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Bioinspired Total Syntheses of Complex Polycyclic Terpenoids:

The Family of Leucosceptroids, (+)-Dictyoxetane and (+)-Dolabellane V

von

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Erklärung

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Eidesstattliche Versicherung

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To my parents,
for all their love and support.

For at the root of the impulse to build molecules is a deep, cherished belief that arguably distinguishes chemistry from other sciences: that there is an art in making, worth nurturing for its own sake.

(Philip Ball)

Parts of this thesis have been published in peer-reviewed journals.

A Divergent Approach to the Marine Diterpenoids (+)-Dictyoxetane and (+)-Dolabellane V
Cedric L. Hugelshofer, Thomas Magauer, *Chem. Eur. J.* ***2016***, 22, 15125–15136.

A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane
Cedric L. Hugelshofer, Thomas Magauer, *J. Am. Chem. Soc.* **2016**, *138*, 6420–6430.
This work was highlighted in *SYNFACTS*: E. M. Carreira, H. Wolleb, *Synfacts* **2016**, *12*, 771.

Total Synthesis of the Leucosceptroid Family of Natural Products
Cedric L. Hugelshofer, Thomas Magauer, *J. Am. Chem. Soc.* **2015**, *137*, 3807–3810.

Strategies for the Synthesis of Antifeedant Leucosceptroid Natural Products
Cedric L. Hugelshofer, Thomas Magauer, *Synlett* **2015**, *26*, 572–579.

Unraveling the Metabolic Pathway in *Leucosceptrum canum* by Isolation of New Defensive Leucosceptroid Degradation Products and Biomimetic Model Synthesis
Shi-Hong Luo,[†] Cedric L. Hugelshofer,[†] Juan Hua, Shu-Xi Jing, Chun-Huan Li, Yan Liu, Xiao-Nia Li, Xu Zhao, Thomas Magauer, Sheng-Hong Li, *Org. Lett.* **2014**, *16*, 6416–6419.

A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (–)-Norleucosceptroid B, and (–)-Leucosceptroid K
Cedric L. Hugelshofer, Thomas Magauer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11351–11355.
This work was highlighted in *SYNFACTS*: E. M. Carreira, M. Westphal, *Synfacts* **2014**, *10*, 1233.

High-Pressure Transformations in Natural Product Synthesis
Cedric L. Hugelshofer, Thomas Magauer, *Synthesis* **2014**, *46*, 1279–1296.

[†] These authors contributed equally to this work.

Parts of this thesis have been presented at scientific conferences.

Syngenta workshop for talented young chemists
Bioinspired Total Syntheses of Complex Polycyclic Terpenoids: The Leucosceptroids and Dictyoxetane (poster). *Stein, Switzerland, Sep. 2016.*

Reaxys PhD Prize Symposium 2016
Bioinspired Total Syntheses of Complex Polycyclic Terpenoids: The Leucosceptroids and Dictyoxetane (poster). *London, United Kingdom, Sep. 2016.*

Gordon Research Conference – Natural Products & Bioactive Compounds
A Divergent and Bioinspired Total Synthesis of (+)-Dictyoxetane and (+)-Dolabellane V (short oral presentation and poster). *Andover, USA, Aug. 2016.*

Hochschule trifft Industrie
Collective Synthesis of Antifeedant Leucosceptroid Natural Products (oral presentation). *Rheinfelden, Switzerland, Oct. 2015.*

Gordon Research Conference – Natural Products
Asymmetric Total Synthesis of the Leucosceptroid Family of Antifeedant Natural Products (selected oral presentation and poster). *Andover, USA, Jul. 2015.*

Kunming Institute of Botany – Chinese Academy of Sciences
A General Entry to Antifeedant Sesterterpenoids (oral presentation). *Kunming, China, Oct. 2014.*

Press-Release

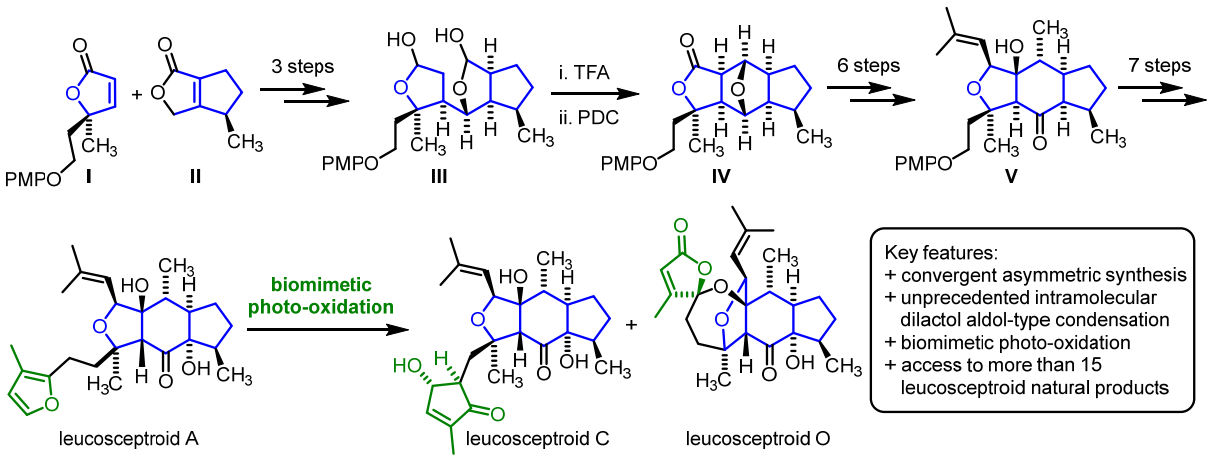
Chemical Synthesis of Antifeedant Natural Products from the Coca Cola tree
Cedric L. Hugelshofer, Klaus Speck, Adriana S. Grossmann, Thomas Magauer. www.beilstein.tv *Jan. 2015*

ABSTRACT

This Ph.D. thesis describes the first collective total synthesis of the leucosceptroid family of natural products, as well as a divergent approach to the marine diterpenes (+)-dictyoxetane and (+)-dolabellane V.

PART I: *Leucosceptrum canum* Smith is a shrub endemic to southwest China and Nepal that harbors sesterterpenoids, designated leucosceptroids A–Q and norleucosceptroids A–H. These compounds were found to act as a potent biological defense against plant-feeding insects. The antifeedant properties together with the novel molecular scaffolds of the leucosceptroids, comprising a 5,6,5-framework with a fully functionalized tetrahydrofuran ring and eight contiguous stereogenic centers, make these natural products highly attractive targets for total synthesis.

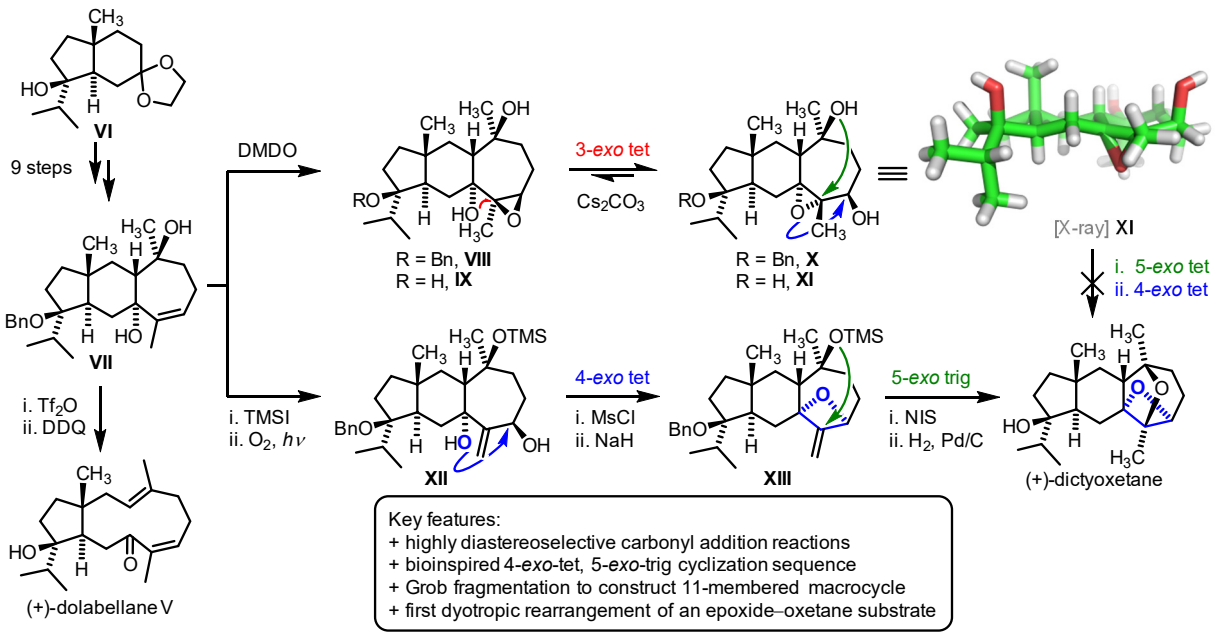
Part I of this thesis presents the evolution of a strategy for the collective synthesis of this family of antifeedant natural products. The elaborated synthetic route commenced with the convergent assembly of the two similarly complex building blocks **I** and **II** (Scheme A). Next, an unprecedented intramolecular dilactol aldol-type condensation of **III** was devised to produce the 5,6,5-framework that is common in all leucosceptroids. Elaboration of the core structure **IV** gave access to gram quantities of the highly functionalized tricycle **V**, which served as the pivotal intermediate for the asymmetric total synthesis of 18 complex leucosceptroid members. The development of a model system helped revealing biogenetic relationships between individual leucosceptroids and could shed light on their biosynthesis. Finally, the biomimetic transformation of leucosceptroid A to leucosceptroids C, K, O and P using singlet oxygen was investigated. Results of these studies corroborated the hypothesis that leucosceptroids A and B are most likely the parent members of the leucosceptroid family of natural products, and photo-oxidation is involved in the metabolic pathway of these antifeedant sesterterpenoids.



Scheme A. Total synthesis of the leucosceptroid family of natural products.

PART II: The second project of this Ph.D. thesis deals with the oxetane-containing natural product (+)-dictyoxetane and the macrocyclic diterpenoid (+)-dolabellane V, for both of which biological activities were unknown and total syntheses had yet to be reported. While only relatively few natural products feature an oxetane, intriguing and strong biological activities are often observed for compounds containing such a structural subunit.

The synthetic efforts towards (+)-dictyoxetane were guided by bioinspired, classical and nonconventional strategies to construct the oxetane, which is embedded in an intricate and unprecedented 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane ring system. At the outset of the bioinspired route, a scalable synthetic approach to key tricycle **VII** was developed starting from known *trans*-hydrindane **VI**. While attempts to prepare (+)-dictyoxetane via epoxides **VIII** and **X** were met with failure, a crucial modification of the originally proposed biosynthesis, involving formation of the oxetane prior to the strained *trans*-tetrahydrofuran ring, eventually enabled construction of the dioxatricyclic substructure. In this respect, use of a highly selective photo-oxidation converted tricycle **VII** into allylic alcohol **XII**, which underwent smooth 4-*exo*-tet cyclization to form oxetane **XIII**. Based on the modified biosynthetic proposal, construction of the synthetically challenging dioxatricyclic framework of (+)-dictyoxetane was then finalized via a 5-*exo* cyclization. Furthermore, the elaborated synthetic route to the full diterpenoid carbon skeleton **VII** emerged as a valuable point of divergence and also allowed disclosing the first total synthesis of (+)-dolabellane V. Notably, a wealth of fascinating reactivity was discovered during the synthetic investigations with putative biogenetic precursors of the dioxatricyclic substructure, and these results culminated in the development of the first strain-releasing type I dyotropic rearrangement of an epoxide–oxetane substrate.



Scheme B. Divergent total synthesis of the marine diterpenoids (+)-dictyoxetane and (+)-dolabellane V.

ACKNOWLEDGEMENTS

The time as a Ph.D. student has certainly been one of the most exciting, interesting, and challenging periods of my life. My mornings in the laboratory repeatedly started with an indescribable and exhilarating feeling that I would be spending the day experimenting and 'making molecules', or simply getting to do something I love. I consider myself very fortunate to have had this exceptional opportunity, and these past years would not nearly have been such a good experience were it not for all the people I was able to spend time with and who supported me.

Foremost, I would like to thank Dr. Thomas Magauer for giving me the opportunity to conduct my Ph.D. studies in his research group, where I was able to expand my chemistry knowledge under his guidance. I am very grateful for the challenging and fascinating projects, and being granted the freedom to implement my own creativity and ideas while working on them. Tommy's enthusiasm for chemistry, confidence in the success of the projects and his tremendous and ceaseless support (amongst countless other things, memorable help with a two hundred millimole scale-up on a weekend), are truly inspiring and have made this an extraordinarily rewarding time as a Ph.D. student. I also specially would like to thank Tommy for appreciating my work and for the large number of instructive and motivating discussions we had.

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
Bn	benzyl
BPO	benzoyl peroxide
br	broad (NMR spectroscopy, IR spectroscopy)
Bu	butyl
CCDC	Cambridge Crystallographic Data Centre
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet (NMR spectroscopy)
d.r.	diastereomeric ratio
dba	tris(dibenzylideneacetone)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyano-1,3-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethylallyl pyrophosphate
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
dmp	tris(dipivaloylmethanato)
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino) ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDCI	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization (mass spectrometry)
equiv	equivalent(s)
ESI	electron spray ionization (mass spectrometry)
Et	ethyl
FPP	farnesyl diphosphate
g	gram(s)
GFPP	geranylfarnesyl diphosphate
GGPP	geranylgeranyl diphosphate
GPP	geranyl diphosphate
h	hour(s)
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence
HWE	Horner-Wodswarth-Emmons
Hz	Hertz (frequency)
i-	*iso* (isomer)
IBX	2-iodoxybenzoic acid
im	imidazole
IPP	isopentenyl pyrophosphate

IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
L_n	ligand(s)
m	medium (IR spectroscopy)
m	multiplet (NMR spectroscopy)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum (pyridine)(hexamethyl phosphoramide)
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MVK	methylvinylketone
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-morpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
p	*para* (isomer)
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
$PhNTf_2$	*N*-phenyl(bistrifluoro methanesulfonimide)
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
q	quartet (NMR spectroscopy)
R	undefined substituent
RCM	ring closing metathesis
R_f	retardation factor
s	strong (IR spectroscopy)
s	singlet (NMR spectroscopy)
SEM	2-(trimethylsilyl)ethoxymethyl
T	temperature
t	triplet (NMR spectroscopy)
t-	(*tert*-) tertiary (isomer)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	*meso*-tetraphenylporphyrin
w	weak (IR spectroscopy)
wt%	weight percent

TABLE OF CONTENTS

THEORETICAL SECTION

EXPERIMENTAL SECTION

THEORETICAL SECTION

1 BIOINSPIRED SYNTHESIS

1.1 General Introduction

In the field of organic chemistry, a biomimetic synthesis or reaction sequence constitutes a transformation that mimics a hypothetical or proven biosynthetic pathway of a natural product.[1] In general, the imitated biosynthetic proposal needs to have a firm basis in known chemical pathways, such as the biosynthesis of terpenoids or polyketides. It is preferable to use the term bioinspired rather than biomimetic synthesis, when the mimicking transformations are conducted with reagents and conditions that are not representative of natural systems. By inducing a specific reaction on a putative biosynthetic intermediate, the transformation might serve as an approach to corroborate a biosynthetic proposal. Alternatively, if the reaction would not succeed, the suggested biosynthesis would remain unsupported and might need to be revised.[2]

The concept of biomimetic synthesis was first introduced in 1917 by Sir Robert Robinson who described the one-pot synthesis of the natural product tropinone (**3**) from glutaraldehyde (**1**), methyl amine and acetone dicarboxylic acid **2** by a Mannich reaction cascade (Scheme 1a).[3] Following this seminal report, numerous other syntheses have been inspired by nature, such as the polyene cyclization cascade to form allopregnanolone (**5**) (Scheme 1b).[4] Heathcock and co-workers realized an impressive cascade of biomimetic steps in total syntheses of several homosecodaphniphyllate congeners starting from simple squalene-type precursors, such as **6** (Scheme 1c).[5] The 'endiandric acid cascade' constitutes a further classic contribution to the field and highlights the beauty of electrocyclizations, which nature uses to build complex natural products.[6] In Nicolaou's bioinspired study, diyne **8** was subjected to Lindlar hydrogenation, whereupon the product underwent sequential, spontaneous 8π conrotatory and 6π disrotatory electrocyclizations and, after a thermally induced intramolecular Diels–Alder reaction, yielded endiandric acid A methyl ester (**9**) (Scheme 1d).[7]

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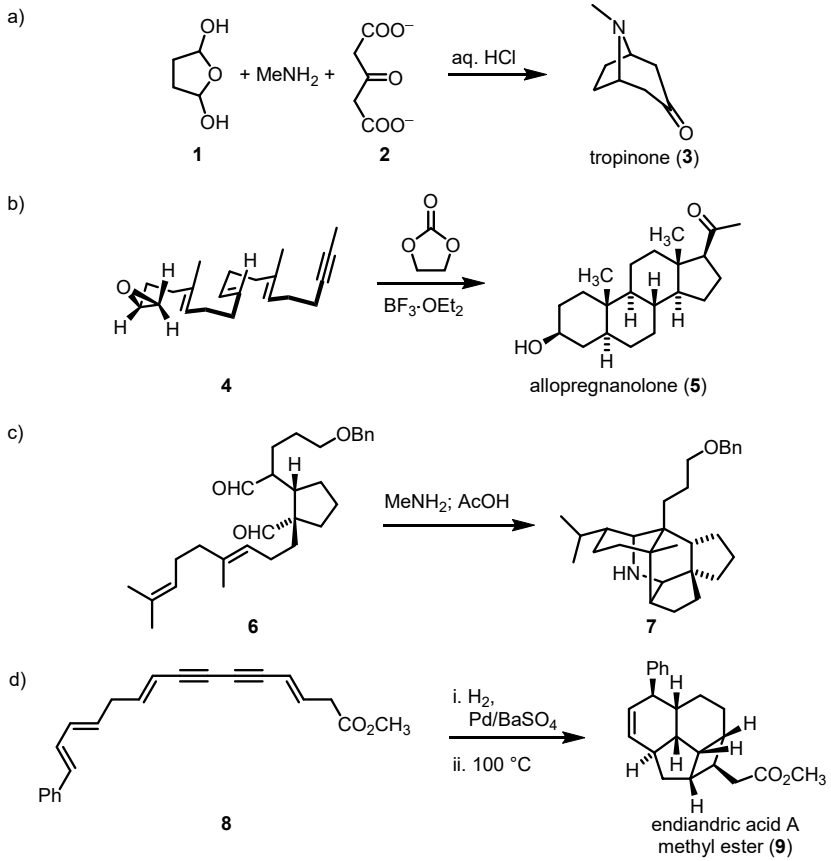
[1] M. C. de la Torre, M. A. Sierra, *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181.
[2] a) E. Gravel, E. Poupon, *Eur. J. Org. Chem.* **2008**, *1*, 27–42; b) M. Razzak, J. K. de Brabander, *Nat. Chem. Biol.* **2011**, *7*, 865–875.
[3] a) R. Robinson, *J. Chem. Soc. Trans.* **1917**, *111*, 762–768; b) A. J. Humphrey, D. O'Hagan, *Nat. Prod. Rep.* **2001**, *18*, 494–502.
[4] a) W. S. Johnson, M. B. Gravestock, B. E. McCarry, *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334; b) S. K. Taylor, *Org. Prep. Proced. Int.* **1992**, *24*, 245–284. c) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730–4756.
[5] a) C. H. Heathcock, S. K. Davidsen, S. Mills, M. A. Sanner, *J. Am. Chem. Soc.* **1986**, *108*, 5650–5651; b) R. B. Ruggeri, M. M. Hansen, C. H. Heathcock, *J. Am. Chem Soc.* **1988**, *110*, 8734–8736; c) J. A. Stafford, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 5433–5434; d) C. H. Heathcock, J. A. Stafford, D. L. Clark, *J. Org. Chem.* **1992**, *57*, 2575–2585; e) C. H. Heathcock, R. B. Ruggeri, K. F. McClure, *J. Org. Chem.* **1992**, *57*, 2585–2594; e) C. H. Heathcock, J. A. Stafford, D. L. Clark, *J. Org. Chem.* **1992**, *57*, 2566–2574; f) C. H. Heathcock, J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, *60*, 1120–1130.
[6] C. M. Beaudry, J. P. Malerich, D. Trauner, *Chem. Rev.* **2005**, *105*, 4757–4778
[7] K. C. Nicolau, N. A. Petasis, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, *104*, 5560–5562.



Scheme 1. Seminal biomimetic syntheses of a) tropinone (**3**), b) allopregnanolone (**5**), c) methyl homosecodaphniphylate precursor **7** and d) endiandric acid A methyl ester (**9**)

As highlighted by these four examples, nature uses relatively small and simple building blocks as precursors for the synthesis of complex molecules. In these processes, cascade reactions frequently occur,[8] where products of one transformation serve as the starting material for a subsequent reaction sequence, thus leading to a rapid increase in structural complexity. Striving to match nature's ingenuity for achieving the total synthesis of natural products is often an intractable ambition in a chemical laboratory. However, it can be advantageous to design synthetic routes bearing biosynthetic considerations in mind, or to devise strategies that feature an individual bioinspired step.[9] Besides providing the recognition and understanding of how nature generates molecular complexity, bioinspired syntheses also stimulate the development of new reactions or result in alternative methods for the preparation of a desired target.[10] Furthermore, employing step-economic cascade reactions can favorably minimize the amount of labor and a general entry to a whole family of natural products might be feasible, if a common biosynthetic precursor can be identified.

[8] a) K. C. Nicolau, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; b) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong and E. A. Anderson, *Chem. Soc. Rev.* **2016**, *45*, 1557–1569.
[9] P. G. Bulger, S. K. Bagal, R. Marquez, *Nat. Prod. Rep.* **2008**, *25*, 254–297.
[10] A. M. Armaly, Y. C. DePorre, E. J. Groso, P. S. Riehl, C. S. Schindler, *Chem. Rev.* **2015**, *115*, 9232–9276.

A wealth of fascinating discoveries have been made and elegant routes to daunting natural products were rendered possible in the pursuit of biomimetic and bioinspired syntheses. In the following section, compelling examples from the recent literature are presented, which highlight conceptually different bioinspired syntheses in the field of terpenoids.

1.2 Bioinspired Syntheses of Terpenoids

1.2.1 Polycyclizations

Arguably, one of the most vibrant areas of bioinspired syntheses of terpene-derived molecules, involve orchestrated, cascade cyclizations of linear precursors to form polycyclic cores of natural products.[11] This strategy is similar to the way nature operates in the biosynthesis of terpenoids (*cf*. Chapter 2.1.1) and stands in stark contrast to traditional syntheses. In the latter case, structural complexity is built up in a stepwise fashion and the idea prevails that each chemical step should introduce a new stereocenter.

Using a strategy that mimics nature, researchers have reported the total synthesis of the meroterpenoid–hybrid hongoquercin B (**10**) from the acyclic precursor **11** (Scheme 2a).[12] In the dual bioinspired route, cyclo-aromatization formed the resorcylate substructure and was directly followed by a stereocontrolled diene epoxide cyclization, which generated the tetracyclic core of the natural product.

As opposed to classical terpenoid biosynthesis, where after cyclization the product then is sequentially oxidized, the order is reversed in the case of ladder polyether metabolites. In the proposed biosynthesis of polyethers, such as the non-traditional polyketide brevetoxin B (**12**), a linear polyene is first oxidized to a polyepoxide (e.g. **13**), which then undergoes a cascade of regio- and stereoselective epoxide-opening events (Scheme 2b).[13] Such dramatic epoxide-opening cascades have enticed many researchers to translate nature's elegant method to the laboratory and develop bioinspired syntheses of challenging polyethers.[14]

The group of McDonald reported an elegant total synthesis of the marine triterpenoid abudinol B (**18**), which features an intriguing structure with cyclic ethers fused to carbacyclic rings (Scheme 2c).[15] In their strategy, the proposed biosynthetic pathway was mimicked starting from a linear squalene-like precursor and by employing a hybrid cascade of epoxide openings and carbacyclizations. Diepoxide **14** was prepared in a short reaction sequence and incorporates an enolsilane for efficient nucleophilic termination of the cascade reaction. In the first stage of the bioinspired tricyclization, the combination

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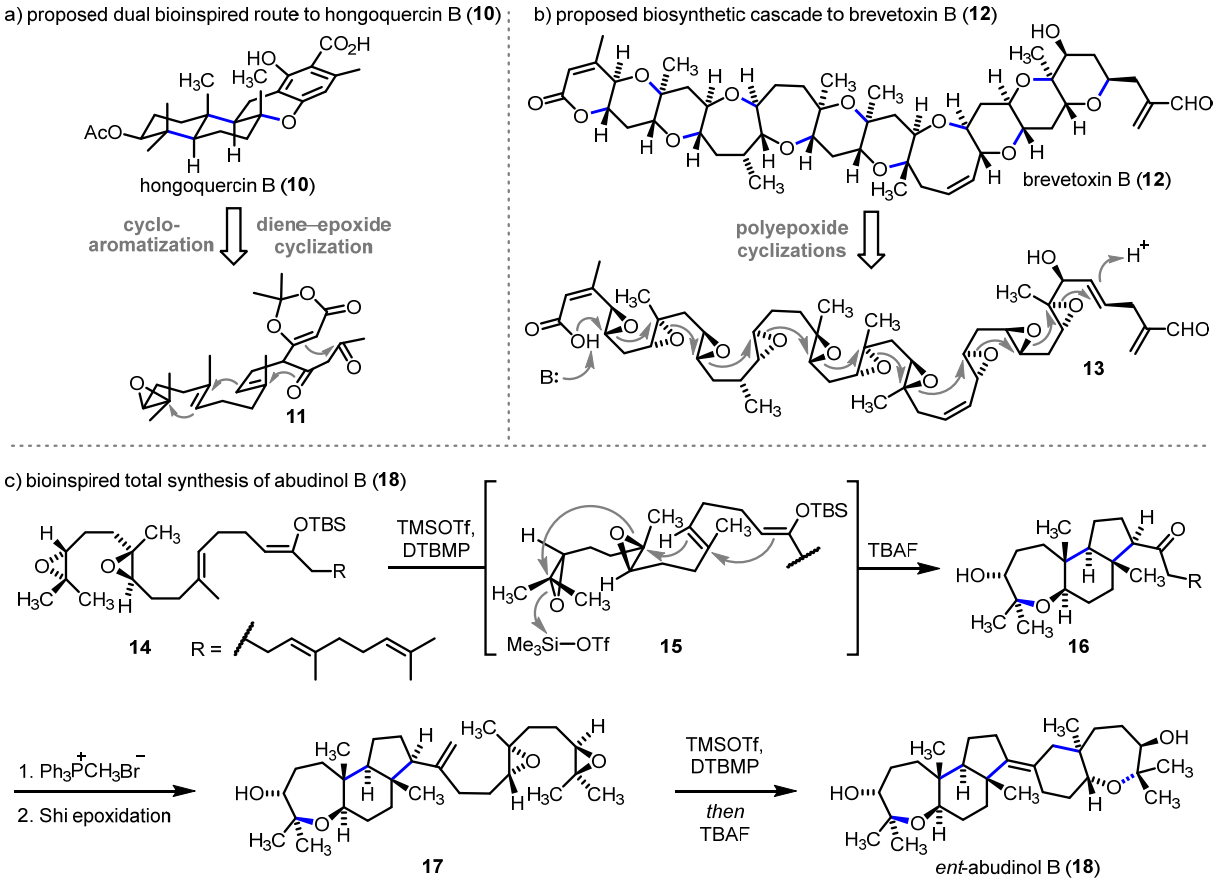
[11] a) G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077; b) P. A. Stadler, A. Eschenmoser, H. Schinz, G. Stork, *Helv. Chim. Acta* **1957**, *40*, 2191–2198; c) W. S. Johnson, K. Wiedhaup, S. F. Brady, G. L. Olson, *J. Am. Chem. Soc.* **1968**, *90*, 5277–5279.
[12] T. N. Barrett, A. G. M. Barrett, *J. Am. Chem. Soc.* **2014**, *136*, 17013–17015.
[13] a) M. S. Lee, G.-W. Qin, K. Nakanishi, M. G. Zagorski, *J. Am. Chem. Soc.* **1989**, *111*, 6234–6241; b) I. Vilotijevic, T. F. Jamison, *Mar. Drugs* **2010**, *8*, 763–809.
[14] a) I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189–1192; b) I. Vilotijevic, T. F. Jamison, *Angew. Chem. Int. Ed.* **2009**, *48*, 5250–5281.
[15] R. Tong, F. E. McDonald, *Angew. Chem. Int. Ed.* **2008**, *47*, 4377–4379.

of trimethylsilyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine led to selective activation of the terminal epoxide and promoted tandem cyclizations to provide tricyclic ketone **16**, after desylation with tetrabutylammonium fluoride. The stereochemical outcome for this major product was found to be consistent with the chair-like conformation shown in **15**. The cascade product **16** was then elaborated to diepoxide **17** in a reaction sequence involving Wittig methylenation and Shi epoxidation. Employing the same activation conditions as before, **17** underwent the hybrid cyclization cascade and afforded *ent*-abudinol B (**18**), albeit accompanied by a partially cyclized by-product arising due to the relatively poor nucleophilicity of the terminating alkene. Despite being a linear synthetic route, the rapid generation of structural complexity using the bioinspired tandem oxa- and carbacyclizations proved highly advantageous and resulted in a concise synthesis of **18**.



Scheme 2. a) Concept of polyolefin carbocyclizations, b) cascade epoxide-opening reactions and c) application to the bioinspired synthesis of abudinol B (**18**).

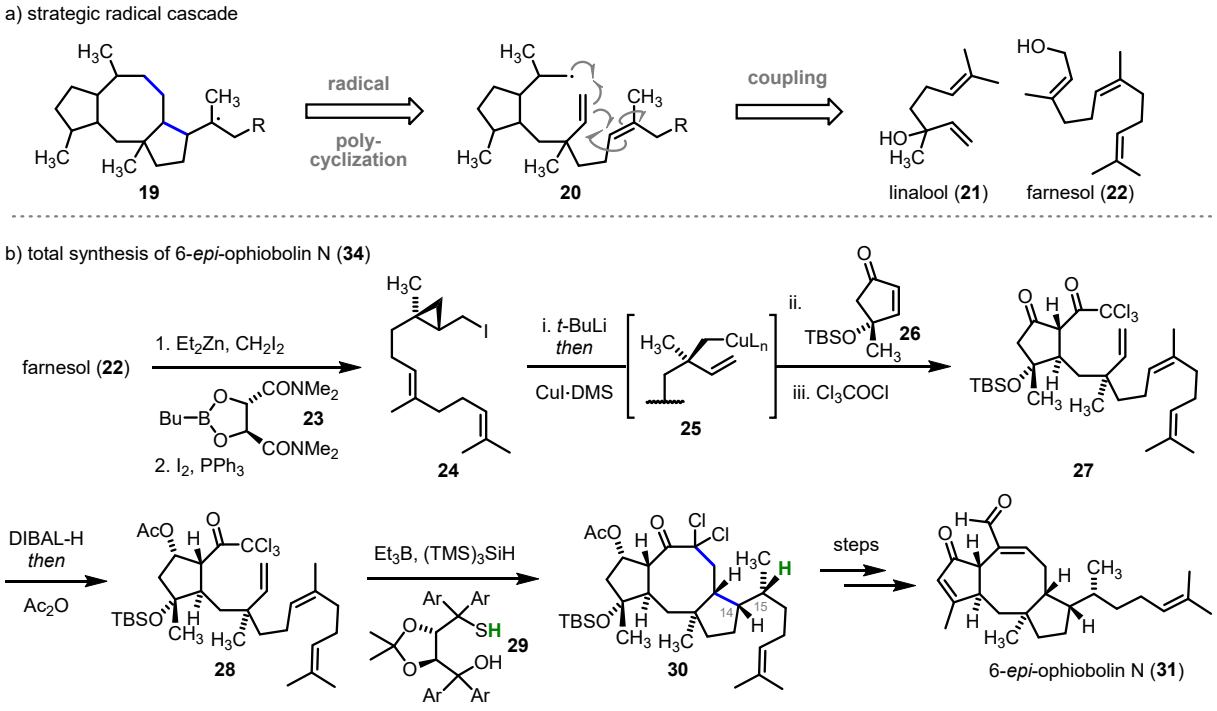
While bioinspired cationic polyene cyclizations constitute a well-studied and powerful approach to access the carbocyclic framework of many terpenoids in a laboratory setting,[4c] this method is often problematic or unsuitable for the synthesis of medium or larger ring frameworks. Alternatively, radical-based bioinspired syntheses of terpenoids have been developed and in some cases these methods can nicely complement the previous cationic approach.[16] Maimone and co-workers recently described a strategy to forge a 5-8-5 fused ring system, as is common in ophiobolin sesterterpenoids, by radical-based cyclization of polyprenyl-derived chains.[17] As outlined in Scheme 3a, the tricyclic framework of **19** was envisioned to be constructed by a cascade 8-*endo*/5-*exo* radical cyclization of **20**, and to this end linalool (**21**) and farnesol (**22**) were identified as suitable starting materials. Thus, the key principle of this strategy involved a bioinspired building block choice, while bond formation was envisioned to take place in a disparate fashion.

The synthesis of the 5-8-5 fused ring system initiated with preparation of iodide **24** via asymmetric cyclopropanation of farnesol (**22**), followed by an Apple reaction (Scheme 3b). Treatment of **24** with *tert*-butyllithium induced lithium-halogen exchange and cyclopropane fragmentation,[18] affording organocopper species **25**, after transmetallation. Addition of the latter species to cyclopentenone **26** (itself prepared in two steps from **21**) occurred diastereoselectively and the intermediate enolate was trapped with trichloroacetyl chloride, yielding trichloroketone **27**. After conversion to acetate **28**, the envisioned key radical cyclization was investigated. A survey of a variety of reaction conditions revealed that the impressive reductive cyclization of **28** to **30** could be effected using triethylborane/air-mediated initiation and employing tris(trimethylsilyl)silane together with a thiol additive. Chiral thiol **29** exerted its influence during the termination of the radical cascade, and was found to improve the diastereoselectivity at C-15 (d.r. = 3.4:1). The remarkably short total synthesis of 6-*epi*-ophiobolin N (**31**) was then completed by incorporation of one further carbon and in few further steps.

1.2.2 Oxidations

A conceptually different approach for the total synthesis of natural products was adopted by researchers who hypothesized that a strategy that holistically mimics nature's two-phase terpenoid synthesis would prove advantageous.[19] Following the first phase (cyclase phase), where the carbon framework is constructed from linear hydrocarbon building blocks, such as by polyene cyclizations, the second phase (oxidase phase) involves divergent oxidation of C=C and C–H bonds to generate structural diversity. Inspired by nature's efficiency in creating a myriad of complex terpenoids, Baran and co-workers

[16] J. Justicia, L. A. de Cienfuegos, A. G. Campaña, D. Miguel, V. Jakoby, A. Gansäuer, J. M. Cuerva, *Chem. Soc. Rev.* **2011**, *40*, 3525–3537.
[17] Z. G. Brill, H. K. Grover, T. J. Maimone, *Science* **2016**, *352*, 1078–1082.
[18] A. B. Charette, J. Naud, *Tetrahedron Lett.* **1998**, *39*, 7259–7262.
[19] K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824–828.



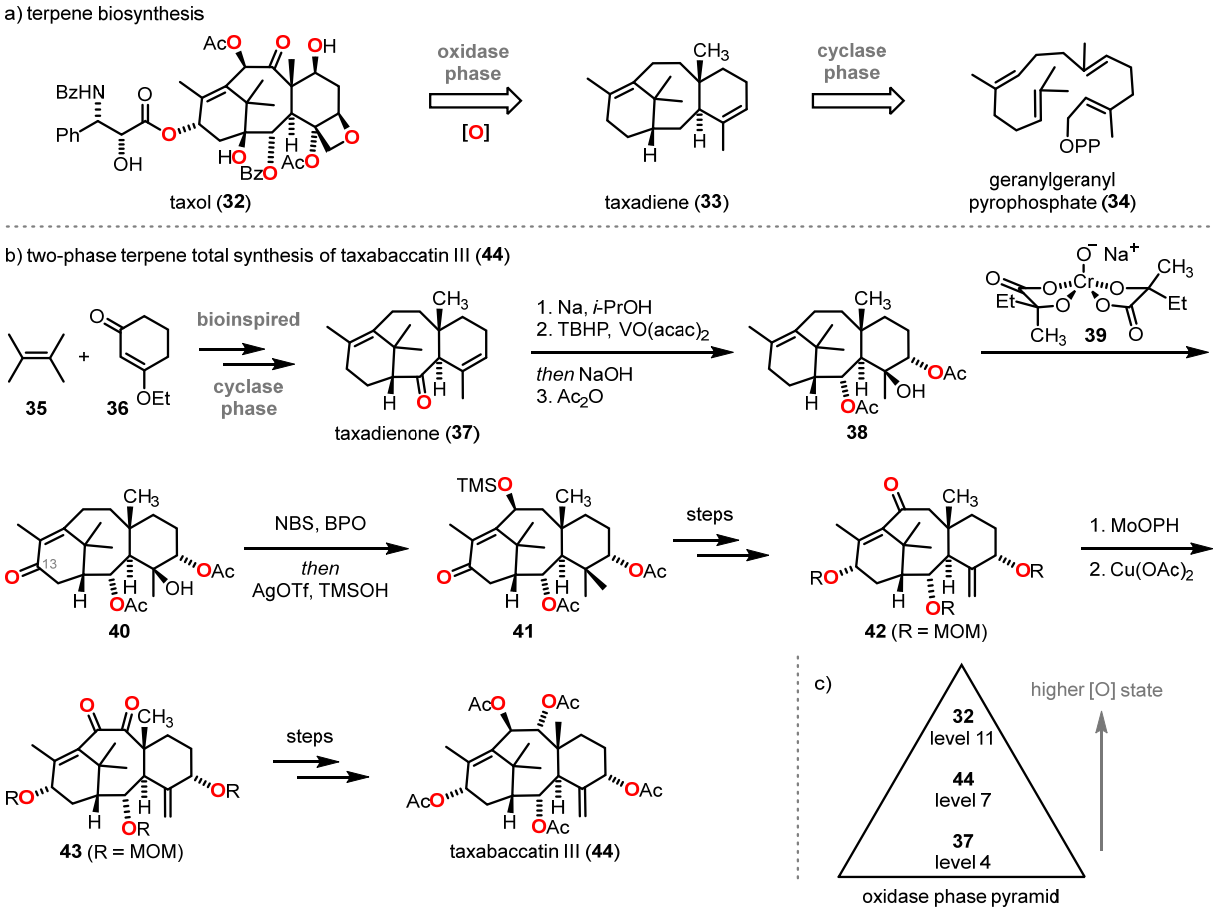
Scheme 3. a) Strategic radical cascade to forge the 5-8-5 tricyclic structure and b) nine-step synthesis of 6-*epi*-ophiobolin N (**31**).

initiated a research program aimed at replicating the biosynthesis of taxanes (Scheme 4a).[20] In 2012, the artificial first phase synthesis of the taxane family of terpenoids was outlined,[21] and taxadienone (**37**) was introduced as the laboratory's synthetic cyclase phase endpoint (Scheme 4b). Since this prelude to an ultimate total synthesis of taxol (**32**), considerable advances have been reported regarding translation of the oxidase phase to the laboratory and in the 'oxidative ascent' of the taxane pyramid (Scheme 4c).[22] In this 'oxidase phase pyramid', the target natural product (**32**) is placed at the apex and the number of C–O bonds decreases upon moving down the pyramid, forming descending levels of oxidation.

In this regard, the successful synthesis of 'level 7' taxabaccatin III (**44**), featuring five oxidized carbon atoms and two degrees of unsaturation, was recently reported starting from taxadienone (**37**).[23] As outlined in Scheme 4b, C–O bonds were sequentially introduced into the carbon framework of **37** using a carefully choreographed sequence of reactions involving epoxidation (**37**→**38**), chromium(V)-mediated allylic oxidation (**38**→**40**), radical-based C–H functionalization (**40**→**41**) and α-hydroxylation (**42**→**43**). These sequential, regio- and stereoselective C–H oxidations highlight that a creative bioinspired synthesis may constitute a huge driving force for the development of novel methods, such as the C–H oxidation with chromium(V)-based reagent **39**, and can stimulate considerable advances in

[20] Y. Ishihara, P. S. Baran, *Synlett* **2010**, 1733–1745.
[21] A. Mendoza, Y. Ishihara, P. S. Baran, *Nat. Chem.* **2012**, *4*, 21–25.
[22] N. C. Wilde, M. Isomura, A. Mendoza, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 4909–4912.
[23] C. Yuan, Y. Jin, N. C. Wild, P. S. Baran, *Angew. Chem. Int. Ed.* **2016**, *55*, 8280–8284.

a field of chemistry.[24] While further ascension of the 'oxidase phase pyramid', to eventually reach taxol (**32**), certainly remains a significant challenge, the completion of this short total synthesis of taxabaccatin III (**44**) constitutes a successful proof of concept of the two-phase terpenoid synthesis principle.

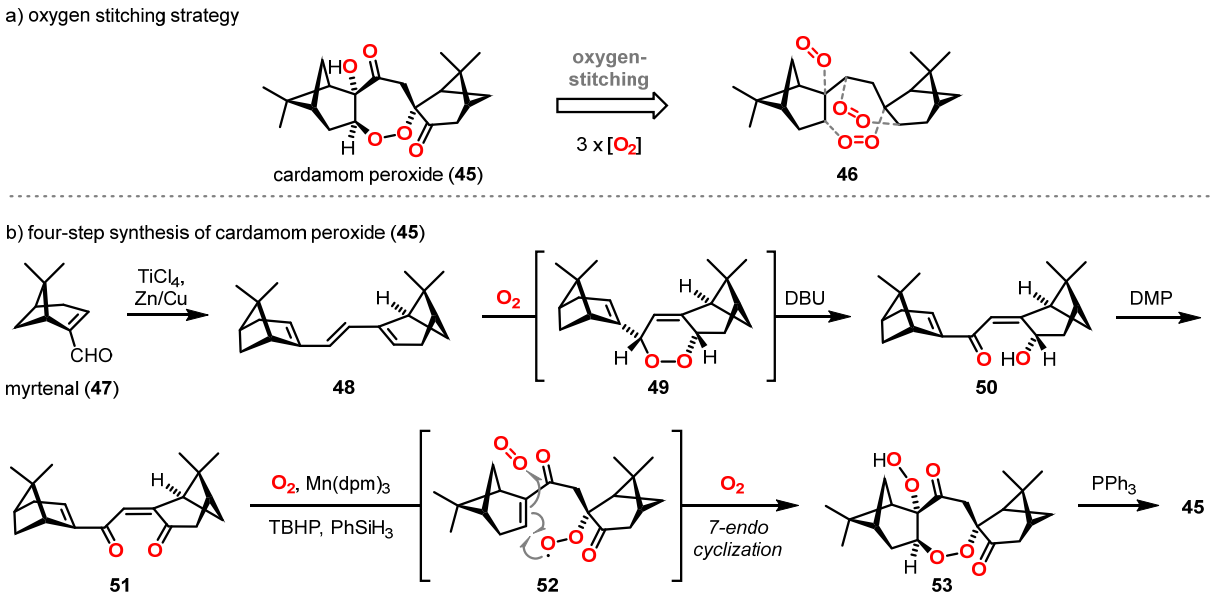


Scheme 4. a) Terpenoid biosynthesis, b) bioinspired two-phase terpene total synthesis of taxabaccatin III (**44**) and c) oxidase phase pyramid.

A quite different total synthesis, but also guided by biosynthetic logic regarding oxidation of a carbon framework, was recently reported of cardamom peroxide (**45**) (Scheme 5a).[25] This natural product features an oxidized, dimeric monoterpene framework and incorporates a bridging seven-membered endoperoxide. While the biosynthetic origin of **45** was unknown at the outset of the studies, it was hypothesized that two monoterpene units and three units of molecular oxygen might be the building blocks. Moreover, the endoperoxide motif was considered to arise from an unusual 7-*endo* cyclization of a peroxy radical (as shown in **52**). To investigate these hypotheses, myrtenal (**47**) was first

[24] a) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783–787; b) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374.
[25] X. Hu, T. J. Maimone, *J. Am. Chem. Soc.* **2014**, *136*, 5287–5290.

dimerized to triene **48** which underwent smooth [4+2] cycloaddition with singlet oxygen. The intermediate endoperoxide **49** was then converted to dienone **51** via Kornblum–DeLaMare rearrangement[26] to **50** and subsequent oxidation. Exposure of **51** to molecular oxygen and a manganese catalyst led to an impressive tandem hydroperoxidation process, which presumably involved the postulated biosynthetic intermediate **52**, and gave diperoxide **53**. A final reduction with triphenylphosphine completed the four-step synthesis of cardamom peroxide (**45**) which corroborated the biosynthetic proposal involving a 7-*endo* cyclization of a peroxy radical.



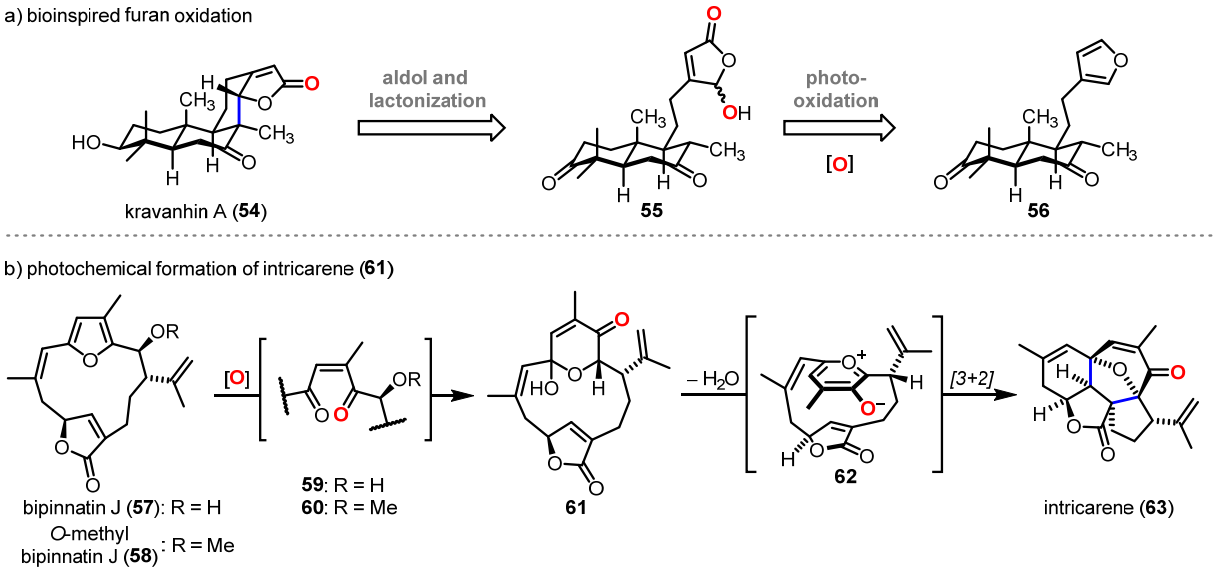
Scheme 5. a) Oxygen stitching blueprint and b) concise total synthesis of cardamom peroxide (**45**).

One of the most widespread applications of singlet oxygen in laboratory syntheses is its use for bioinspired furan oxidations.[27] In this regard, She and co-workers recently reported a short total synthesis of the tetracyclic diterpenoid kravanhin A (**54**) based on retrosynthetic disconnections outlined in Scheme 6a.[28] In their successful plan, **54** was derived from γ-hydroxybutenolide **55** through sequential aldol reaction and lactone formation. In turn, **55** was traced back to furan **56** via a bioinspired photo-oxidation.

A further compelling example involving a bioinspired oxidation concerns the synthesis of the natural product intricarene (**63**), which is a furanocembranoid isolated from Caribbean corals.[29] Diterpenoid **63** was isolated from one of the most irradiated regions of the earth and it thus appears conceivable that photochemical reactions are involved in its biosynthesis. It was hypothesized that intricarene (**63**) might biosynthetically be derived from bipinnatin J (**57**) via intermediate

[26] N. Kornblum, H. E. DeLaMare, *J. Am. Chem. Soc.* **1951**, *73*, 880–881.
[27] a) I. Margaros, T. Montagnon, M. Tofi, E. Pavlakos, G. Vassilikogiannakis, *Tetrahedron* **2006**, *62*, 5308–5317; b) T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res.* **2008**, *41*, 1001−1011.
[28] Z. Zhong, G. Zhao, D. Xu, B. Dong, D. Song, X. Xie, X. She, *Chem. Asian J.* **2016**, *11*, 1542–1547.
[29] J. Marrero, A. D. Rodríguez, C. L. Barnes, *Org. Lett.* **2005**, *7*, 1877–1880.

hydroxypyranone **61**.[30] Elimination of water from the latter species would produce oxidopyrylium species **62** which is well-disposed to undergo a transannular 1,3-dipolar cycloaddition to form **63**. In their seminal work, Trauner and co-workers showed that conversion of bipinnatin J (**57**) to hydroxypyranone **61** could be achieved using either *meta*-chloroperoxybenzoic acid or the biomimetic oxidant singlet oxygen. However, the final cycloaddition to form **63** was found to require temperatures beyond 150 °C, which are conditions that cannot be deemed 'biomimetic'.[30a] In more recent work by the same group,[31] an intriguing discovery was made: Oxidation of the methyl ether derived from bipinnatin J (**58**) with singlet oxygen afforded dione **60**, which upon irradiation with light (mimicking Caribbean sunlight) yielded intricarene (**63**). This surprising outcome was thoroughly investigated with a combination of experiments and theory, and eventually revealed that the oxidopyrylium intermediate can also form under photochemical conditions. Thus, the existence of **63** can be rationalized by invoking a photochemical rather than a thermal, 'non-biomimetic' 1,3-dipolar cycloaddition.



Scheme 6. a) Retrosynthetic analysis of kravanhin A (**54**) based on furan oxidation and b) bioinspired synthesis of intricarene (**63**).

1.2.3 Biosynthetic Relationships

The development of bioinspired syntheses based on a formulated biosynthetic proposal can also help unveil links between apparently related natural products, especially if these coexist in an organism. In some cases, a postulated biosynthetic relationship can invoke a viable intermediate, which might be a natural product in its own right. Alternatively, identification of a common biosynthetic precursor can enable a general entry to a family of natural products.

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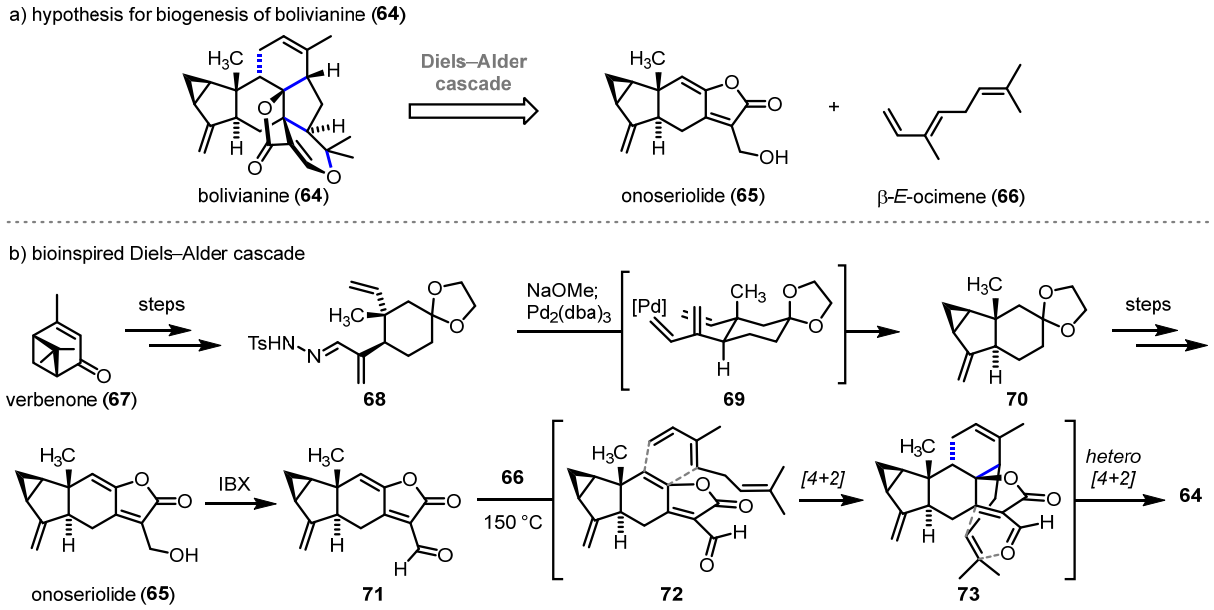
[30] a) P. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, *8*, 5901–5904; b) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401–6404; c) Huang, Q.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545.
[31] D. Stichnoth, P. Kölle, T. J. Kimbrough, E. Riedle, R. de Vivie-Riedle, D. Trauner, *Nat. Commun.* **2014**, *5*, 5597.

Bolivianine (**64**) is a complex sesterterpenoid featuring a daunting heptacyclic skeleton with nine stereogenic centers, which makes it an alluring target for chemical synthesis. Attracted by this challenge, Liu and co-workers established a biosynthetic hypothesis for the formation of bolvianine (**64**) involving a Diels–Alder cascade of onoseriolide (**65**) and β-*E*-ocimene (**66**) (Scheme 7a).[32] This proposal was particularly motivated by the discovery, that the terpenoids **65** and **66** are also present in *Hedyosmum angustifolium*, the small tree from which **64** had been isolated.

Inspired by this hypothesis, a concise synthesis of onoseriolide (**65**) was first developed which started from verbenone (**67**) and included allylic metal carbene species **69** for achieving an intramolecular cyclopropanation (Scheme 7b). After oxidation of **65** to aldehyde **71**, the feasibility of the bioinspired cascade reaction for the preparation of bolvianine (**64**) was investigated. Gratifyingly, it was discovered that heating a mixture of **71** and β-*E*-ocimene (**66**) led to the envisioned Diels–Alder/intramolecular hetero-Diels–Alder cascade, and furnished **64** as the only isolable isomer. Impressively, three cycles, four C–C bonds and five stereogenic centers were generated in this one-pot transformation. While it was put forth that the first cycloaddition reaction (**72**→**73**) might be catalyzed by a Diels–Alderase in nature,[33] investigations on a related system showed, that the intramolecular hetero-Diels–Alder reaction (**73**→**64**) spontaneously took place under ambient conditions.



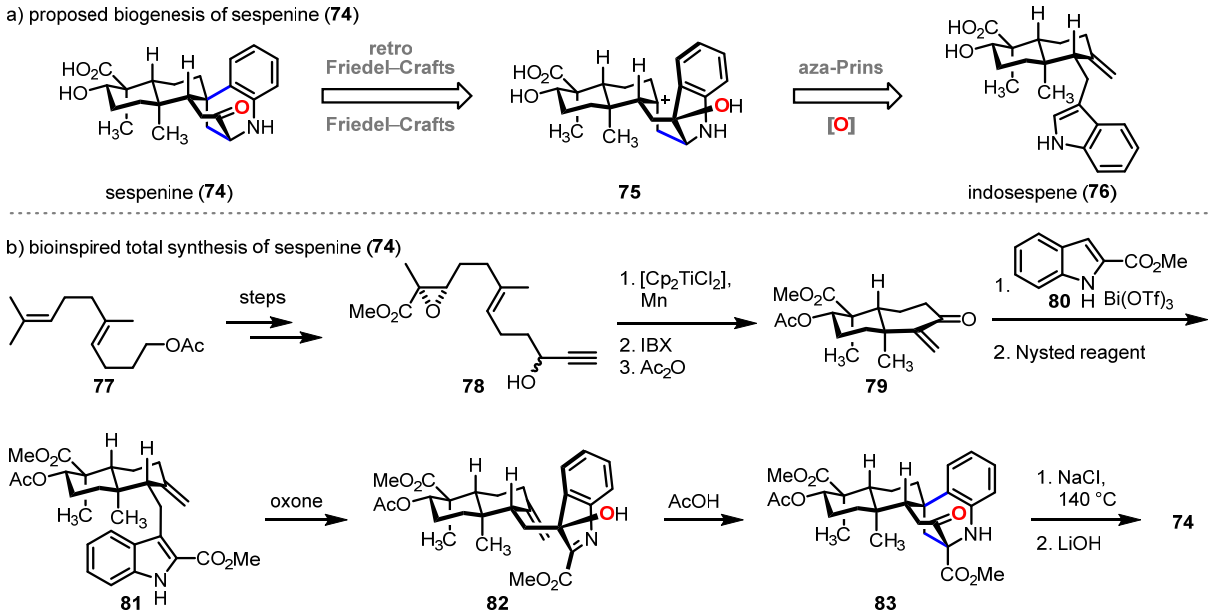
Scheme 7. a) Proposed biogenesis of bolivianine (**64**) and b) bioinspired Diels–Alder cascade in the synthesis of **64**.

[32] a) C. Yuan, B. Du, L. Yang, B. Liu, *J. Am. Chem Soc.* **2013**, *135*, 9291–9294; b) A different hypothesis for the biogenesis of **64** was also reported by the Jullian group, see: L. Acebey, M. Sauvain, S. Beck, C. Moulis, A. Gimenez, V. Jullian, *Org. Lett.* **2007**, *9*, 4693–4696.

[33] a) H. J. Kim, M. W. Ruszczycky, S. Choi, Y. Liu, H. Liu, *Nature* **2011**, *473*, 109–112; b) E. M. Stocking, R. M. Williams, *Angew. Chem. Int. Ed.* **2003**, *42*, 3078−3115; c) M. J. Byrne, N. R. Lees, L.-C. Han, M. W. van der Kamp, A. J. Mulholland, J. E. M. Stach, C. L. Willis, P.R. Race, *J. Am. Chem. Soc.* **2016**, *138*, 6095–6098.

The rare indole sesquiterpenoid sespenine A (**74**) constitutes a further enthralling example, in which identification of a relationship between two natural products proved invaluable for the development of a successful bioinspired total synthesis. It was hypothesized that **74** might biosynthetically originate from indosespene (**76**), which features a similar decalin system as the target natural product (Scheme 8a).[34] After oxidation of the indole C3-position in **76**, a cationic cascade could take place, which would initiate with an aza-Prins cyclization to form the cationic species **75**. Subsequently a Friedel–Crafts annulation followed by retro-Friedel–Crafts fragmentation would form the spiro-tetrahydroquinoline scaffold of **74**.

As outlined in Scheme 8b, Li and co-workers approach to the indosespene-type intermediate **81** commenced with a titanium-catalyzed radical cyclization of epoxide **78** (prepared in seven steps from **77**). After conversion to enone **79**, conjugate addition of indole **80** was promoted by bismuth(III) trifluoromethanesulfonate, and the resulting ketone was treated with Nysted reagent[35] to furnish **81**. The C2-substituent on the indole represents a slight detour from the biosynthetic proposal (*cf.* **76**), but was found to be essential for stabilizing the following synthetic intermediates. Treatment of **81** with oxone led to formation of **82**, which upon exposure to acid cleanly underwent the anticipated cationic cascade reaction and efficiently furnished aniline **83**. Finally, demethoxycarbonylation and subsequent global hydrolysis completed the bioinspired total synthesis of sespenine (**74**).



Scheme 8. a) Proposed biosynthetic relationship of sespenine (**74**) and indosespene (**76**) and b) bioinspired total synthesis of sespenine (**74**).

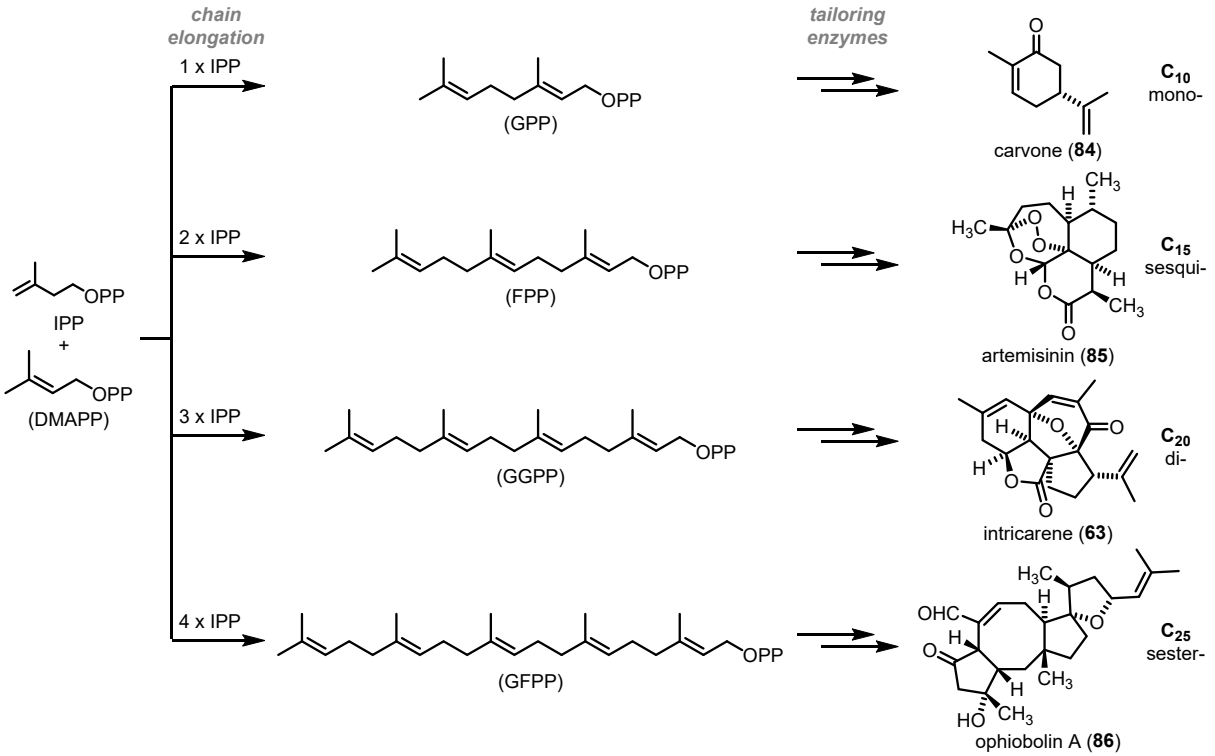
[34] Y. Sun, P. Chen, D. Zhang, M. Baunach, C. Hertweck, A. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 9012–9016.
[35] S. Matsubara, M. Sugihara, K. Utimoto, *Synlett* **1998**, 313–315.

2 PART I: THE LEUCOSCEPTROID FAMILY OF NATURAL PRODUCTS

2.1 Introduction

2.1.1 *trans*-Fused Cyclopentane Terpenoids

Terpenoids constitute the largest class of natural products and play essential roles in mediating a variety of antagonistic and beneficial interactions among organisms in nature.[36] Isopentenyl diphosphate (IPP) stands at the biosynthetic origin of all higher terpenoids, and by isomerization to dimethylallyl diphosphate (DMAPP) is sequentially elongated by prenyltransferases to geranyl diphosphate (GPP, C_{10}), farnesyl diphosphate (FPP, C_{15}), geranylgeranyl diphosphate (GGPP, C_{20}) or geranylfarnesyl diphosphate (GFPP, C_{25}) (Scheme 9).[37] The myriad terpenoid skeletons then arise from these linear precursors by enzyme catalyzed cascade reactions,[38] involving cyclizations, rearrangements, hydrations and selective oxidations.



Scheme 9. Biosynthesis of higher terpenoids.

[36] J. Gershenzon, N. Dudareva, *Nat. Chem. Biol.* **2007**, *3*, 408–414.
[37] P. M. Dewick, *Nat. Prod. Rep.* **2002**, *19*, 181−222.
[38] D. W. Christianson, *Chem. Rev.* **2006**, *106*, 3412–3442.

Based on the great diversity and large number of naturally occurring terpenoids they may be classified according to their number of basic C_5 building blocks. Thus, the exemplary natural products carvone (**84**),[39] artemisinin (**85**),[40] intricarene (**63**)[41] and ophiobolin A (**86**) [42] belong to the subclasses of mono-, sesqui-, di- and sesterterpenoids, respectively.

Within the large family of terpenoid natural products, various members have been discovered that feature a *trans*-fused cyclopentane moiety. Based on the different substitution patterns of the cyclopentane, further distinctions can be made depending on the presence of an *iso*-propyl (or isopropenyl) substituent (type I),[43] both an *iso*-propyl and a tertiary hydroxyl group (type II), or cases where a methyl substitutes the *iso*-propyl substituent and the angular (quaternary) methyl group is missing (type III). The archetypal example of *trans*-fused cyclopentane terpenoid featuring an *iso*-propyl group (type I) is retigeranic acid A (**87**), which was also synthesized in the laboratory by various groups (Figure 1a).[44] Further, natural products with a comparable carbon framework are the sesterterpenoids variecolin (**88**),[45] asperterpenoid (**89**)[46] and recently discovered aspterpenacid A (**90**).[47]

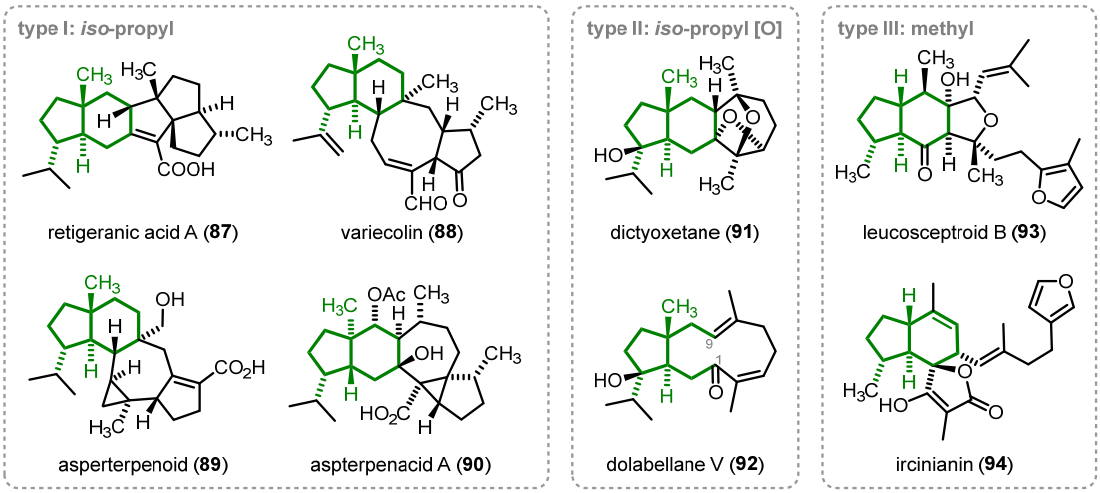


Figure 1. Selected *trans*-fused cyclopentane terpenoids (some members are drawn as the unnatural enantiomer to facilitate comparison).

[39] R. Croteau, *Chem. Rev.* **1987**, *87*, 929–954.
[40] N. J. White, *Science* **2008**, *320*, 330–334.
[41] J. Marrero, A. D. Rodríguez, C. L. Barnes, *Org. Lett.* **2005**, *7*, 1877–1880.
[42] K. Ishibashi, R. Nakamura, *J. Agric. Chem. Soc. Jpn.* **1958**, 32, 739–744.
[43] For a detailed classification of different subtypes of *trans*-hydrindane *iso*-propyl sesterterpenoids, see: D. T. Hog, Dissertation, LMU Munich, 2013.
[44] a) M. Kaneda, R. Takahashi, Y. Iiataka, S. Shibata, *Tetrahedron Lett.* **1972**, *13*, 4609–4611; b) M. Kaneda, R. Takahashi, S. Shibata, *Acta Crystallogr. B* **1974**, *30*, 358–364; for total syntheses of retigeranic acid, see: c) E. J. Corey, M. C. Desai, T. A. Engler, *J. Am. Chem. Soc.* **1985**, *107*, 4339–4341; d) L. A. Paquette, J. Wright, G. J. Drtina, R. A. Roberts, *J. Org. Chem.* **1987**, *52*, 2960–2962; e) T. Hudlicky, L. Radesca-Kwart, L.-q. Li, T. Bryant, *Tetrahedron Lett.* **1988**, *29*, 3283–3286; f) P. A. Wender, S. K. Singh, *Tetrahedron Lett.* **1990**, *31*, 2517–2520.
[45] O. D. Hensens, D. Zink, J. M. Williamson, V. J. Lotti, R. S. L. Chang, M. A. Goetz, *J. Org. Chem.* **1991**, *56*, 3399–3403.
[46] X. Huang, H. Huang, H. Li, X. Sun, H. Huang, Y. Lu, Y. Lin, Y. Long, Z. She, *Org. Lett.* **2013**, *15*, 721–723.
[47] Z. Liu, Y. Chen, S. Chen, Y. Liu, Y. Lu, D. Chen, Y. Lin, X. Huang, Z. She, *Org. Lett.* **2016**, *18*, 1406–1409.

The marine natural products dictyoxetane (**91**) and dolabellane V (**92**) were isolated from *Dictyota dichotoma* and an additional tertiary hydroxyl group was found to decorate the cyclopentane with the *iso*-propyl moiety (Figure 1b).[48] A similar oxidation state of this type II *trans*-fused cyclopentane is also present in many other dolabellane diterpenoids,[49] and in ophiobolin A (**86**) (*vide supra*). While the *trans*-ring junction in dolabellane V (**92**) is comparable to the other presented *trans*-fused cyclopentane terpenoids, it differs in the missing C1–C9 bond (dolabellane numbering).[50] Finally, leucosceptroid B (**93**)[51] and ircinianin (**94**)[52] are examples of terpenoids belonging to the third category of *trans*-fused cyclopentane terpenoids (Figure 1c).

The intriguing scaffolds of *trans*-fused cyclopentane terpenoids pose a formidable challenge for synthetic endeavors, and together with their oftentimes promising biological activities, make these natural products highly attractive targets for chemical synthesis. In the first part of this Ph.D. thesis we focused our efforts on developing a collective total synthesis of the leucosceptroids. Amongst other factors, this family of antifeedant sesterterpenoids is intriguing since all members share a common 5,6,5-tricyclic framework, but only a few feature a type III *trans*-ring junction in the hydrindane portion. Subtle differences in the substitution pattern of the leucosceptroid skeleton seemingly lead to a preference for a *cis*- or *trans*-hydrindane, a circumstance which would certainly prove interesting to be investigated empirically.

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[48] a) K. C. Pullaiah, R. K. Surapaneni, C. B. Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, H. Cun-heng, J. Clardy, *J. Org. Chem.* **1985**, *50*, 3666–3667; b) C. B. Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, H. Cun-heng, J. Clardy, *J. Org. Chem.* **1986**, *51*, 2736–2742.

[49] a) A. D. Rodríguez, E. González, C. Ramírez, *Tetrahedron* **1998**, *54*, 11683–11729; b) M. Hiersemann, H. Helmboldt, *Top. Curr. Chem.* **2005**, *243*, 73–136.

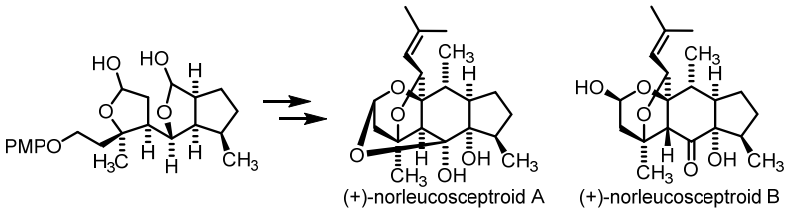
[50] The sesterterpenoids nitiol lacks a similar C–C bond, see: N. Kawahara, M. Nozawa, A. Kurata, T. Hakamatsuka, S. Sekita, M. Satake, *Chem. Pharm. Bull.* **1999**, *47*, 1344–1345

[51] S.-H. Luo, Q. Luo, X.-M. Niu, M.-J. Xie, X. Zhao, B. Schneider, J. Gershenzon, S.-H. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 4471–4475

[52] W. Hofheinz, P. Schönholzer, *Helv. Chim. Acta*, **1977** *60*, 1367–1370.

2.2 Results and Discussion

2.2.1. A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (–)-Norleucosceptroid B, and (–)-Leucosceptroid K



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Terpenoid Synthesis

A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (−)-Norleucosceptroid B, and (−)-Leucosceptroid K**

*Cedric L. Hugelshofer and Thomas Magauer**

Dedicated to Professor Johann Mulzer and Professor Andrew G. Myers

Abstract: *The first asymmetric total synthesis of the antifeedant terpenoids (+)-norleucosceptroid A, (−)-norleucosceptroid B, and (−)-leucosceptroid K has been accomplished. This highly concise synthetic route was guided by our efforts to develop a platform for the collective synthesis of a whole family of antifeedant natural products. The synthesis features a Hauser–Kraus-type annulation followed by an unprecedented, highly efficient intramolecular dilactol aldol-type condensation reaction to produce the 5,6,5 skeleton. The developed synthetic route proceeds for norleucosceptroid A and B in 16 steps (longest linear sequence) from known compounds.*

The cotton bollworm (*Helicoverpa armigera*) and the beet armyworm (*Spodoptera exigua*) are among the most destructive agricultural pests in nature and they affect vegetables and other crops worldwide.[1] Protection against them has been achieved by the use of sex-pheromone traps, insecticides, and transgenic crops. However, resistance to insecticides has developed over the last decade and new chemical agents are necessary to prevent further crop damage from these pests. *Leucosceptrum canum* Smith ("Bird's Coca Cola tree")[2] and *Colquhounia coccinea* var. *mollisa,* plants found in China and Nepal, are remarkably resistant to herbivores and pathogens. Extraction and isolation of the trichomes, flowers, and whole leaves recently led to the discovery of novel sesterterpenoids, designated leucosesterterpenone and leucosesterlactone,[3] leucosceptroids A–O,[4] colquhounoids A–C,[5] and norleucosceptroids A–C, which are classified as pentanor-sesterterpenoids.[6] In general, these compounds display potent antifeedant activity against the cotton bollworm and the beet armyworm and are the first natural sesterterpenoids with biological activity against plant-feeding insects and pathogens. The concept of employing nontoxic antifeedant compounds to protect plants from insect herbivores could emerge as an alternative to conventional synthetic pesticides since the former exhibit high specificity, quick degradation, and lack of impact on nontarget organisms.[7]

The biological properties and novel chemical scaffolds of leucosceptroids and many other sesterterpenoids[8] make these natural products highly attractive targets for chemical synthesis. Recently, Liu and co-workers[9] disclosed the first total synthesis of leucosceptroid B, and Horne and co-workers[10] reported an approach to the core of the leucosceptroids. To date, a general and modifiable strategy that would allow the collective synthesis of this natural product class (comprising 23 members) is not yet available. Structurally, all members of the leucosceptroid family of natural products share a highly functionalized, synthetically challenging 5,6,5 framework that differs in the oxidation state at C11 (OH, H) and the substitution of the C14 ethyl linkage. These attributes were an essential consideration in our initial retrosynthetic analysis of the common ABC core structure and led us to focus on disconnection of the central six-membered ring.

Herein, we describe an enantioselective synthetic route to (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**) that proceeds through the convergent assembly of two building blocks of similar complexity (Scheme 1). Our initial synthetic target was fragment **4**, which could be traced back to **5** through disconnection of the substituents at C4, C5 and C6. The ABC tricycle **5** contains the full retron for a simplifying formal Diels–Alder reaction of the AB dienolate **6** and the C-ring butenolide **7**. We envisaged that both coupling partners could be accessed from simple, readily available building blocks.

In the forward sense, the absolute configuration of fragment **7** was set through a Sharpless asymmetric dihydroxylation reaction starting from **8** (Scheme 2).[11] As shown by Corey, the *p*-methoxyphenyl directing group determined the enantiofacial selectivity and was essential to provide **9** in high enantiomeric excess (> 97 % *ee*).[12] Oxidation of diol **9** using Parikh–Doering conditions[13] and homologation with Bestmann's ylide ($Ph_3P{=}C{=}C{=}O$)[14] formed the butenolide **7** in good overall yield.

The sequence for the preparation of **6** was initiated with the degradation of inexpensive (*R*)-pulegone (**10**)[15] accord-

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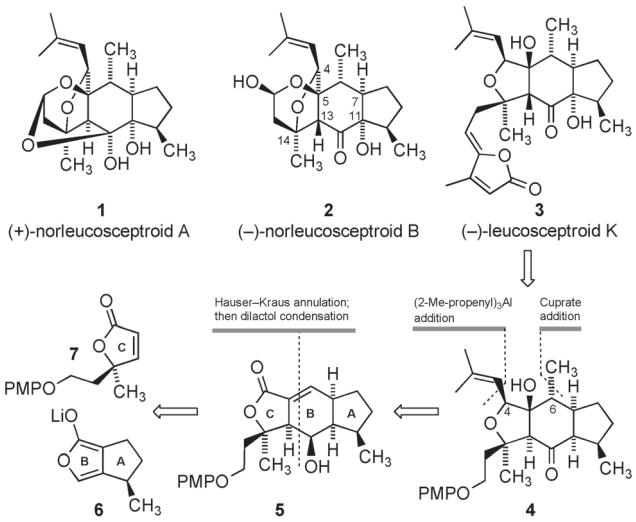
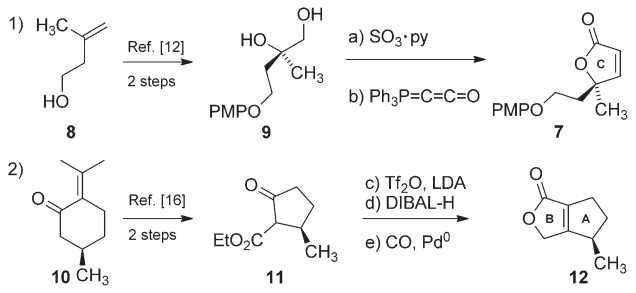
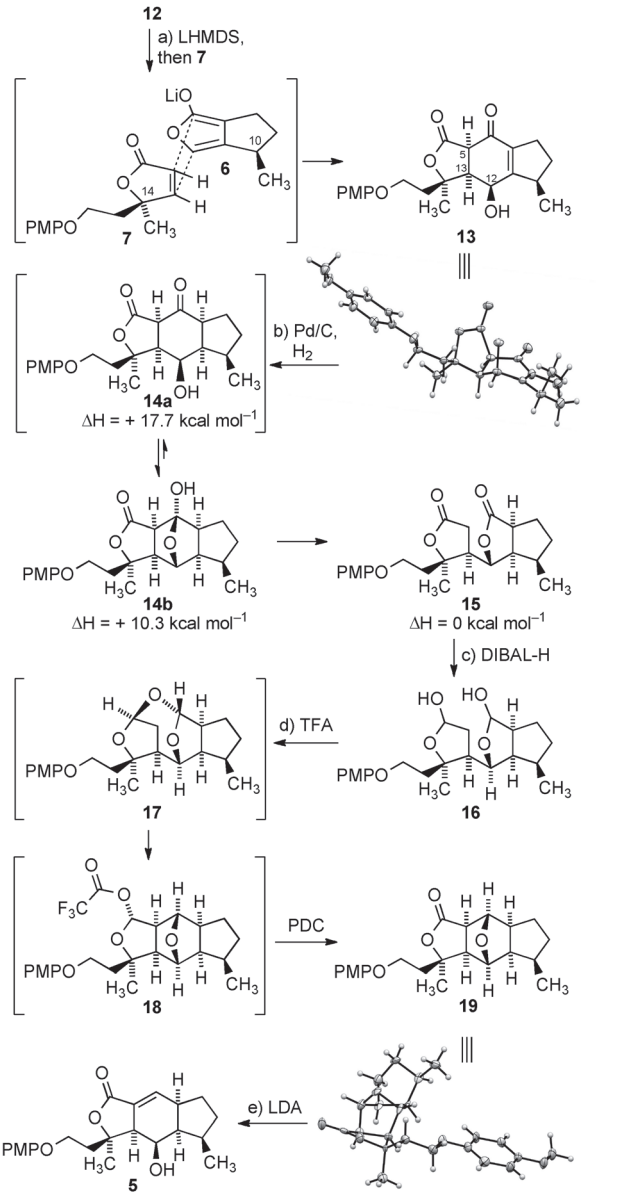


Scheme 1. Selected members of the leucosceptroids family of natural products: (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**); and retrosynthetic analysis. PMP = *p*-methoxyphenyl.



Scheme 2. 1) Preparation of C-ring butenolide **7**. Reagents and conditions: a) SO_3·pyridine, DMSO, NEt_3, CH_2Cl_2, 23 °C, 87%; b) $Ph_3P{=}C{=}C{=}O$, THF, 60 °C, 56%. 2) Preparation of AB segment **12**. Reagents and conditions: c) Tf_2O, LDA, THF, −78 °C to 0 °C; d) DIBAL-H, CH_2Cl_2, −78 °C to 23 °C, 58% over two steps; e) H_2SO_4/HCO_2H, $Pd(PPh_3)_4$, LiCl, $(nBu)_3N$, MeCN, 70 °C, 98%. DIBAL-H = diisobutylaluminium hydride, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide.



Scheme 3. Fragment coupling to give the ABC tricycle **5**. Reagents and conditions: a) LHMDS, THF, then **7**, −78 °C to −30 °C, d.r. = 3:1; b) Pd/C, H_2, MeOH, 57% over two steps; c) DIBAL-H, CH_2Cl_2, −78 °C; d) TFA, CH_2Cl_2, 4 Å molecular sieves, 23 °C, then PDC, 23 °C; e) LDA, THF, −78 °C, 69% over three steps. LHMDS = lithium hexamethyldisilazane, PDC = pyridinium dichromate, TFA = trifluoroacetic acid.

ing to a reported procedure.[16] A combination of lithium diisopropylamide and triflic anhydride was superior to all other investigated conditions (KHMDS/Tf_2O; NEt_3/Tf_2O; DIPEA/Tf_2O; LDA/$PhNTf_2$; LDA/Comins' reagent) for the triflation of the known β-keto ester **11**. Selective reduction of the ester group was readily accomplished with diisobutylaluminium hydride to afford the allyl alcohol in 57% yield over two steps. Palladium(0)-catalyzed insertion of carbon monoxide,[17] generated in situ from the reaction of formic acid with sulfuric acid,[18] gave the AB bicycle **12** in 98% yield.

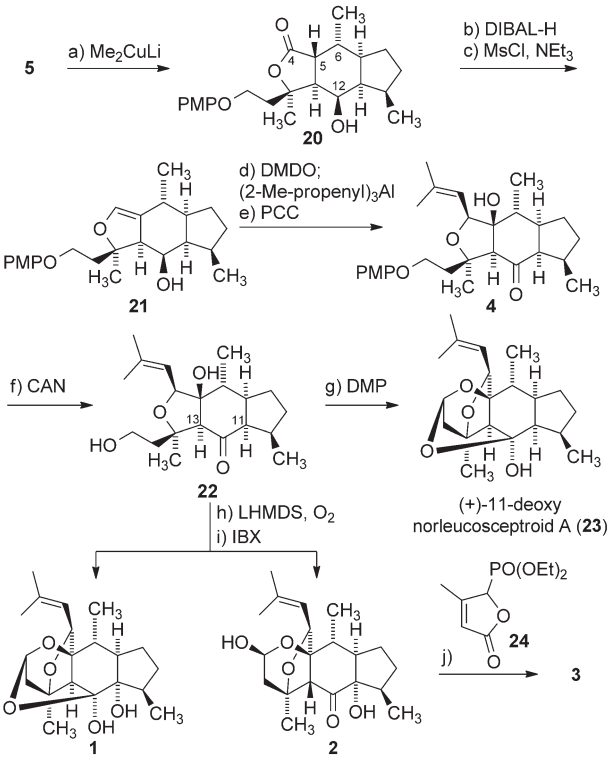
Having developed scalable routes to both ring fragments, we concentrated our efforts on uniting **7** and the AB component **12**-derived lithium isofuran-1-olate **6**, through a Hauser–Kraus-type annulation (Scheme 3).[19,20] Predicting that the reaction would proceed via the transition state shown in Scheme 3, we expected the stereochemical outcome depicted for the ABC tricycle **13**. Although the stereodiscriminating effect of the quaternary center at C14 in **7** was highly uncertain at this stage, we hypothesized that the methyl group at C10 of the AB segment **6** could reinforce the stereofacial selectivity by approaching **7** with its sterically less-hindered bottom face. Indeed, treatment of a solution of **6** in tetrahydrofuran, prepared from **12** using lithium hexamethyldisilazane (2.2 equiv), with equimolar amounts of **7** (−78 °C to −30 °C) led to the formation of enone **13** as a 3:1 mixture of diastereomers. The proposed structure and relative stereochemistry of **13** was unambiguously validated by single-crystal X-ray diffraction. It was necessary to employ excess base to trap **13** as the enolate in order to prevent a retro-Claisen reaction from occurring. The formation of the minor diastereomer can be rationalized by an *exo* approach of **6** from the

lower face of **7** to give the corresponding enone, which possesses the inverse stereochemistry at C5, C12, and C13 compared to **13**, as shown by NMR analysis. We also found that the use of degassed tetrahydrofuran for this transformation suppressed the formation of a *p*-hydroquinone byproduct (see the Supporting Information) and increased the yield of the reaction by approximately 20%.

Initial attempts to directly hydroxylate C5 and introduce the methyl group at C6 were unsuccessful since overoxidation prevailed. However, prior reduction of the enone allowed us to develop an alternative approach that avoided the aforementioned problem. Hydrogenation of **13**[21] using palladium on charcoal under 1 atm of hydrogen occurred exclusively from the convex side of the molecule. After prolonged reaction times or exposure of the crude reaction mixture to triethylamine, we isolated a product with ^{13}C NMR and IR spectra that did not correspond to the expected ketone **14a**. From a molecular model, we concluded that the free hydroxyl group at C12 was well disposed to form hemiacetal **14b**, which could in turn undergo a retro-Claisen condensation to give dilactone **15**. This reaction pathway was also supported by data obtained from density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory with the Gaussian 09 software suite.[22] Although ketone **14a** was never observed experimentally, the intermediate **14b** could be obtained as a single compound and fully characterized. As above, upon exposure of hemiacetal **14b** to mildly basic (NEt_3) or acidic (silica gel) conditions, clean transformation to **15** was observed. To date, more than 4.7 g of dilactone **15** have been prepared in a single batch.

This rather unexpected reaction outcome was taken as a chance to reform the 5,6,5 framework by developing an unprecedented intramolecular dilactol aldol-type condensation within a complex molecular setting.[23] The synthesis of the required dilactol motif through a twofold reduction of **15** (DIBAL-H, CH_2Cl_2, −78 °C) was highly efficient and gave **16** as a mixture of four diastereomers. Careful screening of the reaction parameters (solvent, temperature, reagent) was necessary to realize the intended one-pot condensation–oxidation sequence to give **19**. The optimized procedure involved treating a solution of dilactol **16** in dichloromethane containing 4 Å molecular sieves with trifluoroacetic acid (5 equiv) at 23 °C for 20 min, followed by the addition of pyridinium dichromate to the intermediate 4-*O*-trifluoroacetyl acetal **18**.[24] This afforded the tetracycle **19** as a single diastereomer, the structure of which was unambiguously confirmed by single-crystal X-ray diffraction. Excess acid was required to prevent the reaction from stalling after the intramolecular acetalization of **16** to **17**. The most efficient conditions for the opening of the ether bridge involved the addition of lithium diisopropylamide (1.15 equiv) to a solution of **19** in tetrahydrofuran at −78 °C, which afforded more than 3.0 g of α,β-unsaturated lactone **5** (69% yield over three steps).

Conjugate addition of excess dimethyl cuprate to **5** occurred with excellent diastereoselectivity at C6 and gave rise to **20** as an inconsequential 4:1 mixture of kinetic and thermodynamic epimers at C5 (Scheme 4). Since direct α-hydroxylation followed by lactone reduction proved to be



Scheme 4. Functionalization of the leucosceptroids ABC core and total synthesis of (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**). Reagents and conditions: a) MeLi, CuI, Et_2O, −45 °C to −5 °C, 76%; b) DIBAL-H, CH_2Cl_2, −78 °C; c) MsCl, NEt_3, 1,2-dichloroethane, 75 °C, 53% over two steps; d) DMDO, acetone, CH_2Cl_2, −78 °C to −30 °C, then $AlCl_3$, 2-methyl-1-propenylmagnesium bromide, THF, CH_2Cl_2, −78 °C, 52%; e) PCC, CH_2Cl_2, 4 Å molecular sieves, 23 °C, 87%; f) CAN, pyridine, MeCN, H_2O, 0 °C, 70%; g) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 66%; h) LHMDS, O_2, $P(OEt)_3$, −78 °C to −35 °C; i) IBX, DMSO, 23 °C, 40% **1** and 10% **2** over two steps; j) **24**, KO*t*Bu, THF, 0 °C, then **2**, 0 °C to 23 °C, 70%. CAN = ceric ammonium nitrate, DMDO = dimethyldioxirane, DMP = Dess–Martin periodinane, IBX = 2-iodoxybenzoic acid, MsCl = methanesulfonyl chloride, PCC = pyridinium chlorochromate.

unsuccessful, we envisioned introduction of the C5 hydroxy group via enol ether **21**. The addition of triethylamine (7.5 equiv) to a solution of the crude lactol, derived from **20** by DIBAL-H reduction, and methanesulfonyl chloride (3.5 equiv) in dichloroethane at 75 °C provided **21** in a reproducible manner. These reaction conditions reduced formation of the acetal byproduct that resulted from attack of the C12 hydroxy group on C4 (see the Supporting Information). The epoxide obtained from the reaction of **21** with a solution of dimethyldioxirane in acetone, prepared by the method developed by Taber et al.,[25] was found to be highly unstable and was readily hydrolyzed to the corresponding lactol. We found that the addition of the crude epoxide product as a solution in dichloromethane to a large excess of tris-(2-methyl-1-propenyl) aluminum[26] in tetrahydrofuran at −78 °C delivered the required vinylic appendage from the same side as the epoxide to give the configuration at C4 and C5 depicted in **4**. The observed stereoselectivity of this transformation was attributed to coordination of the organoaluminum reagent to the epoxide to give the alanate and concomitant internal

delivery of the propenyl nucleophile. Introduction of the vinylic appendage at C4 occurred with opposite stereoselectivity when a combination of copper(I) iodide and 2-methyl-1-propenylmagnesium bromide was applied in the analogous reaction.[27]

Subsequent oxidation of the sterically hindered alcohol produced the configurationally stable ketone **4**. We found that H11 and H13 of **4** do not epimerize under basic conditions at 23 °C, however, since the β-hydroxy ketone is perfectly aligned for an E2 elimination, dehydration takes place under more forcing conditions (NEt_3, MeOH, 45 °C). Although *cis*-hydrindanones were calculated to be thermodynamically more stable,[28] and as is corroborated by the structures of most leucosceptroid natural products, (+)-norleucosceptroid A (**1**) features an AB-*cis*-BC-*trans* fusion in which intramolecular hemiacetal formation preserves this conformation from epimerization to the AB-*cis*-BC-*cis* system.

Cleavage of the *p*-methoxyphenyl ether in **4** with ceric(IV) ammonium nitrate followed by oxidation of the primary alcohol **22** with Dess–Martin periodinane afforded (+)-11-deoxynorleucosceptroid A (**23**), which has not yet been isolated from natural sources.[29] Regioselective α-hydroxylation (LHMDS, O_2, $P(OEt)_3$)[30] of **22** afforded two C11 hydroxylated products, which were directly oxidized under mild conditions (IBX, DMSO)[31] without prior purification. NMR analysis of the resulting product mixture revealed that α-hydroxylation had occurred with high stereoselectivity. However, we also recognized that partial epimerization of H13 to the thermodynamically more stable AB-*cis*-BC-*cis* fusion had spontaneously taken place during the α-hydroxylation step. Column chromatography on silica gel thus gave (+)-norleucosceptroid A (**1**), as well as minor amounts of (−)-norleucosceptroid B (**2**). Finally, the union of **2** with phosphonate **24**[32] gave rise to (−)-leucosceptroid K (**3**) in 70 % yield. The spectroscopic data (^1H and ^{13}C NMR, HRMS, $[\alpha]_D$) for **1**–**3**, which are the unnatural enantiomers, were in full agreement with those reported for the naturally occurring substances.

In summary, a general enantioselective synthesis of antifeedant (pentanor-)sesterterpenoids has been developed. This enabled the preparation of three representative antifeedant leucosceptroids; (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**); in a convergent manner with a high level of efficiency. The ability to prepare the ABC tricycle **5** on a multigram scale (3.0 g) paves the way for the synthesis of the remaining leucosceptroids. This work also highlights the fact that the intramolecular aldol condensation of dilactols could be a useful method for organic synthesis. A collective synthesis of the leucosceptroid family and unnatural derivatives thereof is currently underway in our laboratories.

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Keywords: Claisen reaction · leucosceptroids · natural products · terpenoids · total synthesis

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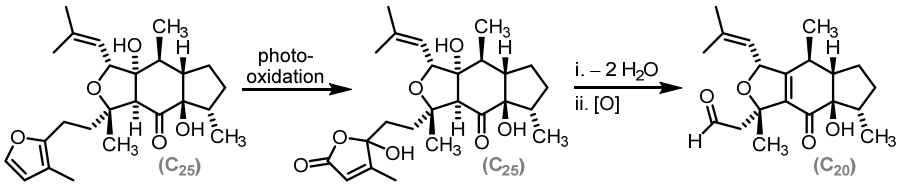
2.2.2. Unraveling the Metabolic Pathway in Leucosceptrum canum by Isolation of New Defensive Leucosceptroid Degradation Products and Biomimetic Model Synthesis

† These authors contributed equally to this work.



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Unraveling the Metabolic Pathway in *Leucosceptrum canum* by Isolation of New Defensive Leucosceptroid Degradation Products and Biomimetic Model Synthesis

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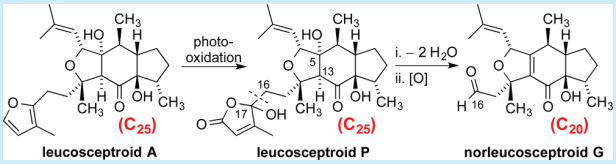
Supporting Information

ABSTRACT: Seven new leucosceptroid degradation products possessing a C_{20}, C_{21}, or C_{25} framework, norleucosceptroids D–H (**1**–**5**), leucosceptroids P (**6**), and Q (**7**), have been isolated from *Leucosceptrum canum*. Their structures were determined by comprehensive NMR, MS, and single-crystal X-ray diffraction analyses. Discovery of these key intermediates, together with the biomimetic oxidation of a model system, supports the hypothesis that two biosynthetic pathways are operative. Antifeedant activity was observed for compounds **1**–**3**.



Terpenoids, the largest class of natural products with highly diversified chemical structures, have been frequently reported to play important physiological and ecological roles in the natural world.[1] To date, degradation of sesterterpenoids in plants is still largely unknown, while the oxidative degradation of other terpenoids has been documented, although the mechanism underlying these transformations is often poorly understood. Known examples include the apocarotenoids (nortetraterpenoids),[2] antifeedant limonoids (tetranortriterpenoids),[3] schinortriterpenoids (nortriterpenoids),[4] and volatile tetra-norterpenoid degradation products of the diterpenoid (*E*,*E*)-geranyllinalool and the sesquiterpenoid (3*S*)-(*E*)-nerolidol, which were shown to attract enemies of herbivores (indirect defense) in a variety of plant species.[5]

Recently, it was found that the glandular trichomes of two Himalayan–Chinese Labiatae species[6] harbor two unique classes of defensive sesterterpenoids, leucosceptroids and colquhounoids, respectively.[7,8] Subsequently, three intriguing antifeedant C_{20} terpenoids, norleucosceptroids A–C,[9] were isolated from *L. canum* and tentatively classified as pentanorsesterterpenoids. Choudhary and co-workers also reported the isolation of three sesterterpenoids from *L. canum* of Nepalese origin,[10] which are structurally quite different from those discovered in Chinese plants.

Synthetic routes to these natural products were reported by three groups. The core structure of leucosceptroids A–D has been prepared by Horne's group,[11a] an asymmetric total synthesis of leucosceptroid B has been achieved by Liu and co-workers,[11b] and most recently Magauer's group reported the total synthesis of norleucosceptroid A, norleucosceptroid B, and leucosceptroid K.[11c,d]

In order to shed light on the metabolic pathways in *L. canum*, the search for key biosynthetic intermediates of norleucosceptroids A–C has been an ongoing topic of interest. Herein, the isolation, structure elucidation, antifeedant activity, and biogenetic relationship of seven new biosynthetic intermediates including two tetranorsesterterpenoids (**1** and **2**), three pentanorsesterterpenoids (**3**–**5**), and two sesterterpenoids (**6** and **7**) are described. Additionally, the oxidative degradation of the furan appendage using an advanced model system was investigated. The obtained results further support the coexistence of two metabolic pathways in leucosceptroid biosynthesis.

For compound **1**, a molecular formula of $C_{21}H_{30}O_4$ was deduced from the high-resolution (HR) EI-MS (*m*/*z* 346.2148 $[M]^+$, calcd 346.2144) and the IR spectrum indicated the presence of two carbonyl groups (1736 and 1709 cm^{-1}). Analysis of the NMR spectra (Tables S1 and S2 and Figures S2–S7 in the Supporting Information) revealed various similarities with those of leucosceptroids B[7] (**9**) and E[8b] (**12**), although the furan or lactone moieties in the C14 side chains were absent and instead a carboxylic acid group was present in **1**. Consideration of all the spectroscopic data suggested that **1** is a tetranorsesterterpenoid lacking C11 and C5 oxygenation. Eventually, a single crystal of **1** was obtained from a mixture of MeOH/water (8:1), and X-ray crystallographic analysis unambiguously established the complete structure of **1** which was named norleucosceptroid D (Figure 1).

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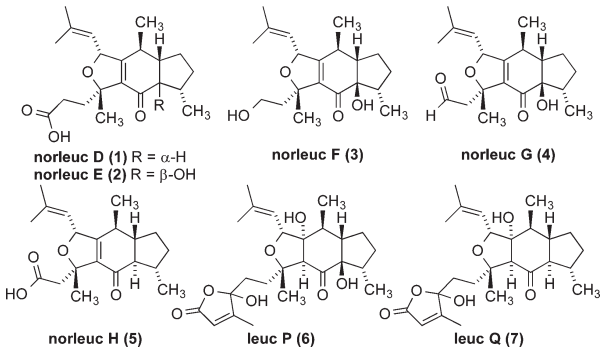


Figure 1. Chemical structures of norleucosceptroids D–H (**1**–**5**), leucosceptroids P (**6**), and Q (**7**).

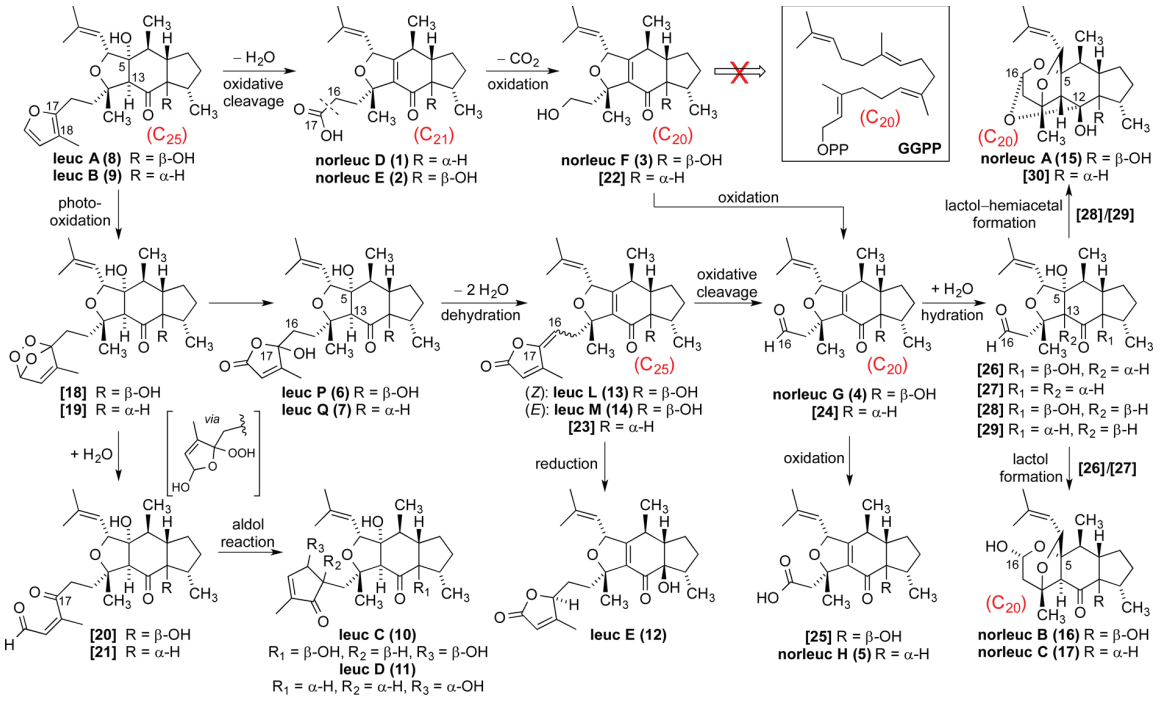
In an analogous fashion, comprehensive NMR, MS, and IR analysis together with comparison of spectroscopic data of previously isolated parent leucosceptroids allowed compounds **2**–**7** to be characterized as shown in Figure 1, and they were named norleucosceptroids E–H (**2**–**5**), leucosceptroids P (**6**), and Q (**7**). A detailed description of the isolation and structure elucidation of all these compounds is provided in the Supporting Information of this report.

During the structure elucidation of the novel leucosceptroids **1**–**7**, a biogenetic relationship between the previously isolated C_{25} sesterterpenoids and C_{20} terpenoids from *L. canum* was recognized (Scheme 1). It is likely that the carboxylic acids norleucosceptroids D (**1**) and E (**2**) directly originate from leucosceptroids A (**8**) and B (**9**), which both are major sesterterpenoids in *L. canum*, by 5,13-dehydration and oxidative cleavage of the furan moiety (scission of the C17/C18 bond). Subsequent decarboxylation and oxidation[12] of tetranorsesterterpenoids **1** and **2** affords the pentanorsesterterpenoids norleucosceptroid F (**3**) and **22**. Oxidation of the latter compounds yields norleucosceptroid G (**4**) and aldehyde **24**, which then may be further oxidized to norleucosceptroid H (**5**) and carboxylic acid **25**.

An alternative degradation pathway of leucosceptroids A (**8**) and B (**9**) is hypothesized to proceed through peroxides **18** and **19**, which arise from the [4 + 2] cycloaddition of singlet oxygen with the furan moiety.[13] A subsequent Kornblum–DeLaMare-type rearrangement[14] of **18** and **19** yields the hydroxy lactones leucosceptroids P (**6**) and Q (**7**), which upon 5,13- and 16,17-dehydration are converted to leucosceptroids L (**13**) and M (**14**) and **23**. While reduction of the C16/C17 bond furnishes leucosceptroid E (**12**), an oxidative cleavage of this bond affords the same aldehydes **4** and **24** as from the $C_{25} \rightarrow C_{21} \rightarrow C_{20}$ decarboxylative pathway. Through hydration of the C5/C13 bond, norleucosceptroid G (**4**) and **24** are then converted to a mixture of intermediates **26**–**29**.[9] While **28** and **29** with the AB-*cis*-BC-*trans* fusion may spontaneously convert to the thermodynamic epimers **26** and **27**, respectively, intramolecular hemiacetal formation can alternatively preserve this conformation from epimerization to the AB-*cis*-BC-*cis* system. Biosynthetically, norleucosceptroids B (**16**) and C (**17**) thus arise from intermediates **26** and **27** through lactol formation between 5-OH and 16-CHO. Similarly, lactol formation between 5-OH and 16-CHO in intermediates **28** and **29**, followed by hemiacetal formation between 16-OH and 12-C=O affords norleucosceptroid A (**15**) and **30**.

Furthermore, the existence of leucosceptroids C (**10**) and D (**11**) also strongly suggests that photooxidation of leucosceptroids A (**8**) and B (**9**) initiates the partial metabolic degradation

Scheme 1. Proposed Metabolic Pathway of Leucosceptroids A (8) and B (9)[a]



[a]For clarity, numbers in parentheses are used for isolated natural products, while numbers in square brackets correspond to intermediates or suspected natural products.

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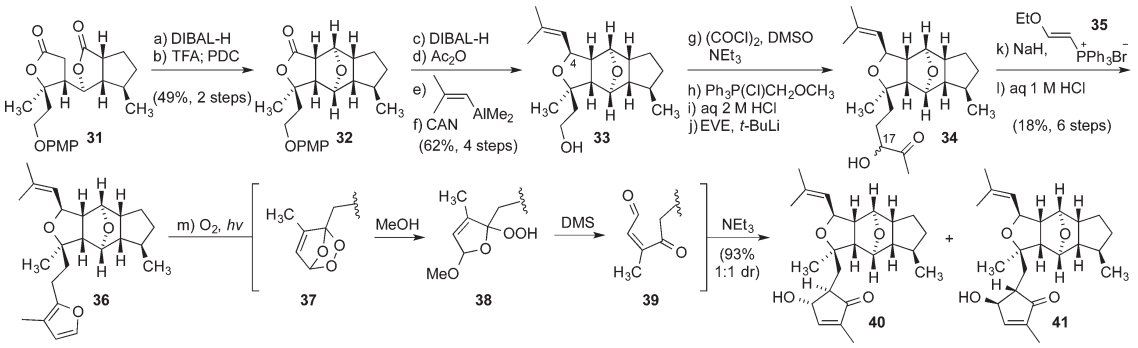
Scheme 2. Model System Synthesis and Biomimetic Furan Photooxidation[a]



[a]DIBAL-H = diisobutylaluminum hydride, TFA = trifluoroacetic acid, PDC = pyridinium dichromate, CAN = ceric ammonium nitrate, DMSO = dimethyl sulfoxide, EVE = ethyl vinyl ether, DMS = dimethyl sulfide.

of these sesterterpenoids. In lieu of the proposed rearrangement of peroxides **18** and **19** to **6** and **7**, respectively, it is envisaged that also nucleophilic addition of water takes place, affording keto aldehydes **20** and **21** via expulsion of hydrogenperoxide from a hemiacetal intermediate. An intramolecular aldol cyclization of the enolized 17-ketone with the aldehyde group in **20** and **21** then gives rise to leucosceptroids C (**10**) and D (**11**).

Although further intermediates remain to be discovered, it is likely that two parallel biosynthetic pathways exist in *L. canum*, leading to the 11-hydroxylated and 11-deoxygenated sesterterpenoids or norsesterterpenoids, respectively. The isolation of intermediates **1**–**7** provides direct evidence that the C_{20} terpenoids, norleucosceptroids A–C (**15**–**17**), are, in fact, sesterterpenoid degradation products and should be classified as pentanorsesterterpenoids rather than diterpenoids which are directly biosynthesized from the universal precursor geranylgeranyl diphosphate (GGPP).

In order to experimentally evaluate the proposed degradation pathway, which is initiated by photooxygenation, a model system was developed. With this objective in mind, known dilactone **31**, available in gram quantities,[11c] was converted to lactone **32** by 2-fold reduction, followed by an intramolecular dilactol aldol-type condensation–oxidation sequence (Scheme 2). DIBAL-H reduction of **32** and acetylation of the resulting lactol afforded an intermediate acetyl acetal as a mixture of diastereomers at C4 (dr = ~2:1). Treatment of this crude product with the mixed organoaluminum reagent, dimethyl-(2-methyl-1-propenyl)aluminum (prepared from aluminum trichloride, methylmagnesium bromide, and 2-methyl-1-propenylmagnesium bromide; see the Supporting Information for details), furnished alcohol **33** as a single diastereomer after cleavage of the *p*-methoxyphenyl ether (62% yield over four steps). Next, Swern oxidation[15] of **33** followed by Wittig–Levine reaction[16] of the so-obtained aldehyde with (methoxymethyl)triphenylphosphonium chloride was carried out, yielding the corresponding C_1–extended aldehyde after acidic hydrolysis. Addition of lithiated ethyl vinyl ether to the latter compound provided α-hydroxy ketone **34** as an inconsequential mixture of diastereomers at C17 (dr = ~1:1). Alkoxide formation in **34** with sodium hydride followed by addition of Wittig salt **35**[17] furnished an intermediate ethoxy acetal, which underwent facile elimination under acidic conditions to afford furan **36**, which constituted the model system of leucosceptroids A (**8**) and B (**9**).

This system was then used to mimic the putative conversion of leucosceptroids A (**8**) and B (**9**) to the hydroxycyclopentenone leucosceptroids C (**10**) and D (**11**) (vide supra), respectively, in a biomimetic manner. Thus, irradiation of an oxygen-sparged solution of furan **36** in methanol containing Rose Bengal as a photosensitizer with light at −78 °C led to rapid consumption of the starting material (<5 min), affording a more polar product, as seen by thin-layer chromatographic analysis. Addition of dimethyl sulfide (DMS) to the putative hydroperoxide **38**, arising from nucleophilic addition of methanol to *endo*-peroxide **37**,[18] followed by warming of the reaction mixture to 23 °C and addition of triethylamine to induce the intramolecular aldol reaction in keto aldehyde **39**, cleanly furnished hydroxy cyclopentenones **40** and **41** as a 1:1 mixture of diastereomers (93% combined yield). It is proposed that, in nature, the conversion from *endo*-peroxide **37** to the hydroxy cyclopentenones would occur via nucleophilic addition of water (instead of methanol) followed by expulsion of hydrogen peroxide to afford keto aldehyde **39** (in the laboratory mimic, peroxide **38** is first reduced with DMS and methanol then serves as the leaving group). The final cyclization step in a natural environment could be catalyzed by an aldolase which is capable of controlling the stereochemical outcome of this aldol reaction.[19] Although the model furan **36** is certainly simplified compared to leucosceptroids A (**8**) and B (**9**), the experimental outcome corroborates the hypothesis that photooxidation occurs readily and might be the first step in the metabolic pathway of the defensive leucosceptroid sesterterpenoids.

Finally, norleucosceptroids D–F (**1**–**3**) were evaluated for their antifeedant activity against a generalist insect, cotton bollworm (*H. armigera*), as previously described.[7] Significant antifeedant activity for **1**–**3** was observed with EC_{50} values of 3.81, 10.86, and 7.35 μg/cm^2, respectively (neem oil: EC_{50} = 2.63 μg/cm^2), suggesting that these leucosceptrane sesterterpenoid degradation products could also be involved in the plant defense against insect enemies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, plant material, crystallographic data, physical-chemical properties, key HMBC correlations and NMR spectra of **1**–**7**. Synthetic procedures, analytical data, and NMR spectra of the biomimetic model synthesis. This

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material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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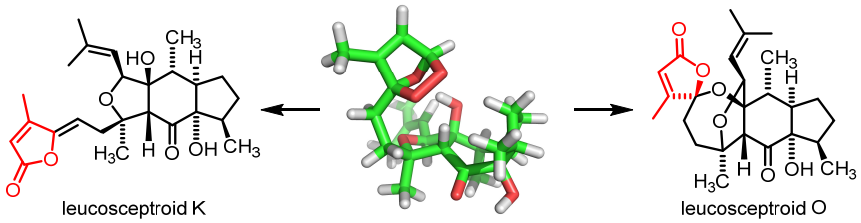
2.2.3. Total Synthesis of the Leucosceptroid Family of Natural Products



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Total Synthesis of the Leucosceptroid Family of Natural Products

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Supporting Information

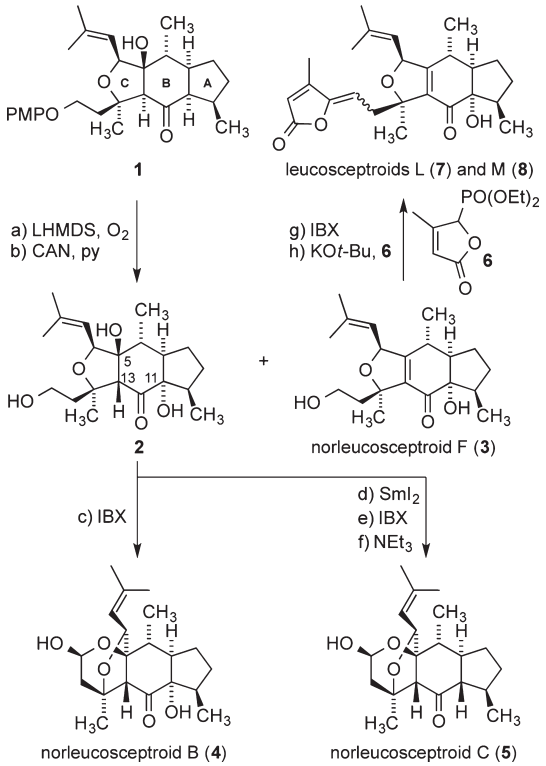
ABSTRACT: A highly efficient strategy enabled the asymmetric total synthesis of 15 antifeedant leucosceptroid natural products. The advanced tricyclic core, available in gram quantity, served as the pivotal intermediate for the preparation of norleucosceptroids B, C, F, and G and leucosceptroids A, B, G, I, J, L, and M. Additionally, the bioinspired oxidative transformation of leucosceptroid A to leucosceptroids C, K, O, and P using singlet oxygen supports the hypothesis that leucosceptroids A and B are most likely the biogenetic precursors of all other members of this natural product family.

Leucosceptroids A–Q and norleucosceptroids A–H are members of families of sesterterpenoids and pentanorsesterterpenoids, respectively, that have been isolated from *Leucosceptrum canum* Smith by Li and co-workers.[1,2] The potent antifeedant activities and novel molecular scaffolds of the leucosceptroids, comprising a 5,6,5-framework with a fully functionalized tetrahydrofuran ring and eight contiguous stereogenic centers, have attracted the attention of several research groups.[3] Concurrent with Ma's work,[3a] we became interested in the biogenetic relationship of the leucosceptroid natural products and hypothesized that two biosynthetic pathways are operative in *L. canum* Smith.[1f] Building upon the previously reported general entry to antifeedant sesterterpenoids,[4] we report the total synthesis of 15 members of the leucosceptroid family. The synthesis of leucosceptroids K (**9**), C (**19**), P (**20**), and O (**23**) was accomplished by the development of experimental conditions that mimic the biosynthetic oxidation, thus corroborating our proposal concerning the metabolic pathway in *L. canum* Smith.

Beginning from the tricyclic core **1**,[4] we first developed an improved route for the synthesis of norleucosceptroid B (**4**), which in the previous approach had been obtained only as a minor byproduct of norleucosceptroid A. As outlined in Scheme 1, we found that α-hydroxylation of **1** prior to cleavage of the *p*-methoxyphenyl ether followed by purification on deactivated silica gel favored the epimerization of H-13 to afford triol **2** together with norleucosceptroid F (**3**). Oxidation (IBX, DMSO, 23 °C)[5] of **2** furnished norleucosceptroid B (**4**), and exposure of **3** to the same conditions afforded norleucosceptroid G (see the Supporting Information for details). The latter was converted to leucosceptroids L (**7**) and M (**8**) (93%, *Z*:*E* = 2:1) by a Horner–Wadsworth–Emmons reaction with phosphonate **6**.[6]

Installation of the AB-*trans*-BC-*cis* ring fusion of norleucosceptroid C (**5**) proved to be unexpectedly challenging. While H-11 and H-13 of tricyclic core **1** were reluctant to undergo epimerization under basic conditions and elimination of OH-5 prevailed, the attempted direct conversion of **4** to **5** failed. Eventually, resorting to triol **2**, where epimerization of H-13 had occurred with ease after the introduction of OH-11,[7] allowed us to prepare the corresponding α-deoxygenated AB-*cis*-BC-*cis* annulated ketone by exposure to samarium(II) iodide.[8] To our surprise, epimerization of H-11 to form the AB-*trans*-BC-*cis* ring system could not be accomplished at this stage. However, oxidation under the established conditions afforded 11-*epi*-norleucosceptroid C, which upon exposure to

Scheme 1. Synthesis of Norleucosceptroids F (3), B (4), and C (5) and Leucosceptroids L (7) and M (8)[a]



[a]Reagents and conditions: (a) LHMDS, O_2, $P(OEt)_3$, THF, −78 to −20 °C; (b) CAN, pyridine, MeCN, H_2O, 0 °C, 21% **2** and 23% **3** over two steps; (c) IBX, DMSO, 23 °C, 56%; (d) SmI_2, THF, MeOH, 23 °C, ≥99%; (e) IBX, DMSO, 23 °C; (f) NEt_3, MeOH, 23 °C, 42% over two steps; (g) IBX, DMSO, 23 °C, 68%; (h) **6**, KO*t*-Bu, 0 to 23 °C, 93%, *Z*:*E* = 2:1.

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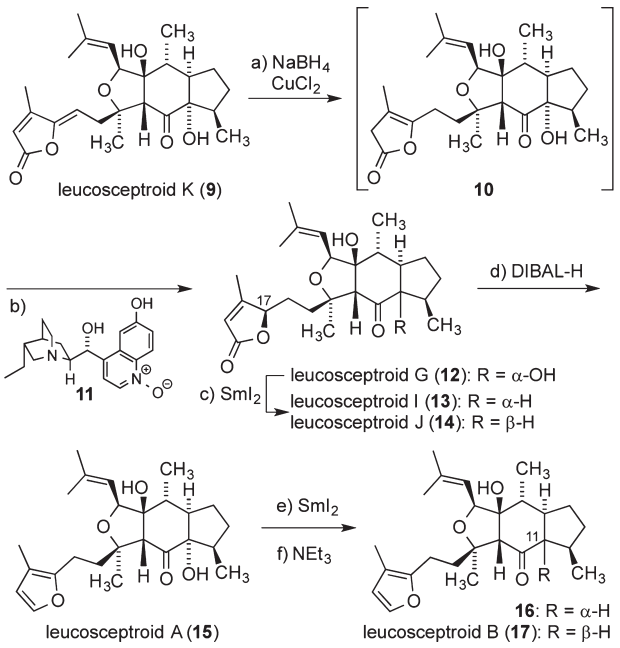
triethylamine in methanol at 23 °C for 24 h was fully converted to norleucosceptroid C (**5**) (42% yield over two steps). Only trace amounts of the 5,13-dehydrated byproduct were formed.

Using our optimized conditions for the extension of norleucosceptroid B,[4] we were able to produce 64 mg of leucosceptroid K (**9**) in a single batch. For its transformation to leucosceptroid G (**12**), we needed to develop a protocol for the selective installation of the remote C-17 stereocenter (Scheme 2). As direct hydrogenation of the C-16/C-17 double bond was

Scheme 2. Preparation of Leucosceptroids A (15), B (17), G (12), I (13), and J (14)[a]



[a]Reagents and conditions: (a) $NaBH_4$, $CuCl_2$, EtOH, 0 °C; (b) **11** (20 mol %), CH_2Cl_2, 0 °C, 70% over two steps, 7:1 d.r.; (c) SmI_2, THF, MeOH, 23 °C, 59%, **13**:**14** = 7:1; (d) DIBAL-H, CH_2Cl_2, −78 °C, then MeOH, aq. 2 M HCl, 23 °C, 75%; (e) SmI_2, THF, MeOH, 23 °C; (f) NEt_3, MeOH, 23 °C, 62%, **16**:**17** = 5:2.

not possible, we were confronted with the challenge of finding conditions to achieve a selective conjugate 1,6-reduction of **9** to β,γ-unsaturated butenolide **10**. Investigation of conditions reported by Baran[9] (sodium borohydride, cobalt(II) chloride) for the reduction of a somewhat similar system revealed that reduction of **9** under the analogous conditions was nonselective and afforded a mixture of products arising from 1,6- and 1,4-reduction. Further investigations using a combination of sodium borohydride with nickel(II) chloride[10] in ethanol were also unsatisfactory. Although the crude product mixture revealed that the reduction occurred with slightly improved selectivity for the desired 1,6-hydride addition, incomplete conversion of the starting material was observed at low temperatures, while partial hydrogenation of the propenyl side chain took place at temperatures above −25 °C. These difficulties prompted us to investigate the use of sodium borohydride in conjunction with copper(II) chloride, a reagent combination that appears to have received only little attention in the literature to date.[11] To our delight, treating an ethanolic solution of leucosceptroid K (**9**) with excess $CuCl_2$ and $NaBH_4$ at 0 °C resulted in the formation of copper boride (Cu_2B) as a finely divided black precipitate[12] and cleanly furnished β,γ-unsaturated butenolide **10**. The use of these conditions proved to be remarkable with respect to both the essentially complete 1,6-selectivity and the tolerance of all other functional groups. The installation of the C-17 stereocenter was then realized by employing a methodology developed by Deng[13] for asymmetric olefin isomerization via proton transfer catalysis. Treating crude β,γ-unsaturated butenolide **10** with cinchona alkaloid-derived catalyst **11** led to the formation of leucosceptroid G (**12**) with good selectivity (7:1 d.r.) in high yield (70% over two steps).[14]

While α-deoxygenation of **12** gave rise to leucosceptroid I (**13**) and traces of its H-11 epimer leucosceptroid J (**14**), DIBAL-H reduction followed by acidic workup furnished leucosceptroid A (**15**) in 75% yield.[15,16] For the synthesis of leucosceptroid B (**17**), **15** was α-deoxygenated to afford known ketone **16**.[3b] Unfortunately, the epimerization conditions that had efficiently converted the AB-*cis*-BC-*cis* ring system to the AB-*trans*-BC-*cis* one in the synthesis of norleucosceptroid C (**5**) (vide supra) proved to be not as successful in this case. While for **5** the AB-*trans* ring fusion might prevent unfavorable interactions between the lactol moiety and the A ring, the absence of such transannular strain in **16** and **17** leads to a much smaller energetic difference between the two H-11 epimers. Discontinuing the epimerization of **16** after 4.5 h completely avoided the elimination of 5-OH and provided **16** and leucosceptroid B (**17**) as a 5:2 mixture (62% yield).[17]

Having developed an efficient route for the preparation of leucosceptroid A (**15**), our next challenge was its biomimetic photo-oxidation[1f] to access leucosceptroids C (**19**), P (**20**), and O (**23**) (Scheme 3). These studies were also guided by our interest in finding the biosynthetic precursor of the intriguing spirocycle **23**, an issue that raised uncertainty at the outset of our investigations since several members were considered as potential candidates. Initial attempts to convert **15** to **19** showed that the [4 + 2] cycloaddition of singlet oxygen with the furan moiety occurred rapidly.[18] However, the reaction appeared to stall during the ensuing efforts to induce the intramolecular aldol reaction that forms the hydroxycyclopentenone ring in **19**. After a detailed analysis of the reaction mixture, it became apparent that the methoxy acetal intermediate (resulting from nucleophilic addition of methanol to *endo*-peroxide **18** followed by reduction with dimethyl sulfide) was remarkably stable and did not convert to the crucial γ-keto aldehyde under the reaction conditions. Hence, an optimized procedure was developed in which the reaction mixture was concentrated at the stage of the methoxy acetal intermediate and the residue was chromatographed on silica gel to unmask the γ-keto aldehyde functionality. The subsequent base-induced intramolecular aldol reaction occurred smoothly and produced leucosceptroid C (**19**) and its diastereomer in 78% yield (1:1 d.r.). Next, the synthesis of leucosceptroid P (**20**) could be accomplished by replacing methanol with a non-nucleophilic solvent and conducting the photo-oxidation in the presence of base. Irradiation of a solution of leucosceptroid A (**15**) in oxygen-saturated dichloromethane containing a catalytic amount of tetraphenylporphyrin (TPP) and *N*,*N*-diisopropylethylamine cleanly produced **20** (85% yield), the product of a Kornblum−DeLaMare-type rearrangement[19] of *endo*-peroxide **18**.

Finally, we turned our attention to the challenge of preparing leucosceptroid O (**23**) in a biomimetic manner. The initial plan to hydrolyze the lactone in leucosceptroid K (**9**) to afford the corresponding γ-keto acid and effect an acid-mediated

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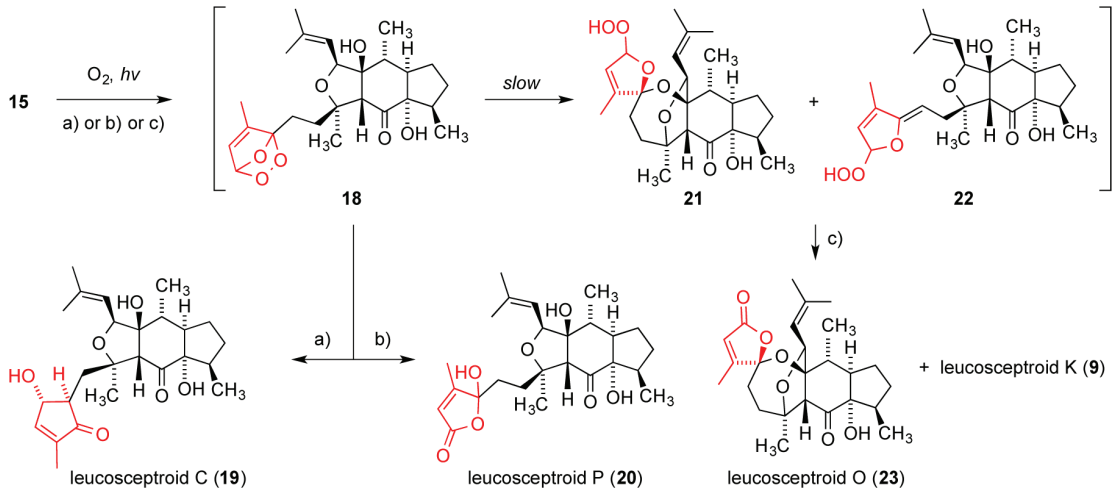
Scheme 3. Bioinspired Photo-oxidation of Leucosceptroid A: Synthesis of Leucosceptroids K (9), C (19), P (20), and O (23)[a]



[a]Reagents and conditions: (a) O_2, *hν*, rose bengal, MeOH, −78 °C, then DMS, 23 °C, then chromatography, then NEt_3, CH_2Cl_2, 23 °C, 78%, 1:1 d.r.; (b) O_2, *hν*, DIPEA, TPP, CH_2Cl_2, −78 °C, 85%; (c) O_2, *hν*, TPP, CD_2Cl_2, −78 to 23 °C, 3 h, then Ac_2O, pyridine, 23 °C, 26% **23** and 34% **9**.

spiroketalization was unsuccessful in our hands.[20] Although leucosceptroid P (**20**) was also regarded as a promising precursor for the synthesis of **23** by virtue of intramolecular ketalization, the envisioned cyclization could not be accomplished under various conditions. After considering several biosynthetic precursors, we hypothesized that all of the leucosceptroid natural products are in fact derived from two parent members, leucosceptroids A (**15**) and B (**17**). Thus, we returned to the biomimetic photo-oxidation and monitored the reaction after exposure of **15** to singlet oxygen by ^{1}H NMR spectroscopy (see the Supporting Information for details). Under strictly anhydrous conditions we were able to observe the clean formation of a 1:1 mixture of diastereomeric *endo*-peroxides **18**.

While standing in solution at 23 °C, **18** slowly (3 h) underwent competing spirocyclization and elimination to afford hydroperoxides **21** and **22**, respectively. Treating this mixture with acetic anhydride and pyridine gave leucosceptroid O (**23**) (26%) and leucosceptroid K (**9**) (34%) after purification by column chromatography on silica gel. Under the assumption that this reaction sequence mimics the biosynthetic oxidation of leucosceptroid A (**15**), it sheds light on the fact that the corresponding *E* isomer of leucosceptroid K (**9**) is unknown. On the basis of a series of optimized structures at the B3LYP/6-31G(d) computational level,[21] we believe that hydrogen bonding between OH-5 and the *endo*-peroxide, as depicted for **18** and **18′** (Figure 1), results in such an orientation that elimination leads to exclusive formation of the *Z* double bond, as observed for leucosceptroid K (**9**). In the case of the photo-oxidation precursor of leucosceptroids L (**7**) and M (**8**),[22] the absence of such a hydrogen-bonding interaction would lead to no preferred orientation of the *endo*-peroxide moiety, resulting in the formation of both double-bond isomers in nature.

In conclusion, our general entry to the synthesis of antifeedant sesterterpenoid natural products enabled the synthesis of 15 complex leucosceptroid members, whose spectroscopic data (^{1}H and ^{13}C NMR, HRMS, $[\alpha]_D$) were in full agreement with those reported for the naturally occurring substances. Additionally, the conducted biomimetic photo-oxidation disclosed that leucosceptroids A and B are most likely the parent members of all other known leucosceptroids.

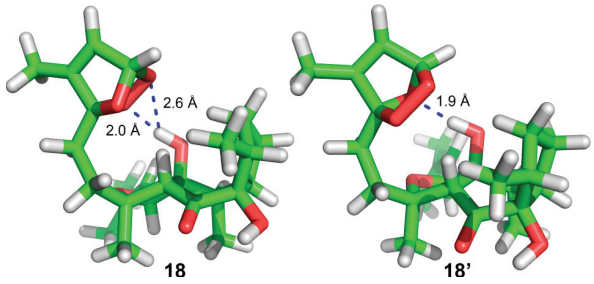


Figure 1. DFT-optimized structures of the diastereomeric *endo*-peroxides **18** and **18′** showing the crucial hydrogen-bonding interaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra of products, comparison of natural and synthetic leucosceptroids, and complete ref 21. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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discussions during the preparation of the manuscript and Giulio Volpin (LMU Munich) for assistance with NMR experiments.

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(14) Treating β,γ-unsaturated butenolide **10** with an achiral base such as triethylamine gave leucosceptroid G (**12**) as a 1:1 mixture of diastereomers at C-17.

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(16) Direct reduction of **9** or **10** to give **15** was unsuccessful. DIBAL-H reduction of the lactone in **10** led to the formation of the corresponding γ-keto aldehyde.

(17) Extending the epimerization time to 24 h gave **16** and **17** in a slightly improved ∼3:1 ratio. However, a considerable amount of the OH-5-eliminated product was formed.

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(22) To date, the 5,13-dehydrated analog of leucosceptroid A (**15**), which would constitute the precursor of leucosceptroids L (**7**) and M (**8**), has not been isolated from natural sources, yet its existence is likely.

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2.2.4. Overview of all Synthesized Leucosceptroid Natural Products

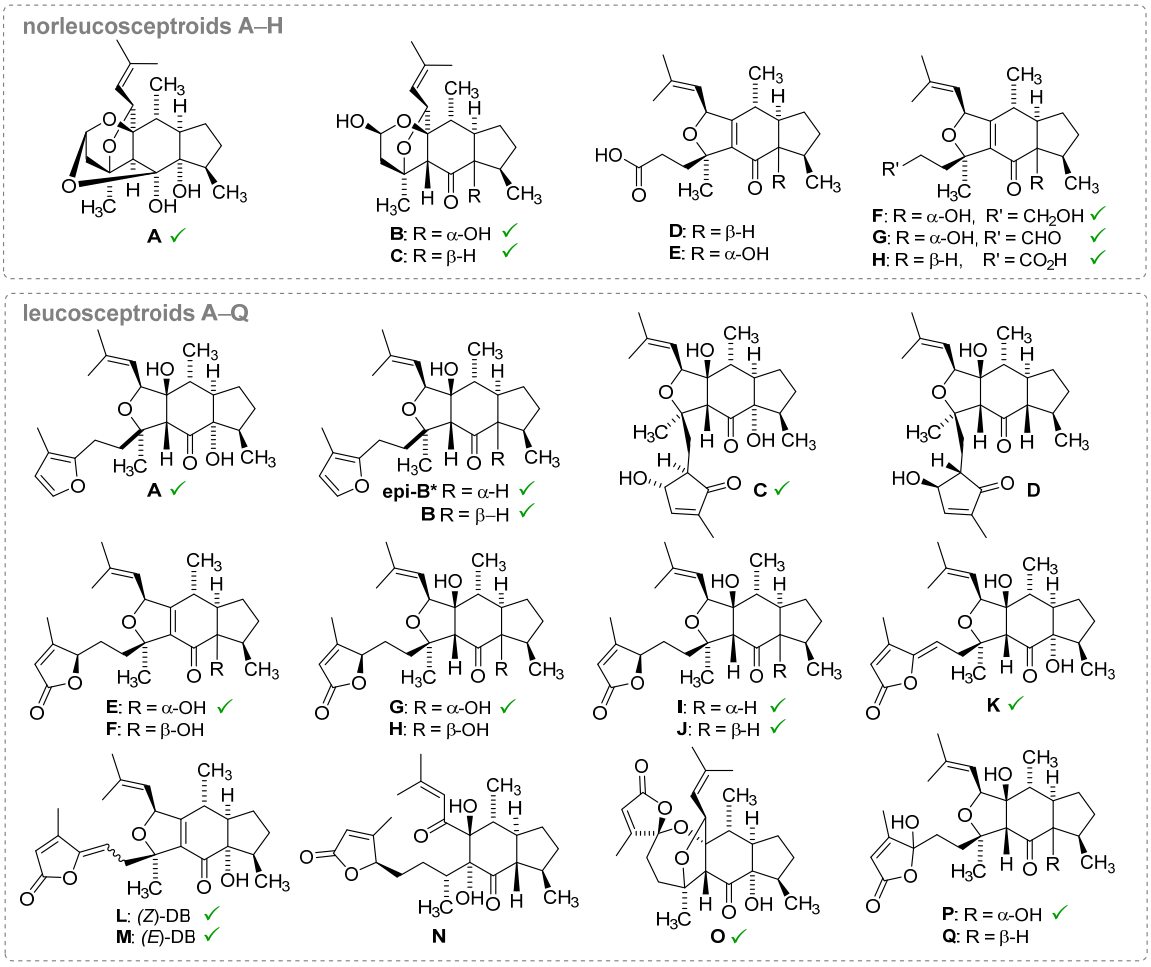
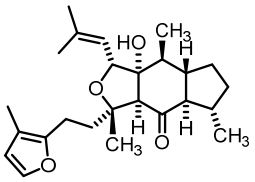
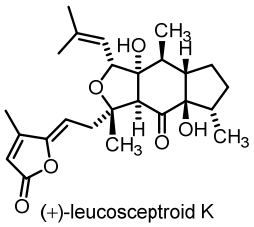


Figure 2. Family of leucosceptroid natural products. Check marks indicate all members which were prepared by the developed synthetic strategy.

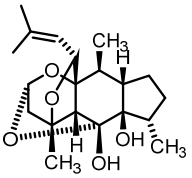
2.3 Strategies for the Synthesis of Antifeedant Leucosceptroid Natural Products



(+)-leucosceptroid B



(+)-leucosceptroid K



(–)-norleucosceptroid A

Strategies for the Synthesis of Antifeedant Leucosceptroid Natural Products

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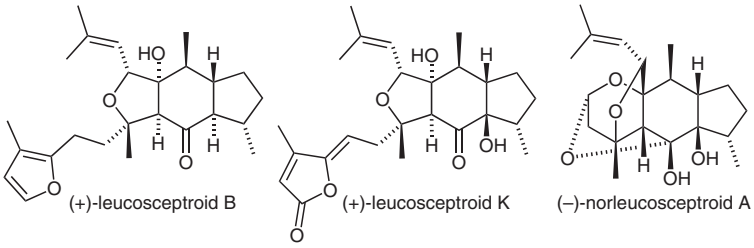

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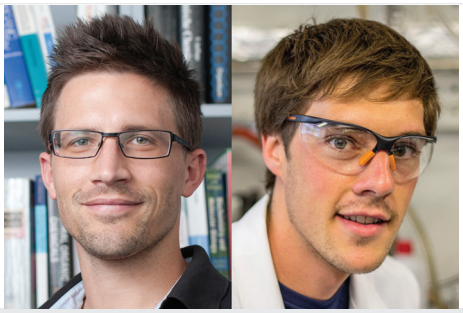
Abstract The evolving pathogen resistance in agricultural pests requires the development of novel chemical agents to maintain efficient pest control. Biological screening of natural products isolated from *Leucosceptrum canum* Smith led to the discovery of active antifeedant sesterterpenoids. This article highlights recent progress towards the synthesis of these natural products.

Key words leucosceptroids, natural products, total synthesis, terpenoids, sesterterpenoids



Thomas Magauer was born in Linz, Austria in 1983. He grew up in Steyr and moved to Vienna in 2002 to study chemistry at the University of Vienna. In 2007, he joined the laboratories of Prof. Johann Mulzer and under his guidance he developed enantioselective syntheses of the complex polyketide kendomycin and the sesquiterpenoid echinopines A and B. After graduating in 2009, he moved to Harvard University, USA, to begin postdoctoral studies with Prof. Andrew G. Myers. At Harvard University he worked on carbohydrates, chiral silicon protecting groups, and developed a synthesis of natural and diverse unnatural antiproliferative trioxacarcins. In 2012, he started his independent research as a Liebig junior research group leader at the LMU Munich. In 2013, he was awarded the Emmy Noether fellowship by the DFG.

Cedric L. Hugelshofer was born in Bern, Switzerland in 1988. He studied chemistry at the University of Basel and joined the group of Prof. Andrew G. Myers at Harvard University, USA, to conduct the research for his Master's thesis. During this time he worked on the development of a methodology for the synthesis of enantiomerically enriched α-quaternary amino acids using pseudoephenamine as a chiral auxiliary. In summer 2013, he joined the laboratories of Dr. Thomas Magauer for his PhD studies and began working on the total synthesis of antifeedant leucosceptroid natural products.

1 Introduction

Bioactive natural products constitute an essential source for the development of new therapeutics and agricultural agents. For these reasons, synthetic organic chemists have been fascinated by the discovery of such compounds for many years. With the advent of efficient synthetic methods, total synthesis is nowadays capable of delivering bioactive natural products in practical quantities[1] whilst allowing for the preparation of structural analogues with an enhanced biological profile. The development of an efficient, modular, and practical synthetic route is a highly creative process, which often is driven by the motivation of developing the 'ideal synthesis'.[2–4] However, pursuit of this ambitious aim does not usually culminate in realizing the actual 'ideal synthesis'. Instead, it allows for the development of multiple approaches for the preparation of a target molecule. Thus an 'intellectual playground' for synthetic organic chemists is created in which everyone strives to outrun the competition by devising a more efficient and elegant synthetic route for addressing the respective molecular complexity.

Current protection measures against the cotton bollworm (*Helicoverpa armigera*) and the beet armyworm (*Spodoptera exigua*), some of the most destructive and widely distributed agricultural pests in nature, are unsatisfactory.[5] These insects have developed pathogen resistance during the past decade, and in order to ensure efficient pest control in the future, the discovery of novel chemical agents

is necessary to replace existing insecticides, sex-pheromone traps, and transgenic crops.[6] Employing antifeedant chemicals (feeding deterrents) to protect plants from insect herbivores is intuitively a very attractive concept and the emergence of antifeedants as an element for safe crop protection is highly desirable due to the specificity, effectiveness, and quick degradation of this alternative protection measure.[7] By extraction and isolation of the trichomes, flowers, and whole leaves of *Leucosceptrum canum Smith* (Labiatae) which is a native plant in China and Nepal, Li and co-workers discovered the first sesterterpenoids which act as a biological defense against plant-feeding insects, displaying nanomolar antifeedant activity against both the cotton bollworm and the beet armyworm. The novel sesterterpenoids were named leucosceptroids A–Q,[8] and norleucosceptroids A–H,[9] which are pentanorsesterterpenoids (Figure 1).[10]

Characteristic for all members of the leucosceptroid family of natural products is a common, highly functionalized tricyclic framework containing a tetrahydrofuran ring (C ring) and eight contiguous stereogenic centers. Differences between the various members arise in the oxidation state at C11 (OH, H), the substitution of the southern hemisphere side chain (C14 linkage), and hydration/dehydration of the C5–C13 bond.

The leucosceptroid natural products and other sesterterpenoids are highly attractive targets for total synthesis[11] based on their intriguing molecular structures combined with their significant biological activity. On these grounds, Horne's laboratory[12] reported an asymmetric approach to the core structure of leucosceptroids in 2011. Two years later, Liu and co-workers[13] accomplished the first total synthesis of leucosceptroid B (**2**). Efforts of our own group[14] have led to the development of a general strategy for the synthesis of this natural product class, which culminated in the total synthesis of (+)-norleucosceptroid A (*ent*-**9**), (–)-norleucosceptroid B (*ent*-**10**) and (–)-leucosceptroid K (*ent*-**5**). Most recently, Ma and co-workers[15] disclosed an efficient route for the first total synthesis of leucosceptroid A (**1**) and the preparation of leucosceptroid B (**2**). Herein, we highlight the recent developments toward the total synthesis of antifeedant sesterterpenoids and focus on the strategies used to construct the synthetically challenging 5,6,5-framework of the leucosceptroids.

2 Synthesis of the Leucosceptroid Core Structure

The synthetic strategy developed by Horne and co-workers relies on an intramolecular Diels–Alder reaction to form the tricyclic leucosceptroid core **12** (Scheme 1). The precursor for the [4+2] cycloaddition was envisaged to be derived from triflate **13** by employing a Sonagashira cross-coupling reaction. In turn, the *cis*-tetrahydrofuran moiety in **13** would be prepared from diol **14** using an oxidative cyclization strategy.

In the forward sense, homoallylic alcohol **15** (derived from D-mannitol diacetonide in two steps) was first converted into ketone **16**. This sequence included several protecting-group manipulations and an oxidative cyclization method developed by Stark and co-workers[16] for the syn-

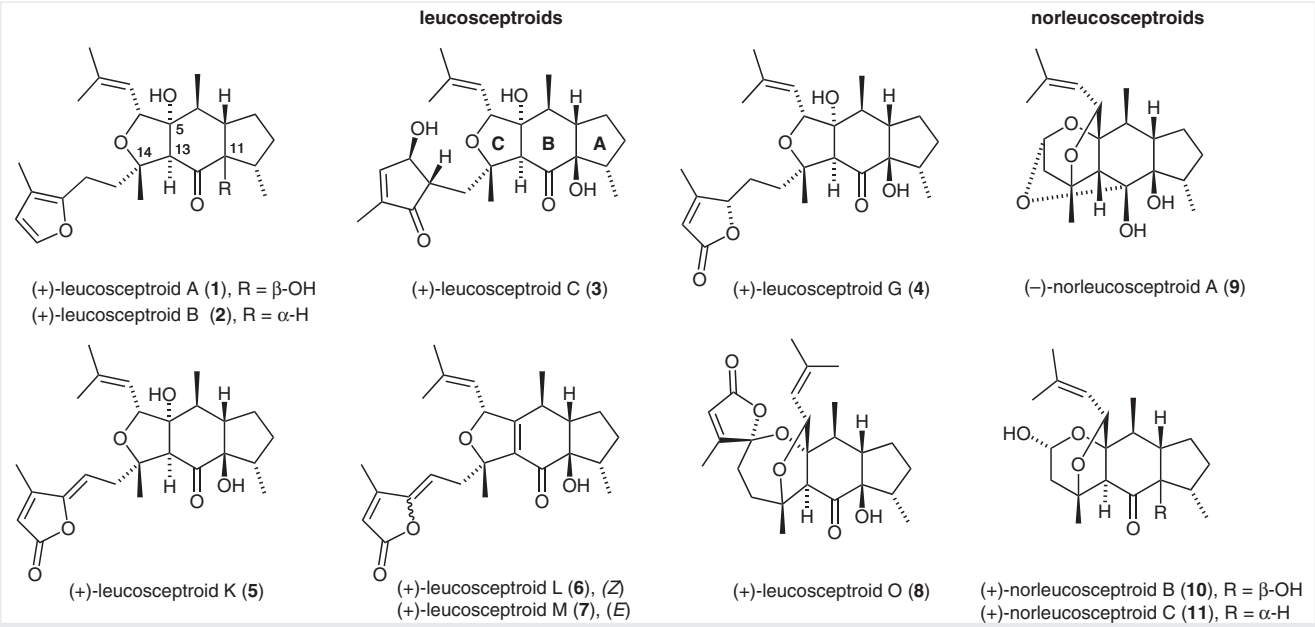
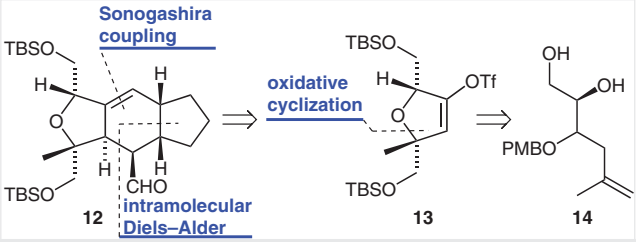


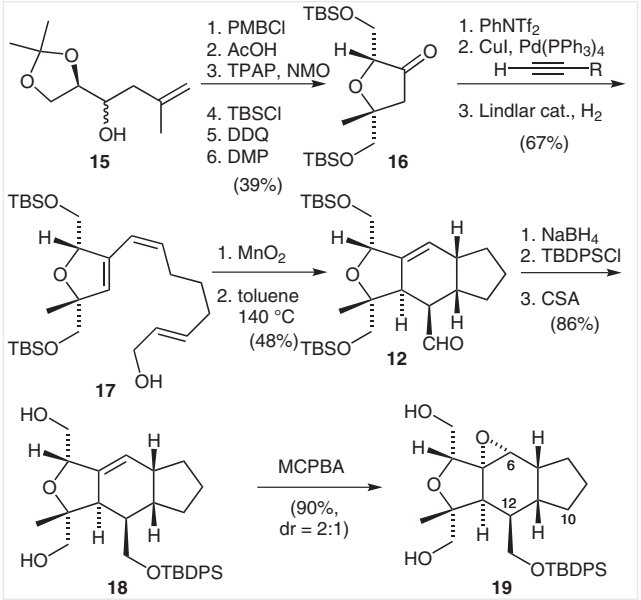
Figure 1 Structures of selected leucosceptroid and norleucosceptroid natural products



Scheme 1 Horne's retrosynthetic analysis of the tricyclic core structure

thesis of *cis*-tetrahydrofuran diols (Scheme 2). Treatment of **16** with *N*-phenyl-bis(trifluoromethanesulfonimide) produced the corresponding triflate which underwent Sonogashira cross-coupling to afford, after semihydrogenation of the alkyne functionality, triene **17**. Oxidation of the allylic alcohol then furnished the crucial Diels–Alder substrate. Heating a solution of this cycloaddition precursor in toluene, gratifyingly furnished the *endo* product **12** as a single diastereomer in good yield. This transformation enabled the efficient construction of the tricyclic core of the leucosceptroid natural products and set three key stereogenic centers in one step. Next, a sequence consisting of aldehyde reduction followed by TBDPS protection of the resulting alcohol and cleavage of the primary TBS ethers gave diol **18**. Epoxidation of the latter compound with MCPBA preferentially occurred from the *endo* face of the *cis*-hydrindane system to yield epoxide **19** as the major compound (dr = 2:1). Unfortunately, all attempts to install the C6 methyl group in **19** by S_N2 epoxide ring opening failed. It was suggested by Horne and co-workers that this is due to the unfavorable attack of a methyl carbanion onto the dialkoxide which is formed upon addition of excess organometallic reagent.

Epoxide **19** ultimately resulted in a dead end, however, Horne showed that construction of the tricyclic leucosceptroid core by means of an intramolecular Diels–Alder reaction is conceptually feasible. Introduction of a chiral alkyne, already containing the C10 methyl group, might allow the synthesis of a more functionalized leucosceptroid core structure. Nevertheless, drawbacks of this route are the need for many protecting-group manipulations, as well as an inevitable C1 degradation for the installation of the C12 ketone.

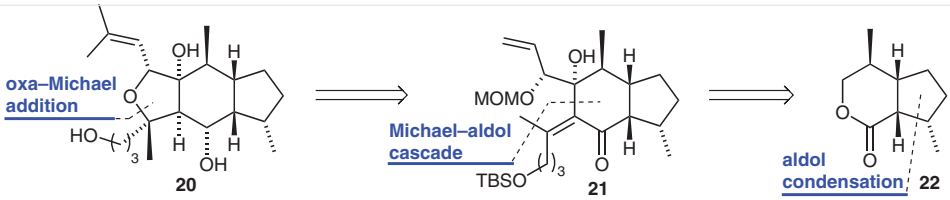


Scheme 2 Asymmetric synthesis of the leucosceptroid core by Horne and co-workers

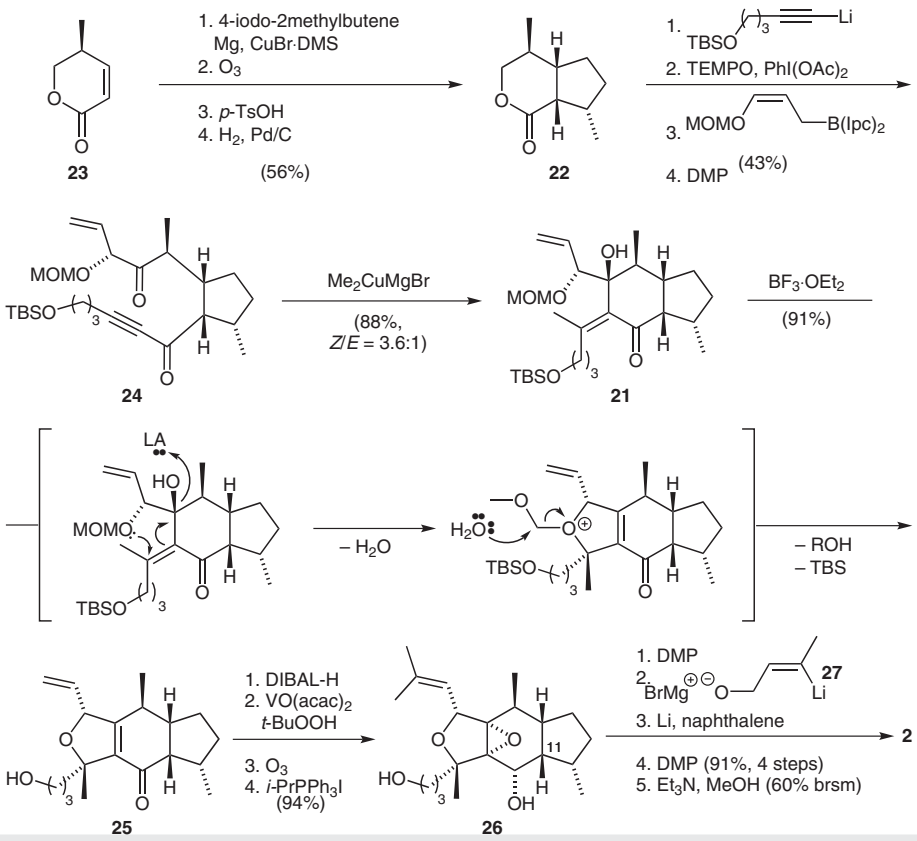
3 Total Synthesis of Leucosceptroid B

A fundamentally different approach to construct the 5,6,5-framework of the leucosceptroids was employed by Liu and co-workers in their synthesis of leucosceptroid B (**2**). They envisioned a late-stage intramolecular oxa-Michael addition to form the highly functionalized tetrahydrofuran (ring C) of the tricyclic core **20** (Scheme 3). The six-membered B ring of bicycle **21** could be accessed via a Michael–aldol cascade, and the A ring in lactone **22** was planned to be prepared by an aldol condensation reaction.

The synthetic endeavor started with conjugate organocuprate addition to α,β-unsaturated lactone **23** (prepared in three steps by an asymmetric Michael addition–elimination reaction[17]), followed by a sequence consisting of ozonolysis, acid-catalyzed aldol condensation, and hydrogenation to afford lactone **22** (Scheme 4). Treatment of **22** with the alkynyl lithium species derived from *tert*-butyldimethyl(pent-4-ynyloxy)silane gave a hydroxy ketone which was efficiently oxidized to the corresponding aldehyde. Asymmetric Brown allylation[18] of the latter compound afforded



Scheme 3 Liu's retrosynthetic disconnections of the tricyclic core **20**



Scheme 4 Total synthesis of leucosceptroid B (**2**) by Liu and co-workers

ynone **24** after Dess–Martin periodinane oxidation. Next, the key sequence of a conjugate 1,4-addition of a methyl carbanion to the ynone and attack of the so-formed allenylcuprate at the ketone was investigated. Optimization of the reaction conditions for this Michael–aldol cascade revealed methyl magnesium bromide and copper(I) iodide to be the best reagent combination for achieving good *Z*/*E* selectivity (3.6:1) and excellent yield (88%) of bicycle **21**. As anticipated, formation of the tetrahydrofuran C ring was then achieved by a boron trifluoride promoted intramolecular oxa-Michael addition. Mechanistically it is suggested that treatment of bicycle **21** with the Lewis acid leads to S_N2' elimination of the allylic hydroxy group once attack of the electron-deficient double bond by the MOM ether takes place. Since direct epoxidation of the enone moiety in **25** failed under basic conditions, stereoselective reduction of the ketone was first performed, thus enabling a hydroxy-directed epoxidation. Subsequent ozonolysis of the terminal double bond and Wittig olefination to install the propenyl side chain furnished diol **26** in very high yield. Oxidation of both the primary and secondary alcohols followed by addition of vinyl lithium **27** to the aldehyde moiety gave rise to the corresponding 1,4-diol. Introduction of the C5 hydroxy group was then achieved by epoxide opening with lithium naphthalene, and the furan moiety was formed in a one-pot oxidation–cyclization–dehydration sequence, affording the H11 epimer of leucosceptroid B (**2**) in excellent yield over four steps. The final epimerization of H11 was plagued by facile elimination of the β-hydroxy ketone under various conditions. Finally, it was discovered that by using triethylamine in methanol at 50 °C, the natural product **2** could be isolated in 21% yield (60% based on recovered starting material) from the thermodynamic product distribution resulting from this reaction.

In conclusion, Liu and co-workers accomplished the first asymmetric total synthesis of leucosceptroid B (**2**) which proceeds in 19 steps from lactone **23**. The developed approach is highly linear and for the stereoselective installment of the C5 hydroxy group additional redox manipulations are required. Although this added several synthetic operations to the overall number of steps, the elegant reaction cascades to forge the B and C rings of the core structure still make this a very attractive strategy.

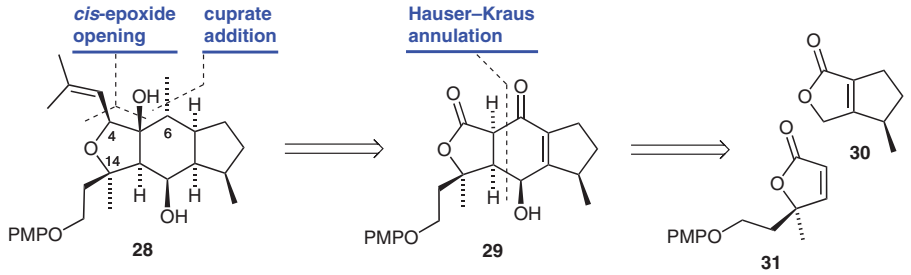
4 Towards the Collective Synthesis of Leucosceptroid Natural Products

With the incentive of devising a concise and practical route for the collective synthesis of leucosceptroid natural products, we considered a convergent assembly of the tricyclic core that would allow for the preparation of large quantities of advanced intermediates for late-stage diversification. The functionalized core structure **28** (Scheme 5) which constituted our initial synthetic target, resembles intermediate **20** in Liu's synthesis. However, the shorter C14 ethyl linkage would also allow the synthesis of the norleucosceptroids. We envisaged preparing **28** by introduction of the C4 propenyl side chain and C6 methyl group with appropriate organometallic reagents in the ABC core structure **29**. In turn, **29** could be formed by a convergent formal [4+2] cycloaddition from two simple coupling partners, AB bicycle **30** and butenolide **31**.

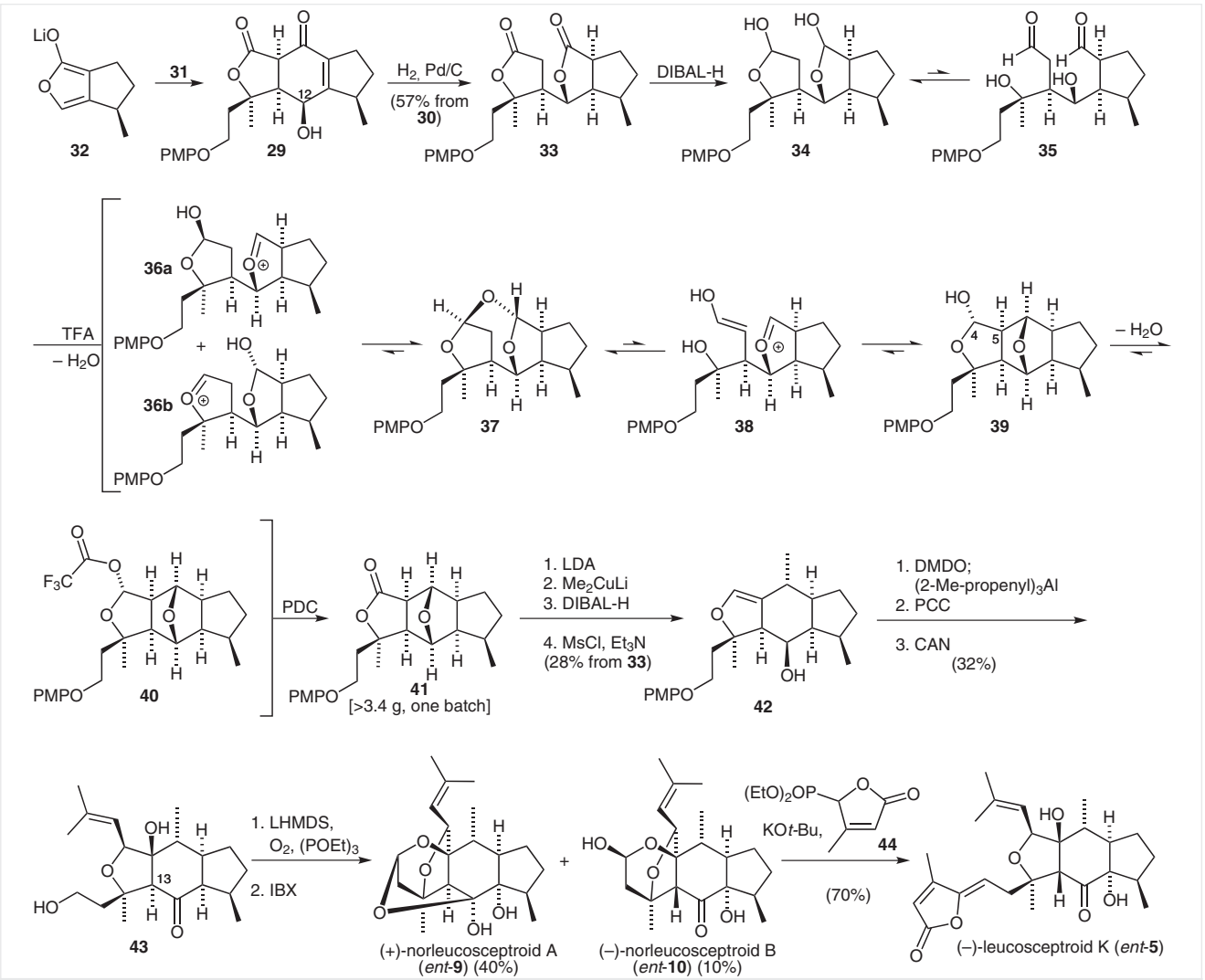
At the outset of our studies we developed highly scalable routes for the synthesis of both AB bicycle **30** (derived from inexpensive (*R*)-pulegone in five steps) and butenolide **31** (four steps from commercially available starting material), allowing facile preparation of decagram quantities of these cycloaddition precursors. The *p*-methoxyphenyl ether in **31** was necessary to set the absolute configuration of this building block[19] and thus serves as the sole, dual-purpose protecting group throughout our synthesis.

Our efforts then focused on assembling tricyclic core **29** via a Hauser–Kraus-type annulation (Scheme 6).[20] We found that treatment of the lithium dienolate **32**, derived from AB bicycle **30**, with the C ring precursor **31**, afforded tricyclic enone **29** as a 3:1 mixture of diastereomers. Surprisingly, hydrogenation of **29** did not afford the corresponding ketone, but instead furnished dilactone **33** as the final product, in a sequence proceeding via a hemiacetal intermediate that then underwent retro-Claisen condensation. Although the importance and potential of this intermediate was not immediately recognized,[21] we later discovered its hidden dialdehyde structure allowing us to develop an intramolecular aldol-type condensation. We envisaged that twofold reduction of dilactone **33** would afford dilactol **34**, which is in equilibrium with dialdehyde **35**. The latter was envisaged to undergo an aldol condensation to reform the 5,6,5-tricyclic system. After DIBAL-H reduction of **33**, ^{1}H NMR analysis of the crude product showed a complex mixture of four dilactol diastereomers **34**, with only trace amounts of aldehyde **35** being observable. Investigation of the reaction parameters revealed that a one-pot condensation–oxidation sequence of dilactol **34** to tetracycle **41** could be carried out in a highly efficient manner. Treating a solution of **34** in dichloromethane containing 4 Å molecular sieves with excess trifluoroacetic acid (5 equiv) led to formation of 4-*O*-trifluoroacetyl acetal **40** (its presence was confirmed by NMR analysis) which upon addition of pyridinium dichromate was oxidized to tetracycle **41**. We believe that the sequence to **40** proceeds through a pair of isomeric oxonium ions **36a** and **36b**, arising from expulsion of one equivalent of water from dilactol **34**, which then both convert into bisacetal **37** as an intermediate. The latter compound could be isolated and characterized when dilactol **34** was treated with substochiometric amounts of trifluoroacetic acid. Equilibration of bisacetal **37** to trace amounts of enol-oxonium ion **38** then allowed an aldol-type reaction to take place, affording ether **39** after lactol formation. Labeling studies revealed that the final conversion of **39** into 4-*O*-trifluoroacetyl acetal **40** does not proceed via formal addition of trifluoroacetic acid to a C4–C5 enol ether, but rather by expulsion of one equivalent of water from **39**, leading to the corresponding oxonium ion which then gets trapped by trifloroacetate. This intramolecular dilactol aldol-type condensation reaction is remarkable since the complex mixture of dilactol diastereomers **34** is converted into a single compound and the reaction proceeds efficiently also on large scale (more than 3.4 g of **41** could be prepared in a single batch). Furthermore, spectroscopically pure tetracycle **41** can be obtained by simply removing the excess solids by filtration.

Continuing the elaboration of the core structure, the ether bridge of **41** was opened under basic conditions, affording the corresponding α,β-unsaturated lactone which allowed introduction of the C6 methyl group by conjugate addition of dimethyl cuprate. Facing the challenge of diastereoselectively introducing the C4 propenyl side chain and C5 hydroxyl group in a *syn* fashion, we prepared enol ether **42** by DIBAL-H reduction of the lactone moiety followed by elimination using methanesulfonyl chloride and triethyl-



Scheme 5 Magauer's retrosynthetic analysis of the functionalized 5,6,5-framework

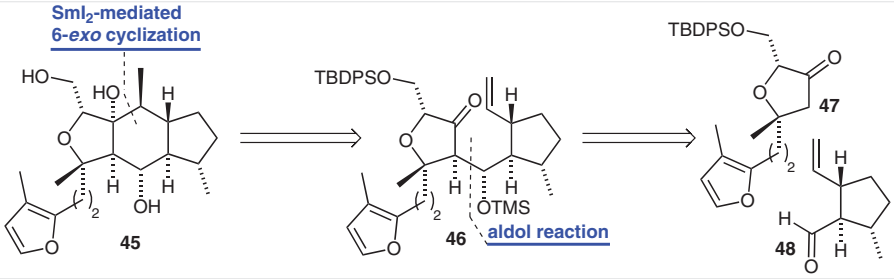


Scheme 6 Total synthesis of (+)-norleucosceptroid A (*ent*-**9**), (–)-norleucosceptroid B (*ent*-**10**) and (–)-leucosceptroid K (*ent*-**5**) proceeding via an unprecedented intramolecular dilactol aldol-type condensation reaction

amine. The labile β-epoxide derived from **42** was most efficiently obtained using a freshly prepared solution of dimethyldioxirane in acetone. Immediate addition of the crude product to excess tris(2-methyl-1-propenyl) aluminum afforded, after oxidation and cleavage of the PMP ether, ketone **43**. Regioselective α-hydroxylation of **43** surprisingly lead to partial epimerization of H13, so that after subsequent oxidation of the primary alcohol both (+)-norleucosceptroid A (*ent*-**9**) and (–)-norleucosceptroid B (*ent*-**10**) were isolated. The nature of how seemingly minor changes in the substitution pattern of the 5,6,5-leucosceptroid framework leads to thermodynamic preference for the AB-*cis*-BC-*cis* or the AB-*cis*-BC-*trans* fusion, is not fully understood and remains a matter of investigation. Finally, condensation of *ent*-**10** with phosphonate **44**, afforded (–)-leucosceptroid K (*ent*-**5**), thus demonstrating the generality of our synthetic route which also allows preparation of further members of the leucosceptroid family. Efforts towards the collective synthesis of this natural product class are currently being pursued in our laboratories.

5 Total Synthesis of Leucosceptroids A and B

Most recently, Ma and co-workers reported a synthetic route to leucosceptroid A (**1**) and B (**2**) in which the tricyclic core was prepared in convergent manner. They envisaged forming the 5,6,5-framework **45** using a late-stage intramolecular ketyl–olefin radical cyclization of ketone **46** (Scheme 7). In turn, **46** could be assembled by an aldol reac-

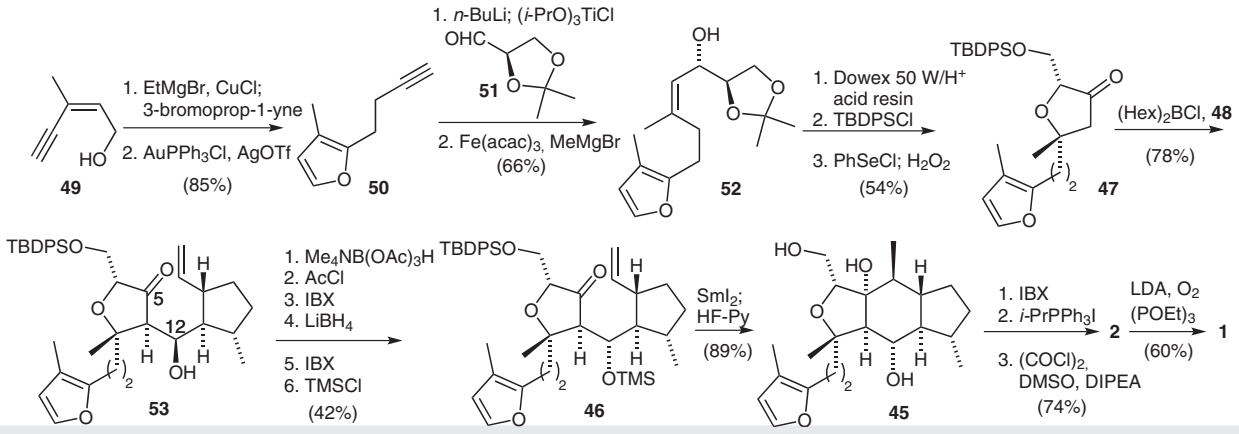


Scheme 7 Ma's retrosynthetic disconnections of the 5,6,5-tricyclic core **45**

tion of aldehyde **48** and dihydrofuranone **47**, a building block that resembles Horne's intermediate **16** but already contains the furan moiety.

In the forward sense, assembly of dihydrofuranone **47** commenced by coupling of enynol **49** with 3-bromoprop-1-yne, followed by gold-catalyzed 5-*exo*-*dig* cyclization to afford furan **50** (Scheme 8). Addition of aldehyde **51** to the titanium acetylide complex derived from **50** gave rise to the corresponding *anti* adduct (dr = 7:1) which was further transformed into allyl alcohol **52** by an iron-catalyzed carbometalation with methylmagnesium bromide. After hydrolysis of the acetal and protection of the primary alcohol as its silyl ether, a PhSeCl-mediated cyclization–oxidation sequence afforded dihydrofuranone **47**. The second aldol reaction partner, aldehyde **48**, was prepared in three steps from (*S*)-citronellal employing MacMillan's SOMO–organocatalysis allylation protocol.[22] While condensation of the lithium enolate derived from **47** with aldehyde **48** failed to afford **53**, it was found that an *anti*-selective boron–aldol reaction [Et_3N, $(hex)_2BCl$] gave **53** in high yield (78%). Next, the crucial SmI_2-mediated intramolecular ketyl–olefin radical cyclization was investigated. Disappointingly, treatment of substrates containing a β-OTMS as found in **53** with SmI_2 (THF, HMPA, *t*-BuOH) only led to a 7-*endo*-*trig* cyclization to produce the undesired 5,7,5-tricyclic compound. It was hypothesized that a repulsive interaction between the axial β-OTMS group and the olefin moiety disfavored the 6-*exo* cyclization. On these grounds, preparation of ketone **46** containing an α-OTMS group (in equatorial position) was envisaged. For the inversion of the C12 hydroxy group in **53**, a five-step redox sequence was required: Reduction of **53** with $Me_4NB(OAc)_3H$, regioselective acylation of the so-obtained 5-OH group, oxidation of 12-OH, followed by reduction of the resulting ketone ($LiBH_4$) furnished the secondary alcohol with the desired stereochemistry. Selective oxidation of 5-OH and protection of 12-OH as the silyl ether then gave ketone **46** containing the desired α-OTMS group. The SmI_2-mediated cyclization of **46** afforded the desired tricyclic triol **45** in excellent yield (89%) after desilylation. Regioselective oxidation of **45** followed by Wittig olefination allowed installation of the propenyl side chain, and Swern oxidation of 12-OH completed the total synthesis of leucosceptroid B (**2**). Finally, α-hydroxylation, employing similar conditions as reported for the introduction of the 11-OH group of the norleucosceptroids, gave leucosceptroid A (**1**).

Ma and co-workers developed a total synthesis of leucosceptroid B (**2**) which proceeded in 18 steps (longest linear sequence) from commercially available enynol **49**. A convergent aldol reaction of two highly functionalized building blocks gave the substrate for the intramolecular ketyl–olefin radical cyclization. Unfortunately, as this cyclization



Scheme 8 Total synthesis of leucosceptroid A (**1**) and B (**2**) employing a SmI_2-mediated radical cyclization

turned out to be unselective for the initial aldol product, many redox manipulations were required to correct the 12-OH stereochemistry and conduct the SmI_2-mediated cyclization in a highly efficient manner.

6 Summary

In conclusion, four quite different strategies for the synthesis of the core structure of antifeedant leucosceptroid natural products have been presented. While the group of Horne employed an intramolecular Diels–Alder reaction, Liu and co-workers developed an oxa-Michael–elimination cascade to forge the tricyclic core. The efforts of our own group culminated in a convergent synthetic route involving a formal [4+2] cycloaddition (Hauser–Kraus-type annulation) followed by an unprecedented intramolecular dilactol aldol-type condensation reaction that allowed us to prepare multigram quantities of the advanced intermediates. Finally, the group of Ma used a SmI_2-mediated intramolecular ketyl–olefin radical cyclization to construct the challenging 5,6,5-leucosceptroid framework. By highlighting the attractiveness of the leucosceptroid natural products and disclosing intricacies associated with their preparation, we hope the work presented herein will stimulate and inspire further organic chemists to develop novel synthetic methods and efficient routes to this fascinating class of natural products.

Acknowledgment

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2.4 Conclusion and Outlook

In Part I of this thesis, a general entry to antifeedant (pentanor-)sesterterpenoids was developed, which culminated in a collective synthesis of the leucosceptroid family of natural products. The key features of the established synthetic route involved convergent assembly of two similarly complex building blocks and the invention of an unprecedented intramolecular aldol condensation of a dilactol. The efficient approach allowed preparation of a highly functionalized core structure on a multigram scale. This pivotal intermediate paved the way for the asymmetric synthesis of 18 complex leucosceptroid natural products. Moreover, we reviewed recent developments toward the total synthesis of leucosceptroids and highlighted the different strategies which have been employed to construct the synthetically challenging 5,6,5-framework.

In collaboration with the group of Prof. Sheng-Hong Li, we focused on unraveling the metabolic pathway in *Leucosceptrum canum*, formulated a biosynthetic proposal and developed a model system to investigate biomimetic furan oxidations. Thus, we were able to suggest links between individual leucosceptroid members and, importantly, identified leucosceptroids A and B as the probable parent members of all other known leucosceptroids. Based on this proposal, we investigated the oxidation of leucosceptroid A using singlet oxygen and could thereby achieve biomimetic syntheses of leucosceptroids C, K, O and P. The results of our studies corroborated the hypothesis that photo-oxidation is involved in the metabolic pathway of the antifeedant leucosceptroids.

In future work, we aim to apply the intramolecular aldol condensation of dilactols in the total synthesis of other complex natural products and establish it as a useful method for organic synthesis. Moreover, the antifeedant properties of the leucosceptroid natural products and of synthetic analogs will be further investigated in collaboration with the group of Prof. Sheng-Hong Li. Together with the research group of Prof. Alexander Adibekian (University of Geneva, Switzerland) it was recently discovered that certain leucosceptroid members bind highly selectively to proteins, which are primarily involved in cancer treatment. These collaborations are expected to provide many more fascinating results in the future.

3 PART II: THE MARINE DITERPENOIDS (+)-DICTYOXETANE AND (+)-DOLABELLANE V

3.1 Introduction

3.1.1 Oxetane-containing Natural Products

Oxetanes are highly polar, four-membered cyclic ethers occurring only in a relatively small number of natural products – many of them being terpenoids. The prime example is taxol (**32**), a complex compound isolated from the bark of the western yew,[53] which has gained major application as a clinical agent in cancer chemotherapy (Figure 3).[54] Notably, replacement of the oxetane in taxol with an azetidine, thietane or selenetane afforded structural analogs with significantly decreased bioactivity compared to the parent compound.[55] The presence of the oxetane ring in taxol thus appears to be essential for the strong anticancer activity, however, the precise role of this four-membered heterocycle remains controversial and obscure.[56]

Notably, several other oxetane-containing natural products, which are structurally distinct from taxol, were also found to exhibit anticancer activity. For example, maoyecrystal I (**95**) was isolated from *Isodon japonicas* and displayed considerable cytotoxicity.[57] Interestingly, a derivative of this natural product in which the oxetane was cleaved methanolytically no longer showed cytotoxic effects against the same cell line. Saharanolide A (**96**), a guaianolide type sesquiterpenoid lactone, was discovered in the organic extract of the leaves of a shrub endemic to Morocco and showed significant cytotoxicity against a human cervix carcinoma cell line.[58] Finally, the extraction of a soft coral of the genus *Pseudopterogorgia* yielded the sesquiterpenoid pseudorigidone A (**97**), which could slow down

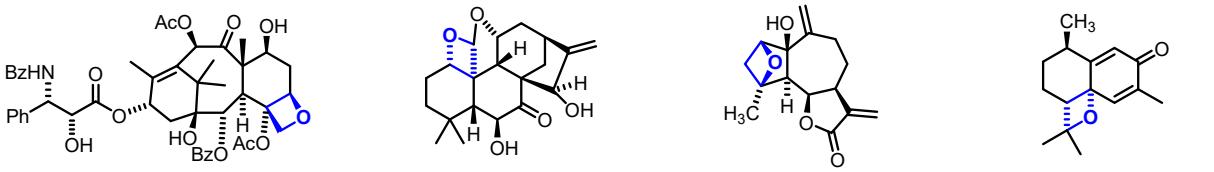

Figure 3. Oxetane-containing natural products exhibiting anticancer activity.

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tumor growth by means of displaying specific inhibitory activity against cell division cycle phosphatases.[59]

Besides anticancer activity, many further oxetane-containing natural products show a wide range of other intriguing pharmacological effects (Figure 4). For example, mitrephorone A (**98**) was isolated from the dried bark of *Mitrephora glabra* and displayed both antimicrobial effects, as well as cytotoxic activity against a panel of different cancer cell lines.[60] Extraction of a fermentation broth of a *Streptomyces* strain allowed isolation of oxetin (**99**), a small molecule displaying antibacterial as well as herbicidal effects.[61] Oxetanocin (**100**) was isolated from a *Bacillus megaterium* soil-bacterium and triggered considerable interest from the scientific community due to its promising anti HIV activity.[62] While thromboxane A_2 (**101**) proved to be a potent inducer of platelet aggregation and constrictor of vascular smooth muscles,[63] bradyoxetin (**102**) was found to be a unique signaling molecule in soybeans.[64] The highly oxygenated natural product trigonothryin C (**103**) showed promising inhibitory activity against HIV and also constitutes one of the first discovered daphnane diterpenoids containing an oxetane.[65] Laureatin (**104**), featuring an oxetane embedded in an eight-membered cyclic ether, was obtained from the extract of the dried seaweed *Laurencia nipponica* and has shown potent activity as a

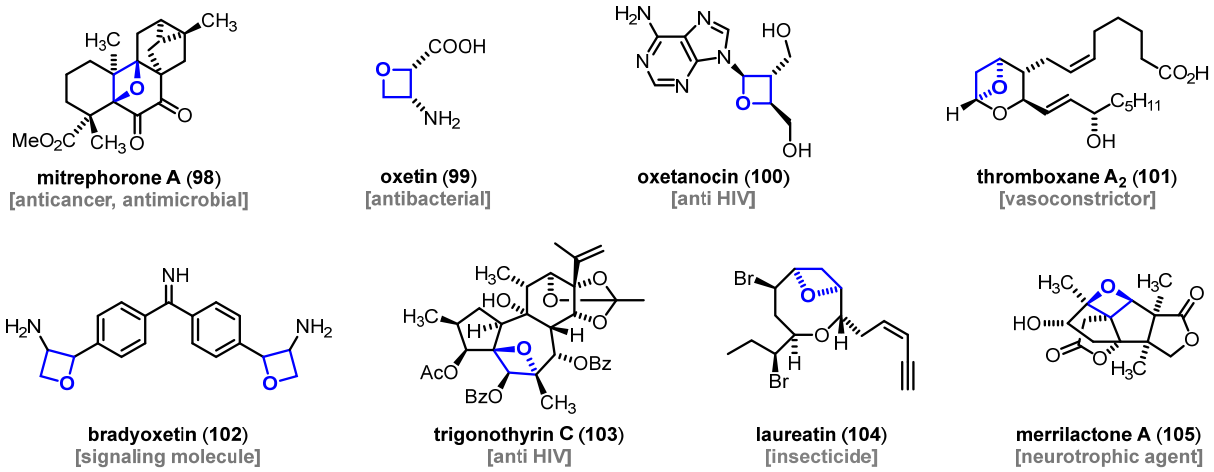

Figure 4. Selected oxetane natural products with varied biologically activities.

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mosquito larvicide.[66] Merrilactone A (**105**) represents a well-known natural product containing a four-membered oxygen hetereocycle.[67] The promising bioactivity of this natural product, namely the stimulation of neuron growth in rats, together with the dense, polycyclic structure has led to considerable synthetic efforts in recent years.[68]

Finally, complex natural products incorporating a highly substituted oxetane are presented, for which distinct biological activities have not yet been reported (Figure 5). For instance, the marine diterpenoid dictyoxetane (**91**) features a structurally beautiful, unique polycyclic ether core that has eluded both total synthesis and investigation of its pharmacological activity for over three decades.[48] Sodwanone W (**106**) was isolated from the sponge *Axinella* and only a cursory examination of its biological effect was undertaken.[69] The resveratrol dimer hopeahainanphenol (**107**) was isolated from the stem bark of *Hopea hainanensis* and in an initial screen showed no acetylcholinesterase inhibitory and antitumor activity.[70] Cephaloziellin B (**108**) is a secondary metabolite from the Chinese liverwort *Cephaloziella kiaeri* and features a rare oxetane–acetal structural motif.[71] While the oxetane and *N*,*O*-hemiacetal motifs embedded in the complex polycyclic structure of stemona-amine B (**109**) were confirmed by X-ray crystallographic analysis, the biological activity of this alkaloid remains unexplored.[72] The daunting structure of the denudatine-type diterpenoid alkaloid epoxynapelline I (**110**), isolated from the roots of *Aconitum nagarum*, was likewise confirmed by X-ray crystallographic analysis.[73] Lastly, asbestinane VII (**111**)[74] and teufruintin C (**112**)[75] have been isolated, yet no biological activity of these oxetane-containing natural products have been reported to date.

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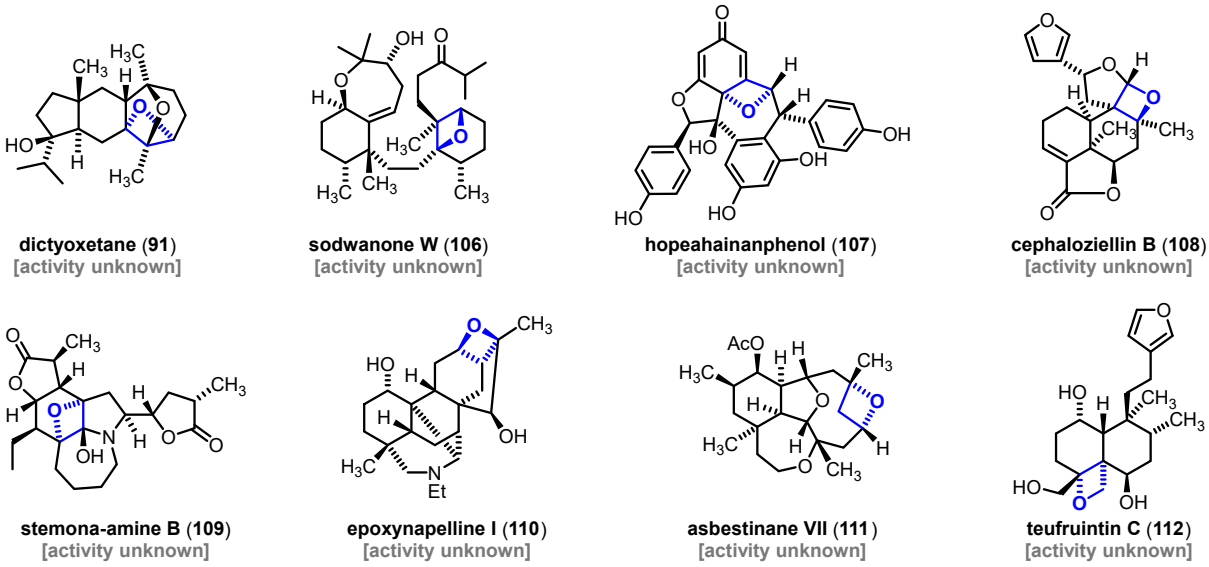

Figure 5. Complex oxetane-containing natural products with unknown biological activites.

As disclosed in this brief overview, numerous oxetane-containing natural products exhibit intriguing biological activities. Although in many cases only a cursory examination of the pharmacological activities has been undertaken, the varied biological effects discovered thus far highlight that the need for more detailed investigations of such natural products is warranted. While bioactive natural products represent a rich source for the development of new therapeutic and agricultural agents,[76] thorough biological studies are often severely hampered by the scarcity of these compounds obtained from natural sources. Thus, it is highly desirable to develop an efficient chemical synthesis that could deliver practical quantities of a natural product for extensive biological investigations.

It is interesting to note that a majority of complex oxetane-containing natural products seem to have been 'forgotten' or 'lost' in the literature, and only a relatively small number of these compounds have attracted synthetic interest. This is unfortunate, since many of the presented natural products display beautiful and challenging structures which certainly constitute formidable synthetic targets. By having highlighted the structural diversity and attractiveness of oxetane-containing natural products, it is hoped that this brief overview might also stimulate and inspire other organic chemists to venture on a synthetic undertaking focusing on such fascinating targets.

On these grounds, in the second part of this Ph.D. thesis we became encouraged to devise a total synthesis of (+)-dictyoxetane, which could finally enable exploration of the bioactivity of this fascinating oxetane-containing natural product. The beautiful and highly complex structure of (+)-dictyoxetane constituted an additional incentive to begin this synthetic endeavor.

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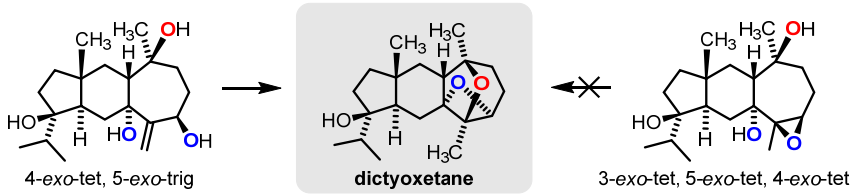
3.2 Results and Discussion

3.2.1 A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane



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A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane

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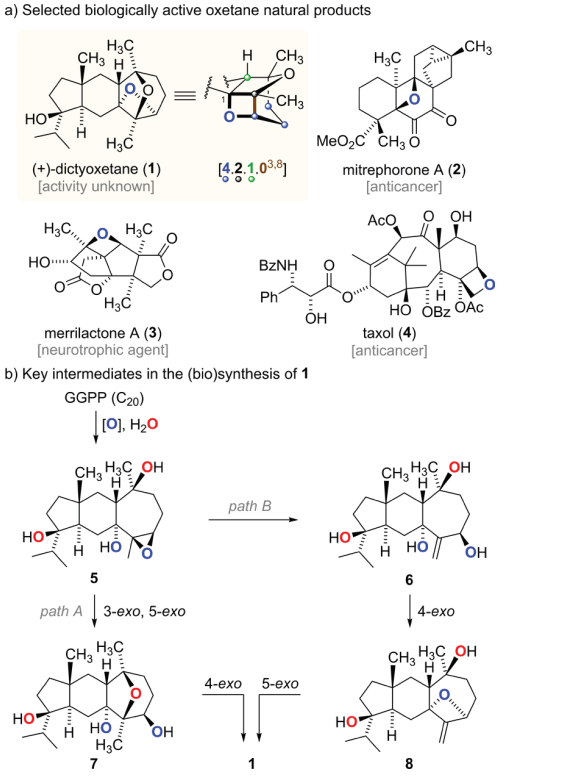
Supporting Information

ABSTRACT: We have developed the first synthesis of the unique oxetane containing diterpene (+)-dictyoxetane. Our retrosynthetic planning was guided by the putative biosynthesis of the unprecedented 2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonane ring system. A bioinspired 4-*exo*-tet, 5-*exo*-trig cyclization sequence enabled the construction of the synthetically challenging dioxatricyclic framework. The overall synthesis proceeds in 15 linear steps from a known and readily available *trans*-hydrindane fragment. In addition, we were able to realize the first dyotropic rearrangement of an epoxide−oxetane substrate.

Natural products containing oxetanes often display strong and intriguing biological activities. However, their occurrence is very rare and less than a dozen have been reported to date (Scheme 1a).[1] Until the development of taxol (**4**) as a potent anticancer agent, medicinal chemistry has focused little study toward this unique structural motif. Oxetanes are highly polar heterocycles that have only recently been identified as efficient hydrogen bond acceptors and valuable surrogates for the *gem*-dimethyl group in drug discovery.[2] (+)-Dictyoxetane (**1**) was first isolated from the brown alga *Dictyota dichotoma* (Krusadai Island, India) in 1985 and contains an oxetane embedded in a synthetically challenging and unique 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system.[3] As biological studies of **1** have not been reported yet and authentic material is currently unavailable,[4] several attempts were made to access the natural product in the chemical laboratory. Despite considerable efforts, only the syntheses of the more accessible *trans*-hydrindane framework[5] and simplified model systems of the dioxatricyclic substructure[6] have been accomplished so far. In seminal work by Hoffmann, promising antitumor activity of the dioxatricyclic subunit against HMO2 (human gastric carcinoma) and HEP G2 (human heptocellular carcinoma) cell lines was revealed, and a putative biosynthesis of **1** (Scheme 1b, path A) was proposed.[6a] It was hypothesized that the cyclization of geranylgeranyl pyrophosphate (GGPP) proceeds analogous to the dollabelane biosynthesis[7] and produces, after transannular cyclization to the 5−6−7 ring system and oxidation, epoxide **5**. A series of consecutive *exo*-tet cyclizations that involve tetrahydrofuran **7** as the key intermediate was suggested to lead to the formation of **1**. While studying the molecular model of **7**, we realized that formation of the strained annulated *trans*-tetrahydrofuran ring might be exceptionally challenging under nonenzymatic conditions.[8] Therefore, we envisioned that the formation of the isomeric allylic alcohol **6** could be a valuable

Scheme 1. Occurrence of Oxetane Natural Products and Bioinspired Synthetic Planning for Dictyoxetane (1)



alternative en route to **1** (Scheme 1b, path B). In this latter scenario, oxetane **8** is first formed via a 4-*exo*-tet cyclization. This ring closure involves a conformational change that places the methylene unit in close proximity to the tertiary alcohol at C10 and thus facilitates the final 5-*exo*-trig cyclization. Herein, we describe our efforts toward (+)-**1** and the first total synthesis of this unique natural product. In order to investigate the individual pathways of the biosynthetic proposals, we decided to directly target protected forms of compound **5** and its isomer **6**.

We first designed a synthetic route to the 5−6−7 ring fragment **14**, which features the full carbon skeleton of **1**, starting from Grainger's *trans*-hydrindane **10** (Scheme 2).[5] The latter can be readily prepared from 2-methylcyclopentenone (**9**), employing a very elegant phosphorane-mediated, pinacol-like rearrangement

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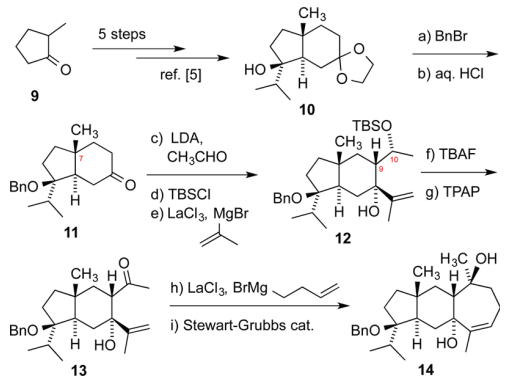
Scheme 2. Synthesis of the Full Carbon Skeleton of Dictyoxetane (1)[a]



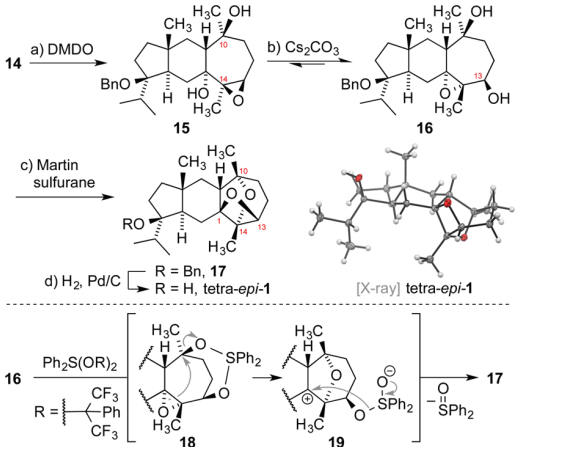
[a]Reagents and conditions: (a) BnBr, KHMDS, THF, −78 to 23 °C; (b) aq. 4 M HCl, THF, 23 °C, 85% over three steps; (c) LDA, CH_3CHO, −78 °C; (d) TBSCl, imidazole, DMAP, DMF, 23 °C, 80% over two steps, 10:1 d.r. at C10; (e) $LaCl_3$·2LiCl, isopropenylmagnesium bromide, THF, 0 °C, 93%; (f) TBAF, THF, 0 to 23 °C; (g) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C, 87% over two steps; (h) $LaCl_3$·2LiCl, 3-butenylmagnesium bromide, THF, 0 °C, 69%, 27% **13**; (i) Stewart−Grubbs cat. (25 mol %), 2,6-dichloro-1,4-benzoquinone, toluene, 111 °C, 55%, 25% recovered diene.

to establish the *trans*-ring junction. As outlined below, the sterically hindered tertiary alcohol of **10** was converted to the corresponding benzyl ether and hydrolysis of the ketal then gave access to multigram quantities (>6 g) of ketone **11**.

Next, a remarkably selective aldol reaction of the lithium enolate derived from **11** with acetaldehyde was carried out. Based on the stereodiscriminating effect of the quaternary center at C7, the aldol product was formed as a single diastereomer at C9 and as an inconsequential 10:1 mixture at C10. After protection of the β-hydroxy ketone as the corresponding silyl ether, the product was treated with isopropenylmagnesium bromide in the presence of the lanthanum(III) chloride bis(lithium chloride) complex[9] furnishing allylic alcohol **12** in high yield and excellent diastereoselectivity.[10] Conducting the analogous transformation in the absence of the lanthanide salt or without prior silyl ether formation proved to be significantly lower yielding and less diastereoselective. Subsequent removal of the silyl ether, followed by Ley−Griffith oxidation (TPAP, NMO),[11] then gave ketone **13** in 87% yield over two steps. Initial attempts to add 3-butenylmagnesium bromide to **13** proved unexpectedly challenging, and very low conversion of the starting material was observed, presumably due to facile enolization of this substrate. Fortunately, this problem could be addressed by premixing the β-hydroxyketone **13** again with lanthanum(III) chloride bis(lithium chloride) complex followed by addition of the Grignard reagent at 0 °C. This modification increased the conversion beyond 70% and provided the corresponding diene as a single diastereomer. To complete the synthesis of the 5−6−7 tricycle **14**, we then investigated the ring-closing metathesis of this diene substrate. After careful screening of the reaction parameters (catalyst, concentration, additives, temperature), the best result for formation of tricycle **14** was achieved using the Stewart−Grubbs catalyst[12] and 2,6-dichloro-1,4-benzoquinone as an additive.[13] The required high temperature (111 °C), high catalyst loading (25 mol %), and prolonged reaction time (40 h) are indicative of the challenge to form a seven-membered ring containing a trisubstituted olefin adjacent to a tertiary alcohol by means of ring-closing metathesis.[14]

Exposure of **14** to an excess of dimethyldioxirane (DMDO) cleanly gave epoxide **15** and traces of the product resulting from α-epoxidation (Scheme 3). With access to **15** we were poised to

Scheme 3. Synthesis of Tetra-*epi*-dictyoxetane (tetra-*epi*-1)[a]



[a]Reagents and conditions: (a) DMDO, acetone, CH_2Cl_2, −78 °C, ≥99%, ≥15:1 d.r.; (b) Cs_2CO_3, MeOH, 60 °C, 22% **15**, 59% **16**; (c) Martin sulfurane, CH_2Cl_2, 0 °C; (d) H_2, Pd/C, THF, 23 °C, 60% over two steps.

investigate the proposed, key *exo*-cyclization sequence to **1**. Numerous attempts to directly activate the epoxide with various acids and fuse the oxygen bridge between C10 and C14 were met with failure. While mild activation of **15** did not lead to any conversion, more forcing conditions (BF_3·OEt_2; $Yb(OTf)_3$; $HClO_4$; *p*-TsOH) led to complete decomposition of the starting material. Eventually, it was discovered that the postulated 3-*exo* rearrangement[6a] could be induced under basic conditions (Cs_2CO_3, MeOH, 60 °C), leading to an approximate 1:2.5 thermodynamic distribution of **15** and **16**, from which the latter could be easily separated by column chromatography on silica gel. At this point we determined that epoxide **16** was also reluctant to undergo further 5-*exo*-cyclization under a variety of acidic ($KHSO_4$; $Yb(OTf)_3$; aq. HCl; $Ti(O\text{-}i\text{-}Pr)_4$; $MgBr_2$·OEt_2), basic (NaH; aq. LiOH), and neutral (CF_3CH_2OH; H_2O[15]) reaction conditions.

These results confirmed our hypothesis that the seemingly simple intramolecular epoxide opening reaction to form the *trans*-tetrahydrofuran of **1** is indeed exceptionally challenging. By analyzing the X-ray structure from deprotected **16** (see Supporting Information for details) we learned that the seven-membered ring adopts a chairlike conformation. Since this places C10-OH in an equatorial position, an energetically unfavorable conformational change would be required to bring C10-OH into close proximity of C14. This result further corroborated our increasing skepticism that the desired 5-*exo*-tet cyclization of epoxide **16** might not be feasible using common activation methods. Finally, in an attempt to eliminate C13-OH in order to both change the ring geometry and generate a more reactive allylic epoxide, we observed a remarkable reaction sequence. Treatment of **16** with Martin sulfurane[16] led to rapid consumption of the starting material and furnished dioxatricycle **17** without detectable amounts of any olefinic byproducts. Hydrogenolysis of the benzyl ether gave 1,10,13,14-tetra-*epi*-

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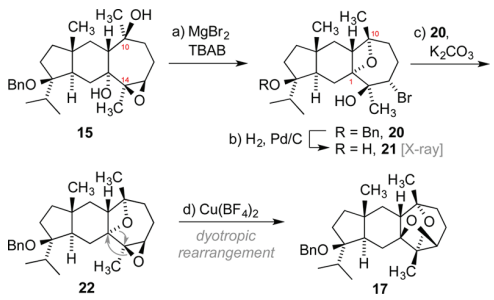
dictyoxetane (tetra-*epi*-**1**), whose structure was unambiguously confirmed by single-crystal X-ray analysis.

To rationalize this intriguing transformation, we compared and analyzed individual reaction intermediates of possible pathways, and the most likely proposed mechanistic scenario is illustrated in Scheme 3. We hypothesize that upon treatment of **16** with Martin sulfurane, the cyclic sulfurane **18** is formed. Driven by the strain release of epoxide opening and formation of a stabilized tertiary carbocation, **18** then rearranges to tetrahydrofuran **19**. Expulsion of diphenyl sulfoxide from **19** generates an alkoxide that immediately traps the carbocation to fuse the oxetane ring between C1 and C13 of dioxatricycle **17**. The direct generation of **17** from epoxide **15**, via in situ equilibration of **16**, can be excluded, as reaction of **15** with Martin sulfurane simply led to dehydration of C10-OH to give the *endo*-cyclic olefin. However, we initially also speculated that epoxide–oxetane **22** might be formed under the reaction conditions and could play a pivotal role during the rearrangement of **16** to dioxatricycle **17** (Scheme 4).

Scheme 4. Synthesis of Dioxatricycle 17 via Dyotropic Rearrangement[a]

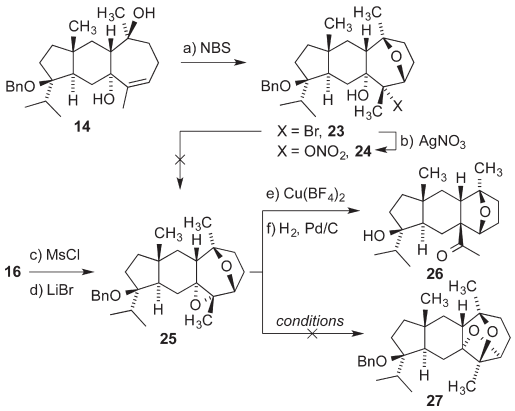


[a]Reagents and conditions: (a) $MgBr_2{\cdot}Et_2O$, TBAB, CH_2Cl_2, 23 °C, 51%; (b) H_2, Pd/C, THF, 23 °C, 83%; (c) **20**, K_2CO_3, MeOH, 0 °C, 94%; (d) $Cu(BF_4)_2{\cdot}xH_2O$, CH_2Cl_2, 23 °C, 36%.

In this context, we discovered that activation of **15** with magnesium bromide ethyl etherate in the presence of tetrabutylammonium bromide (TBAB) promoted smooth bromohydrin formation with concomitant oxetane ring closure between C1 and C10 to furnish **20**. Cleavage of the benzyl ether afforded diol **21** whose crystal structure confirmed the oxetane structural motif. Treatment of bromohydrin **20** with potassium carbonate in methanol provided the epoxide–oxetane **22** in 94% yield. At this stage, we found that **22** is left unreacted upon exposure to Martin sulfurane. Although this result further supported our mechanistic proposal and excluded any pathway based on transient formation of **22**, we were curious if a dyotropic rearrangement to dioxatricycle **17** could be induced by means of Lewis acid activation.[17] After careful experimentation, we discovered that treatment of epoxide–oxetane **22** with copper(II) tetrafluoroborate hydrate[18] promoted a strain-releasing dyotropic rearrangement to give the dioxatricycle **17** (36%) together with byproducts resulting from ring contraction (37%) and oxetane elimination (20%; see Supporting Information for details). To the best of our knowledge, this is the first example of a dyotropic rearrangement involving an epoxide–oxetane substrate.

In an attempt to apply a similar dyotropic rearrangement for the synthesis of **1**, we envisioned to extend this transformation to epoxide–tetrahydrofuran **25** (Scheme 5). Treatment of **14** with

Scheme 5. Attempted Dyotropic Rearrangement of 25[a]

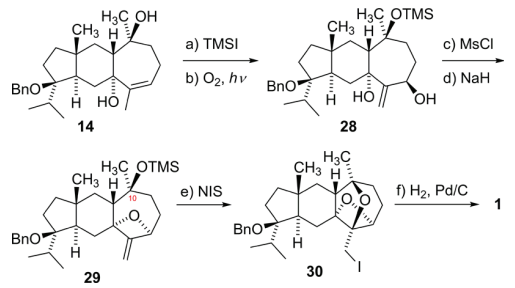


[a]Reagents and conditions: (a) NBS, CH_2Cl_2, 0 °C, ≥99%; (b) $AgNO_3$, $NaHCO_3$, acetone, 23 °C, 60%; (c) MsCl, NEt_3, CH_2Cl_2, −78 °C, 72%; (d) LiBr, Li_2CO_3, DMF, 70 °C, 80%; (e) $Cu(BF_4)_2{\cdot}xH_2O$, CH_2Cl_2, 40 °C; (f) H_2, Pd/C, THF, 23 °C, 90% over two steps.

active halogen sources such as *N*-bromosuccinimide (NBS) exclusively gave regioisomer **23**.[19] Activation of **23** with a panel of silver(I) sources ($AgNO_3$; $AgBF_4$; $AgNTf_2$) or under simple thermal conditions (CF_3CH_2OH, 2,6-lutidine) to promote the desired rearrangement to **27** via **25** was unsuccessful. Although we were able to abstract the tertiary bromide using silver(I) nitrate, exclusive formation of nitrate ester **24** occurred. Epoxide–tetrahydrofuran **25** could be finally prepared from **16** by mesylation and consecutive double S_N2 displacement. However, evaluation of several reaction conditions revealed that dyotropic rearrangement of **25** to **27** is not possible, owing to a competing semipinacol-type rearrangement generating the 5–6–6 tricyclic framework of **26**.[20]

After having failed to convert **15**, **16**, or **25** to the target compound, we returned to our alternative biosynthetic proposal, where we had envisioned constructing the dioxatricyclic substructure by forming the oxetane prior to the strained *trans*-tetrahydrofuran ring. It was found that photo-oxidation of the silyl ether derived from **14**, followed by reduction of the resulting hydroperoxide, gave allylic alcohol **28** as a single regio- and diastereomer in 71% yield (Scheme 6). While the subsequent 4-*exo*-tet cyclization of **28** could be achieved in a single transformation using *p*-toluenesulfonyl chloride and potassium

Scheme 6. Total Synthesis of (+)-Dictyoxetane (1) via Consecutive 4-*exo*-tet and 5-*exo*-trig Cyclizations[a]



[a]Reagents and conditions: (a) TMSI, CH_2Cl_2, 0 to 23 °C, 92%; (b) O_2, *hν*, TPP, DCE, 0 °C; PPh_3, 23 °C, 71%; (c) MsCl, NEt_3, CH_2Cl_2, −78 °C; (d) NaH, THF, 66 °C, 88% over two steps; (e) NIS, CH_2Cl_2, 23 °C; (f) H_2, Pd/C, THF, 23 °C, 80% over two steps.

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tert-butoxide, these conditions proved unreliable and gave irreproducible yields of oxetane **29**. Fortunately, a two-step procedure involving formation of the allylic mesylate and subsequent cyclization under basic conditions in refluxing tetrahydrofuran afforded oxetane **29** in consistently high yields. It was interesting to note that **29** showed severe signal broadening in the ^{1}H NMR spectrum at ambient temperature, indicating that formation of the oxetane had changed the conformation of the seven-membered ring in such a way that the C10-OTMS moiety had been brought into close proximity of the *exo*-methylene and could no longer freely rotate. Thus, exposure of **29** to *N*-iodosuccinimide (NIS) led to smooth cyclization with concomitant silyl ether deprotection, forming the *trans*-tetrahydrofuran of the dioxatricyclic substructure in **30**. The latter product was subjected to hydrogenolysis using palladium on carbon which induced simultaneous dehalogenation of the primary iodide and cleavage of the benzyl ether, furnishing (+)-dictyoxetane (**1**) whose spectroscopic data (^{1}H and ^{13}C NMR, HRMS, IR, $[\alpha]_D$) were in full agreement with those reported for the naturally occurring substance. Moreover, the positive $[\alpha]_D$ value of our synthetic sample established the absolute configuration of the natural product to be as depicted.

In summary, we have developed the first total synthesis of (+)-dictyoxetane (**1**) that contains a unique and synthetically challenging 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system. A crucial modification of the proposed biosynthesis, specifically the use of sequential 4-*exo*-tet and 5-*exo*-trig cyclizations to form the respective oxetane and *trans*-tetrahydrofuran rings, enabled the construction of the complex dioxatricyclic framework. Moreover, we have discovered that epoxide−oxetanes are viable substrates for strain-releasing dyotropic rearrangements. Biological studies of **1** and tetra-*epi*-**1** are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03720.

Experimental details and spectroscopic data (PDF)
X-ray crystallographic data for tetra-*epi*-**1** and **21** (CIF)

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Notes

The authors declare no competing financial interest.

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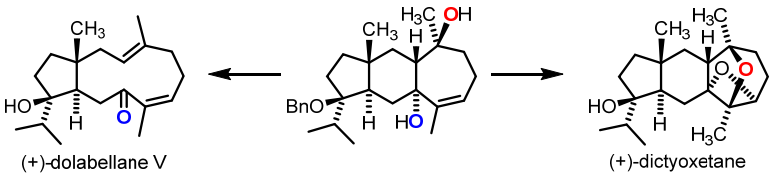
(19) This result further supported our previous assumption that tetrahydrofuran ring formation between C10 and C14 is not directly possible.

(20) Cleavage of the benzyl ether after ring contraction facilitated purification.

3.2.2 A Divergent Approach to the Marine Diterpenoids (+)-Dictyoxetane and (+)-Dolabellane V



Natural Product Synthesis

A Divergent Approach to the Marine Diterpenoids (+)-Dictyoxetane and (+)-Dolabellane V

Cedric L. Hugelshofer and Thomas Magauer*[a]

Abstract: We present a full account of the development of a strategy that culminated in the first total syntheses of the unique oxetane-containing natural product (+)-dictyoxetane and the macrocyclic diterpene (+)-dolabellane V. Our retrosynthetic planning was guided by both classical and nonconventional strategies to construct the oxetane, which is embedded in an unprecedented 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system. Highlights of the successful approach include highly diastereoselective carbonyl addition reactions to assemble the full carbon skeleton, a Grob fragmentation to construct the 11-membered macrocycle of (+)-dolabellane V, and a bioinspired 4-*exo*-tet, 5-*exo*-trig cyclization sequence to form the complex dioxatricyclic framework of (+)-dictyoxetane. Furthermore, an unprecedented strain-releasing type I dyotropic rearrangement of an epoxide-oxetane substrate was developed.

Introduction

Terpenoids constitute the largest class of natural products and many members display unique physical and biological activities, including anticancer, antifeedant, antiviral and antibiotic action.[1] Among these small molecules, only relatively few feature an oxetane structural subunit,[2] as illustrated by the marine oxocene laureatin (**1**) (Figure 1).[3] Taxol (**2**) serves as the archetypal oxetane-containing natural product, which was approved as a novel anticancer agent in 1992 and has spurred medicinal chemists to focus on the unusual four-membered heterocycle.[4] Since then, oxetanes have emerged as potentially attractive structural motifs in drug discovery based on their isosteric relationship with *gem*-dimethyl groups and their outstanding capability to function as hydrogen-bond acceptors.[5] In 1985, chemists isolated a novel natural product, (+)-dictyoxetane (**3**), from a sample of the brown alga *Dictyota dichotoma* collected from the Indian Ocean.[6] Structure elucidation based on X-ray crystallography revealed that this compound features an oxetane embedded in an intricate 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system. From a structural perspective, **3** combines an oxetane motif with a *trans*-hydrindane moiety that is found in various sesterterpenoids,[7] such as leucosceptroid B (**4**)[8] and retigeranic acid A (**5**).[9] A *trans*-fused cyclopentane scaffold is also common in numerous related dolabellanes,[10] as exemplified by (+)-dolabellane V (**6**).[11] Given the lack of biological studies and the challenges of constructing both the unique dioxatricyclic subunit and *trans*-hydrindane moiety of (+)-dictyoxetane (**3**), several attempts were made to prepare the natural product by chemical synthesis. Considerable efforts led to the syntheses of a *trans*-hydrindane framework[12] and simplified model systems of the dioxatricyclic substructure.[13] Based on a crucial modification of the proposed biosynthesis,[14] we recently reported the first total synthesis of (+)-dictyoxetane (**3**).[15] Herein, we disclose a full account of this work and describe the first total synthesis of the natural product (+)-dolabellane V (**6**). Our synthetic journey led us through several unsuccessful approaches to construct the highly substituted oxetane, but ultimately revealed a wealth of interesting reactivity of putative biogenetic precursors of the dioxatricyclic substructure.

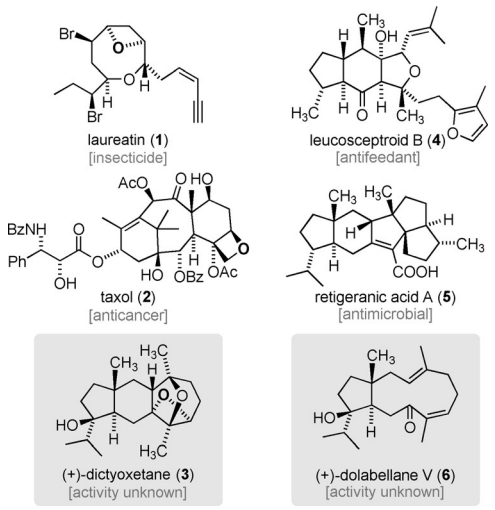


Figure 1. Representative oxetane and *trans*-fused natural products.

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Supporting information for this article, including experimental, computational, and crystallographic details, as well as compound characterization data and copies of ^{1}H and ^{13}C NMR spectra, is available on the WWW under http://dx.doi.org/10.1002/chem.201603061.

56

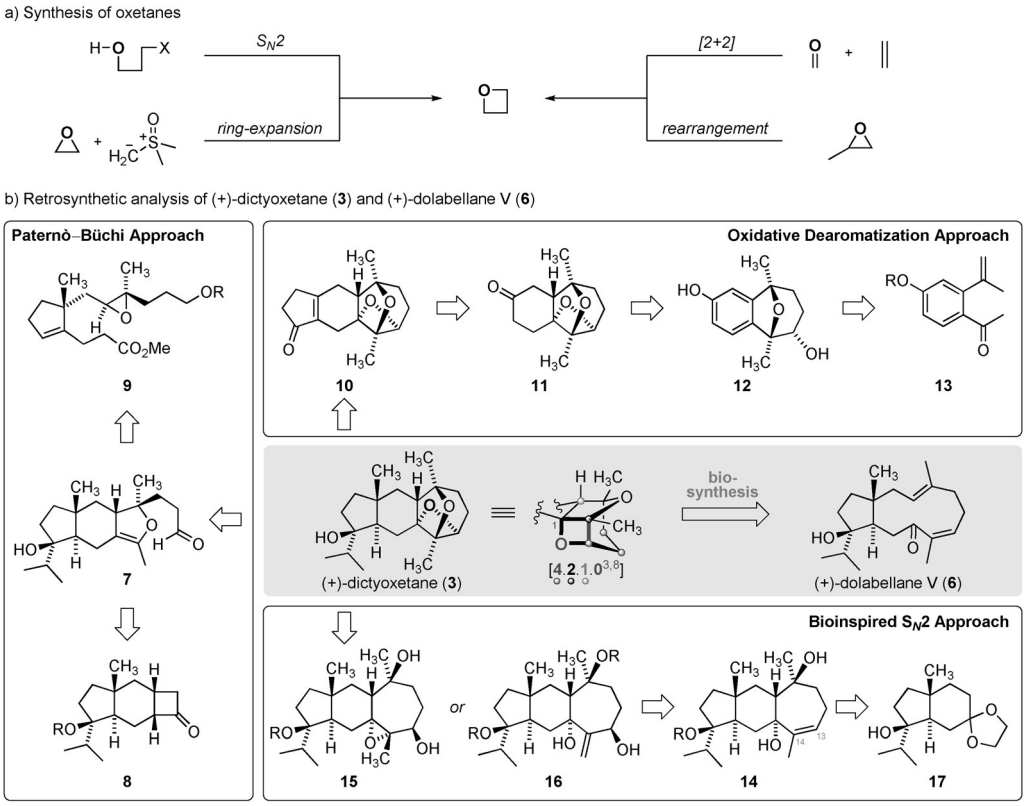
Results and Discussion

Retrosynthetic analysis

Unlike for epoxides or tetrahydrofurans,[16] there is a paucity of synthetic methods to construct oxetanes. As outlined in Scheme 1 a, four general strategies are commonly employed for their synthesis. The intramolecular Williamson etherification (S_N2 displacement)[17] and the [2+2] cycloaddition of a carbonyl and olefin (the Paternò–Büchi reaction)[18] constitute classic synthetic routes towards the four-membered heterocycle. Moreover, oxetanes have been efficiently prepared by ring-expansion of epoxides using sulfoxonium ylides[19] or Wagner–Meerwein type rearrangements of substituted epoxides.[20] Our retrosynthetic analysis of (+)-dictyoxetane (**3**) was primarily guided by taking into consideration the synthetic challenge of constructing the highly substituted oxetane that is part of the 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane ring system. Accordingly, our synthetic plans can be divided into three conceptually different approaches based on the method used to form the oxetane (Scheme 1 b). In an initial synthetic route, we envisioned a late-stage Paternò–Büchi reaction of aldehyde **7** to form the dioxatricyclic ring system of **3**. While the [2+2] photocycloaddition of an alkene and a carbonyl compound constitutes a powerful method for constructing oxetanes, this strategy has enjoyed relatively scarce application in natural product synthesis[21] and certainly would pose a challenging transformation in such a complex molecular setting. Aldehyde **7** was traced back to cyclobutanone **8** or epoxide **9** by a reaction sequence that involves a Baeyer–Villiger oxidation[22] and an ester enolate–epoxide opening reaction, respectively. Given the high risk associated with the endgame of this approach, we also decided to study the Paternò–Büchi reaction on a simplified model system in parallel to our synthetic efforts towards aldehyde **7**.

From an alternative retrosynthetic perspective, we considered installing the *trans*-hydrindane moiety at a final stage and first focus on the challenge of constructing the dioxatricyclic subunit. In this approach, (+)-dictyoxetane (**3**) was traced back to enone **10**; the latter could be obtained through elaboration of the key intermediate, dioxatricycle **11**. We envisaged an intramolecular oxidative dearomatization of phenol **12** as a novel method to forge the oxetane of **11**.[23]

Finally, we were also interested in pursuing a synthetic approach, which is inspired by Hoffmann's biosynthetic proposal.[14] Based on this, (+)-dolabellane V (**6**) is the biogenetic precursor of (+)-dictyoxetane (**3**) by means of a transannular cyclization to forge the 5–6–7 ring system **14**. Stereoselective epoxidation of the C13/C14 olefin in the latter compound, followed by 3-*exo*-tet cyclization would then give epoxide **15** as the key biosynthetic intermediate. For the formation of the dioxatricyclic substructure of **3**, consecutive 5-*exo*-tet and 4-*exo*-tet cyclizations of **15** were proposed. While contemplating the molecular model of **15**, we realized that promotion of the suggested 5-*exo*-tet cyclization might be exceptionally challenging, because this would produce a highly strained *trans*-tetrahydrofuran ring. Therefore, we imagined constructing the oxetane prior

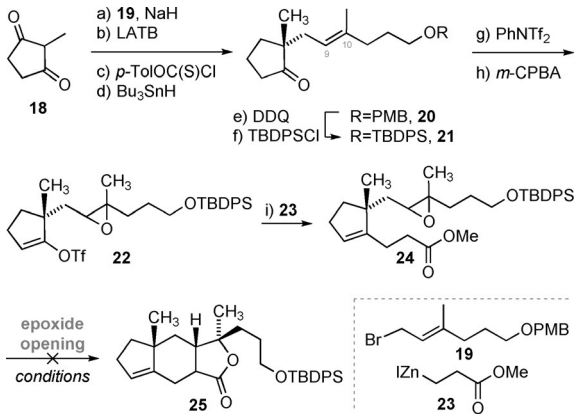


Scheme 1. a) Conventional methods for the construction of oxetanes and b) synthetic planning for (+)-dictyoxetane (**3**) and (+)-dolabellane V (**6**). R = protecting group or H.

to the *trans*-tetrahydrofuran, thus avoiding such a strained intermediate. For this purpose, we identified allylic alcohol **16** as a valuable alternative precursor en route to (+)-dictyoxetane (**3**). To investigate the biosynthetic proposal and our modification thereof, (+)-dictyoxetane (**3**) was traced back to protected forms of epoxide **15** and allylic alcohol **16**, both of which could be obtained through elaboration of tricycle **14**. The latter compound was also considered as an advantageous intermediate, because (+)-dolabellane (**6**) could be derived therefrom through Grob fragmentation.[24] Preparation of the macrocycle through fragmentation of the 5–6–7 ring system thus constitutes the reverse of the biosynthetic pathway, in which transannular cyclization of **6** is suggested to form **14**. We envisioned that tricycle **14** could be constructed from Grainger's *trans*-hydrindane **17**[12] by orchestrating a series of diastereoselective reactions and employing ring-closing metathesis to form the seven-membered carbocycle.

Paternò–Büchi approach

Following the retrosynthetic analysis, we began our synthetic endeavor with the preparation of ester **24** as the precursor for the enolate-epoxide opening reaction (Scheme 2).[25] To this end, the sodium enolate derived from cyclopentanedione **18** was treated with bromide **19**, itself prepared from geraniol on a multigram scale (see the Supporting Information), furnishing the desired diketone in moderate yield (60%) due to competing O-alkylation. Subsequent lithium tri-*tert*-butoxyaluminium hydride mediated reduction and Barton–McCombie deoxygenation[26] of the corresponding alcohol gave ketone **20**.[27]

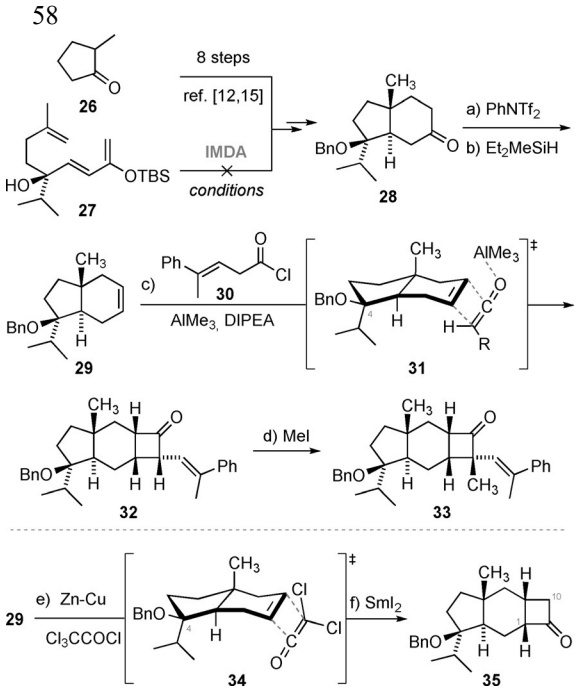


Scheme 2. Synthesis of ester **24** and attempted epoxide opening to prepare lactone **25**. Reagents and conditions: a) **19**, NaH, DMF, 0 to 23 °C, 60%; b) LATB, THF, −60 °C; c) *p*-tolylchlorothionoformate, pyridine, DMAP, CH_2Cl_2, 23 °C; d) Bu_3SnH, AIBN, toluene, 111 °C; e) DDQ, CH_2Cl_2, aq. pH 7 buffer, 0 °C; f) TBDPSCl, imidazole, CH_2Cl_2, 23 °C, 52% over five steps; g) $PhNTf_2$, LDA, THF, −78 to 23 °C, 60%; h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 65%, d.r. = 1:1; i) **23**, SPhos, SPhos Pd G2, THF, DMA, 55 °C, 41%. AIBN = azobisisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyano-*para*-benzoquinone, DMA = *N*,*N*-dimethylacetamide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, LATB = lithium tri-*tert*-butoxyaluminium hydride, LDA = lithium diisopropylamide, *m*-CPBA = *meta*-chloroperoxybenzoic acid, PMB = *p*-methoxybenzyl, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, TBDPS = *tert*-butyldiphenylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Having prepared **20**, we found the *p*-methoxybenzyl ether protecting group to be unstable after the subsequent epoxidation reaction of the C9/C10 double bond due to competing intramolecular epoxide opening. Therefore, **20** was converted into silyl ether **21**, which was then subjected to vinyl triflate formation and subsequent regioselective epoxidation, affording epoxide **22** as a mixture (1:1) of diastereomers.[28] Next, attachment of the ester moiety by homoenolate coupling was achieved by Negishi coupling[29] of **22** with the organozinc species **23**.[30] It is noteworthy that, whereas the use of *N*,*N*-dimethylacetamide as a co-solvent proved crucial to achieve full conversion of the starting material, SPhos Pd G2[31] was required to suppress β-hydride elimination and reduction of the vinyl triflate to the olefin. With **24** in hand, the intramolecular ester enolate-epoxide opening reaction to form lactone **25** was investigated. Unfortunately, treating ester **24** with a variety of lithium or potassium amide bases (LHMDS; KHMDS; LDA), or alkali metal hydrides (NaH; KH) did not lead to opening of the trisubstituted oxirane. Whereas under most investigated conditions the ester enolate simply failed to react, formation of traces of the self-condensation product (intermolecular Claisen reaction) could be observed after prolonged reaction times. We also attempted to increase the reactivity of the epoxide, but found no improvement by employing various weak Lewis acids (TMSCl; $Ti(O\textit{i}\text{-}Pr)_4$; Et_2AlCl), and encountered halohydrin formation when stronger activators ($AlCl_3$; $TiCl_4$) were employed.

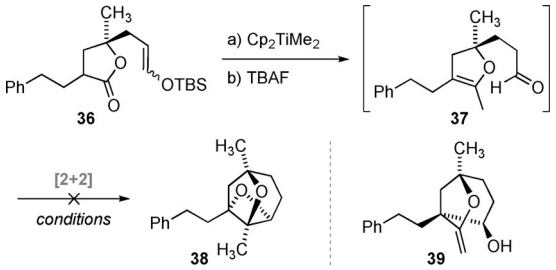
Failure of ester **24** to undergo the envisioned intramolecular epoxide opening required us to develop an alternative strategy for constructing the 5–6–5 tricyclic core of the photocycloaddition precursor **7**. Hence, we were attracted to the possibility of elaborating a *trans*-hydrindane building block through ketene [2+2] cycloaddition to first give a 5–6–4 ring system that could be ring-expanded to the 5–6–5 framework.[33] As outlined in Scheme 3, the synthesis started from ketone **28**,[15] which was first reported in its unprotected form by Grainger and co-workers using an elegant phosphorane-mediated, pinacol-like rearrangement to construct the *trans*-fused hydrindane.[12] While this route proved highly efficient and enabled us to readily prepare multigram quantities (>6 g) of the key building block **28**, we also wanted to determine whether an intramolecular Diels–Alder reaction (IMDA) of triene **27** could be a viable alternative to establish the *trans*-ring junction of **28**.[32] However, exploration of the IMDA of **27** (see the Supporting Information for preparation of this compound) proved unfruitful, and the [4+2] cycloaddition could not be induced under either thermal or high-pressure (14 kbar) conditions.[34]

Ketone **28** was converted into the corresponding vinyl triflate, which was subjected to Pd-catalyzed reduction using a low-boiling silane to afford olefin **29** in 75% yield. This reaction sequence proved far more efficient than sodium borohydride mediated reduction of **28**, followed by elimination of the secondary alcohol, which gave olefin **29** in unsatisfactory yield (15–30%). With ample quantities of **29** in hand, we then investigated the ketene-alkene [2+2] cycloaddition.[33] Given that initial attempts to fuse **29** with various dialkyl ketenes were met with failure, we became interested by Brown's Lewis acid pro-



Scheme 3. Synthesis of olefin **29** and investigation of the ketene [2+2] cycloaddition. Reagents and conditions: a) $PhNTf_2$, KHMDS, THF, −78 °C; b) Et_2MeSiH, $PdCl_2$(dppf), DMF, 60 °C, 75% over two steps; c) **30**, DIPEA, $AlMe_3$, CH_2Cl_2, −65 to −45 °C, 19% **32**, 72% recovered **29**; d) MeI, KO*t*-Bu, THF, *t*-BuOH, −60 to 0 °C, 38%; e) Zn-Cu couple, trichloroacetyl chloride, Et_2O, 23 °C, 48%; f) SmI_2, THF, MeOH, 23 °C, 87%. Bn = benzyl, DIPEA = *N*,*N*-diisopropylethylamine, dppf = 1,1′-bis(diphenylphosphino)ferrocene, KHMDS = potassium bis(trimethylsilyl)amide.

moted ketene-alkene cycloaddition protocol.[35] Moreover, we resorted to acid chloride **30** as the reaction partner because generation of the corresponding ketene is known to be facile,[36] although multiple transformations would be required to then convert the styrene moiety into the desired alkyl side chain. Despite extensive optimization attempts (temperature, concentration, stochiometries, addition rate of **30**) conversion generally remained low, in the best case affording cyclobutanone **32** in 19% yield together with more than 70% of recovered olefin **29**. To make matters worse, we determined that the [2+2] cycloaddition had furnished the undesired cyclobutanone regioisomer, after α-methylation of **32** to give **33**. The outcome of this reaction was unexpected because the [2+2] cycloaddition of dichloroketene with **29** afforded the regioisomeric product **35**. We believe that in transition state **31**, coordination of trimethylaluminium to the ketene might lead to such an orientation that steric clash of the Lewis acid with the C4 isopropyl group is avoided, thus generating cyclobutanone **32** as the preferred regioisomer. For the formation of **35**, we reasoned that, according to transition state **34**, alignment of the dichloroketene to afford the opposite regioisomer is exclusively governed by the chlorine substituents. Considering that a rather lengthy sequence, involving several protecting group manipulations,[37] would be required for functionalization of **35**, we decided to first investigate the Paternò–Büchi reaction on a model system (Scheme 4).

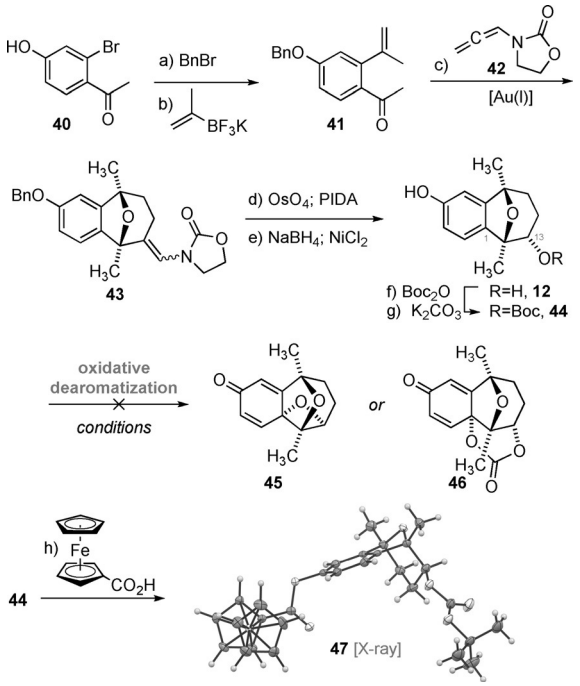


Scheme 4. Synthesis of model aldehyde **37** and attempted Paternò–Büchi reaction. Reagents and conditions: a) Cp_2TiMe_2, toluene, 75 °C, 84%; b) TBAF, THF, −78 °C. TBAF = tetrabutylammonium fluoride.

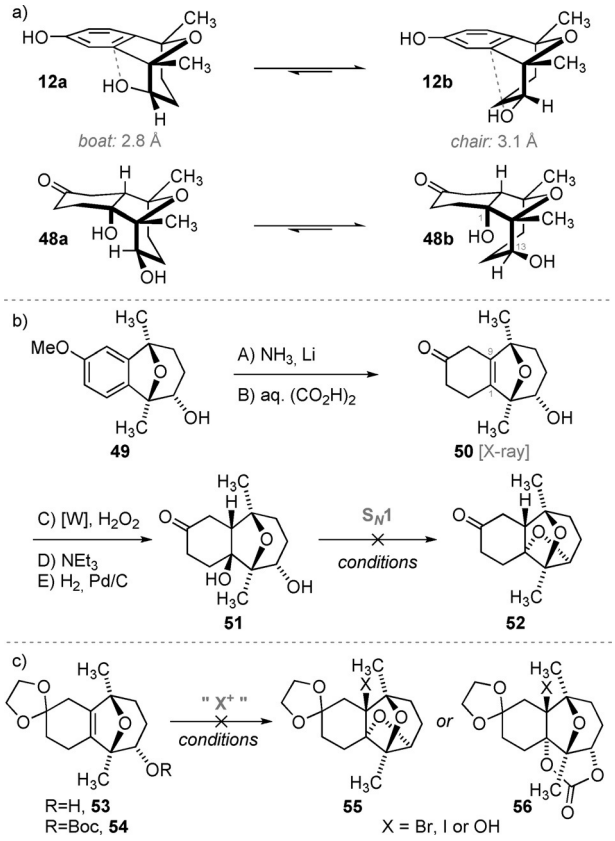
Towards this end, exposure of lactone **36** (see the Supporting Information) to dimethyltitanocene[38] afforded an endocyclic enol ether after prolonged heating, and treatment of the latter intermediate with tetrabutylammonium fluoride unmasked the aldehyde functionality of **37**. Compound **37** proved to be highly unstable under both acidic and basic conditions and readily converted into alcohol **39**, presumably through an intramolecular carbonyl ene reaction.[39] Nevertheless, after a quick aqueous workup of the silyl ether cleavage reaction, **37** was subjected to irradiation with light (254 nm; 300 nm; 250–600 nm) in a variety of solvents (CH_3CN; benzene; acetone). Unfortunately, the desired model dioxatricycle **38** was never observed and instead either complete decomposition of the starting material or formation of alcohol **39** occurred. In light of the fact that preparation of the Paternò–Büchi reaction precursor would involve a long reaction sequence, and based on the results from our model system, which raised great concern that the final [2+2] photocycloaddition would be problematic, we decided to abandon this approach.

Oxidative dearomatization approach

At this juncture, we sought to construct the dioxatricyclic subunit of (+)-dictyoxetane (**3**) at an early stage by intramolecular oxidative dearomatization of phenol **12** as a largely unexplored strategy to form an oxetane (Scheme 5). To this end, bromide **40** was converted into the corresponding benzyl ether and coupled with potassium isopropenyltrifluoroborate to cleanly afford styrene **41**.[40] Next, a gold(I)-catalyzed cascade cycloaddition[41] of **41** with allenamide **42** gave oxa-bridged enamide **43** in 53% yield, together with 45% recovered styrene **41**. Reaction optimization revealed that slow addition of excess allenamide **42** to a solution of **41** and the gold(I) catalyst improved the yield. Nevertheless, incomplete conversion of **41** prevailed under these conditions because of rapid dimerization of the allenamide. The enamine was then oxidatively cleaved[42] and reduction of the resulting ketone together with removal of the benzyl ether could conveniently be achieved in a single transformation by using a combination of sodium borohydride and nickel(II) chloride,[43] furnishing phenol **12** in excellent yield over both steps. With key intermediate **12** in hand, we then explored the intramolecular oxidative dearomatization.[44] Extensive screening using a variety of oxidants (PIDA; PIFA; $^1O_2$;



Scheme 5. Synthesis of phenol **12** and attempted oxidative dearomatization. Reagents and conditions: a) BnBr, K_2CO_3, NaI, CH_3CN, 45 °C, 72% b) potassium isopropenyltrifluoroborate, $Pd(dppf)Cl_2$, NEt_3, *n*-PrOH, 100 °C, 85%; c) **42**, gold(I) catalyst (2 mol%), 4 Å MS, CH_2Cl_2, −15 °C, 53% **43**, 45% recovered **41**; d) OsO_4, NMO, 2,6-lutidine, acetone, H_2O, 23 °C, then PIDA, 23 °C, ≥99%; e) $NaBH_4$, MeOH, −78 °C, then $NiCl_2{\cdot}6H_2O$, 0 °C, ≥99%, d.r. = 10:1; f) Boc_2O, NEt_3, DMAP, CH_2Cl_2, 23 °C; g) K_2CO_3, MeOH, 23 °C, 84% over two steps; h) ferrocenecarboxylic acid, NEt_3, DMAP, EDC, CH_2Cl_2, 23 °C, ≥99%. Boc = *tert*-butyloxycarbonyl, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, NMO = 4-methylmorpholine *N*-oxide, PIDA = phenyliodonium diacetate.



Scheme 6. A) Ring conformations of **12** (interatom distances of DFT-optimized structures) and **48**; B) and C) attempted synthesis of dioxatricycle **52**, **55**, and **56**. Reagents and conditions: a) Li, NH_3, THF, EtOH, −78 to −40 °C; b) oxalic acid, MeOH, H_2O, 23 °C, 86% over two steps; c) $K_2[\{W(=O)(O_2)_2(H_2O)\}_2(\mu\text{-}O)]{\cdot}2H_2O$ (20 mol%), H_2O_2, H_2O, 23 °C; d) NEt_3, MeOH, 45 °C; e) H_2, Pd/C, MeOH, 23 °C, 73% over three steps.

oxone; CAN), base additives and solvents (CH_3CN; H_2O; TFE; CH_3NO_2; CH_2Cl_2; *i*-PrOH) unfortunately only led to decomposition of the starting material and the desired oxetane-dienone **45** was never observed. Reasoning that dearomatization at the C1 position might become feasible by incorporating an extended *O*-nucleophile, phenol **12** was converted into carbonate **44**. Disappointingly, the attempted intramolecular oxidative dearomatization of **44** to form cyclic carbonate **46** could also not be promoted and decomposition again prevailed under the conditions investigated.

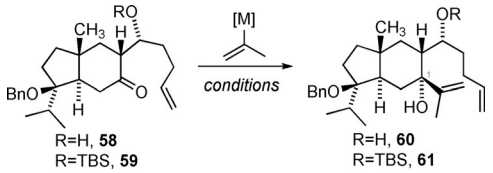
To obtain crystals suitable for X-ray analysis and to gain more insight into the conformation of the dearomatization precursor, carbonate **44** was converted into ferrocenecarboxylate ester **47**, according to Burns' recently reported protocol.[45] Analysis of this X-ray structure revealed that the tetrahydropyran substructure of **47** adopts a chair-like conformation which places the C13-O substituent in an equatorial position and distal from C1. For the intramolecular dearomatization to take place, the tetrahydropyran would first have to undergo an energetically unfavorable change to a boat conformation in which C13-O would be brought in proximity to C1.

Although it was discouraging to recognize that the inherent preference of the phenol to adopt conformer **12b** rendered the intramolecular oxidative dearomatization unfeasible (Scheme 6A), we realized that the chair conformation of diol **48b** could be a valuable alternative for ring-closure. In the latter case, C1-OH would be well suited to form the desired oxetane by intramolecular S_N2 displacement of a C13 leaving group. With this idea in mind, and based on an analogous reaction sequence as above, we prepared anisole **49** (see the Supporting Information for details). As outlined in Scheme 6B, **49** was subjected to Birch reduction[46] and the resulting enol ether was hydrolyzed by using aqueous oxalic acid,[47] cleanly affording ketone **50** in 86% yield over two steps, the structure of which was unambiguously confirmed by single-crystal X-ray analysis. Next, we envisioned a homoallylic alcohol-directed epoxidation[16,48] to install the C1 hydroxyl group with the desired α-configuration. Whereas vanadium-catalyzed epoxidation or treatment of **50** with *meta*-chloroperbenzoic acid led to complex product mixtures, the use of a dinuclear peroxotungstate catalyst[49] furnished one major epoxide. Following opening of this unstable epoxide with triethylamine and hydrogenation of the resulting enone, NOESY NMR experiments indicated that epoxidation occurred from the undesired β-face to give diol **51** as the final product. Not surprisingly, subsequent conversion of **51** into dioxatricycle **52** through an attempted S_N1 reaction failed using a variety of Brønsted or Lewis acids (*p*-TsOH; TFA; TFAA; $Yb(OTf)_3$; $ZnBr_2$; $Cu(BF_4)_2$; $BF_3{\cdot}OEt_2$), pre-

sumably due to a similar conformational restriction as we had encountered in the attempted intramolecular dearomatization. Given that α-face epoxidation of the sterically hindered C1/C9 olefin had failed using alcohol-directed methods, we envisioned installing the desired epoxide via a halohydrin intermediate. To this end, treatment of the enol ether resulting from Birch reduction of **49** with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid gave acetal **53**, which could be converted into carbonate **54** (Scheme 6C). Unfortunately, halohydrin formation in **53** or **54**, as well as all direct haloetherification attempts, met with failure. Finally, exposure of **53** or **54** to *meta*-chloroperbenzoic acid cleanly gave the corresponding tetrasubstituted β-epoxides. However, intramolecular opening of this moiety with the C13-O nucleophile to form **55** or **56** could likewise not be achieved.

In view of the lack of success in elaborating our oxa-bridged 6–7 ring systems, we decided to discontinue this synthetic approach. We realized that early-stage introduction of an α-configured alcohol at C1, prior to formation of the right-hand 6–7 framework of (+)-dictyoxetane (**3**), might prove more rewarding and alleviate problems in constructing this fully substituted carbon center.

Table 1. Selected conditions for isopropenyl addition to **58** and **59**.[a]

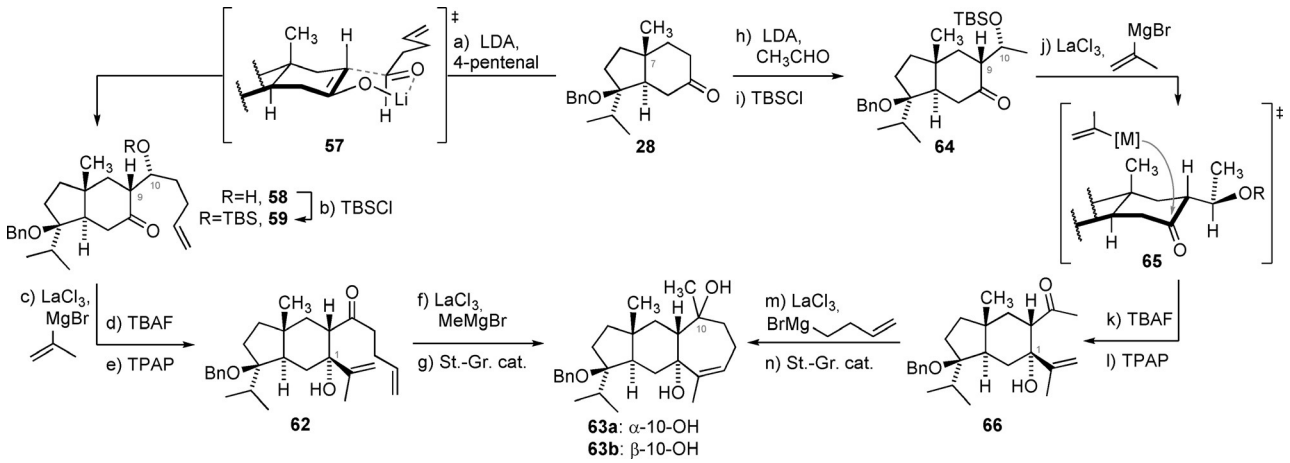


Entry	Ketone	[M]	*T* [°C]	Additive	d.r.[b]
1	**58**	Li	−78	–	n.d.[c]
2	**58**	MgBr	0	–	1:2[c]
3[d]	**58**	MgBr	0	$CeCl_3$	1:2
4	**58**	MgBr	0	$LaCl_3$·2LiCl	1:1
5	**58**	MgBr	−30	$LaCl_3$·2LiCl	3:1
6[e]	**59**	MgBr	0	$LaCl_3$·2LiCl	≥20:1

[a] Unless otherwise stated, all reactions were carried out in THF and by premixing the additive with the ketone for 1 h at 23 °C prior to addition of the organometallic reagent. [b] As determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Incomplete conversion of the starting material. [d] The Grignard reagent was premixed with $CeCl_3$. [e] 91% yield on gram-scale reaction.

Bioinspired S_N2 approach

As outlined in Scheme 7, we began our bioinspired synthetic approach from ketone **28**, which underwent a highly selective aldol reaction with 4-pentenal. Based on the Zimmerman–Traxler transition-state **57**,[50] the aldol product **58** was formed as a single diastereomer at both C9 and C10, and after silyl protection furnished **59** in 72% yield. Initial attempts to add an isopropenyl group to ketone **58** met with limited success, and gave the corresponding tertiary alcohol **60** in both unsatisfactory yields and diastereomeric ratios (Table 1, entries 1–5). Fortunately, employing the silyl protected ketone **59** and premixing it with lanthanum(III) chloride bis(lithium chloride) complex[51] prior to addition of the Grignard reagent, afforded **61** with excellent diastereoselectivity (d.r. ≥ 20:1) and in high yield (entry 6). Following removal of the silyl ether and Ley–Griffith oxidation,[52] ketone **62** was obtained in 88% yield over two steps (Scheme 7). We encountered low conversion of the starting material in the subsequent addition of methylmagnesium bromide to **62**, presumably due to facile enolization of the substrate. In this case, the addition of lanthanum(III) chloride bis(lithium chloride) complex could suppress unwanted enolization with only little success. Although the configuration at the formed C10 stereocenter could not be determined at this stage, the intermediate was subjected to ring-closing metathesis to afford tricycle **63a**. The undesired C1,C10 *cis*-diol rela-



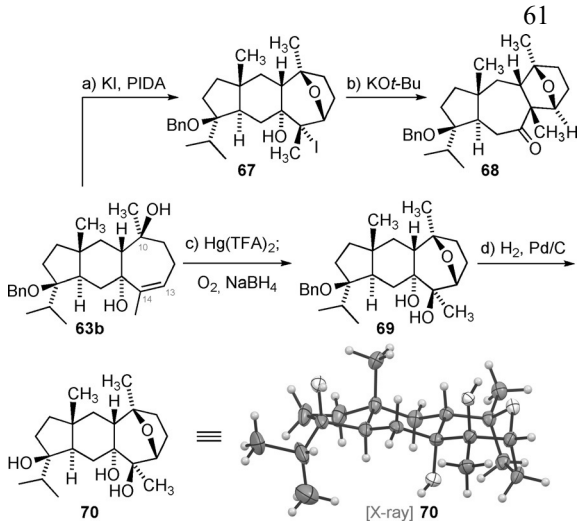
Scheme 7. Selective synthesis of the epimeric 5-6-7 tricycles **63a** and **63b**. Reagents and conditions: a) LDA, 4-pentenal, THF, −78 °C; b) TBSCl, imidazole, DMAP, DMF, 23 °C, 72% over two steps, d.r. ≥ 20:1; c) $LaCl_3$·2LiCl, isopropenylmagnesium bromide, THF, 0 °C, 91%, d.r. ≥ 20:1; d) TBAF, THF, 0 to 23 °C; e) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C, 88% over two steps; f) $LaCl_3$·2LiCl, MeMgBr, THF, 0 °C, 35%, 60% recovered **62**; g) Stewart–Grubbs cat. (20 mol%), 2,6-dichloro-1,4-benzoquinone, toluene, 111 °C, 86% **63a**; h) LDA, CH_3CHO, THF, −78 °C; i) TBSCl, imidazole, DMAP, DMF, 23 °C, 80% over two steps, d.r. = 10:1 at C10; j) $LaCl_3$·2LiCl, isopropenylmagnesium bromide, THF, 0 °C, 93%, d.r. ≥ 20:1 at C1; k) TBAF, THF, 0 to 23 °C; l) TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C, 87% over two steps; m) $LaCl_3$·2LiCl, 3-butenylmagnesium bromide, THF, 0 °C, 69%, 27% recovered **66**; n) Stewart–Grubbs cat. (25 mol%), 2,6-dichloro-1,4-benzoquinone, toluene, 111 °C, 55% **63b**, 25% recovered diene. TBS = *tert*-butyldimethylsilyl, TPAP = tetrapropylammonium perruthenate.

tionship of the latter product was confirmed by formation of a cyclic carbonate (see the Supporting Information for details). In an attempt to generate the desired β-C10-OH stereocenter, as depicted for tricycle **63b**, we inverted the order of the last two reactions. However, first subjecting **62** to ring-closing metathesis, followed by addition of various methyl organometallic reagents to the resulting tricyclic ketone, again resulted in formation of undesired tricycle **63a**.[53] Eventually, we recognized that the desired C10 stereochemistry of tricycle **63b** could presumably be obtained in a modified sequence that simply involves switching the two alkyl substituents that are sequentially introduced by means of the aldol reaction and the second Grignard addition.

On these grounds, the aldol reaction of ketone **28** with acetaldehyde, followed by protection of the resulting secondary alcohol as the *tert*-butyldimethylsilyl ether, efficiently afforded **64** as a single diastereomer at C9 and as an inconsequential 10:1 mixture at C10. Exposure of **64** to isopropenylmagnesium bromide in the presence of lanthanum(III) chloride bis(lithium chloride) complex again furnished the product as a single diastereomer at C1. The diastereoselectivity of this reaction arises from approach of the organometallic species from the sterically less-hindered face, as shown in transition state **65**.[54] Conversion into ketone **66** was then achieved in an analogous fashion as before. For the introduction of the butenyl chain, premixing **66** with the lanthanide salt prior to addition of 3-butenylmagnesium bromide proved to be highly beneficial and, in this case, increased the conversion beyond 70%. Pleasingly, ring-closing metathesis of the resulting diene gave tricycle **63b**, which possesses the desired relative stereochemistry at C10.

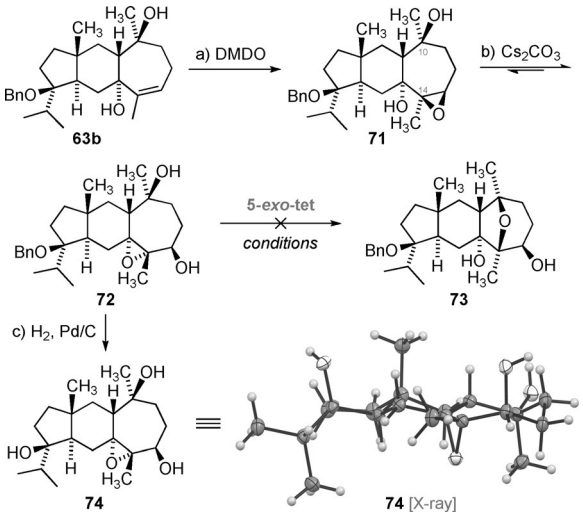
The final metathesis reaction for the formation of the seven-membered ring containing a trisubstituted olefin adjacent to a fully substituted carbon center required careful optimization of the reaction parameters. Whereas first-generation ring-closing metathesis catalysts[55] failed to afford any tricyclic products, initial studies using second-generation Hoveyda–Grubbs[56] or nitro-Grela catalyst[57] gave mixtures of 5–6–7 and undesired 5–6–6 tricycles. Eventually, it was discovered that using the less hindered Stewart–Grubbs catalyst (25 mol%),[58] 2,6-dichloro-1,4-benzoquinone (25 mol%) to avoid olefin isomerization,[59] high dilution (1 mM) and conducting the reaction at elevated temperature (111 °C) gave the best results. It is interesting to note that, under these reaction conditions, the ring-closing metathesis to give **63b** was still incomplete after 40 h (55% yield), whereas the analogous reaction that afforded tricycle **63a** reached full conversion in less than 3 h (86% yield).

Having gained access to tricycle **63b**, which features the full carbon skeleton of (+)-dictyoxetane (**3**) and constitutes a benzyl protected intermediate in the proposed biosynthesis,[14] we began to investigate cyclizations to construct the dioxatricyclic subunit (Scheme 8). Initially, we envisioned that direct halo-etherification would serve to construct the tetrahydrofuran ring between C10 and C14. However, in practice, exposure of tricycle **63b** to active halogen sources (NBS; NIS; KI, PIDA) exclusively gave regioisomer **67** as a result of opening of the intermediate halonium ion at the less hindered C13 position. Whereas iodide **67** was useless for our purpose, we discovered that treatment with potassium *tert*-butoxide led to a very clean semi-pinacol rearrangement[60] and gave **68** in 90% yield. The 5–7–6 carbon framework of the latter product has been found in various dolastane natural products.[61] We also investigated oxymercuration of **63b**,[62] but found the regioselectivity of the etherification to be equally undesired, furnishing diol **69** after oxidative demercuration. Hydrogenolysis of the benzyl ether gave triol **70**, the structure of which was unambiguously confirmed by single-crystal X-ray analysis.



Scheme 8. Cyclizations of tricycle **63b**. Reagents and conditions: a) KI, PIDA, CH_2Cl_2, 0 to 23 °C, 92%; b) KO*t*-Bu, THF, *t*-BuOH, 23 °C, 90%; c) $Hg(TFA)_2$, CH_2Cl_2, MeOH, −78 °C, then $NaBH_4$, O_2, DMF, 0 °C; d) H_2, Pd/C, THF, 23 °C, 31% over two steps. TFA = trifluoroacetate.

Failure to directly form the oxygen bridge between C10 and C14 from tricycle **63b** prompted us to pursue a strategy closely mimicking the proposed biosynthetic *exo*-tet cyclization sequence (Scheme 9).[14] To this end, treatment of **63b** with di-

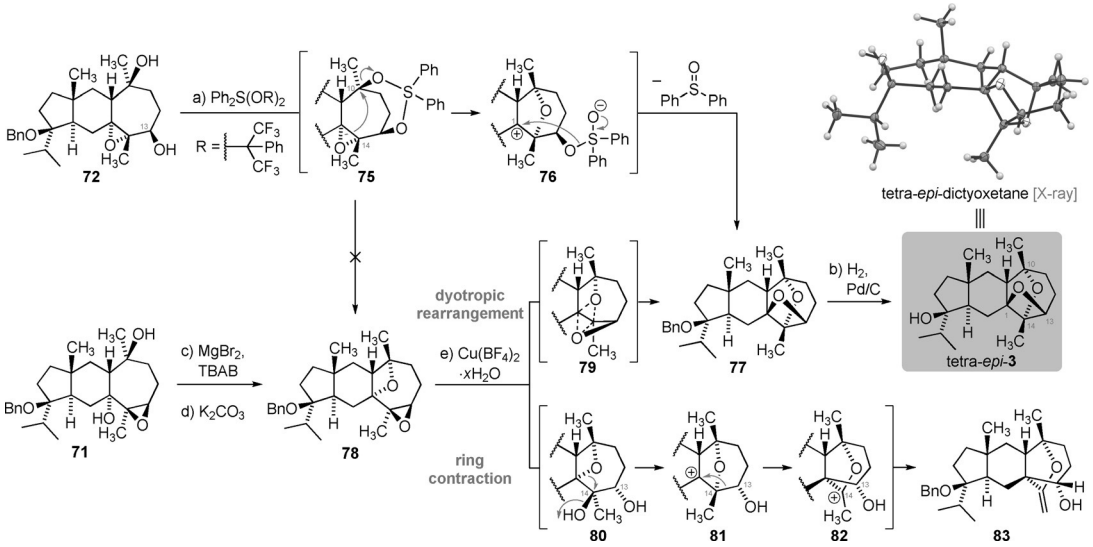


Scheme 9. Investigation of the *exo*-tet cyclization sequence of epoxide **71** according to the proposed biosynthesis. Reagents and conditions: a) DMDO, acetone, CH_2Cl_2, −78 °C, ≥99%, d.r. ≥15:1; b) Cs_2CO_3, MeOH, 60 °C, 59% **72**, 22% recovered **71**; c) H_2, Pd/C, THF, 23 °C, 80%. DMDO = dimethyldioxirane.

methyldioxirane afforded epoxide **71** cleanly and with high selectivity (d.r. $\geq$ 15:1). Attempted tetrahydrofuran formation by activation of the epoxide in **71** with various acids ($BF_3{\cdot}OEt_2$; $Yb(OTf)_3$; $HClO_4$; *p*-TsOH; PPTS; aq. HCl) mostly led to decomposition of the starting material and formation of trace amounts of a product, which we tentatively assigned as an aldehyde resulting from Meinwald ring contraction.[63] Pleasingly, it was discovered that, under basic conditions (Cs_2CO_3; NaOH; LiOH; $LiNEt_2$), **71** underwent the postulated 3-*exo* cyclization, affording a 1:2.5 thermodynamic distribution of **71** and **72**. Encouraged by having realized the first cyclization of the proposed biosynthesis, we next investigated the 5-*exo* cyclization to form *trans*-tetrahydrofuran **73**. Disappointingly, we found this transformation to be unfeasible under a wide range of acidic ($KHSO_4$; $Yb(OTf)_3$; aq. HCl; aq. CH_3CO_2H; $Ti(O\textit{i}\text{-}Pr)_4$; $Sc(OTf)_3$; $MgBr_2{\cdot}OEt_2$), basic (NaH; aq. LiOH) or neutral (CF_3CH_2OH; H_2O; CH_3CN) reaction conditions. Eventually the benzyl ether in epoxide **72** was cleaved and the resulting triol **74** was recrystallized from a mixture of ethyl acetate/hexanes to provide crystals suitable for X-ray analysis. The solid-state structure of **74** confirmed our increasing concerns that the seven-membered ring adopts a chair-like conformation with C10-OH being in an equatorial position. The 5-*exo* cyclization would thus not only produce a highly strained *trans*-tetrahydrofuran ring, but also require an energetically unfavorable conformational change to take place beforehand, making the transformation exceptionally challenging under nonenzymatic conditions.

Finally, we envisioned that elimination of C13-OH would both change the seven-membered ring geometry and provide a more reactive allylic epoxide. Surprisingly, dehydration was not observed upon exposure of epoxide **72** to Martin sulfurane,[64] but rather formation of dioxatricycle **77** took place (Scheme 10). The dioxatricyclic substructure was unambiguously validated by single-crystal X-ray diffraction analysis after conversion into the benzyl deprotected product, 1,10,13,14-tetra-*epi*-dictyoxetane (tetra-*epi*-**3**). We were intrigued by this unexpected rearrangement that formally led to inversion of two sterically encumbered, tertiary oxygen substituents. After contemplating various possible mechanistic pathways and analyzing individual reaction intermediates, we hypothesized that the sequence should be initiated by the formation of cyclic sulfurane **75**. Martin sulfurane dehydration of tertiary alcohols is known to occur through an E_1-like mechanism,[65] thus assisting carbocation formation at C10 and ring-expansion of the epoxide. The latter rearrangement, which forms tetrahydrofuran **76**, is driven by the strain release of the epoxide opening and by generation of a stabilized tertiary carbocation at C1. Finally, expulsion of diphenyl sulfoxide from **76** produces a C13 alkoxide, which cyclizes onto the carbocation and thereby completes the generation of dioxatricycle **77**.

Although this proposed mechanism appeared reasonable in many respects, we were undecided as to whether epoxide-oxetane **78** might also be an intermediate of the unprecedented rearrangement sequence. We initially speculated that, after formation of cyclic sulfurane **75**, the carbocation generated at C10 might be trapped by the epoxide oxygen to form an oxetane and C14 carbocation (instead of tetrahydrofuran **76**). In this latter scenario, diphenyl sulfoxide expulsion and cyclization would then furnish epoxide-oxetane **78**. Aiming at elucidating the possible involvement of **78** as an intermediate during the rearrangement of **72** to dioxatricycle **77**, we made a serendipitous discovery. Exposure of epoxide **71** to excess magnesium bromide ethyl etherate and tetrabutylammonium bromide not only led to the expected bromohydrin formation, but also promoted simultaneous oxetane ring closure between C1 and C10. Treatment of a methanolic solution of this bromohydrin with potassium carbonate then reinstalled the epoxide and afforded epoxide-oxetane **78** in 94% yield. At this juncture, it was discovered that subjecting **78** to the dehydration



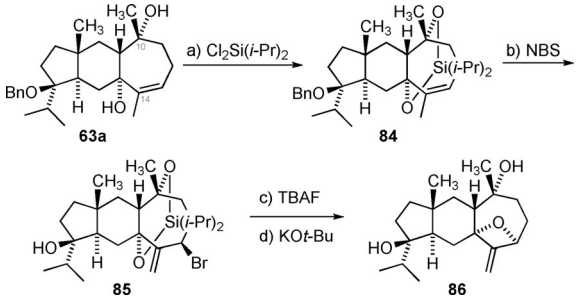
Scheme 10. Synthesis of tetra-*epi*-dictyoxetane (tetra-*epi*-**3**) and investigation of the dyotropic rearrangement of epoxide-oxetane **78**. Reagents and conditions: a) Martin sulfurane, CH_2Cl_2, 0 °C; b) H_2, Pd/C, THF, 23 °C, 60% over two steps from **72**; c) $MgBr_2{\cdot}Et_2O$, TBAB, CH_2Cl_2, 23 °C, 51%; d) K_2CO_3, MeOH, 0 °C, 94%; e) $Cu(BF_4)_2{\cdot}xH_2O$, CH_2Cl_2, 23 °C, 36% **77** and 37% **83**. TBAB = tetrabutylammonium bromide.

conditions with Martin sulfurane left the starting material unchanged. This result led us to exclude a pathway for the formation of dioxatricycle **77** involving the transient formation of **78**, and rather corroborated our mechanistic proposal based on intermediates **75** and **76**.

However, fascinated by the two vicinal and highly strained oxygen heterocycles in **78**, we anticipated that a strain-releasing dyotropic rearrangement could convert epoxide-oxetane **78** into dioxatricycle **77**.[66] Indeed, mild Lewis acid activation of **78** with copper(II) tetrafluoroborate hydrate[67] was found to induce a type I dyotropic rearrangement proceeding through **79** and giving dioxatricycle **77** in 36% yield.

Whereas Mulzer has shown in seminal work that β-lactones efficiently undergo type I dyotropic reactions to afford γ-butyrolactones,[68] the dyotropic rearrangement of an epoxide-oxetane substrate appears to be unprecedented. Moreover, we observed that, under the reaction conditions, epoxide-oxetane **78** was converted into an olefinic byproduct resulting from oxetane elimination (20%, see the Supporting Information) and the ring-contracted enol ether **83** (37% yield). We hypothesized that **83** is formed through initial hydrolysis of the epoxide, affording *anti*-diol **80**. Next, ionization of the C14 tertiary alcohol, followed by a rearrangement, which is driven by the strain release of oxetane opening, leads to tetrahydrofuran **81**. Finally, ring contraction of the latter compound generates the 5–6–6 tricycle **82**, and affords enol ether **83** after elimination.

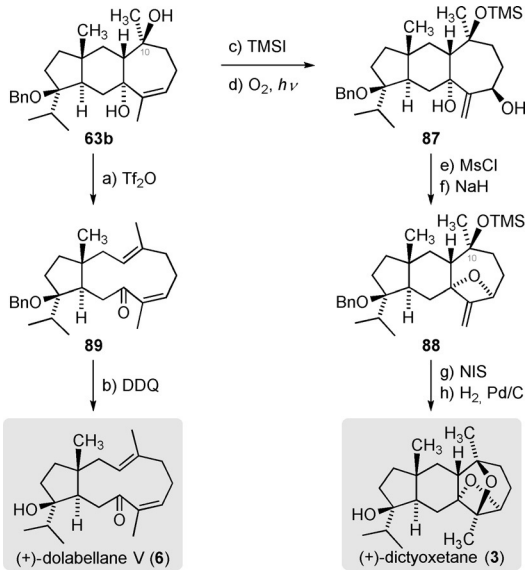
After having failed to induce the putative biomimetic 5-*exo*-tet cyclization of C10-OH onto C14 in epoxide **72**, and based on the fascinating rearrangements we had observed, we returned to our ring-closing metathesis product **63a** with the undesired α-configured C10 alcohol (Scheme 11). We had learnt that ionization of tertiary alcohols occurred readily in our system, and we thus concluded that a reverse cyclization attempt, from C14-OH onto a C10 carbocation, might prove rewarding to fuse the *trans*-tetrahydrofuran ring of (+)-dictyoxetane (**3**). With this idea in mind, we aimed to install a C14 β-configured hydroxyl group in tricycle **63a**. Since dihydroxylation of **63a** was met with failure and epoxidation occurred nonselectively, the 1,3-*cis*-diol was converted into siloxane **84**. During our investigations to form a bromohydrin, we found that exposure of **84** to *N*-bromosuccinimide in wet tetrahydrofuran induced benzyl deprotection and concomitant formation



Scheme 11. Synthesis of oxetane **86** through 4-*exo*-tet cyclization. Reagents and conditions: a) $Cl_2Si(i\text{-}Pr)_2$, imidazole, DMAP, DMF, 23 °C, 97%; b) NBS, THF, H_2O, 23 °C; c) TBAF, THF, 0 to 23 °C; d) KO*t*-Bu, THF, 0 °C, 94% over three steps. NBS = *N*-bromosuccinimide.

of allylic bromide **85**.[69] In a small-scale experiment, we then discovered that treatment of **85** with tetrabutylammonium fluoride led to siloxane deprotection and spontaneous 4-*exo*-tet cyclization, furnishing oxetane **86**. The 4-*exo*-tet cyclization was conveniently brought to completion in larger scale experiments by exposure of the crude silyl deprotected product to potassium *tert*-butoxide. Although we were unable to functionalize the *exo*-cyclic olefin of **86** under various conditions (DMDO; *m*-CPBA; $Hg(OAc)_2$; $Co(acac)_2$, $PhSiH_3$[70]), the ease with which the 4-*exo*-tet cyclization had taken place was deemed an exceedingly valuable discovery.

Having gained much knowledge concerning the structure and unique reactivity of the oxygenated tricycles, we turned to our alternative biosynthetic proposal. By forming the oxetane prior to the strained *trans*-tetrahydrofuran, we expected to succeed in constructing the dioxatricyclic substructure of **3** (Scheme 12). To this end, it was discovered that photo-oxida-



Scheme 12. Sequential 4-*exo*-tet and 5-*exo*-trig cyclizations leading to (+)-dictyoxetane (**3**) and total synthesis of (+)-dolabellane V (**6**). Reagents and conditions: a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; b) DDQ, DCE, aq. pH 7 buffer, 40 °C, 44% over two steps; c) TMSI, CH_2Cl_2, 0 to 23 °C, 92%, d) O_2, *hv*, TPP, DCE, 0 °C, then PPh_3, 23 °C, 71%; e) MsCl, NEt_3, CH_2Cl_2, −78 °C; f) NaH, THF, 66 °C, 88% over two steps; g) NIS, CH_2Cl_2, 23 °C; h) H_2, Pd/C, THF, 23 °C, 80% over two steps. DCE = 1,2-dichloroethane, Ms = methanesulfonyl, NIS = *N*-iodosuccinimide, TMSI = 1-(trimethylsilyl)imidazole, TPP = *meso*-tetraphenylporphyrin.

tion[71] of the silyl ether derived from **63b** afforded allylic alcohol **87** as a single regio- and diastereomer after reduction of the intermediate hydroperoxide using triphenylphosphine. Conversion of **87** into oxetane **88** could not be accomplished under Mitsunobu conditions,[72] and proved unsatisfactory via formation of the secondary tosylate. However, preparation of the allylic mesylate, followed by 4-*exo*-tet cyclization under basic conditions at elevated temperature, cleanly furnished oxetane **88** in an excellent 88% yield over two steps. The ^1H NMR spectrum of **88** revealed severe signal broadening at room temperature, but showed well-resolved resonances upon

heating to 65 °C (see the Supporting Information for details). We concluded that oxetane formation had drastically changed the seven-membered ring conformation and brought the C10-OTMS moiety into close proximity of the *exo*-cyclic olefin, thus impeding its free rotation. As anticipated, this conformational change proved crucial to enable the 5-*exo*-trig cyclization to form the *trans*-tetrahydrofuran. The final ring closure occurred smoothly by using *N*-iodosuccinimide with concomitant trimethylsilyl ether deprotection. Hydrogenolysis of the latter product using palladium on carbon led to simultaneous dehalogenation of the primary iodide and cleavage of the benzyl ether, providing (+)-dictyoxetane (**3**), the analytical data of which were in excellent agreement with those of the natural product.[6, 11]

Moreover, the unexpected reactivity of putative biogenetic precursors of (+)-dictyoxetane (**3**), which had led to displacement of the tertiary C14 alcohol or generated a carbocation at that position, indicated that the envisioned Grob fragmentation to form the 11-membered carbocycle of (+)-dolabellane (**6**) might be a promising endeavor (Scheme 12). Initial attempts to convert the sterically hindered C10-OH of tricycle **63 b** into the corresponding mesylate or tosylate led to complex product mixtures. Gratifyingly, careful experimentation revealed that treating **63 b** with trifluoromethanesulfonic anhydride and 2,6-lutidine at low temperature effectuated the fragmentation in a single step and afforded macrocycle **89**.[73] Finally, cleavage of the benzyl ether under oxidative conditions gave (+)-dolabellane (**6**), the spectroscopic data (^{1}H and ^{13}C NMR, HRMS, IR, $[\alpha]_D$) of which were in full agreement with those reported for the naturally occurring substance.[11] Notably, the fragmentation of tricycle **63 b** also establishes a general entry to many related dolabellane natural products containing a 5–11 bicyclic carbon skeleton.[10, 11, 74]

Conclusion

We have reported the evolution of our strategies aimed at the total syntheses of the marine diterpenes (+)-dictyoxetane (**3**) and (+)-dolabellane V (**6**). Our initial efforts to construct the unique 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane ring system of the former natural product by means of a Paternò–Büchi reaction or intramolecular oxidative dearomatization were unsuccessful. Starting from a readily available *trans*-hydrindane fragment, we finally pursued a bioinspired strategy. For this purpose, we orchestrated a series of substrate-controlled and highly diastereoselective transformations to access the advanced tricyclic core **63 b**. During our attempts to form the dioxatricyclic subunit by mimicking the proposed biosynthetic cyclizations, we gained a crucial understanding of the unique reactivity of the seven-membered ring system and discovered remarkable rearrangements. These studies culminated in the discovery of an unprecedented type I dyotropic reaction of an epoxide-oxetane substrate that gave access to tetra-*epi*-dictyoxetane (tetra-*epi*-**3**). Eventually, a crucial modification of the originally postulated biosynthesis, involving formation of the oxetane prior to the strained *trans*-tetrahydrofuran, enabled construction of the complex dioxatricyclic substructure of (+)-dictyoxetane (**3**). Starting from commercially available 2-methylcyclopentanone (**26**), the asymmetric total syntheses of (+)-dictyoxetane (**3**) and (+)-dolabellane V (**6**) proceeded in 21 (2.6% overall yield) and 17 linear steps (2.5% overall yield), respectively.

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Keywords: oxetane · natural products · rearrangements · terpenoids · total synthesis

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3.3 Conclusion and Outlook

In Part II of this thesis, the first total syntheses of the marine diterpenoids (+)-dictyoxetane and (+)-dolabellane V were accomplished. After unsuccessful attempts to form the 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane ring system of (+)-dictyoxetane via a Paternò−Büchi reaction and a strategy involving intramolecular oxidative dearomatization, we adopted a bioinspired approach. While we were unable to mimic the originally postulated biosynthesis, we devised a crucial modification thereof, which involved formation of the oxetane prior to the strained *trans*-tetrahydrofuran and that eventually enabled us to construct the dioxatricyclic substructure of (+)-dictyoxetane.

The ultimately successful route was designed by keeping in mind the reasons for our failed approaches and by perpetually gaining understanding of the unique reactivity of the oxygenated seven-membered ring system. Moreover, we discovered a host of interesting transformations during our studies, including an unusual sulfur-mediated rearrangement induced by Martin's sulfurane and a strain-releasing dyotropic rearrangement of an epoxide−oxetane substrate.

Biological studies of (+)-dictyoxetane, tetra-*epi*-(−)-dictyoxetane and (+)-dolabellane V are currently underway and will be reported in due course. In future work, we moreover aim to explore dyotropic rearrangements of epoxide−oxetane substrates in a broader context.

EXPERIMENTAL SECTION

4 TABLE OF CONTENTS

5 GENERAL EXPERIMENTAL DETAILS

General Working Methods

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above 23 °C were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass plates precoated with silica gel (0.25 mm, 60-Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or ceric ammonium molybdate solution (CAM), and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by Still et al.,[1] employing silica gel (60 Å, 40–63 µm, *Merck KGaA*). Flash-column chromatography on silica gel using triethylamine pretreated silica gel was performed by preparing the silica gel slurry with triethylamine (10% v/v in corresponding eluent mixture) and flushing the column with the eluent prior to loading the compound on the column. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from Na/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled under nitrogen atmosphere from CaH_2 prior to use. Benzene, dimethylformamide (DMF), dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), toluene and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR) and were used as received. Solvents for extraction, crystallization and flash-column chromatography on silica gel were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride was dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. 4 Å molecular sieves were washed (methanol, acetone, dichloromethane) and then dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the molecular sieves were flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[2] The concentration of freshly prepared dimethyldioxirane solutions[3] was determined by iodometric titration as follows: A 0.02 M aqueous stock solution of sodium thiosulfate pentahydrate (124 mg $Na_2S_2O_3.5H_2O$ in 25 mL H_2O) was prepared in a 25 mL graduated cylinder. A 100 mL flask was charged with water (30 mL), sodium iodide (2.00 g) and glacial acetic acid (1 mL), whereupon the dimethyldioxirane solution (2 mL) was added. The resulting brown mixture was rapidly titrated with the sodium thiosulfate stock solution until disappearance of the yellow iodine colour occurred.

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The concentration of the dimethyldioxirane solution was calculated according to the following equation:

$$c(DMDO) = \frac{M(titrant)\ x\ V(titrant)}{V(DMDO)\ x\ 2}$$

and was generally in the range of 0.04 M to 0.07 M.

NMR spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 800 MHz spectrometer equipped with a CryoProbe™, *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, *Bruker* AXR300, *Varian* VXR400 S and *Bruker* AMX600 spectrometers operating at 800 MHz, 400 MHz, 300 MHz, 400 MHz and 600 MHz for proton nuclei (200 MHz, 100 MHz, 75 MHz, 100 MHz, 150 MHz for carbon nuclei), respectively. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, $CDHCl_2$: δ 5.32, C_6HD_5: 7.16, acetone-d_5: δ 2.05). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, CD_2Cl_2: δ 54.00, C_6D_6: 128.06, acetone-d_6: 29.84). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton) (e.g. "5.21 (t, $^3J_{9/8}$ = 7.3 Hz, 1H, 9-H)"). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Protons of diastereotopic methylene groups are reported as X-H_A and X-H_B, where X-H_A is the more downfield shifted proton. ^{13}C NMR spectroscopic data are reported as follows: Chemical shift in ppm (assigned carbon) (e.g. "159.22 (C-21)"). In cases were resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g. the ^{13}C NMR assignment "18.29 (C-16, C-17), 17.84 (C-16, C-17)" indicates that the resonance at 18.29 is either C-16 or C-17). Additionally to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. All raw FID files were processed and the spectra analyzed using the program *MestReNOVA 9.0* from *Mestrelab Research S. L*.

Mass spectrometry

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionisation mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH.* Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

IR spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in dichloromethane prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, w = weak, br = broad).

Optical rotation

Optical rotation values were recorded on a *PerkinElmer 241* or *Anton Paar MCP 200* polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

Thereby, the wavelength λ is reported in nm and the measuring temperature φ in °C. α represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2·g^{-1}. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

6 EXPERIMENTAL PROCEDURES, X-RAY CRYSTALLOGRAPHIC, COMPUTATIONAL AND SPECTROSCOPIC DATA

6.1 Supporting Information for Chapter 2.2.1

A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (–)-Norleucosceptroid B, and (–)-Leucosceptroid K

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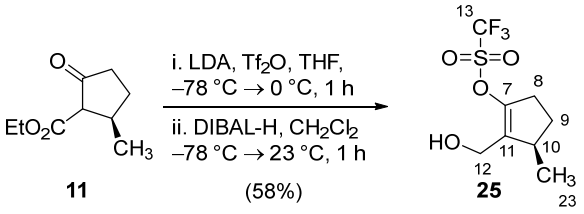
6.1.1 Experimental Procedures

Synthesis of Triflate 25



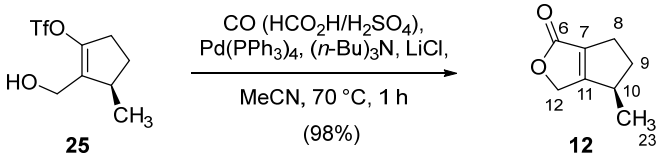
To a solution of diisopropylamine (24.9 mL, 176 mmol, 1.20 eq) in tetrahydrofuran (250 mL) was added *n*-butyllithium solution (2.24 M in hexanes, 73.4 mL, 165 mmol, 1.12 eq) at −78 °C. The resulting mixture was stirred for 5 min at −78 °C, 10 min at 0 °C and finally cooled to −78 °C. A solution of known keto ester **11**[4] (25.0 g, 147 mmol, 1 eq) in tetrahydrofuran (50 mL) was added. After 15 min, the golden solution was treated dropwise with trifluoromethanesulfonic anhydride (29.3 mL, 176 mmol, 1.20 eq) and stirring was continued at −78 °C for 20 min, then at 0 °C for 40 min. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (100 mL), saturated ammonium chloride solution (300 mL) and dichloromethane (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 150 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (10% ethyl acetate in hexanes) and the filtrate was concentrated to afford the crude ester triflate as a light yellow oil which was used in the next step without further purification.

A solution of this crude ester triflate in dichloromethane (300 mL) was treated with diisobutylaluminium hydride solution (1 M in dichloromethane, 323 mL, 323 mmol, 2.20 equiv) at −78 °C. After 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. After 1 h, the mixture was diluted with ethyl acetate (20 mL), saturated aqueous sodium chloride solution (100 mL) and aqueous 1 M hydrogen chloride solution (200 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 150 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in hexanes) to provide triflate **25** as a light yellow oil (22.0 g, 58%).

TLC (10% ethyl acetate in hexanes): R_f = 0.28 (UV, $KMnO_4$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.33 (d, $^2J_{12A/12B}$ = 13.2 Hz, 1H, 12-H_A), 4.13 (d, $^2J_{12B/12A}$ = 13.2 Hz, 1H, 12-H_B), 2.98–2.90 (m, 1H, 10-H), 2.68–2.54 (m, 2H, 8-H), 2.27–2.19 (m, 1H, 9-H_A), 1.58–1.51 (m, 1H, 9-H_B), 1.15 (d, $^3J_{23/10}$ = 6.9 Hz, 3H, 23-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.05 (C-7), 135.25 (C-11), 118.51 (q, $^1J_{13/F}$ = 320 Hz, C-13), 55.52 (C-12), 36.46 (C-10), 30.12 (C-8), 28.94 (C-9), 19.39 (C-23). **HRMS** (EI): calcd for $(C_8H_{11}F_3O_4S)^+$: 260.0330, found: 260.0343. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3356 (br), 2964 (m), 2873 (m) 1420 (s), 1209 (s), 1141 (s), 995 (m) cm^{-1}. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.2 (c = 0.55, $CHCl_3$).

[4] Keto ester **11** was prepared on multi-gram scale according to: a) J. N. Marx, L. R. Norman, *J. Org. Chem.* **1975**, *40*, 1602; b) H. Niwa, K. Kunitani, T. Nagoya, K. Yamada, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3094.

Synthesis of AB-component 12



Note: For safety reasons the following reaction was carried out in three parallel batches (each on 28.2 mmol scale). The crude material of all batches were subsequently combined and purified together. Tetrakis(triphenylphosphine)palladium(0) (2.31 g, 1.98 mmol, 0.07 equiv) was added to a Schlenk flask containing flame-dried lithium chloride (1.31 g, 31.1 mmol, 1.10 equiv). The flask was flushed with argon and tightly sealed with a rubber septum and Teflon tape. A solution of triflate **25** (7.35 g, 28.2 mmol, 1 equiv) in degassed acetonitrile (270 mL) and tributylamine (13.5 mL, 56.5 mmol, 2.00 equiv) were added in sequence via syringe. A second Schlenk flask was connected to the main reaction chamber by a short piece of rubber tubing, enabling gas exchange between the two separated chambers (see **Figure S1**). Sulfuric acid (95–97%, 3.92 mL, 70.6 mmol, 2.50 equiv) was added to this second reaction chamber whereupon both chambers were heated to 70 °C in an oil bath. Formic acid (2.13 mL, 56.5 mmol, 2.00 equiv) was then added dropwise to the Schlenk tube (***Caution**: Addition of formic acid to sulfuric acid leads to significant carbon monoxide overpressure. This reaction should thus be conducted with appropriate precautions and behind a blast shield*). Stirring of the orange suspension was continued at 70 °C for 1 h. The dark orange mixture was allowed to cool to 23 °C and was then partitioned between 1 M aqueous hydrochloric acid solution (250 mL) and dichloromethane (250 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 120 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residues of all three batches were combined, and then purified by flash-column chromatography (20% → 30% ethyl acetate in hexanes) to provide AB-component **12** as an orange oil (11.5 g, 98%).

TLC (25% ethyl acetate in hexanes): R_f = 0.36 (UV, $KMnO_4$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.80–4.71 (m, 2H, 12-H), 3.13–3.04 (m, 1H, 10-H), 2.72–2.65 (m, 1H, 9-H_A), 2.57–2.50 (m, 1H, 8-H_A), 2.48–2.41 (m, 1H, 8-H_B), 2.05–1.98 (m, 1H, 9-H_B), 1.19 (d, $^3J_{23/10}$ = 7.2 Hz, 3H, 23-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 178.03 (C-11), 170.35 (C-6), 136.15 (C-7), 68.42 (C-12), 38.13 (C-9), 37.21 (C-10), 24.53 (C-8), 19.13 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2961 (m), 2932 (m), 1751 (s), 1662 (m), 1348 (m), 1029 (m), 997 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_8H_{10}O_2)^+$: 138.0681, found: 138.0659. $[\alpha]_D^{20}$ = +73.2 (c = 1.05, $CHCl_3$).

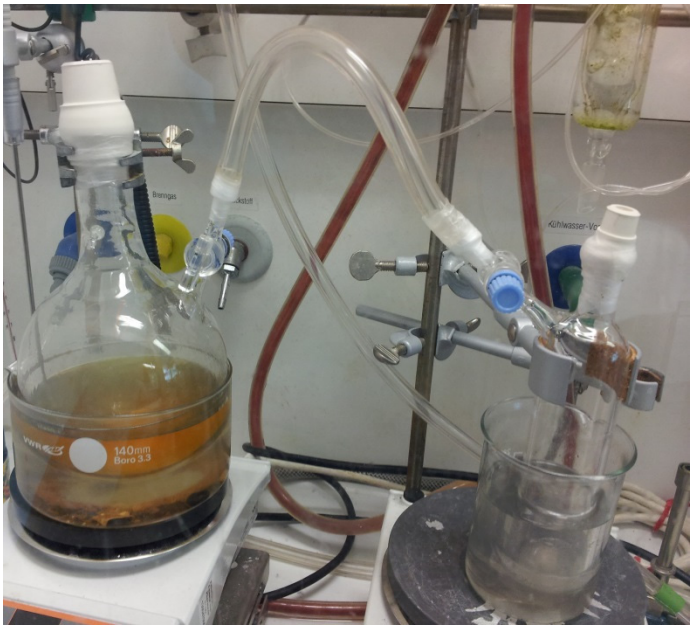
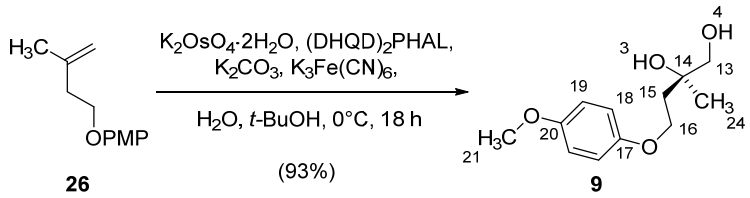


Figure S1. Experimental set up for the synthesis of AB-component **12**. For safety reasons the whole experimental set up is assembled behind a blast shield. The left reaction chamber contains a suspension of tetrakis(triphenylphosphine)palladium(0), triflate **25**, lithium chloride and tributylamine in acetonitrile. A rubber tube connects this chamber to a second Schlenk flask containing sulfuric acid and formic acid for carbon monoxide generation.

Synthesis of Diol 9

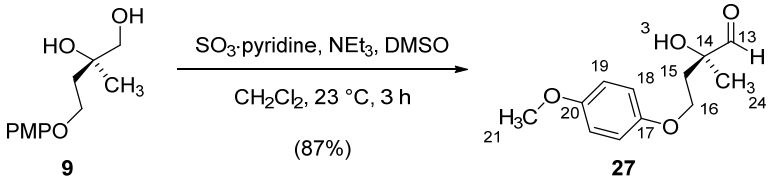


Based on a slightly modified literature procedure,[5] a mixture of $K_3Fe(CN)_6$ (159 g, 484 mmol, 3.00 equiv), K_2CO_3 (66.9 g, 484 mmol, 3.0 equiv), and hydroquinidine 1,4-phthalazinediyl diether (1.26 g, 1.61 mmol, 0.01 equiv) was ground to a fine powder and then was dissolved in a mixture of H_2O–*tert*-butanol (1:1, 800 mL). The orange, biphasic mixture was cooled to 0 °C and potassium osmate(IV) dihydrate (119 mg, 0.32 mmol, 0.002 equiv) was added. After 10 min, a solution of olefin **26**[5] (41.4 g, 161 mmol, 1 equiv) in a mixture of H_2O–*tert*-butanol (1:1, 180 mL) was added and stirring was continued at 0 °C. After 18 h, solid sodium sulfite (203 g, 1.61 mol, 10 equiv) was added and the cooling bath was removed. After 10 min, the reaction mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 150 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% methanol in dichloromethane) to provide diol **9** as a colourless solid (34.0 g, 93%). The characterization data for diol **9** were in agreement with values previously reported.[5]

TLC (5% methanol in dichloromethane): R_f = 0.29 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91–6.78 (m, 4H, 18-H, 19-H), 4.17 (ddd, $^2J_{16A/16B}$ = 9.7 Hz, $^3J_{16A/15A}$ = 7.8 Hz, $^3J_{16A/15B}$ = 4.2 Hz, 1H, 16-H_A), 4.10 (ddd, $^2J_{16B/16A}$ = 9.7 Hz, $^3J_{16B/15B}$ = 6.5 Hz, $^3J_{16B/15A}$ = 4.5 Hz, 1H, 16-H_B), 3.77 (s, 3H, 21-H), 3.54 (dd, $^2J_{13A/13B}$ = 11.1 Hz, $^3J_{13A/4}$ = 6.5 Hz, 1H, 13-H_A), 3.47 (dd, $^3J_{13B/13A}$ = 11.1 Hz, $^3J_{13B/4}$ = 6.5 Hz, 1H, 13-H_B), 2.85 (s, 1H, 3-OH), 2.43 (t, $^3J_{4/13}$ = 6.5 Hz, 1H, 4-OH), 2.10 (ddd, $^2J_{15A/15B}$ = 14.8 Hz, $^3J_{15A/16A}$ = 7.8 Hz, $^3J_{15A/16B}$ = 4.5 Hz, 1H, 15-H_A), 1.91 (ddd, $^3J_{15B/15A}$ = 14.8 Hz, $^3J_{15B/16B}$ = 6.5 Hz, $^3J_{15B/16A}$ = 4.2 Hz, 1H, 15-H_B), 1.25 (s, 3H, 24-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.40 (C-20), 152.43 (C-17), 115.69 (C-18, C-19), 114.87 (C-18, C-19), 72.50 (C-14), 70.22 (C-13), 65.59 (C-16), 55.87 (C-21), 37.74 (C-15), 24.32 (C-24). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3392 (br), 2935 (m) 1508 (s), 1466 (w) 1229 (s), 1038 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{12}H_{18}O_4)^+$: 226.1205, found: 226.1205. $[\alpha]_D^{20}$ = –6.4 (c = 2.80, $CHCl_3$). **Chiral HPLC analysis** using 2-propanol–heptane (7:93) as eluent (flow rate: 1.5 mL/min; column: Phenomenex Lux 5u Amylose-2, 4.6x100 mm, detection: 254 nm; retention times: 16.9 min (major, diol **9**) and 21.8 min (minor, diol ***ent*-9**) and comparison with a racemic sample established that **9** was of ≥97% ee.

[5] E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1995**, 117, 10805.

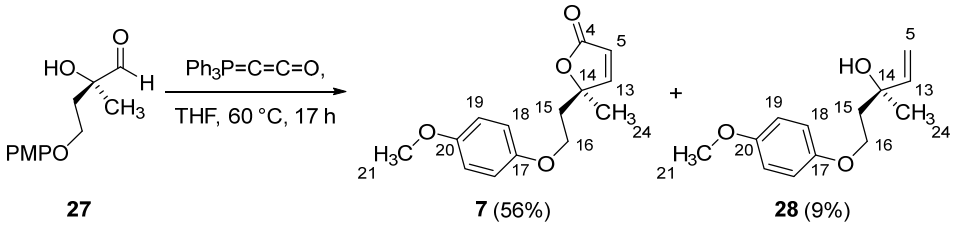
Synthesis of Hydroxy Aldehyde 27



To a solution of diol **9** (33.9 g, 150 mmol, 1 equiv) in a mixture of dichloromethane–dimethyl sulfoxide (4:1, 1.25 L) was added triethylamine (104 mL, 750 mmol, 5.0 equiv), followed by sulfur trioxide pyridine complex (71.6 g, 450 mmol, 3.0 equiv) at 23 °C. The yellow solution was stirred at 23 °C for 3 h. Water (400 mL) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (2 x 150 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% → 35% ethyl acetate in hexanes) to provide hydroxy aldehyde **27** as a colourless solid (29.2 g, 87%).

TLC (35% ethyl acetate in hexanes): R_f = 0.39 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.62 (s, 1H, 13-H), 6.90–6.68 (m, 4H, 18-H, 19-H), 4.08–3.89 (m, 2H, 16-H), 3.75 (s, 3H, 21-H), 3.61 (s, 1H, 3-OH), 2.35 (ddd, $^2J_{15A/15B}$ = 14.5 Hz, $^3J_{15A/16A}$ = 9.5 Hz, $^3J_{15A/16B}$ = 4.7 Hz, 1H, 15-H_A), 2.11–1.99 (m, 1H, 15-H_B), 1.34 (s, 3H, 24-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.50 (C-13), 154.28 (C-20), 152.34 (C-17), 115.55 (C-18, C-19), 114.80 (C-18, C-19), 76.56 (C-14), 63.83 (C-16), 55.86 (C-21), 37.72 (C-15), 23.79 (C-24). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3465 (br), 2933 (m), 1730 (s), 1507 (s), 1228 (s), 1180 (m), 1035 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{12}H_{16}O_4)^+$: 224.1046, found: 224.1040. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –41.0 (c = 1.05, $CHCl_3$).

Synthesis of C-ring Butenolide 7



27 **7** (56%) **28** (9%)

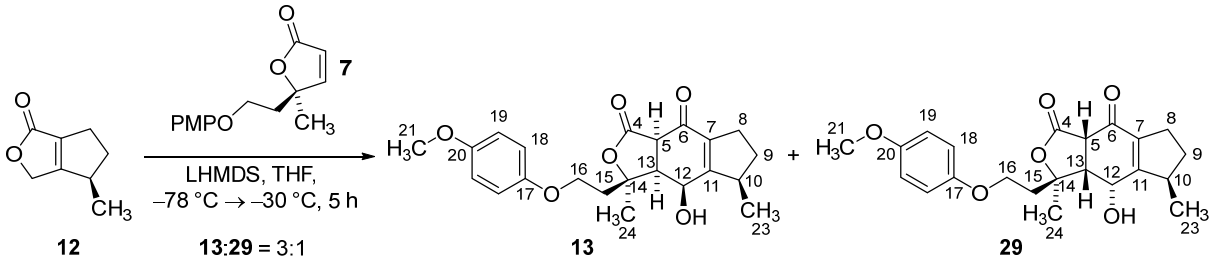
A a solution of hydroxyl aldehyde **27** (26.0 g, 116 mmol, 1 equiv) in tetrahydrofuran (260 mL)was added to a solution of (triphenylphosphoranylidene)ketene[6] (35.0 g, 116 mmol, 1 equiv) in tetrahydrofuran (300 mL) at 50 °C. The resulting mixture was heated to 60 °C in an oil bath. After 17 h, the mixture was cooled to 23 °C and then was concentrated to a third of its volume. Silica gel (ca. 150 mL dry volume) was added and the resulting mixture was evaporated to dryness. The adsorbent material was dry-loaded onto a silica gel column and the product was eluted (35% → 40% ethyl acetate in hexanes) to provide C-ring butenolide **7** as an off-white solid (16.0 g, 56%) and the by-product allylic alcohol **28** as a yellowish oil (2.40 g, 9%).

C-ring butenolide 7: **TLC** (35% ethyl acetate in hexanes): R_f = 0.35 (UV, $KMnO_4$).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, $^3J_{13/5}$ = 5.6 Hz, 1H, 13-H), 6.85–6.73 (m, 4H, 18-H, 19-H), 5.96 (d, $^3J_{5/13}$ = 5.6 Hz, 1H, 5-H), 4.02–3.92 (m, 1H, 16-H_A), 3.90–3.80 (m, 1H, 16-H_B), 3.76 (s, 3H, 21-H), 2.35–2.18 (m, 2H, 15-H), 1.54 (s, 3H, 24-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.60 (C-4), 160.85 (C-13), 154.25 (C-20), 152.41 (C-17), 119.65 (C-5), 115.50 (C-18, C-19), 114.86 (C-18, C-19), 87.68 (C-14), 63.61 (C-16), 55.87 (C-21), 38.08 (C-15), 24.55 (C-24). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934 (m), 1751 (s), 1508 (s), 1469 (w), 1229 (s), 1119 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{14}H_{16}O_4Na)^+$: 271.0946, found: 271.0940. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –96.0 (c = 1.00, CH_2Cl_2).

Allylic alcohol 28: **TLC** (30% ethyl acetate in hexanes): R_f = 0.32 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86–6.79 (m, 4H, 18-H, 19-H), 5.93 (dd, $^3J_{13/5A}$ = 17.2 Hz, $^3J_{13/5B}$ = 10.7 Hz, 1H, 13-H), 5.31 (dd, $^3J_{5A/13}$ = 17.2 Hz, $^2J_{5A/5B}$ = 1.4 Hz, 1H, 5-H_A), 5.10 (dd, $^3J_{5B/13}$ = 10.7 Hz, $^2J_{5B/5A}$ = 1.4 Hz, 1H, 5-H_B), 4.14–4.02 (m, 2H, 16-H), 3.76 (s, 3H, 21-H), 2.77 (br s, 1H, 14-OH), 2.12 (ddd, $^2J_{15A/15B}$ = 14.3 Hz, $^3J_{15A/16A}$ = 8.3 Hz, $^3J_{15A/16B}$ = 5.7 Hz, 1H, 15-H_A), 1.93 (app dt, $^2J_{15B/15A}$ = 14.3 Hz, $^3J_{15B/16}$ = 5.2 Hz, 1H, 15-H_B), 1.35 (s, 3H, 24-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.20 (C-20), 152.62 (C-17), 144.29 (C-13), 115.72 (C-18, C-19), 114.74 (C-18, C-19), 112.59 (C-5), 73.20 (C-14), 66.26 (C-16), 55.82 (C-21), 40.41 (C-15), 28.73 (C-14). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3504 (br), 2932 (m), 1507 (s), 1466 (m), 1226 (s), 1180 (m) 1037 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{13}H_{18}O_3)^+$: 222.1256, found: 222.1251. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +14.0 (c = 1.54, CH_2Cl_2).

[6] a) H. J. Bestmann, D. Sandmeier, *Angew. Chem.* **1975**, *87*, 630; b) *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634; the reagent was prepared according to c) R. Schobert, *Organic Syntheses* **2005**, *82,* 140*; Coll. Vol.* **2009***, 11,* 986.

Synthesis of Major Enone 13

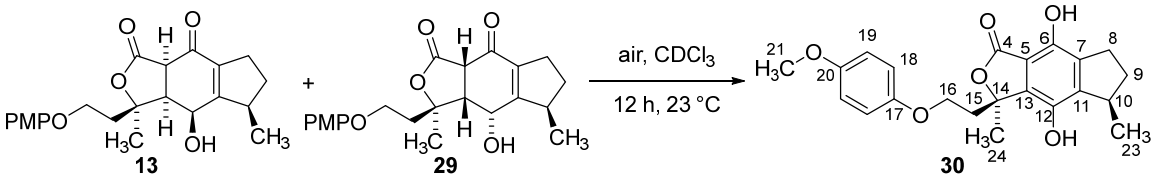


A solution of AB-component **12** (3.00 g, 21.7 mmol, 1 equiv) in degassed tetrahydrofuran (25 mL) was treated with a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 47.8 mL, 47.8 mmol, 2.20 equiv) at −78 °C. After 5 min, the mixture was warmed to 0 °C during which time the solution turned intense orange. After 20 min, the mixture was cooled to −78 °C and a solution of C-ring butenolide **7** (5.39 g, 21.7 mmol, 1 equiv) in degassed tetrahydrofuran (50 mL) was added dropwise over a period of 10 min. The resulting solution was allowed to warm to −30 °C over a period of 5 h, whereupon excess base was quenched by addition of saturated aqueous ammonium chloride solution (250 mL) and the mixture was diluted with dichloromethane (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 120 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude mixture of major enone **13** and minor enone **29** (ca. 3:1 diastereomeric mixture) was immediately used in the next reaction without further purification. Analytically pure samples of both enones **13** and **29** were obtained by careful flash-column chromatography (3% methanol in dichloromethane), followed by further purification by normal-phase semi-preparative HPLC using 2-propanol–heptane (10:90) as eluent (flow rate: 20 mL/min, Varian Dynamax Microsorb 60-8, 21.4x250 mm, detection: 254 nm, retention times: 13.0 min (major enone **13**) and 19.5 min (minor enone **29**)). *Note: Solutions of enones **13** and **29** are susceptible to air oxidation (converting to the corresponding hydroquinone **30**) and thus should be solely handled under inert atmosphere. Dried material of enones **13** and **29** however can be stored over multiple weeks at –30 °C under argon atmosphere without noticeable decomposition.*

Major enone 13: **TLC** (3.5% methanol in dichloromethane): R_f = 0.27 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90–6.75 (m, 4H, 18-H, 19-H), 4.94 (m, 1H, 12-H), 4.26–4.08 (m, 2H, 16-H), 3.70 (s, 3H, 21-H), 3.60 (d, $^3J_{5/13}$ = 7.8 Hz, 1H, 5-H), 3.13–2.95 (m, 1H, 10-H), 2.88 (dd, $^3J_{13/5}$ = 7.8 Hz, $^3J_{13/12}$ = 3.9 Hz, 1H, 13-H), 2.76–2.66 (m, 1H, 8-H_A), 2.65–2.59 (m, 1H, 15-H_A), 2.54–2.38 (m, 2H, 15-H_B, 8-H_B), 2.30–2.11 (m, 1H, 9-H_A), 1.63–1.57 (m, 1H, 9-H_B), 1.55 (s, 3H, 24-H), 1.26 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.15 (C-6), 169.94 (C-4), 166.98 (C-11), 154.21 (C-20), 152.66 (C-17), 139.44 (C-7), 115.45 (C-18, C-19), 114.91 (C-18, C-19), 85.44 (C-14), 64.62 (C-16), 63.43 (C-12), 55.90 (C-21), 51.19 (C-13), 49.12 (C-5), 43.34 (C-10), 34.73 (C-15), 31.56 (C-9), 28.05 (C-8), 25.30 (C-24), 19.40 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2479 (br), 2935 (m), 1766 (s), 1658 (m), 1507 (s), 1230 (s), 1107 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{26}O_6Na)^+$: 409.1627, found: 409.1620. $[\boldsymbol{\alpha}]_D^{20}$ = –8.0 (c = 1.00, CH_2Cl_2).

Minor enone 29: **TLC** (3.5% methanol in dichloromethane): R_f = 0.29 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89–6.80 (m, 4H, 18-H, 19-H), 5.14–5.06 (m, 1H, 12-H), 4.20–4.11 (m, 1H, 16-H_A), 4.11–4.04 (m, 1H, 16-H_B), 3.78 (s, 3H, 21-H), 3.55–3.47 (m, 2H, 5-H, 13-H), 3.33–3.23 (m, 1H, 10-H), 3.07 (br s, 1H, 12-OH), 2.69–2.58 (m, 1H, 8-H_A), 2.58–2.48 (m, 1H, 8-H_B), 2.41–2.26 (m, 2H, 15-H), 2.26–2.14 (m, 1H, 9-H_A), 1.59–1.49 (m, 1H, 9-H_B), 1.40 (s, 3H, 24-H), 1.24 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.18 (C-6), 169.88 (C-4), 168.36 (C-11), 154.70 (C-20), 151.83 (C-17), 136.80 (C-7), 115.51 (C-18, C-19), 115.08 (C-18, C-19), 87.37 (C-14), 64.33 (C-16), 63.67 (C-12), 55.90 (C-21), 51.72 (C-5), 46.87 (C-13), 41.72 (C-10), 40.17 (C-15), 30.76 (C-9), 28.70 (C-8), 25.26 (C-24), 18.65 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3479 (br), 2934 (m), 1763 (s) 1658 (m) 1507 (s), 1230 (s), 1107 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{26}O_6Na)^+$: 409.1627, found: 409.1620. $[\boldsymbol{\alpha}]_D^{20}$ = –28.0 (c = 1.00, CH_2Cl_2).

Air Oxidation of Enones 13 and 29 to Hydroquinone 30

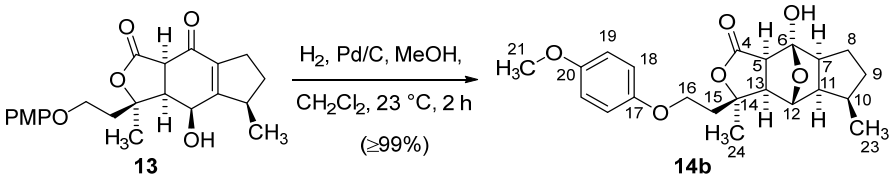


A sample of enones **13** and **29** (ca. 3:1 diastereomeric mixture, 10 mg, 26 µmol) was dissolved in $CDCl_3$ (0.7 mL). The initially colourless solution underwent a colour change to deep red within 12 h under air atmosphere. NMR analysis of this solution showed **30** together with remaining enones **13** and **29**. Concentration of the sample and purification of the resulting residue by flash-column chromatography (30% ethyl acetate in hexanes) afforded hydroquinone **30**.

TLC (30% ethyl acetate in hexanes): R_f = 0.44 (UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (s, 1H, 6-OH), 6.83–6.67 (m, 4H, 18-H, 19-H), 5.19 (s, 1H, 12-OH), 4.05 (dt, $^2J_{16A/16B}$ = 10.0 Hz, $^3J_{16A/15}$ = 6.3 Hz, 1H, 16-H_A), 3.89 (dt, $^2J_{16B/16A}$ = 10.0 Hz, $^3J_{16B/15}$ = 6.3 Hz, 1H, 16-H_B), 3.75 (s, 3H, 21-H), 3.42–3.32 (m, 1H, 10-H), 3.00–2.80 (m, 2H, 8-H), 2.65–2.49 (m, 2H, 15-H), 2.40–2.28 (m, 1H, 9-H_A), 1.89–1.77 (m, 1H, 9-H_B), 1.76 (s, 3H, 24-H), 1.25 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.33 (C-4), 154.38 (C-20), 152.16 (C-17), 146.65 (C-6), 146.32 (C-11), 139.22 (C-12), 136.99 (C-13), 131.94 (C-7), 115.76 (C-18, C-19), 114.78 (C-18, C-19), 110.47 (C-5), 87.24 (C-14), 64.76 (C-16), 55.84 (C-21), 37.72 (C-15), 37.43 (C-10), 34.18 (C-9), 26.85 (C-8), 24.97 (C-24), 19.44 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3435 (br), 2954 (m), 1707 (s), 1507 (s), 1442 (s), 1229 (s), 1184 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{24}O_6Na)^+$: 407.1471, found: 407.1468. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +8.4 (c = 1.00, CH_2Cl_2).

*Note: Solutions of enones **13** and **29** were found to undergo facile oxidation to hydroquinone **30** also under various other conditions. Generally, oxidation of **13** and **29** can be largely avoided by employing degassed solvents and carefully maintaining an inert atmosphere.*

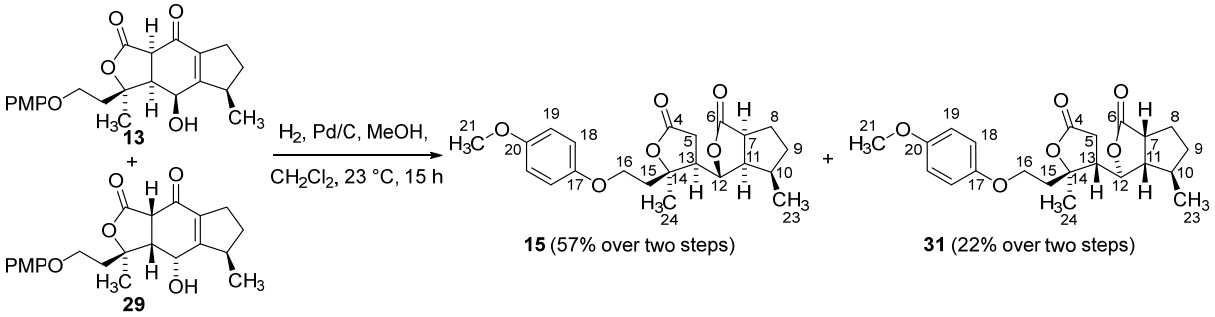
Synthesis of Hemiacetal 14b



To a solution of major enone **13** (120 mg, 311 µmol, 1 equiv) in methanol–dichloromethane (4:1 mixture, 20 mL) was added palladium on carbon (10 wt.%, 33.0 mg, 31 µmol, 0.1 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 2 h, the mixture was diluted with dichloromethane (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated to provide spectroscopically pure hemiacetal **14b** as a colourless solid (120 mg, ≥99%). *Note: Hemiacetal **14b** undergoes a retro-Claisen reaction affording dilactone **15** under both weakly basic and acidic conditions (silica gel).*

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88–6.78 (m, 4H, 18-H, 19-H), 5.27 (s, 1H, 6-OH), 4.72 (s, 1H, 12-H), 4.21–4.03 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.98 (d, $^3J_{5/13}$ = 7.9 Hz, 1H, 5-H), 2.49 (d, $^3J_{13/5}$ = 7.9 Hz, 1H, 13-H), 2.44–2.33 (m, 2H, 7-H, 15-H_A), 2.33–2.17 (m, 3H, 8-H_A, 11-H, 15-H_B), 2.14–2.02 (m, 1H, 10-H), 1.65–1.55 (m, 1H, 9-H_A), 1.55–1.47 (m, 1H, 8-H_B), 1.45 (s, 3H, 24-H), 1.42–1.32 (m, 1H, 9-H_B), 1.10 (d, $^3J_{23/10}$ = 6.8 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.61 (C-4), 154.22 (C-20), 152.68 (C-17), 115.37 (C-18, C-19), 114.90 (C-18, C-19), 107.97 (C-6), 87.73 (C-14), 73.48 (C-12), 64.61 (C-16), 55.88 (C-21), 54.88 (C-13), 52.01 (C-11), 50.75 (C-5), 48.98 (C-7), 38.41 (C-10), 35.49 (C-15), 34.97 (C-9), 27.99 (C-24), 26.35 (C-8), 15.54 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (br), 2949 (m), 1732 (s), 1509 (s), 1228 (s), 1097 (m), 1030 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{27}O_6)^-$: 387.18131, found: 387.18093. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +38.2 (c = 1.00, CH_2Cl_2).

Synthesis of Major Dilactone 15

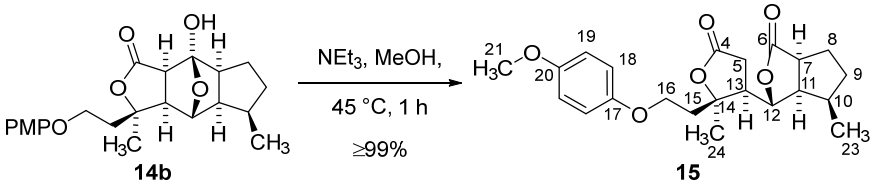


To a solution of crude enones **13** and **29** (ca. 3:1 diastereomeric ratio) in degassed methanol–dichloromethane (4:1 mixture, 500 mL) was added palladium on carbon (10 wt.%, 2.08 g, 1.95 mmol, 0.09 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 1 h and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 15 h, the mixture was sparged with argon before being filtered through a pad of Celite. Triethylamine (6 mL) was added to the filtrate and the mixture was concentrated. The residue was purified by flash-column chromatography (40% → 60% ethyl acetate in hexanes) to provide major dilactone **15** (4.79 g, 57% over two steps from **12**) and minor dilactone **31** as colourless foams (1.87 g, 22% over two steps from **12**).

Major dilactone 15: TLC (40% ethyl acetate in hexanes): R_f = 0.16 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85–6.79 (m, 4H, 18-H, 19-H), 4.52 (dd, $^3J_{12/11}$ = 6.0 Hz, $^3J_{12/13}$ = 1.9 Hz, 1H, 12-H), 4.18–4.07 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 3.10–3.02 (m, 1H, 7-H), 2.67–2.62 (m, 2H, H-5), 2.55–2.48 (m, 1H, 11-H), 2.45–2.38 (m, 1H, 13-H), 2.29 (dt, $^2J_{15A/15B}$ = 15.1 Hz, $^3J_{15A/16}$ = 5.6 Hz, 1H, 15-H_A), 2.25–2.19 (m, 1H, 10-H), 2.19–2.05 (m, 2H, 8-H_A, 15-H_B), 2.05–1.92 (m, 1H, 8-H_B), 1.88–1.79 (m, 1H, 9-H_A), 1.57 (s, 3H, 24-H), 1.33–1.20 (m, 1H, 9-H_B), 1.09 (d, $^3J_{23/10}$ = 6.9 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.74 (C-6), 173.93 (C-4), 154.14 (C-20), 152.73 (C-17), 115.61 (C-18, C-19), 114.84 (C-18, C-19), 86.54 (C-14), 75.55 (C-12), 64.22 (C-16), 55.87 (C-21), 52.43 (C-13), 48.31 (C-11), 44.66 (C-7), 38.65 (C-10), 35.30 (C-15), 32.64 (C-9), 30.42 (C-8), 28.41 (C-5), 26.05 (C-24), 14.18 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (m), 1769 (s), 1508 (s), 1465 (w), 1229 (s), 1106 (w), 1037 (w) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{27}O_6)^-$: 387.18131, found: 387.18093. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +5.2 (c = 1.00, CH_2Cl_2).

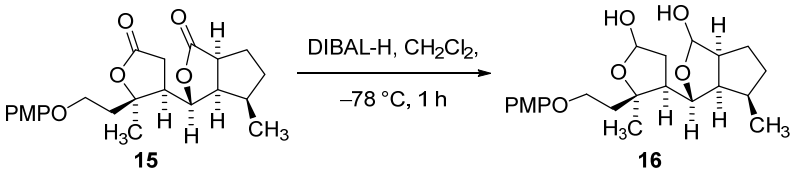
Minor dilactone 31: TLC (40% ethyl acetate in hexanes): R_f = 0.35 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88–6.75 (m, 4H, 18-H, 19-H), 4.32 (dd, $^3J_{12/13}$ = 4.6 Hz, $^3J_{12/11}$ = 3.4 Hz, 1H, 12-H), 4.15 (ddd, $^2J_{16A/16B}$ = 10.3 Hz, $^3J_{16A/15A}$ = 7.2 Hz, $^3J_{16A/15B}$ = 4.5 Hz, 1H, 16-H_A), 4.07 (ddd, $^2J_{16B/16A}$ = 10.3 Hz, $^3J_{16B/15B}$ = 6.3 Hz, $^3J_{16B/15A}$ = 4.6 Hz, 1H, 16-H_B), 3.77 (s, 3H, 21-H), 3.07 (app td, $^3J_{7/11}$ = 9.7 Hz, $^3J_{7/8}$ = 3.9 Hz, 1H, 7-H), 2.86 (td, $^3J_{13/5}$ = 9.9 Hz, $^3J_{13/12}$ = 4.6 Hz, 1H, 13-H), 2.62 (dd, $^3J_{5/13}$ = 9.9 Hz, $^2J_{5A/5B}$ = 2.5 Hz, 2H, 5-H), 2.31–2.11 (m, 4H, 8-H_A, 11-H, 15-H), 2.03–1.91 (m, 2H, 8-H_B, 10-H), 1.87–1.76 (m, 1H, 9-H_A), 1.47 (s, 3H, 24-H), 1.44–1.34 (m, 1H, 9-H_B), 1.05 (d, $^3J_{23/10}$ = 6.8 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.90 (C-6), 173.99 (C-4), 154.37 (C-20), 152.32 (C-17), 115.42 (C-18, C-19), 114.97 (C-18, C-19), 86.34 (C-14), 81.57 (C-12), 63.86 (C-16), 55.89 (C-21), 53.17 (C-11), 48.23 (C-13), 44.14 (C-7), 41.14 (C-10), 39.75 (C-15), 33.77 (C-9), 30.03 (C-5), 28.49 (C-8), 22.49 (C-24), 19.26 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (m), 1767 (s), 1508 (s), 1464 (w), 1230 (s), 1159 (m), 1108 (w), 1038 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{28}O_6K)^+$: 427.15230, found: 427.15176. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.0 (c = 1.00, CH_2Cl_2).

Synthesis of Dilactone 15 by retro-Claisen reaction of Hemiacetal 14b



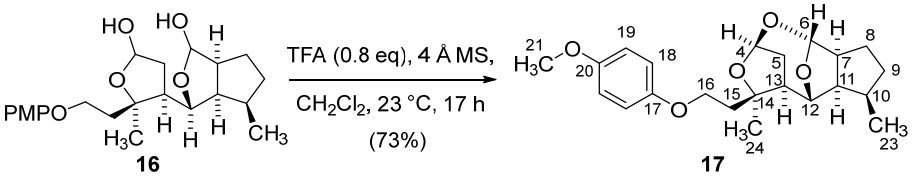
Triethylamine (0.1 mL) was added to a solution of hemiacetal **14b** (110 mg, 283 µmol, 1 equiv) in methanol (12 mL) and the resulting mixture was heated to 45 °C. After 1 h, the mixture was cooled to 23 °C and then was concentrated in vacuo. The residue was purified by flash-column chromatography (3% methanol in dichloromethane) to provide major dilactone **15** as a colourless solid (109 mg, ≥99%).

Synthesis of Dilactol 16



Diisobutylaluminium hydride (1 M solution in dichloromethane, 35.9 mL, 35.9 mmol, 3.00 equiv) was added dropwise to a solution of major dilactone **15** (4.65 g, 12.0 mmol, 1 equiv) in dichloromethane (170 mL) at −78 °C over 10 min. After 1 h, methanol (30 mL) followed by 0.5 M aqueous hydrochloric acid solution (50 mL) were added at −78 °C, and the mixture was then warmed to 23 °C and poured onto saturated aqueous ammonium chloride solution (150 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 80 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide dilactol **16** as a colourless foam (4.71 g) which was used in the next step without further purification.

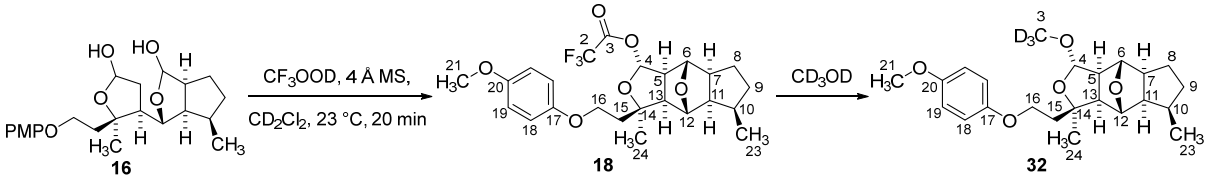
Synthesis of Bisacetal 17 with Substochiometric Amount of TFA



A round-bottomed flask was charged with 4 Å molecular sieves (40 mg) and was flame-dried in vacuo for 4 min. After cooling to 23 °C, the 4 Å molecular sieves were crushed and a solution of crude dilactol **16** (12.3 mg, 31.3 µmol, 1 equiv) in dichloromethane (1.5 mL) was added. The resulting suspension was treated with trifluoroacetic acid (0.90 µL, 12.5 µmol, 0.40 equiv) at 23 °C. After 14 h, TLC analysis of the reaction mixture showed incomplete conversion and another aliquot of trifluoroacetic acid (0.90 µL, 12.5 µmol, 0.40 equiv) was added. After 3 h, solid sodium hydrogencarbonate (20 mg) was added and the mixture was filtered through a pad of sodium sulfate. The filtrate was concentrated to provide spectroscopically pure bisacetal **17** as a colourless solid (8.5 mg, 73%).

TLC (40% ethyl acetate in hexanes): R_f = 0.33 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91–6.75 (m, 4H, 18-H, 19-H), 5.41–5.37 (m, 1H, 4-H), 5.16 (s, 1H, 6-H), 4.93 (app d, *J* = 3.7 Hz, 1H, 12-H), 4.20–3.98 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.83 (app t, *J* = 7.5 Hz, 1H, 7-H), 2.74–2.57 (m, 1H, 15-H_A), 2.45–2.39 (m, 1H, 15-H_B), 2.39–2.32 (m, 1H, 11-H), 2.32–2.24 (m, 2H, 5-H), 2.08–1.97 (m, 2H, 13-H, 10-H), 1.82–1.68 (m, 1H, 8-H_A), 1.68–1.51 (m, 2H, 8-H_B, 9-H_A), 1.33–1.14 (m, 1H, 9-H_B), 1.22 (s, 3H, 24-H), 1.08 (d, $^3J_{23/10}$ = 6.9 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.81 (C-20), 153.34 (C-17), 115.29 (C-18, C-19), 114.77 (C-18, C-19), 109.58 (C-6), 99.59 (C-4), 84.08 (C-14), 79.32 (C-12), 65.77 (C-16), 55.88 (C-21), 54.62 (C-7), 49.70 (C-11), 49.18 (C-13), 37.55 (C-10), 35.56 (C-15), 34.29 (C-9), 32.53 (C-8), 32.06 (C-5), 26.41 (C-24), 16.29 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (w), 1507 (s), 1465 (w), 1229 (s), 1100 (w), 1034 (m), 904 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{30}O_5Na)^+$: 397.19909, found: 397.19816. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +8.5 (c = 0.21, CH_2Cl_2).

Mechanistic Investigation of the Intramolecular Dilactol Aldol-Type Condensation: Synthesis of 4-*O*-Trifluoroacetyl Acetal 18 and Methoxy-d_3 Acetal 32



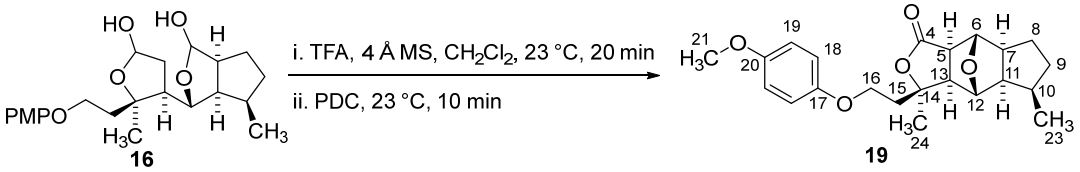
A round-bottomed flask was charged with 4 Å molecular sieves (130 mg) and was flame-dried in vacuo for 4 min. After cooling to 23 °C, a solution of crude dilactol **16** (7.20 mg, 18.3 µmol, 1 equiv) in dichloromethane-d_2 (1.5 mL) was added. The resulting mixture was treated with trifluoroacetic acid-d (6.81 µL, 91.7 µmol, 5.00 equiv) at 23 °C. After 20 min, an aliquot (0.7 mL) was taken and NMR spectra were recorded.

4-*O*-Trifluoroacetyl acetal 18: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.86–6.80 (m, 4H, 18-H, 19-H), 6.20 (s, 1H, 4-H), 4.89 (s, 1H, 12-H), 4.43 (s, 1H, 6-H), 4.17–4.00 (m, 2H, 16-H), 3.76 (s, 3H, 21-H), 2.89 (d, $^3J_{5/13}$ = 7.6 Hz, 1H, 5-H), 2.34 (d, $^3J_{13/5}$ = 7.6 Hz, 1H, 13-H), 2.33–2.21 (m, 2H, 7-H, 15-H_A), 2.18–2.08 (m, 2H, 11-H, 15-H_B), 2.07–1.96 (m, 1H, 10-H), 1.76–1.50 (m, 3H, 8-H, 9-H_A), 1.34 (s, 3H, 24-H), 1.33–1.21 (m, 1H, 9-H_B), 1.06 (d, $^3J_{23/10}$ = 6.9 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, CD_2Cl_2) (*Note: the CF_3CO_2– group is not visible in this spectrum*) δ 154.39 (C-20), 153.42 (C-17), 115.84 (C-18, C-19), 115.21 (C-18, C-19), 107.43 (C-4), 89.85 (C-14), 86.32 (C-6), 78.84 (C-12), 65.48 (C-16), 57.60 (C-13), 56.99 (C-5), 56.27 (C-21), 51.69 (C-11), 48.22 (C-7), 38.11 (C-10), 36.29 (C-15), 35.47 (C-9), 31.93 (C-8), 27.72 (C-24), 15.92 (C-23). **^{19}F NMR** (376 MHz, CD_2Cl_2) δ –76.03.

The remaining reaction mixture was diluted with methanol-d_4 (0.2 mL) and then was filtered through a pad of Celite. The filtrate was concentrated to provide methoxy-d_3 acetal **32**, showing no deuterium incorporation at C-5 and thus confirming that no enol ether is involved in the condensation reaction.

Methoxy-d_3 acetal 32: TLC (20% ethyl acetate in hexanes): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88–6.79 (m, 4H, 18-H, 19-H), 4.74 (s, 1H, 4-H), 4.71 (s, 1H, 12-H), 4.21 (s, 1H, 6-H), 4.18–4.03 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.56 (d, $^3J_{5/13}$ = 7.6 Hz, 1H, 5-H), 2.27–2.20 (m, 1H, 7-H), 2.20–2.09 (m, 3H, 13-H, 15-H), 2.05–1.88 (m, 2H, 10-H, 11-H), 1.68–1.57 (m, 2H, 8-H), 1.54–1.46 (m, 1H, 9-H_A), 1.41–1.33 (m, 1H, 9-H_B), 1.32 (s, 3H, 24-H), 1.06 (d, $^3J_{23/10}$ = 6.6 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) (*Note: the CD_3O– group is not visible in this spectrum*) δ 153.88 (C-20), 153.26 (C-17), 115.48 (C-18, C-19), 114.78 (C-18, C-19), 109.42 (C-4), 86.29 (C-6), 85.26 (C-14), 77.36 (C-12), 65.51 (C-16), 57.60 (C-13), 57.00 (C-5), 55.89 (C-21), 51.48 (C-11), 48.14 (C-7), 37.79 (C-10), 36.69 (C-15), 35.20 (C-9), 31.78 (C-8), 28.27 (C-24), 15.92 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (m), 1507 (s), 1464 (m), 1374 (m), 1229 (s) 1121 (m), 1006 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{23}H_{29}D_3O_5Na)^+$: 414.23357, found: 414.23277.

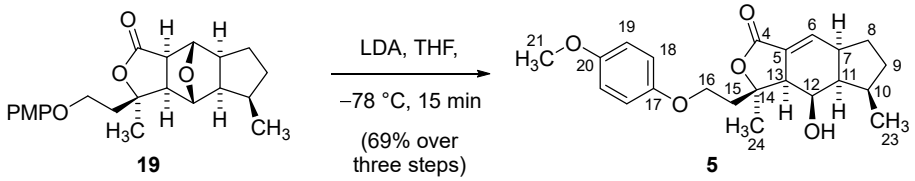
Synthesis of Lactone 19



A round-bottomed flask was charged with 4 Å molecular sieves (21 g) and was flame-dried in vacuo for 5 min. After cooling to 23 °C, the 4 Å molecular sieves were crushed and a solution of crude dilactol **16** (4.71 g, 12.0 mmol, 1 equiv) in dichloromethane (300 mL) was added. The resulting suspension was treated with trifluoroacetic acid (4.46 mL, 60.0 mmol, 5.00 equiv) at 23 °C. After 20 min, pyridinium dichromate (9.03 g, 24.0 mmol, 2.00 equiv) was added in three large portions and stirring was continued at 23 °C. After 10 min, the mixture was filtered through a pad of silica gel (4 cm) and the filter cake was washed with 1% methanol in dichloromethane (ca. 200 mL). The filtrate was concentrated to provide spectroscopically pure lactone **19** as a colourless solid (3.46 g).

TLC (30% ethyl acetate in hexanes): R_f = 0.20 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90–6.77 (m, 4H, 18-H, 19-H), 4.91 (s, 1H, 12-H), 4.56 (s, 1H, 6-H), 4.20–4.04 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 3.04 (d, $^3J_{5/13}$ = 8.1 Hz, 1H, 5-H), 2.38–2.29 (m, 3H, 7-H, 15-H), 2.26 (d, $^3J_{13/5}$ = 8.1 Hz, 1H, 13-H), 2.09–2.01 (m, 1H, 11-H), 2.01–1.95 (m, 1H, 10-H), 1.75–1.62 (m, 2H, 8-H), 1.61–1.50 (m, 1H, 9-H_A), 1.42 (s, 3H, 24-H), 1.39–1.29 (m, 1H, 9-H_B), 1.09 (d, $^3J_{23/10}$ = 6.6 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.26 (C-4), 154.13 (C-20), 152.83 (C-17), 115.42 (C-18, C-19), 114.88 (C-18, C-19), 86.36 (C-14), 86.05 (C-6), 78.86 (C-12), 64.76 (C-16), 55.89 (C-21), 53.91 (C-13), 51.83 (C-5), 51.19 (C-11), 47.99 (C-7), 37.78 (C-10), 35.52 (C-15), 34.99 (C-9), 31.71 (C-8), 28.47 (C-24), 15.80 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 1747 (s), 1509 (s), 1293 (w), 1235 (s), 1097 (m), 1042 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{28}O_5Na)^+$: 395.18344, found: 395.18261. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +60.8 (c = 0.46, CH_2Cl_2).

Synthesis of α,β-Unsaturated Lactone 5

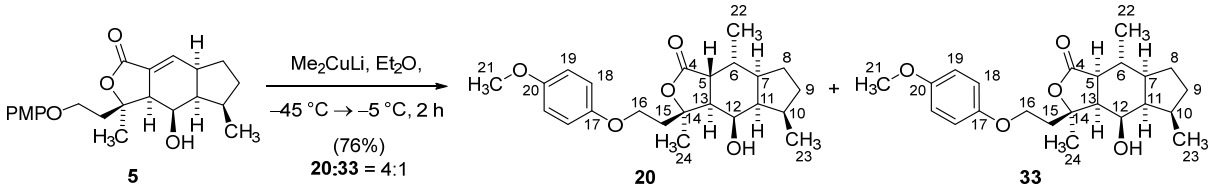


19 **5**

A solution of lactone **19** (3.46 g, 9.29 mmol, 1 equiv) in tetrahydrofuran (100 mL) was treated with a freshly prepared solution of lithium diisopropylamide (0.5 M in tetrahydrofuran, 21.4 mL, 10.7 mmol, 1.15 equiv) at −78 °C. After 15 min, the golden mixture was diluted with saturated aqueous ammonium chloride solution (170 mL) and dichloromethane (60 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 80 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40% ethyl acetate in pentane) to provide α,β-unsaturated lactone **5** as a colourless foam (3.08 g, 69% over three steps from dilactone **15**).

TLC (40% ethyl acetate in hexanes): R_f = 0.35 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (app t, $^3J_{6/7}$ = $^4J_{6/13}$ = 3.5 Hz, 1H, 6-H), 6.87–6.78 (m, 4H, 18-H, 19-H), 4.50 (app dt, $^3J_{12/12OH}$ = 7.4 Hz, $^3J_{12/11}$ = $^3J_{12/13}$ = 2.5 Hz, 1H, 12-H), 4.11 (t, $^3J_{16/15}$ = 6.2 Hz, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.96–2.84 (m, 1H, 7-H), 2.72 (dd, $^4J_{13/6}$ =3.5 Hz, $^3J_{13/12}$ = 2.5 Hz, 1H, 13-H), 2.44–2.36 (m, 2H, 15-H), 2.34–2.23 (m, 1H, 10-H), 2.15–2.05 (m, 2H, 8-H_A, 12-OH), 2.00–1.93 (m, 1H, 11-H), 1.89–1.79 (m, 1H, 9-H_A), 1.67–1.53 (m, 5H, 8-H_B, 9-H_B, 24-H), 1.23 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.06 (C-4), 154.34 (C-20), 152.38 (C-17), 140.82 (C-6), 125.61 (C-5), 115.63 (C-18, C-19), 114.88 (C-18, C-19), 86.90 (C-14), 65.12 (C-12), 64.96 (C-16), 55.87 (C-21), 53.09 (C-13), 47.62 (C-11), 40.87 (C-7), 37.74 (C-10), 36.57 (C-15), 33.04 (C-9), 30.92 (C-8), 28.21 (C-24), 15.24 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3500 (br), 2949 (m), 1750 (s), 1674 (w), 1508 (s), 1230 (s), 1041 (s), 826 (w) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{28}O_5Na)^+$: 395.18344, found: 395.18264. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +61.2 (c = 0.29, CH_2Cl_2).

Synthesis of Lactones 20 and 33



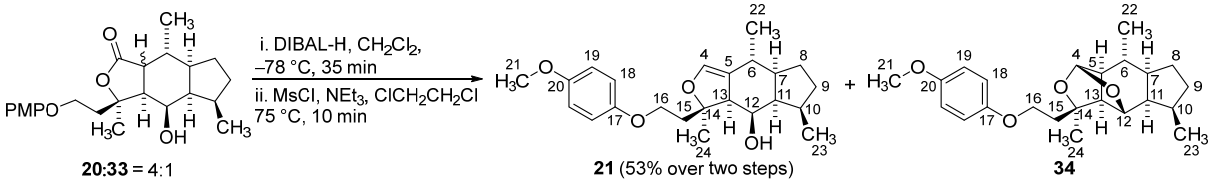
Methyllithium solution (1.6 M in diethyl ether, 40.8 mL, 65.3 mmol, 8.00 equiv) was added to an ice-cooled suspension of copper iodide (6.22 g, 32.6 mmol, 4.00 equiv) in diethyl ether (110 mL). After 30 min, the colourless, slightly cloudy mixture was cooled to −45 °C. A solution of unsaturated lactone **5** (3.04 g, 8.16 mmol, 1 equiv) in diethyl ether (80 mL) was transferred via cannula to the flask containing lithium dimethylcuprate. The transfer was quantitated with diethyl ether (2 x 15 mL). The resulting yellow mixture was allowed to warm to −5 °C over a period of 2 h, and was diluted with saturated aqueous ammonium chloride solution (300 mL) and dichloromethane (100 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (35% ethyl acetate in hexanes) to provide an inconsequential mixture of kinetic and thermodynamic lactone epimers **20** and **33** (**20**:**33** = 4:1) as a yellowish foam (2.40 g, 76%).[7] Analytically pure samples of both lactones **20** and **33** were obtained by careful purification of the epimer mixture by flash-column chromatography (20% ethyl acetate in hexanes).

Kinetic lactone 20: **TLC** (20% ethyl acetate in hexanes): R_f = 0.22 (CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89–6.79 (m, 4H, 18-H, 19-H), 4.41–4.36 (m, 1H, 12-H), 4.14–4.06 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 3.41 (dd, $^3J_{5/13}$ = 14.3 Hz, $^3J_{5/6}$ = 4.9 Hz, 1H, 5-H), 2.58–2.55 (m, 1H, 12-OH), 2.55–2.50 (m, 1H, 15-H_A), 2.41–2.35 (m, 1H, 6-H), 2.24–2.15 (m, 1H, H-10), 2.14–2.10 (m, 1H, 15-H_B), 2.08 (d, $^3J_{13/5}$ = 14.3, 1H, 13-H), 1.95–1.89 (m, 1H, 7-H), 1.89–1.82 (m, 1H, 9-H_A), 1.78–1.70 (m, 3H, 11-H, 8-H), 1.54 (s, 3H, 24-H), 1.47–1.39 (m, 1H, 9-H_B), 1.22 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H), 1.03 (d, $^3J_{22/6}$ = 7.1 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.59 (C-4), 154.43 (C-20), 152.19 (C-17), 115.29 (C-18, C-19), 114.93 (C-18, C-19), 86.29 (C-14), 66.73 (C-12), 65.05 (C-16), 55.87 (C-21), 49.93 (C-13), 47.87 (C-7), 45.37 (C-11), 37.21 (C-10), 36.77 (C-5), 34.67 (C-15), 32.13 (C-9), 30.34 (C-8), 29.46 (C-6), 25.46 (C-24), 16.02 (C-22), 15.72 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3507 (br), 2932 (m), 1747 (s), 1508 (s), 1456 (w), 1382 (w), 1316 (w), 1229 (s), 1034 (m), cm^{-1}. **HRMS** (ESI): calcd for $(C_{23}H_{32}O_5Na)^+$: 411.21474, found: 411.21400. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −12.6 (c = 0.14, CH_2Cl_2).

Thermodynamic lactone 33: **TLC** (30% ethyl acetate in hexanes): R_f = 0.38 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (s, 4H, 18-H, 19-H), 4.47–4.44 (m, 1H, 12-H), 4.24–4.12 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.60–2.49 (m, 2H, 5-H, 15-H_A), 2.31 (dt, $^2J_{15B/15A}$ = 14.1 Hz, $^3J_{15B/16}$ = 7.7 Hz, 1H, 15-H_B), 2.15–2.06 (m, 1H, 10-H), 2.06–2.01 (m, 1H, 13-H), 2.01–1.92 (m, 1H, 6-H), 1.90–1.80 (m, 2H, 7-H, 11-H), 1.78–1.68 (m, 1H, 8-H_A), 1.68–1.53 (m, 2H, 8-H_B, 9-H_A), 1.41 (s, 3H, 24-H), 1.35–1.28 (m, 1H, 9-H_B), 1.29–1.26 (m, 1H, 12-OH), 1.25 (d, $^3J_{22/6}$ = 6.2 Hz, 3H, 22-H), 1.17 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.73 (C-4), 154.07 (C-20), 152.81 (C-17), 115.41 (C-18, C-19), 114.85 (C-18, C-19), 84.06 (C-14), 68.34 (C-12), 64.79 (C-16), 55.88 (C-21), 50.12 (C-13), 46.08 (C-11), 44.12 (C-5), 43.28 (C-7), 38.56 (C-10), 35.01 (C-15), 34.06 (C-9), 33.60 (C-6), 31.06 (C-8), 25.97 (C-24), 22.51 (C-22), 15.67 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3517 (br), 2936 (m), 1758 (s), 1508 (s), 1463 (w), 1230 (s), 1180 (w), 1038 (w) cm^{-1}. **HRMS** (EI): calcd for $(C_{23}H_{32}O_6)^+$: 388.2250, found: 388.2244. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.6 (c = 0.22, CH_2Cl_2).

[7] The analogous reaction conducted on smaller scale (~1.0 mmol) reproducibly afforded the mixture of lactone epimers **20** and **33** in 92% yield.

Synthesis of Enol Ether 21

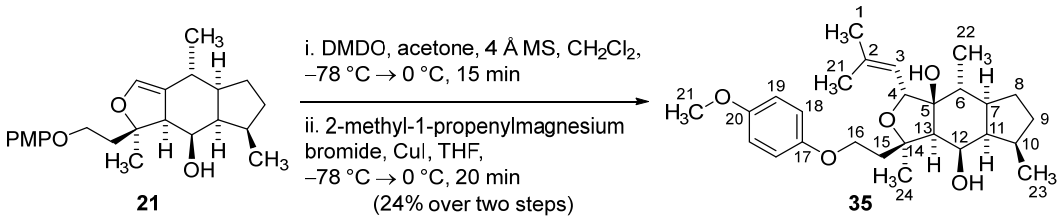


Diisobutylaluminium hydride (1 M solution in dichloromethane, 5.15 mL, 5.15 mmol, 4.00 equiv) was added dropwise to a solution of lactone epimers **20** and **33** (**20**:**33** = 4:1, 500 mg, 1.29 mmol, 1 equiv) in dichloromethane (20 mL) at −78 °C. After 20 min, methanol (5 mL) followed by 1 M aqueous hydrochloric acid solution (10 mL) were added at −78 °C, and the mixture was then warmed to 23 °C and poured onto saturated aqueous ammonium chloride solution (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 25 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide the corresponding lactols as a colourless foam which were used in the next step without further purification. A solution of the crude lactols in 1,2-dichloroethane (35 mL) was treated with methanesulfonyl chloride (347 µL, 4.48 mmol, 3.50 equiv) at 23 °C. After 3 min, the reaction flask was immersed in a preheated oil bath (75 °C) and after further 3 min, triethylamine (1.34 mL, 9.60 mmol, 7.50 equiv) was added dropwise to give a yellow mixture. After 3 min, the flask was lifted out of the oil bath and the mixture was allowed to cool to 23 °C. After 5 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (25 mL) and ether (15 mL). The layers were separated, the aqueous layer was extracted with ether (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes, triethylamine pretreated silica gel) to provide enol ether **21** as a colourless oil (253 mg, 53% over two steps) together with some acetal **34** (not quantitatively isolated) by-product. *Note: Enol ether **21** is an acid- and moisture sensitive compound and, for best results, should be freshly prepared immediately prior to use in the next reaction*.

Enol ether 21: **TLC** (10% ethyl acetate in hexanes): R_f = 0.31 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87–6.79 (m, 4H. 18-H, 19-H), 6.25 (d, $^4J_{4/13}$ = 1.4 Hz, 1H, 4-H), 4.18–4.04 (m, 3H, 12-H, 16-H), 3.77 (s, 3H, 21-H), 2.66–2.55 (m, 1H, 15-H_A), 2.49 (q, $^3J_{6/22}$ = 7.1 Hz, 1H, 6-H), 2.44–2.42 (m, 1H, 13-H), 2.38 (app dt, $^2J_{15B/15A}$ = 14.6 Hz, $^3J_{15B/16}$ = 7.6 Hz, 1H, 15-H_B), 2.15–2.03 (m, 1H, 10-H), 1.98–1.87 (m, 1H, 7-H), 1.87–1.73 (m, 2H, 8-H_A, 9-H_A), 1.73–1.67 (m, 1H, 11-H), 1.55–1.43 (m, 1H, 9-H_B), 1.43–1.34 (m, 2H, 8-H_B, 12-OH), 1.31 (s, 3H, 24-H), 1.17 (d, $^3J_{22/6}$ = 7.1 Hz, 3H, 22-H), 1.14 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.82 (C-20), 153.22 (C-17), 137.34 (C-4), 115.45 (C-18, C-19), 114.76 (C-18, C-19), 114.66 (C-5), 86.45 (C-14), 68.51 (C-12), 65.33 (C-16), 55.89 (C-21), 53.55 (C-13), 48.04 (C-7), 45.11 (C-11), 38.02 (C-10), 33.23 (C-15), 32.18 (2C, C-8, C-9), 30.20 (C-6), 25.71 (C-24), 22.29 (C-22), 15.35 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (m), 2869 (m), 1660 (w), 1506 (s), 1464 (w), 1372 (w), 1264 (m), 1228 (s), 1037 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{23}H_{32}O_4)^+$: 372.23006, found: 372.2303. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -45.3 (c = 0.30, CH_2Cl_2).

Acetal 34: **TLC** (30% ethyl acetate in hexanes): R_f = 0.51 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87–6.77 (m, 4H, 18-H, 19-H), 4.95 (s, 1H, 4-H), 4.54 (s, 1H, 12-H), 4.12–3.97 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.38–2.28 (m, 1H, 15-H_A), 2.28–2.24 (m, 1H, 5-H), 2.14–2.06 (m, 2H, 13-H, 15-H_B), 2.06–1.99 (m, 1H, 10-H), 1.83–1.69 (m, 4H, 6-H, 7-H, 8-H_A, 11-H), 1.68–1.57 (m, 1H, 9-H_A), 1.48–1.39 (m, 1H, 8-H_B), 1.39–1.30 (m, 1H, 9-H_B), 1.29 (s, 3H, 24-H), 1.10 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H), 1.07 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.92 (C-20), 153.04 (C-17), 115.24 (C-18, C-19), 114.85 (C-18, C-19), 102.77 (C-4), 81.40 (C-14), 75.63 (C-12), 65.48 (C-16), 55.92 (C-21), 49.98 (C-5), 47.37 (C-13), 45.14 (C-11), 43.44 (C-7), 38.33 (C-10), 37.10 (C-15), 33.45 (C-9), 33.31 (C-8), 32.19 (C-6), 24.65 (C-24), 23.72 (C-22), 15.81 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2949 (m), 2870 (m), 1507 (s), 1477 (m), 1462 (m), 1375 (w), 1229 (s), 1180 (w), 1106 (w), 1041 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{23}H_{32}O_4Na)^+$: 395.21983, found: 395.21889. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +41.2 (c = 0.23, CH_2Cl_2).

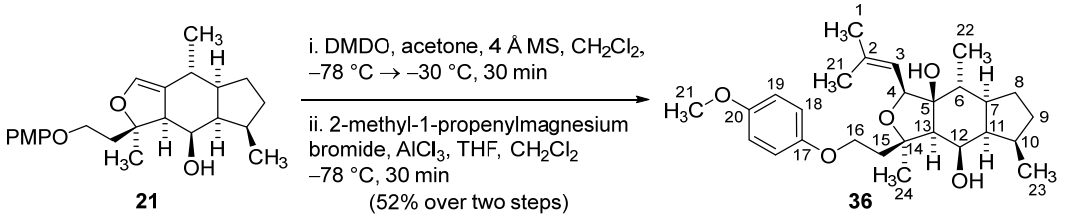
Synthesis of Diol 35 (4-epi)



A round-bottomed flask was charged with 4 Å molecular sieves (50 mg) and then was flame-dried in vacuo for 3 min. After cooling to 23 °C, a solution of enol ether **21** (7.00 mg, 18.8 µmol, 1 equiv) in dichloromethane (1 mL) was added. The resulting suspension was cooled to −78 °C and then was treated with dimethyldioxirane solution (0.040 M in acetone, 0.75 mL, 30.1 µmol, 1.60 equiv). After 3 min, the mixture was warmed to 0 °C and stirring was continued for 12 min. The mixture was concentrated at 23 °C and the residue was dried in vacuo. In a separate flask, a suspension of copper iodide (11.5 mg, 60.2 µmol, 3.2 equiv) in ether (0.5 mL) was treated with 2-methyl-1-propenylmagnesium bromide solution (0.5 M in tetrahydrofuran, 263 µL, 132 µmol, 7.00 equiv) at −78 °C. After 30 min, a solution of the crude epoxide in tetrahydrofuran (0.8 mL) was added dropwise to the reaction mixture. The transfer was quantitated with tetrahydrofuran (2 x 0.2 mL). After 5 min, the mixture was warmed to 0 °C and stirring was continued for 15 min. The mixture was diluted with saturated aqueous ammonium chloride solution (5 mL) and dichloromethane (3 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in pentane) to provide diol **35**, exhibiting the undesired stereochemistry at C4, as a yellowish residue (2.0 mg, 24%).

TLC (30% ethyl acetate in hexanes): R_f = 0.48 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88–6.80 (m, 4H, 18-H, 19-H), 5.13 (d, $^3J_{3/4}$ = 9.6 Hz, 1H, 3-H), 4.73 (d, $^3J_{4/3}$ = 9.6 Hz, 1H, 4-H), 4.48–4.43 (m, 1H, 12-H), 4.38 (s, 1H, 5-OH), 4.18–4.11 (m, 2H, 16-H), 3.95 (d, $^3J_{12OH/12}$ = 7.0 Hz, 1H, 12-OH), 3.77 (s, 3H, 21-H), 2.66 (app dt, $^2J_{15A/15B}$ = 15.1 Hz, $^3J_{15A/16}$ = 7.7 Hz, 1H, 15-H_A), 2.42 (app dt, $^2J_{15B/15A}$ = 15.1 Hz, $^3J_{15B/16}$ = 5.4 Hz, 1H, 15-H_B), 2.25 (q, $^3J_{6/22}$ = 7.2 Hz, 1H, 6-H), 2.20–2.05 (m, 2H, 8-H_A, 10-H), 1.99–1.75 (m, 5H, 7-H, 8-H_B, 9-H_A, 11-H, 13-H), 1.75–1.71 (m, 6H, 1-H, 21-H), 1.64–1.50 (m, 1H, 9-H_B), 1.44 (s, 3H, 24-H), 1.23 (d, $^3J_{23/10}$ = 6.9 Hz, 3H, 23-H), 1.04 (d, $^3J_{22/6}$ = 7.2 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.06 (C-20), 152.75 (C-17), 133.78 (C-2), 125.64 (C-3), 115.38 (C-18, C-19), 114.79 (C-18, C-19), 88.82 (C-5), 87.02 (C-4), 81.51 (C-14), 69.89 (C-12), 65.91 (C-16), 55.88 (C-21), 52.31 (C-13), 50.60 (C-7), 46.09 (C-11), 39.31 (C-6), 37.82 (C-15), 37.47 (C-10), 32.42 (C-9), 31.38 (C-8), 28.07 (C-24), 26.18 (C-1), 20.68 (C-22), 18.52 (C-21), 15.23 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3386 (br), 2929 (m), 1507 (s), 1463 (m), 1375 (m), 1230 (s), 1180 (w), 1039 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{27}H_{40}O_5Na)^+$: 467.27734, found: 467.27667. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +91.8 (c = 0.12, CH_2Cl_2).

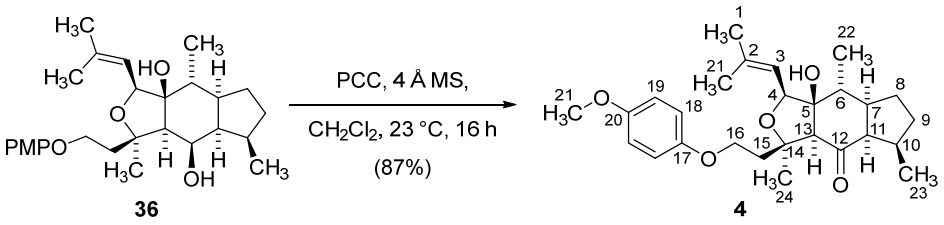
Synthesis of Diol 36



A round-bottomed flask was charged with 4 Å molecular sieves (6 g) and then was flame-dried in vacuo for 4 min. After cooling to 23 °C, a solution of enol ether **21** (250 mg, 0.67 mmol, 1 equiv) in dichloromethane (12 mL) was added. The resulting suspension was cooled to −78 °C and then was treated with a freshly prepared dimethyldioxirane solution (0.036 M in acetone, 26.1 mL, 0.94 mmol, 1.40 equiv). After 10 min, the mixture was warmed to −30 °C and stirring was continued for 20 min. The mixture was concentrated at 23 °C and the residue was dried in vacuo. In a separate flask, an ice-cooled suspension of aluminium trichloride (752 mg, 5.64 mmol, 8.40 equiv) in tetrahydrofuran (4 mL) was treated with 2-methyl-1-propenylmagnesium bromide solution (0.5 M in tetrahydrofuran, 33.8 mL, 16.9 mmol, 25.2 equiv). After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 2 h, the so-obtained organoaluminum reagent was cooled to −78 °C and a solution of the crude epoxide in dichloromethane (20 mL) was added dropwise. The transfer was quantitated with dichloromethane (3 x 4 mL). After 30 min, the cooling bath was removed and the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL), aqueous 1 M hydrogen chloride solution (10 mL) and dichloromethane (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in pentane) to provide diol **36** as a colourless residue (155 mg, 52%).

TLC (30% ethyl acetate in hexanes): R_f = 0.41 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90–6.75 (m, 4H, 18-H, 19-H), 5.33 (d, $^3J_{3/4}$ = 8.9 Hz, 1H, 3-H), 4.38–4.30 (m, 2H, 4-H, 12-H), 4.15 (app t, $^3J_{16/15}$ = 6.5 Hz, 2H, 16-H), 3.99 (d, $^3J_{12OH/12}$ = 8.5 Hz, 1H, 12-OH), 3.76 (s, 3H, 21-H), 3.40 (s, 1H, 5-OH), 2.55–2.37 (m, 2H, 15-H), 2.24–2.11 (m, 1H, 10-H), 2.10–1.99 (m, 2H, 6-H, 8-H_A), 1.99–1.82 (m, 2H, 7-H, 8-H_B), 1.82–1.66 (m, 9H, 1-H, 9-H_A, 11-H, 13-H, 21-H), 1.65–1.52 (m, 1H, 9-H_B), 1.38 (s, 3H, 24-H), 1.22 (d, $^3J_{23/10}$ = 7.0 Hz, 3H, 23-H), 0.97 (d, $^3J_{22/6}$ = 7.3 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.89 (C-20), 152.93 (C-17), 140.39 (C-2), 118.17 (C-3), 115.46 (C-18, C-19), 114.72 (C-18, C-19), 86.12 (C-5), 81.03 (C-14), 77.92 (C-4), 69.06 (C-12), 65.58 (C-16), 55.87 (C-21), 53.34 (C-13), 48.18 (C-7), 47.08 (C-11), 39.01 (C-15), 37.68 (C-10), 37.31 (C-6), 32.03 (C-8), 31.83 (C-9), 27.46 (C-24), 26.65 (C-1), 19.16 (C-22), 19.09 (C-21), 15.19 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (br), 2929 (m), 2872 (m), 1507 (s), 1454 (m), 1376 (w), 1231 (s), 1086 (w), 1039 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{27}H_{40}O_5Na)^+$: 467.27734, found: 467.27690. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.1 (c = 0.22, CH_2Cl_2).

Synthesis of Ketone 4

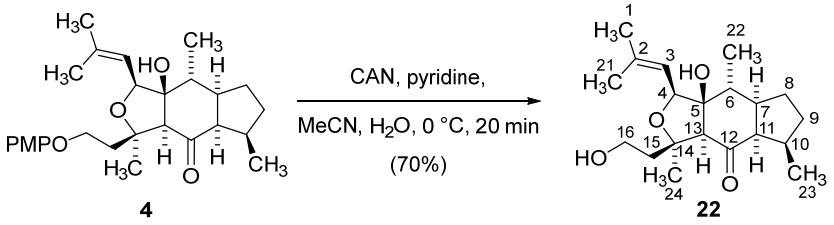


36 **4**

To a solution of diol **36** (147 mg, 0.33 mmol, 1 equiv) in dichloromethane (4.5 mL) were added crushed 4 Å molecular sieves (0.5 g), followed by pyridinium chlorochromate (214 mg, 0.99 mmol, 3.00 equiv) at 23 °C. After 16 h, the mixture was concentrated to half its volume and then was directly loaded onto a short pad of silica gel (5 cm). The product was eluted with 25% ethyl acetate in pentane to provide ketone **4** as a colourless, highly viscous oil (127 mg, 87%).

TLC (30% ethyl acetate in hexanes): R_f = 0.59 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89–6.76 (m, 4H, 18-H, 19-H), 5.28–5.19 (m, 1H, 3-H), 4.46 (d, $^3J_{4/3}$ = 9.0 Hz, 1H, 4-H), 4.15 (t, $^3J_{16/15}$ = 6.7 Hz, 2H, 16-H), 3.75 (s, 3H, 21-H), 2.78 (s, 1H, 13-H), 2.71 (app t, $^3J_{11/7}$ = $^3J_{11/10}$ = 8.5 Hz, 1H, 11-H), 2.58 (s, 1H, 5-OH), 2.57–2.39 (m, 2H, 15-H), 2.34–2.19 (m, 2H, 7-H, 10-H), 2.04–1.79 (m, 3H, 6-H, 8-H), 1.78 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.75 (d, $^4J_{21/3}$ = 1.4 Hz, 3, 21-H), 1.68–1.55 (m, 1H, 9-H_A), 1.55–1.44 (m, 1H, 9-H_B), 1.41 (s, 3H, 24-H), 1.18 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H), 1.12 (d, $^3J_{22/6}$ = 7.3 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.29 (C-12), 153.75 (C-20), 153.13 (C-17), 140.79 (C-2), 118.04 (C-3), 115.67 (C-18, C-19), 114.66 (C-18, C-19), 88.37 (C-5), 80.25 (C-14), 76.93 (C-4), 65.67 (C-16), 62.89 (C-13), 55.87 (C-21), 54.37 (C-11), 50.69 (C-7), 37.99 (C-6), 37.79 (C-15), 37.48 (C-10), 32.62 (C-9), 32.18 (C-8), 29.05 (C-24), 26.57 (C-1), 19.15 (C-21), 18.76 (C-22), 16.84 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3501 (br), 2925 (s), 2872 (m), 1720 (m), 1507 (s), 1462 (m), 1376 (m), 1231 (s), 1179 (w), 1038 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{27}H_{38}O_5Na)^+$: 465.26169, found: 465.26100. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +36.0 (c = 0.19, CH_2Cl_2).

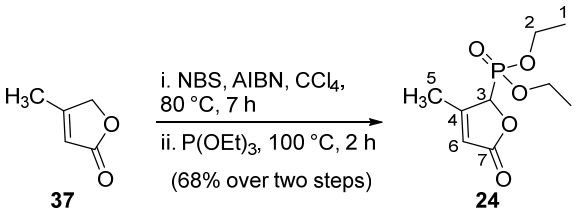
Synthesis of Alcohol 22



An ice-cooled solution of ketone **4** (90.0 mg, 0.20 mmol, 1 equiv) and pyridine (34.5 µl, 0.43 mmol, 2.10 equiv) in a mixture of acetonitrile–water (4:1, 5 mL) was treated with ammonium cerium(IV) nitrate (234 mg, 0.43 mmol, 2.10 equiv). After 20 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (15 mL), water (10 mL) and ethyl acetate (15 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 x 15 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in hexanes) to provide alcohol **22** as a faintly yellow oil (48 mg, 70%).

TLC (30% ethyl acetate in hexanes): R_f = 0.24 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.35–5.29 (m, 1H, 3-H), 4.45 (d, $^3J_{4/3}$ = 9.0 Hz, 1H, 4-H), 4.04–3.94 (m, 1H, 16-H_A), 3.81–3.71 (m, 1H, 16-H_B), 3.62 (br s, 1H, OH), 2.98 (br s, 1H, OH), 2.84 (s, 1H, 13-H), 2.72 (app t, $^3J_{11/7}$ = $^3J_{11/10}$ = 8.7 Hz, 1H, 11-H), 2.52 (ddd, $^2J_{15A/15B}$ = 15.4 Hz, $^3J_{15A/16A}$ = 9.1 Hz, $^3J_{15A/16B}$ = 3.7 Hz, 1H, 15-H_A), 2.36–2.19 (m, 2H, 7-H, 10-H), 2.07 (ddd, $^2J_{15B/15A}$ = 15.4 Hz, $^3J_{15B/16B}$ = 6.0 Hz, $^3J_{15B/16A}$ = 3.1 Hz, 1H, 15-H_B), 2.02–1.79 (m, 3H, 6-H, 8-H), 1.79 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.76 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.68–1.55 (m, 1H, 9-H_A), 1.55–1.44 (m, 1H, 9-H_B), 1.39 (s, 3H, 23-H), 1.16 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H), 1.10 (d, $^3J_{22/6}$ = 7.3 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.49 (C-12), 141.34 (C-2), 117.58 (C-3), 88.10 (C-5), 81.57 (C-14), 77.36 (C-4), 63.02 (C-13), 60.37 (C-16), 54.78 (C-11), 50.63 (C-7), 39.32 (C-15), 38.46 (C-6), 37.36 (C-10), 32.77 (C-9), 32.37 (C-8), 29.76 (C-24), 26.47 (C-1), 19.08 (C-21), 18.76 (C-22), 16.73 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3383 (br), 2927 (s), 2872 (s), 1705 (s), 1451 (m), 1376 (m), 1109 (m), 1047 (m), 975 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{32}O_4Na)^+$: 359.21983, found: 359.21898. $[\alpha]_D^{20}$ = +29.1 (c = 0.09, CH_2Cl_2).

Synthesis of Phosphonate 24[8]

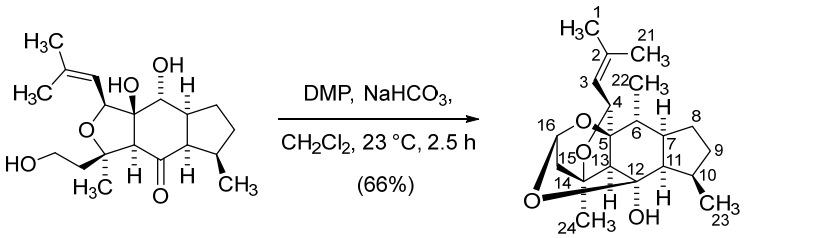


A solution of butenolide **37**[9] (0.80 g, 8.15 mmol, 1 equiv) in carbon tetrachloride (35 mL) was treated with *N*-bromosuccinimide (1.60 g, 8.97 mmol, 1.10 equiv) and 2,2'-azobis(2-methylpropionitrile) (13.4 mg, 0.08 mmol, 0.01 equiv) at 23 °C. The resulting suspension was heated to 80 °C. After 7 h, the faintly orange suspension was allowed to cool to 23 °C and then was filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford a bright orange oil. This crude bromo butenolide was treated with triethylphosphite (1.78 mL, 10.6 mmol, 1.30 equiv) at 23 °C and the resulting dark red mixture was heated to 100 °C. After 2 h, the mixture was allowed to cool to 23 °C and then was directly loaded onto a short pad of silica gel (10 cm). The product was eluted with 5% methanol in dichloromethane to provide phosphonate **24** as a yellow oil (1.30 g, 68% over two steps).
TLC (5% methanol in dichloromethane): R_f = 0.34 ($KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.95–5.91 (m, 1H, 6-H), 5.08 (d, $^2J_{3/P}$ = 15.6 Hz, 1H, 3-H), 4.32–4.08 (m, 4H, 2-H), 2.26 (s, 3H, 5-H), 1.42–1.25 (m, 6H, 1-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.49 (C-7), 164.50 (d, $^2J_{4/P}$ = 4.5 Hz, C-4), 117.84 (d, $^3J_{6/P}$ = 7.2 Hz, C-6), 80.40 (d, $^1J_{3/P}$ = 161 Hz, C-3), 64.48 (d, $^2J_{2/P}$ = 7.0 Hz, C-2), 63.97 (d, $^2J_{2'/P}$ = 7.0 Hz, C-2'), 16.54 (d, $^3J_{1/P}$ = 1.7 Hz, C-1), 16.49 d, $^3J_{1'/P}$ = 1.7 Hz, C-1'), 15.09 (C-5). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 12.09. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2986 (m), 2912 (w), 1784 (s), 1756 (s) 1638 (m), 1443 (w), 1164 (m) 1014 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_9H_{15}O_5P)^+$: 234.06571, found: 234.0951.

[8] Although phosphonate **24** has been described in the literature, neither an experimental procedure nor any analytical data have been reported, see: a) D. C. Harrowven, J. D. Wilden, M. J. Tyte, M. B. Hursthouse, S. J. Coles, *Tetrahedron Letters* **2001**, *42*, 6, 1193. b) D. C. Harrowven, M. J. Tyte, *Tetrahedron Letters* **2001**, *42*, 49, 8709. c) D. C. Harrowven, M. J. Tyte, *Tetrahedron Letters* **2004**, *45*, 10, 2089.

[9] Prepared by the known reduction of citraconic anhydride, see: A. W. Johnson, G. Gowda, A. Hassanali, S. Knox, Z. Monaco, Z. Razavi and G. Rosebery, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1734.

Synthesis of (+)-11-Deoxynorleucosceptroid A (23)

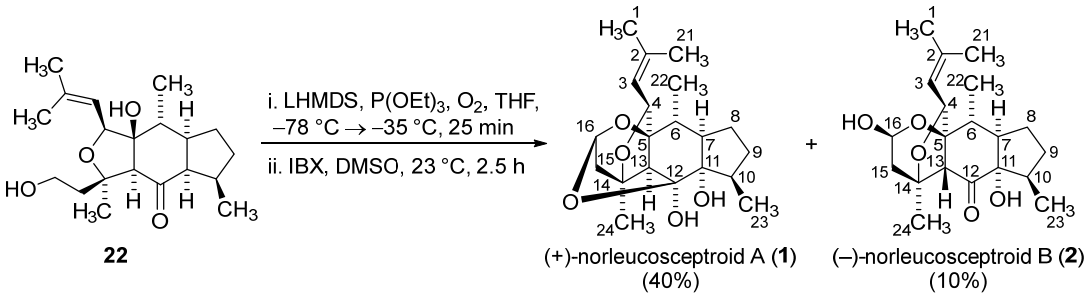


22 (+)-11-deoxynorleucosceptroid A (**23**)

To a solution of **22** (1.06 mg, 3.15 µmol, 1 equiv) in dichloromethane (0.7 mL) was added in sequence sodium bicarbonate (1.16 mg, 13.9 µmol, 4.40 equiv) and Dess-Martin periodinane (2.94 mg, 6.93 µmol, 2.20 equiv) at 23 °C. After 2.5 h, the mixture was diluted with saturated aqueous sodium thiosulfate solution (3 mL), saturated aqueous sodium bicarbonate solution (3 mL) and dichloromethane (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in pentane) to provide (+)-11-deoxynorleucosceptroid A (**23**) as a colourless solid (0.7 mg, 66%).

TLC (30% ethyl acetate in hexanes): R_f = 0.41 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33–5.28 (m, 1H, 3-H), 5.13 (app t, $^3J_{16/15}$ = 2.1 Hz, 1H, 16-H), 4.49 (d, $^3J_{4/3}$ = 9.6 Hz, 1H, 4-H), 2.88 (s, 1H, 12-OH), 2.38–2.26 (m, 1H, 8-H_A), 2.26–2.16 (m, 1H, 10-H), 2.11 (s, 1H, 13-H), 2.10–2.04 (m, 1H, 7-H), 2.04–2.01 (m, 2H, 15-H), 1.98–1.90 (m, 2H, 6-H, 11-H), 1.77 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.79–1.74 (m, 2H, 8-H_B, 9-H_A), 1.73 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.71–1.61 (m, 1H, 9-H_B), 1.55 (s, 3H, 24-H), 1.35 (d, $^3J_{23/10}$ = 7.2 Hz, 3H, 23-H), 0.99 (d, $^3J_{22/6}$ = 7.5 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.14 (C-2), 119.75 (C-3), 98.98 (C-12), 90.96 (C-16), 87.43 (C-5), 77.37 (C-14), 76.92 (C-4), 50.84 (C-7), 49.56 (C-11), 46.82 (C-13), 45.48 (C-15), 37.84 (C-10), 33.45 (C-6), 32.55 (C-9), 30.64 (C-8), 27.14 (C-24), 26.52 (C-1), 18.72 (C-21), 18.38 (C-22), 18.07 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3482 (br), 2930 (s), 2872 (m), 1450 (w), 1377 (m), 1343 (w), 1234 (w), 1158 (m), 1107 (s), 1089 (m), 1000 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{20}H_{30}O_4)^+$: 334.2144, found: 334.2148. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +87.4 (c = 0.04, CH_2Cl_2).

Synthesis of (+)-Norleucosceptroid A (1) and (–)-Norleucosceptroid B (2)



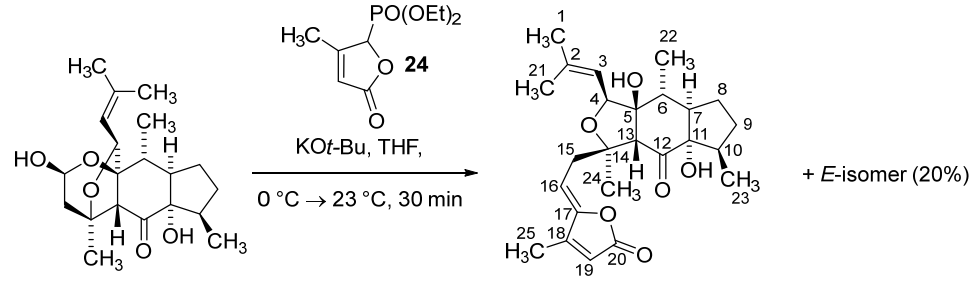
A solution of **22** (46.0 mg, 0.14 mmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with lithium bis(trimethylsilyl)amide solution (1 M in THF, 0.96 mL, 0.96 mmol, 7.0 equiv) at −78 °C. After 5 min, the mixture was warmed to −35 °C. After 55 min, the mixture was cooled to −78 °C, triethyl phosphite (0.14 mL, 0.82 mmol, 6.0 equiv) was added and the argon atmosphere was exchanged for oxygen. After 5 min, the mixture was warmed to −35 °C and stirring was continued for 15 min. The mixture was diluted with saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (15 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude residue was dissolved in dimethyl sulfoxide (0.7 mL) and 2-iodoxybenzoic acid (38.4 mg, 0.14 mmol, 1 equiv) was added at 23 °C. After 2.5 h, the mixture was diluted with water (4 mL) and dichloromethane (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% → 35% ethyl acetate in hexanes) to provide (+)-norleucosceptroid A (**1**) as a colourless solid (18.9 mg, 40% over two steps) and (–)-norleucosceptroid B (**2**) as a colourless oil (4.6 mg, 10% over two steps). For comparison of the analytical data of synthetic (+)-**1** with the reported values for natural (–)-**1**,[10] a small sample was further purified by reversed-phase semi-preparative HPLC using methanol–water (65:35) as eluent (flow rate: 3 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 210 nm; retention time: 17.8 min for (+)-norleucosceptroid A (**1**). For comparison of the analytical data of synthetic (–)-**2** with the reported values for natural (+)-**2**,[10] a small sample was further purified by reversed-phase semi-preparative HPLC using methanol–water (55:45) as eluent (flow rate: 3 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 210 nm; retention time: 12.5 min for (–)-norleucosceptroid B (**2**).

(+)-Norleucosceptroid A (1): **TLC** (40% ethyl acetate in hexanes): R_f = 0.42 (CAM). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 5.29–5.23 (m, 1H, 3-H), 5.09 (d, $^3J_{16/15A}$ = 3.5 Hz, 1H, 16-H), 4.46 (d, $^3J_{4/3}$ = 9.4 Hz, 1H, 4-H), 3.93 (br s, 1H, 12-OH), 3.58 (br s, 1H, 11-OH), 2.60 (d, $^4J_{13/15A}$ = 1.2 Hz, 1H, 13-H), 2.23–2.09 (m, 3H, 7-H, 8-H$_B$, 10-H), 2.02 (d, $^2J_{15B/15A}$ = 13.5 Hz, 1H, 15-H$_B$), 1.89 (ddd, $^2J_{15A/15B}$ = 13.5 Hz, $^3J_{15A/16}$ = 3.5 Hz, $^4J_{15A/13}$ = 1.2 Hz, 1H, 15-H$_A$), 1.86–1.71 (m, 3H, 6-H, 8-H$_A$, 9-H$_B$), 1.72 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.69 (d, $^4J_{21/3}$ = 1.3 Hz, 3H, 21-H), 1.68–1.57 (m, 1H, 9-H$_A$), 1.46 (s, 3H, 24-H), 1.20 (d, $^3J_{23/10}$ = 7.2 Hz, 3H, 23-H), 1.05 (d, $J_{22/6}$ = 7.6 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 137.29 (C-2), 121.98 (C-3), 99.38 (C-12), 91.46 (C-16), 88.33 (C-5), 83.10 (C-11), 77.36 (C-14), 77.17(C-4), 55.88 (C-7), 47.52 (C-10), 46.26 (C-15), 44.51 (C-13), 34.42 (C-6), 31.37 (C-9), 29.54 (C-8), 27.45 (C-24), 26.28 (C-1), 18.98 (C-22), 18.54 (C-21), 15.84 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3448 (br), 2968 (s), 2932 (s), 2877 (m), 1455 (m), 1378 (m), 1263 (m), 1111 (s), 1004 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{29}O_5)^-$: 349.20205, found: 349.20155. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +51.4° (c = 0.29, MeOH).

[10] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768.

(–)-Norleucosceptroid B (2): **TLC** (5% methanol in dichloromethane): R_f = 0.20 (CAM). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 5.54–5.51 (m, 1H, 3-H), 5.45 (app td, $^3J_{16/16OH}$ = 6.6 Hz, $^3J_{16/15}$ = 5.0 Hz, 1H, 16-H), 5.37 (d, $^3J_{16OH/16}$ = 6.6 Hz, 1H, 16-OH), 4.50 (d, $^3J_{4/3}$ = 8.8 Hz, 1H, 4-H), 4.21 (s, 1H, 11-OH), 2.65 (app d, J = 1.9 Hz, 1H), 2.19–2.10 (m, 3H, 8-H_B, 9-H_B, 10-H), 2.08–2.06 (m, 1H, 6-H), 1.95–1.90 (m, 1H, 15-H_B), 1.84–1.78 (m, 1H, 7-H), 1.74 (d, $^4J_{21/3}$ = 1.2 Hz, 3H, 21-H), 1.75–1.69 (m, 2H, 8-H_A, 15-H_A), 1.66 (d, $^4J_{1/3}$ = 1.5 Hz, 3H, 1-H), 1.58 (s, 3H, 24-H), 1.47–1.40 (m, 1H, 9-H_A), 0.98 (d, $J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.95 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 210.78 (C-12), 138.68 (C-2), 122.12 (C-3), 92.15 (C-16), 87.06 (C-11), 86.88 (C-5), 80.74 (C-14), 77.85 (C-4), 64.09 (C-13), 52.54 (C-7), 50.13 (C-15), 48.40 (C-10), 40.62 (C-6), 31.64 (C-9), 30.47 (C-8), 26.13 (C-21), 23.98 (C-24), 18.66 (C-1), 18.52 (C-23), 14.62 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3405 (br), 2962 (s), 2929 (s), 2877 (m), 1704 (s), 1667 (m), 1450 (s), 1378 (s), 1299 (m), 1126 (m), 1075 (s), 1029 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{29}O_5)^-$: 349.20205, found: 349.20211. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –84.4° (c = 0.32, MeOH).

Synthesis of (–)-Leucosceptroid K (3)



An ice-cooled solution of phosphonate **24** (24.1 mg, 103 µmol, 8.00 equiv) in tetrahydrofuran (0.8 mL) was treated with potassium *tert*-butoxide (11.5 mg, 103 µmol, 8.00 equiv). After 35 min, a solution of (–)-norleucosceptroid B (**2**) (4.50 mg, 12.8 µmol, 1 equiv) in tetrahydrofuran (0.4 mL) was added dropwise to the dark red mixture at 0 °C. The transfer was quantitated with tetrahydrofuran (2 x 0.2 mL). After 5 min, the cooling bath was removed and stirring was continued for 25 min. The mixture was diluted with saturated aqueous ammonium chloride solution (5 mL) and dichloromethane (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% → 35% ethyl acetate in hexanes) to provide a 3.5:1 mixture of (–)-leucosceptroid K (**3**) and the corresponding *E*-isomer as a colourless solid (5.0 mg, 90%). Further careful purification of this mixture by flash-column chromatography afforded an analytically pure sample of (–)-leucosceptroid K (**3**).
TLC (40% ethyl acetate in hexanes): R_f = 0.24 (UV/$KMnO_4$). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 6.01 (s, 1H, 19-H), 5.71 (t, $^3J_{16/15}$ = 7.6 Hz, 1H, 16-H), 5.60–5.57 (m, 1H, 3-H), 4.74 (d, $^3J_{4/3}$ = 8.9 Hz, 1H, 4-H), 4.17 (br s, 1H, 11-OH), 3.89 (br s, 1H, 5-OH), 2.82–2.74 (m, 2H, 15-H), 2.72 (s, 1H, 13-H), 2.31–2.24 (m, 1H, 10-H), 2.20 (d, $^4J_{25/19}$ = 1.4 Hz, 3H, 25-H), 2.15–2.02 (m, 3H, 7-H, 8-H_B, 9-H_B), 1.83–1.76 (m, 1H, 6-H), 1.76–1.73 (m, 6H, 1-H, 21-H), 1.73–1.67 (m, 1H, 8-H_A), 1.44–1.38 (m, 1H, 9-H_A), 1.25 (s, 3H, 24-H), 0.98 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.80 (d, $^3J_{23/10}$ = 7.4 Hz, 3H, 23-H). **^{13}C NMR** (150 MHz, acetone) δ 212.40 (C-12), 169.51 (C-20), 156.20 (C-18), 152.63 (C-17), 137.17 (C-2), 122.50 (C-3), 116.61 (C-19), 109.46 (C-16), 85.62 (C-11), 84.52 (C-5), 83.35 (C-14), 77.30 (C-4), 71.70 (C-13), 50.45 (C-7), 46.25 (C-10), 42.27 (C-6), 41.63 (C-15), 31.04 (C-9), 30.62 (C-8), 26.17 (C-21), 24.32 (C-24), 18.84 (C-1), 16.99 (C-23), 14.03 (C-22), 11.72 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3474 (br), 2966 (s), 2937 (s), 2873 (m), 1749 (s), 1694 (m), 1451 (m), 1381 (m), 1286 (m), 1102 (w), 1029 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{34}O_6Na)^+$: 453.22531, found: 453.22462. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –70.4° (c = 0.13, MeOH).

6.1.2 X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[11] and refined by least-squares methods against *F*2 with SHELXL-97.[12] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

C-ring Butenolide 7

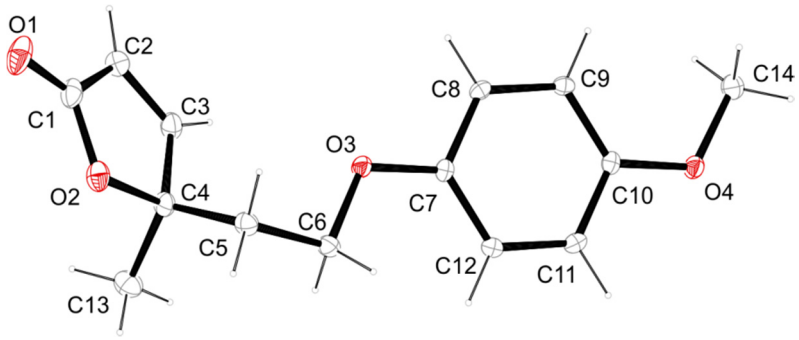
CCDC 1017065 contains the supplementary crystallographic data for C-ring butenolide **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystallographic data for C-ring butenolide **7**.

net formula	$C_{14}H_{16}O_4$
M_r/g mol^{-1}	248.274
crystal size/mm	0.120 × 0.100 × 0.020
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	monoclinic
space group	$P2_1$
a/Å	6.0811(3)
b/Å	6.9682(3)
c/Å	14.9480(7)
α/°	90
β/°	100.7163(16)
γ/°	90
V/Å^3	622.36(5)
Z	2
calc. density/g cm^{-3}	1.32488(11)
μ/mm^{-1}	0.097
absorption correction	multi-scan
transmission factor range	0.9110–0.9585
refls. measured	15617
R_{int}	0.0323
mean σ(*I*)/*I*	0.0210
θ range	3.24–26.41
observed refls.	2333
x, y (weighting scheme)	0.0361, 0.1734
hydrogen refinement	constr
Flack parameter	0.0(9)
refls in refinement	2566
parameters	165
restraints	1

[11] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[12] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.

$R(F_{obs})$	0.0321
$R_w(F^2)$	0.0793
S	1.055
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.214
min electron density/e Å^{-3}	−0.156



Major Enone 13

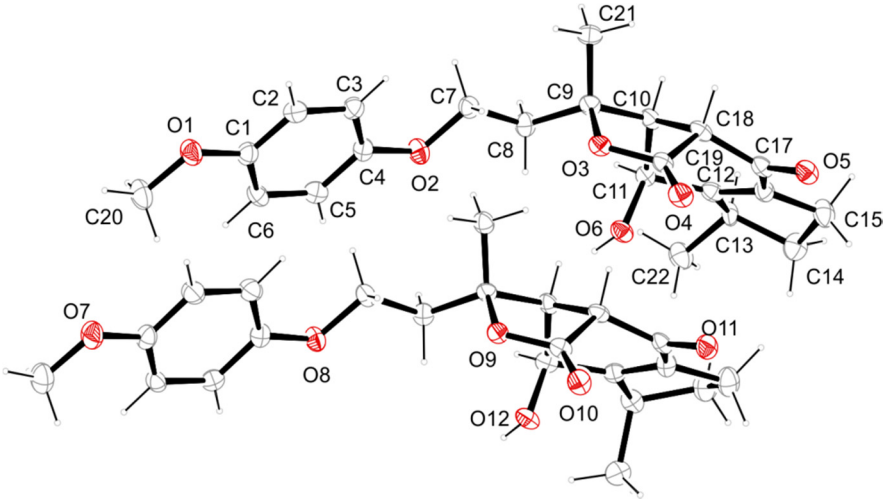
CCDC 1017064 contains the supplementary crystallographic data for major enone **13**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Crystallographic data for major enone **13**.

net formula	$C_{22}H_{26}O_6$
M_r/g mol^{-1}	386.438
crystal size/mm	0.172 × 0.141 × 0.020
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	$P1$
a/Å	7.0158(11)
b/Å	10.4409(18)
c/Å	14.195(3)
α/°	80.818(5)
β/°	87.108(4)
γ/°	70.451(4)
V/Å^3	967.3(3)
Z	2
calc. density/g cm^{-3}	1.3268(4)
μ/mm^{-1}	0.096
absorption correction	multi-scan
transmission factor range	0.8633–0.9585
refls. measured	15768
R_{int}	0.0642
mean σ(I)/I	0.0970
θ range	3.10–26.42
observed refls.	4338
x, y (weighting scheme)	0.0419, 0

hydrogen refinement	mixed
Flack parameter	0.3(8)
refls in refinement	6962
parameters	519
restraints	3
$R(F_{obs})$	0.0506
$R_w(F^2)$	0.1256
S	1.010
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.259
min electron density/e Å^{-3}	−0.223

Correct structure from synthesis, Flack parameter meaningless. C-bound H: constr, O-bound H: refall.



Lactone 19

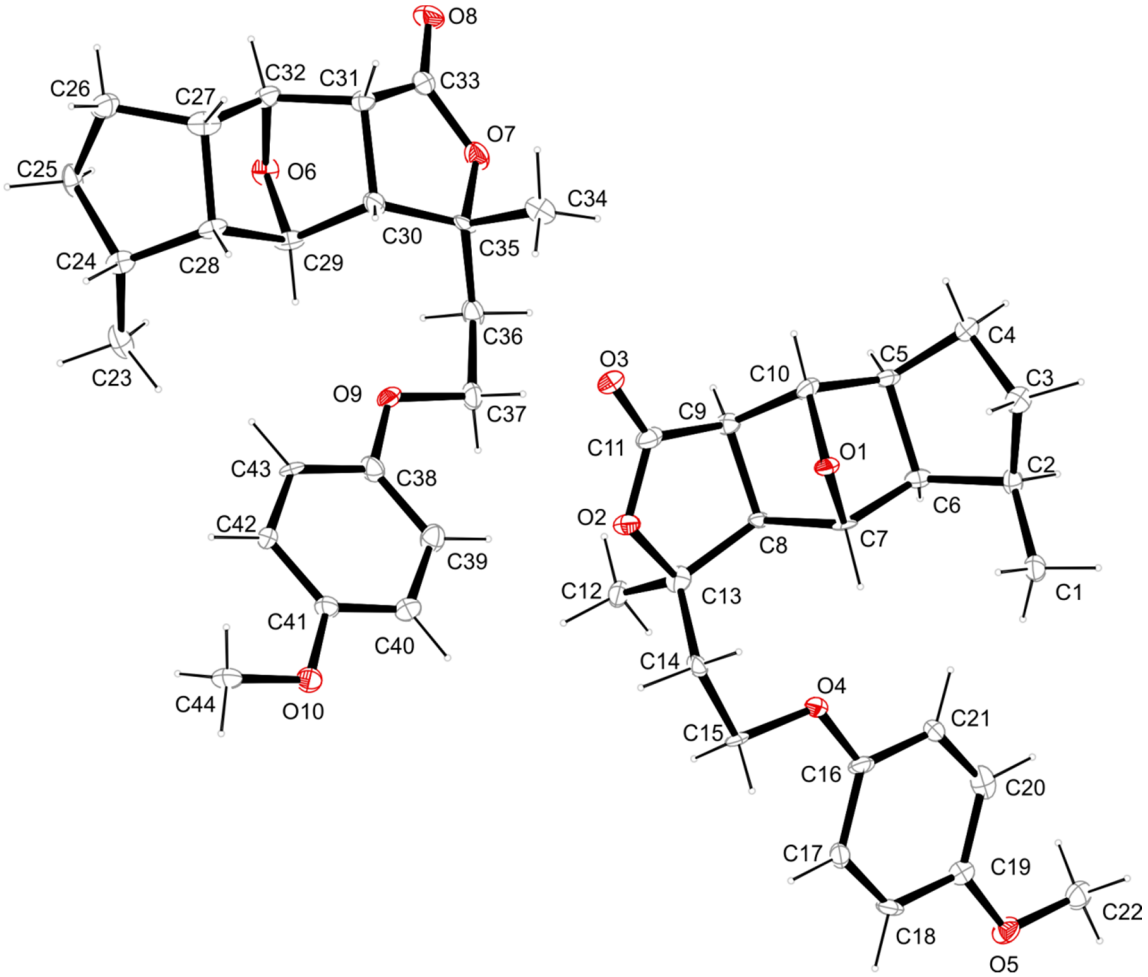
CCDC 1017066 contains the supplementary crystallographic data for lactone **19**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 3. Crystallographic data for lactone **19**.

net formula	$C_{22}H_{28}O_5$
M_r/g mol^{-1}	372.455
crystal size/mm	0.100 × 0.080 × 0.050
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	monoclinic
space group	$P2_1$
a/Å	5.1783(6)
b/Å	31.009(4)
c/Å	11.7951(14)
α/°	90
β/°	99.136(3)
γ/°	90
V/Å^3	1870.0(4)
Z	4

calc. density/g cm^{-3}	1.3230(3)
μ/mm^{-1}	0.093
absorption correction	multi-scan
transmission factor range	0.8676–0.9571
refls. measured	13323
R_{int}	0.0492
mean σ(I)/I	0.0804
θ range	3.16–23.31
observed refls.	3815
x, y (weighting scheme)	0.0207, 6.4528
hydrogen refinement	constr
Flack parameter	1(2)
refls in refinement	4711
parameters	487
restraints	1
$R(F_{obs})$	0.0829
$R_w(F^2)$	0.1694
S	1.188
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.353
min electron density/e Å^{-3}	−0.331

Correct structure derived from synthesis, Flack test meaningless. Poor scattering strength, data only collectable up to a resolution of 0.90 Å.



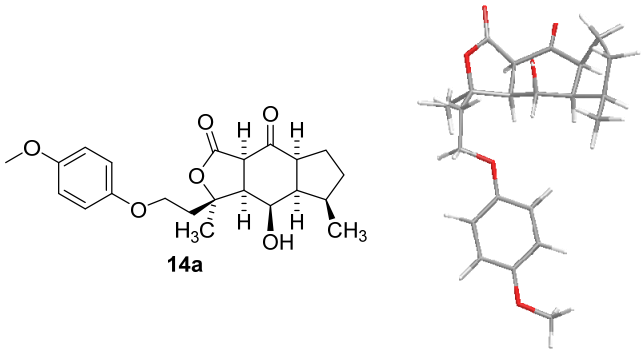
6.1.3 Computational Details

Conformational Search. Conformational searches were performed with MacroModel 10.0 (Schrödinger Release 2013-1**:** MacroModel, version 10.0, Schrödinger, LLC, New York, NY, 2013). An initial subset of reasonable conformers was generated using the molecular mechanics MM3* force field and the 100 structures of lowest energy were documented. A subset of these conformers was then further optimized via DFT calculations.

Density Functional Theory. All DFT calculations were performed using Gaussian 09 (Revision A.02).[13] Each starting structure, already a local minimum with respect to the conformational search potential energy surface, was re-optimized (gas phase) with the B3LYP hybrid functional[14] with the 6-31G(d) basis set.

Computed Geometries and Energies.

Ketone 14a



14a

Computed free energy: -1306.023749 hartree; relative energy with respect to dilactone **15**: +17.7 kcal/mol.

Cartesian coordinates:

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C	-3.549000	-2.575000	3.399000
C	-2.520000	-3.716000	3.497000
C	-4.114000	-2.786000	2.001000
O	-3.361000	-3.661000	1.300000
C	-2.136000	-3.895000	2.001000
C	1.028000	-5.779000	4.160000
O	-0.132000	-5.514000	3.489000
C	-0.195000	-5.631000	2.076000
C	-4.595000	-3.480000	5.649000
C	-4.106000	-5.695000	6.488000
C	-5.607000	-5.704000	6.135000
C	-3.436000	-7.067000	6.353000
C	2.129000	-5.898000	6.322000
C	0.992000	-5.648000	5.550000
C	-3.506000	-4.572000	5.608000
O	-5.108000	-2.277000	1.541000
C	-1.607000	-5.283000	1.594000

[13] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[14] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648. b) P. J. Stephens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, *J. Chem. Phys.* **1994**, *98*, 11623.

C	-4.588000	-2.456000	4.514000
C	4.529000	-6.437000	7.797000
O	4.486000	-6.549000	6.383000
C	2.224000	-6.166000	3.548000
C	3.361000	-6.415000	4.321000
C	3.326000	-6.284000	5.711000
C	-1.148000	-2.808000	1.541000
O	-5.377000	-1.536000	4.529000
C	-3.143000	-4.942000	4.172000
O	-4.318000	-5.286000	3.454000
H	-6.483000	-4.230000	4.759000
H	-6.616000	-3.772000	6.490000
H	-2.998000	-1.604000	3.383000
H	-1.630000	-3.386000	4.083000
H	0.549000	-4.957000	1.601000
H	0.049000	-6.674000	1.774000
H	-4.466000	-2.913000	6.604000
H	-4.012000	-5.371000	7.555000
H	-5.810000	-6.395000	5.287000
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H	-3.555000	-7.498000	5.336000
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H	-3.872000	-7.799000	7.069000
H	2.062000	-5.784000	7.415000
H	0.054000	-5.344000	6.044000
H	-2.581000	-4.193000	6.108000
H	-1.610000	-5.346000	0.481000
H	-2.315000	-6.074000	1.927000
H	3.817000	-7.145000	8.271000
H	4.303000	-5.397000	8.117000
H	5.550000	-6.690000	8.150000
H	2.293000	-6.280000	2.456000
H	4.300000	-6.720000	3.830000
H	-1.559000	-1.780000	1.645000
H	-0.204000	-2.832000	2.127000
H	-0.874000	-2.932000	0.469000
H	-2.421000	-5.785000	4.179000
H	-4.354000	-6.227000	3.326000

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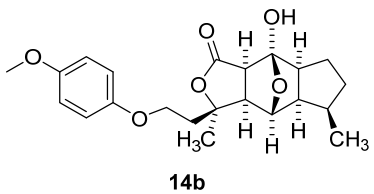
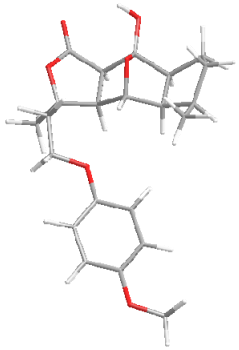
Hemiacetal 14b



14b



Computed free energy: -1306.035562 hartree; relative energy with respect to dilactone **15**: +10.3 kcal/mol.

Cartesian coordinates:

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C	-14.707000	-11.856000	11.608000
O	-14.341000	-17.141000	13.286000
C	-16.502000	-7.475000	13.481000
O	-15.728000	-7.869000	12.359000
C	-14.298000	-10.820000	10.763000
C	-14.656000	-9.499000	11.043000
C	-15.426000	-9.188000	12.165000
C	-15.835000	-10.224000	13.011000
C	-15.477000	-11.545000	12.731000
O	-14.405000	-13.175000	11.414000
O	-15.338000	-19.286000	10.591000
C	-15.682000	-15.563000	9.190000
C	-13.454000	-15.096000	10.298000
C	-13.638000	-13.576000	10.288000
C	-15.103000	-15.218000	15.577000
C	-16.173000	-17.364000	15.761000
C	-13.818000	-14.382000	15.570000
C	-15.507000	-15.892000	11.699000
C	-15.273000	-18.095000	10.779000
O	-14.384000	-17.301000	10.156000
C	-14.743000	-15.931000	10.350000
C	-14.921000	-16.603000	16.219000
C	-16.069000	-17.325000	11.813000
C	-16.412000	-16.910000	14.300000
C	-15.632000	-17.716000	13.236000
C	-14.714000	-15.794000	13.030000
C	-15.713000	-15.515000	14.179000
H	-14.978000	-19.495000	12.959000
H	-16.636000	-6.374000	13.460000
H	-17.509000	-7.944000	13.449000
H	-15.987000	-7.741000	14.428000
H	-13.689000	-11.022000	9.868000
H	-14.328000	-8.689000	10.370000
H	-16.442000	-10.019000	13.906000
H	-15.805000	-12.351000	13.406000
H	-16.075000	-14.528000	9.286000
H	-15.167000	-15.631000	8.206000
H	-16.567000	-16.235000	9.140000
H	-12.788000	-15.384000	11.142000
H	-12.891000	-15.375000	9.376000
H	-12.641000	-13.085000	10.318000
H	-14.144000	-13.261000	9.350000
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H	-17.042000	-17.064000	16.390000
H	-12.971000	-14.917000	15.086000
H	-13.961000	-13.419000	15.033000
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H	-16.316000	-15.128000	11.668000
H	-14.000000	-17.100000	15.842000
H	-14.852000	-16.544000	17.328000
H	-17.165000	-17.394000	11.640000
H	-17.499000	-16.869000	14.062000
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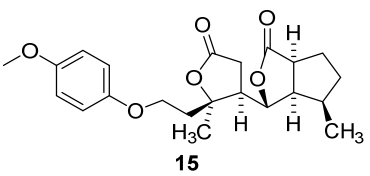
Dilactone 15



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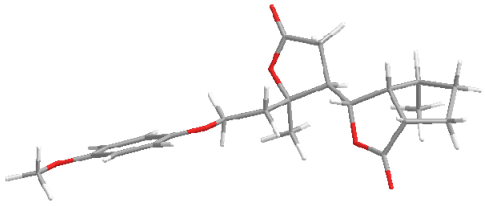

Computed free energy: -1306.051948 hartree

Cartesian coordinates:

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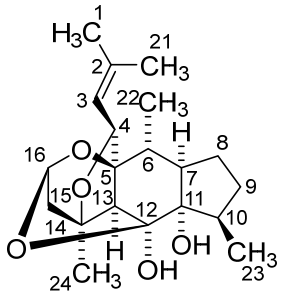
C	-0.817000	0.619000	6.365000
C	-0.618000	2.083000	6.721000
C	-3.143000	0.507000	5.625000
C	-2.910000	-0.637000	6.637000
C	-1.627000	-0.222000	7.388000
C	-2.302000	1.954000	2.241000
C	-2.157000	2.757000	3.540000
C	-2.607000	3.030000	1.223000
O	-2.390000	4.257000	1.737000
C	-1.710000	4.143000	2.993000
C	-3.823000	1.680000	6.358000
O	-3.025000	2.843000	0.107000
C	-2.207000	5.274000	3.902000
C	-0.199000	4.248000	2.725000
C	0.230000	5.509000	1.969000
O	-0.199000	2.505000	7.771000
O	-1.045000	2.884000	5.717000
O	1.634000	5.442000	1.760000
C	2.280000	6.452000	1.102000
C	3.663000	6.321000	0.954000
C	4.409000	7.301000	0.296000
C	3.778000	8.435000	-0.227000
C	2.396000	8.566000	-0.078000
C	1.650000	7.585000	0.580000
O	4.425000	9.444000	-0.885000
C	5.829000	9.376000	-1.083000
H	-0.233000	1.935000	4.070000
H	-1.441000	-0.089000	4.387000
H	0.166000	0.148000	6.134000
H	-3.803000	0.165000	4.794000
H	-2.739000	-1.595000	6.094000
H	-3.771000	-0.786000	7.325000
H	-1.877000	0.382000	8.289000
H	-1.055000	-1.114000	7.727000
H	-3.116000	1.199000	2.310000
H	-1.358000	1.430000	1.971000
H	-3.172000	2.871000	3.978000
H	-4.030000	2.543000	5.694000
H	-4.808000	1.370000	6.773000
H	-3.225000	2.061000	7.213000
H	-1.680000	5.280000	4.881000
H	-2.057000	6.275000	3.443000
H	-3.295000	5.185000	4.115000
H	0.349000	4.213000	3.695000
H	0.137000	3.360000	2.142000
H	-0.295000	5.566000	0.991000
H	-0.016000	6.416000	2.562000
H	4.169000	5.430000	1.362000
H	5.496000	7.162000	0.199000
H	1.890000	9.456000	-0.487000
H	0.562000	7.726000	0.675000
H	6.161000	10.280000	-1.634000
H	6.364000	9.352000	-0.110000
H	6.099000	8.485000	-1.688000

……

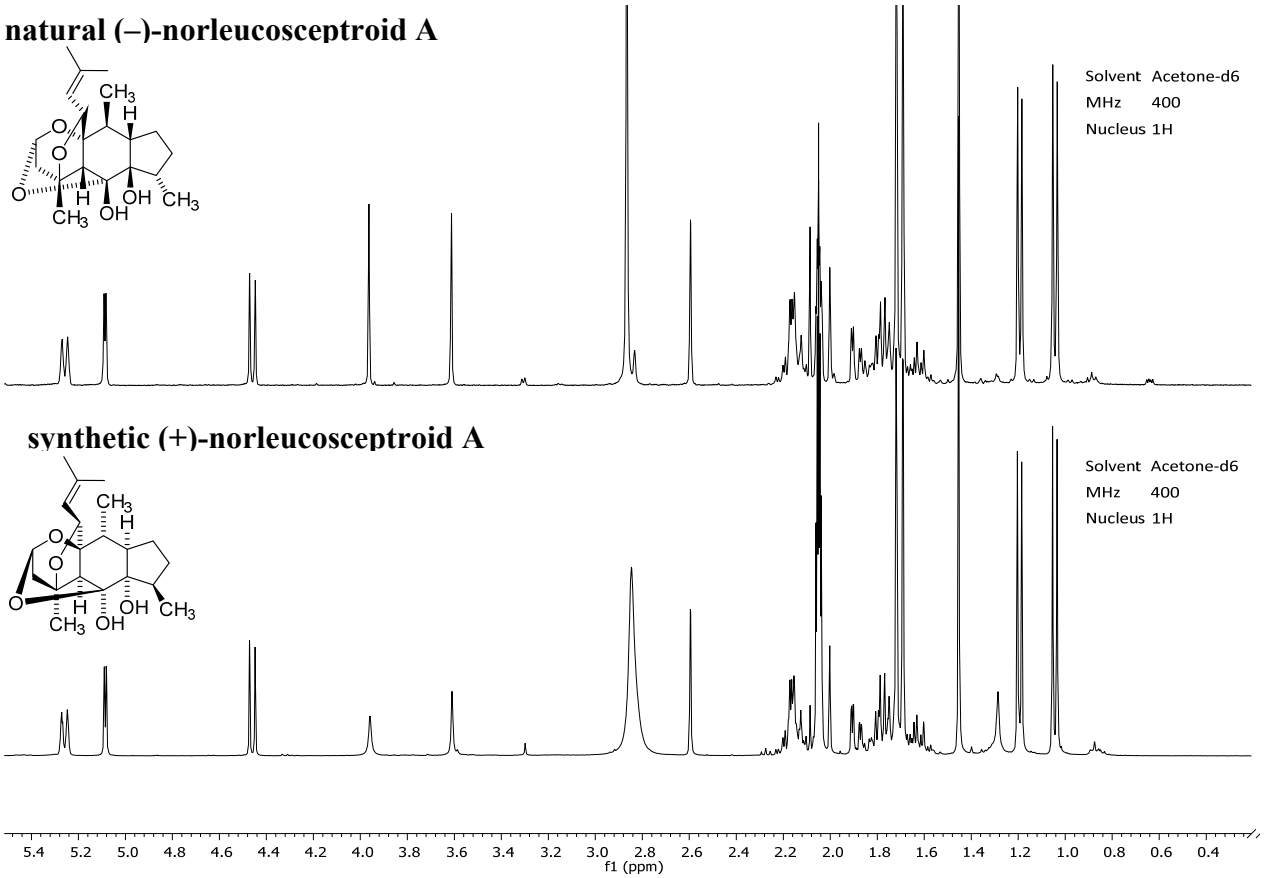
6.1.4 Comparison of ^{1}H and ^{13}C NMR Data for Natural[15] and Synthetic Norleucosceptroid A

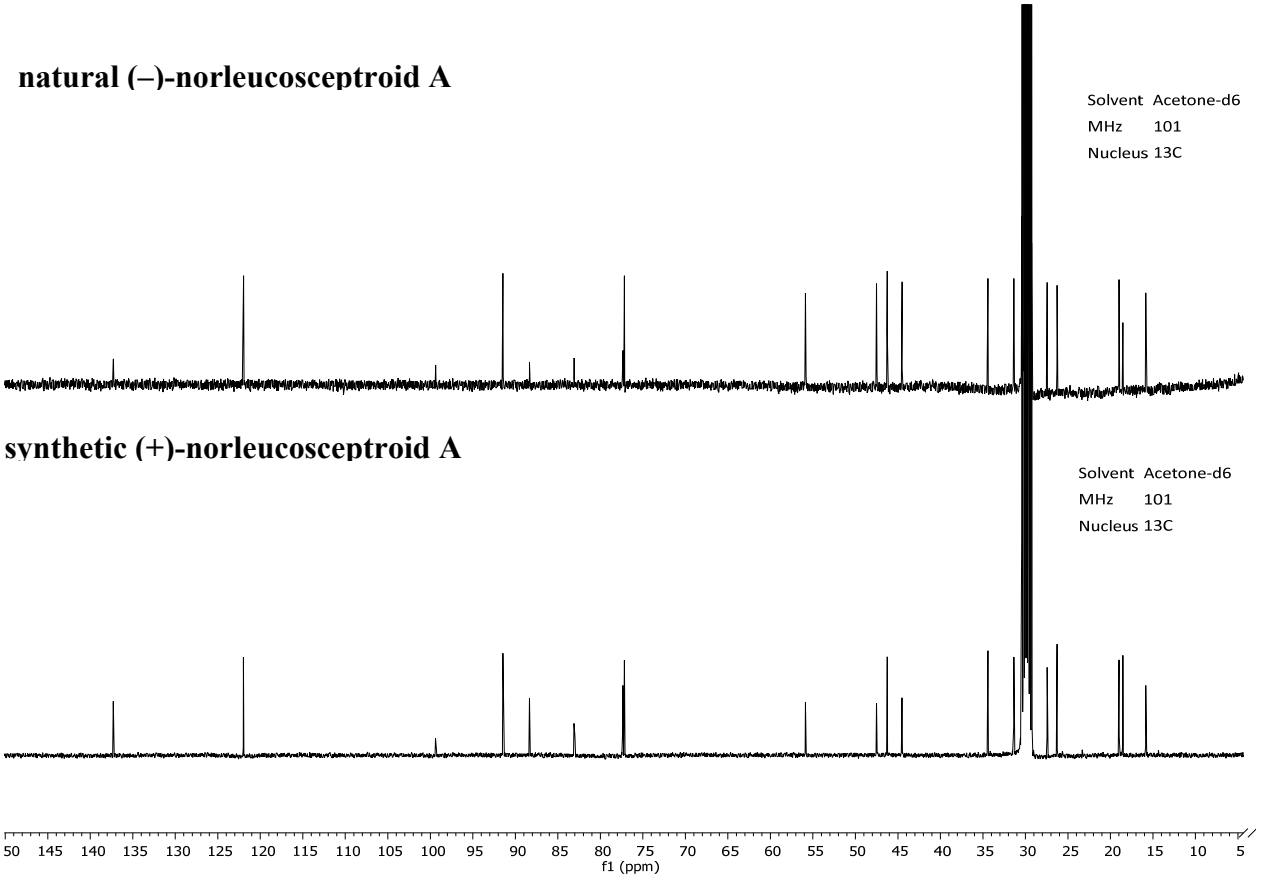


1H Position	Natural (400 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.69 (s, 3H)	1.69 (d, 1.3)	0
3	5.26 (d, 9.4)	5.29–5.23 (m)	
4	4.46 (d, 9.4)	4.46 (d, 9.4)	0
6	1.77 (m)	1.86–1.71 (m)	
7	2.15 (m)	2.23–2.09 (m)	
8α	1.80 (m)	1.86–1.71 (m)	
8β	2.16 (m)	2.23–2.09 (m)	
9α	1.62 (m)	1.68–1.57 (m)	
9β	1.73 (m)	1.86–1.71 (m)	
10	2.13 (m)	2.23–2.09 (m)	
11-OH	3.60 (s)	3.58 (br s)	0.02
12-OH	3.95 (s)	3.93 (br s)	0.02
13	2.59 (s)	2.60 (d, 1.2)	0.1
15a	1.89 (dd, 3.4, 13.6)	1.89 (ddd, 13.5, 3.5, 1.2)	0
15b	2.02, overlapped	2.02 (d, 13.5)	0
16	5.09 (d, 3.3)	5.09 (d, 3.5)	0
21	1.72 (s, 3H)	1.72 (d, 1.4)	0
22	1.04 (d, 7.6, 3H)	1.05 (d, 7.6)	0.01
23	1.19 (d, 7.2, 3H)	1.20 (d, 7.2)	0.01
24	1.45 (s, 3H)	1.46 (s)	0.01

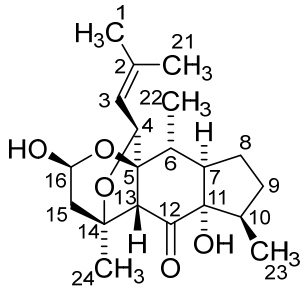
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.5, q	18.5	0
2	137.2, s	137.3	0.1
3	121.9, d	122.0	0.1
4	77.1, d	77.2	0.1
5	88.3, s	88.3	0
6	34.4, d	34.4	0
7	55.8, d	55.9	0.1
8	29.5, t	29.5	0
9	31.3, t	31.4	0.1
10	47.5, d	47.5	0
11	83.0, s	83.1	0.1
12	99.3, s	99.4	0.1
13	44.5, d	44.5	0
14	77.3, s	77.4	0.1
15	46.2, t	46.3	0.1
16	91.4, d	91.5	0.1
21	26.2, q	26.3	0.1
22	18.9, q	19.0	0.1
23	15.8, q	15.8	0
24	27.4, q	27.5	0.1

[15] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768.


natural (–)-norleucosceptroid A
Solvent Acetone-d6
MHz 400
Nucleus 1H
synthetic (+)-norleucosceptroid A
Solvent Acetone-d6
MHz 400
Nucleus 1H
f1 (ppm)


natural (–)-norleucosceptroid A
Solvent Acetone-d6
MHz 101
Nucleus 13C
synthetic (+)-norleucosceptroid A
Solvent Acetone-d6
MHz 101
Nucleus 13C
f1 (ppm)

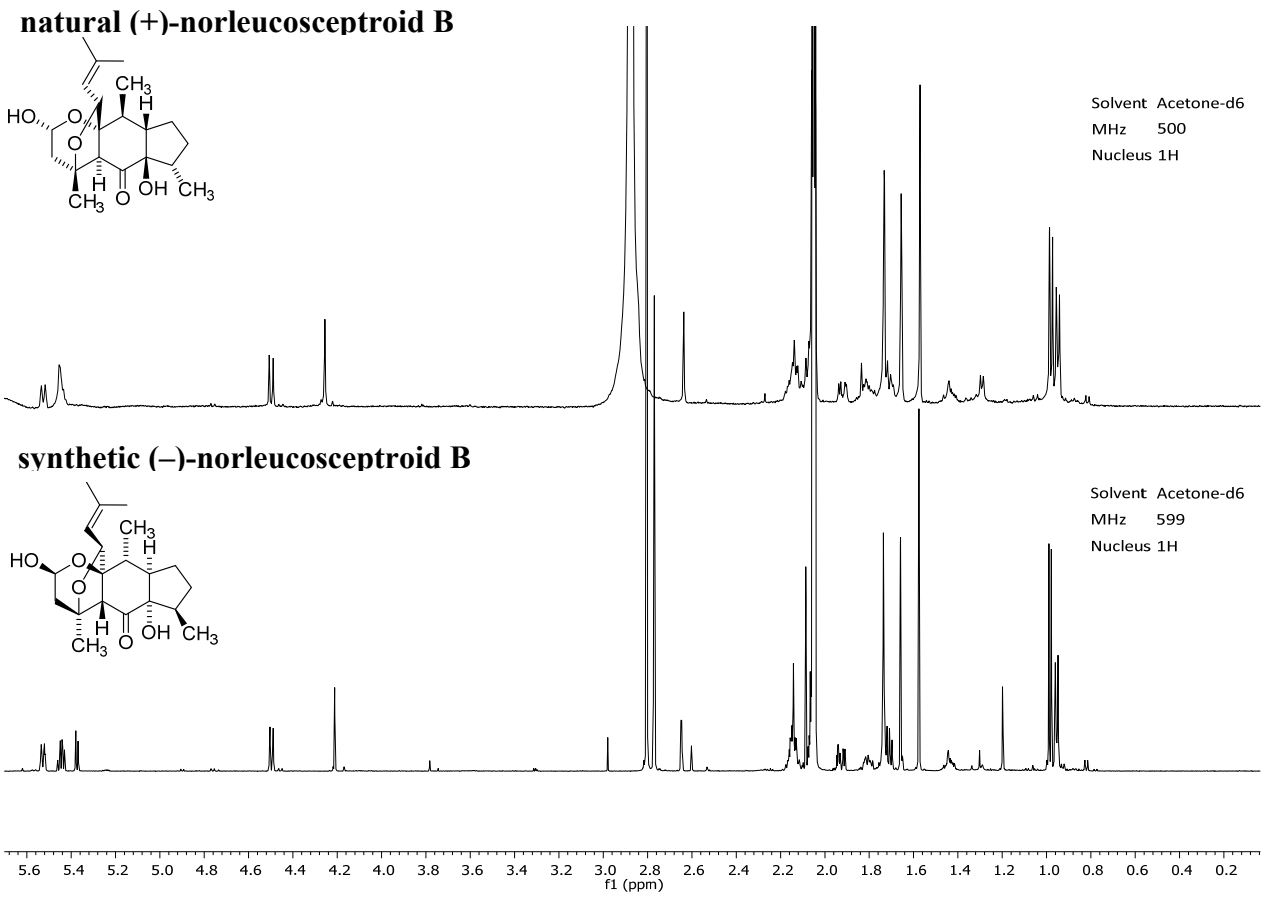
6.1.5 Comparison of ^{1}H and ^{13}C NMR Data for Natural[16] and Synthetic Norleucosceptroid B

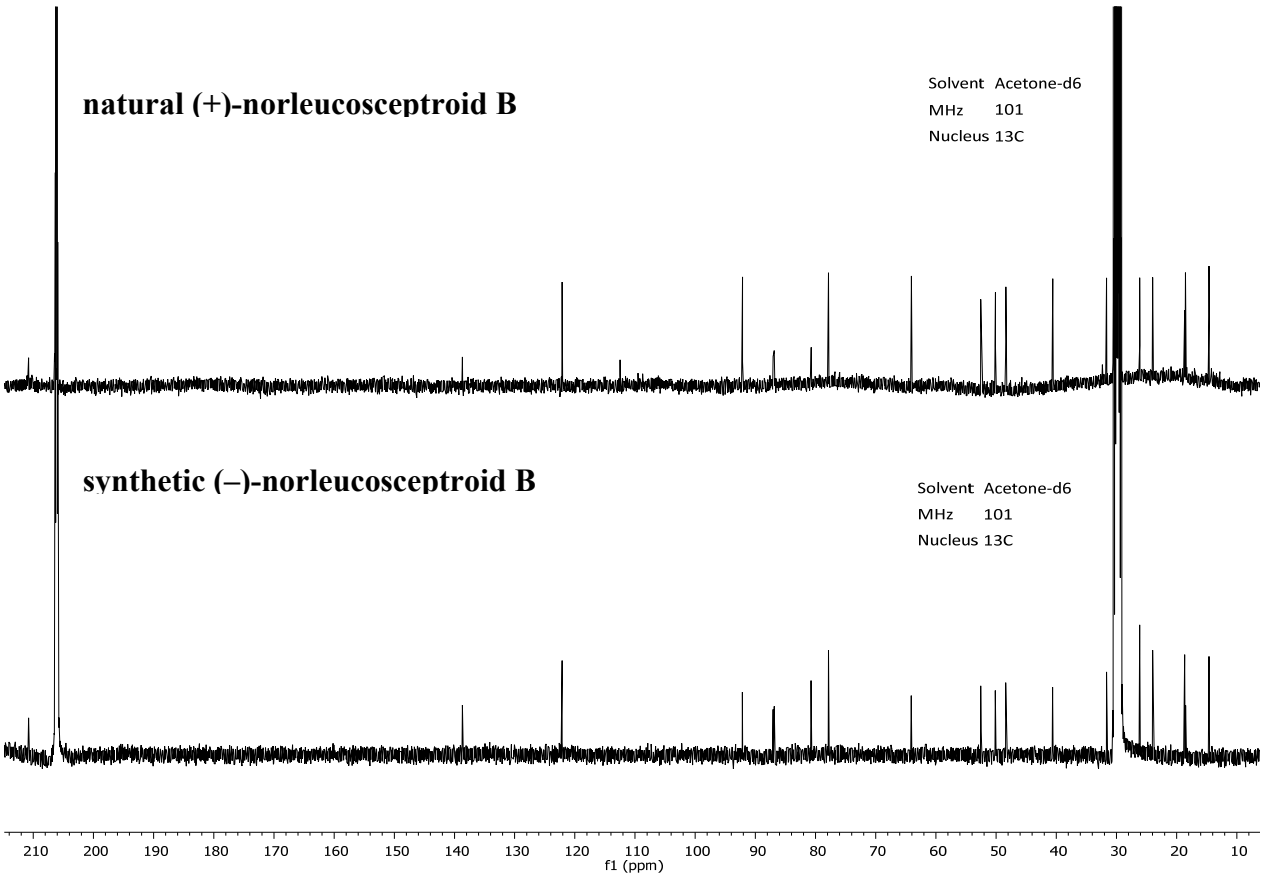


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.65 (s, 3H)	1.66 (d, 1.3, 3H)	0.1
3	5.51 (d, 8.5)	5.53 (d, 8.8)	0.2
4	4.49 (d, 8.5)	4.50 (d, 8.6)	0.1
6	2.06 (m)	2.07–2.03 (m)	
7	1.79 (m)	1.83–1.78 (m)	
8α	1.71 (m)	1.75–1.71 (m)	
8β	2.13 (m)	2.16–2.11 (m)	
9α	1.43 (m)	1.46–1.41 (m)	
9β	2.13 (m)	2.16–2.11 (m)	
10	2.14 (m)	2.16–2.13 (m)	
11-OH	4.25 (s)	4.24 (s)	0.1
13	2.63 (s)	2.64 (s)	0.1
15a	1.69 (m)	1.73–1.68 (m)	
15b	1.91 (m)	1.95–1.88 (m)	
16	5.43 (d, 3.5)	5.47–5.42 (m)	
16-OH	5.44 (s)	5.41 (d, 6.4)	0.3
21	1.72 (s, 3H)	1.73 (d, 3H)	0.1
22	0.97 (d, 7.0, 3H)	0.98 (d, 6.8, 3H)	0.1
23	0.94 (d, 7.5, 3H)	0.95 (d, 7.2, 3H)	0.1
24	1.56 (s, 3H)	1.57 (s, 3H)	0.1

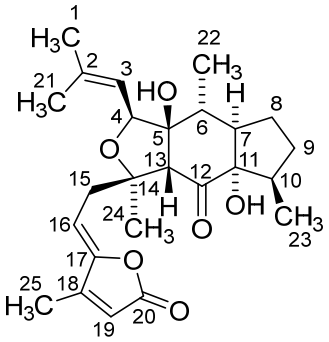
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.6, q	18.7	0.1
2	138.7, s	138.7	0
3	122.1, d	122.1	0
4	77.8, d	77.9	0.1
5	87.0, s	87.0	0
6	40.6, d	40.6	0
7	52.5, d	52.5	0
8	30.5, t	30.5	0
9	31.6, t	31.6	0
10	48.4, d	48.4	0
11	86.9, s	86.9	0
12	210.8, s	210.8	0
13	64.0, d	64.1	0.1
14	80.7, s	80.7	0
15	50.1, t	50.1	0
16	92.1, d	92.2	0.1
21	26.1, q	26.1	0
22	14.6, q	14.6	0
23	18.5, q	18.5	0
24	23.9, q	24.0	0.1

[16] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768.


natural (+)-norleucosceptroid B
Solvent Acetone-d6
MHz 500
Nucleus 1H
synthetic (–)-norleucosceptroid B
Solvent Acetone-d6
MHz 599
Nucleus 1H
f1 (ppm)


natural (+)-norleucosceptroid B
Solvent Acetone-d6
MHz 101
Nucleus 13C
synthetic (–)-norleucosceptroid B
Solvent Acetone-d6
MHz 101
Nucleus 13C
f1 (ppm)

6.1.6 Comparison of ^{1}H and ^{13}C NMR Data for Natural[17] and Synthetic Leucosceptroid K

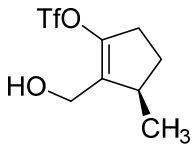


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.73 (d, 1.0)	1.76–1.73 (m)	
3	5.57 (d, 8.9)	5.60–5.57 (m)	
4	4.72 (d, 9.0)	4.74 (d, 8.9)	0.02
5-OH	3.91 (s)	3.89 (br s)	0.02
6	1.76 (m)	1.83–1.76 (m)	
7	2.02 (m)	2.15–2.02 (m)	
8α	1.68 (m)	1.73–1.67 (m)	
8β	2.10 (m)	2.15–2.02 (m)	
9α	1.39 (m)	1.44–1.38 (m)	
9β	2.03 (m)	2.15–2.02 (m)	
10	2.26 (m)	2.31–2.24 (m)	
11-OH	4.19 (s)	4.17 (br s)	0.02
13	2.71 (s)	2.72 (s)	0.1
15a	2.77 (2H, dd,	2.82–2.74 (m, 2H)	
15b	4.7, 7.5)		
16	5.76 (2H, t, 7.6)	5.76 (t, 7.6)	0
19	6.01 (s)	6.01 (s)	0
21	1.73 (s)	1.76–1.73 (m)	
22	0.96 (d, 6.8)	0.98 (d, 6.9)	0.02
23	0.78 (d, 7.4)	0.80 (d, 7.4)	0.02
24	1.23 (s)	1.25 (s)	0.02
25	2.19 (s)	2.20 (d, 1.4)	0.01

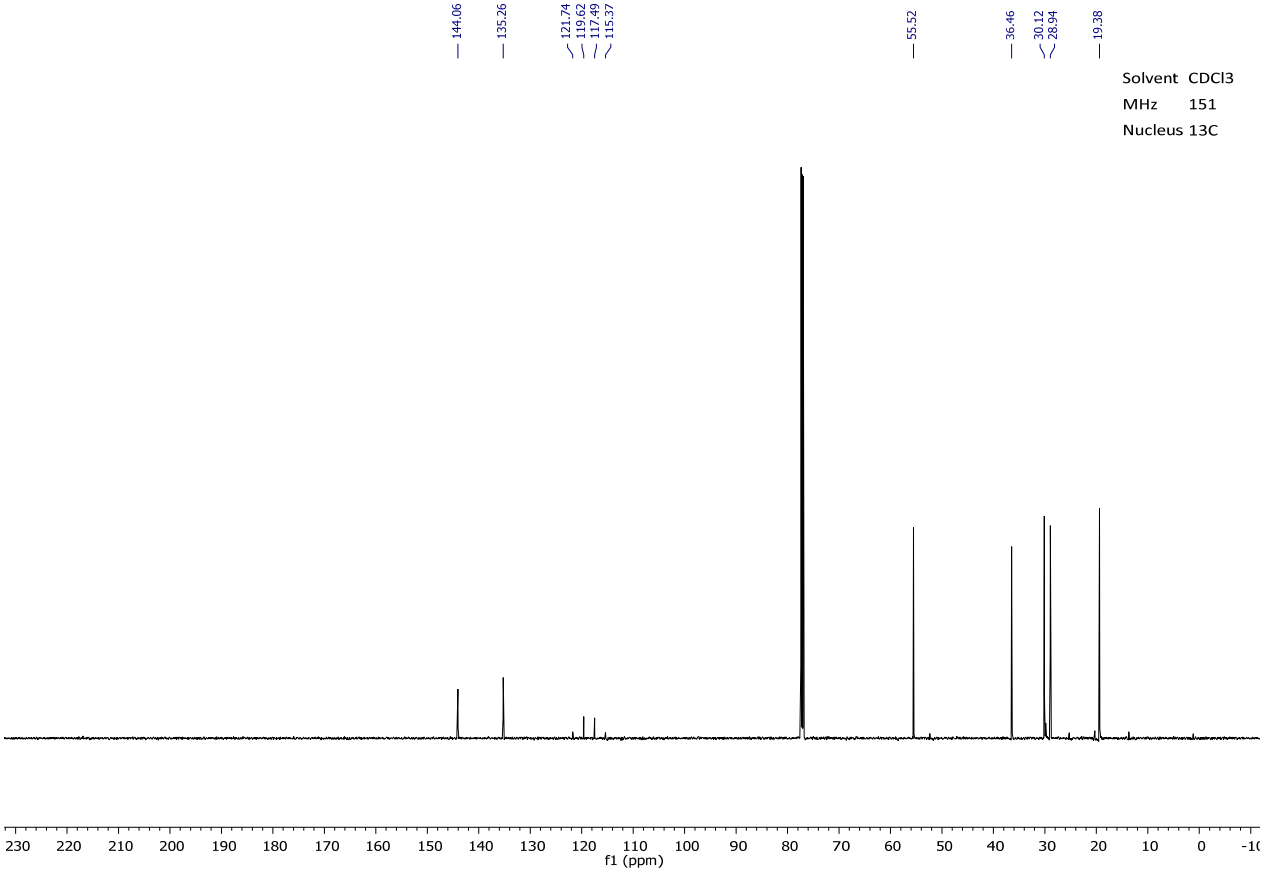
[17] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

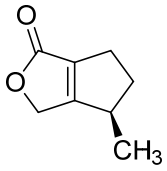
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (150 MHz, acetone-d6)	Δδ (ppm)
1	18.8	18.8	0
2	137.1	137.2	0.1
3	122.4	122.5	0.1
4	77.2	77.3	0.1
5	84.4	84.5	0.1
6	42.2	42.3	0.1
7	50.3	50.5	0.2
8	30.6	30.6	0
9	30.9	31.0	0.1
10	46.1	46.3	0.2
11	85.5	85.6	0.1
12	212.4	212.4	0
13	71.6	71.7	0.1
14	83.3	83.4	0.1
15	41.6	41.6	0
16	109.4	109.5	0.1
17	152.5	152.6	0.1
18	156.2	156.2	0
19	116.6	116.6	0
20	169.5	169.5	0
21	26.1	26.2	0.1
22	14.0	14.0	0
23	16.9	17.0	0.1
24	24.3	24.3	0
25	11.7	11.7	0

6.1.7 ^{1}H and ^{13}C NMR Spectra

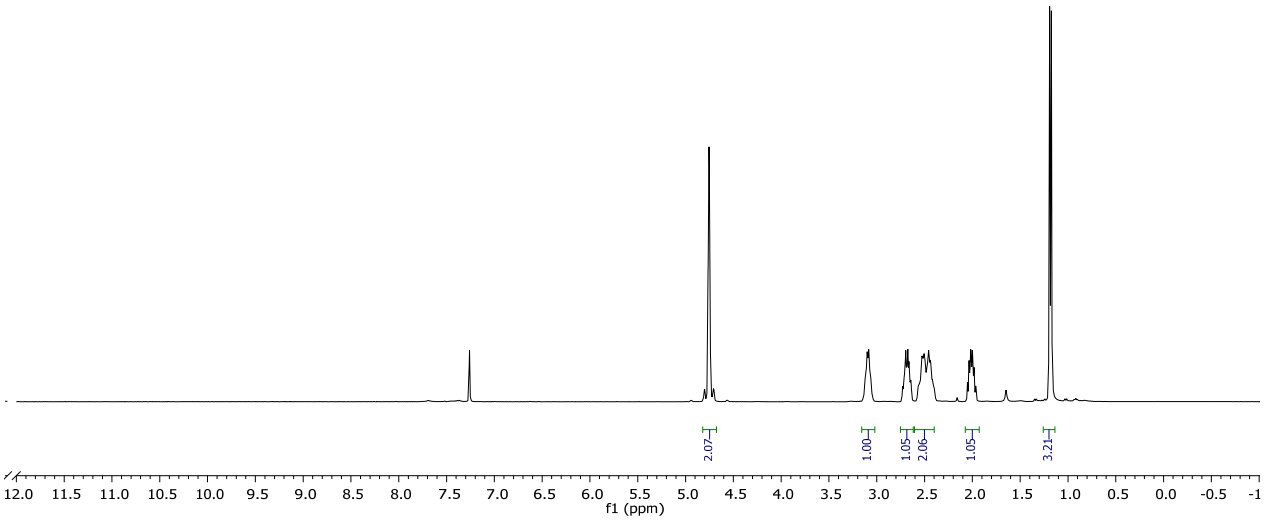

TfO
HO
CH3

Solvent CDCl3
MHz 599
Nucleus 1H
1.00
0.99
1.04
2.07
1.08
2.05
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


144.06
135.26
121.74
119.62
117.49
115.37
55.52
36.46
30.12
28.94
19.38
Solvent CDCl3
MHz 151
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

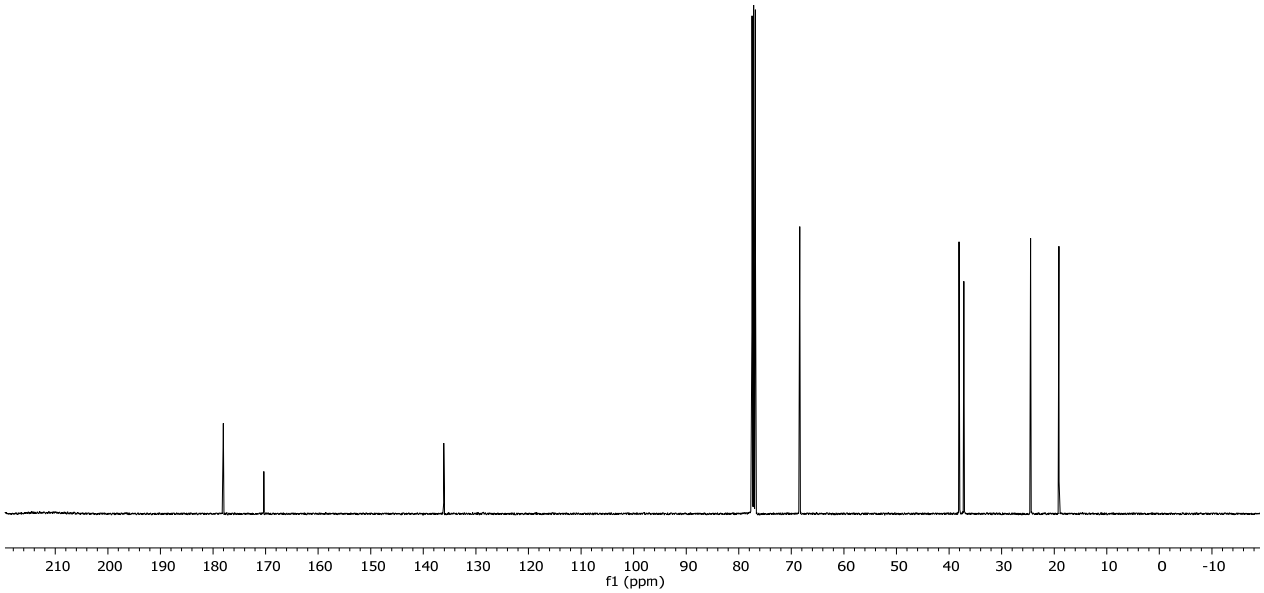


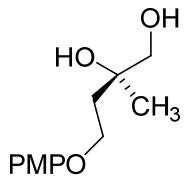
Solvent CDCl3
MHz 400
Nucleus 1H

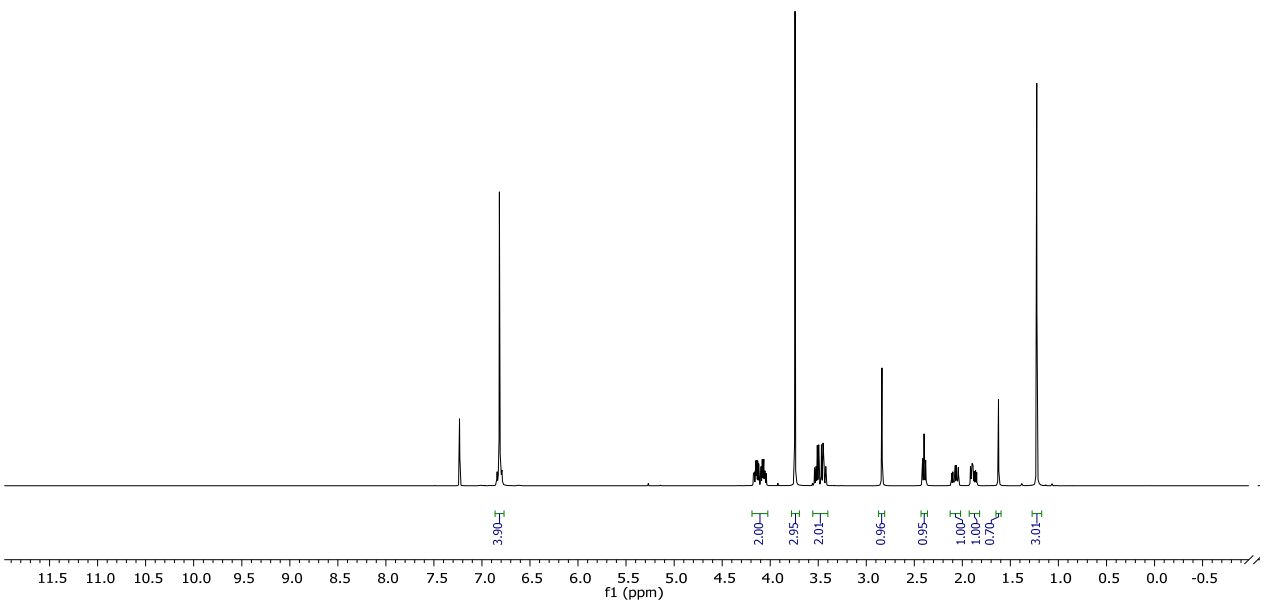


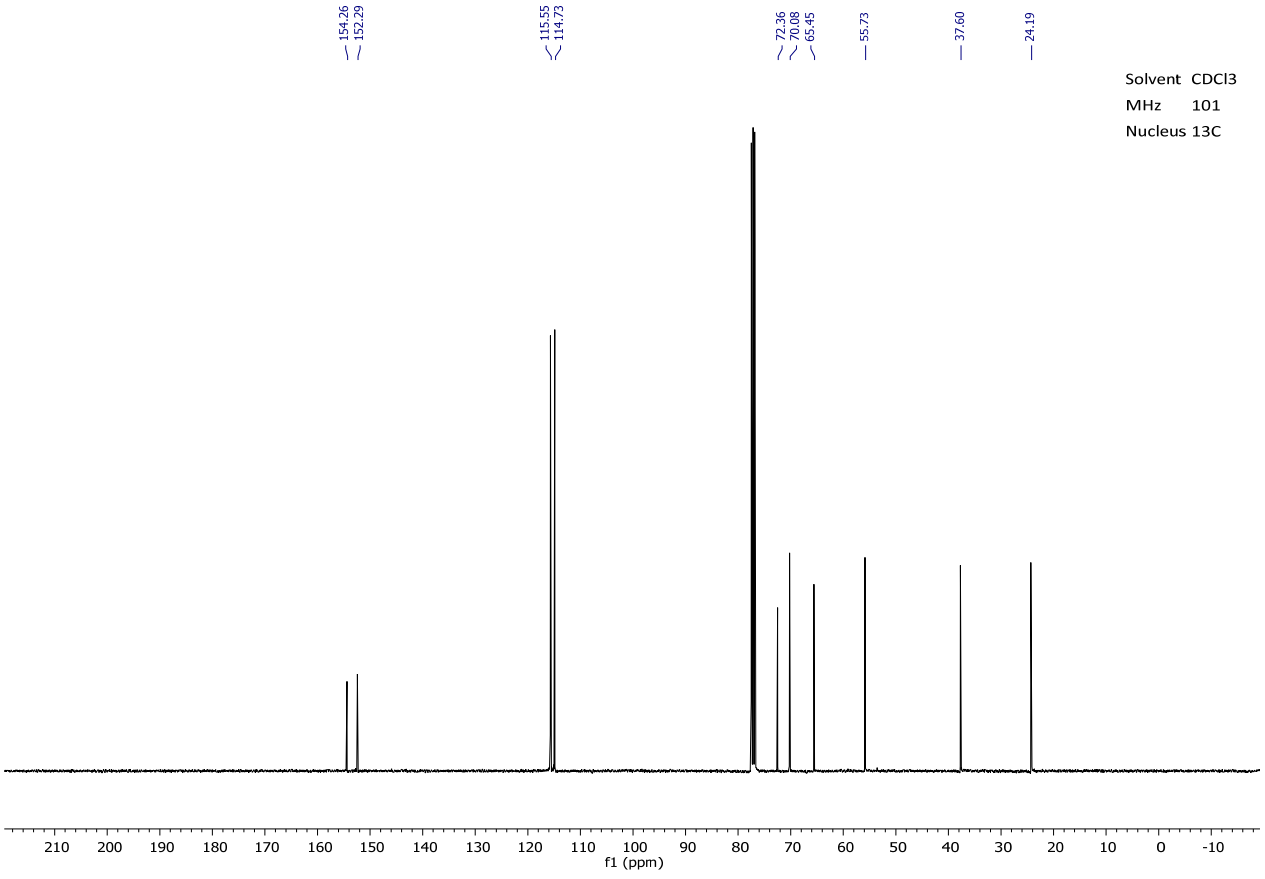
177.93
170.21
135.98
68.28
37.98
37.86
24.37
18.98

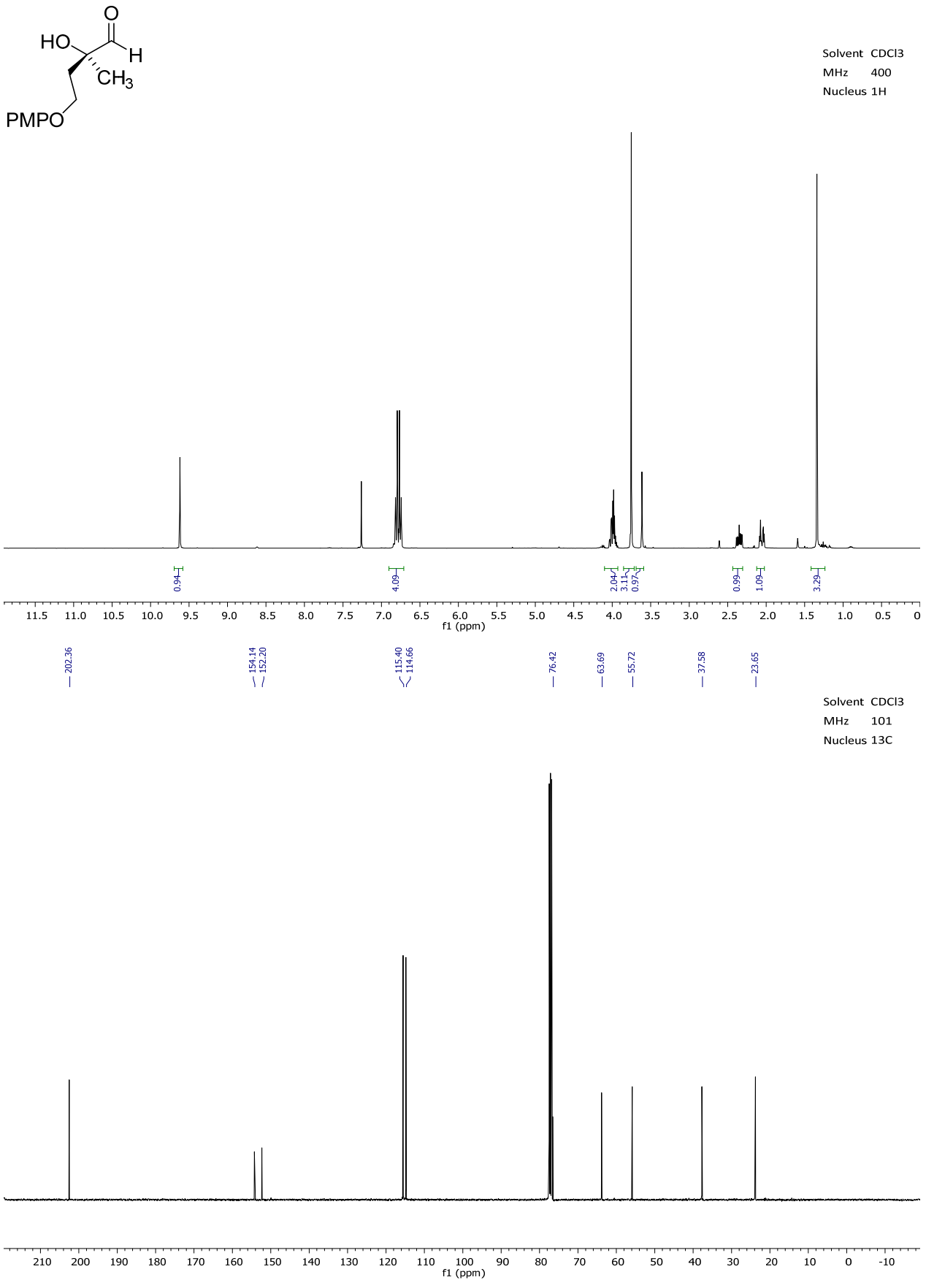
Solvent CDCl3
MHz 101
Nucleus 13C

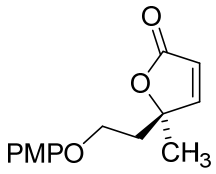



OH
HO
CH3
PMPO

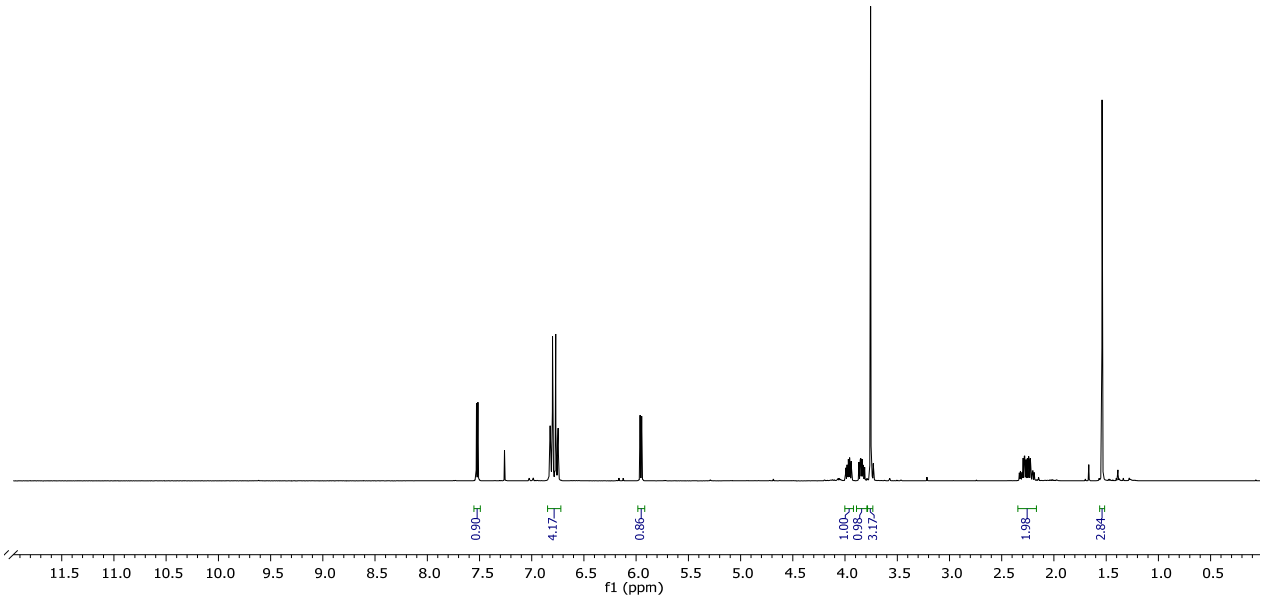

Solvent CDCl3
MHz 400
Nucleus 1H
3.90
2.00
2.95
2.01
0.96
0.95
1.00
1.00
0.70
3.01
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


154.26
152.29
115.55
114.73
72.36
70.08
65.45
55.73
37.60
24.19
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

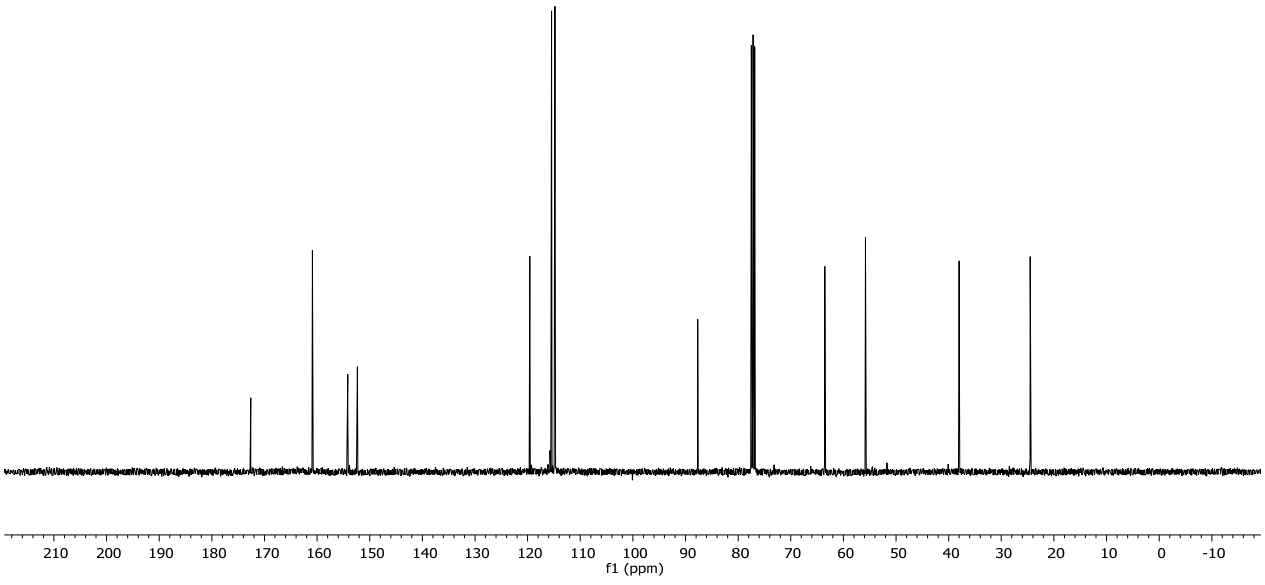

HO
O
H
CH3
PMPO
Solvent CDCl3
MHz 400
Nucleus 1H
0.94
4.09
2.04
3.11
0.97
0.99
1.09
3.29
f1 (ppm)
202.36
154.14
152.20
115.40
114.66
76.42
63.69
55.72
37.58
23.65
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

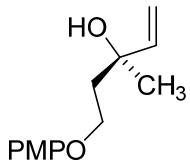


Solvent CDCl3
MHz 400
Nucleus 1H

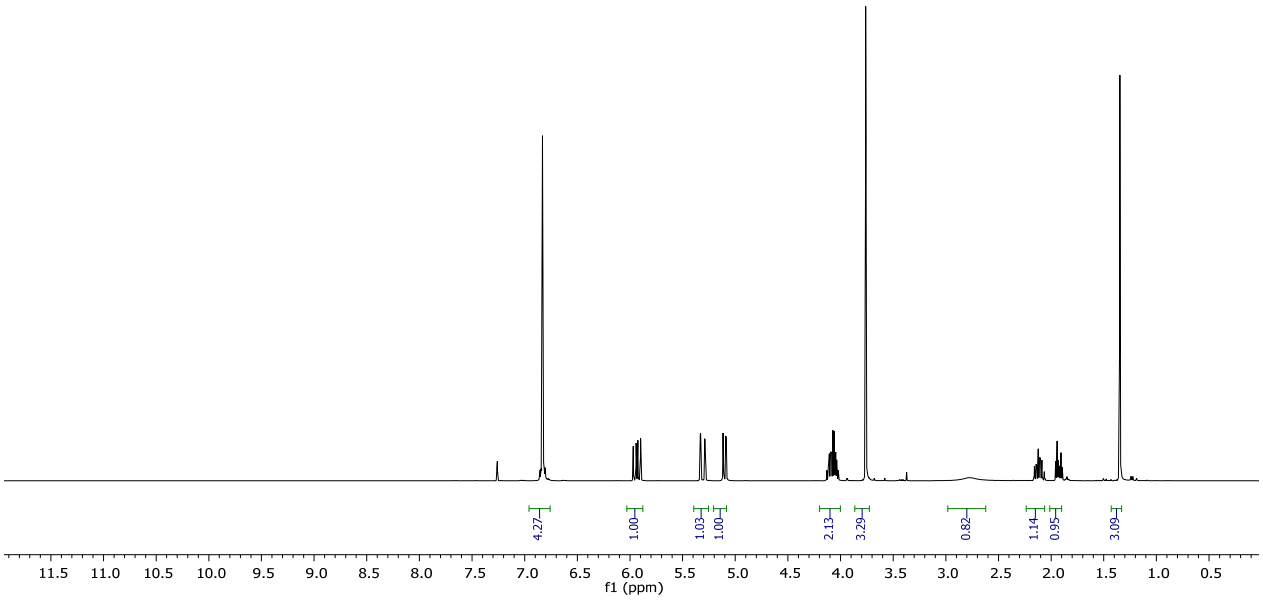


Solvent CDCl3
MHz 101
Nucleus 13C

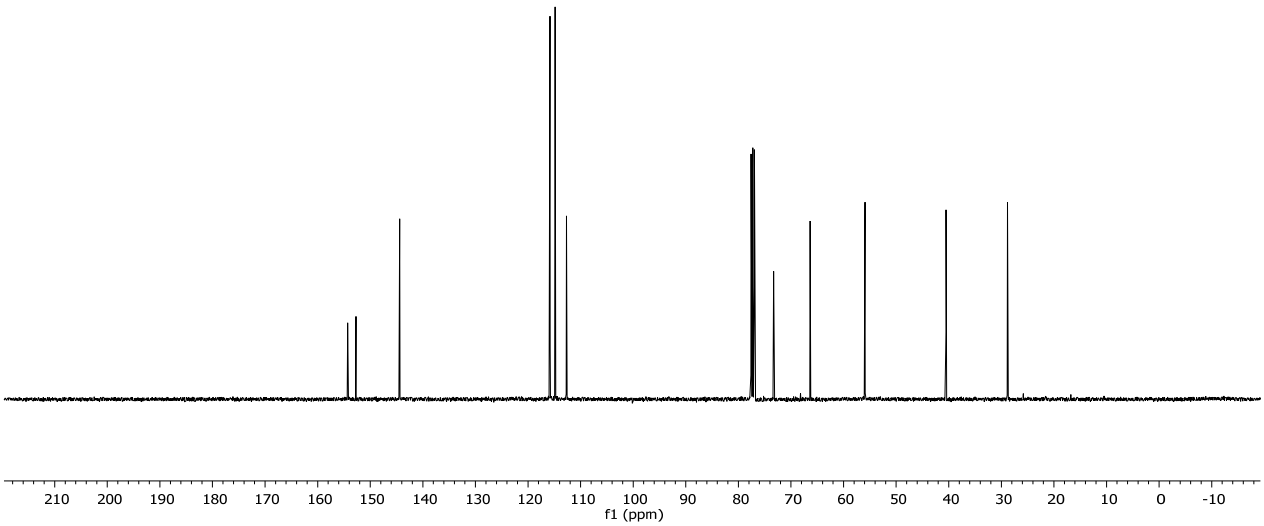


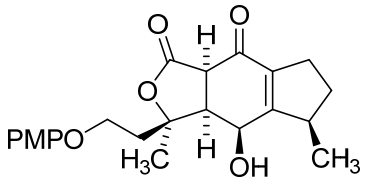


Solvent CDCl3
MHz 400
Nucleus 1H

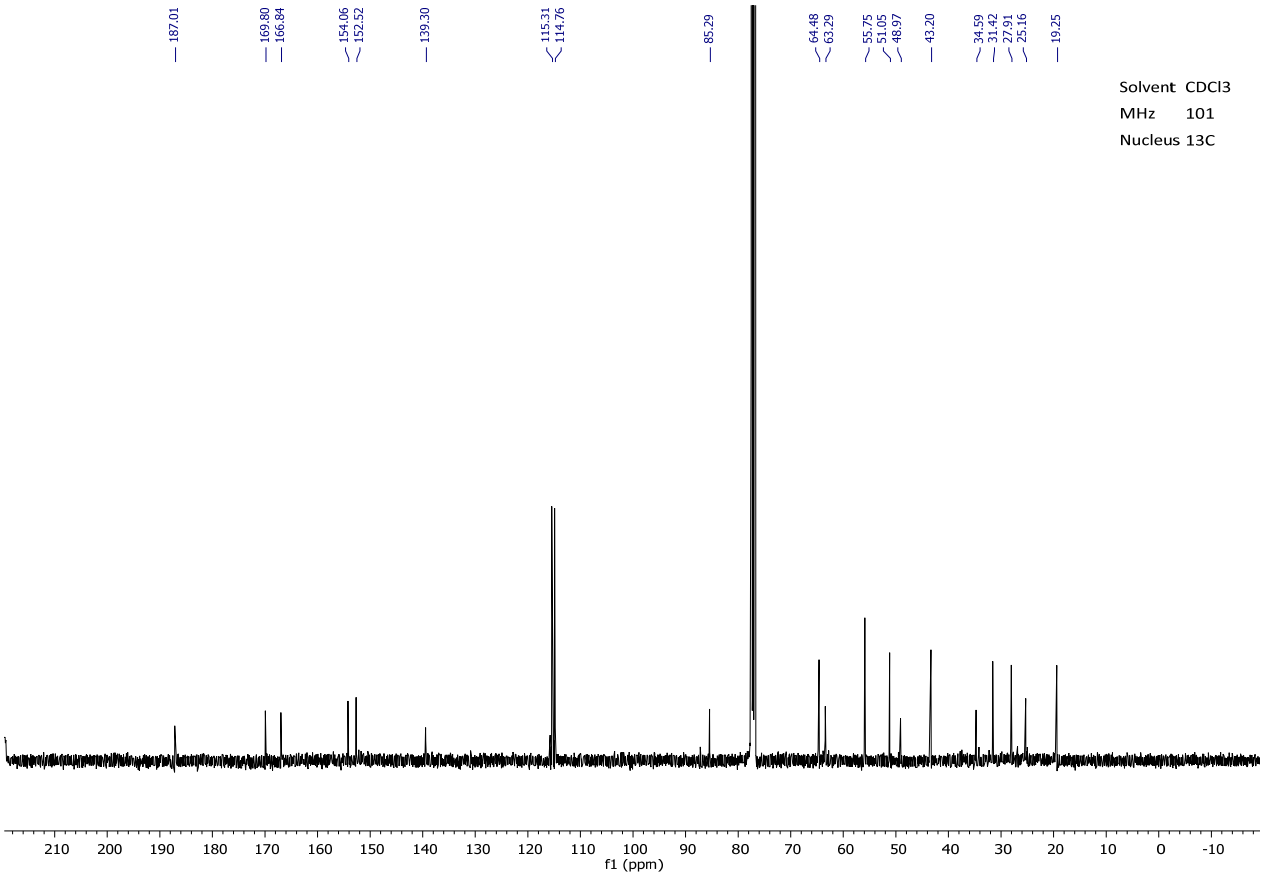


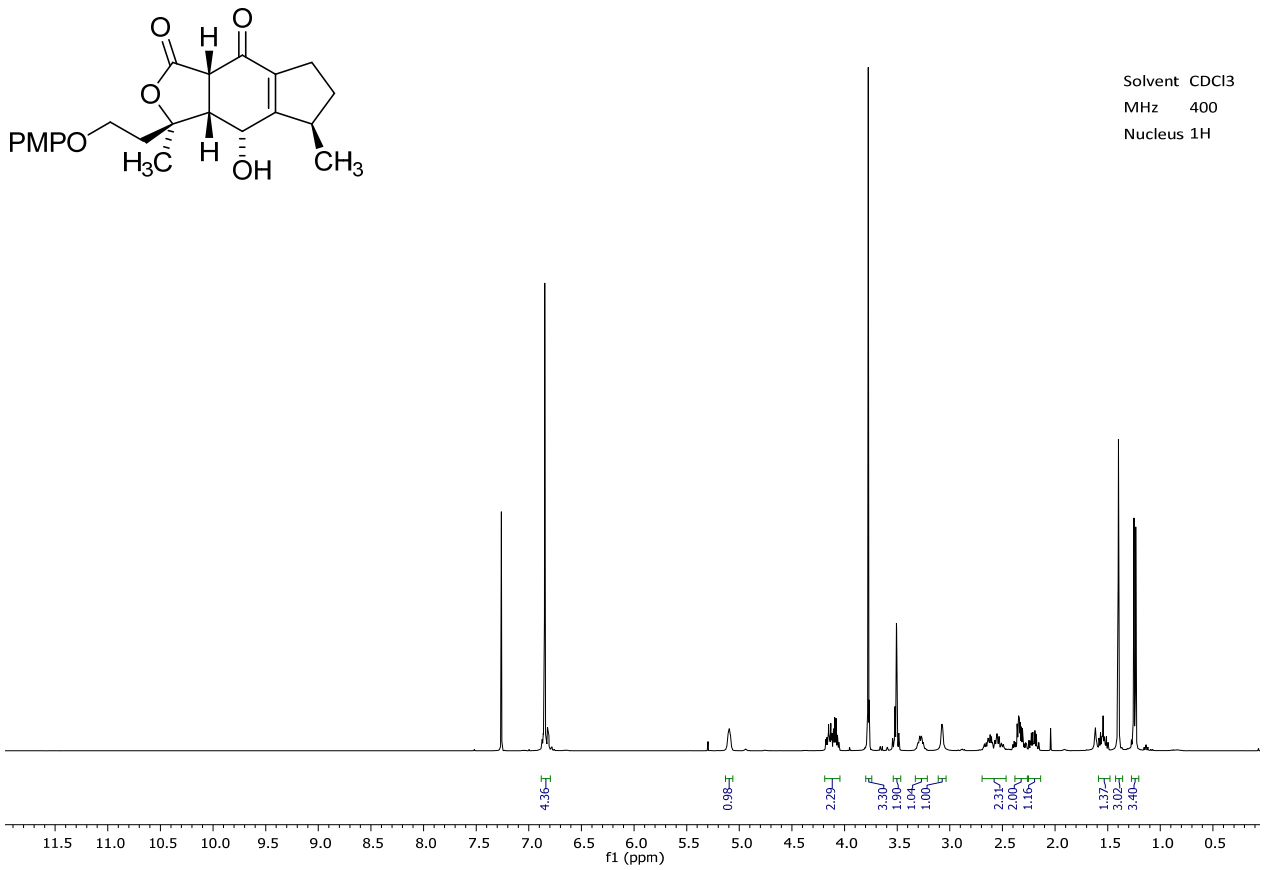
Solvent CDCl3
MHz 101
Nucleus 13C

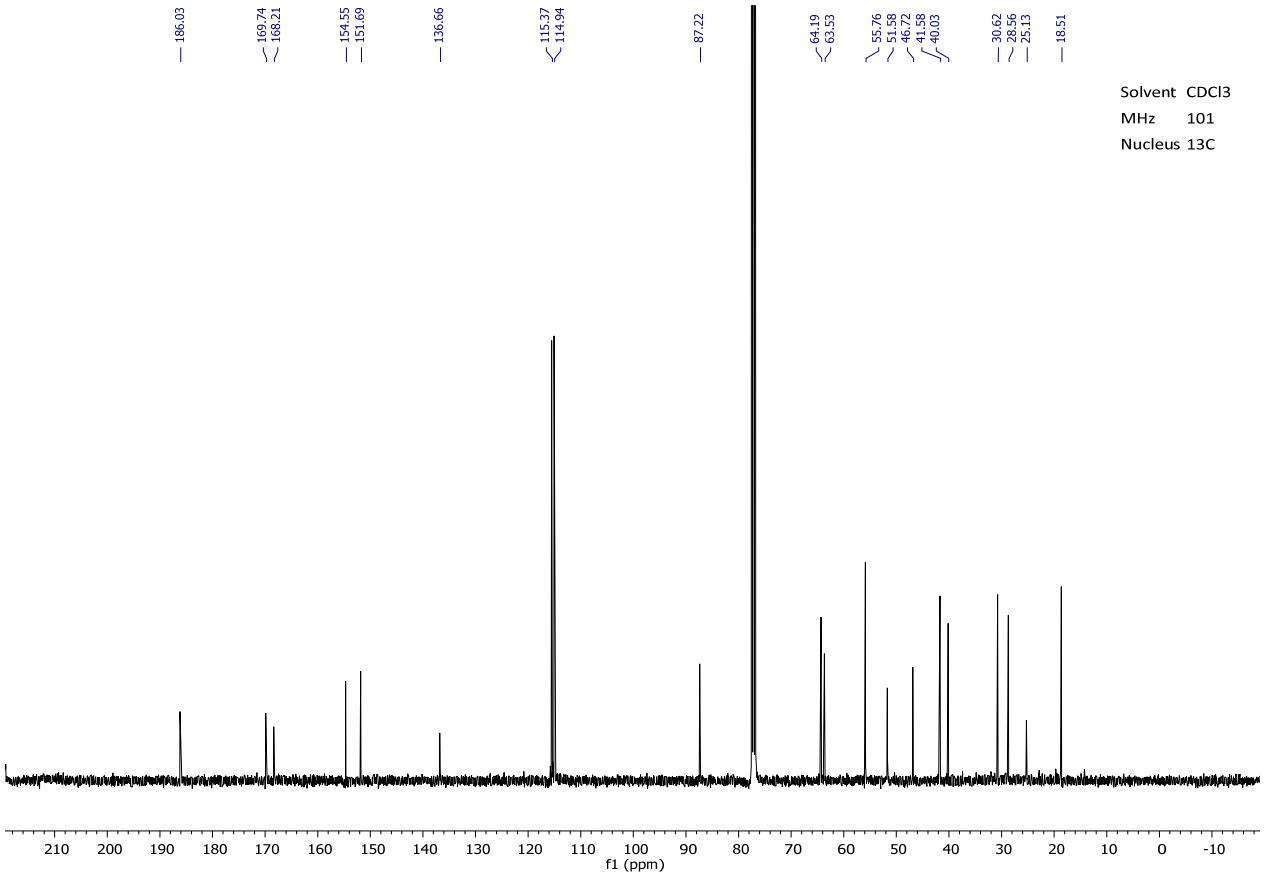


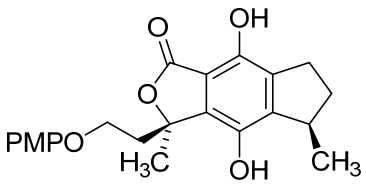

O
H
O
O
PMPO
H3C
H
OH
CH3

Solvent CDCl3
MHz 400
Nucleus 1H
4.05
0.80
1.87
2.83
0.82
0.99
0.92
2.30
1.87
1.13
2.44
2.85
3.26
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

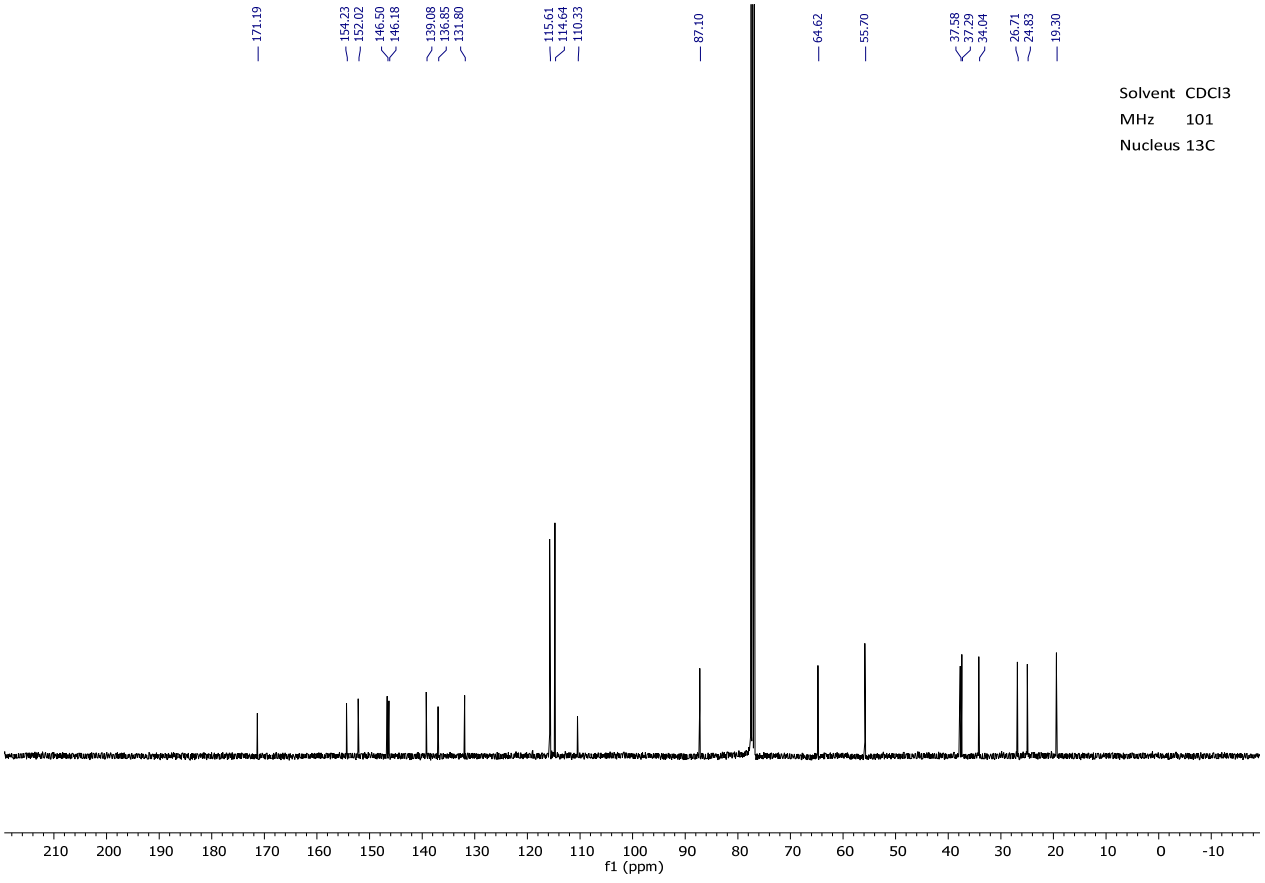

187.01
169.80
166.84
154.06
152.52
139.30
115.31
114.76
85.29
64.48
63.29
55.75
51.05
48.97
43.20
34.59
31.42
27.91
25.16
19.25
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

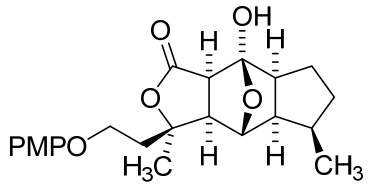

PMPO
H3C
OH
CH3
Solvent CDCl3
MHz 400
Nucleus 1H
f1 (ppm)


186.03
169.74
168.21
154.55
151.69
136.66
115.37
114.94
87.22
64.19
63.53
55.76
51.58
46.72
41.58
40.03
30.62
28.56
25.13
18.51
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

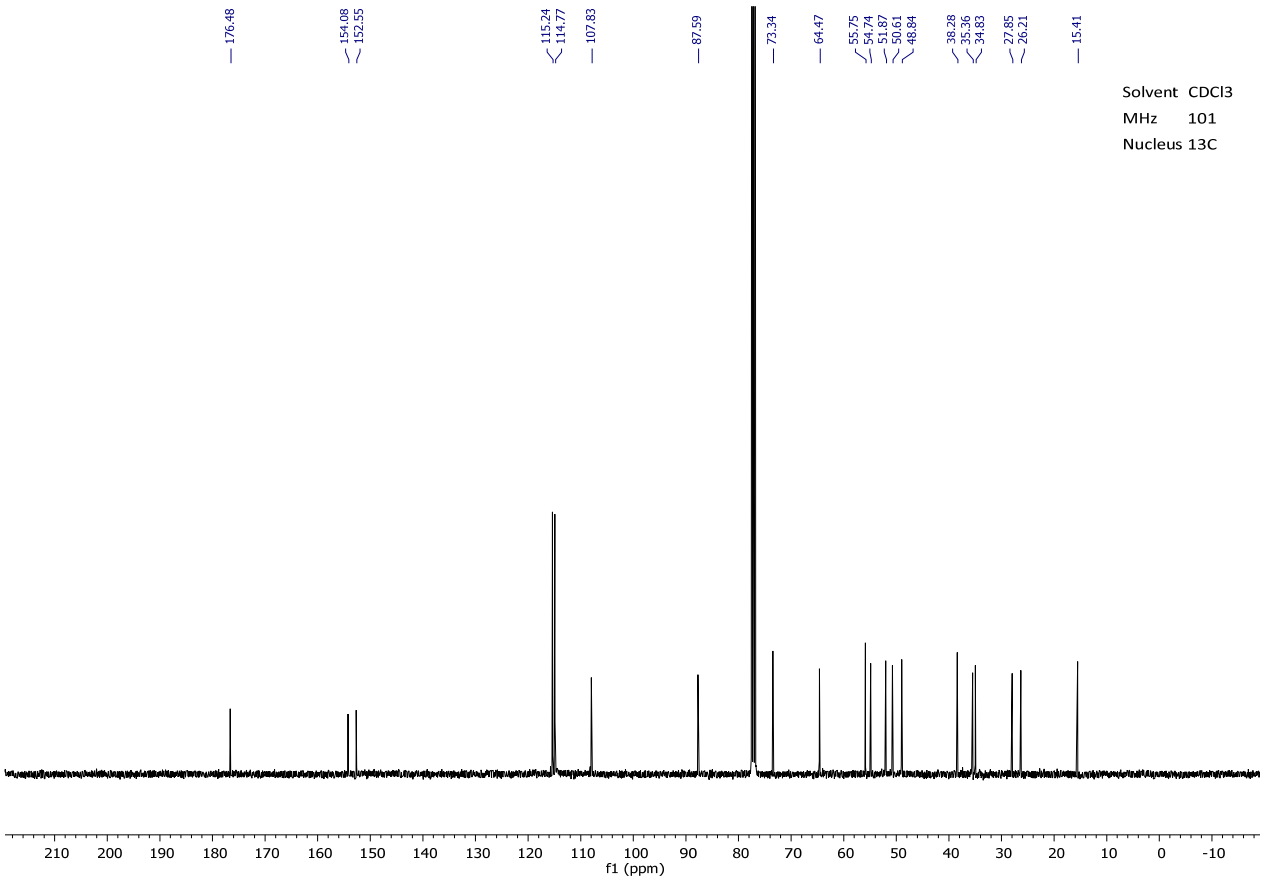

O
OH
O
PMPO
H3C
OH
CH3

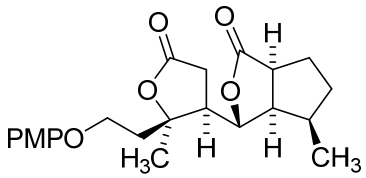
Solvent CDCl3
MHz 400
Nucleus 1H
0.99
4.31
0.97
1.08
1.11
3.26
1.10
2.16
2.21
1.15
1.33
3.04
3.61
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


171.19
154.23
152.02
146.50
146.18
139.08
136.85
131.80
115.61
114.64
110.33
87.10
64.62
55.70
37.58
37.29
34.04
26.71
24.83
19.30
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

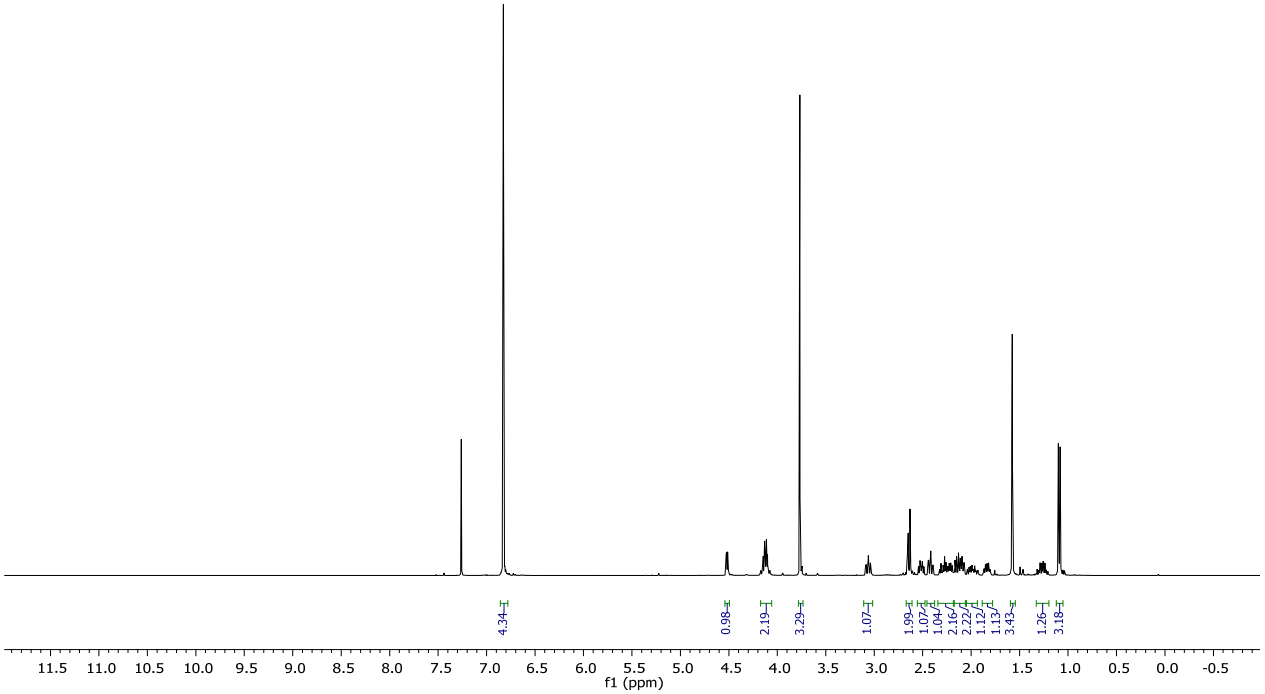

OH
O
H
H
O
O
PMPO
H3C
H
H
CH3

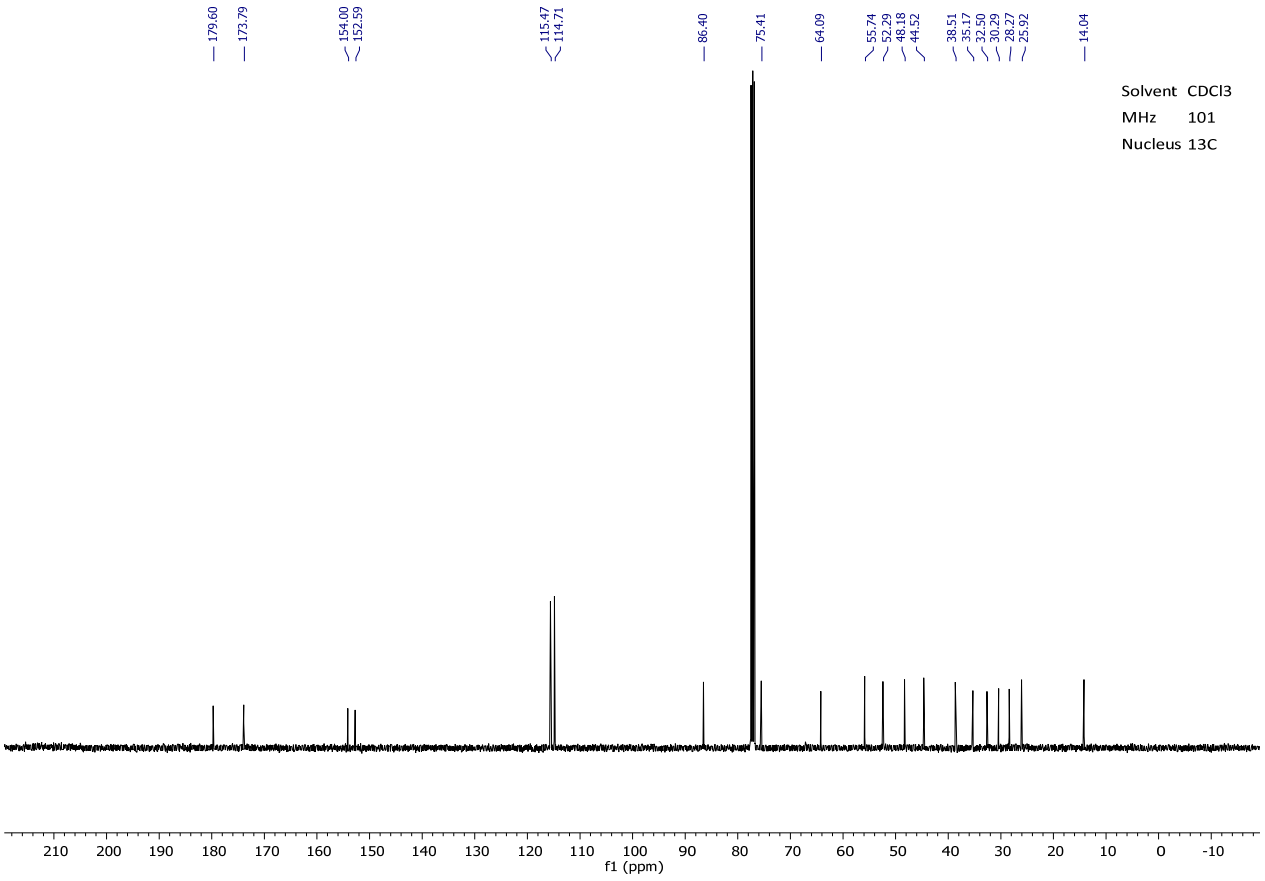
Solvent CDCl3
MHz 400
Nucleus 1H
4.80
0.98
0.99
2.38
3.72
0.99
1.04
2.14
3.33
1.26
1.56
0.96
3.13
1.00
3.16
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


176.48
154.08
152.55
115.24
114.77
107.83
87.59
73.34
64.47
55.75
54.74
51.87
50.61
48.84
38.28
35.36
34.83
27.85
26.21
15.41
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

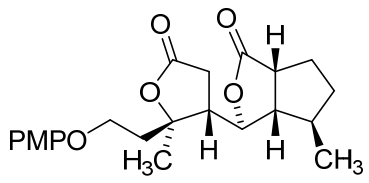


Solvent CDCl3
MHz 400
Nucleus 1H

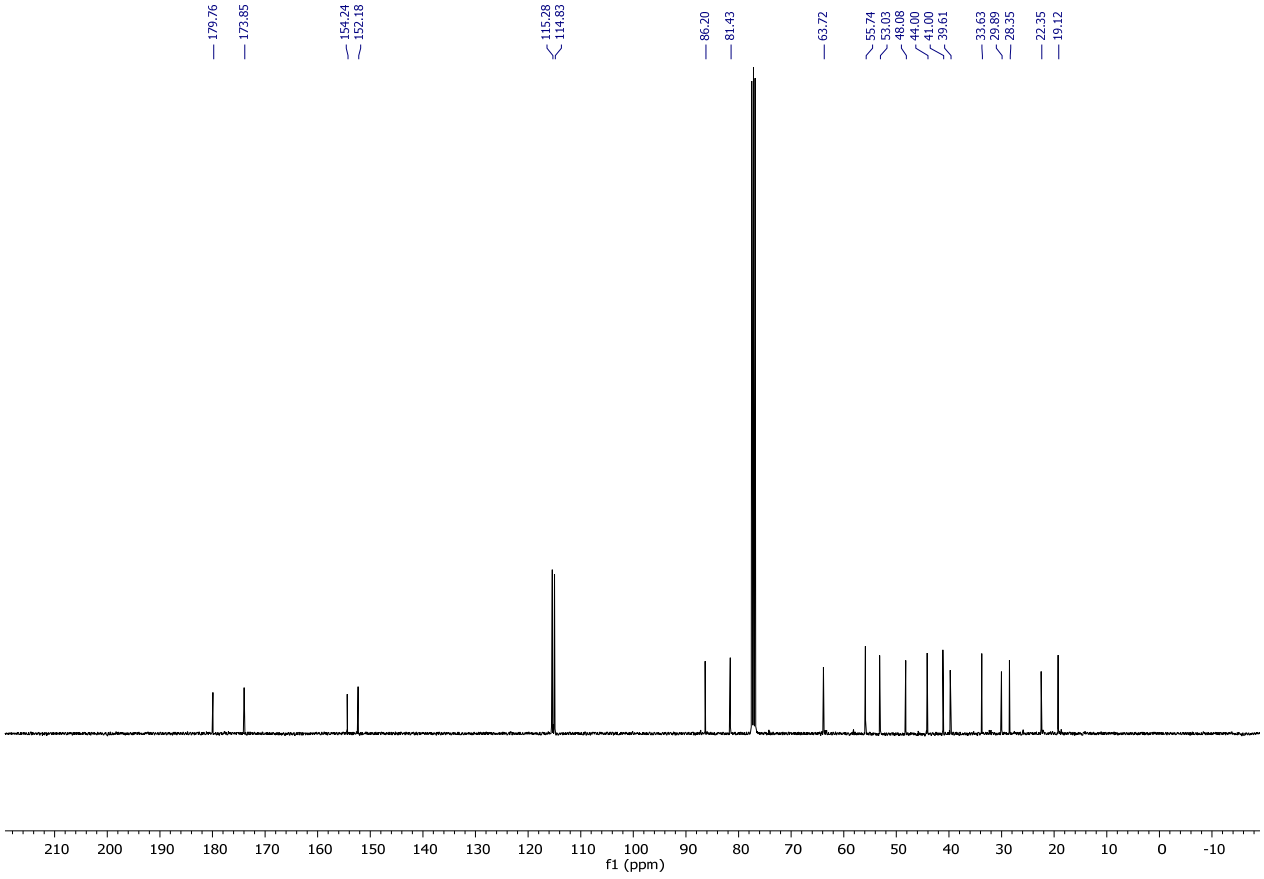


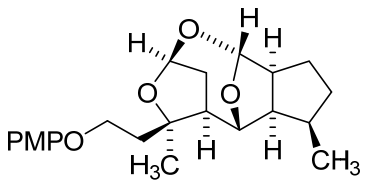


Solvent CDCl3
MHz 101
Nucleus 13C

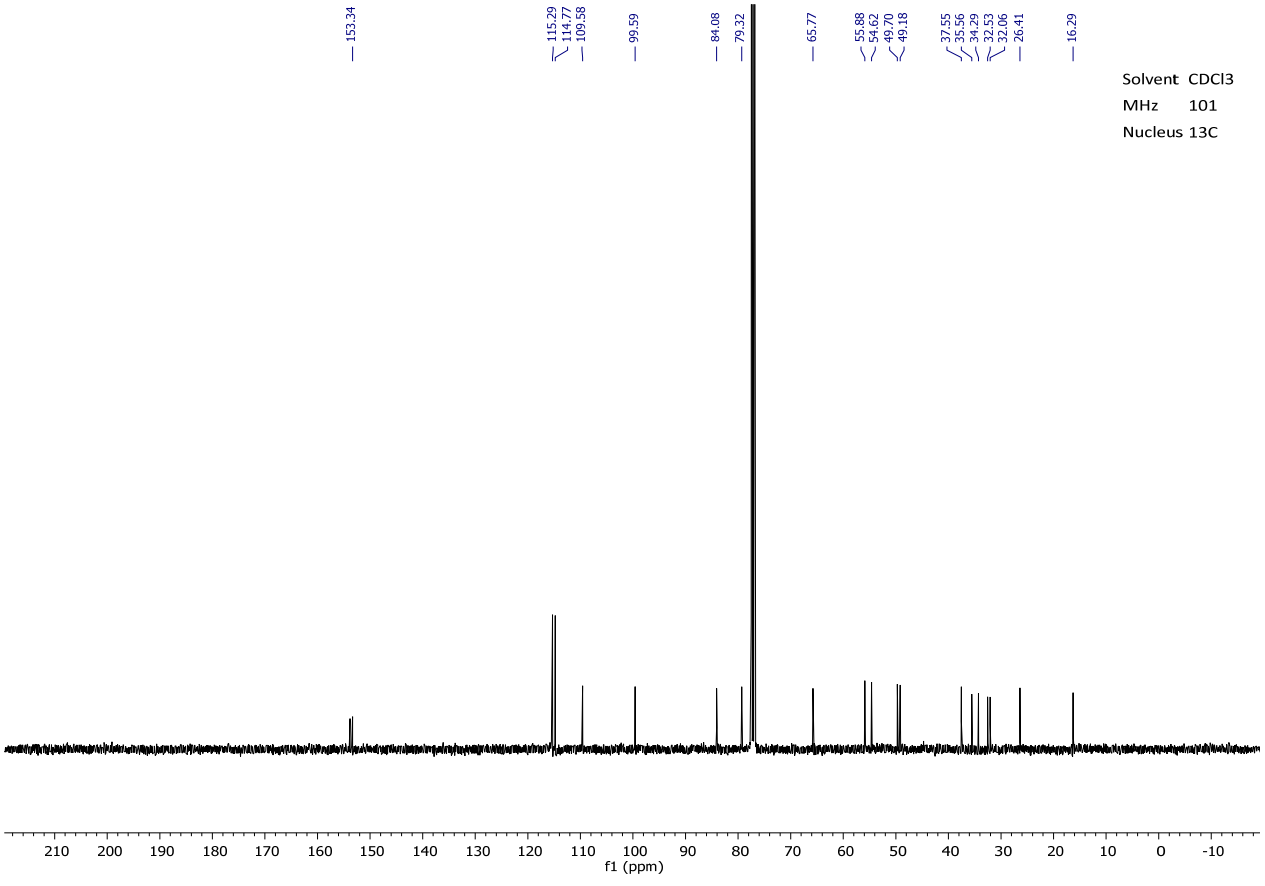

O
O
H
O
O
PMPO
H3C
H
H
CH3

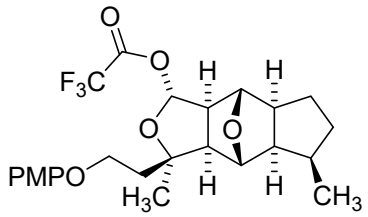
Solvent CDCl3
MHz 400
Nucleus 1H
4.49
0.97
2.34
3.36
0.99
1.00
1.85
4.47
2.21
1.24
2.90
1.14
3.10
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


179.76
173.85
154.24
152.18
115.28
114.83
86.20
81.43
63.72
55.74
53.03
48.08
44.00
41.00
39.61
33.63
29.89
28.35
22.35
19.12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

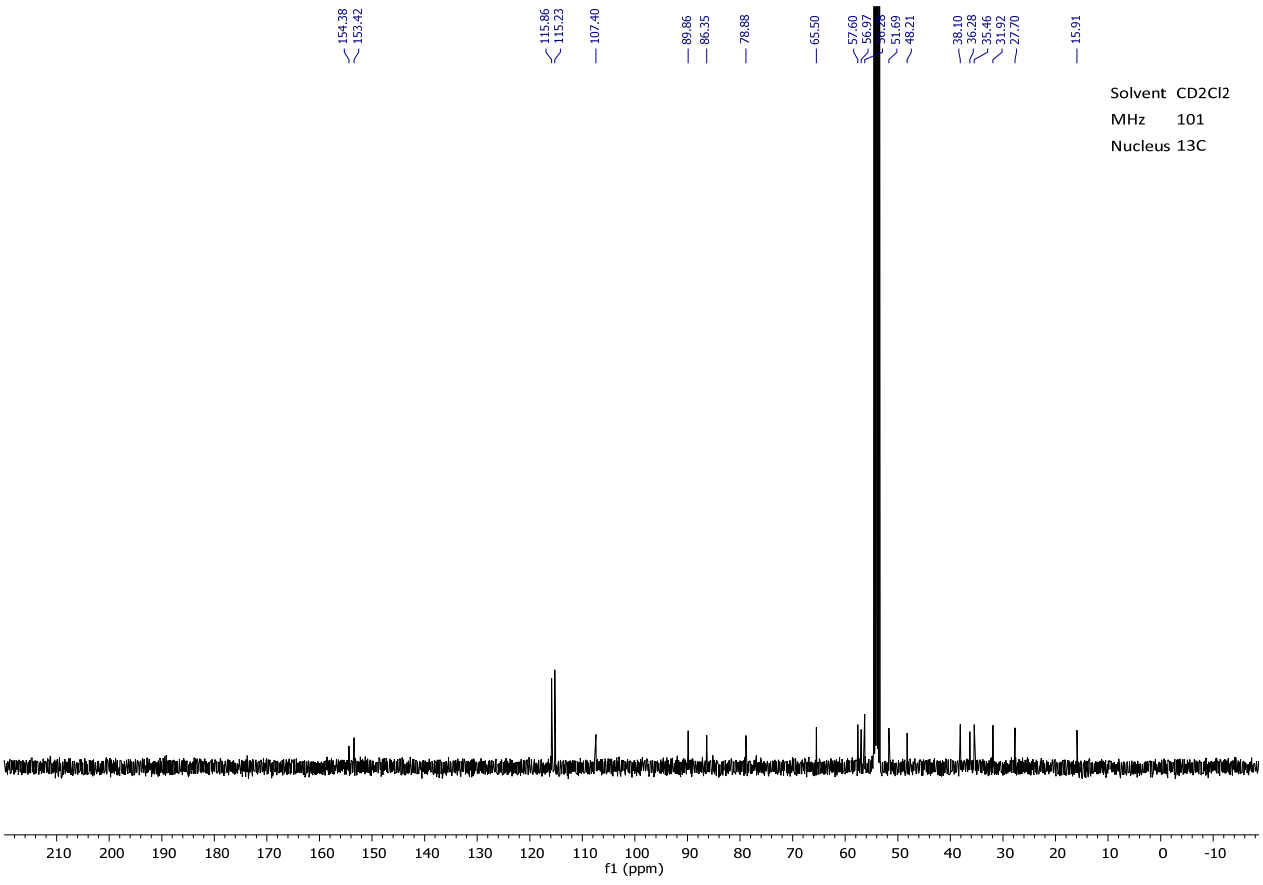

H
O
H
H
O
O
PMPO
H3C
H
H
CH3

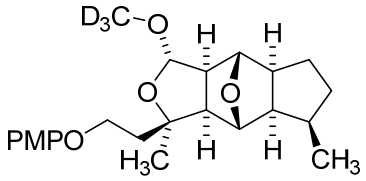
Solvent CDCl3
MHz 400
Nucleus 1H
5.07
1.01
1.04
1.00
2.80
3.80
1.04
1.13
2.46
2.14
2.78
4.21
5.07
3.19
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


153.34
115.29
114.77
109.58
99.59
84.08
79.32
65.77
55.88
54.62
49.70
49.18
37.55
35.56
34.29
32.53
32.06
26.41
16.29
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

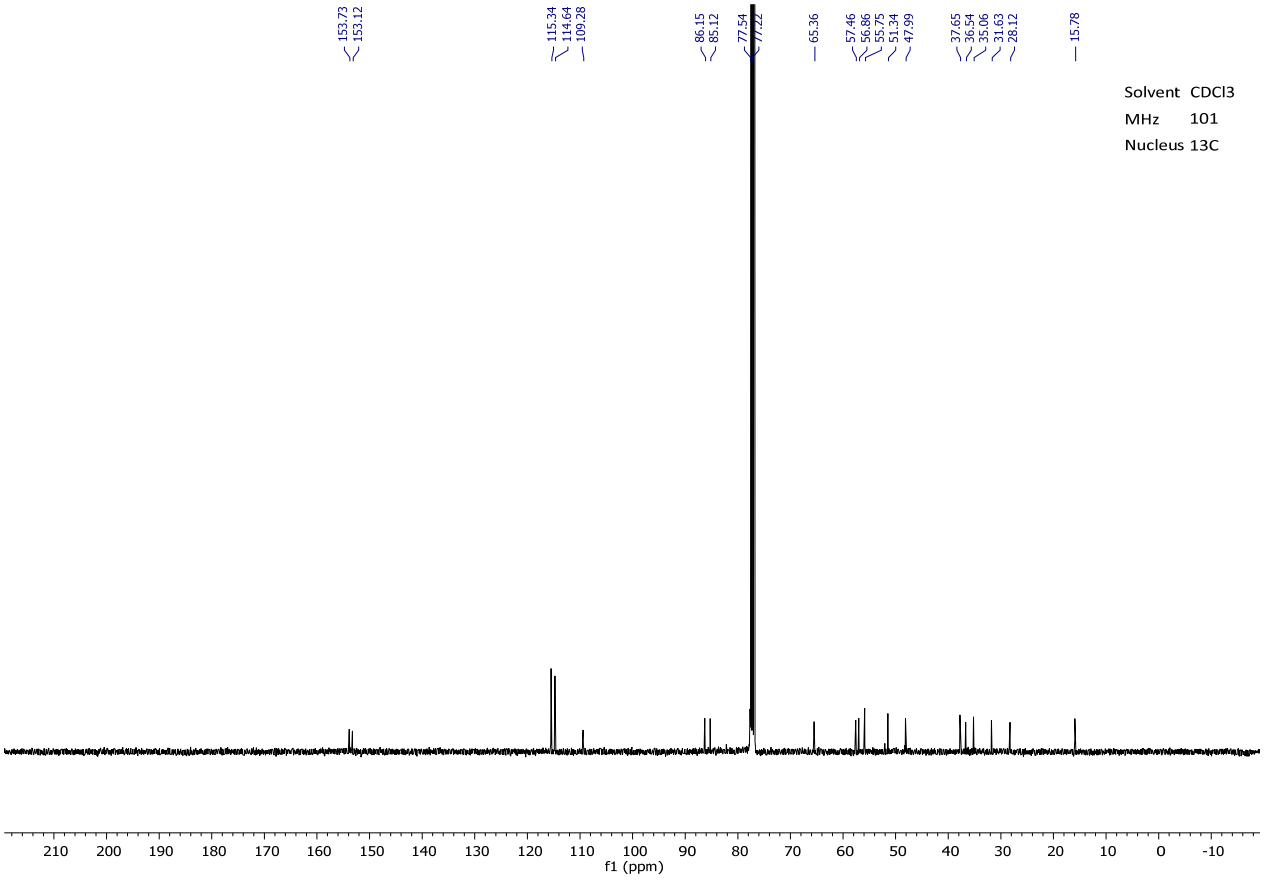

O
O
F3C
H
H
O
O
PMPO
H3C
H
H
CH3

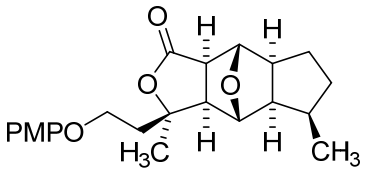
Solvent CD2Cl2
MHz 400
Nucleus 1H
3.98
0.80
0.80
0.76
2.08
3.00
0.81
1.44
1.56
1.82
1.30
2.96
2.41
1.42
3.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


154.38
153.42
115.86
115.23
107.40
89.86
86.35
78.88
65.50
57.60
56.97
51.69
48.21
38.10
36.28
35.46
31.92
27.70
15.91
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

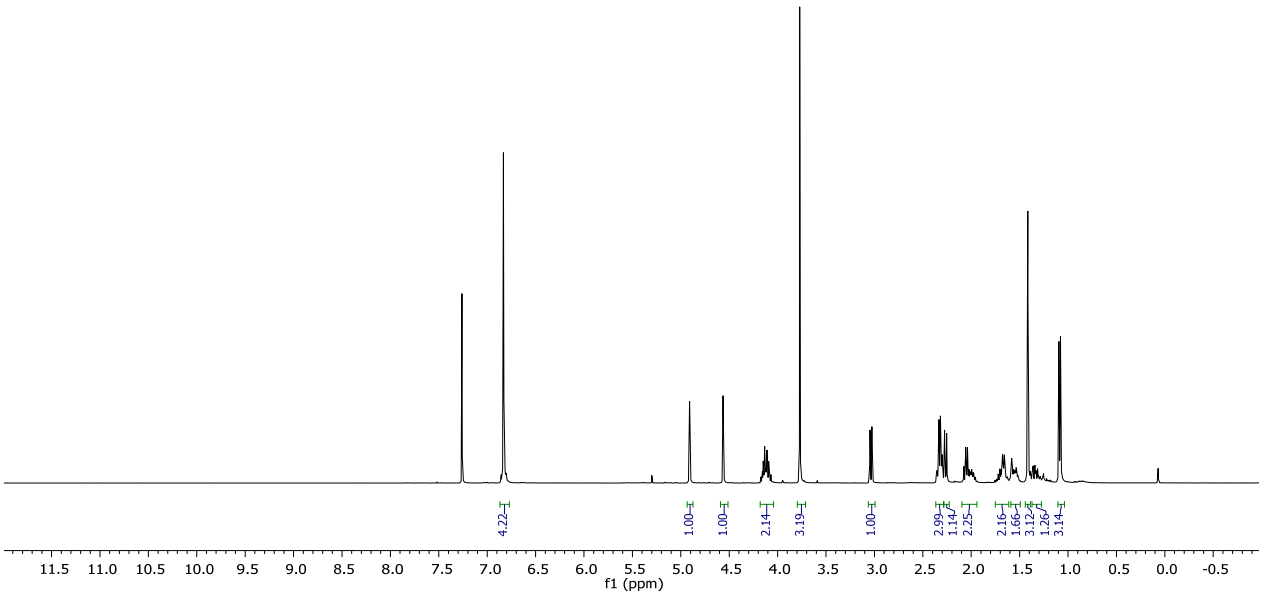

D3C
O
H
H
O
O
PMPO
H3C
H
H
CH3

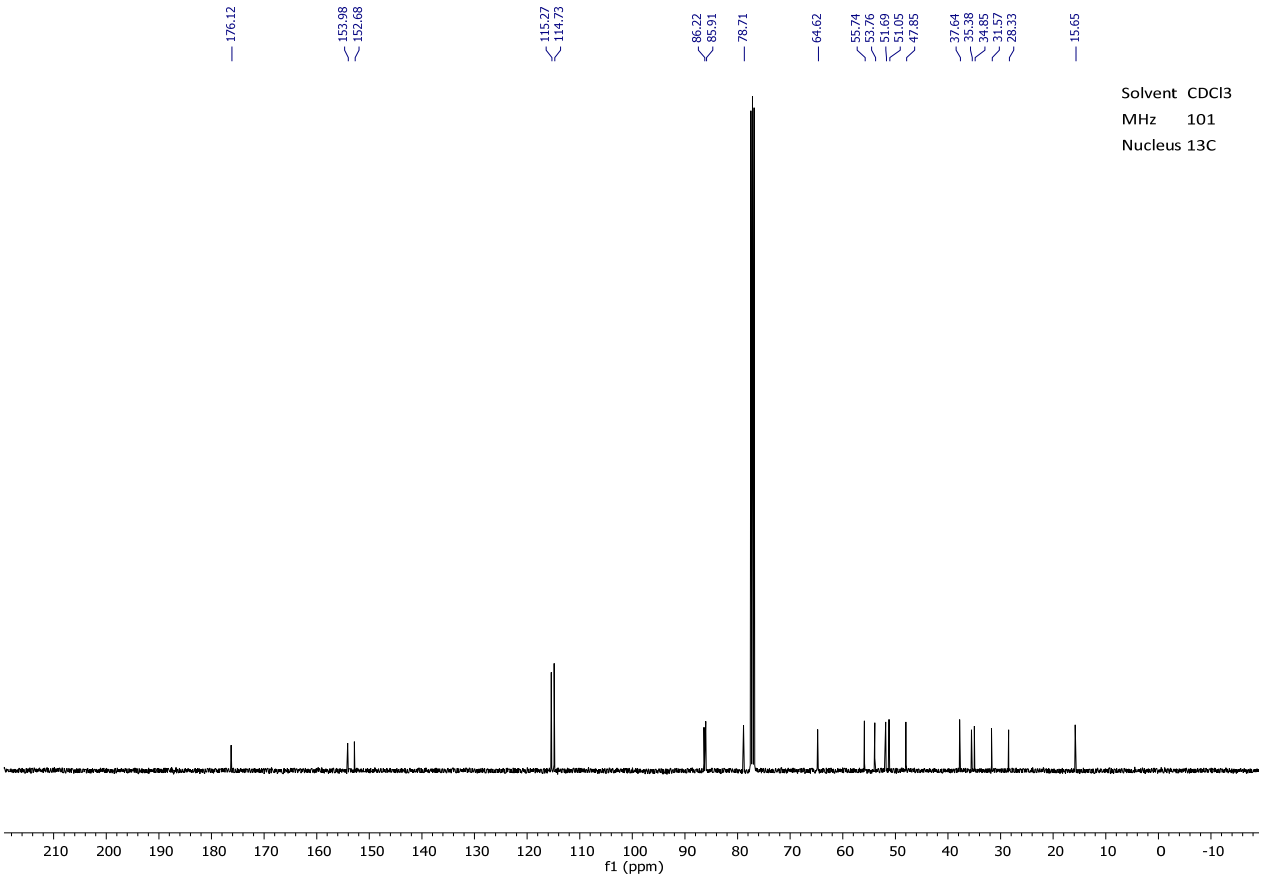
Solvent CDCl3
MHz 400
Nucleus 1H
4.75
0.89
0.91
0.89
2.52
3.53
0.97
1.09
3.14
2.53
1.89
1.21
1.26
3.21
3.08
f1 (ppm)


153.73
153.12
115.34
114.64
109.28
86.15
85.12
77.54
77.22
65.36
57.46
56.86
55.75
51.34
47.99
37.65
36.54
35.06
31.63
28.12
15.78
Solvent CDCl3
MHz 101
Nucleus 13C
f1 (ppm)

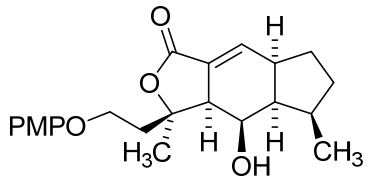


Solvent CDCl3
MHz 400
Nucleus 1H

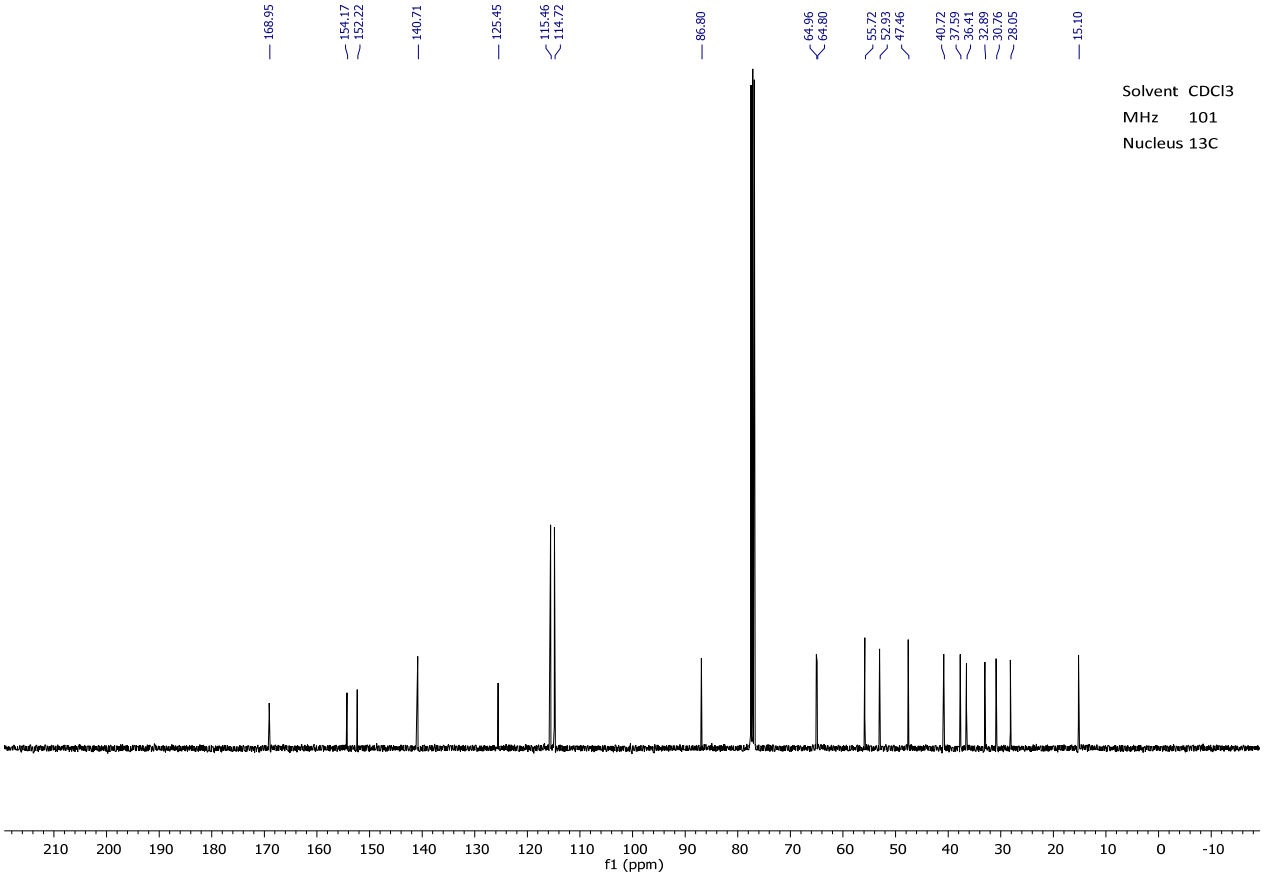


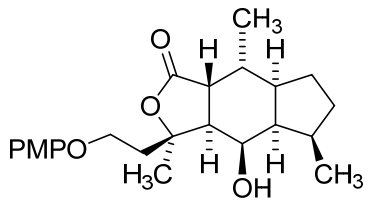


Solvent CDCl3
MHz 101
Nucleus 13C

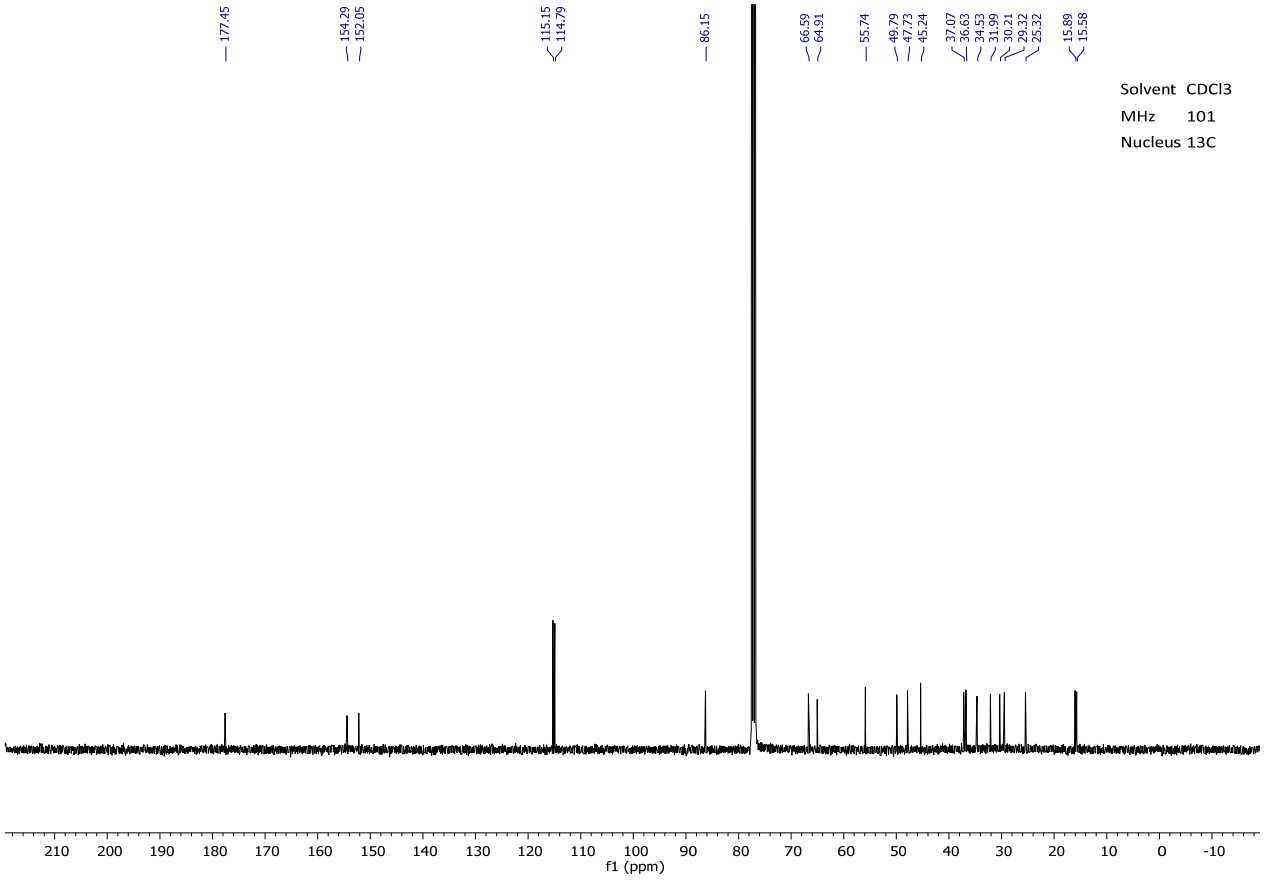

O
H
O
PMPO
H3C
H
OH
H
CH3

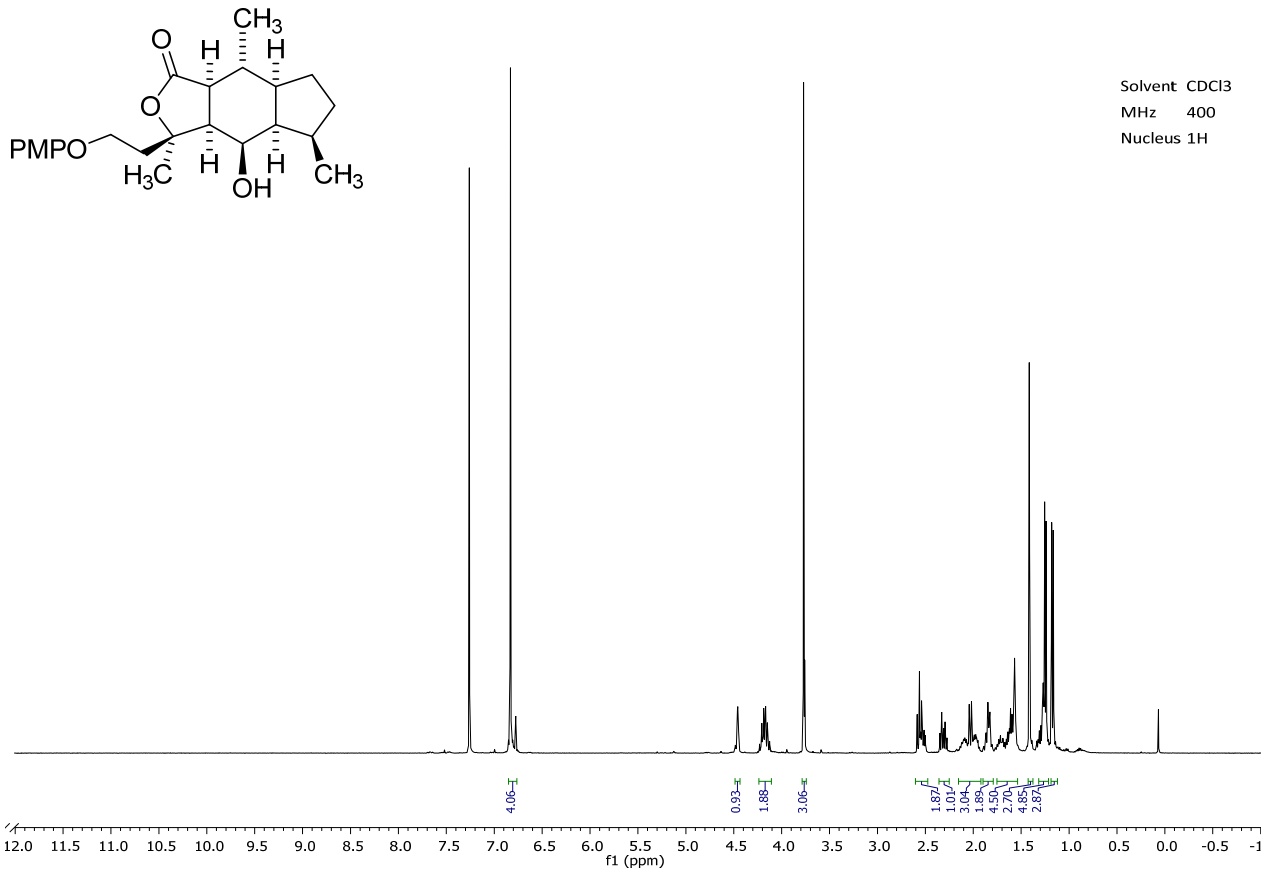
Solvent CDCl3
MHz 400
Nucleus 1H
1.00
4.26
1.00
2.12
3.23
1.01
1.02
1.96
1.27
2.15
1.07
1.07
5.40
3.10
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

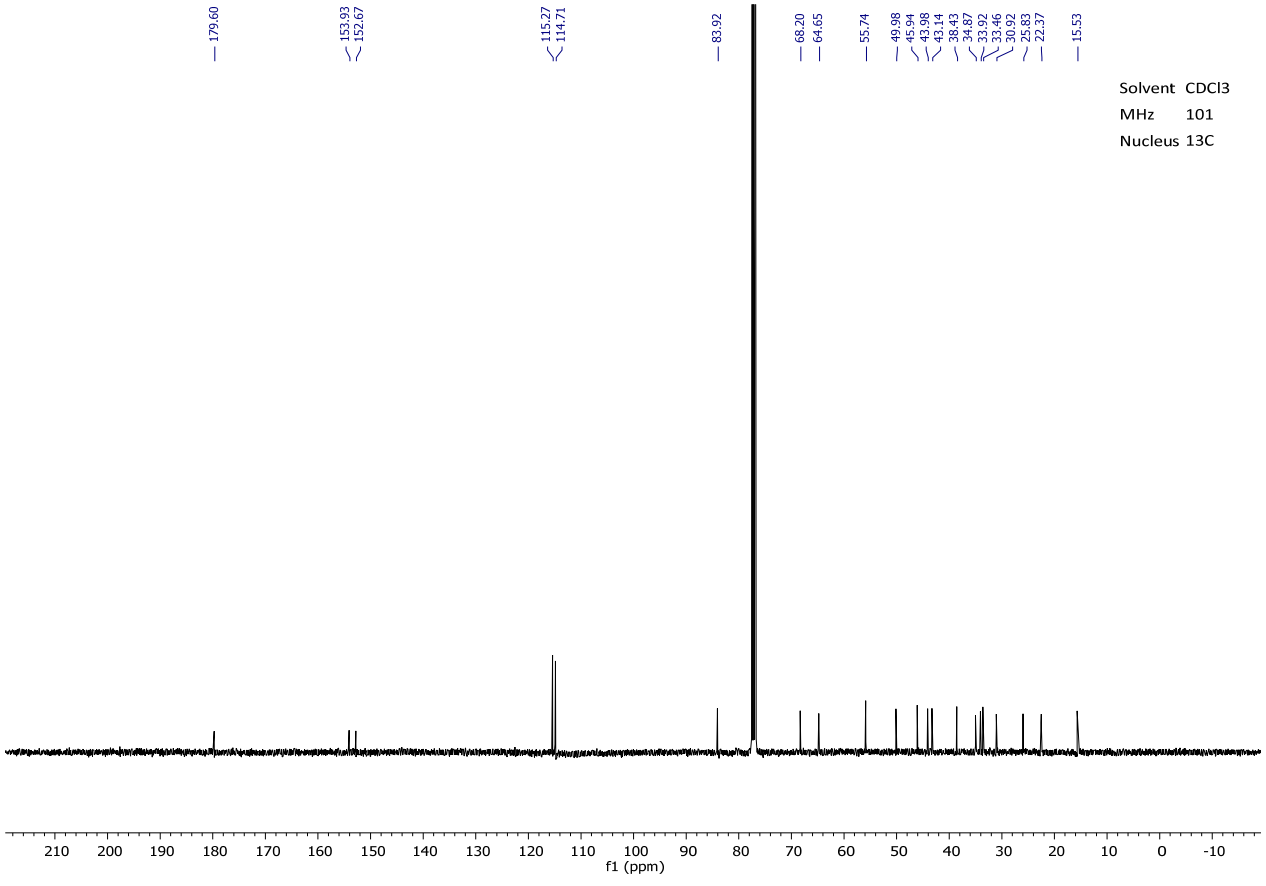

168.95
154.17
152.22
140.71
125.45
115.46
114.72
86.80
64.96
64.80
55.72
52.93
47.46
40.72
37.59
36.41
32.89
30.76
28.05
15.10
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

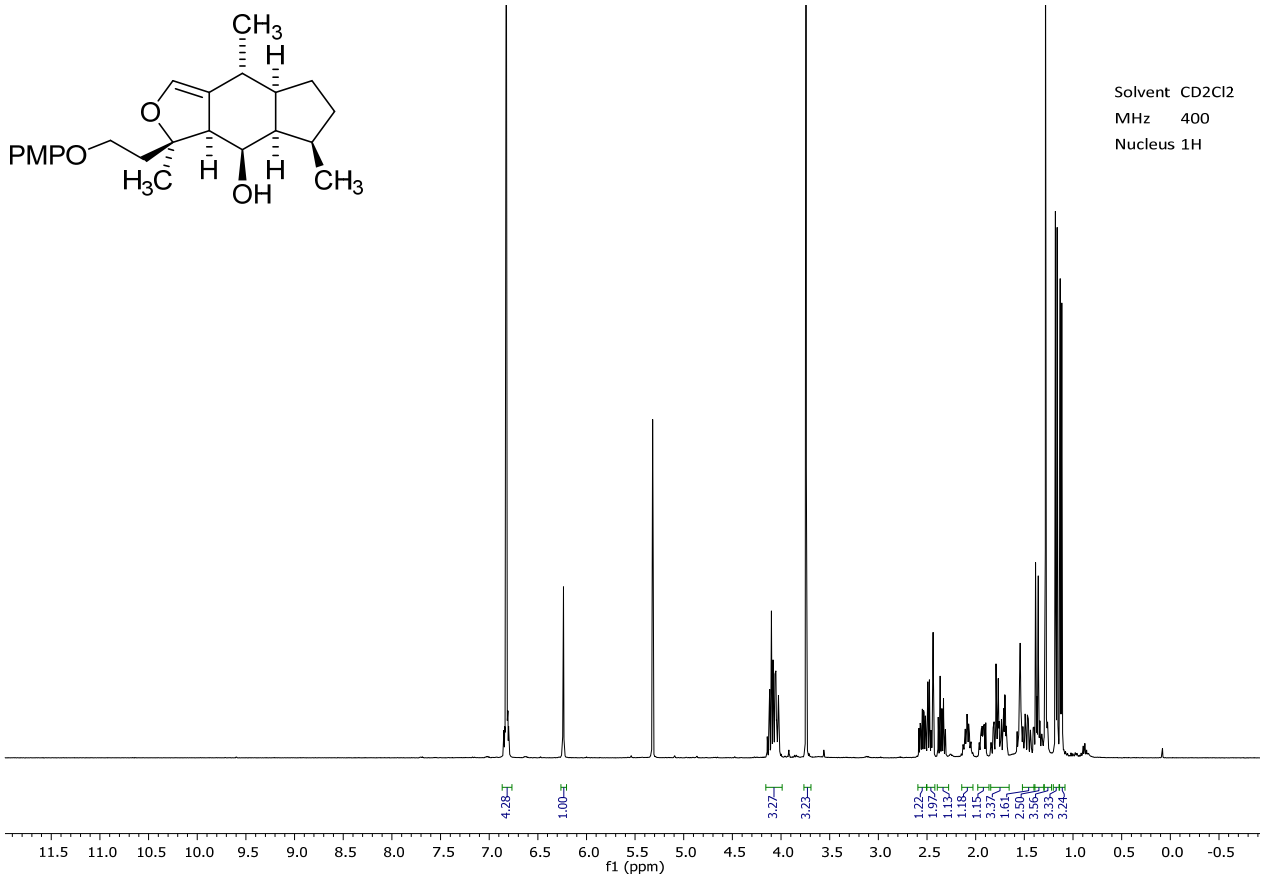

CH3
O
H
H
O
PMPO
H3C
H
H
OH
CH3

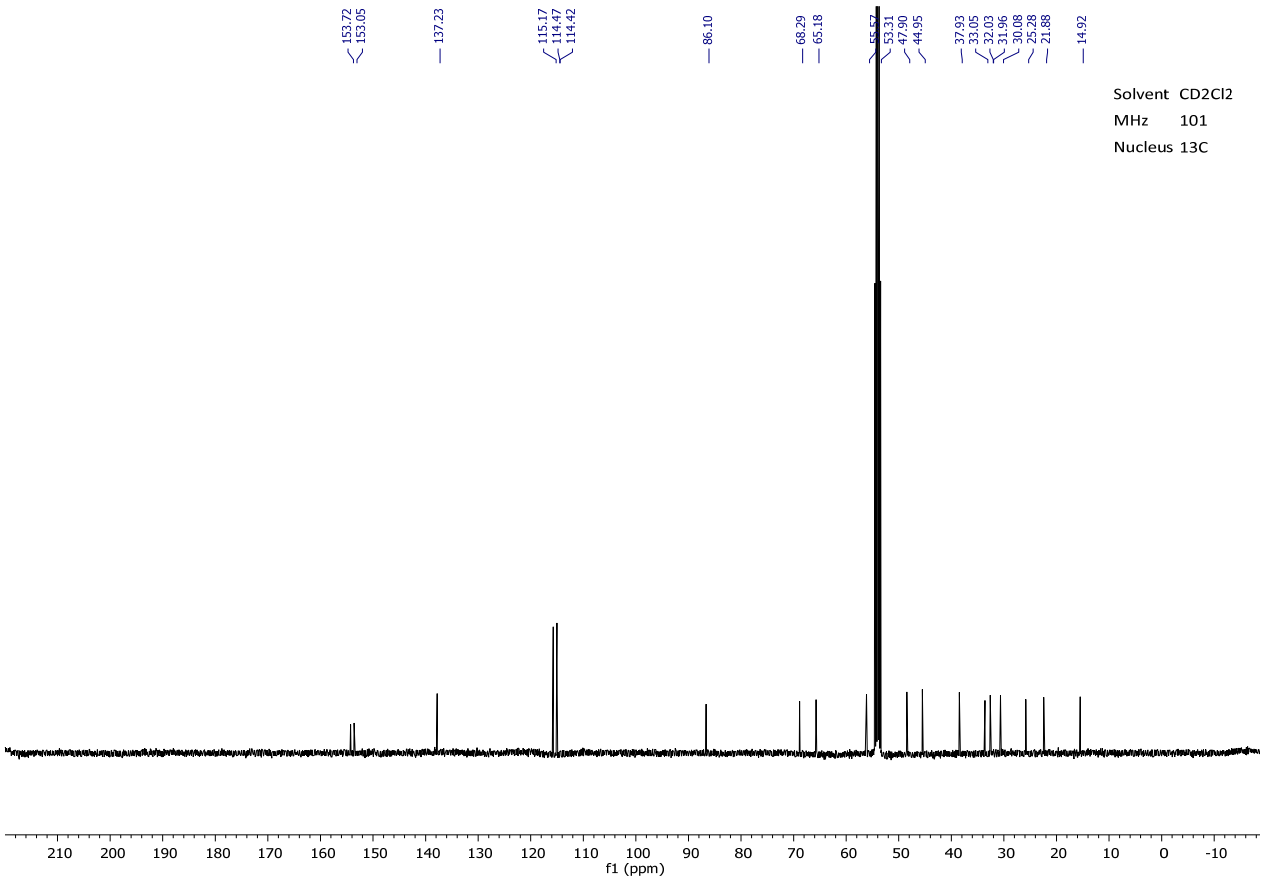
Solvent CDCl3
MHz 599
Nucleus 1H
3.67
0.99
1.99
2.74
1.09
1.97
1.09
1.27
2.13
2.19
2.88
5.43
1.35
2.96
2.82
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


177.45
154.29
152.05
115.15
114.79
86.15
66.59
64.91
55.74
49.79
47.73
45.24
37.07
36.63
34.53
31.99
30.21
29.32
25.32
15.89
15.58
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
O
H
H
O
PMPO
H3C
H
H
OH
CH3
Solvent CDCl3
MHz 400
Nucleus 1H
4.06
0.93
1.88
3.06
1.87
1.01
3.04
1.89
4.50
2.70
4.85
2.87
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


179.60
153.93
152.67
115.27
114.71
83.92
68.20
64.65
55.74
49.98
45.94
43.98
43.14
38.43
34.87
33.92
33.46
30.92
25.83
22.37
15.53
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
H
O
PMPO
H3C
H
OH
H
CH3
Solvent CD2Cl2
MHz 400
Nucleus 1H
4.28
1.00
3.27
3.23
1.22
1.97
1.13
1.18
1.15
3.37
1.61
2.50
3.56
3.33
3.24
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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44.95
37.93
33.05
32.03
31.96
30.08
25.28
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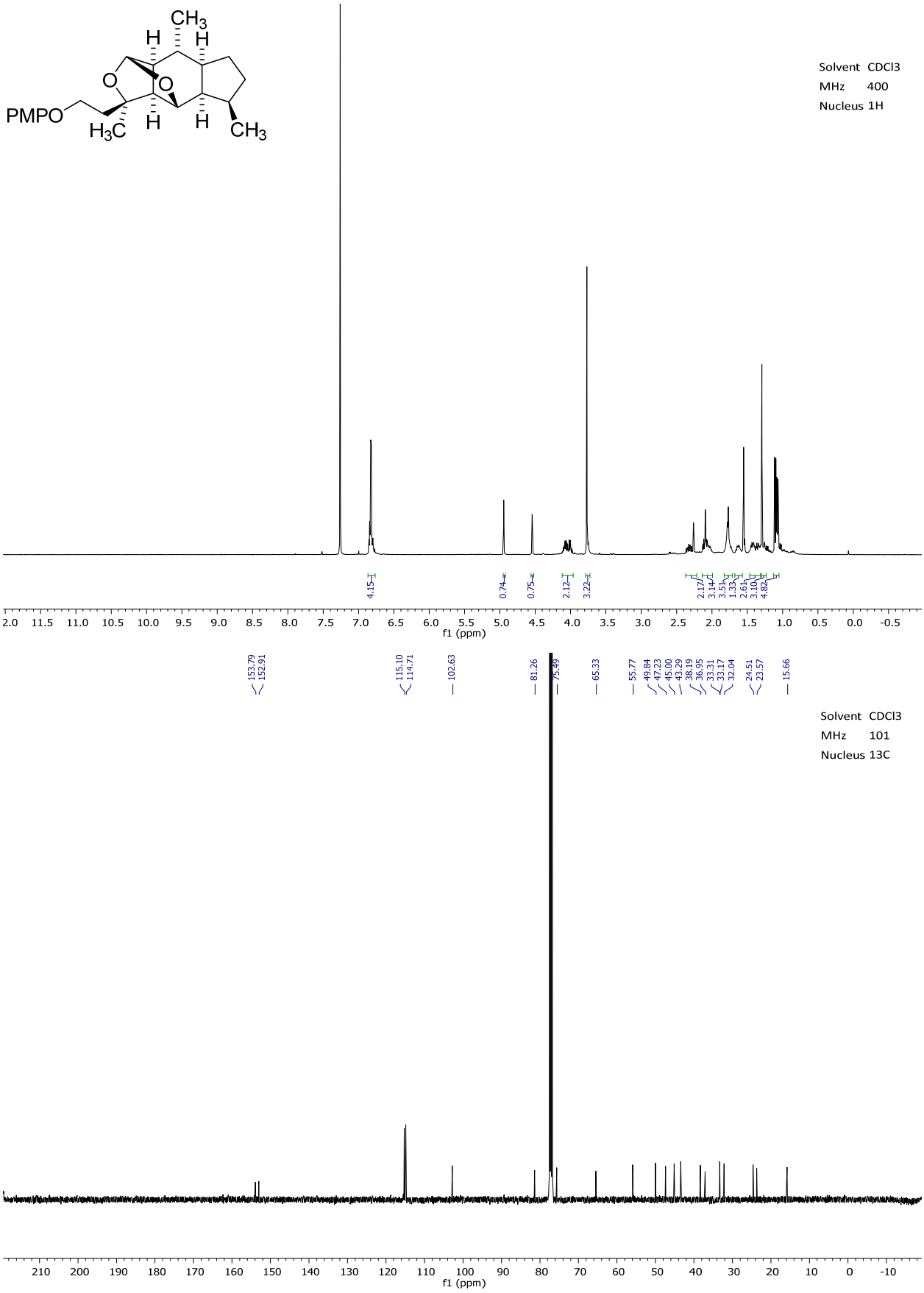
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H
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3.51
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3.10
4.82
f1 (ppm)
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45.00
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38.19
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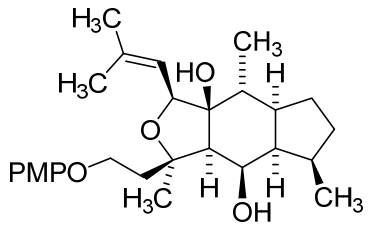
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2.95
0.93
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7.01
2.34
3.00
3.21
3.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
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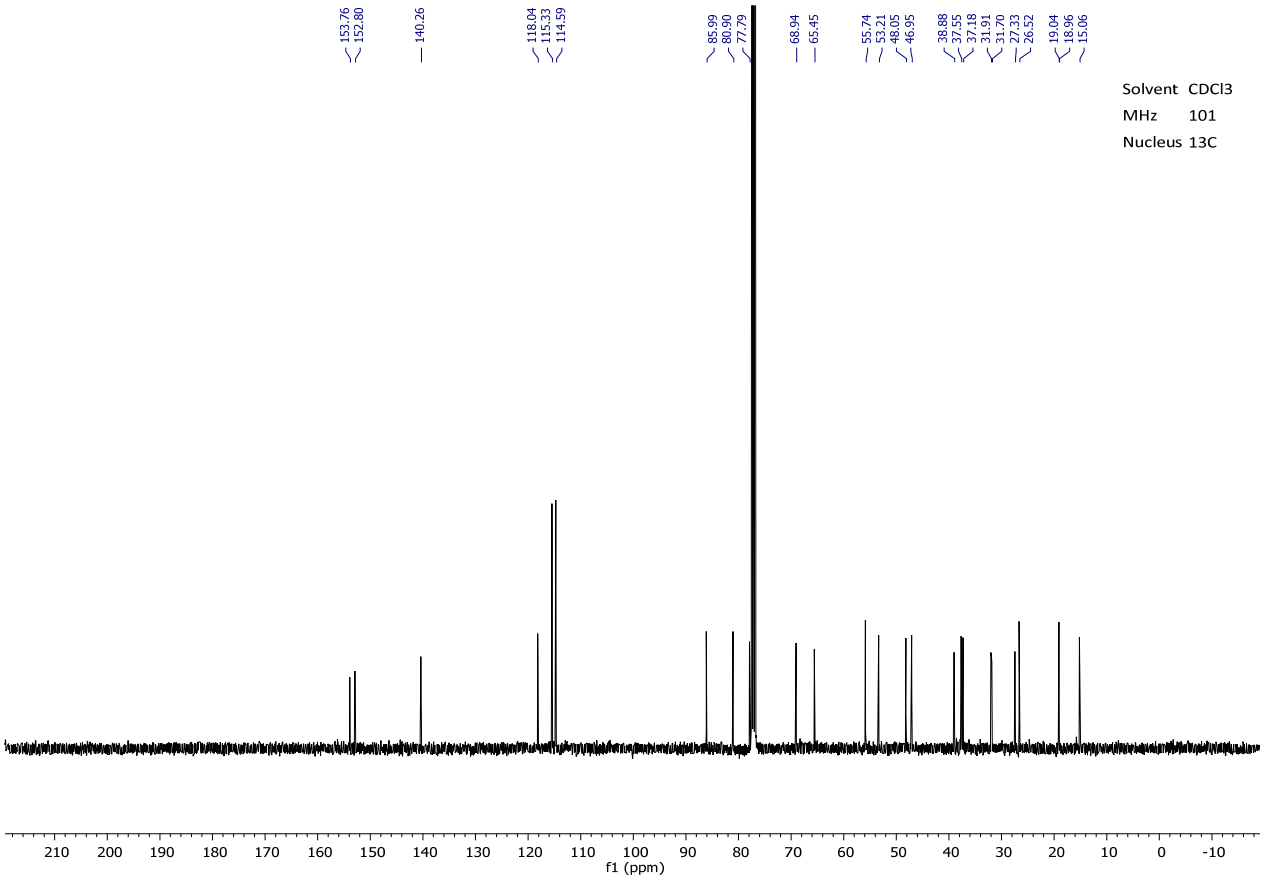
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19.04
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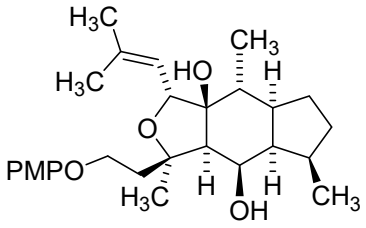
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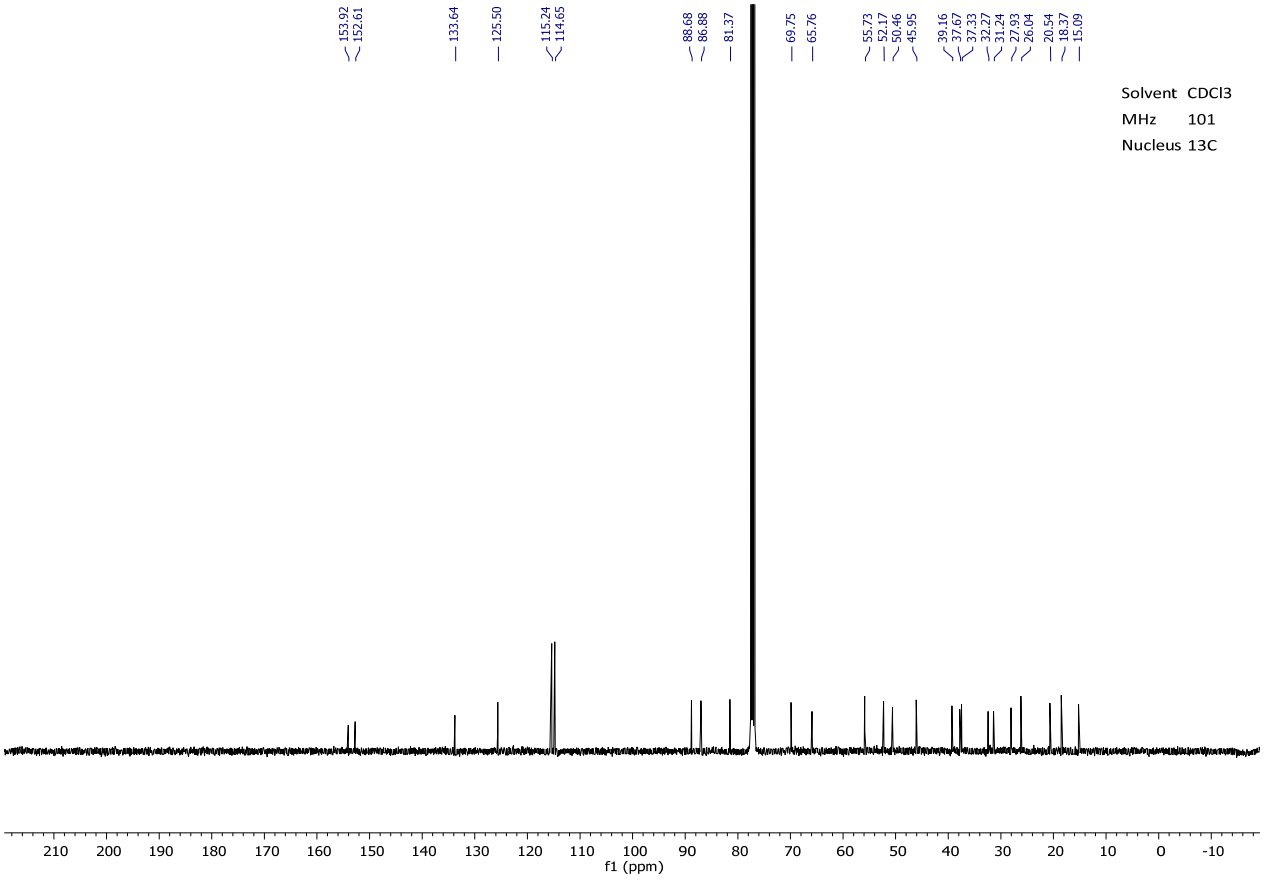
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32.27
31.24
27.93
26.04
20.54
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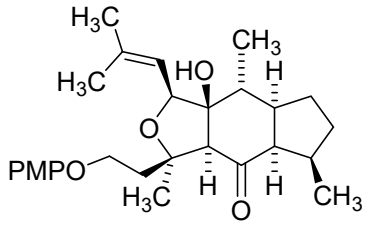
f1 (ppm)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PMPO
H3C
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H
CH3
O

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0.99
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1.13
2.20
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3.56
6.48
2.00
1.34
3.37
3.32
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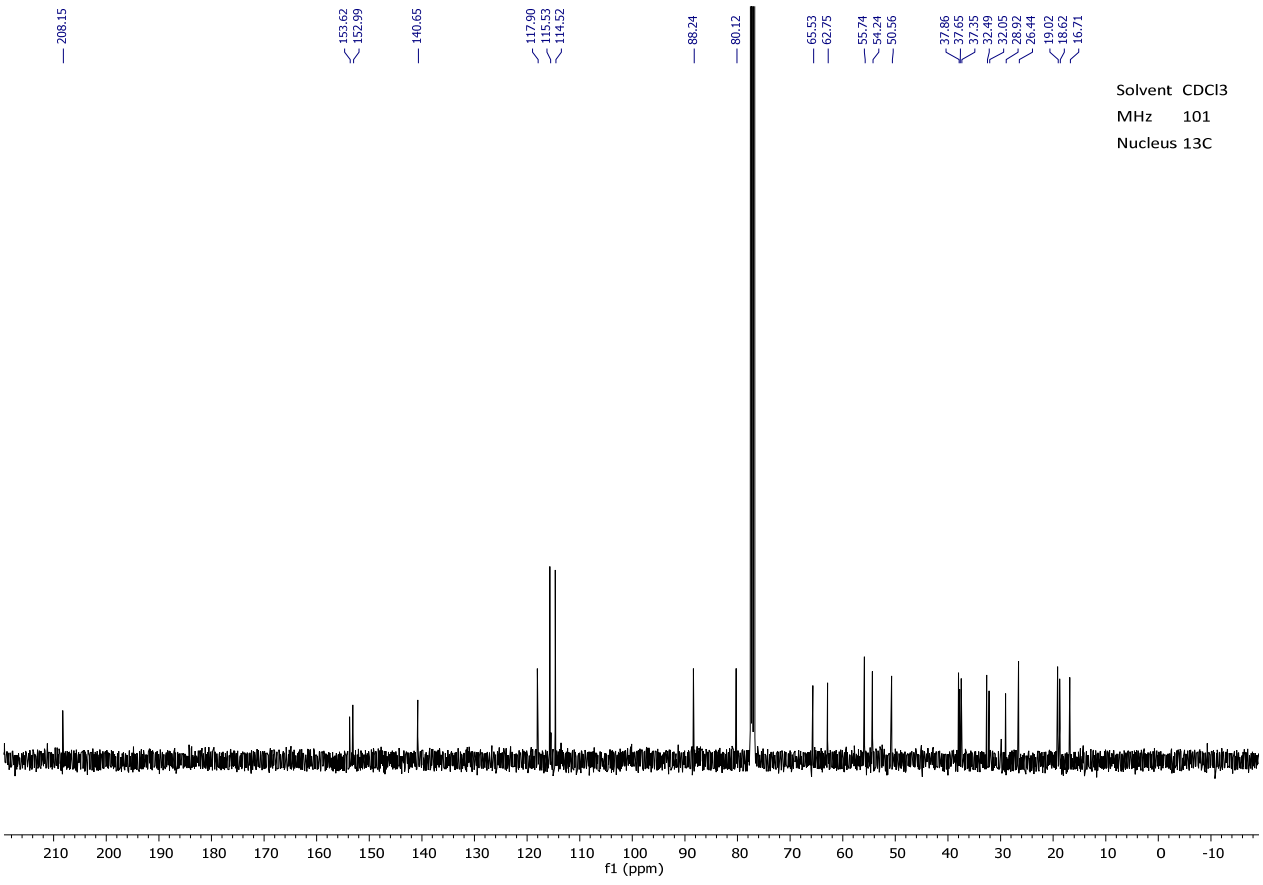
f1 (ppm)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37.65
37.35
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32.05
28.92
26.44
19.02
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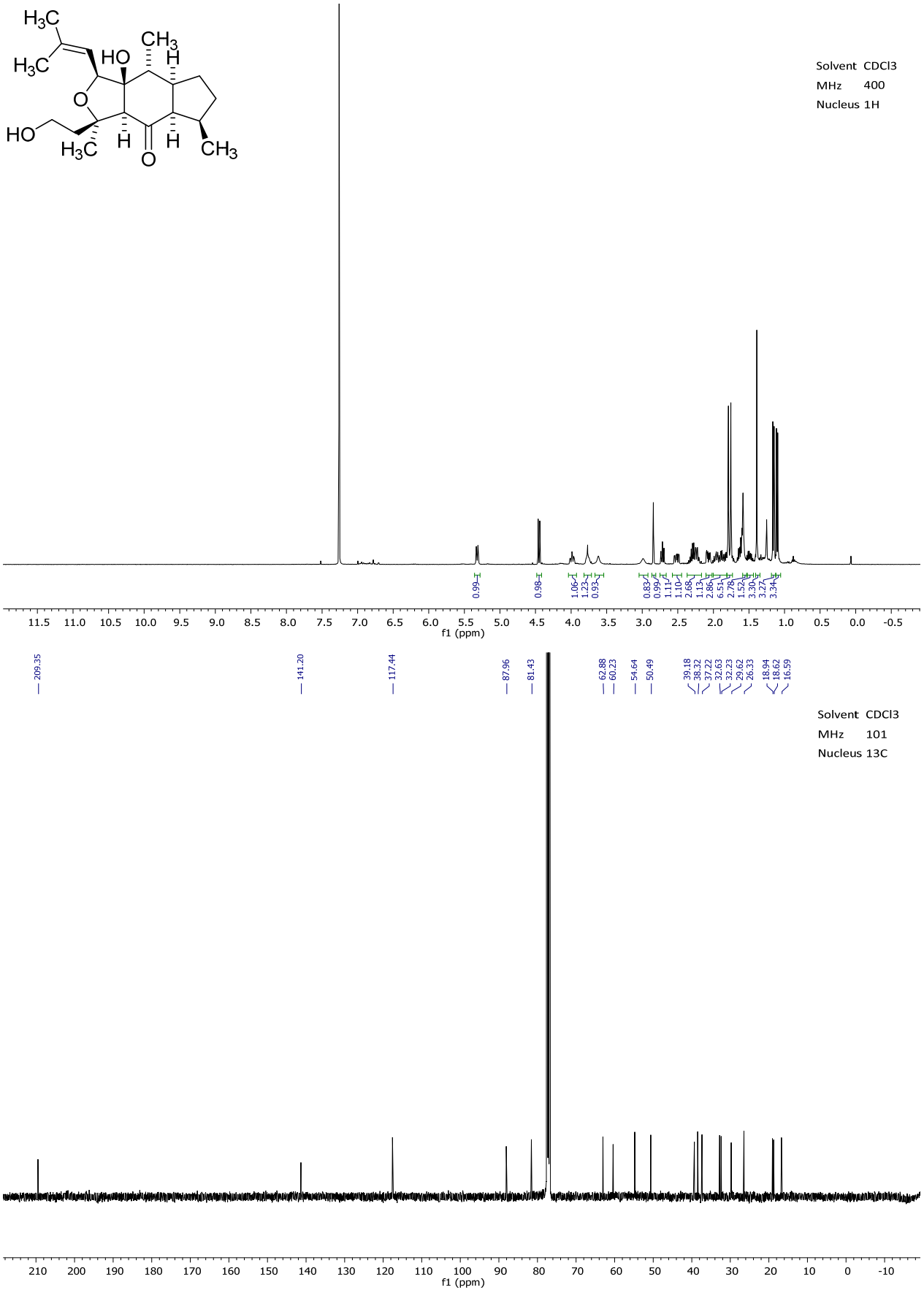
f1 (ppm)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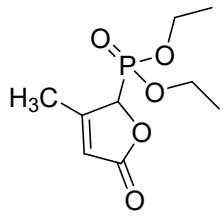
f1 (ppm)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O
H3C
O
O

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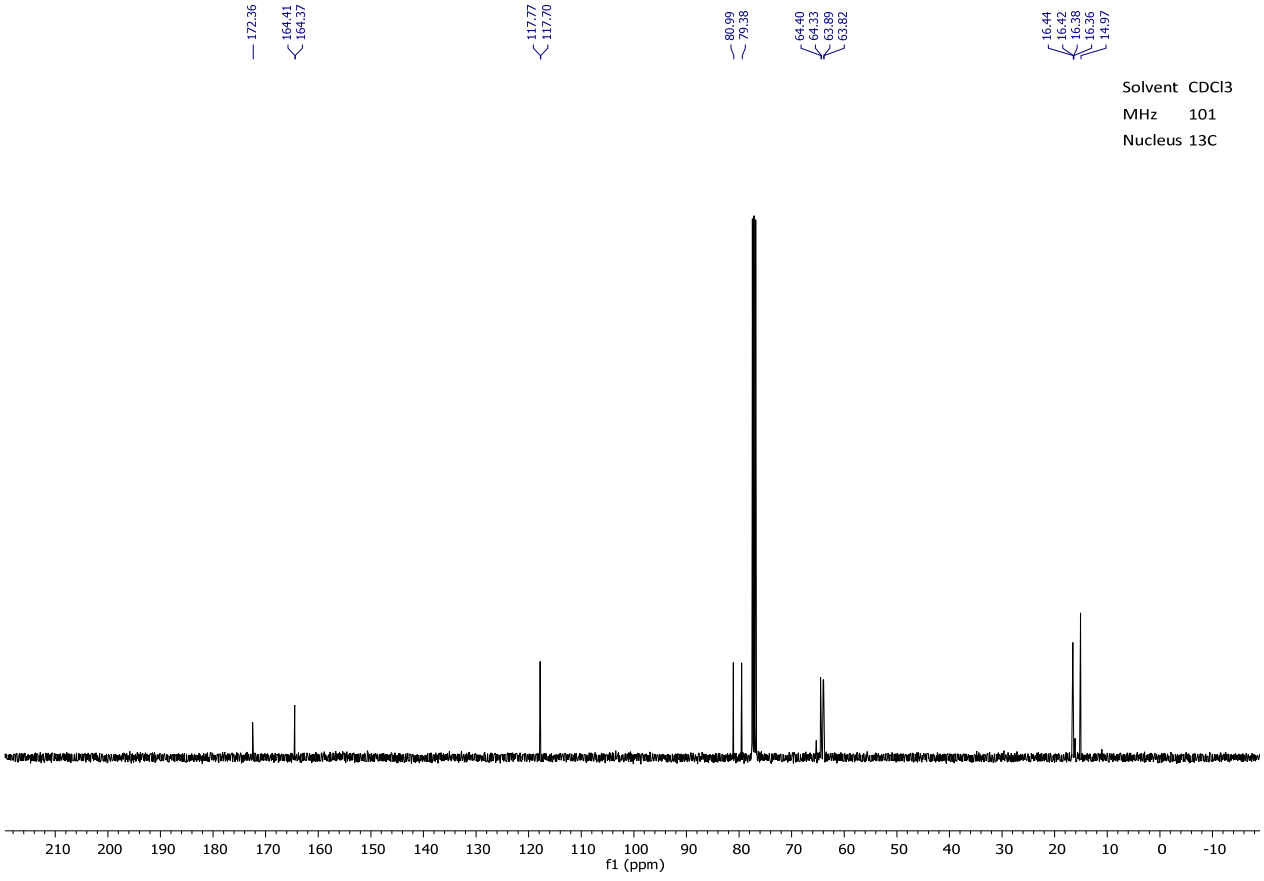
7.47
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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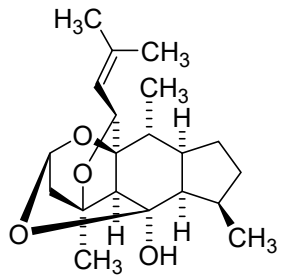
f1 (ppm)



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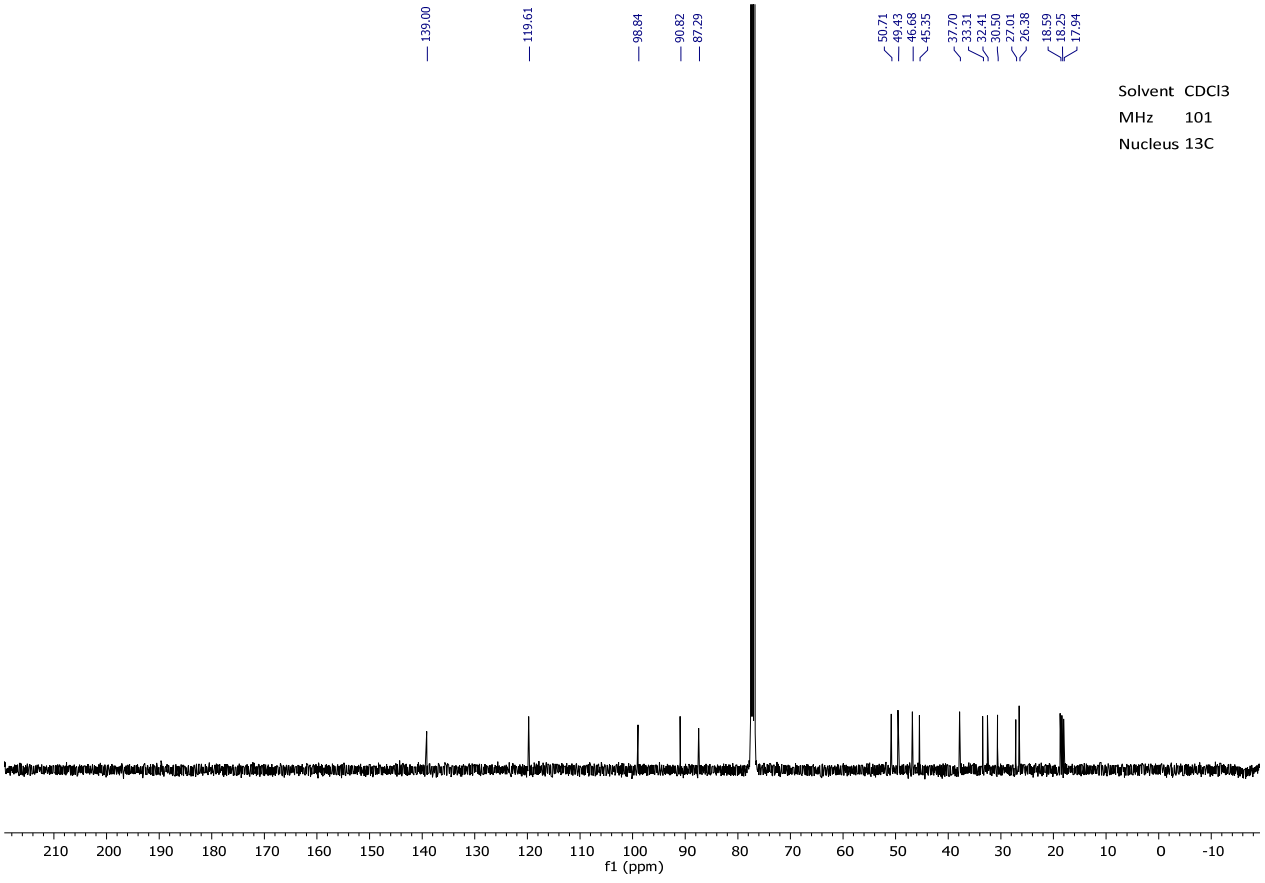
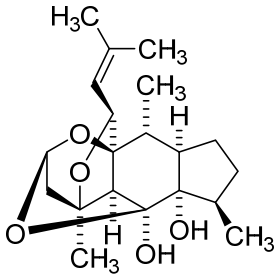
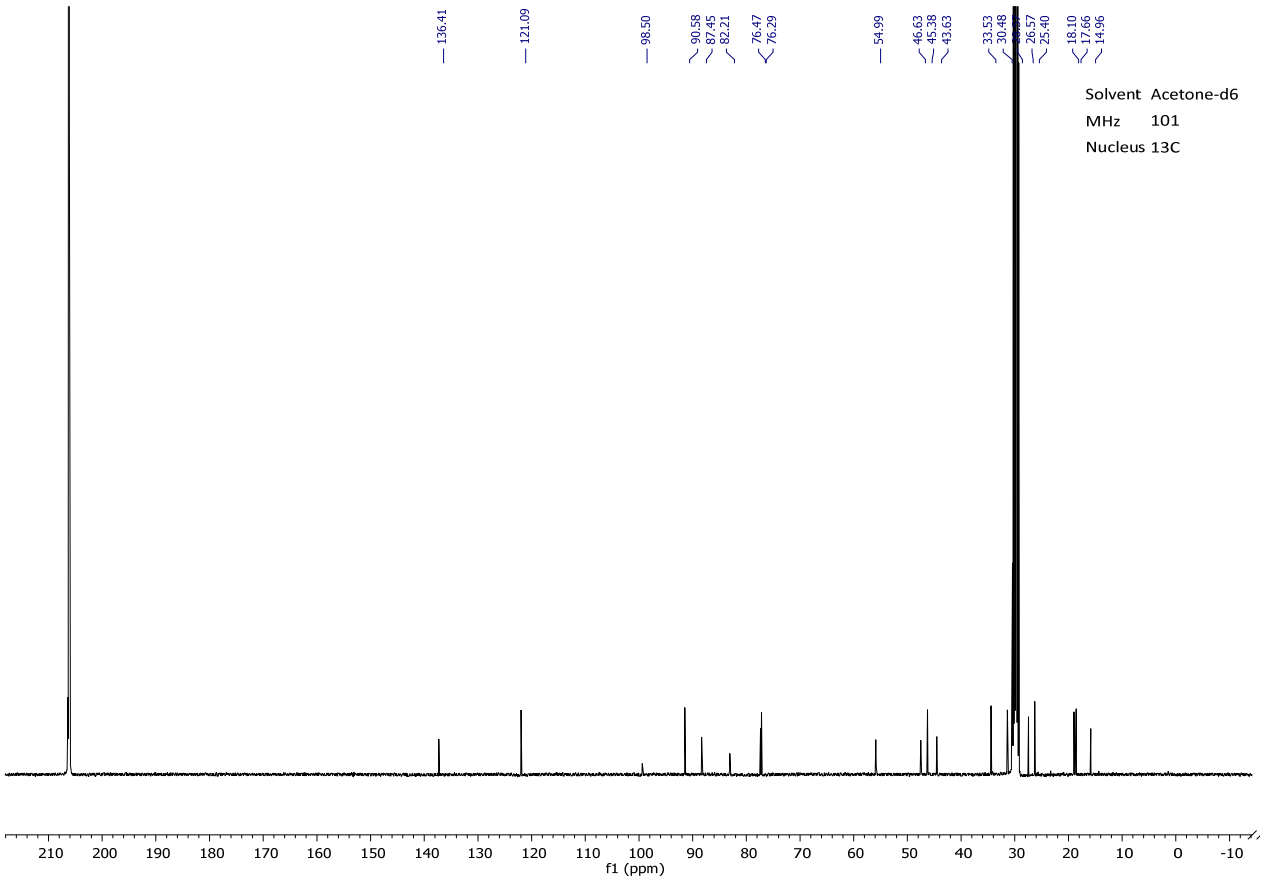
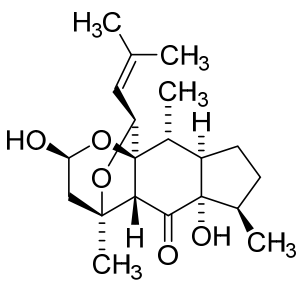




(+)-norleucosceptroid A





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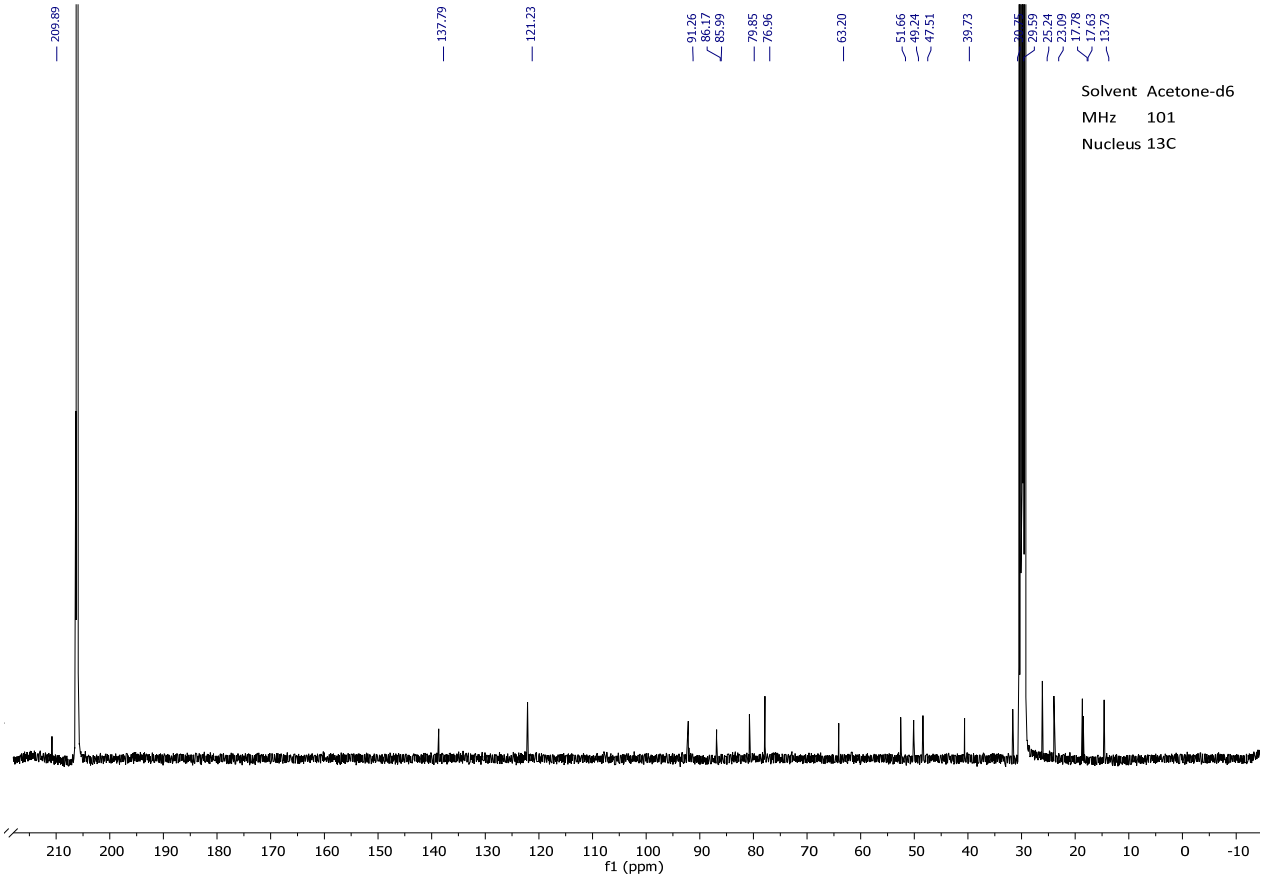
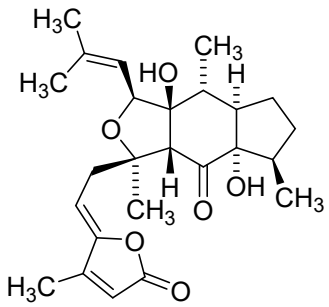
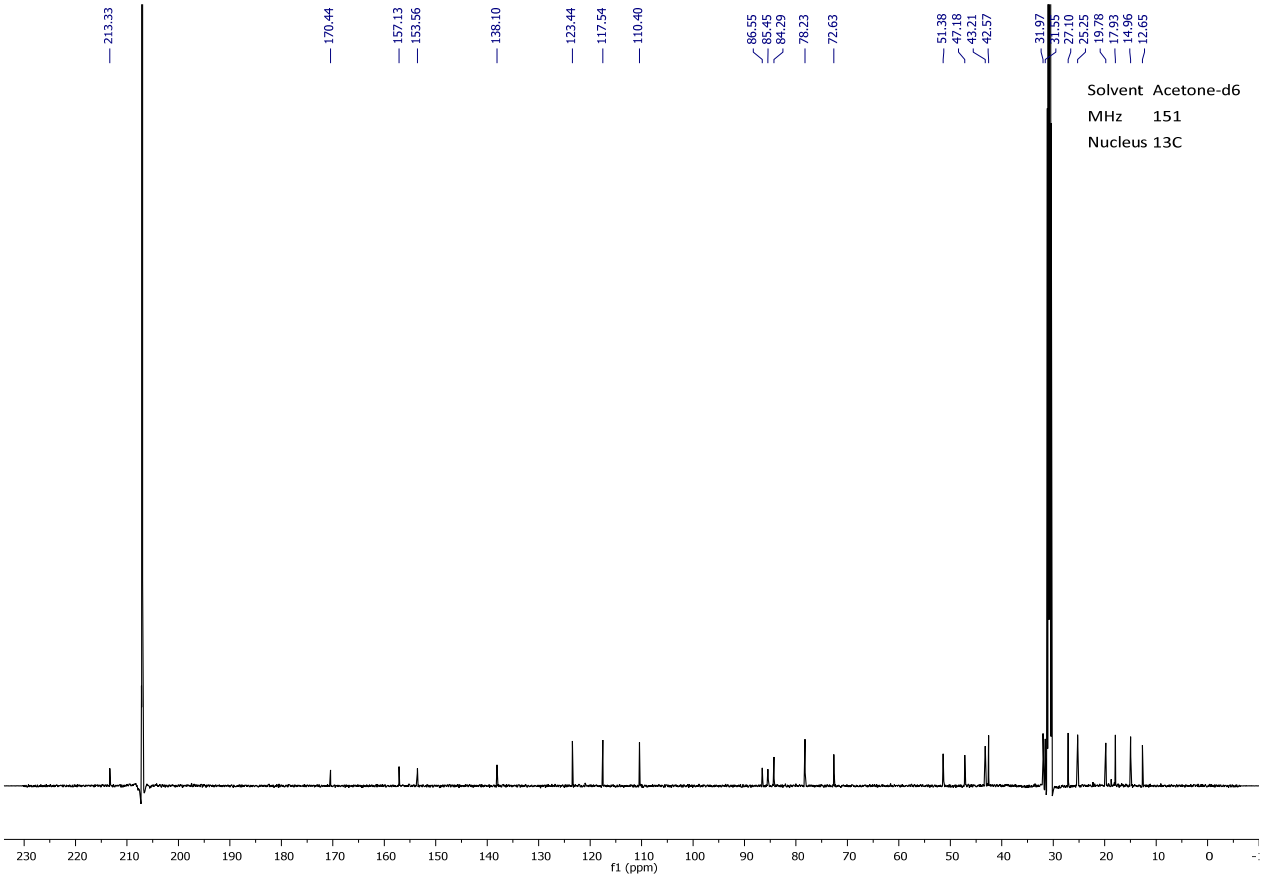




(–)-leucosceptroid K



6.2 Supporting Information for Chapter 2.2.2

Unraveling the Metabolic Pathway in *Leucosceptrum canum* by Isolation of New Defensive Leucosceptroid Degradation Products and Biomimetic Model Synthesis

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[†]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, People's Republic of China*

[∥]*Department of Chemistry and Pharmacy, Ludwig-Maximilians-University Munich, Butenandstrasse 5–13, 81377 Munich, Germany*

[‡]*Graduate University of Chinese Academy of Sciences, Beijing 100039, People's Republic of China*

6.2.1 Natural Product Isolation

Experimental procedures, plant material, crystallographic data, physical-chemical properties, key HMBC correlations, and 1D and 2D NMR spectra (*Figures S1-S47*) of norleucosceptroids D–H (**1**–**5**) and leucosceptroids P–Q (**6**–**7**).

General Experimental Details

Column chromatography was performed employing 200-300 mesh silica gel (Qingdao Marine Chemical Factory, P. R. China). Optical rotation values were measured on a Horiba-SEAP-300 spectropolarimeter. UV spectra were obtained on a Shimadzu-210A double-beam spectrophotometer. IR spectra were recorded on a Bruker-Tensor-27 spectrometer with KBr pellets. NMR experiments were carried out on Bruker AM-400 or DRX-500 spectrometer with TMS as internal standard. Mass spectra were recorded on a VG-Auto-Spec-3000 spectrometer. X-ray diffraction data collection was performed on a Bruker SMART APEX CCD crystallography system. HPLC analysis was performed on an Agilent 1200 series instrument equipped with a quaternary pump, a vacuum degasser, an autosampler, a thermostated column compartment and a diode array detector.

Plant Material

Leaves of *L*. *canum* were collected from Dehong prefecture of Yunnan province, China, in December 2008 and identified by Dr. Zong-Xin Ren. An authentic sample (No. LC-2008-12) was kept in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences. Flowers of *L. canum* were collected from the same place in March 2009, and an authentic sample (No. LC-2009-3) was also kept.

Extraction, Isolation and Purification of Compounds 1–7

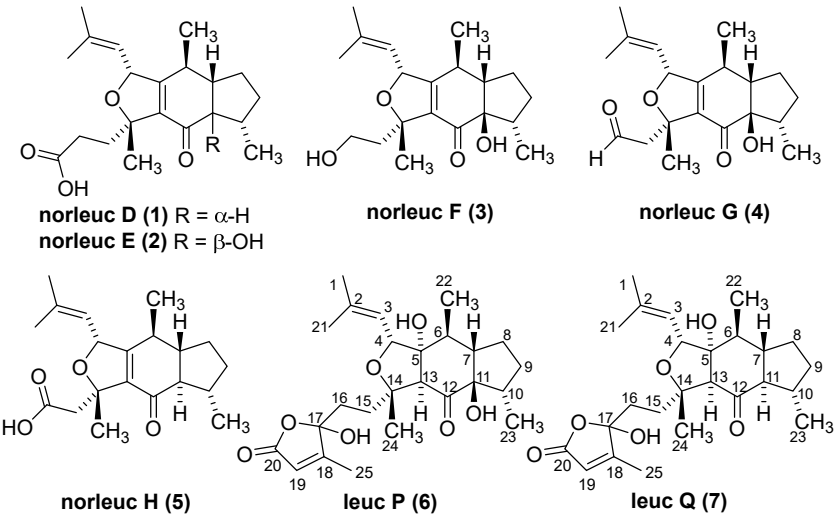
The flowers of *L. canum* were air-dried (25.0 kg) and then soaked in petroleum ether (3 × 50 L) at room temperature for 24 h. The extract was evaporated to dryness under reduced pressure to yield 450 g of an oily residue. This petroleum ether extract was separated by silica gel column chromatography using solvent mixtures of various polarities starting with petroleum ether and progressing to petroleum ether/chloroform (from 10:0 to 0:10, v/v), and then chloroform/acetone (from 10:0 to 0:10, v/v) to give nine fractions A-I. Fraction E (14.2 g) was further chromatographed on a silica gel column using a solvent mixture of petroleum ether/ethyl acetate (19:1, v/v) to give four sub-fractions E1-E4. Subfraction E2 (0.5 g) was repeatedly chromatographed on a silica gel column using petroleum ether/isopropyl alcohol (29:1, v/v) to give **4** (11.9 mg). Fraction F (38.0 g) was further subjected to silica gel column chromatography with petroleum ether/ethyl acetate (15:1, v/v) as eluent to afford another five sub-fractions F1-F5. Subfraction F2 (1.5 g) was repeatedly chromatographed on a silica gel column using petroleum ether/ethyl acetate (9:1, v/v) as eluent and finally purified by reversed-phase semi-preparative HPLC with 75% MeOH/water (flow rate: 3 mL/min, column: ZORBAX SB-C_{18}, 5 μm, 9.4 × 250 mm, detection: UV 238 nm, retention time: t = 12.4 and 14.1 min) to yield compounds **1** (117.8 mg) and **5** (27.5 mg) as colorless oils. Crystallization of **1** with a mixture of MeOH/water (8:1) gave colorless blocks. Subfraction F3 (3.7 g) was repeatedly chromatographed on a silica gel column using petroleum ether/acetone (8:1, v/v) as eluent and finally purified by reversed-phase semi-preparative HPLC with 67% MeOH/water (flow rate: 3 mL/min, column: ZORBAX SB-C_{18}, 5 μm, 9.4 × 250 mm, detection: UV 210 nm, retention time: t = 14.5 min) to yield compound **3** (21.3 mg) as colorless oil. Subfraction F4 (1.5 g) was repeatedly applied on Sephadex LH-20 column eluting with acetone and finally purified by reversed-phase semi-preparative HPLC with 55% MeOH/water (flow rate: 3 mL/min, column: ZORBAX SB-C18, 5um, 9.4 × 250 mm, detection: UV 210 and 238 nm, retention times: t = 7.1 and 12.4 min) to yield compounds **6** (13.2 mg) and **7** (16.2 mg) as colorless oils.

The leaves of *L. canum* (12.5 kg) were air-dried, powdered, and then soaked in petroleum ether (3 × 20 L) at room temperature for 24 h. The extract was evaporated to dryness under reduced pressure to yield 203 g of an oily residue. This petroleum ether extract was separated by silica gel

column chromatography using solvent mixtures of various polarities starting with petroleum ether and progressing to petroleum ether/chloroform (from 10:0 to 0:10, v/v), chloroform/acetone (from 10:0 to 0:10, v/v) to give nine fractions A-I. Fraction F (40.0 g) was subjected to silica gel column chromatography with petroleum ether/ethyl acetate (15:1, v/v) as eluent to afford five subfractions F1-F5. Subfraction F3 (2.9 g) was further subjected to silica gel column chromatography with petroleum ether/acetone (8:1, v/v) as eluent and purified by reversed-phase semipreparative HPLC with 63% MeOH/water (flow rate: 3 mL/min, column: ZORBAX SB-C_{18}, 5 μm, 9.4 × 250 mm, detection: UV 238 nm, retention time: t = 13.1 min) to yield **2** (94.5 mg).

6.2.2 Structure Elucidation of Compounds 1–7

Detailed Description



Compound **1** has a molecular formula of $C_{21}H_{30}O_4$, as deduced from the high resolution (HR) EI-MS (*m*/*z* 346.2148 $[M]^+$, calcd 346.2144) and the IR spectrum indicated the presence of two carbonyl groups (1736 and 1709 cm^{-1}). In the ^1H NMR spectrum (Table S1 and Figure S6), two secondary methyls at δ_H 1.05 (d, *J* = 7.0 Hz) and 1.11 (d, *J* = 6.0 Hz), and three tertiary methyls at δ_H 1.34 (s), 1.77 (s), and 1.79 (s) were clearly visible. In the low-field region, a pair of AB doublets at δ_H 5.20 and 5.53 (*J* = 9.8 Hz) were also observed. Twenty-one carbon resonances were displayed in the ^{13}C NMR spectrum (Table S2 and Figure S7), and were further classified by DEPT experiments as five methyls, four methylenes, six methines, including an oxymethine (δ_C 79.6) and an olefinic methine (δ_C 123.8), and six quaternary carbons, including an oxygenated (δ_C 87.7) and three olefinic (δ_C 138.4, 139.0, and 165.7) quaternary carbons, a carboxylic acid (δ_C 174.9), and an α,β-unsaturated ketone (δ_C 197.2). The above data revealed various similarities with those of leucosceptroids B[18] and E[19], although the furan or lactone moieties in the C-14 side chains were absent and instead a carboxylic group was present in **1**. Consideriation of all the spectroscopic data suggested that **1** was a tetranorsesterterpenoid possessing a combination of the core structures of leucosceptroids B and E (a 5/6/5 ring system with a conjugated ketone but without C-11 oxygenation), which was substituted by an isobutenyl group at the same position (C-4). This inference was further supported by the 2D NMR spectra, including ^1H-^1H COSY, HSQC and HMBC (Figures S8-S11). Especially the HMBC correlations (Figure S1) from the protons of the $–CH_2CH_2–$ moiety (C-15 and C-16) to the carboxylic carbon at δ_C 174.9 (C-17) confirmed that **1** was a C-17-C-18 cleavage product of the C_{25} leucosceptroids. In the

[18] Luo, S. H.; Luo, Q.; Niu, X. M.; Xie, M. J.; Zhao, X.; Schneider, B.; Gershenzon, J.; Li, S. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 4471–4475.

[19] Luo, S. H.; Hua, J.; Niu, X. M.; Liu, Y.; Li, C. H.; Zhou, Y. Y.; Jing, S. X.; Zhao, X.; Li, S. H. *Phytochemistry* **2013**, *86*, 29–35.

ROESY spectrum (Figure S11) of **1**, the correlations of Me-22 with H-4 and H-7, and of Me-23 with H-6, indicated that Me-22, H-4, and H-7 were all β-oriented while Me-23 and H-6 were α-oriented. However, due to overlapping of H-10, H-11, and H-15b (δ_H 2.08-2.11), the configuration of C-11 was difficult to determine by ROESY experiment. Therefore, a single crystal of **1** was obtained from a mixture of MeOH/water (8:1), and X-ray crystallographic analysis with molybdenum radiation was carried out (Figure 2). The result unambiguously established the complete structure of **1** as deduced, and the relative α-configuration of H-11. From a biogenetic point of view, the absolute configuration of **1** should be identical to the parent leucosceptroids.[20] Consequently, compound **1** was characterized as shown in Figure 1, and was named norleucosceptroid D.

Compound **2** was obtained as a colorless oil, having a molecular formula of $C_{21}H_{30}O_5$, as determined by a combination of negative FAB-MS and ^1H and ^{13}C NMR spectra (Figures S12-13), which was confirmed by HR-ESI-MS. The molecular formula differed only in one additional oxygen atom compared to that of **1**, suggesting that **2** was also a tetranorsesterterpenoid. The NMR spectra of **2** (Tables S1 and S2) closely resembled those of **1** except that an oxygenated quaternary carbon at δ_C 86.1 in **2** replaced the methine at δ_C 61.5 (C-11) in **1**, indicating that C-11 of **2** was hydroxylated. This was further confirmed by the HMBC cross peaks from H-7 and Me-23 to the oxygenated quaternary carbon at δ_C 86.1 (Figures S2 and S16). The chemical shift of C-11 of **2** was close to that of leucosceptroids A (δ_C 85.8) and E (δ_C 85.9) but was different from that of leucosceptroids F (δ_C 81.6) and H (δ_C 80.9), indicating that 11-OH of **2** was β-oriented. The relative configurations of the other chrial centers in **2** remained unchanged, based on its similar ROE correlation pattern (Figure S17) with that of **1**. Accordingly, compound **2** was characterized as shown in Figure 1, and was named norleucosceptroid E.

The molecular formula of compound **3** was established as $C_{20}H_{30}O_4$ by the HR-EI-MS and NMR spectra (Figures S18-19), which was just one carbon and oxygen atom less than that of **2**, suggesting that **3** was a pentanorsesterterpenoid. Comparison of the NMR data of **3** (Table S2) with those of **2** indicated that the carboxylic group (C-17) in **2** was absent in **3**, and C-16 (δ_C 59.4) instead was hydroxylated, which was confirmed by the COSY coupling relationship of H_2-15/H_2-16/16-OH (Figure S20) and HMBC correlations from Me-24 to C-15 and H_2-16 to C-14 (Figures S3 and S22). The ROESY spectrum of **3** (Figure S23) displayed the same correlation pattern as that of **2**, and its C-11 chemical shift was also close to that of **2**, indicating the same relative configurations for the two compounds. Thus, **3** was identified as shown in Figure 1, and was named norleucosceptroid F.

For compound **4** the molecular formula of $C_{20}H_{28}O_4$, as indicated from its HR-EI-MS (observed *m/z* 332.1991 $[M]^+$), suggested an additional degree of unsaturation compared to **3**. The ^1H, ^{13}C, ^1H-^1H COSY, HSQC, and HMBC spectra of **4** (Figures S24-S28) established a very similar structure to that of **3**. The exception was that the hydroxymethyl (δ_C 59.4) in **3** was replaced by an aldehyde (δ_C 201.9) in **4**, as supported by the COSY coupling between H_2-15 and the aldehyde proton (H-16), and the HMBC correlations from H_2-15 to C-13, C-14, C-24, and the aldehyde carbon. Compound **4** was therefore identified as shown in Figure 1, and was named norleucosceptroid G.

The EI-MS and HR-EI-MS of **5** indicated a molecular formula of $C_{20}H_{28}O_4$. The NMR data (Tables S1 and S2, Figures S30-S35) of **5** were very similar to those of **4**, with the major differences arising from additional oxygenation at C-16 and deoxygenation at C-11. Comparison of the NMR spectra of **5** with those of **1** showed a close resemblance, except for one missing methylene group in the former compound. In the HMBC spectrum of **5**, the correlations from H_2-15 to C-13, C-14, C-24, and the carboxylic carbon δ_C 171.6 also indicated that C-16 of **5** was carboxylated. Therefore, compound **5** was identified as shown in Figure 1, and was named norleucosceptroid H.

Compounds **6** and **7** were separately isolated as colorless oils by reversed-phase semi-preparative HPLC, and the molecular formulas of $C_{25}H_{36}O_7$ (m/z_{obsd} 448.2435, m/z_{calcd} 448.2461) and $C_{25}H_{36}O_6$ (m/z_{obsd} 431.2424, m/z_{calcd} 431.2433), respectively, were deduced from the HR-ESI-MS and ^{13}C NMR

[20] Luo, S. H.; Weng, L. H.; Xie, M. J.; Li, X. N.; Hua, J.; Zhao, X.; Li, S. H. *Org. Lett.* **2011**, *13*, 1864–1867.

spectra. Strikingly, the same unsaturation degree and a similarity of the NMR spectra of **6** and **7** (Tables S1 and S2) with those of leucosceptroids G and J,[19] respectively, was found. The major difference was that a hemiketal carbon in **6** (δ_C 108.9) and **7** (δ_C 109.1) replaced an oxygenated methine group in leucosceptroids G and J, respectively, suggesting that either C-4 or C-17 of **6** and **7** were oxygenated. In the HMBC spectrum of **6** and **7** (Figures S40 and S46), the simultaneous long-range ^1H–^{13}C correlations from H-19 and Me-25 to the carbon atoms at δ_C 108.9 and δ_C 109.1, respectively, indicated that this hemiketal carbon was ascribable to C-17. The difference between compounds **6** and **7** was determined to be that the hydroxyl group at C-11 in **6** was absent in **7**. The ROESY spectrum of **6** and **7** (Figures S41 and S47) also showed a similar correlation pattern to that of leucosceptroids G and J, respectively, which suggested that the relative configurations of most chiral centers in **6** and **7** remained unchanged. Unfortunately, the stereochemistry of C-17 in **6** and **7** could not be determined by analysis of the ROESY spectra (due to rotation around the side chain carbons C-15 and C-16) and thus remains unclear. The structures of compounds **6** and **7** were determined as shown in Figure 1 and were named leucosceptroids P and Q respectively.

^{1}H NMR Data of Compounds 1–7 in Acetone-d_6

Table S1. ^{1}H NMR Data of Compounds 1−7 in Acetone-d_6 (δ in ppm, J in Hz)[a]

No.	**1**	**2**[b]	**3**[c]	**4**[d]	**5**	**6**[e]	**7**[f]
1[g]	1.79 s	1.79 s	1.80 s	1.84 s	1.77 s	1.71 s	1.69 d (1.5)
3	5.20 d (9.8)	5.13 d (10.0)	5.12 d (10.0)	5.18 d (9.7)	5.08 d (9.9)	5.55 d (8.9)	5.60 brd (8.5)
4	5.53 d (9.8)	5.60 d (10.0)	5.60 d (10.0)	5.73 d (9.8)	5.53 d (9.9)	4.69 d (8.9)	4.42 d (8.5)
6	2.42 m	2.33 m	2.32 m	2.39 m	2.31 m	1.77 m	1.87 m
7	1.88 m	2.13 m	2.13 m	2.17 m	1.88 m	2.03 m	1.81 m
8α	1.46 m	1.67 m	1.67 m	1.71 m	1.46 m	1.69 m	1.29 m
8β	1.90 m	2.12 m	2.12 m	2.18 m	1.90 m	2.09 m	1.81 m
9α	1.31 m	1.40 m	1.41 m	1.44 m	1.33 m	1.40 m	1.30 m
9β	1.95 m	2.14 m	2.14 m	2.19 m	1.97 m	2.00 m	1.93 m
10	2.08 m	2.17 m	2.16 m	2.19 m	2.10 m	2.27 m	2.04 overlap
11	2.11 m	-	-	-	2.05 m	-	1.78 m
13	-	-	-	-	-	2.63 s	2.73 s
15a	1.83 m	2.01 m	2.00 m (2H)	2.69 dd (15.4, 3.2)	2.57 d (14.2)	1.64 m	1.64 m
15b	2.10 m	2.08 m	-	2.76 dd (15.4, 2.7)	2.82 d (14.2)	1.81 m	1.79 m
16a	2.05 m	2.16 m	3.57 m	9.75 s	-	2.18 m	1.96 m
16b	2.33 m	2.39 m	3.62 m	-	-	2.30 m	2.19 m
19	-	-	-	-	-	5.80 s	5.79 brs
21[g]	1.77 s	1.76 s	1.76 s	1.79 s	1.71 s	1.72 s	1.71 d (1.5)
22[g]	1.05 d (7.0)	1.11 d (7.0)	1.12 d (7.0)	1.16 d (7.0)	1.04 d (7.1)	0.96 d (6.8)	0.94 d (7.0)
23[g]	1.11 d (6.0)	0.92 d (7.0)	0.92 d (7.0)	0.89 d (6.6)	1.11 d (6.3)	0.82 d (7.4)	1.12 d (7.0)
24[g]	1.34 s	1.04 s	1.36 s	1.49 s	1.39 s	1.18 s	1.10 s
25[g]	-	-	-	-	-	2.04 s	2.03 brs

[a] ^{1}H NMR of compounds **1**-**3**, **5**-**7** were recorded at 500 MHz; ^{1}H NMR of compound **4** was recorded at 400 MHz. [b] The broad signal around δ_H 3.2 arises from residual water in acetone-d_6 and appears broadened due to the carboxylic acid functionality in **2**. [c] Hydroxyl group signals of **3**: δ_H 4.11 (s, 11-OH), 3.25 (t, J = 5.5 Hz, 16-OH). [d] Hydroxyl group signal of **4**: 4.25 (s, 11-OH). [e] Hydroxyl group signals of **6**: δ_H 4.16 (s, 11-OH), δ_H 3.90 (m, 5-OH). [f] Hydroxyl group signals of **7**: δ_H 4.04 (brs, 5-OH), δ_H 6.34 (brs, 17-OH). [g] integration to 3H.

^{13}C NMR Data of Compounds 1–7 in Acetone-d_6

Table S2. ^{13}C NMR Data of Compounds 1–7 in Acetone-d_6 (125 MHz, δ in ppm)

No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	18.2 q	18.3 q	18.3 q	18.4 q	18.2 q	18.7 q	18.7 q
2	138.4 s	139.0 s	139.3 s	139.6 s	137.5 s	137.0 s	136.9 s
3	123.8 d	123.3 d	123.3 d	122.9 d	124.4 d	122.5 d	122.5 d
4	79.6 d	80.5 d	80.6 d	81.2 d	80.1 d	77.0 d	77.0 d
5	165.7 s	166.6 s	165.7 s	166.8 s	163.5 s	84.2 s	86.2 s
6	37.7 d	33.0 d	33.1 d	33.1 d	37.9 d	42.0 d	47.2 d
7	54.5 d	56.1 d	56.0 d	56.2 d	54.1 d	50.2 d	46.4, d
8	28.6 t	29.3 t	29.4 t	29.7 t	28.6 t	30.5 t	29.0 t
9	32.8 t	32.3 t	32.3 t	32.4 t	32.9 t	30.9 t	32.9 t
10	33.5 d	47.4 d	47.7 d	47.6 d	33.5 d	46.2 d	33.8 d
11	61.5 d	86.1 s	86.0 s	86.1 s	61.6 d	85.5 s	65.1 d
12	197.2 s	197.7 s	197.7 s	197.8 s	197.3 s	212.6 s	210.8 s
13	139.0 s	138.0 s	138.6 s	137.8 s	139.3 s	72.1 d	72.4 d
14	87.7 s	88.3 s	89.0 s	86.7 s	86.5 s	83.2 s	82.2 s
15	34.2 t	34.8 t	42.4 t	52.9 t	43.9 t	38.4 t	37.4 t
16	30.0 t	29.9 t	59.4 t	201.9 d	171.6 s	31.7 t	31.2 t
17	174.9 s	174.9 s	-	-	-	108.9 s	109.1 s
18	-	-	-	-	-	168.4 s	168.3 s
19	-	-	-	-	-	118.4 d	118.3 d
20	-	-	-	-	-	170.9 s	170.7 s
21	26.0 q	25.9 q	25.9 q	26.0 q	26.0 q	26.1 q	26.1 q
22	15.9 q	18.1 q	18.3 q	18.1 q	16.0 q	13.9 q	14.0 q
23	21.3 q	19.2 q	19.1 q	19.3 q	21.4 q	17.1 q	22.0 q
24	27.4 q	26.3 q	26.5 q	27.1 q	27.9 q	23.7 q	22.8 q
25	-	-	-	-	-	12.5 q	12.6 q

Physical-Chemical Properties of Compounds 1–7

Norleucosceptroid D (**1**): colorless blocks; $[\alpha]_D^{20}$ = + 40.9 (*c* = 0.3, MeOH); UV (MeOH) λ_{max} (log ε): 245 (3.52), 203 (3.12) nm; IR (KBr) ν_{max}: 3431, 2968, 2935, 2870, 1736, 1709, 1679, 1631, 1450, 1382, 1313, 1166, 1023, 978 cm^{-1}; EI-MS *m/z* (%): 346 (38) $[M]^+$, 331 (21), 274 (39), 273 (100), 163 (27), 109 (29), 83 (36) , 55 (42); HR-EI-MS: m/z_{obsd} 346.2148 $[M]^+$ (m/z_{calcd} $[C_{21}H_{30}O_4]^+$ = 346.2144).

Norleucosceptroid E (**2**): colorless oil; $[\alpha]_D^{27}$ = + 21.1 (*c* = 0.6, MeOH); UV (MeOH) λ_{max} (log ε): 247 (3.47), 196 (3.29) nm; IR (KBr) ν_{max}: 3437, 2968, 2936, 2876, 1712, 1666, 1452, 1381, 1189, 1045, 837 cm^{-1}; negative FAB-MS *m/z* (%): 361 (68) $[M-H]^-$, 281 (45), 255 (100); HR-ESI-MS: m/z_{obsd} 361.2021 $[M-H]^-$ (m/z_{calcd} $[C_{21}H_{29}O_5]^-$ = 361.2014).

Norleucosceptroid F (**3**): colorless oil; $[\alpha]_D^{26}$ = + 10.8 (*c* = 0.2, MeOH); UV (MeOH) λ_{max} (log ε): 246 (3.41), 202 (3.39), 191 (3.27) nm; IR (KBr) ν_{max}: 3441, 2963, 2932, 2875, 1665, 1461, 1379, 1285, 1046 cm^{-1}; EI-MS *m/z* (%): 334 (50) $[M]^+$, 316 (61), 301 (82), 253 (87) 175 (100); HR-EI-MS: m/z_{obsd} 334.2134 $[M]^+$ (m/z_{calcd} $[C_{20}H_{30}O_4]^+$ = 334.2144).

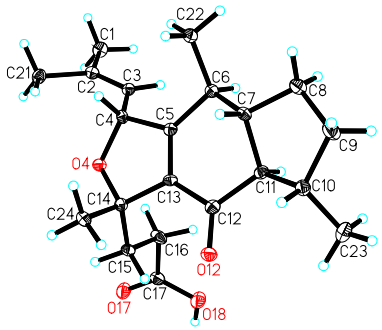
Norleucosceptroid G (**4**): colorless oil; $[\alpha]_D^{17}$ = - 16.6 (*c* = 0.2, MeOH); UV (MeOH) λ_{max} (log ε): 248 (3.49) nm; IR (KBr) ν_{max}: 3434, 2965, 2934, 2875, 1724, 1666, 1452, 1379, 1286, 1126, 1073, 1044, 1010 cm^{-1}; EI-MS *m/z* (%): 332 (31) $[M]^+$, 317 (34), 290 (35), 289 (100), 288 (27), 191 (42), 163 (51), 83 (93), 55 (78); HR-EI-MS: m/z_{obsd} 332.1991 $[M]^+$ (m/z_{calcd} $[C_{20}H_{28}O_4]^+$ = 332.1988).

Norleucosceptroid H (**5**): colorless oil; $[\alpha]_D^{20}$ = + 12.5 (*c* = 0.2, MeOH); UV (MeOH) λ_{max} (log ε): 241 (3.20), 202 (3.10), 196 (2.97) nm; IR (KBr) ν_{max}: 3432, 2953, 2933, 2869, 1711, 1680, 1640, 1451, 1384, 1312, 1164, 1023, 777 cm^{-1}; EI-MS *m/z* (%): 332 (52) $[M]^+$, 317 (41), 274 (29), 273 (100), 163 (28), 109 (34), 83 (89); HR-EI-MS: m/z_{obsd} 332.1991 $[M]^+$ (m/z_{calcd} $[C_{20}H_{28}O_4]$ = 332.1988).

Leucosceptroid P (**6**): colorless oil; $[\alpha]_D^{20}$ = + 38.7 (*c* = 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 208 (3.84) nm; IR (KBr) ν_{max}: 3438, 2967, 2936, 2871, 1747, 1700, 1643, 1452, 1383, 1281, 1245, 1073, 924 cm^{-1}; EI-MS *m/z* (%): 448 (8) $[M]^+$, 412 (24), 397 (12), 364 (27), 290 (53), 289 (100), 271 (55), 270 (32); HR-ESI-MS: m/z_{obsd} 448.2435 $[M]^+$ (m/z_{calcd} $[C_{25}H_{36}O_7]^+$ = 448.2461).

Leucosceptroid Q (**7**): colorless oil; $[\alpha]_D^{26}$ = + 56.3 (*c* = 0.4, MeOH); UV (MeOH) λ_{max} (log ε): 204 (3.98), 195 (3.47) nm; IR (KBr) ν_{max}: 3441, 2962, 2935, 2870, 1746, 1701, 1451, 1377, 1279, 1079, 939, 926 cm^{-1}; negative FAB-MS *m/z* (%): 431 (100) $[M-H]^-$; HR-ESI-MS: m/z_{obsd} 431.2424 $[M-H]^-$ (m/z_{calcd} $[C_{25}H_{35}O_6]^-$ = 431.2433).

Crystal Data of Norleucosceptroid D (1)



X-ray crystallographic structure of norleucosceptroid D (1)

$C_{42}H_{60}O_8$, 2 × *M* = 692.90 g mol^{-1}, colorless blocks, size 0.33 × 0.23 × 0.04 mm^3, Orthorhombic, space group *P2(1)2(1)2(1)*, *a* = 10.142 (2) Å, *b* = 10.495 (2) Å, *c* = 36.579 (8) Å, α = 90°, β = 90°, γ = 90°, *V* = 3893.6 (15) $Å^3$, *T* = -173 °C, *Z* = 4, *d* =1.182 g cm^{-3}, μ(Mo-Kα) = 0.71073 Å, *F*(000) = 1504, 38753 reflections in *h*(-13/13), *k*(-13/13), *l*(-44/48), measured in the range 1.11° ≤ θ ≤28.31°, completeness θ_{max} = 99.7%, 9656 independent reflections, R_{int} = 0.1738, 5125 reflections with *Fo* > 4σ(*Fo*), 461 parameters, 0 restraint, $R1_{obs}$ = 0.0657, $wR2_{obs}$ = 0.1122, $R1_{all}$ = 0.1577, $wR2_{all}$ = 0.1487, GOF = 0.981, Absolute structure parameter 0.0(13), largest difference peak and hole = 0.259 and - 0.316 e $Å^{-3}$. The crystal structure of 1 was solved by direct method using the program SHELXS-97 (G. M. Sheldrick, *SHELXS97 and SHELXL97*, University of Gottingen, Germany, 1997) and subsequent Fourier difference techniques, and refined anisotropically by fullmatrix least-squares on F^2 using SHELXL-97 (G. M. Sheldrick, *SHELXTL*, Version 6.10, Bruker AXS Inc., Madison, Wisconsin, USA, 2000).

Key HMBC Correlations of Compounds 1–5:

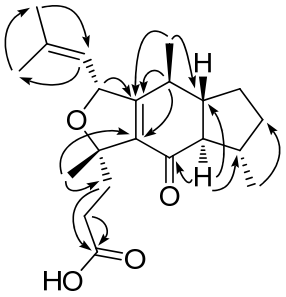


Figure S1. Key HMBC correlations of norleucosceptroid D (**1**).

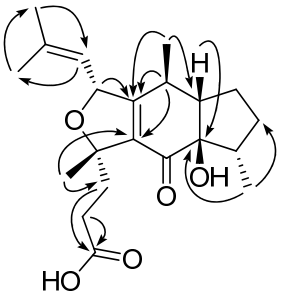


Figure S2. Key HMBC correlations of norleucosceptroid E (**2**).

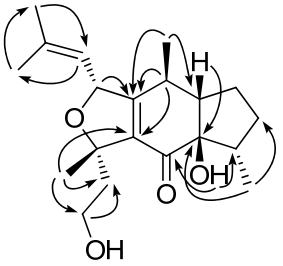


Figure S3. Key HMBC correlations of norleucosceptroid F (**3**).

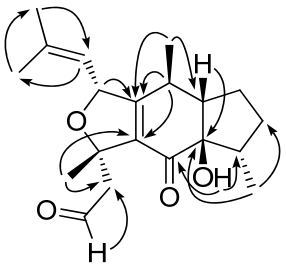


Figure S4. Key HMBC correlations of norleucosceptroid G (**4**).

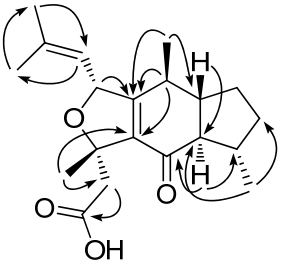


Figure S5. Key HMBC correlations of norleucosceptroid H (**5**).

6.2.3 NMR Spectra of Compounds 1–7

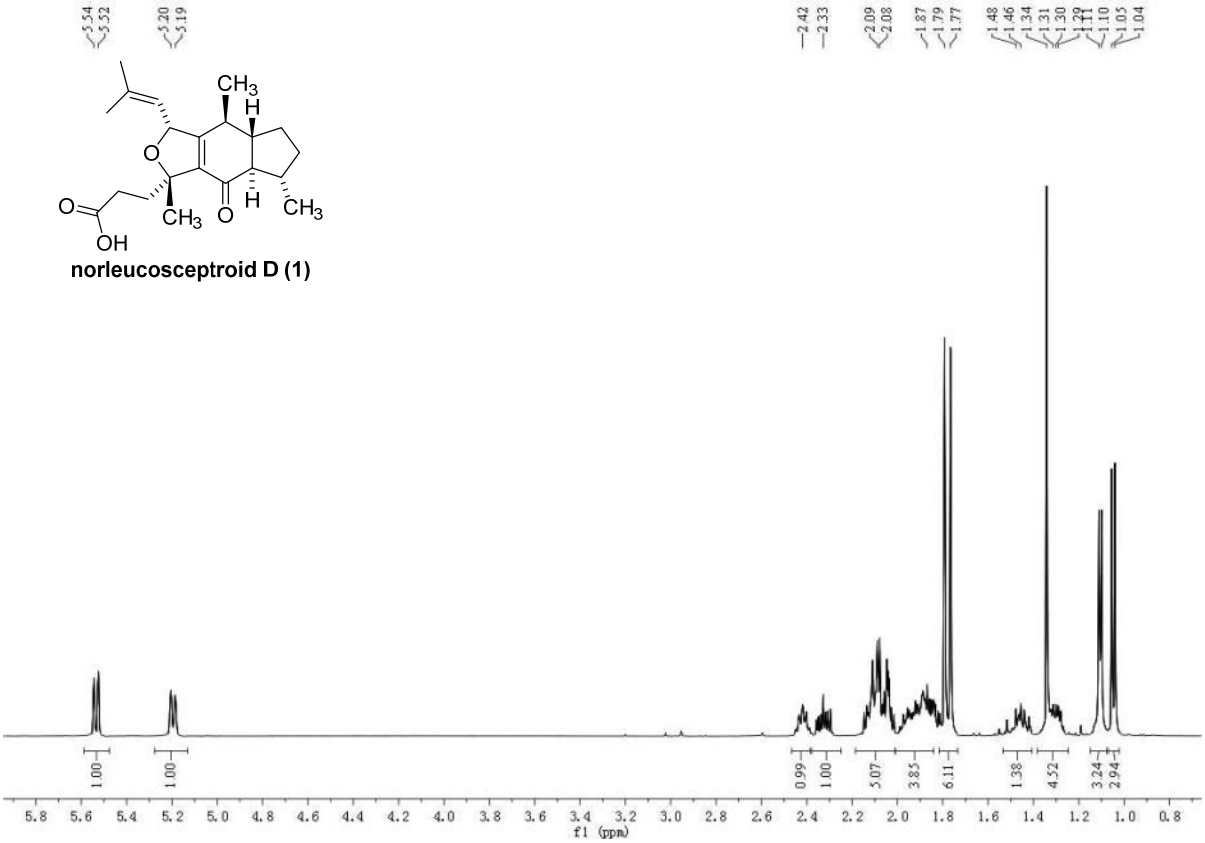


Figure S6. ^{1}H NMR spectrum of norleucosceptroid D (**1**) recorded at 500 MHz in acetone-d_6.

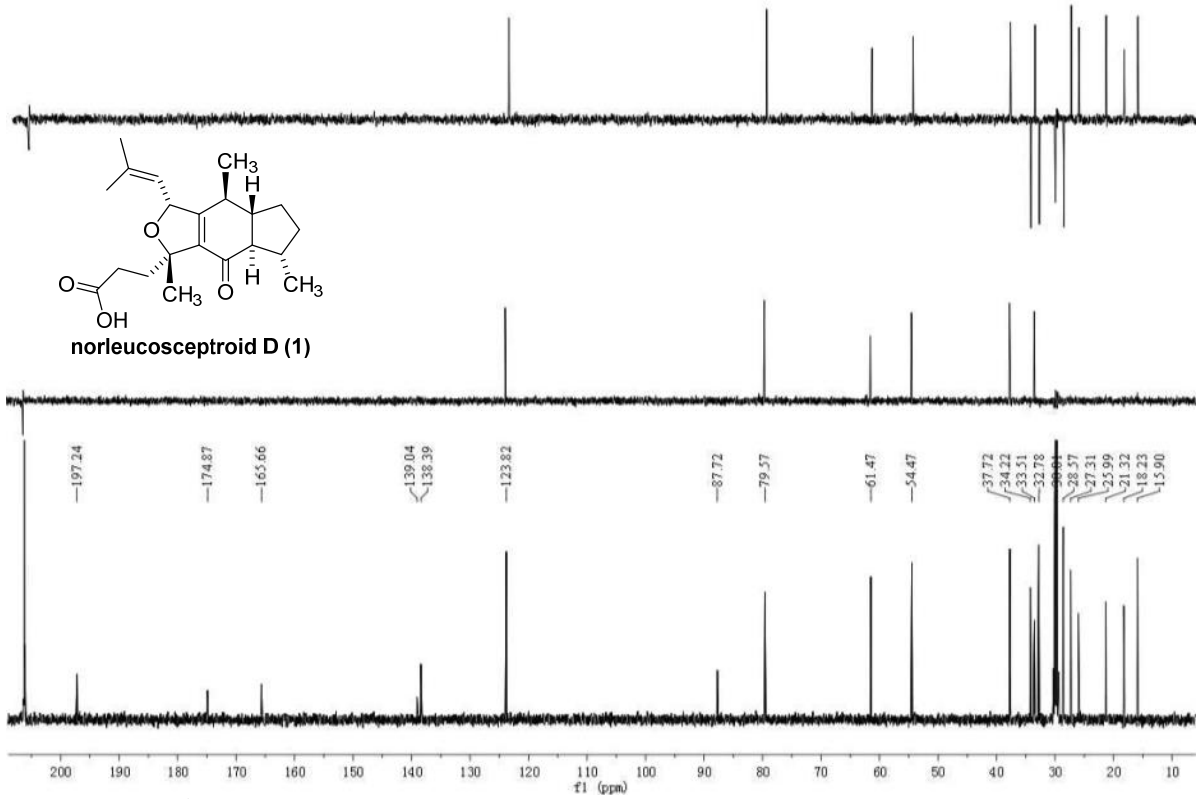


Figure S7. ^{13}C NMR and DEPT spectra of norleucosceptroid D (**1**) recorded at 125 MHz in acetone-d_6.

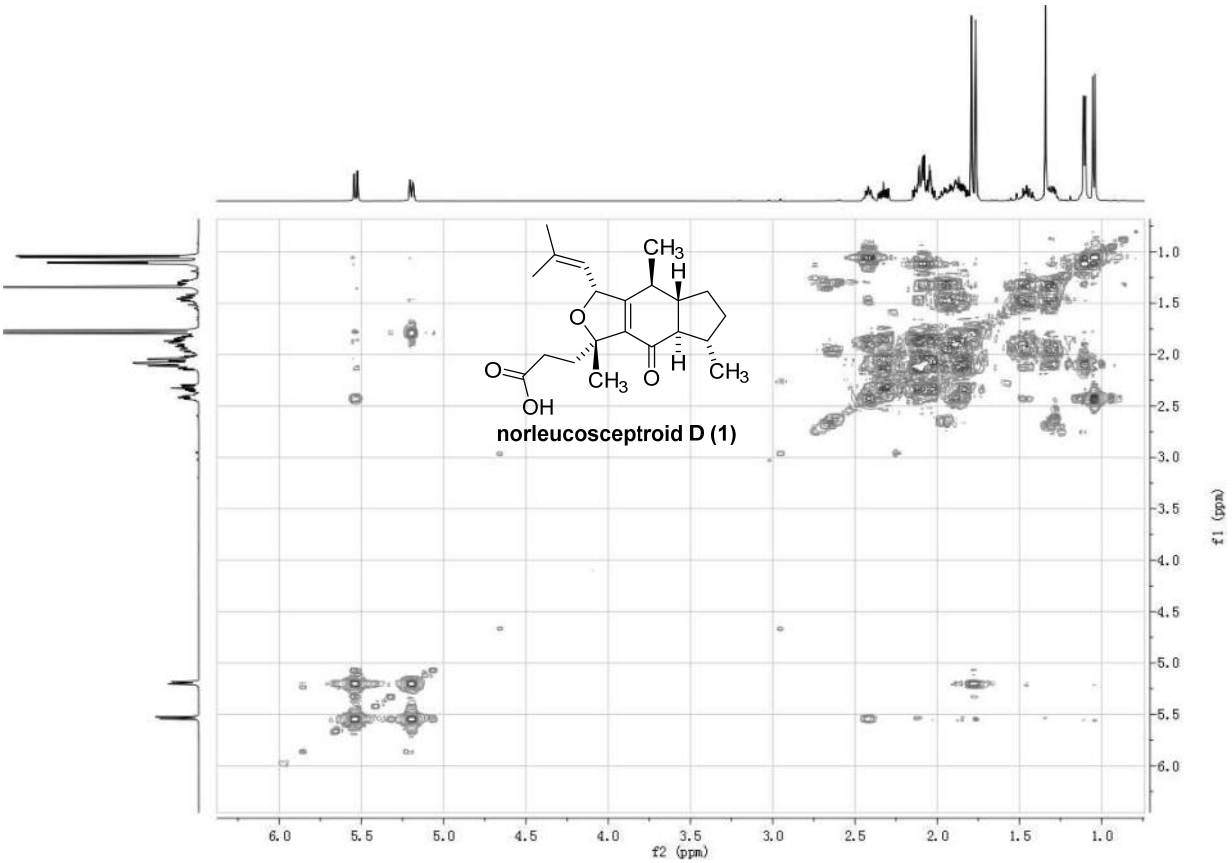


Figure S8. ^{1}H-^{1}H COSY spectrum of norleucosceptroid D (**1**) recorded in acetone-d_6.

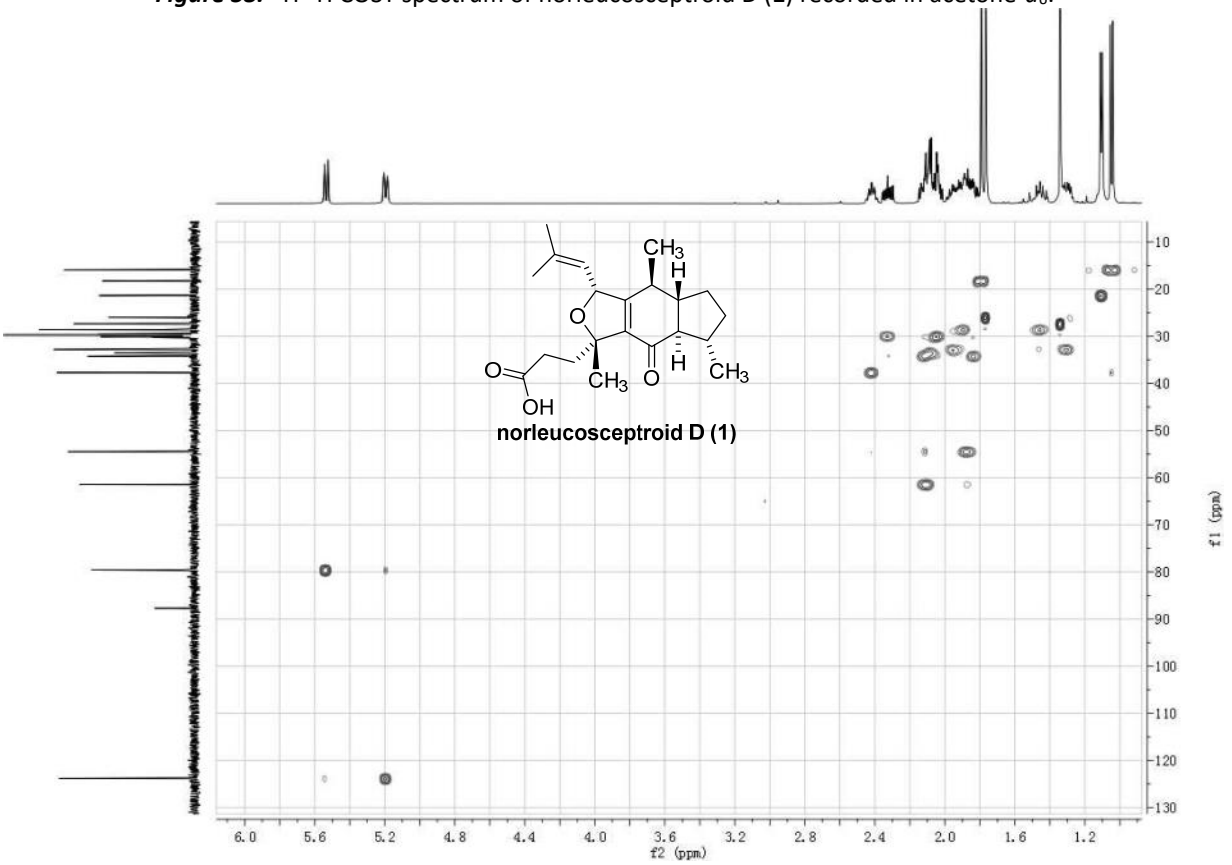


Figure S9. HSQC spectrum of norleucosceptroid D (**1**) recorded in acetone-d_6.

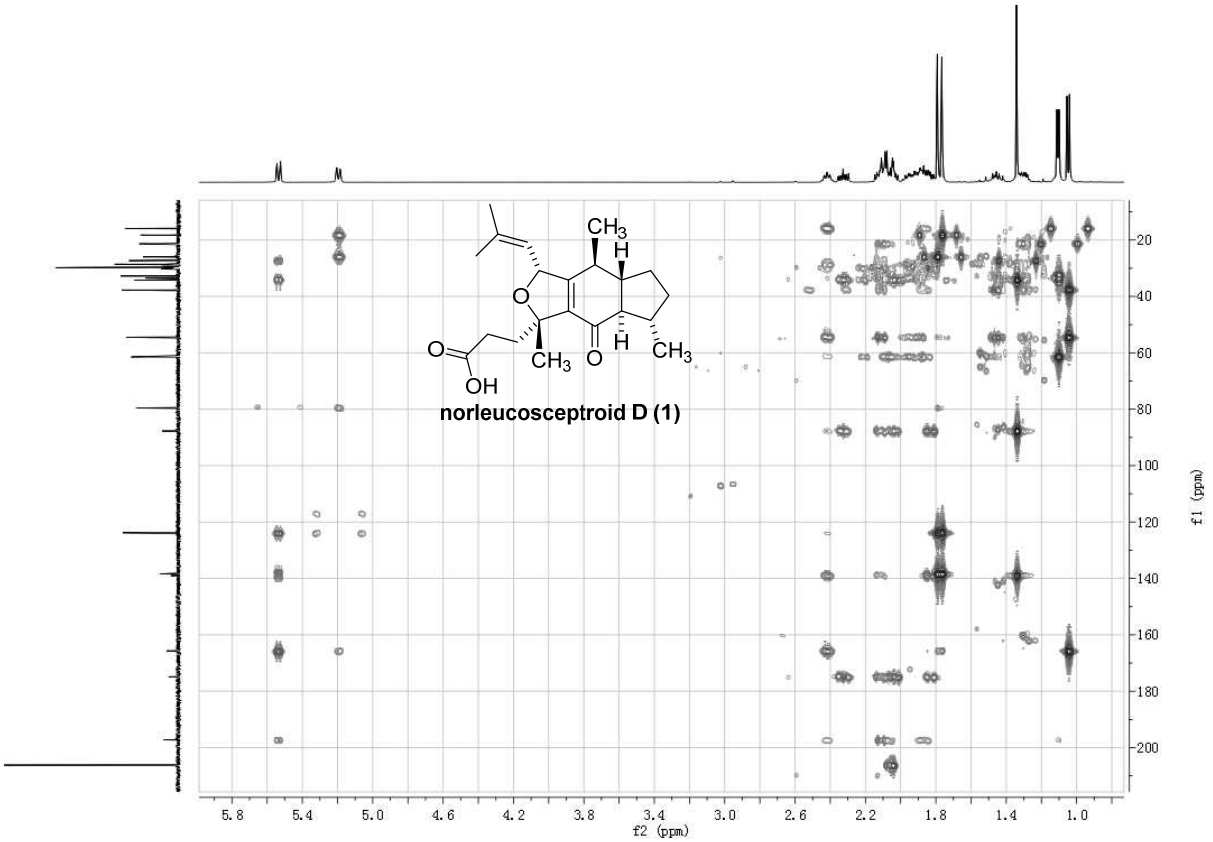


Figure S10. HMBC spectrum of norleucosceptroid D (**1**) recorded in acetone-d_6.

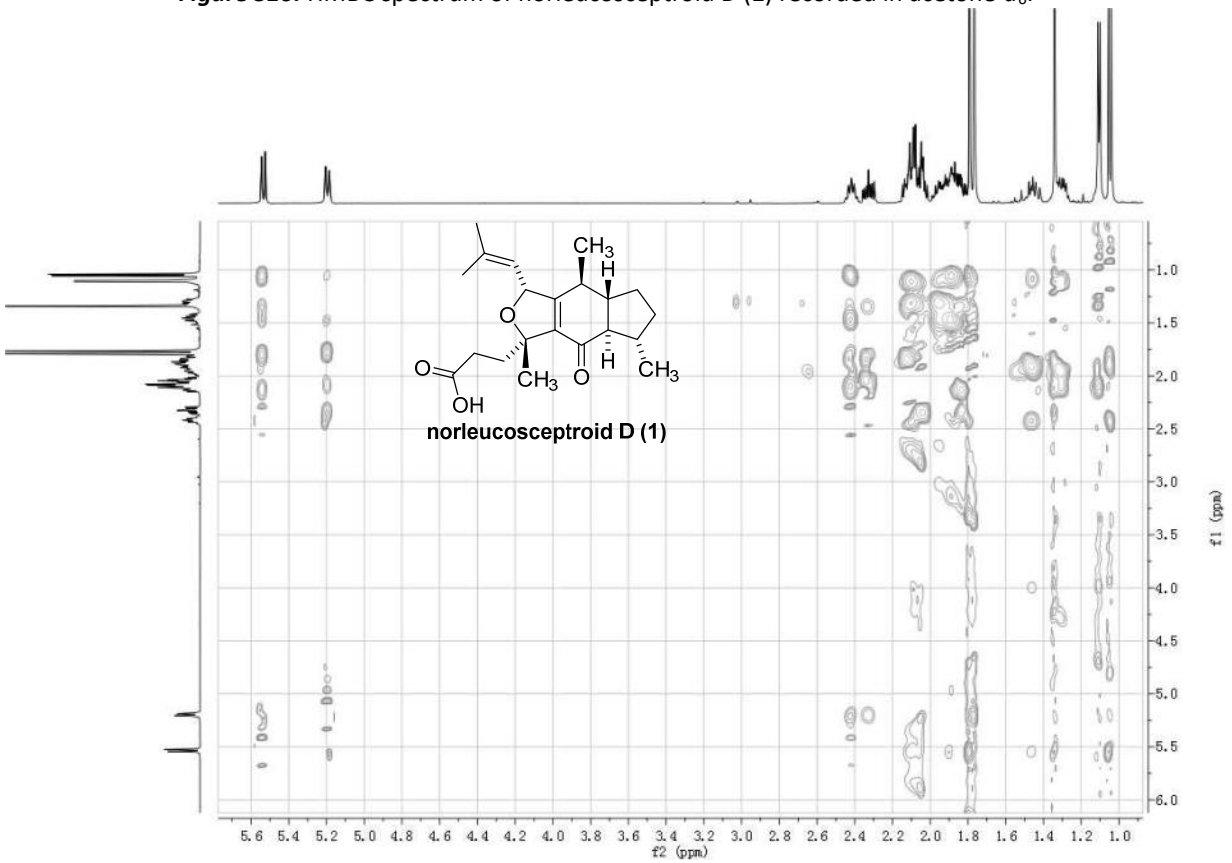


Figure S11. ROESY spectrum of norleucosceptroid D (**1**) recorded in acetone-d_6.

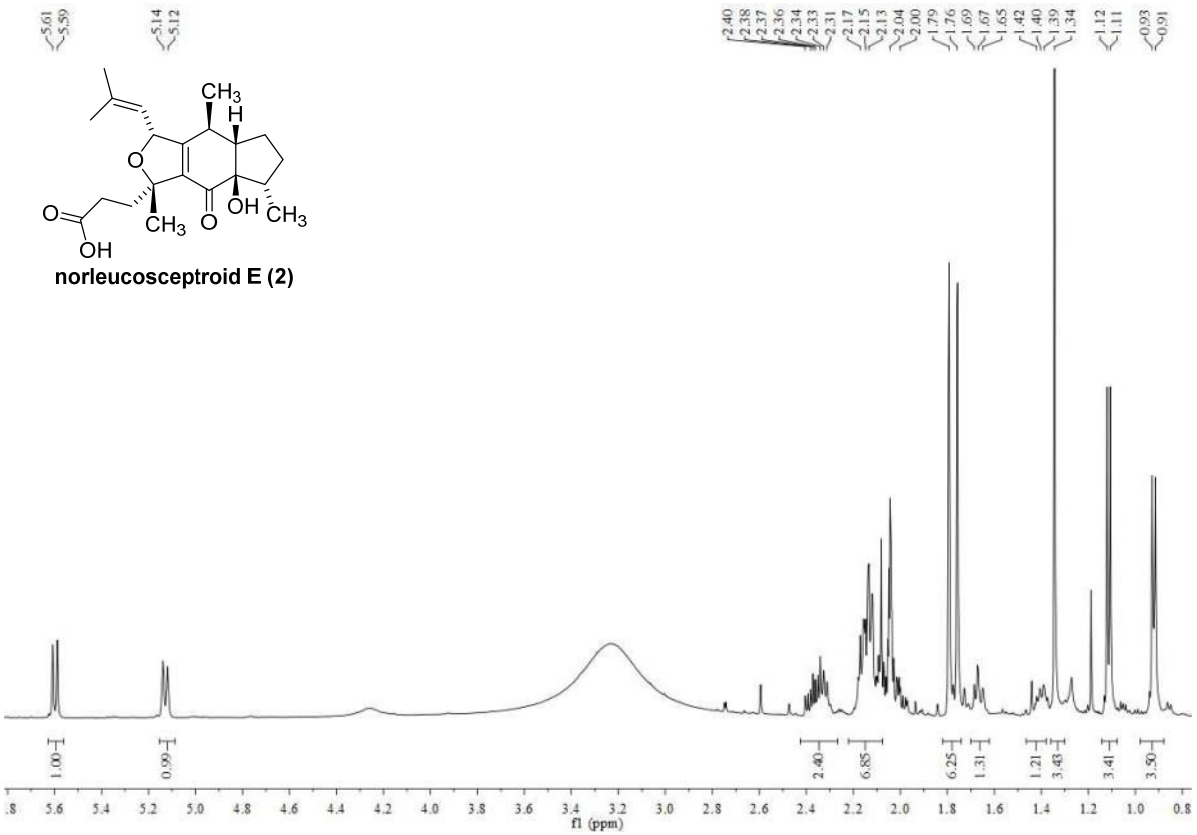


Figure S12. ^{1}H NMR spectrum of norleucosceptroid E (**2**) recorded at 500 MHz in acetone-d_6.

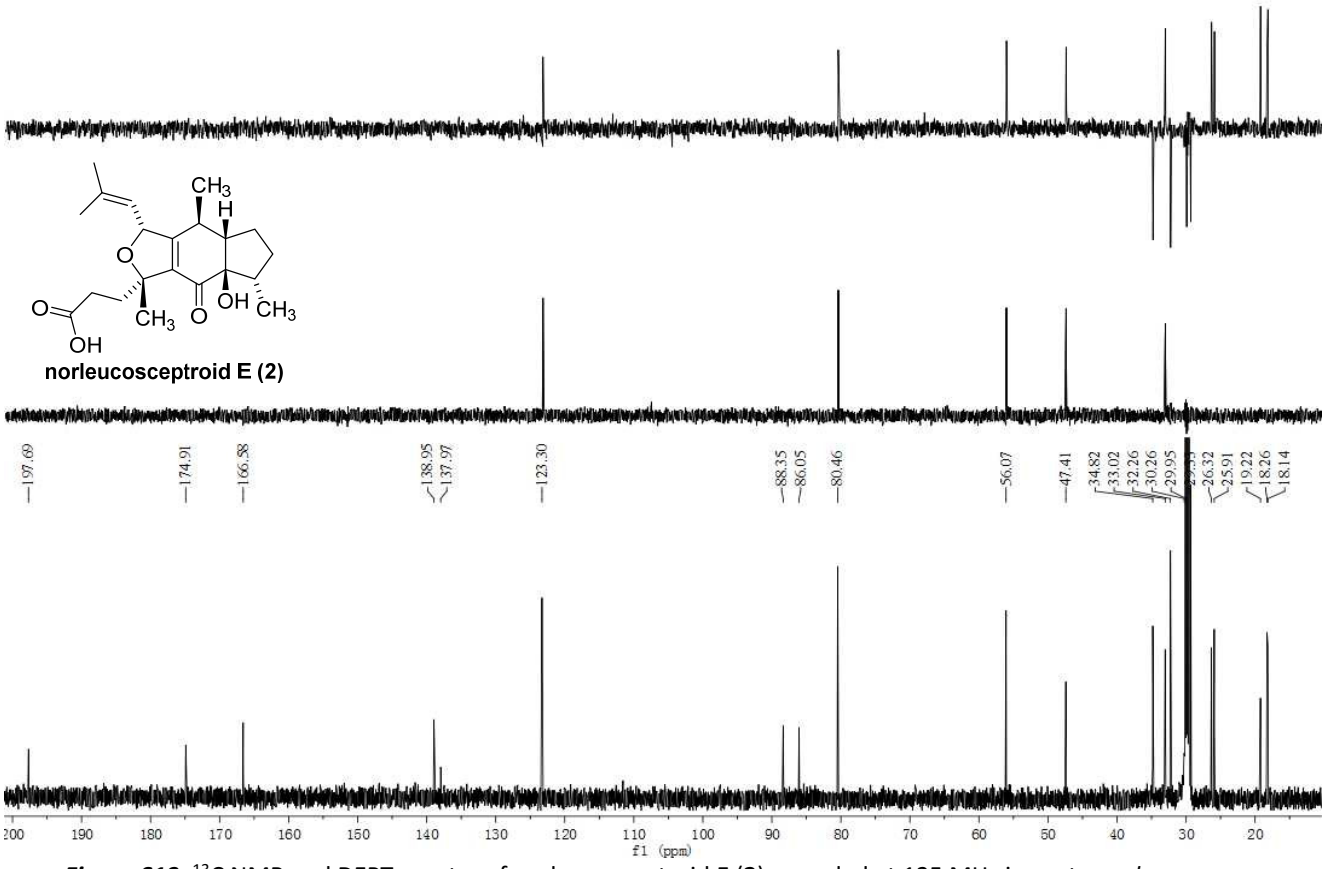


Figure S13. ^{13}C NMR and DEPT spectra of norleucosceptroid E (**2**) recorded at 125 MHz in acetone-d_6.

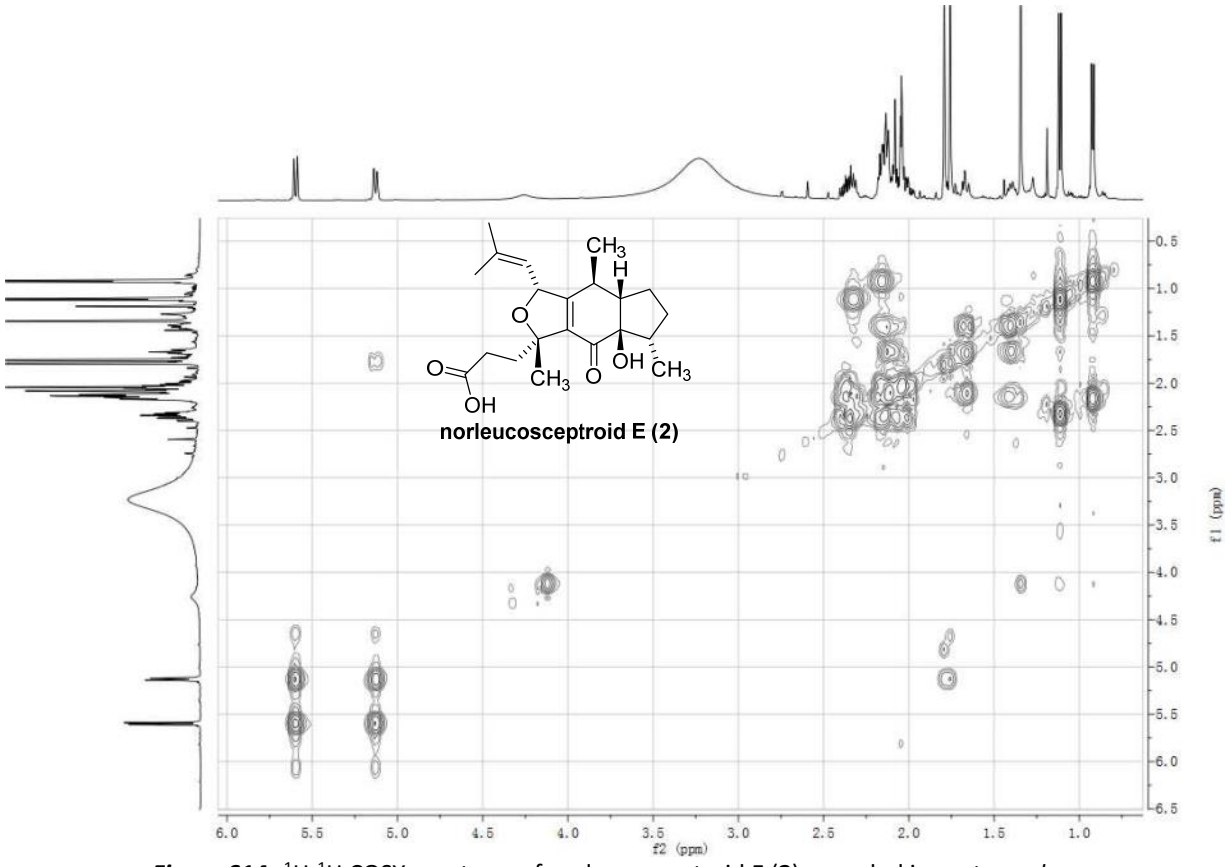


Figure S14. ^{1}H-^{1}H COSY spectrum of norleucosceptroid E (**2**) recorded in acetone-d_6.

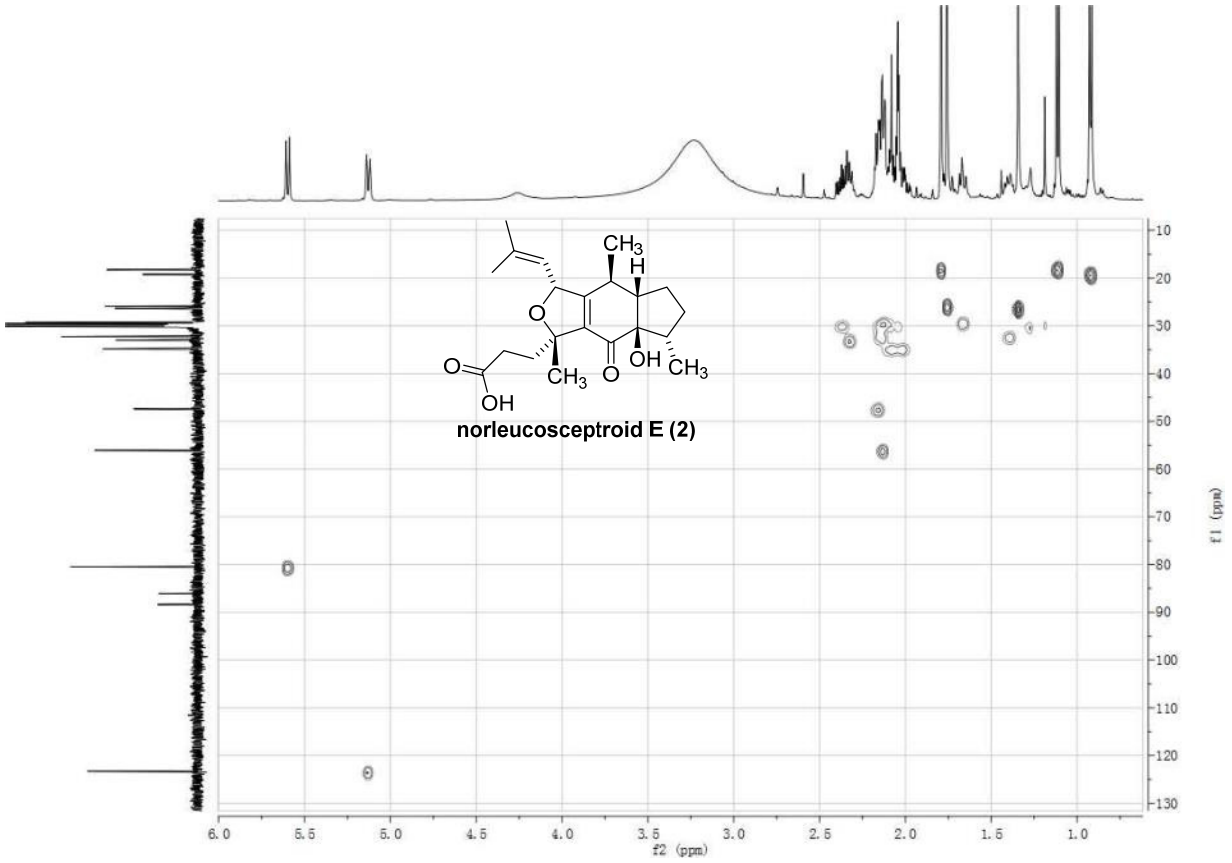


Figure S15. HSQC spectrum of norleucosceptroid E (**2**) recorded in acetone-d_6.

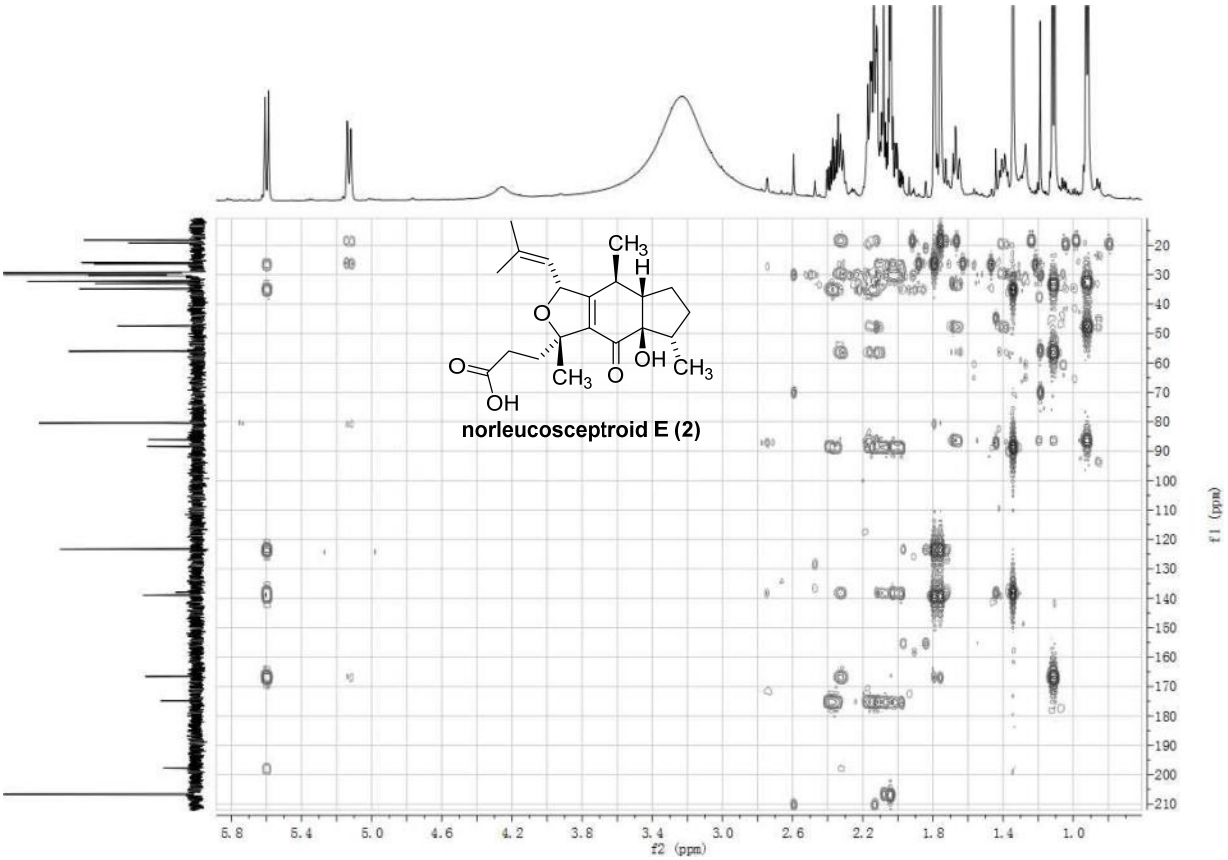


Figure S16. HMBC spectrum of norleucosceptroid E (**2**) recorded in acetone-d_6.

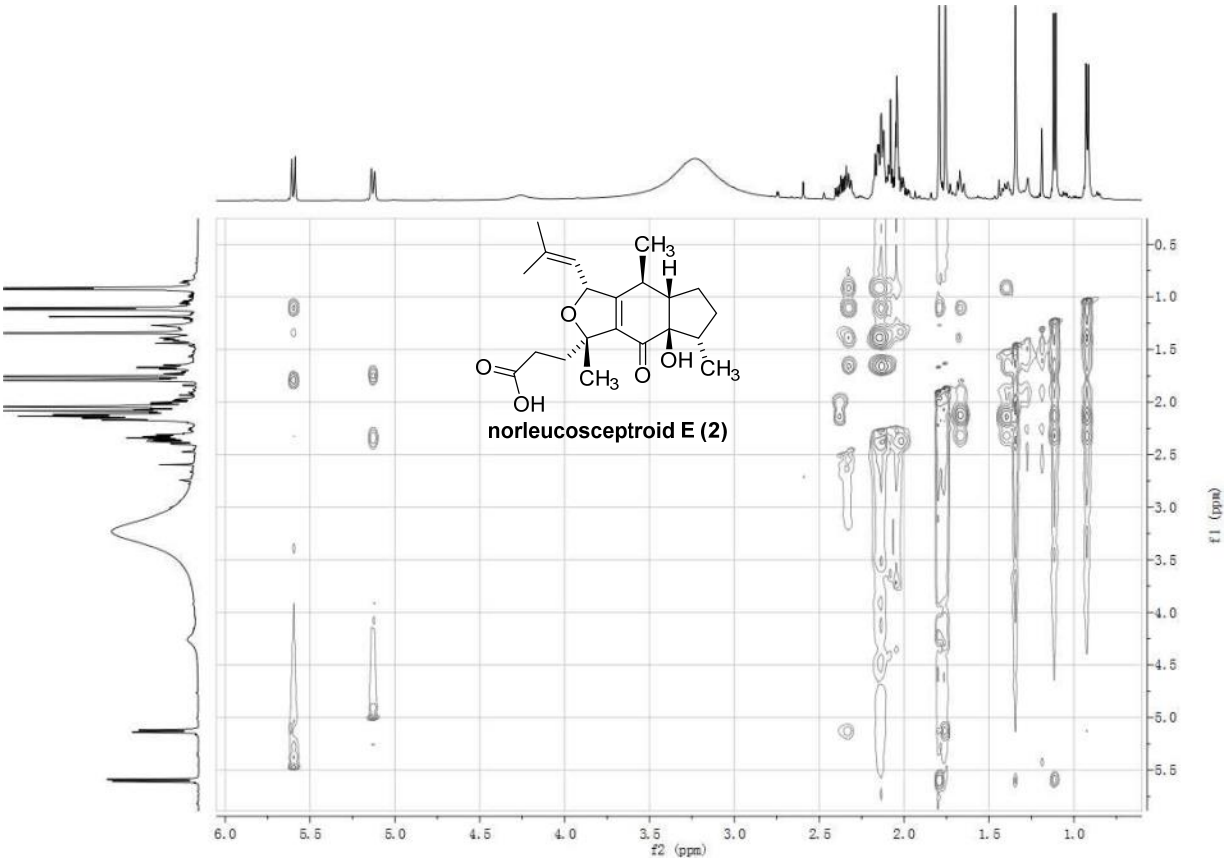


Figure S17. ROESY spectrum of norleucosceptroid E (**2**) recorded in acetone-d_6.

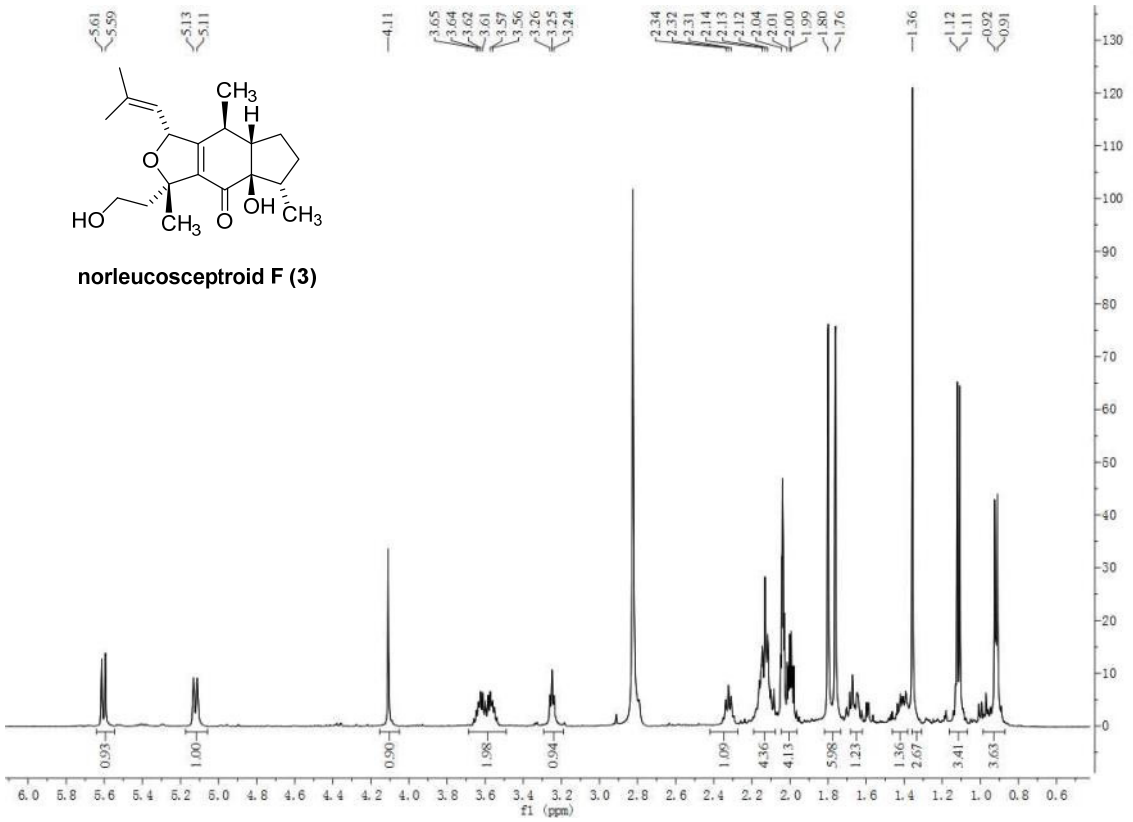


Figure S18. ^{1}H NMR spectrum of norleucosceptroid F (**3**) recorded at 500 MHz in acetone-d_6.

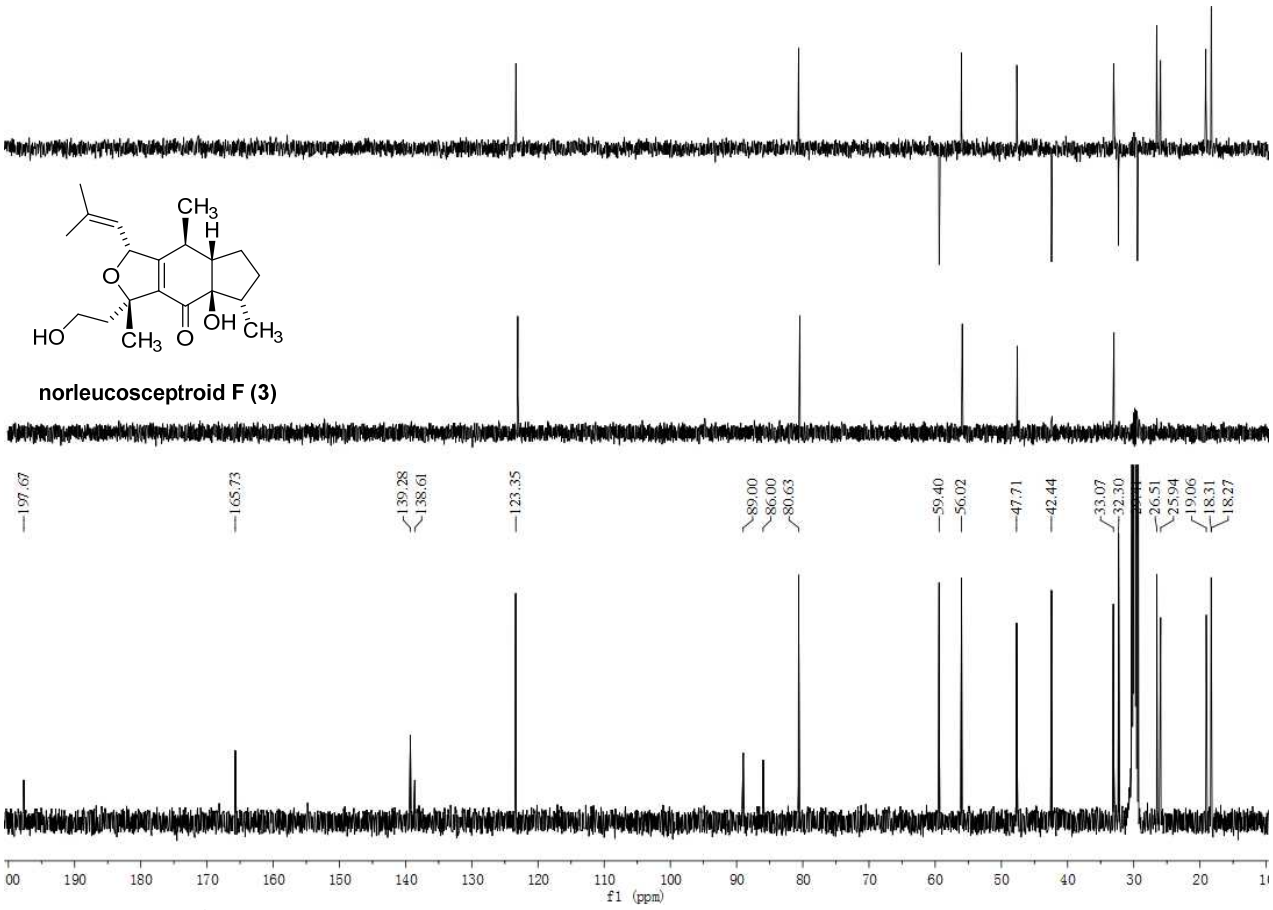


Figure S19. ^{13}C NMR and DEPT spectra of norleucosceptroid F (**3**) recorded at 125 MHz in acetone-d_6.

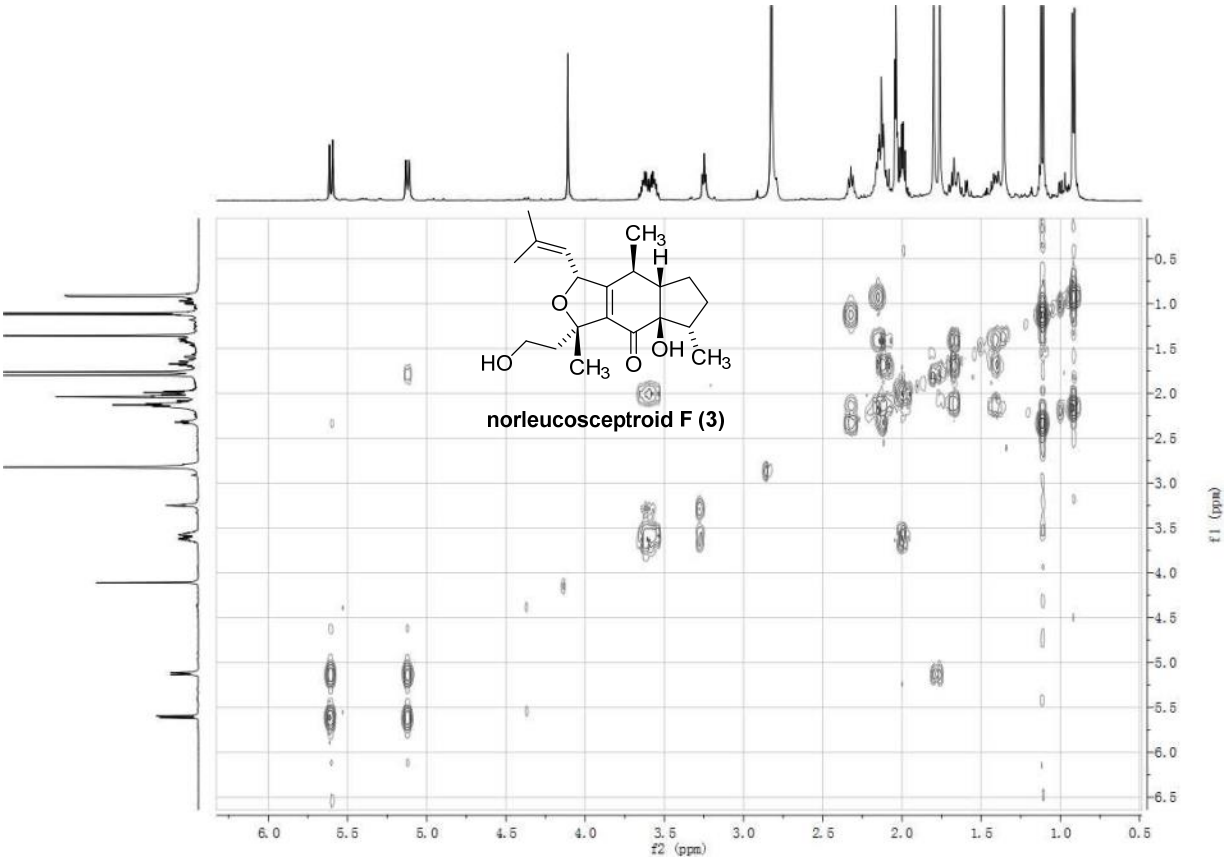


Figure S20. ^{1}H-^{1}H COSY spectrum of norleucosceptroid F (**3**) recorded in acetone-d_6.

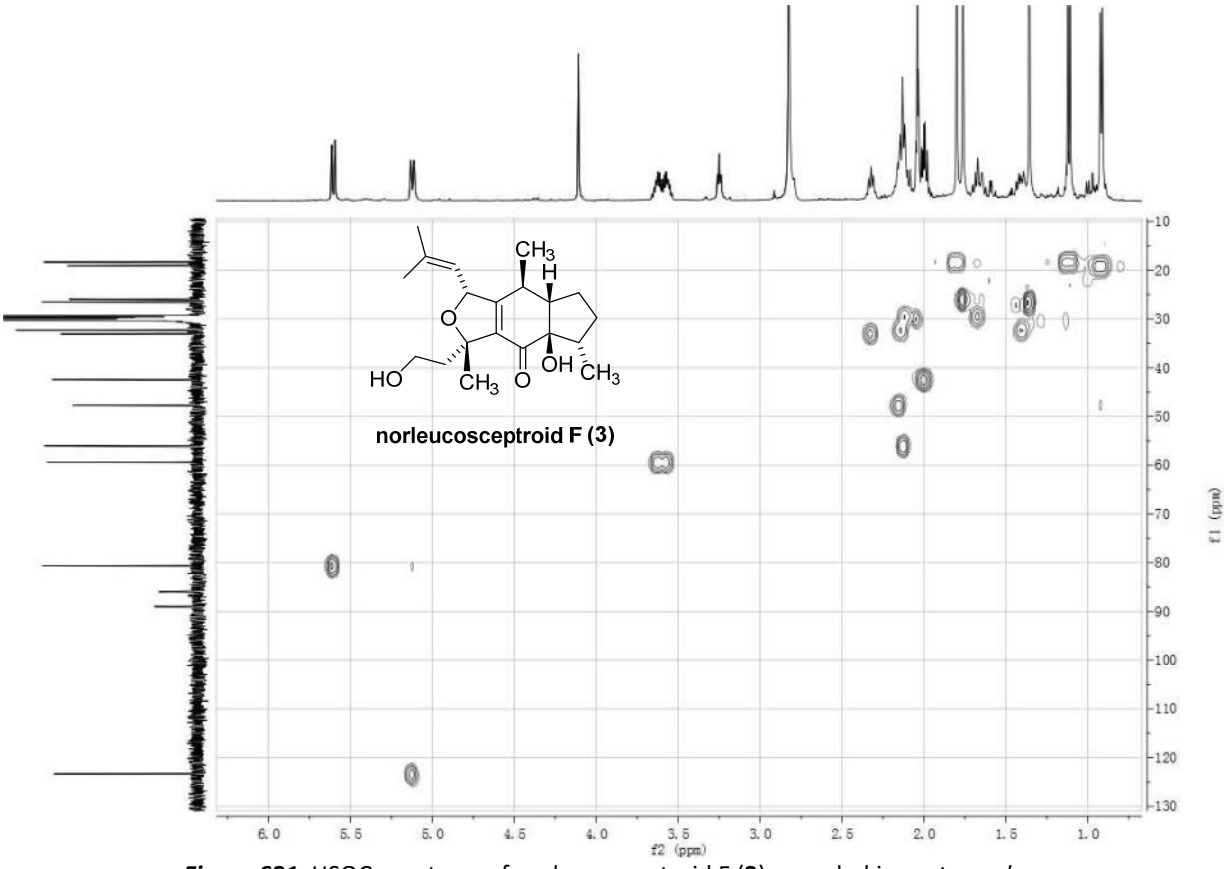


Figure S21. HSQC spectrum of norleucosceptroid F (**3**) recorded in acetone-d_6.

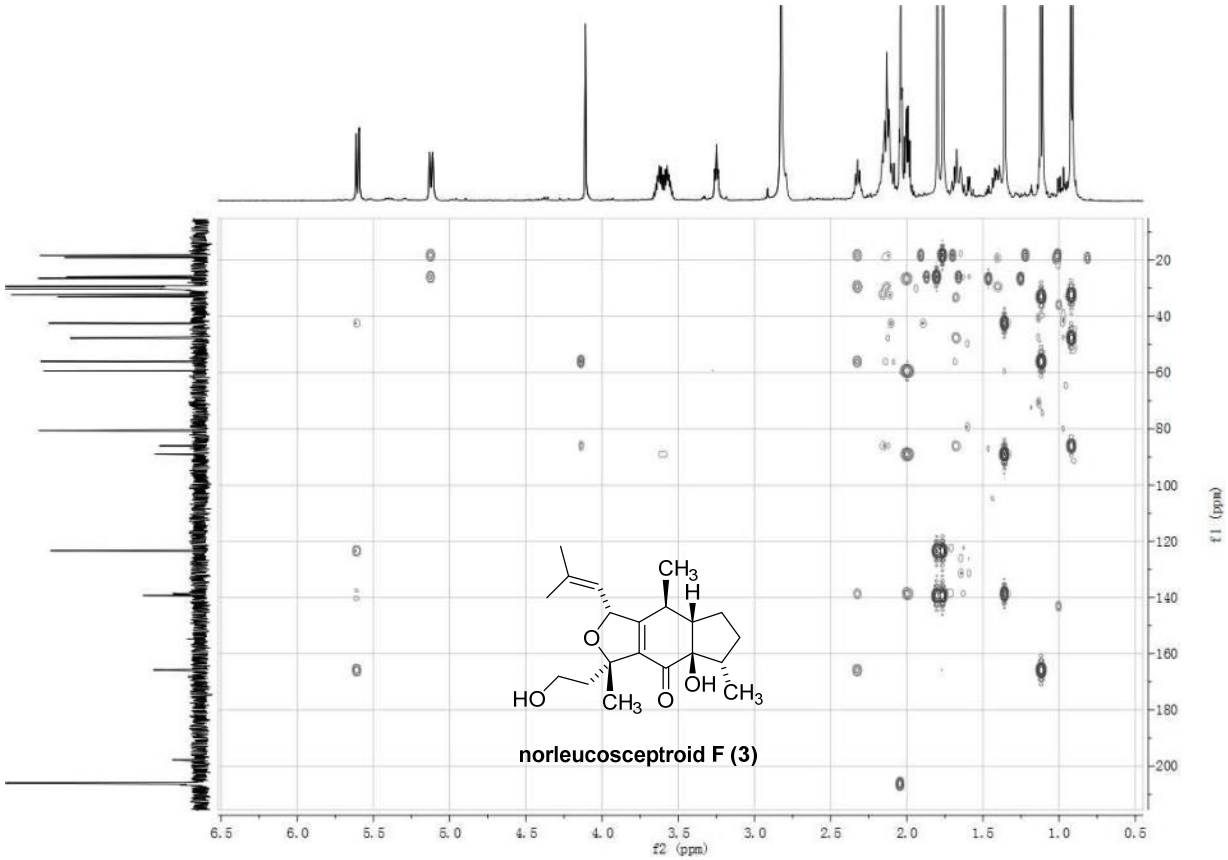


Figure S22. HMBC spectrum of norleucosceptroid F (**3**) recorded in acetone-d_6.

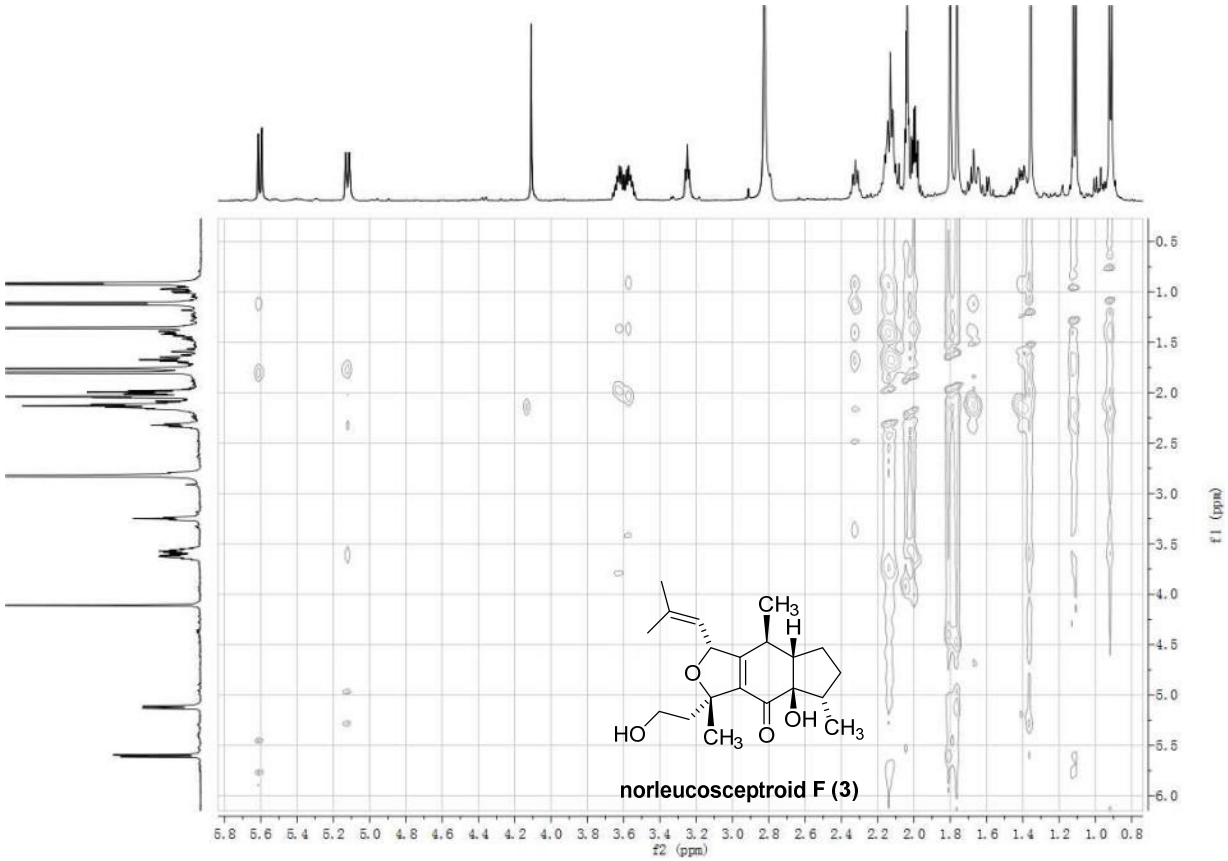


Figure S23. ROESY spectrum of norleucosceptroid F (**3**) recorded in acetone-d_6.

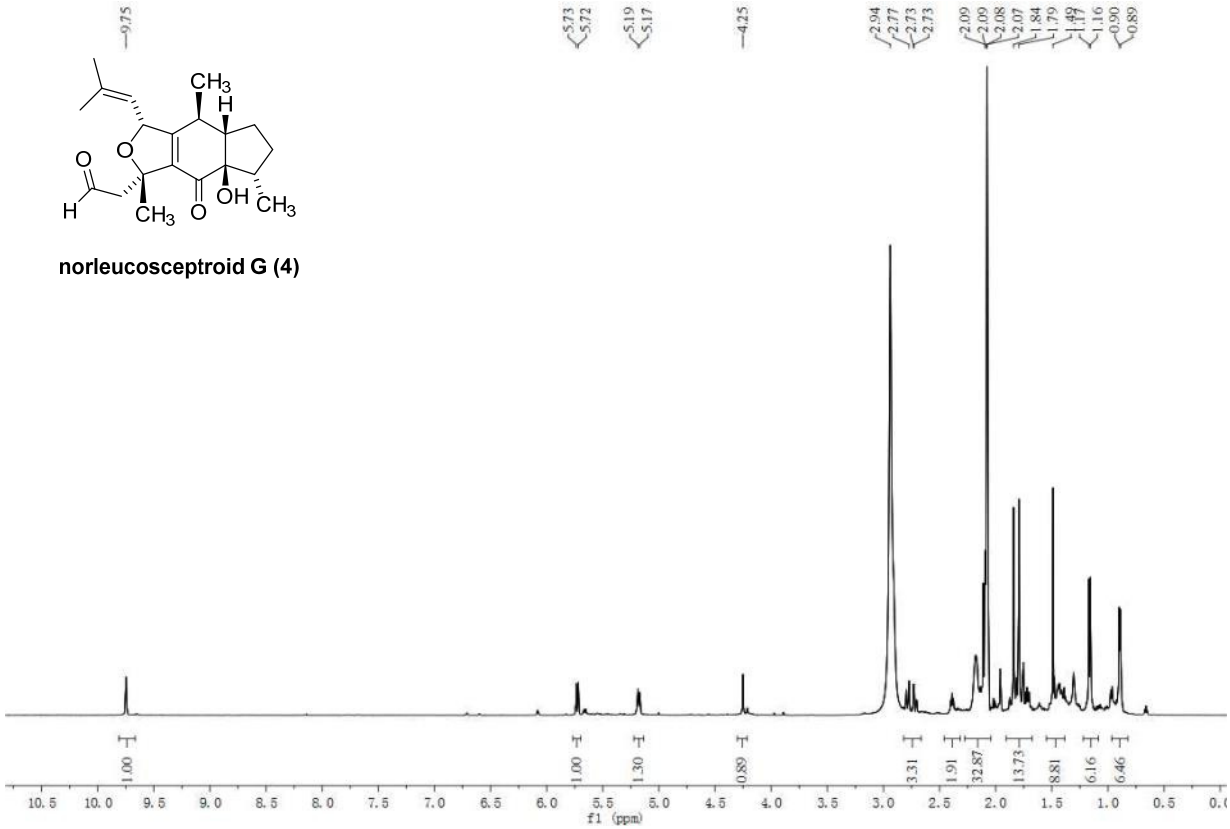


Figure S24. ^{1}H NMR spectrum of norleucosceptroid G (**4**) recorded at 400 MHz in acetone-d_6.

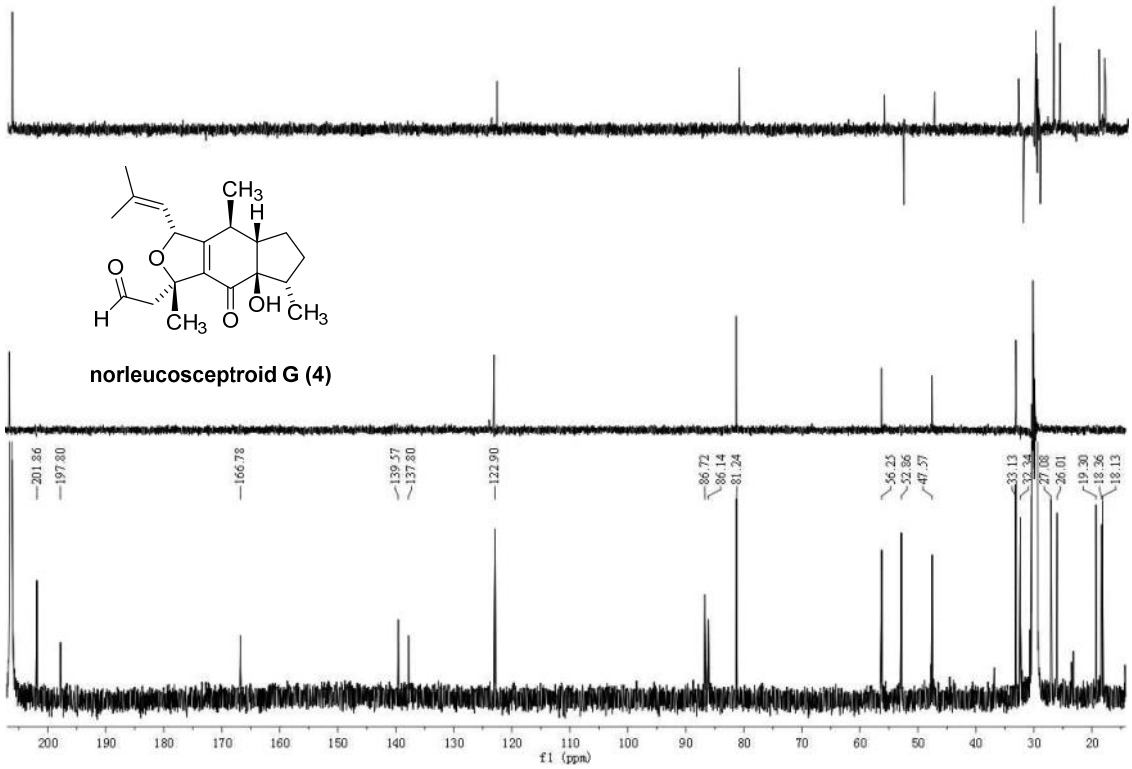


Figure S25. ^{13}C NMR and DEPT spectra of norleucosceptroid G (**4**) recorded at 125 MHz in acetone-d_6.

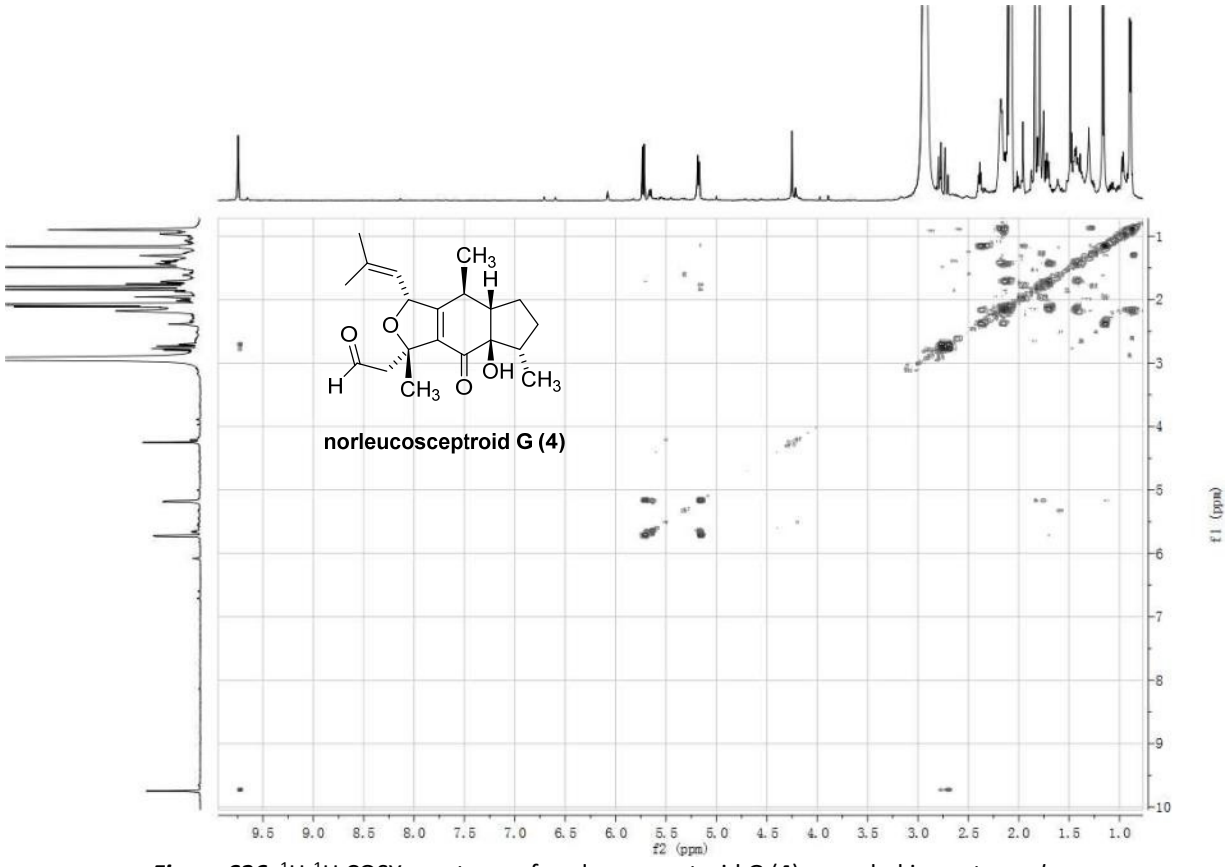


Figure S26. ^{1}H-^{1}H COSY spectrum of norleucosceptroid G (**4**) recorded in acetone-d_6.

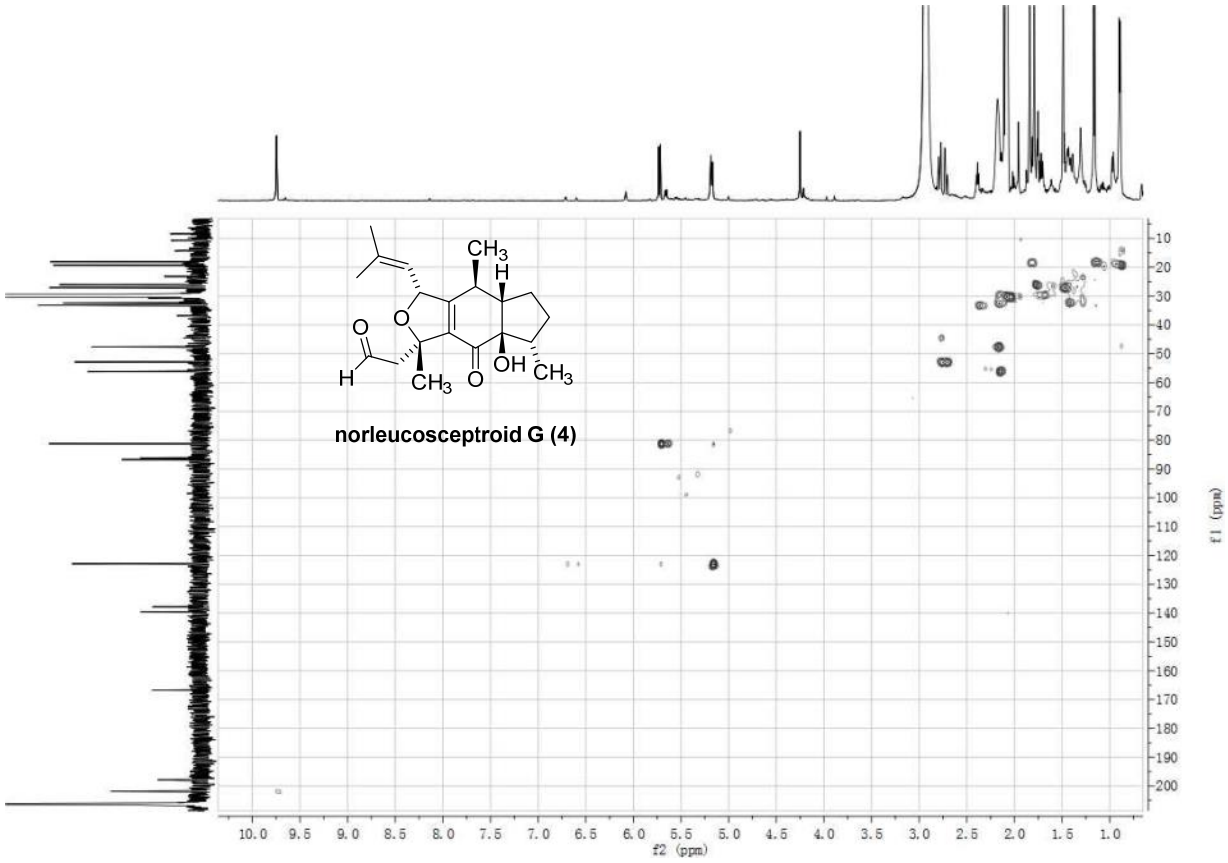


Figure S27. HSQC spectrum of norleucosceptroid G (**4**) recorded in acetone-d_6.

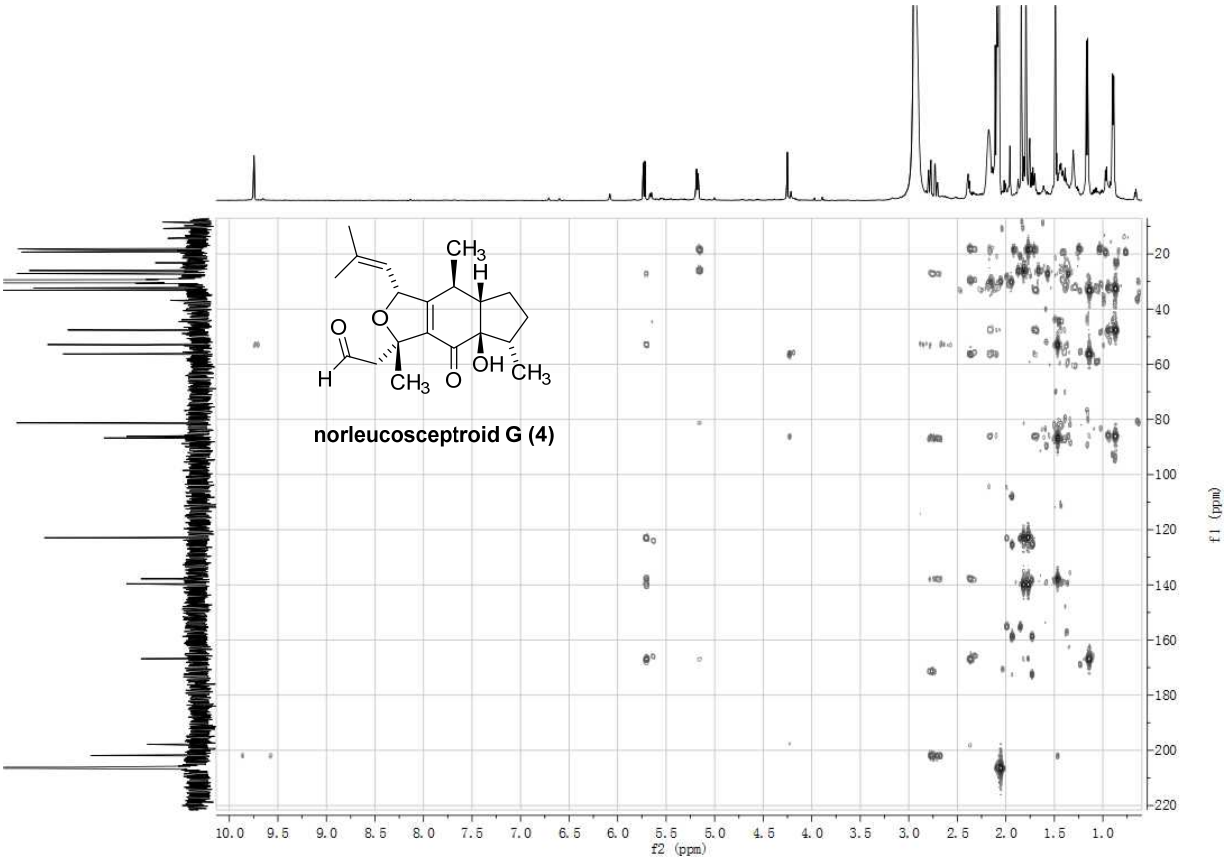


Figure S28. HMBC spectrum of norleucosceptroid G (**4**) recorded in acetone-d_6.

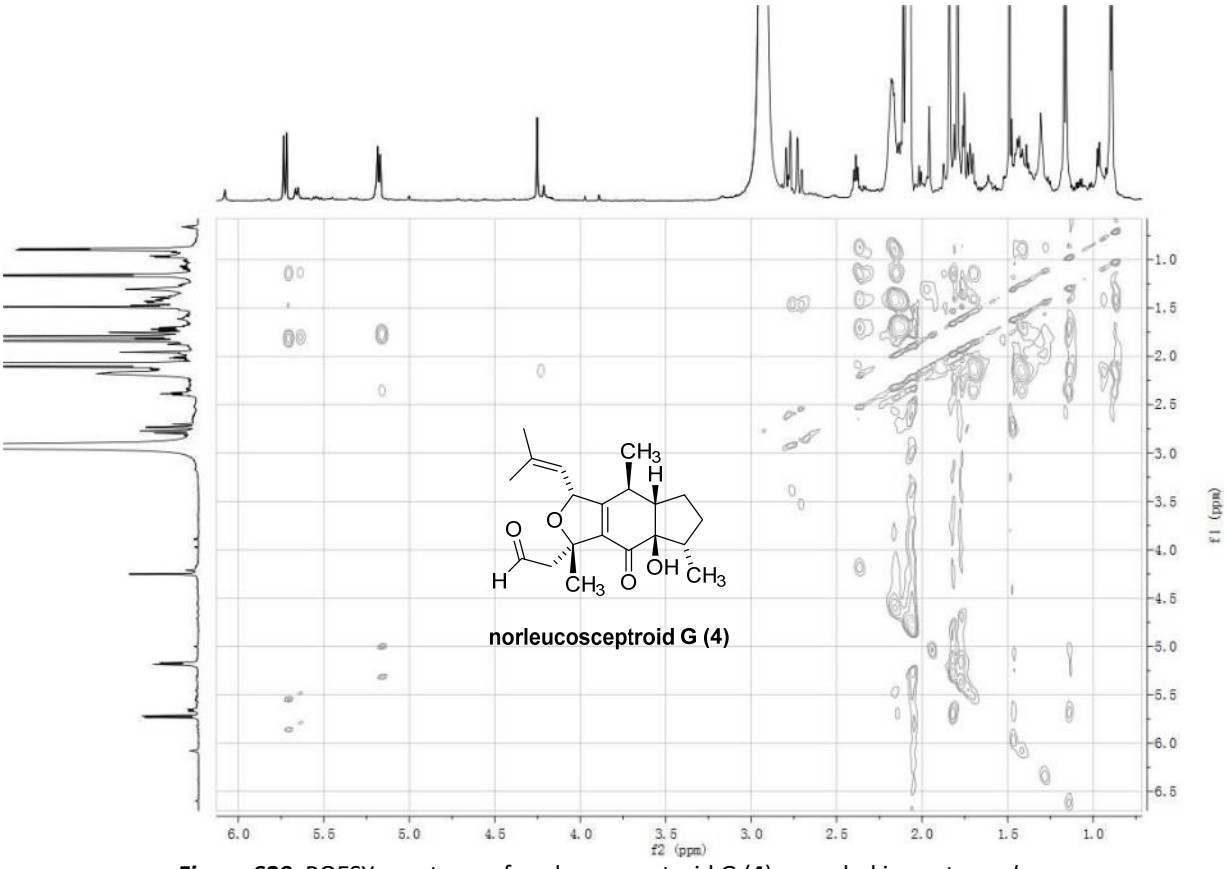


Figure S29. ROESY spectrum of norleucosceptroid G (**4**) recorded in acetone-d_6.

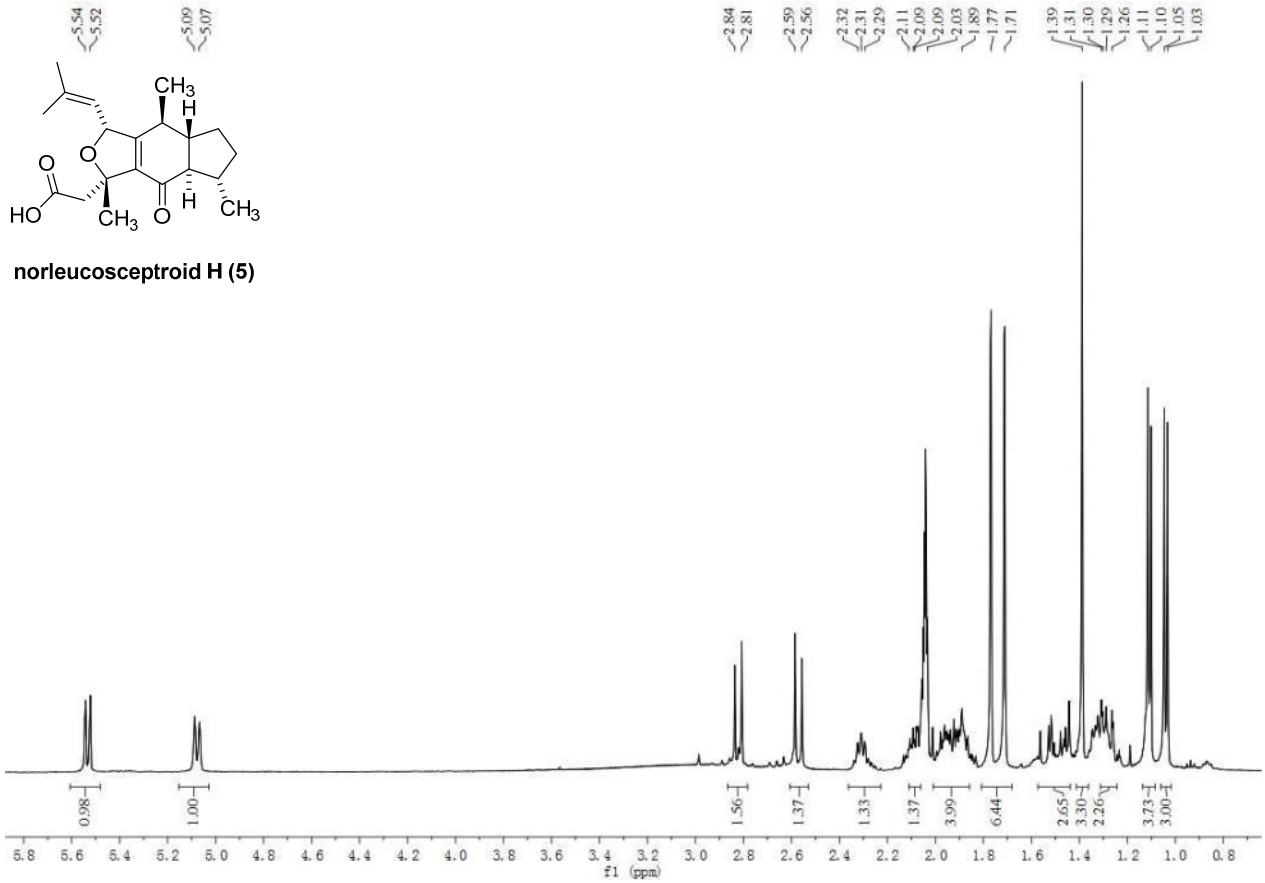


Figure S30. ^{1}H NMR spectrum of norleucosceptroid H (**5**) recorded at 500 MHz in acetone-d_6.

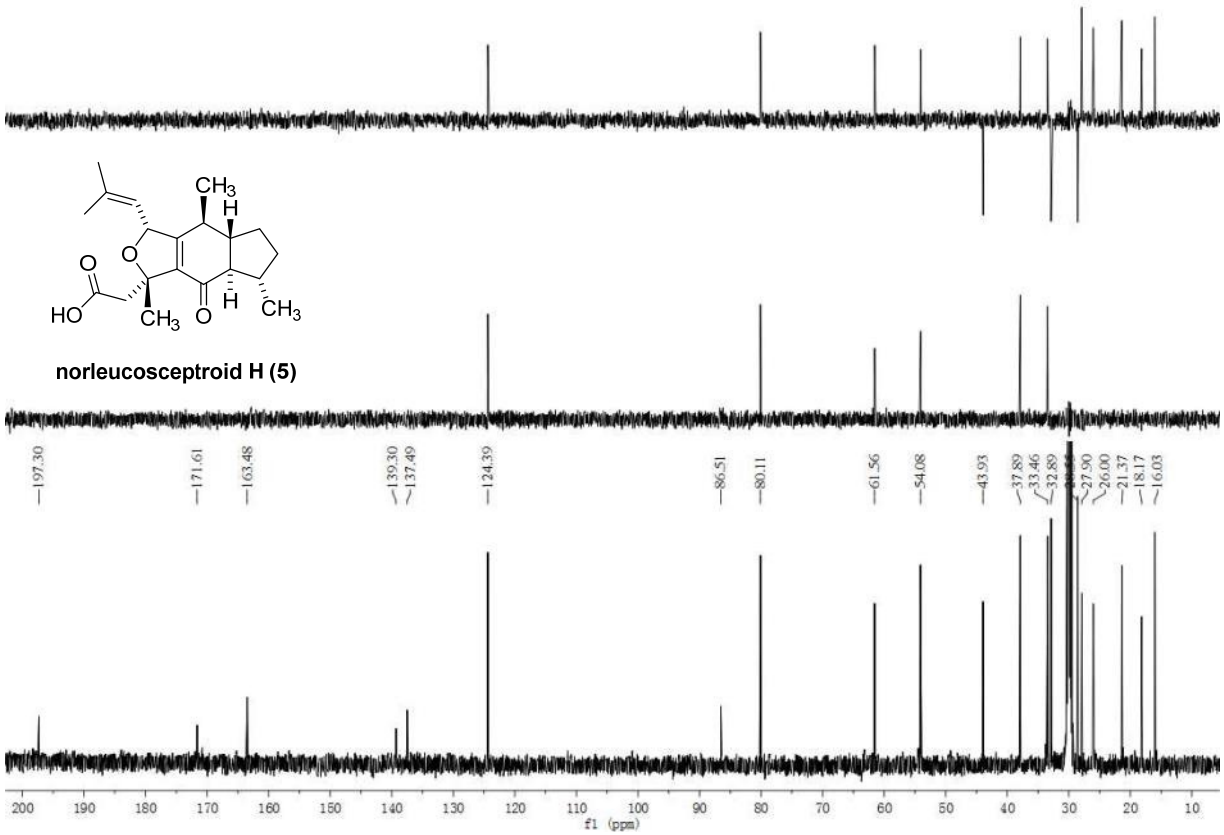


Figure S31. ^{13}C NMR and DEPT spectra of norleucosceptroid H (**5**) recorded at 125 MHz in acetone-d_6.

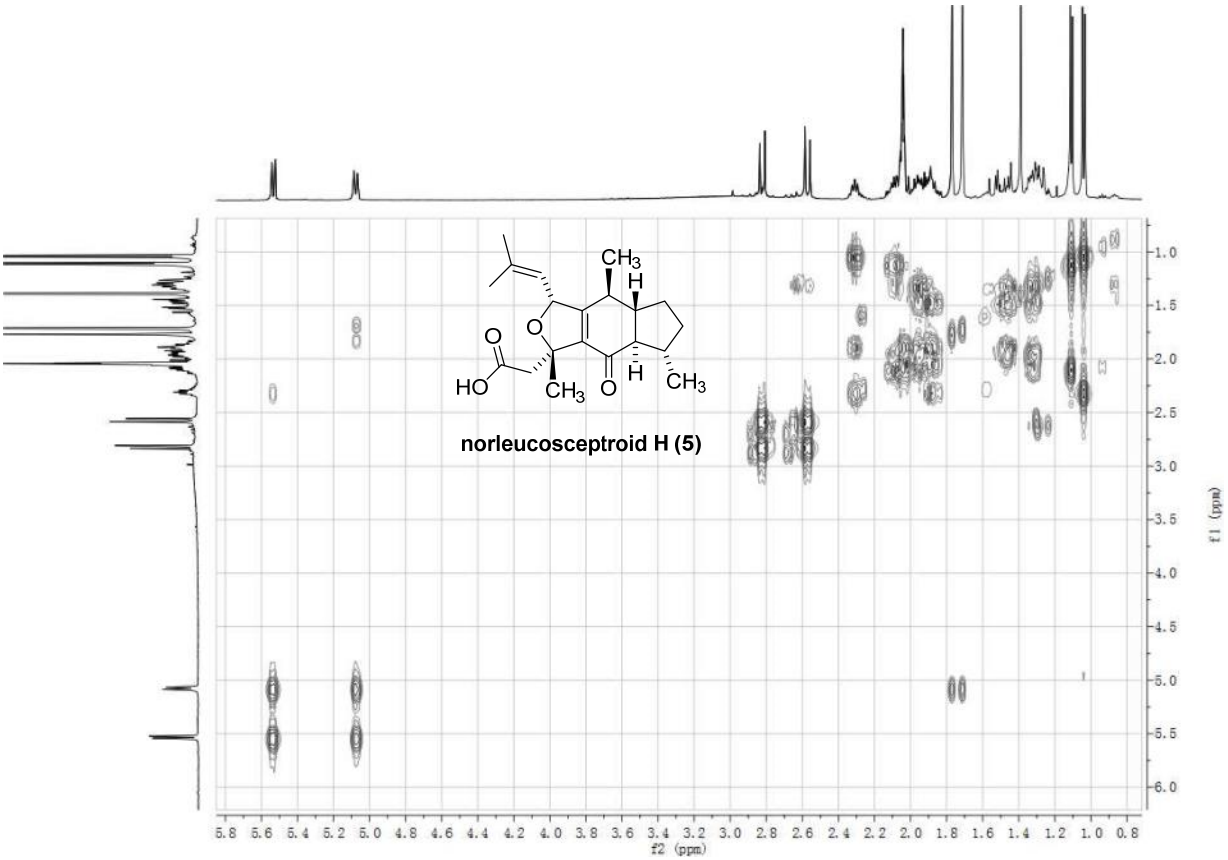


Figure S32. ^{1}H-^{1}H COSY spectrum of norleucosceptroid H (**5**) recorded in acetone-d_6.

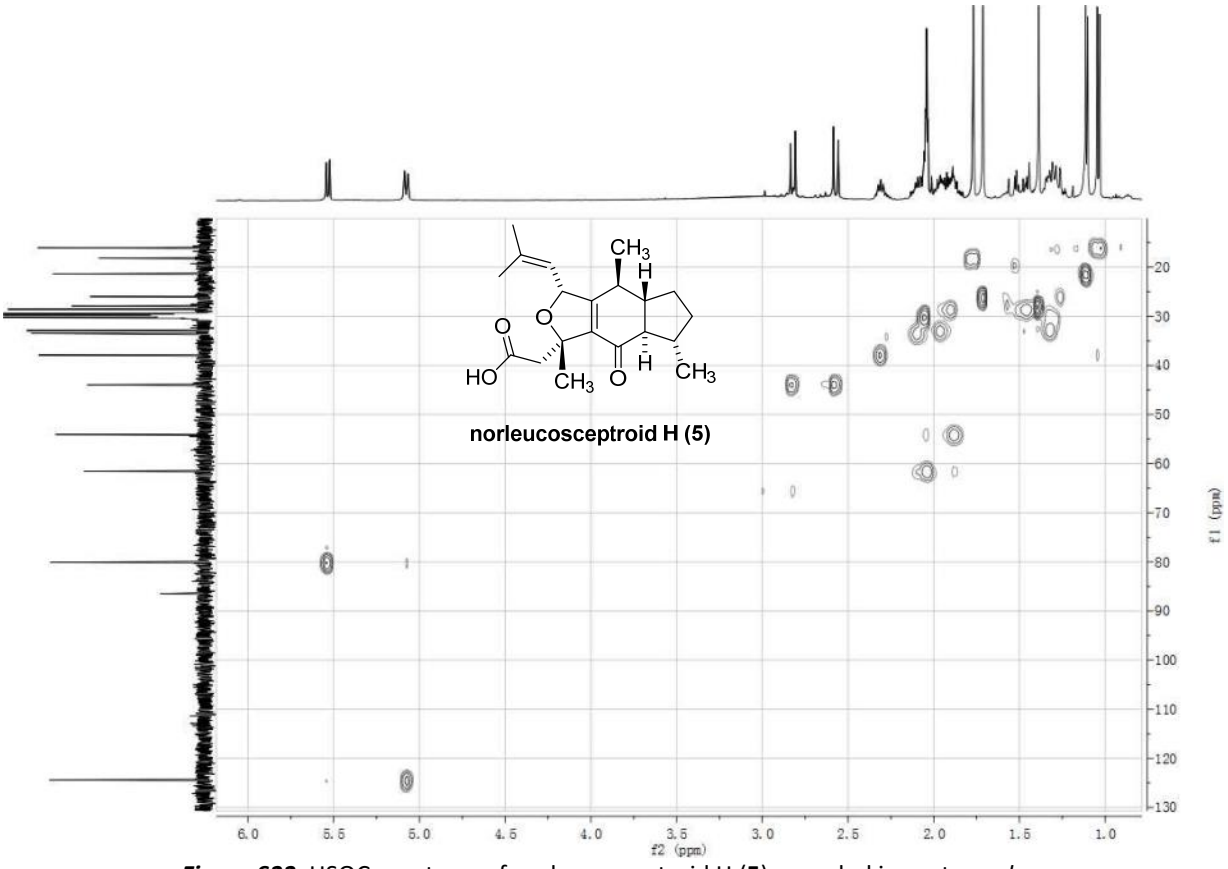


Figure S33. HSQC spectrum of norleucosceptroid H (**5**) recorded in acetone-d_6.

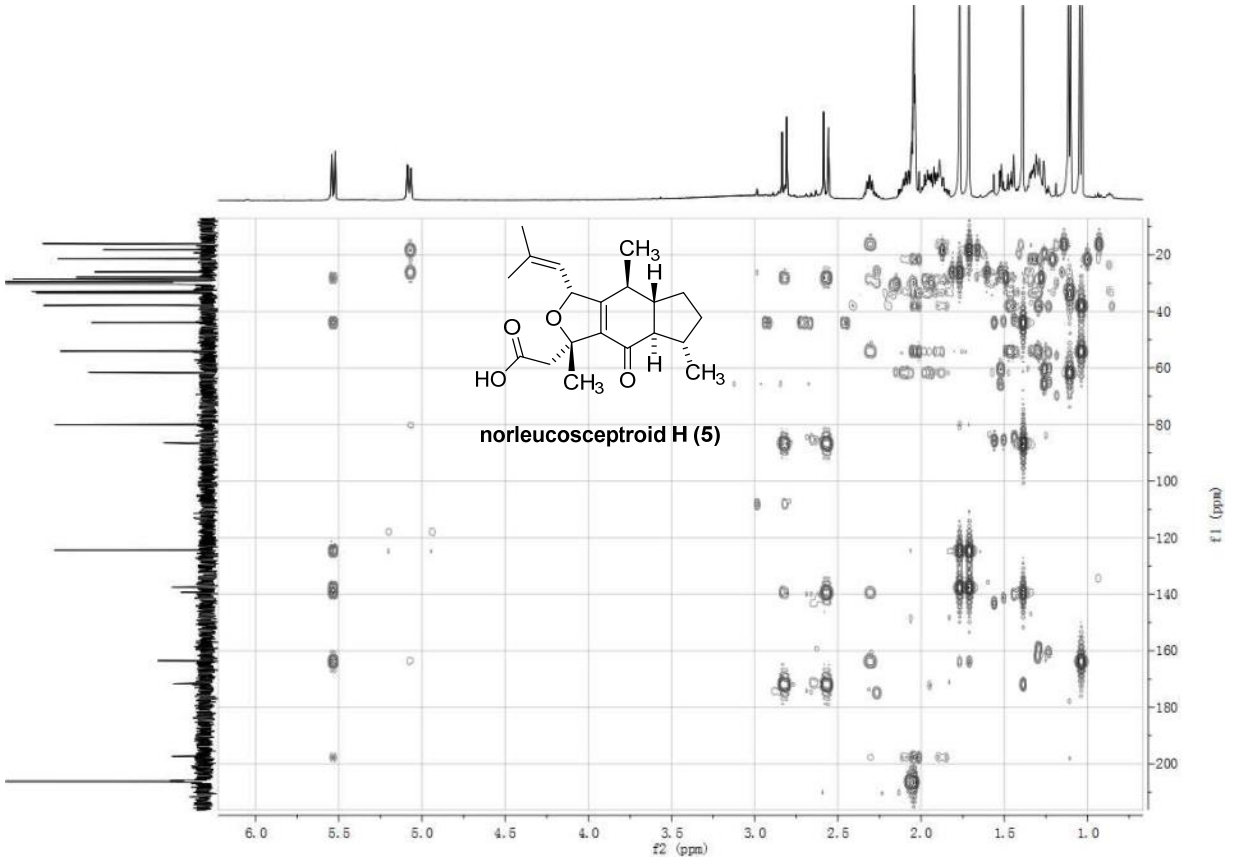


Figure S34. HMBC spectrum of norleucosceptroid H (**5**) recorded in acetone-d_6.

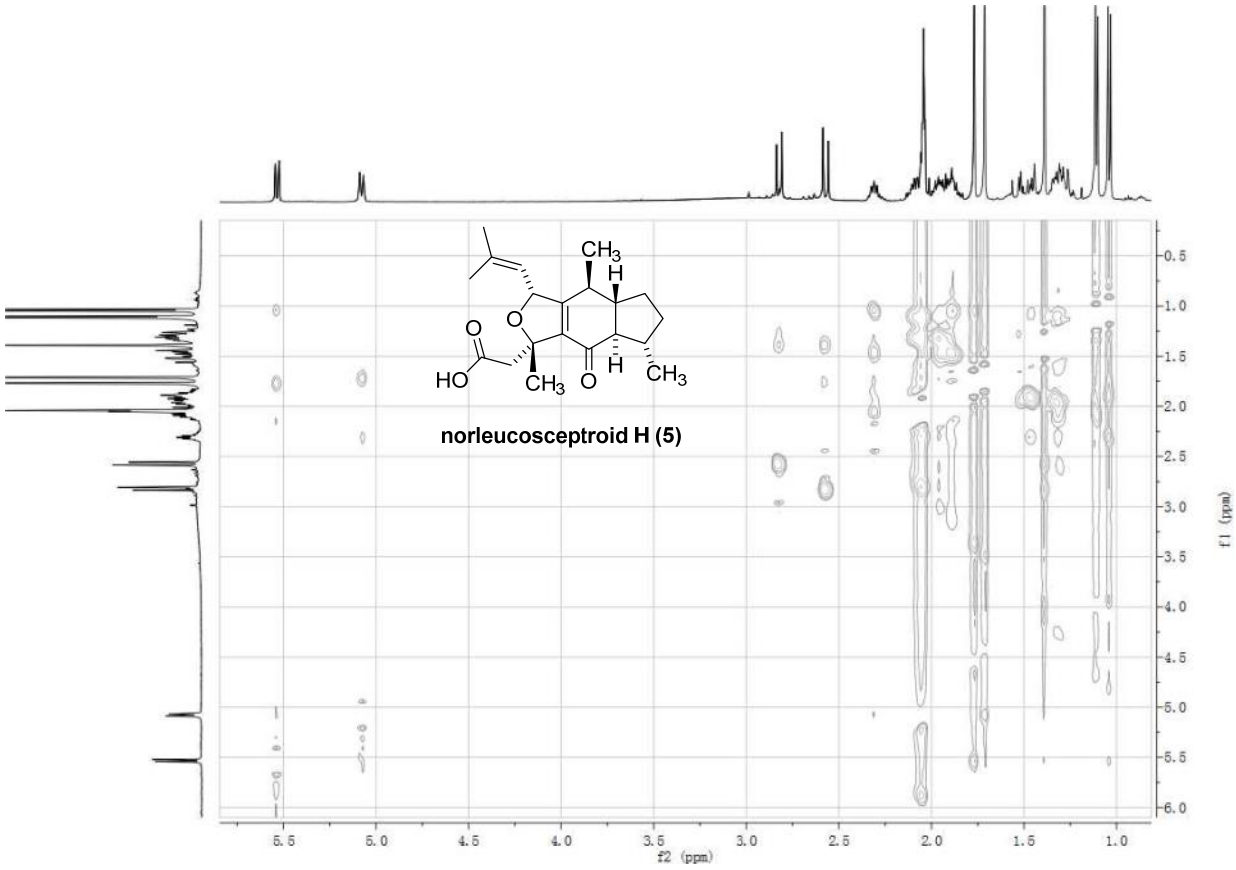


Figure S35. ROESY spectrum of norleucosceptroid H (**5**) recorded in acetone-d_6.

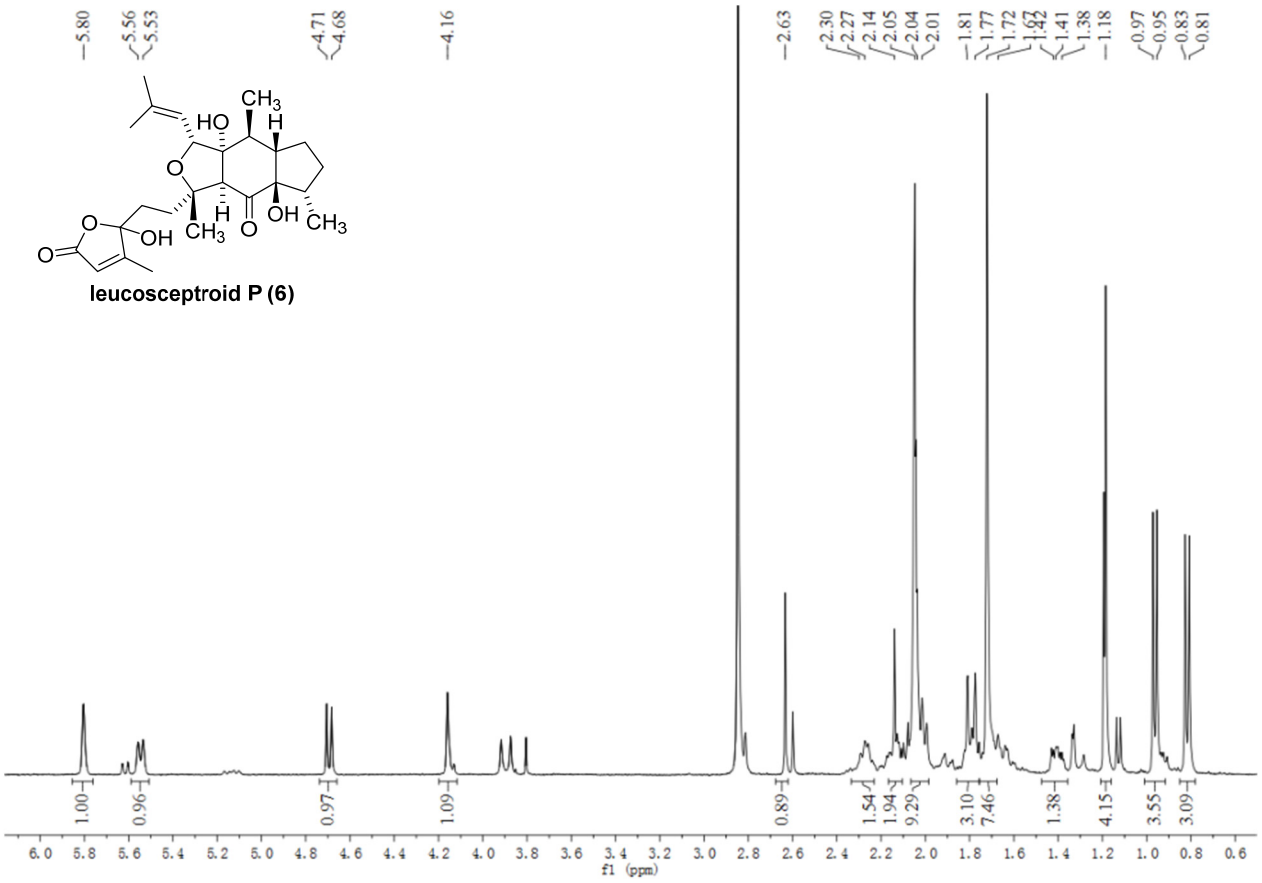


Figure S36. ^{1}H NMR spectrum of norleucosceptroid P (**6**) recorded at 500 MHz in acetone-d_6.

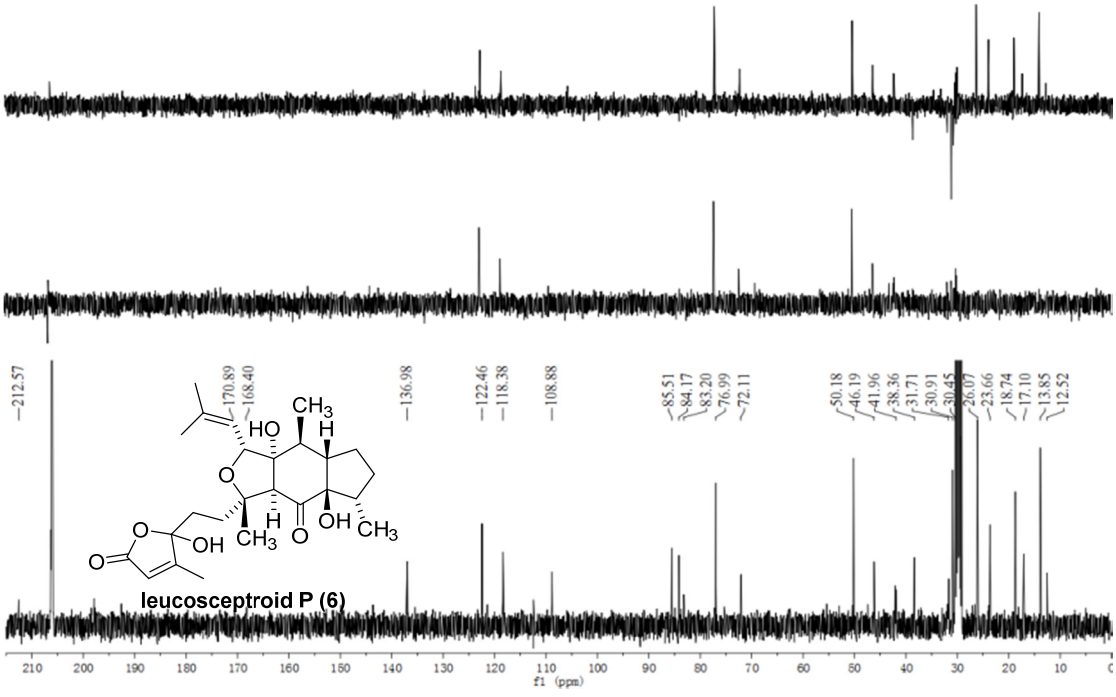


Figure S37. ^{13}C NMR and DEPT spectra of norleucosceptroid P (**6**) recorded at 125 MHz in acetone-d_6.

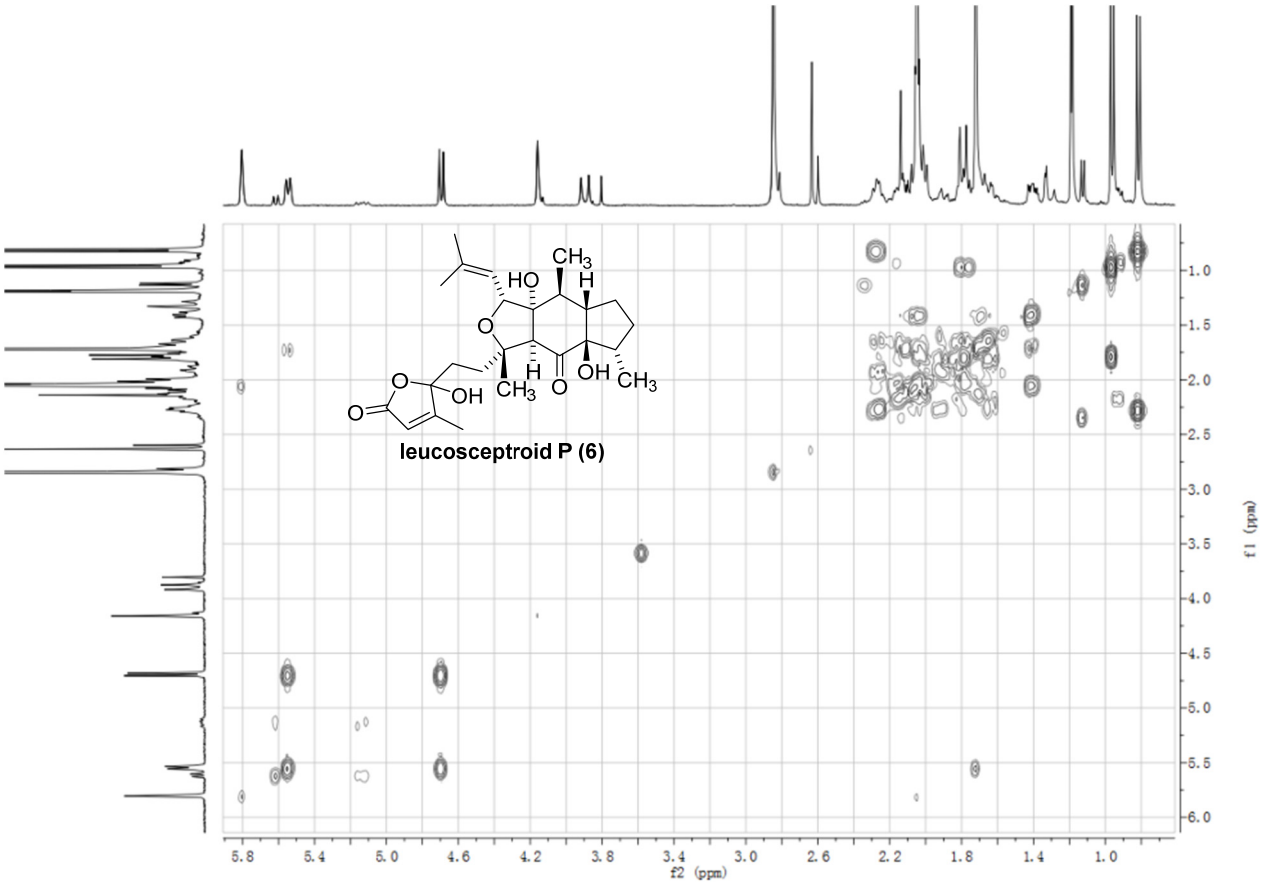


Figure S38. ^{1}H-^{1}H COSY spectrum of leucosceptroid P (**6**) recorded in acetone-d_6.

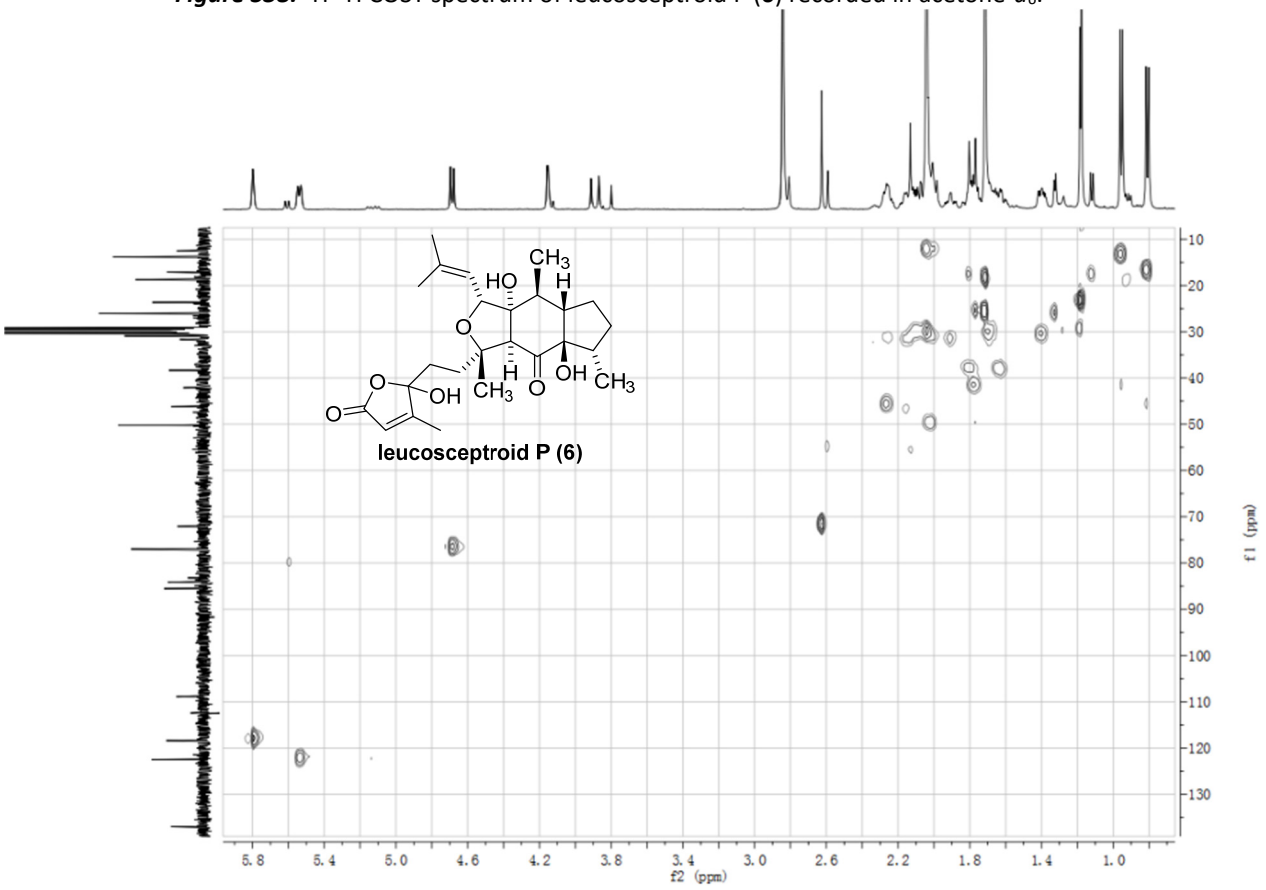


Figure S39. HSQC spectrum of leucosceptroid P (**6**) recorded in acetone-d_6.

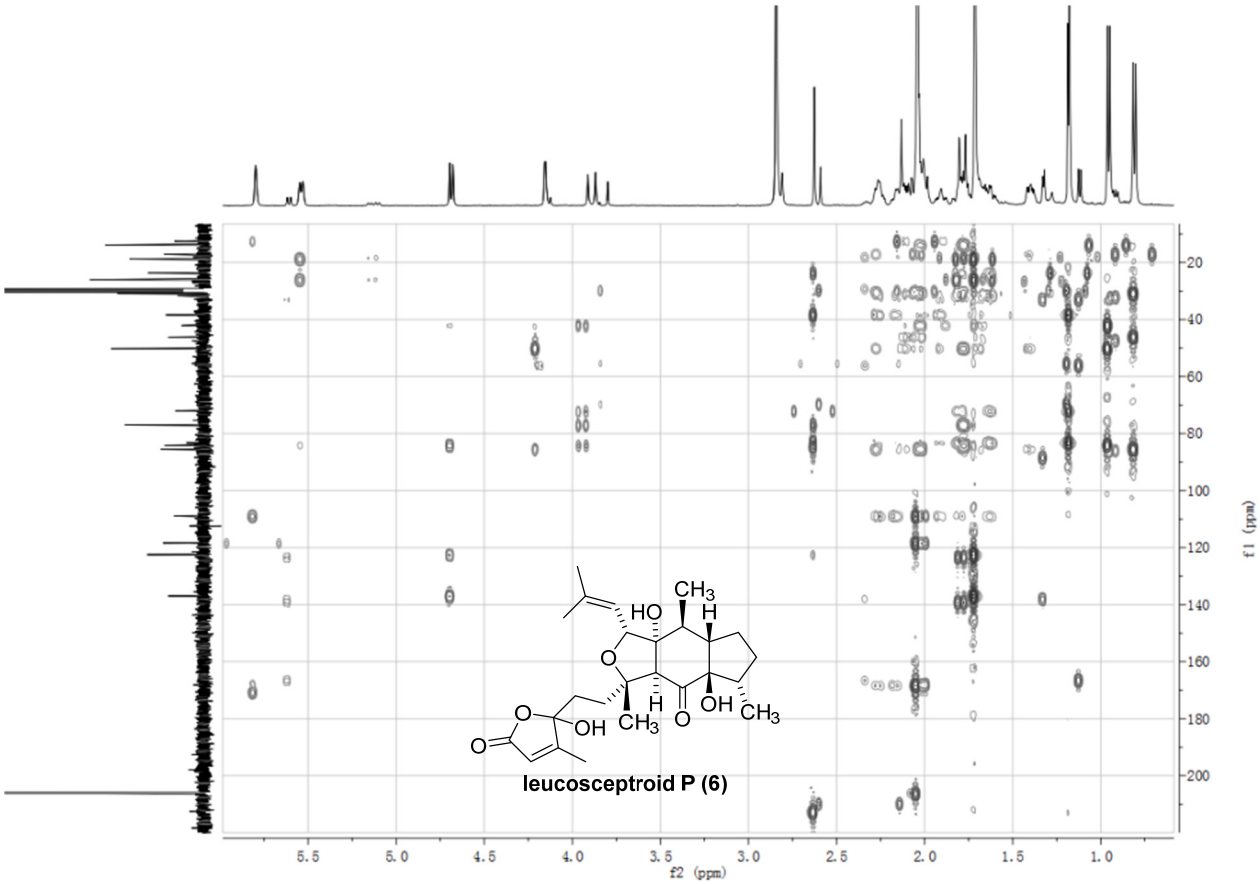


Figure S40. HMBC spectrum of leucosceptroid P (**6**) recorded in acetone-d_6.

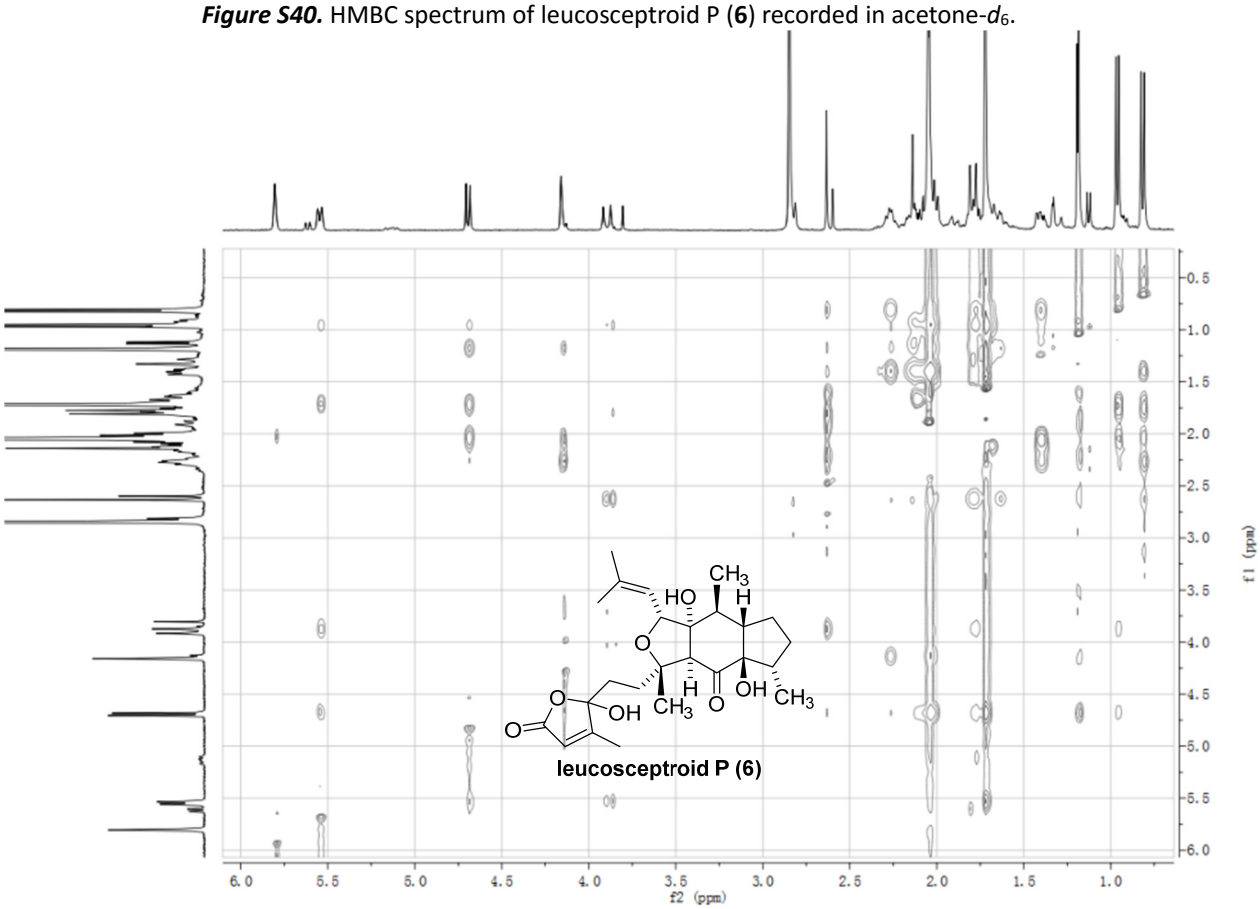


Figure S41. ROESY spectrum of leucosceptroid P (**6**) recorded in acetone-d_6.

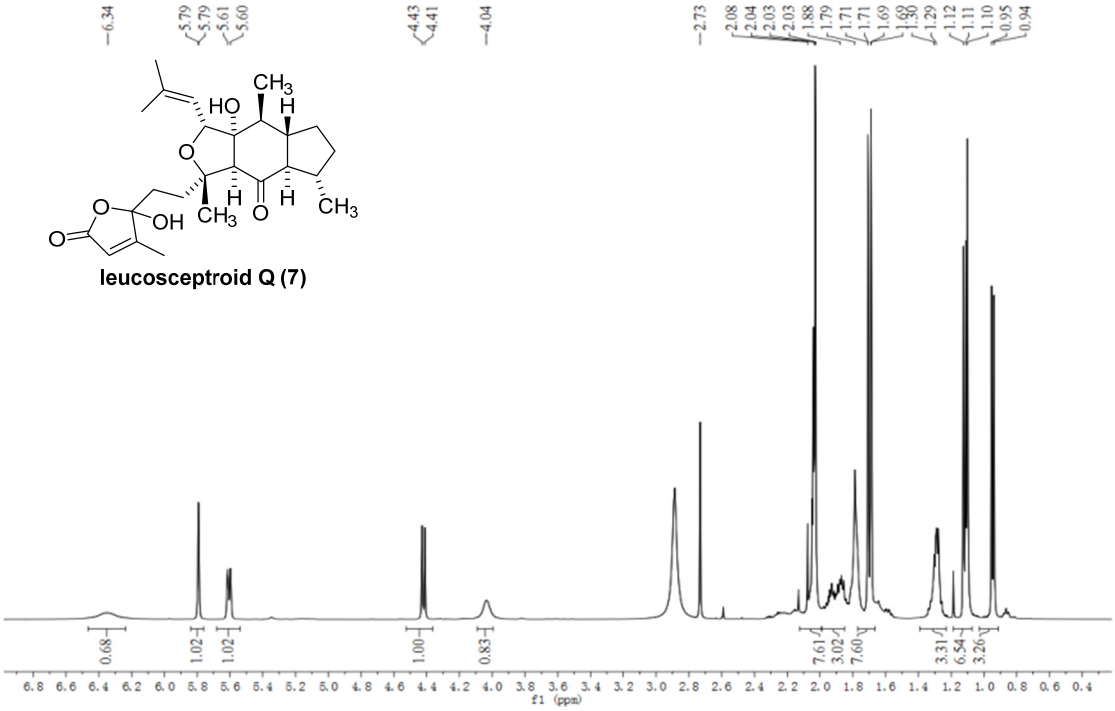


Figure S42. ^{1}H NMR spectrum of norleucosceptroid Q (**7**) recorded at 500 MHz in acetone-d_6.

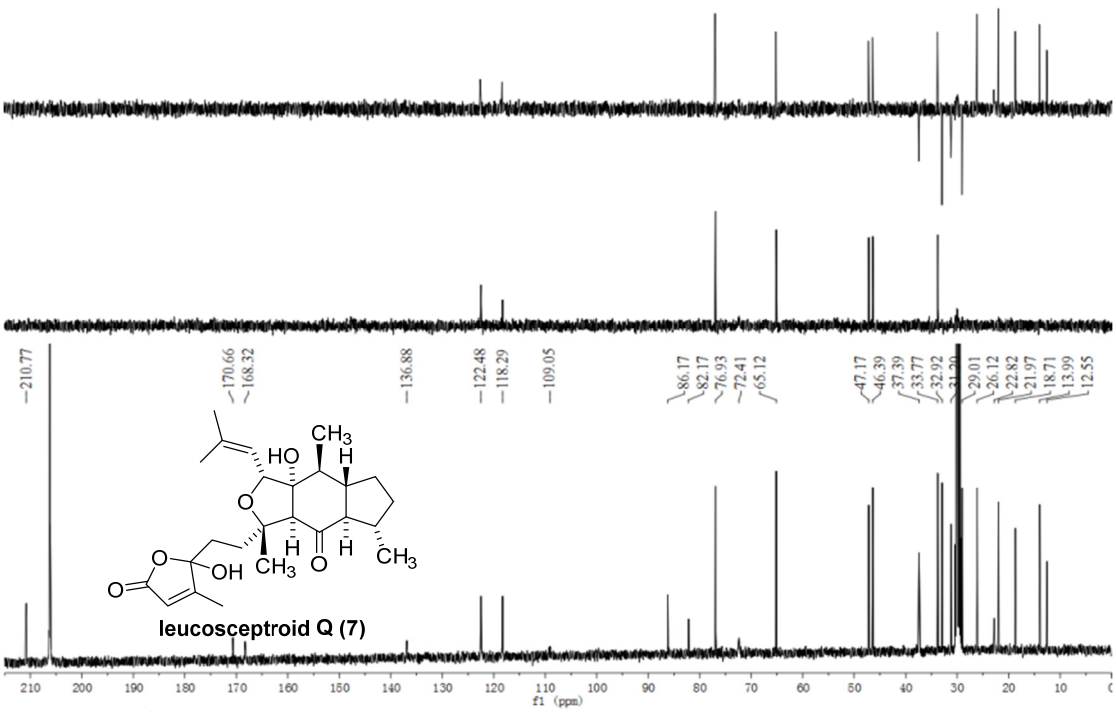


Figure S43. ^{13}C NMR and DEPT spectra of norleucosceptroid Q (**7**) recorded at 125 MHz in acetone-d_6.

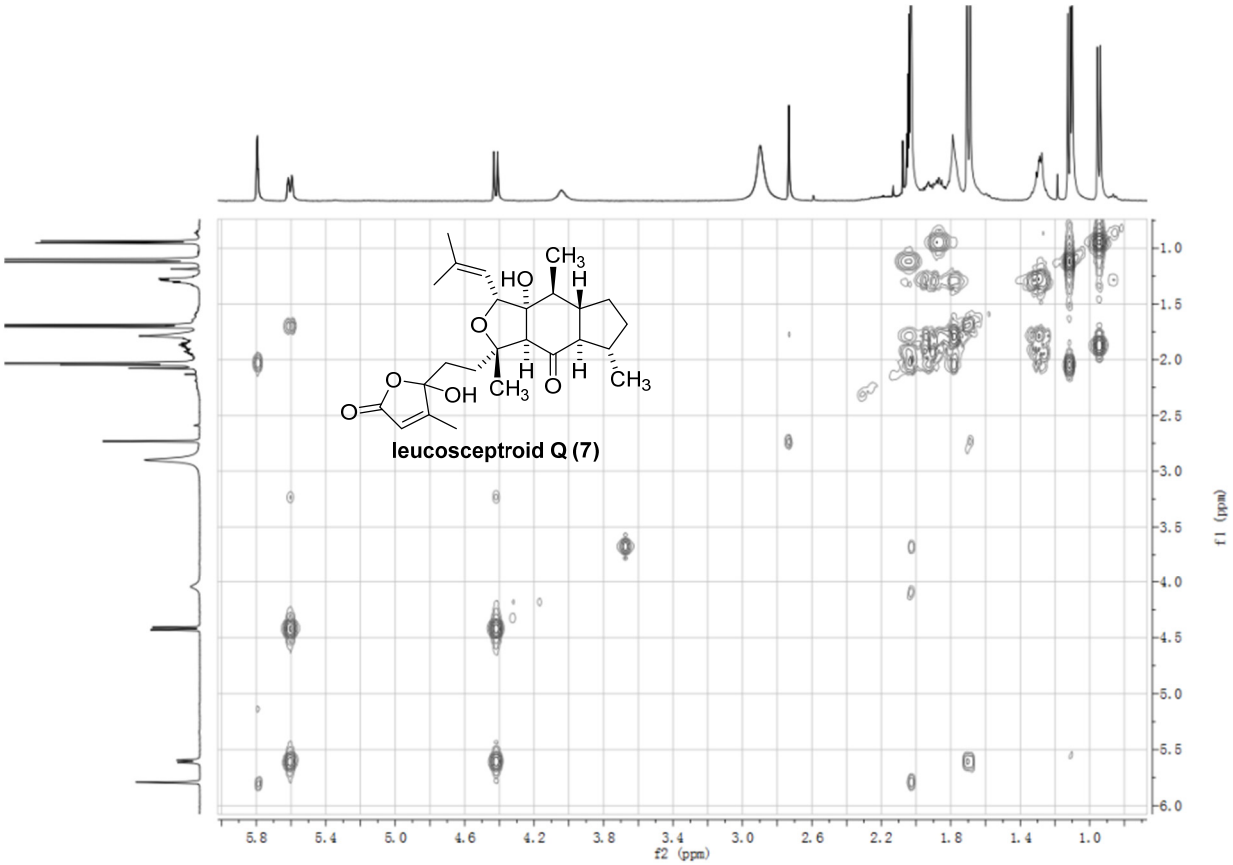


Figure S44. ^{1}H-^{1}H COSY spectrum of leucosceptroid Q (**7**) recorded in acetone-d_6.

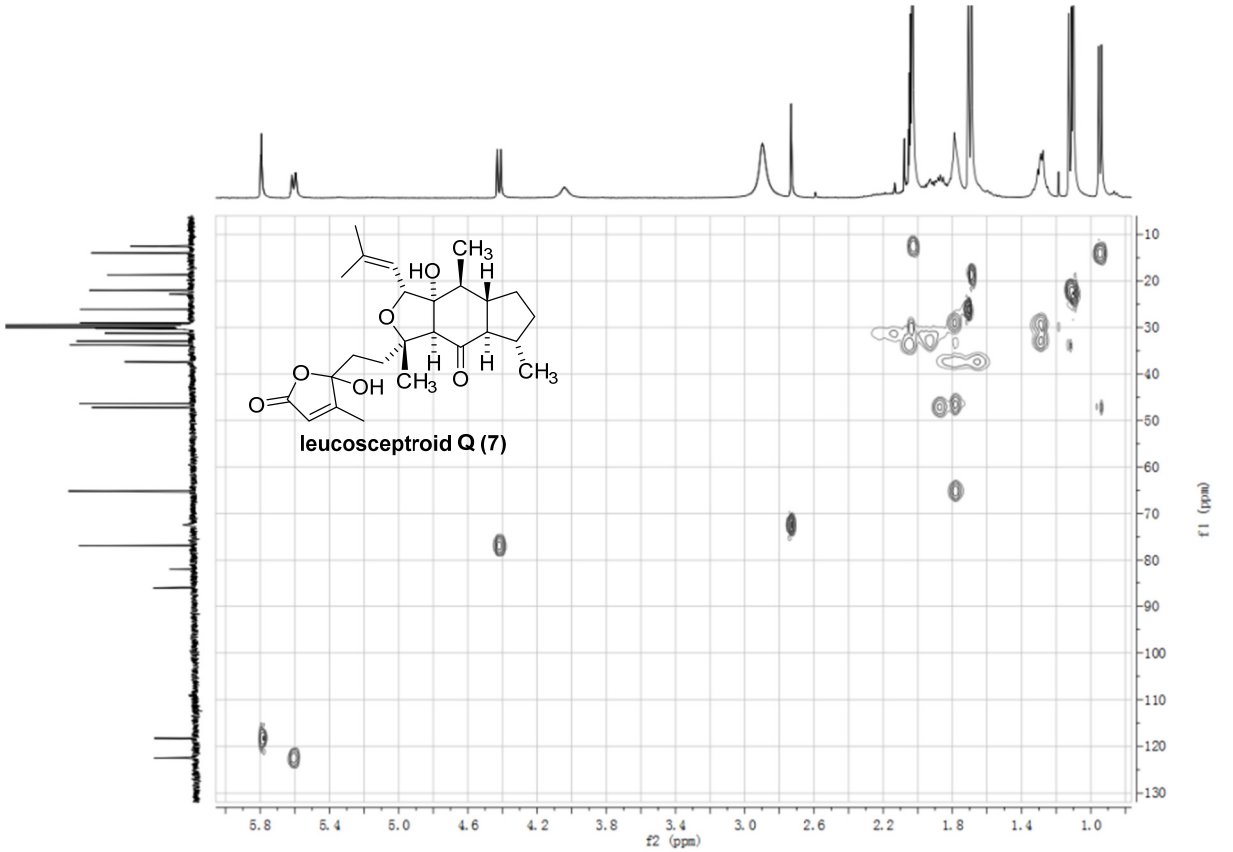


Figure S45. HSQC spectrum of leucosceptroid Q (**7**) recorded in acetone-d_6.

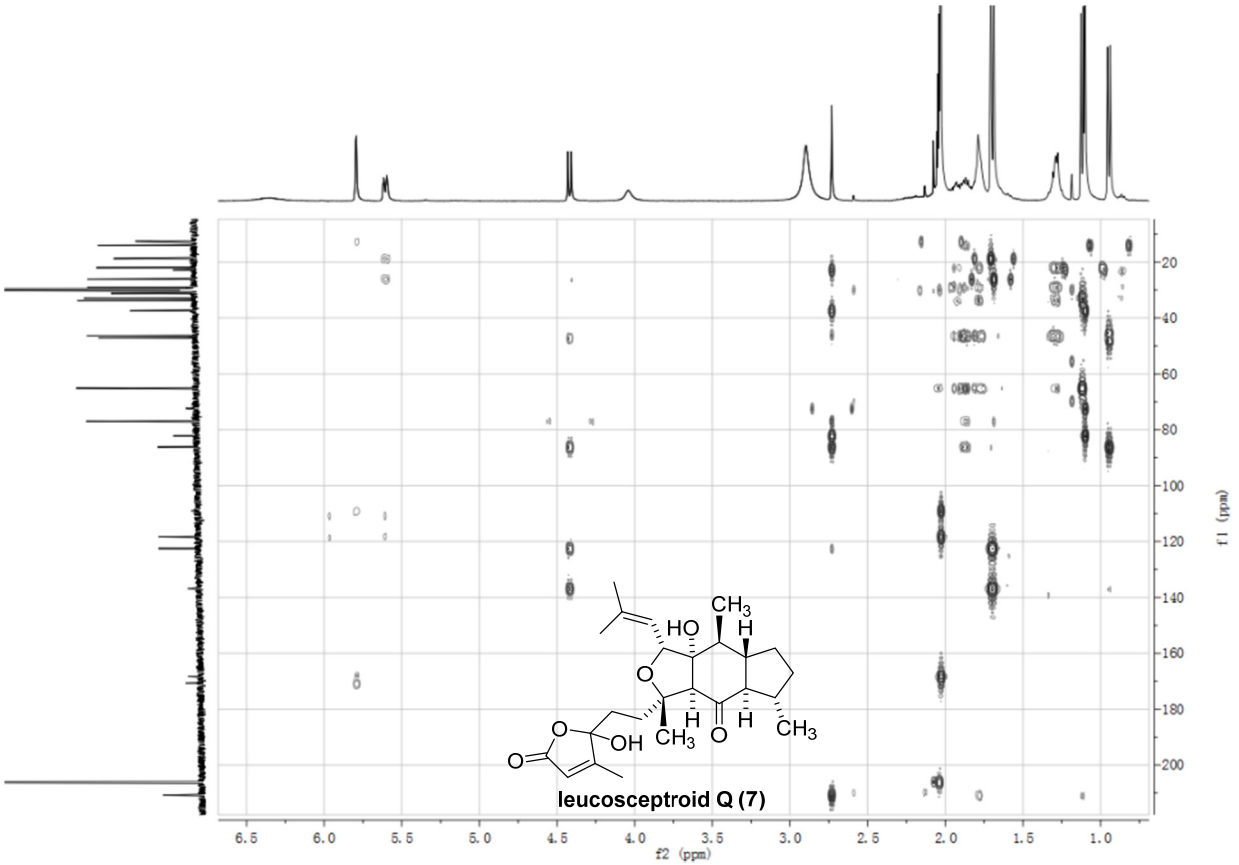


Figure S46. HMBC spectrum of leucosceptroid Q (**7**) recorded in acetone-d_6.

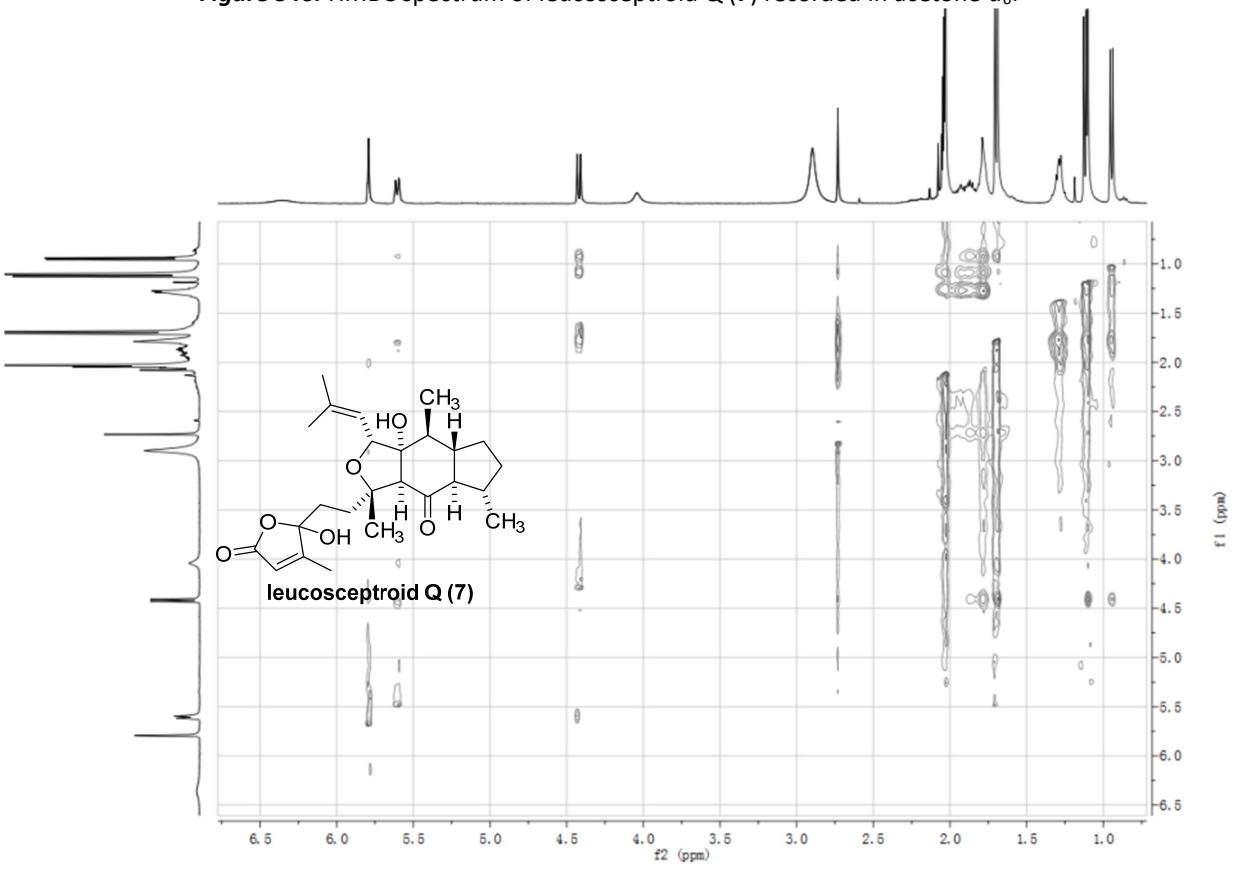
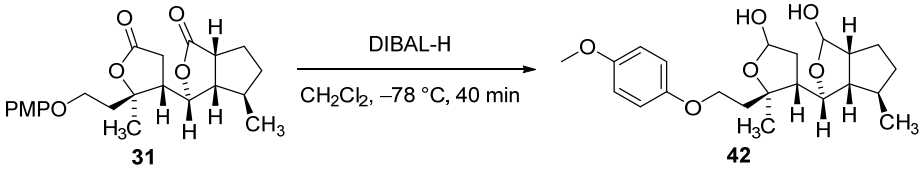


Figure S47. ROESY spectrum of leucosceptroid Q (**7**) recorded in acetone-d_6.

6.2.4 Biomimetic Model Synthesis: Experimental Procedures

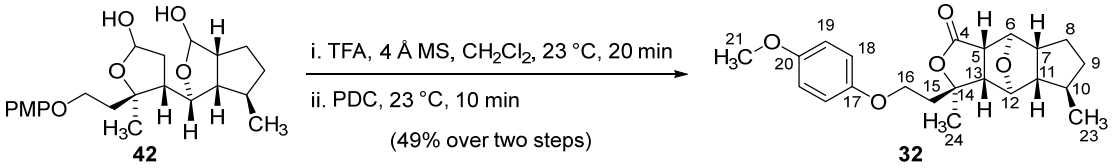
Synthesis of Dilactol 42



Diisobutylaluminium hydride (1 M solution in dichloromethane, 39.4 mL, 39.4 mmol, 3.00 equiv) was added dropwise to a solution of known dilactone **31**[21] (5.10 g, 13.1 mmol, 1 equiv) in dichloromethane (120 mL) at −78 °C over 10 min. After 40 min, methanol (15 mL) followed by 0.5 M aqueous hydrochloric acid solution (70 mL) were added at −78 °C, and the mixture was then warmed to 23 °C and poured onto saturated aqueous ammonium chloride solution (150 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 70 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide dilactol **42** as a colourless foam (5.35 g) which was used in the next step without further purification.

[21] Hugelshofer, C. L.; Magauer, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 11351–11355.

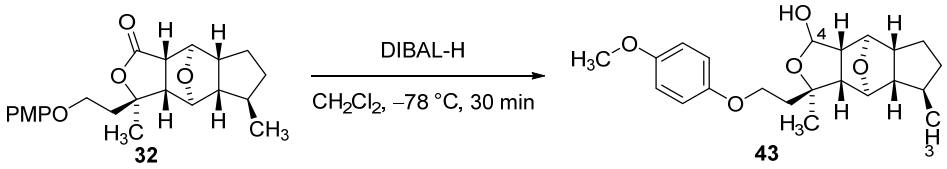
Synthesis of Lactone 32



A round-bottomed flask was charged with 4 Å molecular sieves (20 g) and was flame-dried in vacuo for 5 min. After cooling to 23 °C, the 4 Å molecular sieves were crushed and a solution of crude dilactol **42** (4.13 g, 10.5 mmol, 1 equiv) in dichloromethane (230 mL) was added. The resulting suspension was treated with trifluoroacetic acid (3.91 mL, 52.6 mmol, 5.00 equiv) at 23 °C. After 20 min, pyridinium dichromate (7.92 g, 21.0 mmol, 2.00 equiv) was added in three large portions and stirring was continued at 23 °C. After 10 min, the mixture was filtered through a pad of silica gel (4 cm) and the filter cake was washed with 1% methanol in dichloromethane (ca. 200 mL). The filtrate was concentrated to provide spectroscopically pure lactone **32** as a brownish highly viscous oil (1.91 g, 49% over two steps).

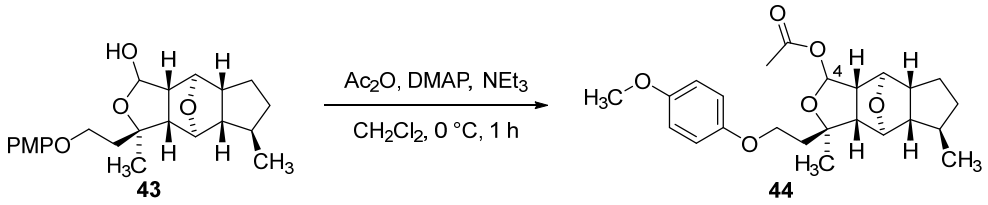
TLC (30% ethyl acetate in hexanes): R_f = 0.37 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87–6.76 (m, 4H, 18-H, 19-H), 4.49 (s, 1H, 6-H), 4.41 (s, 1H, 12-H), 4.08–4.03 (m, 2H, 16-H), 3.77 (s, 3H, 21-H), 2.88 (d, $^3J_{5/13}$ = 8.4 Hz, 1H, 5-H), 2.56 (d, $^3J_{13/5}$ = 8.4 Hz, 1H, 13-H), 2.30–2.21 (m, 1H, 7-H), 2.21–2.03 (m, 2H, 15-H), 1.95–1.85 (m, 1H, 8-H_A), 1.79–1.67 (m, 1H, 9-H_A), 1.68–1.57 (m, 2H, 10-H, 11-H), 1.54 (s, 3H, 24-H), 1.30–1.17 (m, 1H, 8-H_B), 1.06 (d, $^3J_{23/10}$ = 6.2 Hz, 3H, 23-H), 1.01–0.90 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.50 (C-4), 154.25 (C-20), 152.60 (C-17), 115.38 (C-18, C-19), 114.93 (C-18, C-19), 86.34 (C-14), 83.73 (C-6), 81.70 (C-12), 64.19 (C-16), 56.10 (C-11), 55.89 (C-21), 51.83 (C-5), 51.45 (C-13), 48.69 (C-7), 42.53 (C-15), 39.78 (C-10), 35.86 (C-9), 30.87 (C-8), 22.56 (C-24), 19.56 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (m), 1759 (s), 1508 (s), 1461 (w), 1231 (s), 1045 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{22}H_{28}O_5Na)^+$: 395.18344, found: 395.18249. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −20.0 (c = 1.00, CH_2Cl_2).

Synthesis of lactol 43



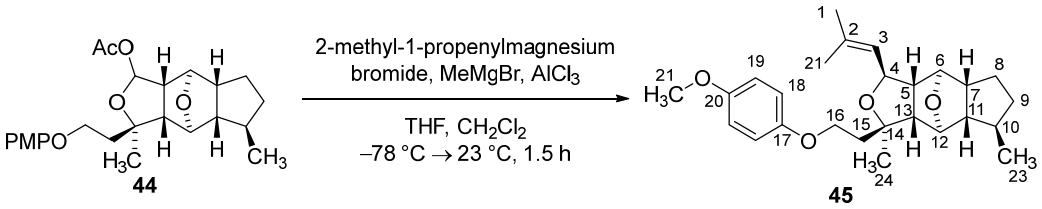
Diisobutylaluminium hydride (1 M solution in dichloromethane, 6.85 mL, 6.85 mmol, 1.50 equiv) was added dropwise to a solution of lactone **32** (1.70 g, 4.56 mmol, 1 equiv) in dichloromethane (50 mL) at −78 °C over 5 min. After 30 min, methanol (10 mL) followed by 0.5 M aqueous hydrochloric acid solution (20 mL) were added at −78 °C, and the mixture was then warmed to 23 °C and poured onto saturated aqueous ammonium chloride solution (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide lactol **43** (ca. 1:1 mixture of diastereomers at C-4) as a yellowish oil (1.75 g) which was used in the next step without further purification.

Synthesis of acetyl acetal 44



To an ice-cooled solution of crude lactol **43** (1.71 g, 4.56 mmol, 1 equiv) in dichloromethane (40 mL) was added 4-(dimethylamino)pyridine (111 mg, 0.91 mmol, 0.20 equiv), triethylamine (1.27 mL, 9.12 mmol, 2.00 equiv) and acetic anhydride (0.86 mL, 9.12 mmol, 2.00 equiv). After 1 h, the mixture was diluted with saturated aqueous sodium chloride solution (40 mL) and dichloromethane (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 25 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide acetyl acetal **44** (ca. 2:1 mixture of diastereomers at C-4) as a yellowish foam (2.1 g) which was used in the next step without further purification.

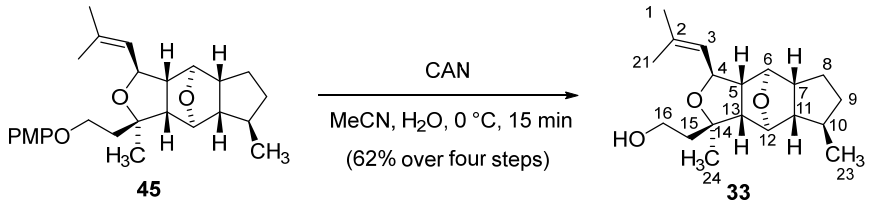
Synthesis of ether 45



An ice-cooled suspension of aluminium trichloride (1.82 g, 13.7 mmol, 3.00 equiv) in tetrahydrofuran (45 mL) was treated with methylmagnesium bromide solution (3.0 M in diethyl ether, 9.12 mL, 27.4 mmol, 6.00 equiv). After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 45 min, 2-methyl-1-propenylmagnesium bromide solution (0.5 M in tetrahydrofuran, 27.4 mL, 13.7 mmol, 3.00 equiv) was added and stirring was continued at 23 °C. After 45 min, the organoaluminum reagent mixture was cooled to −78 °C and a solution of the crude acetyl acetal **44** (1.90 g, 4.56 mmol, 1 equiv) in dichloromethane (25 mL) was added dropwise. The transfer was quantitated with dichloromethane (2 x 7 mL). After 10 min, the mixture was allowed to slowly warm to 23 °C over a period of 1.5 h, whereupon the mixture was diluted with saturated aqueous sodium bicarbonate solution (150 mL) and ethyl acetate (80 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 70 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide ether **45** as a yellowish oil (1.99 g) which was used in the next step without further purification. An analytically pure sample of ether **45** was obtained by purification of the crude material by flash-column chromatography (20% ethyl acetate in hexanes) on silica gel.

TLC (20% ethyl acetate in hexanes): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85–6.80 (m, 4H, 18-H, 19-H), 5.23–5.15 (m, 1H, 3-H), 4.26 (app t, $^3J_{4/3,4/5}$ = 8.5 Hz, 1H, 4-H), 4.09 (s, 1H, 12-H), 4.08–4.02 (m, 2H, 16-H), 3.87 (s, 1H, 6-H), 3.75 (s, 3H, 21-H), 2.33 (d, $^3J_{13/5}$ = 9.2 Hz, 1H, 13-H), 2.18–1.91 (m, 4H, 5-H, 7-H, 15-H), 1.92–1.78 (m, 1H, 8-H_A), 1.74 (s, 3H, 1-H), 1.73 (s, 3H, 21-H), 1.71–1.64 (m, 1H, 9-H_A), 1.63–1.49 (m, 2H, 10-H, 11-H), 1.34 (s, 3H, 24-H), 1.31–1.16 (m, 1H, 8-H_B), 1.03 (d, $^3J_{23/10}$ = 6.1 Hz, 3H, 23-H), 1.00–0.92 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.76 (C-20), 152.98 (C-17), 137.04 (C-2), 124.94 (C-3), 115.22 (C-18, C-19), 114.65 (C-18, C-19), 82.95 (C-14), 81.64 (C-6), 81.31 (C-12), 76.31 (C-4), 65.09 (C-16), 58.17 (C-5), 57.86 (C-13), 57.14 (C-11), 55.78 (C-21), 48.63 (C-7), 42.40 (C-15), 39.53 (C-10), 36.44 (C-9), 30.94 (C-8), 26.09 (C-1), 20.50 (C-24), 19.61 (C-23), 18.59 (C-21). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (m), 1508 (s), 1441 (w), 1379 (w), 1264 (s), 1231 (s), 1040 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{26}H_{36}O_4Na)^+$: 435.25113, found: 435.25062. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −21.0 (c = 1.30, CH_2Cl_2).

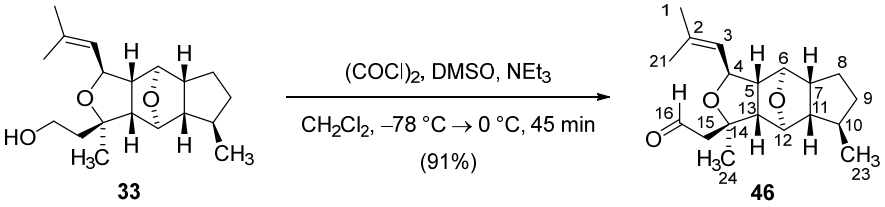
Synthesis of alcohol 33



An ice-cooled solution of crude ether **45** (1.88 g, 4.56 mmol, 1 equiv) in a mixture of acetonitrile–water (4:1, 40 mL) was treated with ammonium cerium(IV) nitrate (5.25 g, 9.58 mmol, 2.10 equiv). After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (100 mL), water (50 mL) and dichloromethane (50 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (35% ethyl acetate in hexanes) on silica gel to provide alcohol **33** as an orange oil (866 mg, 62% over four steps).

TLC (40% ethyl acetate in hexanes): R_f = 0.29 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21–5.14 (m, 1H, 3-H), 4.30–4.24 (m, 1H, 4-H), 4.08 (s, 1H, 12-H), 3.89 (s, 1H, 6-H), 3.84–3.75 (m, 2H, 16-H), 3.20 (br s, 1H, 16-OH), 2.20–2.10 (m, 3H, 5-H, 7-H, 13-H), 1.95–1.74 (m, 4H, 8-H_A, 9-H_A, 15-H), 1.73 (s, 3H, 1-H), 1.72 (s, 3H, 21-H), 1.62–1.55 (m, 1H, 10-H), 1.54–1.48 (m, 1H, 11-H), 1.34 (s, 3H, 24-H), 1.27–1.12 (m, 1H, 8-H_B), 1.03 (d, $^3J_{23/10}$ = 6.5 Hz, 3H, 23-H), 0.99–0.89 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.29 (C-2), 124.60 (C-3), 85.00 (C-14), 81.55 (C-6), 80.92 (C-12), 77.21 (C-4), 59.61 (C-16), 58.18 (C-5), 57.55 (C-13), 57.18 (C-11), 48.57 (C-7), 44.18 (C-15), 39.53 (C-10), 36.38 (C-9), 30.96 (C-8), 26.00 (C-1), 21.36 (C-24), 19.56 (C-23), 18.61 (C-21). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3446 (br), 2947 (s), 2865 (m), 1452 (w), 1376 (m), 1043 (m), 1022 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{19}H_{30}O_3Na)^+$: 329.20926, found: 329.20869. $[\alpha]_D^{20}$ = −32.6 (c = 1.00, CH_2Cl_2).

Synthesis of aldehyde 46

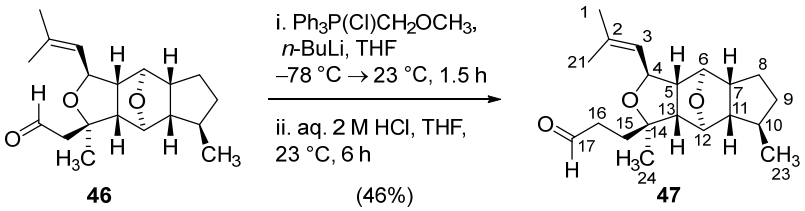


33 **46**

A solution of oxalylchloride (2 M in dichloromethane, 1.71 mL, 3.43 mmol, 3.00 equiv) in dichloromethane (8 mL) was treated with a solution of dimethyl sulfoxide (0.49 mL, 6.85 mmol, 6.00 equiv) in dichloromethane (1 mL) at –78 °C. After 15 min, a solution of alcohol **33** (350 mg, 1.14 mmol, 1 equiv) in dichloromethane (3.7 mL) was added dropwise. After 15 min, triethylamine (1.27 mL, 9.14 mmol, 8.00 equiv) was added and after further 10 min, the mixture was warmed to 0 °C. After 30 min, the mixture was diluted with aqueous pH 7 phosphate buffer solution (30 mL), water (10 mL) and dichloromethane (20 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in hexanes) on silica gel to provide aldehyde **46** as a yellowish oil (316 mg, 91%).

TLC (20% ethyl acetate in hexanes): R_f = 0.45 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (t, $^3J_{16/15}$ = 2.4 Hz, 1H, 16-H), 5.22–5.18 (m, 1H, 3-H), 4.34–4.29 (m, 1H, 4-H), 4.19 (s, 1H, 12-H), 3.92 (s, 1H, 6-H), 2.74–2.59 (m, 2H, 15-H), 2.20–2.10 (m, 3H, 5-H, 7-H, 13-H), 1.92–1.83 (m, 1H, 8-H_A), 1.77 (s, 3H, 1-H), 1.76 (s, 3H, 21-H), 1.75–1.70 (m, 1H, 9-H_A), 1.67–1.58 (m, 1H, 10-H), 1.56–1.50 (m, 1H, 11-H), 1.41 (s, 3H, 24-H), 1.29–1.19 (m, 1H, 8-H_B), 1.06 (d, $^3J_{23/10}$ = 6.6 Hz, 3H, 23-H), 1.04–0.94 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.59 (C-16), 137.76 (C-2), 124.41 (C-3), 81.97 (C-14), 81.66 (C-6), 81.09 (C-12), 76.91 (C-4), 58.12 (C-5), 57.71 (C-13), 57.00 (C-11), 56.32 (C-15), 48.54 (C-7), 39.60 (C-10), 36.40 (C-9), 31.00 (C-8), 26.12 (C-1), 21.88 (C-24), 19.59 (C-23), 18.64 (C-21). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (s), 2868 (w), 1724 (s), 1455 (m), 1376 (m), 1261 (w), 1043 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{19}H_{28}O_3)^+$: 304.2038, found: 304.2030. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –52.9 (c = 0.67, CH_2Cl_2).

Synthesis of C_1-extended aldehyde 47

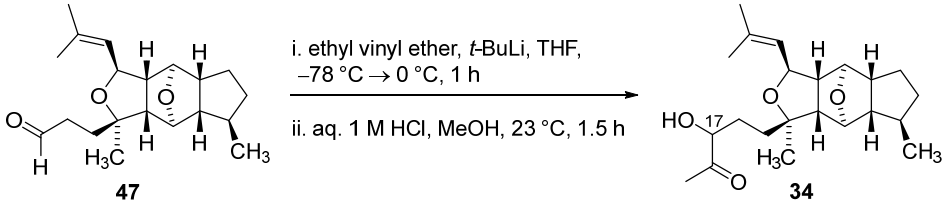


46 **47**

A suspension of (methoxymethyl)triphenylphosphonium chloride (135 mg, 0.39 mmol, 1.60 equiv) in tetrahydrofuran (4 mL) was treated with *n*-butyllithium (2.30 M in hexanes, 161 μL, 0.37 mmol, 1.50 equiv) at –78 °C. After 30 min, a solution of aldehyde **46** (75.0 mg, 0.25 mmol, 1 equiv) in tetrahydrofuran (2.6 mL) was added dropwise to the deep orange mixture. The resulting light yellow, cloudy mixture was then warmed to 23 °C. After 1.5 h, the mixture was diluted with saturated aqueous sodium chloride solution (25 mL), water (10 mL) and ethyl acetate (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the corresponding enol ether as a 1:1 mixture of *E*/*Z*-isomers. The residue was dissolved in tetrahydrofuran (2 mL) and then was treated with aqueous 2 M hydrogen chloride solution (2 mL) at 23 °C. The resulting mixture was vigorously stirred for 6 h, whereupon it was diluted with saturated aqueous sodium chloride solution (10 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (18% ethyl acetate in hexanes) on silica gel to provide C_1-extended aldehyde **47** as a yellowish oil (36 mg, 46%).

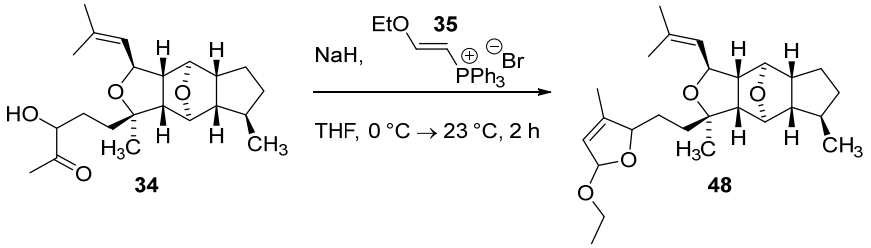
TLC (20% ethyl acetate in hexanes): R_f = 0.34 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (t, $^3J_{17/16}$ = 1.7 Hz, 1H, 17-H), 5.20–5.15 (m, 1H, 3-H), 4.29 (app t, $^3J_{4/3,4/5}$ = 8.5 Hz, 1H, 4-H), 4.09 (s, 1H, 12-H), 3.90 (s, 1H, 6-H), 2.62–2.43 (m, 2H, 16-H), 2.20–1.95 (m, 4H, 5-H, 7-H, 13-H, 15-H_A), 1.92–1.83 (m, 2H, 8-H_A, 15-H_B), 1.79–1.71 (m, 7H, 1-H, 9-H_A, 21-H), 1.66–1.55 (m, 1H, 10-H), 1.51 (app t, *J* = 8.1 Hz, 1H, 11-H), 1.33 (s, 3H, 24-H), 1.29–1.18 (m, 1H, 8-H_B), 1.06 (d, $^3J_{23/10}$ = 6.5 Hz, 3H, 23-H), 1.03–0.94 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.90 (C-17), 137.10 (C-2), 124.68 (C-3), 82.83 (C-14), 81.69 (C-6), 81.00 (C-12), 77.36 (C-4), 58.26 (C-5), 57.29 (C-11), 57.03 (C-13), 48.59 (C-7), 39.59 (C-10), 39.32 (C-16), 36.44 (C-9), 35.32 (C-15), 31.03 (C-8), 26.13 (C-1), 21.33 (C-24), 19.61 (C-23), 18.65 (C-21). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2947 (s), 2864 (m), 1724 (s), 1452 (m), 1376 (m), 1172 (w), 1042 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{20}H_{30}O_3)^+$: 318.2195, found: 318.2199. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –41.1 (c = 0.12, CH_2Cl_2).

Synthesis of α-hydroxy ketone 34



A solution of ethyl vinyl ether (70.0 μL, 72.5 μmol, 7.00 equiv) in tetrahydrofuran (1 mL) was treated with *t*-butyllithium (1.60 M in hexanes, 227 μL, 36.3 μmol, 3.50 equiv) at –78 °C to give a bright yellow solution. After 15 min, the mixture was warmed to 0 °C, whereupon it turned colourless. After 20 min, the so-obtained lithiated ethyl vinyl ether solution was cooled to –78 °C and a solution of C_1-extended aldehyde **47** (33.0 mg, 0.10 mmol, 1 equiv) in tetrahydrofuran was added dropwise. The transfer was quantitated with tetrahydrofuran (2 x 0.3 mL). After 5 min, the mixture was warmed to 0 °C, and after an additional 1 h was diluted with saturated aqueous ammonium chloride solution (7 mL) and dichloromethane (7 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 7 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in methanol (1 mL) and then was treated with with aqueous 0.1 M hydrogen chloride solution (1 mL) at 23 °C. After 1.5 h, the mixture was diluted with water (5 mL) and dichloromethane (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide α-hydroxy ketone **34** (1:1 mixture of diastereomers at C-17) as a yellowish oil (39 mg) which was used in the next step without further purification.

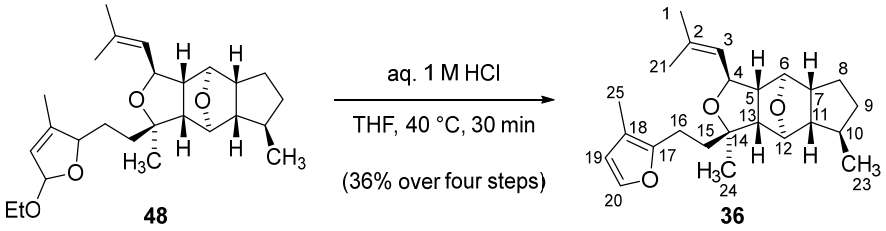
Synthesis of ethoxy acetal 48



A solution of the crude α-hydroxy ketone **34** (1:1 mixture of diastereomers at C-17, 37.7 mg, 104 μmol, 1 equiv) in tetrahydrofuran (1.7 mL) was treated with sodium hydride (60% dispersion in mineral oil, 4.60 mg, 114 μmol, 1.10 equiv) at 0 °C. After 5 min, phopshonium bromide **35**[22] (64.5 mg, 156 mol, 1.50 equiv) was added and the resulting mixture was warmed to 23 °C. After 2 h, the mixture was diluted with saturated aqueous ammonium chloride solution (20 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 12 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel and the filtrate was concentrated to provide ethoxy acetal **48** which was used in the next step without further purification.

[22] Bestmann, H. J.; Roth K.; Ettlinger, M. *Chem. Ber.* **1982**, *115*, 161–171.

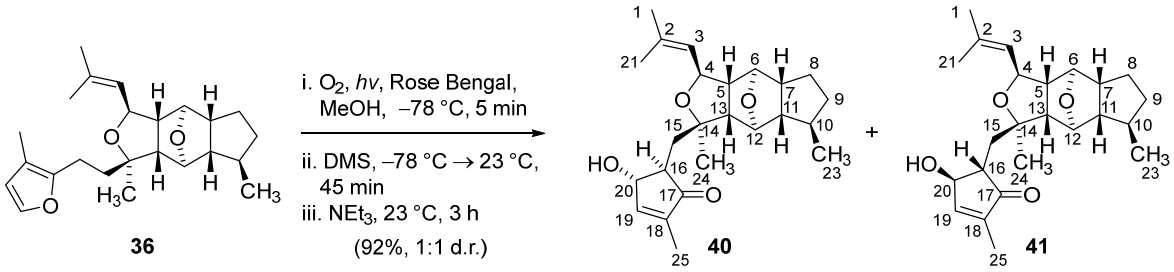
Synthesis of furan 36



A solution of crude ethoxy acetal **48** (19.0 mg, 45.6 μmol, 1 equiv) in tetrahydrofuran (1 mL) was treated with aqueous 1 M hydrogen chloride solution (1 mL) and the resulting mixture was heated to 40 °C. After 30 min, the mixture was cooled to 23 °C, and then was diluted with saturated aqueous sodium chloride solution (15 mL) and dichloromethane (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 7 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes) on silica gel to provide furan **36** as a colourless oil (14 mg, 36% over four steps).

TLC (20% ethyl acetate in hexanes): R_f = 0.59 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, $^3J_{20/19}$ = 1.8 Hz, 1H, 20-H), 6.17 (d, $^3J_{19/20}$ = 1.8 Hz, 1H, 19-H), 5.25–5.19 (m, 1H, 3-H), 4.29 (app t, $^3J_{4/3,4/5}$ = 8.5 Hz, 1H, 4-H), 4.03 (s, 1H, 12-H), 3.89 (s, 1H, 6-H), 2.72–2.64 (m, 2H, 16-H), 2.16–2.07 (m, 2H, 5-H, 7-H), 2.03–1.97 (m, 4H, 13-H, 25-H), 1.94–1.82 (m, 3H, 8-H_A, 15-H), 1.76 (s, 3H, 1-H), 1.75 (s, 3H, 21-H), 1.74–1.70 (m, 1H, 9-H_A), 1.64–1.55 (m, 1H, 10-H), 1.43 (app t, *J* = 8.2 Hz, 1H, 11-H), 1.33 (s, 3H, 24-H), 1.29–1.18 (m, 1H, 8-H_B), 1.05 (d, $^3J_{23/10}$ = 6.6 Hz, 3H, 23-H), 1.03–0.93 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.92 (C-17), 139.78 (C-20), 136.78 (C-2), 125.20 (C-3), 113.65 (C-18), 113.07 (C-19), 83.53 (C-14), 81.75 (C-6), 81.29 (C-12), 76.64 (C-4), 58.25 (C-5), 57.17 (C-11, C-13), 57.12 (C-11, C-13), 48.57 (C-7), 41.65 (C-15), 39.59 (C-10), 36.45 (C-9), 31.00 (C-8), 26.15 (C-1), 21.21 (C-16), 20.60 (C-24), 19.67 (C-23), 18.65 (C-21), 10.06 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (s), 2865 (m), 1514 (w), 1455 (m), 1376 (m), 1276 (s), 1043 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{24}H_{34}O_3)^+$: 370.2508, found: 370.2509. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −36.0 (c = 0.79, CH_2Cl_2).

Synthesis of hydroxy cyclopentenones 40 and 41

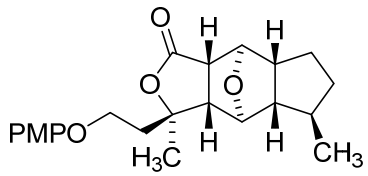


Oxygen was bubbled through a solution of furan **36** (13.0 mg, 35.1 μmol, 1 equiv) and catalytic amount of Rose Bengal (tip of a spatula) in methanol (2.5 mL) at –78 °C. The mixture was irradiated with a Replux Belgium RL 160W (225-235 Volts) lamp, and after 5 min, sparging with oxygen and irradiation was discontinued. Dimethyl sulfide (26.0 μL, 351 mol, 10.0 equiv) was added and the mixture was then warmed to 23 °C. After 45 min, triethylamine (14.6 μL, 105 mol, 3.00 equiv) was added, and after further 3 h, the mixture was concentrated in vacuo. The residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) on silica gel to provide a mixture of hydroxy cyclopentenones **40** and **41** (**40**:**41** = 1:1) as a colourless oil (12.5 mg, 92%). Analytically pure samples of the diastereomeric hydroxy cyclopentenones **40** and **41** were obtained by reversed-phase semi-preparative HPLC using methanol–water (70:30 to 80:20 gradient over 45 min) as eluent (flow rate: 3.5 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 210 nm; retention time: 16.5 min for **40** and 19.5 min for **41**).

Hydroxy cyclopentenone 40: TLC (25% ethyl acetate in hexanes): R_f = 0.23 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22–7.19 (m, 1H, 19-H), 5.22–5.17 (m, 1H, 3-H), 4.46–4.41 (m, 1H, 20-H), 4.31 (app t, $^3J_{4/3,4/5}$ = 8.4 Hz, 1H, 4-H), 4.15 (d, $^3J_{20\text{-}OH/20}$ = 2.0 Hz, 1H, 20-OH), 4.11 (s, 1H, 12-H), 3.87 (s, 1H, 6-H), 2.35 (d, $^2J_{15A/15B}$ = 14.7 Hz, 1H, 15-H_A), 2.25–2.19 (m, 1H, 16-H), 2.16–2.03 (m, 3H, 5-H, 7-H, 13-H), 1.89–1.83 (m, 1H, 8-H_A), 1.83–1.79 (m, 3H, 25-H), 1.76 (s, 3H, 1-H), 1.75 (s, 3H, 21-H), 1.74–1.69 (m, 1H, 9-H_A), 1.65 (dd, $^2J_{15B/15A}$ = 14.7, $^3J_{15B/16}$ = 10.9 Hz, 1H, 15-H_B), 1.61–1.56 (m, 1H, 10-H), 1.56–1.50 (m, 1H, 11-H), 1.41 (s, 3H, 24-H), 1.26–1.15 (m, 1H, 8-H_B), 1.05 (d, $^3J_{23/10}$ = 6.4 Hz, 3H, 23-H), 1.03–0.92 (m, 1H, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.21 (C-17), 155.79 (C-19), 142.34 (C-17), 141.37 (C-2), 122.66 (C-3), 84.01 (C-14), 81.47 (C-6), 81.11 (C-12), 77.36 (C-20), 76.90 (C-4), 58.36 (C-5), 57.02 (C-11), 55.74 (C-13), 53.75 (C-16), 48.64 (C-7), 41.24 (C-15), 39.66 (C-10), 36.45 (C-9), 30.98 (C-8), 26.09 (C-1), 23.08 (C-24), 19.63 (C-23), 18.85 (C-21), 10.43 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3486 (br), 2950 (s), 2865 (m), 1712 (s), 1450 (w), 1379 (w), 1329 (w), 1228 (w) cm^{-1}. **HRMS** (EI): calcd for $(C_{24}H_{34}O_4)^+$: 386.2457, found: 386.2461. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –19.5 (c = 0.24, CH_2Cl_2).

Hydroxy cyclopentenone 41: TLC (25% ethyl acetate in hexanes): R_f = 0.25 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23–7.16 (m, 1H, 19-H), 5.20–5.15 (m, 1H, 3-H), 4.52–4.47 (m, 1H, 20-H), 4.38 (d, $^3J_{20\text{-}OH/20}$ = 2.5 Hz, 1H, 20-OH), 4.31 (app t, $^3J_{4/3,4/5}$ = 8.4 Hz, 1H, 4-H), 4.14 (s, 1H, 12-H), 3.90 (s, 1H, 6-H), 2.48–2.42 (m, 1H, 16-H), 2.31 (dd, $^2J_{15A/15B}$ = 14.2, $^3J_{15B/16}$ = 1.7 Hz, 1H, 15-H_A), 2.24–2.02 (m, 3H, 5-H, 7-H, 13-H), 1.90–1.83 (m, 1H, 8-H_A), 1.82–1.79 (m, 3H, 25-H), 1.78–1.69 (m, 7H, 1-H, 9-H_A, 21-H), 1.65–1.55 (m, 1H, 10-H), 1.54–1.45 (m, 1H, 11-H), 1.45–1.36 (m, 1H, 15-H_B), 1.35 (s, 3H, 24-H), 1.28–1.15 (m, 1H, 8-H_B), 1.04 (d, $^3J_{23/10}$ = 6.6 Hz, 3H, 23-H), 1.01–0.90 (m, 1H, 9-H_B).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.86 (C-17), 155.82 (C-19), 141.98 (C-17), 137.79 (C-2), 124.32 (C-3), 84.02 (C-14), 81.49 (C-6), 80.93 (C-12), 77.36 (C-4), 76.50 (C-20), 60.58 (C-13), 58.09 (C-5), 57.17 (C-11), 54.74 (C-16), 48.68 (C-7), 42.68 (C-15), 39.60 (C-10), 36.44 (C-9), 31.03 (C-8), 26.07 (C-1), 19.56 (C-23), 19.06 (C-24), 18.72 (C-21), 10.37 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3468 (br), 2951 (s), 2867 (m), 1711 (s), 1450 (w), 1379 (w), 1328 (w), 1233 (w) cm^{-1}. **HRMS** (EI): calcd for $(C_{24}H_{34}O_4)^+$: 386.2457, found: 386.2461. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –30.9 (c = 0.19, CH_2Cl_2).

6.2.5 ^{1}H and ^{13}C NMR Spectra of Synthesized Compounds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H
O
O
PMPO
H
H
H3C
CH3

Solvent CDCl3
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Nucleus 1H
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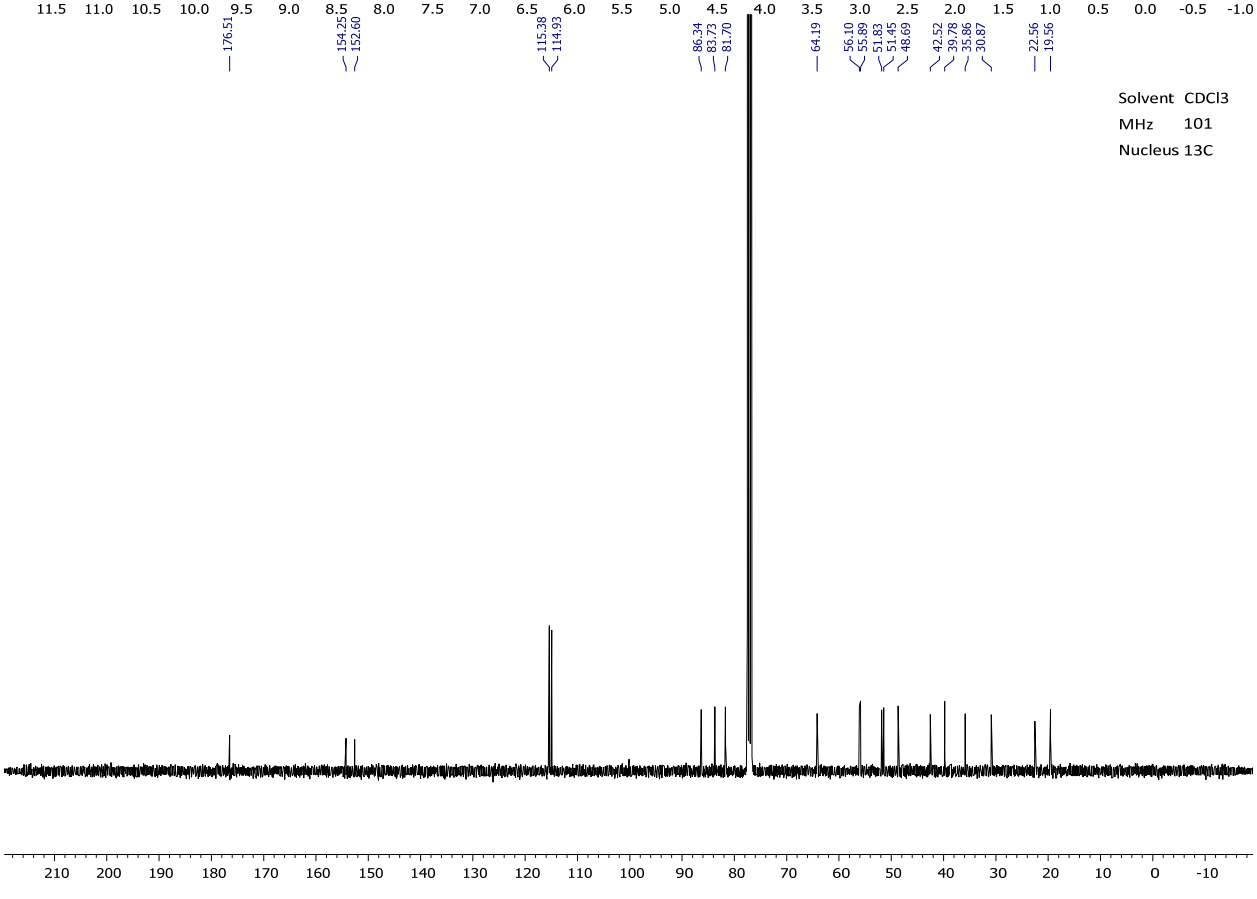
0.95
0.97
2.00
3.27
0.98
0.98
3.76
1.14
1.15
2.61
5.01
1.79
3.00
1.24
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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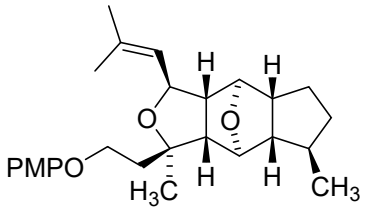
154.25
152.60
115.38
114.93
86.34
83.73
81.70
64.19
56.10
55.89
51.83
51.45
48.69
42.52
39.78
35.86
30.87
22.56
19.56
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10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O
O
PMPO
H
H
CH3
H3C

Solvent CDCl3
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4.60
1.00
0.96
1.06
2.06
0.93
3.48
0.95
3.06
1.53
1.23
7.62
2.23
2.82
1.60
2.91
1.22
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
153.76
152.98
137.04
124.94
115.22
114.66
114.64
82.94
81.64
81.31
76.31
65.09
58.17
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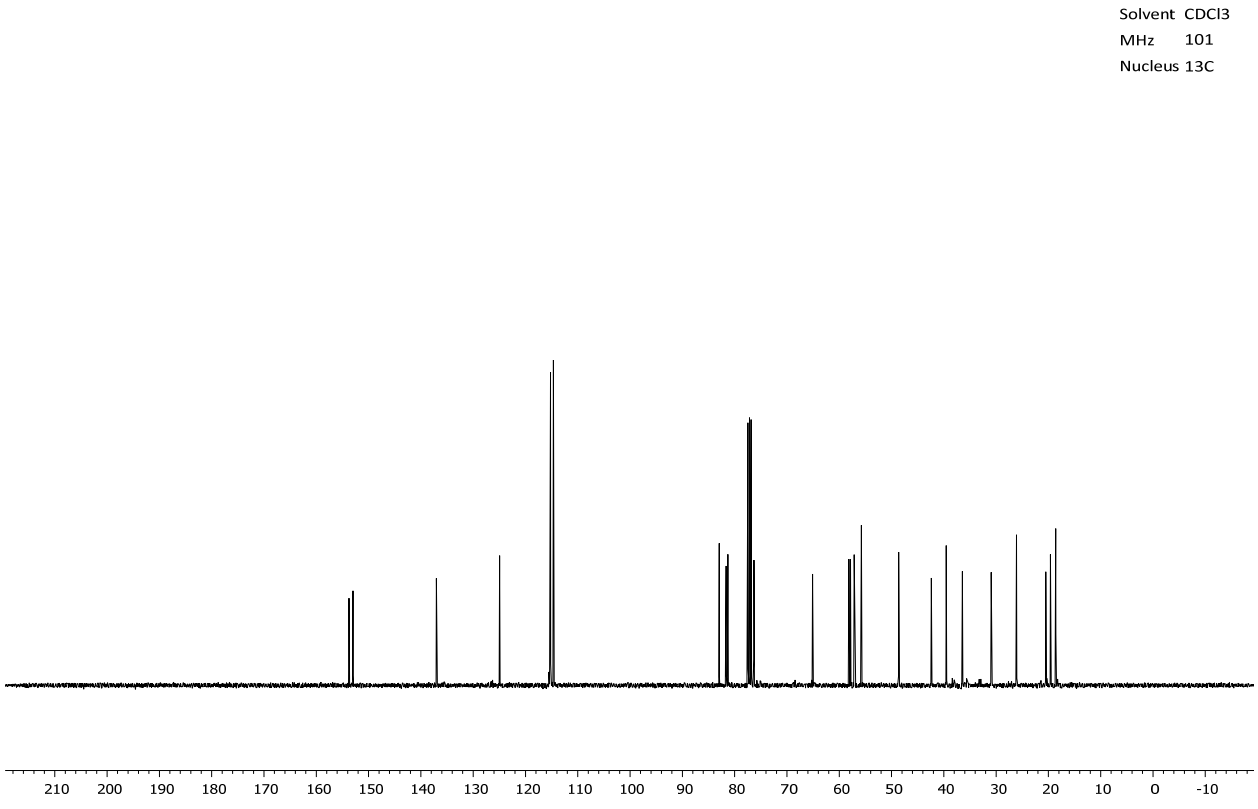
36.44
30.94
26.09
20.50
19.61
18.59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MHz 101
Nucleus 13C
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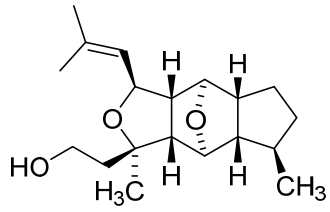
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H
O
O
HO
H
H
H3C
CH3

Solvent CDCl3
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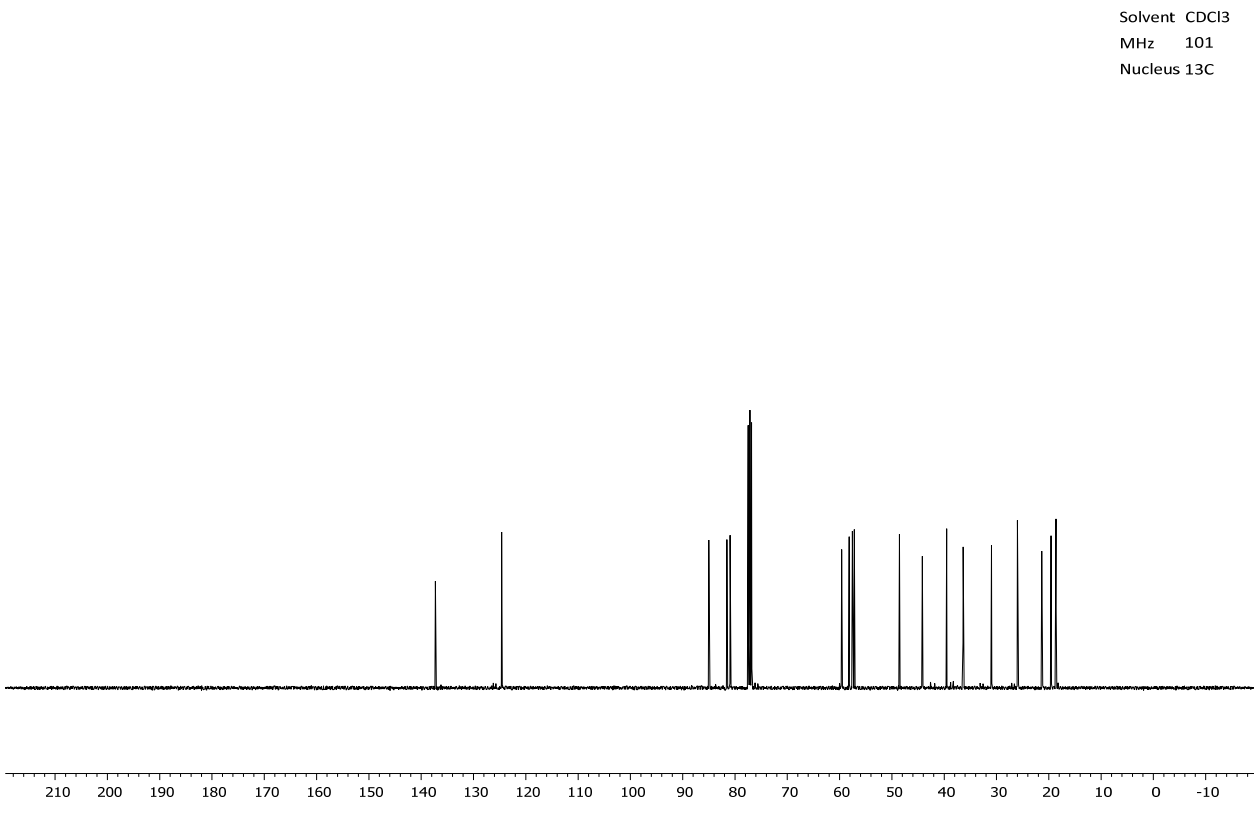
0.94
0.95
0.95
2.08
0.89
2.96
1.98
1.52
7.19
1.10
1.05
2.94
1.36
2.93
1.02
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
137.28
124.60
85.00
81.55
80.92
77.21
59.61
58.18
57.55
57.18
48.57
44.18
39.53
36.38
30.96
26.00
21.36
19.56
18.61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MHz 101
Nucleus 13C
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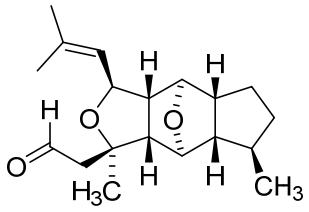
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H
O
O
O
H
H
H3C
CH3

Solvent CDCl3
MHz 400
Nucleus 1H
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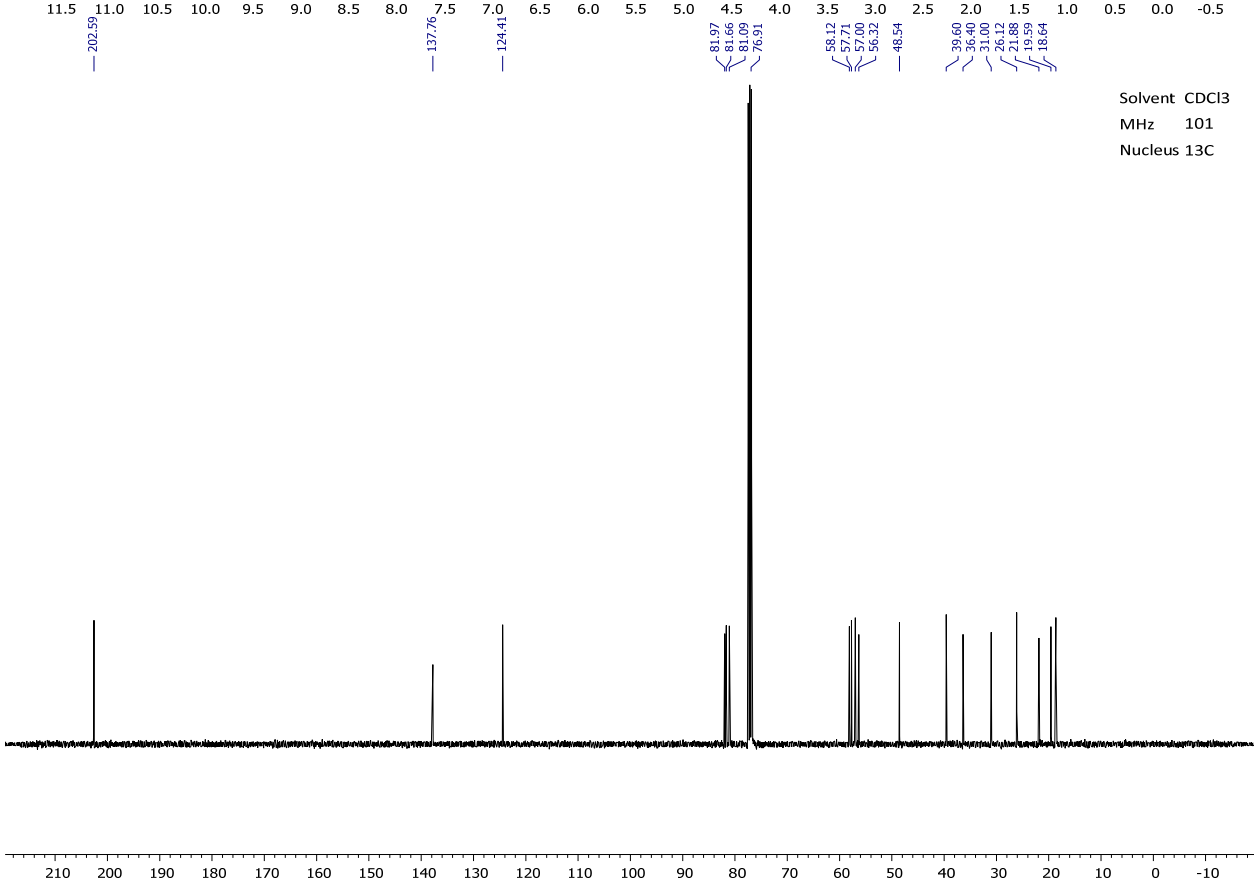
1.07
1.06
1.02
1.03
2.13
3.24
1.25
7.81
1.58
1.17
3.24
1.23
3.24
1.10
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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124.41
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81.66
81.09
76.91
58.12
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57.00
56.32
48.54
39.60
36.40
31.00
26.12
21.88
19.59
18.64
Solvent CDCl3
MHz 101
Nucleus 13C
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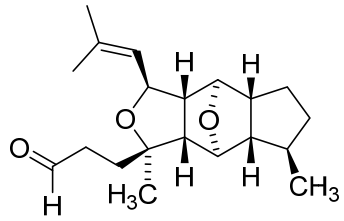
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H
O
O
O
H
H
H
H3C
CH3

Solvent CDCl3
MHz 400
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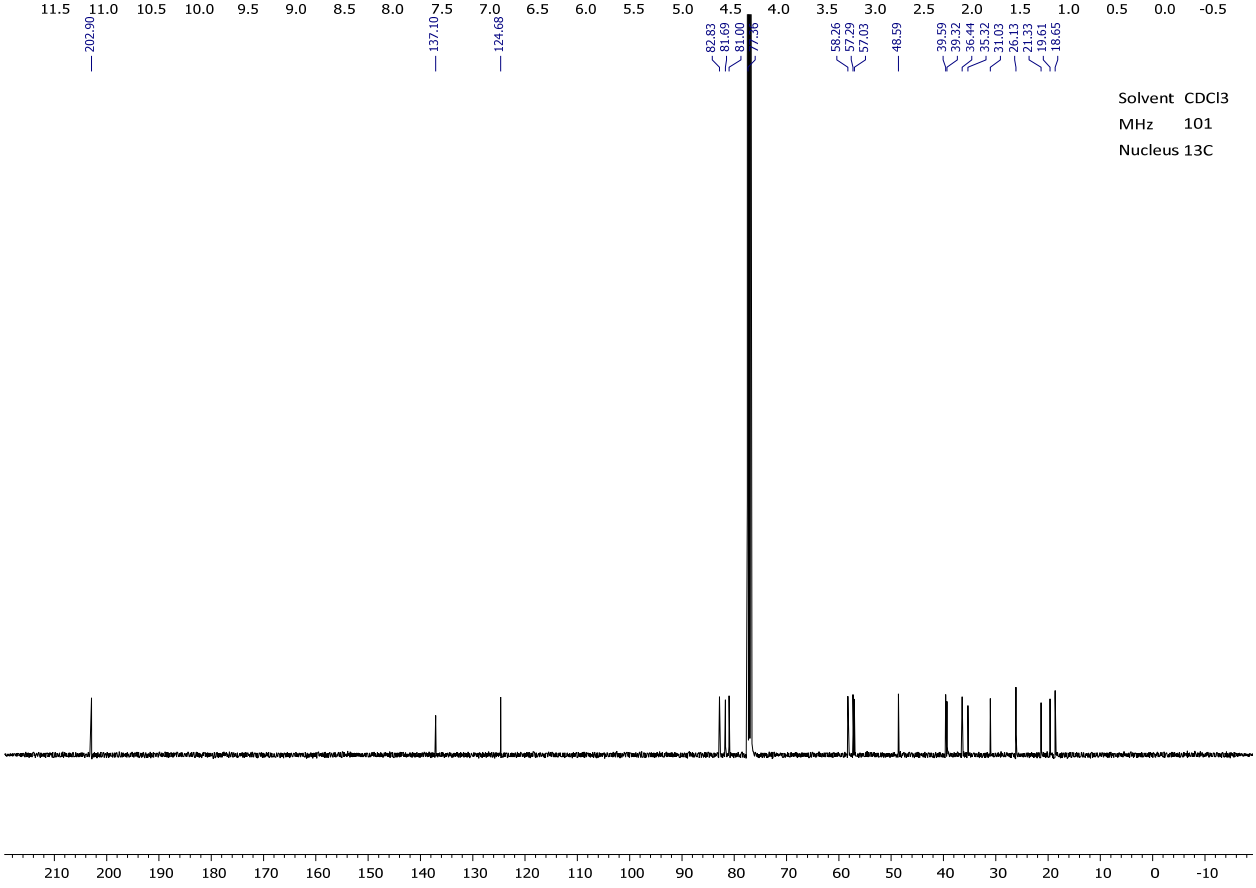
1.13
1.10
1.07
1.12
2.29
2.45
2.34
2.25
8.01
2.06
1.20
3.19
1.61
3.26
1.28
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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81.00
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57.29
57.03
48.59
39.59
39.32
36.44
35.32
31.03
26.13
21.33
19.61
18.65
Solvent CDCl3
MHz 101
Nucleus 13C
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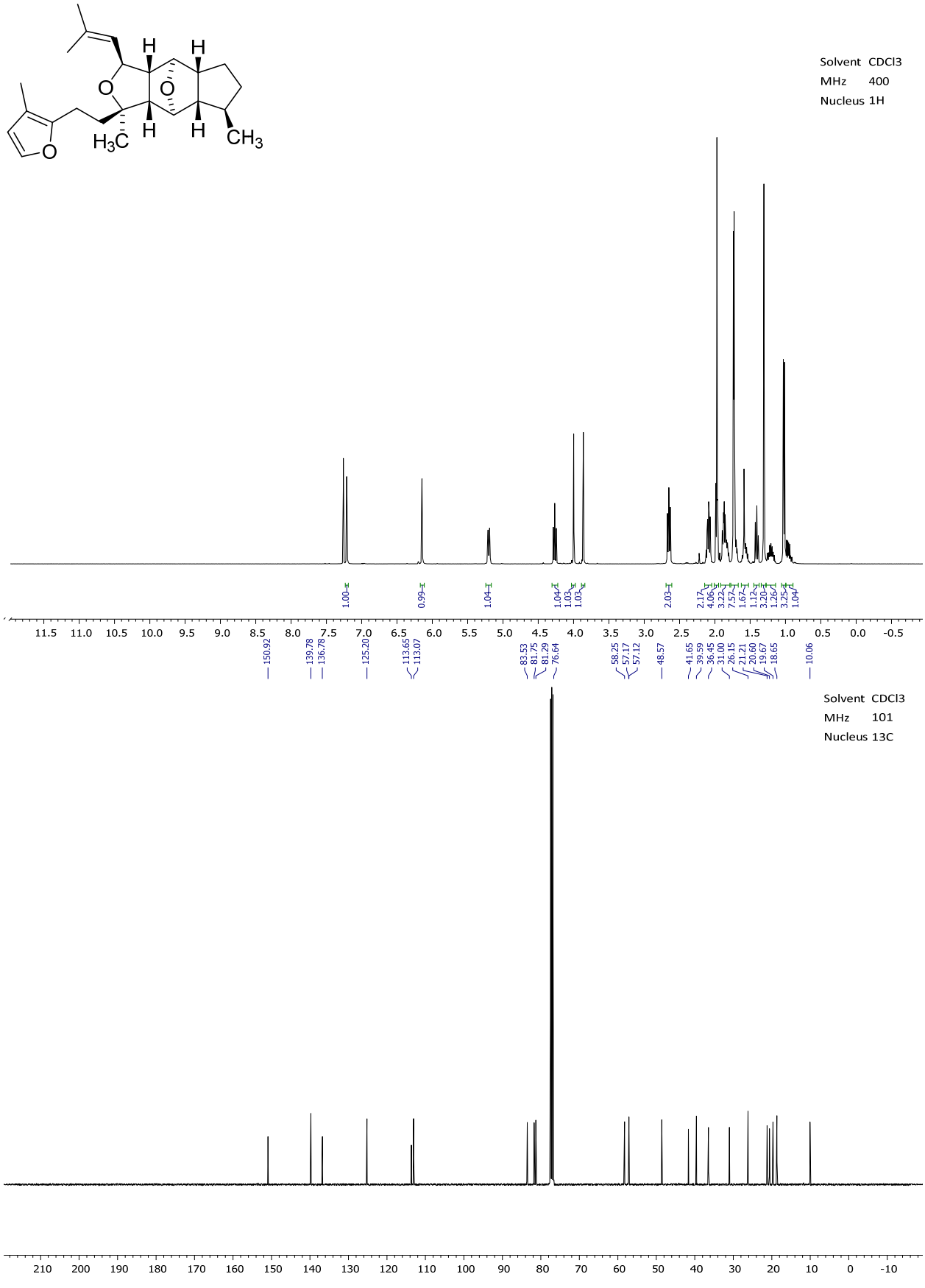
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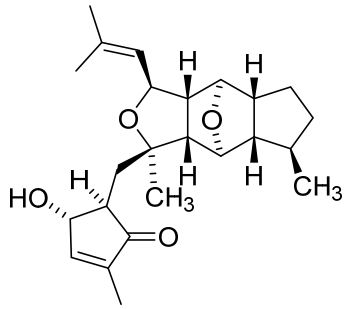
Nucleus 1H
Solvent CDCl3
MHz 101
Nucleus 13C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O
O
H
H
H
HO
CH3
CH3
O

Solvent CDCl3
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Nucleus 1H
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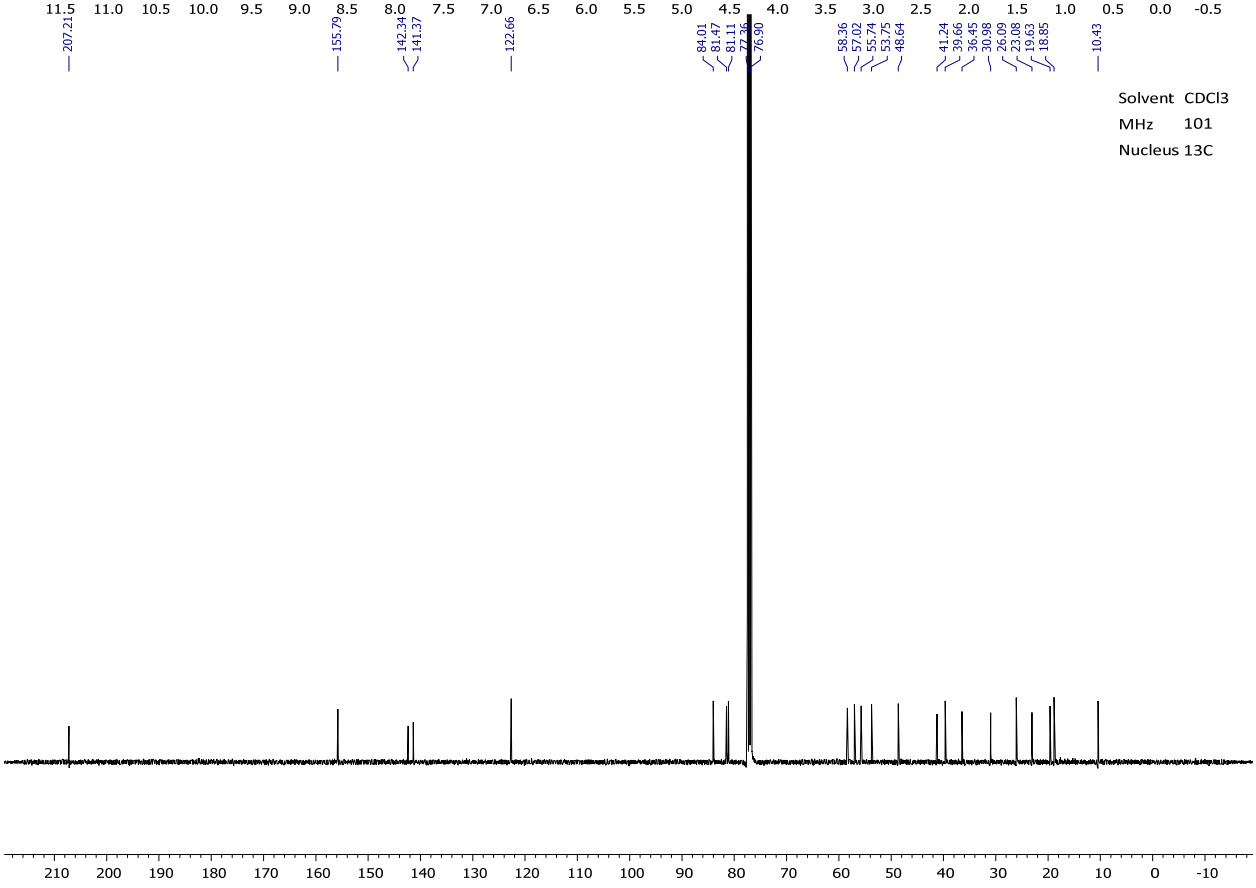
0.97
0.97
0.97
0.95
0.97
0.99
0.96
0.97
2.98
0.88
2.90
5.78
2.32
3.72
2.89
1.51
2.90
0.96
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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76.90
58.36
57.02
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53.75
48.64
41.24
39.66
36.45
30.98
26.09
23.08
19.63
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Solvent CDCl3
MHz 101
Nucleus 13C
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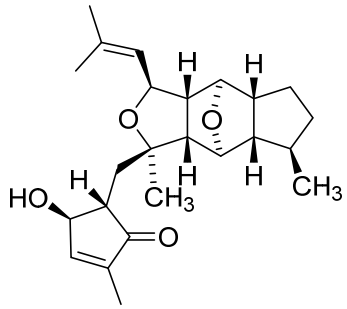
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H
O
O
H
H
H
HO
CH3
CH3
O

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.03
1.00
0.90
1.14
0.95
1.03
1.03
1.01
3.64
1.11
3.22
7.70
3.96
2.86
1.89
3.26
1.69
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
206.86
155.82
141.98
137.79
124.32
84.02
81.49
80.93
77.26
76.50
60.58
58.09
57.17
54.74
48.68
42.68
39.60
36.44
31.03
26.07
19.56
19.06
18.72
10.37
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

6.3 Supporting Information for Chapter 2.2.3

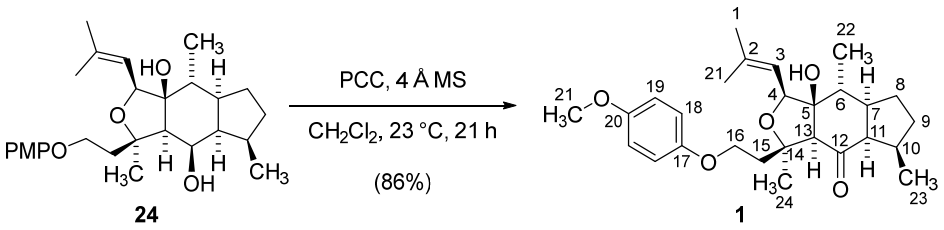
Total Synthesis of the Leucosceptroid Family of Natural Products

Cedric L. Hugelshofer and Thomas Magauer

Department of Chemistry and Pharmacy, Ludwig-Maximilians-University Munich, Butenandtstrasse 5–13, 81377, Munich, Germany

6.3.1 Experimental Procedures

Synthesis of ketone 1

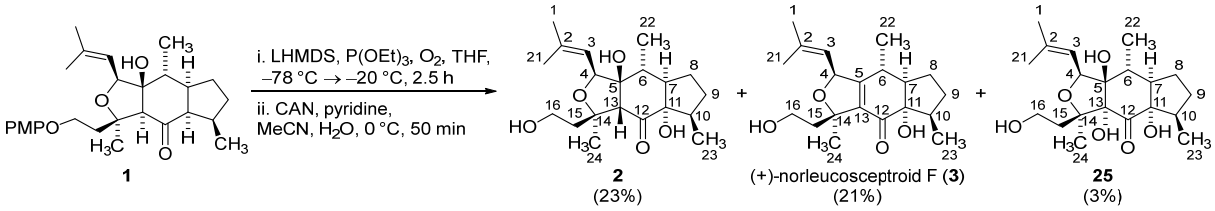


To a solution of diol **24**[23] (1.13 g, 2.54 mmol, 1 equiv) in dichloromethane (24 mL) were added crushed 4 Å molecular sieves (1.5 g), followed by pyridinium chlorochromate (1.53 g, 7.12 mmol, 2.8 equiv) at 23 °C. After 21 h, the mixture was concentrated and then was directly loaded onto a short pad of silica gel (5 cm). The product was eluted with 25% ethyl acetate in pentane to provide ketone **1** as a colourless, highly viscous oil (968 mg, 86%).

TLC (30% ethyl acetate in hexanes): R_f = 0.59 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89–6.76 (m, 4H, 18-H, 19-H), 5.28–5.19 (m, 1H, 3-H), 4.46 (d, $^3J_{4/3}$ = 9.0 Hz, 1H, 4-H), 4.15 (t, $^3J_{16/15}$ = 6.7 Hz, 2H, 16-H), 3.75 (s, 3H, 21-H), 2.78 (s, 1H, 13-H), 2.71 (app t, $^3J_{11/7}$ = $^3J_{11/10}$ = 8.5 Hz, 1H, 11-H), 2.58 (s, 1H, 5-OH), 2.57–2.39 (m, 2H, 15-H), 2.34–2.19 (m, 2H, 7-H, 10-H), 2.04–1.79 (m, 3H, 6-H, 8-H), 1.78 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.75 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.68–1.55 (m, 1H, 9-H_A), 1.55–1.44 (m, 1H, 9-H_B), 1.41 (s, 3H, 24-H), 1.18 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H), 1.12 (d, $^3J_{22/6}$ = 7.3 Hz, 3H, 22-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.29 (C-12), 153.75 (C-20), 153.13 (C-17), 140.79 (C-2), 118.04 (C-3), 115.67 (C-18, C-19), 114.66 (C-18, C-19), 88.37 (C-5), 80.25 (C-14), 76.93 (C-4), 65.67 (C-16), 62.89 (C-13), 55.87 (C-21), 54.37 (C-11), 50.69 (C-7), 37.99 (C-6), 37.79 (C-15), 37.48 (C-10), 32.62 (C-9), 32.18 (C-8), 29.05 (C-24), 26.57 (C-1), 19.15 (C-21), 18.76 (C-22), 16.84 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3501 (br), 2925 (s), 2872 (m), 1720 (m), 1507 (s), 1462 (m), 1376 (m), 1231 (s), 1179 (w), 1038 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{27}H_{38}O_5Na)^+$: 465.26169, found: 465.26100. $[\alpha]_D^{20}$ = +36.0 (c = 0.19, CH_2Cl_2).

[23] C. L. Hugelshofer, T. Magauer, *Angew. Chem., Int. Ed.* **2014**, *53*, 11351.

Synthesis of triol 2, (+)-norleucosceptroid F (3), and tetraol 25



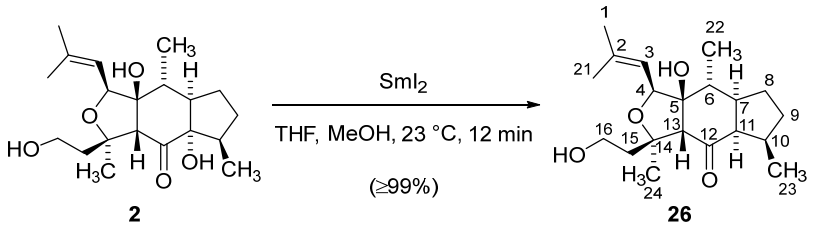
A solution of ketone **1** (710 mg, 1.60 mmol, 1 equiv) in tetrahydrofuran (17 mL) was treated with lithium bis(trimethylsilyl)amide solution (1 M in THF, 6.74 mL, 6.74 mmol, 4.20 equiv) at −78 °C. After 5 min, the mixture was warmed to −35 °C. After 1 h, the mixture was cooled to −78 °C, triethyl phosphite (1.08 mL, 6.42 mmol, 4.00 equiv) was added and the argon atmosphere was exchanged for oxygen. After 5 min, the mixture was warmed to −35 °C and stirring was continued for 2.5 h. The mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL) and dichloromethane (40 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 30 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short pad of silica gel (30% → 50% ethyl acetate in hexanes) and the filtrate was concentrated. The crude product mixture was dissolved in a mixture of acetonitrile–water (4:1, 16 mL), and the resulting mixture was treated with pyridine (171 µl, 2.12 mmol, 2.20 equiv) followed by ammonium cerium(IV) nitrate (1.27 g, 2.31 mmol, 2.40 equiv) at 0 °C. After 35 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (50 mL), water (20 mL) and ethyl acetate (40 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 x 30 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (3% methanol in dichloromethane) on silica gel to provide (+)-norleucosceptroid F (**3**) as a yellowish oil (109 mg, 21% over two steps), triol **2** as a colourless foam (128 mg, 23% over two steps) and traces of tetraol **25** as an off-white solid (15.1 mg, 3% over two steps).

(+)-norleucosceptroid F 3: **TLC** (5% methanol in dichloromethane): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.56 (dd, $^3J_{4/3}$ = 9.9 Hz, $^4J_{4/6}$ = 1.3 Hz, 1H, 4-H), 5.12–5.07 (m, 1H, 3-H), 3.85–3.75 (m, 1H, 16-H_A), 3.73–3.64 (m, 1H, 16-H_B), 3.44 (s, 1H, 11-OH), 3.07 (t, $^3J_{16OH/16}$ = 5.7 Hz, 1H, 16-OH), 2.33–2.11 (m, 4H, 6-H, 7-H, 8-H_A, 10-H), 2.08 (app t, $^3J_{15/16}$ = 5.4 Hz, 2H, 15-H), 1.81 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.79 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.76–1.68 (m, 1H, 8-H_B), 1.48 (s, 3H, 24-H), 1.47–1.38 (m, 2H, 9-H), 1.10 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.92 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.53 (C-12), 166.13 (C-5), 140.73 (C-2), 137.70 (C-13), 121.29 (C-3), 90.16 (C-14), 86.11 (C-11), 80.45 (C-4), 59.95 (C-16), 55.33 (C-7), 47.70 (C-10), 40.66 (C-15), 32.54 (C-6), 32.10 (C-9), 29.26 (C-8), 26.21 (C-1), 26.00 (C-24), 19.54 (C-23), 18.51 (C-21), 17.94 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3456 (br), 2964 (s), 2930 (s), 2877 (m), 1662 (s), 1508 (w), 1494 (w), 1455 (m), 1378 (m), 1280 (m), 1229 (m), 1042 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{20}H_{29}O_4)^+$: 333.20604, found: 333.20693. $[\alpha]_D^{20}$ = +10.4 (c = 0.08, CH_2Cl_2).

Triol 2: **TLC** (5% methanol in dichloromethane): R_f = 0.17 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.48–5.43 (m, 1H, 3-H), 4.59 (d, $^3J_{4/3}$ = 8.7 Hz, 1H, 4-H), 4.03–3.83 (m, 2H, 16-H), 3.46 (br s, 1H, 5-OH, 16-OH) 3.04 (s, 1H, 13-H), 2.96 (br s, 1H, 5-OH, 16-OH) 2.46 (s, 1H, 11-OH), 2.31–1.93 (m, 6H, 7-H, 8-H_A, 9-H_A, 10-H, 15-H), 1.93–1.83 (m, 1H, 6-H), 1.83–1.80 (m, 1H, 8-H_B), 1.79 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.75 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.54–1.44 (m, 1H, 9-H_B), 1.31 (s, 3H, 24-H), 0.97 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.87 (d, $^3J_{23/10}$ = 7.4 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 214.45 (C-12), 140.04 (C-2), 119.40 (C-3), 85.83 (C-11), 84.42 (C-5), 83.30 (C-14), 76.41 (C-4), 68.79 (C-13), 59.80 (C-16), 49.19 (C-7), 47.22 (C-10), 44.35 (C-15), 39.23 (C-6), 30.58 (C-9), 29.80 (C-8), 26.35 (C-1), 24.46 (C-24), 19.09 (C-21), 17.01 (C-23), 14.08 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3397 (br), 2945 (s), 2873 (m), 1661 (s), 1455 (s), 1380 (s), 1231 (m), 1098 (s), 1018 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{32}O_5Na)^+$: 375.21474, found: 375.21397. $[\alpha]_D^{20}$ = −117.4 (c = 0.06, CH_2Cl_2).

Tetraol 25: **TLC** (5% methanol in dichloromethane): R_f = 0.15 (CAM). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 5.40 (d, $^3J_{3/4}$ = 9.5 Hz, 1H, 3-H), 4.93 (s, 1H, 13-OH), 4.83 (d, $^3J_{4/3}$ = 9.5 Hz, 1H, 4-H), 4.12 (s, 1H, 5-OH), 3.91 (s, 1H, 11-OH), 3.88–3.82 (m, 1H, 16-H_A), 3.66–3.56 (m, 1H, 16-H_B), 3.56–3.50 (m, 1H, 16-OH), 2.54–2.41 (m, 1H, 15-H_A), 2.40–2.31 (m, 1H, 7-H), 2.25–2.12 (m, 1H, 10-H), 2.05–1.81 (m, 3H, 8-H_A, 9-H_A, 15-H_B), 1.76 (s, 3H, 21-H), 1.74 (s, 3H, 1-H), 1.64–1.42 (m, 3H, 6-H, 8-H_B, 9-H_B), 1.36 (s, 3H, 24-H), 1.14 (d, $^3J_{22/6}$ = 7.2 Hz, 3H, 22-H), 1.05 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 208.15 (C-12), 139.71 (C-2), 119.65 (C-3), 87.13 (C-13), 86.82 (C-11), 86.75 (C-14), 85.53 (C-5), 76.48 (C-4), 60.01 (C-16), 56.85 (C-7), 49.98 (C-10), 44.59 (C-6), 40.36 (C-15), 34.05 (C-9), 32.51 (C-8), 26.36 (C-1), 22.66 (C-24), 20.29 (C-22), 18.89 (C-21), 16.65 (C-23). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3340 (br), 2943 (s), 2832 (m), 1720 (m), 1449 (m), 1377 (m), 1268 (m), 1117 (m), 1023 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{31}O_6)^-$: 367.21261, found: 367.21286. $[\alpha]_D^{20}$ = –17.8 (c = 0.34, MeOH).

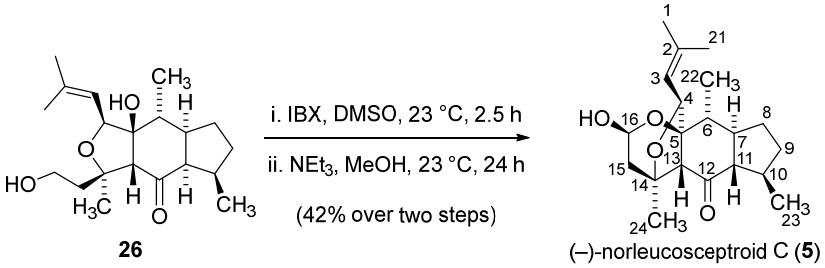
Synthesis of diol 26



A solution of triol **2** (10.0 mg, 28.4 µmol, 1 equiv) in a mixture of tetrahydrofuran–methanol (4:1, 1.2 mL) was treated with samarium(II) iodide solution (0.1 M in THF, 1.31 mL, 131 µmol, 4.60 equiv) at 23 °C. The resulting dark blue mixture turned turquois within about 20 s and then nearly colourless after further 20 s. After 12 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and dichloromethane (3 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a short pad of Celite and the filtrate was concentrated to provide spectroscopically pure diol **26** (9.5 mg, ≥99%).

TLC (5% methanol in dichloromethane): R_f = 0.36 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.52–5.46 (m, 1H, 3-H), 4.63 (d, $^3J_{4/3}$ = 8.7 Hz, 1H, 4-H), 3.94–3.87 (m, 2H, 16-H), 3.24 (br s, 1H, 16-OH), 3.08–3.03 (m, 2H, 5-OH, 13-H), 2.74 (dd, ^3J = 10.8 Hz, ^3J = 7.2 Hz, 1H, 11-H), 2.64–2.54 (m, 1H, 10-H), 2.25–2.15 (m, 1H, 7-H), 2.11–1.92 (m, 3H, 8-H_A, 15-H), 1.79 (d, $^4J_{1/3}$ = 1.5 Hz, 3H, 1-H), 1.77 (d, $^4J_{21/3}$ = 1.5 Hz, 3H, 21-H), 1.71–1i.65 (m, 1H, 6-H), 1.64–1.52 (m, 3H, 8-H_B, 9-H), 1.20 (s, 3H, 24-H), 0.97 (d, $^3J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.89 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 214.78 (C-12), 139.56 (C-2), 119.84 (C-3), 85.03 (C-5), 82.94 (C-14), 76.02 (C-4), 70.62 (C-13), 59.55 (C-16), 56.42 (C-11), 44.58 (C-15), 44.04 (C-6), 40.62 (C-7), 36.52 (C-10), 33.18 (C-9), 30.85 (C-8), 26.34 (C-1), 22.80 (C-24), 19.14 (C-21), 17.04 (C-23), 13.40 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3400 (br), 2963 (s), 2936 (m), 1682 (s), 1452 (s), 1377 (s), 1265 (s), 1072 (m), 1026 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{32}O_4Na)^+$: 359.21983, found: 359.21975. $[\alpha]_D^{20}$ = –102.2 (c = 0.14, CH_2Cl_2).

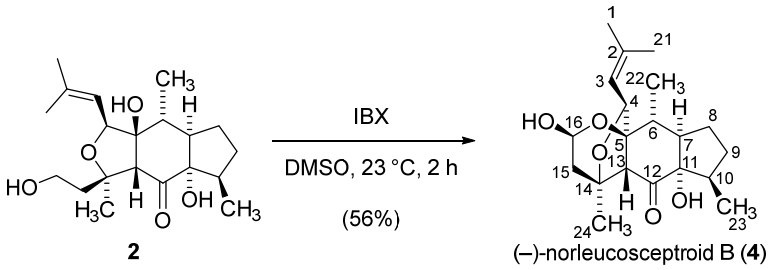
Synthesis of (–)-norleucosceptroid C (5)



A solution of diol **26** (9.5 mg, 28.4 µmol, 1 equiv) in dimethyl sulfoxide (0.6 mL) was treated with 2-iodoxybenzoic acid (8.8 mg, 31.2 µmol, 1.10 equiv) at 23 °C. After 2.5 h, the mixture was diluted with pH 7 buffer solution (5 mL) and dichloromethane (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short pad of silica gel (30% ethyl acetate in hexanes) and the filtrate was concentrated. The crude product (as seen by ^{1}H NMR analysis, this α-H11 epimer of norleucosceptroid C exists in its lactol and open-chained aldehyde form in solution, ~2:1 ratio) was dissolved in methanol (1 mL) and triethylamine (0.15 mL) was added at 23 °C. After 24 h, the mixture was concentrated (23 °C waterbath) and the residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) on silica gel to provide (–)-norleucosceptroid C (**5**) as a colourless oil (4.0 mg, 42% over two steps).

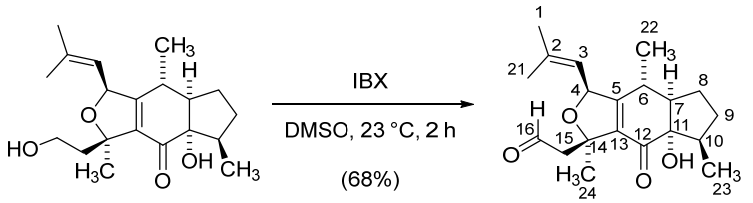
TLC (40% ethyl acetate in hexanes): R_f = 0.32 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 5.54 (d, $^3J_{3/4}$ = 8.5 Hz, 1H, 3-H), 5.44–5.38 (m, 2H, 16-H, 16-OH), 4.38 (d, $^3J_{4/3}$ = 8.5 Hz, 1H, 4-H), 2.92 (s, 1H, 13-H), 2.25–2.16 (m, 2H, 10-H, 11-H), 2.16–2.10 (m, 1H, 6-H), 1.96–1.90 (m, 1H, 9-H$_A$), 1.90–1.84 (m, 1H, 8-H$_A$), 1.84–1.80 (m, 1H, 15-H$_A$), 1.71 (s, 3H, 21-H), 1.63 (s, 3H, 1-H), 1.61 (s, 3H, 24-H), 1.57–1.54 (m, 1H, 15-H$_B$), 1.52–1.45 (m, 1H, 7-H), 1.41–1.35 (m, 1H, 8-H$_B$), 1.30–1.23 (m, 1H, 9-H$_B$), 0.96 (d, $^3J_{23/10}$ = 6.4 Hz, 3H, 23-H), 0.91 (d, $^3J_{22/6}$ = 7.1 Hz, 3H, 22-H). **^{13}C NMR** (200 MHz, Acetone-d_6) δ 205.89 (C-12), 138.50 (C-2), 122.23 (C-3), 92.30 (C-16), 91.42 (C-5), 79.31 (C-14), 76.51 (C-4), 65.28 (C-13), 64.60 (C-11), 51.35 (C-7), 49.72 (C-15), 44.54 (C-6), 32.53 (C-10), 31.72 (C-9), 30.14 (C-8) 26.10 (C-21), 22.29 (C-24), 19.95 (C-23), 18.74 (C-1), 14.22 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3406 (br), 2958 (s), 2932 (s), 2871 (m), 1719 (s), 1670 (w), 1451 (m), 1375 (m), 1333 (m) 1065 (m), 1030 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{20}H_{30}O_4)^+$: 334.2144, found: 334.2135. $[\alpha]_D^{20}$ = –26.4 (c = 0.11, MeOH).

Synthesis of (–)-norleucosceptroid B (4)



A solution of triol **2** (108 mg, 306 µmol, 1 equiv) in dimethyl sulfoxide (1 mL) was treated with 2-iodoxybenzoic acid (90.1 mg, 322 µmol, 1.05 equiv) at 23 °C. After 2 h, the mixture was diluted with pH 7 buffer solution (10 mL) and dichloromethane (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 10 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash-column chromatography (35% ethyl acetate in hexanes) on silica gel to provide (–)-norleucosceptroid B (**4**) as a colourless foam (60.0 mg, 56%).
TLC (5% methanol in dichloromethane): R_f = 0.20 (CAM). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 5.54–5.51 (m, 1H, 3-H), 5.45 (app td, $^3J_{16/16OH}$ = 6.6 Hz, $^3J_{16/15}$ = 5.0 Hz, 1H, 16-H), 5.37 (d, $^3J_{16OH/16}$ = 6.6 Hz, 1H, 16-OH), 4.50 (d, $^3J_{4/3}$ = 8.8 Hz, 1H, 4-H), 4.21 (s, 1H, 11-OH), 2.64 (br s, 1H, 13-H), 2.19–2.10 (m, 3H, 8-H_B, 9-H_B, 10-H), 2.08–2.06 (m, 1H, 6-H), 1.95–1.90 (m, 1H, 15-H_B), 1.84–1.78 (m, 1H, 7-H), 1.74 (d, $^4J_{21/3}$ = 1.2 Hz, 3H, 21-H), 1.75–1.69 (m, 2H, 8-H_A, 15-H_A), 1.66 (d, $^4J_{1/3}$ = 1.5 Hz, 3H, 1-H), 1.58 (s, 3H, 24-H), 1.47–1.40 (m, 1H, 9-H_A), 0.98 (d, $J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.95 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 210.78 (C-12), 138.68 (C-2), 122.12 (C-3), 92.15 (C-16), 87.06 (C-11), 86.88 (C-5), 80.74 (C-14), 77.85 (C-4), 64.09 (C-13), 52.54 (C-7), 50.13 (C-15), 48.40 (C-10), 40.62 (C-6), 31.64 (C-9), 30.47 (C-8), 26.13 (C-21), 23.98 (C-24), 18.66 (C-1), 18.52 (C-23), 14.62 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3405 (br), 2962 (s), 2929 (s), 2877 (m), 1704 (s), 1667 (m), 1450 (s), 1378 (s), 1299 (m), 1126 (m), 1075 (s), 1029 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{20}H_{29}O_5)^-$: 349.20205, found: 349.20211. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –84.4 (c = 0.32, MeOH).

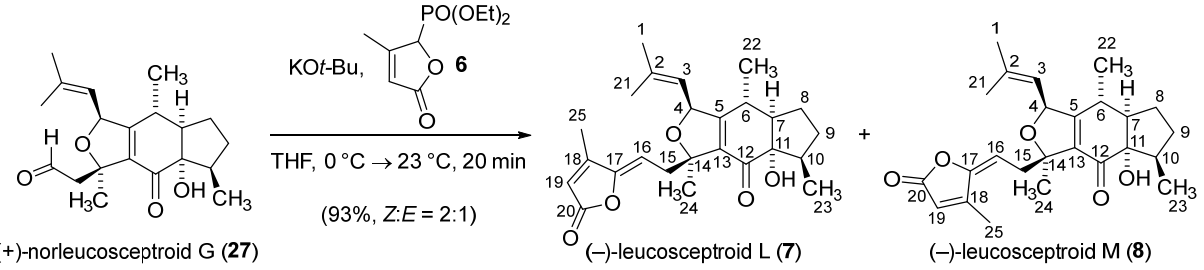
Synthesis of (+)-norleucosceptroid G (27)



(+)-norleucosceptroid F (**3**) (+)-norleucosceptroid G (**27**)

A solution of (+)-norleucosceptroid F (**3**) (90.0 mg, 269 µmol, 1 equiv) in dimethyl sulfoxide (1.5 mL) was treated with 2-iodoxybenzoic acid (86.7 mg, 309 µmol, 1.15 equiv) at 23 °C. After 2 h, the mixture was diluted with pH 7 buffer solution (10 mL) and dichloromethane (7 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 7 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in hexanes) on silica gel to provide (+)-norleucosceptroid G (**27**) as an off-white solid (61.1 mg, 68%).
TLC (30% ethyl acetate in hexanes): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 9.73 (t, $^3J_{16/15}$ = 3.0 Hz, 1H, 16-H), 5.70 (d, $^3J_{4/3}$ = 9.8 Hz, 1H, 4-H), 5.15 (d, $^3J_{3/4}$ = 9.8 Hz, 1H, 3-H), 4.18 (s, 1H, 11-OH), 2.76 (dd, $^2J_{15A/15B}$ = 15.4 Hz, $^3J_{15A/16}$ = 2.6 Hz, 2H, 15-H_A), 2.69 (dd, $^2J_{15B/15A}$ = 15.4 Hz, $^3J_{15B/16}$ = 3.2 Hz, 2H, 15-H_B), 2.41–2.32 (m, 1H, 6-H), 2.22–2.08 (m, 4H, 7-H, 8-H_A, 9-H_A, 10-H), 1.82 (s, 3H, 21-H), 1.77 (s, 3H, 1-H), 1.75–1.64 (m, 1H, 8-H_B), 1.47 (s, 3H, 24-H), 1.45–1.35 (m, 1H, 9-H_B), 1.14 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.87 (d, $^3J_{23/10}$ = 6.7 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 201.69 (C-16), 197.69 (C-12), 166.70 (C-5), 139.48 (C-2), 137.75 (C-13), 122.83 (C-3), 86.65 (C-14), 86.05 (C-11), 81.17 (C-4), 56.15 (C-7), 52.81 (C-15), 47.55 (C-10), 33.09 (C-6), 32.28 (C-9), 29.36 (C-8), 27.01 (C-24), 25.94 (C-1), 19.18 (C-23), 18.30 (C-21), 18.10 (C-22). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (br), 2957 (s), 1720 (m), 1663 (s), 1604 (s), 1524 (s), 1488 (s), 1390 (m), 1318 (m), 1240 (s), 1109 (s), 1073 (s) cm^{-1}. **HRMS** (EI): calcd for $(C_{20}H_{28}O_4)^+$: 332.1988, found: 332.1990. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.2 (c = 1.00, MeOH).

Synthesis of (–)-leucosceptroid L (7) and (–)-leucosceptroid M (8)



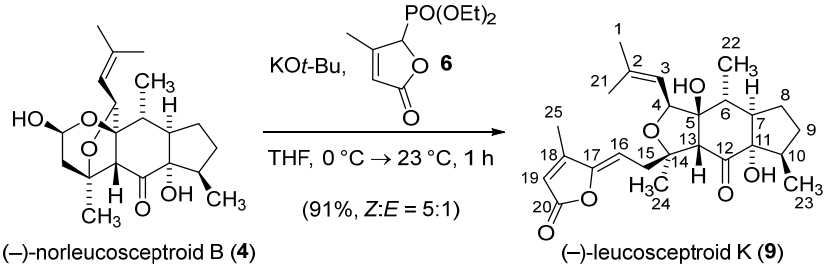
An ice-cooled solution of phosphonate **6**[24] (133 mg, 569 µmol, 3.50 equiv) in tetrahydrofuran (2.5 mL) was treated with potassium *tert*-butoxide (63.8 mg, 569 µmol, 3.50 equiv). After 30 min, a solution of (+)-norleucosceptroid G (**27**) (54.0 mg, 162 µmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise to the dark red mixture at 0 °C. The transfer was quantitated with tetrahydrofuran (3 x 0.5 mL). After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 20 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 10 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (45% ethyl acetate in hexanes) on silica gel to provide a 2:1 mixture of (–)-leucosceptroid L (**7**) and (–)-leucosceptroid M (**8**) as a colourless oil (62.0 mg, 93%). Analytically pure samples of (–)-leucosceptroid L (**7**) and (–)-leucosceptroid M (**8**) were obtained by reversed-phase semi-preparative HPLC using methanol–water (55:45) as eluent (flow rate: 3 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 254 nm; retention times: 15.7 min for **8** and 29.2 min for **7**).

(–)-leucosceptroid L (7): **TLC** (40% ethyl acetate in hexanes): R_f = 0.28 (UV/$KMnO_4$). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 6.00 (s, 1H, 19-H), 5.66 (dd, $^3J_{4/3}$ = 9.6 Hz, $^4J_{4/6}$ = 1.3 Hz, 1H, 4-H), 5.44 (app t, $^3J_{16/15}$ = 7.9 Hz, 1H, 16-H), 5.18–5.14 (m, 1H, 3-H), 4.13 (s, 1H, 11-OH), 2.90 (dd, $^2J_{15B/15A}$ = 15.3 Hz, $^3J_{15B/16}$ = 8.0 Hz, 1H, 15-H_B), 2.73 (dd, $^2J_{15A/15B}$ = 15.3 Hz, $^3J_{15A/16}$ = 7.1 Hz, 1H, 15-H_A), 2.38–2.32 (m, 1H, 6-H), 2.16 (d, $^4J_{25/19}$ = 1.4 Hz, 3H, 25-H), 2.15–2.09 (m, 4H, 7-H, 8-H_B, 9-H_B, 10-H), 1.82 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.77 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.68–1.62 (m, 1H, 8-H_A), 1.42 (s, 3H, 24-H), 1.37–1.33 (m, 1H, 9-H_B), 1.14 (d, $^3J_{22/6}$ = 7.0 Hz, 3H, 22-H), 0.84 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 197.48 (C-12), 169.38 (C-20), 166.55 (C-5), 155.81 (C-18), 152.44 (C-17), 139.28 (C-2), 137.77 (C-13), 123.35 (C-3), 116.79 (C-19), 109.14 (C-16), 88.68 (C-14), 86.02 (C-11), 80.85 (C-4), 56.03 (C-7), 47.49 (C-10), 36.80 (C-15), 32.97 (C-6), 32.22 (C-9), 29.46 (C-8), 26.79 (C-24), 26.06 (C-1), 18.86 (C-23), 18.36 (C-21), 18.20 (C-22), 11.63 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3440 (br), 2965 (s), 2928 (m), 1769 (s), 1666 (s), 1445 (w), 1378 (m), 1260 (s), 1070 (s), 1024 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{32}O_5Na)^+$: 435.21474, found: 435.21443. $[\alpha]_D^{20}$ = –102.4 (c = 0.09, CH_2Cl_2).

[24] Prepared according to: a) D. C. Harrowven, J. D. Wilden, M. J. Tyte, M. B. Hursthouse, S. J. Coles, *Tetrahedron Letters* **2001**, *42*, 6, 1193. b) C. L. Hugelshofer, T. Magauer, *Angew. Chem., Int. Ed.* **2014**, *53*, 11351.

(–)-leucosceptroid M (8): **TLC** (40% ethyl acetate in hexanes): R_f = 0.28 (UV/$KMnO_4$). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 6.06–6.04 (m, 1H, 19-H), 5.66 (dd, $^3J_{4/3}$ = 9.6 Hz, $^4J_{4/6}$ = 1.4 Hz, 1H, 4-H), 5.66–5.64 (m, 1H, 16-H), 5.13–5.09 (m, 1H, 3-H), 4.13 (s, 1H, 11-OH), 3.08 (dd, $^2J_{15B/15A}$ = 15.2 Hz, $^3J_{15B/16}$ = 9.7 Hz, 1H, 15-H_B), 2.73 (dd, $^2J_{15A/15B}$ = 15.2 Hz, $^3J_{15A/16}$ = 7.4 Hz, 1H, 15-H_A), 2.40 (d, $^4J_{25/19}$ = 1.4 Hz, 3H, 25-H), 2.39–2.33 (m, 1H, 6-H), 2.17–2.08 (m, 4H, 7-H, 8-H_B, 9-H_B, 10-H), 1.82 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.76 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.67–1.63 (m, 1H, 8-H_A), 1.42 (s, 3H, 24-H), 1.36–1.32 (m, 1H, 9-H_B), 1.13 (d, $^3J_{22/6}$ = 7.0 Hz, 3H, 22-H), 0.81 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 197.81 (C-12), 169.00 (C-20), 167.35 (C-5), 155.80 (C-18), 151.73 (C-17), 139.64 (C-2), 137.32 (C-13), 122.91 (C-3), 120.02 (C-19), 113.26 (C-16), 88.98 (C-14), 85.96 (C-11), 80.72 (C-4), 56.09 (C-7), 47.34 (C-10), 35.80 (C-15), 32.95 (C-6), 32.15 (C-9), 29.46 (C-8), 27.25 (C-24), 25.98 (C-1), 18.88 (C-23), 18.34 (C-21), 18.06 (C-22), 15.54 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3440 (br), 2964 (s), 2929 (m), 2877 (w), 1760 (s), 1661 (s), 1452 (w), 1378 (w), 1260 (s), 1079 (s), 1020 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{32}O_5Na)^+$: 435.21474, found: 435.21444. $[\alpha]_D^{20}$ = –42.5 (c = 0.07, CH_2Cl_2).

Synthesis of (–)-leucosceptroid K (9)

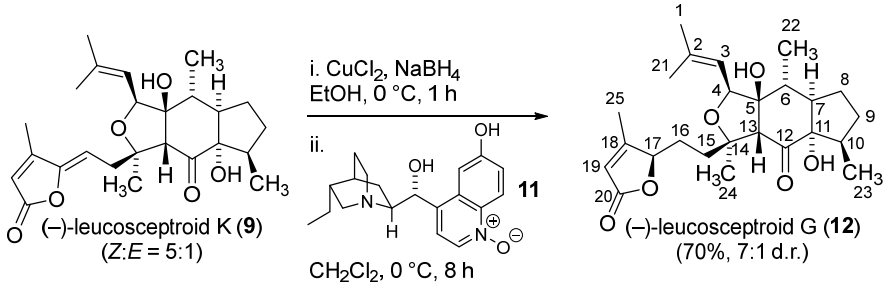


An ice-cooled solution of phosphonate **6**[25] (152 mg, 651 µmol, 4.00 equiv) in tetrahydrofuran (2.5 mL) was treated with potassium *tert*-butoxide (73.0 mg, 651 µmol, 4.00 equiv). After 30 min, a solution of (–)-norleucosceptroid B (**4**) (57.0 mg, 163 µmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise to the dark red mixture at 0 °C. The transfer was quantitated with tetrahydrofuran (3 x 0.5 mL). After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 1 h, the mixture was diluted with saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (10 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (4 x 10 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (45% ethyl acetate in hexanes) on silica gel to provide a 5:1 mixture of (–)-leucosceptroid K (**9**) and the corresponding *E*-isomer as a colourless oil (63.5 mg, 91%). Further careful purification of this mixture by flash-column chromatography on silica gel afforded an analytically pure sample of (–)-leucosceptroid K (**9**).

TLC (40% ethyl acetate in hexanes): R_f = 0.24 (UV/$KMnO_4$). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 6.01 (s, 1H, 19-H), 5.71 (t, $^3J_{16/15}$ = 7.6 Hz, 1H, 16-H), 5.60–5.57 (m, 1H, 3-H), 4.74 (d, $^3J_{4/3}$ = 8.9 Hz, 1H, 4-H), 4.17 (br s, 1H, 11-OH), 3.89 (br s, 1H, 5-OH), 2.82–2.74 (m, 2H, 15-H), 2.72 (s, 1H, 13-H), 2.31–2.24 (m, 1H, 10-H), 2.20 (d, $^4J_{25/19}$ = 1.4 Hz, 3H, 25-H), 2.15–2.02 (m, 3H, 7-H, 8-H_B, 9-H_B), 1.83–1.76 (m, 1H, 6-H), 1.76–1.73 (m, 6H, 1-H, 21-H), 1.73–1.67 (m, 1H, 8-H_A), 1.44–1.38 (m, 1H, 9-H_A), 1.25 (s, 3H, 24-H), 0.98 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.80 (d, $^3J_{23/10}$ = 7.4 Hz, 3H, 23-H). **^{13}C NMR** (150 MHz, Acetone-d_6) δ 212.40 (C-12), 169.51 (C-20), 156.20 (C-18), 152.63 (C-17), 137.17 (C-2), 122.50 (C-3), 116.61 (C-19), 109.46 (C-16), 85.62 (C-11), 84.52 (C-5), 83.35 (C-14), 77.30 (C-4), 71.70 (C-13), 50.45 (C-7), 46.25 (C-10), 42.27 (C-6), 41.63 (C-15), 31.04 (C-9), 30.62 (C-8), 26.17 (C-21), 24.32 (C-24), 18.84 (C-1), 16.99 (C-23), 14.03 (C-22), 11.72 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3474 (br), 2966 (s), 2937 (s), 2873 (m), 1749 (s), 1694 (m), 1451 (m), 1381 (m), 1286 (m), 1102 (w), 1029 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{34}O_6Na)^+$: 453.22531, found: 453.22462. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –70.4 (c = 0.13, MeOH).

[25] Prepared according to: a) D. C. Harrowven, J. D. Wilden, M. J. Tyte, M. B. Hursthouse, S. J. Coles, *Tetrahedron Letters* **2001**, *42*, 6, 1193. b) C. L. Hugelshofer, T. Magauer, *Angew. Chem., Int. Ed.* **2014**, *53*, 11351.

Synthesis of (–)-leucosceptroid G (12)

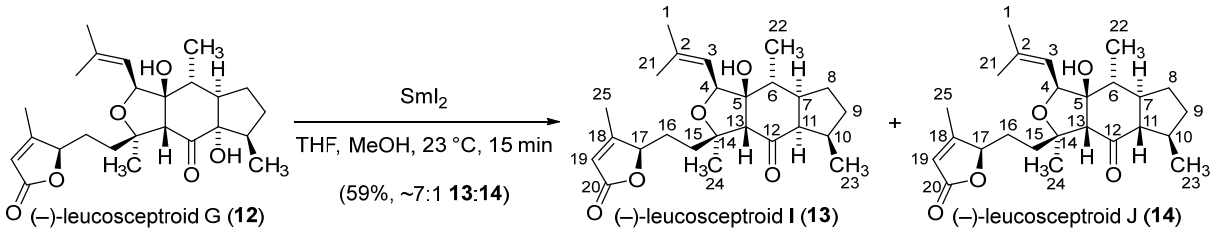


A solution of (–)-leucosceptroid K (**9**) (*Z*:*E* = 5:1, 40.0 mg, 92.9 µmol, 1 equiv) in ethanol (2.5 mL) was treated with copper(II) chloride (62.5 mg, 46.5 µmol, 5.00 equiv), followed by sodium borohydride (35.1 mg, 92.9 µmol, 10.0 equiv) at 0 °C. The mixture gradually turned into a deep brown suspension. After 20 min, a second portion of sodium borohydride (17.6 mg, 46.5 µmol, 5.00 equiv) was added, and after further 30 min, the mixture turned clear and a fine black precipitate formed. After 2 min, the mixture was diluted with pH 7 buffer solution (15 mL) and dichloromethane (15 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 10 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in dichloromethane (2.2 mL) and cinchona alkaloid catalyst **11**[26] (6.1 mg, 18.6 µmol, 0.20 equiv) was added at 0 °C. Stirring was continued at 0 °C for 8 h, whereupon the mixture was concentrated (23 °C waterbath). The residue was purified by flash-column chromatography (4% methanol in dichloromethane) on silica gel to provide a 7:1 mixture of (–)-leucosceptroid G (**12**) and the corresponding C-17 diastereomer as a colourless solid (28.1 mg, 70% over two steps). An analytically pure sample of (–)-leucosceptroid G (**12**) was obtained by reversed-phase semi-preparative HPLC purification using methanol–water (37:63 to 55:45 gradient over 140 min) as eluent (flow rate: 4.5 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 210 nm; retention time: 55 min for **12** and 57 min for the minor diastereomer).

TLC (5% methanol in dichloromethane): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 5.83–5.80 (m, 1H, 19-H), 5.54 (d, $^3J_{3/4}$ = 8.9 Hz, 1H, 3-H), 5.05–4.99 (m, 1H, 17-H), 4.69 (d, $^3J_{4/3}$ = 8.9 Hz, 1H, 4-H), 4.16 (s, 1H, 11-OH), 3.87 (s, 1H, 5-OH), 2.65 (s, 1H, 13-H), 2.32–2.18 (m, 2H, 10-H, 16-H_A), 2.14–2.09 (m, 4H, 8-H_A, 25-H), 2.06–1.98 (m, 2H, 7-H, 9-H_A), 1.83–1.74 (m, 3H, 6-H, 15-H), 1.72 (s, 6H, 1-H, 21-H), 1.69–1.59 (m, 2H, 8-H_B, 16-H_B), 1.46–1.35 (m, 1H, 9-H), 1.19 (s, 3H, 24-H), 0.96 (d, $^3J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.82 (d, $^3J_{23/10}$ = 7.4 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 212.76 (C-12), 173.20 (C-20), 170.39 (C-18), 136.87 (C-2), 122.64 (C-3), 117.16 (C-19), 85.54 (C-11), 85.05 (C-17), 84.22 (C-5), 83.44 (C-14), 76.94 (C-4), 72.09 (C-13), 50.19 (C-7), 46.22 (C-10), 42.09 (C-6), 39.30 (C-15), 30.94 (C-9), 30.47 (C-8), 27.57 (C-16), 26.14 (C-21), 23.72 (C-24), 18.79 (C-1), 17.16 (C-23), 13.93 (C-22), 13.85 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3451 (br), 2962 (s), 2933 (s), 2877 (m), 1735 (s), 1694 (s), 1447 (m), 1381 (m), 1298 (m), 1102 (w), 1026 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{36}O_6Na)^+$: 455.24096, found: 455.24086. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –176.0 (c = 0.04, MeOH).

[26] Cinchona alkaloid catalyst **11** was prepared starting from hydroquinine according to: Y. Wu, R. P. Singh, L. Deng, *J. Am. Chem. Soc.* **2011**, *133,* 12458.

Synthesis of (–)-leucosceptroid I (13) and (–)-leucosceptroid J (14)

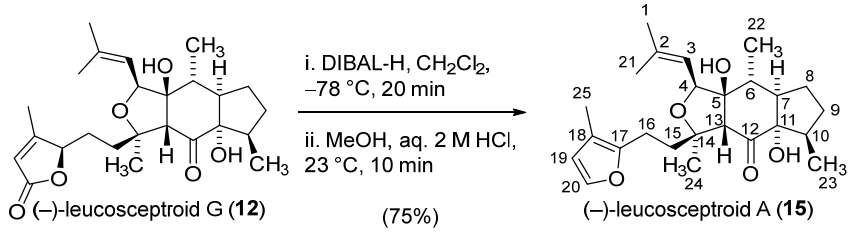


A solution of of (–)-leucosceptroid G (**12**) (2.1 mg, 4.85 µmol, 1 equiv) in a mixture of tetrahydrofuran–methanol (3:1, 0.8 mL) was treated with samarium(II) iodide solution (0.1 M in THF, 0.49 mL, 48.5 µmol, 10 equiv) at 23 °C. The resulting dark blue mixture turned nearly colourless within 1 min. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and dichloromethane (3 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a short pad of Celite and the filtrate was concentrated to provide an approximate 7:1 mixture of (–)-leucosceptroid I (**13**) and (–)-leucosceptroid J (**14**) as a colourless oil (1.2 mg, 59%). Analytically pure samples of (–)-leucosceptroid I (**13**) and (–)-leucosceptroid J (**14**) were obtained by reversed-phase semi-preparative HPLC using methanol–water (52:48 to 70:30 gradient over 50 min) as eluent (flow rate: 3.5 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 230 nm; retention times: 40.1 min for **13** and 45.1 min for **14**).

(–)-leucosceptroid I (13): TLC (5% methanol in dichloromethane): R_f = 0.36 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 5.83–5.81 (m, 1H, 19-H), 5.59–5.56 (m, 1H, 3-H), 5.02–4.99 (m, 1H, 17-H), 4.74 (d, $^3J_{4/3}$ = 8.8 Hz, 1H, 4-H), 3.92 (s, 1H, 5-OH), 2.88 (dd, ^3J = 10.9, ^3J = 7.0 Hz, 1H, 11-H), 2.66 (s, 1H, 13-H), 2.47–2.42 (m, 1H, 10-H), 2.42–2.36 (m, 1H, 7-H), 2.26–2.20 (m, 1H, 16-H$_A$), 2.12–2.11 (m, 3H, 25-H), 2.04–2.01 (m, 1H, 8-H$_A$), 1.81–1.75 (m, 1H, 15-H$_A$), 1.75–1.71 (m, 7H, 1-H, 15-H$_B$, 21-H), 1.64–1.51 (m, 4H, 6-H, 8-H$_B$, 9-H$_A$, 16-H$_B$), 1.51–1.46 (m, 1H, 9-H$_B$), 1.13 (s, 3H, 24-H), 0.96 (d, $^3J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.90 (dd, $^3J_{23/10}$ = 7.2 Hz, 3H, 23-H). **^{13}C NMR** (200 MHz, Acetone-d_6) δ 213.17 (C-12), 173.18 (C-20), 170.38 (C-18), 136.61 (C-2) 122.94 (C-3), 117.14 (C-19), 85.70 (C-5), 85.07 (C-17), 82.63 (C-14), 77.04 (C-4), 73.86 (C-13), 56.38 (C-11), 46.25 (C-6), 41.57 (C-7), 38.70 (C-15), 37.09 (C-10), 33.48 (C-9), 31.43 (C-8), 27.29 (C-16), 26.19 (C-1), 22.14 (C-24), 18.78 (C-21), 16.89 (C-23), 13.85 (C-22, C-25), 13.79 (C-22, C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3466 (br), 2931 (s), 2874 (m), 1757 (s), 1739 (s), 1687 (m), 1449 (m), 1378 (m), 1297 (w), 1034 (m) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{40}O_5N)^+$: 434.29010, found: 434.29033. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –128.8 (c = 0.04, MeOH).

(–)-leucosceptroid J (14): TLC (5% methanol in dichloromethane): R_f = 0.36 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 5.83–5.79 (m, 1H, 19-H), 5.62–5.59 (m, 1H, 3-H), 5.01–4.96 (m, 1H, 17-H), 4.42 (d, $^3J_{4/3}$ = 8.5 Hz, 1H, 4-H), 3.98 (s, 1H, 5-OH), 2.74 (s, 1H, 13-H), 2.22–2.16 (m, 1H, 16-H$_A$), 2.10 (s, 3H, 25-H), 2.08–2.05 (m, 1H, 10-H), 1.96–1.91 (m, 1H, 9-H$_A$), 1.90–1.86 (m, 1H, 6-H), 1.84–1.76 (m, 5H, 7-H, 8-H$_A$, 11-H, 15-H), 1.72 (s, 3H, 1-H), 1.70 (s, 3H, 21-H), 1.62–1.55 (m, 1H, 16-H$_B$), 1.34–1.26 (m, 2H, 8-H$_B$, 9-H$_B$), 1.13 (d, $^3J_{23/10}$ = 6.7 Hz, 3H, 23-H), 1.11 (s, 3H, 24-H), 0.96 (d, $^3J_{22/6}$ = 7.0 Hz, 3H, 22-H). *Note: The small amount of **14** obtained after HPLC separation did not allow acquisition of a ^{13}C NMR spectrum with satisfactory signal to noise ratio. The chemical shifts of some carbon atoms (C-12, C-20) thus had to be determined from the HMBC spectrum.* **^{13}C NMR** (200 MHz, Acetone-d_6) δ 210. 73 (C-12), 173.21 (C-20), 170.5 (C-18), 136.71 (C-2), 122.68 (C-3), 117.06 (C-19), 86.22 (C-5), 85.20 (C-17), 82.40 (C-14), 76.88 (C-4), 72.44 (C-13), 65.18 (C-11), 47.17 (C-6), 46.44 (C-7), 38.62 (C-15), 33.82 (C-10), 32.96 (C-9), 29.05 (C-8), 27.31 (C-16), 26.15 (C-1), 22.86 (C-24), 22.02 (C-23), 18.74 (C-21), 14.05 (C-22), 13.85 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3484 (br), 2931 (s), 2870 (m), 1736 (s), 1697 (m), 1640 (m), 1452 (m), 1266 (s), 1164 (m), 1038 (w) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{40}O_5N)^+$: 434.29010, found: 434.29039.

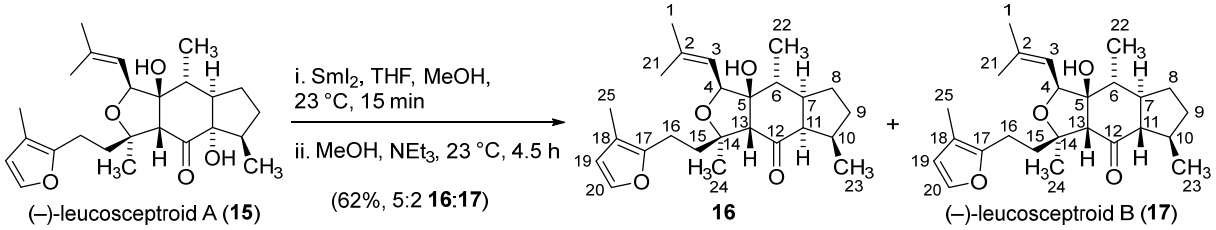
Synthesis of (–)-leucosceptroid A (15)



A solution of of (–)-leucosceptroid G (**12**) (19.8 mg, 45.8 µmol, 1 equiv) in dichloromethane (2.5 mL) was treated with diisobutylaluminium hydride solution (1 M in dichloromethane, 229 µL, 229 µmol, 5.00 equiv) at −78 °C. After 20 min, methanol (0.4 mL) and aqueous 2 M hydrogen chloride solution (0.4 mL) were added whereupon the mixture was warmed to 23 °C. After 10 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (7 mL) and dichloromethane (7 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in hexanes) on silica gel to provide (–)-leucosceptroid A (**15**) as a colourless solid (14.2 mg, 75%).

TLC (20% ethyl acetate in hexanes): R_f = 0.31 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, $^3J_{20/19}$ = 1.7 Hz, 1H, 20-H), 6.14 (d, $^3J_{19/20}$ = 1.7 Hz, 1H, 19-H), 5.41 (d, $^3J_{3/4}$ = 8.4 Hz, 1H, 3-H), 4.60 (d, $^3J_{4/3}$ = 8.4 Hz, 1H, 4-H), 2.74 (app t, *J* = 9.2, 2H, 16-H), 2.69 (s, 1H, 13-H), 2.67 (s, 1H, 11-OH), 2.39 (s, 1H, 5-OH), 2.27–1.98 (m, 6H, 7-H, 8-H_A, 9-H_A, 10-H, 15-H), 1.96 (s, 3H, 25-H), 1.93–1.81 (m, 2H, 6-H, 8-H_B), 1.80 (s, 3H, 1-H), 1.76 (s, 3H, 21-H), 1.55–1.44 (m, 1H, 9-H_B), 1.31 (s, 3H, 24-H), 0.96 (d, $^3J_{22/6}$ = 6.9 Hz, 3H, 22-H), 0.86 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.22 (C-12), 150.45 (C-17), 140.25 (C-2), 139.94 (C-20), 119.19 (C-3), 113.83 (C-18), 112.99 (C-19), 86.01 (C-11), 85.03 (C-5), 82.94 (C-14), 76.51 (C-4), 69.34 (C-13), 49.91 (C-7), 47.39 (C-10), 42.38 (C-15), 39.03 (C-6), 30.86 (C-9), 29.95 (C-8), 26.48 (C-1), 22.88 (C-24), 21.10 (C-16), 19.19 (C-21), 16.77 (C-23), 14.47 (C-22), 10.00 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3455 (s), 2963 (s), 2929 (s), 2875 (m), 1680 (s), 1446 (m), 1385 (m), 1326 (m), 1273 (m), 1101 (m), 1064 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{25}H_{36}O_5)^+$: 416.2563, found: 416.2591. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –150.2 (c = 0.14, $CHCl_3$).

Synthesis of ketone 16 and (–)-leucosceptroid B (17)

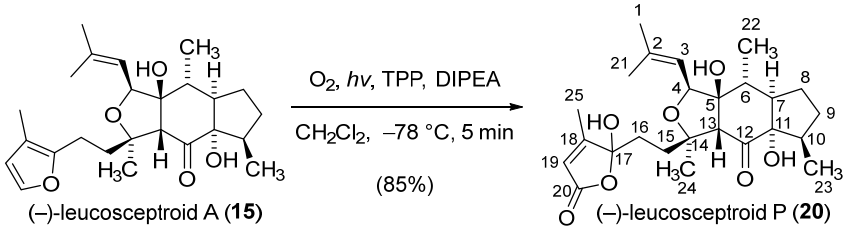


A solution of of (–)-leucosceptroid A (**15**) (2.0 mg, 4.80 µmol, 1 equiv) in a mixture of tetrahydrofuran–methanol (4:1, 0.9 mL) was treated with samarium(II) iodide solution (0.1 M in THF, 0.72 mL, 72.0 µmol, 15 equiv) at 23 °C. The resulting dark blue mixture turned nearly colourless within 2 min. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and dichloromethane (3 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in methanol (0.8 mL) and triethylamine (80 µL) was added at 23 °C. After 4.5 h, the mixture was concentrated (23 °C waterbath) and the residue was filtered through a short pad of silica gel (20% ethyl acetate in hexanes) to provide a 5:2 mixture of ketone **16** and (–)-leucosceptroid B (**17**) as a colourless oil (1.2 mg, 62%). Analytically pure samples of ketone **16** and (–)-leucosceptroid B (**17**) were obtained by reversed-phase semi-preparative HPLC using methanol–water (72:28 to 80:20 gradient over 30 min) as eluent (flow rate: 4.5 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 230 nm; retention times: 14.2 min for **16** and 19.1 min for **17**).

Ketone 16: TLC (20% ethyl acetate in hexanes): R_f = 0.42 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.20 (d, $^3J_{20/19}$ = 1.8 Hz, 1H, 20-H), 6.14 (d, $^3J_{19/20}$ = 1.8 Hz, 1H, 19-H), 5.47–5.43 (m, 1H, 3-H), 4.71 (d, $^3J_{4/3}$ = 8.9 Hz, 1H, 4-H), 2.81–2.75 (m, 2H, 11-H, 16-H_A), 2.74 (s, 1H, 13-H), 2.73–2.67 (m, 1H, 16-H_B), 2.55–2.49 (m, 1H, 10-H), 2.25–2.20 (m, 1H, 7-H), 2.19 (s, 1H, 5-OH), 2.11–2.06 (m, 1H, 15-H_A), 2.06–1.98 (m, 2H, 8-H_A, 15-H_B), 1.97 (s, 3H, 25-H), 1.80 (d, $^4J_{1/3}$ = 1.5 Hz, 3H, 1-H), 1.78 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.69–1.55 (m, 4H, 6-H, 8-H_B, 9-H), 1.19 (s, 3H, 24-H), 0.96 (d, $^3J_{22/6}$ = 6.7 Hz, 3H, 22-H), 0.95 (d, $^3J_{23/10}$ = 7.1 Hz, 3H, 23-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 212.73 (C-12), 150.67 (C-17), 139.88 (C-20), 139.28 (C-2), 120.24 (C-3), 113.73 (C-18), 112.94 (C-19), 85.48 (C-5), 82.83 (C-14), 76.58 (C-4), 71.94 (C-13), 56.02 (C-11), 44.19 (C-6), 42.05 (C-15), 41.10 (C-7), 36.63 (C-10), 33.04 (C-9), 30.96 (C-8), 26.49 (C-1), 21.90 (C-24), 20.86 (C-16), 19.17 (C-21), 16.77 (C-23), 13.45 (C-22), 9.98 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3470 (br), 2926 (s), 2848 (m), 1691 (s), 1456 (s), 1377 (m), 1265 (m), 1149 (m), 1054 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{25}H_{36}O_4)^+$: 400.2614, found: 400.2616. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –101.5 (c = 0.09, $CHCl_3$).

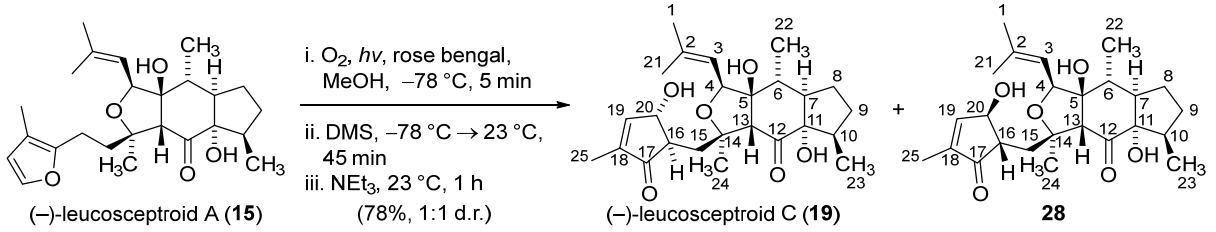
(–)-leucosceptroid B (17): TLC (20% ethyl acetate in hexanes): R_f = 0.40 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.20 (d, $^3J_{20/19}$ = 1.8 Hz, 1H, 20-H), 6.13 (d, $^3J_{19/20}$ = 1.8 Hz, 1H, 19-H), 5.49–5.46 (m, 1H, 3-H), 4.38 (d, $^3J_{4/3}$ = 8.6 Hz, 1H, 4-H), 2.76 (s, 1H, 13-H), 2.75–2.71 (m, 2H, 16-H), 2.31 (s, 1H, 5-OH), 2.15–2.10 (m, 1H, 10-H), 2.10–2.06 (m, 2H, 15-H), 1.98–1.93 (m, 4H, 9-H_A, 25-H), 1.92–1.87 (m, 1H, 6-H), 1.85–1.80 (m, 1H, 8-H_A), 1.79 (d, $^4J_{1/3}$ = 1.4 Hz, 3H, 1-H), 1.78–1.75 (m, 1H, 11-H), 1.74 (d, $^4J_{21/3}$ = 1.4 Hz, 3H, 21-H), 1.66–1.59 (m, 1H, 7-H), 1.37–1.29 (m, 2H, 8-H_B, 9-H_B), 1.22 (s, 3H, 24-H), 1.16 (d, $^3J_{23/10}$ = 6.7 Hz, 3H, 23-H), 0.96 (d, $^3J_{22/6}$ = 7.1 Hz, 3H, 22-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 209.61 (C-12), 150.73 (C-17), 139.85 (C-20), 139.16 (C-2), 120.07 (C-3), 113.74 (C-18), 112.97 (C-19), 86.48 (C-5), 82.10 (C-14), 76.07 (C-4), 70.87 (C-13), 64.91 (C-11), 46.11 (C-7), 45.01 (C-6), 41.62 (C-15), 33.06 (C-10), 32.39 (C-9), 28.78 (C-8), 26.44 (C-1), 22.99 (C-24), 21.87 (C-23), 20.85 (C-16), 19.09 (C-21), 14.07 (C-22), 10.00 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3514 (s), 2956 (m), 2925 (s), 2855 (m), 1701 (s), 1668 (m), 1511 (m), 1451 (s), 1375 (m), 1272 (m), 1147 (m), 1051 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{25}H_{36}O_4)^+$: 400.2614, found: 400.2630. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –56.0 (c = 0.03, $CHCl_3$).

Synthesis of (–)-leucosceptroid P (20)



Oxygen was bubbled through a solution of (–)-leucosceptroid A (**15**) (11.0 mg, 26.4 µmol, 1 equiv) in dichloromethane (3.5 mL) containing a catalytic amount of tetraphenylporphyrin (TPP, tip of a spatula) and *N*,*N*-diisopropylethylamine (22.9 µL, 132 µmol, 5.00 equiv) at –78 °C. The mixture was irradiated with a Replux Belgium RL 160W (225–235 Volts) lamp, and after 5 min, sparging with oxygen and irradiation was discontinued. The cooling bath was removed, and after 15 min the mixture was concentrated. The residue was purified by flash-column chromatography (5% methanol in dichloromethane) on silica gel to provide (–)-leucosceptroid P (**20**) as a colourless oil (10.1 mg, 85%.).
*Note: since (–)-leucosceptroid P (**20**) exists as a 1:1 mixture of diastereomers at C-17, the three hydroxyl groups show a double set of signals in the ^{1}H NMR spectrum, and most carbon atoms show a second set of signals with mostly less than 0.1 ppm deviation in the ^{13}C NMR spectrum. The signal of the second diastereomer is marked with an asterisk.*
TLC (5% methanol in dichloromethane): R_f = 0.17 (CAM). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 6.34, 6.30* (s, 1H, 17-OH), 5.81 (br s, 1H, 19-H), 5.58–5.51 (m, 1H, 3-H), 4.70 (d, $^{3}J_{4/3}$ = 8.9 Hz, 1H, 4-H), 4.18, 4.17* (s, 1H, 11-OH), 3.93, 3.89* (s, 1H, 5-OH), 2.63 (s, 1H, 13-H), 2.32–2.22 (m, 2H, 10-H, 16-H$_A$), 2.22–1.97 (m, 7H, 7-H, 8-H$_A$, 9-H$_A$, 16-H$_B$, 25-H), 1.97–1.75 (m, 2H, 6-H, 15-H$_A$), 1.72 (s, 6H, 1-H, 21-H), 1.69–1.54 (m, 2H, 8-H$_B$, 15-H$_B$), 1.45–1.35 (m, 1H, 9-H$_B$), 1.19 (s, 3H, 24-H), 0.96 (d, $^{3}J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.82 (d, $^{3}J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 212.69, 212.60* (C-12), 170.65, 170.61* (C-20), 168.27, 168.21* (C-18), 137.00 (C-2), 122.52, 122.49* (C-3), 118.41, 118.38* (C-19), 108.93, 108.85* (C-17), 85.53 (C-11), 84.19 (C-5), 83.30, 83.24* (C-14), 77.02, 77.00* (C-4), 72.16, 72.06* (C-13), 50.18 (C-7), 46.21, 46.16* (C-10), 42.18, 42.02* (C-6), 38.43, 38.38* (C-15), 31.75, 31.68* (C-16), 30.94 (C-9), 30.53 (C-8) 26.13 (C-21), 23.72, 23.70* (C-24), 18.80 (C-1), 17.17, 17.13* (C-23), 13.91 (C-22), 12.60, 12.55* (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3427 (br), 2967 (s), 1745 (s), 1694 (s), 1445 (m), 1380 (m), 1264 (s), 1102 (m), 1020 (m), 937 (m) cm^{-1}. **HRMS** (EI): calcd for $(C_{25}H_{36}O_7Na)^+$: 471.23587, found: 471.23564. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –111.3 (c = 0.56, MeOH).

Synthesis of (–)-leucosceptroid C (19) and cyclopentenone 28

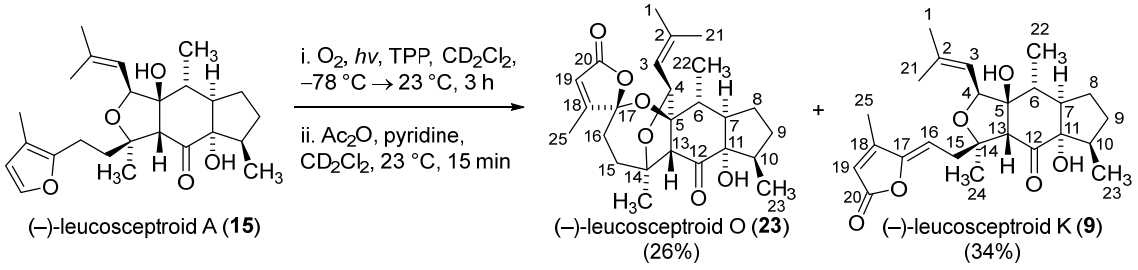


Oxygen was bubbled through a solution of (–)-leucosceptroid A (**15**) (8.8 mg, 21.1 μmol, 1 equiv) in methanol (1.6 mL) containing a catalytic amount of rose bengal (tip of a spatula) at –78 °C. The mixture was irradiated with a Replux Belgium RL 160W (225–235 Volts) lamp, and after 4 min, sparging with oxygen and irradiation was discontinued. Dimethyl sulfide (15.6 μL, 211 mol, 10.0 equiv) was added and the mixture was then warmed to 23 °C. After 45 min, triethylamine (14.7 μL, 106 mol, 4.00 equiv) was added, and after further 35 min, the mixture was concentrated in vacuo. The residue was purified by flash-column chromatography (40% → 50% ethyl acetate in hexanes) on silica gel to provide two main fractions. The less polar fraction (R_f = 0.15, 40% ethyl acetate in hexanes) contained traces of a 1:1 mixture of (–)-leucosceptroid C (**19**) and cyclopentenone **28**, while the more polar fraction (R_f = 0.07, 40% ethyl acetate in hexanes) contained the corresponding γ-keto aldehyde (the aldol reaction precursor). The residue from the more polar fraction was dissolved in dichloromethane (1.5 mL) and triethylamine (40 μL) was added at 23 °C. After 1 h, the mixture was concentrated (23 °C waterbath) and the residue was purified by flash-column chromatography (40% → 50% ethyl acetate in hexanes) on silica gel to provide a further 1:1 mixture of (–)-leucosceptroid C (**19**) and cyclopentenone **28** (7.1 mg, 78% total yield). Analytically pure samples of (–)-leucosceptroid C (**19**) and cyclopentenone **28** were obtained by reversed-phase semi-preparative HPLC using methanol–water (40:60 to 80:20 gradient over 80 min) as eluent (flow rate: 4.0 mL/min; column: Nucleosil 100-7 C18, 10x250 mm; detection: 238 nm; retention times: 32.9 min for **19** and 35.9 min for **28**).

(–)-leucosceptroid C (19): TLC (5% methanol in dichloromethane): R_f = 0.28 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 7.21–7.19 (m, 1H, 19-H), 5.62–5.59 (m, 1H, 3-H), 4.80 (d, $^3J_{4/3}$ = 8.8 Hz, 1H, 4-H), 4.65–4.62 (m, 1H, 20-H), 4.34 (d, $^3J_{20OH/20}$ = 3.7 Hz, 1H, 20-OH), 4.26 (s, 1H, 11-OH), 4.12 (s, 1H, 5-OH), 2.77 (s, 1H, 13-H), 2.43 (app dt, $^3J_{16/15B}$ = 11.2 Hz, $^3J_{16/15A}$ = $^3J_{16/20}$ = 2.3 Hz, 1H, 16-H), 2.32 (dd, $^2J_{15A/15B}$ = 14.2 Hz, $^3J_{15A/16}$ = 2.3 Hz, 1H, 15-H_A), 2.30–2.27 (m, 1H, 10-H), 2.15–2.09 (m, 1H, 8-H_A), 2.09–2.04 (m, 2H, 7-H, 9-H_A), 1.90 (dd, $^2J_{15B/15A}$ = 14.2 Hz, $^3J_{15B/16}$ = 11.2 Hz, 1H, 15-H_B), 1.83–1.79 (m, 1H, 6-H), 1.76 (s, 6H, 1-H, 21-H), 1.73 (app t, $^4J_{25/19}$ = 1.8 Hz, 3H, 25-H), 1.72–1.67 (m, 1H, 8-H_B), 1.44–1.40 (m, 1H, 9-H_B), 1.30 (s, 3H, 24-H), 0.98 (d, $^3J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.83 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (200 MHz, Acetone-d_6) δ 212.21 (C-12), 206.87 (C-17), 156.80 (C-19), 141.83 (C-18), 138.12 (C-2), 121.85 (C-3), 85.57 (C-11), 84.20 (C-5), 83.73 (C-14), 77.49 (C-4), 76.79 (C-20), 73.53 (C-13), 54.02 (C-16) 50.32 (C-7), 46.23 (C-10), 44.29 (C-15), 41.93 (C-6), 30.98 (C-9), 30.51 (C-8), 26.14 (C-21), 23.54 (C-24), 18.84 (C-1), 17.21 (C-23), 13.93 (C-22), 10.14 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3443 (br), 2965 (s), 2935 (s), 1699 (s), 1449 (m), 1381 (m), 1331 (m), 1234 (m), 1104 (m), 1023 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{36}O_6Na)^+$: 455.24096, found: 455.24091. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –128.0 (c = 0.06, MeOH).

Cyclopentenone 28: TLC (5% methanol in dichloromethane): R_f = 0.28 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 7.23–7.21 (m, 1H, 19-H), 5.60–5.58 (m, 1H, 3-H), 5.01 (s, 1H, 5-OH), 4.93 (d, $^3J_{20OH/20}$ = 3.4 Hz, 1H, 20-OH), 4.73–4.71 (m, 1H, 20-H), 4.69 (d, $^3J_{4/3}$ = 8.9 Hz, 1H, 4-H), 4.19 (s, 1H, 11-OH), 2.81 (s, 1H, 13-H), 2.45–2.41 (m, 1H, 16-H), 2.34–2.26 (m, 2H, 10-H, 15-H_A), 2.16–2.06 (m, 3H, 7-H, 8-H_A, 9-H_A), 1.87–1.81 (m, 1H, 6-H), 1.78–1.74 (m, 7H, 1-H, 8-H_B, 21-H), 1.73 (app t, $^4J_{25/19}$ = 1.6 Hz, 3H, 25-H), 1.63 (dd, $^2J_{15B/15A}$ = 14.8 Hz, $^3J_{15B/16}$ = 12.1 Hz, 1H, 15-H_B), 1.44–1.38 (m, 1H, 9-H_B), 1.29 (s, 3H, 24-H), 0.98 (d, $^3J_{22/6}$ = 6.8 Hz, 3H, 22-H), 0.83 (d, $^3J_{23/10}$ = 7.5 Hz, 3H, 23-H). **^{13}C NMR** (200 MHz, Acetone-d_6) δ 213.72 (C-12), 207.83 (C-17), 157.67 (C-19), 141.79 (C-18), 137.84 (C-2), 121.79 (C-3), 85.50 (C-11), 84.22 (C-5), 83.86 (C-14), 76.86 (C-4), 76.38 (C-20), 69.79 (C-13), 52.20 (C-16), 49.95 (C-7), 46.42 (C-10), 43.16 (C-15), 41.05 (C-6), 30.86 (C-9), 30.28 (C-8), 26.18 (C-1, C-24), 18.82 (C-21), 17.35 (C-23), 14.05 (C-22), 10.12 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3388 (br), 2961 (s), 2935 (s), 2878 (m), 1698 (s), 1449 (m), 1381 (m), 1328 (m), 1264 (m), 1103 (m), 1029 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{36}O_6Na)^+$: 455.24096, found: 455.24089. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –146.6 (c = 0.08, MeOH).

Synthesis of (–)-leucosceptroid O (23) and (–)-leucosceptroid K (9)



Oxygen was bubbled through a solution of (–)-leucosceptroid A (**15**) (4.9 mg, 11.8 µmol, 1 equiv) in CD_2Cl_2 (0.8 mL) containing a catalytic amount of tetraphenylporphyrin (TPP, tip of a spatula) at –78 °C. The mixture was irradiated with a Replux Belgium RL 160W (225–235 Volts) lamp, and after 2 min, sparging with oxygen and irradiation was discontinued. The cooling bath was removed, and the mixture was transferred to a NMR tube. Conversion of the initially formed *endo*-peroxide **18** was monitored by ^{1}H NMR spectroscopy at 23 °C (see Figure 1 on the following page). After 3 h, the mixture was transferred back to a round-bottomed flask and the NMR tube was rinsed with dichloromethane (2 x 0.1 mL). Acetic anhydride (10.1 µL, 118 µmol, 10.0 equiv), followed by pyridine (4.8 µL, 58.9 µmol, 5.00 equiv) were added. After 15 min, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and dichloromethane (3 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (35% ethyl acetate in hexanes) on silica gel to provide (–)-leucosceptroid O (**23**) (1.3 mg, 26%) and (–)-leucosceptroid K (**9**) (1.7 mg, 34%). The characterization data for (–)-leucosceptroid K (**9**) were in full agreement with the values reported above.

(–)-leucosceptroid O (23): TLC (40% ethyl acetate in hexanes): R_f = 0.31 (CAM). **^{1}H NMR** (800 MHz, Acetone-d_6) δ 5.84 (q, $^4J_{19/25}$ = 1.6 Hz, 1H, 19-H), 5.62–5.60 (m, 1H, 3-H), 5.24 (d, $^3J_{4/3}$ = 9.0 Hz, 1H, 4-H), 4.45 (s, 1H, 11-OH), 3.50 (s, 1H, 13-H), 2.47 (ddd, $^2J_{16A/16B}$ = 14.5 Hz, $^3J_{16A/15A}$ = 12.7 Hz, $^3J_{16A/15B}$ = 4.7 Hz, 1H, 16-H_A), 2.33–2.29 (m, 1H, 10-H), 2.25 (d, $^4J_{25/19}$ = 1.6 Hz, 3H, 25-H), 2.14–2.10 (m, 1H, 8-H_A), 2.02–1.95 (m, 2H, 7-H, 9-H_A), 1.94–1.87 (m, 1H, 15-H_A), 1.80–1.76 (m, 4H, 1-H, 16-H_B), 1.75 (d, $^4J_{21/3}$ = 1.3 Hz, 3H, 21-H), 1.74–1.68 (m, 2H, 6-H, 15-H_B), 1.59–1.52 (m, 1H, 8-H_B), 1.42–1.36 (m, 1H, 9-H_B), 1.32 (s, 3H, 24-H), 0.93 (d, $^3J_{22/6}$ = 6.7 Hz, 3H, 22-H), 0.85 (d, $^3J_{23/10}$ = 7.3 Hz, 3H, 23-H). **^{13}C NMR** (200 MHz, Acetone-d_6) δ 208.01 (C-12), 170.79 (C-18), 170.41 (C-20), 137.99 (C-2), 122.17 (C-3), 116.33 (C-19), 110.34 (C-17), 91.15 (C-5), 85.05 (C-11), 84.12 (C-14), 79.00 (C-4), 65.35 (C-13), 51.29 (C-7), 45.75 (C-10), 44.04 (C-6), 38.95 (C-15), 31.39 (C-8), 31.16 (C-16), 31.00 (C-9), 27.01 (C-24), 26.23 (C-1), 18.99 (C-21), 16.84 (C-23), 14.33 (C-22), 13.16 (C-25). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3436 (br), 2957 (m), 2925 (s), 2873 (m), 1764 (s), 1700 (s), 1448 (m), 1377 (s), 1224 (s), 1173 (m), 1106 (m), 1081 (s) cm^{-1}. **HRMS** (ESI): calcd for $(C_{25}H_{38}O_6N)^+$: 448.26991, found: 448.26994. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –89.6 (c = 0.03, MeOH).

6.3.2 ^{1}H NMR Monitoring of Leucosceptroid O (23) Synthesis

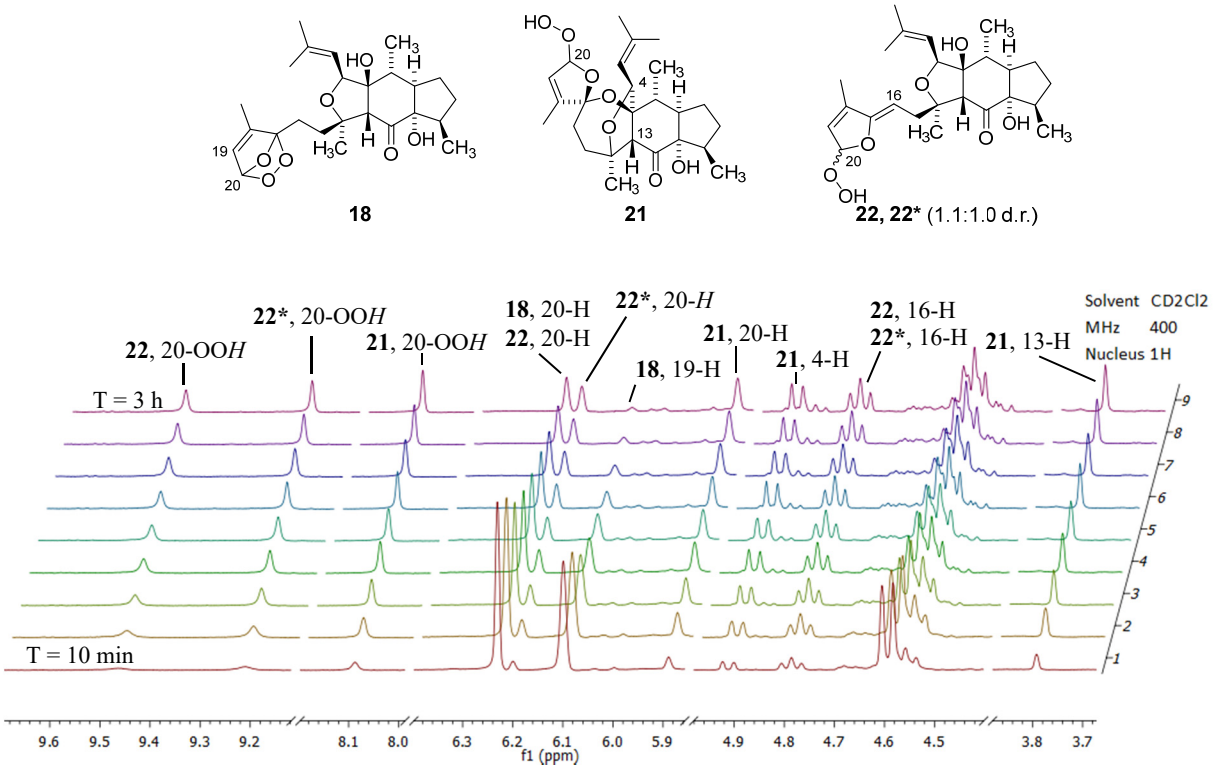


Figure 1. Monitoring the photo-oxidation of leucosceptroid A (**15**) by ^{1}H NMR spectroscopy (400 MHz, CD_2Cl_2).

The first ^{1}H NMR spectrum (recorded approximately 10 min after end of irradiation and warming of the reaction mixture to 23 °C) shows the *endo*-peroxide **18** as the main component [6.25 ppm (s, 1H, 20-H) and 6.10 ppm (s, 1H, 19-H)]. The ensuing spectra (recorded in approximate 20 min intervals) show a gradual intensity decline of *endo*-peroxide **18** while the intensity of hydroperoxide **21** [8.09 ppm (s, 1H, 20-OO*H*), 5.53 ppm (s, 1H, 20-H), 4.92 ppm (d $^{3}J_{4/3}$ = 8.9 Hz, 1H, 4-H) and 3.80 ppm (s, 1H, 13-H)] and hydroperoxide **22** (1.1:1.0 mixture of diastereomers at C20) [9.47 ppm (s, 1H, 20-OO*H*), 9.22* ppm (s, 1H, 20-OO*H*), 6.25 ppm (s, 1H, 20-H), 6.21* ppm (s, 1H, 20-H, minor) and 4.80 ppm (t, $^{3}J_{16/15}$ = 8.0 Hz, 1H ,16-H, diastereomers overlap)] increase. Spectrum 9 (recorded after approximately 3 h reaction time) shows essentially full consumption of *endo*-peroxide **18**.

The approximate 1:1:1.3 ratio of formed hydroperoxides is consistent with the isolated yields of leucosceptroid K (**9**) and leucosceptroid O (**23**). Hydroperoxide **22** is visibly a 1:1 mixture of diastereomers at C-20 (the –*OOH* resonances of the two diastereomers occur at 9.47 and 9.22 ppm in the ^{1}H NMR spectrum). While **21** appears as a single compound by ^{1}H NMR analysis, the stereochemistry at C-20 could not be unambiguously determined and its existence as a mixture of C-20 diastereomers (with overlapping ^{1}H NMR resonances) cannot be excluded. Hydroperoxides **21** and **22** were found to be moderately stable in solution, but eluded isolation and purification.

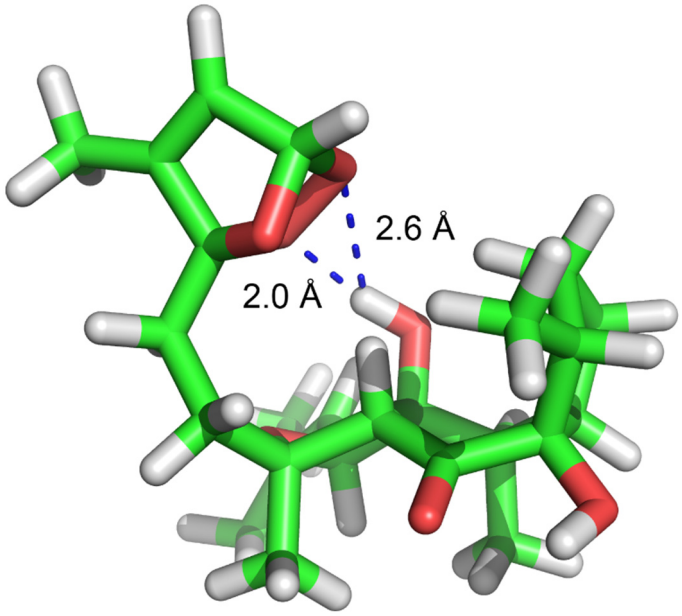
6.3.3 Computational Details

Conformational Search. Conformational searches were performed with Spartan'10 (Spartan'10, Wavefunction, Inc., Irvine CA). An initial subset of reasonable conformers was generated using the molecular mechanics MMFF force field[27] and the 100 structures of lowest energy were documented. A subset of these conformers was then further optimized via DFT calculations.

Density Functional Theory. All DFT calculations were performed using Gaussian 09 (Revision A.02).[28] Each starting structure, already a local minimum with respect to the conformational search potential energy surface, was optimized (gas phase) with the B3LYP hybrid functional[29] employing the 6-31G(d) basis set.

Computed Geometries and Energies.

***Endo*-peroxide 18**



Computed sum of electronic and thermal Enthalpies = –1500.119263 hartee.

Cartesian coordinates:

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C 0	-0.308300	-2.945800	-1.816700

[27] T. A. Halgren, *J. Comput. Chem.* **1996,** *17*, 490.

[28] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[29] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648. b) P. J. Stephens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, *J. Chem. Phys.* **1994**, *98*, 11623.

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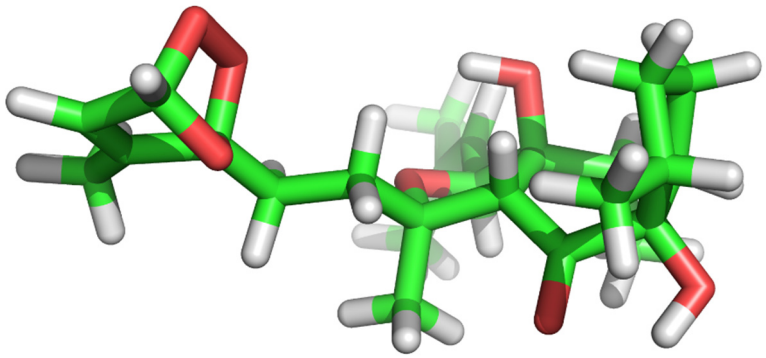
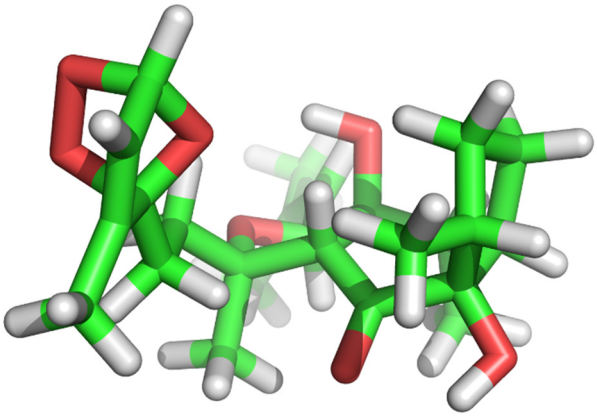
Further structures within 1.50 kcal/mol relative energy with respect to the found global minimum conformer **18** are depicted below:

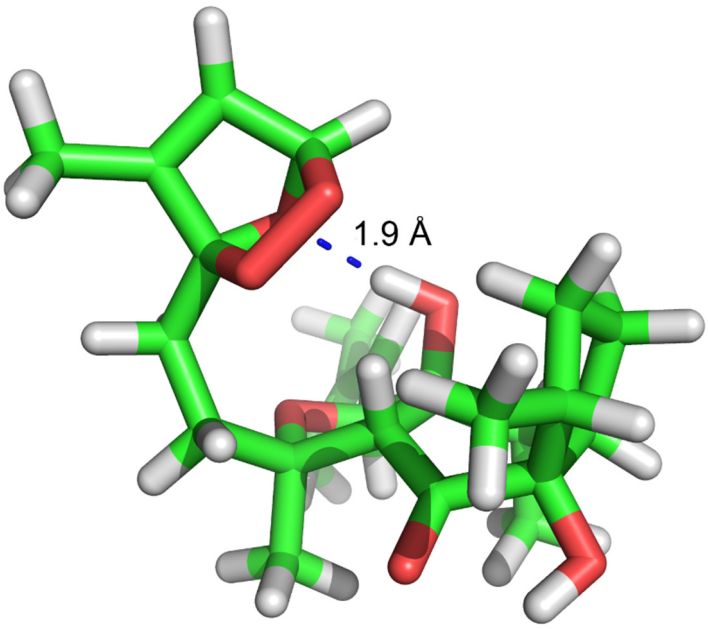


Relative energy: +1.25 kcal/mol



Relative energy: +1.48 kcal/mol

***Endo*-peroxide 18'**



Computed sum of electronic and thermal Enthalpies = –1500.118497 hartee.

Cartesian coordinates:

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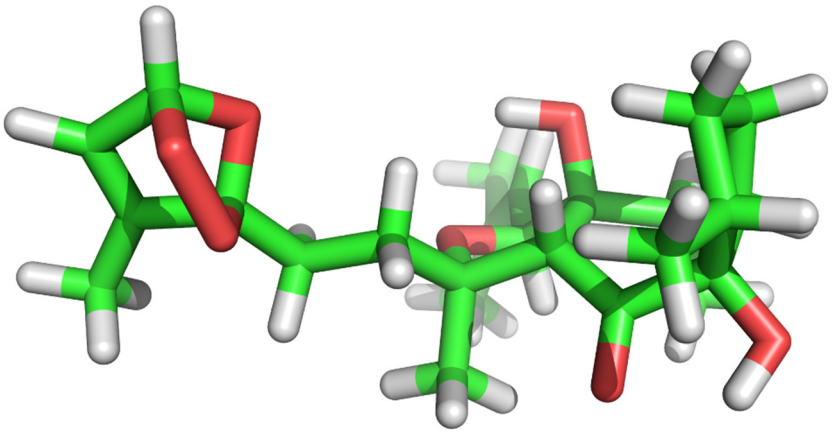
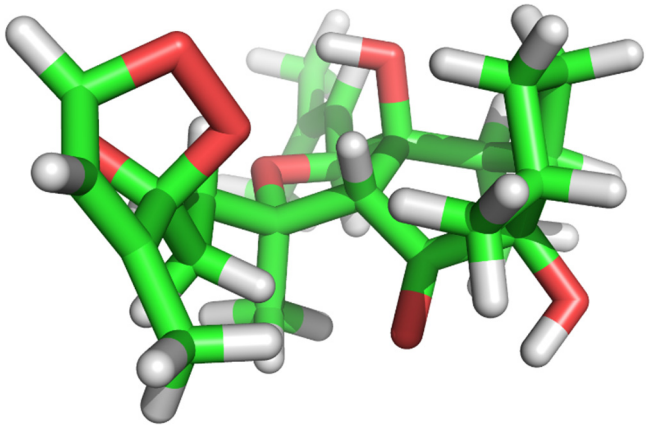
C 0	1.311200	0.528700	2.253600
C 0	-1.071300	0.880800	2.900400
O 0	-1.369200	-1.912800	2.344000
O 0	-0.477100	0.377100	-1.671300
C 0	2.498500	1.080700	1.436600
O 0	2.869000	-1.674800	-0.923100
C 0	3.055800	-0.460500	-1.703300
C 0	4.474300	0.001300	-1.472100
C 0	4.474600	0.478100	-0.220800
O 0	2.871400	-1.143000	0.455100
C 0	3.016800	0.300900	0.246500
O 0	2.285400	0.480600	-0.970100
C 0	5.607800	0.897400	0.655200
H 0	0.342500	-0.806600	0.214500
H 0	-3.602700	-2.092700	-1.223700

H	0	-2.881500	0.239100	-1.890100
H	0	-1.689100	-4.400200	-0.702000
H	0	-0.113900	-3.722700	-2.444500
H	0	0.297100	-2.244700	-1.580000
H	0	-1.477000	-1.422500	-3.011900
H	0	-2.352800	-2.953600	-2.909900
H	0	-2.198400	1.952300	0.743100
H	0	-0.368600	-4.449800	1.433600
H	0	0.817200	-3.336500	0.726000
H	0	0.589600	-4.941400	0.028400
H	0	-4.025100	1.204000	0.068700
H	0	-4.726500	-0.369100	-0.314000
H	0	-3.644600	-0.217500	1.060900
H	0	-2.797700	-3.178400	1.758700
H	0	-1.024300	2.659100	-1.938600
H	0	-1.368300	4.798200	-2.776800
H	0	-2.652600	5.705300	-1.950600
H	0	-0.966500	6.062900	-1.596100
H	0	-2.053300	4.016900	1.432000
H	0	-1.440900	5.595900	0.932200
H	0	-3.116300	5.175900	0.599100
H	0	1.460000	-0.530000	2.488000
H	0	1.354500	1.060700	3.211100
H	0	-2.127300	0.868900	2.616800
H	0	-0.925800	0.083300	3.630300
H	0	-0.852200	1.846600	3.369200
H	0	0.425100	0.635800	-1.403400
H	0	2.261600	2.084900	1.071700
H	0	3.341000	1.183300	2.129300
H	0	2.664500	-0.643900	-2.702000
H	0	5.315100	-0.200100	-2.124400
H	0	5.473900	1.918500	1.034100
H	0	6.556600	0.856300	0.112500
H	0	5.689800	0.237300	1.528800

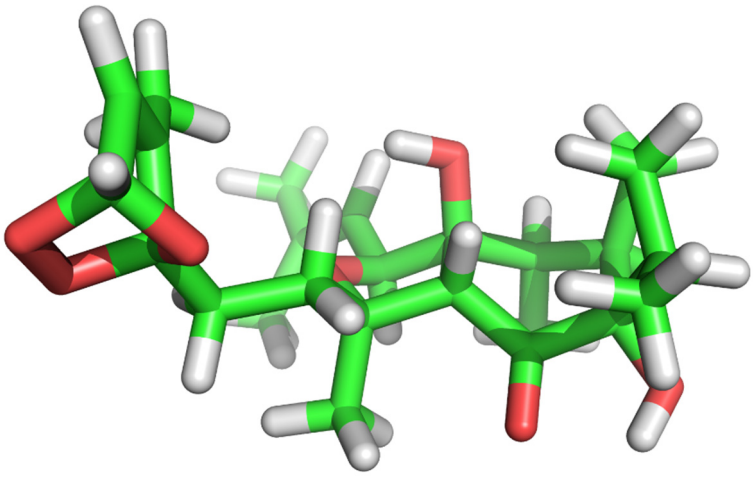
Further structures within 1.50 kcal/mol relative energy with respect to the found global minimum conformer **18'** are depicted below:



Relative energy: +0.83 kcal/mol



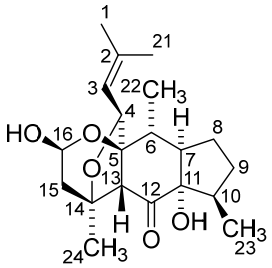
Relative energy: +0.84 kcal/mol



Relative energy: +1.25 kcal/mol

6.3.4 Comparison of ^{1}H and ^{13}C NMR data

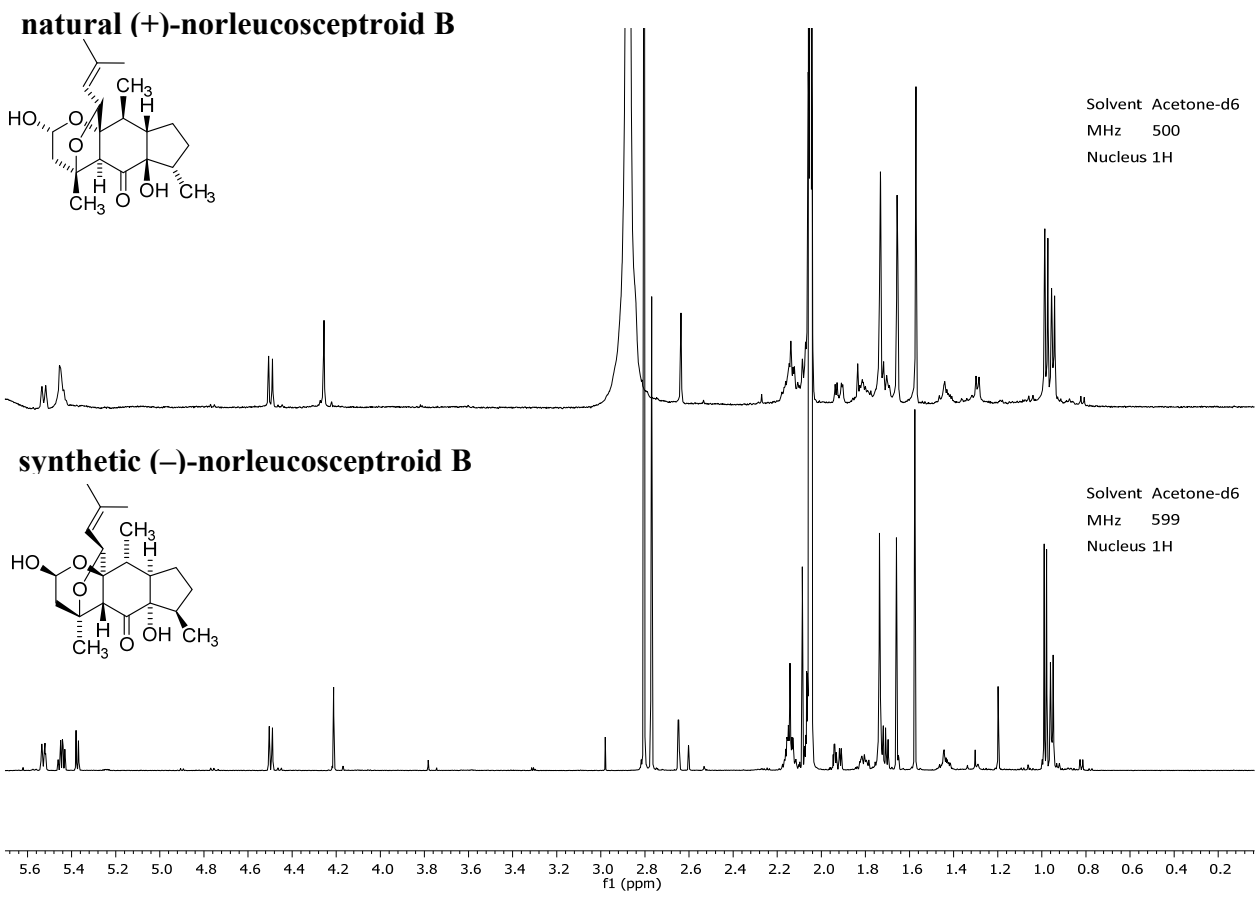
Natural[30] and synthetic norleucosceptroid B

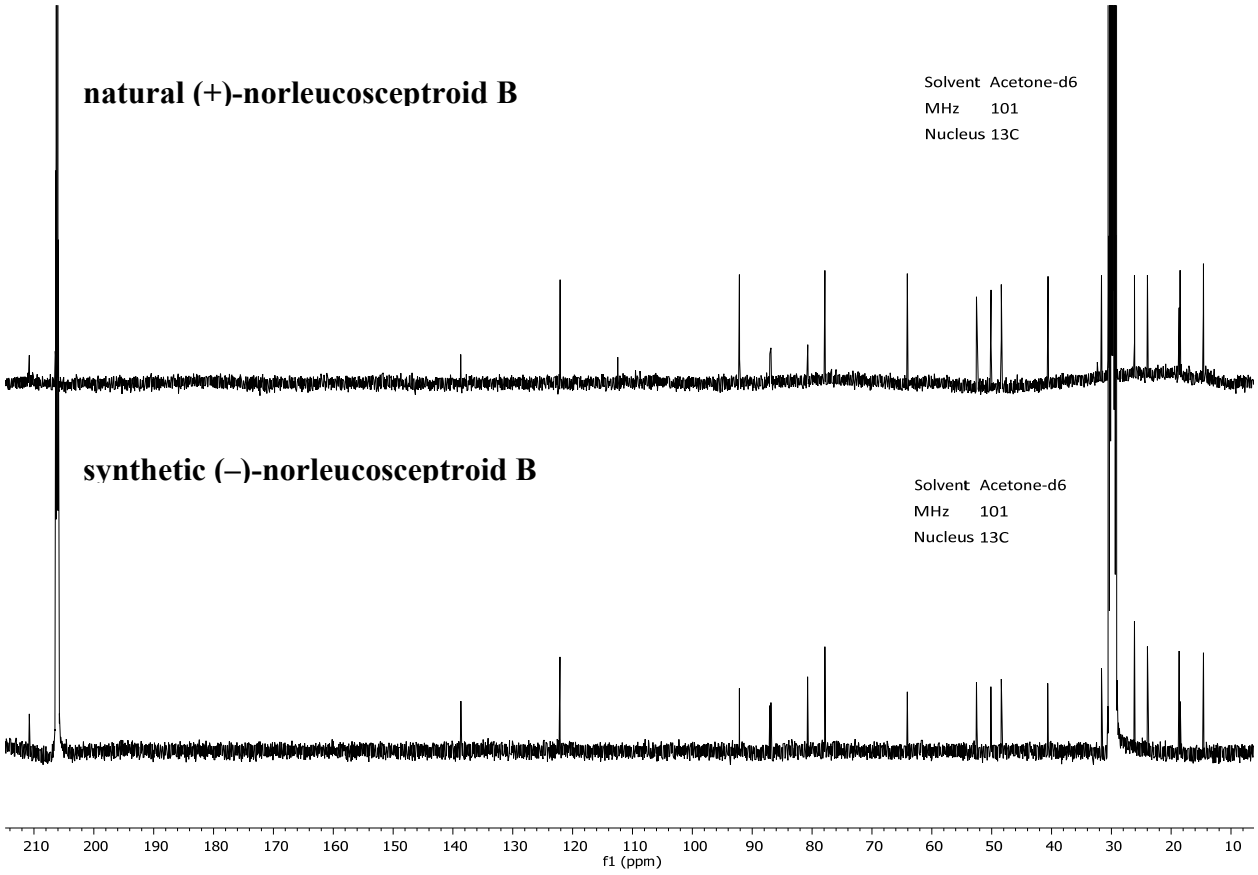


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.65 (s, 3H)	1.66 (d, 1.3, 3H)	0.01
3	5.51 (d, 8.5)	5.53 (d, 8.8)	0.02
4	4.49 (d, 8.5)	4.50 (d, 8.6)	0.01
6	2.06 (m)	2.07–2.03 (m)	
7	1.79 (m)	1.83–1.78 (m)	
8α	1.71 (m)	1.75–1.71 (m)	
8β	2.13 (m)	2.16–2.11 (m)	
9α	1.43 (m)	1.46–1.41 (m)	
9β	2.13 (m)	2.16–2.11 (m)	
10	2.14 (m)	2.16–2.13 (m)	
11-OH	4.25 (s)	4.24 (s)	0.01
13	2.63 (s)	2.64 (s)	0.01
15a	1.69 (m)	1.73–1.68 (m)	
15b	1.91 (m)	1.95–1.88 (m)	
16	5.43 (d, 3.5)	5.47–5.42 (m)	
16-OH	5.44 (s)	5.41 (d, 6.4)	0.03
21	1.72 (s, 3H)	1.73 (d, 3H)	0.01
22	0.97 (d, 7.0, 3H)	0.98 (d, 6.8, 3H)	0.01
23	0.94 (d, 7.5, 3H)	0.95 (d, 7.2, 3H)	0.01
24	1.56 (s, 3H)	1.57 (s, 3H)	0.01

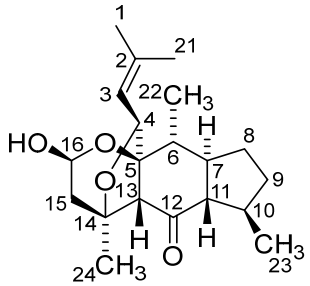
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.6	18.7	0.1
2	138.7	138.7	0
3	122.1	122.1	0
4	77.8	77.9	0.1
5	87.0	87.0	0
6	40.6	40.6	0
7	52.5	52.5	0
8	30.5	30.5	0
9	31.6	31.6	0
10	48.4	48.4	0
11	86.9	86.9	0
12	210.8	210.8	0
13	64.0	64.1	0.1
14	80.7	80.7	0
15	50.1	50.1	0
16	92.1	92.2	0.1
21	26.1	26.1	0
22	14.6	14.6	0
23	18.5	18.5	0
24	23.9	24.0	0.1

[30] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768.


natural (+)-norleucosceptroid B
Solvent Acetone-d6
MHz 500
Nucleus 1H
synthetic (–)-norleucosceptroid B
Solvent Acetone-d6
MHz 599
Nucleus 1H
f1 (ppm)


natural (+)-norleucosceptroid B
Solvent Acetone-d6
MHz 101
Nucleus 13C
synthetic (–)-norleucosceptroid B
Solvent Acetone-d6
MHz 101
Nucleus 13C
f1 (ppm)

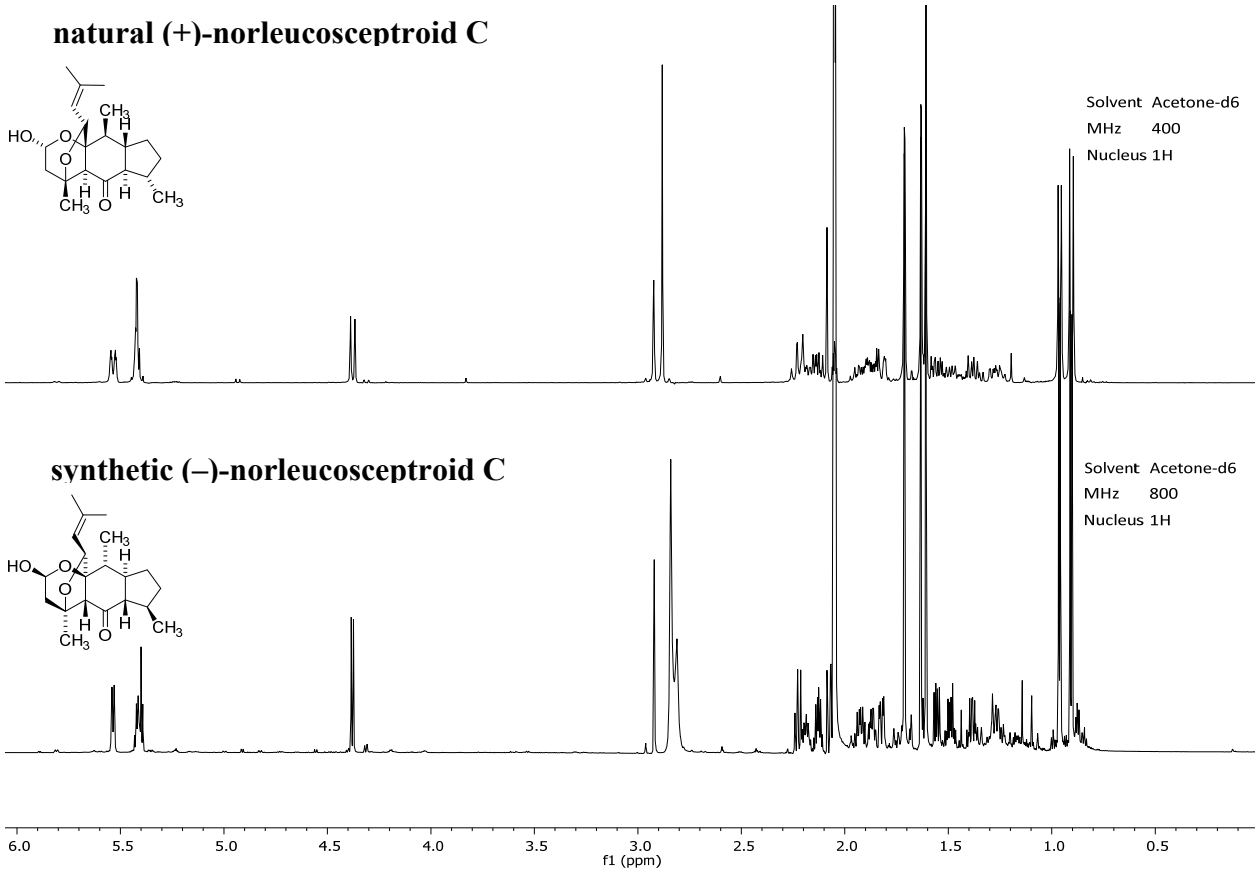
Natural[31] and synthetic norleucosceptroid C

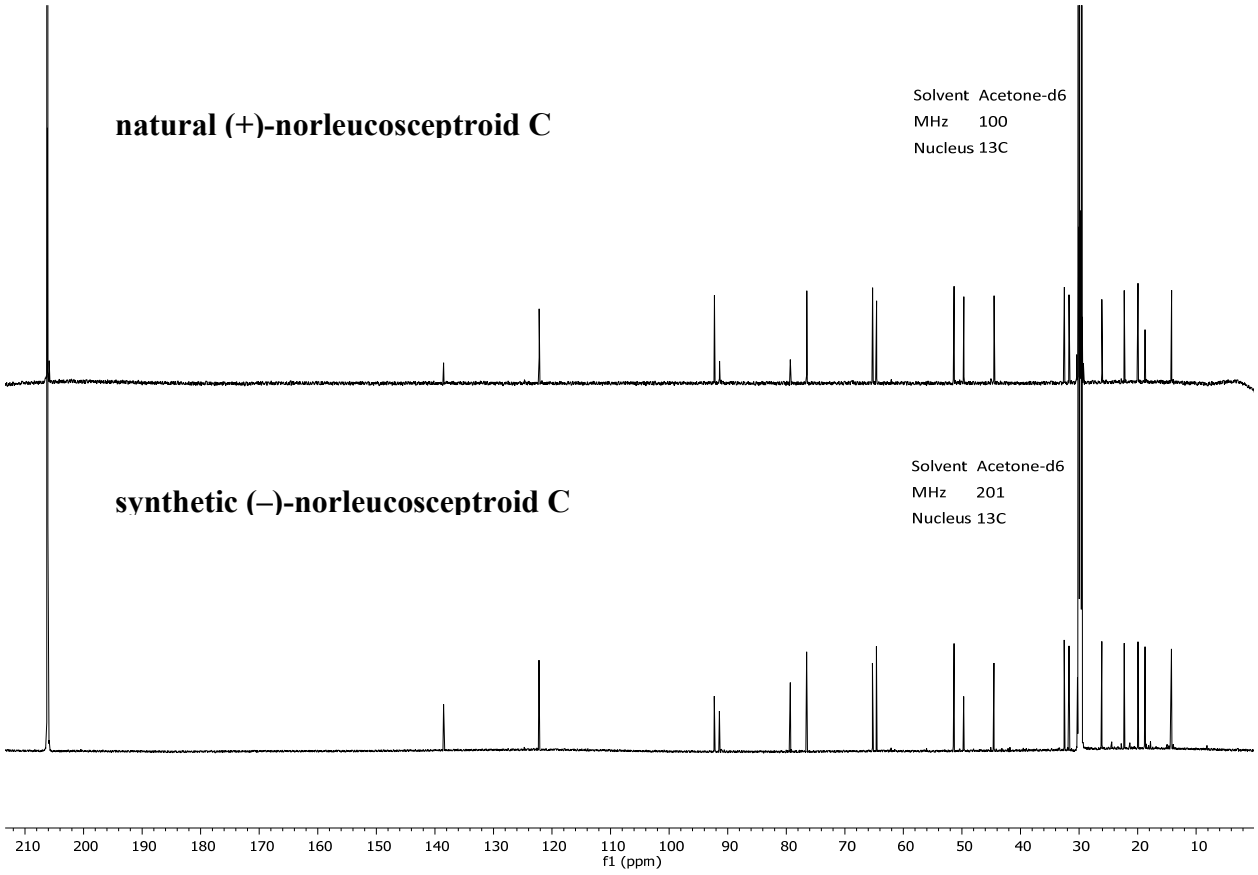


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (800 MHz, acetone-d6)	Δδ (ppm)
1	1.63 (s, 3H)	1.63 (s, 3H)	0
3	5.53, (br d, 8.4)	5.54 (d, 8.5)	0.01
4	4.38 (d, 8.4)	4.38 (d, 8.5)	0
6	2.12 (m)	2.16–2.10 (m)	
7	1.48 (m)	1.52–1.45 (m)	
8α	1.37 (m)	1.41–1.35 (m)	
8β	1.86 (m)	1.90–1.84 (m)	
9α	1.26 (m)	1.30–1.23 (m)	
9β	1.92 (m)	1.96–1.60 (m)	
10	2.19 (m)	2.25–2.16 (m)	
11	2.21 (m)	2.25–2.16 (m)	
13	2.92 (s)	2.92 (s)	0
15a	1.52 (m)	1.57–1.54 (m)	
15b	1.82 (m)	1.84–1.80 (m)	
16	5.42 (d, 4.0)	5.44–5.38 (m)	
16-OH	5.40 (s)	5.44–5.38 (m)	
21	1.71 (s, 3H)	1.71 (s, 3H)	0
22	0.90 (d, 7.1, 3H)	0.91 (d, 7.1, 3H)	0.01
23	0.96 (d, 6.2, 3H)	0.96 (d, 6.4, 3H)	0
24	1.61 (s, 3H)	1.61 (s, 3H)	0

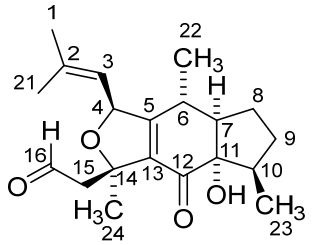
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (200 MHz, acetone-d6)	Δδ (ppm)
1	18.7	18.7	0
2	138.5	138.5	0
3	122.2	122.2	0
4	76.5	76.5	0
5	91.4	91.4	0
6	44.5	44.5	0
7	51.3	51.4	0.1
8	30.1	30.1	0
9	31.7	31.7	0
10	32.5	32.5	0
11	64.6	64.6	0
12	205.9	205.9	0
13	65.2	65.3	0.1
14	79.3	79.3	0
15	49.7	49.7	0
16	92.2	92.3	0.1
21	26.1	26.1	0
22	14.2	14.2	0
23	19.9	20.0	0.1
24	22.2	22.3	0.1

[31] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768.


natural (+)-norleucosceptroid C
Solvent Acetone-d6
MHz 400
Nucleus 1H
synthetic (–)-norleucosceptroid C
Solvent Acetone-d6
MHz 800
Nucleus 1H
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


natural (+)-norleucosceptroid C
Solvent Acetone-d6
MHz 100
Nucleus 13C
synthetic (–)-norleucosceptroid C
Solvent Acetone-d6
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Natural[32] and synthetic norleucosceptroid G

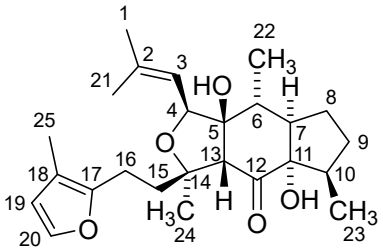


1H Position	Natural (400 MHz, acetone-d6)	Synthetic (400 MHz, acetone-d6)	Δδ (ppm)
1	1.84 (s, 3H)	1.82 (s, 3H)	0.02
3	5.18 (d, 9.7)	5.15 (d, 9.8)	0.03
4	5.73 (d, 9.8)	5.70 (d, 9.8)	0.03
6	2.39 (m)	2.41–2.32 (m)	
7	2.17 (m)	2.22–2.08 (m)	
8α	1.71 (m)	1.75–1.64 (m)	
8β	2.18 (m)	2.22–2.08 (m)	
9α	1.44 (m)	1.45–1.35 (m)	
9β	2.19 (m)	2.22–2.08 (m)	
10	2.19 (m)	2.22–2.08 (m)	
11-OH	4.25 (s)	4.18 (s)	0.07
15a	2.69 (dd, 15.4, 3.2)	2.69 (dd, 15.4, 3.2)	0
15b	2.76 (dd, 15.4, 2.7)	2.76 (dd, 15.4, 2.6)	0
16	9.75 (s)	9.73 (t, 3.0)	0.02
21	1.79 (s, 3H)	1.77 (s, 3H)	0.02
22	1.16 (d, 7.0, 3H)	1.14 (d, 6.9, 3H)	0.02
23	0.86 (d, 6.6, 3H)	0.87 (d, 6.7, 3H)	0.01
24	1.49 (s, 3H)	1.47 (s, 3H)	0.02

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.4	18.3	0.1
2	139.6	139.5	0.1
3	122.9	122.8	0.1
4	81.2	81.2	0
5	166.8	166.7	0.1
6	33.1	33.1	0
7	56.2	56.2	0
8	29.7	29.4	0.3
9	32.4	32.3	0.1
10	47.6	47.6	0
11	86.1	86.1	0
12	197.8	197.7	0.1
13	137.8	137.8	0
14	86.7	86.7	0
15	52.9	52.8	0.1
16	201.9	201.7	0.2
21	26.0	25.9	0.1
22	18.1	18.1	0
23	19.3	19.2	0.1
24	27.1	27.0	0.1

[32] S.H. Luo, C. L. Hugelshofer, J. Hua, S.-X. Jing, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, T. Magauer, S.H. Li, *Org. Lett.* **2014**, *16*, 16, 6416.

Natural[33] and synthetic leucosceptroid A

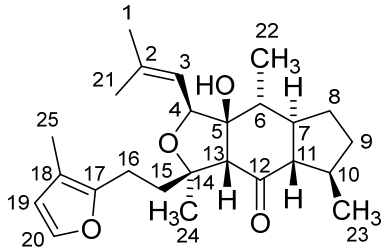


1H Position	Natural (500 MHz, $CDCl_3$)	Synthetic (400 MHz, $CDCl_3$)	Δδ (ppm)
1	1.76 (s, 3H)	1.76 (s, 3H)	0
3	5.42 (d, 8.7)	5.41 (d, 8.4)	0.01
4	4.60 (d, 8.7)	4.60 (d, 8.4)	0
5-OH	2.47 (s)	2.39 (s)	0.08
6	1.87 (m)	1.93–1.81 (m)	
7	2.11 (m)	2.27–1.98 (m)	
8α	1.82 (m)	1.93–1.81 (m)	
8β	2.16 (m)	2.27–1.98 (m)	
9α	1.50 (m)	1.55–1.44 (m)	
9β	2.01 (m)	2.27–1.98 (m)	
10	2.22 (m)	2.27–1.98 (m)	
11-OH	2.79 (s)	2.67 (s)	0.12
13	2.69 (s)	2.69 (s)	0
15	2.06 (dd, 8.1, 8.5)	2.27–1.98 (m)	
16	2.74 (dd, 8.1, 8.5)	2.74 (app t, 9.2)	0
19	6.15 (d, 1.2)	6.15 (d, 1.7)	0
20	7.21 (d, 1.2)	7.21 (d, 1.7)	0
21	1.80 (s, 3H)	1.80 (s, 3H)	0
22	0.96 (d, 6.9, 3H)	0.96 (d, 6.9, 3H)	0
23	0.86 (d, 7.3, 3H)	0.86 (d, 7.3, 3H)	0
24	1.31 (s, 3H)	1.31 (s, 3H)	0
25	1.97 (s, 3H)	1.96 (s, 3H)	0.01

13C Position	Natural (125 MHz, $CDCl_3$)	Synthetic (100 MHz, $CDCl_3$)	Δδ (ppm)
1	19.0	19.2	0.2
2	140.0	140.3	0.3
3	119.1	119.2	0.1
4	76.3	76.5	0.2
5	84.8	85.0	0.2
6	38.9	39.0	0.1
7	49.7	49.9	0.2
8	29.8	30.0	0.2
9	30.6	30.9	0.03
10	47.1	47.4	0.03
11	85.8	86.0	0.2
12	213.1	213.2	0.1
13	69.3	69.3	0
14	82.8	82.9	0.1
15	42.2	42.4	0.2
16	20.9	21.1	0.2
17	150.3	150.5	0.2
18	113.6	113.8	0.2
19	112.8	112.9	0.1
20	139.8	139.9	0.1
21	26.3	26.5	0.2
22	14.2	14.5	0.3
23	16.6	16.8	0.2
24	22.7	22.9	0.2
25	9.8	10.0	0.2

[33] S.-H. Luo, Q. Luo, X.-M. Niu, M.-J. Xie, X. Zhao, B. Schneider, J. Gershenzon, S.-H. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 4471.

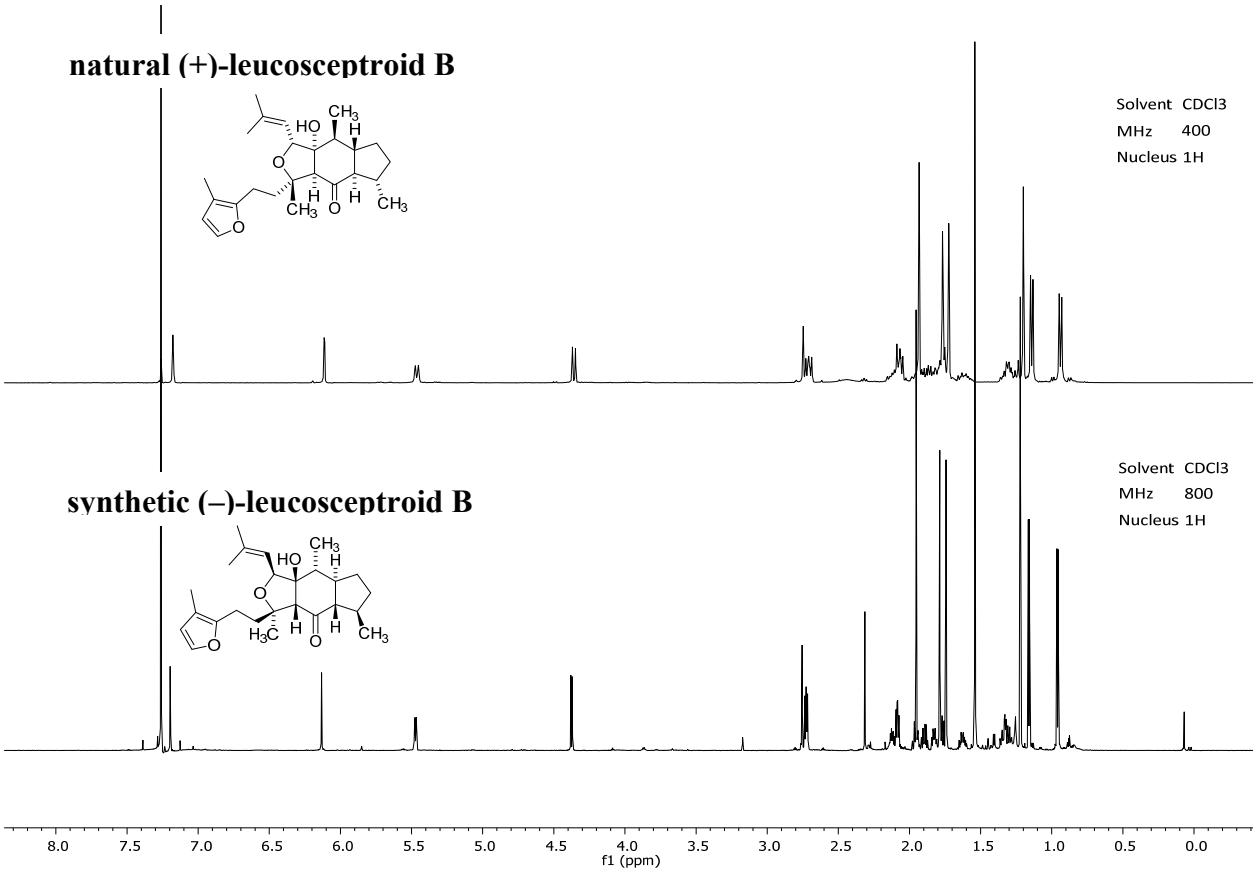
Natural[34] and synthetic leucosceptroid B

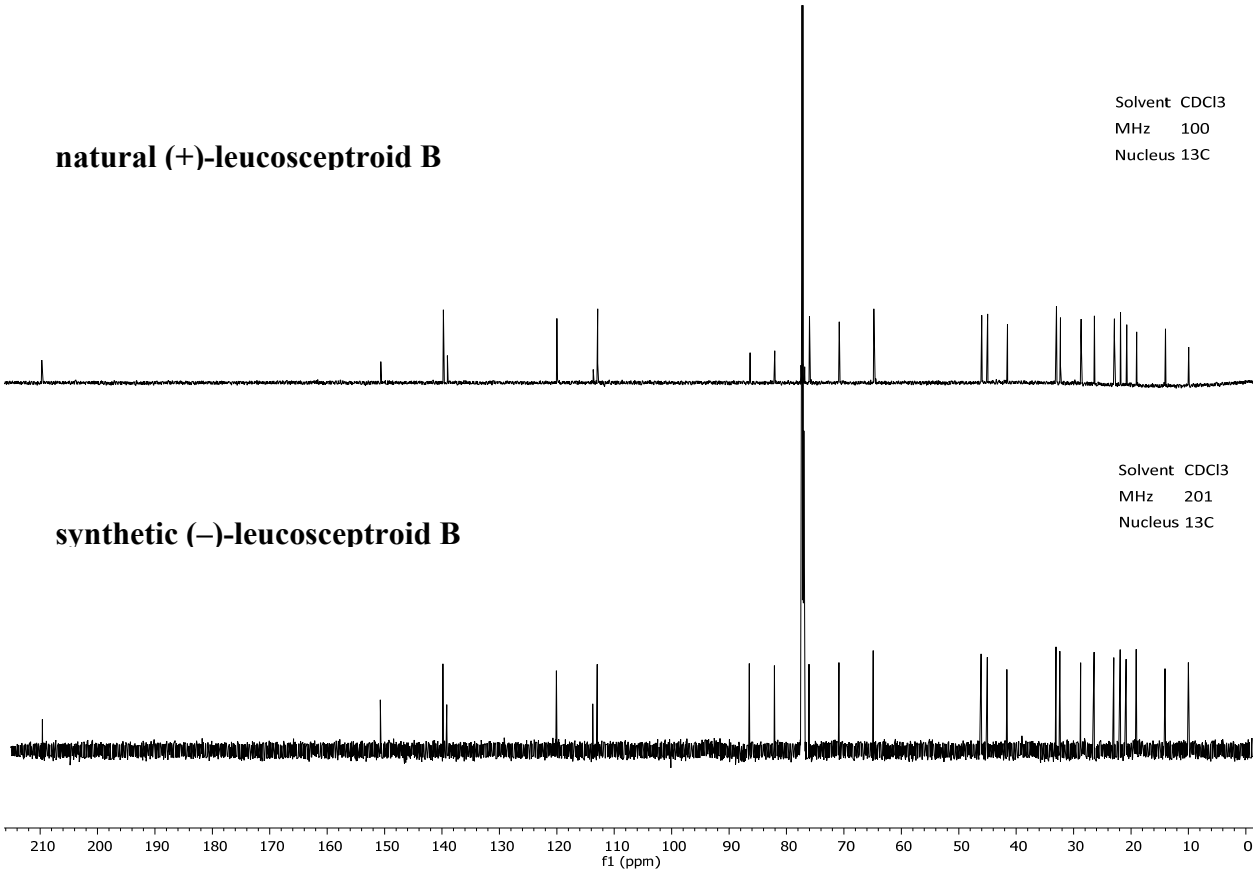


1H Position	Natural (500 MHz, $CDCl_3$)	Synthetic (800 MHz, $CDCl_3$)	Δδ (ppm)
1	1.72 (s, 3H)	1.74 (d, 1.4)	0.02
3	5.46 (d, 9.0)	5.49–5.46 (m)	
4	4.35 (d, 9.0)	4.38 (d, 8.6)	0.03
5-OH	-	2.31 (s)	
6	1.87 (m)	1.92–1.87 (m)	
7	1.61 (m)	1.66–1.59 (m)	
8α	1.28 (m)	1.37–1.29 (m)	
8β	1.81 (m)	1.85–1.80 (m)	
9α	1.31 (m)	1.37–1.29 (m)	
9β	1.93 (m)	1.98–1.93 (m)	
10	2.11 (m)	2.15–2.10 (m)	
11	1.76 (m)	1.78–1.75 (m)	
13	2.74 (s)	2.76 (s)	0.02
15	2.07 (t, 8.6)	2.10–2.06 (m)	
16	2.71 (t, 8.6)	2.75–2.71 (m)	
19	6.10 (d, 1.5)	6.13 (d, 1.8)	0.03
20	7.16 (d, 1.5)	7.20 (d, 1.8)	0.04
21	1.77 (s, 3H)	1.79 (d, 1.4)	0.02
22	0.94 (d, 7.0, 3H)	0.96 (d, 7.1, 3H)	0.02
23	1.14 (d, 6.5, 3H)	1.16 (d, 6.7, 3H)	0.02
24	1.20 (s, 3H)	1.22 (s, 3H)	0.02
25	1.93 (s, 3H)	1.95 (s, 3H)	0.02

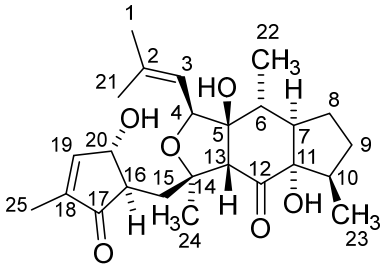
13C Position	Natural (125 MHz, $CDCl_3$)	Synthetic (200 MHz, $CDCl_3$)	Δδ (ppm)
1	18.8	19.1	0.3
2	138.8	139.2	0.4
3	119.9	120.1	0.2
4	75.8	76.1	0.3
5	86.2	86.5	0.3
6	44.8	45.0	0.2
7	45.8	46.1	0.3
8	28.5	28.8	0.3
9	32.1	32.4	0.3
10	32.8	33.1	0.3
11	64.6	64.9	0.3
12	209.4	209.6	0.2
13	70.7	70.9	0.2
14	81.9	82.1	0.2
15	41.4	41.6	0.2
16	20.6	20.9	0.3
17	150.5	150.7	0.2
18	133.4	113.7	0.3
19	112.7	113.0	0.3
20	139.6	139.8	0.2
21	26.1	26.4	0.3
22	13.8	14.1	0.3
23	21.6	21.9	0.3
24	22.6	23.0	0.4
25	9.7	10.0	0.3

[34] S.-H. Luo, Q. Luo, X.-M. Niu, M.-J. Xie, X. Zhao, B. Schneider, J. Gershenzon, S.-H. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 4471.


natural (+)-leucosceptroid B
Solvent CDCl3
MHz 400
Nucleus 1H
synthetic (–)-leucosceptroid B
Solvent CDCl3
MHz 800
Nucleus 1H
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


natural (+)-leucosceptroid B
Solvent CDCl3
MHz 100
Nucleus 13C
synthetic (–)-leucosceptroid B
Solvent CDCl3
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

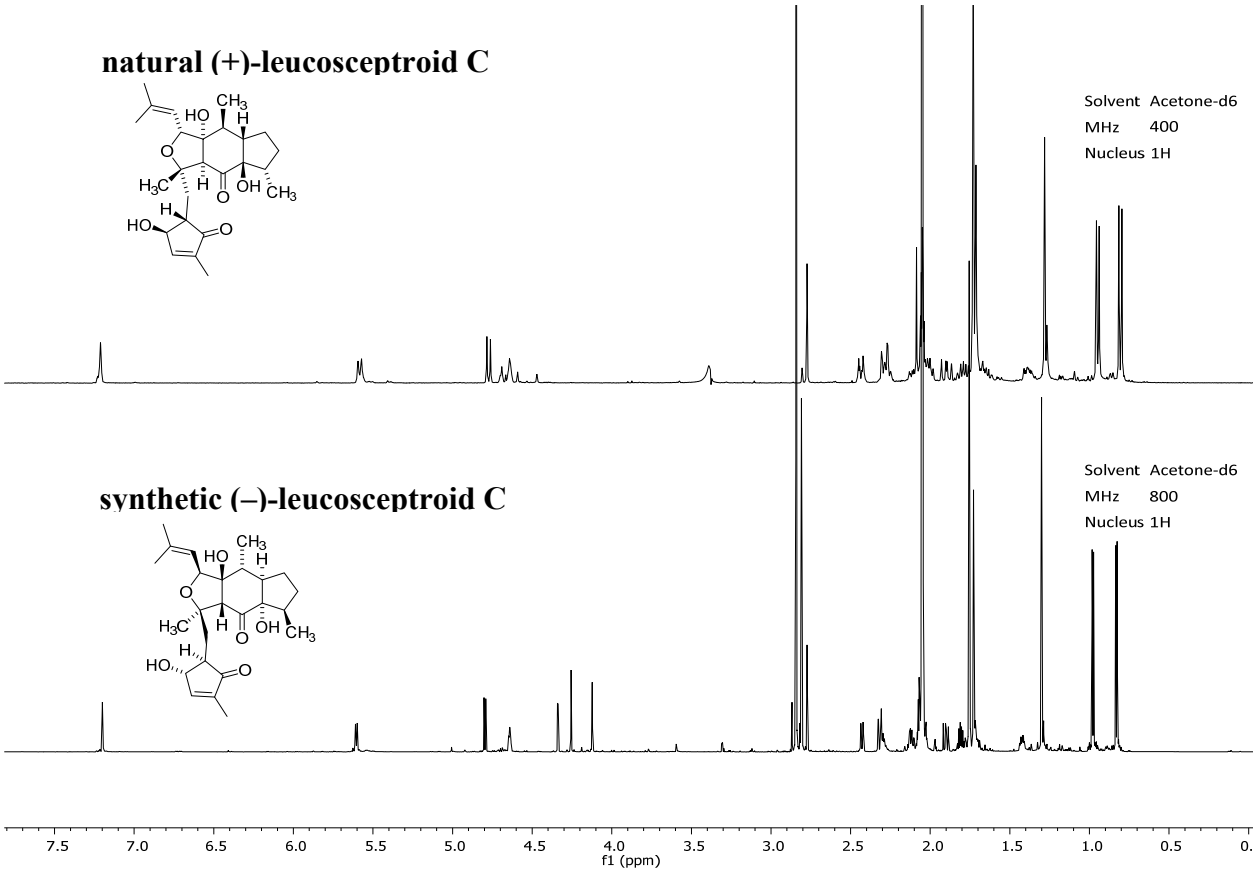
Natural[35] and synthetic leucosceptroid C

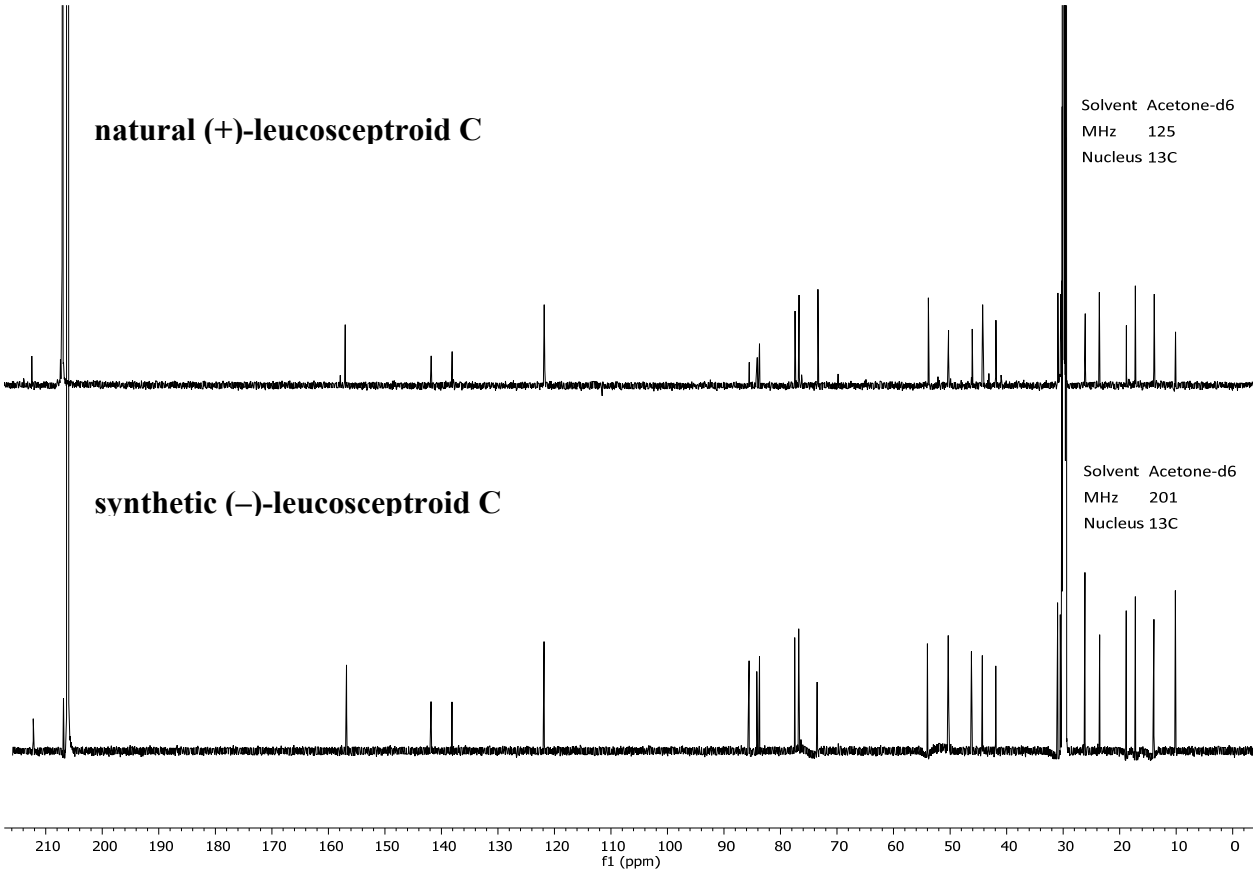


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (800 MHz, acetone-d6)	Δδ (ppm)
1	1.72 (s, 3H)	1.76 (s, 3H)	0.04
3	5.57 (d, 8.8)	5.62–5.59 (m)	
4	4.76 (d, 8.8)	4.80 (d, 8.8)	0.04
5-OH	4.46 (s)	4.12 (s)	0.34
6	1.78 (m)	1.83–1.79 (m)	
7	2.00 (m)	2.09–2.04 (m)	
8α	1.64 (m)	1.72–1.67 (m)	
8β	2.08 (m)	2.15–2.09 (m)	
9α	1.38 (m)	1.44–1.40 (m)	
9β	2.03 (m)	2.09–2.04 (m)	
10	2.25 (m)	2.30–2.27 (m)	
11-OH	4.58 (s)	4.26 (s)	0.32
13	2.76 (s)	2.77 (s)	0.01
15a	2.28 (dd, 14.0, 2.5)	2.32 (dd, 14.2, 2.3)	0.04
15b	1.89 (dd, 14.0, 10.5)	1.90 (dd, 14.2, 11.2)	0.01
16	2.43 (dt, 10.5, 2.5)	2.43 (app dt, 11.2, 2.3)	0
19	7.20 (br s)	7.21–7.19 (m)	
20	4.63 (br s)	4.65–4.62 (m)	
20-OH	4.68 (d, 2.8)	4.34 (d, 3.7)	0.34
21	1.72 (s, 3H)	1.76 (s, 3H)	0.04
22	0.94 (d, 6.8, 3H)	0.98 (d, 6.8, 3H)	0.04
23	0.79 (d, 7.4, 3H)	0.83 (d, 7.3, 3H)	0.04
24	1.27 (s, 3H)	1.30 (s, 3H)	0.03
25	1.70 (br s, 3H)	1.73 (app t, 1.8, 3H)	0.03

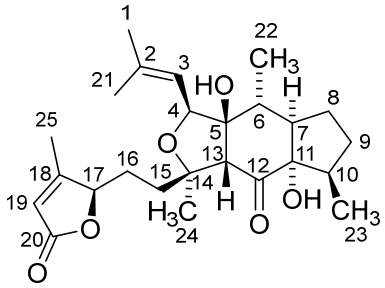
[35] S.-H. Luo, L.-H. Weng, M.-J. Xie, X.-N. Li, J. Hua, X. Zhao, S.-H. Li, *Org. Lett.* **2011**, *13*, 1864.

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (200 MHz, acetone-d6)	Δδ (ppm)
1	18.8	18.8	0
2	138.0	138.1	0.1
3	121.8	121.9	0.1
4	77.4	77.5	0.1
5	84.1	84.2	0.1
6	41.8	41.9	0.1
7	50.2	50.3	0.1
8	30.4	30.5	0.1
9	30.9	31.0	0.1
10	46.0	46.2	0.2
11	85.5	85.6	0.1
12	212.5	212.2	0.3
13	73.3	73.5	0.2
14	83.7	83.7	0
15	44.2	44.3	0.1
16	53.8	54.0	0.2
17	207.4	206.9	0.5
18	141.8	141.8	0
19	157.0	156.8	0.2
20	76.7	76.8	0.1
21	26.0	26.1	0.1
22	13.8	13.9	0.1
23	17.2	17.2	0
24	23.6	23.5	0.1
25	10.0	10.1	0.1


natural (+)-leucosceptroid C
Solvent Acetone-d6
MHz 400
Nucleus 1H
synthetic (–)-leucosceptroid C
Solvent Acetone-d6
MHz 800
Nucleus 1H
f1 (ppm)


natural (+)-leucosceptroid C
Solvent Acetone-d6
MHz 125
Nucleus 13C
synthetic (–)-leucosceptroid C
Solvent Acetone-d6
MHz 201
Nucleus 13C
f1 (ppm)

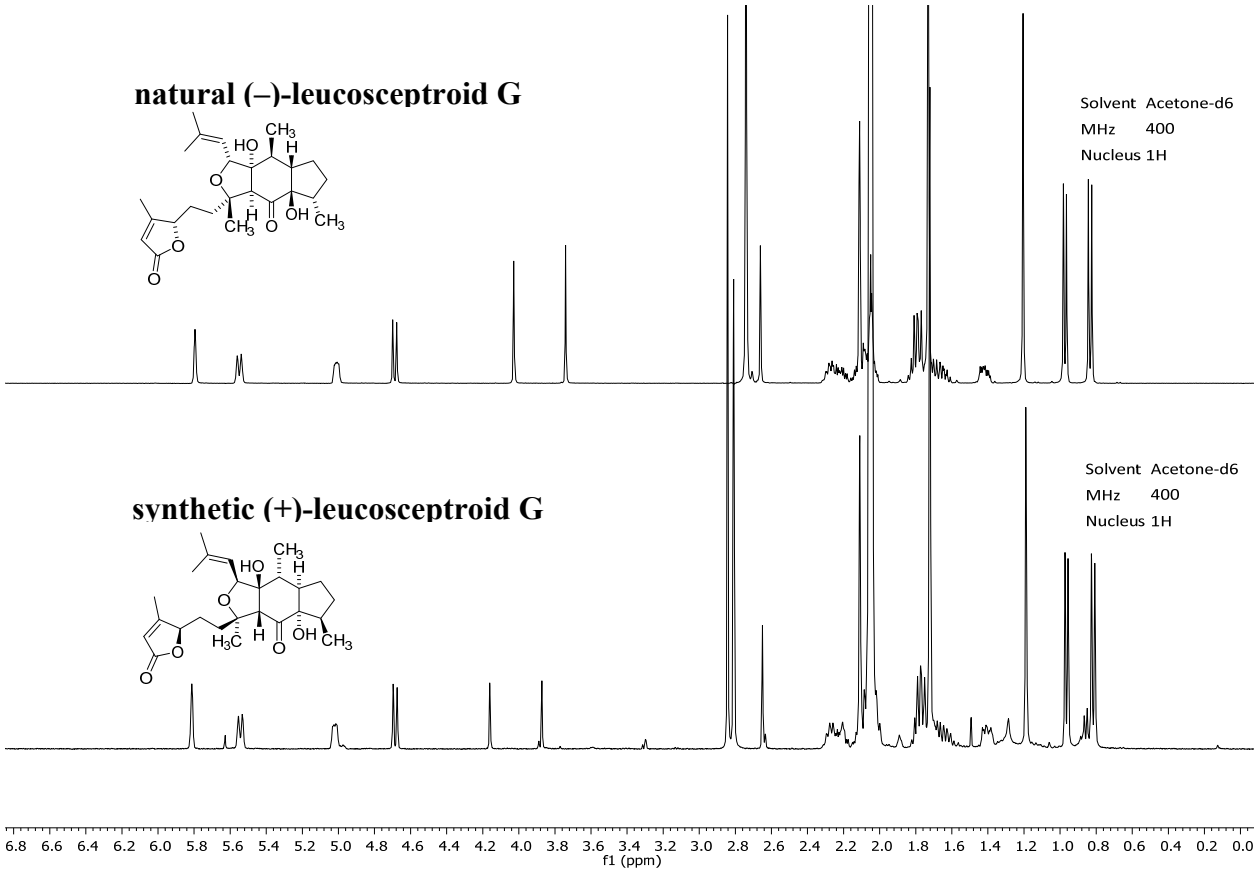
Natural[36] and synthetic leucosceptroid G

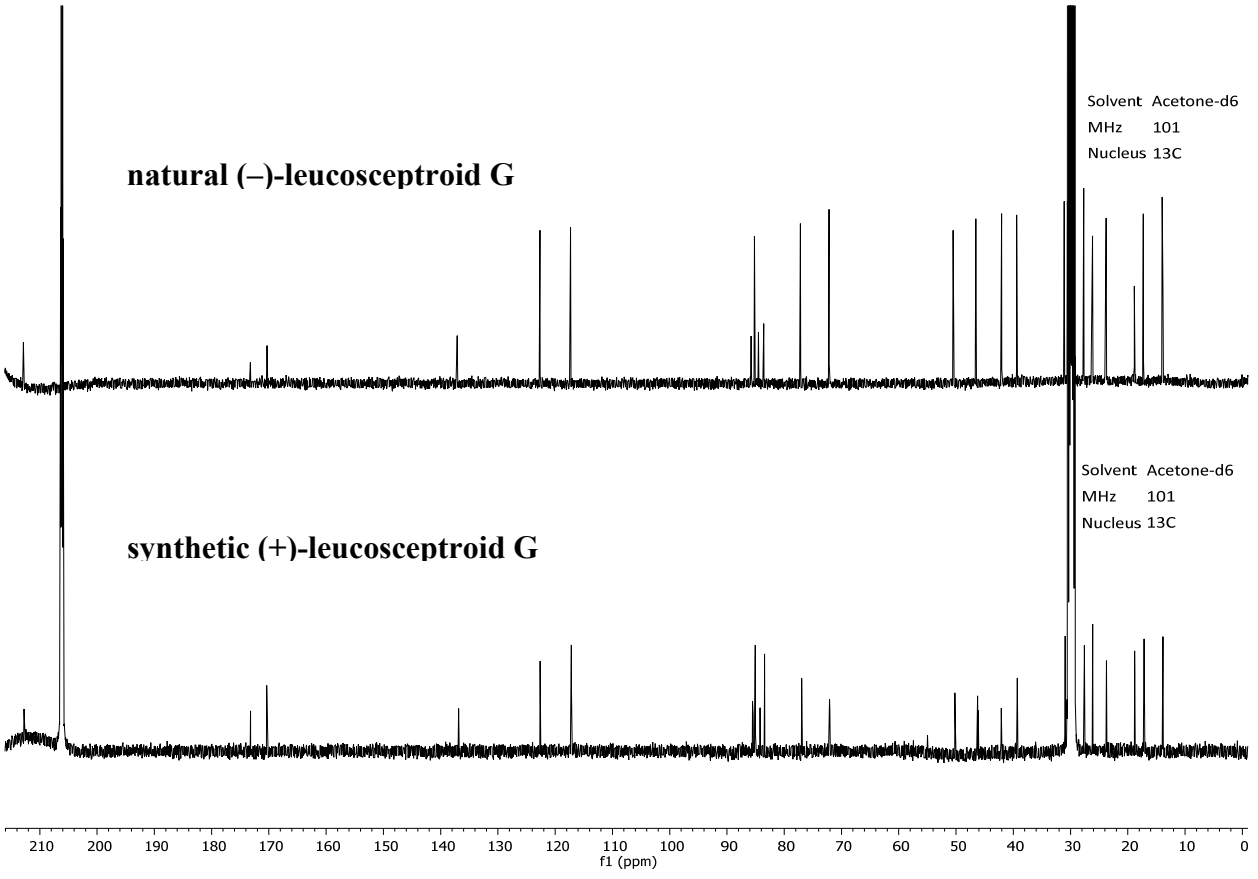


1H Position	Natural (400 MHz, acetone-d6)	Synthetic (400 MHz, acetone-d6)	Δδ (ppm)
1	1.71 (s, 3H)	1.72 (s, 3H)	0.01
3	5.54 (d, 8.8)	5.54 (d, 8.9)	0
4	4.68 (d, 8.8)	4.69 (d, 8.9)	0.01
5-OH	3.73 (s)	3.87 (s)	0.14
6	1.78 (m)	1.83–1.74 (m)	
7	2.01 (m)	2.06–1.98 (m)	
8α	1.69 (m)	1.69–1.59 (m)	
8β	2.09 (m)	2.14–2.09 (m)	
9α	1.40 (m)	1.46–1.35 (m)	
9β	2.03 (m)	2.06–1.98 (m)	
10	2.27 (m)	2.32–2.18 (m)	
11-OH	4.02 (s)	4.16 (s)	0.14
13	2.65 (s)	2.65 (s)	0
15a	1.76 (m)	1.83–1.74 (m)	
15b	-	1.83–1.74 (m)	
16a	1.63 (m)	1.69–1.59 (m)	
16b	2.20 (m)	2.32–2.18 (m)	
17	5.00 (br s)	5.05–4.99 (m)	
19	5.78 (br s)	5.83–5.80 (m)	
21	1.71 (s, 3H)	1.72 (s, 3H)	0.01
22	0.96 (d, 6.8, 3H)	0.96 (d, 6.8, 3H)	0
23	0.82 (d, 7.3, 3H)	0.82 (d, 7.4, 3H)	0
24	1.20 (s, 3H)	1.19 (s, 3H)	0.01
25	2.11 (br s, 3H)	2.11 (br s, 3H)	0

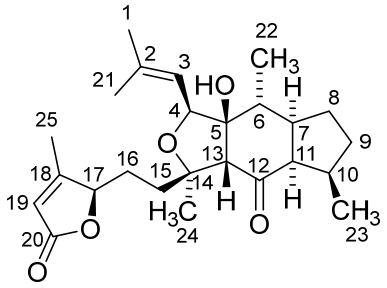
[36] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

13C Position	Natural (100 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.8	18.8	0
2	137.1	136.9	0.2
3	122.6	122.6	0
4	77.1	76.9	0.2
5	84.5	84.2	0.3
6	42.0	42.1	0.1
7	50.5	50.2	0.3
8	30.5	30.5	0
9	31.1	30.9	0.2
10	46.5	46.2	0.3
11	85.8	85.5	0.3
12	212.8	212.8	0
13	72.1	72.1	0
14	83.6	83.4	0.2
15	39.4	39.3	0.1
16	27.7	27.6	0.1
17	85.2	85.1	0.1
18	170.3	170.4	0.1
19	117.3	117.2	0.1
20	173.2	173.2	0
21	26.1	26.1	0
22	14.0	13.9	0.1
23	17.3	17.2	0.1
24	23.8	23.7	0.1
25	13.8	13.9	0.1


natural (–)-leucosceptroid G
Solvent Acetone-d6
MHz 400
Nucleus 1H
synthetic (+)-leucosceptroid G
Solvent Acetone-d6
MHz 400
Nucleus 1H
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0
f1 (ppm)


natural (–)-leucosceptroid G
Solvent Acetone-d6
MHz 101
Nucleus 13C
synthetic (+)-leucosceptroid G
Solvent Acetone-d6
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

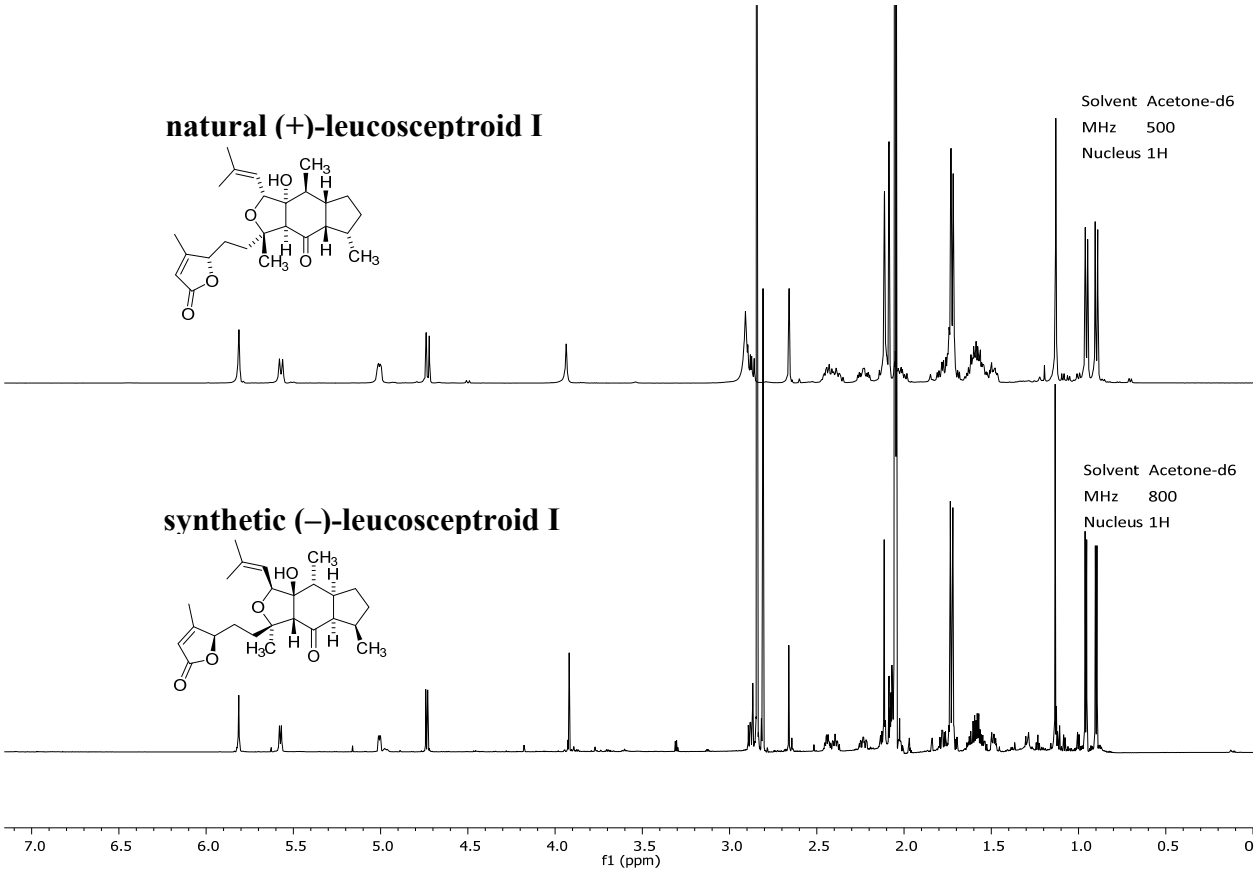
Natural[37] and synthetic leucosceptroid I

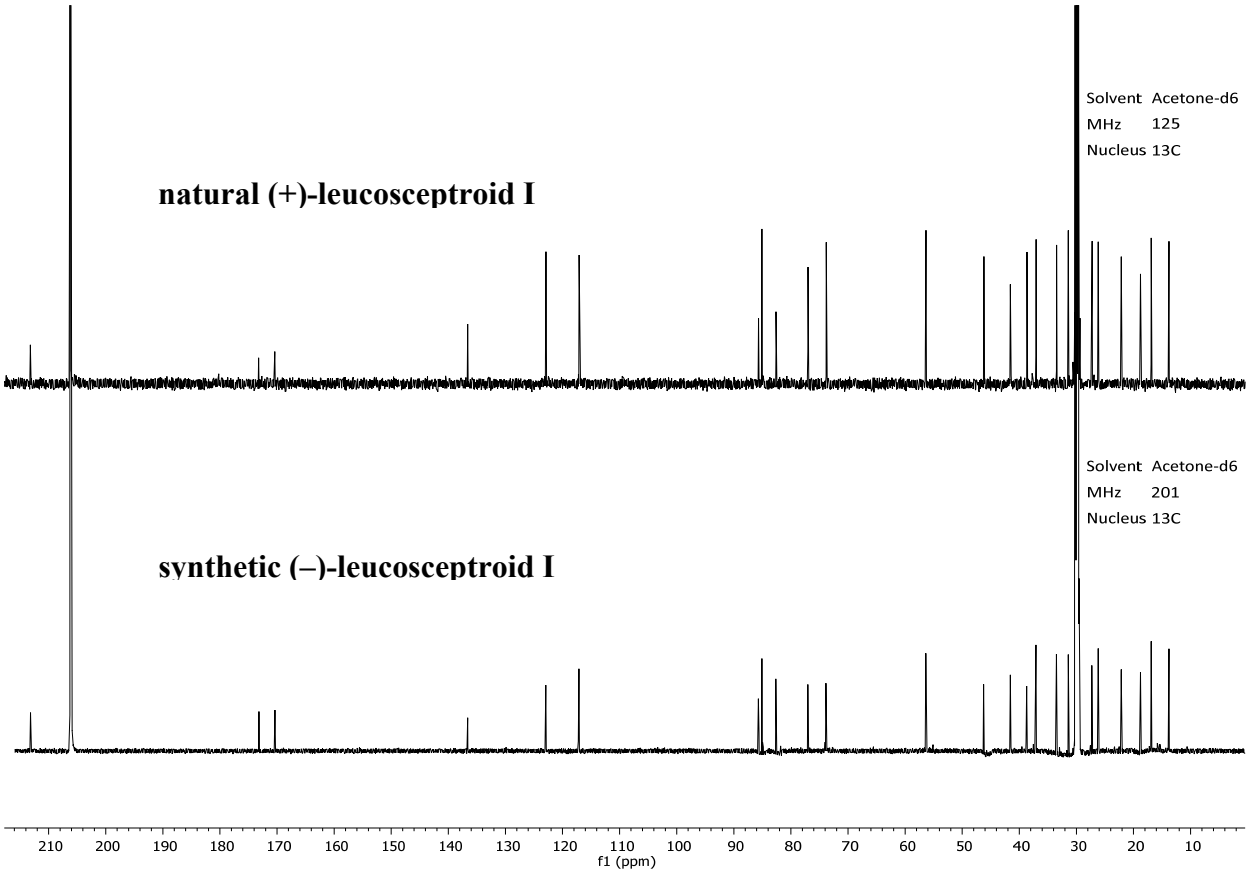


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (800 MHz, acetone-d6)	Δδ (ppm)
1	1.72 (d, 1.0, 3H)	1.72 (d, 1.3, 3H)	0
3	5.56 (d, 9.0)	5.59–5.56 (m)	
4	4.72 (d, 9.0)	4.74 (d, 8.8)	0.02
5-OH	3.93 (s)	3.92 (s)	0.01
6	1.58 (m)	1.64–1.51 (m)	
7	2.38 (m)	2.42–2.36 (m)	
8α	1.53 (m)	1.64–1.51 (m)	
8β	2.01 (m)	2.04–2.01 (m)	
9α	1.47 (m)	1.51–1.46 (m)	
9β	1.60 (m)	1.64–1.51 (m)	
10	2.42 (m)	2.47–2.42 (m)	
11	2.87 (dd, 11.0, 7.0)	2.88 (dd, 10.9, 7.0)	0.01
13	2.65 (s)	2.66 (s)	0.01
15a	1.77 (m)	1.81–1.75 (m)	
15b	-	1.75–1.71 (m)	
16a	1.57 (m)	1.64–1.51 (m)	
16b	2.22 (m)	2.26–2.20 (m)	
17	5.00 (br s)	5.02–4.99 (m)	
19	5.80 (br s)	5.83–5.81 (m)	
21	1.71 (d, 1.5, 3H)	1.73 (d, 1.3, 3H)	0.02
22	0.94 (d, 7.0, 3H)	0.96 (d, 6.8, 3H)	0.02
23	0.89 (d, 7.5, 3H)	0.90 (d, 7.2, 3H)	0.01
24	1.12 (s, 3H)	1.13 (s, 3H)	0.01
25	2.10 (br s, 3H)	2.11 (br s, 3H)	0.01

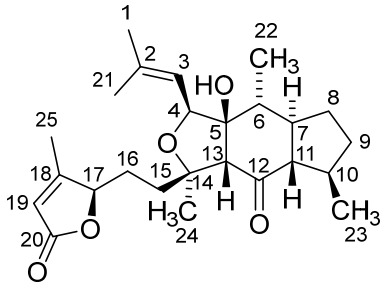
[37] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (200 MHz, acetone-d6)	Δδ (ppm)
1	18.7	18.8	0.1
2	136.6	136.6	0
3	122.9	122.9	0
4	77.0	77.0	0
5	85.6	85.7	0.1
6	46.2	46.3	0.1
7	41.5	41.6	0.1
8	31.4	31.4	0
9	33.4	33.5	0.1
10	37.0	37.1	0.1
11	56.3	56.4	0.1
12	213.2	213.2	0
13	73.8	73.9	0.1
14	82.6	82.6	0
15	38.6	38.7	0.1
16	27.2	27.3	0.1
17	85.0	85.1	0.1
18	170.4	170.4	0
19	117.1	117.1	0
20	173.2	173.2	0
21	26.1	26.2	0.1
22	13.8	13.9	0.1
23	16.9	16.9	0
24	22.1	22.1	0
25	13.7	13.8	0.1


natural (+)-leucosceptroid I
Solvent Acetone-d6
MHz 500
Nucleus 1H
synthetic (–)-leucosceptroid I
Solvent Acetone-d6
MHz 800
Nucleus 1H
f1 (ppm)


natural (+)-leucosceptroid I
Solvent Acetone-d6
MHz 125
Nucleus 13C
synthetic (–)-leucosceptroid I
Solvent Acetone-d6
MHz 201
Nucleus 13C
f1 (ppm)

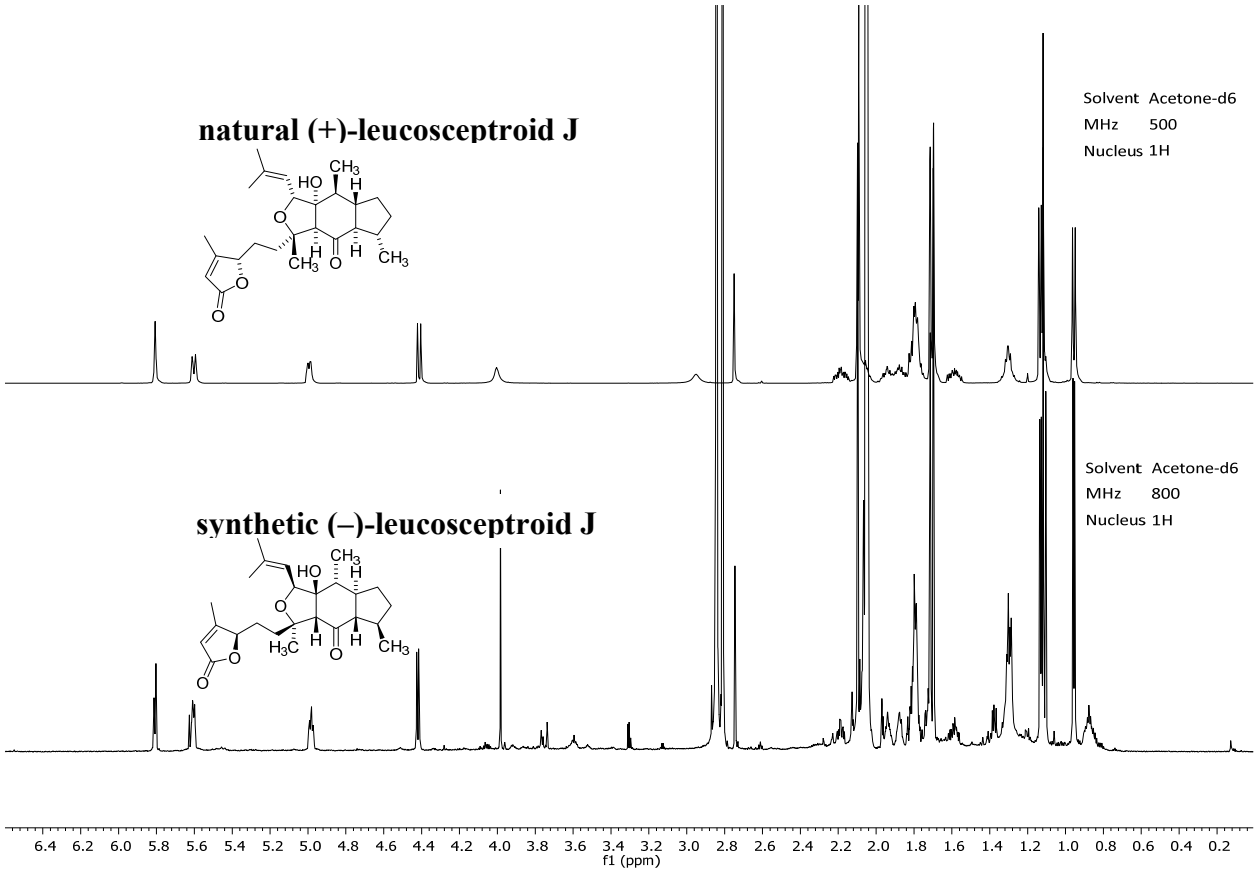
Natural[38] and synthetic leucosceptroid J

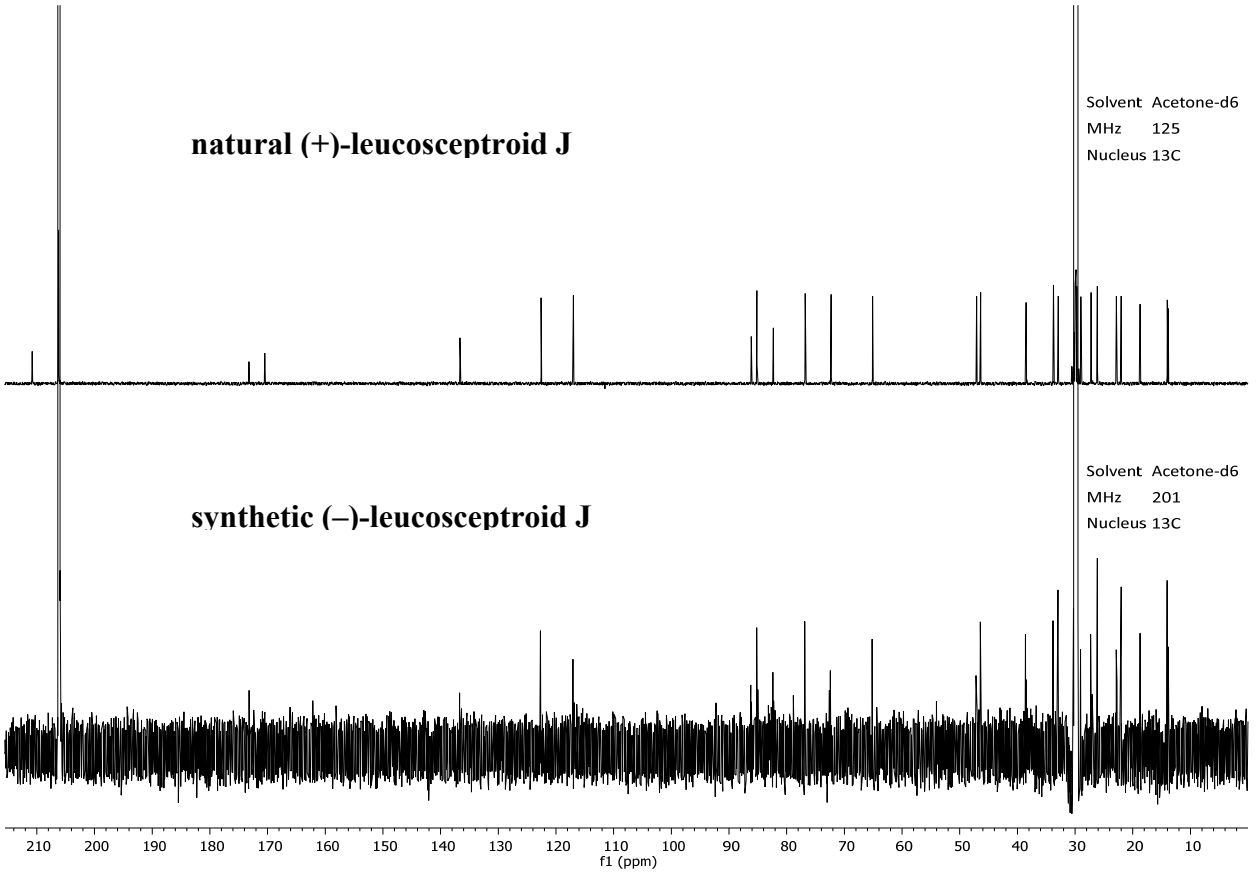


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.68 (d, 1.5, 3H)	1.70 (s, 3H)	0.02
3	5.59 (d, 8.5)	5.62–5.59 (m)	
4	4.40 (d, 8.5)	4.42 (d, 8.5)	0.02
5-OH	3.99 (s)	3.98 (s)	0.01
6	1.86 (m)	1.90–1.86 (m)	
7	1.76 (m)	1.84–1.76 (m)	
8α	1.29 (overlap)	1.34–1.26 (m)	
8β	1.78 (m)	1.84–1.76 (m)	
9α	1.29 (overlap)	1.34–1.26 (m)	
9β	1.93 (m)	1.96–1.91 (m)	
10	2.04 (m)	2.08–2.05 (m)	
11	1.77 (m)	1.84–1.76 (m)	
13	2.73 (s)	2.74 (s)	0.01
15a	1.79 (m, 2H)	1.84–1.76 (m)	
15b	-	1.84–1.76 (m)	
16a	1.57 (m)	1.62–1.55 (m)	
16b	2.17 (m)	2.22–2.16 (m)	
17	4.98 (br s)	5.01–4.96 (m)	
19	5.79 (br s)	5.83–5.79 (m)	
21	1.70 (d, 1.5, 3H)	1.72 (s, 3H)	0.02
22	0.94 (d, 7.0, 3H)	0.96 (d, 7.0, 3H)	0.02
23	1.23 (d, 7.0, 3H)	1.13 (d, 6.7, 3H)	0.1
24	1.10 (s, 3H)	1.11 (s, 3H)	0.01
25	2.08 (br s, 3H)	2.10 (s, 3H)	0.02

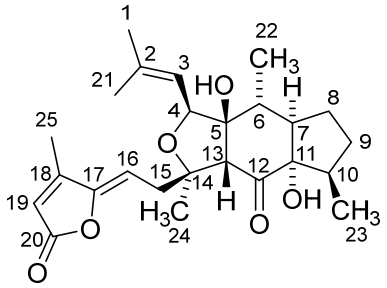
[38] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (150 MHz, acetone-d6)	Δδ (ppm)
1	18.7	18.7	0
2	136.7	136.7	0
3	122.6	122.7	0.1
4	76.8	76.9	0.1
5	86.2	86.2	0
6	47.1	47.2	0.1
7	46.4	46.4	0
8	29.0	29.1	0.1
9	32.9	33.0	0.1
10	33.8	33.8	0
11	65.1	65.2	0.1
12	210.8	210.7	0.1
13	72.3	72.4	0.1
14	82.4	82.4	0
15	38.5	38.6	0.1
16	27.2	27.3	0.1
17	85.2	85.2	0
18	170.5	170.5	0
19	117.0	117.1	0.1
20	173.3	173.2	0.1
21	26.2	26.2	0
22	14.0	14.1	0.1
23	22.0	22.0	0
24	22.8	22.9	0.1
25	13.8	13.9	0.1


natural (+)-leucosceptroid J
Solvent Acetone-d6
MHz 500
Nucleus 1H
synthetic (–)-leucosceptroid J
Solvent Acetone-d6
MHz 800
Nucleus 1H
6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)


natural (+)-leucosceptroid J
Solvent Acetone-d6
MHz 125
Nucleus 13C
synthetic (–)-leucosceptroid J
Solvent Acetone-d6
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Natural[39] and synthetic leucosceptroid K

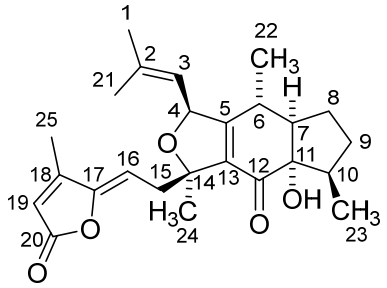


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.73 (d, 1.0, 3H)	1.76–1.73 (m, 3H)	
3	5.57 (d, 8.9)	5.60–5.57 (m)	
4	4.72 (d, 9.0)	4.74 (d, 8.9)	0.02
5-OH	3.91 (s)	3.89 (br s)	0.02
6	1.76 (m)	1.83–1.76 (m)	
7	2.02 (m)	2.15–2.02 (m)	
8α	1.68 (m)	1.73–1.67 (m)	
8β	2.10 (m)	2.15–2.02 (m)	
9α	1.39 (m)	1.44–1.38 (m)	
9β	2.03 (m)	2.15–2.02 (m)	
10	2.26 (m)	2.31–2.24 (m)	
11-OH	4.19 (s)	4.17 (br s)	0.02
13	2.71 (s)	2.72 (s)	0.01
15	2.77 (dd, 4.7, 7.5)	2.82–2.74 (m)	
16	5.76 (2H, t, 7.6)	5.76 (t, 7.6)	0
19	6.01 (s)	6.01 (s)	0
21	1.73 (s, 3H)	1.76–1.73 (m, 3H)	
22	0.96 (d, 6.8, 3H)	0.98 (d, 6.9, 3H)	0.02
23	0.78 (d, 7.4, 3H)	0.80 (d, 7.4, 3H)	0.02
24	1.23 (s, 3H)	1.25 (s, 3H)	0.02
25	2.19 (s, 3H)	2.20 (d, 1.4, 3H)	0.01

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (150 MHz, acetone-d6)	Δδ (ppm)
1	18.8	18.8	0
2	137.1	137.2	0.1
3	122.4	122.5	0.1
4	77.2	77.3	0.1
5	84.4	84.5	0.1
6	42.2	42.3	0.1
7	50.3	50.5	0.2
8	30.6	30.6	0
9	30.9	31.0	0.1
10	46.1	46.3	0.2
11	85.5	85.6	0.1
12	212.4	212.4	0
13	71.6	71.7	0.1
14	83.3	83.4	0.1
15	41.6	41.6	0
16	109.4	109.5	0.1
17	152.5	152.6	0.1
18	156.2	156.2	0
19	116.6	116.6	0
20	169.5	169.5	0
21	26.1	26.2	0.1
22	14.0	14.0	0
23	16.9	17.0	0.1
24	24.3	24.3	0
25	11.7	11.7	0

[39] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

Natural[40] and synthetic leucosceptroid L

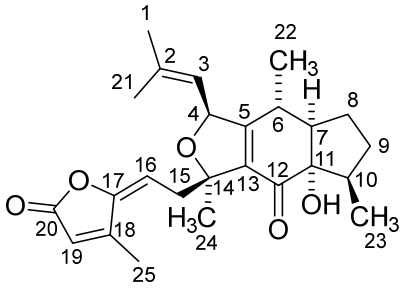


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.81 (s, 3H)	1.82 (d, 1.2, 3H)	0.1
3	5.15 (d, 9.6)	5.16 (d, 9.7)	0.1
4	5.66 (d, 9.6)	5.66 (dd, 9.7, 0.9)	0
6	2.34 (m)	2.83–2.32 (m)	
7	2.14 (m)	2.15–2.10 (m)	
8α	1.64 (m)	1.67–1.63 (m)	
8β	2.11 (m)	2.15–2.10 (m)	
9α	1.34 (m)	1.37–1.33 (m)	
9β	2.12 (m)	2.15–2.10 (m)	
10	2.13 (m)	2.15–2.10 (m)	
11-OH	4.15 (s)	4.13 (s)	0.2
15a	2.72 (dd, 15.4, 7.2)	2.73 (dd, 15.4, 7.1)	0.1
15b	2.89 (dd, 15.4, 8.0)	2.90 (dd, 15.4, 8.0)	0.1
16	5.44 (t, 7.5)	5.44 (t, 7.5)	0
19	6.00 (s)	6.00 (s)	0
21	1.77 (s, 3H)	1.78 (d, 1.0, 3H)	0.1
22	1.13 (d, 7.0, 3H)	1.14 (d, 7.0, 3H)	0.1
23	0.83 (d, 7.0, 3H)	0.84 (d, 7.0, 3H)	0.1
24	1.41 (s, 3H)	1.42 (s, 3H)	0.1
25	2.14 (s, 3H)	2.16 (d, 1.3, 3H)	0.2

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (150 MHz, acetone-d6)	Δδ (ppm)
1	18.3	18.4	0.1
2	139.2	139.3	0.1
3	123.3	123.4	0.1
4	80.8	80.9	0.1
5	166.5	166.6	0.1
6	33.0	33.0	0
7	56.0	56.0	0
8	29.5	29.5	0
9	32.2	32.2	0
10	47.5	47.5	0
11	86.0	86.0	0
12	197.4	197.5	0.1
13	137.7	137.8	0.1
14	88.6	88.7	0.1
15	36.8	36.8	0
16	109.0	109.1	0.1
17	152.4	152.4	0
18	155.7	155.8	0.1
19	116.7	116.8	0.1
20	169.3	169.4	0.1
21	26.0	26.1	0.1
22	18.2	18.2	0
23	18.7	18.9	0.2
24	26.7	26.8	0.1
25	11.5	11.6	0.1

[40] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

Natural[41] and synthetic leucosceptroid M

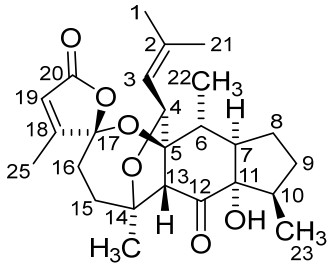


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (600 MHz, acetone-d6)	Δδ (ppm)
1	1.81 (s, 3H)	1.82 (d, 1.2, 3H)	0.1
3	5.11 (d, 9.6)	5.11 (d, 9.7)	0
4	5.66 (d, 8.7)	5.67 (dd, 9.6, 1.2)	0.1
6	2.35 (m)	2.39–3.44 (m)	
7	2.14 (m)	2.17–2.08 (m)	
8α	1.65 (m)	1.66–1.63 (m)	
8β	2.12 (m)	2.17–2.08 (m)	
9α	1.34 (m)	1.37–1.32	
9β	2.10 (m)	2.17–2.08 (m)	
10	2.11 (m)	2.17–2.08 (m)	
11-OH	4.14 (s)	4.13 (s)	0.1
15a	2.72 (dd, 15.1, 7.4)	2.73 (dd, 15.2, 7.4)	0.1
15b	3.07 (dd, 15.3, 9.8)	3.08 (dd, 15.2, 9.7)	0.1
16	5.64 (t, 9.4)	5.66-5.64 (m)	
19	6.05 (s)	6.06 (s)	0.1
21	1.75 (s, 3H)	1.76 (d, 1.1, 3H)	0.1
22	1.13 (d, 7.0, 3H)	1.13 (d, 7.0, 3H)	0
23	0.80 (d, 7.0, 3H)	0.81 (d, 7.0, 3H)	0.1
24	1.42 (s, 3H)	1.42 (s, 3H)	0
25	2.39 (s, 3H)	2.40 (d, 1.3, 3H)	0.1

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (150 MHz, acetone-d6)	Δδ (ppm)
1	18.4	18.3	0.1
2	139.7	139.6	0.1
3	123.0	122.9	0.1
4	80.8	80.7	0.1
5	167.4	167.4	0
6	33.0	33.0	0
7	56.2	56.1	0.1
8	29.4	29.4	0
9	32.2	32.2	0
10	47.3	47.3	0
11	86.0	86.0	0
12	197.9	197.8	0.1
13	137.3	137.3	0
14	89.0	89.0	0
15	35.8	35.8	0
16	113.4	113.3	0.1
17	151.8	151.7	0.1
18	155.9	155.8	0.1
19	120.1	120.0	0.1
20	169.1	169.0	0.1
21	26.1	26.0	0.1
22	18.1	18.1	0
23	19.0	18.9	0.1
24	27.3	27.3	0
25	15.6	15.5	0.1

[41] S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, 86, 29.

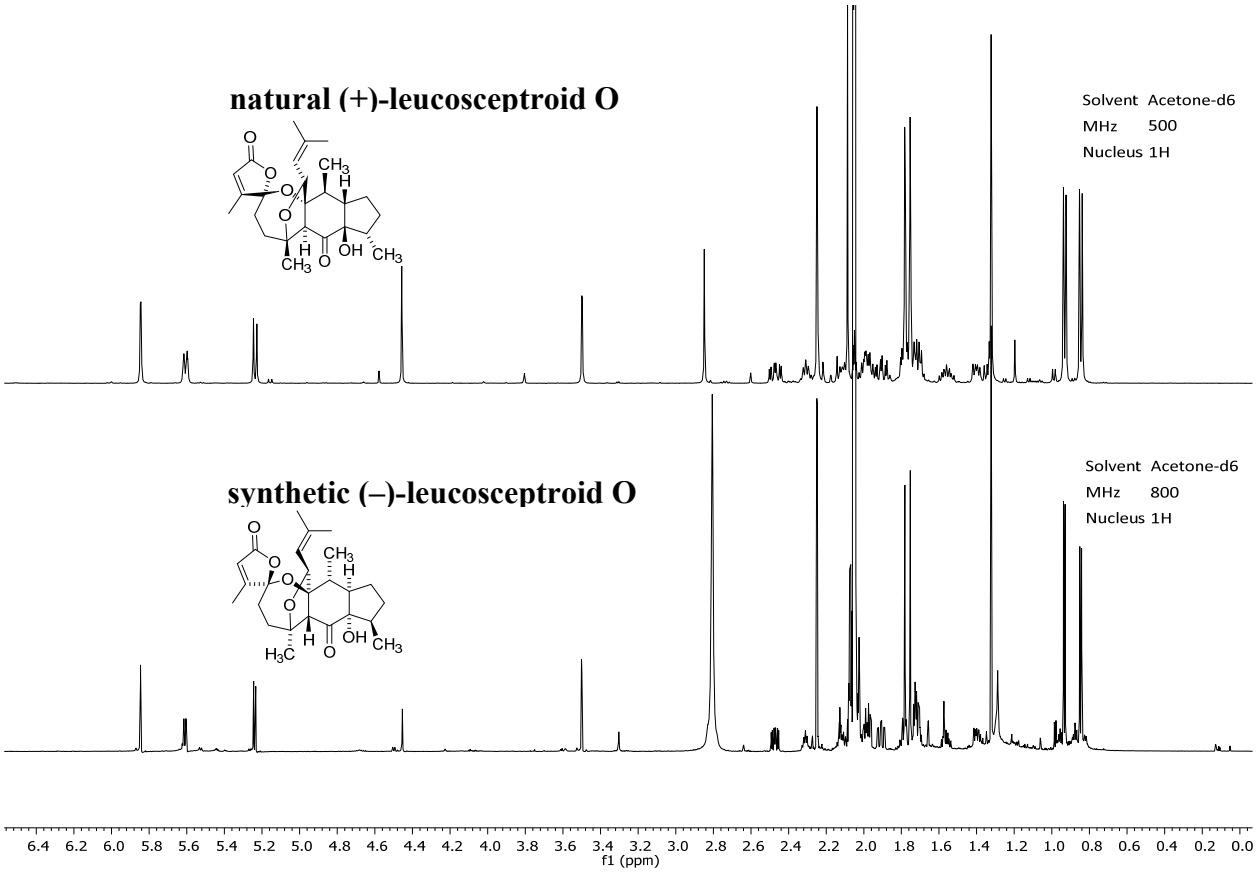
Natural[42] and synthetic leucosceptroid O

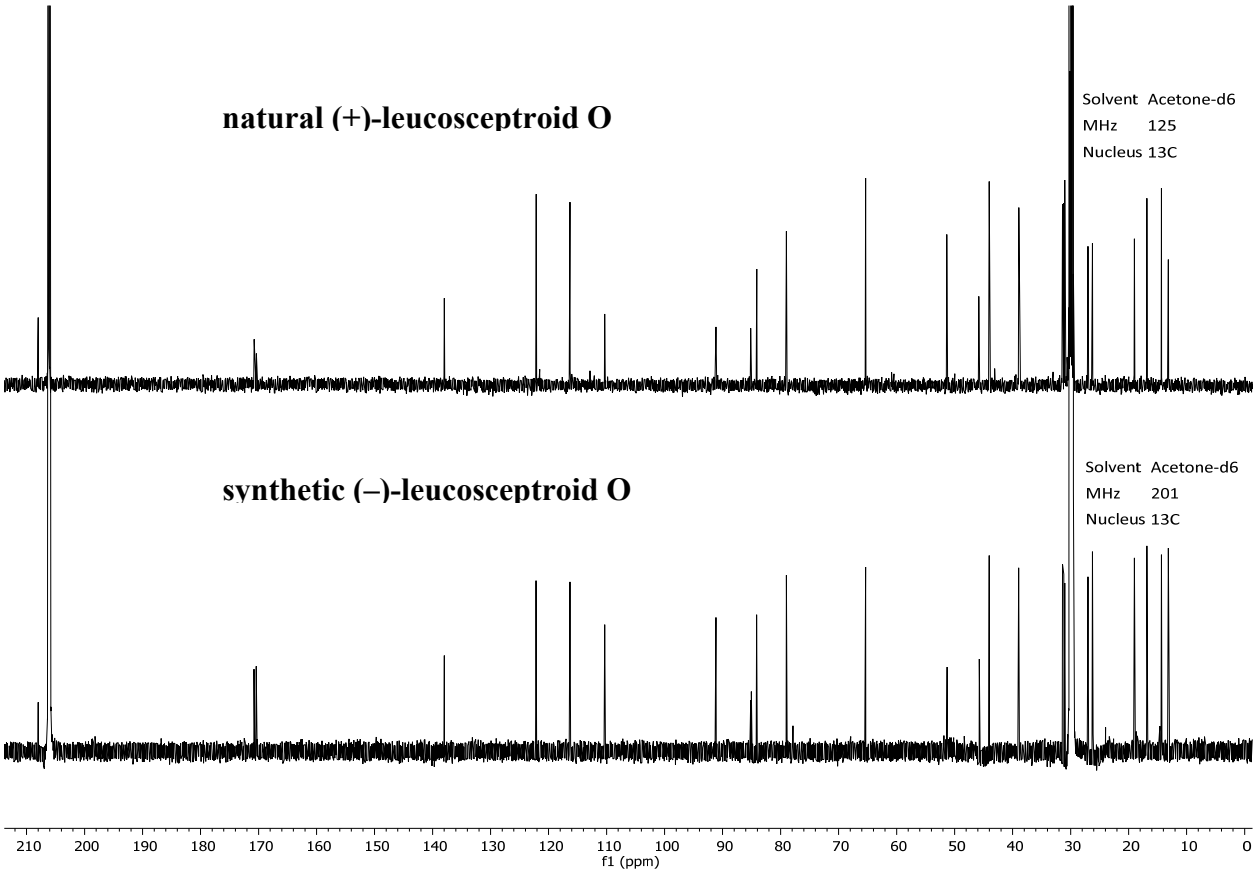


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (800 MHz, acetone-d6)	Δδ (ppm)
1	1.74 (s, 3H)	1.75 (d, 1.3, 3H)	0.01
3	5.60 (d, 9.0)	5.62–5.60 (m)	
4	5.23 (d, 9.0)	5.24 (d, 9.0)	0.01
6	1.71 (m)	1.74–1.68 (m)	
7	1.97 (m)	2.02–1.95 (m)	
8α	1.56 (m)	1.59–1.52 (m)	
8β	2.12 (m)	2.14–2.10 (m)	
9α	1.39 (m)	1.42–1.36 (m)	
9β	1.99 (m)	2.02–1.95 (m)	
10	2.30 (m)	2.33–2.29 (m)	
11-OH	4.46 (s)	4.45 (s)	0.01
13	3.49 (s)	3.50 (s)	0.01
15a	1.70 (m)	1.74–1.68 (m)	
15b	1.90 (m)	1.94–1.87 (m)	
16a	1.78 (m)	1.80–1.76 (m)	
16b	2.46 (m)	2.47 (ddd, 14.5, 12.7, 4.7)	0.01
19	5.84 (s)	5.84 (q, 1.6)	0
21	1.77 (s, 3H)	1.78 (d, 1.3, 3H)	0.01
22	0.92 (d, 6.7, 3H)	0.93 (d, 6.7, 3H)	0.01
23	0.84 (d, 7.3, 3H)	0.85 (d, 7.3, 3H)	0.01
24	1.31 (s, 3H)	1.32 (s, 3H)	0.01
25	2.24 (s, 3H)	2.25 (d, 1.6, 3H)	0.01

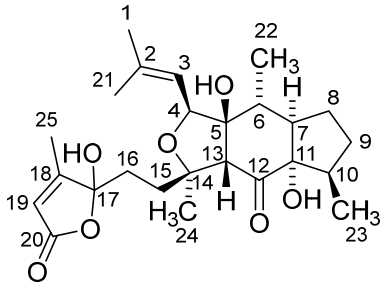
13C Position	Natural (125 MHz, acetone-d6)	Synthetic (200 MHz, acetone-d6)	Δδ (ppm)
1	18.9	19.0	0.1
2	137.9	138.0	0.1
3	122.1	122.2	0.1
4	78.9	79.0	0.1
5	91.1	91.2	0.1
6	44.0	44.0	0
7	51.3	51.3	0
8	31.4	31.4	0
9	30.9	31.0	0.1
10	45.8	45.8	0
11	85.1	85.1	0
12	208.0	208.0	0
13	65.3	65.4	0.1
14	84.1	84.1	0.1
15	38.9	39.0	0.1
16	31.1	31.2	0.1
17	110.3	110.3	0
18	170.7	170.8	0.1
19	116.3	116.3	0
20	170.4	170.4	0
21	26.2	26.2	0
22	14.3	14.3	0
23	16.8	16.8	0
24	27.0	27.0	0
25	13.1	13.2	0.1

[42] S.-H. Luo, J. Hua, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Tetrahedron Lett*. **2013**, *54*, 235.


natural (+)-leucosceptroid O
Solvent Acetone-d6
MHz 500
Nucleus 1H
synthetic (–)-leucosceptroid O
Solvent Acetone-d6
MHz 800
Nucleus 1H
f1 (ppm)


natural (+)-leucosceptroid O
Solvent Acetone-d6
MHz 125
Nucleus 13C
synthetic (–)-leucosceptroid O
Solvent Acetone-d6
MHz 201
Nucleus 13C
f1 (ppm)

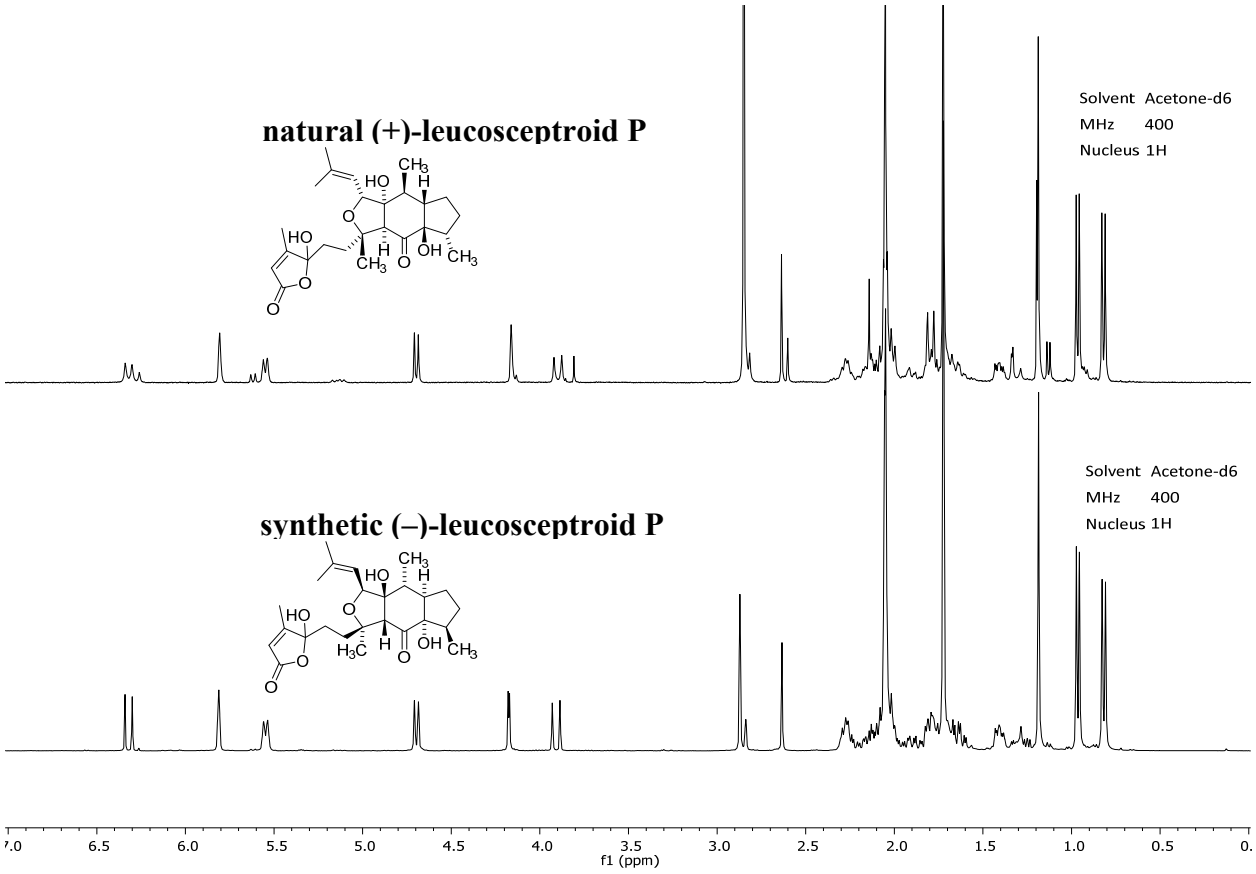
Natural[43] and synthetic leucosceptroid P

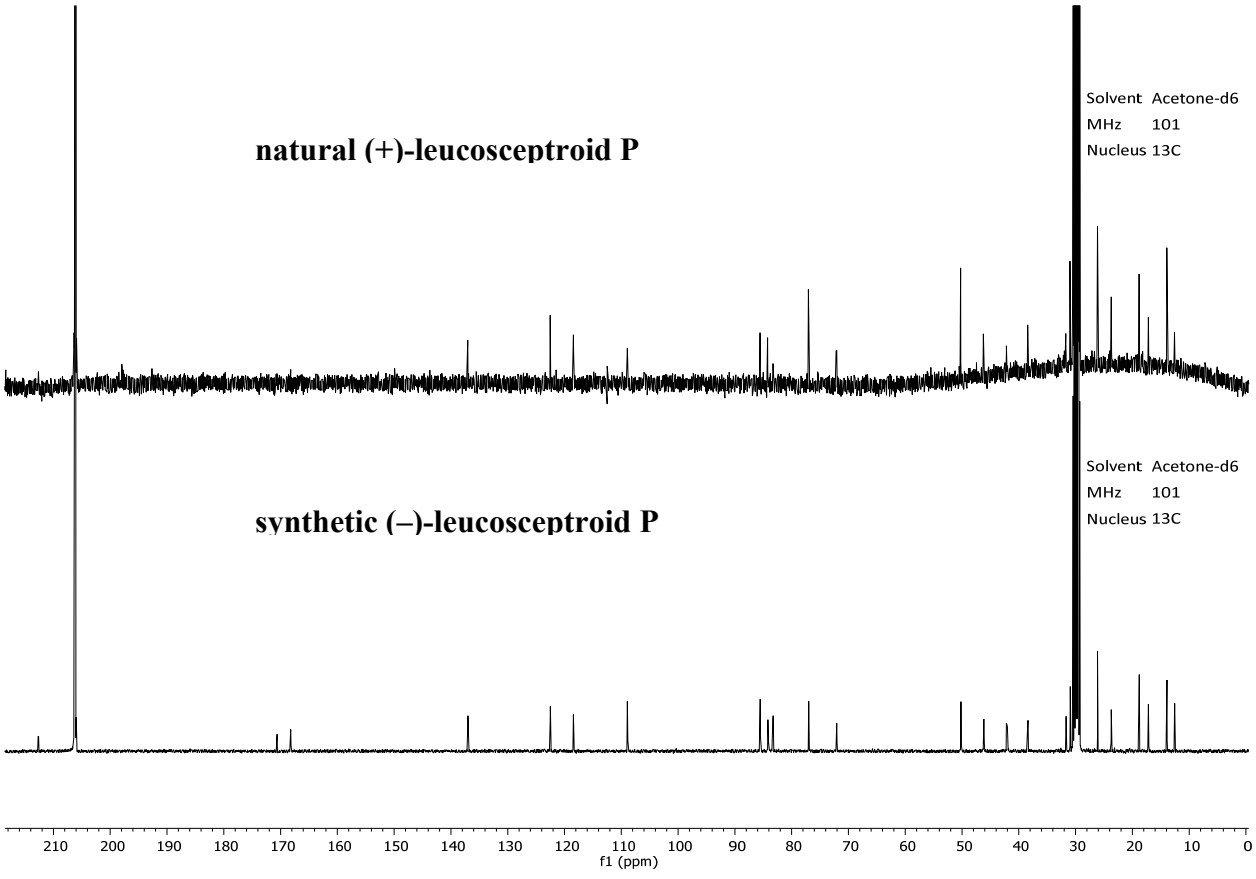


1H Position	Natural (500 MHz, acetone-d6)	Synthetic (400 MHz, acetone-d6)	Δδ (ppm)
1	1.71 (s, 3H)	1.72 (s, 3H)	0.01
3	5.55 (d, 8.9)	5.58–5.51 (m)	
4	4.69 (d, 8.9)	4.70 (d, 8.9)	0.01
5-OH	3.90 (m)	3.93 (s)	0.03
6	1.77 (m)	1.97–1.75 (m)	
7	2.03 (m)	2.22–1.97 (m)	
8α	1.69 (m)	1.69–1.54 (m)	
8β	2.09 (m)	2.22–1.97 (m)	
9α	1.40 (m)	1.45–1.35 (m)	
9β	2.00 (m)	2.22–1.97 (m)	
10	2.27 (m)	2.32–2.22 (m)	
11-OH	4.16 (s)	4.18 (s)	0.02
13	2.63 (s)	2.63 (s)	0
15a	1.64 (m)	1.69–1.54 (m)	
15b	1.81 (m)	1.97–1.75 (m)	
16a	2.18 (m)	2.22–1.97 (m)	
16b	2.30 (m)	2.32–2.22 (m)	
17-OH	-	6.34 (s)	
19	5.80 (s)	5.81 (br s)	0.01
21	1.72 (s, 3H)	1.72 (s, 3H)	0
22	0.96 (d, 6.8, 3H)	0.96 (d, 6.8, 3H)	0
23	0.82 (d, 7.4, 3H)	0.82 (d, 7.3, 3H)	0
24	1.18 (s, 3H)	1.19 (s, 3H)	0.01
25	2.04 (s, 3H)	2.05 (overlapped, 3H)	0.01

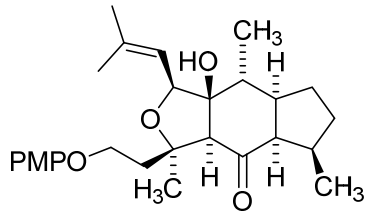
[43] S.H. Luo, C. L. Hugelshofer, J. Hua, S.-X. Jing, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, T. Magauer, S.H. Li, *Org. Lett.* **2014**, *16*, 16, 6416.

13C Position	Natural (125 MHz, acetone-d6)	Synthetic (100 MHz, acetone-d6)	Δδ (ppm)
1	18.7	18.8	0.1
2	137.0	137.0	0
3	122.5	122.5	0
4	77.0	77.0	0
5	84.2	84.2	0
6	42.0	42.2	0.2
7	50.2	50.2	0
8	30.5	30.5	0
9	30.9	30.9	0
10	46.2	46.2	0
11	85.5	85.5	0
12	212.6	212.7	0.1
13	72.1	72.2	0.1
14	83.2	83.3	0.1
15	38.4	38.4	0
16	31.7	31.8	0.1
17	108.9	108.9	0
18	168.4	168.3	0.1
19	118.4	118.4	0
20	170.9	170.7	0.2
21	26.1	26.1	0
22	13.9	13.9	0
23	17.1	17.2	0.1
24	23.7	23.7	0
25	12.5	12.6	0.1

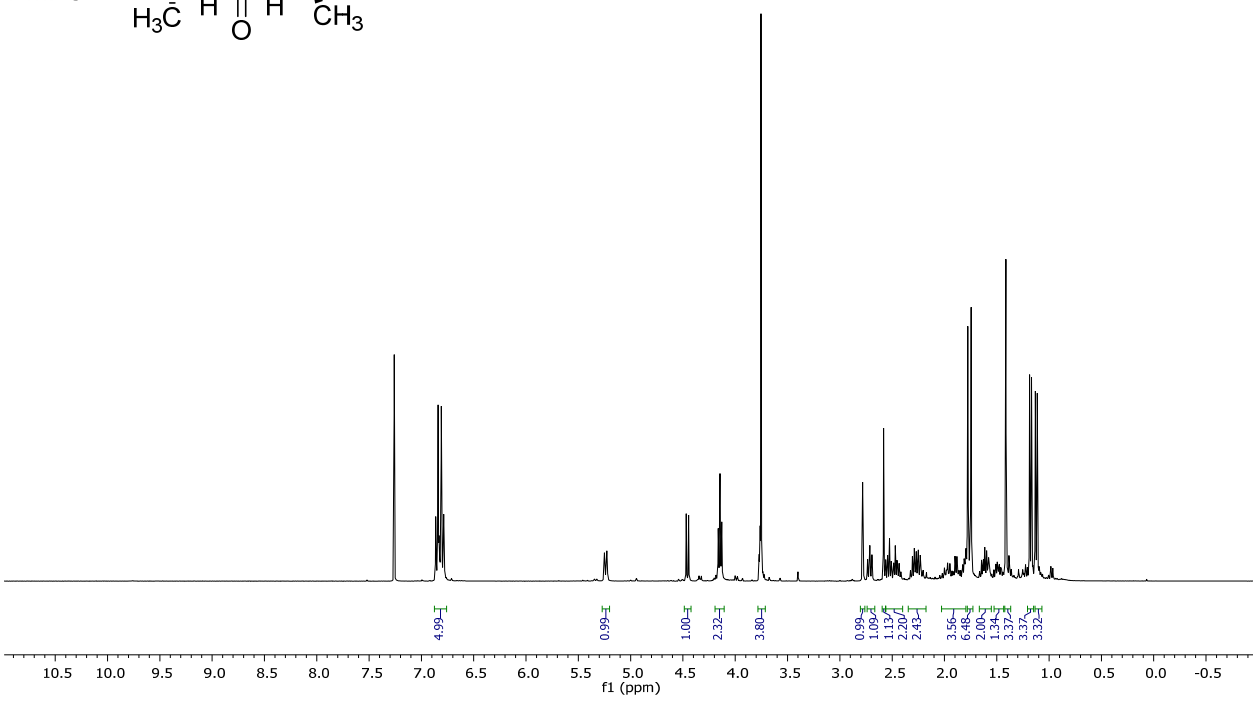

natural (+)-leucosceptroid P
Solvent Acetone-d6
MHz 400
Nucleus 1H
synthetic (–)-leucosceptroid P
Solvent Acetone-d6
MHz 400
Nucleus 1H
f1 (ppm)

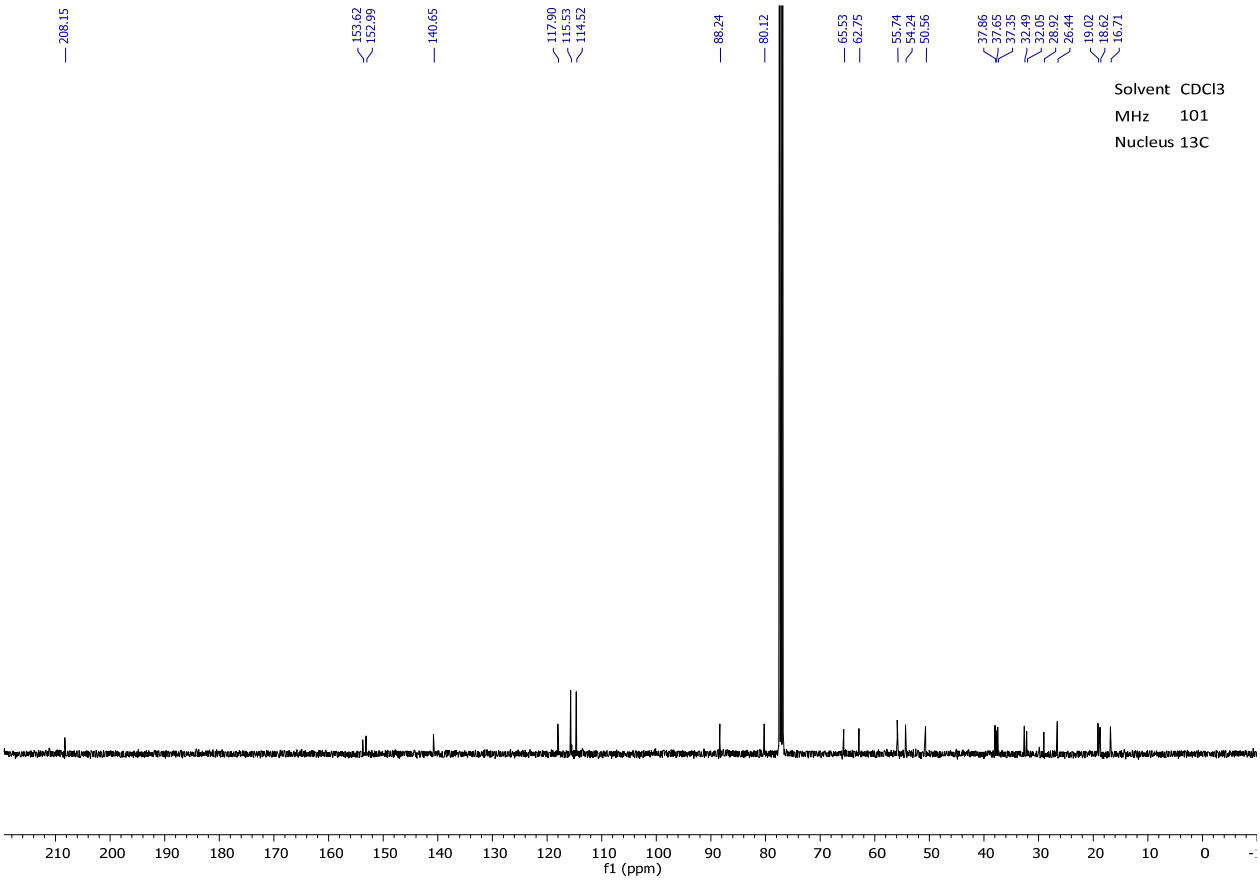

natural (+)-leucosceptroid P
Solvent Acetone-d6
MHz 101
Nucleus 13C
synthetic (–)-leucosceptroid P
Solvent Acetone-d6
MHz 101
Nucleus 13C
f1 (ppm)

6.3.5 ^{1}H and ^{13}C NMR Spectra

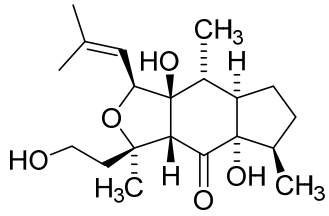


Solvent CDCl3
MHz 400
Nucleus 1H

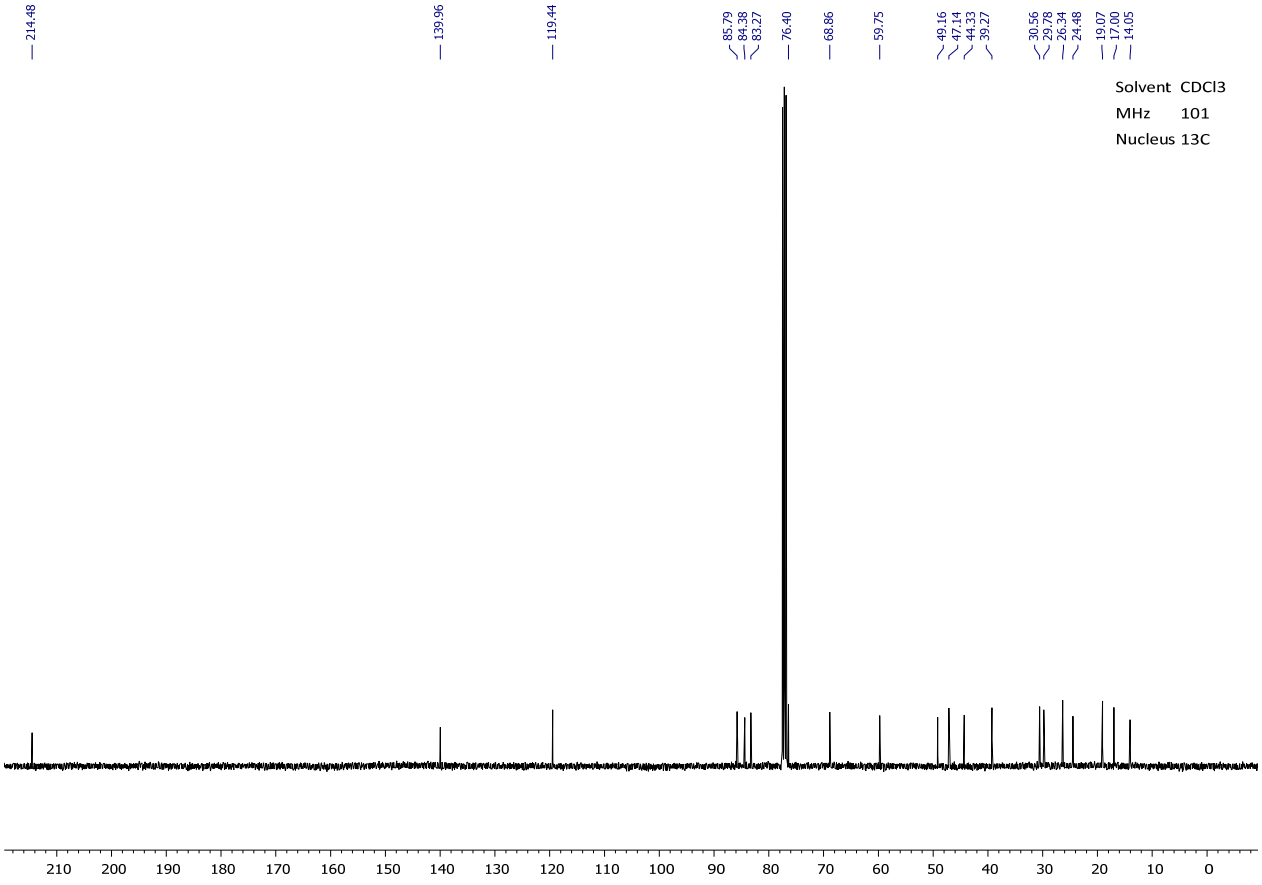


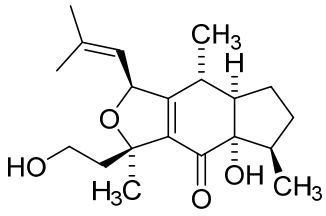


Solvent CDCl3
MHz 101
Nucleus 13C

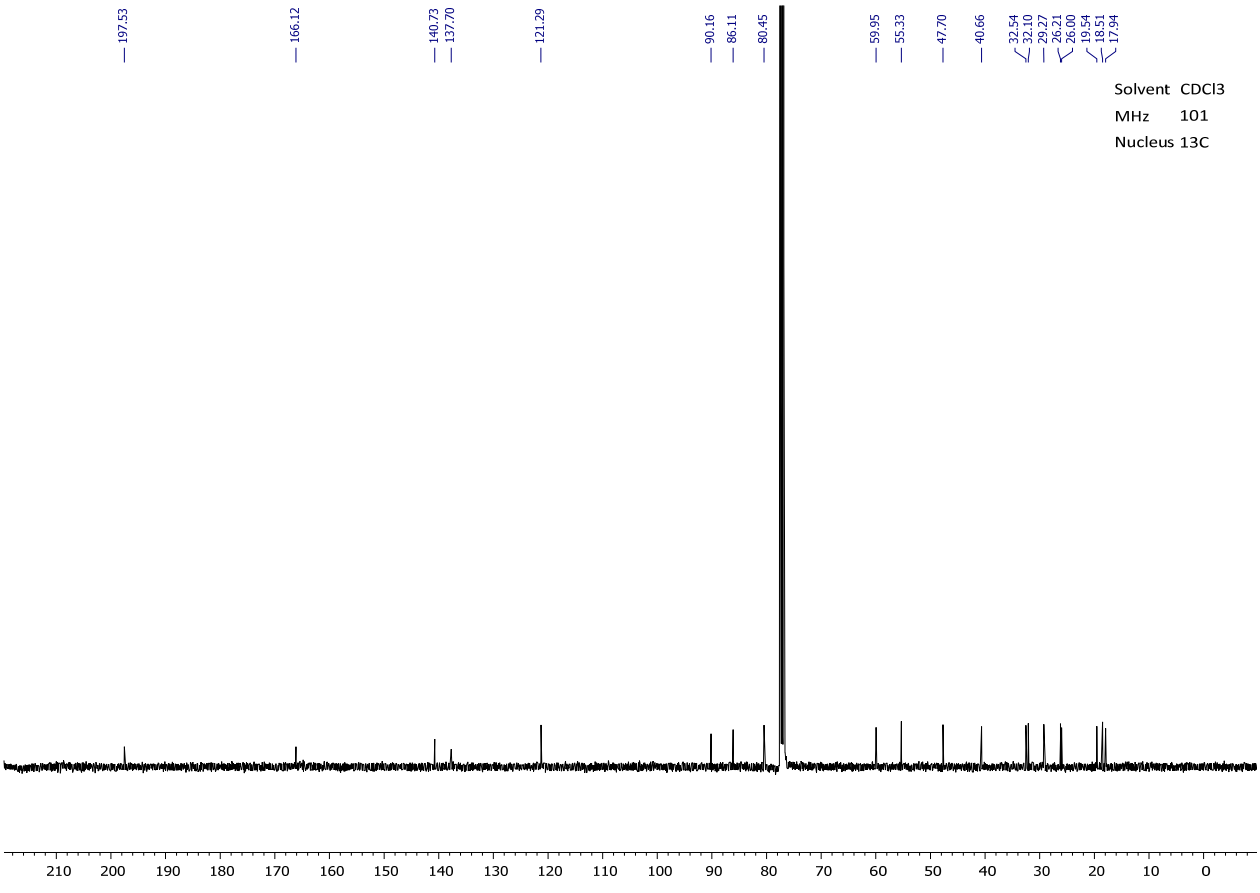

CH3
HO
H
O
HO
H3C
H
O
OH
CH3

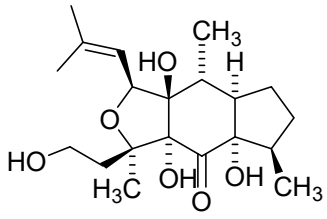
Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.96
2.25
0.73
1.09
0.65
0.99
7.54
1.97
7.64
2.68
3.32
3.16
3.20
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


214.48
139.96
119.44
85.79
84.38
83.27
76.40
68.86
59.75
49.16
47.14
44.33
39.27
30.56
29.78
26.34
24.48
19.07
17.00
14.05
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

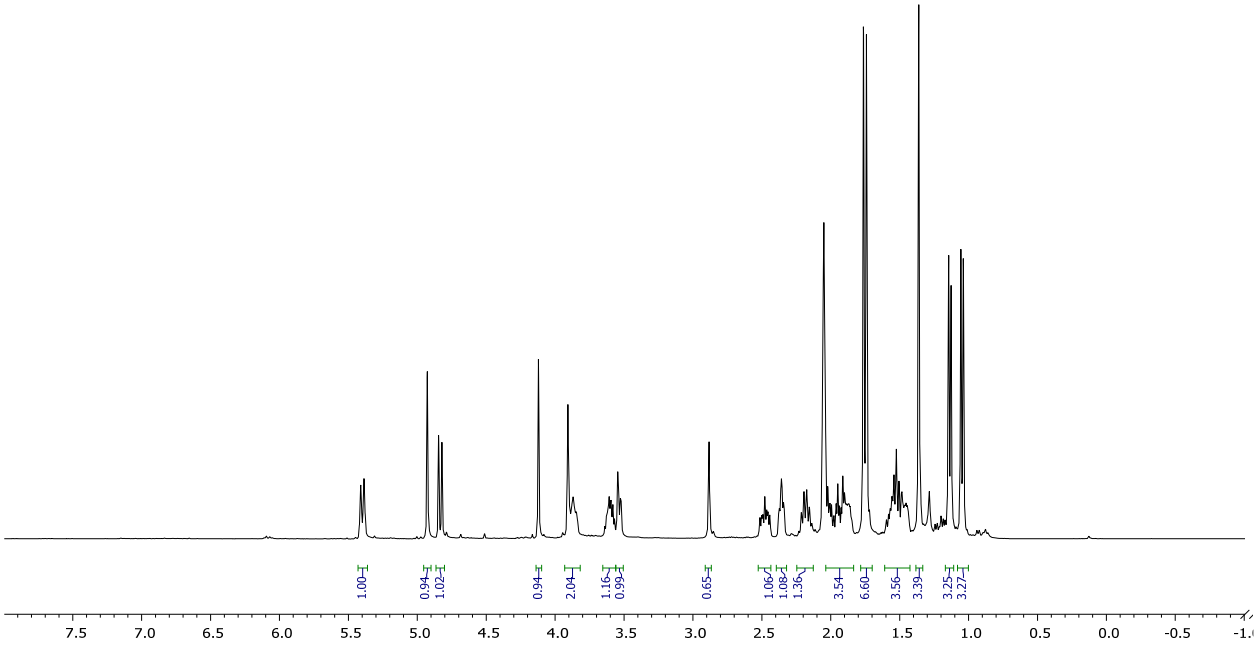


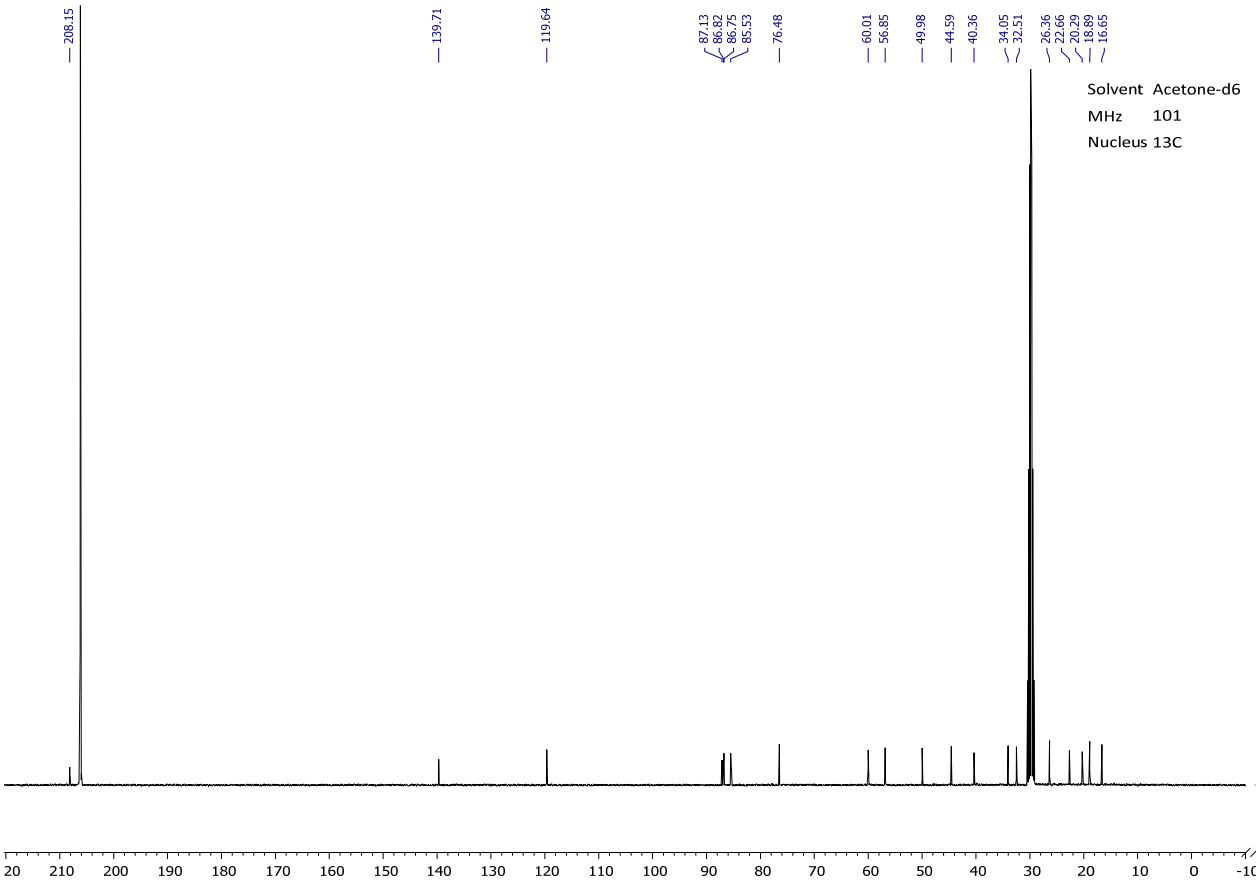
(+)-norleucosceptroid F

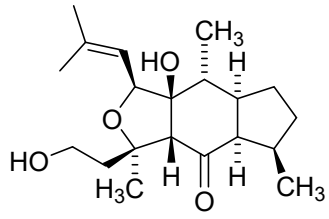




Solvent Acetone-d6
MHz 400
Nucleus 1H






CH3
HO
H
O
HO
H3C
H
H
O
CH3

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.88
2.20
0.80
1.66
0.95
1.03
1.16
3.61
6.43
3.84
2.78
2.83
3.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
214.78
139.56
119.84
85.03
82.94
76.02
70.63
59.55
56.42
44.58
44.04
40.62
36.52
33.18
30.85
26.34
22.80
19.14
17.04
13.40
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Nucleus 13C
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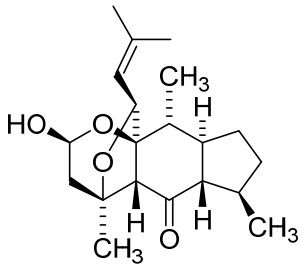

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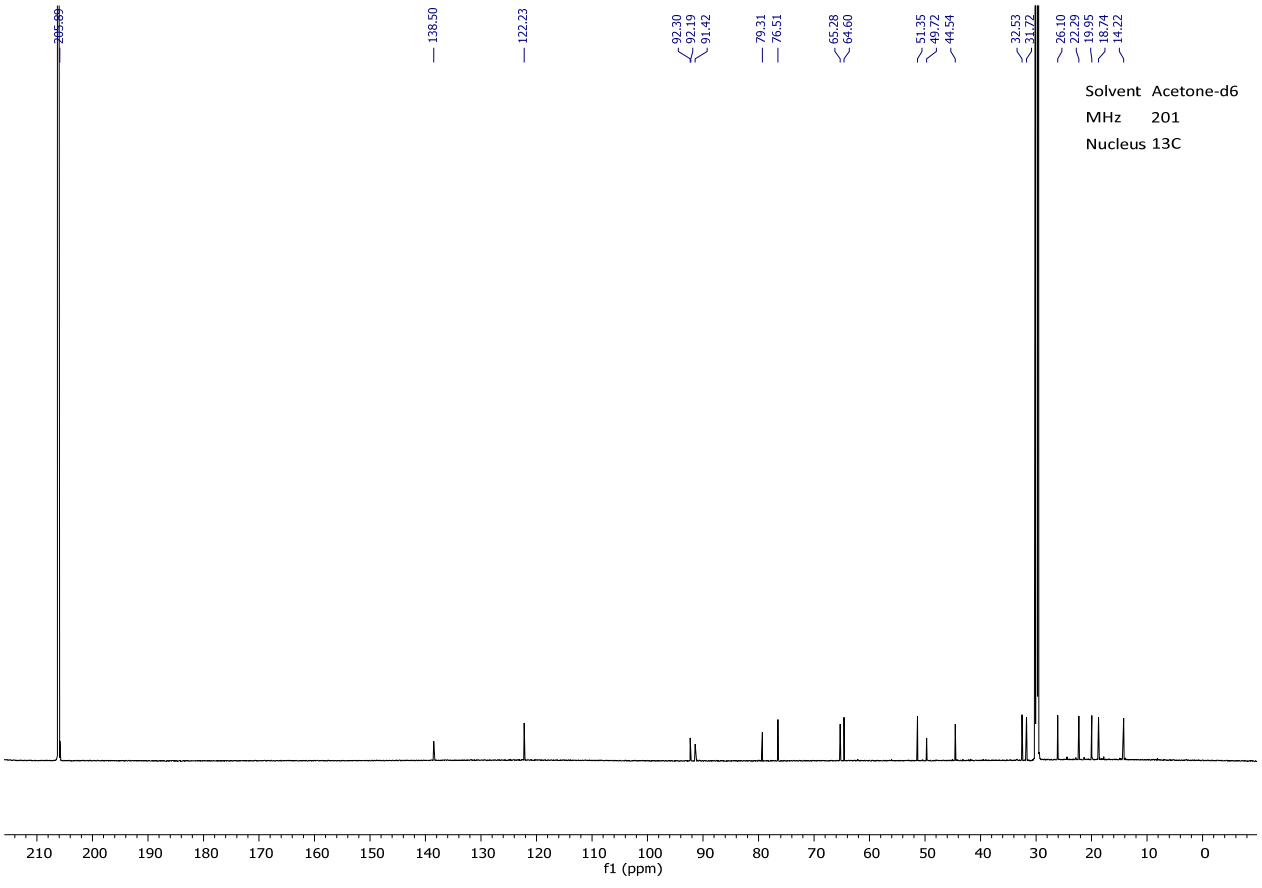

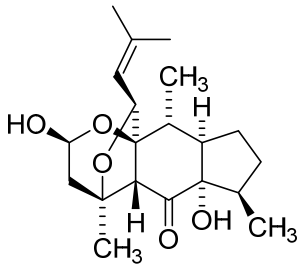

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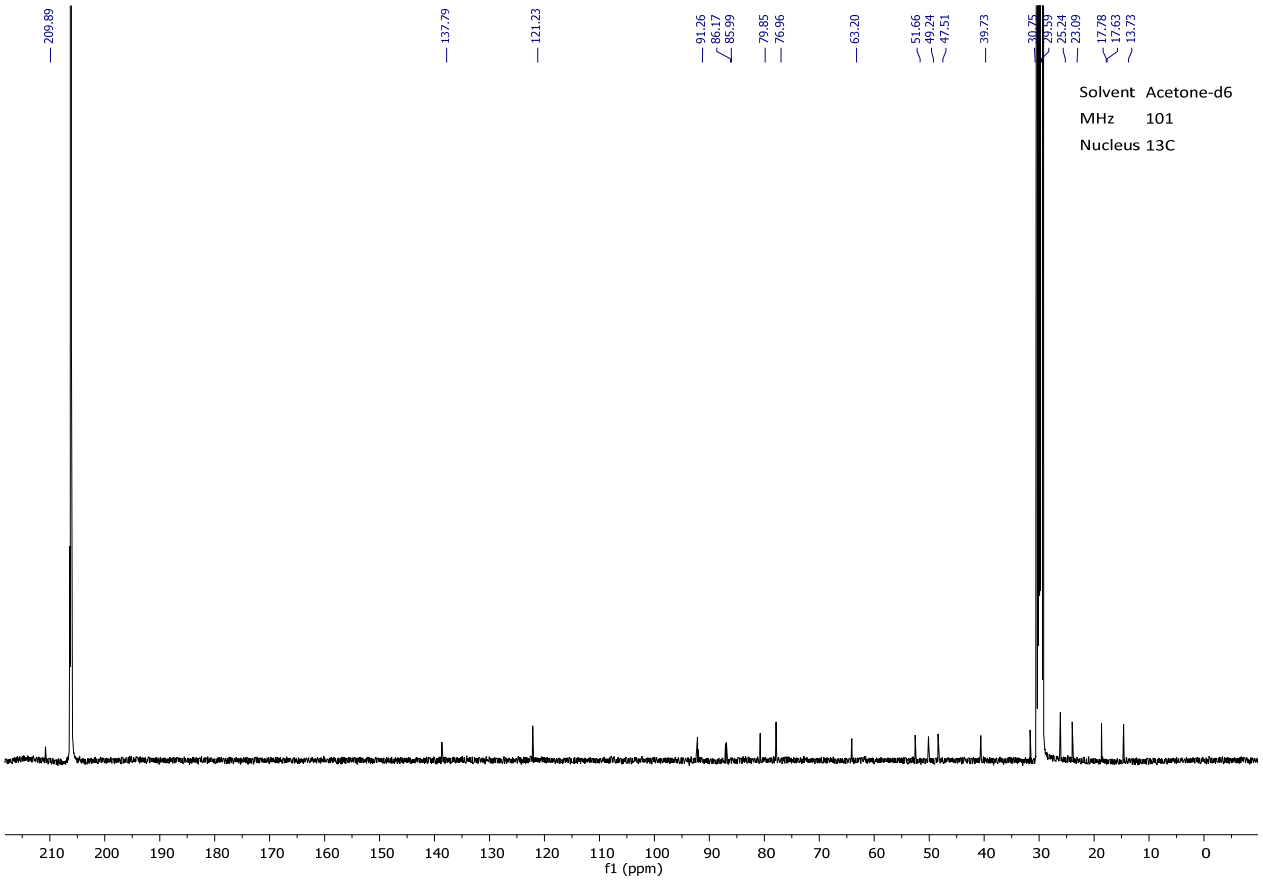
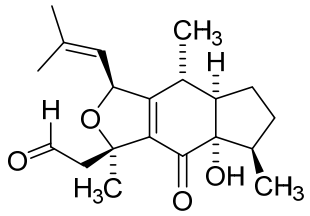
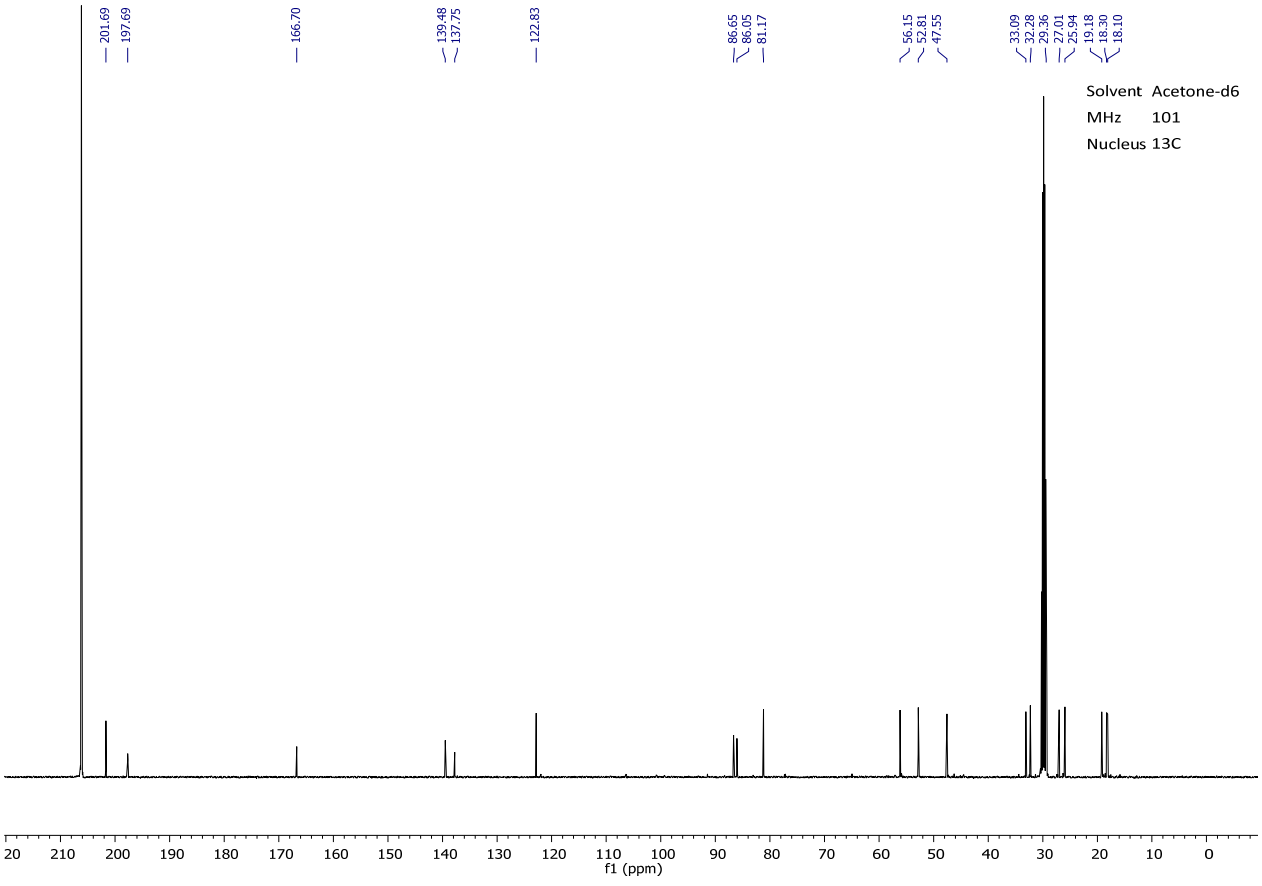
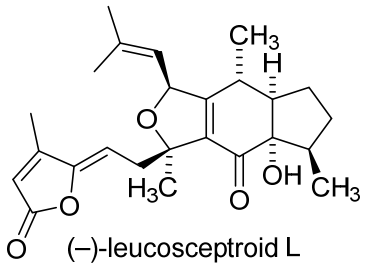




(+)-norleucosceptroid G





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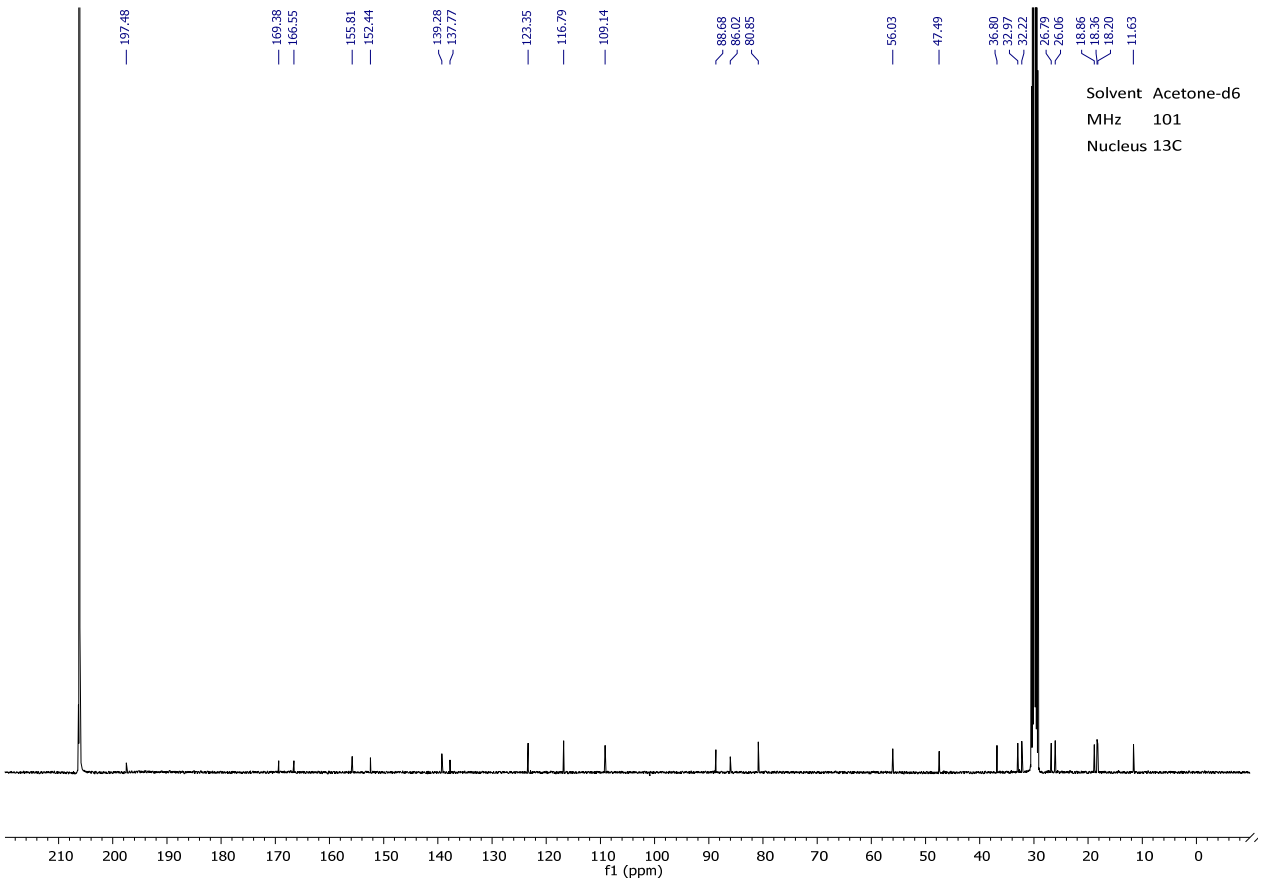
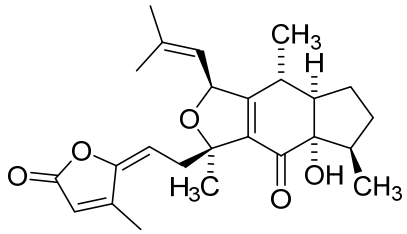
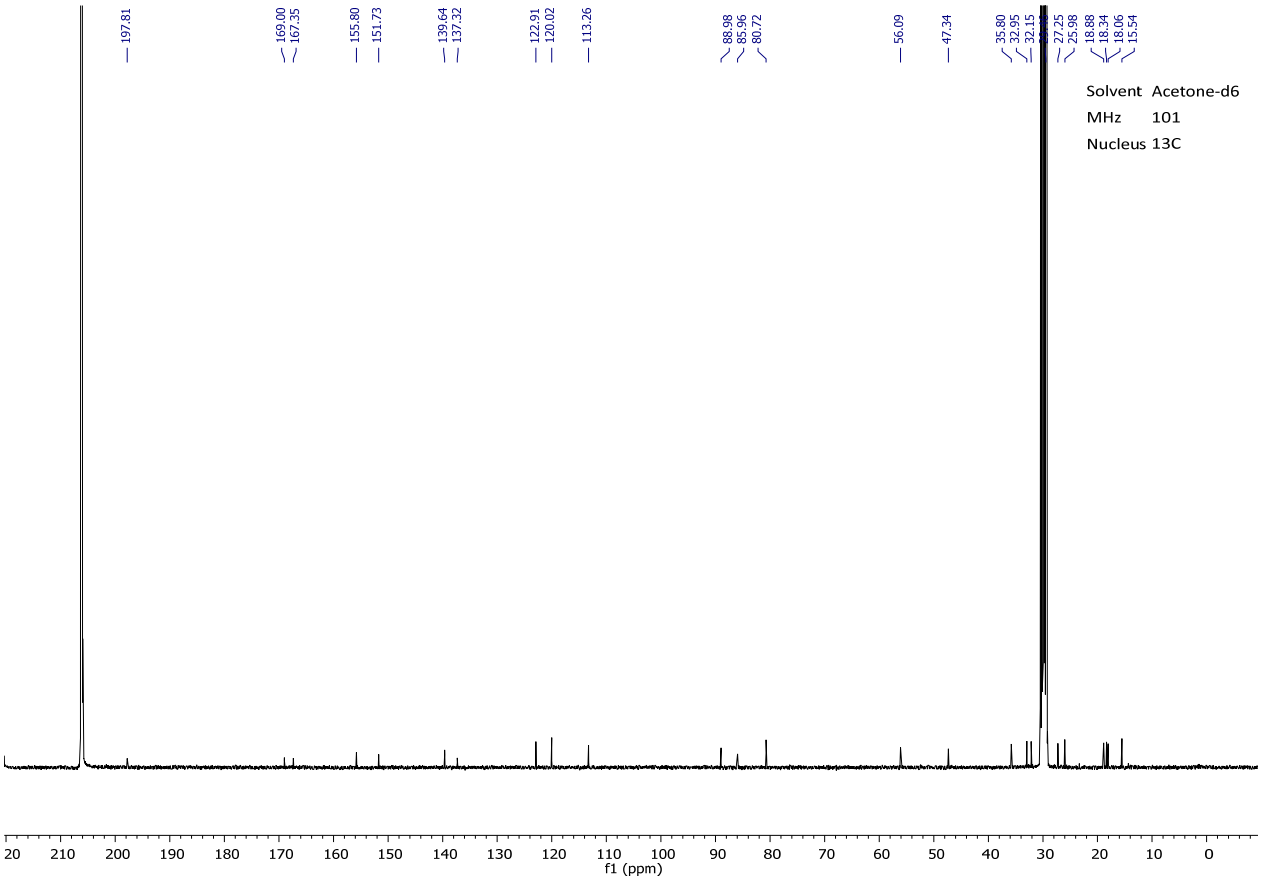
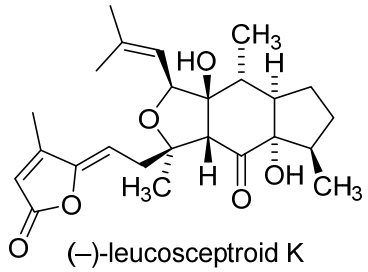


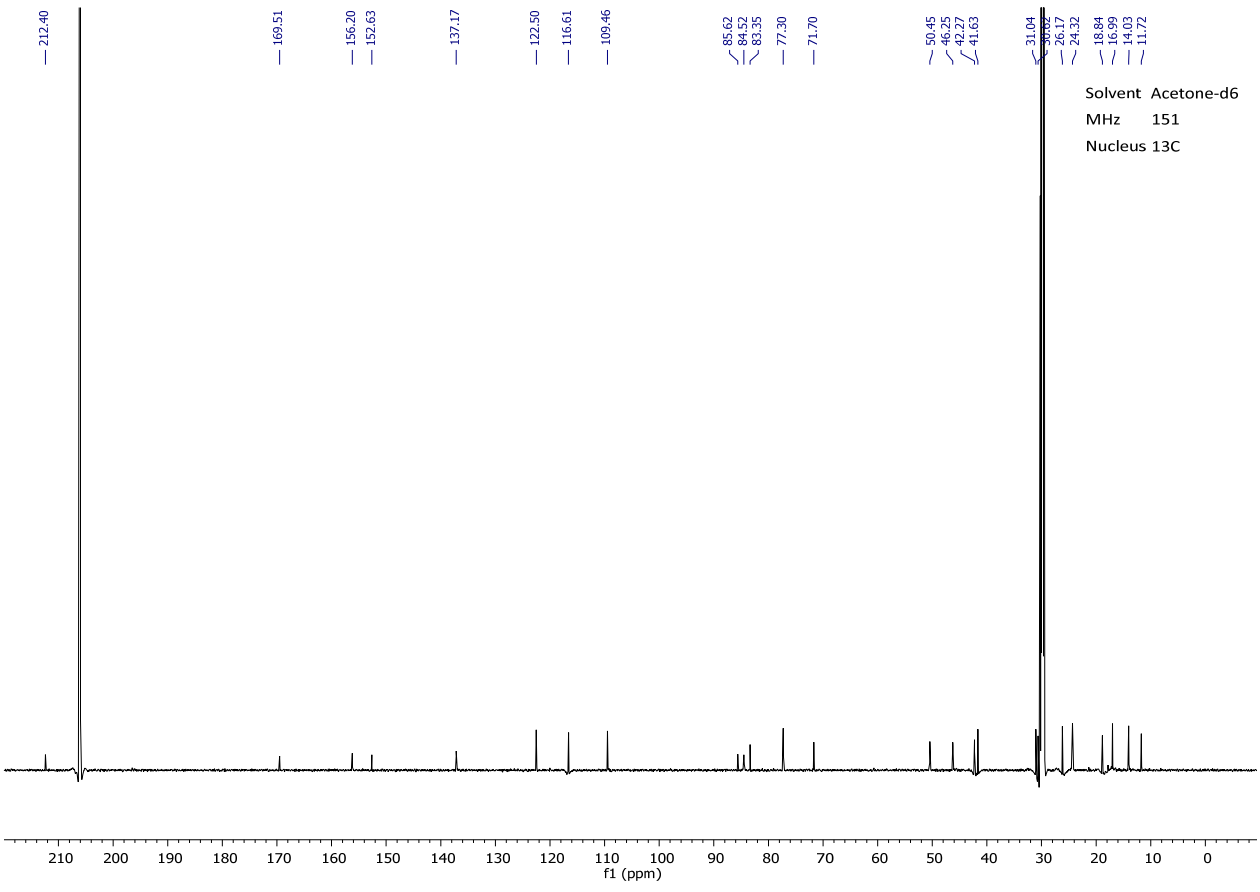


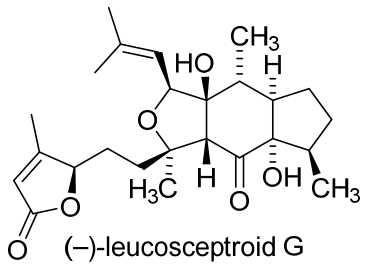
(–)-leucosceptroid M





(–)-leucosceptroid K





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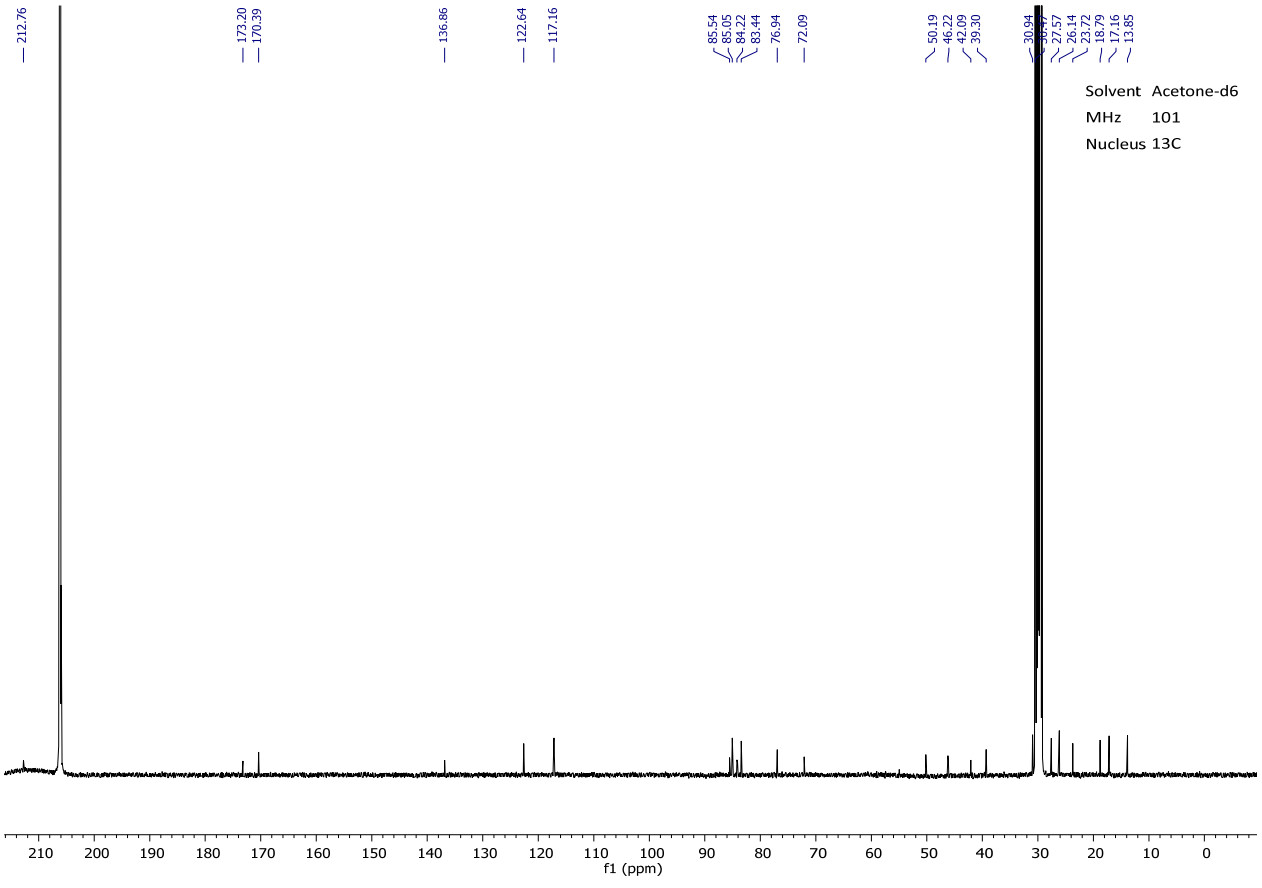
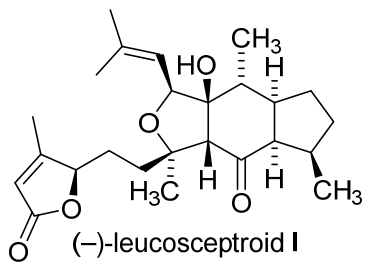
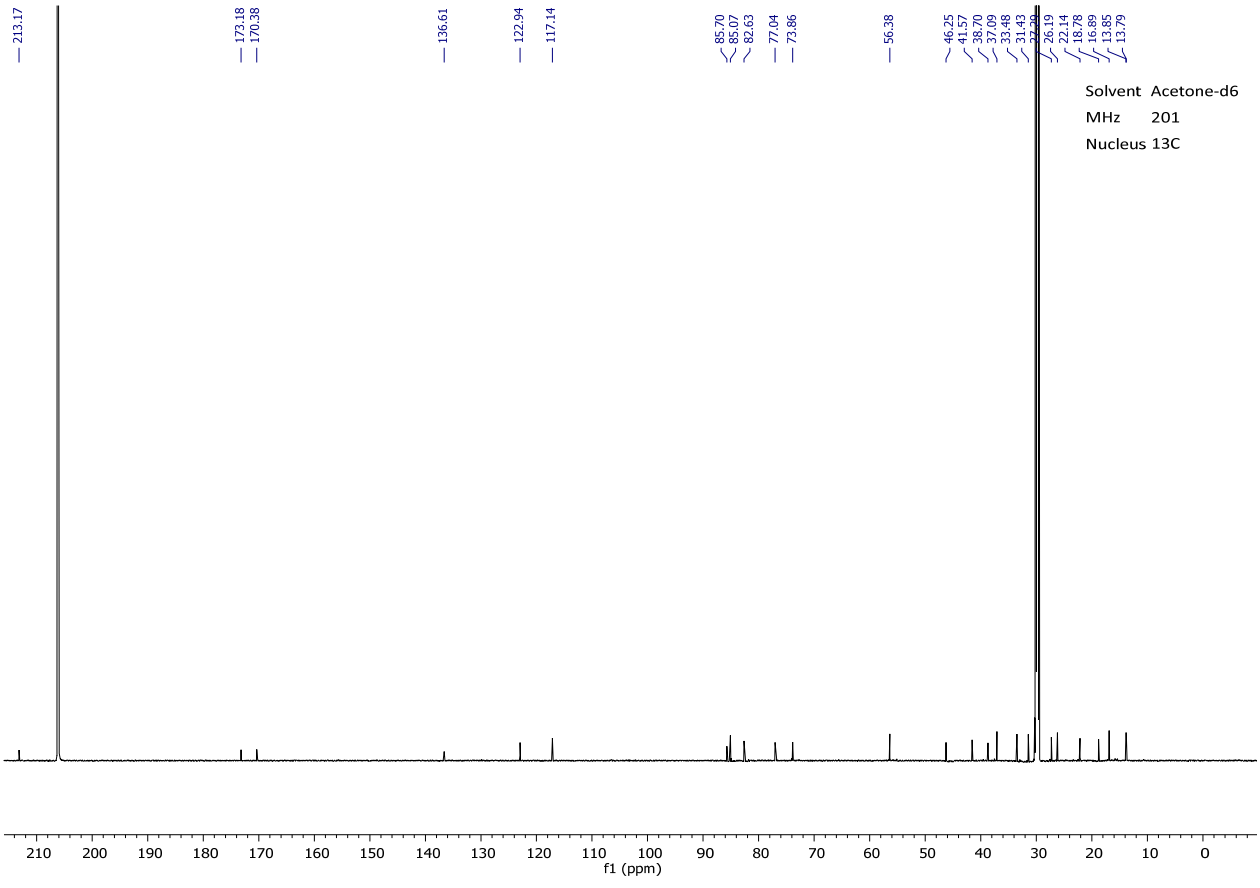
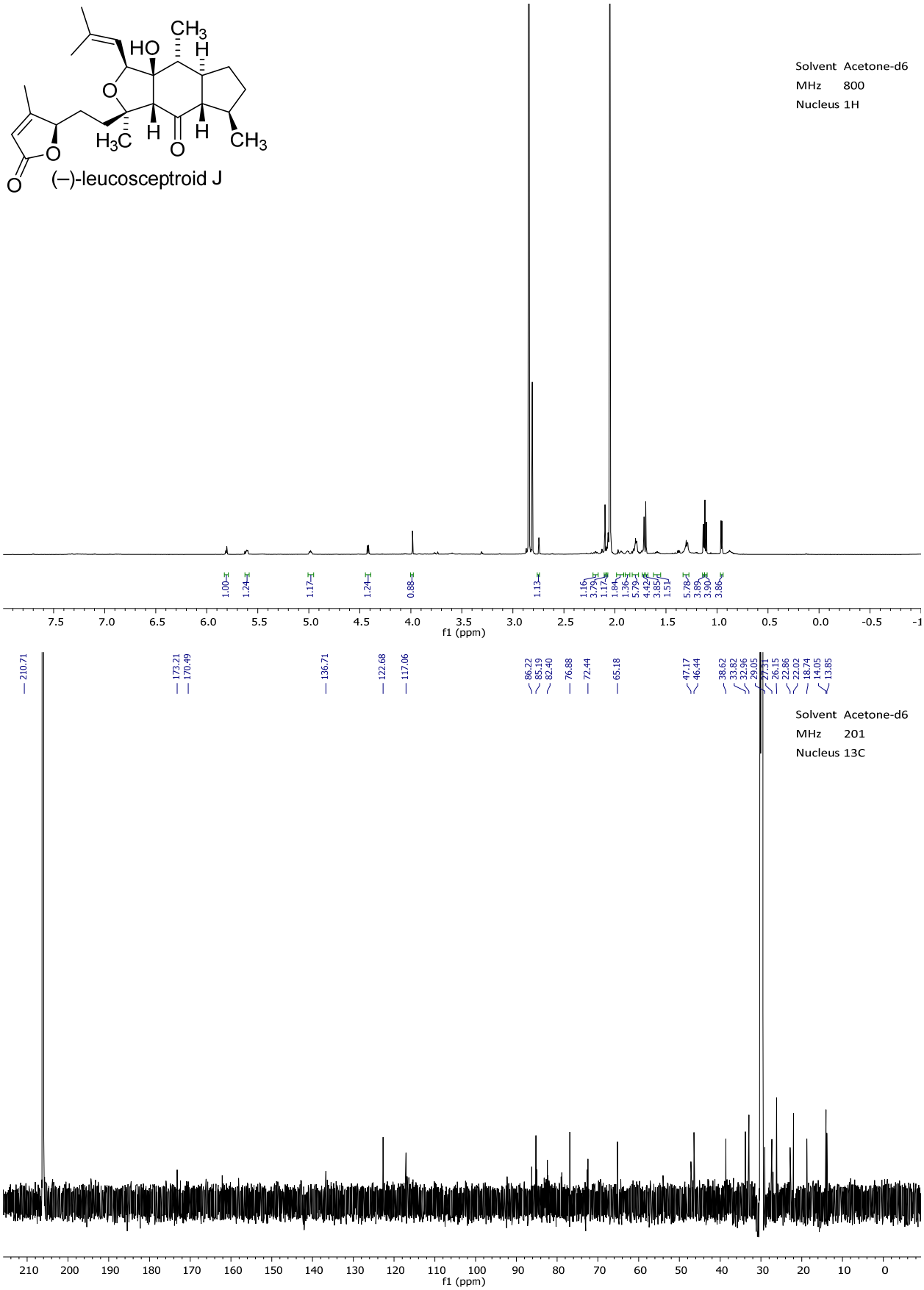




(–)-leucosceptroid I




(–)-leucosceptroid J
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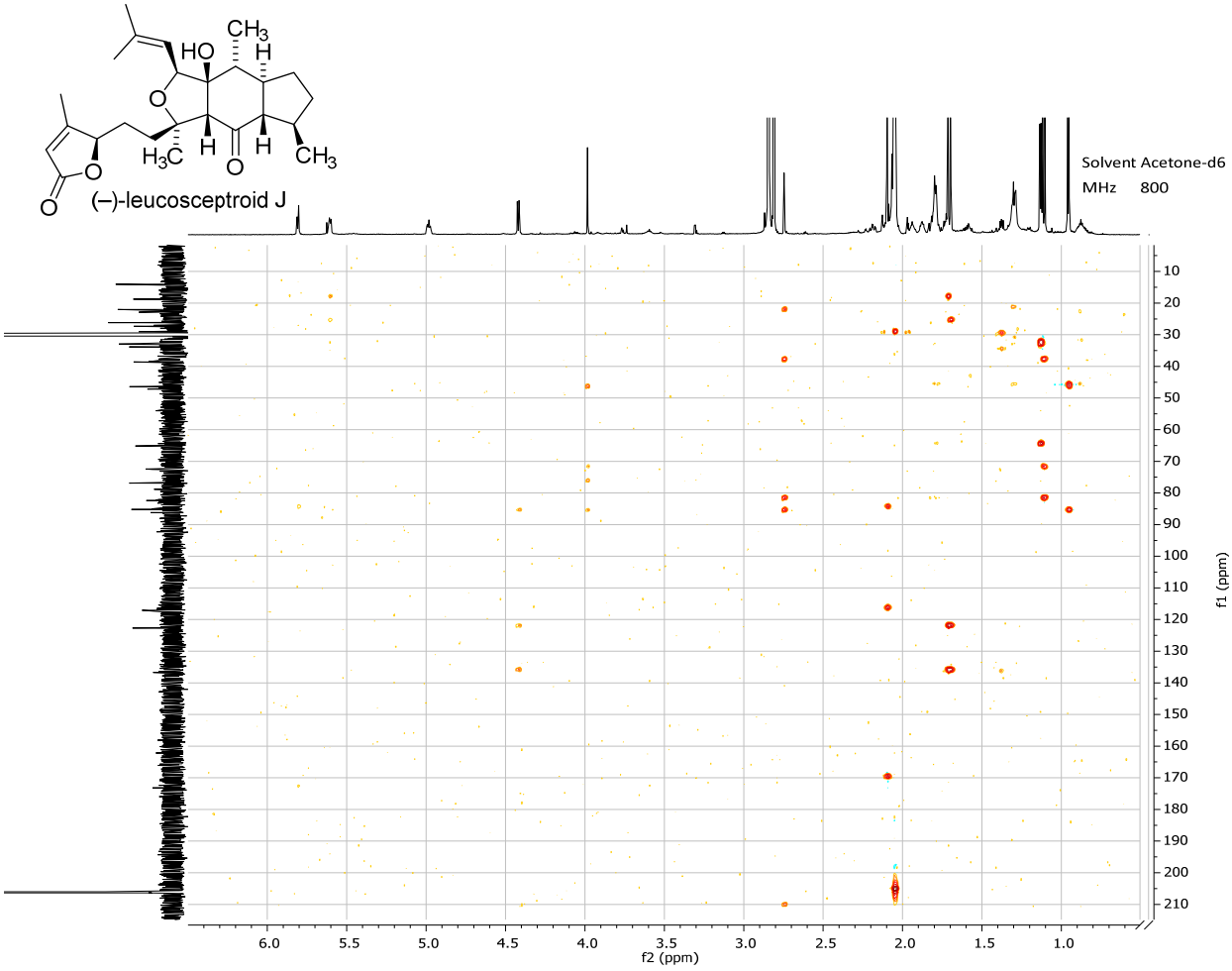
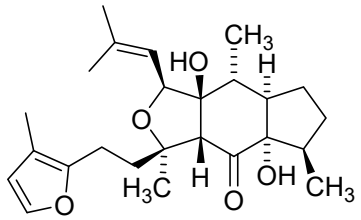
MHz 800
Nucleus 1H
f1 (ppm)
Solvent Acetone-d6
MHz 201
Nucleus 13C
f1 (ppm)


(–)-leucosceptroid J
Solvent Acetone-d6
MHz 800
f2 (ppm)
f1 (ppm)



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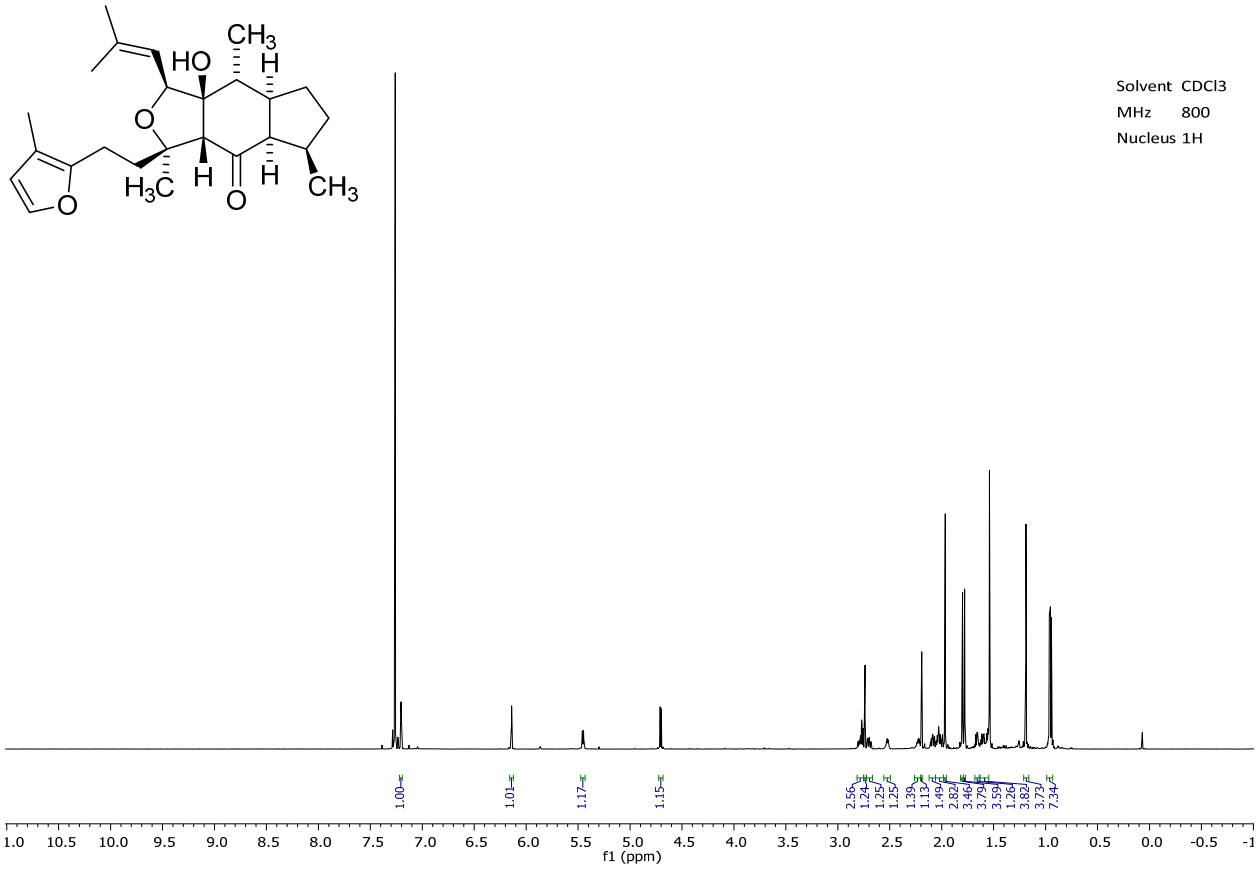
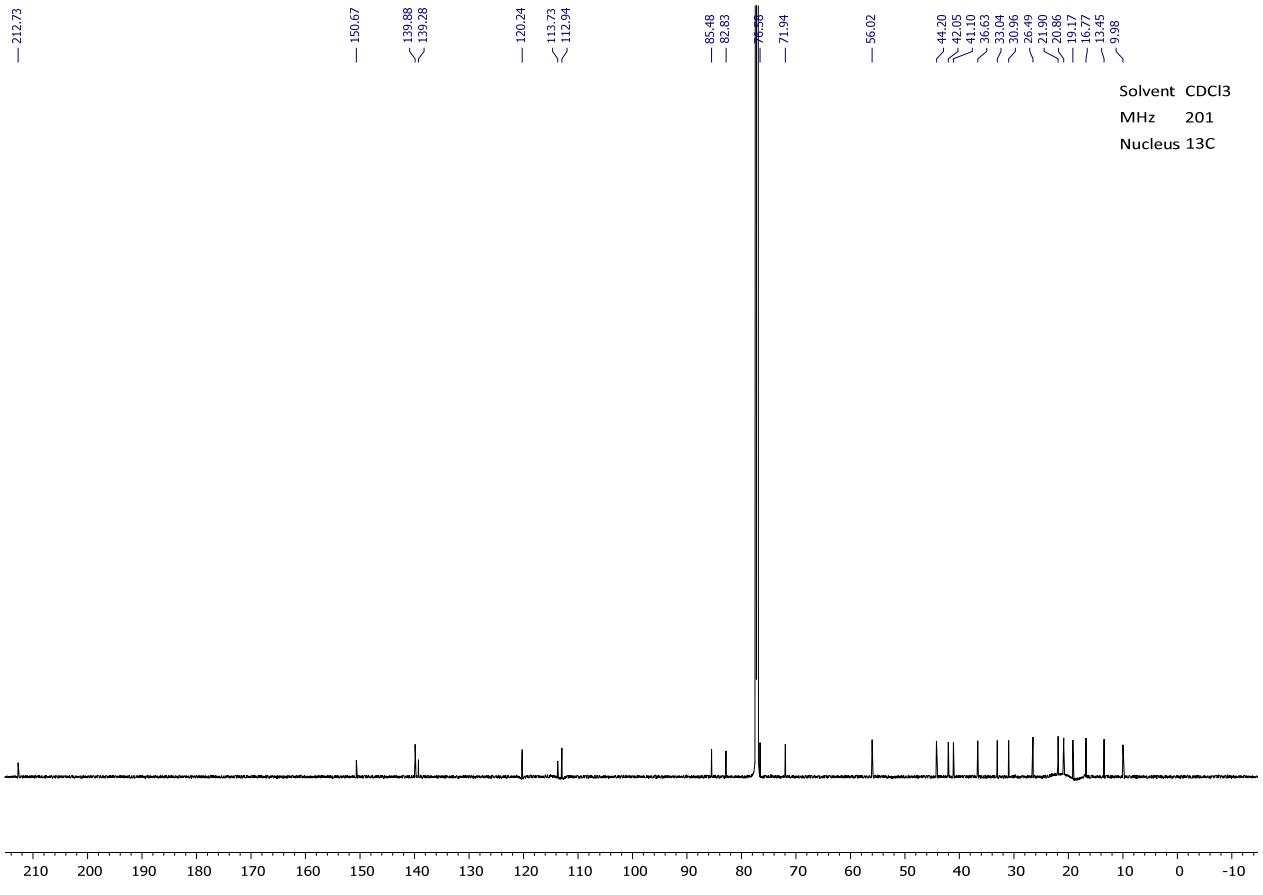
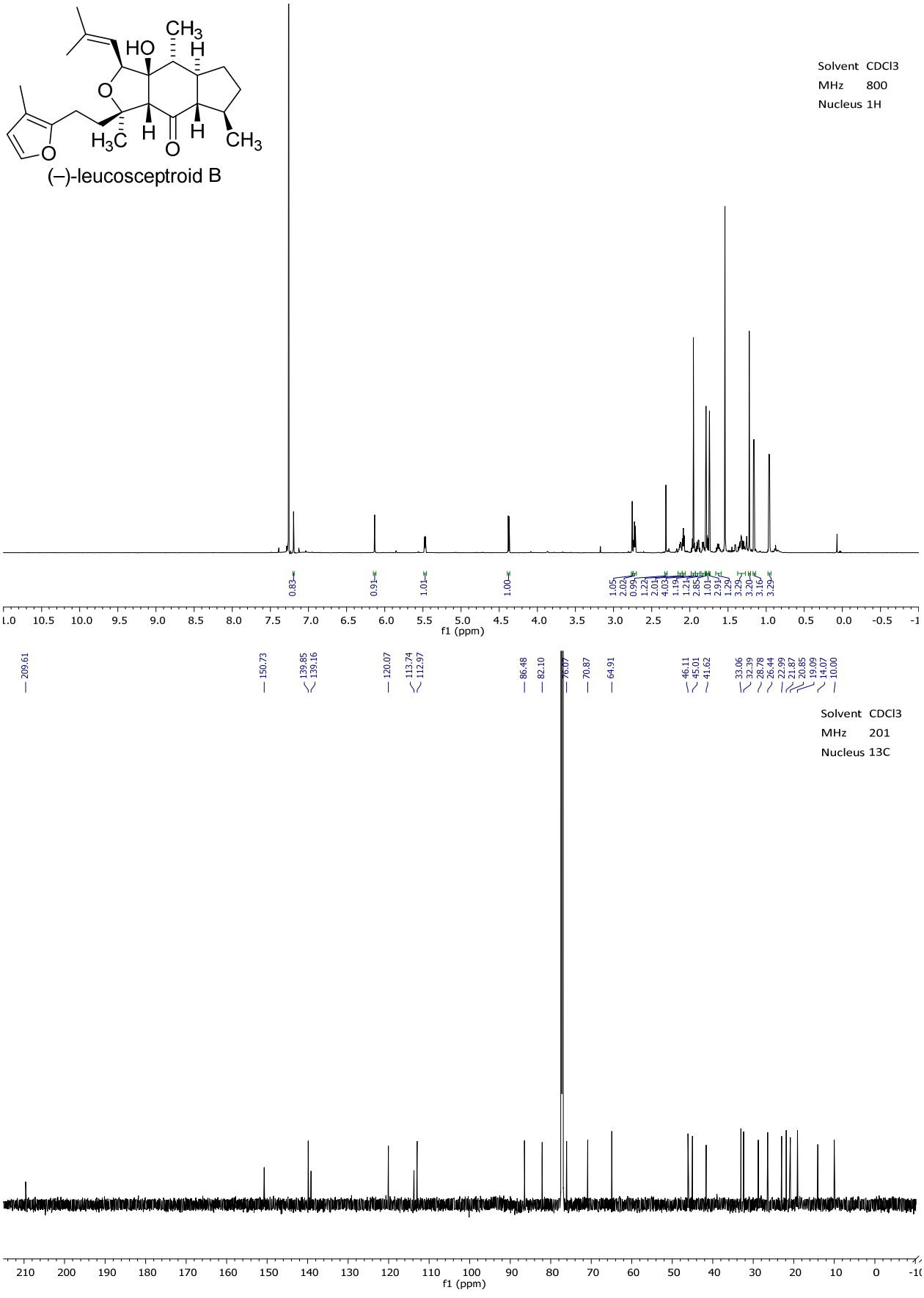
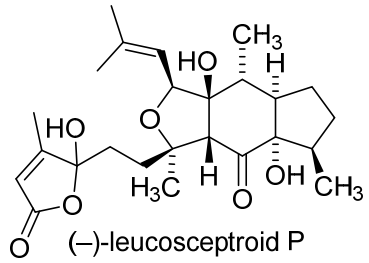
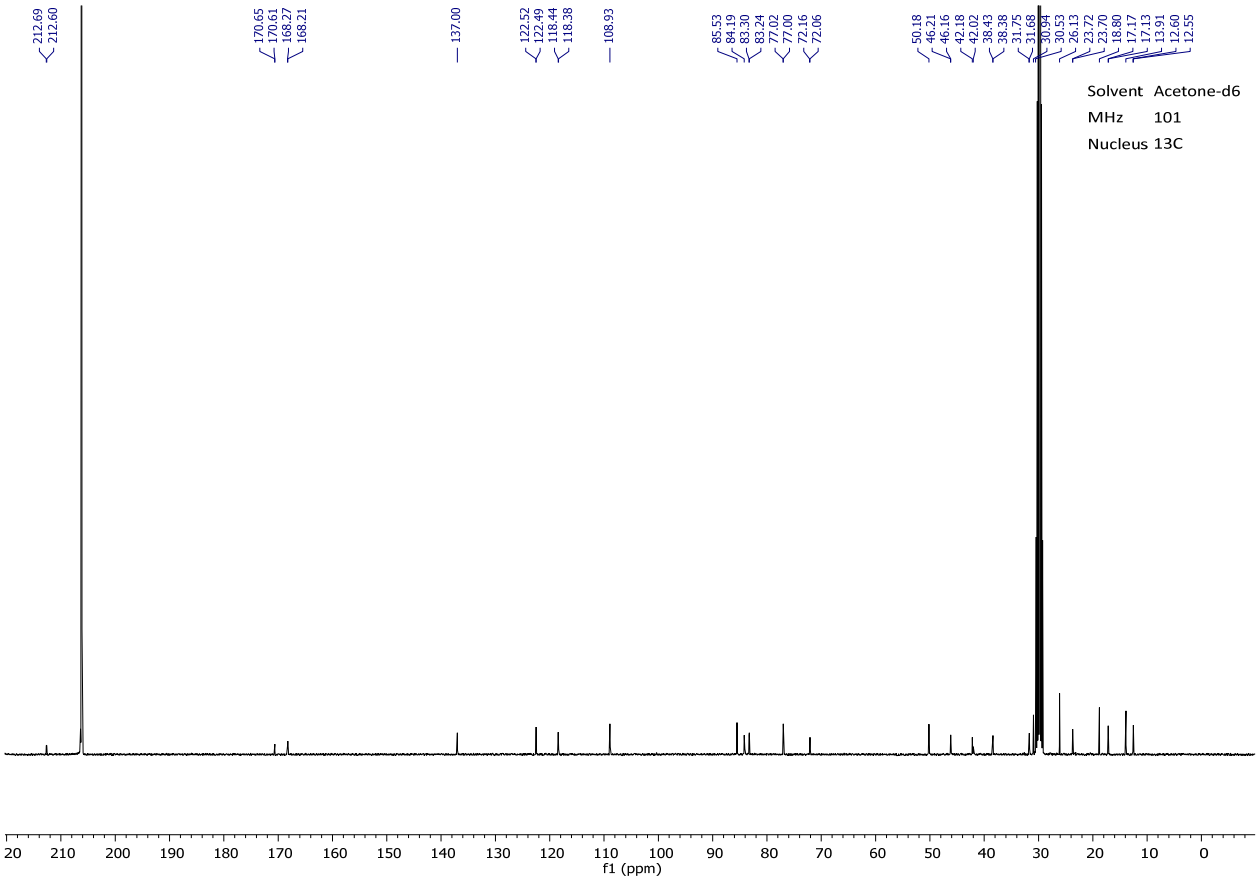

CH3
HO
H
O
H3C
H
O
H
CH3
O
Solvent CDCl3
MHz 800
Nucleus 1H
1.00
1.01
1.17
1.15
2.56
1.24
1.25
1.25
1.39
1.13
1.49
2.82
3.46
3.78
3.59
1.26
3.82
3.73
7.34
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

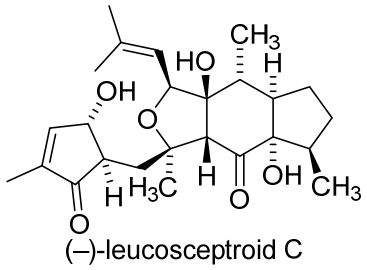

212.73
150.67
139.88
139.28
120.24
113.73
112.94
85.48
82.83
76.58
71.94
56.02
44.20
42.05
41.10
36.63
33.04
30.96
26.49
21.90
20.86
19.17
16.77
13.45
9.98
Solvent CDCl3
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


CH3
HO
H
O
H3C
H
O
H
CH3
O
(–)-leucosceptroid B
Solvent CDCl3
MHz 800
Nucleus 1H
0.83
0.91
1.01
1.00
1.05
2.02
0.99
1.22
2.01
4.03
1.19
1.21
2.85
1.01
2.91
1.29
3.29
3.20
3.16
3.29
f1 (ppm)
209.61
150.73
139.85
139.16
120.07
113.74
112.97
86.48
82.10
76.07
70.87
64.91
46.11
45.01
41.62
33.06
32.39
28.78
26.44
22.99
21.87
20.85
19.09
14.07
10.00
Solvent CDCl3
MHz 201
Nucleus 13C
f1 (ppm)

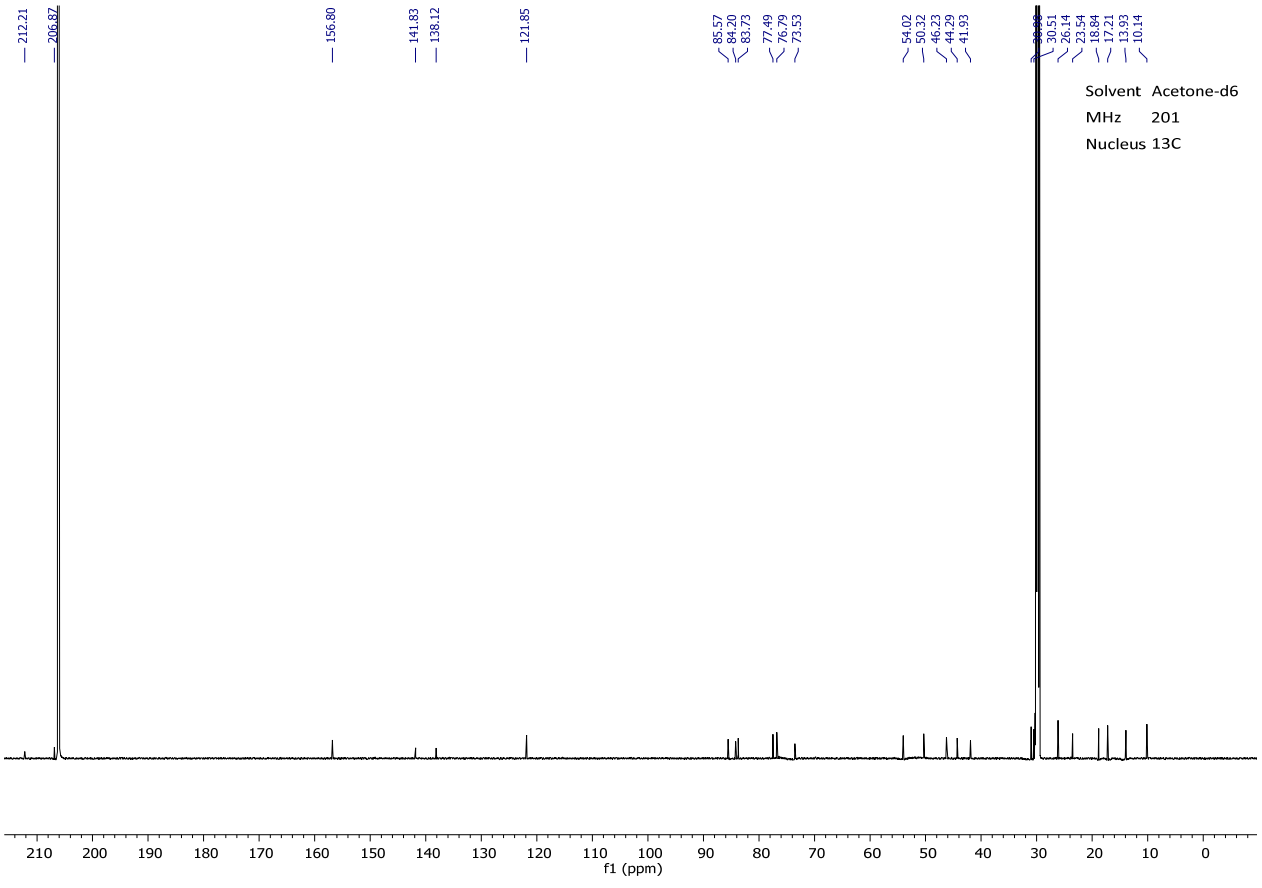


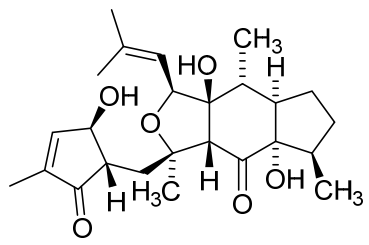
(–)-leucosceptroid P



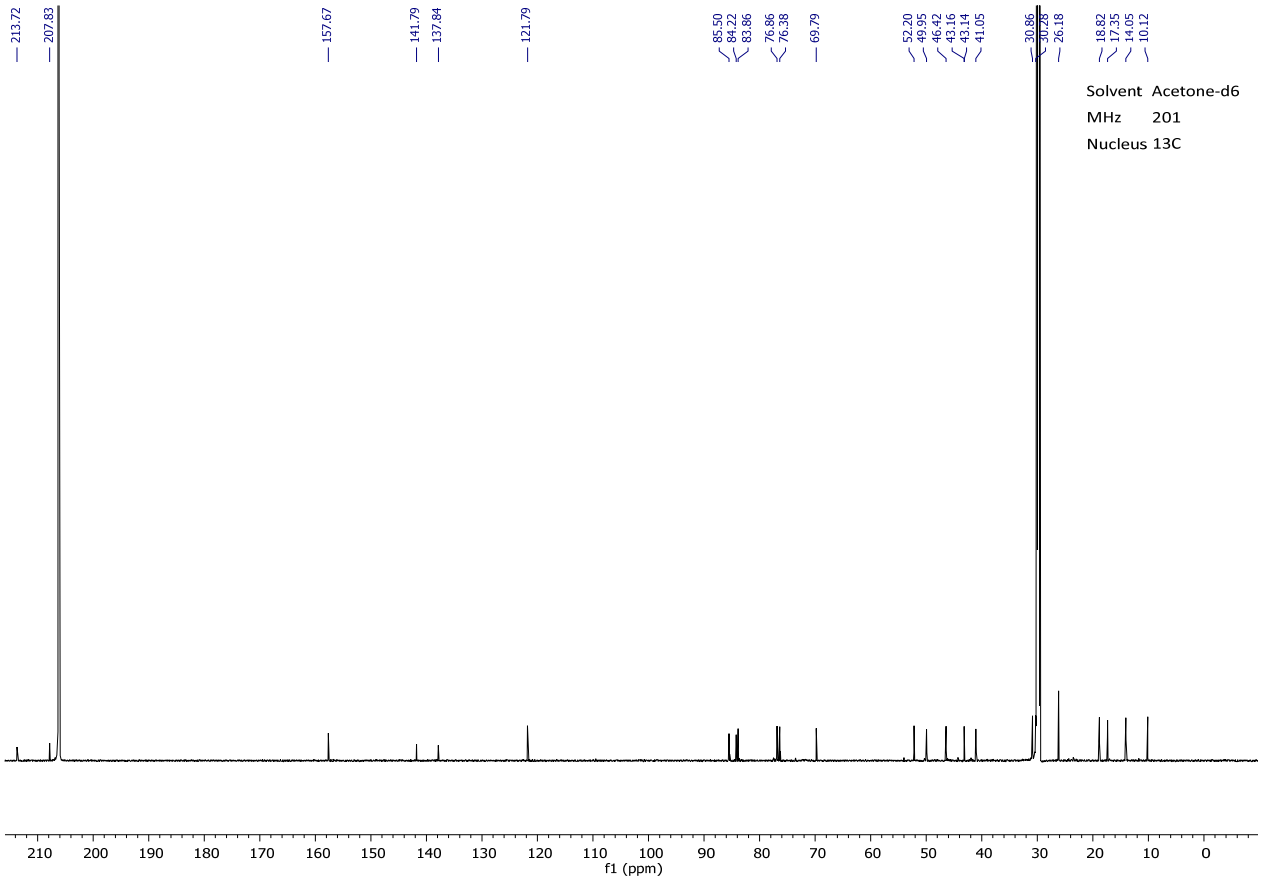


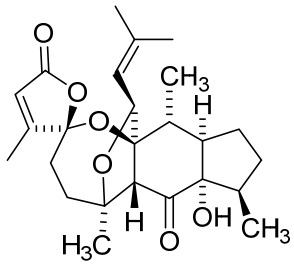
(–)-leucosceptroid C



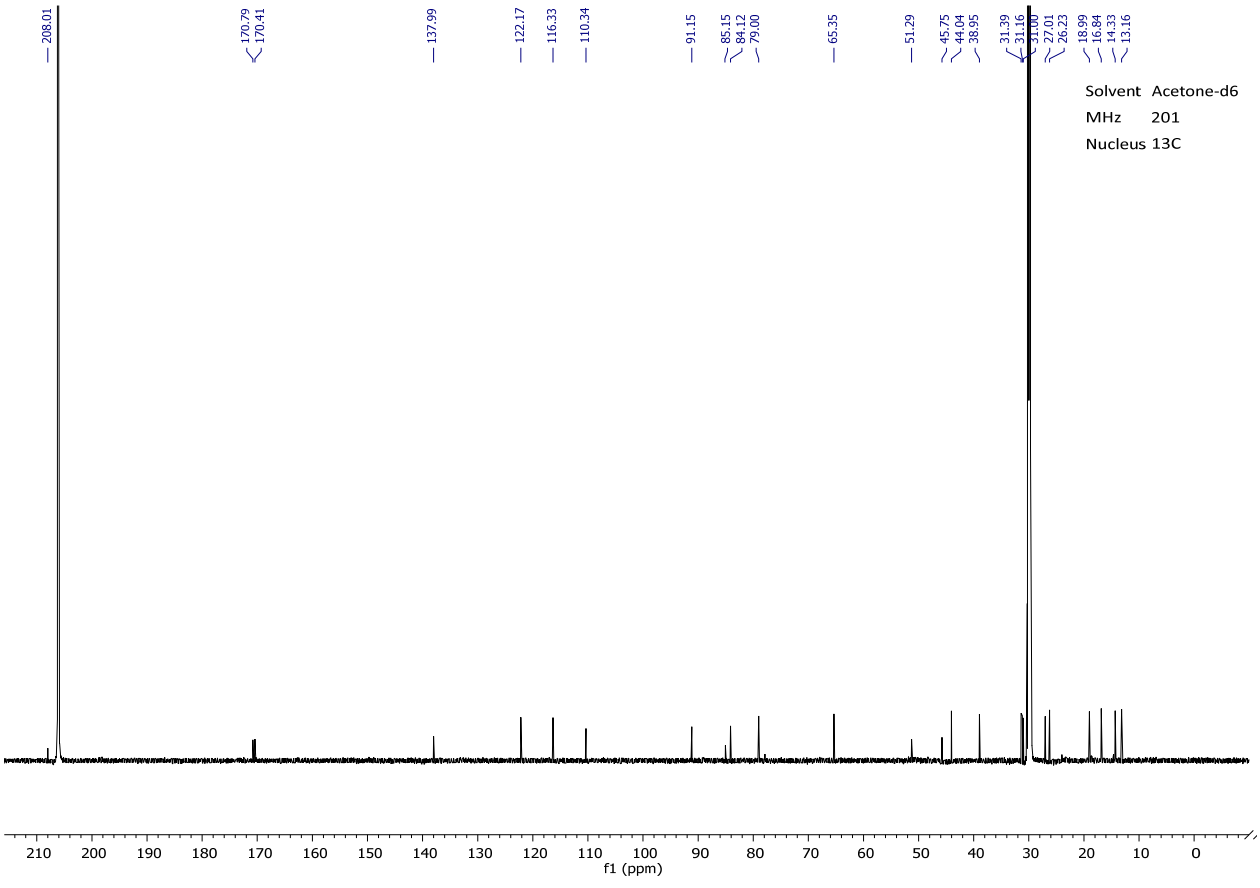

CH3
HO
H
OH
O
H
H3C
H
O
OH
CH3
O

Solvent Acetone-d6
MHz 800
Nucleus 1H
0.86
1.02
0.71
0.67
0.92
1.01
0.72
0.79
1.00
2.32
2.66
1.03
8.34
4.06
0.97
1.31
3.24
3.59
3.55
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


213.72
207.83
157.67
141.79
137.84
121.79
85.50
84.22
83.86
76.86
76.38
69.79
52.20
49.95
46.42
43.16
43.14
41.05
30.86
30.28
26.18
18.82
17.35
14.05
10.12
Solvent Acetone-d6
MHz 201
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(–)-leucosceptroid O



6.4 Supporting Information for Chapter 3.2.1

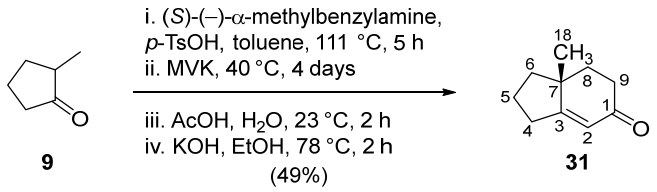
A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane

Cedric L. Hugelshofer and Thomas Magauer

Department of Chemistry and Pharmacy, Ludwig-Maximilians-University Munich, Butenandtstrasse 5–13, 81377, Munich, Germany

6.4.1 Experimental Procedures

Synthesis of enone 31



Based on the known preparation of enone **31**,[44] a round-bottomed flask was charged with 2-methylcyclopentanone (**9**) (28.0 mL, 260 mmol, 1 equiv), (*S*)-(–)-α-methylbenzylamine (33.5 mL, 260 mmol, 1.00 equiv), *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol, 0.002 equiv) and toluene (50 mL). The flask was then equipped with a Dean-Stark apparatus and the mixture was heated to 111 °C. After 5 h, the removal of water was judged to be complete (approximately 4.3 mL water collected) and the mixture was cooled to 0 °C. Methyl vinyl ketone (25.3 mL, 312 mmol, 1.20 equiv) was added, and after 1 h, the mixture was warmed to 40 °C. After 2 days, a further portion of methyl vinyl ketone (21.1 mL, 260 mmol, 1.00 equiv) was added and stirring was continued at 40 °C. After further 2 days, the mixture was cooled to 0 °C, and a solution of acetic acid (22.3 mL, 389 mmol, 1.50 equiv) in water (30 mL) was added. The resulting biphasic mixture was warmed to 23 °C and stirred vigorously. After 2 h, the mixture was diluted with saturated aqueous sodium chloride solution (50 mL), water (50 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 70 mL) and the combined organic extracts were washed sequentially with aqueous 1 M hydrogen chloride solution (50 mL) and saturated aqueous sodium chloride solution (60 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the diketone which was used in the next step without further purification.

A solution of the crude diketone (assuming 260 mmol) in ethanol (280 mL) was treated with potassium hydroxide (24.8 g, 442 mmol, 1.70 equiv) at 23 °C, and the resulting mixture was heated to 78 °C. After 2 h, the mixture was cooled to 0 °C and was acidified by addition of acetic acid (ca. 25 mL, pH~6). The resulting mixture was concentrated until a thick paste resulted. Water (150 mL) and a mixture of diethyl ether–pentane (1:1 v/v, 100 mL) was added. The layers were separated, the aqueous layer was extracted with diethyl ether–pentane (1:1 v/v, 4 x 70 mL) and the combined organic extracts were washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% → 30% ethyl acetate in hexanes) to provide enone **31** (19.0 g, 49%) as an orange oil. The characterization data for **31** were in agreement with values previously reported.[44a,45] The absolute configuration (*R*) of enone **31** was derived from the sign of the optical rotation, and **31** was estimated to be of ≥80% ee by comparison with the literature values (Lit.:[44a] $[\alpha]_D^{20}$ = –108° (c = 3.50, EtOH); Lit.:[45] $[\alpha]_D^{20}$ = –94° (c = 1.00, EtOH)).

TLC (20% ethyl acetate in hexanes): R_f = 0.32 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78–5.76 (m, 1H, 2-H), 2.76–2.64 (m, 1H, 4-H_A), 2.61–2.42 (m, 2H, 4-H_B, 9-H_A), 2.39–2.31 (m, 1H, 9-H_B), 2.03 (ddd, $^2J_{8A/8B}$ = 13.0 Hz, $^3J_{8A/9B}$ = 5.3 Hz, $^3J_{8A/9A}$ = 2.1 Hz, 1H, 8-H_A), 1.97–1.75 (m, 4H, 5-H, 6-H_A, 8-H_B), 1.53–1.43 (m, 1H, 6-H_B), 1.16 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.79 (C-1), 178.76 (C-3), 121.42 (C-2), 42.82 (C-7), 40.94 (C-6), 36.17 (C-8), 33.93 (C-9), 30.84 (C-4), 22.49 (C-18), 21.26 (C-5). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2960 (m), 2928 (m), 2861 (m), 1667 (s), 1454 (w), 1421 (w), 1296 (w), 1222 (w), 1202 (w) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{10}H_{14}O)^+$: 150.1045, found: 150.1044. $[\alpha]_D^{20}$ = –94.8° (c = 2.00, EtOH).

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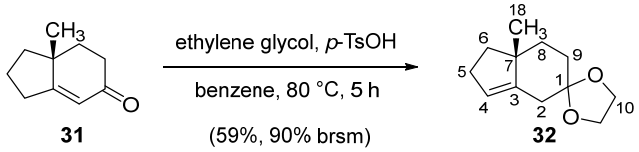
[44] a) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273. b) G. Revial, M. Pfau, *Org. Synth.* **1992**, *70*, 35.

[45] E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686.

Synthesis of ketal 32



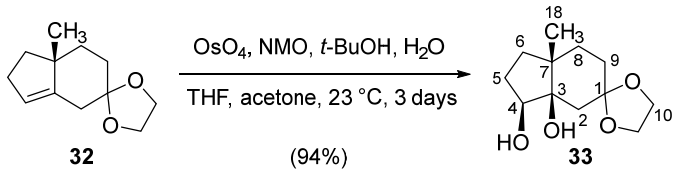
Based on the known preparation of ketal **32**,[46] a round-bottomed flask was charged with enone **31** (9.21 g, 61.3 mmol, 1 equiv), ethylene glycol (20.5 mL, 368 mmol, 6.00 equiv), *p*-toluenesulfonic acid monohydrate (1.17 g, 6.13 mmol, 0.10 equiv) and benzene (150 mL). The flask was equipped with a Dean-Stark apparatus and the mixture was heated to 80 °C. After 5 h, the removal of water was judged to be complete and the mixture was cooled to 23 °C. The mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (150 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 70 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% → 30% ethyl acetate in hexanes) to provide recovered enone **31** (3.19 g, 35%) and ketal **32** (7.00 g, 59%, 90% brsm) as a yellow oil. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for ketal **32** were in full agreement with values previously reported for the racemic compound.[47]

TLC (20% ethyl acetate in hexanes): R_f = 0.53 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32–5.28 (m, 1H, 4-H), 4.05–3.88 (m, 4H, 10-H), 2.48–2.19 (m, 4H, 2-H, 5-H), 1.91–1.74 (m, 2H, 6-H_A, 9-H_A), 1.75–1.61 (m, 3H, 6-H_B, 8-H_A, 9-H_B), 1.59–1.49 (m, 1H, 8-H_B), 1.06 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.40 (C-3), 122.63 (C-4), 109.87 (C-1), 64.65 (C-10), 64.51 (C-10'), 45.14 (C-7), 40.31 (C-6), 37.72 (C-8), 36.25 (C-2), 31.86 (C-9), 30.51 (C-5), 22.36 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944 (s), 2880 (m), 1455 (w), 1353 (w), 1306 (w), 1257 (w), 1177 (w), 1115 (m), 1090 (s), 1020 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{12}H_{18}O_2)^+$: 194.1307, found: 194.1293. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –18.7° (c = 0.83, CH_2Cl_2).

[46] a) D. Becker, N. C. Brodsky, J. Kalo, *J. Org. Chem.* **1978**, *43*, 2557. b) D. Becker, J. Kalo, N. C. Brodsky, *J. Org. Chem.* **1978**, *43*, 2562.

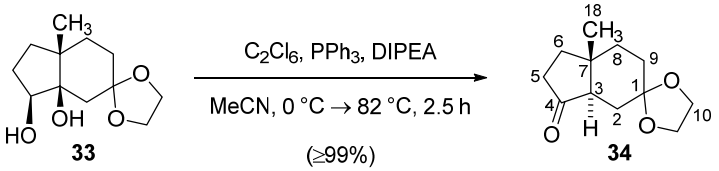
[47] B. Defaut, T. B. Parsons, N. Spencer, L. Male, B. M. Kariuki, R. S. Grainger, *Org. Biomol. Chem.* **2012**, *10*, 4926.

Synthesis of diol 33



Based on a slightly modified literature procedure,[47] a solution of ketal **32** (8.10 g, 41.7 mmol, 1 equiv) in tetrahydrofuran (24 mL), *tert*-butanol (70 mL), water (12 mL) and acetone (12 mL) was treated sequentially with 4-methylmorpholine *N*-oxide (5.86 g, 50.0 mmol, 1.20 equiv) and osmium tetroxide solution (2.5 wt.% in *t*-BuOH, 10.2 mL, 1.04 mmol, 0.03 equiv) at 23 °C. After 3 days, sodium sulfite (15.8 g, 125 mmol, 3.00 equiv) and water (20 mL) were added. After 15 min, the mixture was diluted with more water (100 mL) and ethyl acetate (100 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (6 x 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (7% methanol in dichloromethane) to provide diol **33** (8.94 g, 94%) as a brownish oil which solidified upon standing. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for diol **33** were in full agreement with values previously reported for the racemic compound.[47]
TLC (5% methanol in dichloromethane): R_f = 0.24 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.22–4.15 (m, 1H, 4-H), 4.00–3.89 (m, 4H, 10-H), 2.96 (br s, 1H, 3-OH), 2.49 (d, $^{3}J_{4OH/4}$ = 3.9 Hz, 1H, 4-OH), 2.13–2.02 (m, 1H, 5-H_A), 1.76–1.42 (m, 9H, 2-H, 5-H_B, 6-H, 8-H, 9-H), 1.07 (s, 3H, 18-H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 109.24 (C-1), 80.23 (C-3), 76.67 (C-4), 64.50 (C-10), 64.27 (C-10'), 42.45 (C-7), 40.25 (C-2), 34.02 (C-6), 32.54 (C-8), 30.45 (C-9), 28.82 (C-5), 21.58 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (br), 2954 (m), 1465 (m), 1428 (m), 1341 (m), 1265 (s), 1122 (m), 1091 (s), 1069 (s), 1032 (s), 1012 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+Na], $C_{12}H_{20}O_4Na)^+$: 251.12593, found: 251.12550. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –61.8° (c = 0.33, CH_2Cl_2).

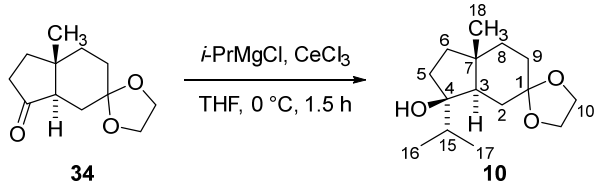
Synthesis of hydrindanone 34



Based on the literature procedure,[47] a suspension of triphenylphosphine (17.3 g, 66.1 mmol, 2.20 equiv) in acetonitrile (200 mL) was treated with hexachloroethane (15.7 g, 66.1 mmol, 2.20 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was warmed to 23 °C. After 30 min, the mixture was cooled to 0 °C, whereupon *N*,*N*-diisopropylethylamine (22.9 mL, 132 mmol, 4.40 equiv), followed by a solution of diol **33** (6.86 g, 30 mmol, 1 equiv) in acetonitrile (120 mL) was added dropwise over a period of 10 min. After 1 h, the reaction flask was placed in a preheated (82 °C) oil bath. After 1.5 h, the mixture was allowed to cool to 23 °C, and then was diluted with diethyl ether (300 mL). The organic layer was washed with water (2 x 100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide hydrindanone **34** (6.32 g, ≥99%) as a yellowish oil which solidified upon standing. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for hydrindanone **34** were in full agreement with values previously reported for the racemic compound.[47]

TLC (30% ethyl acetate in hexanes): R_f = 0.38 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.02–3.85 (m, 4H, 10-H), 2.40–2.20 (m, 3H, 3-H, 5-H), 1.98–1.91 (m, 1H, 2-H_A), 1.90–1.57 (m, 6H, 6-H, 8-H, 9-H), 1.45 (app t, $^{2}J_{2B/2A} = {}^{3}J_{2B/3}$ = 13.1 Hz, 1H, 2-H_B), 0.87 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 216.44 (C-4), 109.56 (C-1), 64.62 (C-10), 64.33 (C-10'), 57.34 (C-3), 38.72 (C-7), 35.93 (C-5, C-6, C-8), 35.88 (C-5, C-6, C-8), 35.39 (C-5, C-6, C-8), 31.70 (C-9), 29.86 (C-2), 17.03 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (m), 2882 (m), 1737 (s), 1459 (m), 1354 (m), 1287 (m), 1194 (m), 1110 (s), 1080 (m), 1016 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{12}H_{19}O_3$)$^{+}$: 211.13342, found: 211.13297. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –92.6° (c = 1.00, CH_2Cl_2).

Synthesis of *trans*-hydrindane 10

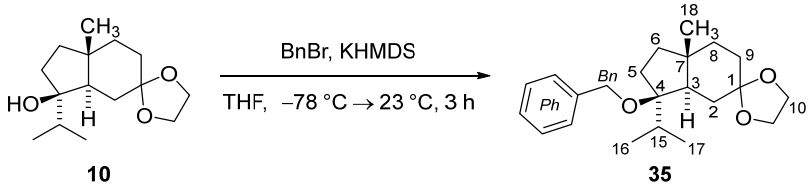


Based on a slightly modified literature procedure,[47] a solution of hydrindanone **34** (6.31 g, 30 mmol, 1 equiv) in tetrahydrofuran (250 mL) was treated with anhydrous cerium(III) trichloride (11.1 g, 45 mmol, 1.50 equiv) at 23 °C. After 1.5 h, the colourless suspension was cooled to 0 °C, whereupon a solution of isopropylmagnesium chloride (2 M in THF, 33.8 mL, 67.5 mmol, 2.25 equiv) was added over a period of 10 min. After 1.5 h, the mixture was diluted with pH 7 buffer solution (300 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 70 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide *trans*-hydrindane **10** (8.10 g) as a brownish oil which was used in the next step without further purification.

An analytically pure sample of *trans*-hydrindane **10** was obtained by flash-column chromatography on silica gel (30% ethyl acetate in hexanes). The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for *trans*-hydrindane **10** were in full agreement with values previously reported for the racemic compound.[47]

TLC (30% ethyl acetate in hexanes): R_f = 0.37 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.98–3.91 (m, 4H, 10-H), 2.00 (dd, $^{2}J_{5A/5B}$ = 14.3 Hz, $^{3}J_{5A/6B}$ = 9.6 Hz, 1H, 5-H_A), 1.86–1.52 (m, 9H, 2-H, 3-H, 5-H_B, 6-H_A, 8-H_A, 9-H, 15-H), 1.38 (app td, $^{2}J_{8B/8A}$ = $^{3}J_{8B/9A}$ = 13.4 Hz, $^{3}J_{8B/9B}$ = 4.3 Hz, 1H, 8-H_B), 1.16–1.05 (m, 4H, 6-H_B, 18-H), 1.04 (s, 1H, 4-OH), 0.95 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H), 0.90 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 110.81 (C-1), 83.30 (C-4), 64.47 (C-10), 64.29 (C-10'), 51.09 (C-3), 41.56 (C-7), 39.42 (C-6), 37.47 (C-15), 37.29 (C-8), 36.73 (C-5), 31.61 (C-2, C-9), 31.56 (C-2, C-9), 18.47 (C-16, C-17), 18.31 (C-18), 17.65 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3508 (br), 2953 (s), 2877 (s), 1459 (m), 1348 (m), 1292 (m), 1254 (m), 1192 (m), 1145 (s), 1089 (s), 1020 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{26}O_3$)$^{+}$: 254.1882, found: 254.1876. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –12.6° (c = 1.00, CH_2Cl_2).

Synthesis of benzyl ether 35



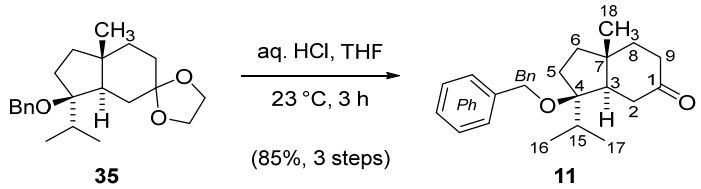
10 **35**

A solution of crude *trans*-hydrindane **10** (6.50 g, 25.6 mmol, 1 equiv) in tetrahydrofuran (21 mL) was treated sequentially with potassium bis(trimethylsilyl)amide solution (1 M in THF, 30.7 mL, 30.7 mmol, 1.20 equiv) and benzyl bromide (4.59 mL, 38.3 mmol, 1.50 equiv) at –78 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 3 h, the mixture was diluted with saturated aqueous ammonium chloride solution (150 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide benzyl ether **35** (8.82 g) as a yellowish oil which was used in the next step without further purification.

An analytically pure sample of benzyl ether **35** was obtained by flash-column chromatography on silica gel (5% → 10% ethyl acetate in hexanes).

TLC (10% ethyl acetate in hexanes): R_f = 0.33 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H, *Ph*), 4.45–4.37 (m, 2H, *Bn*), 3.98–3.92 (m, 4H, 10-H), 2.33–2.20 (m, 1H, 15-H), 2.22–2.11 (m, 1H, 5-H_A), 1.95–1.75 (m, 5H, 2-H, 3-H, 5-H_B, 9-H_A), 1.66–1.53 (m, 3H, 6-H_A, 8-H_A, 9-H_B), 1.41 (app td, $^2J_{8B/8A}$ = $^3J_{8B/9A}$ = 13.4 Hz, $^3J_{8B/9B}$ = 4.5 Hz, 1H, 8-H_B), 1.20–1.09 (m, 1H, 6-H_B), 1.07 (s, 3H, 18-H), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.34 (*Ph*), 128.23 (*Ph*), 126.79 (*Ph*), 126.68 (*Ph*), 111.05 (C-1), 87.58 (C-4), 64.40 (C-10), 64.28 (C-10'), 62.43 (*Bn*), 48.33 (C-3), 41.86 (C-7), 40.17 (C-6), 36.87 (C-8), 34.43 (C-5), 33.75 (C-2), 33.01 (C-15), 31.74 (C-9), 18.48 (C-16, C-17), 18.19 (C-18), 18.15 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 2877 (m), 1454 (m), 1385 (m), 1263 (m), 1198 (m), 1143 (m), 1085 (s), 1061 (s), 1040 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{22}H_{32}O_3$)$^+$: 344.2351, found: 344.2338. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +32.2° (c = 1.06, CH_2Cl_2).

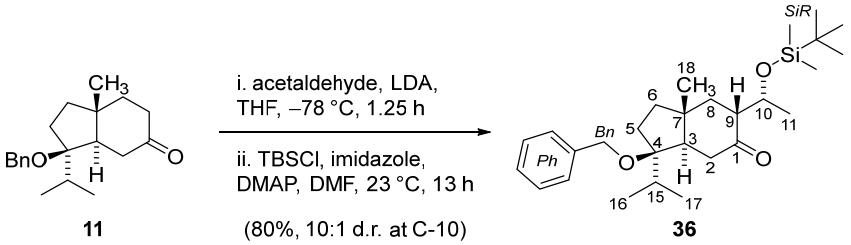
Synthesis of ketone 11



A solution of crude benzyl ether **35** (8.82 g, 25.6 mmol, 1 equiv) in tetrahydrofuran (100 mL) was treated with aqueous 4 M hydrogen chloride solution (30 mL) and the resulting mixture was stirred vigorously at 23 °C. After 3 h, the mixture was diluted with water (50 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% → 20% ethyl acetate in hexanes) to provide ketone **11** (6.51 g, 85% over three steps) as a yellowish oil which solidified upon standing.

TLC (10% ethyl acetate in hexanes): R_f = 0.29 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29–7.16 (m, 5H, *Ph*), 4.39–4.33 (m, 2H, *Bn*), 2.70 (dd, $^2J_{2A/2B}$ = 16.1 Hz, $^3J_{2A/3}$ = 14.2 Hz, 1H, 2-H_A), 2.44–2.36 (m, 2H, 2-H_B, 9-H_A), 2.33–2.28 (m, 1H, 9-H_B), 2.28–2.16 (m, 2H, 5-H_A, 15-H), 1.85 (dd, $^2J_{5B/5A}$ = 13.8 Hz, $^3J_{5B/6B}$ = 8.1 Hz, 1H, 5-H_B), 1.82–1.75 (m, 2H, 3-H, 8-H_A), 1.65 (dd, $^2J_{6A/6B}$ = 12.0 Hz, $^3J_{6A/5A}$ = 7.9 Hz, 1H, 6-H_A), 1.55–1.48 (m, 1H, 8-H_B), 1.20–1.13 (m, 4H, 6-H_B, 18-H), 0.89 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.86 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.61 (C-1), 139.84 (*Ph*), 128.34 (*Ph*), 127.05 (*Ph*), 126.84 (*Ph*), 87.40 (C-4), 62.61 (*Bn*), 49.63 (C-3), 41.74 (C-7), 41.55 (C-2), 39.94 (C-6), 37.72 (C-9), 37.29 (C-8), 35.08 (C-5), 33.06 (C-15), 18.26 (C-16, C-17), 18.15 (C-18), 17.78 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (m), 2876 (m), 1706 (s), 1454 (m), 1387 (m), 1220 (w), 1111 (m), 1085 (m), 1056 (s), 1028 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+NH_4], $C_{20}H_{32}O_2N)^+$: 318.24330, found: 318.24334. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +15.6° (c = 1.05, CH_2Cl_2).

Synthesis of silyl ether 36



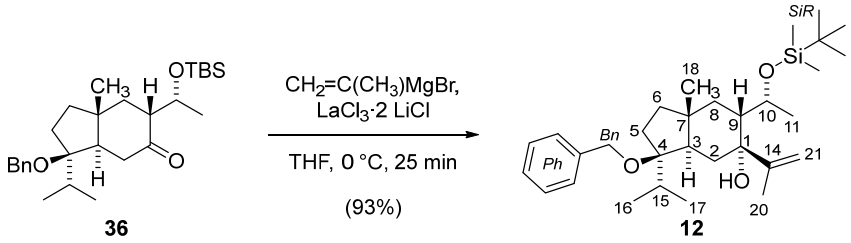
11 **36**

A solution of ketone **11** (1.28 g, 4.26 mmol, 1 equiv) in tetrahydrofuran (12 mL) was treated with a freshly prepared solution of lithium diisopropylamide (1 M in THF, 4.69 mL, 4.69 mmol, 1.10 equiv) at −78 °C (addition to the inner wall of the reaction flask, such that the solution was cooled before reaching the reaction mixture). After 45 min, a solution of acetaldehyde (0.29 mL, 5.11 mmol, 1.20 equiv) in tetrahydrofuran (4 mL) was added dropwise over a period of 5 min. After 40 min, TLC analysis indicated incomplete conversion of ketone **11**, and therefore a further portion of acetaldehyde (71.7 µL, 1.28 mmol, 0.30 equiv) in tetrahydrofuran (0.5 mL) was added dropwise over a period of 2 min. After further 30 min, the mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to provide the aldol product which was used in the next step without further purification.

A solution of the crude aldol product (assuming 4.26 mmol) in dimethyl formamide (8.5 mL) was treated sequentially with imidazole (0.93 g, 13.6 mmol, 3.20 equiv), 4-dimethylaminopyridine (52.0 mg, 0.43 mmol, 0.10 equiv) and *tert*-butyldimethylchlorosilane (0.90 g, 5.96 mmol, 1.40 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 13 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (40 mL), water (20 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to provide silyl ether **36** (1.57 g, 80% over two steps, inconsequential 10:1 d.r. at C-10) as a colourless oil which solidified upon standing.

TLC (5% ethyl acetate in hexanes): R_f = 0.43 (CAM). *Note: Traces of the minor C-10 diastereomer are visible in the ^{1}H and ^{13}C NMR spectra, but solely the resonances of the major diastereomer are listed below.* **^{1}H NMR** (800 MHz, C_6D_6) δ 7.31–7.28 (m, 2H, *Ph*), 7.26–7.23 (m, 2H, *Ph*), 7.15–7.13 (m, 1H, *Ph*), 4.7–4.67 (m, 1H, 10-H), 4.17–4.09 (m, 2H, *Bn*), 2.75–2.69 (m, 1H, 2-H_A), 2.66–2.61 (m, 1H, 9-H), 2.60 (dd, $^2J_{2B/2A}$ = 15.5 Hz, $^3J_{2B/3}$ = 3.9 Hz, 1H, 2-H_B), 2.09 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/9}$ = 6.5 Hz, 1H, 8-H_A), 2.05–1.99 (m, 1H, 5-H_A), 1.84 (h, $^3J_{15/16\text{-}17}$ = 6.9 Hz, 1H, 15-H), 1.67 (dd, $^3J_{3/2A}$ = 14.3 Hz, $^3J_{3/2B}$ = 3.9 Hz, 1H, 3-H), 1.57–1.49 (m, 2H, 5-H_B, 6-H_A), 1.43 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 12.6 Hz, 1H, 8-H_B), 1.25 (d, $^3J_{11/10}$ = 6.2 Hz, 3H, 11-H), 1.11 (s, 3H, 18-H), 1.08–1.02 (m, 1H, 6-H_B), 0.99 (s, 9H, *SiR*), 0.78 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.68 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.10 (s, 6H, *SiR*). **^{13}C NMR** (200 MHz, C_6D_6) δ 210.42 (C-1), 140.13 (*Ph*), 128.57 (*Ph*), 127.33 (*Ph*), 127.17 (*Ph*), 87.58 (C-4), 67.51 (C-10), 62.84 (*Bn*), 52.95 (C-9), 50.46 (C-3), 41.94 (C-7), 41.90 (C-2), 40.38 (C-6), 38.07 (C-8), 34.86 (C-5), 32.90 (C-15), 26.15 (*SiR*), 19.85 (C-11), 18.85 (C-18), 18.32 (*SiR*), 18.10 (C-16, C-17), 17.72 (C-16, C-17), –4.36 (*SiR*), –4.76 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 2930 (s), 2857 (m), 1700 (s), 1471 (m), 1387 (m), 1254 (s), 1109 (s), 1066 (s), 1043 (s), 1006 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–*t*Bu], $C_{24}H_{37}O_3Si)^+$: 401.2512, found: 401.2516. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +26.4° (c = 0.33, CH_2Cl_2).

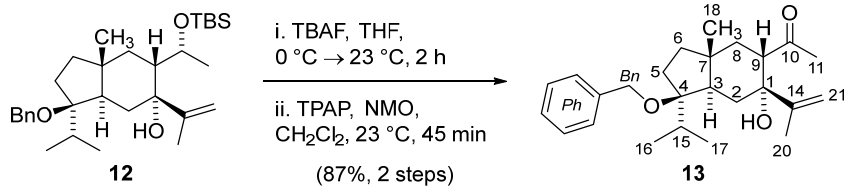
Synthesis of allylic alcohol 12



A solution of silyl ether **36** (1.56 g, 3.40 mmol, 1 equiv, 10:1 d.r. at C-10) in tetrahydrofuran (3.5 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 7.39 mL, 3.40 mmol, 1.00 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon isopropenylmagnesium bromide solution (0.5 M in THF, 20.4 mL, 10.2 mmol, 3.00 equiv) was added dropwise over a period of 20 min (syringe pump). After complete addition, stirring was continued for 5 min, before the mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to provide allylic alcohol **12** (1.58 g, 93%) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.32 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.37 (m, 2H, *Ph*), 7.25–7.19 (m, 2H, *Ph*), 7.13–7.06 (m, 1H, *Ph*), 5.50 (d, $^2J_{21A/21B}$ = 2.2 Hz, 1H, 21-H_A), 4.93–4.88 (m, 1H, 21-H_B), 4.33–4.22 (m, 2H, *Bn*), 3.81–3.72 (m, 1H, 10-H), 3.59 (d, $^4J_{1OH/2A}$ = 1.3 Hz, 1H, 1-OH), 2.32–2.19 (m, 2H, 2-H_A, 3-H), 2.16–2.00 (m, 2H, 5-H_A, 15-H), 1.98–1.88 (m, 2H, 8-H_A, 9-H), 1.75 (s, 3H, 20-H), 1.72–1.61 (m, 3H, 2-H_B, 5-H_B, 6-H_A), 1.53 (d, $^2J_{8B/8A}$ = 8.5 Hz, 1H, 8-H_B), 1.34–1.24 (m, 4H, 6-H_B, 11-H), 1.21 (s, 3H, 18-H), 1.01 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.99–0.92 (m, 12H, 16-H, 17-H, *SiR*), 0.04 (s, 3H, *SiR*), 0.00 (s, 3H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 153.45 (C-14), 140.70 (*Ph*), 128.52 (*Ph*), 127.33 (*Ph*), 127.14 (*Ph*), 110.27 (C-21), 88.71 (C-4), 78.59 (C-1), 74.41 (C-10), 63.20 (*Bn*), 45.17 (C-3), 42.50 (C-9), 42.28 (C-7), 41.66 (C-8), 41.34 (C-6), 38.01 (C-2), 34.25 (C-5), 33.19 (C-15), 25.99 (*SiR*), 22.55 (C-11), 20.24 (C-20), 19.11 (C-18), 18.53 (C-16, C-17), 18.34 (C-16, C-17), 18.13 (*SiR*), –4.11 (*SiR*), –4.87 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3461 (br), 2954 (s), 2930 (s), 2858 (m), 1454 (m), 1386 (s), 1254 (s), 1118 (m), 1060 (s), 1028 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{31}H_{53}O_3Si)^+$: 501.37640, found: 501.37617. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +20.0°(c = 0.20, CH_2Cl_2).

Synthesis of β-hydroxyketone 13

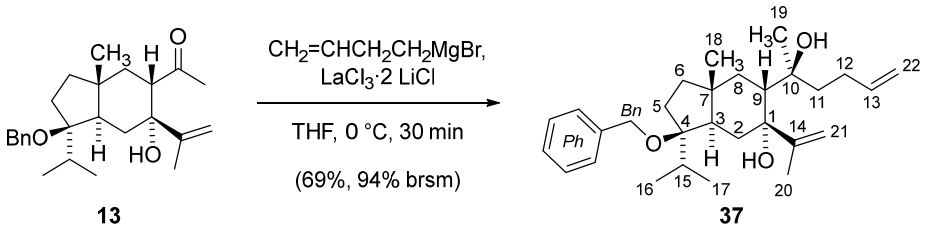


A solution of allylic alcohol **12** (1.57 g, 3.13 mmol, 1 equiv) in tetrahydrofuran (30 mL) was treated with tetrabutylammonium fluoride solution (1 M in THF, 4.70 mL, 4.70 mmol, 1.50 equiv) at 0 °C. After 1.5 h, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 30 min, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (80 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude diol which was used in the next step without further purification.

A solution of the crude diol (assuming 3.13 mmol) in dichloromethane (24 mL) was treated sequentially with 4 Å molecular sieves (600 mg), 4-methylmorpholine *N*-oxide (0.55 g, 4.70 mmol, 1.50 equiv) and tetrapropylammonium perruthenate (77.0 mg, 0.21 mmol, 0.07 equiv) at 23 °C. After 45 min, the mixture was concentrated to a small volume and the black oily residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to provide β-hydroxyketone **13** (1.05 g, 87% over two steps) as a yellowish oil which solidified upon standing.

TLC (10% ethyl acetate in hexanes): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.38–7.33 (m, 2H, *Ph*), 7.24–7.18 (m, 2H, *Ph*), 7.13–7.06 (m, 1H, *Ph*), 5.21–5.18 (m, 1H, 21-H_A), 4.91 (br s, 1H, 1-OH), 4.83–4.80 (m, 1H, 21-H_B), 4.30–4.20 (m, 2H, *Bn*), 2.97 (dd, $^3J_{9/8A}$ = 12.7 Hz, $^3J_{9/8B}$ = 3.8 Hz, 1H, 9-H), 2.43–2.35 (m, 1H, 3-H), 2.09–1.99 (m, 2H, 5-H_A, 15-H), 1.98–1.93 (m, 2H, 2-H), 1.69–1.67 (m, 3H, 20-H), 1.67–1.57 (m, 5H, 5-H_B, 8-H_A, 11-H), 1.50 (dd, $^2J_{6A/6B}$ = 11.6 Hz, $^3J_{6A/5A}$ = 7.9 Hz, 1H, 6-H_A), 1.38 (dd, $^2J_{8B/8A}$ = 12.2 Hz, $^3J_{8B/9}$ = 3.8 Hz, 1H, 8-H_B), 1.18–1.08 (m, 1H, 6-H_B), 1.07 (s, 3H, 18-H), 1.05 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 215.29 (C-10), 152.16 (C-14), 140.91 (*Ph*), 128.91 (*Ph*), 127.72 (*Ph*), 127.58 (*Ph*), 110.84 (C-21), 88.90 (C-4), 77.24 (C-1), 63.56 (*Bn*), 50.80 (C-9), 45.54 (C-3), 42.21 (C-7), 40.81 (C-6), 40.34 (C-8), 36.02 (C-2), 34.50 (C-5), 33.47 (C-15), 30.69 (C-11), 20.15 (C-20), 19.18 (C-18), 18.87 (C-16, C-17), 18.62 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (br), 2958 (s), 1695 (s), 1639 (w), 1453 (s), 1386 (s), 1182 (m), 1163 (m), 1086 (m), 1058 (s), 1027 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{27}H_{39}O_5$)$^-$: 443.27975, found: 443.28067. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +15.6° (c = 0.50, CH_2Cl_2).

Synthesis of diene 37

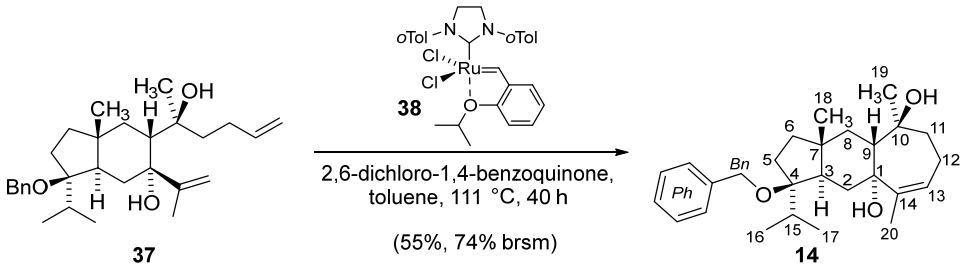


Grignard stock solution preparation: A suspension of magnesium turnings (0.32 g, 13.0 mmol, 1 equiv) in tetrahydrofuran (8 mL) was treated dropwise with a solution of 4-bromo-1-butene (1.32 mL, 13.0 mmol, 1.00 equiv) in tetrahydrofuran (5 mL) over a period of 10 min so as to maintain a gentle reflux. After complete addition, stirring was continued at 23 °C for 1 h, before the mixture was filtered (argon atmosphere) and used immediately in the following reaction.

In a separate flask, a solution of β-hydroxyketone **13** (1.00 g, 2.60 mmol, 1 equiv) in tetrahydrofuran (3 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 5.65 mL, 2.60 mmol, 1.00 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon freshly prepared 3-butenylmagnesium bromide solution (assuming 0.70 M in THF, 11.1 mL, 7.80 mmol, 3.00 equiv) was added dropwise over a period of 20 min (syringe pump). After end of the addition, stirring was continued for 10 min, before the mixture was diluted with pH 7 buffer solution (70 mL), saturated aqueous sodium chloride solution (30 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% → 20% ethyl acetate in hexanes) to provide recovered β-hydroxyketone **13** (0.27 g, 27%) as a yellowish oil and diene **37** (0.79 g, 69%, 94% brsm) as a yellowish foam.

TLC (10% ethyl acetate in hexanes): R_f = 0.20 (CAM). *Note:* diene **37** *shows signal broadening in both the ^{1}H and ^{13}C NMR spectra due to hindered rotation of the sidechains.* **^{1}H NMR** (400 MHz, C_6D_6) δ 7.39–7.34 (m, 2H, *Ph*), 7.25–7.18 (m, 2H, *Ph*), 7.14–7.07 (m, 1H, *Ph*), 5.78–5.56 (m, 2H, 13-H, 21-H_A), 5.08–4.90 (m, 2H, 22-H), 4.84 (br s, 1H, 21-H_B), 4.34–4.19 (m, 2H, *Bn*), 4.13 (br s, 1H, 1-OH, 10-OH), 2.34–2.13 (m, 2H, 2-H_A, 3-H), 2.13–1.93 (m, 3H, 5-H_A, 9-H, 15-H), 1.93–1.83 (m, 2H, 12-H), 1.78–1.51 (m, 9H, 2-H_B, 5-H_B, 6-H_A, 8-H, 11-H_A, 20-H), 1.34–1.18 (m, 5H, 6-H_B, 11-H_B, 19-H), 1.11 (br s, 3H, 18-H), 1.02 (br d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 155.66 (C-14), 140.66 (*Ph*), 138.78 (C-13), 128.50 (*Ph*), 127.27 (*Ph*), 127.13 (*Ph*), 114.63 (C-22), 109.81 (C-21), 88.78 (C-4), 79.82 (C-1), 77.52 (C-10), 63.17 (*Bn*), 44.92 (C-3), 42.41 (C-6, C-7, C-9, C-11), 42.18 (C-6, C-7, C-9, C-11), 41.35 (C-6, C-7, C-9, C-11), 41.18 (C-6, C-7, C-9, C-11), 39.48 (C-2), 38.18 (C-8), 34.20 (C-5), 33.23 (C-15), 29.18 (C-12), 26.47 (C-19), 20.59 (C-20), 19.02 (C-18), 18.55 (C-16, C-17), 18.30 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3366 (br), 2944 (s), 2873 (s), 1639 (m), 1453 (s), 1385 (s), 1345 (m), 1142 (m), 1059 (s), 906 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{31}H_{47}O_5$)$^-$: 499.34235, found: 499.34308. $[\alpha]_D^{20}$ = +11.3° (c = 0.30, CH_2Cl_2).

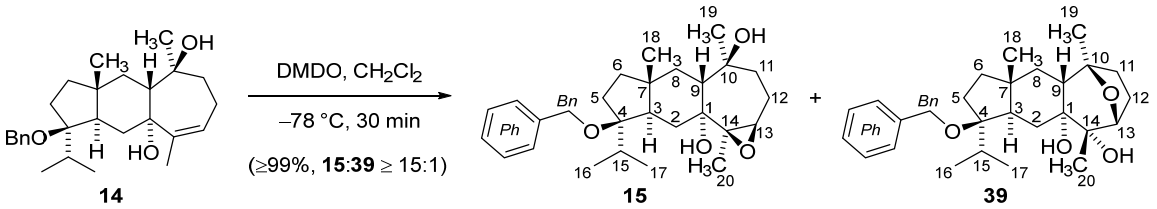
Synthesis of tricycle 14



A solution of diene **37** (0.42 g, 0.95 mmol, 1 equiv) in degassed (sparged with argon for 60 min prior to use) toluene (900 mL) was treated with 2,6,-dichloro-1-4-benzoquinone (33.7 mg, 0.19 mmol, 0.20 equiv) and Stewart–Grubbs catalyst **38** (109.0 mg, 0.19 mmol, 0.20 equiv). The resulting orange mixture was then heated to 111 °C, whereupon it turned dark brown. After 24 h, a further portion of Stewart–Grubbs catalyst **38** (27.2 mg, 47.7 µmol, 0.05 equiv) was added and stirring was continued at 111 °C. After further 16 h, the mixture was allowed to cool to 23 °C and then was concentrated in vacuo. The residue was purified by flash-column chromatography on silica gel (25% → 30% ethyl acetate in hexanes) to provide recovered diene **37** (106 mg, 25%) as a yellow oil and tricycle **14** (0.22 g, 55%, 74% brsm) as an off-white foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.15 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.38–7.32 (m, 2H, *Ph*), 7.22–7.18 (m, 2H, *Ph*), 7.11–7.07 (m, 1H, *Ph*), 5.60–5.56 (m, 1H, 13-H), 4.30–4.23 (m, 2H, *Bn*), 2.37–2.30 (m, 1H, 12-H_A), 2.24 (dd, $^3J_{9/8B}$ = 12.6 Hz, $^3J_{9/8A}$ = 3.8 Hz, 1H, 9-H), 2.16 (d, $^2J_{2A/2B}$ = 12.5 Hz, 1H, 2-H_A), 2.08–2.01 (m, 3H, 5-H_A, 8-H_A, 15-H), 1.93–1.85 (m, 2H, 2-H_B, 3-H), 1.74–1.57 (m, 9H, 5-H_B, 6-H_A, 8-H_B, 11-H, 12-H_B, 20-H), 1.27 (s, 3H, 19-H), 1.22–1.17 (m, 1H, 6-H_B), 1.13 (s, 3H, 18-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.82 (br s, 1H, 1-OH), 0.75 (br s, 1H, 10-OH). **^{13}C NMR** (200 MHz, C_6D_6) δ 141.17 (C-14), 140.59 (*Ph*), 131.05 (C-13), 128.52 (*Ph*), 127.16 (*Ph*), 127.11 (*Ph*), 88.69 (C-4), 76.60 (C-1), 74.78 (C-10), 63.08 (*Bn*), 46.53 (C-9), 46.08 (C-11), 45.88 (C-3), 41.56 (C-7), 41.42 (C-6), 39.52 (C-8), 38.25 (C-2), 34.26 (C-5), 33.22 (C-15), 28.12 (C-19), 22.28 (C-12), 21.39 (C-20), 18.61 (C-16, C-17), 18.53 (C-18), 18.36 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (br), 2955 (s), 2873 (m), 1453 (m), 1386 (m), 1306 (m), 1090 (m), 1063 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_5$)$^-$: 471.31105, found: 471.31184. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.3° (c = 0.87, CH_2Cl_2).

Synthesis of epoxide 15

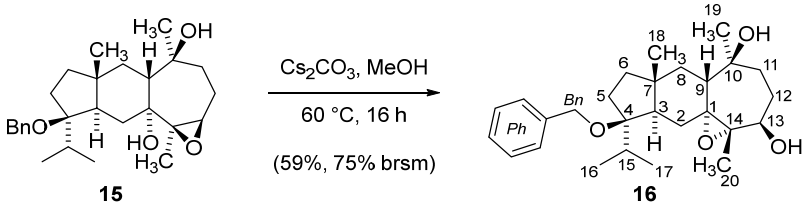


A solution of tricycle **14** (100 mg, 0.24 mmol, 1 equiv) in dichloromethane (4 mL) was treated dropwise over a period of 5 min with freshly prepared dimethyldioxirane solution (0.064 M in acetone, 5.68 mL, 0.36 mmol, 1.50 equiv) at –78 °C. After 15 min, more dimethyldioxirane solution (0.064 M in acetone, 5.68 mL, 0.36 mmol, 1.50 equiv) was added. After 15 min, the mixture was allowed to warm to 23 °C, and then was concentrated. Residual water was removed by azeotropic distillation using benzene (3 x 15 mL), to provide a pure mixture of epoxide **15** and tetrahydrofuran **39** (104 mg, ≥99%, **15**:**39** ≥ 15:1)[48] as an off-white foam which was used in the next step without further purification.
A small quantity of this mixture was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide analytically pure samples of epoxide **15** and tetrahydrofuran **39**.
Epoxide **15**: **TLC** (30% ethyl acetate in hexanes): R_f = 0.16 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.37–7.34 (m, 2H, *Ph*), 7.15–7.13 (m, 2H, *Ph*), 7.07–7.03 (m, 1H, *Ph*), 4.31–4.24 (m, 2H, *Bn*), 2.90 (dd, $^3J_{13/12A}$ = 8.4 Hz, $^3J_{13/12B}$ = 3.9 Hz, 1H, 13-H), 2.49 (app t, $^2J_{2A/2B}$ = $^3J_{2A/3}$ = 14.1 Hz, 1H, 2-H_A), 2.12 (dd, $^3J_{9/8B}$ = 12.7 Hz, $^3J_{9/8A}$ = 4.3 Hz, 1H, 9-H), 2.06–1.99 (m, 4H, 2-H_B, 5-H_A, 8-H_A, 15-H), 1.95–1.89 (m, 1H, 12-H_A), 1.72–1.67 (m, 1H, 11-H_A), 1.66–1.54 (m, 4H, 3-H, 5-H_B, 6-H_A, 12-H_B), 1.46 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 12.7 Hz, 1H, 8-H_B), 1.40–1.36 (m, 1H, 11-H_B), 1.23 (s, 3H, 19-H), 1.17 (s, 6H, 18-H, 20-H), 1.16–1.11 (m, 1H, 6-H_B), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.88 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.37 (*Ph*), 128.55 (*Ph*), 127.08 (*Ph*), 126.93 (*Ph*), 88.51 (C-4), 77.36 (C-1), 74.75 (C-10), 69.25 (C-13), 63.88 (C-14), 63.15 (*Bn*), 45.72 (C-3), 41.83 (C-7), 41.37 (C-11), 41.21 (C-6), 41.14 (C-9), 38.89 (C-8), 36.47 (C-2), 34.25 (C-5), 33.26 (C-15), 27.52 (C-19), 21.74 (C-12), 19.50 (C-18, C-20), 18.60 (C-16, C-17), 18.44 (C-16, C-17), 18.23 (C-18, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3484 (br), 2943 (m), 2876 (m), 1456 (s), 1387 (s), 1201 (m), 1139 (m), 1088 (m), 1062 (s), 1002 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_6$)$^-$: 487.30596, found: 487.30672. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –16.6° (c = 0.18, CH_2Cl_2).

Tetrahyodrofuran **39**: **TLC** (30% ethyl acetate in hexanes): R_f = 0.42 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.40–7.36 (m, 2H, *Ph*), 7.25–7.22 (m, 2H, *Ph*), 7.12–7.08 (m, 1H, *Ph*), 4.31–4.27 (m, 2H, *Bn*), 3.73 (d, $^3J_{13/12B}$ = 7.6 Hz, 1H, 13-H), 2.56–2.51 (m, 2H, 11-H_A, 14-OH), 2.44–2.38 (m, 1H, 12-H_A), 2.33 (dd, $^3J_{3/2A}$ = 12.4 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 2.11–2.03 (m, 2H, 5-H_A, 15-H), 1.87 (dd, $^3J_{9/8A}$ = 13.1 Hz, $^3J_{9/8B}$ = 3.2 Hz, 1H, 9-H), 1.86–1.80 (m, 1H, 12-H_B), 1.69–1.63 (m, 2H, 2-H_A, 5-H_B), 1.60–1.53 (m, 3H, 2-H_B, 6-H_A, 8-H_A), 1.40–1.30 (m, 2H, 8-H_B, 11-H_B), 1.27 (s, 3H, 19-H), 1.25–1.19 (m, 1H, 6-H_B), 1.12 (s, 3H, 18-H), 1.10 (s, 3H, 20-H), 1.01 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.64 (*Ph*), 128.52 (*Ph*), 127.31 (*Ph*), 127.19 (*Ph*), 88.53 (C-4), 83.89 (C-13), 83.23 (C-10), 75.61 (C-1), 72.98 (C-14), 63.18 (*Bn*), 46.63 (C-9), 45.02 (C-3), 42.60 (C-7), 40.87 (C-6), 37.69 (C-8), 33.86 (C-5), 32.95 (C-15), 32.42 (C-2), 32.18 (C-11), 28.08 (C-12), 25.64 (C-19), 24.62 (C-20), 19.71 (C-18), 18.71 (C-16, C-17), 18.65 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3404 (br), 2935 (s), 2869 (m), 1712 (w), 1453 (s), 1378 (s), 1256 (m), 1113 (m), 1048 (m), 1030 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_6$)$^-$: 487.30596, found: 487.30674. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.8° (c = 0.23, CH_2Cl_2).

[48] Epoxidation of tricycle **14** with *m*-CPBA (CH_2Cl_2, 0 °C) gave an unfavourable 2:3 mixture of epoxide **15** and tetrahydrofuran **39**.

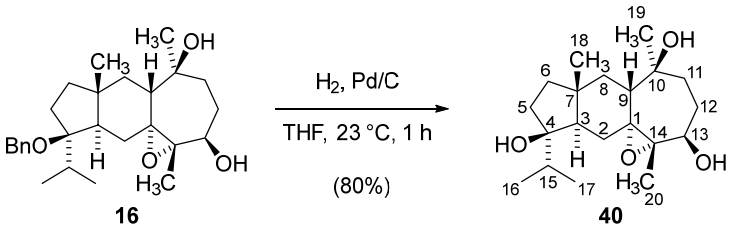
Synthesis of epoxide 16



A solution of epoxide **15** (94.0 mg, 0.22 mmol, 1 equiv) in methanol (12 mL) was treated with cesium carbonate (1.79 g, 5.48 mmol, 25.0 equiv) and the resulting mixture was heated to 60 °C. After 16 h, the mixture was allowed to cool to 23 °C and then was diluted with pH 7 buffer solution (30 mL) and ethyl acetate (25 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (50% ethyl acetate in hexanes) to provide recovered epoxide **15** (21.0 mg, 22%) as a colourless oil and epoxide **16** (55.0 mg, 59%, 75% brsm) as a colourless oil.

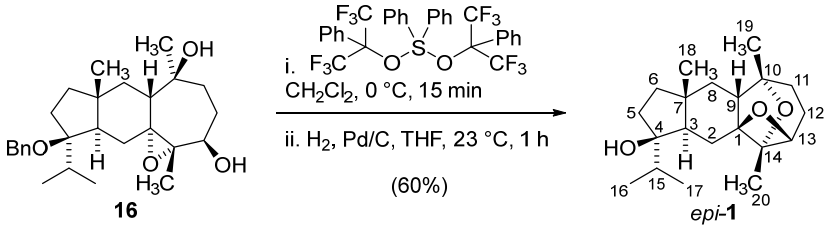
TLC (50% ethyl acetate in hexanes): R_f = 0.15 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.38–7.33 (m, 2H, *Ph*), 7.27–7.21 (m, 2H, *Ph*), 7.15–7.10 (m, 1H, *Ph*), 4.27–4.18 (m, 2H, *Bn*), 3.92–3.88 (m, 1H, 13-H), 2.29 (dd, $^2J_{8A/8B}$ = 12.4 Hz, $^3J_{8A/9}$ = 4.1 Hz, 1H, 8-H_A), 2.23–2.13 (m, 2H, 2-H_A, 9-H), 2.08–1.95 (m, 2H, 5-H_A, 15-H), 1.86–1.77 (m, 3H, 2-H_B, 3-H, 11-H_A), 1.74–1.65 (m, 1H, 12-H_A), 1.65–1.51 (m, 3H, 5-H_B, 6-H_A, 8-H_B), 1.47 (s, 3H, 20-H), 1.44–1.35 (m, 2H, 11-H_B, 12-H_B), 1.27 (s, 3H, 19-H), 1.23–1.14 (m, 1H, 6-H_B), 1.12 (s, 3H, 18-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.85 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.55 (*Ph*), 128.54 (*Ph*), 127.24 (*Ph*), 127.19 (*Ph*), 88.26 (C-4), 76.33 (C-13), 74.70 (C-10), 67.17 (C-14), 66.39 (C-1), 63.03 (*Bn*), 48.63 (C-3), 46.83 (C-9), 41.83 (C-7, C-8), 41.55 (C-7, C-8), 41.19 (C-6), 36.95 (C-11), 34.40 (C-5), 33.57 (C-2), 33.09 (C-15), 27.67 (C-12), 25.53 (C-19), 23.19 (C-20), 18.85 (C-18), 18.33 (C-16, C-17), 17.99 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3383 (br), 2954 (s), 2929 (s), 1451 (m), 1382 (m), 1346 (w), 1091 (s), 1059 (s), 1030 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_6$)$^-$: 487.30596, found: 487.30682. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.0° (c = 0.20, CH_2Cl_2).

Synthesis of triol 40



A solution of epoxide **16** (7.5 mg, 17.5 µmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 46.6 mg, 43.7 µmol, 2.50 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (9% methanol in dichloromethane) to provide triol **40** (4.7 mg, 80%) as a colourless solid. Recrystallization (ethyl acetate/hexanes) of the product gave crystals suitable for X-ray diffraction.
TLC (9% methanol in dichloromethane): R_f = 0.15 (CAM). **^{1}H NMR** (800 MHz, CD_2Cl_2) δ 4.21 (dd, $^3J_{13/12B}$ = 4.8 Hz, $^3J_{13/12A}$ = 2.5 Hz, 1H, 13-H), 2.17–2.13 (m, 2H, 8-H_A, 9-H), 2.04–2.00 (m, 1H, 5-H_A), 1.87–1.80 (m, 2H, 2-H_A, 11-H_A), 1.76–1.61 (m, 5H, 5-H_B, 6-H_A, 12-H, 15-H), 1.53–1.48 (m, 5H, 3-H, 11-H_B, 20-H), 1.46 (dd, $^2J_{2B/2A}$ = 14.0 Hz, $^3J_{2B/3}$ = 3.2 Hz, 1H, 2-H_B), 1.41 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 13.3 Hz, 1H, 8-H_B), 1.20 (s, 3H, 19-H), 1.18–1.11 (m, 1H, 6-H_B), 1.05 (s, 3H, 18-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.88 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, CD_2Cl_2) δ 83.97 (C-4), 76.79 (C-13), 75.36 (C-10), 67.30 (C-14), 66.40 (C-1), 51.39 (C-3), 46.85 (C-9), 42.09 (C-8), 41.33 (C-7), 40.40 (C-6), 37.94 (C-15), 37.21 (C-11), 37.15 (C-5), 31.69 (C-2), 27.76 (C-12), 25.34 (C-19), 23.15 (C-20), 18.90 (C-18), 18.55 (C-16, C-17), 17.78 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3424 (br), 2957 (s), 2924 (s), 2867 (m), 1455 (m), 1382 (m), 1261 (m), 1095 (s), 1005 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{22}H_{37}O_6$)$^-$: 397.25901, found: 397.26046. $[\alpha]_D^{20}$ = +9.4° (c = 0.11, MeOH).

Synthesis of 1,10,13,14-tetra-*epi* dictyoxetane (*epi*-1)



A solution of epoxide **16** (5.0 mg, 11.7 µmol, 1 equiv) in dichloromethane (1.2 mL) was treated with Martin sulfurane (7.9 mg, 11.7 µmol, 1.00 equiv) at 0 °C. After 15 min, the mixture was diluted with pH 7 buffer solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (10% ethyl acetate in hexanes) to provide dioxatricycle **17**[49] which was used in the next step without further purification.

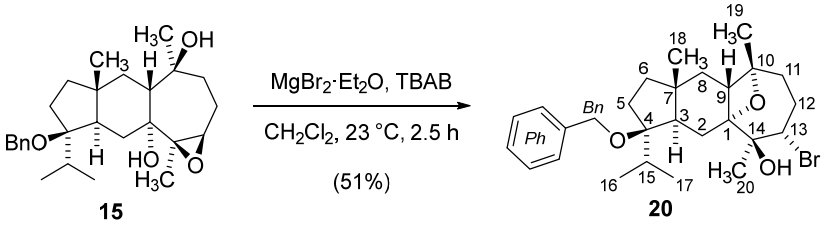
A solution of the crude dioxatricycle **17** (assuming 11.7 µmol) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 24.9 mg, 23.4 µmol, 2.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (35% ethyl acetate in hexanes) to provide 1,10,13,14-tetra-*epi* dictyoxetane (*epi*-**1**) (2.3 mg, 60% over two steps) as a colourless solid.

Recrystallization (ethyl acetate/hexanes) of the product gave crystals suitable for X-ray diffraction.

TLC (40% ethyl acetate in hexanes): R_f = 0.26 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 4.29 (br d, $^3J_{13/12A}$ = 3.6 Hz, 1H, 13-H), 2.08–2.02 (m, 2H, 2-H_A, 9-H), 2.02–1.96 (m, 2H, 2-H_B, 11-H_A), 1.86–1.78 (m, 2H, 5-H_A, 12-H_A), 1.74–1.61 (m, 3H, 5-H_B, 11-H_B, 12-H_B), 1.56 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/9}$ = 6.5 Hz, 1H, 8-H_A), 1.49–1.43 (m, 2H, 6-H_A, 15-H), 1.30 (s, 3H, 20-H), 1.19 (s, 3H, 19-H), 1.09 (s, 3H, 18-H), 1.02 (dd, $^3J_{3/2B}$ = 14.0 Hz, $^3J_{3/2A}$ = 3.6 Hz, 1H, 3-H), 0.92–0.85 (m, 5H, 6-H_B, 8-H_B, 16-H, 17-H), 0.78 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.69 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 96.98 (C-1), 82.90 (C-4), 82.37 (C-14), 81.52 (C-13), 81.15 (C-10), 51.95 (C-9), 50.37 (C-3), 41.47 (C-7), 41.15 (C-8), 39.80 (C-6), 37.65 (C-15), 36.83 (C-5), 33.06 (C-11), 28.72 (C-2), 24.18 (C-12), 24.11 (C-19), 18.53 (C-18), 18.49 (C-16, C-17), 17.80 (C-16, C-17), 17.29 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3455 (m), 2958 (s), 2932 (s), 2852 (m), 1454 (m), 1384 (m), 1275 (m), 1189 (m), 1121 (m), 1062 (m), 1020 (m), 974 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_3$)$^+$: 320.2351, found: 320.2351. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –90.0° (c = 0.07, CH_2Cl_2).

[49] This intermediate could also be obtained via the dyotropic rearrangement of epoxide-oxetane **22**, see "Synthesis of dioxatricycle **17**" for characterization of this product.

Synthesis of bromohydrin 20



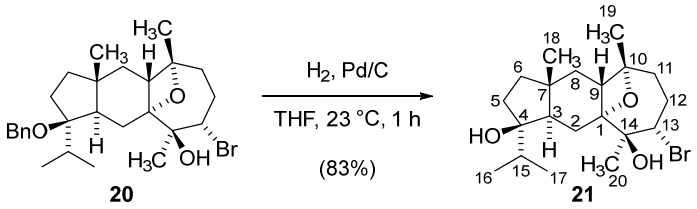
15 **20**

A solution of epoxide **15** (25.0 mg, 58.3 µmol, 1 equiv) in dichloromethane (3 mL) was treated sequentially with magnesium bromide ethyl etherate (90.4 mg, 350 µmol, 6.00 equiv) and tetrabutylammonium bromide (113 mg, 350 µmol, 6.00 equiv) at 0 °C. After 10 min, the mixture was warmed to 23 °C.[50] After 2.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (8% ethyl acetate in hexanes) to provide bromohydrine **20** (14.5 mg, 51%) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.39 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.45–7.42 (m, 2H, *Ph*), 7.27–7.23 (m, 2H, *Ph*), 7.11–7.08 (m, 1H, *Ph*), 4.68 (d, $^3J_{13/12A}$ = 13.2 Hz, 1H, 13-H), 4.37–4.27 (m, 2H, *Bn*), 2.65 (app t, $^2J_{2A/2B} = {}^3J_{2A/3}$= 13.9 Hz, 1H, 2-$H_A$), 2.42–2.35 (m, 1H, 12-$H_A$), 2.33 (dd, $^3J_{9/8A}$ = 10.5 Hz, $^3J_{9/8B}$ = 6.6 Hz, 1H, 9-H), 2.11–2.04 (m, 3H, 5-H_A, 12-H_B, 15-H), 2.00 (dd, $^3J_{3/2A}$= 13.9 Hz, $^3J_{3/2B}$ = 4.1 Hz, 1H, 3-H), 1.76–1.69 (m, 3H, 2-H_B, 5-H_B, 14-OH), 1.65 (dd, $^2J_{6A/6B}$ = 11.9 Hz, $^3J_{6A/5A}$ = 7.7 Hz, 1H, 6-H_A), 1.63–1.58 (m, 2H, 8-H), 1.36 (s, 3H, 20-H), 1.35–1.28 (m, 1H, 11-H_A), 1.24–1.19 (m, 4H, 6-H_B, 18-H), 1.13–1.07 (m, 1H, 11-H_B), 1.06 (s, 3H, 19-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.73 (*Ph*), 128.58 (*Ph*), 127.19 (*Ph*), 127.08 (*Ph*), 88.25 (C-4), 84.37 (C-1), 81.33 (C-10), 76.97 (C-14), 69.48 (C-13), 63.38 (*Bn*), 44.71 (C-3), 41.71 (C-6), 40.53 (C-7), 40.49 (C-11), 38.90 (C-9), 37.35 (C-8), 35.61 (C-5), 33.77 (C-15), 32.83 (C-12), 30.56 (C-2), 25.65 (C-19), 20.21 (C-18), 18.40 (C-16, C-17), 17.76 (C-16, C-17), 17.48 (br, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3432 (br), 2952 (s), 2865 (m), 1453 (m), 1375 (s), 1197 (w), 1129 (m), 1098 (m), 1060 (m), 1027 (w) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{79}BrO_5$)$^-$: 549.22156, found: 549.22240; calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{81}BrO_5$)$^-$: 551.21952, found: 551.22035. $[\alpha]_D^{20}$ = –28.5° (c = 0.71, CH_2Cl_2).

[50] Reaction monitoring by TLC analysis (30% ethyl acetate in hexanes) showed gradual conversion of epoxide **15** (R_f = 0.15) to a putative bromo-triol intermediate (R_f = 0.30), which then reacted further to bromohydrin **20** (R_f = 0.80).

Synthesis of diol 21

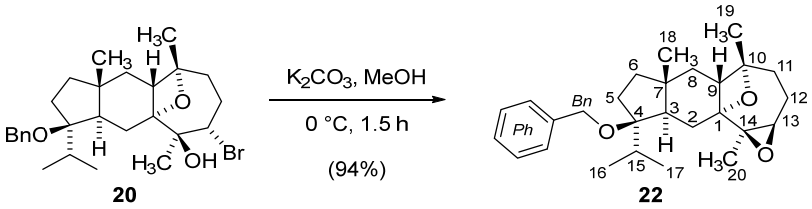


A solution of bromohydrin **20** (4.0 mg, 8.14 µmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 8.7 mg, 8.14 µmol, 1.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide diol **21** (2.7 mg, ≥99%) as a colourless solid.

Recrystallization (ethyl acetate/hexanes) of the product gave crystals suitable for X-ray diffraction.

TLC (30% ethyl acetate in hexanes): R_f = 0.35 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 4.68 (dd, $^3J_{13/12A}$ = 13.2 Hz, $^3J_{13/12B}$ =2.0 Hz, 1H, 13-H), 2.47–2.33 (m, 1H, 12-H_A), 2.33–2.23 (m, 2H, 2-H_A, 9-H), 2.11–2.04 (m, 1H, 12-H_B), 1.99–1.88 (m, 2H, 5-H_A, 14-OH), 1.79–1.64 (m, 3H, 3-H, 5-H_B, 6-H_A), 1.57–1.42 (m, 7H, 2-H_B, 8-H, 15-H, 20-H), 1.36–1.27 (m, 1H, 11-H_A), 1.21 (s, 3H, 18-H), 1.17–1.03 (m, 2H, 6-H_B, 11-H_B), 1.00 (s, 3H, 19-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.86 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.71 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 84.05 (C-1), 83.49 (C-4), 81.48 (C-10), 77.14 (C-14), 69.31 (C-13), 47.64 (C-3), 40.92 (C-6), 40.45 (C-11), 40.24 (C-7), 38.89 (C-9), 37.97 (C-8, C-15), 37.92 (C-8, C-15), 37.04 (C-5), 32.84 (C-12), 28.48 (C-2), 25.58 (C-19), 20.19 (C-18), 18.36 (C-16, C-17), 17.66 (2C, C-16, C-17, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (br), 2954 (s), 2869 (m), 1468 (m), 1447 (m), 1374 (m), 1129 (m), 1094 (m), 1074 (m), 986 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{22}H_{36}{}^{79}BrO_5)^-$: 459.17461, found: 459.17549; calcd for ([M+CH_3COO], $C_{22}H_{36}{}^{81}BrO_5)^-$: 461.17257, found: 461.17345. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –52.5° (c = 0.35, CH_2Cl_2).

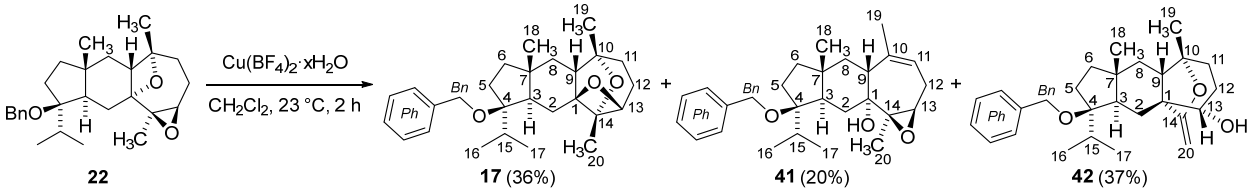
Synthesis of epoxide–oxetane 22



A solution of bromohydrin **20** (14.0 mg, 28.5 µmol, 1 equiv) in methanol (1.5 mL) was treated with potassium carbonate (9.8 mg, 71.2 µmol, 2.50 equiv) at 0 °C. After 1.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide epoxide–oxetane **22** (11.0 mg, 94%) as a colourless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.35 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 4.34–4.21 (m, 2H, *Bn*), 2.86–2.77 (m, 1H, 9-H), 2.73 (dd, $^3J_{13/12B}$ = 7.8 Hz, $^3J_{13/12A}$ = 3.1 Hz, 1H, 13-H), 2.45 (dd, $^2J_{2A/2B}$ = 14.8 Hz, $^3J_{2A/3}$ = 13.0 Hz, 1H, 2-H_A), 2.08–1.95 (m, 4H, 3-H, 5-H_A, 12-H_A, 15-H), 1.93–1.80 (m, 3H, 2-H_B, 11-H_A, 12-H_B), 1.72–1.62 (m, 3H, 5-H_B, 8-H), 1.62–1.54 (m, 1H, 6-H_A), 1.29 (s, 3H, 20-H), 1.28–1.17 (m, 2H, 6-H_B, 11-H_B), 1.11 (s, 3H, 19-H), 1.10 (s, 3H, 18-H), 1.02 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.61 (*Ph*), 128.61 (*Ph*), 127.14 (*Ph*), 126.90 (*Ph*), 88.18 (C-4), 83.25 (C-10), 82.82 (C-1), 66.30 (C-14), 63.25 (*Bn*), 61.39 (C-13), 45.27 (C-3), 41.07 (C-6), 40.69 (C-7), 38.70 (C-11), 37.36 (C-8), 35.44 (C-5), 35.20 (C-9), 33.63 (C-15), 32.64 (C-2), 26.31 (C-19), 25.30 (C-12), 19.67 (C-18), 19.15 (C-20), 18.29 (C-16, C-17), 17.67 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2940 (s), 2873 (m), 1496 (m), 1453 (s), 1376 (s), 1298 (w), 1149 (m), 1089 (m), 1055 (s), 1028 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2821, found: 410.2822. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.3° (c = 0.67, CH_2Cl_2).

Synthesis of dioxatricycle 17



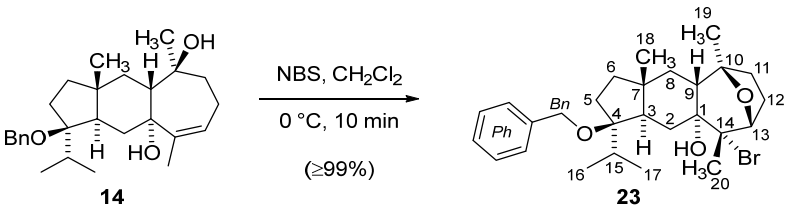
A solution of epoxide-oxetane **22** (7.0 mg, 17.0 µmol, 1 equiv) in dichloromethane (1 mL) was treated with copper(II) tetrafluoroborate hydrate (4.4 mg, 17.0 µmol, 1.00 equiv) at 23 °C. After 2 h, the yellow mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% → 20% ethyl acetate in hexanes) to provide dioxatricycle **17** (2.5 mg, 36%) as a colourless solid, olefin **41** (1.4 mg, 20%) as a colourless oil, and enol ether **42** (2.6 mg, 37%) as a yellowish oil.

Dioxatricycle **17**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.45 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.40–7.34 (m, 2H, *Ph*), 7.24–7.18 (m, 2H, *Ph*), 7.14–7.08 (m, 1H, *Ph*), 4.31–4.17 (m, 3H, 13-H, *Bn*), 2.49–2.38 (m, 2H, 2-H), 2.10–1.91 (m, 4H, 5-H_A, 9-H, 11-H_A, 15-H), 1.87–1.79 (m, 1H, 12-H_A), 1.76–1.62 (m, 2H, 11-H_B, 12-H_B), 1.62–1.50 (m, 2H, 5-H_B, 8-H_A), 1.48–1.39 (m, 1H, 6-H_A), 1.38 (s, 3H, 20-H), 1.24–1.17 (m, 4H, 3-H, 19-H), 1.05 (s, 3H, 18-H), 1.02–0.92 (m, 5H, 6-H_B, 8-H_B, 16-H, 17-H), 0.77 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.43 (*Ph*), 128.58 (*Ph*), 127.15 (*Ph*), 126.96 (*Ph*), 97.31 (C-1), 87.70 (C-4), 82.52 (C-14), 81.38 (C-13), 81.21 (C-10), 62.76 (*Bn*), 52.00 (C-9), 47.78 (C-3), 41.83 (C-7), 40.73 (C-6, C-8), 40.63 (C-6, C-8), 34.86 (C-5), 33.17 (C-11, C-15), 33.14 (C-11, C-15), 30.89 (C-2), 24.19 (C-19), 24.12 (C-12), 18.47 (C-16, C-17), 18.38 (C-18), 18.08 (C-16, C-17), 17.71 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (s), 2930 (s), 1454 (m), 1385 (m), 1273 (w), 1189 (m), 1089 (m), 1057 (m), 1027 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2821, found: 410.2816. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –4.4° (c = 0.36, CH_2Cl_2).

Olefin **41**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.38 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.43–7.35 (m, 2H, *Ph*), 7.15–7.11 (m, 2H, *Ph*), 7.09–7.03 (m, 1H, *Ph*), 5.45–5.38 (m, 1H, 11-H), 4.37–4.24 (m, 2H, *Bn*), 2.85–2.76 (m, 2H, 9-H, 13-H), 2.50–2.36 (m, 2H, 2-H_A, 12-H_A), 2.33 (dd, $^2J_{2B/2A}$ = 14.1 Hz, $^3J_{2B/3}$ = 3.2 Hz, 1H, 2-H_B), 2.16–1.97 (m, 4H, 3-H, 5-H_A, 12-H_B, 15-H), 1.77 (app t, $^2J_{8A/8B}$ = $^3J_{8A/9}$ = 12.5 Hz, 1H, 8-H_A), 1.69–1.60 (m, 4H, 5-H_B, 19-H), 1.60–1.53 (m, 1H, 6-H_A), 1.49 (dd, $^2J_{8B/8A}$ = 12.5 Hz, $^3J_{8B/9}$ = 4.9 Hz, 1H, 8-H_B), 1.22 (s, 3H, 20-H), 1.22–1.17 (m, 4H, 6-H_B, 18-H), 1.08 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.53 (C-10, *Ph*), 140.48 (C-10, *Ph*), 128.54 (*Ph*), 127.04 (*Ph*), 127.00 (*Ph*), 124.86 (C-11), 88.59 (C-4), 75.15 (C-1), 65.40 (C-13), 63.49 (C-14), 63.18 (*Bn*), 44.91 (C-3), 41.95 (C-7), 41.19 (C-6), 40.94 (C-8), 37.88 (C-9), 34.25 (C-5), 33.33 (C-15), 32.69 (C-2), 27.47 (C-12), 22.33 (C-19), 19.95 (C-20), 18.56 (C-16, C-17), 18.50 (C-18), 18.33 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3474 (br), 2958 (s), 2933 (s), 2857 (m), 1453 (m), 1385 (m), 1198 (w), 1087 (m), 1055 (s), 1027 (m), 1000 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{41}O_5$)$^-$: 469.2954, found: 469.2962. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –19.6° (c = 0.21, CH_2Cl_2).

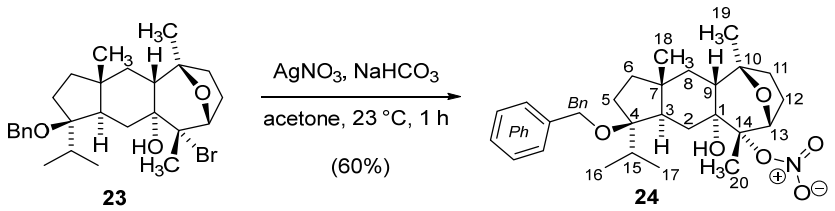
Enol ether **42**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.45–7.39 (m, 2H, *Ph*), 7.26–7.21 (m, 2H, *Ph*), 7.14–7.08 (m, 1H, *Ph*), 4.57–4.55 (m, 1H, 20-H_A), 4.36–4.22 (m, 2H, *Bn*), 3.87 (d, $^2J_{20B/20A}$ = 1.3 Hz, 1H, 20-H_B), 3.23–3.13 (m, 1H, 13-H), 2.27 (dd, $^2J_{2A/2B}$ = 14.5 Hz, $^3J_{2A/3}$ = 3.1 Hz, 1H, 2-H_A), 2.09–1.98 (m, 2H, 5-H_A, 15-H), 1.93 (dd, $^2J_{2B/2A}$ = 14.5 Hz, $^3J_{2B/3}$ = 12.9 Hz, 1H, 2-H_B), 1.79–1.71 (m, 1H, 12-H_A), 1.69–1.63 (m, 1H, 3-H), 1.63–1.54 (m, 1H, 5-H_B), 1.54–1.45 (m, 3H, 6-H_A, 11-H_A, 12-H_B), 1.40 (dd, $^2J_{8A/8B}$ = 11.9 Hz, $^3J_{8A/9}$ = 5.3 Hz, 1H, 8-H_A), 1.30 (dd, $^3J_{9/8B}$ = 12.0 Hz, $^3J_{9/8A}$ = 5.3 Hz, 1H, 9-H), 1.18–1.08 (m, 4H, 6-H_B, 8-H_B, 11-H_B, 13-OH), 1.06 (d, ^3J = 6.9 Hz, 3H, 16-H, 17-H), 1.02 (s, 3H, 19-H), 1.00 (s, 3H, 18-H), 0.89 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 164.57 (C-14), 140.55 (*Ph*), 128.58 (*Ph*), 127.33 (*Ph*), 127.23 (*Ph*), 88.40 (C-4), 83.11 (C-10), 78.75 (C-20), 74.36 (C-13), 63.15 (*Bn*), 55.24 (C-1), 47.25 (C-9), 46.37 (C-3), 42.03 (C-7), 40.85 (C-6), 38.86 (C-8), 37.72 (C-11), 34.09 (C-5), 33.42 (C-15), 30.73 (C-12), 26.47 (C-2), 20.56 (C-19), 18.67 (C-18), 18.41 (C-16, C-17), 18.38 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3457 (br), 2934 (s), 2856 (m), 1664 (m), 1454 (m), 1379 (m), 1219 (w), 1197 (w), 1087 (m), 1060 (s), 1028 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2821, found: 410.2813. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.5° (c = 0.27, CH_2Cl_2).

Synthesis of bromide 23



A solution of tricycle **14** (14.5 mg, 35.1 µmol, 1 equiv) in dichloromethane (1.5 mL) was treated with *N*-bromosuccinimide (6.9 mg, 38.1 µmol, 1.10 equiv) at 0 °C. After 10 min, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide spectroscopically pure bromide **23** (17.3 mg, ≥99%) as a colourless oil.
TLC (5% ethyl acetate in hexanes): R_f = 0.34 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.38–7.35 (m, 2H, *Ph*), 7.24–7.21 (m, 2H, *Ph*), 7.13–7.09 (m, 1H, *Ph*), 4.27–4.21 (m, 3H, 13-H, *Bn*), 2.78–2.73 (m, 1H, 12-H_A), 2.56–2.51 (m, 1H, 11-H_A), 2.27 (dd, $^3J_{3/2A}$ = 12.4 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 2.10–2.07 (m, 1H, 9-H), 2.06–2.00 (m, 2H, 5-H_A, 15-H), 1.99–1.93 (m, 1H, 12-H_B), 1.88 (app t, $^2J_{2A/2B}$ = $^3J_{2A/3}$ = 12.8 Hz, 1H, 2-H_A), 1.81–1.78 (m, 4H, 2-H_B, 20-H), 1.77 (d, $^4J_{1OH/9}$ = 1.9 Hz, 1H, 1-OH), 1.65–1.60 (m, 1H, 5-H_B), 1.59–1.51 (m, 2H, 6-H_A, 8-H_A), 1.32–1.27 (m, 2H, 8-H_B, 11-H_B), 1.19–1.13 (m, 4H, 6-H_B, 19-H), 1.06 (s, 3H, 18-H), 0.99 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.42 (*Ph*), 128.55 (*Ph*), 127.39 (*Ph*), 127.26 (*Ph*), 88.37 (C-4), 85.99 (C-13), 83.99 (C-10, C-14), 83.89 (C-10, C-14), 76.48 (C-1), 63.27 (*Bn*), 47.53 (C-9), 44.58 (C-3), 42.74 (C-7), 40.65 (C-6), 38.14 (C-8), 34.01 (C-2), 33.89 (C-5), 32.97 (C-15), 31.87 (C-11), 30.28 (C-12), 28.93 (C-20), 25.54 (C-19), 19.69 (C-18), 18.67 (2C, 16-C, 17-C). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3547 (m), 2937 (s), 2869 (m), 1452 (m), 1377 (m), 1276 (m), 1195 (m), 1117 (m), 1056 (s), 1018 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{79}BrO_5$)$^-$: 549.22156, found: 549.22233; calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{81}BrO_5$)$^-$: 551.21952, found: 551.22023. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +62.3° (c = 0.10, CH_2Cl_2).

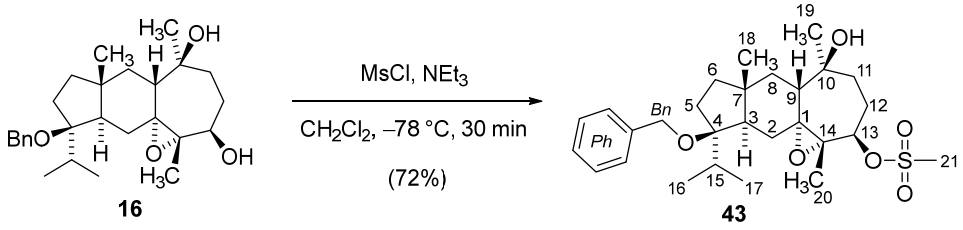
Synthesis of nitrate ester 24



A solution of bromide **23** (17.3 mg, 35.1 µmol, 1 equiv) in acetone (1.5 mL) was treated with sodium hydrogen carbonate (14.7 mg, 175 µmol, 5.00 equiv) and silver nitrate (17.9 mg, 105 µmol, 3.00 equiv) at 23 °C. Gradual formation of a greyish precipitate was observed. After 1 h, the suspension was filtered through a pad of cotton wool and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide nitrate ester **24** (10.0 mg, 60%) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.20 (CAM). **^{1}H NMR** (600 MHz, C_6D_6) δ 7.37–7.33 (m, 2H, *Ph*), 7.26–7.22 (m, 2H, *Ph*), 7.14–7.10 (m, 1H, *Ph*), 4.87 (d, $^3J_{13/12B}$ = 7.7 Hz, 1H, 13-H), 4.21 (app s, 2H, *Bn*), 2.46–2.40 (m, 1H, 11-H_A), 2.39–2.33 (m, 1H, 12-H_A), 2.07 (dd, $^3J_{3/2A}$ = 12.5 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 2.04–1.95 (m, 2H, 5-H_A, 15-H), 1.84 (dd, $^3J_{9/8A}$ = 13.0 Hz, $^3J_{9/8B}$ = 3.3 Hz, 1H, 9-H), 1.80–1.71 (m, 2H, 2-H_A, 12-H_B), 1.62 (dd, $^2J_{2B/2A}$ = 13.5 Hz, $^3J_{2B/3}$ = 2.8 Hz, 1H, 2-H_B), 1.60–1.54 (m, 1H, 5-H_B), 1.49–1.43 (m, 2H, 6-H_A, 8-H_A), 1.39 (br s, 1H, 1-OH), 1.38 (s, 3H, 20-H), 1.31–1.24 (m, 1H, 11-H_B), 1.22 (dd, $^2J_{8B/8A}$ = 11.8 Hz, $^3J_{8B/9}$ = 3.3 Hz, 1H, 8-H_B), 1.15 (s, 3H, 19-H), 1.12–1.05 (m, 1H, 6-H_B), 1.00 (s, 3H, 18-H), 0.92 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.87 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.29 (*Ph*), 128.57 (*Ph*), 127.48 (*Ph*), 127.36 (*Ph*), 92.15 (C-14), 88.21 (C-4), 83.26 (C-10), 79.65 (C-13), 76.77 (C-1), 63.18 (*Bn*), 47.12 (C-9), 44.34 (C-3), 42.30 (C-7), 40.57 (C-6), 36.92 (C-8), 33.79 (C-5), 32.97 (C-15), 32.44 (C-11), 32.36 (C-2), 28.17 (C-12), 25.27 (C-19), 20.28 (C-20), 19.51 (C-18), 18.60 (C-16, C-17), 18.56 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3603 (w), 2937 (m), 2865 (m), 1627 (s), 1453 (m), 1381 (m), 1290 (s), 1197 (m), 1117 (m), 1060 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{42}NO_8$)$^-$: 532.29104, found: 532.29170. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +42.0° (c = 0.33, CH_2Cl_2).

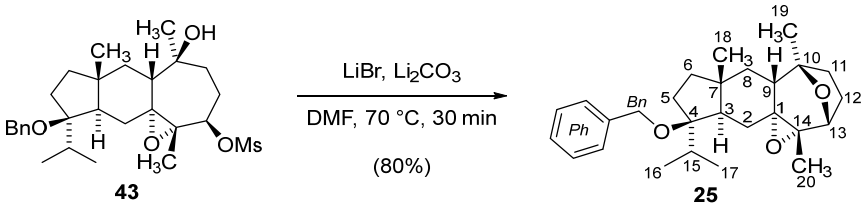
Synthesis of mesylate 43



A solution of epoxide **16** (18.0 mg, 42.0 µmol, 1 equiv) in dichloromethane (1.2 mL) was treated sequentially with triethylamine (23.3 µL, 0.17 mmol, 4.00 equiv) and methanesulfonyl chloride (6.5 µL, 84.0 µmol, 2.00 equiv) at –78 °C. After 30 min, the cooling bath was removed and the mixture was immediately diluted with pH 7 buffer solution (10 mL) and ethyl acetate (15 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (50% ethyl acetate in hexanes) to provide mesylate **43** (15.3 mg, 72%) as a colourless oil.

TLC (50% ethyl acetate in hexanes): R_f = 0.25 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.33–7.30 (m, 2H, *Ph*), 7.21–7.18 (m, 2H, *Ph*), 7.11–7.07 (m, 1H, *Ph*), 5.06 (dd, $^3J_{13/12A}$ = 5.8 Hz, $^3J_{13/12B}$ =1.5 Hz, 1H, 13-H), 4.23–4.16 (m, 2H, *Bn*), 2.41 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/9}$ = 4.8 Hz, 1H, 8-H_A), 2.29–2.22 (m, 2H, 2-H_A, 9-H), 2.13 (s, 3H, 21-H), 2.04–1.94 (m, 2H, 5-H_A, 15-H), 1.94–1.84 (m, 2H, 11-H_A, 12-H_A), 1.77 (dd, $^2J_{2B/2A}$ = 14.9 Hz, $^3J_{2B/3}$ = 3.2 Hz, 1H, 2-H_B), 1.67 (dd, $^3J_{3/2A}$ = 13.6 Hz, $^3J_{3/2B}$ = 3.2 Hz, 1H, 3-H), 1.62–1.57 (m, 2H, 5-H_B, 6-H_A), 1.56–1.49 (m, 2H, 8-H_B, 12-H_B), 1.40 (s, 3H, 20-H), 1.32–1.28 (m, 1H, 11-H_B), 1.24 (s, 3H, 19-H), 1.16–1.10 (m, 1H, 6-H_B), 1.08 (s, 3H, 18-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.82 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.32 (*Ph*), 128.58 (*Ph*), 127.31 (*Ph*), 127.26 (*Ph*), 88.27 (C-4), 87.56 (C-13), 74.28 (C-10), 66.18 (C-1), 63.82 (C-14), 63.19 (*Bn*), 48.20 (C-3), 45.64 (C-9), 41.72 (C-8), 41.34 (C-6), 41.12 (C-7), 38.23 (C-21), 38.15 (C-11), 34.52 (C-2), 33.61 (C-5), 33.20 (C-15), 25.43 (C-12), 23.90 (C-19), 22.36 (C-20), 18.50 (C-18), 18.26 (C-16, C-17), 17.84 (C16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3517 (br), 2957 (s), 2929 (s), 1454 (m), 1353 (s), 1173 (s), 1087 (m), 1064 (m), 970 (w), 898 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{30}H_{45}O_8S$)$^-$: 565.28351, found: 565.28434. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.4° (c = 0.23, CH_2Cl_2).

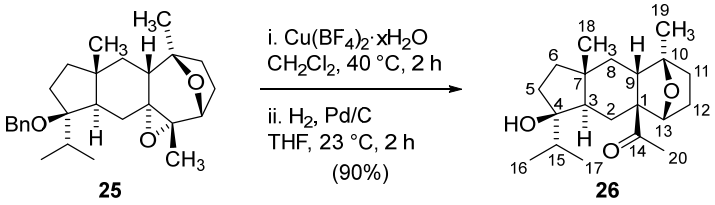
Synthesis of epoxide-tetrahydrofuran 25



A solution of mesylate **43** (2.0 mg, 4.0 µmol, 1 equiv) in dimethyl formamide (0.7 mL) was treated sequentially with lithium bromide (24.0 mg, 0.28 mmol, 70.0 equiv) and lithium carbonate (4.4 mg, 59.2 µmol, 15.0 equiv), and the resulting mixture was heated to 70 °C. After 30 min, the mixture was allowed to cool to 23 °C, whereupon it was diluted with saturated aqueous sodium chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to provide epoxide-tetrahydrofuran **25** (1.3 mg, 80%) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.20 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.39–7.36 (m, 2H, *Ph*), 7.30–7.27 (m, 2H, *Ph*), 7.16–7.15 (m, 1H, *Ph*), 4.27–4.21 (m, 2H, *Bn*), 4.17 (d, $^3J_{13/12B}$ = 6.4 Hz, 1H, 13-H), 2.16–2.08 (m, 3H, 9-H, 11-H_A, 12-H_A), 2.05–1.96 (m, 4H, 2-H_A, 3-H, 5-H_A, 15-H), 1.76–1.68 (m, 1H, 12-H_B), 1.65–1.62 (m, 1H, 2-H_B), 1.61–1.57 (m, 1H, 5-H_B), 1.54 (dd, $^2J_{6A/6B}$ = 11.6 Hz, $^3J_{6A/5A}$ = 7.8 Hz, 1H, 6-H_A), 1.46 (dd, $^2J_{8A/8B}$ = 11.8 Hz, $^3J_{8A/9}$ = 3.5 Hz, 1H, 8-H_A), 1.35–1.30 (m, 1H, 8-H_B), 1.28 (s, 3H, 19-H), 1.20–1.15 (m, 5H, 6-H_B, 11-H_B, 20-H), 1.10 (s, 3H, 18-H), 0.96 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.56 (*Ph*), 128.50 (*Ph*), 127.19 (*Ph*), 127.13 (*Ph*), 87.68 (C-4), 80.71 (C-10), 80.05 (C-13), 68.36 (C-14), 67.23 (C-1), 62.85 (*Bn*), 49.16 (C-3), 45.26 (C-9), 43.14 (C-7), 40.82 (C-6), 39.38 (C-8), 33.97 (C-5), 33.08 (C-15), 30.91 (C-11), 29.67 (C-12), 29.14 (C-2), 26.36 (C-19), 19.74 (C-18), 18.39 (C-16, C-17), 18.16 (C-16, C-17), 17.77 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (s), 1497 (w), 1453 (s), 1376 (s), 1263 (m), 1199 (m), 1137 (m), 1085 (m), 1061 (s), 1036 (s), 990 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{24}H_{31}O_3$)$^+$: 367.2273, found: 367.2264. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +54.0° (c = 0.10, CH_2Cl_2).

Synthesis of 5-6-6 tricycle 26

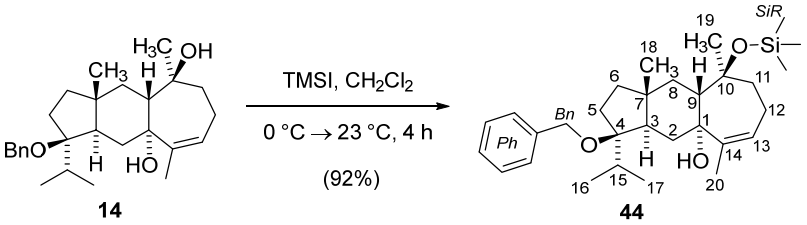


A solution of epoxide-tetrahydrofuran **25** (1.0 mg, 2.44 µmol, 1 equiv) in dichloromethane (1 mL) was treated with copper(II) tetrafluoroborate hydrate (1.2 mg, 4.87 µmol, 2.00 equiv) and the resulting mixture was heated to 40 °C. After 2 h, the mixture was allowed to cool to 23 °C, and was then diluted with pH 7 buffer solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the benzyl protected 5-6-6 tricycle which was used in the next step without further purification.

A solution of the benzyl ether (assuming 2.44 µmol) in tetrahydrofuran (2 mL) was treated with palladium on carbon (10 wt.%, 5.2 mg, 4.87 µmol, 2.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 2 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (40% ethyl acetate in hexanes) to provide 5-6-6 tricycle **26** (0.7 mg, 90% over two steps) as a colourless oil.

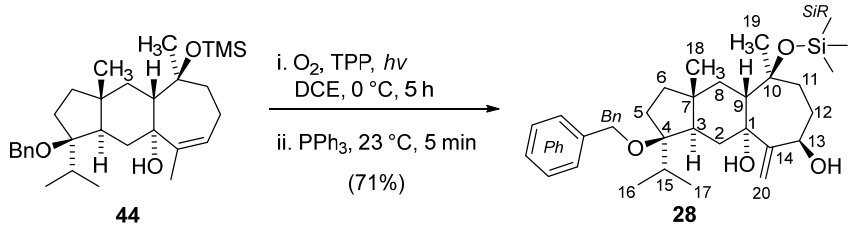
TLC (40% ethyl acetate in hexanes): R_f = 0.22 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 4.22 (d, $^3J_{13/12}$ = 5.3 Hz, 1H, 13-H), 3.29–3.25 (m, 1H, 9-H), 1.91 (s, 3H, 20-H), 1.85–1.77 (m, 2H, 5-H_A, 11-H_A), 1.69 (dd, $^2J_{8A/8B}$ = 12.8 Hz, $^3J_{8A/9}$ = 10.4 Hz, 1H, 8-H_A), 1.63–1.56 (m, 3H, 2-H_A, 12-H), 1.50–1.44 (m, 2H, 5-H_B, 6-H_A), 1.43–1.38 (m, 1H, 15-H), 1.38–1.35 (m, 1H, 2-H_B), 1.34 (s, 3H, 19-H), 1.17–1.08 (m, 2H, 3-H, 11-H_B), 1.00 (s, 3H, 18-H), 0.94–0.88 (m, 1H, 6-H_B), 0.84 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.83–0.80 (m, 1H, 8-H_B), 0.78 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.52 (br s, 1H, 4-OH). **^{13}C NMR** (200 MHz, C_6D_6) δ 206.79 (C-14), 88.78 (C-10), 82.99 (C-13), 82.69 (C-4), 59.57 (C-1), 49.25 (C-3), 41.92 (C-7), 41.15 (C-9), 40.50 (C-6), 38.96 (C-8), 37.90 (C-15), 37.64 (C-5), 30.51 (C-11), 26.02 (C-12), 24.86 (C-20), 23.86 (C-2), 20.89 (C-19), 19.69 (C-18), 18.40 (C-16, C-17), 17.80 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3499 (br), 2958 (s), 2872 (m), 1705 (s), 1469 (m), 1382 (m), 1281 (w), 1197 (m), 998 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{20}H_{33}O_3$)$^+$: 321.24297, found: 321.24329. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –29.1° (c = 0.12, CH_2Cl_2).

Synthesis of silyl ether 44



A solution of tricycle **14** (140 mg, 339 µmol, 1 equiv) in dichloromethane (1.5 mL) was treated with *N*-trimethylsilylimidazole (0.50 mL, 3.39 mmol, 10.0 equiv) at 0 °C. After 5 min, the mixture was warmed to 23 °C. After 4 h, the mixture was diluted with pH 7 buffer solution (35 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide silyl ether **44** (151 mg, 92%) as a colourless oil.
TLC (10% ethyl acetate in hexanes): R_f = 0.49 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.37–7.31 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 5.66–5.60 (m, 1H, 13-H), 4.30–4.21 (m, 2H, *Bn*), 2.55–2.43 (m, 1H, 12-H_A), 2.34 (dd, $^3J_{9/8B}$ = 12.5 Hz, $^3J_{9/8A}$ = 3.8 Hz, 1H, 9-H), 2.23 (dd, $^2J_{8A/8B}$ = 12.2 Hz, $^3J_{8A/9}$ = 3.8 Hz, 1H, 8-H_A), 2.17 (d, $^2J_{2A/2B}$ = 11.5 Hz, 1H, 2-H_A), 2.10–1.99 (m, 2H, 5-H_A, 15-H), 1.95–1.86 (m, 3H, 2-H_B, 3-H, 11-H_A), 1.81–1.57 (m, 8H, 5-H_B, 6-H_A, 8-H_B, 11-H_B, 12-H_B, 20-H), 1.46 (s, 3H, 19-H), 1.32–1.20 (m, 1H, 6-H_B), 1.18 (s, 3H, 18-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.94 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H), 0.86 (br s, 1H, 1-OH), 0.17 (s, 9H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 141.15 (C-14), 140.62 (*Ph*), 131.16 (C-13), 128.49 (*Ph*), 127.11 (*Ph*), 127.08 (*Ph*), 88.69 (C-4), 79.83 (C-10), 76.72 (C-1), 63.03 (*Bn*), 47.81 (C-9), 45.96 (C-3), 45.83 (C-11), 41.66 (C-6, C-17), 41.53 (C-6, C-7), 39.78 (C-8), 38.52 (C-2), 34.25 (C-5), 33.21 (C-15), 28.43 (C-19), 22.42 (C-12), 21.39 (C-20), 18.70 (C-18), 18.63 (C-16, C-17), 18.39 (C-16, C-17), 2.86 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3464 (br), 2955 (s), 2857 (m), 1453 (m), 1379 (m), 1249 (m), 1151 (w), 1105 (m), 1086 (m), 1027 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–H_2O], $C_{30}H_{46}O_2Si)^+$: 466.3267, found: 466.3249. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.8° (c = 0.86, CH_2Cl_2).

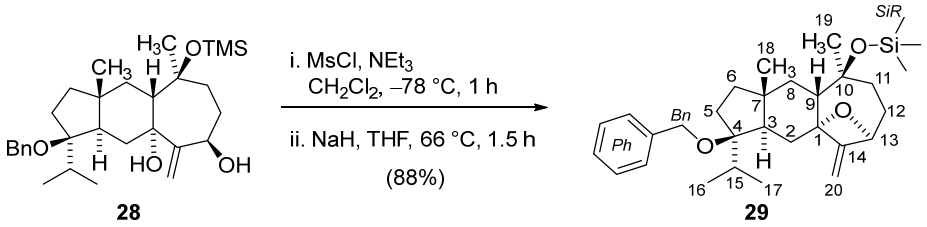
Synthesis of allylic alcohol 28



A stream of pure oxygen gas was bubbled below the liquid surface of a solution of silyl ether **44** (75.0 mg, 155 µmol, 1 equiv) in dichloroethane (20 mL) containing a catalytic amount of tetraphenylporphyrin (TPP, tip of a spatula) at 0 °C. After 3 min, the mixture was irradiated with a Replux Belgium RL 160W (225–235 Volts) lamp. After 5 h, TLC analysis (20% ethyl acetate in hexanes) indicated complete conversion of silyl ether **44** (R_f = 0.80) to the hydroperoxide intermediate (R_f = 0.29). Sparging with oxygen and irradiation was discontinued, triphenylphosphine (81.2 mg, 309 µmol, 2.00 equiv) was added and the mixture was then allowed to warm to 23 °C. After 5 min, TLC analysis (20% ethyl acetate in hexanes) indicated complete reduction of the hydroperoxide intermediate and formation of allylic alcohol **28** (R_f = 0.23). The mixture was concentrated in vacuo, and the residue was purified by flash-column chromatography on silica gel (10% → 20% ethyl acetate in hexanes) to provide allylic alcohol **28** (55.0 mg, 71%) as a colourless foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.23 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.39–7.36 (m, 2H, *Ph*), 7.22–7.18 (m, 2H, *Ph*), 7.10–7.07 (m, 1H, *Ph*), 5.17–5.11 (m, 1H, 20-H_A), 4.74 (br s, 1H, 20-H_B), 4.29–4.23 (m, 2H, *Bn*), 4.21–4.18 (m, 1H, 13-H), 2.64 (br d, $^3J_{9/8B}$ = 12.6 Hz, 1H, 9-H), 2.40–2.35 (m, 1H, 2-H_A), 2.12–2.03 (m, 3H, 5-H_A, 8-H_A, 15-H), 1.97 (dd, $^3J_{3/2A}$ = 13.2 Hz, $^3J_{3/2B}$ = 2.9 Hz, 1H, 3-H), 1.93–1.89 (m, 2H, 12-H), 1.70–1.57 (m, 6H, 2-H_B, 5-H_B, 6-H_A, 8-H_B, 11-H), 1.35 (s, 3H, 19-H), 1.32 (s, 3H, 18-H), 1.28–1.22 (m, 1H, 6-H_B), 1.06 (br s, 1H, 1-OH), 1.04 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H), 0.80–0.77 (m, 1H, 13-OH), 0.16 (s, 9H, *SiR*). **^{13}C NMR** (200 MHz, C_6D_6) δ 160.21 (C-14), 140.49 (*Ph*), 128.52 (*Ph*), 127.65 (*Ph*), 127.22 (*Ph*), 111.37 (C-20), 88.65 (C-4), 79.35 (C-10), 76.91 (C-1), 75.47 (br, C-13), 63.39 (*Bn*), 46.82 (2C, C-3, C-9), 43.68 (br, C-2), 42.81 (C-7), 41.16 (C-6), 39.29 (C-11), 37.85 (C-8), 34.08 (C-5), 33.23 (C-15), 29.82 (C-12), 26.99 (C-18), 19.42 (C-19), 18.72 (C-16, C-17), 18.59 (C-16, C-17), 2.91 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3463 (br), 2953 (s), 2869 (m), 1453 (m), 1385 (m), 1248 (s), 1118 (m), 1041 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{27}H_{41}O_4Si)^+$: 457.2774, found: 457.2781. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.5° (c = 0.83, CH_2Cl_2).

Synthesis of oxetane 29



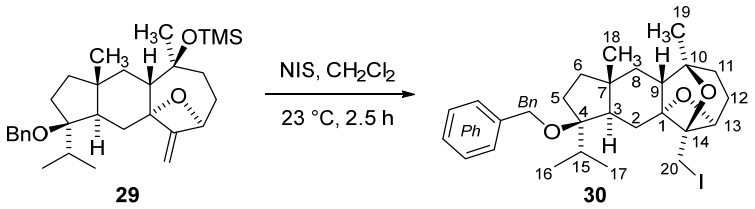
A solution of allylic alcohol **28** (27.0 mg, 53.9 µmol, 1 equiv) in dichloromethane (2.5 mL) was treated sequentially with triethylamine (172 µL, 1.24 mmol, 23.0 equiv) and methanesulfonyl chloride (41.7 µL, 0.54 mmol, 10.0 equiv) at –78 °C. After 1 h, the cooling bath was removed and the mixture was immediately diluted with saturated aqueous sodium hydrogen carbonate solution (25 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude allylic mesylate which was used in the next step without further purification.

A solution of the crude allylic mesylate (assuming 53.9 µmol) in tetrahydrofuran (4 mL) was treated with sodium hydride (60 wt.% in mineral oil, 10.8 mg, 0.27 mmol, 5.00 equiv) at 23 °C. The resulting mixture was heated to 66 °C, whereupon a further portion of sodium hydride (60 wt.% in mineral oil, 10.8 mg, 0.27 mmol, 5.00 equiv) was added. After 1.5 h, the mixture was cooled to 0 °C and *carefully* diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide oxetane **29** (23.0 mg, 88% over two steps) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.50 (CAM). *Note: Due to hindered rotation of the C10–OTMS group, oxetane **29** shows severe signal broadening in NMR spectra recorded at room temperature. Better resolved spectra could be obtained at 65 °C. However, some carbon atoms are still not visible in the ^{13}C NMR spectrum due to signal broadening. Most protons could therefore also not be assigned.*

^{1}H NMR (400 MHz, C_6D_6, 65 °C) δ 7.37–7.33 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.11–7.05 (m, 1H, *Ph*), 4.96–4.91 (m, 1H, 13-H), 4.65 (dd, *J* = 2.0 Hz, 1.2 Hz, 1H, 20-H_A), 4.47 (app t, *J* = 1.2 Hz, 1H, 20-H_B), 4.35–4.26 (m, 2H, *Bn*), 2.33 (dd, *J* = 14.1 Hz, 3.2 Hz, 1H), 2.26–2.17 (m, 1H), 2.14–2.04 (m, 4H), 2.00–1.82 (m, 3H), 1.72–1.50 (m, 5H), 1.42 (br s, 3H, 19-H), 1.25–1.17 (m, 1H), 1.15 (s, 3H, 18-H), 1.04 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.16 (s, 9H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6, 65 °C) δ 156.66, 140.66, 128.51, 127.47, 127.17, 99.29, 88.61, 84.25, 63.57, 51.60, 45.44, 42.29, 41.41, 39.61, 37.06, 34.14, 33.39, 29.93, 18.99, 18.40, 18.27, 2.98. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 1454 (m), 1374 (m), 1349 (m), 1248 (s), 1159 (w), 1110 (s), 1084 (s), 1057 (s), 1027 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{30}H_{46}O_3Si)^+$: 482.3216, found: 482.3211. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +4.2° (c = 0.30, CH_2Cl_2).

Synthesis of iodide 30

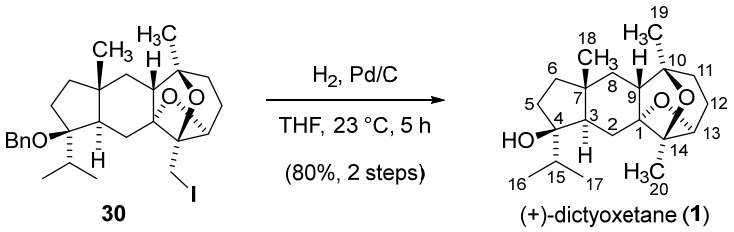


A solution of oxetane **29** (22.0 mg, 45.6 µmol, 1 equiv) in dichloromethane (2 mL) was treated with *N*-iodosuccinimide (12.3 mg, 54.7 µmol, 1.20 equiv) and the resulting pink mixture was stirred at 23 °C under exclusion of light. After 1.5 h, TLC analysis indicated incomplete conversion of oxetane **29**, and therefore a further portion of *N*-iodosuccinimide (3.1 mg, 13.7 µmol, 0.30 equiv) was added. After 1 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated (under exclusion of light) to provide the crude iodide **30** which was used in the next step without further pruficiation.

An analytically pure sample of iodide **30** could be obtained by *rapid* purification by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) in the dark.

TLC (10% ethyl acetate in hexanes): R_f = 0.43 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.42–7.38 (m, 2H, *Ph*), 7.28–7.24 (m, 2H, *Ph*), 7.14–7.10 (m, 1H, *Ph*), 4.29–4.24 (m, 2H, *Bn*), 4.21 (d, $^3J_{13/12B}$ = 3.9 Hz, 1H, 13-H), 3.04 (d, $^2J_{20A/20B}$ = 10.6 Hz, 1H, 20-H_A), 2.90 (d, $^2J_{20B/20A}$ = 10.6 Hz, 1H, 20-H_B), 2.15–2.12 (m, 1H, 3-H), 2.12–2.07 (m, 1H, 5-H_A), 2.06–2.02 (m, 1H, 15-H), 1.97 (dd, $^2J_{2A/2B}$ = 12.5 Hz, $^3J_{2A/3}$ = 2.7 Hz, 1H, 2-H_A), 1.84 (app t, $^2J_{2B/2A}$ = $^3J_{2B/3}$ = 12.5 Hz, 1H, 2-H_B), 1.75–1.69 (m, 1H, 11-H_A), 1.69–1.59 (m, 4H, 5-H_B, 9-H, 12-H), 1.56–1.53 (m, 1H, 8-H_A), 1.50 (dd, $^3J_{6A/5A}$ = 11.7 Hz, $^2J_{6A/6B}$ = 7.9 Hz, 1H, 6-H_A), 1.35 (dd, $^2J_{11B/11A}$ = 13.0 Hz, $^3J_{11B/12A}$ = 8.0 Hz, 1H, 11-H_B), 1.24–1.22 (m, 1H, 8-H_B), 1.21 (s, 3H, 19-H), 1.19–1.14 (m, 1H, 6-H_B), 1.09–1.06 (m, 6H, 16-H, 17-H, 18-H), 0.96 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.42 (*Ph*), 128.56 (*Ph*), 128.29 (*Ph*), 127.34 (*Ph*), 95.57 (C-1), 87.21 (C-4), 82.11 (C-14), 81.04 (C-13), 80.23 (C-10), 63.03 (*Bn*), 53.68 (C-9), 45.70 (C-3), 42.99 (C-7), 40.14 (C-6), 35.08 (C-8), 34.50 (C-5), 33.07 (C-15), 30.81 (C-2), 26.77 (C-19), 24.90 (C-11), 24.19 (C-12), 19.88 (C-18), 18.46 (C-16, C-17), 18.42 (C-16, C-17), 5.45 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (s), 2926 (s), 2857 (m), 1729 (w), 1453 (m), 1378 (m), 1348 (m), 1191 (m), 1147 (m), 1022 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{37}O_3I)^+$: 536.1787, found: 536.1773.

Synthesis of (+)-dictyoxetane (1)



A solution of the crude iodide **30** (assuming 45.6 µmol, 1 equiv) in tetrahydrofuran (5 mL) was treated with palladium on carbon (10 wt.%, 97.1 mg, 91.2 µmol, 2.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C.[51] After 5 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide (+)-dictyoxetane (**1**) (11.7 mg, 80% over two steps) as a colourless oil.

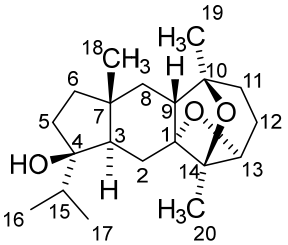
TLC (40% ethyl acetate in hexanes): R_f = 0.43 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 4.25 (br d, $^3J_{13/12A}$ = 3.9 Hz, 1H, 13-H), 2.04 (dd, $^3J_{3/2B}$ = 12.9 Hz, $^3J_{3/2A}$ = 2.8 Hz, 1H, 3-H), 1.94–1.86 (m, 1H, 5-H_A), 1.86–1.67 (m, 4H, 2-H_A, 5-H_B, 11-H_A, 12-H_A), 1.67–1.51 (m, 5H, 6-H_A, 8-H_A, 9-H, 12-H_B, 15-H), 1.48–1.39 (m, 2H, 2-H_B, 11-H_B), 1.30 (s, 3H, 20-H), 1.28 (s, 3H, 19-H), 1.27–1.24 (m, 1H, 8-H_B), 1.12 (s, 3H, 18-H), 1.10–1.05 (m, 1H, 6-H_B), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.89 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.54 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 97.05 (C-1), 82.45 (C-4), 81.17 (C-13), 80.77 (C-14), 79.78 (C-10), 53.30 (C-9), 47.89 (C-3), 42.67 (C-7), 39.72 (C-6), 36.68 (C-15), 35.43 (C-5), 35.08 (C-8), 28.00 (C-2), 27.06 (C-19), 25.13 (C-11), 24.03 (C-12), 20.05 (C-18), 18.58 (C-16, C-17), 17.68 (C-16, C-17), 16.49 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3484 (br), 2956 (s), 2928 (s), 2862 (m), 1452 (m), 1388 (m), 1375 (m), 1292 (w), 1148 (m), 1067 (m), 1019 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_3$)$^+$: 320.2351, found: 320.2349. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +29.1° (c = 1.00, $CHCl_3$). (Lit.:[52] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.0° (c = 3.00, $CHCl_3$).

^{1}H NMR (800 MHz, $CDCl_3$) δ 4.38 (br d, $^3J_{13/12A}$ = 3.3 Hz, 1H, 13-H), 2.04 (ddd, $^2J_{5A/5B}$ = 14.5 Hz, $^3J_{5A/6B}$ = 9.6 Hz, $^3J_{5A/6A}$ = 1.1 Hz, 1H, 5-H_A), 1.86–1.79 (m, 4H, 2-H_A, 3-H, 11-H_A, 12-H_A), 1.77–1.71 (m, 2H, 5-H_B, 15-H), 1.69–1.59 (m, 3H, 6-H_A, 9-H, 12-H_B), 1.54–1.47 (m, 3H, 2-H_B, 8-H_A, 11-H_B), 1.40 (dd, $^2J_{8B/8A}$ = 11.5 Hz, $^3J_{8B/9}$ = 3.4 Hz, 1H, 8-H_B), 1.37 (s, 3H, 20-H), 1.30 (s, 3H, 19-H), 1.21–1.15 (m, 1H, 6-H_B), 1.09 (s, 3H, 18-H), 1.08 (br s, 1H, 4-OH), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.90 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 97.41 (C-1), 82.87 (C-4), 81.45 (C-13), 80.81 (C-14), 80.23 (C-10), 52.80 (C-9), 48.14 (C-3), 42.65 (C-7), 39.19 (C-6), 36.73 (C-15), 35.97 (C-5), 34.73 (C-8), 27.78 (C-2), 26.86 (C-19), 24.76 (C-11), 23.51 (C-12), 20.13 (C-18), 18.70 (C-16, C-17), 17.64 (C-16, C-17), 16.30 (C-20).

[51] Reaction monitoring by TLC analysis (30% ethyl acetate in hexanes) showed gradual conversion of iodide **30** (R_f = 0.77) to the dehalogenated intermediate (R_f = 0.69) (usually within 1-2 h), which then was further reduced to (+)-dictyoxetane (**1**) (R_f = 0.34). Occasionally the reaction was found to stall after complete dehalogenation. In these cases, the mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was then resubmitted to the analogous hydrogenation conditions with fresh palladium on carbon.

[52] a) K. C. Pullaiah, R. K. Surapaneni, C. B. Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, H. Cun-heng, J. Clardy, *J. Org. Chem.* **1985**, *50*, 3665. b) C. B. Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, H. Cunheng, J. Clardy, *J. Org. Chem.* **1986**, *51,* 2736.

6.4.2 ^{1}H and ^{13}C NMR Comparison of Natural[52] and Synthetic (+)-Dictyoxetane



^{1}H Position	Natural (360 MHz, C_6D_6)	Synthetic (400 MHz, C_6D_6)	Δδ (ppm)
3	2.03 (dd, 13.0, 2.5)	2.04 (dd, 12.9, 2.6)	0.01
5a	1.90 (dd, 14.0, 9.5)	1.90 (dd, 14.0, 9.5)	0
13	4.25 (br d)	4.25 (br d)	0
16	0.95 (d, 6.5)	0.95 (d, 6.8)	0
17	0.88 (d, 6.5)	0.89 (d, 6.8)	0.01
18	1.11 (s, 3H)	1.12 (s, 3H)	0.01
19	1.27 (s, 3H)	1.28 (s, 3H)	0.01
20	1.29 (s, 3H)	1.30 (s, 3H)	0.01

Resonances of all other protons occur as overlapping multiplets and are not listed in this table.

^{13}C Position	Natural (50 MHz, $CDCl_3$)	Synthetic (200 MHz, $CDCl_3$)	Δδ (ppm)
1	97.2	97.4	0.2
2	27.6	27.8	0.2
3	48.0	48.1	0.1
4	82.7	82.9	0.2
5	35.9	36.0	0.1
6	39.1	39.2	0.2
7	42.5	42.6	0.1
8	34.6	34.7	0.1
9	52.6	52.8	0.2
10	80.1	80.2	0.1
11	24.6	24.8	0.2
12	23.4	23.5	0.1
13	81.3	81.4	0.1
14	80.6	80.8	0.2
15	36.6	36.7	0.1
16	17.5	17.6	0.1
17	18.5	18.7	0.2
18	20.0	20.1	0.1
19	26.7	26.9	0.2
20	16.1	16.3	0.1

6.4.3 X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[53] and refined by least-squares methods against *F*2 with SHELXL-97.[54] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Triol 40

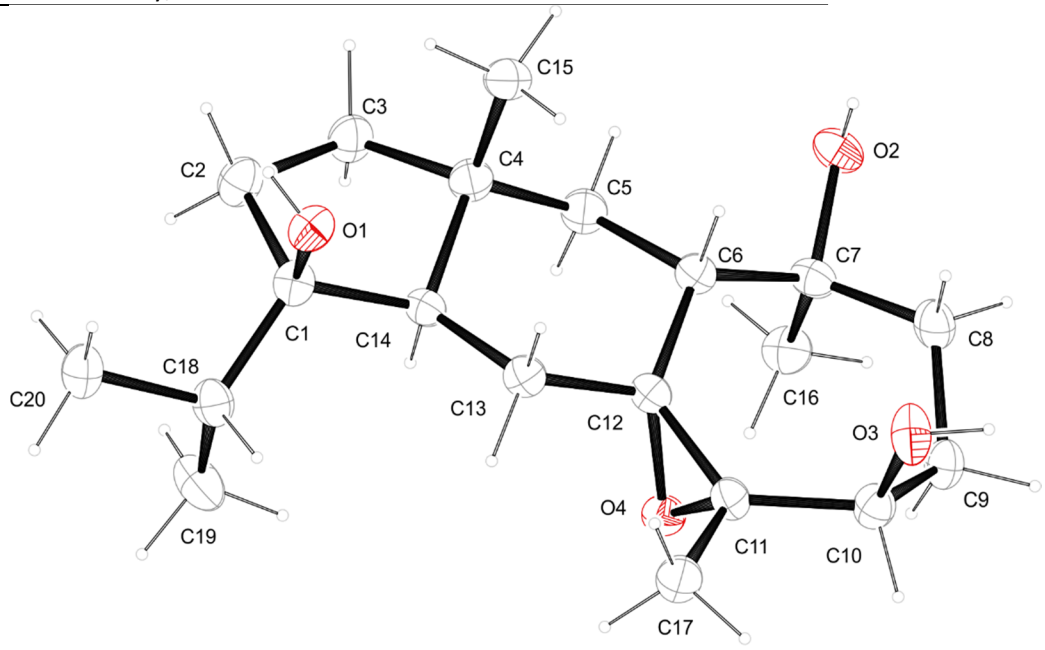
CCDC 1473419 contains the supplementary crystallographic data for triol **40**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4. Triol **40**

net formula	$C_{20}H_{34}O_4$
M_r/g mol^{-1}	338.47
crystal size/mm	0.100 × 0.050 × 0.040
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	8.5285(6)
b/Å	14.0549(9)
c/Å	15.1362(10)
α/°	90
β/°	90
γ/°	90
V/Å^3	1814.3(2)
Z	4
calc. density/g cm^{-3}	1.239
μ/mm^{-1}	0.084
absorption correction	Multi-Scan
transmission factor range	0.8239–0.9580
refls. measured	7152
R_{int}	0.0244
mean σ(*I*)/*I*	0.0332
θ range	3.101–25.364
observed refls.	2889
x, y (weighting scheme)	0.0354, 0.6797
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	−0.6(5)
refls in refinement	3234
parameters	234
restraints	0

[53] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[54] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.

$R(F_{obs})$	0.0367
$R_w(F^2)$	0.0916
S	1.101
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.143
min electron density/e Å^{-3}	−0.212



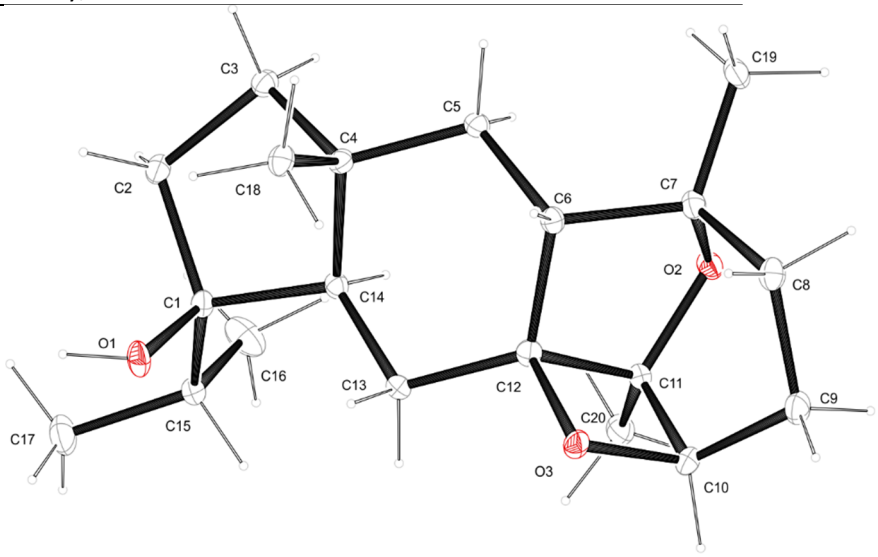
1,10,13,14-tetra-*epi* dictyoxetane (*epi*-1)

CCDC 1473420 contains the supplementary crystallographic data for 1,10,13,14-tetra-*epi* dictyoxetane (*epi*-**1**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5. 1,10,13,14-tetra-*epi* dictyoxetane (*epi*-**1**)

net formula	$C_{20}H_{32}O_3$
M_r/g mol^{-1}	320.45
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.3848(4)
b/Å	9.4448(7)
c/Å	28.5710(19)
α/°	90
β/°	90
γ/°	90
V/Å^3	1722.9(2)
Z	4
calc. density/g cm^{-3}	1.235
μ/mm^{-1}	0.081

absorption correction	Multi-Scan
transmission factor range	0.8980–0.9585
refls. measured	31378
R_{int}	0.0372
mean σ(*I*)/*I*	0.0206
θ range	3.038–26.405
observed refls.	3373
x, y (weighting scheme)	0.0383, 0.6304
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	−0.1(3)
refls in refinement	3507
parameters	217
restraints	0
$R(F_{obs})$	0.0338
$R_w(F^2)$	0.0856
S	1.102
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.263
min electron density/e Å^{-3}	−0.183



Diol 21

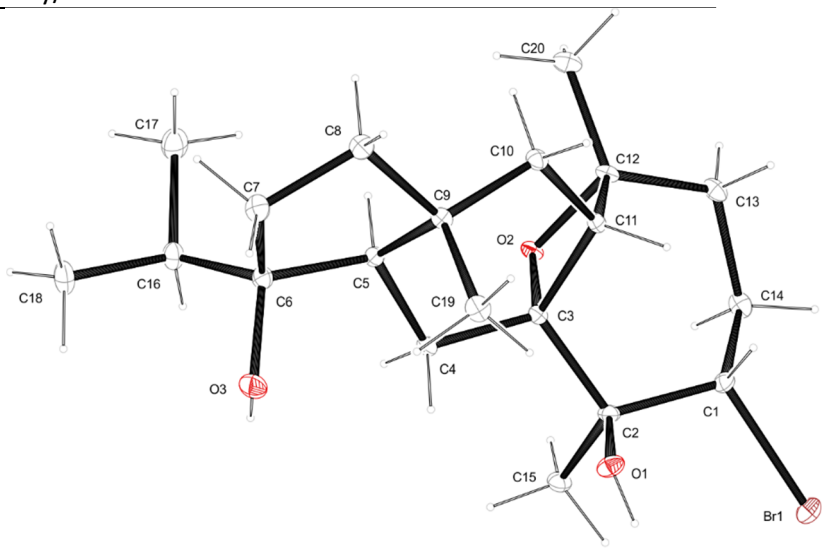
CCDC 1473421 contains the supplementary crystallographic data for diol **21**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 6. **Diol 21**

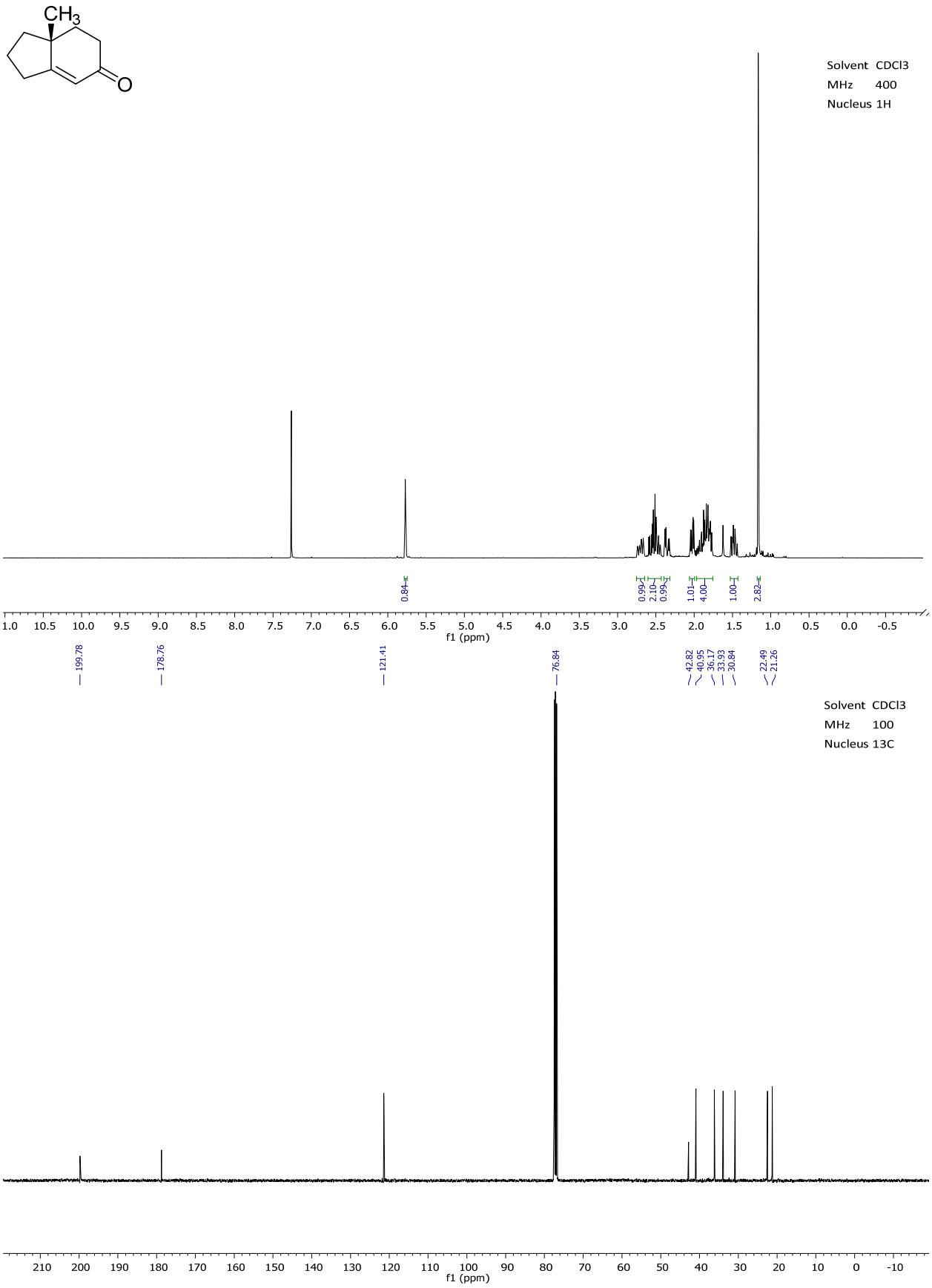
net formula	$C_{20}H_{33}BrO_3$
M_r/g mol^{-1}	401.38
crystal size/mm	0.070 × 0.050 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	7.2444(5)
b/Å	10.8801(7)

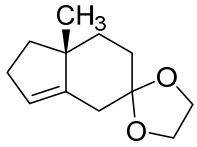
c/Å	23.8676(15)
α/°	90
β/°	90
γ/°	90
V/Å^3	1881.2(2)
Z	4
calc. density/g cm^{-3}	1.417
μ/mm^{-1}	2.200
absorption correction	Multi-Scan
transmission factor range	0.6527–0.6985
refls. measured	33734
R_{int}	0.0687
mean σ(*I*)/*I*	0.0441
θ range	3.172–28.271
observed refls.	4453
x, y (weighting scheme)	0.0293, 0.8784
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	0.107(5)
refls in refinement	4655
parameters	230
restraints	0
$R(F_{obs})$	0.0301
$R_w(F^2)$	0.0740
S	1.062
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.337
min electron density/e Å^{-3}	−0.499
net formula	$C_{20}H_{32}O_3$
M_r/g mol^{-1}	320.45
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.3848(4)
b/Å	9.4448(7)
c/Å	28.5710(19)
α/°	90
β/°	90
γ/°	90
V/Å^3	1722.9(2)
Z	4
calc. density/g cm^{-3}	1.235
μ/mm^{-1}	0.081
absorption correction	Multi-Scan
transmission factor range	0.8980–0.9585
refls. measured	31378
R_{int}	0.0372
mean σ(*I*)/*I*	0.0206
θ range	3.038–26.405
observed refls.	3373
x, y (weighting scheme)	0.0383, 0.6304

hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	−0.1(3)
refls in refinement	3507
parameters	217
restraints	0
$R(F_{obs})$	0.0338
$R_w(F^2)$	0.0856
S	1.102
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.263
min electron density/e Å^{-3}	−0.183

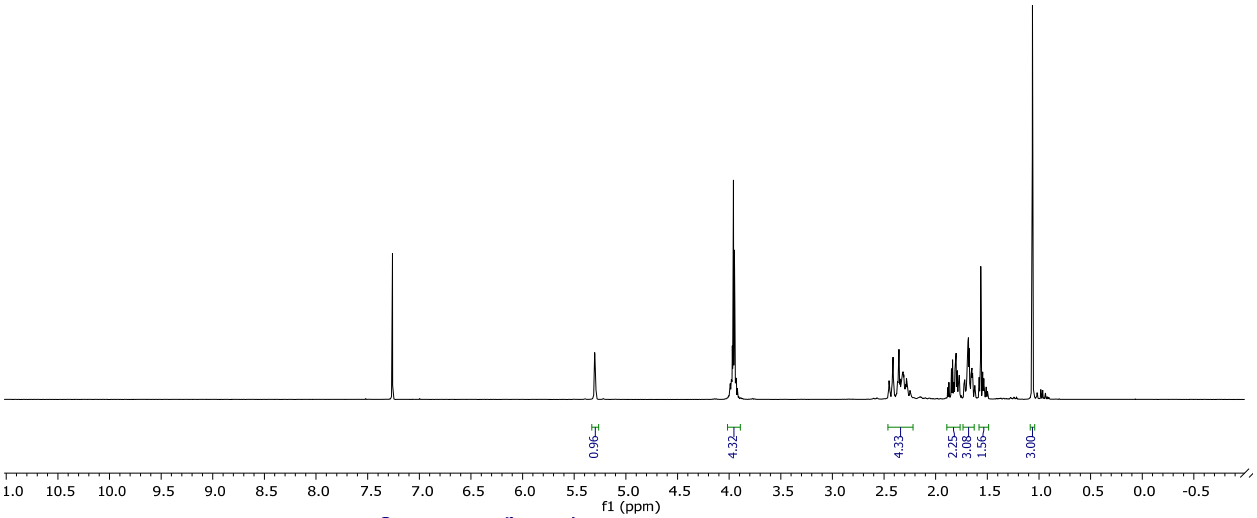


6.4.4 ^{1}H and ^{13}C NMR Spectra

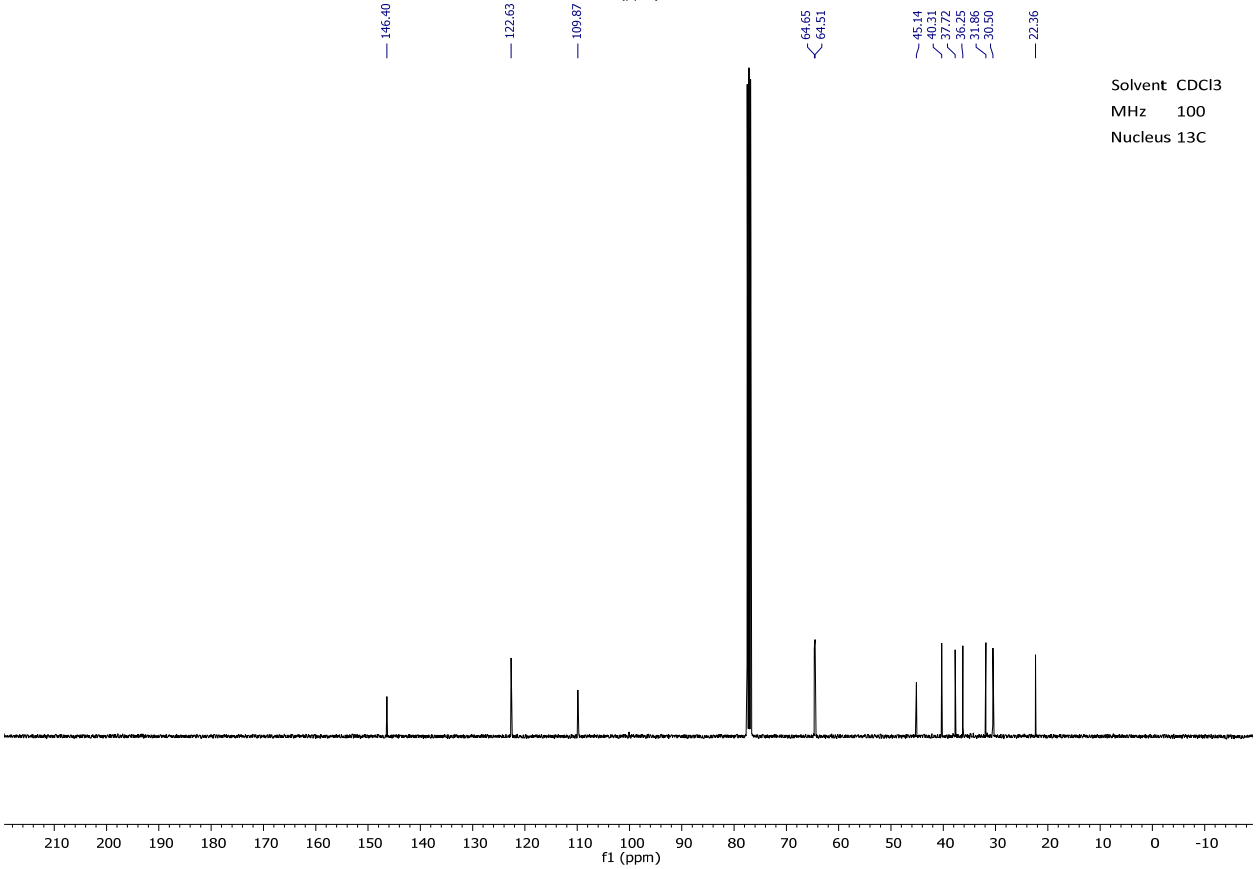

CH3
O
Solvent CDCl3
MHz 400
Nucleus 1H
0.84
0.99
2.10
0.99
1.01
4.00
1.00
2.82
f1 (ppm)
199.78
178.76
121.41
76.84
42.82
40.95
36.17
33.93
30.84
22.49
21.26
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)

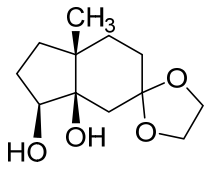


Solvent CDCl3
MHz 400
Nucleus 1H

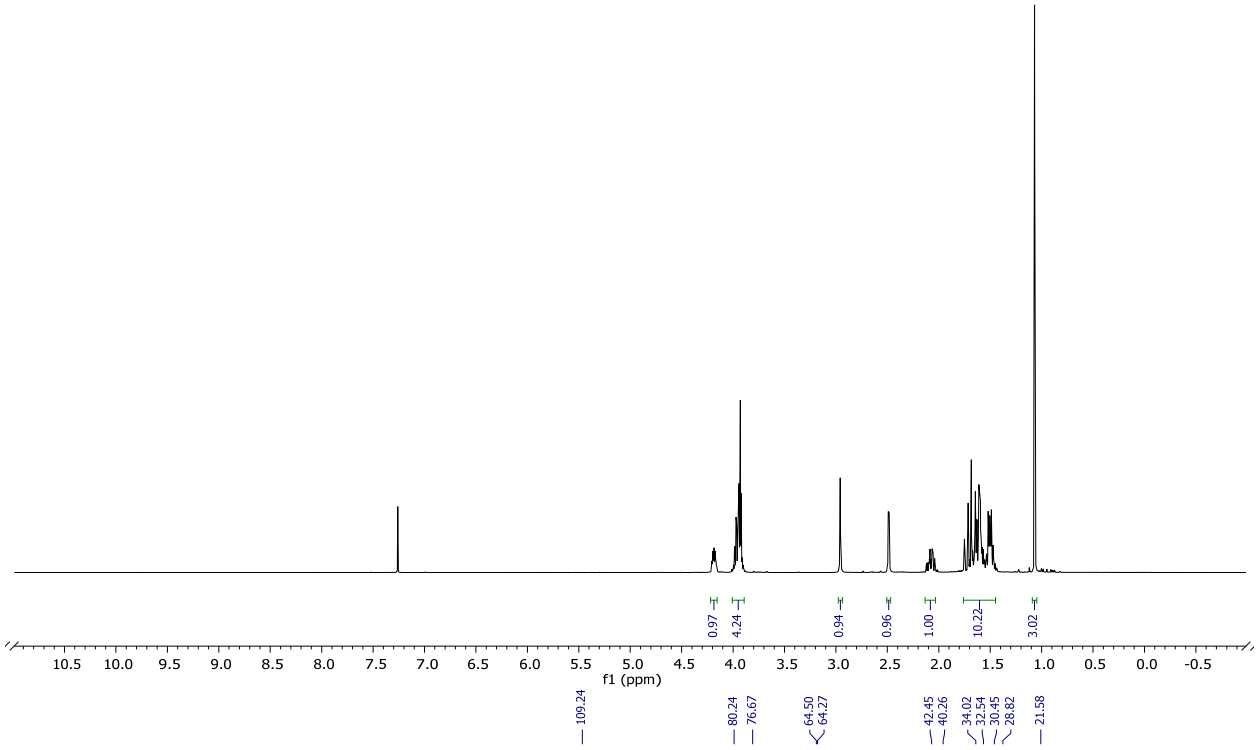


Solvent CDCl3
MHz 100
Nucleus 13C



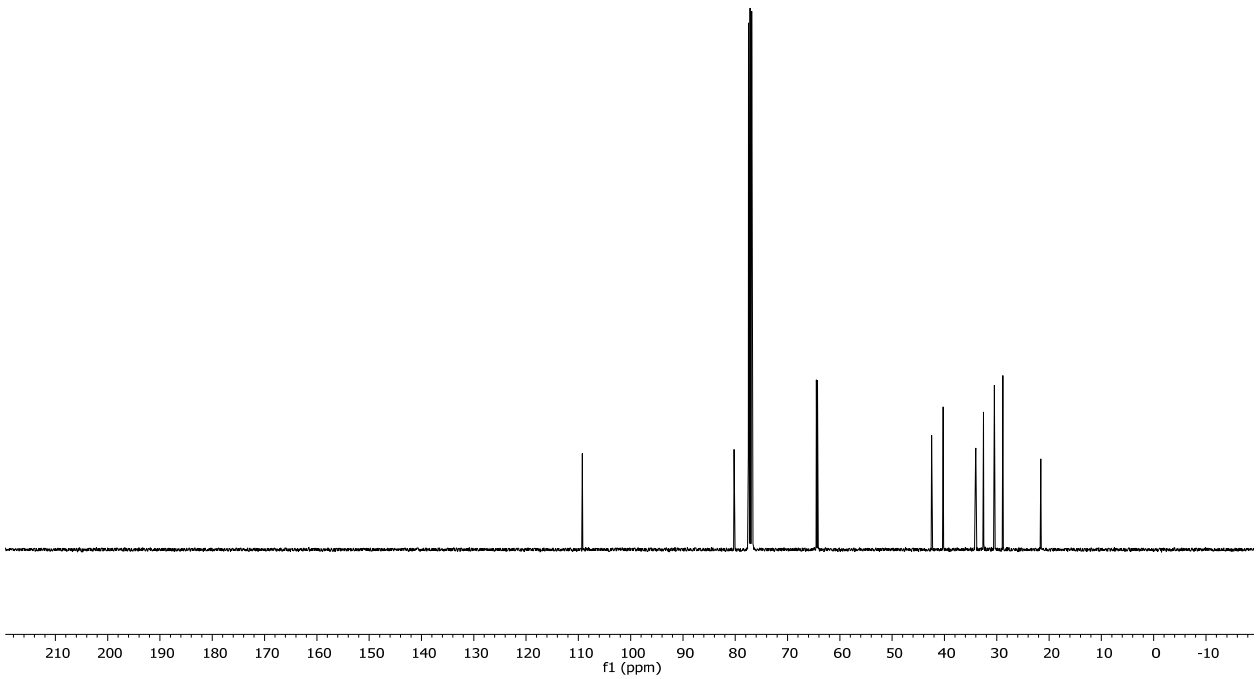


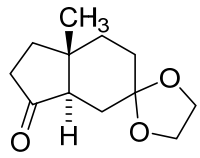
Solvent CDCl3
MHz 400
Nucleus 1H



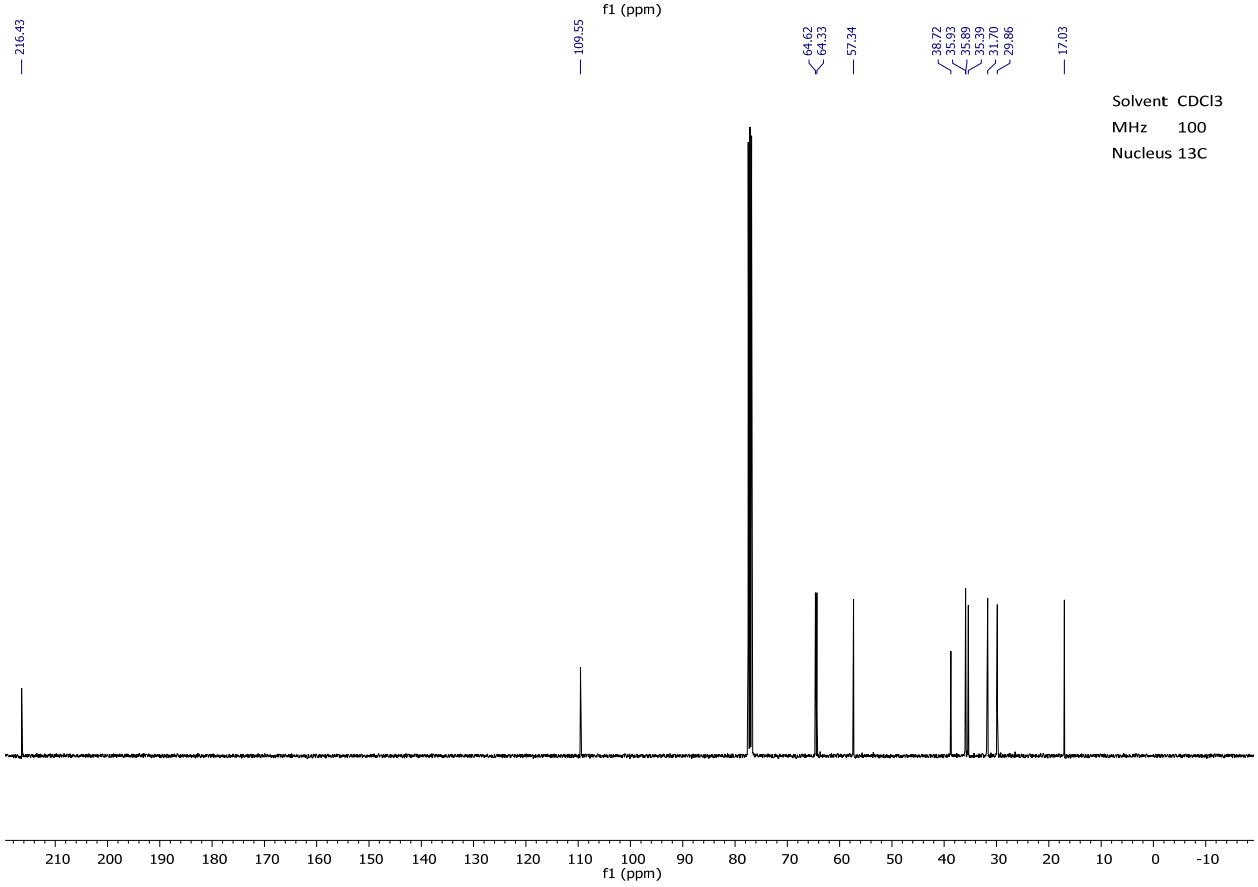
109.24
80.24
76.67
64.50
64.27
42.45
40.26
34.02
32.54
30.45
28.82
21.58

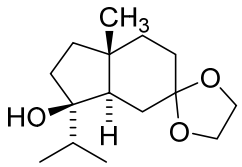
Solvent CDCl3
MHz 100
Nucleus 13C



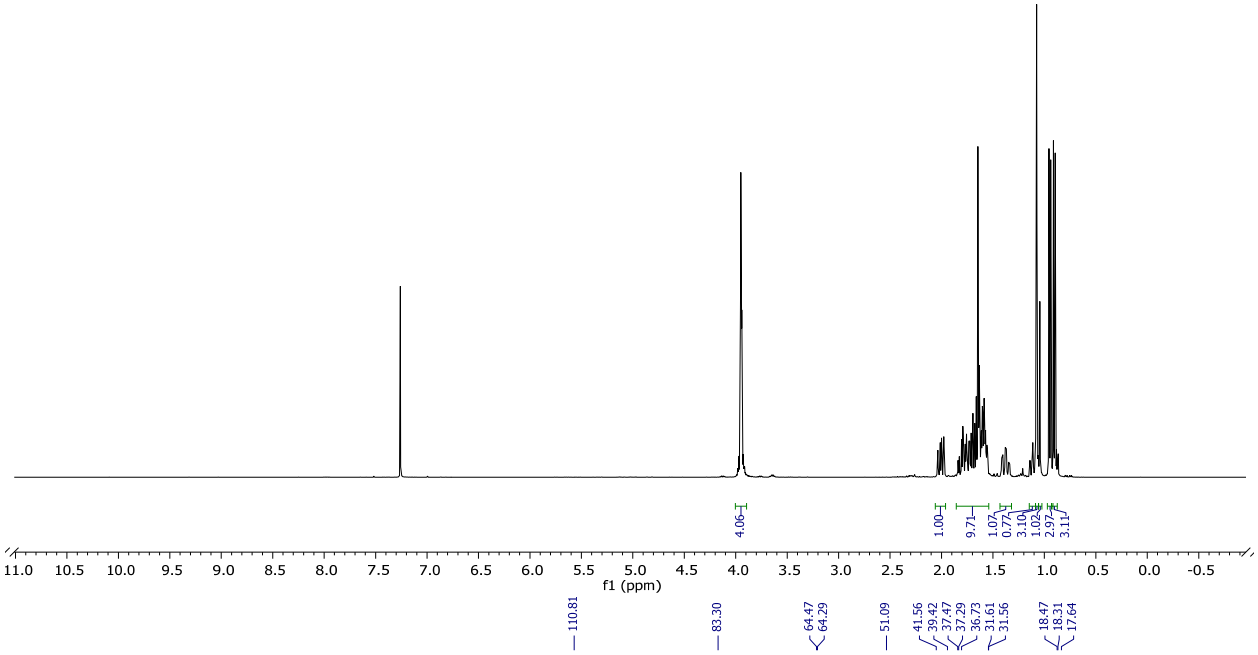

CH3
O
O
O
H

Solvent CDCl3
MHz 400
Nucleus 1H
4.15
3.06
7.63
1.07
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


216.43
109.55
64.62
64.33
57.34
38.72
35.93
35.89
35.39
31.70
29.86
17.03
Solvent CDCl3
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

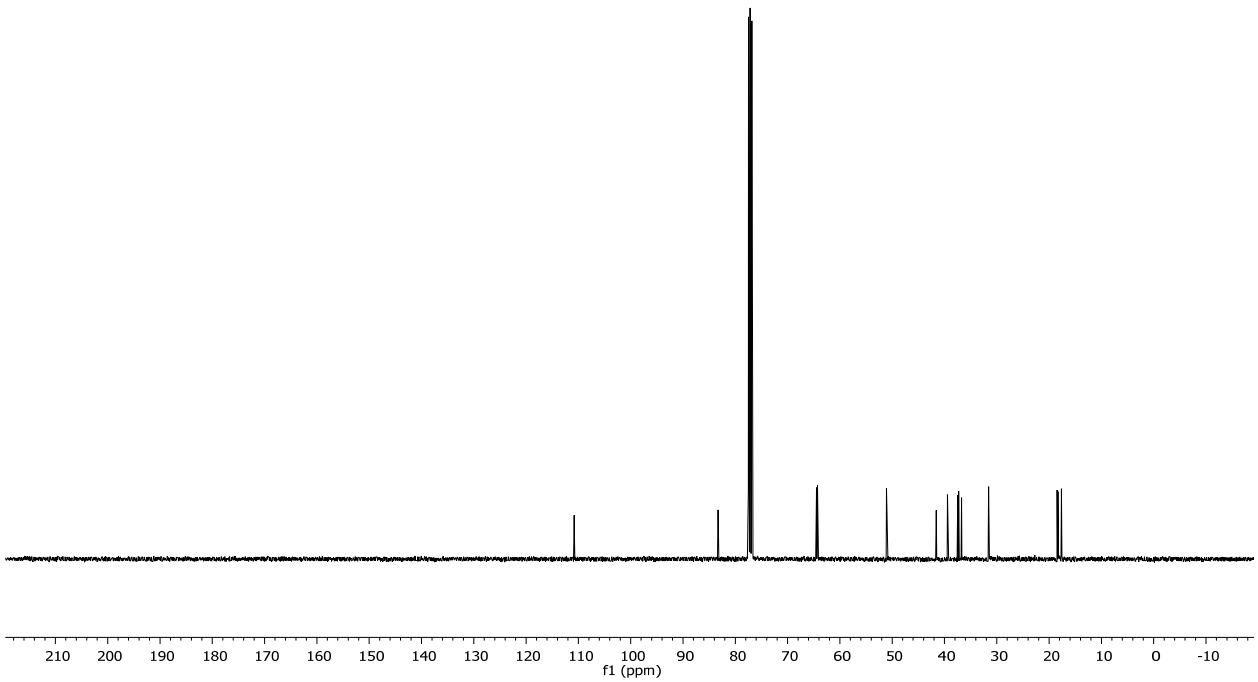


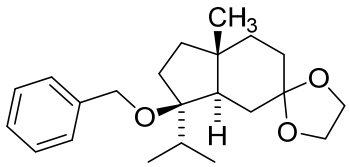
Solvent CDCl3
MHz 400
Nucleus 1H



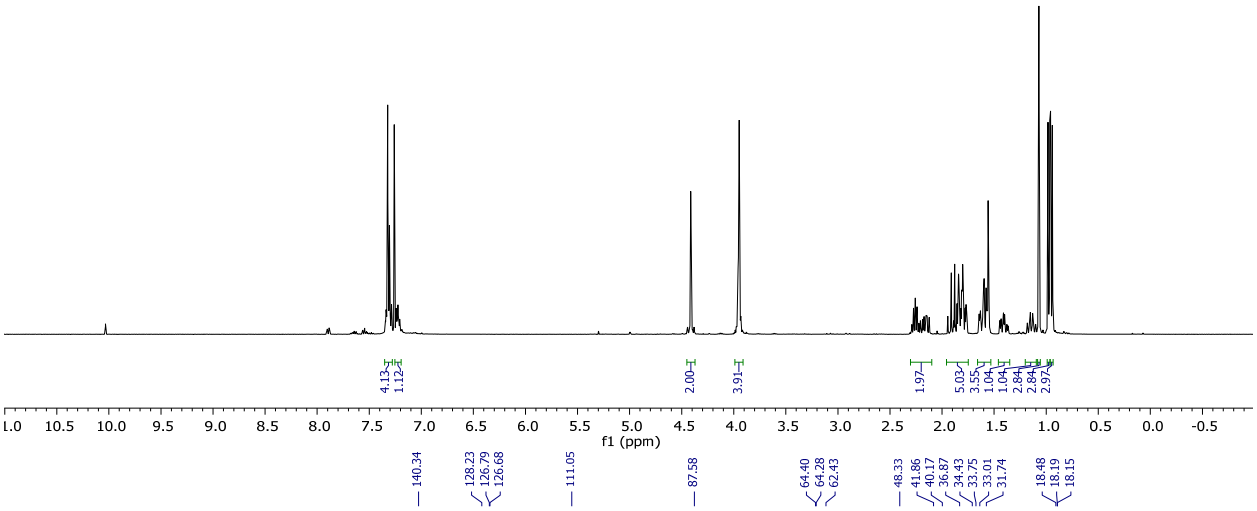
110.81
83.30
64.47
64.29
51.09
41.56
39.42
37.47
37.29
36.73
31.61
31.56
18.47
18.31
17.64

Solvent CDCl3
MHz 100
Nucleus 13C

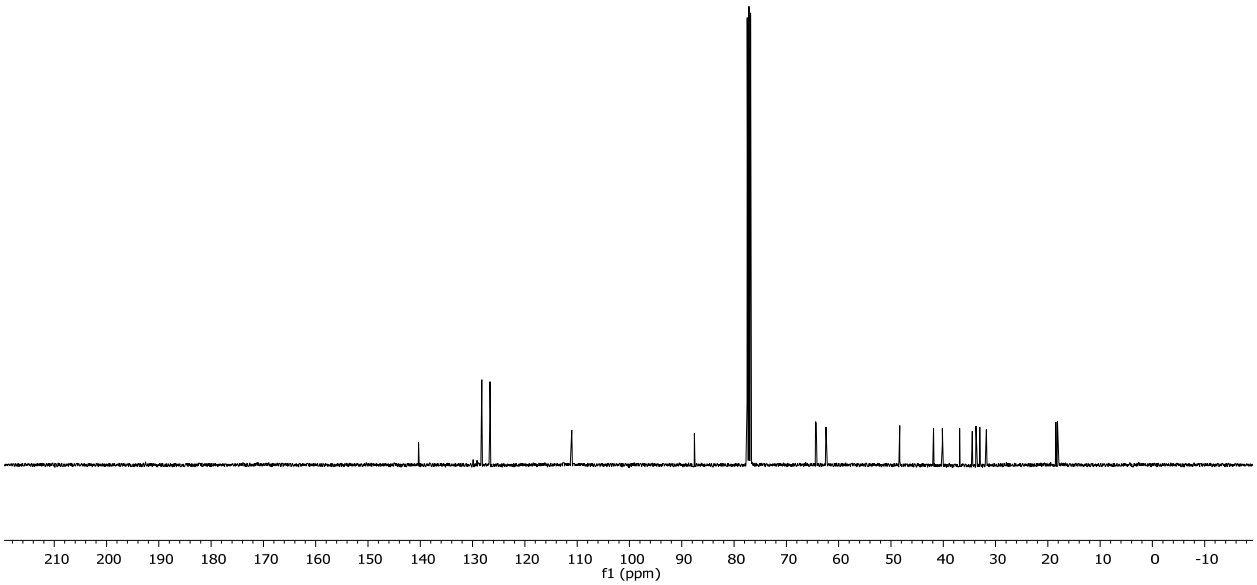


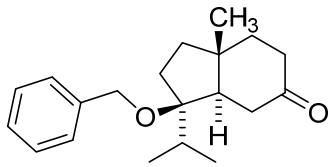


Solvent CDCl3
MHz 400
Nucleus 1H

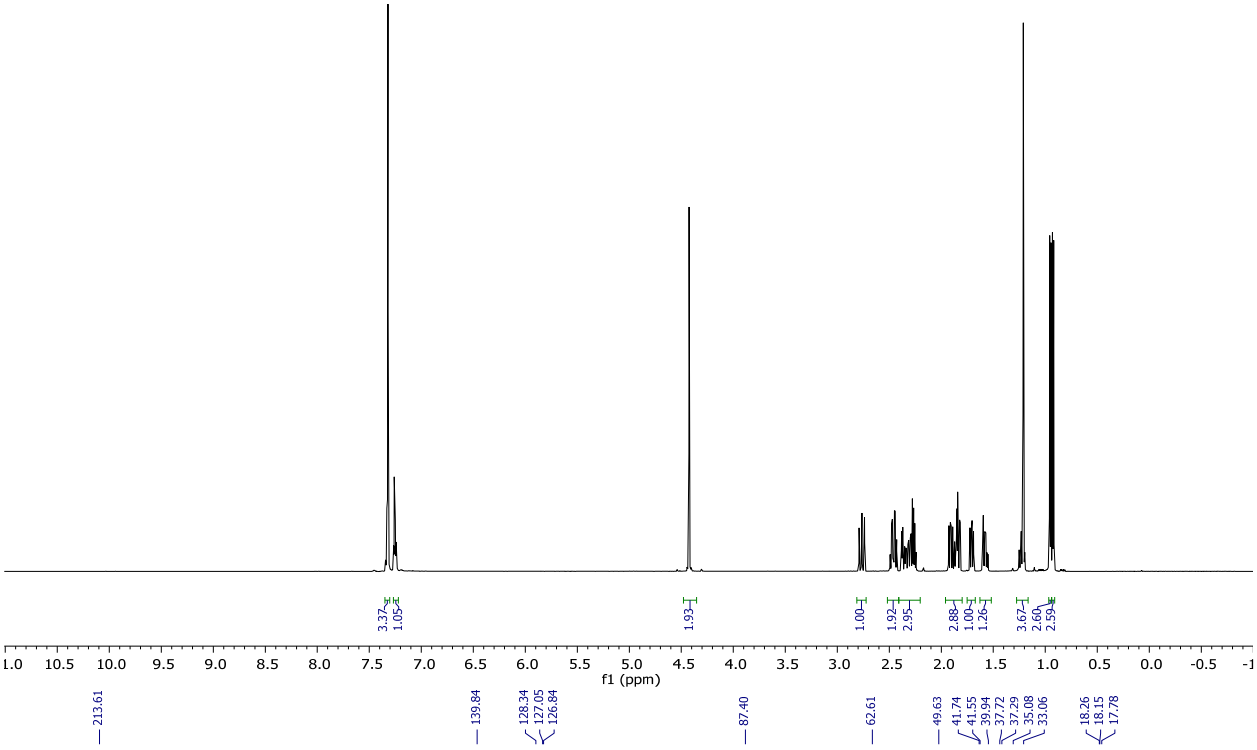


Solvent CDCl3
MHz 100
Nucleus 13C

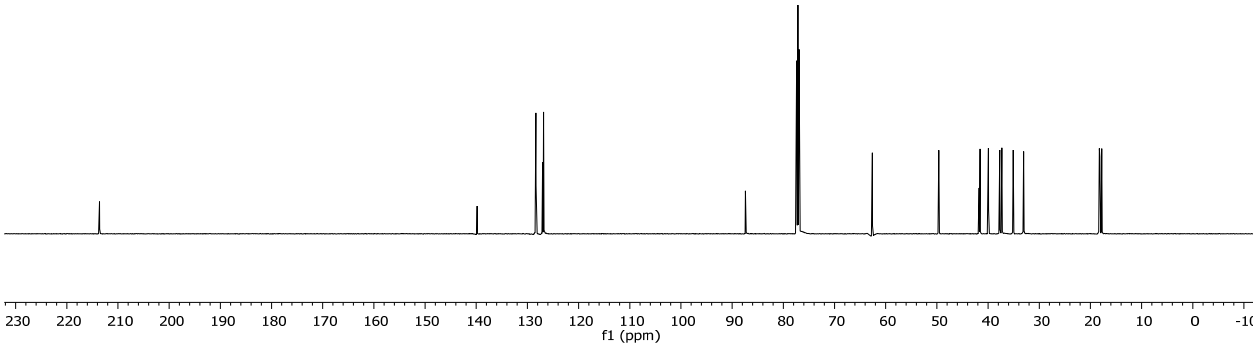


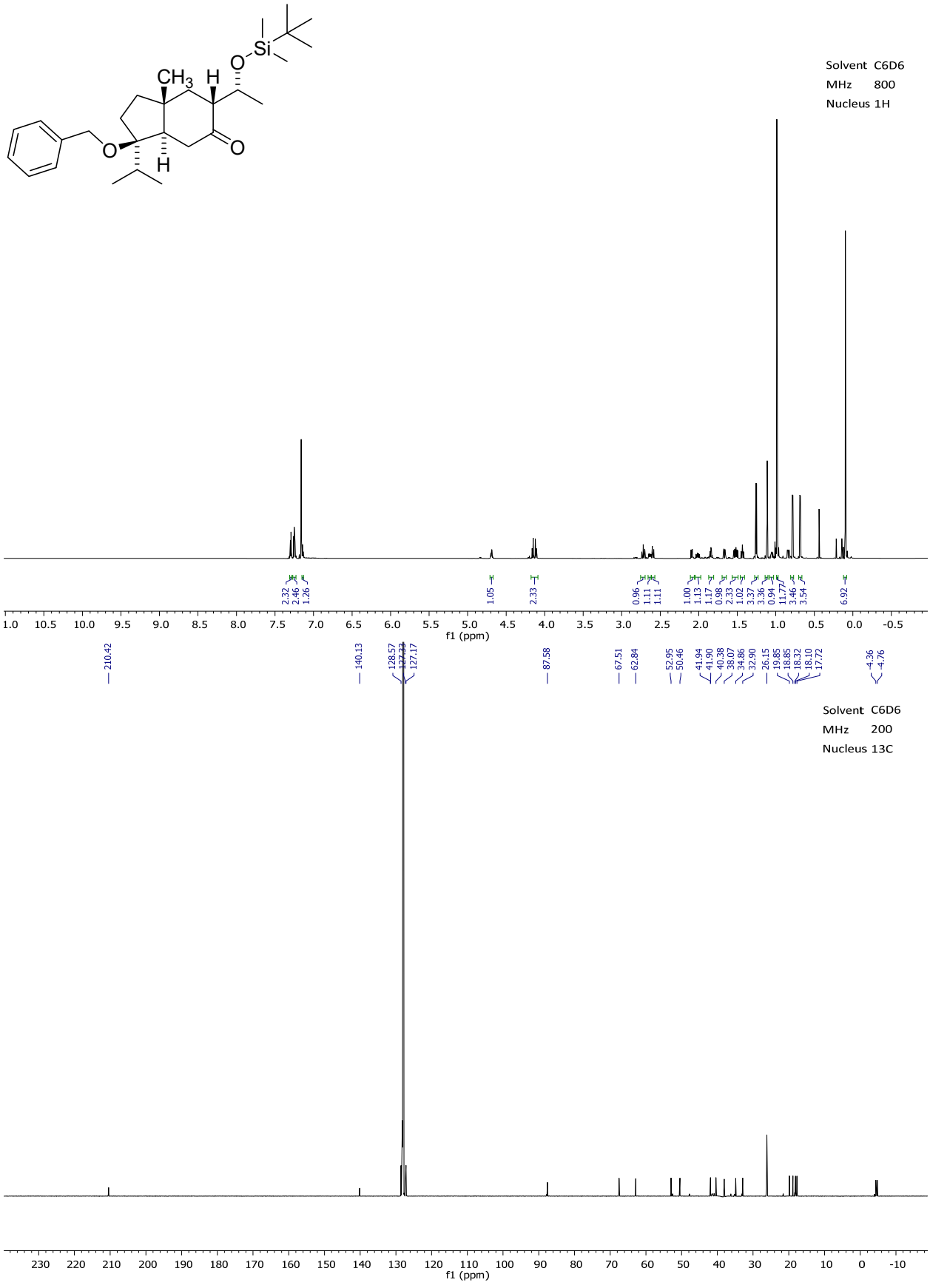


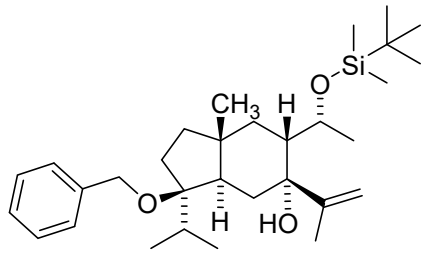
Solvent CDCl3
MHz 600
Nucleus 1H



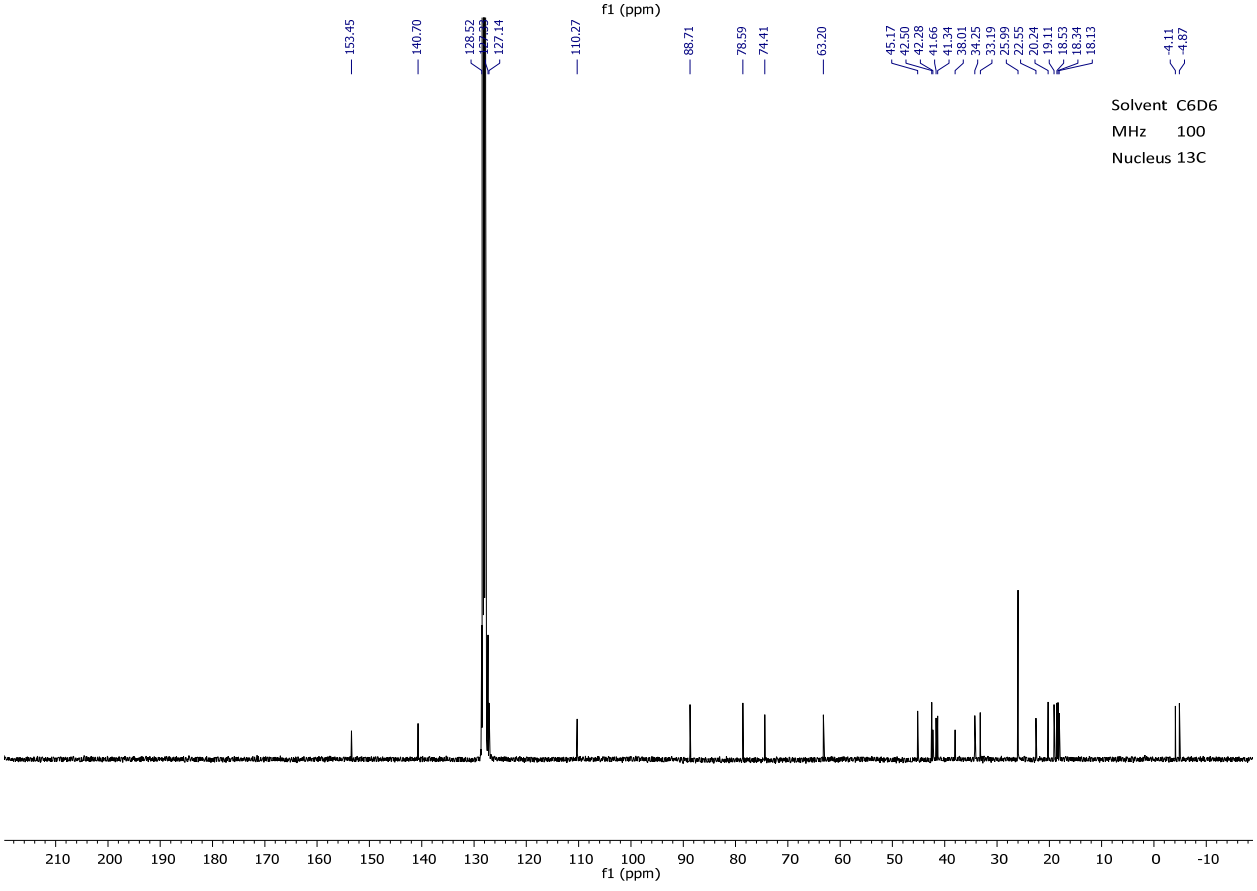
Solvent CDCl3
MHz 150
Nucleus 13C

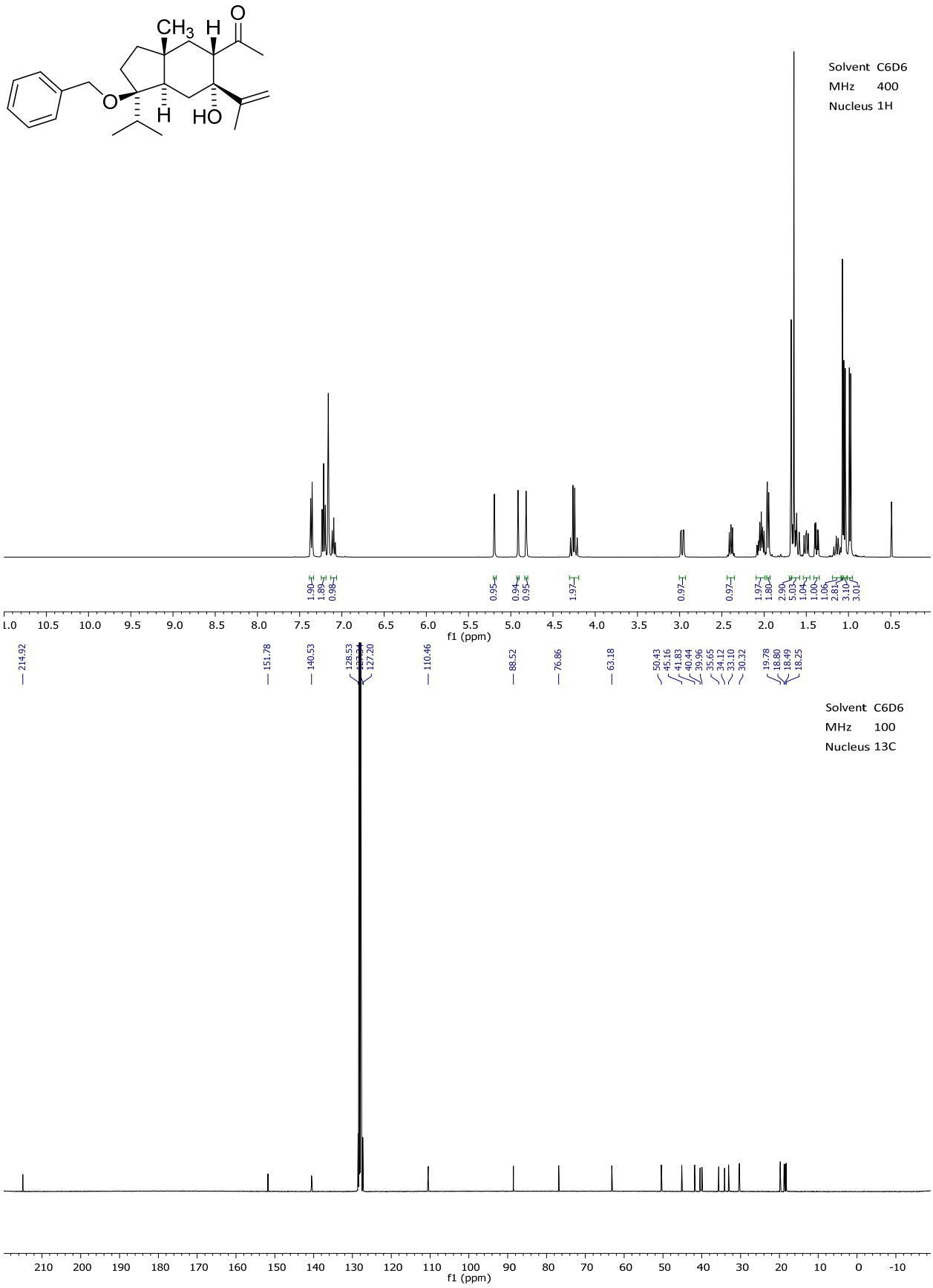


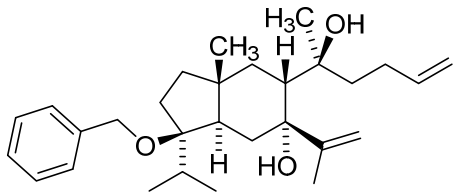

Si
O
CH3
H
O
O
H
Solvent C6D6
MHz 800
Nucleus 1H
2.32
2.46
1.26
1.05
2.33
0.96
1.11
1.11
1.00
1.13
1.17
0.98
2.33
1.02
3.37
3.36
0.94
11.77
3.46
3.54
6.92
f1 (ppm)
210.42
140.13
128.57
127.33
127.17
87.58
67.51
62.84
52.95
50.46
41.94
41.90
40.38
38.07
34.86
32.90
26.15
19.85
18.85
18.32
18.10
17.72
-4.36
-4.76
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)


Si
O
CH3
H
O
H
HO

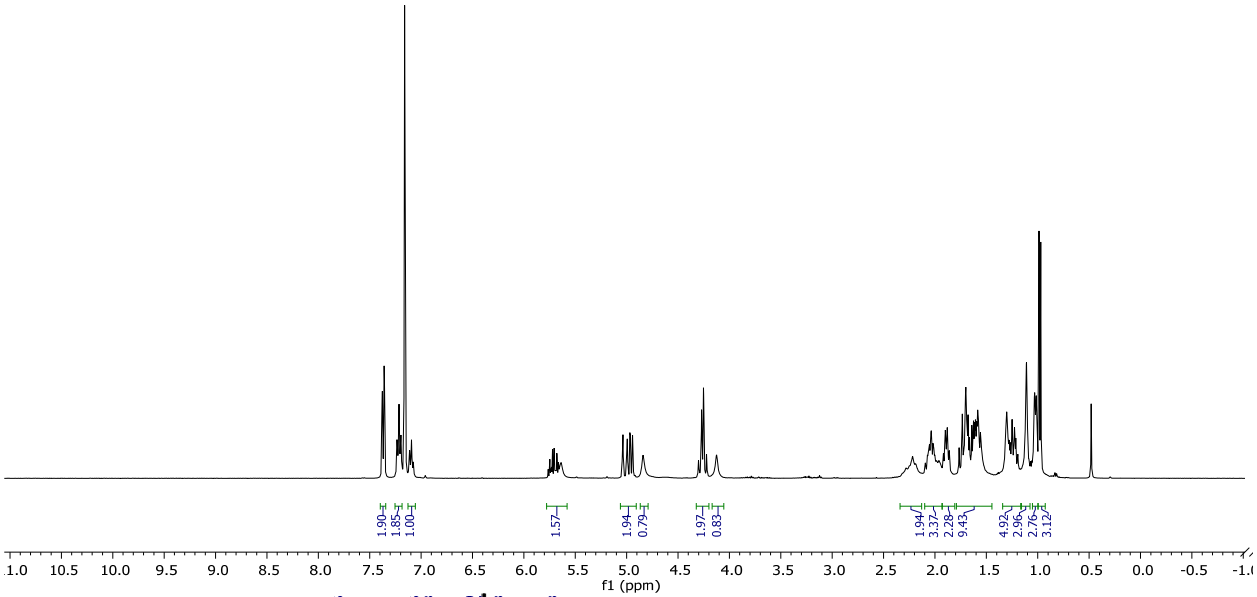
Solvent C6D6
MHz 400
Nucleus 1H
2.00
2.08
1.08
0.96
0.99
2.07
1.00
1.00
2.04
2.04
1.82
2.95
3.17
0.95
3.72
2.95
3.03
12.24
3.03
3.05
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

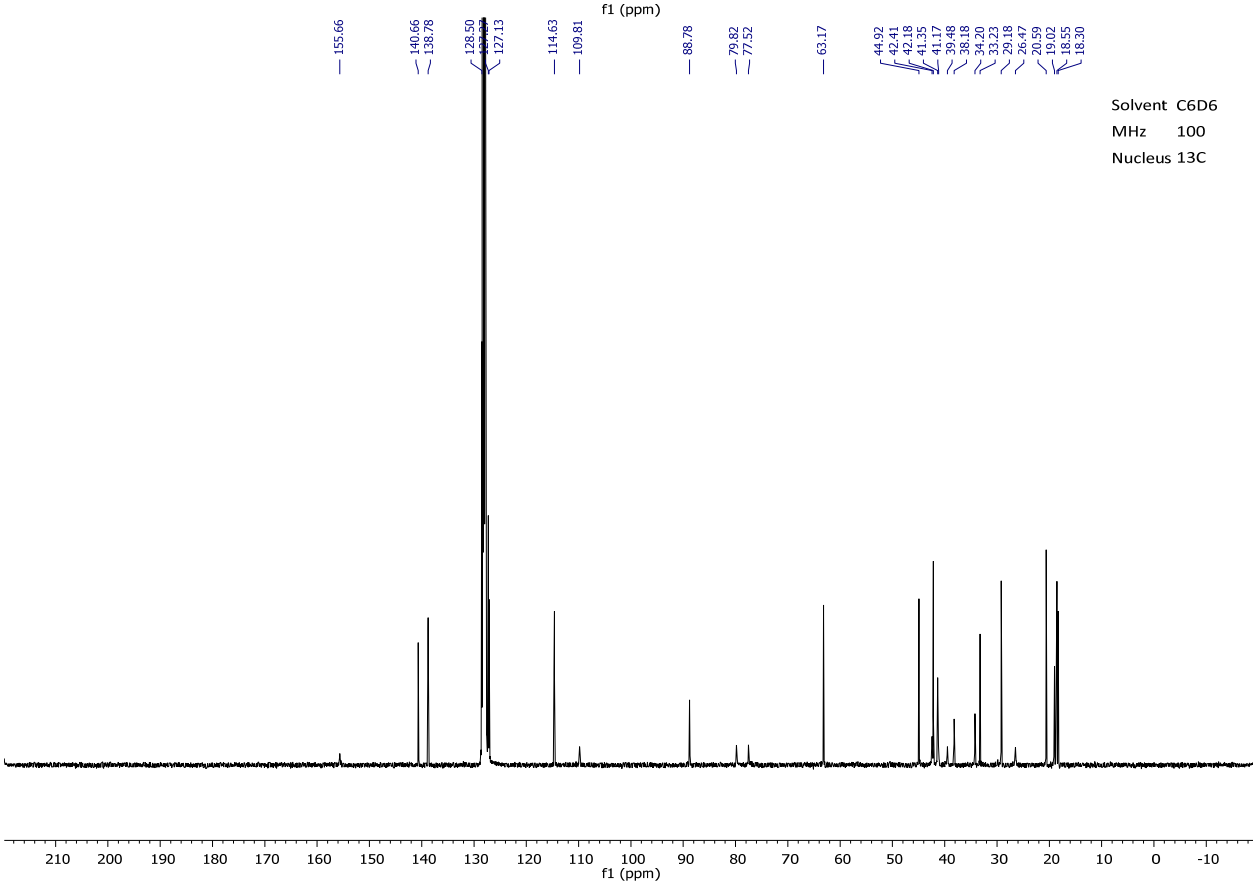

153.45
140.70
128.52
127.14
110.27
88.71
78.59
74.41
63.20
45.17
42.50
42.28
41.66
41.34
38.01
34.25
33.19
25.99
22.55
20.24
19.11
18.53
18.34
18.13
-4.11
-4.87
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
H
O
O
H
HO
Solvent C6D6
MHz 400
Nucleus 1H
1.90
1.89
0.98
0.95
0.94
0.95
1.97
0.97
0.97
1.97
1.80
2.90
5.03
1.04
1.00
1.06
2.81
3.10
3.01
f1 (ppm)
214.92
151.78
140.53
128.53
127.20
110.46
88.52
76.86
63.18
50.43
45.16
41.83
40.44
39.96
35.65
34.12
33.10
30.32
19.78
18.80
18.49
18.25
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

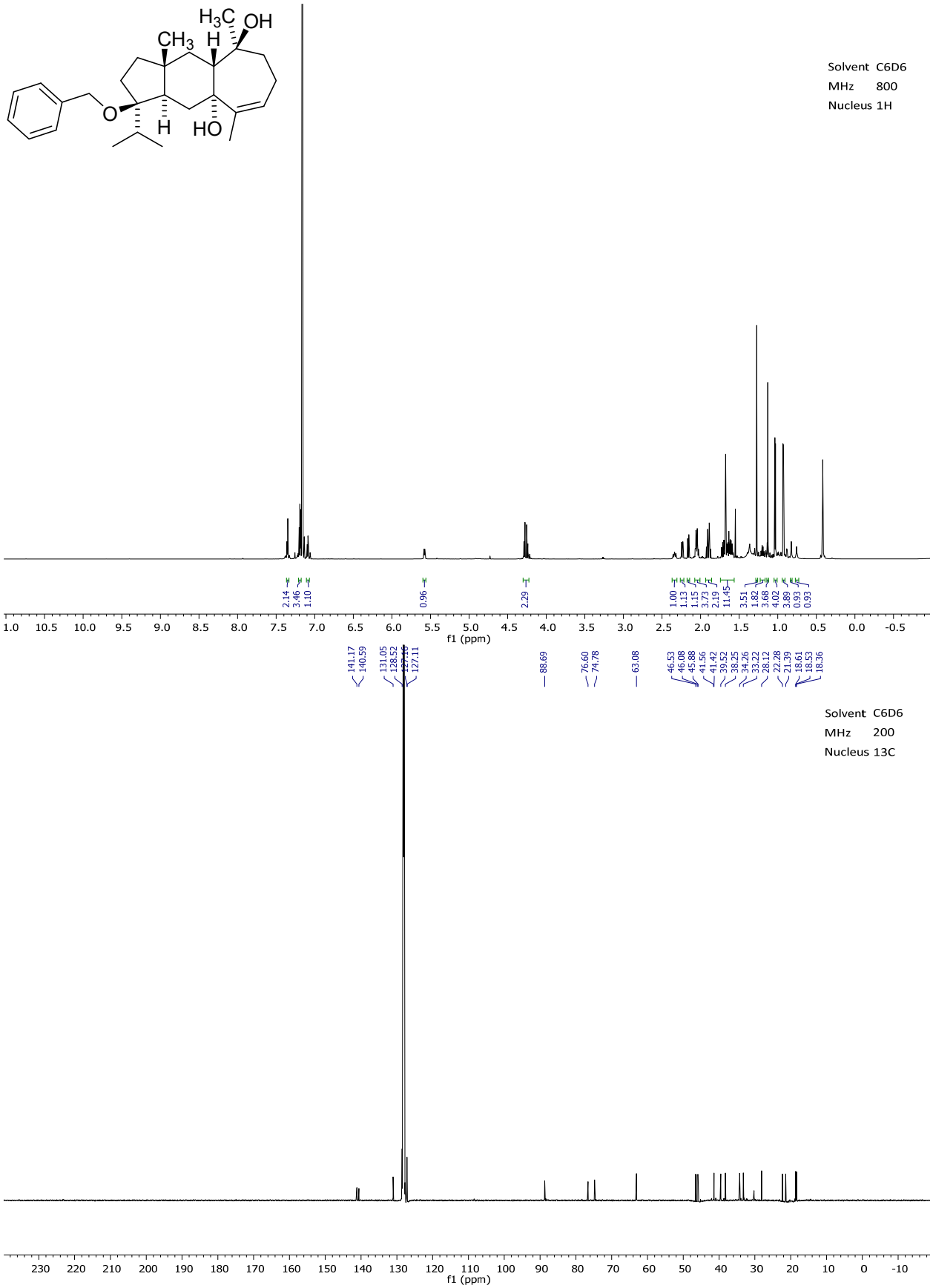


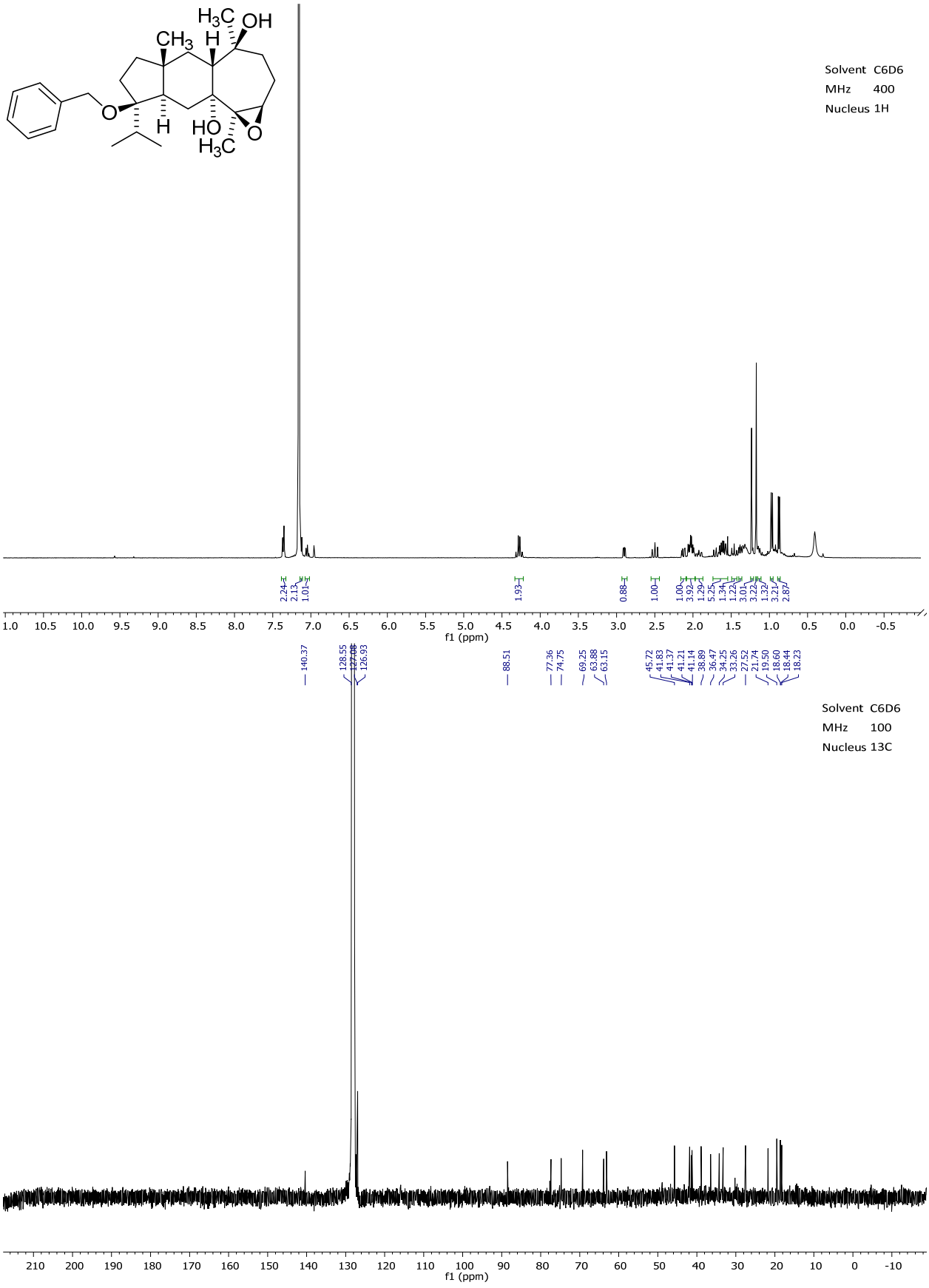
Solvent C6D6
MHz 400
Nucleus 1H

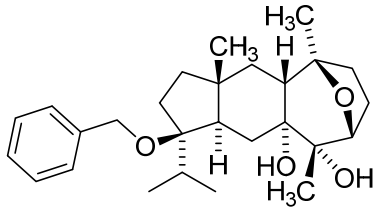




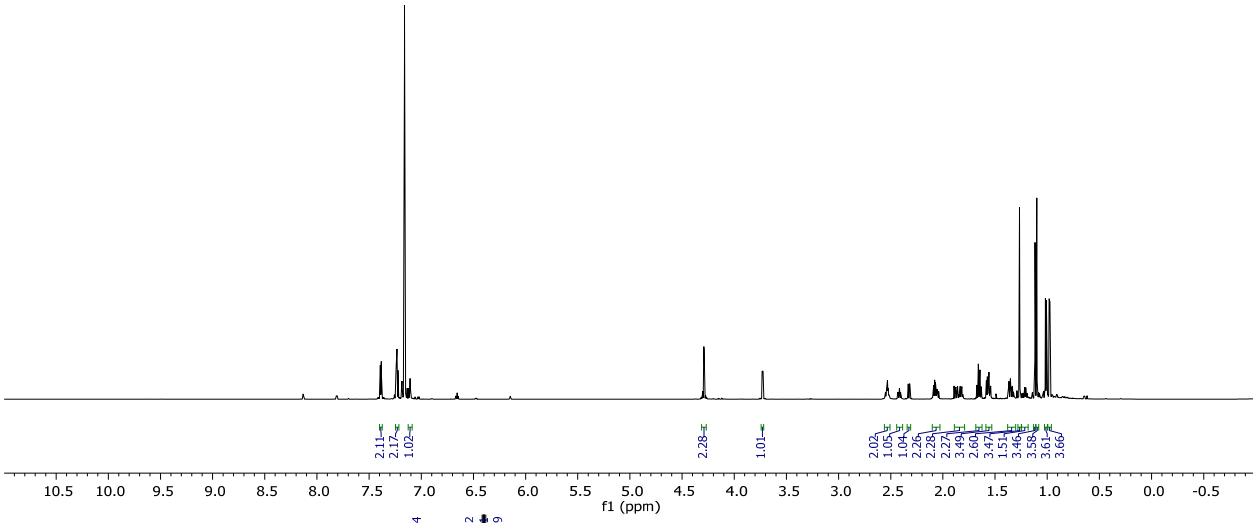
Solvent C6D6
MHz 100
Nucleus 13C

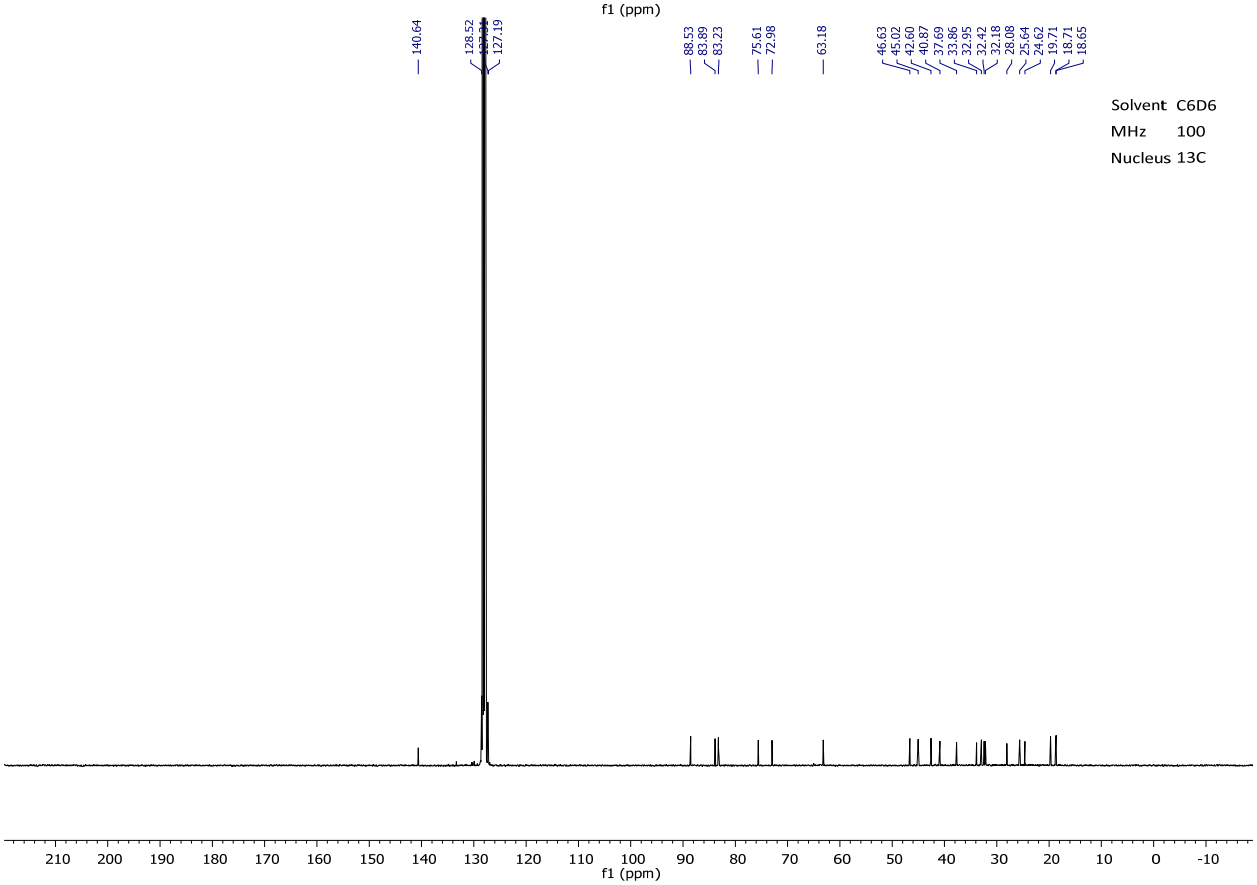

H3C OH
CH3 H
O
H HO
Solvent C6D6
MHz 800
Nucleus 1H
2.14
3.46
1.10
0.96
2.29
1.00
1.13
1.15
3.73
2.19
11.45
3.51
1.82
3.68
4.02
3.89
0.93
0.93
f1 (ppm)
141.17
140.59
131.05
128.52
127.46
127.11
88.69
76.60
74.78
63.08
46.53
46.08
45.88
41.56
41.42
39.52
38.25
34.26
33.22
28.12
22.28
21.39
18.61
18.53
18.36
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)


Solvent C6D6
MHz 400
Nucleus 1H
f1 (ppm)
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

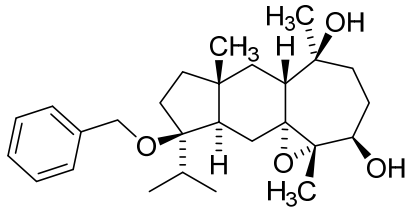


Solvent C6D6
MHz 800
Nucleus 1H

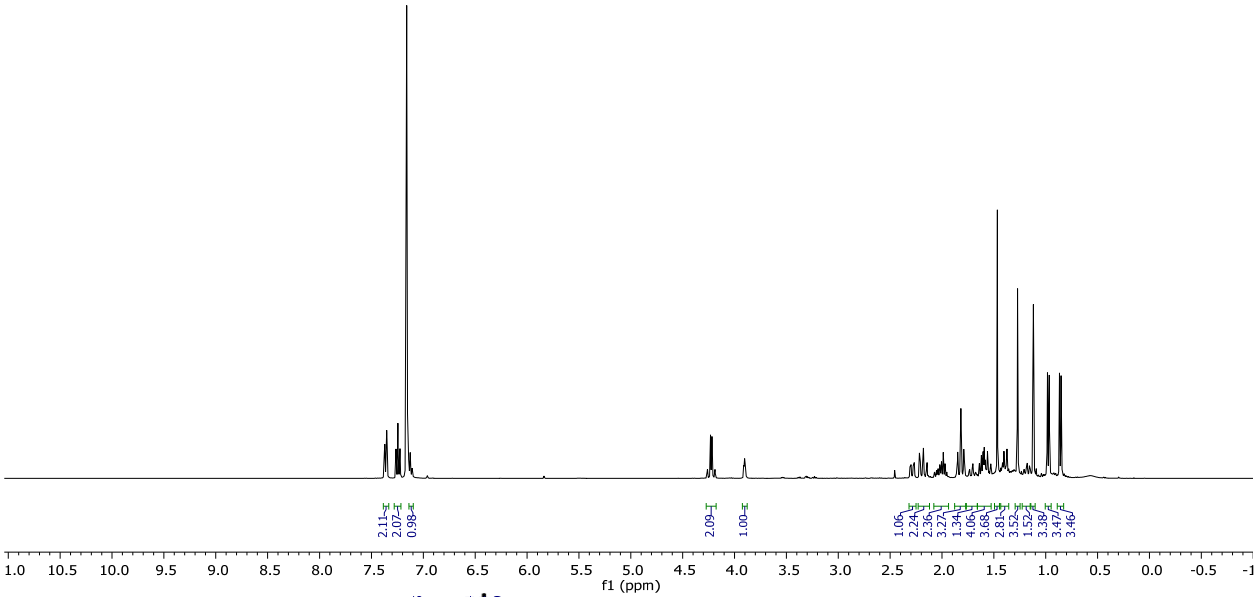


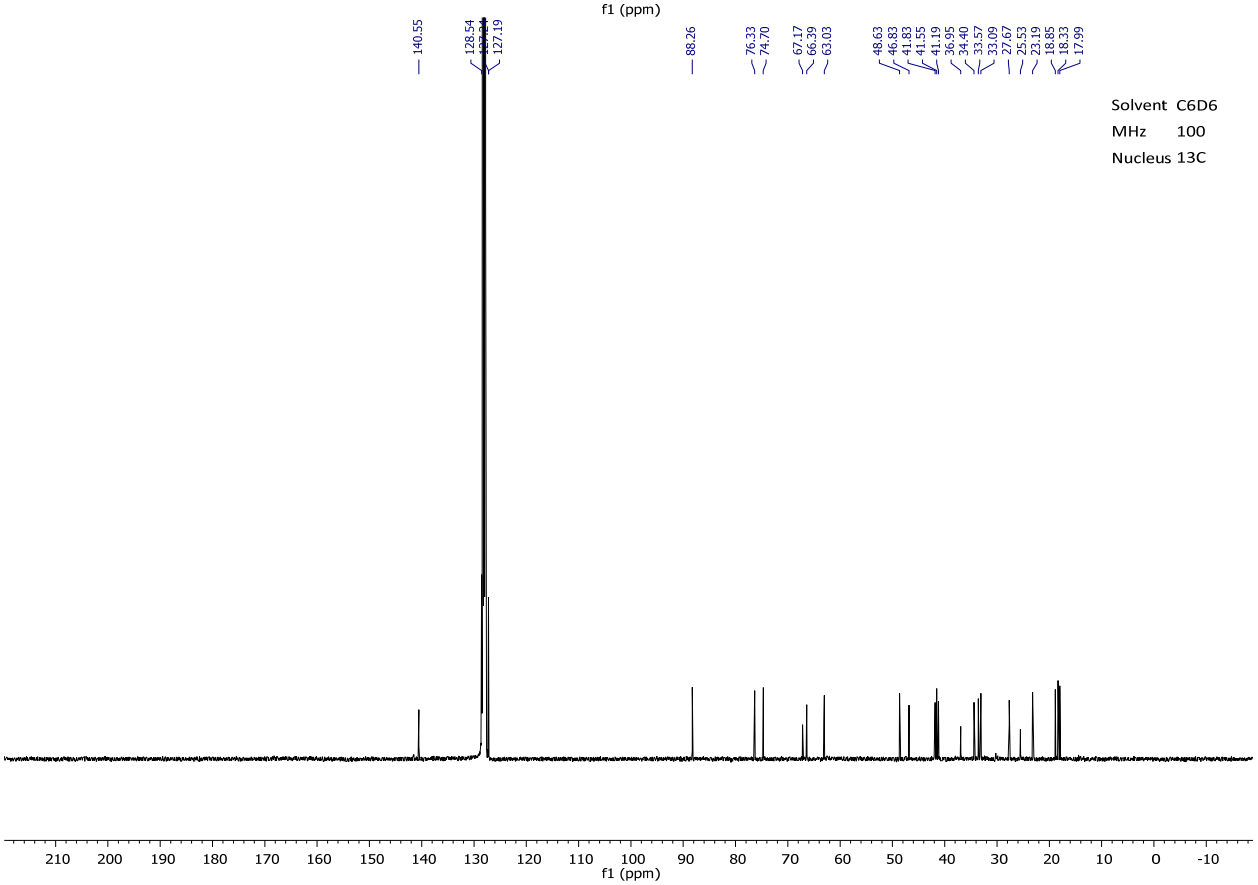


Solvent C6D6
MHz 100
Nucleus 13C

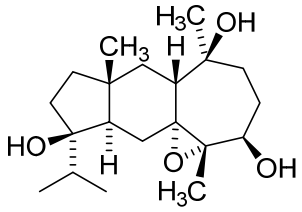


Solvent C6D6
MHz 400
Nucleus 1H

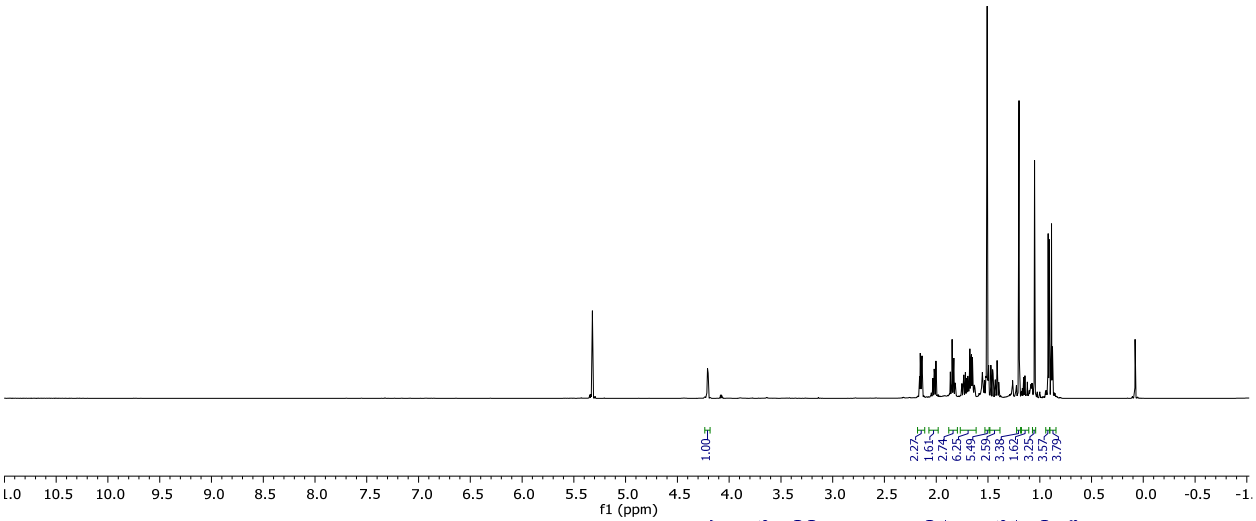


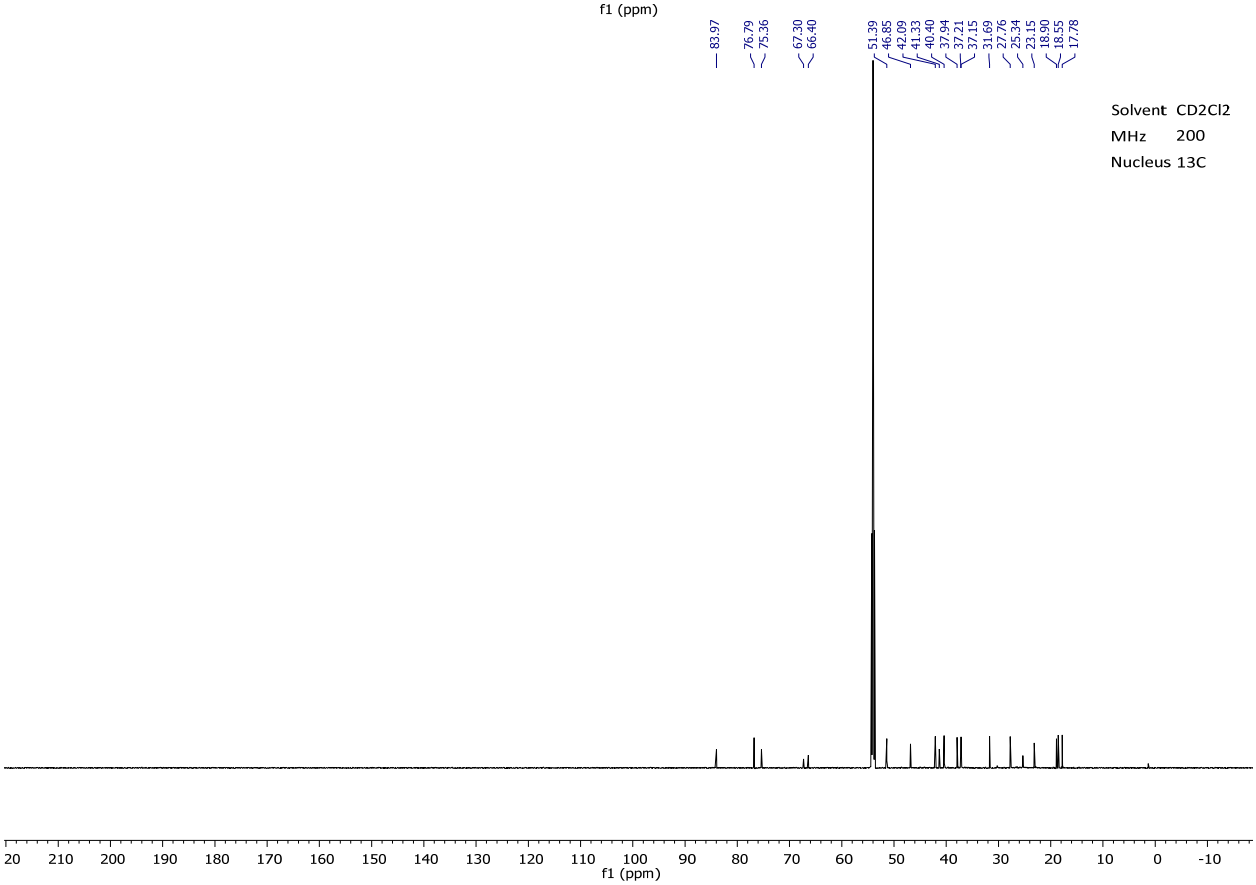


Solvent C6D6
MHz 100
Nucleus 13C

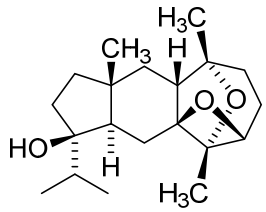


Solvent CD2Cl2
MHz 800
Nucleus 1H

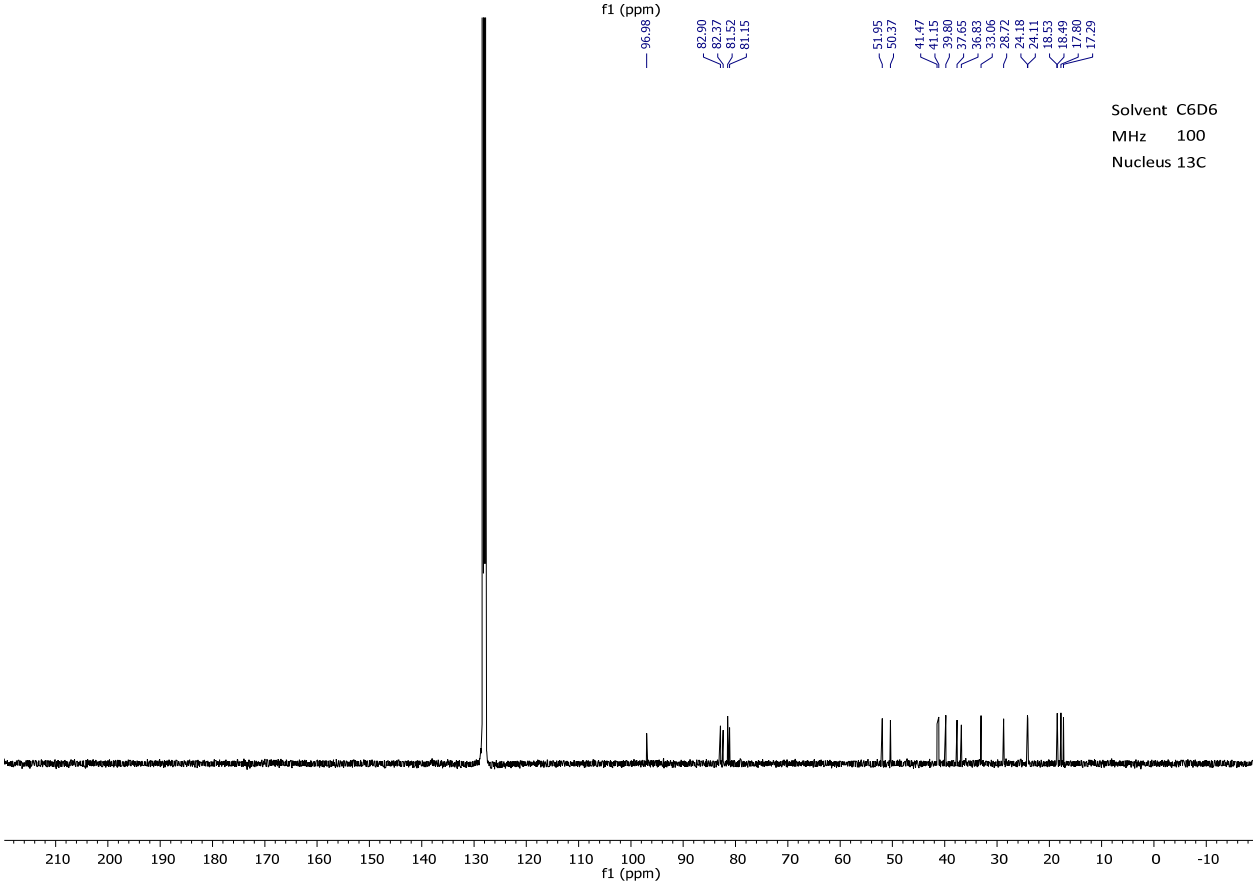


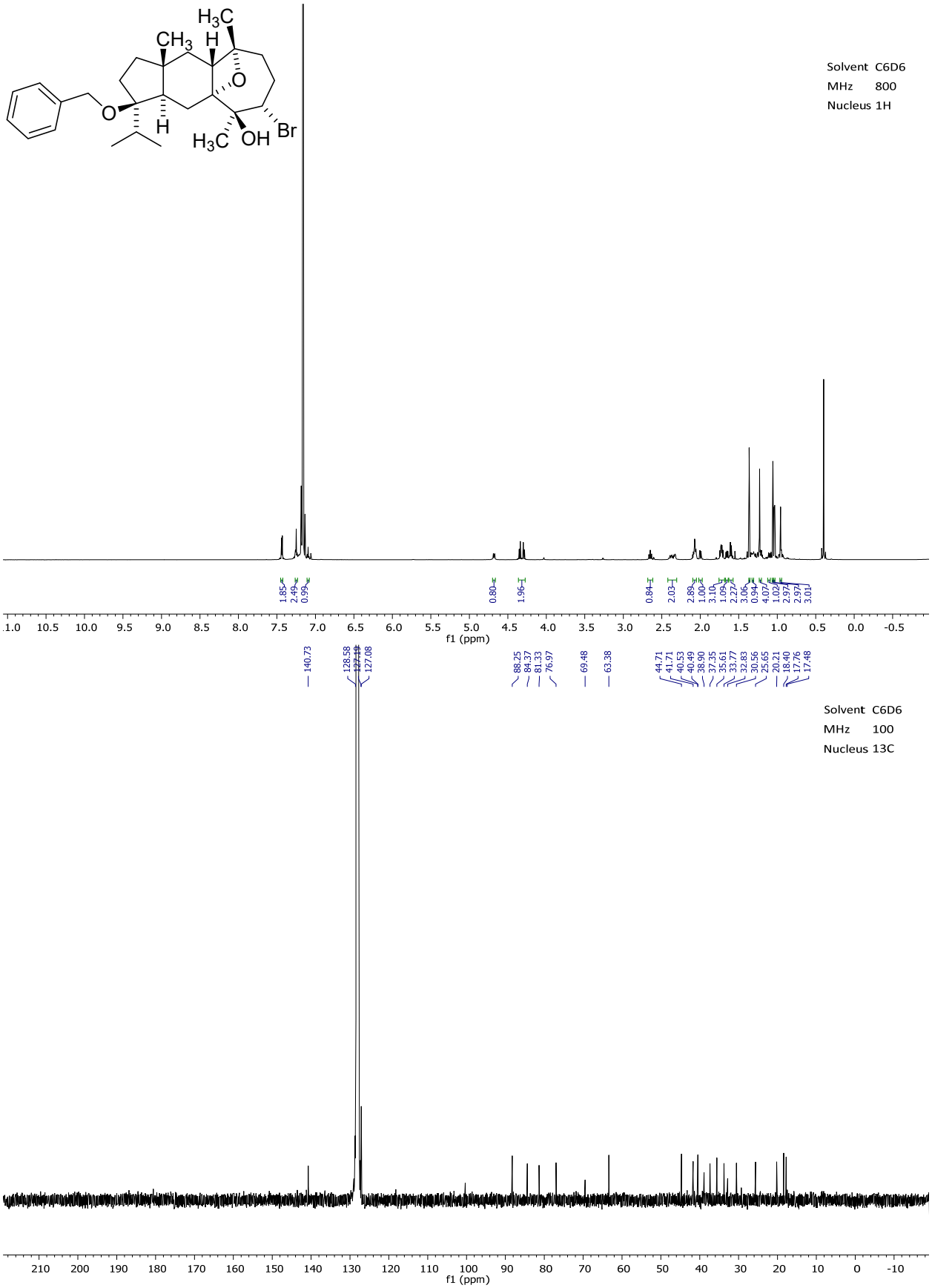


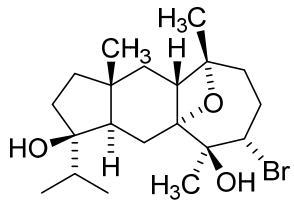
Solvent CD2Cl2
MHz 200
Nucleus 13C


H3C
CH3
H
O
O
HO
H
H3C

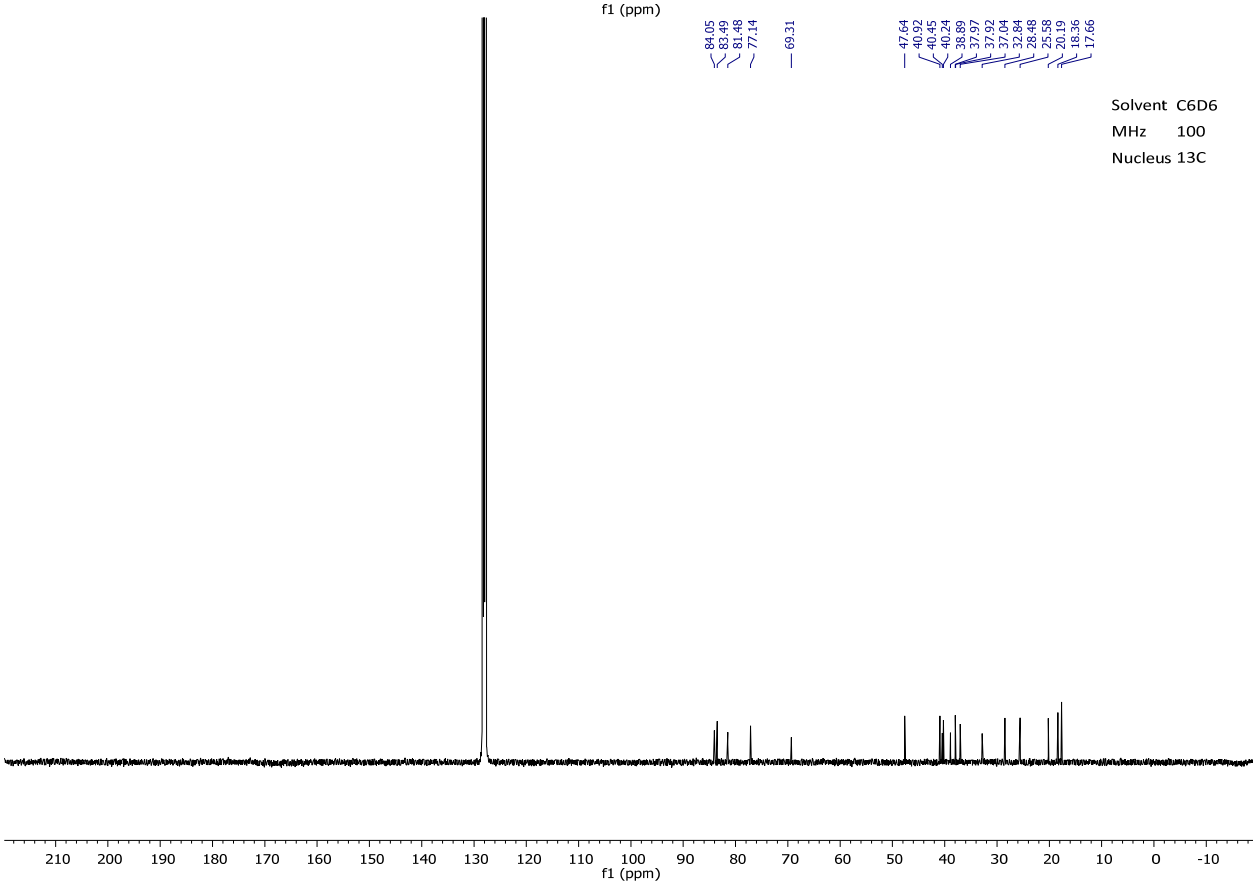
Solvent C6D6
MHz 800
Nucleus 1H
1.00
2.15
2.21
2.21
3.15
3.13
1.12
2.25
3.30
3.23
3.23
1.17
5.71
0.99
f1 (ppm)

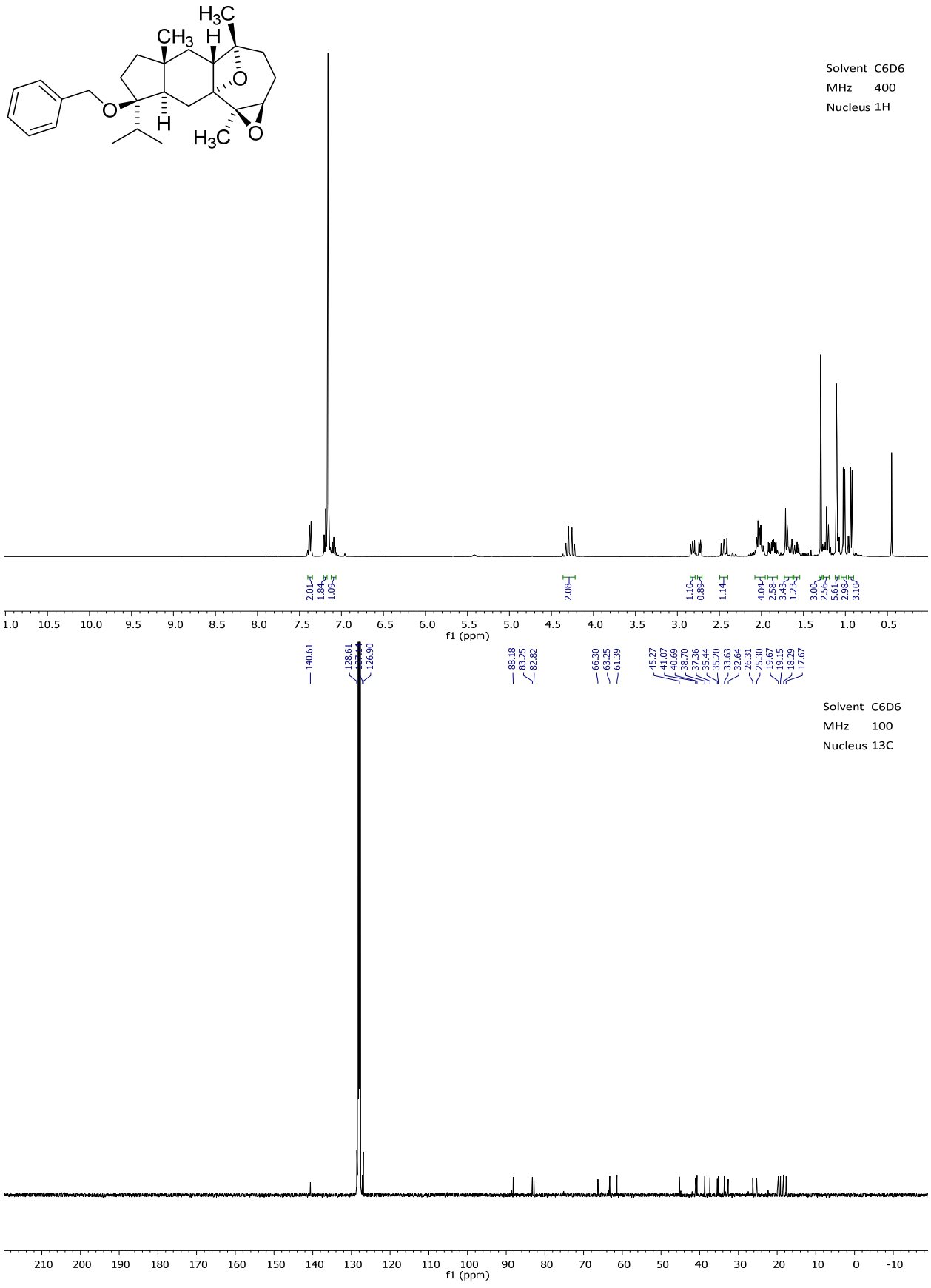

96.98
82.90
82.37
81.52
81.15
51.95
50.37
41.47
41.15
39.80
37.65
36.83
33.06
28.72
24.18
24.11
18.53
18.49
17.80
17.29
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

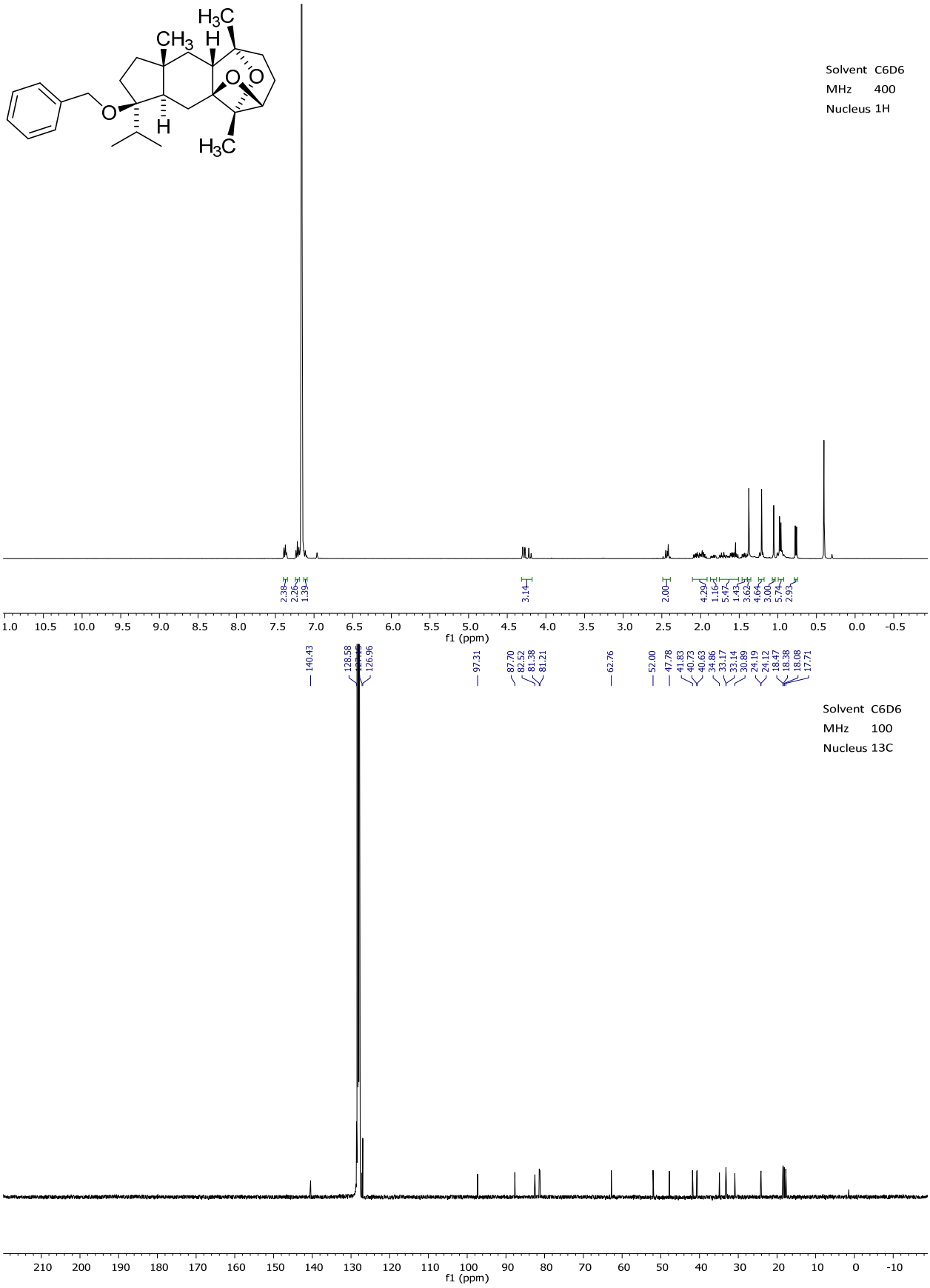

H3C
CH3
H
O
O
H
H3C
OH
Br
Solvent C6D6
MHz 800
Nucleus 1H
1.85
2.49
0.99
0.80
1.96
0.84
2.03
2.89
1.00
3.10
1.09
2.27
3.06
0.94
4.07
1.02
2.97
2.97
3.01
f1 (ppm)
140.73
128.58
127.19
127.08
88.25
84.37
81.33
76.97
69.48
63.38
44.71
41.71
40.53
40.49
38.90
37.35
35.61
33.77
32.83
30.56
25.65
20.21
18.40
17.76
17.48
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

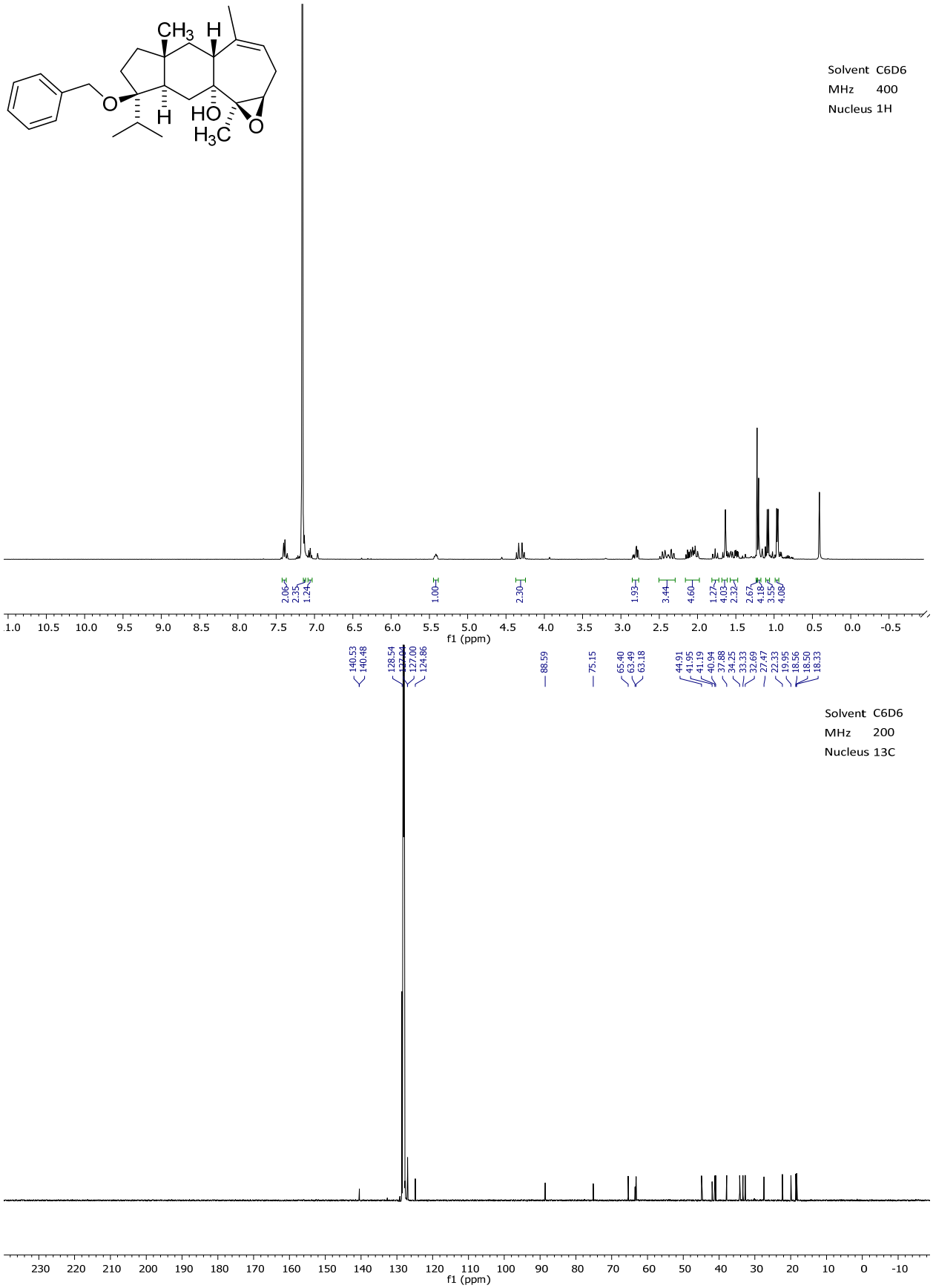

H3C
CH3
H
O
HO
H
H3C
OH
Br

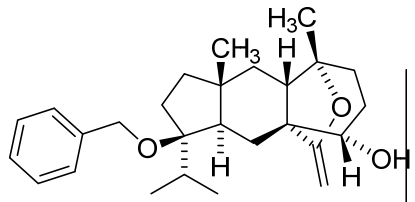
Solvent C6D6
MHz 400
Nucleus 1H
1.00
1.07
2.02
1.05
2.06
3.24
7.37
1.41
3.09
2.10
3.06
3.14
3.21
0.93
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


84.05
83.49
81.48
77.14
69.31
47.64
40.92
40.45
40.24
38.89
37.97
37.92
37.04
32.84
28.48
25.58
20.19
18.36
17.66
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

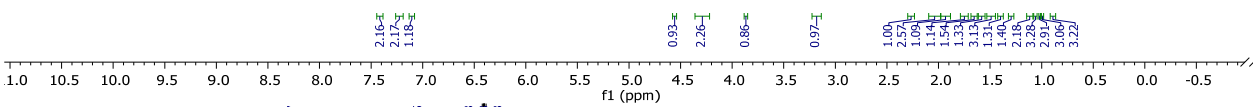

Solvent C6D6
MHz 400
Nucleus 1H
f1 (ppm)
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

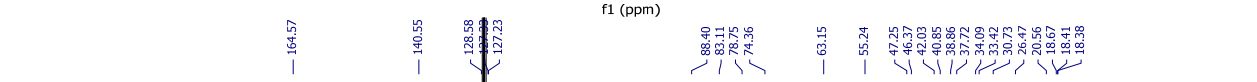

Solvent C6D6
MHz 400
Nucleus 1H
f1 (ppm)
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


CH3 H
O
H
HO
H3C
O
Solvent C6D6
MHz 400
Nucleus 1H
2.06
2.35
1.24
1.00
2.30
1.93
3.44
4.60
1.27
4.03
2.32
2.67
4.18
3.55
4.08
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
140.53
140.48
128.54
127.00
124.86
88.59
75.15
65.40
63.49
63.18
44.91
41.95
41.19
40.94
37.88
34.25
33.33
32.69
27.47
22.33
19.95
18.56
18.50
18.33
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

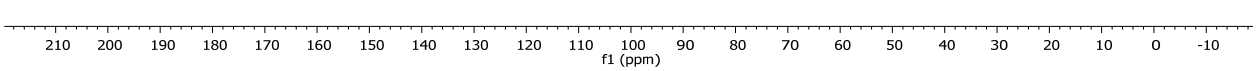


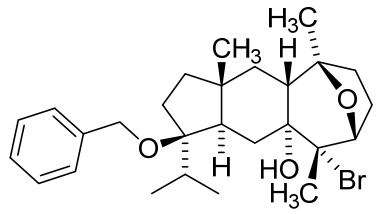
Solvent C6D6
MHz 400
Nucleus 1H



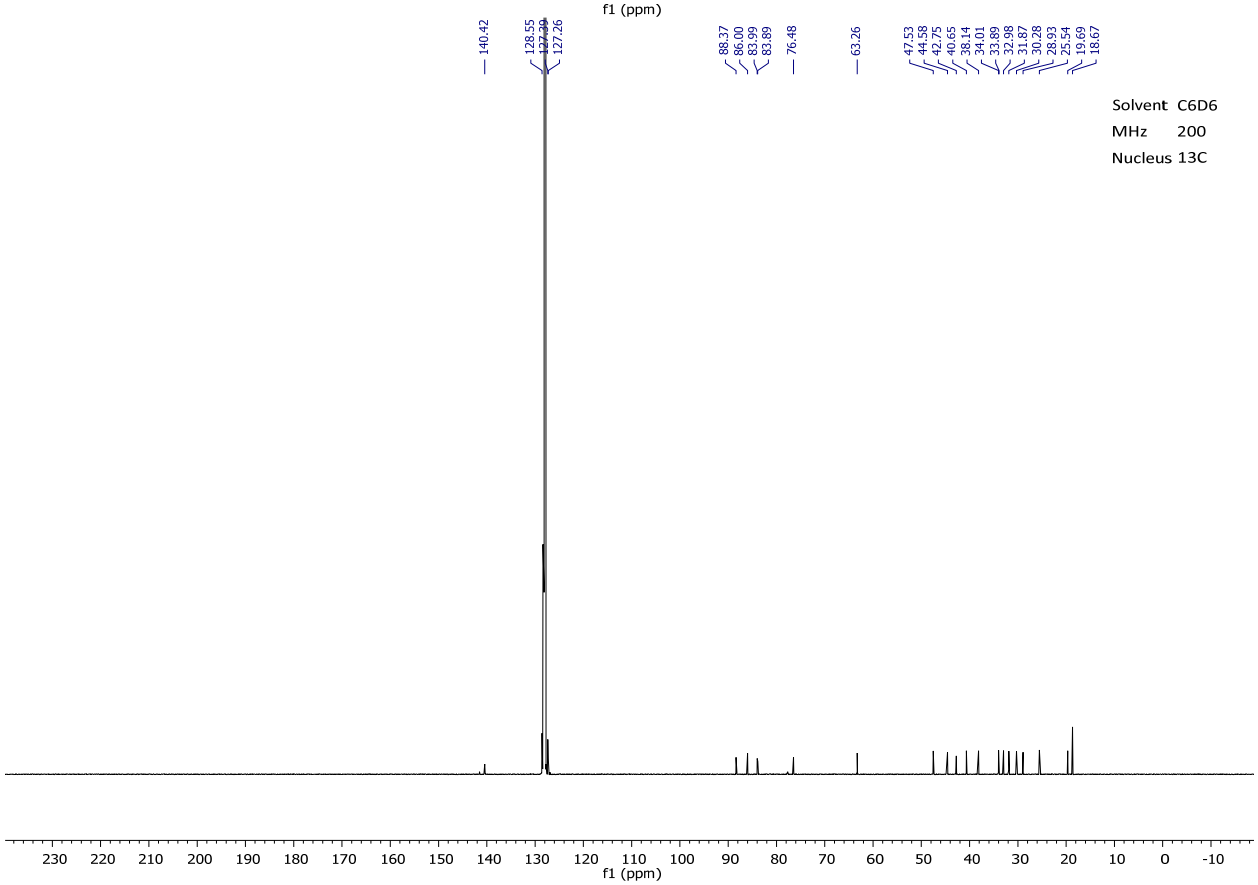


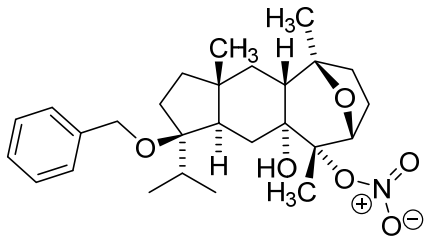
Solvent C6D6
MHz 100
Nucleus 13C



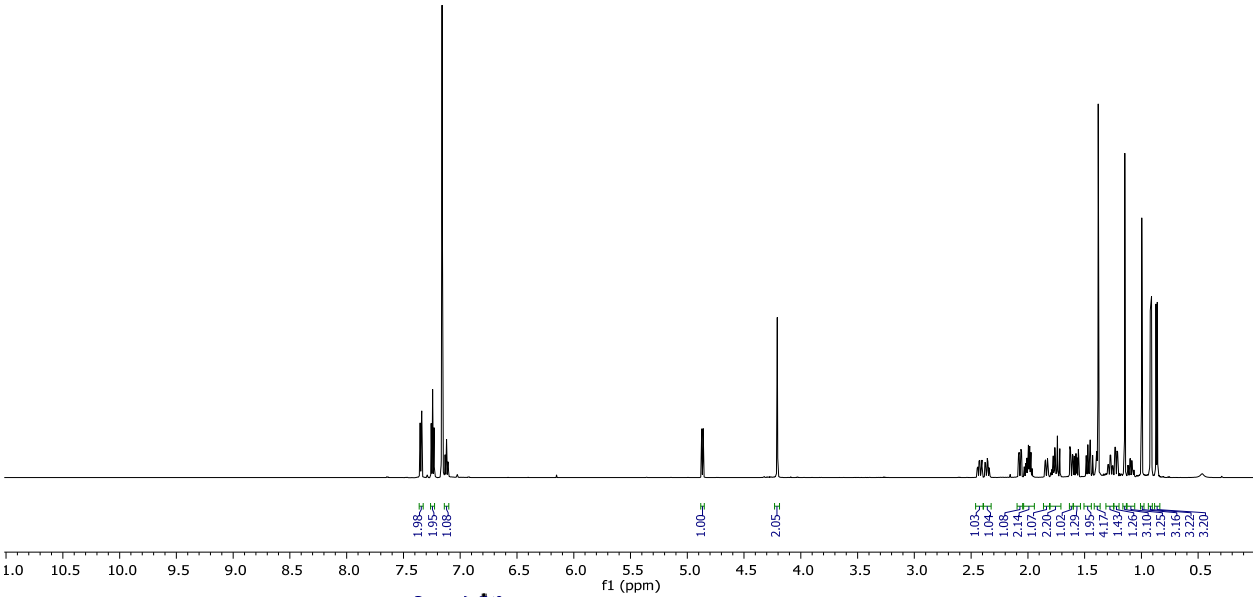

H3C
CH3
H
O
O
H
HO
H3C
Br

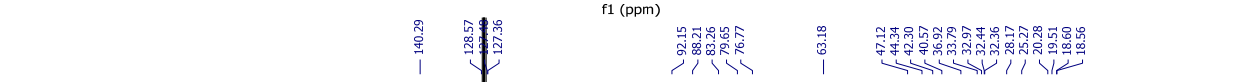
Solvent C6D6
MHz 800
Nucleus 1H
2.09
2.15
0.85
3.24
0.98
0.98
1.00
1.00
2.14
1.06
1.06
5.49
1.04
2.29
2.26
4.46
3.24
3.34
3.41
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


140.42
128.55
127.39
127.26
88.37
86.00
83.99
83.89
76.48
63.26
47.53
44.58
42.75
40.65
38.14
34.01
33.89
32.98
31.87
30.28
28.93
25.54
19.69
18.67
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Solvent C6D6
MHz 600
Nucleus 1H

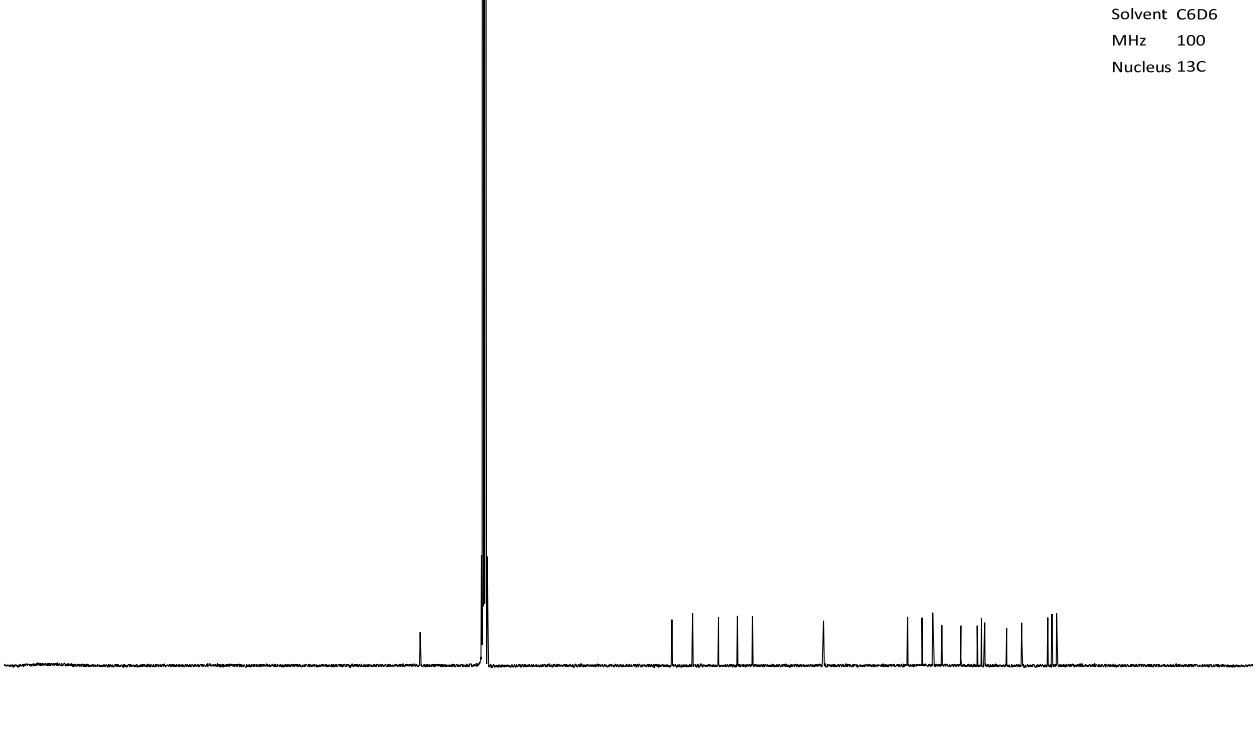


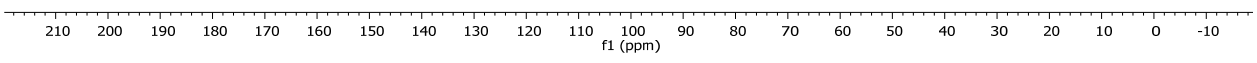


f1 (ppm)

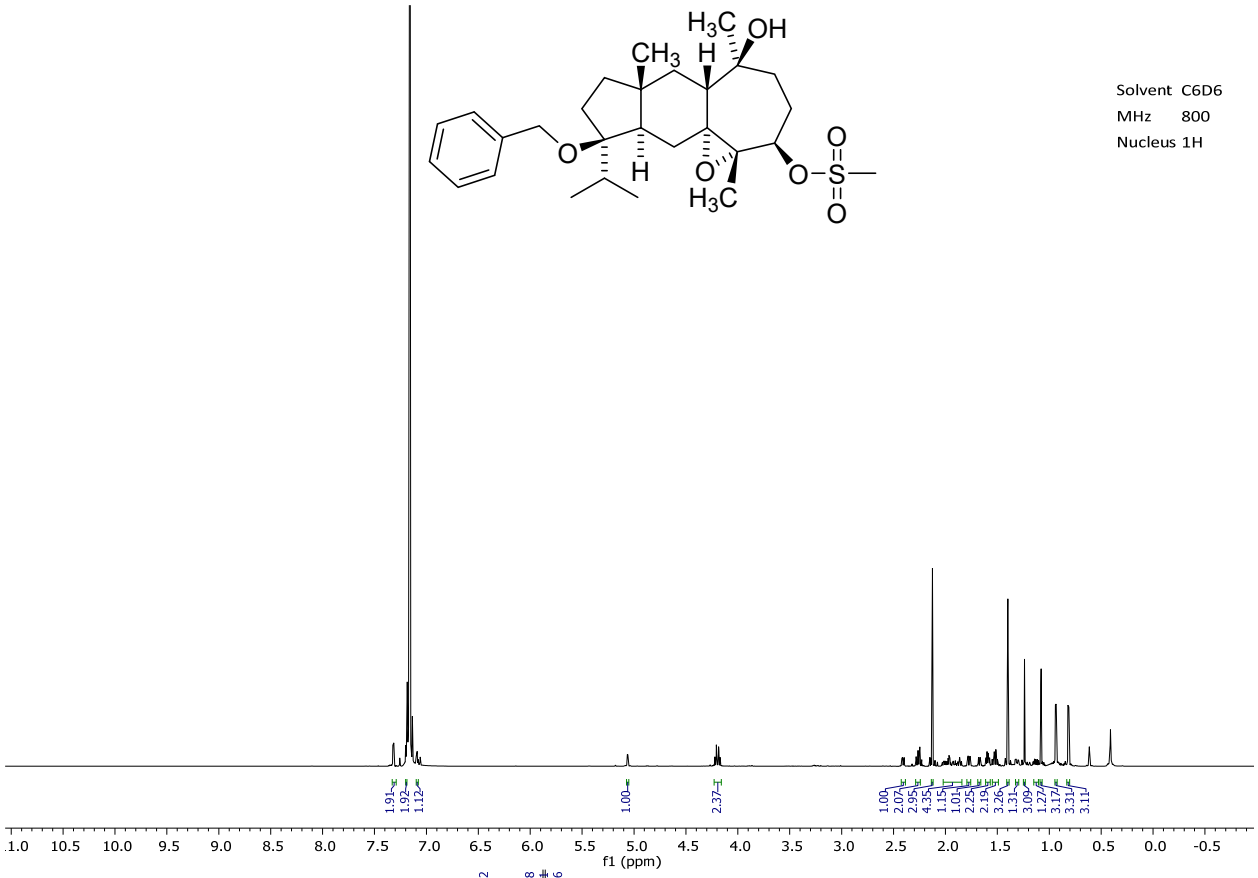
140.29 128.57 128.36 127.36 92.15 88.21 83.26 79.65 76.77 63.18 47.12 44.34 42.30 40.57 36.92 33.79 32.97 32.44 32.36 28.17 25.27 20.28 19.51 18.60 18.56

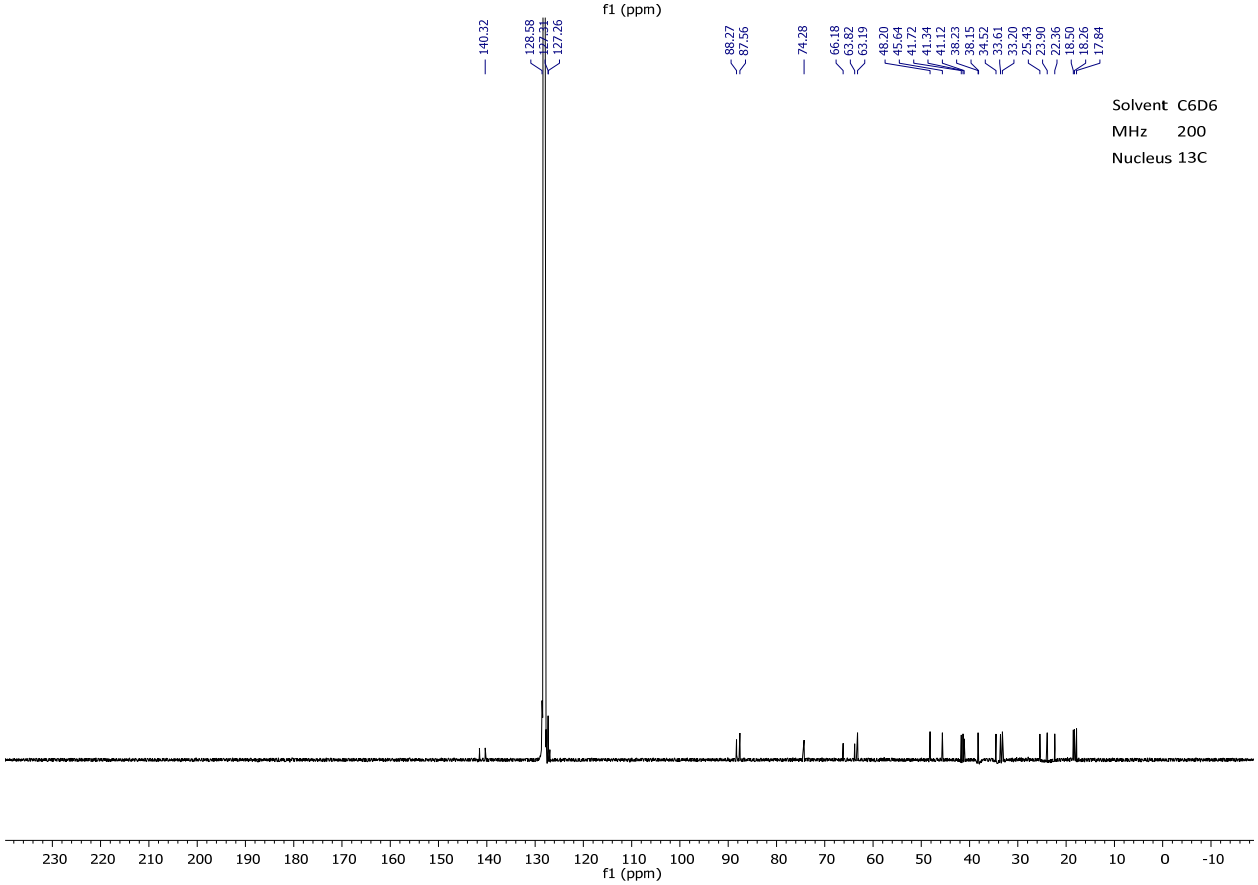
Solvent C6D6
MHz 100
Nucleus 13C

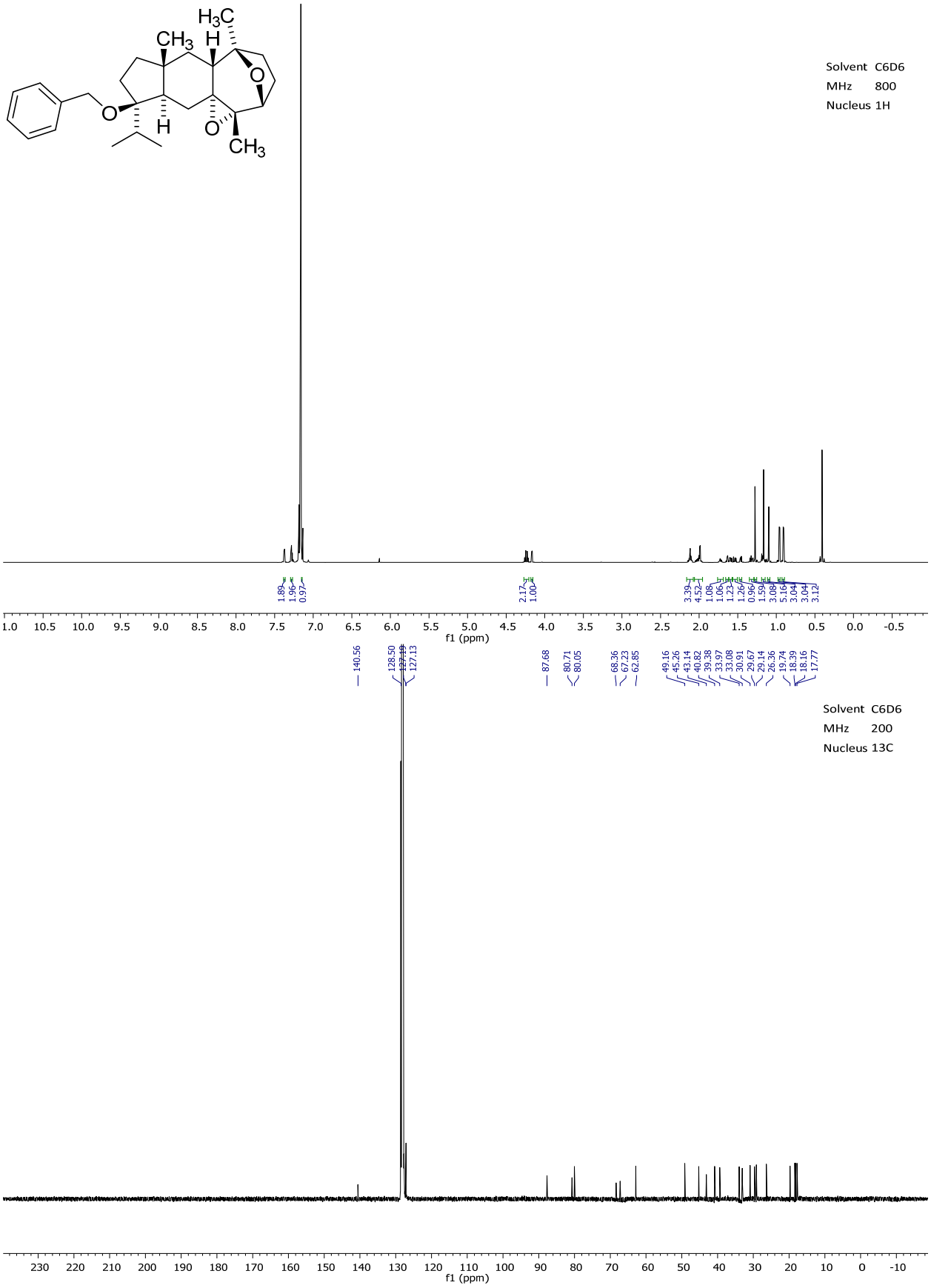


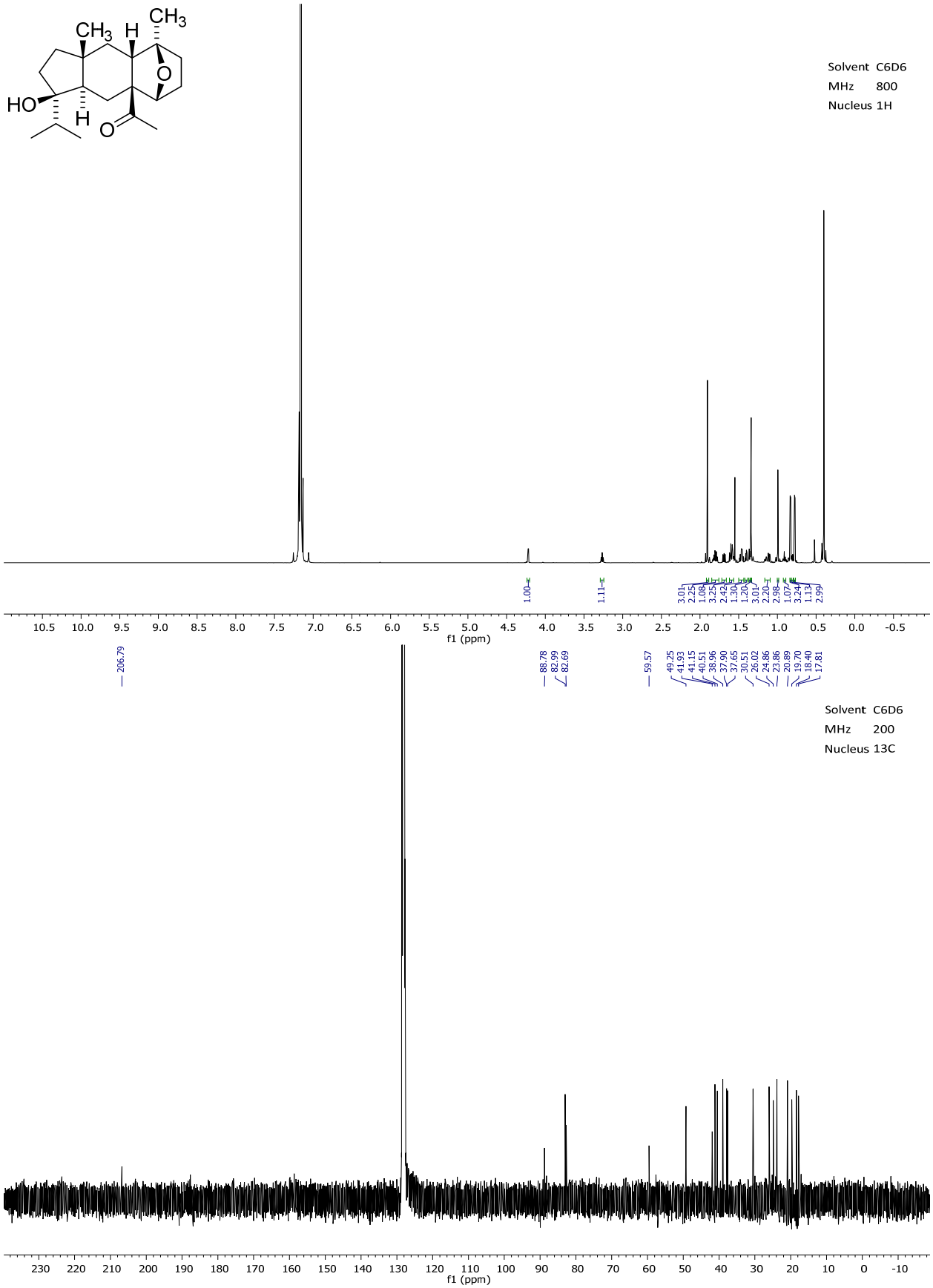


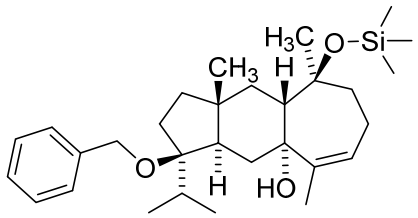
f1 (ppm)


Solvent C6D6
MHz 800
Nucleus 1H
f1 (ppm)

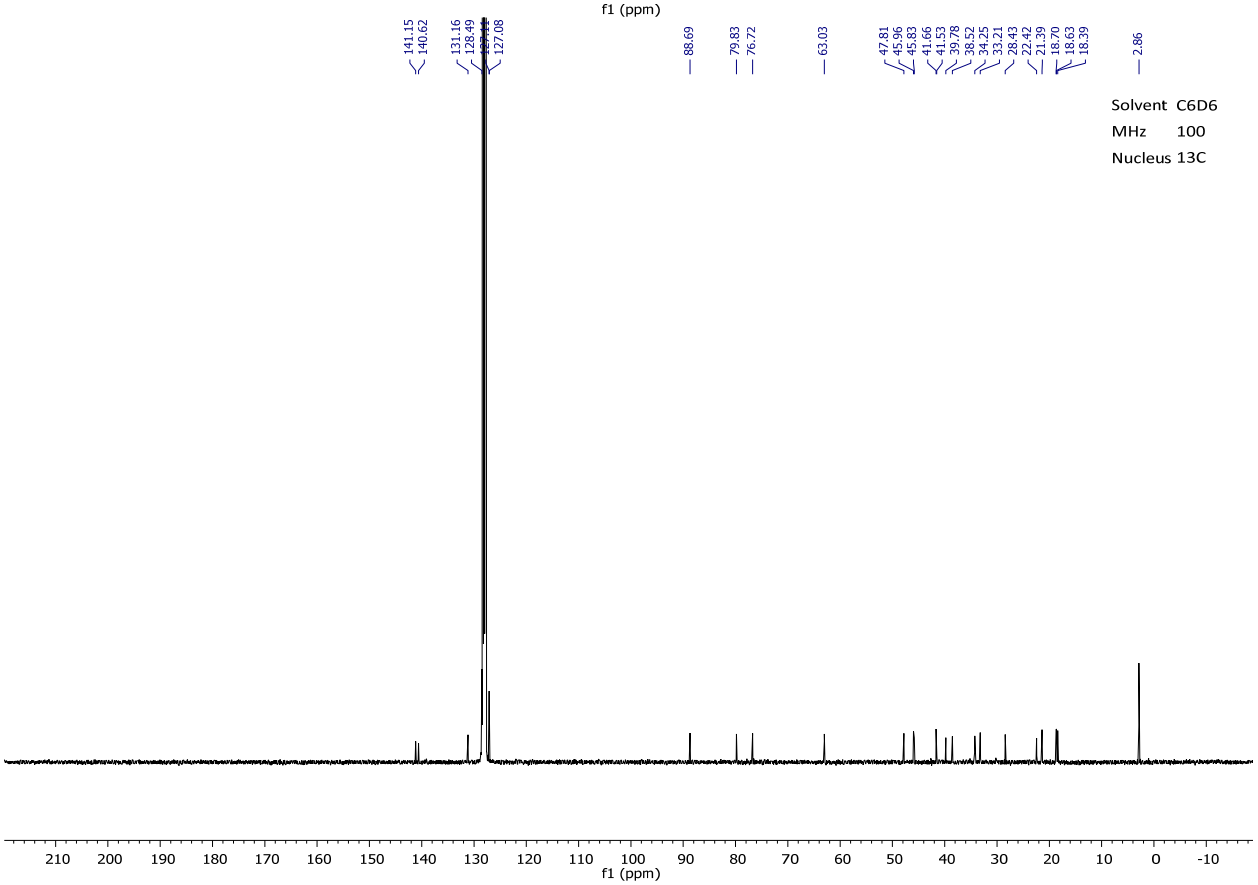

Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)

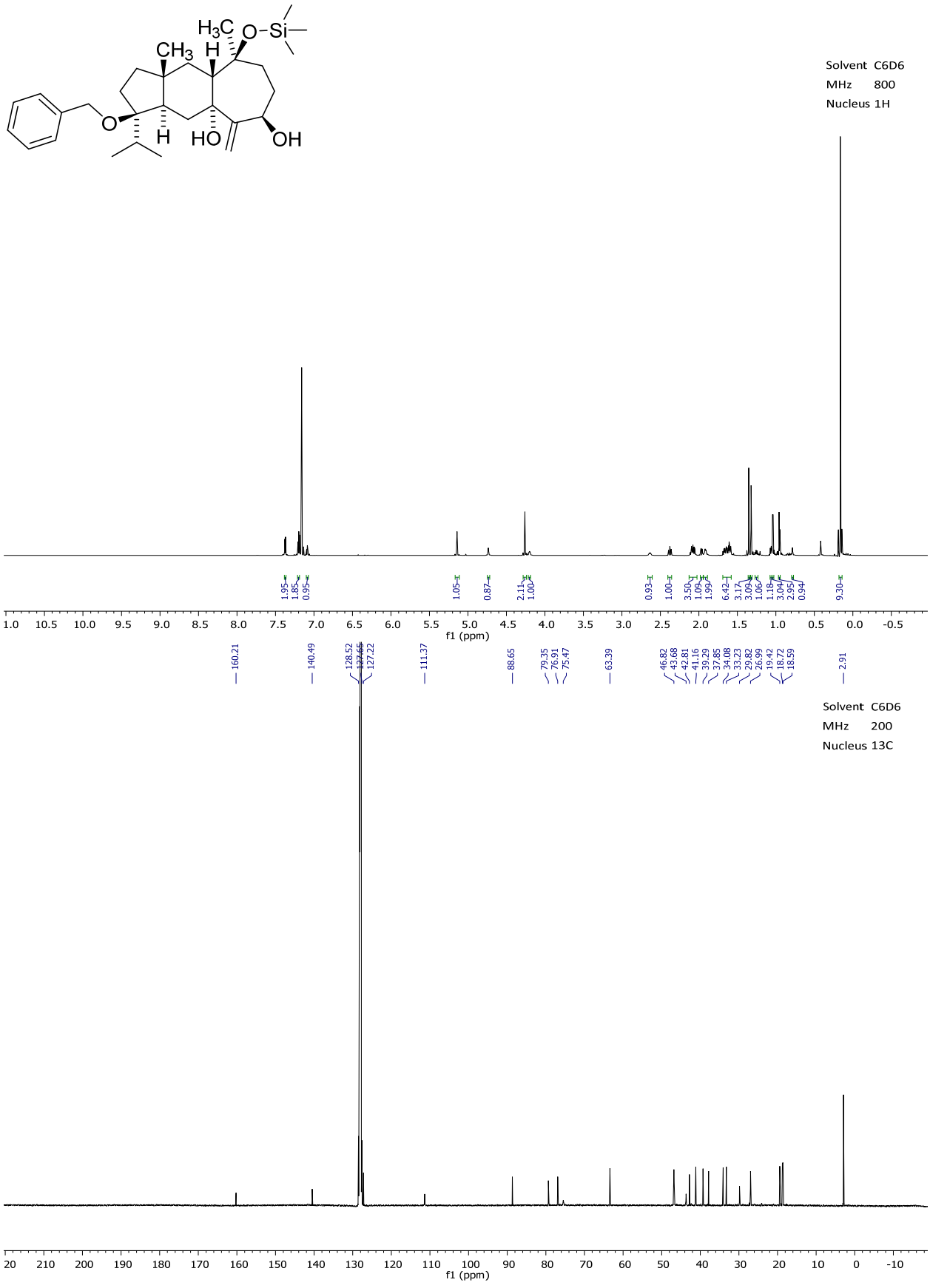

Solvent C6D6
MHz 800
Nucleus 1H
f1 (ppm)
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)

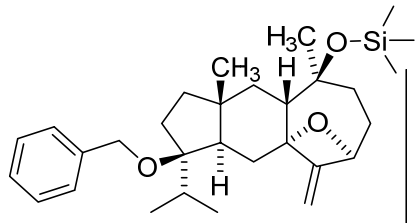

CH3
H
CH3
HO
H
O
O
Solvent C6D6
MHz 800
Nucleus 1H
1.00
1.11
3.01
2.25
1.08
3.25
2.42
1.30
1.20
3.01
2.20
2.98
1.07
3.24
1.13
2.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
206.79
88.78
82.99
82.69
59.57
49.25
41.93
41.15
40.51
38.96
37.90
37.65
30.51
26.02
24.86
23.86
20.89
19.70
18.40
17.81
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
O
Si
CH3
H
O
H
HO

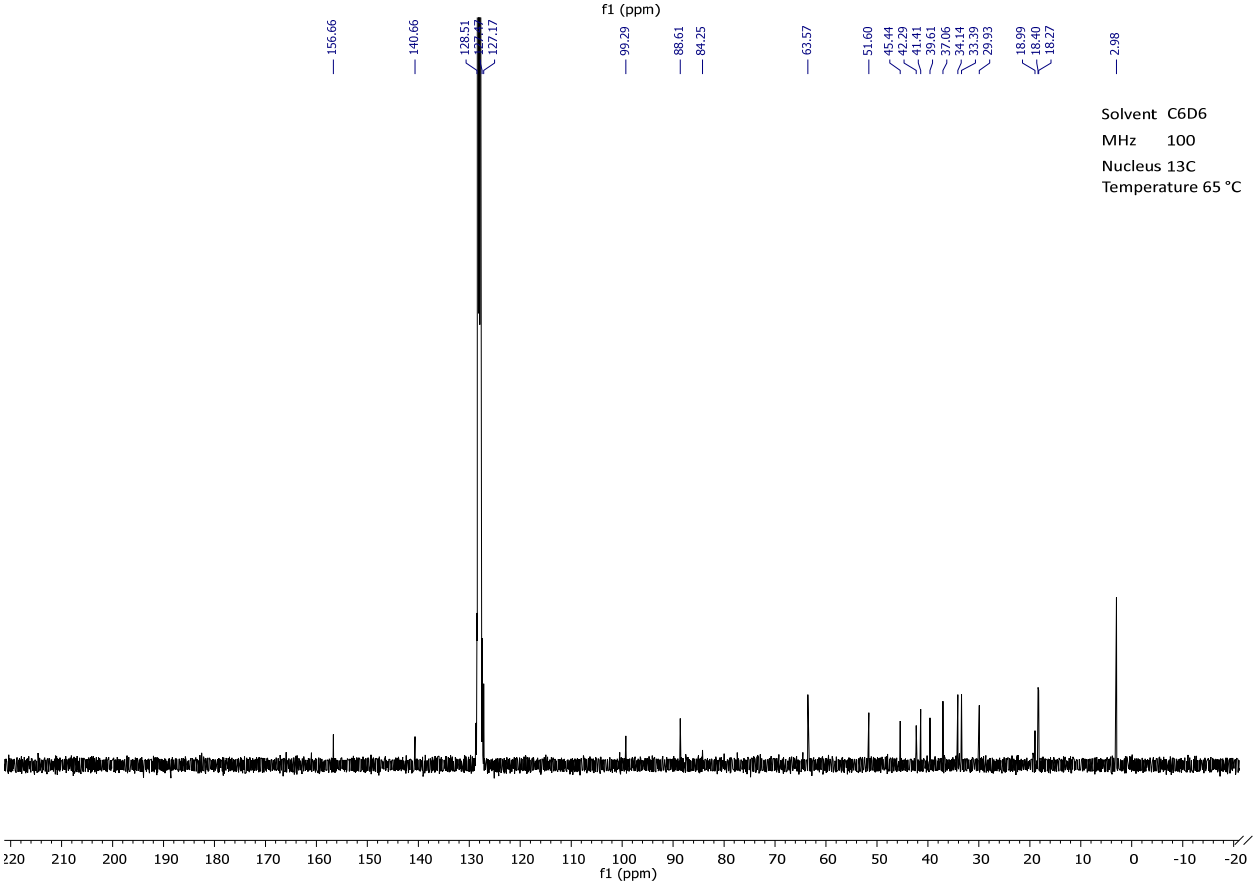
Solvent C6D6
MHz 400
Nucleus 1H
2.23
2.52
1.20
1.00
2.48
1.00
1.06
1.03
1.09
2.36
3.12
8.45
3.20
1.26
3.19
3.24
3.47
1.12
9.00
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

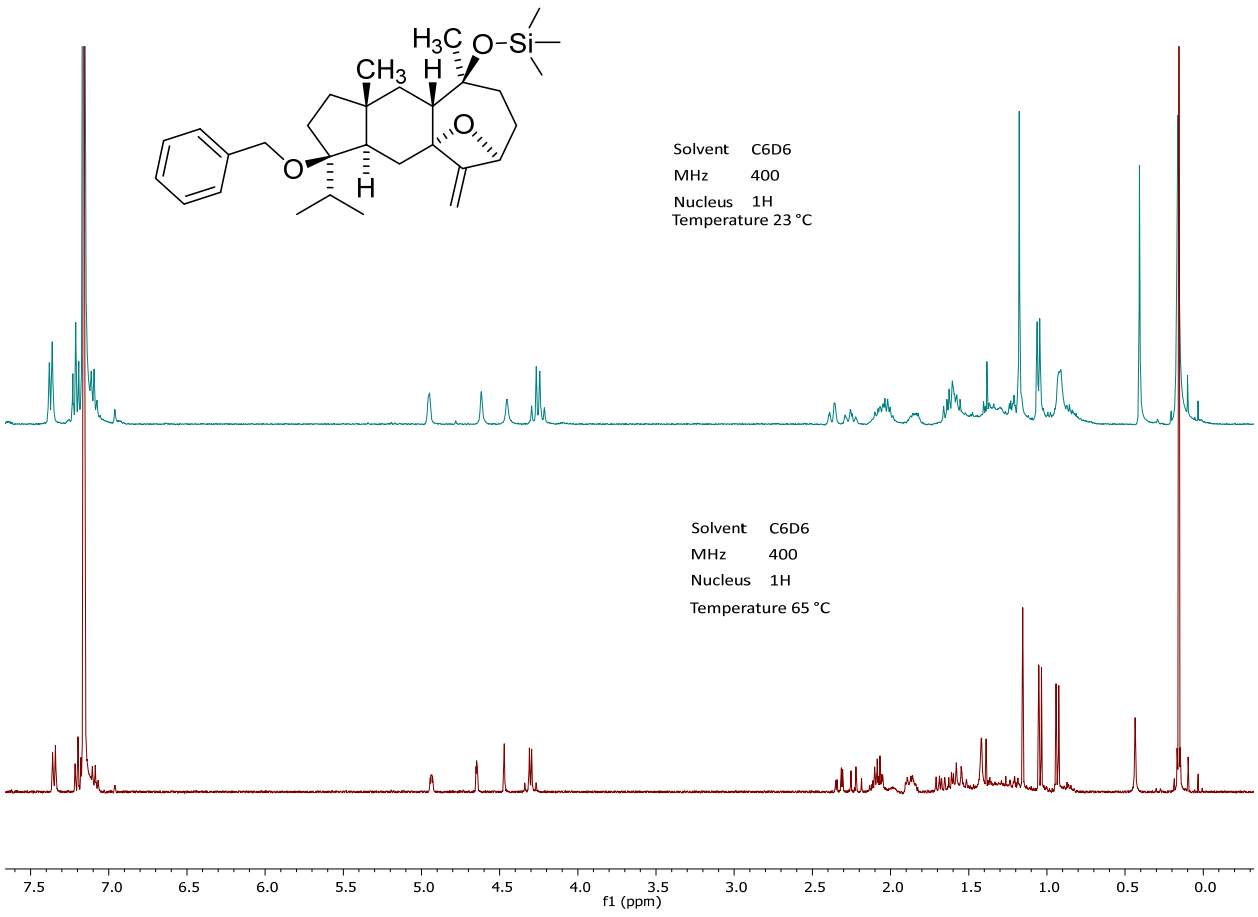

141.15
140.62
131.16
128.49
128.44
127.08
88.69
79.83
76.72
63.03
47.81
45.96
45.83
41.66
41.53
39.78
38.52
34.25
33.21
28.43
22.42
21.39
18.70
18.63
18.39
2.86
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

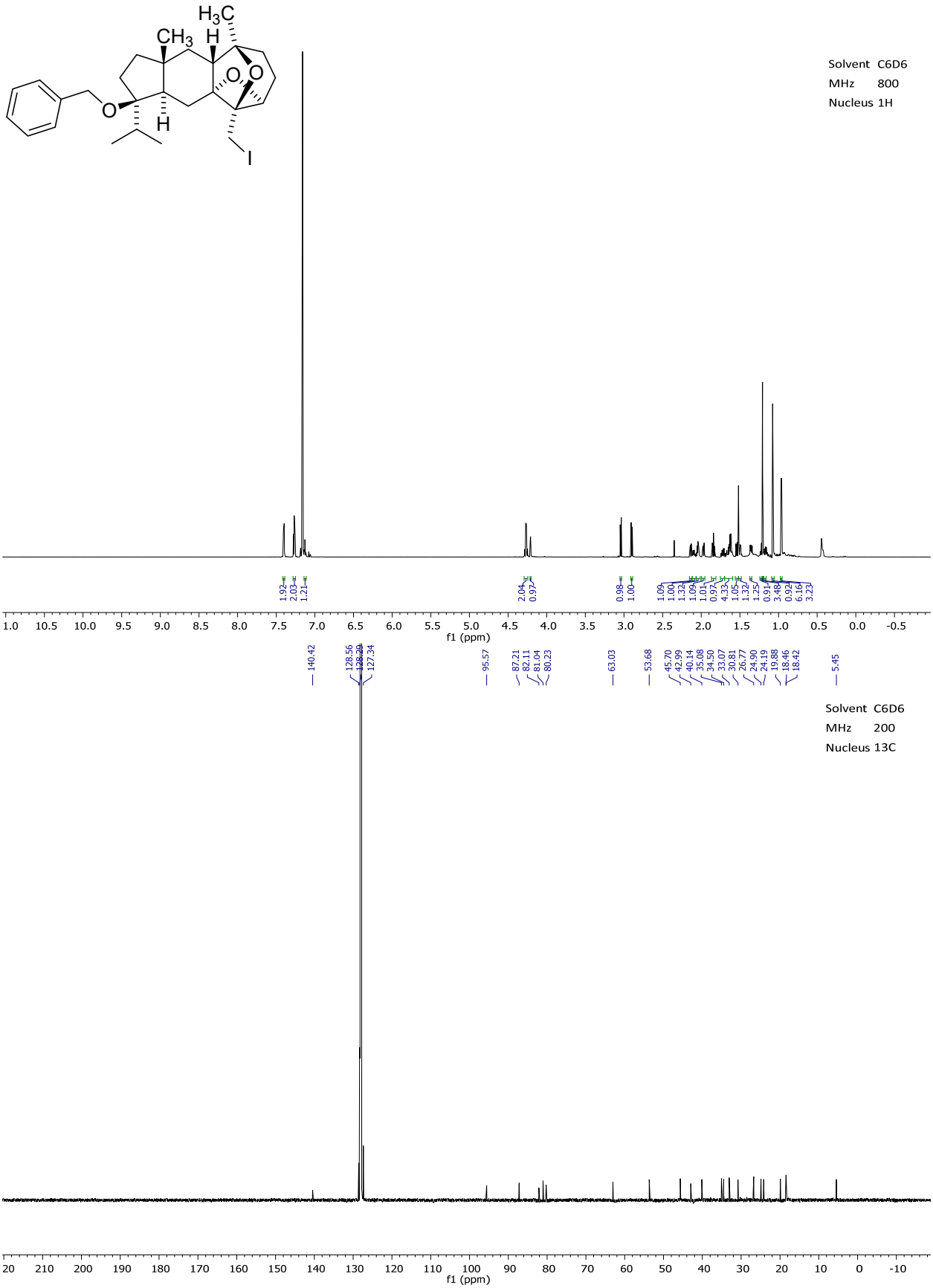

H3C
O-Si
CH3
H
O
H
HO
OH
Solvent C6D6
MHz 800
Nucleus 1H
1.95
1.85
0.95
1.05
0.87
2.11
1.00
0.93
1.00
3.50
1.05
1.99
6.42
3.17
3.09
1.06
1.18
3.04
2.95
0.94
9.30
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
160.21
140.49
128.52
127.65
127.22
111.37
88.65
79.35
76.91
75.47
63.39
46.82
43.68
42.81
41.16
39.29
37.85
34.08
33.23
29.82
26.99
19.42
18.72
18.59
2.91
Solvent C6D6
MHz 200
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

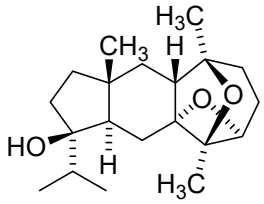

H3C
O-Si
CH3
H
O
O
H

Solvent C6D6
MHz 400
Nucleus 1H
Temperature 65 °C
2.21
2.15
1.16
1.00
0.98
0.98
2.33
1.01
0.99
3.59
0.55
2.46
5.84
3.21
2.18
3.28
3.28
3.22
9.71
f1 (ppm)


156.66
140.66
128.51
127.17
99.29
88.61
84.25
63.57
51.60
45.44
42.29
41.41
39.61
37.06
34.14
33.39
29.93
18.99
18.40
18.27
2.98
Solvent C6D6
MHz 100
Nucleus 13C
Temperature 65 °C
f1 (ppm)

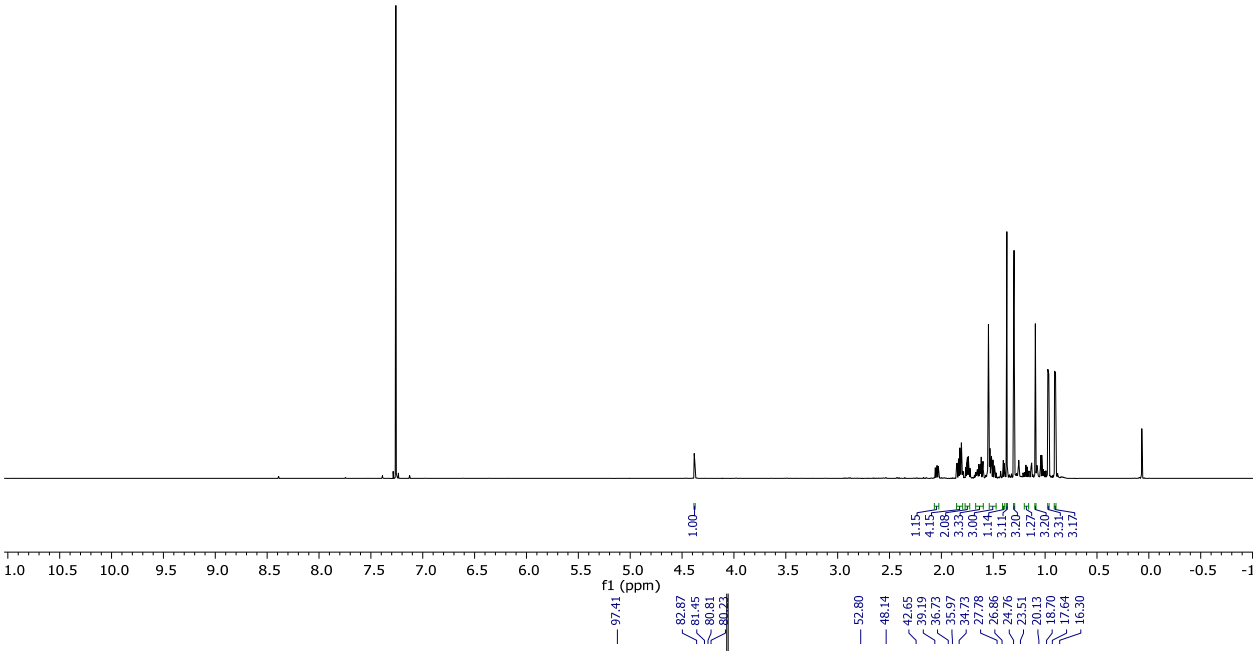

H3C
O-Si
CH3
H
O
O
H
Solvent C6D6
MHz 400
Nucleus 1H
Temperature 23 °C
Solvent C6D6
MHz 400
Nucleus 1H
Temperature 65 °C
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Solvent C6D6
MHz 800
Nucleus 1H
f1 (ppm)
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)



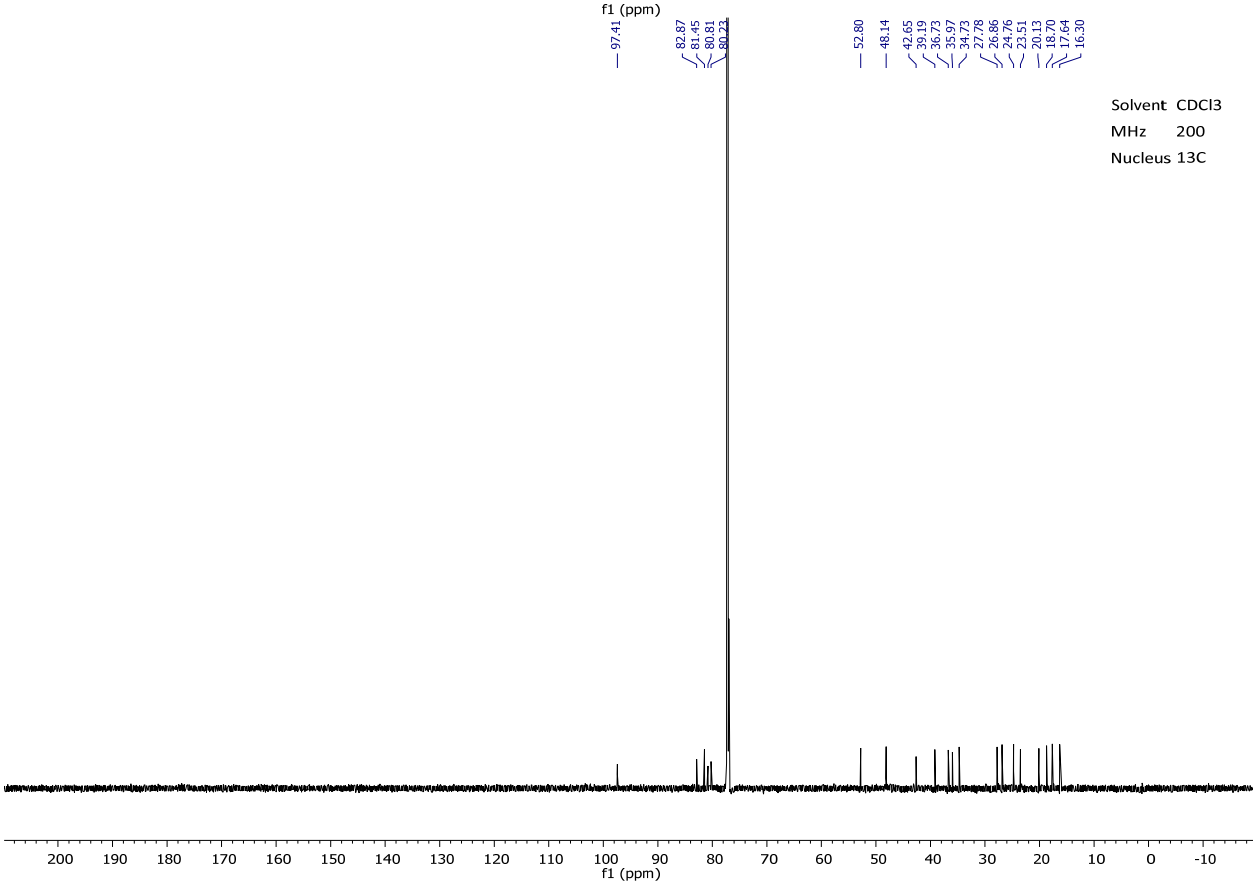
dictyoxetane (**1**)

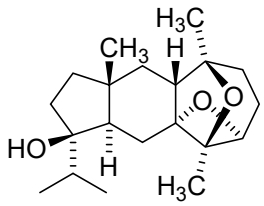
Solvent CDCl3
MHz 800
Nucleus 1H



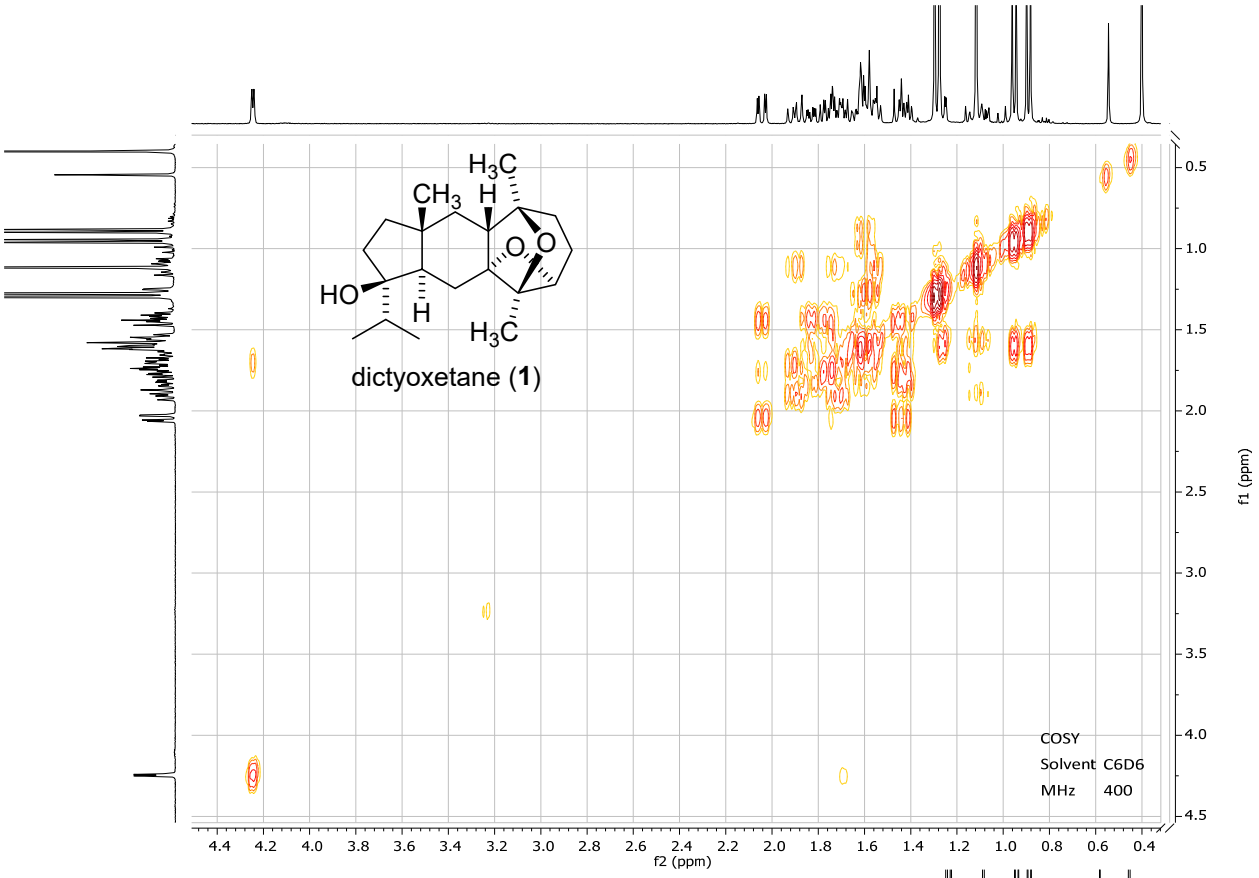
97.41
82.87
81.45
80.81
80.23
52.80
48.14
42.65
39.19
36.73
35.97
34.73
27.78
26.86
24.76
23.51
20.13
18.70
17.64
16.30

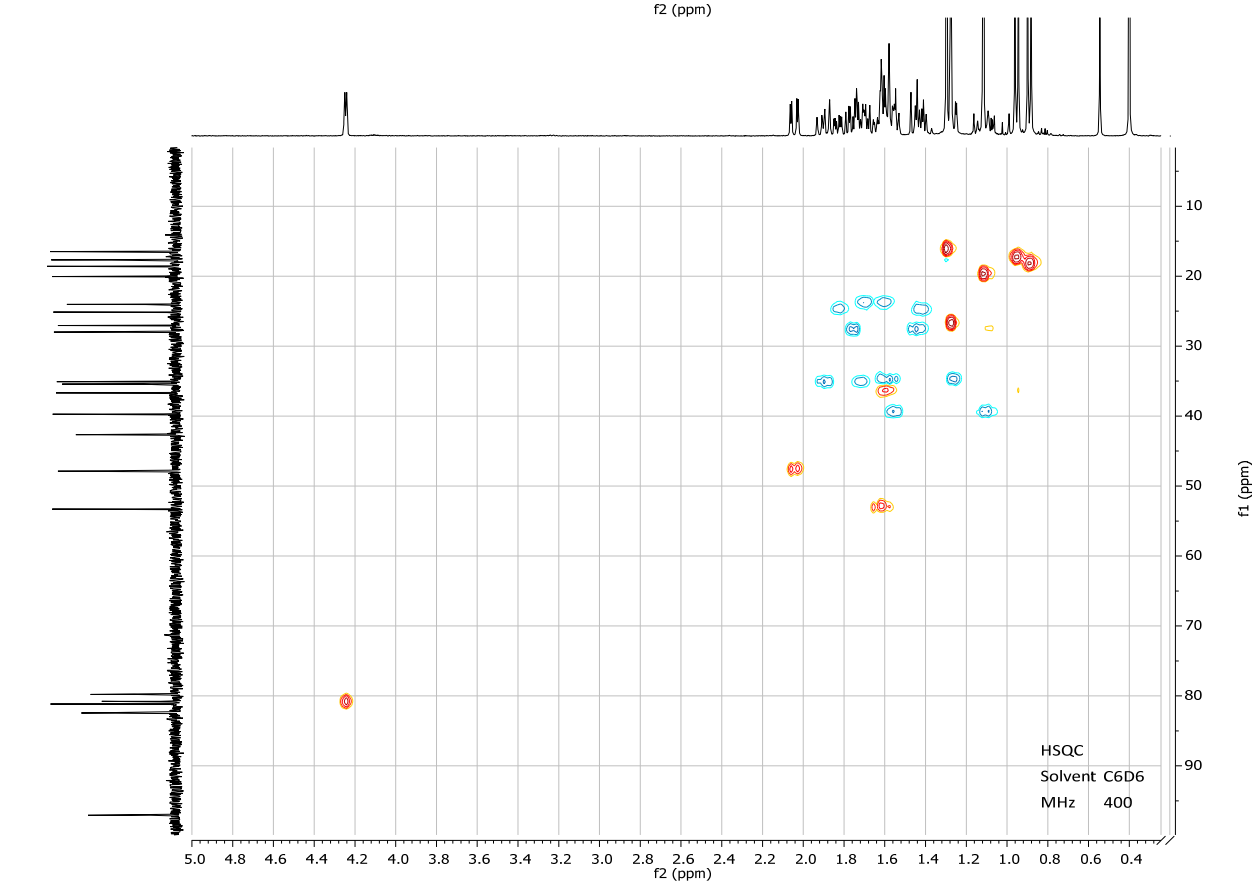
Solvent CDCl3
MHz 200
Nucleus 13C

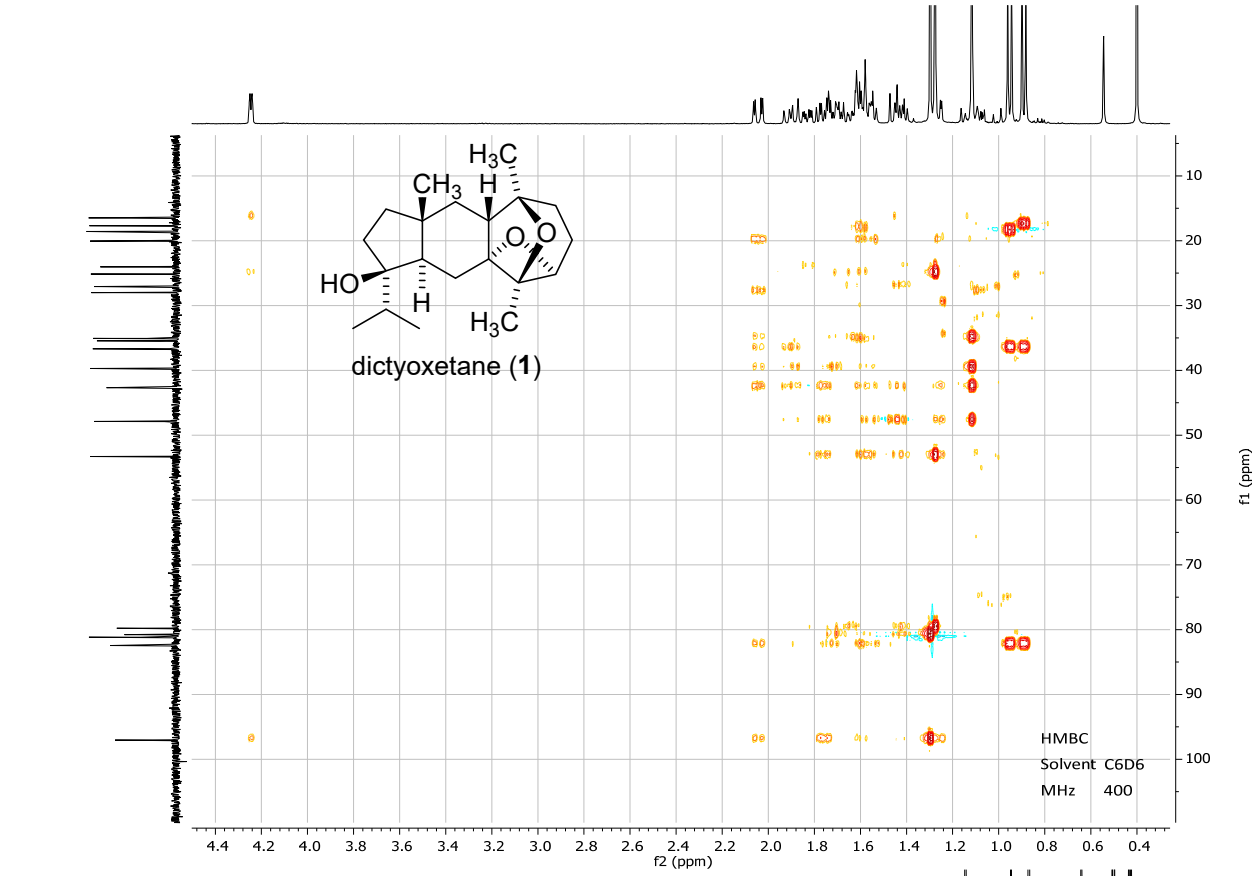


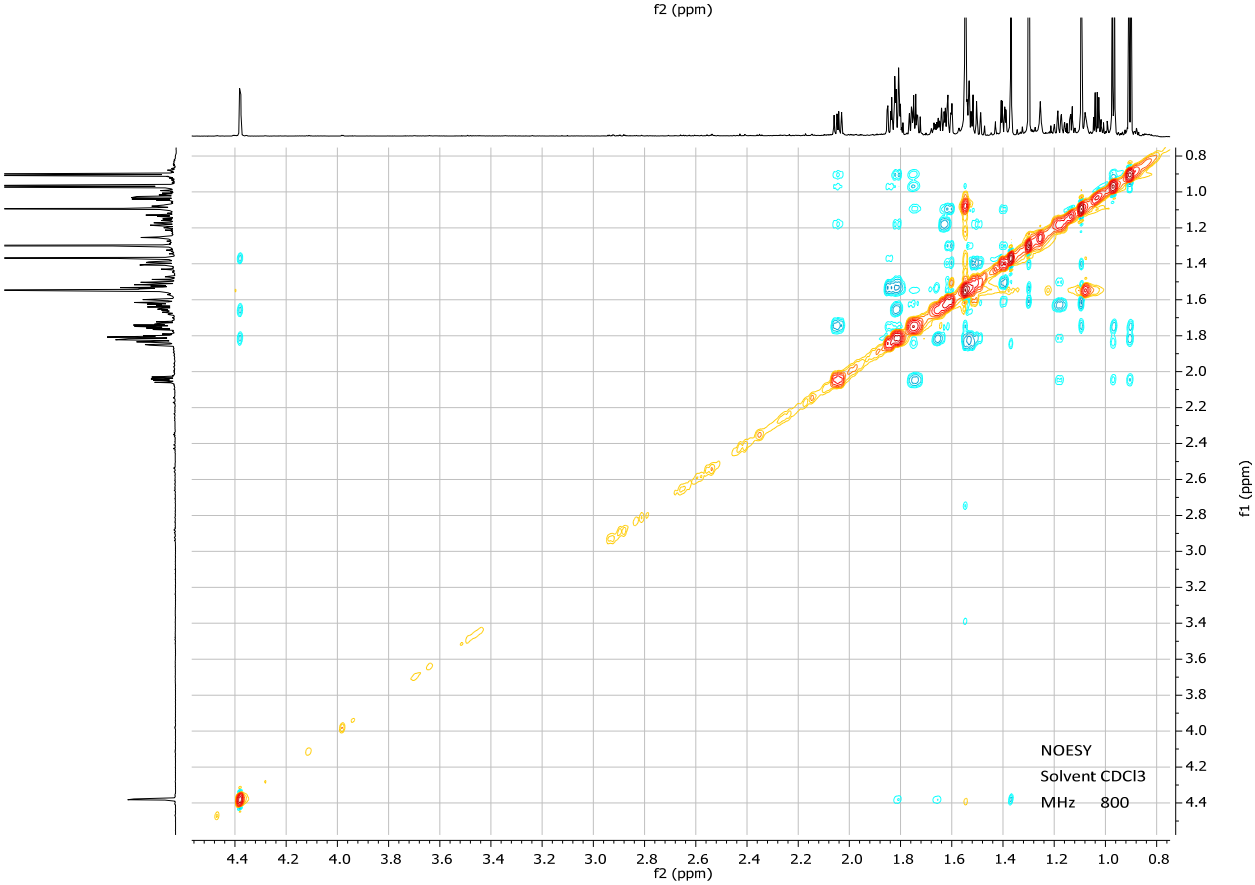


dictyoxetane (**1**)


H3C
CH3
H
O
O
HO
H
H3C
dictyoxetane (1)
COSY
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)


HSQC
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)


H3C
CH3
H
O
O
HO
H
H3C
dictyoxetane (1)
HMBC
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)


NOESY
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)

6.5 Supporting Information for Chapter 3.2.2

A Divergent Approach to the Marine Diterpenoids (+)-Dictyoxetane and (+)-Dolabellane V

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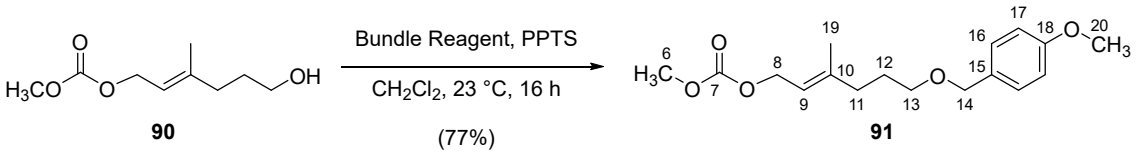
6.5.1 Experimental Procedures: Paternò–Büchi Approach

Enolate–Epoxide Opening Route

Synthesis of benzyl ether 91



90 **91**

Bundle reagent preparation:[55] A solution of 4-methoxybenzyl alcohol (32.5 g, 235 mmol, 1.50 equiv) in diethyl ether (150 mL) was treated with sodium hydride (60 wt.% in mineral oil, 0.94 g, 23.5 mmol, 0.15 equiv) at 0 °C. After gas evolution had ceased (ca. 3 min), the mixture was warmed to 23 °C for 15 min, and then was cooled to 0 °C. Trichloroacetonitrile (23.5 mL, 235 mmol, 1.50 equiv) was added dropwise over a period of 10 min, and the mixture was allowed to warm to 23 °C. After 1 h, the mixture was diluted with saturated aqueous sodium bicarbonate solution (120 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 70 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated (25 °C, waterbath) to afford the crude Bundle reagent as a yellow oil.

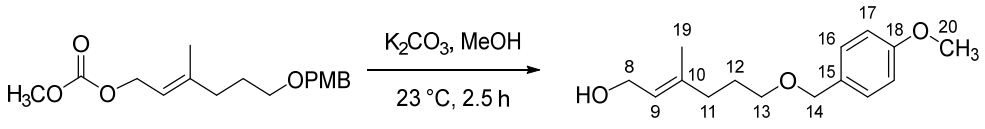
A solution of the crude Bundle reagent (assuming 235 mmol) in dichloromethane (200 mL) was added to known alcohol **90**[56] (29.5 g, 157 mmol, 1 equiv) at 0 °C. Pyridinium *p*-toluenesulfonate (3.94 g, 15.7 mmol, 0.1 equiv) was added, and after 10 min, the mixture was allowed to warm to 23 °C. After 16 h, the suspension was filtered through a pad of Celite and the filtrate was concentrated to afford a thick slurry. Saturated aqueous sodium bicarbonate solution (150 mL) and diethyl ether/hexanes (1:1, 100 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether/hexanes (1:1, 2 x 100 mL), and the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes) on silica gel to provide benzyl ether **91** as a colourless oil (37.2 g, 77%).

TLC (10% ethyl acetate in hexanes): R_f = 0.19 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, $^3J_{16/17}$ = 8.2 Hz, 2H, 16-H), 6.89 (d, $^3J_{17/16}$ = 8.2 Hz, 2H, 17-H), 5.39 (t, $^3J_{9/8}$ = 7.1 Hz, 1H, 9-H), 4.66 (d, $^3J_{8/9}$ = 7.1 Hz, 2H, 8-H), 4.44 (s, 2H, 14-H), 3.81 (s, 3H, 20-H), 3.79 (s, 3H, 6-H), 3.44 (t, $^3J_{13/12}$ = 6.5 Hz, 2H, 13-H), 2.13 (t, $^3J_{11/12}$ = 7.8 Hz, 2H, 11-H), 1.79–1.69 (m, 5H, 12-H, 19-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.15 (C-18), 155.90 (C-7), 142.85 (C-10), 130.63 (C-15), 129.31 (C-16), 117.98 (C-9), 113.78 (C-17), 72.60 (C-14), 69.44 (C-13), 64.69 (C-8), 55.29 (C-20), 54.71 (C-6), 36.02 (C-11), 27.65 (C-12), 16.48 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953 (m), 2855 (m), 1746 (s), 1613 (m), 1513 (s), 1443 (m), 1248 (s), 1098 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{17}H_{24}O_5)^+$: 308.1618, found: 308.1618.

[55] a) T. Iversen, D. R. Bundle, *J. Chem. Soc., Chem. Commun.* **1981**, 1240. b) R. Chegondi, M. M. L. Tan, P. R. Hanson, *J. Org. Chem.* **2011**, *76*, 3909.

[56] A. Guzman-Martinez, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10634.

Synthesis of allylic alcohol 92

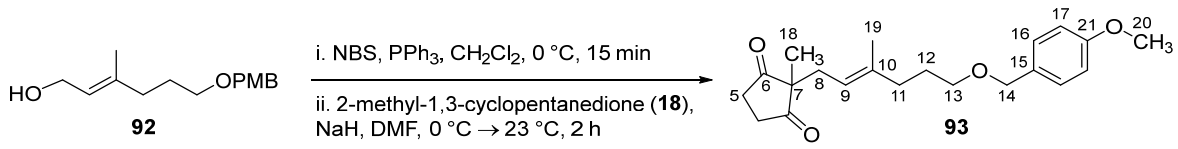


91 (≥99%) **92**

A solution of benzyl ether **91** (37.0 g, 120 mmol, 1 equiv) in methanol (300 mL) was treated with potassium carbonate (2.82 g, 20.4 mmol, 0.17 equiv) at 0 °C. After 5 min, the cloudy mixture was allowed to warm to 23 °C. After 2.5 h, the mixture was concentrated to a volume of ca. 70 mL, and was diluted with saturated aqueous ammonium chloride solution (150 mL) and ethyl acetate (100 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford spectroscopically pure allylic alcohol **92** (30.4 g, ≥99%) as a yellowish oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.23 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, $^3J_{16/17}$ = 8.2 Hz, 2H, 16-H), 6.88 (d, $^3J_{17/16}$ = 8.2 Hz, 2H, 17-H), 5.40 (t, $^3J_{9/8}$ = 7.1 Hz, 1H, 9-H), 4.43 (s, 2H, 14-H), 4.14 (app t, $^3J_{8/8OH}$ = $^3J_{8/9}$ = 6.2 Hz, 2H, 8-H), 3.81 (s, 3H, 20-H), 3.43 (t, $^3J_{13/12}$ = 6.5 Hz, 2H, 13-H), 2.09 (t, $^3J_{11/12}$ = 7.8 Hz, 2H, 11-H), 1.78–1.68 (m, 2H, 12-H), 1.67 (s, 3H, 19-H), 1.16 (t, $^3J_{8OH/8}$ = 5.4 Hz, 1H, 8-OH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.24 (C-18), 139.47 (C-10), 130.76 (C-15), 129.42 (C-16), 123.66 (C-9), 113.87 (C-17), 72.69 (C-14), 69.64 (C-13), 59.51 (C-8), 55.42 (C-20), 36.13 (C-11), 27.86 (C-12), 16.34 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3391 (br), 2940 (m), 2857 (m), 1612 (m), 1513 (s), 1301 (m), 1247 (s), 1097 (s), 1034 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{22}O_3)^+$: 250.1564, found: 250.1565.

Synthesis of diketone 93

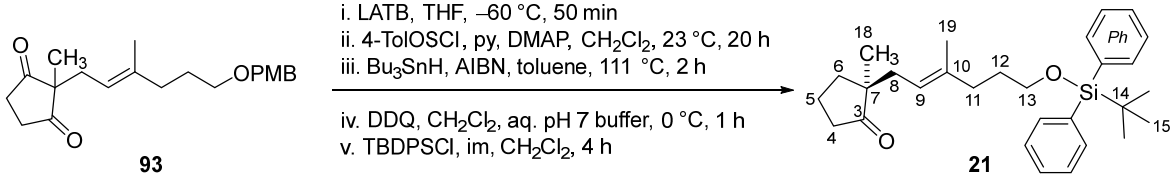


A solution of allylic alcohol **92** (6.00 g, 24.0 mmol, 1 equiv) in dichloromethane (150 mL) was treated with triphenylphosphine (7.54 g, 28.8 mmol, 1.20 equiv), followed by *N*-bromosuccinimide (5.12 g, 28.8 mmol, 1.20 equiv) at 0 °C. After 15 min, the orange mixture was diluted with water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to a volume of ca. 20 mL. The oily residue was filtered through a short pad of Celite with some subernatant hexanes (to precipitate triphenylphosphine oxide). The filtercake was washed with diethyl ether and the filtrate was concentrated to provide the crude allylic bromide **19** which was immediately used in the next step.

A suspension of sodium hydride (60 wt.% in mineral oil, 1.15 g, 28.8 mmol, 1.20 equiv) in dimethylformamide (50 mL) was treated portionwise with 2-methyl-1,3-cyclopentanedione (**18**) (3.22 g, 28.8 mmol, 1.20 equiv) at 0 °C. The mixture was warmed to 23 °C for 15 min before being cooled to 0 °C, whereupon a solution of the crude allylic bromide **19** (assuming 24.0 mmol) in dimethylformamide (10 mL) was added. The transfer was quantitated with dimethylformamide (2 x 4 mL). The resulting mixture was allowed to warm to 23 °C over a period of 2 h, and then was diluted with saturated aqueous ammonium chloride solution (250 mL) and ethyl acetate (70 mL). The layers were separated and the aqueous layer was extracted with ethylacetate (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) on silica gel to provide diketone **93** as a yellowish oil (6.18 g, 60%). *Note: As determined by analysis of the crude ^{1}H NMR, an approximate 3:1 mixture of C- and O-alkylated products was formed in this reaction.*

TLC (20% ethyl acetate in hexanes): R_f = 0.14 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, $^3J_{16/17}$ = 8.4 Hz, 2H, 16-H), 6.90 (d, $^3J_{17/16}$ = 8.4 Hz, 2H, 17-H), 4.96 (t, $^3J_{9/8}$ = 7.9 Hz, 1H, 9-H), 4.43 (s, 2H, 14-H), 3.83 (s, 3H, 20-H), 3.40 (t, $^3J_{13/12}$ = 6.5 Hz, 2H, 13-H), 2.79–2.58 (m, 4H, 5-H), 2.35 (d, $^3J_{8/9}$ = 7.9 Hz, 2H, 8-H), 2.03 (t, $^3J_{11/12}$ = 7.6 Hz, 2H, 11-H), 1.71–1.61 (m, 2H, 12-H), 1.59 (s, 3H, 19-H), 1.12 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 217.07 (C-6), 159.22 (C-21), 140.08 (C-10), 130.70 (C-15), 129.40 (C-16), 117.31 (C-9), 113.87 (C-17), 72.70 (C-14), 69.64 (C-13), 57.05 (C-7), 55.40 (C-20), 36.36 (C-11), 35.70 (C-5), 35.30 (C-8), 28.18 (C-12), 18.64 (C-18), 16.19 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944 (m), 2865 (m), 1722 (s), 1612 (m), 1513 (s), 1452 (m), 1247 (m), 1094 (m), 1034 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{21}H_{29}O_4$)$^+$: 345.20658, found: 345.20638.

Synthesis of ketone 21



Note: A protecting group swap had to be carried out at this stage since the PMB group was found to be instable after epoxidation of the C9/C10 double bond.

A solution of diketone **93** (4.74 g, 13.8 mmol, 1 equiv) in tetrahydrofuran (50 mL) was treated dropwise with a solution of lithium *tri-tert*-butoxyaluminium hydride (3.95 g, 15.5 mmol, 1.13 equiv) in tetrahydrofuran (40 mL) over a period of 10 min at –60 °C. After 50 min, the mixture was carefully diluted with methanol (2 mL), followed by aqueous 1 M hydrogen chloride solution (200 mL) and ethyl acetate (150 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered (40% ethyl acetate in hexanes) through a short pad of silica gel and the filtrate was concentrated to provide the hydroxy ketone (4.27 g), which was used in the next step without further purification.

A solution of this hydroxy ketone (4.27 g, 12.3 mmol, 1 equiv) in dichloromethane (30 mL) was treated sequentially with pyridine (4.98 mL, 61.6 mmol, 5.00 equiv), 4-dimethylaminopyridine (151 mg, 1.23 mmol, 0.1 equiv) and 4-tolyl chlorothionoformate (4.51 mL, 29.6 mmol, 2.40 equiv) at 0 °C. After 5 min, the mixture was allowed to warm to 23 °C. After 20 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (60 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered (20% ethyl acetate in hexanes) through a short pad of silica gel and the filtrate was concentrated to provide the crude thioate, which was used in the next step without further purification.

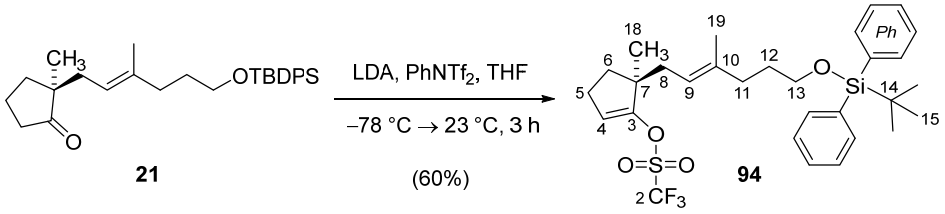
A solution of this crude thioate (assuming 12.3 mmol) in toluene (80 mL) was treated with azobisisobutyronitrile (202 mg, 1.23 mmol, 0.10 equiv) and tributyltin hydride (7.29 mL, 27.1 mmol, 2.20 equiv). The resulting mixture was heated to 111 °C for 2 h, then was cooled to 23 °C and was concentrated. The residue was filtered (15% $\rightarrow$ 20% ethyl acetate in hexanes) through a short pad of silica gel and the filtrate was concentrated to provide a mixture of ketone **20** together with co-polar *p*-cresol (5.11 g, ca. 1:1.8 ratio). This mixture was used in the next step without further purification.

A mixture of crude ketone **20** (assuming 12.3 mmol) in dichloromethane (30 mL) and aqueous pH 7 buffer solution (3 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.07 g, 13.5 mmol, 1.10 equiv) at 0 °C. After 1 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (70 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered (30% ethyl acetate in hexanes) through a short pad of silica gel and the filtrate was concentrated to provide the primary alcohol (1.77 g), which was used in the next step without further purification.

A solution of the crude primary alcohol (1.77 g, 8.42 mmol, 1 equiv) in dichloromethane (20 mL) was treated with imidazole (1.72 g, 25.2 mmol, 3.00 equiv), followed by *tert*-butyldiphenylchlorosilane (3.27 mL, 12.6 mmol, 1.50 equiv) at 0 °C. After 5 min, the mixture was allowed to warm to 23 °C. After 4 h, the mixture was diluted with water (40 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) on silica gel to provide ketone **21** as a colourless oil (3.20 g, 52% over five steps).

TLC (10% ethyl acetate in hexanes): R_f = 0.44 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H, *Ph*), 7.45–7.34 (m, 6H, *Ph*), 5.09–5.02 (m, 1H, 9-H), 3.63 (t, $^3J_{13/12}$ = 6.6 Hz, 2H, 13-H), 2.32–2.10 (m, 2H, 4-H), 2.10–2.03 (m, 4H, 8-H, 11-H), 1.91–1.77 (m, 3H, 5-H, 6-H_A), 1.69–1.58 (m, 3H, 6-H_B, 12-H), 1.56 (s, 3H, 13-H), 1.05 (s, 9H, 15-H), 0.96 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 223.96 (C-3), 138.07 (C-10), 135.69 (*Ph*), 134.18 (*Ph*), 129.66 (*Ph*), 127.72 (*Ph*), 119.62 (C-9), 63.70 (C-13), 49.11 (C-7), 37.97 (C-4), 36.28 (C-11), 35.18 (C-6), 34.78 (C-8), 31.04 (C-12), 27.00 (C-15), 21.97 (C-18), 19.36 (C-14), 18.95 (C-5), 16.28 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (m), 2931 (m), 2857 (m), 1735 (s), 1471 (m), 1427 (s), 1106 (s), 1091 (s), 1064 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–CH_3], $C_{28}H_{37}O_2Si)^+$: 433.2563, found: 433.2566.

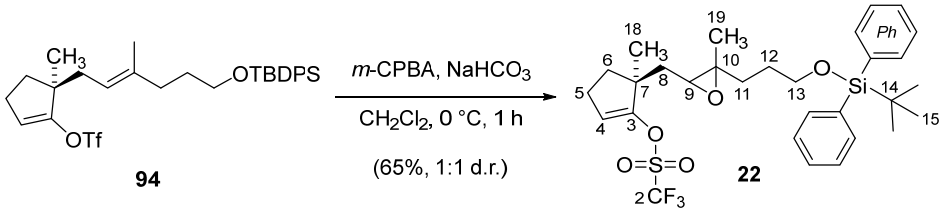
Synthesis of triflate 94



A solution of ketone **21** (2.13 g, 4.75 mmol, 1 equiv) in tetrahydrofuran (12 mL) was treated with a freshly prepared solution of lithium diisopropylamide (0.94 M in THF, 7.07 mL, 6.65 mmol, 1.40 equiv) at −78 °C. After 45 min, a solution of *N*-phenylbis(trifluoromethanesulfonimide) (2.37 g, 6.65 mmol, 1.40 equiv) in tetrahydrofuran (5 mL) was added dropwise. After 15 min, the mixture was allowed to warm to 23 °C over a period of 2.5 h. The orange mixture was diluted with saturated aqueous ammonium chloride solution (150 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (3% ethyl acetate in hexanes) on silica gel to provide triflate **94** as a colourless oil (1.66 g, 60%).

TLC (3% ethyl acetate in hexanes): R_f = 0.37 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 4H, *Ph*), 7.38–7.27 (m, 6H, *Ph*), 5.46 (t, $^3J_{4/5}$ = 2.6 Hz, 1H, 4-H), 5.05–4.98 (m, 1H, 9-H), 3.56 (t, $^3J_{13/12}$ = 6.5 Hz, 2H, 13-H), 2.26–2.08 (m, 2H, 5-H), 2.07–1.95 (m, 4H, 8-H, 11-H), 1.85–1.75 (m, 1H, 6-H_A), 1.63–1.52 (m, 3H, 6-H_B, 12-H), 1.50 (s, 3H, 19-H), 1.03 (s, 3H, 18-H), 0.98 (s, 9H, 15-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.45 (C-3), 137.96 (C-10), 135.70 (*Ph*), 134.20 (*Ph*), 129.66 (*Ph*), 127.72 (*Ph*), 119.56 (C-9), 118.6 (q, $^1J_{2/F}$ = 320 Hz, C-2), 113.37 (C-4), 63.70 (C-13), 47.17 (C-7), 36.47 (C-8, C-11), 36.29 (C-8, C-11), 33.83 (C-6), 31.04 (C-12), 26.99 (C-15), 25.75 (C-5), 24.29 (C-18), 19.36 (C-14), 16.28 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2933 (m), 2858 (m), 1655 (w), 1420 (s), 1248 (m), 1208 (s), 1141 (s), 1109 (s), 1049 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–*t*Bu], $C_{26}H_{30}O_4F_3SSi)^+$: 523.1586, found: 523.1583.

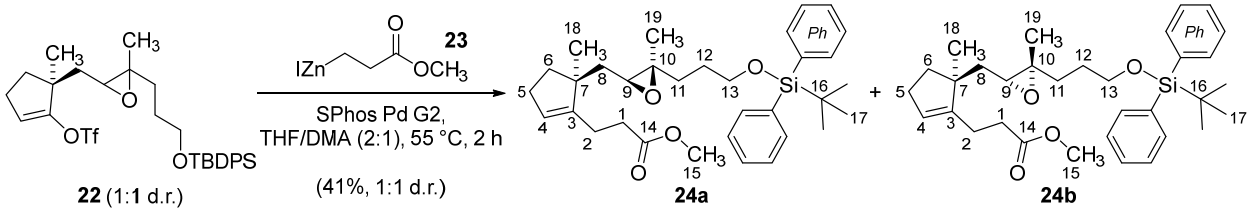
Synthesis of epoxide 22



A solution of triflate **94** (220 mg, 0.38 mmol, 1 equiv) in dichloromethane (4 mL) was treated with sodium hydrogen carbonate (35.0 mg, 0.42 mmol, 1.10 equiv) and *meta*-chloroperoxybenzoic acid (109 mg, 0.47 mmol, 1.25 equiv) at 0 °C. After 1 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (25 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (8% ethyl acetate in hexanes) on silica gel to provide epoxide **22** (1:1 mixture of diastereomers) as a colourless oil (146 mg, 65%).

TLC (10% ethyl acetate in hexanes): R_f = 0.34 (CAM). *In cases where the proton or carbon atoms show a double set of signals, the signal of the second diastereomer is marked with an asterisk.* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H, *Ph*), 7.46–7.34 (m, 6H, *Ph*), 5.67 (t, $^3J_{4/5}$ = 2.6 Hz, 1H, 4-H), 5.62* (t, $^3J_{4/5}$ = 2.6 Hz, 1H, 4-H), 3.71–3.59 (m, 2H, 13-H), 2.75 (t, $^3J_{9/8}$ = 6.1 Hz, 1H, 9-H), 2.69* (dd, $^3J_{9/8A}$ = 7.6 Hz, $^3J_{9/8B}$ = 3.6 Hz, 1H, 9-H), 2.43–2.34 (m, 2H, 5-H), 2.21–2.03 (m, 1H, 6-H_A), 1.88–1.74 (m, 1H, 6-H_B), 1.73–1.44 (m, 6H, 8-H, 11-H, 12-H), 1.23 (s, 3H, 19-H), 1.22 (s, 3H, 18-H), 1.05 (s, 9H, 15-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.31 (C-3), 153.39* (C-3), 135.68 (*Ph*), 134.00 (*Ph*), 129.74 (*Ph*), 127.77 (*Ph*), 118.6 (q, $^1J_{2/F}$ = 320 Hz, C-2), 114.72 (C-4), 113.76* (C-4), 63.78 (C-13), 63.74* (C-13), 60.31 (C-10), 60.12* (C-10), 60.06 (C-9), 59.85* (C-9), 46.26 (C-7), 45.71* (C-7), 37.22 (C-8), 36.72* (C-8), 35.24 (C-11), 35.12* (C-11), 34.46 (C-6), 34.03* (C-6), 28.31 (C-12), 28.29* (C-12), 26.97 (C-15), 25.75 (C-5), 25.66* (C-5), 25.28 (C-8), 23.86* (C-8), 19.34 (C-14), 16.86 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (m), 2859 (m), 1421 (s), 1248 (m), 1211 (s), 1140 (s), 1110 (s), 1048 (m) cm^{-1}. **HRMS** (ESI): calcd for ($[M+NH_4]$, $C_{30}H_{43}O_5F_3NSSi)^+$: 614.25833, found: 614.25845.

Synthesis of ester 24



*Preparation of organozinc reagent **23**:* A suspension of zinc dust (367 mg, 5.61 mmol, 1.50 equiv) in tetrahydrofuran (1 mL) was treated with 1,2-dibromoethane (1 drop) and the resulting mixture was heated to 65 °C for 3 min. After cooling to 23 °C, chlorotrimethylsilane (1 drop) was added, whereupon foaming of the mixture was observed. After 15 min, a solution of methyl 3-iodopropanoate (800 mg, 3.74 mmol, 1 equiv) in tetrahydrofuran (2.5 mL) was added and stirring of the resulting mixture was continued at 23 °C under exclusion of light. After 2 h, the mixture was filtered (argon atmosphere) into a flame-dried flask, and the molarity of the organozinc reagent **23** solution was determined to be 1.10 M by iodometric titration.

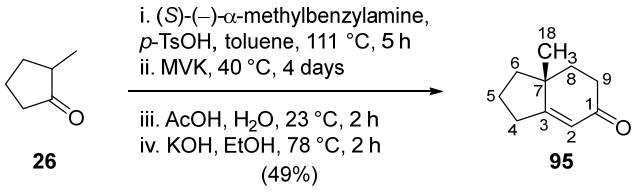
A solution of epoxide **22** (1:1 d.r., 218 mg, 0.37 mmol, 1 equiv) in tetrahydrofuran and dimethylacetamide (1:1 v/v, 2 mL) was treated with SPhos (15.0 mg, 36.5 µmol, 0.10 equiv) and SPhos Pd G2 (26.3 mg, 36.5 µmol, 0.10 equiv). Freshly prepared organozinc reagent **23** solution (1.10 M in THF, 1.33 mL, 1.46 mmol, 4.00 equiv) was then added and the resulting mixture was warmed to 55 °C. After 2 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (25 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (8% ethyl acetate in hexanes) on silica gel to provide esters **24a** and **24b** as a colourless oil (1:1 d.r., 80 mg, 41%). Analytically pure samples of the diastereomers **24a** and **24b** could be obtained by further careful purification by flash-column chromatography (3% ethyl acetate in hexanes) on silica gel. *The relative stereochemistry of **24a** and **24b** could not be determined and is depicted arbitrary.*

24a: TLC (10% ethyl acetate in hexanes): R_f = 0.26 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70–7.62 (m, 4H, *Ph*), 7.46–7.34 (m, 6H, *Ph*), 5.35–5.28 (m, 1H, 4-H), 3.72–3.58 (m, 5H, 13-H, 15-H), 2.66–2.61 (m, 1H, 9-H), 2.59–2.48 (m, 2H, 1-H), 2.30–2.13 (m, 4H, 2-H, 5-H), 2.02–1.92 (m, 1H, 6-H_A), 1.73–1.38 (m, 7H, 6-H_B, 8-H, 11-H, 12-H), 1.21 (s, 3H, 19-H), 1.09 (s, 3H, 18-H), 1.04 (s, 9H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.99 (C-14), 148.60 (C-3), 135.69 (*Ph*), 134.05 (*Ph*), 129.70 (*Ph*), 127.76 (*Ph*), 123.22 (C-4), 63.88 (C-13), 61.10 (C-9), 59.82 (C-10), 51.76 (C-15), 49.18 (C-7), 38.00 (C-8), 37.14 (C-6), 35.36 (C-11), 32.55 (C-1), 29.77 (C-5), 28.41 (C-12), 26.99 (C-17), 25.89 (C-18), 21.93 (C-2), 19.35 (C-16), 16.96 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (s), 2931 (m), 2857 (m), 1740 (s), 1428 (m), 1158 (m), 1110 (s), 1040 (w) cm^{-1}. **HRMS** (ESI): calcd for ([M+NH_4], $C_{33}H_{50}NO_4Si)^+$: 552.35091, found: 552.35103.

24b: TLC (10% ethyl acetate in hexanes): R_f = 0.23 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H, *Ph*), 7.45–7.34 (m, 6H, *Ph*), 5.33–5.26 (m, 1H, 4-H), 3.72–3.59 (m, 5H, 13-H, 15-H), 2.66 (t, $^3J_{9/8}$ = 6.5 Hz, 1H, 9-H), 2.57–2.51 (m, 2H, 1-H), 2.29–2.18 (m, 4H, 2-H, 5-H), 1.95–1.86 (m, 1H, 6-H_A), 1.70–1.48 (m, 7H, 6-H_B, 8-H, 11-H, 12-H), 1.22 (s, 3H, 19-H), 1.05 (s, 3H, 18-H), 1.04 (s, 9H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.04 (C-14), 148.97 (C-3), 135.69 (*Ph*), 134.04 (*Ph*), 129.72 (*Ph*), 127.76 (*Ph*), 122.76 (C-4), 63.88 (C-13), 61.11 (C-9), 60.55 (C-10), 51.75 (C-15), 48.71 (C-7), 37.53 (C-8), 37.12 (C-6), 35.32 (C-11), 32.58 (C-1), 29.78 (C-5), 28.41 (C-12), 27.00 (C-17), 25.70 (C-18), 21.92 (C-2), 19.36 (C-16), 17.02 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (m), 2931 (m), 2856 (m), 1739 (s), 1428 (m), 1158 (m), 1106 (s), 1039 (w) cm^{-1}. **HRMS** (ESI): calcd for ([M+NH_4], $C_{33}H_{50}NO_4Si)^+$: 552.35091, found: 552.35100.

Synthesis of Key Building Block Ketone 28

Synthesis of enone 95[57]



A round-bottomed flask was charged with 2-methylcyclopentanone (**26**) (28.0 mL, 260 mmol, 1 equiv), (*S*)-(–)-α-methylbenzylamine (33.5 mL, 260 mmol, 1.00 equiv), *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol, 0.002 equiv) and toluene (50 mL). The flask was then equipped with a Dean-Stark apparatus and the mixture was heated to 111 °C. After 5 h, the removal of water was judged to be complete (approximately 4.3 mL water collected) and the mixture was cooled to 0 °C. Methyl vinyl ketone (25.3 mL, 312 mmol, 1.20 equiv) was added, and after 1 h, the mixture was warmed to 40 °C. After 2 days, a further portion of methyl vinyl ketone (21.1 mL, 260 mmol, 1.00 equiv) was added and stirring was continued at 40 °C. After further 2 days, the mixture was cooled to 0 °C, and a solution of acetic acid (22.3 mL, 389 mmol, 1.50 equiv) in water (30 mL) was added. The resulting biphasic mixture was warmed to 23 °C and stirred vigorously. After 2 h, the mixture was diluted with saturated aqueous sodium chloride solution (50 mL), water (50 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 70 mL) and the combined organic extracts were washed sequentially with aqueous 1 M hydrogen chloride solution (50 mL) and saturated aqueous sodium chloride solution (60 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the diketone, which was used in the next step without further purification.

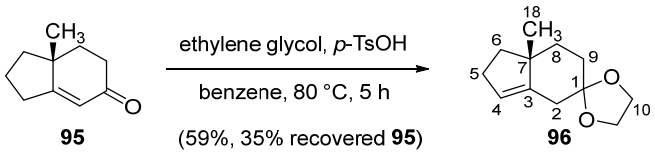
A solution of the crude diketone (assuming 260 mmol) in ethanol (280 mL) was treated with potassium hydroxide (24.8 g, 442 mmol, 1.70 equiv) at 23 °C, and the resulting mixture was heated to 78 °C. After 2 h, the mixture was cooled to 0 °C and was acidified by addition of acetic acid (ca. 25 mL, pH~6). The resulting mixture was concentrated until a thick paste resulted. Water (150 mL) and a mixture of diethyl ether–pentane (1:1 v/v, 100 mL) was added. The layers were separated, the aqueous layer was extracted with diethyl ether–pentane (1:1 v/v, 4 x 70 mL) and the combined organic extracts were washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% to 30% ethyl acetate in hexanes) to provide enone **95** (19.0 g, 49%) as an orange oil. The characterization data for **95** were in agreement with values previously reported.[44a,58] The absolute configuration (*R*) of enone **95** was derived from the sign of the optical rotation, and **95** was estimated to be of ≥80% ee by comparison with the literature values (Lit.:[44a] $[\alpha]_D^{20}$ = –108° (c = 3.50, EtOH); Lit.:[45] $[\alpha]_D^{20}$ = –94° (c = 1.00, EtOH)).

TLC (20% ethyl acetate in hexanes): R_f = 0.32 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78–5.76 (m, 1H, 2-H), 2.76–2.64 (m, 1H, 4-H_A), 2.61–2.42 (m, 2H, 4-H_B, 9-H_A), 2.39–2.31 (m, 1H, 9-H_B), 2.03 (ddd, $^2J_{8A/8B}$ = 13.0 Hz, $^3J_{8A/9B}$ = 5.3 Hz, $^3J_{8A/9A}$ = 2.1 Hz, 1H, 8-H_A), 1.97–1.75 (m, 4H, 5-H, 6-H_A, 8-H_B), 1.53–1.43 (m, 1H, 6-H_B), 1.16 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.79 (C-1), 178.76 (C-3), 121.42 (C-2), 42.82 (C-7), 40.94 (C-6), 36.17 (C-8), 33.93 (C-9), 30.84 (C-4), 22.49 (C-18), 21.26 (C-5). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2960 (m), 2928 (m), 2861 (m), 1667 (s), 1454 (w), 1421 (w), 1296 (w), 1222 (w), 1202 (w) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{10}H_{14}O)^+$: 150.1039, found: 150.1044. $[\alpha]_D^{20}$ = –94.8° (c = 2.00, EtOH).

[57] a) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273. b) G. Revial, M. Pfau, *Org. Synth.* **1992**, *70*, 35.

[58] E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686.

Synthesis of ketal 96[59]



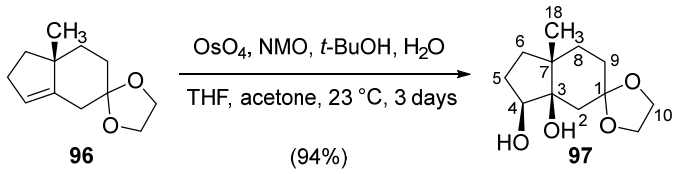
A round-bottomed flask was charged with enone **95** (9.21 g, 61.3 mmol, 1 equiv), ethylene glycol (20.5 mL, 368 mmol, 6.00 equiv), *p*-toluenesulfonic acid monohydrate (1.17 g, 6.13 mmol, 0.10 equiv) and benzene (150 mL). The flask was equipped with a Dean-Stark apparatus and the mixture was heated to 80 °C. After 5 h, the removal of water was judged to be complete and the mixture was cooled to 23 °C. The mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (150 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 70 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% to 30% ethyl acetate in hexanes) to provide recovered enone **95** (3.19 g, 35%) and ketal **96** (7.00 g, 59%) as a yellow oil. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for ketal **96** were in full agreement with values previously reported for the racemic compound.[60]

TLC (20% ethyl acetate in hexanes): R_f = 0.53 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32–5.28 (m, 1H, 4-H), 4.05–3.88 (m, 4H, 10-H), 2.48–2.19 (m, 4H, 2-H, 5-H), 1.91–1.74 (m, 2H, 6-H_A, 9-H_A), 1.75–1.61 (m, 3H, 6-H_B, 8-H_A, 9-H_B), 1.59–1.49 (m, 1H, 8-H_B), 1.06 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.40 (C-3), 122.63 (C-4), 109.87 (C-1), 64.65 (C-10), 64.51 (C-10'), 45.14 (C-7), 40.31 (C-6), 37.72 (C-8), 36.25 (C-2), 31.86 (C-9), 30.51 (C-5), 22.36 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944 (s), 2880 (m), 1455 (w), 1353 (w), 1306 (w), 1257 (w), 1177 (w), 1115 (m), 1090 (s), 1020 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{12}H_{18}O_2$)$^+$: 194.1301, found: 194.1293. $[\alpha]_D^{20}$ = –18.7° (c = 0.83, CH_2Cl_2).

[59] a) D. Becker, N. C. Brodsky, J. Kalo, *J. Org. Chem.* **1978**, *43*, 2557. b) D. Becker, J. Kalo, N. C. Brodsky, *J. Org. Chem.* **1978**, *43*, 2562.

[60] B. Defaut, T. B. Parsons, N. Spencer, L. Male, B. M. Kariuki, R. S. Grainger, *Org. Biomol. Chem.* **2012**, *10*, 4926.

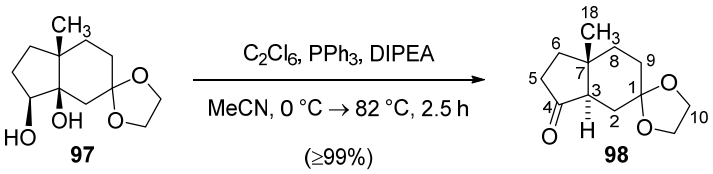
Synthesis of diol 97[47]



A solution of ketal **96** (8.10 g, 41.7 mmol, 1 equiv) in tetrahydrofuran (24 mL), *tert*-butanol (70 mL), water (12 mL) and acetone (12 mL) was treated sequentially with 4-methylmorpholine *N*-oxide (5.86 g, 50.0 mmol, 1.20 equiv) and osmium tetroxide solution (2.5 wt.% in *t*-BuOH, 10.2 mL, 1.04 mmol, 0.03 equiv) at 23 °C. After 3 days, sodium sulfite (15.8 g, 125 mmol, 3.00 equiv) and water (20 mL) were added. After 15 min, the mixture was diluted with more water (100 mL) and ethyl acetate (100 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (6 x 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (7% methanol in dichloromethane) to provide diol **97** (8.94 g, 94%) as a brownish oil which solidified upon standing. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for diol **97** were in full agreement with values previously reported for the racemic compound.[47]

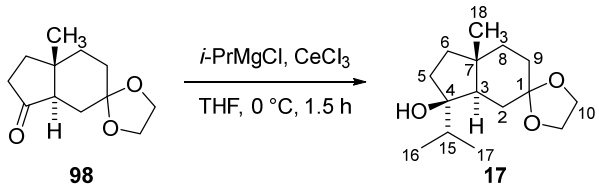
TLC (5% methanol in dichloromethane): R_f = 0.24 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.22–4.15 (m, 1H, 4-H), 4.00–3.89 (m, 4H, 10-H), 2.96 (br s, 1H, 3-OH), 2.49 (d, $^{3}J_{4OH/4}$ = 3.9 Hz, 1H, 4-OH), 2.13–2.02 (m, 1H, 5-H_A), 1.76–1.42 (m, 9H, 2-H, 5-H_B, 6-H, 8-H, 9-H), 1.07 (s, 3H, 18-H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 109.24 (C-1), 80.23 (C-3), 76.67 (C-4), 64.50 (C-10), 64.27 (C-10'), 42.45 (C-7), 40.25 (C-2), 34.02 (C-6), 32.54 (C-8), 30.45 (C-9), 28.82 (C-5), 21.58 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (br), 2954 (m), 1465 (m), 1428 (m), 1341 (m), 1265 (s), 1122 (m), 1091 (s), 1069 (s), 1032 (s), 1012 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+Na], $C_{12}H_{20}O_4Na)^+$: 251.12593, found: 251.12550. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –61.8° (c = 0.33, CH_2Cl_2).

Synthesis of hydrindanone 98[47]



A suspension of triphenylphosphine (17.3 g, 66.1 mmol, 2.20 equiv) in acetonitrile (200 mL) was treated with hexachloroethane (15.7 g, 66.1 mmol, 2.20 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was warmed to 23 °C. After 30 min, the mixture was cooled to 0 °C, whereupon *N*,*N*-diisopropylethylamine (22.9 mL, 132 mmol, 4.40 equiv), followed by a solution of diol **97** (6.86 g, 30 mmol, 1 equiv) in acetonitrile (120 mL) was added dropwise over a period of 10 min. After 1 h, the reaction flask was placed in a preheated (82 °C) oil bath. After 1.5 h, the mixture was allowed to cool to 23 °C, and then was diluted with diethyl ether (300 mL). The organic layer was washed with water (2 x 100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide hydrindanone **98** (6.32 g, ≥99%) as a yellowish oil which solidified upon standing. The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for hydrindanone **98** were in full agreement with values previously reported for the racemic compound.[47] **TLC** (30% ethyl acetate in hexanes): R_f = 0.38 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.02–3.85 (m, 4H, 10-H), 2.40–2.20 (m, 3H, 3-H, 5-H), 1.98–1.91 (m, 1H, 2-H_A), 1.90–1.57 (m, 6H, 6-H, 8-H, 9-H), 1.45 (app t, $^{2}J_{2B/2A} = {}^{3}J_{2B/3}$ = 13.1 Hz, 1H, 2-H_B), 0.87 (s, 3H, 18-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 216.44 (C-4), 109.56 (C-1), 64.62 (C-10), 64.33 (C-10'), 57.34 (C-3), 38.72 (C-7), 35.93 (C-5, C-6, C-8), 35.88 (C-5, C-6, C-8), 35.39 (C-5, C-6, C-8), 31.70 (C-9), 29.86 (C-2), 17.03 (C-18). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (m), 2882 (m), 1737 (s), 1459 (m), 1354 (m), 1287 (m), 1194 (m), 1110 (s), 1080 (m), 1016 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{12}H_{19}O_3$)$^{+}$: 211.13342, found: 211.13297. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –92.6° (c = 1.00, CH_2Cl_2).

Synthesis of *trans*-hydrindane 17[47]

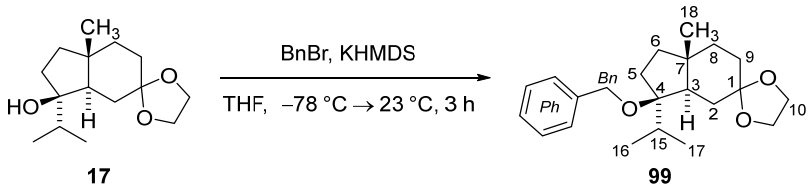


A solution of hydrindanone **98** (6.31 g, 30 mmol, 1 equiv) in tetrahydrofuran (250 mL) was treated with anhydrous cerium(III) trichloride (11.1 g, 45 mmol, 1.50 equiv) at 23 °C. After 1.5 h, the colourless suspension was cooled to 0 °C, whereupon a solution of isopropylmagnesium chloride (2 M in THF, 33.8 mL, 67.5 mmol, 2.25 equiv) was added over a period of 10 min. After 1.5 h, the mixture was diluted with pH 7 buffer solution (300 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 70 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide *trans*-hydrindane **17** (8.10 g) as a brownish oil, which was used in the next step without further purification.

An analytically pure sample of *trans*-hydrindane **17** was obtained by flash-column chromatography on silica gel (30% ethyl acetate in hexanes). The ^{1}H NMR, ^{13}C NMR, IR and HMRS data for *trans*-hydrindane **17** were in full agreement with values previously reported for the racemic compound.[47]

TLC (30% ethyl acetate in hexanes): R_f = 0.37 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.98–3.91 (m, 4H, 10-H), 2.00 (dd, $^{2}J_{5A/5B}$ = 14.3 Hz, $^{3}J_{5A/6B}$ = 9.6 Hz, 1H, 5-H_A), 1.86–1.52 (m, 9H, 2-H, 3-H, 5-H_B, 6-H_A, 8-H_A, 9-H, 15-H), 1.38 (app td, $^{2}J_{8B/8A}$ = $^{3}J_{8B/9A}$ = 13.4 Hz, $^{3}J_{8B/9B}$ = 4.3 Hz, 1H, 8-H_B), 1.16–1.05 (m, 4H, 6-H_B, 18-H), 1.04 (s, 1H, 4-OH), 0.95 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H), 0.90 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 110.81 (C-1), 83.30 (C-4), 64.47 (C-10), 64.29 (C-10'), 51.09 (C-3), 41.56 (C-7), 39.42 (C-6), 37.47 (C-15), 37.29 (C-8), 36.73 (C-5), 31.61 (C-2, C-9), 31.56 (C-2, C-9), 18.47 (C-16, C-17), 18.31 (C-18), 17.65 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3508 (br), 2953 (s), 2877 (s), 1459 (m), 1348 (m), 1292 (m), 1254 (m), 1192 (m), 1145 (s), 1089 (s), 1020 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{26}O_3$)$^{+}$: 254.1877, found: 254.1876. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –12.6° (c = 1.00, CH_2Cl_2).

Synthesis of benzyl ether 99

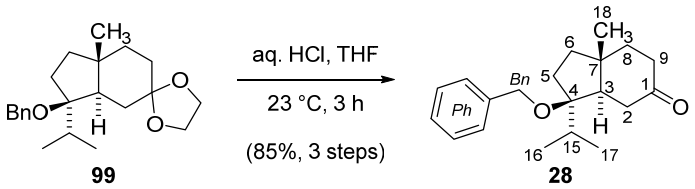


A solution of crude *trans*-hydrindane **17** (6.50 g, 25.6 mmol, 1 equiv) in tetrahydrofuran (21 mL) was treated sequentially with potassium bis(trimethylsilyl)amide solution (1 M in THF, 30.7 mL, 30.7 mmol, 1.20 equiv) and benzyl bromide (4.59 mL, 38.3 mmol, 1.50 equiv) at –78 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 3 h, the mixture was diluted with saturated aqueous ammonium chloride solution (150 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide benzyl ether **99** (8.82 g) as a yellowish oil, which was used in the next step without further purification.

An analytically pure sample of benzyl ether **99** was obtained by flash-column chromatography on silica gel (5% to 10% ethyl acetate in hexanes).

TLC (10% ethyl acetate in hexanes): R_f = 0.33 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H, *Ph*), 4.45–4.37 (m, 2H, *Bn*), 3.98–3.92 (m, 4H, 10-H), 2.33–2.20 (m, 1H, 15-H), 2.22–2.11 (m, 1H, 5-H_A), 1.95–1.75 (m, 5H, 2-H, 3-H, 5-H_B, 9-H_A), 1.66–1.53 (m, 3H, 6-H_A, 8-H_A, 9-H_B), 1.41 (app td, $^2J_{8B/8A}$ = $^3J_{8B/9A}$ = 13.4 Hz, $^3J_{8B/9B}$ = 4.5 Hz, 1H, 8-H_B), 1.20–1.09 (m, 1H, 6-H_B), 1.07 (s, 3H, 18-H), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.34 (*Ph*), 128.23 (*Ph*), 126.79 (*Ph*), 126.68 (*Ph*), 111.05 (C-1), 87.58 (C-4), 64.40 (C-10), 64.28 (C-10'), 62.43 (*Bn*), 48.33 (C-3), 41.86 (C-7), 40.17 (C-6), 36.87 (C-8), 34.43 (C-5), 33.75 (C-2), 33.01 (C-15), 31.74 (C-9), 18.48 (C-16, C-17), 18.19 (C-18), 18.15 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 2877 (m), 1454 (m), 1385 (m), 1263 (m), 1198 (m), 1143 (m), 1085 (s), 1061 (s), 1040 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{22}H_{32}O_3$)$^+$: 344.2346, found: 344.2338. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +32.2° (c = 1.06, CH_2Cl_2).

Synthesis of ketone 28

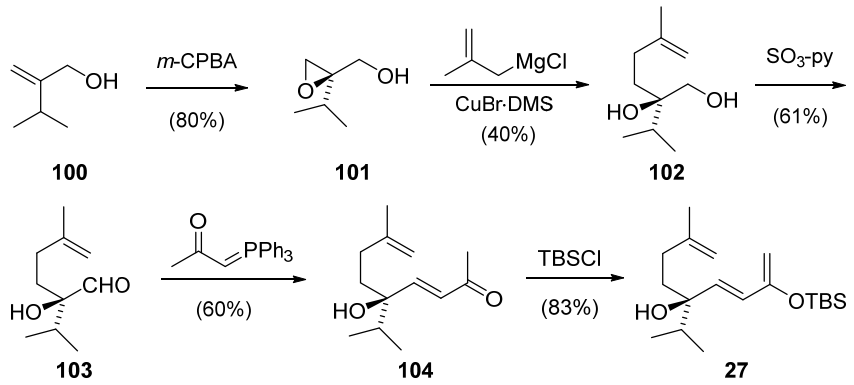


A solution of crude benzyl ether **99** (8.82 g, 25.6 mmol, 1 equiv) in tetrahydrofuran (100 mL) was treated with aqueous 4 M hydrogen chloride solution (30 mL) and the resulting mixture was stirred vigorously at 23 °C. After 3 h, the mixture was diluted with water (50 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% to 20% ethyl acetate in hexanes) to provide ketone **28** (6.51 g, 85% over three steps) as a yellowish oil which solidified upon standing.

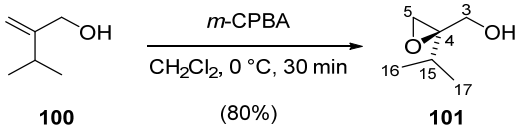
TLC (10% ethyl acetate in hexanes): R_f = 0.29 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29–7.16 (m, 5H, *Ph*), 4.39–4.33 (m, 2H, *Bn*), 2.70 (dd, $^2J_{2A/2B}$ = 16.1 Hz, $^3J_{2A/3}$ = 14.2 Hz, 1H, 2-H_A), 2.44–2.36 (m, 2H, 2-H_B, 9-H_A), 2.33–2.28 (m, 1H, 9-H_B), 2.28–2.16 (m, 2H, 5-H_A, 15-H), 1.85 (dd, $^2J_{5B/5A}$ = 13.8 Hz, $^3J_{5B/6B}$ = 8.1 Hz, 1H, 5-H_B), 1.82–1.75 (m, 2H, 3-H, 8-H_A), 1.65 (dd, $^2J_{6A/6B}$ = 12.0 Hz, $^3J_{6A/5A}$ = 7.9 Hz, 1H, 6-H_A), 1.55–1.48 (m, 1H, 8-H_B), 1.20–1.13 (m, 4H, 6-H_B, 18-H), 0.89 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.86 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.61 (C-1), 139.84 (*Ph*), 128.34 (*Ph*), 127.05 (*Ph*), 126.84 (*Ph*), 87.40 (C-4), 62.61 (*Bn*), 49.63 (C-3), 41.74 (C-7), 41.55 (C-2), 39.94 (C-6), 37.72 (C-9), 37.29 (C-8), 35.08 (C-5), 33.06 (C-15), 18.26 (C-16, C-17), 18.15 (C-18), 17.78 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (m), 2876 (m), 1706 (s), 1454 (m), 1387 (m), 1220 (w), 1111 (m), 1085 (m), 1056 (s), 1028 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+NH_4], $C_{20}H_{32}O_2N)^+$: 318.24330, found: 318.24334. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +15.6° (c = 1.05, CH_2Cl_2).

Synthesis of the Diels–Alder Reaction Precursor 27

Triene **27** was prepared according to the following synthetic route (all yields are unoptimized).



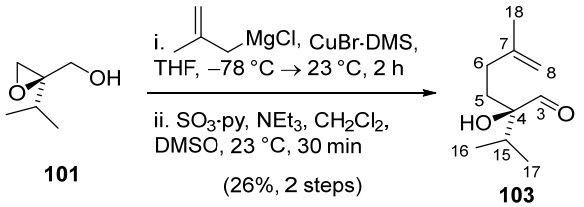
Synthesis of epoxide 101



A solution of known allylic alcohol **100**[61] (2.00 g, 20.0 mmol, 1 equiv) in dichloromethane (70 mL) was treated with *meta*-chloroperoxybenzoic acid (5.05 g, 22.0 mmol, 1.10 equiv) at 0 °C. After 30 min, the mixture was diluted with diethyl ether (100 mL) and the resulting suspension was filtered through a pad of Celite. The filtrate was washed sequentially with saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (50% diethyl ether in pentane) to provide epoxide **101** (1.85 g, 80%) as a colourless liquid, which was used in the next step without further purification.

[61] W. Ma, J. Fang, J. Ren, Z. Wang, *Org. Lett.* **2015**, *17*, 4180.

Synthesis of aldehyde 103



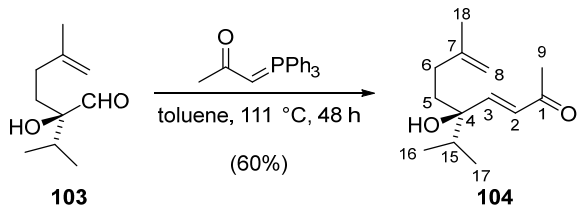
101 **103**

Grignard stock solution preparation: A suspension of magnesium turnings (0.47 g, 20.0 mmol, 1 equiv) in tetrahydrofuran (15 mL) was treated dropwise with a solution of 3-chloro-2-methyl-1-propene (1.96 mL, 20.0 mmol, 1.00 equiv) in tetrahydrofuran (5 mL) over a period of 20 min so as to maintain a gentle reflux. After complete addition, stirring was continued at 23 °C for 6 h, before the mixture was filtered (argon atmosphere) and used immediately in the following reaction.

In a separate flask, a solution of epoxide **101** (800 mg, 6.89 mmol, 1 equiv) in tetrahydrofuran (10 mL) was treated with copper(I) bromide dimethyl sulfide complex (283 mg, 1.38 mmol, 0.20 equiv) and the resulting mixture was cooled to –78 °C. The freshly prepared 2-methylallylmagnesium chloride solution (assuming 0.70 M in THF, 19.7 mL, 13.8 mmol, 2.00 equiv) was added dropwise over a period of 10 min. After 30 min, the mixture was warmed to 23 °C. After 1.5 h, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (30 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (40% ethyl acetate in hexanes) to provide crude diol **102** (500 mg) as a colourless oil, which was used in the next step without further purification.

A solution of crude diol **102** (500 mg, 2.90 mmol, 1 equiv) in dichloromethane (24 mL) and dimethyl sulfoxide (6 mL) was treated sequentially with triethylamine (2.02 mL, 14.5 mmol, 5.00 equiv) and sulfur trioxide pyridine complex (1.39 g, 8.71 mmol, 3.00 equiv) at 23 °C. After 30 min, the mixture was diluted with water (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (10% diethyl ether in pentane) to provide the crude aldehyde **103** (300 mg, 26% over two steps) as a colourless oil, which was used in the next step without further purification.

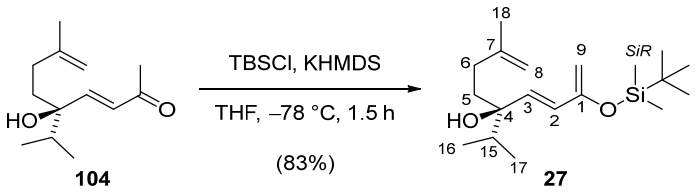
Synthesis of enone 104



103 **104**

A solution of aldehyde **103** (118 mg, 0.69 mmol, 1 equiv) in toluene (1.4 mL) was treated with 1-(triphenylphosphoranylidene)-2-propanone (441 mg, 1.39 mmol, 2.00 equiv) and the resulting suspension was heated to 111 °C. After 24 h, the mixture was cooled to 23 °C, whereupon a further portion of 1-(triphenylphosphoranylidene)-2-propanone (441 mg, 1.39 mmol, 2.00 equiv) was added. The suspension was then heated to 111 °C. After 24 h, the mixture was cooled to 23 °C, and then was concentrated in vacuo. The residue was purified by flash-column chromatography on silica gel (20% to 30% ethyl acetate in hexanes) to provide enone **104** (87.0 mg, 60%) as a yellowish oil.
TLC (20% ethyl acetate in hexanes): R_f = 0.19 (UV/CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 6.66 (d, $^3J_{3/2}$ = 15.9 Hz, 1H, 3-H), 6.24 (d, $^3J_{2/3}$ = 15.9 Hz, 1H, 2-H), 4.63 (br s, 1H, 8-H_A), 4.59 (br s, 1H, 8-H_B), 2.19 (s, 3H, 9-H), 2.01–1.92 (m, 1H, 6-H_A), 1.88–1.78 (m, 1H, 6-H_B), 1.77–1.57 (m, 6H, 5-H, 15-H, 18-H), 0.86–0.80 (m, 6H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.17 (C-1), 150.81 (C-3), 146.02 (C-7), 129.35 (C-2), 110.40 (C-8), 77.89 (C-4), 36.90 (C-15), 36.07 (C-5), 31.77 (C-6), 28.28 (C-9), 22.78 (C-18), 17.77 (C-16, C-17), 16.64 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3477 (br), 2966 (s), 1673 (s), 1645 (s), 1440 (w), 1360 (m), 1262 (s), 1177 (w), 1090 (w) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{13}H_{22}O_2$)$^+$: 210.1614, found: 210.1620.

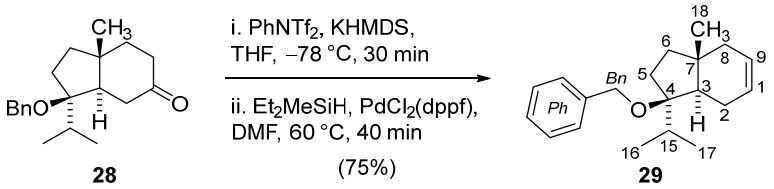
Synthesis of triene 27



A solution of enone **104** (25.0 mg, 0.12 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was treated sequentially with potassium bis(trimethylsilyl)amide solution (1 M in THF, 0.36 mL, 0.36 mmol, 3.00 equiv) and *tert*-butyldimethylchlorosilane (53.8 mg, 0.36 mmol, 3.00 equiv) at –78 °C. After 1.5 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to provide triene **27** (32.0 mg, 83%) as a yellowish oil.
TLC (10% ethyl acetate in hexanes): R_f = 0.50 (UV/CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 6.28 (d, $^3J_{2/3}$ = 15.3 Hz, 1H, 2-H), 6.20 (d, $^3J_{3/2}$ = 15.3 Hz, 1H, 3-H), 4.80 (br s, 1H, 8-H_A), 4.77 (br s, 1H, 8-H_B), 4.38 (s, 1H, 9-H_A), 4.36 (s, 1H, 9-H_B), 2.18–1.99 (m, 2H, 6-H), 1.75–1.58 (m, 6H, 5-H, 15-H, 18-H), 1.01 (s, 9H, *SiR*), 0.92–0.86 (m, 6H, 16-H, 17-H), 0.16 (s, 3H, *SiR*), 0.15 (s, 3H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 155.40 (C-1), 146.45 (C-7), 135.06 (C-3), 127.50 (C-2), 110.17 (C-8), 95.68 (C-9), 77.28 (C-4), 37.49 (C-15), 37.32 (C-5), 32.17 (C-6), 26.00 (*SiR*), 22.76 (C-18), 18.51 (*SiR*), 17.87 (C-16, C-17), 16.86 (C-16, C-17), –3.36 (*SiR*), –4.43 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3480 (br), 2958 (s), 2931 (s), 1593 (m), 1471 (m), 1310 (s), 1253 (s), 1024 (s), 1004 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–CH_3], $C_{18}H_{33}O_2Si)^+$: 309.2250, found: 309.2254.

Ketene–Alkene [2+2] Cycloaddition Route

Synthesis of olefin 29



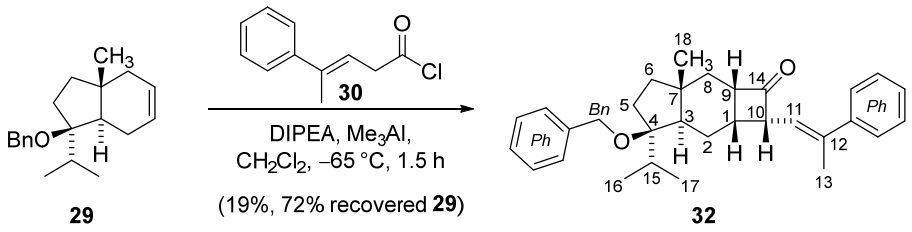
28 **29**

A solution of ketone **28** (320 mg, 1.07 mmol, 1 equiv) in tetrahydrofuran (8 mL) was treated slowly with with potassium bis(trimethylsilyl)amide solution (1 M in THF, 2.13 mL, 2.13 mmol, 2.00 equiv) at –78 °C (addition to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture). After 15 min, *N*-phenyl-bis(trifluoromethanesulfonimide) (685 mg, 1.92 mmol, 1.80 equiv) was added in one portion. After 30 min, the cooling bath was removed and the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and diethyl ether (25 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica (3% ethyl acetate in hexanes) to provide the crude vinyl triflate (colourless oil which solidified upon standing), which was used in the next step without further purification.

A solution of the crude vinyl triflate (assuming 1.07 mmol) in dimethylformamide (5.3 mL) was treated sequentially with diethylmethylsilane (464 µL, 3.20 mmol, 3.00 equiv) and Pd(dppf)Cl_2 (39.0 mg, 0.05 mmol, 0.05 equiv). The resulting mixture was heated to 60 °C whereupon it turned dark red in colour. After 40 min, the mixture was cooled to 23 °, and then was diluted with water (40 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 x 25 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (2% ethyl acetate in hexanes) to provide olefin **29** (262 mg, 75% over two steps) as a colourless oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.57 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H, *Ph*), 7.26–7.21 (m, 1H, *Ph*), 5.72–5.68 (m, 1H, 1-H), 5.59–5.55 (m, 1H, 9-H), 4.47–4.41 (m, 2H, *Bn*), 2.45–2.37 (m, 1H, 2-H_A), 2.28 (h, $^3J_{15/16\text{-}17}$ = 6.8 Hz, 1H, 15-H), 2.12 (ddd, $^2J_{5A/5B}$ = 13.6 Hz, $^3J_{5A/6B}$ = 12.5 Hz, $^3J_{5A/6A}$ = 7.7 Hz, 1H, 5-H_A), 2.09–1.93 (m, 3H, 2-H_B, 8-H), 1.81 (dd, $^2J_{5B/5A}$ = 13.6 Hz, $^3J_{5B/6B}$ = 8.1 Hz, 1H, 5-H_B), 1.67 (dd, $^2J_{6A/6B}$ = 11.8 Hz, $^3J_{6A/5A}$ = 7.7 Hz, 1H, 6-H_A), 1.61 (dd, $^3J_{3/2A}$ = 12.0 Hz, $^3J_{3/2B}$ = 4.7 Hz, 1H, 3-H), 1.22–1.14 (m, 1H, 6-H_B), 0.99 (s, 3H, 18-H), 0.96–0.92 (m, 6H, 16-H, 17-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 140.52 (*Ph*), 128.26 (*Ph*), 128.15 (C-1), 126.82 (2C, *Ph*), 125.89 (C-9), 87.65 (C-4), 62.61 (*Bn*), 46.42 (C-3), 41.93 (C-8), 40.59 (2C, C-6, C-7), 34.36 (C-5), 33.36 (C-15), 25.97 (C-2), 18.84 (C-18), 18.28 (C-16, C-17), 17.72 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2958 (s), 2924 (s), 2886 (m), 1496 (m), 1453 (s), 1385 (s), 1226 (m), 1150 (m), 1085 (m), 1063 (s) cm^{-1}. **HRMS** (ESI and EI): mass not found. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –38.0° (c = 0.70, CH_2Cl_2).

Synthesis of cyclobutanone 32



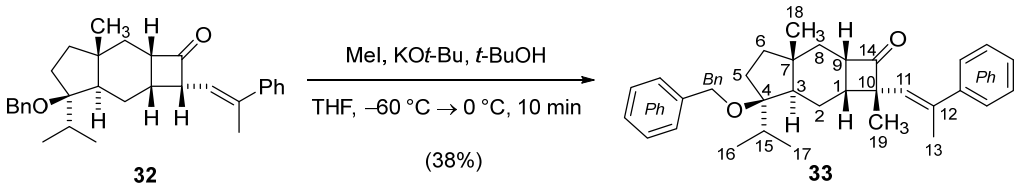
Based on Brown's Lewis acid promoted [2+2] cycloaddition protocol,[62] a solution of olefin **29** (103 mg, 0.36 mmol, 1 equiv) and *N*,*N*-diisopropylethylamine (0.19 mL, 1.09 mmol, 3.00 equiv) in dichloromethane (0.3 mL) was treated dropwise with trimethylaluminium solution (2 M in toluene, 1.09 mL, 2.17 mmol, 6.00 equiv) at –65 °C. A solution of the known acid chloride **30**[62] (176 mg, 0.91 mmol, 2.50 equiv) in dichloromethane (0.3 mL) was added dropwise over a period of 45 min (syringe pump). After complete addition, the mixture was warmed to –45 °C for 45 min. The mixture was then carefully diluted with triethylamine (0.5 mL) and methanol (0.5 mL). After warming to 23 °C, aqueous 1 M hydrogen chloride solution (15 mL) and diethyl ether (15 mL) were added. The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% to 10% ethyl acetate in hexanes) to provide recovered olefin **29** (74 mg, 72%) as a colourless oil, and cyclobutanone **32** (30 mg, 19%) as a yellowish oil.[63] *Note: At this stage cyclobutanone **32** remained contaminated with minor unidentified impurities which could only be removed after α-methylation (vide infra).*

TLC (10% ethyl acetate in hexanes): R_f = 0.39 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.18 (m, 10H, *Ph*), 5.92–5.86 (m, 1H, 11-H), 4.38–4.30 (m, 3H, 10-H, *Bn*), 3.55–3.44 (m, 1H, 9-H), 3.13–3.03 (m, 1H, 1-H), 2.22–1.95 (m, 6H, 2-H_A, 5-H_A, 13-H, 15-H), 1.90–1.68 (m, 4H, 2-H_B, 5-H_B, 8-H), 1.62 (dd, $^2J_{6A/6B}$ = 12.1 Hz, $^3J_{6B/5A}$ = 7.6 Hz, 1H, 6-H_A), 1.30 (dd, $^3J_{3/2A}$ = 13.9 Hz, $^3J_{3/2B}$ = 4.3 Hz, 1H, 3-H), 1.21–1.10 (m, 1H, 6-H_B), 1.00 (s, 3H, 18-H), 0.75 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.72 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 214.13 (C-14), 142.57 (C-12), 140.31 (*Ph*), 140.02 (*Ph*), 128.29 (*Ph*), 128.23 (*Ph*), 127.25 (*Ph*), 126.94 (*Ph*), 126.85 (*Ph*), 125.86 (*Ph*), 119.63 (C-11), 87.76 (C-4), 62.77 (*Bn*), 61.14 (C-10), 53.58 (C-9), 45.85 (C-3), 40.67 (C-6), 40.59 (C-7), 37.52 (C-8), 35.09 (C-5), 33.27 (C-15), 27.93 (C-1), 20.91 (C-2, C-18), 20.86 (C-2, C-18), 18.03 (C-16, C-17), 17.36 (C-16, C-17), 17.11 (C-13). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (m), 2874 (m), 1766 (s), 1700 (m), 1600 (w), 1446 (m), 1386 (m), 1266 (m), 1062 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{31}H_{38}O_2$)$^+$: 442.2866, found: 442.2859. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +50.4° (c = 0.90, CH_2Cl_2).

[62] C. M. Rasik, M. K. Brown, *Angew. Chem. Int. Ed.* **2014**, *53*, 14522.

[63] Despite extensive optimization attempts of this [2+2] cycloaddition reaction, the conversion remained low in all cases and ≥70% starting material was recovered.

Synthesis of α-methylated cyclobutanone 33

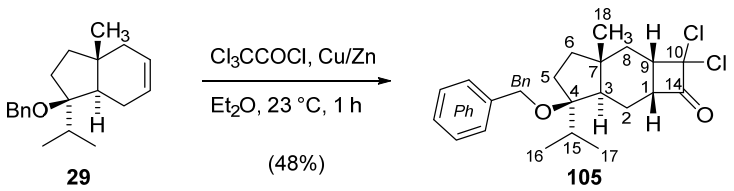


A solution of cyclobutanone **32** (18.0 mg, 40.7 µmol, 1 equiv) in tetrahydrofuran (0.7 mL) and *tert*-butanol (0.05 mL) was treated sequentially with iodomethane (10.1 µL, 163 µmol, 4.00 equiv) and potassium *tert*-butoxide (5.0 mg, 44.7 µmol, 1.10 equiv) at –60 °C. The resulting bright yellow solution was warmed to 0 °C.[64] After 10 min, the mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (7% ethyl acetate in hexanes) to provide α-methylated cyclobutanone **33** (7.0 mg, 38%) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.40 (UV/CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.40–7.20 (m, 10H, *Ph*), 6.05–6.03 (m, 1H, 11-H), 4.39–4.33 (m, 2H, *Bn*), 3.57–3.52 (m, 1H, 9-H), 2.57 (app t, $^3J_{1/2A}$ = $^3J_{1/9}$ = 9.4 Hz, 1H, 1-H), 2.25–2.19 (m, 1H, 2-H_A), 2.14–2.09 (m, 4H, 13-H, 15-H), 2.03 (ddd, $^2J_{5A/5B}$ = 13.7 Hz, $^3J_{5A/6B}$ = 12.6 Hz, $^3J_{5A/6A}$ = 7.8 Hz, 1H, 5-H_A), 1.88–1.84 (m, 2H, 2-H_B, 8-H_A), 1.74 (dd, $^2J_{5B/5A}$ = 13.7 Hz, $^3J_{5B/6B}$ = 7.9 Hz, 1H, 5-H_B), 1.60 (dd, $^2J_{8B/8A}$ = 13.2 Hz, $^3J_{8B/9}$ = 7.6 Hz, 1H, 8-H_B), 1.57 (dd, $^2J_{6A/6B}$ = 12.3 Hz, $^3J_{6A/5A}$ = 7.8 Hz, 1H, 6-H_A), 1.47 (s, 3H, 19-H), 1.35 (dd, $^3J_{3/2A}$ = 13.7 Hz, $^3J_{3/2A}$ = 4.4 Hz, 1H, 3-H), 1.11–1.05 (m, 1H, 6-H_B), 0.96 (s, 3H, 18-H), 0.74 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.59 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 215.71 (C-14), 143.65 (*Ph*), 140.42 (*Ph*), 137.64 (C-12), 128.29 (*Ph*), 128.20 (*Ph*), 127.09 (*Ph*), 126.91 (*Ph*), 126.82 (*Ph*), 125.91 (*Ph*), 125.52 (C-11), 87.87 (C-4), 65.59 (C-10), 62.67 (*Bn*), 52.30 (C-9), 45.81 (C-3), 40.43 (C-6, C-7), 40.40 (C-6, C-7), 37.19 (C-8), 36.44 (C-1), 34.69 (C-5), 33.21 (C-15), 25.00 (C-19), 20.99 (C-2), 19.98 (C-18), 18.02 (C-13), 17.72 (C-16, C-17), 17.57 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (s), 2924 (s), 2857 (m), 1766 (s), 1495 (m), 1454 (s), 1379 (m), 1193 (w), 1084 (m), 1053 (s), 1026 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M–H], $C_{32}H_{39}O_2$)$^-$: 455.29555, found: 455.29615. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –35.4° (c = 1.00, CH_2Cl_2).

[64] TLC analysis at this stage indicated that product formation as well as considerable decomposition of the starting material had occurred.

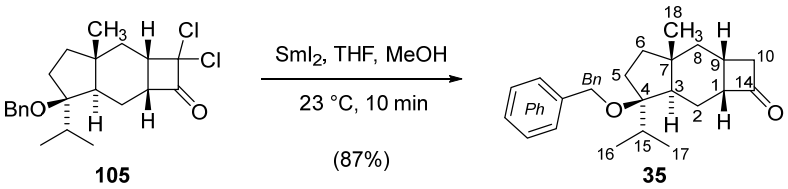
Synthesis of dichlorocyclobutanone 105



A vigorously stirred suspension of olefin **29** (60.0 mg, 0.21 mmol, 1 equiv) and zinc-copper couple (92.5 mg, 0.72 mmol, 3.40 equiv) in diethyl ether (0.7 mL) was treated dropwise with a solution of trichloroacetyl chloride (37.7 µL, 0.34 mmol, 1.60 equiv) in diethyl ether (0.4 mL) over a period of 45 min (syringe pump) at 23 °C. After complete addition, stirring was continued for 15 min, before the mixture was diluted with diethyl ether (4 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 5 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) to provide dichlorocyclobutanone **105** (40.0 mg, 48%) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.47 (UV/CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.32–7.11 (m, 5H, *Ph*), 4.19–4.03 (m, 2H, *Bn*), 3.50 (dd, $^3J_{1/9}$ = 10.5 Hz, $^3J_{1/2B}$ = 7.8 Hz, 1H, 1-H), 2.64–2.55 (m, 1H, 9-H), 2.02 (dd, $^2J_{2A/2B}$ = 14.8 Hz, $^3J_{2A/3}$ = 4.3 Hz, 1H, 2-H_A), 1.87–1.65 (m, 4H, 2-H_B, 5-H_A, 8-H_A, 15-H), 1.44 (dd, $^2J_{5A/5B}$ = 13.8 Hz, $^3J_{5A/6B}$ = 8.1 Hz, 1H, 5-H_B), 1.32–1.12 (m, 3H, 3-H, 6-H_A, 8-H_B), 0.94–0.81 (m, 4H, 6-H_B, 16-H, 17-H), 0.69–0.61 (m, 6H, 16-H, 17-H, 18-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 195.30 (C-14), 140.34 (*Ph*), 128.52 (*Ph*), 127.33 (*Ph*), 127.11 (*Ph*), 88.53 (C-10), 87.44 (C-4), 62.92 (*Bn*), 54.34 (C-1), 46.82 (C-3), 43.34 (C-9), 41.14 (C-7), 40.66 (C-8), 39.91 (C-6), 33.93 (C-5), 33.14 (C-15), 20.60 (C-2), 18.02 (C-16, C-17), 17.98 (C-18), 17.64 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (m), 2940 (m), 2862 (m), 1800 (s), 1454 (m), 1387 (m), 1269 (m), 1194 (m), 1086 (m), 1064 (s), 1028 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{19}H_{21}O_2Cl_2)^+$: 351.0919, found: 351.0914. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –19.6° (c = 1.33, CH_2Cl_2).

Synthesis of cyclobutanone 35

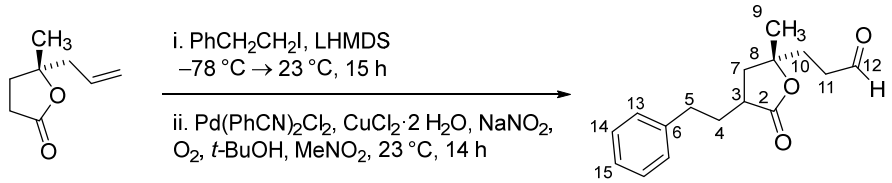


A solution of dichlorocyclobutanone **105** (29.0 mg, 73.3 µmol, 1 equiv) in a mixture of tetrahydrofuran/methanol (10:1 v/v, 1.1 mL) was treated with samarium(II) iodide solution (0.1 M in THF, 3.67 mL, 367 µmol, 5.00 equiv) at 23 °C. After 10 min, the mixture was diluted with pH 7 buffer solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 7 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes) to provide cyclobutanone **35** (20.3 mg, 87%) as a yellowish oil which solidified upon standing.

TLC (10% ethyl acetate in hexanes): R_f = 0.35 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5H, *Ph*), 4.46–4.34 (m, 2H, *Bn*), 3.51–3.42 (m, 1H, 1-H), 3.22 (ddd, $^2J_{10A/10B}$ = 16.0 Hz, $^3J_{10A/9}$ = 9.2 Hz, $^4J_{10A/1}$ = 2.3 Hz, 1H, 10-H_A), 2.71–2.59 (m, 1H, 9-H), 2.40 (app dt, $^2J_{10B/10A}$ = 16.0 Hz, $^3J_{10B/9}$ = $^4J_{10B/1}$ = 2.0 Hz, 1H, 10-H_B), 2.29–2.19 (m, 2H, 8-H_A, 15-H), 2.14–1.99 (m, 2H, 2-H_A, 5-H_A), 1.93–1.76 (m, 2H, 2-H_B, 5-H_B), 1.54 (dd, $^2J_{6A/6B}$ = 12.0 Hz, $^3J_{6A/5A}$ =7.7 Hz, 1H, 6-H_A), 1.33 (dd, $^3J_{3/2B}$ = 13.1 Hz, $^3J_{3/2A}$ = 4.4 Hz, 1H, 3-H), 1.13–0.93 (m, 8H, 6-H_B, 8-H_B, 16-H, 17-H, 18-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.85 (C-14), 140.37 (*Ph*), 128.27 (*Ph*), 126.89 (*Ph*), 126.82 (*Ph*), 87.67 (C-4), 62.72 (*Bn*), 58.56 (C-1), 52.59 (C-10), 47.20 (C-3), 45.06 (C-8), 42.01 (C-7), 40.05 (C-6), 34.13 (C-5), 33.32 (C-15), 22.17 (C-9), 20.81 (C-2), 18.28 (C-16, C-17), 18.13 (C-18), 17.78 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 2881 (m), 1772 (s), 1454 (m), 1384 (m), 1270 (w), 1153 (w), 1084 (m), 1068 (s), 1032 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{19}H_{23}O_2$)$^+$: 283.1698, found: 283.1693. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.5° (c = 0.66, CH_2Cl_2).

Model System

Synthesis of aldehyde 107



106 **107**

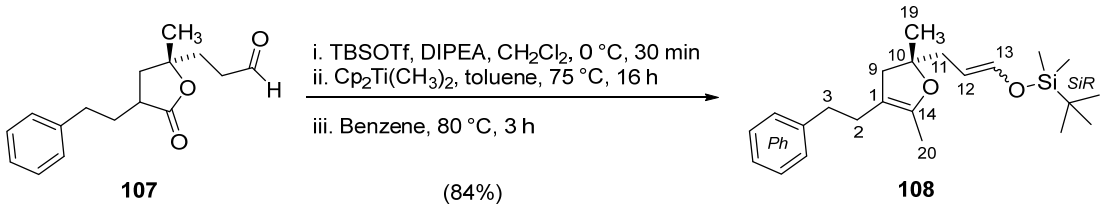
A solution of (racemic) known lactone **106**[65] (700 mg, 4.99 mmol, 1 equiv) in tetrahydrofuran (20 mL) was treated with lithium bis(trimethylsilyl)amide solution (1 M in THF, 7.99 mL, 7.99 mmol, 1.60 equiv), followed by (2-iodoethyl)benzene (0.80 mL, 5.49 mmol, 1.10 equiv) at –78 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 15 h, the mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica (15% ethyl acetate in hexanes) to provide the alkylated lactone (501 mg, 41%, yield unoptimized), which was used in the next step without further purification.

A round-bottomed flask was charged with bis(benzonitrile)palladium(II) dichloride (39.2 mg, 0.10 mmol, 0.05 equiv), copper(II) chloride dihydrate (17.4 mg, 0.10 mmol, 0.05 equiv) and sodium nitrite (3.5 mg, 0.05 mmol, 0.03 equiv).[66] The flask was flushed with oxygen for 1 min, whereupon a solution of the lactone (500 mg, 2.05 mmol, 1 equiv) in oxygen-sparged *tert*-butanol (22 mL) and nitromethane (1.5 mL) was added. The resulting mixture was sparged with oxygen gas for 3 min, and stirring was then continued under oxygen atmosphere whereupon the mixture turned dark brown in colour. After 14 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (50 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40% ethyl acetate in hexanes) to provide aldehyde **107** (372 mg, 28% over two steps, 1:1 d.r.) as a yellowish oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.29 (UV/CAM). *In cases where the proton or carbon atoms show a double set of signals, the signal of the second diastereomer is marked with an asterisk.* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85–9.83 (m, 1H), 9.83–9.81* (m, 1H), 7.36–7.27 (m, 2H), 7.27–7.18 (m, 3H), 2.86–2.57 (m, 5H), 2.36–2.19 (m, 2H), 2.13–1.96 (m, 2H), 1.92–1.71 (m, 2H), 1.44 (s, 3H), 1.35* (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.88, 200.83*, 178.26, 178.08*, 140.79, 128.69, 128.53, 126.40, 83.13, 83.08*, 40.82, 40.09*, 39.78, 39.46*, 38.84, 38.78*, 33.53, 33.49*, 33.44, 32.96*, 32.51, 31.94*, 26.63, 25.13*. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2937 (m), 1761 (s), 1723 (s), 1452 (m), 1383 (m), 1186 (m), 907 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{16}H_{20}O_3)^+$: 260.1407, found: 260.1407.

[65] M. Wada, M. Honna, Y. Kuramoto, N. Miyoshi, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2265.
[66] Z. K. Wickens, K. Skakuj, B. Morandi, R. H. Grubbs, *J. Am. Chem. Soc.* **2014**, *136*, 890.

Synthesis of enol ether 108



A solution of aldehyde **107** (368 mg, 1.41 mmol, 1 equiv) in dichloromethane (9 mL) was treated sequentially with *N,N*-diisopropylethylamine (0.59 mL, 3.39 mmol, 2.40 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfante (0.36 mL, 1.55 mmol, 1.10 equiv) at –78 °C. After 30 min, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (5 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide the silyl enol ether **36** (mixture of *E*-/*Z*-alkene isomers), which was used in the next step without further purification.

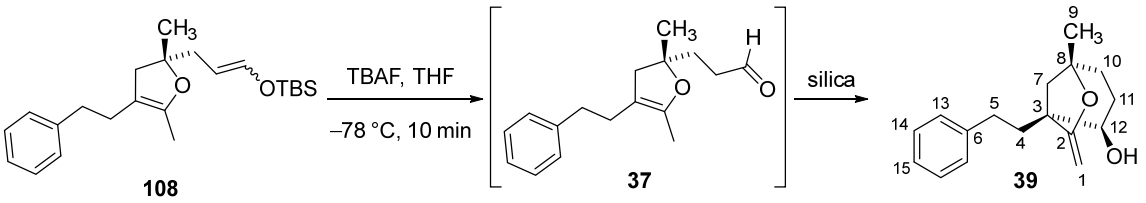
A dimethyltitanocene solution in toluene was freshly prepared based on the procedure of J. Payack et al.[67] and determined to contain 8.2 wt.% dimethyltitanocene by ^{1}H NMR analysis. A solution of the crude silyl enol ether **36** (assuming 1.41 mmol) in toluene (2 mL) was treated with the freshly prepared dimethyltitanocene solution (8.4 mL, ca. 2.82 mmol, 2.00 equiv) and the resulting mixture was heated to 75 °C. After 16 h, the mixture was allowed to cool to 23 °C and was diluted with hexanes (20 mL). The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes, triethylamine pretreated silica gel) to provide a mixture of *exo*- and *endo*-cyclic enol ethers.

In order to isomerize the *exo*-cyclic enol ether, the mixture was dissolved in benzene (8 mL) and the resulting solution was heated to 80 °C. After 3 h, the mixture was cooled to 23 °C and then was concentrated to provide enol ether **108** (442 mg, 84%, 4:3 mixture of *E*-/*Z*-alkene isomers) as a yellow oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.23 (UV/CAM). *In cases where the proton or carbon atoms show a double set of signals due to the E-/Z-alkene isomers, the signal of the second isomer is marked with an asterisk. The C-2, C-3, C-9 and C-11 carbon atoms could not be unambiguously assigned.* **^{1}H NMR** (400 MHz, C_6D_6) δ 7.22–7.06 (m, 5H, *Ph*), 6.37–6.29 (m, 1H, 12-H), 5.31–5.23 (m, 1H, 13-H), 4.77–4.71* (m, 1H, 13-H), 2.73–2.09 (m, 8H, 2-H, 3-H, 9-H, 11-H), 1.53 (br s, 3H, 20-H), 1.51* (br s, 3H, 20-H), 1.41 (s, 3H, 19-H), 1.29* (s, 3H, 19-H), 0.95 (s, 9H, *SiR*), 0.93* (s, 9H, *SiR*), 0.09 (s, 3H, *SiR*), 0.03 (s, 3H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 147.17 (C-14), 147.13* (C-14), 142.71 (C-12), 142.59 (*Ph*), 142.55* (*Ph*), 140.50* (C-12), 128.87 (*Ph*), 128.56 (*Ph*), 126.13 (*Ph*), 107.22 (C-13), 106.25* (C-13), 104.28 (C-1), 104.17* (C-1), 83.90 (C-10), 83.59* (C-10), 44.54, 44.02*, 39.78, 36.19*, 35.36, 29.26, 29.15*, 27.13 (C-19), 27.08* (C-19), 25.89 (*SiR*), 25.82* (*SiR*), 18.50 (*SiR*), 18.47* (*SiR*), 11.53 (C-20), 11.46* (C-20), –5.08 (*SiR*), –5.27 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3028 (w), 2955 (s), 2929 (s), 2858 (m), 1660 (s), 1454 (m), 1254 (s), 1169 (s), 1103 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{23}H_{36}O_2Si)^+$: 372.2479, found: 372.2474.

[67] J. F. Payack, D. L. Hughes, D. Cai, I. F. Cottrell, T. R. Verhoeven, *Org. Synth.* **2002**, *79*, 19.

Synthesis of aldeyde 37 and alcohol 39



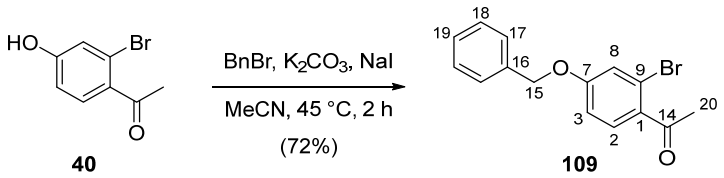
A solution of enol ether **108** (30.0 mg, 80.5 µmol, 1 equiv) in tetrahydrofuran (1 mL) was treated with tetrabutylammonium fluoride solution (1 M in THF, 0.11 mL, 105 µmol, 1.30 equiv) at–78 °C. After 10 min, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide aldehyde **37**, which (due to its instability) was used in the next step without further purification. Aldehyde **37** was found to readily undergo ene reaction (e.g. on silica gel) to afford alcohol **39**. Thus, for all investigations of the intramolecular Paternò-Büchi reaction (see main text), **37** was prepared immediately prior to use by TBAF deprotection of enol ether **108**.

Alcohol 39: **TLC** (30% ethyl acetate in hexanes): R_f = 0.33 (UV/CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.24–7.08 (m, 5H, 13-H, 14-H, 15-H), 4.42–4.40 (m, 1H, 1-H_A), 3.64–3.62 (m, 1H, 1-H_B), 3.37–3.28 (m, 1H, 12-H), 2.66 (app td, $^2J_{5A/5B}$ = $^3J_{5A/4B}$ = 12.8 Hz, $^3J_{5A/4A}$ = 5.1 Hz, 1H, 5-H_A), 2.39 (app td, $^2J_{5B/5A}$ = $^3J_{5B/4A}$ = 12.8 Hz, $^3J_{5B/4B}$ = 4.5 Hz, 1H, 5-H_B), 2.19–2.09 (m, 1H, 4-H_A), 1.81–1.73 (m, 1H, 11-H_A), 1.67 (ddd, $^2J_{4B/4A}$ = 13.7 Hz, $^3J_{4B/5A}$ = 12.8 Hz, $^3J_{4B/5B}$ = 4.5 Hz, 1H, 4-H_B), 1.51–1.31 (m, 3H, 7-H_A, 10-H_A, 11-H_B), 1.13 (s, 3H, 9-H), 1.08–0.93 (m, 3H, 7-H_B, 10-H_B, 12-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 165.80 (C-2), 142.96 (C-6), 128.82 (C-13, C-14), 128.74 (C-13, C-14), 126.21 (C-15), 81.30 (C-8), 78.33 (C-1), 70.14 (C-12), 53.35 (C-3), 45.66 (C-7), 36.65 (C-10), 34.45 (C-4), 31.51 (C-5), 30.91 (C-11), 24.77 (C-9). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3447 (br), 3026 (w), 2931 (s), 2866 (m), 1666 (s), 1453 (s), 1380 (s), 1299 (m), 1204 (m), 1179 (m), 1045 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{17}H_{22}O_2$)$^+$: 258.1614, found: 258.1617.

6.5.2 Experimental Procedures: Oxidative Dearomatization Approach

Synthesis of Phenol 12

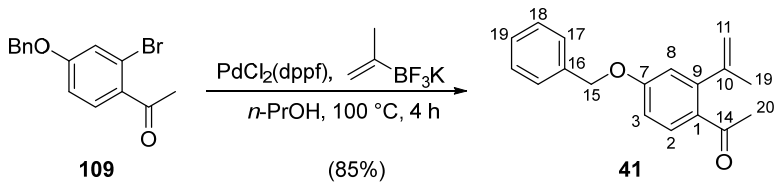
Synthesis of benzyl ether 109



A solution of bromide **40** (1.87 g, 8.71 mmol, 1 equiv) in acetonitrile (30 mL) was treated sequentially with potassium carbonate (1.32 g, 9.58 mmol, 1.10 equiv), sodium iodide (391 mg, 2.61 mmol, 0.30 equiv) and benzyl bromide (1.35 mL, 11.3 mmol, 1.30 equiv) at 23 °C. The resulting suspension was then warmed to 45 °C. After 2 h, the mixture was cooled to 23 °C, and diluted with water (30 mL), saturated aqueous ammonium chloride solution (40 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in hexanes) to provide benzyl ether **109** (1.92 g, 72%) as a yellowish solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.38 (UV/ $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, $^3J_{2/3}$ = 8.7 Hz, 1H, 2-H), 7.43–7.33 (m, 5H, 17-H, 18-H, 19-H), 7.25 (d, $^4J_{8/3}$ = 2.5 Hz, 1H, 8-H), 6.94 (dd, $^3J_{3/2}$ = 8.7 Hz, $^4J_{3/8}$ = 2.5 Hz, 1H, 3-H), 5.09 (s, 2H, 15-H), 2.63 (s, 3H, 20-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.30 (C-14), 161.13 (C-7), 135.83 (C-16), 133.06 (C-1), 131.80 (C-2), 128.89 (C-17, C-18), 128.56 (C-19), 127.65 (C-17, C-18), 121.40 (C-9), 120.64 (C-8), 113.92 (C-3), 70.55 (C-15), 30.20 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3064 (w), 3032 (w), 2922 (w), 1687 (s), 1591 (s), 1558 (m), 1488 (m), 1453 (m), 1381 (m), 1355 (s), 1299 (m), 1251 (s), 1222 (s), 1021 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{13}O_2Br)^+$: 304.0093, found: 304.0105.

Synthesis of styrene 41

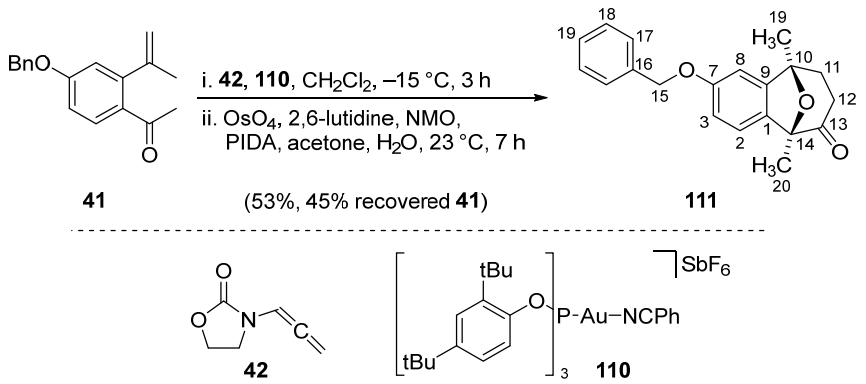


109 (85%) **41**

A mixture of benzyl ether **109** (2.14 g, 7.01 mmol, 1 equiv), potassium isopropenyltrifluoroborate (1.25 g, 8.41 mmol, 1.20 equiv), triethylamine (980 µL, 7.01 mmol, 1.00 equiv) and $PdCl_2$(dppf) (128 mg, 0.18 mmol, 0.025 equiv) in degassed (sparged with argon gas for 30 min prior to use) *n*-propanol (50 mL) was heated to 100 °C. After 4 h, the mixture was cooled to 23 °C and was then diluted with water (60 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (4 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 x 20 mL). The washed organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes) to provide styrene **41** (1.59 g, 85%) as a yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.37 (UV/$KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, $^3J_{2/3}$ = 8.6 Hz, 1H, 2-H), 7.49–7.29 (m, 5H, 17-H, 18-H, 19-H), 6.89 (dd, $^3J_{3/2}$ = 8.6 Hz, $^4J_{3/8}$ = 2.6 Hz, 1H, 3-H), 6.84 (d, $^4J_{8/3}$ = 2.6 Hz, 1H, 8-H), 5.16–5.13 (m, 1H, 11-H_A), 5.11 (s, 2H, 15-H), 4.90–4.87 (m, 1H, 11-H_B), 2.49 (s, 3H, 20-H), 2.10–2.07 (m, 3H, 19-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.20 (C-14), 160.91 (C-7), 146.29 (C-10), 146.14 (C-9), 136.40 (C-16), 131.56 (C-1), 131.16 (C-8), 128.82 (C-17, C-18), 128.36 (C-19), 127.69 (C-17, C-18), 115.67 (C-8), 115.38 (C-11), 112.91 (C-3), 70.24 (C-15), 29.66 (C-20), 24.14 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3078 (m), 2972 (m), 2915 (m), 1678 (s), 1594 (s), 1561 (s), 1454 (m), 1354 (m), 1306 (m), 1249 (s), 1218 (s), 1102 (m), 1055 (m), 1016 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{18}H_{18}O_2$)$^+$: 266.1301, found: 266.1313.

Synthesis of ketone 111



A mixture of flame-dried 4 Å MS (800 mg), styrene **41** (1.51 g, 5.67 mmol, 1 equiv) and gold catalyst **110**[68] (67.0 mg, 57.0 µmol, 0.01 equiv) in dichloromethane (10 mL) was cooled to –15 °C, whereupon a solution of known allenamide **42**[69] (710 mg, 5.67 mmol, 1.00 equiv) in dichloromethane (15 mL) was added dropwise over a period of 1 h. After complete addition, TLC analysis indicated incomplete conversion of styrene **41**. A second portion of gold catalyst **110** (67.0 mg, 57.0 µmol, 0.01 equiv) was added, followed by dropwise addition of a solution of allenamide **42** (710 mg, 5.67 mmol, 1.00 equiv) in dichloromethane (15 mL) over a period of 1 h. After end of the second addition, TLC analysis still indicated incomplete conversion of styrene **41**. The mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography (60% to 70% ethyl acetate in hexanes) to provide recovered styrene **41** (0.68 g, 45%) as a yellow oil, and enamide **43** (1.17 g, 53%, mixture of *E*-/*Z*- alkene isomers) as an off-white foam, which was used in the next step without further purification.

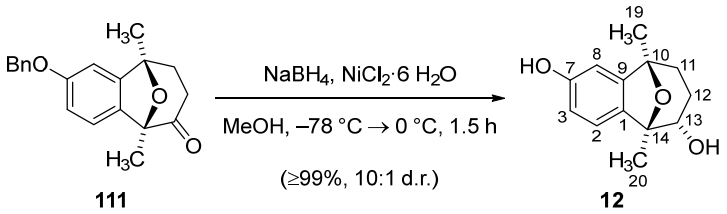
A solution of enamide **43** (1.17 g, 2.99 mmol, 1 equiv) in acetone (24 mL) and water (3 mL) was treated with 2,6-lutidine (700 µL, 5.98 mmol, 2.00 equiv), 4-methylmorpholine *N*-oxide (525 mg, 4.48 mmol, 1.50 equiv) and with osmium tetroxide solution (2.5 wt.% in *tert*-butanol, 880 µL, 0.09 mmol, 0.03 equiv) at 23 °C. After 7 h, (diacetoxyiodo)benzene (1.44 g, 4.48 mmol, 1.50 equiv) was added at 23 °C. After 45 min, the yellow cloudy mixture was diluted with saturated aqueous sodium thiosulfate solution (70 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes) to provide ketone **111** (866 mg, 53% over two steps) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.15 (UV/$KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5H, 17-H, 18-H, 19-H), 7.04 (d, $^3J_{2/3}$ = 8.1 Hz, 1H, 2-H), 6.88 (dd, $^3J_{3/2}$ = 8.1 Hz, $^4J_{3/8}$ = 2.2 Hz, 1H, 3-H), 6.85 (d, $^4J_{8/3}$ = 2.2 Hz, 1H, 8-H), 5.08 (s, 2H, 15-H), 2.44–2.28 (m, 2H, 11-H_A, 12-H_B), 2.20–2.07 (m, 1H, 12-H_B), 2.02–1.92 (m, 1H, 11-H_A), 1.70 (s, 3H, 19-H), 1.59 (s, 3H, 20-H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 204.66 (C-13), 160.31 (C-7), 147.86 (C-9), 136.70 (C-16), 135.71 (C-1), 128.80 (C-17, C-18), 128.32 (C-19), 127.71 (C-17, C-18), 121.84 (C-2), 113.82 (C-3), 108.09 (C-8), 87.88 (C-14), 83.39 (C-10), 70.64 (C-15), 37.20 (C-11), 33.19 (C-12), 23.58 (C-19), 16.47 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2981 (m), 2932 (m), 1721 (s), 1608 (m), 1592 (m), 1482 (m), 1453 (m), 1376 (m), 1348 (m), 1279 (m), 1224 (m), 1202 (m), 1074 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–CO], $C_{19}H_{20}O_2)^+$: 280.1463, found: 280.1460.

[68] a) H. Faustino, I. Alonso, J. L. Mascareñas, F. Lopez, *Angew. Chem. Int. Ed.* **2013**, *52*, 6526. b) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721.

[69] T. W. Bousfield, M. C. Kimber, *Tetrahedron Letters* **2015**, *56*, 350.

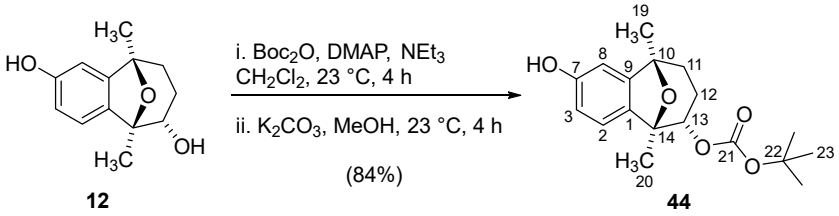
Synthesis of phenol 12



A solution of ketone **111** (120 mg, 389 µmol, 1 equiv) in methanol (3 mL) was treated with sodium borohydride (36.8 mg, 973 µmol, 2.50 equiv) at –78 °C. After 1 h, TLC analysis indicated complete conversion of the ketone starting material to a more polar product (i.e. complete reduction of the ketone to the corresponding alcohol). The mixture was warmed to 0 °C, whereupon nickel(II) chloride hexahydrate (185 mg, 778 µmol, 2.00 equiv) and more sodium borohydride (58.9 mg, 1.56 mmol, 4.00 equiv) were added, whereupon a black precipitate formed. Four further portions of sodium borohydride (36.8 mg, 973 µmol, 2.50 equiv) were added in 10 min intervals, whereupon TLC analysis indicated complete conversion of the polar intermediate to an even more polar product (i.e. complete benzyl ether cleavage). The mixture was diluted with saturated aqueous ammonium chloride solution (40 mL) and ethyl acetate (50 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% methanol in dichloromethane) to provide phenol **12** (86 mg, ≥99%, 10:1 d.r.) as a colorless oil. *Note: Traces of the minor diastereomer are visible in the ^{1}H and ^{13}C NMR spectra, but solely the resonances of the major diastereomer are listed below.*

TLC (10% methanol in dichloromethane): R_f = 0.30 (UV/CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (d, $^{3}J_{2/3}$ = 7.9 Hz, 1H, 2-H), 6.71 (dd, $^{3}J_{3/2}$ = 7.9 Hz, $^{4}J_{3/8}$ = 2.3 Hz, 1H, 3-H), 6.58 (d, $^{4}J_{8/3}$ = 2.3 Hz, 1H, 8-H), 5.53 (br s, 1H, 7-OH), 3.71–3.62 (m, 1H, 13-H), 1.92–1.80 (m, 2H, 11-H_A, 12-H_A), 1.59 (s, 3H, 20-H), 1.57–1.48 (m, 4H, 11-H_B, 19-H), 0.63–0.50 (m, 1H, 12-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.18 (C-7), 148.23 (C-9), 135.18 (C-1), 121.82 (C-2), 113.93 (C-3), 107.37 (C-8), 84.67 (C-14), 82.51 (C-10), 71.24 (C-13), 34.89 (C-11), 29.04 (C-12), 22.93 (C-19), 20.21 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3345 (br), 3055 (m), 2976 (m), 2933 (m), 1618 (m), 1453 (m), 1376 (m), 1265 (s), 1150 (m), 1058 (m), 1038 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M–H], $C_{13}H_{15}O_3)^-$: 219.10267, found: 219.10283.

Synthesis of carbonate 44



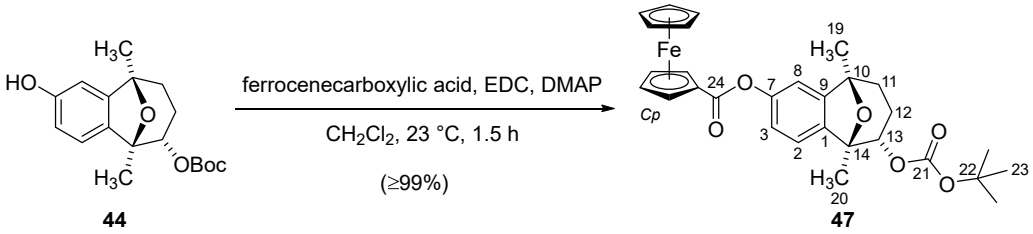
12 **44**

A solution of phenol **12** (77.1 mg, 0.35 mmol, 1 equiv) in dichloromethane (4 mL) was treated sequentially with triethylamine (0.73 mL, 5.25 mmol, 15.0 equiv), 4-dimethylaminopyridine (8.55 mg, 0.07 mol, 0.20 equiv) and di-*tert*-butyl dicarbonate (535 mg, 2.45 mmol, 7.00 equiv) at 23 °C. After 4 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (40 mL) and diethyl ether (30 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica (10% ethyl acetate in hexanes) to provide the *bis*-Boc protected compound, which was used in the next step without further purification.

A solution of the *bis*-Boc protected compound (assuming 0.35 mmol) in methanol (3 mL) was treated with potassium carbonate (48.4 mg, 0.35 mmol, 1.00 equiv) at 23 °C. After 4 h, the mixture was diluted with saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) to provide carbonate **44** (94.0 mg, 84% over two steps) as a colorless foam.

TLC (30% ethyl acetate in hexanes): R_f = 0.33 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.06 (d, $^3J_{2/3}$ = 7.9 Hz, 1H, 2-H), 6.72 (dd, $^3J_{3/2}$ = 7.9 Hz, $^4J_{3/8}$ = 2.3 Hz, 1H, 3-H), 6.56 (d, $^4J_{8/3}$ = 2.3 Hz, 1H, 8-H), 4.89 (s, 1H, 7-OH), 4.69 (dd, $^3J_{13/12A}$ = 10.4 Hz, $^3J_{13/12B}$ = 5.5 Hz, 1H, 13-H), 1.94–1.85 (m, 2H, 11-H_A, 12-H_B), 1.56 (s, 3H, 19-H), 1.56–1.52 (m, 4H, 11-H_B, 20-H), 1.47 (s, 9H, 23-H), 0.83–0.75 (m, 1H, 12-H_B). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 155.94 (C-7), 153.41 (C-21), 147.97 (C-9), 135.51 (C-1), 122.52 (C-2), 114.13 (C-3), 106.89 (C-8), 83.14 (C-14), 82.81 (C-10), 82.17 (C-22), 75.33 (C-13), 34.42 (C-11), 27.96 (C-23), 25.04 (C-12), 22.87 (C-19), 20.30 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3368 (br), 2977 (m), 2934 (m), 1739 (s), 1710 (m), 1619 (m), 1459 (m), 1369 (m), 1315 (m), 1277 (s), 1255 (m), 1159 (s), 1095 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{18}H_{24}O_5)^+$: 320.1618, found: 320.1619.

Synthesis of ferrocenecarboxylate ester 47



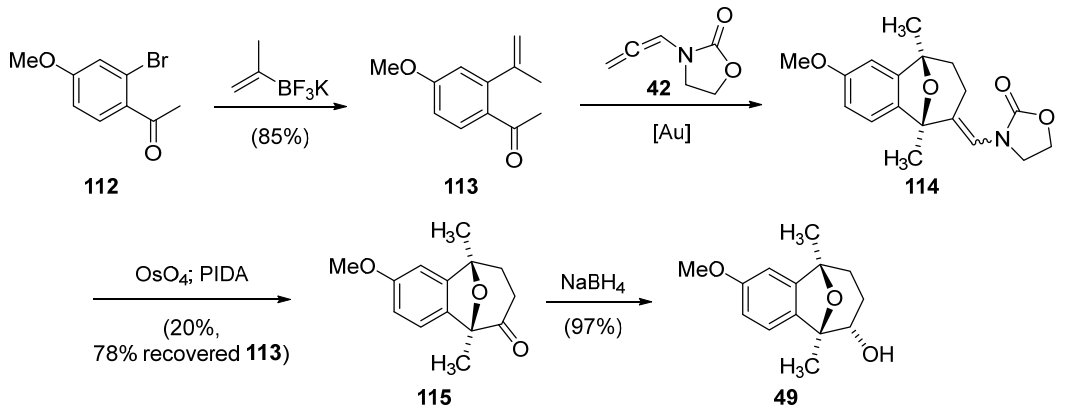
44 **47**

A solution of carbonate **44** (20.0 mg, 62.4 µmol, 1 equiv) in dichloromethane (1 mL) was treated sequentially with triethylamine (10.4 µL, 74.9 µmol, 1.20 equiv), 4-dimethylaminopyridine (7.63 mg, 62.4 µmol, 1.00 equiv), ferrocenecarboxylic acid (17.2 mg, 74.9 µmol, 1.20 equiv), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (14.4 mg, 74.9 µmol, 1.20 equiv) at 23 °C. After 1.5 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (5 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 8 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in hexanes) to provide ferrocenecarboxylate ester **47** (33 mg, ≥99%) as an orange solid.

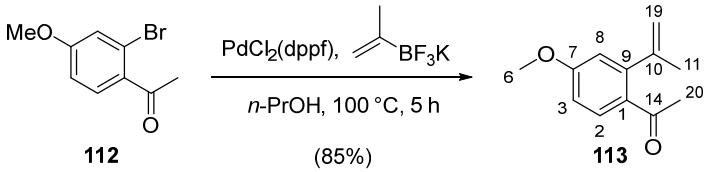
Recrystallization of the product from ethyl acetate/hexanes gave crystals suitable for X-ray diffraction. **TLC** (20% ethyl acetate in hexanes): R_f = 0.31 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27–7.25 (m, 1H, 2-H), 7.10 (dd, $^3J_{3/2}$ = 7.9 Hz, $^4J_{3/8}$ = 2.1 Hz, 1H, 3-H), 6.90 (dd, $^4J_{8/3}$ = 2.1 Hz, $^5J_{8/2}$ = 0.5 Hz, 1H, 8-H), 4.97–4.95 (m, 2H, *Cp*), 4.72 (dd, $^3J_{13/12A}$ = 10.3 Hz, $^3J_{13/12B}$ = 5.7 Hz, 1H, 13-H), 4.52–4.50 (m, 2H, *Cp*), 4.31 (s, 5H, *Cp*), 1.99–1.89 (m, 2H, 11-H_A, 12-H_B), 1.63–1.60 (m, 4H, 11-H_B, 19-H), 1.59 (s, 3H, 20-H), 1.48 (s, 9H, 23-H), 0.91–0.81 (m, 1H, 12-H_B). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.53 (C-24), 153.36 (C-21), 151.13 (C-7), 147.52 (C-9), 140.40 (C-1), 122.47 (C-2), 120.78 (C-3), 113.17 (C-8), 83.25 (C-14), 82.95 (C-10), 82.18 (C-22), 75.08 (C-13), 72.12 (*Cp*), 70.78 (*Cp*), 70.12 (*Cp*), 34.36 (C-11), 27.96 (C-23), 25.03 (C-12), 22.92 (C-19), 20.24 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (m), 2933 (m), 1731 (s), 1454 (m), 1375 (m), 1312 (m), 1277 (s), 1256 (s), 1185 (s), 1160 (s), 1097 (s), 1051 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+NH_4], $C_{29}H_{36}O_6NFe)^+$: 550.18920, found: 550.18843.

Birch Reduction Route

Anisole **49** was prepared according to the following synthetic route.



Synthesis of styrene 113

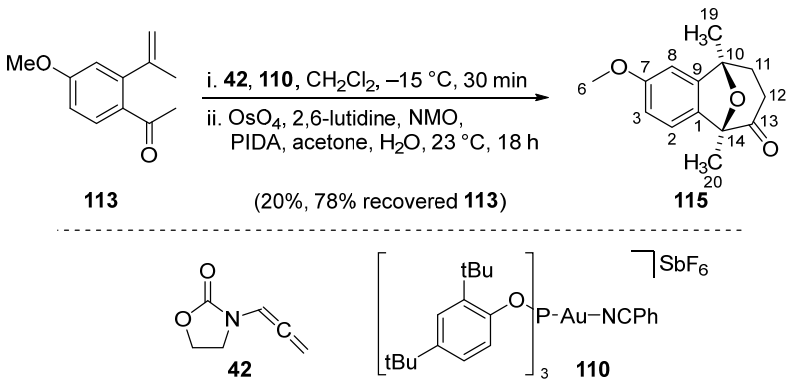


A mixture of the known bromide **112**[70] (6.00 g, 26.2 mmol, 1 equiv), potassium isopropenyltrifluoroborate (4.84 g, 32.7 mmol, 1.25 equiv), triethylamine (3.64 mL, 26.2 mmol, 1.00 equiv) and $PdCl_2$(dppf) (575 mg, 0.79 mmol, 0.03 equiv) in degassed (sparged with argon gas for 30 min prior to use) *n*-propanol (200 mL) was heated to 100 °C. After 5 h, the mixture was cooled to 23 °C and was then diluted with water (150 mL) and diethyl ether (100 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (4 x 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (3 x 100 mL). The washed organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate in hexanes) to provide styrene **113** (4.23 g, 85%) as a yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.48 (UV/$KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, $^3J_{2/3}$ = 8.5 Hz, 1H, 2-H), 6.82 (dd, $^3J_{3/2}$ = 8.5 Hz, $^4J_{3/8}$ = 2.6 Hz, 1H, 3-H), 6.75 (d, $^4J_{8/3}$ = 2.6 Hz, 1H, 8-H), 5.16–5.12 (m, 1H, 19-H_A), 4.90–4.87 (m, 1H, 19-H_B), 3.85 (s, 3H, 6-H), 2.49 (s, 3H, 20-H), 2.11–2.07 (m, 3H, 11-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.99 (C-14), 161.64 (C-7), 146.29 (C-10), 146.06 (C-9), 131.30 (C-1), 131.06 (C-2), 115.13 (C-19), 114.60 (C-8), 112.05 (C-3), 55.43 (C-6), 29.51 (C-20), 24.05 (C-11). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3079 (w), 2969 (w), 1677 (s), 1595 (s), 1560 (m), 1457 (m), 1354 (m), 1303 (m), 1247 (s), 1227 (s), 1181 (m), 1060 (m), 1027 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{12}H_{14}O_2$)$^+$: 190.0988, found: 190.0978.

[70] Q. Chen, X. Huo, H. Zheng, X. She, *Synlett* **2012**, *23*, 1349.

Synthesis of ketone 115

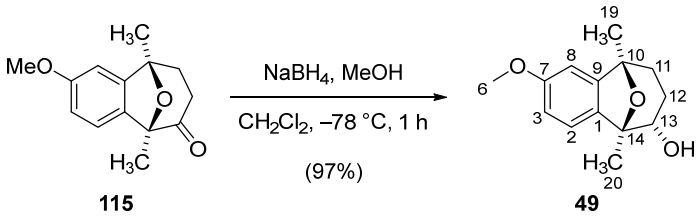


A mixture of flame-dried 4 Å MS (700 mg), styrene **113** (6.69 g, 35.2 mmol, 2.00 equiv) and gold catalyst **110**[68] (270 mg, 0.105 mmol, 0.013 equiv) in dichloromethane (90 mL) was cooled to –15 °C, whereupon known allenamide **42**[69] (2.20 g, 17.6 mmol, 1 equiv) was added. After 30 min, the cooling bath was removed and the deep red mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography (30% to 80% ethyl acetate in hexanes) to provide recovered styrene **113** (5.20 g, 78%) as a yellow oil, and the enamide product (1.49 g, 27%, mixture of *E*-/*Z*-alkene isomers) as a yellow solid, which was used in the next step without further purification.

A solution of the enamide (1.40 g, 4.44 mmol, 1 equiv) in acetone (36 mL) and water (4 mL) was treated with 2,6-lutidine (1.03 mL, 8.88 mmol, 2.00 equiv), 4-methylmorpholine *N*-oxide (780 mg, 6.66 mmol, 1.50 equiv) and with osmium tetroxide solution (4 wt.% in water, 543 µL, 0.09 mmol, 0.02 equiv) at 23 °C. After 18 h, (diacetoxyiodo)benzene (2.15 g, 6.66 mmol, 1.50 equiv) was added at 23 °C. After 1 h, the yellow cloudy mixture was diluted with saturated aqueous sodium thiosulfate solution (100 mL) and diethyl ether (50 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes) to provide ketone **115** (820 mg, 20% over two steps) as a colorless solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.40 (UV/$KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04 (d, $^3J_{2/3}$ = 8.2 Hz, 1H, 2-H), 6.80 (dd, $^3J_{3/2}$ = 8.2 Hz, $^4J_{3/8}$ = 2.1 Hz, 1H, 3-H), 6.75 (d, $^4J_{8/3}$ = 2.1 Hz, 1H, 8-H), 3.84 (s, 3H, 6-H), 2.42–2.27 (m, 2H, 11-H_A, 12-H_A), 2.18–2.06 (m, 1H, 12-H_B), 2.01–1.94 (m, 1H, 11-H_B), 1.71 (s, 3H, 19-H), 1.58 (s, 3H, 20-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.60 (C-13), 160.95 (C-7), 147.64 (C-9), 135.23 (C-1), 121.66 (C-2), 112.87 (C-3), 106.88 (C-8), 87.67 (C-14), 83.25 (C-10), 55.63 (C-6), 37.02 (C-11), 33.02 (C-12), 23.44 (C-19), 16.33 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2980 (w), 2934 (w), 1718 (s), 1609 (m), 1592 (m), 1483 (m), 1278 (m), 1228 (m), 1072 (m), 1047 (m), 1022 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{14}H_{16}O_3$)$^+$: 232.1094, found: 232.1087.

Synthesis of anisole 49

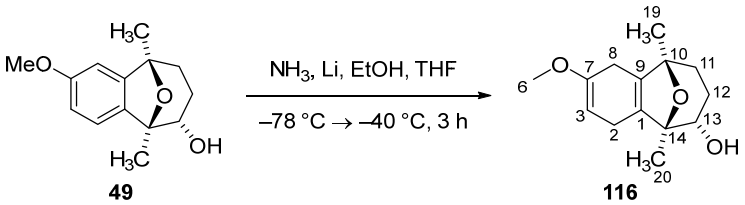


115 **49**

A solution of ketone **115** (820 mg, 3.53 mmol, 1 equiv) in a mixture of methanol (9 mL) and dichloromethane (9 mL) was treated with sodium borohydride (267 mg, 7.06 mmol, 2.00 equiv) at –78 °C. After 1 h, saturated aqueous ammonium chloride solution (40 mL) and ethyl acetate (50 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40% ethyl acetate in hexanes) to provide anisole **49** (800 mg, 97%) as a colorless foam.

TLC (40% ethyl acetate in hexanes): R_f = 0.24 (UV/CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.07 (d, $^3J_{2/3}$ = 8.1 Hz, 1H, 2-H), 6.80 (dd, $^3J_{3/2}$ = 8.1 Hz, $^4J_{3/8}$ = 2.4 Hz, 1H, 3-H), 6.65 (d, $^4J_{8/3}$ = 2.4 Hz, 1H, 8-H), 3.83 (s, 3H, 6-H), 3.68–3.64 (m, 1H, 13-H), 1.90–1.81 (m, 2H, 11-H_A, 12-H_A), 1.60 (s, 3H, 20-H), 1.58 (s, 3H, 19-H), 1.56–1.51 (m, 1H, 11-H_B), 1.06 (br s, 1H, 13-OH), 0.59–0.50 (m, 1H, 12-H_B). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.17 (C-7), 148.07 (C-9), 135.44 (C-1), 121.63 (C-2), 111.98 (C-3), 106.36 (C-8), 84.57 (C-14), 82.46 (C-10), 71.25 (C-13), 55.72 (C-6), 35.00 (C-11), 29.17 (C-12), 23.00 (C-19), 20.25 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3433 (br), 2970 (m), 2932 (m), 1614 (m), 1593 (m), 1485 (m), 1453 (m), 1428 (m), 1355 (m), 1278 (m), 1227 (m), 1216 (m), 1057 (s), 1024 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{14}H_{18}O_3)^+$: 234.1250, found: 234.1249.

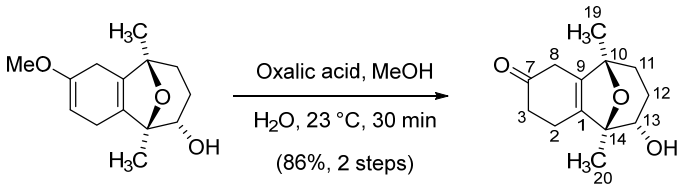
Synthesis of enol ether 116



49 **116**

Lithium metal (815 mg, 117 mmol, 25.0 equiv) was added portionwise to freshly condensed ammonia (100 mL) at –78 °C, whereupon the mixture turned deep blue. After 15 min, a solution of anisole **49** (1.10 g, 4.69 mmol, 1 equiv) in tetrahydrofuran (15 mL) was added dropwise at –78 °C. The mixture was then slowly warmed to –40 °C over a period of 3 h, whereupon ethanol (25 mL) was added, after which the blue colour faded. The cooling bath was then removed, and the ammonia was allowed to evaporate overnight. The resulting residue was dissolved in saturated aqueous sodium hydrogen carbonate solution (150 mL) and ethyl acetate (70 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 x 70 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (2 x 40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to afford the crude enol ether **116** (1.10 g) as a colourless oil, which was used in the next step without further purification.

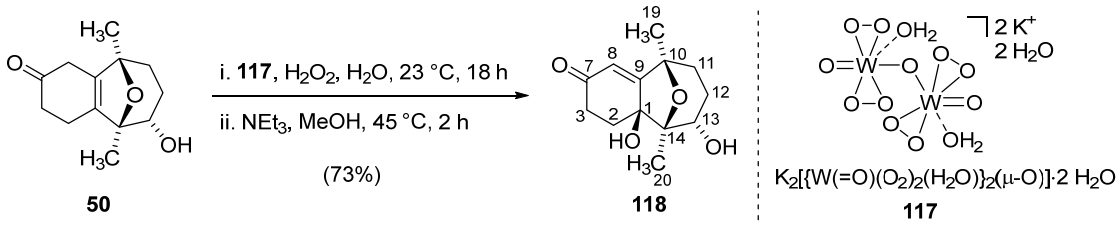
Synthesis of ketone 50



116 **50**

A solution of the crude enol ether **116** (270 mg, 1.14 mmol, 1 equiv) in methanol (17 mL) was treated with a solution of oxalic acid (309 mg, 3.43 mmol, 3.00 equiv) in water (3 mL) at 23 °C. After 30 min, the mixture was diluted with water (10 mL) and ethyl acetate (50 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (4 x 50 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (6% methanol in dichloromethane) to provide ketone **50** (219 mg, 86% over two steps) as a colorless oil which solidified upon standing.
Recrystallization of the product from diethyl ether/hexanes gave crystals suitable for X-ray diffraction. **TLC** (5% methanol in dichloromethane): R_f = 0.20 (UV/CAM). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 3.54–3.48 (m, 1H, 13-H), 2.96–2.88 (m, 1H, 8-H_A), 2.70–2.62 (m, 1H, 8-H_B), 2.59–2.49 (m, 4H, 2-H, 3-H), 1.94–1.86 (m, 1H, 12-H_A), 1.56–1.43 (m, 2H, 11-H), 1.34 (s, 3H, 20-H), 1.30–1.22 (m, 1H, 12-H_B), 1.20 (s, 3H, 19-H). **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 209.49 (C-7), 137.40 (C-1), 136.52 (C-9), 86.26 (C-14), 83.68 (C-10), 71.20 (C-13), 38.79 (C-3), 36.50 (C-8), 31.22 (C-11), 29.20 (C-12), 23.41 (C-2), 21.99 (C-19), 19.35 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3432 (br), 2968 (m), 2931 (m), 1712 (s), 1448 (m), 1373 (m), 1182 (m), 1065 (m), 1053 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{13}H_{18}O_3$)$^+$: 222.1250, found: 222.1250.

Synthesis of enone 118



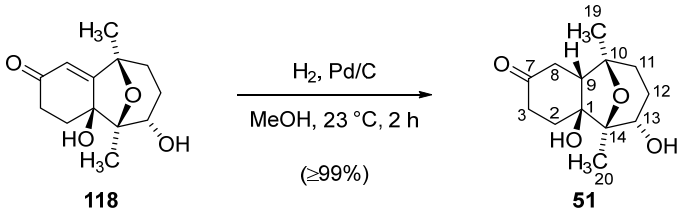
A mixture of ketone **50** (42.0 mg, 189 µmol, 1 equiv) in water (0.4 mL) was treated sequentially with tungstate catalyst **117**[71] (26.2 mg, 37.8 µmol, 0.20 equiv) and hydrogen peroxide solution (30 wt.% in water, 38.6 µL, 378 µmol, 2.00 equiv) at 23 °C. After 18 h, the mixture was diluted with saturated aqueous sodium chloride solution (10 mL) and ethyl acetate (15 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the crude epoxide, which was used in the next step without further purification.

A solution of the crude epoxide (assuming 189 µmol) in methanol (4 mL) was treated with triethylamine (0.25 mL) and the resulting mixture was heated to 45 °C. After 2 h, the mixture was cooled to 23 °C and then was concentrated in vacuo. The residue was purified by flash-column chromatography (7% methanol in dichloromethane) to provide enone **118** (32.6 mg, 73% over two steps) as a colorless foam.

TLC (5% methanol in dichloromethane): R_f = 0.13 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 5.73 (s, 1H, 8-H), 3.81 (dd, $^3J_{13/12A}$ = 11.6 Hz, $^3J_{13/12B}$ = 6.2 Hz, 1H, 13-H), 2.91–2.85 (m, 1H, 3-H_A), 2.56–2.51 (m, 1H, 2-H_A), 2.45–2.40 (m, 1H, 3-H_B), 2.24 (br s, 1H, OH), 2.04 (ddd, $^2J_{2B/2A}$ = 14.2 Hz, $^3J_{2B/3A}$ = 5.4 Hz, $^3J_{2B/3B}$ = 1.7 Hz, 1H, 2-H_B), 1.93–1.85 (m, 2H, 11-H_A, 12-H_A), 1.74 (br s, 1H, OH), 1.66–1.62 (m, 1H, 11-H_B), 1.59–1.52 (m, 1H, 12-H_B), 1.47 (s, 3H, 19-H), 1.44 (s, 3H, 20-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 199.87 (C-7), 172.00 (C-9), 120.15 (C-8), 85.75 (C-14), 80.70 (C-10), 77.87 (C-1), 73.40 (C-13), 37.63 (C-11), 32.96 (C-3), 27.78 (C-12), 27.19 (C-2), 23.79 (C-19), 17.59 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3428 (br), 2936 (m), 2876 (m), 1667 (s), 1446 (m), 1376 (m), 1330 (m), 1292 (m), 1206 (m), 1121 (m), 1068 (s), 1007 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{13}H_{19}O_4$)$^+$: 239.12833, found: 239.12788.

[71] a) N. J. Campbell, A. C. Dengel, C. J. Edwards, W. P. Griffith, J. *Chem. Soc. Dalton Trans.* **1989**, 1203. b) K. Kamata, K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2004**, *10*, 4728.

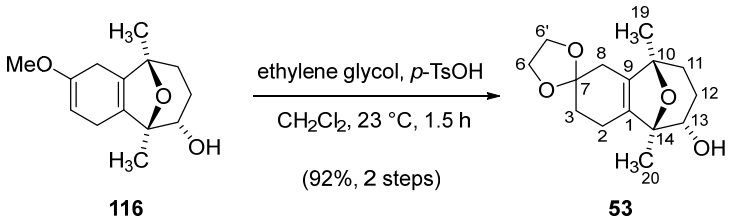
Synthesis of diol 51



A solution of enone **118** (21.0 mg, 881 µmol, 1 equiv) in methanol (5 mL) was treated with palladium on carbon (10 wt.%, 13.1 mg, 12.3 µmol, 0.15 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 2 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 2 h, the mixture was diluted with dichloromethane (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated to provide spectroscopically pure diol **51** as a colourless oil (22 mg, ≥99%).

TLC (5% methanol in dichloromethane): R_f = 0.11 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 3.82 (dd, $^3J_{13/12A}$ = 11.1 Hz, $^3J_{13/12B}$ = 6.9 Hz, 1H, 13-H), 2.62–2.56 (m, 1H, 3-H_A), 2.52 (app td, $^2J_{2A/2B}$ = $^3J_{2A/3A}$ = 14.4 Hz, $^3J_{2A/3B}$ = 4.0 Hz, 1H, 2-H_A), 2.41 (dd, $^2J_{8A/8B}$ = 15.6 Hz, $^3J_{8A/9}$ = 13.9 Hz, 1H, 8-H_A), 2.38–2.31 (m, 2H, 3-H_B, 8-H_B), 2.09 (dd, $^3J_{9/8A}$ = 13.9 Hz, $^3J_{9/8B}$ = 6.4 Hz, 1H, 9-H), 2.01–1.96 (m, 1H, 12-H_A), 1.85–1.81 (m, 1H, 2-H_B), 1.80 (br s, 1H, 13-OH), 1.77–1.68 (m, 2H, 11-H_A, 12-H_B), 1.68–1.60 (m, 2H, 1-OH, 11-H_B), 1.41 (s, 3H, 20-H), 1.29 (s, 3H, 19-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 212.18 (C-7), 86.21 (C-14), 82.27 (C-1), 80.33 (C-10), 74.29 (C-13), 58.00 (C-9), 38.33 (C-8), 34.20 (C-3), 32.30 (C-11), 27.49 (C-12), 26.91 (C-19), 26.45 (C-2), 19.84 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3426 (br), 2962 (m), 2931 (m), 1702 (s), 1448 (m), 1401 (m), 1378 (m), 1222 (m), 1184 (m), 1114 (m), 1067 (s), 977 (s) cm^{-1}. **HRMS** (ESI): calcd for ($[M+HCO_2]$, $C_{14}H_{21}O_6)^-$: 285.13381, found: 285.13452.

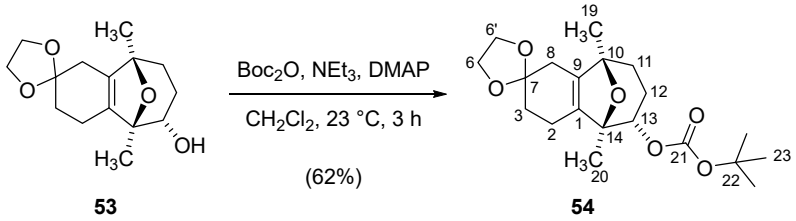
Synthesis of acetal 53



A solution of the crude enol ether **116** (315 mg, 1.33 mmol, 1 equiv) in dichloromethane (3 mL) was treated with ethylene glycol (0.37 mL, 6.66 mmol, 5.00 equiv) and *p*-toluenesulfonic acid monohydrate (25.4 mg, 0.13 mmol, 0.10 equiv) at 23 °C. After 1.5 h, the mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (2 x 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% methanol in dichloromethane) to provide acetal **53** (327 mg, 92% over two steps) as a colorless oil.

TLC (5% methanol in dichloromethane): R_f = 0.27 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04–3.94 (m, 4H, 6-H, 6'-H), 3.55–3.47 (m, 1H, 13-H), 2.40–2.27 (m, 3H, 2-H, 8-H_A), 2.05–1.98 (m, 1H, 8-H_B), 1.92–1.73 (m, 3H, 3-H, 12-H_A), 1.57–1.51 (m, 1H, 11-H_A), 1.48–1.41 (m, 1H, 11-H_B), 1.38 (s, 3H, 20-H), 1.37–1.32 (m, 1H, 12-H_B), 1.27–1.24 (m, 1H, 13-OH), 1.23 (s, 3H, 19-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.32 (C-9), 135.96 (C-1), 109.09 (C-7), 85.79 (C-14), 83.61 (C-10), 71.29 (C-13), 64.78 (C-6, C-6'), 64.59 (C-6, C-6'), 32.48 (C-8), 31.23 (C-3), 31.11 (C-11), 28.60 (C-12), 21.83 (C-19), 21.78 (C-2), 19.16 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444 (br), 2929 (s), 1447 (m), 1372 (m), 1274 (m), 1112 (s), 1062 (s), 1037 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{22}O_4)^+$: 266.1513, found: 266.1512.

Synthesis of carbonate 54

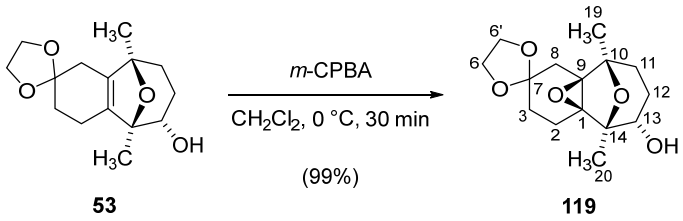


53 **54**

A solution of acetal **53** (54.0 mg, 0.20 mmol, 1 equiv) in dichloromethane (2.5 mL) was treated sequentially with triethylamine (0.28 mL, 2.03 mmol, 10.0 equiv), 4-dimethylaminopyridine (5.0 mg, 0.04 mmol, 0.20 equiv) and di-*tert*-butyl dicarbonate (133 mg, 0.61 mmol, 3.00 equiv) at 23 °C. After 3 h, TLC analysis indicated still incomplete conversion of acetal **53**, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (30 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in hexanes) to provide carbonate **54** (46.0 mg, 62%) as a colorless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.40 (CAM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.53–4.48 (m, 1H, 13-H), 4.04–3.95 (m, 4H, 6-H, 6'-H), 2.40–2.20 (m, 3H, 2-H, 8-H_A), 2.05–1.91 (m, 2H, 8-H_B, 12-H_A), 1.87–1.74 (m, 2H, 3-H), 1.62–1.56 (m, 1H, 11-H_A), 1.50–1.41 (m, 11H, 11-H_B, 12-H_B, 23-H), 1.30 (s, 3H, 20-H), 1.23 (s, 3H, 19-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.52 (C-21), 136.66 (C-9), 135.76 (C-1), 108.99 (C-7), 84.69 (C-14), 83.97 (C-10), 81.87 (C-22), 75.11 (C-13), 64.77 (C-6, C-6'), 64.64 (C-6, C-6'), 32.45 (C-8), 31.26 (C-3), 30.58 (C-11), 27.95 (C-23), 24.95 (C-12), 21.74 (C-19), 21.04 (C-2), 19.14 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (m), 2932 (m), 1738 (s), 1449 (w), 1371 (m), 1315 (m), 1277 (s), 1254 (s), 1163 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{30}O_6$)$^+$: 366.2037, found: 366.2034.

Synthesis of epoxide 119



53 **119**

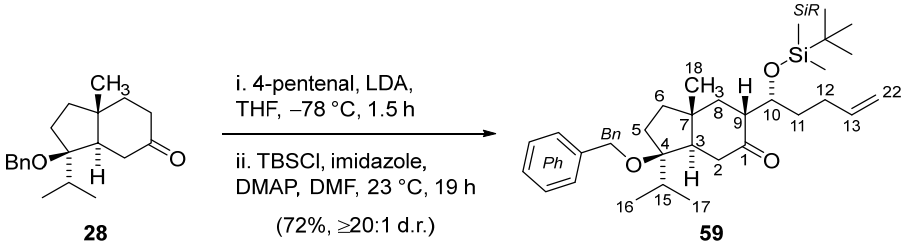
A solution of acetal **53** (97.0 mg, 0.36 mmol, 1 equiv) in dichloromethane (2 mL) was treated with *meta*-chloroperoxybenzoic acid (126 mg, 0.55 mmol, 1.50 equiv) at 0 °C. After 30 min, the mixture was diluted with ethyl acetate (30 mL) and the organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (2 x 15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (4% methanol in dichloromethane) to provide epoxide **119** (102 mg, 99%) as a colorless foam.

TLC (5% methanol in dichloromethane): R_f = 0.19 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 4.00–3.88 (m, 4H, 6-H, 6'-H), 3.66 (dd, $^3J_{13/12A}$ = 11.1 Hz, $^3J_{13/12B}$ = 6.0 Hz, 1H, 13-H), 2.41–2.36 (m, 1H, 2-H_A), 2.12 (d, $^2J_{8A/8B}$ = 15.4 Hz, 1H, 8-H_A), 2.11–2.01 (m, 2H, 2-H_B, 12-H_A), 1.93 (dd, $^2J_{8B/8A}$ = 15.4 Hz, $^4J_{8B/3B}$ = 2.0 Hz, 1H, 8-H_B), 1.82–1.67 (m, 4H, 3-H_A, 11-H, 12-H_B), 1.55–1.51 (m, 1H, 3-H_B), 1.31 (s, 3H, 20-H), 1.19 (s, 3H, 19-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 107.88 (C-7), 80.25 (C-14), 78.26 (C-10), 72.77 (C-13), 65.14 (C-9), 64.69 (C-6, C-6'), 64.62 (C-1), 64.41 (C-6, C-6'), 32.55 (C-11), 32.03 (C-8), 27.70 (C-3), 26.60 (C-12), 19.82 (C-2), 18.43 (C-19), 15.85 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3458 (br), 2931 (s), 2883 (m), 1447 (s), 1367 (s), 1204 (m), 1131 (s), 1107 (s), 1031 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{15}H_{22}O_5)^+$: 282.1462, found: 282.1454.

6.5.3 Experimental Procedures: Bioinspired S_N2 Approach

Synthesis of Tricycle 63a

Synthesis of silyl ether 59

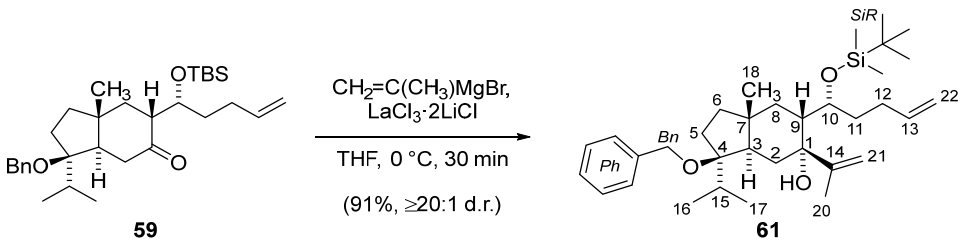


A solution of ketone **28** (1.00 g, 3.33 mmol, 1 equiv) in tetrahydrofuran (9.5 mL) was treated with a freshly prepared solution of lithium diisopropylamide (1 M in THF, 3.66 mL, 3.66 mmol, 1.10 equiv) at −78 °C (addition to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture). After 40 min, a solution of 4-pentenal (0.41 mL, 3.99 mmol, 1.20 equiv) in tetrahydrofuran (4.3 mL) was added dropwise over a period of 5 min. After 1.5 h, the orange mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude aldol product **58**, which was used in the next step without further purification.

A solution of the crude aldol product **58** (assuming 3.33 mmol) in dimethyl formamide (6.7 mL) was treated sequentially with imidazole (0.68 g, 9.99 mmol, 3.00 equiv), 4-dimethylaminopyridine (40.7 mg, 0.33 mmol, 0.10 equiv) and *tert*-butyldimethylchlorosilane (0.65 g, 4.33 mmol, 1.30 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 19 h, the mixture was diluted with pH 7 buffer solution (40 mL), water (20 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) to provide silyl ether **59** (1.20 g, 72% over two steps) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.29 (CAM). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H, *Ph*), 5.89–5.80 (m, 1H, 13-H), 5.06–5.01 (m, 1H, 22-H_A), 4.97–4.93 (m, 1H, 22-H_B), 4.43–4.39 (m, 2H, *Bn*), 4.31–4.25 (m, 1H, 10-H), 2.77–2.70 (m, 1H, 2-H_A), 2.65–2.59 (m, 1H, 9-H), 2.42 (dd, $^2J_{2B/2A}$ = 16.1 Hz, $^3J_{2B/3}$ = 3.9 Hz, 1H, 2-H_B), 2.34–2.15 (m, 3H, 5-H_A, 12-H_A, 15-H), 2.08–2.00 (m, 2H, 8-H_A, 12-H_B), 1.89 (dd, $^2J_{5B/5A}$ = 14.0 Hz, $^3J_{5B/6B}$ =8.1 Hz, 1H, 5-H_B), 1.75–1.70 (m, 2H, 3-H, 6-H_A), 1.48–1.41 (m, 3H, 8-H_B, 11-H), 1.28–1.20 (m, 1H, 6-H_B), 1.19 (s, 3H, 18-H), 0.94 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.92 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.88 (s, 9H, *SiR*), 0.06 (s, 3H, *SiR*), 0.03 (s, 3H, *SiR*). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 212.78 (C-1), 139.84 (*Ph*), 139.05 (C-13), 128.35 (*Ph*), 127.06 (*Ph*), 126.89(*Ph*) , 114.51 (C-14), 87.57 (C-4), 70.78 (C-10), 62.58 (*Bn*), 52.32 (C-9), 49.85 (C-3), 41.82 (C-7), 41.71 (C-2), 40.25 (C-6), 37.55 (C-8), 34.78 (C-5), 33.00 (C-15), 32.90 (C-11), 31.10 (C-12), 26.04 (*SiR*), 18.72 (C-18), 18.34 (C-16, C-17), 18.21 (*SiR*), 17.84 (C-16, C-17), –4.31 (*SiR*), –4.45 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (s), 2924 (s), 2856 (m), 1700 (s), 1471 (m), 1387 (m), 1255 (m), 1067 (s), 1046 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{31}H_{51}O_3Si)^+$: 499.36075, found: 499.36045. $[\alpha]_D^{20}$ = +28.8° (c = 1.00, CH_2Cl_2).

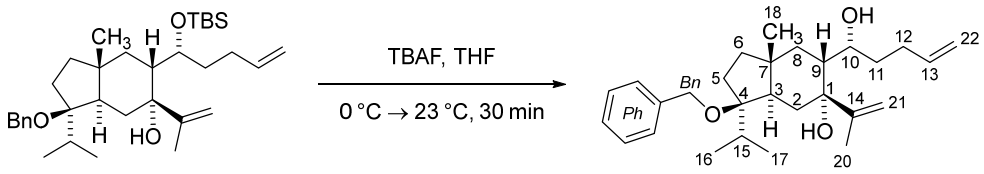
Synthesis of allylic alcohol 61



A solution of silyl ether **59** (1.15 g, 2.31 mmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 5.01 mL, 2.31 mmol, 1.00 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon isopropenylmagnesium bromide solution (0.5 M in THF, 13.8 mL, 6.92 mmol, 3.00 equiv) was added dropwise over a period of 20 min (syringe pump). After end of the addition, stirring was continued for 10 min, before the mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) to provide allylic alcohol **61** (1.14 g, 91%) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.26 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.40–7.37 (m, 2H, *Ph*), 7.24–7.19 (m, 2H, *Ph*), 7.12–7.08 (m, 1H, *Ph*), 5.87–5.81 (m, 1H, 13-H), 5.30–5.27 (m, 1H, 21-H_A), 5.12–5.08 (m, 1H, 22-H_A), 5.02–4.99 (m, 1H, 22-H_B), 4.90–4.87 (m, 1H, 21-H_B), 4.30–4.24 (m, 2H, *Bn*), 3.80–3.76 (m, 1H, 10-H), 2.70 (br s, 1H, 1-OH), 2.27 (app t, $^2J_{2A/2B} = {}^3J_{2A/3}$ = 13.4 Hz, 1H, 2-H_A), 2.24–2.15 (m, 3H, 3-H, 11-H_A, 12-H_A), 2.13–2.00 (m, 4H, 5-H_A, 9-H, 12-H_B, 15-H), 1.87 (app t, $^2J_{8A/8B} = {}^3J_{8A/9}$ = 12.4 Hz, 1H, 8-H_A), 1.74 (s, 3H, 20-H), 1.70 (dd, $^2J_{8B/8A}$ = 12.4 Hz, $^3J_{8B/9}$ = 3.9 Hz, 1H, 8-H_B), 1.69–1.62 (m, 3H, 5-H_B, 6-H_B, 11-H_B), 1.58 (dd, $^2J_{2B/2A}$ = 13.4 Hz, $^3J_{2B/3}$ = 2.3 Hz, 1H, 2-H_B), 1.31–1.24 (m, 1H, 6-H_B), 1.22 (s, 3H, 18-H), 0.99 (s, 9H, *SiR*), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.09 (s, 3H, *SiR*), 0.06 (s, 3H, *SiR*). **^{13}C NMR** (200 MHz, C_6D_6) δ 152.59 (C-14), 140.63 (*Ph*), 139.09 (C-13), 128.54 (*Ph*), 127.34 (*Ph*), 127.18 (*Ph*), 114.73 (C-22), 110.38 (C-21), 88.64 (C-4), 78.51 (C-1), 76.72 (C-10), 63.20 (*Bn*), 45.26 (C-3), 42.67 (C-7), 41.43 (C-9), 41.26 (C-6), 40.11 (C-8), 38.20 (C-2), 34.67 (C-11), 34.18 (C-5), 33.17 (C-15), 31.82 (C-12), 26.18 (*SiR*), 20.18 (C-20), 19.11 (C-18), 18.58 (C-16, C-17), 18.42 (C-16, C-17), 18.37 (*SiR*), –4.02 (*SiR*), –4.06 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (m), 2953 (s), 2928 (s), 2857 (m), 1713 (m), 1471 (m), 1386 (m), 1360 (m), 1254 (m), 1058 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{34}H_{57}O_3Si)^+$: 541.40770, found: 541.40760. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +25.0° (c = 1.00, CH_2Cl_2).

Synthesis of diol 120



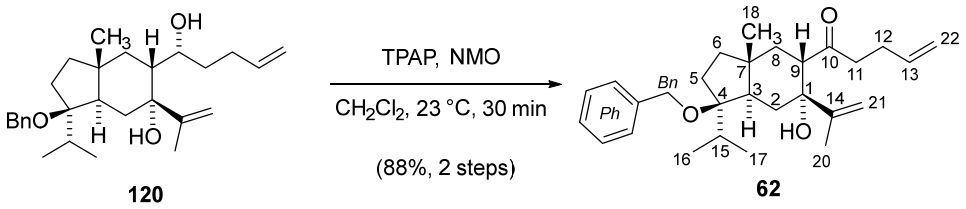
61 **120**

A solution of allylic alcohol **61** (0.41 g, 0.76 mmol, 1 equiv) in tetrahydrofuran (7 mL) was treated with tetrabutylammonium fluoride solution (1 M in THF, 0.91 mL, 0.91 mmol, 1.20 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 25 min, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (30 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide diol **120** as a yellowish oil, which was used in the next step without further purification.

An analytically pure sample of diol **120** was obtained by flash-column chromatography (7% ethyl acetate in hexanes).

TLC (10% ethyl acetate in hexanes): R_f = 0.11 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.37–7.35 (m, 2H, *Ph*), 7.22–7.19 (m, 2H, *Ph*), 7.11–7.08 (m, 1H, *Ph*), 5.81 (app ddt, $^3J_{13/22A}$ = 17.0 Hz, $^3J_{13/22B}$ = 10.2 Hz, $^3J_{13/12}$ = 6.7 Hz, 1H, 13-H), 5.21–5.19 (m, 1H, 21-H_A), 5.06 (app dq, $^3J_{22A/13}$ = 17.0 Hz, $^2J_{22A/22B}$ = $^4J_{22A/12}$ = 1.7 Hz, 1H, 22-H_A), 4.99–4.97 (m, 1H, 22-H_B), 4.76–4.74 (m, 1H, 21-H_B), 4.28–4.23 (m, 2H, *Bn*), 3.54–3.51 (m, 1H, 10-H), 2.65 (br s, 1H, 1-OH, 10-OH), 2.26–2.16 (m, 2H, 2-H_A, 12-H_A), 2.11 (dd, $^3J_{3/2A}$ = 12.9 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 2.10–1.99 (m, 4H, 5-H_A, 9-H, 12-H_B, 15-H), 1.74–1.71 (m, 3H, 20-H), 1.68–1.51 (m, 6H, 2-H_B, 5-H_B, 6-H_A, 8-H_A, 11-H), 1.42 (dd, $^2J_{8B/8A}$ = 12.4 Hz, $^3J_{8B/9}$ = 4.4 Hz, 1H, 8-H_B), 1.22–1.16 (m, 1H, 6-H_B), 1.12 (s, 3H, 18-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.96 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 155.33 (C-14), 140.54 (*Ph*), 139.19 (C-13), 128.53 (*Ph*), 127.29 (*Ph*), 127.19 (*Ph*), 114.81 (C-22), 109.27 (C-21), 88.53 (C-4), 78.40 (C-1), 75.58 (C-10), 63.16 (*Bn*), 45.08 (C-3), 42.66 (C-9), 42.31 (C-7), 41.72 (C-8), 41.05 (C-6), 38.22 (C-2), 35.18 (C-11), 34.18 (C-5), 33.21 (C-15), 31.15 (C-12), 20.15 (C-20), 18.98 (C-18), 18.57 (C-16, C-17), 18.35 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3395 (br), 2956 (m), 2933 (m), 1639 (m), 1453 (m), 1386 (m), 1059 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{30}H_{45}O_5$)$^-$: 485.32670, found: 485.32744. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.8° (c = 0.39, CH_2Cl_2).

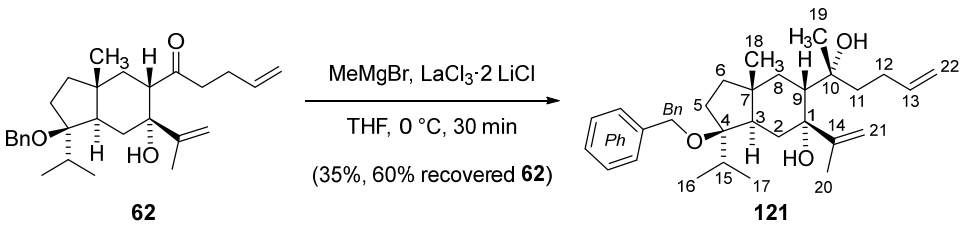
Synthesis of ketone 62



A solution of the crude allylic alcohol **120** (assuming 0.76 mmol) in dichloromethane (9 mL) was treated sequentially with 4 Å molecular sieves (200 mg), 4-methylmorpholine *N*-oxide (133 mg, 1.41 mmol, 1.50 equiv) and tetrapropylammonium perruthenate (26.6 mg, 75.8 µmol, 0.10 equiv) at 23 °C. After 30 min, the mixture was concentrated to a small volume and the residue was purified by flash-column chromatography (10% ethyl acetate in hexanes) to provide ketone **62** (283 mg, 88% over two steps) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.40 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.38–7.35 (m, 2H, *Ph*), 7.24–7.20 (m, 2H, *Ph*), 7.12–7.09 (m, 1H, *Ph*), 5.64 (app ddt, $^3J_{13/22A}$ = 16.6 Hz, $^3J_{13/22B}$ = 10.3 Hz, $^3J_{13/12}$ = 6.4 Hz, 1H, 13-H), 5.20–5.19 (m, 1H, 21-H_A), 4.96–4.90 (m, 3H, 1-OH, 22-H), 4.83–4.79 (m, 1H, 21-H_B), 4.31–4.22 (m, 2H, *Bn*), 2.98 (dd, $^3J_{9/8A}$ = 12.8 Hz, $^3J_{9/8B}$ = 3.8 Hz, 1H, 9-H), 2.41 (dd, $^3J_{3/2A}$ = 11.6 Hz, $^3J_{3/2B}$ = 3.8 Hz, 1H, 3-H), 2.23–2.10 (m, 3H, 11-H_A, 12-H), 2.09–2.02 (m, 3H, 5-H_A, 11-H_B, 15-H), 2.02–1.93 (m, 2H, 2-H), 1.69–1.62 (m, 5H, 5-H_B, 8-H_A, 20-H), 1.51 (dd, $^2J_{6A/6B}$ = 11.7 Hz, $^3J_{6A/5A}$ = 7.9 Hz, 1H, 6-H_A), 1.40 (dd, $^2J_{8B/8A}$ = 12.2 Hz, $^3J_{8B/9}$ = 3.8 Hz, 1H, 8-H_B), 1.18–1.11 (m, 1H, 6-H_B), 1.10 (s, 3H, 18-H), 1.05 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-), 0.99 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 216.15 (C-10), 151.64 (C-14), 140.55 (*Ph*), 137.30 (C-13), 128.54 (*Ph*), 127.35 (*Ph*), 127.21 (*Ph*), 115.41 (C-22), 110.66 (C-21), 88.57 (C-4), 76.92 (C-1), 63.21 (*Bn*), 50.08 (C-9), 45.18 (C-3), 42.64 (C-11), 41.83 (C-7), 40.44 (C-6), 40.17 (C-8), 35.58 (C-2), 34.12 (C-5), 33.11 (C-15), 27.47 (C-12), 19.79 (C-20), 18.86 (C-18), 18.49 (C-16, C-17), 18.26 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (m), 2955 (s), 2857 (s), 1694 (s), 1640 (m), 1453 (s), 1386 (s), 1088 (s), 1058 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{28}H_{41}O_3$)$^+$: 425.30557, found: 425.30540. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.4° (c = 0.97, CH_2Cl_2).

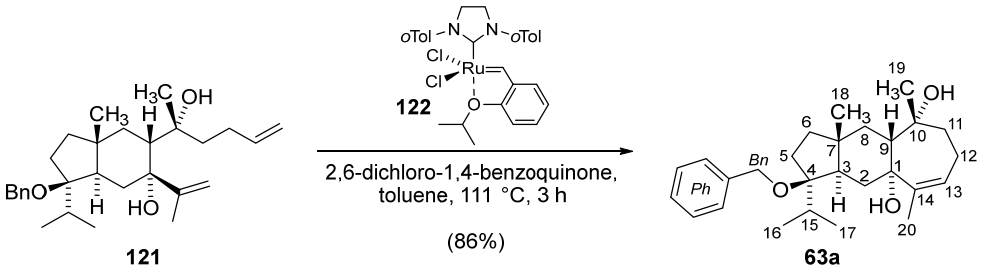
Synthesis of diene 121



62 **121**

A solution of ketone **62** (350 mg, 0.82 mmol, 1 equiv) in tetrahydrofuran (1.5 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 1.88 mL, 0.87 mmol, 1.05 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon methylmagnesium bromide solution (3 M in Et_2O, 0.69 mL, 2.06 mmol, 2.50 equiv) was added dropwise over a period of 20 min (syringe pump). After end of the addition, stirring was continued for 20 min, before the mixture was diluted with pH 7 buffer solution (40 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (4 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexanes) to provide recovered ketone **62** (208 mg, 60%) as a colourless oil and diene **121** (127 mg, 35%) as a colourless oil which solidified upon standing. **TLC** (15% ethyl acetate in hexanes): R_f = 0.23 (CAM). *Note: diene* **121** *shows sever signal broadening in both the ^{1}H and ^{13}C NMR spectra due to hindered rotation of the sidechains. Some carbon atoms are thus not visible in the ^{13}C NMR spectrum.* **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.31 (m, 2H, *Ph*), 7.24–7.18 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 5.92–5.74 (m, 1H, 13-H), 5.24–5.15 (br m, 1H, 21-H_A), 5.13–5.03 (m, 1H, 22-H_A), 5.03–4.94 (m, 1H, 22-H_B), 4.69 (br s, 1H, 21-H_B), 4.31–4.17 (m, 2H, *Bn*), 2.36–1.45 (m, 17H, 2-H, 3-H, 5-H, 6-H_A, 8-H, 9-H, 11-H, 12-H, 15-H, 20-H), 1.27–1.14 (m, 4H, 6-H_B, 19-H), 1.11 (s, 3H, 18-H), 1.02–0.87 (m, 6H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.52 (*Ph*), 139.51 (C-13), 128.53 (*Ph*), 127.26 (*Ph*), 127.20 (*Ph*), 114.36 (C-22), 108.52 (C-21), 88.52 (C-4), 79.46 (C-1), 76.66 (C-10), 63.13 (*Bn*), 45.16 (C-9), 42.44 (C-7), 41.20 (C-6), 39.91 (br, C-8, C-11), 34.15 (C-5), 33.17 (C-15), 28.62 (C-12), 26.58 (br, C-19), 20.46 (C-20), 18.92 (C-18), 18.58 (C-16, C-17), 18.36 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3392 (br), 2939 (s), 2874 (s), 1639 (m), 1453 (s), 1385 (s), 1347 (m), 1200 (m), 1120 (m), 1086 (s), 1062 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{29}H_{44}O_3$)$^+$: 440.3285, found: 440.3277. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +16.7° (c = 0.23, CH_2Cl_2).

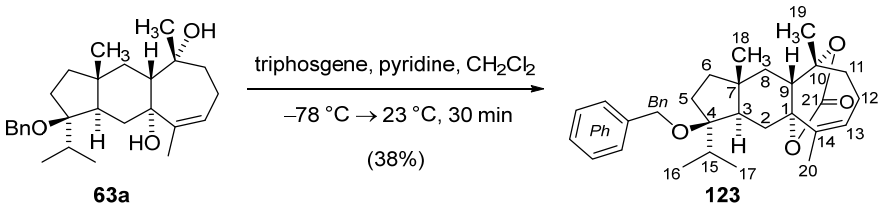
Synthesis of tricycle 63a



A solution of diene **121** (115 mg, 0.26 mmol, 1 equiv) in degassed (sparged with argon for 60 min prior to use) toluene (270 mL) was treated with 2,6-dichloro-1-4-benzoquinone (9.2 mg, 52.2 µmol, 0.20 equiv) and Stewart–Grubbs catalyst **122** (29.8 mg, 52.2 µmol, 0.20 equiv). The resulting orange mixture was then heated to 111 °C, whereupon it turned dark brown. After 3 h, the mixture was allowed to cool to 23 °C and then was concentrated in vacuo. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide tricycle **63a** (93.0 mg, 86%) as an off-white solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.24 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.40–7.35 (m, 2H, *Ph*), 7.23–7.19 (m, 2H, *Ph*), 7.12–7.07 (m, 1H, *Ph*), 5.59–5.55 (m, 1H, 13-H), 4.35–4.26 (m, 2H, *Bn*), 3.14 (br s, 1H, 1-OH, 10-OH), 2.27 (br s, 1H, 1-OH, 10-OH), 2.16 (dd, $^2J_{2A/2B}$ = 13.9 Hz, $^3J_{2A/3}$ =2.7 Hz, 1H, 2-H_A), 2.12–2.04 (m, 3H, 3-H, 5-H_A, 15-H), 2.01 (dd, $^3J_{9/8A}$ = 12.5 Hz, $^3J_{9/8B}$ = 4.5 Hz, 1H, 9-H), 1.95–1.88 (m, 3H, 2-H_B, 8-H_A, 11-H_A), 1.87–1.79 (m, 5H, 12-H, 20-H), 1.73–1.65 (m, 3H, 5-H_B, 8-H_B, 11-H_B), 1.61 (dd, $^2J_{6A/6B}$ = 11.6 Hz, $^3J_{6A/5A}$ = 7.8 Hz, 1H, 6-H_A), 1.28–1.21 (m, 1H, 6-H_B), 1.11–1.07 (m, 6H, 16-H, 17-H, 18-H), 1.05 (s, 3H, 19-H), 0.99 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 144.02 (C-14), 140.72 (*Ph*), 129.04 (C-13), 128.52 (*Ph*), 128.41 (*Ph*), 127.15 (*Ph*), 127.10 (*Ph*), 88.76 (C-4), 78.31 (C-1), 76.72 (C-10), 63.10 (*Bn*), 46.14 (C-11), 44.67 (C-3), 43.93 (C-9), 41.59 (C-7), 41.50 (C-6), 38.93 (C-8), 37.29 (C-2), 34.40 (C-5), 33.27 (C-15), 30.01 (C-19), 23.60 (C-12), 21.90 (C-20), 19.20 (C-18), 18.53 (C-16, C-17), 18.30 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3322 (br), 2951 (s), 2874 (m), 1454 (m), 1389 (m), 1204 (m), 1084 (m), 1062 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_5$)$^-$: 471.31105, found: 471.31185. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.4° (c = 1.00, CH_2Cl_2).

Synthesis of cyclic carbonate 123



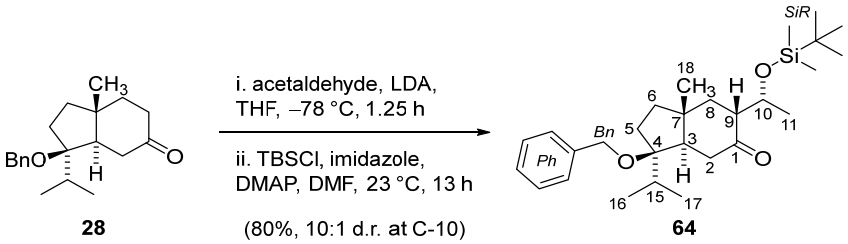
63a **123**

A solution of tricycle **63a** (1.5 mg, 3.6 µmol, 1 equiv) in dichloromethane (0.8 mL) was treated sequentially with pyridine (2.9 µL, 36.4 µmol, 10.0 equiv) and triphosgene (2.2 mg, 7.3 µmol, 2.00 equiv) at –78 °C. After 10 min, the mixture was warmed to 23 °C. After further 20 min, the mixture was diluted with pH 7 buffer solution (10 mL), and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (15% ethyl acetate in hexanes) to provide cyclic carbonate **123** (0.6 mg, 38%) as a colourless solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.25 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.34–7.31 (m, 2H, *Ph*), 7.21–7.18 (m, 2H, *Ph*), 7.11–7.07 (m, 1H, *Ph*), 5.29–5.25 (m, 1H, 13-H), 4.25–4.15 (m, 2H, *Bn*), 2.49 (d, $^2J_{2A/2B}$ = 11.2 Hz, 1H, 2-H_A), 2.36 (dd, $^3J_{9/8A}$ = 12.2 Hz, $^3J_{9/8B}$ = 5.4 Hz, 1H, 9-H), 2.04–1.97 (m, 2H, 5-H_A, 15-H), 1.93–1.85 (m, 3H, 2-H_B, 3-H, 11-H_A), 1.81–1.74 (m, 1H, 12-H_A), 1.70–1.67 (m, 3H, 20-H), 1.61 (dd, $^2J_{5B/5A}$ = 13.9 Hz, $^3J_{5B/6B}$ = 8.4 Hz, 1H, 5-H_B), 1.49–1.42 (m, 2H, 6-H_A, 12-H_B), 1.36–1.29 (m, 2H, 8-H), 1.13 (ddd, $^2J_{11B/11A}$ = 14.9 Hz, $^3J_{11B/12A}$ = 5.8 Hz, $^3J_{11B/12B}$ = 2.9 Hz, 1H, 11-H_B), 1.09–1.03 (m, 4H, 6-H_B, 16-H, 17-H), 0.98 (s, 3H, 18-H), 0.94 (s, 3H, 19-H), 0.92 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 149.49 (C-21), 140.26 (*Ph*), 137.11 (C-14), 128.60 (*Ph*), 127.46 (*Ph*), 127.35 (*Ph*), 126.71 (C-13), 88.32 (C-4), 85.50 (C-1, C-10), 85.47 (C-1, C-10), 63.17 (*Bn*), 44.22 (C-3), 41.56 (C-11), 41.36 (C-7), 40.61 (C-6), 39.04 (C-8), 36.47 (C-9), 34.03 (C-5), 33.25 (C-15), 32.98 (C-2), 28.35 (C-19), 22.18 (C-12), 20.22 (C-20), 18.65 (C-18), 18.46 (C-16, C-17), 18.06 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (m), 2862 (m), 1737 (s), 1454 (m), 1382 (m), 1303 (m), 1201 (m), 1116 (m), 1051 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{25}H_{31}O_4$)$^+$: 395.2223, found: 395.2219.

Synthesis of Tricycle 63b

Synthesis of silyl ether 64



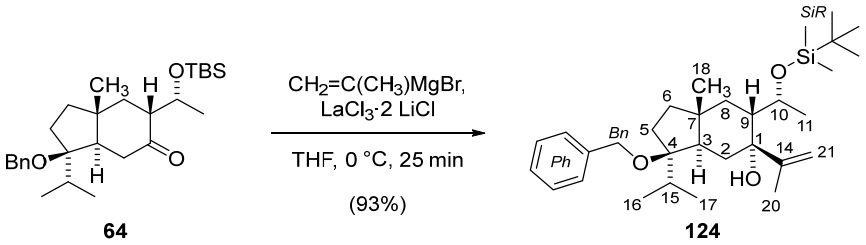
28 (80%, 10:1 d.r. at C-10) **64**

A solution of ketone **28** (1.28 g, 4.26 mmol, 1 equiv) in tetrahydrofuran (12 mL) was treated with a freshly prepared solution of lithium diisopropylamide (1 M in THF, 4.69 mL, 4.69 mmol, 1.10 equiv) at −78 °C (addition to the inner wall of the reaction flask, such that the solution was cooled before reaching the reaction mixture). After 45 min, a solution of acetaldehyde (0.29 mL, 5.11 mmol, 1.20 equiv) in tetrahydrofuran (4 mL) was added dropwise over a period of 5 min. After 40 min, TLC analysis indicated incomplete conversion of ketone **28**, and therefore a further portion of acetaldehyde (71.7 µL, 1.28 mmol, 0.30 equiv) in tetrahydrofuran (0.5 mL) was added dropwise over a period of 2 min. After further 30 min, the mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the aldol product, which was used in the next step without further purification.

A solution of the crude aldol product (assuming 4.26 mmol) in dimethyl formamide (8.5 mL) was treated sequentially with imidazole (0.93 g, 13.6 mmol, 3.20 equiv), 4-dimethylaminopyridine (52.0 mg, 0.43 mmol, 0.10 equiv) and *tert*-butyldimethylchlorosilane (0.90 g, 5.96 mmol, 1.40 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 13 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (40 mL), water (20 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to provide silyl ether **64** (1.57 g, 80% over two steps, inconsequential 10:1 d.r. at C-10) as a colourless oil which solidified upon standing.

TLC (5% ethyl acetate in hexanes): R_f = 0.43 (CAM). *Note: Traces of the minor C-10 diastereomer are visible in the ^{1}H and ^{13}C NMR spectra, but solely the resonances of the major diastereomer are listed below.* **^{1}H NMR** (800 MHz, C_6D_6) δ 7.31–7.28 (m, 2H, *Ph*), 7.26–7.23 (m, 2H, *Ph*), 7.15–7.13 (m, 1H, *Ph*), 4.70–4.67 (m, 1H, 10-H), 4.17–4.09 (m, 2H, *Bn*), 2.75–2.69 (m, 1H, 2-H_A), 2.66–2.61 (m, 1H, 9-H), 2.60 (dd, $^2J_{2B/2A}$ = 15.5 Hz, $^3J_{2B/3}$ = 3.9 Hz, 1H, 2-H_B), 2.09 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/9}$ = 6.5 Hz, 1H, 8-H_A), 2.05–1.99 (m, 1H, 5-H_A), 1.84 (h, $^3J_{15/16\text{-}17}$ = 6.9 Hz, 1H, 15-H), 1.67 (dd, $^3J_{3/2A}$ = 14.3 Hz, $^3J_{3/2B}$ = 3.9 Hz, 1H, 3-H), 1.57–1.49 (m, 2H, 5-H_B, 6-H_A), 1.43 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 12.6 Hz, 1H, 8-H_B), 1.25 (d, $^3J_{11/10}$ = 6.2 Hz, 3H, 11-H), 1.11 (s, 3H, 18-H), 1.08–1.02 (m, 1H, 6-H_B), 0.99 (s, 9H, *SiR*), 0.78 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.68 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.10 (s, 6H, *SiR*). **^{13}C NMR** (200 MHz, C_6D_6) δ 210.42 (C-1), 140.13 (*Ph*), 128.57 (*Ph*), 127.33 (*Ph*), 127.17 (*Ph*), 87.58 (C-4), 67.51 (C-10), 62.84 (*Bn*), 52.95 (C-9), 50.46 (C-3), 41.94 (C-7), 41.90 (C-2), 40.38 (C-6), 38.07 (C-8), 34.86 (C-5), 32.90 (C-15), 26.15 (*SiR*), 19.85 (C-11), 18.85 (C-18), 18.32 (*SiR*), 18.10 (C-16, C-17), 17.72 (C-16, C-17), –4.36 (*SiR*), –4.76 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 2930 (s), 2857 (m), 1700 (s), 1471 (m), 1387 (m), 1254 (s), 1109 (s), 1066 (s), 1043 (s), 1006 (m) cm^{-1}. **HRMS** (EI): calcd for ([M–*t*Bu], $C_{24}H_{37}O_3Si)^+$: 401.2512, found: 401.2516. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +26.4° (c = 0.33, CH_2Cl_2).

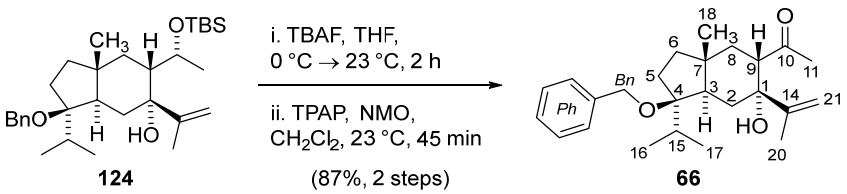
Synthesis of allylic alcohol 124



A solution of silyl ether **64** (1.56 g, 3.40 mmol, 1 equiv, 10:1 d.r. at C-10) in tetrahydrofuran (3.5 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 7.39 mL, 3.40 mmol, 1.00 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon isopropenylmagnesium bromide solution (0.5 M in THF, 20.4 mL, 10.2 mmol, 3.00 equiv) was added dropwise over a period of 20 min (syringe pump). After complete addition, stirring was continued for 5 min, before the mixture was diluted with pH 7 buffer solution (50 mL), saturated aqueous sodium chloride solution (20 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to provide allylic alcohol **124** (1.58 g, 93%) as a colourless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.32 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.37 (m, 2H, *Ph*), 7.25–7.19 (m, 2H, *Ph*), 7.13–7.06 (m, 1H, *Ph*), 5.50 (d, $^2J_{21A/21B}$ = 2.2 Hz, 1H, 21-H_A), 4.93–4.88 (m, 1H, 21-H_B), 4.33–4.22 (m, 2H, *Bn*), 3.81–3.72 (m, 1H, 10-H), 3.59 (d, $^4J_{1OH/2A}$ = 1.3 Hz, 1H, 1-OH), 2.32–2.19 (m, 2H, 2-H_A, 3-H), 2.16–2.00 (m, 2H, 5-H_A, 15-H), 1.98–1.88 (m, 2H, 8-H_A, 9-H), 1.75 (s, 3H, 20-H), 1.72–1.61 (m, 3H, 2-H_B, 5-H_B, 6-H_A), 1.53 (d, $^2J_{8B/8A}$ = 8.5 Hz, 1H, 8-H_B), 1.34–1.24 (m, 4H, 6-H_B, 11-H), 1.21 (s, 3H, 18-H), 1.01 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.99–0.92 (m, 12H, 16-H, 17-H, *SiR*), 0.04 (s, 3H, *SiR*), 0.00 (s, 3H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 153.45 (C-14), 140.70 (*Ph*), 128.52 (*Ph*), 127.33 (*Ph*), 127.14 (*Ph*), 110.27 (C-21), 88.71 (C-4), 78.59 (C-1), 74.41 (C-10), 63.20 (*Bn*), 45.17 (C-3), 42.50 (C-9), 42.28 (C-7), 41.66 (C-8), 41.34 (C-6), 38.01 (C-2), 34.25 (C-5), 33.19 (C-15), 25.99 (*SiR*), 22.55 (C-11), 20.24 (C-20), 19.11 (C-18), 18.53 (C-16, C-17), 18.34 (C-16, C-17), 18.13 (*SiR*), –4.11 (*SiR*), –4.87 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3461 (br), 2954 (s), 2930 (s), 2858 (m), 1454 (m), 1386 (s), 1254 (s), 1118 (m), 1060 (s), 1028 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+H], $C_{31}H_{53}O_3Si)^+$: 501.37640, found: 501.37617. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +20.0° (c = 0.20, CH_2Cl_2).

Synthesis of ketone 66

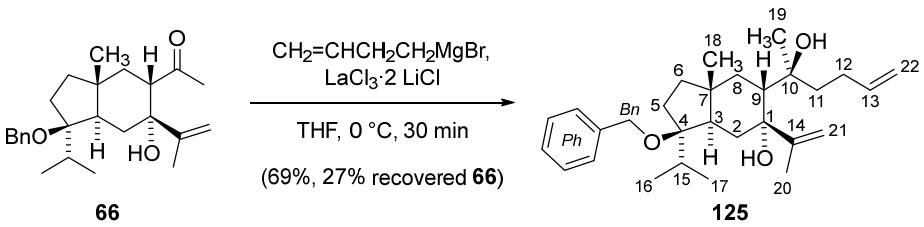


A solution of allylic alcohol **124** (1.57 g, 3.13 mmol, 1 equiv) in tetrahydrofuran (30 mL) was treated with tetrabutylammonium fluoride solution (1 M in THF, 4.70 mL, 4.70 mmol, 1.50 equiv) at 0 °C. After 1.5 h, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 30 min, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (80 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude diol, which was used in the next step without further purification.

A solution of the crude diol (assuming 3.13 mmol) in dichloromethane (24 mL) was treated sequentially with 4 Å molecular sieves (600 mg), 4-methylmorpholine *N*-oxide (0.55 g, 4.70 mmol, 1.50 equiv) and tetrapropylammonium perruthenate (77.0 mg, 0.21 mmol, 0.07 equiv) at 23 °C. After 45 min, the mixture was concentrated to a small volume and the black oily residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to provide ketone **66** (1.05 g, 87% over two steps) as a yellowish oil which solidified upon standing.

TLC (10% ethyl acetate in hexanes): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.38–7.33 (m, 2H, *Ph*), 7.24–7.18 (m, 2H, *Ph*), 7.13–7.06 (m, 1H, *Ph*), 5.21–5.18 (m, 1H, 21-H_A), 4.91 (br s, 1H, 1-OH), 4.83–4.80 (m, 1H, 21-H_B), 4.30–4.20 (m, 2H, *Bn*), 2.97 (dd, $^3J_{9/8A}$ = 12.7 Hz, $^3J_{9/8B}$ = 3.8 Hz, 1H, 9-H), 2.43–2.35 (m, 1H, 3-H), 2.09–1.99 (m, 2H, 5-H_A, 15-H), 1.98–1.93 (m, 2H, 2-H), 1.69–1.67 (m, 3H, 20-H), 1.67–1.57 (m, 5H, 5-H_B, 8-H_A, 11-H), 1.50 (dd, $^2J_{6A/6B}$ = 11.6 Hz, $^3J_{6A/5A}$ = 7.9 Hz, 1H, 6-H_A), 1.38 (dd, $^2J_{8B/8A}$ = 12.2 Hz, $^3J_{8B/9}$ = 3.8 Hz, 1H, 8-H_B), 1.18–1.08 (m, 1H, 6-H_B), 1.07 (s, 3H, 18-H), 1.05 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 215.29 (C-10), 152.16 (C-14), 140.91 (*Ph*), 128.91 (*Ph*), 127.72 (*Ph*), 127.58 (*Ph*), 110.84 (C-21), 88.90 (C-4), 77.24 (C-1), 63.56 (*Bn*), 50.80 (C-9), 45.54 (C-3), 42.21 (C-7), 40.81 (C-6), 40.34 (C-8), 36.02 (C-2), 34.50 (C-5), 33.47 (C-15), 30.69 (C-11), 20.15 (C-20), 19.18 (C-18), 18.87 (C-16, C-17), 18.62 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (br), 2958 (s), 1695 (s), 1639 (w), 1453 (s), 1386 (s), 1182 (m), 1163 (m), 1086 (m), 1058 (s), 1027 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{27}H_{39}O_5$)$^-$: 443.27975, found: 443.28067. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +15.6° (c = 0.50, CH_2Cl_2).

Synthesis of diene 125



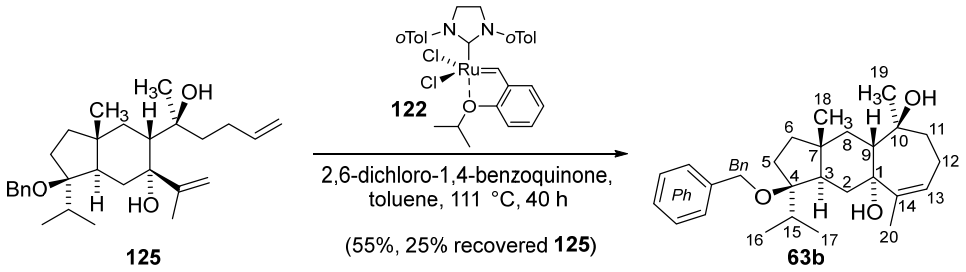
66 **125**

Grignard stock solution preparation: A suspension of magnesium turnings (0.32 g, 13.0 mmol, 1 equiv) in tetrahydrofuran (8 mL) was treated dropwise with a solution of 4-bromo-1-butene (1.32 mL, 13.0 mmol, 1.00 equiv) in tetrahydrofuran (5 mL) over a period of 10 min so as to maintain a gentle reflux. After complete addition, stirring was continued at 23 °C for 1 h, before the mixture was filtered (argon atmosphere) and used immediately in the following reaction.

In a separate flask, a solution of ketone **66** (1.00 g, 2.60 mmol, 1 equiv) in tetrahydrofuran (3 mL) was treated with lanthanum(III) chloride bis(lithium chloride) complex solution (0.46 M in THF, 5.65 mL, 2.60 mmol, 1.00 equiv) at 23 °C. After 1 h, the brownish solution was cooled to 0 °C, whereupon freshly prepared 3-butenylmagnesium bromide solution (assuming 0.70 M in THF, 11.1 mL, 7.80 mmol, 3.00 equiv) was added dropwise over a period of 20 min (syringe pump). After end of the addition, stirring was continued for 10 min, before the mixture was diluted with pH 7 buffer solution (70 mL), saturated aqueous sodium chloride solution (30 mL) and diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (5 x 40 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% to 20% ethyl acetate in hexanes) to provide recovered ketone **66** (0.27 g, 27%) as a yellowish oil and diene **125** (0.79 g, 69%) as a yellowish foam.

TLC (10% ethyl acetate in hexanes): R_f = 0.20 (CAM). *Note:* diene **125** *shows signal broadening in both the ^{1}H and ^{13}C NMR spectra due to hindered rotation of the sidechains.* **^{1}H NMR** (400 MHz, C_6D_6) δ 7.39–7.34 (m, 2H, *Ph*), 7.25–7.18 (m, 2H, *Ph*), 7.14–7.07 (m, 1H, *Ph*), 5.78–5.56 (m, 2H, 13-H, 21-H_A), 5.08–4.90 (m, 2H, 22-H), 4.84 (br s, 1H, 21-H_B), 4.34–4.19 (m, 2H, *Bn*), 4.13 (br s, 1H, 1-OH, 10-OH), 2.34–2.13 (m, 2H, 2-H_A, 3-H), 2.13–1.93 (m, 3H, 5-H_A, 9-H, 15-H), 1.93–1.83 (m, 2H, 12-H), 1.78–1.51 (m, 9H, 2-H_B, 5-H_B, 6-H_A, 8-H, 11-H_A, 20-H), 1.34–1.18 (m, 5H, 6-H_B, 11-H_B, 19-H), 1.11 (br s, 3H, 18-H), 1.02 (br d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^{3}J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 155.66 (C-14), 140.66 (*Ph*), 138.78 (C-13), 128.50 (*Ph*), 127.27 (*Ph*), 127.13 (*Ph*), 114.63 (C-22), 109.81 (C-21), 88.78 (C-4), 79.82 (C-1), 77.52 (C-10), 63.17 (*Bn*), 44.92 (C-3), 42.41 (C-6, C-7, C-9, C-11), 42.18 (C-6, C-7, C-9, C-11), 41.35 (C-6, C-7, C-9, C-11), 41.18 (C-6, C-7, C-9, C-11), 39.48 (C-2), 38.18 (C-8), 34.20 (C-5), 33.23 (C-15), 29.18 (C-12), 26.47 (C-19), 20.59 (C-20), 19.02 (C-18), 18.55 (C-16, C-17), 18.30 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3366 (br), 2944 (s), 2873 (s), 1639 (m), 1453 (s), 1385 (s), 1345 (m), 1142 (m), 1059 (s), 906 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{31}H_{47}O_5$)$^-$: 499.34235, found: 499.34308. $[\alpha]_D^{20}$ = +11.3° (c = 0.30, CH_2Cl_2).

Synthesis of tricycle 63b

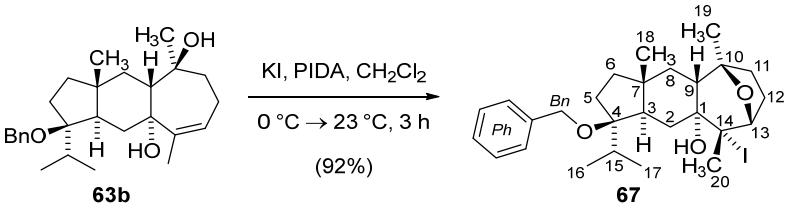


A solution of diene **125** (0.42 g, 0.95 mmol, 1 equiv) in degassed (sparged with argon for 60 min prior to use) toluene (900 mL) was treated with 2,6-dichloro-1-4-benzoquinone (33.7 mg, 0.19 mmol, 0.20 equiv) and Stewart–Grubbs catalyst **122** (109.0 mg, 0.19 mmol, 0.20 equiv). The resulting orange mixture was then heated to 111 °C, whereupon it turned dark brown. After 24 h, a further portion of Stewart–Grubbs catalyst **122** (27.2 mg, 47.7 µmol, 0.05 equiv) was added and stirring was continued at 111 °C. After further 16 h, the mixture was allowed to cool to 23 °C and then was concentrated in vacuo. The residue was purified by flash-column chromatography on silica gel (25% to 30% ethyl acetate in hexanes) to provide recovered diene **125** (106 mg, 25%) as a yellow oil and tricycle **63b** (0.22 g, 55%) as an off-white foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.15 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.38–7.32 (m, 2H, *Ph*), 7.22–7.18 (m, 2H, *Ph*), 7.11–7.07 (m, 1H, *Ph*), 5.60–5.56 (m, 1H, 13-H), 4.30–4.23 (m, 2H, *Bn*), 2.37–2.30 (m, 1H, 12-H_A), 2.24 (dd, $^3J_{9/8B}$ = 12.6 Hz, $^3J_{9/8A}$ = 3.8 Hz, 1H, 9-H), 2.16 (d, $^2J_{2A/2B}$ = 12.5 Hz, 1H, 2-H_A), 2.08–2.01 (m, 3H, 5-H_A, 8-H_A, 15-H), 1.93–1.85 (m, 2H, 2-H_B, 3-H), 1.74–1.57 (m, 9H, 5-H_B, 6-H_A, 8-H_B, 11-H, 12-H_B, 20-H), 1.27 (s, 3H, 19-H), 1.22–1.17 (m, 1H, 6-H_B), 1.13 (s, 3H, 18-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.82 (br s, 1H, 1-OH), 0.75 (br s, 1H, 10-OH). **^{13}C NMR** (200 MHz, C_6D_6) δ 141.17 (C-14), 140.59 (*Ph*), 131.05 (C-13), 128.52 (*Ph*), 127.16 (*Ph*), 127.11 (*Ph*), 88.69 (C-4), 76.60 (C-1), 74.78 (C-10), 63.08 (*Bn*), 46.53 (C-9), 46.08 (C-11), 45.88 (C-3), 41.56 (C-7), 41.42 (C-6), 39.52 (C-8), 38.25 (C-2), 34.26 (C-5), 33.22 (C-15), 28.12 (C-19), 22.28 (C-12), 21.39 (C-20), 18.61 (C-16, C-17), 18.53 (C-18), 18.36 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3462 (br), 2955 (s), 2873 (m), 1453 (m), 1386 (m), 1306 (m), 1090 (m), 1063 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_5$)$^-$: 471.31105, found: 471.31184. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.3° (c = 0.87, CH_2Cl_2).

Elaboration of Tricycle 63b

Synthesis of iodide 67

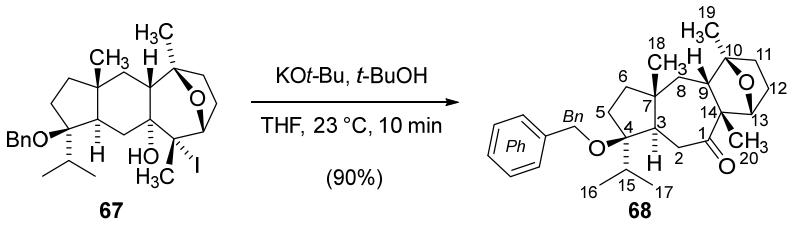


A solution of tricycle **63b** (3.0 mg, 7.3 µmol, 1 equiv) in dichloromethane (1 mL) was treated sequentially with potassium iodide (2.7 mg, 16.0 µmol, 2.20 equiv) and (diacetoxyiodo)benzene (2.6 mg, 8.0 µmol, 1.10 equiv) at 0 °C. After 10 min, the mixture was warmed to 23 °C. After 3 h, the mixture was diluted with pH 7 buffer solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) to provide iodide **67** (3.6 mg, 92%) as a colourless oil.[72]

TLC (5% ethyl acetate in hexanes): R_f = 0.32 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.38–7.33 (m, 2H, *Ph*), 7.25–7.20 (m, 2H, *Ph*), 7.13–7.07 (m, 1H, *Ph*), 4.40 (d, $^3J_{13/12B}$ = 7.7 Hz, 1H, 13-H), 4.29–4.20 (m, 2H, *Bn*), 2.93–2.83 (m, 1H, 12-H_A), 2.59–2.49 (m, 1H, 11-H_A), 2.29–2.18 (m, 2H, 3-H, 9-H), 2.09–1.98 (m, 6H, 5-H_A, 12-H_B, 15-H, 20-H), 1.94 (app t, $^2J_{2A/2B}$ = $^3J_{2A/3}$ = 13.2 Hz, 1H, 2-H_A), 1.72 (dd, $^2J_{2B/2A}$ = 13.2 Hz, $^3J_{2B/3}$ = 2.7 Hz, 1H, 2-H_B), 1.66–1.49 (m, 3H, 5-H_B, 6-H_A, 8-H_A), 1.38 (d, $^4J_{1OH/9}$ = 2.0 Hz, 1H, 1-OH), 1.32–1.22 (m, 2H, 8-H_B, 11-H_B), 1.20–1.11 (m, 4H, 6-H_B, 19-H), 1.06 (s, 3H, 18-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.92 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.39 (*Ph*), 128.55 (*Ph*), 127.39 (*Ph*), 127.27 (*Ph*), 88.30 (C-4), 87.77 (C-13), 84.10 (C-10), 78.94 (C-14), 77.13 (C-1), 63.26 (*Bn*), 46.54 (C-9), 44.53 (C-3), 42.97 (C-7), 40.59 (C-6), 38.40 (C-8), 36.21 (C-2), 33.92 (C-5), 33.04 (C-15), 32.10 (C-20), 31.83 (C-12), 31.63 (C-11), 25.70 (C-19), 19.71 (C-18), 18.72 (C-16, C-17), 18.70 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3527 (m), 2935 (s), 2861 (m), 1452 (s), 1376 (s), 1345 (m), 1275 (m), 1191 (m), 1116 (m), 1061 (s), 1015 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{42}IO_5$)$^-$: 597.20769, found: 597.20840. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +49.7° (c = 0.12, CH_2Cl_2).

[72] Alternatively, iodide **67** could be cleanly prepared by using NIS (CH_2Cl_2, 0 °C).

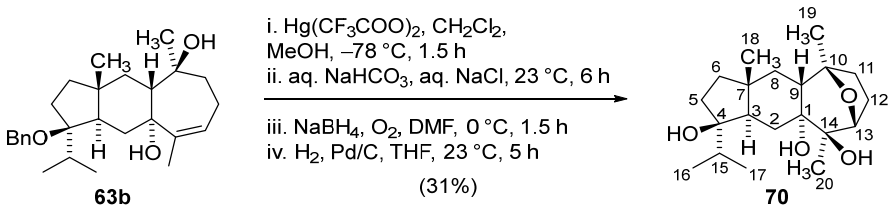
Synthesis of cycloheptanone 68



A solution of iodide **67** (3.5 mg, 6.5 µmol, 1 equiv) in tetrahydrofuran (1 mL) and *tert*-butanol (0.05 mL) was treated with potassium *tert*-butoxide (2.2 mg, 19.5 µmol, 3.00 equiv) at 23 °C. After 10 min, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes) to provide cycloheptanone **68** (2.4 mg, 90%) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.24 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.36–7.31 (m, 2H, *Ph*), 7.27–7.22 (m, 2H, *Ph*), 7.14–7.09 (m, 1H, *Ph*), 4.26 (d, $^3J_{13/12B}$ = 5.9 Hz, 1H, 13-H), 4.24–4.11 (m, 2H, *Bn*), 3.00 (app t, $^2J_{2A/2B}$ = $^3J_{2A/3}$ = 12.4 Hz, 1H, 2-H_A), 2.71 (dd, $^2J_{2B/2A}$ = 12.4 Hz, $^3J_{2B/3}$ = 1.6 Hz, 1H, 2-H_B), 2.26–2.15 (m, 1H, 12-H_A), 2.05–1.86 (m, 3H, 5-H_A, 12-H_B, 15-H), 1.71–1.58 (m, 2H, 9-H, 11-H_A), 1.57–1.46 (m, 3H, 3-H, 5-H_B, 8-H_A), 1.36–1.28 (m, 4H, 6-H_A, 19-H), 1.25 (s, 3H, 20-H), 1.21–1.13 (m, 1H, 11-H_B), 1.11–1.07 (m, 4H, 6-H_B, 18-H), 1.05 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 1.01–0.92 (m, 1H, 8-H_B), 0.79 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 213.82 (C-1), 140.13 (*Ph*), 128.63 (*Ph*), 127.43 (*Ph*), 127.29 (*Ph*), 88.99 (C-4), 87.71 (C-10), 83.77 (C-13), 63.35 (*Bn*), 63.12 (C-14), 52.71 (C-9), 51.05 (C-3), 44.21 (C-7, C-8), 44.16 (C-7, C-8), 41.46 (C-6), 40.41 (C-2), 34.16 (C-5), 33.57 (C-15), 31.51 (C-11), 28.38 (C-19), 26.89 (C-12), 21.05 (C-20), 19.10 (C-18), 18.24 (C-16, C-17), 17.72 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2964 (s), 2924 (s), 2884 (m), 1686 (s), 1453 (m), 1382 (m), 1084 (s), 1061 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2816, found: 410.2796. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –15.0° (c = 0.08, CH_2Cl_2).

Synthesis of triol 70



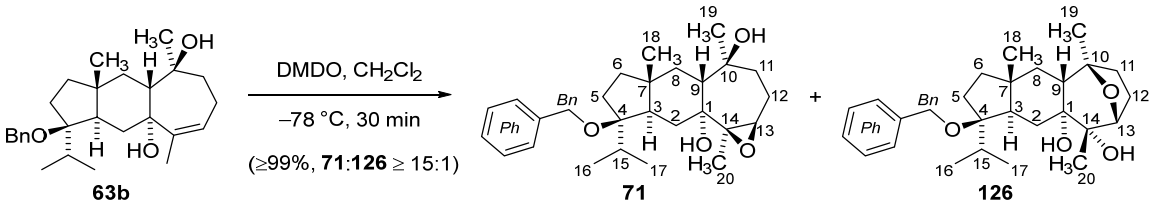
A solution of tricycle **63b** (9.1 mg, 22.1 µmol, 1 equiv) in dichloromethane (1 mL) and methanol (20 µL) was treated with mercury(II) trifluoroacetate (11.3 mg, 26.5 µmol, 1.20 equiv) at –78 °C. After 1.5 h, the cooling bath was removed and saturated aqueous sodium hydrogen carbonate solution (1 mL) and saturated aqueous sodium chloride solution (1 mL) were added. The resulting biphasic mixture was stirred vigorously at 23 °C. After 6 h, the mixture was diluted with pH 7 buffer solution (5 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the organomercury product, which was used in the next step without further purification.

A solution of sodium borohydride (2.5 mg, 66.3 µmol, 3.00 equiv) in dimethyl formamide (1.5 mL) was sparged with a stream of pure oxygen gas at 0 °C for 20 min. A solution of the crude organomercury product (assuming 22.1 µmol) in dimethyl formamide (0.7 mL) was then added dropwise over a period of 1 h (syringe pump) at 0 °C, during which time oxygen-sparging of the mixture was continued. After complete addition, the mixture was warmed to 23 °C for 15 min, before it was diluted with aqueous 0.5 M hydrogen chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (20% ethyl acetate in hexanes) to provide diol **69**, which was used in the next step without further purification.

A solution of the crude diol **69** (assuming 22.1 µmol) in tetrahydrofuran (4 mL) was treated with palladium on carbon (10 wt.%, 23.5 mg, 22.1 µmol, 1.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a stream of pure hydrogen gas through a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 5 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography (50% ethyl acetate in hexanes) to provide triol **70** (2.3 mg, 31% over three steps) as a colourless solid.

Recrystallization of the product from ethyl acetate/hexanes gave crystals suitable for X-ray diffraction. **TLC** (50% ethyl acetate in hexanes): R_f = 0.14 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 3.91 (d, $^3J_{13/12B}$ = 8.0 Hz, 1H, 13-H), 3.03 (br s, 1H, 14-OH), 2.26–2.18 (m, 2H, 11-H_A, 12-H_A), 1.94–1.88 (m, 2H, 9-H, 2-H_A), 1.87–1.80 (m, 2H, 5-H_A, 12-H_B), 1.72–1.67 (m, 1H, 5-H_B), 1.57–1.54 (m, 1H, 6-H_A), 1.52 (dd, $^3J_{3/2A}$ = 13.6 Hz, $^3J_{3/2B}$ = 3.1 Hz, 1H, 3-H), 1.43 (h, $^3J_{15/16\text{-}17}$ = 6.8 Hz, 1H, 15-H), 1.33–1.27 (m, 2H, 8-H_A, 11-H_B), 1.20 (s, 3H, 19-H), 1.18–1.10 (m, 2H, 2-H_B, 8-H_B), 1.08 (s, 3H, 18-H), 1.02 (s, 3H, 20-H), 1.01–0.96 (m, 1H, 6-H_B), 0.90 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.76 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.50 (br s, 1H, 1-OH), 0.44 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 84.55 (C-13), 83.20 (C-4), 83.06 (C-10), 76.46 (C-1), 73.30 (C-14), 47.42 (C-3), 45.21 (C-9), 42.06 (C-7), 40.12 (C-6), 37.35 (C-8), 36.59 (C-15), 34.45 (C-5), 31.65 (C-11), 29.05 (C-2), 27.69 (C-12), 25.63 (C-19), 19.93 (C-18), 18.76 (C-16, C-17), 17.88 (C-16, C-17), 16.75 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3474 (br), 2932 (s), 2860 (s), 1466 (m), 1376 (m), 1344 (s), 1327 (m), 1188 (m), 1102 (m), 1037 (s), 1005 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{22}H_{37}O_6$)$^-$: 397.25901, found: 397.26061. $[\alpha]_D^{20}$ = –41.7° (c = 0.08, CH_2Cl_2).

Synthesis of epoxide 71

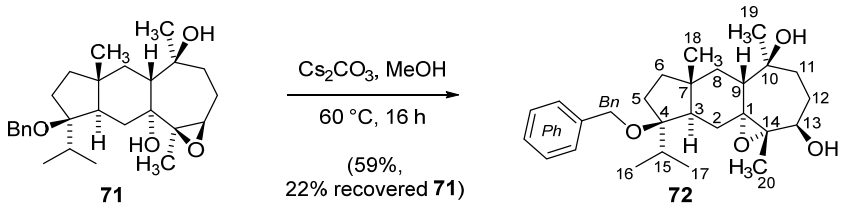


A solution of tricycle **63b** (100 mg, 0.24 mmol, 1 equiv) in dichloromethane (4 mL) was treated dropwise over a period of 5 min with freshly prepared dimethyldioxirane solution (0.064 M in acetone, 5.68 mL, 0.36 mmol, 1.50 equiv) at –78 °C. After 15 min, more dimethyldioxirane solution (0.064 M in acetone, 5.68 mL, 0.36 mmol, 1.50 equiv) was added. After 15 min, the mixture was allowed to warm to 23 °C, and then was concentrated. Residual water was removed by azeotropic distillation using benzene (3 x 15 mL), to provide a pure mixture of epoxide **71** and tetrahydrofuran **126** (104 mg, ≥99%, **71**:**126** ≥ 15:1) as an off-white foam, which was used in the next step without further purification.[73]
A small quantity of this mixture was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide analytically pure samples of epoxide **71** and tetrahydrofuran **126**.
Epoxide **71**: **TLC** (30% ethyl acetate in hexanes): R_f = 0.16 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.37–7.34 (m, 2H, *Ph*), 7.15–7.13 (m, 2H, *Ph*), 7.07–7.03 (m, 1H, *Ph*), 4.31–4.24 (m, 2H, *Bn*), 2.90 (dd, $^3J_{13/12A}$ = 8.4 Hz, $^3J_{13/12B}$ = 3.9 Hz, 1H, 13-H), 2.49 (app t, $^2J_{2A/2B}$ = $^3J_{2A/3}$ = 14.1 Hz, 1H, 2-H_A), 2.12 (dd, $^3J_{9/8B}$ = 12.7 Hz, $^3J_{9/8A}$ = 4.3 Hz, 1H, 9-H), 2.06–1.99 (m, 4H, 2-H_B, 5-H_A, 8-H_A, 15-H), 1.95–1.89 (m, 1H, 12-H_A), 1.72–1.67 (m, 1H, 11-H_A), 1.66–1.54 (m, 4H, 3-H, 5-H_B, 6-H_A, 12-H_B), 1.46 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 12.7 Hz, 1H, 8-H_B), 1.40–1.36 (m, 1H, 11-H_B), 1.23 (s, 3H, 19-H), 1.17 (s, 6H, 18-H, 20-H), 1.16–1.11 (m, 1H, 6-H_B), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.88 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.37 (*Ph*), 128.55 (*Ph*), 127.08 (*Ph*), 126.93 (*Ph*), 88.51 (C-4), 77.36 (C-1), 74.75 (C-10), 69.25 (C-13), 63.88 (C-14), 63.15 (*Bn*), 45.72 (C-3), 41.83 (C-7), 41.37 (C-11), 41.21 (C-6), 41.14 (C-9), 38.89 (C-8), 36.47 (C-2), 34.25 (C-5), 33.26 (C-15), 27.52 (C-19), 21.74 (C-12), 19.50 (C-18, C-20), 18.60 (C-16, C-17), 18.44 (C-16, C-17), 18.23 (C-18, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3484 (br), 2943 (m), 2876 (m), 1456 (s), 1387 (s), 1201 (m), 1139 (m), 1088 (m), 1062 (s), 1002 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_6$)$^-$: 487.30596, found: 487.30672. $[\alpha]_D^{20}$ = –16.6° (c = 0.18, CH_2Cl_2).

Tetrahyodrofuran **126**: **TLC** (30% ethyl acetate in hexanes): R_f = 0.42 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.40–7.36 (m, 2H, *Ph*), 7.25–7.22 (m, 2H, *Ph*), 7.12–7.08 (m, 1H, *Ph*), 4.31–4.27 (m, 2H, *Bn*), 3.73 (d, $^3J_{13/12B}$ = 7.6 Hz, 1H, 13-H), 2.56–2.51 (m, 2H, 11-H_A, 14-OH), 2.44–2.38 (m, 1H, 12-H_A), 2.33 (dd, $^3J_{3/2A}$ = 12.4 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 2.11–2.03 (m, 2H, 5-H_A, 15-H), 1.87 (dd, $^3J_{9/8A}$ = 13.1 Hz, $^3J_{9/8B}$ = 3.2 Hz, 1H, 9-H), 1.86–1.80 (m, 1H, 12-H_B), 1.69–1.63 (m, 2H, 2-H_A, 5-H_B), 1.60–1.53 (m, 3H, 2-H_B, 6-H_A, 8-H_A), 1.40–1.30 (m, 2H, 8-H_B, 11-H_B), 1.27 (s, 3H, 19-H), 1.25–1.19 (m, 1H, 6-H_B), 1.12 (s, 3H, 18-H), 1.10 (s, 3H, 20-H), 1.01 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.64 (*Ph*), 128.52 (*Ph*), 127.31 (*Ph*), 127.19 (*Ph*), 88.53 (C-4), 83.89 (C-13), 83.23 (C-10), 75.61 (C-1), 72.98 (C-14), 63.18 (*Bn*), 46.63 (C-9), 45.02 (C-3), 42.60 (C-7), 40.87 (C-6), 37.69 (C-8), 33.86 (C-5), 32.95 (C-15), 32.42 (C-2), 32.18 (C-11), 28.08 (C-12), 25.64 (C-19), 24.62 (C-20), 19.71 (C-18), 18.71 (C-16, C-17), 18.65 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3404 (br), 2935 (s), 2869 (m), 1712 (w), 1453 (s), 1378 (s), 1256 (m), 1113 (m), 1048 (m), 1030 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{43}O_6$)$^-$: 487.30596, found: 487.30674. $[\alpha]_D^{20}$ = +18.8° (c = 0.23, CH_2Cl_2).

[73] Epoxidation of tricycle **63b** with *m*-CPBA (CH_2Cl_2, 0 °C) gave an unfavourable 2:3 mixture of epoxide **71** and tetrahydrofuran **126**.

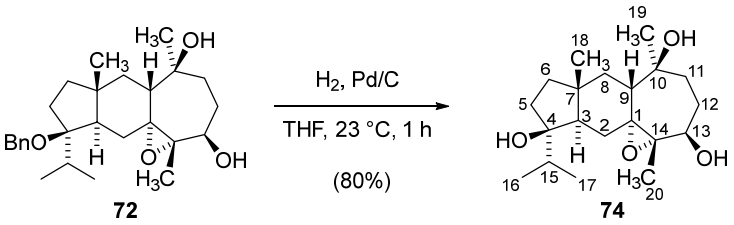
Synthesis of epoxide 72



A solution of epoxide **71** (94.0 mg, 0.22 mmol, 1 equiv) in methanol (12 mL) was treated with cesium carbonate (1.79 g, 5.48 mmol, 25.0 equiv) and the resulting mixture was heated to 60 °C. After 16 h, the mixture was allowed to cool to 23 °C and then was diluted with pH 7 buffer solution (30 mL) and ethyl acetate (25 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (50% ethyl acetate in hexanes) to provide recovered epoxide **71** (21.0 mg, 22%) as a colourless oil and epoxide **72** (55.0 mg, 59%) as a colourless oil.

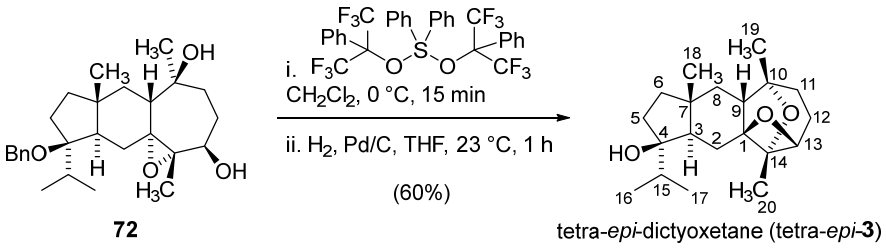
TLC (50% ethyl acetate in hexanes): R_f = 0.15 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.38–7.33 (m, 2H, *Ph*), 7.27–7.21 (m, 2H, *Ph*), 7.15–7.10 (m, 1H, *Ph*), 4.27–4.18 (m, 2H, *Bn*), 3.92–3.88 (m, 1H, 13-H), 2.29 (dd, $^2J_{8A/8B}$ = 12.4 Hz, $^3J_{8A/9}$ = 4.1 Hz, 1H, 8-H_A), 2.23–2.13 (m, 2H, 2-H_A, 9-H), 2.08–1.95 (m, 2H, 5-H_A, 15-H), 1.86–1.77 (m, 3H, 2-H_B, 3-H, 11-H_A), 1.74–1.65 (m, 1H, 12-H_A), 1.65–1.51 (m, 3H, 5-H_B, 6-H_A, 8-H_B), 1.47 (s, 3H, 20-H), 1.44–1.35 (m, 2H, 11-H_B, 12-H_B), 1.27 (s, 3H, 19-H), 1.23–1.14 (m, 1H, 6-H_B), 1.12 (s, 3H, 18-H), 0.98 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.85 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.55 (*Ph*), 128.54 (*Ph*), 127.24 (*Ph*), 127.19 (*Ph*), 88.26 (C-4), 76.33 (C-13), 74.70 (C-10), 67.17 (C-14), 66.39 (C-1), 63.03 (*Bn*), 48.63 (C-3), 46.83 (C-9), 41.83 (C-7, C-8), 41.55 (C-7, C-8), 41.19 (C-6), 36.95 (C-11), 34.40 (C-5), 33.57 (C-2), 33.09 (C-15), 27.67 (C-12), 25.53 (C-19), 23.19 (C-20), 18.85 (C-18), 18.33 (C-16, C-17), 17.99 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3383 (br), 2954 (s), 2929 (s), 1451 (m), 1382 (m), 1346 (w), 1091 (s), 1059 (s), 1030 (s) cm^{-1}. **HRMS** (ESI): calcd for ($[M+CH_3COO]$, $C_{29}H_{43}O_6)^-$: 487.30596, found: 487.30682. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.0° (c = 0.20, CH_2Cl_2).

Synthesis of triol 74



A solution of epoxide **72** (7.5 mg, 17.5 µmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 46.6 mg, 43.7 µmol, 2.50 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (9% methanol in dichloromethane) to provide triol **74** (4.7 mg, 80%) as a colourless solid. Recrystallization of the product from ethyl acetate/hexanes gave crystals suitable for X-ray diffraction. **TLC** (9% methanol in dichloromethane): R_f = 0.15 (CAM). **^{1}H NMR** (800 MHz, CD_2Cl_2) δ 4.21 (dd, $^3J_{13/12B}$ = 4.8 Hz, $^3J_{13/12A}$ = 2.5 Hz, 1H, 13-H), 2.17–2.13 (m, 2H, 8-H_A, 9-H), 2.04–2.00 (m, 1H, 5-H_A), 1.87–1.80 (m, 2H, 2-H_A, 11-H_A), 1.76–1.61 (m, 5H, 5-H_B, 6-H_A, 12-H, 15-H), 1.53–1.48 (m, 5H, 3-H, 11-H_B, 20-H), 1.46 (dd, $^2J_{2B/2A}$ = 14.0 Hz, $^3J_{2B/3}$ = 3.2 Hz, 1H, 2-H_B), 1.41 (app t, $^2J_{8B/8A}$ = $^3J_{8B/9}$ = 13.3 Hz, 1H, 8-H_B), 1.20 (s, 3H, 19-H), 1.18–1.11 (m, 1H, 6-H_B), 1.05 (s, 3H, 18-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.88 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, CD_2Cl_2) δ 83.97 (C-4), 76.79 (C-13), 75.36 (C-10), 67.30 (C-14), 66.40 (C-1), 51.39 (C-3), 46.85 (C-9), 42.09 (C-8), 41.33 (C-7), 40.40 (C-6), 37.94 (C-15), 37.21 (C-11), 37.15 (C-5), 31.69 (C-2), 27.76 (C-12), 25.34 (C-19), 23.15 (C-20), 18.90 (C-18), 18.55 (C-16, C-17), 17.78 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3424 (br), 2957 (s), 2924 (s), 2867 (m), 1455 (m), 1382 (m), 1261 (m), 1095 (s), 1005 (s) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{22}H_{37}O_6$)$^-$: 397.25901, found: 397.26046. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +9.4° (c = 0.11, MeOH).

Synthesis of 1,10,13,14-tetra-*epi* dictyoxetane (tetra-*epi*-3)



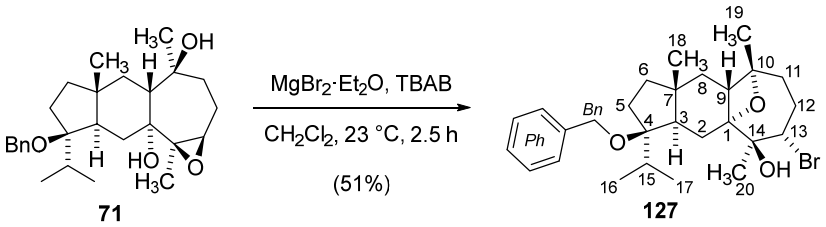
A solution of epoxide **72** (5.0 mg, 11.7 µmol, 1 equiv) in dichloromethane (1.2 mL) was treated with Martin sulfurane (7.9 mg, 11.7 µmol, 1.00 equiv) at 0 °C. After 15 min, the mixture was diluted with pH 7 buffer solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through a pad of silica gel (10% ethyl acetate in hexanes) to provide dioxatricycle **77**,[74] which was used in the next step without further purification.

A solution of the crude dioxatricycle **77** (assuming 11.7 µmol) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 24.9 mg, 23.4 µmol, 2.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (35% ethyl acetate in hexanes) to provide 1,10,13,14-tetra-*epi* dictyoxetane (tetra-*epi*-**3**) (2.3 mg, 60% over two steps) as a colourless solid.

Recrystallization of the product from ethyl acetate/hexanes gave crystals suitable for X-ray diffraction. **TLC** (40% ethyl acetate in hexanes): R_f = 0.26 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 4.29 (br d, $^3J_{13/12A}$ = 3.6 Hz, 1H, 13-H), 2.08–2.02 (m, 2H, 2-H_A, 9-H), 2.02–1.96 (m, 2H, 2-H_B, 11-H_A), 1.86–1.78 (m, 2H, 5-H_A, 12-H_A), 1.74–1.61 (m, 3H, 5-H_B, 11-H_B, 12-H_B), 1.56 (dd, $^2J_{8A/8B}$ = 12.6 Hz, $^3J_{8A/9}$ = 6.5 Hz, 1H, 8-H_A), 1.49–1.43 (m, 2H, 6-H_A, 15-H), 1.30 (s, 3H, 20-H), 1.19 (s, 3H, 19-H), 1.09 (s, 3H, 18-H), 1.02 (dd, $^3J_{3/2B}$ = 14.0 Hz, $^3J_{3/2A}$ = 3.6 Hz, 1H, 3-H), 0.92–0.85 (m, 5H, 6-H_B, 8-H_B, 16-H, 17-H), 0.78 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.69 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 96.98 (C-1), 82.90 (C-4), 82.37 (C-14), 81.52 (C-13), 81.15 (C-10), 51.95 (C-9), 50.37 (C-3), 41.47 (C-7), 41.15 (C-8), 39.80 (C-6), 37.65 (C-15), 36.83 (C-5), 33.06 (C-11), 28.72 (C-2), 24.18 (C-12), 24.11 (C-19), 18.53 (C-18), 18.49 (C-16, C-17), 17.80 (C-16, C-17), 17.29 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3455 (m), 2958 (s), 2932 (s), 2852 (m), 1454 (m), 1384 (m), 1275 (m), 1189 (m), 1121 (m), 1062 (m), 1020 (m), 974 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_3$)$^+$: 320.2346, found: 320.2351. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –90.0° (c = 0.07, CH_2Cl_2).

[74] This intermediate could also be obtained via the dyotropic rearrangement of epoxide-oxetane **78**, see "Synthesis of dioxatricycle **77**" for characterization of this product.

Synthesis of bromohydrin 127

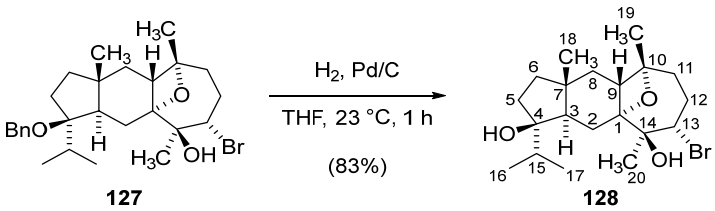


A solution of epoxide **71** (25.0 mg, 58.3 µmol, 1 equiv) in dichloromethane (3 mL) was treated sequentially with magnesium bromide ethyl etherate (90.4 mg, 350 µmol, 6.00 equiv) and tetrabutylammonium bromide (113 mg, 350 µmol, 6.00 equiv) at 0 °C. After 10 min, the mixture was allowed to warm to 23 °C.[75] After 2.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (8% ethyl acetate in hexanes) to provide bromohydrine **127** (14.5 mg, 51%) as a colourless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.39 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.45–7.42 (m, 2H, *Ph*), 7.27–7.23 (m, 2H, *Ph*), 7.11–7.08 (m, 1H, *Ph*), 4.68 (d, $^3J_{13/12A}$ = 13.2 Hz, 1H, 13-H), 4.37–4.27 (m, 2H, *Bn*), 2.65 (app t, $^2J_{2A/2B} = {}^3J_{2A/3}$= 13.9 Hz, 1H, 2-$H_A$), 2.42–2.35 (m, 1H, 12-$H_A$), 2.33 (dd, $^3J_{9/8A}$ = 10.5 Hz, $^3J_{9/8B}$ = 6.6 Hz, 1H, 9-H), 2.11–2.04 (m, 3H, 5-H_A, 12-H_B, 15-H), 2.00 (dd, $^3J_{3/2A}$= 13.9 Hz, $^3J_{3/2B}$ = 4.1 Hz, 1H, 3-H), 1.76–1.69 (m, 3H, 2-H_B, 5-H_B, 14-OH), 1.65 (dd, $^2J_{6A/6B}$ = 11.9 Hz, $^3J_{6A/5A}$ = 7.7 Hz, 1H, 6-H_A), 1.63–1.58 (m, 2H, 8-H), 1.36 (s, 3H, 20-H), 1.35–1.28 (m, 1H, 11-H_A), 1.24–1.19 (m, 4H, 6-H_B, 18-H), 1.13–1.07 (m, 1H, 11-H_B), 1.06 (s, 3H, 19-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.73 (*Ph*), 128.58 (*Ph*), 127.19 (*Ph*), 127.08 (*Ph*), 88.25 (C-4), 84.37 (C-1), 81.33 (C-10), 76.97 (C-14), 69.48 (C-13), 63.38 (*Bn*), 44.71 (C-3), 41.71 (C-6), 40.53 (C-7), 40.49 (C-11), 38.90 (C-9), 37.35 (C-8), 35.61 (C-5), 33.77 (C-15), 32.83 (C-12), 30.56 (C-2), 25.65 (C-19), 20.21 (C-18), 18.40 (C-16, C-17), 17.76 (C-16, C-17), 17.48 (br, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3432 (br), 2952 (s), 2865 (m), 1453 (m), 1375 (s), 1197 (w), 1129 (m), 1098 (m), 1060 (m), 1027 (w) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{79}BrO_5$)$^-$: 549.22156, found: 549.22240; calcd for ([M+CH_3COO], $C_{29}H_{42}{}^{81}BrO_5$)$^-$: 551.21952, found: 551.22035. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –28.5° (c = 0.71, CH_2Cl_2).

[75] Reaction monitoring by TLC analysis (30% ethyl acetate in hexanes) showed gradual conversion of epoxide **71** (R_f = 0.15) to a putative bromo-triol intermediate (R_f = 0.30), which then reacted further to bromohydrin **127** (R_f = 0.80).

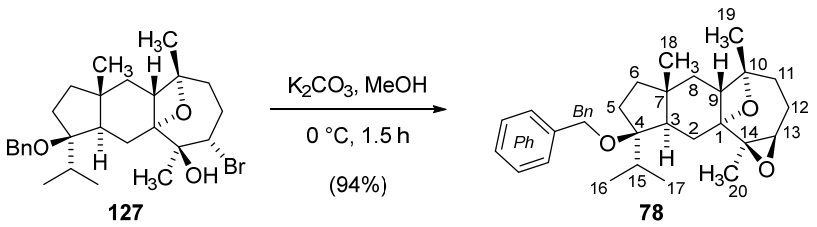
Synthesis of diol 128



A solution of bromohydrin **127** (4.0 mg, 8.14 µmol, 1 equiv) in tetrahydrofuran (2.5 mL) was treated with palladium on carbon (10 wt.%, 8.7 mg, 8.14 µmol, 1.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C. After 1 h, the mixture was diluted with ethyl acetate (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide diol **128** (2.7 mg, ≥99%) as a colourless solid.

Recrystallization of the product from ethyl acetate/hexanes gave crystals suitable for X-ray diffraction. **TLC** (30% ethyl acetate in hexanes): R_f = 0.35 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 4.68 (dd, $^3J_{13/12A}$ = 13.2 Hz, $^3J_{13/12B}$ =2.0 Hz, 1H, 13-H), 2.47–2.33 (m, 1H, 12-H_A), 2.33–2.23 (m, 2H, 2-H_A, 9-H), 2.11–2.04 (m, 1H, 12-H_B), 1.99–1.88 (m, 2H, 5-H_A, 14-OH), 1.79–1.64 (m, 3H, 3-H, 5-H_B, 6-H_A), 1.57–1.42 (m, 7H, 2-H_B, 8-H, 15-H, 20-H), 1.36–1.27 (m, 1H, 11-H_A), 1.21 (s, 3H, 18-H), 1.17–1.03 (m, 2H, 6-H_B, 11-H_B), 1.00 (s, 3H, 19-H), 0.91 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.86 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.71 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 84.05 (C-1), 83.49 (C-4), 81.48 (C-10), 77.14 (C-14), 69.31 (C-13), 47.64 (C-3), 40.92 (C-6), 40.45 (C-11), 40.24 (C-7), 38.89 (C-9), 37.97 (C-8, C-15), 37.92 (C-8, C-15), 37.04 (C-5), 32.84 (C-12), 28.48 (C-2), 25.58 (C-19), 20.19 (C-18), 18.36 (C-16, C-17), 17.66 (2C, C-16, C-17, C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3460 (br), 2954 (s), 2869 (m), 1468 (m), 1447 (m), 1374 (m), 1129 (m), 1094 (m), 1074 (m), 986 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{22}H_{36}{}^{79}BrO_5)^-$: 459.17461, found: 459.17549; calcd for ([M+CH_3COO], $C_{22}H_{36}{}^{81}BrO_5)^-$: 461.17257, found: 461.17345. $[\alpha]_D^{20}$ = –52.5° (c = 0.35, CH_2Cl_2).

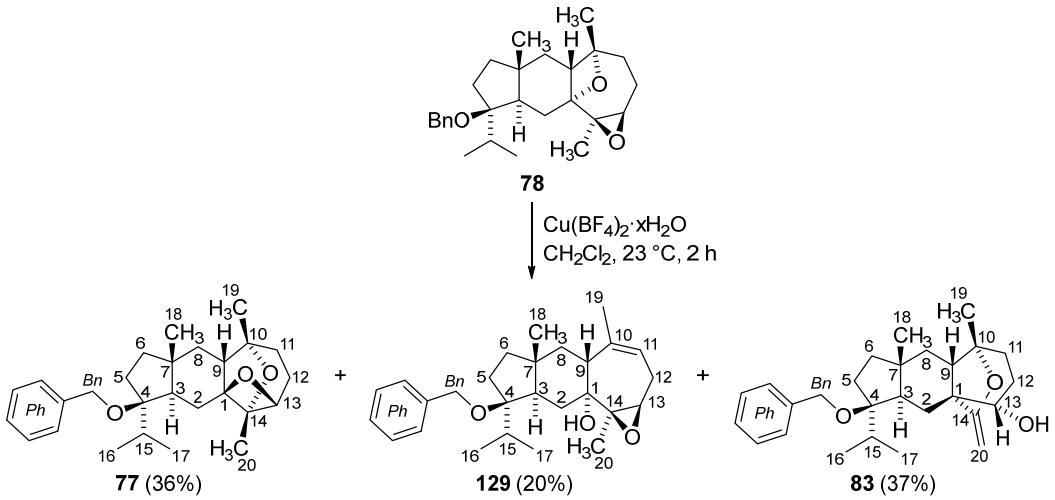
Synthesis of epoxide–oxetane 78



A solution of bromohydrin **127** (14.0 mg, 28.5 µmol, 1 equiv) in methanol (1.5 mL) was treated with potassium carbonate (9.8 mg, 71.2 µmol, 2.50 equiv) at 0 °C. After 1.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to provide epoxide–oxetane **78** (11.0 mg, 94%) as a colourless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.35 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 4.34–4.21 (m, 2H, *Bn*), 2.86–2.77 (m, 1H, 9-H), 2.73 (dd, $^3J_{13/12B}$ = 7.8 Hz, $^3J_{13/12A}$ = 3.1 Hz, 1H, 13-H), 2.45 (dd, $^2J_{2A/2B}$ = 14.8 Hz, $^3J_{2A/3}$ = 13.0 Hz, 1H, 2-H_A), 2.08–1.95 (m, 4H, 3-H, 5-H_A, 12-H_A, 15-H), 1.93–1.80 (m, 3H, 2-H_B, 11-H_A, 12-H_B), 1.72–1.62 (m, 3H, 5-H_B, 8-H), 1.62–1.54 (m, 1H, 6-H_A), 1.29 (s, 3H, 20-H), 1.28–1.17 (m, 2H, 6-H_B, 11-H_B), 1.11 (s, 3H, 19-H), 1.10 (s, 3H, 18-H), 1.02 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.61 (*Ph*), 128.61 (*Ph*), 127.14 (*Ph*), 126.90 (*Ph*), 88.18 (C-4), 83.25 (C-10), 82.82 (C-1), 66.30 (C-14), 63.25 (*Bn*), 61.39 (C-13), 45.27 (C-3), 41.07 (C-6), 40.69 (C-7), 38.70 (C-11), 37.36 (C-8), 35.44 (C-5), 35.20 (C-9), 33.63 (C-15), 32.64 (C-2), 26.31 (C-19), 25.30 (C-12), 19.67 (C-18), 19.15 (C-20), 18.29 (C-16, C-17), 17.67 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2940 (s), 2873 (m), 1496 (m), 1453 (s), 1376 (s), 1298 (w), 1149 (m), 1089 (m), 1055 (s), 1028 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2816, found: 410.2822. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.3° (c = 0.67, CH_2Cl_2).

Synthesis of dioxatricycle 77



A solution of epoxide–oxetane **78** (7.0 mg, 17.0 µmol, 1 equiv) in dichloromethane (1 mL) was treated with copper(II) tetrafluoroborate hydrate (4.4 mg, 17.0 µmol, 1.00 equiv) at 23 °C. After 2 h, the yellow mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% to 20% ethyl acetate in hexanes) to provide dioxatricycle **77** (2.5 mg, 36%) as a colourless solid, olefin **129** (1.4 mg, 20%) as a colourless oil, and enol ether **83** (2.6 mg, 37%) as a yellowish oil.

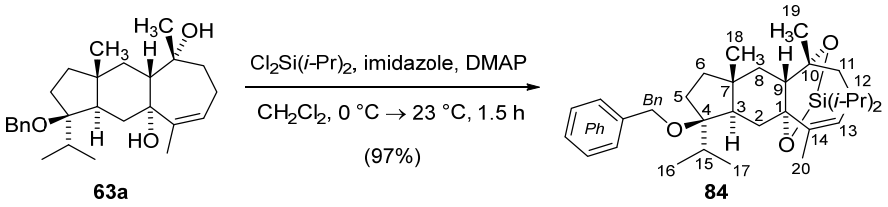
Dioxatricycle **77**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.45 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.40–7.34 (m, 2H, *Ph*), 7.24–7.18 (m, 2H, *Ph*), 7.14–7.08 (m, 1H, *Ph*), 4.31–4.17 (m, 3H, 13-H, *Bn*), 2.49–2.38 (m, 2H, 2-H), 2.10–1.91 (m, 4H, 5-H_A, 9-H, 11-H_A, 15-H), 1.87–1.79 (m, 1H, 12-H_A), 1.76–1.62 (m, 2H, 11-H_B, 12-H_B), 1.62–1.50 (m, 2H, 5-H_B, 8-H_A), 1.48–1.39 (m, 1H, 6-H_A), 1.38 (s, 3H, 20-H), 1.24–1.17 (m, 4H, 3-H, 19-H), 1.05 (s, 3H, 18-H), 1.02–0.92 (m, 5H, 6-H_B, 8-H_B, 16-H, 17-H), 0.77 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 140.43 (*Ph*), 128.58 (*Ph*), 127.15 (*Ph*), 126.96 (*Ph*), 97.31 (C-1), 87.70 (C-4), 82.52 (C-14), 81.38 (C-13), 81.21 (C-10), 62.76 (*Bn*), 52.00 (C-9), 47.78 (C-3), 41.83 (C-7), 40.73 (C-6, C-8), 40.63 (C-6, C-8), 34.86 (C-5), 33.17 (C-11, C-15), 33.14 (C-11, C-15), 30.89 (C-2), 24.19 (C-19), 24.12 (C-12), 18.47 (C-16, C-17), 18.38 (C-18), 18.08 (C-16, C-17), 17.71 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (s), 2930 (s), 1454 (m), 1385 (m), 1273 (w), 1189 (m), 1089 (m), 1057 (m), 1027 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2816, found: 410.2816. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –4.4° (c = 0.36, CH_2Cl_2).

Olefin **129**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.38 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.43–7.35 (m, 2H, *Ph*), 7.15–7.11 (m, 2H, *Ph*), 7.09–7.03 (m, 1H, *Ph*), 5.45–5.38 (m, 1H, 11-H), 4.37–4.24 (m, 2H, *Bn*), 2.85–2.76 (m, 2H, 9-H, 13-H), 2.50–2.36 (m, 2H, 2-H_A, 12-H_A), 2.33 (dd, $^2J_{2B/2A}$ = 14.1 Hz, $^3J_{2B/3}$ = 3.2 Hz, 1H, 2-H_B), 2.16–1.97 (m, 4H, 3-H, 5-H_A, 12-H_B, 15-H), 1.77 (app t, $^2J_{8A/8B}$ = $^3J_{8A/9}$ = 12.5 Hz, 1H, 8-H_A), 1.69–1.60 (m, 4H, 5-H_B, 19-H), 1.60–1.53 (m, 1H, 6-H_A), 1.49 (dd, $^2J_{8B/8A}$ = 12.5 Hz, $^3J_{8B/9}$ = 4.9 Hz, 1H, 8-H_B), 1.22 (s, 3H, 20-H), 1.22–1.17 (m, 4H, 6-H_B, 18-H), 1.08 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.53 (C-10, *Ph*), 140.48 (C-10, *Ph*), 128.54 (*Ph*), 127.04 (*Ph*), 127.00 (*Ph*), 124.86 (C-11), 88.59 (C-4), 75.15 (C-1), 65.40 (C-13), 63.49 (C-14), 63.18 (*Bn*), 44.91 (C-3), 41.95 (C-7), 41.19 (C-6), 40.94 (C-8), 37.88 (C-9), 34.25 (C-5), 33.33 (C-15), 32.69 (C-2), 27.47 (C-12), 22.33 (C-19), 19.95 (C-20), 18.56 (C-16, C-17), 18.50 (C-18), 18.33 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3474 (br), 2958 (s), 2933 (s), 2857 (m), 1453 (m), 1385 (m), 1198 (w), 1087 (m), 1055 (s), 1027 (m), 1000 (m) cm^{-1}. **HRMS** (ESI): calcd for ([M+CH_3COO], $C_{29}H_{41}O_5$)$^-$: 469.2954, found: 469.2962. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –19.6° (c = 0.21, CH_2Cl_2).

Enol ether **83**: **TLC** (20% ethyl acetate in hexanes): R_f = 0.28 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.45–7.39 (m, 2H, *Ph*), 7.26–7.21 (m, 2H, *Ph*), 7.14–7.08 (m, 1H, *Ph*), 4.57–4.55 (m, 1H, 20-H_A), 4.36–4.22 (m, 2H, *Bn*), 3.87 (d, $^2J_{20B/20A}$ = 1.3 Hz, 1H, 20-H_B), 3.23–3.13 (m, 1H, 13-H), 2.27 (dd, $^2J_{2A/2B}$ = 14.5 Hz, $^3J_{2A/3}$ = 3.1 Hz, 1H, 2-H_A), 2.09–1.98 (m, 2H, 5-H_A, 15-H), 1.93 (dd, $^2J_{2B/2A}$ = 14.5 Hz, $^3J_{2B/3}$ = 12.9 Hz, 1H, 2-H_B), 1.79–1.71 (m, 1H, 12-H_A), 1.69–1.63 (m, 1H, 3-H), 1.63–1.54 (m, 1H, 5-H_B), 1.54–1.45 (m, 3H, 6-H_A, 11-H_A, 12-H_B), 1.40 (dd, $^2J_{8A/8B}$ = 11.9 Hz, $^3J_{8A/9}$ = 5.3 Hz, 1H, 8-H_A), 1.30 (dd, $^3J_{9/8B}$ = 12.0 Hz, $^3J_{9/8A}$ = 5.3 Hz, 1H, 9-H), 1.18–1.08 (m, 4H, 6-H_B, 8-H_B, 11-H_B, 13-OH), 1.06 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 1.02 (s, 3H, 19-H), 1.00 (s, 3H, 18-H), 0.89 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (100 MHz, C_6D_6) δ 164.57 (C-14), 140.55 (*Ph*), 128.58 (*Ph*), 127.33 (*Ph*), 127.23 (*Ph*), 88.40 (C-4), 83.11 (C-10), 78.75 (C-20), 74.36 (C-13), 63.15 (*Bn*), 55.24 (C-1), 47.25 (C-9), 46.37 (C-3), 42.03 (C-7), 40.85 (C-6), 38.86 (C-8), 37.72 (C-11), 34.09 (C-5), 33.42 (C-15), 30.73 (C-12), 26.47 (C-2), 20.56 (C-19), 18.67 (C-18), 18.41 (C-16, C-17), 18.38 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3457 (br), 2934 (s), 2856 (m), 1664 (m), 1454 (m), 1379 (m), 1219 (w), 1197 (w), 1087 (m), 1060 (s), 1028 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_3$)$^+$: 410.2816, found: 410.2813. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.5° (c = 0.27, CH_2Cl_2).

Elaboration of Tricycle 63a

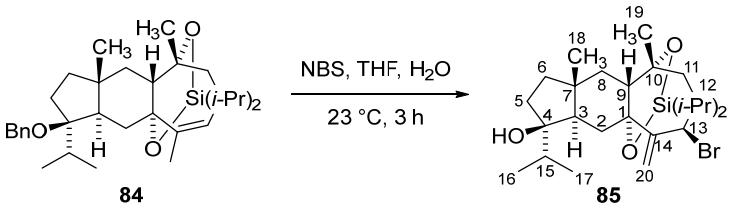
Synthesis of siloxane 84



A solution of tricycle **63a** (37.0 mg, 82.4 µmol, 1 equiv) in dimethyl formamide (1 mL) was treated sequentially with imidazole (84.1 mg, 1.24 mmol, 15.0 equiv), 4-dimethylaminopyridine (1.0 mg, 8.2 µmol, 0.10 equiv) and dichlorodiisopropylsilane (44.6 µL, 247 µmol, 3.00 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 1.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (3% ethyl acetate in hexanes) to provide siloxane **84** (42.0 mg, 97%) as a colourless oil.

TLC (3% ethyl acetate in hexanes): R_f = 0.42 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.41–7.35 (m, 2H, *Ph*), 7.23–7.17 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 5.51–5.43 (m, 1H, 13-H), 4.36–4.24 (m, 2H, *Bn*), 2.42 (dd, $^2J_{2A/2B}$ = 13.7 Hz, $^3J_{2A/3}$ = 2.7 Hz, 1H, 2-H_A), 2.36 (dd, $^3J_{9/8A}$ = 12.1 Hz, $^3J_{9/8B}$ = 5.0 Hz, 1H, 9-H), 2.21 (app td, $^2J_{11A/11B}$ = $^3J_{11A/12A}$ = 13.8 Hz, $^3J_{11A/12B}$ = 3.3 Hz, 1H, 11-H_A), 2.16–1.98 (m, 4H, 3-H, 5-H_A, 12-H_A, 15-H), 1.90–1.81 (m, 6H, 2-H_B, 11-H_B, 8-H_A, 20-H), 1.80–1.59 (m, 4H, 5-H_B, 6-H_A, 8-H_B, 12-H_B), 1.31–1.00 (m, 27H, 6-H_B, 16-H, 17-H, 18-H, 19-H, *Si(i-Pr)$_2$*). **^{13}C NMR** (100 MHz, C_6D_6) δ 142.13 (C-14), 140.62 (*Ph*), 128.54 (*Ph*), 127.28 (*Ph*), 127.15 (*Ph*), 126.43 (C-13), 88.73 (C-4), 80.26 (C-1), 77.49 (C-10), 63.18 (*Bn*), 47.18 (C-11), 44.49 (C-3), 42.04 (C-9), 41.80 (C-6), 41.57 (C-7), 39.48 (C-8), 37.30 (C-2), 34.29 (C-5), 33.27 (C-15), 32.79 (C-19), 24.39 (C-12), 20.78 (C-20), 19.31 (C-18), 18.56 (C-16, C-17, *Si(i-Pr)$_2$*), 18.52 (C-16, C-17, *Si(i-Pr)$_2$*), 18.40 (C-16, C-17, *Si(i-Pr)$_2$*), 18.28 (C-16, C-17, *Si(i-Pr)$_2$*), 17.83 (C-16, C-17, *Si(i-Pr)$_2$*), 17.70 (C-16, C-17, *Si(i-Pr)$_2$*), 15.66 (C-16, C-17, *Si(i-Pr)$_2$*), 14.59 (C-16, C-17, *Si(i-Pr)$_2$*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943 (s), 2863 (s), 1463 (m), 1385 (w), 1372 (w), 1248 (w), 1148 (m), 1116 (m), 1011 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{33}H_{52}O_3Si)^+$: 524.3680, found: 524.3686. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +17.6° (c = 1.00, CH_2Cl_2).

Synthesis of allylic bromide 85

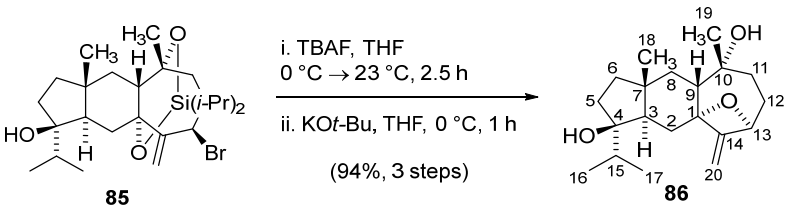


A solution of siloxane **84** (20.0 mg, 38.1 µmol, 1 equiv) in tetrahydrofuran (1 mL) and water (0.5 mL) was treated with *N*-bromosuccinimide (33.9 mg, 191 µmol, 5.00 equiv) at 23 °C. After 2 h, TLC analysis indicated incomplete conversion of siloxane **84**, and therefore a further portion of *N*-bromosuccinimide (33.9 mg, 191 µmol, 5.00 equiv) was added. After 1 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated to provide the crude allylic bromide **85**, which was used in the next step without further pruficiation.

An analytically pure sample of allylic bromide **85** was obtained by flash-column chromatography (8% ethyl acetate in hexanes).

TLC (10% ethyl acetate in hexanes): R_f = 0.33 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 5.51 (d, $^2J_{20A/20B}$ = 1.4 Hz, 1H, 20-H_A), 4.94 (d, $^2J_{20B/20A}$ = 1.4 Hz, 1H, 20-H_B), 4.81–4.75 (m, 1H, 13-H), 2.89–2.80 (m, 1H, 9-H), 2.24–2.06 (m, 2H, 2-H_A, 12-H_A), 1.99 (dd, $^3J_{3/2A}$ = 12.9 Hz, $^3J_{3/2B}$ = 2.8 Hz, 1H, 3-H), 1.95–1.63 (m, 9H, 2-H_B, 5-H, 6-H_A, 8-H, 11-H, 12-H_B), 1.62–1.53 (m, 1H, 15-H), 1.35 (s, 3H, 18-H), 1.26–1.01 (m, 18H, 6-H_B, 19-H, *Si(i-Pr)$_2$*), 0.96 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.92 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.54 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 158.24 (C-14), 118.50 (C-20), 83.40 (C-4), 79.15 (C-1), 77.55 (C-10), 57.23 (br, C-13), 48.00 (C-3), 42.52 (C-2, C-9, C-11), 42.39 (C-2, C-9, C-11), 42.33 (C-2, C-9, C-11), 41.80 (C-7), 40.69 (C-6), 39.77 (br, C-8), 37.52 (C-15), 35.59 (C-5), 34.22 (C-12), 29.94 (C-19), 20.01 (C-18), 18.61 (C-16, C-17, *Si(i-Pr)$_2$*), 18.32 (C-16, C-17, *Si(i-Pr)$_2$*), 18.31 (C-16, C-17, *Si(i-Pr)$_2$*), 17.82 (C-16, C-17, *Si(i-Pr)$_2$*), 17.54 (C-16, C-17, *Si(i-Pr)$_2$*), 17.31 (C-16, C-17, *Si(i-Pr)$_2$*), 16.13 (C-16, C-17, *Si(i-Pr)$_2$*), 15.18 (C-16, C-17, *Si(i-Pr)$_2$*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3492 (br), 2943 (s), 2865 (s), 1463 (m), 1385 (w), 1257 (w), 1127 (m), 1014 (s) cm^{-1}. **HRMS** (ESI and EI): mass not found.

Synthesis of allylic oxetane 86



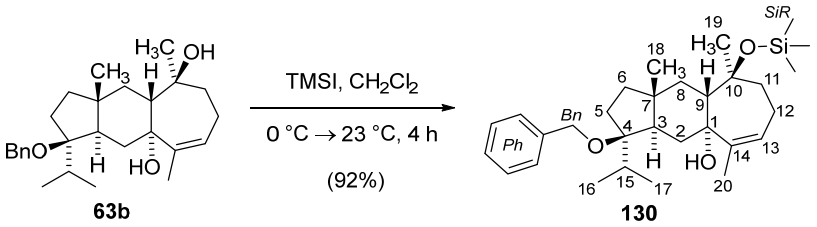
A solution of the crude allylic bromide **85** (assuming 38.1 µmol, 1 equiv) in tetrahydrofuran (1 mL) was treated with tetrabutylammonium fluoride solution (1 M in THF, 113 µL, 381 µmol, 10.0 equiv) at 0 °C. After 5 min, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 2.5 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude triol, which was used in the next step without further purification.

A solution of this crude triol (assuming 38.1 µmol, 1 equiv) in tetrahydrofuran (1 mL) was treated with potassium *tert*-butoxide (21.4 mg, 191 µmol, 5.00 equiv) at 0 °C. After 1 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate in hexanes) to provide allylic oxetane **86** (11.5 mg, 94% over three steps) as a colourless oil.

TLC (30% ethyl acetate in hexanes): R_f = 0.31 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 4.94–4.91 (m, 1H, 13-H), 4.64 (app t, $^2J_{20A/20B}$ = $^3J_{20A/13}$ = 1.6 Hz, 1H, 20-H_A), 4.40 (app t, $^2J_{20B/20A}$ = $^3J_{20B/13}$ = 1.6 Hz, 1H, 20-H_B), 4.08 (br s, 1H, 10-OH), 2.14–1.97 (m, 4H, 2-H_A, 8-H_A, 11-H_A, 12-H_A), 1.93 (app t, $^2J_{2B/2A}$ = $^3J_{2B/3}$ = 14.1 Hz, 1H, 2-H_B), 1.87–1.75 (m, 2H, 5-H_A, 8-H_B), 1.68–1.54 (m, 4H, 5-H_B, 6-H_A, 9-H, 11-H_B), 1.48–1.38 (m, 2H, 3-H, 15-H), 1.27 (s, 3H, 19-H), 1.26–1.21 (m, 1H, 12-H_B), 1.14–1.07 (m, 1H, 6-H_B), 1.06 (s, 3H, 18-H), 0.87 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.79 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.60 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 155.20 (C-14), 100.41 (C-20), 96.29 (C-1), 85.57 (C-13), 83.03 (C-4), 74.11 (C-10), 48.82 (C-9), 47.52 (C-3), 41.62 (C-7), 40.65 (C-6), 38.75 (C-8), 38.23 (C-5, C-11, C-15), 38.14 (C-5, C-11, C-15), 37.27 (C-5, C-11, C-15), 35.38 (C-2), 29.38 (C-19), 28.37 (C-12), 19.09 (C-18), 18.23 (C-16, C-17), 17.61 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3472 (br), 2927 (s), 2865 (m), 1718 (m), 1457 (m), 1378 (m), 1264 (m), 1130 (s), 1100 (s), 1070 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_3$)$^+$: 320.2346, found: 320.2344. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –52.0° (c = 0.78, CH_2Cl_2).

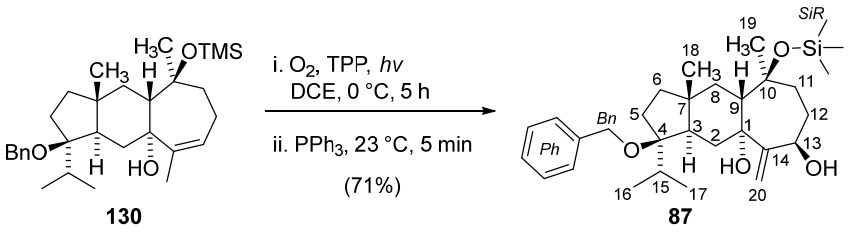
Total Synthesis of (+)-Dictyoxetane (3)

Synthesis of silyl ether 130



A solution of tricycle **63b** (140 mg, 339 µmol, 1 equiv) in dichloromethane (1.5 mL) was treated with *N*-trimethylsilylimidazole (0.50 mL, 3.39 mmol, 10.0 equiv) at 0 °C. After 5 min, the mixture was warmed to 23 °C. After 4 h, the mixture was diluted with pH 7 buffer solution (35 mL) and diethyl ether (20 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide silyl ether **130** (151 mg, 92%) as a colourless oil.
TLC (10% ethyl acetate in hexanes): R_f = 0.49 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.37–7.31 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.12–7.06 (m, 1H, *Ph*), 5.66–5.60 (m, 1H, 13-H), 4.30–4.21 (m, 2H, *Bn*), 2.55–2.43 (m, 1H, 12-H_A), 2.34 (dd, $^3J_{9/8B}$ = 12.5 Hz, $^3J_{9/8A}$ = 3.8 Hz, 1H, 9-H), 2.23 (dd, $^2J_{8A/8B}$ = 12.2 Hz, $^3J_{8A/9}$ = 3.8 Hz, 1H, 8-H_A), 2.17 (d, $^2J_{2A/2B}$ = 11.5 Hz, 1H, 2-H_A), 2.10–1.99 (m, 2H, 5-H_A, 15-H), 1.95–1.86 (m, 3H, 2-H_B, 3-H, 11-H_A), 1.81–1.57 (m, 8H, 5-H_B, 6-H_A, 8-H_B, 11-H_B, 12-H_B, 20-H), 1.46 (s, 3H, 19-H), 1.32–1.20 (m, 1H, 6-H_B), 1.18 (s, 3H, 18-H), 1.03 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.94 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H), 0.86 (br s, 1H, 1-OH), 0.17 (s, 9H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6) δ 141.15 (C-14), 140.62 (*Ph*), 131.16 (C-13), 128.49 (*Ph*), 127.11 (*Ph*), 127.08 (*Ph*), 88.69 (C-4), 79.83 (C-10), 76.72 (C-1), 63.03 (*Bn*), 47.81 (C-9), 45.96 (C-3), 45.83 (C-11), 41.66 (C-6, C-17), 41.53 (C-6, C-7), 39.78 (C-8), 38.52 (C-2), 34.25 (C-5), 33.21 (C-15), 28.43 (C-19), 22.42 (C-12), 21.39 (C-20), 18.70 (C-18), 18.63 (C-16, C-17), 18.39 (C-16, C-17), 2.86 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3464 (br), 2955 (s), 2857 (m), 1453 (m), 1379 (m), 1249 (m), 1151 (w), 1105 (m), 1086 (m), 1027 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–H_2O], $C_{30}H_{46}O_2Si$)$^+$: 466.3267, found: 466.3249. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.8° (c = 0.86, CH_2Cl_2).

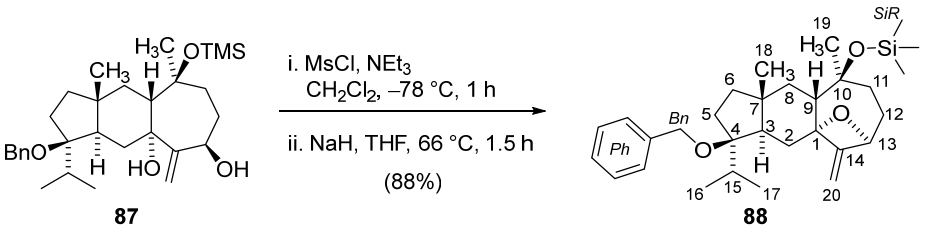
Synthesis of allylic alcohol 87



A stream of pure oxygen gas was bubbled below the liquid surface of a solution of silyl ether **130** (75.0 mg, 155 µmol, 1 equiv) in dichloroethane (20 mL) containing a catalytic amount of tetraphenylporphyrin (TPP, tip of a spatula) at 0 °C. After 3 min, the mixture was irradiated with a Replux Belgium RL 160W (225–235 Volts) lamp. After 5 h, TLC analysis (20% ethyl acetate in hexanes) indicated complete conversion of silyl ether **130** (R_f = 0.80) to the hydroperoxide intermediate (R_f = 0.29). Sparging with oxygen and irradiation was discontinued, triphenylphosphine (81.2 mg, 309 µmol, 2.00 equiv) was added and the mixture was then allowed to warm to 23 °C. After 5 min, TLC analysis (20% ethyl acetate in hexanes) indicated complete reduction of the hydroperoxide intermediate and formation of allylic alcohol **87** (R_f = 0.23). The mixture was concentrated in vacuo, and the residue was purified by flash-column chromatography on silica gel (10% to 20% ethyl acetate in hexanes) to provide allylic alcohol **87** (55.0 mg, 71%) as a colourless foam.

TLC (20% ethyl acetate in hexanes): R_f = 0.23 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.39–7.36 (m, 2H, *Ph*), 7.22–7.18 (m, 2H, *Ph*), 7.10–7.07 (m, 1H, *Ph*), 5.17–5.11 (m, 1H, 20-H_A), 4.74 (br s, 1H, 20-H_B), 4.29–4.23 (m, 2H, *Bn*), 4.21–4.18 (m, 1H, 13-H), 2.64 (br d, $^3J_{9/8B}$ = 12.6 Hz, 1H, 9-H), 2.40–2.35 (m, 1H, 2-H_A), 2.12–2.03 (m, 3H, 5-H_A, 8-H_A, 15-H), 1.97 (dd, $^3J_{3/2A}$ = 13.2 Hz, $^3J_{3/2B}$ = 2.9 Hz, 1H, 3-H), 1.93–1.89 (m, 2H, 12-H), 1.70–1.57 (m, 6H, 2-H_B, 5-H_B, 6-H_A, 8-H_B, 11-H), 1.35 (s, 3H, 19-H), 1.32 (s, 3H, 18-H), 1.28–1.22 (m, 1H, 6-H_B), 1.06 (br s, 1H, 1-OH), 1.04 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.95 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H), 0.80–0.77 (m, 1H, 13-OH), 0.16 (s, 9H, *SiR*). **^{13}C NMR** (200 MHz, C_6D_6) δ 160.21 (C-14), 140.49 (*Ph*), 128.52 (*Ph*), 127.65 (*Ph*), 127.22 (*Ph*), 111.37 (C-20), 88.65 (C-4), 79.35 (C-10), 76.91 (C-1), 75.47 (br, C-13), 63.39 (*Bn*), 46.82 (2C, C-3, C-9), 43.68 (br, C-2), 42.81 (C-7), 41.16 (C-6), 39.29 (C-11), 37.85 (C-8), 34.08 (C-5), 33.23 (C-15), 29.82 (C-12), 26.99 (C-18), 19.42 (C-19), 18.72 (C-16, C-17), 18.59 (C-16, C-17), 2.91 (*SiR*). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3463 (br), 2953 (s), 2869 (m), 1453 (m), 1385 (m), 1248 (s), 1118 (m), 1041 (s) cm^{-1}. **HRMS** (EI): calcd for ([M–*i*Pr], $C_{27}H_{41}O_4Si)^+$: 457.2774, found: 457.2781. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +28.5° (c = 0.83, CH_2Cl_2).

Synthesis of oxetane 88

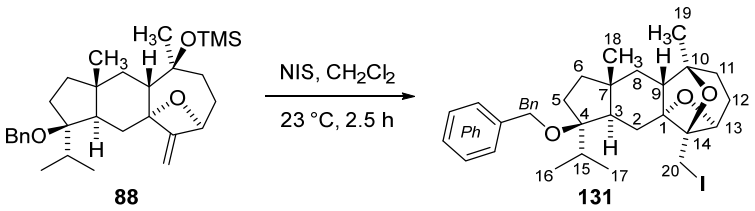


A solution of allylic alcohol **87** (27.0 mg, 53.9 µmol, 1 equiv) in dichloromethane (2.5 mL) was treated sequentially with triethylamine (172 µL, 1.24 mmol, 23.0 equiv) and methanesulfonyl chloride (41.7 µL, 0.54 mmol, 10.0 equiv) at –78 °C. After 1 h, the cooling bath was removed and the mixture was immediately diluted with saturated aqueous sodium hydrogen carbonate solution (25 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude allylic mesylate, which was used in the next step without further purification.

A solution of the crude allylic mesylate (assuming 53.9 µmol) in tetrahydrofuran (4 mL) was treated with sodium hydride (60 wt.% in mineral oil, 10.8 mg, 0.27 mmol, 5.00 equiv) at 23 °C. The resulting mixture was heated to 66 °C, whereupon a further portion of sodium hydride (60 wt.% in mineral oil, 10.8 mg, 0.27 mmol, 5.00 equiv) was added. After 1.5 h, the mixture was cooled to 0 °C and *carefully* diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (15 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide oxetane **88** (23.0 mg, 88% over two steps) as a colourless oil. **TLC** (10% ethyl acetate in hexanes): R_f = 0.50 (CAM). *Note: Due to hindered rotation of the C10–OTMS group, oxetane **88** shows severe signal broadening in NMR spectra recorded at 23 °C. Better resolved spectra could be obtained at 65 °C. However, some carbon atoms are still not visible in the ^{13}C NMR spectrum due to signal broadening. Most protons could therefore also not be assigned.*

^{1}H NMR (400 MHz, C_6D_6, 65 °C) δ 7.37–7.33 (m, 2H, *Ph*), 7.22–7.17 (m, 2H, *Ph*), 7.11–7.05 (m, 1H, *Ph*), 4.96–4.91 (m, 1H, 13-H), 4.65 (dd, *J* = 2.0 Hz, 1.2 Hz, 1H, 20-H_A), 4.47 (app t, *J* = 1.2 Hz, 1H, 20-H_B), 4.35–4.26 (m, 2H, *Bn*), 2.33 (dd, *J* = 14.1 Hz, 3.2 Hz, 1H), 2.26–2.17 (m, 1H), 2.14–2.04 (m, 4H), 2.00–1.82 (m, 3H), 1.72–1.50 (m, 5H), 1.42 (br s, 3H, 19-H), 1.25–1.17 (m, 1H), 1.15 (s, 3H, 18-H), 1.04 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.93 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.16 (s, 9H, *SiR*). **^{13}C NMR** (100 MHz, C_6D_6, 65 °C) δ 156.66, 140.66, 128.51, 127.47, 127.17, 99.29, 88.61, 84.25, 63.57, 51.60, 45.44, 42.29, 41.41, 39.61, 37.06, 34.14, 33.39, 29.93, 18.99, 18.40, 18.27, 2.98. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (s), 1454 (m), 1374 (m), 1349 (m), 1248 (s), 1159 (w), 1110 (s), 1084 (s), 1057 (s), 1027 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{30}H_{46}O_3Si)^+$: 482.3211, found: 482.3211. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +4.2° (c = 0.30, CH_2Cl_2).

Synthesis of iodide 131

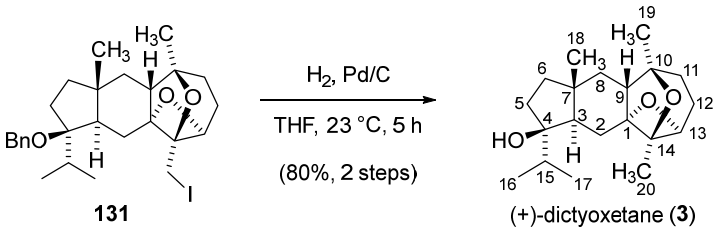


A solution of oxetane **88** (22.0 mg, 45.6 µmol, 1 equiv) in dichloromethane (2 mL) was treated with *N*-iodosuccinimide (12.3 mg, 54.7 µmol, 1.20 equiv) and the resulting pink mixture was stirred at 23 °C under exclusion of light. After 1.5 h, TLC analysis indicated incomplete conversion of oxetane **88**, and therefore a further portion of *N*-iodosuccinimide (3.1 mg, 13.7 µmol, 0.30 equiv) was added. After 1 h, the mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered through a pad of Celite and the filtrate was concentrated (under exclusion of light) to provide the crude iodide **131**, which was used in the next step without further pruficiation.

An analytically pure sample of iodide **131** could be obtained by *rapid* purification by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) in the dark.

TLC (10% ethyl acetate in hexanes): R_f = 0.43 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.42–7.38 (m, 2H, *Ph*), 7.28–7.24 (m, 2H, *Ph*), 7.14–7.10 (m, 1H, *Ph*), 4.29–4.24 (m, 2H, *Bn*), 4.21 (d, $^3J_{13/12B}$ = 3.9 Hz, 1H, 13-H), 3.04 (d, $^2J_{20A/20B}$ = 10.6 Hz, 1H, 20-H_A), 2.90 (d, $^2J_{20B/20A}$ = 10.6 Hz, 1H, 20-H_B), 2.15–2.12 (m, 1H, 3-H), 2.12–2.07 (m, 1H, 5-H_A), 2.06–2.02 (m, 1H, 15-H), 1.97 (dd, $^2J_{2A/2B}$ = 12.5 Hz, $^3J_{2A/3}$ = 2.7 Hz, 1H, 2-H_A), 1.84 (app t, $^2J_{2B/2A}$ = $^3J_{2B/3}$ = 12.5 Hz, 1H, 2-H_B), 1.75–1.69 (m, 1H, 11-H_A), 1.69–1.59 (m, 4H, 5-H_B, 9-H, 12-H), 1.56–1.53 (m, 1H, 8-H_A), 1.50 (dd, $^3J_{6A/5A}$ = 11.7 Hz, $^2J_{6A/6B}$ = 7.9 Hz, 1H, 6-H_A), 1.35 (dd, $^2J_{11B/11A}$ = 13.0 Hz, $^3J_{11B/12A}$ = 8.0 Hz, 1H, 11-H_B), 1.24–1.22 (m, 1H, 8-H_B), 1.21 (s, 3H, 19-H), 1.19–1.14 (m, 1H, 6-H_B), 1.09–1.06 (m, 6H, 16-H, 17-H, 18-H), 0.96 (d, ^3J = 6.7 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 140.42 (*Ph*), 128.56 (*Ph*), 128.29 (*Ph*), 127.34 (*Ph*), 95.57 (C-1), 87.21 (C-4), 82.11 (C-14), 81.04 (C-13), 80.23 (C-10), 63.03 (*Bn*), 53.68 (C-9), 45.70 (C-3), 42.99 (C-7), 40.14 (C-6), 35.08 (C-8), 34.50 (C-5), 33.07 (C-15), 30.81 (C-2), 26.77 (C-19), 24.90 (C-11), 24.19 (C-12), 19.88 (C-18), 18.46 (C-16, C-17), 18.42 (C-16, C-17), 5.45 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (s), 2926 (s), 2857 (m), 1729 (w), 1453 (m), 1378 (m), 1348 (m), 1191 (m), 1147 (m), 1022 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{37}O_3I)^+$: 536.1782, found: 536.1773.

Synthesis of (+)-dictyoxetane (3)



A solution of the crude iodide **131** (assuming 45.6 µmol, 1 equiv) in tetrahydrofuran (5 mL) was treated with palladium on carbon (10 wt.%, 97.1 mg, 91.2 µmol, 2.00 equiv) at 23 °C. An atmosphere of hydrogen was maintained by sparging the mixture with a stream of hydrogen gas using a stainless steel needle for 5 min and vigorous stirring of the suspension was then continued under hydrogen atmosphere at 23 °C.[76] After 5 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to provide (+)-dictyoxetane (**3**) (11.7 mg, 80% over two steps) as a colourless oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.43 (CAM). **^{1}H NMR** (400 MHz, C_6D_6) δ 4.25 (br d, $^3J_{13/12A}$ = 3.9 Hz, 1H, 13-H), 2.04 (dd, $^3J_{3/2B}$ = 12.9 Hz, $^3J_{3/2A}$ = 2.8 Hz, 1H, 3-H), 1.94–1.86 (m, 1H, 5-H_A), 1.86–1.67 (m, 4H, 2-H_A, 5-H_B, 11-H_A, 12-H_A), 1.67–1.51 (m, 5H, 6-H_A, 8-H_A, 9-H, 12-H_B, 15-H), 1.48–1.39 (m, 2H, 2-H_B, 11-H_B), 1.30 (s, 3H, 20-H), 1.28 (s, 3H, 19-H), 1.27–1.24 (m, 1H, 8-H_B), 1.12 (s, 3H, 18-H), 1.10–1.05 (m, 1H, 6-H_B), 0.95 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.89 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.54 (br s, 1H, 4-OH). **^{13}C NMR** (100 MHz, C_6D_6) δ 97.05 (C-1), 82.45 (C-4), 81.17 (C-13), 80.77 (C-14), 79.78 (C-10), 53.30 (C-9), 47.89 (C-3), 42.67 (C-7), 39.72 (C-6), 36.68 (C-15), 35.43 (C-5), 35.08 (C-8), 28.00 (C-2), 27.06 (C-19), 25.13 (C-11), 24.03 (C-12), 20.05 (C-18), 18.58 (C-16, C-17), 17.68 (C-16, C-17), 16.49 (C-20). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3484 (br), 2956 (s), 2928 (s), 2862 (m), 1452 (m), 1388 (m), 1375 (m), 1292 (w), 1148 (m), 1067 (m), 1019 (m) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_3$)$^+$: 320.2346, found: 320.2349. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +29.1° (c = 1.00, $CHCl_3$). (Lit.:[77] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +35.0° (c = 3.00, $CHCl_3$).

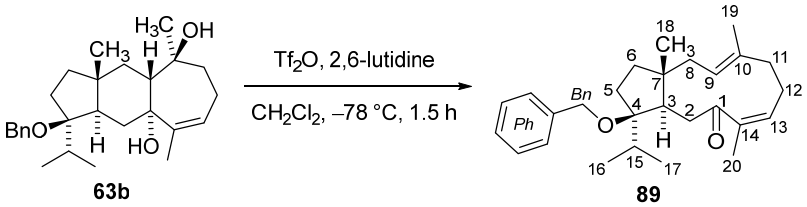
^{1}H NMR (800 MHz, $CDCl_3$) δ 4.38 (br d, $^3J_{13/12A}$ = 3.3 Hz, 1H, 13-H), 2.04 (ddd, $^2J_{5A/5B}$ = 14.5 Hz, $^3J_{5A/6B}$ = 9.6 Hz, $^3J_{5A/6A}$ = 1.1 Hz, 1H, 5-H_A), 1.86–1.79 (m, 4H, 2-H_A, 3-H, 11-H_A, 12-H_A), 1.77–1.71 (m, 2H, 5-H_B, 15-H), 1.69–1.59 (m, 3H, 6-H_A, 9-H, 12-H_B), 1.54–1.47 (m, 3H, 2-H_B, 8-H_A, 11-H_B), 1.40 (dd, $^2J_{8B/8A}$ = 11.5 Hz, $^3J_{8B/9}$ = 3.4 Hz, 1H, 8-H_B), 1.37 (s, 3H, 20-H), 1.30 (s, 3H, 19-H), 1.21–1.15 (m, 1H, 6-H_B), 1.09 (s, 3H, 18-H), 1.08 (br s, 1H, 4-OH), 0.97 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.90 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 97.41 (C-1), 82.87 (C-4), 81.45 (C-13), 80.81 (C-14), 80.23 (C-10), 52.80 (C-9), 48.14 (C-3), 42.65 (C-7), 39.19 (C-6), 36.73 (C-15), 35.97 (C-5), 34.73 (C-8), 27.78 (C-2), 26.86 (C-19), 24.76 (C-11), 23.51 (C-12), 20.13 (C-18), 18.70 (C-16, C-17), 17.64 (C-16, C-17), 16.30 (C-20).

[76] Reaction monitoring by TLC analysis (30% ethyl acetate in hexanes) showed gradual conversion of iodide **131** (R_f = 0.77) to the dehalogenated intermediate (R_f = 0.69) (usually within 1-2 h), which then was further reduced to (+)-dictyoxetane (**3**) (R_f = 0.34). Occasionally the reaction was found to stall after complete dehalogenation. In these cases, the mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was then resubmitted to the analogous hydrogenation conditions with fresh palladium on carbon.

[77] a) K. C. Pullaiah, R. K. Surapaneni, C. B. Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, H. Cun-heng, J. Clardy, *J. Org. Chem.* **1985**, *50*, 3665. b) C. B. Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, H. Cunheng, J. Clardy, *J. Org. Chem.* **1986**, *51,* 2736.

Total Synthesis of (+)-Dolabellane V (6)

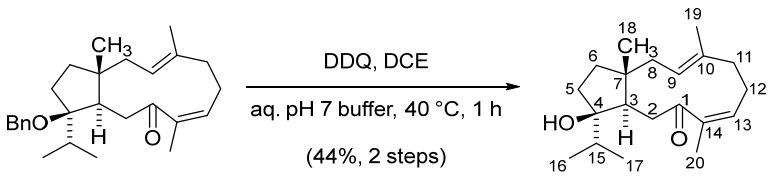
Synthesis of macrocycle 89



63b **89**

A solution of tricycle **63b** (6.5 mg, 15.8 µmol, 1 equiv) in dichloromethane (1 mL) was treated sequentially with 2,6-lutidine (36.7 µL, 315 µmol, 20.0 equiv) and trifluoromethanesulfonic anhydride (13.1 µL, 78.8 µmol, 5.00 equiv) at –78 °C. After 1.5 h, the mixture was diluted with pH 7 buffer solution (15 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl
ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to provide macrocycle **89** (4.0 mg) as a colourless oil. *Note: At this stage macrocycle **89** remained contaminated with minor, unidentified impurities and the yield was thus determined after subsequent benzyl deprotection.*
TLC (10% ethyl acetate in hexanes): R_f = 0.47 (CAM). **^{1}H NMR** (800 MHz, C_6D_6) δ 7.35–7.33 (m, 2H, *Ph*), 7.24–7.21 (m, 2H, *Ph*), 7.12–7.08 (m, 1H, *Ph*), 5.30–5.26 (m, 1H, 13-H), 5.17–5.13 (m, 1H, 9-H), 4.30–4.20 (m, 2H, *Bn*), 3.25–3.19 (m, 1H, 12-H_A), 2.87–2.80 (m, 2H, 2-H), 2.48 (dd, $^3J_{3/2A}$ = 6.0 Hz, $^3J_{3/2B}$ = 3.2 Hz, 1H, 3-H), 2.23 (dd, $^2J_{8A/8B}$ = 13.5 Hz, $^3J_{8A/9}$ = 11.2 Hz, 1H, 8-H_A), 2.03 (h, $^3J_{15/16\text{-}17}$ = 6.8 Hz, 1H, 15-H), 2.00–1.95 (m, 1H, 11-H_A), 1.94–1.89 (m, 1H, 8-H_B), 1.83–1.78 (m, 1H, 5-H_A), 1.77–1.73 (m, 1H, 12-H_B), 1.69 (s, 3H, 19-H), 1.67–1.58 (m, 5H, 5-H_B, 11-H_B, 20-H), 1.57–1.53 (m, 1H, 6-H_A), 1.37–1.32 (m, 1H, 6-H_B), 1.14 (s, 3H, 18-H), 1.12–1.10 (m, 6H, 16-H, 17-H). **^{13}C NMR** (200 MHz, C_6D_6) δ 204.98 (C-1), 140.54 (*Ph*), 139.14 (C-14), 135.74 (C-10), 133.56 (C-13), 128.58 (*Ph*), 128.29 (*Ph*), 127.21 (*Ph*), 122.46 (C-9), 90.41 (C-4), 63.38 (*Bn*), 45.57 (C-7), 45.43 (C-3), 43.29 (C-8), 42.05 (C-6), 39.64 (C-11), 38.32 (C-2), 33.45 (C-15), 32.15 (C-5), 23.43 (C-12), 22.85 (C-18), 20.90 (C-20), 18.43 (C-16, C-17), 17.12 (C-16, C-17), 16.63 (C-19). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2927 (s), 2875 (s), 1694 (s), 1635 (w), 1454 (s), 1379 (s), 1207 (w), 1085 (m), 1049 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{27}H_{38}O_2$)$^+$: 394.2866, found: 394.2888.

Synthesis of (+)-dolabellane V (6)

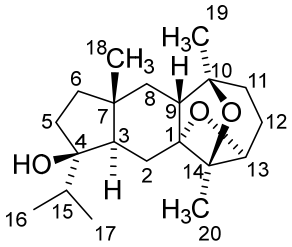


89 (+)-dolabellane V (**6**)

A solution of macrocycle **89** (4.0 mg, 10.1 µmol, 1 equiv) in dichloroethane (1 mL) and aqueous pH 7 buffer solution (0.1 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (11.5 mg, 50.7 µmol, 5.00 equiv) and the resulting brown mixture heated to 40 °C. After 1 h, the mixture was cooled to 23 °C and saturated aqueous sodium hydrogen carbonate solution (1 mL) was added. After 1 h, the mixture was diluted with more saturated aqueous sodium hydrogen carbonate solution (10 mL) and diethyl ether (10 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexanes) to provide (+)-dolabellane V (**6**) (2.1 mg, 44% over two steps) as a colourless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.29 (CAM). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 5.57 (app t, $^3J_{13/12A}$ = $^3J_{13/12B}$ = 8.6 Hz, 1H, 13-H), 5.04–4.99 (m, 1H, 9-H), 2.81–2.73 (m, 1H, 12-H_A), 2.71 (dd, $^2J_{2A/2B}$ = 14.9 Hz, $^3J_{2A/3}$ = 8.5 Hz, 1H, 2-H_A), 2.24–2.19 (m, 1H, 12-H_B), 2.18 (d, $^2J_{2B/2A}$ = 14.7 Hz, 1H, 2-H_B), 2.12 (dd, $^2J_{8A/8B}$ = 13.4 Hz, $^3J_{8A/9}$ = 10.7 Hz, 1H, 8-H_A), 2.04–1.98 (m, 2H, 3-H, 11-H_A), 1.95 (br s, 3H, 20-H), 1.90–1.78 (m, 3H, 8-H_B, 11-H_B, 15-H), 1.76–1.70 (m, 2H, 5-H_A, 6-H_A), 1.57 (br s, 3H, 19-H), 1.53–1.45 (m, 2H, 5-H_B, 6-H_B), 1.11 (s, 3H, 18-H), 1.00 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H), 0.99 (d, ^3J = 6.8 Hz, 3H, 16-H, 17-H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 207.54 (C-1), 138.09 (C-14), 135.80 (C-13), 135.24 (C-10), 122.51 (C-9), 87.88 (C-4), 48.12 (C-3), 44.72 (C-7), 43.20 (C-8), 40.82 (C-6), 37.92 (C-11), 37.32 (C-2), 34.54 (C-15), 31.33 (C-5), 25.07 (C-12), 24.78 (C-18), 21.43 (C-20), 18.29 (C-16, C-17), 17.78 (C-19), 17.59 (C-16, C-17). **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3512 (br), 2929 (s), 2870 (s), 1681 (s), 1627 (m), 1454 (s), 1380 (s), 1268 (m), 1203 (m), 1156 (m), 1082 (m), 1033 (s) cm^{-1}. **HRMS** (EI): calcd for ([M], $C_{20}H_{32}O_2)^+$: 304.2400, found: 304.2404. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +22.2° (c = 0.35, $CHCl_3$). (Lit.:[52] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.2° (c = 6.16, $CHCl_3$).

6.5.4 ^{1}H and ^{13}C NMR Comparison of Natural[52] and Synthetic (+)-Dictyoxetane

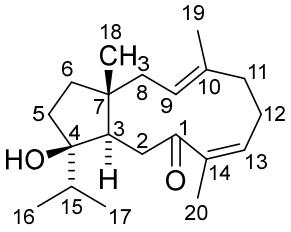


^{1}H Position	Natural (360 MHz, C_6D_6)	Synthetic (400 MHz, C_6D_6)	Δδ (ppm)
3	2.03 (dd, 13.0 Hz, 2.5 Hz, 1H)	2.04 (dd, 12.9 Hz, 2.6 Hz, 1H)	0.01
5a	1.90 (dd, 14.0 Hz, 9.5 Hz, 1H)	1.90 (dd, 14.0 Hz, 9.5 Hz, 1H)	0
13	4.25 (br d, 1H)	4.25 (br d, 1H)	0
16	0.95 (d, 6.5 Hz, 3H)	0.95 (d, 6.8 Hz, 3H)	0
17	0.88 (d, 6.5 Hz, 3H)	0.89 (d, 6.8 Hz, 3H)	0.01
18	1.11 (s, 3H)	1.12 (s, 3H)	0.01
19	1.27 (s, 3H)	1.28 (s, 3H)	0.01
20	1.29 (s, 3H)	1.30 (s, 3H)	0.01

Resonances of all other protons occur as overlapping multiplets and are not listed in this table.

^{13}C Position	Natural (50 MHz, $CDCl_3$)	Synthetic (200 MHz, $CDCl_3$)	Δδ (ppm)
1	97.2	97.4	0.2
2	27.6	27.8	0.2
3	48.0	48.1	0.1
4	82.7	82.9	0.2
5	35.9	36.0	0.1
6	39.1	39.2	0.2
7	42.5	42.6	0.1
8	34.6	34.7	0.1
9	52.6	52.8	0.2
10	80.1	80.2	0.1
11	24.6	24.8	0.2
12	23.4	23.5	0.1
13	81.3	81.4	0.1
14	80.6	80.8	0.2
15	36.6	36.7	0.1
16	17.5	17.6	0.1
17	18.5	18.7	0.2
18	20.0	20.1	0.1
19	26.7	26.9	0.2
20	16.1	16.3	0.1

6.5.5 ^{1}H and ^{13}C NMR Comparison of Natural[52] and Synthetic (+)-Dolabellane V



^{1}H Position	Natural ($CDCl_3$)	Synthetic (800 MHz, $CDCl_3$)	Δδ (ppm)
2a	2.70 (dd, 15.0 Hz, 8.5 Hz, 1H)	2.71 (dd, 14.9 Hz, 8.5 Hz, 1H)	0.01
2b	2.18 (dd, 15.0 Hz, 1.5 Hz, 1H)	2.18 (d, 14.7 Hz, 1H)	0
8a	2.12 (dd, 13.0 Hz, 11.0 Hz, 1H)	2.12 (dd, 13.4 Hz, 10.7 Hz, 1H)	0
9	5.02 (dd, 10.5 Hz, 5.0 Hz, 1H)	5.04–4.99 (m, 1H)	0
12a	2.76 (m, 1H)	2.81–2.73 (m, 1H)	0
12b	2.22 (m, 1H)	2.24–2.19 (m, 1H)	0
13	5.58 (t, 8.5 Hz, 1H)	5.57 (app t, 8.6 Hz, 1H)	0.01
16	1.00 (d, 7.0 Hz, 3H)	1.00 (d, 6.8 Hz, 3H)	0
17	0.99 (d, 7.0 Hz, 3H)	0.99 (d, 6.8 Hz, 3H)	0
18	1.11 (s, 3H)	1.11 (s, 3H)	0
19	1.57 (br s, 3H)	1.57 (br s, 3H)	0
20	1.95 (br s, 3H)	1.95 (br s, 3H)	0

Resonances of all other protons occur as overlapping multiplets and are not listed in this table.

^{13}C Position	Natural ($CDCl_3$)	Synthetic (200 MHz, $CDCl_3$)	Δδ (ppm)
1	207.4	207.5	0.1
2	37.1	37.3	0.2
3	47.9	48.1	0.2
4	87.6	87.9	0.3
5	31.0	31.3	0.3
6	40.6	40.8	0.2
7	44.4	44.7	0.3
8	43.0	43.2	0.2
9	122.2	122.5	0.3
10	134.9	135.2	0.3
11	37.6	37.9	0.3
12	24.9	25.1	0.2
13	135.6	135.8	0.2
14	137.8	138.1	0.3
15	34.2	34.5	0.3
16	18.1	18.3	0.2
17	17.4	17.6	0.2
18	24.5	24.8	0.3
19	17.6	17.8	0.2
20	21.2	21.4	0.2

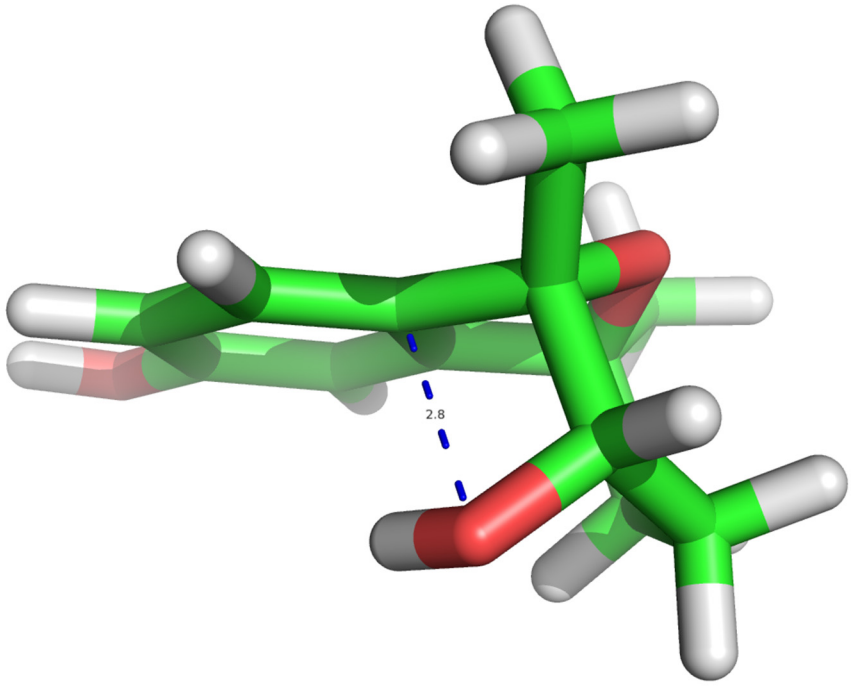
6.5.6 Computational Details

Conformational Search. Conformational searches were performed with Spartan'14 (Spartan'14, Wavefunction, Inc., Irvine CA). An initial subset of reasonable conformers was generated using the molecular mechanics MMFF force field[78] and the 100 structures of lowest energy were documented. A subset of these conformers was then further optimized via DFT calculations.

Density Functional Theory. All DFT calculations were performed using Gaussian 09 (Revision A.02).[79] Each starting structure, already a local minimum with respect to the conformational search potential energy surface, was optimized (gas phase) with the B3LYP hybrid functional[80] employing the 6-31G(d) basis set. The interatom distances are displayed in [Å].

Computed Geometries and Energies.

Phenol 12a (*boat*)



Computed sum of electronic and thermal Enthalpies = –730.386037 hartee.

Cartesian coordinates:

C	0	-2.88789	0.64727	0.17941
C	0	-2.86044	-0.54898	-0.44168
C	0	-1.72743	-1.25598	-0.58773
C	0	-0.60432	-0.73556	-0.08309
C	0	-0.60918	0.44649	0.53017

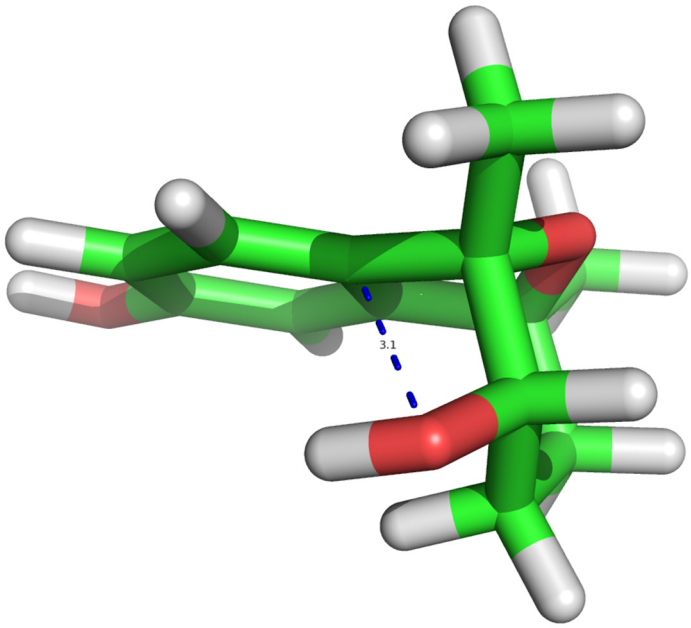
[78] T. A. Halgren, *J. Comput. Chem.* **1996**, *17*, 490.

[79] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[80] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648. b) P. J. Stephens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, *J. Chem. Phys.* **1994**, *98*, 11623.

C	0	-1.73842	1.14953	0.66922
O	0	-4.05646	1.33375	0.29982
C	0	0.82146	-1.21982	-0.11766
C	0	1.48998	-0.68721	-1.39112
C	0	2.23702	0.62827	-1.14656
C	0	1.50563	1.54849	-0.15169
C	0	0.80699	0.74458	0.95548
O	0	1.38565	-0.54474	0.98911
C	0	0.90612	1.39256	2.3313
C	0	0.96536	-2.72547	0.06438
O	0	0.52531	-0.48646	-2.40046
H	0	-3.79852	-0.95837	-0.85338
H	0	-1.71842	-2.22139	-1.11617
H	0	-1.72611	2.12794	1.17326
H	0	-4.77249	0.81881	-0.10615
H	0	2.21235	-1.43473	-1.79661
H	0	2.4466	1.16127	-2.10316
H	0	3.23679	0.37707	-0.71304
H	0	0.76198	2.18507	-0.68583
H	0	2.25208	2.25065	0.2895
H	0	0.46653	2.41541	2.32844
H	0	0.37048	0.78886	3.099
H	0	1.96857	1.48069	2.65357
H	0	0.53126	-3.27928	-0.79841
H	0	2.03757	-3.0145	0.14934
H	0	0.44907	-3.06901	0.98965
H	0	-0.16624	0.10164	-2.07974

Phenol 12b (*chair*)



Computed sum of electronic and thermal Enthalpies = –730.395359 hartee.

Cartesian coordinates:

C	0	-2.80609	0.72783	-0.27842
C	0	-2.70736	-0.52479	-0.76818
C	0	-1.57928	-1.24847	-0.67078
C	0	-0.53611	-0.68254	-0.05581
C	0	-0.61143	0.55634	0.43311
C	0	-1.73497	1.27415	0.32856
O	0	-3.96697	1.42633	-0.40477
C	0	0.8601	-1.18293	0.20169
C	0	1.72688	-0.81281	-1.0004
C	0	1.66321	0.68745	-1.3153
C	0	1.63046	1.5409	-0.03347
C	0	0.73399	0.89028	1.02759
O	0	1.28117	-0.38428	1.28583
C	0	0.6683	1.69139	2.32189
C	0	0.94325	-2.65291	0.59523
O	0	1.26638	-1.52916	-2.12227
H	0	-3.58152	-0.97073	-1.2723
H	0	-1.51221	-2.26566	-1.08563
H	0	-1.77957	2.29874	0.72815
H	0	-4.62255	0.876	-0.86305
H	0	2.78238	-1.11876	-0.81265
H	0	0.73759	0.89891	-1.90314
H	0	2.51558	0.98871	-1.96848
H	0	1.26941	2.56979	-0.26827
H	0	2.66522	1.63893	0.37311
H	0	0.24911	2.70776	2.14731
H	0	0.02846	1.18079	3.07727
H	0	1.68258	1.81653	2.7644
H	0	0.59868	-3.32078	-0.22538
H	0	1.99068	-2.93741	0.8445
H	0	0.31237	-2.86281	1.48893
H	0	0.31634	-1.38605	-2.19413

6.5.7 X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[81] and refined by least-squares methods against *F*2 with SHELXL-97.[82] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

Ferrocenecarboxylate ester 47

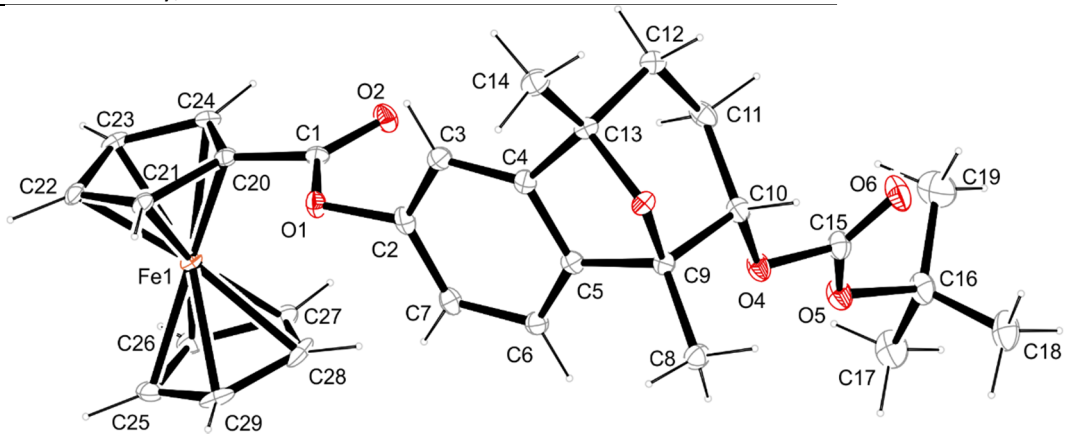
CCDC 1487773 contains the supplementary crystallographic data for ferrocenecarboxylate ester **47**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 7. Ferrocenecarboxylate ester **47**

net formula	$C_{29}H_{32}FeO_6$
M_r/g mol^{-1}	532.39
crystal size/mm	0.100 × 0.060 × 0.020
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	'P -1'
a/Å	7.6264(4)
b/Å	9.9775(5)
c/Å	17.2839(9)
α/°	81.9015(15)
β/°	82.8026(14)
γ/°	80.2118(14)
V/Å^3	1276.16(11)
Z	2
calc. density/g cm^{-3}	1.385
μ/mm^{-1}	0.633
absorption correction	multi-scan
transmission factor range	0.7005–0.7452
refls. measured	30263
R_{int}	0.0508
mean σ(*I*)/*I*	0.0393
θ range	2.860–25.44
observed refls.	3908
x, y (weighting scheme)	0.0315, 1.6799
hydrogen refinement	constr
refls in refinement	4685
parameters	330
restraints	0

[81] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[82] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.

$R(F_{obs})$	0.0412
$R_w(F^2)$	0.0949
S	1.070
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.401
min electron density/e Å^{-3}	−0.275



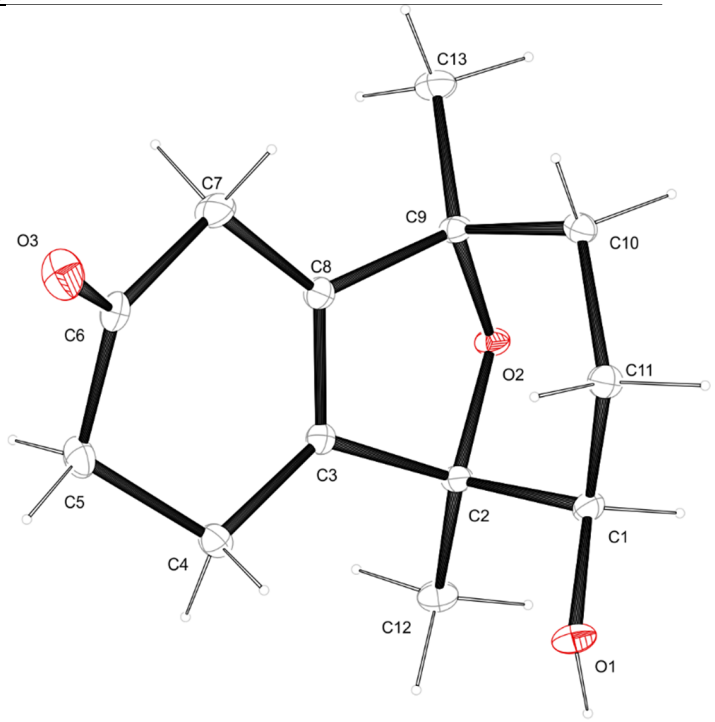
Ketone 50

CCDC 1487774 contains the supplementary crystallographic data for ketone **50**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Ketone **50**

net formula	$C_{13}H_{18}O_3$
M_r/g mol^{-1}	222.27
crystal size/mm	0.100 × 0.080 × 0.050
T/K	153.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21/n 1'
a/Å	8.4612(2)
b/Å	8.7254(3)
c/Å	15.5121(4)
α/°	90
β/°	101.4305(8)
γ/°	90
V/Å^3	1122.50(6)
Z	4
calc. density/g cm^{-3}	1.315
μ/mm^{-1}	0.092
absorption correction	Multi-Scan
transmission factor range	0.9235–0.9593
refls. measured	20718
R_{int}	0.0299

mean σ(*I*)/*I*	0.0192
θ range	3.555–28.279
observed refls.	2503
x, y (weighting scheme)	0.0487, 0.5201
hydrogen refinement	C-H: constr, O-H: refall
refls in refinement	2772
parameters	151
restraints	0
$R(F_{obs})$	0.0392
$R_w(F^2)$	0.1081
S	1.073
$shift/error_{max}$	0.001
max electron density/e Å^{-3}	0.386
min electron density/e Å^{-3}	−0.232

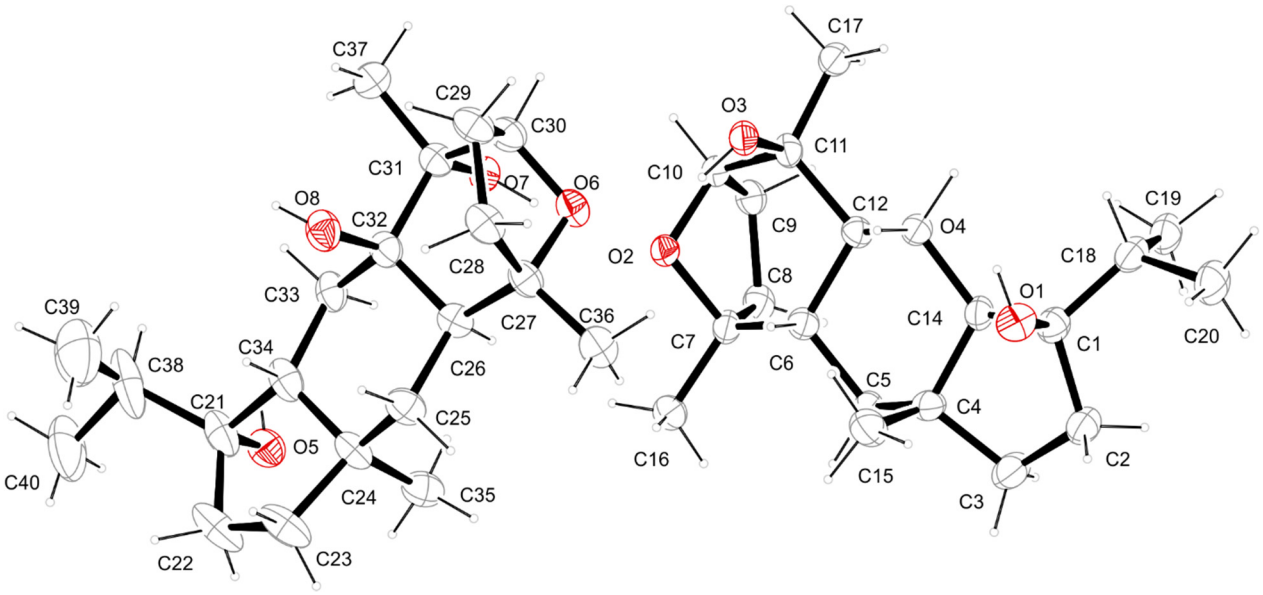


Triol 70

CCDC 1487775 contains the supplementary crystallographic data for triol **70**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 3. Triol **70**

net formula	$C_{20}H_{34}O_4$
M_r/g mol^{-1}	338.47
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 2'
a/Å	12.7886(4)
b/Å	31.7041(12)
c/Å	10.3424(5)
α/°	90
β/°	90
γ/°	90
V/Å^3	4193.3(3)
Z	8
calc. density/g cm^{-3}	1.072
μ/mm^{-1}	0.073
absorption correction	multi-scan
transmission factor range	0.8863–0.9579
refls. measured	49722
mean σ(I)/I	0.0590
θ range	2.500–25.058
observed refls.	5958
x, y (weighting scheme)	0.0815, 0.8800
hydrogen refinement	constr
Flack parameter	−0.7(6)
refls in refinement	7414
parameters	448
restraints	0
$R(F_{obs})$	0.0598
$R_w(F^2)$	0.1540
S	1.104
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.341
min electron density/e Å^{-3}	−0.259



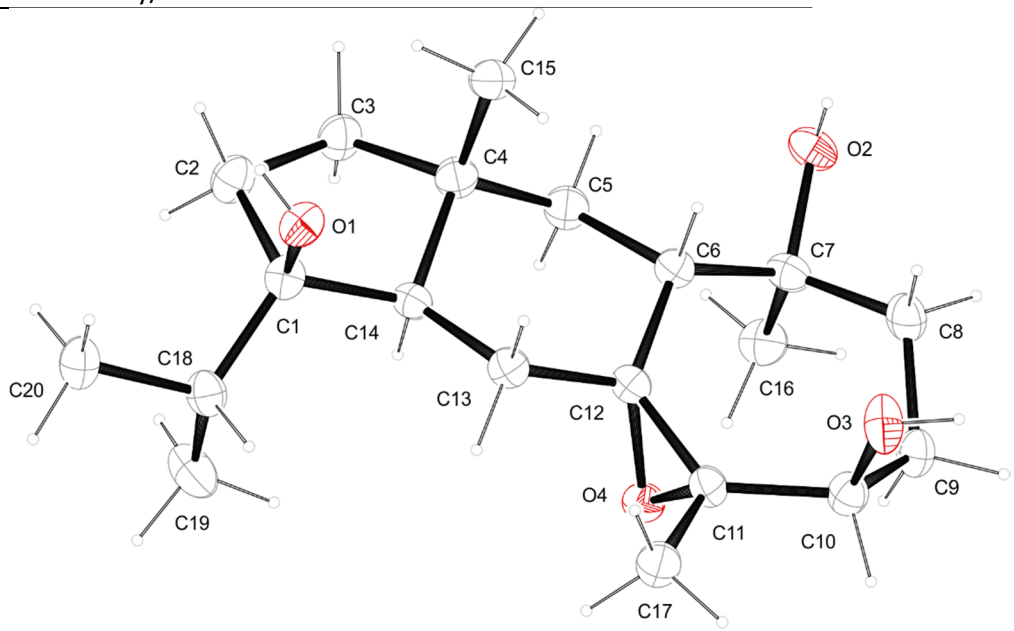
Triol 74

CCDC 1473419 contains the supplementary crystallographic data for triol **74**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4. Triol **74**

net formula	$C_{20}H_{34}O_4$
M_r/g mol^{-1}	338.47
crystal size/mm	0.100 × 0.050 × 0.040
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	8.5285(6)
b/Å	14.0549(9)
c/Å	15.1362(10)
α/°	90
β/°	90
γ/°	90
V/Å^3	1814.3(2)
Z	4
calc. density/g cm^{-3}	1.239
μ/mm^{-1}	0.084
absorption correction	Multi-Scan
transmission factor range	0.8239–0.9580
refls. measured	7152
R_{int}	0.0244
mean σ(*I*)/*I*	0.0332
θ range	3.101–25.364

observed refls.	2889
x, y (weighting scheme)	0.0354, 0.6797
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	−0.6(5)
refls in refinement	3234
parameters	234
restraints	0
$R(F_{obs})$	0.0367
$R_w(F^2)$	0.0916
S	1.101
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.143
min electron density/e Å^{-3}	−0.212

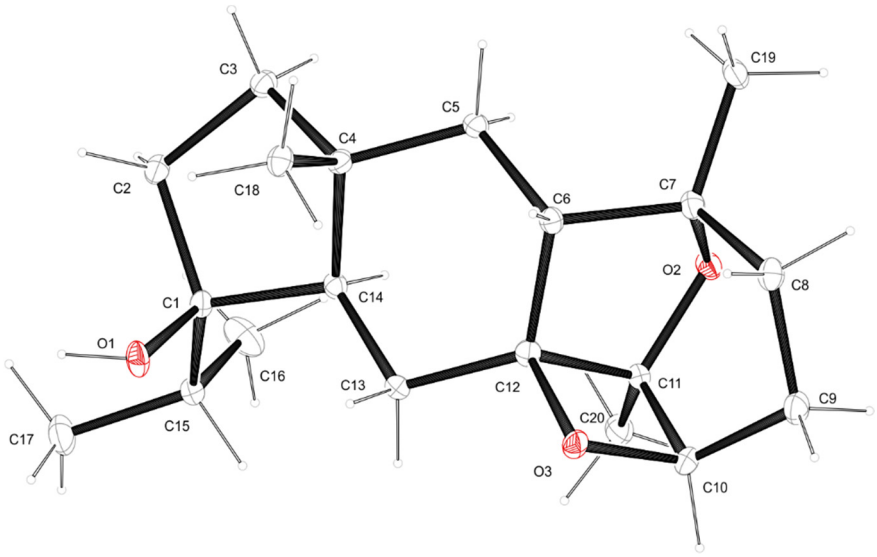


Tetra-*epi* dictyoxetane (tetra-*epi*-3)

CCDC 1473420 contains the supplementary crystallographic data for 1,10,13,14-tetra-*epi* dictyoxetane (tetra-*epi*-**3**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5. 1,10,13,14-tetra-*epi* dictyoxetane (tetra-*epi*-**3**)

net formula	$C_{20}H_{32}O_3$
M_r/g mol^{-1}	320.45
crystal size/mm	0.100 × 0.030 × 0.020
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.3848(4)
b/Å	9.4448(7)
c/Å	28.5710(19)
α/°	90
β/°	90
γ/°	90
V/Å^3	1722.9(2)
Z	4
calc. density/g cm^{-3}	1.235
μ/mm^{-1}	0.081
absorption correction	Multi-Scan
transmission factor range	0.8980–0.9585
refls. measured	31378
R_{int}	0.0372
mean σ(I)/I	0.0206
θ range	3.038–26.405
observed refls.	3373
x, y (weighting scheme)	0.0383, 0.6304
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	−0.1(3)
refls in refinement	3507
parameters	217
restraints	0
$R(F_{obs})$	0.0338
$R_w(F^2)$	0.0856
S	1.102
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.263
min electron density/e Å^{-3}	−0.183



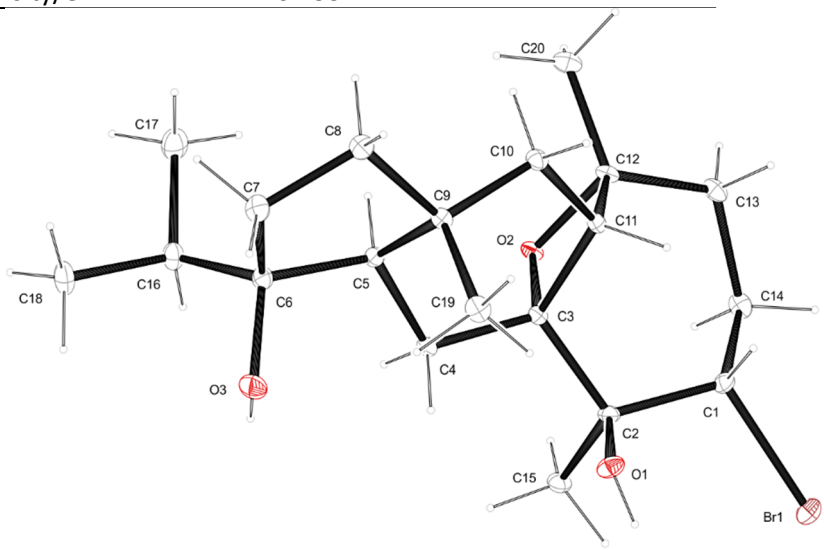
Diol 128

CCDC 1473421 contains the supplementary crystallographic data for diol **128**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

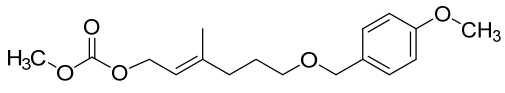
Table 6. Diol **128**

net formula	$C_{20}H_{33}BrO_3$
M_r/g mol^{-1}	401.38
crystal size/mm	0.070 × 0.050 × 0.030
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	7.2444(5)
b/Å	10.8801(7)
c/Å	23.8676(15)
α/°	90
β/°	90
γ/°	90
V/Å^3	1881.2(2)
Z	4
calc. density/g cm^{-3}	1.417
μ/mm^{-1}	2.200
absorption correction	Multi-Scan
transmission factor range	0.6527–0.6985
refls. measured	33734
R_{int}	0.0687
mean σ(*I*)/*I*	0.0441
θ range	3.172–28.271

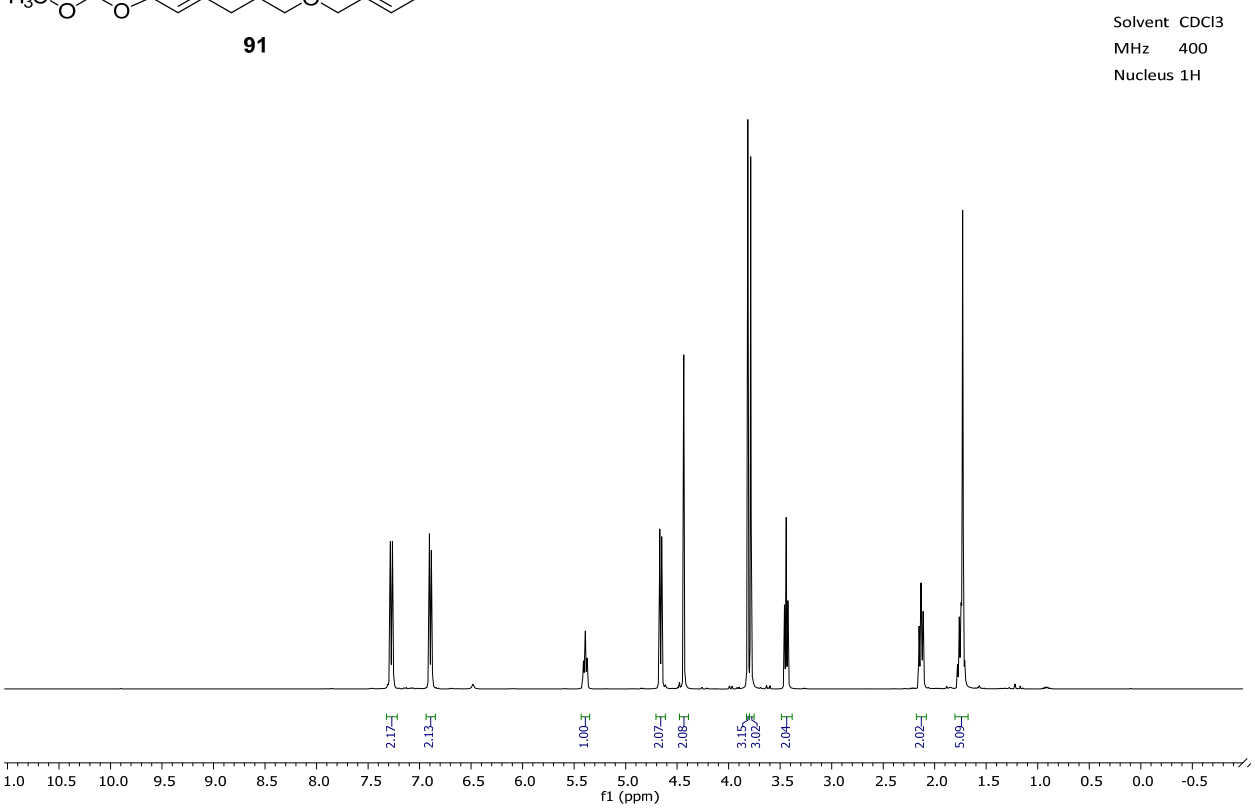
observed refls.	4453
x, y (weighting scheme)	0.0293, 0.8784
hydrogen refinement	C-H: constr, O-H: refall
Flack parameter	0.107(5)
refls in refinement	4655
parameters	230
restraints	0
$R(F_{obs})$	0.0301
$R_w(F^2)$	0.0740
S	1.062
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.337
min electron density/e Å^{-3}	−0.499

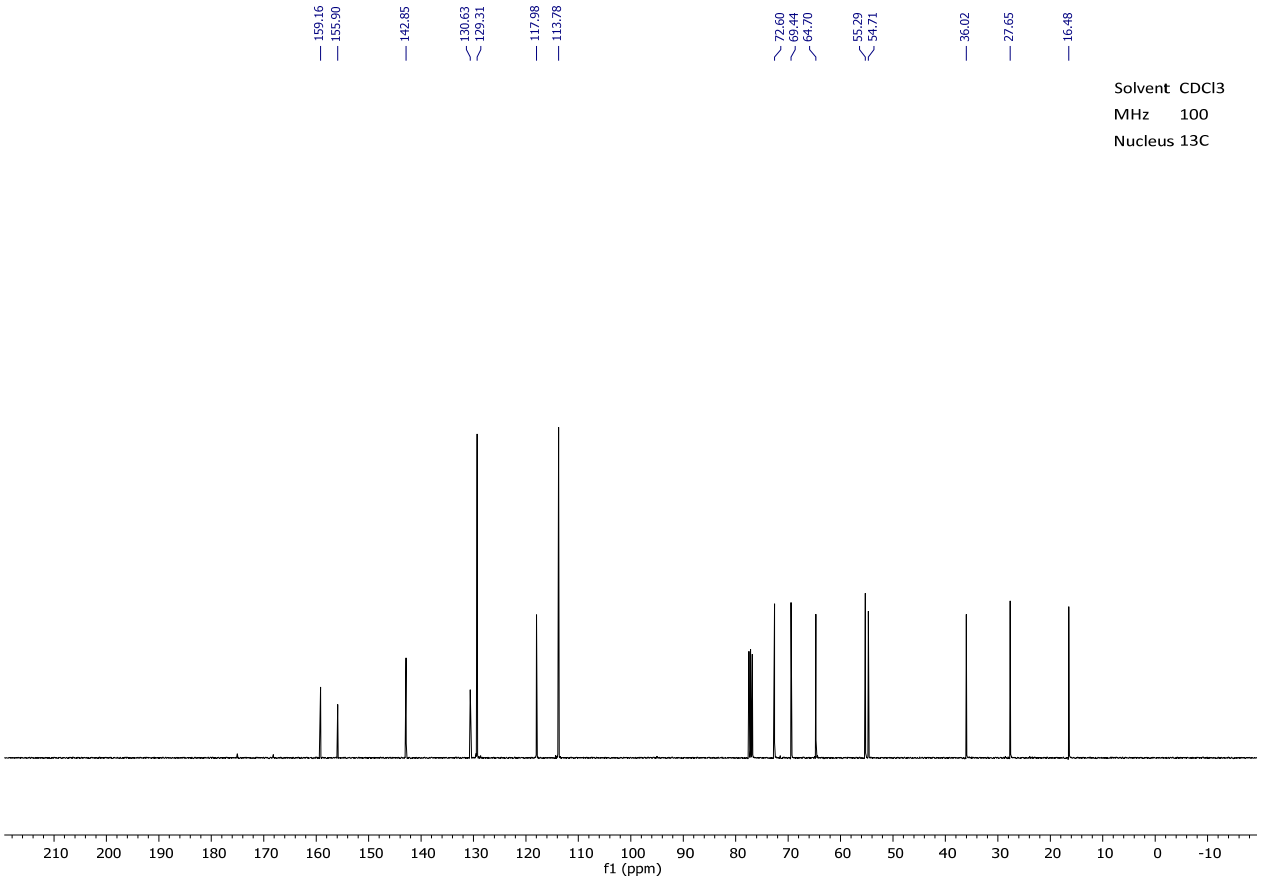


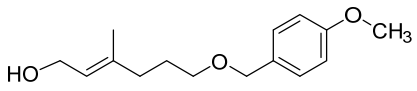
6.5.8 ^{1}H and ^{13}C NMR Spectra



91

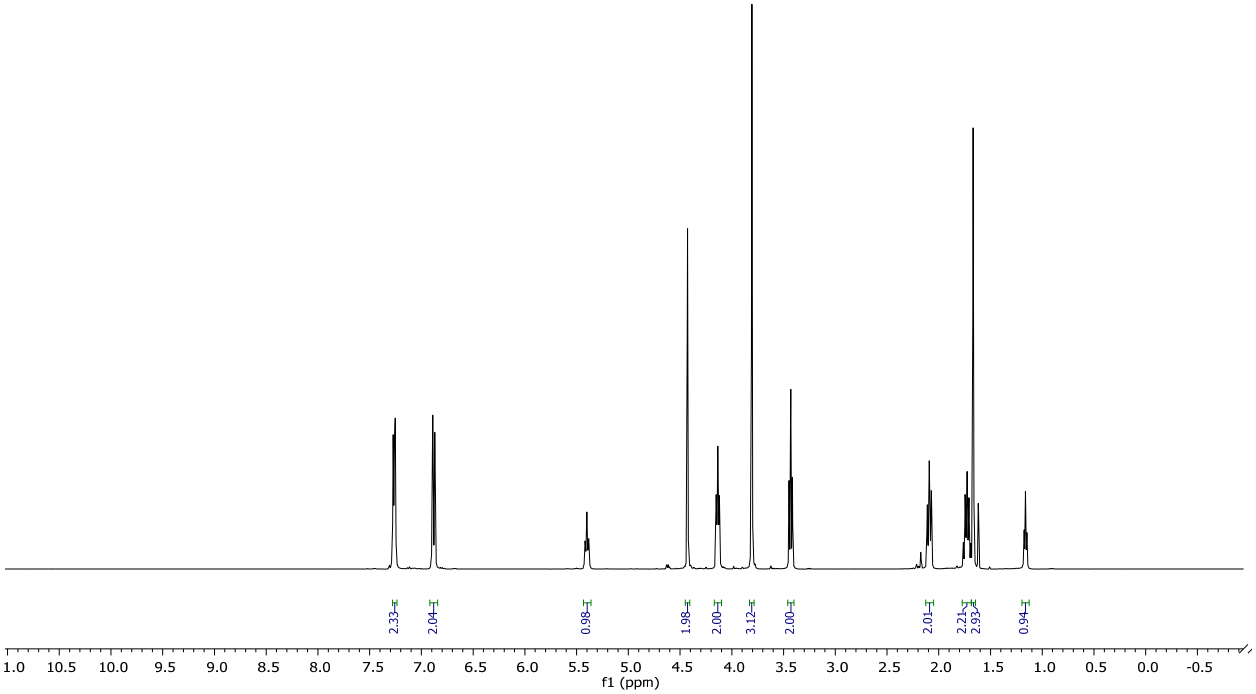

Solvent CDCl3
MHz 400
Nucleus 1H
2.17
2.13
1.00
2.07
2.08
3.15
3.02
2.04
2.02
5.09
f1 (ppm)


Solvent CDCl3
MHz 100
Nucleus 13C
159.16
155.90
142.85
130.63
129.31
117.98
113.78
72.60
69.44
64.70
55.29
54.71
36.02
27.65
16.48
f1 (ppm)



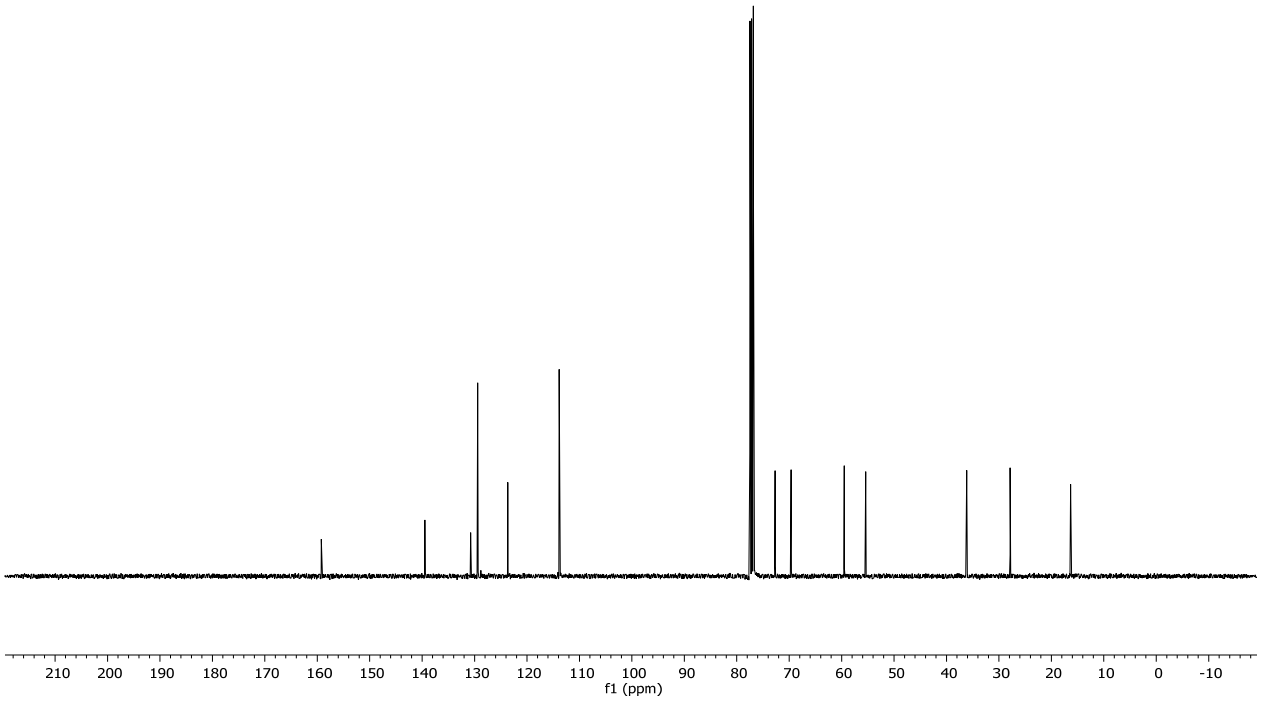
92

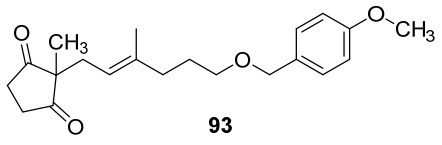
Solvent CDCl3
MHz 400
Nucleus 1H



159.24
139.47
130.76
129.41
123.66
113.87
72.69
69.64
59.51
55.42
36.13
27.86
16.34

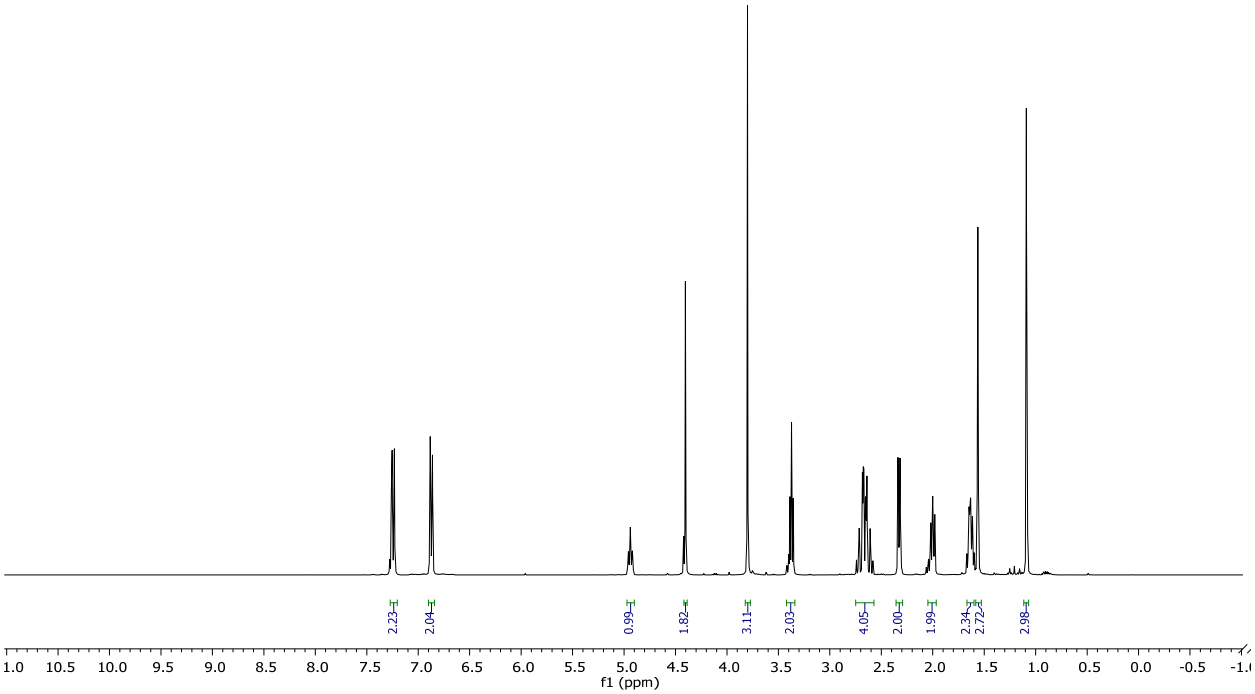
Solvent CDCl3
MHz 100
Nucleus 13C



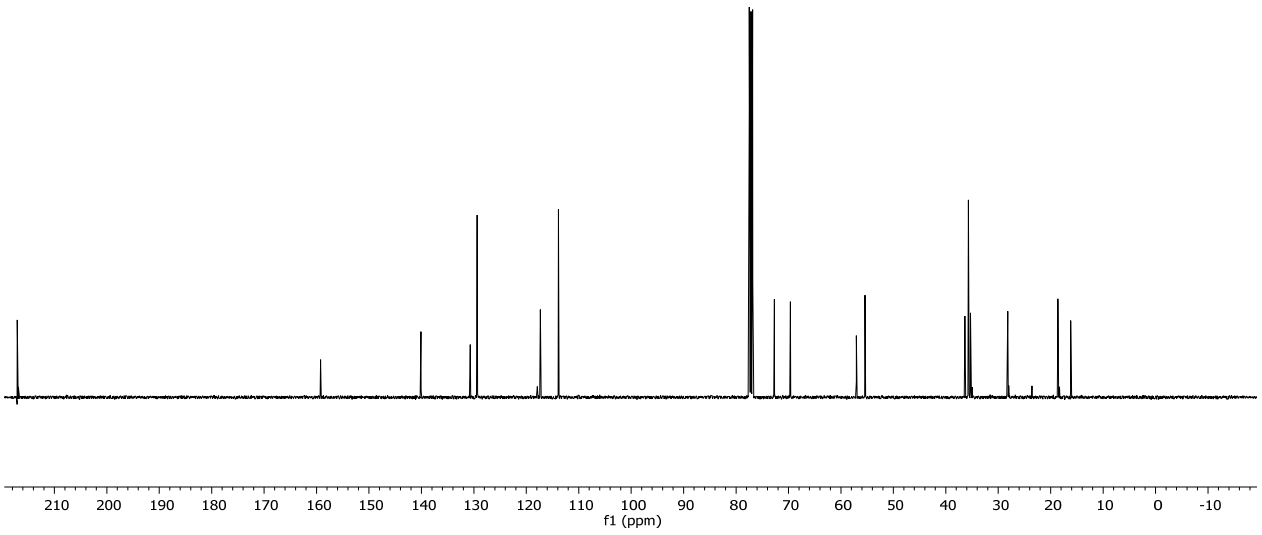


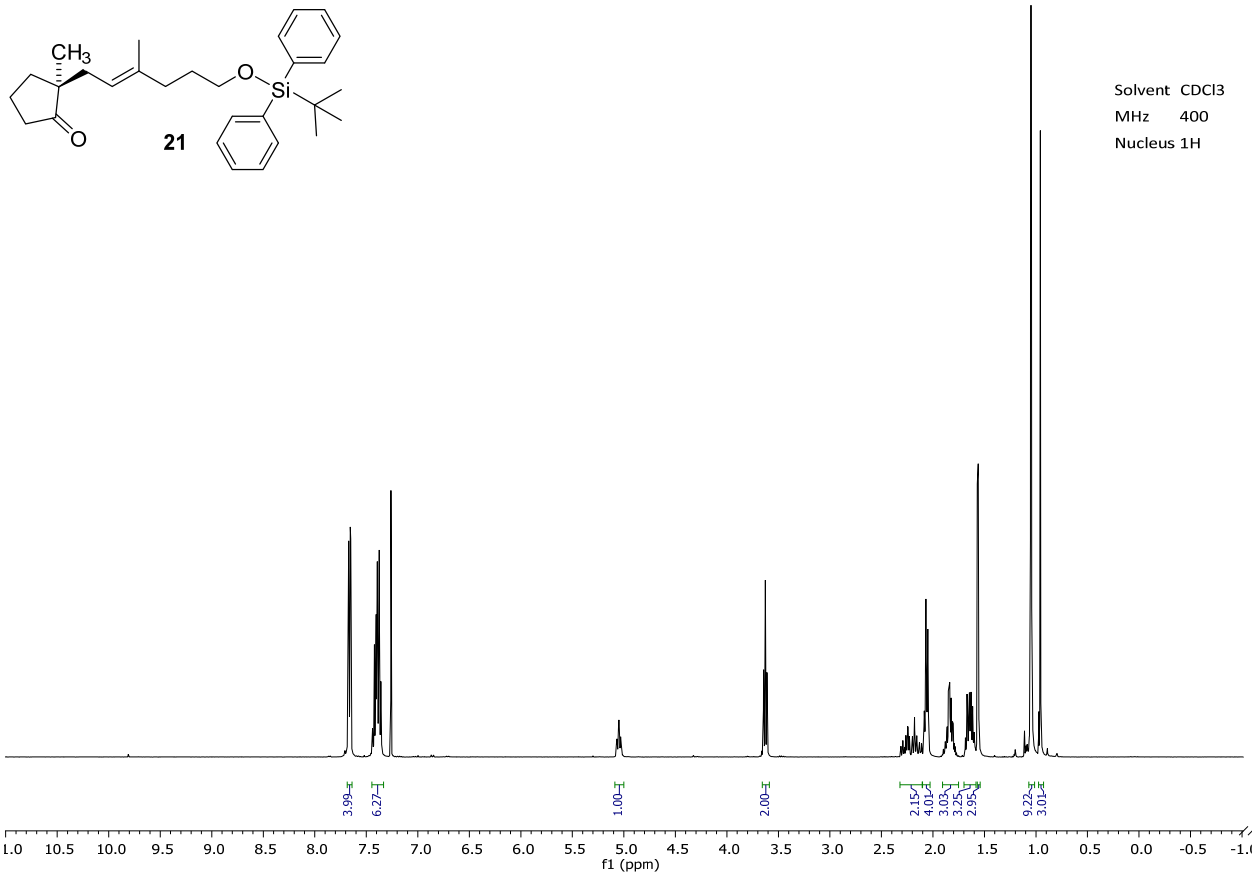
93

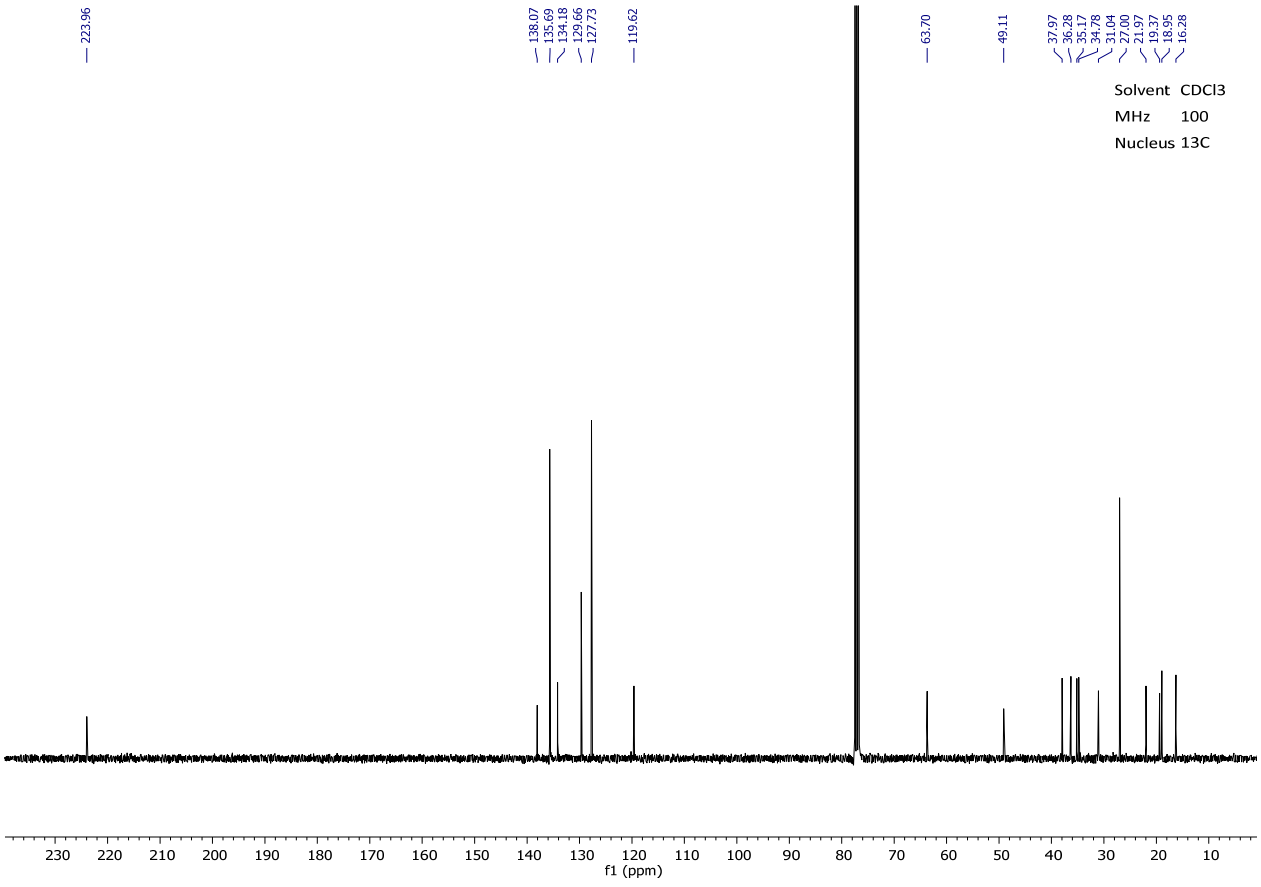
Solvent CDCl3
MHz 400
Nucleus 1H

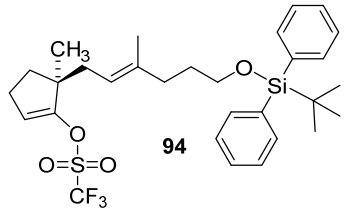


Solvent CDCl3
MHz 100
Nucleus 13C



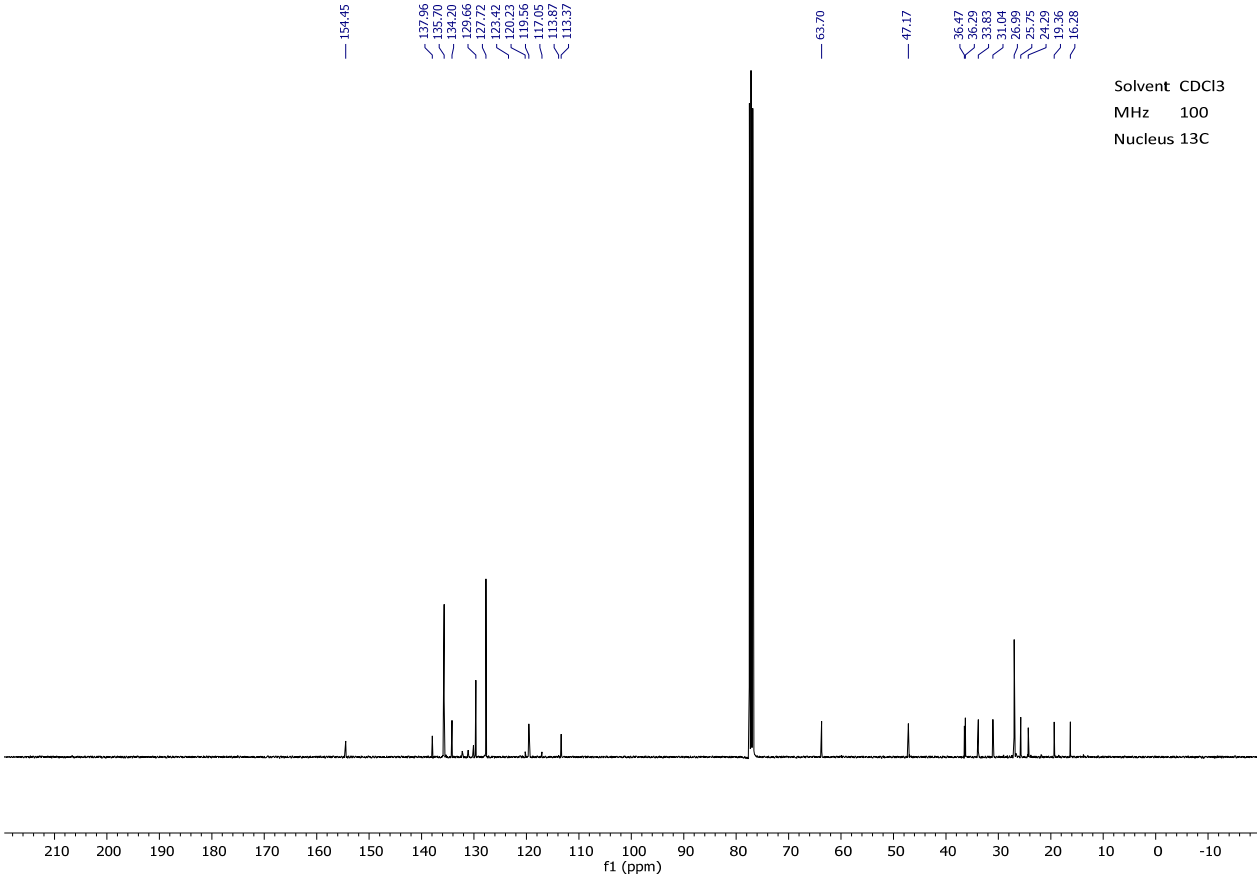

CH3
O
Si
O
21
Solvent CDCl3
MHz 400
Nucleus 1H
3.99
6.27
1.00
2.00
2.15
4.01
3.03
3.25
2.95
9.22
3.01
f1 (ppm)

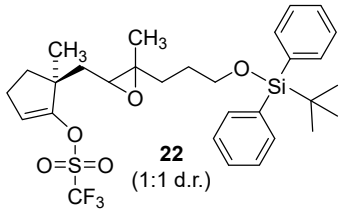

223.96
138.07
135.69
134.18
129.66
127.73
119.62
63.70
49.11
37.97
36.28
35.17
34.78
31.04
27.00
21.97
19.37
18.95
16.28
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


CH3
O
Si
O
O=S=O
CF3

94

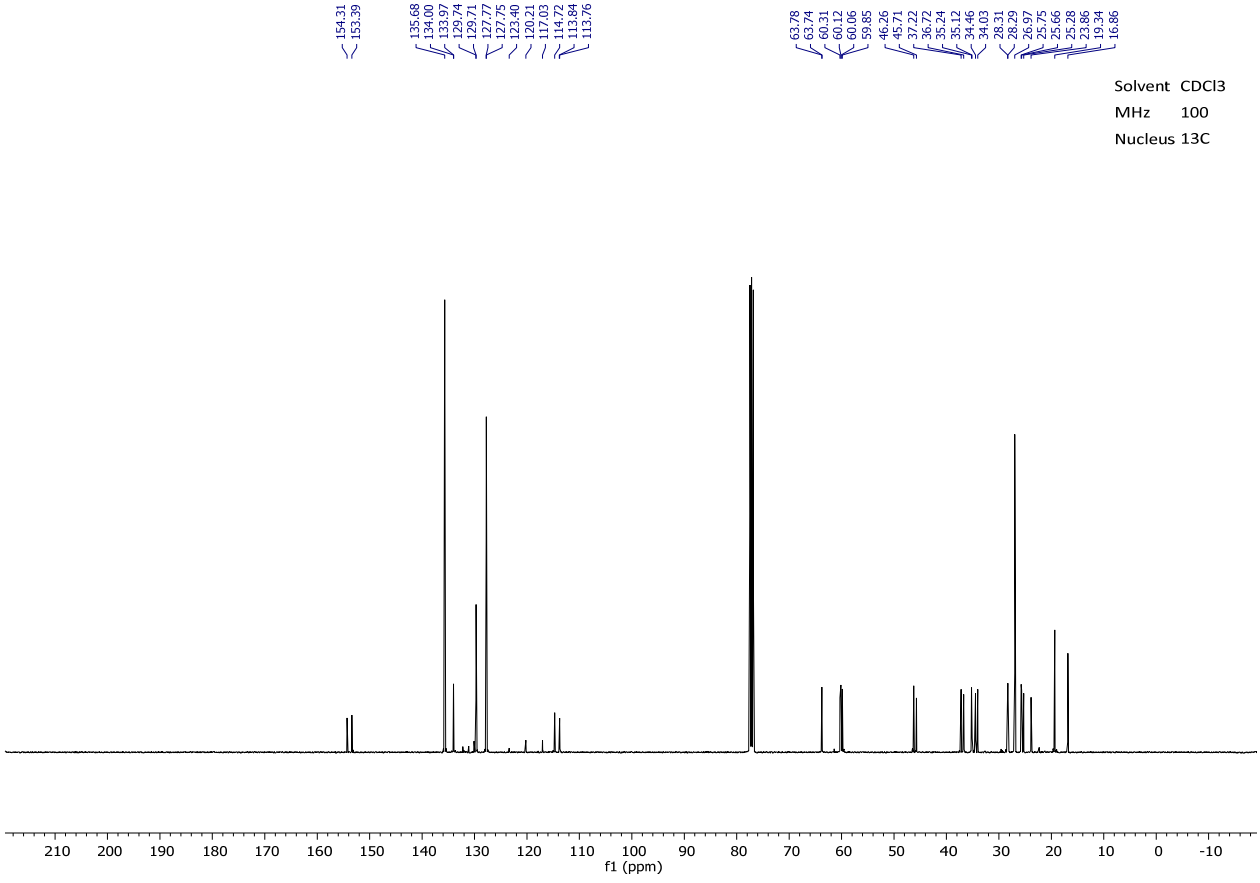
Solvent CDCl3
MHz 400
Nucleus 1H
4.55
7.40
0.87
1.00
2.05
1.92
4.07
1.00
3.24
2.82
2.97
9.93
f1 (ppm)

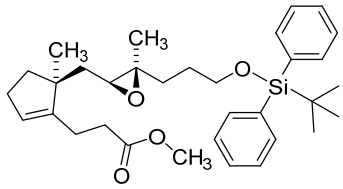

154.45
137.96
135.70
134.20
129.66
127.72
123.42
120.23
119.56
117.05
113.87
113.37
63.70
47.17
36.47
35.29
33.83
31.04
26.99
25.75
24.29
19.36
16.28
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


CH3
CH3
O
O
Si
O
O=S=O
CF3

22
(1:1 d.r.)

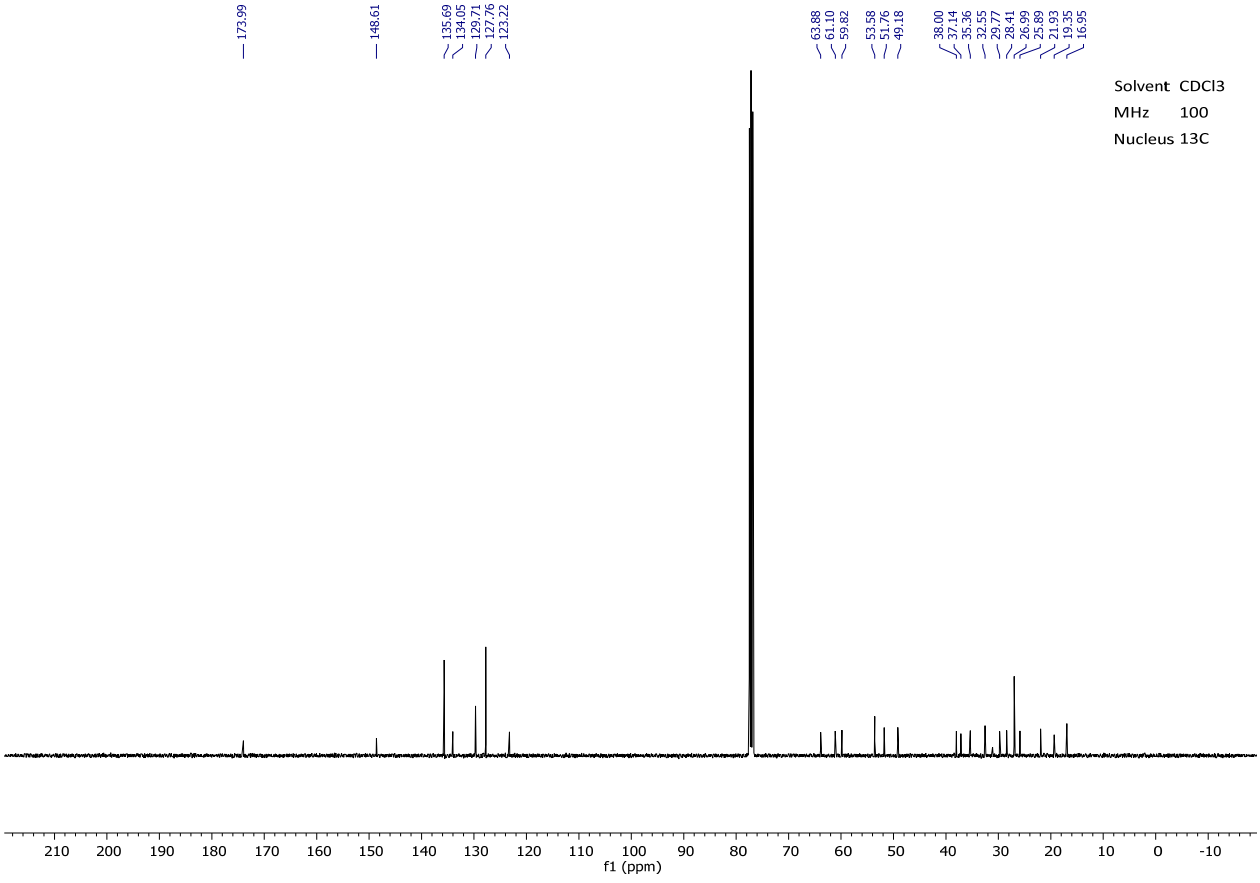
Solvent CDCl3
MHz 400
Nucleus 1H
4.07
6.22
0.48
0.44
2.00
0.45
0.55
1.85
0.98
1.56
5.84
2.75
2.69
8.80
f1 (ppm)

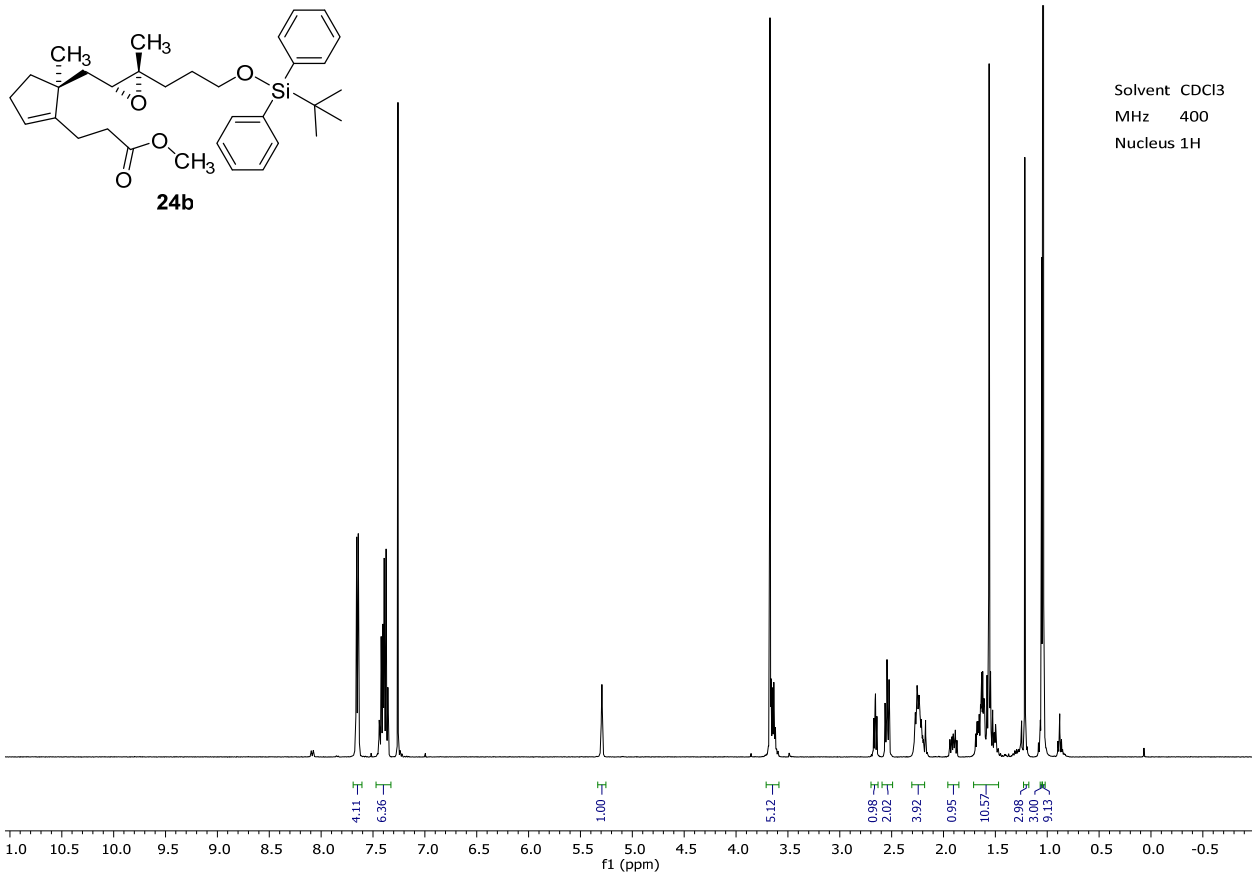

154.31
153.39
135.68
134.00
133.97
129.74
129.71
127.77
127.75
123.40
120.21
117.03
114.72
113.84
113.76
63.78
63.74
60.31
60.12
60.06
59.85
46.26
45.71
37.22
36.72
35.24
35.12
34.46
34.03
28.31
28.29
26.97
25.75
25.66
25.28
23.86
19.34
16.86
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)

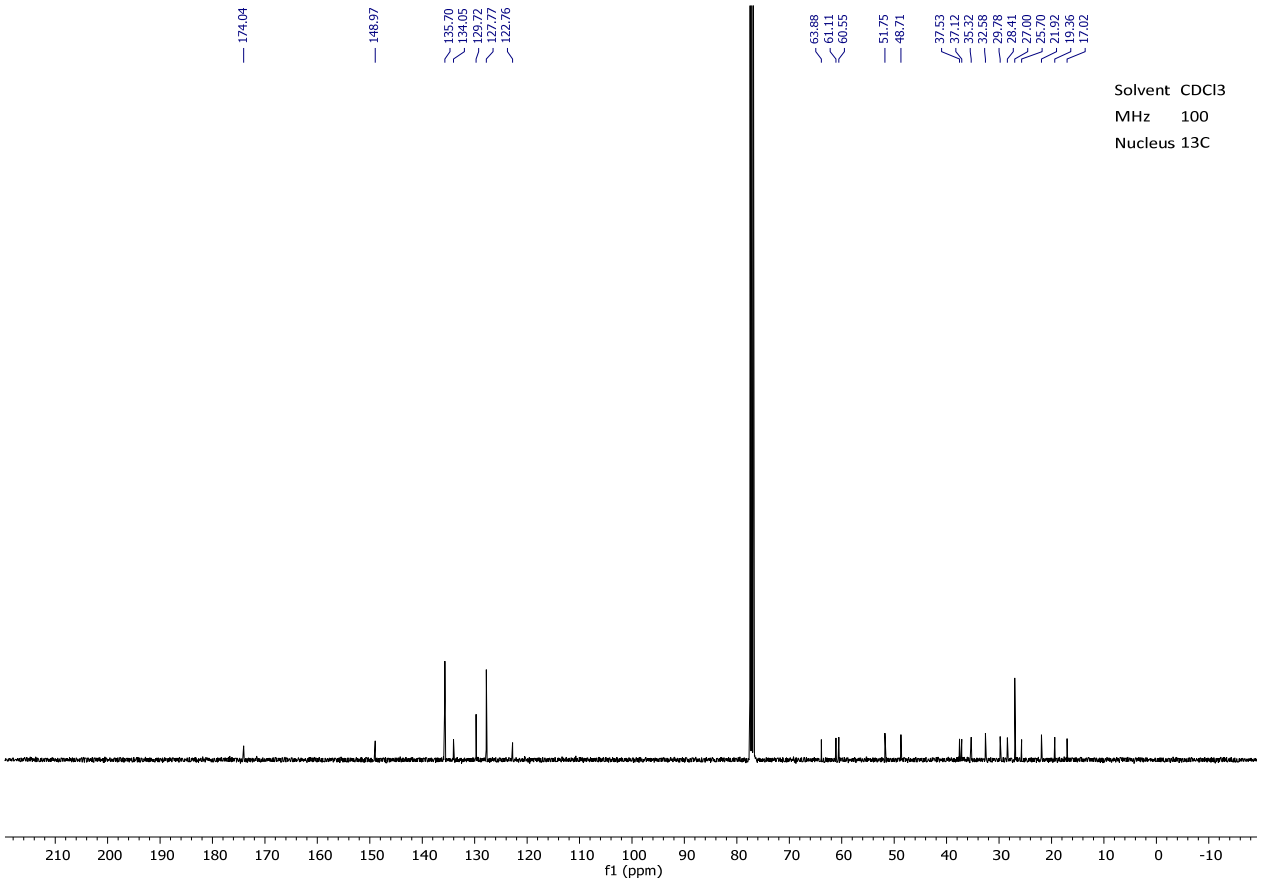

CH3
CH3
O
Si
O
O
O
CH3

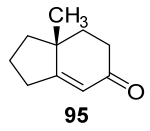
24a

Solvent CDCl3
MHz 400
Nucleus 1H
4.26
6.49
1.00
5.20
0.94
1.96
3.99
0.94
8.88
3.08
3.05
9.60
f1 (ppm)


173.99
148.61
135.69
134.05
129.71
127.76
123.22
63.88
61.10
59.82
53.58
51.76
49.18
38.00
37.14
35.36
32.55
29.77
28.41
26.99
25.89
21.93
19.35
16.95
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)

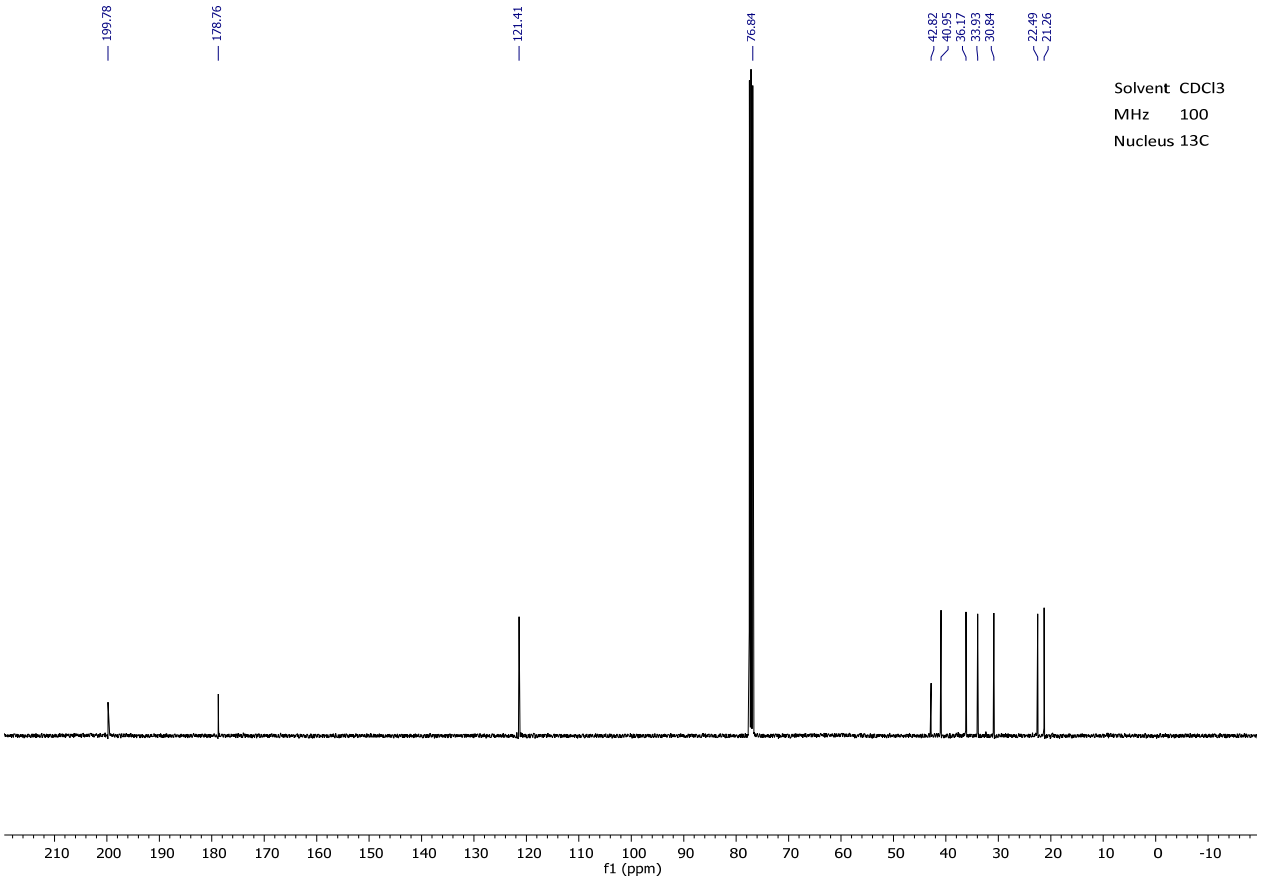

CH3
CH3
O
O
Si
O
CH3
O
24b
Solvent CDCl3
MHz 400
Nucleus 1H
4.11
6.36
1.00
5.12
0.98
2.02
3.92
0.95
10.57
2.98
3.00
9.13
f1 (ppm)

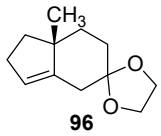

174.04
148.97
135.70
134.05
129.72
127.77
122.76
63.88
61.11
60.55
51.75
48.71
37.53
37.12
35.32
32.58
29.78
28.41
27.00
25.70
21.92
19.36
17.02
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


CH3
O

95

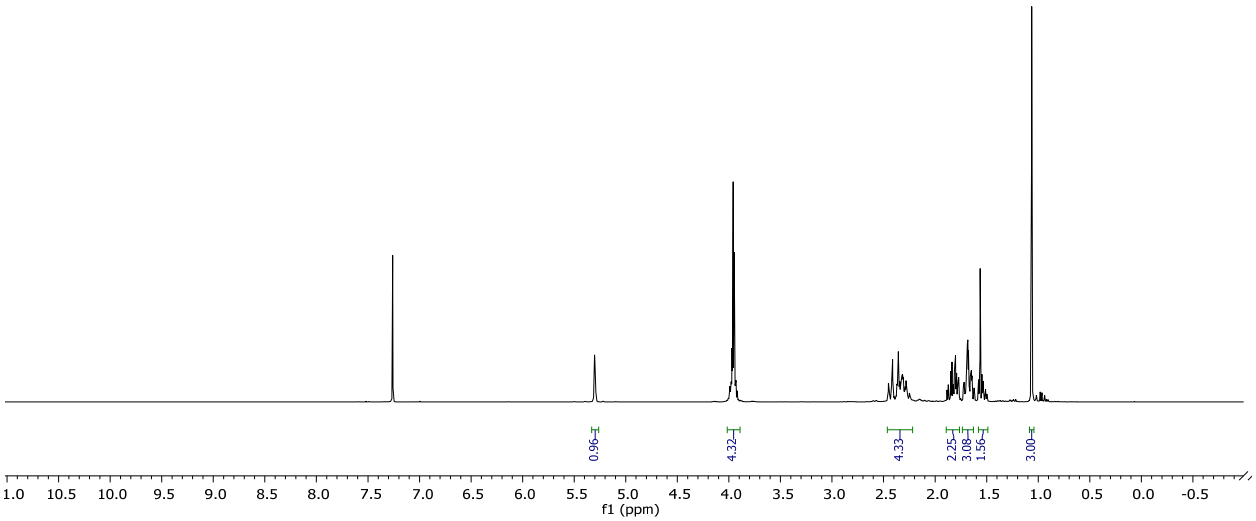
Solvent CDCl3
MHz 400
Nucleus 1H
0.84
0.99
2.10
0.99
1.01
4.00
1.00
2.82
f1 (ppm)

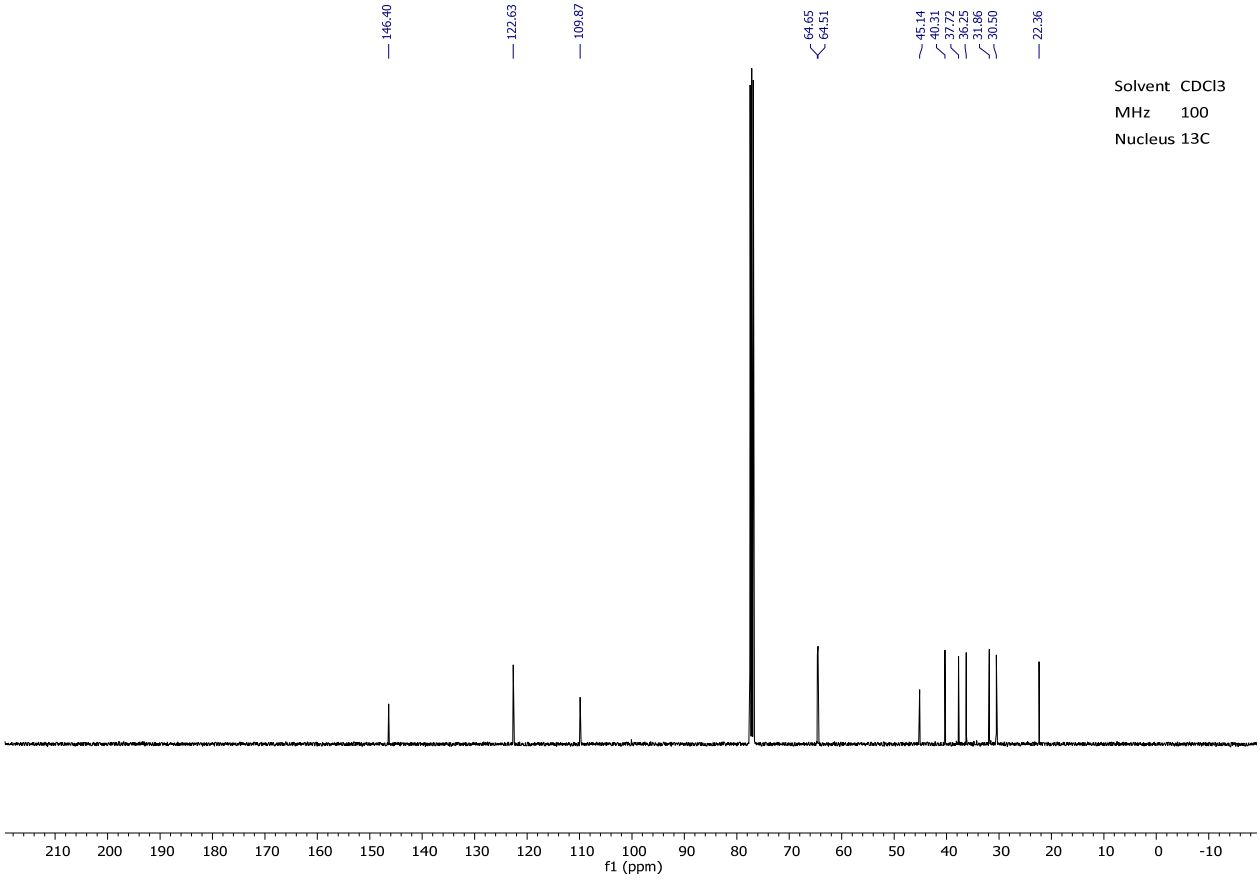

199.78
178.76
121.41
76.84
42.82
40.95
36.17
33.93
30.84
22.49
21.26
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)

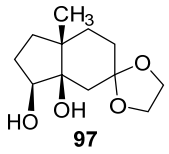


96

Solvent CDCl3
MHz 400
Nucleus 1H

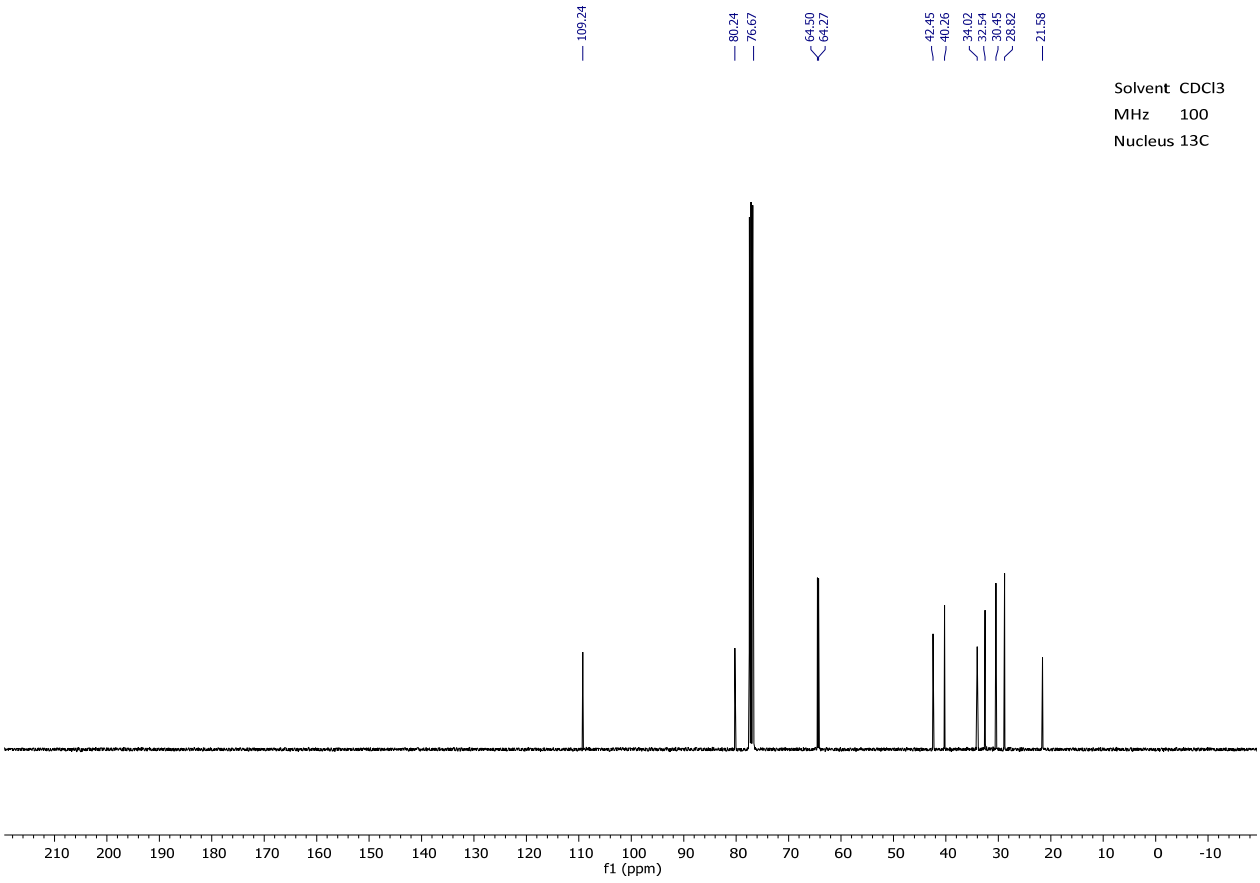


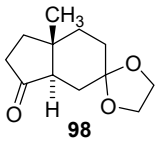



CH3
O
HO
OH
O

97

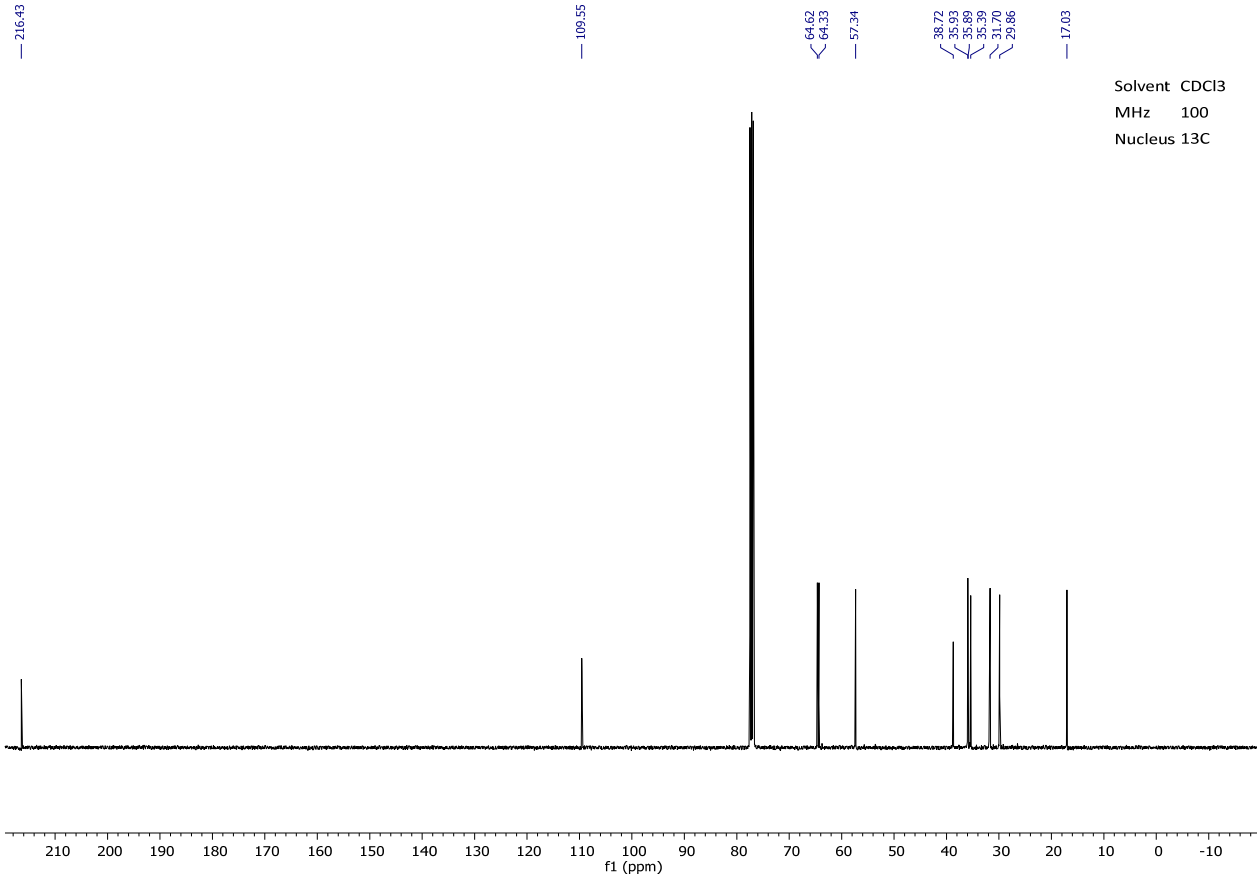
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
4.24
0.94
0.96
1.00
10.22
3.02
f1 (ppm)

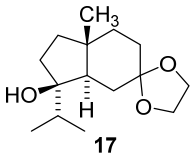

109.24
80.24
76.67
64.50
64.27
42.45
40.26
34.02
32.54
30.45
28.82
21.58
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


CH3
O
O
H
O

98

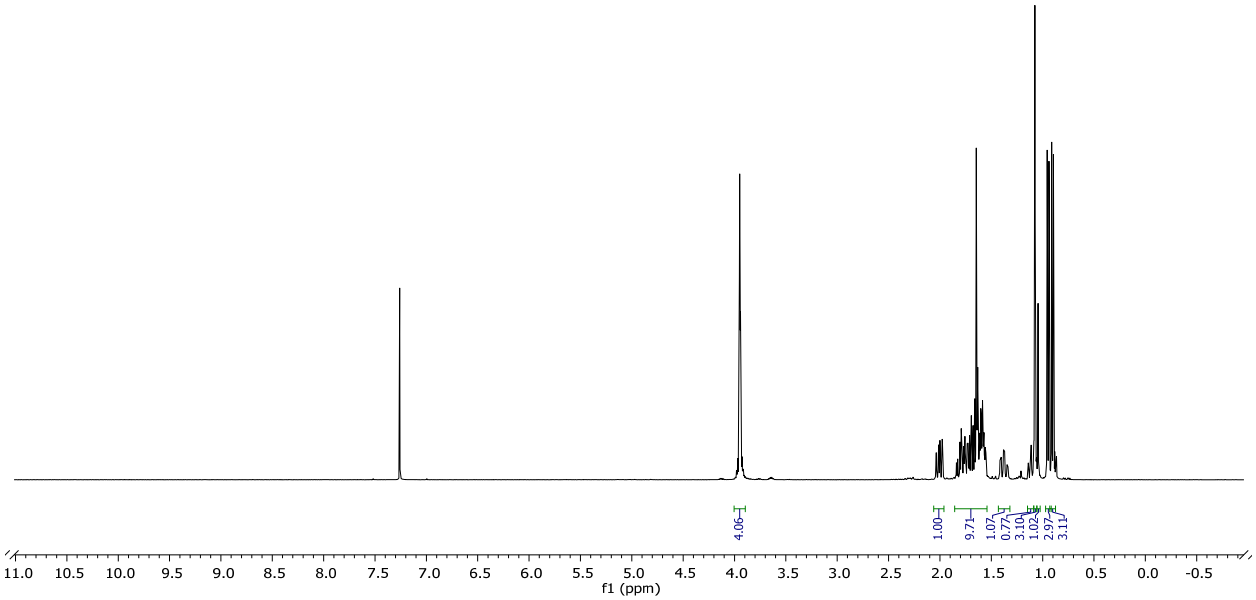
Solvent CDCl3
MHz 400
Nucleus 1H
4.15
3.06
7.63
1.07
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


216.43
109.55
64.62
64.33
57.34
38.72
35.93
35.89
35.39
31.70
29.86
17.03
Solvent CDCl3
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

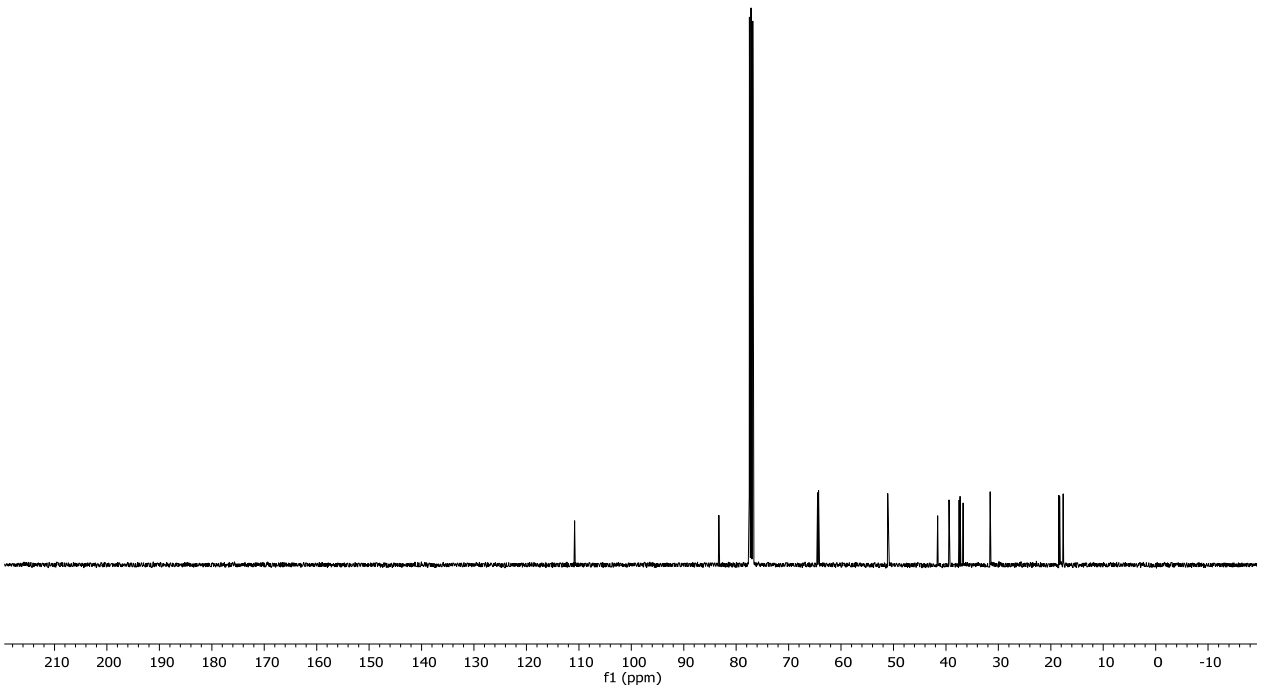


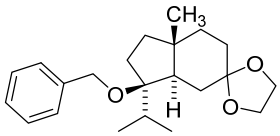
17

Solvent CDCl3
MHz 400
Nucleus 1H



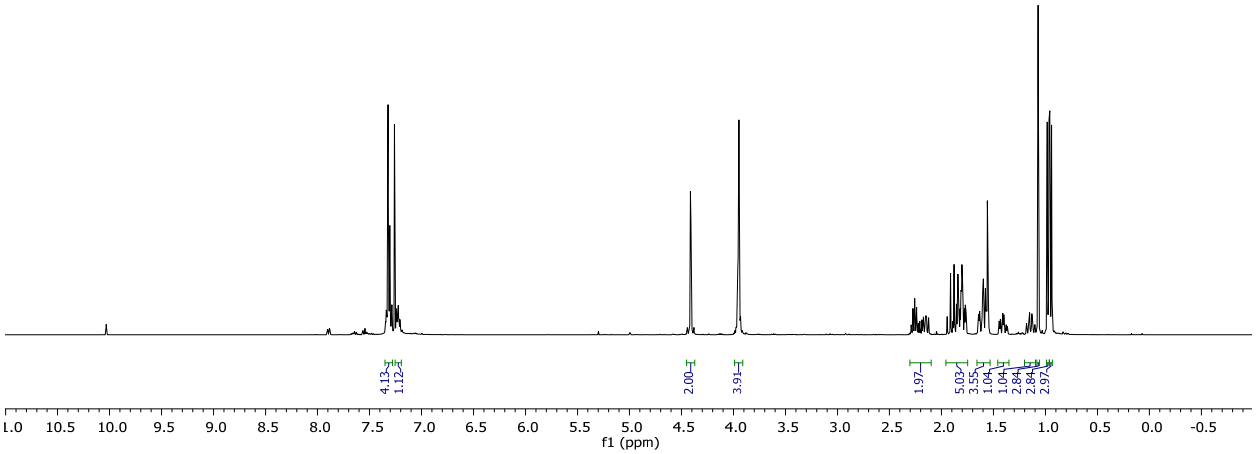
Solvent CDCl3
MHz 100
Nucleus 13C



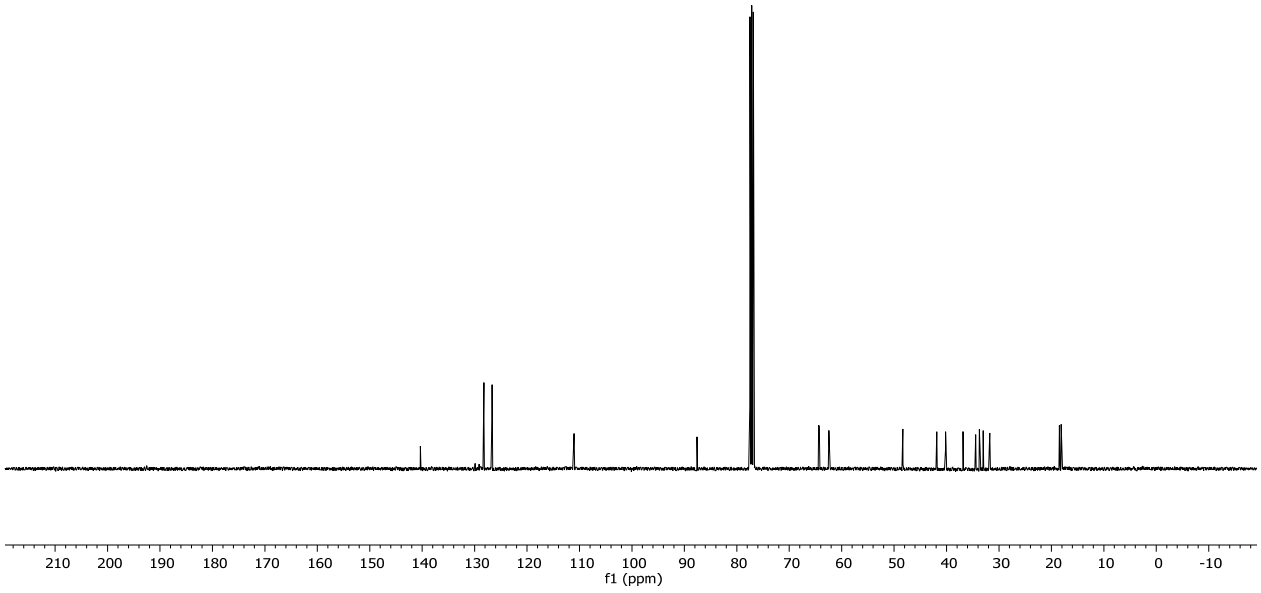


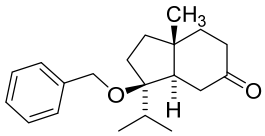
99

Solvent CDCl3
MHz 400
Nucleus 1H

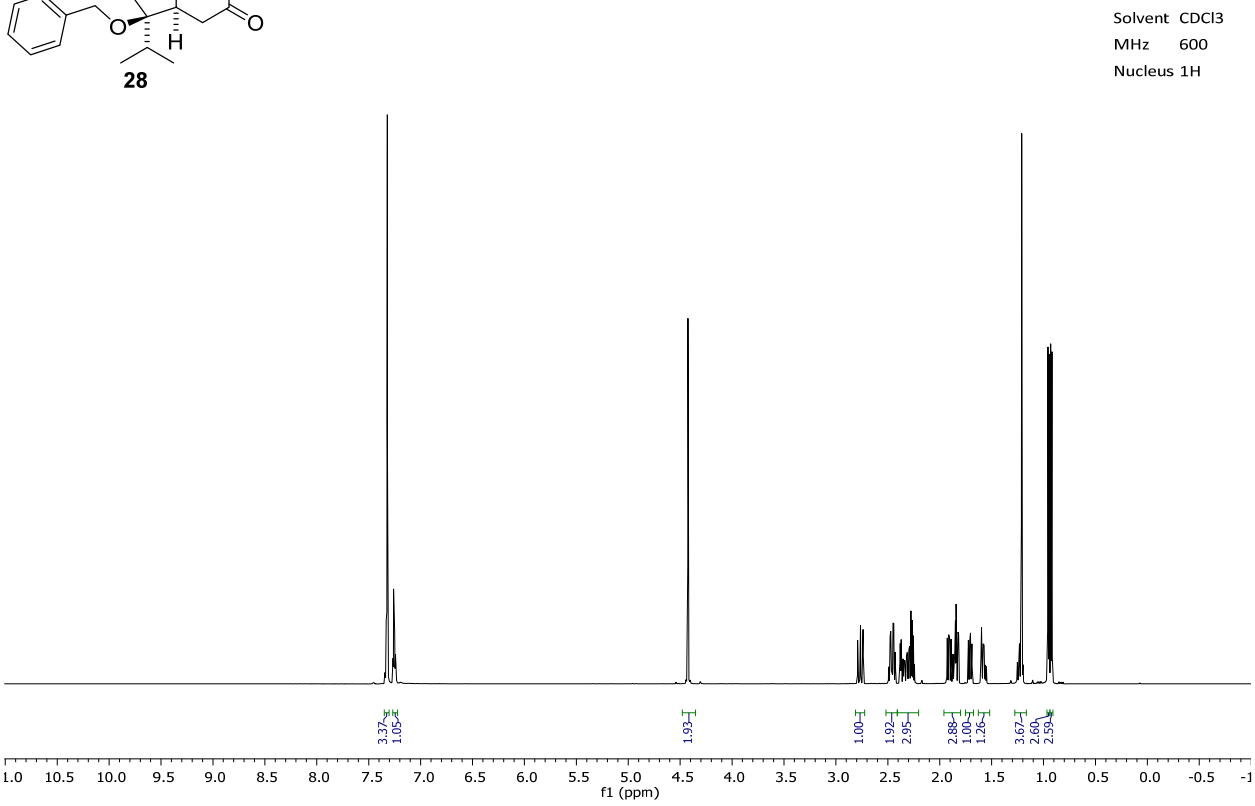


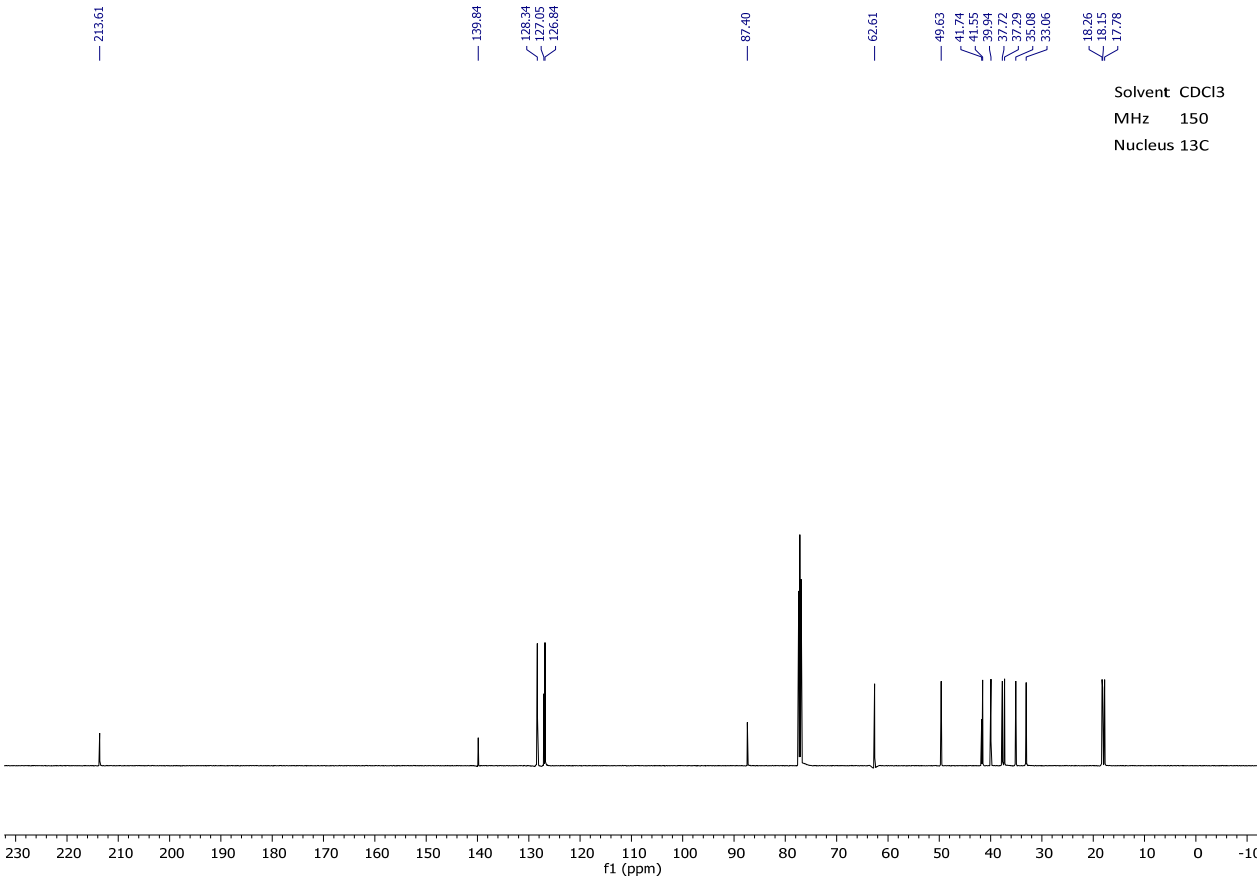
Solvent CDCl3
MHz 100
Nucleus 13C

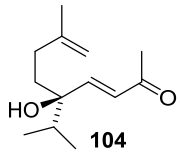



CH3
O
H
O

28

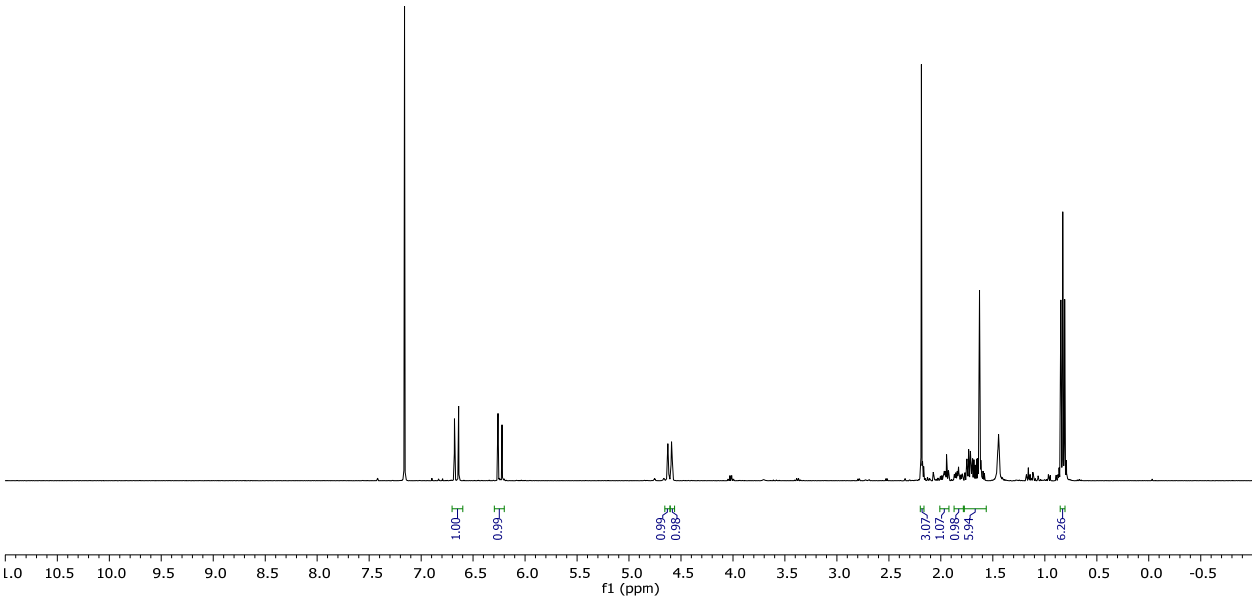

Solvent CDCl3
MHz 600
Nucleus 1H
3.37
1.05
1.93
1.00
1.92
2.95
2.88
1.00
1.26
3.67
2.60
2.59
f1 (ppm)

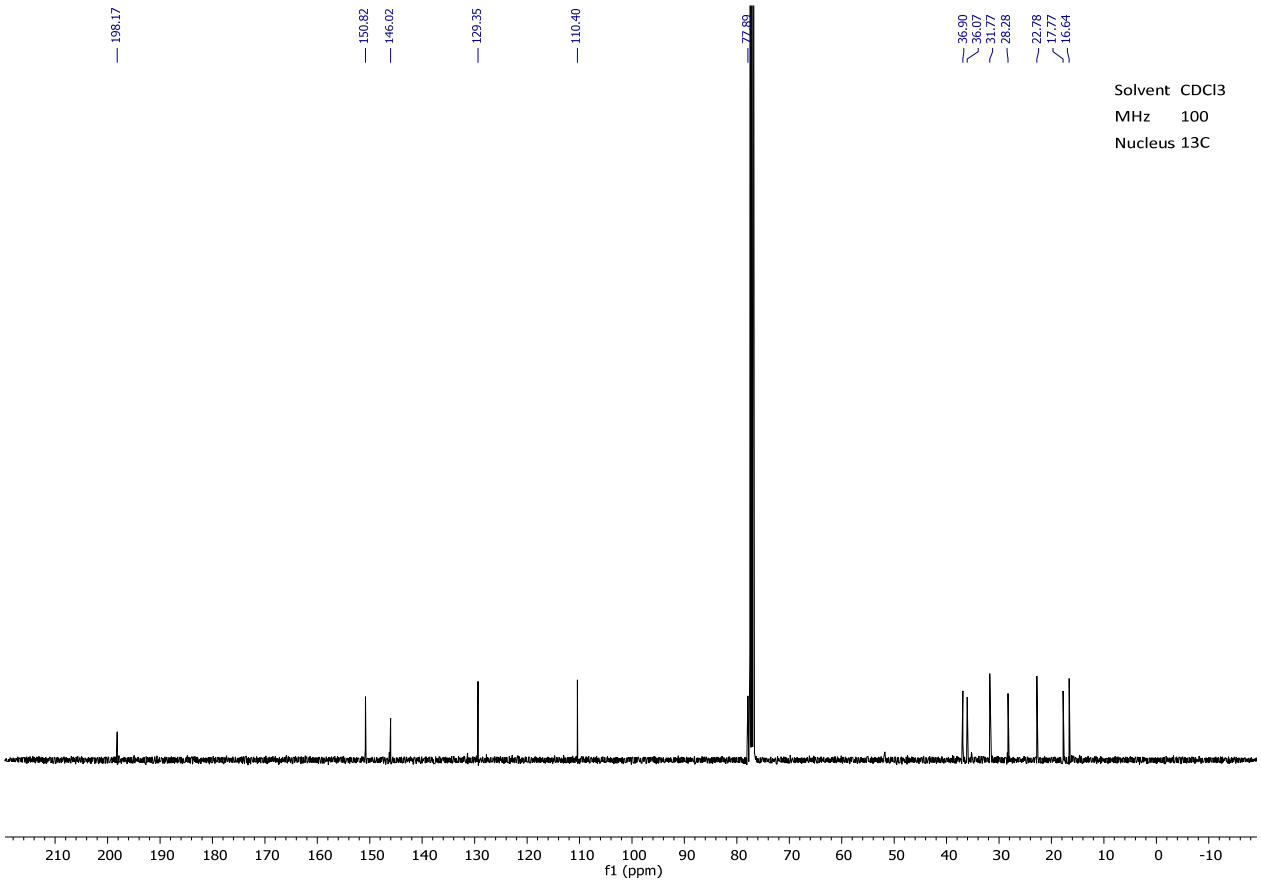

213.61
139.84
128.34
127.05
126.84
87.40
62.61
49.63
41.74
41.55
39.94
37.72
37.29
35.08
33.06
18.26
18.15
17.78
Solvent CDCl3
MHz 150
Nucleus 13C
f1 (ppm)



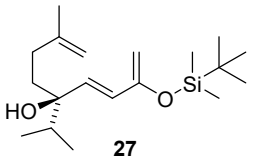
104

Solvent C6D6
MHz 400
Nucleus 1H



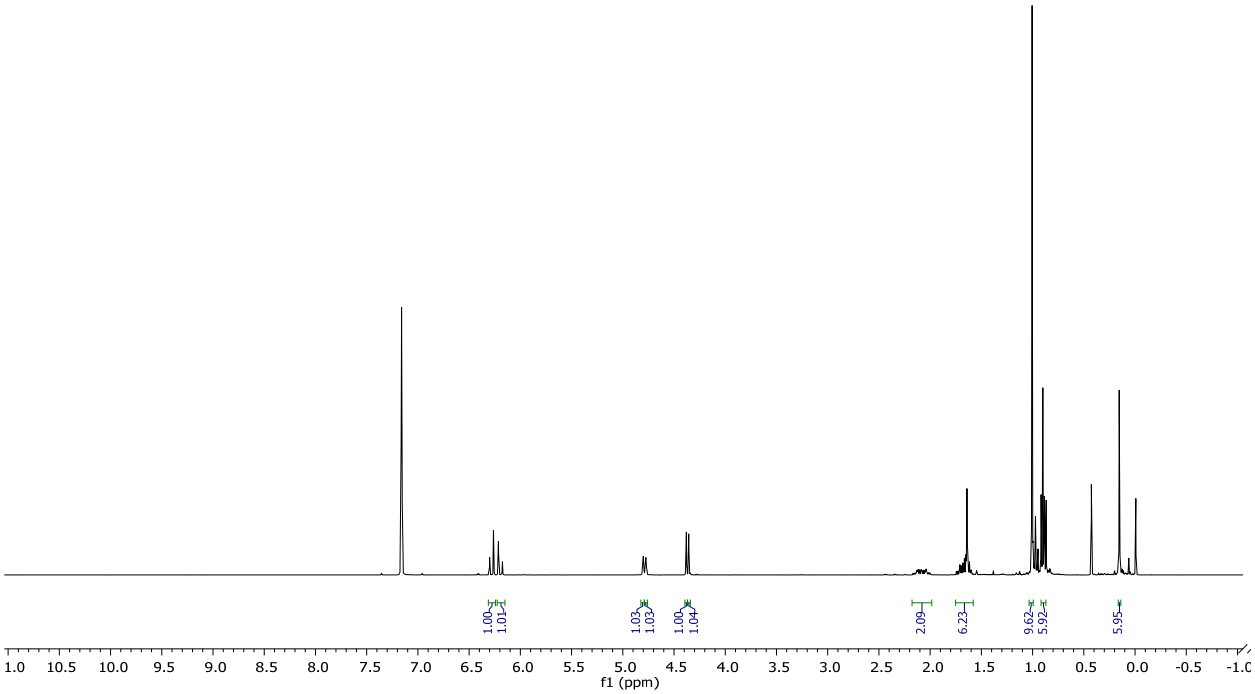


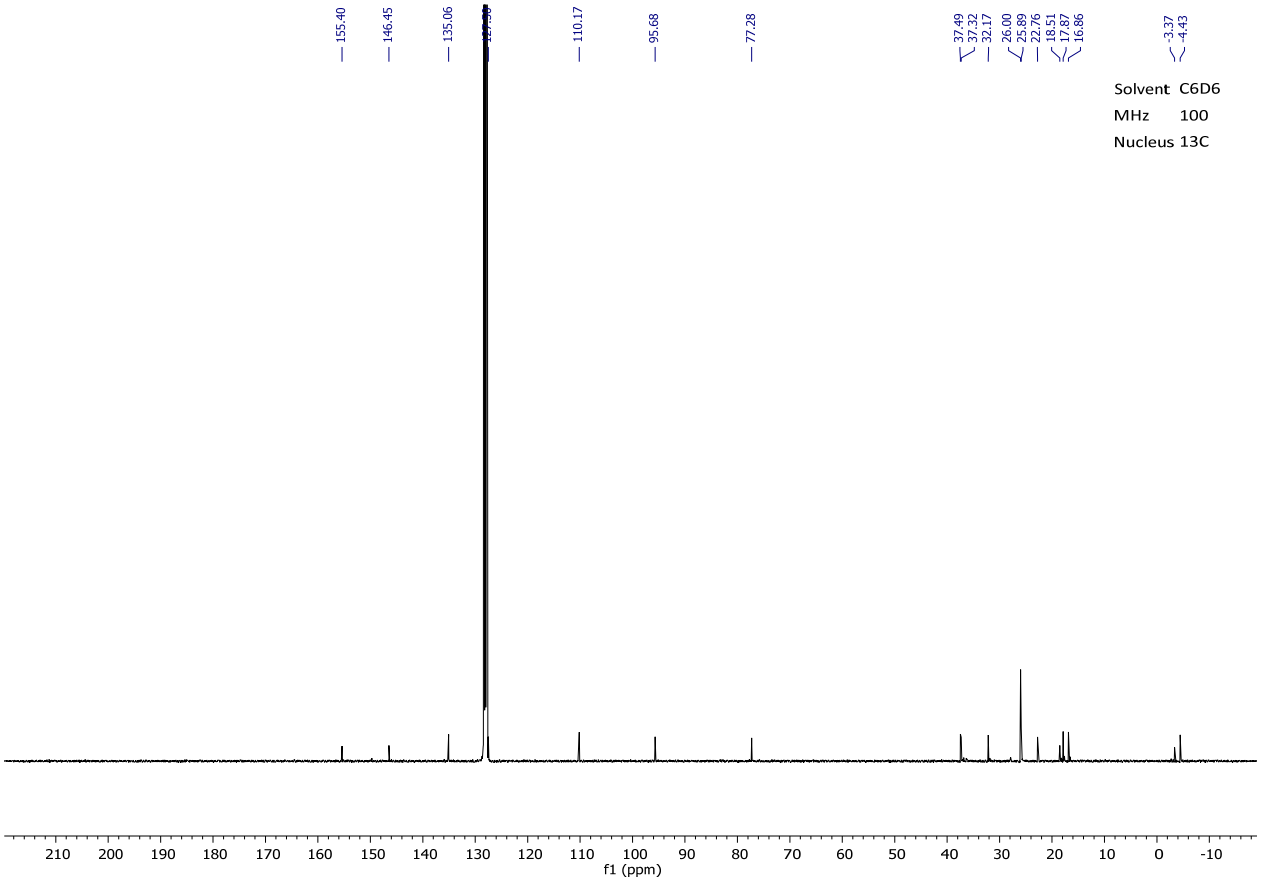
Solvent CDCl3
MHz 100
Nucleus 13C



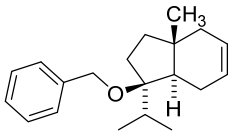
27

Solvent C6D6
MHz 400
Nucleus 1H



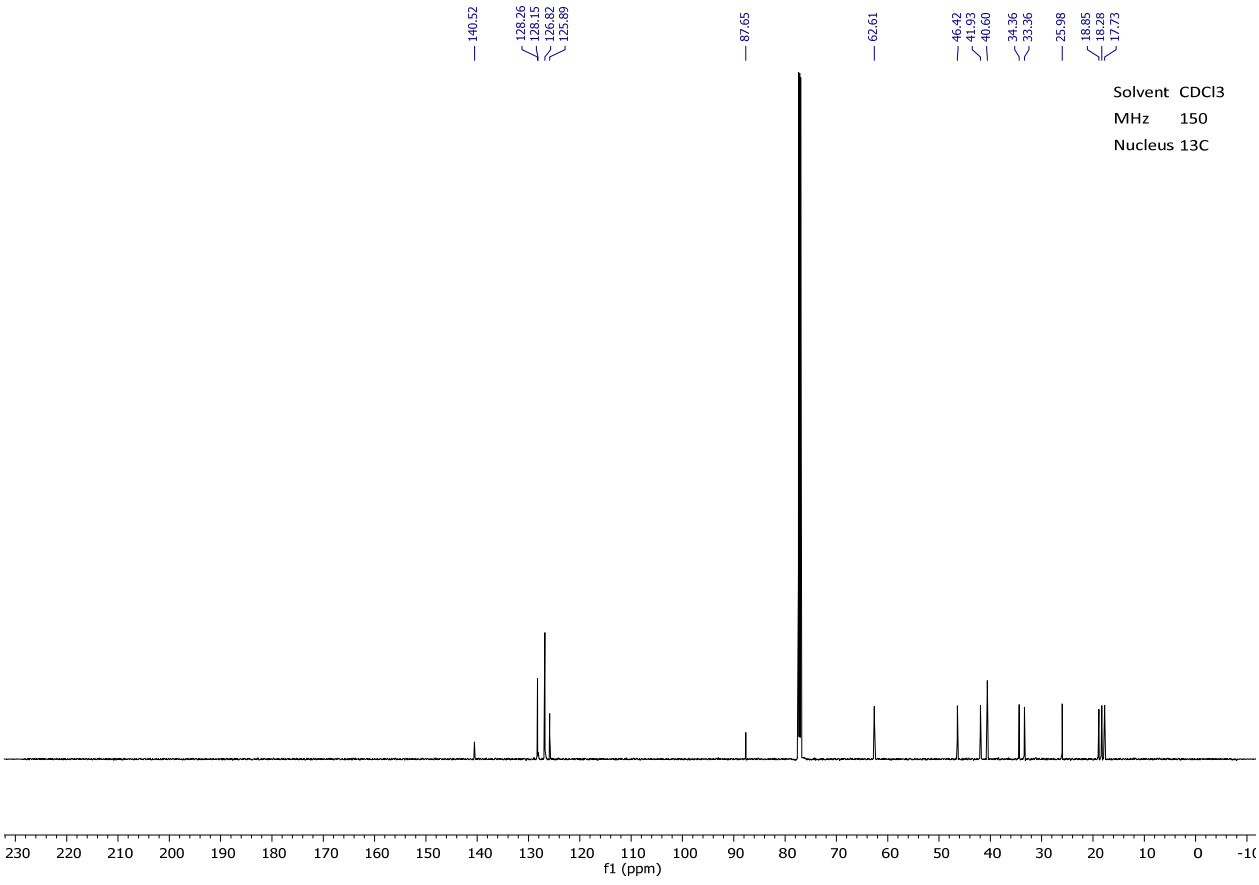


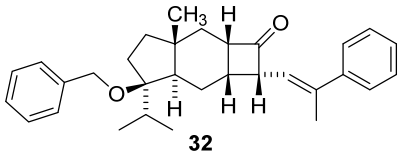
Solvent C6D6
MHz 100
Nucleus 13C


CH3
O
H

29

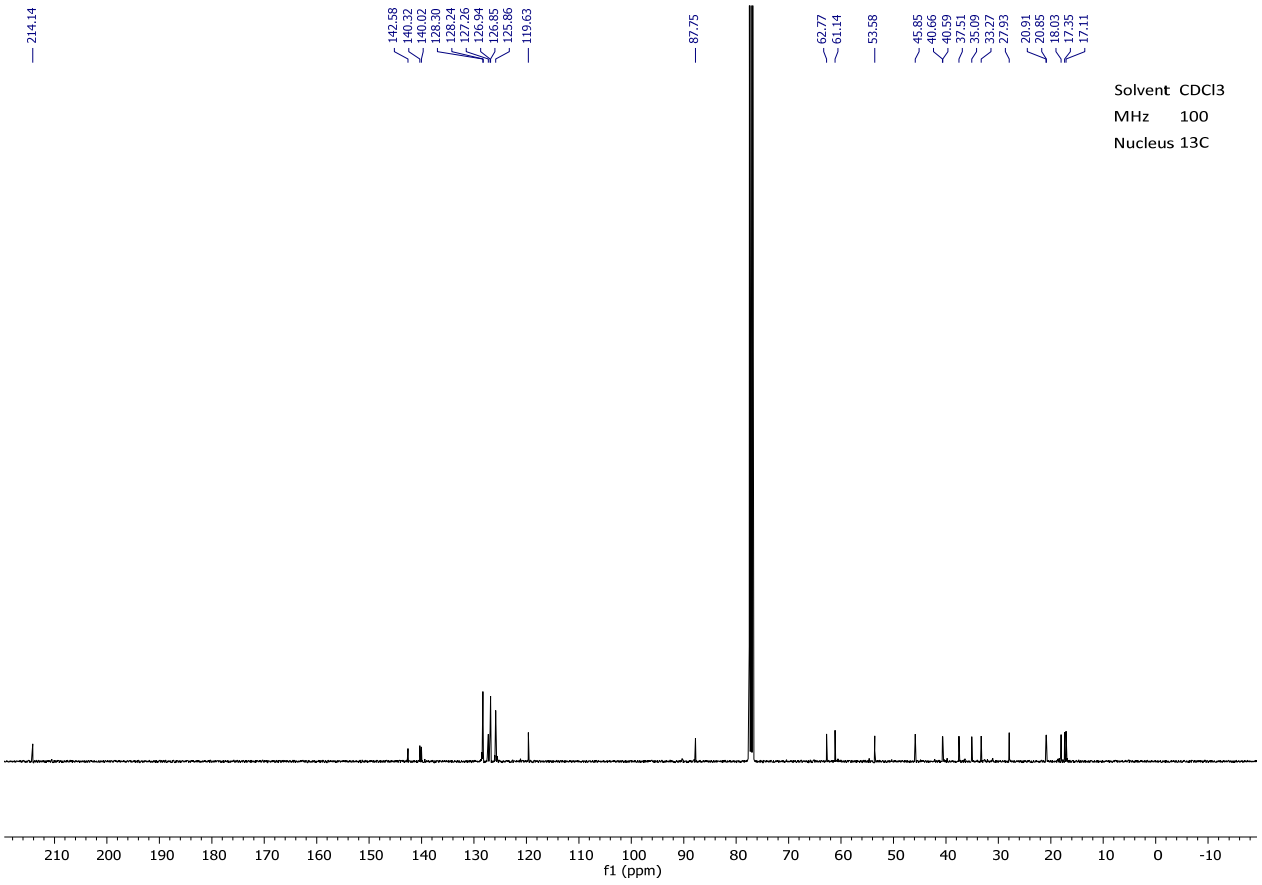
Solvent CDCl3
MHz 600
Nucleus 1H
4.05
0.99
0.99
0.98
2.09
1.03
1.08
3.68
1.02
1.05
1.01
1.03
3.07
6.27
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

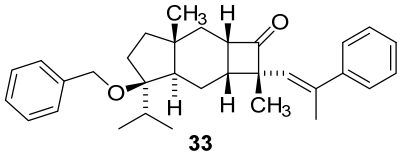

140.52
128.26
128.15
126.82
125.89
87.65
62.61
46.42
41.93
40.60
34.36
33.36
25.98
18.85
18.28
17.73
Solvent CDCl3
MHz 150
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
H
O
O
H
H
H

32

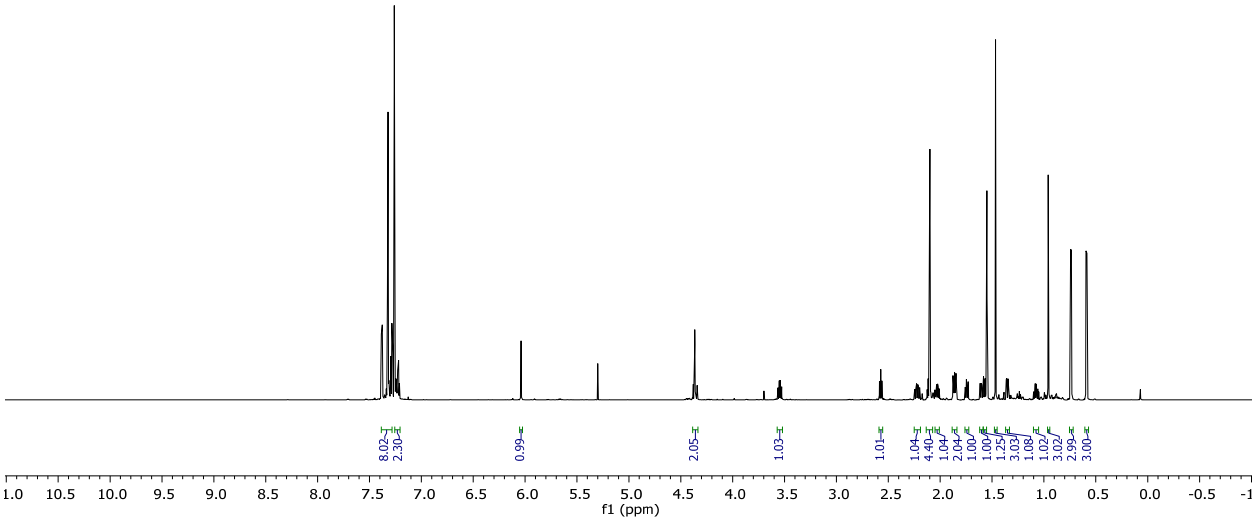
Solvent CDCl3
MHz 400
Nucleus 1H
12.85
1.00
3.08
1.04
1.04
6.45
4.37
1.14
1.19
1.11
2.29
2.95
3.04
f1 (ppm)

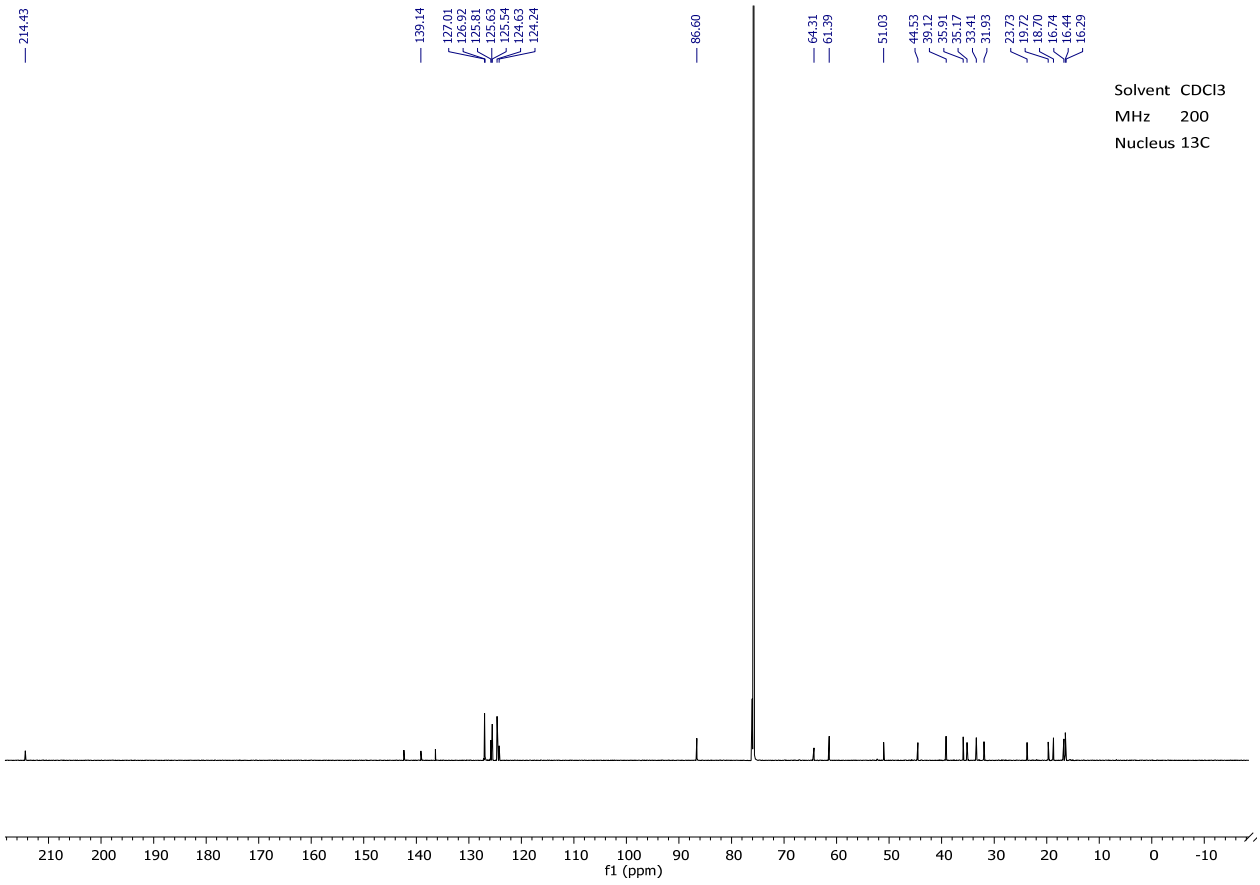

214.14
142.58
140.32
140.02
128.30
128.24
127.26
126.94
126.85
125.86
119.63
87.75
62.77
61.14
53.58
45.85
40.66
40.59
37.51
35.09
33.27
27.93
20.91
20.85
18.03
17.35
17.11
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)

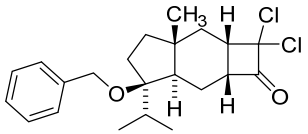


33

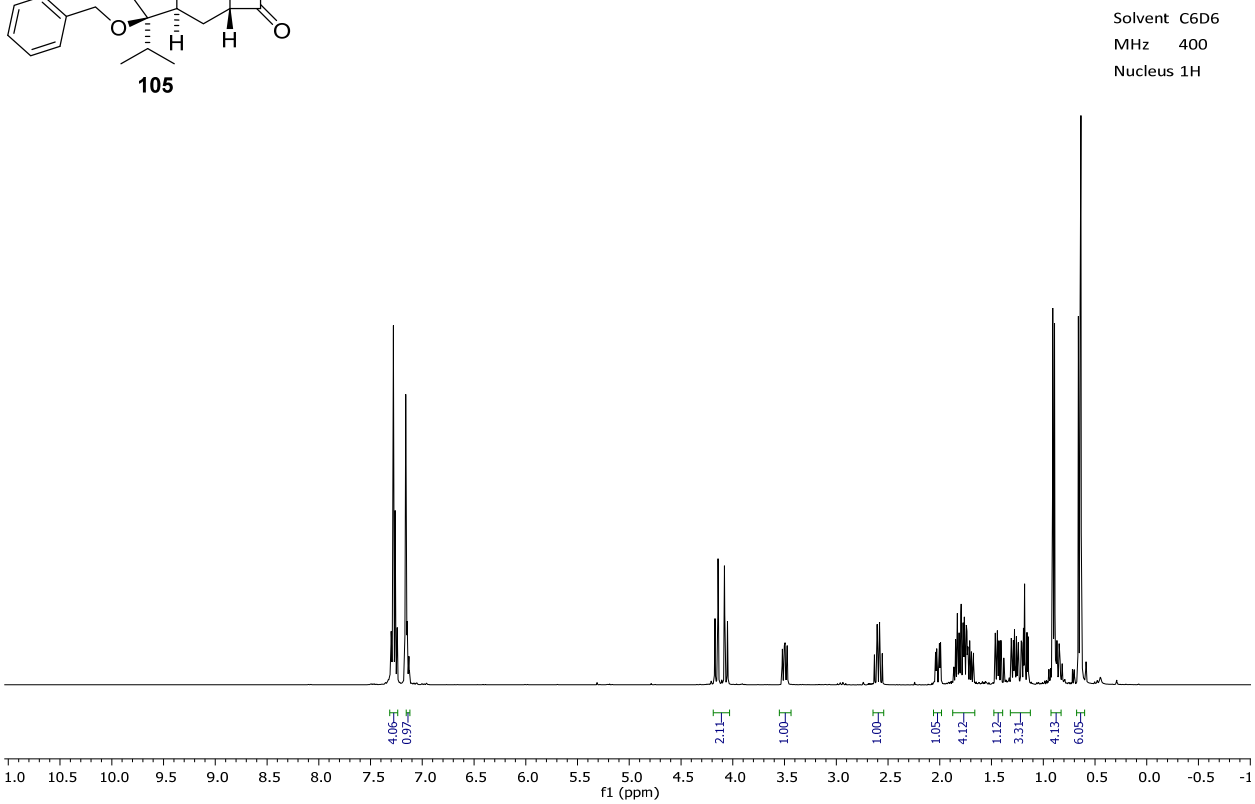
Solvent CDCl3
MHz 800
Nucleus 1H

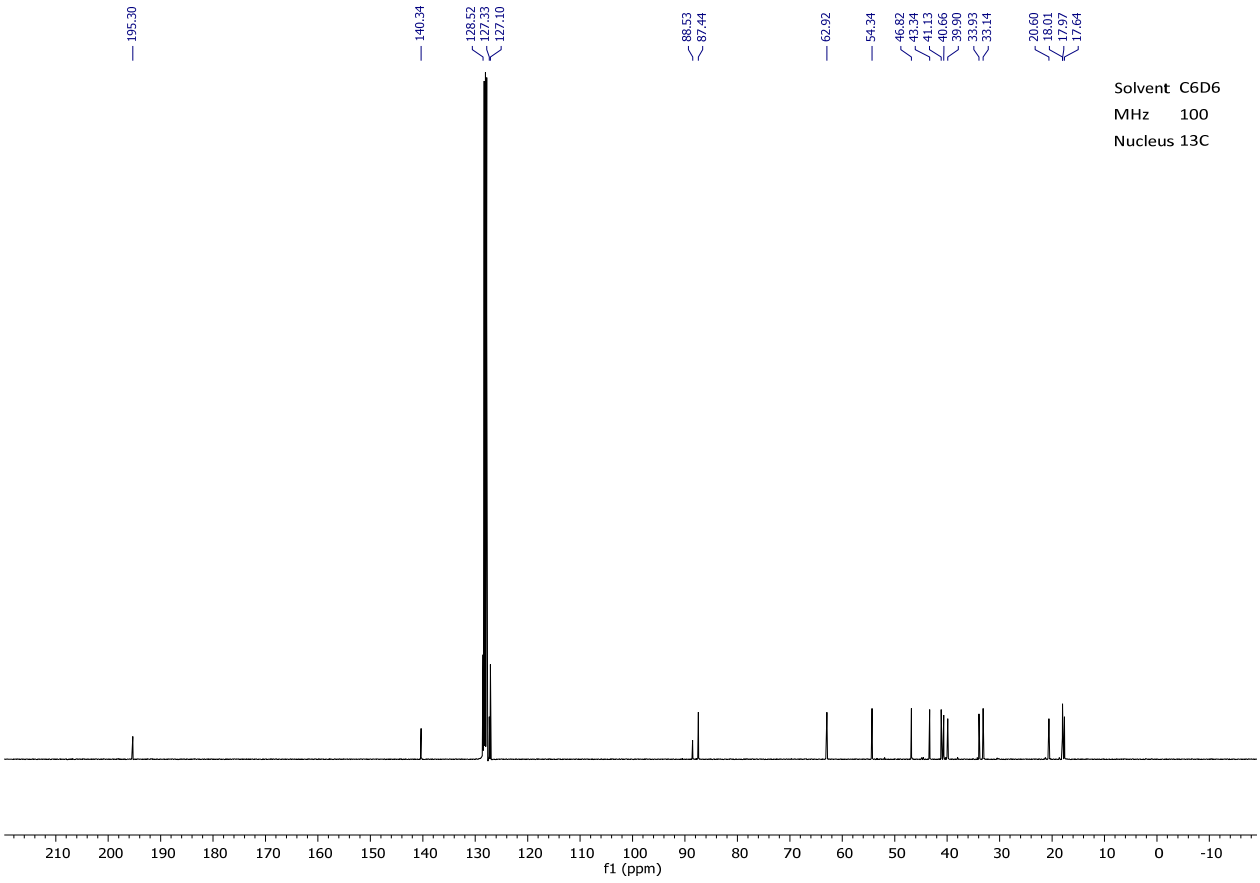


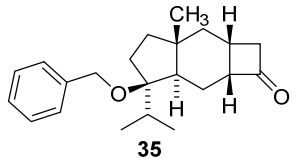



CH3
H
Cl
Cl
O
H
H
O

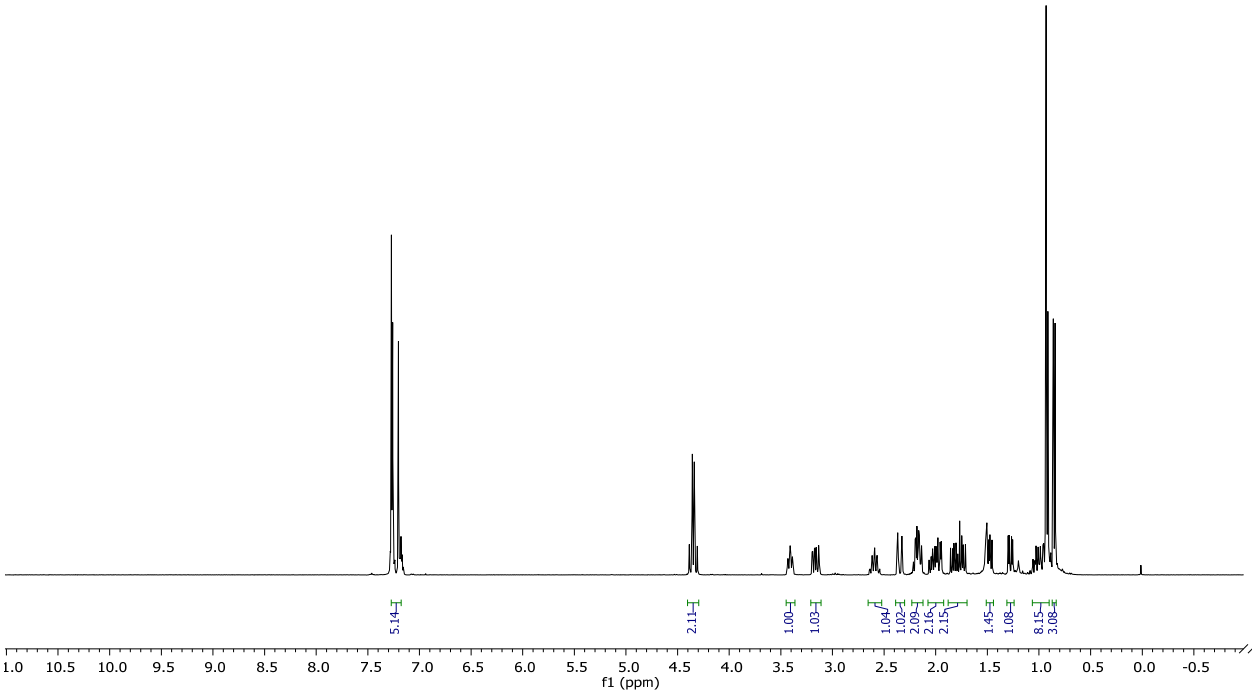
105

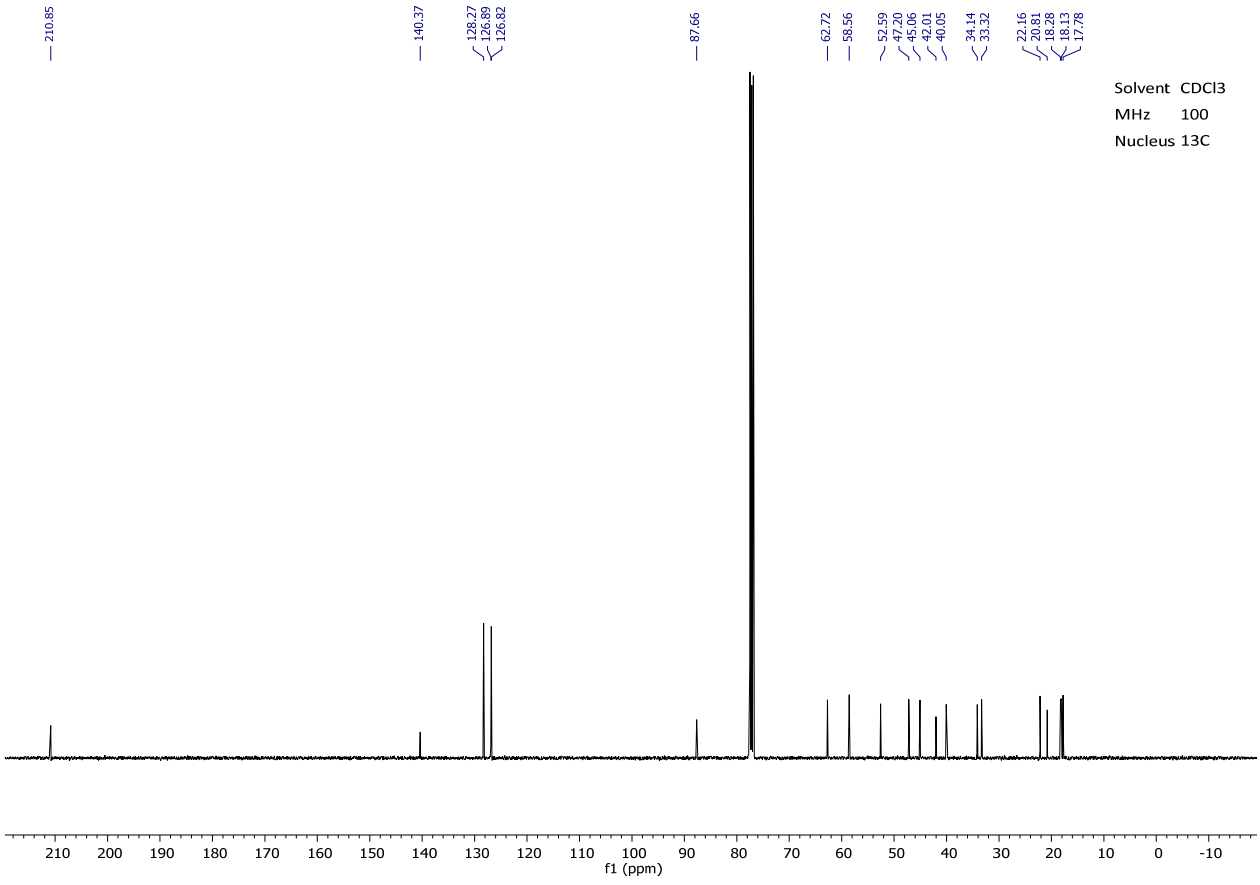

Solvent C6D6
MHz 400
Nucleus 1H
4.06
0.97
2.11
1.00
1.00
1.05
4.12
1.12
3.31
4.13
6.05
f1 (ppm)

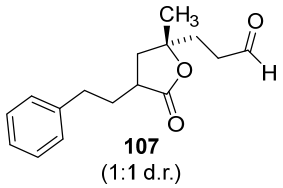

195.30
140.34
128.52
127.33
127.10
88.53
87.44
62.92
54.34
46.82
43.34
41.13
40.66
39.90
33.93
33.14
20.60
18.01
17.97
17.64
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


CH3
H
O
H
H
O

35

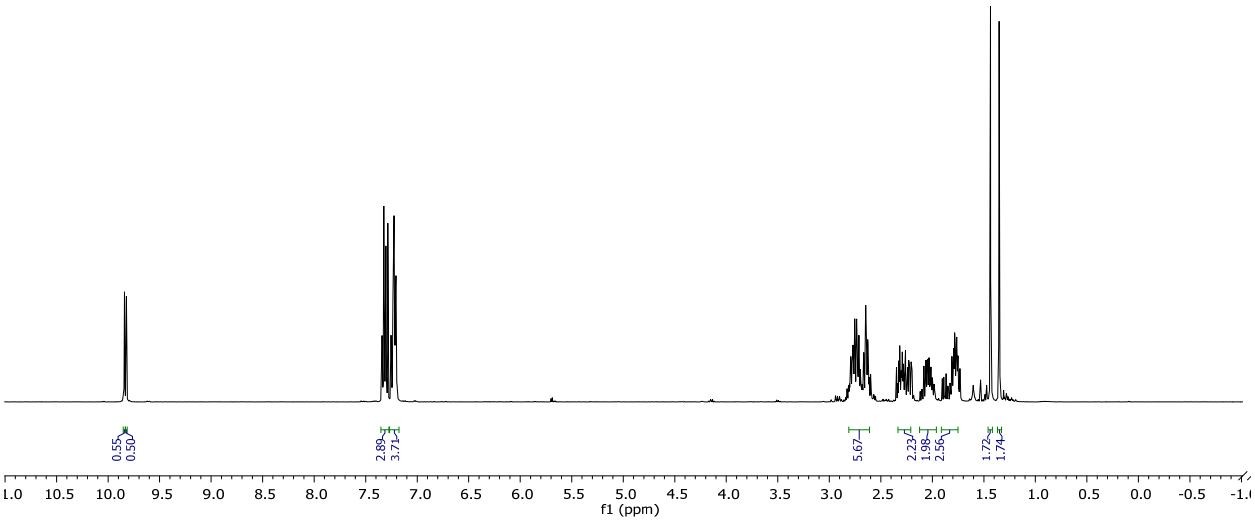

Solvent CDCl3
MHz 400
Nucleus 1H
5.14
2.11
1.00
1.03
1.04
1.02
2.09
2.16
2.15
1.45
1.08
8.15
3.08
f1 (ppm)

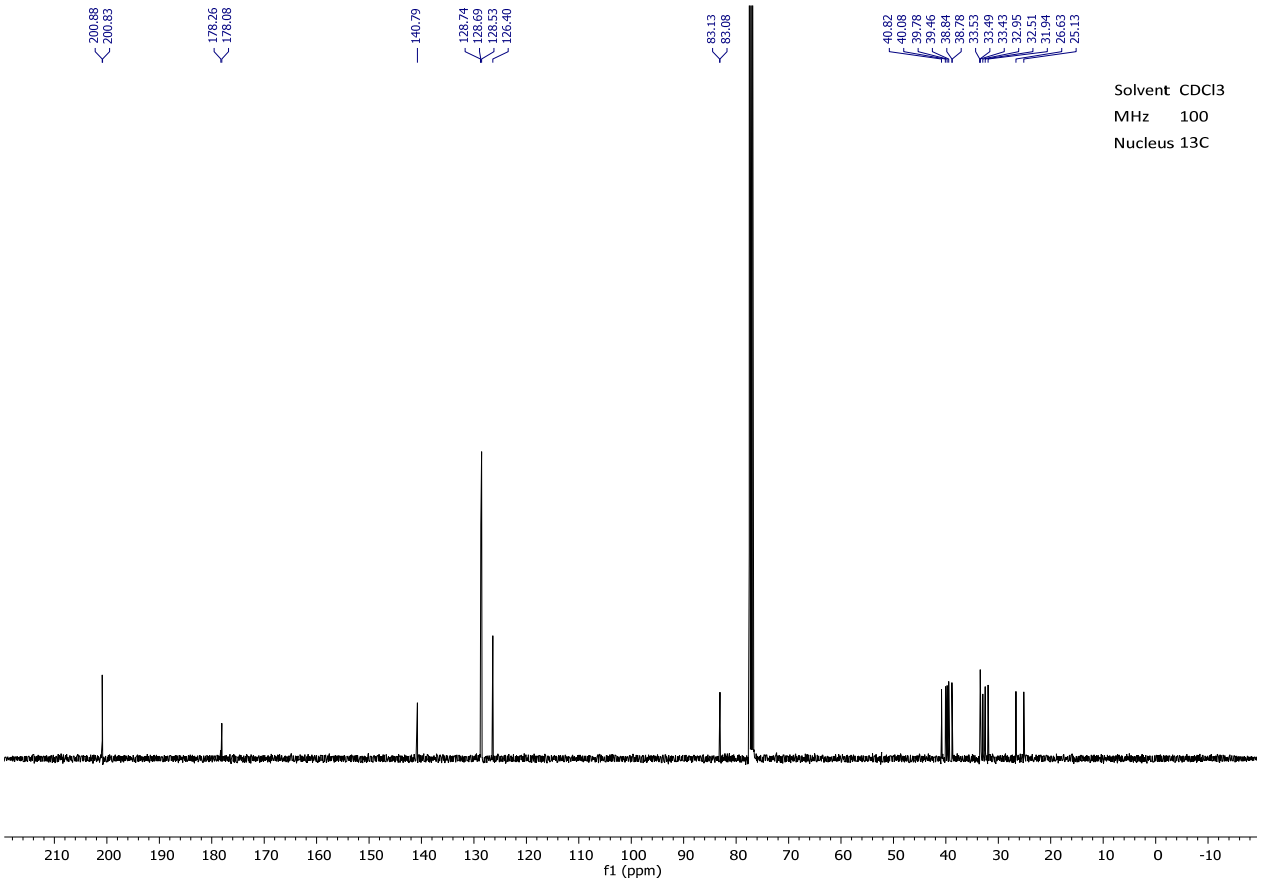

210.85
140.37
128.27
126.89
126.82
87.66
62.72
58.56
52.59
47.20
45.06
42.01
40.05
34.14
33.32
22.16
20.81
18.28
18.13
17.78
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)



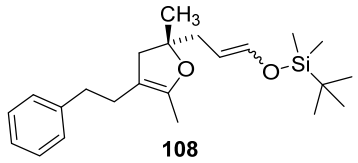
107
(1:1 d.r.)

Solvent CDCl3
MHz 400
Nucleus 1H



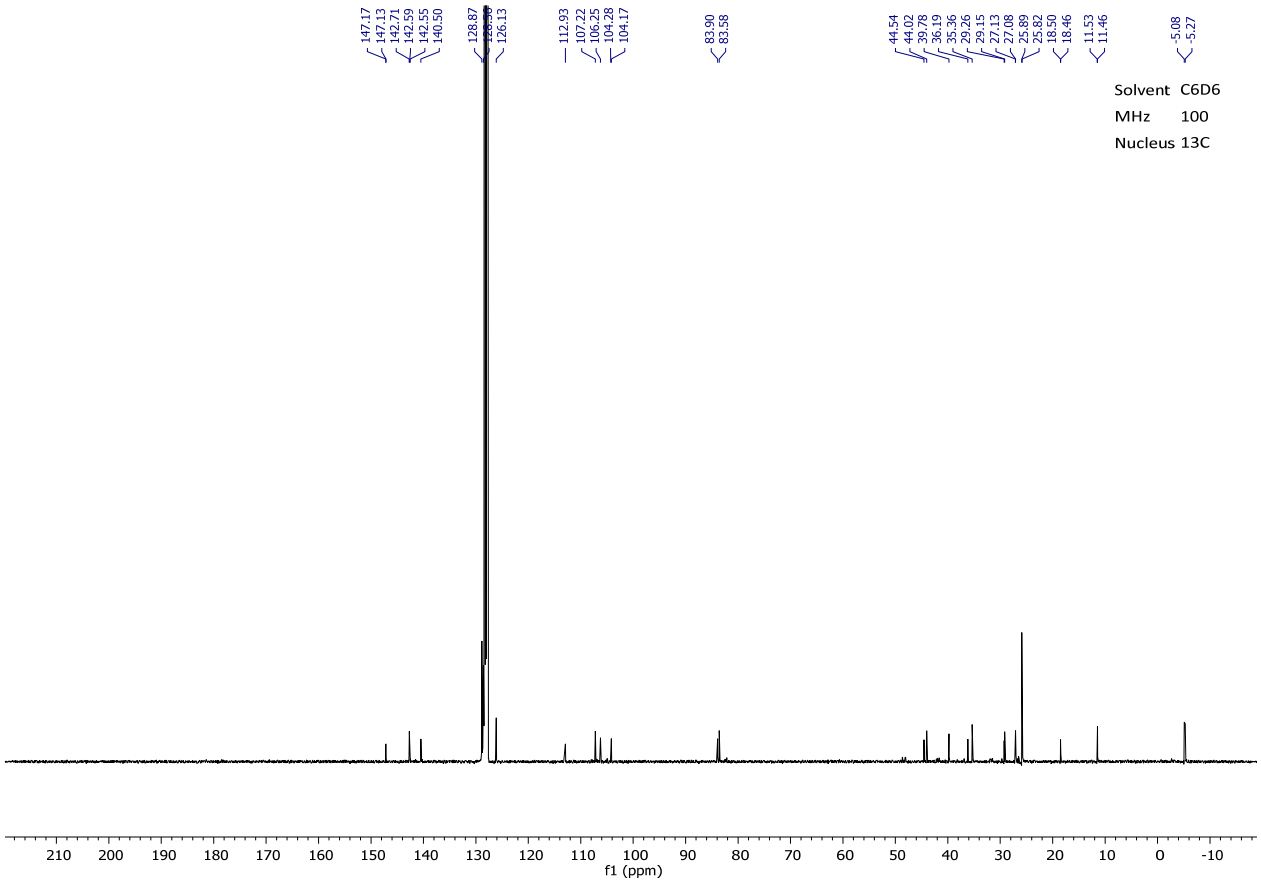


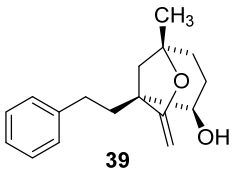
Solvent CDCl3
MHz 100
Nucleus 13C


CH3
O
O
Si

108

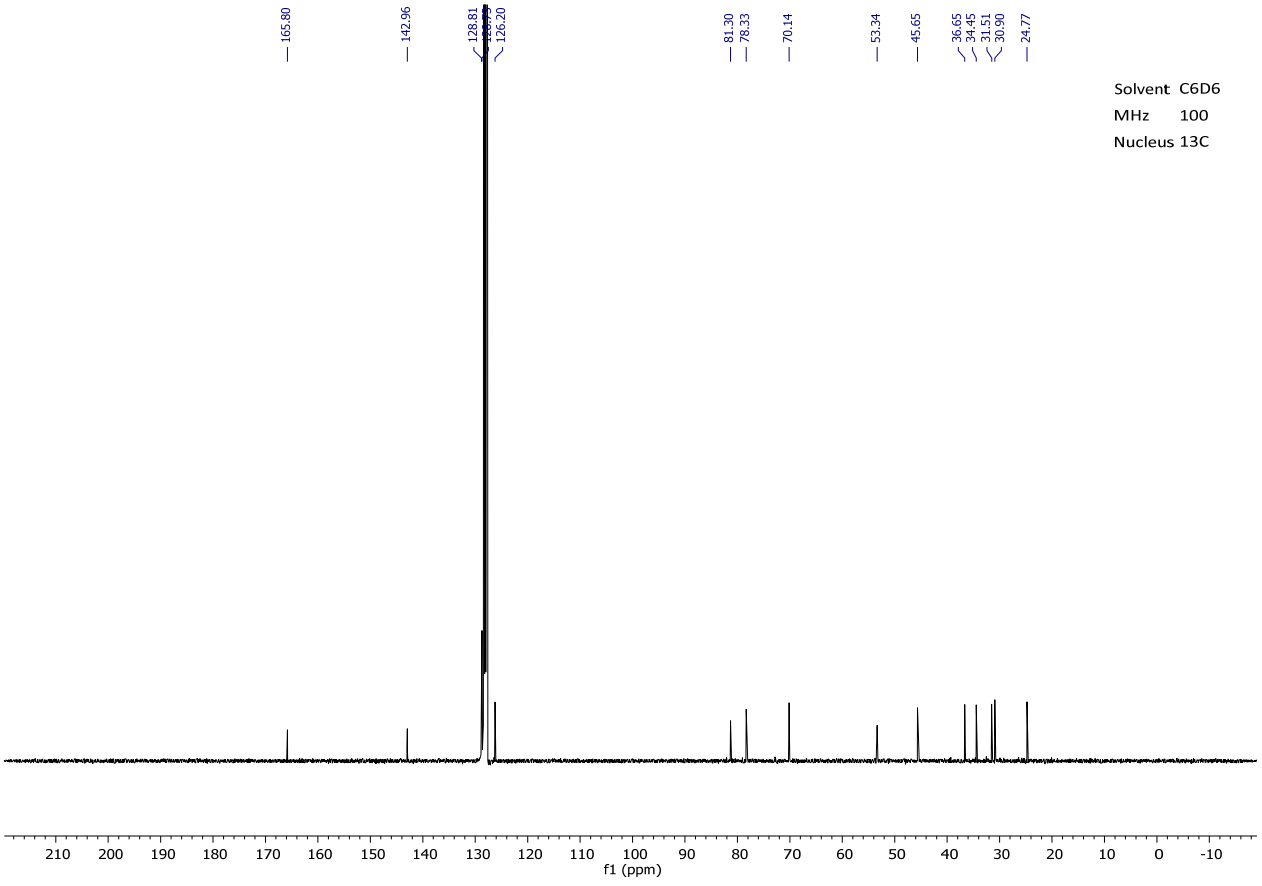
Solvent C6D6
MHz 400
Nucleus 1H
1.33
4.10
1.00
0.58
0.43
0.86
2.50
0.63
4.41
1.21
1.81
1.29
1.82
9.76
3.44
2.83
f1 (ppm)

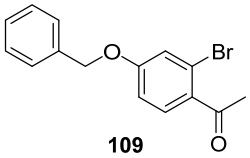

147.17
147.13
142.71
142.59
142.55
140.50
128.87
126.13
112.93
107.22
106.25
104.28
104.17
83.90
83.58
44.54
44.02
39.78
36.19
35.36
29.26
29.15
27.13
27.08
25.89
25.82
18.50
18.46
11.53
11.46
-5.08
-5.27
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


CH3
O
OH

39

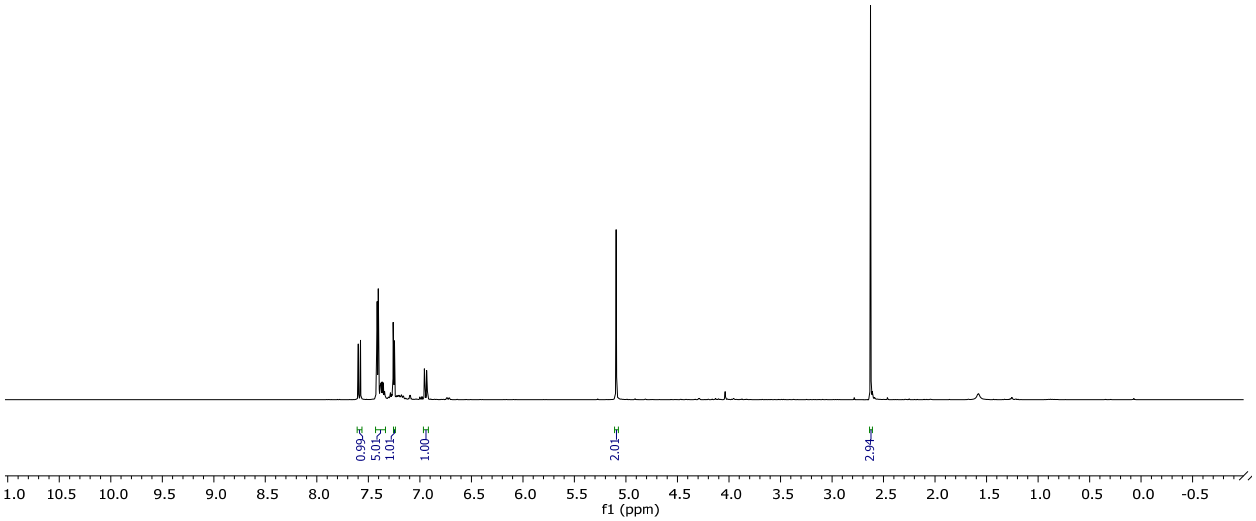
Solvent C6D6
MHz 400
Nucleus 1H
4.01
1.11
1.00
1.01
1.02
1.02
1.02
1.06
1.08
1.07
3.32
3.06
3.20
f1 (ppm)


165.80
142.96
128.81
126.20
81.30
78.33
70.14
53.34
45.65
36.65
34.45
31.51
30.90
24.77
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)

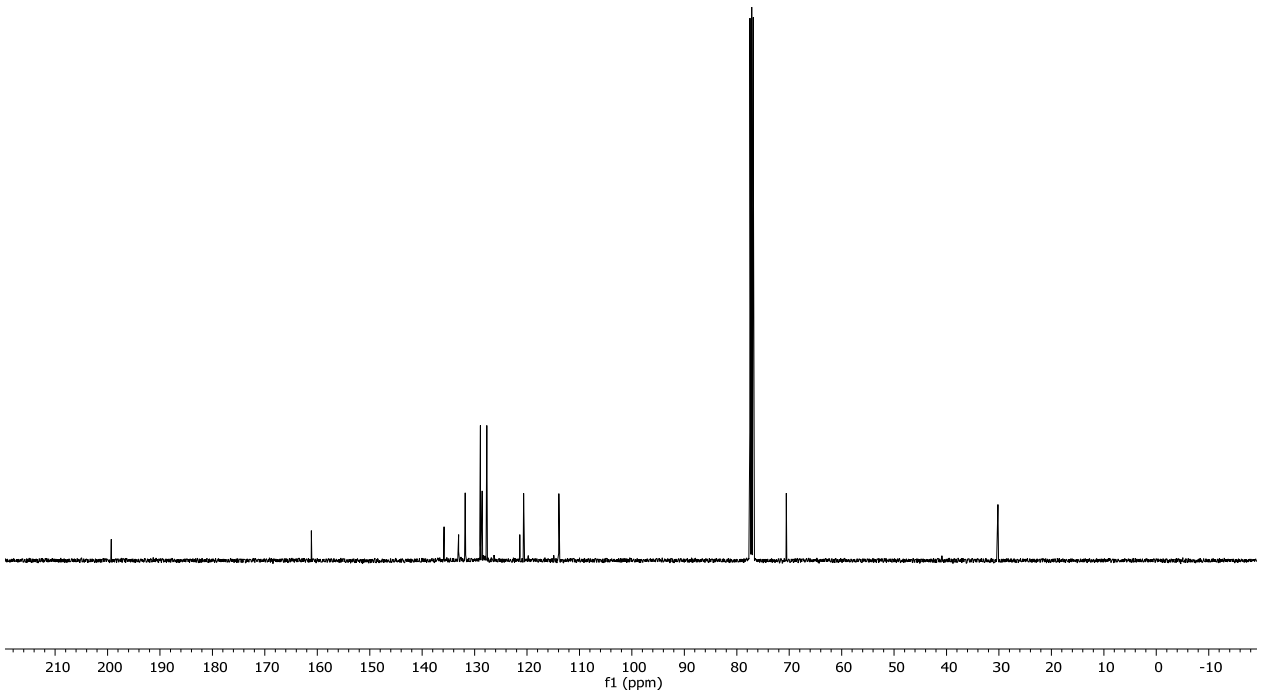


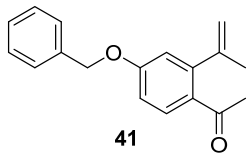
109

Solvent CDCl3
MHz 400
Nucleus 1H



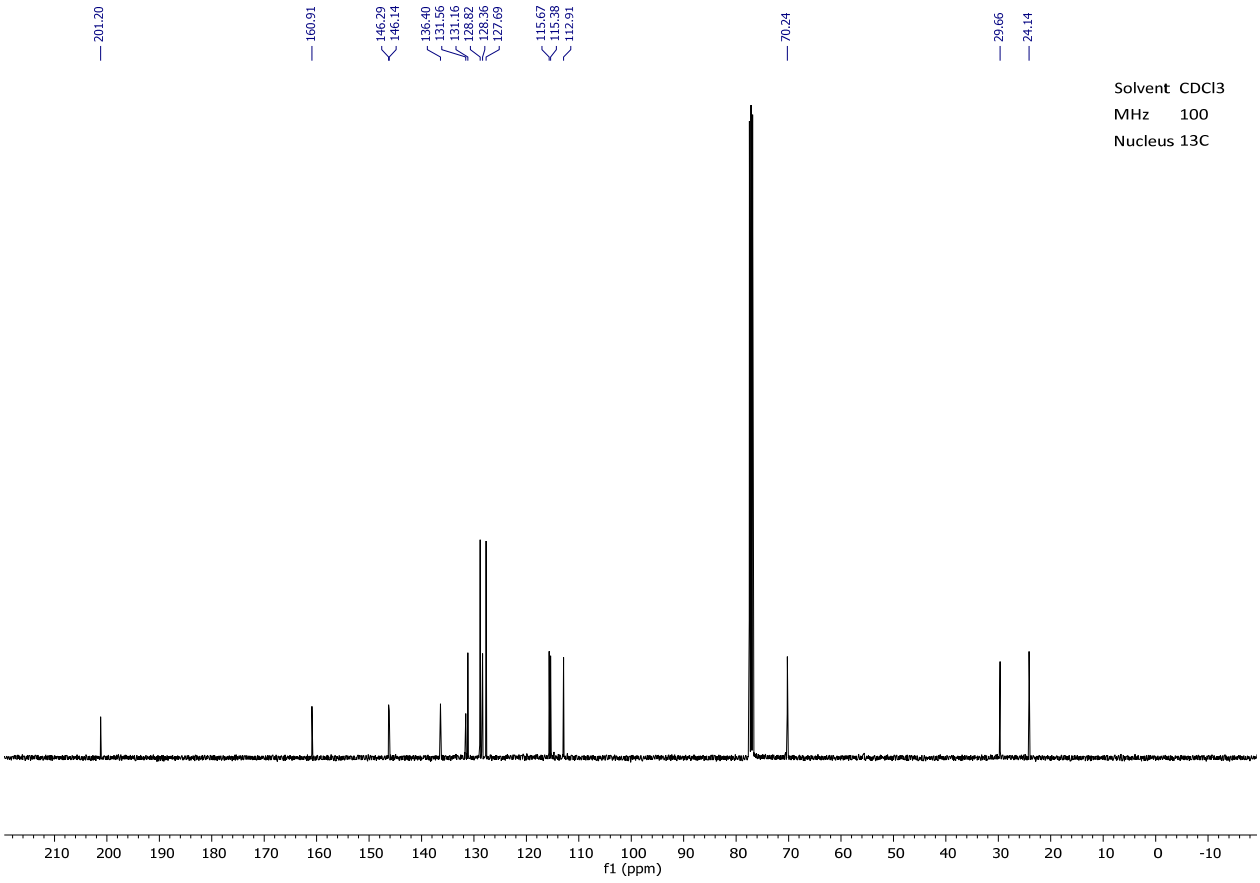
Solvent CDCl3
MHz 100
Nucleus 13C

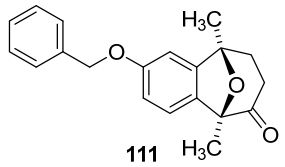



O
O

41

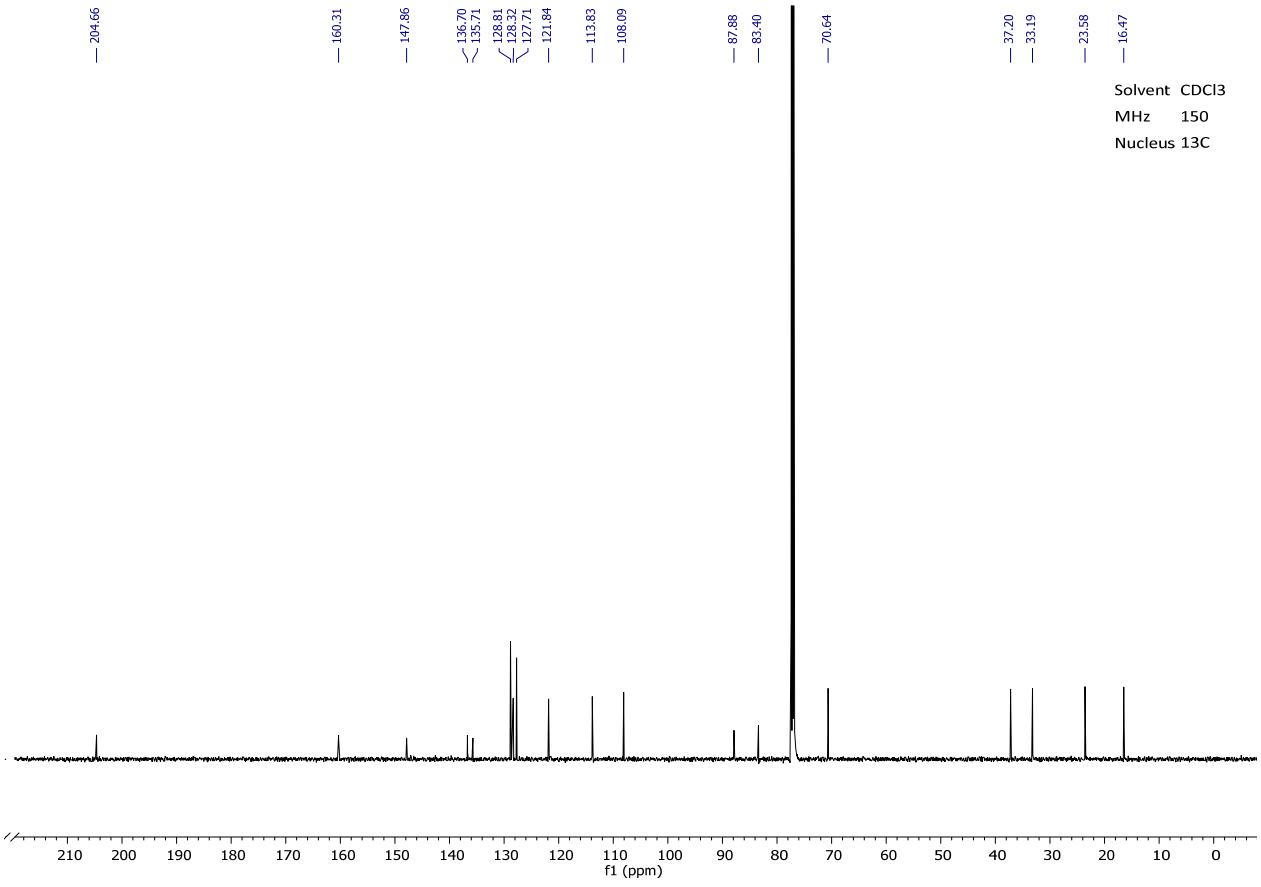
Solvent CDCl3
MHz 400
Nucleus 1H
1.05
5.09
0.99
0.98
1.02
2.09
1.00
2.99
3.02
f1 (ppm)

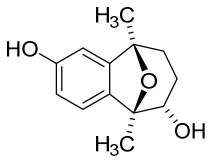

201.20
160.91
146.29
146.14
136.40
131.56
131.16
128.82
128.36
127.69
115.67
115.38
112.91
70.24
29.66
24.14
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


H3C
O
O
O
H3C

111

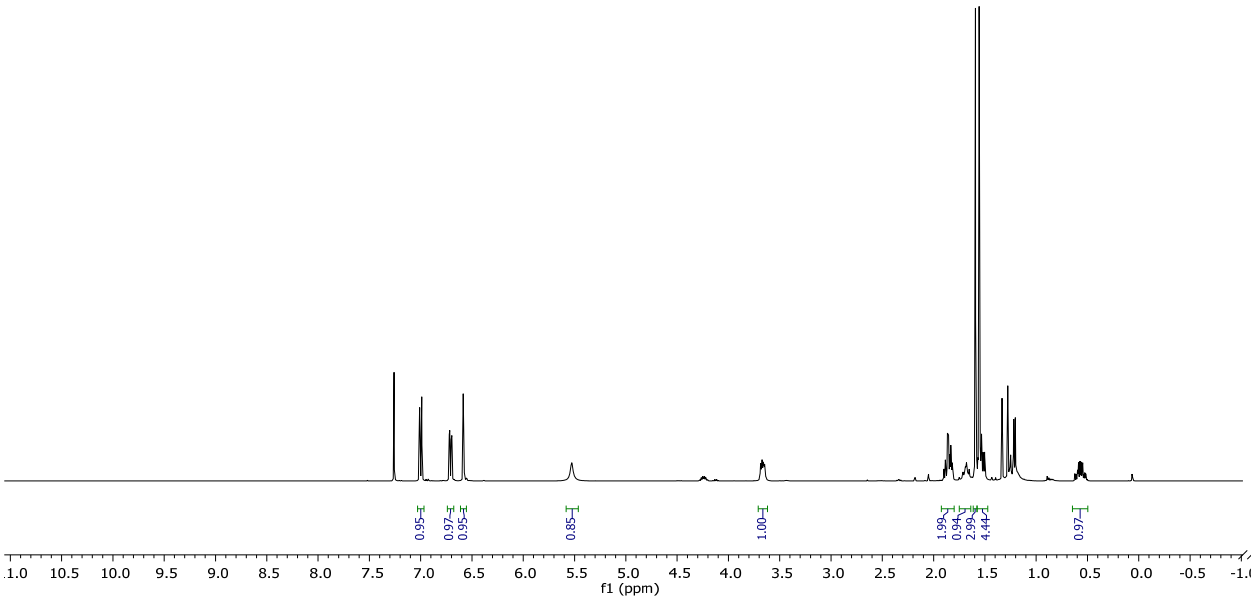
Solvent CDCl3
MHz 400
Nucleus 1H
4.98
1.00
2.01
2.04
2.08
1.05
1.02
3.04
2.92
f1 (ppm)

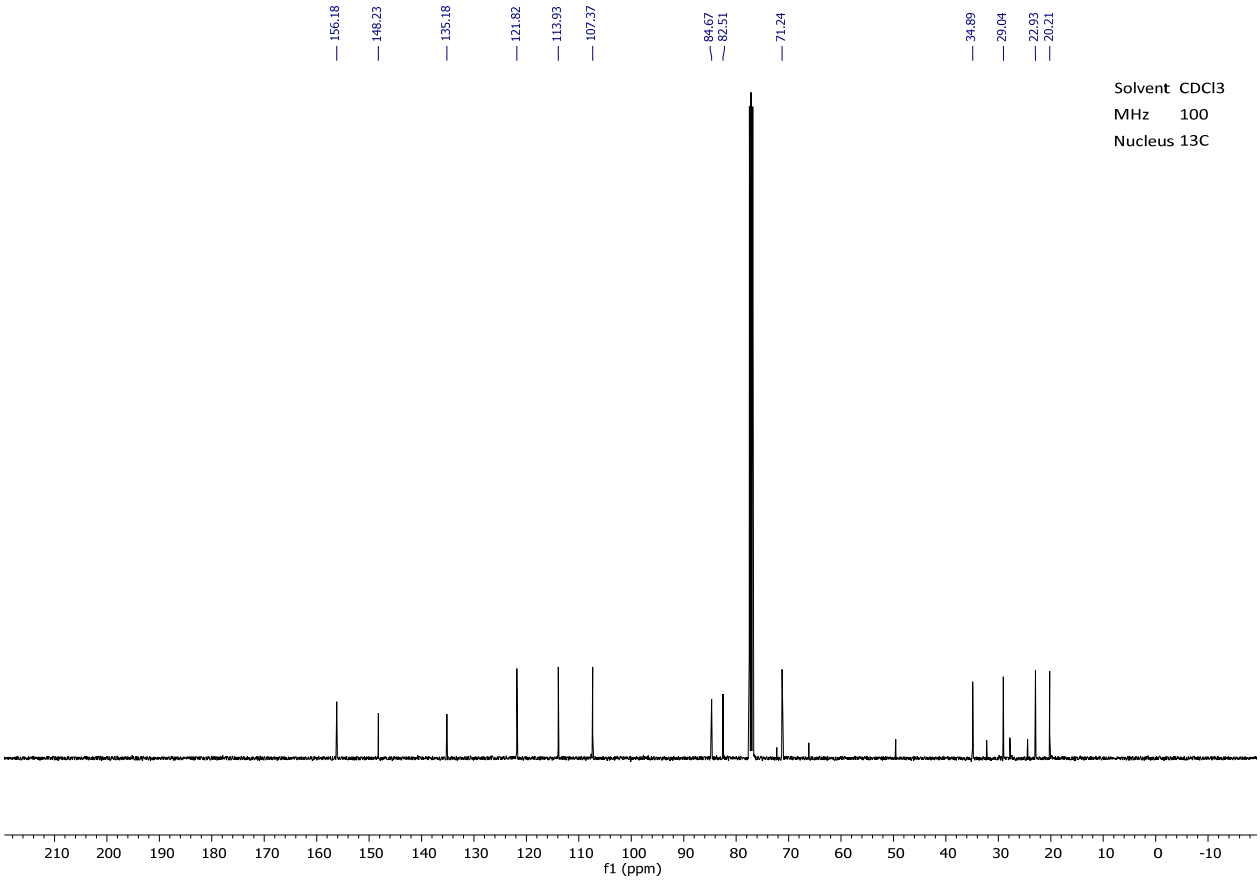

204.66
160.31
147.86
136.70
135.71
128.81
128.32
127.71
121.84
113.83
108.09
87.88
83.40
70.64
37.20
33.19
23.58
16.47
Solvent CDCl3
MHz 150
Nucleus 13C
f1 (ppm)

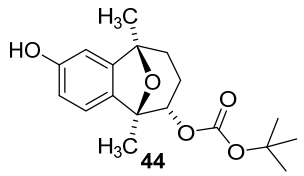


12

Solvent CDCl3
MHz 400
Nucleus 1H

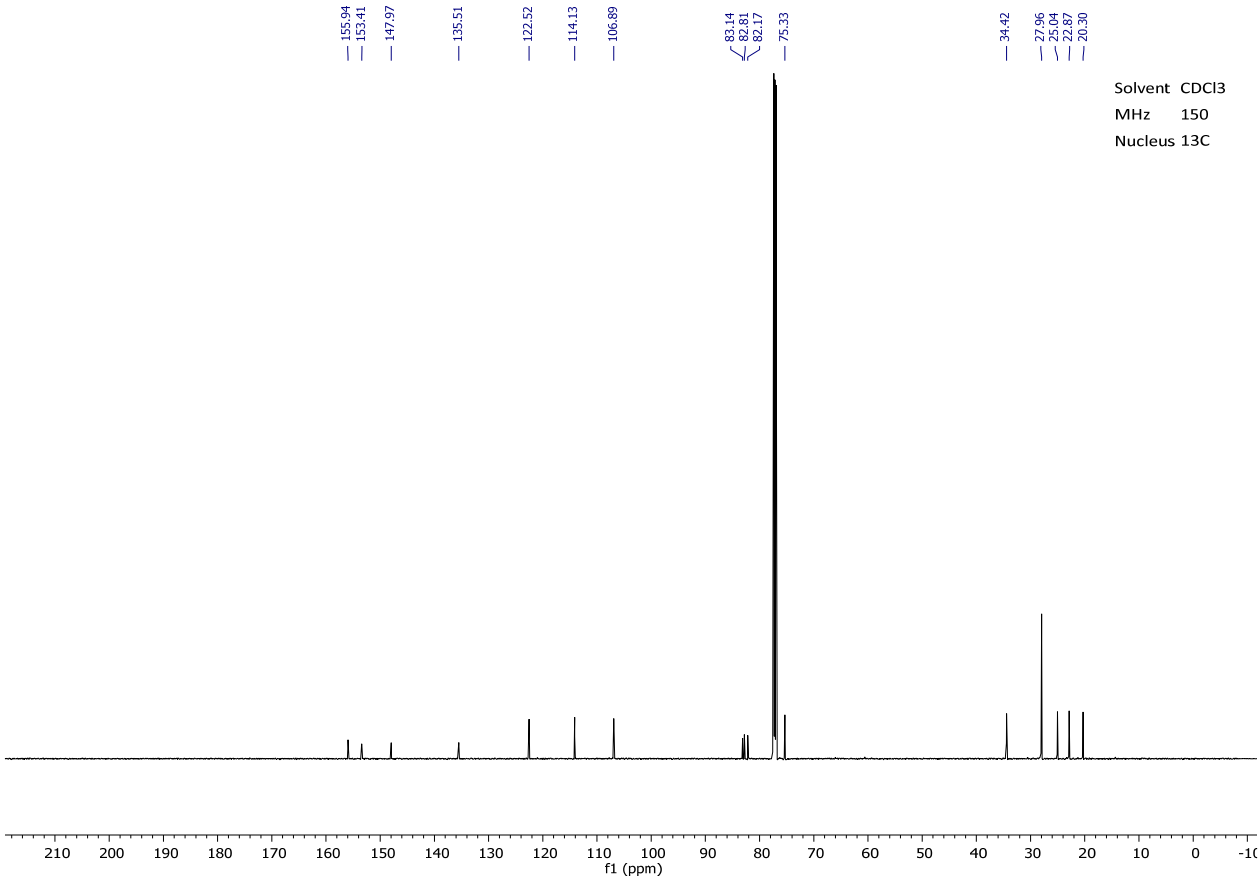


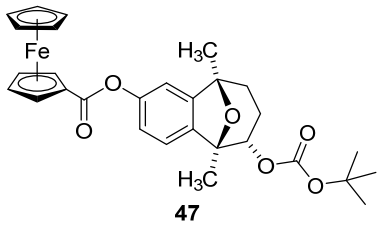



H3C
HO
O
O
O
O
H3C

44

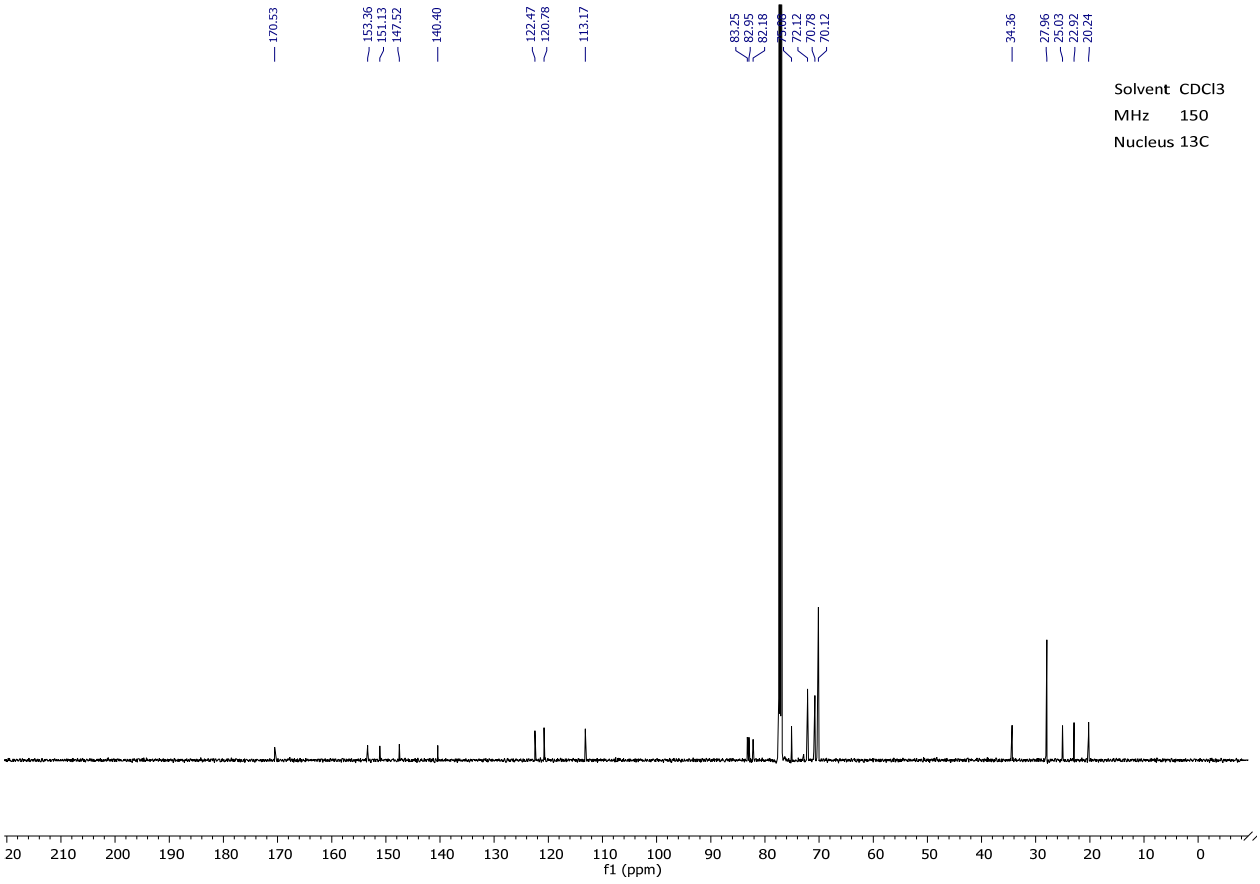
Solvent CDCl3
MHz 600
Nucleus 1H
1.00
1.01
0.99
0.97
1.01
2.07
3.08
4.06
9.12
1.07
f1 (ppm)

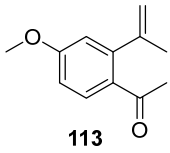

155.94
153.41
147.97
135.51
122.52
114.13
106.89
83.14
82.81
82.17
75.33
34.42
27.96
25.04
22.87
20.30
Solvent CDCl3
MHz 150
Nucleus 13C
f1 (ppm)


Fe
H3C
O
O
O
O
O
O
H3C

47

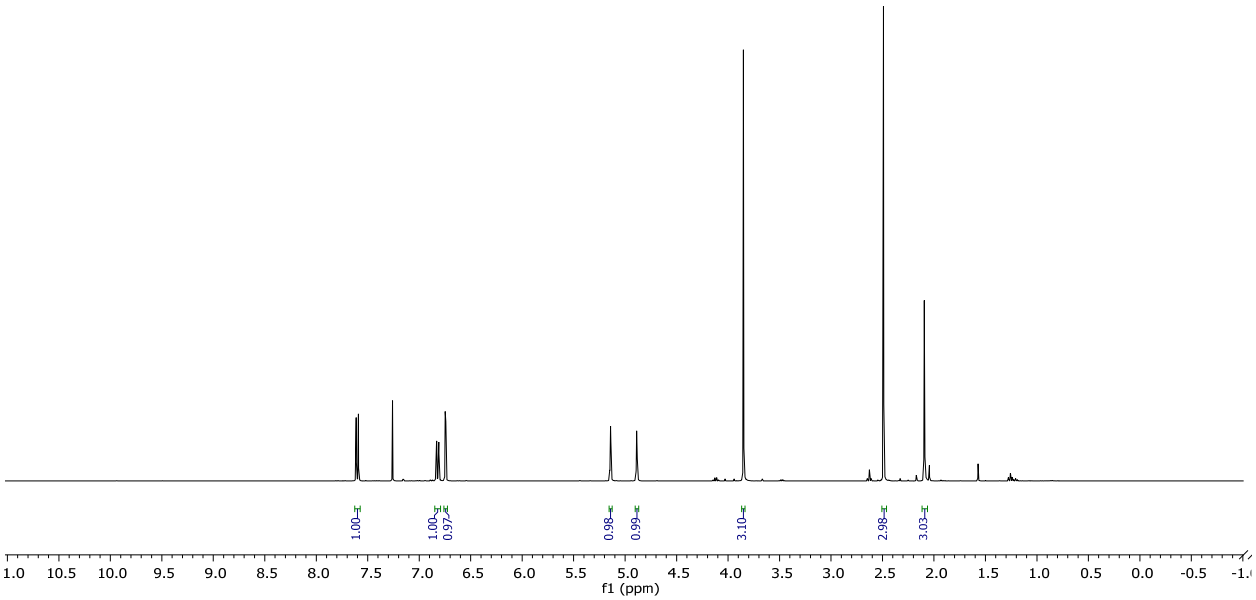
Solvent CDCl3
MHz 600
Nucleus 1H
1.05
1.01
1.00
2.06
1.02
2.12
5.39
2.09
3.95
3.17
9.34
1.05
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


170.53
153.36
151.13
147.52
140.40
122.47
120.78
113.17
83.25
82.95
82.18
77.00
72.12
70.78
70.12
34.36
27.96
25.03
22.92
20.24
Solvent CDCl3
MHz 150
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



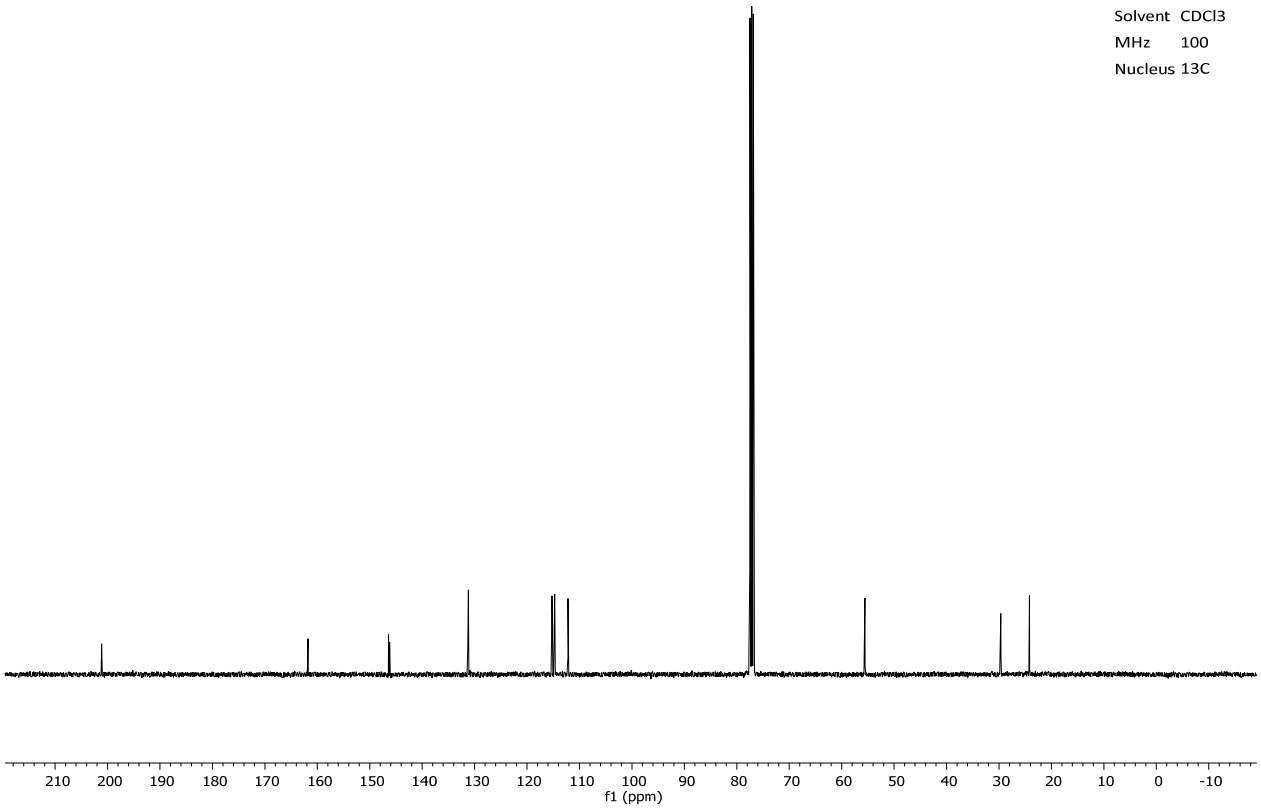
113

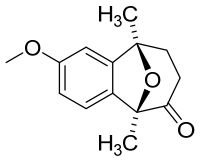
Solvent CDCl3
MHz 400
Nucleus 1H



201.12
161.77
146.42
146.20
131.30
131.20
115.26
114.74
112.18
55.57
29.65
24.18

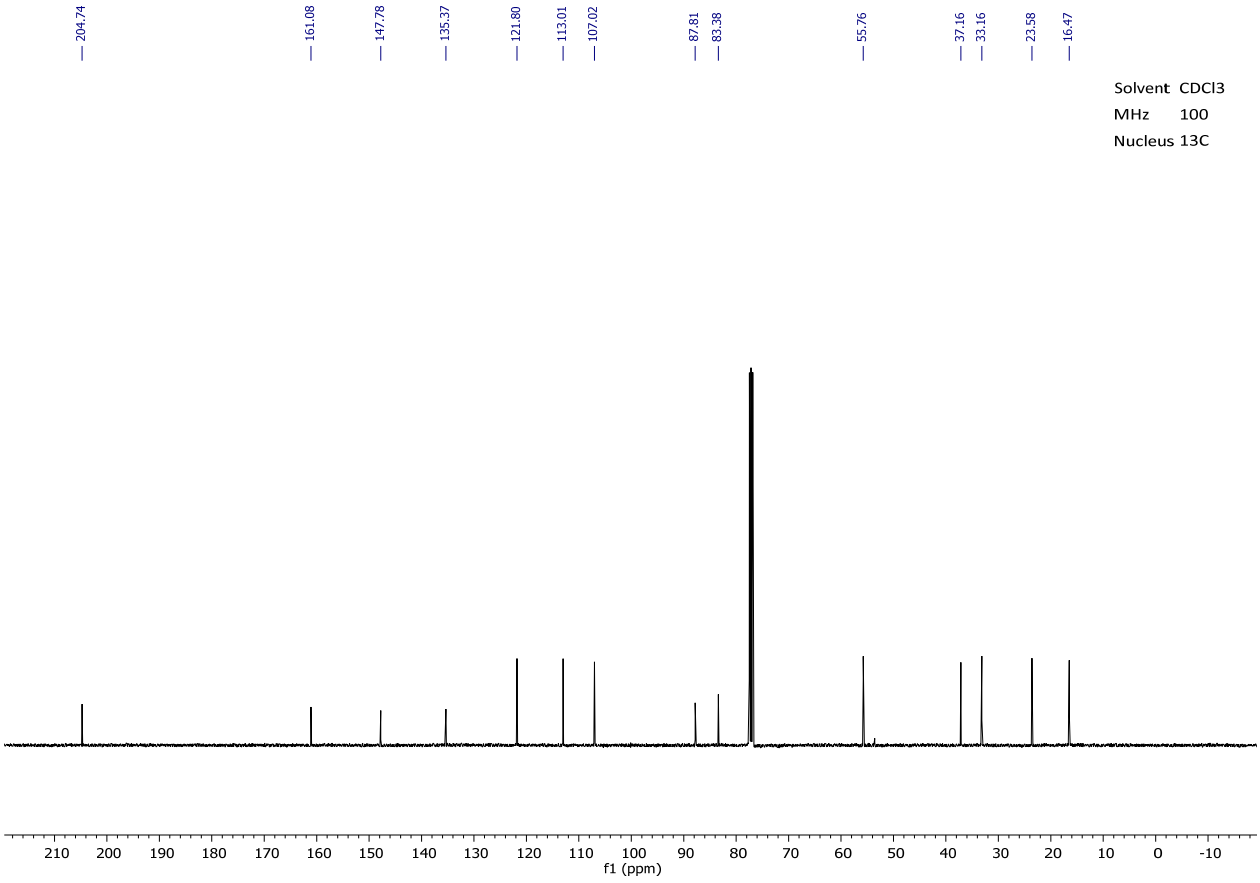
Solvent CDCl3
MHz 100
Nucleus 13C

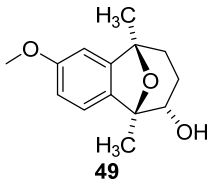



H3C
O
O
O
H3C

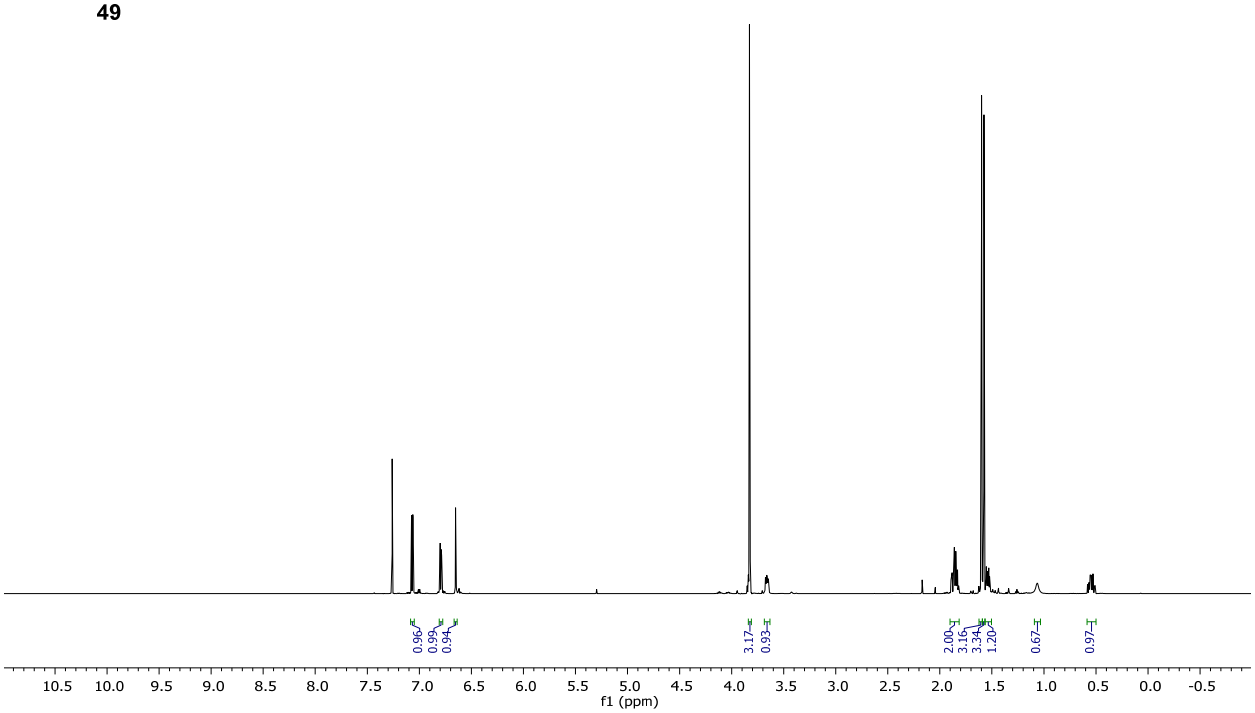
115

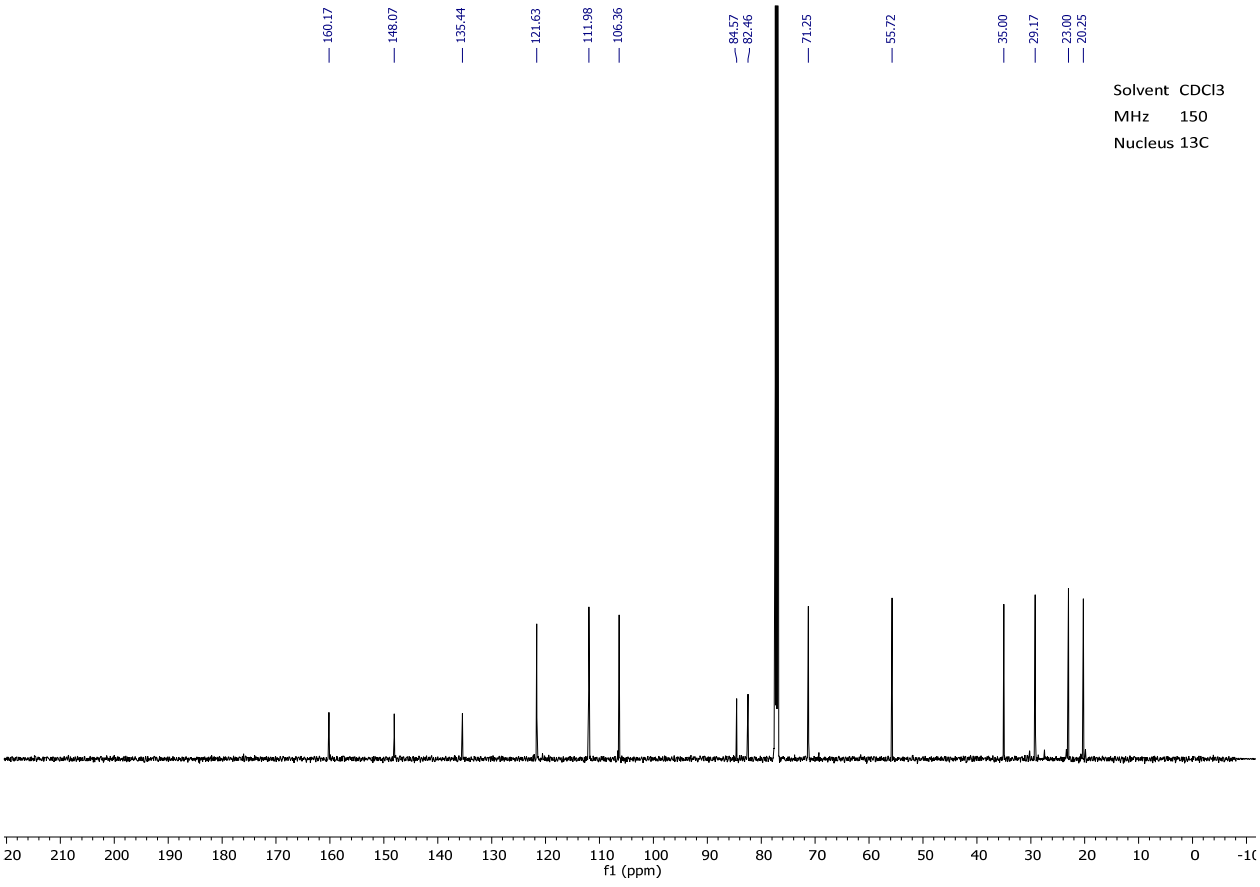
Solvent CDCl3
MHz 400
Nucleus 1H
0.97
0.99
0.98
3.00
2.03
1.04
1.00
3.02
3.16
f1 (ppm)

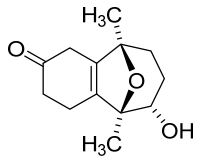

204.74
161.08
147.78
135.37
121.80
113.01
107.02
87.81
83.38
55.76
37.16
33.16
23.58
16.47
Solvent CDCl3
MHz 100
Nucleus 13C
f1 (ppm)


H3C
O
O
OH
H3C

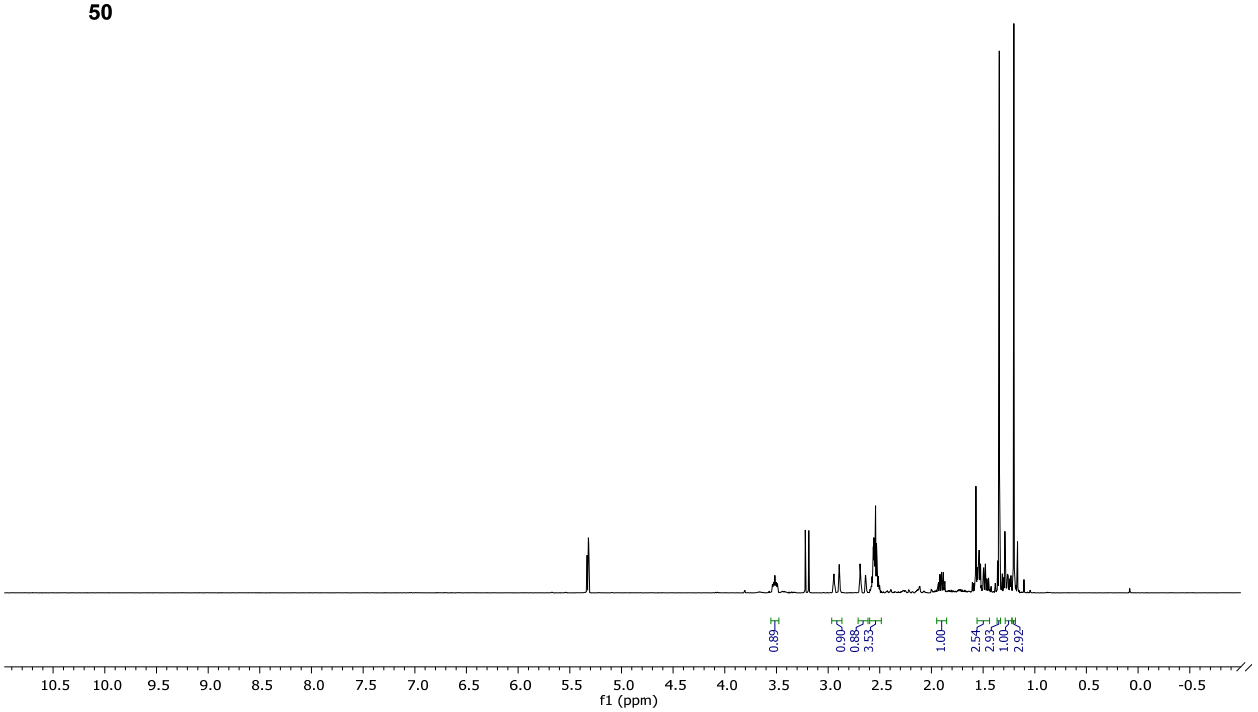
49

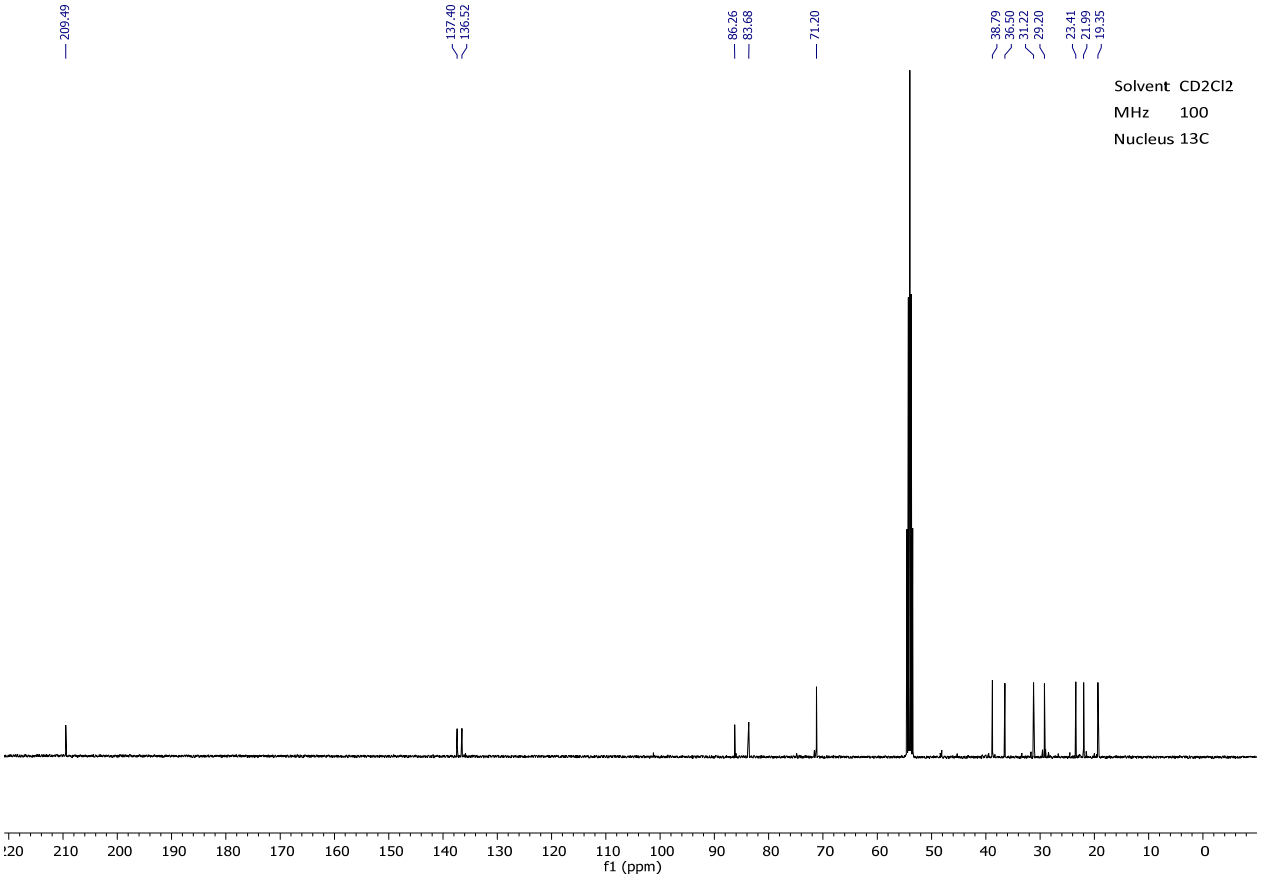

Solvent CDCl3
MHz 600
Nucleus 1H
0.96
0.99
0.94
3.17
0.93
2.00
3.16
3.34
1.20
0.67
0.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

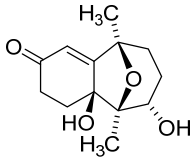

160.17
148.07
135.44
121.63
111.98
106.36
84.57
82.46
71.25
55.72
35.00
29.17
23.00
20.25
Solvent CDCl3
MHz 150
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H3C
O
O
OH
H3C

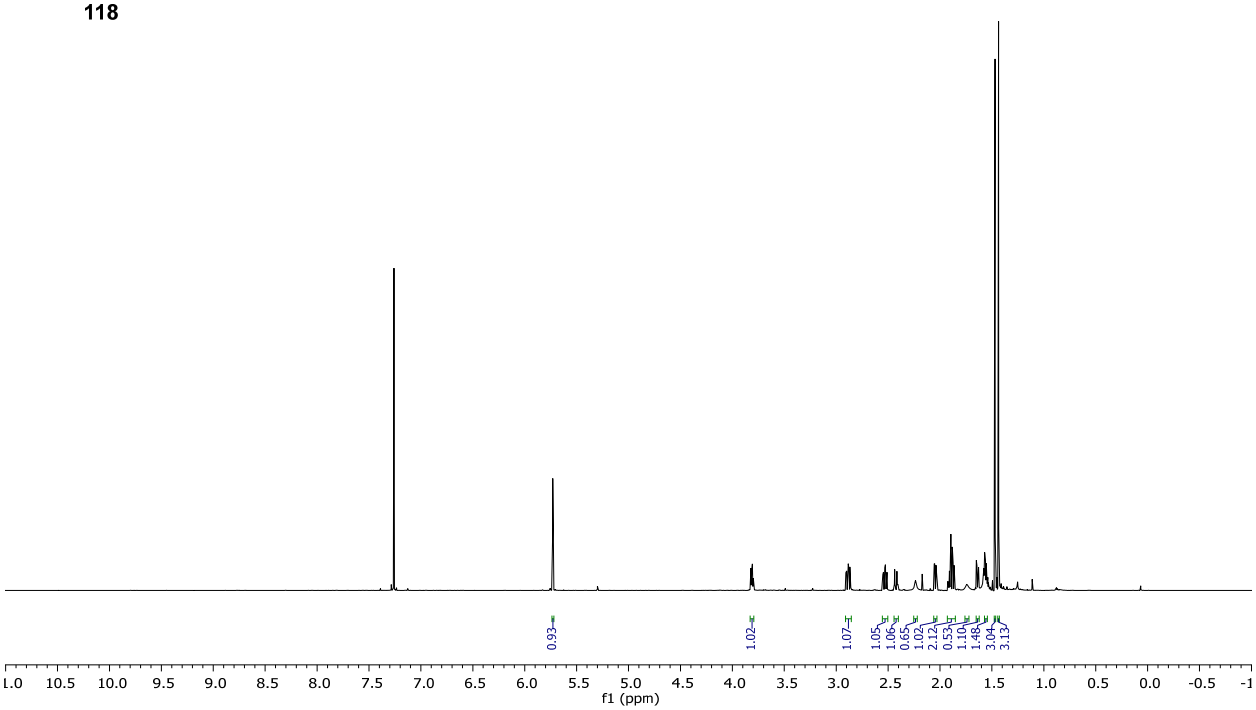
50

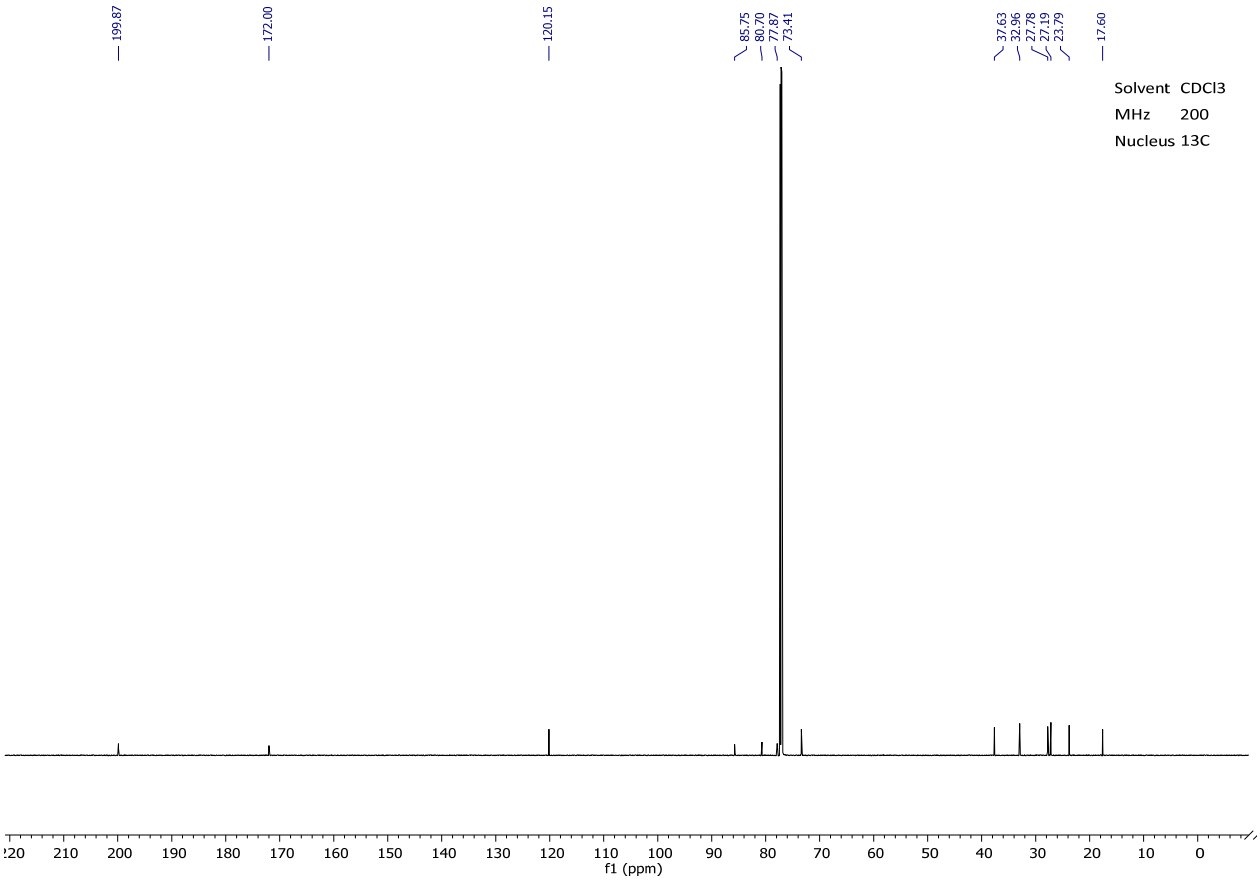

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.89
0.90
0.88
3.53
1.00
2.54
2.93
1.00
2.92
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

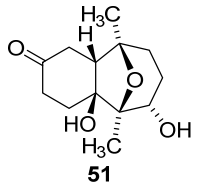

209.49
137.40
136.52
86.26
83.68
71.20
38.79
36.50
31.22
29.20
23.41
21.99
19.35
Solvent CD2Cl2
MHz 100
Nucleus 13C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H3C
O
O
HO
OH
H3C

118

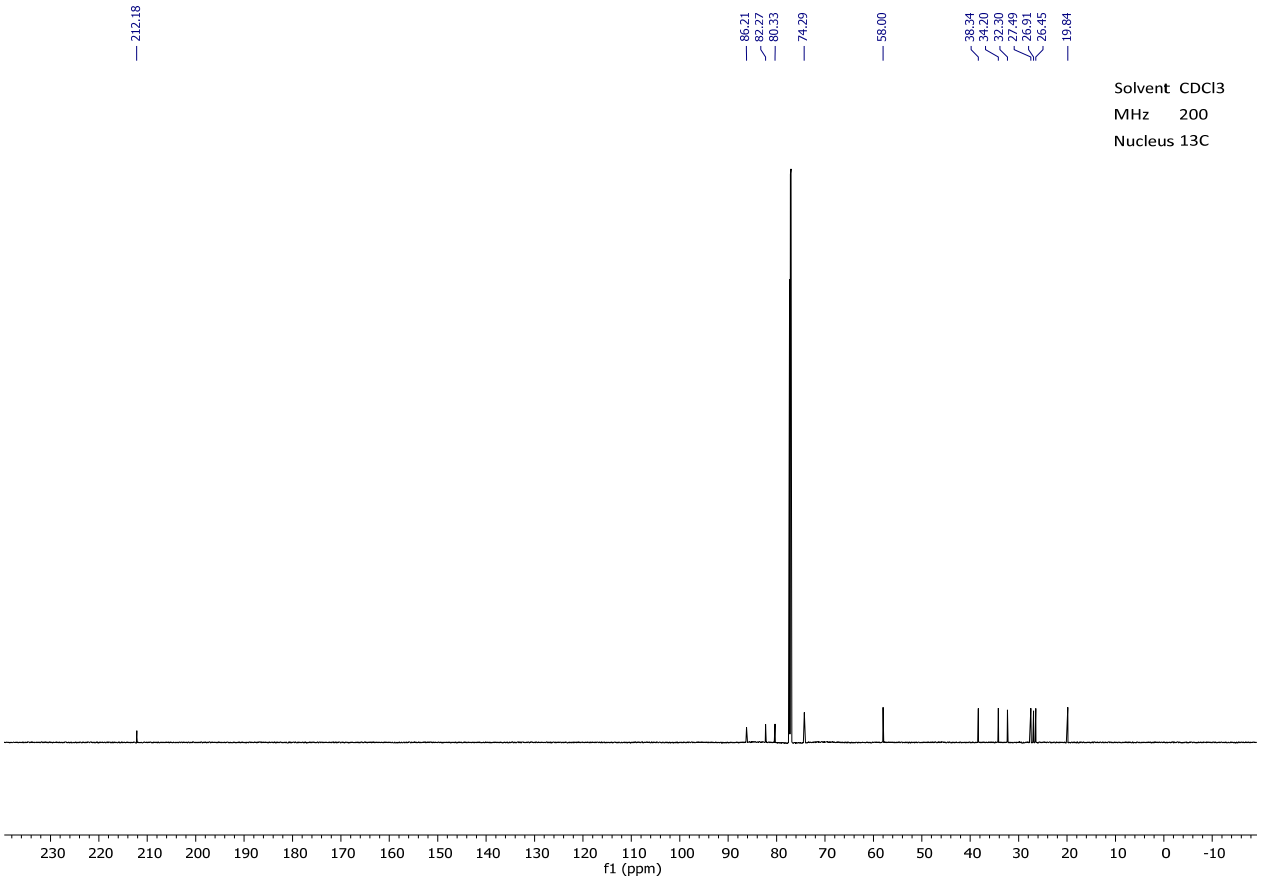

Solvent CDCl3
MHz 800
Nucleus 1H
0.93
1.02
1.07
1.05
1.06
0.65
1.02
2.12
0.53
1.10
1.48
3.04
3.13
f1 (ppm)

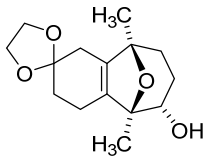

199.87
172.00
120.15
85.75
80.70
77.87
73.41
37.63
32.96
27.78
27.19
23.79
17.60
Solvent CDCl3
MHz 200
Nucleus 13C
f1 (ppm)


H3C
H
O
O
HO
OH
H3C

51

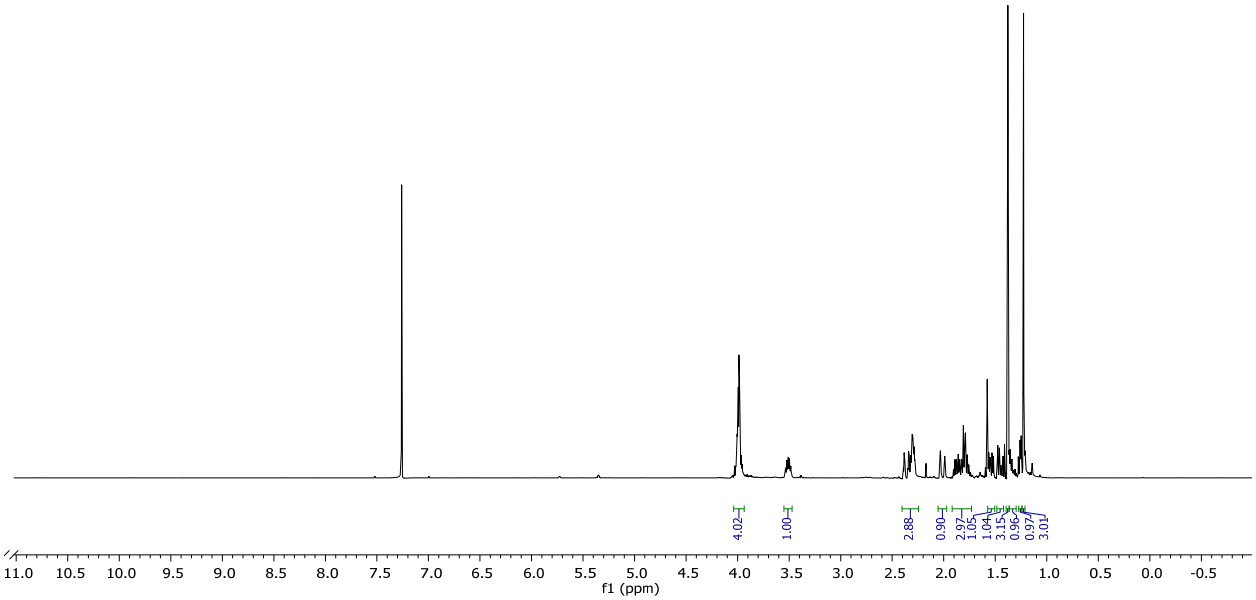
Solvent CDCl3
MHz 800
Nucleus 1H
1.00
1.03
1.03
1.02
2.00
1.00
0.99
1.11
0.84
2.19
2.18
3.00
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

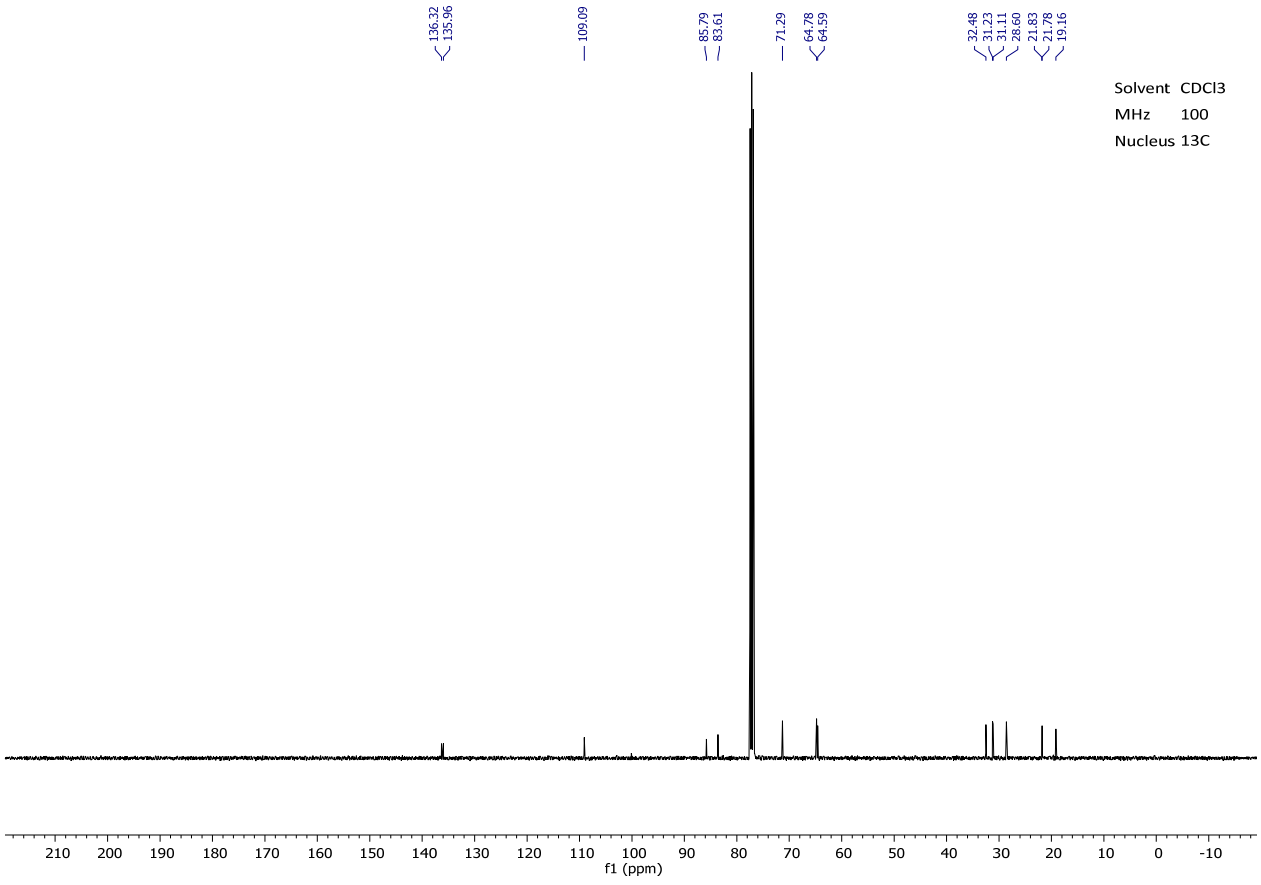

212.18
86.21
82.27
80.33
74.29
58.00
38.34
34.20
32.30
27.49
26.91
26.45
19.84
Solvent CDCl3
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

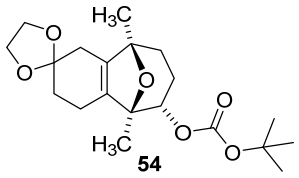


53

Solvent CDCl3
MHz 400
Nucleus 1H

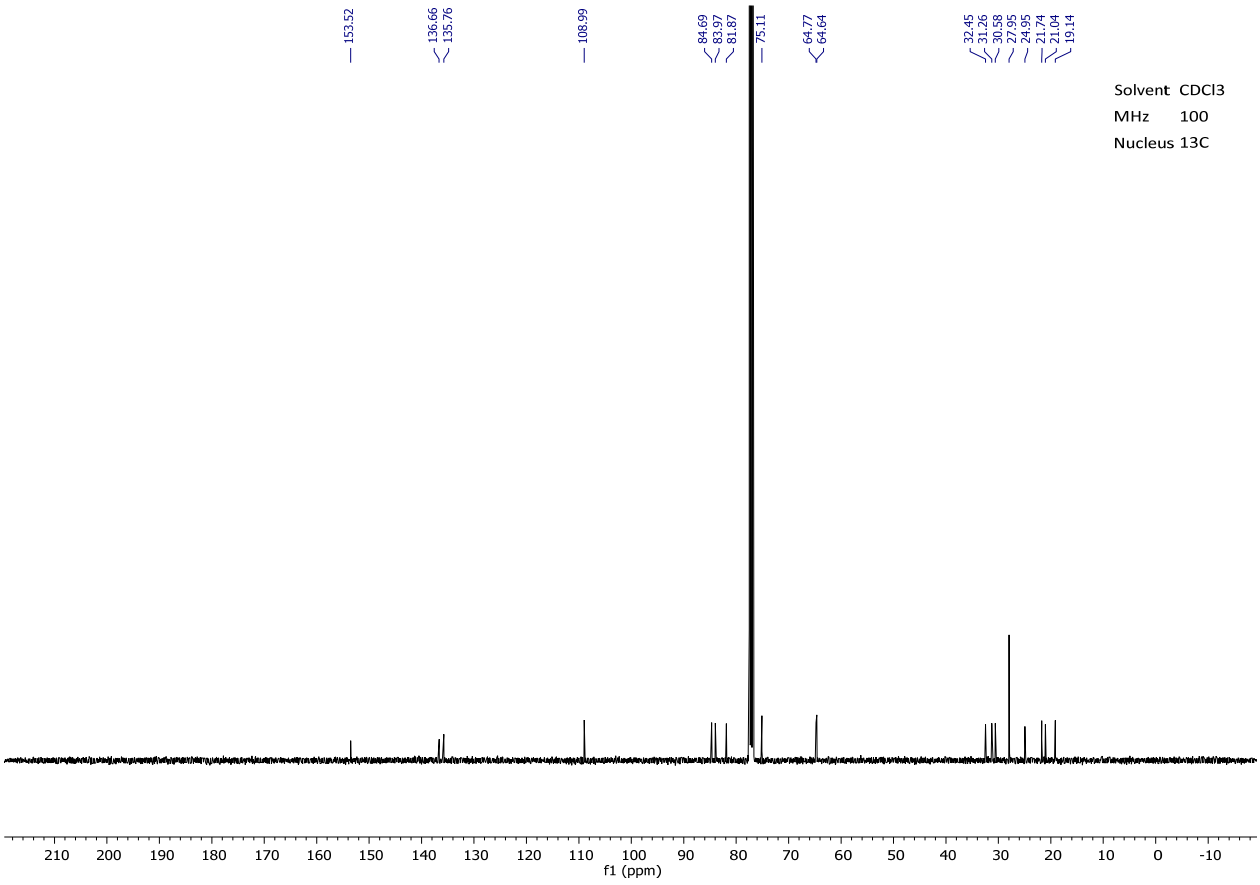


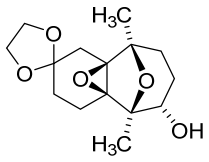



H3C
O
O
O
O
O
O
H3C

54

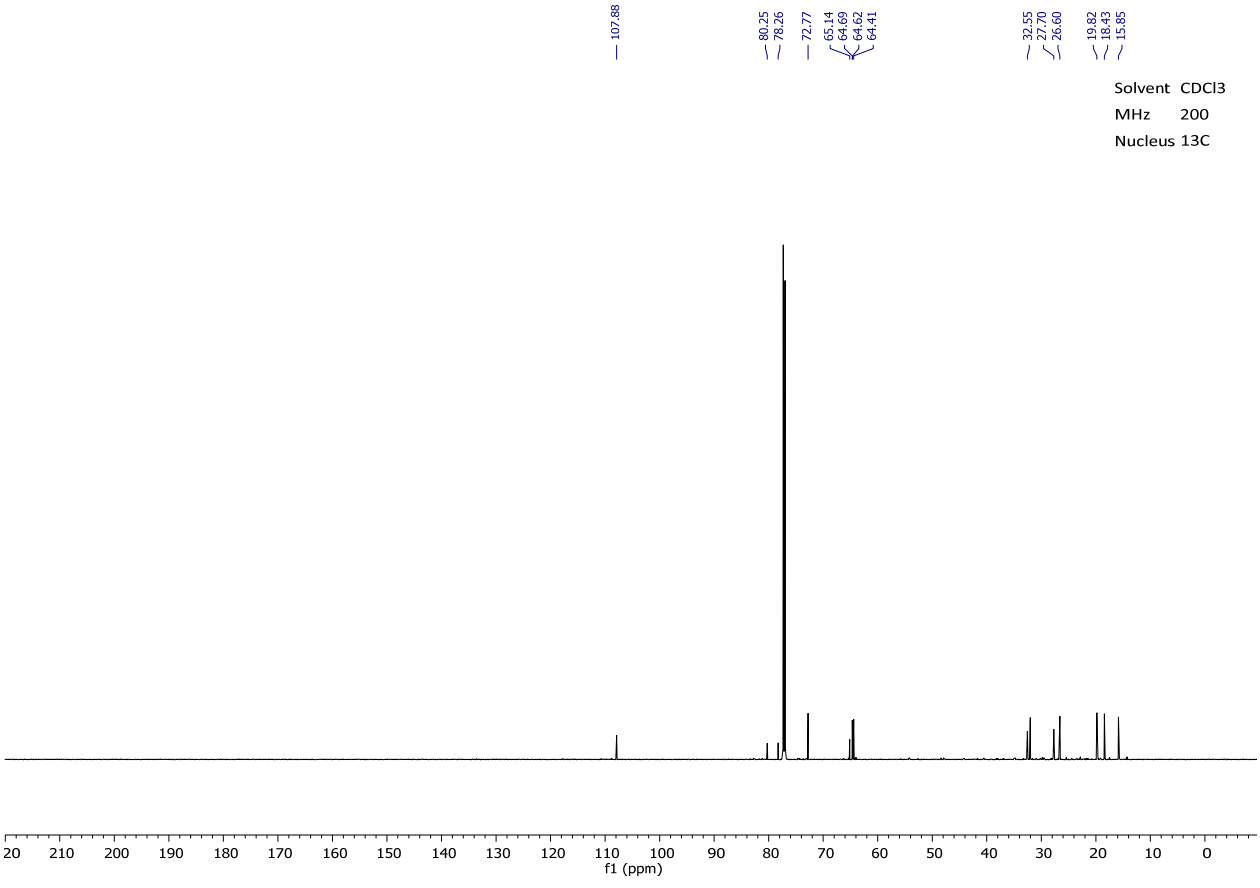
Solvent CDCl3
MHz 400
Nucleus 1H
1.00
4.21
3.08
2.10
2.05
0.96
11.34
3.04
3.09
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

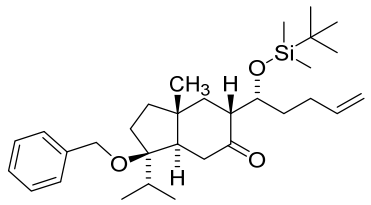

153.52
136.66
135.76
108.99
84.69
83.97
81.87
75.11
64.77
64.64
32.45
31.26
30.58
27.95
24.95
21.74
21.04
19.14
Solvent CDCl3
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
O
O
O
O
OH
H3C

119

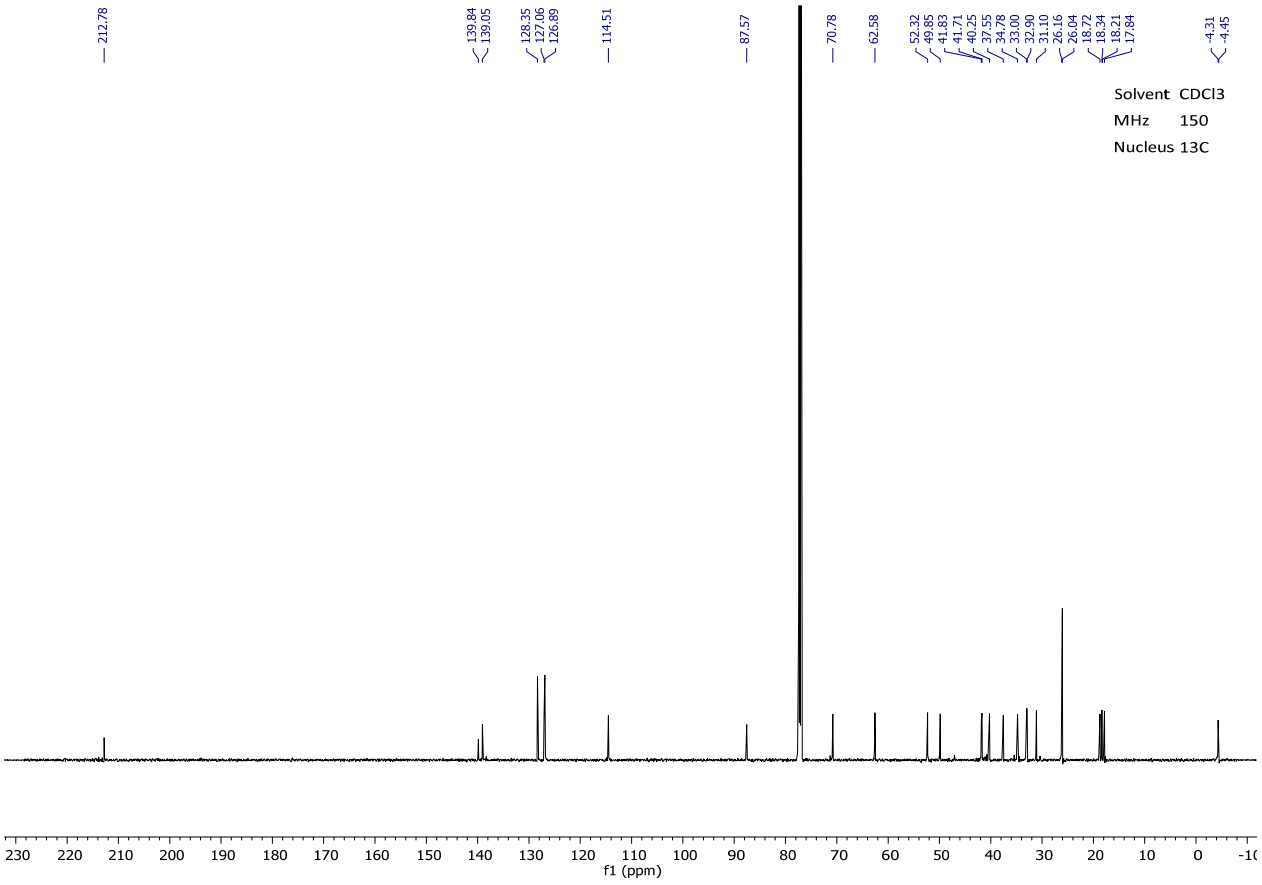
Solvent CDCl3
MHz 800
Nucleus 1H
4.05
1.00
0.97
0.99
2.01
2.06
4.41
1.13
3.12
2.76
f1 (ppm)

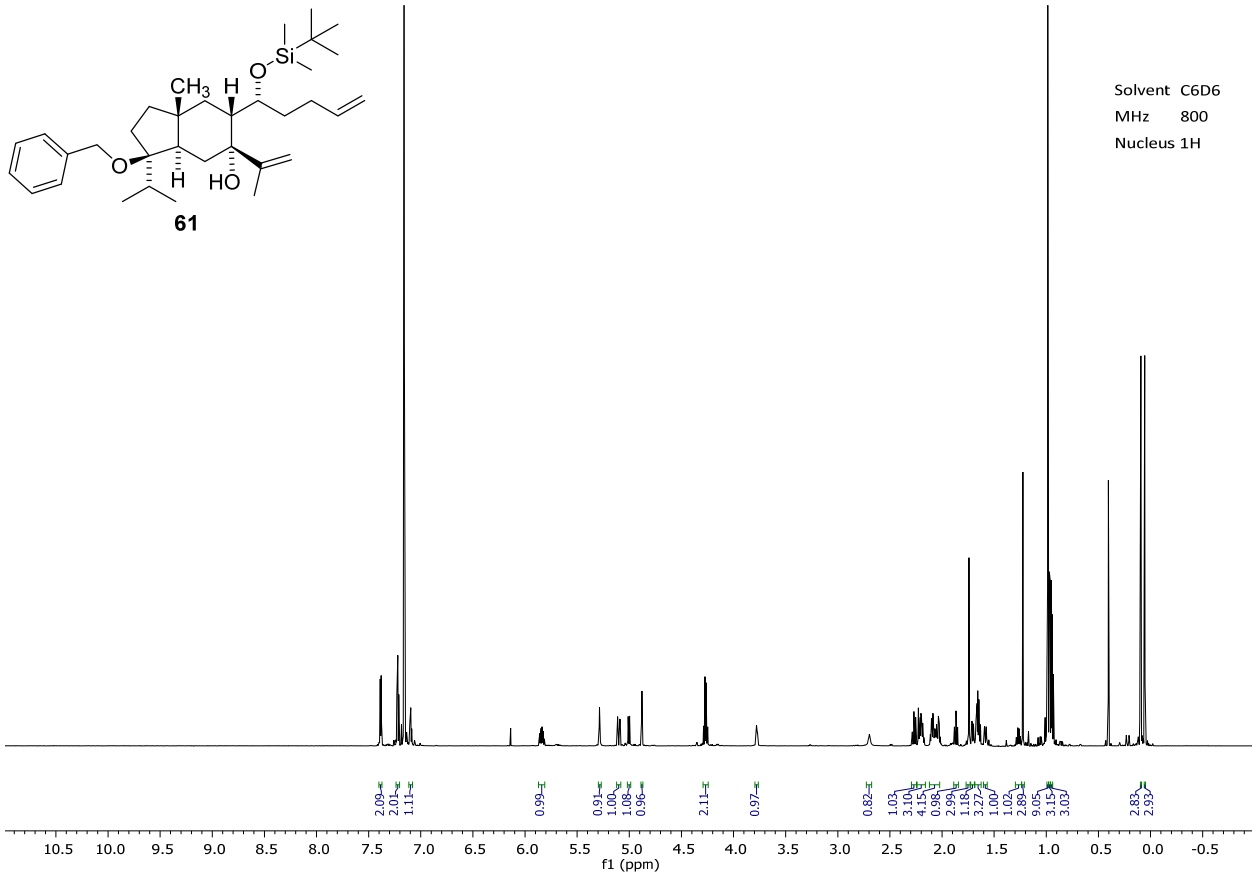

107.88
80.25
78.26
72.77
65.14
64.69
64.62
64.41
32.55
27.70
26.60
19.82
18.43
15.85
Solvent CDCl3
MHz 200
Nucleus 13C
f1 (ppm)


CH3
H
O
Si
O
O
H

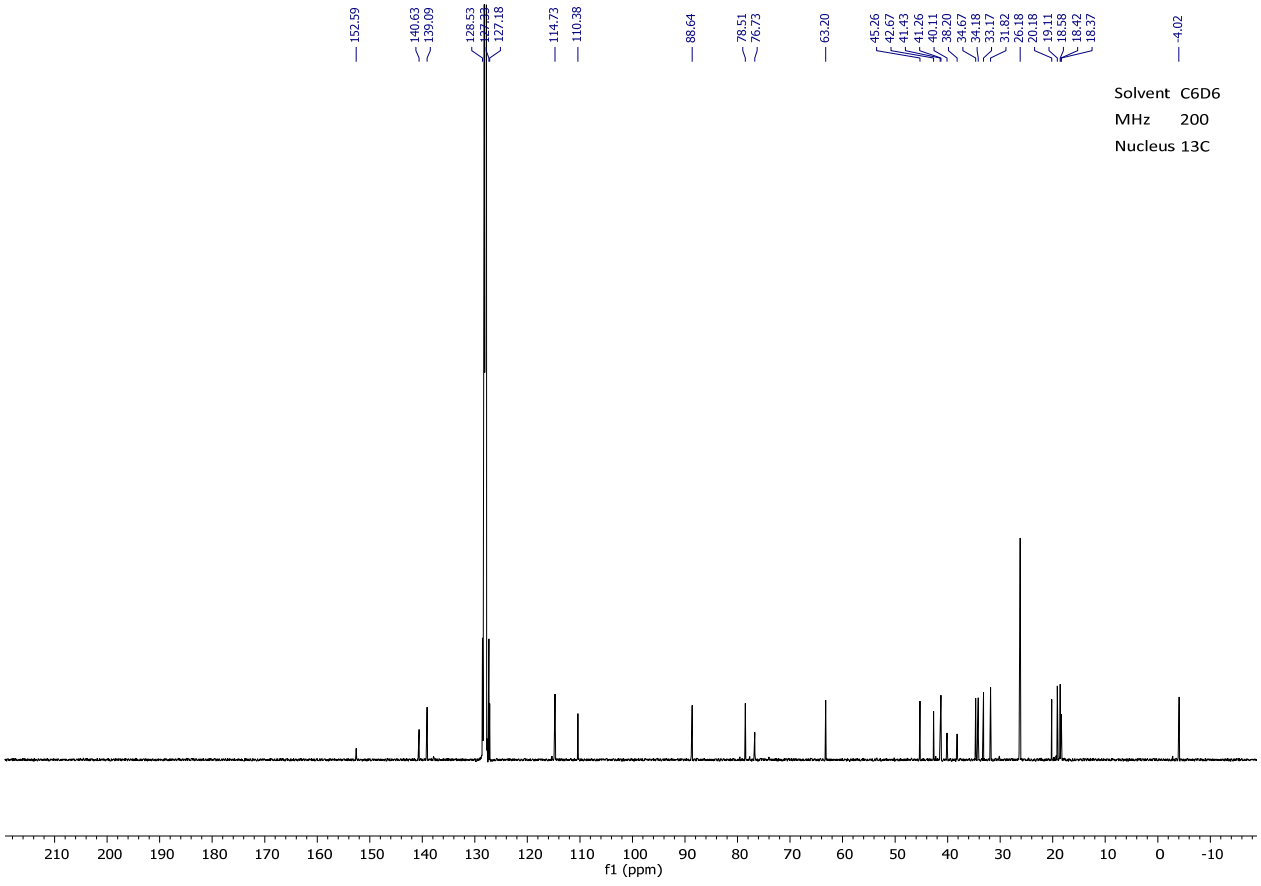
59

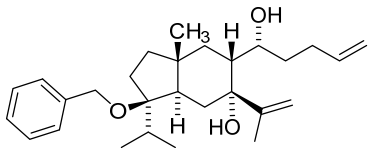
Solvent CDCl3
MHz 600
Nucleus 1H
4.04
0.97
1.00
1.04
1.07
2.02
0.93
1.01
0.94
1.01
3.14
1.97
1.03
1.99
2.91
0.95
2.81
3.19
2.96
9.01
2.89
2.95
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


212.78
139.84
139.05
128.35
127.06
126.89
114.51
87.57
70.78
62.58
52.32
49.85
41.83
41.71
40.25
37.55
34.78
33.00
32.90
31.10
26.16
26.04
18.72
18.34
18.21
17.84
-4.31
-4.45
Solvent CDCl3
MHz 150
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Solvent C6D6
MHz 800
Nucleus 1H
f1 (ppm)

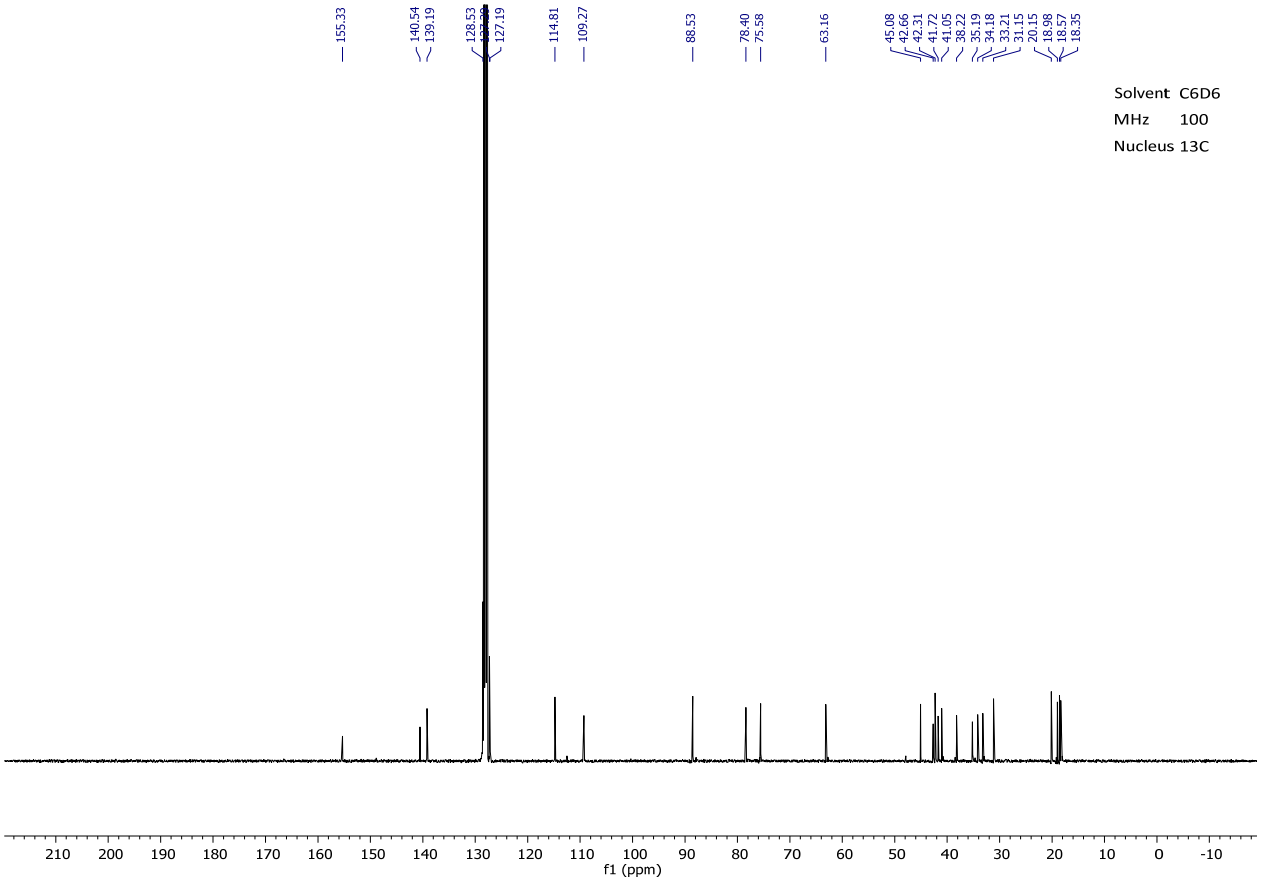
61

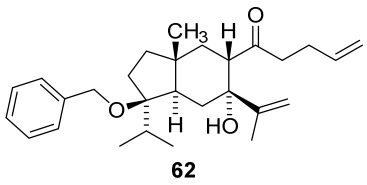

Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)


CH3
H
OH
O
H
HO

120

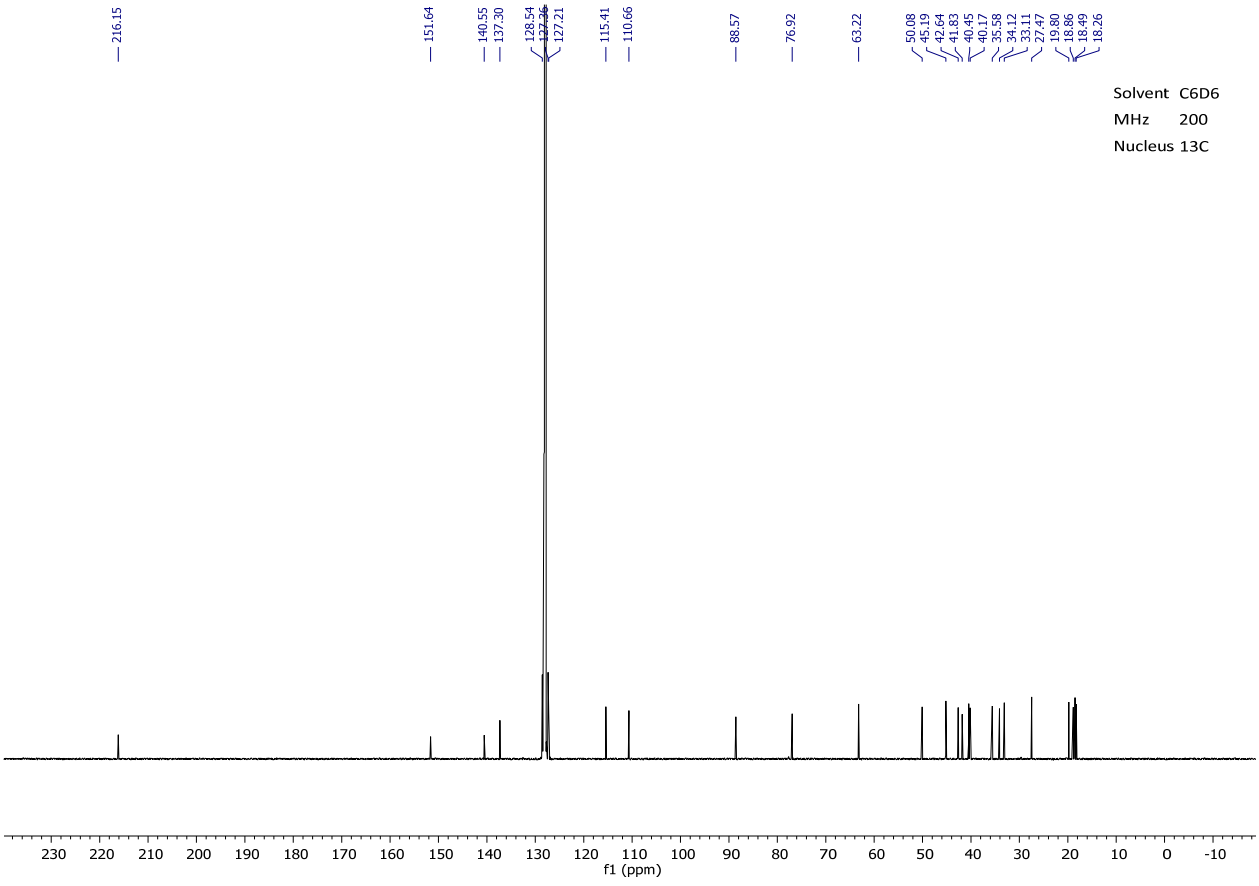
Solvent C6D6
MHz 800
Nucleus 1H
2.05
2.09
1.00
1.05
0.96
1.07
1.06
1.04
2.36
1.04
0.43
2.15
1.05
4.52
3.09
6.25
1.07
1.11
3.13
3.23
3.28
f1 (ppm)

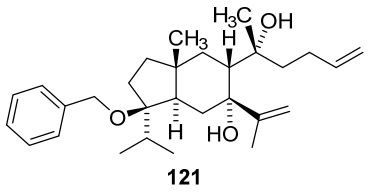

155.33
140.54
139.19
128.53
127.19
114.81
109.27
88.53
78.40
75.58
63.16
45.08
42.66
42.31
41.72
41.05
38.22
35.19
34.18
33.21
31.15
20.15
18.98
18.57
18.35
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


CH3
H
O
O
H
HO

62

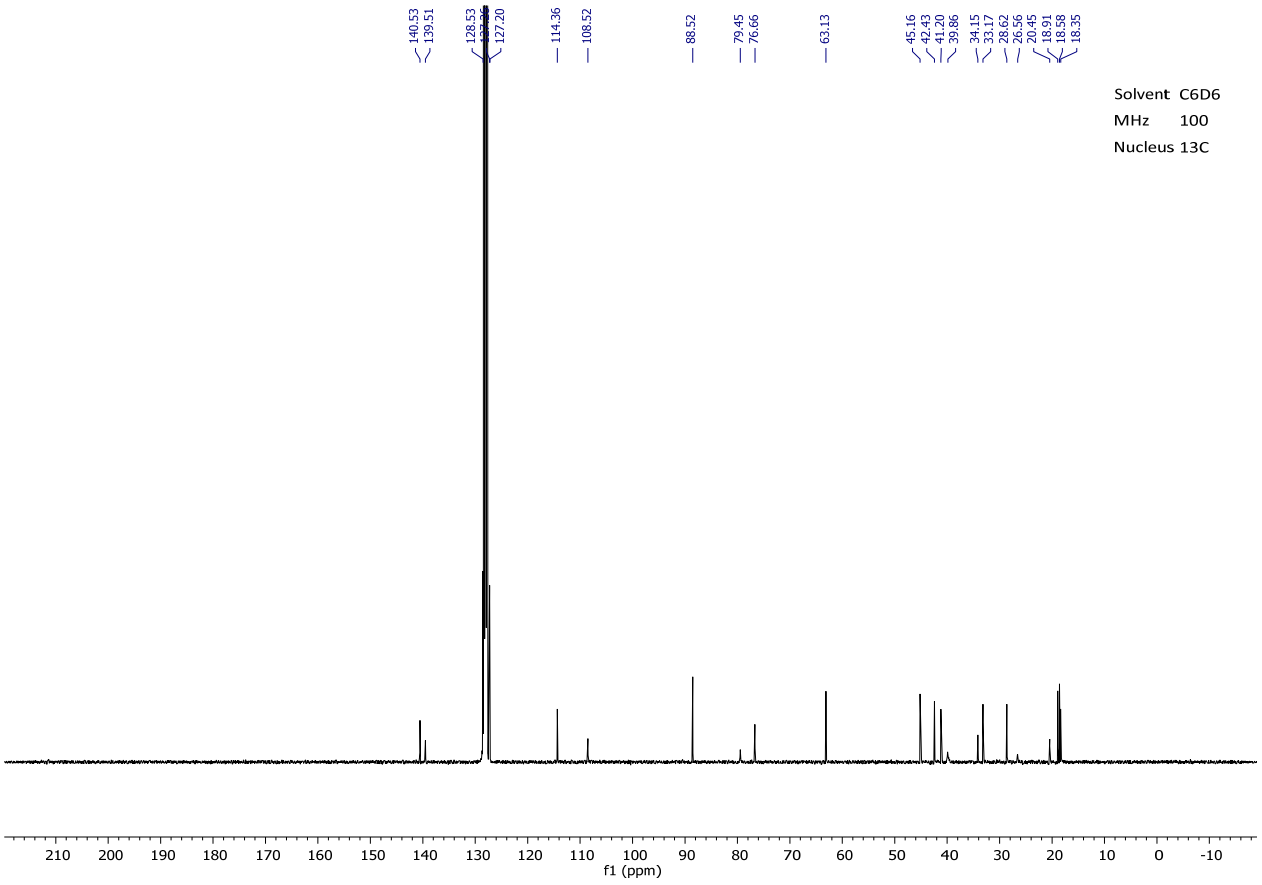
Solvent C6D6
MHz 800
Nucleus 1H
2.00
2.05
1.00
0.99
1.01
3.03
1.01
2.11
1.01
0.99
3.08
3.09
2.08
5.12
1.01
1.01
1.10
2.97
3.04
3.16
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

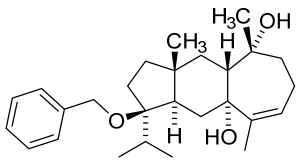

216.15
151.64
140.55
137.30
128.54
127.26
127.21
115.41
110.66
88.57
76.92
63.22
50.08
45.19
42.64
41.83
40.45
40.17
35.58
34.12
33.11
27.47
19.80
18.86
18.49
18.26
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
OH
CH3
H
O
H
HO

121

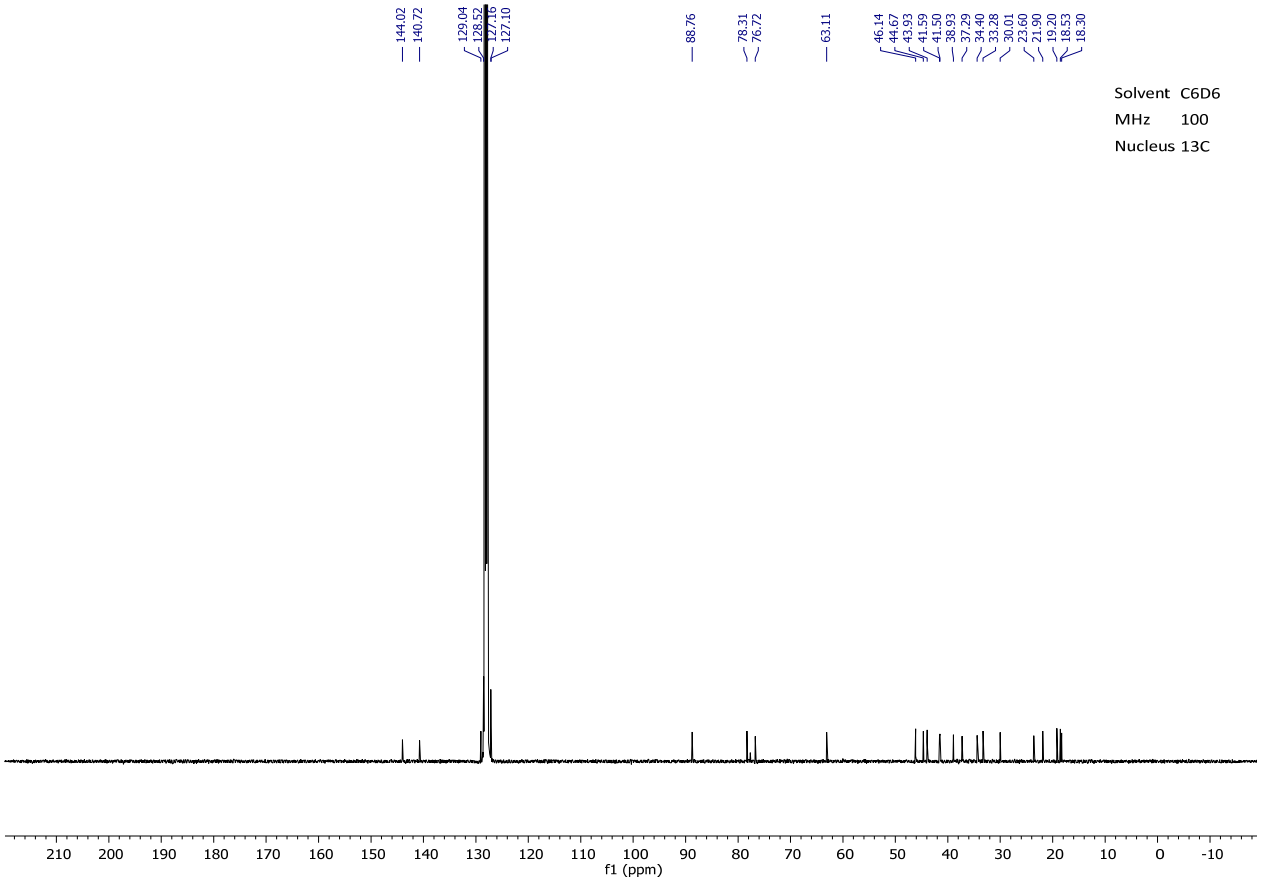
Solvent C6D6
MHz 400
Nucleus 1H
1.84
1.82
1.00
0.87
0.38
0.99
1.01
0.89
1.85
17.14
3.52
3.16
5.91
f1 (ppm)

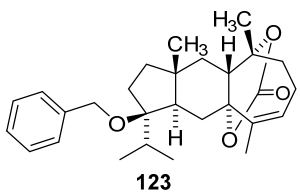

140.53
139.51
128.53
127.20
114.36
108.52
88.52
79.45
76.66
63.13
45.16
42.43
41.20
39.86
34.15
33.17
28.62
26.56
20.45
18.91
18.58
18.35
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C
OH
CH3
H
O
H
HO

63a

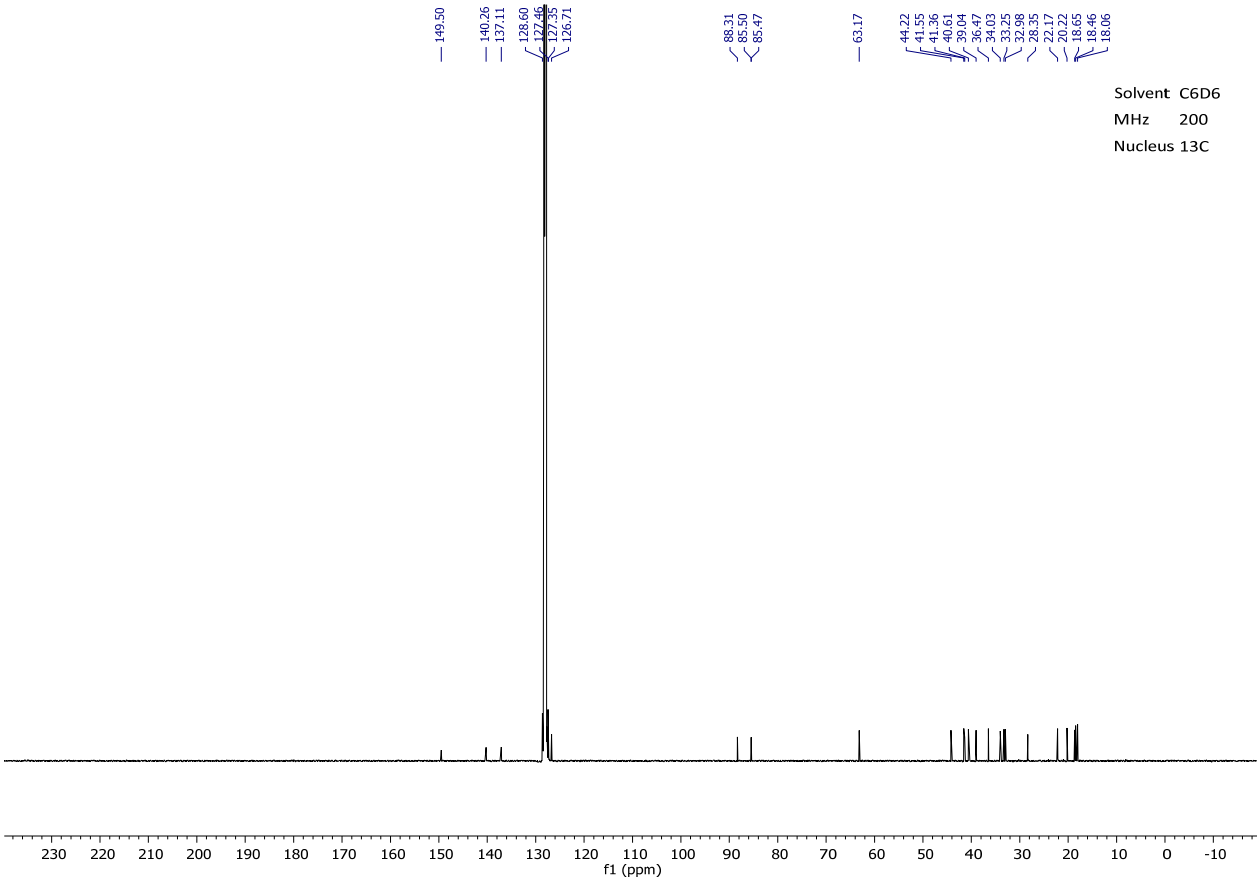
Solvent C6D6
MHz 800
Nucleus 1H
2.01
1.99
1.04
1.00
2.10
0.81
1.04
3.24
1.13
3.08
5.18
3.19
1.30
1.42
6.14
3.06
3.23
f1 (ppm)

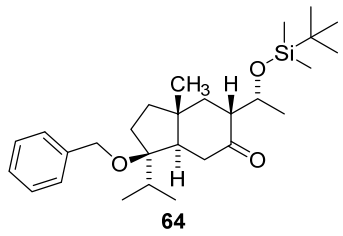

144.02
140.72
129.04
128.52
127.76
127.10
88.76
78.31
76.72
63.11
46.14
44.67
43.93
41.59
41.50
38.93
37.29
34.40
33.28
30.01
23.60
21.90
19.20
18.53
18.30
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C
CH3
H
O
O
H
O

123

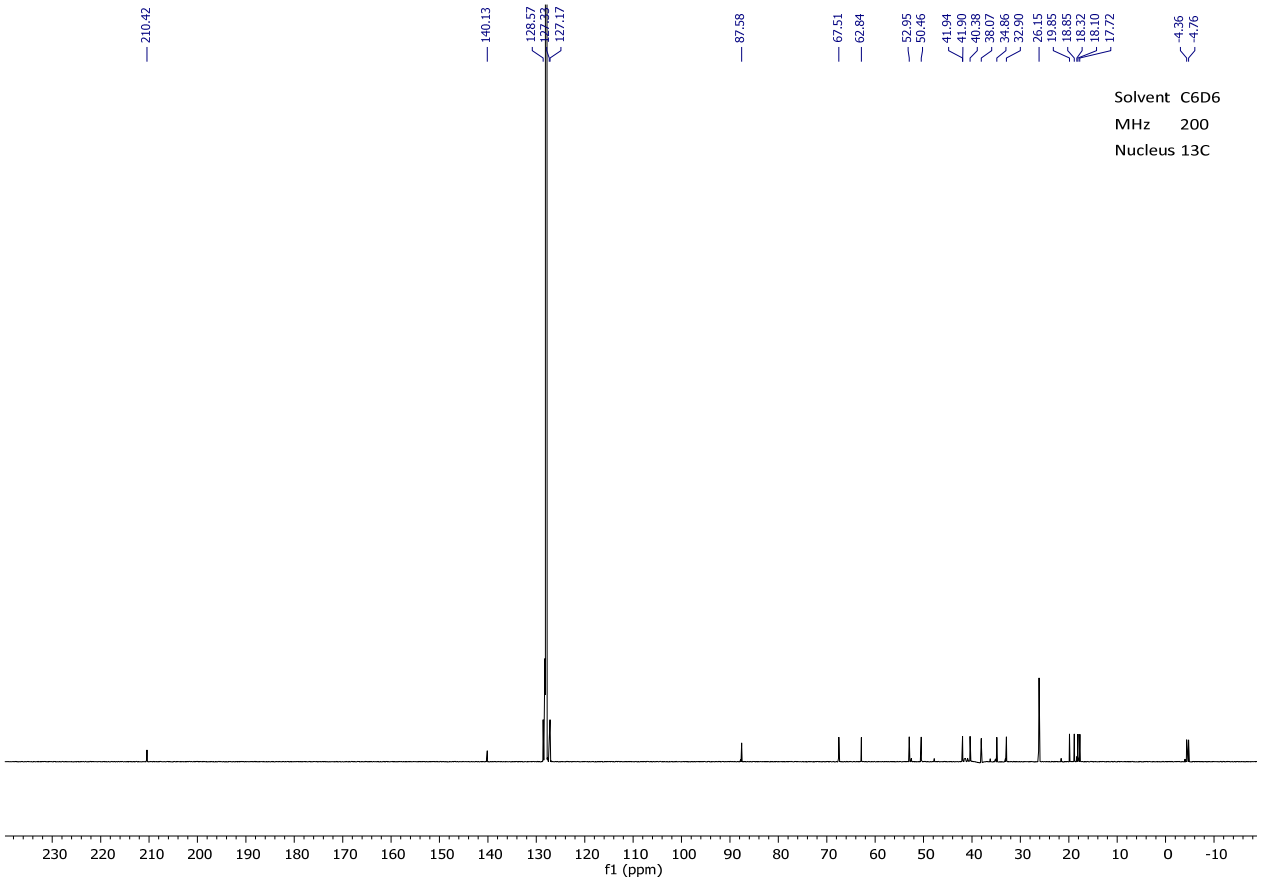
Solvent C6D6
MHz 800
Nucleus 1H
2.00
2.83
1.00
1.01
2.13
0.91
1.01
2.07
3.11
1.04
3.04
1.13
2.19
2.37
1.10
4.42
3.08
3.03
3.33
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

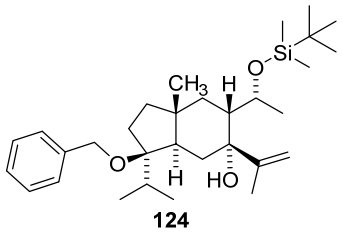

149.50
140.26
137.11
128.60
127.46
127.35
126.71
88.31
85.50
85.47
63.17
44.22
41.55
41.36
40.61
39.04
36.47
34.03
33.25
32.98
28.35
22.17
20.22
18.65
18.46
18.06
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3
H
O
Si
O
O
H

64

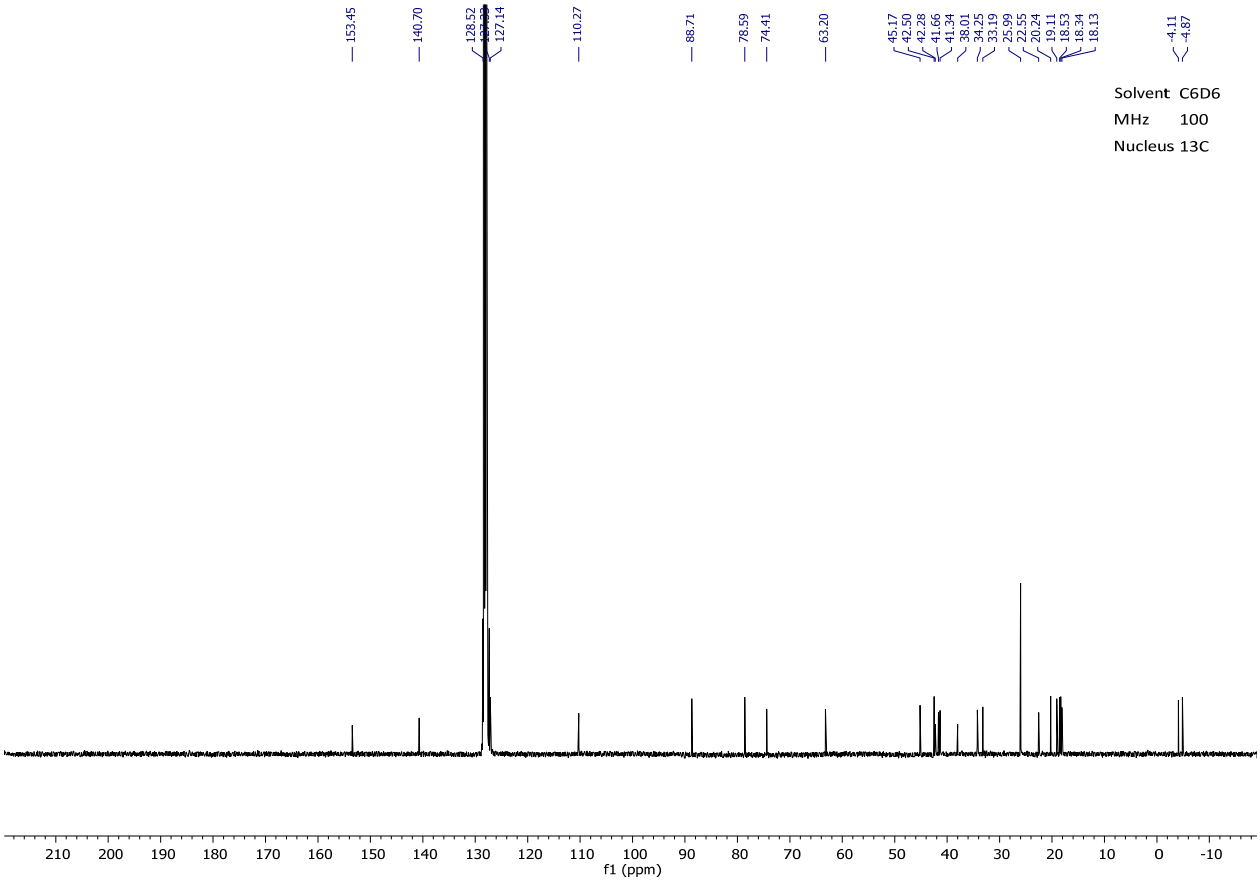
Solvent C6D6
MHz 800
Nucleus 1H
2.32
2.46
1.26
1.05
2.33
0.96
1.11
1.11
1.00
1.13
1.17
0.98
2.33
1.02
3.37
3.36
0.94
11.77
3.46
3.54
6.92
f1 (ppm)

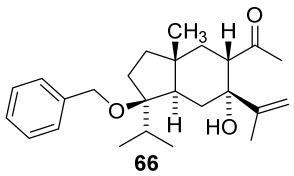

210.42
140.13
128.57
127.17
87.58
67.51
62.84
52.95
50.46
41.94
41.90
40.38
38.07
34.86
32.90
26.15
19.85
18.85
18.32
18.10
17.72
-4.36
-4.76
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)


CH3
H
O
Si
O
H
HO

124

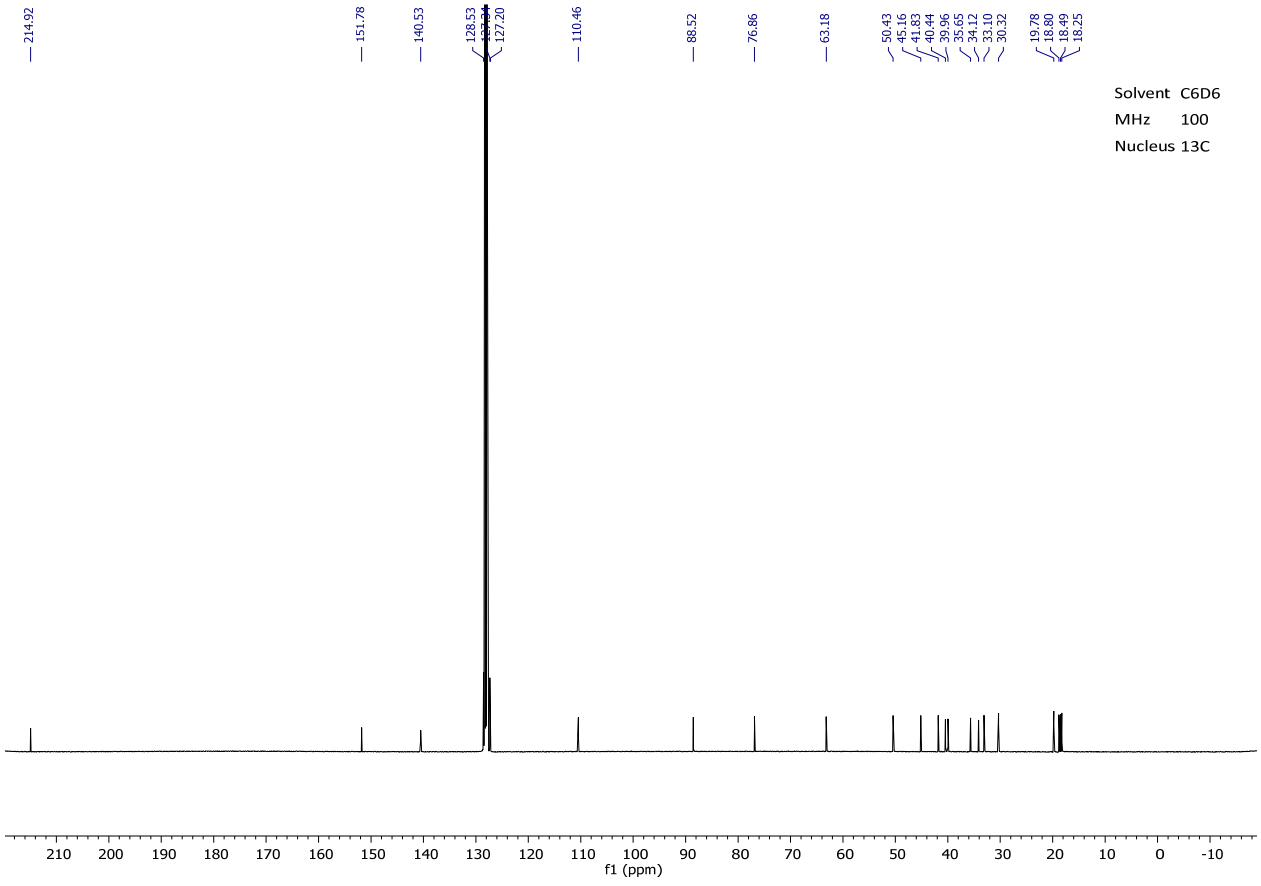
Solvent C6D6
MHz 400
Nucleus 1H
2.00
2.08
1.08
0.96
0.99
2.07
1.00
1.00
2.04
2.04
1.82
2.95
3.17
0.95
3.72
2.95
3.03
12.24
3.03
3.05
f1 (ppm)

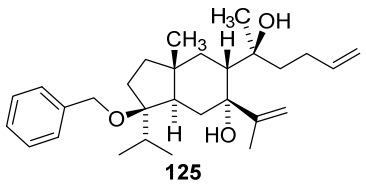

153.45
140.70
128.52
127.14
110.27
88.71
78.59
74.41
63.20
45.17
42.50
42.28
41.66
41.34
38.01
34.25
33.19
25.99
22.55
20.24
19.11
18.53
18.34
18.13
-4.11
-4.87
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


CH3
H
O
O
H
HO

66

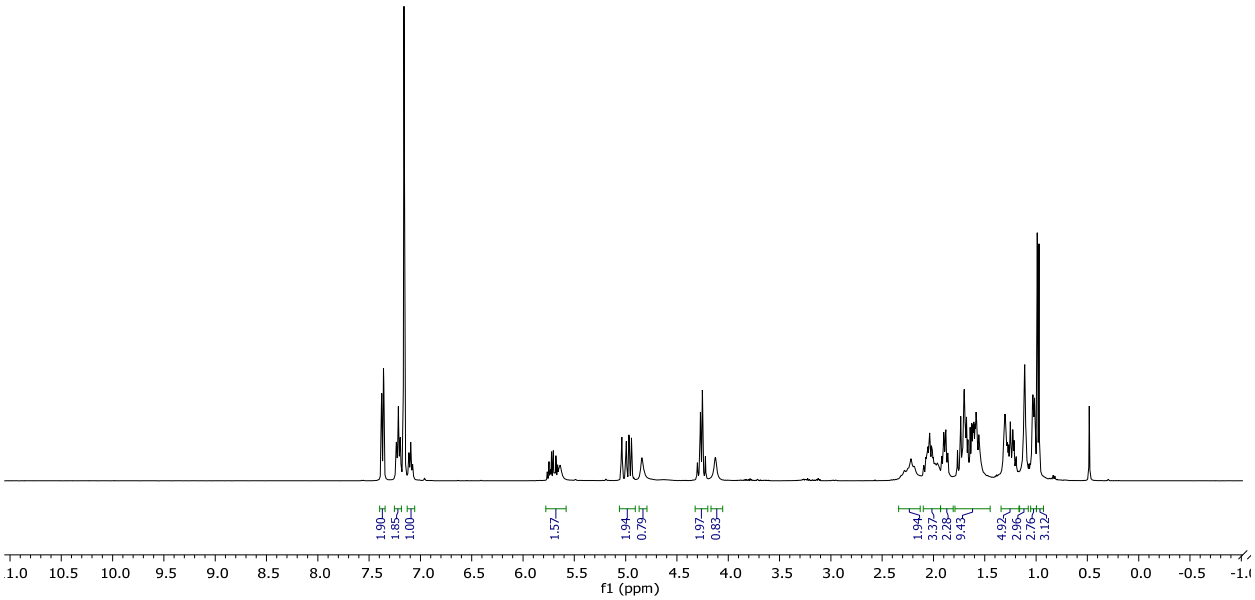
Solvent C6D6
MHz 400
Nucleus 1H
1.90
1.89
0.98
0.95
0.94
0.95
1.97
0.97
0.97
1.97
1.80
2.90
5.03
1.04
1.00
1.06
2.81
3.10
3.01
f1 (ppm)

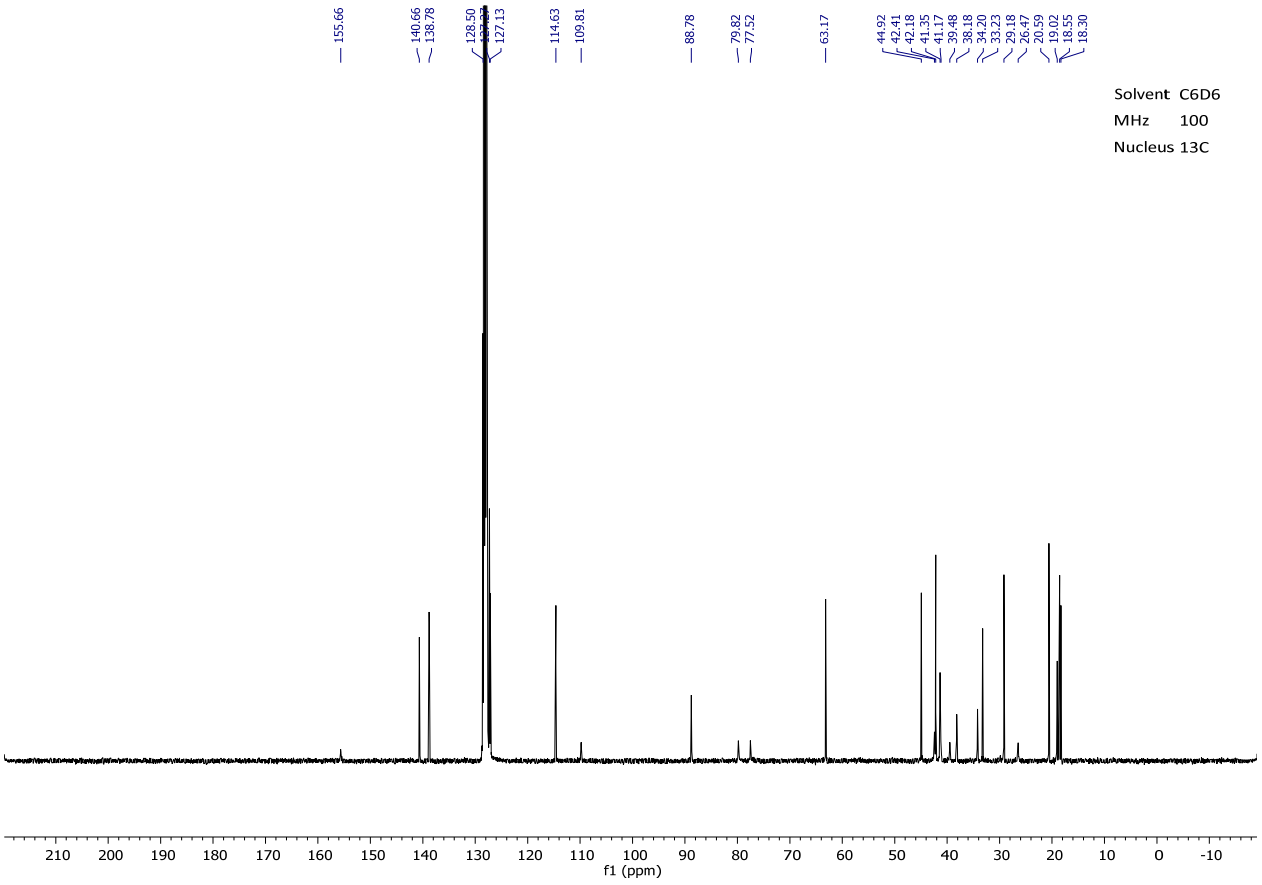

214.92
151.78
140.53
128.53
127.20
110.46
88.52
76.86
63.18
50.43
45.16
41.83
40.44
39.96
35.65
34.12
33.10
30.32
19.78
18.80
18.49
18.25
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)



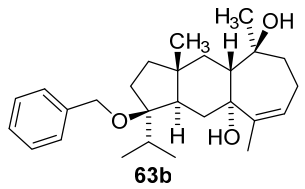
125

Solvent C6D6
MHz 400
Nucleus 1H



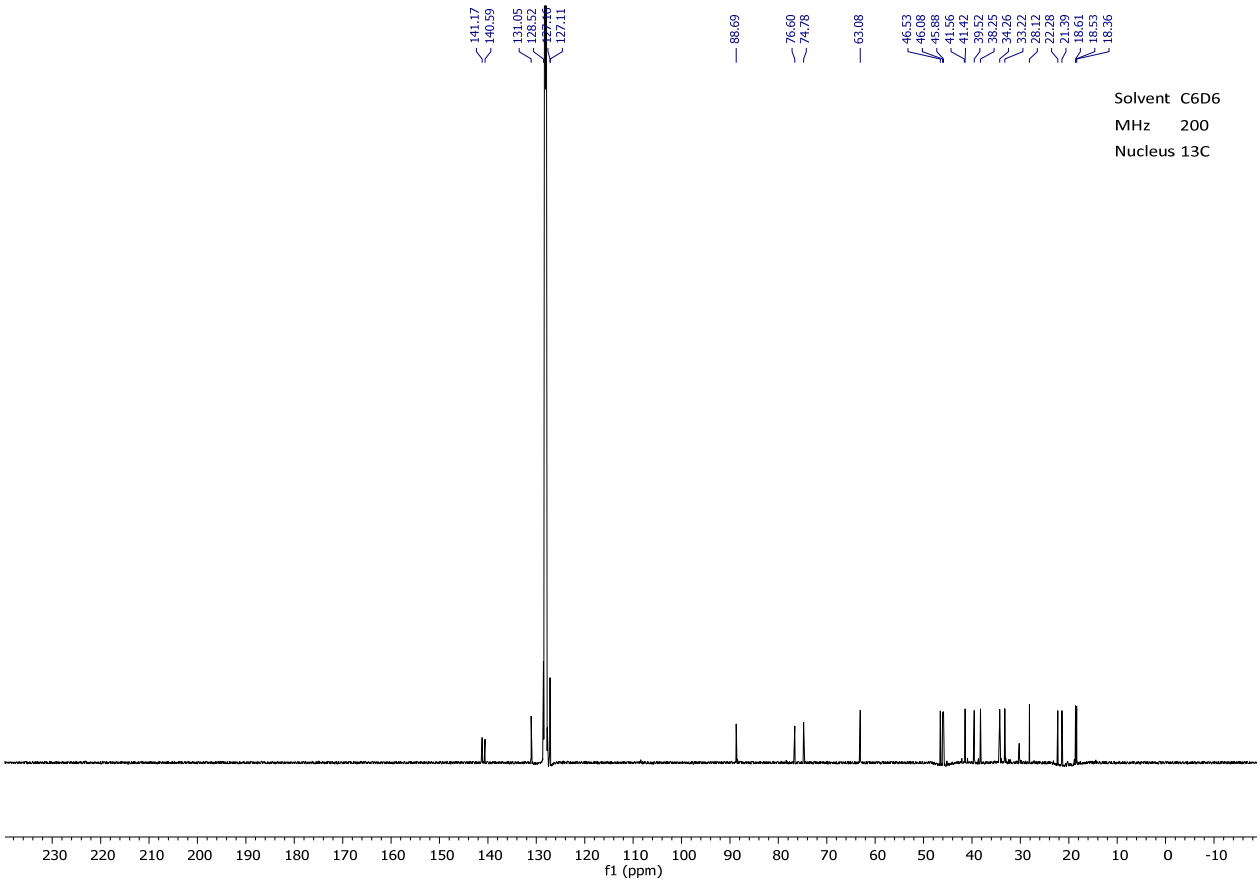


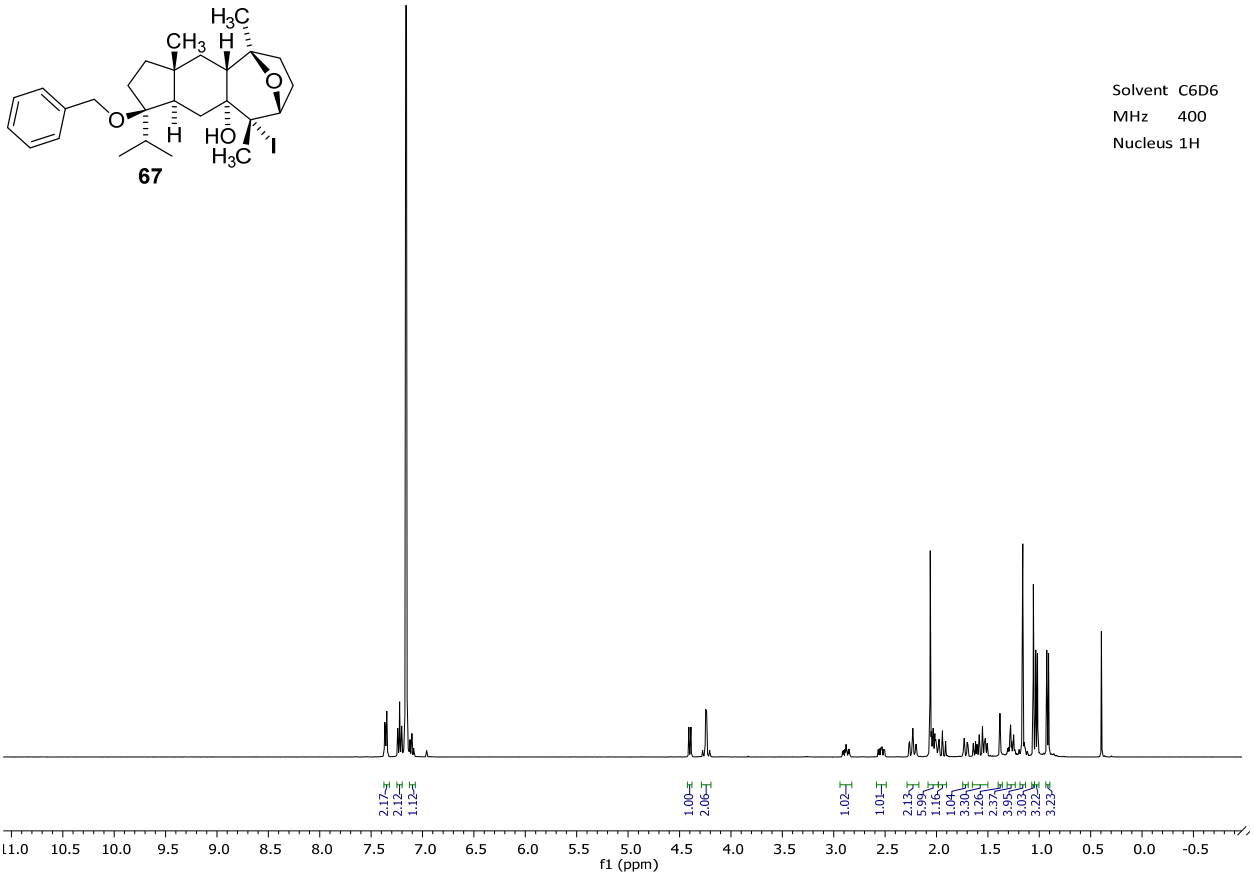
Solvent C6D6
MHz 100
Nucleus 13C

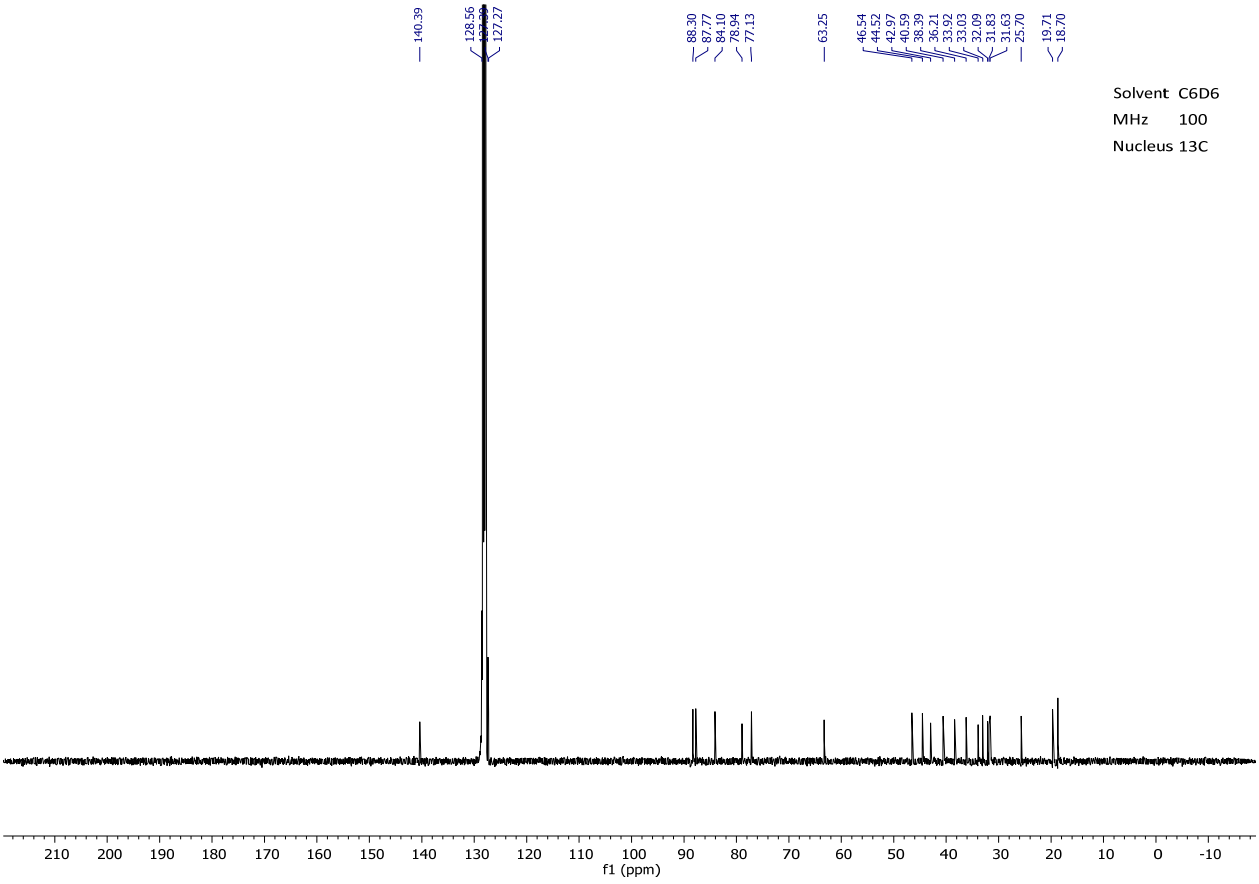

H3C OH
CH3 H
O
H HO

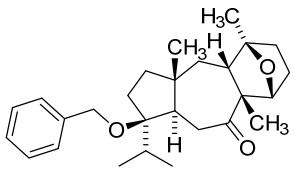
63b

Solvent C6D6
MHz 800
Nucleus 1H
2.14
3.46
1.10
0.96
2.29
1.00
1.13
1.15
3.73
2.19
11.45
3.51
1.82
3.68
4.02
3.89
0.93
0.93
f1 (ppm)


141.17
140.59
131.05
128.52
127.46
127.11
88.69
76.60
74.78
63.08
46.53
46.08
45.88
41.56
41.42
39.52
38.25
34.26
33.22
28.12
22.28
21.39
18.61
18.53
18.36
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)

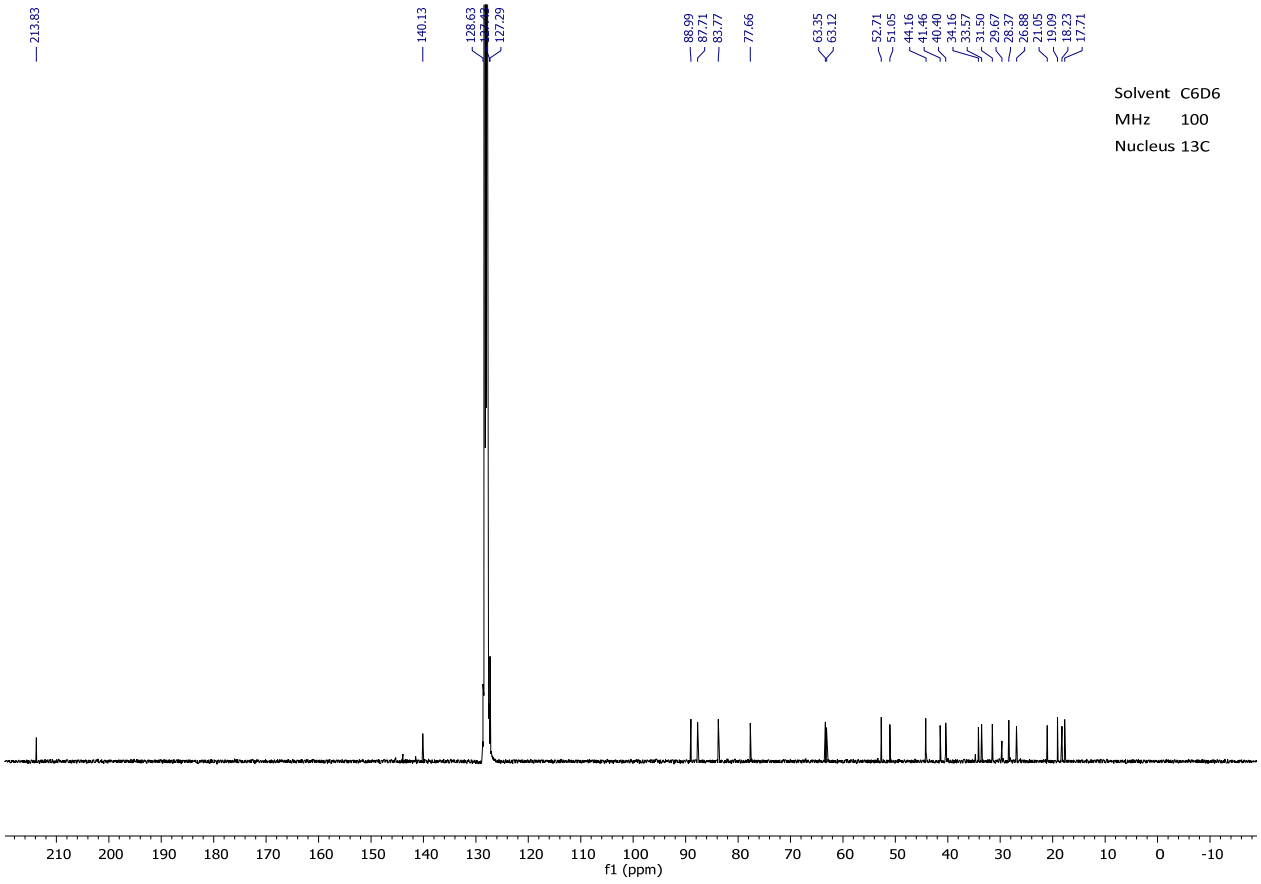

H3C
CH3
H
O
O
H
HO
H3C
I
67
Solvent C6D6
MHz 400
Nucleus 1H
2.17
2.12
1.12
1.00
2.06
1.02
1.01
2.13
5.99
1.16
1.04
3.30
1.26
2.37
3.95
3.05
3.22
3.23
f1 (ppm)

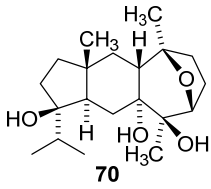

140.39
128.56
128.39
127.27
88.30
87.77
84.10
78.94
77.13
63.25
46.54
44.52
42.97
40.59
38.39
36.21
33.92
33.03
32.09
31.83
31.63
25.70
19.71
18.70
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)



68

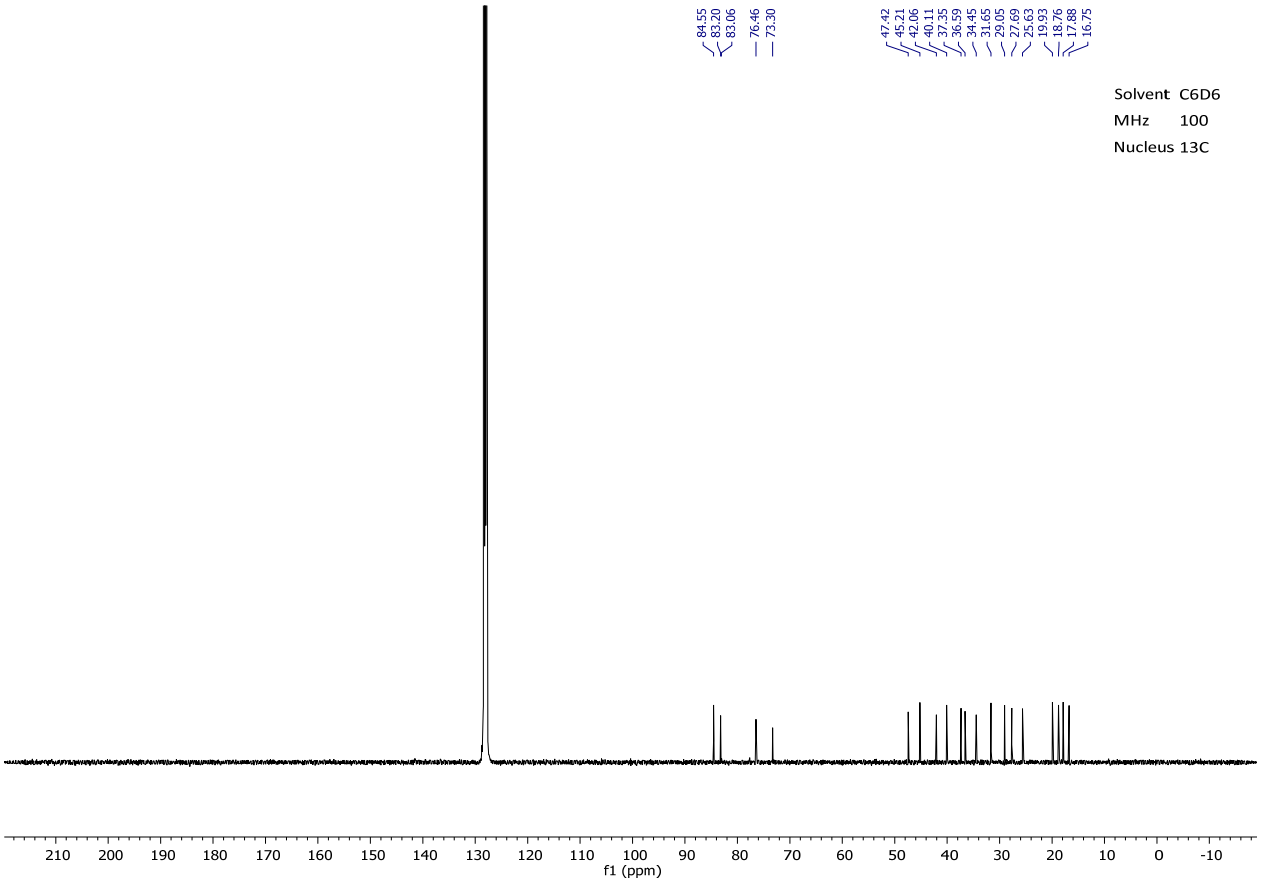
Solvent C6D6
MHz 400
Nucleus 1H
2.05
2.02
1.34
1.00
2.05
0.97
0.95
0.98
2.78
2.05
3.04
4.37
3.08
1.37
3.83
3.39
1.10
2.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

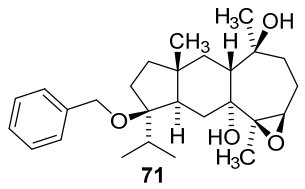

213.83
140.13
128.63
127.29
88.99
87.71
83.77
77.66
63.35
63.12
52.71
51.05
44.16
41.46
40.40
34.16
33.57
31.50
29.67
28.37
26.88
21.05
19.09
18.23
17.71
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
CH3
H
O
HO
H
HO
H3C
OH

70

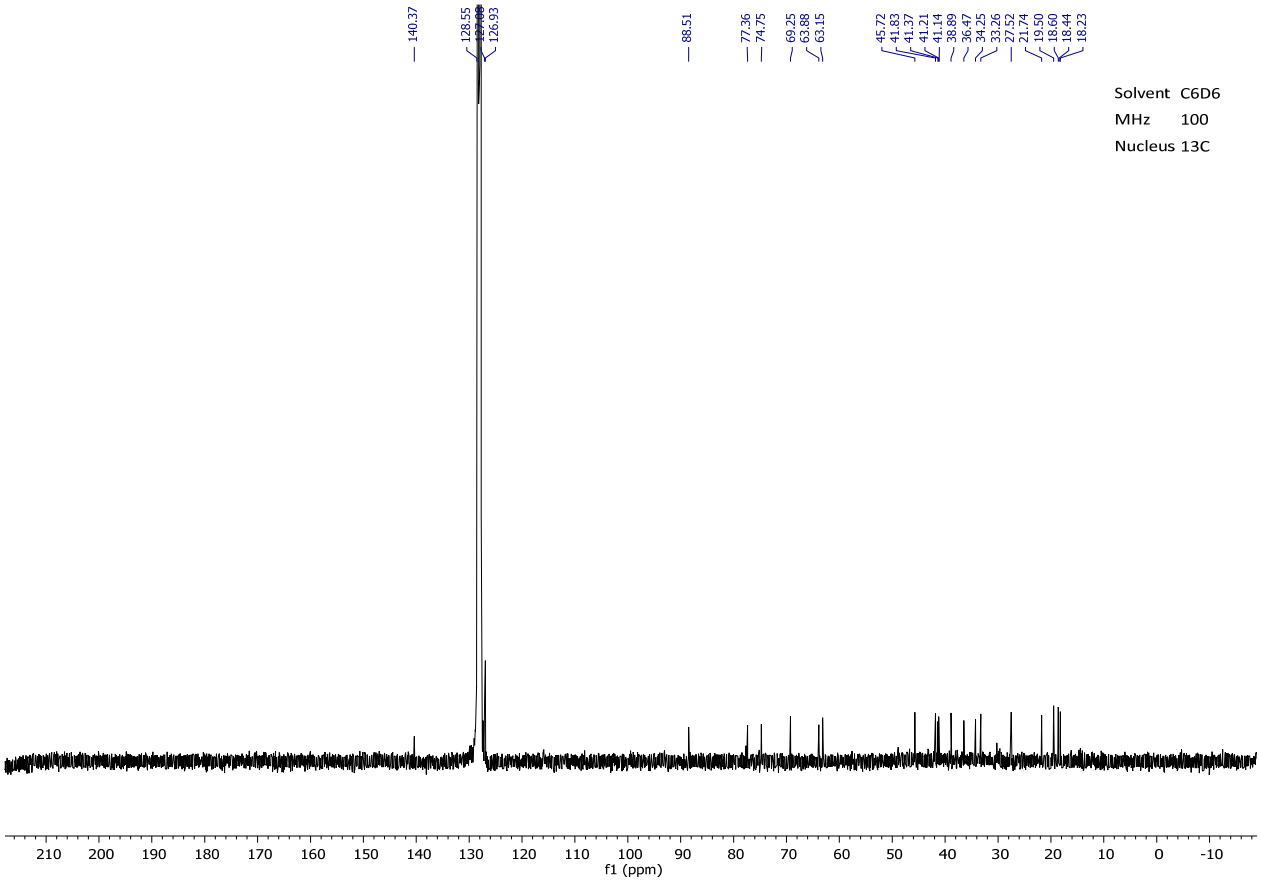
Solvent C6D6
MHz 800
Nucleus 1H
1.00
0.89
2.01
1.95
2.00
0.93
0.99
1.01
0.99
2.24
2.96
2.13
2.94
2.95
1.47
3.01
2.91
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

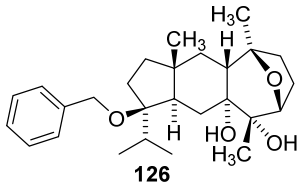

84.55
83.20
83.06
76.46
73.30
47.42
45.21
42.06
40.11
37.35
36.59
34.45
31.65
29.05
27.69
25.63
19.93
18.76
17.88
16.75
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C OH
CH3 H
O
H
HO
H3C
O

71

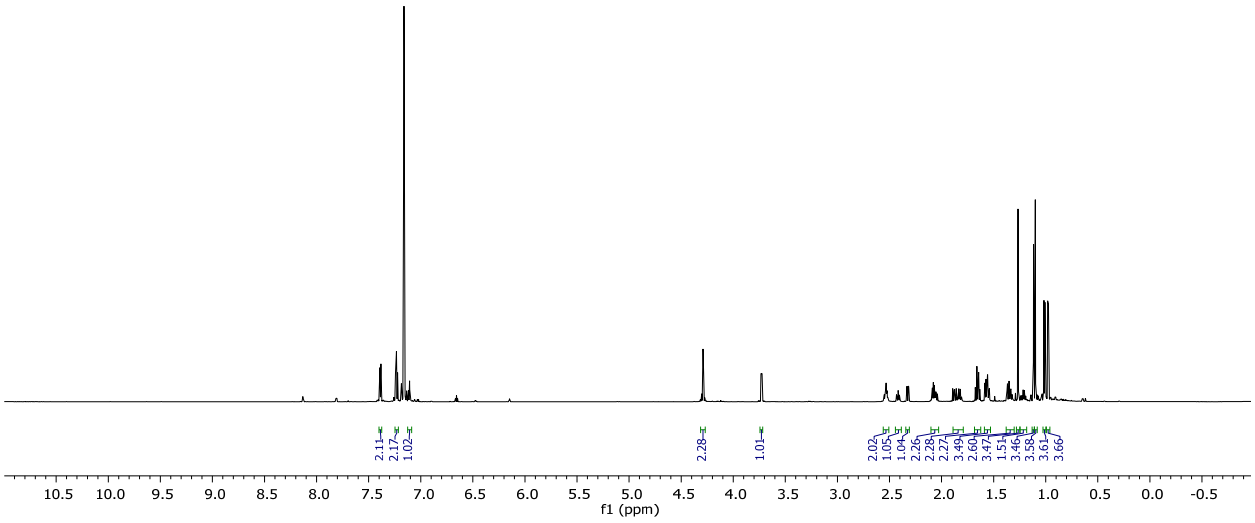
Solvent C6D6
MHz 400
Nucleus 1H
2.24
2.13
1.01
1.93
0.88
1.00
1.00
3.92
1.29
5.25
1.34
1.22
3.01
3.22
1.32
3.21
2.87
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

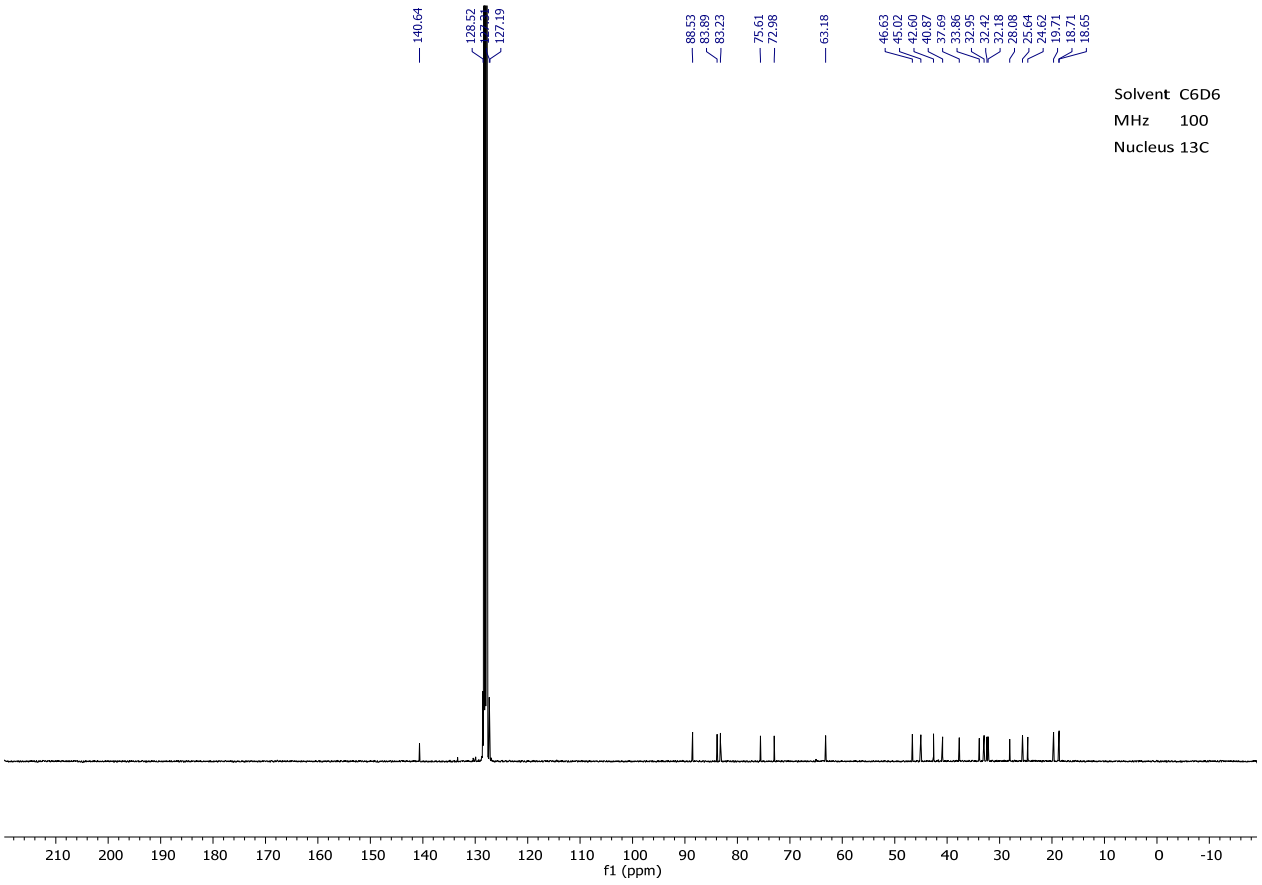

140.37
128.55
126.93
88.51
77.36
74.75
69.25
63.88
63.15
45.72
41.83
41.37
41.21
41.14
38.89
36.47
34.25
33.26
27.52
21.74
19.50
18.60
18.44
18.23
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



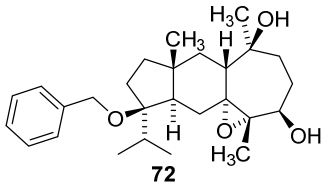
126

Solvent C6D6
MHz 800
Nucleus 1H

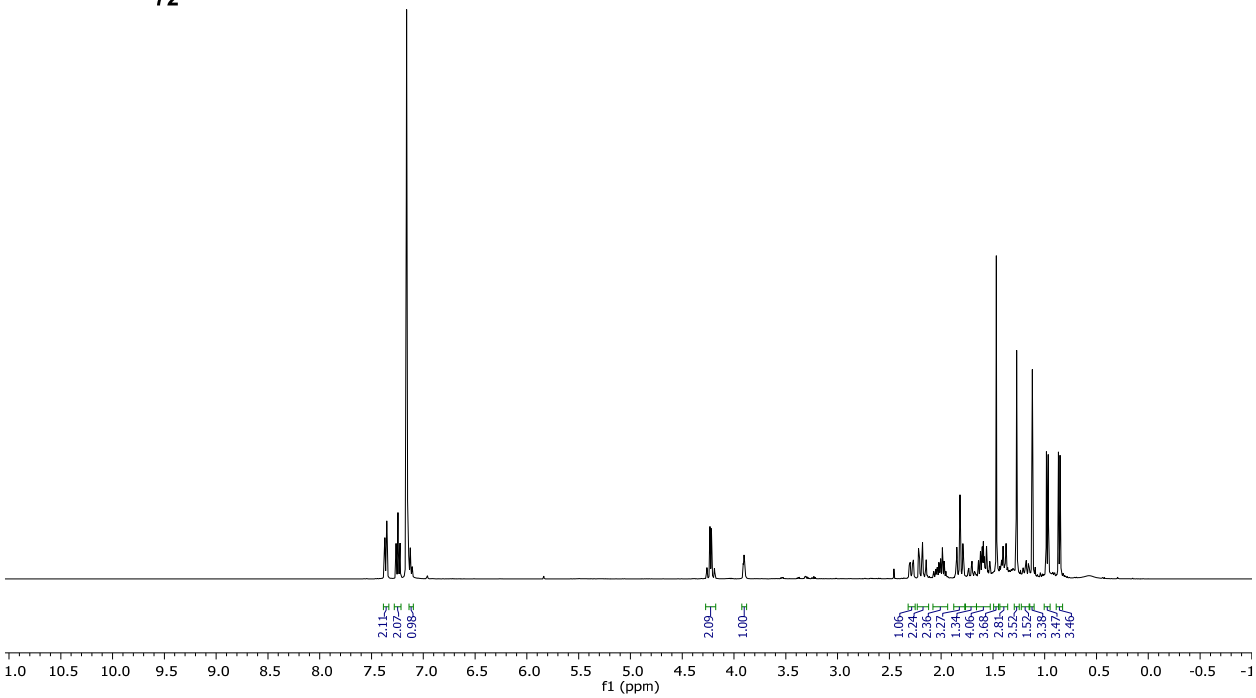


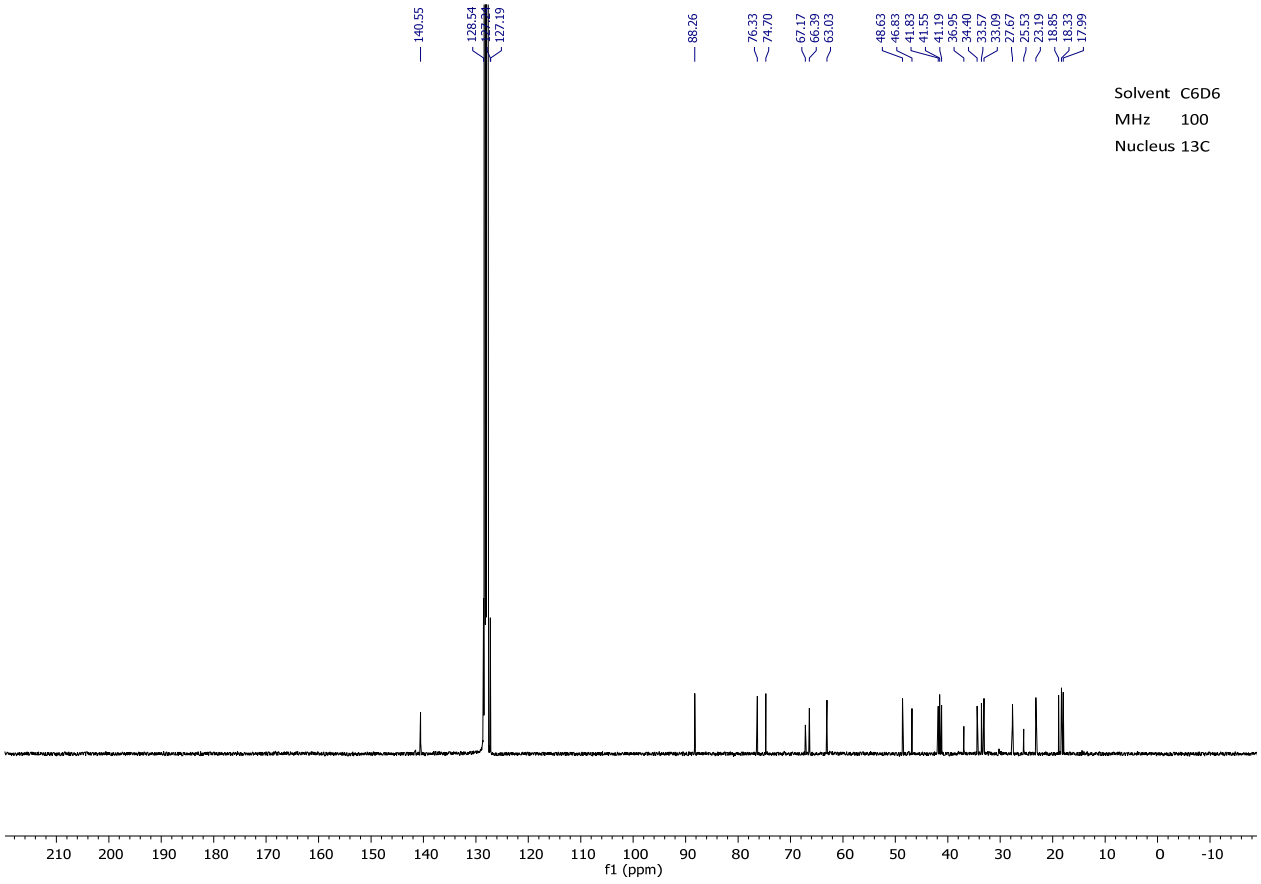


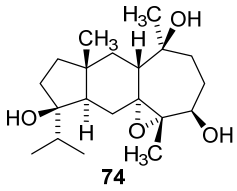
Solvent C6D6
MHz 100
Nucleus 13C


H3C OH
CH3 H
O
H
O
H3C
OH

72

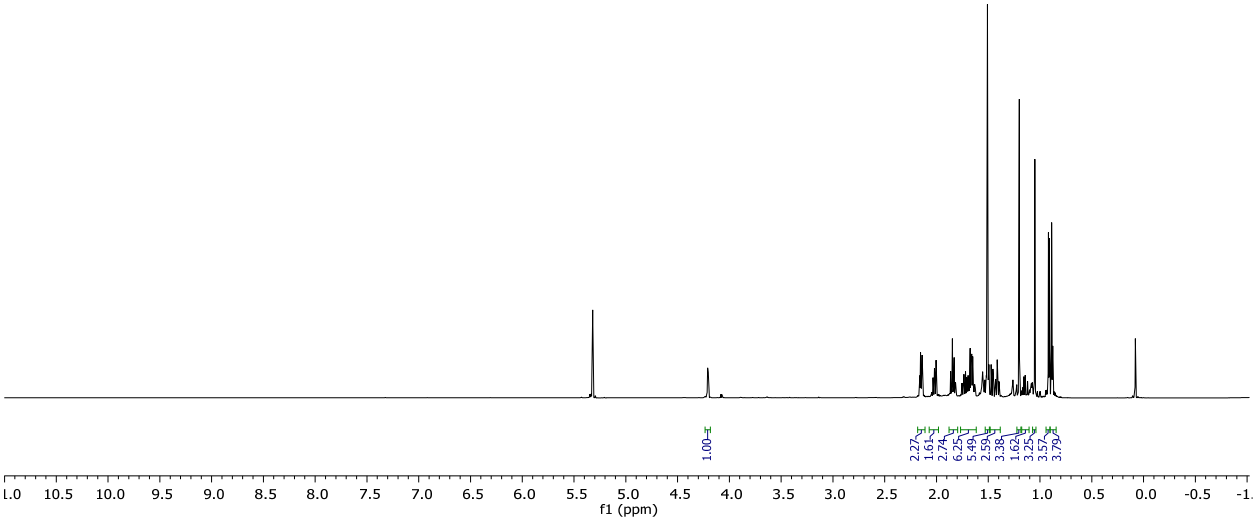

Solvent C6D6
MHz 400
Nucleus 1H
2.11
2.07
0.98
2.09
1.00
1.06
2.24
2.36
3.27
1.34
4.06
3.68
2.81
3.52
1.52
3.38
3.47
3.46
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

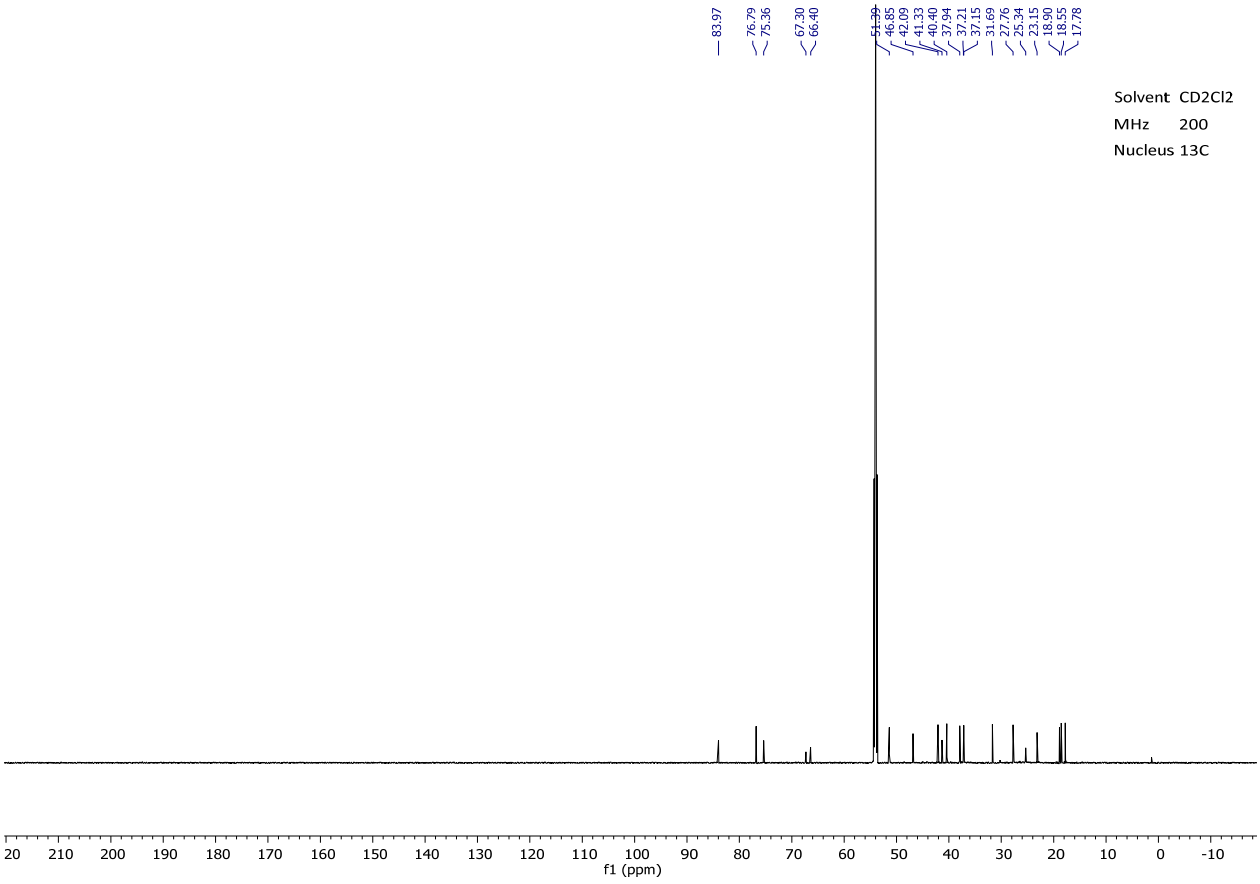

140.55
128.54
128.24
127.19
88.26
76.33
74.70
67.17
66.39
63.03
48.63
46.83
41.83
41.55
41.19
36.95
34.40
33.57
33.09
27.67
25.53
23.19
18.85
18.33
17.99
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



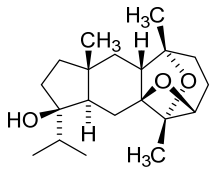
74

Solvent CD2Cl2
MHz 800
Nucleus 1H

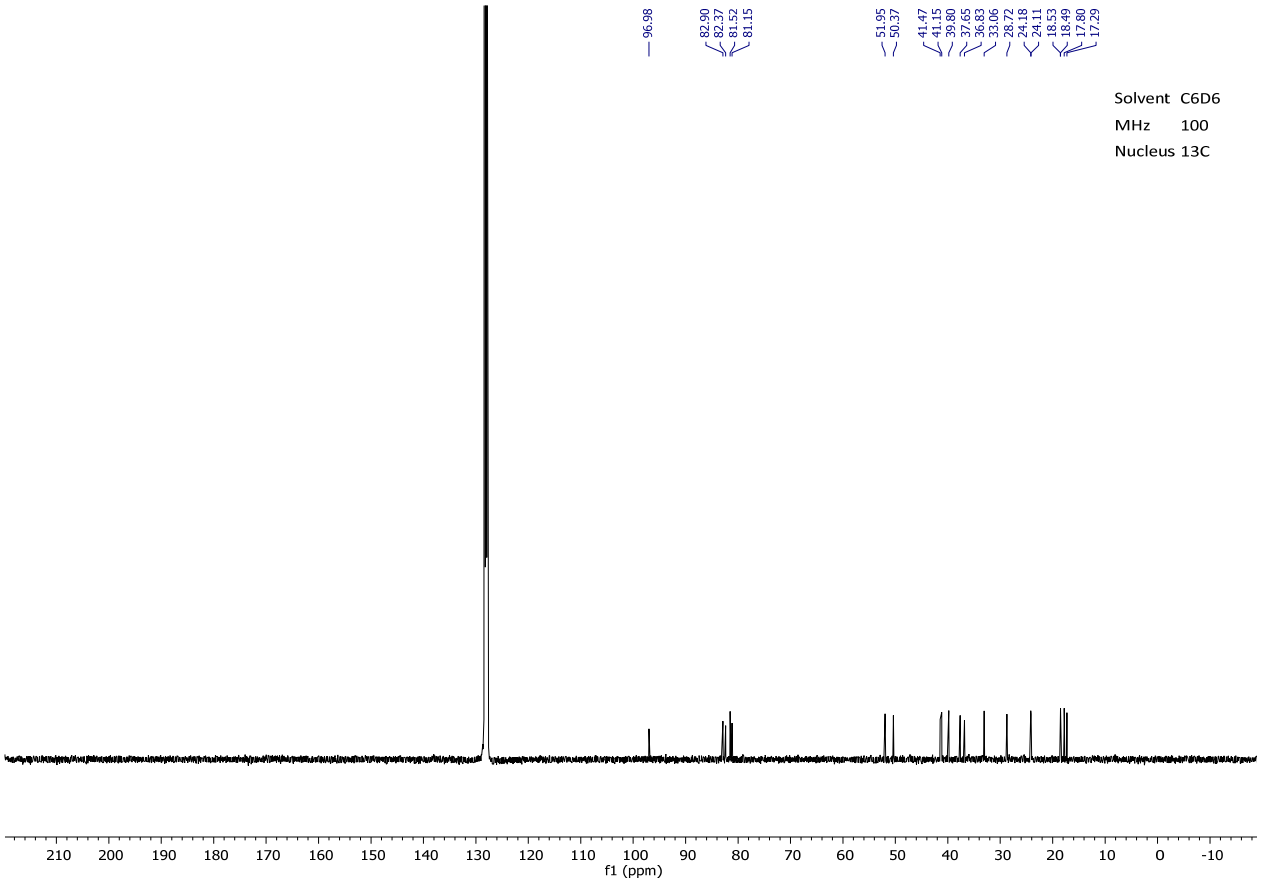


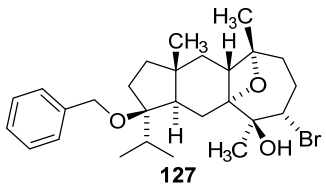


Solvent CD2Cl2
MHz 200
Nucleus 13C



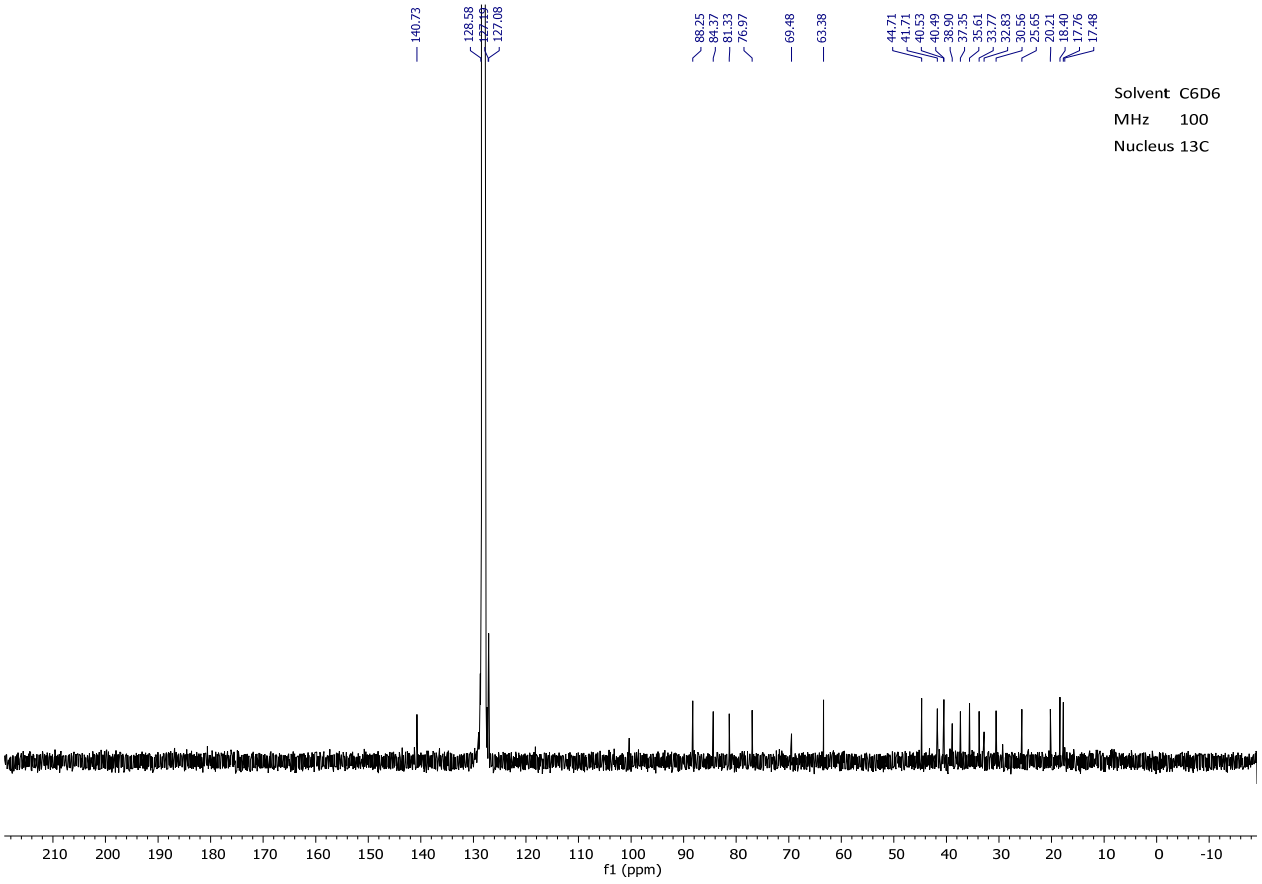
tetra-*epi*-dictyoxetane (tetra-*epi*-**3**)

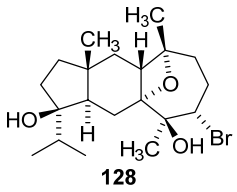



H3C
CH3
H
O
O
H
H3C
OH
Br

127

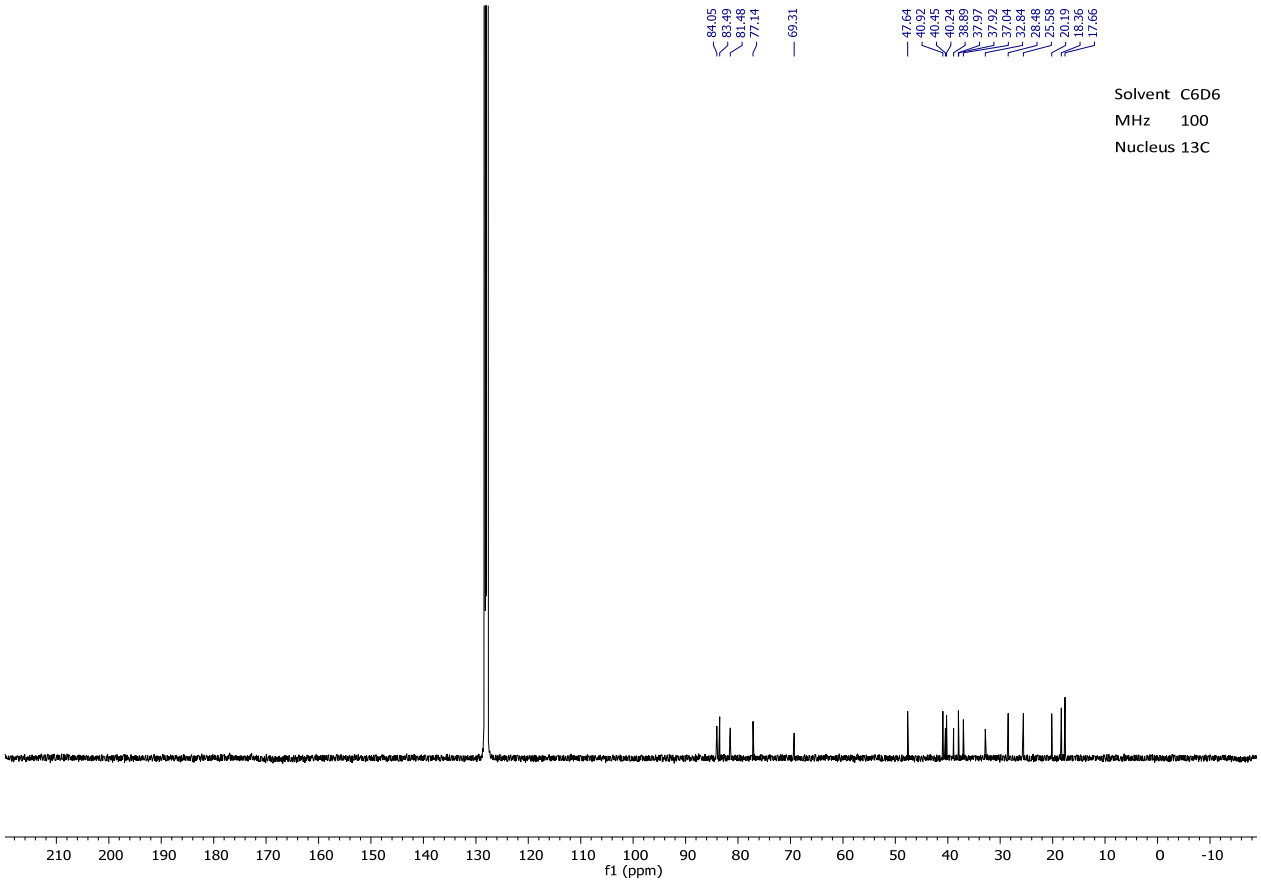
Solvent C6D6
MHz 800
Nucleus 1H
1.85
2.49
0.99
0.80
1.96
0.84
2.03
2.89
1.00
3.10
1.09
2.27
3.06
0.94
4.07
1.02
2.97
2.97
3.01
f1 (ppm)

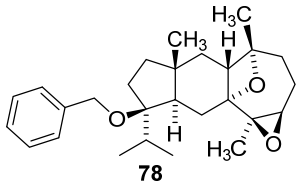

140.73
128.58
127.08
88.25
84.37
81.33
76.97
69.48
63.38
44.71
41.71
40.53
40.49
38.90
37.35
35.61
33.77
32.83
30.56
25.65
20.21
18.40
17.76
17.48
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C
CH3
H
O
HO
H
H3C
OH
Br

128

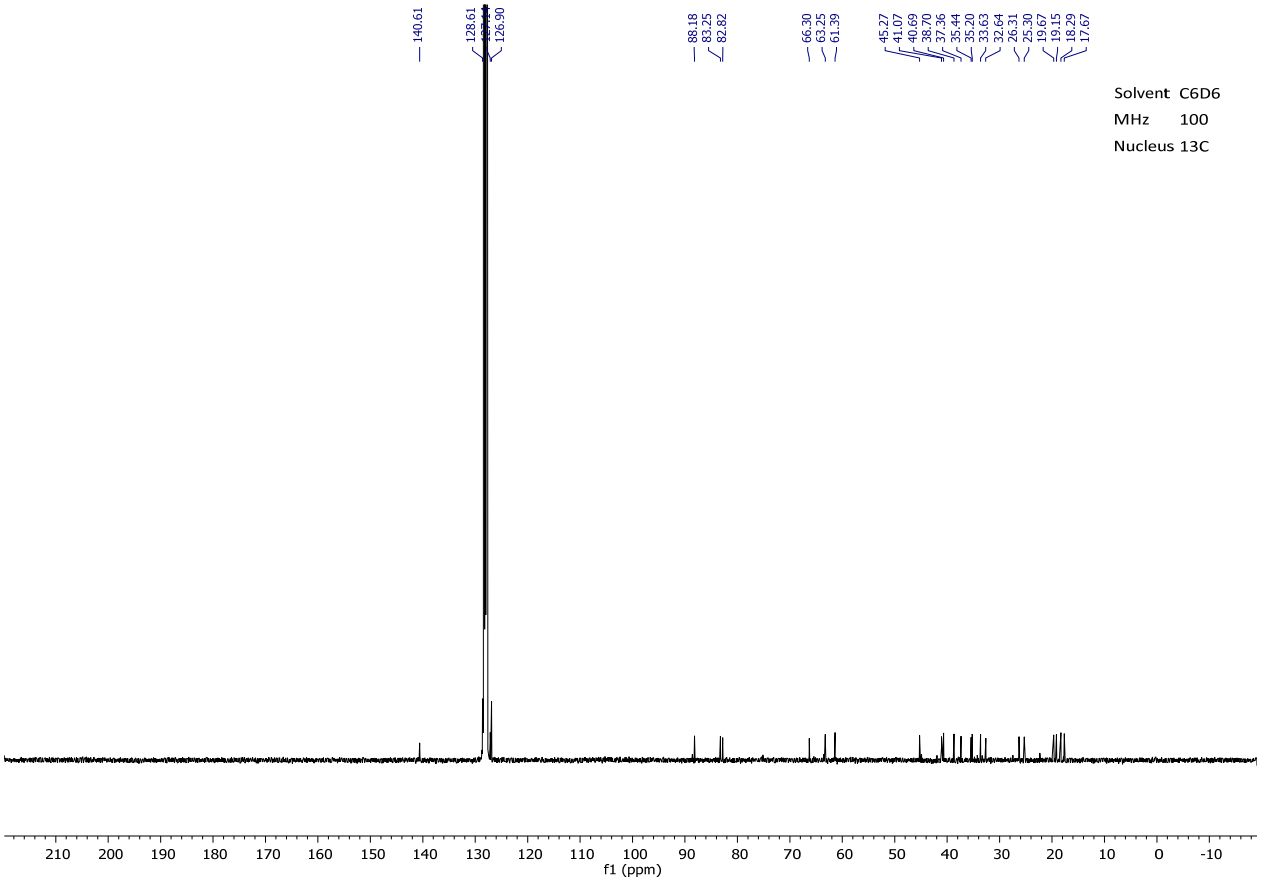
Solvent C6D6
MHz 400
Nucleus 1H
1.00
1.07
2.02
1.05
2.06
3.24
7.37
1.41
3.09
2.10
3.06
3.14
3.21
0.93
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

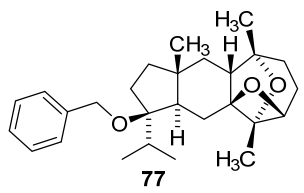

84.05
83.49
81.48
77.14
69.31
47.64
40.92
40.45
40.24
38.89
37.97
37.92
37.04
32.84
28.48
25.58
20.19
18.36
17.66
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
CH3
H
O
O
H
H3C
O

78

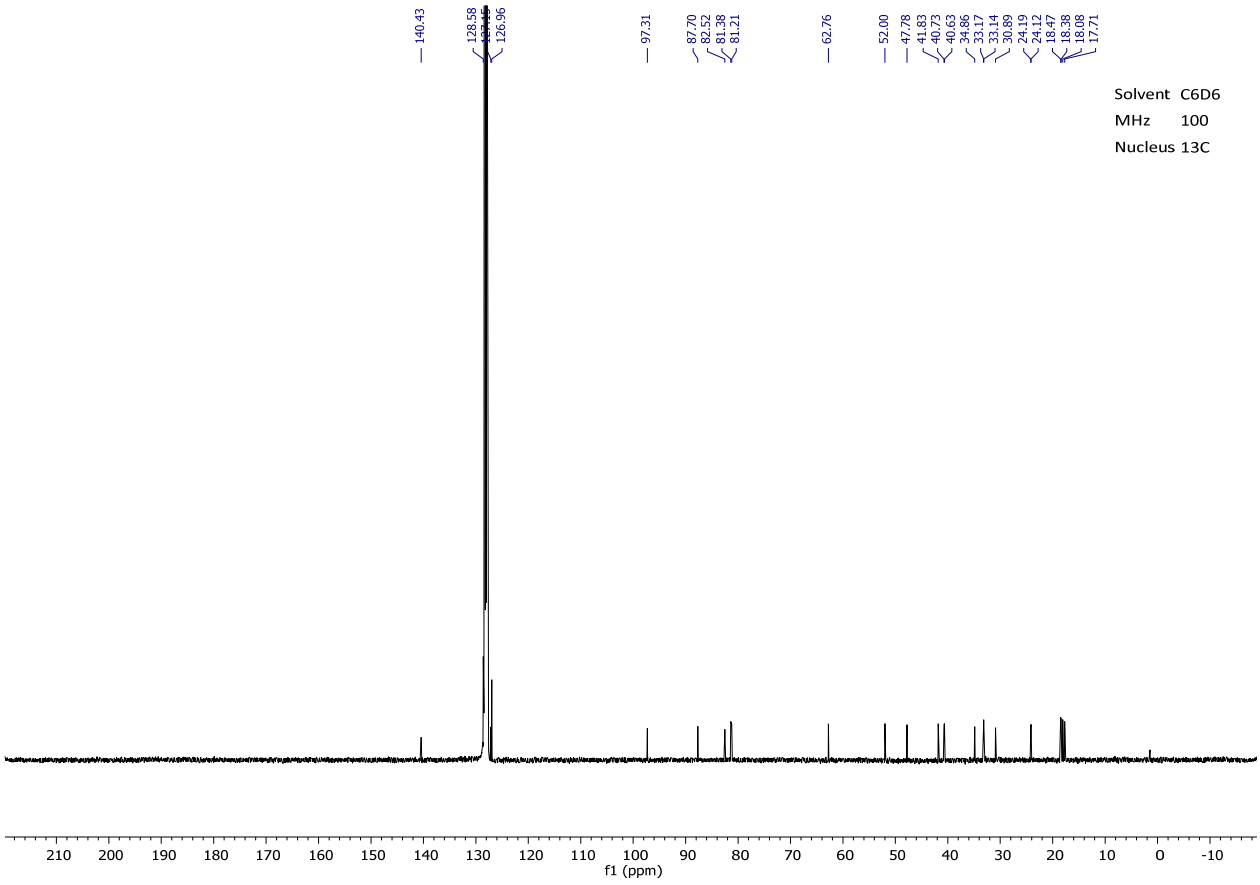
Solvent C6D6
MHz 400
Nucleus 1H
2.01
1.84
1.09
2.08
1.10
0.89
1.14
4.04
2.58
3.43
1.23
3.00
2.56
5.61
2.98
3.10
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

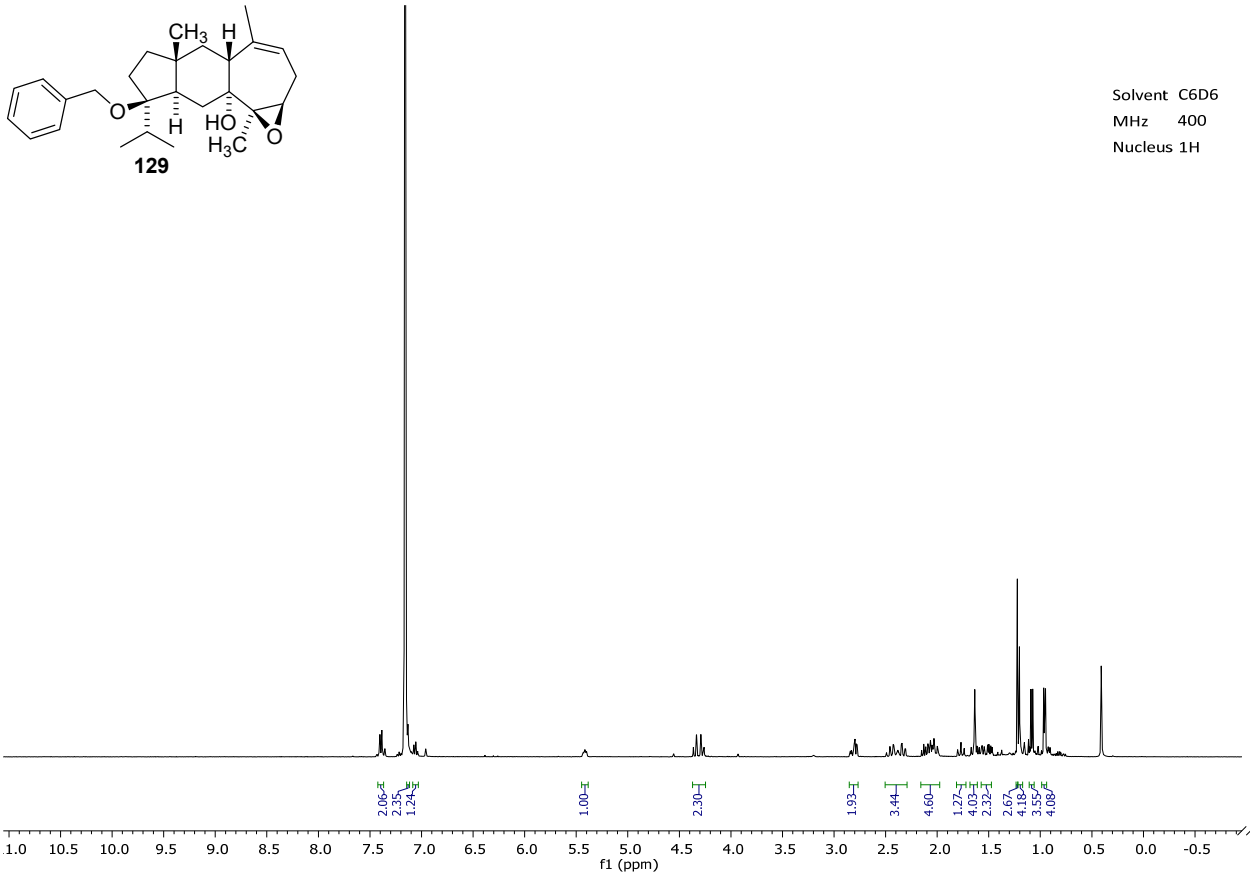

140.61
128.61
126.90
88.18
83.25
82.82
66.30
63.25
61.39
45.27
41.07
40.69
38.70
37.36
35.44
35.20
33.63
32.64
26.31
25.30
19.67
19.15
18.29
17.67
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

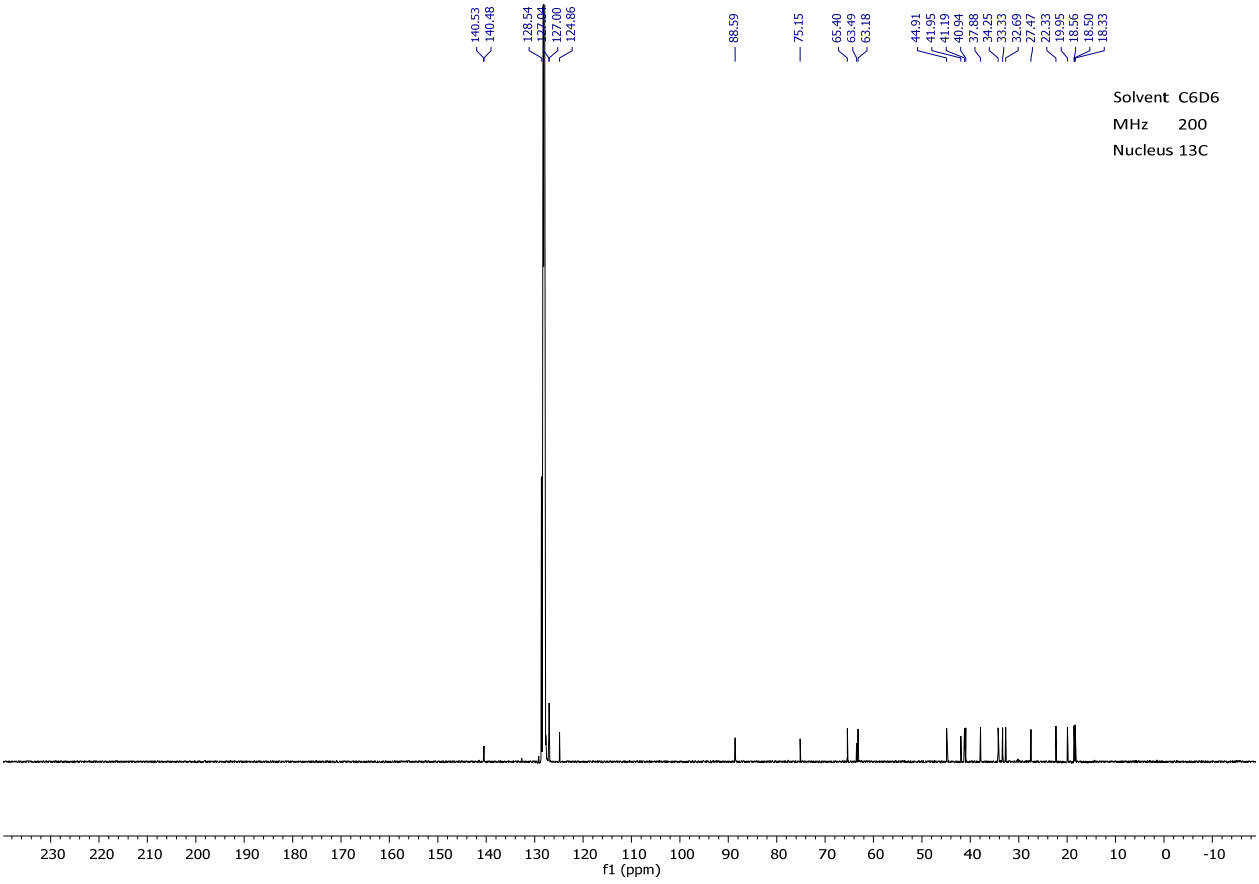

H3C
CH3
H
O
O
O
H
H3C

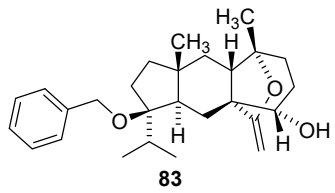
77

Solvent C6D6
MHz 400
Nucleus 1H
2.38
2.26
1.39
3.14
2.00
4.29
1.16
5.47
1.43
3.62
4.64
3.00
5.74
2.93
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


140.43
128.58
126.96
97.31
87.70
82.52
81.38
81.21
62.76
52.00
47.78
41.83
40.73
40.63
34.86
33.17
33.14
30.89
24.19
24.12
18.47
18.38
18.08
17.71
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

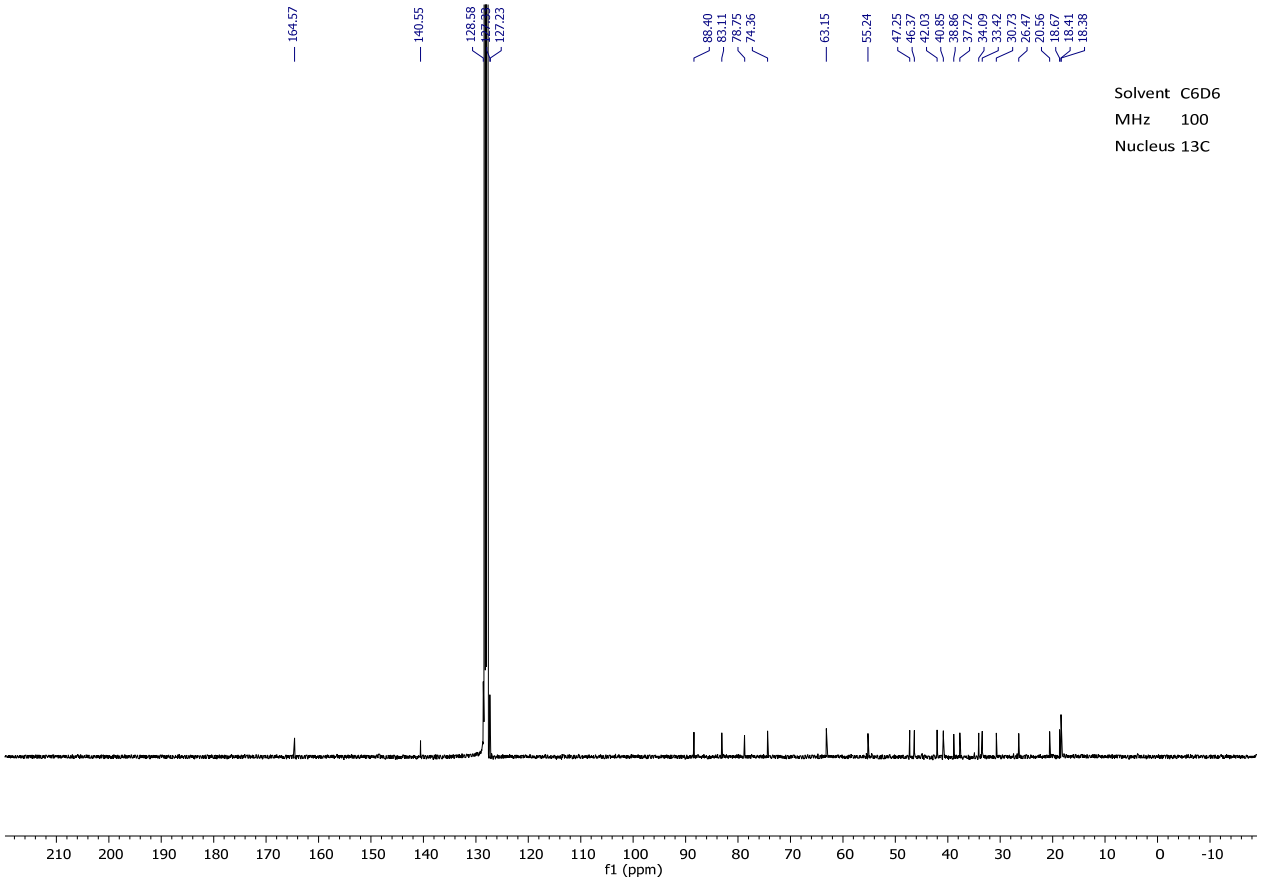

CH3 H
O
H
HO
H3C
O
129
Solvent C6D6
MHz 400
Nucleus 1H
2.06
2.35
1.24
1.00
2.30
1.93
3.44
4.60
1.27
4.03
2.32
2.67
4.18
3.55
4.08
f1 (ppm)

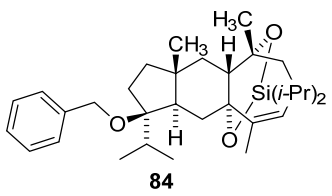

140.53
140.48
128.54
127.04
127.00
124.86
88.59
75.15
65.40
63.49
63.18
44.91
41.95
41.19
40.94
37.88
34.25
33.33
32.69
27.47
22.33
19.95
18.56
18.50
18.33
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)


H3C
CH3
H
O
O
H
H
OH

83

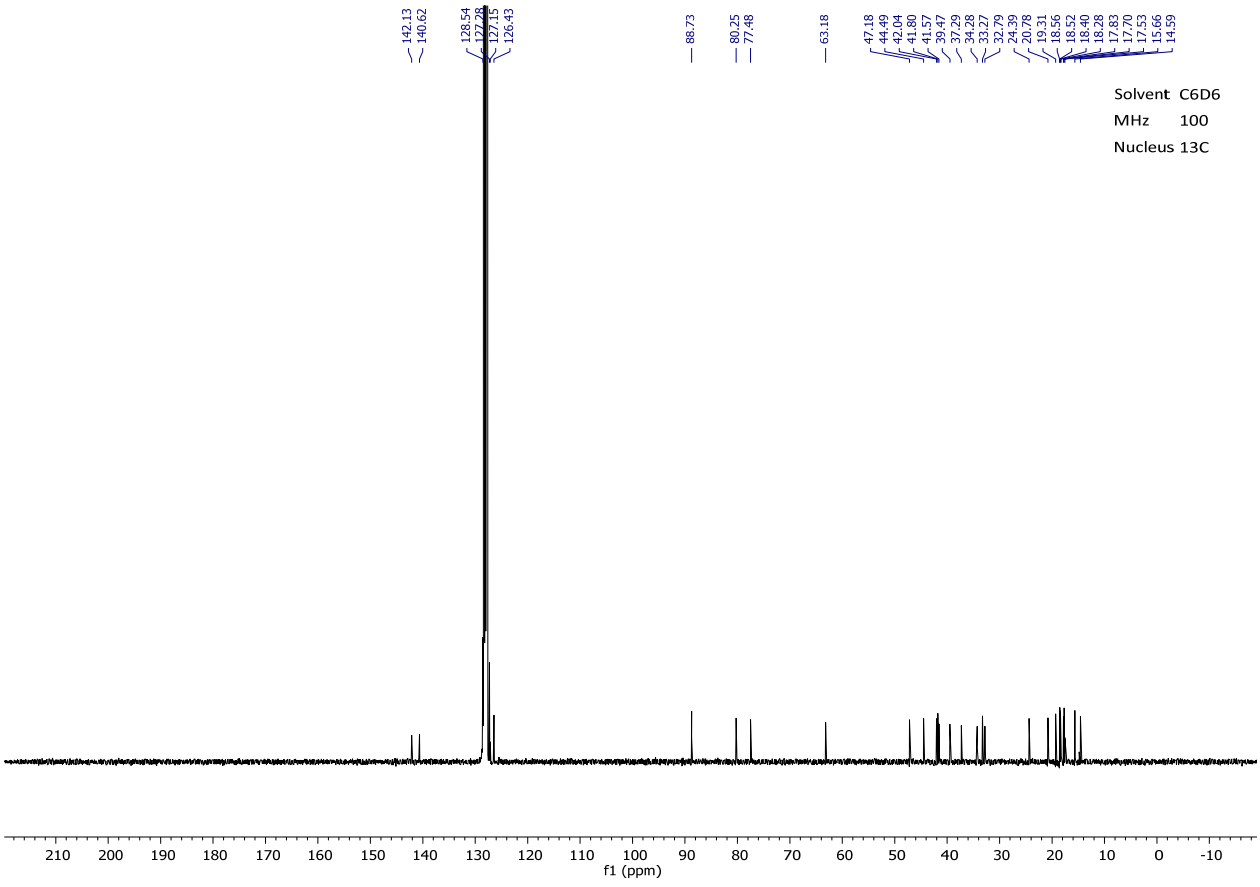
Solvent C6D6
MHz 400
Nucleus 1H
2.16
2.17
1.18
0.93
2.26
0.86
0.97
1.00
2.57
1.09
1.14
1.54
1.33
3.15
1.31
1.40
2.18
3.28
2.91
3.06
3.22
f1 (ppm)

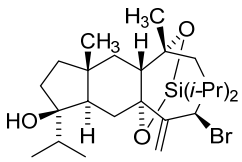

164.57
140.55
128.58
127.23
88.40
83.11
78.75
74.36
63.15
55.24
47.25
46.37
42.03
40.85
39.86
37.72
34.09
33.42
30.73
26.47
20.56
18.67
18.41
18.38
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C
O
CH3
H
Si(i-Pr)2
O
H
O

84

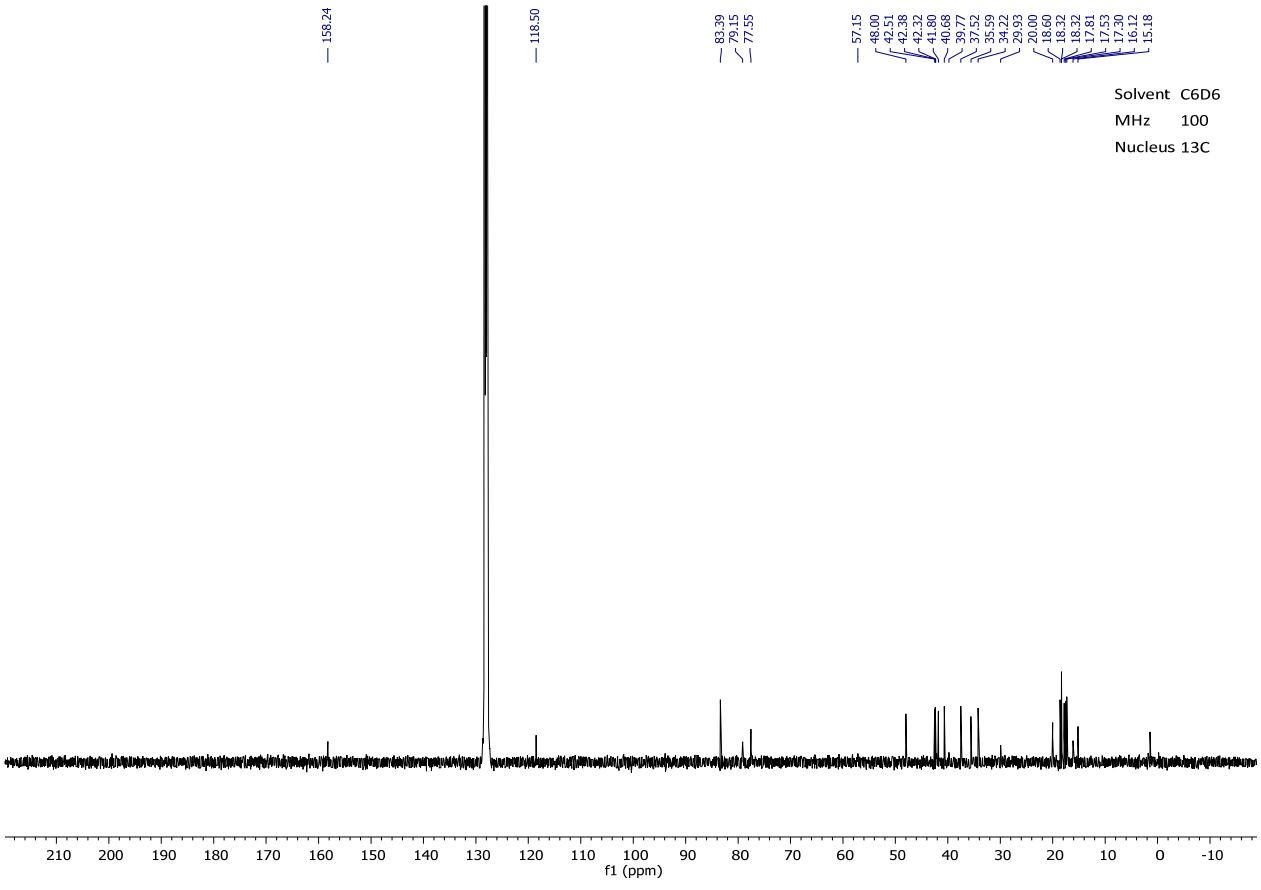
Solvent C6D6
MHz 400
Nucleus 1H
1.93
2.04
1.00
0.96
1.97
0.93
0.99
1.02
4.02
5.55
4.57
27.88
f1 (ppm)

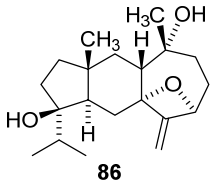

142.13
140.62
128.54
127.28
127.15
126.43
88.73
80.25
77.48
63.18
47.18
44.49
42.04
41.80
41.57
39.47
37.29
34.28
33.27
32.79
24.39
20.78
19.31
18.56
18.52
18.40
18.28
17.83
17.70
17.53
15.66
14.59
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C
O
CH3
H
Si(i-Pr)2
HO
H
O
Br

85

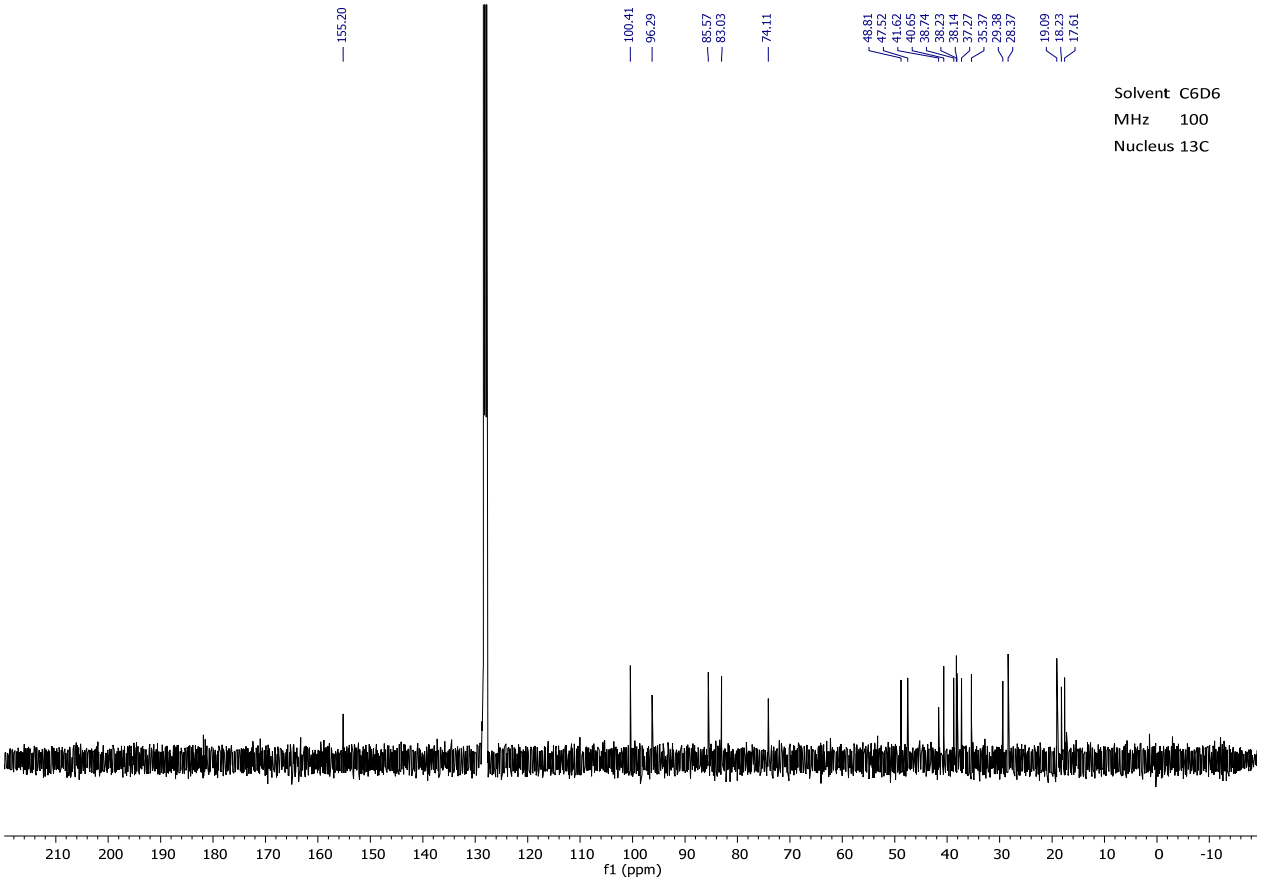
Solvent C6D6
MHz 400
Nucleus 1H
0.91
0.86
0.90
0.86
2.00
0.98
8.80
1.39
3.55
18.69
3.43
3.52
0.71
f1 (ppm)

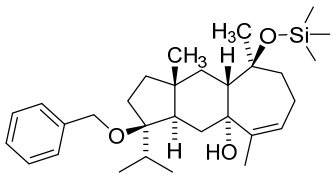

158.24
118.50
83.39
79.15
77.55
57.15
48.00
42.51
42.38
42.32
41.80
40.68
39.77
37.52
35.59
34.22
29.93
20.00
18.60
18.32
18.32
17.81
17.53
17.30
16.12
15.18
Solvent C6D6
MHz 100
Nucleus 13C
f1 (ppm)


H3C OH
CH3 H
O
HO
H

86

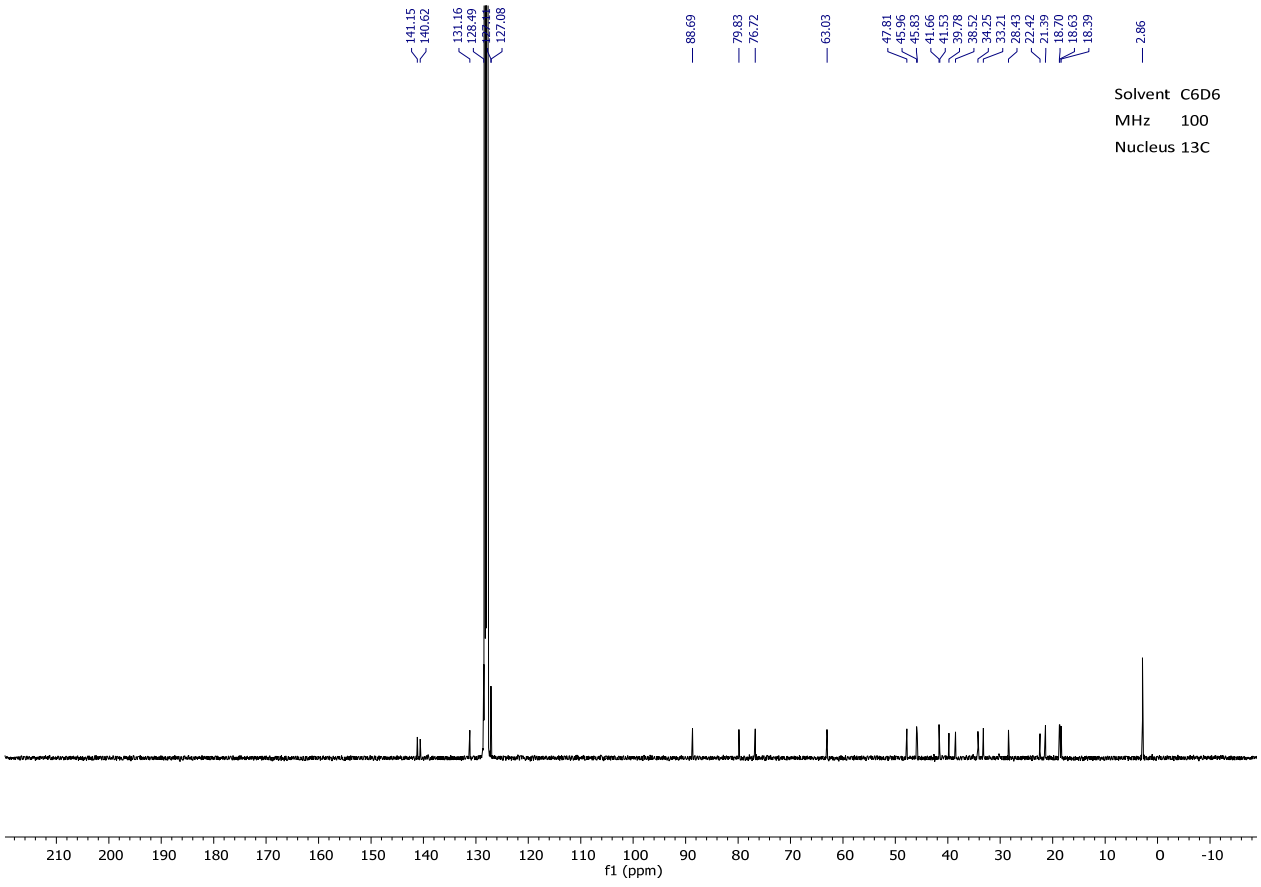
Solvent C6D6
MHz 400
Nucleus 1H
1.00
0.98
1.00
0.94
4.11
1.17
2.79
3.55
2.21
3.04
1.23
1.32
3.21
3.23
3.11
0.80
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

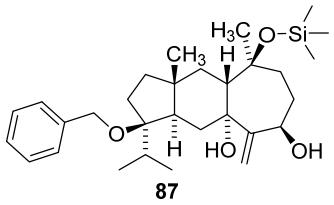

155.20
100.41
96.29
85.57
83.03
74.11
48.81
47.52
41.62
40.65
38.74
38.23
38.14
37.27
35.37
29.38
28.37
19.09
18.23
17.61
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
O-Si
CH3
H
O
H
HO

130

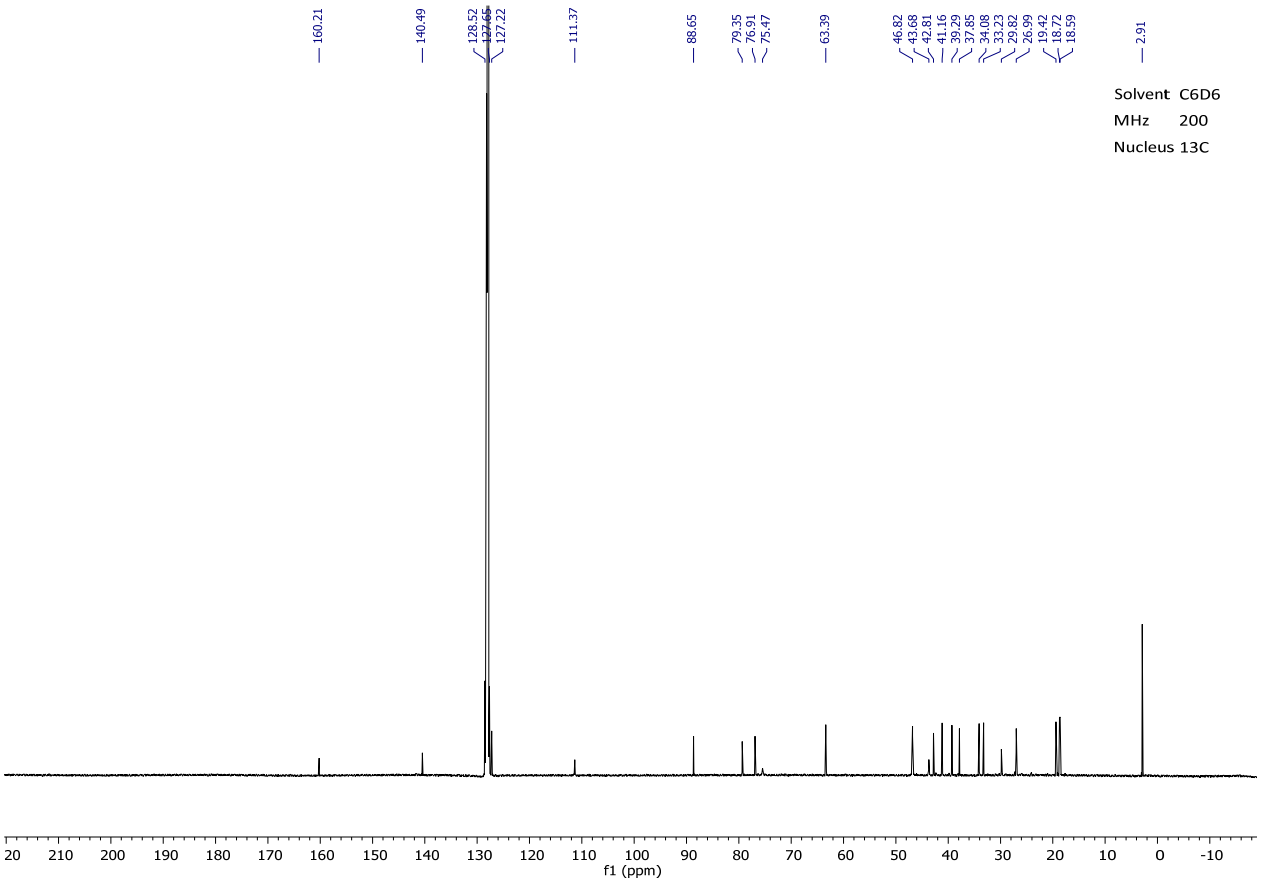
Solvent C6D6
MHz 400
Nucleus 1H
2.23
2.52
1.20
1.00
2.48
1.00
1.06
1.03
1.09
2.36
3.12
8.45
3.20
1.26
3.19
3.24
3.47
1.12
9.00
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

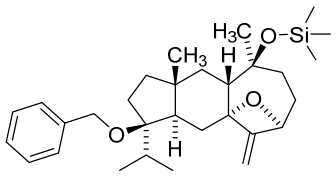

141.15
140.62
131.16
128.49
127.08
88.69
79.83
76.72
63.03
47.81
45.96
45.83
41.66
41.53
39.78
38.52
34.25
33.21
28.43
22.42
21.39
18.70
18.63
18.39
2.86
Solvent C6D6
MHz 100
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H3C
O-Si
CH3
H
O
H
HO
OH

87

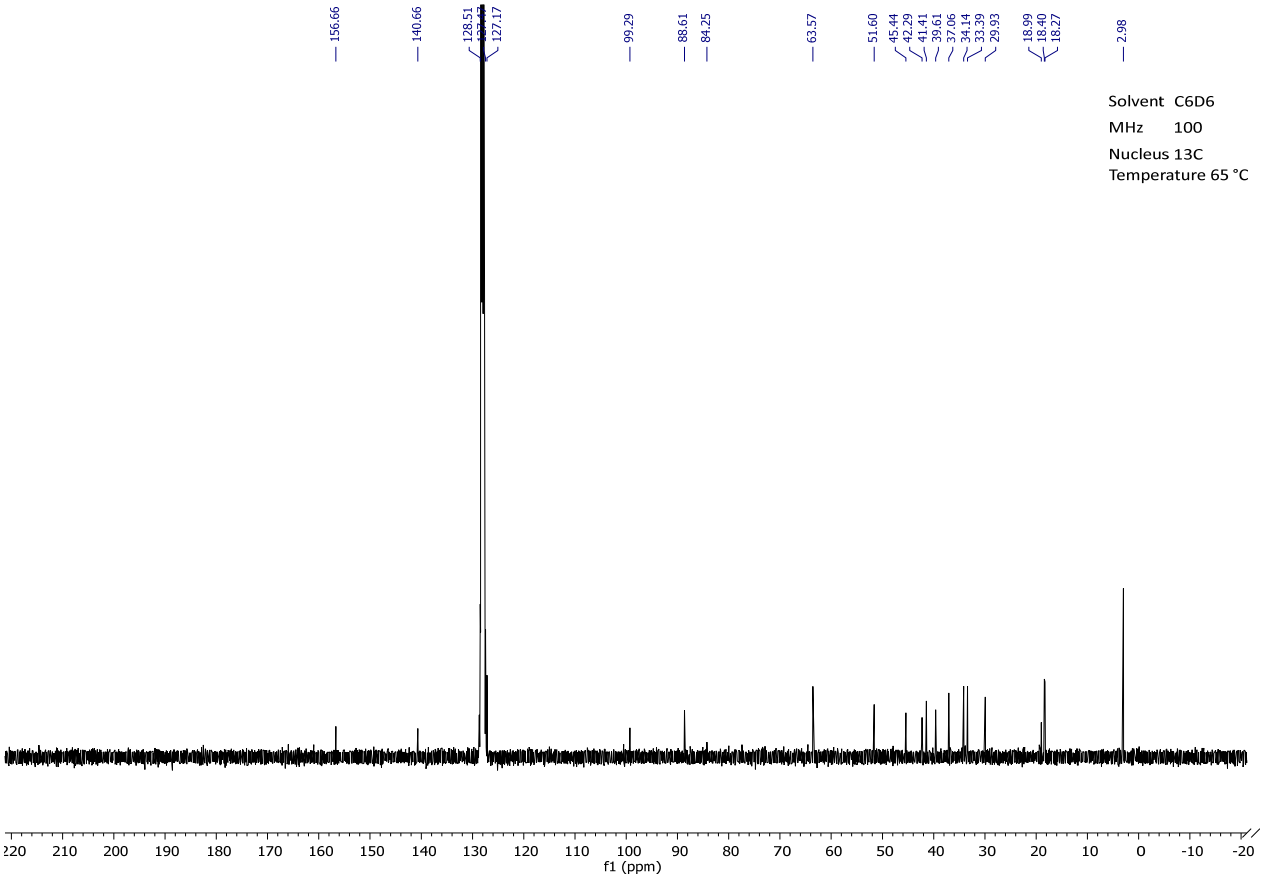
Solvent C6D6
MHz 800
Nucleus 1H
1.95
1.85
0.95
1.05
0.87
2.11
1.00
0.93
1.00
3.50
1.09
1.99
6.42
3.17
3.09
1.06
1.18
3.04
2.95
0.94
9.30
f1 (ppm)

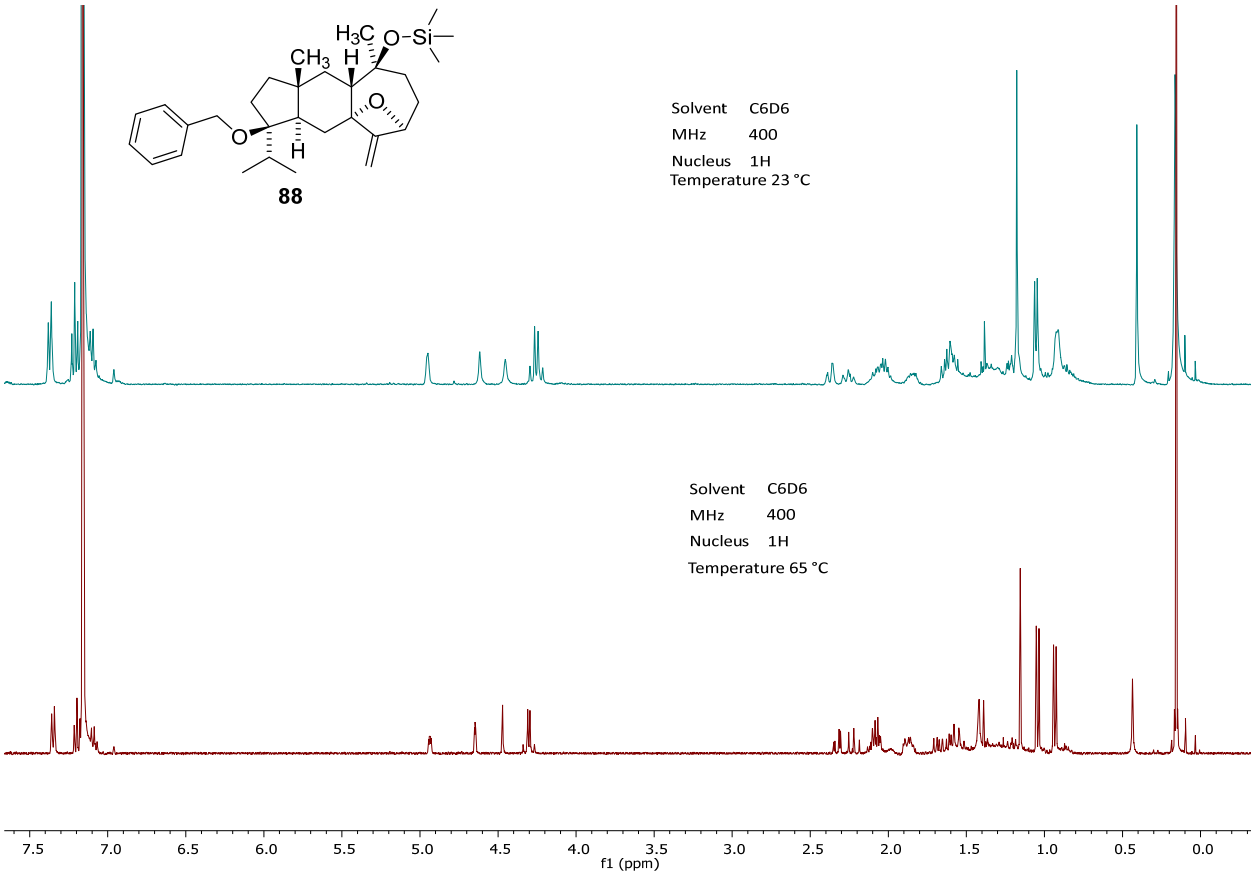

160.21
140.49
128.52
127.65
127.22
111.37
88.65
79.35
76.91
75.47
63.39
46.82
43.68
42.81
41.16
39.29
37.85
34.08
33.23
29.82
26.99
19.42
18.72
16.59
2.91
Solvent C6D6
MHz 200
Nucleus 13C
f1 (ppm)

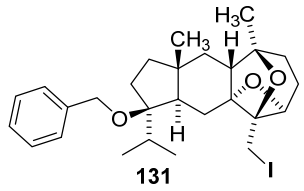

H3C
O-Si
CH3
H
O
O
H

88

Solvent C6D6
MHz 400
Nucleus 1H
Temperature 65 °C
2.21
2.15
1.16
1.00
0.98
0.98
2.33
1.01
0.99
3.59
0.55
2.46
5.84
3.21
2.18
3.28
3.28
3.22
9.71
f1 (ppm)

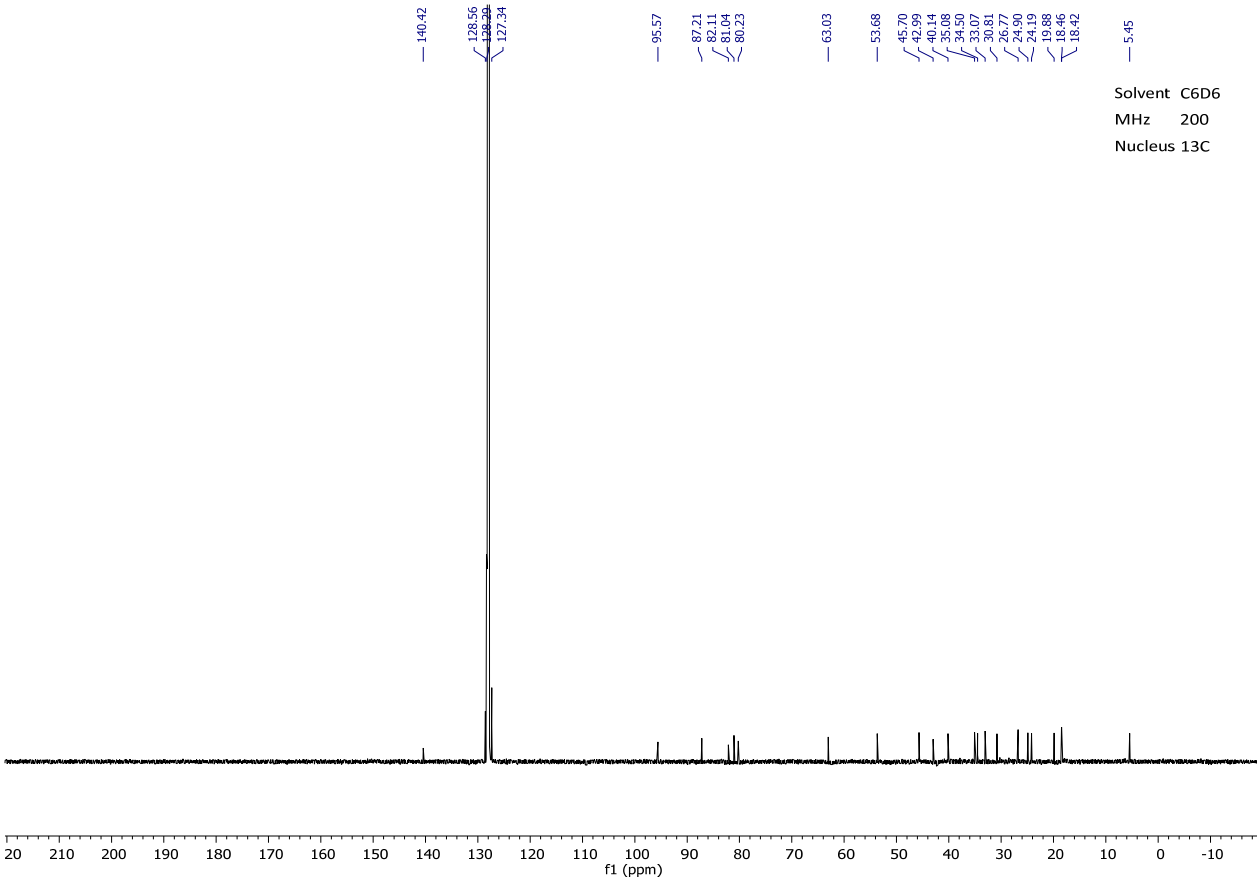

156.66
140.66
128.51
127.17
99.29
88.61
84.25
63.57
51.60
45.44
42.29
41.41
39.61
37.06
34.14
33.39
29.93
18.99
18.40
18.27
2.98
Solvent C6D6
MHz 100
Nucleus 13C
Temperature 65 °C
f1 (ppm)

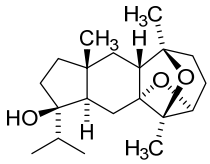

H3C O-Si
CH3 H
O
O
H
88
Solvent C6D6
MHz 400
Nucleus 1H
Temperature 23 °C
Solvent C6D6
MHz 400
Nucleus 1H
Temperature 65 °C
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


H3C
CH3
H
O
O
O
H
I

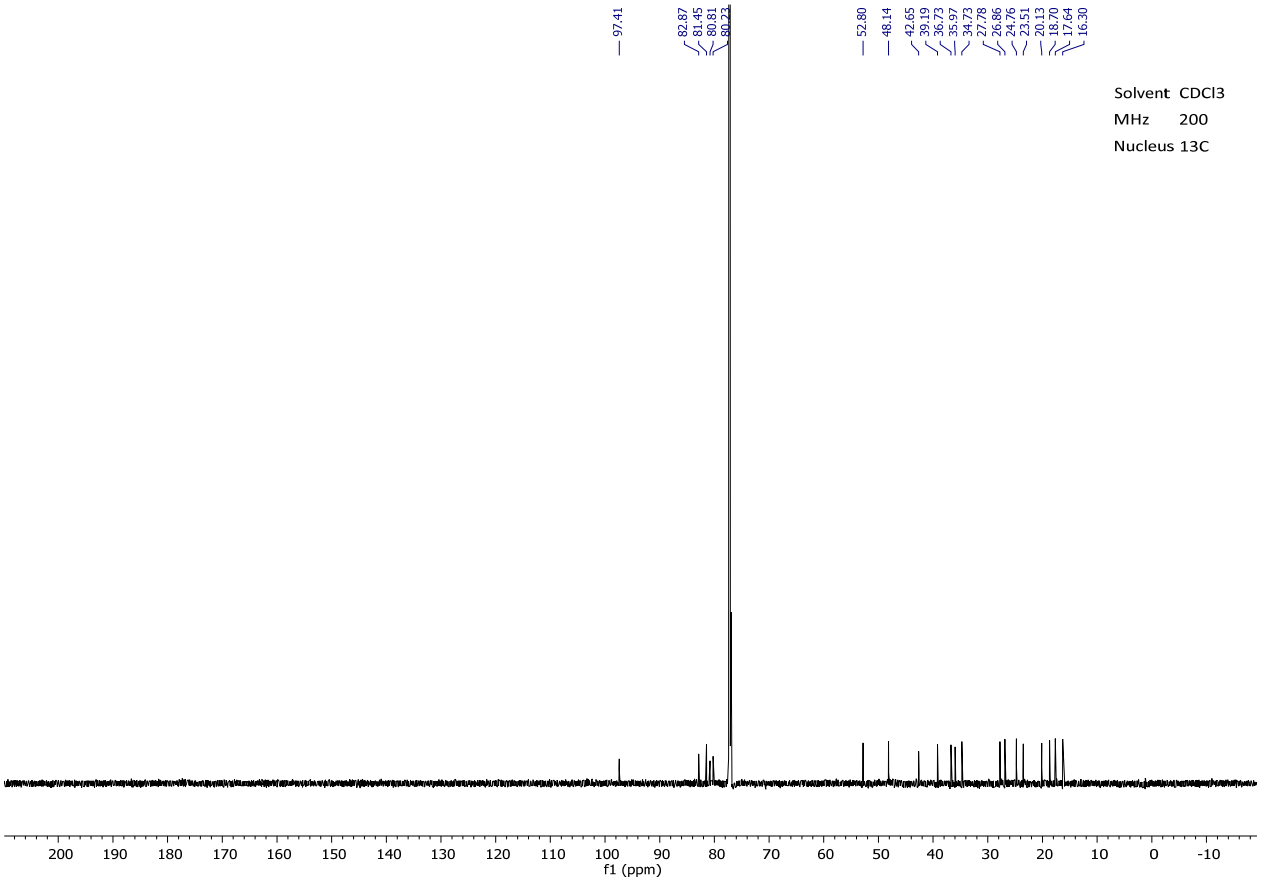
131

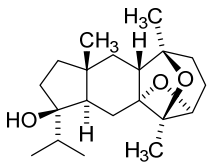
Solvent C6D6
MHz 800
Nucleus 1H
1.92
2.03
1.21
2.04
0.97
0.98
1.00
1.09
1.00
1.32
1.09
1.01
0.97
4.33
1.05
1.32
1.25
0.91
3.48
0.92
6.16
3.23
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


140.42
128.56
128.29
127.34
95.57
87.21
82.11
81.04
80.23
63.03
53.68
45.70
42.99
40.14
35.08
34.50
33.07
30.81
26.77
24.90
24.19
19.88
18.46
18.42
5.45
Solvent C6D6
MHz 200
Nucleus 13C
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

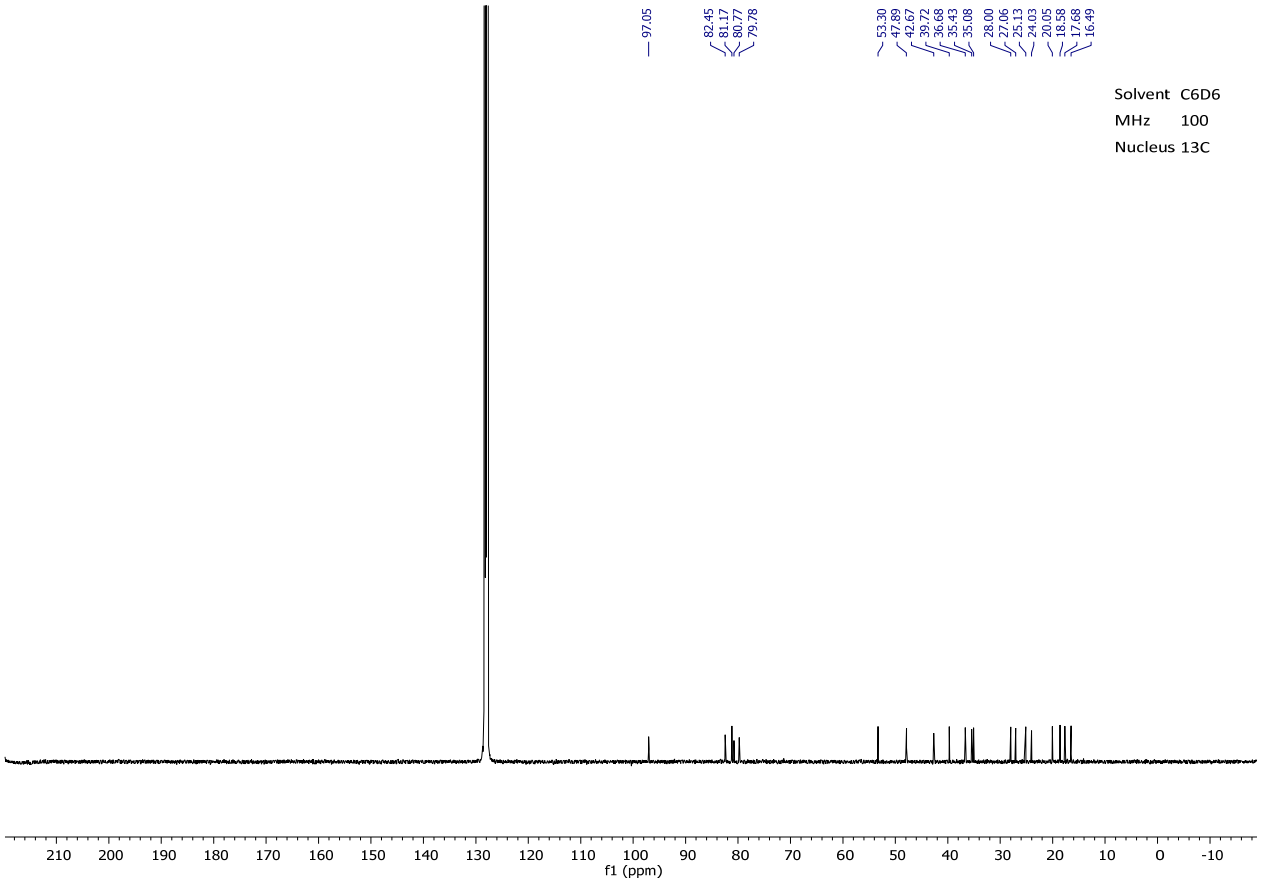


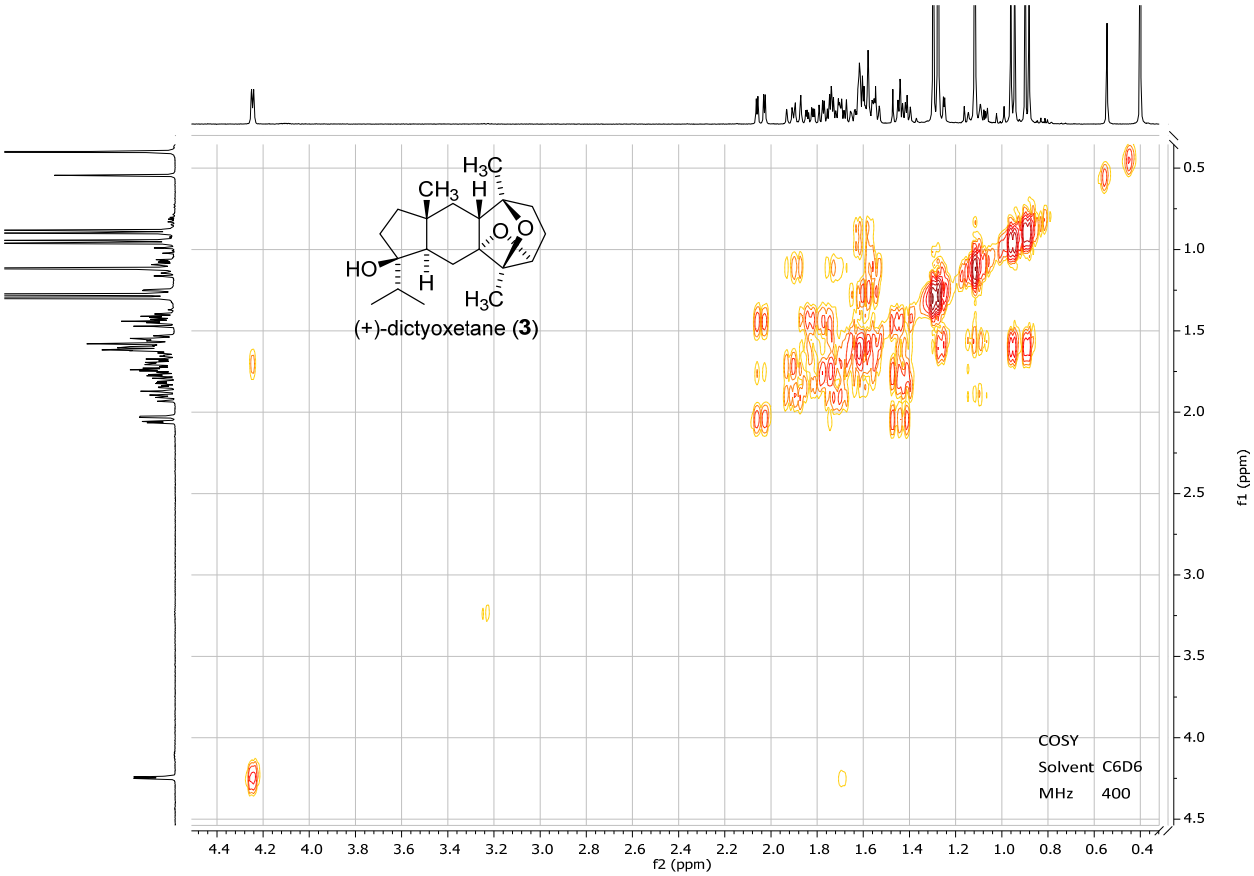
(+)-dictyoxetane (**3**)

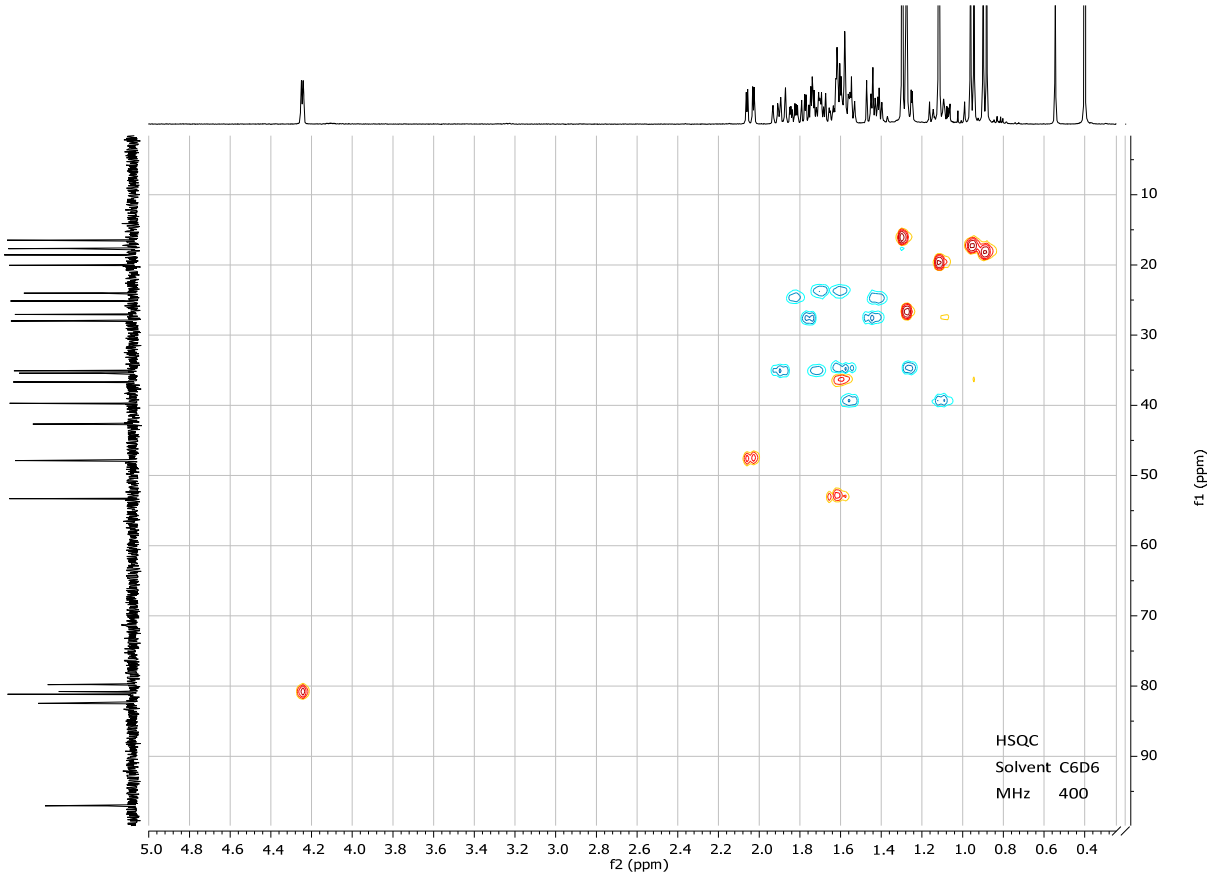


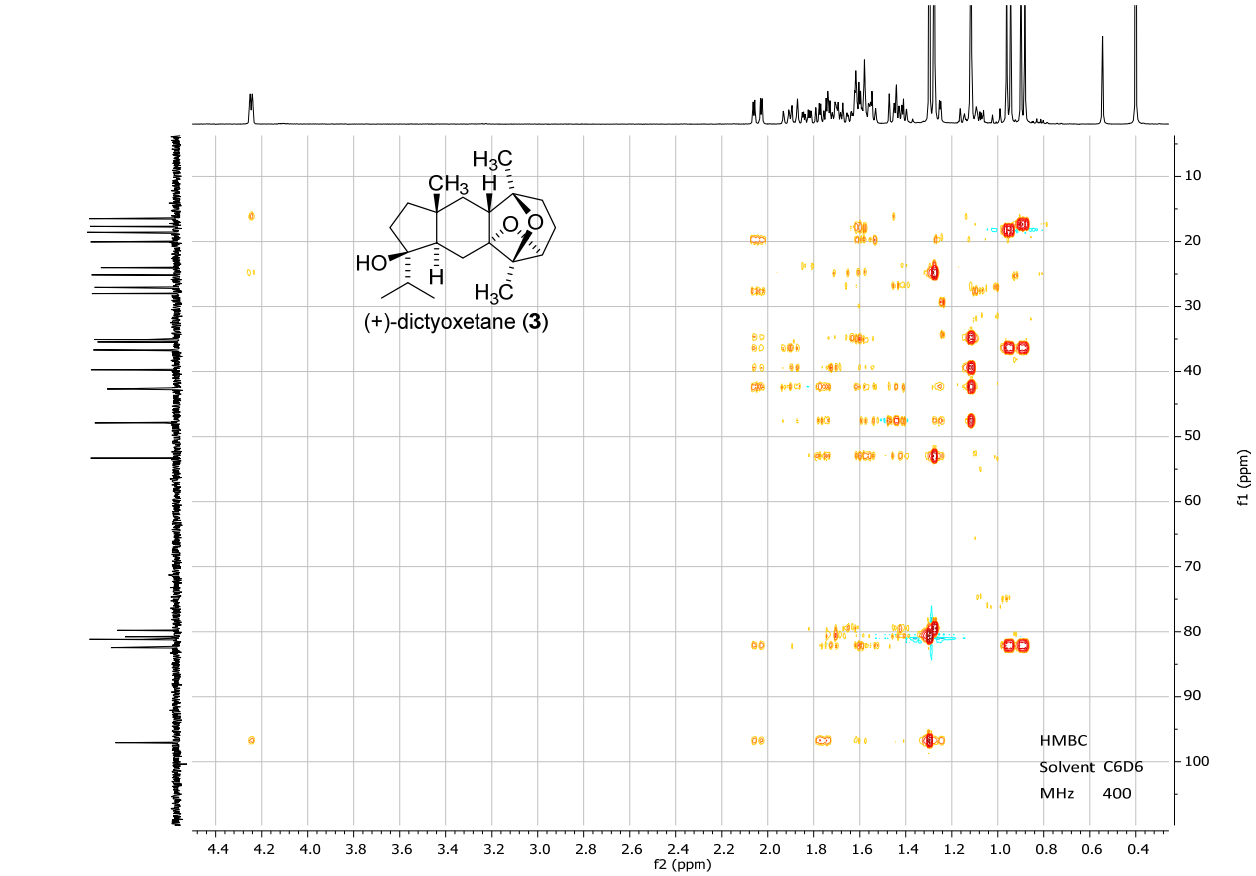


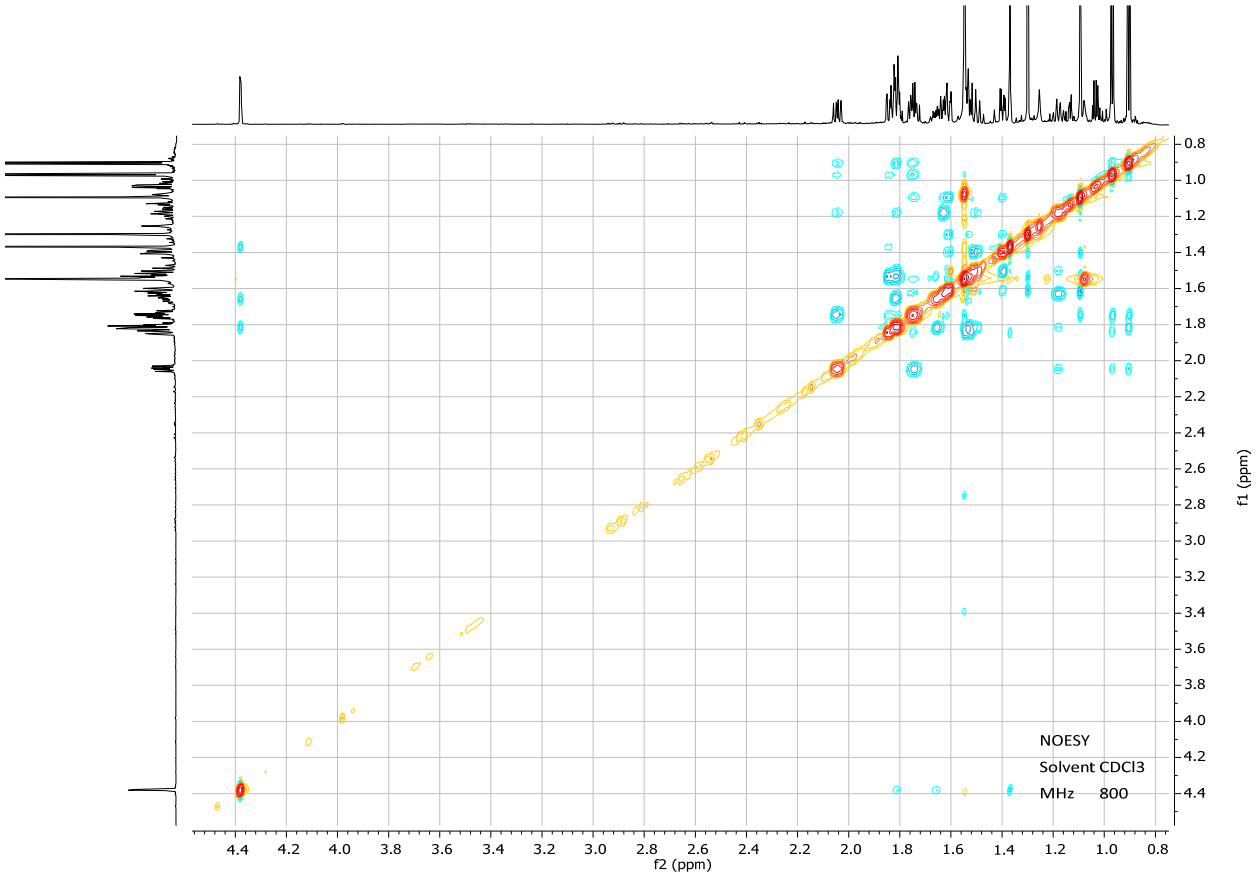
(+)-dictyoxetane (**3**)

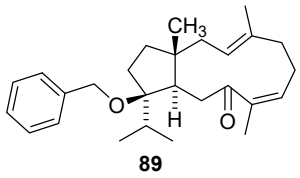



H3C
CH3
H
O
O
HO
H
H3C
(+)-dictyoxetane (3)
COSY
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)


HSQC
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)

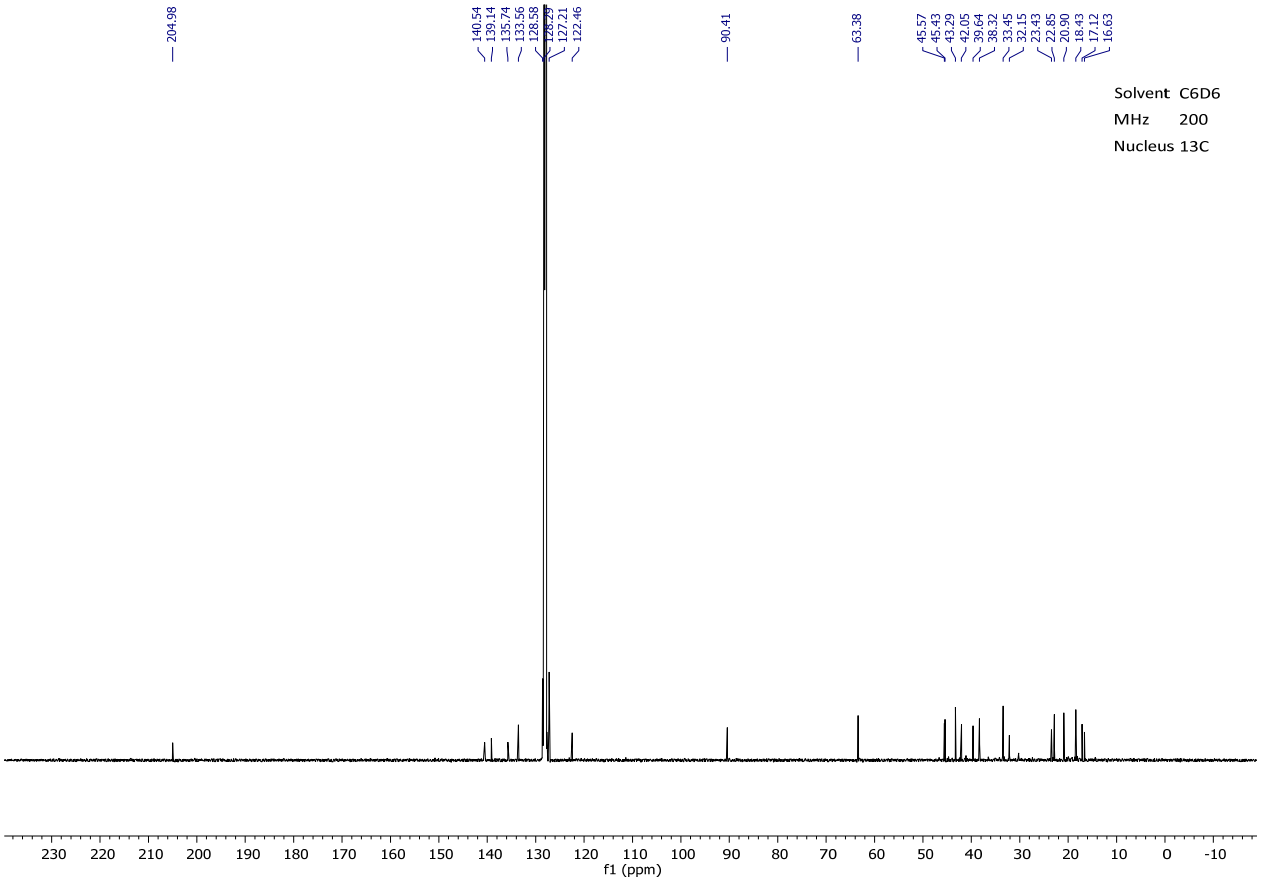

(+)-dictyoxetane (3)
HMBC
Solvent C6D6
MHz 400
f2 (ppm)
f1 (ppm)

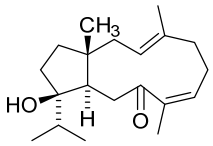

NOESY
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)


CH3
O
H
O

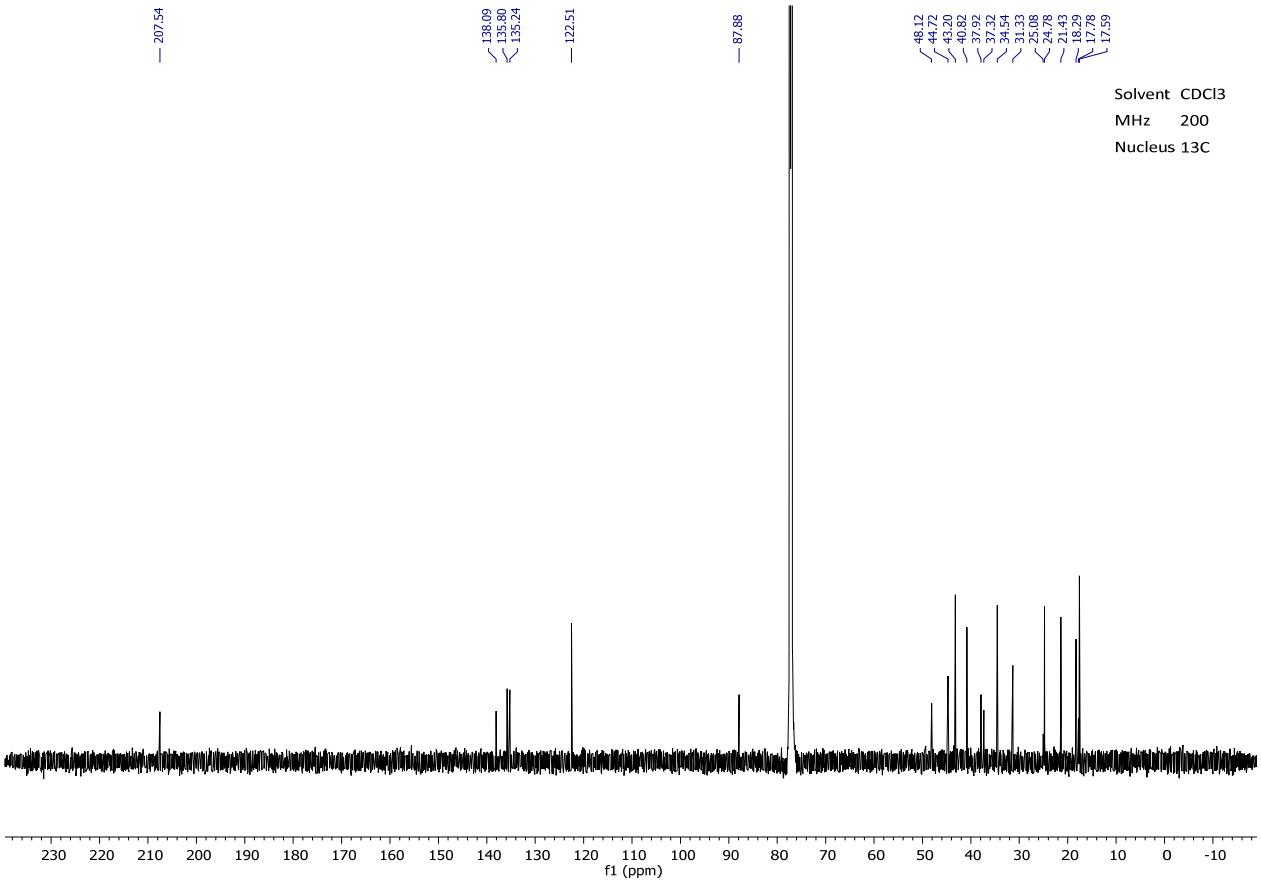
89

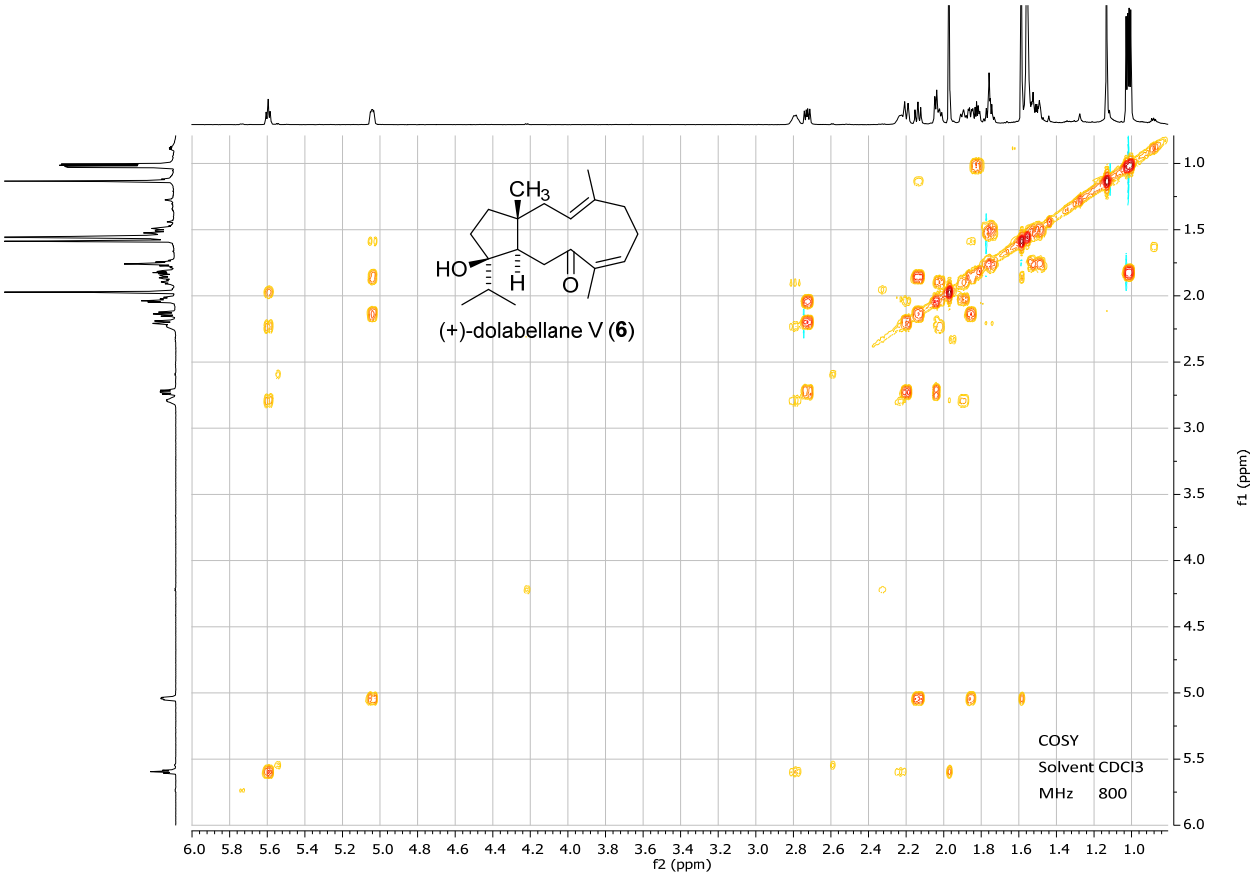
Solvent C6D6
MHz 800
Nucleus 1H
1.93
2.10
1.20
1.03
0.99
2.16
0.97
2.02
0.95
0.97
0.91
0.89
1.15
0.93
1.04
2.94
5.35
1.17
1.13
3.04
6.04
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

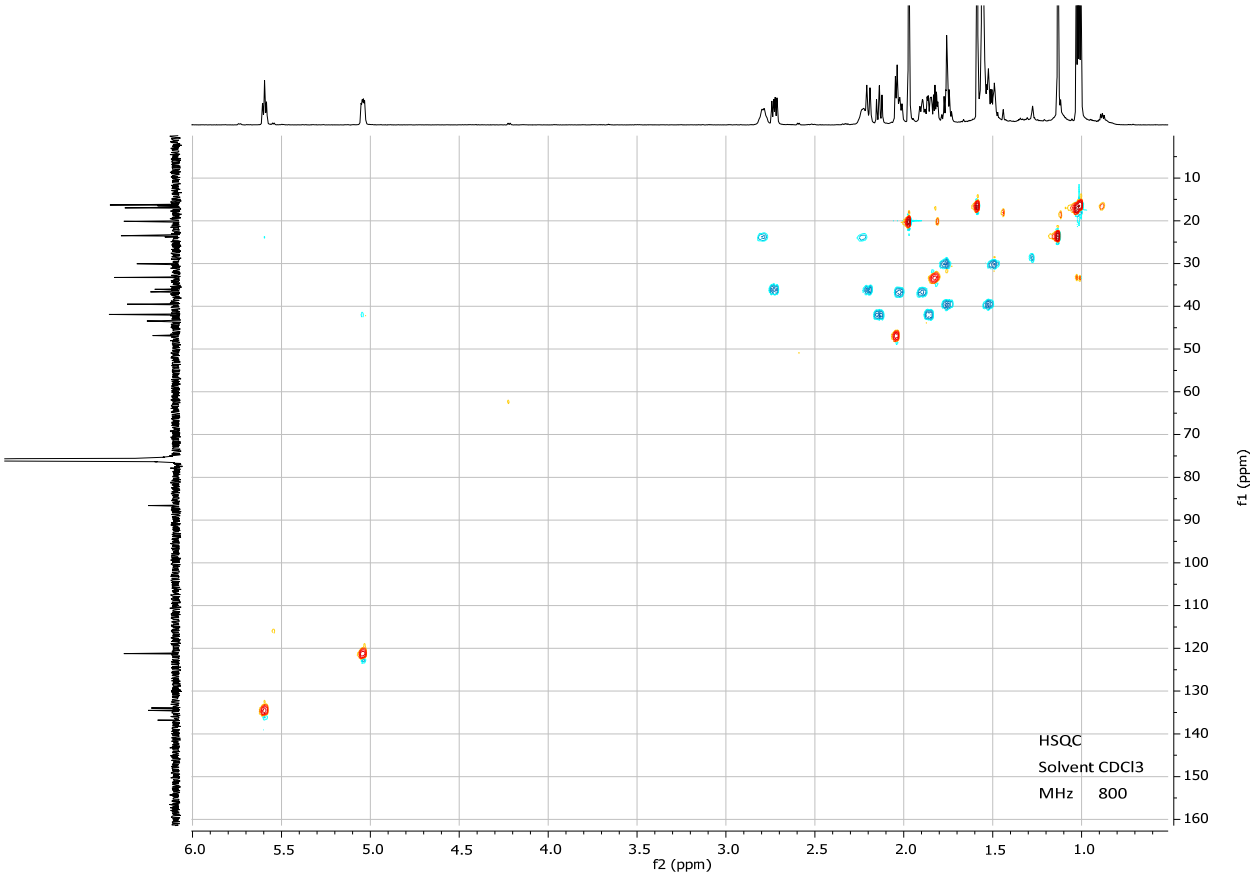

204.98
140.54
139.14
135.74
133.56
128.58
126.29
127.21
122.46
90.41
63.38
45.57
45.43
43.29
42.05
39.64
38.32
33.45
32.15
23.43
22.85
20.90
18.43
17.12
16.63
Solvent C6D6
MHz 200
Nucleus 13C
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

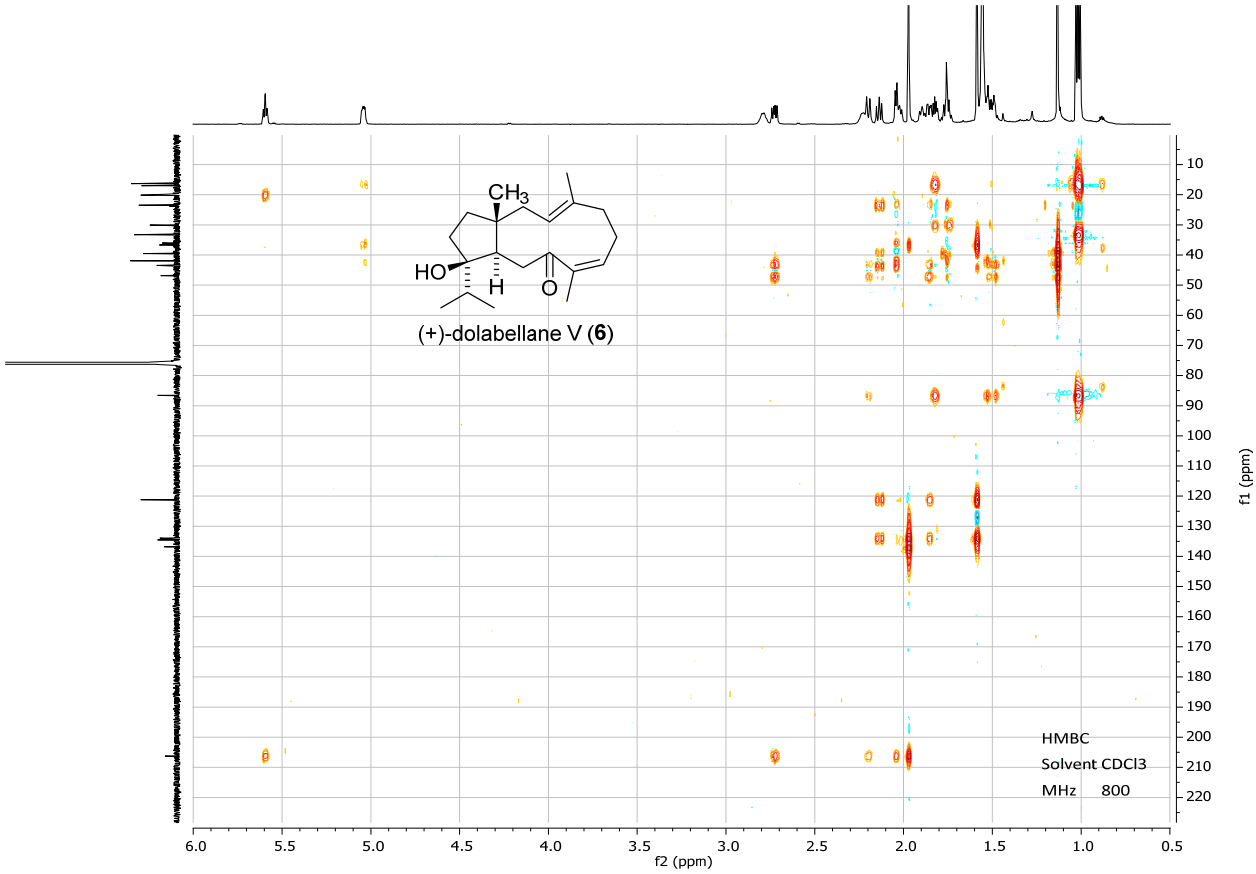


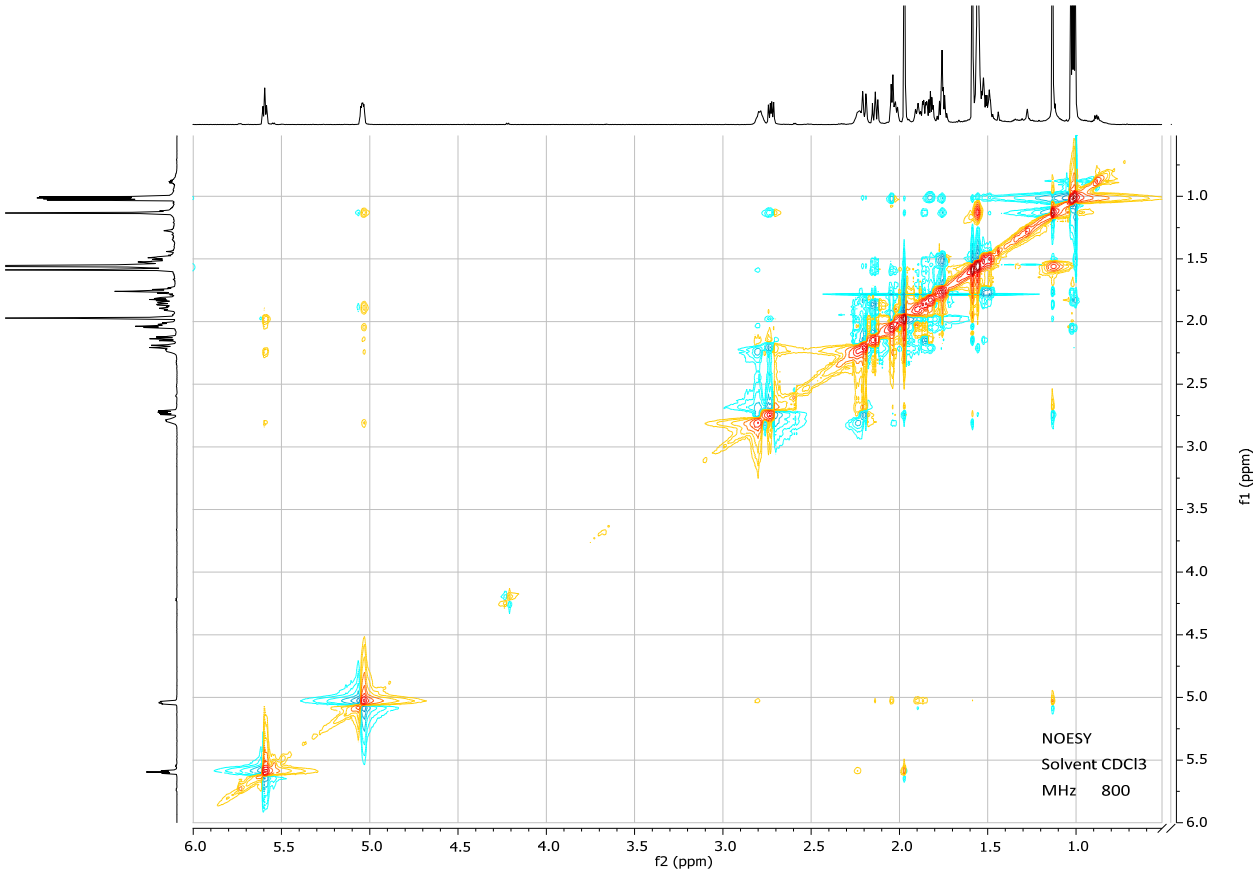
(+)-dolabellane V (**6**)




CH3
HO
H
O
(+)-dolabellane V (6)
COSY
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)


HSQC
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)


CH3
HO
H
O
(+)-dolabellane V (6)
HMBC
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)


NOESY
Solvent CDCl3
MHz 800
f2 (ppm)
f1 (ppm)

Cedric L. Hugelshofer

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Date of Birth:	July 27th, 1988
Place of Birth:	Bern, Switzerland
Nationalities:	Swiss and British
Languages:	German (native), English (native) Spanish (basic), French (basic)

EDUCATION

LMU Munich, Germany PhD student in the group of Dr. Thomas Magauer	Bioinspired total syntheses of antifeedant sesterterpenoids and complex dolabellane diterpenoids	Jul. 13 – present
Harvard University, USA Master's thesis research in the group of Prof. Andrew G. Myers	Development of a methodology for the synthesis of enantiomerically enriched α-quaternary amino acids	Mar. 12 – Aug. 12
University of Basel, Switzerland M. Sc. Chemistry (final grade: 5.9*) B. Sc. Chemistry (final grade: 5.7*)	With focus on organic chemistry	Sep. 08 – Feb. 12
Gymnasium Burgdorf, Switzerland Swiss Federal Maturity (high school) (Final grade: 5.4*)	With a focus on biology and chemistry	Aug. 04 – Jun. 07

* Grading scheme: 6.0 = excellent; 5.5 = very good; 5.0 = good; 4.5 = quite good; 4.0 = pass; < 4.0 = fail

EMPLOYMENT AND INTERNSHIPS

Research stay Research group of Prof. S.-H. Li, Kunming Institute of Botany, China	Collaborative investigation of the metabolic pathway of antifeedant leucosceptroid natural products in *L. canum*	Oct. 2014
Research stay / Civil service Empa – Swiss Federal Laboratories for Materials Science and Technology, Dübendorf, Switzerland	Studies on the gas–solid reaction of carbon dioxide with alanates, and the reversible hydrogen sorption reaction in borohydrides using transition metal dopants	Nov. 12 – Mar. 13
Internship Research group of Prof. Karl Gademann, University of Basel	Research towards the total synthesis of the cyathane diterpene cyrneine A	Sep. 11 – Oct. 11
Internship Research group of Prof. Helma Wennemers, University of Basel	Synthesis and conformational analysis of (4*S*)- and (4*R*)-guanidinylated proline derivatives	Aug. 11 – Sep. 11
Voluntary work Southern African Wildlife College, South Africa	Assistance with various tasks in a nature conservation project and behavioural monitoring of game	May 08 – Jun. 08
Military service Lyss, Spiez, Payerne	Obligatory military service and training to be a corporal (nuclear, biological and chemical defense)	Nov. 07 – Apr. 08

PUBLICATIONS

10. A Divergent Approach to the Marine Diterpenoids (+)-Dictyoxetane and (+)-Dolabellane V
    Cedric L. Hugelshofer, Thomas Magauer, *Chem. Eur. J.* ***2016****, just accepted.*
9. A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane
    Cedric L. Hugelshofer, Thomas Magauer, *J. Am. Chem. Soc.* **2016**, *138*, 6420–6430.
    This work was highlighted in *SYNFACTS*: E. M. Carreira, M. Westphal, *Synfacts* **2016**, *12*, 771.
8. Total Synthesis of the Leucosceptroid Family of Natural Products
    Cedric L. Hugelshofer, Thomas Magauer, *J. Am. Chem. Soc.* **2015**, *137*, 3807–3810.
7. Strategies for the Synthesis of Antifeedant Leucosceptroid Natural Products
    Cedric L. Hugelshofer, Thomas Magauer, *Synlett* **2015**, *26*, 572–579.
6. Unraveling the Metabolic Pathway in *Leucosceptrum canum* by Isolation of New Defensive Leucosceptroid Degradation Products and Biomimetic Model Synthesis
    Shi-Hong Luo,[†] Cedric L. Hugelshofer,[†] Juan Hua, Shu-Xi Jing, Chun-Huan Li, Yan Liu, Xiao-Nia Li, Xu Zhao, Thomas Magauer, Sheng-Hong Li, *Org. Lett.* **2014**, *16*, 6416–6419.
5. A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (–)-Norleucosceptroid B, and (–)-Leucosceptroid K
    Cedric L. Hugelshofer, Thomas Magauer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11351–11355.
    This work was highlighted in *SYNFACTS*: E. M. Carreira, M. Westphal, *Synfacts* **2014**, *10*, 1233.
4. Gas–Solid Reaction of Carbon Dioxide with Alanates
    Cedric L. Hugelshofer, Andreas Borgschulte, Elsa Callini, Santhosh K. Matam , Jeffrey Gehrig, Daniel T. Hog, Andreas Züttel, *J. Phys. Chem. C* **2014**, *118*, 15940–15945.
3. High-Pressure Transformations in Natural Product Synthesis
    Cedric L. Hugelshofer, Thomas Magauer, *Synthesis* **2014**, *46*, 1279–1296.
2. The Role of Ti in Alanates and Borohydrides: Catalysis and Metathesis
    Elsa Callini, Andreas Borgschulte, Cedric L. Hugelshofer, Anibal J. Ramirez-Cuesta, Andreas Züttel, *J. Phys. Chem. C* **2014**, *118*, 77–84.
1. Synthesis of Quaternary α-Methyl α-Amino Acids by Asymmetric Alkylation of Pseudoephenamine Alaninamide Pivaldimine
    Cedric L. Hugelshofer, Kevin T. Mellem, Andrew G. Myers, *Org. Lett.* **2013**, *15*, 3134–3137.

    Chemical Synthesis of Antifeedant Natural Products from the Coca Cola tree
    Cedric L. Hugelshofer, Klaus Speck, Adriana S. Grossmann, Thomas Magauer. Press-release: www.beilstein.tv (Jan. 2015).

[†] These authors contributed equally to this work.

PRESENTATIONS

- **Gordon Research Conference – Natural Products and Bioactive Compounds**
  A Divergent and Bioinspired Total Synthesis of (+)-Dictyoxetane and (+)-Dolabellane V (short oral presentation and poster). *Andover, New Hampshire, USA, Aug. 2016.*
- **Hochschule trifft Industrie**
  Collective Synthesis of Antifeedant Leucosceptroid Natural Products. *Rheinfelden, Basel, Switzerland, Oct. 2015.*
- **Gordon Research Conference – Natural Products**
  Asymmetric Total Synthesis of the Leucosceptroid Family of Antifeedant Natural Products (selected oral presentation and poster). *Andover, New Hampshire, USA, Jul. 2015.*
- **Kunming Institute of Botany – Chinese Academy of Sciences**
  A General Entry to Antifeedant Sesterterpenoids. *Kunming, Yunnan, China, Oct. 2014.*

FELLOWSHIPS AND AWARDS

- Reaxys PhD Prize Finalist — 2016
- Kekulé Mobility Fellowship (Fonds der Chemischen Industrie) — Nov. 2013 – present

TEACHING EXPERIENCE

LMU Munich, Germany Jul. 2013 – present

- Assistance and tutoring of "Heterocyclic Chemistry" lecture
- Teaching undergraduate students basic organic chemistry in various practical courses
- Supervision of interns (Bachelor's and Master's students)

PERSONAL INTERESTS

Travelling	Discovering and experiencing new cultures and places	• Fascinated by the variety of different cultures and impressive natural sceneries found on earth • Backpacking in China, Southeast Asia, Bolivia, USA, South Africa and many countries within Europe
Sports and nature	Running, snowboarding, tennis, and hiking	• Marathon running (Munich 2015: 2h 53min, top 70) • Enjoying trips to the mountains or forests, often also combined with sport
Photography	Nature and experimental photography	• Passionate nature photographer, always looking for interesting subjects and lighting