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Studies in Natural Product Synthesis:

Toward the Total Synthesis of Maoecrystal V and Caribenol A and Total Synthesis of Sandresolide B and the Proposed Structure of Trichodermatide A

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Erklärung

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Eidesstattliche Versicherung

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Irina Albrecht

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Publications

Parts of this dissertation have been published in peer-reviewed journals

1. I. Baitinger, P. Mayer, D. Trauner, *Org. Lett.* **2010**, *12*, 5656–5659.
   Toward the Total Synthesis of Maoecrystal V: Establishment of Contiguous Quaternary Stereocenters.

2. I. T. Chen, I. Baitinger, L. Schreyer, D. Trauner, *Org. Lett.* **2014**, *16*, 166–169.
   Total Synthesis of Sandresolide B and Amphilectolide.

3. E. Myers, E. Herrero-Gómez, I. Albrecht, J. Lachs, P. Mayer, M. Hanni, C. Ochsenfeld, D. Trauner, *J. Org. Chem.* **2014**, *79*, 9812–9817.
   Total Synthesis of the Proposed Structure of Trichodermatide A.

Table of contents

Summary

I. Toward the Total Synthesis of Maoecrystal V

The diterpenoid maoecrystal V (**I**) was discovered in the Chinese medical herb, *Isodon eriocalyx*. In comparison to related natural products, its molecular skeleton has been highly modified by bond-breaking and rearrangements, rendering access through total synthesis highly attractive (Figure I).

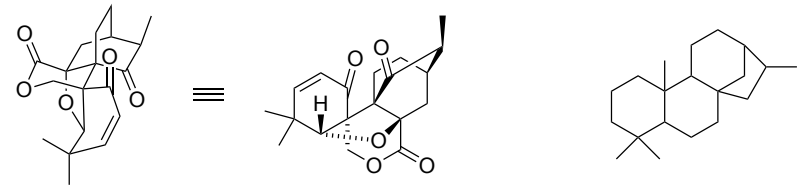
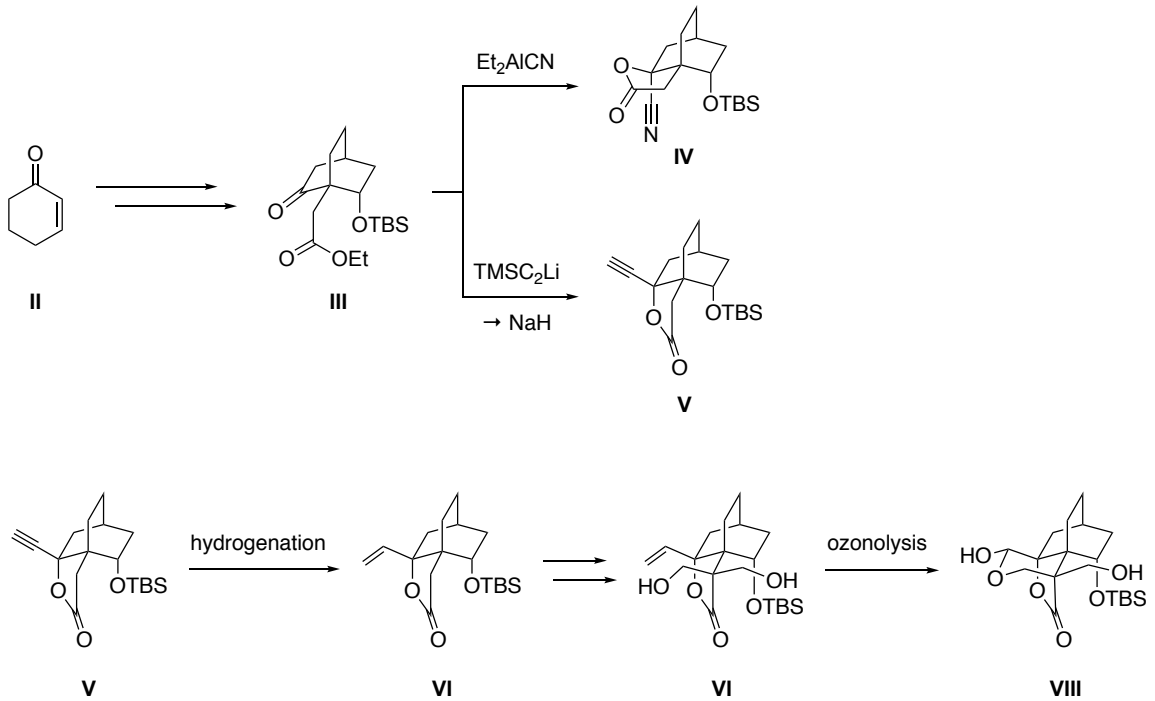


Figure I. Molecular structure of maoecrystal V, originating from an *ent*-kaurane

Synthetic efforts toward the dense architecture of the target molecule are described, based on a strategy employing small electrophiles and nucleophiles. The central elements of the synthesis comprise the formation of the central [2.2.2]bicyclooctanone by an intramolecular aldol addition, a stereoselective introduction of a C1 equivalent to form alkyne **V** as well as a double alkylation of lactone **VI** in the proximity of tetrasubstituted carbon atoms. The developed robust synthesis has led to advanced precursor **VIII** to the natural product (Scheme I).

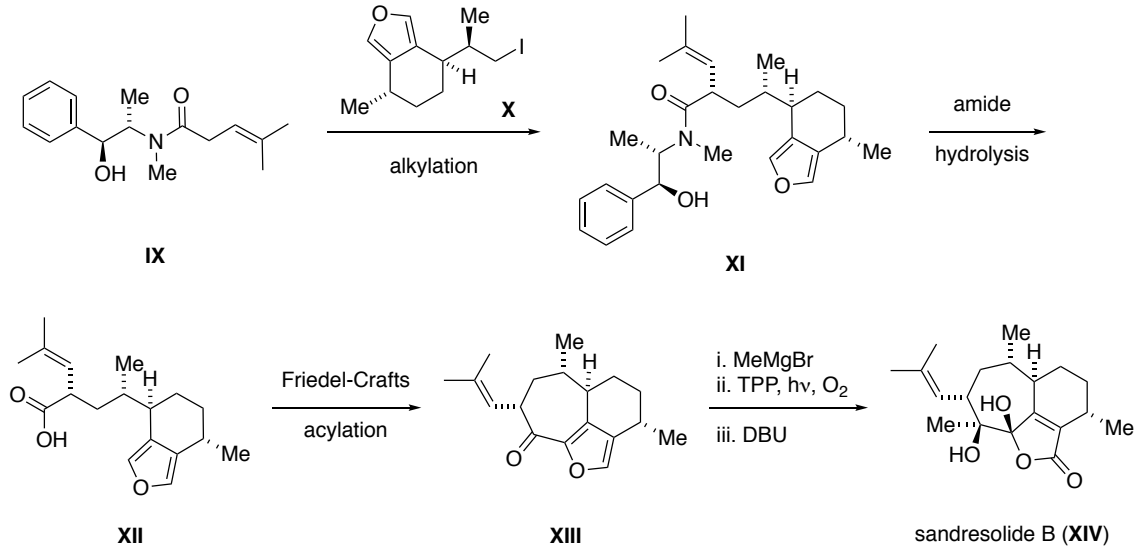


Scheme I. Studies toward the total synthesis of maoecrystal V

II. Total Synthesis of Sandresolide B and Toward the Total Synthesis of Caribenol A

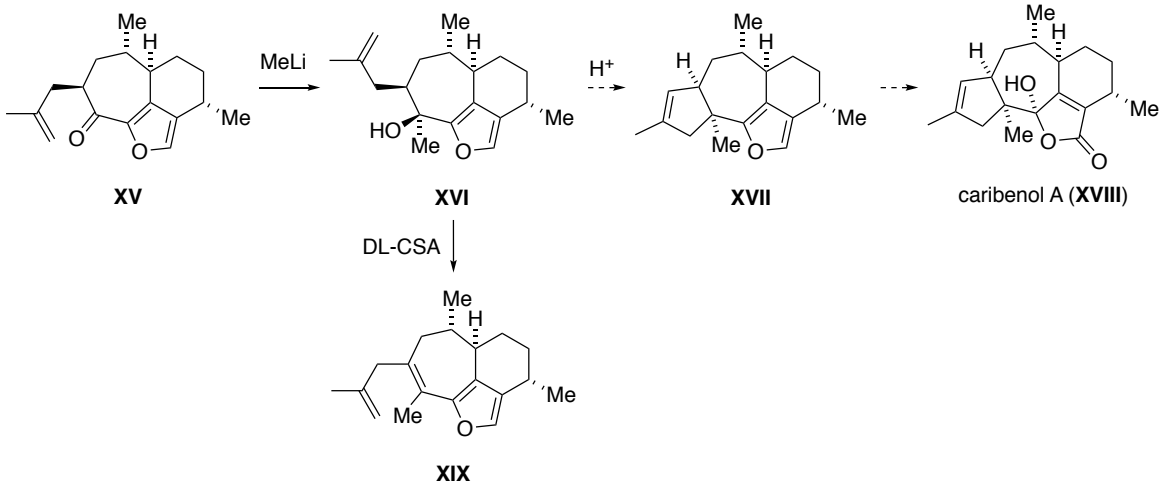
Sandresolide B (**XIV**) and caribenol A (**XVIII**) both were found in the soft coral, *Pseudopterogorgia elisabethae* that was collected in Caribbean Sea waters. Close structural resemblance of their carbon skeletons prompted the investigation of a common synthetic approach, which is described herein.

Following stereoselective Myers alkylation of advanced furan intermediate **X** as well as a later Friedel–Crafts acylation of **XII**, the implementation of developed biomimetic oxidation conditions led to the total synthesis of sandresolide B (**XIV**, Scheme II).



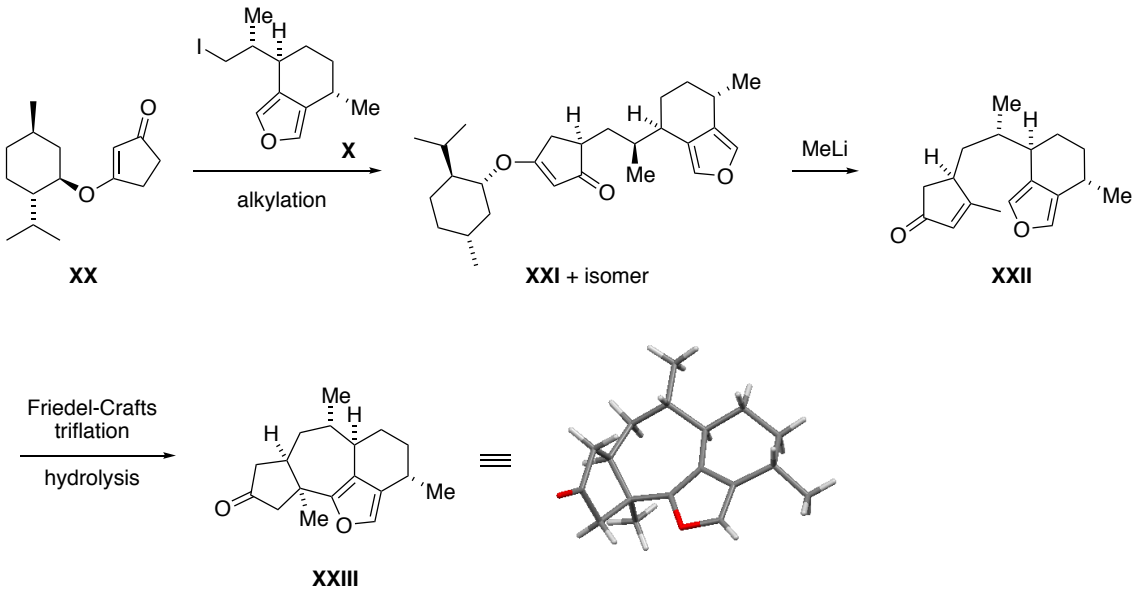
Scheme II. Total synthesis of sandresolide B

For caribenol A (**XVIII**), initially a strategy based on precursor **XV** prepared analogously to sandresolide B (**XIV**) was examined (Scheme III). The formation of the required five-membered ring via a carbenium ion which is intramolecularly trapped by the *exo* double bond of the side chain did not proceed, but led to elimination product **XIX**.



Scheme III. Initial synthetic approach toward caribenol A

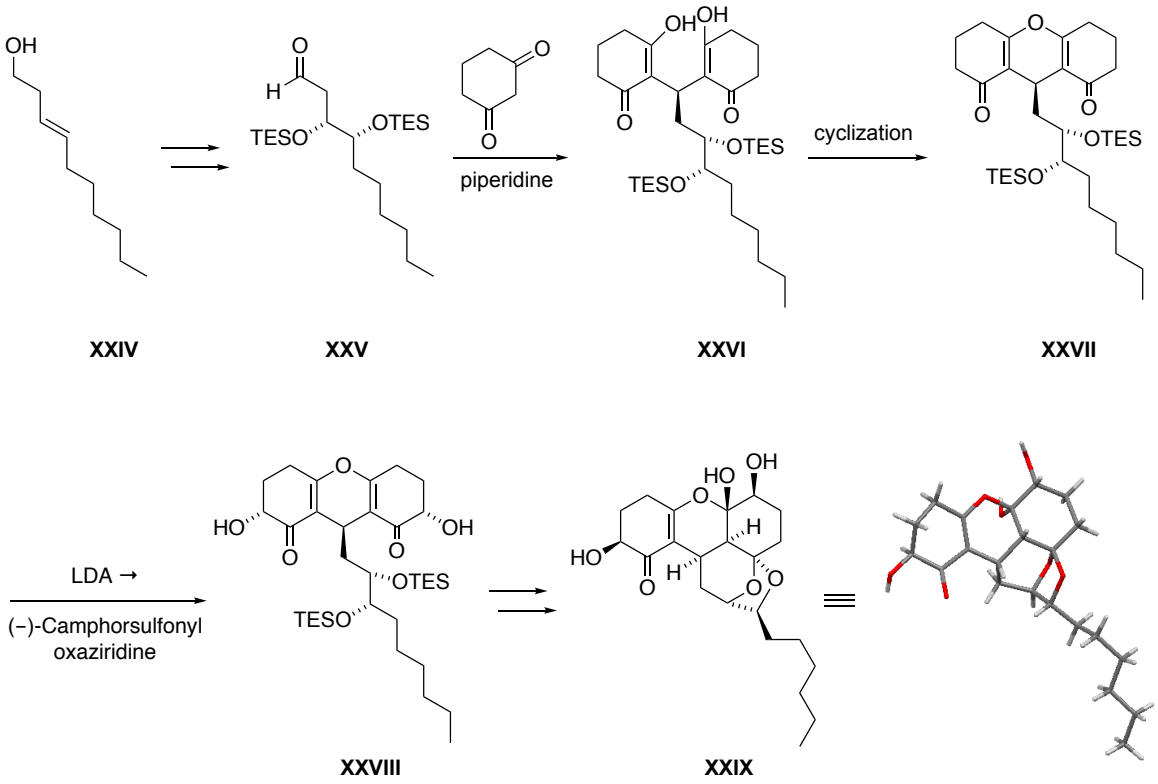
A revised approach has been elaborated, proceeding through auxiliary-controlled alkylation of enol ether **XX** and Stork–Danheiser reaction to yield cyclopentenone **XXII**. Eventually, the efficient construction of the carbon skeleton **XXIII** of caribenol A (**XVIII**) was accomplished via Friedel–Crafts triflation of **XXII** and verified by x-ray crystallographic measurements (Scheme IV).



Scheme IV. Revised synthetic approach toward caribenol A

III. Total Synthesis of the Proposed Structure of Trichodermatide A

Trichodermatide A (**XXIX**), an unprecedented polyketide, was isolated together with three further congeners from the marine-derived fungus, *Trichoderma reseii*. The synthesis of the published structure was approached via a highly symmetrical intermediate **XXVIII** that was formed by a Knoevenagel condensation/Michael addition cascade as well as stereoselective bis(α-hydroxylation). Conditions were developed to realize the isomerization of the symmetrical intermediate **XXVIII** to yield the reported structure of trichodermatide A (**XXIX**). X-ray crystallography confirmed the connectivity of the synthesized molecule (Scheme V).



Scheme V. Total synthesis of the proposed structure of Trichodermatide A

The NMR spectra of the synthesized material did not match those published for the natural product. We conclude that trichodermatide A is an isomer of the reported structure, as recently verified by the Hiroya group.

I. Toward the Total Synthesis of Maoecrystal V

1. Introduction

Throughout human history, plants and their extracts have been instrumental in medicinal applications.[1] Most of the efficacy is ascribed to the presence of secondary metabolites rather than other constituents commonly found in all types of organisms: building blocks, energy sources, enzymes, structural materials or hereditary elements.[2] Taking into account the metabolic cost for the biosynthesis of secondary metabolites, it is considered likely that plants produce these natural products to obtain an advantage when facing environmental challenges.[2,3] Particularly, secondary metabolites assist in the survival of the plant facing threats from herbivores, pathogens, other plants, and radical damage or even simply lack of nutrients. Previous research found that many secondary metabolites have a very specific effect in other organisms and often show high complementarity to enzyme receptors.[4]

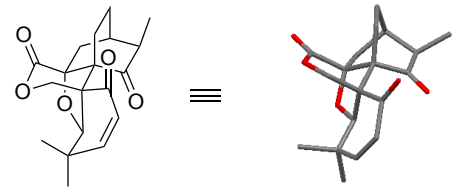
Hence, it is not surprising, that natural products find use in modern medicine and continue to be part of various therapies. Considering the period 1981–2014 alone, 51% of newly approved drugs were either natural products, their derivatives, mimics or molecules containing natural product pharmacophores.[5] The role as privileged scaffolds stems from the high structural diversity obtained via selective evolution according to their biological resources.[2] To explore further potential therapies, research programs directed into isolation and characterization of natural products aim at uncovering new substances. Selected examples will be discussed in the individual chapters of the thesis.

2. Isolation and Structure

With the isolation of over 1,000 *ent*-kauranoids, including over 700 new ones, the group of Prof. Han-Dong Sun at the Kunming Botanical Institute has contributed to research in identification of chemical substances from the *Isodon* genus of plants.[6] These plants are rich in terpenoids and their extracts have been used as traditional medicine for a long time,[7,8] hence raising the interest in this species and its natural product constituents.[9]

In 1994, upon search for bioactive compounds, 5 mg of maoecrystal V (**1**) were isolated from 11.9 kg of dried powdered leaves from *Isodon eriocalyx* (Dunn.) Hara. The structure was tentatively established based on extensive analysis of MS, IR and NMR data. These results were not published, as the isolationists sought to verify the tentative structure, which

would have implied an unprecedented rearrangement of the *ent*-kaurane carbon framework. Eventually, after a single crystal could be obtained, the unusual structure of maoecrystal V (**1**) could be confirmed by x-ray analysis and disclosed in 2004.[10]



maoecrystal V (**1**)

Figure 1.1. Molecular and x-ray structure of maoecrystal V

The absolute configuration was postulated based on closely related natural products that were previously isolated from the same botanical origin, where the relative configuration had been determined. Maoecrystal V (**1**) originates from an *ent*-kaurane structure, exhibiting a highly modified skeletal and oxidation pattern. The most distinct features include a [2.2.2]bicyclooctanone and a strained cyclic ether, all embedded within a system of five interwoven rings. The rings comprise a spirocyclic δ-lactone as well as a *trans*-fused cyclohexenone, which add to the compact framework. Moreover, the close proximity of three adjacent quaternary stereocenters makes maoecrystal V (**1**) a challenging target for total synthesis.

3. Maoecrystal Natural Products Family

To understand the remarkable position of maoecrystal V (**1**) among its congeners, the family of this natural product should be considered. The maoecrystal molecules are members of the *ent*-kaurane diterpenoids[11] originating from *I. eriocalyx*. As representatives of an important genus of the *Labiatae* (=*Lamiaceae*) family,[8] *Isodon* species have been the source of 11 groups of diterpenoids to date.[12] The members of the maoecrystal family can be assigned to four groups, classified by the oxidation and skeletal patterns. The first and largest category are the mono-7,20-epoxy-*ent*-kauranes, a subgroup of the C20-oxygenated-*ent*-kauranes: maoecrystal B–G (**2**–**7**),[13,14] I–K (**8**–**10**),[15,16] *epi*-maoecrystal P (**11**),[17] maoecrystal Q–T (**12**–**15**),[18,19] maoecrystal X (**16**) and Y (**17**).[20] Although the *ent*-kaurane carbon skeleton is intact, this group features an oxymethine at C20 forming an epoxy ring with C7. In addition, C15 is commonly oxidized to a ketone or a hydroxyl group.[12]

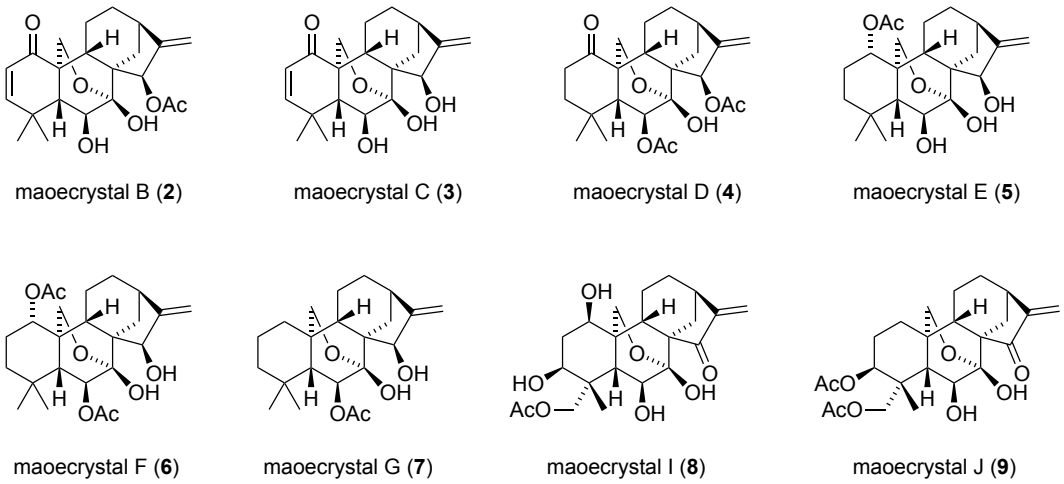


Figure 1.2. Structures of mono-7,20-epoxy-*ent*-kauranes, maoecrystal B–G, I and J

Maoecrystal I (**8**) and J (**9**) stand out in terms of their biological activities as both have been found to inhibit the root growth of lettuce seedlings. This effect was hypothetically attributed to the α-methylene group conjugated to a carbonyl group, acting as a Michael acceptor for the addition of a thiol-containing enzyme.[15] Furthermore, maoecrystal I (**8**) exhibited inhibition of the Wnt signaling pathway, as well as selective cytotoxicity toward the colon carcinoma cell lines SW480, HCT116 and HT29.[21]

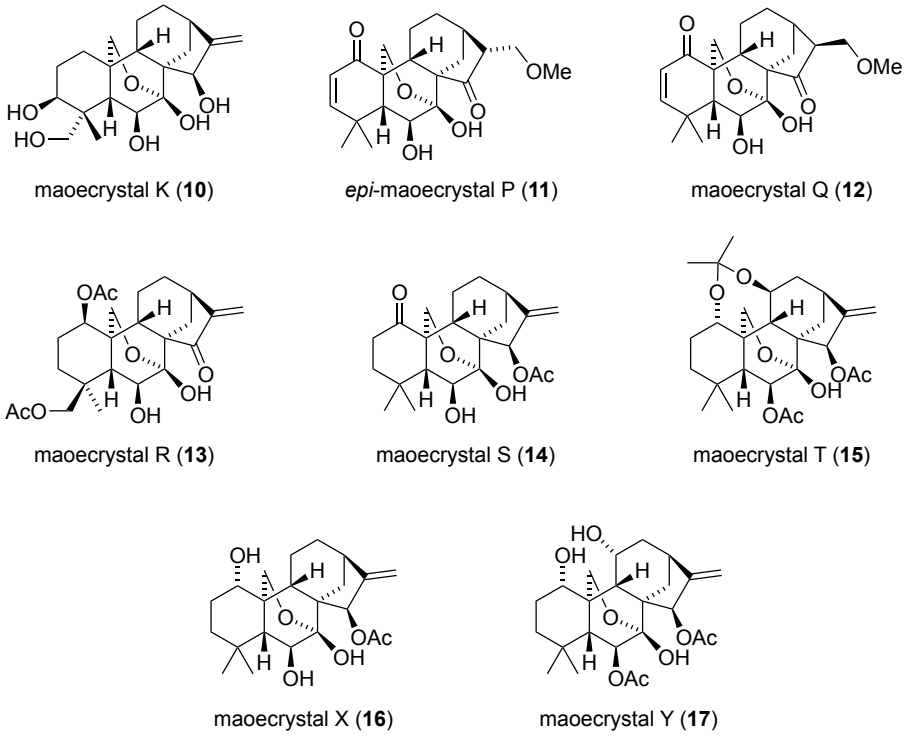


Figure 1.3. Structures of mono-7,20-epoxy-*ent*-kauranes, maoecrystal K, *epi*-P, Q–T, X and Y

Three maoecrystal molecules are part of mono-3,20-epoxy-*ent*-kauranes, the second subgroup of C20-oxygenated *ent*-kauranes: maoecrystal A (**18**),[13] U (**19**)[17] and P (**20**)[22]. Similar to the class of mono-7,20-epoxy-*ent*-kauranes, the positions C6, C7 and C15 are oxygenated. Differentiating structural features include a ketone group at C1 and C15, as well as oxygenation at C3.

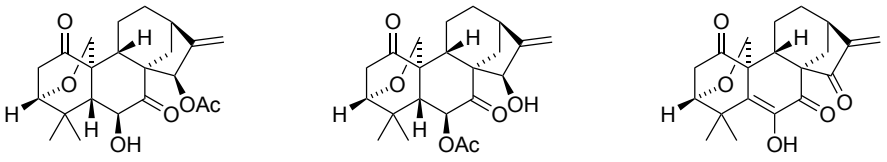
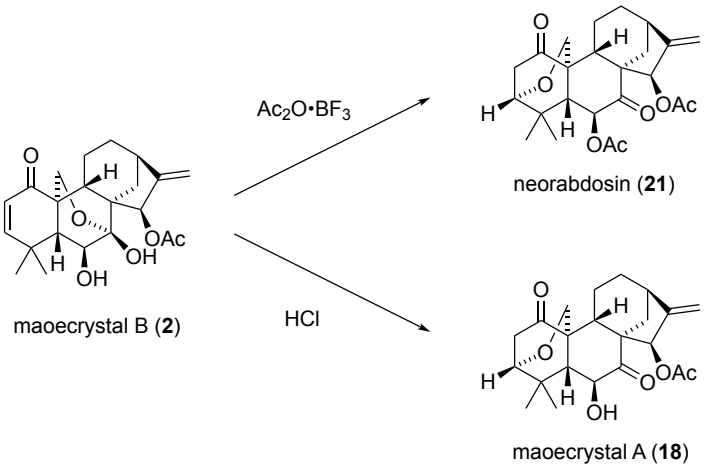


Figure 1.4. Structures of mono-3,20-epoxy-*ent*-kauranes maoecrystal A, U and P

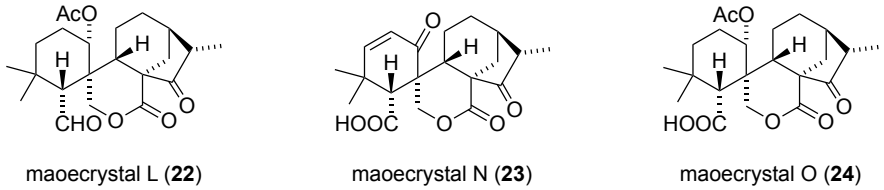
These natural products are believed to arise from 7,20-epoxy-*ent*-kauranoids containing an α,β-unsaturated ketone group, where an intramolecular Michael addition takes place at C3.[8] Evidence to support this biosynthetic assumption have been provided by Sun and co-workers, who converted maoecrystal B (**2**) into neorabdosin (**21**) in the presence of $Ac_2O{\cdot}BF_3$ and obtained maoecrystal A (**18**) when exposing maoecrystal B (**2**) to HCl.[13]



Scheme 1.1. Conversion of maoecrystal B into neorabdosin and maoecrystal A

With respect to bioactivity, maoecrystal P (**20**) showed significant cytotoxicity against human tumor T24 cells, a characteristic that is presumably due to the presence of the α,β-unsaturated ketone at C15.[22]

Another sizeable structural type is represented by the 6,7-seco-*ent*-kauranes. In this group, the C6–C7 bond has been oxidatively cleaved to provide spirolactone (7,20-lactone)-type natural products. The aldehyde that is anticipated to form at C6 during the biosynthesis, is present in maoecrystal L (**22**), or is further oxidized to a carboxyl group, as in maoecrystal N (**23**), *epi*-N (**25**), O (**24**) and W (**26**).[20,23] All members of this family feature a substructure composed of four rings and a ketone at C15 as well as a reduced olefin group at C16/C17.



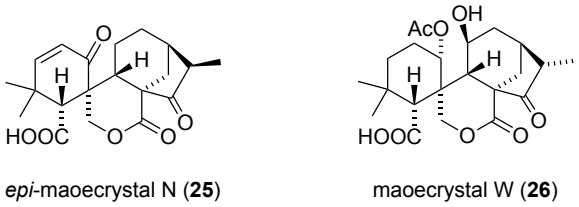


Figure 1.5. Structures of 6,7-seco-*ent*-kauranes, maoecrystal L, N, O *epi*-N and W

Maoecrystal M (**27**),[24] categorized into the class of *ent*-kauranoid dimers, bears a symmetrical structure, which is unique among dimers isolated from the genus *Isodon*. A [2+2]-cycloaddition reaction involving the exocyclic double bonds at C16/C17 has presumably afforded the unusual four-membered ring.[8]

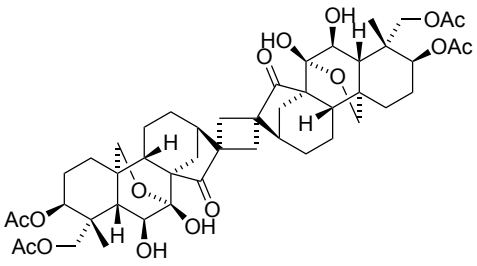
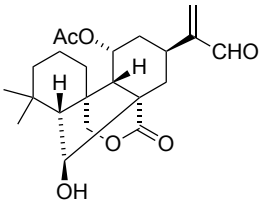


Figure 1.6. Structure of the *ent*-kauranoid dimer, maoecrystal M

The fourth structural class of the maoecrystal family, miscellaneous *ent*-kauranoids, encompasses those members that cannot easily be integrated into any of the other categories.[8] During biosynthesis, the carbon skeletons of both maoecrystal V (**1**)[10] and maoecrystal Z (**28**),[7] have undergone multiple modifications, consequently making these

natural products currently only accessible by total synthesis. Regarding maoecrystal Z (**28**), considerable cytotoxicity has been observed against human tumor cell lines K562, MCF7, A2780 with IC_{50} values of 2.90 μg/mL, 1.63 μg/mL, 1.45 μg/mL, respectively.[7] Noteworthy structural features are the dense tetracyclic carbon ring system and six vicinal stereogenic centers.



maoecrystal Z (**28**)

Figure 1.7. Structure of the miscellaneous *ent*-kauranoid, maoecrystal Z

Maoecrystal V (**1**) is referred to in the literature as the most modified naturally occurring *ent*-kauranoid from the genus *Isodon*, emphasizing its extraordinary status within the maoecrystal family. The unprecedented 6,7-seco-6-nor-15(8→9)-abeo-5,8-epoxy-*ent*-kaurene backbone includes only 19 carbon atoms, one carbon atom being lost during the biosynthesis of this diterpenoid.[10]

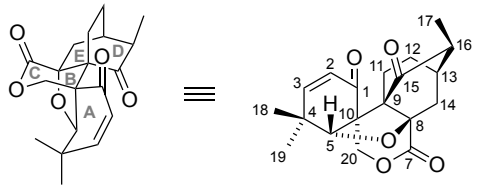
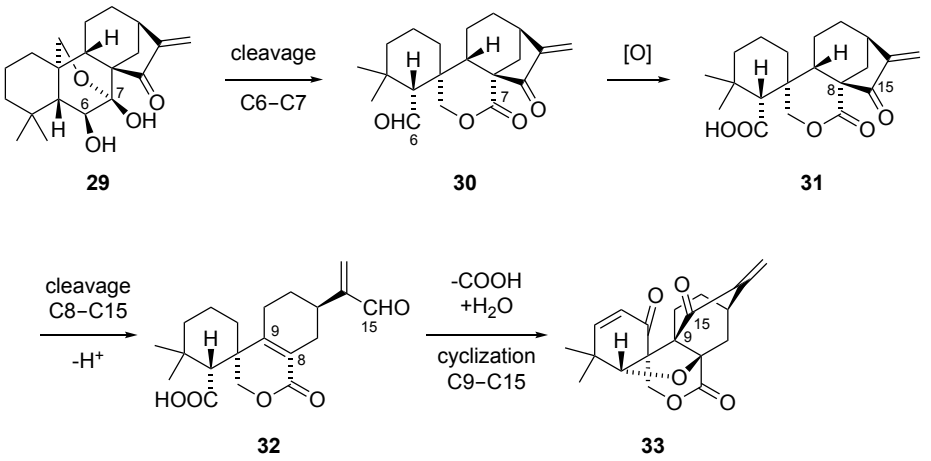


Figure 1.8. Structures and labelling of maoecrystal V

4. Biosynthetic Hypothesis

Sun and co-workers formulated a hypothesis on the biosynthetic pathway toward maoecrystal V (**1**), starting from prevailing 7,20-epoxy-*ent*-kaurane **29**.[7] In the initial step, oxidative cleavage of the C6–C7 bond would lead to spirolactone **30**. The aldehyde group would undergo further oxidation to carboxylic acid **31**. An additional cleavage of the C8–C15 bond would afford intermediate **32**. Subsequent decarboxylation in the presence of water would trigger a rearrangement to form the pentacyclic core structure of maoecrystal V (**33**).



Scheme 1.2. Proposed biosynthesis of maoecrystal V

5. Bioactivity

The bioactivity of maoecrystal V (**1**) was assessed *in vitro* with respect to cytotoxicity. Among the four human tumor cell lines K562, A549, BGC-823 and HeLa evaluated in the assay, low IC_{50} values of 0.02 µg/mL were obtained toward HeLa cells. The cytotoxic effect was observed at significantly lower concentrations than for the standard treatment *cis*-platin (IC_{50} of 0.99 µg/mL). Toward the other four cell lines investigated, very high IC_{50} values were measured (Table 1.1).[10] Therefore, maoecrystal V (**1**) can be regarded as non-cytotoxic toward those cell lines, indicating a highly selective activity profile.

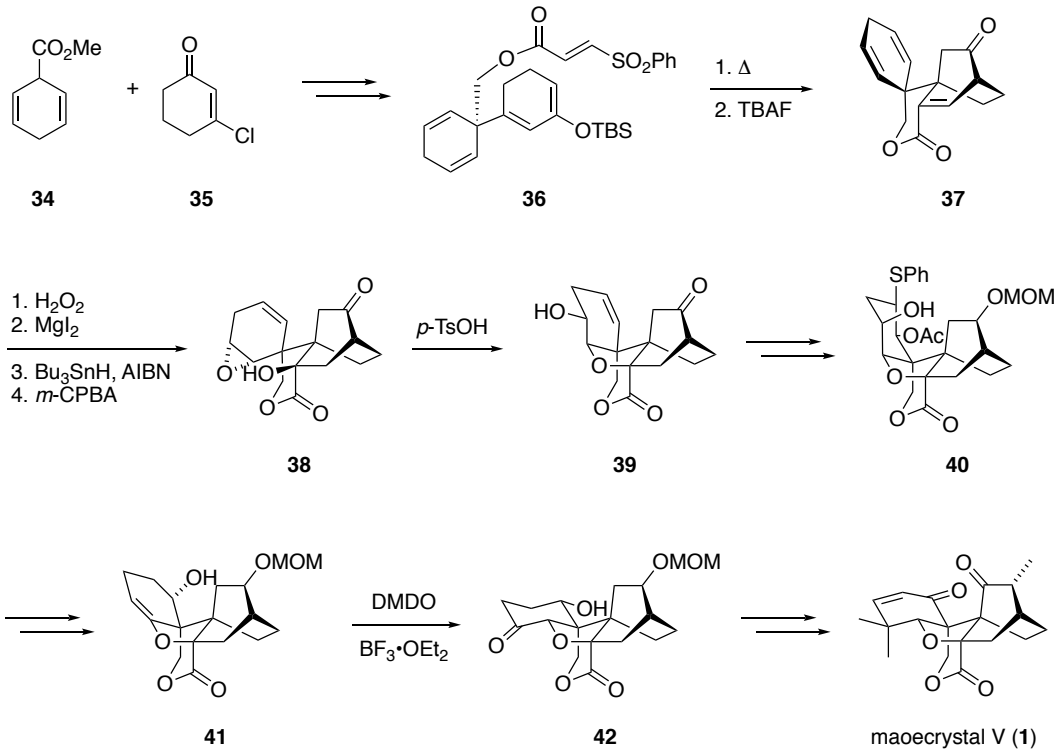
	IC_{50} (µg/mL)			
test substance	**K562**	**A549**	**BGC-823**	**HeLa**
maoecrystal V (**1**)	6.43×10^4	2.63×10^5	1.47×10^4	0.02
cis-platin	0.38	1.61	0.25	0.99

Table 1.1. Results of cytotoxicity screening for maoecrystal V

6. Review of Total Syntheses of Maoecrystal V

Maoecrystal V (**1**) displaying potent activity combined with low toxicity and a chemically interesting structure caused high interest in the development of a total synthesis, particularly as only small amounts were available from its natural source. In addition to our contributions to this research problem in 2010,[25] numerous approaches toward the target have been published,[26-37] with five research groups succeeding in completion of the total synthesis.[38-44] Four of these syntheses proceeded via a Diels–Alder strategy to address the challenge of constructing the [2.2.2]bicyclooctanone ring element. Here, only completed total syntheses are discussed.

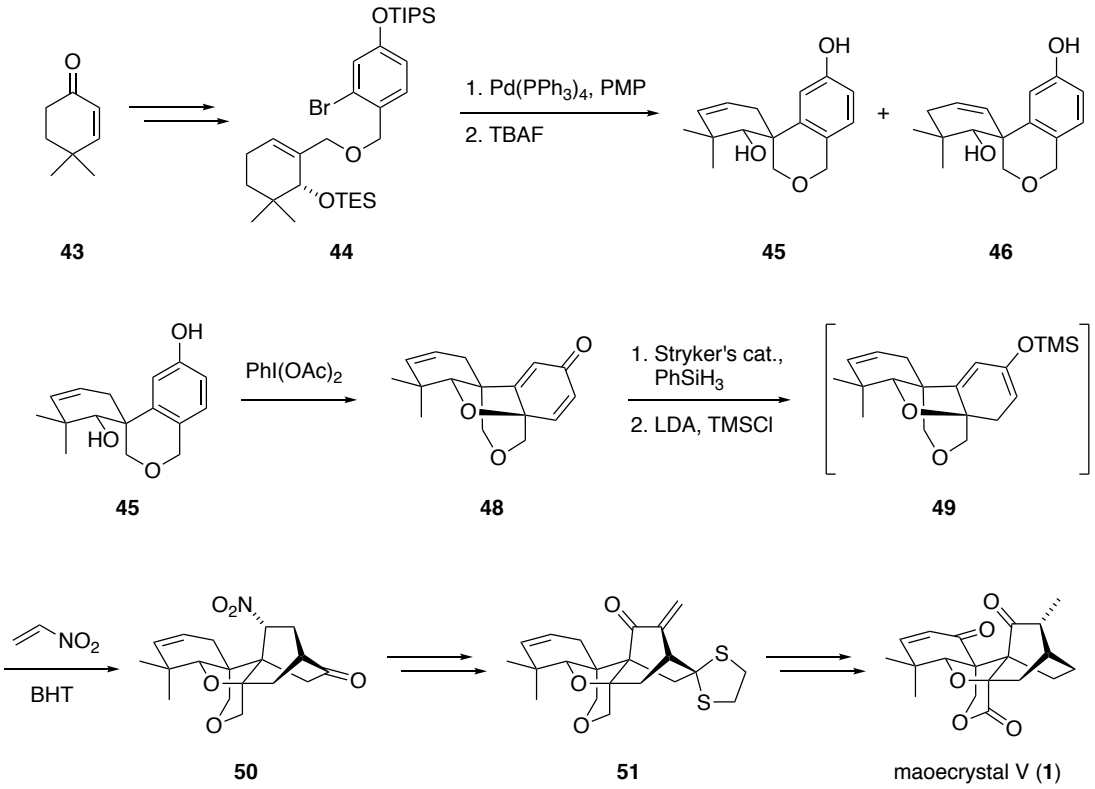
In 2012, Danishefsky accomplished the total synthesis of maoecrystal V (**1**) utilizing an intramolecular Diels–Alder reaction (IMDA) strategy for expedient access to the framework.[38] Starting from commercially available **34**, IMDA substrate **36** was synthesized, which upon heating underwent cycloaddition and elimination of phenylsulfinate, furnishing maoecrystal V core **37** including [2.2.2]bicyclooctane and lactone motifs (Scheme 1.3). Further modification by chemoselective epoxidation, oxirane opening and directed epoxidation gave rise to molecule **38**. In a key step, epoxide **38** underwent cyclization upon treatment with *p*-TsOH to furnish the tetrahydrofuranoid ring, albeit forming a *cis* junction with the cyclohexene. To obtain the correct connectivity for maoecrystal V (**1**), epimerization of the C5 stereocenter was effected by a series of transformations. *Exo*-glycal **41** was synthesized and subjected to DMDO and $BF_3 \cdot OEt_2$ initiating epoxidation followed by rearrangement to form compound **42** with the desired *trans* ring junction. Having the core system set-up, the synthesis of maoecrystal V (**1**) was completed by installation of the *gem*-dimethyl unsaturated ketone functionality on the cyclohexane ring as well as the ketone and α-methyl group of the [2.2.2]bicyclooctane. In summary, the synthesis of maoecrystal V (**1**) proceeded via an IMDA as key step to obtain four of the five rings present in the target molecule. Although the tetrahydrofuranoid was formed with the undesired ring fusion, a correction could be effected.



Scheme 1.3. Danishefsky group's total synthesis of maoecrystal V

In 2014, the Thomson group reported an enantioselective synthesis of maoecrystal V (**1**) based on a Diels–Alder approach to form the key [2.2.2]bicyclooctane motif.[39] This transformation was carried out at an advanced stage of the synthesis, as late installation of the THF ring with the bicyclooctane already in place proved challenging in previous studies. The first key step in the synthesis was a diastereoselective formation of the spirocenter at C10 by Heck reaction of precursor **44**, which in turn could be obtained from dimethyl-cyclohexenone **43** (Scheme 1.4). Subjection of TES-protected **44** to $Pd(PPh_3)_4$ and penta-methylpiperidine (PMP) followed by TBAF yielded two alkene isomers, the major product **45** carrying a double bond in the 2,3-position. Interestingly, only isomer **45** could undergo oxidative cyclodearomatization, forming the required tetrahydrofuran ring upon treatment with $PhI(OAc)_2$. Under the same reaction conditions, oxidation of the minor isomer **46** was observed. Completion of the maoecrystal V (**1**) backbone was achieved by generating enol ether **49**, which was reacted with nitroethylene in a Diels–Alder cycloaddition yielding [2.2.2]bicyclooctane **50** as a single diastereomer. Adjustment of functionalities of the carbocyclic core led to maoecrystal V (**1**) in six further steps, including two late-stage C–H oxidations. As in initial investigations, α-methylation of a C15 ketone formed a mixture of inseparable epimers, Thomson and co-workers chose to prepare *exo*-enone **51**. Reduction of the methylene group by $NaBH_4$ from the accessible face opposite of the dithiane gave

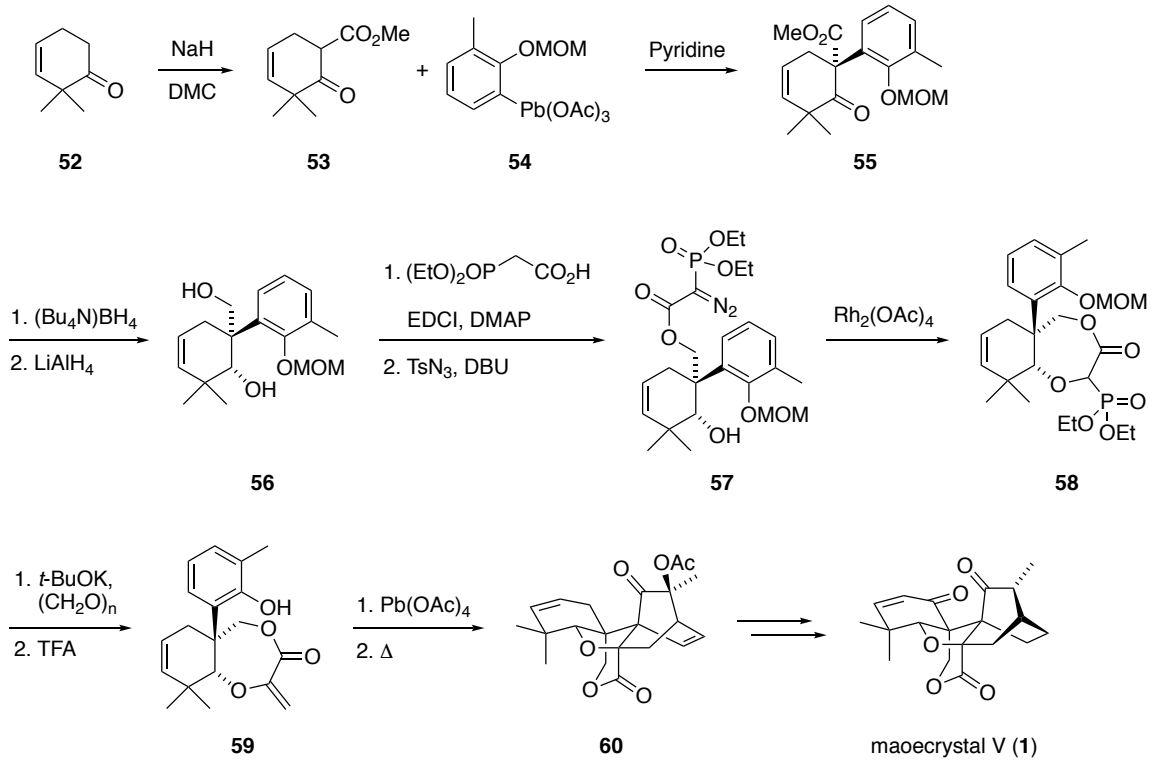
rise to the desired diastereomer as the main product, which was carried on to maoecrystal V (**1**).



Scheme 1.4. Thomson group's total synthesis of maoecrystal V

The first total synthesis of maoecrystal V (**1**) was accomplished in 2010 by Yang and co-workers, who built up the intertwined ring system of the target molecule through IMDA of an elegantly designed precursor.[40,41] To construct the quaternary center at C10, β-ketoester **53**, available from ketone **52**, was subjected to an oxidative arylation with lead compound **54** (Scheme 1.5). The envisioned reduction to *cis*-diol **56** could be implemented stepwise by first obtaining the desired C5 alcohol by reaction with Bu_4NBH_4, then reducing the ester with $LiAlH_4$. Esterification of the primary alcohol and treatment with TsN_3 furnished diazophosphate **57**. In a key step, **57** underwent O–H bond insertion to give phosphonate ester **58**, which could be transformed into enone **59** by Horner–Wadsworth–Emmons reaction with paraformaldehyde, followed by MOM deprotection. Enone **59** set the stage for oxidative dearomatization in the presence of $Pb(OAc)_4$ to diastereomeric hydroquinone acetates, which readily underwent IMDA to furnish [2.2.2]bicyclooctane, lactone and tetrahydrofurane functionalities of the target molecule in one transformation. Although the cycloaddition was facially unselective, desired product **60** could be isolated in 36% yield. Radical functionalization of the A ring, cleavage of the acetoxy group, reduction of the

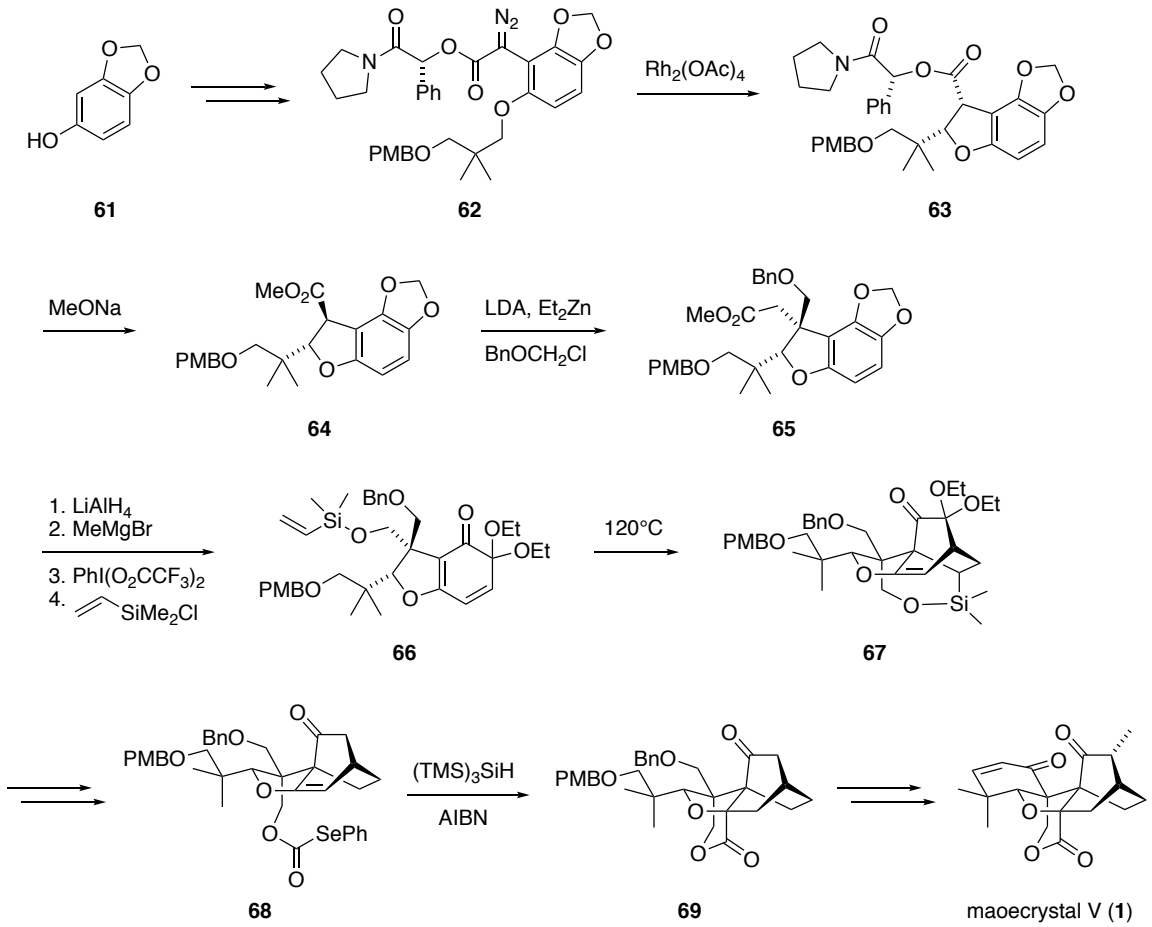
alkene, and oxidation resulted in the C16 epimer of maoecrystal V (**1**). Equilibration of misconfigured stereocenter in *epi*-maoecrystal V with DBU led to a 1:1 mixture of epimers, from which maoecrystal V (**1**) could be isolated, thus completing a concise synthesis.



Scheme 1.5. Yang group's total synthesis of maoecrystal V

In 2014, Zakarian and co-workers successfully addressed two major challenges: formation of the [2.2.2]bicyclooctanone and installation of the strained furan.[42,43] As an enantio-determining step, early installation of the furan by Rh-catalyzed C–H insertion was envisioned. After initial attempts by means of chiral catalyst systems, modification with chiral auxiliaries achieved the desired results. The synthesis started from sesamol (**61**), which was transformed into diazo compound **62** (Scheme 1.6). Pyrrolamides of mandelic acid were found to be effective in controlling diastereoselectivity in the C–H insertion and, in the presence of Rh(II) acetate, furan **63** was formed with 84% *ee*. Full epimerization of C10 was achieved by methanolysis, which also led to cleavage of the amide. The quaternary stereocenter was installed by reacting a zinc enolate, generated from ester **64**, with benzyl chloromethyl ether. Constructing the [2.2.2]bicyclooctanone unit was carried out through an IMDA, where the dienophile was an ethylene equivalent tethered to the molecule. The required substrate was prepared by $PhI(O_2CCF_3)_2$ oxidation of the phenol obtained after deprotection of compound **65** and reaction with vinyldimethylchlorosilane. Upon heating,

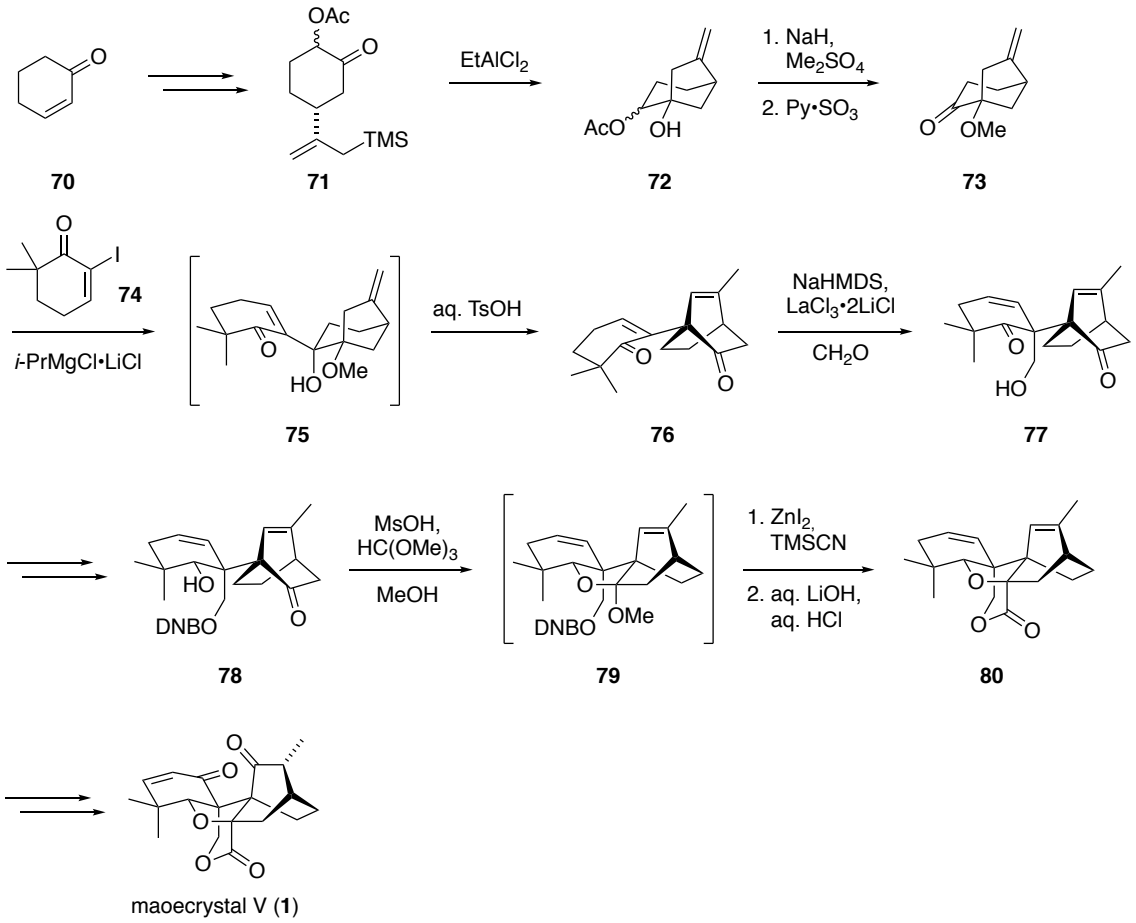
cycloaddition delivered the required key structural element in 96% yield. The silyl tether and both ethoxy groups were removed by subsequent transformations. Installation of the required lactone was envisioned to be effected by radical cyclization: the required seleno-carbonate **68** was formed and subjected to $(TMS)_3SiH$/AIBN, where radical cyclization proved successful to obtain the anticipated lactone **69**. Completion of the synthesis included diastereoselective methylation of the bicyclooctanone and installation of the cyclo-hexenone. The optical rotation values were in accordance with the measurements published by the isolationists, confirming the assigned absolute configuration.



Scheme 1.6. Zakarian group's total synthesis of maoecrystal V

In contrast to previously published total syntheses of maoecrystal V (**1**), in 2016, Baran and co-workers reported their second-generation approach to establish the [2.2.2]bicyclooctane framework through a pinacol-type rearrangement, analogous to the proposed biosynthetic route.[44] Allylsilane **71**, accessed from cyclohexenone (**70**), underwent a Baldwin-disfavored cyclization uniquely in the presence of $EtAlCl_2$, a large number of Lewis acids being screened (Scheme 1.7). The formed [3.2.1]bicycle **72** was methylated and oxidized to obtain

key precursor **73**. Addition of dimethylcyclohexenone fragment **74**, which contributes all of the carbon atoms for the maoecrystal V A ring, could be achieved by using the corresponding Grignard reagent. At this stage, intermediate **75** was subjected to aqueous TsOH and the remarkable 1,2-shift led to the desired [2.2.2]bicyclooctanone, while simultaneously the methylene double bond isomerized into the endocyclic position. Installation of the final quarternary center could be realized chemoselectively by the addition of $LaCl_3 \cdot 2LiCl$ to the 1,4-sodium enolate of **76**, favoring aldol reaction with formaldehyde at the sterically hindered C10 position. Subsequent modifications allowed selective reduction of the C5 ketone to afford alcohol **78**. Treatment of compound **78** with $CH(OMe)_3$/MeOH and methanesulfonic acid formed the furanoid ring, which reacted with ZnI_2 and TMSCN to introduce the final carbon atom. The lactone ring was formed under hydrolytic conditions, furnishing the natural product's backbone. To complete the synthesis, an oxidation/iodination sequence installed the required oxidation and unsaturation patterns.



Scheme 1.7. Baran group's total synthesis of maoecrystal V

The synthetic maoecrystal V (**1**) was subjected to cytotoxicity screenings against various cancer cell lines, but showed no significant activity against any cell line, including HeLa.[44] These observations support the finding that a cytotoxic mode of action is observed in compounds carrying an enone with exomethylene.[9]

The accomplished syntheses not only provided enough material for more thorough biological testing, but would also open up avenues for the synthesis of potentially more active non-natural analogues of the natural product.

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7. Results

7.1. Toward the Total Synthesis of Maoecrystal V: Establishment of Contiguous Quaternary Stereocenters

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Within the published results, work in the context of the thesis comprises the elaboration starting from acetonide 9.

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Toward the Total Synthesis of Maoecrystal V: Establishment of Contiguous Quaternary Stereocenters

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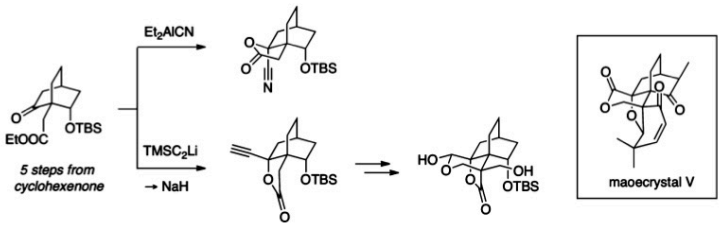
Received October 9, 2010

ABSTRACT

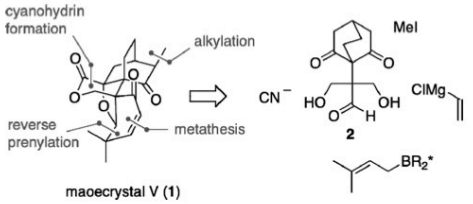


A synthetic strategy toward maoecrystal V has been identified. It has been shaped by the necessity to maneuver in sterically hindered molecular environments.

Maoecrystal V is a recently reported natural product with several unusual and attractive features (Scheme 1). Following its isolation from the Chinese medicinal herb *Isodon eriocalyx* by Sun and co-workers, it was shown to have significant cytotoxic properties, in particular against HeLa cancer cells.[1] The molecule appears to be a rearranged and oxidatively modified *ent*-kaurane diterpene that features a dense network of interwoven rings including a six-membered lactone, a tetrahydrofuran, a cyclohexenone, and a bicyclo[2.2.2]octane moiety. This ring system contains four highly substituted carbon atoms, three of which are contiguous, making maoecrystal V one of the most sterically compressed natural products known.

As a consequence, maoecrystal V has received considerable attention in the synthetic community. To date, five synthetic approaches have been published, all of which rely on a Diels−Alder reaction for the establishment of the bicyclo[2.2.2]octane ring system.[2]

Scheme 1. Structure and Retrosynthetic Analysis of Maoecrystal V



Herein, we report an alternative synthetic strategy, which employs a range of small nucleophiles and electrophiles to

(1) Li, S. H.; Wang, J.; Niu, X. M.; Shen, Y. H.; Zhang, H. J.; Sun, H. D.; Li, M. L.; Tian, Q. E.; Lu, Y.; Peng, C.; Zheng, Q. T. *Org. Lett.* **2004**, *6*, 4327–4330.

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deal with the steric hindrance of the maoecrystal ring system. Thus far, our efforts have yielded a structure with four of the five rings of maoecrystal V in place and, most importantly, the two contiguous quaternary carbons and adjacent tertiary alcohol moiety that make this natural product such a challenging synthetic target.

Our initial retrosynthetic analysis centered around the highly symmetric bicyclo[2.2.2]octane derivative **2**, which already incorporates two of the three quaternary carbons of the target molecule (Scheme 1). We envisioned an asymmetric reverse prenylation,[3] cyanohydrin formation, and olefin metathesis[4] as key components of our synthetic plan.

The synthesis of the bicyclo[2.2.2]octane system started with a diastereomeric mixture of cyclohexenones **3**, easily obtained via alkylation of cyclohexenone with ethyl bromoacetate, followed by Sakurai allylation.[5] Ozonolysis of **3** yielded the corresponding aldehydes **4**, which, when subjected to acidic conditions, cleanly underwent intramolecular aldol addition to afford hydroxy bicyclo[2.2.2]octanone **5** as a 7:1 mixture of *endo* and *exo* isomers.[6] Following silylation, this mixture could be separated, and the major diastereomer **6** was further processed. It should be noted that an asymmetric version of this general synthetic approach to bicyclo[2.2.2]octanes has been developed by Kitahara et al.[5]

At this stage, we decided to explore a departure from the retrosynthetic analysis outlined above and attempt the installation of the requisite tertiary alcohol through cyanohydrin formation. Treatment of ketone **6** with Nagata's reagent (Et_2AlCN)[7] not only resulted in the formation of the cyanohydrin but also effected transesterification to yield lactone **7**.

Unfortunately, X-ray analysis of this product determined that the undesired diastereomer had formed (Figure 1). Since

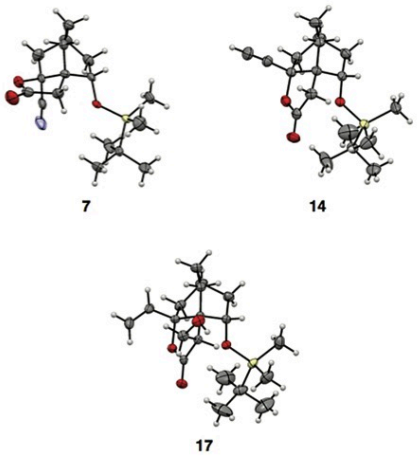
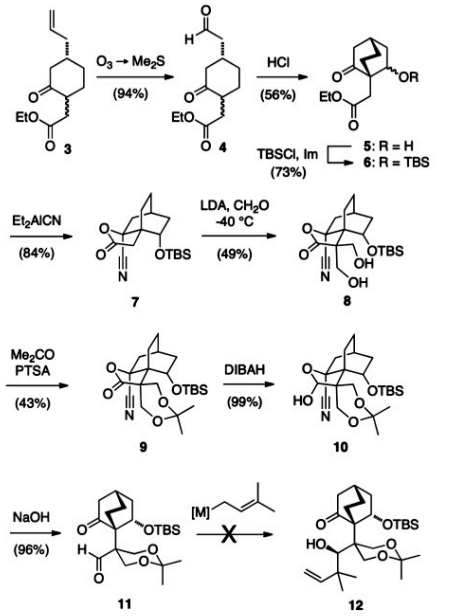


Figure 1. X-ray structures of key bicyclo[2.2.2.]octanes **7**, **14**, and **17**.

the addition of cyanide under Nagata conditions is known to be reversible,[7b] this result could reflect the relative thermodynamic stability of the initially formed cyanohydrins.

With lactone **7** in hand, we investigated the installment of the second quaternary carbon through double aldol addition to formaldehyde, a very small electrophile.[8] Ultimately, this was effected by gradually warming **7** with a large excess of LDA and formaldehyde, the latter obtained through thermal depolymerization of dry paraformaldehyde. Under these conditions, 1,3-diol **8** was isolated in 49% yield (Scheme 2). This remarkable reaction presumably proceeds

Scheme 2. Opening Sequence and First-Generation Approach to Maoecrystal V



through an initial deprotonation and aldol addition, followed by what is, in essence, a Fráter−Seebach alkylation.[9] Pro-

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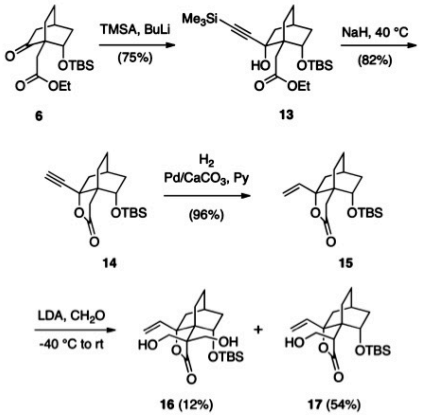
tection of the resulting diol **8** as an acetal yielded **9**, which could be selectively reduced with DIBAH[10] to furnish the lactol **10**. Upon treatment with 2 M aqueous NaOH, the lactol moiety underwent fragmentation with loss of cyanide to afford keto aldehyde **11**. The stereochemically undesired cyanohydrin in **7** therefore serves as a protecting group for a carbonyl group. Since **11** resembles the symmetrical aldehyde **2** (cf. Scheme 1), we decided to explore its participation in a reverse prenylation reaction. To date, however, we have not been able to effect this transformation.

While these studies were ongoing, we investigated the addition of other small nucleophiles to ketone **6** to overcome the undesired stereoselectivity of the Nagata cyanohydrin formation (Scheme 3).

Scheme 3. Overcoming the Undesired Stereoselectivity

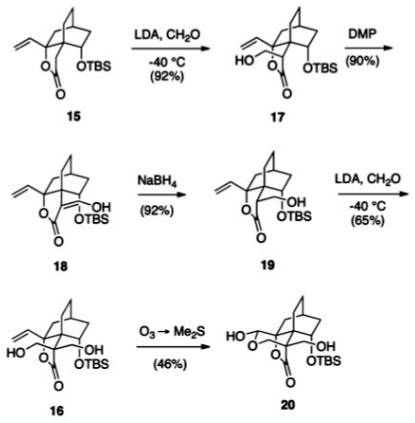


Potassium cyanide, TMSCN, and 2-furyllithium gave unsatisfactory results, and vinyl magnesium bromide or the corresponding organocerium reagent proved unreactive. The slender anion of TMS-acetylene (TMSA), however, added cleanly to the bicyclic ketone **6** and, this time, gave only the desired stereoisomer **13**.[11] Treatment of the tertiary alcohol with NaH resulted in lactone formation with concomitant desilylation to afford tricyclic lactone **14**, the structure of which was confirmed by X-ray crystallography (Figure 1). Lindlar reduction of **14** gave lactone **15**, whose vinyl group serves as a synthetic equivalent of a carbonyl group.

Unfortunately, the double aldol addition of **15** to formaldehyde proved more challenging than the corresponding transformation of **7**, presumably due to its different steric environment. Under optimized conditions, we only obtained low yields of the 1,3-diol **16**, together with larger amounts of the monoaddition product **17**. The structure of **17** was again established by X-ray crystallography (Figure 1).

Given the low yield of the double addition product **16**, we decided to take a stepwise approach (Scheme 4). A single

Scheme 4. Stepwise Approach to the Two-Fold Aldol Addition



hydroxymethylation of lactone **15** under carefully controlled conditions (−40 °C) gave aldol addition product **17** in good yield and as a single diastereomer. The high diastereoselectivity of this reaction is probably due to the "open-book effect" of the 1-oxabicyclo[4.3.0]nonane subunit, which results in addition from the convex side.

All attempts to carry out a second addition using **17** as a starting material, however, gave unsatisfactory results. We reasoned that this was due to the considerable steric hindrance that would be encountered in the formation of the requisite dianion through double deprotonation of **17**. We therefore oxidized **17** to the corresponding 1,3-dicarbonyl compound, which primarily exists in its enolized form **18**. Once again, steric hindrance interfered with a subsequent attempt to C-alkylate. Selective reduction of **18** with sodium borohydride, however, was possible and gave hydroxymethyl lactone **19**, a diastereomer of **17**, as a single isomer. With the α-proton now more accessible, Fráter−Seebach-type double deprotonation and hydroxymethylation proceeded with relative ease to yield **16** in satisfactory yield.

Ozonolysis of **16** yielded lactol/lactone **20** as a single diastereomer. This compound features the two contiguous quaternary carbons and the adjacent tertiary alcohol (in the form of a lactone) characteristic of maoecrystal V. It also provides three functional handles in three different oxidation states that could be used to carry on the synthesis.

In summary, we have outlined a synthetic strategy toward maoecrystal V that addresses issues that any synthesis of this

(9) (a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828. (b) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277. (c) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197–200.

(10) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871–8872.

(11) (a) Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185–1191. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624.

fascinating target will face. So far, our approach has yielded an advanced intermediate, compound **20**, which has suitably differentiated functional groups and features four of the five rings of the target. Attempts to streamline our synthetic route and render it asymmetric are currently underway. The continuation of our synthetic endeavor will most likely require additional strategies to overcome steric hindrance, such as high-pressure reactions or intramolecularization.

Acknowledgment. This work was generously supported by the Fonds der Chemischen Industrie (graduate scholarship for I.B.) The help of Braulio Vargas Möller and Harald Budde (undergraduate research internship) is gratefully acknowledged.

Note Added in Proof. Since this paper was accepted, the first total synthesis of maoecrystal V has been published, also following a Diels−Alder approach: Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745−16746.

Note Added after ASAP Publication. Figure 1 contained an error in the version published ASAP November 18, 2010; the correct version reposted December 10, 2010.

Supporting Information Available: Spectroscopic and analytical data for compounds **3**−**20**. Crystallographic data for compounds **7**, **14**, and **17** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 796309, 796310, and 796311, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

OL102446U

Toward the Total Synthesis of Maoecrystal V: Establishment of Contiguous Quaternary Stereocenters

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Supporting Information

General Experimental Details

Unless otherwise specified, all reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was performed using the analytical grade solvents indicated and Merck silica gel (40-63 μm, 60 Å) as the stationary phase. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating: potassium permanganate and ceric ammonium molybdate. Tetrahydrofurane (THF), and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Diiosopropylamine was distilled from and stored over CaH_2. *n*-Butyllithium (*n*-BuLi) was titrated with diphenylacetic acid prior to use. All other solvents, as well as starting materials and reagents were used without further purification from commercial sources.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) spectra were recorded at 18 °C in base filtered $CDCl_3$ on Varian Mercury spectrometers operating at 300 Hz, 400 MHz and 600 MHz for proton nuclei (75 MHz, 100 MHz and

150 MHz for carbon nuclei). For ^{1}H NMR spectra signals arising from residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemicals shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defiened as: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet br=broad or combinations of the above. The residual $CHCl_3$ peak (δ 7.26) was used as reference for ^{1}H NMR spectra. The central peak (δ 77.16) of the $CDCl_3$ 'triplet' was used as reference for proton-decoupled ^{13}C NMR spectra.

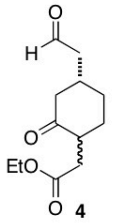
Low- and high-resolution electrospray (ESI) mass spectra were obtained on a Varian MAT 711 MS instrument operating in either positive or negative ionization modes. Fast atom bombardment (FAB) mass spectra were measured on a VG ProSpec Mass Spectrometer.

Melting points were measured on a Büchi melting point B-540 system and are uncorrected.

X-ray analysis measurements of **7** were made on a Bruker APEX^{1} CCD area detector with graphite monochromated Mo-K_α radiation (λ = 0.71069 Å). The data collections for **14** and **17** were performed on an Oxford Diffraction Xcalibur diffractometer at 173 K using graphite monochromated Mo-K_α-radiation (λ = 0.71073 Å).

Experimental Procedures

Aldehydes 4



4

Ozone was bubbled into a mixture of **3** (26.5 g, 118 mmol), $NaHCO_3$ (0.33g, 4 mmol), CH_2Cl_2 (200 mL) and MeOH (200 mL) at −78 °C until a blue color developed. Excess ozone was then removed by bubbling N_2 through the mixture. Me_2S (14.5 mL, 12.2 g, 197 mmol) was added and the mixture was left to stir overnight at rt The mixture was then concentrated *in vacuo* and purified by flash

column chromatography (hexanes/EtOAc = 2/1) to give 25.3 g (112 mmol, 94 %) of **4** as a colorless oil.

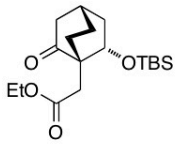
TLC: R_f = 0.22 (hexanes/EtOAc = 2/1) [$KMnO_4$]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, ^3J = 7.1 Hz, 3H), 1.35-2.92 (m, 12H,), 4.08 (q, ^3J = 7.1 Hz, 2H), 9.68-9.72 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, only shifts of major diastereomer are listed): δ = 14.2, 31.6, 32.2, 34.1, 34.4, 46.4, 47.5, 50.4, 60.5, 172.4, 200.5, 208.9.

HRMS (FAB+): calcd for $C_{12}H_{18}O_4Na$ [$(M+Na)^+$]: 249.1097, found: 249.1098

***t*-Butyldimethylsilyloxybicyclo[2.2.2]octanone 6**



6

A mixture of **4** (6.27 g, 27.7 mmol), 2 N HCl aq (5.54 mL, 11.1 mmol), and acetone (105 mL) was heated at reflux for 10 min. After cooling, $NaHCO_3$ (0.931 g, 11.1 mmol) and water (2.5 mL) were added and the mixture was concentrated *in vacuo*. The residue was extracted with ethyl ether (3 × 40 mL), washed with saturated $NaHCO_3$ aq (10 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a mixture of diastereomers **5** and **5a** (3.54 g, 15.6 mmol, 56%), which was carried on without further purification.

A solution of the hydroxybicyclo[2.2.2]octanones **5** and **5a** obtained above (3.76 g 16.6 mmol), *t*-butyldimethylsilyl chloride (3.0 g, 19.9 mmol) and imidazole (1.70 g, 24.9 mmol) in DMF (20 mL) was stirred overnight at rt The mixture was poured into water (200 mL) and extracted with ethyl ether (3 × 100 mL). The organic phase was washed with 2 N HCl aq (100 mL), water (3 × 80 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 19/1) to give 3.65 g **6** (10.7 mmol, 65%) as well as 0.50 g **6a** (1.46 mmol, 9%), both as colorless oils. 0.46 g (2.05 mmol, 12%) of the starting materials **5** and **5a** could be reisolated.

6:

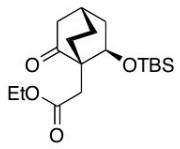
TLC: R_f = 0.55 (hexanes/EtOAc = 5/1) [$KMnO_4$]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.04 (s, 3H), 0.82 (s, 9H), 1.24 (t, ^3J = 7.1 Hz, 3H), 1.48-1.57 (m, 1H), 1.60-1.74 (m, 3H), 1.86 (ddd, ^2J = 13.9 Hz, ^3J = 11.3, 7.1 Hz, 1H), 2.09 (ddt, ^2J = 13.9 Hz, ^3J = 8.2, 2.2 Hz, 1H), 2.17-2.24 (m, 2H), 2.31-2.38 (m, 1H), 2.51 (d, ^2J = 16.0 Hz, 1H), .2.61 (d, ^2J = 16.0 Hz, 1H), 4.10 (q, ^3J = 7.1 Hz, 2H), 4.33 (d, ^3J = 7.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.1, 14.4, 17.9, 24.0, 25.3, 25.8, 27.5, 33.9, 37.6, 44.0, 50.9, 60.2, 70.2, 172.5, 212.8.

HRMS (FAB+): calcd for $C_{18}H_{32}O_4SiNa$ [$(M+Na)^+$]: 363.1962, found: 363.1963

6a:



6a

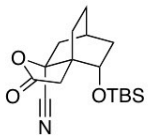
TLC: R_f = 0.50 (hexanes/EtOAc = 5/1) [$KMnO_4$]

^{1}H-NMR (400 MHz, $CDCl_3$, observed): δ = 0.00 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.25 (t, ^3J = 7.1 Hz, 3H), 1.52-1.65 (m, 3H), 1.76-1.87 (m, 1H), 2.04-2.25 (m, 5H), 2.32 (d, ^2J = 16.7 Hz, 1H), .2.43 (d, ^2J = 16.7 Hz, 1H), 4.10 (q, ^3J = 7.1 Hz, 2H), 4.34 (d, ^3J = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.0, −4.1, 14.3, 18.0, 22.8, 24.9, 25.9, 27.5, 34.8, 38.6, 43.9, 52.2, 60.1, 67.4, 172.0, 212.8.

HRMS (FAB+): calcd for $C_{18}H_{32}O_4SiNa$ [$(M+Na)^+$]: 363.1962, found 363.1963

Lactone 7



7

To a solution of **6** (6.92 g, 20.3 mmol) in 100 mL toluene at 0 °C was added a 1 M solution of diethylaluminium cyanide in toluene (26.5 mL, 26.5 mmol). The reaction mixture was stirred at 0 °C for 3 h, then warmed to rt After 9 h, the reaction mixture was poured into a mixture of 3 M NaOH aq (400 mL) and 200 mL ice and the aqueous phase was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 9/1) affording 5.47 g (17.0 mmol, 84%) of **7** as a white, crystalline solid.

TLC: R_f = 0.16 (hexanes/EtOAc = 9/1) [$KMnO_4$]

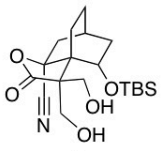
m.p.: 130 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.38 (ddd, ^2J = 13.7 Hz, ^3J = 10.8, 1.3 Hz, 1H), 1.46-1.55 (m, 1H), 1.56-1.64 (m, 1H), 1.76 (ddd, ^2J = 13.7 Hz, ^3J = 10.7, 8.0 Hz, 1H), 1.80 (dd, ^2J = 14.0 Hz, ^3J = 6.7 Hz, 1H), 1.91 (d, ^2J = 14.3 Hz, 1H), 2.03 (virt. q, $J \approx$ 4.9 Hz, 1H), 2.04 (d, ^2J = 16.7 Hz, 1H), 2.21 (dddd, ^2J = 14.0 Hz, ^3J = 9.1, 4.9 Hz, ^4J = 2.0 Hz, 1H), 2.58 (ddd, ^2J = 14.3 Hz, ^3J = 4.9 Hz, ^4J = 2.2 Hz, 1H), 3.08 (d, ^2J = 16.7 Hz, 1H), 3.98 (dd, ^3J = 6.7 Hz, 9.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.3, 18.1, 24.6, 25.1, 25.7, 25.8, 35.1, 37.0, 37.2, 47.5, 67.4, 76.6, 119.8, 174.6.

HRMS (FAB+): calcd for $C_{17}H_{27}O_3NSiNa$ [$(M+Na)^+$]: 344.1652, found: 344.1661

Diol 8



8

A LDA solution was prepared by dissolving diisopropylamine (1.35 mL, 0.97 g, 9.59 mmol) in THF (4 mL) at −78 °C and adding a 2.39 M solution of *n*-butyllithium in hexanes (3.65 mL, 8.71 mmol) dropwise. After stirring at −78 °C for 30 min the reaction mixture was warmed to 0 °C for 10 min and cooled to −78 °C again. To a solution of **7** (400 mg, 1.24 mmol) in THF (40 mL) was added gradually the prepared LDA solution at −78 °C. After addition was completed, stirring was continued for 30 min and the temperature was then raised to −40 °C for 30 min. A stream of formaldehyde gas, generated by thermolysis (160 °C) of paraformaldehyde was introduced through a cannula in a stream of N_2 for 10 min. The reaction mixture was quenched by addition of saturated NH_4Cl aq (4 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were filtered through celite and washed with EtOAc. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1 → 1/1) to give 232 mg **8** (0.61 mmol, 49%) as a white, crystalline solid.

TLC: R_f = 0.14 (hexanes/EtOAc = 2/1) [$KMnO_4$]

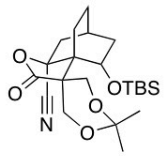
m.p.: 164 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 3H), 0.20 (s, 3H), 0.97 (s, 9H), 1.47-1.64 (m, 3H), 1.89-1.96 (m, 2H), 2.04-2.14 (m, 2H), 2.28 (dddd, ^2J = 13.8 Hz, ^3J = 8.9, 5.0 Hz, ^4J = 1.9 Hz, 1H), 2.68 (ddd, ^2J = 14.2 Hz, ^3J = 5.4 Hz, ^4J = 2.2 Hz, 1H), 2.96 (dd, ^3J = 9.1, 3.5 Hz, 1H), 3.40 (dd, ^3J = 8.4, 5.7 Hz, 1H), 3.85 (dd, ^2J = 12.1 Hz, ^3J = 9.1 Hz, 1H), 4.15 (dd, ^2J = 12.3 Hz, ^3J = 8.4 Hz, 1H), 4.22 (dd, ^2J = 12.1 Hz, ^3J = 3.5 Hz, 1H), 4.49 (dd, ^3J = 8.9, 7.3 Hz, 1H), 4.67 (dd, ^2J = 12.3 Hz, ^3J = 5.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −3.6, −3.5, 18.6, 23.9, 24.3, 24.6, 26.0, 38.2, 38.9, 51.2, 56.0, 64.0, 64.7, 71.3, 73.9, 121.4, 174.9.

HRMS (FAB+): calcd for $C_{19}H_{31}O_5NSiNa$ [$(M+Na)^+$]: 404.1864, found: 404.1863

Acetal 9



9

Diol **8** (52.0 mg, 136 µmol) was dissolved in DMF (2 mL) and 2,2-dimethoxypropane (0.85 mL, 0.71 g, 6.81 mmol) and p-toluenesulfonic acid (0.51 mg, 2.72 µmol) were added. After stirring the resulting solution at rt for 48 h, pyridine (0.1 mL) and water (15 mL) were added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (hexanes/EtOAc = 3/1) afforded 24.7 mg **9** (58.9 µmol, 43%) as a white solid.

TLC: R_f = 0.38 (hexanes/EtOAc = 2/1) [$KMnO_4$]

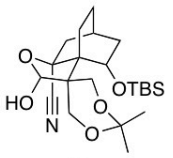
m.p.: 201 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 1.34-1.58 (m, 10H), 1.83 (dddd, , ^2J = 13.7 Hz, ^3J = 6.4, 2.6 Hz, ^4J = 1.4 Hz, 1H), 1.89 (d, ^2J = 14.3 Hz, 1H), 1.97-2.07 (m, 1H), 2.26 (dddd, , ^2J = 13.7 Hz, ^3J = 9.0, 4.8 Hz, ^4J = 2.1 Hz, 1H), 2.65 (ddd, ^2J = 14.3 Hz, ^3J = 5.3 Hz, ^4J = 1.5 Hz, 1H), 3.86 (d, ^2J = 3.6 Hz, 2H), 4.19 (d, ^2J = 12.3 Hz, 1H), 4.25 (dd, ^3J = 9.8, 6.4 Hz, 1H), 4.98 (d, ^2J = 12.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −4.4, −3.5, 18.1, 22.2, 22.6, 23.8, 24.5, 25.1, 26.0, 38.9, 39.3, 49.5, 50.3, 60.1, 60.6, 68.9, 73.0, 99.5, 121.2, 175.7.

HRMS (FAB+): calcd for $C_{22}H_{35}O_5NSi$ [$(M+H)^+$]: 422.2354, found: 422.2358

Lactol 10



10

To a solution of **9** (35 mg, 0.083 mmol) in DCM (2 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAH in DCM. After stirring for 30 min at this temperature, the reaction was quenched by addition of water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with 0.5 M aqueous HCl (5 mL), then brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 2/1) affording 35 mg (0.083 mmol, 99%) of **10** as a white, crystalline solid.

TLC: R_f = 0.31 (hexanes/EtOAc = 2/1) [CAM]

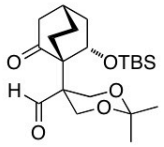
m.p.: 181 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 3H), 0.17 (s, 3H), 0.95 (s, 9H), 1.18-1.24 (m, 2H), 1.37 (s, 3H), 1.46 (s, 3H), 1.49-1.56 (m, 1H), 1.64-1.71 (m, 1H), 1.81-1.91 (m, 2H), 1.93-2.05 (m, 1H), 2.07-2.17 (m, 1H), 2.45-2.55 (m, 1H), 3.64 (d, *J* = 3.0, 1H), 3.83 (d, *J* = 11.2, 1H), 4.02-4.11 (m, 2H), 4.33 (dd, *J* = 3.2, 12.9, 1H), 4.61 (d, *J* = 12.9, 1H), 5.83 (d, *J* = 3.0, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = −4.3, −3.5, 18.1, 18.6, 21.8, 24.4, 24.8, 26.0, 29.5, 39.2, 40.4, 48.4, 50.1, 61.8, 65.1, 70.1, 75.1, 97.8, 103.3, 123.4.

HRMS (ESI−): calcd for $C_{23}H_{38}NO_7Si$ [(M+HCOO)$^-$]: 468.2418, found: 468.2413.

Keto Aldehyde 11



11

To a solution of **10** (50 mg, 0.118 mmol) in EtOH (2 mL) at rt was added 2 M aqueous NaOH and the reaction was stirred for 30 min. This mixture was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with water (10 mL), then brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 5/1) affording 45 mg (0.114 mmol, 96%) of **11** as a colourless oil.

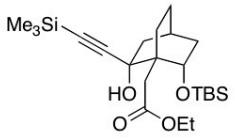
TLC: R_f = 0.72 (hexanes/EtOAc = 2/1) [CAM]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3H), 0.14 (s, 3H), 0.80 (s, 9H), 1.30 (s, 3H), 1.35 (s, 3H), 1.35-1.50 (m, 1H), 1.60-1.77 (m, 3H), 2.01-2.15 (m, 3H), 2.17-2.22 (m, 1H), 2.31-2.40 (m, 1H), 3.94-4.04 (m, 2H), 4.16-4.28 (m, 3H), 9.89 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, observed): δ = −4.3, −3.0, 17.9, 22.2, 25.0, 26.0, 26.8, 38.2, 44.9, 51.2, 57.6, 60.9, 61.9, 70.9, 98.4, 204.6, 212.7.

HRMS (ESI+): calcd for $C_{21}H_{36}O_5SiNa$ [$(M+Na)^+$]: 419.2230, found: 419.2223

Alcohol 13



13

A solution of (trimethylsilyl)acetylene (0.395 mL, 2.77 mmol) in THF (5 mL) was treated at −78 °C with a 1.5 M solution of *n*-butyllithium in hexanes (1.76 mL, 2.64 mmol). After stirring for 30 min at this temperature, this solution was added dropwise to a solution of **6** (0.45 g, 1.32 mmol) in THF (15 mL) at −78 °C and left to stir for 20 min at this temperature. The reaction was warmed to rt and then quenched by addition of saturated NH_4Cl aq (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 20/1) affording 0.436 g (0.994 mmol, 75%) of **13** as a colourless oil.

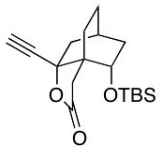
TLC: R_f = 0.74 (hexanes/EtOAc = 10/1) [CAM]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.15 (s, 9H), 0.87 (s, 9H), 1.24 (t, *J* = 7.1, 3H), 1.33-1.40 (m, 1H), 1.42-1.50 (m, 1H), 1.53-1.62 (m, 2H), 1.69-1.77 (m, 1H), 1.78-1.83 (m, 1H), 1.89-2.00 (m, 2H), 2.51-2.31 (m, 1H), 2.60 (d, *J* = 15.2, 1H), 2.90 (d, *J* = 15.2, 1H), 4.17-4.00 (m, 2H), 4.50 (dd, *J* = 2.0, 9.0, 1H), 4.85 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.2, −4.4, 0.0, 14.4, 17.7, 23.8, 24.6, 25.2, 25.8, 35.3, 38.1, 41.0, 47.1, 60.0, 71.4, 72.9, 87.5, 108.8, 172.9.

HRMS (ESI+): calcd for $C_{23}H_{42}O_4Si_2Na$ $[(M+Na)^+]$: 461.2519, found: 461.2515

Lactone 14



14

NaH (159 mg, 60% in mineral oil, 3.98 mmol) was suspended in a solution of **13** (436 mg, 0.994 mmol) in THF (20 mL) and the reaction was stirred for 3 h at 40 °C. After cooling to rt, the reaction mixture was poured into 1 M HCl (5 mL) and ice, then extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 10/1) affording 0.262 g (0.817 mmol, 82%) of **15** as a white, crystalline solid.

TLC: R_f = 0.47 (hexanes/EtOAc = 5/1) [CAM]

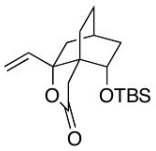
m.p.: 150 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.35-148 (m, 2H), 1.58-1.68 (m, 1H), 1.88-2.08 (m, 4H), 2.13-2.22 (m, 2H), 2.32-2.38 (m, 1H), 2.57-2.62 (m, 2H), 3.82 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.6, 17.8, 23.9, 25.7, 25.8, 37.7, 38.0, 39.2, 44.3, 73.7, 73.9, 81.0, 84.9, 176.0.

HRMS (ESI+): calcd for $C_{18}H_{29}O_3Si$ $[(M+H)^+]$: 321.1881 found: 321.1882

Lactone 15



15

A solution of **14** (190 mg, 0.539 mmol) in pyridine (10 mL) was vigorously stirred in hydrogen with 6.3 mg (0.059 mg) of a 5% palladium-on-calcium carbonate catalyst, poisoned with 3.5% lead at atmospheric pressure and rt After 30 min, the catalyst was removed and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to give 183 mg (0.567 mmol, 96 %) of **15** as a white, crystalline solid.

TLC: R_f = 0.48 (hexanes/EtOAc = 5/1) [CAM]

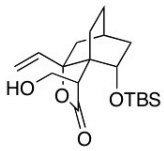
m.p.: 131 °C

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 0.07 (s, 6H), 0.90 (s, 9H), 1.36 (ddd, *J* = 6.9, 10.7, 13.4, 1H), 1.46-1.52 (m, 1H), 1.65-1.77 (m, 3H), 1.91-2.11 (m, 5H), 2.34 (d, *J* = 16.2, 1H), 3.77 (d, *J* = 8.9, 1H), 5.15 (d, *J* = 0.9, 10.8, 1H), 5.32 (dd, *J* = 0.9, 16.9, 1H), 6.03 (dd, *J* = 10.8, 16.9, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = −4.9, −4.6, 17.8, 24.4, 24.7, 25.8, 25.9, 35.6, 36.7, 40.3, 43.4, 74.6, 85.7, 114.3, 140.5, 176.9.

HRMS (ESI+): calcd for $C_{18}H_{34}O_3NSi$ $[(M+NH_4)^+]$: 340.2308, found: 340.2303

Alcohol 17



17

A LDA solution was prepared by dissolving diisopropylamine (0.67 mL, 0.477 g, 4.71 mmol) in THF (2 mL) at −78 °C and adding a 2.34 M solution of *n*-butyllithium in hexanes (1.99 mL, 4.65 mmol) dropwise. After stirring at −78 °C for 30 min the reaction mixture was warmed to 0 °C for 10 min and cooled to −78 °C again. To a

solution of **15** (100 mg, 0.31 mmol) in THF (3 mL) was added gradually the prepared LDA solution at −78 °C. After addition was completed, stirring was continued for 30 min and the temperature was then raised to −40 °C for 30 min. A stream of formaldehyde gas, generated by thermolysis (160 °C) of paraformaldehyde was introduced through a cannula in a stream of N_2 for 10 min. The reaction mixture was quenched by addition of saturated NH_4Cl aq (4 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were filtered through celite and washed with EtOAc. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (hexanes/EtOAc = 2/1) to give 101 mg **17** (0.29 mmol, 92%) as a white, crystalline solid.

TLC: R_f = 0.25 (hexanes/EtOAc = 2/1) [CAM]

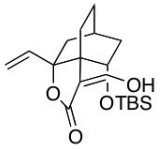
m.p.: 169 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6H), 0.88 (s, 9H), 1.30-1.40 (m, 1H), 1.45-1.60 (m, 1H), 1.62-1.75 (m, 3H), 1.82-2.00 (m, 3H), 2.08-2.17 (m, 1H), 2.34-2.47 (m, 2H), 3.66-3.79 (m, 2H), 3.83-3.93 (m, 1H), 5.11 (d, *J*=10.8, 1H), 5.31 (d, *J*=16.9, 1H), 6.12 (dd, *J*=10.9, 16.9, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.4, 17.7, 21.2, 24.3, 25.5, 25.8, 36.6, 39.8, 44.9, 50.1, 61.3, 76.1, 86.0, 114.5, 142.8, 178.6.

HRMS (ESI−): calcd for $C_{19}H_{32}O_4SiCl$ $[(M+Cl)^-]$: 387.1758, found: 387.1863

Dicarbonyl 18



18

To a solution of **17** (130 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $NaHCO_3$ (43 mg, 0.517 mmol), then DMP (219 mg, 0.517 mmol) and the mixture was left to stir at rt for 2 h. The reaction was quenched by addition of conc. Na_2SO_3 aq : sat. $NaHCO_3$ aq : water = 5 mL : 5 mL : 5 mL and stirred vigorously for 20 min. After extracting the aqueous phase with EtOAc (3 × 20 mL), the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, and

evaporated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to give **18** (116 mg, 0.331 mmol, 90%) as a colorless oil.

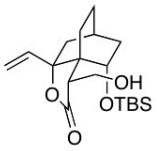
TLC: R_f = 0.65 (hexanes/EtOAc = 2/1) [CAM]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = −0.08-0.12 (m, 6H), 0.81-0.94 (m, 9H), 1.16-2.19 (m, 12H), 3.03 (s, 1H), 4.17-4.20 (m, 1H), 5.10-5.38 (m, 2H), 5.92-6.08 (m, 1H), 9.99 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of enol and aldehyde): δ = −5.2, −4.8, −4.1, −3.9, 17.7, 17.8, 22.4, 23.7, 24.0, 24.8, 25.5, 25.7, 25.8, 25.9, 26.0, 29.9, 36.2, 39.3, 40.2, 45.8, 47.8, 54.2, 69.2, 84.6, 86.6, 108.6, 114.9, 115.3, 139.9, 140.4, 152.6, 173.6, 176.4, 199.4.

HRMS (ESI−): calcd for $C_{19}H_{29}O_4Si$ [$(M-H)^-$]: 349.1841, found: 363.1836

Hydroxymethyl lactone 19



19

Sodium borohydride (32 mg, 0.855 mmol) was added to a solution of **18** (100 mg, 0.285 mmol) in EtOH (2 mL) at 0 °C and the mixture was left to stir at rt for 1 h. The reaction was quenched by neutralization with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Purification of the residue by flash column chromatography (hexanes/EtOAc = 2/1) yielded **19** (92 mg, 0.261 mmol, 92%) as a colorless oil.

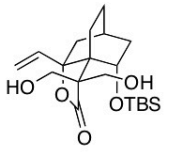
TLC: R_f = 0.28 (hexanes/EtOAc = 2/1) [CAM]

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.38-1.44 (m, 1H), 1.46-1.52 (m, 1H), 1.63-1.77 (m, 3H), 1.87-1.93 (m, 1H), 1.96-2.02 (m, 2H), 2.11-2.14 (m, 1H), 2.69 (dd, *J*=6.0, 8.8, 1H), 3.66 (dd, *J*=6.0, 10.9, 1H), 3.92 (d, *J*=8.2, 1H), 4.08 (dd, *J*=8.8, 10.9, 1H), 5.18 (dd, *J*=0.9, 10.8, 1H), 5.34 (dd, *J*=0.9, 16.9, 1H), 6.03 (dd, *J*=10.9, 16.9, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = −4.0, −3.4, 18.0, 24.2, 24.3, 25.3, 26.0, 35.6, 39.4, 45.7, 46.5, 58.7, 70.3, 85.0, 114.8, 139.8, 179.1.

HRMS (ESI+): calcd for $C_{19}H_{32}O_4SiNa$ [$(M+Na)^+$]: 375.1968, found: 375.1962

Diol 16



16

A LDA solution was prepared by dissolving diisopropylamine (0.23 mL, 0.165 g, 1.63 mmol) in THF (1.5 mL) at −78 °C and adding a 2.34 M solution of *n*-butyllithium in hexanes (1.58 mL, 6.76 mmol) dropwise. After stirring at −78 °C for 30 min the reaction mixture was warmed to 0 °C for 10 min and cooled to −78 °C again. To a solution of **19** (40 mg, 0.113 mmol) in THF (1.5 mL) was added gradually the prepared LDA solution at −78 °C. After addition was completed, stirring was continued for 20 min and the temperature was then raised to −40 °C for 20 min. A stream of formaldehyde gas, generated by thermolysis (160 °C) of paraformaldehyde was introduced through a cannula in a stream of N_2 for 10 min. The reaction mixture was quenched by addition of saturated NH_4Cl aq (2 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were filtered through celite and washed with EtOAc. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (hexanes/EtOAc = 1/1) to give 28 mg **16** (0.073 mmol, 65%) as a colorless oil.

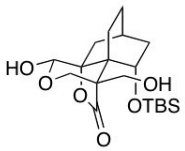
TLC: R_f = 0.15 (hexanes/EtOAc = 2/1) [CAM]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.09-0.16 (m, 6H), 0.91 (s, 9H), 1.23-1.55 (m, 4H), 1.65-2.00 (m, 6H), 2.25-2.30 (m, 1H), 2.52 (s br, 1H), 3.09 (s br, 1H), 3.91-3.97 (m, 1H), 4.02-4.06 (m, 1H), 4.11-4.14 (m, 1H), 4.15-4.21 (m, 1H), 4.23-4.28 (m, 1H), 5.11 (dd, *J*=1.1, 10.9, 1H), 5.35 (dd, *J*=1.1, 17.0, 1H), 6.33 (dd, *J*=10.9, 16.9, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −4.2, −2.7, 18.2, 20.6, 24.5, 24.6, 26.1, 37.3, 38.7, 48.6, 51.6, 62.7, 63.5, 70.9, 85.4, 113.6, 144.1, 179.8.

HRMS (ESI+): calcd for $C_{20}H_{34}O_5SiNa$ [$(M+Na)^+$]: 405.2073, found: 405.2067

Lactol/Lactone 20



20

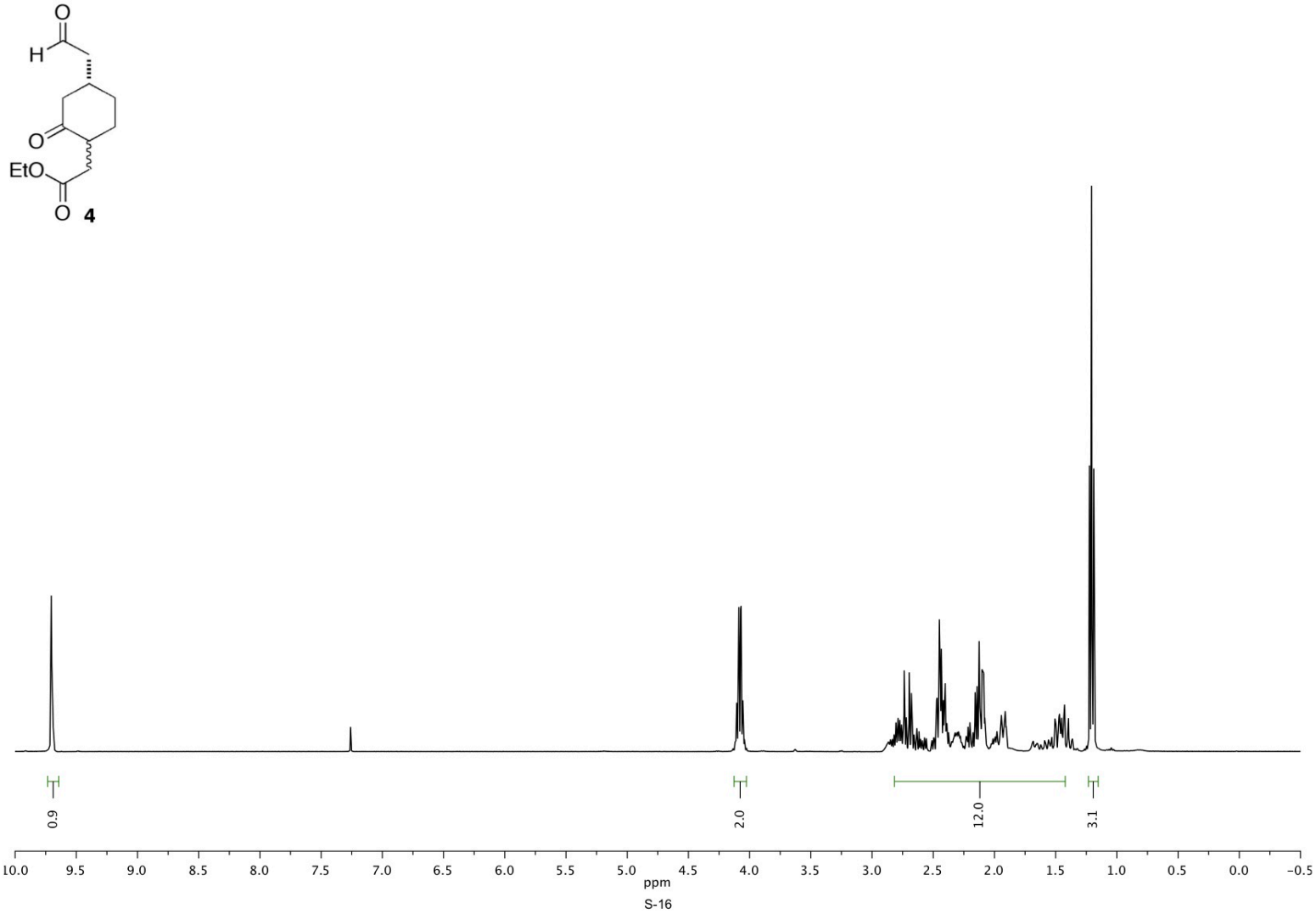
Ozone was bubbled into a mixture of **16** (30 mg, 0.078 mmol), $NaHCO_3$ (6.6 mg, 0.078 mmol), CH_2Cl_2 (1 mL) and MeOH (1 mL) for 10 min. Excess ozone was then removed by bubbling N_2 through the mixture. Me_2S (0.02 mL, 20 mg, 0.314 mmol) was added and the mixture was left to stir overnight at rt The mixture was then concentrated *in vacuo* and purified by flash column chromatography (hexanes/EtOAc = 2/1) to give 14 mg (0.036 mmol, 46 %) of **20** as a colorless oil.

TLC: R_f = 0.11 (hexanes/EtOAc = 2/1) [CAM]

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.15-1.28 (m, 1H), 1,47-1.61 (m, 2H), 1.64-1.74 (m, 1H), 1.83-1.88 (m, 1H), 1.95-2.10 (m, 3H), 2.14-2.21 (m, 1H), 2.59-2.69 (m, 1H), 2.76 (d, *J*=12.8, 1H), 3.50-3.57 (m, 1H), 3.97 (d, *J*=7.3, 1H), 4.03-4.10 (m, 2H), 4.19 (d, *J*=11.2, 1H), 4.83 (d, *J*=12.7, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = −4.1, −3.7, 18.0, 19.6, 23.8, 24.8, 26.0, 31.0, 39.3, 45.1, 48.2, 59.1, 64.4, 70.0, 83.9, 94.0, 178.8.

HRMS (ESI+): calcd for $C_{19}H_{33}O_6SiNa$ $[(M+H)^+]$: 385.2041, found: 385.2042.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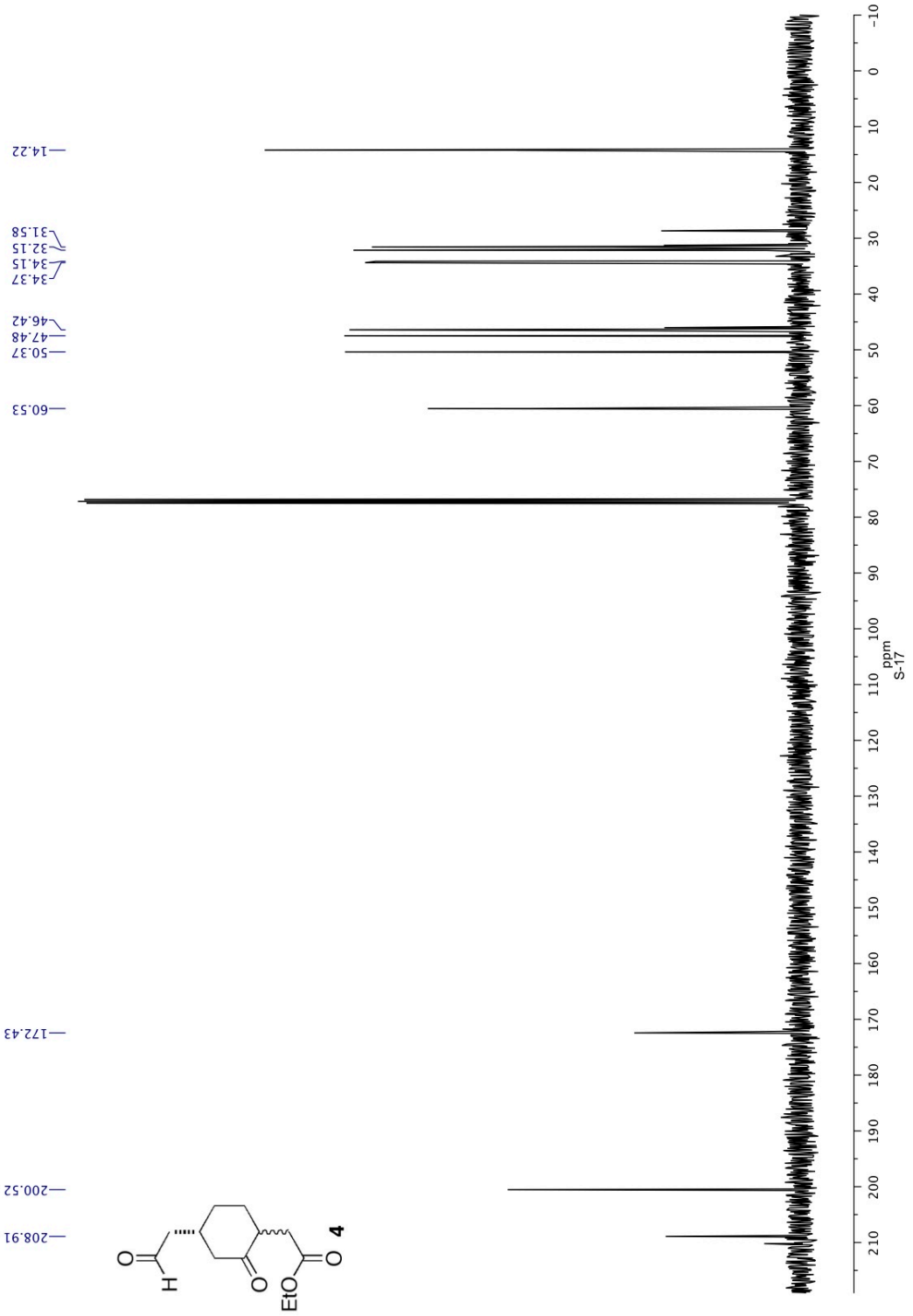
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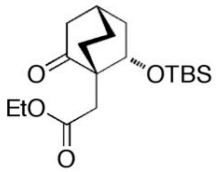
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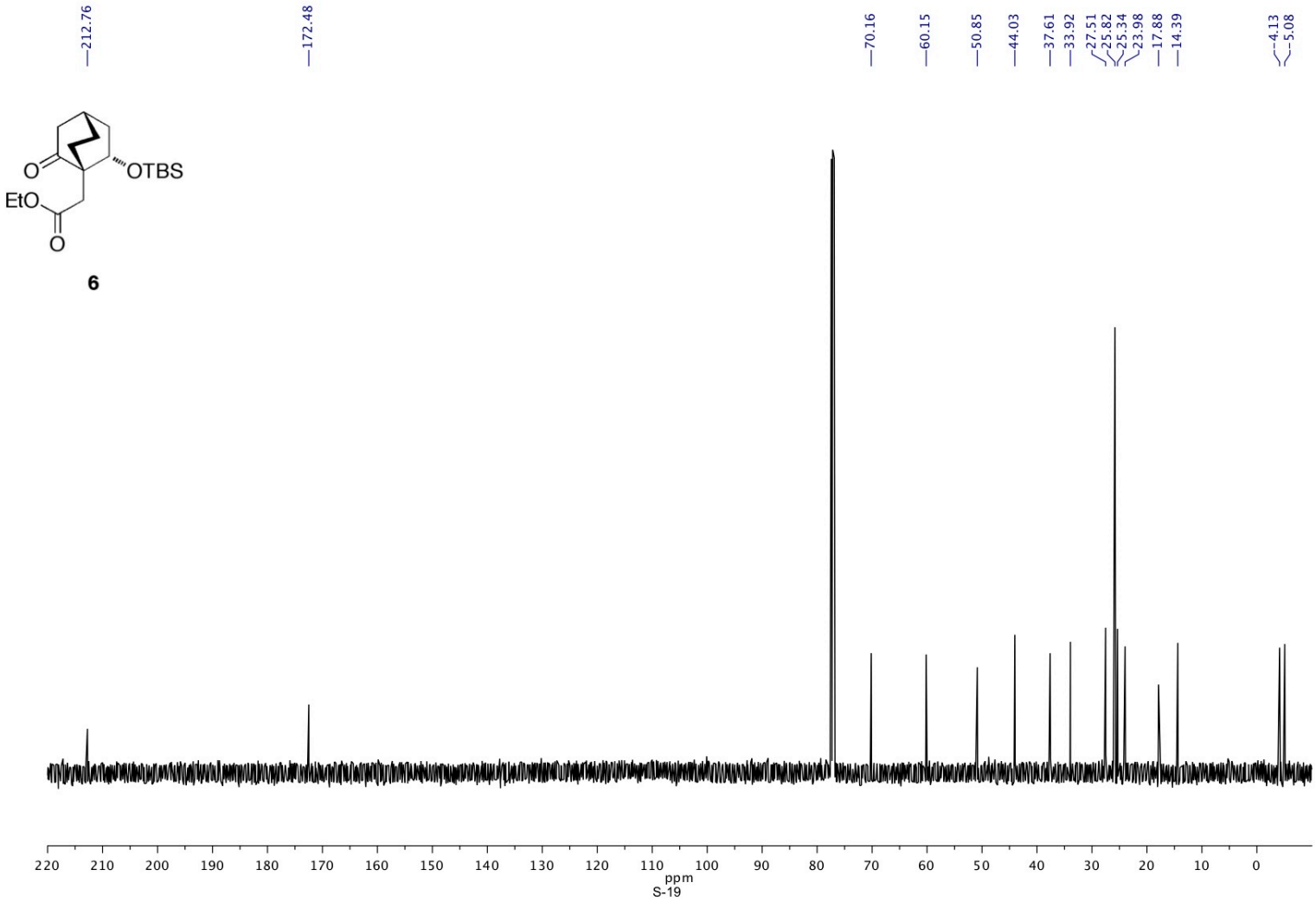
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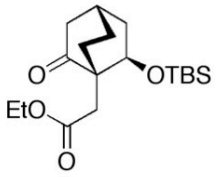
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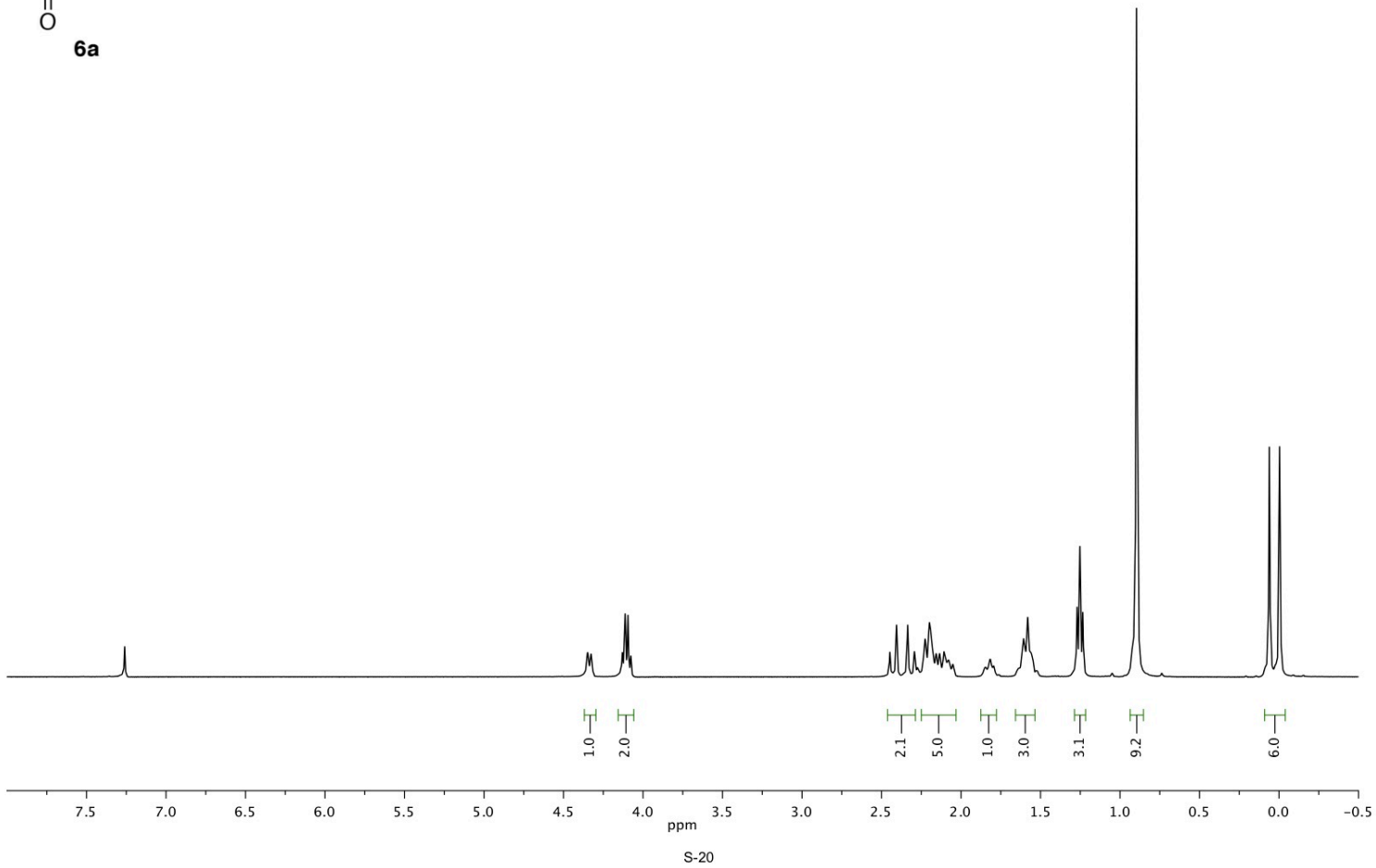
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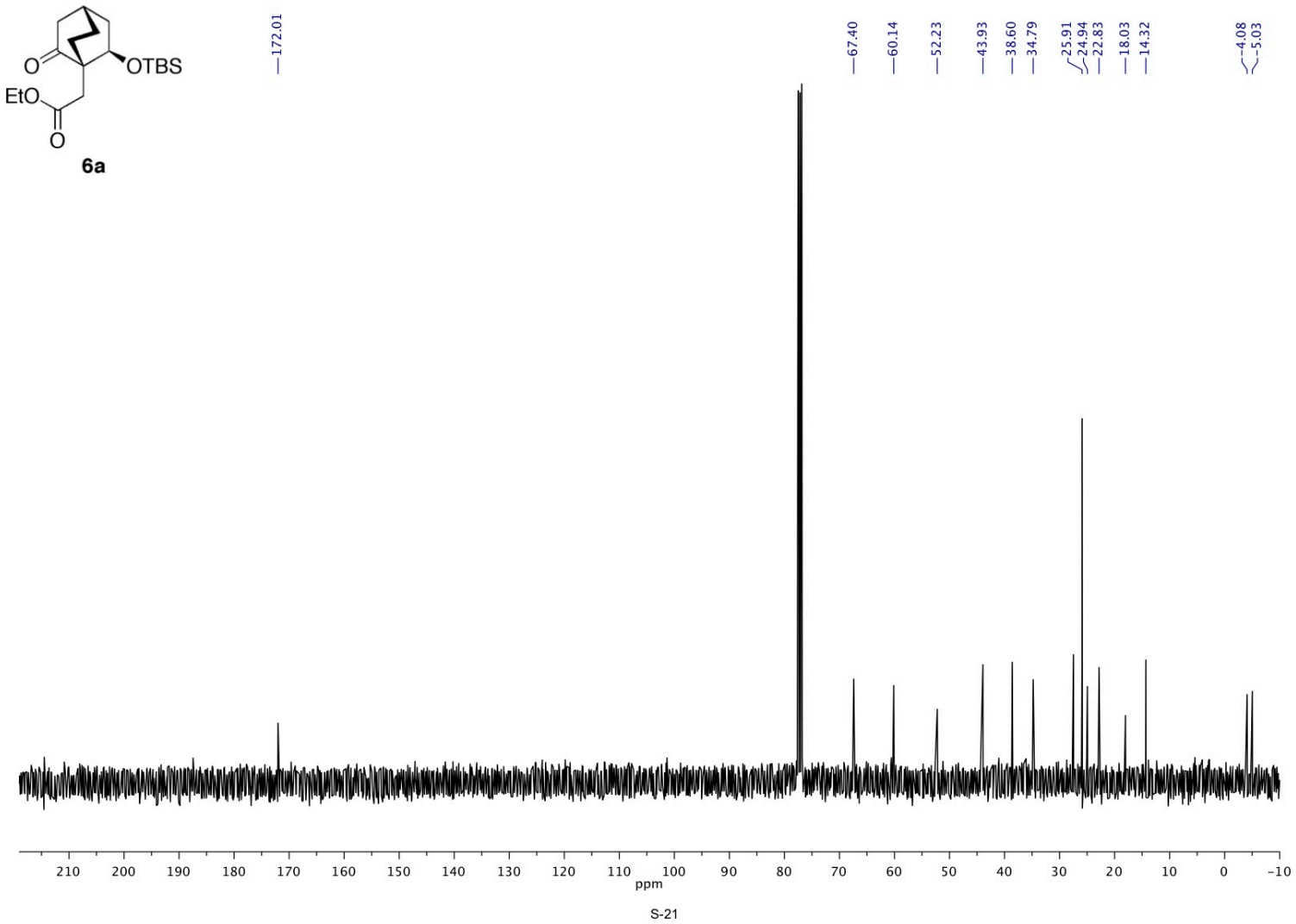
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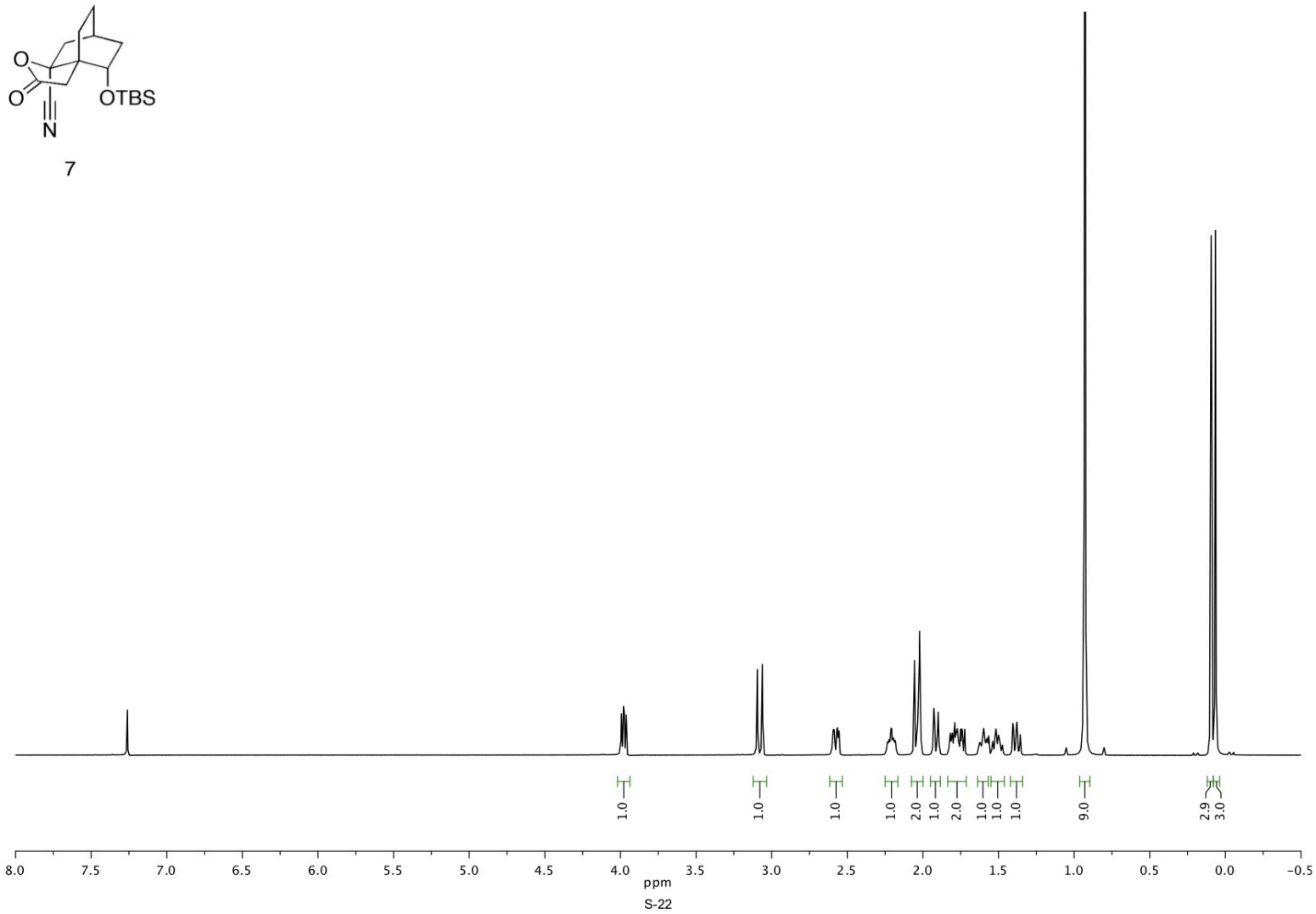
S-21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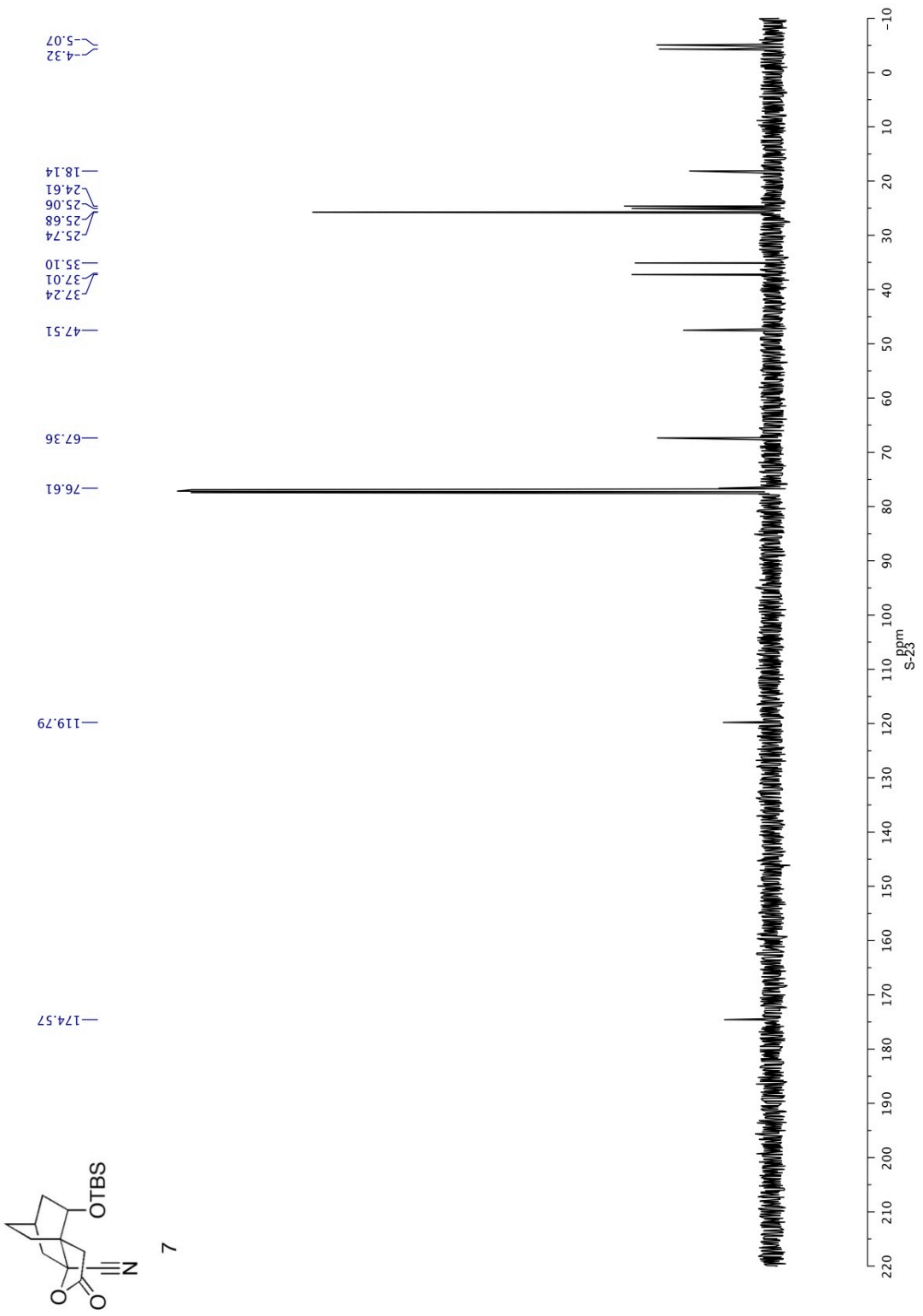
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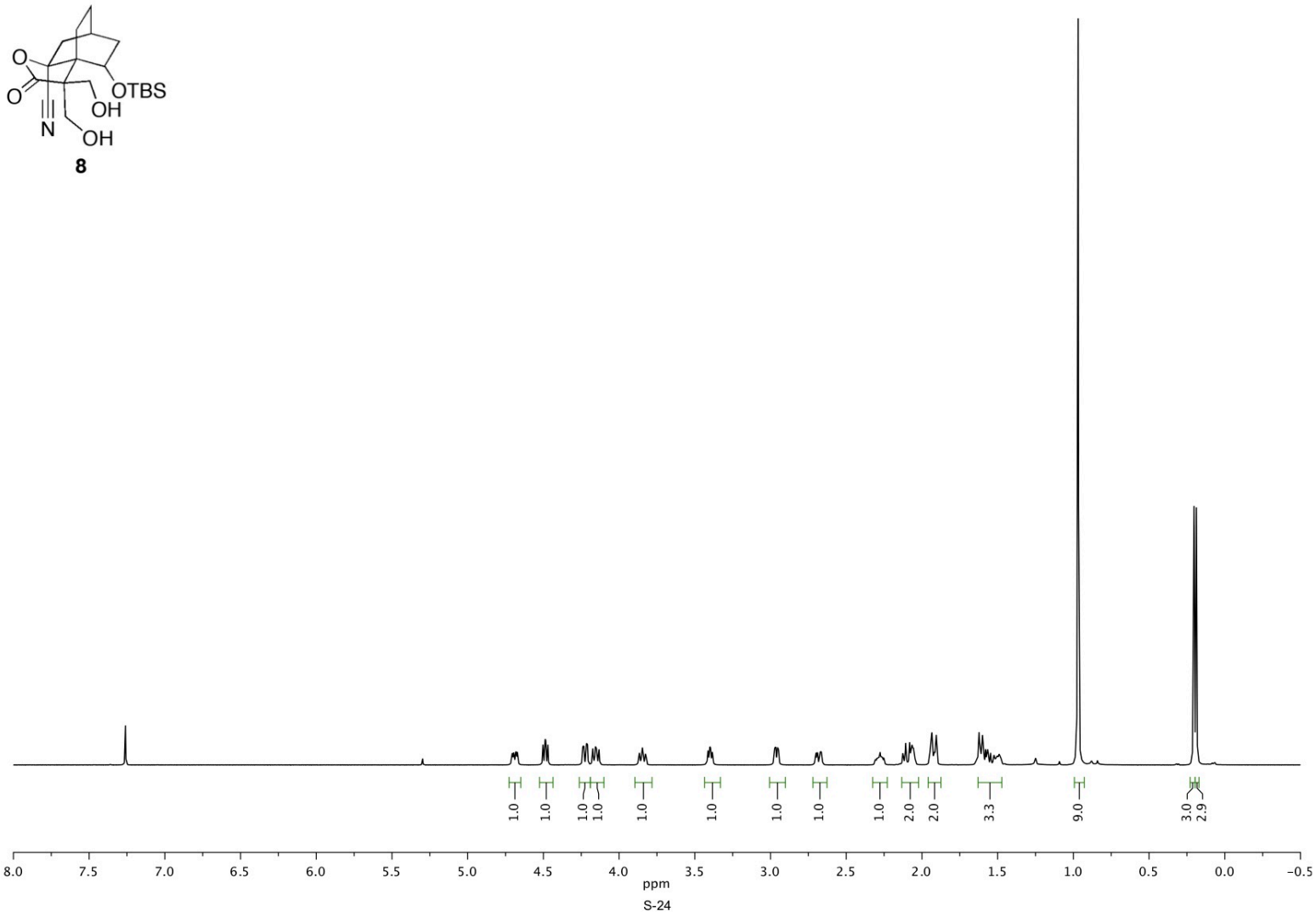
S-23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O
N
OTBS
OH
OH
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1.0
1.0
1.0
1.0
1.0
1.0
2.0
2.0
3.3
9.0
3.0
2.9
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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1.0
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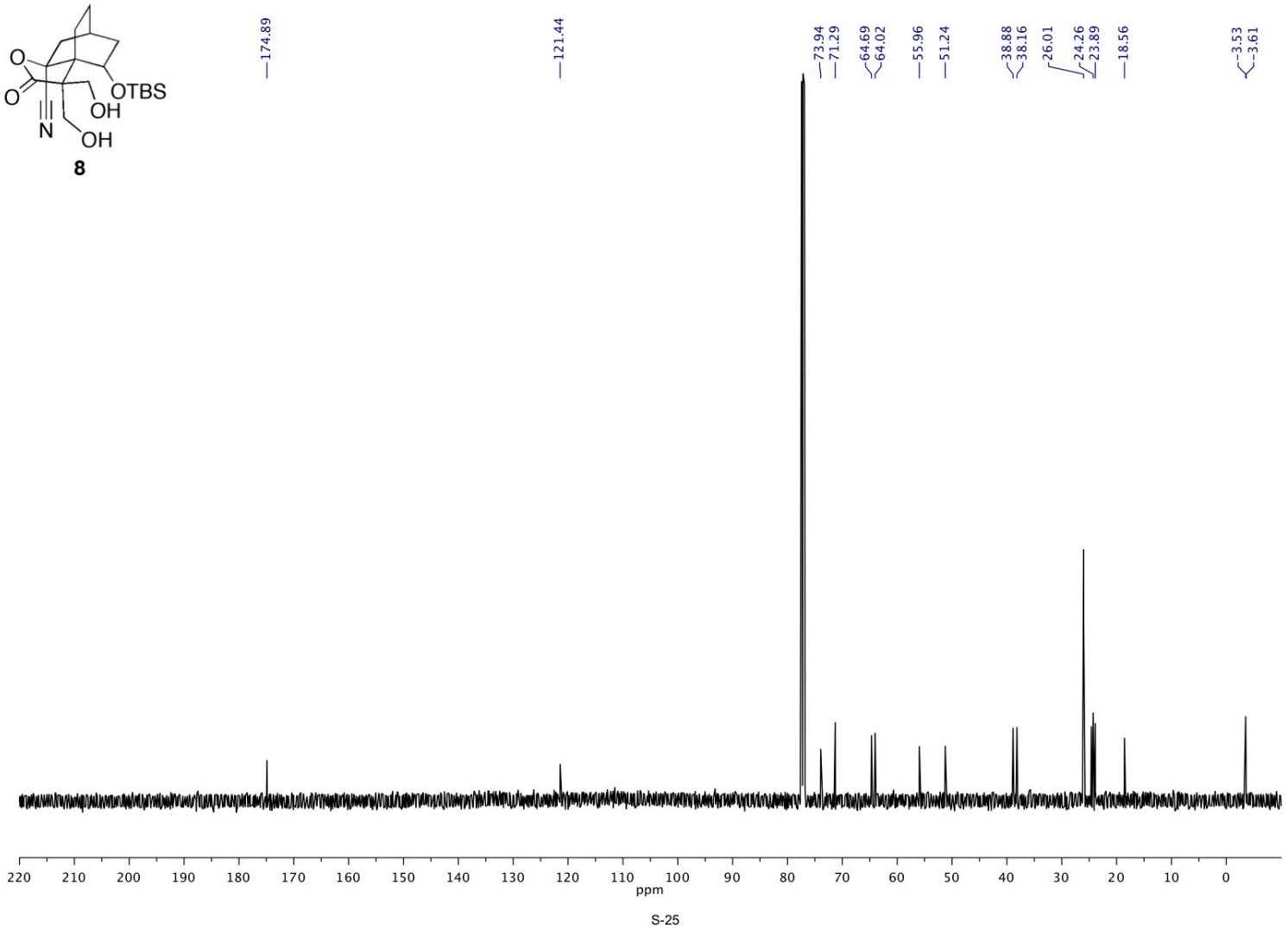
0.0
-0.5
ppm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O
OTBS
OH
N
OH
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121.44
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71.29
64.69
64.02
55.96
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38.88
38.16
26.01
24.26
23.89
18.56
-3.53
-3.61
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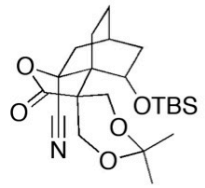
ppm

S-25


O
O
N
O
O
OTBS

9

1.0
1.1
0.9
2.0
1.0
1.1
1.0
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1.1
10.1
9.0
3.0
3.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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2.0
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1.0
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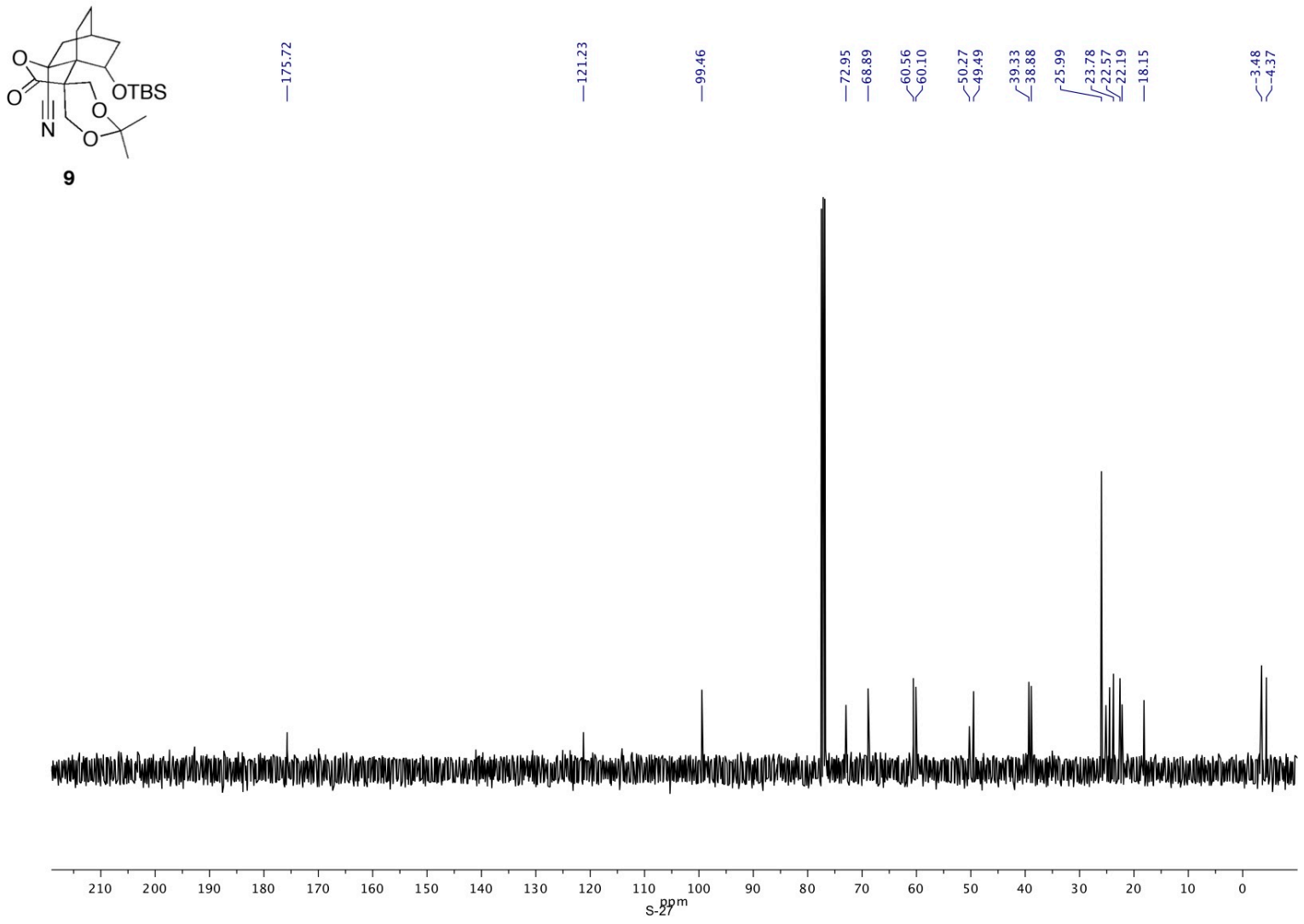
0.0
-0.5
ppm


OTBS
O
O
N
O
O
9
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121.23
99.46
72.95
68.89
60.56
60.10
50.27
49.49
39.33
38.88
25.99
23.78
22.57
22.19
18.15
-3.48
-4.37
210
200
190
180
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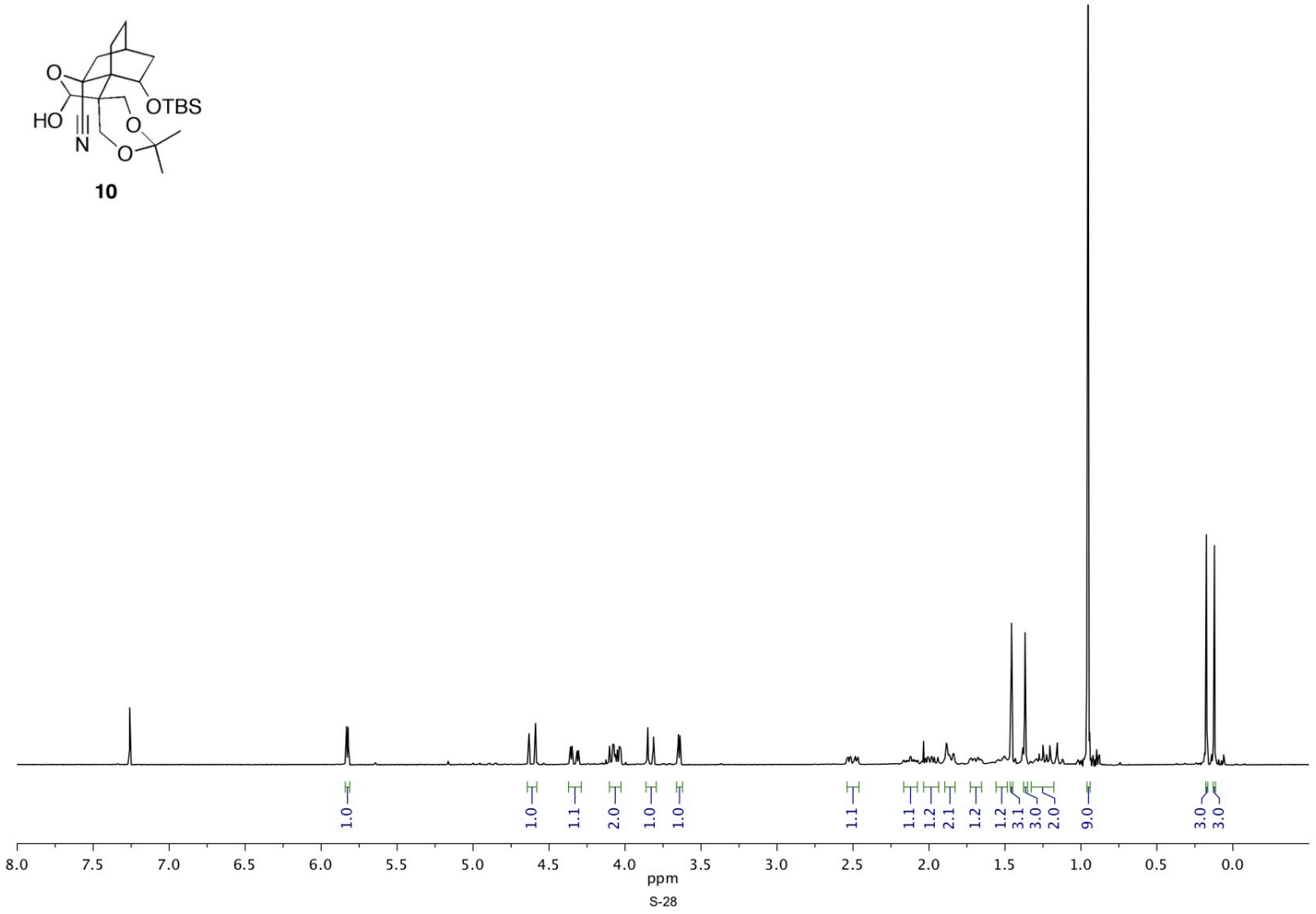
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
HO
N
O
O
OTBS
10
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1.0
1.1
2.0
1.0
1.0
1.1
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2.1
1.2
1.2
3.1
3.0
2.0
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3.0
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7.0
6.5
6.0
5.5
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3.0
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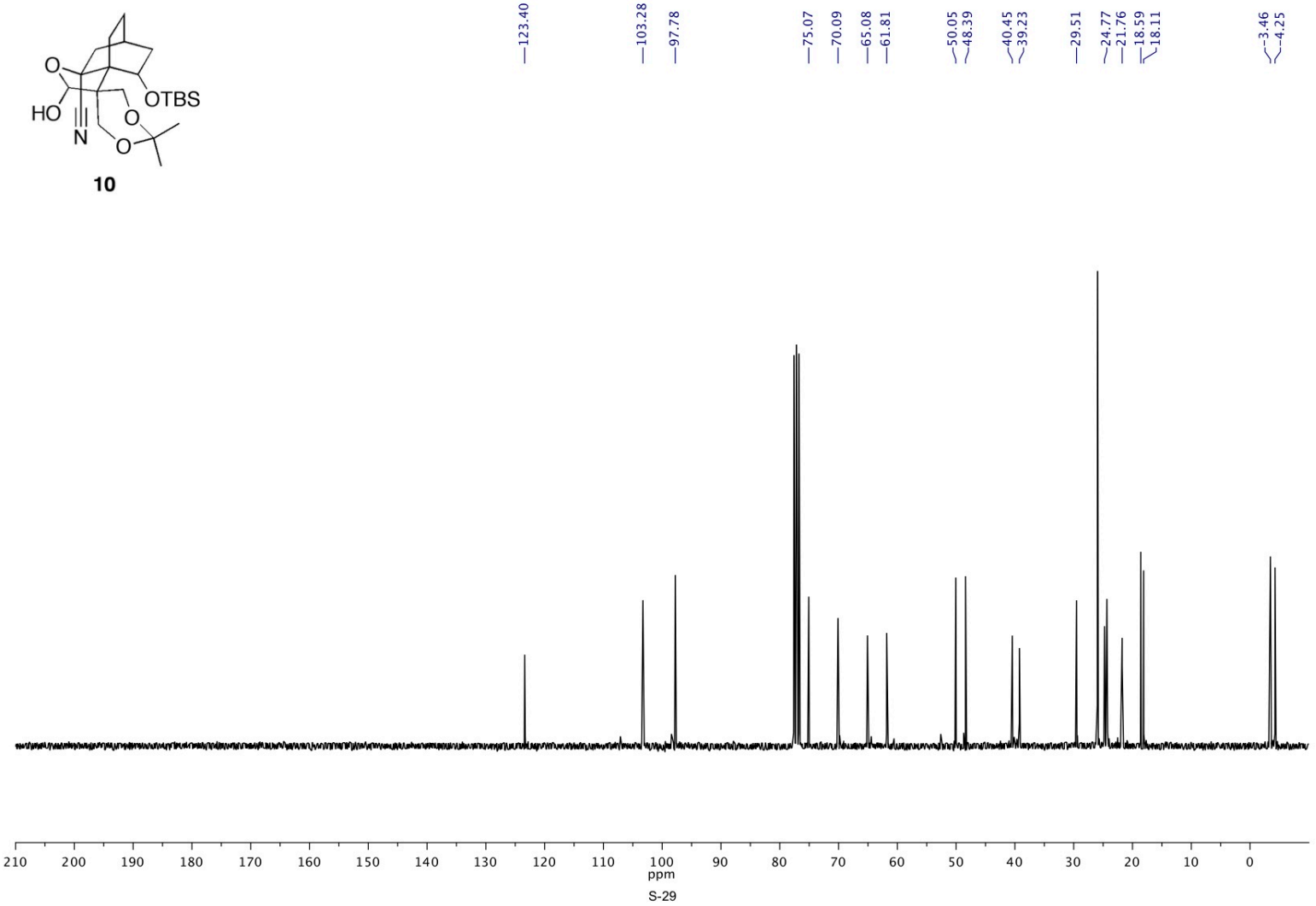
1.0
0.5
0.0
ppm
S-28


O
HO
N
O
O
O
OTBS
10
123.40
103.28
97.78
75.07
70.09
65.08
61.81
50.05
48.39
40.45
39.23
29.51
24.77
21.76
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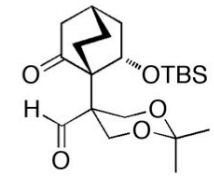
18.11
-3.46
-4.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm
S-29


O
OTBS
H
O
O
O

11

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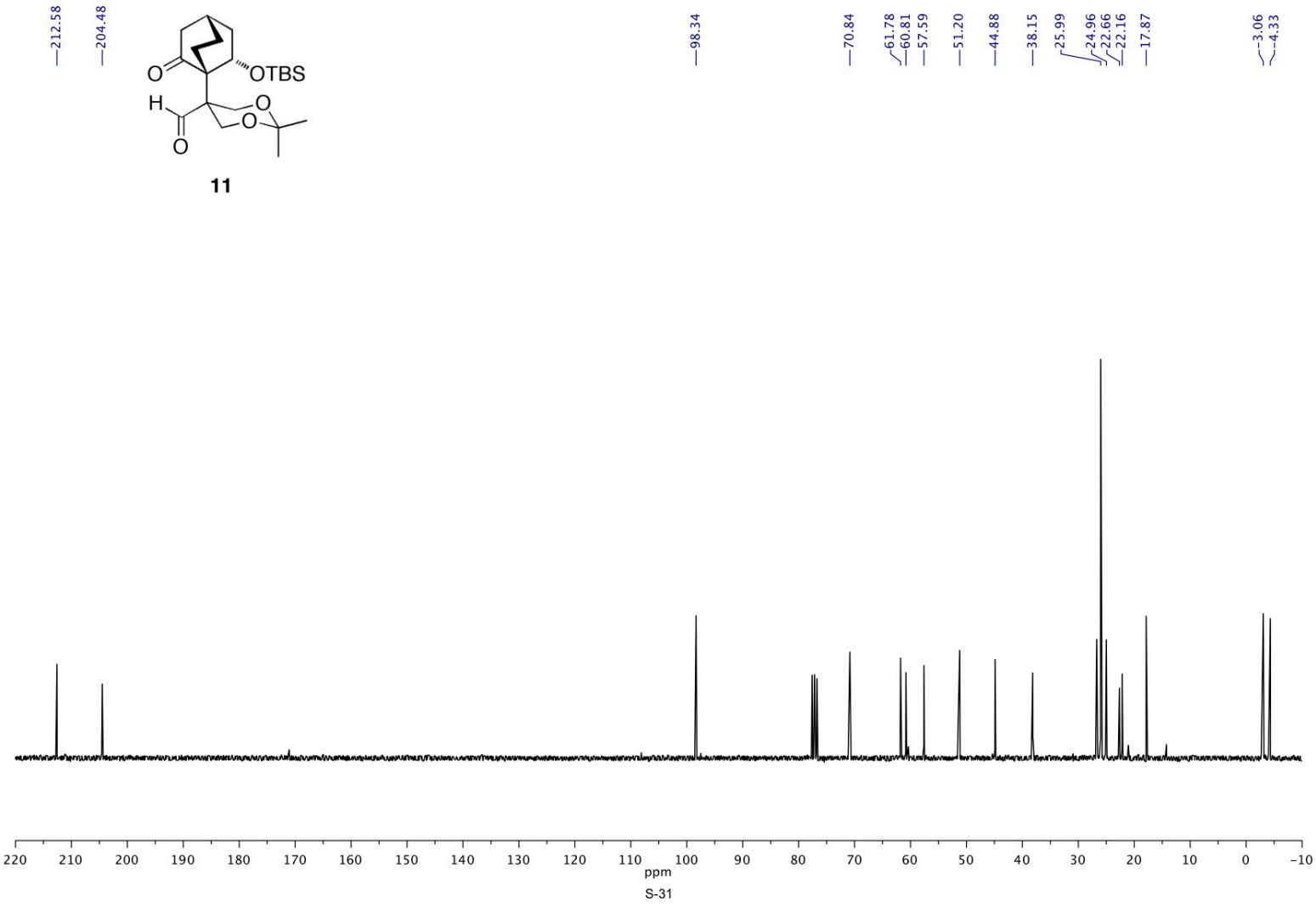
3.2
2.2
1.2
1.2
3.0
3.2
1.3
3.0
3.1
9.2
3.1
2.9
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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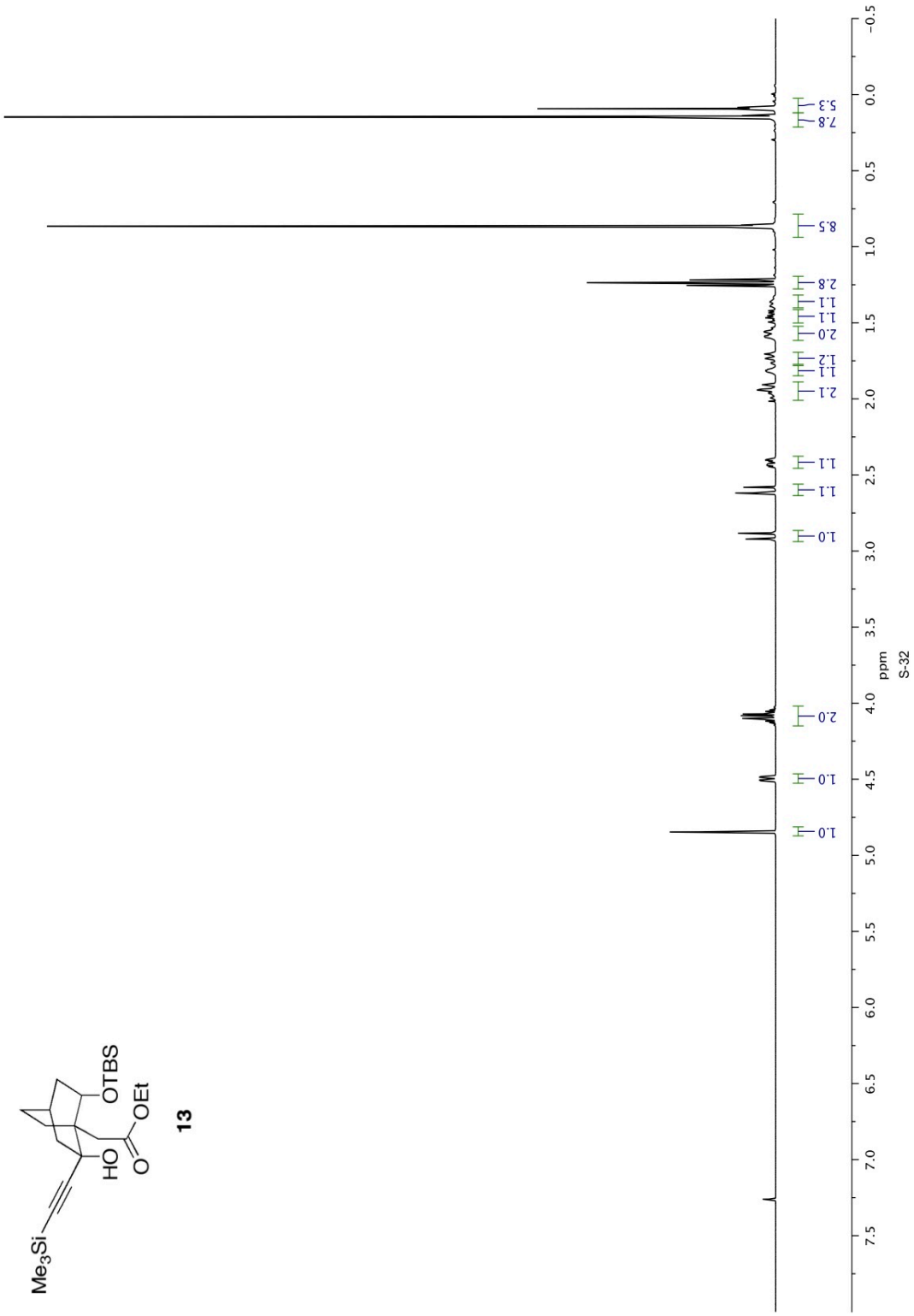
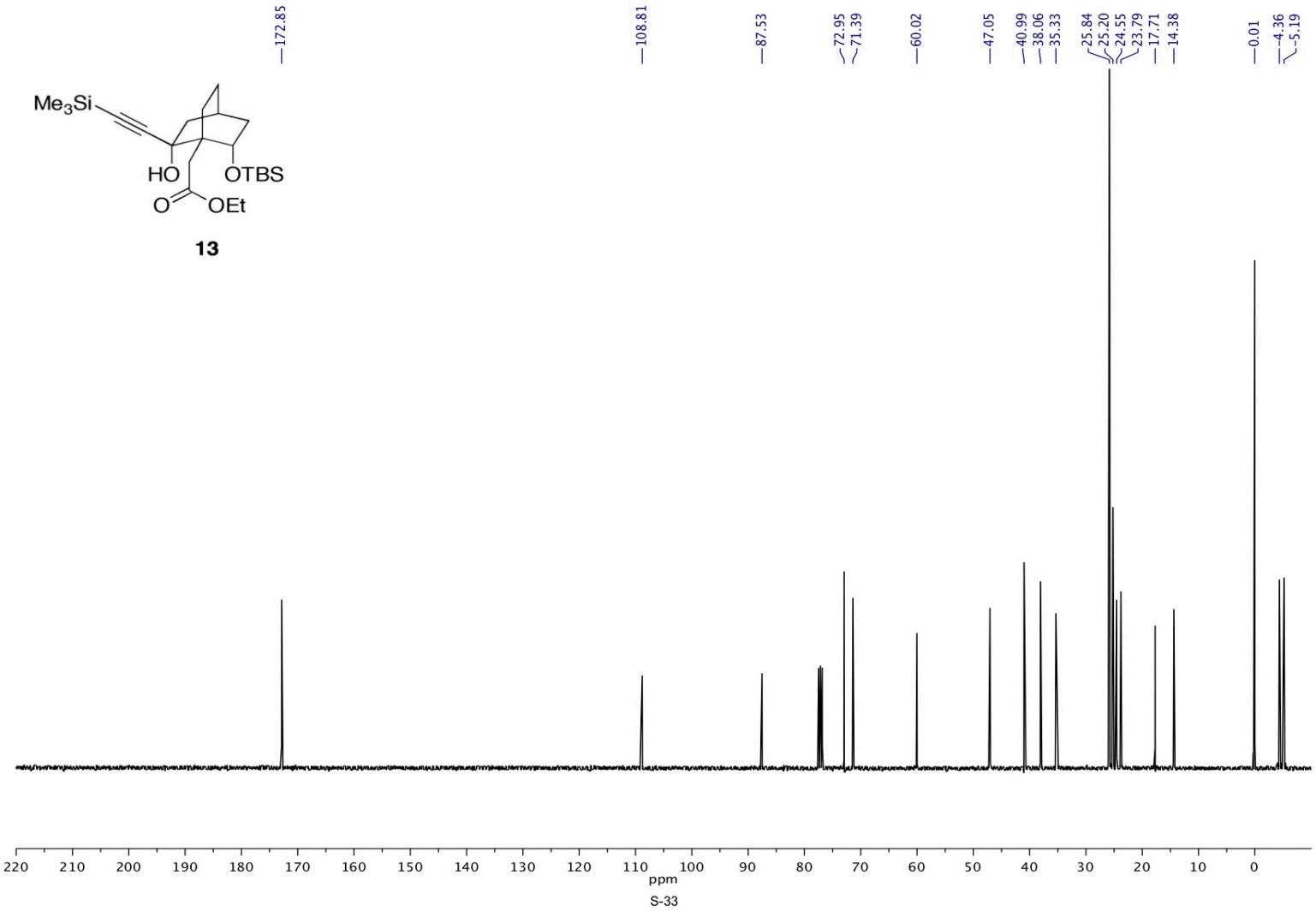
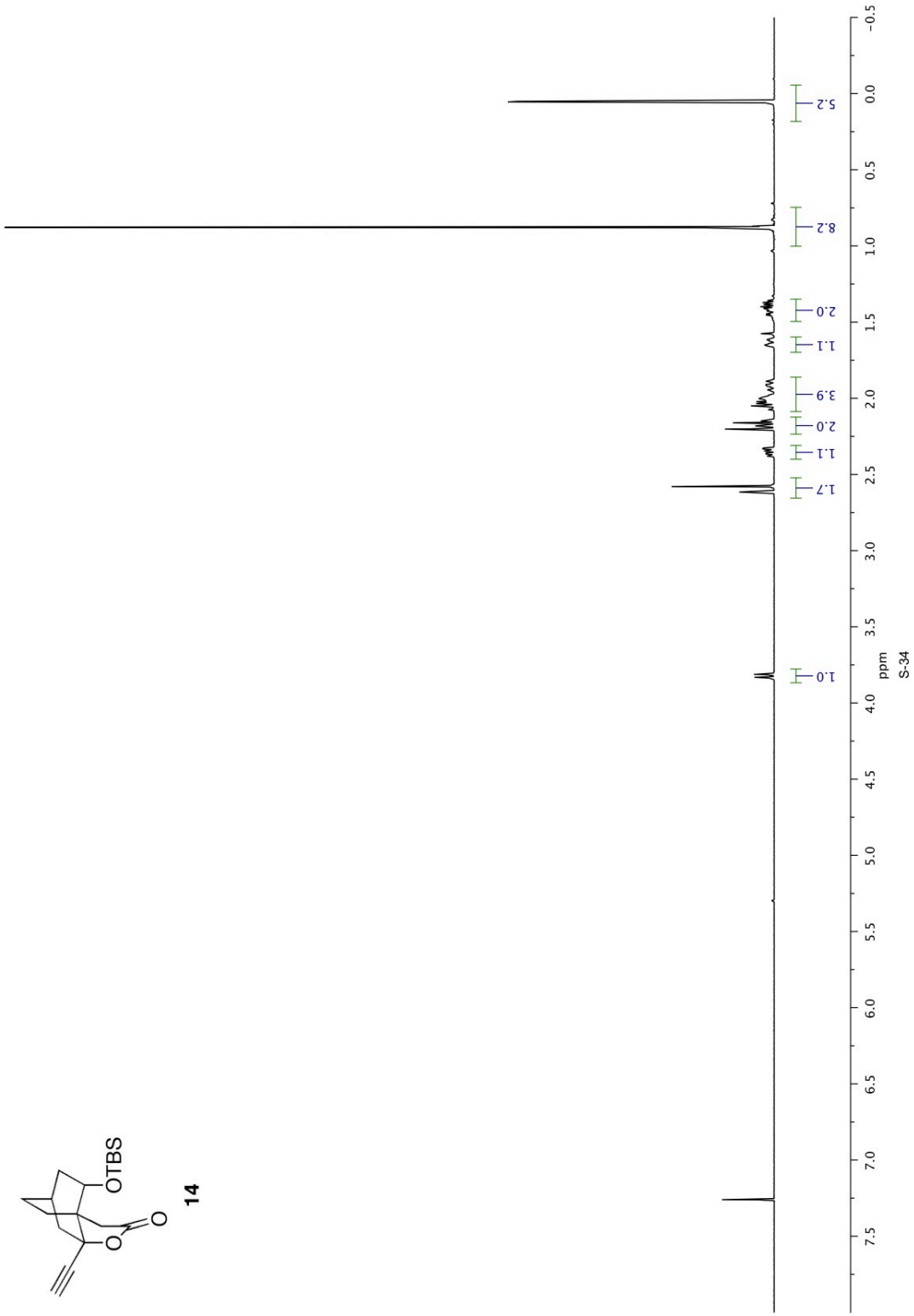
204.48
98.34
70.84
61.78
60.81
57.59
51.20
44.88
38.15
25.99
24.96
22.66
22.16
17.87
-3.06
-4.33
OTBS
H
O
O
O
O
11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

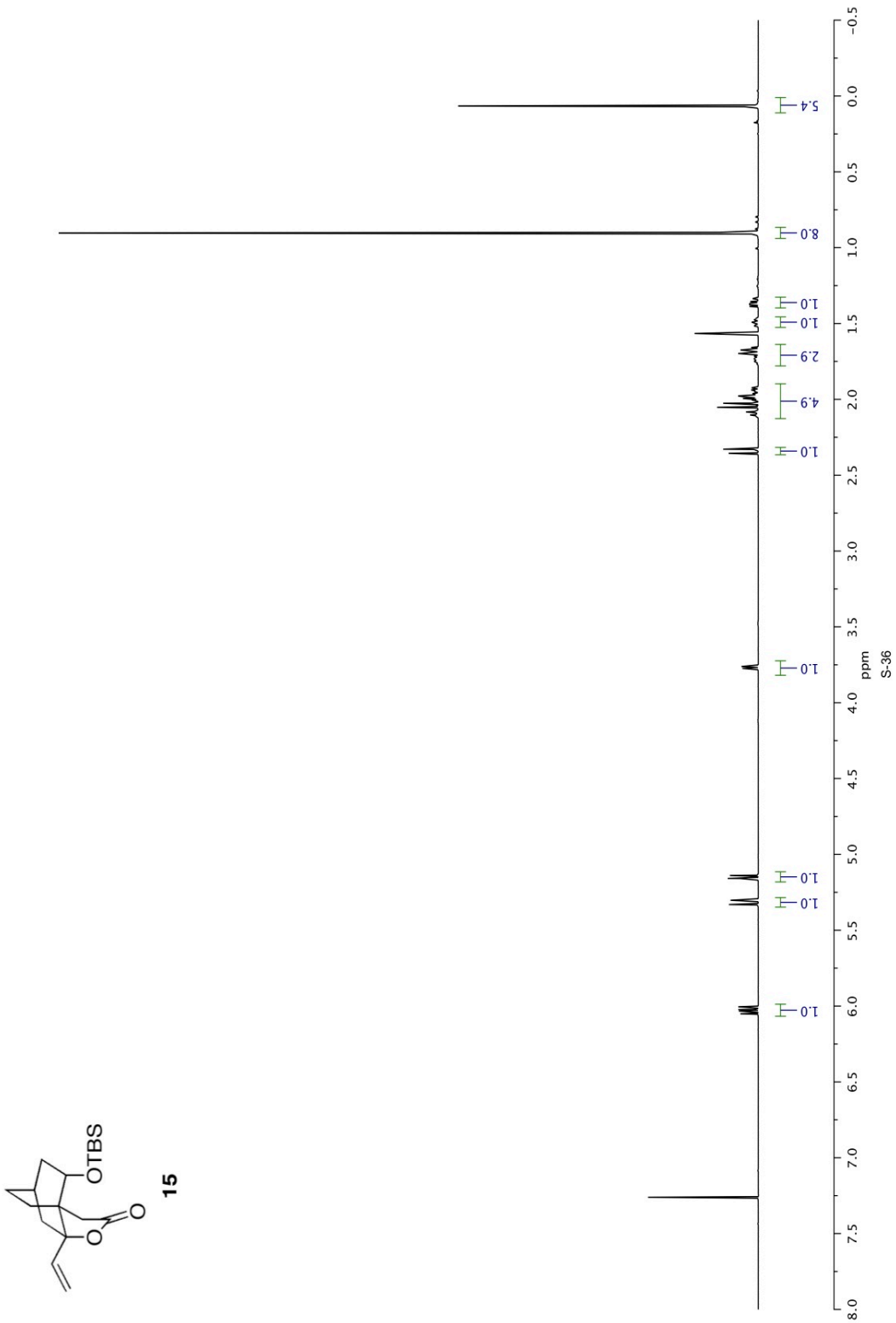
S-31


Me3Si
HO
OTBS
O
OEt
13
5.3
7.8
8.5
2.8
1.1
1.1
2.0
1.2
1.1
2.1
1.1
1.1
1.0
2.0
1.0
1.0
ppm
S-32


172.85
108.81
87.53
72.95
71.39
60.02
47.05
40.99
38.06
35.33
25.84
25.20
24.55
23.79
17.71
14.38
0.01
-4.36
-5.19
Me3Si
HO
OTBS
O
OEt
13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


OTBS
O
O
14
5.2
8.2
2.0
1.1
3.9
2.0
1.1
1.7
1.0
ppm
S-34

OTBS
O
O
14
176.03
84.87
80.96
73.90
73.71
44.30
37.99
37.73
25.93
25.86
25.69
23.93
17.80
-4.57
-4.93
ppm
S-35


OTBS
O
O
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5.4
8.0
1.0
1.0
2.9
4.9
1.0
1.0
1.0
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1.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
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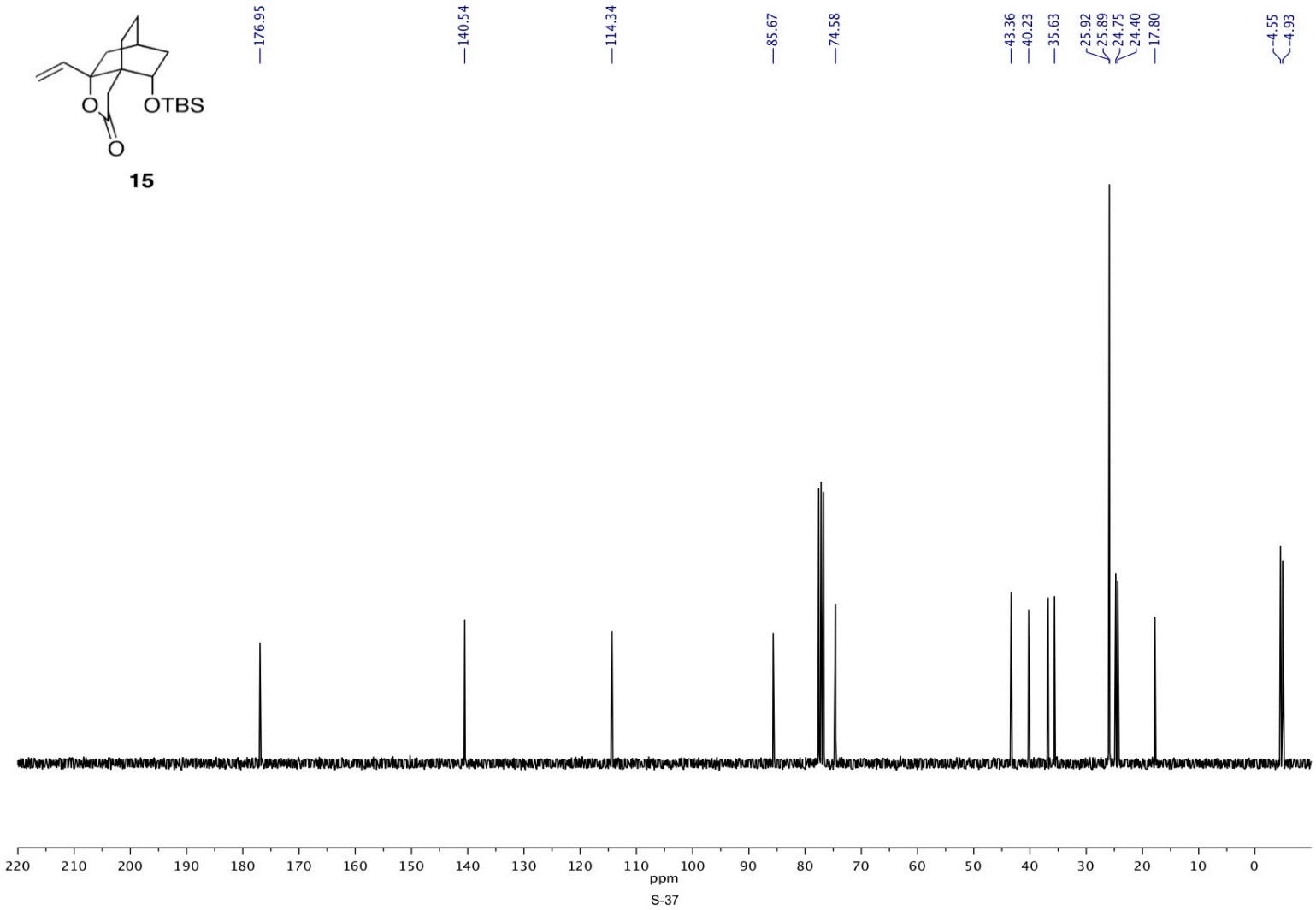
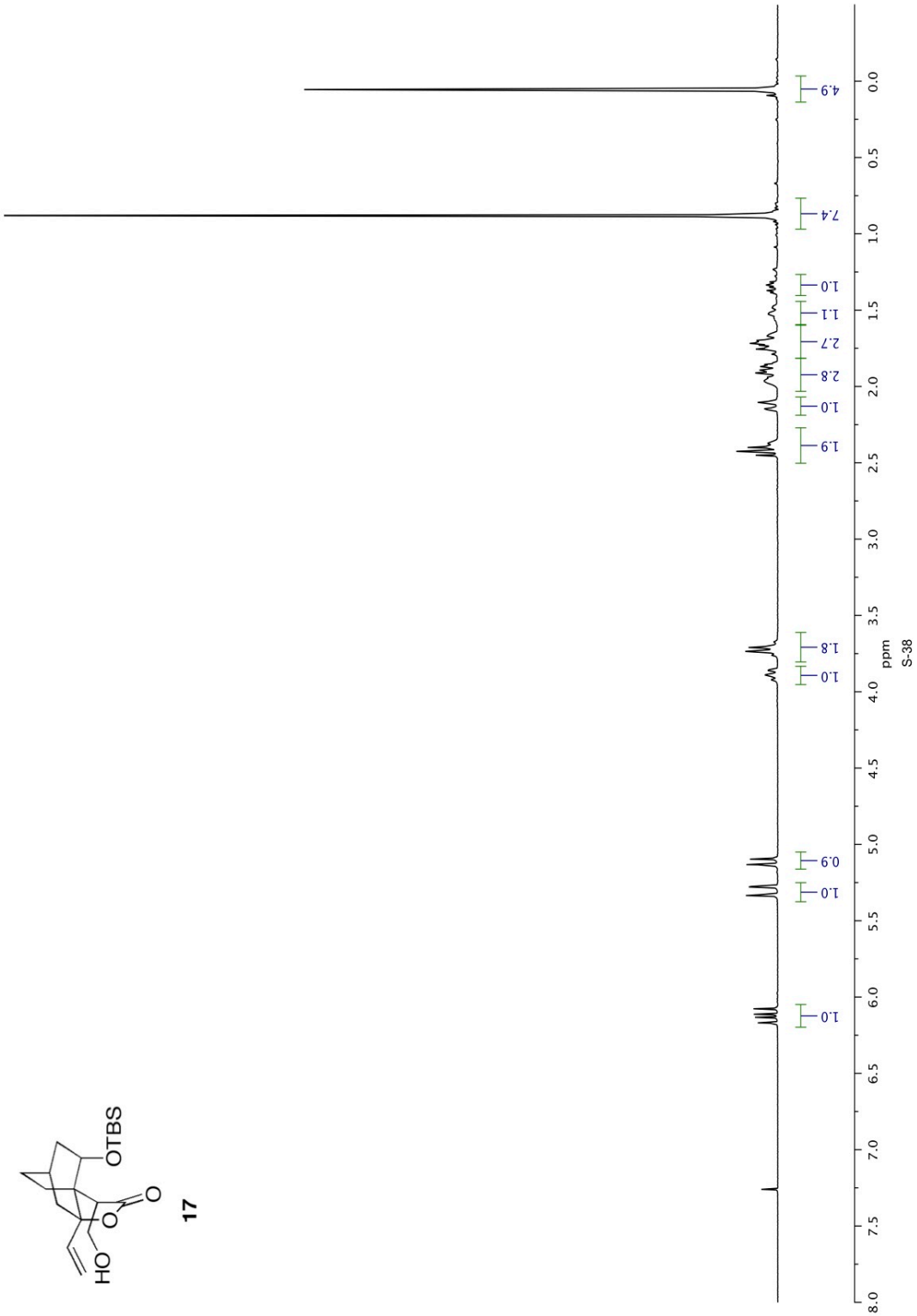
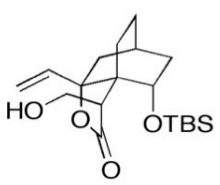
1.5
1.0
0.5
0.0
−0.5
ppm
S-36


OTBS
O
O
15
176.95
140.54
114.34
85.67
74.58
43.36
40.23
35.63
25.92
25.89
24.75
24.40
17.80
-4.55
-4.93
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm
S-37


OTBS
HO
O
O
17
4.9
7.4
1.0
1.1
2.7
2.8
1.0
1.9
1.8
1.0
0.9
1.0
1.0
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
ppm
S-38


HO
O
OTBS
O

17

178.61
142.84
114.53
86.01
76.10
61.34
50.09
44.87
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36.59
25.81
25.47
24.29
21.21
17.74
-4.36
-4.96
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

S-39

OH
OTBS
O
O
18
4.6
7.6
12.6
0.5
1.1
2.5
1.6
1.0
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
ppm
S-40

-5.20
-4.85
-4.08
-3.92
17.78
17.83
22.39
25.50
29.86
32.91
36.21
39.27
40.16
45.79
47.76
54.24
69.20
84.63
86.59
114.88
115.34
139.91
140.36
152.64
173.58
176.45
199.37
OH
OTBS
O
O
18
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm
S-41

OH
OTBS
O
O
19
5.5
8.3
1.1
1.1
3.1
1.1
1.9
1.0
1.0
1.0
1.0
1.0
1.0
1.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
2.5
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1.5
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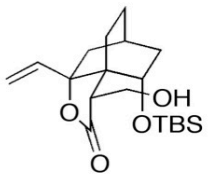
−0.5
ppm
S-42


OH
OTBS
O
O

19

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139.76
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85.00
70.32
58.67
46.53
45.75
39.36
35.63
25.99
25.34
24.33
24.18
17.99
-3.38
-4.01
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

S-43

OH
OTBS
HO
O
O
16
1.0
1.0
1.0
0.9
1.0
0.9
0.9
1.0
1.0
1.1
5.8
4.0
7.7
4.6
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
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1.0
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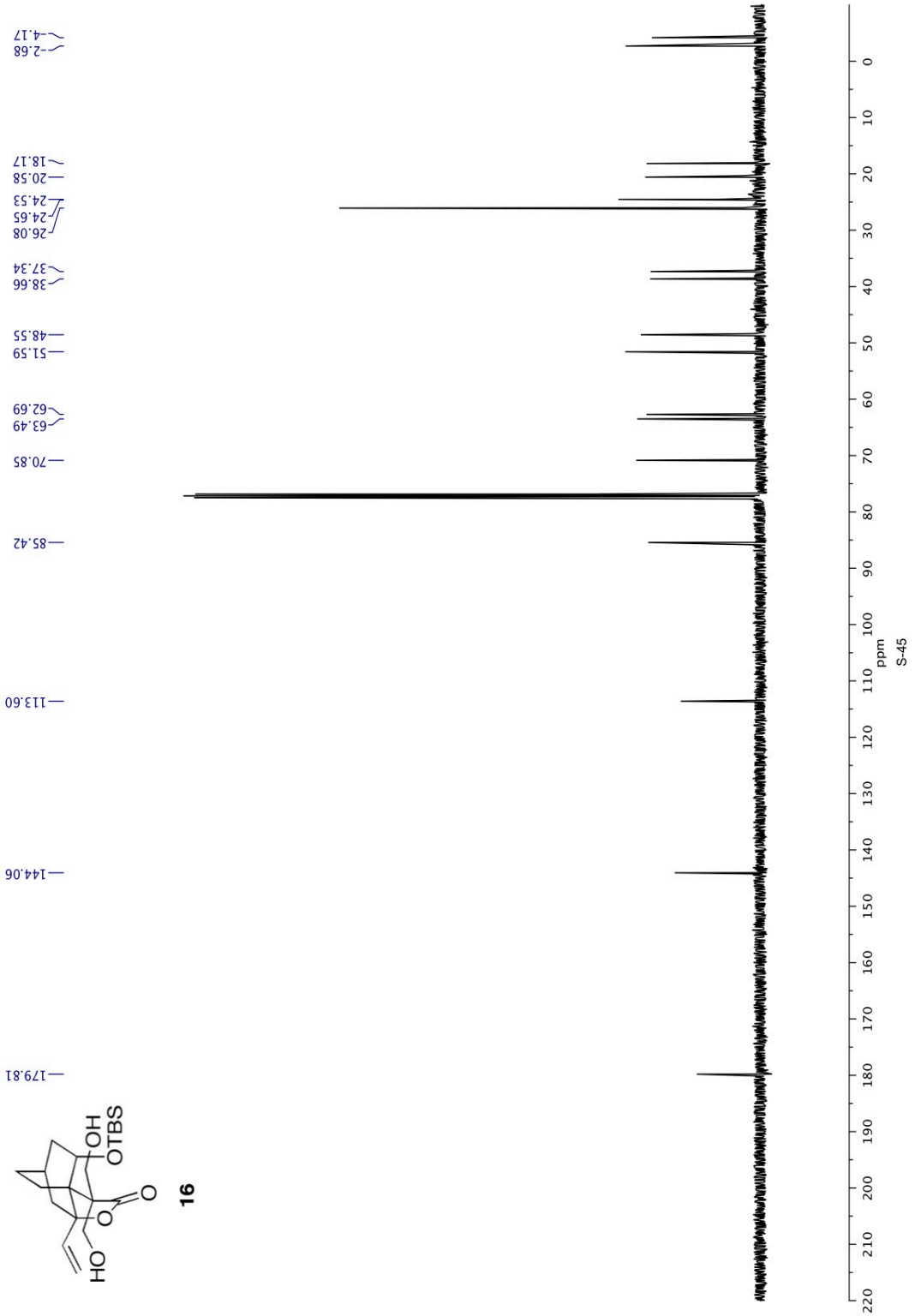
0.0
ppm
S-44


179.81
144.06
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85.42
70.85
63.49
62.69
51.59
48.55
38.66
37.34
26.08
24.65
24.53
20.58
18.17
-2.68
-4.17
OH
OTBS
HO
O
O
16
ppm
S-45

OH
OTBS
O
O
O
HO
20
3.0
2.7
8.9
1.1
2.3
1.1
1.1
3.0
1.0
1.0
1.0
1.1
1.0
2.0
1.1
1.0
ppm
S-46

-4.13
-3.72
17.98
19.61
23.84
30.99
39.27
45.12
48.24
59.15
64.45
69.98
83.87
94.05
178.81
OH
OTBS
HO
O
20
ppm
S-47

II. Total Synthesis of Sandresolide B and Studies toward Caribenol A

1. Introduction and Background

Natural products from marine sources display a vast structural diversity, generated by the rich variety of source organisms in their respective habitats.[1] One remarkable source of such natural products is the *Pseudopterogorgia* species of the gorgonians, which are the most common octocorals in the Caribbean Sea.[2] While *P. americana* is the most widespread among the 15 known species, *P. elisabethae* has received the strongest interest from natural product researchers due to the high variety of diterpenoids encountered in this invertebrate. Accounting for more than 20 diterpenoid skeletal variants found over the past 40 years (as exemplified in Figure 2.1),[3-5] *P. elisabethae* demonstrates its biosynthetic capability to form diverse structural variants from basic starting materials.

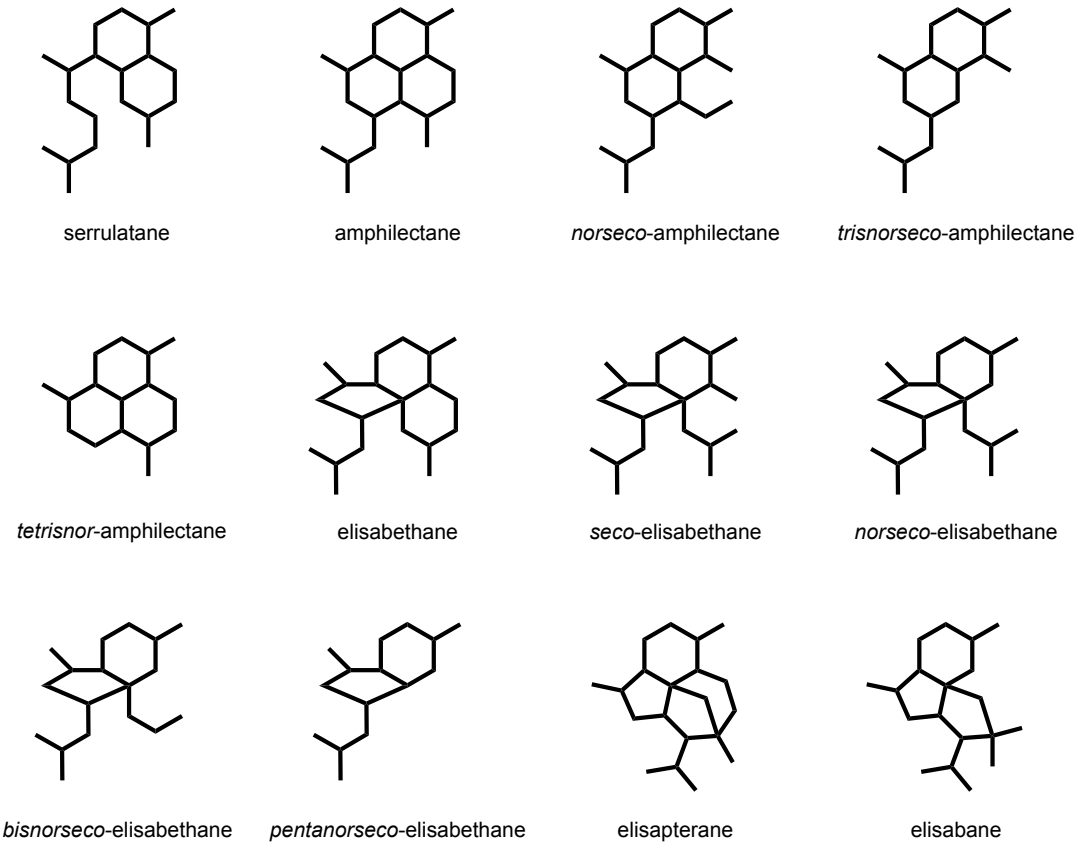


Figure 2.1. Terpenoid carbon skeletons originating from *Pseudopterogorgia elisabethae*[3-5]

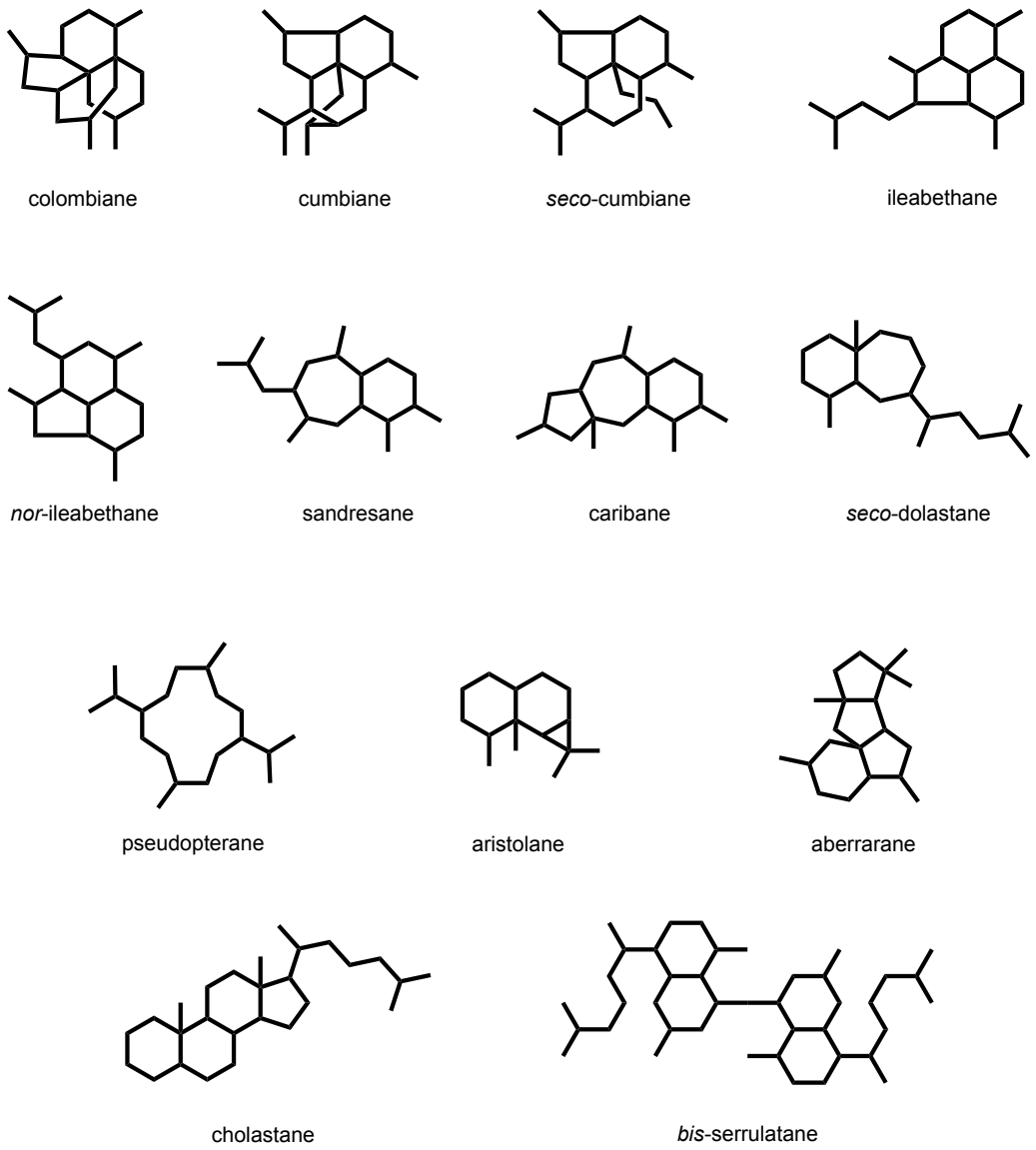
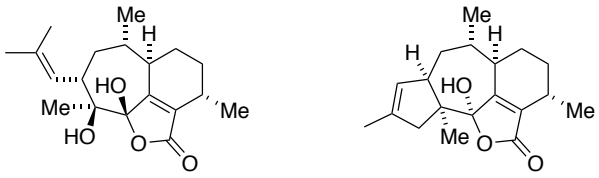


Figure 2.1. *(cont.)* Terpenoid carbon skeletons originating from *Pseudopterogorgia elisabethae*[3-5]

The natural products of relevance to the work described here, sandresolide B[6] (**81**) and caribenol A[7] (**82**), are shown in Figure 2.2. One of the distinguishing features of these natural products is their ring systems comprising a hydroxybutenolide moiety. This moiety is synthetically accessible from furans, and we were intrigued to use a furan-based strategy for the total syntheses of these two molecules. Moreover, the close structural resemblance of the carbon backbones indicated that a common synthetic approach could potentially be applied to both natural products.



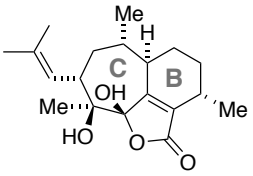
sandresolide B (**81**) caribenol A (**82**)

Figure 2.2. Structures of sandresolide B and caribenol A

2. Isolation and Structure

The group of Abimael D. Rodríguez in Puerto Rico has intensively explored novel structures of natural products from *P. elisabethae*. Although the primary focus was to uncover structurally novel metabolites, the researchers also evaluated biological activity of the newly-discovered natural products in the areas of inflammation, infectious diseases and cancer.

During an underwater expedition in the Eastern Caribbean Sea in 1996, Rodríguez and co-workers collected a specimen of *P. elisabethae* near San Andrés Island, Columbia. When reexamining the extracts of a 1.0 kg dry weight sample, the group discovered sandresolide B (**81**) (Figure 2.3), an investigation they published in 1999.[6] The structural assignment was established by a combination of extensive 1D and 2D NMR experiments, along with IR, UV and HRMS analyses. The distinctively unique structure of the novel norditerpene features a network of a seven-carbon ring joined to a six-membered ring, both of which are fused to a 5-hydroxyfuranone. In total, sandresolide B (**81**) contains six stereocenters as well as an unsaturated isobutenyl side chain.

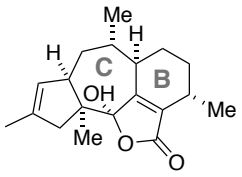


sandresolide B (**81**)

Figure 2.3. Structure and carbon ring nomenclature (amphilectane based) of sandresolide B

As part of a campaign in 2002, Rodríguez and co-workers examined the chemotype of a *P. elisabethae* specimen collected near Old Providence Island in the proximity of Nicaragua. From the hexane-soluble part of the gorgonian extract, which was subjected to a series of

purification steps, 9.0 mg of caribenol A (**82**) could be isolated.[7] The structure of the molecule was derived from the comprehensive analysis of 2D NMR experiments. X-ray diffraction studies confirmed the structure and determined the relative configuration (Figure 2.4).



caribenol A (**82**)

Figure 2.4. Structure and carbon ring nomenclature (amphilectane based) of caribenol A

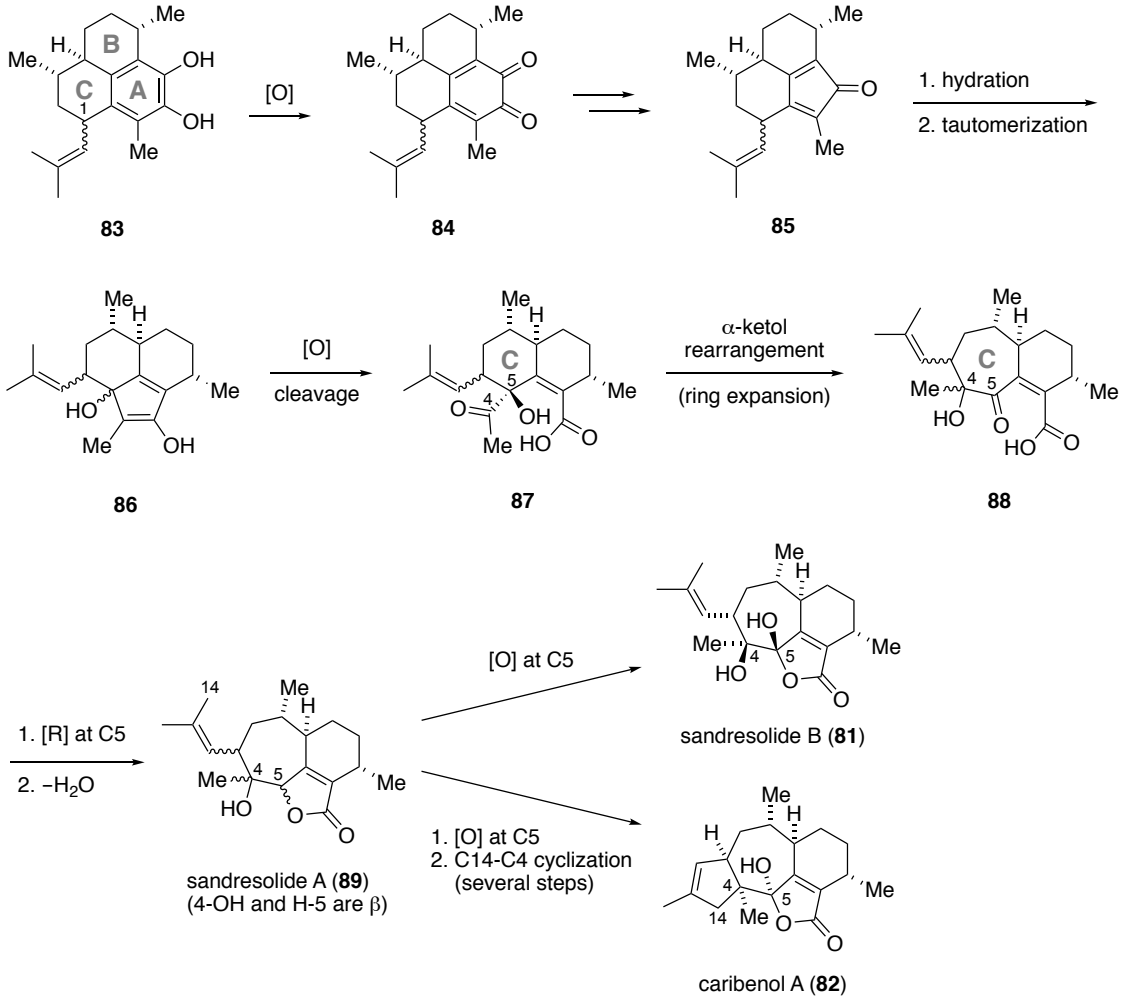
Caribenol A (**82**) comprises a polycyclic core, with three adjacent all-carbon rings forming a 5,7,6-tricarbocyclic skeleton. As in sandresolide B (**81**), an additional lactone hemiketal bridges rings B and C of this unique norditerpene, and the molecule carries six chiral centers.

3. Biosynthetic Considerations

Rodríguez and co-workers have postulated a biosynthetic pathway illustrating plausible interconnections between the frameworks of sandresolide B (**81**) and caribenol A (**82**).[7] Catechol **83** can be regarded as the common starting point for further skeletal modifications toward both natural products. This polycyclic structure is known as both C1 epimers and has been confirmed as a direct biosynthetic precursor of the anti-inflammatory pseudopterosins using radiolabeling studies.[8]

Rodríguez proposes that the biosynthesis starts with an oxidation to form *o*-quinone **84**, followed by further skeletal modifications yielding cyclopentadienone **85** (Scheme 2.1). This intermediate initially undergoes hydration and tautomerizes to dienol **86**. Its polycyclic structure is likely the precursor to the unique carbon skeleton embedding a seven-membered ring. The key transformation is triggered by oxidative cleavage of the enol, resulting in hydroxyketone **87** which undergoes an α-ketol rearrangement giving **88**. The overall degradation and rearrangement sequence leads to the expansion of ring C to a seven-membered ring. Reduction of the ketone at C5 allows the condensation to the respective butenolide **89**, which also has been isolated as the natural product sandresolide A with C4-

OH and C5-H being on the same face. The congener sandresolide B (**81**) arises from oxidation at C5. Caribenol A (**82**) is potentially obtained from **89** by oxidation at C5 and a C14–C4 cyclization in several steps.



Scheme 2.1. Proposed biosynthesis of sandresolide B and caribenol A

4. Biological Properties of Sandresolide B and Caribenol A

Gorgonian corals have very few predators[9] – a striking observation considering the abundance of these soft corals as well as the high predation intensity of their habitats.[10,11] To date, no definite explanation of the reasons behind this observation exists. Multiple research activities have not reached a definitive conclusion on the role of sclerites in animal tissue as a means of physical defense, or the sufficiency of nutritional value for feeding purposes. Interestingly, it was demonstrated via fish feeding assays that the addition of organic extracts from gorgonians at natural volumetric concentrations to food pellets

deterred consumption.[12] Consequently, organic compounds have been commonly regarded as the primary defense instrument of these species. Additional evidence points toward the function of secondary metabolites to inhibit settlement of larvae, to aid in resistance to fungi, as well as to deter overgrowth by other organisms.[13-15]

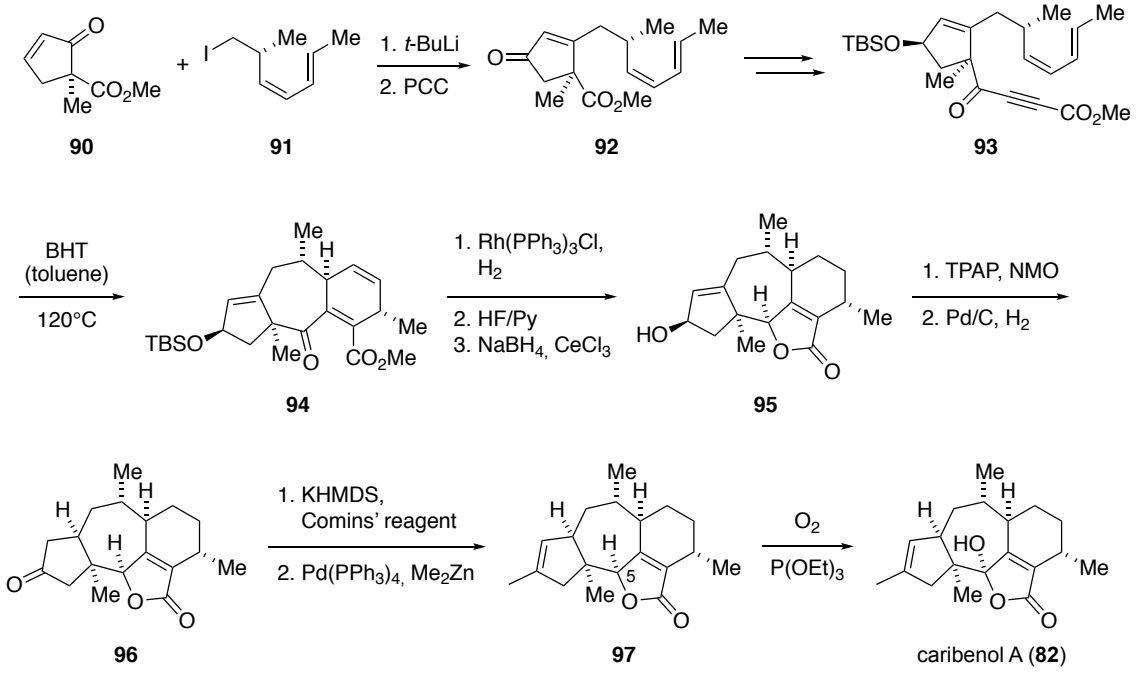
As a result, natural products originating from the gorgonians have received considerable interest with regard to their pharmacological profiles, and potent biological activities associated with these natural products have been identified, as summarized in a review by Kerr.[16] Many natural products from the *P. elisabethae* family have been demonstrated to possess anti-tuberculosis activity. Accordingly, newly isolated metabolites are commonly evaluated against *Mycobacterium tuberculosis*.[17] For sandresolide B (**81**), however, no screening of biological activity has been reported. On the other hand, caribenol A (**82**) has been evaluated for inhibitory activity against *M. tuberculosis* H37Rv, demonstrating a MIC value of >128 μg/mL. It was also found to possess weak *in vitro* antiplasmodial activity against chloroquine-resistant malaria parasite *Plasmodium falciparum* W2 with an IC_{50} value of 20 μg/mL.[7]

5. Previous Synthetic Efforts toward Caribenol A

The attractive combination of novel molecular architectures together with potentially useful pharmacological activities of sandresolide B (**81**) and caribenol A (**82**) have motivated numerous research laboratories to explore chemical syntheses of these scarce substances.

Other than our contributions, total syntheses have not been reported for either sandres–olide B (**81**), or other members of its family.[18] For caribenol A (**82**), in addition to the synthesis published by our group,[19] two groups have succeeded in the chemical syntheses of the target molecule. In the following section, the key transformations of completed total syntheses will be discussed.

The approach by Yang and co-workers was designed to expediently construct the tricyclic carbon skeleton of caribenol A (**82**) in order to provide a model route to further molecular variants.[20] An intramolecular Diels–Alder reaction (IMDA) was planned as a key step in the total synthesis. By selecting favorable starting materials, two of the six stereocenters required for the target molecule could already be incorporated during the opening sequence.

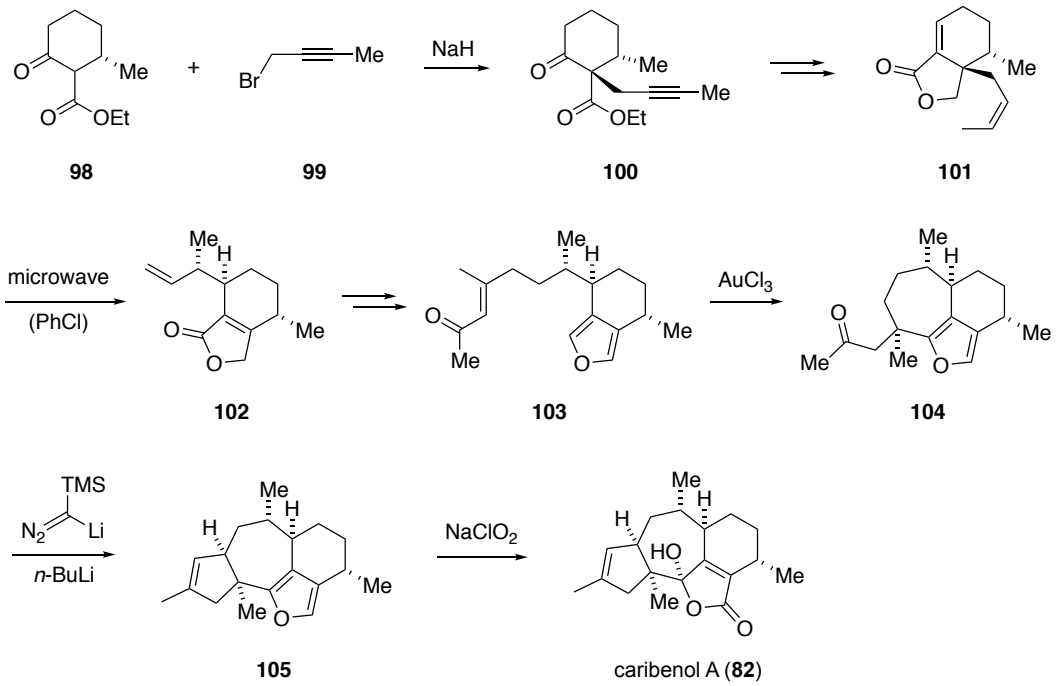


Scheme 2.2. Yang group's total synthesis of caribenol A

In an initial step, iodide **91**, after treatment with *t*-BuLi was added to enone **90** to yield intermediate **92** after oxidative rearrangement (Scheme 2.2). Subsequent transformations were aimed at installing an activated alkyne for the reaction with the electron-rich diene as well as converting the carbonyl group of an enone into silyl ether **93**. The key IMDA reaction could be effected by addition of BHT in catalytic amounts to form the tricyclic core **94** of caribenol A (**82**). As a result of the selected geometry of the diene scaffold **93**, two further stereocenters were generated as required. Subsequent chemoselective hydrogenation, reduction and esterification reactions yielded furan-2-one **95**, which could be transformed into intermediate **96** upon oxidation and hydrogenation. Completion of the carbon backbone **97** was achieved by Pd-catalyzed coupling of $ZnMe_2$ to the previously generated enol triflate. Biomimetic and stereoselective installation of the hydroxyl group at C5 could be successfully performed through oxidation with molecular oxygen in the presence of a base and $P(OEt)_3$, leading to caribenol A (**82**). The authors stated that with a successful synthesis route established, their goal was the creation of a library based on the natural product to allow for further medicinal analysis and structure-activity investigation.

More recently, the group of Luo succeeded in the synthesis of caribenol A (**82**) in the context of a campaign to develop a general synthetic route to serrulatane- and amphilectane-based natural products.[21] The starting material **98** was prepared by 1,4-addition of a methyl group to cyclohexenone, and subsequent trapping of the resulting enolate with Mander's reagent

(Scheme 2.3). The outcome of the addition was controlled by a chiral ligand and the installed stereocenter acted as a template to govern the stereocenters formed later in the synthesis. Substrate **100**, prepared by alkylation of β-ketoester **98**, was transformed into lactone **101** in a four-step sequence to set up the precursor for the first key step. Upon heating to 200 °C under microwave conditions, precursor **101** underwent a thermal Cope rearrangement to furnish **102**. The desired relative stereochemical outcome of the newly formed stereocenters was thereby controlled by the *cis*-geometry of the pendant alkene in the substrate.



Scheme 2.3. Luo group's total synthesis of caribenol A

After formation of the furan moiety as well as extension of the side chain to a total of eight carbon atoms, intermediate **103** was subjected to the second key transformation of the synthesis. In a gold-mediated closure of the seven-membered carbon ring, the nucleophilic furan added intramolecularly to the Au(III)-activated enone with good diastereoselectivity. Completion of the carbon backbone was achieved by reaction with diazo(trimethylsilyl)-methyllithium, and C-H insertion of the resulting carbene to yield cyclopentene **105**, which was oxidized using sodium chlorite to access caribenol A (**82**).

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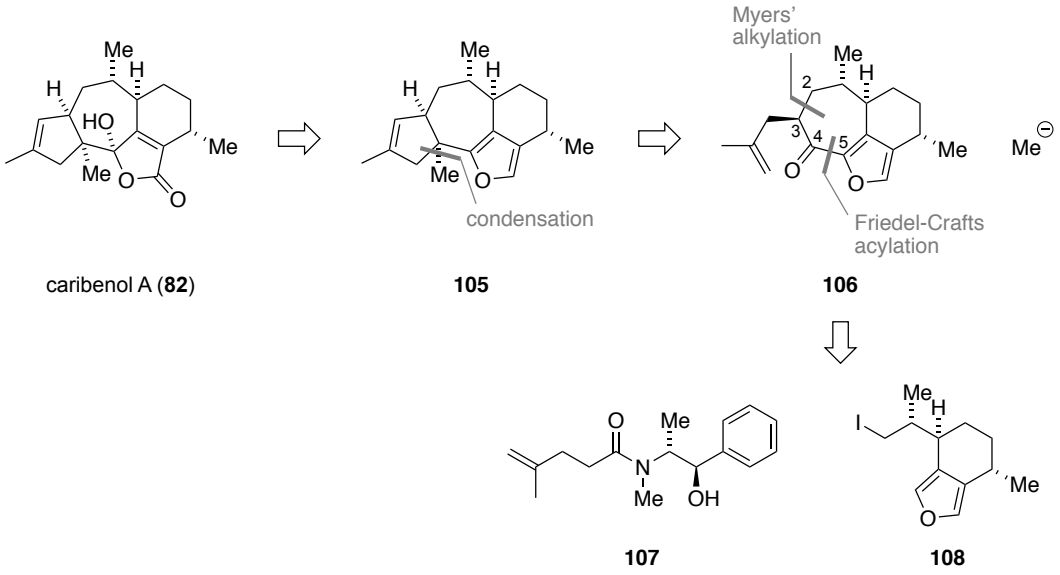
6. Results

6.1. Synthetic Studies toward Caribenol A

6.1.1. Initial Synthetic Approach

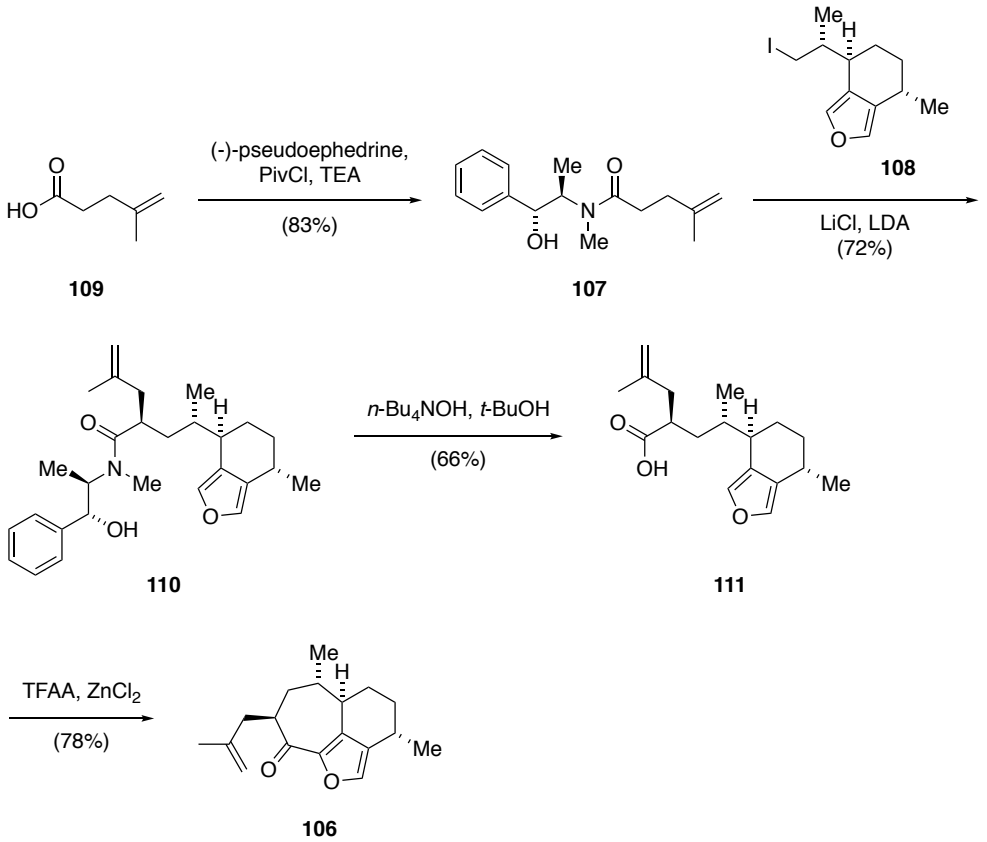
In the initial retrosynthetic analysis, the characteristic hydroxybutenolide moiety of caribenol A (**82**) was traced back to furan **105** through oxidation (Scheme 2.4). Further disconnections follow the proposed biosynthetic pathway and include the addition of a methyl and an alkene group onto a carbonyl group within intermediate **106**. The C4 carbonyl is instrumental for a Friedel–Crafts acylation to form the C4–C5 bond. The seven-membered ring is further dissected at C2/C3 through an asymmetric Myers' alkylation[1] as employed by us in the synthesis of sandresolide B (**81**).[2] Corresponding starting materials include iodide **108**, previously constructed by our group in the total synthesis of sandresolide B (**81**),[2] as well as amide **107**.



Scheme 2.4. Initial retrosynthetic analysis of caribenol A

Based on the experience previously gathered for the alkylation of β-branched alkyl iodide **108**,[2] pseudoephedrine was selected as a suitable chiral auxiliary. Thus, (–)-pseudoephedrine was N-acylated with literature known acid **109**[3] (Scheme 2.5). The reaction proceeded via activation of the carboxylic acid **109** as the mixed anhydride, which reacted smoothly with (–)-pseudoephedrine to form amide **107**. After deprotonation of **107** with LDA to the corresponding lithium enolate, reaction with iodide **108** yielded alkylation product **110**. Adding LiCl to the reaction is crucial to allow for stereoselective conversion as a secondary lithium alkoxide associated with solvent molecules is believed to shield one

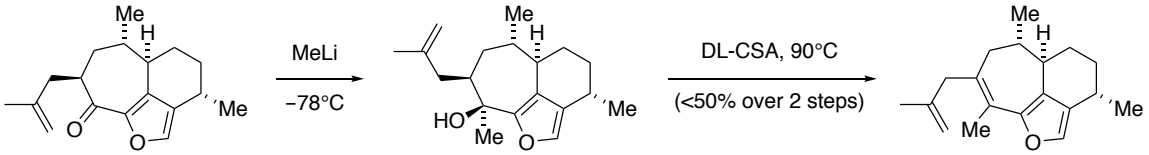
face of the enolate. Additionally, O-alkylation at the auxiliary's hydroxyl group is suppressed.[4] To cleave off the auxiliary, a standard protocol was employed, involving *t*-butyl ammonium hydroxide formed in situ from *n*-butyl ammonium hydroxide and the *t*-butyl alcohol.[4] This reagent allowed to avoid epimerization of the newly-formed stereocenter. Carboxylic acid **111** was subjected to intramolecular Friedel–Crafts acylation with the furan as the nucleophile. Due to the presence of trifluoroacetic anhydride and excess zinc chloride rapid conversion to the desired furyl ketone **106** was achieved.



Scheme 2.5. Preparation of the key intermediate **106**

Having synthesized the key intermediate **106**, the completion of the carbon skeleton by formation of the final cyclopentene ring was examined. According to our initial strategy, formation of a tertiary alcohol by addition of a methyl group to the ketone was required. In the event, using excess methyl lithium in combination with short reaction times - the conditions that have proved effective during optimization of sandresolide B (**81**) synthesis - successfully led to tertiary alcohol **112** (Scheme 2.6). Although full characterization was not carried out with this unstable compound, good stereoselectivity was observed as confirmed by NOE experiments. It was rationalized that exposure of this tertiary alcohol to acidic conditions would proceed through elimination of water to form a carbenium ion that

could be intramolecularly trapped by the *exo* double bond of the side chain, forming the required five-membered ring. Thus, several acidic conditions were screened, including DL-camphorsulfonic acid, *p*-toluenesulfonic acid and pyridinium *p*-toluenesulfonate, as well as heating of the reaction mixtures. In all cases, strong coloration of the reaction mixture was observed, whereby upon quenching only the thermodynamic elimination product **113**, which presents the newly-formed double bond in conjugation to the furan, could be obtained (Scheme 2.6). Presumably, the position of the formed positive charge relative to the furan rendered a highly stable carbenium ion, thus disfavoring nucleophilic attack by the side-chain double bond.



106 **112** **113**

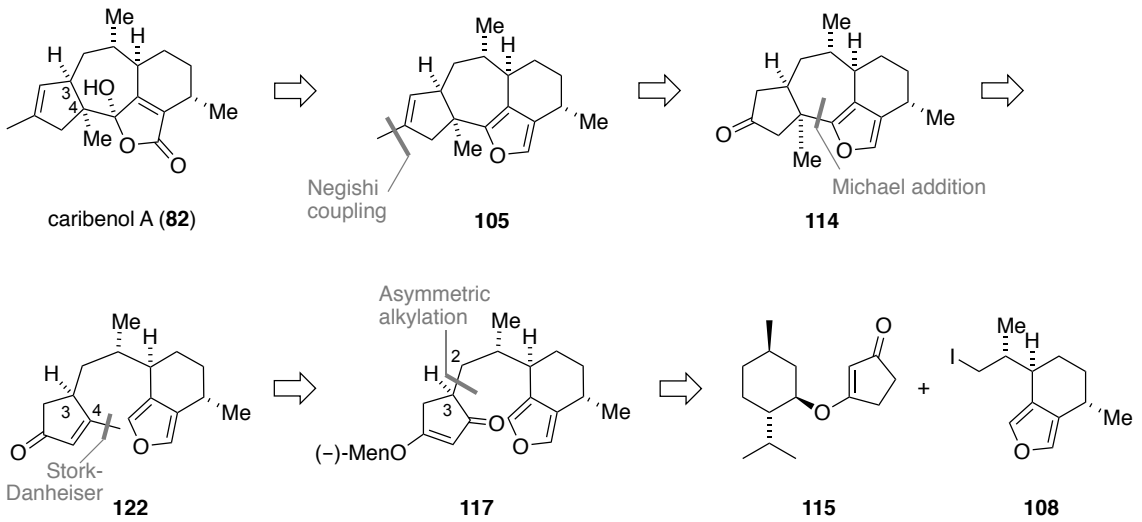
Scheme 2.6. Attempted construction of caribenol A carbon backbone

At this stage, possible workarounds such as already transforming the furan into the butenolide to suppress the stabilizing effect of the furan on the carbenium ion were not considered feasible. Firstly, competing side reactions with the butenolide during methyl additions would be expected. Additionally, the experiences gained with the furan system indicated that the cyclization to the cyclopentene ring does not advance easily despite the intramolecular nature of this reaction. Consequently, a revised strategy was designed to ensure the five-membered ring is in place early in the reaction sequence.

6.1.2. Revised Approach toward Caribenol A

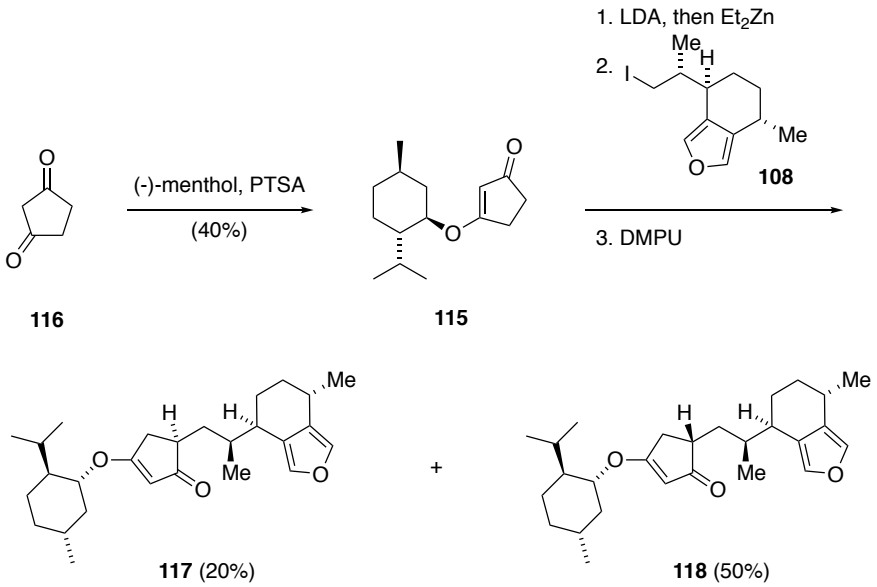
Upon revision, the retrosynthetic analysis retains the oxidation of the furan in intermediate **105** as a late step (Scheme 2.7). Further disconnections include a Negishi cross-coupling to install the alkenyl methyl group via an enol intermediate obtainable from the ketone moiety within intermediate **114**. The seven-membered ring was envisioned to be connected by means of a Michael addition between a cyclopentenone and an electron-rich furan. Working backwards, the cyclopentenone with the suitable 3,4-substitution pattern would be obtained through a Stork–Danheiser reaction[5] of the alkoxy-substituted 1,3-cyclopentadione **117**. The five-membered ring was envisioned to be introduced as part of a single building block

in an asymmetric alkylation to form the C2–C3 bond. In summary, the target molecule can be traced back retrosynthetically to the precursors **108** and **115**.



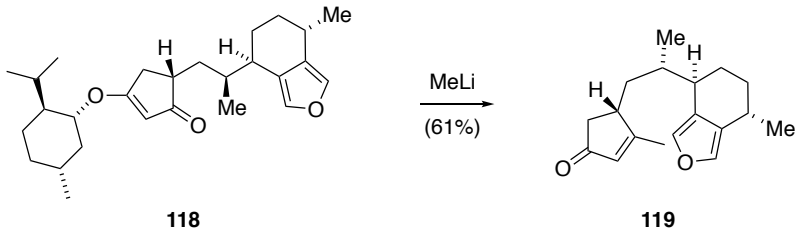
Scheme 2.7. Revised retrosynthetic analysis of caribenol A

To execute the proposed synthesis, the literature-known intermediate **115** was prepared by condensation of (–)-menthol with 1,3-cyclopentanedione (**116**)[6] (Scheme 2.8). Upon re-examining previous work toward caribenol A (**82**) conducted in our group using (+)-menthol,[7] the (–)-stereoisomer of the auxiliary was selected to achieve the required *R*-configuration outcome of the subsequent alkylation reaction. Enone **115** was treated with LDA to form the respective lithium enolate followed by diethyl zinc and readily displaced the iodide in **108** with good overall yield. It was key to perform the reaction under concentrated conditions to overcome the steric hindrance of the reactive site at the iodide and drive the reaction forward. Addition of diethyl zinc is assumed to lead to the formation of lithium alkoxydiethylzincate and was necessary to avoid self-coupling,[8] considering that a nine-fold excess of the nucleophile was employed. Upon separation of the obtained mixture of diastereomers by preparative HPLC, the desired isomer **117** could be isolated in only 20% yield, along with 50% of its epimer, **118**. This selectivity is most likely a result of the steric hindrance caused by the methyl group in the β-position, overriding the steric influence imposed by the relatively more distant menthol group. The outcome was even further shifted toward the undesired epimer when probing the reaction with (+)-menthol as the auxiliary. Optimization of the chiral auxiliary appended to the enone substrate should provide improved stereoselectivity of the reaction.



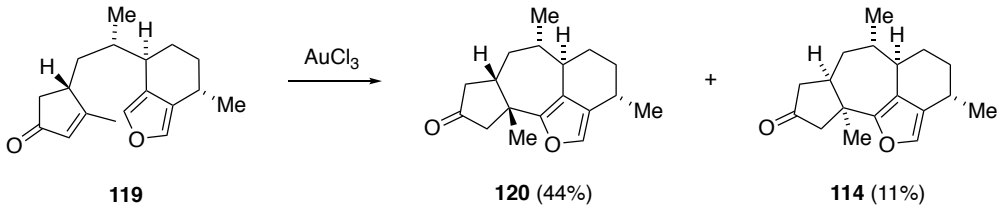
Scheme 2.8. Asymmetric alkylation of iodide precursor **108**

Despite the low yield of the alkylation reaction, sufficient quantities of **117** were accessible to continue examining the proposed total synthesis. Epimer **118** was carried along as a model system, allowing for screening of reaction conditions. Subjecting vinylogous ester **118** to methyllithium resulted in clean conversion through a Stork–Danheiser reaction to the respective cyclopentenone **119** (Scheme 2.9).



Scheme 2.9. Stork–Danheiser reaction to cyclopentenone **119**

The devised completion of the target molecule's carbon skeleton required intramolecular conjugate addition of the furan onto the enone, a transformation that could be achieved by activation of the Michael system. However, initial attempts to conduct this transformation in the presence of Brønsted acids with different pKa values (such as camphorsulfonic acid, formic acid) or Lewis acids (such as BF_3) failed. Fortunately, promising results were observed in the presence of $AuCl_3$ (Scheme 2.10).

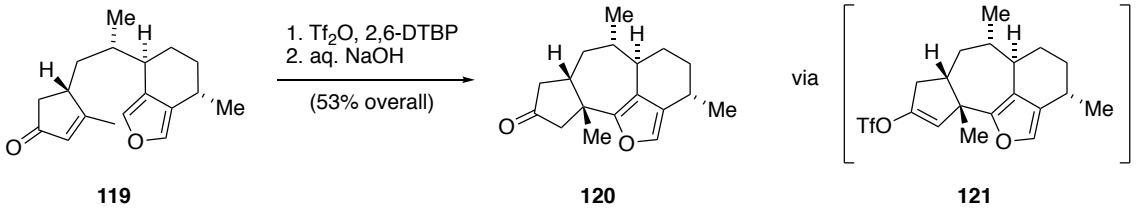


119 **120** (44%) **114** (11%)

Scheme 2.10. $AuCl_3$-mediated intramolecular addition of the furan onto the Michael system

Nevertheless, while the ring closure could be initiated, it was not possible to drive the reaction to satisfactory levels of conversion. The desired 7-membered ring containing product **120** could be obtained in low yields which varied between 33 and 44%. Interestingly, small amounts of diastereomer **114** were also formed with yields up to 11% during this reaction, indicating epimerization of the stereocenter at the cyclopentenone. In the attempt to drive the reaction to completion, further Lewis acid equivalents were added sequentially over the course of days, but considerable amounts of starting material remained unreacted. On the other hand, elevating the reaction temperature to 40°C resulted in decomposition of the substrate within less than an hour. These results seemed to confirm the enone's anticipated poor reactivity due to substitution at the 4-position.

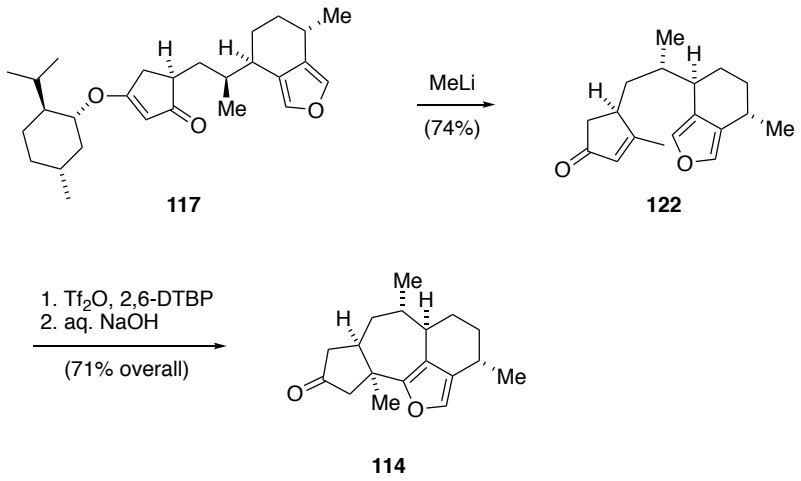
Eventually, the problematic step could be overcome using Friedel–Crafts triflation conditions developed in our group for robust 1,4-addition involving sterically hindered systems.[9] Treating enone **119** with 2,6-di-*tert*-butylpyridine followed by triflic anhydride smoothly afforded the tetracyclic intermediate **120** upon hydrolysis to the ketone by aqueous sodium hydroxide (Scheme 2.11). The structure of diastereomer **120** has been verified by NOESY experiments. It carries the fused seven-membered ring *cis* to the cyclopentanone, whereas a hypothetical *trans* isomer would have to overcome high ring strain.



119 **120** **121**

Scheme 2.11. Optimization of the conjugate addition conditions using the test system **119**

When the optimized conditions were applied to the correct diastereomer, the reaction sequence of Stork–Danheiser reaction, Friedel–Crafts triflation and hydrolysis led to the desired ketone **114** in good yields (Scheme 2.12).



Scheme 2.12. Constructing the tetracyclic framework **114** of caribenol A

The structure of the crystalline product **114** was confirmed by single-crystal x-ray diffraction experiment. The resulting structure (Figure 2.5) shows that while the rings B and C as well as the furan form a flat, sheet-like structure, the cyclopentanone rises above this plane. The structure confirms that all the stereocenters are in place and in accordance with the connectivity for caribenol A (**82**).

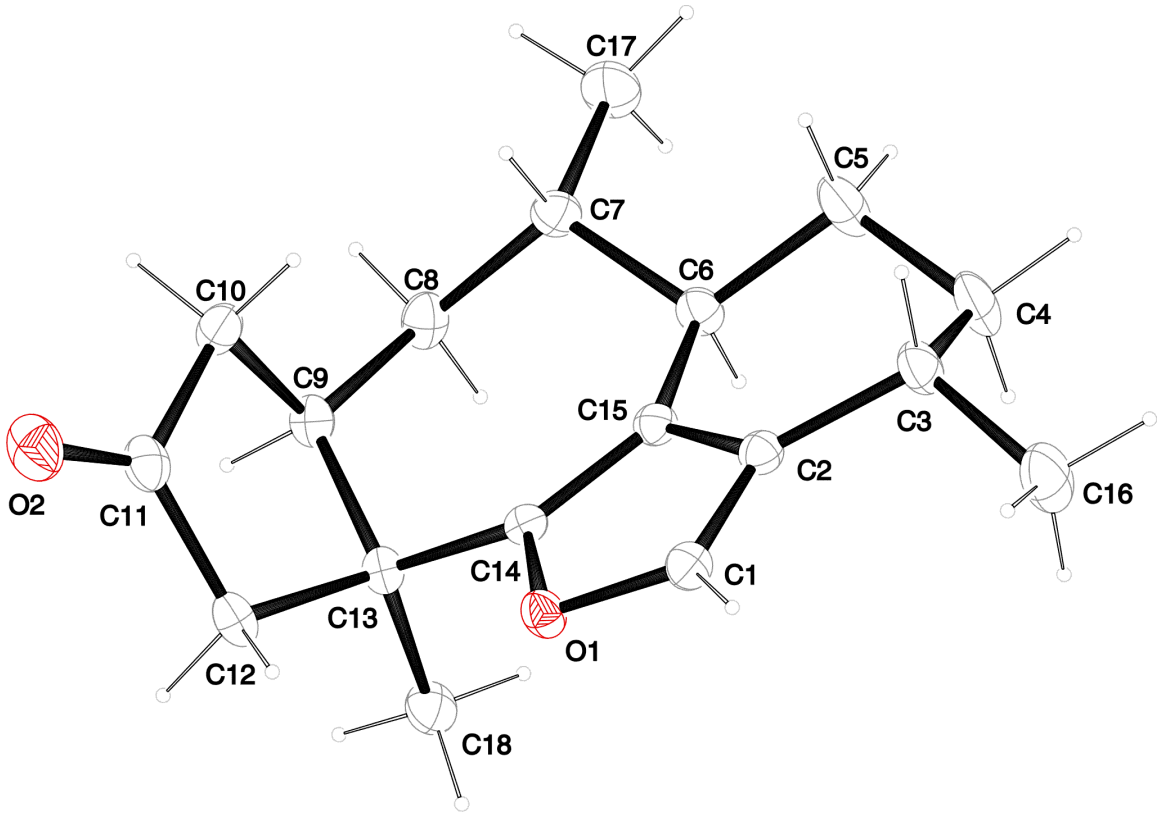
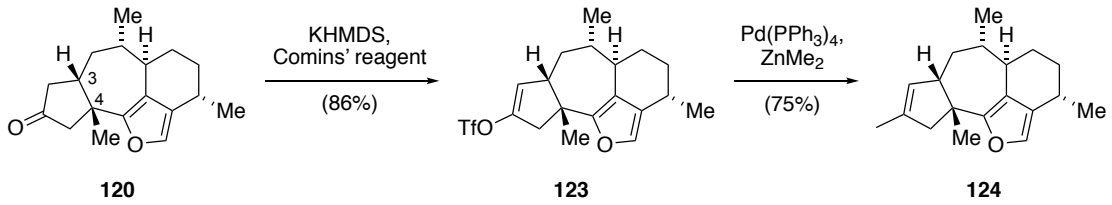


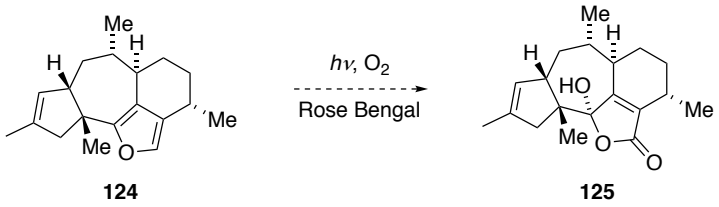
Figure 2.5. X-ray structure of tetracycle **114**

The remaining transformations required to complete the total synthesis included conversion of the cyclopentanone motif into a methyl-substituted cyclopentene, and oxidation of the furan. As before, reaction conditions were studied using the undesired diastereomer **120**, which shows opposite configuration at C3 and C4, owing to material availability. A sterically hindered base was selected to abstract the more accessible proton of the substrate. Regioselective deprotonation of cyclopentanone **120** by KHMDS, and subjection of the resulting potassium enolate to Comins' reagent,[10] provided triflate **123**, which was cross-coupled with dimethyl zinc in the presence of tetrakis(triphenylphosphine)palladium(0)[11] (Scheme 2.13). The resulting Negishi cross-coupling allowed to obtain the required cyclopentene **124** in 75% yield.



Scheme 2.13. Negishi coupling sequence using the test system **120**

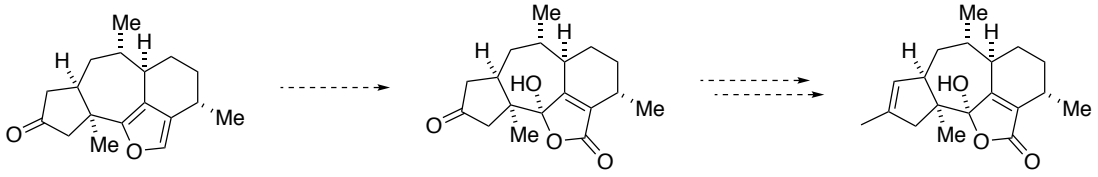
The stage was then set for probing the key oxidation sequence to obtain the hydroxybutenolide system of caribenol A (**82**). Unfortunately, applying biomimetic oxidation conditions which have reliably yielded hydroxybutenolides from the respective furan systems in late stages of total syntheses[12] to furan **124** only resulted in decomposition of the material (Scheme 2.14).



124 **125**

Scheme 2.14. Attempted furan oxidation using the test system **124**

Presumably, an ene reaction with the electron-rich double bond embedded into the cyclopentene was occurring during the attempted furan oxidation. Thus, for completion of the total synthesis, the issue of selectivity of furan oxidation would have to be overcome by altering the reaction sequence. Starting from the cyclopentanone compound **114**, initial furan oxidation followed by installing the methyl substituent should proceed smoothly according to previous results (Scheme 2.15).[11]



114 **126** caribenol A (**82**)

Scheme 2.15. Proposed route for completion of caribenol A

The above hypothesis has been validated by the subsequent research in our group,[13] leading to caribenol A (**82**). Moreover, in 2016, Luo and co-workers have identified conditions to access the hydroxybutenolide directly from the furan in the final step of their total synthesis.[14]

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6.1.3. Experimental Section

General Experimental Details

Unless stated otherwise, all reactions were carried out in oven-dried or flame-dried glassware under a positive pressure of nitrogen or argon. Tetrahydrofuran (THF), and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from and stored over CaH_2. *n*-Butyllithium (*n*-BuLi) was titrated with diphenylacetic acid prior to use. Lithium chloride (LiCl) was heated at 140 ºC under high vacuum for 16 h prior to use. Molecular sieves (MS) were activated at 200 ºC and cooled under inert atmosphere. Nitromethane was purchased from Acros and stored over 3 Å molecular sieves. All other solvents as well as starting materials and reagents were used as obtained from commercial sources without further purification.

Flash column chromatography was performed employing silica gel 60 (40-60 μm) as the stationary phase and the analytical grade solvents indicated. Reactions and chromatography fractions were monitored by analytical thin layer chromatography (TLC) using Merck silica gel 60 F_{254} glass plates. The eluted plates were visualized using a 254 nm UV lamp and/or by treatment with potassium permanganate ($KMnO_4$) or ceric ammonium molybdate (CAM) solution followed by heating.

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded at 25 °C on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are calibrated using residual non-deuterated solvent as an internal reference. ^1H NMR data are reported as follows: chemical shift (δ) (multiplicity, coupling constant(s) *J* (Hz), relative integral). Multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; br=broad, or combinations of the above. Where coincident coupling constants have been observed in the NMR spectrum, the apparent multiplicity of the proton resonance concerned is reported. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the solvent. All raw NMR data is available on request. Additional supporting spectra can be found in the NMR spectra section.

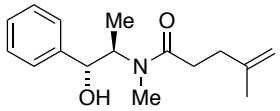
Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (electron ionization, EI) or on a Thermo Finnigan LTQ FT (electrospray ionization, ESI) instrument.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System) instrument equipped with an attenuated total reflection (ATR) measuring unit. IR data is reported as absorption frequency (cm^{-1}).

X-ray analysis measurements were performed on an α Oxford Diffraction Xcalibur diffractometer at 173 K using graphite monochromated Mo-Kα-radiation (λ = 0.71073 Å).

Experimental Procedures and Product Characterization

Pseudoephedrine amide 107

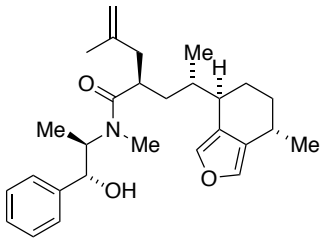


107

To a solution of **109** (1.42 g, 12.4 mmol) in MeCN (60 mL) was added triethylamine (4.14 mL, 3.02 g, 29.9 mmol) and the solution was left to stir for 10 min at room temperature. After cooling to 0 °C, pivaloyl chloride (1.83 mL, 1.79 g, 14.9 mmol) was added, and the suspension was diluted by addition of THF (12 mL). A solution of (−)-pseudoephedrine (2.05 g, 12.4 mmol) and triethylamine (1.72 mL, 1.26 g, 12.4 mmol) in THF (30 mL) was added quickly to the reaction mixture via cannula. The reaction mixture was left to come to 15 °C over 1.5 h, at which point H_2O (15 mL) were added. Volatiles were removed *in vacuo* at 70 mbar and the residue was diluted by addition of 50 mL of 0.5 M aqueous NaOH and 60 mL of 10% MeOH in CH_2Cl_2. The aqueous phase was separated and extracted with 10% MeOH in CH_2Cl_2 (3 × 60 mL). The combined organic phases were washed with 1 M aqueous NaOH (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (30% acetone/hexanes), to afford 2.69 g (10.3 mmol, 83%) of **107** as a colorless oil and as a 2:1 mixture of rotamers.

TLC: R_f = 0.24 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.10 (m, 5H), 4.68 (s, 1H), 4.64 – 4.57 (m, 1H), 4.55 – 4.17 (m, 2.6H), 4.00 – 3.88 (m, 0.4H), 2.87 – 2.72 (m, 3H), 2.52 – 2.17 (m, 4H), 1.69 (s, 3H), 1.05 – 0.90 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] (major rotamer) = 174.7, 144.8, 142.4, 128.3, 127.6, 126.5, 110.0, 76.3, 58.3, 33.1, 32.6, 32.6, 22.7, 14.4. IR (film): ν_{max} [cm^{-1}] = 3376, 3071, 2968, 2934, 1618, 1451, 1404. HRMS (ESI+): calcd for $C_{16}H_{24}NO_2$ ([M+H]$^+$) 262.1802, found 262.1801. Optical Rotation: $[\alpha]_D^{25}$ = –67° (c 1.59, CH_2Cl_2).

Myers alkylation product 110

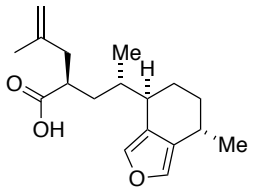


110

To a suspension of lithium chloride (1.43 g, 33.7 mmol) and diisopropylamine (0.92 mL, 0.68 g, 6.51 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 3.92 mL, 6.27 mmol) dropwise. The resulting reaction mixture was warmed to 0 °C for 5 min, and then cooled back to −78 °C. A solution of amide **107** (0.82 g, 3.13 mmol) in THF (15 mL), cooled to 0 °C, was then added dropwise by cannula. The reaction mixture was stirred for 1 h at −78 °C, and was then warmed to 0 °C for 15 min, then to room temperature for 5 min. After cooling the reaction mixture back to 0 °C, a solution of iodide **108** (0.733 g, 2.41 mmol) in THF (5 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 16 hours, then quenched with a 1:1 mixture of sat. aqueous NH_4Cl/H_2O (30 mL), and extracted with EtOAc (3 × 50 mL). The combined organic phased were dried over Na_2SO_4 then concentrated, and the resulting residue was purified by flash column chromatography (10 to 60% EtOAc/hexanes) to provide 0.756 g (1.73 mmol, 72%) **110** as a yellow oil.

TLC: R_f = 0.27 (30% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.42 – 7.22 (m, 5H), 7.17 (t, J = 1.6 Hz, 1H), 6.96 (t, J = 1.7 Hz, 1H), 4.82 – 4.75 (m, 1H), 4.74 – 4.68 (m, 1H), 4.66 – 4.58 (m, 1H), 4.38 (s, 1H), 4.17 – 4.07 (m, 1H), 2.94 – 2.74 (m, 4H), 2.68 – 2.47 (m, 2H), 2.46 – 2.32 (m, 1H), 2.15 – 2.06 (m, 1H), 1.97 – 1.87 (m, 1H), 1.85 – 1.64 (m, 5H), 1.60 – 1.41 (m, 2H), 1.40 – 1.04 (m, 8H), 0.77 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 178.3, 143.4, 142.6, 137.5, 137.2, 128.8, 128.4, 127.7, 126.4, 124.9, 112.2, 76.4, 58.3, 40.6, 38.7, 37.1, 37.0, 34.3, 34.1, 33.0, 28.1, 23.6, 23.0, 21.2, 15.8, 14.6. HRMS (ESI+) calcd for $C_{28}H_{40}NO_3$ ($[M+H]^+$) 438.3008, found 438.3003.

Acid 111

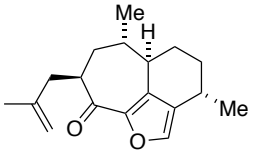


111

To **110** (0.748 g, 1.71 mmol) were added *t*-BuOH (5 mL), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 5.55 g, 8.55 mmol) and water (15 mL), and the mixture was heated at reflux for 20 h. After cooling to room temperature, the resulting mixture was treated with 0.5 M aqueous NaOH (20 mL), then extracted with EtOAc (40 mL). The separated aqueous layer was again extracted with EtOAc (2 × 40 mL), then adjusted to pH = 1 by the addition of a 1 M aqueous HCl solution. The resulting solution was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with H_2O (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (40% EtOAc/hexanes solution containing 1% AcOH) and the fractions containing product were washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated to afford 326 mg (1.12 mmol, 66%) of **111** as a colorless oil.

^{1}H NMR (599 MHz, $CDCl_3$): δ [ppm] = 7.17 (t, *J* = 1.6 Hz, 1H), 7.11 (t, *J* = 1.6 Hz, 1H), 4.80 (s, 1H), 4.76 (s, 1H), 2.80 – 2.74 (m, 1H), 2.70 (tt, *J* = 8.8, 6.0 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.39 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.19 (dd, *J* = 14.2, 5.9 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.90 (dtd, *J* = 12.4, 4.7, 2.3 Hz, 1H), 1.75 (s, 3H), 1.73 – 1.67 (m, 1H), 1.67 – 1.63 (m, 1H), 1.58 (ddd, *J* = 13.7, 7.5, 5.8 Hz, 1H), 1.33 – 1.30 (m, 1H), 1.21 – 1.14 (m, 4H), 0.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 180.6, 142.8, 137.4, 137.4, 128.9, 125.0, 112.6, 40.9, 36.8, 36.5, 34.6, 33.0, 29.9, 28.1, 23.4, 22.5, 21.2, 15.6. IR (film): ν_{max} [cm^{-1}] = 2954, 2922, 2852, 1706, 1651, 1455. HRMS (EI): calcd for $C_{18}H_{26}O_3$ ($[M]^+$) 290.1882, found 290.1875. Optical Rotation: $[\alpha]_D^{25}$ = +13° (c 0.50, CH_2Cl_2).

Ketone 106

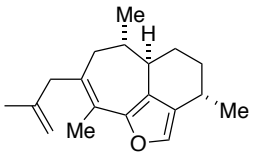


106

To a solution of **111** (260 mg, 0.895 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added trifluoroacetic anhydride (0.174 mL, 263 mg, 1.25 mmol) via a Teflon cannula. After warming the reaction mixture to room temperature for 10 min, a solution of $ZnCl_2$ (1 M in THF, 1.79 mL, 1.79 mmol) was added dropwise. The reaction mixture was left to stir for 30 min at room temperature, then heated to 40 °C for 1 h, and quenched upon cooling to room temperature by addition of 1 M aqueous HCl (10 mL). The organic layer was separated and washed with sat. aqueous $NaHCO_3$ (30 mL), water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 190 mg (0.701 mmol, 78%) of **106** as a colorless oil.

TLC: R_f = 0.35 (20% EtOAc/hexanes). ^{1}H NMR (599 MHz, $CDCl_3$): δ [ppm] = 7.38 (d, *J* = 1.6 Hz, 1H), 4.84 (s, 1H), 4.73 (s, 1H), 2.73 – 2.58 (m, 3H), 2.41 (ddd, *J* = 11.2, 9.3, 5.7 Hz, 1H), 2.22 (dddd, *J* = 12.5, 5.6, 4.4, 2.1 Hz, 1H), 2.10 (ddd, *J* = 13.8, 10.0, 0.8 Hz, 1H), 1.96 (dtd, *J* = 13.0, 4.7, 2.1 Hz, 1H), 1.82 – 1.66 (m, 6H), 1.31 (tdd, *J* = 13.1, 11.2, 2.1 Hz, 1H), 1.25 – 1.20 (m, 4H), 1.08 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 191.3, 147.9, 143.2, 141.8, 135.7, 130.3, 113.2, 44.2, 40.1, 38.7, 36.3, 35.6, 32.8, 29.7, 27.9, 22.2, 20.9, 20.4. IR (film): ν_{max} [cm^{-1}] = 2931, 1738, 1672, 1366, 1216. HRMS (ESI+) calcd for $C_{18}H_{25}O_2$ ([M+H]$^+$) 273.1855, found 273.1849.

Alkene 113



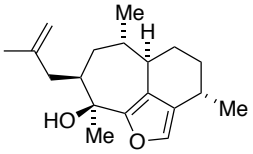
113

A solution of **106** (10 mg, 36.7 µmol) in THF (4 mL) was cooled to −78 °C and methyllithium (1.6 M in Et_2O, 92 µL, 147 µmol) was added dropwise. The reaction mixture was left to stir at −78 °C for 10 min, warmed to room temperature, then quenched by the addition of sat. aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with Et_2O (2 ×

10 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was redissolved in 4 mL toluene, heated to 90 °C and a solution of D,L-camphorsulfonic acid (0.05 M in toluene, 0.73 mL, 36.7 µmol) was added. The reaction mixture was left to stir for 30 min at 90 °C, warmed to room temperature, and concentrated. The residue was filtered over a silica plug which was then rinsed with a 1:1 mixture of hexanes/Et_2O (30 mL) to afford **113** as a minor by-product (colorless oil, <5 mg).

TLC: R_f = 0.64 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.05 (d, *J* = 1.7 Hz, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 2.95 (d, *J* = 15.4 Hz, 1H), 2.65 (d, *J* = 15.4 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.36 – 2.19 (m, 3H), 2.17 (s, 3H), 1.83 – 1.70 (m, 3H), 1.64 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.10 – 1.03 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6): δ [ppm] = 150.2, 143.5, 135.1, 132.1, 129.3, 123.8, 122.4, 111.2, 45.1, 44.7, 42.2, 37.9, 33.8, 30.5, 28.2, 22.7, 21.6, 20.6, 15.3. IR (film): ν_{max} [cm^{-1}] = 2959, 2928, 2872, 1762, 1648, 1454.

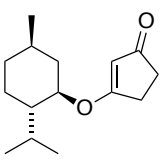
The desired product **112** could be characterized as a minor component:



112

^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.00 (d, *J* = 1.8 Hz, 1H), 4.84 (s, 1H), 4.77 (s, 1H), 2.63 (dd, *J* = 13.4, 2.7 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.33 (s, 1H), 2.14 (dd, *J* = 13.3, 11.0 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.94 – 1.85 (m, 2H), 1.75 – 1.58 (m, 5H), 1.54 – 1.45 (m, 4H), 1.12 – 0.99 (m, 5H), 0.89 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6): δ [ppm] = 153.3, 145.0, 134.8, 129.4, 117.7, 112.6, 74.3, 42.4, 38.8, 37.4, 37.0, 34.8, 33.4, 30.8, 28.4, 22.1, 21.0, 20.9.

Menthol enol ether 115

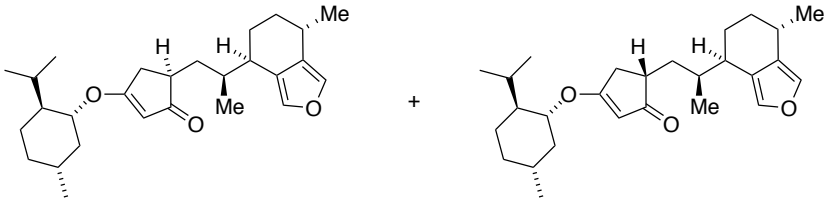


115

A solution of 1,3-cyclopentadione (**116**, 5.00 g, 50.9 mmol), (−)-menthol (9.06 g, 58.0 mmol) and *p*-toluenesulfonic acid (1.04 g, 5.47 mmol) in benzene (150 mL) was refluxed at 120 °C for 8 h using a Dean-Stark adapter. The solution was cooled to room temperature, and washed with sat. aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with EtOAc (2 × 70 mL), and the combined organic phases were washed with brine (60 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (25% to 60% EtOAc/hexanes) to afford 4.85 g (20.5 mmol, 40%) of **115** as a colorless solid.

TLC: R_f = 0.32 (25% EtOAc/hexanes). ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 5.36 (s, 1H), 3.78 (td, *J* = 10.7, 4.3 Hz, 1H), 2.17 – 2.03 (m, 4H), 2.03 – 1.92 (m, 2H), 1.49 – 1.40 (m, 2H), 1.38 – 1.29 (m, 1H), 1.23 – 1.09 (m, 1H), 0.90 – 0.79 (m, 5H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H), 0.67 – 0.61 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6): δ [ppm] = 203.5, 188.1, 104.6, 81.8, 47.7, 39.7, 34.4, 34.1, 31.1, 28.8, 26.7, 23.8, 22.2, 20.7, 16.9. IR (film): ν_{max} [cm^{-1}] = 2952, 2925, 2868, 1705, 1678, 1585. HRMS (EI): calcd for $C_{15}H_{24}O_2$ ([M]$^+$) 236.1776, found 236.1767. Optical Rotation: $[\alpha]_D^{25}$ = –156° (c 2.50, CH_2Cl_2).

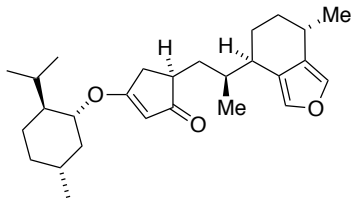
Alkylation products 117 and 118



117 **118**

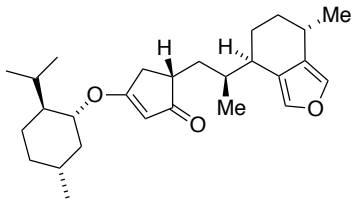
To a solution of diisopropylamine (0.86 mL, 0.62 g, 6.12 mmol) in THF (6 mL) cooled to −78 °C was added *n*-BuLi (1.6 M in hexanes, 3.64 mL, 5.82 mmol) dropwise. The solution was warmed to 0 °C over a period of 20 min, then cooled back to −78 °C. Enone **115** (1.17 g, 4.93 mmol) in THF (3 mL) was added dropwise, and the reaction mixture was stirred for 20 min at −78 °C, then Et_2Zn (0.58 mL, 0.69 g, 5.62 mmol) was added dropwise. After 5 min, iodide **108** (0.15 g, 0.49 mmol) in THF (2 mL), followed by dry DMPU (2.97 mL, 3.16 g, 24.7 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 20 h. EtOAc (30 mL) was added, and the ensuing mixture was washed with 1 M aqueous HCl (20 mL) then H_2O (20 mL), and the combined aqueous phases were extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with sat. aqueous $NaHCO_3$ (40 mL), H_2O (40 mL), and brine (30 mL), dried over Na_2SO_4

and concentrated. The residue was purified by flash column chromatography (10% acetone/hexanes), followed by HPLC (EtOAc/hexanes 10% to 18% v/v gradient elution) to afford 102 mg (0.247 mmol, 50%) of **118** and 41 mg (0.099 mmol, 20%) of **117**, both as colorless oil.



117

TLC: R_f = 0.39 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, CH_2Cl_2): δ [ppm] = 7.18 (t, *J* = 1.6 Hz, 1H), 7.14 (t, *J* = 1.6 Hz, 1H), 5.25 (s, 1H), 3.99 (td, *J* = 10.7, 4.3 Hz, 1H), 2.82 (ddd, *J* = 17.4, 7.2, 1.1 Hz, 1H), 2.78 – 2.70 (m, 1H), 2.63 – 2.46 (m, 2H), 2.31 (ddd, *J* = 17.5, 3.0, 1.1 Hz, 1H), 2.17 – 2.07 (m, 2H), 2.06 – 1.94 (m, 2H), 1.91 (dtd, *J* = 12.3, 4.8, 2.2 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.76 – 1.65 (m, 2H), 1.55 – 1.46 (m, 2H), 1.37 – 1.25 (m, 2H), 1.21 – 1.16 (m, 4H), 1.12 – 1.02 (m, 2H), 0.98 – 0.88 (m, 7H), 0.87 – 0.82 (m, 3H), 0.78 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ [ppm] = 208.6, 188.6, 137.7, 137.6, 129.4, 125.6, 103.3, 82.7, 47.9, 43.7, 39.9, 37.0, 36.6, 36.4, 35.3, 34.6, 33.3, 31.7, 28.4, 26.9, 24.1, 23.4, 22.1, 21.3, 20.7, 16.9, 16.0. IR (film): ν_{max} [cm^{-1}] = 2954, 2927, 2869, 1675, 1581. HRMS (ESI+): calcd for $C_{27}H_{41}O_3$ ([M+H]$^+$) 413.3056, found 413.3049. Optical Rotation: $[\alpha]_D^{25}$ = –67° (c 1.75, CH_2Cl_2).

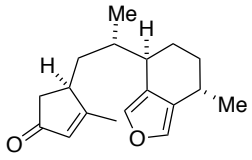


118

TLC: R_f = 0.38 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, CD_2Cl_2): δ [ppm] = 7.18 (t, *J* = 1.6 Hz, 1H), 7.17 (t, *J* = 1.6 Hz, 1H), 5.24 (s, 1H), 3.99 (td, *J* = 10.7, 4.3 Hz, 1H), 2.73 (ddd, *J* = 17.5, 7.3, 1.1 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.62 – 2.46 (m, 2H), 2.31 (ddd, *J* = 17.4, 3.0, 1.1 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.05 – 1.83 (m, 4H), 1.83 – 1.75 (m, 1H), 1.75 – 1.68 (m, 2H), 1.56 – 1.47 (m, 2H), 1.36 – 1.26 (m, 2H), 1.22 – 1.16 (m, 4H), 1.11 – 1.01 (m, 2H), 0.96 – 0.89 (m, 7H), 0.89 – 0.85 (m, 3H), 0.78 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ [ppm] = 208.5, 188.5, 137.7, 137.6, 129.3, 125.4, 103.5, 82.6, 47.9, 43.7,

39.8, 38.8, 37.2, 36.0, 35.1, 34.6, 33.3, 31.7, 28.3, 26.8, 24.3, 24.0, 22.1, 21.3, 20.8, 16.9, 14.6. IR (film): ν_{max} [cm^{-1}] = 2962, 2925, 2860, 1691, 1590. HRMS (ESI+): calcd for $C_{27}H_{41}O_3$ ($[M+H]^+$) 413.3056, found 413.3049. Optical Rotation: $[\alpha]_D^{25}$ = –48° (c 1.40, CH_2Cl_2).

Enone 122

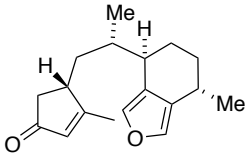


122

To a solution of **117** (10.3 mg, 25.0 µmol) in THF (1 mL) at −78 °C was added dropwise methyllithium (1.6 M in Et_2O, 0.14 mL, 225 µmol) and the reaction mixture was stirred for 1.5 h. The dry ice bath was removed, then 0.4 M aqueous $NaHSO_4$ (0.6 mL) was added, and the resulting reaction mixture was left to stir for 5 min before being diluted with 30% Et_2O/hexanes (10 mL). The organic phase was separated, then washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford 5 mg (18.4 µmol, 74%) of cyclopentenone **122** as a colorless oil.

TLC: R_f = 0.21 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.11 (t, J = 1.6 Hz, 1H), 7.03 (t, J = 1.6 Hz, 1H), 5.80 – 5.76 (m, 1H), 2.46 – 2.32 (m, 2H), 2.25 (dd, J = 17.9, 6.6 Hz, 1H), 2.20 – 2.12 (m, 1H), 1.87 (dd, J = 17.9, 2.0 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.50 – 1.58 (m, 1H), 1.44 (t, J = 1.1 Hz, 3H), 1.40 – 1.31 (m, 2H), 1.16 – 1.00 (m, 5H), 0.73 – 0.59 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6): δ [ppm] = 206.2, 179.5, 137.8, 137.7, 131.0, 128.8, 124.5, 42.4, 41.9, 39.0, 38.3, 35.3, 33.2, 28.3, 24.7, 21.2, 16.7, 14.9. IR (film): ν_{max} [cm^{-1}] = 2955, 2923, 2851, 1692, 1619. HRMS (ESI): calcd for $C_{18}H_{25}O_2$ ($[M+H]^+$) 273.1855, found 273.1850. Optical Rotation: $[\alpha]_D^{25}$ = +59° (c 0.30, CH_2Cl_2).

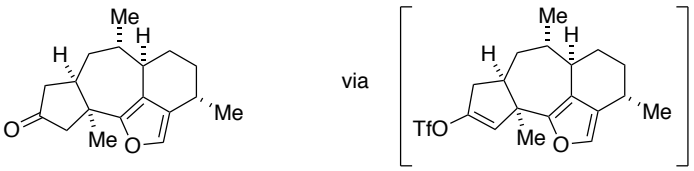
Enone 119



119

To a solution of **118** (84.2 mg, 204 μmol) in THF (4.5 mL) at −78 °C was added dropwise MeLi (1.6 M in Et_2O, 1.02 mL, 1.63 mmol) and the reaction mixture was warmed to 0 °C over 3 h. After addition of 0.4 M aqueous $NaHSO_4$ (6 mL), the reaction mixture left to stir for 5 min before dilution with 30% Et_2O/hexanes (50 mL). The organic phase was separated, then washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford 42 mg (154 μmol, 76%) of cyclopentenone **119** as a colorless oil. TLC: R_f = 0.21 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.13 (t, J = 1.6 Hz, 1H), 7.01 (t, J = 1.6 Hz, 1H), 5.80 – 5.75 (m, 1H), 2.56 – 2.49 (m, 1H), 2.46 – 2.37 (m, 1H), 2.26 (dd, J = 18.0, 6.6 Hz, 1H), 2.20 – 2.12 (m, 1H), 1.92 (dd, J = 18.0, 2.3, 1H), 1.75 – 1.61 (m, 2H), 1.51 – 1.34 (m, 5H), 1.19 – 0.99 (m, 5H), 0.75 – 0.61 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6): δ [ppm] = 206.3, 179.5, 137.8, 137.6, 130.9, 128.8, 125.0, 42.2, 42.1, 37.7, 35.1, 35.0, 33.2, 28.3, 23.1, 21.2, 16.8, 16.2. IR (film): ν_{max} [cm^{-1}] = 2956, 2925, 2869, 1711, 1692, 1619. HRMS (EI+): calcd for $C_{18}H_{24}O_2$ ([M]$^+$) 272.1776, found 272.1767. Optical Rotation: $[\alpha]_D^{25}$ = +35° (c 2.35, CH_2Cl_2)

Ketone 115



114 **114a**

To a solution of **122** (7 mg, 25.7 μmol) in MeCN (5 mL) at room temperature powdered 3 Å molecular sieves (200 mg) were added, and the resulting suspension was left to stir for 1 h. After cooling to −20 °C, di-*tert*-butylpyridine (9.8 μL, 43.7 μmol) was added, followed by dropwise addition of triflic anhydride (17.1 μL, 103 μmol). The reaction mixture was warmed to −10 °C over the course of 30 min, at which point sat. aqueous $NaHCO_3$ (5 mL) was added. After warming to room temperature, the resulting mixture was filtered through

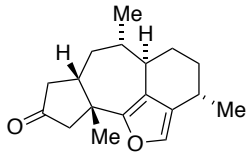
a pad of Celite™ that was subsequently rinsed with CH_2Cl_2 (20 mL). The emulsion was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (2% EtOAc/hexanes) afforded 5 mg (12.4 µmol, 48%) of triflate **114a** as a colorless oil along with 2 mg (7.34 µmol, 28%) of tetracycle **114** as a white solid. The triflate **114a** was carried on to the hydrolysis step.

To a solution of **114a** (5 mg, 12.4 µmol) in dioxane (1.5 mL) at room temperature was added a solution of sat. aqueous NaOH in water (2% w/w, 1.5 mL) and the reaction mixture was left to stir for 1 h. After addition of water (20 mL), the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (10% EtOAc/hexanes) afforded 3 mg (11.0 µmol, 89%) of tetracycle **114** as a white solid. Overall, 5 mg (18.4 µmol, 71%) of tetracycle **114** could be obtained starting from **122**.

TLC: R_f = 0.59 (20% EtOAc/hexanes). ^{1}H NMR (600 MHz, C_6D_6): δ [ppm] = 6.91 (d, J = 1.8 Hz, 1H), 3.38 (dt, J = 17.6, 1.2 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.14 (dd, J = 17.9, 12.8 Hz, 1H), 1.97 – 1.83 (m, 3H), 1.74 – 1.69 (m, 1H), 1.67 – 1.58 (m, 2H), 1.50 (ddd, J = 15.1, 5.7, 2.1 Hz, 1H), 1.39 – 1.28 (m, 2H), 1.09 (s, 3H), 1.06 – 0.90 (m, 5H), 0.78 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6): δ [ppm] = 213.7, 152.0, 135.6, 129.3, 119.3, 52.0, 44.9, 44.9, 41.7, 40.7, 37.1, 33.4, 32.4, 30.6, 28.6, 25.6, 21.3, 20.9. IR (film): ν_{max} [cm^{-1}] = 2953, 2922, 2873, 1740. HRMS (ESI): calcd for $C_{18}H_{25}O_2$ ([M+H]$^+$) 273.1855, found 273.1848. Optical Rotation: $[\alpha]_D^{25}$ = –33° (c 0.24, CH_2Cl_2).

Crystallographic data for compound **114** has been deposited at the Cambridge Crystallographic Data Centre (CCDC number 1522399) and can be obtained free of charge from the website www.ccdc.cam.ac.uk/structures/.

Ketone 120



120

To a solution of **119** (15 mg, 55.1 µmol) in MeCN (5 mL) at room temperature powdered 3 Å molecular sieves (200 mg) were added, and the resulting suspension was left to stir for

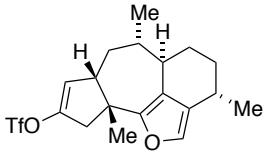
1 h. After cooling to −20 °C, di-*tert*-butylpyridine (21.0 µL, 93.6 µmol) was added, followed by dropwise addition of triflic anhydride (37.0 µL, 219 µmol). The reaction mixture was warmed to −10 °C over the course of 30 min, at which point sat. aqueous $NaHCO_3$ (5 mL) was added. After warming to room temperature, the resulting mixture was filtered through a pad of Celite™ that was subsequently rinsed with CH_2Cl_2 (40 mL). The emulsion was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was taken up in dioxane (2 mL), a solution of sat. aqueous NaOH in water (2% w/w, 1.5 mL) was added and the reaction mixture was left to stir for 1 h at room temperature. After addition of water (20 mL), the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (10% EtOAc/hexanes) afforded 8 mg (29.4 µmol, 53%) of tetracycle **120** as a colorless oil.

TLC: R_f = 0.60 (20% EtOAc/hexanes). ^{1}H NMR (600 MHz, C_6D_6): δ [ppm] = 6.98 (d, J = 1.8 Hz, 1H), 2.49 – 2.38 (m, 2H), 2.38 – 2.34 (m, 1H), 2.20 (dq, J = 18.0, 1.2 Hz, 1H), 1.85 – 1.74 (m, 3H), 1.73 – 1.64 (m, 2H), 1.31 (d, J = 0.8 Hz, 3H), 1.30 – 1.25 (m, 1H), 1.25 – 1.16 (m, 2H), 1.10 – 1.01 (m, 4H), 0.99 – 0.94 (m, 1H), 0.79 (d, J = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6): δ [ppm] = 214.6, 152.9, 135.5, 129.7, 119.4, 50.2, 46.4, 45.1, 44.7, 43.4, 42.5, 38.8, 33.6, 30.1, 28.3, 26.7, 21.4, 21.4. IR (film): ν_{max} [cm^{-1}] = 2954, 2917, 2868, 1742. HRMS (EI+): calcd for $C_{18}H_{24}O_2$ ([M]$^+$) 272.1776, found 272.1771. Optical Rotation: $[\alpha]_D^{25}$ = –55° (c 1.0, CH_2Cl_2).

120 **114**

To a solution of **119** (9 mg, 33.0 µmol) in MeCN (2 mL) was added $AuCl_3$ (10 N in MeCN, 0.1 ml, 1 mg, 3.30 µmol) and the solution was left to stir for 48 h at room temperature. The reaction mixture concentrated and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 4 mg (14.7 µmol, 44%) of **120** as a colorless oil along with 1 mg (3.7 µmol, 11%) of **114** as a white solid.

Enol triflate 123

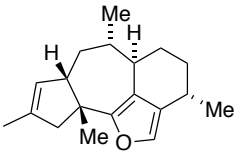


123

To a solution of **120** (18 mg, 66.1 µmol) in THF (7 mL) at −78 °C was added KHMDS (0.5 M in toluene, 0.145 mL, 72.7 µmol). After stirring at this temperature for 30 min, a solution of Comins' reagent (29 mg, 72.7 µmol) in THF (2 mL) was added and the mixture was left to stir for 3 h at −78 °C. The reaction was treated with sat. aqueous NH_4Cl (7 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (2% EtOAc/hexanes) to afford 23 mg (56.9 µmol, 86%) of **123** (mixture of diastereomers) as a colorless oil.

^{1}H NMR (600 MHz, C_6D_6): δ [ppm] (major diastereomer) = 7.01 (d, *J* = 1.8 Hz, 1H), 5.14 (td, *J* = 2.8, 1.0 Hz, 1H), 2.73 – 2.68 (m, 1H), 2.51 – 2.45 (m, 1H), 2.42 (dd, *J* = 16.1, 1.0 Hz, 1H), 2.06 (dq, *J* = 11.4, 2.9 Hz, 1H), 1.77 – 1.84 (m, 2H), 1.76 – 1.71 (m, 1H), 1.43 (s, 3H), 1.32 – 1.27 (m, 1H), 1.24 – 1.17 (m, 2H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.08 – 1.03 (m, 1H), 0.98 – 0.93 (m, 1H), 0.82 (dd, *J* = 6.6, 1.0 Hz, 3H). ^{13}C NMR (150 MHz, C_6D_6): δ [ppm] = 152.1, 148.0, 136.1, 128.3, 122.1, 119.2 (q, *J* = 320.8 Hz, CF_3), 52.6, 44.3, 44.3, 44.1, 42.2, 38.0, 33.8, 29.7, 29.5, 28.0, 21.7, 21.5. Signal for C-OTf not observed. These findings are in accordance with the characterization of similar molecules. (Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *Journal of the American Chemical Society* **2010**, *132*, 13608).

Methylcyclopentene 124



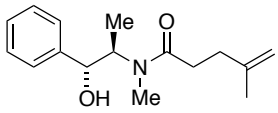
124

To a degassed solution of **123** (20 mg, 49.5 µmol) and $Pd(PPh_3)_4$ (5.7 mg, 4.95 µmol) in THF (7 mL) at room temperature was added Me_2Zn (1.2 M in toluene, 0.12 mL, 148 µmol) dropwise. The reaction mixture was stirred for 1 h at this temperature, at which point sat.

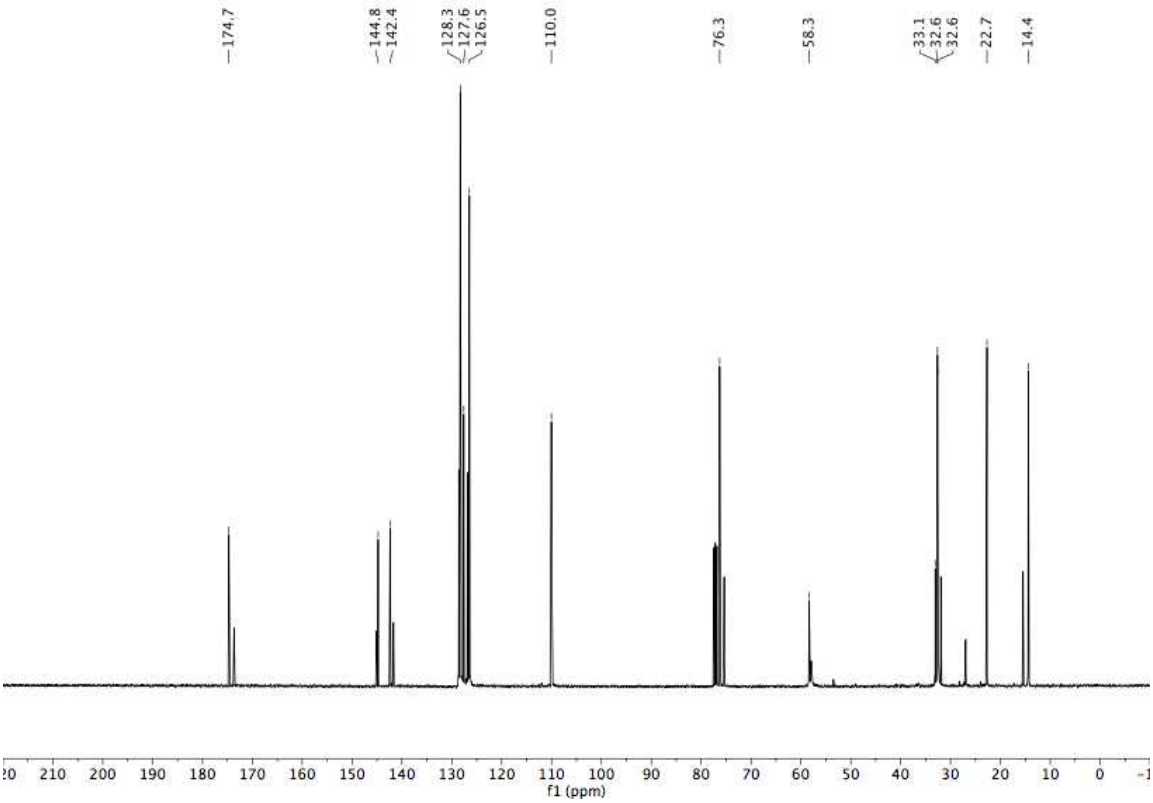
aqueous NH_4Cl solution (3 mL) was added. After extraction with Et_2O (3 × 10 mL), the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (1% EtOAc/hexanes) to afford 10 mg (37.0 µmol, 75%) of **124** as a colorless oil.

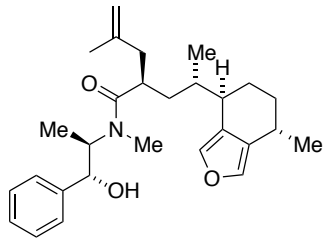
TLC: R_f = 0.87 (2% EtOAc/hexanes). ^{1}H NMR (400 MHz, C_6D_6): δ [ppm] = 7.13 (d, J = 1.8 Hz, 1H), 5.22 – 5.19 (m, 1H), 2.69 – 2.62 (m, 1H), 2.60 – 2.52 (m, 1H), 2.46 – 2.38 (m, 1H), 2.33 (d, J = 15.9 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.85 – 1.91 (m, 1H), 1.81 – 1.74 (m, 1H), 1.66 (d, J = 0.6 Hz, 3H), 1.62 – 1.56 (m, 4H), 1.50 – 1.39 (m, 2H), 1.22 – 1.00 (m, 5H), 0.94 (d, J = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 154.9, 137.4, 135.1, 129.2, 127.8, 117.6, 56.6, 49.9, 45.8, 44.6, 43.5, 37.6, 33.8, 29.8, 29.6, 27.9, 21.8, 21.7, 16.8. HRMS (ESI) calcd for $C_{19}H_{27}O$ ($[M+H]^+$) 271.2062, found 271.2055.

NMR Spectra



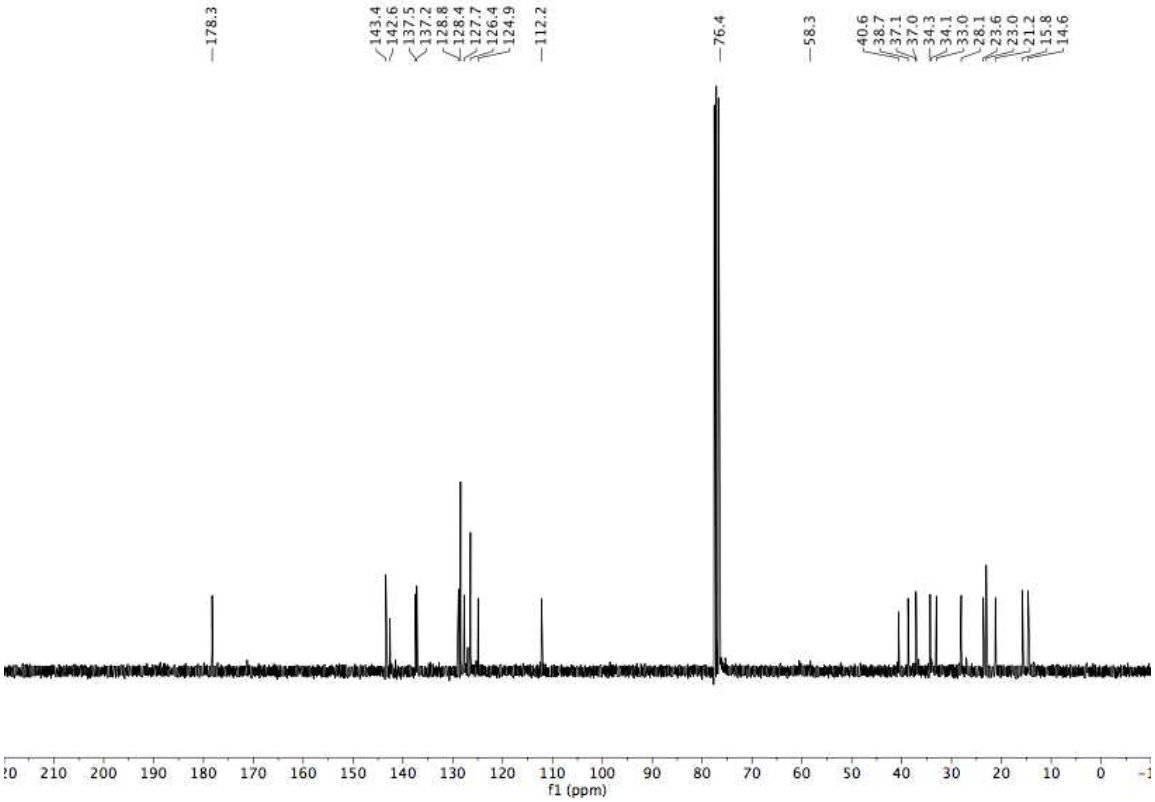
107

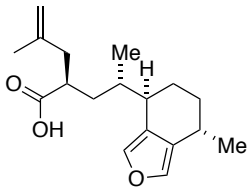



Me
H
O
N
Me
Me
Me
O
OH

110

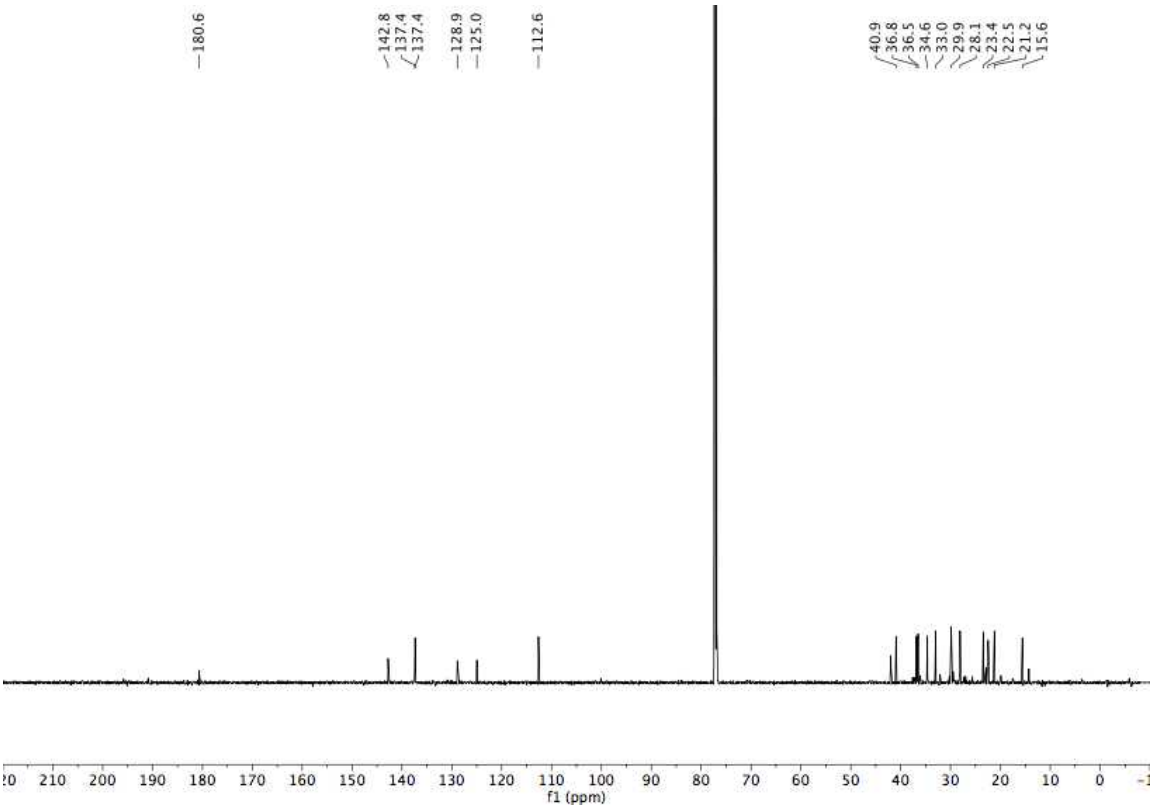
4.93
0.74
0.75
1.04
1.06
1.11
1.06
0.99
3.99
2.04
1.09
1.02
1.09
4.94
1.93
7.86
2.64
f1 (ppm)

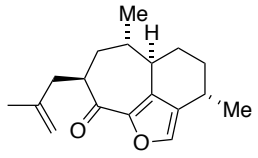

178.3
143.4
142.6
137.5
137.2
128.8
128.4
127.7
126.4
124.9
112.2
76.4
58.3
40.6
38.7
37.1
37.0
34.3
34.1
33.0
28.1
23.6
23.0
21.2
15.8
14.6
f1 (ppm)


Me
H
O
OH
Me
O

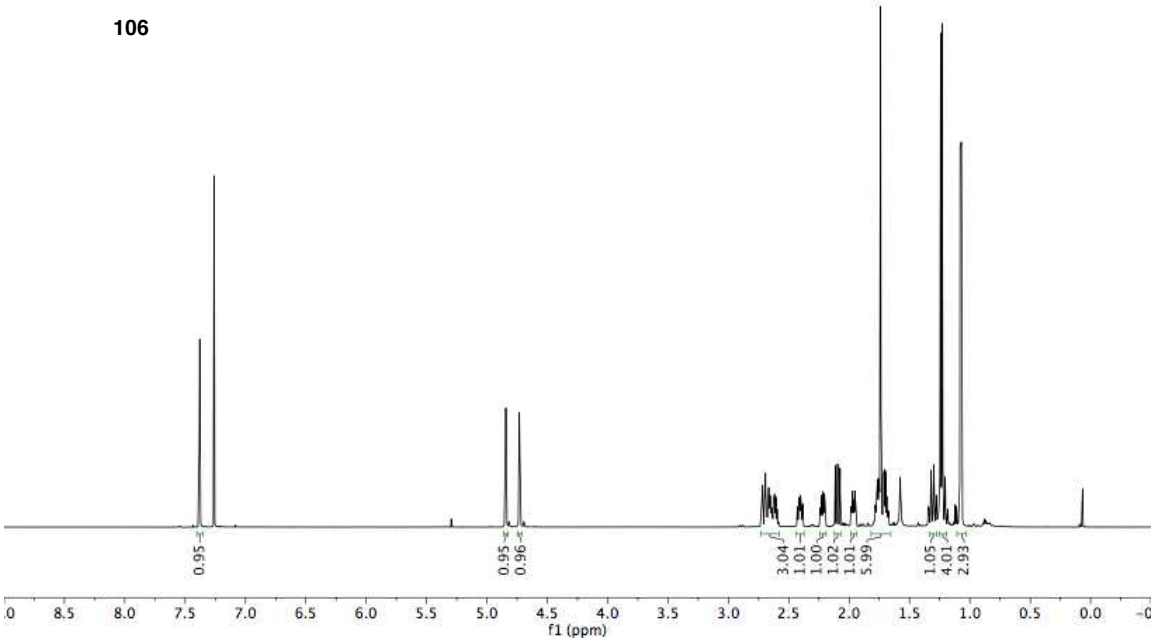
111

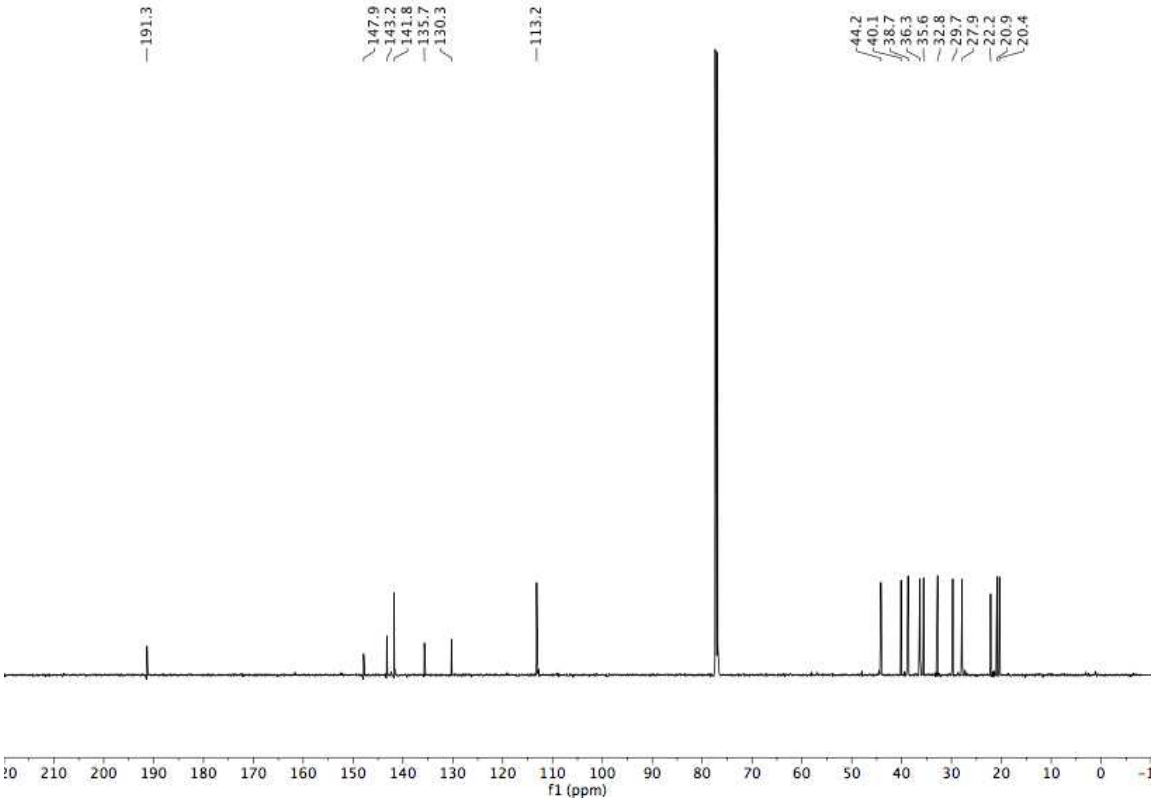
0.78
0.76
0.97
1.01
0.97
1.02
1.03
1.00
1.15
0.94
1.04
2.76
1.08
1.06
1.01
1.18
4.07
3.10
f1 (ppm)


180.6
142.8
137.4
137.4
128.9
125.0
112.6
40.9
36.8
36.5
34.6
33.0
29.9
28.1
23.4
22.5
21.2
15.6
f1 (ppm)


Me
H
Me
O
O

106


0.95
0.95
0.96
3.04
1.01
1.00
1.02
1.01
5.99
1.05
4.01
2.93
f1 (ppm)


191.3
147.9
143.2
141.8
135.7
130.3
113.2
44.2
40.1
38.7
36.3
35.6
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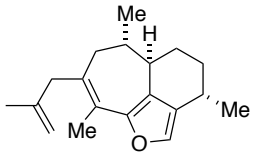
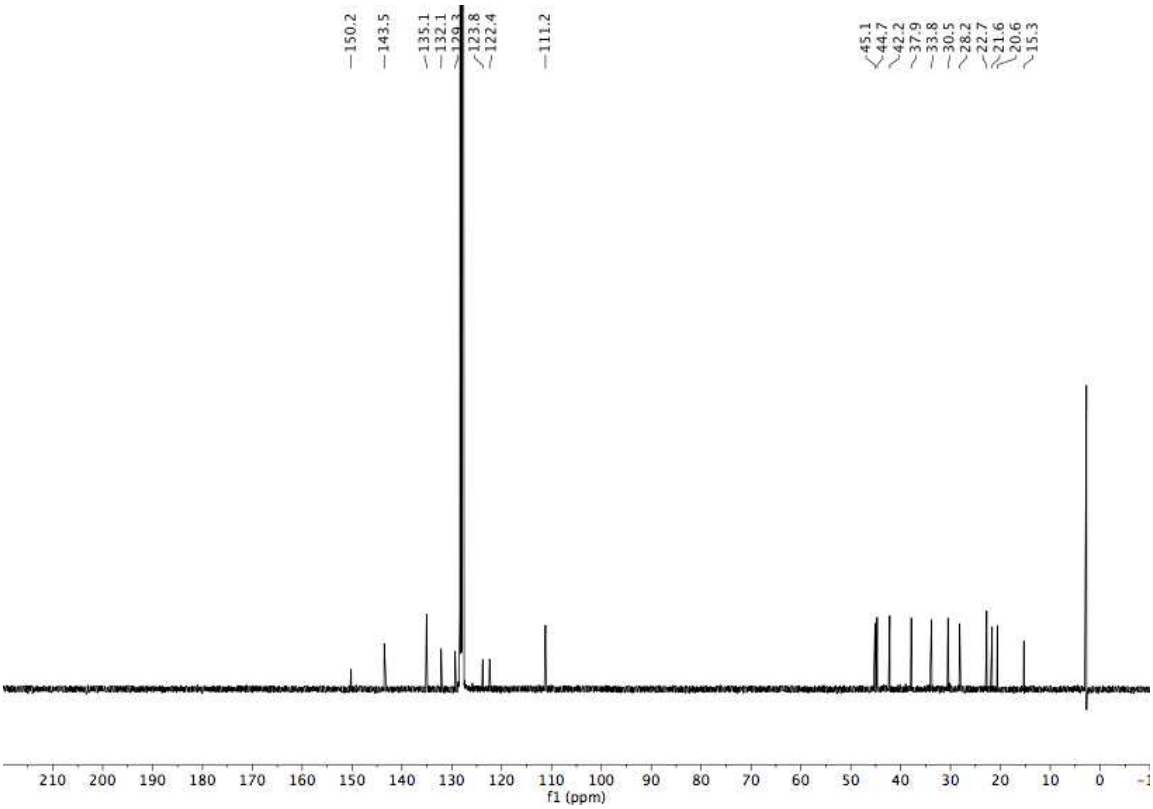
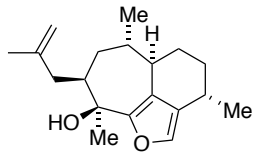
29.7
27.9
22.2
20.9
20.4
f1 (ppm)


Me
H
Me
Me
O

113

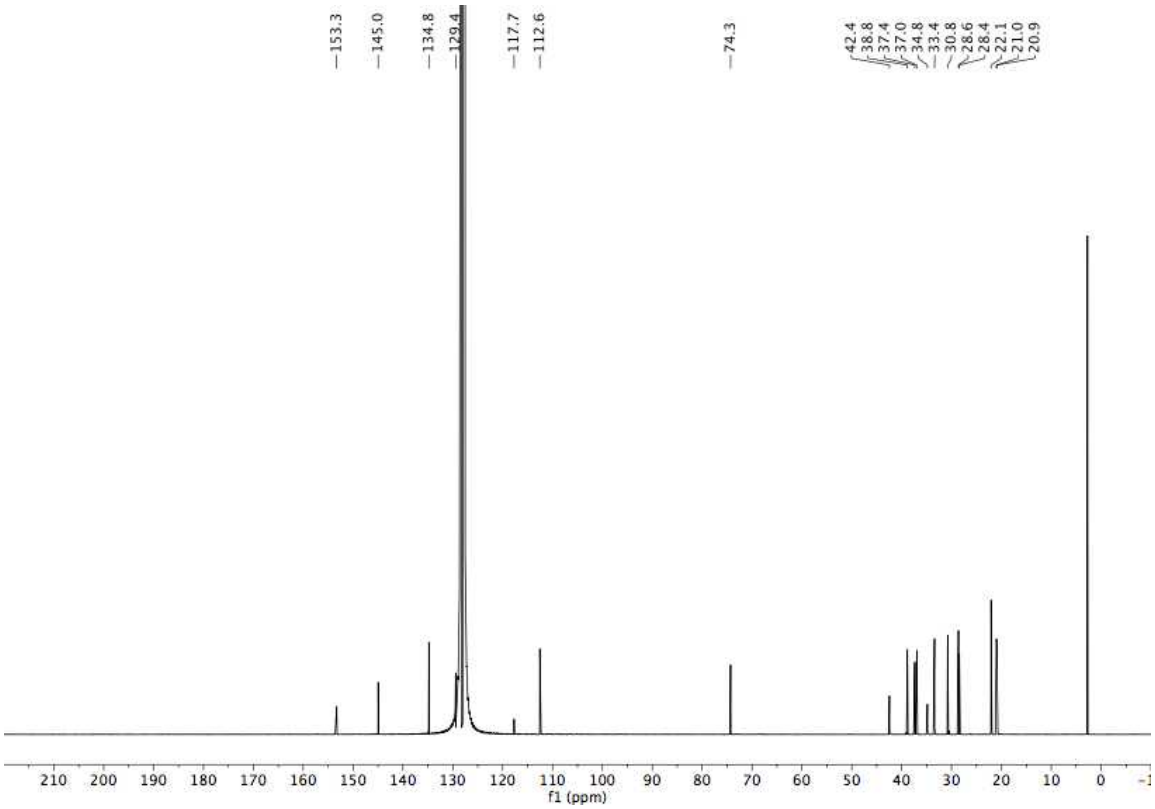
0.76
0.92
0.94
1.01
1.00
1.00
2.94
3.02
3.03
3.01
3.00
1.88
3.01
0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

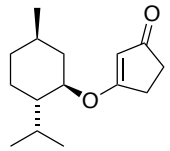

150.2
143.5
135.1
132.1
129.2
123.8
122.4
111.2
45.1
44.7
42.2
37.9
33.8
30.5
28.2
22.7
21.6
20.6
15.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
H
HO
Me
O
Me

112

0.77
0.93
0.90
1.00
1.00
0.92
1.01
1.92
1.97
4.93
3.81
4.91
3.02
f1 (ppm)


153.3
145.0
134.8
129.4
117.7
112.6
74.3
42.4
38.8
37.4
37.0
34.8
33.4
30.8
28.6
28.4
22.1
21.0
20.9
f1 (ppm)



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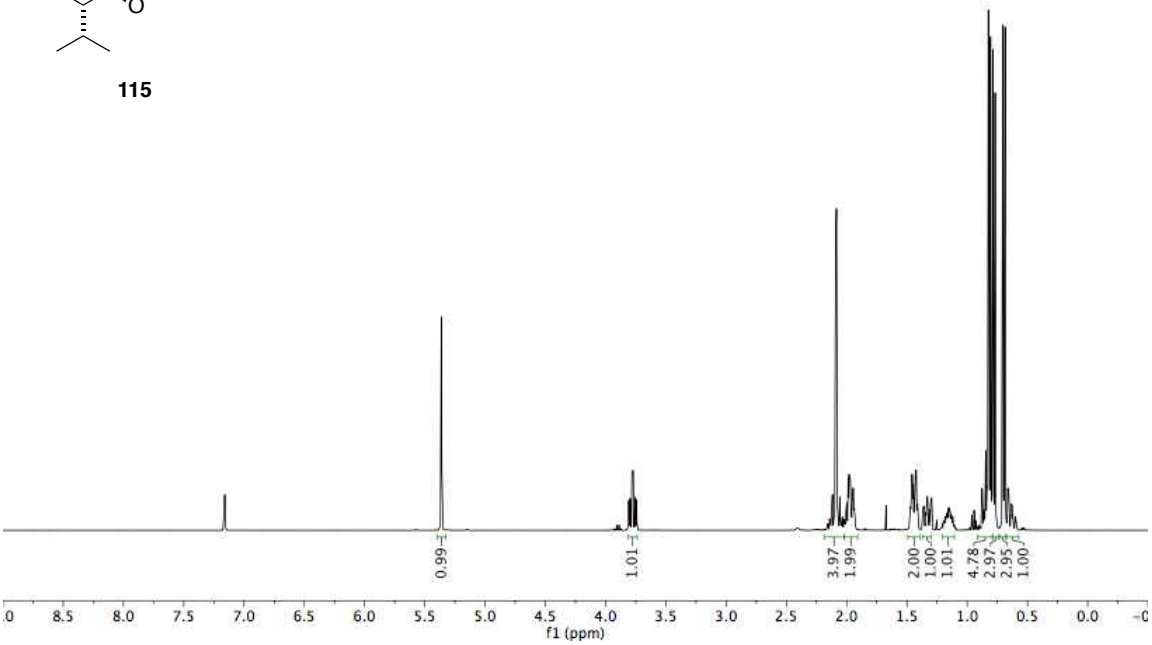
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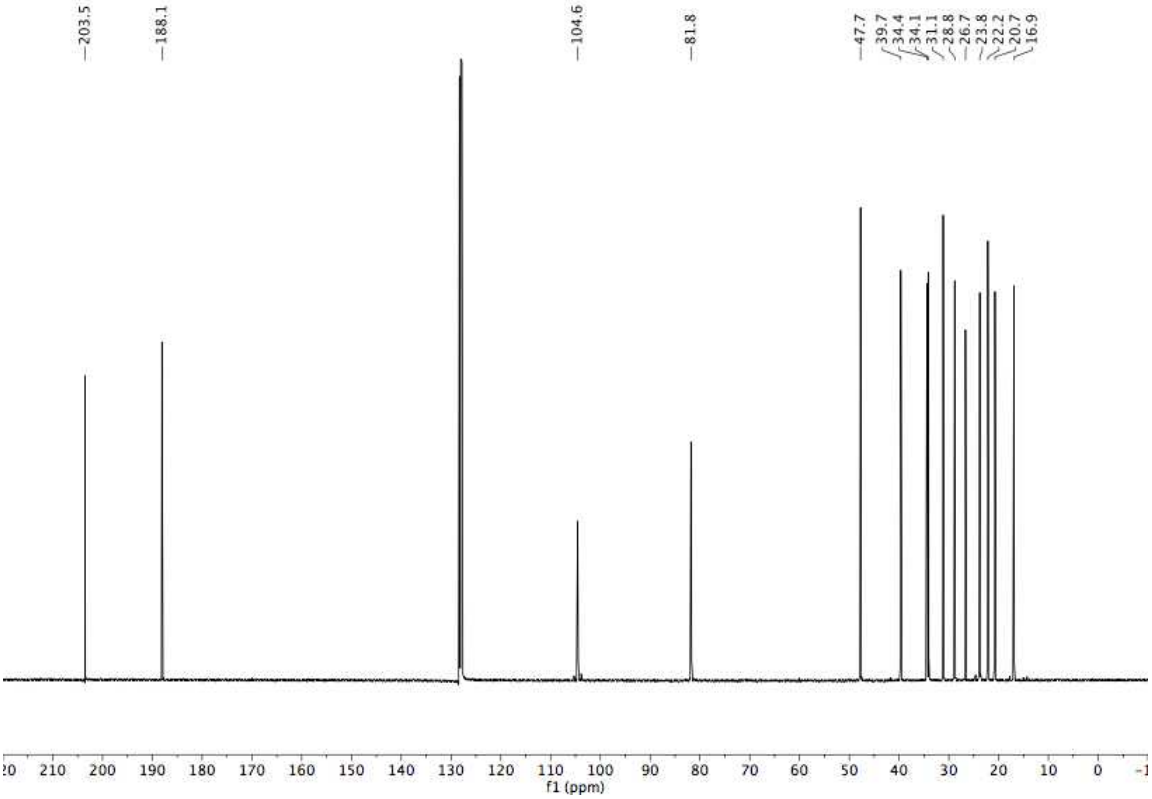
1.00
f1 (ppm)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104.6
81.8
47.7
39.7
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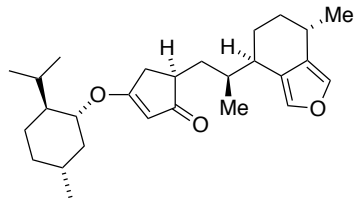
34.1
31.1
28.8
26.7
23.8
22.2
20.7
16.9
f1 (ppm)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H
H
O
Me
O
O

117

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0.95
1.00
0.94
0.95
2.01
1.00
2.00
2.01
1.01
1.00
1.98
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2.02
4.05
2.00
7.00
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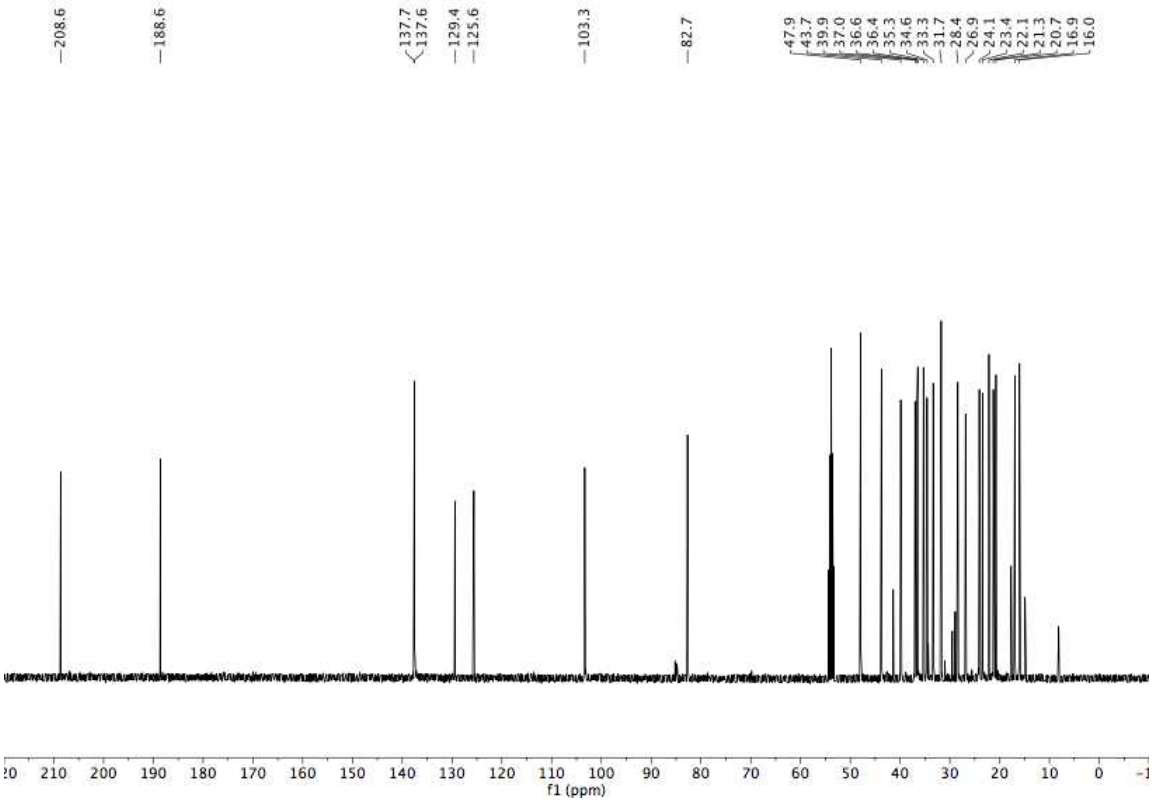
f1 (ppm)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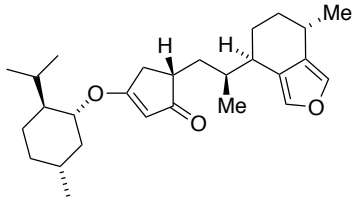
137.6
129.4
125.6
103.3
82.7
47.9
43.7
39.9
37.0
36.6
36.4
35.3
34.6
33.3
31.7
28.4
26.9
24.1
23.4
22.1
21.3
20.7
16.9
16.0
f1 (ppm)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H
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O
Me
O
O

118

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0.97
0.88
1.98
1.01
1.00
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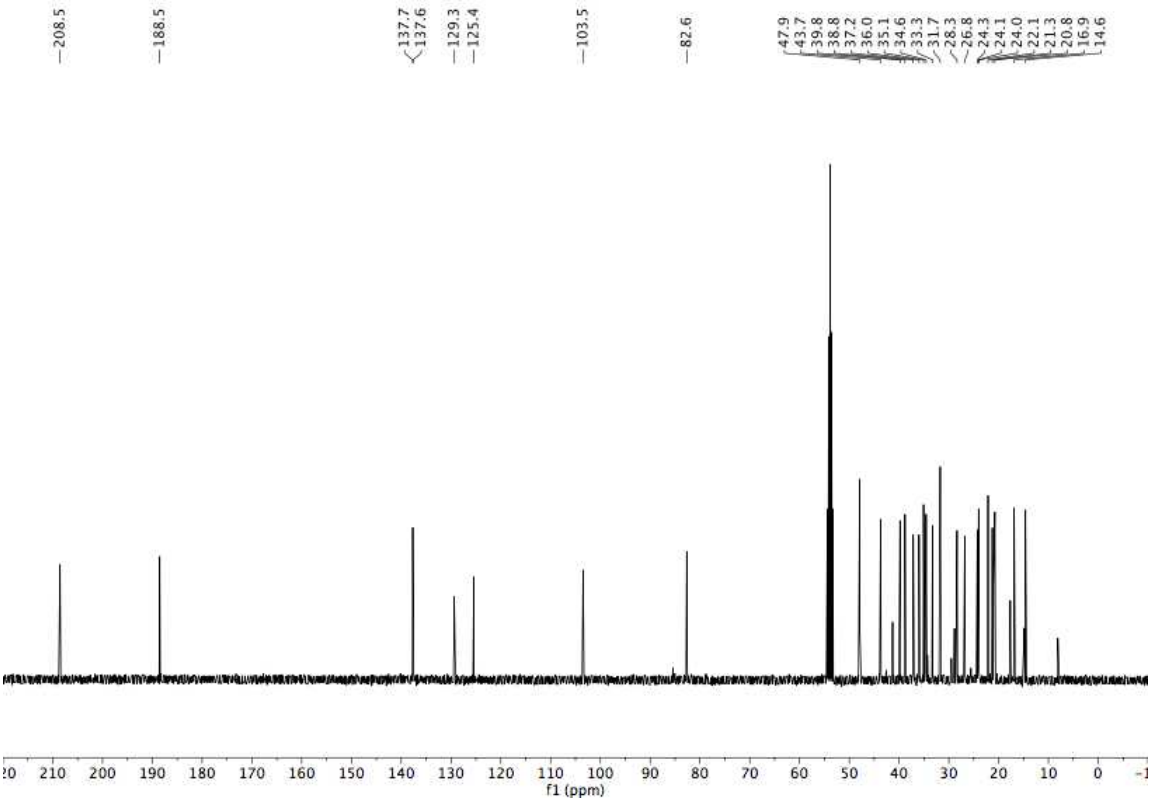
2.03
2.04
2.00
4.02
1.99
7.03
3.00
2.92
f1 (ppm)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137.6
129.3
125.4
103.5
82.6
47.9
43.7
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37.2
36.0
35.1
34.6
33.3
31.7
28.3
26.8
24.3
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24.0
22.1
21.3
20.8
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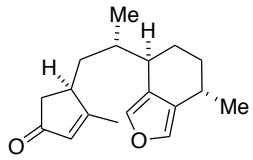
14.6
f1 (ppm)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H
Me
O
O

122

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1.01
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1.04
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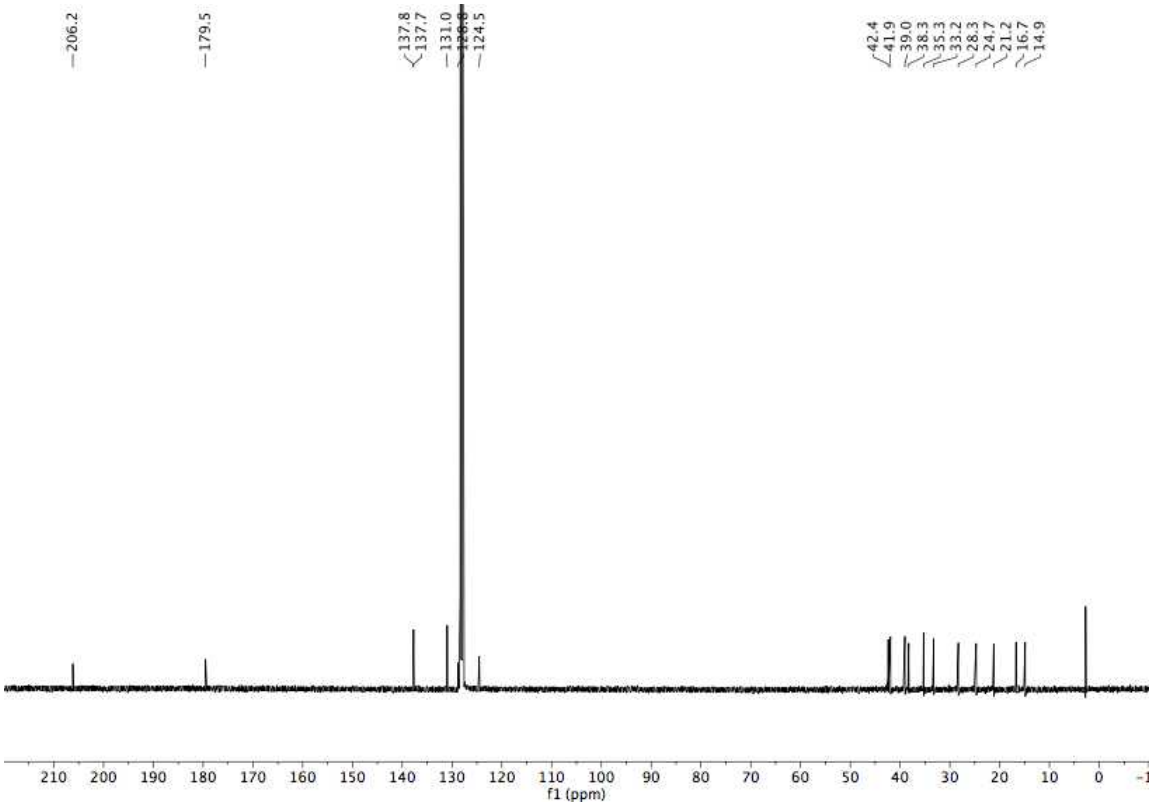
5.00
3.82
f1 (ppm)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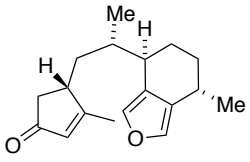
f1 (ppm)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H
Me
O
O

119

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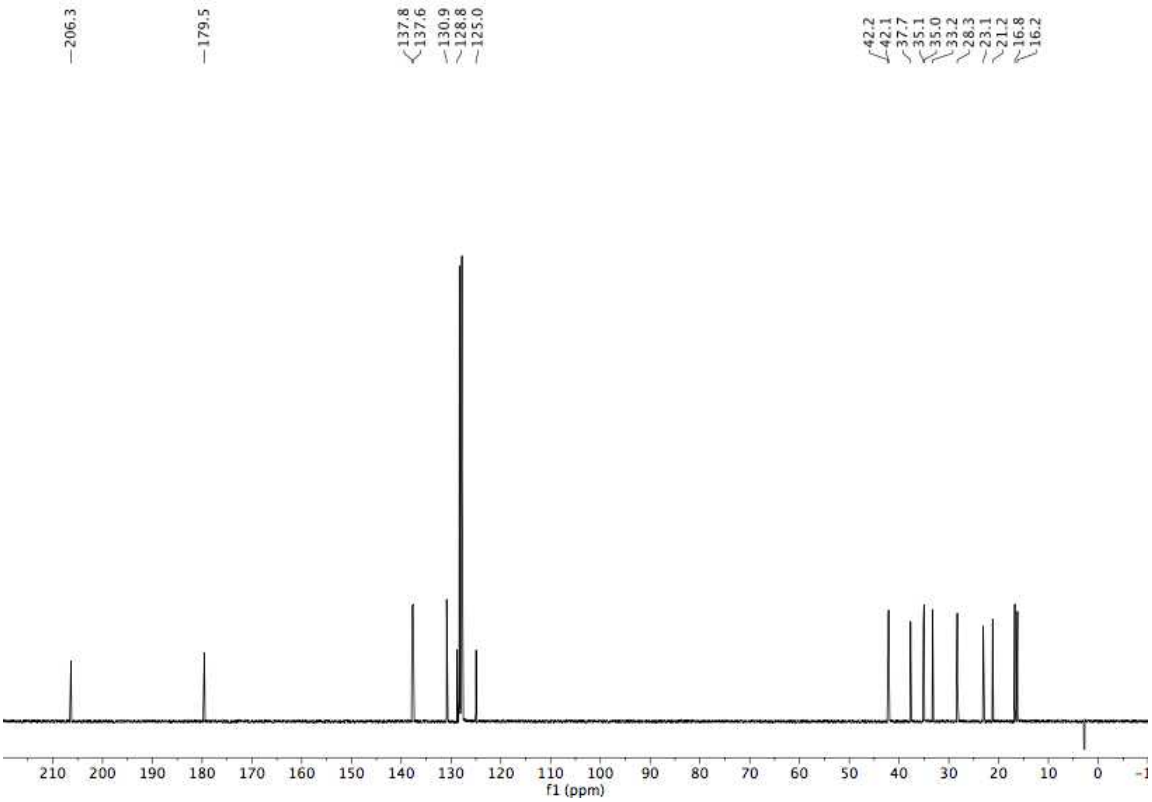
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28.3
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21.2
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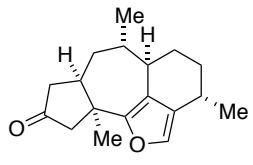
16.2
f1 (ppm)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H
O
Me
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Me

114

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3.05
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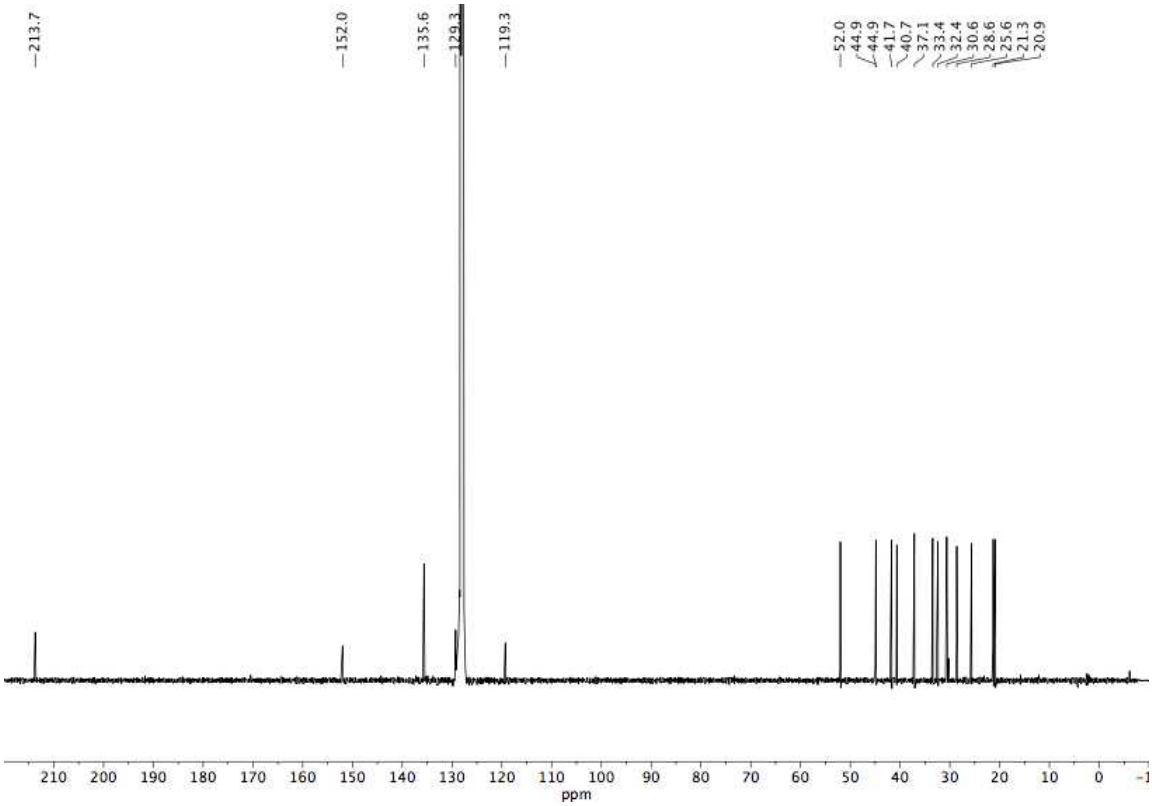
2.80
f1 (ppm)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52.0
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41.7
40.7
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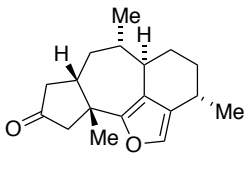
30.6
28.6
25.6
21.3
20.9
ppm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H
O
Me
O
Me

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3.02
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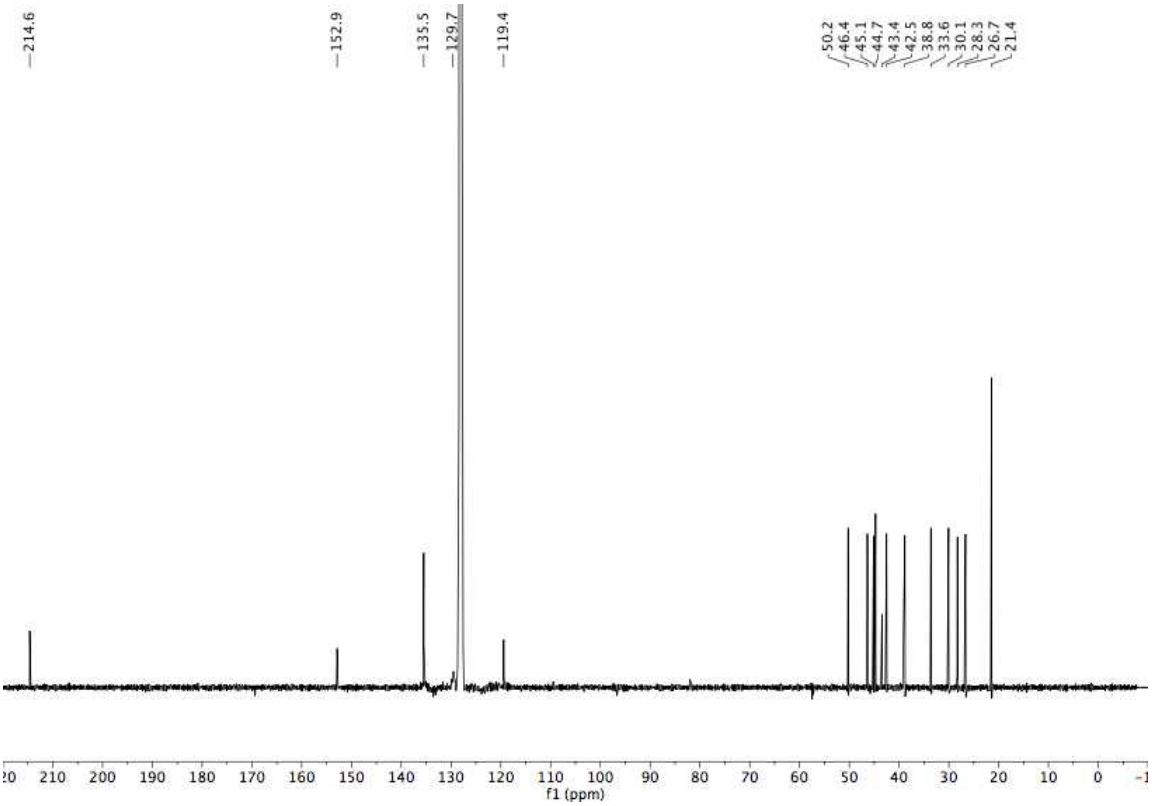
1.98
3.91
1.02
2.92
f1 (ppm)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38.8
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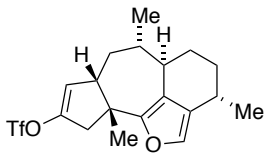
30.1
28.3
26.7
21.4
f1 (ppm)


Me
H
H
TfO
Me
O
Me

123

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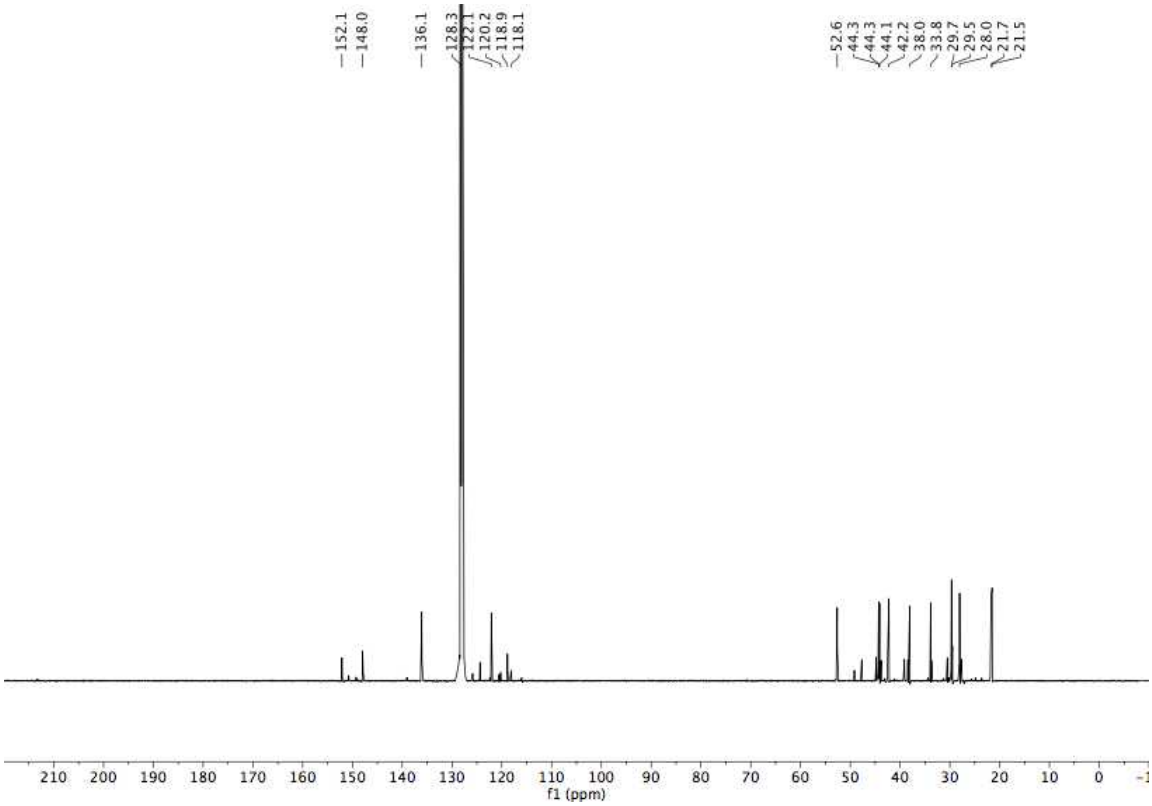
0.21
0.21
0.80
1.02
1.05
0.99
1.00
2.19
1.16
2.38
0.85
1.08
2.10
2.95
1.03
1.03
3.00
f1 (ppm)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118.1
52.6
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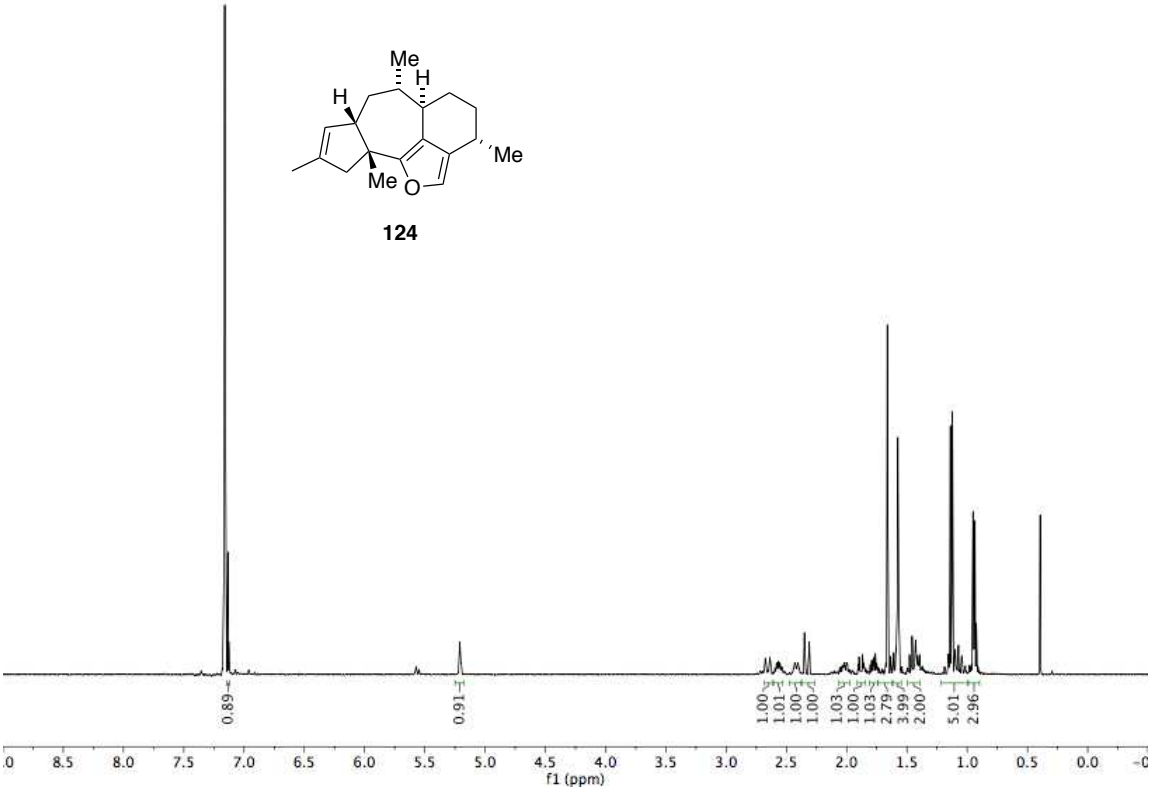
42.2
38.0
33.8
29.7
29.5
28.0
21.7
21.5
f1 (ppm)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Me
Me
O
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1.00
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2.00
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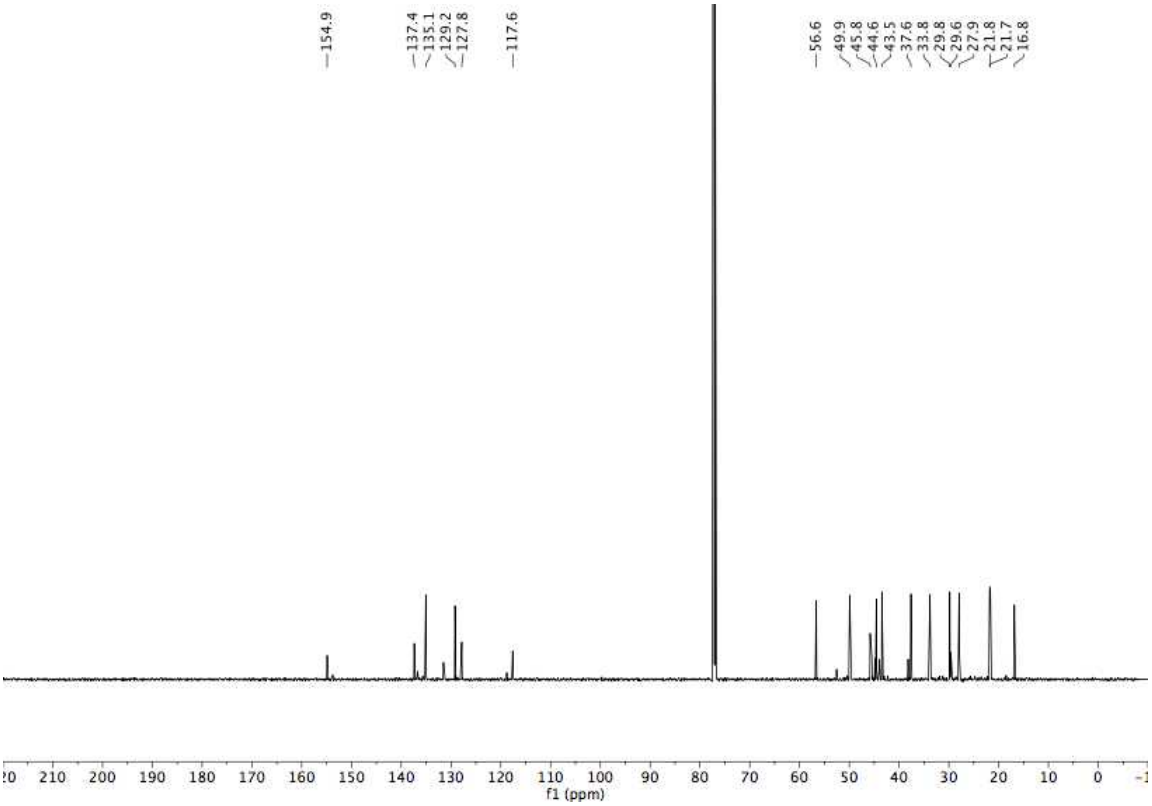
2.96
f1 (ppm)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127.8
117.6
56.6
49.9
45.8
44.6
43.5
37.6
33.8
29.8
29.6
27.9
21.8
21.7
16.8
f1 (ppm)

6.2. Total Synthesis of Sandresolide B and Amphilectolide

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Author contribution statement

I.B. optimized the reactions for the total synthesis of sandresolide B for compounds **7**, **9**, **10**, **12**, **13**, **14**, **21**, **22**, **23** and **24**, the results being documented in the supporting information. I.B. developed conditions for the final reaction sequence leading to the formation of sandresolide B and characterized this molecule. I.B. has written a part of the manuscript and provided input for the publication.

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Total Synthesis of Sandresolide B and Amphilectolide

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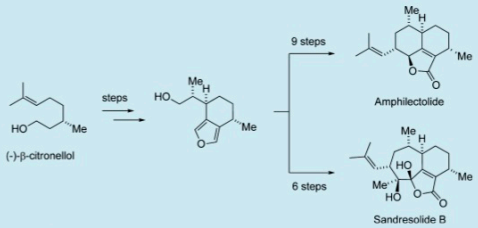
Department of Chemistry and Center of Integrated Protein Science, University of Munich, Butenandtstrasse 5 - 13 (F4.086), 81377 Munich, Germany

Supporting Information



ABSTRACT: The total synthesis of the diterpenoids sandresolide B and amphilectolide from a common furan building block is presented. Key steps include palladium-mediated carbonylation, lanthanide catalyzed ring closure, Myers alkylation, intramolecular Friedel–Crafts acylation, photooxygenation, and a Kornblum–DeLaMare rearrangement.

The Caribbean octocoral *Pseudopterogorgia elisabethae* is a chemically prolific species that has attracted the interest of natural product chemists for years.[1] Since the 1980s, when the Fenical group first isolated natural products from this family, over 40 marine metabolites have been isolated from *Pseudopterogorgia elisabethae*. Many of these natural products have been collected, isolated, and structurally elucidated by the Rodríguez group, and they feature a broad spectrum of biological activity against inflammation, tuberculosis, cancer, and antiplasmodial activity.[1]

Our synthetic interest in compounds from the *Pseudopterogorgia elisabethae* family arises from the recognition that, although structurally diverse, these natural products also share structural patterns that could be accessed through a common building block. From the outset, our prior experience with furans and their oxidized variants guided our focus toward amphilectolide, the sandresolides, and the caribenols (Figure 1).[2] Interestingly, **1**–**6** were all obtained from deep-sea

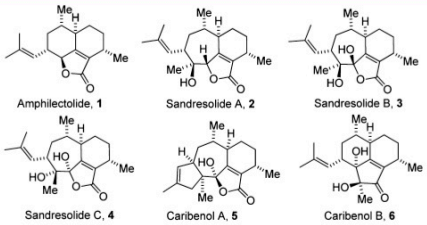


Figure 1. Selected diterpenoids from *Pseudopterogorgia elisabethae*.

expeditions near San Andrés island, Colombia, by Rodríguez and co-workers. Amphilectolide, **1**, was structurally elucidated in 2000,[3] and sandresolides A and B, **2** and **3**, were first reported in 1999.[4] Sandresolide C, **4**, a diastereomer of sandresolide B, **3**, with respect to the hydroxyl and acetal stereochemistry, was disclosed in 2009.[5] These compounds also bear a structural resemblance to the caribenols **5** and **6**, reported in 2007.[6] Amphilectolide, **1**, sandresolide C, **4**, and caribenols A and B, **5** and **6**, are active against *Mycobacterium tuberculosis* $H_{37}R_V$ (41%, 15%, 61%, and 94% growth inhibition at 6.25 μg/mL, respectively).[5] Sandresolide C, **4**, also shows an IC_{50} of 18 μg/mL against the *Plasmodium falciparum* W2 (chloroquine-resistant) strain. Curiously, an evaluation of sandresolides A and B, **2** and **3**, has not been reported. It is possible that material limitations have hampered full biological evaluation of sandresolides A and B, **2** and **3**, enhancing their value as synthetic targets.

To date, the only total synthesis reported within this collection of natural products is the total synthesis of caribenol A, **5**, by the Yang group.[7] We report herein the first total synthesis of amphilectolide, **1**, and sandresolide B, **3**.

Retrosynthetically, we envisioned that all natural products in Figure 1 could be accessed from a common furan **7**. In the case of amphilectolide, **1**, this could be done via allylic alcohol **8**, whereas in the case of sandresolide B, **3**, this could be achieved via carboxylic acid **9** (Scheme 1). The nucleophilic furan moiety in **8** and **9** would be used to close the six- or seven-membered ring in **1** and **3** via allylic alkylation or Friedel–Crafts acylation, respectively. In the final steps of the syntheses, the butenolide

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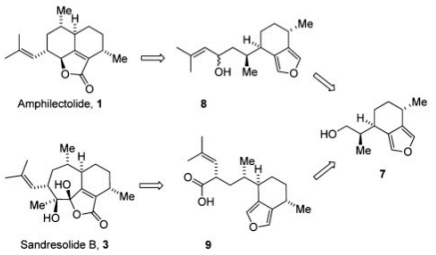
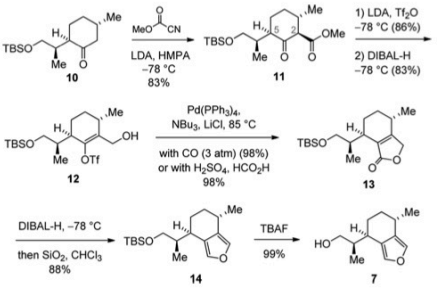
Scheme 1. Retrosynthetic Analysis of Amphilectolide, 1, and Sandresolide B, 3



or hydroxybutenolide would be oxidatively elaborated from the furan.

Our access to furan building block **7** relies on a general strategy developed by Molander to anneal furan rings to ketones.[8] The synthesis commences with the preparation of ketone **10**, available in eight steps from (−)-*β*-citronellol (Scheme 2).[9] Ketone **10** was homologated with Mander's

Scheme 2. Preparation of Key Furan Building Block 7

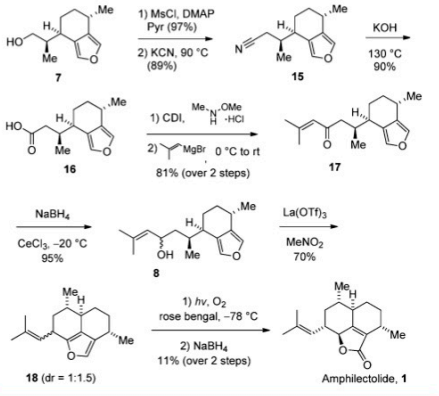


reagent to provide **11**,[10] the relative stereochemistry of which was established by NOE correlations. Conversion of **11** into the corresponding enol triflate required a low temperature and a strong base, and reduction of the resulting ester provided carbonylation precursor **12**.

Initial experiments were guided by known butenolide-producing couplings on simpler substrates. All known protocols at the time proceeded using catalytic amounts of palladium and carbon monoxide (CO) at ambient pressure. In our case, no reaction was observed under these conditions, presumably due to steric constraints. Therefore we employed conditions using CO at elevated pressures (3−5 bar) to achieve a 98% yield of desired butenolide **13**. Even under these conditions, complete conversion required 48 hours of heating at reflux in acetonitrile. Subsequently, this key step was met with even further improvement using CO generated *in situ*.[11] To our delight, the conversion also proceeded in 98% yield and could now take place without the use of a toxic gas canister. Completion of furan building block **7** involved the reduction of butenolide **13**, followed by mild dehydration and cleavage of the TBS protecting group.

With gram quantities of **7** in hand, we proceeded to synthesize amphilectolide, **1** (Scheme 3). Mesylation of furan **7**

Scheme 3. Total Synthesis of Amphilectolide, 1



was followed by homologation with potassium cyanide to furnish nitrile **15**. While direct addition of 2-methyl-2-propenylmagnesium bromide provided enone **17** in 20% yield, we ultimately took a three-step approach involving saponification and conversion to the corresponding Weinreb amide, followed by Grignard addition to furnish unstable enone **17**. Immediate reduction of **17** was carried out under Luche conditions to afford allylic alcohol **8**, a suitable precursor for ring closure.

After gaining access to the allylic alcohol **8**, ring closure was investigated under a variety of protic and Lewis acidic conditions. Lanthanum(III) triflate[12] provided the best yields, although the diastereoselectivity was poor, as it was in all reaction conditions screened. The lanthanum(III) triflate mediated ring closure was verified to proceed via an SN_1 mechanism. When the two diastereomers of precursor **8** were separated and either was subjected to the Lewis acid, the same 1:1.5 ratio of diastereomers of **18** resulted. Unfortunately, the two diastereomers of **18** could not be separated and individually characterized.

The final steps for amphilectolide, **1**, consisted of a challenging furan oxidation, followed by reduction, to provide the butenolide moiety of **1**. We screened conditions, including the use of peracids,[13] magnesium bis(monoperoxyphthalate) hexahydrate,[14] and photooxygenation using Rose Bengal as a sensitizer.[15] For the latter, rapid consumption of starting material was observed to provide a number of unstable products. Therefore, we explored a variety of reductive, acidic, and basic workup conditions to encourage the collapse of the presumed intermediate endoperoxides. After many failed attempts, the total synthesis of amphilectolide, **1**, was completed via photooxygenation of a diastereomeric mixture of **18** in the presence of Hünig's base, followed by immediate reduction with sodium borohydride. This procedure provided a complex mixture of products, from which amphilectolide, **1**, could be isolated in low yield. All spectra of synthetic amphilectolide, **1**, were in accordance with the reported natural product.[3]

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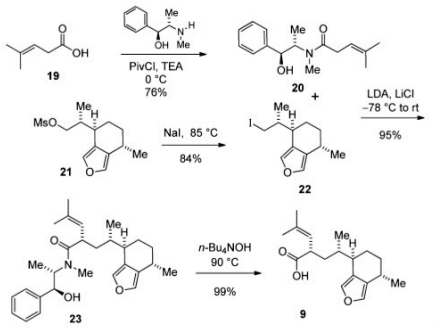
Building on our experiences gained during the synthesis of amphilectolide, **1**, we then proceeded to synthesize sandresolide B, **3**, in a shorter sequence and with better yields. To this end, we employed a Myers asymmetric alkylation, which is known to be effective in sterically encumbered systems.[16]

In anticipation of the Myers alkylation, we prepared (+)-pseudoephedrine derivative **20** via known acid **19** (Scheme 4).[17] Double deprotonation of **20** provided a highly

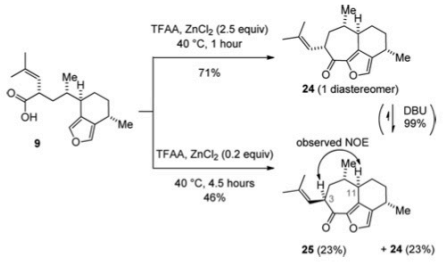
Scheme 4. Myers Alkylation to Access Ring-Closure Precursor 9



nucleophilic enolate, and lithium chloride was added to both accelerate the reaction and suppress *O*-alkylation.[18] Addition of iodide **22**, prepared via a Finkelstein reaction from mesylate **21**, allowed for the preparation of amide **23** in 95% yield and as a single diastereomer. This compound could be saponified to acid **9** using tetrabutylammonium hydroxide at high temperature.[18]

With key acid **9** in hand, we proceeded to install the seven-membered ring of the sandresolides using an intramolecular Friedel–Crafts acylation (Scheme 5). Ring closure was

Scheme 5. Ring Closure and NOE Correlations To Characterize 25



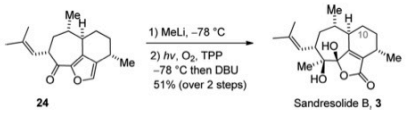
investigated using various activation methods with Lewis and Brønsted acids. The only conditions that provided desired product **24** entailed activation of the acid with trifluoroacetic anhydride followed by gentle heating with zinc chloride. Short reaction times and stoichiometric zinc chloride were key to this ring closure; after 1 hour, epimerization of the stereocenter next to the carbonyl group produced **25**.

We pursued a few avenues to establish the relative stereochemistry of diastereomers **24** and **25**. NOESY measurements were taken on the separable diastereomers, and **25** held the key correlation to establish the structure: protons at C(3) and C(11) showed correlations at δ 3.44 and δ 2.45 respectively.

We also established that **25** is the thermodynamically more stable product: treatment of either diastereomer with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected clean conversion to **25**. This finding was confirmed through a conformational search using Macromodel (10 000 step Monte Carlo search, solvent-free OPLS algorithm),[19] which indicated that the undesired diastereomer **25** was thermodynamically more stable by 6.7 kcal/mol. The above findings explain why short reaction times are critical to obtain a diastereomerically clean ring closure: our desired product **24** is the kinetic product.

Completion of sandresolide B, **3**, required a stereoselective addition of a methyl organometallic reagent to the carbonyl of **24**, followed by furan oxidation to form the hydroxybutenolide moiety (Scheme 6). The addition of methyl magnesium

Scheme 6. Completion of Sandresolide B, 3



bromide proceeded smoothly to form the corresponding unstable benzylic tertiary alcohol. We originally hoped to obtain both diastereomers, since one could lead to sandresolide B, **3**, and the other to sandresolide C, **4**. Interestingly, substrate control led to the predominant formation of the precursor of sandresolide B, **3**, which was immediately subjected to photooxygenation. The photooxygenation conditions used in amphilectolide, **1**, did not allow for the clean and reliable formation of sandresolide B, **3**. Optimization led to tetraphenylporphyrine as a photosensitizer,[20] running the reaction without methanol (previously used to solubilize Rose Bengal) to avoid the potential formation of alkoxybutenolides,[15] and using DBU to collapse the *endo* peroxide via a Kornblum–DeLaMare rearrangement.[21] Of the bases screened for this rearrangement, only DBU allowed for the efficient formation of sandresolide B, **3**. These highly optimized conditions provided sandresolide B, **3**, from **24** in 51% yield over two steps.

The proton NMR data of sandresolide B, **3**, were in accordance with the literature except for the axial proton at C(10), which was reported to have the same chemical shift as the equatorial proton in the isolation paper.[4] Our suspicions of a misassignment arose because the axial and equatorial protons are consistently found with different shifts of approximately δ 1.3 and δ 2.0 respectively for all compounds in this project, as well as in the reported spectra of amphilectolide, **1**, and sandresolide C, **4**. The HSQC of sandresolide B, **3**, shows a correlation between the carbon at δ 28.2 and protons at δ 1.27 and δ 2.00 while the reported HMBC correlates the carbon at δ 28.2 with two protons at δ 2.00.[4] Correspondence with the isolationist, Abimael D. Rodríguez, served to confirm the minor misassignment in the isolation paper, verifying that our spectral data for sandresolide B, **3**, matched those of the isolated natural product.

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In summary, we have developed a scaleable route to a valuable furan building block, **7**, which has been used for the first total syntheses of amphilectolide, **1**, and sandresolide B, **3**. Key steps include palladium-mediated carbonylative butenolide formations, a Myers alkylation, a lanthanum(III) triflate-catalyzed ring closure, an intramolecular Friedel–Crafts acylation, photooxygenations, and a Kornblum–DeLaMare rearrangement. The use of our key furan building block **7** in the synthesis of a number of other diterpenoids isolated from *Pseudopterogorgia elisabethae*, such as caribenols A and B, **5** and **6**, is under active investigation in our laboratories and will be reported in due course.[6]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data for all new compounds. 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.

■ ACKNOWLEDGMENTS

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Total Synthesis of Sandresolide B and Amphilectolide

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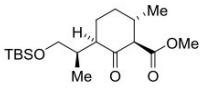
Supporting Information

General Experimental Details: All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was carried out with Merck 40–60 μM 60 Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} plates and visualized with potassium permanganate, ceric ammonium molybdate, or anisaldehyde. Tetrahydrofuran (THF), and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. *n*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

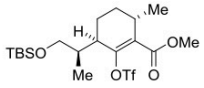
Instrumentation: FT-IR spectra were obtained as neat samples on a Perkin-Elmer BXII-FTIR spectrometer. Proton and carbon NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) (unless otherwise noted) on a Varian Mercury 400 MHz or 600 MHz or Bruker Avance III HD 400 MHz spectrometer, reported in ppm and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. High resolution mass spectra (HRMS) were obtained at Ludwig-Maximilians-Universität using electron impact (EI) or electrospray ionization (ESI).



(1*R*,3*R*,6*S*)-methyl 3-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-6-methyl-2-oxocyclohexanecarboxylate (11). To a solution of 12.0 mL (8.63 g, 85.3 mmol) diisopropylamine in 400 mL THF cooled to −78 °C was added 51.6 mL (82.5 mmol) of *n*BuLi (1.6 M in hexanes) dropwise. The solution was allowed to come to 0 °C for 2 hours, at which point it was cooled back to −78 °C. A solution of 7.82 g (27.5 mmol) **10** in 100 mL THF was then added dropwise and the reaction mixture was stirred for another hour before addition of 14.8 mL (15.3 g, 85.2 mmol) hexamethylphosphoramide (HMPA) followed by 6.76 mL (7.25 g, 85.3 mmol) methyl cyanoformate (Mander's reagent). The solution became pale yellow and after 15 minutes at −78 °C, was quenched with H_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with NaCl (saturated), dried over Na_2SO_4, filtered,

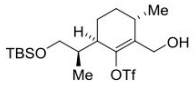
and evaporated. Purification by flash column chromatography (5 to 15% Et_2O/hexanes) afforded 7.81 g of **11** (83%) as a pale yellow oil.

Rf: 0.41, 10% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 3.76 (s, 3H), 3.49 (dd, 1H, *J* = 9.9, 5.5 Hz), 3.37 (dd, 1H, *J* = 9.9, 7.8 Hz), 3.04 (dd, 1H, *J* = 12.2, 1.2 Hz), 2.53 (m, 1H), 2.25 (m, 2H), 1.99 (m, 2H), 1.45 (m, 2H), 1.02 (d, 3H, *J* = 6.4 Hz), 0.87 (s, 9H), 0.80 (d, 3H, *J* = 7.0 Hz), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz): δ 207.05, 170.53, 65.77, 65.70, 52.01, 49.97, 37.56, 33.34, 33.05, 26.46, 26.07, 21.24, 18.42, 12.77, −5.23, −5.33. IR: 2955, 2930, 2857, 1748, 1472, 1359, 1251, 1090 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{34}O_4SiNa$ ([M + Na]$^+$) 365.2124, found 365.2117. $[\alpha]^{25}_D$ +8.4 (*c* = 1.0, $CHCl_3$).



(3*R*,6*S*)-methyl 3-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-enecarboxylate (S1). To a solution of 0.45 mL (3.24 mmol) DIA in 50 mL THF at 0 °C was added 1.30 mL (3.24 mmol) *n*BuLi (2.5 M in hexanes). The yellow solution was stirred for 20 minutes, then cooled to −78 °C and a solution of 0.701 g (2.16 mmol) **11** in 10 mL THF was added dropwise. After an hour, 0.55 mL (3.24 mmol) Tf_2O was added dropwise. The solution became a darker yellow color and after 15 minutes, complete consumption of starting material was observed by TLC. The reaction mixture was then quenched with $NaHCO_3$ (saturated). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and evaporated then purified by flash column chromatography (5 to 10% EtOAc/hexanes, 1% TEA) to afford 833 mg of **S1** (86%) as a pale yellow oil, (92% based on recovered starting material (borsm), reverse reaction may have occurred on column).

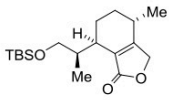
Rf: 0.59, 10% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 3.81 (s, 3H), 3.53 (dd, 1H, *J* = 10.0, 6.0 Hz), 3.41 (m, 1H), 2.86 (m, 1H), 2.75 (m, 1H), 2.20 (m, 1H), 1.81 (m, 2H), 1.53 (m, 1H), 1.31 (m, 1H), 1.11 (d, 3H, *J* = 6.9 Hz), 0.88 (s, 9H), 0.76 (d, 3H, *J* = 7.0 Hz), 0.03 (s, 6H). ^{13}C NMR (100 MHz): δ 165.49, 152.14, 131.16, 118.46 (q, *J* = 320.2 Hz, CF_3), 65.19, 52.12, 37.94, 35.49, 32.16, 28.64, 25.93, 20.32, 20.14, 18.34, 11.46, −5.38, −5.55. IR: 2933, 2859, 1733, 1472, 1422, 1246, 1140, 1068 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{33}O_6F_3SSiNa$ ([M + Na]$^+$) 497.1617, found 497.1611. $[\alpha]^{25}_D$ −5.3 (*c* = 0.87, $CHCl_3$).



(3*S*,6*R*)-6-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (12). A solution of 10.1 g (21.3

mmol) **S1** in 600 mL DCM was cooled to to −78 °C, and then 60.2 mL of DIBAL-H (6.02 mmol, 1.0 M in $PhCH_3$) was added dropwise. After 1 hour of stirring, the reaction mixture was warmed to room temperature for 10 minutes, at which point it was quenched with a 1:1 mixture of H_2O/Rochelle's Salt (saturated) and diluted with DCM. The layers were stirred vigorously until no emulsion was present. The layers were then separated and the aqueous layer was extracted twice with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (10 to 20% EtOAc/hexanes and 1% TEA) afforded 7.90 g of **12** (83%) as a clear, colorless oil.

Rf: 0.55, 25% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 4.36 (d, 1H, *J* = 12.7 Hz), 4.24 (dd, 1H, *J* = 12.7, 1.9 Hz), 3.50 (dd, 1H, *J* = 10.0, 6.2 Hz), 3.42 (dd, 1H, *J* = 10.0, 8.8 Hz), 2.85 (m, 1H), 2.55 (m, 1H), 2.17 (m, 1H), 1.80 (br m, 2H), 1.69 (br s, 1H, *O*H), 1.45 (m, 1H), 1.29 (m, 1H), 1.19 (d, 3H, *J* = 7.0 Hz), 0.88 (s, 9H), 0.74 (d, 3H, *J* = 7.0 Hz), 0.03 (m, 6H). ^{13}C NMR (100 MHz): δ 147.37, 136.36, 118.53 (q, *J* = 319.9 Hz, CF_3), 65.38, 58.41, 38.45, 35.20, 32.35, 29.91, 25.93, 21.17, 19.58, 18.33, 11.22, −5.35, −5.50. IR: 3342, 2931, 1673, 1473, 1415, 1248, 1140, 1090, 972, 883, 819, 775, 667 cm $^{-1}$. HRMS (ESI) calcd for $C_{18}H_{33}O_5ClF_3SiS$ ($[M + Cl]^-$) 481.1459, found 481.1458. $[\alpha]^{25}_D$ −12 (*c* = 0.33, $CHCl_3$).



(4*S*,7*R*)-7-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4-methyl-4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (13). We present two procedures to provide this compound in 98% yield.

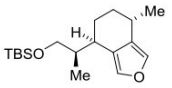
1) To a solution of 7.90 g (17.7 mmol) **12** in 90 mL MeCN was added 2.45 g (2.12 mmol) $Pd(PPh_3)_4$, 0.825 g (19.5 mmol) LiCl (dried under high vacuum), and 8.43 mL (6.56 g, 35.4 mmol) NBu_3. The solution was degassed with N_2 for 20 minutes, then transferred to a Paar bomb. The apparatus was filled with CO (3 bar) and flushed three times, then filled with 3 bar CO and heated to 85 °C. The solution became orange after 5 minutes. After 48 hours, the solution was cooled to room temperature and the apparatus was flushed with N_2 before it was opened. The solvent was evaporated, and flash column chromatography (10% EtOAc/hexanes) afforded 5.6 g (98%) of **13** as a light yellow oil.

2) To a solution of 2.67 g (5.98 mmol) **12** in MeCN (95 mL, previously degassed by 3 freeze–pump–thaw cycles) in a 300 mL Schlenk tube was subsequently added 2.80 mL (2.22 g, 11.8 mmol) NBu_3, 829 mg (0.72 mmol) $Pd(PPh_3)_4$ and 279 mg (6.58 mmol) LiCl (previously dried *in vacuo* at 200 °C overnight). 1.00 mL (1.84 g, 96% w/w, 18.0 mmol) H_2SO_4 was placed in a 50 mL Schlenk tube. Both Schlenk tubes were connected with each other by a plastic tube (1.5 cm outer diameter, 0.2 cm thickness). The septa on both Schlenk tubes were sealed with Teflon® tape, Parafilm® and secured with springs (see

Figure 1). A blast shield was placed in front of the reaction setup as a precautionary measure. Both Schlenk tubes were then heated to 75 °C, at which point 0.71 mL (0.87 g, 95% w/w, 17.9 mmol) HCO_2H was added to the stirred H_2SO_4 *via* syringe. After 23 hours, both Schlenk tubes were cooled to room temperature and the reaction mixture was filtered through a silica pad, which was washed with EtOAc. The solvents were removed *in vacuo*, and the crude product was purified by flash column chromatography (9 to 13 to 17% EtOAc/*n*-pentane), yielding 1.90 g (98%) of **13** as a colorless oil.

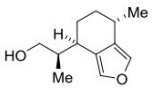
Figure 1. Experimental setup for in situ generation of CO

Rf: 0.55, 25% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 4.73 (ddd, 1H, *J* = 17.1, 3.3, 1.0 Hz) 4.66 (ddd, 1H, *J* = 17.1, 2.6, 1.5 Hz), 3.52 (dd, 1H, *J* = 10.0, 6.5 Hz), 3.48 (dd, 1H, *J* = 10.0, 8.3 Hz), 2.79 (br m, 2H), 2.51 (m, 1H), 1.98 (m, 1H), 1.78 (m, 1H), 1.43 (m, 1H), 1.28 (m, 1H), 1.11 (d, 3H, *J* = 7.1 Hz), 0.88 (s, 9H), 0.65 (d, 3H, *J* = 6.9 Hz), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz): δ 173.72, 166.28, 127.73, 70.02, 65.98, 34.13, 33.43, 30.88, 30.47, 26.07, 21.37, 18.77, 18.40, 11.51, −5.17, −5.32. IR: 2929, 1750, 1661, 1462, 1254, 1086, 1020 cm $^{-1}$. HRMS (ESI) calcd for $C_{18}H_{33}O_3Si$ ($[M + H]^+$) 325.2199, found 325.2194. $[\alpha]^{25}_D$ +43 (*c* = 0.33, $CHCl_3$).



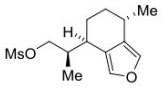
***tert*-butyldimethyl((*R*)-2-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)propoxy)silane (14)**. A solution of 5.61 g (17.3 mmol) **13** in 180 mL $PhCH_3$ was cooled to to −78 °C, and then 27.7 mL of a DIBAL-H solution in $PhCH_3$ (1.0 M, 27.7 mmol) was added dropwise, the solution was left to stir for 30 min. After warming the reaction mixture to 0 °C, it was quenched with a 1:1 mixture of H_2O/Rochelle's Salt (saturated) and diluted with DCM. The layers were stirred vigorously until no emulsion was present. The layers were then separated and the aqueous layer was extracted twice with DCM. The combied organic layers were washed with NaCl (saturated), dried over Na_2SO_4, filtered, and evaporated. To the crude mixture were added 35.5 g silica gel and ~300 mL $CHCl_3$, then stirred for 16 hours. This mixture was then filtered, washed with Et_2O, and evaporated. Purification by flash column chromatography (5% EtOAc/hexanes) afforded 4.67 g of **14** (88%) as a clear, colorless oil.

Rf: 0.61, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.18 (s, 1H), 7.14 (s, 1H), 3.55 (m, 2H), 2.90 (m, 1H), 2.58 (m, 1H), 2.07 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.28 (m, 1H), 1.21 (d, 3H, *J* = 7 Hz and m, 1H), 0.90 (s, 9H), 0.79 (d, 3H, *J* = 7 Hz), 0.06 (d, 6H, *J* = 2 Hz). ^{13}C NMR (100 MHz): δ 137.26, 137.11, 128.78, 125.04, 66.17, 39.12, 33.42, 32.70, 27.86, 25.93, 23.34, 21.13, 18.30, 11.87, −5.32, −5.38. IR: 2956, 2856, 1462, 1415, 1361, 1250, 1208, 1141, 1089 cm $^{-1}$. HRMS (EI) calcd for $C_{18}H_{32}O_2Si$ ($[M]^+$) 308.2172, found 308.2172. $[\alpha]^{25}_D$ +56 (*c* = 0.33, $CHCl_3$).



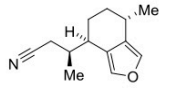
(*R*)-2-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)propan-1-ol (7). A solution of 4.60 g (14.9 mmol) **14** in 150 mL THF was cooled to 0 °C, and then 20.9 mL (20.9 mmol) of a tetrabutylammonium fluoride (TBAF) solution (1.0 M in THF) was added dropwise. After 1 hour, the solution was then warmed to room temperature and stirred for another 30 minutes. The reaction mixture was then quenched with $NaHCO_3$ (saturated), diluted with Et_2O, and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers was washed with NaCl (saturated), dried over Na_2SO_4, filtered, and evaporated. Flash column chromatography (25% EtOAc/hexanes) afforded 2.90 g (quantitative yield) of **7** as a clear, colorless oil.

Rf: 0.35, 25% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 7.19 (s, 1H), 7.17 (s, 1H), 3.63 (m, 2H), 2.89 (m, 1H), 2.59 (m, 1H), 2.11 (m, 1H), 1.90 (m, 1H), 1.76 (m, 1H), 1.51 (br s, 1H), 1.34 (m, 2H), 1.22 (d, 3H, J = 9 Hz), 0.88 (d, 3H, J = 9 Hz). ^{13}C NMR (75 MHz): δ 137.34, 137.15, 128.75, 124.62, 66.27, 39.35, 33.76, 32.63, 27.83, 23.67, 21.11, 12.12. IR: 3333, 2956, 1538, 1453, 1374, 1232, 1129, 1024, 890 cm $^{-1}$. HRMS (EI) calcd for $C_{12}H_{18}O_2$ ($[M]^+$) 194.1307, found 194.1303. $[\alpha]^{25}_D$ +76 (c = 0.40, $CHCl_3$).



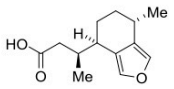
(*R*)-2-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)propyl methanesulfonate (21). To a solution of 3.05 g (15.7 mmol) **7** in 300 mL DCM was added 3.27 mL (2.38 g, 23.5 mmol) NEt_3 and 1.46 mL (2.16g, 18.8 mmol) mesyl chloride. The solution was stirred at room temperature for 30 minutes, and quenched with $NaHCO_3$ (saturated), extracted with $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (25% EtOAc/hexanes) afforded 4.14 g (97%) of **21** as a slightly tan oil.

Rf: 0.66, 40% EtOAc/hexanes. ^{1}H NMR (400 MHz): δ 7.19 (d, 1H, J = 1.6 Hz), 7.17 (d, 1H, J = 1.6 Hz), 4.23 (dd, 1H, J = 9.7 Hz), 4.15 (dd, 1H, J = 9.7 Hz), 3.02 (s, 3H), 2.89 (m, 1H), 2.57 (m, 1H), 2.35 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.33 (ddd, 1H, J = 14 Hz), 1.21 (m, 4H), 0.94 (d, 3H, J = 7 Hz). ^{13}C NMR (75 MHz): δ 137.61, 137.18, 128.57, 123.46, 72.42, 37.34, 36.50, 33.68, 32.35, 27.70, 23.79, 21.05, 12.14. IR: 2959, 2361, 1540, 1455, 1353, 1129, 1042 cm $^{-1}$. HRMS (ESI) calcd for $C_{13}H_{20}O_4SCl$([M + $Cl]^-$) 307.0771, found 307.0775. $[\alpha]^{25}_D$ +49 (c = 0.47, $CHCl_3$).



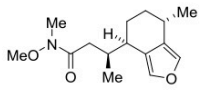
(*S*)-3-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)butanenitrile (15). To a solution of 130 mg (0.477 mmol) of **21** in 12 mL DMF (anhydrous) in a pressure tube was added 68 mg (1.049 mmol) of KCN. The mixture was heated to 70 °C for 2.5 hours, then to 95 °C for 4 hours. The reaction mixture was then cooled to 70 °C for 16 hours, quenched with $NaHCO_3$ (saturated), and diluted with Et_2O. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (15% EtOAc/hexanes) afforded 86 mg (89%) of **15** as a white solid.

Rf: 0.61, 25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.20 (d, 1H, *J* = 1.6 Hz), 7.17 (d, 1H, *J* = 1.5 Hz), 2.86 (m, 1H), 2.58 (m, 1H), 2.34 (m, 2H), 2.31 (m, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.35 (ddd, 1H, *J* = 11 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 1.05 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz): δ 137.67, 137.30, 128.42, 123.11, 119.22, 36.49, 34.31, 32.09, 27.61, 23.91, 22.15, 21.02, 15.50. IR: 3104, 2942, 2243, 1541, 1457, 1328, 1266, 1122, 1035 cm $^{-1}$. HRMS (EI) calcd for $C_{13}H_{17}NO$ ($[M]^+$) 203.1310, found 203.1303. $[\alpha]^{25}_D$ +41 (*c* = 0.33, $CHCl_3$).



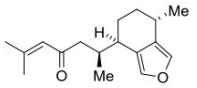
(*S*)-3-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)butanoic acid (16). To a solution of 45 mg (0.22 mmol) **15** in 4.0 mL ethylene glycol and 1.0 mL H_2O in a sealed tube was added 0.99 g (17.6 mmol) KOH. The reaction mixture was heated to 130 °C for 2 hours and after 2 hours, the light yellow solution was cooled to room temperature, then diluted with H_2O and extracted with EtOAc. The organic layer was extracted once more with H_2O and the combined aqueous layers were then acidified with HCl (2.0 M) until the pH was adjusted to 4. The resulting aqueous solution was then extracted once with EtOAc and the resulting organic layer was dried over $MgSO_4$, filtered, and evaporated. Filtration through a silica pad (70% EtOAc/hexanes) afforded 44 mg (90%) of **16** as a pale yellow solid.

Rf: 0.10, 25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.20 (t, 1H, *J* = 1.6 Hz), 7.18 (t, 1H, *J* = 1.6 Hz), 2.76 (m, 1H), 2.57 (m, 1H), 2.44 (m, 2H), 2.33 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.36 (ddd, 1H, *J* = 14 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 0.94 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (150 MHz): δ 179.33, 137.45, 137.37, 128.60, 124.05, 39.04, 37.02, 33.52, 32.53, 27.79, 23.85, 21.01, 15.27. IR: 2928, 1708, 1538, 1455, 1413, 1291, 1129, 1044 cm $^{-1}$. HRMS (EI) calcd for $C_{13}H_{18}O_3$ ($[M]^+$) 222.1256, found 222.1245. $[\alpha]^{25}_D$ +67 (*c* = 0.33, $CHCl_3$).



(*S*)-*N*-methoxy-*N*-methyl-3-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)butanamide (S2). A solution of 70 mg (0.32 mmol) **16** in 15 mL DCM (anhydrous) was cooled to 0 °C, and then 112 mg (0.69 mmol) of 1,1 carbonyldiimidazole (CDI) was added portionwise over 70 minutes, warming to room temperature after a few minutes. The yellow solution was then cooled to 0 °C, and then 61 mg (0.63 mmol) of *N,O*-Dimethylhydroxylamine hydrochloride was added. The solution was warmed to room temperature and after 40 minutes, another 30 mg (0.31 mmol) of *N,O*-Dimethylhydroxylamine hydrochloride was added. The reaction mixture was stirred for another 16 hours at room temperature, and then another 10 mg of *N,O*-Dimethylhydroxylamine hydrochloride was added and after 1.5 hours, the mixture was quenched with NH_4Cl (saturated) and diluted with DCM. The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated), then NaCl (saturated), dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (30% EtOAc/hexanes) afforded 79 mg (94%) of **S2** as a clear, colorless oil.

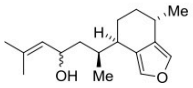
Rf: 0.59, 40% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.21 (t, 1H, *J* = 1.6 Hz), 7.17 (t, 1H, *J* = 1.6 Hz), 3.68 (s, 3H), 3.19 (s, 3H), 2.72 (m, 1H), 2.58 (m, 1H), 2.56 (m, 1H), 2.44 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.37 (ddd, 1H, *J* = 13 Hz), 1.21 (m, 1H and d, 3H, *J* = 6.7 Hz), 0.90 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (150 MHz): δ 174.07, 137.53, 137.22, 128.63, 124.43, 61.19, 37.36, 36.43, 33.04, 32.69, 27.85, 24.07, 21.05, 15.41. IR: 2929, 1666, 1455, 1378, 1177, 1128, 1042 cm $^{-1}$. HRMS (EI) calcd for $C_{15}H_{23}NO_3$ ($[M]^+$) 265.1678, found 265.1674. $[\alpha]^{25}_D$ +10 (*c* = 0.60, $CHCl_3$).



(*S*)-2-methyl-6-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)hept-2-en-4-one (17). A solution of 200 mg **S2** (0.75 mmol) in 50 mL THF was cooled to 0 °C and then 4.0 mL (3.0 mmol) of a 0.5 M 2-methyl-1-propenylmagnesium bromide solution in THF was added dropwise. The reaction mixture was warmed to room temperature for 10 minutes, then quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was washed with NaCl (saturated), dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (5% EtOAc/hexanes) afforded 169 mg (86%) of **17** as a clear, colorless oil that was unstable in $CHCl_3$ and $CDCl_3$.

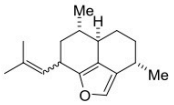
Rf: 0.59, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz, C_6D_6): δ 7.10 (t, 1H, *J* = 1.6 Hz), 7.09 (t, 1H, *J* = 1.1 Hz), 5.83 (quintet, 1H, *J* = 1.3 Hz), 2.63 (m, 1H), 2.57 (m, 1H), 2.40 (m, 1H), 2.27 (dd, 1H, *J* = 15.8 Hz), 2.18 (dd, 1H, *J* = 15.8 Hz), 2.14 (d, 3H, *J* = 1.1 Hz), 1.64 (m, 1H), 1.54 (m, 1H), 1.49 (d, 3H, *J* = 1.3 Hz), 1.18 (ddd, 1H, *J* = 12.9 Hz), 1.05

(m, 1H and d, 3H, J = 6.7 Hz), 0.90 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 198.65, 153.43, 137.56, 137.24, 128.39, 124.29, 124.05, 48.73, 37.21, 27.83, 26.82, 24.28, 20.74, 20.17, 15.47. IR: 2928, 2367, 1686, 1633, 1447, 1377, 1266, 1129, 1043 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{23}O_2$ ([M - H]$^-$) 259.1698, found 259.1704.



(6*S*)-2-methyl-6-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)hept-2-en-4-ol (8). A solution of 167 mg (0.64 mmol) **17** in 35.0 mL DCM (anhydrous) was cooled to −40 °C and then 8.0 mL (3.2 mmol) of a freshly prepared 0.4 M $CeCl_3$ solution in MeOH was added dropwise. The reaction mixture was stirred for 10 minutes before 121 mg (3.2 mmol) of $NaBH_4$ was added, and then the mixture was allowed to gradually warm to −25 °C over 50 minutes at which point it was quenched slowly with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (10% EtOAc/hexanes) afforded 159 mg (95%) of **8** as a clear, colorless oil that was a mixture of diastereomers.

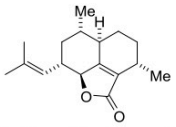
Rf: 0.21, 10% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.16 (t, 1 H, J = 1.6 Hz), 7.14 (dd, 1 H, J = 3.4 Hz), 5.19 (m, 0.6H), 5.18 (m, 0.4H), 4.47 (m, 1H), 2.76 (m, 0.4H), 2.67 (m, 0.6H), 2.56 (m, 1H), 2.07 (m, 0.6H), 1.88 (m, 1.4H), 1.73 (2 sets of dd, 6H, J = 1.3 Hz), 1.62 (br m, 1.4H), 1.59 (m, 0.6H), 1.33 (m, 2H), 1.25 (t, 1H J = 3.4 Hz), 1.20 (d, 3H, J = 6.7 Hz), 1.15 (m, 1H), 0.85 (2 sets of d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.56, 134.77, 67.14, 66.74, 42.37, 42.33, 37.68, 37.38, 32.94, 32.88, 32.57, 27.94, 25.81, 25.75, 23.82, 23.74, 21.02, 18.24, 18.16, 15.69, 15.04. IR: 3358, 2959, 2361, 1672, 1538, 1449, 1376, 1265, 1129, 1044 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{26}O_2$ ([M]$^+$) 262.1933, found 262.1926.



(3*S*,5a*R*,6*S*)-3,6-dimethyl-8-(2-methylprop-1-en-1-yl)-4,5,5a,6,7,8-hexahydro-3H-naphtho[1,8-bc]furan (18). To a solution of 22 mg **8** (0.084 mmol) in 6 mL $MeNO_2$ was added 1.5 mL of a freshly prepared solution of 1 mg / mL $La(OTf)_3$ in $MeNO_2$ over 5 minutes. The pink reaction mixture was stirred for 15 minutes until it was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The layers were separated and the organic layer was washed with $NaHCO_3$ (saturated) until no pink color remained. It was then washed with NaCl (saturated), dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (0.1 to 2 to 5% EtOAc/hexanes) afforded

14 mg (70%) of **18** as a clear, colorless oil that was a 0.4:0.6 mixture of diastereomers at the position of ring closure. (Inseparable by flash column chromatography or HPLC).

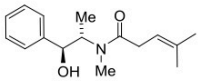
Rf: 0.48, hexanes. ^{1}H NMR (400 MHz, C_6D_6): δ 7.08 (dd, 0.4H, *J* = 2.6 Hz), 7.07 (dd, 0.6 H, *J* = 2.5 Hz), 5.31 (dq, 0.4H, *J* = 13.8 Hz), 5.23 (dq, 0.6H, *J* = 13.7 Hz), 3.73 (m, 1H), 2.57 (m, 1H), 1.96 (br m, 0.6H), 1.83 (m, 2.4H), 1.70 (m, 6H), 1.47 (m, 0.6H), 1.34 (m, 1H), 1.30 (m, 1.4H), 1.16 (doublet with shoulder, 3H, *J* = 10.2 Hz), 1.10 (br m, 2H), 0.91 (d with shoulder, 3H, *J* = 9.5 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 150.30, 136.52, 136.42, 132.44, 120.98, 109.90, 40.86, 40.28, 39.99, 39.82, 36.10, 35.42, 33.74, 33.63, 33.22, 32.19, 28.33, 28.26, 27.37, 25.56, 25.43, 21.72, 18.16, 18.03, 17.77, 17.66. IR: 2955, 2361, 1650, 1550, 1452, 1375, 1309, 1256, 1130, 1088 cm $^{-1}$. HRMS (EI) calcd for $C_{17}H_{24}O$ ($[M]^+$) 244.1827, found 244.1839.



(3*S*,5a*R*,6*S*,8*S*,8a*S*)-3,6-dimethyl-8-(2-methylprop-1-en-1-yl)-3,4,5,5a,6,7,8,8a-octahydro-2H-naphtho[1,8-bc]furan-2-one, amphilectolide (1). To a solution of 30 mg (0.12 mmol) **18** in 6 mL DCM was added 6 mg (0.006 mmol) Rose Bengal, 3 mL MeOH, and 0.10 mL (0.60 mmol) DIEA. The solution was cooled to −78 °C and irradiated with a UV lamp (Replux Belgium RL 160 W, 225 – 235 Volts). O_2 was bubbled through for 15 minutes, then the reaction mixture was quickly evaporated at 30 °C, taken up in 6 mL EtOH; 23 mg (0.60 mmol) of $NaBH_4$ was then added. After 10 minutes, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, diluted with Et_2O, washed with NaCl (saturated), dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography (6% Et_2O/hexanes followed by 5% EtOAc/hexanes) afforded 3.3 mg (11%) (**1**) as a white solid.

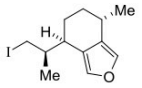
^{1}H NMR isolation	^{1}HNMR current	^{13}C NMR isolation	^{13}C NMR current
5.07, br dd (1.2, 9.0)	5.07, dt (1.4, 9.0)	172.9	172.93
4.35, d (10.5)	4.35, d (9.0)	165.0	165.05
2.42, m	2.42, m	134.5	134.53
2.23, m	2.24, m	128.1	128.11
2.16, m	2.17, m	125.2	125.15
2.01, m	2.05, m	83.6	83.64
1.86, m	1.91, m	44.1	44.11
1.72, br s	1.72, d (1.44)	41.0	40.95
1.62, br d (0.9)	1.63 d (1.38)	39.5	39.51
1.56, m	1.56, m	38.4	38.36
1.23, d (7.2)	1.23, d (8.0)	31.2	31.19
1.20, m	1.20, m	27.3	27.32
1.13, m	1.13, m	27.2	27.17

1.11, m	1.11, m	25.8	25.85
1.06, m	1.06, m	19.1	19.12
1.04, d (7.2)	1.04, d (6.5)	18.3	18.33
		17.8	17.83



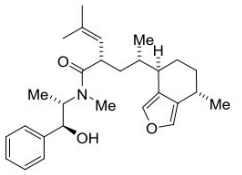
***N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,4-dimethylpent-3-enamide (20)**. A solution of 1.16 g (10.2 mmol) **19** and 2.5 mL (18.2 mmol) triethylamine (TEA) in 20 mL MeCN was cooled to 0 °C, and then 1.9 mL (15.3 mmol) of pivaloyl chloride was added. To the resulting white slurry was added 5 mL THF to enhance solubility. The reaction mixture turned yellow, and after 20 minutes, a solution of 1.7 g (10.2 mmol) of (+) pseudoephedrine and 1.4 mL (10.2 mmol) of TEA in 15 mL THF was added. The reaction mixture was warmed to room temperature and stirred for another 75 minutes, at which point it was quenched with water. The volatiles were removed by rotary evaporation, and then a solution of NaOH (0.5 M) was added. This solution was extracted with a mixture of 10% methanol in DCM twice, and the resulting organic layer was washed with a 1.0 M NaOH solution. The organic layer was then dried over $MgSO_4$, filtered, and evaporated and the crude oil purified by flash column chromatography (60% EtOAc/hexanes) to provide 2.04 g (76%) **20** as a white solid that was a 1:2 mixture of rotamers.

Rf: 0.31, 60% EtOAc/hexanes. ^{1}H NMR (300 MHz) of major rotamer: δ 7.32 (m, 5H), 5.21 (t, 1H, J = 7.1 Hz), 4.60 (dd, 1H, J = 7.7 Hz), 4.48 (br s, 1H), 4.39 (m, 1H), 3.03 (d, 2H, J = 6.7 Hz), 2.79 (s, 3H), 1.74 (s, 3H), 1.63 (s, 3H), 1.13 (d, 3H, J = 7.0 Hz). ^{13}C NMR (75 MHz) of major rotamer: δ 174.35, 142.48, 134.92, 128.30, 127.56, 126.38, 116.58, 75.42, 58.62, 34.56, 33.17, 25.69, 18.06, 14.39. IR: 3373, 2916, 2363, 1633, 1453, 1403, 1262, 1115 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{24}NO_2$ ([M + H]$^+$) 262.1807, found 262.1802. $[\alpha]^{25}_D$ +116 (c = 0.38, $CHCl_3$).



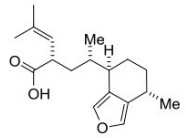
(4*R*,7*S*)-4-((*R*)-1-iodopropan-2-yl)-7-methyl-4,5,6,7-tetrahydroisobenzofuran (22). To a solution of 4.03 g (14.8 mmol) **21** in 200 mL acetone (anhydrous) in a pressure tube was added 11.1 g (74.0 mmol) of NaI. The mixture was excluded from light and heated to 85 °C for 2.5 hours. The mixture was left to come to room temperature, then quenched with H_2O and diluted with Et_2O. The layers were separated and the organic layer was washed with NaCl (saturated), dried over Na_2SO_4, filtered, and evaporated. Flash column chromatography (2% EtOAc/hexanes) afforded 3.78 g (84%) of **22** as a light-sensitive oil.

Rf: 0.38, hexanes. ^{1}H NMR (400 MHz): δ 7.18 (d, 1H, *J* = 1.6 Hz), 7.16 (d, 1H, *J* = 1.6 Hz), 3.25 (dd, 2H, *J* = 7.0 Hz), 2.96 (m, 1H), 2.56 (m, 1H), 2.12 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.25 (m, 5H), 0.99 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz): δ 137.46, 137.31, 128.56, 124.04, 39.63, 36.68, 32.25, 27.72, 23.14, 21.10, 15.98, 13.42. IR: 2854, 1455, 1376, 1194, 1045 cm $^{-1}$. HRMS (EI) calcd for $C_{12}H_{17}IO$ ([M]$^{+}$) 304.0324, found 304.0322. $[\alpha]^{25}_{D}$ +31 (*c* = 0.37, $CHCl_3$).



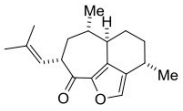
(*S*)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,4-dimethyl-2-((*S*)-2-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)propyl)pent-3-enamide (23). A suspension of 3.14 mL (2.25 g, 22.2 mmol) diisopropylamine and 3.56 g (84.0 mmol) LiCl in 20 mL THF was cooled to −78 °C, and 13.5 mL (21.6 mmol) of *n*BuLi (1.6 M in hexanes) were added dropwise. The resulting reaction mixture was warmed to 0 °C for 5 minutes, and then cooled to −78 °C. A solution of 2.82 mg (10.8 mmol) of chiral auxiliary **20** in 35 mL THF cooled to 0 °C was then added dropwise by cannula. The reaction mixture turned bright yellow. The reaction mixture was stirred for 1 hour at −78 °C, and was then warmed to 0 °C for 15 minutes, then to room temperature for 5 minutes. The reaction mixture was cooled to 0 °C, and a solution of 1.83 g (6.02 mmol) of iodide **22** was added dropwise. The reaction mixture was warmed to room temperature and the flask was covered with foil to protect it from light. After 19 hours at room temperature, the reaction mixture was quenched with a 1:1 solution of water: NH_4Cl (saturated) and the resulting mixture was extracted four times with EtOAc. The combined organic extracts were dried over Na_2SO_4, evaporated and the crude oil was purified by flash column chromatography (10 to 60% EtOAc/hexanes) to provide 2.51 g (95%) **23** as a yellow oil that was a 2:1 mixture of rotamers. Excess chiral auxiliary **20** was also recovered (815 mg).

Rf: 0.39, 40% EtOAc/hexanes. ^{1}H NMR (600 MHz) of major rotamer: δ 7.35 (m, 5H), 7.18 (s, 1H), 7.12 (s, 1H), 5.10 (d, 1H, *J* = 9.7 Hz), 4.64 (m, 1H), 4.38 (br s, 1H), 3.78 (m, 1H), 3.41 (m, 1H), 2.81 (s, 3H), 2.67 (m, 1H), 2.58 (m, 1H), 1.90 (m, 2H), 1.74 (m, 2H), 1.66 (d, 1H, *J* = 4.5 Hz), 1.37 (m, 2H), 1.20 (m, 9H), 0.88 (m, 3H), 0.81 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (150 MHz) of major rotamer: δ 176.89, 142.52, 137.22, 137.16, 133.34, 128.84, 128.70, 128.25, 127.47, 126.77, 126.23, 124.80, 123.66, 76.50, 57.87, 40.93, 37.38, 37.33, 33.85, 32.89, 27.99, 27.94, 25.70, 23.77, 21.00, 18.15, 15.63, 14.40. IR: 3376, 2929, 2871, 2361, 1628, 1452, 1405, 1264, 1127, 1044 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{39}NO_3$ ([M]$^{+}$) 437.2930, found 437.2931. $[\alpha]^{25}_{D}$ +117 (*c* = 0.40, $CHCl_3$).



(*S*)-4-methyl-2-((*S*)-2-((4*R*,7*S*)-7-methyl-4,5,6,7-tetrahydroisobenzofuran-4-yl)propyl)pent-3-enoic acid (9). To 2.51 g (5.74 mmol) of compound **23** were added 20 mL of *t*-BuOH, 57.4 g of an aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 28.7 mmol) and 50 mL of water and the mixture was heated to 100 °C at reflux for 20 hours. After cooling the reaction mixture to room temperature, it was partitioned between a 0.5 M solution of NaOH and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The pH of the aqueous layer was adjusted to pH = 1 by addition of a 0.5 M HCl aqueous solution. The aqueous layer was then extracted three more times with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated. The crude material was purified using flash column chromatography (40% EtOAc/hexanes and 1% AcOH) and the fractions containing product were washed with $NaHCO_3$ (saturated), then dried over Na_2SO_4, filtered, and evaporated to afford 1.66 g (99%) of **9** as a pale yellow oil.

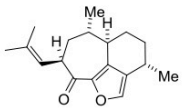
Rf: 0.46, 60% EtOAc/Hexanes. ^{1}H NMR (600 MHz): δ 7.16 (t, 1H, *J* = 1.6 Hz), 7.09 (t, 1H, *J* = 1.5 Hz), 5.13 (d, 1H *J* = 9.5 Hz), 3.38 (m, 1H), 2.67 (m, 1H), 2.55 (m, 2H), 1.87 (m, 3H), 1.74 (d with shoulder, 4H *J* = 1.3 Hz), 1.69 (d, 3H *J* = 1.4 Hz), 1.43 (m, 1H), 1.31 (m, 1H), 1.20 (d, 3H, *J* = 6.7 Hz), 1.17 (m, 1H), 0.86 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (150 MHz): δ 181.04, 137.22, 137.18, 135.51, 128.79, 124.71, 122.24, 42.85, 37.22, 36.70, 33.98, 32.85, 27.93, 25.77, 23.54, 20.99, 18.21, 15.52. IR: 2959, 2926, 1710, 1448, 1377, 1292, 1130, 1044 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{26}O_3$ ($[M]^+$) 290.1882, found 290.1883. $[\alpha]^{25}_D$ +78 (*c* = 0.63, $CHCl_3$).



(3*S*,5a*R*,6*S*,8*S*)-3,6-dimethyl-8-(2-methylprop-1-en-1-yl)-4,5,5a,6,7,8-hexahydrocyclohepta[cd]isobenzofuran-9(3H)-one (24). A solution of 300 mg (1.03 mmol) **9** in 200 mL DCM was cooled to 0 °C, and then 0.201 mL (303 mg, 1.44 mmol) of trifluoroacetic anhydride was added using a teflon cannula. The reaction mixture was warmed to room temperature, and after 10 minutes, 2.06 mL of a 1.0 M solution of $ZnCl_2$ (2.06 mmol) in THF was added dropwise. The pale yellow reaction mixture was stirred at room temperature for 30 minutes, then warmed to 40 °C for 1 hour. The reaction mixture was then quenched with an aqueous solution of 1.0 M HCl, the layers were

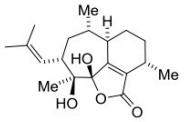
separated, and the organic layer was subsequently washed with a saturated aqueous solution of $NaHCO_3$ and NaCl (saturated). The organic layers were then dried over Na_2SO_4, filtered, and evaporated. The crude material was purified using flash column chromatography (10% EtOAc/hexanes) to afford 200 mg (71%) of **24** as a crystalline white solid.

Rf: 0.58, 25% EtOAc/hexanes. ^{1}H NMR (600 MHz): δ 7.38 (d, 1H, *J* = 1.6 Hz), 5.28 (dm, 1H *J* = 8.7 Hz), 3.47 (m, 1H), 2.65 (m, 1H), 2.35 (m, 1H), 2.13 (m, 1H), 2.03 (m, 1H), 1.86 (m, 3H), 1.78 (s, 3H), 1.65 (s, 3H), 1.24 (m with d, 5H *J* = 6.6 Hz), 1.13 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR (150 MHz): δ 190.36, 147.51, 142.16, 134.31, 133.74, 129.52, 123.73, 50.20, 43.61, 41.37, 38.66, 32.90, 28.68, 27.25, 25.78, 21.59, 21.23, 18.12. IR: 2955, 2923, 1650, 1525, 1442, 1400, 1284 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}O_2$ ($[M]^+$) 272.1776, found 272.1773. $[\alpha]^{25}_D$ +14 (*c* = 0.30, $CHCl_3$).



(3*S*,5a*R*,6*S*,8*R*)-3,6-dimethyl-8-(2-methylprop-1-en-1-yl)-4,5,5a,6,7,8-hexahydrocyclohepta[cd]isobenzofuran-9(3H)-one (25). To a solution of 17 mg (0.062 mmol) **24** in 2 mL $PhCH_3$ was added 0.028 mL DBU (0.19 mmol) and the solution was stirred at room temperature for 48 hours, then concentrated and purified by flash column chromatography (10% EtOAc/hexanes) to obtain 17 mg (quantitative yield) of **25** as a yellow oil.

^{1}H NMR (600 MHz): δ 7.38 (d, 1H, *J* = 1.5 Hz), 5.43 (d, 1H *J* = 9.1 Hz), 3.45 (m, 1H), 2.62 (m, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.77 (s, 3H), 1.62 (s, 3H), 1.61 (m, 1H), 1.30 (m, 1H), 1.24 (m with d, 4H *J* = 6.7 Hz), 1.12 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (150 MHz): δ 190.26, 147.79, 141.60, 135.49, 133.39, 130.02, 122.44, 46.13, 39.97, 39.61, 35.81, 32.61, 29.46, 27.68, 25.99, 20.76, 20.59, 18.11.

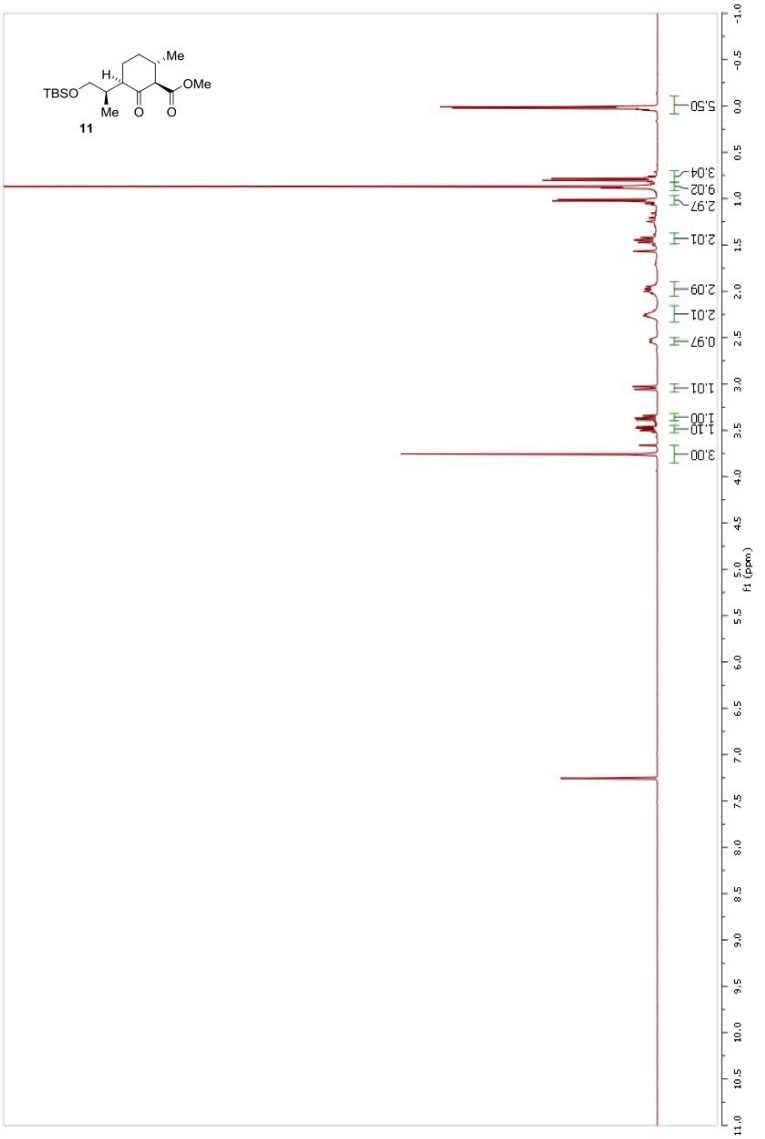


(3*S*,5a*R*,6*S*,8*S*,9*S*,9a*S*)-9,9a-dihydroxy-3,6,9-trimethyl-8-(2-methylprop-1-en-1-yl)-4,5,5a,6,7,8,9,9a-octahydrocyclohepta[cd]isobenzofuran-2(3H)-one, sandresolide B (3). A solution of 30 mg (0.11 mmol) of **9** in 12 mL THF was cooled to −78 °C, and then 0.147 mL (0.44 mmol) of a 3.0 M solution of methylmagnesium bromide in Et_2O was added. After 10 minutes at −78 °C, the reaction mixture was left to come to room temperature over 20 minutes and was then quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted twice with

Et_2O. The combined organic layers were washed with NaCl (saturated), dried over Na_2SO_4, filtered, and evaporated. Crude material was taken on directly due to instability and was dissolved in 8 mL DCM. To this solution was added one spatula edge of tetraphenylporphyrine. The solution was then cooled to −78 °C, and oxygen was bubbled through while the flask was irradiated with a UV lamp (Replux Belgium RL 160 W, 225 – 235 Volts). After 10 minutes, 0.1 mL (0.66 mmol) of DBU was added and the reaction mixture was allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (30% acetone/hexanes) to give 18 mg (51%) of sandresolide B (**3**) as a white solid.

^{1}H NMR isolation	^{1}H NMR current	^{13}C NMR isolation	^{13}C NMR current
5.05 br d, (10.0 Hz)	5.05 br d (9.9 Hz)	170.8	170.7
3.02 ddd (10.0, 8.5, 3.9 Hz)	3.01 ddd (9.9, 8.2, 3.6 Hz)	162.0	161.9
2.53, m	2.55, m	134.8	134.7
2.18, m	2.19, m	132.4	132.4
2.08, m	2.08, m	124.3	124.3
2.00, m	2.00, m	108.2	108.2
2.00, m*	1.27, m	77.2	77.3
1.92, m	1.92, m	46.0	46.1
1.77, d, 1.2 Hz	1.77, d, (1.9 Hz)	43.9	43.9
1.72, d, 1.1 Hz	1.73, d, (1.4 Hz)	43.8	43.8
1.57, m	1.57 (m)	33.3	33.2
1.24, m	1.28 (m)	31.7	31.7
1.24, d, (6.5 Hz)	1.24 (d, 7.0 Hz)	28.2	28.2
1.18, m	1.18 (m)	27.5	27.5
1.12, s	1.11 (s)	26.2	26.3
0.94, d, (6.8 Hz)	0.95, d, (6.9 Hz)	21.0	21.0
		19.1	19.1
		18.4	18.5
		16.9	16.9

* Error in isolation paper as discussed in manuscript, confirmed through correspondence with the isolationist.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OMe
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3.00
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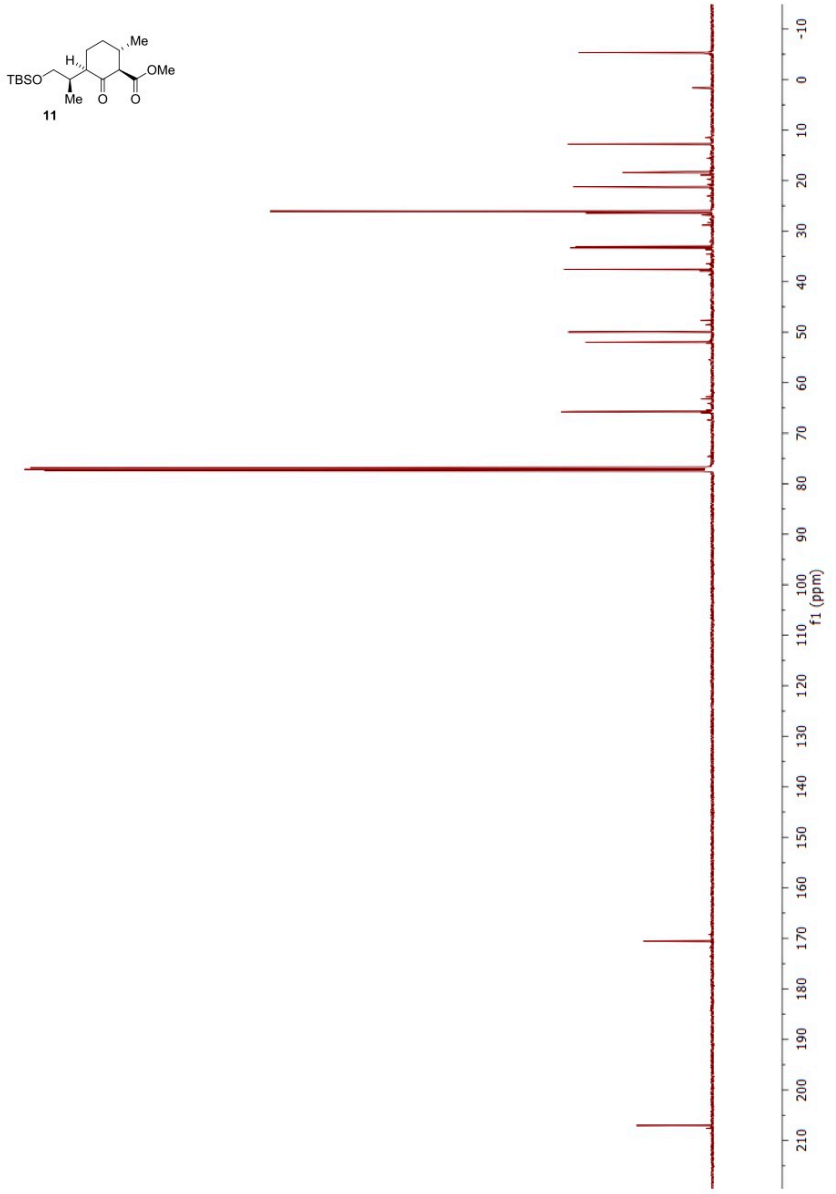
S15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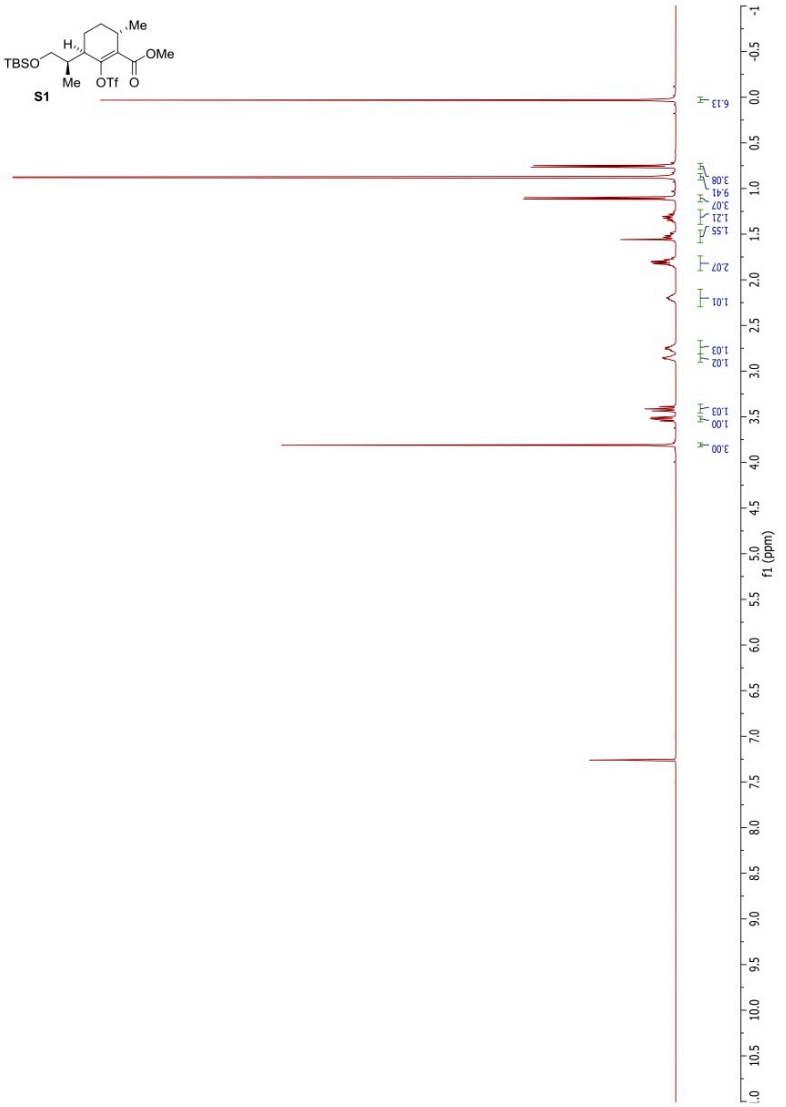
f1 (ppm)

S16



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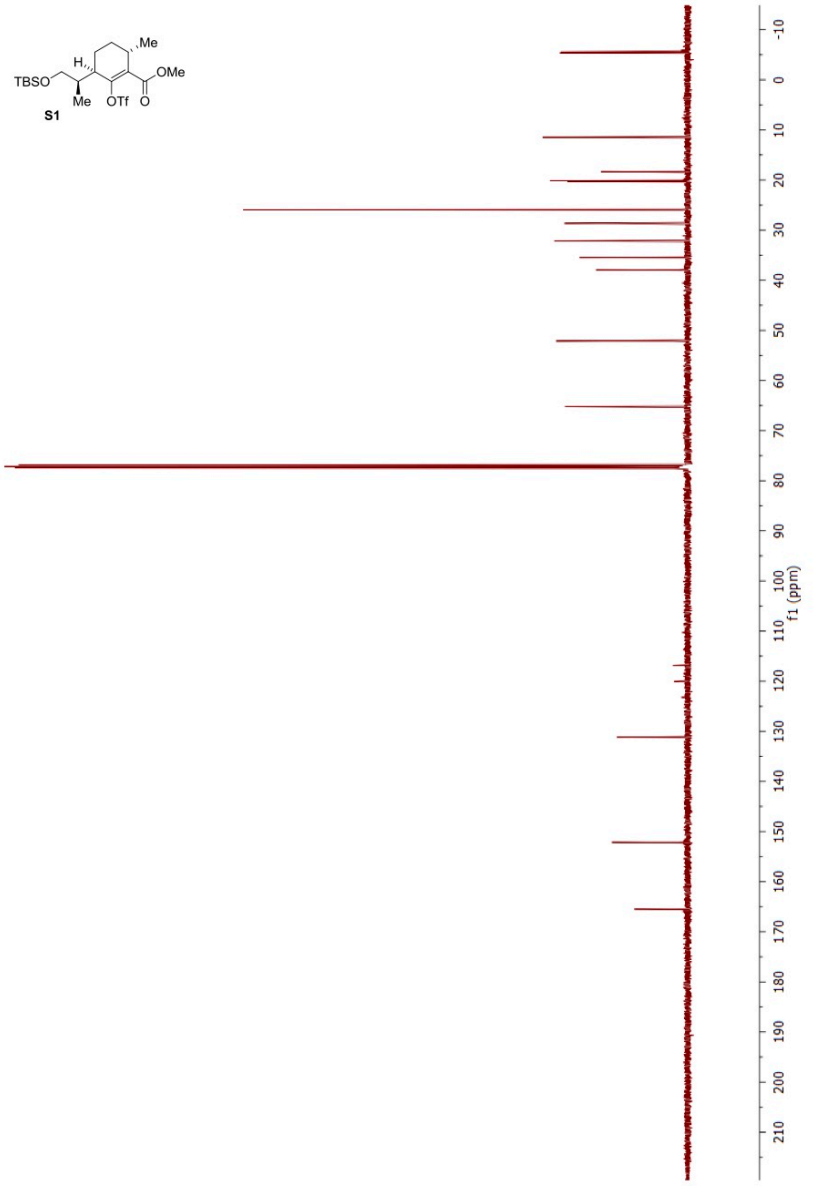
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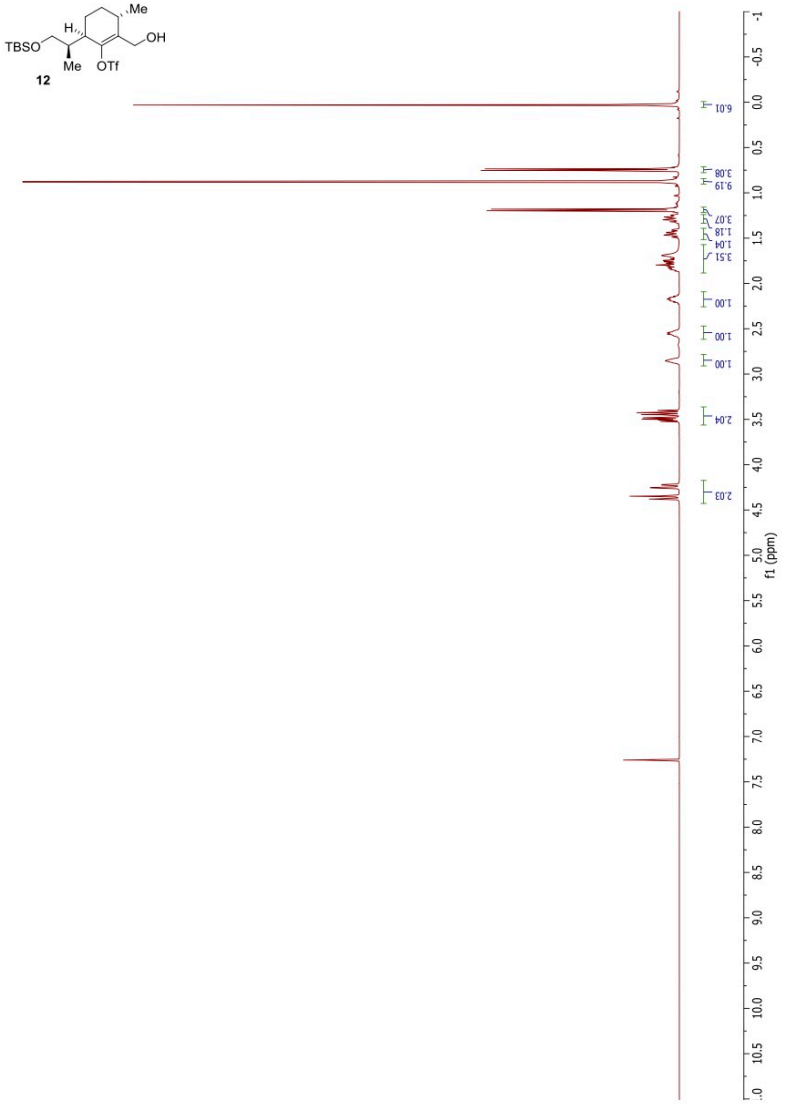
f1 (ppm)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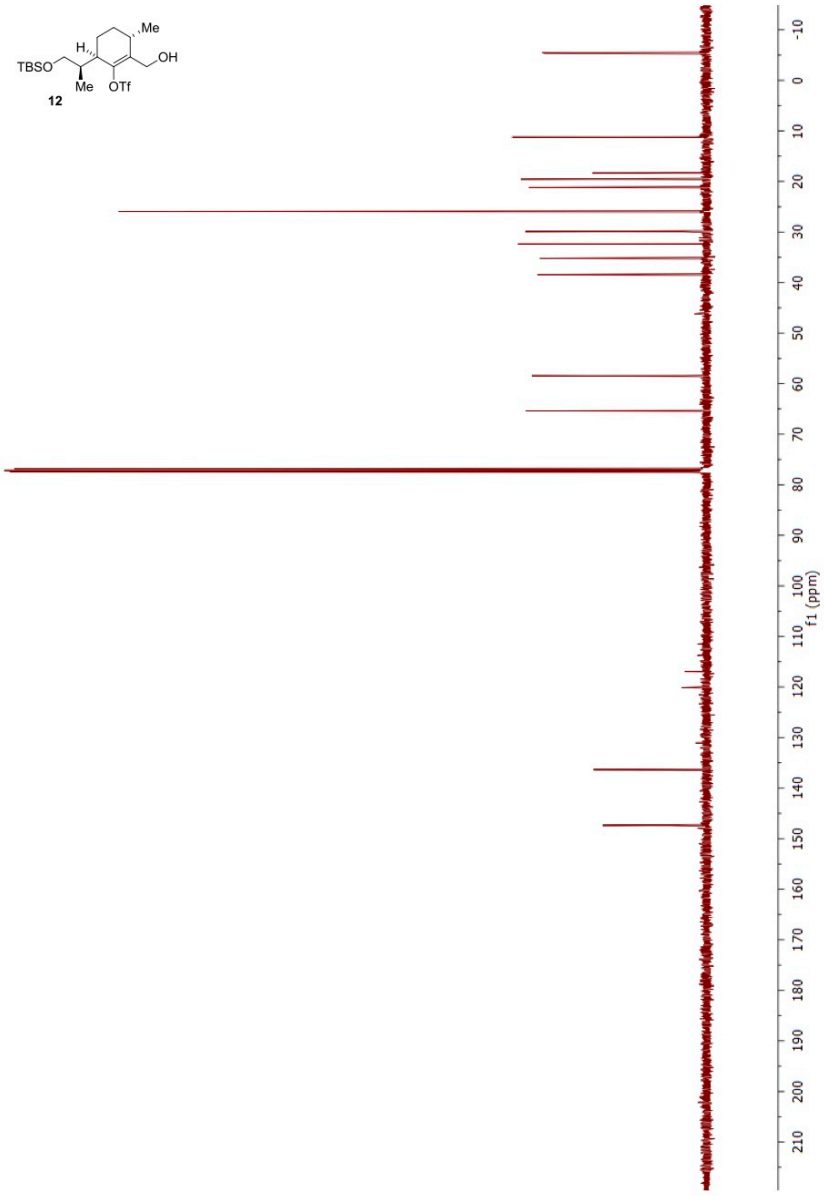
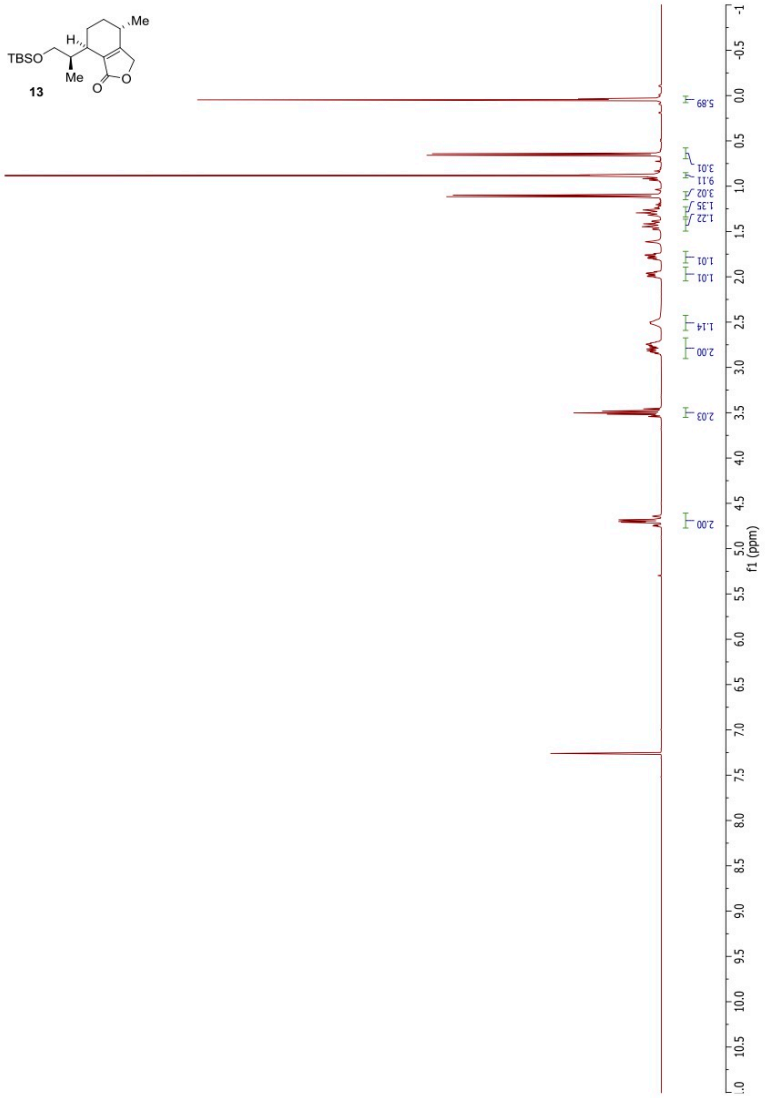
f1 (ppm)



S20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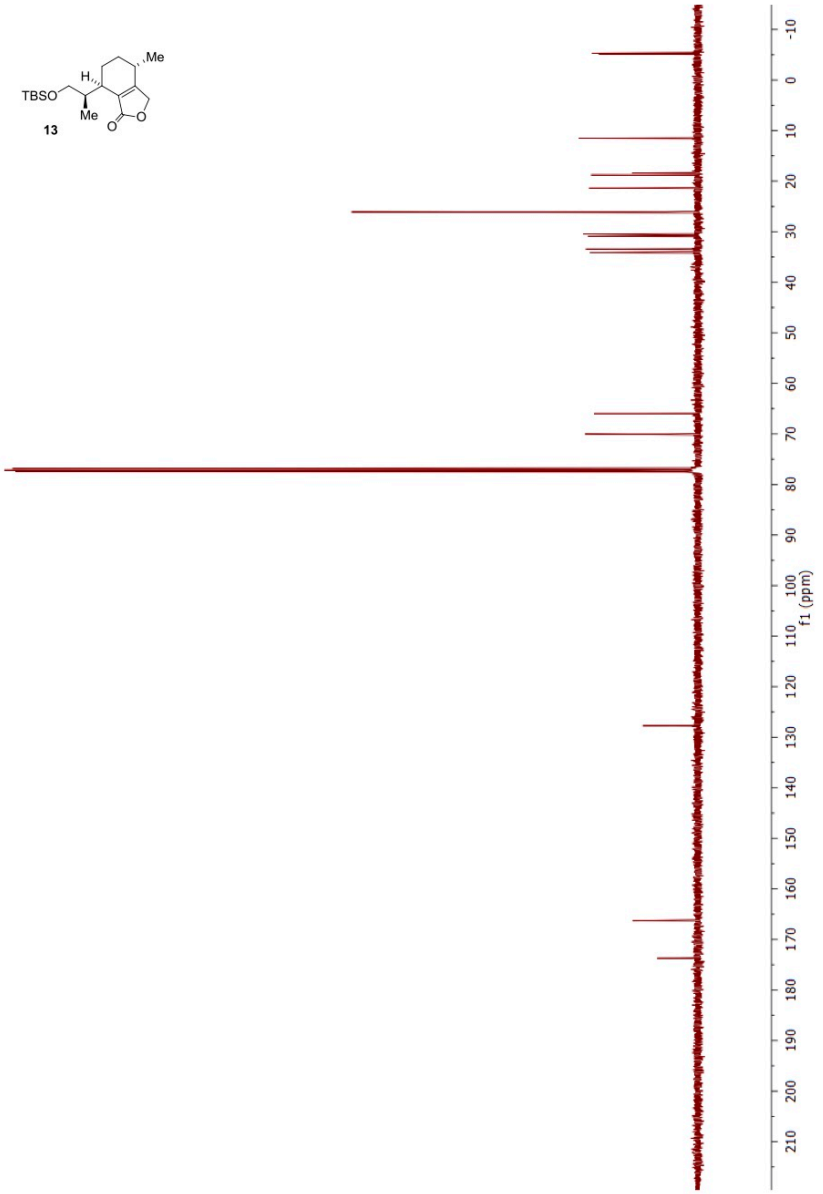
S21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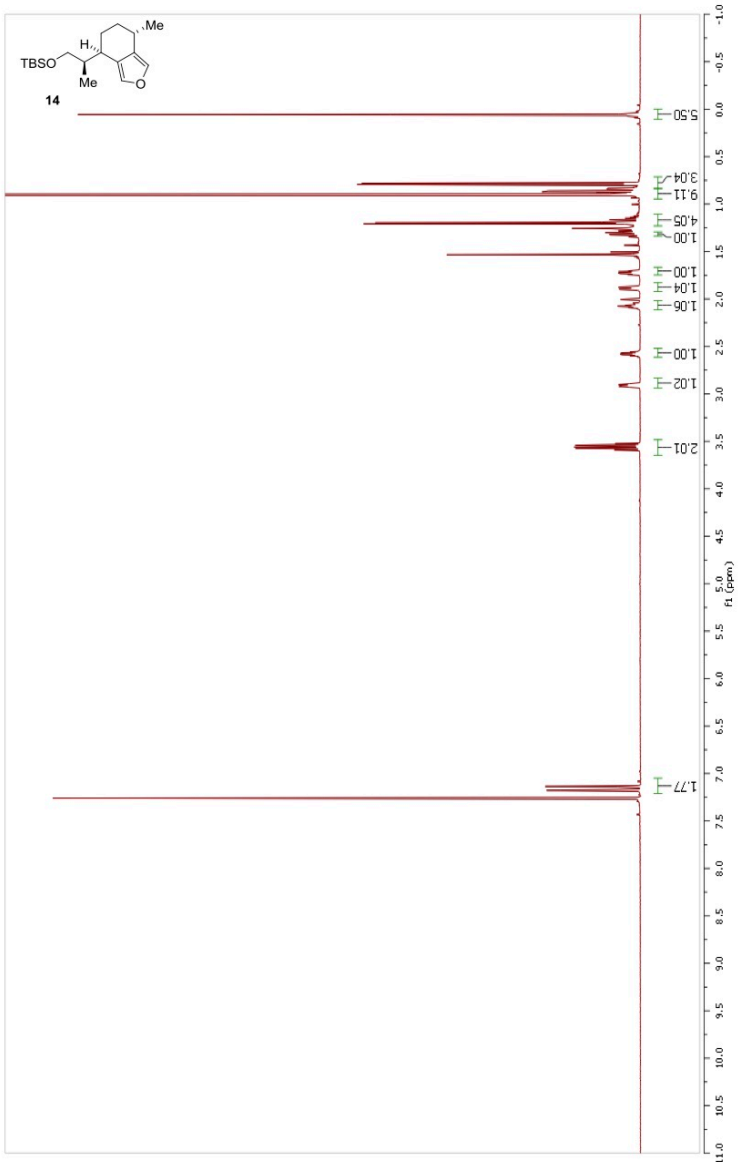
f1 (ppm)

S22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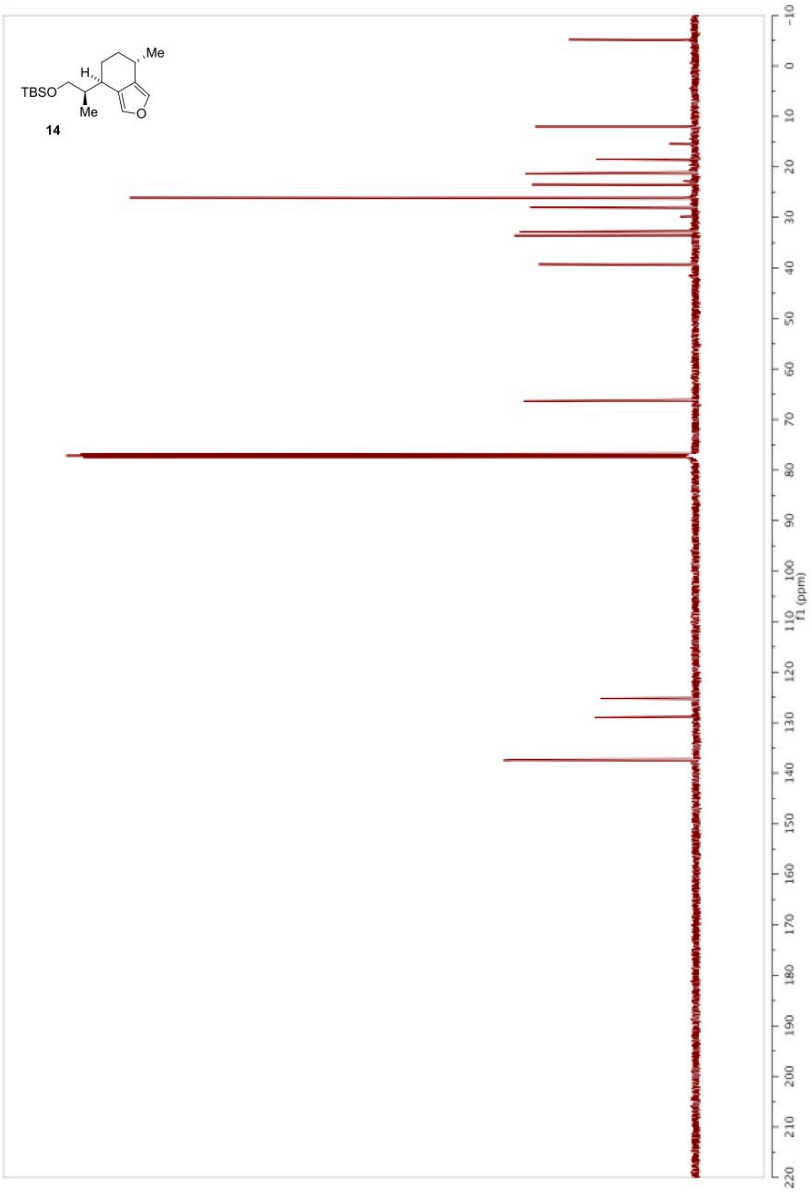
S23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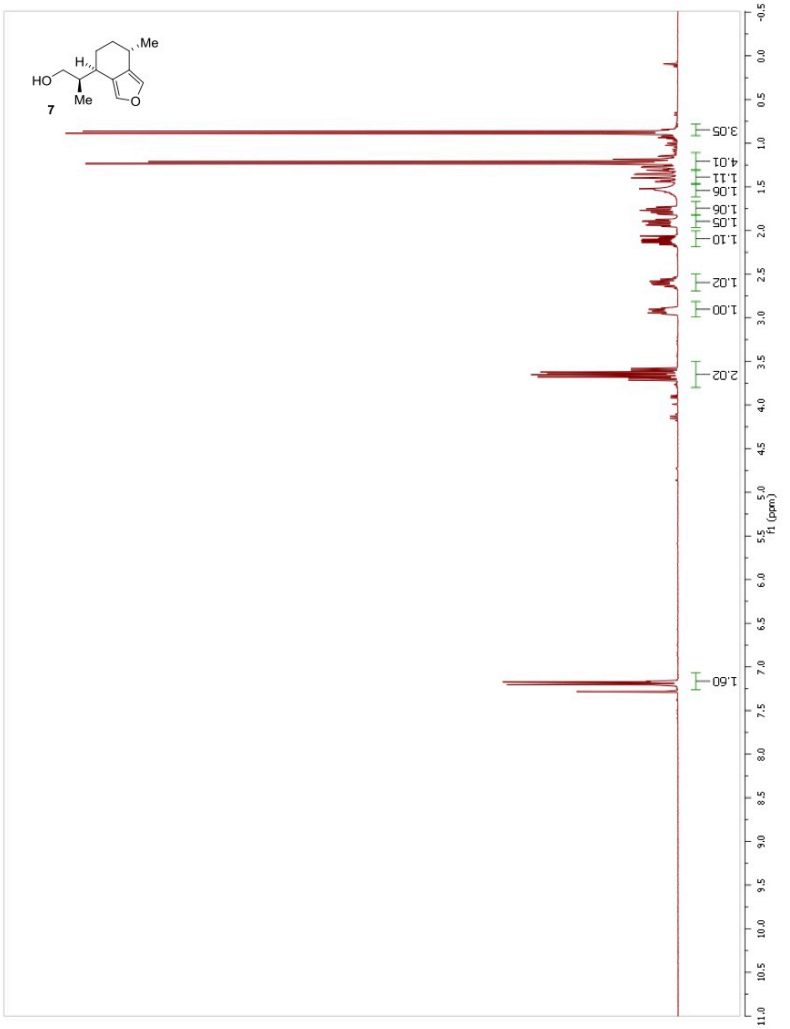
f1 (ppm)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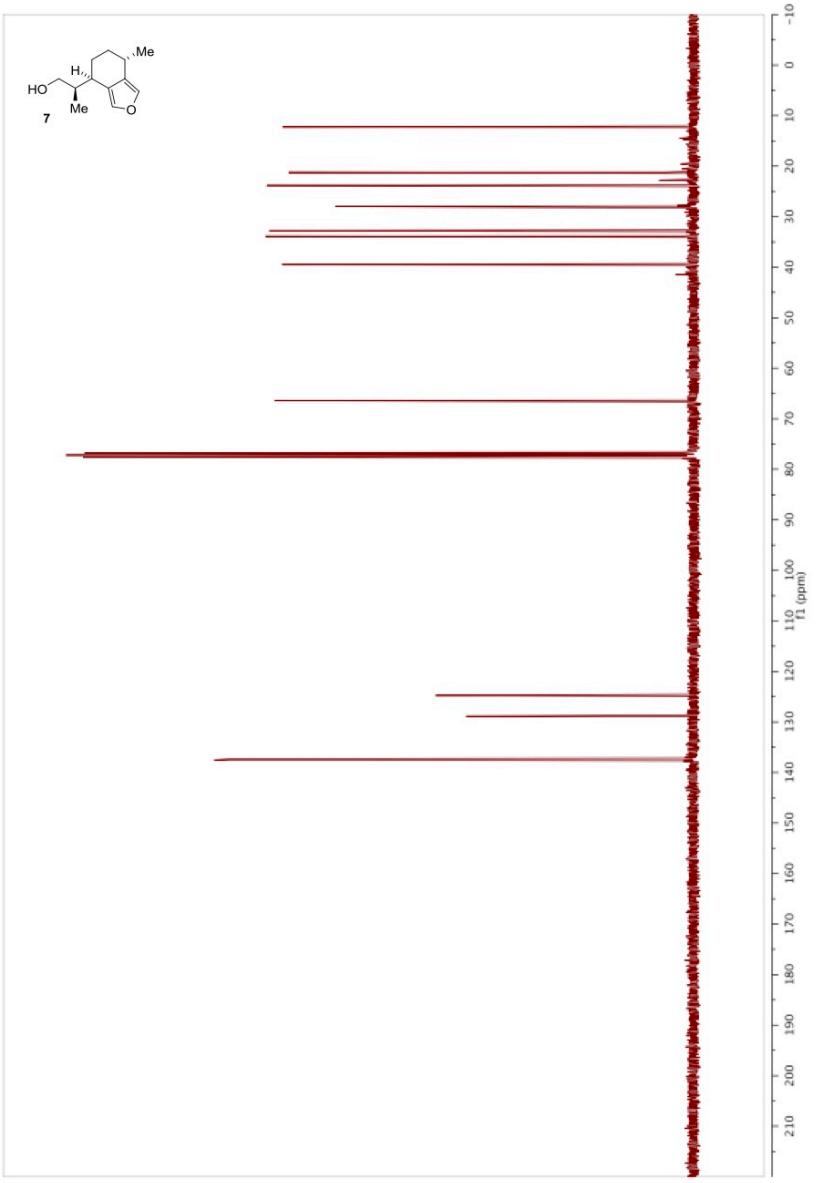
f1 (ppm)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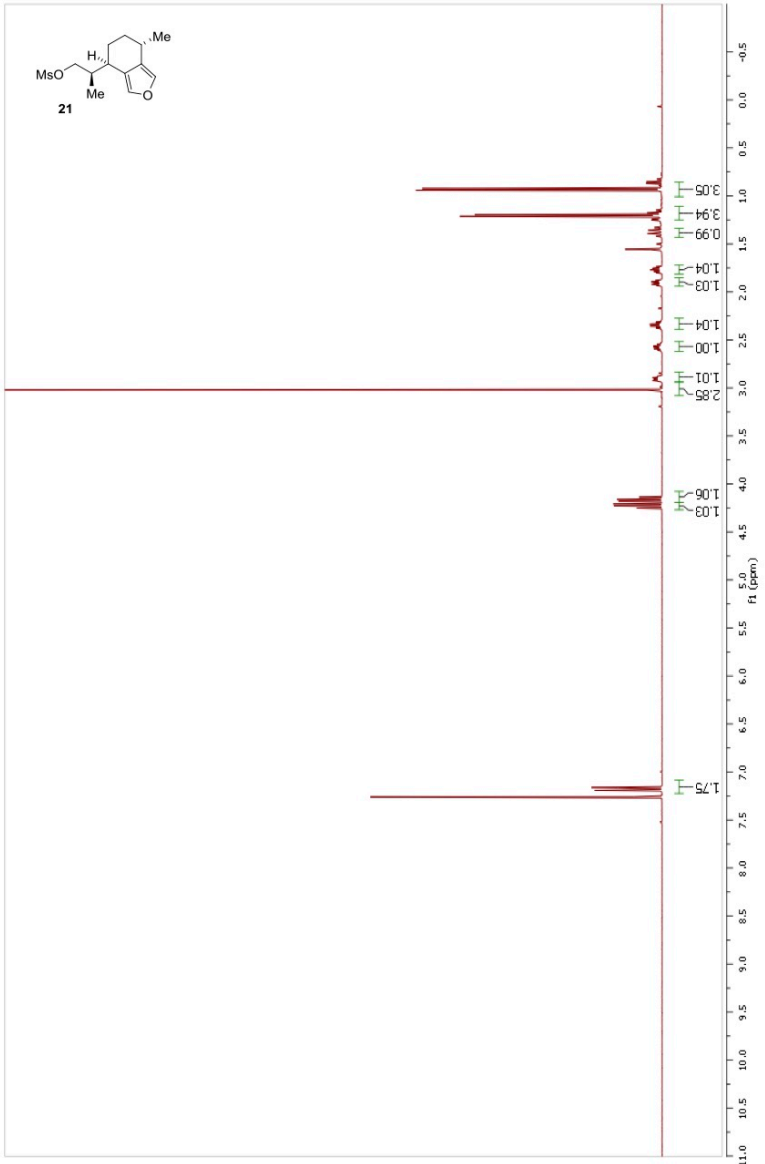
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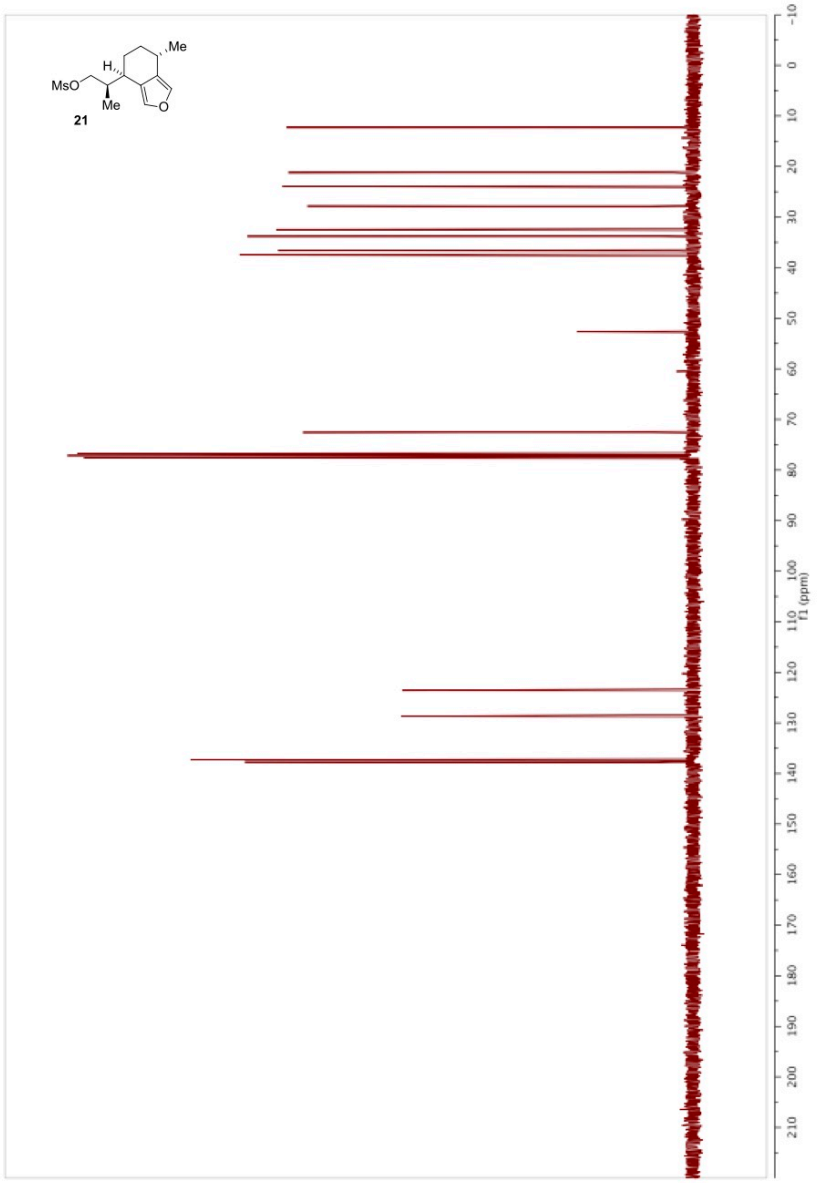
F1 (ppm)

S27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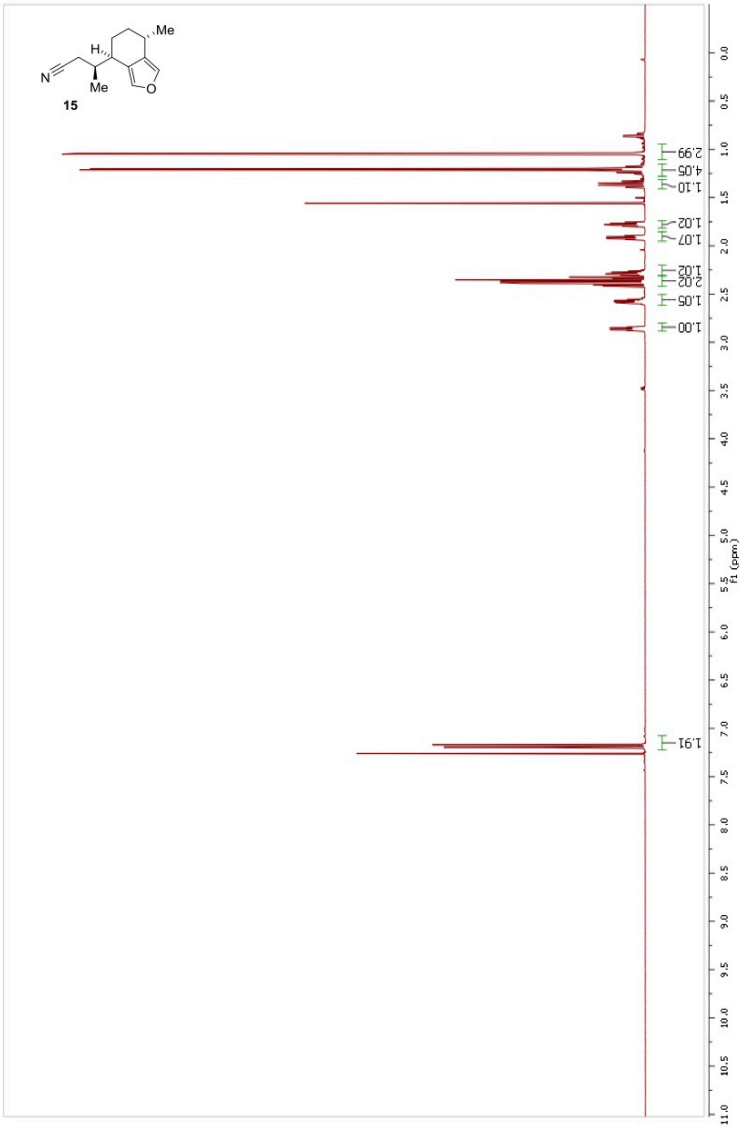
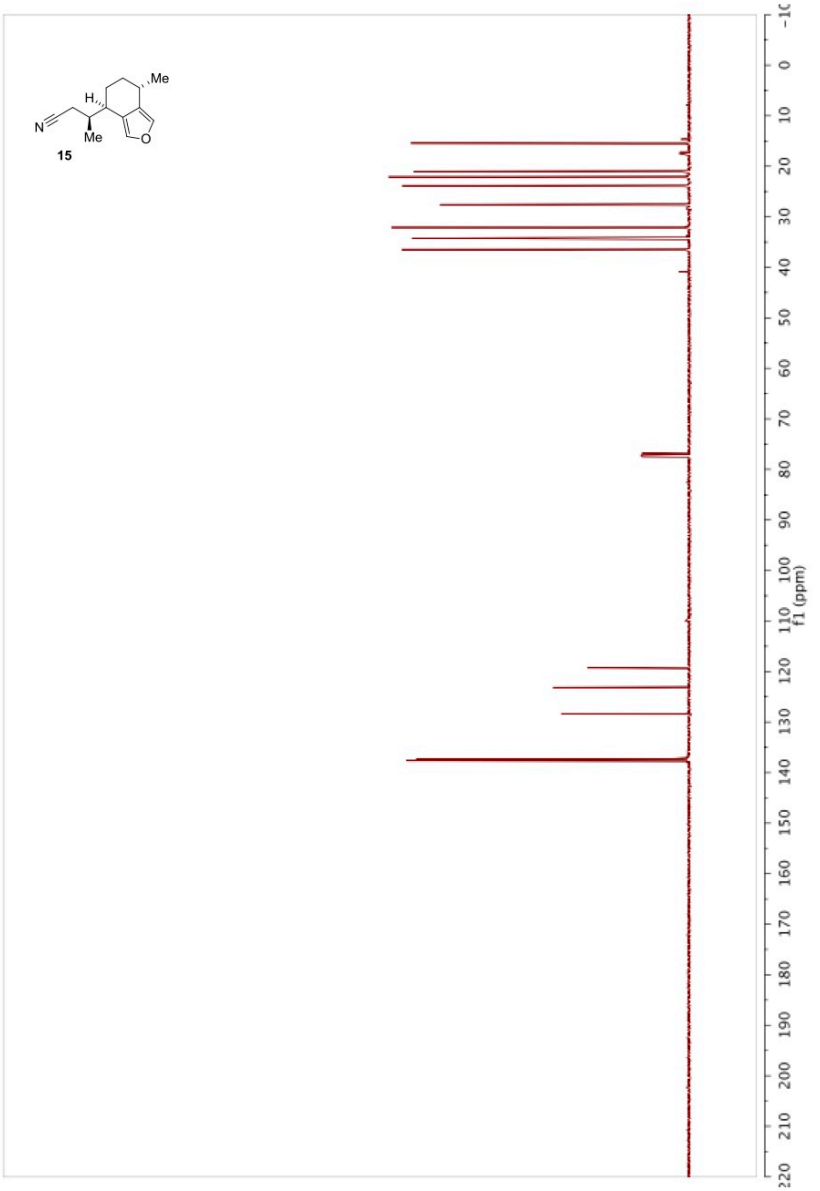
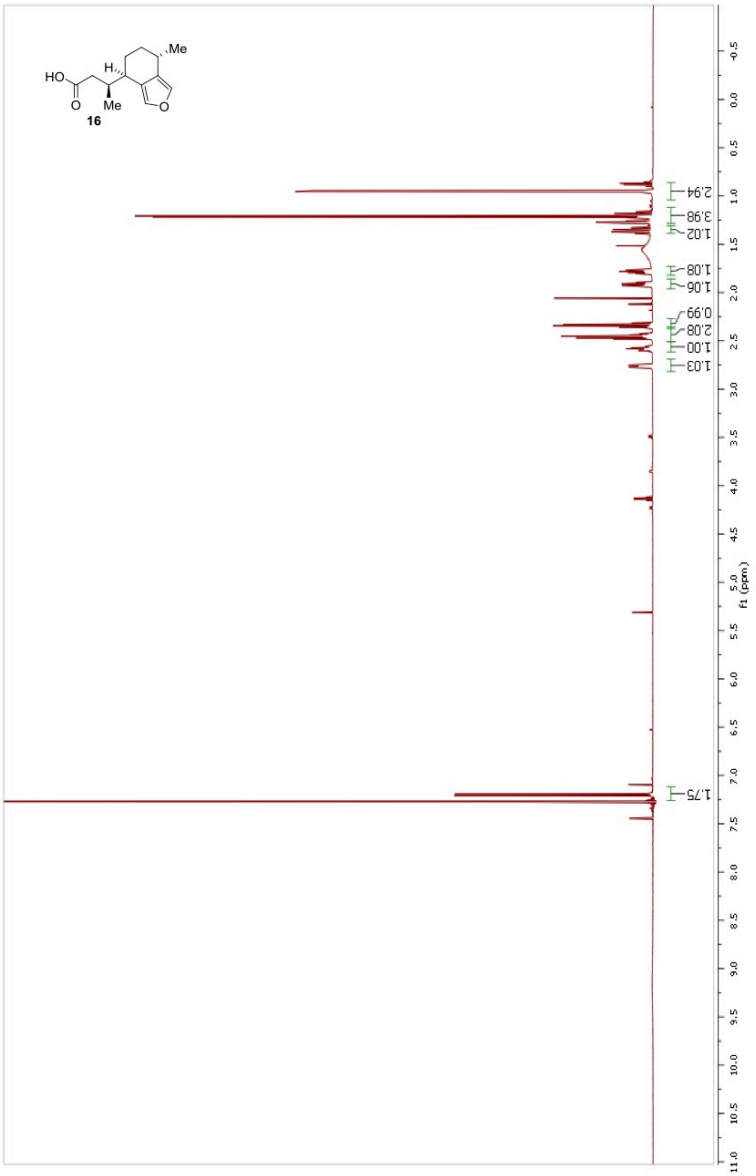


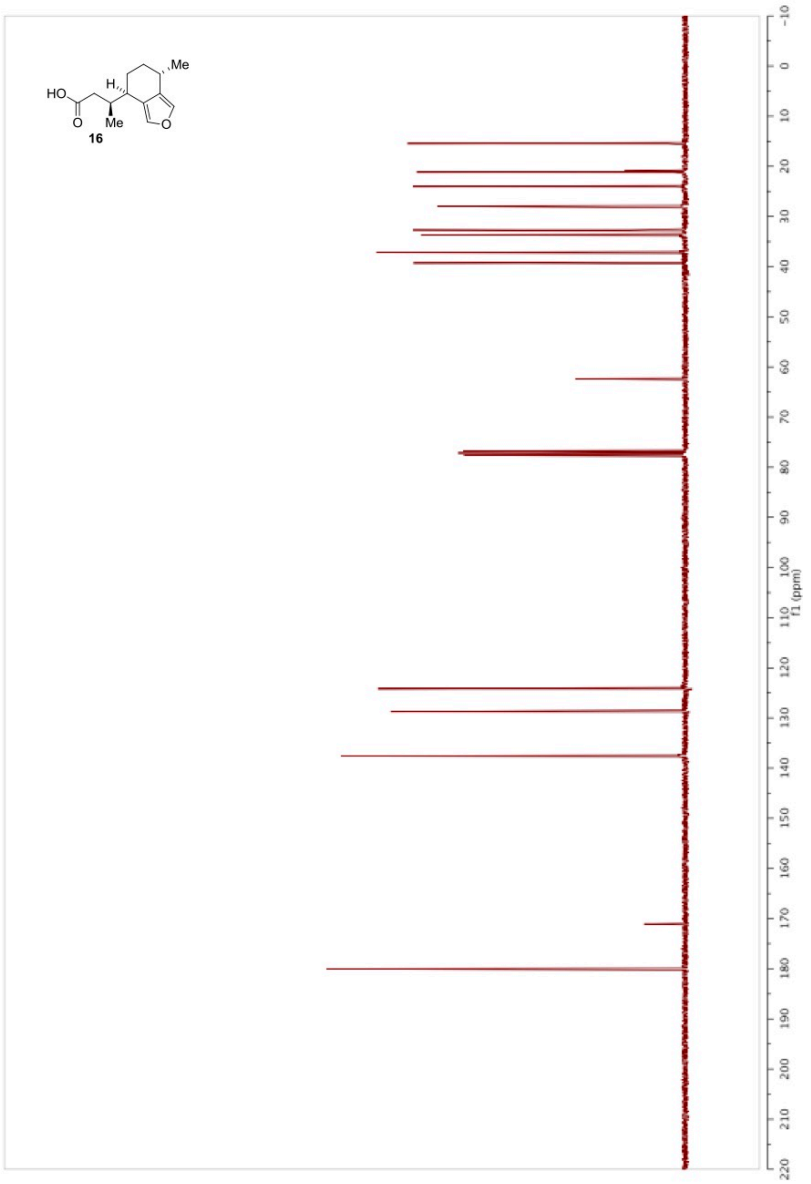
S29

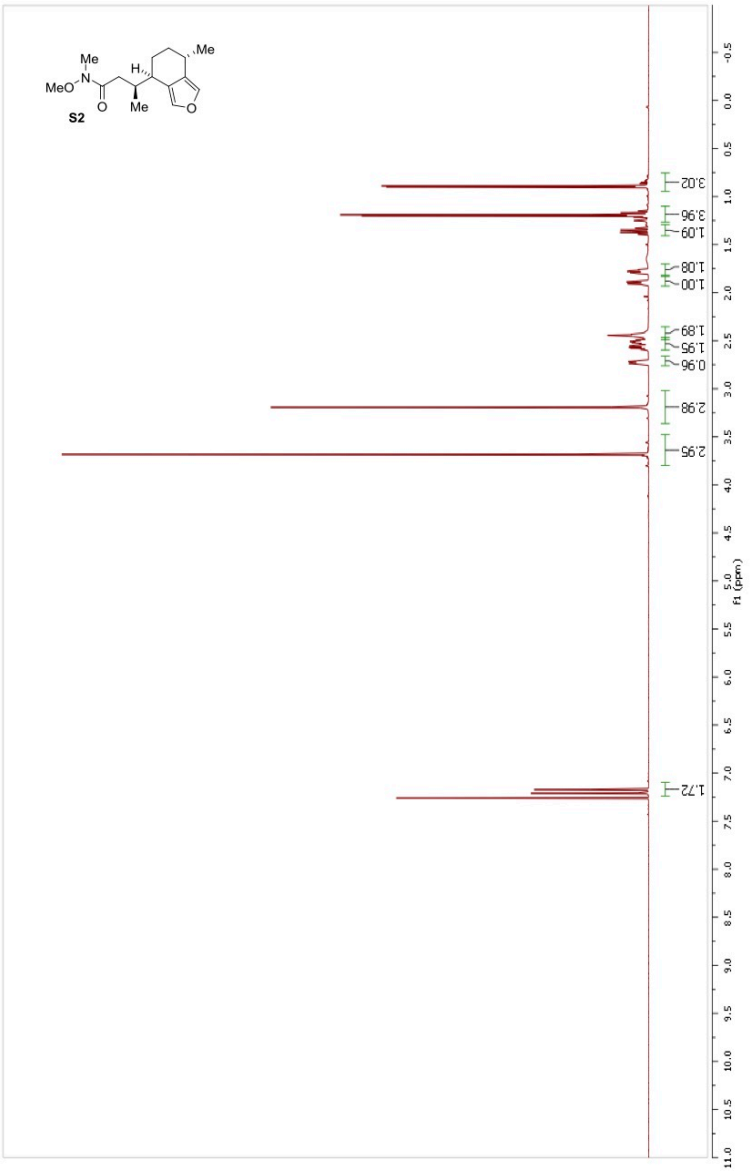


S30

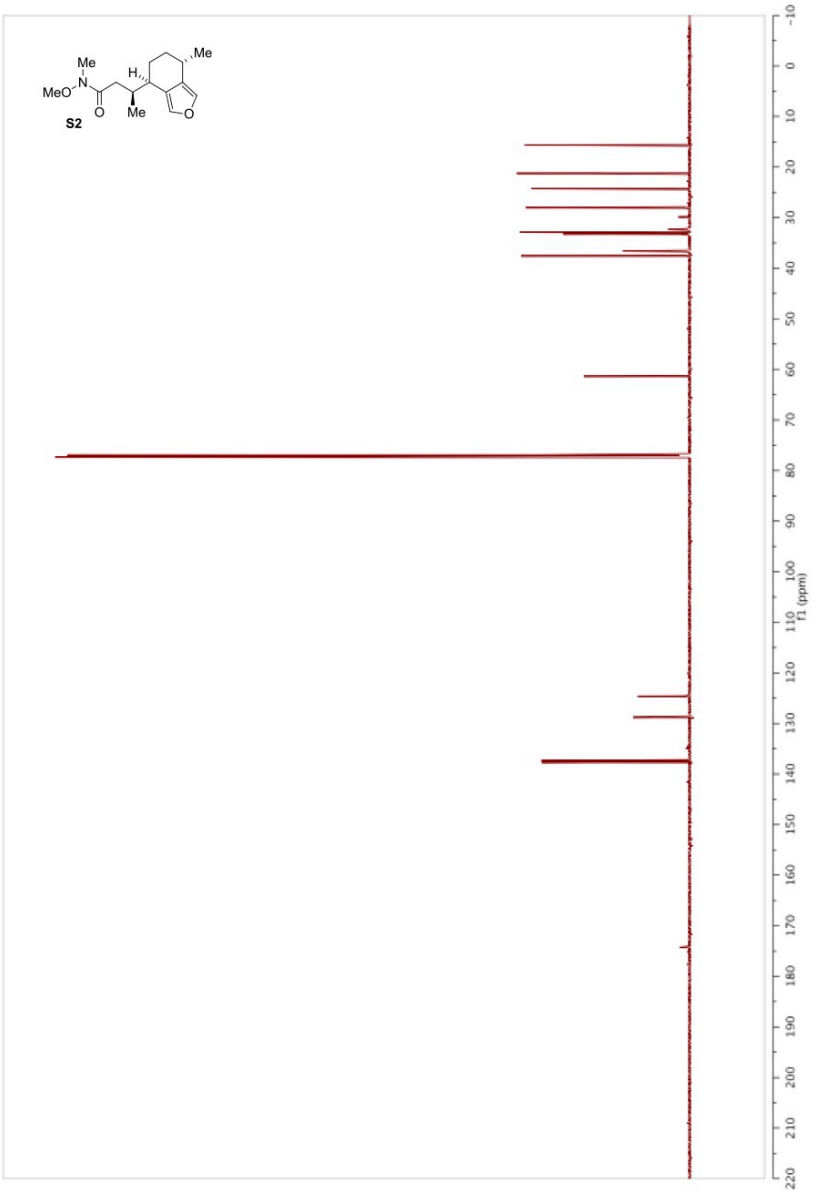


S31

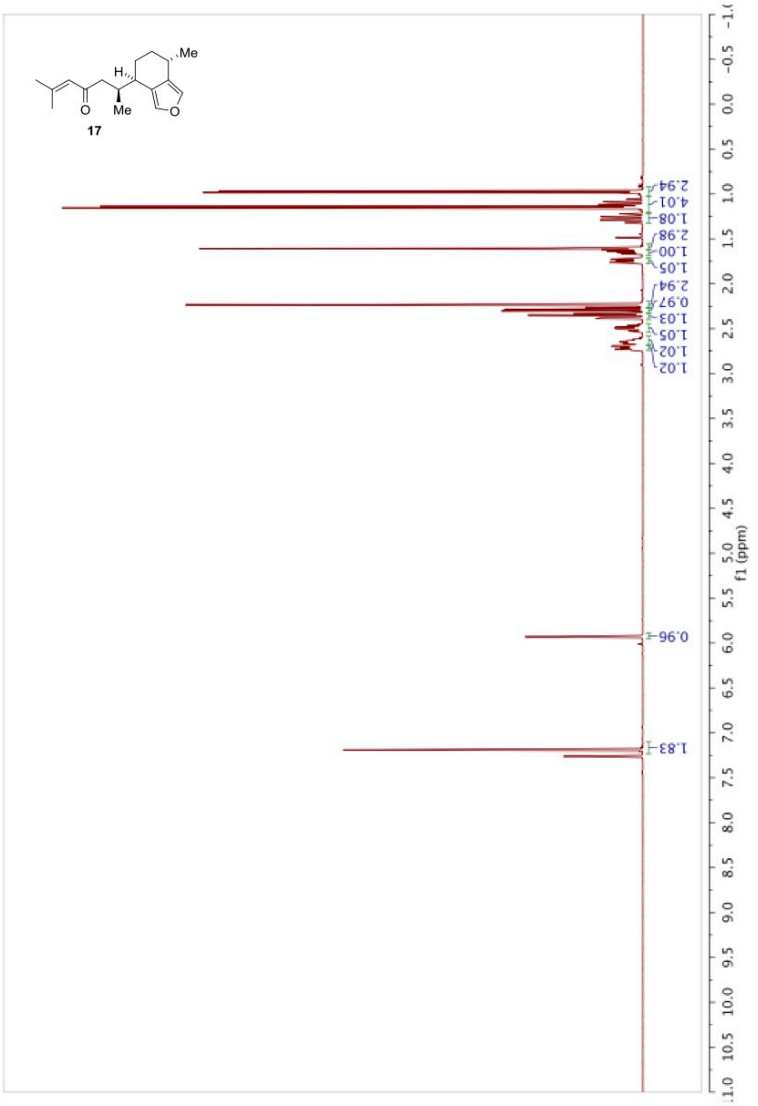

HO
O
Me
H
Me
O
16
f1 (ppm)

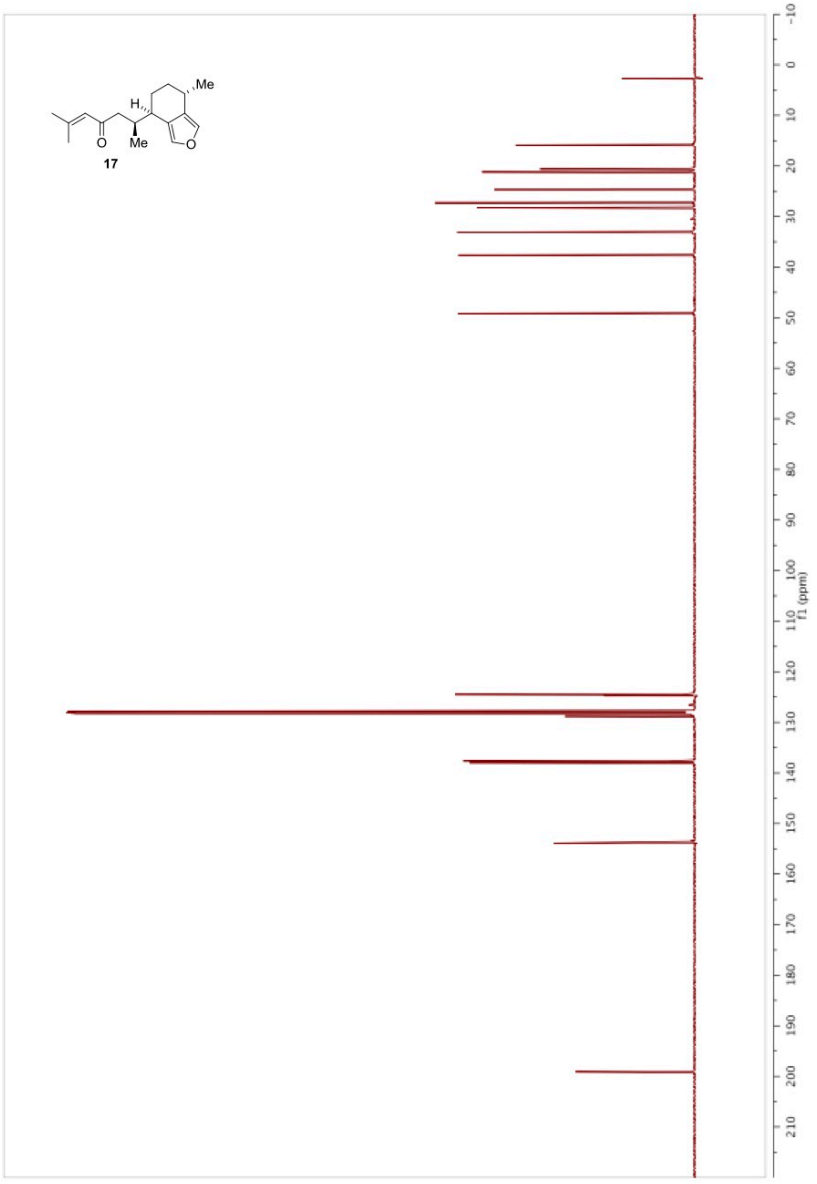

Me
MeO
N
O
H
Me
Me
O
S2
3.02
3.96
1.09
1.08
1.00
1.89
1.95
0.96
2.98
2.95
1.72
f1 (ppm)

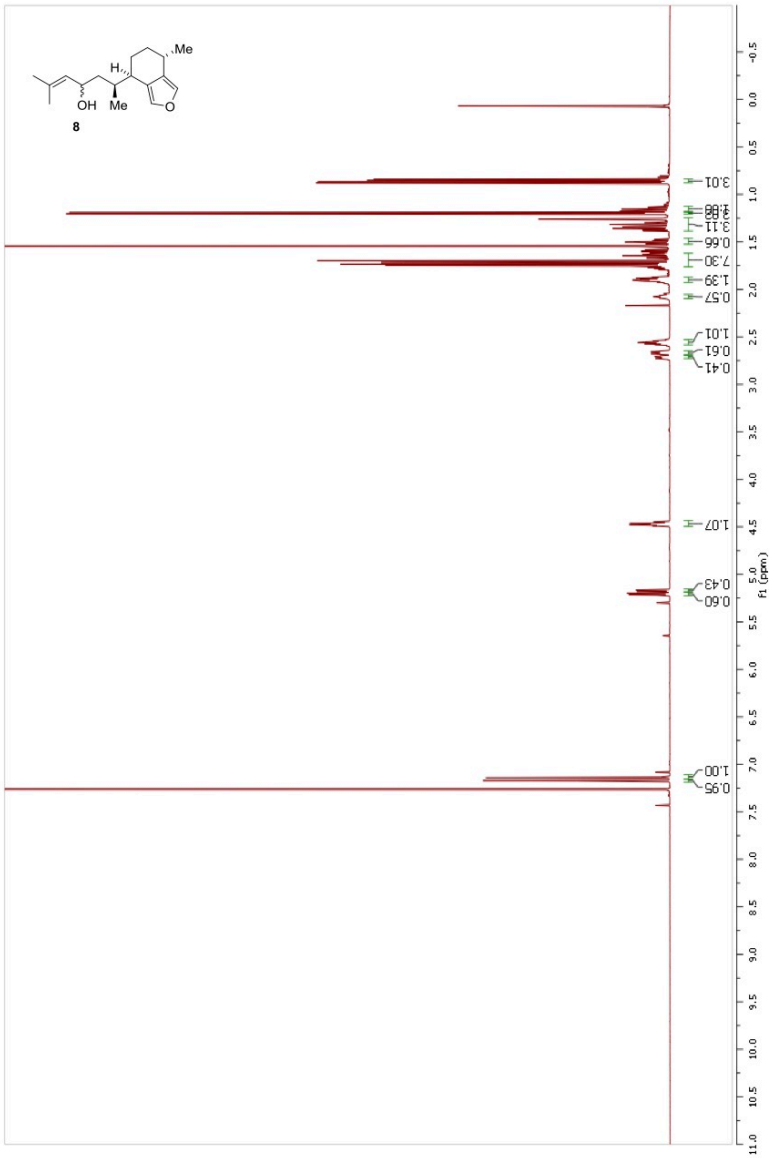
S33



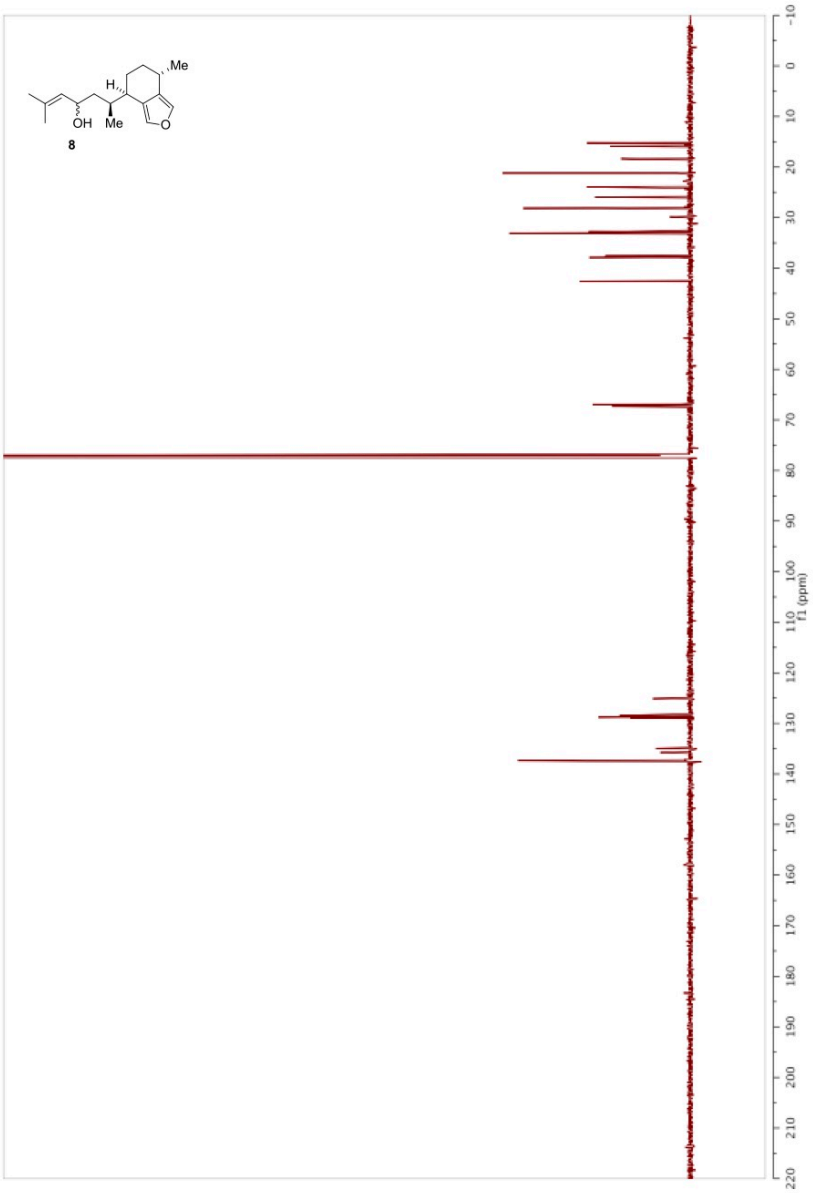
S34

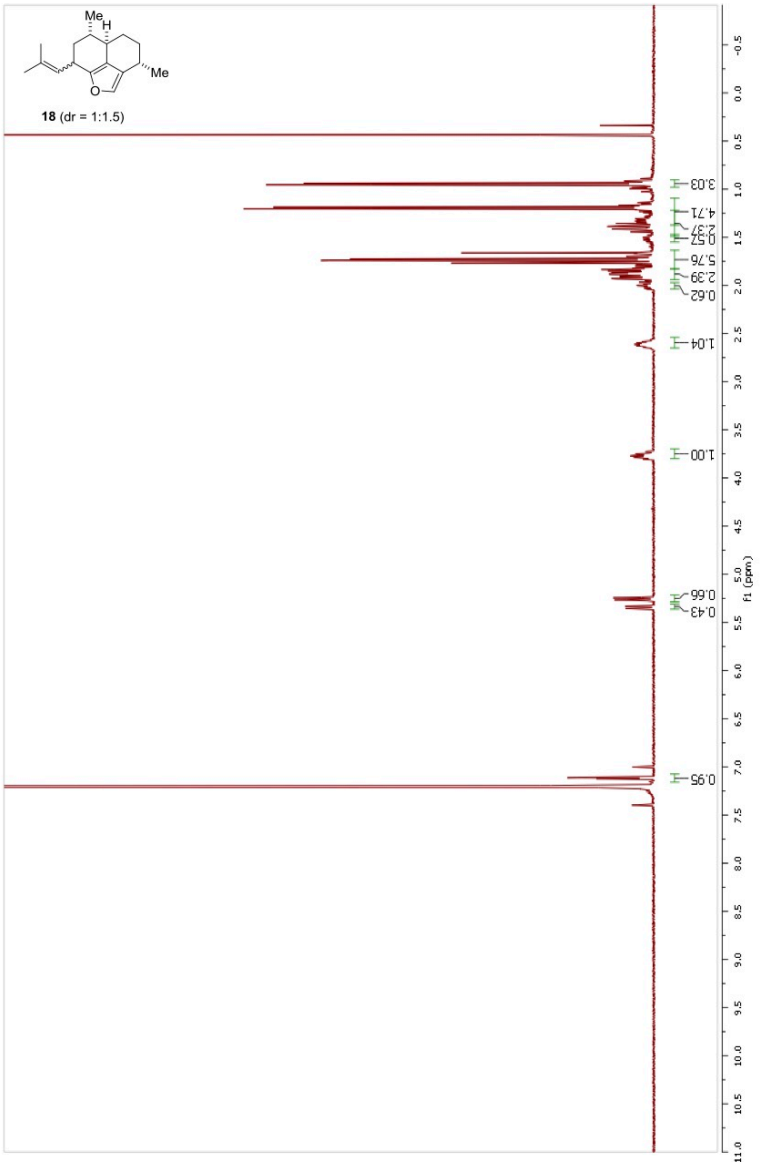

Me
H
O
Me
O
17
2.94
4.01
1.08
2.98
1.00
1.05
2.94
0.97
1.03
1.05
1.02
1.02
0.96
1.83
f1 (ppm)


Me
H
O
Me
O
17
f1 (ppm)

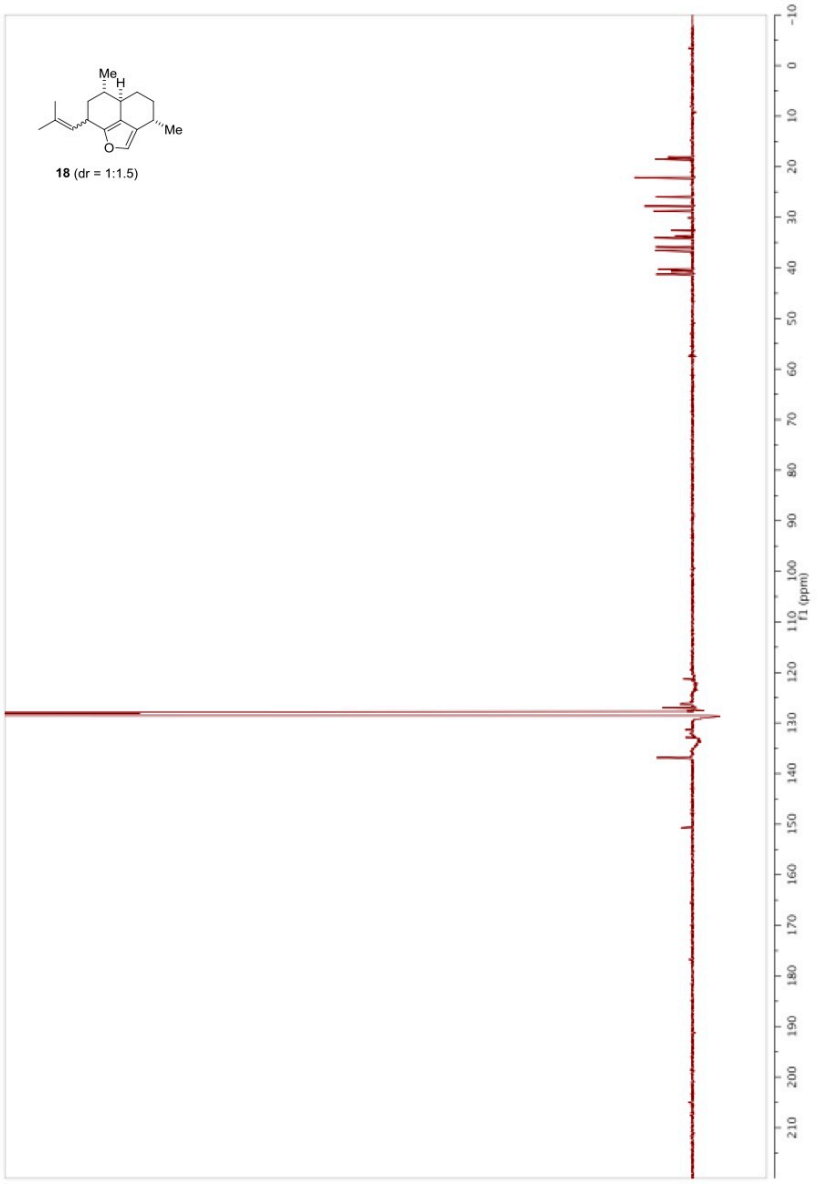

Me
H
OH
Me
O
8
3.01
1.88
3.11
0.66
7.30
1.39
0.57
1.01
0.61
0.41
1.07
0.43
0.60
0.95
1.00
f1 (ppm)

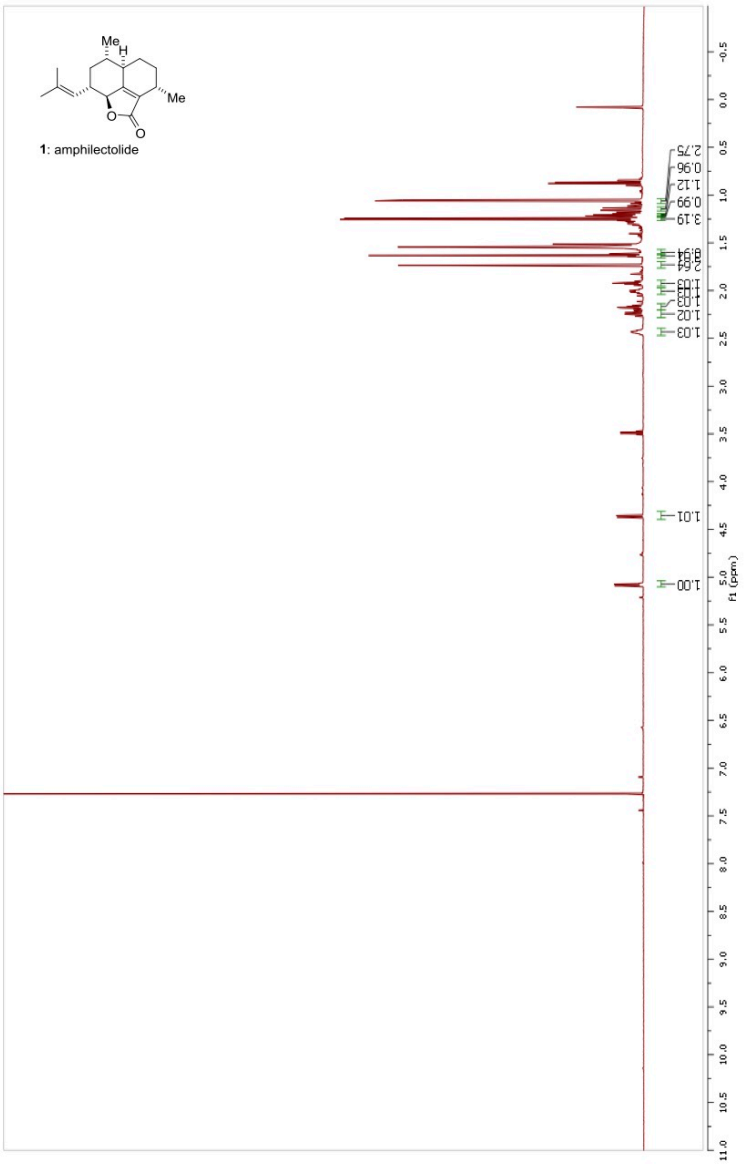
S37


Me
H
OH
Me
O
8
f1 (ppm)

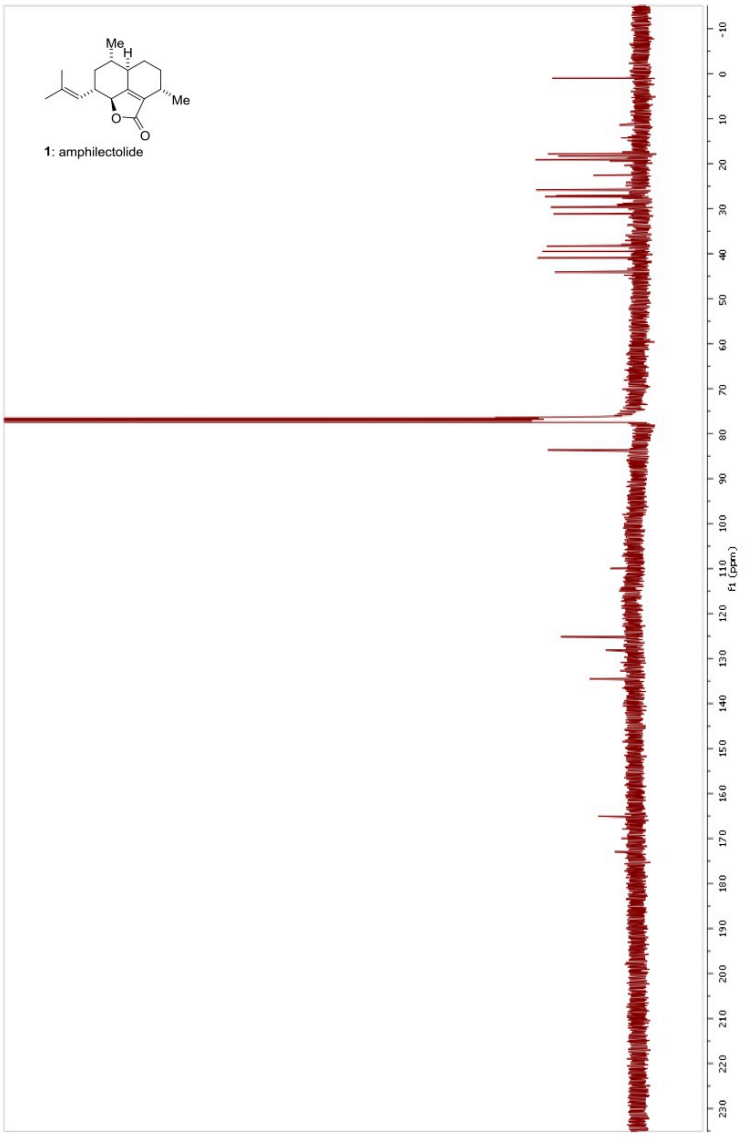

Me
H
Me
O
18 (dr = 1:1.5)
3.03
4.71
2.57
2.37
5.76
2.39
0.62
1.04
1.00
0.66
0.43
0.95
f1 (ppm)

S39

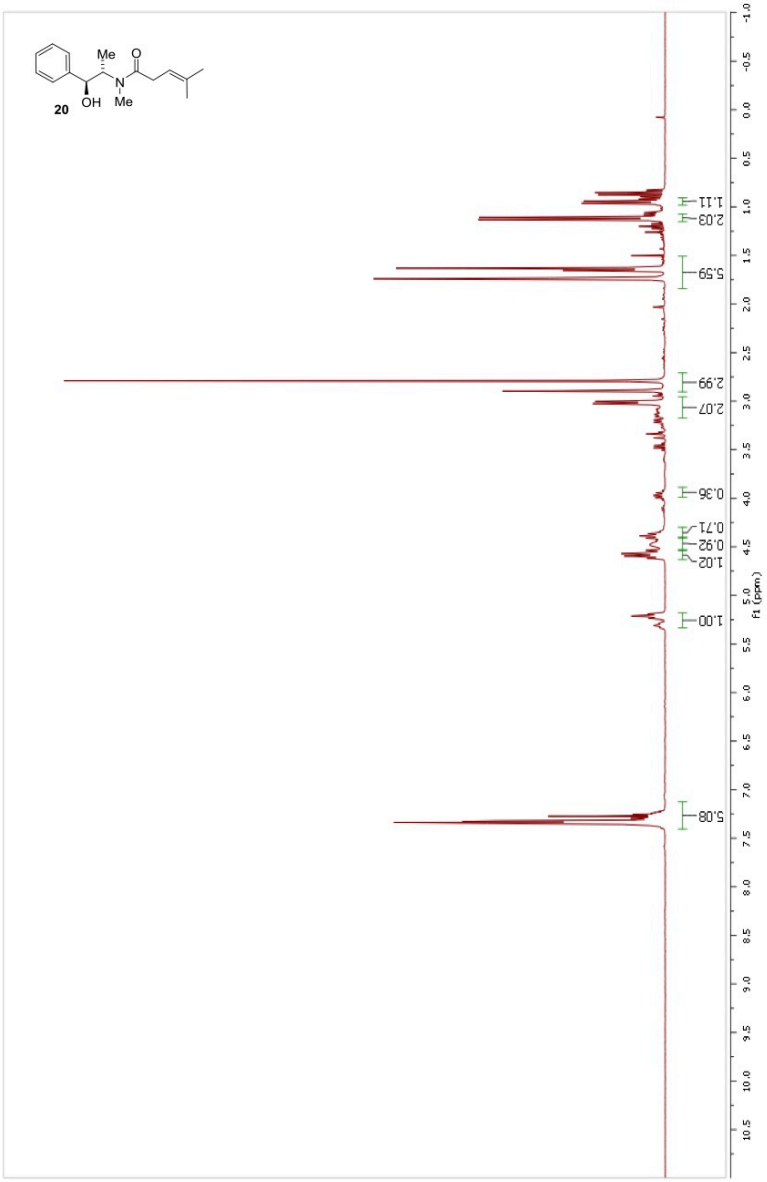

Me
H
Me
O
18 (dr = 1:1.5)
f1 (ppm)


Me
H
Me
O
O
1: amphilectolide
3.19
0.99
1.12
0.96
2.75
8.92
2.84
2.68
1.03
1.03
1.03
1.02
1.03
1.01
1.00
f1 (ppm)

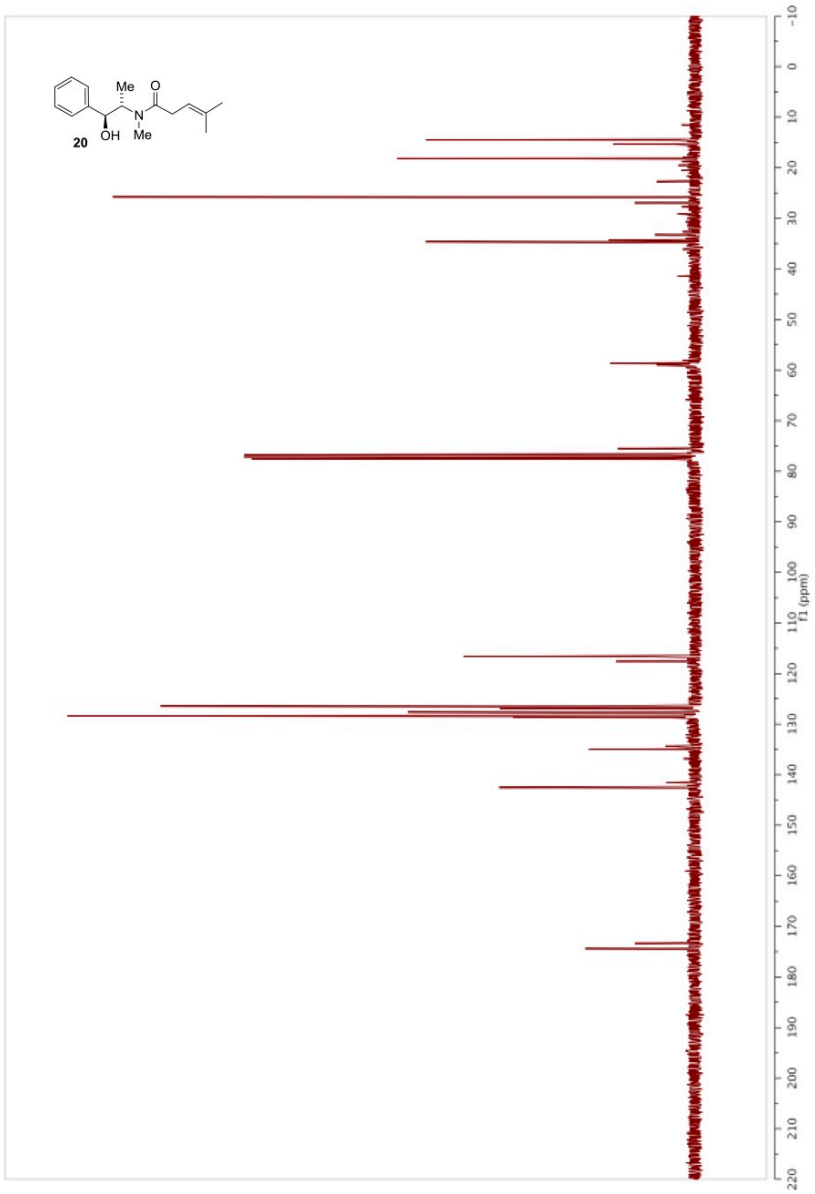
S41

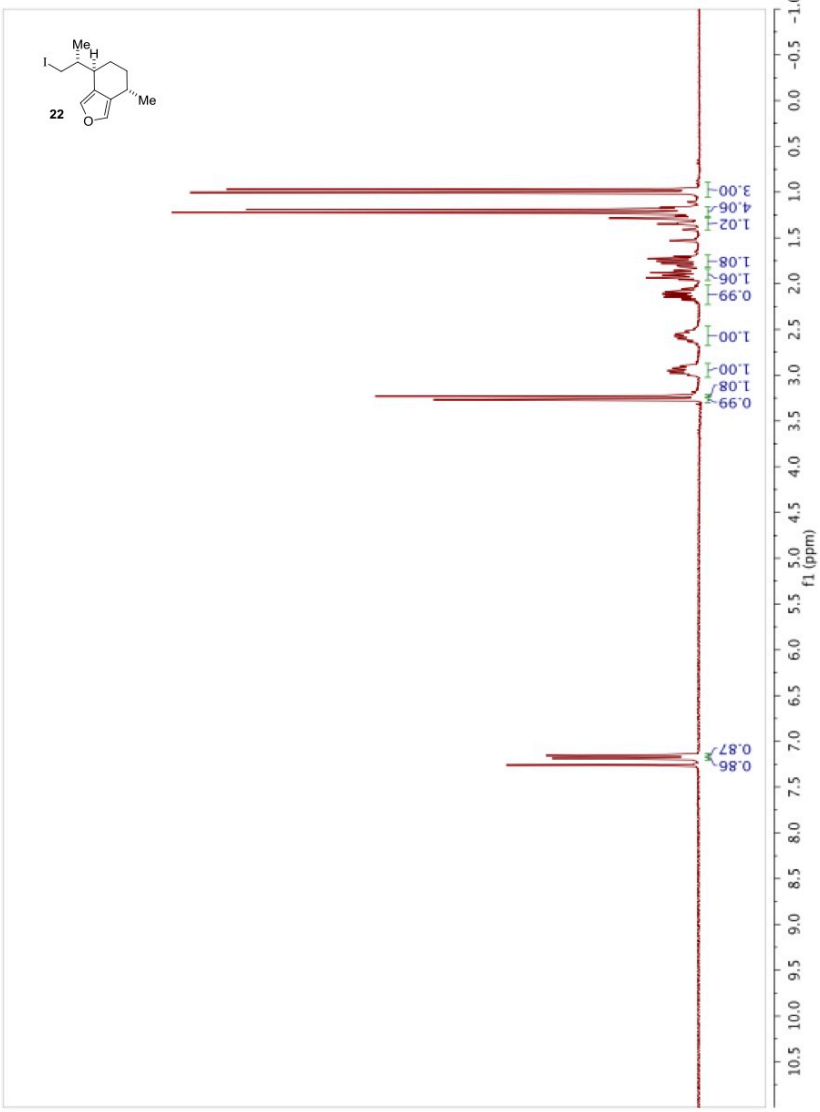


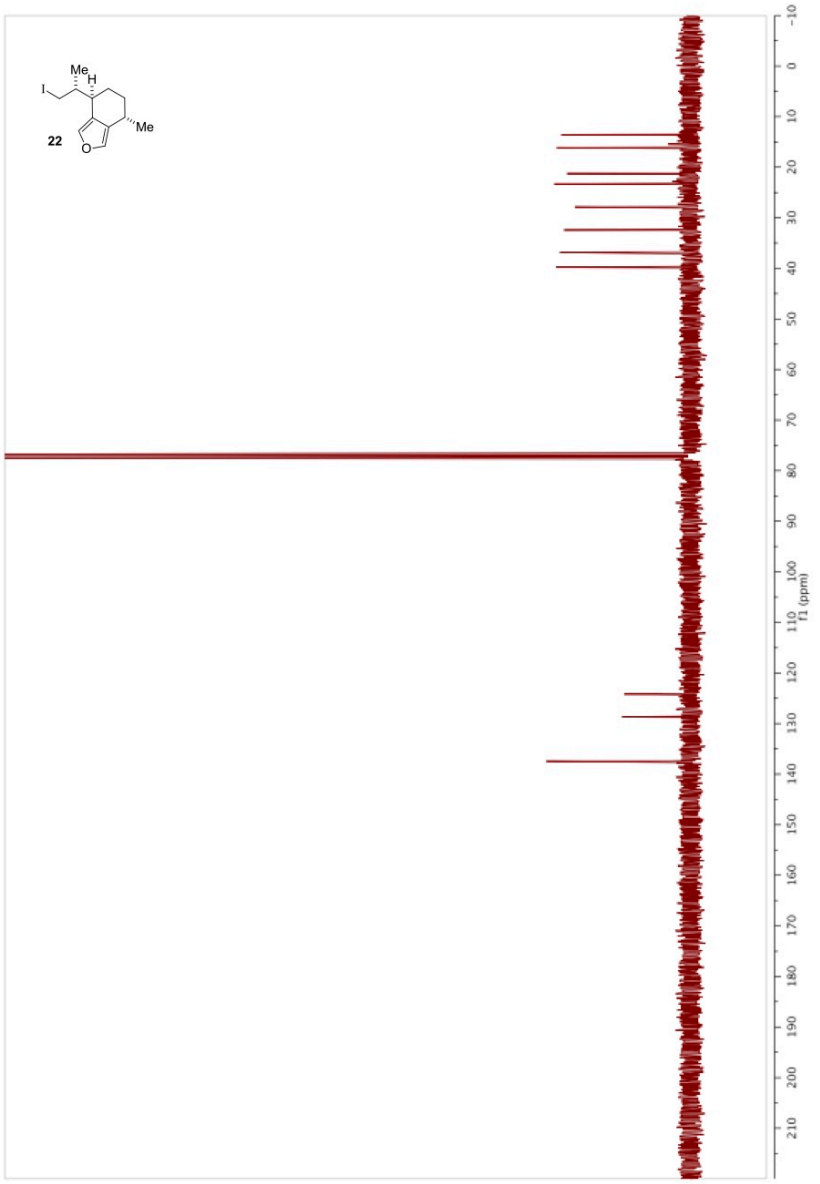
S42

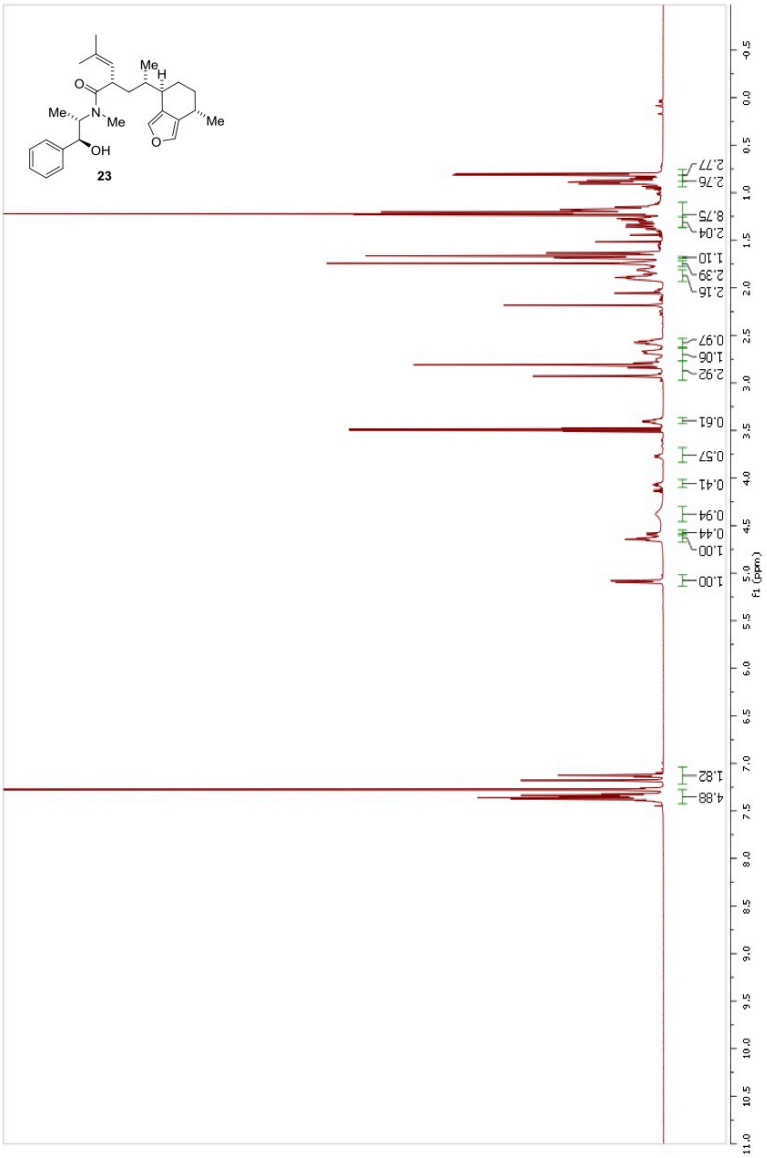

Me
O
N
Me
OH
Me
20
1.11
2.03
5.59
2.99
2.07
0.36
0.71
0.92
1.02
1.00
5.08
f1 (ppm)

S43

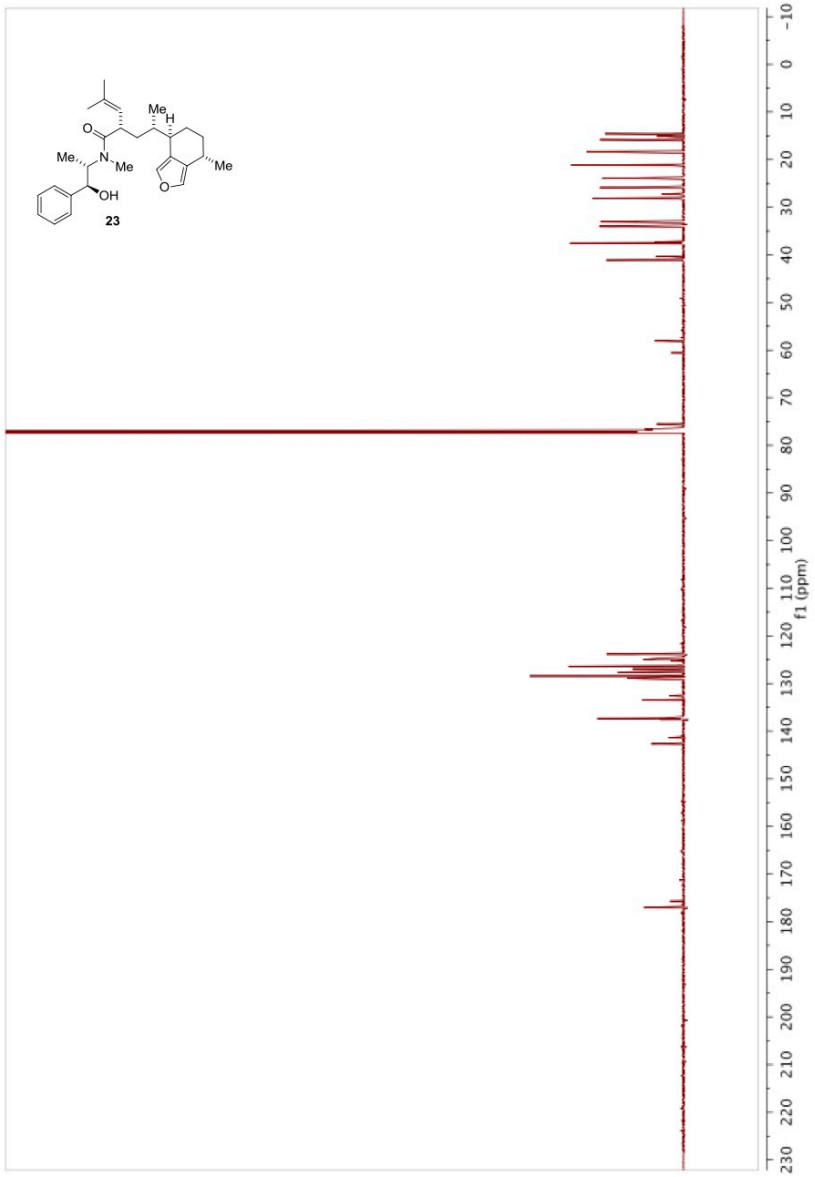

Me
O
N
Me
20
OH
f1 (ppm)

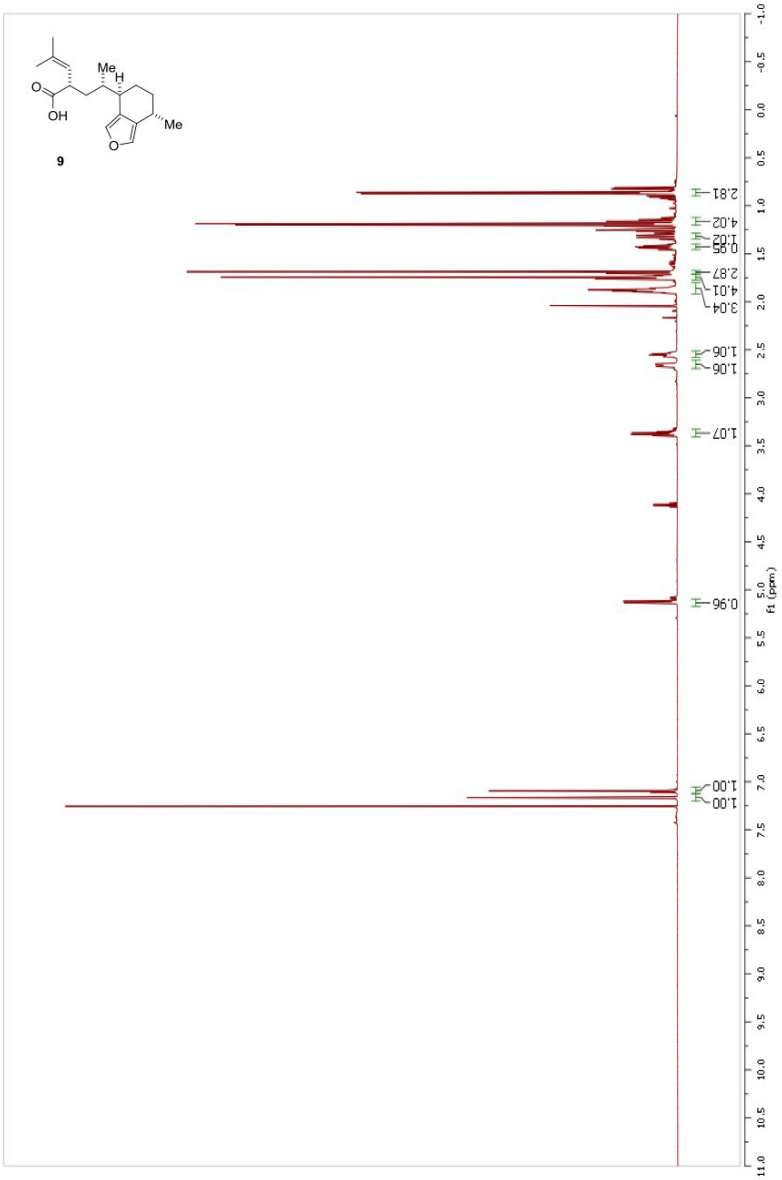

Me
H
I
Me
22
O
3.00
4.06
1.02
1.08
1.06
0.99
1.00
1.00
1.08
0.99
0.87
0.86
f1 (ppm)

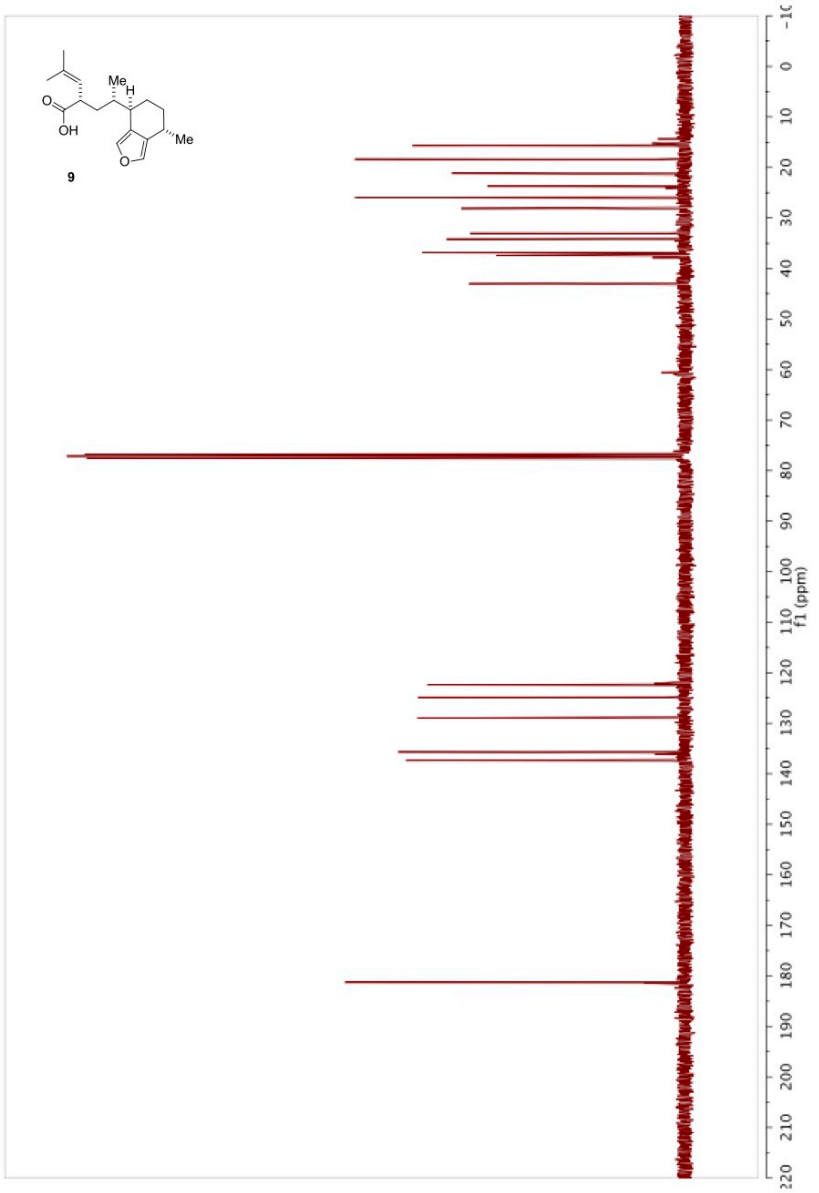

Me
H
I
Me
22
O
f1 (ppm)


Me
H
O
Me
N
Me
Me
OH
O
23
2.77
2.76
8.75
2.04
1.10
2.39
2.16
0.97
1.06
2.92
0.61
0.57
0.41
0.94
0.44
1.00
1.00
1.82
4.88
f1 (ppm)

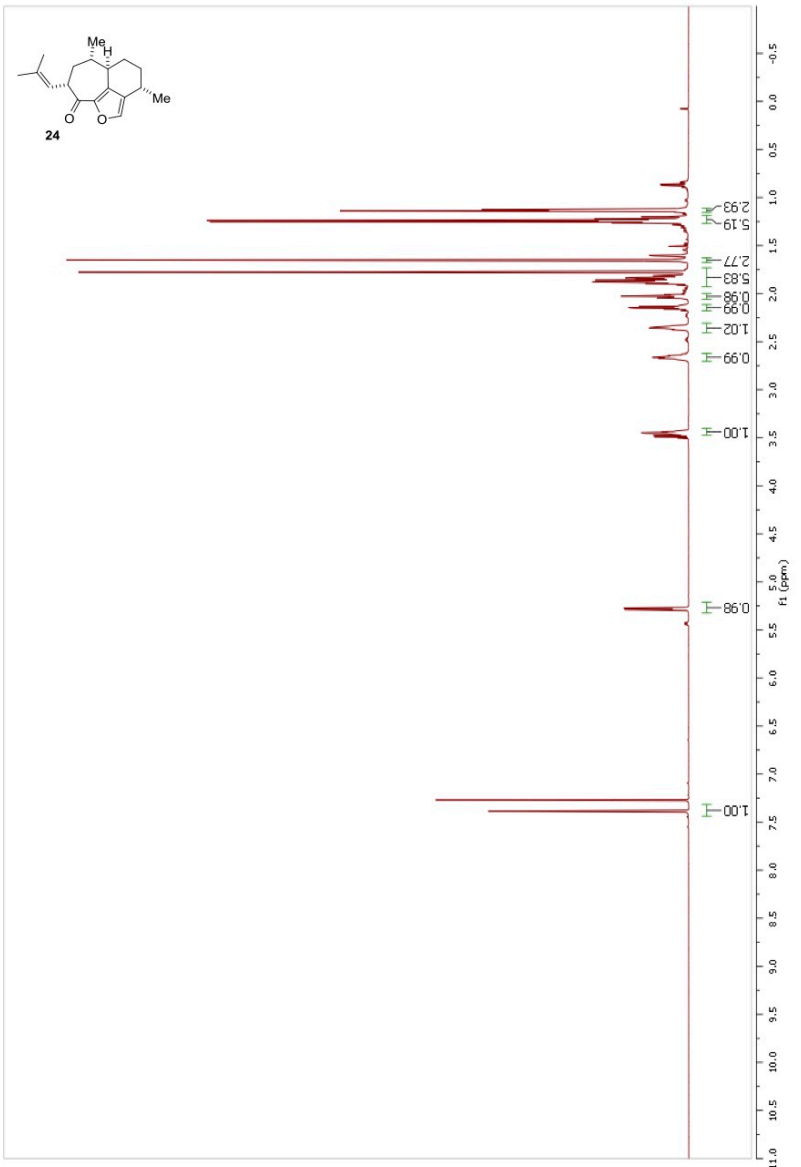
S47


Me
H
O
N
Me
Me
Me
O
OH
23
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)

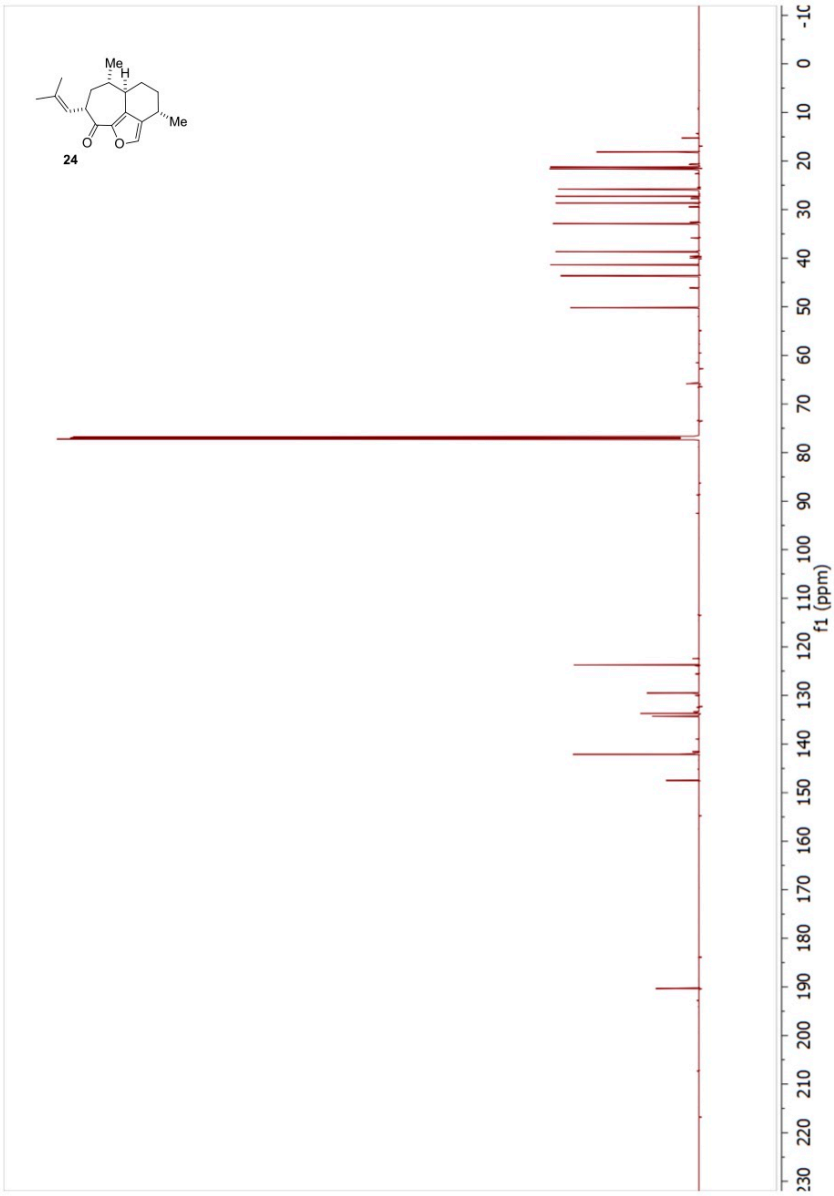

Me
H
O
OH
Me
O
9
2.81
4.02
1.02
0.95
2.87
4.01
3.04
1.06
1.06
1.07
0.96
1.00
1.00
f1 (ppm)

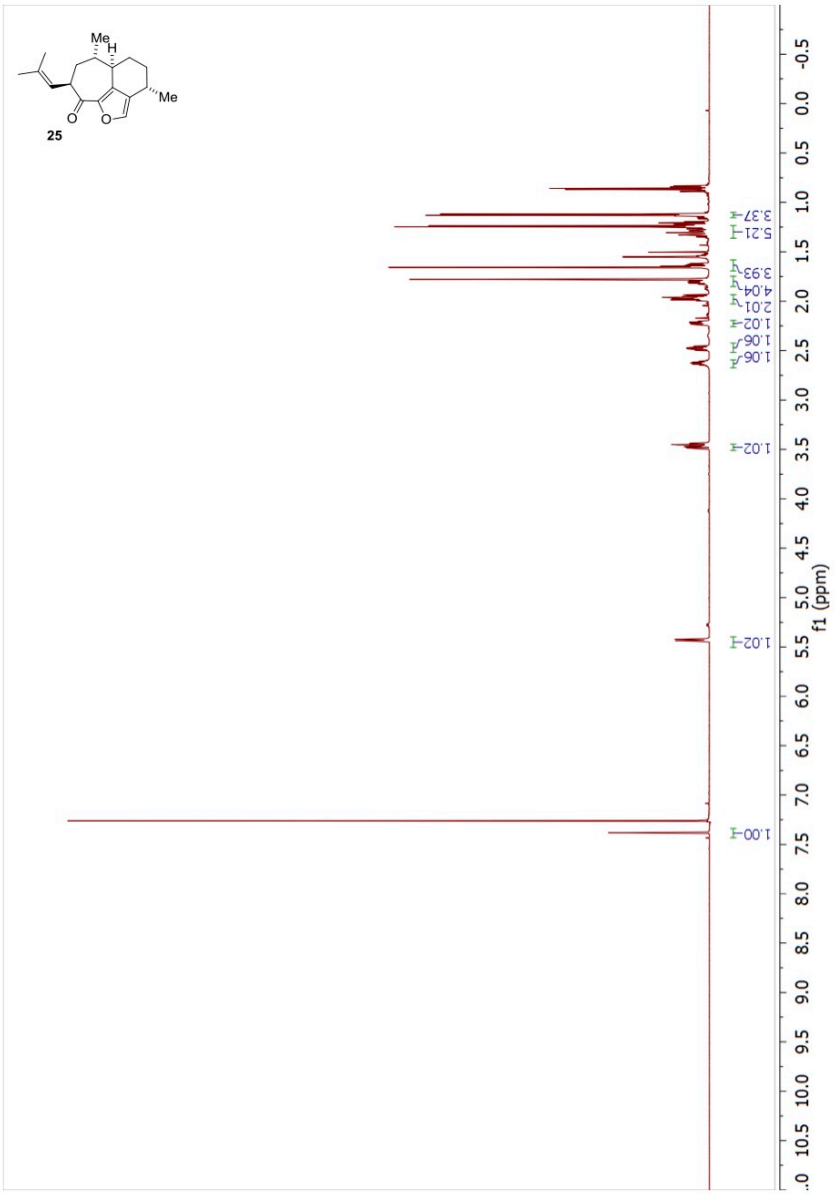


S50

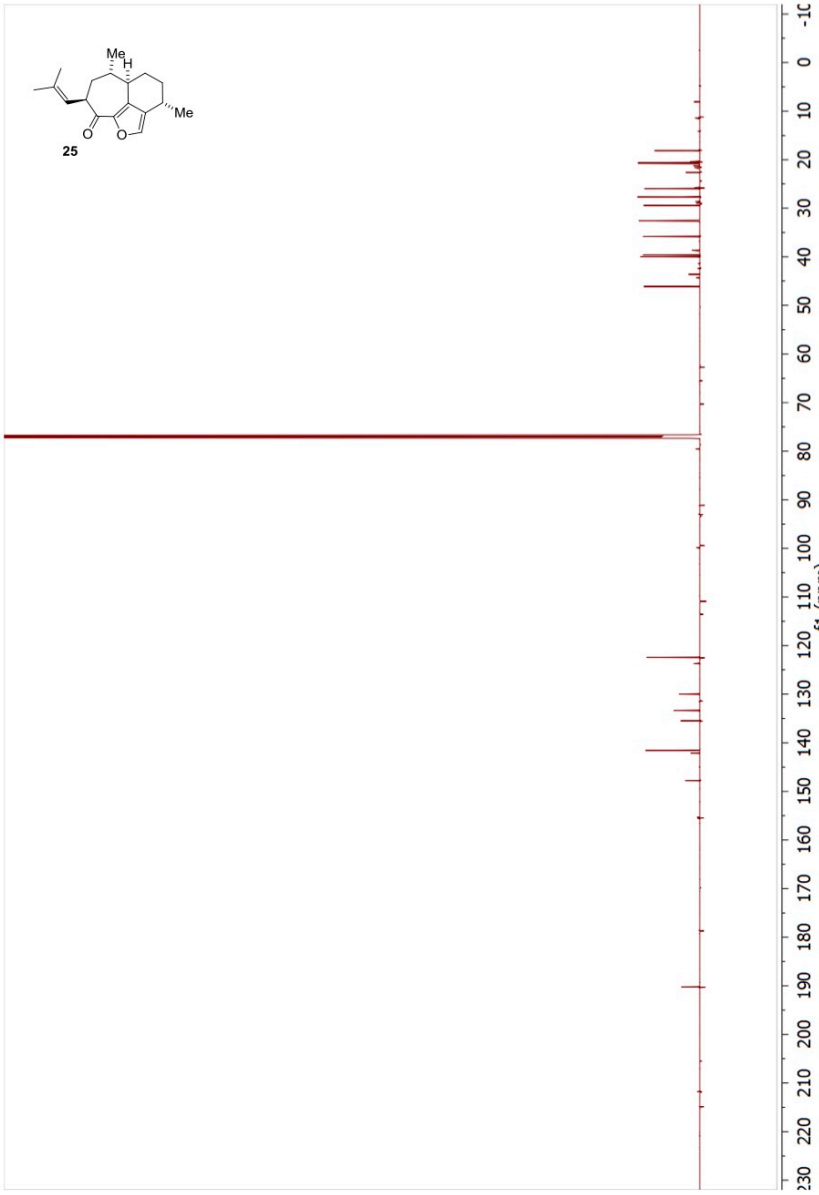


S51

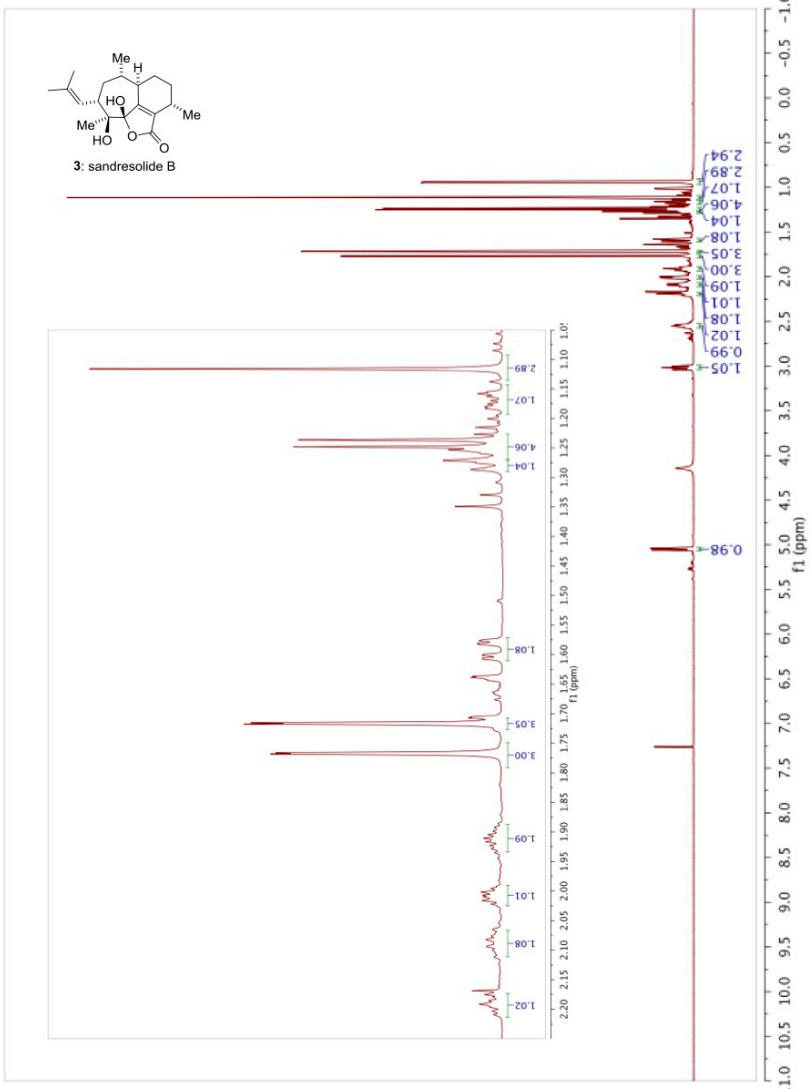

Me
H
Me
O
O
24
f1 (ppm)



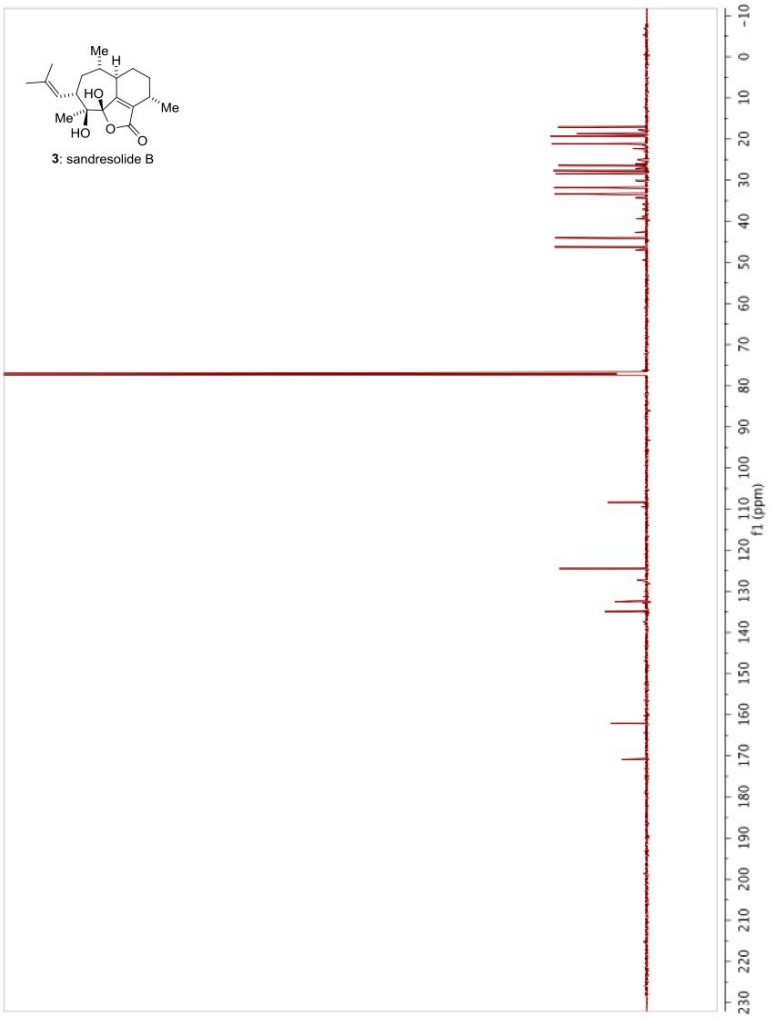
S53

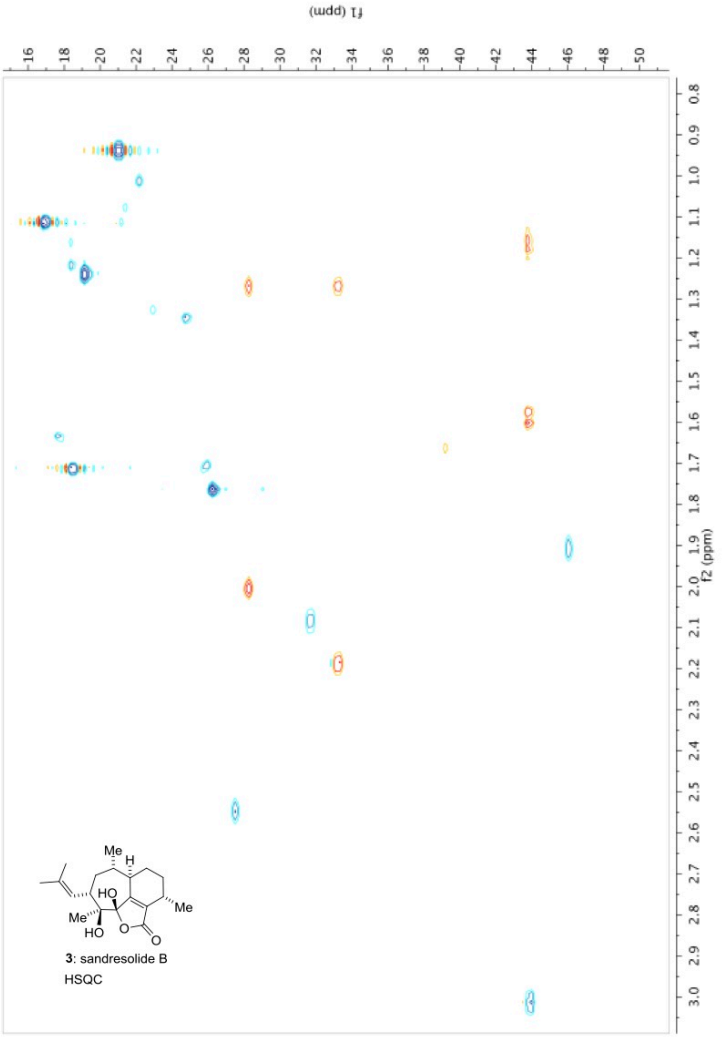


S54

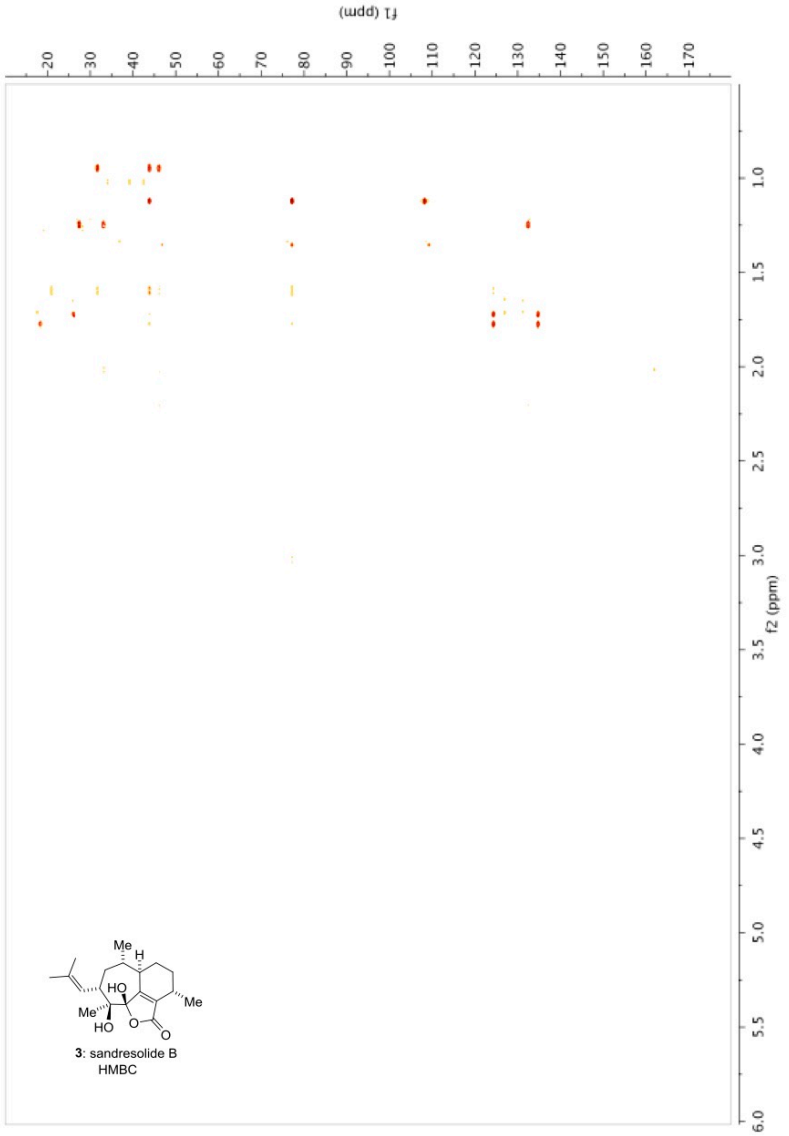

Me
H
HO
Me
Me
HO
O
O
3: sandresolide B
2.94
2.89
1.07
4.06
1.04
1.08
3.05
3.00
1.09
1.01
1.08
1.02
0.99
1.05
0.98
f1 (ppm)

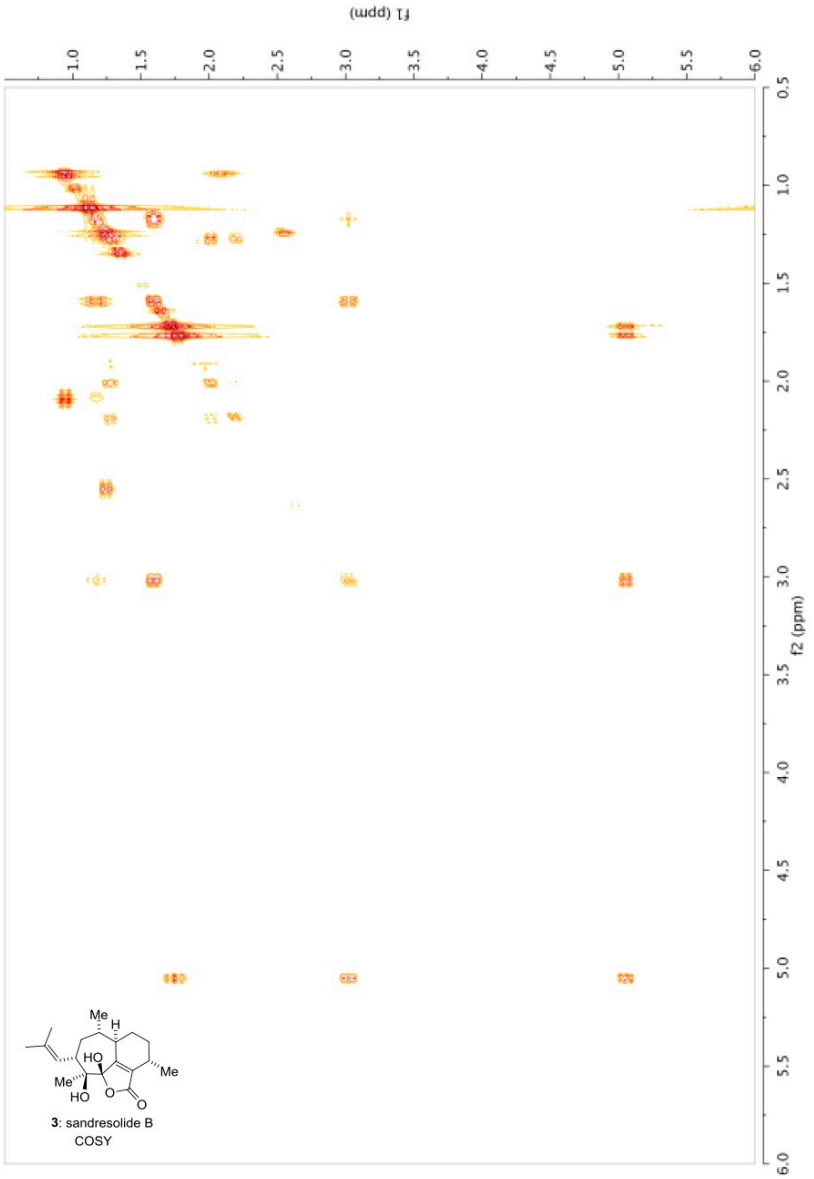
S55


Me
H
HO
Me
Me
HO
O
O
3: sandresolide B
f1 (ppm)



S57


f1 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Me
H
HO
Me
Me
HO
O
O
3: sandresolide B
HMBC

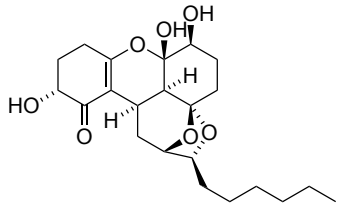

f1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Me
H
HO
Me
Me
HO
O
O
3: sandresolide B
COSY

III. Total Synthesis of the Proposed Structure of Trichodermatide A

1. Introduction, Isolation and Structure

Fungi of the genus *Trichoderma* have, in addition to potent cellulase activity,[1] an array of bioactive chemical compounds.[2]

Upon searching for bioactive metabolites in *T. reesei*, Pei and co-workers reported the isolation of trichodermatide A (**127**) in 2008 (Figure 3.1).[3] The compound was extracted from *T. reesei,* which was collected from marine mud in the tideland of Lianyungang, China. Structural assignment was achieved by 1D and 2D NMR spectroscopy, mass spectroscopy and CD spectral analysis.



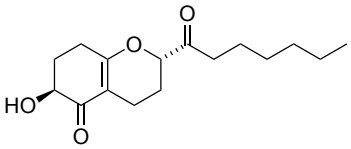
trichodermatide A (**127**)

Figure 3.1. Structure of trichodermatide A as proposed in 2008

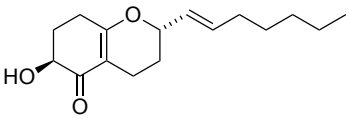
Trichodermatide A (**127**) is an unprecedented polyketide featuring a ketal-containing skeleton. Structural features of trichodermatide A (**127**) include an α-hydroxy vinylogous ester as well as a hexyl chain. The molecule contains eight stereogenic centers, seven of which are contiguous.

In terms of its biological properties, trichodermatide A (**127**) exhibits weak cytotoxicity against the A375-S2 melanoma cell line with an IC_{50} value of 102.2 μg/mL.[3]

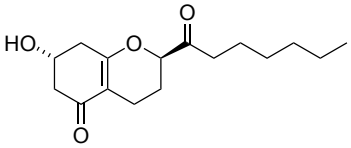
Along with trichodermatide A (**127**), three other structurally related compounds, trichodermatide B–D (**128**–**130**), were isolated. In 2018, two further congeners, trichodermatide E (**131**) and F (**132**), have been found in *T. applanatum* (Figure 3.2).[4] All members of the trichodermatide family carry the structural element of a cyclohexenone ring, fused to a pyran, along with an aliphatic side chain.



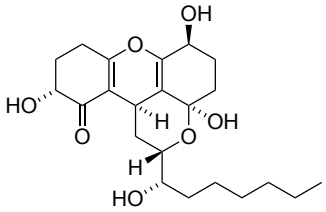
trichodermatide B (**128**)



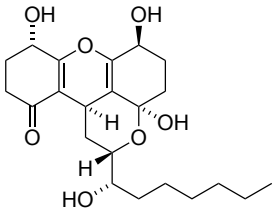
trichodermatide C (**129**)



trichodermatide D (**130**)



trichodermatide E (**131**)



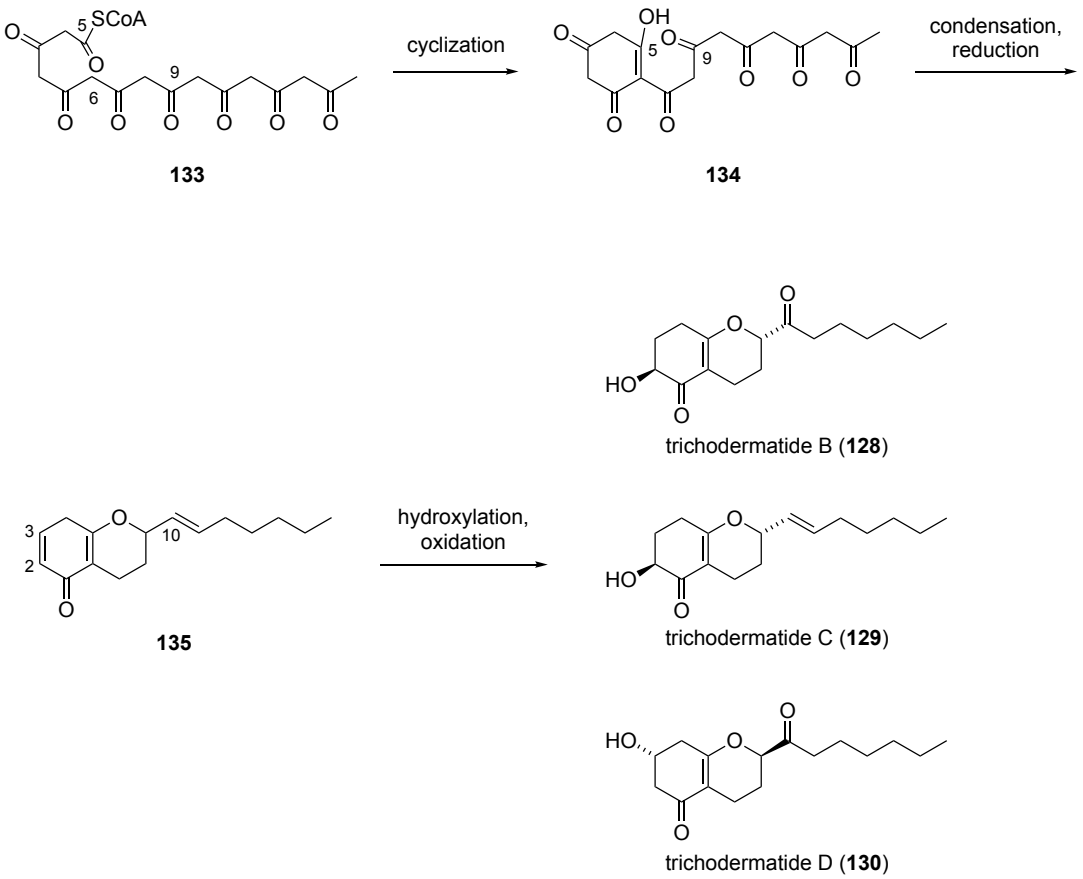
trichodermatide F (**132**)

Figure 3.2. Structures of trichodermatide B–F

2. Proposed Biosynthesis

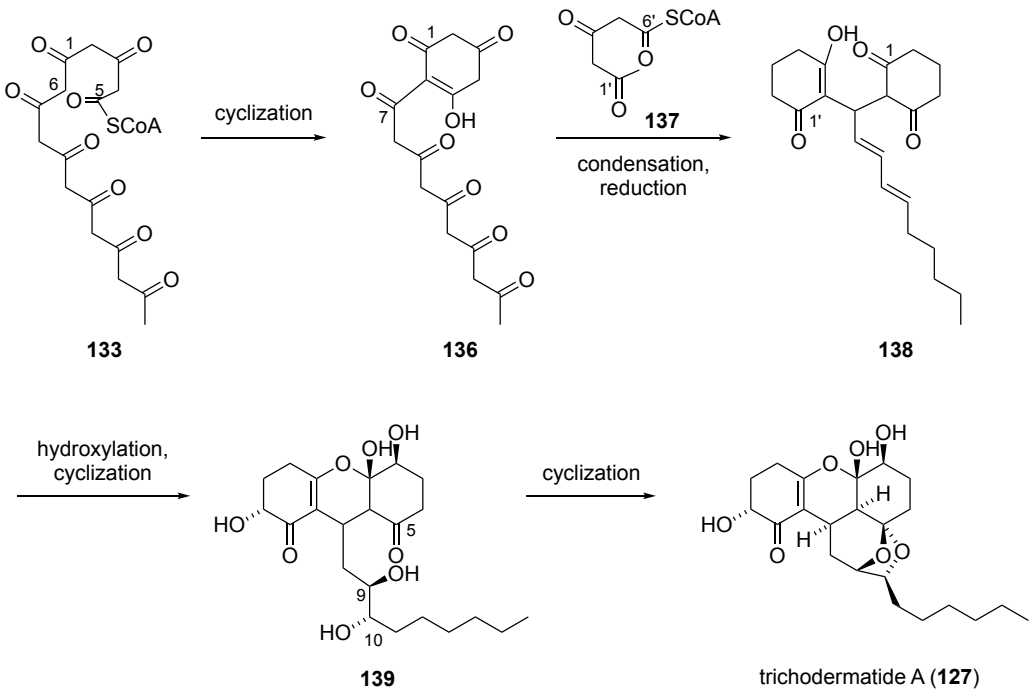
Based on biosynthetic pathways of similar octaketides isolated from fungal sources,[5,6] Pei and co-workers postulated a biosynthetic origin of trichodermatide A–D (**127**–**130**).[3] That trichodermatide A (**127**) is composed of 22 carbon atoms, while only 16 carbon atoms are present in the structures of trichodermatide B–D (**128**–**130**), points toward diverging biosynthetic pathways.

For the 16-carbon members of the family, the starting point of the hypothesized biosynthesis is the linear 16 carbon atom chain conjugated to coenzyme A (**133**), which proceeds to form the first ring through a Claisen condensation between C5 and C6 to give biosynthetic intermediate **134** (Scheme 3.1). This intermediate then undergoes a second cyclization through formation of a bond between C5 and C9 as well as reduction of the carbonyl groups, furnishing intermediate **135**. Trichodermatide B (**128**), C (**129**) and D (**130**) are suggested to arise from oxidation of **135** at C10 and hydroxylation at C2 and C3, respectively.



Scheme 3.1. Proposed biosynthesis of trichodermatide B–D

For trichodermatide A (**127**, Scheme 3.2), the initial Claisen condensation of octaketide **133** is also proposed to occur, followed by condensation with an additional triketide unit to form intermediate **138**. Reduction of the carbonyl groups, and ring closure through bond formation between C1' and C1 would then furnish tricyclic structure **139**. Following hydroxylation, the vicinal diol at C9/C10 would cyclize onto the carbonyl at C5, resulting in the direct formation of the unique ketal moiety.



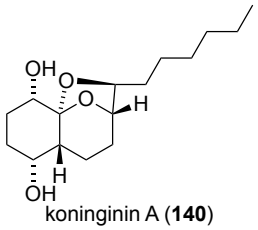
Scheme 3.2. Proposed biosynthesis of trichodermatide A

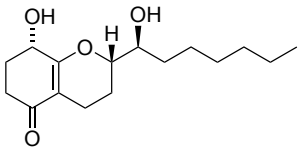
3. Structurally Related Natural Products

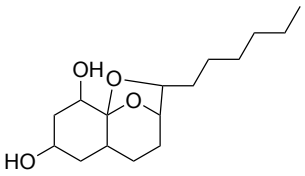
The koninginins[7-18] are the largest class of known structural relatives of the trichodermatides. With the exception of few members of the koninginin family (koninginin A (**140**), C (**142**), G (**146**), N (**153**) and O (**154**)), the main structural element found in this class is the α,β-unsaturated cyclohexenone fused to a pyran ring yielding the characteristic vinylogous ester moiety present in all trichodermatides. The koninginins commonly feature a linear six carbon atom chain (Figure 3.3).

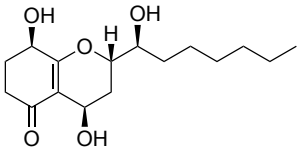
In addition to the above-described moieties, the following oxidation patterns are prevalent in the koninginins: the central cyclohexane is hydroxylated either at C2 or C4, C10 is often hydroxylated, and the C7 position can occasionally be hydroxylated.

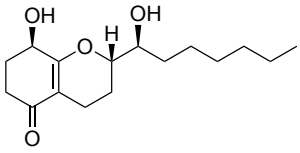
Notable variations of the koninginin structures include the reduction of the cyclohexenone, as present in koninginin A (**140**), C (**142**) and G (**146**), as well as replacement of the pyran with a furan system, as in koninginin N (**153**) and O (**154**).

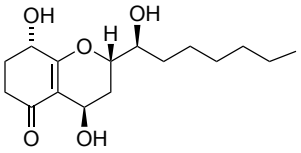

koninginin A (**140**)

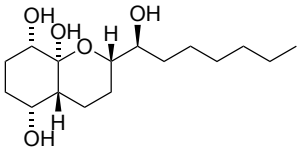

koninginin B (**141**)

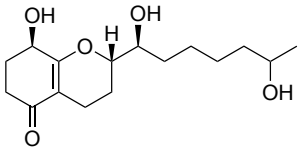

koninginin C (**142**)


koninginin D (**143**)


koninginin E (**144**)


koninginin F (**145**)


koninginin G (**146**)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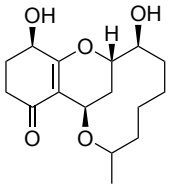
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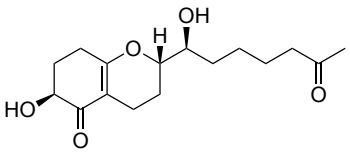
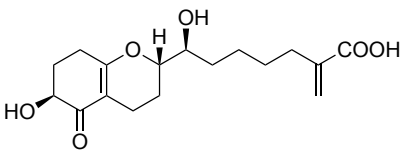
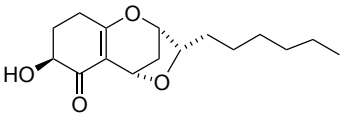

koninginin J (**149**)


koninginin K (**150**)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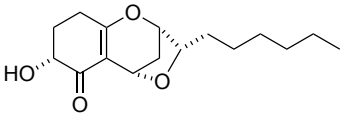
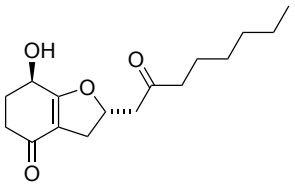
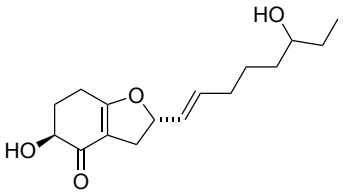
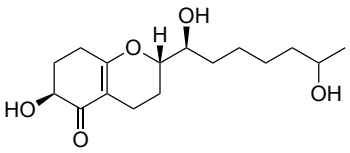
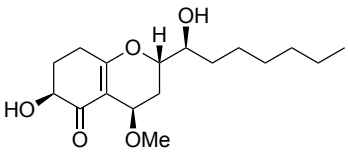
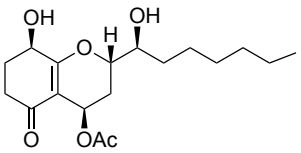

koninginin M (**152**)


koninginin N (**153**)


koninginin O (**154**)


koninginin P (**155**)


koninginin Q (**156**)


koninginin R (**157**)

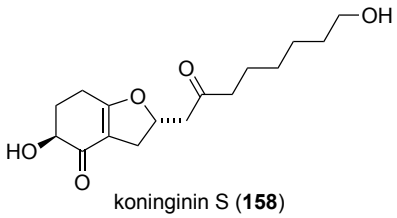
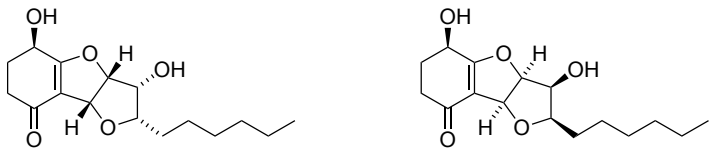

koninginin S (**158**)

Figure 3.3. Structures of koninginin A–S

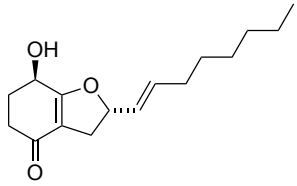
Not surprisingly, the koninginins were also isolated from *Trichoderma* species. Fungi of this genus are reported to be involved in biological control of antagonistic microorganisms[19-21] and benefiting plant growth.[22] Consequently, the search for metabolites with agrochemical potential has been the driver behind continuous investigations. Koninginin A–E (**140**–**144**)[7-11] were initially found in the endophytic fungus *T. koningii*. All representatives inhibit the growth of etiolated wheat coleoptiles, like the congener koninginin G (**146**)[13] from *T. aureovide*. Koninginin I (**148**), J (**149**) and K (**150**) have been isolated from *T. neokoningii* but were found not effective in assays for nematicidal activity.[15] In 2015, koninginin L (**151**) and M (**152**) have been reported after isolation from *T. koningii* and their absolute configuration determined by x-ray analysis.[16] Related compounds, koninginin N–Q (**153**–**156**), were isolated from *T. koningiopsis* and have demonstrated weak antifungal activity with MIC of 128 µg/mL (nyrstatin with MIC of 32 µg/mL).[17] Moderate antifungal activity has also been demonstrated by koninginin R (**157**) and S (**158**), which have been isolated from *T. koningiopsis*.[18] As notable bioactivities, the koninginins E (**144**) and F (**145**) were found to inhibit effectively phospholipase A2 as well as inhibiting edema-inducing, myotoxic as well as enzymatic activities of the total venom of the jararacussu snake.[12]

The trichodermaketones are one further, albeit relatively small, family of structural relatives to the trichodermatides. Following screening a library of marine microbial extracts for biological activity, compounds **159**–**162** were isolated from *T. koningii* (Figure 3.4). Of the isolated compounds, a biological effect was only found for trichodermaketone A (**159**), which showed synergistic antifungal activity with ketoconazole.[23]

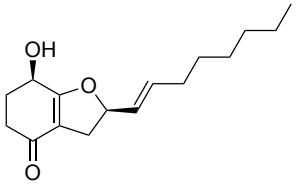


trichodermaketone A (**159**)

trichodermaketone B (**160**)



trichodermaketone C (**161**)



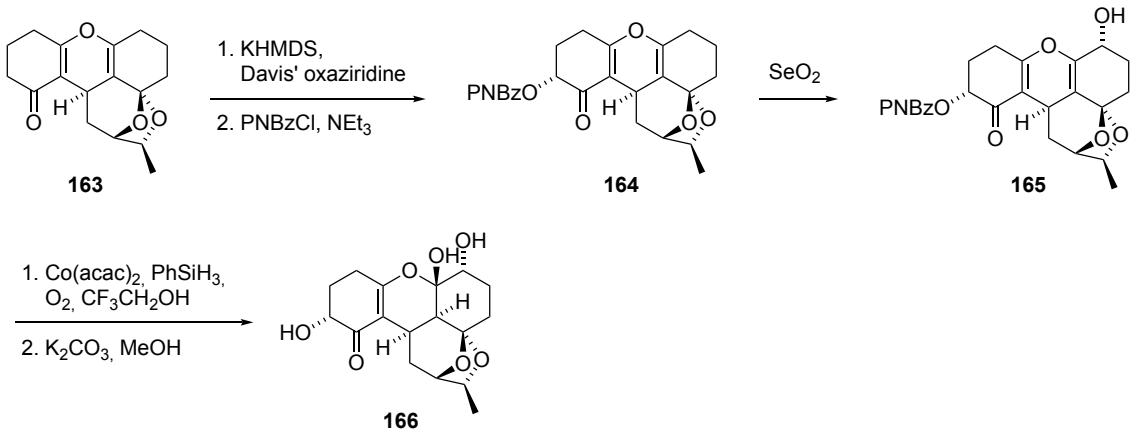
trichodermaketone D (**162**)

Figure 3.4. Structures of trichodermaketone A–D

All trichodermaketones feature a tetrahydrobenzofurano-4-one structural motif, which Zhang and co-workers proposed to be generated by different cyclases compared to those involved in the biosynthesis of the trichodermatides.[23] The trichodermaketones A (**159**) and B (**160**) contain a novel bis(tetrahydrofuran) tricyclic skeleton, not previously reported in polyketides.

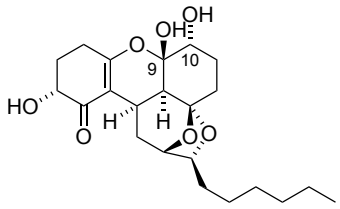
4. Total Syntheses of the Trichodermatides

The trichodermatides have attracted interest as a target to explore methodologies for selective installation of the respective oxygenated structures. Hsung and co-workers accessed the proposed structure of trichodermatides B (**128**) and C (**129**), but found deviations in the ^{1}H and ^{13}C NMR spectroscopic data of their synthesized material in comparison to the reported data.[24] With regards to trichodermatide A (**127**), the Hiroya group has initially reported the total synthesis in 2013 with spectroscopic data identical to the natural product.[25] The results reported by our group[26] caused Hiroya and co-workers to initiate a structural reevaluation of trichodermatide A (**127**), leading to them proposing revised structure **167** of trichodermatide A in 2015[27] (Figure 3.5). Based on an analogous system bearing a shortened alkyl chain to facilitate crystallization, the group concluded the alternative structure was a C10 epimer of the originally reported configuration. In the synthesis of Hiroya and co-workers, ketone **163** was subjected to α-hydroxylation through generation of the enolate and treatment with Davis' oxaziridine (Scheme 3.3). Nitrobenzoylation allowed for x-ray analysis, confirming the formation of the desired diastereomer **164**. Reaction of **164** with SeO_2 proceeded with an allylic oxidation to give alcohol **165**, which underwent selective hydration to hemiacetal **166** in 83% yield. The structure could be confirmed by x-ray analysis before removal of the nitrobenzoate.



Scheme 3.3. Hiroya group's synthesis of trichodermatide A analogue **166**

Hiroya and co-workers concluded that the functionalization of the original synthetic trichodermatide A was identical to the analog with the shortened alkyl chain and therefore proposed structure **167** for trichodermatide A (Figure 3.5). Further support of their findings was provided by NOESY experiments of their synthetic trichodermatide A (**167**), showing correlations between H10 and C9-OH, while ^{1}H and ^{13}C NMR spectra were identical to those reported for the isolated material.[27]



167

Figure 3.5. Confirmed structure for trichodermatide A

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5. Results

5.1. Total Synthesis of the Proposed Structure of Trichodermatide A

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E. Myers, E. Herrero-Gómez, I. Albrecht, J. Lachs, P. Mayer, M. Hanni, C. Ochsenfeld, D. Trauner, *J. Org. Chem.* **2014**, *79*, 9812–9817.

Author contribution statement

I.A. worked on an early protective-group free synthetic approach toward the target molecule. In this course, I.A. developed the α-hydroxylation conditions that were employed in the final total synthesis of the proposed structure of trichodermatide A. I.A. performed the R_f, IR and HRMS characterization of compounds **11**, **12**, **13**, **15**, **16**, **17** and **1** as well as NMR characterization of compound **12**. I.A. provided critical feedback to the manuscript.

The computational details within the supporting information have been excluded in this context. Please refer to the original supporting information document of the publication for full details.

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Total Synthesis of the Proposed Structure of Trichodermatide A

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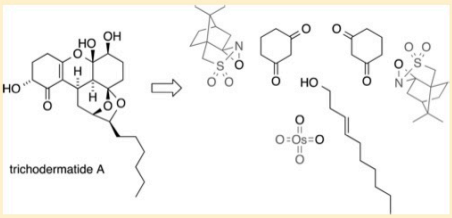
Supporting Information

ABSTRACT: A short total synthesis of the published structure of racemic trichodermatide A is reported. Our synthesis involves a Knoevenagel condensation/Michael addition sequence, followed by the formation of tricyclic hexahydroxanthene-dione and a diastereoselective bis-hydroxylation. The final product, the structure of which was confirmed by X-ray crystallography, has NMR spectra that are very similar, but not identical, to those of the isolated natural product. Quantum chemically computed ^{13}C shifts agree well with the present NMR measurements.



The trichodermatides are a family of natural products with unusual features that have attracted considerable attention in the chemical community (Figure 1). Isolated

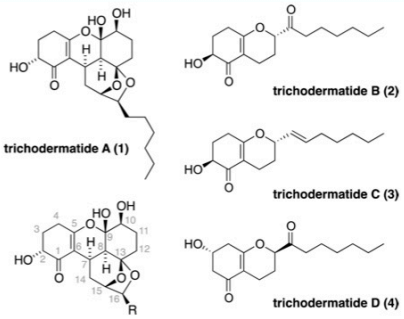
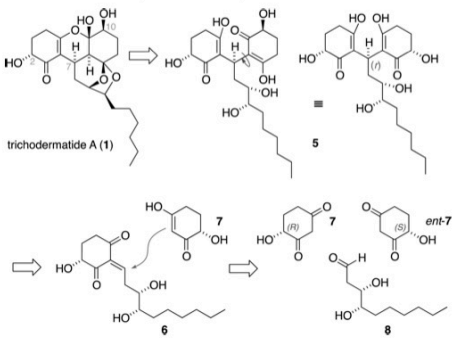


Figure 1. Proposed structures of the trichodermatides.

from the marine-derived fungus *Trichoderma reesei* by Pei and co-workers, these compounds have shown a variety of interesting bioactivities.[1] Trichodermatide A, whose relative and absolute configuration was elucidated using a combination of NMR spectroscopy and CD measurements, has a particularly interesting structure featuring a pentacyclic ring system with eight stereocenters. Hiroya and co-workers have recently reported its first total synthesis.[2]

The highly unusual carbon skeleton and the intricate stereochemical features of trichodermatide A are best revealed through a retrosynthetic analysis (Scheme 1). Hydrolysis of

Scheme 1. Retrosynthetic Analysis of Trichodermatide A



the acetal and cleavage of the hemiacetal affords alkylidene-bis-1,3-cyclohexanedione derivative **5**, shown here in its enolized form and as two conformers. The conformer on the right side emphasizes that C7 (trichodermatide numbering) is a pseudo-asymmetric center. Dissection of **5** via a retro-Michael reaction (→6), and then a retro-Knoevenagel condensation, affords two 6-hydroxy-cyclohexane-1,3-diones of opposite absolute configurations, **7** and *ent*-**7**, and chiral dihydroxy aldehyde **8**.

In the forward direction, the formation of alkylidene-bis-1,3-diones from aldehydes and 1,3-diones via Knoevenagel

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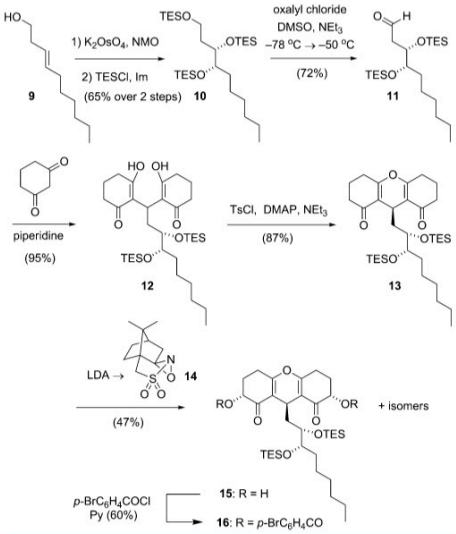
condensation and Michael addition is a well-documented process.[3] However, we deemed it unlikely that such a reaction would proceed cleanly with a racemate of 4-hydroxy-cyclohexane-1,3-dione **7** or a protected derivative thereof. We, therefore, decided to simplify the synthetic plan by introducing the two hydroxy groups at C2 and C10 (trichodermatide A numbering) at a later stage. It was hoped that, by trapping the two cyclohexane-1,3-dione moieties in a stiff polycyclic form, we would be able to carry out a 2-fold hydroxylation with a high degree of diastereoselectivity.

Our synthesis of racemic trichodermatide A started with the dihydroxylation[4] of known (*E*)-3-decen-1-ol **9** (Scheme 2).[5]

Scheme 2. Synthesis of Hexahydroxanthene-dione 15



Triple silylation of the resultant racemic triol using triethyl chlorosilane gave **10**, which could be selectively deprotected and oxidized under Swern conditions.[6] This gave aldehyde **11** contaminated with 10−15% of the silyl ether **10**, from which it could not be separated. However, this impurity did not interfere in the subsequent Knoevenagel condensation/Michael addition sequence using 1,3-cyclohexadione, which afforded alkylidene-bis-cyclohexane-1,3-dione **12** in excellent yield. Optimized conditions for this transformation included the use of piperidine as a catalyst and the presence of an excess amount of 1,3-cyclohexadione.

With **12** in hand, dehydrative cyclization to the vinylogous anhydride **13** was investigated. This cyclization was effected cleanly when a slight excess of tosyl chloride in methylene chloride was added dropwise to a solution of **12**, in the presence of a base (NEt_3) and a catalytic amount of DMAP. Generation of the bis-lithium enolate and subsequent addition of Davis' (+)-(camphorsulfonyl)oxaziridine[7] **14** resulted in 2-fold hydroxylation, yielding the desired compound **15** as the major diastereomer. This result indicated that hexahydroxanthene-dione **13** with its bulky side chain exerts a considerable degree of substrate control, overwhelming the reagent control of enantiomerically pure oxaziridine **14**. The structure of **15** was unequivocally confirmed by conversion into its bis-bromobenzoate **16** and single-crystal X-ray analysis.[8] The attractive "scorpion-like" structure of **16** in the solid state is shown in Figure 2.

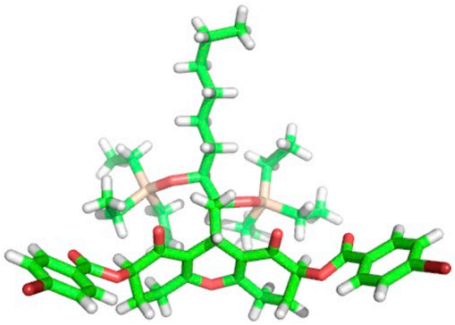
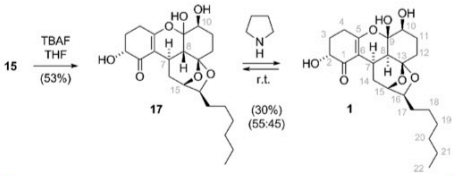


Figure 2. X-ray structure of **16**.

With ample amounts of **15** in hand, we studied its desilylation and isomerization to trichodermatide A. The latter seemingly only requires hydrolysis, followed by diastereotopos-selective acetal formation and diastereoselective hemiacetal formation. We anticipated that both of these operations could be carried out under thermodynamic control.

When a solution of **15** in THF was treated with an excess amount of TBAF (10 equiv) and the mixture was allowed to stir overnight at room temperature, conversion to a more polar compound was observed. To our surprise, this compound, which was isolated as an oil, turned out to be 8-*epi*-trichodermatide **17** (Scheme 3). The *trans* relationship between protons at C7 and C8 was evident from the large coupling constant found in the ^{1}H NMR spectrum.

Scheme 3. Synthesis of 1, the Proposed Structure of Trichodermatide A



Convinced that trichodermatide A represents a thermodynamic minimum, we next investigated the isomerization of **17** to the desired target compound. Several ways in which this could be achieved can be imagined, including retro-Michael/Michael addition and cycloreversion/cycloaddition. In the event, we found that stirring a solution of **17** in CH_2Cl_2 in the presence of excess pyrrolidine at room temperature overnight gave a 55:45 mixture of the starting material **17** and a new isomer (Scheme 3).[9] This isomer was isolated as a

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white solid, facilitating its purification and structure elucidation.

Intriguingly, the NMR spectra of this new isomer closely, but not fully, matched the spectra of enantiomerically pure **1** reported by Pei and co-workers.[1] The most remarkable difference was found for the signals at C8, the ^{13}C signal of which was found to resonate at 42.2 ppm instead of the reported value of 38.1 ppm (150 MHz, d_6-DMSO). The proton at C8 is also shifted from 1.60 to 1.94 ppm (600 MHz, d_6-DMSO). The analysis of 2D-NMR spectra measured in d_6-DMSO was confounded by extensive signal overlap, but 2D-NMR in CD_3Cl showed the same key NOESY correlations between H7 and H8, H16 and H7, H8 and H10, and OH9 and H11, as reported by Pei and co-workers.[1] HMBC correlations between OH9 and C8, OH9 and C9, and H2 and C1 were also found. The identity of our compound with the reported structure of trichodermatide A (**1**) was firmly established using single-crystal X-ray analysis.[10] The structure of racemic **1** in the solid state is shown in Figure 3.

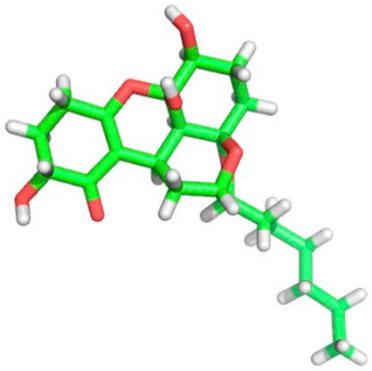

Figure 3. X-ray structure of **1**.

The batch of crystals with similar morphology from which the single crystal for analysis was picked was redissolved and subjected to NMR spectroscopy. The spectra thus obtained were identical to those previously recorded.

Since the NMR spectra of our racemic material do not fully match the spectra reported for trichodermatide A, the question arises whether the real natural product could be a closely related isomer of **1**. Indeed, several stereoisomers of **1** and constitutional isomers involving different acetals can be imagined. This number is even larger, when one takes the possibility into account that the α-hydroxy ketone moieties epimerize. In principle, all stereocenters in trichodermatide A, with the exception of C15 and C16, could epimerize under relatively mild conditions.

To explore this possibility, we calculated the relative stability and NMR spectra of 13 possible stereoisomers with their alkyl side chain at C17 truncated to a methyl group (see the Supporting Information).[11] According to our quantum-chemical calculations, the published structure of trichodermatide A indeed represents the lowest energy isomer of the series by about 0.7 kcal/mol (results from the B3LYP/6-31G(d) and RI-MP2/SVP calculations; see the Supporting Information for details). The ^{13}C NMR chemical shifts of the different isomers were calculated at the MP2/SVP level of theory, with the structures reoptimized using the RI-MP2/SVP level of theory. In addition, calculations of ^{13}C NMR shifts were carried out at the MP2/TZVP (frag) + HF/TZVP(full)-HF/TZVP(frag) level of theory starting from the measured X-ray structure.[12−15] Here, the intermediate reference method[16] was utilized in the calculation of the NMR shieldings. All NMR computations employ gauge-including atomic orbitals (GIAO).[17] Basis sets as large as def2-TZVP need to be used for the NMR calculations. Furthermore, ^{13}C shifts were computed for optimized structures in the absence of solvent and including three explicit DMSO solvent molecules.

Computed shifts for the reported structure of trichodermatide A were compared both to our experimental NMR data (obtained from **1**) and to the one reported by Pei and co-workers.[1] The agreement of theoretical vs experimental shifts was better for our data set. The standard deviation (STD) was found to be 1.6 ppm, in contrast to a STD of 2.8 ppm for isolated trichodermatide. The inclusion of three DMSO molecules lowers the standard deviation of the computed carbon shifts with respect to present NMR measurements by roughly 0.4 ppm, within the intermediate reference method, with both the SVP and def2-TZVP basis set. With respect to C8, where the mismatch between reported and synthesized results was more evident, the computed shift was found to be in good agreement with our experimental value (41.8 ppm vs 42.2 ppm). Unfortunately, comparison of the calculated spectra of the other 12 isomers with the reported spectra of the natural product was inconclusive and did not allow for structural reassignment. Direct comparison of our synthetic material with the natural product was also impossible due to the unavailability of a sample from the isolation group.

In summary, we have synthesized the proposed structure of trichodermatide A (**1**) as a racemate and confirmed its identity by X-ray crystallography. While our NMR spectra came close, they did not fully match the published spectra. A sample of the natural product for direct comparison was not available. The recently reported total synthesis of trichodermatide A by Hiroya et al.[2] does not represent structural proof, since epimerizations similar to the one in Scheme 3 could have happened under their conditions as well. Interestingly, the proposed structures of the simpler congeners trichodermatides B (**2**) and C (**3**) have been recently synthesized by Hsung and co-workers,[18] and the spectra of the synthetic, racemic compounds were found to be in disagreement with the published ones as well. According to our work, it is possible that natural trichodermatide A is also an isomer of compound **1**, but we cannot confidently say which one it is.

■ EXPERIMENTAL SECTION

All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was performed using the analytical grade solvents indicated and silica gel (40−63 μm, 60 Å) as the stationary phase. Reactions and chromatography fractions were monitored with Merck silica gel 60 F254 glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip, followed by heating: potassium permanganate and ceric ammonium molybdate. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from and stored over CaH_2. *n*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other solvents, as well as starting

materials and reagents, were used without further purification from commercial sources.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ or CD_2Cl_2 on spectrometers operating at 300 Hz, 400 and 600 MHz for proton nuclei (75 MHz, 100 and 150 MHz for carbon nuclei). For ^{1}H NMR spectra, signals arising from residual proton forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemicals shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral], where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad, or combinations of the above. The residual peaks of $CHCl_3$ (δ 7.24 ppm) or CH_2Cl_2 peak (δ 5.32 ppm) were used as reference for ^{1}H NMR spectra (for $CDCl_3$ or CD_2Cl_2, respectively). The central peak (δ 77.16 ppm) of the $CDCl_3$ "triplet" was used as reference for proton-decoupled ^{13}C NMR spectra. Mass spectroscopy (MS) experiments were performed either on an electron ionization (EI) or on an electrospray ionization (ESI) instrument using a time-of-flight analyzer. Infrared (IR) spectra were recorded on an FTIR system equipped with an attenuated total reflection (ATR) measuring unit. Suitable crystals for single-crystal diffractometry were selected by means of a polarization microscope and placed on the tip of a glass fiber. The data collections were performed on four-circle diffractometers at 293 K (**16**) and 173 K (**1**) using MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods with SIR97[19] and refined by least-squares methods against F^2 with SHELXL-97.[20] In **16**, the disorder of ethyl groups has been described by split models. All nondisordered non-hydrogen atoms were refined anisotropically; all disordered atoms have been refined isotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms.

Alcohol 9. Under a nitrogen atmosphere, a solution of commercially available 3-decyn-1-ol (5.17 g, 33.52 mmol) in THF (9 mL) was added to a solution of $LiAlH_4$ (3.78 g, 100.55 mmol) in diglyme (50 mL) and THF (15 mL) at 0 °C. The mixture was heated at reflux for 72 h, then cooled to room temperature, and slowly quenched with water and 10% NaOH. This mixture was then poured into 10% aq. HCl and extracted into hexane. The combined organic layers were washed with water, then brine, dried over $MgSO_4$, and concentrated *in vacuo*. Vacuum distillation (bp 70 °C, 6.5×10^{-1} mbar) provided alkene **9** as a colorless oil (4.12 g, 79%). R_f = 0.57 (hexanes/EtOAc 7:3). The analytical data for **9** matched those provided in the literature.[21]

3,4-*syn*-Decane-1,3,4-triol. NMO (0.56 g, 4.82 mmol) and $K_2OsO_4{\cdot}2H_2O$ (12 mg, 0.032 mmol) were added to a solution of alkene **9** (0.50 g, 3.2 mmol) in acetone/H_2O (1:1, 10 mL). The resulting solution was stirred at room temperature for 12 h. A saturated solution of sodium sulfite (20 mL) was added, and the mixture was allowed to stir for 15 min. CH_2Cl_2 (50 mL) was added, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated ammonium chloride (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2/MeOH 19:1 as eluent) to give the corresponding triol as a clear oil (0.43 g, 71% yield). R_f = 0.38 ($CHCl_3$/MeOH 17:3). The analytical data for 3,4-*syn*-decane-1,3,4-triol matched those given in the literature.[19]

Silyl Ether 10. Imidazole (34.9 g, 512.8 mmol) was added to a 500 mL flask containing a solution of 3,4-*syn*-decane-1,3,4-triol (12.18 g, 64.1 mmol) in 250 mL of DMF. The solution was cooled to 0 °C, and TESCl (64.4 mL, 384.6 mmol) was added dropwise over a period of 10 min. The resulting solution was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was poured into water (2500 mL), and the resulting aqueous mixture was extracted into diethyl ether (3 × 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over $MgSO_4$, and concentrated under reduced vacuum. The crude residue was purified using silica gel column chromatography (hexanes as eluent) to give the protected triol **10** as a clear oil (31.4 g, 92% yield). The analytical data for **10** are as follows: R_f = 0.33 (hexanes/EtOAc 99:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77−3.59 (m, 3H), 3.54 (m, 1H), 1.87 (dtd, J(H,H) = 13.5, 8.3, 2.6 Hz, 1H), 1.60 (m, 1H), 1.51−1.38 (m, 2H), 1.34−1.10 (m, 8H), 0.98−0.89 (m, 27H), 0.86 (t, J(H,H) = 7.0 Hz, 3H), 0.62−0.45 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.2, 71.6, 60.0, 33.6, 31.8, 30.2, 29.5, 26.6, 22.6, 14.1, 6.92 (3C), 6.86 (3C), 6.7 (3C), 5.15 (3C), 5.07 (3C), 4.4 ppm (3C); HRMS (ESI): m/z calcd for $C_{28}H_{64}O_3Si_3$ + Na^+: 555.4061 [M + Na^+]; found: 555.4055.

Aldehyde 11. Oxalyl chloride (2.61 mL, 30.47 mmol) was added to a 500 mL flask containing 175 mL of dry CH_2Cl_2 under N_2. The solution was cooled to −78 °C, and DMSO (2.76 mL, 39.00 mmol) was added dropwise. The resulting solution was stirred for 15 min at −78 °C. TES-protected triol **10** (12.98 g, 24.37 mmol) was added to the solution dropwise over 30 min. The resulting solution was then allowed to warm slowly to −55 °C and was then stirred at that temperature for approximately 90 min. The solution was then cooled to −78 °C, NEt_3 (16.95 mL, 121.85 mmol) was added slowly over a 5 min period, and the solution was allowed to warm to 0 °C over 1 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (300 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced vacuum. The crude residue was purified using silica gel column chromatography (hexanes, then 3% EtOAc in hexanes as eluent) to give 8.14 g of a pale yellow liquid. The ^{1}H NMR spectrum of the material showed that it contained the aldehyde **11** and the TES-protected triol **10** in a molar ratio of 9:1. The material was used directly in the next step. The analytical data for pure sample of **11** are as follows: R_f = 0.30 (hexanes/EtOAc 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (dd, J(H,H) = 2.9, 1.9 Hz, 1H), 4.18 (dt, J(H,H) = 8.4, 4.2 Hz, 1H), 3.59 (ddd, J(H,H) = 8.8, 4.5, 2.7 Hz, 1H), 2.65 (ddd, J(H,H) = 15.8, 4.0, 1.9 Hz, 1H), 2.44 (ddd, J(H,H) = 15.8, 8.3, 2.9 Hz, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.34−1.13 (m, 8H), 0.96−0.89 (m, 18H), 0.86 (t, J(H,H) = 7.0 Hz, 3H), 0.60−0.52 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 74.8, 70.5, 45.7, 31.8, 30.3, 29.4, 26.4, 22.6, 14.1, 6.8 (3C), 6.7 (3C), 5.0 (3C), 4.9 (3C); IR (thin film): ν = 2953, 2935, 2913, 2876, 1730, 1458, 1238, 1091, 1003, 720 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{48}O_3Si_2$ + Na^+: 439.3040 [M + Na^+]; found: 439.3033.

Alkylidene-bis-cyclohexane-1,3-dione 12. Crude aldehyde **11** (17.62 mmol as determined using ^{1}H NMR spectroscopy; contaminated with TES-protected triol **10**) was dissolved in CH_2Cl_2 (250 mL). 1,3-Cyclohexadione (8.77 g, 78.27 mmol) and piperidine (200 mL, 1.96 mmol) were added, and the resulting solution was stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified directly by silica gel column chromatography (1−5% EtOAc in hexanes, gradient) to give the title compound as a white solid (10.4 g, 95% yield). Analytic data for **12** are as follows: R_f = 0.36 (hexanes/EtOAc 17:3); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 12.96 (s, 1H), 12.31 (s, 1H), 4.12 (dd, J(H,H) = 10.9, 3.3 Hz, 1H), 3.56 (ddd, J(H,H) = 9.2, 4.3, 2.2 Hz, 1H), 3.42 (ddd, J(H,H) = 10.4, 4.3, 2.2 Hz, 1H), 2.81 (ddd, J(H,H) = 13.6, 11.0, 2.3 Hz, 1H), 2.50−2.38 (m, 4H), 2.34−2.23 (m, 4H), 1.95−1.71 (m, 4H), 1.56 (m, 1H), 1.47 (m, 1H), 1.37 (ddd, J(H,H) = 13.9, 10.4, 3.4 Hz, 1H), 1.32−1.07 (m, 8H), 1.00−0.91 (m, 18H), 0.88 (t, J(H,H) = 7.0 Hz, 3H), 0.62−0.54 ppm (m, 12H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 193.1, 192.5, 191.0, 190.6, 120.0, 117.2, 75.7, 74.2, 34.2, 33.9, 33.6, 33.0, 32.4, 31.4, 30.9, 30.2, 27.3, 25.9, 23.2, 20.5, 20.3, 14.4, 7.4 (3C), 7.3 (3C), 5.8 (3C), 5.7 ppm (3C); IR (thin film): ν = 2951, 2933, 2875, 1578, 1424, 1378, 1194, 1005, 980, 932, 908, 894, 738, 724 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{62}O_6Si_2$ + Na^+: 645.3983 [M + Na^+]; found: 645.3969.

Vinylogous Anhydride 13. NEt_3 (31.55 mmol, 4.4 mL) and DMAP (0.63 mmol, 77 mg) were added to a solution of bis(1,3-cyclohexadione) compound **12** (6.31 mmol, 3.93 g) in CH_2Cl_2 (150 mL) at room temperature. A solution of TsCl (6.94 mmol, 1.32 g) in CH_2Cl_2 (10 mL) was then added dropwise, and the solution was stirred for 2 h. The reaction mixture was poured into saturated

aqueous $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with another portion of CH_2Cl_2 (150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified using silica gel column chromatography using 10% EtOAc/Hexanes containing 1% NEt_3 to give the title compound **13** as an oil (3.3 g, 87% yield). The compound was not stable, even when stored at −20 °C and so needs to be consumed within a few days. Analytic data for 13 are as follows: R_f = 0.19 (hexanes/EtOAc 17:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (br dd, J(H,H) = 9.0, 2.7 Hz, 1H), 3.58 (ddd, J(H,H) = 9.5, 4.2, 2.0 Hz, 1H), 3.46 (ddd, J(H,H) = 8.8, 4.1, 2.4 Hz, 1H), 2.58−2.20 (m, 8H), 2.05−1.90 (m, 4H), 1.62−1.48 (m, 2H), 1.40−1.10 (m, 10H), 1.02−0.84 (m, 18H), 0.84 (t, J(H,H) = 7.0 Hz, 3H), 0.80−0.47 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 196.4, 165.3, 165.0, 118.6, 117.9, 75.6, 72.7, 39.1, 37.1, 37.1, 31.4, 30.3, 29.6, 27.4, 27.2, 26.8, 22.6, 21.9, 20.3, 19.9, 14.1, 7.10 (3C), 7.07 (3C), 5.33 (3C), 5.32 ppm (3C); IR (thin film): ν = 2952, 2874, 1672, 1378, 1173, 1130, 1093, 742 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{60}O_5Si_2$ + Na^+: 627.3877 [M + Na^+]; found: 627.3863.

Diol 15. THF (5 mL) and diisopropylamine (1.19 mmol, 0.167 mL) were added to a 50 mL Schlenk flask under an N_2 atmosphere, and the resulting solution was cooled to 0 °C. 2.5 M *n*BuLi in hexanes (1.19 mmol, 0.47 mL) was added, and the resulting mixture was allowed to stir at 0 °C for approximately 20 min. The solution was then cooled to −78 °C (dry ice/acetone), and the diketone **13** (0.496 mmol, 300 mg) was added dropwise as a solution in THF (1 mL). The mixture was stirred at that temperature for 20 min. A solution of Davis oxaziridine **14** (1.49 mmol, 341 mg) in THF (2 mL) was added dropwise, and once all of it had been added, the flask was removed from the −78 °C cooling bath and placed in an ice bath. After 5 min, the reaction mixture was poured into a flask containing 10 mL of phosphate-buffered H_2O (300 mM, pH 7). CH_2Cl_2 (100 mL), and 100 mL of phosphate-buffered H_2O (300 mM, pH 7) was then added. The organic layer was separated, and the aqueous layer was extracted with another portion of CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was then triturated using 10% EtOAc in hexanes (2 × 5 mL), the insoluble oxaziridine byproduct being discarded. The resulting oil was purified by silica gel column chromatography to give the title compound **15** (150 mg, 47% yield). Other fractions contained a mixture of other diastereomers (∼30 mg, ∼10% yield, slightly more polar than title compound) and a mixture of monohydroxylated compounds (∼30 mg, ∼10% yield, which were slightly less polar than the title compound). Analytic data for **15** are as follows: R_f = 0.39 (hexanes/EtOAc 3:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.07−4.13 ppm (m, 2H), 4.01 (br d, J(H,H) = 8.0 Hz, 1H), 3.82 (d, J(H,H) = 1.8 Hz, 1H), 3.78 (d, J(H,H) = 1.7 Hz, 1H), 3.43−3.47 (m, 2H), 2.68−2.77 (m, 2H), 2.41−2.49 (m, 4H), 1.83−1.93 (m, 2H), 1.76 (ddd, J(H,H) = 14.4, 8.1, 1.6 Hz, 1H), 1.31−1.43 (m, 2H), 1.46 (m, 1H), 1.18−1.28 (m, 6H), 1.04−1.09 (m, 2H), 0.97 (app t, J(H,H) = 8.0 Hz, 6H), 0.90 (app t, J(H,H) = 8.0 Hz, 6H), 0.85 (t, J(H,H) = 7.0 Hz, 3H), 0.43−0.68 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.2, 197.4, 164.4, 164.1, 115.3, 114.3, 75.4, 73.0, 71.6, 71.5, 35.4, 31.8, 30.3, 30.2, 29.9, 29.6, 26.8, 26.2, 26.0, 23.6, 22.6, 14.0, 7.04 (3C), 7.00 (3C), 5.4 (3C), 5.3 ppm (3C); IR (thin film): ν = 3480, 2951, 2874, 1671, 1374, 1361, 1170, 1089, 1075, 1003, 723 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{60}O_7Si_2$ + Na^+: 659.3775 [M + Na^+]; found: 659.3760.

Bis-bromobenzoate 16. NEt_3 (55 mL, 0.392 mmol) and DMAP (2.0 mg, 0.016 mmol) were added to a solution of **15** (50 mg, 0.079 mmol) in CH_2Cl_2 (2 mL). The solution was cooled to 0 °C, and *p*-bromobenzoyl chloride (51 mg, 0.235 mmol) was added in one portion. The resulting solution was allowed to stir at that temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was poured into sat. aq. $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was further extracted with two portions of CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography (hexanes/ethyl acetate 4:1 as eluent) to give the title compound as an oil (47 mg, 60% yield). Analytic data for **16** are as follows: R_f = 0.35 (hexanes/EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91−7.94 ppm (m, 4H), 7.55−7.59 (m, 4H), 5.56 (dd, J(H,H) = 11.7, 5.1 Hz, 1H), 5.52 (dd, J(H,H) = 11.3, 5.0 Hz, 1H), 4.02 (dd, J(H,H) = 8.0, 3.0 Hz, 1H), 3.41−3.48 (m, 2H), 2.79−2.87 (m, 2H), 2.55−2.63 (m, 2H), 2.39−2.45 (m, 2H), 2.26−2.34 (m, 2H), 1.67 (ddd, J(H,H) = 13.9, 8.8, 1.8 Hz, 1H), 1.50 (m, 1H), 1.42 (ddd, J(H,H) = 13.9, 9.8, 3.0 Hz, 1H), 1.36 (m, 1H), 1.18−1.28 (m, 6H), 1.02−1.10 (m, 2H), 0.90−0.96 (m, 18H), 0.84 (t, J(H,H) = 8.0 Hz, 3H), 0.50−0.68 ppm (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.1, 190.3, 164.9, 164.8, 164.0, 163.4, 131.7 (4C), 131.4 (2C), 131.4 (2C), 128.7, 128.5, 128.4, 128.3, 117.0, 116.5, 75.5, 72.85, 72.82, 72.4, 36.4, 31.8, 30.2, 29.6, 27.1 (2C), 26.9, 25.8, 25.5, 23.3, 22.6, 14.0, 7.1 (6C), 5.4 (3C), 5.3 ppm (3C); IR (thin film): ν = 2954, 1728, 1690, 1267, 1167, 1116, 1101, 1012, 749 cm^{-1}; HRMS (ESI): m/z calcd for $C_{48}H_{66}Br_2O_9Si_2$ + Na^+: 1023.2510 [M + Na^+]; found: 1023.2511. Single crystals suitable for X-ray crystallography were obtained by recrystallization from hexanes.

Compound 17. Under an atmosphere of N_2, TBAF as a 1 M solution in THF (20 mmol, 20 mL) was added using a syringe to a dry flask containing triethylsilyl-protected tetraol **15** (1 mmol, 0.65 g). The resulting light-brown solution was stirred overnight at room temperature. The reaction mixture was poured into a flask containing 300 mL of phosphate-buffered H_2O (300 mM, pH 7), and resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (CH_2Cl_2/acetone 3:1 as eluent) to give the title compound **17** as a foamy solid, together with a minor isomer that could not be fully characterized (222 mg, 53% yield). Analytic data for **17** are as follows: R_f = 0.20 (CH_2Cl_2/acetone 3:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.21 ppm (t, J(H,H) = 2.6 Hz, 1H; H15), 4.17 (t, J(H,H) = 6.6 Hz, 1H; H16), 4.05 (dd, J(H,H) = 12.9, 5.6 Hz, 1H; H2), 3.97 (br. s, 1H; OH), 3.95 (t, J(H,H) = 3.0 Hz, 1H; H10), 3.85 (br. s, 1H; OH), 2.93 (br. app. t, J(H,H) = 12.5 Hz, 1H; H7), 2.74 (ddd, J(H,H) = 14.0, 5.0, 2.5 Hz, 1H; H14), 2.64 (dddd, J(H,H) = 17.5, 12.6, 5.2, 3.0 Hz, 1H; H4), 2.44 (dddd, J(H,H) = 17.5, 5.2, 2.0, 2.0 Hz, 1H; H4′), 2.35 (dddd, J(H,H) = 12.7, 5.4, 5.4, 2.2 Hz, 1H; H3), 2.18 (ddd, J(H,H) = 13.8, 13.8, 5.4 Hz, 1H; H12), 2.05 (d, J(H,H) = 12.5 Hz, 1H; H8), 1.98 (dddd, J(H,H) = 14.7, 14.7, 4.5, 2.5 Hz, 1H; H11), 1.91 (m, 1H; H11′), 1.80 (dddd, J(H,H) = 12.7, 12.7, 12.7, 5.5 Hz, 1H; H3′), 1.60−1.66 (m, 2H; H12′, H14′), 1.43−1.56 (m, 2H; H17, H17′), 1.21−1.35 (m, 9H; OH, H18−H21, H18′−H21′), 0.87 ppm (t, J(H,H) = 6.8 Hz, 3H; H22, H22′, H22″); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.2 (C1), 169.1(CS), 111.5 (C6), 106.3 (C13), 98.8 (C9), 80.8 (C16), 77.7 (C15), 71.3 (C2), 69.7 (C10), 42.7 (C8), 35.5 (C17), 31.7 (alkyl chain), 31.0 (C14), 29.8 (C3), 29.1 (alkyl chain), 27.4 (C4), 26.7 (C12), 25.3 (alkyl chain), 24.9 (C11), 22.6 (alkyl chain), 22.2 (C7), 14.0 ppm (C22); IR (thin film): ν = 3410 (brd), 1627, 1592 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{32}O_7$: 408.2148 [M]; found: 408.2108.

Compound 1, Proposed as Trichodermatide A. Pyrrolidine (6 mL, 0.0735 mmol) was added to a solution of **17** (10 mg, 0.0245 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was stirred overnight at room temperature. The reaction mixture was poured into a flask containing 10 mL of phosphate-buffered H_2O (300 mM, pH 7), and the resulting biphasic mixture was stirred vigorously for 15 min. CH_2Cl_2 (10 mL) was added, and the layers were separated. The aqueous layer was extracted with another portion of CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude material showed that it consisted of a 55:45 mixture of starting material **17** and the required isomer **1** (R_f = 0.19, CH_2Cl_2/acetone 3:1). Compound **1** was purified using silica gel flash chromatography (CH_2Cl_2/acetone 3:1 as eluent), followed by trituration in CH_3CN. Trichodermatide A **1** was obtained as a white solid (3 mg, 30% yield). ^{1}H and ^{13}C NMR spectral data for **1** are provided in the

Supporting Information. In $CDCl_3$, **1** exists predominantly as one isomer; in d_6-DMSO, **1** exists as a mixture of isomers. IR (thin film): ν = 3339 (brd), 1647, 1596 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{31}O_7$: 407.2070 [M − H^+]; found: 407.2075. X-ray quality crystals were obtained by recrystallization from acetonitrile.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, X-ray data of **1** and **16**, Cartesian coordinates of optimized isomers, figures, and computed ^{13}C NMR shifts. 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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(8) X-Ray crystal structure of **16**: CCDC 985618. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K.; E-mail: deposit@ccdc.cam.ac.uk.

(9) A minor isomer that could not be identified was observed in the NMR solution of **17** and **1**. Signals for a minor isomer were also detected by Pei and co-workers (ref 1).

(10) X-Ray crystal structure of **1**: CCDC 985619. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K.; E-mail: deposit@ccdc.cam.ac.uk.

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Total Synthesis of the Proposed Structure of Trichodermatide A

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Supporting Information

Table of Contents

1. Spectral Data for 1:

^{1}H NMR data of synthetic material **1** (600 MHz, $CDCl_3$)

Chemical Shift (ppm)	Multiplicity	Assignment
4.42	s	OH (tertiary)
4.28	br. s	15
4.18	t, *J*(H,H) = 6.5 Hz	16
4.12	dd, *J*(H,H) = 13.3, 5.6 Hz	2 (axial)
3.87	br. s	OH
3.72	dd, *J*(H,H) = 11.6, 5.0 Hz	10
3.18	ddd, *J* (H,H)= 11.9, 7.1, 6.8 Hz	7
2.64	dddd, *J*(H,H) = 18.1, 12.6, 4.9, 1.8 Hz	4a (pseudo-axial)
2.51	dddd, *J*(H,H) = 18.1, 5.0, 2.0, 1.8 Hz	4b (pseudo-equitorial)
2.39	dddd, *J*(H,H) = 12.6, 5.6, 4.9, 2.0 Hz	3a (equatorial)
2.30	br. s.	OH
2.17	ddd, *J* (H,H)= 14.0, 6.8, 1.7 Hz	14a (equatorial)
2.05	dddd, *J*(H,H) = 12.6, 7.7, 4.5, 3.4 Hz	11a (equatorial)
1.92-1.87	m (2H)	12a, 12b
1.85-1.78	m (2H)	3b (axial), 14b (axial)
1.78	d, *J*(H,H) = 7.1 Hz	8

1.73	ddd, *J* (H,H)= 12.6, 11.6, 6.3 Hz	11b (axial)
1.54	m	17a
1.48	m	17b
1.42-1.25	m (8H)	18a/b, 19a/b, 20a/b, 21a/b
0.90	t, *J*(H,H) = 7.0 Hz	22

^{13}C NMR data of synthetic material **1** (150 MHz, $CDCl_3$)

Chemical Shift	**Assignment**
198.1	quat., 1
168.1	quat., 5
112.0	quat., 6
105.9	quat., 13
97.9	quat., 9
79.0	CH, 16
78.2	CH, 15
72.0	CH, 10
71.2	CH, 2
41.8	CH, 8
35.5	CH_2, 17
31.9	CH_2, 12
31.7	CH_2, 18-21
30.1	CH_2, 14

29.1	CH_2, 18-21
29.0	CH_2, 3
27.6	CH_2, 11
27.3	CH_2, 4
25.2	CH_2, 18-21
22.5	CH_2, 18-21
21.5	CH, 7
14.0	CH_3, 22

Comparison Trichodermatide A (Isolated)[1] and (Synthetic **1**)

^{13}C NMR (150 MHz, DMSO-d_6)

Isolated (DMSO)	**Synthetic (DMSO)**	**Synthetic ($CDCl_3$)**	**Assignment**
197.7	197.7	198.3	quat., 1
167.9	167.7	168.3	quat., 5
111.7	111.9	112.1	quat., 6
106.2	105.5	106.0	quat., 13
100.0	99.0	98.0	quat., 9
77.5	77.5	79.1	CH, 16
77.1	77.1	78.4	CH, 15
68.2	70.7	72.2	CH, 10
70.7	70.6	71.3	CH, 2
38.1	42.3	42.0	CH, 8

35.4	35.4	35.7	CH_2, 17
24.8 (suspected misassignment)	32.1	32.1	CH_2, 12
28.8	31.3	31.9	CH_2, 18-21
29.5	29.4	30.2	CH_2, 14
28.4	29.1	29.3	CH_2, 18-21
29.4	28.7	29.2	CH_2, 3
26.5	28.2	27.7	CH_2, 11
27.4	27.5	27.5	CH_2, 4
31.4 (suspected misassignment)	24.8	25.3	CH_2, 18-21
22.1	22.2	22.7	CH_2, 18-21
21.7	22.1	21.7	CH, 7
14.1	14.0	14.2	CH_3, 22

HMBC correlations (600 MHz, $CDCl_3$)

Proton assignment	Correlates with these carbon atoms
OH (tertiary)	8, 9
15	7, 13, 17
16	Saturated Chain, 13, 15
2	1, 3, 4
10	9, 11
7	1, 5, 6, 8, 9, 14
4a	2, 3, 5, 6
4b	2, 3, 5, 6
3a	1, 2, 4, 5
14a	7, 8, 16
11a	9, 10, 12, 13
12a and 12b	8, 10, 11, 13
14b	16
3b	1, 2, 4,
8	7, 9, 13, 14
11b	10
17a and 17b	Saturated Chain

NOESY (600 MHz, $CDCl_3$)

Assignment	**Close in space to**
OH(tertiary)	11b, 14b
2	3a, 4a
3a	2, 3b
3b	3a
4a	4b
4b	4a
7	8, 14a, 16
8	7, 10
10	8, 11a, 12b
11a	11b, 10
11b	11a
12a	12b
12b	10, 12a
14a	7, 14b, 15, 16
14b	14a, 15
15	14a, 14b, 17a, 17b,
16	7, 14a, 17a, 17b
17a	17b
17b	17a

2. Crystallographic data for 16:

net formula	$C_{48}H_{66}Br_2O_9Si_2$
M_r/g mol^{-1}	1003.011
crystal size/mm	0.32 × 0.24 × 0.11
T/K	293(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12$
a/Å	28.0291(6)
b/Å	25.3002(5)
c/Å	13.8427(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	9816.4(4)
Z	8
calc. density/g cm^{-3}	1.35737(6)
μ/mm^{-1}	1.753
absorption correction	'multi-scan'
transmission factor range	0.79077–1.00000
refls. measured	45391
R_{int}	0.0380

mean σ(*I*)/*I*	0.1198
θ range	4.22–26.35
observed refls.	11272
x, y (weighting scheme)	0.0298, 0
hydrogen refinement	constr
Flack parameter	0.013(5)
refls in refinement	19645
parameters	1113
restraints	0
$R(F_{obs})$	0.0405
$R_w(F^2)$	0.0730
S	0.816
$shift/error_{max}$	0.002
max electron density/e $Å^{-3}$	1.008
min electron density/e $Å^{-3}$	−0.733

Disordered ethyl groups have been handled by split models.

The following figures show the two symmetrically independent molecules in the asymmetric unit (only major part of disordered groups shown).

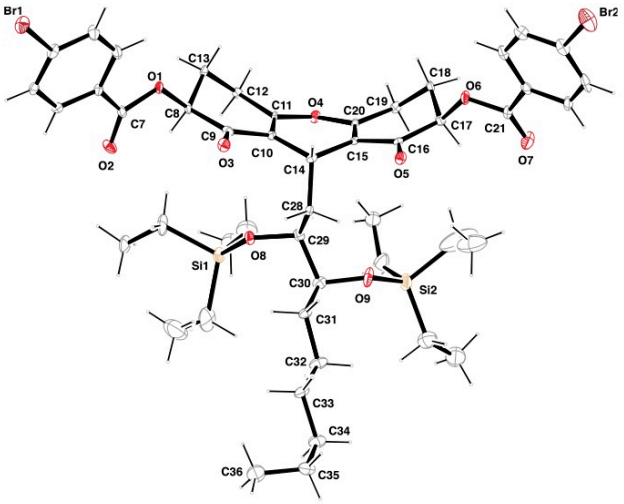


Figure 1: Form A of **16**

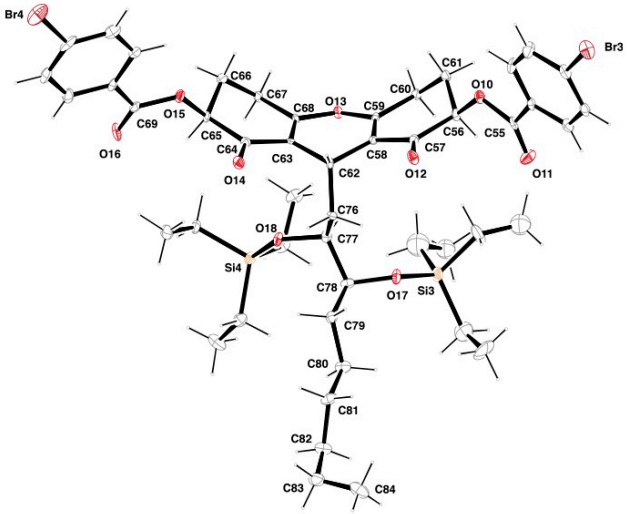


Figure 2: Form B of **16**

3. Crystallographic data for 1:

net formula	$C_{22}H_{32}O_7$
M_r/g mol^{-1}	408.485
crystal size/mm	0.22 × 0.05 × 0.02
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	5.1037(3)
b/Å	12.7494(7)
c/Å	31.1738(17)
α/°	90
β/°	92.531(3)
γ/°	90
V/Å^3	2026.47(19)
Z	4
calc. density/g cm^{-3}	1.33891(13)
μ/mm^{-1}	0.099
absorption correction	none
refls. measured	10107
R_{int}	0.1724

mean σ(*I*)/*I*	0.1634
θ range	3.20–24.00
observed refls.	1502
x, *y* (weighting scheme)	0.0473, 0
hydrogen refinement	constr
refls in refinement	3152
parameters	266
restraints	0
$R(F_{obs})$	0.0625
$R_w(F^2)$	0.1292
S	0.939
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.290
min electron density/e Å^{-3}	−0.269

Crystal had poor scattering strength; data with theta > 24° omitted.

Centrosymmetric space group.

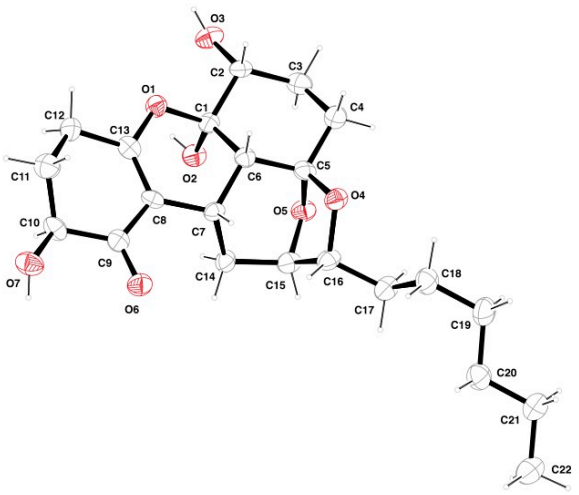
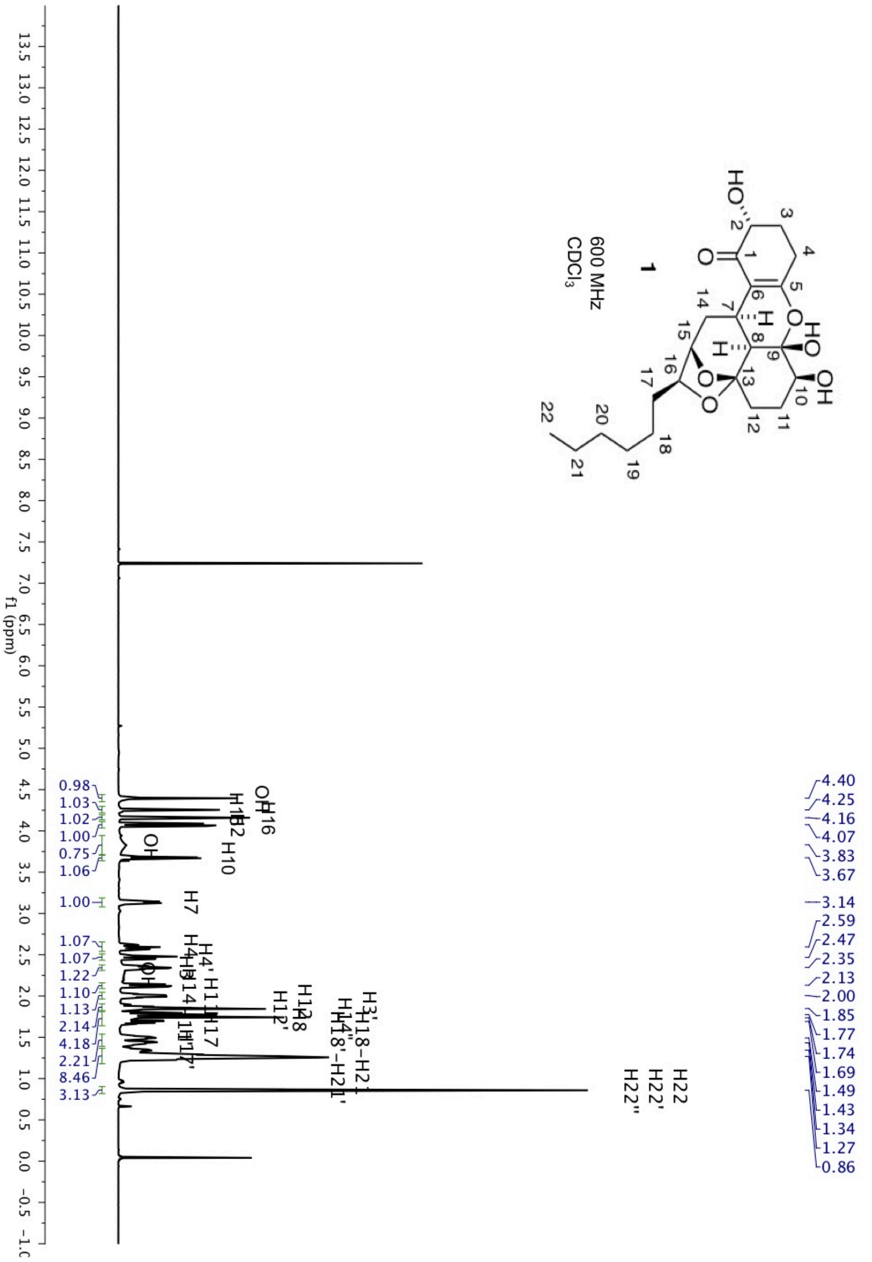
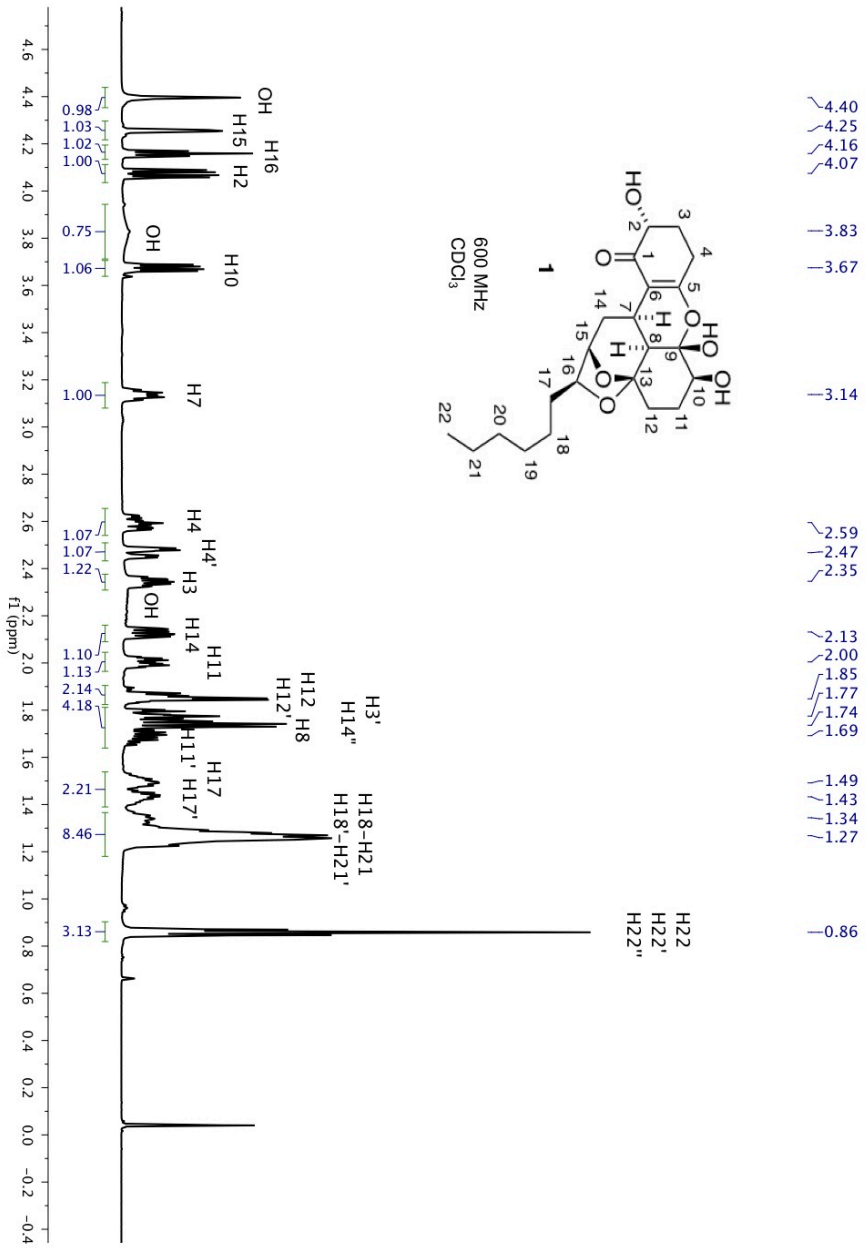


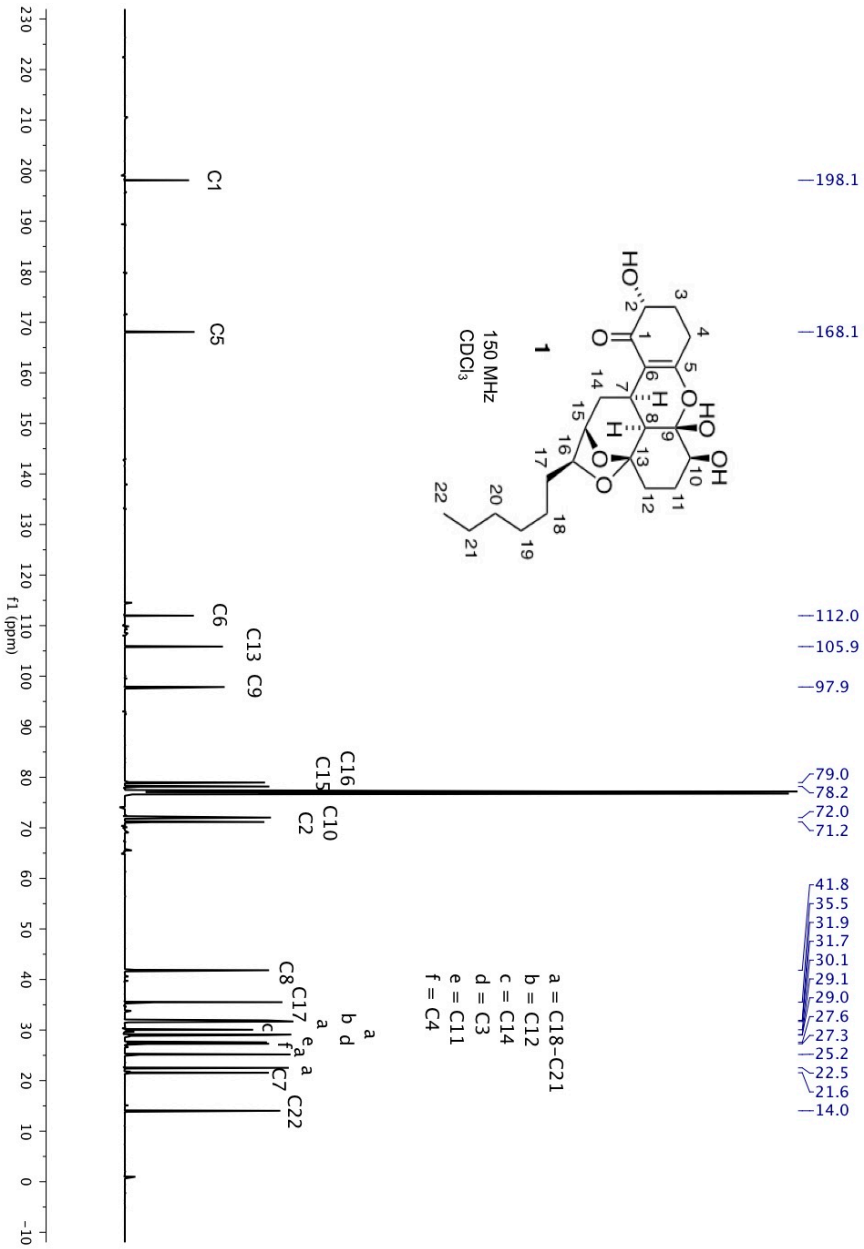
Figure 3: X-ray structure of **1**

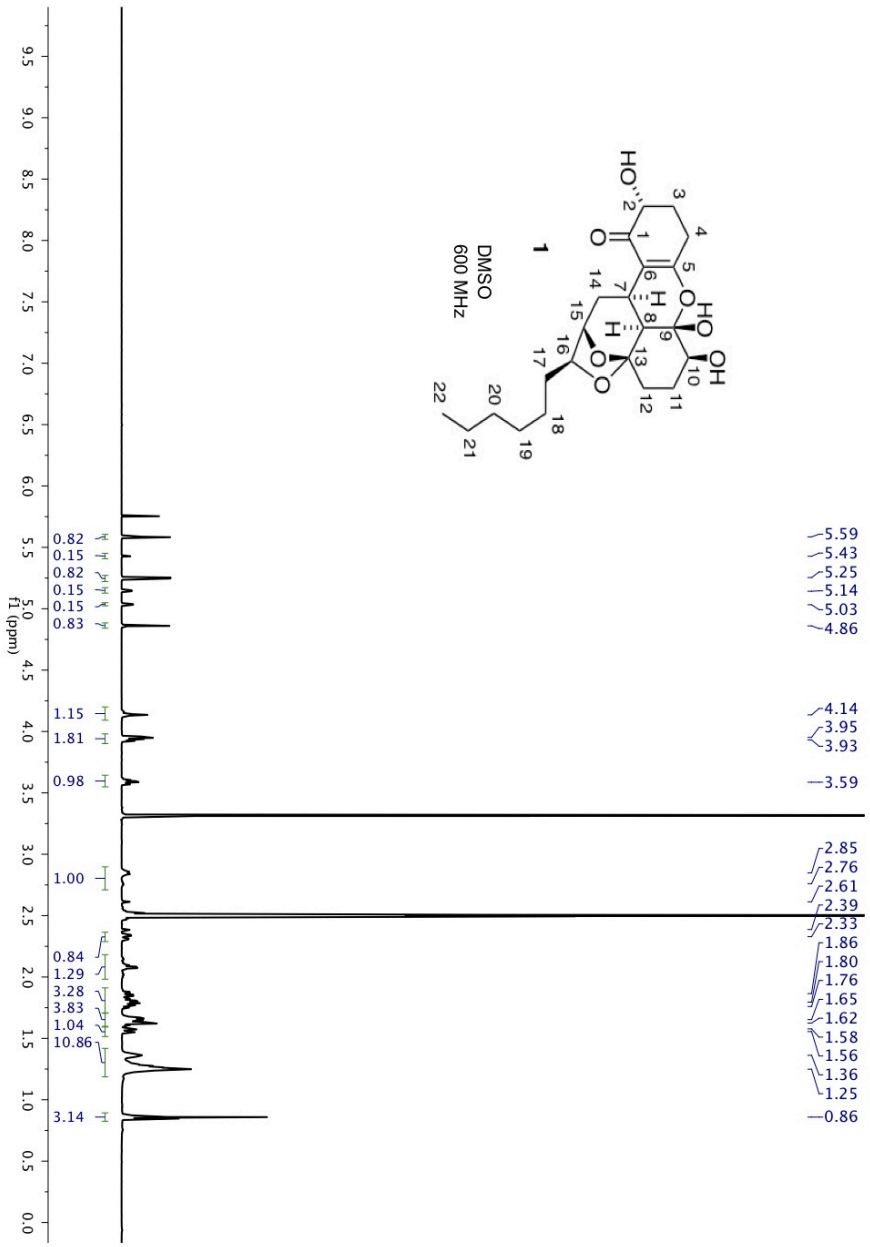
4. NMR spectra

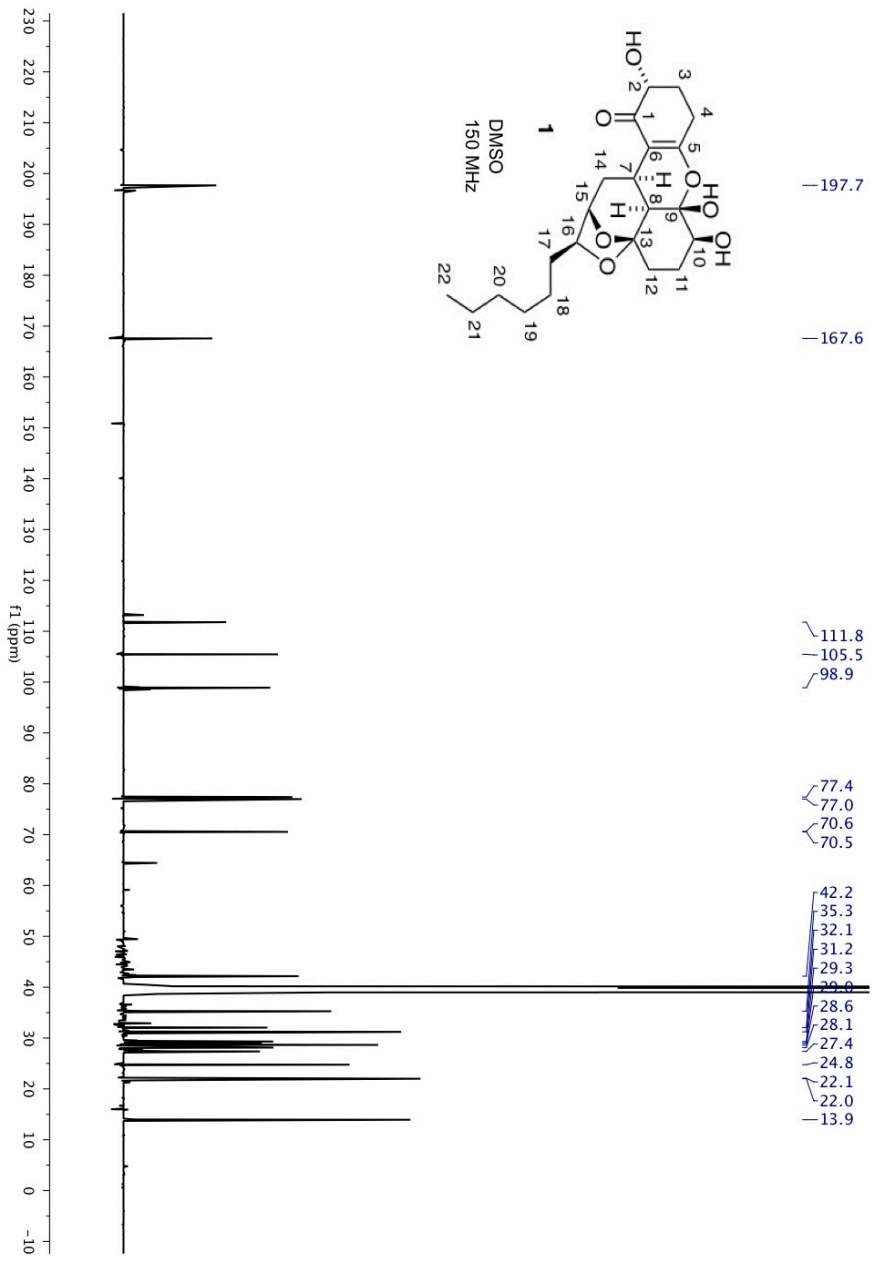

1
600 MHz
CDCl3
f1 (ppm)


600 MHz
CDCl3
1
OH
H15
H16
H2
OH
H10
H7
H4
H4'
H3
OH
H14
H11
H12'
H12
H8
H3'
H14"
H11'
H17'
H17
H18-H21
H18'-H21'
H22
H22'
H22"
0.98
1.03
1.02
1.00
0.75
1.06
1.00
1.07
1.07
1.22
1.10
1.13
2.14
4.18
2.21
8.46
3.13
4.40
4.25
4.16
4.07
3.83
3.67
3.14
2.59
2.47
2.35
2.13
2.00
1.85
1.77
1.74
1.69
1.49
1.43
1.34
1.27
0.86
f1 (ppm)

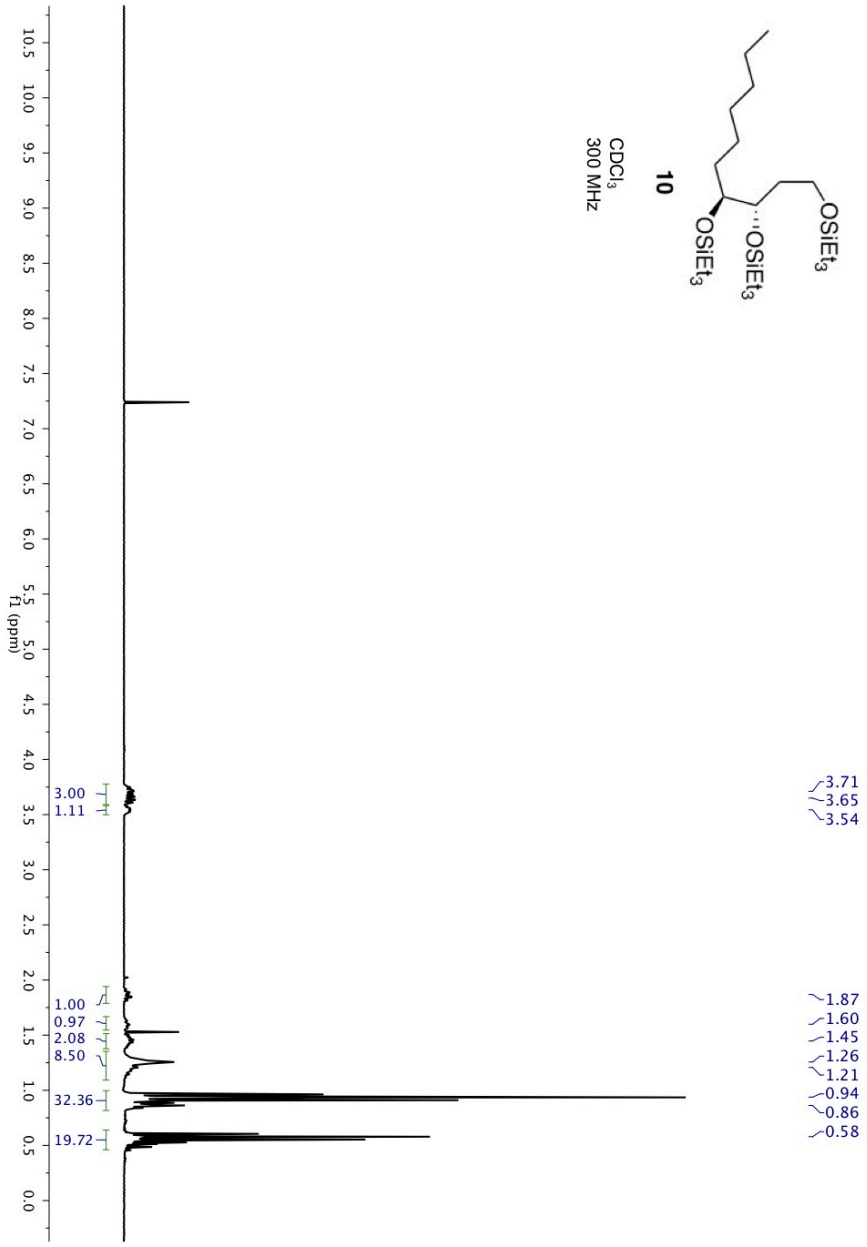
15

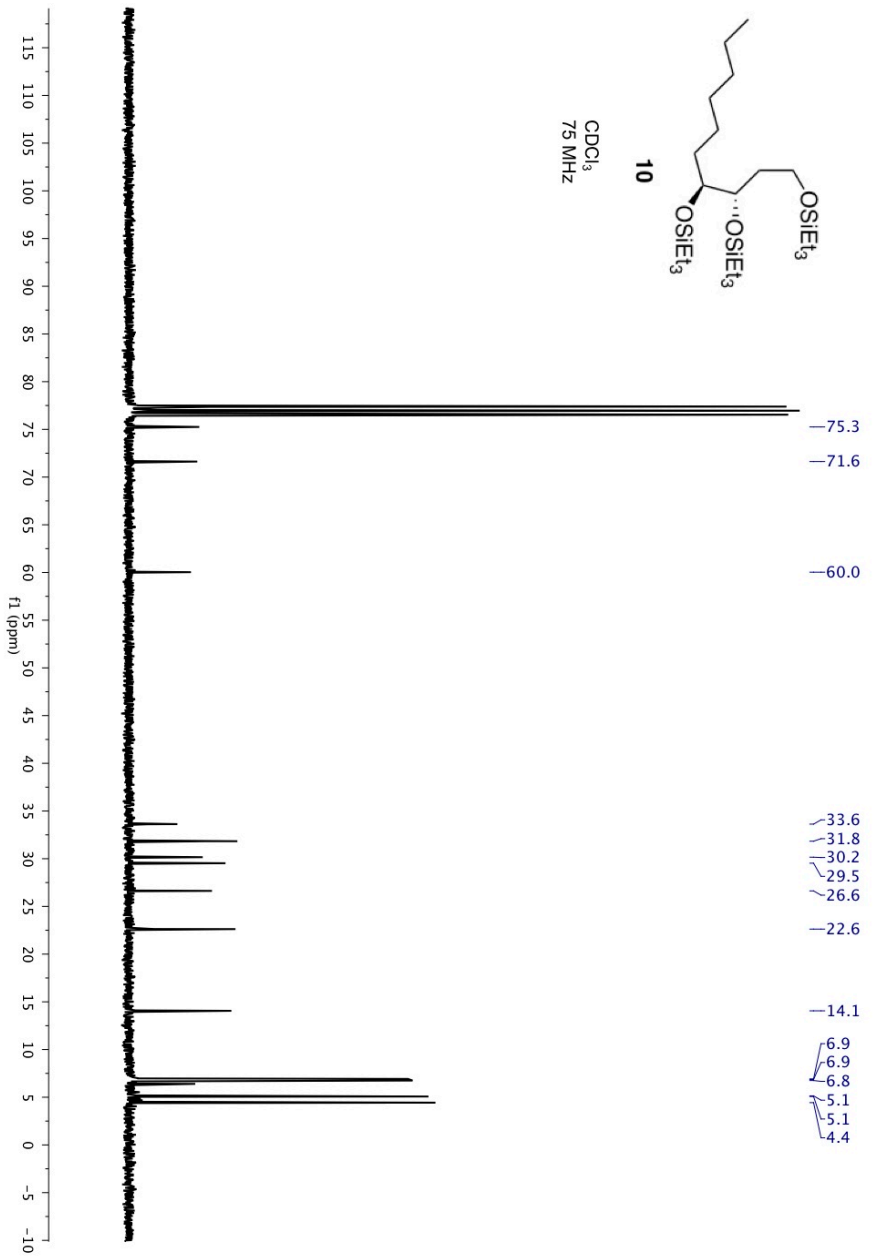

150 MHz
CDCl3
1
HO
OH
O
O
O
O
H
H
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
C1
C5
C6
C13
C9
C16
C15
C10
C2
C8
C17
C7
C22
a
b
c
d
e
f
a = C18–C21
b = C12
c = C14
d = C3
e = C11
f = C4
198.1
168.1
112.0
105.9
97.9
79.0
78.2
72.0
71.2
41.8
35.5
31.9
31.7
30.1
29.1
29.0
27.6
27.3
25.2
22.5
21.6
14.0
f1 (ppm)


DMSO
600 MHz
1
f1 (ppm)
0.82
0.15
0.82
0.15
0.15
0.83
1.15
1.81
0.98
1.00
0.84
1.29
3.28
3.83
1.04
10.86
3.14
5.59
5.43
5.25
5.14
5.03
4.86
4.14
3.95
3.93
3.59
2.85
2.76
2.61
2.39
2.33
1.86
1.80
1.76
1.65
1.62
1.58
1.56
1.36
1.25
0.86

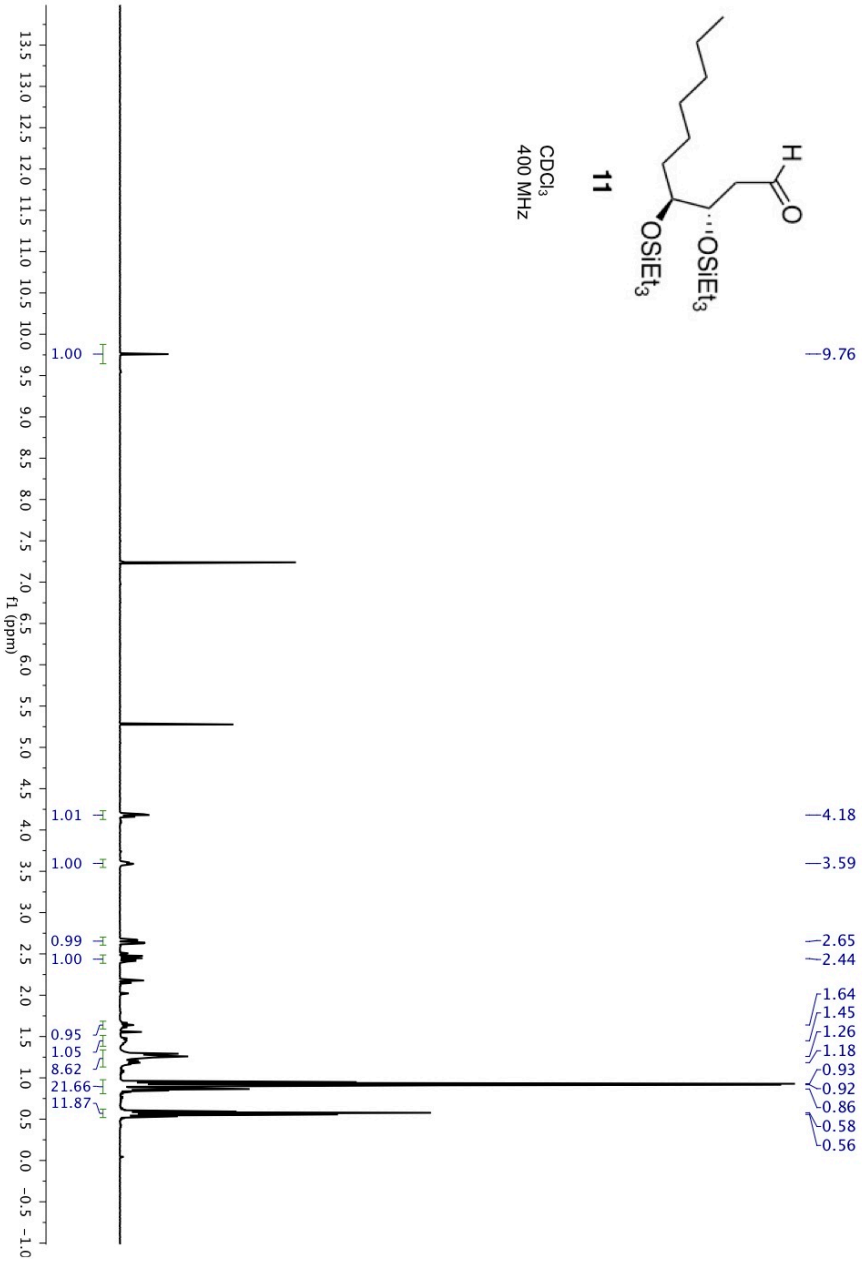

DMSO
150 MHz
1
f1 (ppm)
197.7
167.6
111.8
105.5
98.9
77.4
77.0
70.6
70.5
42.2
35.3
32.1
31.2
29.3
28.6
28.1
27.4
24.8
22.1
22.0
13.9

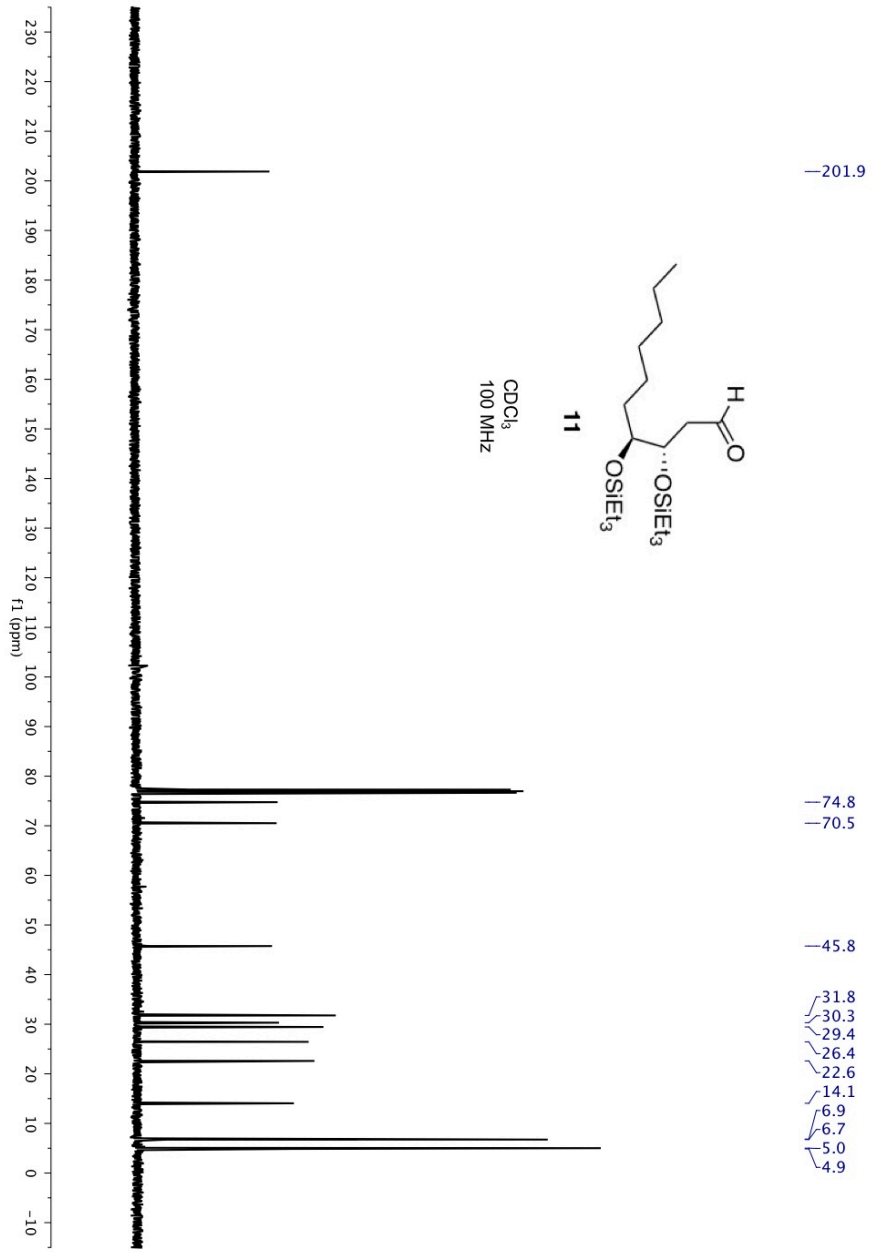
18

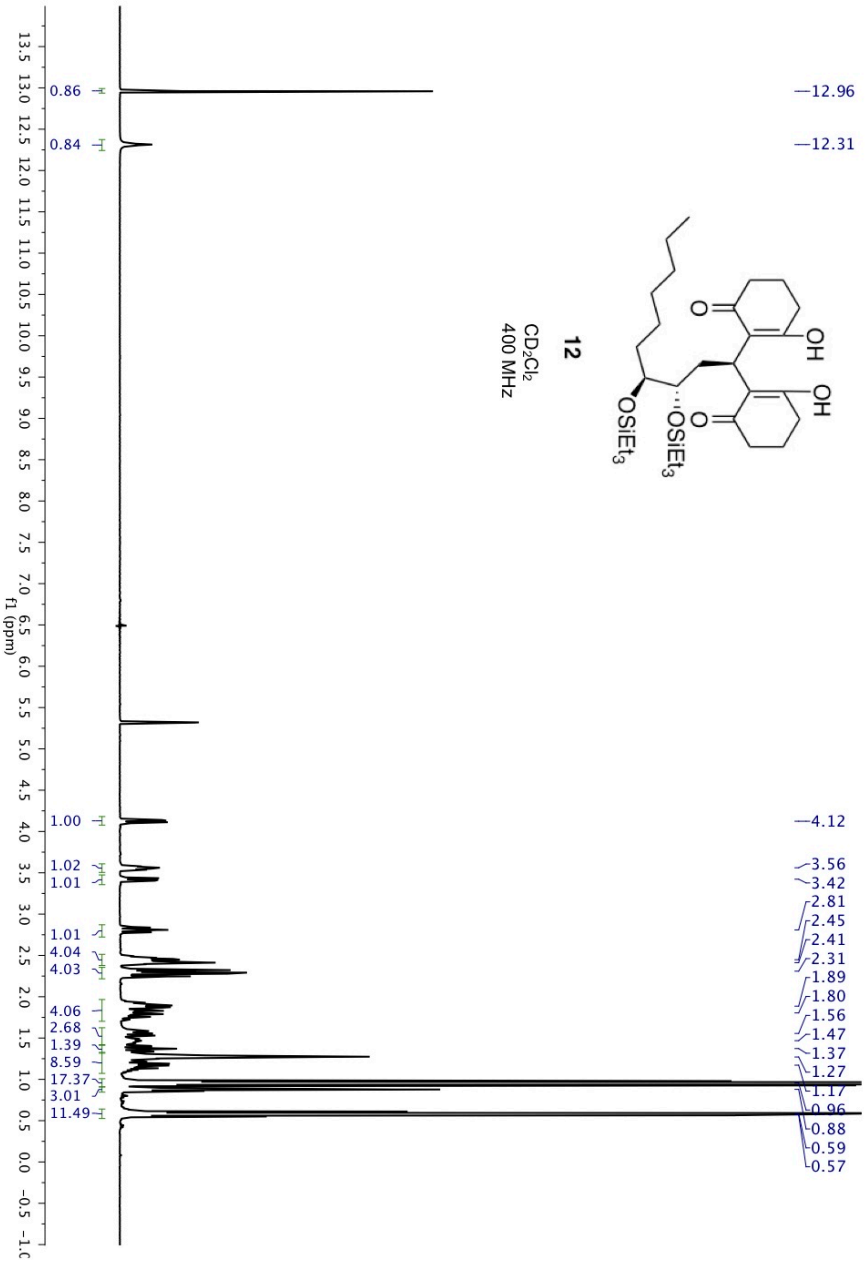

10
CDCl3
300 MHz
OSiEt3
OSiEt3
OSiEt3
f1 (ppm)
3.00
1.11
1.00
0.97
2.08
8.50
32.36
19.72
3.71
3.65
3.54
1.87
1.60
1.45
1.26
1.21
0.94
0.86
0.58

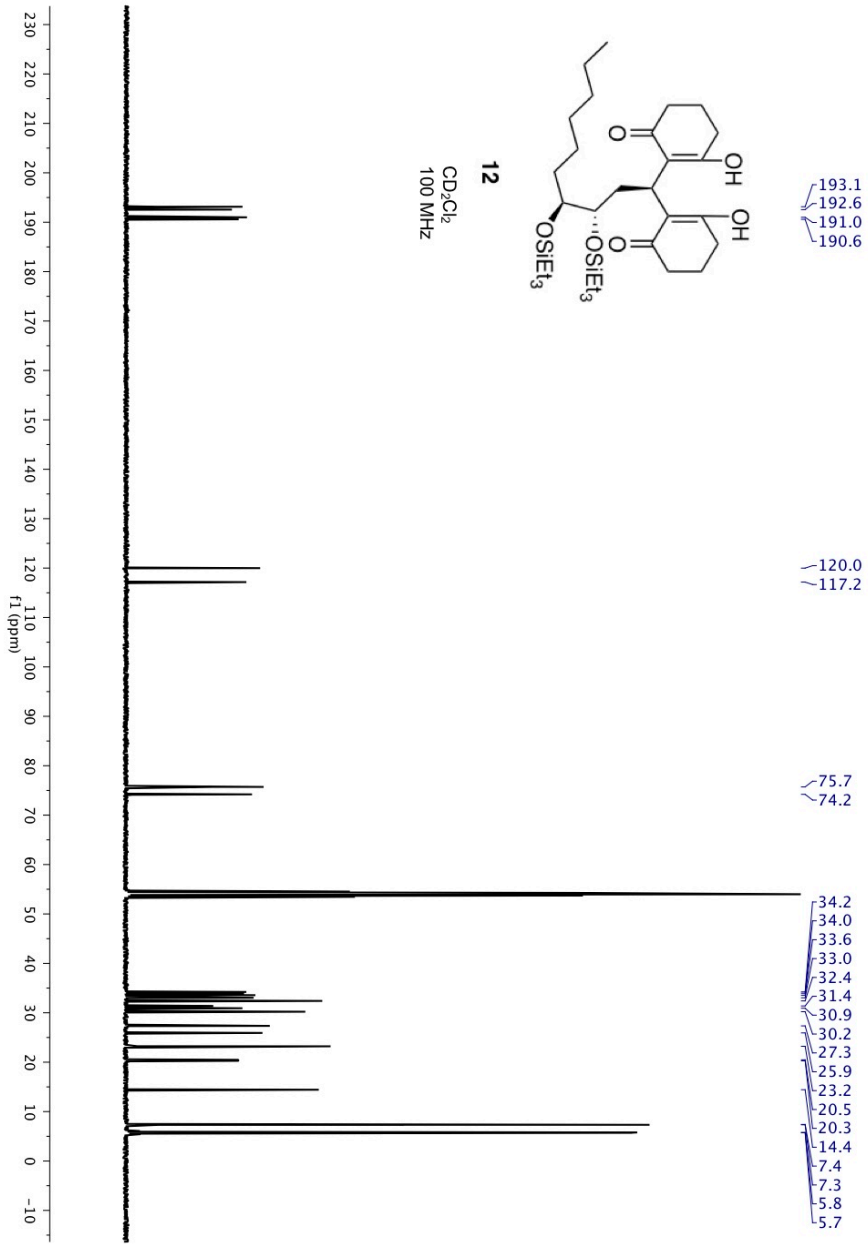

10
CDCl3
75 MHz
OSiEt3
OSiEt3
OSiEt3
f1 (ppm)
75.3
71.6
60.0
33.6
31.8
30.2
29.5
26.6
22.6
14.1
6.9
6.9
6.8
5.1
5.1
4.4

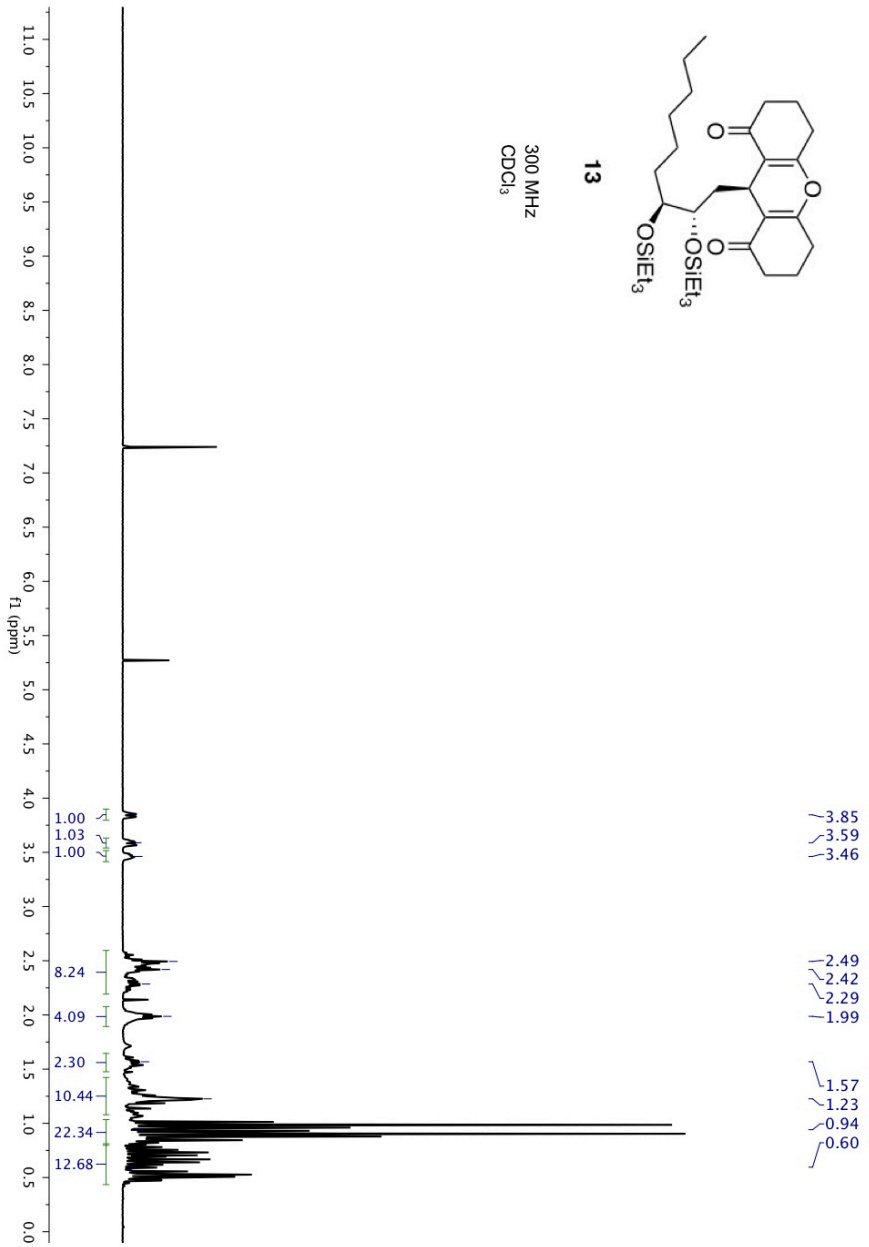
20

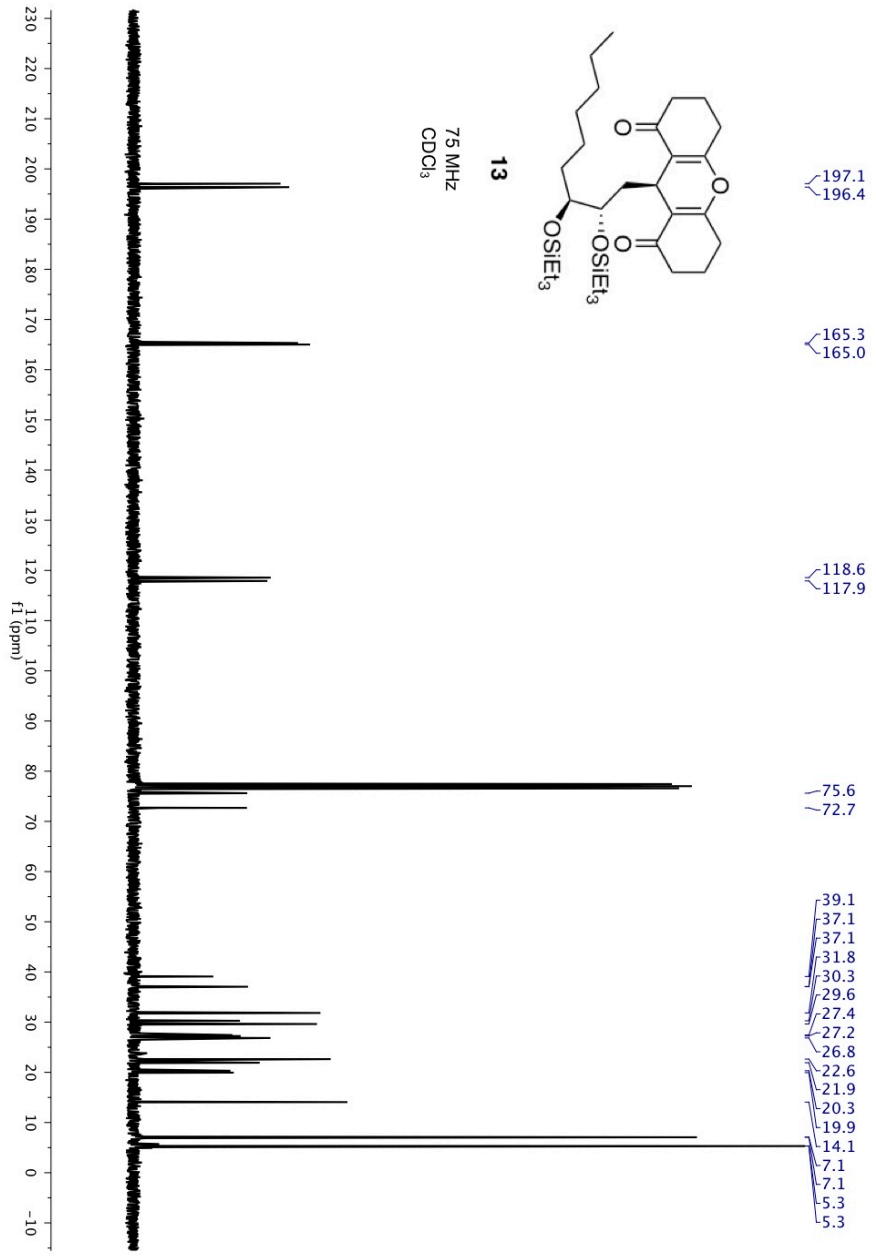

11
CDCl3
400 MHz
OSiEt3
OSiEt3
O
H
f1 (ppm)
1.00
1.01
1.00
0.99
1.00
0.95
1.05
8.62
21.66
11.87
9.76
4.18
3.59
2.65
2.44
1.64
1.45
1.26
1.18
0.93
0.92
0.86
0.58
0.56

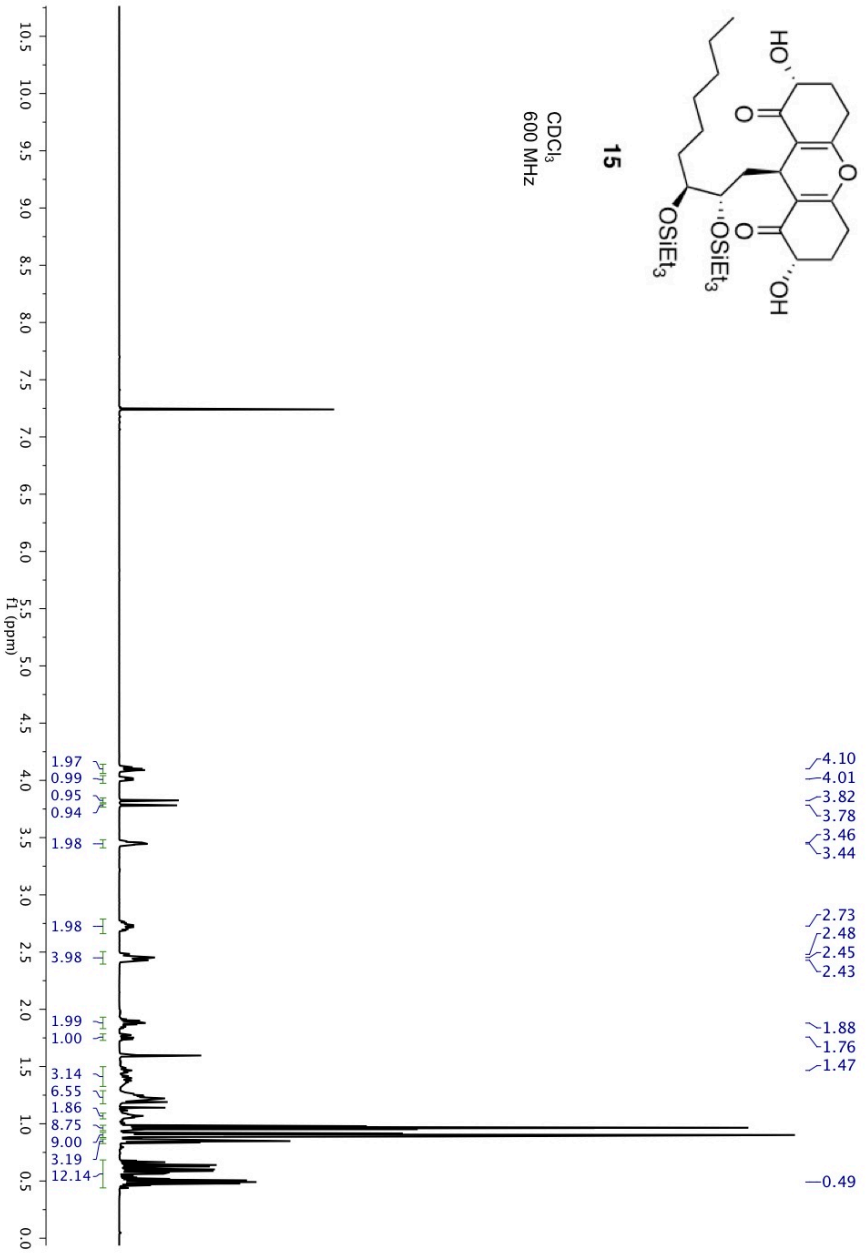

CDCl3
100 MHz
11
OSiEt3
OSiEt3
H
O
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
201.9
74.8
70.5
45.8
31.8
30.3
29.4
26.4
22.6
14.1
6.9
6.7
5.0
4.9

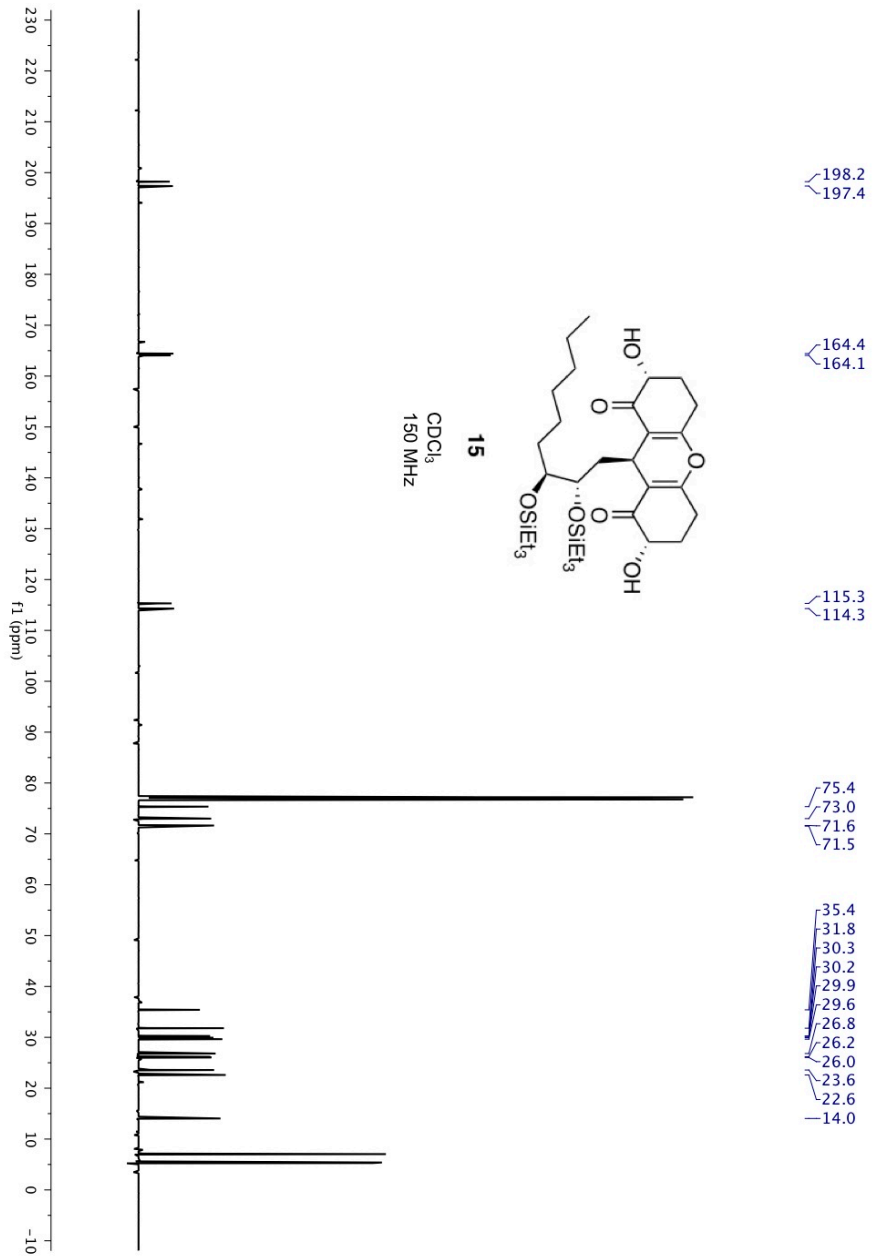

12
CD2Cl2
400 MHz
OH
OH
O
O
OSiEt3
OSiEt3
f1 (ppm)
0.86
0.84
1.00
1.02
1.01
1.01
4.04
4.03
4.06
2.68
1.39
8.59
17.37
3.01
11.49
12.96
12.31
4.12
3.56
3.42
2.81
2.45
2.41
2.31
1.89
1.80
1.56
1.47
1.37
1.27
1.17
0.96
0.88
0.59
0.57


12
CD_2Cl_2
100 MHz
OH
OH
O
O
OSiEt3
OSiEt3
193.1
192.6
191.0
190.6
120.0
117.2
75.7
74.2
34.2
34.0
33.6
33.0
32.4
31.4
30.9
30.2
27.3
25.9
23.2
20.5
20.3
14.4
7.4
7.3
5.8
5.7
f1 (ppm)

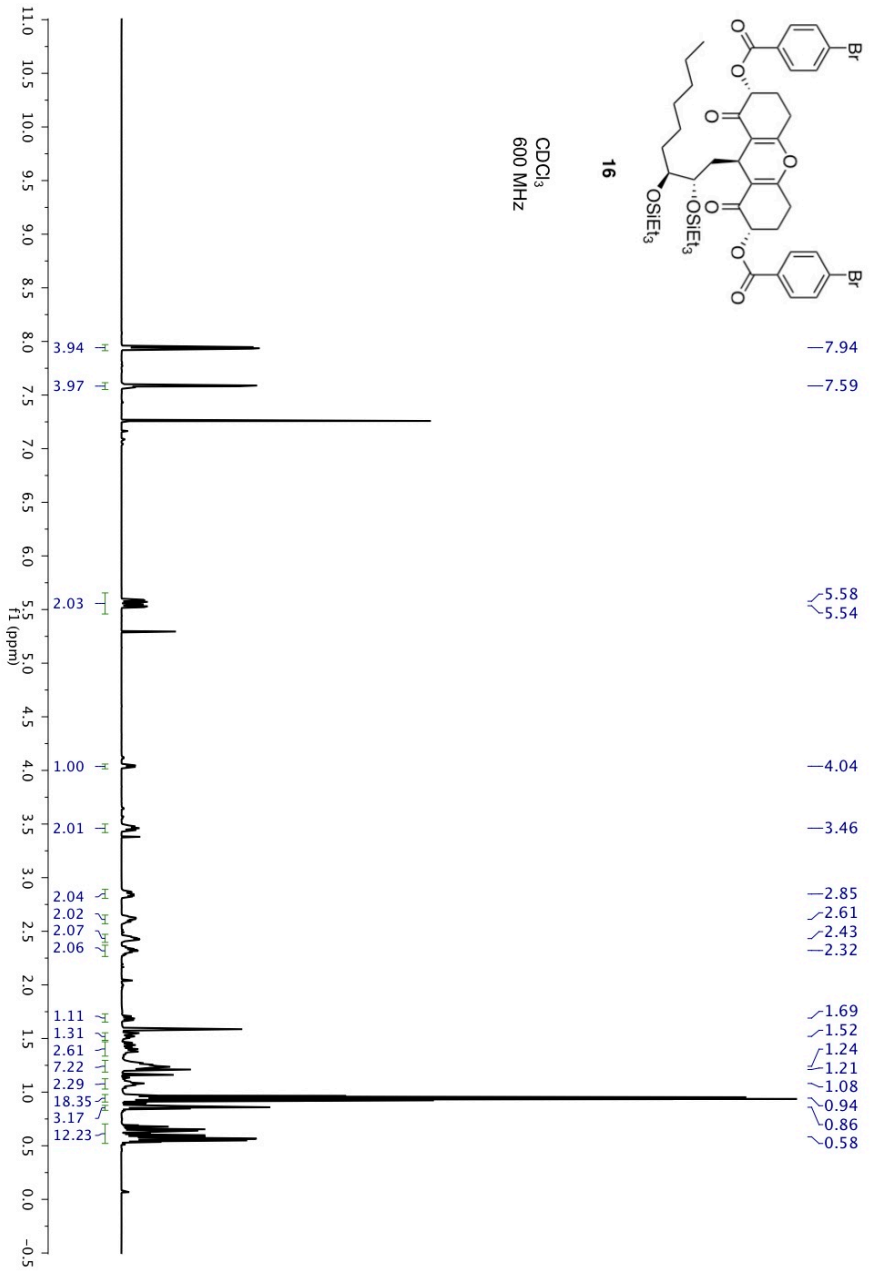

13
300 MHz
CDCl3
OSiEt3
OSiEt3
O
O
O
f1 (ppm)
1.00
1.03
1.00
8.24
4.09
2.30
10.44
22.34
12.68
3.85
3.59
3.46
2.49
2.42
2.29
1.99
1.57
1.23
0.94
0.60

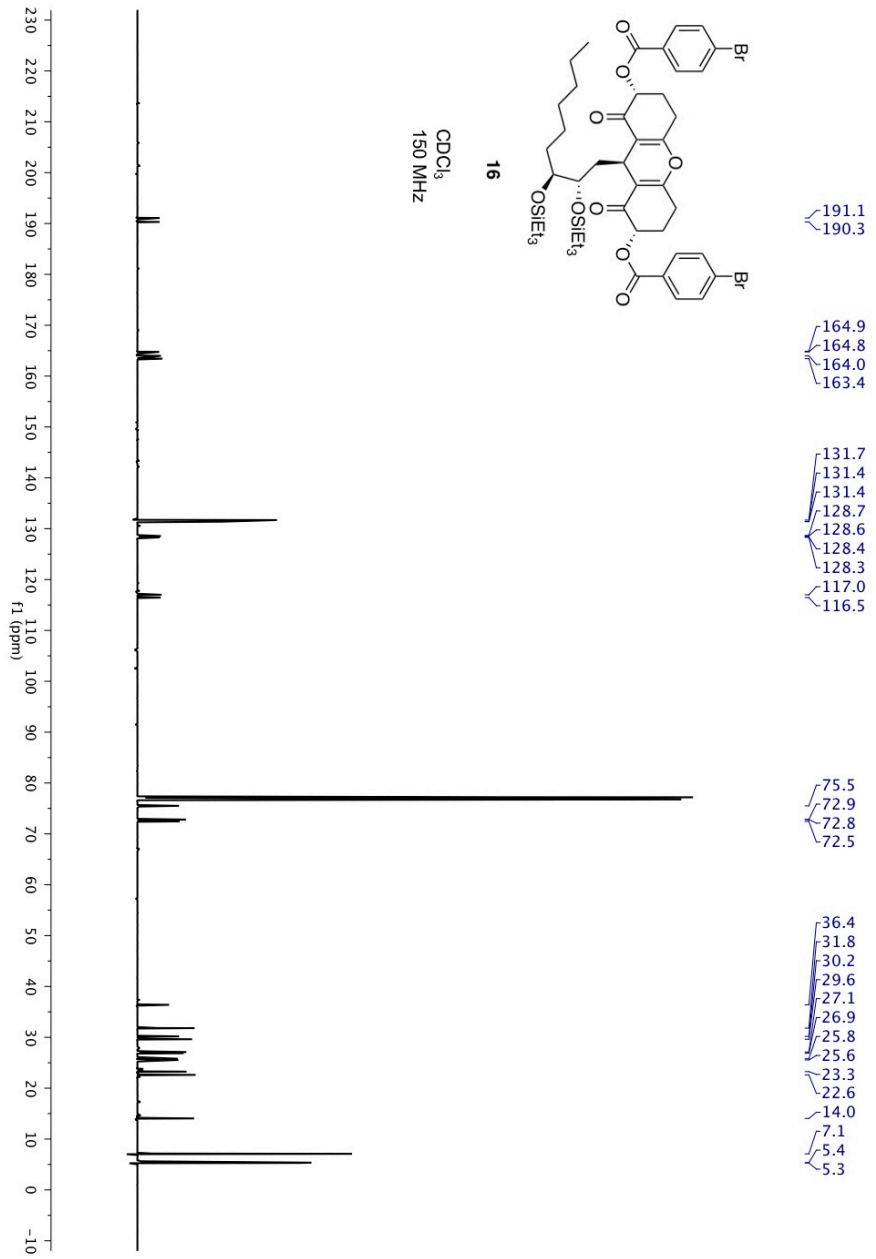

13
75 MHz
CDCl3
OSiEt3
OSiEt3
197.1
196.4
165.3
165.0
118.6
117.9
75.6
72.7
39.1
37.1
37.1
31.8
30.3
29.6
27.4
27.2
26.8
22.6
21.9
20.3
19.9
14.1
7.1
7.1
5.3
5.3
f1 (ppm)

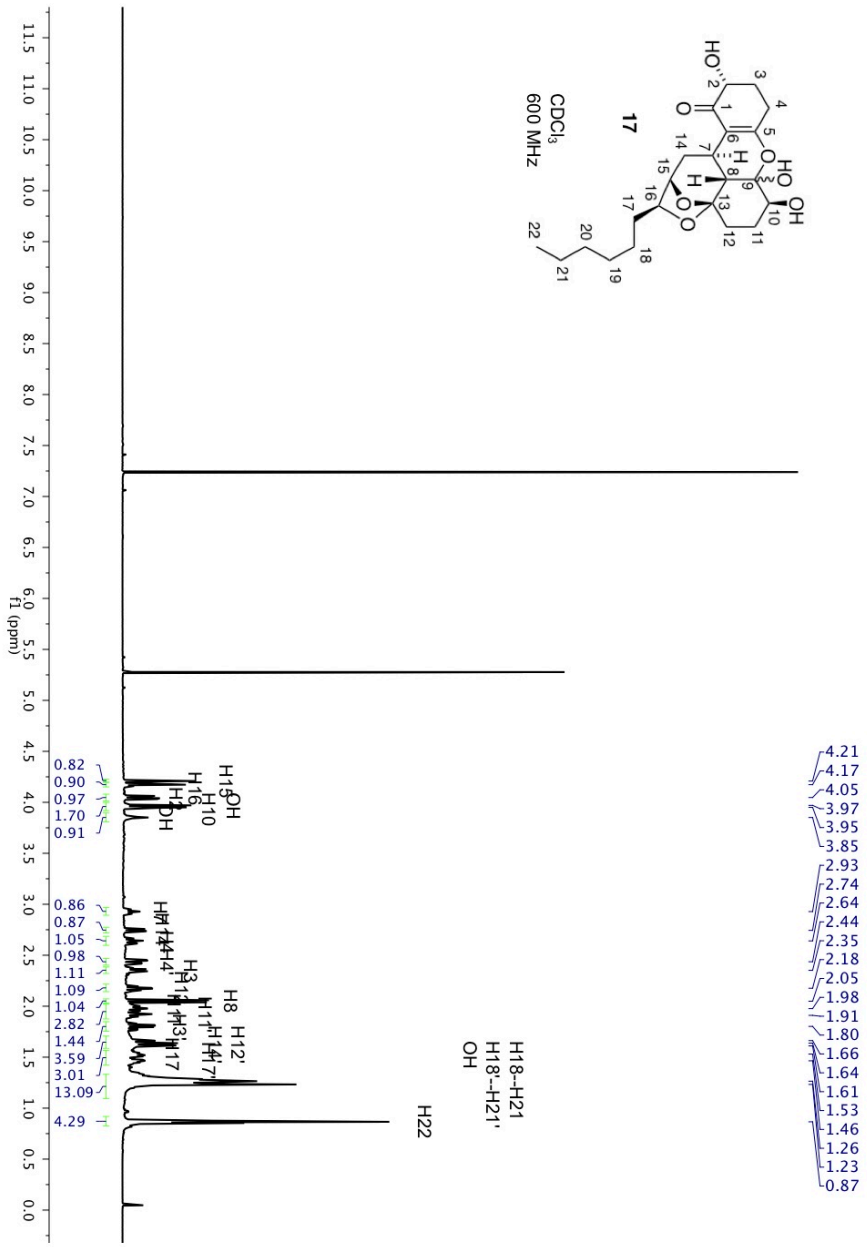

15
CDCl3
600 MHz
HO
O
OSiEt3
O
OSiEt3
OH
f1 (ppm)
1.97
0.99
0.95
0.94
1.98
1.98
3.98
1.99
1.00
3.14
6.55
1.86
8.75
9.00
3.19
12.14
4.10
4.01
3.82
3.78
3.46
3.44
2.73
2.48
2.45
2.43
1.88
1.76
1.47
0.49

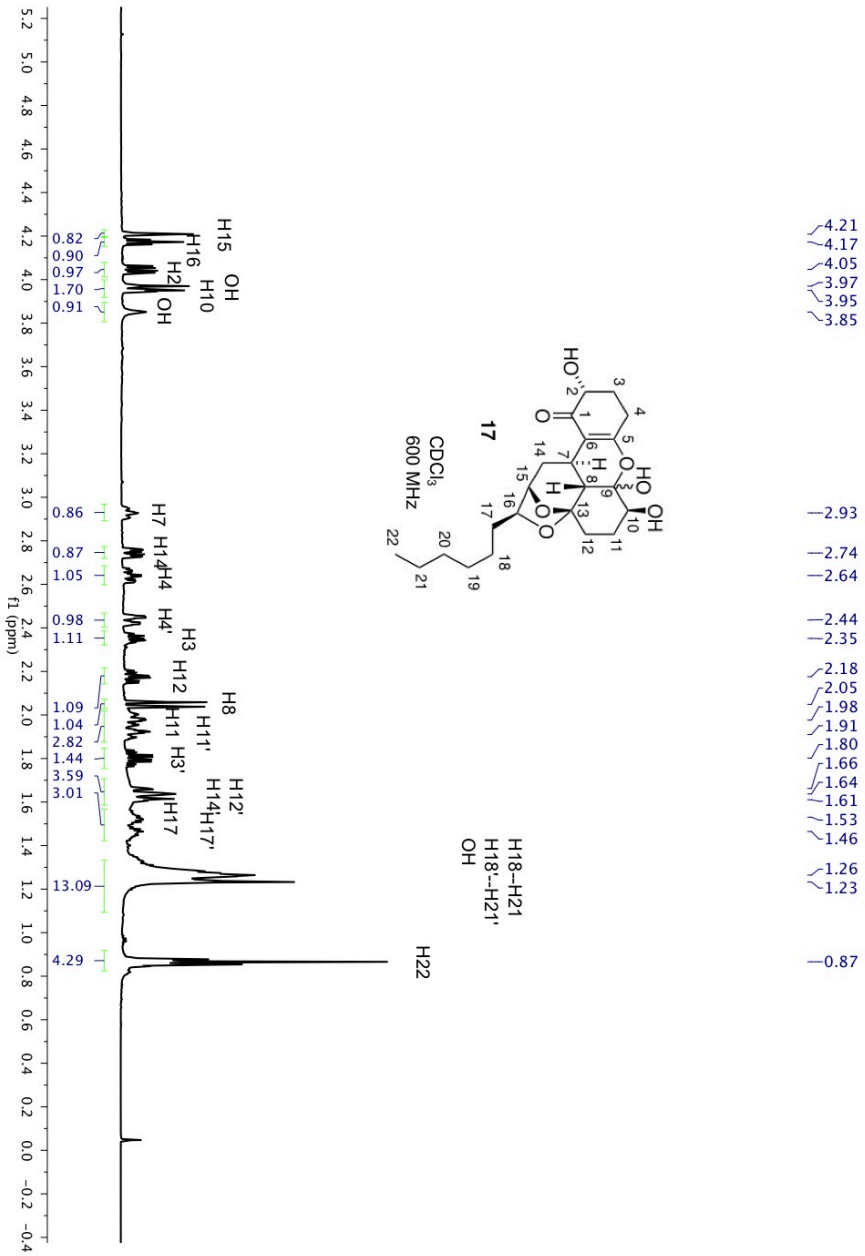

198.2
197.4
164.4
164.1
115.3
114.3
75.4
73.0
71.6
71.5
35.4
31.8
30.3
30.2
29.9
29.6
26.8
26.2
26.0
23.6
22.6
14.0
15
CDCl3
150 MHz
HO
O
OSiEt3
OSiEt3
O
O
OH
f1 (ppm)

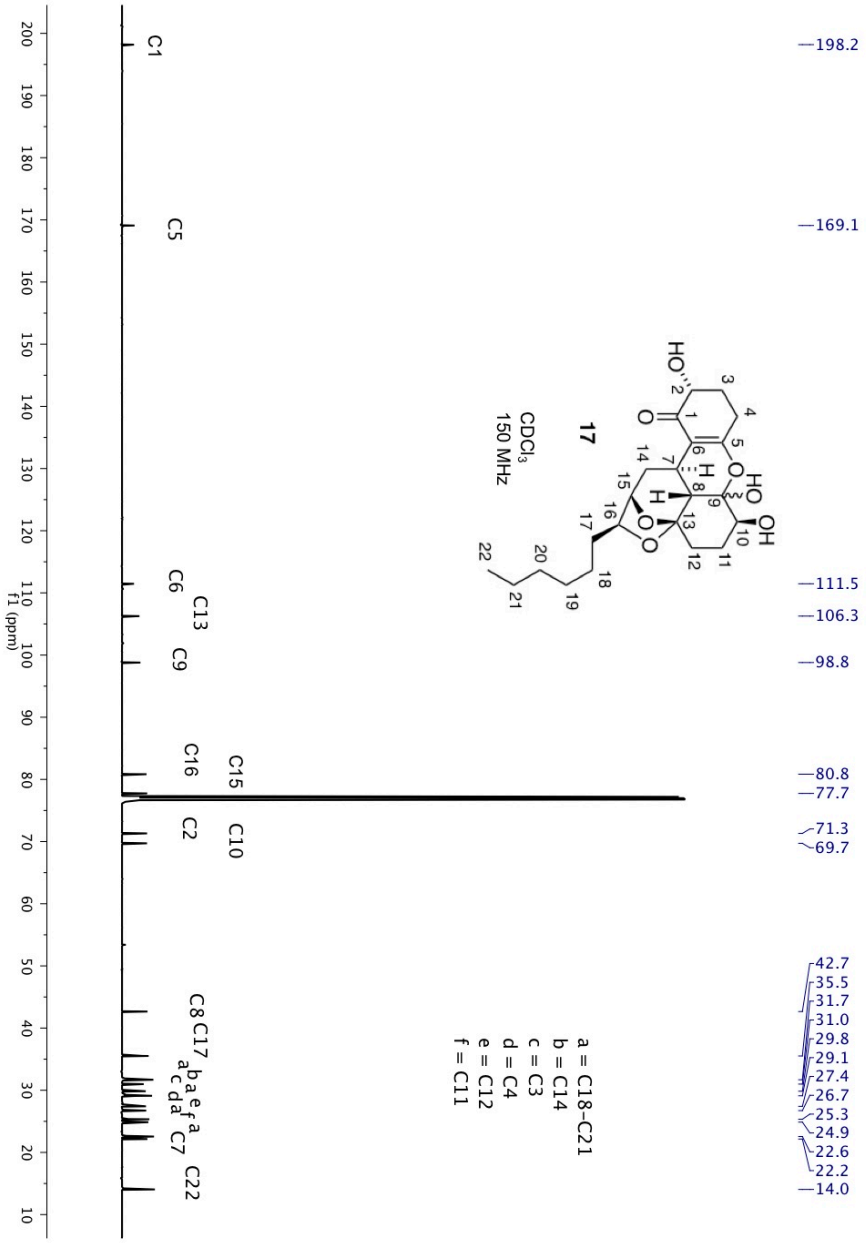
28


CDCl3
600 MHz
16
Br
Br
OSiEt3
OSiEt3
f1 (ppm)
3.94
3.97
2.03
1.00
2.01
2.04
2.02
2.07
2.06
1.11
1.31
2.61
7.22
2.29
18.35
3.17
12.23
7.94
7.59
5.58
5.54
4.04
3.46
2.85
2.61
2.43
2.32
1.69
1.52
1.24
1.21
1.08
0.94
0.86
0.58


CDCl3
150 MHz
16
OSiEt3
OSiEt3
Br
Br
191.1
190.3
164.9
164.8
164.0
163.4
131.7
131.4
131.4
128.7
128.6
128.4
128.3
117.0
116.5
75.5
72.9
72.8
72.5
36.4
31.8
30.2
29.6
27.1
26.9
25.8
25.6
23.3
22.6
14.0
7.1
5.4
5.3
f1 (ppm)


17
CDCl3
600 MHz
f1 (ppm)
H22
H18--H21
H18'--H21'
OH
H8
H12'
H10
H16
H15
OH
OH
0.82
0.90
0.97
1.70
0.91
0.86
0.87
1.05
0.98
1.11
1.09
1.04
2.82
1.44
3.59
3.01
13.09
4.29
4.21
4.17
4.05
3.97
3.95
3.85
2.93
2.74
2.64
2.44
2.35
2.18
2.05
1.98
1.91
1.80
1.66
1.64
1.61
1.53
1.46
1.26
1.23
0.87


17
CDCl3
600 MHz
HO
OH
OH
H15
H16
H2
H10
H7
H14
H4
H4'
H3
H12
H8
H11
H11'
H3'
H17
H12'
H14'
H17'
H18--H21
H18'--H21'
OH
H22
0.82
0.90
0.97
1.70
0.91
0.86
0.87
1.05
0.98
1.11
1.09
1.04
2.82
1.44
3.59
3.01
13.09
4.29
4.21
4.17
4.05
3.97
3.95
3.85
2.93
2.74
2.64
2.44
2.35
2.18
2.05
1.98
1.91
1.80
1.66
1.64
1.61
1.53
1.46
1.26
1.23
0.87
f1 (ppm)


198.2
169.1
111.5
106.3
98.8
80.8
77.7
71.3
69.7
42.7
35.5
31.7
31.0
29.8
29.1
27.4
26.7
25.3
24.9
22.6
22.2
14.0
17
CDCl3
150 MHz
a = C18–C21
b = C14
c = C3
d = C4
e = C12
f = C11
C1
C5
C6
C13
C9
C16
C15
C10
C2
C8
C17
C7
C22
f1 (ppm)

(1) Sun, Y.; Tian, L.; Huang, J.; Ma, H.-Y.; Zheng, Z.; Lv, A.-L.; Yasukawa, K.; Pei, Y.-H. *Org. Lett.* **2008**, *10*, 393-396.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	azobis(*iso*-butyronitrile)
atm	standard atmosphere (1.01325 bar)
b	broad
B3LYP	Becke, three-parameter, Lee-Yang-Parr
BHT	butylated hydroxytoluene = 2,6-bis(1,1-dimethylethyl)-4-methylphenol
Bn	benzyl
Bu	butyl
n-BuLi	*n*-butyllithium
CAM	ceric ammonium nitrate
cat.	catalytic
CD	circular dichroism
CoA	coenzyme A
cont.	continued
m-CPBA	*meta*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAH	DIBAL-H = diisobutylaluminum hydride
DIEA	*N,N*-diisopropylethylamine
DMAP	(4-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1H)-one
DMSO	dimethyl sulfoxide
DNB	2,4-dinitrobenzyl
DTBP	di-*tert*-butyl peroxide
EDCl	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide
EI	electron ionization
ESI	electrospray ionization

Et	ethyl
FTIR	fourier-transform infrared spectroscopy
GGPP	geranylgeranyl pyrophosphate
$h\nu$	ultraviolet irradiation
HF	Hartree-Fock
HMBC	heteronuclear multiple bond correlation experiment
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
KHMDS	potassium hexamethyldisilazide
HSQC	heteronuclear single quantum correlation experiment
HWE	Horner–Wadsworth–Emmons
IMDA	intramolecular Diels–Alder
IR	infrared spectroscopy
LDA	lithium diisopropylamide
m	multiplet
MIC	minimum inhibitory concentration
m.p.	melting point
Me	methyl
MOM	methoxy methyl ether
MS	mass spectrometry
MsOH	methanesulfonic acid
MP2	second-order Møller–Plesset perturbation theory
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
[O]	oxidant
OPLS	optimized potential for liquid simulations
PCC	pyridinium chlorochromate
Ph	phenyl
pK_a	logarithmic acid dissociation constant
PivCl	pivaloyl chloride
PMB	*p*-methoxybenzyl

PMP	pentamethylpiperidine
PNBzCl	*p*-nitrobenzoyl chloride
ppm	parts per million
i-Pr	isopropyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
RI	resolution-of-the-identity
R_f	retention factor
s	singlet
SVP	split valence polarization
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethysilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TZVP	valence triple-zeta polarization
Wnt	wingless/integrated