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**Studies Towards Total Synthesis of Polyketide
Natural Products and Alkaloids**

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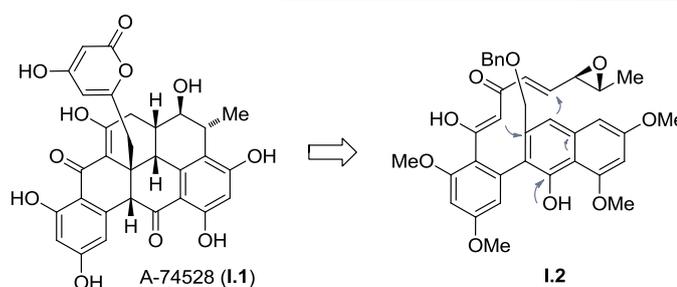
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–For my family–

SUMMARY

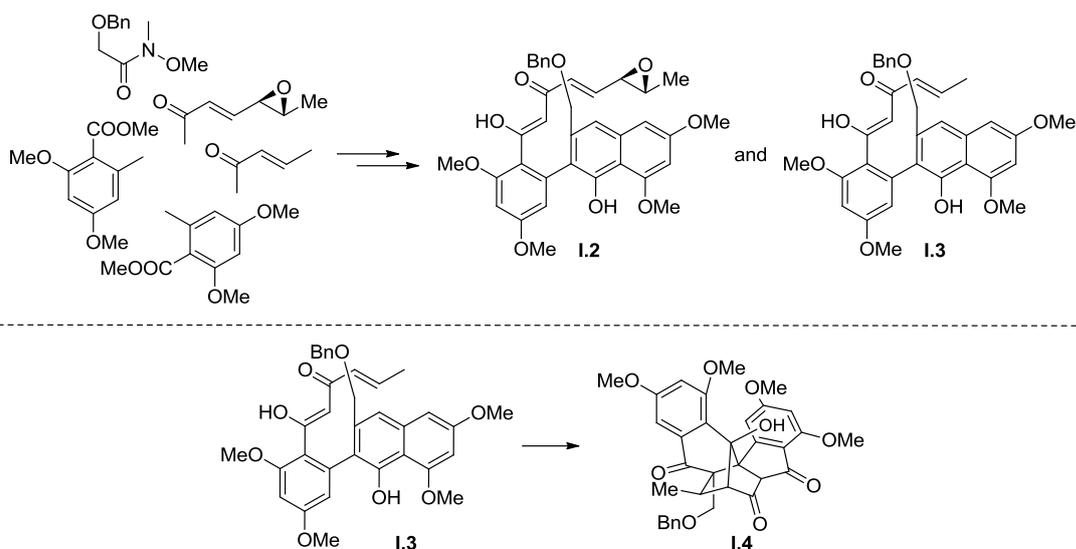
Chapter I: Synthetic Studies Toward A-74528

A-74528 (**I.1**) is an unusual natural product which has recently been isolated from *Streptomyces* sp. SANK 61196 by Ogita and co-workers (Scheme A).^[1] Although **I.1** was found to activate the interferon system *via* inhibition of 2',5'-oligoadenylate phosphodiesterase (2'-PDE),^[1] no synthetic approaches to A-74528 (**I.1**) have been reported. With its 30 carbon atoms, A-74528 (**I.1**) is one of the most complex and largest aromatic polyketides known to date. Structurally, A-74528 (**I.1**) consists of a hexacyclic core with an appended α -pyrone moiety. Its unprecedented carbon skeleton contains two acyl resorcinol motifs typical of type II polyketides, which flank the perhydropyrene core. This heptacyclic system also features six contiguous stereocenters, one of which is quaternary.



Scheme A. Type II polyketide A-74528 (**I.1**) and its possible precursor **I.2**.

This research project is centered on the development of a biomimetic synthesis of **I.1** and its precursors. We found it fascinating to test the limits of biomimetic synthesis and to explore whether a complex polyketide pathway could be emulated in the laboratory.^[2] As a key step of our synthesis an intramolecular Michael-Michael cascade of intermediate **I.1** was envisioned, the synthesis of which demanded advanced biaryl chemistry techniques (Scheme A). These investigations initially focused on challenging transition-metal catalyzed cross-coupling reactions and, eventually, led to a synthetic strategy based on potentially biomimetic condensation chemistry, thus providing the key intermediates epoxide **I.2** and enone **I.3** (Scheme B). At this point, extensive experimentations towards a Michael-Michael cyclization of the model system **I.3** were undertaken. Although, the desired system could not be isolated thus far, other interesting reactions of **I.3** have been observed, leading to, for example, the dearomatized compound **I.4** in a cascade reaction (Scheme B).^[3] This biomimetic approach could serve to unveil more interesting facets of polyketide type II chemistry.

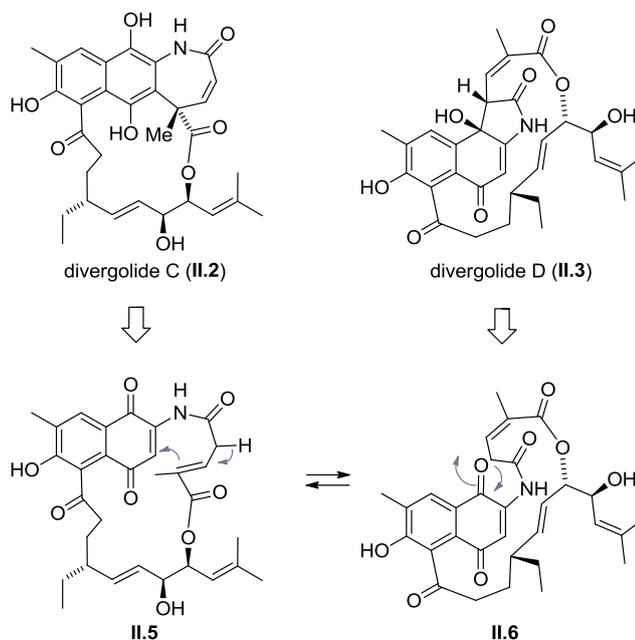
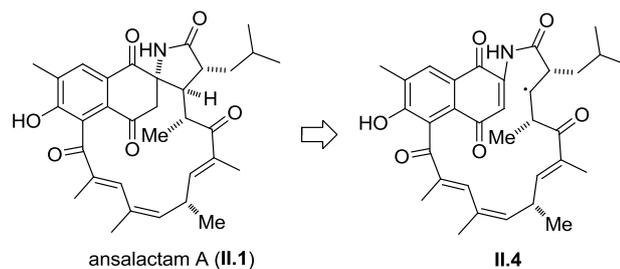


Scheme B. Synthetic progress toward A-74528 (**I.1**).

Chapter II: Synthetic Studies Toward Ansalactam A, Divergolides C and D

Ansalactam A (**II.1**) and divergolides C and D (**II.2** and **II.3**) are macrolactam natural products which belong to the ansamycin polyketide family. The intriguing structures of these three ansa macrolides attracted our interest. Thus, as a part of this PhD thesis, we envisaged to test biomimetic steps, which are involved in the biogeneses of all three natural products.

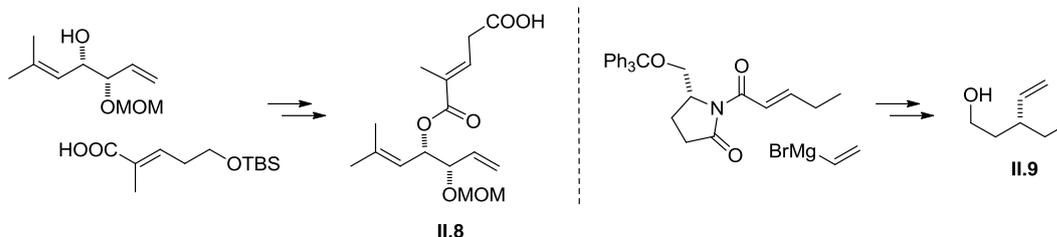
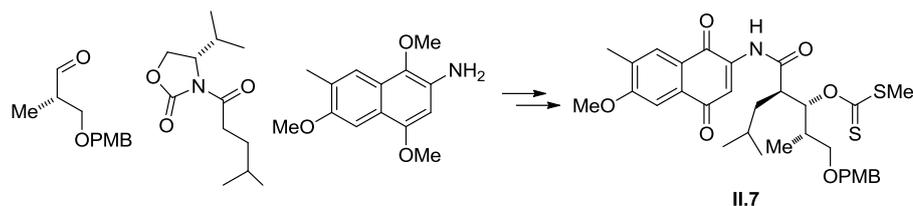
Ansalactam A (**II.1**) was isolated by Moore and co-workers in 2011 from *Streptomyces* sp., derived from marine sediments.^[4] As we suppose, its fascinating biosynthesis presumably involves a radical cyclization of an open ring radical system **II.4**, forming the 5-membered lactam ring (Scheme C). On the other hand, divergolides C and D (**II.2** and **II.3**) were isolated by Hertweck and co-workers in 2011 from an endophyte (*Streptomyces* sp. HKI0576) of the mangrove tree *Bruguiera gymnorrhiza*.^[5] Hertweck and co-workers discovered, that divergolides C and D (**II.2** and **II.3**) originate from a similar bioprecursor. We believe, that the biomimetic total synthesis of both divergolides could be achieved starting from the intermediates **II.5** and **II.6**, which may interconvert into each other by an transesterification and double bond isomerisation process, providing swift access to both natural products (Scheme C).



Scheme C. Type I polyketides ansalactam A (II.1) and divergolides C and D (II.2 and II.3), as well as their possible precursor II.4, II.5 and II.6.

In the case of ansalactam A (II.1), our synthetic strategy involves the aforementioned biomimetic radical 5-*exo*-trig ring closure at an early stage of the synthesis. So far, as a part of this PhD thesis, an efficient synthesis of the naphthoquinone system II.7 was successfully achieved (Scheme D). Suitable reaction conditions for the proposed radical ring closure have been investigated.

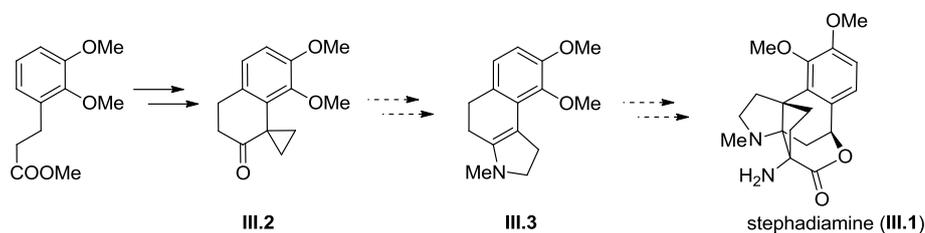
In the envisioned synthesis of the divergolides II.2 and II.3 we also aimed to prove our biomimetic hypothesis. It was planned to access both compounds II.2 and II.3 from a common intermediate, structurally similar to the isomers II.5 and II.6, by means of a base mediated Michael addition (for II.2), an aldol reaction (for II.3) and, finally, a transesterification. This dissertation includes the development of the syntheses of the eastern side chain II.8 and the western side chain II.9 (Scheme D).



Scheme D. Synthetic progress towards ansalactam A (**II.1**) and divergolides C and D (**II.2** and **II.3**).

Chapter III: Synthetic Studies Toward Stephdiamine

The hasubanan alkaloids are a subgroup of the famous natural product class of morphine alkaloids, which have historically been an inspiration and challenge for synthetic chemists. Many natural products of the morphine family show strong biological activities. One of the members of the hasubanan subgroup is stephdiamine (**III.1**). Stephdiamine was isolated from *Stephania japonica* as a minor component in 1984 by Ibuka and co-workers.^[6] With its 15 carbon atom skeleton stephdiamine (**III.1**) is so far the only isolated representative of the *nor*-C-hasubanan alkaloids. Structurally, stephdiamine (**III.1**) consists of a pentacyclic core, bearing one benzene ring, two amine portions and a lactone functionality. This pentacyclic structure features four stereocenters, one of which is a benzylic all-carbon quaternary center and two are nitrogen containing tetrasubstituted carbon (NTC) centers (Scheme E).



Scheme E. Envisioned total synthesis of stephdiamine (**III.1**).

Inspired by the beautiful structure of **III.1** and the challenge to introduce two NTC centers, one of the projects of this PhD thesis was the development of a synthetic entry to **III.1** and its precursors. The precursor tetralone system **III.2** has been synthesized in just six synthetic steps,

including a C–H activation step.^[7] First attempts toward the assembly of enamine system **III.3** have been made (Scheme E).

ACKNOWLEDGEMENTS

I would like to thank Prof. Dirk Trauner for the tremendous opportunity to do my PhD in his group. I am especially thankful for the diverse and interesting projects I was allowed to work on in the last years and for the scientific freedom that was always provided to me and contributed the most to my learning. Most importantly, it is Dirk Trauners inspiration, enthusiasm and support (even in all personal living conditions) that made my PhD journey a memorable experience.

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ABBREVIATIONS

6-31G(d)	Pople type basis set (computational chemistry)
9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstrom
Ac	acetyl
α_D	specific rotation
ACP	acyl carrier protein
AD	asymmetric dihydroxylation
AHBA	3-amino-5-hydroxy-benzoic acid
AIBN	azobisisobutyronitrile
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
a. u.	Hartree atomic unit(s)
Aux	auxiliary
B3LYP	Becke, 3-parameter, Lee-Yang-Parr (DFT functional)
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOM	benzyl methyl ether
bp	boiling point
Bu	butyl
Bz	benzoyl
<i>c</i>	concentration
CAN	ceric ammonium nitrate
CCDC	Cambridge crystallographic data center
CDI	carbonyldiimideazole
CoA	coenzyme A
COSY	¹ H correlation spectroscopy (NMR)
d	day(s)
<i>d</i>	deutero
δ	chemical shift (NMR)
Δ	delta, difference
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

<i>de</i>	diastereomeric excess
deg	degree(s)
DFT	density functional theory
DH	dehydrogenase
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPEPhos	bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
<i>dr</i>	diastereomeric ratio
E	free energy
<i>E</i>	entgegen (opposite, <i>trans</i>)
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
<i>ee</i>	enantiomeric excess
EI	electron ionization
eq.	equivalent(s)
<i>er</i>	enantiomeric ratio
ER	enoyl reductase
ESI	electrospray ionisation (HRMS)
Et	ethyl
FA	formic acid
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond connectivity (NMR)
HMDS	hexamethyldisilazide
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HSP	heat shock protein(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence (NMR)
Hz	hertz (frequency)
<i>i</i>	iso (isomer)

IC ₅₀	half maximal inhibitory concentration
im	imidazole
Ipc	isopinocampheyl
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
<i>J</i>	coupling constant (NMR)
K	Kelvin
KR	ketoreductase
KS	ketosynthase
λ	lambda, wave length unit
<i>L</i>	litre(s)
L	any ligand
l	length
LAH	lithium aluminum hydride
LC	liquid chromatography
LDA	lithium <i>N,N</i> -diisopropylamide
m	meter(s)
<i>m</i>	meta
M	molar (<i>c</i>)
Me	methyl
min	minute(s)
MM3	molecular modeling 3 force field
MMFF	Merck Molecular Force Field
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
ms	molecular sieves
μ w	microwave
<i>n</i>	normal (isomer)
N	normal (<i>c</i>)
$\tilde{\nu}$	frequency (IR)
NADPH	reduced nicotinamide adenine dinucleotide phosphate
nd	not detected
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
nOe (NOE)	nuclear Overhauser effect (enhancement) (NMR)

NOESY	nuclear Overhauser enhancement spectroscopy (NMR)
NTC	nitrogen containing tetrasubstituted carbon
Nu	undefined nucleophile
<i>o</i>	ortho
<i>p</i>	para
PDE	phosphodiesterase
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation.
Ph	phenyl
pin	pinacol
PKS	polyketide synthase
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
ppm	parts per million (NMR)
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
PRCG	polak-riberie conjugate gradient (Macro Model)
py	pyridine
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
quant	quantitative(ly)
R	undefined substituent
RCM	ring closing metathesis
R _f	retention factor (TLC)
RNA	ribonucleic acid
RNaseL	2-5A-dependent ribonuclease L
rt	room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
<i>sec</i>	secondary
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
<i>t</i>	(<i>tert</i>) tertiary (isomer)
T3P	propylphosphonic anhydride
TBAB	tetra- <i>N</i> -butylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TE	thioesterase
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tos	<i>para</i> -toluenesulfonyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
t _R	retention time (HPLC, GC)
TS	transition state
UV	ultra-violet
W	watt
wt	weight
Z	zusammen (together, <i>cis</i>)

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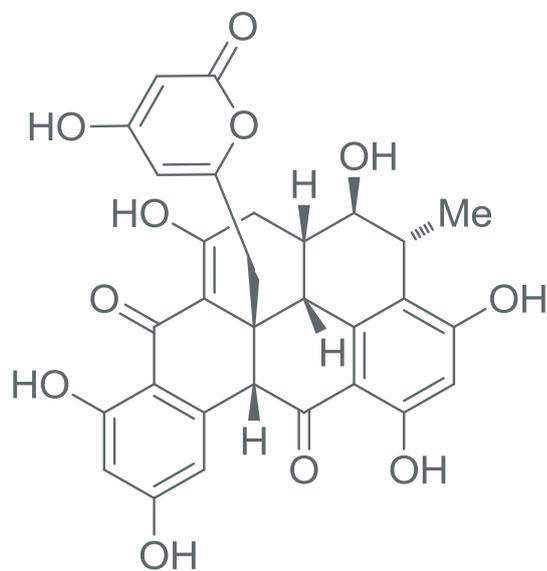
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CHAPTER I

'SYNTHETIC STUDIES TOWARD

A-74528'



CHAPTER I: SYNTHETIC STUDIES TOWARD A-74528

1. Introduction

1.1. Type II Polyketide Natural Products

Polyketides are a large and structurally diverse class of natural products, which are grouped together based on their biosynthetic relationship, strongly connected to classical fatty acid synthesis. Among them, many aromatic natural products formed by type II polyketide synthase (PKS) are known to possess pharmacologically important activities and some of them have been proven as clinically useful drugs.^[8] Thus, anthracyclines, such as doxorubicin (**I.5**) and daunorubicin (**I.6**), are effective chemotherapeutics used in the treatment of certain cancer types.^[9] Whereas tetracyclines and their derivatives, among them most prominent tetracycline (**I.7**) itself, form one of the most important classes of antibiotics (Figure I.1).^[10]

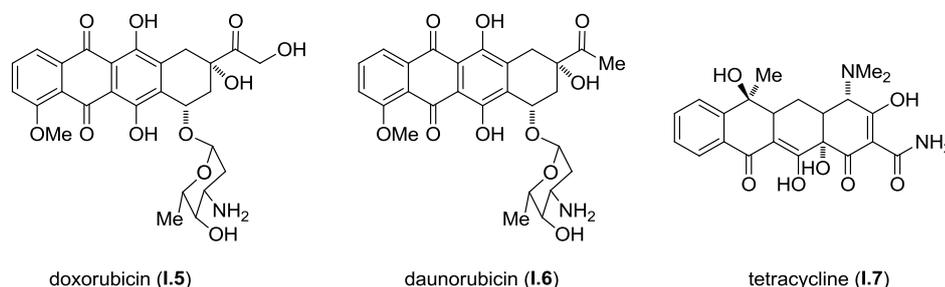
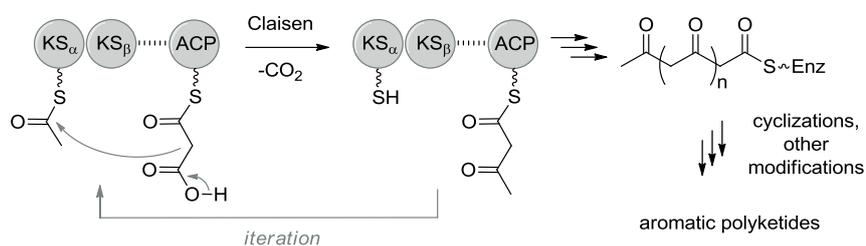


Figure I.1. Prominent type II polyketides: doxorubicin (**I.5**), daunorubicin (**I.6**) and tetracycline (**I.7**).

Polyketides of this type are derived from poly- β -keto chains formed by type II PKS. Similar to type II bacterial and plant fatty acid synthases, type II PKS is a complex of individual monofunctional proteins of iterative type. The 'minimal' iterative PKS consists of two ketosynthase units (KS_{α} and KS_{β}) and an acyl carrier protein (ACP) (Scheme I.1).^[8] In analogy to classic fatty acid synthesis, the key step in the formation of poly- β -keto chain is the decarboxylative Claisen condensation of malonyl-CoA extender units with an acyl starter, which is catalyzed by PKS. In this process, carbon dioxide attached to the malonyl-CoA unit activates the α -position and facilitates the decarboxylative Claisen condensation without the need for a strong base. In this transformation, the KS_{α} subunit of the 'minimal' type II PKS system catalyzes the Claisen condensation, whereas the KS_{β} subunit, lacking the active site cysteine residue, is believed to be responsible for the loading and decarboxylation steps, and

plays a major role in the control of the chain length of the synthesized polyketide chain.^[11] The third unit in the 'minimal' PKS system, ACP, serves as an anchor for the poly- β -keto chain. In contrast to fatty acid synthesis, the reductive enzymes, such as ketoreductases (KR), dehydrogenases (DH) and enoylreductases (ER) do not have to be present in the type II PKS. Unlike fatty acid synthesis, in which each elongation step is followed by a sequence of reductive transformations, the assembly of the reduction sequence for aromatic compounds is largely or even completely omitted. In the course of this transformation, a highly reactive β -carbonyl chain is provided, which is stabilized on the enzyme surface until the appropriate chain length is achieved. In some cases, distinct carbonyl functions can be reduced by a KR of type II PKS system, which is believed to control the first cyclization process of the β -carbonyl-chain. These very reactive intermediates possess various possibilities for intramolecular Claisen or aldol reactions. Therefore, the folding mode of the β -carbonyl-chain is crucial for the regioselectivity of post-PKS cyclizations promoted by various cyclases and aromatases, providing structurally diverse aromatic compounds (Scheme I.1). Interestingly, although the starter units in type II polyketide biosynthesis can vary, no report exists of an aromatic PKS employing chain extender unit other than malonyl-CoA.^[11-12]



Scheme I.1. Basic mechanism for the biosynthesis of aromatic polyketides by 'minimal' PKS synthase.

This process, with its broad variety of folding modes of the β -carbonyl chains, enables the specific formation of diverse aromatic structures. Due to the reactivity of the proposed poly- β -keto intermediates, as well as the involvement of a multi-enzyme complex rather than of a single enzyme in the polyketide biosynthesis, the investigation of this biosynthetic machinery is a challenging task. Since the reactive intermediates are difficult to isolate and characterize, in most cases one can only speculate about their origin. Nevertheless, on certain occasions, biomimetic total synthesis of type II polyketides can serve as a powerful tool to analyze proposed biosynthetic intermediates and to gain deeper insights into the steps involved in the biosynthesis of these natural products.

1.2. Structure, Isolation and Biological Properties

A-74528 (**I.1**) is an unusual type II polyketide, isolated in 2005 by Ogita and co-workers from *Streptomyces* sp. SANK 61196 during a screening for 2'-PDE inhibitors in microbial extracts (Figure I.2).^[1] It is described as a pale yellow solid, which is soluble in methanol and dimethylsulfoxide (DMSO). Despite several efforts, A-74528 could not be crystallized due to its instability. Thus, structural elucidation of the molecule was performed using ¹H- and ¹³C-NMR spectroscopy as well as 2D-NMR experiments, among them the 2D-INADIQUATE technique.^[1]

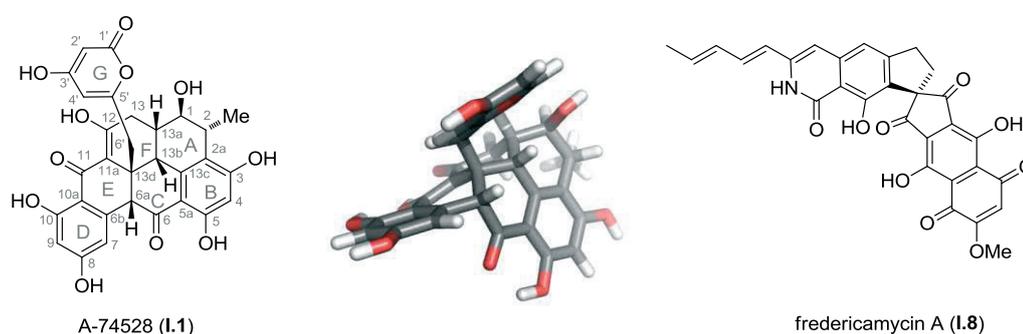


Figure I.2. Structures and relative stereochemistry of fredericamycin (**I.8**) and A-74528 (**I.1**), as well as the MM3 force field model of A-74528.^a

Structurally, A-74528 (**I.1**) is one of the most complex and largest aromatic polyketides known. It consists of a hexacyclic core with an appendent α -pyrone moiety. Its unprecedented carbon skeleton contains two acyl resorcinol motifs, which are typical of type II polyketides, flanking a perhydropyrene core. Unusual for a type II polyketide natural product is the fact that the tetracyclic core features six contiguous stereocenters, one of which is quaternary. In addition, the C1-secondary alcohol on ring A is present in a position not typical for a polyketide, a fact that needs to be accounted for in any proposed biosynthetic pathway. With the exception of fredericamycin A (**I.8**), A-74528 is the only isolated C-30 type II polyketide so far (Figure I.2).

In terms of its biological profile, A-74528 (**I.1**) was found to activate the 2-5A interferon system, which is considered to be one of the major pathways involved in anti-tumor and anti-viral response in human cells.^[13] The enzyme RNaseL, which degrades viral and cellular RNA upon activation and thus shuts down the protein biosynthesis in viral cells, is mobilized by binding 2',5'-oligoadenylates (2-5A). Since the action of 2-5A can be deactivated by 2',5'-specific phosphodiesterase (2'-PDE), overabundance of 2'-PDE in tumor and viral cells prevents

^aThe nomenclature of the A-74528 ring system was adopted from Ogita and co-workers. The MM3 force field calculations were performed using MacroModel (Version 9.0): MM3* FF/gas phase/PRCG/500 steps.

their apoptosis. A-74528 (**I.1**) showed an inhibitory effect on human 2'-PDE with an IC₅₀ value of 34 µg/ml, possessing dose-dependent reduction of viral replication without any cytotoxic effects in the absence of a viral infection. This is very promising, since the ability of viruses to take control over host cells by incorporating their own RNA into the genome of the host is one of the challenges in the design of selective antiviral drugs, as they should be able to specifically remold virus replication with no or minimal effect on host cells. Thus, especially in the case of multidrug resistance, new drugs with novel mechanisms of action are required. Hence, the capacity of A-74528 to interrupt the action of 2'-PDE provides a potential therapy against cancer and viral infections.^[1,13]

1.3. Project Aims

As highlighted above, the biomimetic synthesis of type II polyketide natural products can provide useful information about key steps in the actual biosynthetic pathway of a particular natural product. Inspired by the intriguing and complex structure of A-74528 (**I.1**), the speculations about its biosynthesis, and the fact that no synthetic approach toward A-74528 (**I.1**) has been reported to date, we found this molecule a perfect target to test the limits of biomimetic synthesis. It was our aim to explore whether a complex polyketide pathway of a C-30 polyketide like **I.1** could be emulated in the laboratory. Thus, the goal of this project was to devise and execute a biomimetic synthesis of A-74528. To establish this synthesis, a development of new chemistry including a, as we suppose biomimetic, Michael-Michael cascade was essential. In addition, we planned to contribute to the elucidation of the biosynthetic pathway of the natural product by isolating, characterizing and analyzing our synthetic intermediates during the synthesis of A-74528 and using them for the identification of biosynthetic precursors.

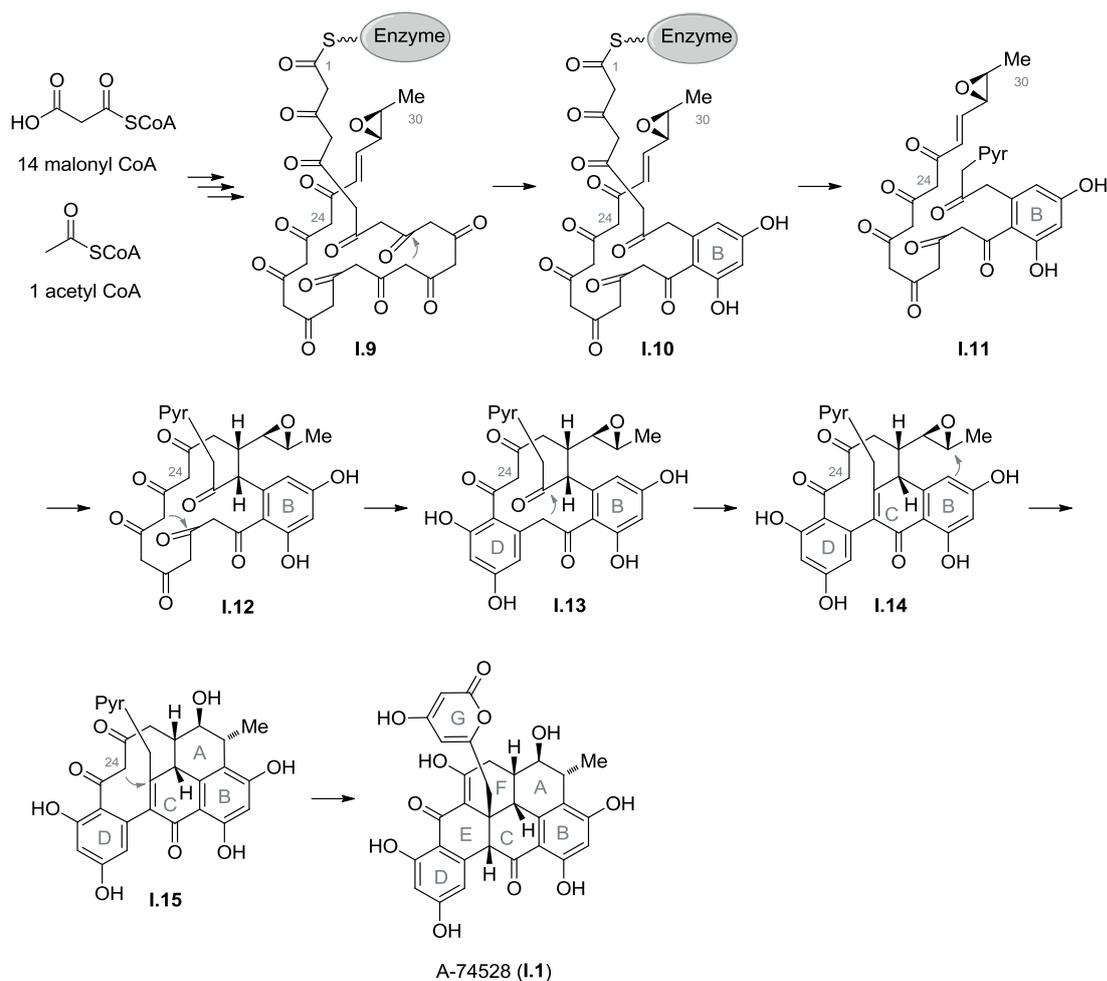
The synthetic studies toward A-74528 as well as the discoveries and challenges of the envisioned synthetic pathway are discussed in detail in the next section.

2. Background

2.1. Proposed Biogenesis of A-74528

The described unique biological profile as well as its structural novelty aroused interest in the biosynthesis of A-74528 (**I.1**).^[2] Its highly oxidized polyphenolic structure suggests its formation by a type II PKS system, incorporating a C-30 carbon chain and unique oxidation and cyclization processes. In 2010, Khosla and co-workers published their extensive work on the mechanistic analysis of the biosynthesis of A-74528 (**I.1**).^[2] Using biosynthetic engineering techniques, such as cloning and sequencing of the complete A-74528 gene cluster as well as functional expression in a heterologous *Streptomyces* host, they were able to characterize the type II PKS genes responsible for A-74528 biosynthesis. Interestingly, the A-74528 PKS genes possessed high end-to-end sequence similarity to their fredericamycin A analogues, suggesting that A-74528 is a pentadecaketide. Thus far, fredericamycin A (**I.8**) and A-74528 (**I.1**) are the only known natural products incorporating a C-30 carbon chain in their biosynthesis, which is the longest polyketide chain length known to be constructed by a type II PKS system. Although fredericamycin A is structurally unrelated to A-74528, Khosla and co-workers were able to show that the A-74528 gene cluster can produce either of the two natural products **I.1** or **I.8**, rectifying the generally accepted 'one cluster one antibiotic' paradigm.^[2]

Based on their results, the Khosla group was able to propose a biosynthetic pathway responsible for the formation of A-74528 (**I.1**) (Scheme I.2). Specifically, they suggest that the unusual oxygenation pattern in A-74528 results from an epoxide-opening reaction. Assuming that the epoxide had been installed at the C28-C29 bond of the C-30 chain at the earliest stages of the biosynthesis, the enzyme bound intermediate **I.9** is believed to serve two purposes. On one hand, presence of an epoxide in **I.9** can be responsible for the regio- and stereocontrol of the first cyclization process in the biosynthesis. On the other hand, the epoxide could act as a recognition element to distinguish between the two metabolic pathways to fredericamycin A and A-74528. Khosla supposes that, following epoxidation, the carbon chain undergoes six sequential cyclization reactions, first forming the B ring of the natural product in the enzyme bound intermediate **I.10**. After the formation of the α -pyrone moiety in **I.11**, a closure to a 16-membered macrocycle **I.12** via a Michael reaction occurs, at which point the ring D in **I.13** is assembled via an aldol condensation process. Thereafter, aldol condensation provides biaryl system **I.14**, which finally undergoes an epoxide-opening process to intermediate **I.15**. In the final step of the proposed biosynthesis, a Michael addition affords the natural product (Scheme I.2).^[2]

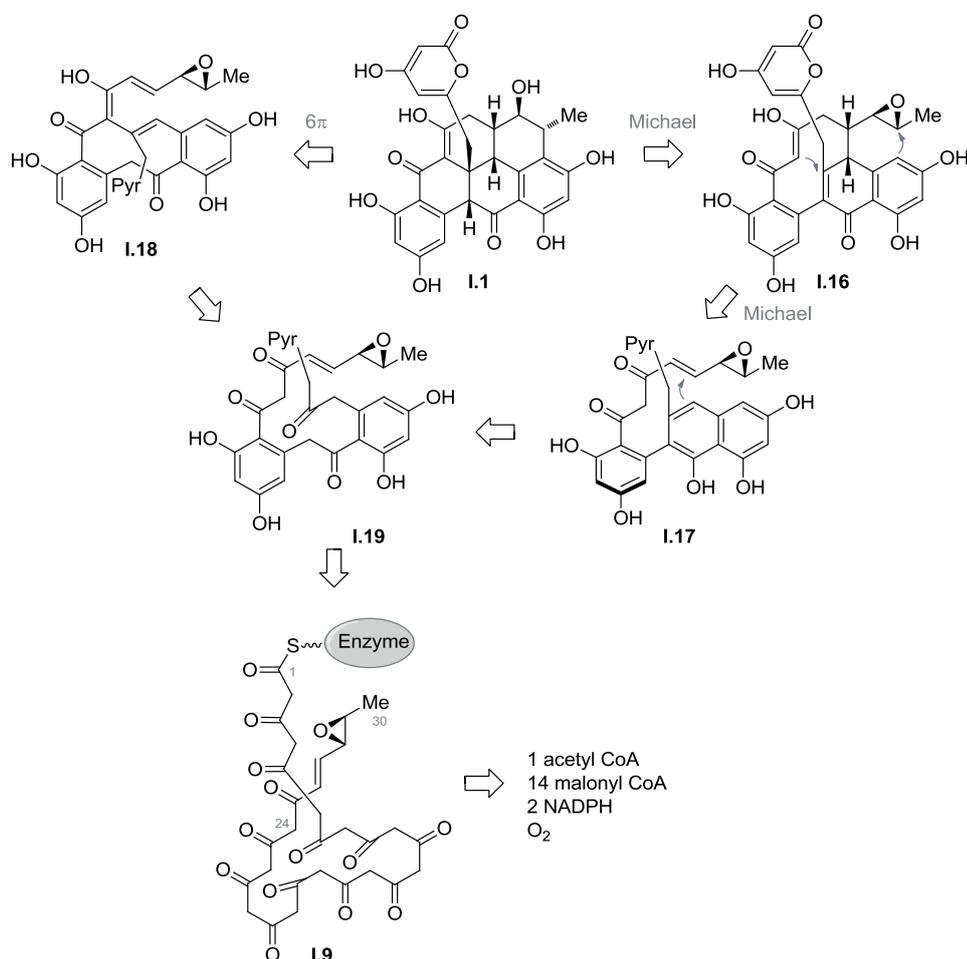


Scheme I.2. Mechanism of the biosynthesis of A-74528 proposed by Khosla and co-workers.^{b[2]}

Although Khosla's group was able to characterize individual enzymes involved in the biosynthesis of **I.1**, it is still not clear which precise enzymes of the multi-enzyme complex are involved in the specific tailoring and cyclization steps. This leaves room for speculation on both, the exact biosynthetic mechanism and the sequence of the cyclization processes of the C-30 epoxy polyketide **I.9**. We believe that it is also conceivable that A-74528 (**I.1**) stems directly from a strained enone **I.16**, which engages in a transannular Michael addition and epoxide opening (Scheme I.3). Compound **I.16** could in turn arise from a dearomatizing intramolecular Michael addition involving aryl naphthalene **I.17**. Alternatively, A-74528 (**I.1**) could also arise from a disrotatory 6π -electrocyclization of intermediate **I.18**, followed by conjugate addition and attack on the epoxide. Naphthalene **I.17** as well as triene **I.18** could both be formed by intramolecular condensation from the partially aromatized polyketide **I.19**, which we consider to be a key intermediate in both pathways. However, as intermediate **I.19** has the potential to engage in a number of cyclization modes, proposed by Khosla and us, the exact sequence of

^bScheme I.2 was assembled based on the publication of Zaleta-Rivera *et al.*: K. Zaleta-Rivera, L. K. Charkoudian, C. P. Ridley, C. Khosla, *J. Am. Chem. Soc.* **2010**, *132*, 9122–9128.

cyclization events remains to be delineated. The question is whether this intermediate first forms a 6-, 10-, 12-, or 14-membered ring. Finally, compound **I.19** itself could originate from epoxy polyketide **I.9**, assembled by the type II PKS from acetyl and malonyl coenzyme A (Scheme I.3).^c



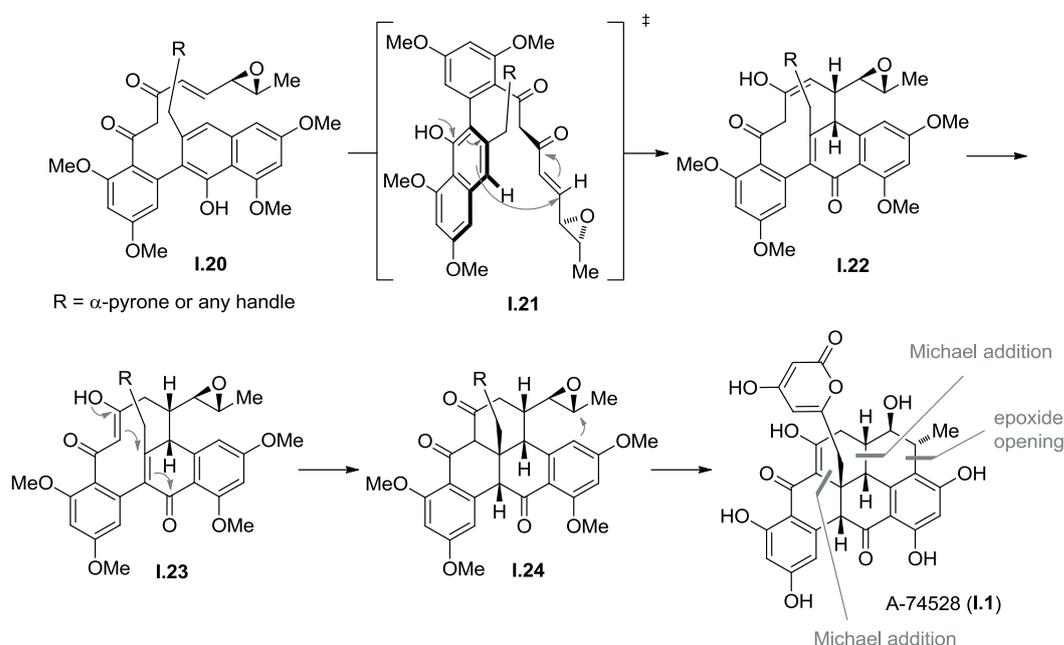
Scheme I.3. Alternative biosynthetic analysis of A-74528.

The enormous chain length of the biosynthetic polyketide precursor **I.9**, its flexibility, as well as the variety of potential folding modes of the C-30 carbon chain and, thus, cyclization possibilities of this highly reactive intermediate, pave the way for further speculations on the exact formation of this natural product. This could potentially involve myriad of stepwise and/or concerted cyclization processes, which will not be discussed herein. The focus of our synthetic approach was centered on the biosynthetic considerations involving the double Michael reaction strategy, as the described dearomatizing reaction cascade was fascinating to us due to its challenging nature (Scheme I.3).

^cPart of this discussion was already published in: A. Hager, D. Mazunin, P. Mayer, D. Trauner, *Org. Lett.* **2011**, *13*, 1386–1389.

2.2. Strategy and Retrosynthetic Analysis^d

Based on the biosynthetic considerations discussed before (*vide supra*, Chapter 2, Section 2.1), the synthetic strategy we have chosen involves an intramolecular Michael-Michael addition step of biaryl intermediate **I.20**, which we consider to be a key intermediate in the biosynthesis of A-74528 (**I.1**) (Scheme I.4). Due to the atropisomerism in biaryl **I.20**, two diastereomeric transition states are possible in the first dearomatizing Michael addition step of the electron-rich naphthol system. The corresponding transition state **I.21** (here chosen arbitrary) should result in the formation of only one diastereomer **I.22**. The completion of the double Michael sequence would provide the partially dearomatized pentacyclic compound **I.24**, which upon epoxide opening will furnish the skeleton of the natural product (Scheme I.4).



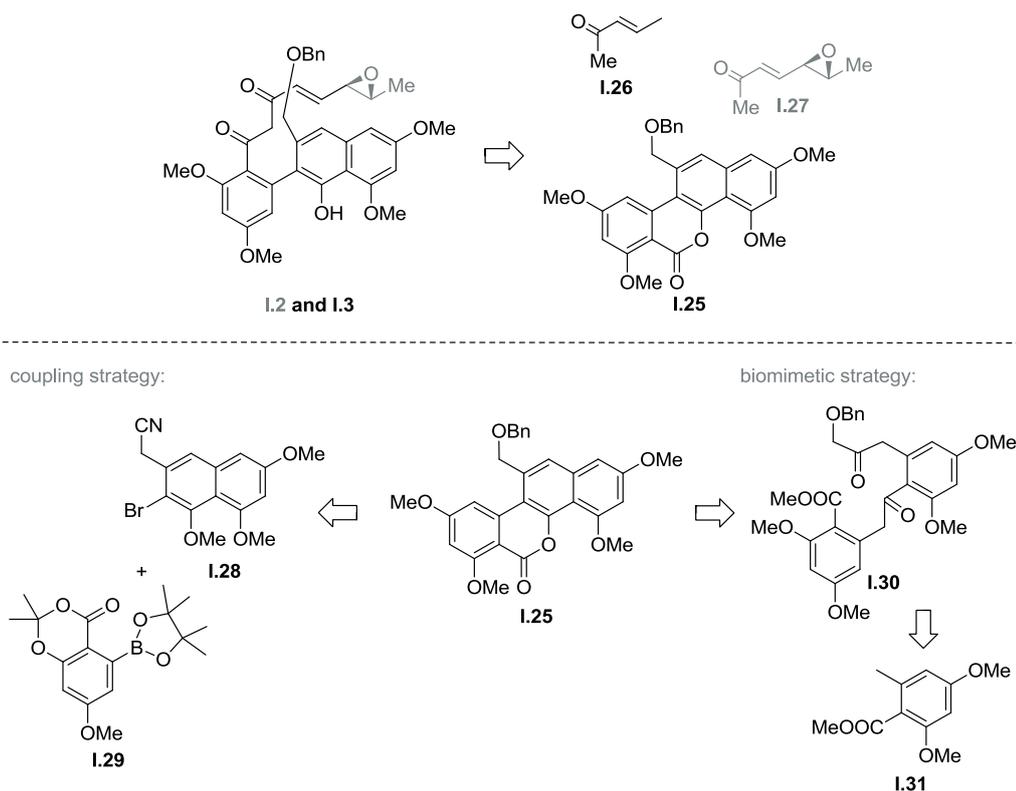
Scheme I.4. Envisioned key steps in the synthesis of A-74528 (**I.1**).

This synthetic approach toward A-74528 (**I.1**) is both novel and challenging in nature. Not only does it involve a dearomatizing Michael addition step, which is scarcely represented in literature and, to the best of our knowledge, has not been applied in total synthesis so far. In addition, it also comprises the epoxy-diketo structure **I.20** as one of the key intermediates, the reactivity and conformation of which is difficult to estimate.

One of the major challenges posed by this synthetic strategy is the assembly of the biaryl system **I.2**, analogous to **I.20**, or its less complex analog **I.3** (Scheme I.5). Both systems can be retrosynthetically traced back to lactone **I.25** and the corresponding side chains **I.26** and **I.27**.

^dPart of this discussion was already published in: A. Hager, D. Mazunin, P. Mayer, D. Trauner, *Org. Lett.* **2011**, *13*, 1386–1389.

At this stage, we envisaged two synthetic strategies toward lactone **I.25**. In the first approach we planned to address the lactone assembly using advanced metal-mediated biaryl coupling strategy, wherein lactone **I.25** could be derived from bromonaphthalene system **I.28** and the requisite aromatic coupling partner **I.29**. Alternatively, in our second approach, we envisaged to construct lactone **I.25** using a biomimetic sequence, which involves several condensation reactions. In this context, lactone **I.25** can arise from linear diketone **I.30**, which in turn can be traced back to the orsellinic acid derivative **I.31** (Scheme I.5).



Scheme I.5. Retrosynthetic strategy.

Both strategies conceal their own perils. Firstly, the envisioned Suzuki-Miyaura cross coupling between naphthalene **I.28** and boronic ester **I.29** could pose a challenge due to the steric demand of the coupling partners providing an *o,o'*-substituted biaryl system as the coupled product. In addition, the electron-rich nature of both substrates **I.28** and **I.29** could complicate oxidative addition, the critical initial step in palladium-catalyzed coupling reactions. In the case of the biomimetic strategy based on condensation chemistry, problems can arise as a result of the highly reactive nature of polyketide intermediates such as diketone **I.30**, demanding sophisticated control of the selectivity in the envisioned cyclization reaction.

The detailed results of both synthetic approaches are described in the following chapter.

3. Results and Discussion^e

3.1. Cross-Coupling Strategy

Initially, we focused our research on the proposed transition-metal-catalyzed cross-coupling strategy. This approach calls for the independent construction of the two Suzuki-Miyaura coupling partners, naphthalene **I.28** and boronic ester **I.29** (Figure I.3).

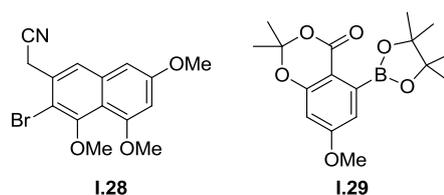


Figure I.3. Building blocks involved in the cross coupling strategy.

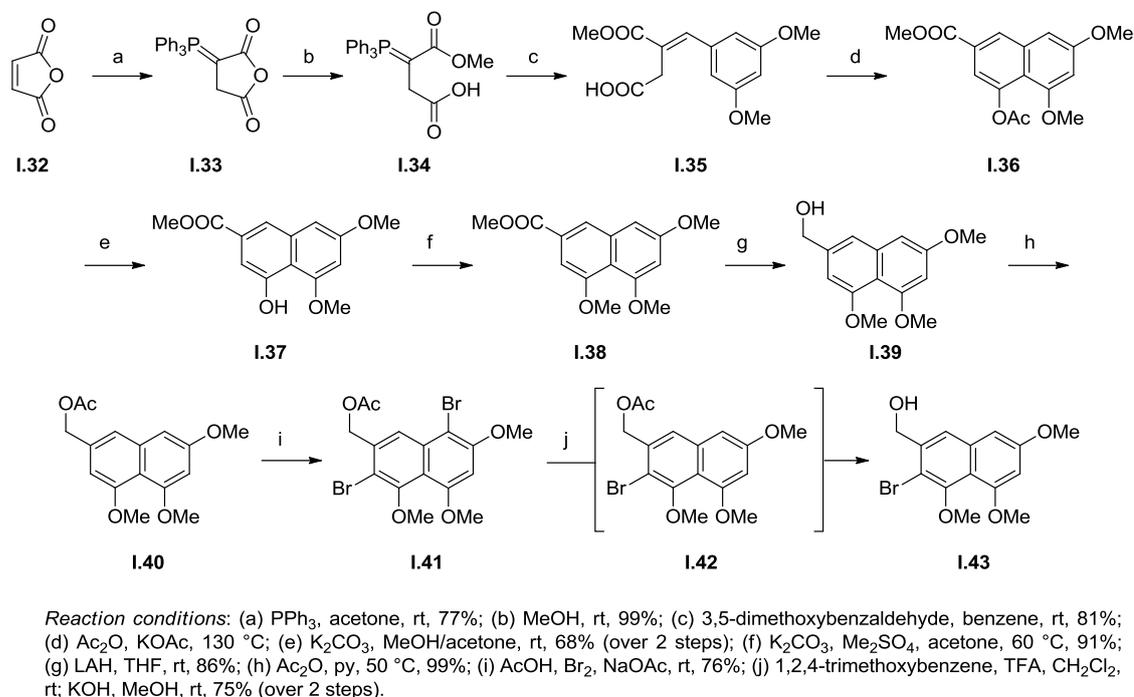
3.1.1. Assembly of the Aromatic Coupling Partners

The synthesis of coupling partners **I.28** and **I.29**, as outlined in the retrosynthetic analysis (*vide supra*, Scheme I.5) utilizes well-established protocols in the first instance. Thus, the synthesis of the naphthalene **I.28** started with maleic anhydride **I.32**, which underwent a Michael addition reaction with triphenylphosphine and, following deprotonation, provided the ylen **I.33** (Scheme I.6).^[14] Regioselective opening of anhydride **I.33** with methanol afforded monomethyl ester **I.34**. It is likely, that the electron-withdrawing effect of the phosphorous substituent increases the electrophilicity of the adjacent carbonyl group and results in the observed regiochemical outcome. The ylen **I.34** was subjected to Wittig conditions with 3,5-dimethoxybenzaldehyde as the reaction partner, providing the unsaturated acid **I.35** as a single *E*-isomer.^[15]

Next, acid **I.35** underwent a smooth intramolecular Friedel-Crafts acylation to naphthalene **I.36**. At this stage, ester hydrolysis furnished naphthol **I.37**, which was then protected as methyl ether, giving permethylated naphthalene **I.38**. Following reduction of the methyl ester and acetylation of the resultant benzylic alcohol **I.39**, naphthyl intermediate **I.40** was dibrominated, providing a highly substituted naphthalene system **I.41**. It is plausible that the first bromination occurs at the more electron-rich ring, bearing two methoxy substituents, and that bromination at the kinetically favored position next to the benzylic acetate unit then follows.^[16] At this point, in

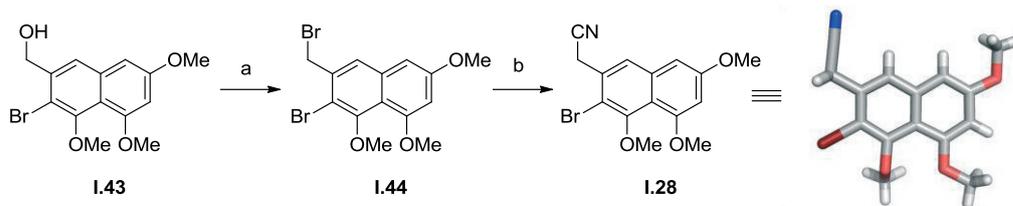
^ePart of this work was already published in: A. Hager, D. Mazunin, P. Mayer, D. Trauner, *Org. Lett.* **2011**, *13*, 1386–1389.

order to gain entry to the required anchor for the envisioned Suzuki-Miyaura coupling, a regioselective debromination reaction had to be performed. This was achieved using the more electron-rich 1,2,4-trimethoxybenzene as the reagent, which under acidic conditions undergoes a bromine transfer reaction with dibromide **I.41** via an electrophilic aromatic substitution process, also known as a variant of the halogen dance reaction.^[16] Under these conditions, an inseparable mixture of monobrominated **I.42** and 1-bromo-2,4,5-trimethoxybenzene was obtained, the separation of which was easily achieved after the removal of the acetate portion, providing literature known benzylic alcohol **I.43** (Scheme I.6).^[17] Overall, the synthetic sequence was performed on gram scale according to the procedures published by Greene and coworkers in 2010, providing the desired naphthalene portion in a high 19% overall yield in 11 lengthy, yet practical steps.^[17-18]



Scheme I.6. Synthesis of the naphthalene system **I.43**.

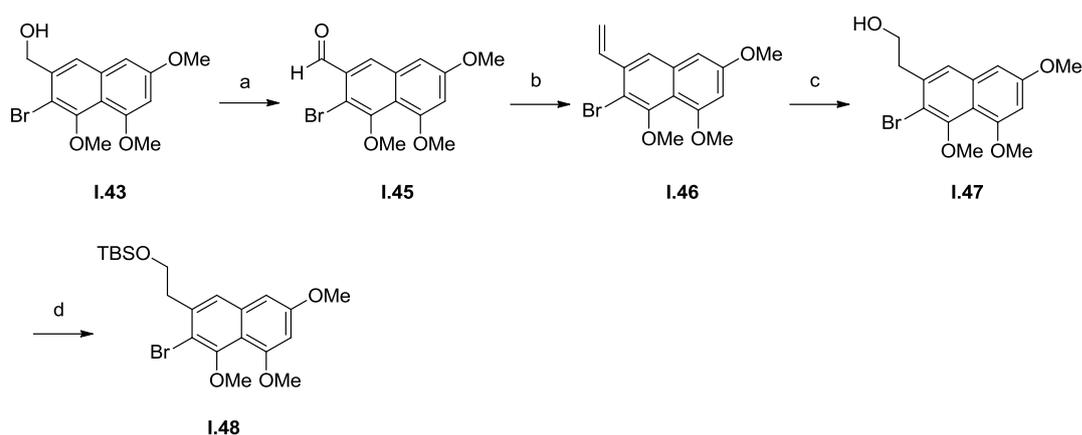
With **I.43** in hand, the synthesis of the naphthalene coupling partner **I.28** was completed in two steps (Scheme I.7). In this context, benzylic alcohol **I.43** was converted under Appel conditions to dibromide **I.44** in excellent yield. This intermediate was then transformed to the corresponding nitrile **I.28**, which could serve as a handle for the construction of the α -pyrone system present in the A-74528 structure. In addition to extensive NMR analysis, the structure of nitrile **I.28** was conclusively confirmed by means of X-ray crystallography.



Reaction conditions: (a) PPh_3 , CBr_4 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 89%; (b) KCN , EtOH , H_2O , $75\text{ }^\circ\text{C}$, 99%.

Scheme 1.7. Completion of the synthesis of naphthalene coupling portion **1.28** and its X-ray structure.

In order to be able to perform more extensive and rigorous Suzuki-Miyaura cross-coupling studies, we prepared analogs of naphthalene **1.28**, which are also suitable precursors for A-74528 synthesis (Scheme 1.8). Towards this goal, benzylic alcohol **1.43** was converted to the corresponding aldehyde **1.45** via a Dess-Martin oxidation. Wittig olefination of **1.45** furnished alkene **1.46**, which was hydroborated to alcohol **1.47**. TBS-ether **1.48** was finally obtained in excellent yield by means of a simple silyl protection.



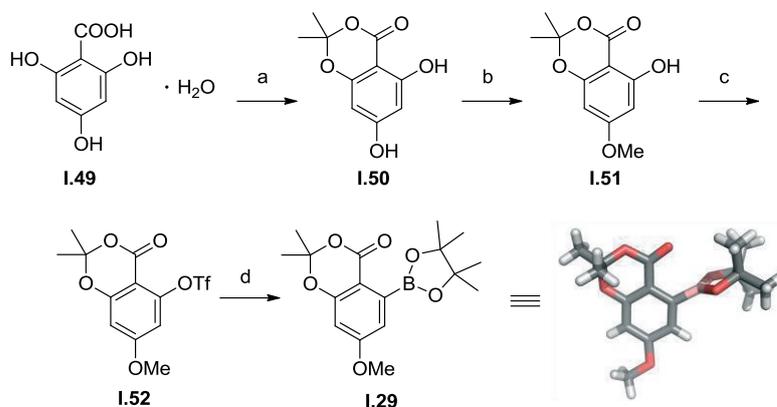
Reaction conditions: (a) DMP, CH_2Cl_2 , rt, 87%; (b) $\text{Ph}_3\text{PCH}_3\text{Br}$, NaHMDS, THF, rt, 97%; (c) 9-BBN, THF, rt, 71%; (d) TBSCl, im, CH_2Cl_2 , rt, 99%.

Scheme 1.8. Synthesis of naphthalene derivatives **1.47** and **1.48**.

The second coupling partner, boronic ester **1.29**, was obtained from trihydroxybenzoic acid **1.49** following a known protocol (Scheme 1.9).^[19] After formation of acetal **1.50**, the less sterically hindered alcohol was protected as a methyl ether under Mitsunobu conditions, providing hydroxybenzene **1.51**. Treatment of **1.51** with triflic anhydride in the presence of pyridine then afforded aryl triflate **1.52** in excellent yield.^[19c,19d] With the *ortho*-substituted, and thus sterically demanding, triflate **1.52** in hand, the synthesis of boronate **1.29**^f was accomplished using a Masuda coupling protocol^[19a,19b] with pinacolborane as the coupling partner. In spite of its high instability, boronic ester **1.29** could be crystallized and resolved by

^fAlthough the Suzuki-Miyaura coupling was performed several times, the obtained yields were always lower than those reported in the literature: M. Altenmöller, J. Podlech, D. Fenske, *Eur. J. Org. Chem.* **2006**, 1278–1284. One explanation for this observation could be the high instability of boronate **1.29** under column chromatography conditions.

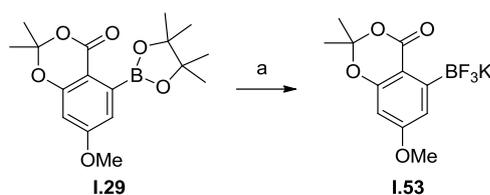
X-ray crystallographic analysis. The performed X-ray crystallography confirmed the supposed structure of **I.29**, which was proposed based on NMR (Scheme I.9).



Reaction conditions: (a) TFA, TFAA, acetone, rt, 34%; (b) PPh_3 , MeOH, DIAD, THF, rt, 86%; (c) Tf_2O , py, $-10 \rightarrow 0$ °C, 92%; (d) pinacolborane, NEt_3 , $\text{Pd}(\text{PPh}_3)_4$, 1,4-dioxane, 75 °C, 45%.

Scheme I.9. Synthesis of boronic ester **I.29** and its X-ray structure.

As pointed out in several publications by Molander and co-workers,^[20] the stability of a boron-containing coupling partner can be increased by converting it to the corresponding trifluoroborate, a protected equivalent of the appropriate boronic acid. The use of trifluoroborates simplifies the purification process, as they can be easily crystallized in the most cases. In addition, trifluoroborates can tolerate harsher conditions than the corresponding boronic acids. In the presence of water, reaction intermediates similar to those generated by boronic acid precursors are formed. With this in mind, boronic ester **I.29** was treated with potassium bifluoride and, pleasingly potassium trifluoroborate **I.53** was obtained in high yield (Scheme I.10).



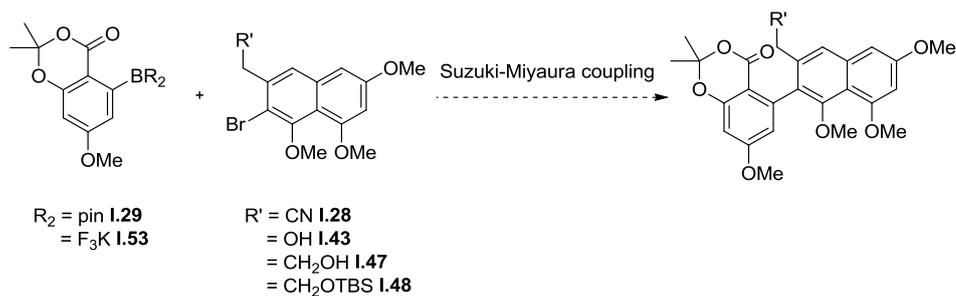
Reaction conditions: (a) KHF_2 , MeOH, H_2O , rt, 94%.

Scheme I.10. Synthesis of trifluoroborate **I.53**.

With both coupling partners in hand, studies of the projected Suzuki-Miyaura biaryl coupling could be performed, which is described in the next section.

3.1.2. Suzuki-Miyaura Coupling

One of the most powerful methods in organic chemistry for C-C bond formation is the Suzuki-Miyaura coupling reaction. It possesses a broad substrate scope and wide tolerance for functional groups. Thus, we envisioned to achieve the synthesis of the desired biaryl system *via* a Suzuki-Miyaura coupling of boronic ester **I.29**, or the corresponding trifluoroborate **I.53** with bromide **I.28** or its derivatives **I.43**, **I.47** or **I.48** (Scheme I.11).



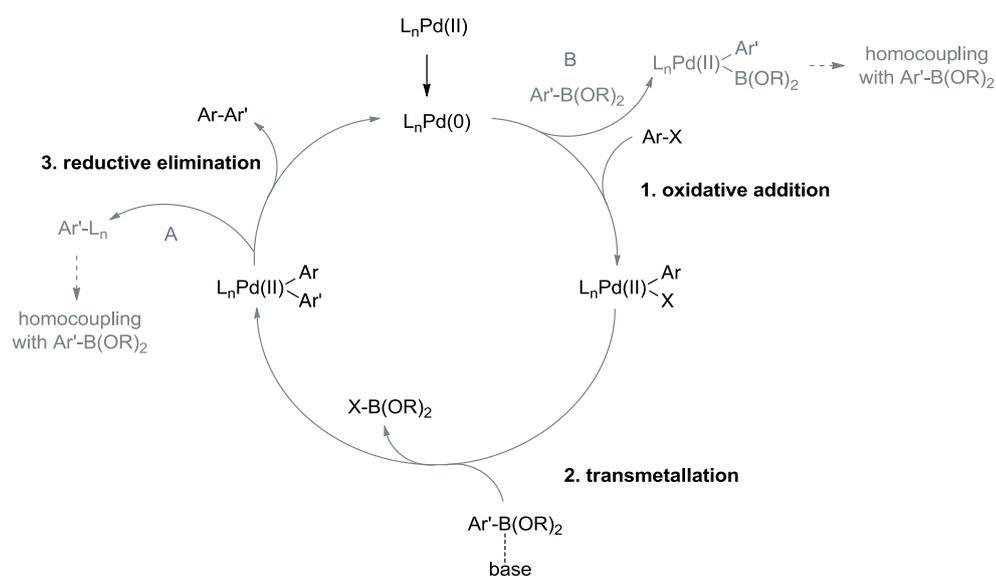
Scheme I.11. Envisioned Suzuki-Miyaura coupling.

The mechanism of this coupling reaction is well established and consists of three main steps: 1. Oxidative addition of an organo-halide or triflate to a palladium(0) species; 2. Transmetalation step between the organo-boron compound and the palladium II intermediate; and finally 3. Reductive elimination, delivering the desired product and regenerating the palladium(0) catalyst (Scheme I.12).^[21] Several criteria can have a huge impact on the kinetics of each individual step in the mechanism, which need to be accounted for in the envisioned aryl-aryl Suzuki-Miyaura coupling process.

Oxidative addition is considered to be the rate determining step in the catalytic cycle. In this step, palladium is oxidized and the substrate reduced. Therefore, organohalides with electron-donating substituents undergo oxidative addition more slowly than those with electron-withdrawing groups.^[21a] As bromide **I.28** and its derivatives **I.43**, **I.47** and **I.48** are electron-rich coupling partners, steps had to be taken to enhance the rate of the oxidative addition. This is possible, for example, by employing palladium complexes with sterically demanding ligands, such as DPEphos^[22], RuPhos^[23], SPhos^[23-24], *Pt*-Bu₃^[21e], PEPPSI^[25]-ligands and others^[21d,21e,24,26], which were shown to be highly reactive towards the oxidative addition due to the faster formation of the coordinatively unsaturated reactive palladium(0) species.^[21d] Due to the aromatic nature of the coupling partner **I.28**, competing β -hydride elimination following oxidative addition did not pose any danger.

Bulky ligands also have favorable effect on metal-metal exchange and reductive elimination step kinetics.^[21d,21e] Although much is known about the mechanistic details of

oxidative addition, less information is available about the transmetallation step. This may be caused by the high dependence of the rate of this step on the organometallic reagent used and the reaction conditions employed. In general, organic groups located on boron are weakly nucleophilic and undergo the transmetallation step only slowly. The rate of transmetallation reaction can be enhanced by addition of bases, such as Na_2CO_3 , NEt_3 , NHCO_3 , Cs_2CO_3 , Ti_2CO_3 and other, which increase the nucleophilicity of the organic group *via* coordination to boronic esters and/or deprotonation of boronic acids.^[21a] Hence, the choice of an appropriate base is essential for the success of the desired coupling.



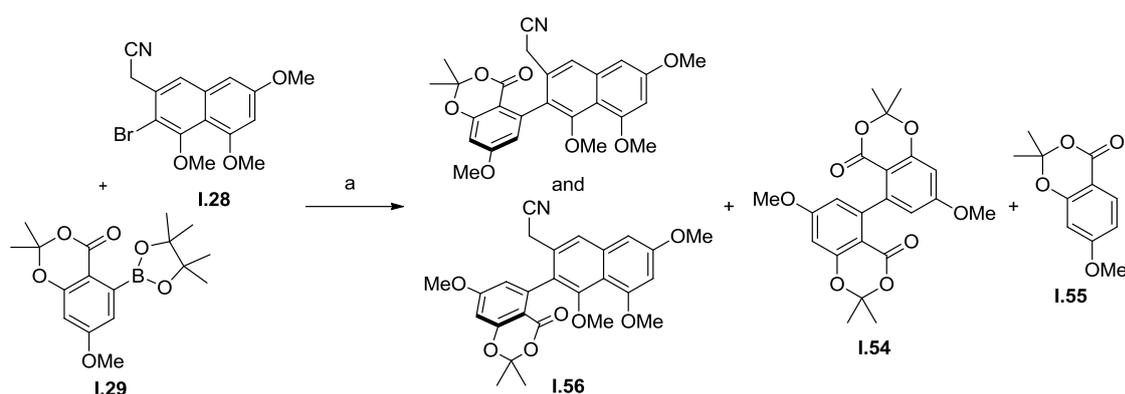
Scheme I.12. Simplified mechanism of aryl-aryl Suzuki-Miyaura reaction with possible side reactions A and B.

Furthermore, steric hindrance of both coupling partners can have an enormous decelerating impact on transmetallation, resulting in low yields of the product.^[21a,21d] This is especially true for *o*-substituted arylboronic species, such as boronic ester **I.29** and trifluoroborate **I.53**. Having sterically hindered coupling partners **I.28** and **I.29** and anticipating the formation of sterically hindered *o,o,o'*-biaryl system, we had to reckon with the formation of byproducts, such as homocoupled biaryls. In many cases undesired homocoupling of either two aryl halides or two aryl boronic species may compete with the formation of the desired cross-coupled product. In particular, electron-donating substituents on the aryl boronic species, as in boronic ester **I.29**, enhance the aryl-aryl exchange between the palladium(II) species and its phosphine ligands. This process results in the formation of phosphine-substituted aryl species, which in turn can undergo an oxidative addition and lead to homocoupling reaction (Scheme I.12, side reaction A).^[21a,21e] The formation of biaryls by homocoupling of aryl boronic species can also be induced by concentration effects. In the case of low concentration of aryl halide, the reactive palladium

species may undergo oxidative addition with aryl boronic species, also leading to homocoupling as the side reaction (Scheme I.12, side reaction B).^[27]

We were less concerned about the reductive elimination step of the coupling, which is known to be fast in the case of biaryl synthesis due to presumed π -orbital participation during the bond-forming process. Finally, we anticipated that aqueous reaction, typical in a Suzuki-Miyaura coupling, could also promote the competitive hydrolytic deboronation process potentially necessitating anhydrous conditions.

As explained, linkage of the two components through Suzuki-Miyaura coupling required careful optimization. In spite of a wide screening of reaction conditions, different ligands (e.g. PPh_3 , DPEPhos, RuPhos, PEPPSI-*i*-Pr, dba, dppf) and bases (e.g. K_3PO_4 , CsCO_3 , $\text{KO}t\text{-Bu}$, $\text{Ba}(\text{OH})_2$, NEt_3 , K_2CO_3 ; see Table IV.1, experimental section) and altering of the coupling partners, we were not able to achieve the formation of the desired *o,o,o'*-biaryl product. In most cases, due to the reasons described above, only the homocoupled product **I.54** of aryl boronic species **I.29** and protodeboronated benzene **I.55** were isolated. The isolation of the protodeboronated species led to assumption that the transmetallation step had indeed taken place however, no product could be detected. Eventually, we settled on a protocol that involved microwave irradiation and tetrakis(triphenylphosphine) palladium(0) as catalyst. To our delight, despite the aqueous nature of these conditions, **I.28** could be coupled with **I.29** to afford biaryl **I.56** as a racemic mixture of atropisomers in good yield (Scheme I.13). In addition to the main product, a small amount of homocoupled product **I.54** and deboronated benzene **I.55** was formed during the reaction.



Reaction conditions: (a) $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , TBAB, toluene/water, μ -wave, 120°C , 200 W, **I.56**: 68%, **I.54**: 26%, **I.55**: 16%.

Scheme I.13. Successful Suzuki-Miyaura coupling under μ -wave conditions.

The use of trifluoroborate **I.53** instead of the boronic ester **I.29** as the coupling partner did not decrease the yield of the undesired protodeboronation product and, in fact, resulted in diminished isolated yields of biaryl **I.56** (not shown).^[3] This successful coupling is one of the

few examples of the formation of a triply *o,o,o'*-substituted biaryl bond in acceptable yield through microwave forced transition-metal catalyzed cross coupling.^[28]

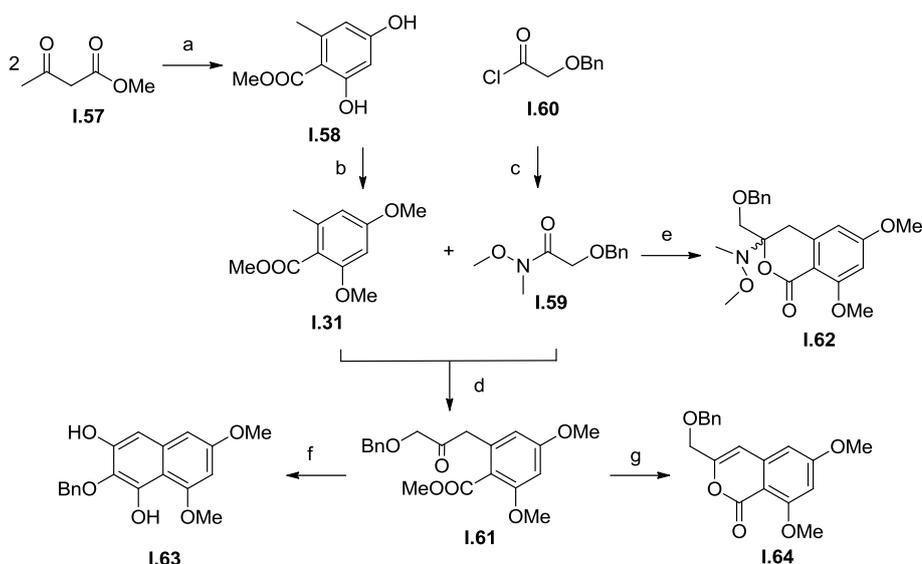
It is widely known that microwave irradiation can be superior to conventional heating protocols.^[29] As a result of shorter reaction times, application of microwave irradiation conditions limits the decomposition of reaction partners and/or products. It is likely that the dissociation of a phosphine ligand from the palladium center is accelerated under microwave irradiation. This results in faster formation of the unsaturated reactive palladium(0) species, thus favoring the oxidative addition step and facilitating the catalytic cycle. Water as a reaction medium is often an excellent solvent for microwave-induced transformations, and we also found that a mixture of water and toluene as solvent, together with catalytic amounts of *tetra-N*-butylammonium bromide (TBAB) as phase transfer catalyst were efficient reaction conditions. All attempts with other naphthalene derivatives, such as alcohols **I.43** and **I.47** as well as TBS-ether **I.48**, provided only trace amounts of the corresponding biaryl systems.

Although we were able to find a satisfactory solution for the cross coupling, we nevertheless realized that this synthetic approach was too long and unpractical to support a total synthesis of A-74528 (**I.1**), particularly in light of the subsequent functionalization necessary to complete the synthesis. Therefore, we explored an alternative pathway, which relied on the proposed biosynthesis and involved sophisticated condensation chemistry.

3.2. Condensation Strategy

The second approach to the desired biaryl system commenced with the application of well-established condensation chemistry of methyl acetoacetate (**I.57**) (Scheme I.14).^[30] Upon double deprotonation of methyl acetoacetate with sodium hydroxide and *n*-butyl lithium, the corresponding anion underwent a condensation reaction with a second equivalent of methyl acetoacetate forming, under strongly acidic conditions, exclusively methyl ester **I.58**, despite of the possibility of numerous alternative condensation pathways. Methyl ester **I.58** thus obtained was treated with excess of dimethyl sulfate, giving rise to dimethylether **I.31** in good yield.^[30c] Condensation of the corresponding benzyl anion of **I.31** with Weinreb amide **I.59**, prepared in one step from acid chloride **I.60** according to a literature known protocol,^[31] gave ketone **I.61** upon quenching the reaction at -78 °C. Interestingly, when the reaction was performed at -78 °C and allowed to slowly warm to room temperature prior to the aqueous quench, no product was formed. Instead, formation of ester **I.62** was observed, in which the elimination of the Weinreb amide portion had not taken place.

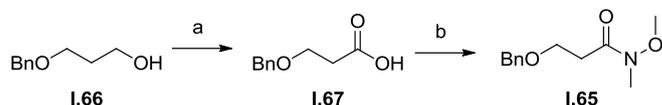
Treatment of ketone **I.61** with strong bases, such as sodium hydroxide, yielded the highly substituted but, unfortunately, undesired naphthalene structure **I.63** via an intramolecular Claisen condensation. However, when milder conditions were applied, ketone **I.61** underwent enolization of the benzylic position and intramolecular *O*-condensation, providing the desired isocumarin **I.64**, in which the carbonyl group is activated towards nucleophilic addition (Scheme I.14).



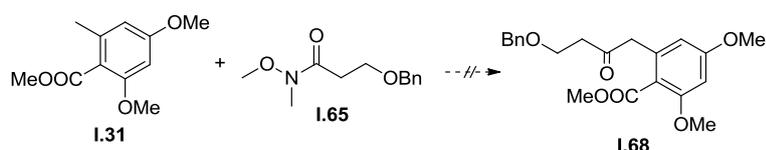
Reaction conditions: (a) NaH, THF, 0 °C; \rightarrow *n*-BuLi, -78 °C \rightarrow rt \rightarrow 60 °C; \rightarrow HCl, 51%; (b) Me₂SO₄, K₂CO₃, acetone, 60 °C, 99%; (c) ClCH₂N(OMe)Me, py, CHCl₃, 0 °C \rightarrow rt, 97%; (d) LDA, THF, -78 °C; HCl, 73%; (e) LDA, THF, -78 °C \rightarrow rt, 14%; (f) NaH, THF, 0 °C \rightarrow rt, 26%; (g) DBU, CH₂Cl₂, rt, 95%.

Scheme I.14. Synthesis of active ester **I.64** via condensation reactions.

In order to have a longer handle in the benzylic position of the active ester **I.64**, suitable for the formation of the pyrone ring in A-74528, we envisioned to use literature known Weinreb amide **I.65**.^[32] Starting from monoprotected alcohol **I.66**, Weinreb amide **I.65** was synthesized in two steps according to a known protocol involving Jones oxidation to acid **I.67** and its conversion to **I.65** in a 1,1'-carbonyldiimidazole-mediated coupling (Scheme I.15).

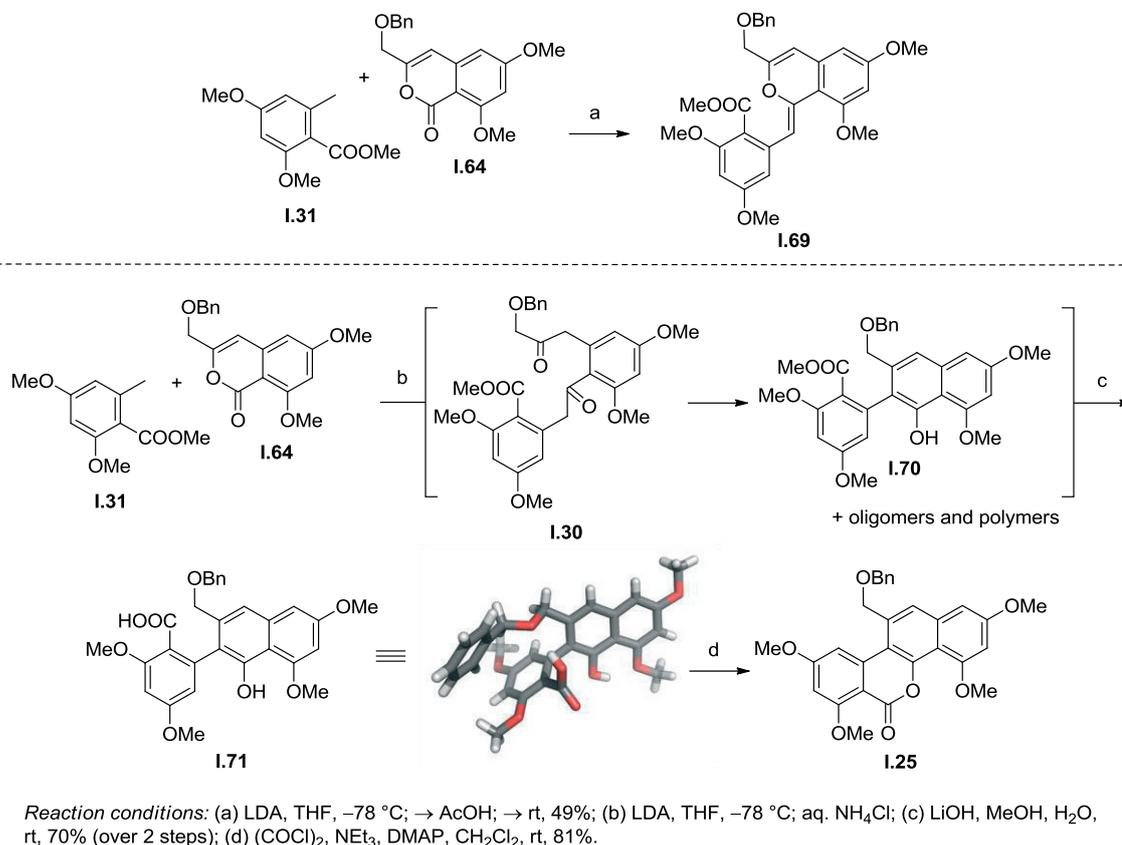


Reaction conditions: (a) Jones reagent, acetone, 0 °C, 83%; (b) ClCH₂N(OMe)Me, CDI, CH₂Cl₂, rt, 68%.



Scheme I.15. Synthesis of Weinreb amide **I.65** and attempts for its conversion to ketone **I.68**.

Unfortunately, all attempts to condense the resulting Weinreb amide **I.65** with the lithium anion of the permethylated orsellinic acid **I.31** did not lead to the formation of the desired ketone **I.68**. The likely cause of this result is the elimination of a benzoate anion in both Weinreb amide **I.65** as well as the desired product **I.68** *via* an E1cb mechanism.



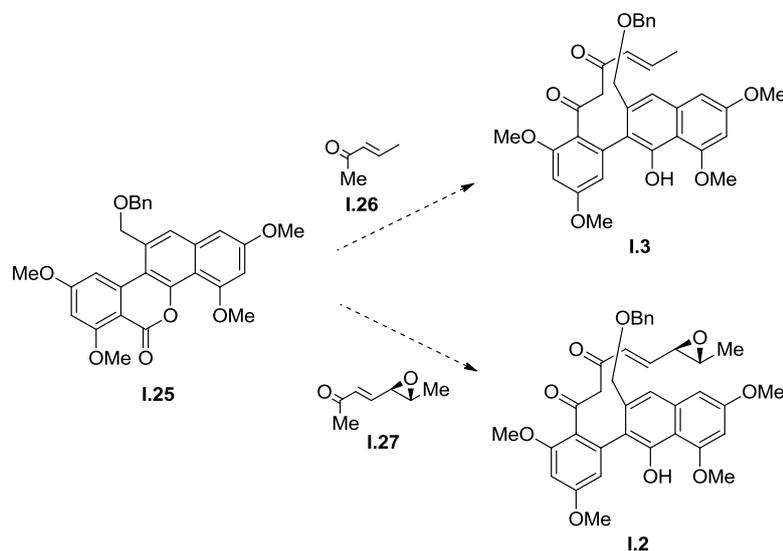
Scheme I.16. Synthesis of the biaryl acid **I.71** and lactone **I.25**.

Nevertheless, with gram quantities of active ester **I.64** in hand, we commenced with the assembly of the desired biaryl skeleton (Scheme I.16). As such, the Claisen condensation of isocumarin **I.64** with orsellinic acid derivative **I.31** had to be carefully optimized. For instance, if the reaction of lithium anion of **I.31** with active ester **I.64** was quenched with acetic acid at $-78\text{ }^{\circ}\text{C}$, undesired double enol ether **I.69** was obtained, in which the envisioned condensation had not proceeded to completion. However, by quenching the reaction under neutral conditions with an aqueous ammonium chloride solution and precooling the solution of active ester **I.64** to $-78\text{ }^{\circ}\text{C}$ prior to the reaction, the condensation process was successfully driven to completion and afforded the desired system. Mechanistically, **I.64** engaged in a Claisen-type condensation with an anion of **I.31** providing intermediate diketone **I.30**. This material underwent cyclization upon work-up to yield in addition to biaryl methyl ester **I.70**, the desired acid **I.71** as well as a complex mixture of oligomers and polymers. Direct saponification of this mixture prompted the transformation of the undesired products to the envisioned biaryl acid **I.71**, which was isolated

as a mixture of atropisomers in good yield. The structure of biaryl **I.71** was established using ^1H -, ^{13}C - and 2D-NMR techniques and confirmed by its X-ray crystal structure. Treatment of the acid **I.71** with oxalyl chloride in the presence of base then gave achiral phenolic δ -lactone **I.25**, our key intermediate for A-74528 synthesis.

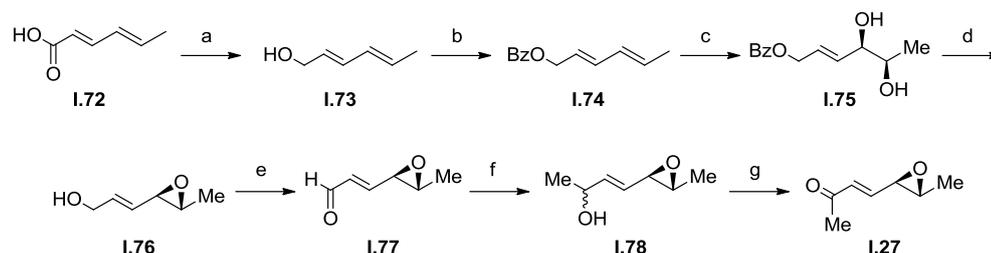
The synthesis of acid **I.71** could be reliably performed on gram scale, providing the desired biaryl building block in only six steps. In comparison, the synthesis of the corresponding intermediate **I.56** using the Suzuki-Miyaura approach (*vide supra*, section 3.1.) required a 16-step protocol and was limited in its scale due to the reduced capacity of the microwave reactor used in the last step. Hence, with the condensation approach to lactone **I.25** firmly established, a solid foundation was set for the synthesis of A-74528 (**I.1**).

With this developed approach to **I.25**, the intended installation of a side-chain corresponding to C24-C30 of the natural product could be explored (Scheme I.17). We thought, that the biaryl system **I.3**, which could be derived from lactone **I.25** and the commercially available enone **I.26**, would represent a useful model system for the desired Michael-Michael reaction. In the case of the real system **I.2**, the unknown epoxy side chain **I.27** had to be connected to lactone **I.25**. As a result, a scalable and reliable synthesis of side chain **I.27** had to be achieved first.



Scheme I.17. Planned installation of side chains **I.26** and **I.27**.

The enone side-chain **I.27** was synthesized in cooperation with D. Mazunin in the course of his Masters research project and will be only briefly discussed herein (Scheme I.18).^g The synthesis commenced with a known sequence of transformations.^[33] Specifically, sorbic acid **I.72** was reduced to alcohol **I.73**, which, after protection as benzoyl ester **I.74**, was subjected to Sharpless asymmetric dihydroxylation, providing diol **I.75** in good yield and high enantiomeric excess. The formation of the *trans*-epoxide **I.76** was achieved using conditions established by Stephenson and co-workers, wherein sequential inter- and intramolecular S_N2 processes led to the formation of the known product **I.76**.^[34]



Reaction conditions: (a) LAH, Et₂O, 88%; (b) BzCl, py, 60%; (c) AD-mix-β, *t*-BuOH/H₂O, 63% (*ee* = 90%); (d) MeC(OMe)₃, CH₂Cl₂, rt; then: AcBr, rt; then: K₂CO₃, MeOH, rt, 80%; (e) DMP, CH₂Cl₂, 0 °C, 85%; (f), MeLi, Et₂O, -78 °C, 75%; (g) DMP, CH₂Cl₂, 0 °C, 86%, (*ee* = 75%).

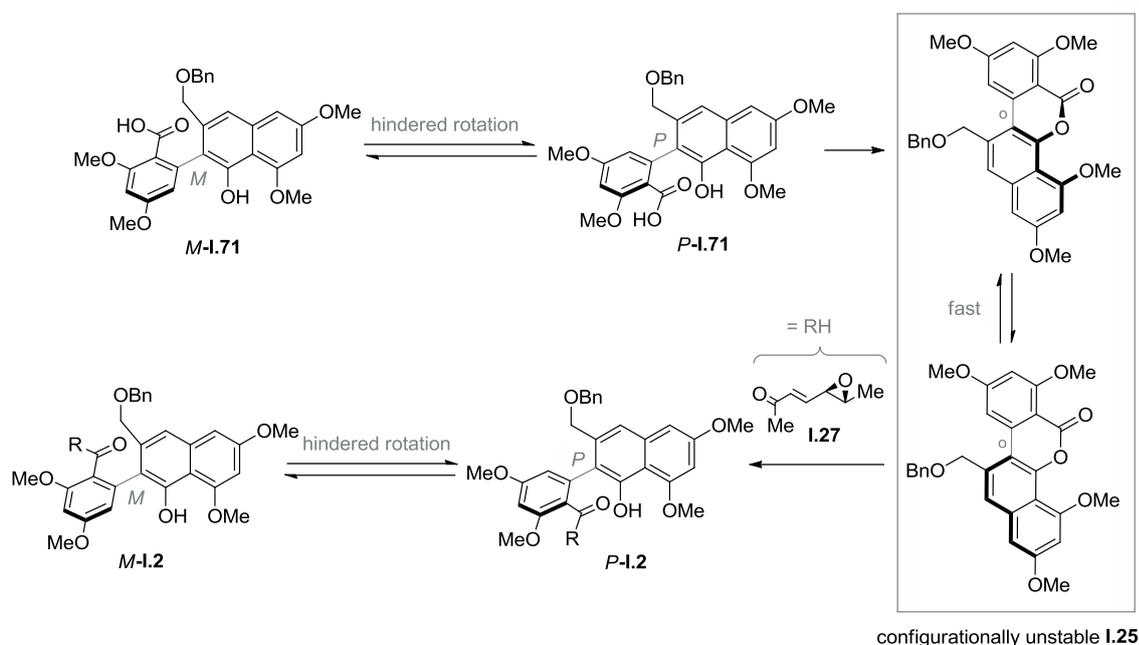
Scheme I.18. Synthesis of the epoxy side chain **I.27**.^[34]

Finally, we were able to establish a synthetic route to epoxide **I.27**, which was accomplished in three steps from epoxyalcohol **I.76**. Thus, a Dess-Martin periodinane mediated oxidation of alcohol **I.76** provided aldehyde **I.77**, which was converted to secondary alcohol **I.78** by means of a direct methyl lithium addition. Although alcohol **I.78** was isolated as a mixture of diastereoisomers, simple oxidation provided the desired enantiomerically-enriched side chain **I.27** in excellent yield (Scheme I.18).^[34] Unfortunately, during the previous steps, a racemization process as a side reaction must have taken place resulting in a drop in the *ee* value from 90% in side chain **I.27** to 75% in the final product as indicated by chiral HPLC analysis. Presumably, the observed racemization occurred *via* an intramolecular epoxide opening in a conjugate fashion with the free alcohol in **I.78** as the nucleophile.

At this stage, with sufficient quantities of side chain **I.27**, fragment coupling toward double Michael precursors **I.3** and **I.2** could be attempted. However, before these results are discussed, some stereochemical considerations concerning the axial chirality of the substrates involved have to be accounted for.

^gThe synthesis of the epoxy side chain **I.27** was carried out by D. Mazunin as a part of his Masters project under the supervision of A. Hager. The experimental procedures of this sequence are not included in the presented work. For detailed experimental information and mechanistic discussion, see: A. Hager, D. Mazunin, P. Mayer, D. Trauner, *Org. Lett.* **2011**, *13*, 1386–1389 and D. Mazunin, Masters Thesis, Ludwig-Maximilians-Universität, München, **2010**.

The phenomenon of axial chirality is caused by the hindered rotation around an aryl-aryl bond. This rotational ability is in turn governed by the steric demand of the substituents on the aromatic rings, and is temperature-dependent. An essential premise for axial chirality is the fact that these substituents have to be different on the two sides of the axis.^[35] *Ortho*-substituents, in particular, increase the rotation barrier as a result of their sterical clash, although cases of axial chirality induced by *meta*-substituents are also known. Among *ortho*-substituted compounds, mono-*ortho*-substituted non-bridged biaryl systems are not able to form rotationally stable isomers at room temperature. Biaryls possessing two *ortho*-substituents are more hindered in their rotation at room temperature, though in most cases rotation can still take place within a few hours, depending on the size of the substituents. In contrast, tri-*ortho*-substituted biaryls, such as biaryl acid **I.71**, possess a rotationally stable axis at room temperature, as two of these substituents have to pass each other in the transition state of the rotation.



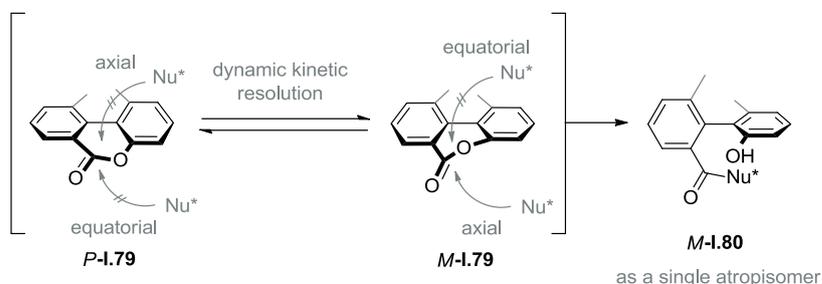
Scheme I.19. Stereochemical considerations concerning the desired lactone opening process.

In contrast to open biaryl systems, bridged biaryls represent a special case. If bearing a 5-membered *ortho*-bridge, the corresponding axis is not rotationally hindered. In the case of a 6-membered *ortho*-bridge, the rotational barrier is higher, yet, rotation is still possible and thus the axis is stereochemically labile.^[35c] In the context of the intermediates in our synthesis, this has the following consequences (Scheme I.19): 1. the biaryl axis in acid **I.71** is rotationally hindered at room temperature, and, therefore, exists as two atropisomers, **M-I.71** and **P-I.71**; 2. The conversion of acid **I.71** to lactone **I.25** bearing an *o,o'*-6-membered biaryl bridge provides an achiral molecule, in which the rotation of the biaryl axis occurs rapidly. However, following the desired lactone-opening reaction with, for instance, epoxy side-chain **I.27**, the compound

obtained will once again be chiral and exists in its two atropisomeric forms *M*-**I.2** and *P*-**I.2** at room temperature (Scheme I.19).

These stereochemical properties of biaryl compounds can serve as a useful tool in stereoselective biaryl synthesis, which is known as atroposelective lactone cleavage.^[35c] The key intermediates of this method are stereochemically labile lactone-bridged biaryls, such as **I.25**. The atropoenantio- or atropodiastereoselective cleavage of the lactone bridge can be achieved *via* a nucleophilic lactone opening reaction involving different chiral nucleophiles. In most cases, the use of chiral *O*-, *N*- or *H*-based nucleophiles has been reported.^[35c]

The transformation of stereochemically unstable lactones into chiral biaryls can be regarded as an example of a dynamic kinetic resolution (Scheme I.20). As has been shown by quantum chemical calculations, axial attack of the nucleophile on the lactone system is strongly favored over the equatorial one.^[35c] Thus, due to steric reasons, the chiral nucleophile is only able to react with one of the atropisomers of lactone **I.79**, for example *M*-**I.79**, discriminating between the two possible diastereomeric transition states of the lactone opening. The reactive atropisomer *M*-**I.79** is constantly delivered by the rapid equilibrium of the atropoisomerization process. In this manner, a complete conversion of 'racemic' lactone **I.79** to the chiral open ring system **I.80** is possible, allowing for an almost complete control of the stereochemistry of the biaryl axis.

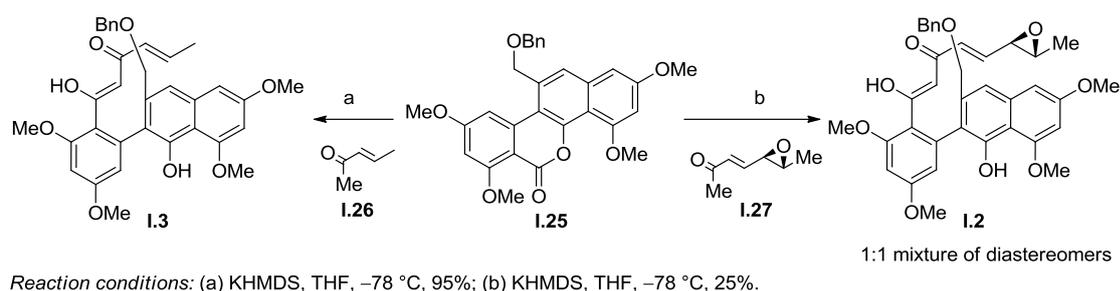


Scheme I.20. Proposed mechanism of the lactone cleavage with chiral nucleophiles.^{h[35c]}

We envisioned to apply the described lactone-opening concept for the synthesis of A-74528 precursor **I.2** using the epoxy side-chain **I.27** as the chiral *C*-based nucleophile. To the best of our knowledge, there is no literature report on lactone cleavage with chiral *C*-nucleophiles. Towards this end, we were able to show that the achiral tetracyclic lactone **I.25** could be linked with the potassium enolate of achiral methyl-1-propenyl ketone **I.26**, a *C*-based nucleophile (Scheme I.21). This transformation furnished the 1,3-diketone model system **I.3** in good yield, which exists mostly in its enolized form, and, due to the achiral nature of the applied

^hThis scheme was adopted from: G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5327.

nucleophile, as a racemic mixture of two atropisomers. We were now intrigued to test whether the analogous transformation could be carried out with the enolate of the enantiomerically enriched epoxy ketone **I.27**. Unfortunately, the condensation of the chiral potassium enolate of ketone **I.27** with **I.25** gave aryl naphthol **I.2** as an inseparable mixture of diastereomers with respect to the biaryl axis. It is likely that the stereogenic centers in the epoxide moiety in **I.27** are too far away to effect dynamic kinetic resolution and induce diastereoselectivity in the ring-opening reaction. The low yield of this transformation is presumably caused by the instability of the epoxy side chain **I.27** towards bases and nucleophiles.



Scheme I.21. Assembly of diketones **I.2** and **I.3** via lactone opening.

Even though the chiral lactone cleavage was unsuccessful, some interesting spectroscopic results were observed in the course of this study. The described chirality switch from chiral acid **I.71** to achiral lactone **I.25** and back to chiral compound **I.3** could be clearly appreciated by means of $^1\text{H-NMR}$ spectroscopy (Figure I.4). Featuring a chiral rotational-hindered axis, acid **I.71** possesses diastereotopic protons in both of its benzylic methylene groups. These protons exhibit a typical diastereotopic coupling characteristics in the $^1\text{H-NMR}$ spectrum, i.e. the protons of each methylene group couple to each other producing in each case two doublets with a roof effect. When converted to rotationally unstable lactone **I.25**, the biaryl no longer contains chiral elements in its structure. As a result the four formerly diastereotopic methylene protons are now enantiotopic and appear in the $^1\text{H-NMR}$ spectrum as two distinct singlets. Finally, following lactone cleavage, the resulting biaryl axis in **I.3** is rotationally stable at room temperature, making the methylene group protons diastereotopic. Consequently, the corresponding $^1\text{H-NMR}$ spectrum shows a complex coupling pattern of these four protons H_A , H_B , H_C and H_D , which appears as a multiplet. This comparison of spectroscopic data provides a good evidence for axial chirality of biaryl compounds.

With the Michael systems **I.2** and **I.3** in hand, required for the construction of the A-74528 core, investigation into their capacity to engage in the desired double Michael addition cascade could now be undertaken.

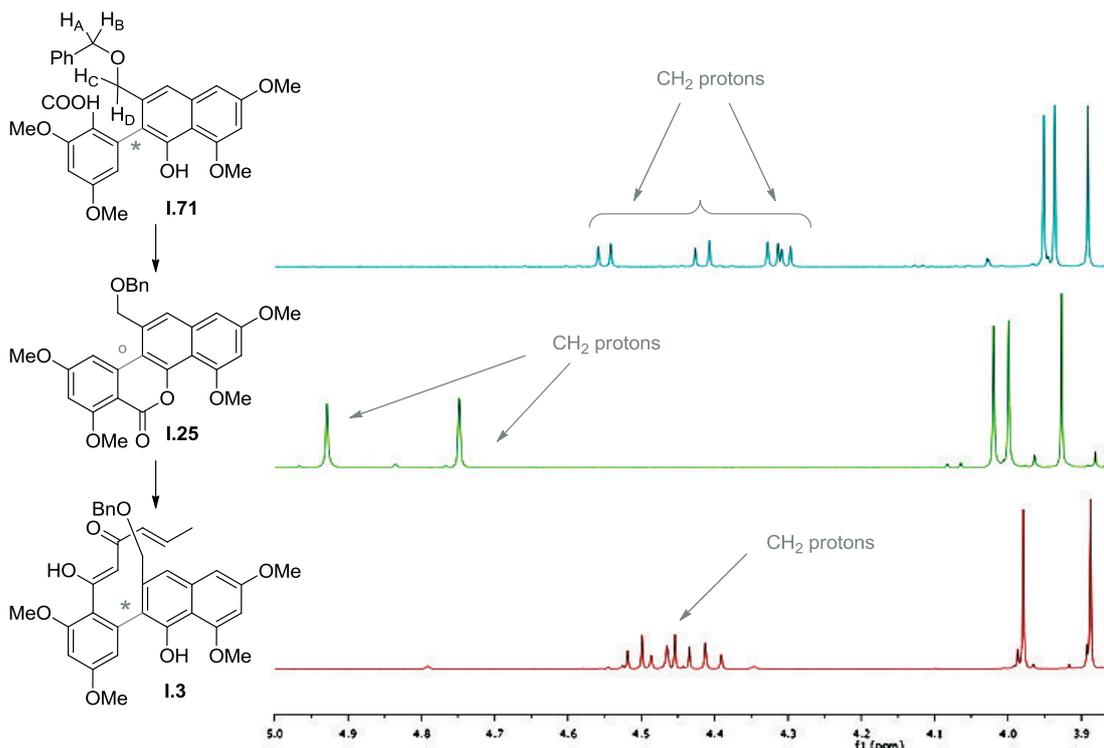
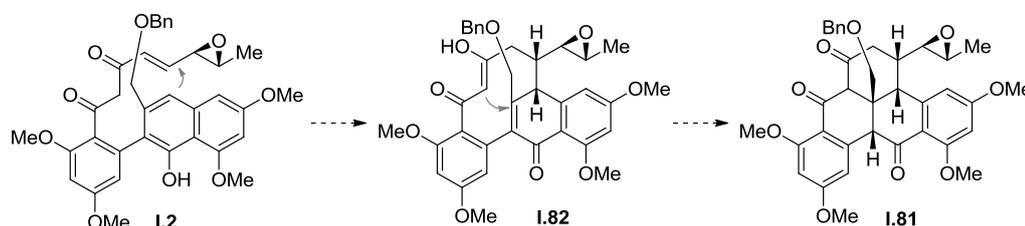


Figure I.4. Chemical shifts and comparison of coupling behavior of biaryl compounds **I.71**, **I.25** and **I.3** in $^1\text{H-NMR}$ spectra (400 MHz, CDCl_3).

3.3. Toward the Michael-Michael Cascade

Inspired by the proposed biogenesis of A-74528 (**I.1**) and driven by the question how far we can push the boundaries of biomimetic synthesis of complex type II polyketide natural products, the key step we have chosen for the assembly of the A-74528 core is a double Michael addition cascade of epoxy intermediate **I.2** providing the desired polycyclic system **I.81** via enone **I.82** (Scheme I.22).

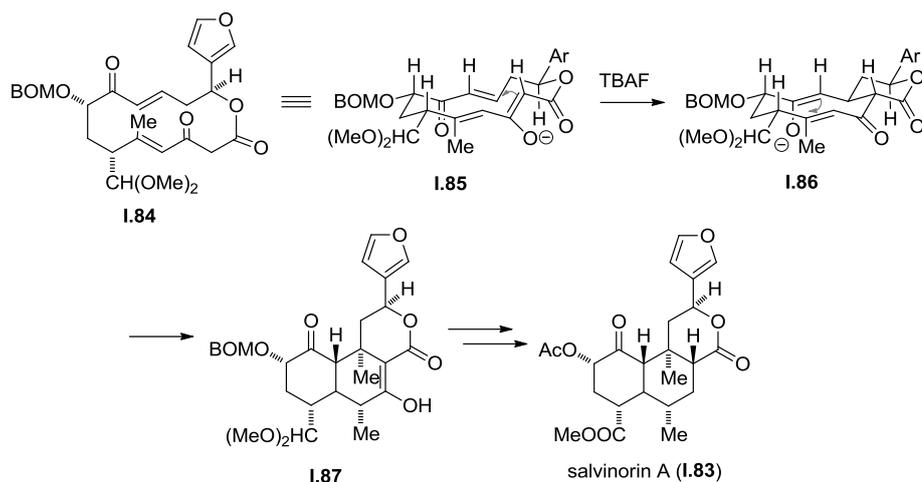


Scheme I.22. Intended biomimetic Michael-Michael cascade reaction.

Michael addition reactions, along with aldol condensation processes, belong to the most powerful C-C bond forming transformations in organic chemistry. The history of Michael reactions dates back to 1880s and is strongly connected to the research of the American chemist Arthur Michael, the eponym to this reaction.^[36] Since its discovery, this transformation has been

used in numerous syntheses of natural products. One of the most distinguished applications of this nucleophilic attack on α,β -unsaturated systems is its utilization in cascade processes, enabling the formation of several C-C bonds in a single operation.^[37] These cascade reactions can be either inter- or intramolecular, may be initiated by other reactions, can involve more than two Michael reactions and may be reflexive, in which both reactants serve as acceptor and donor.^[38]

One of the recent examples of an intramolecular Michael cascade reaction employed in a total synthesis of a natural product is the synthesis of κ opioid receptor agonist salvinorin A (**I.83**), published by D. Evans and co-workers in 2007.^[39] For their featured key transannular cyclization process, they synthesized Michael system **I.84**, which upon treatment with TBAF at -78 °C underwent a reflexive double Michael cascade. Under these conditions enolate **I.85** was first formed, which underwent the first Michael addition. This resulted in the generation of enolate **I.86**, which in turn was able to cyclize intramolecularly forming the core structure **I.87** of salvinorin A (**I.83**) (Scheme I.23).



Scheme I.23. Intramolecular double-Michael-addition as a key step in Evans' salvinorin A synthesis.^[39]

One interesting aspect that needs to be accounted for in our proposed key step is that during the projected reflexive intramolecular Michael-Michael cascade the naphthalene portion in **I.2** will require undergoing a partial dearomatization process. This leads us to the following question: To which extent the electron rich naphthol system of **I.2** can be described as an aromatic structure or considered to be an enol: i.e. how nucleophilic is it? It was our aim to answer this question as part of our studies. To the best of our knowledge, so far there are no reports of a dearomatizing Michael addition, involved in the total synthesis of a natural product. However, some examples of dearomatization during a Michael reaction^[40] and aldol addition^[41]

have been published. Thus, the desired key step would represent the first case of a dearomatizing Michael addition reaction applied in the total synthesis of a natural product.

In general, nucleophilic attack on the C-C double bond of the Michael system can be triggered by both acids and bases. In the first instance, we intended to explore the desired double Michael cascade on the model system **I.3**, lacking the delicate epoxide function in the side-chain (Scheme I.24). Towards this end, more than 50 diverse reaction conditions were tested, including various weak and soft Brønsted bases and acids, Lewis acids, organocatalysts, heating and microwave conditions, transition metal catalysts and radical initiators.ⁱ The most interesting results which have been obtained over the course of these investigations are discussed next.



Scheme I.24. Model system for the proposed double-Michael addition.

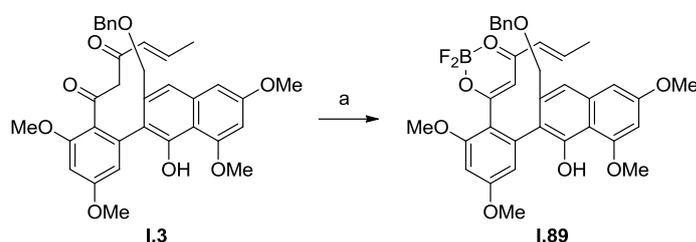
3.3.1. Acidic Conditions

Over the course of the screening of acidic conditions, Lewis acids, such as phenylboronic acid, aluminum chloride and boron trifluoride etherate complex, as well as protic acids, such as PPTS, acetic acid, hydrochloric acid and trifluoroacetic acid, all which are known to promote Michael additions, have been used in a variety of solvent systems. In almost all cases only partial or full decomposition of the starting material took place and no identifiable products could be obtained. Nevertheless, when diketone **I.3** was treated with boron trifluoride diethyl ether complex at 0 °C, the corresponding difluoroborate complex **I.89** was formed in 26% yield (Scheme I.25).

Intrigued by this observation, the structure of the complex **I.89** was fully elucidated using conventional ¹H-, ¹³C- and ¹⁹F-NMR spectroscopy as well as 2D-NMR methods, and mass spectrometry. Surprisingly, unlike the ¹H- and ¹³C- spectra, the ¹⁹F-NMR spectrum of difluoroborate **I.89** indicated the existence of two stereoisomers of **I.89** showing two separate sets of signals. Each of these isomers possesses a typical AB quartet coupling pattern of two

ⁱFor detailed information on the screened conditions, see Table A in the appendix of this work.

diastereotopic fluorines. This fact is likely to be caused by the keto-enol tautomerism between the two keto groups in the side chain.



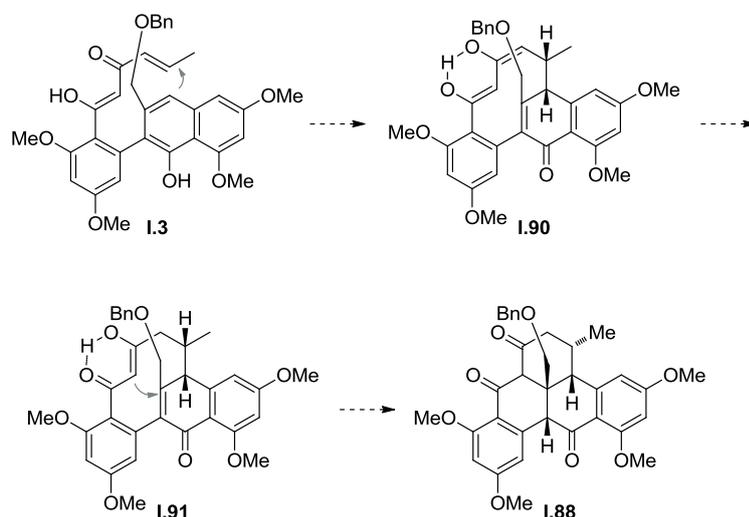
Reaction conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, THF, 0 °C, 28%.

Scheme 1.25. Formation of the difluoroborate **1.89**.

As the desired Michael-Michael reactivity could not be induced by means of acid promoters, we were prompted to explore other conditions with the hope of triggering the desired cyclization. Specifically, bases and radical reagents were investigated in great detail.

3.3.2. Basic, Radical and Miscellaneous Conditions

We speculated that deprotonation of the naphthol hydroxyl group in **1.3** with a base would increase the nucleophilicity of the *para*-carbon atom, forcing the desired nucleophilic attack (Scheme 1.26).

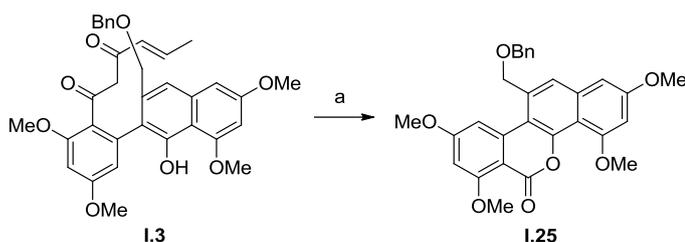


Scheme 1.26. Mechanistic considerations regarding the desired double Michael addition.

Unfortunately, the pKa values of both the naphthol hydroxyl group and the benzylic enol fall in the similar region of around 10. As the diketone usually exists in its enolized form, as confirmed by NMR, we assumed that the desired deprotonation would be difficult to control, ultimately resulting in an equilibrium between the two deprotonated forms. However,

concerning the desired transformation this could also be an advantage since the first Michael attack in **I.3** would produce enolate **I.90** (or the corresponding enol), which would need to tautomerize to the enolate **I.91** before it could undergo the second Michael addition. Thus, equilibrium conditions such as weak bases and protic solvents might be beneficial in this context.

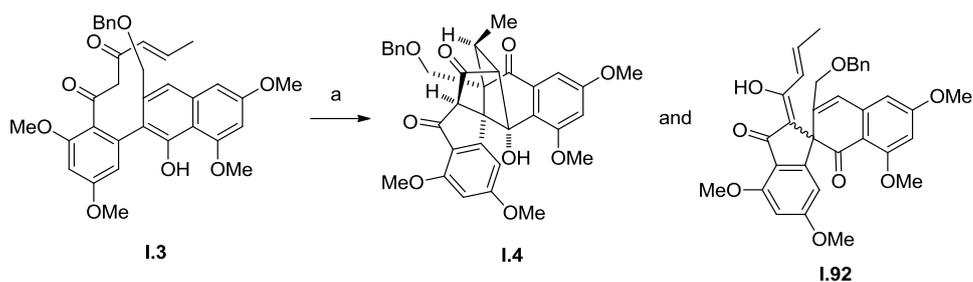
Our base screen started with weak bases, such as cesium fluoride, lithium perchlorate, potassium carbonate, lithium hydroxide, and TBAF, as well as amine bases, such as piperidine, triethylamine, DABCO and DBU, in addition to strong bases, such as LDA. In a similar fashion to reactions carried out under acidic conditions, in most cases either decomposition of diketone **I.3** was observed or the starting material was re-isolated. In some reactions using a weak base, a retro-Claisen condensation occurred, resulting in elimination of the side-chain and providing the lactone **I.25** as the main product (Scheme I.27). For example, treatment of diketone **I.3** with cesium fluoride in acetonitrile at elevated temperatures afforded lactone **I.25** in a high 65% yield (Scheme I.27), wherein the original lactone intermediate **I.25** had been obtained.



Reaction conditions: (a) CsF, MeCN, 60 °C, 65%

Scheme I.27. Unexpected formation of the lactone **I.25** via a retro-Claisen reaction of diketone **I.3**.

Interestingly, the use of TBAF as base led to another interesting observation. Upon stirring diketone **I.3** over several days in a DMF/THF mixture in the presence of TBAF and air, two new complex structures were isolated. Despite all attempts, the isolated material could not be crystallized and X-ray structural analysis could not be performed. Nevertheless, the structure of the isolated products could be elucidated by extensive NMR analysis, suggesting that one of the products is a complex dearomatized polycyclic system **I.4**, whereas the other is a simpler spiro-cyclic system **I.92** (Scheme I.28).



Reaction conditions: (a) TBAF, THF/DMF, air, rt, 7d, **1.4**: 15%, **1.92**: 25%.

Scheme 1.28. Formation of unexpected products **1.4** and **1.92**.

The ^1H -NMR spectrum of the newly isolated compound **1.4** suggested that an addition to the Michael system of the side chain in **1.3** had taken place. The rationale behind this assumption was the absence of the signals for the unsaturated Michael system of the side chain, in addition to an up-field shift of the terminal methyl group with a changed coupling pattern. A closer look at the ^{13}C -NMR spectrum of the compound indicated a remarkable up-field shift of several carbons, which had previously appeared in the spectrum of the starting material in the aromatic or unsaturated region. For example, C-A in the newly formed spiro center of **1.4** was shifted to 69.2 ppm, whereas in the starting material **1.3** the corresponding signal appeared at 119.8 ppm (Figure I.5). This fact suggested to us that a dearomatization of one or more rings had indeed taken place. Encouraged by this observation and, assuming that the desired Michael-Michael addition had occurred, further spectroscopic analysis was performed. Unfortunately, it was clear from the high resolution ESI spectrometry data that the compound isolated was not the desired product. Indeed, the obtained mass of 585.2117 g/mol implied the incorporation of an additional oxygen atom in the new structure. Finally, the identification of the complex structure was accomplished using 2D-NMR spectroscopy (COSY, NOESY, HMBC, HSQC). Through the detailed analysis of the NOESY signals, we were able to assign the relative configuration of all stereogenic centers in **1.4** (Figure I.5).^j

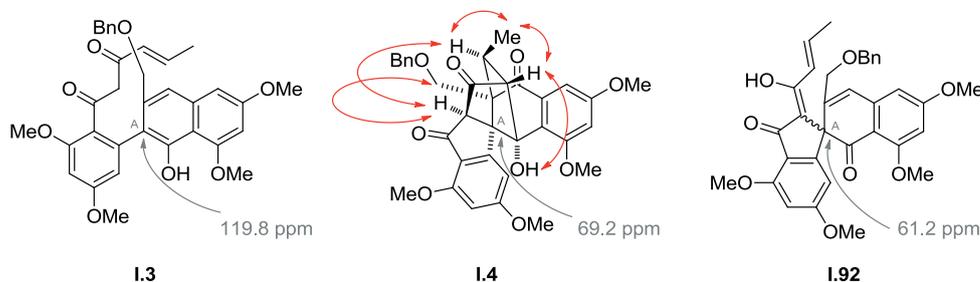
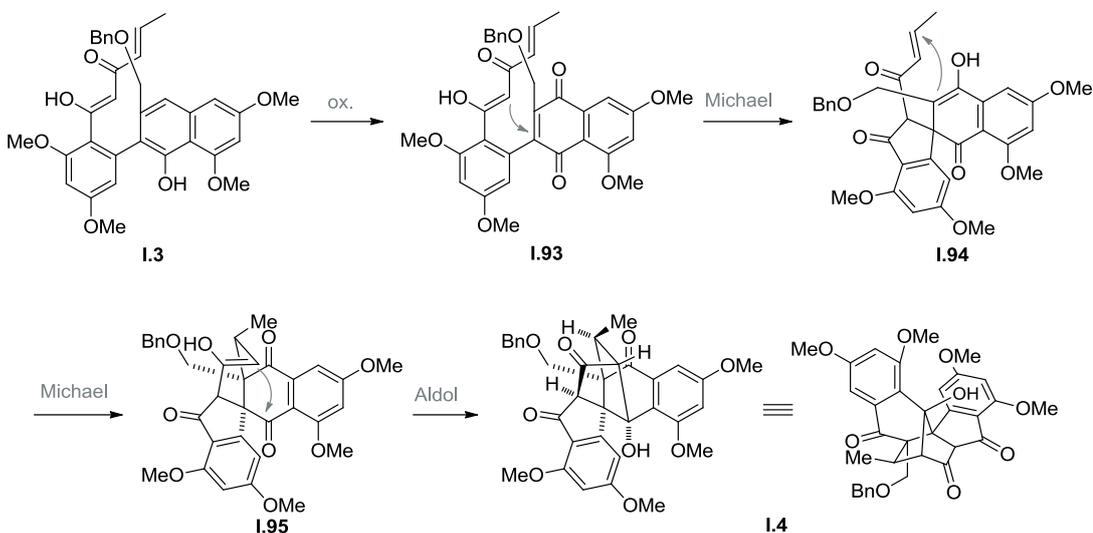


Figure I.5. Proposed structures of isolated compounds **1.4** and **1.92**; Important NOESY correlations in **1.4** leading to the assumption of the relative stereochemistry (red), as well as comparison of chemical shifts of carbon A in starting material and products (grey).

^jDetailed spectroscopic analysis as well as 2D-NMR-spectra are summarized in the experimental section of this work.

In the case of the second isolated product, the changes in the ^1H - and ^{13}C -NMR spectra were more subtle. It was easy to realize that the Michael system was still intact and that two of the aromatic rings were unchanged. However, a thorough inspection of the 2D-NMR spectra led us to the assumption that the isolated compound had the partially dearomatized structure **I.92**. The change of the NMR shift of the former biaryl carbon atom C-A was particularly conspicuous (Figure I.5). Whereas in the starting material it appears at 119.8 ppm in the ^{13}C -spectrum, the dearomatization causes an up-field shift to 61.2 ppm in **I.92**, making the dearomatization obvious.

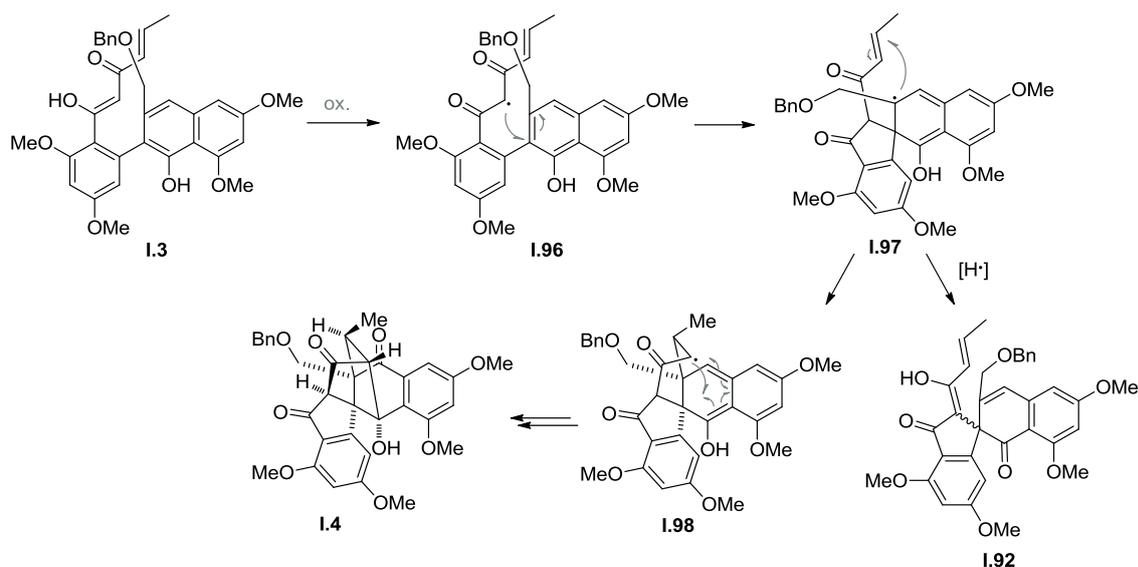
Initially, in order to explain the formation of these unexpected compounds, we assumed the involvement of an air oxidation of biaryl **I.3**, leading to the corresponding naphthoquinone **I.93** (Scheme I.29). At this point, naphthoquinone **I.93** could serve as an electrophile for the Michael addition of the diketone, producing the spiro-compound **I.94**. The enol moiety in **I.94** could then in turn attack the side chain in a Michael fashion, thus forming the pentacycle **I.95** which possesses a further nucleophilic enol functionality. Finally, an aldol addition of this enol unit to the ketone of the former quinone portion would furnish the isolated structure **I.4**. Although we attempted to prove this hypothesis by selective synthesis of naphthoquinone **I.93** under various oxidative conditions, we were not able to successfully achieve its selective formation.



Scheme I.29. Proposed mechanism for the formation of **I.93**.

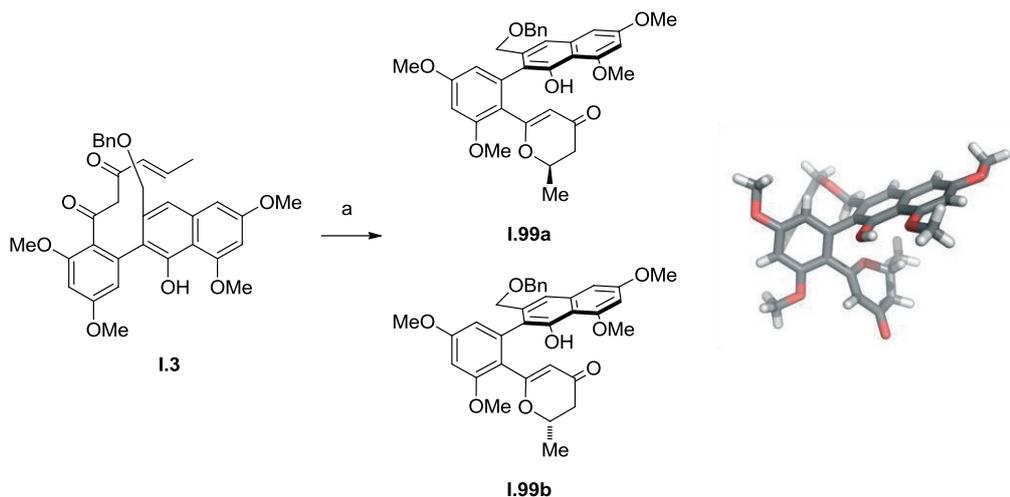
Based on the isolated structure **I.92** and assuming that this might be a precursor to structure **I.4**, it is plausible that the entire process is of radical nature (Scheme I.30). Thus, it is conceivable that diketone **I.3** could form a stabilized diketo radical **I.96** in the presence of oxygen, which then could undergo a radical cyclization process with the more electron-rich naphthalene ring, forming the tertiary radical **I.97**. This radical could be reduced with a source of hydrogen, possibly the starting material itself, delivering the spiro-cyclic compound **I.92**. On

the other hand, radical **I.97** could also be involved in further cyclization reactions. More specifically, attacking the C-C double bond of the Michael system in the side chain, it would produce a stabilized radical **I.98**. Subsequent radical cyclization on the enol and oxidation of the *para*-position with oxygen will furnish the complex structure **I.4**. In order to prove the radical nature of the mechanism, a radical inhibitor could be added to the reaction mixture to prevent the reaction taking place. This will form part of future work and help to elucidate the proposed mechanism in detail.



Scheme 1.30. A radical pathway for the formation of **I.4** and its putative precursor **I.92**.

In addition to the described reactions, treatment of Michael system **I.3** with bases, e.g. triethylamine at elevated temperatures led to the isolation of another interesting structure. After extensive NMR analysis, this product was identified as γ -pyrone **I.99**, which had been formed as a 1:1 mixture of diastereomers (Scheme I.31). To our delight, the proposed structure was eventually conclusively verified by X-ray crystallography analysis. This structure is presumably formed *via* an intramolecular *O*-addition of the enolate of β -diketone **I.3** to the Michael system of the side chain. In addition, high temperature experiments that were performed in the hope of achieving the synthesis of pentacyclic system **I.88** also resulted in the isolation of **I.99** as the major product. More specifically, when enone **I.3** was heated in 1,2-dichlorobenzene at 160 °C for several hours, both diastereoisomers of γ -pyrone **I.99** were isolated in 50% yield. The same observation was made when enone **I.3** was heated at 120 °C in a microwave reactor, affording traces of the diastereomeric γ -pyrone mixture. The reaction of **I.3** in other solvents such as benzene, DMSO, dichlorobenzene at different temperatures was performed. However, in the most cases, only partial decomposition of the starting material occurred and no other reaction took place.



Reaction conditions: (a) Δ or base, up to 50% of the diastereomeric mixture

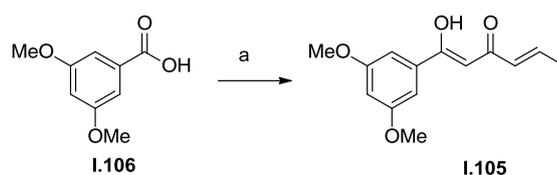
Scheme I.31. Formation of the diastereomeric γ -pyrones **I.99a** and **I.99b**.

The so called oxa-Michael reactions possess a lot of synthetic potential as their products, such as β -hydroxyketones or γ -pyrones are common motifs in polyketide natural products, making them valuable building blocks in total synthesis. Even though the first conjugate addition of an alcohol to an acceptor system was published already in 1878 by Loyd,^[42] this transformation did not get a lot of attention in the synthetic community until recent years.^[43] Typical pitfalls related to the oxa-Michael additions are the reversibility of the addition step and the poor nucleophilicity of the employed alcohols, resulting in low yields of the product and poor enantioselectivity. However, in recent years, especially in the field of organocatalysis,^[44] some interesting developments have been achieved. It was shown that proline-based catalysts^[45] can provide the desired β -oxy-compounds in high enantiomeric purity^[45-46] when employed in cascade reactions.^[47] In addition, List and co-workers were able to achieve enantioselective addition of hydrogen peroxide to Michael systems, promoted by cinchona alkaloid derivatives.^[48]

These recent developments persuaded us to look into the intramolecular γ -pyrone formation in more detail (Scheme I.31). We were hoping to achieve an organocatalytic, diastereoselective synthesis of **I.99**. Based on the concept of activating the Michael system in **I.3** in form of the corresponding chiral imminium ion **I.100**, we envisioned to apply typical imminium ion catalysts (Scheme I.32).^[49]

When the reaction was performed in DMSO without additives, diketone **I.3** did not undergo any transformation (Table I.1, entry 1). Addition of a base, such as triethylamine to the reaction mixture, provided the γ -pyrone **I.99** in 35% yield as a 1:1 mixture of diastereoisomers, which was used as a control experiment. When L-proline **I.101** was used as catalyst, the yield of the reaction increased to 80% in DMSO as the solvent. In contrast, protic solvents, such as *i*-propanol resulted in the formation of only trace amounts of the product (entries 3 and 4, Table I.1). The use of L-proline (**I.101**) or lithium proline (**I.102**) did not lead to any improvement of the diastereocontrol of the reaction. However, when Jørgensen's catalyst (**I.103**) was employed, a 2:1 mixture of diastereomers **I.99a** and **I.99b** was isolated, however the isolated yield dropped to 20%. Finally, slightly better results could be achieved using MacMillan's catalyst (**I.104**) in DMSO giving a 2.2:1 ratio of diastereomeric γ -pyrones **I.99** (entry 7, Table I.1). Unfortunately, the yield of the transformation decreased under these conditions providing only 35% of the product. Interestingly, both the diastereoselectivity and the yield of the reaction were reduced when the conditions of mixed catalysis of L-proline (**I.101**) and MacMillan's catalyst (**I.104**) were applied, providing only 20% yield of γ -pyrone as a 1.3:1 mixture of diastereomers (Table I.1). In summary, the best yield of the transformation could be achieved with L-proline (**I.101**) as the catalyst in DMSO as the reaction medium. The best diastereoselectivity of the reaction was observed using MacMillan's catalyst (**I.104**), albeit the yield of the product was lower (grey lines, Table I.1).

In order to gain a better insight of the factors that affect this transformation, we decided to explore this reaction on a simpler and, thus, more easily available system. We presumed that the observed low diastereoselectivity could be partially caused by the biaryl axis of **I.3**. To exclude this effect, we planned to test this reaction on an achiral system. Towards this end, diketone **I.105** was synthesized starting from commercially available dimethoxybenzoic acid **I.106** in only one step *via* the corresponding acid chloride (Scheme I.33). With the enone **I.105** in hand we could explore its potential in the enantioselective organocatalytic oxa-Michael addition reaction.

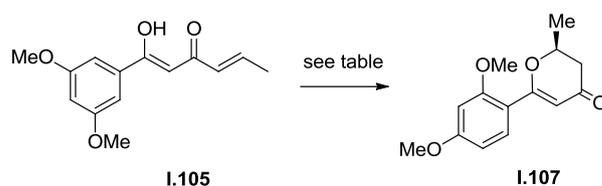


Reaction conditions: (a) (COCl)₂, DMF, rt; then: KHMDS, **I.26**, THF, rt, 55%.

Scheme I.33. Synthesis of the diketone **I.105**, a simpler system for stereoselective oxa-Michael addition.

As in the case of biaryl system **I.3**, several organocatalysts were explored in the formation of γ -pyrone **I.107** (Table I.2). As before, the best yield of the transformation was achieved using L-proline (**I.101**) as catalyst. In general, the yields of the intramolecular oxa-Michael reaction of the simpler system **I.105** were lower than those with biaryl system **I.3** as the starting material.

Table I.2. Screening conditions applied for envisioned enantioselective synthesis of γ -pyrone **I.107**.



Entry	Catalyst	Solvent	Yield	<i>er</i> I.107a : I.107b ^a
1	–	DMSO	–	–
2	I.101	DMSO	55%	1:1
3	I.102	DMSO	30%	1:1
4	I.103	DMSO	15%	1:1
5	I.104	DMSO	40%	1:1
6	I.104/I.101	DMSO	20%	1:1

^aThe enantiomeric ratio (*er*) was measured on chiral normal phase HPLC (Nucleocel DELTA S, 250 x 4.6 mm, isocratic elution, hexanes (A)/*i*-propanol (B), 96% A, flow rate: 0.5 mL/min, detection at 300 nm, $t_R(\mathbf{I.107a}) = 52.9$ min, $t_R(\mathbf{I.107b}) = 57.5$ min).

As mentioned above, List and co-workers have shown that cinchona alkaloid derived organocatalysts, such as *R*-**I.108** and *S*-**I.108** can be used to achieve enantioselective addition of oxygen-based nucleophiles to Michael acceptors (Figure I.6).^[48] In combination with chiral binol derived phosphoric acids, such as **I.109**, even better yields and enantiomeric excess could be observed. Based on these results, we explored the implementation of these catalysts in the synthesis of γ -pyrone **I.107**. Unfortunately, even with these catalytic systems no reliable and conclusive results were achieved, as in the most cases decomposition of starting material was observed.

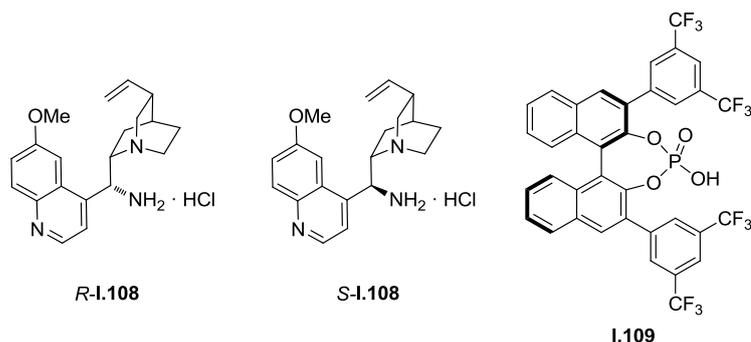


Figure I.6. Additional catalysts used for the enantioselective oxa-Michael reaction.

One potential explanation for the lack of enantio- and diastereomeric induction in the described oxa-Michael additions can be the reversibility of the reaction, a common drawback of these transformations. Although the initial attack of the oxygen atom could in principle be stereoselective in the presence of a chiral catalyst, the thermodynamic equilibrium between product and starting material eventually leads to racemic product in poor yield. On the other hand, due to the intramolecular nature of the γ -pyrone formation, this uncatalyzed cyclization might proceed faster than the implementation of the starting material into the catalytic cycle, essential for a stereocontrolled process.

Going back to the desired intramolecular Michael-Michael addition reaction of **I.3** envisioned to form the basic core of A-74528 (**I.1**) other methods for this cyclization were tested. Among them, well explored radical-inducing agents such as $\text{Mn}(\text{OAc})_3$,^[54] $\text{K}_3\text{Fe}(\text{CN})_6$,^[55] $\text{Pb}(\text{OAc})_4$,^[56] $[\text{Fe}(\text{DMF})_3\text{Cl}_2][\text{FeCl}_4]$ ^[57] were employed. Unfortunately, in most cases only complex mixtures were obtained and no formation of the desired product could be observed. These unsuccessful attempts are not described in detail in this chapter; further information can be found in the Table A in the appendix of this thesis.

In conclusion, although many interesting results have been achieved towards to the envisioned Michael-Michael addition cascade for the synthesis of the core structure of A-74528 (**I.1**), all attempts to force the formation of the desired system were unsuccessful. Based on the obtained results, there are several options for the explanation for the failed Michael-Michael cascade. The first is related to the electronics of the starting material. It is therefore possible that the naphthol portion in the model system **I.3** is not nucleophilic enough to undergo the desired dearomatizing attack. On the other hand, the electrophilicity of the acceptor side chain might be impaired by the fact that the compound exists in its enol form in the solution, as indicated by ¹H-NMR spectroscopy. Nonetheless, we believe, that the main reason for these disappointing results lies in the conformation of the starting material (Figure I.7). A close inspection of the structure of enone **I.3** as well as isolated byproducts indicates that, due to the enol form of the starting material, the system is significantly less flexible than originally anticipated.

Specifically, the X-ray structure of γ -pyrone **I.99** shows that the desired reaction centers, the carbon atom in the *para*-position to the aromatic hydroxy group and the former unsaturated carbon atom on the side chain, are pointing away from each other. In analogy, this might be also the case in the open system **I.3**, suggesting, that both reaction centers are too far away to undergo the desired Michael addition as the inducing step of the envisioned cascade. Overall, we believe that these illustrated conformational aspects of the system **I.3** inhibit the Michael-Michael cascade even under applied reaction conditions, which are typically efficient at inducing keto-enol tautomerism and changing the conformation of the molecule.

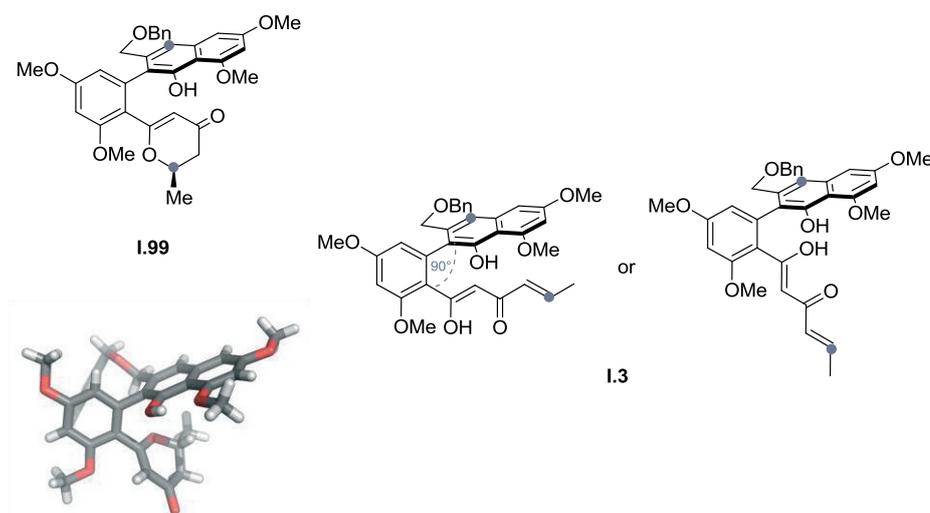


Figure I.7. Conformational considerations relating to the envisioned Michael-Michael cascade of enone **I.3**. The involved carbons are pointing away from each other in both drawn conformers of **I.3** (grey dots) embedding an angle of 90° , as suggested by the X-ray structure of γ -pyrone **I.99**.

Consequently, based on these results, any other strategy for the total synthesis of A-74528 (**I.1**) will have to account for this fact and less strained intermediates will have to be used. This could be achieved using systems, in which, for example one of the aromatic rings in **I.3** is open, thus allowing for more flexibility in the system.

The results achieved with the model system **I.3** as well as the conformational analysis of the structures **I.99** and **I.3** suggesting an inopportune situation for the desired Michael-Michael addition forced us to abandon the studies with the real system **I.2** containing the epoxy side-chain. We figured that a new strategy is required to achieve a total synthesis of A-74528.

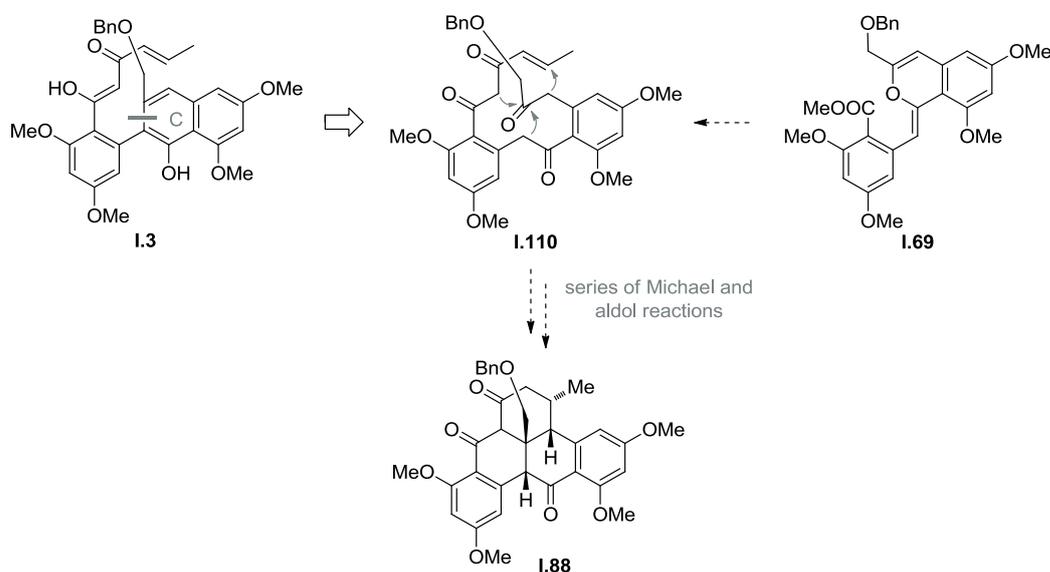
4. Summary, Conclusions and Future Work

In summary, several synthetic strategies toward a total synthesis of the complex C-30 polyketide A-74528 (**I.1**) involving biomimetic steps have been developed and executed. Focusing on a dearomatizing intramolecular Michael-Michael addition as the key step for the synthesis, a range of highly substituted biaryl compounds have been synthesized, which might serve as valuable intermediates in the total synthesis of A-74528 (**I.1**). Initially, the biaryl compounds were successfully prepared using a sterically and electronically challenging Suzuki-Miyaura coupling strategy that needed for careful and extensive optimization. In addition, a successful strategy toward biomimetic synthesis of biaryl compounds based on condensation chemistry was developed. As a result, the desired Michael-Michael biaryl precursor **I.2**, incorporating the epoxy side-chain **I.27** as well as the model system **I.1** bearing a shorter side-chain were synthesized using a novel, scalable and robust synthetic route.

The application of biomimetic condensation chemistry in the biaryl synthesis showed that biomimetic laboratory synthesis of type II polyketides without any enzymatic control is possible to some extent. However, all efforts to convert the biaryl intermediates to our target molecule *via* a more complicated biomimetic Michael-Michael cyclization cascade were unsuccessful, forcing us to change our biosynthetic hypothesis. The reason for these unexpected results might lie in the strained nature of biaryls **I.2** and **I.3** caused by the dominant rigid enol form of the molecules. Nevertheless, we believe that incorporation of the intramolecular Michael-Michael cyclization in the biosynthesis of A-74528 (**I.1**) is still possible, although the corresponding precursor may have to be forced to adopt the correct conformation with the help of an enzyme. Presumably, this could be simulated in the laboratory by using capsule techniques, in which the Michael system **I.3** would be pushed into the required conformation.

Although the envisioned Michael-Michael cascade was unsuccessful, some interesting results have been achieved along the way. Among them, highly complex fused structure **I.4** and its proposed precursor **I.92** have been isolated. Mechanistic considerations led to the assumption that both molecules were formed involving a radical mechanism. In addition, an interesting intramolecular oxa-Michael addition leading to the formation of γ -pyrone **I.99** was observed. In this context, studies for the stereoselective synthesis of **I.99**, as well as the synthesis of a simpler model γ -pyrone **I.107** have been performed. Thus, a screen of organocatalysts was conducted in order to achieve diastereo- and enantioselectivity in this transformation. Unfortunately, this process could not be successfully optimized due to the possibly reversible nature of the oxa-Michael addition.

In terms of future work, it is important to account for the aforementioned identified disadvantages of the proposed biomimetic Michael-Michael cyclization reaction. Based on these considerations a more flexible system as a precursor for the A-74528 core has to be designed. Such a system could be, for instance, tetraketone **I.110**, in which the ring C of the former naphthalene system in the model structure **I.3** is disconnected, thus importing more flexibility to the precursor (Scheme I.34). This tetraketo system **I.110** could undergo a series of Michael and aldol reactions, during the course of which the residual three rings of the model core **I.88** would be formed. Due to the reactive nature of the precursor, it is difficult to speculate which cyclization process would occur first. In general, this approach would bring several advantages, one of them being the increased flexibility of the system and, the other, the avoidance of the interesting, albeit challenging, dearomatization process. We believe that the polyketone **I.110** can be made starting from 'protected' diketone **I.69**, the synthesis of which had already been achieved in the course of biaryl synthesis studies (*vide supra*). It is likely that, tetraketone **I.69** will be highly reactive and difficult to handle, suggesting the need for its generation in situ. The similarity of tetraketone **I.110** to the biomimetic polyketone precursors, its high reactivity and the diversity of reaction modes it could undergo, makes the described alternative route both challenging and fascinating from the biomimetic point of view.

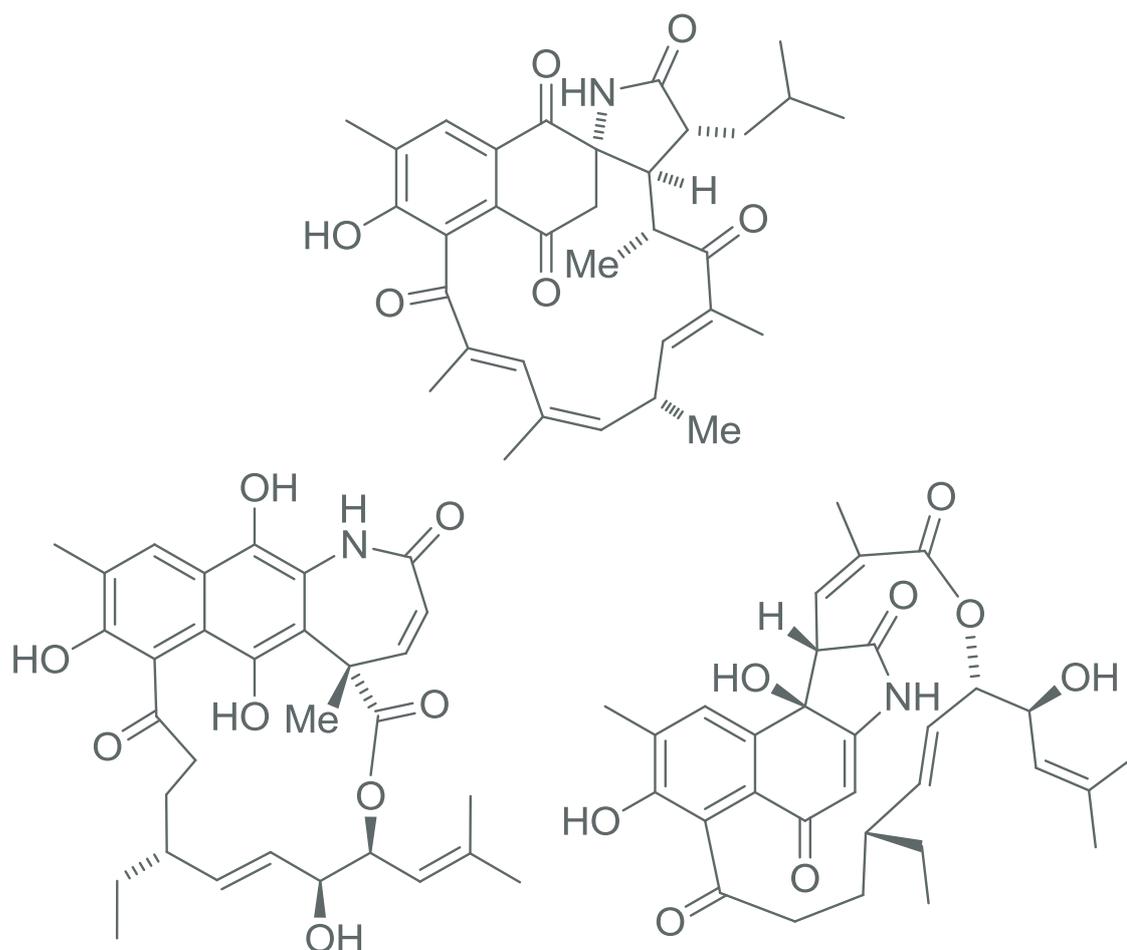


Scheme I.34. Alternative retrosynthetic considerations toward the basic core of A-74528.

In this context, a reduction of the ester portion in **I.69** was performed providing cyclic acetal **I.111**, which, dissolved in deuterated chloroform, rapidly transforms into the alcohol **I.112** (Scheme I.35). Unfortunately, due to the chemical instability of **I.111** and **I.112**, they were only characterized by $^1\text{H-NMR}$. However, both compounds could be implemented in the new synthetic route to A-74528 (**I.1**), since both of them could presumably be converted to the triketone **I.110** in additional steps.

CHAPTER II

'SYNTHETIC STUDIES TOWARD ANSALACTAM A, DIVERGOLIDES C and D'



CHAPTER II: SYNTHETIC STUDIES TOWARD ANSALACTAM A, DIVERGOLIDES C AND D

5. Introduction and Background

5.1. Type I Polyketide Natural Products

Much more structural diversity than encountered with fatty acids and type II polyketides can be found within the type I polyketide natural products. Typically, type I polyketides are characterized by their partially reduced structures possessing several stereocenters. One of the most famous polyketide groups are the macrolides, which usually are made by type I polyketide synthase (PKS). Macrolides are macrocyclic lactones or lactams featuring in the majority of cases 12-, 14-, and 16-membered ring systems and are known to show clinically important activities with distinguished modes of action.^[8] Some of the macrolide structures have been proven as clinical useful antibiotics, for instance erythromycin A (**II.10**),^[58] rapamycin (**II.11**)^[59] and avermectines^[60] (Figure II.1).

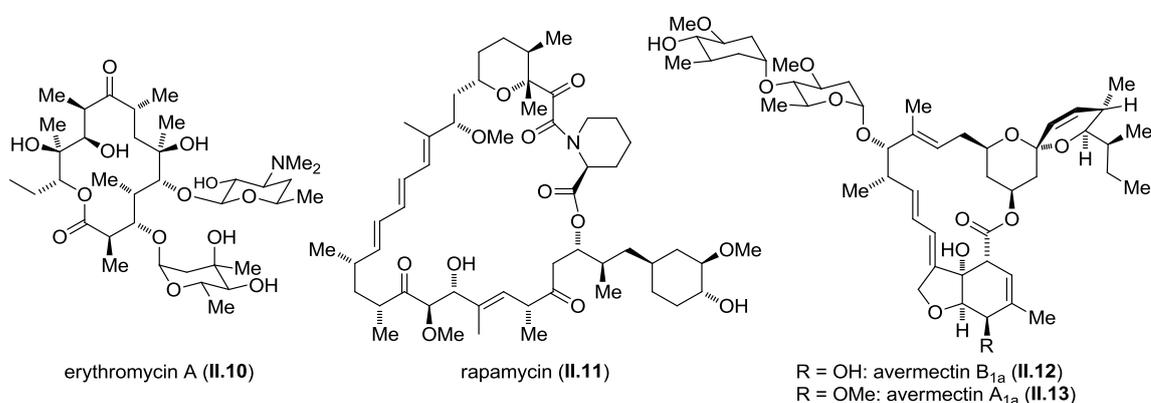


Figure II.1. Prominent type I polyketide natural products: erythromycin A (**II.10**), rapamycin (**II.11**) and avermectines B_{1a} and A_{1a} (**II.12** and **II.13**).^[8]

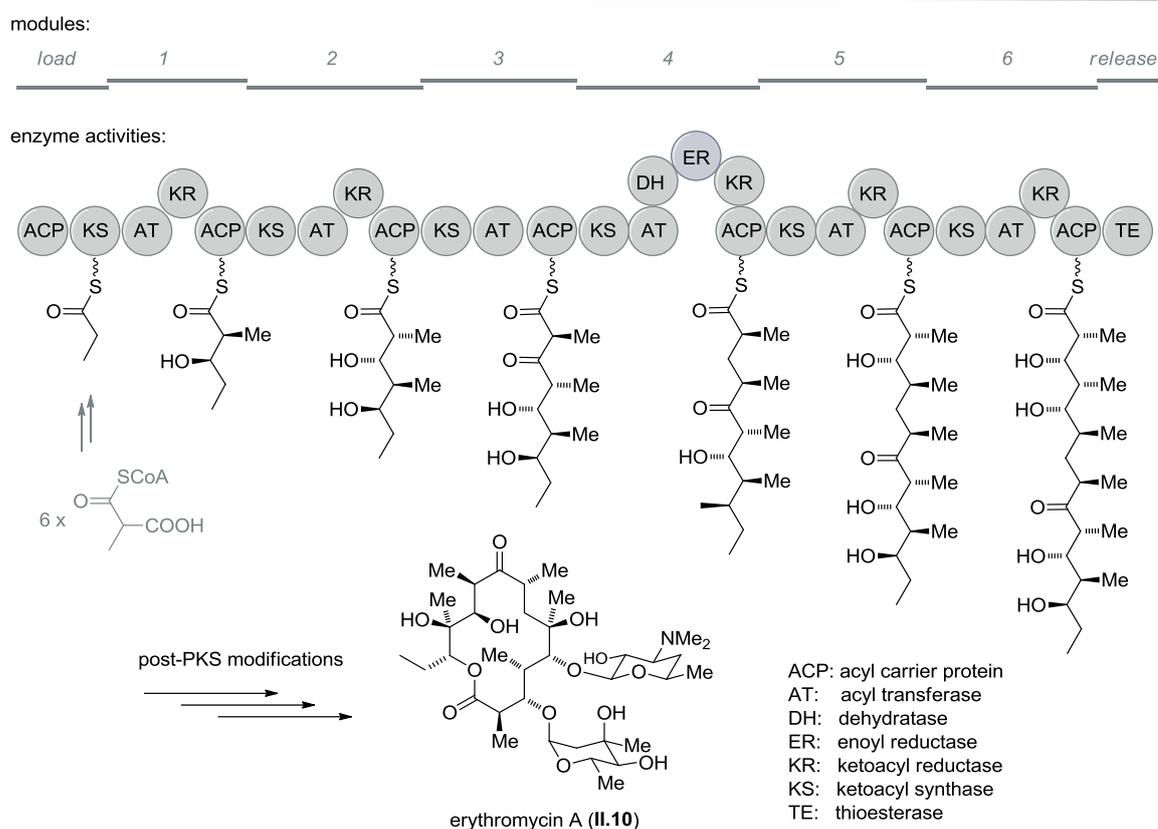
More than 40% of the known antibiotics target protein synthesis of the pathogens. Among them, the most prominent macrolide antibiotic, erythromycin A (**II.10**), isolated from actinomycete *Saccharopolyspora Erythraea*, inhibits the growth of bacteria by binding to their ribosome and thus blocking their protein biosynthesis (Figure II.1).^[61] The immunosuppressant rapamycin (**II.11**) was initially extracted from *Streptomyces Hygroscopicus* and is broadly used to prevent rejection after organ transplantation. Rapamycin (**II.11**) forms a complex with mammalian target of rapamycin (mTOR) inhibiting protein synthesis required for T-cell

activation, thus inhibiting the immune response.^[62] One of the recent examples for clinically used macrolide structures are avermectines, represented here by avermectin B_{1a} (**II.12**) and A_{1a} (**II.13**). Ivermectin, a synthetic derivative of avermectines, is an extremely potent agent used at low dosages against worm parasites in humans, *e.g.* *Onchocerca volvulus*, pathogen of river blindness. The biological target of avermectines and its derivatives are the glutamate gated chloride channels unique to nematodes, resulting in blocking of electrical activity in nerve and muscle cells and death (Figure II.1).^[8]

In contrast to fatty acids, type I polyketides are characterized by partial, complete or no reduction of the corresponding polyketide chain. They display a mixture of hydroxyl groups, carbonyl groups, double bonds and other residues in their structures, meaning that the three stage reductive process involving alcohol formation by keto reductase (KR), dehydration by dehydrase (DH) and reduction of the double bond by enoyl reductase (ER) is not always taking place during the chain assembly.^[8] Type I PKS systems are, in contrast to type II PKS complexes, large multifunctional proteins with individual functional domains, which are mostly non-iterative. They operate as a biological assembly line of multifunctional proteins organized as discrete modules. Each module possesses special enzyme activities, which are necessary in that particular extension cycle. The polyketide chain, which is attached to an ACP unit, is modified according to the enzyme activities of the corresponding unit and then passed to another ACP of the next module.^[63] Although the enzymatic background in fatty acid and type II polyketide as well as in the type I polyketide syntheses differs, the chemical key step in the formation of the corresponding poly- β -keto chains is always the same being the decarboxylative Claisen condensation of mostly malonyl-CoA extender units with an acyl starter catalyzed by ketoacyl synthase (KS). In contrast to this, as mentioned above the modifying processes catalyzed by KR, DH or ER are not all active during the particular cycle in type I polyketide synthesis and are highly controlled by the corresponding module, leading to partial or no reduction of the polyketide chain. Typically, the linear sequence of modules in the PKS type I enzymes corresponds to the structural sequence in the produced polyketide chain.^[12b]

One classical example for a typical type I polyketide biosynthesis is the enzymatic assembly of erythromycin A (**II.10**) (Scheme II.1).^[8] Erythromycin A is a 14-membered lactone which is composed by propionate units delivered by propionyl-CoA as a starter unit and 6 methylmalonyl-CoA molecules as extenders. Scheme II.1 shows the particular sequence of the chain formation corresponding to **II.10**. All reduction modes of the newly formed carbonyl group can be found in this type I PKS system. Thus, module 1 possesses only KR activity delivering a β -hydroxy chain after the accomplished cycle. On the contrary, module 3 of the assembly line does not reduce the carbonyl group at all, whereas module 4 functions similarly to fatty acid synthase and possesses KR, ER and DH activities reducing the complete newly

formed carbonyl system to a methylene group. After completion of the chain synthesis, the polyketide is released by thioesterase (TE) forming in this case a lactone bond. Following post PKS processes, such as oxidations and glycosylations afford finally the antibiotic erythromycin A (**II.10**).^[8]



Scheme II.1. Type I PKS system involved in the biosynthesis of erythromycin A (**II.10**) and its modules as well as the essential enzyme activities.^k

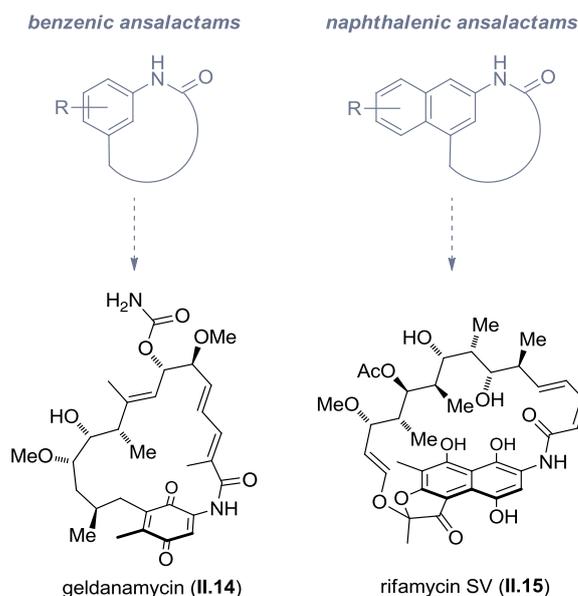
Not only the versatile reductive properties of the type I PKS systems but also their ability to incorporate various starter acyl units as well as, in contrast to type II PKS, extender units,^[64] results in the formation of intriguing and synthetically inspiring polyketide structures.^[65]

5.2. Ansa Macrolides

Over the years our group got interested in the total synthesis of type I polyketide natural products. In particular recently, our work was focused on the synthesis of ansa macrolide natural products, a subgroup of macrolide polyketides.^[66] Ansa macrolides are a complex group of mostly bioactive natural products, which are predominantly isolated from actinomycetes.^[8] The name ansa macrolides, as introduced by Lüttringhaus^[67] and further utilized by Prelog and Oppolzer,^[68] is inspired by the 'basket' like shape of these molecules possessing a 'handle'

^kThis scheme is adopted from P. M. Dewick, *Medicinal Natural Products; A Biosynthetic Approach*, third ed., Wiley-VCH, Weinheim, **2009**.

(Latin: *ansa* = handle). As the name already implies, the 'handle' of these 'basket like' structures is a polyketide chain. The 'basket' itself can be formed by different rigid building blocks, such as highly substituted benzene and quinone rings in benzenic macrolides, e.g. geldanamycin (**II.14**), or alternatively, as represented in naphthalenic ansamycines, substituted naphthalene and naphthoquinone moieties, e.g. rifamycin SV (**II.15**) (Scheme II.2).^[69] The macrocycle in ansa macrolides is typically connected *via* an amide bond, meaning that, in contrast to other macrolides, ansa macrolides are lactams.



Scheme II.2. Classification of ansa macrolides according to their 'basket' moiety and the most prominent representatives of this macrolactam group: geldanamycin (**II.14**) and rifamycin SV (**II.15**)

Following the description of biological properties of macrolides one already might assume that also the ansalactams show diverse biological activities. Indeed, rifamycins are an important group of therapeutically used antibiotics applied in the treatment of tuberculosis and leprosy. Rifamycins bind to bacterial RNA polymerase thus sterically blocking the RNA synthesis in the bacteria.^[70] Geldanamycin (**II.14**) is a famous anti-cancer drug candidate. It inhibits heat shock proteins 90 (HSP90) preferentially in cancer cells, thus interfering with protein biosynthesis and leading to their apoptosis.^[71]

Inspired by the outstanding biological activities of ansalactams and by their intriguing structural properties, we were prompted to develop synthetic pathways to novel ansa macrolides, which will be described in the next section.

5.3. Structure, Isolation and Biological Properties

In 2011, the groups of R. Moore^[4] and C. Hertweck^[5] isolated independently from each other several new ansa macrolide natural products from different *Streptomyces* strains. Moore and co-workers were investigating a *Streptomyces* sp. strain CNH-189 isolated from marine sediments collected in California. LC/MS analysis of the crude culture extract showed several absorption bands typical for highly conjugated aromatic compounds. After an extensive HPLC separation of initially 60 L culture extract, they were able to enrich 70 mg of a novel ansa macrolide, which they called according to its structural properties ansalactam A (**II.1**) (Figure II.2). The structural elucidation of the molecule was performed using detailed ¹H-, ¹³C- and 2D-NMR analysis and finally confirmed *via* X-ray structure of the natural product. In addition to this, Moore and co-workers were also able to assign the absolute stereochemistry of macrolide **II.1** applying Mosher's method to several hydroxyl derivatives of the natural product.^[4]

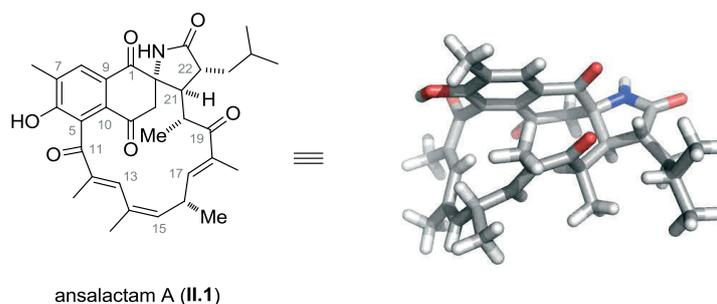


Figure II.2. Structure assigned to ansalactam A (**II.1**)¹ and the corresponding X-ray structure illustrating the 'basket' like shape of the molecule.^[4]

Almost simultaneously, Hertweck and co-workers published their results on the investigations of mangrove trees.^[5] Mangrove trees are tropic and subtropic trees growing in saline coastal sediments. Among them, *Bruguiera gymnorrhiza* is the dominant mangrove species found along the Chinese coast. The bark and roots of this species are known to have been used in Chinese folk medicine to treat diarrhea, throat inflammation and hemostasis.^[72] While the bioactive chemical components from the tree itself have been extensively studied, less information is available on the biosynthetic potential of the entophytes of the tree. Thus, Hertweck's group was investigating the *Streptomyces* sp. stem HKI0576 from the stem of the tree. The first HPLC-MS analysis showed a complex metabolome of the entophyte. After fermentation of 200 L culture extract they were able to isolate several ansa macrolides in amounts adequate for structural elucidation. According to the proposed diverse biogenesis of these natural products, which will be discussed later, they were called divergolides A-D (**II.16**,

¹The structure numbering is according to the one introduced by Moore and co-workers in: M. C. Wilson, S.-J. Nam, T. A. M. Gulder, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2011**, *133*, 1971–1977.

II.17, **II.2** and **II.3**). The structural elucidation of the compounds was carried out using extensive ^1H -, ^{13}C - and 2D-NMR techniques. In addition, the structural assignment of divergolide A (**II.16**) was confirmed by X-ray crystallography (Figure II.3).^[5]

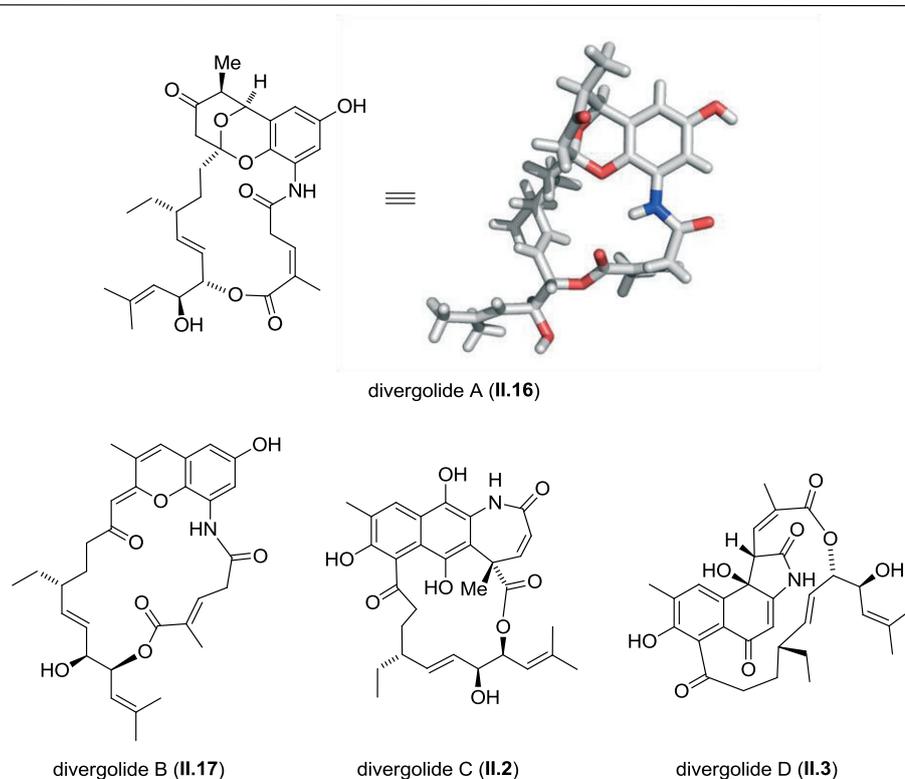


Figure II.3. Structures assigned to divergolides A-D by Hertweck and co-workers, as well as the X-ray structure of divergolide A (**II.16**) confirming the initial assignment.^[5]

Biologically, Hertweck and co-workers could show that all four divergolides display interesting biological activities. Among them, divergolide A (**II.16**) exhibits the strongest activity against *Mycobacterium vaccae*, and divergolide D (**II.3**) is strongly active against *Bacillus subtilis* and *Staphylococcus aureus*, whereas divergolide C (**II.2**) is the only divergolide found to be active against *Enterococcus faecalis*. In addition, a cytotoxicity screen against 40 tumor cell lines revealed that among all isolated divergolides, only divergolide D (**II.3**) showed promising activities against several of them. Thus, it was toxic to lung (LXFA 629L), pancreatic (PANC-1), renal (RXF 486L) and sarcoma (Saoc-2) cancer cell lines with IC_{50} values ranging from 1.0 to 2.0 μM . Owing to their biological activities, divergolides could contribute to further development of anti-tumor and anti-infective drugs.^[5] In the case of ansalactam A (**II.1**), no biological evaluation was reported, so far.

Along the lines of the work established in our group, we focused our interest on the synthesis of ansalactam A (**II.1**) and divergolides C and D (**II.2** and **II.3**).^[66] All three compounds belong to the group of naphthalenic ansalactams and show similar naphthalene

building blocks in their 'basket' moiety, which are biosynthetically in all three cases derived from 3-amino-5-hydroxy-benzoic acid (AHBA).

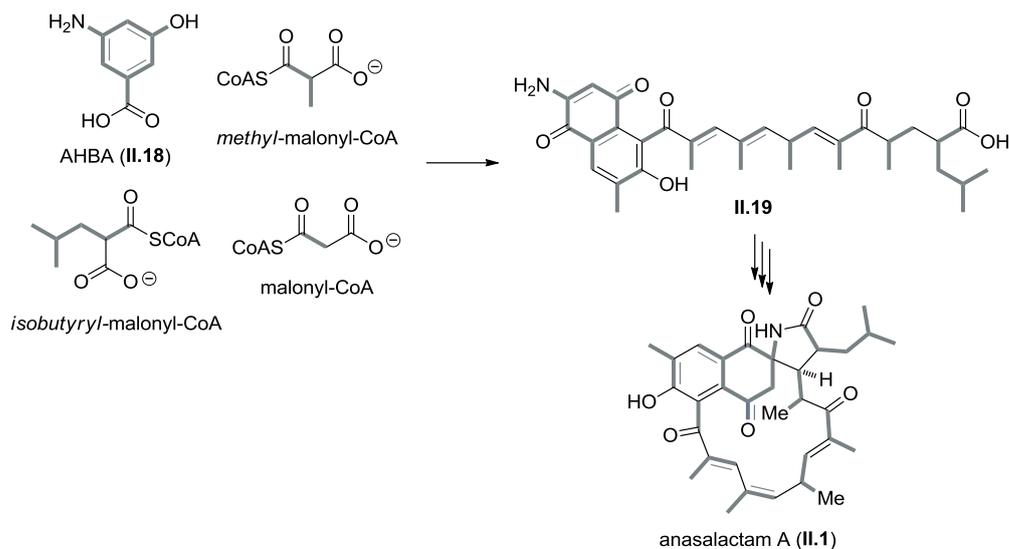
Structurally, ansalactam A (**II.1**) possesses a spiro γ -lactam functionality, which is connected to a highly substituted reduced naphthoquinone portion and bridged, typically for type I macrolides, by a polyketide chain forming a 16-membered ring (Figure II.2). The 'handle' of the molecule features in addition to two carbonyl groups three trisubstituted double bonds. Two of these double bonds in the C12 and C17 positions are *E*-configured, while the one in C14 position shows a *Z*-configuration as was verified by the corresponding ROESY correlations. The tetracyclic core of this type I polyketide possesses five stereogenic centers, four of them are contiguous. Interestingly, the spiro-system shows an isobutyryl side-chain at C22 position, which is unusual for this type of polyketides.^[4]

In analogy to ansalactam A (**II.1**), both divergolides C and D (**II.2** and **II.3**) feature tetracyclic scaffolds (Figure II.3). The basket building block in all three molecules is similar. In contrast to ansalactam A (**II.1**), the corresponding naphthalenic portion of divergolide C (**II.2**) is at the oxidation state of a hydroquinone, whereas divergolide D (**II.3**) possesses a highly substituted naphthoquinone derivative in its 'basket' like structure. Divergolide C (**II.2**) features adjacent to the naphthalene portion a 7-membered lactam ring, which is bridged by a polyketide chain forming a 15-membered cyclic lactone. The molecule bears three double bonds, one of which is trisubstituted. In addition to this, divergolide C (**II.2**) has four stereogenic centers one being benzylic and quaternary. The stereocenter attached to the oxygen atom of the lactone portion features an isobutenyl side-chain, which is unusual as an extender unit in type I polyketide synthesis. On the contrary to divergolide C (**II.2**), the scaffold of divergolide D (**II.3**) shows a 5-membered lactam ring attached to the naphthoquinone carbonyl group forming a tertiary alcohol. The tricyclic 'basket' portion is linked by a polyketide chain, which forms a 19-membered acyclic lactone. As being the case for divergolide C (**II.2**), the molecule features three double bonds, one of which is *Z*-configured. Additionally, five stereogenic centers can be found in divergolide D, two of which being secondary alcohol derivatives placed in allylic positions and one, as pointed out earlier, is benzylic and quaternary.^[5]

5.4. Proposed Biogenesis

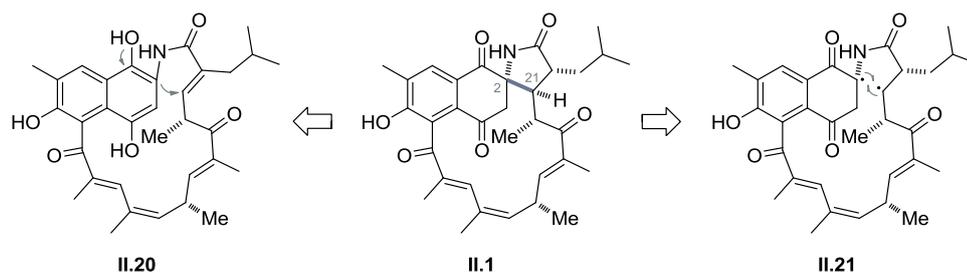
As the structural similarities might already suggest, the biosynthesis of the newly isolated ansa macrolides is somewhat related. Both research groups suspected the incorporation of AHBA (**II.18**) in the biosynthesis of the naphthalene cores. This assumption could be confirmed by the Moore group using high throughput identification of AHBA synthases. 3-amino-5-hydroxybenzoic acid (AHBA), a naturally occurring amino acid, serves as a starter unit in many

ansa macrolide biosyntheses.^[4,73] It was shown, that AHBA is biosynthetically made by a variant of the shikimate pathway, the aminoshikimate way.^[74] In the case of ansalactam A (**II.1**), based on ¹³C-labeling studies and comparison to rifamycin and naphthomycin biosyntheses, Moore and co-workers suggested that the carbon backbone **II.19** of ansalactam A is made biosynthetically incorporating one malonate, six methylmalonate and one 2-isobutyrylmalonate extender units consecutively attached to the AHBA acyl starter by a type I PKS system (Scheme II.3).^[4]



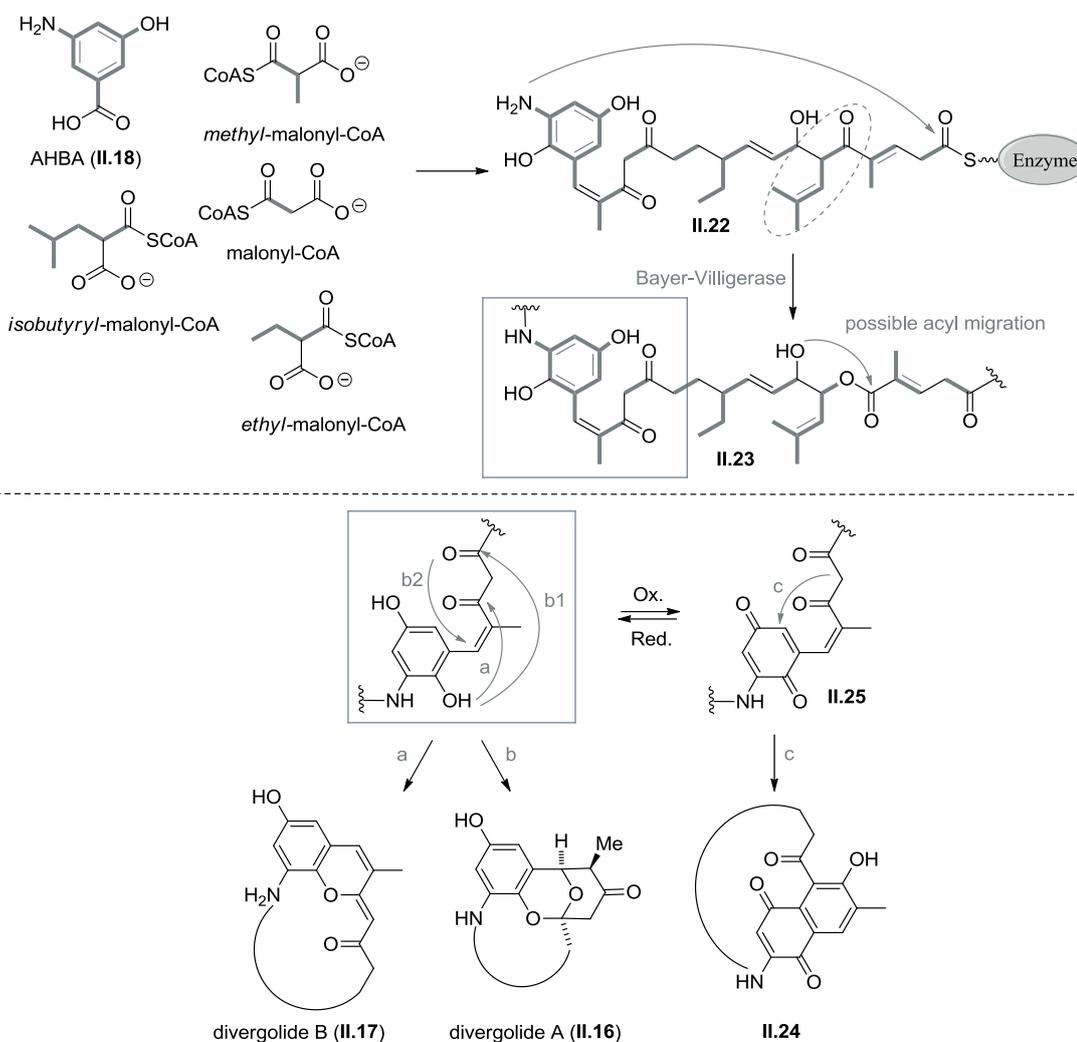
Scheme II.3. Biosynthesis of the carbon skeleton **II.19**, the precursor of ansalactam A (**II.1**), according to Moore and co-workers.^[4]

Unfortunately, Moore and co-workers did not provide an explanation for the formation of the spiro γ -lactam functionality in the structure of ansalactam A (**II.1**). The bond formed between C2 and C21 is in the β -position to the amide functionality of the lactam ring. We believe that there are two possibilities how this bond might be installed in the course of the biosynthesis (Scheme II.4). On one hand, it is possible that a nucleophilic enol-like attack of the naphthohydroquinone into the Michael system of the side chain in the possible precursor molecule similar to **II.20** causes the formation of the aforesaid bond. On the other hand, it appears to be conceivable that the C2-C21 bond could be installed in a radical fashion involving a stabilized radical intermediate similar to **II.21** (Scheme II.4). Though, it remains unclear how this radical intermediate might be formed and whether the lactam bond is already closed or the reaction takes place in the corresponding open ring system.



Scheme II.4. Postulated formation of the C2-C21 bond in the spiro γ -lactam functionality of **II.1** involving Michael addition and radical cyclization as possible key steps.

In the case of divergolides A-D (**II.16**, **II.17**, **II.2** and **II.3**), Hertweck and co-workers were not able to perform isotope labeling experiments due to the small amounts of natural products available from the parent organisms. However, they proposed a possible scenario for the formation of these natural products (Scheme II.5).^[5]

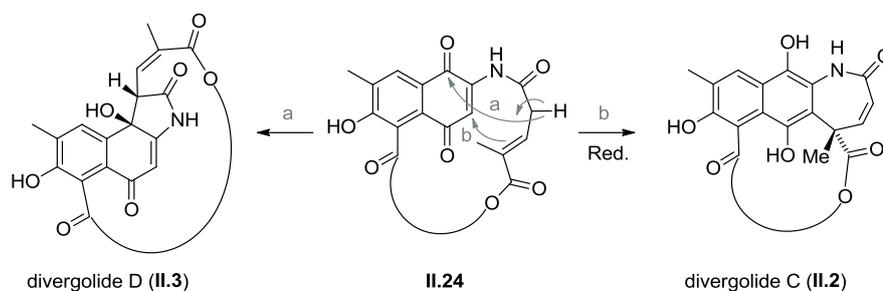


Scheme II.5. Suggested biogenesis of divergolides A-D (**II.16**, **II.17**, **II.2** and **II.3**).^{[5]m}

^mThis scheme was adopted from: L. Ding, A. Maier, H.-H. Fiebig, H. Görls, W.-H. Lin, G. Peschel, C. Hertweck, *Angew. Chem. Int. Ed.* **2011**, *50*, 1630–1634.

As they suggest, the carbon skeleton **II.22** of all four divergolides is formed by the same polyketide chain. In analogy to the biosynthesis of ansalactam A (**II.1**), AHBA (**II.18**) is used as the acyl starter unit, which is then condensed by type I PKS with two methylmalonyl-CoA, three malonyl-CoA, one ethylmalonyl-CoA and one isobutyryl-CoA extender units. A Baeyer-Villigerase oxidizes this carbon backbone giving corresponding ester **II.23**. As they suppose, possible acyl migration enables the formation of the different ester functionalities in all four divergolides. The high degree of flexibility of the highly reactive polyketide precursor enables three different types of cyclization reactions, which give rise to three different 'basket' moieties found in divergolides A-C. Specifically, cyclizations involving oxygen attack of the phenolic hydroxyl group form the exomethylene-2*H*-benzopyran of **II.17** (path a, Scheme II.5) and the ring system of **II.16** (path b, Scheme II.5), respectively. The naphthoquinone portion **II.24** found in divergolides C and D might be formed after an oxidation process by a Michael addition of the side chain into the accordant benzoquinone **II.25** (path c, Scheme II.5).^[5]

After the formation of the naphthoquinone **II.24** the stage is set for the installation of the 7- and 5-membered lactam rings corresponding to divergolide C and D systems (Scheme II.6). Accordingly, an aldol attack of the aliphatic side chain onto one of the carbonyl portions in the naphthoquinone system **II.24** forms the 5-membered lactam system of divergolide D **II.3** (path a, Scheme II.6). Whereas a vinylogous attack, proceeding after a conjugated deprotonation, gives rise to the 7-membered lactam system of divergolide C (**II.2**) (path b, Scheme II.6).^[5]

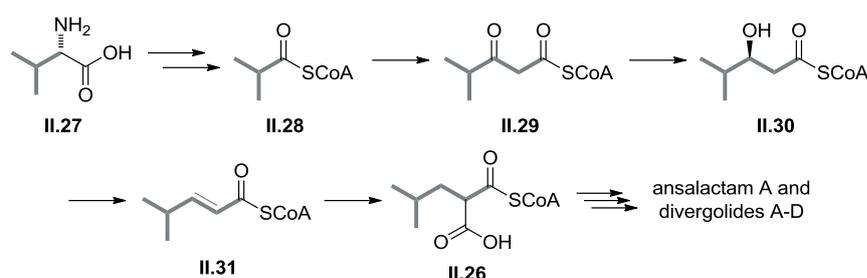


Scheme II.6. Formation of divergolides C and D (**II.2** and **II.3**) via two different cyclization modes.^{[5]n}

Most fascinating fact in Hertweck's proposed biosynthesis of divergolides is the assumption that all four natural products fit into one biosynthetic scheme starting from one shared precursor **II.23**. The flexible and diverse cyclization modes of this precursor finally lead to divergolides, named after the proposed biosynthetic pathway. Yet, it is still not clear, whether the proposed acyl migration in **II.23** takes place prior to or during the cyclization processes, leaving room for further speculations.

ⁿThis scheme was adopted from: L. Ding, A. Maier, H.-H. Fiebig, H. Görls, W.-H. Lin, G. Peschel, C. Hertweck, *Angew. Chem. Int. Ed.* **2011**, *50*, 1630–1634.

A comparison of biosynthetic pathways of all five natural shows interesting analogies. For instance, an AHBA derived acyl starter unit is involved in the synthesis of ansalactam A (**II.1**) as well as in the biogenesis of divergolides A-D (**II.16**, **II.17**, **II.2** and **II.3**).^[4-5,74] All natural products biogeneses involve interesting and diverse cyclization modes leading to the formation of the rigid 'basket' structures. Remarkably, these newly isolated ansa macrolides all share a novel branched PKS extender unit. This isobutyryl malonyl-CoA unit was observed for the first time in this class of natural products.^[4-5] Based on [D_7]-isobutyrate and [D_8]-valine feeding experiments as well as on extensive genome analysis, Hertweck and co-workers concluded that the isobutyryl based extender unit **II.26** is derived from valine **II.27**, which is processed in the first steps to isobutyryl-CoA (**II.28**) (Scheme II.7). Next, isobutyryl-CoA is elongated to **II.29** by the action of KS III. Further transformation to hydroxyl-CoA ester **II.30** catalyzed by 3-hydroxybutyryl-CoA dehydrogenase (HBDH) give after elimination of water dimethylcrotonyl-CoA (**II.31**). The newly identified crotonyl-CoA reductase/carboxylase promotes a reductive carboxylation to provide the novel isobutyryl malonyl-CoA extender unit (**II.26**).^[75]



Scheme II.7. Formation of the unusual isobutyryl malonyl-CoA extender unit **II.26** proposed by Hertweck's group.^[75]

The enormous flexibility of the described biosynthetic pathways leading to the ansa macrolides **II.1-III.3**, **II.16** and **II.17** as well as the variety of potential cyclization possibilities, especially in the case of formation of divergolides C and D (**II.2** and **II.3**) sparked our interest. Specifically, the naphthalene based ansamycines, ansalactam A (**II.1**), divergolide C (**II.2**) and divergolide D (**II.3**) drew our attention. Thus, we intended to develop synthetic ways based on the described biomimetic steps leading to the formation of these natural products using similar precursors.

5.5. Project Aims

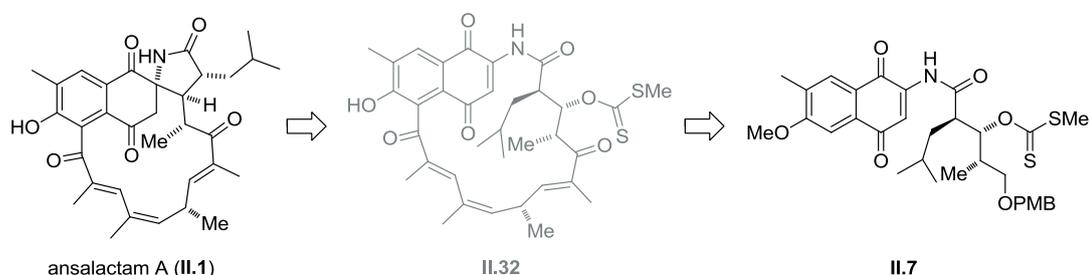
The first goal of this project was to develop a biomimetic pathway to a model precursor of ansalactam A (**II.1**) and to test the proposed radical cyclization reaction forming the spiro γ -lactam functionality. Secondly, we envisioned to develop a synthetic entry to divergolides C and D (**II.2** and **II.3**) starting from the same advanced intermediate. As key steps of the projected

route we planned to apply the supposed biomimetic conjugate and aldol additions forming the 5-membered and 7-membered lactam rings of the natural products.

The synthetic progress toward ansalactam A and divergolides C and D, as well as the discoveries and challenges of the envisioned synthetic pathways are discussed in detail in the next sections.

6. Results and Discussion – Ansalactam A

Along the lines of the proposed biosynthetic spiro γ -lactam formation described above, we intended to incorporate this biomimetic ring closure into our synthetic studies toward ansalactam A (**II.1**). Since we considered the radical mechanism to be more likely involved in the biosynthesis our attempts were focused on the synthesis of the appropriate precursor capable of radical formation. To be able to approve the envisaged biomimetic step, we decided to perform the screening for this reaction on an easier accessible model system **II.7**, which lacks the macrocycle of the possible natural product precursor **II.32**. As a handle for the intended radical formation, we have chosen to install a xanthate functionality in the β -position to the amide bond in **II.7**. Xanthates have been extensively used for directed radical formations (Scheme II.8).^[76]



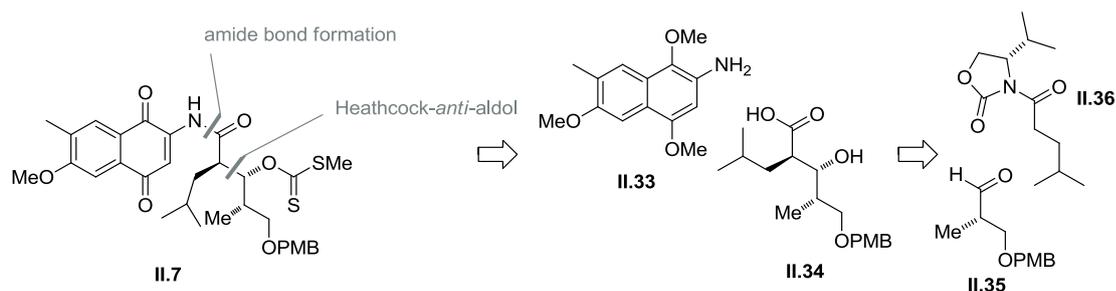
Scheme II.8. Retrosynthetic considerations regarding the model precursor **II.7** for the spiro γ -lactam formation in ansalactam A (**II.1**).

A suitable strategy had to be developed for the synthesis of the model system **II.7**, which account for the highly substituted *anti-syn*-pattern of the aliphatic side chain attached to the aromatic portion. The acquisition of the naphthoquinone system is discussed in the following section.

6.1. Synthesis of the Model Precursor

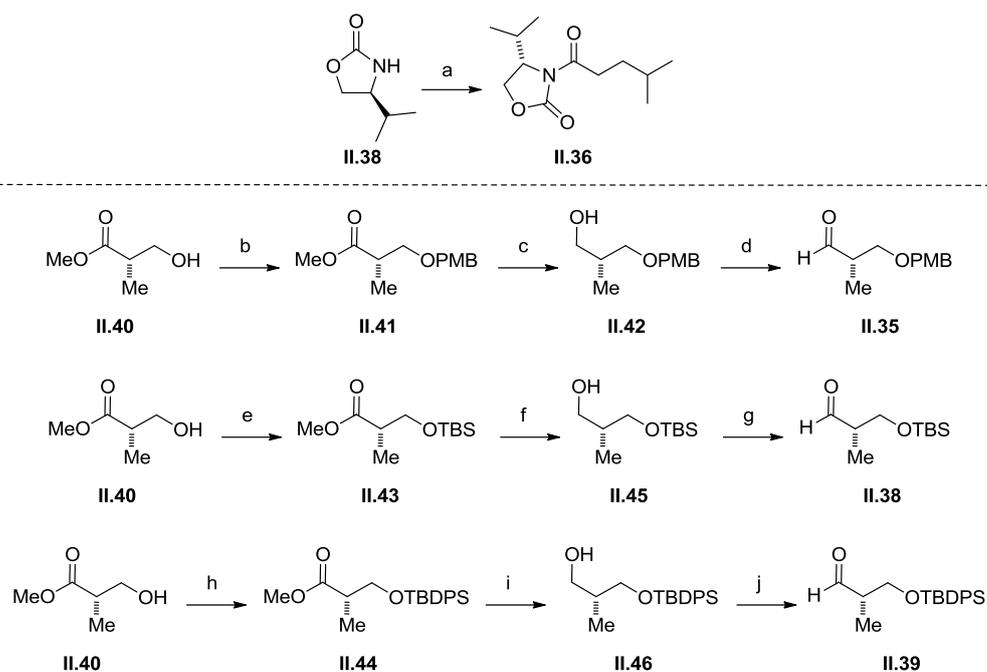
In our retrosynthetic considerations we envisioned the assembly of the model system **II.7** through an amide bond formation between the corresponding aminonaphthalene portion **II.33** and the appropriated β -hydroxy-acid **II.34**.^o This side chain in turn, can be traced back to the (*S*)-Roche ester derived aldehyde **II.35** and acylated Evans auxiliary **II.36**. The desired *anti-syn*-substitution relationship was planned to be installed in a Heathcock-*anti*-aldol reaction (Scheme II.9).

^oThis work was performed in cooperation with C. Kuttruff, a PhD student in the Trauner group. The assembly of the naphthalenic portion **II.33** and its derivatives was a part of the PhD thesis of C. K. and will not be discussed herein.



Scheme II.9. Retrosynthetic analysis of the model naphthoquinone system **II.7**.

The first steps of the synthesis of the β -hydroxy acid **II.34** follow well-established literature known protocols (Scheme II.10). The acylated L-valine based Evans auxiliary **II.36** was could be obtained according to a procedure by Joullié *et al.*^[77] A nucleophilic addition of lithium anion of Evans auxiliary **II.37**^[78] to 4-methylvaleric acid, which was activated *in-situ* by pivaloyl chloride forming the corresponding mixed anhydride, gave the desired product in 89% yield on gram scale.



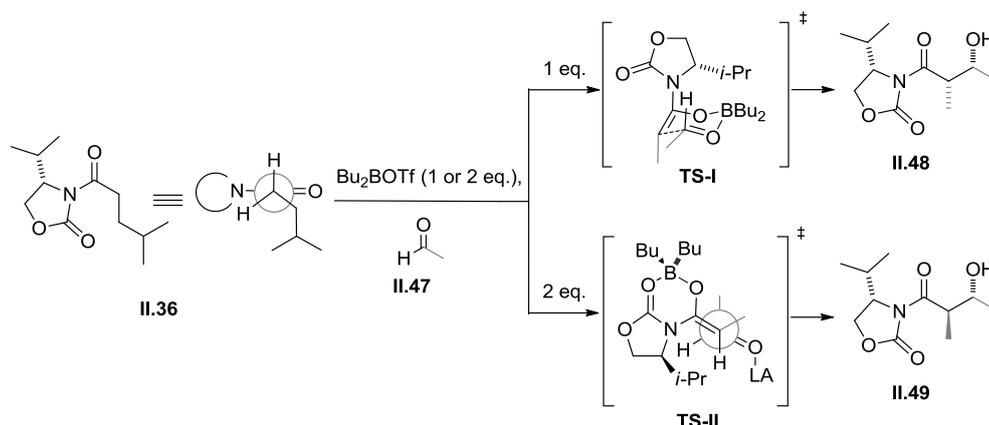
Reaction conditions: (a) 4-methylvaleric acid, NEt₃, pivaloyl chloride, 0 °C, THF; *n*-BuLi, THF, -78 °C, 80%; (b) PMBOH, PPTS, trichloroacetonitrile, Et₂O, CH₂Cl₂, rt, 94%; (c) LAH, THF, 0 °C, 92%; (d) DMP, CH₂Cl₂, rt, 93%; (e) TBSCl, im, CH₂Cl₂, rt, 99%; (f) DIBAL-H, CH₂Cl₂, -78 °C, 86%; (g) DMP, CH₂Cl₂, rt, 84%; (h) TBDPSCI, im, CH₂Cl₂, rt, 93%; (i) DIBAL-H, CH₂Cl₂, -78 °C, 82%; (j) DMP, CH₂Cl₂, rt, quant.

Scheme II.10. Synthesis of the aldol reaction partners imide **II.36** and aldehydes **II.35**, **II.38** and **II.39**.

As electrophilic reaction partners for the envisioned aldol reaction, three aldehydes **II.35**, **II.38** and **II.39** containing different protecting groups at the terminal alcohol position were synthesized (Scheme II.10). This variation of protecting groups should allow for more flexibility in the investigation of the appropriate Heathcock-*anti*-aldol conditions. Thus, in the first case, the (*S*)-Roche ester (**II.40**) was protected as its PMB ether **II.41** and, following literature known

procedures,^[79] converted to the aldehyde **II.35** via the corresponding alcohol **II.42**, which was oxidized with Dess-Martin periodinane. A similar literature protocol was used for the synthesis of the analogous silyl protected aldehyde derivatives.^[80] Hence, the protection of (*S*)-Roche ester (**II.40**) as TBS- and TBDPS-ethers **II.43** and **II.44** was followed by the reduction of the ester functionality with DIBAL-H affording the corresponding alcohols **II.45** and **II.46** in high yields. The TBS- and TBDPS-protected aldehydes **II.38** and **II.39** were obtained using Dess-Martin periodinane promoted oxidation of the primary alcohol in **II.45** and **II.46**, respectively, and were used without further purification in the Heathcock-*anti*-aldol screening.

With both reaction partners in hand, attempts toward the projected synthesis of β -hydroxy acid **II.34** were performed. One of the major challenges in the following aldol reaction is the selective installation of the three contiguous stereocenters showing an *anti-syn*-relationship. Specifically, we figured it might cause some problems due to the sterically demanding *iso*-butyl substituent in the α -position to the carboxy group in **II.34**. In this context, we decided that the best method to face this problem would be the well established Heathcock-*anti*-aldol reaction (Scheme II.11).^[81]



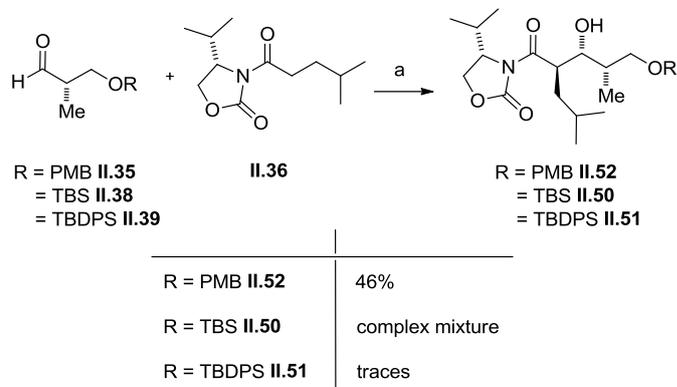
Scheme II.11. Mechanistic rationale behind the Evans and non-Evans aldol reactions.

The Heathcock-*anti* aldol reaction is a variation of the Evans aldol^[82] reaction. Both methods have been used extensively for stereospecific formation of β -hydroxy carbonyl compounds containing an α -substituent.^[83] The stereospecificity of these reactions is controlled by a chirality transfer from the Evans auxiliary, in our case L-valine derived auxiliary, attached to the nucleophilic reaction partner.^[84] In most cases, the auxiliary based stereochemistry control overrides the substrate selectivity. The *syn*-/*anti*- relationship in the product of both reactions can be controlled by the amount of the Lewis acid involved in the transformation.^[85] Thus, a deprotonation of the most stable conformer of oxazolidinone **II.36**, in the Newman projection of which the sterical hindrance between the alkyl chain and the auxiliary is minimized, leads to the exclusive formation of *Z*-enolate (Scheme II.11). In the case of the classical *syn*-Evans aldol

reaction, which proceeds in the presence of only one equivalent of di-*n*-butylboron triflate, this enolate is believed to react with any aldehyde **II.47** in a closed transition state **TS-I** according to the Zimmerman-Traxler^[86] model.^[83] Dipole minimization leads to a transition state, in which both carbonyl groups point in opposite directions. This 6-membered transition state is preferred over other possible and leads to high enolate face selectivity of the reaction providing preferentially *syn*-product **II.48** (Scheme II.11).

In the case of the non-Evans-Heathcock-*anti*-aldol reaction, which was first reported in 1991, the addition of two equivalents of di-*n*-butylboron triflate is assumed to furnish the formation of an open transition state **TS-II** most stable in the antiperiplanar conformation leading to the formation of the *anti*-product **II.49** (Scheme II.11).^[81]

Following the Heathcock-*anti*-aldol reaction, the linkage of the two reaction partners was performed. Using the TBS- and TBDPS-protected aldehydes **II.38** and **II.39**, no or only traces of the corresponding β -hydroxy compounds **II.50** and **II.51** were observed. However, when the reaction was performed using the PMB-protected electrophile **II.35**, aldol product **II.52** was formed in moderate 46% yield (Scheme II.12). In this case, the auxiliary controlled stereochemical outcome of the reaction matches the expected substrate controlled stereochemical outcome, which can be predicted by the Felkin-Anh model.

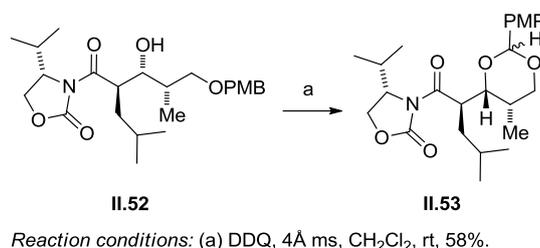


Reaction conditions: (a) 2 eq. Bu₂BOTf, DIPEA, 3Å ms, Et₂O, -78 °C

Scheme II.12. Screening of substrates best suitable for *anti*-aldol reaction.

The described transformation required careful optimization. The resulting product **II.52** could only be obtained, when excess reagent was quenched with pH 7 phosphate buffer. Other work up procedures led to the re-isolation of starting materials. The moderate yield as well as the need for neutral work up conditions is presumably caused by a competing retro-aldol process. Supposedly, the retro-aldol reaction of substrate **II.52** is preferred specifically in this case caused by the sterically demanding α -*iso*-propyl substituent leading to sterically adverse situation in the final product.

In order to prove the stereochemical relationship between the three contiguous substituents in the β -hydroxy chain, the corresponding cyclic PMP-acetal **II.53** was synthesized. Thus, treatment of the aldol product **II.52** with DDQ under strictly anhydrous conditions in the presence of molecular sieves provided the corresponding unstable PMP-ether **II.53** as a single diastereomer in 58% yield (Scheme II.13).



Scheme II.13. Synthesis of the PMP-acetal **II.53**.

Using ¹H-, ¹³C- and 2D-NMR methods an extensive analysis of compound **II.53** was performed. However, caused by the overlap of several signals in the proton NMR spectrum, only limited conclusions could be made. Specifically significant was one signal in the NOESY spectrum showing a clear correlation between the methyl substituent in C4 position and the protons of the PMP group (Figure II.4).

Assuming that the most stable diastereomer of **II.53** would be the one with a configuration at the newly formed benzylic stereocenter leading to the structure with the most sterically demanding substituents in the equatorial position, led to the following assumptions: Knowing that the stereocenter at C4 is *S*-configured, four possible diastereomers can be formed during the described aldol reaction. Two of them possess a 2,3-*anti*-3,4-*syn* and 2,3-*syn*-3,4-*syn* relationship between the substituents at C2, C3 and C4 and *R*-configuration at the benzylic stereocenter, as shown in **II.53-A**, **II.53-B** (Figure II.4). The other show a 2,3-*syn*-3,4-*anti* and 2,3-*anti*-3,4-*anti* relationships between the substituents at C2, C3 and C4 and *S*-configuration at the benzylic stereocenter, as shown in **II.53-C** and **II.53-D**, respectively (Figure II.4). The most stable chair conformations of these diastereomers indicate that the observation of the detected C4-methyl-PMP NOESY-correlation could only be made with the diastereomers **II.53-A** and **II.53-B** possessing a *syn* relationship between the C3 and C4 substituents. In the case of 3,4-*anti* configured diastereomers **II.53-C** and **II.53-D** the corresponding protons are too far away from each other to be able to cause the observed NOESY signal (Figure II.4). From this logic, we were able to conclude that the stereocenter at C3 was *R*-configured. However, at this stage of the project we were not able to proof the stereochemistry of the C2 position, which according to the mechanistic model of the Heathcock-*anti*-aldol should be *R*-configured as shown in **II.53-A**.

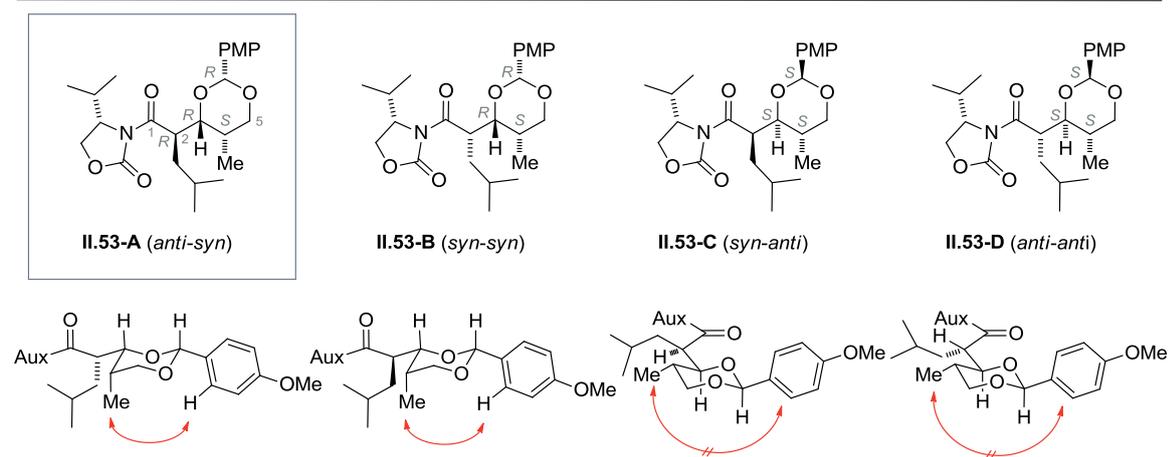
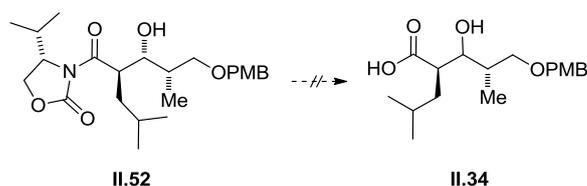


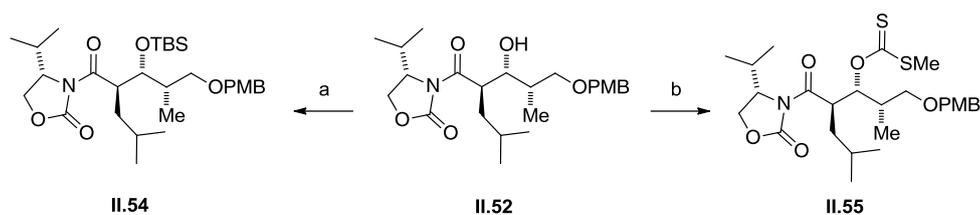
Figure II.4. Stereochemical analysis of the four possible isomers of PMP-ether **II.53** based on the observed NOESY-correlation (red).

In order to obtain the free β -hydroxy acid **II.34**, the hydrolysis of the Evans auxiliary in **II.52** was approached (Scheme II.14). Based on our earlier observations, which showed that **II.52** is prone to undergo a retro-aldol reaction, it was not surprising that the desired hydrolysis turned out to be problematic. All applied conditions (among them NaOH, LiOH, LiOH/H₂O₂, HCl/H₂O, MeO⁻, Me₃SnOH, EtS⁻ and others)^[87] led to decomposition of the starting material.



Scheme II.14. Approached cleavage of Evans auxiliary in oxazolidinone **II.52**.

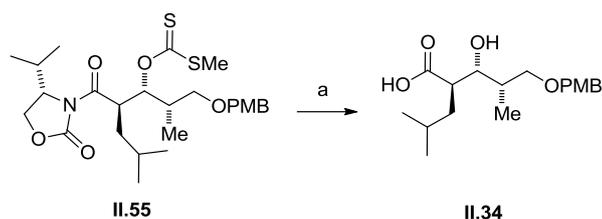
Based on these results, we decided to protect the free hydroxy group of oxazolidinone **II.52**, which would help to avoid the retro-aldol pathway. Among screened conditions, only the subjecting of the starting material **II.52** to tributylsilyl triflate in the presence of 2,6-lutidine led to the formation of isolable amounts of TBS-ether **II.54** (Scheme II.15). Unfortunately, the yield of the reaction could not be improved and we had to reconsider our choice of the protecting group. Finally, we found appropriate conditions for 'protection' of the secondary alcohol in **II.52** as a xanthate in **II.55**.



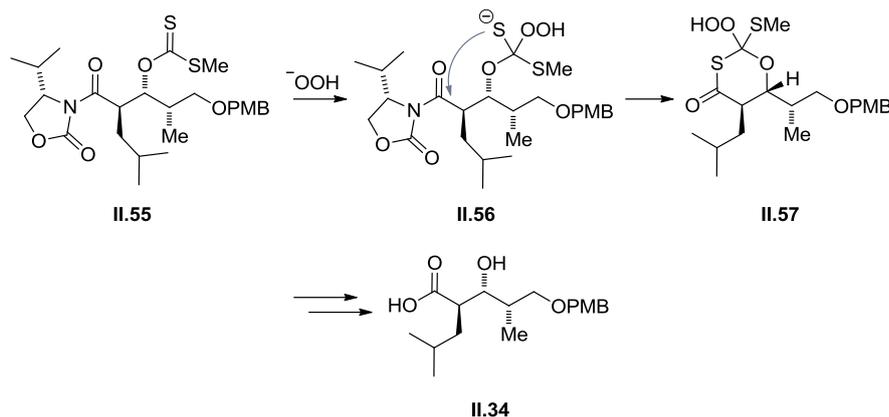
Reaction conditions: (a) TBSOTf, 2,6-lutidine, CH₂Cl₂, -10 °C → rt, 29%; (b) CS₂, NaHMDS, -78 °C; → MeI, 0 °C → rt, 60%.

Scheme II.15. Protection of oxazolidinone **II.52** as TBS-ether **II.54** and xanthate **II.55**.

We were hoping that the xanthate group in **II.55** would stay intact or at least help to promote the hydrolytical cleavage of the Evans auxiliary preventing retro-aldol reaction. Fortunately, treatment of xanthate **II.55** in basic hydrogen peroxide solution provided the highly temperature sensitive β -hydroxy acid **II.34** in 95% yield. We think that an intramolecular acyl transfer mechanism is the key to overcome the undesired retro-aldol reaction (Scheme II.16). Thus, we suppose that the peroxy anion first attacks the xanthate group in **II.55** forming the anionic intermediate **II.56**, which allows for an intramolecular auxiliary cleavage *via* the formation of a 6-membered ring in **II.57** giving finally after additional hydrolysis the desired product **II.34**.



Reaction conditions: (a) H₂O₂, LiOH, THF/H₂O, 0 °C → rt, 95%.

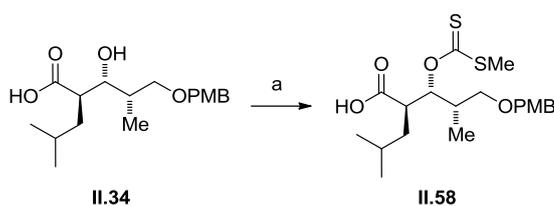


Scheme II.16. Cleavage of the Evans auxiliary promoted by the xanthate group of **II.55** and the proposed mechanism.

The hydrolytical cleavage of the Evans auxiliary in substrates with sterically demanding substituents in the α -position is known to be problematic. There are some literature examples of intramolecularly promoted auxiliary hydrolyses, for instance with the assistance of an appendent hydroxyl group.^[88] So far, no general cleavage method for sterically challenging substrates has

been reported. The detour *via* described xanthate formation leading to intramolecular effect in the hydrolytical cleavage of the Evans auxiliary might represent a suitable general method of choice also for other sterically hindered substrates.

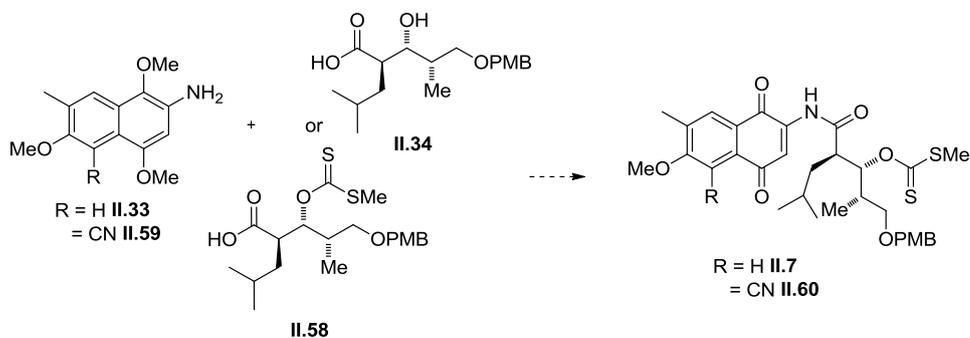
As we intended to have a xanthate functionality also in the model system for the radical cyclization, the acid **II.34** was converted to the corresponding xanthate derivative **II.58** using the same protocol as for the formation of **II.55**. Treatment of acid **II.34** with carbon disulfide as a solvent in the presence of NaHMDS followed by methylation with methyl iodide provided the acid **II.58** in 84% yield (Scheme II.17).



Reaction conditions: (a) CS₂, NaHMDS, -78 °C; → MeI, 0 °C → rt, 84%.

Scheme II.17. Synthesis of the xanthate **II.58**.

With the acids **II.34** and **II.58** in hand, the synthesis of the model system was completed (Scheme II.18). As a coupling partner the naphthalenic amines **II.33** and **II.59^p** core were chosen. Accordingly, first attempts aiming for the construction of amides **II.7** and **II.60** were made.

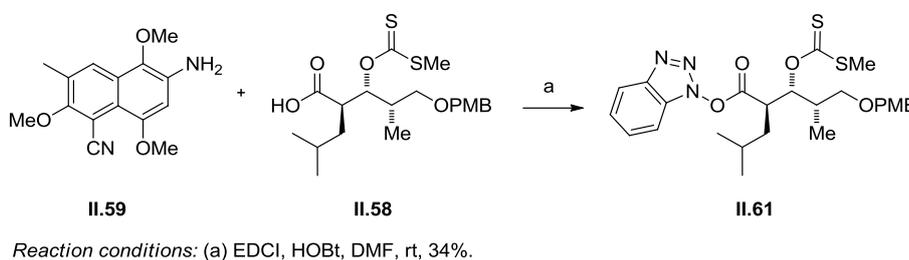


Scheme II.18. Envisioned assembly of the model system **II.7** a precursor for the proposed biomimetic radical cyclization step.

Initially, we focused on classical amide coupling conditions to achieve the desired transformation. However, all attempts in this direction, standard protocols such as EDCI/HOBt, EDCI/HOBt/DIPEA, EDCI/DMAP, PyBOP/DIPEA and T3P (propylphosphoric anhydride)/pyridine together with a variation of coupling partners and solvents, did not lead to the formation of the desired amides. In most cases, especially in the presence of a base in the reaction

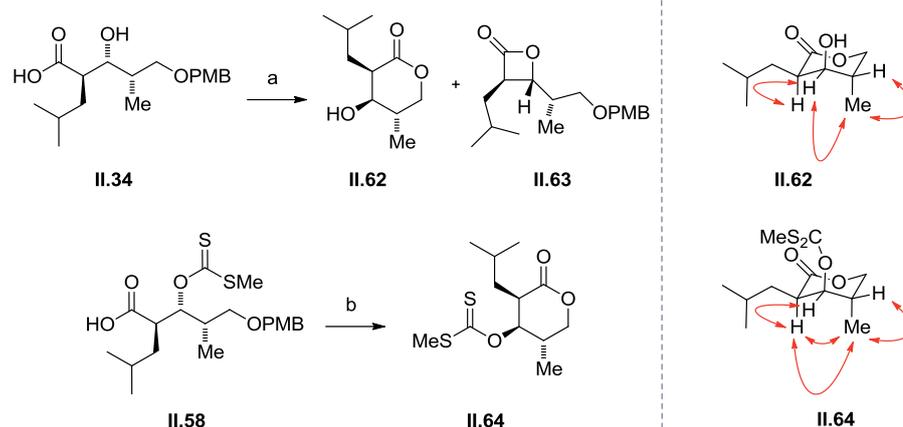
^pBoth naphthalenic systems **II.33** and **II.59** were kindly provided by C. Kuttruff. For experimental procedures for the preparation of both compounds see: C. A. Kuttruff, PhD Thesis, Ludwig-Maximilians-Universität, München, 2012.

mixture, decomposition of the acid coupling partners **II.34** and **II.58** was observed whereas the naphthalenic coupling partners remained intact. Apparently, the amide coupling was slower than the base mediated retro aldol reaction leading to xanthate removal in **II.58** and decomposition of both acid coupling partners **II.34** and **II.58**. Interestingly, when a solution of naphthalene **II.59** and xanthate **II.58** in dry DMF was subjected to EDCI/HOBt coupling conditions, formation of the HOBt-ester **II.61** in low yields was observed (Scheme II.19). In further attempts, even if the more reactive HOBt-ester **II.61** was used as a potential coupling partner, the desired amide products could not be obtained. Over prolonged reaction times and at elevated temperatures only decomposition of the aliphatic coupling partners **II.34** and **II.58** was observed. Based on these results, a new strategy was developed.



Scheme II.19. Synthesis of the reactive HOBt-ester **II.61**.

In order to have a more reactive derivative of acids **II.34** and **II.58**, synthesis of the corresponding acid chlorides was approached. Unfortunately, classical reagents used for acid chloride formation such as thionyl chloride or benzenesulfonyl chloride did not give any product. Treatment of acid **II.34** with Ghosez's reagent led to the cleavage of the PMB-group forming a 6-membered lactone **II.62** in 51% yield. As a byproduct the β -lactone **II.63** was isolated (Scheme II.20). The formation of both cyclic lactones *via* an intramolecular ring closure implied that the corresponding acid chloride was formed in the course of the process, but then trapped intramolecularly. A similar PMB-deprotection process was also observed, when xanthate **II.58** was subjected to the same reaction conditions providing the 6-membered lactone **II.64** in 65% yield. Both 6-membered lactones **II.62** and **II.64** were used to verify the proposed stereochemistry of acid **II.34**. Indeed, the observed NOESY correlations in the presumably most stable chair conformations of **II.62** and **II.64** confirmed the stereochemical assumptions of the *anti-syn* relationship in **II.34** (Scheme II.20).

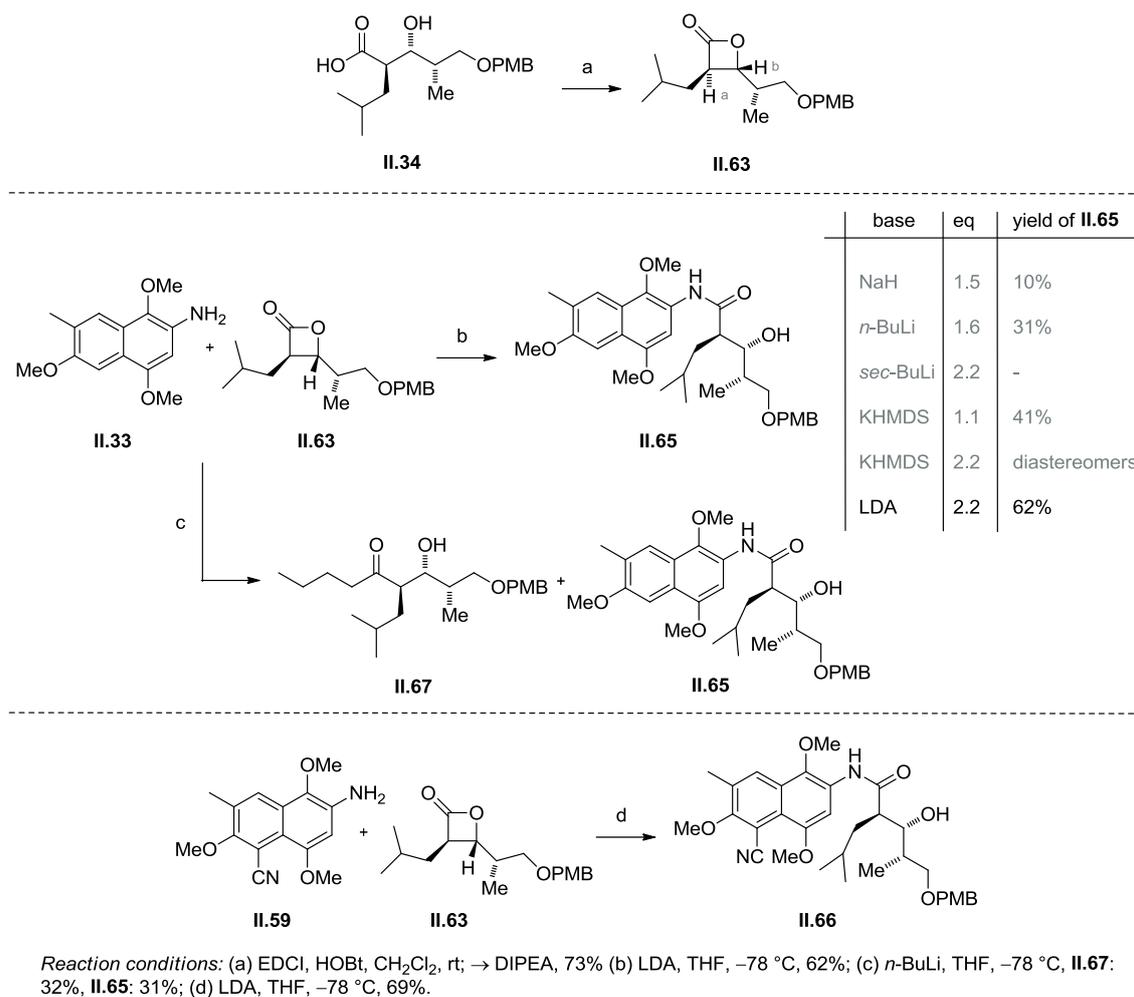


Reaction conditions: (a) 1-chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez's reagent), CH_2Cl_2 , rt, **II.62**: 51%, **II.63**: 16%; (b) 1-chloro-*N,N*,2-trimethyl-1-propenylamine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt}$, 65%.

Scheme II.20. Synthesis of the lactones **II.62**, **II.63** and **II.64** and stereochemical analysis based on the observed NOESY correlations in the spectra of **II.62** and **II.64** (red).

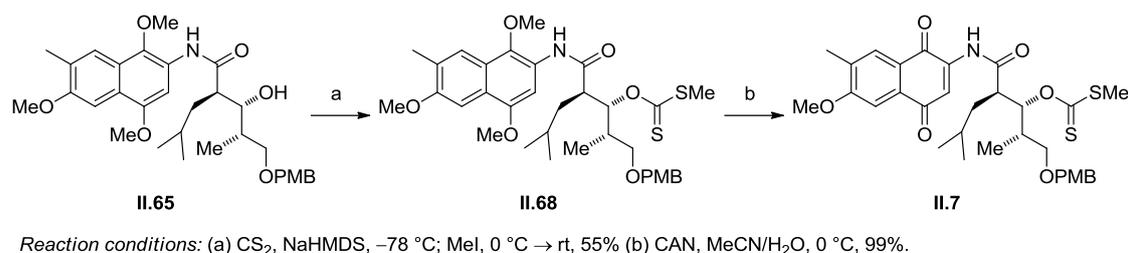
The synthesis of β -lactone **II.63** turned out to be of great importance. On the basis of this result, we decided to use this lactone as electrophile in our synthetic approach. We believed that the deprotonated aminonaphthalene **II.33** could open the β -lactone **II.63** providing the entry to the desired amide. For this purpose, the protocol for the formation of **II.63** was improved. Intramolecular EDCI/HOBt coupling involving a late addition (after 12 hours) of DIPEA furnished β -lactone **II.63** in 73% yield (Scheme II.21). The missing NOESY-correlation of protons Ha and Hb indicated also in this structure the anti relationship between the *iso*-propyl and the oxygen substituents. With the lactone **II.63** in hand, different bases to achieve the formation of the amides **II.65** and **II.66** were tested.

The best results giving 62% of the desired amide **I.65** were achieved using LDA as a base for the deprotonation of amine **II.33** (Scheme II.21). The use of 2 equivalents of LDA turned out to be crucial for the yield of the reaction. Presumably, the second equivalent of the base deprotonates the newly formed amide, preventing possible retro aldol process. Interestingly, when KHMDS was used as a base, a diastereomeric mixture of **II.65** was isolated. Treating the starting materials with *n*-BuLi at low temperatures led to a nucleophilic attack of the base into the β -lactone system, providing ketone **II.67** and the amide **II.65** as a byproduct. The optimized LDA conditions were also used for the reaction of the cyano naphthalene **II.59** with **II.63**. Under these conditions, the corresponding amide **II.66** could be isolated in satisfying 69% yield.



Scheme II.21. Synthesis of the β -lactone **II.63** and its application in the syntheses of amides **II.65** and **II.66**.

With the developed strategy for the synthesis of the amide **II.65** the envisioned formation of naphthoquinone **II.7** was accomplished in only two additional steps (Scheme II.22). Xanthate formation, using carbon disulfide as solvent, provided xanthate **II.68** in moderate yields. Finally, a high yielding cautious CAN-promoted deprotection and oxidation of the hydroquinone moiety completed the synthesis of the model system **II.7**.



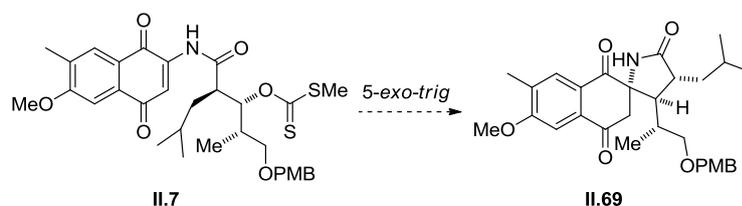
Scheme II.22. Last steps in the synthesis of the precursor for the proposed biomimetic radical cyclization.

With the requisite xanthate precursor **II.7** in hand, suitable for the envisioned directed radical formation, investigations of ability of **II.7** to engage in the radical cyclization process were made.

6.2. Toward the Radical Cyclization

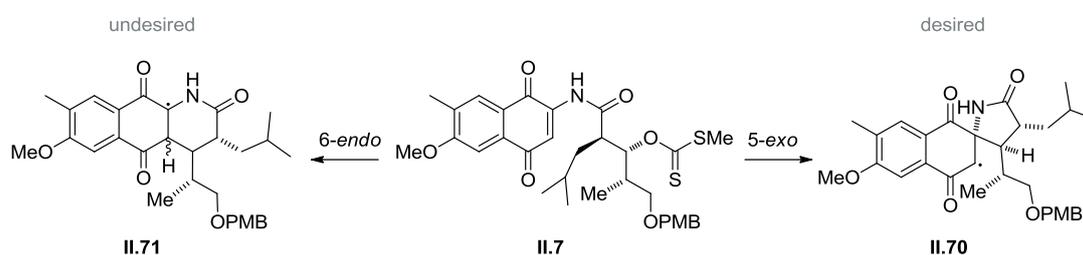
Radical mediated transformations represent a powerful method for C-C bond formation and have been broadly used in organic synthesis.^[89] Among them, radical cyclization reactions were extensively studied for the construction especially of 5- and 6-membered ring systems. Based on experimentally obtained results, rules for the cyclization modes were postulated, known as Baldwin's rules. According to this assumptions, the cyclizations can be classified into two main groups: *endo* and *exo* cyclizations.^[89b] Caused by the high reactivity of radical intermediates, radical reactions are mostly kinetically controlled. In general, 5-*exo* cyclizations are faster than the 6-*endo* cyclizations within the same system, and represent the main pathway. The success of a particular cyclization mode in a defined ring system depends on the hybridization of the bond, which is attacked by a radical. The preferable approach angle for the cyclization on a sp²-hybridized system, as is in our case, is 109°. Although the regiochemistry of radical cyclizations was subject of intense investigations, still there are many open questions. For instance, it was shown, that not only the kinetic control is crucial for the regiochemical outcome of these reactions. In some cases the thermodynamic stability of the resultant radical intermediates can lead to kinetically unfavored yet thermodynamically preferred 6-*endo* cyclizations.^[90] In addition, introduction of heteroatoms such as oxygen, sulfur or nitrogen, changes the flexibility and bond length in the corresponding systems as well as the rate constant for the ring closure, eventually leading to unexpected cyclization modes.^[90]

Although radical cyclizations can face regioselectivity problems described above, they have been successfully utilized as key steps in several natural product syntheses.^[37,91] Our envisioned biomimetic approach toward the synthesis of ansalactam A (**II.1**) is based on a radical 5-*exo-trig* cyclization of the radical induced in the side chain onto a naphthoquinone in **II.7** providing spiro- γ -lactone **II.69** (Scheme II.23).



Scheme II.23. Envisioned radical key step: formation of the spiro- γ -lactam portion of ansalactam A (**II.1**).

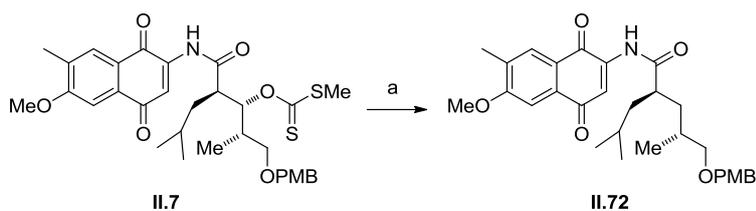
Several examples for radical cyclizations onto quinone derivatives have been reported in the literature.^[92] To our knowledge, formation of spiro systems involving amino-naphthoquinones have not been described, so far. Hoping for a kinetically controlled pathway and adequate flexibility of the aliphatic chain in **II.7**, we envisioned to cause the spiro- γ -lactone formation promoted by an appropriate radical starter. Nevertheless, thermodynamic aspects of this reaction had to be considered. This raises the question of determining the most stable radical intermediate. For our system, there are two possibilities: is it the secondary radical **II.70** formed by the desired 5-*exo* cyclization, which is additionally stabilized by the adjacent carbonyl functionality or is it the tertiary radical **II.71**, which is highly stabilized by amino and carbonyl groups, resulting from the undesired 6-*endo* cyclization process? (Scheme II.24).



Scheme II.24. Two possible cyclization pathways of model system **II.7**.

From the thermodynamic point of view, the formation of the more substituted radical **II.71** additionally stabilized by its carbonyl and amino substituents will be preferred in the approached reaction. However, does this thermodynamic argument have the ability to outbalance the kinetic control observed in the most radical cyclization processes? We figured that the envisioned reaction would be an example for a fine balance between the two possible pathways and thus difficult to predict.

In order to find out which ring closure is preferred, xanthate **II.7** was subjected to radical forming conditions. Addition of AIBN and tributyltin hydride solution to a solution of xanthate in benzene or toluene at elevated temperatures, only led to decomposition of starting material. However, when the order of the addition was reversed, and a solution of xanthate was added to AIBN and tributyltin hydride solution at elevated temperatures, an exclusive formation of the Barton-McCombie product **II.72** was observed (Scheme II.25). The formation of this product can be reasoned by a high concentration of tributyltin hydride in the course of the reaction.



Reaction conditions: (a) AIBN, Bu₃SnH, benzene, 80 °C, 72%.

Scheme II.25. Observed Barton-McCombie reaction resulting in the formation of the deoxygenated naphthoquinone **II.72**.

The desired formation of the spiro γ -lactam **II.69** could not be achieved, so far. Several protocols still have to be tested to effect the desired transformation. Subtle optimization of radical reaction conditions is needed. For instance, variation of solvents, temperature, order of addition and concentrations can have a great influence on the reaction outcome^[90] and might assist in the formation of the spiro compound **II.69**. Additionally, other radical starters and hydride sources, such as silicon based hydrides^[93] can be used and might change the course of the reaction.

One additional aspect of the aimed radical cyclization needs to be considered. The starting material **II.7** is an amide that can theoretically exist as four isomers with respect to the orientation of the amide substituents and quinone moiety (Figure II.5). The isomers **II.7-A** and **II.7-D** show a sterically adverse situation, as in the case of **II.7-A** both amide residues clash into each other and in the structure **II.7-D** the lone pairs of both carbonyl groups would electronically repel each other. This considerations based on a simple conformational analysis suggest that it is unlikely that these two isomers significantly participate in the main population of the molecule. The situation in the isomers **II.7-B** and **II.7-C** is less obvious. The *anti*-isomer **II.7-C**, with respect to the alkyl substituents, is considered to be more stable for the most amide systems in comparison to the corresponding *syn*-isomer **II.7-B**. Transferred to the desired reaction, this would mean that in the presumably more stable *anti*-isomer **II.7-C** the induced radical center in the β -position to the amide functionality, would be turned away from the double bond that needs to be attacked in order for the cyclization to occur. In that case, the desired radical cyclization would be disfavored by the geometrical properties of the starting material. Based on these considerations, we intended to find out which of these two isomers is the most populated in the reaction mixture. For this purpose, a conformational search for both isomers **II.7-B** and **II.7-C** followed by DFT optimization (B3LYP/6-31G(d) basis set) were performed.⁹

First a conformational search on both isomers using MMFF force field with MacroModel (Version 9.0; MMFF/gas phase/PRCG/500 steps) was made.^[47] Then, in both cases significant conformers were picked and redundant isomers were discarded. Using this approach, 20

⁹The DFT optimizations were performed with the help of E. Herero-Gómez, a postdoctoral researcher in the Trauner laboratories.

conformers for *anti*-isomer **II.7-C** were selected for further calculations. In the case of *syn*-isomer **II.7-B**, 30 conformers were subjected to further investigations. For *syn*-isomer **II.7-B**, the rotation around the C-N-CO bond had to be fixed during the conformational search, in order to avoid its rotation to the *anti*-isomer **II.7-C**.

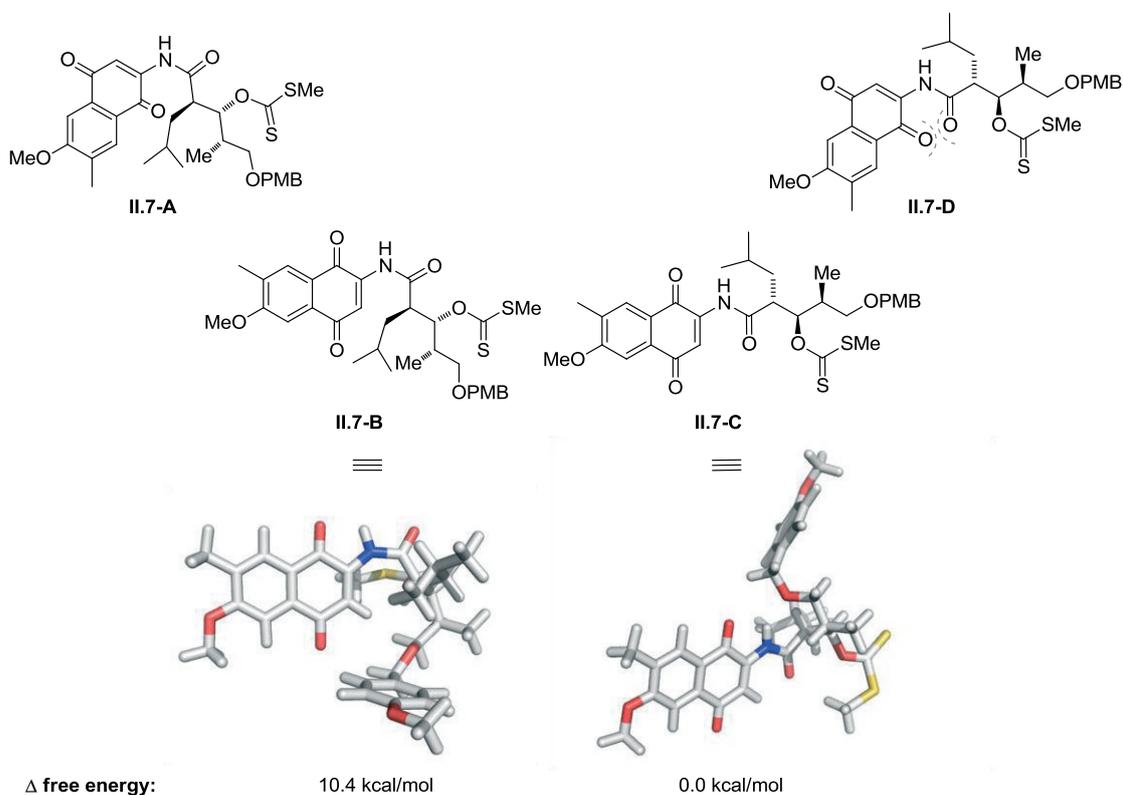


Figure II.5. Structure of four possible isomers of **II.7** and DFT structures of **II.7-B** and **II.7-C** with corresponding differences of the free energy.

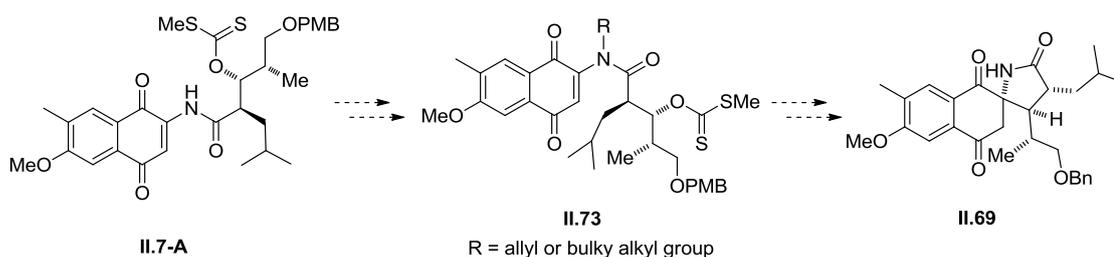
Selected structures were optimized using DFT calculations at B3LYP/6-31G(d) level. This level of theory has proven to possess the best cost-output benefit for sulfur containing structures and has been widely applied to organic molecules.^[94] One major conformer for *anti*-isomer **II.7-C** was found with an additional conformer close in energy within a range of 1 kcal/mol (difference of free energy of 1 kcal/mol at 25 °C corresponds to 85% of the lower energy conformer in the mixture). In the case of *syn*-isomer **II.7-B**, one major conformer and three other, which are close in energy within a range of 1 kcal/mol were identified. The difference of free energy of the two most stable conformers of *anti*-isomer **II.7-C** and *syn*-isomer **II.7-B** was calculated showing that the *syn*-isomer **II.7-B** is 10.4 kcal/mol higher in its relative free energy than the lowest energy *anti*-isomer **II.7-C**. According to the Boltzmann distribution consideration, this means that most likely no significant percentage of the *syn*-isomer will be present in the reaction mixture at 25 °C (difference of free energy of 3 kcal/mol at 25 °C corresponds to ~1% of the relative contribution of the higher energy conformer). This calculations imply, that for the reaction to occur the *anti*-

isomer **II.7-C** need first to rotate to the higher energy *syn*-isomer **II.7-B**, which would probably need more than 10.4 kcal/mol. Still, the overall process might be thermodynamically favored depending on the stability of the formed product.

7. Summary, Conclusions and Future Work – Ansalactam A.

In summary, a model system **II.7** suitable for the biomimetic radical cyclization process forming the spiro- γ -lactam portion of ansalactam A (**II.1**) was synthesized. A scalable and reliable synthetic sequence for naphthoquinone **II.7** was established, in which problems caused by sterically unfavorable *i*-propyl substituent in the α -position, present in all synthesized intermediates leading to undesired retro-aldol processes, were successfully overcome. Additionally, first attempts toward the envisioned radical cyclization were made. The desired cyclization was not achieved so far, but several reaction conditions remain to be tested, which might lead to the desired 5-*exo-trig* cyclization.

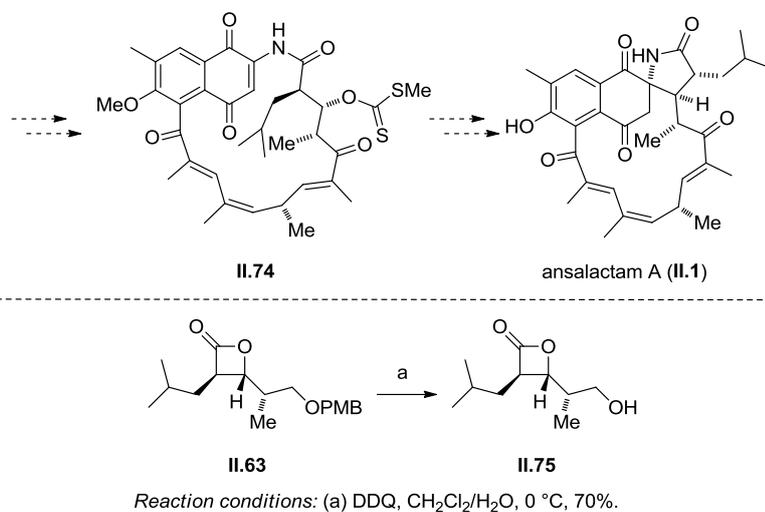
To gain more insight on the proposed cyclization process, DFT calculations of **II.7** were performed. The results of these calculations showed that the desired SYN-conformation **II.7-B** of the amide **II.7** is rather unfavored in comparison to the ANTI-system **II.7-A**, which might complicate the envisioned process. For the future work it is important to account for the described configurational disadvantages. Based on the calculations, it might be necessary to fix the undesired amide SYN-conformation in naphthoquinone **II.7**. This could be achieved *via* two different approaches. On one hand, an additional amide substituent in **II.7** could be introduced, which would favor the SYN conformation in the system. For instance, an allyl or a bulky alkyl substituent on the nitrogen forming compound analogous to **II.73** can be used for this purposes (Scheme II.26).



Scheme II.26. Possible strategy toward the radical ring closure based on the synthesis of postulated SYN-stable substituted amide **II.73**.

On the other hand, prior to the radical key step it might also be helpful to close the macrocycle of the natural product, in which the SYN-amide would be favored, for example, represented by a system similar to **II.74** depicted in scheme II.27. Based on these considerations, the corresponding macrolactam system **II.74** needs to be synthesized. Along this lines, we could show that the PMB-protected β -lactone **II.63** can be easily deprotected using

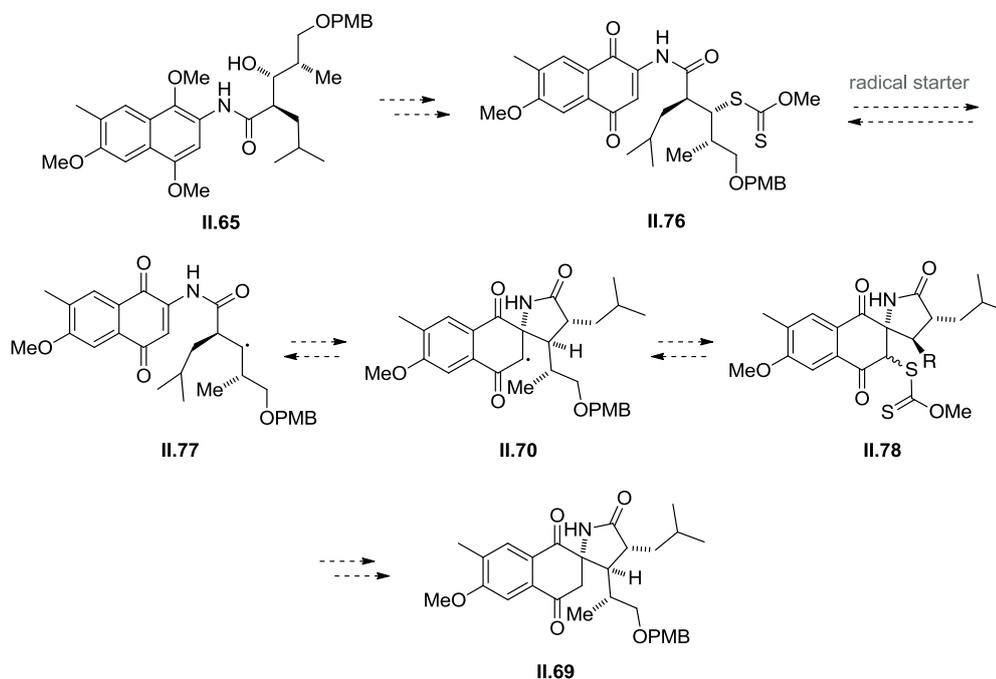
DDQ in the presence of water. This primary alcohol **II.75** can serve as a handle for the installation of the remaining side chain (Scheme II.27).



Scheme II.27. Revised strategy for the key radical ring closure based on the macrocycle **II.74** as key intermediate, as well as the synthesis of the possible intermediate **II.75** with a free handle for further chain assembly

To overcome the observed Barton-McCombie side reaction, hydrogen atom donors, which are milder than tributyltin hydride, can be used. For instance, bulky silanes, e. g. tris(trimethylsilyl)silane ((TMS)₃SiH),^[95] were shown to be less reactive in radical chain reactions avoiding a quick trapping of the newly formed radicals. In addition, it might be helpful to apply a xanthate transfer reaction in the envisioned cyclization step (Scheme II.28). Zard and co-workers could show that the radical reaction of 'reversed' xanthates can be performed without any hydrogen radical source avoiding the formation of Barton-McCombie products.^[76] For this purpose, a system similar to **II.76** needs to be synthesized (Scheme II.28). Reaction of this system with a suitable radical starter would lead to an easy rupture of the carbon-sulfur bond. In this case, the cleavage of the carbon-oxygen bond in the xanthate is unfavored caused by the instability of the newly formed methyl radical. In the absence of a hydrogen radical source, the radical **II.77** cannot be quenched irreversibly. On the contrary, a reaction with a sulfur based xanthate radical is reversible and would provide equilibrium dependent amounts of radical **II.77** prolonging its lifetime in the reaction mixture. This radical will then have enough time to be captured by the less reactive double bond of the naphthoquinone system forming **II.70**. The newly formed, more stable radical **II.70** in turn, can react with the xanthate radical generating **II.78**, which then can be reduced to the desired system **II.69**. The described process is similar to the Kharash halogen transfer reaction,^[96] in the course of which a halogen atom traps the newly formed radical. Intramolecular processes are known to proceed even more easily than the intermolecular xanthate transfer reactions. This reaction can give access to scaffolds, which can be made only with difficulties or not at all using reductive radical conditions. One

limitation of the described alternative might be the reversibility of this thermodynamically controlled process. Thus, a mixture of 5-*exo* and 6-*endo* products might be obtained, depending on the stability of involved radicals.^[76]

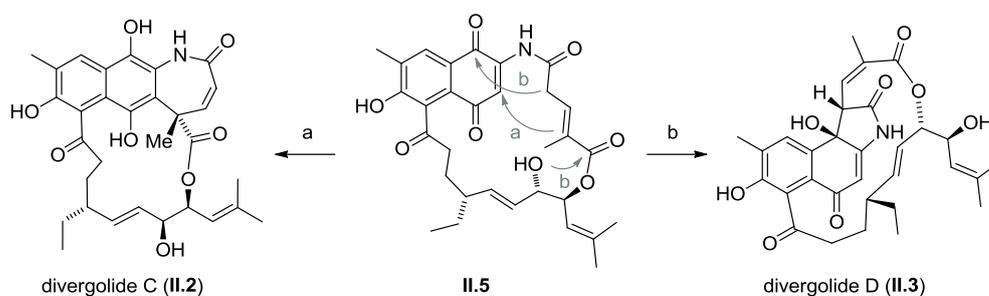


Scheme II.28. Xanthate transfer reaction for the formation of **II.69**.

As summarized above, for the biomimetic synthesis of ansalactam A (**II.1**) still exciting opportunities are open. However, in all described approaches the sterically adverse situation employing an *iso*-butyl substituent needs to be considered.

8. Results and Discussion – Divergolides C and D.[†]

As described earlier, Hertweck and co-workers suggested a biosynthetic pathway for the formation of divergolides C and D (**II.2** and **II.3**), which is based on a common precursor for both molecules.^[5] Inspired by this hypothesis, we decided to develop a biomimetic synthesis of the two natural products, which is based on the macrolactam **II.5** as the common key precursor (Scheme II.29). Along these lines, the macrolactam **II.5** could undergo an intramolecular Michael addition onto the naphthoquinone system forming the 7-membered ring of divergolide C (**II.2**, pathway a in Scheme II.29). Alternatively, an intramolecular aldol addition onto the naphthoquinone portion of **II.5** combined with an acyl shift could produce divergolide D (**II.3**, pathway b in Scheme II.29).



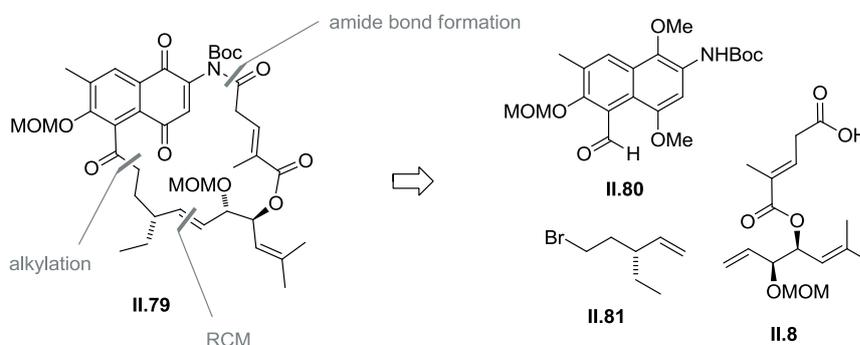
Scheme II.29. Two possible cyclization modes of the macrolactam **II.5** leading to the formation of divergolides C and D.

Based on these considerations, we decided to synthesize a protected analog of macrolactam **II.5** and test its ability to undergo the described cyclization processes. Thus, we have chosen system **II.79** as our key target, which incorporates MOM protected alcohol groups and a Boc-protected amide portion (Scheme II.30). The envisioned cyclization could then be performed as two discrete reactions. The acyl transfer could be controlled by selective protection or deprotection of the allylic alcohol groups, respectively. Or, more biomimetically, the intermediate **II.79** could be globally deprotected and exposed to the appropriate reaction conditions, *e.g.* treatment with a weak base could lead to the synthesis of both natural products in a one pot process.

Retrosynthetically, the intermediate **II.79** can be traced back to three major building blocks. A naphthalene building block **II.80**, similar to the one used in the ansalactam A (**II.1**) approach, could be connected to the two aliphatic side chains **II.81** and **II.82** by means of an alkylation

[†]This project was carried out in cooperation with D. Hager and C. Kuttruff, both PhD students in the Trauner group.

reaction and an amide bond formation, respectively. The macrocycle could be finally closed using ring closing Grubbs metathesis (RCM) of the two least hindered double bonds setting the stage for the desired key step (Scheme II.30). The described sequence is flexible and could also be changed in its order.

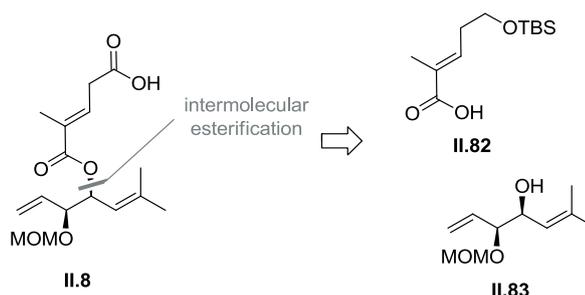


Scheme II.30. Retrosynthesis of the macrolactam precursor **II.79**.

The aim of this project was the development of a suitable synthetic strategy leading to the required aliphatic side chains **II.81** and **II.8**.^s

8.1. Synthesis of the Eastern Side-Chain

In our retrosynthetic considerations we envisioned to assemble the eastern side chain by an intermolecular esterification of α,β -unsaturated TBS-protected acid **II.82** and MOM-protected allylic alcohol **II.83** (Scheme II.31).

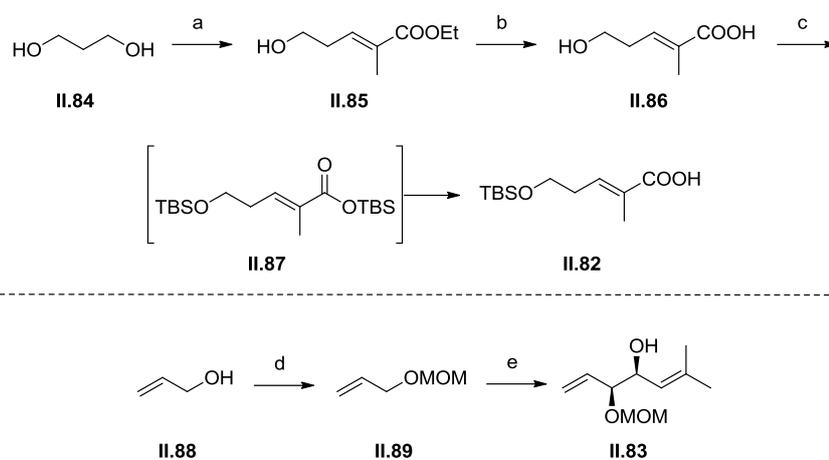


Scheme II.31. Retrosynthetic analysis of the acid side chain **II.8**.

Following this retrosynthetic plan, the synthesis of the TBS-protected acid **II.82** commences with the literature known oxidative desymmetrizing Wittig olefination of 1,3-propanediol **II.84** (Scheme II.32).^[97] Treatment of **II.84** with excess of manganese dioxide in the presence of

^sThe synthesis of the naphthalene portion **II.80** was part of the theses of D. Hager and C. Kuttruff. The assembly of all three building blocks was investigated by D. Hager. For detailed discussion and experimental procedures see: D. Hager, PhD Thesis, Ludwig-Maximilians-Universität, München, **2012**; C. A. Kuttruff, PhD Thesis, Ludwig-Maximilians-Universität, München, **2012**.

(carbethoxyethylidene)triphenylphosphorane provided exclusively the *E*-isomer of unsaturated ethyl ester **II.85** in 66% yield. Basic hydrolysis of the ethyl ester **II.85** gave the corresponding hydroxyl acid **II.86** in high yields, which was then exposed to a protection-deprotection sequence necessary for the formation of the desired side chain. Thus, treatment of acid **II.86** with tributyldimethylsilyl triflate provided the rather unstable double silylated TBS-ester **II.87**, which was isolated and used without further purification. Selective, potassium carbonate promoted deprotection provided quantitatively the TBS-protected unsaturated acid **II.82** over two steps.



Reaction conditions: (a) $\text{Ph}_3\text{PCCH}_3\text{COOEt}$, MnO_2 , CH_2Cl_2 , rt, 66%; (b) KOH , $\text{MeOH}/\text{H}_2\text{O}$, 80°C , 98%; (c) TBSOTf , 2,6-lutidine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt}$; $\rightarrow \text{K}_2\text{CO}_3$, MeOH , $0^\circ\text{C} \rightarrow \text{rt}$, quant.; (d) MOMCl , DIPEA , $0^\circ\text{C} \rightarrow \text{rt}$, 40%; (e) *sec*- BuLi , THF , -78°C ; $\rightarrow (+)\text{-B}(\text{Ipc})_2\text{OMe}$ in THF ; $\rightarrow \text{BF}_3 \cdot \text{OEt}_2$; \rightarrow 3-methylcroton aldehyde in THF ; $\rightarrow \text{rt}$, 68%, *er* = 92:8.

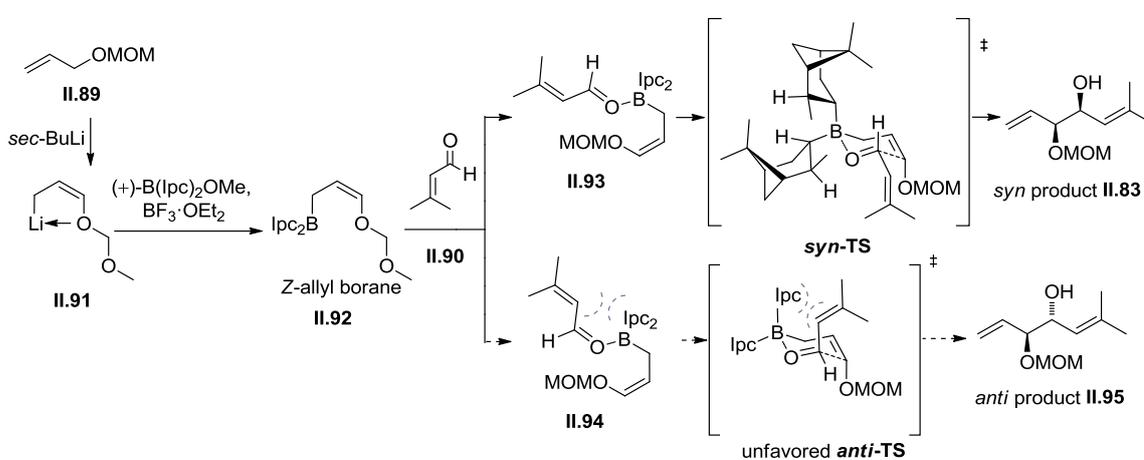
Scheme II.32. Synthesis of acid **II.82** and allylic alcohol **II.83**.

The synthesis of the corresponding coupling partner **II.83** was accomplished in two steps. In the first step, allyl alcohol **II.88** was protected as MOM-ether **II.89** using a literature reported protocol.^[98] Purification of the product turned out to be problematic, as the reaction mixture had to be carefully fractionally distilled several times over a vigreux column to obtain MOM-ether **II.89**, pure enough to be used in the next step. Next, diastereo- and enantioselective Brown allylation of 3-methylcroton aldehyde (**II.90**) was performed using a procedure adopted from literature known protocols for similar compounds.^[98a] This transformation provided the desired alcohol coupling partner **II.83** in 68% yield as a single diastereomer with an enantiomeric ratio of 92:8 (Scheme II.32).[†]

The two stereocenters generated during the new C-C bond formation are set with a high degree of stereoselectivity. This observed stereoselectivity results from several stereochemical

[†]The enantiomeric ratio (*er*) was determined on chiral normal phase HPLC (Nucleocel DELTA S, 250 x 4.6 mm, isocratic elution, hexanes (A)/*i*-propanol (B), 95% A, flow rate: 1 mL/min, detection at 210 nm, $t_{\text{R}}(\text{II.83-A}) = 5.65$ min, $t_{\text{R}}(\text{II.83-B}) = 6.48$ min).

properties of the intermediates involved in the transformation, which are depicted in scheme II.33.^[99]

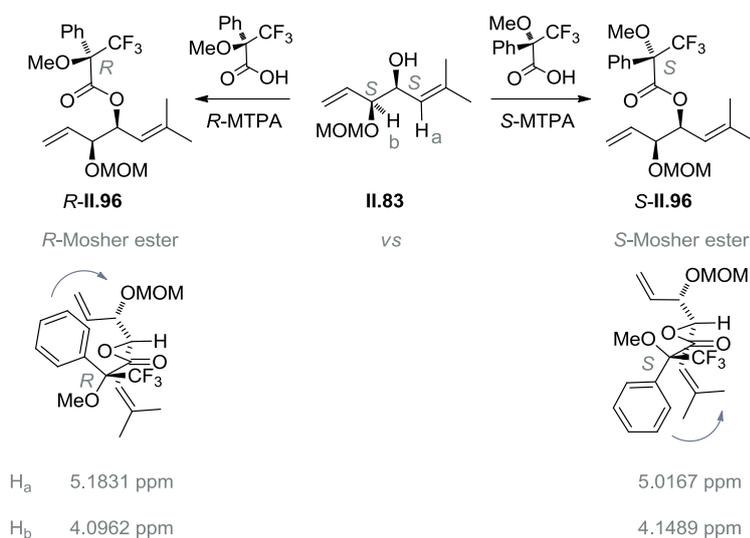


Scheme II.33. Stereochemical considerations leading to the formation of mostly *syn*-S,S-allyl alcohol **II.83** in the course of Brown allyl addition reaction.

The *syn* selectivity, which represents the simple diastereoselectivity of this addition process, can be explained taking two considerations into account. First, the lithiated species **II.91** generated from MOM allyl ether **II.89** exists in the configurationally stable *Z*-form. This is stabilized by coordination of lithium by the appendent MOM group forming a five membered ring system.^[98a] Consequently, the configurational stability of **II.91** enables the stereoselective formation of the *Z*-allyl borane **II.92**, which is essential for the successful formation of the *syn* product. Secondly, the allyl borane species **II.92** is believed to react with aldehydes *via* a chair-like transition state similar to the Zimmerman-Traxler^[86] model used for aldol reactions. The allyl borane **II.92** can be engaged into *syn*- and *anti*- transition states giving rise to two diastereoisomeric allylic alcohols. However, the *syn*-TS is favored over the *anti*-TS, in which the arrangement of the aldehyde substituent in the *pseudo*-equatorial position is not possible.^[99] The corresponding *pseudo*-axial substituent causes adverse interaction with the axial isocampheyl (Ipc) ligand in *anti*-TS making this thermodynamically unfavored.^[100] In addition to the adverse thermodynamic situation of the *anti*-TS, it should be emphasized, that the pathway leading to the formation of the *anti*-TS is also kinetically disfavored. Prior to the formation of both transition states a precoordination of the aldehyde to the boron allyl species takes place forming intermediates **II.93** and **II.94**. Whereas the more advantageous species **II.93** showing an *E*-configuration with respect to the CO double bond leads to the formation of the *syn*-TS, the correspondent *Z*-species **II.94** is more sterically congested due to the location of the metal center *syn* to the aldehyde substituent. In consequence of the described thermodynamic and kinetic criteria, the formation of the *syn* diastereomer **II.83** is favored over the formation of the *anti*-product **II.95**. On the other hand, the described transformation is also enantioselective owing this fact to the chiral diisocampheyl ligands. Thus, only the depicted

syn-TS is believed to be dominant in this reaction. This is caused by pandered sterical situation of the Ipc ligands. Both equatorial methyl substituents of the ligands are occupying the least hindered positions pointing away from the methylene protons of the allyl species (not shown).^[100-101] This leads to the favored *Si*-face addition to the aldehyde giving rise to the *S,S*-allyl alcohol **II.83** shown in Scheme II.33. As a result, the described stereochemical considerations lead to the formation of the desired *syn-S,S*-allyl alcohol as a single diastereomer with an enantiomeric excess of 84%.

The verification of the diastereo- and enantioselectivity of this reaction was performed using Mosher's ester analysis for the determination of the absolute configuration of the allylic alcohol **II.83**.^[102] On this purpose, corresponding *R*- and *S*-Mosher esters *R*-**II.96** and *S*-**II.96** were synthesized, which differ in the chemical shifts in their ¹H-NMR spectra because of their diastereomeric nature (Scheme II.34).

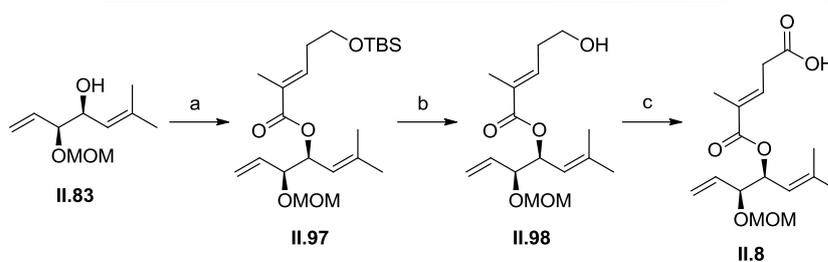


Scheme II.34. Mosher ester analysis used for the determination of absolute configuration of the allylic alcohol stereocenter in **II.83**.

The common accepted considerations regarding the NMR-properties of both Mosher ester diastereomers are empirically based.^[102] It is assumed that the most important conformations of the esters dominating the spectroscopic features of the molecules are those shown in scheme II.34, in which the ester usually adopts the *s-trans* arrangement about the OCO bond and the CF₃ portion, as well as the methane protons are both *syn*-coplanar with the CO bond. The shielding effect of the aryl group present in the Mosher ester moiety affects the protons residing above or below the plane of the aromatic system in these particular conformations. Consequently, assuming that the allylic alcohol portion is *S*-configured, as suggested by the described transition state, the *R*-Mosher ester *R*-**II.96** would show a higher chemical shift of the H_a proton, which is not shielded in the *R*-**II.96**. In contrast, *S*-**II.96**, in which the mentioned H_a

is shielded by the aryl ring, would show an up-field shift of Ha signal in the $^1\text{H-NMR}$ spectrum. In fact, this effect could be observed in the spectra of the synthesized compounds: *R*-**II.96** showed a chemical shift of 5.1831 ppm for Ha and *S*-**II.96** showed an up-field effect shifting the same proton to 5.0167 ppm verifying the assumed *S*-configuration of the allylic alcohol center. In addition, the methine proton Hb showed a similar trend in the NMR spectra. Being shielded by the aryl group in *R*-**II.96** it is chemically shifted to 4.0962 ppm, whereas in *S*-**II.96** Hb points away from the aryl portion possessing a higher chemical shift of 4.1489 ppm (Scheme II.34). Although the observed effects are subtle, they support the assumption of the *S*-configuration of the allylic alcohol stereocenter in **II.83**.

With both esterification partners, acid **II.82** and allylic alcohol **II.83** in hand, the aliphatic eastern side chain of divergolides C and D (**II.2** and **II.3**) was assembled in three steps (Scheme II.35). Application of the Yamaguchi esterification conditions gave the ester **II.97** in 78% yield. The following TBS-deprotection using TBAF at 0 °C provided reliable access to the free alcohol **II.98**, which was oxidized to the free acid **II.8** under Jones conditions. It should be noted, that the employed Jones oxidation was the only oxidative protocol which was found to be successful on this particular system. Other oxidative reagents such as DMP, TPAP/NMO/H₂O, TPAP/BAIB/H₂O lead to complete decomposition of the starting material **II.98** (Scheme II.35). The $^1\text{H-NMR}$ spectrum showed that the obtained acid **II.8** exists in solution as two isomers, presumably caused by the migration of the double bond of the α,β -unsaturated ester system to the 2,4-position next to the free acid moiety.



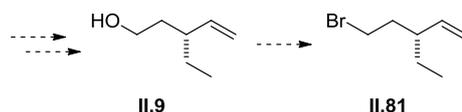
Reaction conditions: (a) 2,4,6-trichlorobenzoyl chloride, NEt₃, toluene; → **II.82**, DMAP, rt, 78%; (b) TBAF, THF, 0 °C → rt, 84%; (c) Jones reagent, acetone, 0 °C, 92%.

Scheme II.35. Completion of the assembly of the aliphatic eastern side chain **II.8**.

After the synthesis of the eastern side chain **II.8** was successfully accomplished, investigations toward the assembly of the western aliphatic side chain **II.81** were made.

8.2. Synthesis of the Western Side-Chain^u

We envisioned to access the bromide **II.81** from the corresponding alcohol **II.9**, which, as we figured, could be easily converted into the desired compound **II.81** using for instance Appel conditions (Scheme II.36).



Scheme II.36. Envisioned synthesis of bromide **II.81** from alcohol **II.9**.

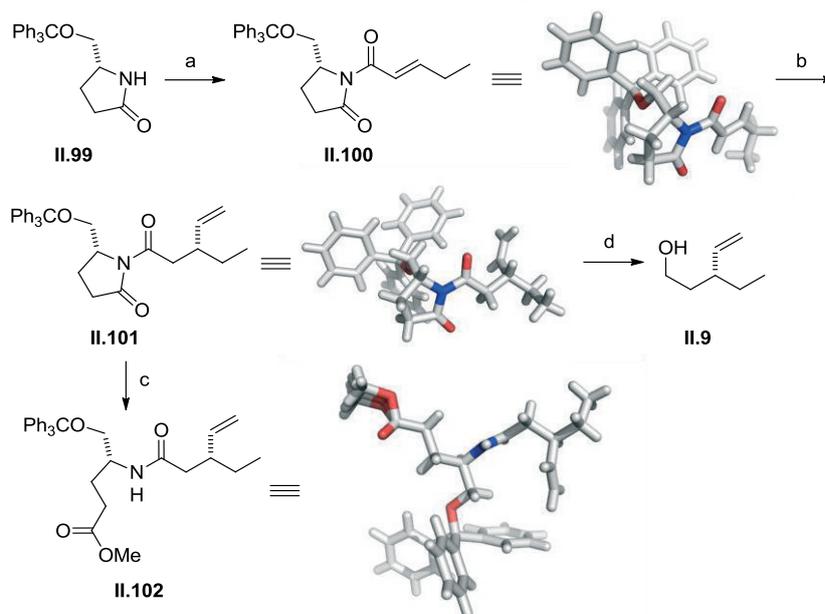
Although a few procedures leading to the alcohol **II.9** or its enantiomer are reported in the literature, its synthesis turned out to be more challenging than initially believed. Negishi and co-workers reported a five step procedure for the synthesis of **II.9**. The final transformation in their sequence included a lipase catalyzed acetylation as an additional purification step.^[103] Thus, this procedure did not seem practical to us. Searching for alternatives, we looked closer onto the zirconium catalyzed asymmetric carbomagnesation procedure developed by Hoveyda and his group.^[104] After initial investigations, Hoveyda's procedure turned out to be not suitable in a practical way as the expensive zirconium catalyst had to be used in high loading quantities and the enantioselectivity was not reliable.^v

Finally, aiming for a reliable and scalable protocol for the formation of alcohol **II.9**, we focused on a procedure, which involved auxiliary controlled diastereoselective 1,4-addition of a monoorganocopper reagent. This protocol was briefly sketched by Hoveyda group and used to approve the proposed absolute stereochemistry of the zirconium mediated transformation.^[104a] Unfortunately, they did not report a detailed procedure for the auxiliary promoted route. Since it is known that conjugate additions can be reliably controlled by Koga's auxiliary,^[105] we have chosen this amide as source of chiral information.^[106] Acylation of the amide **II.99^w** with activated *trans*-2-pentenoic acid, which was prepared *in-situ* using pivaloyl chloride, provided the unsaturated imide **II.100** in high yields. The subsequent conjugate addition of the vinyl cuprate onto imide **II.100** proceeded smoothly giving the correspondent alkene on gram scale in 90% yield (Scheme II.37).

^uThis work was performed together with D. Hager, a PhD student in the Trauner group.

^vThe initial investigations of the Hoveyda route were performed by D. Hager and C. Kuttruff. For further information, see: D. Hager, PhD Thesis, Ludwig-Maximilians-Universität, München, **2012**; C. A. Kuttruff, PhD Thesis, Ludwig-Maximilians-Universität, München, **2012**.

^wKoga's auxiliary was kindly provided by D. Hager and C. Kuttruff.



Reaction conditions: (a) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$; \rightarrow *trans*-2-pentenoic acid, pivaloyl chloride, NEt_3 , THF, $-78\text{ }^{\circ}\text{C}$ \rightarrow rt; 86%; (b) vinyl magnesium bromide, $\text{CuBr}\cdot\text{SMe}_2$, THF, $-40\text{ }^{\circ}\text{C}$, 90%; (c) LiOMe, THF, $0\text{ }^{\circ}\text{C}$ \rightarrow rt, 45%; (d) LiOMe, THF, $0\text{ }^{\circ}\text{C}$ \rightarrow rt; \rightarrow LAH, ca 70%;

Scheme II.37. Synthesis of the alcohol **II.9**, a precursor for the western side-chain of divergolides C and D as well as the X-ray structures of intermediates **II.100**, **II.101** and **II.102** verifying the absolute stereochemistry.

The stereochemical control of this transformation is not understood. For instance, the facial selectivity of the addition can be completely switched using different Lewis acids and copper reagents. Presumably, under the described conditions in the presence of dimethylsulfate, the oxygen of the large trityl group may precoordinate the vinyl copper reagent leading to the *Si*-face attack, hence providing exclusively the diastereomer **II.101** with the *R*-configuration on the newly formed stereocenter. Other explanations for the reported stereochemical outcome induced by the chiral amide **II.99** are also available.^[105-106] The absolute stereochemistry of **II.101** was established using X-ray crystallography technique knowing the configuration of the stereocenter in the appendent auxiliary moiety.

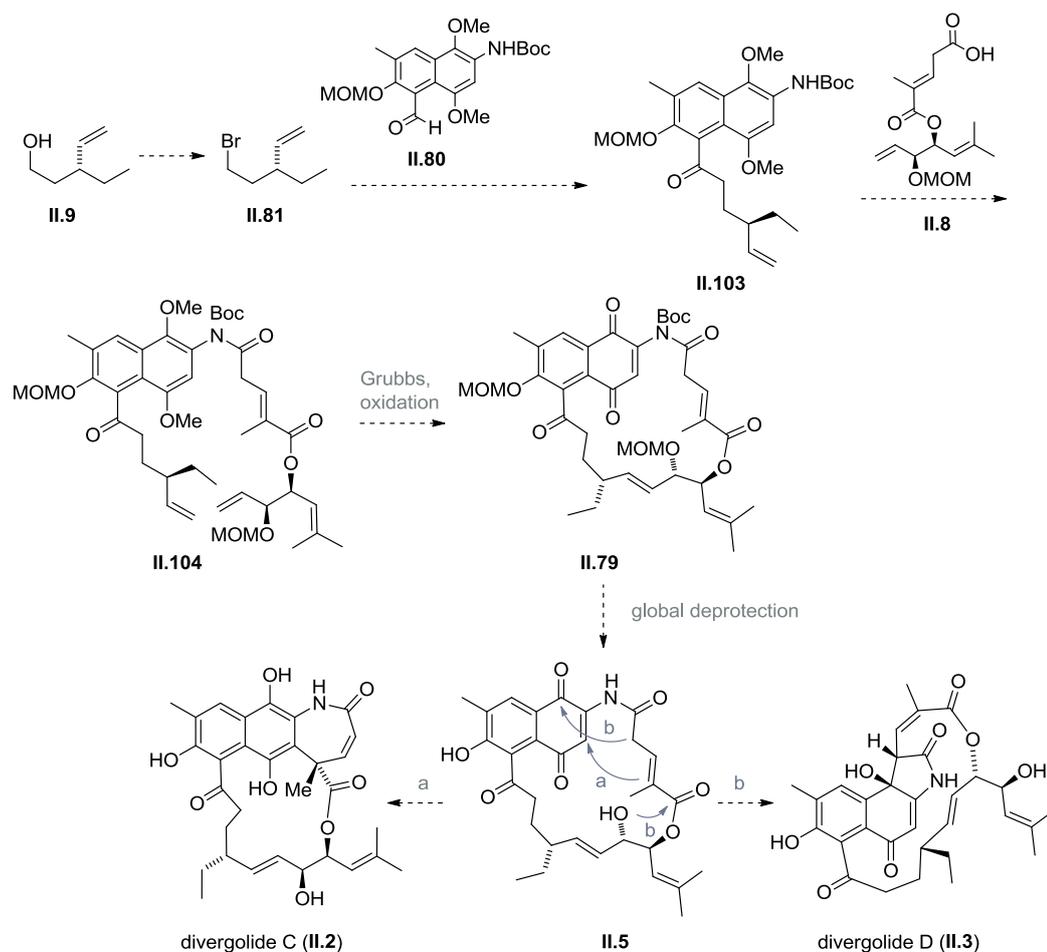
Not many literature reports exist on the cleavage of Koga's auxiliary. In the most cases, harsh conditions such as boiling HCl or strong basic conditions were used.^[105-106] Based on this fact the liberation of the synthesized chain needed for careful optimization. Using lithium methanolate, the auxiliary was only partially cleaved providing the open amide **II.102** as the main product (Scheme II.37). However, careful optimization showed that a combination of methanolate addition followed by LAH reduction of the complex reaction mixture gave the volatile alcohol **II.9** in 70% yield over the described two steps. Due to the volatile nature of the product the yields reported are only approximate, since the reactions were only performed on small scale and some material was lost during the removal of the solvent.

With the alcohol **II.9** in hands, further investigations toward the formation of the western side chain **II.81** and its attachment to the naphthalene system **II.80** can be performed. Both directions are further examined by D. Hager.

9. Summary, Conclusions and Future Work – Divergolides C and D

In summary, the eastern side chain **II.8** for the synthesis of divergolides C and D has been synthesized. The developed reliable and scalable route incorporates an asymmetric Brown allylation, as well as oxidative desymmetrizing Wittig reaction and a Yamaguchi esterification as key steps.

In addition, the asymmetric synthesis of alcohol **II.9** was accomplished delivering a direct precursor for the formation of the western side chain **II.81** of divergolides C and D. This synthetic route involves a diastereoselective conjugate addition of monoorganocopper reagent to the chiral imide **II.100** derived from Koga's auxiliary. The stereochemistry of the product could be confirmed by X-ray crystallography of several intermediates.



Scheme 11.38. Further directions in the biomimetic total synthesis of divergolides C and D (**II.2** and **II.3**)

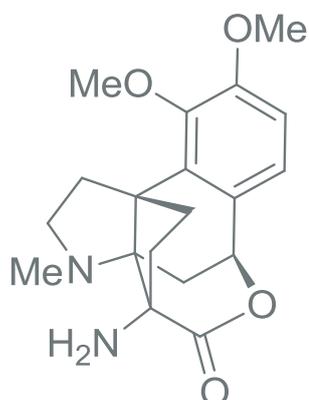
Continuing the proposed biomimetic total synthesis of divergolides C and D (**II.2** and **II.3**), we will have to target the transformation of the alcohol **II.9** into bromide **II.81**, which then could be attached to aldehyde **II.80** (Scheme II.38). Next, the resultant ketone **II.103** should be able to undergo an amide bond formation with the western side chain **II.8** to provide the RCM precursor **II.104**. This intermediate will presumably exist as a mixture of isomers regarding to the *syn-anti*-amide bond isomerism and to the sterically and thus rotationally hindered ketone portion attached to the naphthalene system. These facts could complicate the envisioned Grubbs ring closing metathesis, which should deliver after following oxidation the protected precursor **II.79**. Global deprotection would then provide access to the proposed biomimetic precursor of divergolides C and D, which would be able to undergo earlier discussed cyclization reactions leading to the formation of both natural products (Scheme II.38).

The described synthetic studies involving the formation of bromide **II.81** and the attachment of both side chains to the naphthalenic coupling partner as well as the assembly of the macrocycle **II.79** are currently being investigated in our laboratories by D. Hager.^x

^xFor further information, see: D. Hager, PhD Thesis, Ludwig-Maximilians-Universität, München, 2012

CHAPTER III

'SYNTHETIC STUDIES TOWARD STEPHADIAMINE'^y



^yThis project was performed in cooperation with D. Hager, a PhD student in the Trauner Group. This chapter was written together and can be found also in his PhD thesis.^[107] Both authors contributed equally to this work.

CHAPTER III: SYNTHETIC STUDIES TOWARD STEPHADIAMINE

10. Introduction

10.1. Alkaloid Natural Products

The history of alkaloid natural products and their connection to humankind is long and ambivalent. Mostly isolated from plant sources,^[108] these natural products and their parent organisms have been and are still used as food spices, currency, ritual tools, hallucinogenic drugs and poison.^[109] One of the most prominent and early applications of an alkaloidal poison is reported in the context of the execution of Socrates in 399 BC by means of drinking an extract of poison hemlock (*Conium maculatum*), the main biologically active compound of which is coniine (**III.4**).^[110] Other poisonous alkaloid containing plants and the corresponding natural products have also been misused. Curare for example, with its main neurotoxic ingredient tubocurarine (**III.5**), was used as an arrow poison by South American indigenous people.^[8] Strychnine (**III.6**), gained from *Strychnos nux-vomica*, was applied as doping agent, analgesic and poison.^[111] Furthermore, the addictive effect of tobacco and the hallucinogenic nature of *Atropa belladonna* are based on the biologically active alkaloids being nicotine (**III.7**)^[112] and atropine (**III.8**)^[8] respectively (Figure III.1).

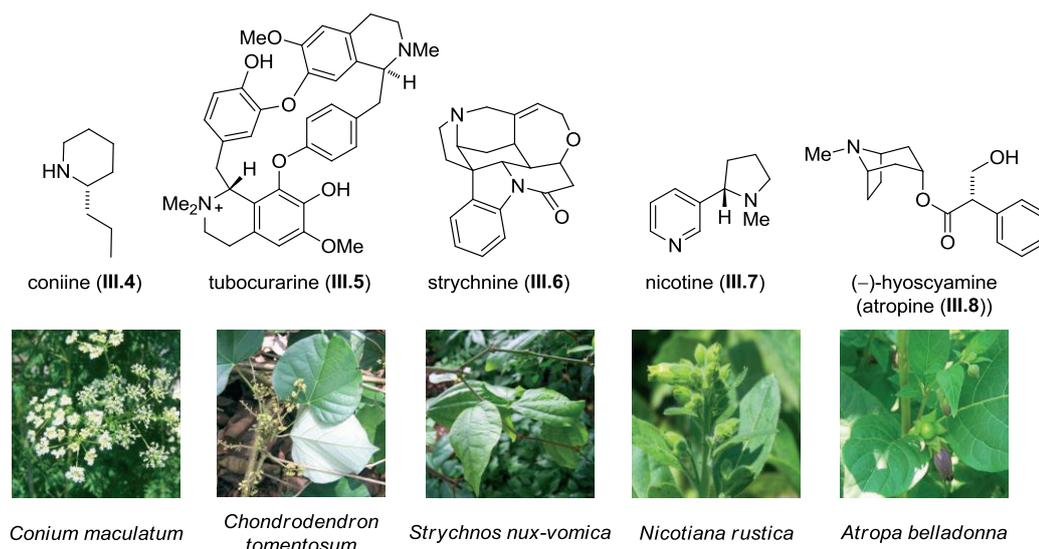


Figure III.1. Famous alkaloid structures: coniine (**III.4**), tubocurarine (**III.5**), strychnine (**III.6**), nicotine (**III.7**), and atropine (**III.8**), as well as their natural sources: *Conium maculatum*,^[113] *Chondrodendron tomentosum*,^[114] *Strychnos nux-vomica*,^[113] *Nicotiana rustica*,^[113] *Atropa belladonna*^[113].

Although a limited number of simple amino acid derived building blocks are involved in the biogenesis of alkaloids, the incorporation of other, polyketide and terpenoid structures allow for a broad structural diversity and complexity within these natural products.^[8,108] As a result, a variety of biological activities are known among alkaloids. For example, as such, they can activate, block or deactivate ion channels, or alternatively bind to DNA, thus affecting protein biosynthesis.^[115]

One of the most famous and historically important alkaloids is (–)-morphine (**III.9**), the main component of opium (Figure III.2).^[116] Its ambiguous biological activities are both, blessing and curse to humankind: on one hand **III.9** acts as a painkiller, whereas on the other, it causes sincere addiction. Most likely, opium poppy (*Papaver somniferum*), the main source of (–)-morphine, was cultivated and used by Sumerians as medicine and hallucinogenic drug already more than 4000 years ago.^[117] In the following centuries, the use of opium, the dry milky juice of the opium poppy fruit, became widely common in China and the Arabian countries and later throughout the whole world. The addiction to (–)-morphine (**III.9**) provoked wars and is still one of the major problems worldwide. However, (–)-morphine is used as one of the most potent analgesic drugs up to date.^[116]

Although *Papaver somniferum* has been cultivated for centuries, it was only in 1804 that (–)-morphine was isolated and identified as the main biologically active ingredient of opium poppy by Sertürner (Figure III.2).^[118] Since then, several biological studies and chemical syntheses of morphine and its analogs have been performed.^[119] In fact, this natural product and its intriguing structure is still an inspiration for synthetic chemists even today.

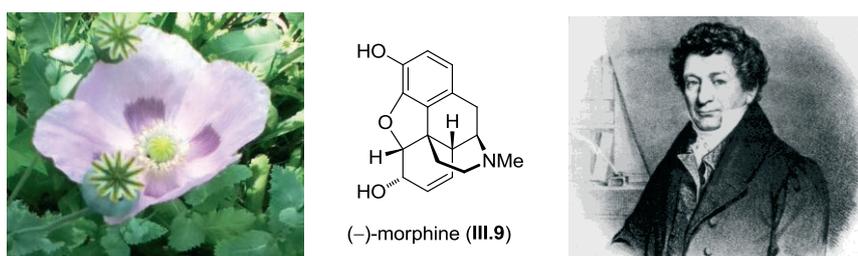


Figure III.2. *Papaver somniferum*,^[113] the natural source of (–)-morphine (**III.9**) (left), the structure of **III.9** (middle) and a portrait of F. Sertürner^[120] (right).

During the last centuries, many other alkaloids with the common morphinan skeleton have been isolated and characterized (Figure III.3).^[108,121] The backbone of morphinans features a benzylic all carbon quaternary center in C13 and a nitrogen containing stereocenter at C9 position, which is always *R*-configured. In 1964, Inubushi and co-workers were able to isolate a new alkaloid showing a modified morphinan skeleton.^[122] Hasubanonine (**III.10**) eventually

turned out to be the parent compound of the new class of hasubanan natural products, all possessing the typical hasubanan skeleton, isomeric to the morphinans. Mostly isolated from various *Stephania* species, which were also used in traditional Chinese medicine, more than 40 compounds have been identified to date.^[121] In contrast to the morphinans, in the hasubanan skeleton the nitrogen substituent is moved from C9 to the C14 position, forming a 5-membered ring, which now possesses a nitrogen containing tetrasubstituted carbon center (NTC). The resulting aza-propellane skeleton can vary in its oxidation states. In addition, the hasubanans differ from morphinans in their absolute stereochemistry as they represent the opposite enantiomeric series of the skeleton.^[123] Although the biological activities of hasubanan alkaloids are not as remarkable as those of the morphine derived structures, they have been the subject of extensive chemical research since the 1970s, culminating in various total syntheses of these natural products.^[124]

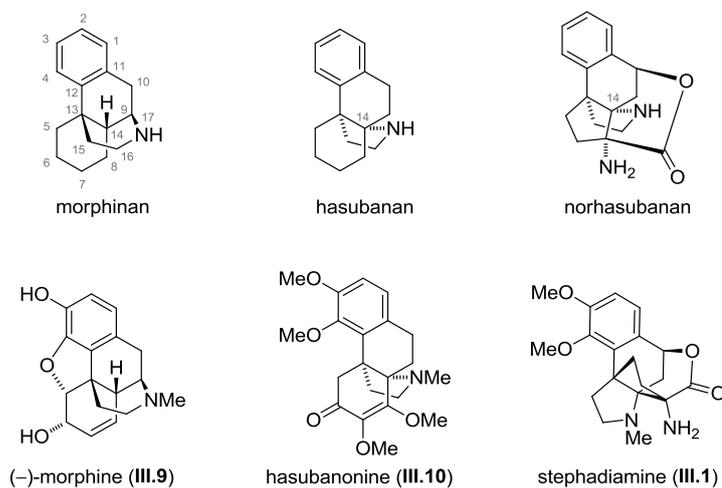


Figure III.3. The structures of morphinan, hasubanan and norhasubanan skeletons, as well as the corresponding parent compounds morphine (III.9), hasubanone (III.10) and stephadiamine (III.1).

Along with the investigations of the *Stephania* species, another new alkaloid type, related to the morphinans, was discovered. Thus far, the only identified representative of these norhasubanan alkaloids is stephadiamine (III.1).^[6] As in the case of hasubanans, the norhasubanan core possesses the opposite configuration to the morphinan skeleton and an NTC center at C14 position. Additionally, one of the rings is rearranged forming a pentacyclic system with a second NTC center, featuring a primary amine (Figure III.3).

Many synthetic routes to morphinan and hasubanan structures have been developed in the last century and still a huge synthetic interest in this type of compounds exists. Thus, it is surprising that no synthetic approach to the norhasubanan stephadiamine (III.1) has yet been

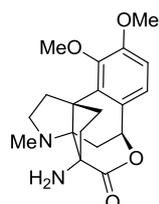
published. Therefore, the goal of this work was the development of the first and efficient total synthesis of stephadiamine (**III.1**) with the potential of an enantioselective NTC installation.

10.2. Stephadiamine – Isolation and Structure

The common scrambler *Stephania japonica*, often found in south-east Asia and the Pacific region, is known to possess various medicinal properties. Parts of this plant and its extracts are used in the Chinese and Taiwanese folk medicine as anti-diarrheal, anti-febrile drugs and as a remedy against malaria and cholera.^[6,125] Biological investigations of alcoholic extracts of this species have shown that *S. japonica* is a rich source of hasubanan alkaloids.^[126] In the course of metabolom investigations of *S. japonica* in 1984, Ibuka and co-workers were able to isolate and characterize a minor component of the ethanolic plant extract representing a novel type of alkaloidal structure, the pentacyclic stephadiamine (**III.1**), which was isolated as a colorless solid (Figure III.4).^[6]



Stephania japonica



stephadiamine (**III.1**)

Figure III.4. Leaves of *Stephania japonica*^[127] (left) and the structure of stephadiamine (**III.1**) (right).

The quantity of the obtained novel natural product was not adequate for detailed chemical degradation studies. Nevertheless, Ibuka and co-workers were able to elucidate the structure of the molecule using IR and ¹H-NMR spectroscopic analysis, as well as mass spectrometry. Eventually, they were able to obtain X-ray structures of stephadiamine (**III.1**) and its derivative *N-p*-bromobenzoyl stephadiamine (**III.11**), clarifying the connectivity and the absolute stereochemistry of the compound (Figure III.5).^[6] Structurally, the lactonic C-norhasubanan **III.1** is not a member of the hasubanan alkaloid family in the strict sense. This type of skeleton has not been previously found in nature and to our knowledge, **III.1** is the only representative of norhasubanan alkaloids identified thus far.

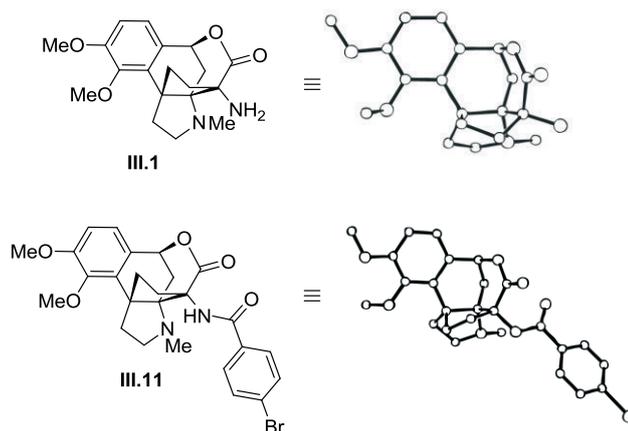


Figure III.5. Structure (left) and X-ray analysis (right) of stephadiamine (**III.1**) and *N*-*p*-bromobenzoylstephadiamine (**III.11**).^z

The basic pentacyclic core of the natural product **III.1** features a tetralin system, which is connected to a 6-membered lactone moiety and a pyrrolidine ring bridged by two methylene groups forming a propellane structure (Figure III.6). Stephadiamine (**III.1**) possesses four stereogenic centers, two of which are benzylic. An all-carbon quaternary stereocenter at C13 and an oxygen containing chiral center at C10 positions are joined by two NTC stereocenters at the C7 and C14 position. One of the latter includes a tertiary amine portion, whereas the second bears a primary amine as the nitrogen substituent. In contrast to hasubanan alkaloids, the former ring C is rearranged to a 5-membered system and the 6-membered lactone moiety forms the new ring E (Figure III.6). In addition, hasubanan alkaloids show only one nitrogen atom, whereas stephadiamine (**III.1**) possesses two nitrogen functionalities.

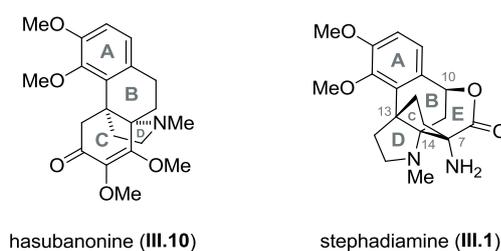


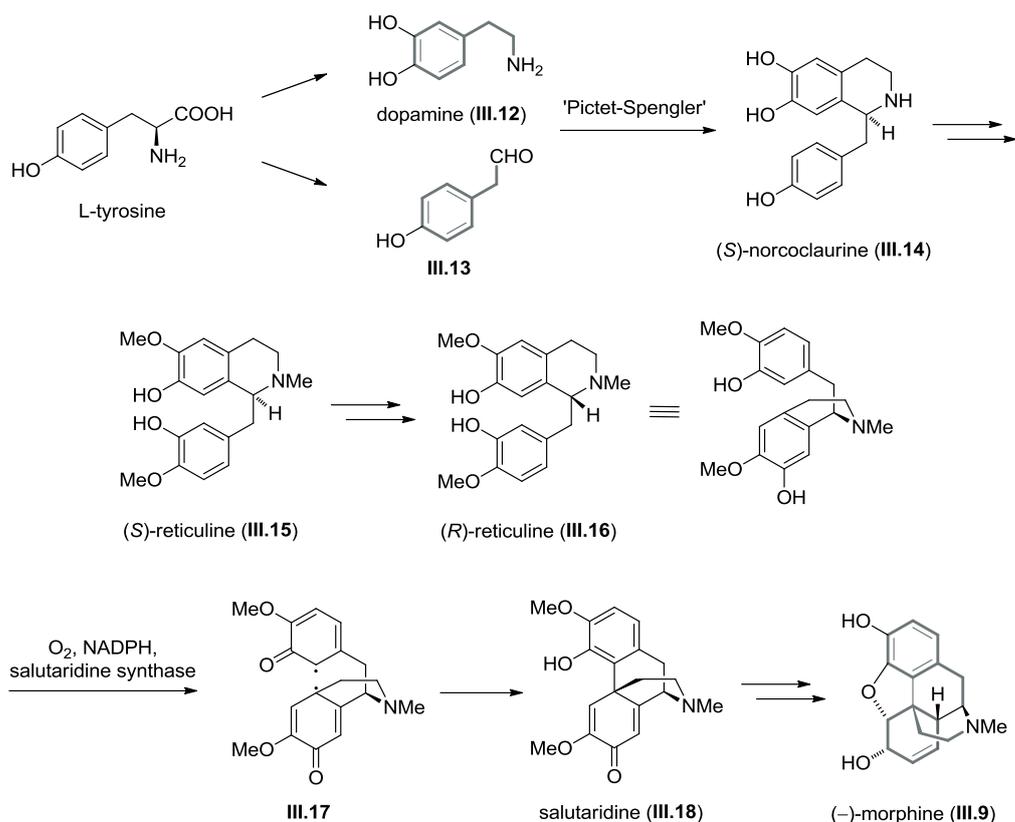
Figure III.6. Skeletons of hasubanonine (**III.10**) and stephadiamine (**III.1**).

The synthetic challenge presented by the complex structure of **III.1** and specifically its two contiguous NTC centers as well as the fact that stephadiamine (**III.1**) has not been synthesized thus far, prompted us to develop a total synthesis of this natural product.

^zUnfortunately, the 3D coordinates for both structures have not been disposed in the CCDC data base. Thus, only qualitative pictures from the corresponding publication can be shown here.

10.3. Stephadamine – Biosynthetic Considerations

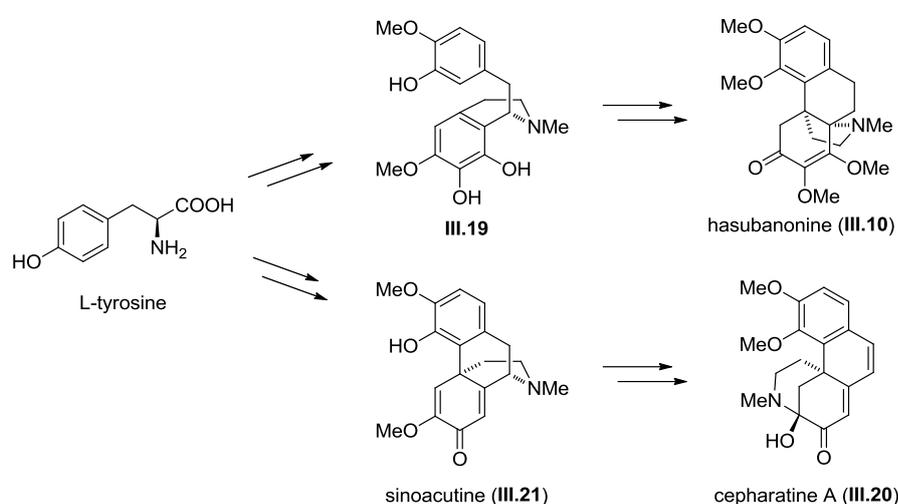
The structural resemblance of the morphinan, hasubanan and norhasubanan skeletons discloses a connection of the biogenesis of the natural products belonging to these three classes of alkaloids. The broad interest in morphine (**III.9**) culminated in extensive studies on the biosyntheses of several benzyltetrahydroisoquinoline alkaloids.^[128] It was shown that in nature, **III.9** is derived from dopamine (**III.12**) and 4-hydroxyphenylacetaldehyde (**III.13**), two simple building blocks originating from the amino acid tyrosine (Scheme III.1).^[8]



Scheme III.1. Biosynthesis of (-)-morphine (**III.9**).

It was suggested that both building blocks combine in an enzyme promoted Pictet-Spengler-type reaction to the benzyltetrahydroisoquinoline core of (S)-norcoclaurine (**III.14**), which is then oxidized and methylated to yield (S)-reticuline (**III.15**). An enzyme catalyzed oxidation/reduction process forms its enantiomer (R)-reticuline (**III.16**), a key compound in all morphinan alkaloid biosyntheses. Compound **III.16** is cyclized *via* an enzymatically formed diradical **III.17** to salutaridine (**III.18**) by a selective intramolecular *o,p*-phenoloxidative coupling, which is one of the most important reactions in morphinan biosyntheses. In **III.18**, the major framework of (-)-morphine (**III.9**) is already established.^[129] Further enzyme catalyzed transformations afford **III.9**.^[8]

In the case of the parent hasubanan alkaloid hasubanonine (**III.10**), the biogenesis is less investigated. Feeding experiments of ^{14}C -labelled isoquinolines to *S. japonica* performed by Battersby in the early 1980s led to the proposal that, in analogy to morphine biogenesis, phenoxidative coupling of tyrosine derived isoquinoline **III.19**, an oxidized version of (*R*)-reticuline (**III.16**), is involved in the formation of hasubanonine (**III.10**) (Scheme III.2). However, the detailed sequence of the transformations involved in the biosynthesis of hasubanonine (**III.10**), especially the installation of the 5-membered pyrrolidine moiety, is yet to be explained.^[130] In the case of cepharatine A (**III.20**), another hasubanan alkaloid, Zhang and co-workers suggested the incorporation of sinoacutine (**III.21**), the enantiomer of salutaridine (**III.18**), which is involved in the morphine synthesis (Scheme III.2).^[125]



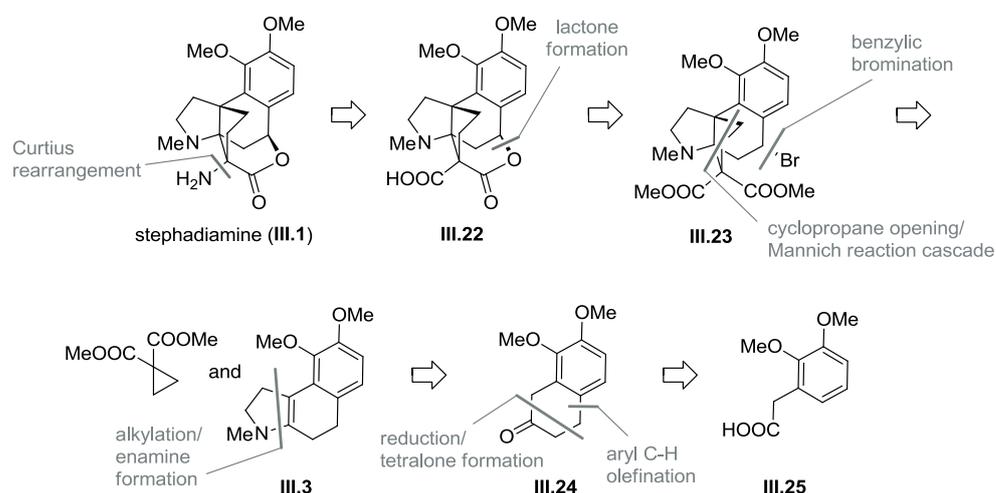
Scheme III.2. Proposed biosyntheses of hasubanan alkaloids hasubanonine (**III.10**) and cepharatine A (**III.20**).

Unfortunately, the biogenesis of our target compound stephadiamine (**III.1**) was not investigated. However, its resemblance to the morphinan and hasubanan structures again suggests an incorporation of L-tyrosine. Further speculations along these lines would result in the assumption that a Pictet-Spengler-type reaction and a phenoxidative coupling are also involved in the stephadiamine biogenesis. In addition, a skeletal rearrangement leading to dearomatization and ring contraction to form rings C and E would have to take place.

10.4. Strategy and Retrosynthetic Analysis

One of the major challenges posed by the envisioned total synthesis of stephadiamine (**III.1**) is the assembly of the two contiguous NTC centers. Among many methods for the synthesis of NTC centers, Curtius rearrangement is a powerful tool for NTC formation and has been applied successfully in total syntheses of various alkaloids, even in sterically hindered

cases.^[131] The retrosynthetic strategy we have chosen involves a Curtius rearrangement, which would introduce the NTC center in C7 position comprising a primary amine as substituent. Thus, stephadiamine (**III.1**) could be traced back to carboxylic acid **III.22** (Scheme III.3). At this stage, we envisaged to introduce the lactone moiety in **III.22** by means of an intramolecular bromine replacement leading to diester **III.23** as a logical precursor. The propellane skeleton of bromide **III.23** could be assembled by means of a benzylic bromination and a homoconjugated addition/Mannich cascade, involving dimethyl cyclopropane-1,1-dicarboxylate and enamine **III.3** as reaction partners. In turn, enamine **III.3** could be derived from β -tetralone **III.24** through a stepwise enamine formation/alkylation sequence. The tetralone system **III.24** is known to be accessible from the simple commercially available building block 2-(2,3-dimethoxyphenyl)acetic acid (**III.25**) in several steps involving a C-H activation process and a cyclization reaction.^[7]



Scheme III.3. Retrosynthetic analysis of stephadiamine (**III.1**).

The synthetic approach toward stephadiamine (**III.1**) is both novel and challenging in its nature. Not only does it involve a cyclopropane opening/Mannich cascade, which is scarcely represented in literature and, to our knowledge, has never been used in total synthesis thus far. The strategy also requires the formation of enamine **III.3** as one of the intermediates, which is known to be oxygen and temperature sensitive.^[132] In addition, the assembly of tetralone **III.24** relies on a novel type of chemistry involving a C-H activation process.

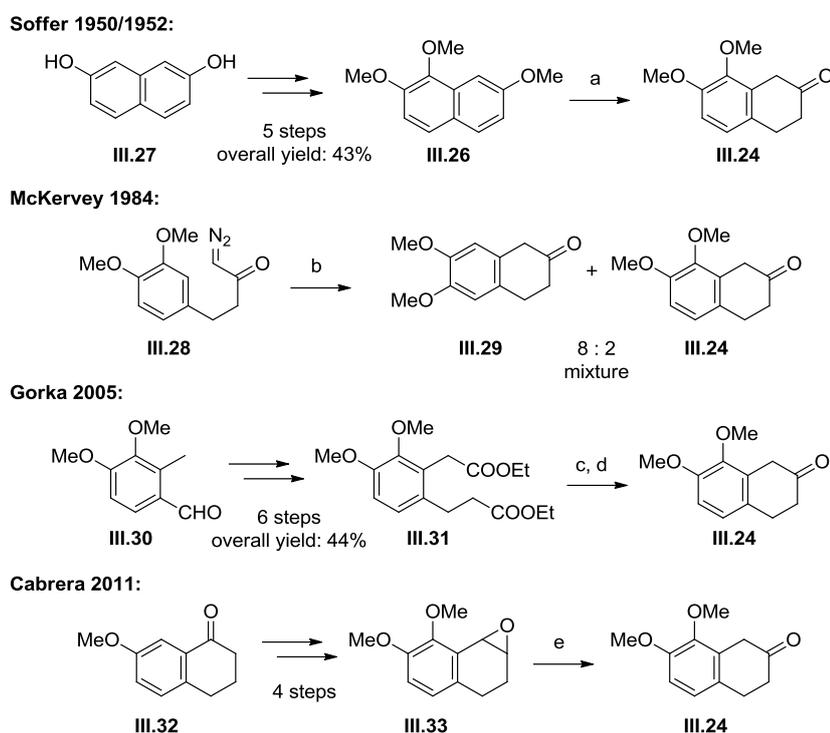
Despite its challenging nature, the envisioned approach offers a high flexibility. For example, the cyclopropane opening reaction requires an activation of dimethyl cyclopropane-1,1-dicarboxylate with a Lewis acid.^[133] At this stage, the use of a chiral Lewis acid holds promise to even access **III.1** in enantiopure form. Furthermore, the assembly of enamine **III.3** starting from β -tetralone **III.24** can proceed *via* several different approaches by interchanging

alkylation and enamine formation processes. Hence, β -tetralone **III.24** represents a key intermediate, which could function as a branching point for various synthetic approaches toward the total synthesis of stephadiamine **III.1**.

11. Results and Discussion^{aa}

11.1. Assembly of β -tetralone

Along the lines of the proposed retrosynthetic strategy (*vide supra*, scheme III.3), our first goal in the total synthesis of stephadiamine **III.1** was to access dimethoxy β -tetralone **III.24**. Several syntheses of this compound are described in the literature, which will be shortly discussed herein (Scheme III.4).



Reaction conditions: (a) Na, EtOH, 31%; (b) $\text{Rh}_2(\text{OCOCF}_3)_4$, 96% of a 8:2 mixture; (c) $\text{KO}t\text{-Bu}$, benzene, Δ , 55%; (d) NaCl, H_2O , DMSO, Δ , 73%; (e) H_2SO_4 , EtOH, Δ .

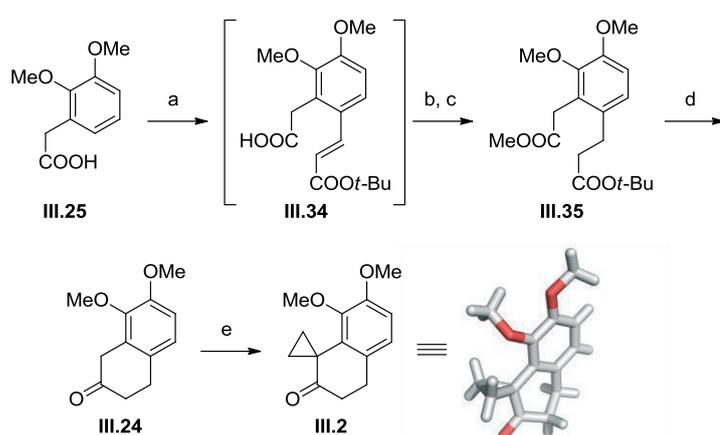
Scheme III.4. Literature known syntheses of β -tetralone **III.24**.

The earliest synthesis was published in 1950/1952 by Soffer and his group during their work toward morphine synthesis. It was focused on the dearomatization of trimethoxynaphthalene **III.26** under Birch conditions as a key step.^[134] Unfortunately, they needed five steps to synthesize **III.26** starting from dihydroxynaphthalene **III.27** and the final dearomatization step provided the desired tetralone **III.24** in an unsatisfactory yield of only 31%. More than 30 years later, McKervey and co-workers published a rhodium(II) catalyzed C-H insertion of diazoketone **III.28** providing the desired 5,6-dimethoxytetralone (**III.24**) only as a minor regioisomer and mostly the undesired *para*-cyclized product **III.29**.^[135] In 2005, Gorka

^{aa}The experimental work of this chapter was performed together with N. Vrielink, an undergraduate researcher in the Trauner laboratories.

and co-workers synthesized **III.24** starting from benzaldehyde **III.30**.^[136] First, they assembled the diester **III.31** in six steps and then cyclized it in a low yielding two step protocol to **III.24**. A shorter route to β -tetralone **III.24** was developed by Cabrera and co-workers in 2011, who converted the commercially available 7-methoxy-1-tetralone (**III.32**) to epoxide **III.33** in four steps. In the final step, under strongly acidic conditions, the epoxide **III.33** was opened to β -tetralone **III.24**.^[137]

All of the routes described thus far, include low yielding steps, and/or employ expensive catalysts. In addition, the starting materials are not easily available and the key intermediates have to be prepared in several steps. Eventually, it seemed that the best, shortest and most elegant way to assemble **III.24** would be a synthesis based on a procedure published by Yu and co-workers in 2010.^[7] Thus, we were able to synthesize β -tetralone **III.24** along an optimized route in only four steps (Scheme III.5).



Reaction conditions: (a) Pd(OAc)₂, *p*-benzoquinone, *tert*-butyl acrylate, *tert*-amylalcohol, KHCO₃, O₂, 3 bar, 85 °C; (b) Pd/C, H₂, MeOH, rt; (c) TMSCHN₂, toluene/MeOH, 0 °C → rt, 84% (over 3 steps); (d) KO*t*-Bu, Et₂O, rt; → AcOH/HCl, 110 °C, 70%; (e) 1,2-dibromoethane, NaH, DMF, 0 °C → -78 °C, 88%.

Scheme III.5. Synthesis of β -tetralone **III.24**^[7] and the assembly of the corresponding cyclopropane **III.2**.

The synthesis commences with a palladium catalyzed aryl C-H olefination of dimethoxyphenylacetic acid **III.25** with *tert*-butyl acrylate as a coupling partner. This step needed for careful optimization as procedure reported by Yu and co-workers led only to mixtures of starting material and traces of product. However, application of oxygen overpressure of 3 bar in an autoclave apparatus furnished the corresponding unsaturated ester **III.34** exclusively. Without further purification, a reduction/esterification sequence was performed providing the diester **III.35** in 84% over three steps. The synthesis of β -tetralone **III.24** was accomplished by means of a cyclization/decarboxylation process, which gave **III.24** in 70% yield. This short protocol provided the desired β -tetralone **III.24** in only four steps,

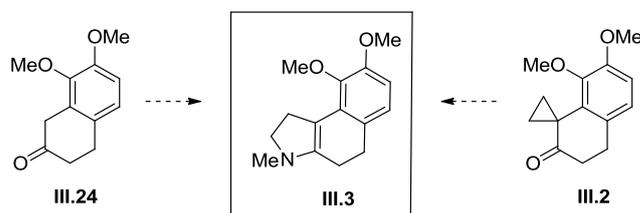
three of which were carried out without column chromatography, in an overall yield of 59% on multigram scale.

Next, β -tetralone **III.24** was converted to the corresponding cyclopropane **III.2** in 88% yield, which could serve as an alternative precursor for the assembly of enamine **III.3** (*vide supra*, Scheme III.3). The structure of **III.2** was confirmed by X-ray crystallographic analysis (Scheme III.5).

With β -tetralone **III.24** and cyclopropane **III.2** in hands first attempts toward the synthesis of enamine structure **III.3** were undertaken.

11.2. Toward Tricyclic Enamine

As outlined in the retrosynthetic analysis, the preparation of enamine **III.3**, a key intermediate in the total synthesis of stephadiamine **III.1**, could start directly from tetralone **III.24** following an amination/alkylation sequence (Scheme III.6). Alternatively, it is also reasonable that the formation of **III.3** could be achieved by means of a cyclopropane-opening reaction of **III.2**, followed by a cyclization with methylamine as nucleophile.

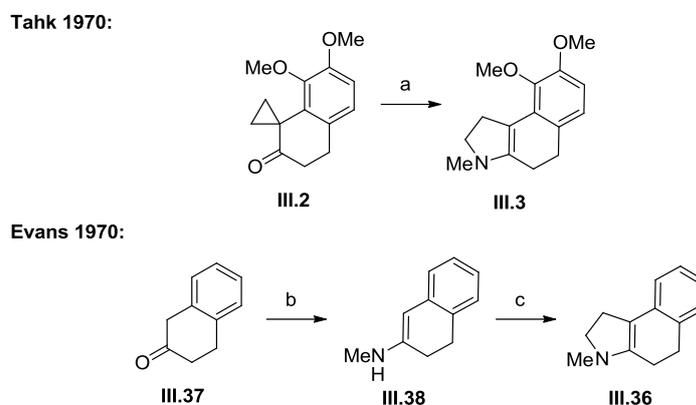


Scheme III.6. Envisioned assembly of the tricyclic enamine structure **III.3**.

11.2.1. Previous Work on the Formation of the Key Enamine

The enamine **III.3** shows a methoxy substitution pattern typical of morphinan and hasubanan alkaloids (*vide supra*, Section 10.1). Thus, the synthesis of this portion was of great interest to synthetic chemists. It is therefore surprising that the compound **III.3** was synthesized only once by Tahk and co-workers in 1970 in the context of their work on cephamine (Scheme III.7).^[132b] The enamine **III.3**, which was described as air sensitive, was made from cyclopropane **III.2** by a homoconjugated addition of methylamine followed by cyclization. To achieve this transformation, Tahk and co-workers had to apply harsh conditions including heating as well as high pressure and long reaction times. Unfortunately, only analytical amounts

of the product **III.3** could be isolated and characterized despite the fact that 1 g of starting material was employed in this reaction.



Reaction conditions: (a) MeNH₂, CaO, benzene, 100 °C, 7d, analytical amounts; (b) MeNH₂, Et₂O, TiCl₄, rt, 99%; (c) *i*-PrMgCl, bromochloroethane, THF, 100%.

Scheme III.7. Literature known syntheses of enamine **III.3** and its derivatives.

In the same year, Evans and co-workers published their work on the synthesis of the hasubanan carbocyclic system.^[132a,138] One of the key intermediates used in this approach was enamine **III.36**, which lacks the two methoxy groups present in **III.3** (Scheme III.7). Starting from tetralone **III.37**, Evans *et al.* achieved the assembly of enamine **III.36** via enamine **III.38** by a two step protocol involving amination of **III.37** and alkylation of **III.38** with bromochloroethane. This procedure is high yielding and could be performed on gram scale.

In addition to the described protocols, the formation of enamines of type **III.3** was the subject of two other publications.^[139] Both are based on the sequence established by Evans and co-workers. Yet, the synthesis of a system containing two methoxy groups as present in **III.3** using the Evans protocol has not been reported to date.

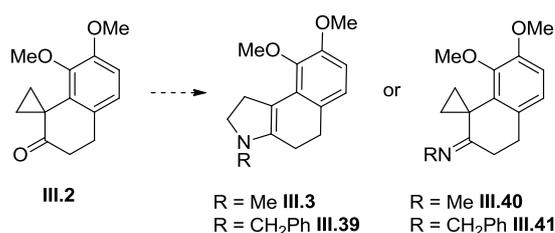
Whith this information in hand, the synthesis of enamine **III.3** was attempted.

11.2.2. Studies Toward Enamine System

Initially, attempts in the synthesis of enamine **III.3** focused on the homoconjugated addition of amine nucleophiles to cyclopropane **III.2** as described by Tahk and co-workers (*vide supra*, Scheme III.7). In order to improve the yields of the transformation, a variety of different reactions was performed. Thus, cyclopropane **III.2** was subjected to several conditions involving the nucleophiles methylamine or benzylamine with the expectation that enamines **III.3** and **III.39** or the corresponding imines **III.40** and **III.41** would be formed (Table III.1). First, focusing on methylamine as nucleophilic reaction partner, conditions with methylamine solutions and methyl amine hydrochloride salt were investigated (entries 1-7, Table III.1). As it

is known that acids such as ytterbium triflate or *p*-toluenesulfonic acid can activate cyclopropane substituted ketones and force the cyclopropane opening, they were used as additives in some cases of the screening.^[133] Despite different temperatures and solvents applied in the attempts, only starting material could be re-isolated in the most cases without observing the formation of the desired products. In the presence of acidic additives (entries 1 and 2, Table III.1), decomposition and formation of complex mixtures occurred.

Table III.1. Screening conditions applied for synthesis of enamine **III.3** and **III.39** and corresponding imines **III.40** and **III.41**.



Entry	Amine	Solvent	Additive	T	Observation
1	MeNH ₂ /THF	MeCN	Yb(OTf) ₃	80 °C	complex mixture
2	MeNH ₂ /THF	toluene	<i>p</i> -TosOH	80 °C	decomposition
3	MeNH ₂ /THF	THF	–	rt	sm ^a
4	MeNH ₂ /THF	THF	–	μw/100 °C	sm
5	MeNH ₂ ·HCl	benzene	–	μw/100 °C	sm
6	MeNH ₂ /THF	xylene	–	140 °C	sm
7	MeNH ₂ ·HCl	benzene	–	150 °C	sm
8	MeNH ₂ (g)	toluene	Yb(OTf) ₃	80 °C	complex mixture
9	MeNH ₂ (g)	–	–	100 °C	III.40:III.2 (1.5:1) ^b
10	PhCH ₂ NH ₂	Et ₂ O	–	rt	sm
11	PhCH ₂ NH ₂	xylene	–	140 °C	decomposition
12	PhCH ₂ NH ₂	benzene	4Å ms ^c	90 °C	complex mixture
13	PhCH ₂ NH ₂	Et ₂ O	TiCl ₄	–15 °C	sm

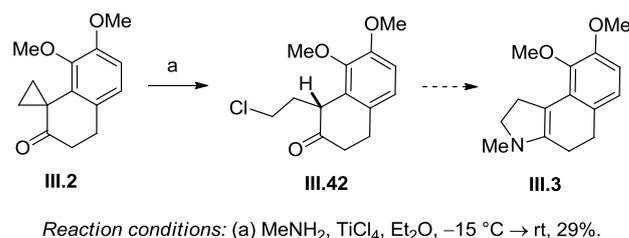
^asm = starting material

^bAs determined by ¹H-NMR spectroscopy.

^cms = molecular sieves

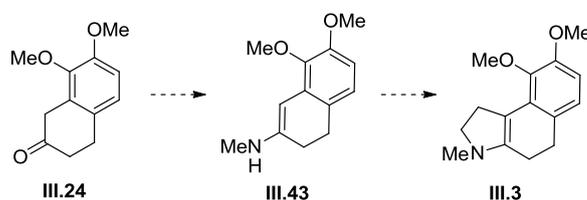
As Tahk and co-workers used freshly condensed methylamine gas, a closer examination of these conditions was undertaken (entries 8 and 9, Table III.1). Methylamine gas was condensed at –78 °C in a high pressure vessel and cyclopropane **III.2** was dissolved therein. Heating in the presence of ytterbium triflate with toluene as solvent lead to the formation of complex mixtures (entry 8, Table III.1). But when methylamine was used as solvent without any additives at

tetrachloride at room temperature (Scheme III.8). Under these conditions, the cyclopropane ring was opened by a chloride anion, presumably after the activation of the keto group by titanium chloride. Methyl amine is most likely not involved in the formation of **III.42**. Further development and optimization of this reaction could prove **III.42** as a building block for the synthesis of enamine **III.3**. Accordingly, treatment of **III.42** with methyl amine could force an intramolecular ring closure and provide an elegant synthetic entry to enamine **III.3** (Scheme III.8).



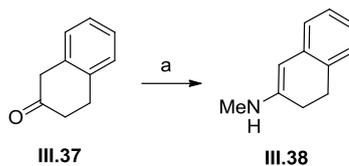
Scheme III.8. Cyclopropane opening reaction leading to the formation of chloride **III.42** and envisioned formation of enamine **III.3**.

At this stage of the synthesis, we decided to test the conditions for the enamine formation published by Evans and co-workers.^[132a] We first aimed for the formation of the enamine **III.43** starting from β -tetralone **III.24**, which should then be alkylated, thus forming the desired compound **III.3** (Scheme III.9).



Scheme III.9. Envisioned stepwise formation of **III.3** via enamine **III.43** as possible precursor.

Following this strategy, we tried to reproduce the reaction of unsubstituted β -tetralone **III.37** to enamine **III.38** as described by Evans *et al.* (*vide supra*, Scheme III.7). Unfortunately, treatment of commercially available **III.37** with methylamine solution in the presence of titanium tetrachloride at room temperature did not lead to the formation of the desired enamine **III.38**. In addition, conditions such as MeNH₂/amberlite-12/toluene/ Δ T,^[140] MeNH₂/TiCl₄/NEt₃/DCM,^[141] and MeNH₂·HCl/*p*-TosOH/toluene/ Δ T^[142] proved unsuccessful as only starting material was recovered. Eventually, we found that heating of β -tetralone (**III.37**) with neat methylamine at 100 °C in an autoclave apparatus (7 bar) furnished the desired enamine **III.38** in quantitative yields (Scheme III.10).



Reaction conditions: (a) MeNH₂ (g), -78 °C → 100 °C, 7 bar, quant.

Scheme III.10. Formation of the enamine structure **III.38**.

This reaction of **III.37** was monitored by ¹H-NMR spectroscopy of the crude reaction mixture (Figure III.8). A comparison of the crude spectrum with the spectrum of the starting material **III.37** indicated the formation of a new compound. Thus, the newly formed compound lacks the benzylic methylene protons H2 present in the starting material **III.37**. Instead, a new peak for H2 at 5.25 ppm indicates the formation of the unsaturated enamine system **III.38**. Furthermore, the new methyl group (H11) attached to a nitrogen atom was detected in the ¹H-NMR spectrum at 2.80 ppm. All of these new signals suggest the quantitative formation of the desired enamine **III.38**. Due to the instability of the compound further characterization attempts were not performed.

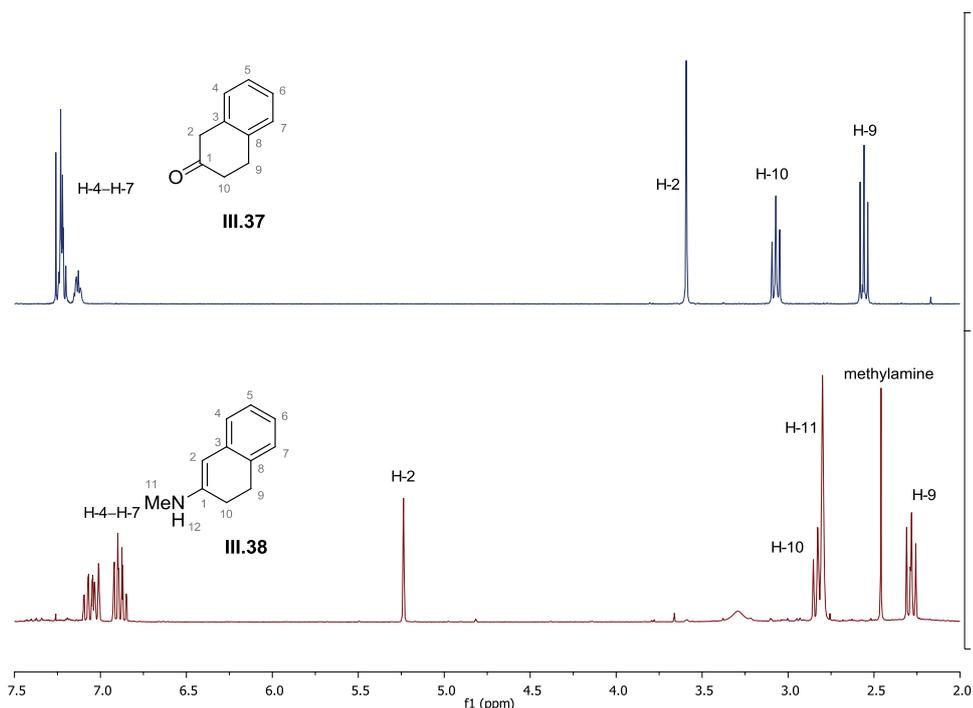
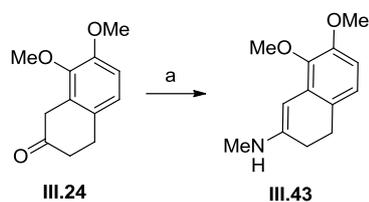


Figure III.8. ¹H-NMR spectra (in CDCl₃) of β-tetralone **III.37** and the desired product enamine **III.38**.^{bb}

Having successfully established conditions for the enamine formation, the same procedure was applied to the dimethoxytetralone system **III.24**. Treatment of dimethoxytetralone **III.24**

^{bb}In the case of enamine **III.38**, the assignment of the protons is speculative, since it is based on chemical shifts of the signals and comparison to the starting material.

with freshly condensed methylamine at high temperatures in an autoclave apparatus led to the quantitative formation of the desired dimethoxyenamine **III.43** (Scheme III.11).



Reaction conditions: (a) MeNH₂ (g), -78 °C → 100 °C, 7 bar, quant.

Scheme III.11. Formation of dimethoxytetralone **III.43**.

Again, successful conversion could be followed by ¹H-NMR spectroscopy (Figure III.9). In analogy to the spectrum of enamine **III.38**, the ¹H-spectrum of **III.43** shows a new peak at 5.47 ppm corresponding to the enamine proton H2 and lacks a methylene group, which is present in the starting material (peak H2 in the spectrum of **III.24**). In addition, another new peak suggesting the presence of a methyl group attached to a nitrogen atom appears (peak H13 in **III.43** spectrum). Hence, the crude proton spectrum of the performed reaction indicates the formation of the desired compound **III.43**. Also in this case, no further characterization could be performed due to the instability of the obtained product.

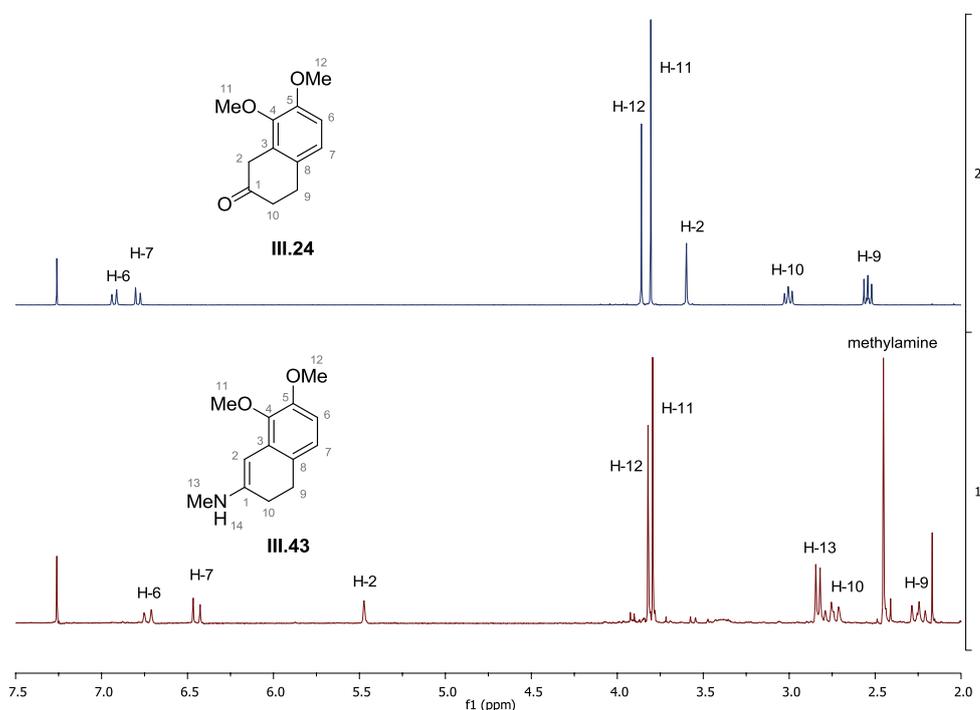
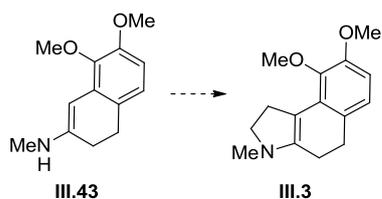


Figure III.9. ¹H-NMR spectra (in CDCl₃) of tetralone **III.24** and crude enamine **III.43**.^{cc}

^{cc}The assignment of the protons present in **III.24** was performed using 2D-NMR spectroscopic experiments. In the case of enamine **III.43**, the assignment is speculative, since it is based on chemical shifts of the signals and comparison to the starting material.

At this point, we envisioned the alkylation of enamine **III.43** to access the tricyclic enamine **III.3**, a key intermediate in the total synthesis of stephadiamine **III.1** (Scheme III.12). Several conditions, among them the alkylation condition developed by Evans, were investigated using the crude enamine **III.43**. Thus far, no conclusive results were obtained. This topic is currently being investigated by N. Vrieling as a part of her Master's project in the Trauner laboratories.



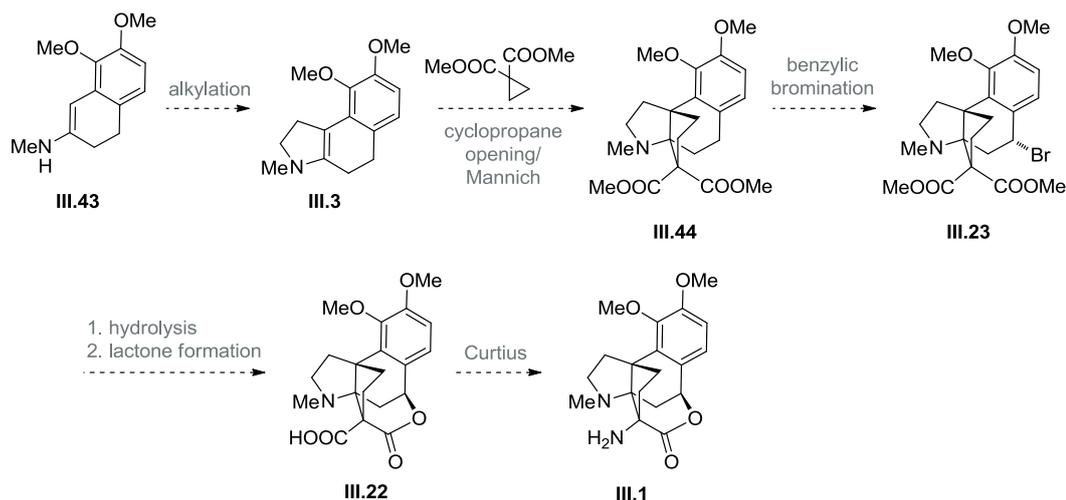
Scheme III.12. Envisioned installation of the ethylene bridge forming enamine **III.3**.

12. Summary, Conclusions and Future Work – Stephadiamine

In summary, first attempts toward the total synthesis of the norhasubanan stephadiamine **III.1** have been made. The literature known synthetic route to β -tetralone **III.24**, one of the key-intermediates in the envisioned synthesis, was optimized. Following these high yielding and reliable procedures, **III.24** could be synthesized in multigram quantities in 59% yield over four steps. In addition, the cyclopropane system **III.2** was prepared, which could possibly serve as a valuable precursor for the formation of enamine **III.3**.

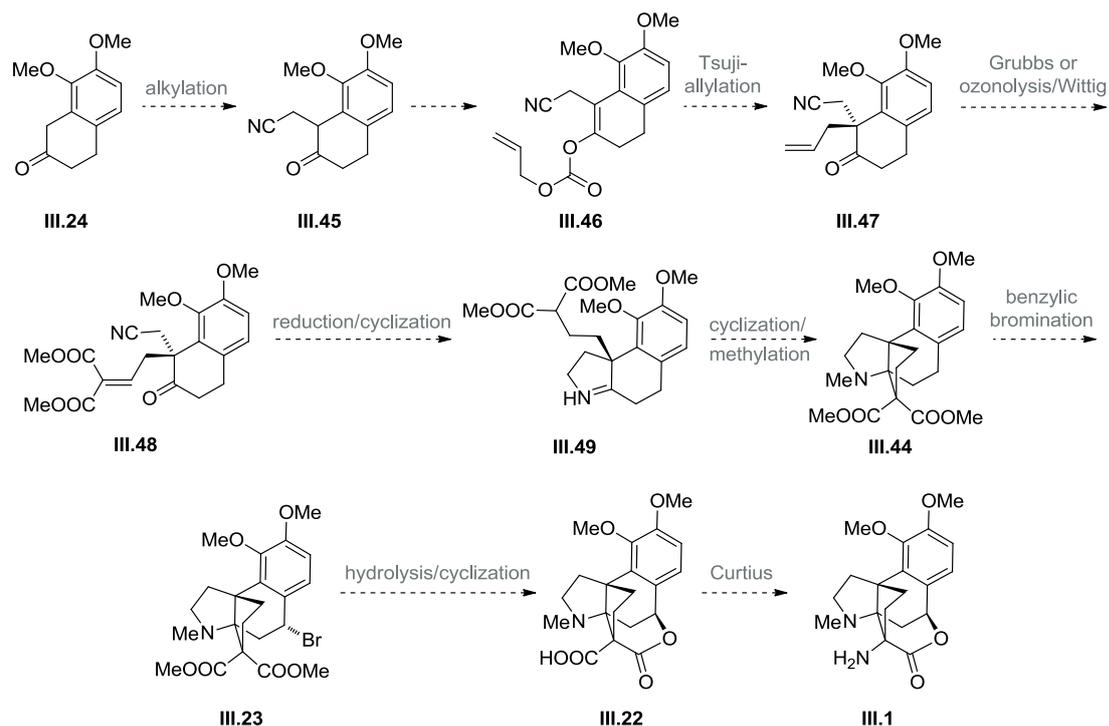
Furthermore, first experiments aiming for the formation of the tricyclic enamine system **III.3** were performed. Although these attempts remained unsuccessful, some promising results were obtained implying the formation of imine structure **III.40**. Additionally, the cyclopropane **III.2** could be opened with titanium tetrachloride presumably forming the primary chloride **III.42**, which in future could open alternative routes for the synthesis of enamine **III.3**. Finally, we were able to accomplish the syntheses of rather unstable bicyclic enamine structures **III.38** and **III.43**, precursors for the formation of the desired tricyclic enamine systems **III.3** and **III.36**. Alkylation reactions of **III.43** were performed to install the ethylene bridge, unfortunately with no success so far.

In the future, with this molecule in hand, first attempts toward the cyclopropane opening/Mannich cascade could be made (Scheme III.13). This key step of the synthesis would provide access to the propellane skeleton **III.44** featuring the first NTC center of **III.1**. Intermolecular cyclopropane opening reactions are enhanced by activation of the adjacent carbonyl group with Lewis acids, such as ytterbium or scandium triflates.^[133] This fact would also provide the potential to apply chiral Lewis acid catalysis to form the correspondent quaternary benzylic stereocenter in enantioselective manner, eventually leading to an asymmetric synthesis of stephadiamine **III.1**. Following, selective bromination of **III.44** in the benzylic position should lead to bromide **III.23**, which in turn can be converted to lactone **III.22** by means of hydrolysis and lactone formation. The final step in the total synthesis of **III.1** is envisioned to be a Curtius rearrangement forming the second NTC center of **III.1**. This route is currently under investigation by N. Vrieling as a part of a Master's thesis in the Trauner laboratories.



Scheme III.13. Envisioned synthetic route to Stephadamine **III.1** via cyclopropane opening/aminoalkylation strategy.

Alternatively, as the pursued synthetic route proved to be more challenging than originally anticipated, a second synthetic strategy for the synthesis of **III.1** starting from β -tetralone **III.24** was developed (Scheme III.14). The new route would start with an alkylation of **III.24** forming nitrile **III.45**. Alkylations of this type on similar systems are known in the literature and can be performed using enamine catalysis to avoid double alkylation processes.^[143] Next, nitrile **III.45** could be converted to enol ether **III.46**, which in turn should smoothly undergo Tsuji allylation forming the benzylic quaternary stereocenter in **III.47** even in an asymmetric way.^[144] Enantioselective Tsuji allylation is a powerful method for installation of hindered stereocenters^[145] and was applied successfully in total synthesis.^[146] The diester moiety present in **III.48** could then be introduced using either Grubbs metathesis or an ozonolysis/Wittig olefination sequence. The propellane motif of **III.44** is likely to be incorporated into **III.48** by means of a reduction of the Michael system and the nitrile portion,^[143b] followed by an intramolecular imine formation to give **III.49**, which would then cyclize in a Mannich fashion to propellane **III.44**. Most likely, these transformations could take place as a cascade reaction in a one pot process providing **III.44** directly from nitrile **III.48**. Finally, after *N*-methylation, the same sequence as described in the first synthetic strategy toward stephadamine **III.1** could be employed to accomplish the synthesis of the natural product. This sequence involves benzylic bromination of **III.44**, hydrolysis and intramolecular lactone formation of (\rightarrow **III.23**) as well as a Curtius rearrangement of acid **III.22**.^[131c,147]



Scheme III.14. Alternative possible synthetic route to stephadiamine **III.1**.

The second strategy includes the powerful enantioselective Tsuji allylation and the cascade reduction/double cyclization reaction as key steps, which form the first NTC-center of stephadiamine. Thus, this strategy is a short and efficient alternative way representing a modern and interesting route for the first asymmetric synthesis of **III.1**. Overall, the versatile β -tetralone **III.24** turned out to be a flexible key building block and could serve as starting material in alternative entries to **III.1** leaving room for further investigations.

CHAPTER IV

'EXPERIMENTAL PROCEDURES'

CHAPTER IV: EXPERIMENTAL PROCEDURES

General Experimental Procedures

Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in oven-dried glassware (180 °C oven temperature). Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled prior to use from sodium benzophenone ketyl. Triethylamine (NEt₃) and diisopropylamine (*i*-Pr₂NH) were distilled from and stored over CaH₂. *n*-Butyllithium (*n*-BuLi) was titrated using iodine prior to use. All other solvents as well as starting materials and reagents were obtained from commercial sources and used without further purification. Hexanes refers to fractions of isohexanes which boil between 40 and 80 °C.

Organic extracts were dried over Na₂SO₄ unless otherwise noted. 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 F₂₅₄ glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip (potassium permanganate, ceric ammonium molybdate, and anisaldehyde) followed by heating.

All microwave irradiation experiments were carried out in a CEM Explorer™ microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL Pyrex vessels sealed with CEM plastic crimp tops equipped with magnetic stirrers. The temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperature using nitrogen jet.

Unless otherwise specified, proton (¹H) and carbon (¹³C) spectra were recorded at 18 °C in base filtered CDCl₃ on Varian Mercury spectrometers operating at 300 MHz, 400 MHz and 600 MHz for proton nuclei (75 MHz, 100 MHz and 150 MHz for carbon nuclei). ¹H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral, functional group] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet br = broad or combinations of the above. The residual CHCl₃ peak (δ 7.26), residual DMSO peak (δ 2.50) or the residual CD₂Cl₂ peak (δ 5.32) were used as references for ¹H NMR spectra. The central peak (δ 77.16) of the CDCl₃ 'triplet', the central peak (δ 39.52) of the DMSO-*d*₆ 'heptet' and the central peak (δ 53.84) of CD₂Cl₂ peak 'pentet'

were used as references for proton-decoupled ^{13}C NMR spectra. The assignment of the proton and carbon atoms in the molecules is based on a range of performed 2D-NMR experiments (COSY, HMBC, HSQC, NOESY). The numbering of the proton and carbon atoms does not correspond to the IUPAC nomenclature.

Infrared spectra (IR, $\tilde{\nu}$) were recorded on a Perkin-Elmer BXII-FTIR spectrometer equipped with an attenuated total reflection (ATR) measuring unit. Samples were analyzed as neat materials. IR data is reported in frequency of absorption (cm^{-1}). The corresponding IR bands are characterized as follows: w = weak, m = medium, s = strong, br = broad or combinations thereof.

A Thermo Finnigan MAT 95 mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a Thermo Finnigan LTQ FT instrument operating in either positive or negative ionization modes.

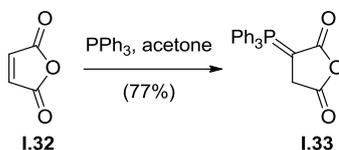
Melting points (mp) were measured on a Büchi melting point B-540 or SRS MPA120 EZ-Melt systems and are uncorrected.

Optical rotations were measured at the given temperature (T in $^{\circ}\text{C}$) on a Perkin-Elmer 241 or Krüss P8000-T polarimeter at the sodium-D line (589 nm) and the concentrations (c) (g/100 mL) indicated using spectroscopic grade solvents. The measurements were carried out in a cell with a path length (l) of 0.5 dm. Specific rotations $[\alpha]_{\text{D}}$ were calculated using the equation $[\alpha]_{\text{D}} = 100 \cdot \alpha / (c \cdot l)$ and are given in $10^{-1} \cdot \text{deg} \cdot \text{cm}^2 \cdot \text{g}^{-1}$.

High performance liquid chromatography (HPLC) was performed with HPLC grade solvents and deionized water that was purified on a TKA MicroPure water purification system. All solvents were degassed with helium gas prior to use. Unless noticed otherwise, all experiments were carried out at room temperature; the column used is specified as appropriate. Analytical HPLC spectra were recorded on a ultra high performance liquid chromatography (UHPLC) system from the Agilent 1260 Infinity series (1260 degasser, 1260 Binary Pump VL, 1260 ALS auto sampler, 1260 TCC thermostatted column compartment, 1260 DAD diode array detector), which was computer-controlled through Agilent ChemStation software. Preparative HPLC was performed on a computer-operated Varian system (Galaxie Chromatography Software, two PrepStar pumps Model SD-1, manual injection, ProStar 335 Photo Diode Array Detector, 380-LC Evaporative Light Scattering Detector).

Specific Experimental Procedures and Product Characterization

Preparation of the Wittig reagent **I.33**^[14,15b,15c]



3-(Triphenylphosphoranylidene)butanedioic anhydride (I.33). To a magnetically stirred solution of triphenylphosphine (78.7 g, 300 mmol) in dry acetone (290 mL) was added dropwise at room temperature a solution of maleic anhydride **I.32** (29.4 g, 300 mmol) in dry acetone (150 mL). After complete addition, the reaction mixture was stirred for 10 min. The newly formed solid product was filtered off and washed with cold acetone (600 mL) providing 82.8 g (230 mmol, 77%) of the Wittig reagent **I.33** as a white solid.

$R_f = 0.76$, 85:10:5 $\text{CHCl}_3/\text{MeOH}/\text{AcOH}$.

mp: 166–168 °C (acetone).

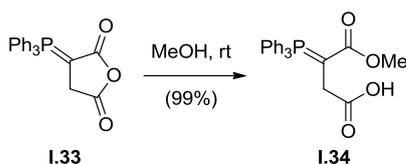
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.70\text{--}7.63$ (m, 3H), 7.63–7.58 (m, 6H), 7.57–7.51 (m, 6H), 3.21 (s, 2H).

^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 174.8$ (d, $^3\text{P}J = 19.7$ Hz), 167.5 (d, $^2\text{P}J = 18.0$ Hz), 133.4(4) (d, $^2\text{P}J = 10.6$ Hz, 6 x C), 133.3(8) (d, $^4\text{P}J = 3.0$ Hz, 3 x C), 129.5 (d, $^3\text{P}J = 12.7$ Hz, 6 x C), 124.2 (d, $^1\text{P}J = 93.1$ Hz, 3 x C), 37.2 (d, $^2\text{P}J = 11.7$ Hz), 33.8 (d, $^1\text{P}J = 135.5$ Hz).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3000$ (w), 1790 (m), 1701 (s), 1482 (w), 1436 (m), 1320 (s), 1250 (w), 1162 (m), 1107 (s).

HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{18}\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$ 361.0988, found 361.0989.

Preparation of phosphorane **I.34**^[14,15b,15c]



4-Methoxy-4-oxo-3-(triphenylphosphoranylidene)butanoic acid (I.34). The ylene **I.33** (30.0 g, 83.3 mmol) was suspended in dry methanol (150 mL) and stirred at room temperature

for 24 h. Removal of the solvent *in vacuo* provided 32.6 g (83.0 mmol, 99%) of the product **I.34** as a beige solid.

$R_f = 0.32$, 85:10:5 CHCl₃/MeOH/AcOH.

mp: 70–71 °C (MeOH).

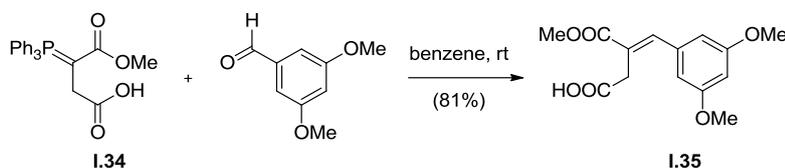
¹H NMR (300 MHz, CDCl₃): δ /ppm = 7.69–7.60 (m, 10H), 7.57–7.42 (m, 5H), 3.35 (s, 3H), 2.90 (d, ³*J* = 14.9 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃): δ /ppm = 173.2 (d, ²*P**J* = 6.4 Hz), 171.7 (d, ³*P**J* = 6.9 Hz), 133.8 (d, ²*P**J* = 9.8 Hz, 6 x C), 133.5 (d, ⁴*P**J* = 2.8 Hz, 3 x C), 129.5 (d, ³*P**J* = 12.6 Hz, 6 x C), 123.4 (d, ¹*P**J* = 89.8 Hz, 3 x C), 51.8 (s), 39.5 (d, ¹*P**J* = 90.6 Hz), 35.2 (d, ²*P**J* = 5.0 Hz).

IR: $\tilde{\nu}$ /cm⁻¹ = 2906 (w), 1729 (m), 1603 (m), 1483 (w), 1435 (m), 1318 (m) 1150 (m), 1100 (s).

HRMS (ESI) calculated for C₂₃H₂₂O₄P [M+H]⁺ 393.1250, found 393.1249.

Preparation of acid **I.35**^[15a,17]



(E)-4-(3,5-Dimethoxyphenyl)-3-(methoxycarbonyl)but-3-enoic acid (I.35). To a magnetically stirred solution of phosphorane **I.34** (57.8 g, 147 mmol) in dry benzene (100 mL) was added 3,5-dimethoxybenzaldehyde (11.9 g, 71.6 mmol). After the reaction was stirred for 4 d at room temperature, the solvent was removed *in vacuo* and the resulting crude solid was purified by flash column chromatography (50:1 CH₂Cl₂/FA). In order to remove residual formic acid the combined collected fractions were extracted with aqueous half saturated NaHCO₃ solution (3 x 150 mL). The obtained aqueous layer was washed with CH₂Cl₂ (1 x 200 mL) and acidified with concentrated HCl solution (to pH = 4). After back extraction of the product with CH₂Cl₂ (3 x 100 mL) the combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford 16.3 g (58.2 mmol, 81%) of the acid **I.35** as a white solid.

$R_f = 0.19$, 50:1 CH₂Cl₂/FA.

mp: 103 °C (CH₂Cl₂).

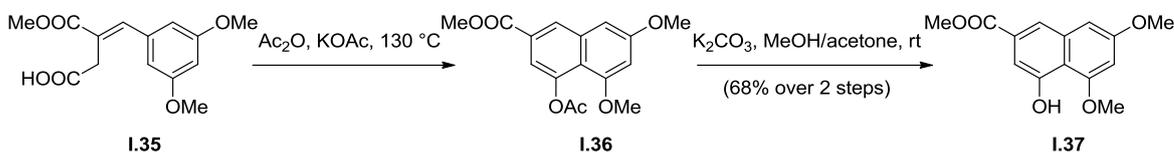
^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.86 (s, 1H), 6.51–6.50 (m, 2H), 6.47 (d, 4J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 6H), 3.59 (s, 2H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ/ppm = 172.1, 167.3, 160.5 (2 x C), 140.7, 136.4, 126.7, 107.0 (2 x C), 101.0, 55.3 (2 x C), 52.2, 33.7.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3084 (w), 2945 (w), 2841 (w), 1700 (s), 1590 (s), 1429 (m), 1279 (s), 1205 (s), 1154 (s).

HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{16}\text{O}_6$ $[\text{M}]^+$ 280.0947, found 280.0931.

Preparation of naphthalene **I.37**^[17]



Methyl 4-acetoxy-5,7-dimethoxy-2-naphthoate (I.36). A solution of acid **I.35** (5.00 g, 17.8 mmol) and potassium acetate (1.79 g, 18.2 mmol) in acetic anhydride (180 mL) was stirred at 130 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water (500 mL) and stirred for an additional 30 min. Then, the mixture was extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (2 x 200 mL) and brine (250 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude naphthalene **I.36** was used in the next step without further purification.

For full characterization of naphthalene **I.36**, an analytic sample was purified by flash column chromatography (1:4→1:0 EtOAc/hexanes gradient elution)

R_f = 0.44, 1:2 EtOAc/hexanes.

mp: 153–154 °C (EtOAc).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 8.31 (d, 4J = 1.3 Hz, 1H), 7.48 (d, 4J = 1.7 Hz, 1H), 6.84 (d, 4J = 2.2 Hz, 1H), 6.59 (d, 4J = 2.2 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 6H), 2.36 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 170.1, 166.5, 158.9, 156.3, 147.0, 137.1, 128.5, 128.1, 117.3, 116.7, 101.7, 100.2, 56.3, 55.5, 52.4, 21.0.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3064 (w), 2993 (w), 2950 (w), 2847 (w), 1771(m), 1719 (s), 1610 (m), 1447 (m), 1393 (w), 1271 (s), 1210 (s), 1129 (s).

HRMS (ESI) calculated for $C_{16}H_{20}O_6N$ $[M+NH_4]^+$ 322.1285, found 322.1286.

Methyl 4-hydroxy-5,7-dimethoxy-2-naphthoate (I.37). To a suspension of the crude naphthalene **I.36** in MeOH (45 mL) and acetone (45 mL) was added K_2CO_3 (7.01 g, 50.7 mmol) in one portion and the reaction mixture was stirred for 1 h at room temperature before being quenched by slow addition of water (100 mL) and aqueous HCl solution (5%, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL), the combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained yellow solid was washed with cold acetone (100 mL) to give 3.19 g (12.2 mmol, 67% over two steps) of naphthol **I.37** as a white solid.

$R_f = 0.45$, 1:2 EtOAc/hexanes.

mp: 162 °C (acetone).

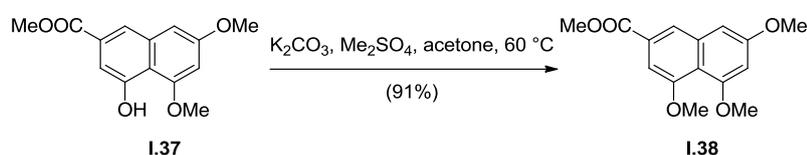
1H NMR (600 MHz, $CDCl_3$): δ /ppm = 9.12 (s, 1H), 7.90 (d, $^4J = 1.5$ Hz, 1H), 7.28 (d, $^4J = 1.6$ Hz, 1H), 6.78 (d, $^4J = 2.2$ Hz, 1H), 6.52 (d, $^4J = 2.1$ Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ /ppm = 167.2, 158.2, 157.0, 154.9, 136.8, 129.7, 120.6, 113.1, 108.0, 100.7, 100.0, 56.4, 55.5, 52.3.

IR: $\tilde{\nu}/cm^{-1} = 3377$ (m), 2941 (w), 1711 (s), 1614 (m), 1587 (m), 1429 (m), 1370 (s), 1285 (m), 1200 (s), 1160 (s), 1128 (s).

HRMS (ESI) calculated for $C_{14}H_{13}O_5$ $[M-H]^-$ 261.0768, found 261.0766.

Preparation of naphthalene **I.38**^[17-18]



Methyl 4,5,7-trimethoxy-2-naphthoate (I.38). A magnetically stirred mixture of naphthol **I.37** (15.0 g, 57.2 mmol), K_2CO_3 (23.3 g, 172 mmol) and dimethylsulfate (36.1 g, 27.1 mL, 126 mmol) in dry acetone (500 mL) was heated at 60 °C for 48 h. The solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (250 mL). The organic layer was washed with water (200 mL) and the water phase was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were washed with water (200 mL), aqueous NH_3 solution (10wt%, 200 mL) and aqueous

NaOH solution (5%, 200 mL), then dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide 14.4 g (52.3 mmol, 91%) of trimethoxynaphthalene **I.38** as a white solid.

R_f = 0.56, 1:2 EtOAc/hexanes.

mp: 144–145 °C (CH₂Cl₂).

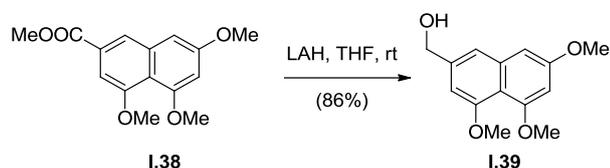
¹H NMR (600 MHz, CDCl₃): δ/ppm = 8.02 (dd, ⁴J = 1.5 Hz, ⁴J = 0.4 Hz, 1H), 7.25 (d, ⁴J = 1.5 Hz, 1H), 6.79 (d, ⁴J = 2.3 Hz, 1H), 6.59 (d, ⁴J = 2.3 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ/ppm = 167.4, 158.7, 158.3, 157.6, 137.4, 128.4, 122.9, 115.3, 103.0, 101.0, 100.1, 56.4(2), 56.4(1), 55.4, 52.3.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2997 (w), 2955 (w), 2843 (w), 1717 (m), 1704 (m), 1622 (m), 1589 (s), 1433 (m), 1378 (s), 1355 (m), 1267 (s), 1194 (s), 1100 (s).

HRMS (ESI) calculated for C₁₅H₁₇O₅ [M+H]⁺ 277.1071, found 277.1070.

Preparation of alcohol **I.39**^[17-18]



4,5,7-Trimethoxy-2-hydroxymethyl-naphthalene (I.39). To a magnetically stirred suspension of lithium aluminum hydride (3.97 g, 105 mmol) in dry THF (130 mL) was added dropwise a solution of ester **I.38** (14.4 g, 52.3 mmol) in THF (400 mL) at room temperature. The reaction was stirred at room temperature for 1 h before being quenched at 0 °C by addition of saturated aqueous NH₄Cl solution (100 mL) and water (100 mL). After stirring at room temperature for 20 min, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 350 mL). The combined organic fractions were dried over Na₂SO₄ and concentrated *in vacuo* providing the crude product. Purification of the crude material by recrystallization from EtOAc/hexanes gave 11.2 g (45.1 mmol, 86%) of alcohol **I.39** as a white solid.

R_f = 0.11, 1:2 EtOAc/hexanes.

mp: 117–118 °C (EtOAc/hexanes).

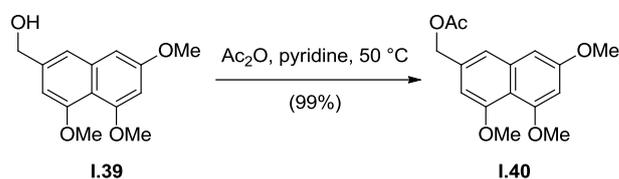
^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.19 (s, 1H), 6.68 (s, 1H), 6.65 (d, $^4J = 2.3$ Hz, 1H), 6.48 (d, $^4J = 2.3$ Hz, 1H), 4.74 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 158.5, 158.4, 157.7, 139.8, 138.2, 117.5, 112.6, 103.1, 99.1, 98.8, 65.6, 56.3(6), 56.3(5), 55.4.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3302 (m), 2921 (w), 2850 (w), 1610 (m), 1582 (s), 1446 (m), 1374 (m), 1343 (m), 1256 (m), 1200 (s), 1127 (s), 1150 (s), 1035 (s).

HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$ 249.1121, found 249.1122.

Preparation of acetate **I.40**^[17-18]



(4,5,7-Trimethoxynaphthalen-2-yl)methyl acetate (I.40). A solution of alcohol **I.39** (8.10 g, 32.7 mmol) and acetic anhydride (6.67 g, 6.17 mL, 65.3 mmol) in dry pyridine (57 mL) was stirred at 50 °C for 3 h. After addition of water (150 mL), the mixture was extracted with diethyl ether (3 x 250 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (200 mL), water (200 mL) and aqueous HCl solution (0.1M, 200 mL), followed by an additional wash with water (200 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* providing 9.45 g (32.5 mmol, 99%) of acetate **I.40** as a beige solid.

R_f = 0.45, 1:2 EtOAc/hexanes.

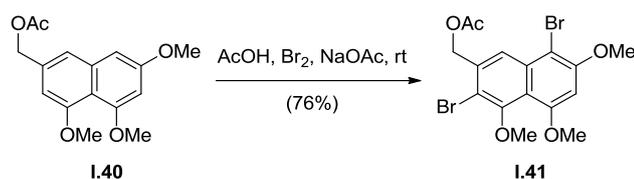
mp: 88–91 °C (diethyl ether).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.25 (d, $^4J = 0.9$ Hz, 1H), 6.70 (d, $^4J = 2.3$ Hz, 1H), 6.66 (d, $^4J = 1.4$ Hz, 1H), 6.50 (d, $^4J = 2.3$ Hz, 1H), 5.18 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 171.1, 158.6, 158.4, 157.8, 138.1, 134.7, 119.4, 113.0, 104.0, 99.3, 99.1, 66.6, 56.4(3), 56.4(2), 55.4, 21.2.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2938 (w), 2361 (w), 1738 (m), 1591 (s), 1451 (m), 1386 (m), 1272 (m), 1238 (s), 1198 (s), 1161 (s), 1120 (s), 1048 (s).

HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{18}\text{O}_5$ $[\text{M}]^+$ 290.1154, found 290.1149.

Preparation of dibromide I.41^[17-18]

(3,8-Dibromo-4,5,7-trimethoxynaphthalen-2-yl)methyl acetate (I.41). To a magnetically stirred solution of acetate **I.40** (5.60 g, 19.3 mmol) and sodium acetate (3.96 g, 48.3 mL, 65.3 mmol) in acetic acid (53 mL) was added dropwise a solution of bromine (7.10 g, 2.28 mL, 44.4 mmol) in acetic acid (83 mL) at room temperature. The reaction was stirred for 15 min, then diluted with CH_2Cl_2 (300 mL) and the mixture was washed with water (180 mL), saturated aqueous NaHCO_3 solution (3 x 150 mL) and water (180 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained yellow solid was recrystallized from EtOAc providing 6.53 g (14.6 mmol, 76%) of the dibromide **I.41** as a yellow solid.

$R_f = 0.30$, 1:2 EtOAc/hexanes.

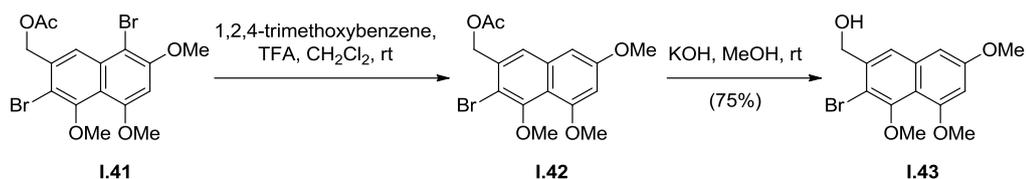
mp: 179 °C (EtOAc).

^1H NMR (600 MHz, CDCl_3): δ /ppm = 8.06 (s, 1H), 6.71 (s, 1H), 5.32 (d, $^4J = 0.7$ Hz, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 3.87 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ /ppm = 171.7, 156.7, 154.8, 153.9, 135.6, 134.1, 122.7, 117.2, 114.4, 100.2, 96.2, 66.3, 61.9, 57.1, 56.8, 21.1.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2926$ (w), 2844 (w), 1741 (s), 1605 (m), 1589 (m), 1460 (w), 1353 (s), 1342 (m), 1220 (s), 1212 (s), 1125 (s), 1028 (m).

HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{16}^{79}\text{Br}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 468.9257, found 468.9258.

Preparation of alcohol I.43^[16-18]

(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)methyl acetate (I.42). A solution of dibromide **I.41** (9.32 g, 20.8 mmol), 1,2,4-trimethoxybenzene (3.85 g, 3.41 mL, 22.9 mmol) and trifluoroacetic acid (11.9 g, 8.01 mL, 104 mmol) in dry CH_2Cl_2 (225 mL) was stirred at room

temperature for 28 h. CH_2Cl_2 (200 mL) was added and the mixture was washed with saturated aqueous NaHCO_3 solution (2 x 200 mL), followed by water (200 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:4 EtOAc/hexanes) provided an inseparable mixture of the debrominated acetate **I.42** and 1-bromo-2,4,5-trimethoxybenzene, which was used in the next step without further purification.

(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)methanol (I.43). A solution of the above prepared acetate **I.42** and KOH (4.7 g, 83.8 mmol) in methanol (145 mL) was stirred at room temperature for 15 min. After the addition of aqueous diluted HCl solution (150 mL) the aqueous layer was extracted with EtOAc (2 x 150 mL), and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The obtained crude product was purified by flash column chromatography (1:5 EtOAc/hexanes) to give 5.13 g (15.7 mmol, 75% over two steps) of the alcohol **I.43** as a white solid.

$R_f = 0.46$, 1:2 EtOAc/hexanes.

mp: 99 °C (EtOAc/hexanes).

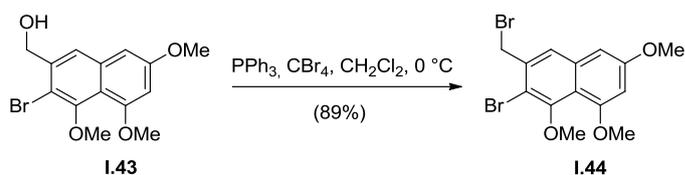
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.53$ (s, 1H), 6.69 (d, $^4J = 2.3$ Hz, 1H), 6.53 (d, $^4J = 2.3$ Hz, 1H), 4.83 (s, 2H), 3.97 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 158.7$, 156.7, 153.5, 138.9, 136.9, 122.4, 116.2, 113.0, 99.7, 99.0, 65.6, 61.8, 56.3, 55.4.

IR: $\tilde{\nu}/\text{cm}^{-1} = 3510$ (w), 3248 (w), 2925 (w), 2841 (w), 1621 (m), 1582 (s), 1443 (m), 1387 (m), 1339 (s), 1255 (m), 1208 (s), 1163 (s), 1123 (s).

HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{16}^{79}\text{BrO}_4$ $[\text{M}+\text{H}]^+$ 327.0226, found 327.0228.

Preparation of bromide **I.44**



2-Bromo-3-(bromomethyl)-1,6,8-trimethoxynaphthalene (I.44). A magnetically stirred solution of alcohol **I.43** (583 mg, 1.78 mmol) and tetrabromomethane (650 mg, 1.96 mmol) in dry CH_2Cl_2 (18 mL) was cooled to 0 °C, and then, triphenylphosphine (514 mg, 1.96 mmol) was

added in two portions. The reaction was immediately allowed to warm to room temperature and stirred for 2 h. Then, the mixture was concentrated *in vacuo* and the resulting crude oil was purified by flash column chromatography (1:4 EtOAc/hexanes) to give 615 mg (1.58 mmol, 89%) of bromide **I.44** as a beige solid.

$R_f = 0.69$, 1:2 EtOAc/hexanes.

mp: 178–179 °C (EtOAc/hexanes).

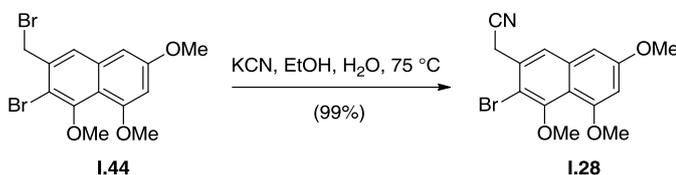
$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.58$ (s, 1H), 6.68 (d, $^4J = 2.2$ Hz, 1H), 6.55 (d, $^4J = 2.1$ Hz, 1H), 4.73 (s, 2H), 3.97 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 158.9$, 156.7, 154.3, 136.7, 136.0, 125.4, 116.9, 114.5, 100.4, 98.9, 61.8, 56.4, 55.5, 34.6.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2940$ (w), 2843 (w), 1622 (m), 1578 (s), 1446 (m), 1389 (m), 1336 (s), 1260 (s), 1207 (s), 1163 (s), 1120 (s), 956 (s).

HRMS (EI) calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3^{79}\text{Br}_2$ $[\text{M}]^+$ 387.9315, found 387.9303.

Preparation of cyanide **I.28**



2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)acetonitrile (I.28). To a magnetically stirred solution of bromide **I.44** (465 mg, 1.19 mmol) in EtOH (20 mL) and water (6 mL) was added KCN (116 mg, 1.79 mmol) at room temperature. The reaction mixture was heated to 75 °C and stirred at this temperature for 1 h. After the reaction was cooled to room temperature, saturated aqueous NaHCO_3 solution (30 mL) was added and the resulting biphasic mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 400 mg (1.18 mmol, 99%) of cyanide **I.28** as a white solid that was used without further purification.

$R_f = 0.59$, 1:2 EtOAc/hexanes.

mp: 44–45 °C (EtOAc).

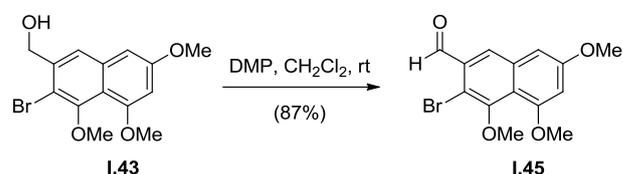
^1H NMR (600 MHz, CDCl_3): δ /ppm = 7.66 (s, 1H), 6.74 (d, $^4J = 2.3$ Hz, 1H), 6.57 (d, $^4J = 2.3$ Hz, 1H), 3.98 (s, 3H), 3.96 (d, $^4J = 0.9$ Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ /ppm = 159.2, 156.7, 154.4, 136.8, 128.9, 123.4, 117.4, 116.5, 113.6, 100.3, 98.9, 61.9, 56.4, 55.6, 25.7.

IR: $\tilde{\nu}/\text{cm}^{-1} = 3016$ (w), 2926 (w), 2839 (w), 1618 (m), 1599 (m), 1574 (s), 1446 (m), 1387 (m), 1335 (s), 1258 (m), 1162 (s), 1098 (s).

HRMS (ESI) calculated for $\text{C}_{15}\text{H}_{15}\text{NO}_3^{79}\text{Br}$ $[\text{M}+\text{H}]^+$ 336.0230, found 336.0234.

Preparation of aldehyde **I.45**^[148]



3-Bromo-4,5,7-trimethoxy-2-naphthaldehyde (I.45). To a magnetically stirred solution of alcohol **I.43** (200 mg, 1.53 mmol) in wet CH_2Cl_2 (90 mL) was added Dess-Martin periodinane (2.00 g, 4.74 mmol) at room temperature. The reaction was stirred at room temperature for 10 min before it was quenched with water (65 mL), aqueous saturated NaHCO_3 solution (65 mL) and aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (65 mL). The biphasic mixture was stirred 15 min, until both layers became colorless. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude product was subjected to flash column chromatography (1:4 EtOAc/hexanes) to provide 432 mg (1.33 mmol, 87%) of aldehyde **I.45** as a yellow solid.

$R_f = 0.48$, 1:4 EtOAc/hexanes.

mp: 162 °C (EtOAc/hexanes).

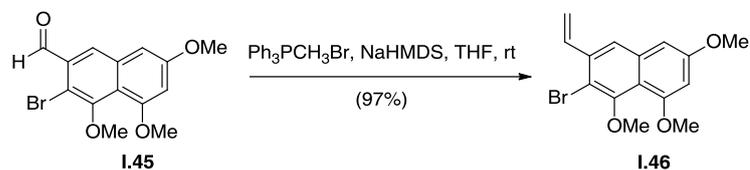
^1H NMR (300 MHz, CDCl_3): δ /ppm = 10.49 (s, 1H), 8.05 (s, 1H), 6.83 (d, $^4J = 2.3$ Hz, 1H), 6.67 (d, $^4J = 2.3$ Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.91 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ /ppm = 192.6, 159.2, 156.7, 154.4, 136.1, 132.0, 126.0, 120.1, 113.9, 102.6, 100.6, 62.1, 56.5, 55.6.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2985$ (w), 1737 (s), 1447 (w), 1273 (m), 1250 (s), 1098 (w), 1044 (s).

HRMS (ESI) calculated for $C_{14}H_{13}O_4^{79}Br$ $[M]^+$ 323.9992, found 323.9984.

Preparation of alkene **I.46**^[148]



2-Bromo-1,6,8-trimethoxy-3-vinylnaphthalene (I.46). To a magnetically stirred suspension of methyltriphenylphosphonium bromide (414 mg, 1.15 mmol) in dry THF (21 mL) was added NaHMDS solution (1M in toluene, 1.15 mL, 1.15 mmol) at room temperature and the mixture was stirred for 1 h. Thereafter, a solution of aldehyde **I.45** (250 mg, 770 μmol) in dry THF (10 mL) was added and the reaction was stirred for an additional 1 h before it was diluted with diethyl ether (30 mL). The organic layer was washed with water (3 x 30 mL) and brine (3 x 30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was subjected to flash column chromatography (1:5 EtOAc/hexanes) providing 234 mg (730 μmol , 97%) of the aldehyde **I.46** as colorless solid.

$R_f = 0.75$, 1:4 EtOAc/hexanes.

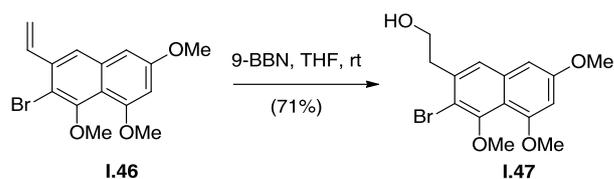
mp: 71–72 $^\circ\text{C}$ (EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 7.63$ (s, 1H), 7.17 (ddd, $^3\text{trans}J = 17.3$ Hz, $^3\text{cis}J = 10.9$ Hz, $^4J = 0.5$ Hz, 1H), 6.71 (d, $^4J = 2.3$ Hz, 1H), 6.52 (d, $^4J = 2.3$ Hz, 1H), 5.76 (dd, $^3\text{trans}J = 17.3$ Hz, $^2J = 1.3$ Hz, 1H), 5.39 (dd, $^3\text{cis}J = 10.9$ Hz, $^2J = 1.3$ Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 158.6$, 156.7, 153.6, 137.4, 136.8, 136.7, 120.9, 116.9, 116.5, 114.6, 99.8, 98.9, 61.7, 56.4, 55.5.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2980$ (w), 2932 (w), 2827 (w), 1615 (s), 1574 (s), 1398 (m), 1349 (m), 1335 (s), 1260 (m), 1209 (s), 1163 (s), 1127 (s), 1097 (m), 1049 (s).

HRMS (ESI) calculated for $C_{15}H_{15}O_3^{79}Br$ $[M]^+$ 322.0199, found 322.0202.

Preparation of alcohol I.47^[148]

2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)ethanol (I.47). A solution of alkene **I.46** (100 mg, 310 μmol) and 9-Borabicyclo[3.3.1]nonane (0.5M in THF, 740 μL , 370 μmol) in dry THF (0.4 mL) was stirred at room temperature for 2 h before it was diluted with aqueous NaOH solution (6M, 0.1 mL) and water (0.12 mL). The mixture was cooled to 0 °C and aqueous H₂O₂ solution (30wt%, 0.12 mL) was added dropwise. After being stirred at room temperature for 1 h, water (10 mL) was added and the phases were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL) and the combined organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude product was subjected to flash column chromatography (1:2 EtOAc/hexanes) to afford 76.0 mg (220 μmol , 71%) of alcohol **I.47** as a colorless oil.

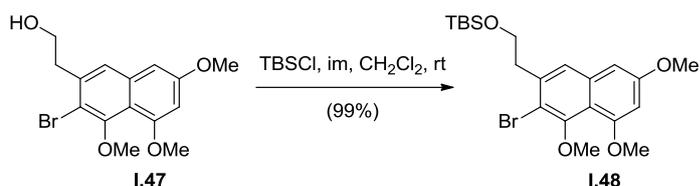
R_f = 0.35, 1:2 EtOAc/hexanes.

¹H NMR (400 MHz, CDCl₃): δ /ppm = 7.38 (d, ⁴J = 0.4 Hz, 1H), 6.66 (d, ⁴J = 2.3 Hz, 1H), 6.51 (d, ⁴J = 2.2 Hz, 1H), 3.97 (s, 3H), 3.96 (t, ³J = 6.5 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.15 (td, ³J = 6.5 Hz, ⁴J = 0.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ /ppm = 158.7, 156.8, 153.9, 137.0, 136.7, 124.7, 115.9(2), 115.9(3), 99.4(2), 99.4(4), 62.1, 61.8, 56.3, 55.5, 40.0.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3350 (w), 2934 (w), 2838 (w), 1619 (s), 1593 (m), 1575 (s), 1450 (m), 1389 (m), 1337 (s), 1259 (m), 1208 (m), 1150 (s), 1119 (s), 1056 (s).

HRMS (ESI) calculated for C₁₅H₁₈O₄⁷⁹Br [M+H]⁺ 341.0383, found 341.0384.

Preparation of TBS-ether I.48^[148]

(2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)ethoxy)(tert-butyl)dimethylsilane (I.48). A solution of alcohol **I.47** (29.0 mg, 80.0 μmol), *tert*-butyldimethylsilyl chloride (15.0 mg, 100 μmol) and imidazole (13.0 mg, 200 μmol) in dry CH_2Cl_2 (0.1 mL) was stirred at room temperature for 24 h. During this time a white precipitate was formed, which was removed by a filtration. After the filter cake was washed with CH_2Cl_2 (10 mL), the organic layer was concentrated *in vacuo* to provide crude product. Subjection of this material to flash column chromatography (1:6 EtOAc/hexanes) gave 36.1 mg (79.4 μmol , 99%) of the TBS ether **I.48** as a yellow solid.

$R_f = 0.80$, 1:5 EtOAc/hexanes.

mp: 46–47 °C (EtOAc/hexanes).

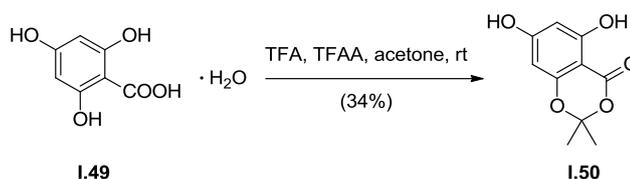
^1H NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 7.36$ (s, 1H), 6.63 (d, $^4J = 2.3$ Hz, 1H), 6.50 (d, $^4J = 2.2$ Hz, 1H), 3.96 (s, 3H), 3.90 (t, $^3J = 6.9$ Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.09 (t, $^3J = 6.9$ Hz, 2H), 0.86 (s, 9H), -0.04 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 158.5$, 156.7, 153.5, 137.6, 136.6, 125.1, 116.1, 115.7, 99.2, 98.4, 62.8, 61.7, 56.3, 55.5, 40.3, 26.1 (3 x C), 18.5, -5.2 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2928$ (m), 1620 (m), 1577 (m), 1464 (m), 1296 (m), 1337 (m), 1258 (m), 1209 (m), 1162 (m), 1124 (m), 1088 (s), 1062 (m), 1045 (s).

HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{32}\text{O}_4^{79}\text{Br}^{28}\text{Si}$ $[\text{M}+\text{H}]^+$ 455.1248, found 455.1250.

Preparation of acetone **I.50**^[19c,19d]



5,7-Dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (I.50). To a magnetically stirred solution of 2,4,6-trihydroxybenzoic acid (**I.49**) (10.0 g, 53.2 mmol) in trifluoroacetic acid (80 mL) were slowly added dry acetone (7.90 g, 10.0 mL, 136 mmol) and trifluoroacetic acid anhydride (50 mL) at 0 °C. After being warmed to room temperature, the reaction was stirred for 24 h. Then, the mixture was concentrated *in vacuo* and the residual crude oil was re-dissolved in saturated aqueous NaHCO_3 solution (300 mL). The aqueous solution was extracted with EtOAc (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a dark yellow oil. Subjection of this material to flash column

chromatography (1:2 EtOAc/hexanes) provided 3.82 g (18.2 mmol, 34%) of the acetonide **I.50** as a white solid.

$R_f = 0.13$, 1:2 EtOAc/hexanes.

mp: 199 °C (EtOAc/hexanes).

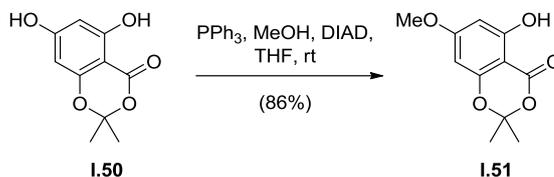
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 10.45$ (s, 1H), 6.08 (d, $^4J = 2.2$ Hz, 1H), 5.96 (d, $^4J = 2.2$ Hz, 1H), 2.18 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 165.3$, 164.1, 163.4, 157.4, 107.2, 97.8, 95.7, 93.4, 25.8 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3178$ (m), 2595 (w), 1627 (s), 1601 (s), 1503 (m), 1478 (m), 1430 (m), 1316 (m), 1267 (s), 1159 (s), 1160 (s), 1056 (m).

HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{O}_5$ $[\text{M}]^+$ 210.0523, found 210.0522.

Preparation of hydroxybenzene **I.51**^[19c]



5-Hydroxy-7-methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (I.51). To a magnetically stirred solution of acetonide **I.50** (3.82 g, 18.1 mmol), triphenylphosphine (5.10 g, 19.4 mmol) and methanol (622 mg, 790 μL , 19.4 mmol) in dry THF (60 mL) was slowly added diisopropyl azodicarboxylate (3.92 g, 19.4 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was then stirred for 2 h before EtOAc (300 mL) was added. The organic layer was washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the crude product. Subjection of this material to flash column chromatography (1:9 EtOAc/hexanes) provided 3.47 g (15.5 mmol, 86%) of phenol **I.51** as a white solid.

$R_f = 0.30$, 1:3 EtOAc/hexanes.

mp: 107–108 °C (EtOAc/hexanes).

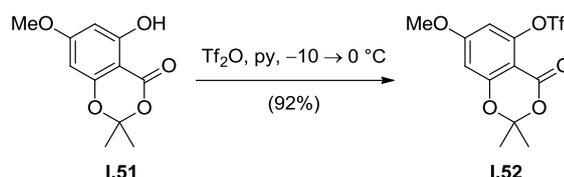
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 10.45$ (s, 1H), 6.15 (d, $^4J = 2.3$ Hz, 1H), 6.00 (d, $^4J = 2.3$ Hz, 1H), 3.82 (s, 3H), 1.73 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 167.8, 165.3, 163.3, 157.0, 107.0, 95.9, 94.8, 93.2, 55.9, 25.8 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3854 (w), 3182 (w), 2362 (w), 2340 (w), 1700 (s), 1642 (s), 1585 (m), 1506 (m), 1357 (m), 1273 (m), 1168 (s).

HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{12}\text{O}_5$ $[\text{M}]^+$ 224.0679, found 224.0676.

Preparation of triflate **I.52**^[19c]



7-Methoxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (I.52). A magnetically stirred solution of phenol **I.51** (3.47 g, 15.5 mmol) in dry pyridine (50 mL) was cooled to at -10 °C and trifluorosulfonic anhydride (4.80 g, 2.86 mL, 17.0 mmol) was added slowly. The reaction was stirred at 0 °C for 2 h before being quenched with ice water (100 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL) and the combined organic fractions were washed with aqueous HCl solution (0.1M, 150 mL), saturated aqueous NaHCO_3 solution (150 mL), water (150 mL) and brine (150 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude product was subjected to flash column chromatography (1:6 EtOAc/hexanes) to provide 5.09 g (14.3 mmol, 92%) of the triflate **I.52** as a yellow solid.

R_f = 0.60, 1:3 EtOAc/hexanes.

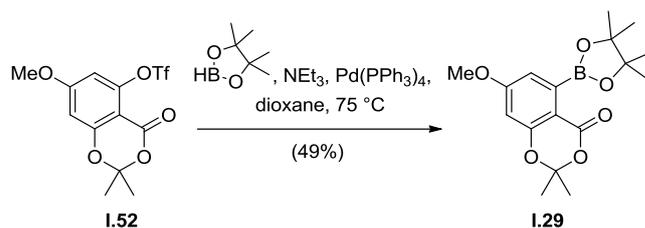
mp: 69 – 70 °C (EtOAc/hexanes).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 6.53 (d, 4J = 2.3 Hz, 1H), 6.48 (d, 4J = 2.4 Hz, 1H), 3.88 (s, 3H), 1.74 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 165.7, 159.0, 157.2, 150.1, 118.9 (q, ^{1F}J = 321.1 Hz, CF_3), 106.7, 105.5, 101.3, 101.1, 56.4, 25.7 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2993 (w), 1730 (m), 1627 (m), 1578 (m), 1424 (m), 1378 (w), 1286 (m), 1220 (s), 1154 (m), 1238 (m), 1058 (s), 1038 (s).

HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_7\text{SNa}$ $[\text{M}+\text{Na}]^+$ 379.0070, found 379.0069.

Preparation of boronic ester **I.29^[19a,19b]****7-Methoxy-2,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-benzo[d]**

[1,3]dioxin-4-one (I.29). A magnetically stirred solution of triflate **I.52** (663 mg, 1.86 mmol), freshly distilled triethylamine (560 mg, 770 μ L, 5.58 mmol) and tetrakis(triphenylphosphine) palladium(0) (107 mg, 93.0 μ mol) in dry dioxane (112 mL) was degassed with argon for 10 min at room temperature and then, pinacolborane (2.62 g, 2.97 mL, 20.5 mmol) was added dropwise. After being stirred at 75 °C for 1.5 h, the mixture was concentrated *in vacuo* and the obtained dark brown oil was purified by a quick flash column chromatography (1:10 EtOAc/hexanes, silica gel was deactivated prior to use with 0.1:1:10 NEt₃/EtOAc/hexanes) to provide 304 mg (910 μ mol, 49%) of the boronic ester **I.29** as a yellow crystalline solid.

R_f = 0.67, 1:2 EtOAc/hexanes.

¹H NMR (600 MHz, CDCl₃): δ /ppm = 6.66 (d, ⁴J = 2.4 Hz, 1H), 6.39 (d, ⁴J = 2.4 Hz, 1H), 3.83 (s, 3H), 1.71 (s, 6H), 1.42 (s, 12H).

¹³C NMR (150 MHz, CDCl₃): δ /ppm = 165.7, 162.0, 157.3, 113.8, 108.8, 106.3, 101.7, 84.6 (2 x C), 55.8, 26.0 (2 x C), 24.9 (4 x C). (C-B signal is obscured or overlapping).

HRMS (ESI) calculated for C₁₇H₂₃O₆¹¹BNa [M+Na]⁺ 357.1480, found 357.1480.

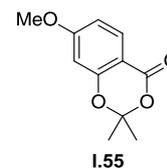
As a byproduct, traces of protodeborylated benzene **I.55** were isolated:

7-Methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (I.55).

Colorless oil.

R_f = 0.71, 1:2 EtOAc/hexanes.

¹H NMR (600 MHz, CDCl₃): δ /ppm = 7.86 (d, ³J = 8.7 Hz, 1H), 6.64 (dd, ³J = 8.8 Hz, ⁴J = 2.4 Hz, 1H), 6.42 (d, ⁴J = 2.3 Hz, 1H), 3.84 (s, 3H), 1.72 (s, 6H).

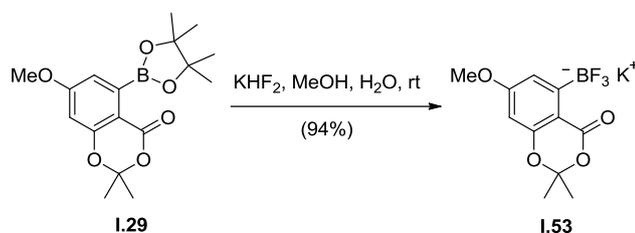


¹³C NMR (150 MHz, CDCl₃): δ /ppm = 166.4, 161.1, 158.1, 131.3, 110.4, 106.4(3), 106.3(8), 101.2, 55.9, 25.9 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3084 (w), 3002 (w), 2946 (w), 2850 (w), 1716 (s), 1613 (s), 1585 (s), 1505 (m), 1446 (s), 1375 (m), 1298 (s), 1250 (s), 1208 (s), 1152 (s), 1108 (s), 1047 (s).

HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{12}\text{O}_4$ $[\text{M}]^+$ 208.0736, found 208.0727.

Preparation of trifluoroborate **I.53**

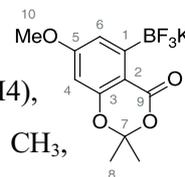


Potassium trifluoro(7-methoxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)borate (I.53). A solution of boronic ester **I.29** (110 mg, 330 μmol) and potassium bifluoride (64.0 mg, 820 μmol) in MeOH (0.11 mL) and water (0.22 mL) was stirred at room temperature for 2 h. The mixture was cooled to 0 °C and kept at this temperature for 20 min before the freshly formed precipitate was collected. The obtained white solid was washed with cold MeOH to provide 97.0 mg (310 μmol , 94%) of trifluoroborate **I.53** as a white powder.

R_f = 0.05, 1:2 EtOAc/hexanes.

mp: 224 °C (MeOH).

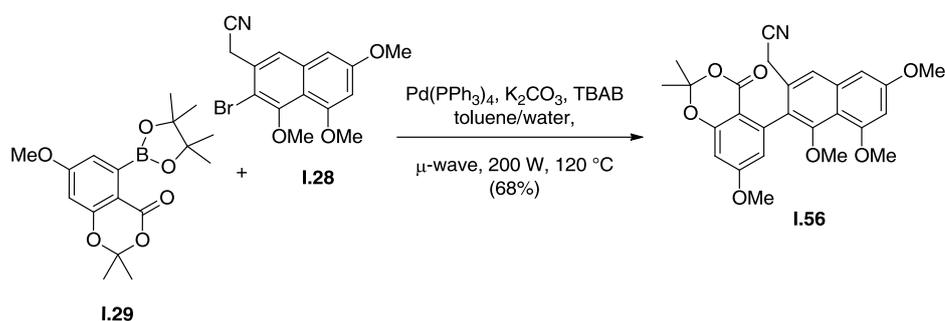
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ/ppm = 6.87 (d, $^4J = 2.7$ Hz, 1H, Ar-H, H4), 6.30 (d, $^4J = 2.7$ Hz, 1H, Ar-H, H6), 3.75 (s, 3H, OCH_3 , H10), 1.58 (s, 6H, CH_3 , H8).



^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ/ppm = 163.6 (CO, C9), 157.8 (Ar- C_q -B, C1), 114.6 (Ar-C, C4), 109.3 (Ar- C_q , C5), 103.7 (Ar- C_q , C2), 103.4 (C_q , C7) 99.0 (Ar-C, C6), 98.3 (Ar- C_q , C3), 55.1 (OCH_3 , C10), 25.3 (CH_3 , 2 x C8).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2999 (w), 2942 (w), 1733 (m), 1601 (m), 1567 (m), 1408 (w), 1339 (w), 1250 (s), 1199 (s), 1252 (s), 1058 (s).

HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{11}\text{O}_4^{11}\text{BF}_3$ $[\text{M}]^-$ 275.0708, found 275.0706.

Preparation of biaryl **I.56**

To effect the formation of biaryl **I.56** several Suzuki-coupling conditions were screened. Selected screening conditions are summarized in table IV.1. It was found that microwave conditions were required in order for the reaction to proceed.

Table IV.1. Selected conditions used for the Suzuki coupling of bromide **I.28** with boronate **I.29**

Entry	Catalyst	Base	Ligand	Solvent	Additive	T [°C]	Product
1	Pd ₂ (dba) ₃	Cs ₂ CO ₃	DPEPhos	toluene	ms ^a	50	n. p. ^b
2	Pd ₂ (dba) ₃	K ₃ PO ₄	RuPhos	dioxane	ms ^a	50	n. p. ^b
3	PEPPSI-IPr	KOtBu	–	<i>i</i> PrOH	-	rt	n. p. ^b
4	PEPPSI-IPr	Ba(OH) ₂	–	<i>i</i> PrOH	-	65	n. p. ^b
5	PEPPSI-IPr	K ₂ CO ₃	–	MeOH	-	65	n. p. ^b
6	PEPPSI-IPr	KOtBu	–	<i>t</i> BuOH	ms ^a	65	n. p. ^b
7	Pd(PPh ₃) ₄	K ₂ CO ₃	–	water/toluene	TBAB	120, μw	68%

^ams = molecular sieves (4Å). ^bn. p. = no product formation.

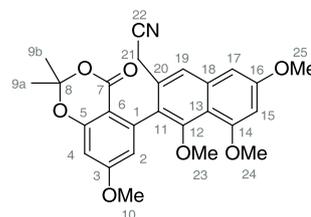
2-(4,5,7-Trimethoxy-3-(7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)naphthalen-2-yl)acetonitrile (I.56**).** To a magnetically stirred solution of cyanide **I.28** (50.0 mg, 150 μmol) in toluene (1 mL) and water (1 mL) was added boronate ester **I.29** (160 mg, 480 μmol) followed by K₂CO₃ (62.0 mg, 450 μmol), tetra-*N*-butylammonium bromide (13.0 mg, 40.0 μmol), and tetrakis(triphenylphosphine)palladium(0) (35.0 mg, 30.0 μmol). The ensuing mixture was stirred at 120 °C in a CEM microwave reactor operating at 200 W (maximum power) for 2 h. After this, the reaction mixture was cooled to room temperature, then, diluted with CH₂Cl₂ (10 mL) and washed with water (7 mL) followed by aqueous HCl solution (10wt%, 7 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a dark brown oil. Subjection of this material to flash column chromatography

(1:9→1:4→1:2→1:0 EtOAc/hexanes, gradient elution) provided 47.0 mg (101 μ mol, 68%) of biaryl **I.56** as a white solid.

R_f = 0.39, 1:2 EtOAc/hexanes.

mp 76–79 °C.

^1H NMR (600 MHz, CDCl_3): δ /ppm = 7.66 (br s, 1H, Ar-H, H19), 6.80 (d, 4J = 2.3 Hz, 1H, Ar-H, H17), 6.55–6.53 (m, 3H, Ar-H, H2, H4, H15), 3.95 (s, 3H, OCH_3 , H24 or H25), 3.93 (s, 3H, OCH_3 , H24 or H25), 3.86 (s, 3H, OCH_3 , H10), 3.56 (dd, 2J = 18.8 Hz, 4J = 1.1 Hz, 1H, CH_2 , H21), 3.53 (s, 3H, OCH_3 , H23), 3.39 (dd, 2J = 18.8 Hz, 4J = 0.7 Hz, 1H, CH_2 , H21), 1.76 (s, 3H, CH_3 , H9), 1.73 (s, 3H, CH_3 , H9).



^{13}C NMR (150 MHz, CDCl_3): δ /ppm = 165.1 (Ar- C_q , C3), 159.5 (CO, C7), 158.8 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 157.3 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 153.1 (Ar- C_q , C12), 141.2 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 137.7 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 128.8 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 128.0 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 122.5 (Ar-C, C19), 118.0 (CN, C22), 115.5 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 114.0 (Ar-C, C2 or C4), 106.3 (Ar- C_q , C1 or C5 or C6 or C11 or C13 or C14 or C16 or C18 or C20), 105.7 (C $_q$, C8), 101.9 (Ar-C, C2 or C4), 99.7 (Ar-C, C15), 99.2 (Ar-C, C17), 62.3 (Ar-C-OMe, C23), 56.2 (Ar-C-OMe, C24 or C25), 56.0 (Ar-C-OMe, C10), 55.6 (Ar-C-OMe, C24 or C25), 26.8 (CH_3 , C9a or C9b), 25.1 (CH_3 , C9a or C9b), 22.3 (CH_2 , C21) (one signal obscured or overlapping).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2936 (w), 2362 (w), 1730 (m), 1605 (s), 1575 (s), 1454 (m), 1391 (s), 1339 (s), 1278 (s), 1204 (s), 1130 (s), 1053 (s).

HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{26}\text{NO}_7$ [$\text{M}+\text{H}$] $^+$ 464.1704, found 464.1705.

As byproducts, 26.0 mg (62.7 μ mol, 26%) of homocoupling product **I.54** and 16.0 mg (76.8 μ mol, 16%) of protodeborylated benzene **I.55** were isolated:

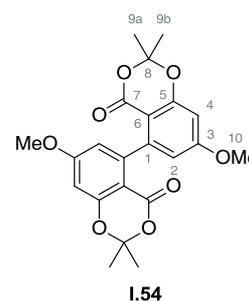
7,7'-Dimethoxy-2,2,2',2'-tetramethyl-4H,4'H-[5,5'-bibenzo[d][1,3]dioxine]-4,4'-dione (I.54).

Yellow oil.

$R_f = 0.49$, 1:2 EtOAc/hexanes.

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.48$ (d, $^4J = 2.5$ Hz, 2H, Ar-H, H4), 6.46 (d, $^4J = 2.5$ Hz, 2H, Ar-H, H2), 3.86 (s, 6H, OCH_3 , H10), 1.76 (s, 6H, CH_3 , H9), 1.73 (s, 6H, CH_3 , H9).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 165.0$ (2 x Ar- C_q , C3), 160.1 (2 x CO, C7), 158.4 (2 x Ar- C_q , C6), 145.3 (2 x Ar- C_q , C5), 112.5 (2 x Ar-C, C4), 105.9 (2 x Ar- C_q , C1), 105.9 (2 x C_q , C8), 100.8 (2 x Ar-C, C2), 55.8 (2 x OCH_3 , C10), 27.3 (2 x CH_3 , C9), 24.2 (2 x CH_3 , C9).



IR: $\tilde{\nu}/\text{cm}^{-1} = 3588$ (w), 1005 (w), 2361 (w), 2340 (w), 1700 (s), 1419 (m), 1359 (s), 1221 (s).

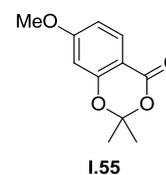
HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{23}\text{O}_8$ $[\text{M}+\text{H}]^+$ 415.1387, found 415.1387.

7-Methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (I.55).

Colorless oil.

$R_f = 0.71$, 1:2 EtOAc/hexanes.

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.86$ (d, $^3J = 8.7$ Hz, 1H), 6.64 (dd, $^3J = 8.8$ Hz, $^4J = 2.4$ Hz, 1H), 6.42 (d, $^4J = 2.3$ Hz, 1H), 3.84 (s, 3H), 1.72 (s, 6H).

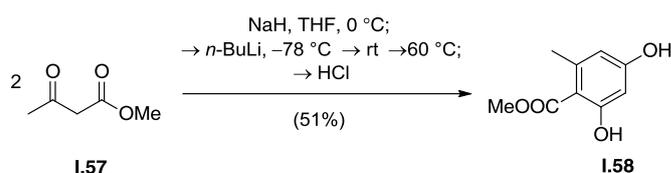


$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 166.4$, 161.1, 158.1, 131.3, 110.4, 106.4(3), 106.3(8), 101.2, 55.9, 25.9 (2 x C).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3084$ (w), 3002 (w), 2946 (w), 2850 (w), 1716 (s), 1613 (s), 1585 (s), 1505 (m), 1446 (s), 1375 (m), 1298 (s), 1250 (s), 1208 (s), 1152 (s), 1108 (s), 1047 (s).

HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{12}\text{O}_4$ $[\text{M}]^+$ 208.0736, found 208.0727.

Preparation of orsellinic ester I.58^[30d]



Methyl 2,4-dihydroxy-6-methylbenzoate (I.58). After NaH (60wt% suspension in mineral oil, 25.8 g, 650 mmol) was washed with *n*-pentane (3 x 100 mL), it was suspended in dry THF

(250 mL) and methylacetoacetate (**I.57**) (50.0 g, 46.5 mL, 430 mmol) was added dropwise at 0 °C (Caution! Gas evolution!). The mixture was cooled to -78 °C and *n*-BuLi solution (2.5M in hexanes, 160 mL, 400 mmol) was added dropwise. The reaction was warmed to room temperature and stirred overnight before being warmed to 60 °C and stirred for an additional 24 h at this temperature. After the mixture was cooled to 0 °C, aqueous concentrated HCl solution was added dropwise, until the pH of the solution was adjusted to 2. Then, the mixture was stirred for an additional 12 h at room temperature before the layers were separated and the aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the crude product, which was subjected to flash column chromatography (1:6→1:4→1:2 EtOAc/hexanes gradient elution) giving 19.8 g (109 mmol, 51%) of the methyl ester **I.58** as a white solid.

R_f = 0.38, 1:2 EtOAc/hexanes.

mp: 136 °C (EtOAc/hexanes).

¹H NMR (600 MHz, CDCl₃): δ/ppm = 11.75 (s, 1H), 6.28 (d, ⁴J=2.6 Hz, 1H), 6.23 (d, ⁴J=2.6 Hz, 1H), 5.35 (br s, 1H), 3.92 (s, 3H), 2.49 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ/ppm = 172.3, 165.4, 160.4, 144.1, 111.5, 105.8, 101.4, 52.0, 24.4.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3365 (w), 3308 (w), 2958 (w), 1599 (s), 1581 (s), 1443 (m), 1379 (w), 1310 (s), 1242 (s), 1198 (m), 1120 (s).

HRMS (ESI) calculated for C₉H₁₀O₄ [M]⁺ 182.0574, found 182.0577.

As a minor byproduct the free orsellinic acid (**I.113**) was isolated:

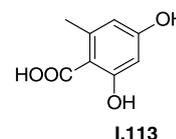
2,4-Dihydroxy-6-methylbenzoic acid (**I.113**).

White solid.

R_f = 0.06, 1:2 EtOAc/hexanes.

Mp: 184–185 °C (EtOAc/hexanes).

¹H NMR (400 MHz, DMSO-*d*₆): δ/ppm = 10.13 (s, 1H), 6.17 (dd, ⁴J=2.5 Hz, ⁴J=0.8 Hz, 1H), 6.12 (dd, ⁴J=2.5 Hz, ⁴J=0.4 Hz, 1H), 2.39 (s, 3H).

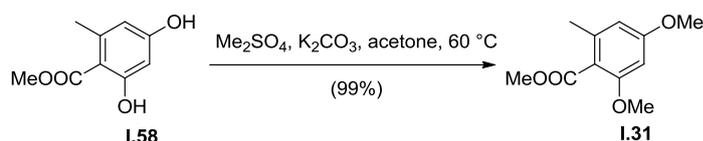


¹³C NMR (100 MHz, DMSO-*d*₆): δ/ppm = 173.3, 164.5, 162.0, 142.9, 111.0, 104.8, 100.5, 23.5.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3371 (w), 2939 (w), 1619 (s), 1454 (s), 1359 (m), 1250 (s), 1207 (s), 1166 (s), 1062 (m).

HRMS (ESI) calculated for $\text{C}_8\text{H}_8\text{O}_4$ $[\text{M}]^+$ 168.0417, found 168.0425.

Preparation of dimethyl ether **I.31**^[30c]



Methyl 2,4-dimethoxy-6-methylbenzoate (I.31). A magnetically stirred solution of phenol **I.58** (19.8 g, 109 mmol), dimethylsulfate (35.7 g, 26.8 mL, 283 mmol) and K_2CO_3 (90.0 g, 653 mmol) in dry acetone (400 mL) was refluxed for 12 h. After filtration of the solid, residual acetone was removed *in vacuo* and the obtained oil was re-dissolved in diethyl ether (500 mL). The ether phase was washed with aqueous NaOH solution (1M, 2 x 250 mL), dried over Na_2SO_4 and filtered. Evaporation of the solvent provided 22.6 g (108 mmol, 99%) of dimethyl ether **I.31** as a light yellow solid.

R_f = 0.63, 1:3 EtOAc/hexanes.

mp: 41 °C (EtOAc/hexanes).

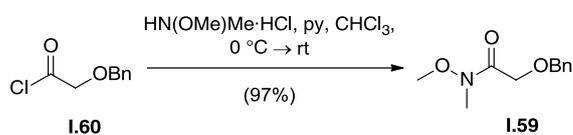
^1H NMR (300 MHz, CDCl_3): δ/ppm = 6.31 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ/ppm = 168.9, 161.5, 158.6, 138.4, 116.6, 106.8, 96.3, 56.0, 55.5, 52.1, 20.0.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2950 (w), 2841 (w), 1723 (m), 1604 (m), 1586 (m), 1456 (m), 1326 (m), 1264 (s), 1201 (s), 1099 (s), 1092 (s), 1050 (s).

HRMS (ESI) calculated for $\text{C}_{11}\text{H}_{14}\text{O}_4$ $[\text{M}]^+$ 210.0887, found 210.0871.

Preparation of Weinreb amide **I.59**^[31]



2-(Benzyloxy)-*N*-methoxy-*N*-methylacetamide (I.59). To a magnetically stirred solution of acid chloride **I.60** (25.0 g, 135 mmol) and methoxy(methyl)amine hydrochloride (14.5 g, 149 mmol) in dry chloroform (1300 mL) was added dropwise dry pyridine (12.8 g, 13.1 mL, 163 mmol) at 0 °C. After the reaction was stirred at room temperature for 24 h, the solution was concentrated *in vacuo* and the obtained crude material was re-dissolved in diethyl ether/CH₂Cl₂ mixture (1:1, 700 mL). The organic layer was washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Subjection of thus obtained crude material to flash column chromatography (1:2→1:1 EtOAc/hexanes, gradient elution) provided 27.4 g (131 mmol, 97%) of amide **I.59** as a colorless oil.

R_f = 0.29, 1:2 EtOAc/hexanes.

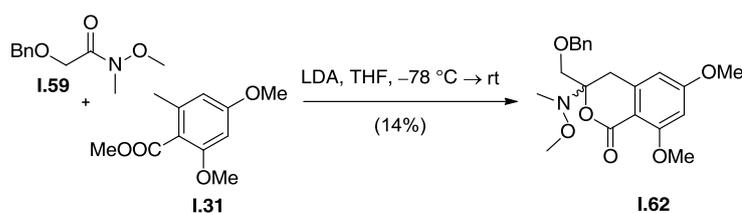
¹H NMR (300 MHz, CDCl₃): δ/ppm = 7.43–7.27 (m, 5H), 4.67 (s, 2H), 4.28 (s, 2H), 3.63 (s, 3H), 3.19 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ/ppm = 171.2, 137.7, 128.5 (2 x C), 128.2 (2 x C), 128.0, 73.4, 67.2, 61.5, 32.5.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2938 (w), 1675 (s), 1453 (m), 1391 (m), 1328 (m), 1268 (w), 1178 (m), 1136 (m), 1086 (s), 990 (s).

HRMS (ESI) calculated for C₁₁H₁₆O₃N [M+H]⁺ 210.1125, found 210.1113.

Preparation of amine I.62

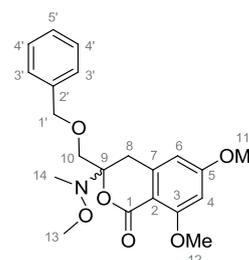


3-((Benzyloxy)methyl)-6,8-dimethoxy-3-((methoxy(methyl)amino)methyl)-3,4-dihydro naphthalen-1(2H)-one (I.62). To a magnetically stirred solution of freshly distilled diisopropylamine (97.0 mg, 0.135 mL, 960 μmol) in dry THF (2.5 mL) was added *n*-BuLi (2.4M in hexanes, 400 μL, 960 μmol), and the mixture was stirred for 10 min at room temperature. After the LDA solution was cooled to –78 °C, a solution of benzoate **I.31** (100 mg, 480 μmol) in dry THF (1.3 mL) was added slowly through a thin cannula and the resulting orange mixture was stirred at –78 °C for 5 min. Then, a solution of Weinreb amide **I.59** (100 mg, 480 μmol) in dry THF (1.25 mL) was added slowly and the reaction was stirred at –78

°C for an additional 10 min before being warmed to 0 °C. After 30 min at 0 °C, the mixture was warmed to room temperature and stirred for an additional 30 min, before a saturated aqueous NH₄Cl solution (5 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 7 mL). The combined organic phases were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude mixture was purified by flash column chromatography (1:1 EtOAc/hexanes) to give 26.0 mg (65.0 μmol, 14%) of amine **I.62** as yellow oil.

R_f = 0.43, 1:2 EtOAc/hexanes.

¹H NMR (300 MHz, CDCl₃): δ/ppm = 7.39–7.22 (m, 5H, Ar-H, H3', H4', H5'), 6.36 (d, ⁴J = 2.3 Hz, 1H, Ar-H, H4), 6.28 (d, ⁴J = 2.3 Hz, 1H, Ar-H, H6), 4.53 (s, 2H, CH₂, H1'), 3.90 (s, 3H, OCH₃, H12), 3.85 (s, 3H, OCH₃, H11), 3.75 (d, ²J = 10.2 Hz, 1H, CH₂, H10), 3.56 (d, ²J = 10.3 Hz, 1H, CH₂, H10), 3.44 (s, 3H, OCH₃, H13), 3.37 (d, ²J = 16.7 Hz, 1H, CH₂, H8), 3.26 (d, ²J = 16.7 Hz, 1H, CH₂, H8), 2.70 (s, 3H, NCH₃, H14).

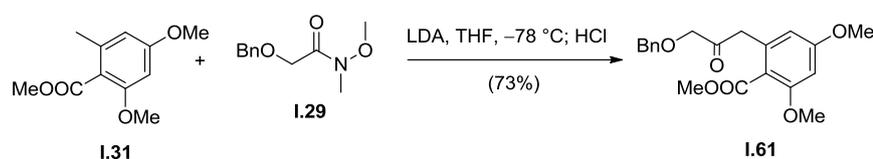


¹³C NMR (75 MHz, CDCl₃): δ/ppm = 164.6 (Ar-C_q, C5), 163.1 (Ar-C_q, C3), 161.3 (CO, C1), 142.54 (Ar-C_q, C2), 137.7 (Ar-C_q, C2'), 128.5 (Ar-C, 2 x C3' or 2 x C4'), 127.9(4) (Ar-C, 2 x C3' or 2 x C4'), 127.9(1) (Ar-C_q, C5'), 106.6 (Ar-C_q, C7), 104.5 (Ar-C, C6), 97.4 (Ar-C, C4), 96.4 (C_q, C9), 73.7 (CH₂, C1'), 69.5 (CH₂, C10), 61.0 (OCH₃, C13), 56.3 (OCH₃, C12), 55.6 (OCH₃, C11), 36.6 (NCH₃, C14), 32.8 (CH₂, C8)

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2985 (w), 2256 (w), 1736 (s), 1606 (w), 1447 (w), 1372 (m), 1230 (s), 1162 (w), 1098 (w), 1044 (s).

HRMS (ESI) calculated for C₂₁H₂₆O₆N [M+H]⁺ 388.1755, found 388.1757.

Preparation of ketone **I.61**



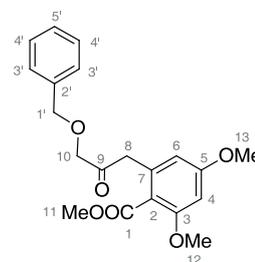
Methyl 2-(3-(benzyloxy)-2-oxopropyl)-4,6-dimethoxybenzoate (I.61). To a magnetically stirred solution of diisopropylamine (545 mg, 0.760 mL, 5.39 mmol) in dry THF (10 mL) was added *n*-BuLi (1.5M in hexanes, 3.59 mL, 5.39 mmol), and the resulting mixture was stirred for 10 min at room temperature. After the LDA solution was cooled to –78 °C, a solution of

methylbenzoate **I.31** (1.03 g, 4.90 mmol) in dry THF (5 mL) was added slowly through a thin cannula and the orange mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Weinreb amide **I.31** (1.54 g, 7.35 mmol) was dissolved in dry THF (5 mL) and was then added dropwise to the solution of the anion. Stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 2 h before the yellow reaction mixture was quenched by adding aqueous HCl solution (2M, 20 mL), and then warmed to room temperature. The biphasic mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a crude yellow oil. Subjection of this material to flash column chromatography (1:4→1:2 EtOAc/hexanes, gradient elution) provided 1.28 g (3.57 mmol, 73%) of ketone **I.61** as a white solid.

$R_f = 0.35$, 1:2 EtOAc/hexanes.

mp: 49–50 $^{\circ}\text{C}$ (EtOAc/hexanes).

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 7.36\text{--}7.26$ (m, 5H, Ar-H, H3', H4' and H5'), 6.41 (d, $^4J = 2.3$ Hz, 1H, Ar-H, H4), 6.32 (d, $^4J = 2.3$ Hz, 1H, Ar-H, H6), 4.59 (s, 2H, CH_2 , H1'), 4.16 (s, 2H, CH_2 , H10), 3.81 (s, 3H, OCH_3 , H12), 3.80 (s, 3H, OCH_3 , H11 or H13), 3.80 (s, 3H, OCH_3 , H11 or H13), 3.78 (s, 2H, CH_2 , H8).

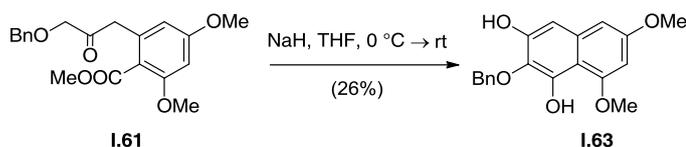


^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 205.0$ (CO, C9), 168.1 (CO, C1), 162.0 (Ar- C_q , C5), 159.4 (Ar- C_q , C3), 137.5 (Ar- C_q , C2'), 135.4 (Ar- C_q , C7), 128.6 (2 x Ar-CH, C3' or C4'), 128.1 (3 x Ar-CH, C3' or C4' and C5') 115.9 (Ar-CH, C2), 107.9 (Ar-CH, C6), 98.1 (Ar-CH, C4), 74.7 (CH_2 , C10), 73.5 (CH_2 , C1'), 56.2 (OCH_3 , C11 or C12 or C13), 55.6 (OCH_3 , C11 or C12 or C13), 52.2 (OCH_3 , C11 or C12 or C13), 45.0 (CH_2 , C8).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2948$ (w), 2840 (w), 1723 (m), 1602 (s), 1585 (m), 1455 (m), 1427 (m), 1314 (m), 1272 (s), 1203 (s), 1090 (s), 1047 (s).

HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{22}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 381.1309, found 381.1306.

Preparation of naphthalene **I.63**



2-(Benzyloxy)-6,8-dimethoxynaphthalene-1,3-diol (I.63). To a magnetically stirred solution of ketone **I.61** (100 mg, 280 μmol) in dry THF (4 mL) was added NaH (60wt% suspension in mineral oil, 22.4 mg, 560 μmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h before a saturated aqueous NH_4Cl solution (2 mL) and water (2 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 7 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained yellow oil was purified by flash column chromatography (1:1 EtOAc/hexanes) to give 24.0 mg (73.5 μmol , 26%) of naphthalene **I.63** as a beige solid.

R_f = 0.44, 1:2 EtOAc/hexanes.

mp: 130 °C (EtOAc/hexanes).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 9.34 (s, 1H), 7.49–7.42 (m, 2H), 7.41–7.33 (m, 3H), 6.66 (s, 1H), 6.54 (d, 4J = 1.9 Hz, 1H), 6.33 (d, 4J = 1.9 Hz, 1H), 5.83 (s, 1H), 5.19 (s, 2H), 4.03 (s, 3H), 3.86 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 157.6, 157.3, 150.2, 146.4, 137.5, 134.0, 130.0, 128.9 (2 x C), 128.8 (2 x C), 128.7, 106.5, 100.5, 98.7, 95.9, 75.4, 56.3, 55.4.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3477 (m), 3309 (w), 3020 (w), 2938 (w), 1626 (m), 1600 (m), 1517 (w), 1446 (m), 1388 (m), 1370 (m), 1314 (m), 1279 (m), 1202 (s), 1150 (s), 1118 (m), 1050 (s).

HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{18}\text{O}_5$ $[\text{M}]^+$ 326.1154, found 326.1147.

As a byproduct 18.0 mg (55.2 μmol , 20%) of isocumarin **I.64** were isolated:

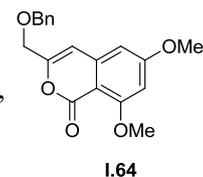
3-((Benzyloxy)methyl)-6,8-dimethoxy-1H-isochromen-1-one (I.64).

White solid.

R_f = 0.28, 1:1 EtOAc/hexanes.

mp: 112–113 °C (EtOAc/hexanes).

^1H NMR (300 MHz, CDCl_3): δ/ppm = 7.38–7.26 (m, 5H), 6.46 (d, 4J = 2.1 Hz, 1H), 6.41 (br s, 1H), 6.37 (d, 4J = 2.2 Hz, 1H), 4.65 (s, 2H), 4.32 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H).

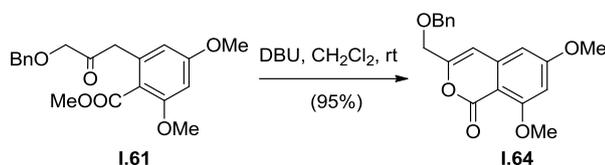


^{13}C NMR (75 MHz, CDCl_3): δ/ppm = 165.6, 163.5, 158.9, 154.9, 141.8, 137.5, 128.6, 128.6, 128.1, 128.0, 128.0, 103.6, 103.5, 100.4, 98.9, 73.3, 68.0, 56.4, 55.8.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2847 (w), 2362 (w), 1715 (s), 1676 (m), 1596 (s), 1574 (m), 1454 (m), 1426 (m), 1367 (m), 1346 (m), 1290 (m), 1238 (m), 1213 (s), 1162 (s), 1101 (s), 1055 (m).

HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{18}\text{O}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 349.1046, found 349.1045.

Preparation of isocumarin **I.64**



3-((Benzyloxy)methyl)-6,8-dimethoxy-1H-isochromen-1-one (I.64). To a magnetically stirred solution of ketone **I.61** (1.25 g, 3.49 mmol) in dry CH_2Cl_2 (24 mL) was added diazabicycloundecen (1.86 g, 1.82 mL, 12.2 mmol) at room temperature. The resulting reaction mixture was stirred for 12 h before a saturated aqueous NH_4Cl solution (25 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained yellow oil was purified by flash column chromatography (1:2 EtOAc/hexanes) to give 1.08 g (3.31 mmol, 95%) of isocumarin **I.64** as white solid.

R_f = 0.28, 1:1 EtOAc/hexanes.

mp: 112–113 °C (EtOAc/hexanes).

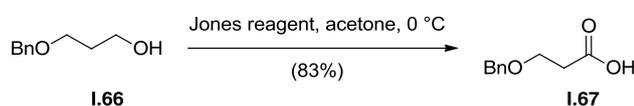
^1H NMR (300 MHz, CDCl_3): δ /ppm = 7.38–7.26 (m, 5H), 6.46 (d, 4J = 2.1 Hz, 1H), 6.41 (br s, 1H), 6.37 (d, 4J = 2.2 Hz, 1H), 4.65 (s, 2H), 4.32 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ /ppm = 165.6, 163.5, 158.9, 155.0, 141.8, 137.5, 128.7 (2 x C), 128.1, 128.0 (2 x C), 103.6, 103.6, 100.4, 98.9, 73.4, 68.0, 56.5, 55.8.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2847 (w), 2362 (w), 1715 (s), 1676 (m), 1596 (s), 1574 (m), 1454 (m), 1426 (m), 1367 (m), 1346 (m), 1290 (m), 1238 (m), 1213 (s), 1162 (s), 1101 (s), 1055 (m).

HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{18}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 349.1046, found 349.1045.

Preparation of acid **I.67**^[32]



3-(Benzyloxy)propanoic acid (I.67). To a magnetically stirred solution of benzyloxypropanol **I.66** (2.50 g, 15.0 mmol) in acetone (75 mL) was added dropwise freshly prepared Jones reagent (8N) at 0 °C until the reaction mixture remained orange. After being stirred at 0 °C for 3 h, the reaction was filtered over Celite and the organic phase was washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The obtained crude material was subjected to flash column chromatography (1:1 EtOAc/hexanes) providing 2.25 g (12.5 mmol, 83%) of free acid **I.67** as a white solid.

R_f = 0.14, 1:1 EtOAc/hexanes.

mp: 33–34 °C (EtOAc/hexanes).

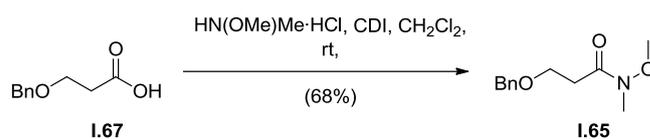
¹H NMR (400 MHz, CDCl₃): δ/ppm = 7.38–7.27 (m, 5H), 4.56 (s, 2H), 3.76 (t, ³J = 6.3 Hz, 2H), 2.68 (t, ³J = 6.3 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ/ppm = 177.1, 137.9, 128.6 (2 x C), 127.9(0), 127.8(7) (2 x C), 73.4, 65.3, 35.0.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3032 (w), 2906 (m), 2871 (m), 2634 (w), 1695 (s), 1499 (w), 1421 (m), 1336 (m), 1230 (m), 1119 (s).

HRMS (ESI) calculated for C₁₀H₁₁O₃ [M]⁻ 179.0714, found 179.0713.

Preparation of Weinreb amide **I.65**^[149]



3-(Benzyloxy)-N-methoxy-N-methylpropanamide (I.65). A solution of acid **I.67** (2.11 g, 11.7 mmol), 1,1'-carbonyldiimidazole (2.28 g, 14.1 mmol) and methoxy(methyl)amine hydrochloride (1.37 g, 14.1 mmol) in dry CH₂Cl₂ (31 mL) was stirred at room temperature for 3 h. After the mixture was washed with water (20 mL) and brine (20 mL), the combined aqueous phases were re-extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:1 EtOAc/hexanes) providing 1.77 g (7.93 mmol, 68%) of amide **I.65** as a colorless oil.

R_f = 0.28, 1:1 EtOAc/hexanes.

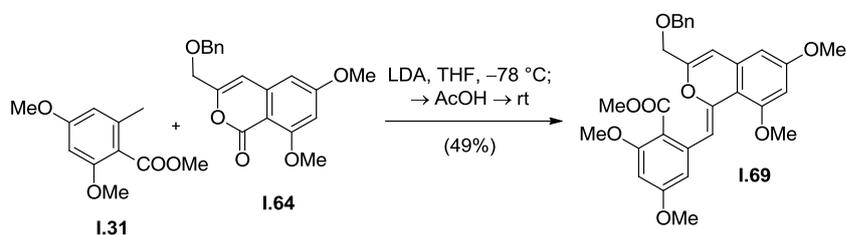
^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.36–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.55 (s, 2H), 3.81 (t, 3J = 6.6 Hz, 2H), 3.68 (s, 3H), 3.19 (s, 3H), 2.77 (t, 3J = 5.7, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 172.5, 138.5, 128.5 (2 x C), 127.8 (2 x C), 127.7, 73.4, 66.1, 61.4, 32.6, 32.2.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3030 (w), 2937 (w), 2868 (w), 2362 (w), 1680 (s), 1453 (m), 1420 (m), 1383 (m), 1178 (m), 1096 (s), 1028 (m), 992 (s).

HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{N}$ $[\text{M}+\text{H}]^+$ 224.1281, found 224.1280.

Preparation of dienole ether **I.69**

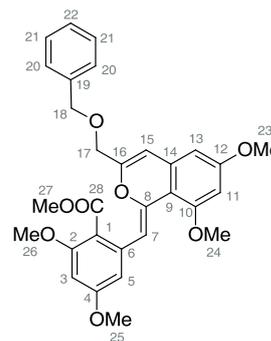


(Z)-3-((Benzyloxy)methyl)-1-(3,5-dimethoxy-2-methylbenzylidene)-6,8-dimethoxy-1H-isochromene (I.69). To a magnetically stirred solution of diisopropylamine (71.3 mg, 93.8 μL , 552 μmol) in dry THF (4 mL) was added *n*-BuLi (1.6M in hexanes, 320 μL , 506 μmol), and the mixture was stirred for 10 min at room temperature. After the LDA solution was cooled to $-78\text{ }^\circ\text{C}$ a solution of benzoate **I.31** (97.0 mg, 460 μmol) in dry THF (2 mL) was added slowly through a thin cannula. The resulting orange mixture was stirred at $-78\text{ }^\circ\text{C}$ for 20 min before a solution of isocumarine **I.64** (150 mg, 460 μmol) in dry THF (27 mL) was added fastly through a thick cannula. The purple mixture was stirred for 1 h, then acetic acid (6 mL) was added and the reaction was warmed to room temperature. After stirring was continued for 4 h, the reaction was concentrated *in vacuo* and the resulting yellow oil was re-dissolved in diethyl ether/EtOAc mixture (1:1, 100 mL). Then, the organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing the crude product. Subjection of this material to flash column chromatography (1:2→1:1→1:0 EtOAc/hexanes, gradient elution) gave 117 mg (226 μmol , 49%) of dienol ether **I.69** as a yellow solid.

R_f = 0.49, 1:2 EtOAc/hexanes.

mp: 67–68 $^\circ\text{C}$ (EtOAc/hexanes).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.37 (d, 4J = 2.1 Hz, 1H, Ar-H, H5), 7.33–7.30 (m, 4H, Ar-H, H20 and H21), 7.30–7.27 (m, 1H, Ar-H, H22) 6.79 (s, 1H, CH, H7), 6.39 (d, 4J = 2.3 Hz, 1H, Ar-H, H11), 6.29 (d, 4J = 2.1 Hz, 1H, Ar-H, H3), 6.18 (d, 4J = 2.4 Hz, 1H, Ar-H, H13), 5.89 (s, 1H, Ar-H, H15), 4.58 (s, 2H, CH_2 , H18), 4.19 (s, 2H, CH_2 , H17), 3.90 (s, 3H, OCH_3 , H24), 3.89 (s, 3H, OCH_3 , H27), 3.82 (s, 3H, OCH_3 , H23), 3.79 (s, 3H, OCH_3 , H26), 3.70 (s, 3H, OCH_3 , H25).

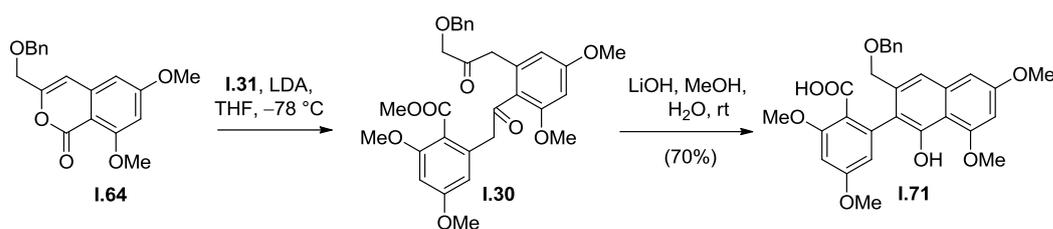


^{13}C NMR (100 MHz, CDCl_3): δ/ppm = 169.6 (CO or Ar- C_q , C10), 161.1(2) (Ar- C_q , C4), 161.0(7) (Ar- C_q , C12), 158.1 (CO or Ar- C_q , C28), 157.4 (Ar- C_q , C2), 151.6 (C_q , C16), 147.6 (C_q , C8), 137.7 (Ar- C_q , C19), 136.3 (Ar- C_q , C6 or C14), 133.9 (Ar- C_q , C6 or C14), 128.6 (2 x Ar-C, C20 or C21), 128.1 (2 x Ar-C, C20 or C21), 128.0 (Ar-C, C22), 110.2 (Ar- C_q , C1), 108.9 (Ar- C_q , C9), 104.8 (Ar-C, C5), 103.6 (CH, C15), 102.9 (CH, C7), 101.5 (Ar-H, C13), 99.0 (Ar-H, C11), 96.7 (Ar-H, C3), 72.4 (CH_2 , C18), 68.5 (CH_2 , C17), 56.0 (OCH_3 , C26), 55.8 (OCH_3 , C24), 55.5 (OCH_3 , C23), 55.4 (OCH_3 , C25), 52.3 (OCH_3 , C27).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2926 (w), 2842 (w), 2360 (w), 1723 (m), 1585 (s), 1453 (m), 1424 (m), 1349 (m), 1261 (m), 1201 (s), 1150 (s), 1095 (s).

HRMS (ESI) calculated for $\text{C}_{30}\text{H}_{31}\text{O}_8$ $[\text{M}+\text{H}]^+$ 519.2013, found 519.2015.

Preparation of ketone I.30 biaryl I.71



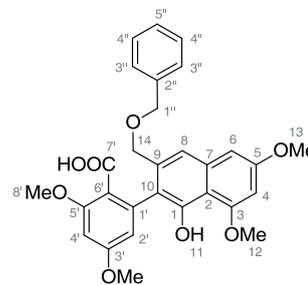
2-(3-((Benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxybenzoic acid (I.71). To a magnetically stirred solution of freshly distilled diisopropylamine (807 mg, 1.10 mL, 7.97 mmol) in dry THF (32 mL) was added *n*-BuLi (2.5M in hexanes, 2.94 mL, 7.35 mmol), and the mixture was stirred for 10 min at room temperature. After the LDA solution was cooled to $-78\text{ }^\circ\text{C}$, a solution of benzoate **I.31** (1.29 g, 6.13 mmol) in dry THF (30 mL) was added slowly through a thin cannula and the resulting orange mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min. In the meantime, isocoumarin **I.64** was dissolved in dry THF (290 mL) and precooled to $-78\text{ }^\circ\text{C}$. The cold isocoumarin solution was poured quickly in one portion to the

solution of the lithium anion. Stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 2 h before the yellow reaction mixture was quenched by adding a saturated aqueous NH_4Cl solution (200 mL) and then warmed to room temperature. The biphasic mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford crude yellow oil. Subjection of this material to flash column chromatography (1:4 \rightarrow 1:2 \rightarrow 1:1 \rightarrow 1:0 EtOAc/hexanes, then 9:1 MeOH/EtOAc, gradient elution) provided **I.30** in trace quantities in addition to two fractions, A and B (A: $R_f = 0.1$ 1:1 EtOAc/hexanes, 1.18 g, mixture of carboxylic acid **I.71** and methyl ester **I.70**; B: $R_f = 0.02$ 1:1 EtOAc/hexanes, 1.59 g, mixture of oligomers). All of these mixtures were converted into acid **I.71** as follows: After concentration *in vacuo*, the fractions were separately dissolved in MeOH/water/ CH_2Cl_2 mixtures (A: 9 mL:3 mL:1 mL; B: 12 mL:4 mL:1 mL) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (A: 134 mg, 3.19 mmol; B: 180 mg, 4.30 mmol) was added. The two reaction mixtures were stirred overnight at room temperature and then aqueous HCl solution (2M) was added until the pH was adjusted to 3. The aqueous layers were extracted with CH_2Cl_2 (each reaction 3 x 70 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford acid **I.71** (combined yield: 2.18 g, 4.32 mmol, 70% over two steps) as a beige solid.

$R_f = 0.10$, 1:1 EtOAc/hexanes.

mp: $157\text{ }^{\circ}\text{C}$ (CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 9.38$ (s, 1H, OH, H11), 7.29–7.24 (m, 3H, Ar-H, H4" and H5"), 7.25 (s, 1H, Ar-H, H8), 7.10–7.08 (m, 2H, Ar-H, H3"), 6.70 (d, $^4J = 2.2$ Hz, 1 H, Ar-H, H6), 6.57 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H4'), 6.47 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H4), 6.34 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H2'), 4.55 (d, $^2J = 10.3$ Hz, 1H, CH_2 , H14), 4.42 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H1"), 4.32 (d, $^2J = 11.7$ Hz, 1H, CH_2 , H1"), 4.30 (d, $^2J = 10.2$ Hz, 1H, CH_2 , H14), 3.95 (s, 3H, OCH_3 , H12), 3.94 (s, 3H, OCH_3 , H8'), 3.89 (s, 3H, OCH_3 , H13), 3.78 (s, 3H, OCH_3 , H9').



IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3382 (w), 2936 (w), 2362 (w), 2338 (w), 1735 (w), 1596 (m), 1453 (m), 1363 (m), 1340 (m), 1250 (m), 1204 (s), 1109 (s), 1044 (s).

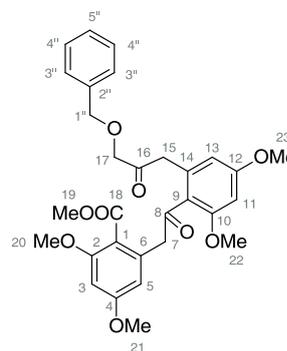
HRMS (ESI) calculated for $\text{C}_{29}\text{H}_{28}\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 527.1676, found 527.1675.

1-(benzyloxy)-3-{2-[2-(3,5-dimethoxy-2-methylphenyl)acetyl]-3,5-dimethoxyphenyl}propan-2-one-methanedione (I.30).

Colorless oil.

R_f = 0.18, 1:2 EtOAc/hexanes.

^1H NMR (400 MHz, CDCl_3): δ/ppm = 7.35–7.27 (m, 5H, Ar-H, H3" and H4" and H5"), 6.41 (d, $^3J = 2.3$ Hz, 1H, Ar-H, H11), 6.36 (s, 2H, Ar-H, H3 and H5), 6.29 (d, $^3J = 2.3$ Hz, 1H, Ar-H, H13), 4.55 (s, 2H, CH_2 , H1"), 4.22 (s, 2H, CH_2 , H7), 4.17 (s, 2H, CH_2 , H17), 3.86 (s, 3H, OCH_3 , H22), 3.81 (s, 3H, OCH_3 , H23), 3.78 (s, 3H, OCH_3 , CH_{20} or H21), 3.76 (s, 3H, OCH_3 , H20 or H21), 3.70 (s, 3H, OCH_3 , H19), 3.70 (s, 2H, CH_2 , H15).



^{13}C NMR (100 MHz, CDCl_3): δ/ppm = 205.5 (CO, C16), 201.2 (CO, C8), 168.2 (CO, C18), 162.0 (Ar- C_q , C12), 161.6 (Ar- C_q , C2 or C4), 159.8 (Ar- C_q , C10), 158.7 (Ar- C_q , C2 or C4), 137.7 (Ar- C_q , C2"), 136.5 (Ar- C_q , C6 or C14), 136.3 (Ar- C_q , C6 or C14), 128.5 (2 x Ar-CH, C3" or C4"), 128.1 (2 x Ar-CH, C3" or C4"), 127.9 (Ar-CH, C5"), 122.5 (Ar- C_q , C9), 116.6 (Ar- C_q , C1), 109.0 (Ar-CH, C13), 107.8 (Ar-CH, C3 or C5), 97.6(4) (Ar-CH, C3 or C5 or C11), 97.6(0) (Ar-CH, C3 or C5 or C11), 74.9 (CH_2 , C17), 73.4 (CH_2 , C1"), 56.1 (OCH_3 , C20 or C21 or C22 or C23), 55.8 (OCH_3 , C20 or C21 or C22 or C23), 55.6 (OCH_3 , C20 or C21 or C22 or C23), 55.5 (OCH_3 , C20 or C21 or C22 or C23), 52.0 (OCH_3 , C19), 49.2 (CH_2 , C7), 44.7 (CH_2 , C15).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2944 (w), 2841 (w), 2362 (w), 2338 (w), 1727 (s), 1599 (s), 1454 (m), 1425 (m), 1313 (m), 1240 (m), 1203 (s), 1086 (s), 1046 (s).

HRMS (ESI) calculated for $\text{C}_{30}\text{H}_{32}\text{O}_9\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 559.1939, found 559.1942.

The methyl ester **1.70** was isolated as a minor byproduct in traces and characterized:

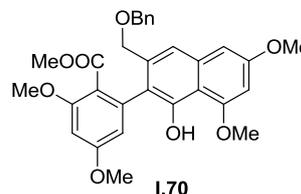
3-[(benzyloxy)methyl]-2-(3,5-dimethoxy-2-methylphenyl)-6,8-dimethoxynaphthalen-1-ol-methanedione (I.70).

White solid.

$R_f = 0.13$, 1:1 EtOAc/hexanes.

mp: 90–91 °C (EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ /ppm = 9.32 (s, 1H), 7.41 (s, 1H), 7.38–7.26 (m, 5H), 6.74 (d, $^3J = 2.2$ Hz, 1H), 6.51 (d, $^3J = 2.3$ Hz, 1H), 6.44 (d, $^3J = 2.2$ Hz, 1H), 6.39 (d, $^3J = 2.3$ Hz, 1H), 4.53 (d, $^2J = 11.7$ Hz, 1H), 4.46 (m, 3H), 3.97 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H), 3.42 (s, 3H).

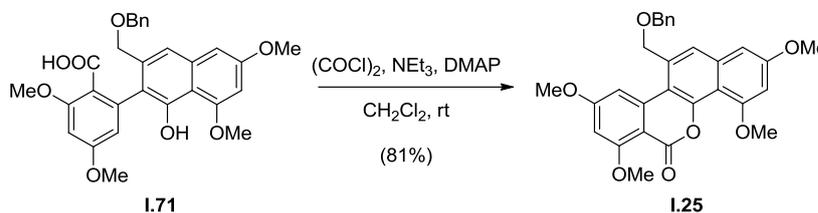


^{13}C NMR (100 MHz, CDCl_3): δ /ppm = 168.0, 161.6, 158.3, 158.0, 157.3, 151.1, 138.7, 138.0, 137.6, 136.8, 128.4 (2 x C), 127.8 (2 x C), 127.6, 119.0, 117.3, 116.0, 109.7, 107.1, 99.7, 98.2, 97.8, 72.7, 70.5, 56.2, 56.0, 55.6, 55.5, 51.9.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2944$ (w), 2363 (w), 1675 (m), 1599 (s), 1454 (m), 1424 (m), 1264 (m), 1201 (m), 1100 (s), 1095 (s).

HRMS (ESI) calculated for $\text{C}_{30}\text{H}_{30}\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 541.1833, found 541.1836.

Preparation of lactone **I.25**



11-((Benzyloxy)methyl)-2,4,7,9-tetramethoxy-6H-dibenzo[*c,h*]chromen-6-one (I.25**)**. To a magnetically stirred solution of acid **I.71** (60.0 mg, 120 μmol) in dry CH_2Cl_2 (0.6 mL) was added at room temperature oxalyl chloride (2M solution in CH_2Cl_2 , 60.0 μL , 120 μmol). The resulting dark brown mixture was stirred at room temperature for 10 min before triethylamine (24.0 μL , 180 μmol) and dimethylaminopyridine (700 μg , 6.00 μmol) were added. After stirring was continued for 1 h, the ensuing mixture was concentrated *in vacuo* and subjected to column chromatography (1:2→1:0 EtOAc/hexanes, gradient elution) to afford 47.0 mg (96.6 μmol , 81%) of lactone **I.25** as a pale yellow solid.

$R_f = 0.18$, 1:1 EtOAc/hexanes.

mp: 182 °C (EtOAc/hexanes).

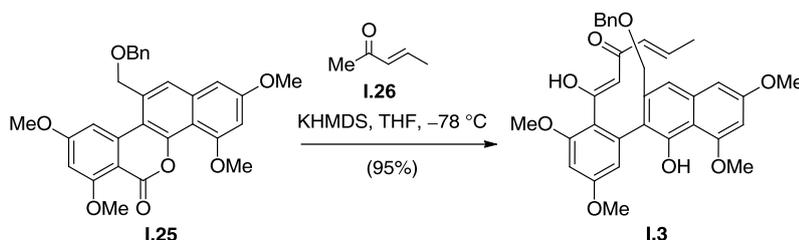
^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.74 (d, 4J = 2.2 Hz, 1H), 7.57 (s, 1H), 7.42–7.29 (m, 5H), 6.72 (d, 4J = 2.3 Hz, 1H), 6.60 (d, 4J = 2.3 Hz, 1H), 6.57 (d, 4J = 2.2 Hz, 1H), 4.93 (s, 2H), 4.75 (s, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ/ppm = 165.2, 163.3, 160.1, 158.9, 157.7, 150.5, 140.3, 138.0, 136.7, 131.6, 128.6 (2 x C), 128.0, 127.9(6) (2 x C), 127.7, 113.3, 111.0, 104.3, 102.9, 100.4, 98.7, 98.5, 72.5, 72.2, 56.6 (2 x C), 55.8, 55.6.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3371 (w), 2933 (w), 2339 (w), 1720 (m), 1623 (m), 1595 (s), 1582 (s), 1453 (m), 1390 (m), 1348 (m), 1246 (m), 1206 (s), 1126 (m), 1050 (s), 1012 (s).

HRMS (ESI) calculated for $\text{C}_{29}\text{H}_{27}\text{O}_7$ $[\text{M}+\text{H}]^+$ 487.1751, found 487.1751.

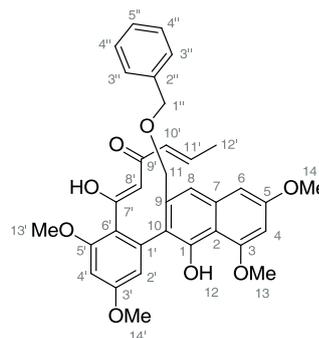
Preparation of diketone **I.3**



(1Z,4E)-1-(2-(3-((benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxy phenyl)-1-hydroxyhexa-1,4-dien-3-one (I.3). To a magnetically stirred solution of KHMDS (0.5M in toluene, 2.26 mL, 1.13 mmol) in dry THF (1.5 mL) was added dropwise a solution of (*E*)-3-penten-2-one (**I.26**) (85% pure, 130 μL , 120 mg, 1.13 mmol) in dry THF (1.5 mL) at -78 $^{\circ}\text{C}$. The ensuing mixture was stirred at -78 $^{\circ}\text{C}$ for 20 min before a solution of lactone **I.25** (275 mg, 570 μmol) in dry THF (2 mL) was added. After being stirred at -78 $^{\circ}\text{C}$ for 2 h, the mixture was quenched by adding a saturated aqueous NH_4Cl solution (10 mL), and then warmed to room temperature. The ensuing biphasic mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a crude yellow oil. Subjection of this material to flash column chromatography (1:1 \rightarrow 1:0 EtOAc/hexanes, gradient elution) provided 308 mg (540 μmol , 95%) of ketone **I.3** as a yellow oil.

R_f = 0.59, 2:1 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): δ/ppm = 9.31 (s, 1H, OH, H12), 7.37 (s, 1H, Ar-H, H8), 7.31 (m, 4H, Ar-H, H3" and H4"),



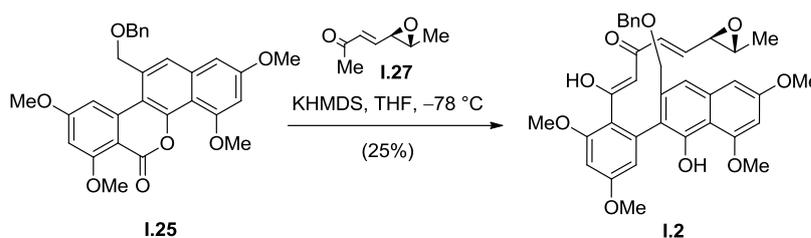
7.27–7.24 (m, 1H, Ar-H, H5"), 6.72 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H6), 6.60 (dq, $^3J = 15.5$ Hz, $^3J = 7.0$ Hz, 1H, CH, H11'), 6.52 (d, $^4J = 2.3$ Hz, 1H, Ar-H, H4'), 6.44 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H4), 6.38 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H2'), 5.67 (dq, $^3J = 15.5$ Hz, $^4J = 1.7$ Hz, 1H, CH, H10'), 5.67 (s, 1H, CH, H8'), 4.50 (d, $^2J = 11.7$ Hz, 1H, CH₂, H1''), 4.46 (dd, $^2J = 12.9$ Hz, $^3J = 0.8$ Hz, 1H, CH₂, H11), 4.43 (d, $^2J = 11.7$ Hz, 1H, CH₂, H1''), 4.39 (d, $^2J = 12.9$ Hz, 1H, CH₂, H11), 3.98 (s, 3H, OCH₃, H13), 3.89 (s, 3H, OCH₃, H14), 3.85 (s, 3H, OCH₃, H13'), 3.76 (s, 3H, OCH₃, H14'), 1.77 (dd, $^3J = 7.0$ Hz, $^4J = 1.6$ Hz, 3H, CH₃, H12').

¹³C NMR (150 MHz, CDCl₃): δ /ppm = 192.1 (CO, C7'), 177.2 (CO, C9'), 161.4 (Ar-C_q, C3'), 158.4 (Ar-C_q, C5'), 157.9 (Ar-C_q, C5), 157.3 (Ar-C_q, C3), 150.8 (Ar-C_q, C1), 138.7 (Ar-C_q, C2''), 138.4 (CH, C11'), 137.9 (Ar-C_q, C1'), 137.6 (Ar-C_q, C9), 136.8 (Ar-C_q, C7), 128.4 (2 x Ar-CH, C3'' or C4''), 128.0 (CH, C10'), 127.9 (2 x Ar-CH, C3'' or C4''), 127.5 (Ar-CH, C5''), 122.1 (Ar-C_q, C6'), 119.8 (Ar-C_q, C10), 116.3 (Ar-CH, C8), 109.8 (Ar-C_q, C2), 107.5 (Ar-CH, C2'), 102.6 (CH, C8'), 99.8 (Ar-CH, C6), 98.4 (Ar-CH, C4'), 97.9 (Ar-CH, C4), 72.8 (CH₂, C1''), 70.7 (CH₂, C11), 56.3 (OCH₃, C13), 56.0 (OCH₃, C14), 55.6 (OCH₃, C14 or C14'), 55.5 (OCH₃, C14 or C14'), 18.5 (CH₃, C12').

IR: $\tilde{\nu}$ /cm⁻¹ = 2984 (w), 1737 (s), 1588 (w), 1372 (m), 1220 (s), 1159 (m), 1046 (s).

HRMS (ESI) calculated for C₃₄H₃₅O₈ [M+H]⁺ 571.2326, found 571.2325.

Preparation of diketone **I.2**



(1Z,4E)-1-(2-(3-((Benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxy phenyl)-1-hydroxyhexa-1,4-dien-3-one (I.2). To a magnetically stirred solution of KHMDS (0.5M in toluene, 160 μ L, 80.0 μ mol) in dry THF (100 μ L) at -78 °C was added dropwise a solution of ketone **I.27** (10.0 mg, 80.0 μ mol, ee = 75%) in dry THF (100 μ L). The ensuing mixture was stirred at -78 °C for 20 min before a solution of lactone **I.25** (20.0 mg, 40.0 μ mol) in dry THF (500 μ L) was added. After stirring at -78 °C for 2 h, the reaction was quenched by adding a saturated aqueous NH₄Cl solution (5 mL), and then warmed to room temperature. The biphasic mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a crude yellow oil. Subjection of this material to flash column chromatography

(1:1→1:0 EtOAc/hexanes, gradient elution) provided 36.0 mg (9.79 μmol , 25%) of ketone **I.2** as a yellow oil. The compound was characterized as a mixture of diastereoisomers ($dr = 1:1$).

$R_f = 0.55$, 2:1 EtOAc/hexanes.

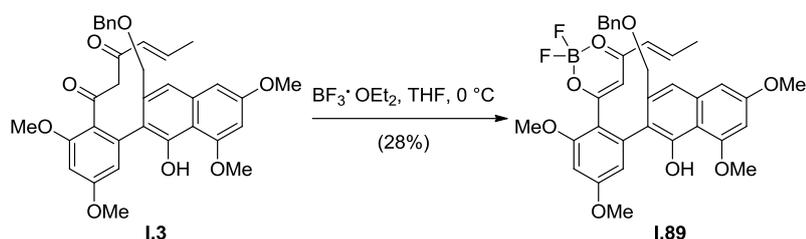
^1H NMR (600 MHz, CDCl_3) (mixture of two diastereomers, both diastereomers quoted): $\delta/\text{ppm} = 9.27(3)$ (s, 1H), 9.27(0) (s, 1H), 7.32 (s, 1H), 7.27–7.26 (m, 3H), 7.21 (m, 2H), 6.68 (d, $^3J = 2.1$ Hz, 1H), 6.47 (d, $^3J = 1.7$ Hz, 1H), 6.39 (m, 1H), 6.33 (m, 1H), 6.30–6.22 (m, 1H), 5.89 (d, $^3J = 15.5$ Hz, 1H), 5.68(8) (s, 1H), 5.68(5) (s, 1H), 4.45–4.34 (m, 4H), 3.93 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 3.01 (d, $^3J = 7.02$ Hz, 1H), 2.81 (dq, $^3J = 5.2$ Hz, $^3J = 2.0$ Hz, 1H), 1.28 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3) (mixture of two diastereomers, both diastereomers quoted): $\delta/\text{ppm} = 194.1$, 194.0(8), 173.6, 173.5, 161.6(2), 161.6(0), 158.5, 158.4(6), 157.9(5), 157.9(4), 157.3(0), 157.2(9), 150.7(4), 150.7(0), 138.7, 138.1, 138.0, 137.7(9), 137.7(8), 137.5, 136.8, 128.6, 128.4(3), 128.4(0) (2 x C), 127.8 (2 x C), 127.5, 122.2(3), 122.2(0), 119.6(7), 119.6(2), 116.4(6), 116.4(4), 109.7(4), 109.7(3), 107.6, 107.5(9), 103.9(5), 103.9(0), 99.8(3), 99.8(1), 98.3(8), 98.3(6), 97.9(4), 97.9(2), 72.7(7), 70.6(8), 58.2, 58.1, 57.8, 57.7, 56.3(3), 56.3(1), 56.0, 55.6, 55.5, 31.1, 29.9, 17.7(3), 17.7(0).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3391$ (w), 2987 (w), 1652 (m), 1633 (m), 1585 (s), 1452 (m), 1364 (m), 1345 (m), 1206 (m), 1156 (s), 1108 (m), 1044 (m).

HRMS (ESI) calculated for $\text{C}_{36}\text{H}_{38}\text{O}_9$ $[\text{M}+\text{H}]^+$ 613.2432, found 613.2429.

Preparation of difluoroborate complex **I.89**

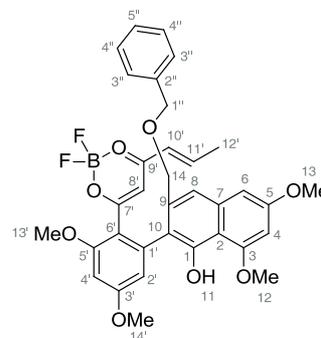


(1Z,4E)-1-(2-(3-((benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxy phenyl)-1-((difluoroboryl)oxy)hexa-1,4-dien-3-one (I.89**)**. To a magnetically stirred solution of diketone **I.3** (20.0 mg, 35.0 μmol) in dry THF (1.25 mL) was added slowly trifluoroborate diethyl etherate complex (2.70 mg, 2.0 μL , 39.0 μmol) at 0 °C. The resulting mixture was stirred for 1 h before it was warmed to room temperature. Stirring was continued for 2 h, then EtOAc (10 mL) was added and the organic phase was washed with brine (10 mL),

dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing yellow oil. Subjection of this material to flash column chromatography (1:3→1:2→2:1→1:0 EtOAc/hexanes, gradient elution) gave 6.00 mg (9.70 μmol , 28%) of complex **1.89** as a yellow film.

$R_f = 0.79$, 2:1 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 9.31$ (s, 1H, OH, H11), 7.39 (s, 1H, Ar-H, H8), 7.32–7.28 (m, 4H, Ar-H, H3'' and H4''), 7.26–7.23 (m, 1H, Ar-H, H5''), 7.10–7.04 (m, 1H, CH, H11'), 6.74 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H6), 6.53 (d, $^4J = 2.3$ Hz, 1H, Ar-H, H4'), 6.45 (d, $^4J = 2.3$ Hz, 1H, Ar-H, H4 or H2'), 6.44 (d, $^4J = 2.2$ Hz, 1H, Ar-H, H4 or H2'), 6.13 (s, 1H, CH, H8'), 5.86 (dq, $^3J = 15.2$ Hz, $^4J = 1.6$ Hz, 1H, CH, H10'), 4.53 (d, $^2J = 11.8$ Hz, 1H, CH_2 , H1'') 4.47 (dd, $^2J = 12.4$ Hz, $^4J = 0.7$ Hz, 1H, CH_2 , H14), 4.44 (dd, $^2J = 12.4$ Hz, $^4J = 0.6$ Hz, 1H, CH_2 , H14), 4.43 (d, $^2J = 11.8$ Hz, 1H, CH_2 , H1''), 3.96 (s, 3H, OCH_3 , H12), 3.89 (s, 3H, OCH_3 , H13 or H13'), 3.89 (s, 3H, OCH_3 , H13 or H13'), 3.76 (s, 3H, OCH_3 , H14'), 1.86 (dd, $^3J = 7.0$ Hz, $^4J = 1.6$ Hz, 3H, CH_3 , H12'), .



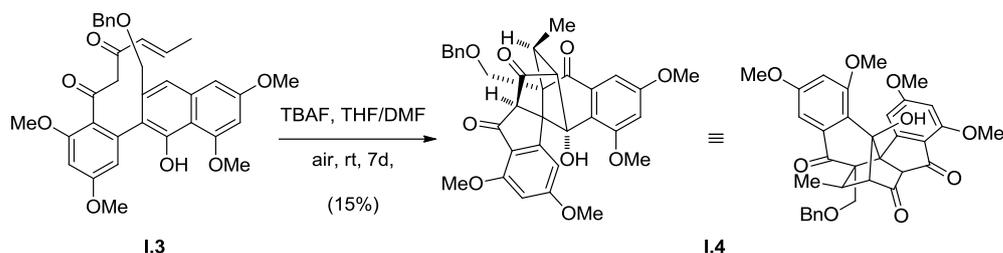
^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 185.7$ (CO, C7' or C9'), 179.0 (CO, C7' or C9'), 163.3 (Ar-C_q, C3'), 160.1 (Ar-C_q, C5'), 158.0 (Ar-C_q, C5), 157.3 (Ar-C_q, C3), 150.5 (Ar-C_q, C1), 147.5 (CH, C11'), 140.8 (Ar-C_q, C7 or C9 or C1' or C6'), 138.7 (Ar-C_q, C2''), 136.9 (Ar-C_q, C7 or C9 or C1' or C6'), 136.8 (Ar-C_q, C7 or C9 or C1' or C6'), 128.4 (2 x Ar-CH, C3'' or C4''), 127.8 (2 x Ar-CH, C3'' or C4''), 127.5 (Ar-CH, C5''), 126.4 (CH, C10'), 119.3 (Ar-C_q, C10), 117.5 (Ar-CH, C8), 117.3 (Ar-C_q, C7 or C9 or C1' or C6'), 109.9 (Ar-C_q, C2), 108.8 (Ar-C_q, C2'), 103.2 (CH, C8'), 99.9 (Ar-CH, C6), 98.4 (Ar-CH, C4'), 98.2 (Ar-CH, C4), 72.7 (CH_2 , C1''), 70.9 (CH_2 , C14), 56.4 (OCH_3 , C12), 56.2 (OCH_3 , C13 or C13'), 55.7 (OCH_3 , C14'), 55.5 (OCH_3 , C13 or C13'), 19.1 (CH_3 , C12').

^{19}F NMR (300 MHz, CDCl_3): $\delta/\text{ppm} =$ First set of signals: $-140.4(0)$ (d, $^{2\text{FF}}J = -80.8$ Hz, BF_2), -141.0 (d, $^{2\text{FF}}J = -80.9$ Hz, BF_2); Second set of signals: $-140.3(5)$ (d, $^{2\text{FF}}J = -81.0$ Hz, BF_2), -140.9 (d, $^{2\text{FF}}J = -80.6$ Hz, BF_2). In the fluorine NMR two sets of signals are observed, which presumably can be explained by the existence of two isomers of **1.89** (keto-enol-tautomers).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2985$ (w), 1737 (s), 1447 (w), 1372 (m), 1280 (s), 1098 (w), 1044 (s).

HRMS (ESI) calculated for $\text{C}_{34}\text{H}_{33}\text{O}_8\text{BF}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 641.2129, found 641.2128.

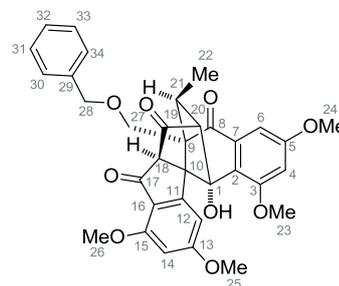
Preparation of alcohol I.4



12-((Benzyloxy)methyl)-4b-hydroxy-2,4,8,10-tetramethoxy-14-methyl-4bH-5,12-methanobenzo [5,6]pentaleno[1,6a-a]naphthalene-6,7,13(5H,6aH,12H)-trione (I.4). To a magnetically stirred solution of *tetra-N*-butylammonium fluoride (1M in THF, 70.0 μL , 70.0 μmol) in dry THF (1.5 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise a solution of ketone **I.3** (20.0 mg, 35.0 μmol) in dry THF (1.2 mL) and DMF (2.5 mL). The ensuing mixture was warmed to room temperature and stirred for 6 days. The resulting yellow solution was then concentrated *in vacuo* and directly subjected to flash column chromatography (1:2 \rightarrow 1:1 \rightarrow 2:1 \rightarrow 1:0 EtOAc/hexanes, then MeOH, gradient elution) providing 3.00 mg (5.14 μmol , 15%) of alcohol **I.4** as a white solid.

R_f 0.19, 2:1 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): δ /ppm = 7.27 (d, $^3J = 2.5$ Hz, 1H, Ar-H, H6), 7.24–7.21 (m, 3H, Ar-H, H31, H32 and H33), 7.08–7.05 (m, 2H, Ar-H, H30, H34), 6.70 (d, $^3J = 2.4$ Hz, 1H, Ar-H, H4), 6.31 (d, $^3J = 1.9$ Hz, 1H, Ar-H, H14), 6.03 (d, $^3J = 1.9$ Hz, 1H, Ar-H, H12), 5.39 (s, 1H, OH), 4.51 (d, $^2J = 12.1$ Hz, 1H, CH₂, H28), 4.43 (d, $^2J = 12.1$ Hz, 1H, CH₂, H28), 4.31 (s, 1H, CH, H18), 4.03 (d, $^2J = 10.7$ Hz, 1H, CH₂, H27), 3.98 (d, $^2J = 10.7$ Hz, 1H, CH₂, H27), 3.90 (s, 3H, OCH₃, H24), 3.88 (s, 3H, OCH₃, H26), 3.82 (s, 3H, OCH₃, H23), 3.62 (s, 3H, OCH₃, H25), 2.82 (q, $^3J = 7.6$ Hz, 1H, CH, H21), 2.78 (s, 1H, CH, H20), 0.62 (d, $^3J = 7.6$ Hz, 3H, CH₃, H22).



^{13}C NMR (150 MHz, CDCl_3): δ /ppm = 202.1 (CO, C19), 197.3 (CO, C8), 189.9 (CO, C17), 165.9 (Ar-C_q, C13), 161.1 (Ar-C_q, C5), 159.4 (Ar-C_q, C15), 158.7 (Ar-C_q, C3), 149.7 (Ar-C_q, C7 or C11), 137.7 (Ar-C_q, C29), 134.3 (Ar-C_q, C7 or C11), 128.5 (2 x Ar-CH, C31 and C33), 127.8 (Ar-CH, C32), 127.4 (2 x Ar-CH, C30 and C34), 121.3 (Ar-C_q, C2), 120.9 (Ar-C_q, C16), 105.9 (Ar-CH, C4), 102.4 (Ar-CH, C12), 100.2 (Ar-CH, C6), 98.3 (Ar-CH, C14), 83.9 (COH, C1), 73.7 (CH₂, C28), 69.2 (C_q, C10), 68.2(3) (CH or CH₂, C20 or C27), 68.2(2) (CH or CH₂, C20 or C27), 63.0 (CH, C18), 59.6 (C_q, C9), 56.3 (OCH₃, C23), 56.0 (OCH₃, C24 or C26), 55.9 (OCH₃, C24 or C26), 55.7 (OCH₃, C25), 38.4 (CH, C21), 14.0 (CH₃, C22).

Table IV.2. NMR-data (including COSY, HSQC and HMBS couplings as well as NOESY correlations) of alcohol **I.4**.

Nr	δ_C /ppm	δ_H /ppm	COSY	HSQC	HMBC	NOESY
1	83.9	–	–	–	–	–
2	121.3	–	–	–	–	–
3	158.7	–	–	–	–	–
4	105.9	6.70	H6	C4	C2, C3, C5, C6	H23, H24
5	161.1	–	–	–	–	–
6	100.2	7.27	H4	C6	C2, C4, C8	H24
7	149.7 or 134.3	–	–	–	–	–
8	197.3	–	–	–	–	–
9	59.6	–	–	–	–	–
10	69.2	–	–	–	–	–
11	149.7 or 134.3	–	–	–	–	–
12	102.4	6.03	H14	C12	C10, C13, C14, C16	H25
13	165.9	–	–	–	–	–
14	98.3	6.31	H12	C14	C12, C13, C15, C16	H25, H26
15	159.4	–	–	–	–	–
16	120.9	–	–	–	–	–
17	189.9	–	–	–	–	–
18	63.0	4.31	–	C18	C20 or C27, C30, C34, C29	H21, H27
19	202.1	–	–	–	–	–
20	68.2(3) 68.2(2)	or 2.78	–	C20 or C27	C9, C10, C15, C18, C19	H22, OH- C1
21	38.4	2.82	H22	C21	C1, C8, C9, C19, C20 or C27, C22	H20, H23
22	14.0	0.62	H21	C22	C9, C21, C20 or C27	H20, H21
23	56.3	3.82	–	C23	C3	H4, OH-C1
24	56.0	3.90	–	C24 or C26	C5	H4, H6
25	55.7	3.62	–	C25	C13	H12, H14
26	56.0 or 55.9	3.88	–	C24 or C26	C15	H14
27	68.2(3) 68.2(2)	or 4.03 (H27a) and 4.98 (H27b)	–	C20 or C27	C8, C9, C10, C21, C28	each other
28	73.7	4.51 (H28a), 4.43 (H28b)	H30, H34 and to each other	C28	C20 or C27, C29, C30, C34	each other
29	137.7	–	–	–	–	–
30	127.4	7.08–7.05	H31, H32, H33	C30, C34	C30–C34, C28	H31–H33
31	128.5	7.24–7.21	H30, H34	C31–C33	C30–C34	H30, H34

32	127.7	7.24–7.21	H30, H34	C31–C33	C30–C34	H30, H34
33	128.5	7.24–7.21	H30, H34	C31–C33	C30–C34	H30, H34
34	127.4	7.08–7.05	H31, H32, H33	C30, C34	C30–C34, 28	H31–H33
OH	OH-C1	5.39	–	–	C1, C2, C10	H20, H23

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2926 (w), 2253 (w), 1766 (w), 1696 (m), 1605 (w), 1468 (w), 1334 (w), 1209 (m), 1161 (m), 903 (s).

HRMS (ESI) calculated for $\text{C}_{34}\text{H}_{33}\text{O}_9$ $[\text{M}+\text{H}]^+$ 585.2119, found 585.2117.

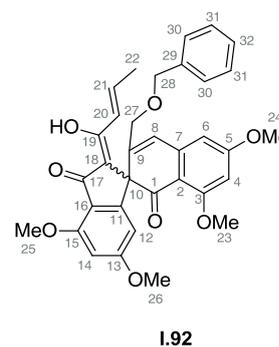
As a second product, 5.00 mg (8.79 μmol , 25%) of the spiro compound **I.92** were isolated and characterized:

(2Z)-3'-[(benzyloxy)methyl]-2-[(2E)-1-hydroxybut-2-en-1-ylidene]-4,6,6',8'-tetramethoxy-2,3-dihydro-1'H-spiro[indene-1,2'-naphthalene]-1',3-dione (I.92).

Beige solid.

R_f = 0.12, 1:1 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.32–7.23 (m, 3H, Ar-H, H31 and H32), 7.21–7.18 (m, 2H, Ar-H, H30), 6.96 (t, 4J = 1.7 Hz, 1H, CH, H8), 6.76 (dq, 3J = 14.0 Hz, 3J = 7.0 Hz, 1H, CH, H21), 6.51 (d, 4J = 2.3 Hz, 1H, Ar-H, H6), 6.42 (d, 4J = 2.3 Hz, 1H, Ar-H, H4), 6.31 (d, 4J = 1.9 Hz, 1H, Ar-H, H14), 6.18 (d, 4J = 1.9 Hz, 1H, Ar-H, H12), 5.55 (dq, 3J = 15.1 Hz, 4J = 1.7 Hz, 1H, CH, H20), 4.38 (d, 2J = 11.8 Hz, 1H, CH_2 , H28), 4.34 (d, 2J = 11.8 Hz, 1H, CH_2 , H28), 3.99 (dd, 2J = 15.2 Hz, 4J = 1.8 Hz, 1H, CH_2 , H27), 3.95 (s, 3H, OCH_3 , H24), 3.92 (s, 3H, OCH_3 , H25), 3.84 (s, 3H, OCH_3 , H23), 3.69 (s, 3H, OCH_3 , H26), 3.57 (dd, 2J = 15.2 Hz, 4J = 1.6 Hz, 1H, CH_2 , H27), 1.70 (dd, 3J = 7.0 Hz, 4J = 1.6 Hz, 3H, CH_3 , H22).

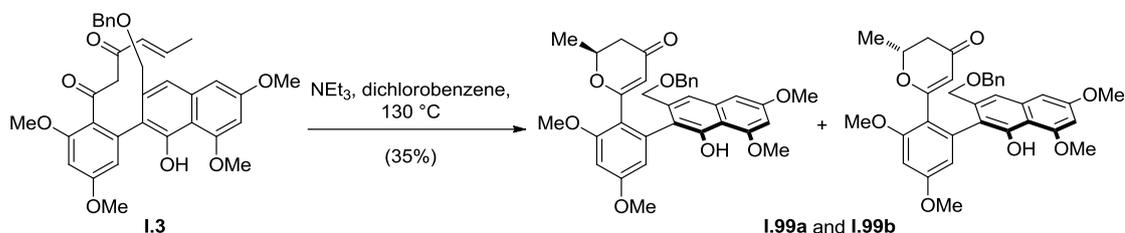


^{13}C NMR (100 MHz, CDCl_3): δ/ppm = 195.5 (CO, C17), 193.4 (CO, C1), 166.5 (Ar- C_q , C13), 165.9 (Ar- C_q , C5), 164.4 (C-OH, C19), 163.6 (Ar- C_q , C3), 159.6 (Ar- C_q , C15), 154.3 (Ar- C_q , C11), 145.5 (C_q , C7 or C9), 142.3 (C_q , C7 or C9), 139.6 (CH, C21), 137.9 (Ar- C_q , C29), 128.5 (2 x Ar-C, C31), 127.8 (Ar-C, C32), 127.6 (2 x Ar-C, C30), 123.1 (CH, C20), 122.4 (CH, C8), 119.7 (Ar- C_q , C16), 113.2 (C_q , C18), 110.8 (Ar- C_q , C2), 105.2 (Ar-C, C6), 100.1 (Ar-C, C12), 98.3(7) (Ar-C, C4), 98.3(6) (Ar-C, C14), 72.9 (CH_2 , C28), 68.7 (CH_2 , C27), 61.2 (C_q , C10), 56.1(4) (OCH_3 , C23), 56.1(1) (OCH_3 , C24 or C25), 55.9 (OCH_3 , C26), 55.8 (OCH_3 , C24 or C25), 19.1 (CH_3 , C22).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2985 (w), 2257 (w) 1736 (s), 1447 (w), 1373 (m), 1280 (s), 1098 (w), 1044 (s).

HRMS (ESI) calculated for $\text{C}_{34}\text{H}_{33}\text{O}_8$ $[\text{M}+\text{H}]^+$ 569.2170, found 569.2164.

Preparation of γ -pyrone **I.99a** and **I.99b**



6-(2-{3-[(Benzyloxy)methyl]-1-hydroxy-6,8-dimethoxynaphthalen-2-yl}-4,6-

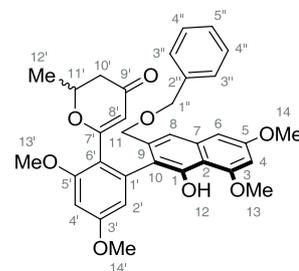
dimethoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyran-4-one (**I.99**). To a magnetically stirred solution of ketone **I.3** (20.0 mg, 35.0 μmol) in dry dichlorobenzene (1.2 mL) was added dry NEt_3 (10.0 μL , 70.0 μmol) and the reaction was heated to 130 $^\circ\text{C}$. The ensuing mixture was refluxed at this temperature for 48 h, and then, the resulting brown liquid was directly subjected to flash column chromatography (0:1 \rightarrow 2:1 \rightarrow 1:1 \rightarrow 1:2 \rightarrow 1:0 EtOAc/hexanes, gradient elution) providing 7.00 mg (12.3 μmol , 35%, 1:1 mixture of two diastereoisomers) of γ -pyrone **I.99** as a viscous colorless oil.

For characterization purposes an analytical amount of diastereomeric mixture of **I.99a** and **I.99b** was separated on preparative HPLC (VARIAN Dynamax, 250 x 21.4 mm, water (A)/methanol (B), 0 min 30% A, 40 min 23% A, 15.8 mL/min, $t_{\text{R}}(\text{I.99a})$ = 41.01 min, $t_{\text{R}}(\text{I.99b})$ = 46.67 min).

R_f = 0.69, 2:1 EtOAc/hexanes (both diastereoisomers).

Diastereoisomer **I.99a**.

^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ /ppm = 9.30 (s, 1H, OH, H12), 7.35 (s, 1H, Ar-H, H8), 7.35–7.30 (m, 2H, Ar-H, H3" or H4" and/or H5"), 7.28–7.27 (m, 3H, Ar-H, H3" or H4" and H5"), 6.90 (d, 3J = 2.3 Hz, 1H, Ar-H, H6), 6.64 (d, 3J = 2.3 Hz, 1H, Ar-H, H4'), 6.58 (d, 3J = 2.2 Hz, 1H, Ar-H, H4), 6.36 (d, 3J = 2.3 Hz, 1H, Ar-H, H2'), 5.20 (s, 1H, CH, H8'), 4.43 (d, 2J = 12.0 Hz, 1H, CH_2 , H1''), 4.40 (d, 2J = 12.0 Hz, 1H, CH_2 , H1'), 4.27 (d, 2J = 13.7 Hz, 1H, CH_2 , H11), 4.23 (d, 2J = 13.6 Hz, 1H, CH_2 , H11), 3.98 (s, 3H, OCH_3 , H13), 3.85 (s, 3H, OCH_3 , H14), 3.84–3.81 (m, 1H, CH, H11'), 3.81 (s, 3H, OCH_3 , H13'), 3.76 (s, 3H, OCH_3 , H14'), 2.12 (ddq, 2J = 16.7 Hz,



$^3J = 3.5$ Hz, $^4J = 0.7$ Hz, 1H, CH₂, H10'), 1.96 (dd, $^2J = 16.9$ Hz, $^3J = 13.0$ Hz, 1H, CH₂, H10'), 0.88 (d, $^3J = 6.4$ Hz, 3H, CH₃, H12').

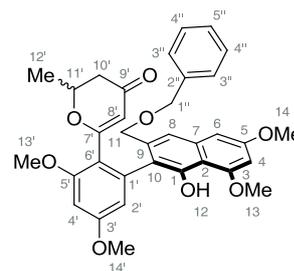
^{13}C NMR (150 MHz, DMSO-*d*₆): δ /ppm = 191.8 (CO, C9'), 169.4 (C_q, C7'), 161.1 (Ar-C_q, C3'), 158.2 (Ar-C_q, C5'), 157.6 (Ar-C_q, C5), 157.0 (Ar-C_q, C3), 150.7 (Ar-C_q, C1), 138.7 (Ar-C_q, C7 or C1'), 138.3 (Ar-C_q, C2''), 136.5 (Ar-C_q, C9), 136.0 (Ar-C_q, C7 or C1'), 128.2 (2 x Ar-CH, C3'' or C4''), 127.4 (Ar-CH, C5''), 127.3 (2 x Ar-CH, C3'' or C4''), 118.8 (Ar-C_q, C10), 116.4 (Ar-C_q, C6'), 115.0 (Ar-CH, C8), 109.0 (Ar-C_q, C2), 107.9 (Ar-CH, C2'), 107.2 (CH, C8'), 99.4 (Ar-CH, C6), 97.7(4) (Ar-CH, C4'), 97.6(8) (Ar-CH, C4), 75.1 (CH, C11'), 71.7 (CH₂, C1''), 69.5 (CH₂, C11), 56.4 (OCH₃, C13), 55.9 (OCH₃, C13'), 55.4 (OCH₃, C14'), 55.3 (OCH₃, C14), 42.1 (CH₂, C10'), 19.2 (CH₃, C12').

IR: $\tilde{\nu}/\text{cm}^{-1} = 3392$ (m), 1602 (s), 1326 (m), 1205 (m), 1158 (s), 1110 (m), 1026 (m).

HRMS (ESI) calculated for C₃₄H₃₅O₈ [M+H]⁺ 571.2326, found 571.2325.

Diastereoisomer I.99b.

^1H NMR (400 MHz, DMSO-*d*₆): δ /ppm = 9.18 (s, 1H, OH, H12), 7.41 (s, 1H, Ar-H, H8), 7.38–7.24 (m, 5H, Ar-H, H3'', H4'' and H5''), 6.93 (d, $^3J = 2.2$ Hz, 1H, Ar-H, H6), 6.64 (d, $^3J = 2.3$ Hz, 1H, Ar-H, H4'), 6.55 (d, $^3J = 2.2$ Hz, 1H, H4), 6.36 (d, $^3J = 2.3$ Hz, 1H, Ar-H, H2'), 5.26 (s, 1H, CH, H8'), 4.53–4.46 (m, 2H, CH₂, H1''), 4.40–4.32 (m, 2H, CH₂, H11), 3.95 (s, 3H, OCH₃, H13), 3.85 (s, 3H, OCH₃, H14), 3.80 (s, 3H, OCH₃, H13'), 3.75 (s, 3H, OCH₃, H14'), 3.38 (ddd, $^3J = 13.4$ Hz, $^3J = 6.4$ Hz, $^3J = 3.7$ Hz, 1H, CH, H11'), 2.21–2.03 (m, 2H, CH₂, H10'), 0.97 (d, $^3J = 6.3$ Hz, 3H, CH₃, H12').

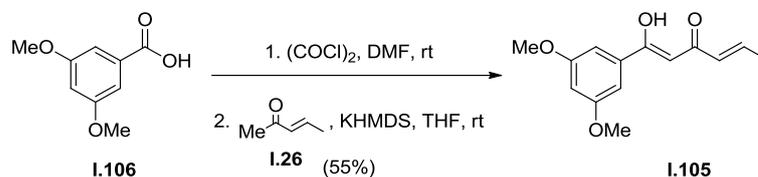


^{13}C NMR (100 MHz, DMSO-*d*₆): δ /ppm = 192.1 (CO, C9'), 169.5 (C_q, C7'), 161.2 (Ar-C_q, C3'), 158.0 (Ar-C_q, C5'), 157.7 (Ar-C_q, C5), 156.9 (Ar-C_q, C3), 150.0 (Ar-C_q, C1), 138.9 (Ar-C_q, C7 or C1'), 138.4 (Ar-C_q, C2''), 137.2 (Ar-C_q, C9), 136.0 (Ar-C_q, C7 or C1'), 128.2 (2 x Ar-CH, C3'' or C4''), 127.3(9) (Ar-CH, C5''), 127.3(7) (2 x Ar-CH, C3'' or C4''), 118.7 (Ar-C_q, C10), 116.5 (Ar-C_q, C6'), 114.7 (Ar-CH, C8), 108.8 (Ar-C_q, C2), 107.8 (CH, C2' or C8'), 107.7 (CH, C2' or C8'), 99.5 (Ar-CH, C6), 97.6,(2 x Ar-CH, C4 and C4'), 75.6 (CH, C11'), 71.9 (CH₂, C1''), 69.8 (CH₂, C11), 56.3 (OCH₃, C13), 55.9 (OCH₃, C13'), 55.4 (OCH₃, C14 or C14'), 55.3 (OCH₃, C14 or C14'), 42.2 (CH₂, C10'), 19.4 (CH₃, C12').

IR: $\tilde{\nu}/\text{cm}^{-1} = 3389$ (w), 2935 (w), 2065 (w), 1655 (m), 1632 (m), 1595 (s), 1452 (m), 1364 (s), 1326 (s), 1249 (m), 1205 (s), 1109 (s), 1043 (s).

HRMS (ESI) calculated for $C_{34}H_{35}O_8$ $[M+H]^+$ 571.2326, found 571.2325.

Preparation of dienone **I.105**



(E)-1-(3,5-dimethoxyphenyl)hex-4-ene-1,3-dione (I.105). To a magnetically stirred solution of 3,5-dimethoxybenzoic acid (**I.106**) (500 mg, 30.1 mmol) in dry CH_2Cl_2 (50 mL) was added oxalyl chloride solution (2M in CH_2Cl_2 , 29.5 mmol, 6.02 mL) and dry DMF (0.1 mL). The mixture was stirred at room temperature for 15 min, concentrated *in vacuo* and the obtained acid chloride was dried under high vacuum. To a solution of KHMDS (0.5M in toluene, 4.51 mmol, 9.02 mL) in dry THF (7.5 mL) was added dropwise a solution of enone **I.26** (85wt%, 380 mg, 4.51 mmol, 0.44 mL) in dry THF (7.5 mL) at $-78^\circ C$. After being stirred for 15 min at this temperature, a solution of the above prepared acid chloride in dry THF (17.5 mL) was added through a thick cannula at $-78^\circ C$. The mixture was stirred for 40 min at $-78^\circ C$, before aqueous saturated NH_4Cl solution (100 mL) was added and the biphasic mixture was warmed to room temperature. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing the crude product. Subjection of this material to flash column chromatography (1:3→1:0 EtOAc/hexanes, gradient elution) gave 412 mg (1.66 mmol, 55%) of dienone **I.105** as a yellow oil and 70.0 mg (0.421 mmol, 14%) of the recovered carboxylic acid **I.106**.

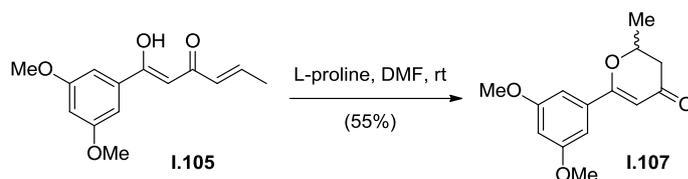
$R_f = 0.82$, 1:1 EtOAc/hexanes.

1H NMR (600 MHz, $CDCl_3$): $\delta/ppm = 7.05$ (d, $^4J = 2.3$ Hz, 2H), 6.96 (dq, $^3J = 15.4$ Hz, $^3J = 6.9$ Hz, 1H), 6.62 (t, $^4J = 2.3$ Hz, 1H), 6.10 (s, 1H), 6.03 (dq, $^3J = 15.4$ Hz, $^4J = 1.5$ Hz, 1H), 3.84 (s, 6H), 1.95 (dd, $^3J = 7.0$ Hz, $^4J = 1.7$ Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): $\delta/ppm = 188.9$, 180.3, 161.0 (2 x C), 140.4, 138.5, 127.9, 105.2 (2 x C), 104.9, 96.4, 55.7 (2 x C), 18.6.

IR: $\tilde{\nu}/cm^{-1} = 2934$ (w), 1652 (m), 1591 (m), 1454 (m), 1427 (m), 1348 (m), 1303 (m), 1203 (s), 1160 (s), 1045 (m).

HRMS (ESI) calculated for $C_{14}H_{15}O_4$ $[M-H]^-$ 247.0976, found 247.0981.

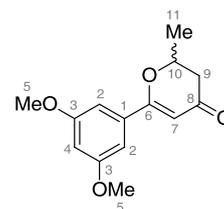
Preparation of enone **I.107**

6-(3,5-dimethoxyphenyl)-2-methyl-2H-pyran-4(3H)-one (I.107). A solution of dienone **I.105** (20.0 mg, 81.0 μmol) and L-proline (1.90 mg, 16.0 μmol) in dry DMF (0.3 mL) was stirred at room temperature for 6 d. After being concentrated *in vacuo*, the crude product was subjected to flash column chromatography (1:2 \rightarrow 1:0 EtOAc/hexanes, gradient elution) providing 11.0 mg (44.3 μmol , 55%, *er* = 1:1) of enone **I.107** as a yellow oil and 3.00 mg (12.1 μmol , 15%) of the starting material **I.105**.

The enantiomeric ratio (*er*) was measured on chiral HPLC (Nucleocel DELTA S, 250 x 4.6 mm, isocratic elution, hexanes (A)/*i*-propanol (B), 96% A, flow rate: 0.5 mL/min, detection at 300 nm, t_{R} (**I.107a**) = 52.9 min, t_{R} (**I.107b**) = 57.5 min).

R_{f} = 0.5, 1:1 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): δ /ppm = 6.87 (d, 4J = 2.3 Hz, 2H, Ar-H, H2), 6.58 (t, 4J = 2.3 Hz, 1H, Ar-H, H4), 5.97 (s, 1H, CH, H7), 4.69 (dq, 3J = 12.7 Hz, 3J = 6.3 Hz, 3J = 4.2 Hz, 1H, CH, H10), 3.82 (s, 6H, OCH_3 , H5), 2.62–2.49 (m, 2H, CH_2 , H9), 1.58 (d, 3J = 6.4 Hz, 3H, CH_3 , H11).

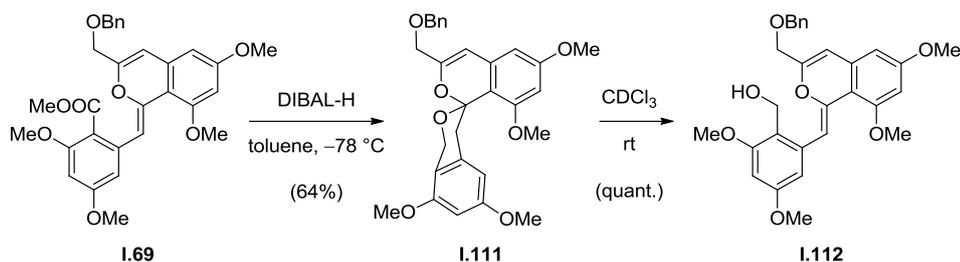


^{13}C NMR (150 MHz, CDCl_3): δ /ppm = 193.6 (CO, C8), 170.3 (Ar- C_q , C1 or C6), 161.0 (2 x Ar- C_q , C3), 135.0 (Ar- C_q , C1 or C6), 104.8 (2 x Ar-CH, C2), 103.9 (Ar-CH, C4), 102.5 (br s, CH, C7), 76.3 (CH, C10), 55.7 (2 x OCH_3 , C5), 43.2 (br, CH_2 , C9), 20.6 (CH_3 , C11).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2985 (w), 2360 (w), 2256 (w), 1732 (s), 1447 (w), 1374 (m), 1239 (s), 1045 (s).

HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{17}\text{O}_4$ [$\text{M}+\text{H}$] $^+$ 249.1121, found 249.1121.

Preparation of alcohol I.112



(Z)-2-((3-((benzyloxy)methyl)-6,8-dimethoxy-1*H*-isochromen-1-ylidene)methyl)-4,6-dimethoxy phenyl)methanol (I.112). To a magnetically stirred solution of ester **I.69** (10.0 mg, 19.0 μmol) in dry toluene (1 mL) was added dropwise a solution of diisobutylaluminum hydride (1.2M in toluene, 23.0 μmol , 20.0 μL) at $-78\text{ }^\circ\text{C}$. The ensuing mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. Then, aqueous saturated NH_4Cl solution (5 mL) was added and the biphasic mixture was warmed to room temperature. After addition of EtOAc (7 mL), the layers were separated and the organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a crude colorless oil. Subjection of this material to flash column chromatography (1:4 \rightarrow 1:0 EtOAc/hexanes, gradient elution) provided 6.00 mg (12.0 μmol , 64%) acetal **I.111** as a colorless oil. When **I.111** was dissolved in deuterated chloroform, a quantitative conversion to the open alcohol **I.112** took place within 24 h. Due to the chemical instability of the material, both compounds were characterized only by $^1\text{H-NMR}$ spectroscopy.

(R)-3'-((benzyloxy)methyl)-6,6',8,8'-tetramethoxyspiro[isochroman-3,1'-isochromene] (I.111).

$R_f = 0.5$, 1:2 EtOAc/hexanes.

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.32\text{--}7.26$ (m, 5H), 6.37 (d, $^3J = 2.4$ Hz, 1H), 6.32–6.31 (m, 2H), 6.27 (d, $^3J = 2.4$ Hz, 1H), 5.96 (s, 1H), 4.83 (d, $^2J = 14.7$ Hz, 1H), 4.79 (d, $^2J = 14.7$ Hz, 1H), 4.57 (d, $^2J = 12.0$ Hz, 1H), 4.52 (d, $^2J = 12.1$ Hz, 1H), 4.37 (d, $^2J = 16.7$ Hz, 1H), 4.10 (dd, $^2J = 13.4$ Hz, $^4J = 0.8$ Hz, 1H), 4.03 (d, $^2J = 13.4$ Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.05 (d, $^2J = 16.7$ Hz, 1H).

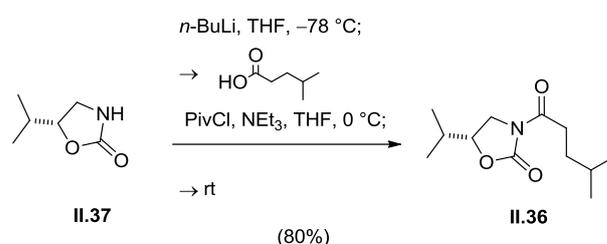
(Z)-2-((3-((benzyloxy)methyl)-6,8-dimethoxy-1*H*-isochromen-1-ylidene)methyl)-4,6-dimethoxy phenyl)methanol (I.112).

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.49$ (s, 1H), 7.44–7.42 (m, 2H), 7.37–7.35 (m, 2H), 7.31–7.29 (m, 2H), 7.11 (d, $^3J = 2.1$ Hz, 1H), 6.71 (d, $^3J = 2.3$ Hz, 1H), 6.50 (d, $^3J = 2.3$ Hz,

1H), 6.45 (d, $^3J = 2.1$ Hz, 1H), 5.09 (s, 2H), 4.87 (s, 2H), 4.73 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H).

HRMS (ESI) calculated for $C_{29}H_{30}O_7Na$ $[M+Na]^+$ 513.1884, found 513.1883.

Preparation of oxazolidinone **II.36**^[77,150]



(R)-5-isobutyl-3-(4-methylpentanoyl)oxazolidin-2-one (II.36). To a magnetically stirred solution of **II.37** (6.00 g, 46.5 mmol) in dry THF (200 mL) was added dropwise a solution of *n*-BuLi (2.5M in hexanes, 58.1 mmol, 23.2 mL) at $-78\text{ }^\circ\text{C}$. The ensuing mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min. In a separate flask, triethylamine (8.23 g, 81.3 mmol, 11.3 mL) and pivaloyl chloride (7.70 g, 63.9 mmol, 7.87 mL) were added subsequently to a solution of 4-methylvaleric acid (6.75 g, 58.1 mmol, 7.33 mL) in dry THF (300 mL) at $0\text{ }^\circ\text{C}$. After stirring at $0\text{ }^\circ\text{C}$ for 30 min, the acid anhydride mixture was added slowly to the $-78\text{ }^\circ\text{C}$ cold lithio-oxazolidinone species, which was kept at $-78\text{ }^\circ\text{C}$. The reaction mixture was warmed to room temperature over a period of 2 h, then, water (500 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (100 mL), water (100 mL) and brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford crude colorless oil. Subjection of this material to flash column chromatography (1:8 \rightarrow 1:6 \rightarrow 1:0 EtOAc/hexanes, gradient elution) provided 8.40 g (37.0 mmol, 80%) of acylated oxazolidinone **II.36** as a colorless oil.

$R_f = 0.6$, 1:4 EtOAc/hexanes.

$[\alpha]_D^{24} = +85.4$ ($c = 1.0$, CHCl_3).

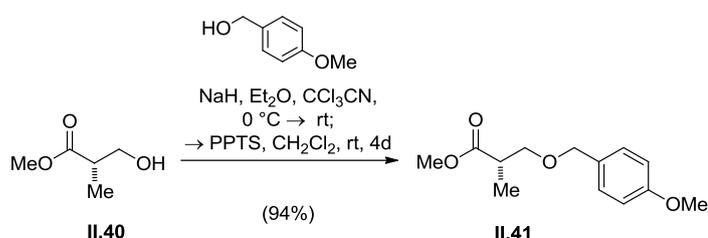
$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 4.43$ (ddd, $^3J = 8.3$ Hz, $^3J = 3.8$ Hz, $^3J = 3.1$ Hz, 1H), 4.26 (dd, $^3J = 8.8$ Hz, $^3J = 8.8$ Hz, 1H), 4.20 (dd, $^3J = 9.1$ Hz, $^3J = 3.0$ Hz, 1H), 3.04–2.94 (m, 1H), 2.90–2.81 (m, 1H), 2.37 (m, 1H), 1.66–1.58 (m, 1H), 1.59–1.50 (m, 2H), 0.94–0.89 (m, 9H), 0.87 (d, $^3J = 6.9$ Hz, 3H).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 173.8, 154.2, 63.4, 58.5, 33.8, 33.4, 28.5, 27.9, 22.5(0), 22.4(6), 18.1, 14.8$.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2958 (m), 2873 (w), 1785 (s), 1699 (s), 1468 (w), 1386 (s), 1301 (m), 1228 (w), 1199 (s), 1060 (m).

HRMS (EI) calculated for $\text{C}_{12}\text{H}_{21}\text{O}_3\text{N}^+$ $[\text{M}]^+$ 227.1521, found 227.1522.

Preparation of methylpropanoate **II.41**^[79]



(S)-Methyl-3-(4-methoxybenzyl)oxy-2-methylpropanoate (II.41). To a magnetically stirred suspension of NaH (60wt% suspension in mineral oil, 609 mg, 15.2 mmol) in dry diethyl ether (80 mL) was slowly added a solution of 4-methoxybenzyl alcohol (20.7 g, 150 mmol) in diethyl ether (50 mL) at 0 °C. The ensuing mixture was warmed to room temperature and stirred for 30 min before it was cooled to 0 °C and trichloroacetonitrile (21.6 g, 150 mmol, 15.0 mL) was added dropwise over 15 min. After 1 h, the reaction was allowed to warm to room temperature and stirred for an additional 3 h. Then, the solution was concentrated *in vacuo* providing crude orange oil, to which a MeOH/hexane mixture (150 mL, 1:275) was added. After being stirred for 30 min, the heterogeneous mixture was filtered and the filtrate was concentrated to give 4-methoxybenzyl trichloroacetimidate as crude yellow oil, which was used without further purification. Thus obtained 4-methoxybenzyl trichloroacetimidate was dissolved in dry CH_2Cl_2 (70 mL) and added to a magnetically stirred solution of (S)-Roche ester **II.40** (10.0 mg, 84.7 mmol, 9.34 mL) in dry CH_2Cl_2 (70 mL) at 0 °C followed by an addition of PPTS (1.06 mg, 4.23 mmol). The reaction was stirred at 0 °C for 1 h and was then allowed to warm to room temperature at which it was stirred for an additional 6 d. After filtration, the filtrate was extracted with EtOAc/hexanes mixture (50 mL, 2:8) followed by CH_2Cl_2 (50 mL). The combined organic layers were washed with aqueous saturated NaHCO_3 solution (150 mL) and brine (150 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to provide a crude yellow oil. Subjection of this material to flash column chromatography (1:97→1:9→1:0 EtOAc/hexanes, gradient elution) provided 19.0 g (79.8 mmol, 94%) of methylpropanoate **II.41** as a colorless oil.

$R_f = 0.57$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +11.4$ ($c = 1.0$, CH_2Cl_2).

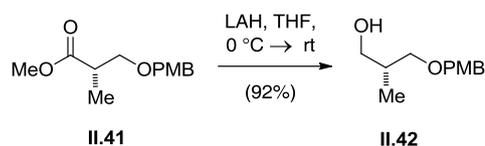
^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.25–7.22 (m, 2H), 6.89–6.86 (m, 2H), 4.46 (d, 2J = 11.8 Hz, 1H), 4.44 (d, 2J = 11.8 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.63 (dd, 2J = 9.2 Hz, 3J = 7.3 Hz, 1H), 3.46 (dd, 2J = 9.2 Hz, 3J = 6.0 Hz, 1H), 2.80–2.73 (m, 1H), 1.18–1.16 (d, 3J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ/ppm = 175.4, 159.3, 130.4, 129.3 (2 x C), 113.9 (2 x C), 72.9, 71.8, 55.4, 51.8, 40.3, 14.1.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2950 (w), 1859 (w), 2360 (w), 1735 (s), 1612 (m), 1586 (w), 1512 (s), 1459 (m), 1362 (w), 1240 (s), 1198 (m), 1173 (s), 1985 (s).

HRMS (EI) calculated for $\text{C}_{13}\text{H}_{18}\text{O}_4$ $[\text{M}]^+$ 238.1205, found 238.1197.

Preparation of alcohol **II.42**^[79a]



(R)-3-(4-Methoxybenzyloxy)-2-methyl-1-propanol (II.42). To a magnetically stirred suspension of lithium aluminum hydride (767 mg, 27.7 mmol) in THF (43.0 mL) was added dropwise a solution of ester **II.41** (6.00 g, 25.2 mmol) in THF (43.0 mL) at 0 °C. The ensuing mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The reaction was stirred at room temperature for 1 h before it was cooled to 0 °C and quenched by sequential addition of water (2 mL), aqueous NaOH solution (1 M, 2 mL) and water (2 mL). Then, the biphasic solution was allowed to warm to room temperature and Na_2SO_4 was added. After being stirred for 30 min, the reaction mixture was filtered through a glass frit and the filter cake was washed with diethyl ether. The filtrate was concentrated *in vacuo* to provide crude colorless oil. Subjection of this material to flash column chromatography (1:3→1:0 EtOAc/hexanes, gradient elution) gave 4.88 g (23.2 mmol, 92%) of alcohol **II.42** as a colorless oil.

R_f = 0.24, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +13.2$ (c = 1.0, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.26–7.23 (m, 2H), 6.90–6.87 (m, 2H), 4.46 (d, 2J = 11.6 Hz, 1H), 4.44 (d, 2J = 11.6 Hz, 1H), 3.81 (s, 3H), 3.62 (ddd, 2J = 10.7 Hz, 3J = 4.3 Hz, 3J = 0.7 Hz, 1H), 3.58 (dd, 2J = 10.7 Hz, 3J = 7.3 Hz, 1H), 3.53 (ddd, 2J = 9.1 Hz, 3J = 4.6 Hz,

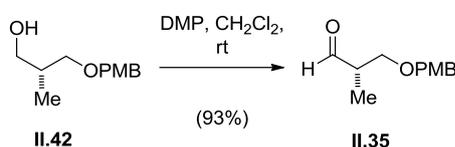
$^3J = 0.7$ Hz, 1H), 3.39 (dd, $^2J = 9.1$ Hz, $^3J = 8.2$ Hz, 1H), 2.11–2.02 (m, 1H), 0.87 (d, $^3J = 7.0$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 159.4, 130.2, 129.3$ (2 x C), 114.0 (2 x C), 75.3, 73.2, 68.1, 55.4, 35.7, 13.6.

IR: $\tilde{\nu}/\text{cm}^{-1} = 3396$ (w), 2861 (w), 1612 (m), 1586 (w), 1511 (s), 1463 (m), 1362 (m), 1302 (m), 1244 (s), 1173 (m), 1086 (s), 1040 (s).

HRMS (EI) calculated for $\text{C}_{12}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$ 210.1256, found 210.1254.

Preparation of aldehyde **II.35**^[79a]



(S)-3-(4-Methoxybenzyl)oxy-2-methyl-1-propanal (II.35). To a magnetically stirred solution of alcohol **II.42** (265 mg, 1.26 mmol) in wet CH_2Cl_2 (5.5 mL) was slowly added Dess-Martin periodinane (802 mg, 1.89 mmol) at room temperature. The ensuing mixture was stirred for 30 min, then, three 0.5 mL portions of CH_2Cl_2 were added subsequently over the course of 15 min. After being stirred for an additional 10 min, the reaction was diluted with diethyl ether (20 mL) and aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (15 mL) followed by aqueous saturated NaHCO_3 solution (7 mL) were added. The biphasic mixture was vigorously stirred for an additional 10 min, the organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with aqueous saturated NaHCO_3 solution (40 mL), water (40 mL) and brine (40 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to provide the crude aldehyde **II.35** (243 mg, 93%) as a pale yellow oil. This material was used immediately in a Heathcock anti-aldol reaction without further purification.

$R_f = 0.58$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +29.4$ ($c = 1.0$, CH_2Cl_2).

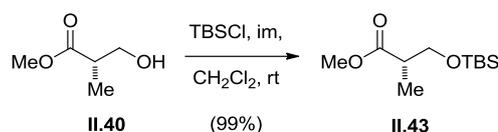
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 9.71$ (d, $^3J = 1.6$ Hz, 1H), 7.25–7.21 (m, 2H), 6.88 (m, 2H), 4.46 (br s, 2H), 3.81 (s, 3H), 3.65 (dd, $^2J = 9.4$ Hz, $^3J = 6.8$ Hz, 1H), 3.61 (dd, $^2J = 9.4$ Hz, $^3J = 5.3$ Hz, 1H), 2.70–2.59 (m, 1H), 1.12 (d, $^3J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 204.1, 159.4, 130.1, 129.4$ (2 x C), 113.9 (2 x C), $73.1, 69.9, 55.4, 46.9, 10.9$.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2936$ (w), 2837 (w), 2726 (w), 1819 (w), 1721 (m), 1612 (m), 1512 (s), 1457 (w), 1360 (w), 1302 (w), 1250 (s), 1173 (m), 1091 (s), 1032 (s).

HRMS (EI) calculated for $\text{C}_{12}\text{H}_{16}\text{O}_3$ $[\text{M}]^+$ 208.1099, found 208.1078.

Preparation of TBS ether **II.43**^[80a]

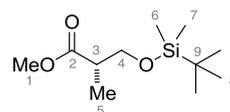


(S)-Methyl 3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate (II.43). A solution of (*S*)-Roche ester (**II.40**) (5.00 g, 42.3 mmol, 4.67 mL), *tert*-butyldimethylsilyl chloride (7.66 g, 50.8 mmol) and imidazole (7.20 g, 106 mmol) in dry CH_2Cl_2 (150 mL) was stirred at room temperature overnight. After the white precipitate was filtered off, the reaction was concentrated *in vacuo* providing a crude oil. Subjection of this material to flash column chromatography (1:2 EtOAc/hexanes) yielded 9.68 g (41.7 mmol, 99%) of TBS ether **II.43** as a colorless oil.

$R_f = 0.85$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +21.0$ ($c = 1.0$, CH_2Cl_2).

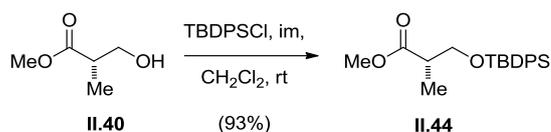
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 3.77$ (dd, $^2J = 9.7$ Hz, $^3J = 6.9$ Hz, 1H, CH_2 , H4), 3.67 (s, 3H, OCH_3 , H1), 3.65 (dd, $^2J = 9.7$ Hz, $^3J = 6.0$ Hz, 1H, CH_2 , H4), 2.69 – 2.61 (m, 1H, CH, H3), 1.14 (d, $^3J = 7.1$ Hz, 3H, CH_3 , H5), 0.87 (s, 9H, CH_3 , H8), 0.04 (s, 3H, SiCH_3 , H6 or H7), 0.03 (s, 3H, SiCH_3 , H6 or H7).



^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 175.6$ (CO, C2), 65.4 (CH_2 , C4), 51.6 (OCH_3 , C1), 42.7 (CH, C3), 25.9 (3 x CH_3 , C8), 18.9 (C_q , C9), 13.6 (CH_3 , C5), $-5.3(45)$ (SiCH_3 , C6 or C7), $-5.3(47)$ (SiCH_3 , C6 or C7).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2953$ (w), 2930 (w), 2858 (w), 1741 (m), 1463 (w), 1361 (w), 1253 (m), 1198 (m), 1176 (m), 1092 (m).

HRMS (EI) calculated for $\text{C}_{10}\text{H}_{21}\text{O}_3\text{Si}$ $[\text{M}-\text{CH}_3]^+$ 217.1260, found 217.1251.

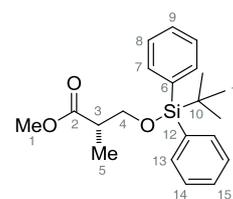
Preparation of TBDPS ether II.44^[80c]

(S)-Methyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate II.44. A solution of (*S*)-Roche ester **II.40** (1.00 g, 8.47 mmol, 930 μL), *tert*-butyldiphenylsilyl chloride (2.79 g, 10.2 mmol, 2.60 mL) and imidazole (1.44 g, 21.2 mmol) in dry CH_2Cl_2 (30 mL) was stirred at room temperature overnight. After the white precipitate was filtered off, the reaction was concentrated *in vacuo* providing crude oil. Subjection of this material to flash column chromatography (1:8 \rightarrow 1:2 EtOAc/hexanes, gradient elution) gave 2.80 g (7.86 mmol, 93%) of TBDPS ether **II.44** as a colorless oil.

$R_f = 0.78$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +12.6$ ($c = 1.0$, CH_2Cl_2).

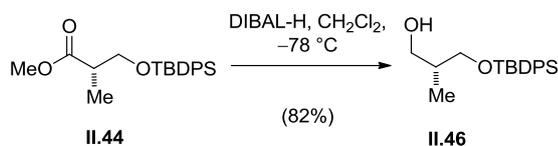
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.69\text{--}7.59$ (m, 4H, Ar-H, H7 or H8 or H13 or H14), 7.44–7.41 (m, 2H, Ar-H, H9 or H15), 7.40–7.37 (m, 4H, Ar-H, H7 or H8 or H13 or H14), 3.83 (dd, $^2J = 9.8$ Hz, $^3J = 6.9$ Hz, 1H, CH_2 , H4), 3.72 (dd, $^2J = 9.8$ Hz, $^3J = 5.8$ Hz, 1H, CH_2 , H4), 3.68 (s, 3H, OCH_3 , H1), 2.78–2.66 (m, 1H, CH, H3), 1.16 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H5), 1.03 (s, 9H, CH_3 , H11).



^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 175.5$ (CO, C2), 135.7(22) (2 x Ar-CH, C7 or C8 or C13 or C14), 135.7(15) (2 x Ar-CH, C7 or C8 or C13 or C14), 133.7 (Ar- C_q , C6 or C12), 133.6 (Ar- C_q , C6 or C12), 129.8 (Ar-CH, C9 or C15), 127.8 (4 x Ar-CH, C9 or C15 and C7 or C8 or C13 or C14), 66.1 (CH_2 , C4), 51.7 (OCH_3 , C1), 42.6 (CH, C3), 26.9 (3 x CH_3 , C11), 19.4 (C_q , C10), 13.6 (CH_3 , C5).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3071$ (w), 2931 (w), 2857 (w), 1738 (m), 1472 (w), 1427 (w), 1388 (w), 1247 (w), 1198 (w), 1175 (w), 1104 (m), 1084 (m).

HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{32}\text{NO}_3\text{Si}$ $[\text{M}+\text{NH}_4]^+$ 374.2146, found 374.2146.

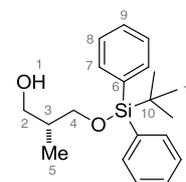
Preparation of alcohol II.46^[80c]

(R)-3-((Tert-butyldiphenylsilyloxy)-2-methylpropan-1-ol (II.46). To a magnetically stirred solution of ester **II.44** (1.00 g, 2.81 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of diisobutylaluminum hydride (1M in CH_2Cl_2 , 12.1 mL, 12.1 mmol) at $-78\text{ }^\circ\text{C}$. The ensuing mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1.5 h, then water (2 mL) and diethyl ether (50 mL) were added and the mixture was allowed to warm to room temperature. After the reaction was stirred for 10 min, water (2 mL) and aqueous NaOH solution (1M, 2 mL) were added subsequently followed by addition Na_2SO_4 . The mixture was stirred for an additional 20 min, before being filtered and concentrated *in vacuo* providing crude product. Subjection of this material to flash column chromatography (1:6 EtOAc/hexanes) gave 754 mg (2.30 mmol, 82%) of alcohol **II.46** as a colorless oil.

$R_f = 0.57$, 1:4 EtOAc/hexanes.

$[\alpha]_D^{24} = +4.0$ ($c = 1.0$, CH_2Cl_2).

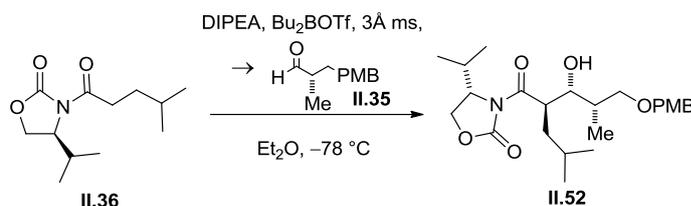
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.70\text{--}7.65$ (m, 4H, Ar-H, H7 or H8), 7.45–7.43 (m, 2H, Ar-H, H9), 7.41–7.38 (m, 4H, Ar-H, H7 or H8), 3.73 (dd, $^2J = 10.1$ Hz, $^3J = 4.5$ Hz, 1H, CH_2 , H2 or H4), 3.69–3.66 (m, 2H, CH_2 , H2 or H4), 3.60 (dd, $^2J = 10.1$ Hz, $^3J = 7.7$ Hz, 1H, CH_2 , H2 or H4), 2.04–1.95 (m, 1H, CH, H3), 1.06 (s, 9H, CH_3 , H11), 0.83 (d, $^3J = 7.0$, 3H, CH_3 , H5).



^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 135.7(4)$ (2 x Ar-CH, C7 or C8), 135.7(2) (2 x Ar-CH, C7 or C8), 133.3 (Ar- C_q , C6), 133.2(9) (Ar- C_q , C6), 129.9 (2 x Ar-CH, C9), 127.9(12) (2 x Ar-CH, C7 or C8), 127.9(10) (2 x Ar-CH, C7 or C8), 68.9 (CH_2 , C2 or C4), 67.9 (CH_2 , C2 or C4), 37.4 (CH, C3), 27.0 (3 x CH_3 , C11), 19.3 (C_q , C10), 13.3 (CH_3 , C5).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3365$ (w), 2958 (w), 2929 (w), 2857 (w), 1740 (w), 1472 (w), 1427 (w), 1240 (w), 1105 (m), 1029 (m).

HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{29}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 329.1931, found 329.1931.

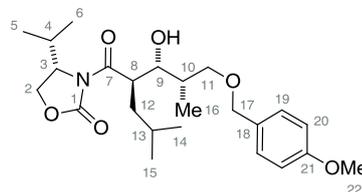
Preparation of alcohol **II.52**

(S)-3-((2R,3R,4S)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methylpentanoyl)-4-isopropylloxazolidin-2-one (II.52). A solution of acyl oxazolidinone **II.36** (1.07 g, 4.70 mmol) in dry diethyl ether (15 mL) was stirred over 3Å molecular sieves for 20 min before it was cooled to 0 °C. Subsequently, diisopropylethylamine (717 mg, 5.55 mmol, 0.94 mL) and freshly distilled dibutylboron triflate (2.58 g, 9.40 mmol, 3.15 mL) were added dropwise. The mixture was stirred for 30 min at 0 °C before it was cooled to -78 °C and a solution of aldehyde **II.35** (990 mg, 4.75 mmol) in diethyl ether (5 mL) was added, which was pre-dried over 3Å molecular sieves beforehand. The ensuing mixture was stirred at -78 °C for 2 h, then, aqueous pH-7-phosphate buffer (0.1M, 3.5 mL) and methanol (10 mL) were added in one portion. The reaction was warmed to room temperature and after being stirred for 10 min, aqueous hydrogen peroxide solution (30wt%, 4 mL) and methanol (8 mL) were added in one portion. The reaction was stirred for 30 min at 0 °C and 1 h at room temperature. After addition of EtOAc (150 mL), the mixture was washed with aqueous saturated NaHCO₃ solution (150 mL) and brine (150 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* providing crude product. Subjection of this material to flash column chromatography (1:9→1:3→1:0 EtOAc/hexanes, gradient elution) gave 940 mg (2.16 mmol, 46%) of alcohol **II.52** as a colorless oil.

R_f = 0.38, 1:3 EtOAc/hexanes.

[α]_D²⁴ = +29.6 (c = 1.0, CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ/ppm = 7.25–7.20 (m, 2H, Ar-H, H19), 6.88–6.84 (m, 2H, Ar-H, H20), 4.46–4.40 (m, 3H, CH and CH₂, H3 and H17), 4.30–4.19 (m, 3H, CH and CH₂, H2 and H8), 3.86–3.83 (m, 1H, CH, H9), 3.80 (s, 3H, OCH₃, H22), 3.47 (dd, ²J = 9.1 Hz, ³J = 6.0 Hz, 1H, CH₂, H11), 3.42 (dd, ²J = 9.1 Hz, ³J = 5.1 Hz, 1H, CH₂, H11), 2.83 (d, ³J = 7.9 Hz, 1H, OH), 2.47–2.44 (m 1H, CH, H4), 1.98–1.93 (m, 1H, CH, H10), 1.69 (ddd, ²J = 13.4 Hz, ³J = 10.1 Hz, ³J = 5.0 Hz, 1H, CH₂, H12), 1.51–1.44 (m, 1H, CH, H13), 1.21 (ddd, ²J = 13.3 Hz, ³J = 8.8 Hz, ³J = 4.4 Hz, 1H, CH₂, H12), 1.01 (d, ³J = 7.0 Hz, 3H, CH₃, H16), 0.92–0.87 (m, 12H, CH₃, H5, H6, H14 and H15).

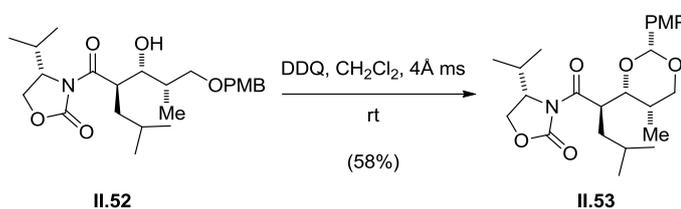


^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 177.0 (CO, C7), 159.3 (Ar- C_q , C21), 154.7 (CO, C1), 130.5 (Ar- C_q , C18), 129.4 (2 x Ar-CH, C19), 113.9 (2 x Ar-CH, C20), 75.9 (CH, C9), 73.9 (CH₂, C11), 73.1 (CH₂, C17), 63.3 (CH₂, C2), 59.4 (CH, C3), 55.4 (OCH₃, C22), 44.0 (CH, C8), 38.5 (CH₂, C12), 36.2 (CH, C10), 28.5 (CH, C4), 26.4 (CH, C13), 23.4 (CH₃, C14 or C15), 22.4 (CH₃, C14 or C15), 18.2 (CH₃, C5 or C6), 14.7 (CH₃, C5 or C6), 10.3 (CH₃, C16).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3500 (w), 2958 (w), 2870 (w), 1776 (s), 1736 (m), 1696 (m), 1611 (w), 1512 (m), 1384 (s), 1300 (m), 1245 (s), 1200 (s), 1093 (m).

HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{37}\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 458.2513, found 458.2516.

Preparation of PMP ether **II.53**

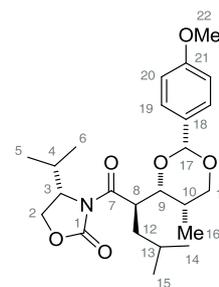


(5R)-5-Isobutyl-3-((2R)-2-((2R,5S)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyl pentanoyl)oxazolidin-2-one (II.53). To a magnetically stirred solution of alcohol **II.52** (100 mg, 230 μmol) in dry CH_2Cl_2 (3.5 mL) were added 4 Å molecular sieves and the mixture was stirred for 30 min at 0 °C before a solution of pre-dried 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (77.0 mg, 340 μmol) in dry CH_2Cl_2 (0.75 mL) was added dropwise. The reaction was stirred at 0 °C for an additional 2.5 h, then CH_2Cl_2 (10 mL) was added. The mixture was filtered over Celite, washed with aqueous saturated NaHCO_3 solution (10 mL) and aqueous saturated $\text{Na}_2\text{SO}_3/\text{NaHSO}_3$ solution, dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing 60.0 mg (134 μmol , 58%) of PMP ether **II.53** as a colorless oil. Due to the chemical instability of the compound, purification using column chromatography could not be performed. The obtained NMR-spectra are partially contaminated with traces of other diastereomer, starting material and benzaldehyde.

R_f = 0.5, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +7.7$ (c = 0.5, CDCl_3).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.34–7.32 (m, 2H, Ar-H, H19), 6.83–6.80 (m, 2H, Ar-H, H20), 5.32 (s, 1H, CH, H17), 4.65–4.61 (m, 1H, CH, H8), 4.38 (ddd, 3J = 8.3 Hz, 3J = 3.5 Hz, 3J = 2.6 Hz, 1H, CH, H3), 4.13 (dd, 3J = 8.7 Hz, 3J = 8.7 Hz, 1H, CH₂, H2), 4.07–4.02 (m, 3H, CH and CH₂, H2 and H9)



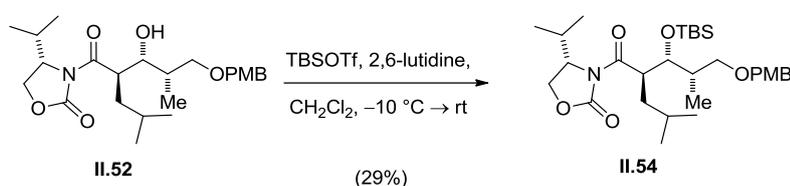
and H11), 4.00 (dd, $^2J = 11.3$ Hz, $^3J = 1.5$ Hz, 1H, CH₂, H11), 3.78 (s, 3H, OCH₃, H22), 2.09–2.04 (m, 1H, CH, H4), 1.73–1.68 (m, 2H, CH and CH₂, H10 and H12), 1.45–1.40 (m, 1H, CH, H13), 1.31 (d, $^3J = 6.9$ Hz, 3H, CH₃, H16), 1.12 (ddd, $^2J = 13.2$ Hz, $^2J = 10.1$ Hz, $^3J = 3.0$ Hz, 1H, CH₂, H12), 0.94 (d, $^3J = 6.5$ Hz, 3H, CH₃, H14 or H15), 0.90 (d, $^3J = 6.6$ Hz, 3H, CH₃, H14 or H15), 0.68 (d, $^3J = 7.1$ Hz, 3H, CH₃, H5 or H6), 0.22 (d, $^3J = 6.9$ Hz, 3H, CH₃, H5 or H6).

¹³C NMR (150 MHz, CDCl₃): δ /ppm = 176.5 (CO, C7), 160.1 (Ar-C_q, C21), 153.7 (CO, C1), 131.4 (Ar-C_q, C18), 128.1 (2 x Ar-CH, C19), 113.6 (2 x Ar-CH, C20), 102.5 (CH, C17), 83.2 (CH, C9), 73.8 (CH₂, C11), 62.8 (CH₂, C2), 59.0 (CH, C3), 55.5 (OCH₃, C22), 42.6 (CH, C8), 37.2 (CH₂, C12), 30.0 (CH, C10), 28.3 (CH, C4), 26.6 (CH, C13), 24.2 (CH₃, C14 or C15), 22.2 (CH₃, C14 or C15), 17.9 (CH₃, C5 or C6), 13.8 (CH₃, C5 or C6), 11.3 (CH₃, C16).

IR: $\tilde{\nu}$ /cm⁻¹ = 2958 (m), 2870 (w), 1776 (s), 1736 (m), 1693 (s), 1614 (m), 1518 (m), 1385 (s), 1370 (s), 1300 (m), 1220 (s), 1199 (s), 1156 (m), 1115 (s), 1028 (s).

HRMS (ESI) calculated for C₂₄H₃₆NO₆ [M+H]⁺ 434.2537, found 434.2540.

Preparation of TBS ether II.54

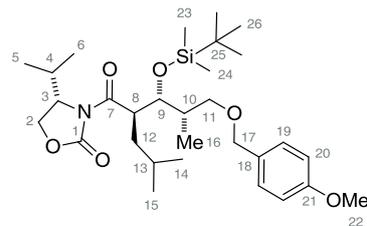


(R)-3-((2R,3R,4S)-3-((*Tert*-butyldimethylsilyl)oxy)-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl pentanoyl)-5-isobutyloxazolidin-2-one (II.54). To a magnetically stirred solution of alcohol **II.52** (30.08 mg, 69.0 μ mol) and 2,6-lutidine (13.0 mg, 124 μ mol, 14.0 μ L) in dry CH₂Cl₂ (0.4 mL) was added dropwise *tert*-butyldimethylsilyl triflate (26.0 mg, 97.0 μ mol, 22.0 μ L) at 0 °C and the ensuing mixture was warmed to room temperature over 1 h. After being stirred at room temperature for an additional 2 h, the reaction was diluted with diethyl ether (10 mL) and washed with aqueous HCl solution (2M, 7 mL) and aqueous saturated NaHCO₃ solution (7 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to obtain a crude mixture. Subjection of this material to flash column chromatography (1:6 EtOAc/hexanes) afforded 11.0 mg (20.0 μ mol, 29%) of the TBS ether **II.54** as a colorless oil.

R_f = 0.75, 1:3 EtOAc/hexanes.

$[\alpha]_D^{22} = +2.7$ ($c = 0.5$, CH₂Cl₂).

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.21–7.14 (m, 2H, Ar-H, H19), 6.89–6.81 (m, 2H, Ar-H, H20), 4.45 (dt, $^3J = 8.4$ Hz, $^3J = 3.1$ Hz, 1H, CH, H3), 4.42 (dd, $^3J = 5.2$ Hz, $^3J = 1.1$ Hz, 1H, CH, H9), 4.38 (d, $^2J = 11.5$ Hz, 1H, CH_2 , H17), 4.29 (d, $^2J = 11.5$ Hz, 1H, CH_2 , H17), 4.22 (dd, $^2J = 8.8$ Hz, $^3J = 8.8$ Hz, 1H, CH_2 , H2), 4.15 (dd, $^2J = 9.1$ Hz, $^3J = 2.9$ Hz, 1H, CH_2 , H2), 4.10–4.08 (m, 1H, CH, H8), 3.80 (s, 3H, OCH_3 , H22), 3.21 (dd, $^2J = 8.8$ Hz, $^3J = 8.8$ Hz, 1H, CH_2 , H11), 3.10 (dd, $^2J = 8.8$ Hz, $^3J = 5.7$ Hz, 1H, CH_2 , H11), 2.28–2.20 (m, 1H, CH, H4), 1.93 (ddd, $^2J = 13.3$ Hz, $^3J = 11.5$ Hz, $^3J = 5.1$ Hz, 1H, CH_2 , H12), 1.86–1.79 (m, 1H, CH, H10), 1.61–1.57 (m, 1H, CH_2 , H12), 1.38–1.29 (m, 1H, CH, H13), 0.90 (s, 9H, CH_3 , H26), 0.89 (d, $^3J = 4.0$ Hz, 3H, CH_3 , H16), 0.87–0.83 (m, 9H, CH_3 , H14, H15 and H5 or H6), 0.72 (d, $^3J = 6.9$ Hz, 3H, CH_3 , H5 or H6), 0.16 (s, 3H, SiCH_3 , H23 or H24), 0.06 (s, 3H, SiCH_3 , H23 or H24).

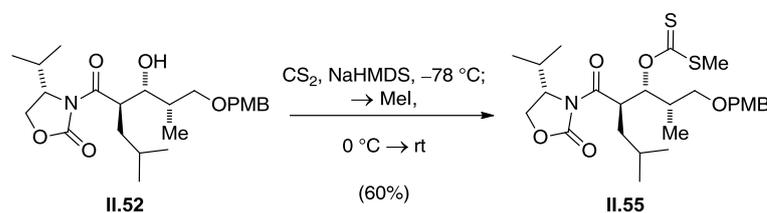


^{13}C NMR (150 MHz, CDCl_3): δ/ppm = 173.9 (CO, C7), 159.2 (Ar- C_q , C21), 153.7 (CO, C1), 130.9 (Ar- C_q , C18), 129.4 (2 x Ar-CH, C19), 113.8 (2 x Ar-CH, C20), 73.7 (CH_2 , C11), 72.7 (CH_2 , C17), 69.6 (CH, C9), 63.1 (CH_2 , C2), 58.8 (CH, C3), 55.4 (OCH_3 , C22), 49.4 (CH, C8), 36.4 (CH, C10), 34.5 (CH_2 , C12), 28.5 (CH, C4), 27.9 (CH, C13), 26.2 (3 x CH_3 , C26), 23.8 (CH_3 , C14 or C15), 22.2 (CH_3 , C14 or C15), 18.5 (C_q , C25), 18.2 (CH_3 , C5 or C6), 14.4 (CH_3 , C5 or C6), 11.7 (CH_3 , C16), -3.8 (SiCH_3 , C23 or C24), -5.2 (SiCH_3 , C23 or C24).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2957 (w), 1856 (w), 1776 (m), 1694 (w), 1612 (w), 1513 (w), 1386 (w), 1263 (m), 1248 (m), 1204 (m), 1090 (m).

HRMS (ESI) calculated for $\text{C}_{30}\text{H}_{51}\text{NO}_6^{28}\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 572.3378, found 572.3380.

Preparation of xanthate II.55



O-((2*S*,3*R*,4*R*)-4-((*S*)-4-Isopropyl-2-oxooxazolidine-3-carbonyl)-1-((4-methoxybenzyl)oxy)-2,6-dimethylheptan-3-yl) *S*-methyl carbonodithioate (II.55). To a magnetically stirred solution of alcohol **II.52** (5.30 g, 12.2 mmol) in carbon disulfide (200 mL) was added dropwise a solution of NaHMDS (1M in THF, 17.0 mmol, 17.0 mL) at -78 °C and the ensuing mixture was stirred at this temperature for 1 h. After dropwise addition of MeI (25.9 g, 183 mmol, 11.4 mL) at -78 °C, the reaction mixture was allowed to warm to 0 °C and was stirred for 3 h

before the ice bath was removed. Then, the reaction was stirred at room temperature for 1 h before carbon disulfide was evaporated *in vacuo*. The residue was dissolved in diethyl ether (1 L) and washed with water (500 mL), aqueous HCl solution (1M, 500 mL) and brine (500 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford crude yellow oil. Subjection of this material to flash column chromatography (1:9→1:4 EtOAc/hexanes, gradient elution) provided 3.88 g (7.38 mmol, 60%) xanthate **II.55** as a yellow oil.

R_f = 0.61, 1:3 EtOAc/hexanes.

[α]_D²⁴ = +70.1 (*c* = 1.0, CH₂Cl₂).

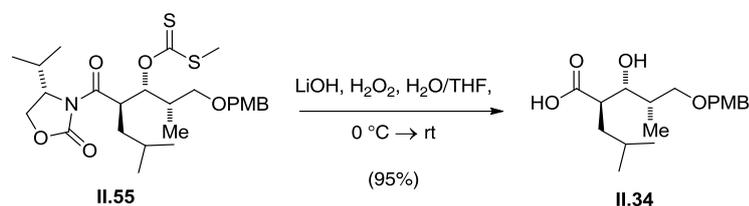
¹H NMR (600 MHz, CDCl₃): δ/ppm = 7.27–7.24 (m, 2H), 6.88–6.84 (m, 2H), 6.33 (dd, ³*J* = 9.1 Hz, ³*J* = 2.4 Hz, 1H), 4.71 (m, 1H), 4.43–4.38 (m, 2H), 4.32 (d, ²*J* = 11.2 Hz, 1H), 4.22–4.18 (m, 2H), 3.80 (s, 3H), 3.37 (dd, ²*J* = 9.2 Hz, ³*J* = 7.1 Hz, 1H), 3.28 (dd, ²*J* = 9.2 Hz, ³*J* = 6.1 Hz, 1H), 2.51 (s, 3H), 2.33–2.21 (m, 2H), 1.83–1.76 (m, 1H), 1.46–1.39 (m, 1H), 1.29–1.22 (m, 1H), 1.08 (d, ³*J* = 7.0 Hz, 3H), 0.90–0.84 (m, 12H).

¹³C NMR (150 MHz, CDCl₃): δ/ppm = 192.3, 173.8, 159.3, 153.9, 130.6, 129.6 (2 x C), 113.8 (2 x C), 84.5, 73.1, 72.4, 63.1, 59.3, 55.4, 42.8, 39.4, 36.8, 28.8, 26.5, 23.8, 22.2, 18.9, 18.5, 14.7, 11.2.

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2960 (w), 2871 (w), 1776 (m), 1735 (m), 1699 (m), 1612 (w), 1512 (m), 1464 (w), 1385 (m), 1371 (m), 1236 (s), 1200 (s), 1092 (m), 1039 (s).

HRMS (ESI) calculated for C₂₆H₃₉O₆N³²S₂Na [M+Na]⁺ 548.2111, found 548.2119.

Preparation of acid **II.34**



(2R,3R,4S)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methylpentanoic acid (II.34). To a magnetically stirred mixture of LiOH (1M in water, 41.4 mmol, 41.4 mL) and H₂O₂ solution (30wt% in water, 82.8 mmol, 9.20 mL) was added dropwise a solution of **II.55** (544 mg, 1.04 mmol) in THF (27.0 mL) at 0 °C and the ensuing mixture was warmed to room temperature. After stirring at room temperature for 19 h, the reaction was extracted with CH₂Cl₂

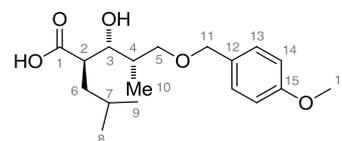
(2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Thus obtained mixture of starting material and free Evans-auxiliary was subjected in a second cycle to reaction conditions listed above. The residual water layer was acidified to pH = 1 using aqueous HCl solution (1M) and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford 320 mg (990 μmol , 95% after 2 reaction cycles) of the free acid **II.34** as a white solid.

$R_f = 0.09$, 1:3 EtOAc/hexanes.

mp: 80–82 °C (CH_2Cl_2).

$[\alpha]_D^{24} = +18.8$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.24\text{--}7.22$ (m, 2H, Ar-H, H13), 6.88–6.86 (m, 2H, Ar-H, H14), 4.46 (d, $^2J = 11.5$ Hz, 1H, CH_2 , H11), 4.42 (d, $^2J = 11.5$ Hz, 1H, CH_2 , H11), 3.89 (dd, $^3J = 7.0$ Hz, $^3J = 3.5$ Hz, 1H, CH, H3), 3.80 (s, 3H, CH_3 , H16), 3.56 (dd, $^2J = 9.2$ Hz, $^3J = 3.9$ Hz, 1H, CH_2 , H5), 3.49 (dd, $^2J = 9.2$ Hz, $^3J = 5.4$ Hz, 1H, CH_2 , H5), 2.66–2.61 (m, 1H, CH, H2), 1.93–1.88 (m, 1H, CH, H4), 1.69–1.58 (m, 2H, CH_2 and CH, H6 and H7), 1.22 (ddd, $^2J = 13.3$ Hz, $^3J = 8.9$ Hz, $^3J = 4.4$ Hz, 1H, CH_2 , H6), 1.00 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H10), 0.92 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H8 or H9), 0.90 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H8 or H9).

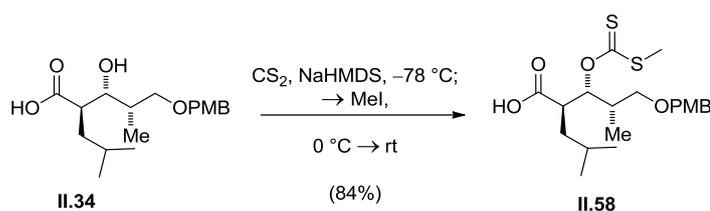


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 179.0$ (CO, C1), 159.5 (Ar- C_q , C15), 129.9 (Ar- C_q , C12), 129.5 (2 x Ar-CH, C13), 114.0 (2 x Ar-CH, C14), 75.3 (CH, C3), 74.6 (CH_2 , C5), 73.4 (CH_2 , C11), 55.4 (OCH_3 , C16), 47.4 (CH, C2), 38.7 (CH_2 , C6), 36.2 (CH, C4), 26.2 (CH, C7), 23.5 (CH_3 , C8 or C9), 21.8 (CH_3 , C8 or C9), 10.8 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2850$ (w), 2390 (w), 1694 (m), 1512 (m), 1246 (s), 1034 (m).

HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{28}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 347.1829, found 347.1832.

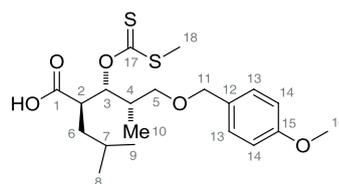
Preparation of acid **II.58**



(2*R*,3*R*,4*S*)-2-Isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((methylthio)carbonothioyl)oxy)pentanoic acid (II.58). To a magnetically stirred solution of acid **II.34** (100 mg, 310 μmol) in carbon disulfide (5.00 mL) was added dropwise a solution of NaHMDS (1M in THF, 860 μmol , 0.860 mL) at $-78\text{ }^\circ\text{C}$ and the ensuing mixture was stirred at this temperature for 1 h. After dropwise addition of MeI (660 mg, 4.65 mmol) at $-78\text{ }^\circ\text{C}$, the reaction was allowed to warm to $0\text{ }^\circ\text{C}$ and was stirred for 3 h before the ice bath was removed. The reaction was stirred at room temperature for an additional 1 h before carbon disulfide was evaporated *in vacuo*. The residue was dissolved in diethyl ether (150 mL) and washed with aqueous HCl solution (1M, 50.0 mL), water (50.0 mL) and brine (50.0 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford crude yellow oil. Subjection of this material to flash column chromatography (1:2 \rightarrow 1:0 EtOAc/hexanes, gradient elution) provided 108 mg (261 μmol , 84%) of a single diastereoisomer of acid **II.58** as a colorless oil.

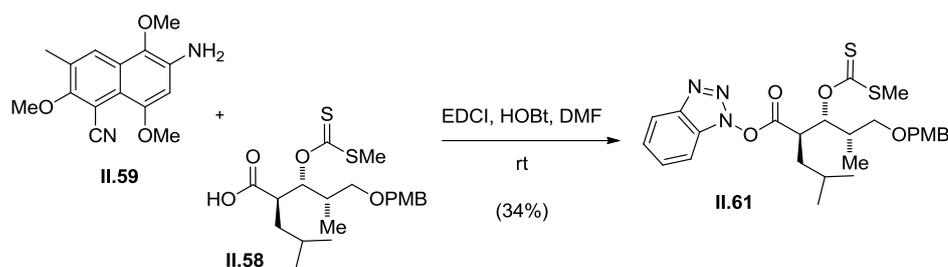
$R_f = 0.2$, 1:2 EtOAc/hexanes.

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.27\text{--}7.24$ (m, 2H, Ar-H, H13), 6.89–6.87 (m, 2H, Ar-H, H14), 6.13 (dd, $^3J = 5.9$ Hz, $^3J = 5.9$ Hz, 1H, CH, H3), 4.47–4.39 (m, 2H, CH_2 , H11), 3.81 (s, 3H, CH_3 , H16), 3.43 (m, 2H, CH_2 , H5), 3.01–2.98 (ddd, $^2J = 10.4$ Hz, $^3J = 5.9$ Hz, $^3J = 4.6$ Hz, 1H, CH_2 , H2), 2.53 (s, 3H, CH_3 , H18), 2.32 (ddt, $^3J = 12.9$ Hz, $^3J = 12.6$ Hz, $^3J = 6.6$ Hz, 1H, CH, H4), 1.70 (ddd, $^2J = 13.6$ Hz, $^3J = 10.2$ Hz, $^3J = 5.1$ Hz, 1H, CH_2 , H6), 1.65–1.55 (m, 1H, CH, H7), 1.29–1.21 (m, 1H, CH_2 , H6), 1.00 (d, $^3J = 6.9$ Hz, 3H, CH_3 , H10), 0.92–0.81 (m, 6H, CH_3 , H8 and H9).



$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 215.9$ (CS, C17), 175.5 (CO, C1), 159.5 (Ar- C_q , C15), 129.7 (Ar- C_q and 2 x Ar-CH, C12, C13), 114.1 (2 x Ar-CH, C14), 84.2 (CH, C3), 73.3 (CH_2 , C11), 72.4 (CH_2 , C5), 55.4 (OCH_3 , C16), 46.4 (CH, C2), 37.7 (CH_2 , C6), 36.8 (CH, C4), 26.2 (CH, C7), 23.4 (CH_3 , C8 or C9), 21.8 (CH_3 , C8 or C9), 18.8 (SCH_3 , C18), 13.0 (CH_3 , C10).

Preparation of HOBt-ester II.61

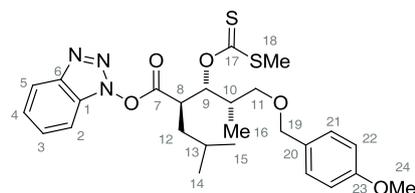


(2*R*,4*S*)-1*H*-Benzo[*d*][1,2,3]triazol-1-yl 2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((methyl thio)carbonothioyl)oxy)pentanoate (II.61). A solution of naphthalene **II.59** (10.0 mg, 41.0 μmol), acid **II.58** (25.5 mg, 62.0 μmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt (12.0 mg, 62.0 μmol) and 1-hydroxybenzotriazole (7.00 mg, 49.0 μmol) in dry DMF (0.5 mL) was stirred for 36 h at room temperature before EtOAc (10 mL) was added. The organic phase was washed with water (3 x 15 mL), aqueous LiCl solution (10wt%, 3 x 15 mL) and brine (2 x 15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Subjection of thus obtained crude material to flash column chromatography (1:4→1:1→1:0 EtOAc/hexanes, gradient elution) provided 14.0 mg (20.9 μmol , 34%) of HOBt-ester **II.61** as a colorless oil.

$R_f = 0.73$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +48.6$ ($c = 0.3$, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 8.06\text{--}8.00$ (m, 1H, Ar-H, H2 or H3 or H4 or H5), 7.53–7.48 (m, 1H, Ar-H, H2 or H3 or H4 or H5), 7.44–7.39 (m, 2H, Ar-H, H2 or H3 or H4 or H5), 7.29–7.26 (m, 2H, Ar-H, H21), 6.87–6.85 (m, 2H, Ar-H, H22), 6.41–6.39 (m, 1H, CH, H9), 4.46 (d, $^2J = 11.4$ Hz, 1H, CH_2 , H19), 4.42 (d, $^2J = 11.4$ Hz, 1H, CH_2 , H19), 3.79 (s, 3H, OCH_3 , H24), 3.55–3.51 (m, 1H, CH, H8), 3.50 (dd, $^2J = 9.4$ Hz, $^3J = 4.9$ Hz, 1H, CH_2 , H11), 3.46 (dd, $^2J = 9.4$ Hz, $^3J = 7.1$ Hz, 1H, CH_2 , H11), 2.59 (s, 3H, SCH_3 , H18), 2.48–2.40 (m, 1H, CH, H10), 1.96–1.82 (m, 2H, CH and CH_2 , H13 and H12), 1.55–1.50 (m, 1H, CH_2 , H12), 1.10 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H16), 1.03 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H14 or H15), 1.01 (d, $^3J = 6.4$ Hz, 3H, CH_3 , H14 or H15).

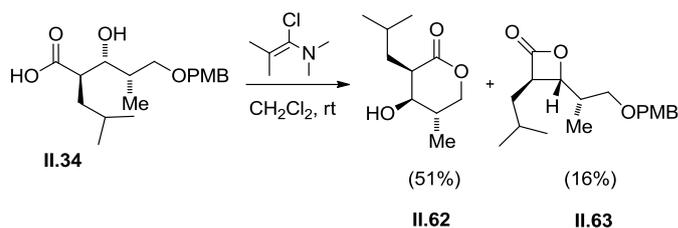


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 216.0$ (CS, C17), 169.3 (CO, C7), 159.4 (Ar- C_q , C23), 143.6 (Ar- C_q , C1 or C6), 130.2 (Ar- C_q , C20), 129.7 (2 x Ar-CH, C21), 128.8 (Ar-CH, C2 or C3 or C4 or C5), 128.7 (Ar- C_q , C1 or C6), 124.9 (Ar-CH, C2 or C3 or C4 or C5), 120.6 (Ar-CH, C2 or C3 or C4 or C5), 113.9 (2 x Ar-CH, C22), 108.6 (Ar-CH, C2 or C3 or C4 or C5), 82.9 (CH, C9), 73.2 (CH_2 , C19), 72.1 (CH_2 , C11), 55.4 (OCH_3 , C24), 44.9 (CH, C8), 38.2 (CH_2 , C12), 37.1 (CH, C10), 26.4 (CH, C13), 23.3 (CH_3 , C14 or C15), 21.8 (CH_3 , C14 or C15), 19.2 (SCH_3 , C18), 12.6 (CH_3 , C16).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2960$ (w), 2925 (w), 2855 (w), 1812 (w), 1612 (w), 1513 (m), 1465 (w), 1369 (w), 1247 (m), 1201 (s), 1173 (w), 1020 (s).

HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{S}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 554.1754, found 554.1757.

Preparation of lactone II.62



(3R,4R,5S)-4-hydroxy-3-isobutyl-5-methyltetrahydro-2H-pyran-2-one (II.62). To a magnetically stirred solution of hydroxyacid **II.34** (34.0 mg, 105 μmol) in dry CH_2Cl_2 (1 mL) was added dropwise Ghosez's reagent (34.0 mg, 252 μmol , 32.0 μL) at 0 °C. The reaction was stirred at this temperature for 15 min, then EtOAc (5 mL) was added and the mixture was warmed to room temperature. After the solvent was removed *in vacuo*, the obtained crude material was subjected to flash column chromatography (1:8 EtOAc/hexanes) providing 14.0 mg (53.8 μmol , 51%) of lactone **II.62** as colorless oil and 5.00 mg (16.3 μmol , 16%) of β -lactone **II.63** as a yellow oil.

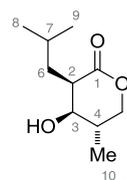
(3R,4R,5S)-4-hydroxy-3-isobutyl-5-methyltetrahydro-2H-pyran-2-one (II.62).

Colorless oil.

$R_f = 0.5$, 1:2 EtOAc/hexanes.

$[\alpha]_D^{21} = -85.6$ ($c = 0.25$, CHCl_3).

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 4.39$ (dd, $^2J = 11.6$ Hz, $^3J = 5.8$ Hz, 1H, CH_2 , H5), 3.89–3.84 (m, 2H, CH and CH_2 , H3 and H5), 2.57 (ddd, $^3J = 7.6$ Hz, $^3J = 6.4$ Hz, $^3J = 4.0$ Hz, 1H, CH, H2), 2.17–2.13 (m, 1H, CH, H4), 1.85–1.73 (m, 2H, CH and CH_2 , H7 and H6), 1.51–1.47 (m, 1H, CH_2 , H6), 1.10 (d, $^3J = 7.1$ Hz, 3H, CH_3 , H10), 0.96 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H8 or H9), 0.93 (d, $^3J = 6.4$ Hz, 3H, CH_3 , H8 or H9).



$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta/\text{ppm} = 173.6$ (CO, C1), 73.1 (COH, C3), 70.2 (CH_2 , C5), 41.5 (CH, C2), 36.9 (CH, C4), 34.5 (CH_2 , C6), 25.2 (CH, C7), 23.1 (CH_3 , C8 or C9), 22.3 (CH_3 , C8 or C9), 15.3 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3470$ (w), 3020 (w), 2960 (w), 1733 (m), 1388 (w), 1214 (m), 1164 (w), 1110 (w).

HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$ 187.1329, found 187.1334.

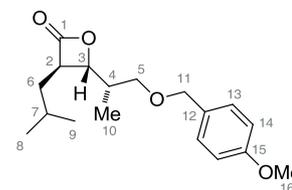
(3*R*,4*R*)-4-((*S*)-1-Hydroxypropan-2-yl)-3-isobutyloxetan-2-one (II.63).

Yellow oil.

$R_f = 0.61$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +20.5$ ($c = 1.0$, CH_2Cl_2).

$^1\text{H NMR}$ (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.24\text{--}7.21$ (m, 2H, Ar-H, H13), 6.90–6.86 (m, 2H, Ar-H, H14), 4.42–4.38 (m, 2H, CH_2 , H11), 4.13 (dd, $^3J = 7.4$ Hz, $^3J = 4.0$ Hz, 1H, CH, H3), 3.81 (s, 3H, OCH_3 , H16) 3.46–3.42 (m, 2H, CH and CH_2 , H2 and H5), 3.32

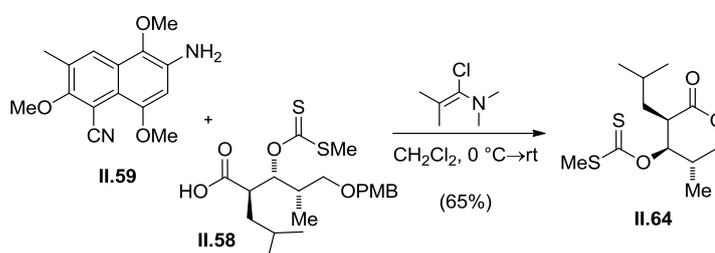


(dd, $^2J = 9.4$ Hz, $^3J = 7.6$ Hz, 1H, CH_2 , H5), 2.14–2.07 (m, 1H, CH, H4), 1.71–1.66 (m, 2H, CH and CH_2 , H7 and H6), 1.57–1.52 (m, 1H, CH_2 , H6), 1.04 (d, $^3J = 6.8$ Hz, 3H, CH_3 , H10), 0.88 (d, $^3J = 6.4$ Hz, 3H, CH_3 , H8 or H9), 0.86 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H8 or H9).

$^{13}\text{C NMR}$ (150 MHz, CDCl_3): $\delta/\text{ppm} = 172.3$ (CO, C1), 159.5 (Ar- C_q , C15), 130.1 (Ar- C_q , C12), 129.6 (2 x Ar-CH, C13), 114.0 (2 x Ar-CH, C14), 80.9 (CH, C3), 73.3 (CH_2 , C11), 71.7 (CH_2 , C5), 55.4 (OCH_3 , C16), 53.0 (CH, C2), 37.8 (CH, C4), 37.5 (CH_2 , C6), 26.2 (CH, C7), 22.6 (CH_3 , C8 or C9), 22.4 (CH_3 , C8 or C9), 12.5 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2957$ (w), 2932 (w), 2870 (w), 1800 (s), 1611 (m), 1512 (s), 1464 (m), 1360 (w), 1301 (w), 1246 (s), 1172 (m), 1112 (s), 1086 (s).

HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 329.1729, found 329.1725.

Preparation of lactone II.64

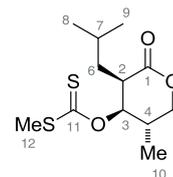
***O*-((3*R*,4*R*,5*S*)-3-Isobutyl-5-methyl-2-oxotetrahydro-2*H*-pyran-4-yl) *S*-methyl carbonodithioate (II.64).** To a magnetically stirred solution of xanthate **II.58** (25.0 mg, 62.0 μmol) in dry CH_2Cl_2 (2 mL) was added dropwise Ghosez's reagent (9.00 mg, 66.0 μmol , 9.00 μL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then a solution of naphthalene **II.59** (10.0 mg, 41.0 μmol) in dry CH_2Cl_2 (1 mL) was added and the reaction was warmed to room temperature. After the reaction was stirred for 12 h, CH_2Cl_2 (10 mL) was added and the organic solution was

washed with aqueous saturated NH_4Cl solution (10 mL) and water (10 mL). The CH_2Cl_2 phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:8→1:4→1:2→1:1 EtOAc/hexanes, gradient elution) providing 11.0 mg (40.0 μmol , 65%) of lactone **II.64** as a colorless oil.

$R_f = 0.78$, 1:2 EtOAc/hexanes.

$[\alpha]_D^{21} = -70.7$ ($c = 0.5$, CHCl_3).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 5.74$ (dd, $^3J = 3.3$ Hz, $^3J = 2.5$ Hz, 1H, CH, H3), 4.40 (dd, $^2J = 11.8$ Hz, $^3J = 6.4$ Hz, 1H, CH_2 , H5), 3.90 (dd, $^2J = 11.8$ Hz, $^3J = 9.1$ Hz, 1H, CH_2 , H5), 2.77 (ddd, $^3J = 8.0$ Hz, $^3J = 6.0$ Hz, $^3J = 3.5$ Hz, 1H, CH, H2), 2.53 (s, 3H, SMe, H12), 2.47–2.39 (m, 1H, CH, H4), 1.81 (ddd, $^2J = 14.3$ Hz, $^3J = 8.5$ Hz, $^3J = 6.0$ Hz, 1H, CH_2 , H6), 1.74–1.65 (m, 1H, CH, H7), 1.42 (ddd, $^2J = 14.0$ Hz, $^3J = 7.9$ Hz, $^3J = 5.9$ Hz, 1H, CH_2 , H6), 1.19 (d, $^3J = 7.2$ Hz, 3H, CH_3 , H10), 0.96–0.88 (m, 6H, CH_3 , H8 and H9).

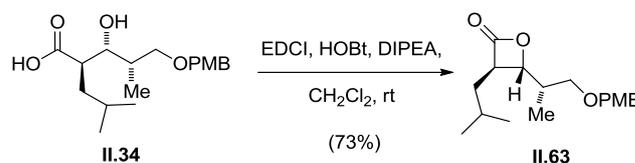


^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 215.2$ (CS, C11), 172.3 (CO, C1), 83.2 (CH, C3), 70.0 (CH_2 , C5), 39.5 (CH, C2), 34.6 (CH_2 , C6), 33.9 (CH, C4), 25.1 (CH, C7), 23.1 (CH_3 , C8 or C9), 22.0 (CH_3 , C8 or C9), 19.0 (SCH₃, C12), 14.8 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2958$ (w), 1751 (s), 1467 (w), 1382 (w), 1202 (s), 1154 (w), 1093 (w), 1055 (s).

HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{17}\text{O}_2$ $[\text{M}-\text{OCSSMe}]^+$ 169.1229, found 169.1223.

Preparation of β -lactone **II.63**



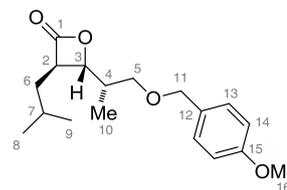
(3R,4R)-3-Isobutyl-4-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)oxetan-2-one (II.63). A solution of hydroxyacid **II.34** (320 mg, 986 μmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (227 mg, 1.18 mmol) and 1-hydroxybenzotriazole (196 mg, 1.48 mmol) in dry CH_2Cl_2 (32 mL) was stirred for 12 h at room temperature before diisopropylethylamine (141 mg, 1.09 mmol, 190 μL) was added dropwise. The mixture was stirred for an additional 8 h at room temperature, then EtOAc (100 mL) was added and the organic phase was washed with aqueous saturated NH_4Cl solution (100 mL) and brine (100 mL). After being dried over Na_2SO_4 , filtered and concentrated *in vacuo*, the obtained crude

material was subjected to flash column chromatography (1:9→1:0 EtOAc/hexanes, gradient elution) providing 220 mg (718 μmol , 73%) of β -lactone **II.63** as a yellow oil.

$R_f = 0.61$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{24} = +20.5$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 7.24\text{--}7.21$ (m, 2H, Ar-H, H13), 6.90–6.86 (m, 2H, Ar-H, H14), 4.42–4.38 (m, 2H, CH_2 , H11), 4.13 (dd, $^3J = 7.4$ Hz, $^3J = 4.0$ Hz, 1H, CH, H3), 3.81 (s, 3H, OCH_3 , H16) 3.46–3.42 (m, 2H, CH and CH_2 , H2 and H5), 3.32 (dd, $^2J = 9.4$ Hz, $^3J = 7.6$ Hz, 1H, CH_2 , H5), 2.14–2.07 (m, 1H, CH, H4), 1.71–1.66 (m, 2H, CH and CH_2 , H7 and H6), 1.57–1.52 (m, 1H, CH_2 , H6), 1.04 (d, $^3J = 6.8$ Hz, 3H, CH_3 , H10), 0.88 (d, $^3J = 6.4$ Hz, 3H, CH_3 , H8 or H9), 0.86 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H8 or H9).

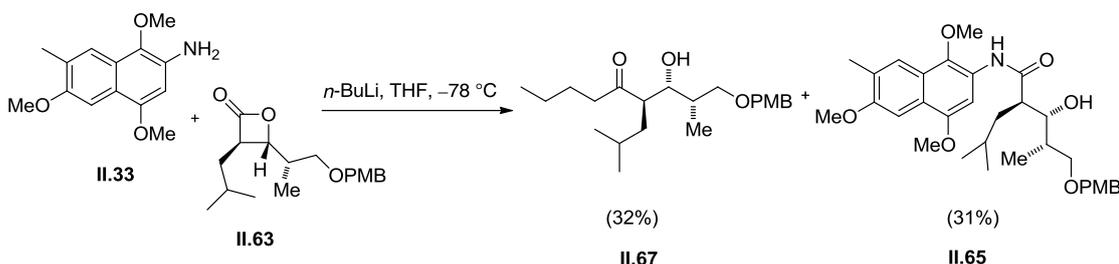


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 172.3$ (CO, C1), 159.5 (Ar- C_q , C15), 130.1 (Ar- C_q , C12), 129.6 (2 x Ar-CH, C13), 114.0 (2 x Ar-CH, C14), 80.9 (CH, C3), 73.3 (CH_2 , C11), 71.7 (CH_2 , C5), 55.4 (OCH_3 , C16), 53.0 (CH, C2), 37.8 (CH, C4), 37.5 (CH_2 , C6), 26.2 (CH, C7), 22.6 (CH_3 , C8 or C9), 22.4 (CH_3 , C8 or C9), 12.5 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2957$ (w), 2932 (w), 2870 (w), 1800 (s), 1611 (m), 1512 (s), 1464 (m), 1360 (w), 1301 (w), 1246 (s), 1172 (m), 1112 (s), 1086 (s).

HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 329.1729, found 329.1725.

Preparation of ketone **II.67** and amide **II.65**



(2*S*,3*R*,4*R*)-3-Hydroxy-4-isobutyl-1-((4-methoxybenzyloxy)-2-methylnonan-5-one (**II.67**).

To a magnetically stirred solution of naphthalene **II.33** (12.0 mg, 49.0 μmol) in dry THF (0.5 mL) was added dropwise a solution of *n*-BuLi (2.4M in hexanes, 35.0 μL , 84.0 μmol) at -78 °C. The reaction was stirred for 20 min before a solution of β -lactone **II.63** (16.0 mg, 52.0 μmol) in dry THF (0.5 mL) was added dropwise. After the mixture was stirred at -78 °C for 1 h, then a mixture of aqueous pH-7-phosphate buffer (0.1M, 5 mL) and *i*-PrOH (5 mL) was

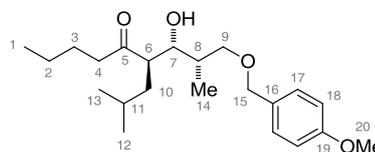
added in one portion. The biphasic mixture was warmed to room temperature, the layers were separated and the aqueous layer was extracted with EtOAc (1 x 15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:9→1:6→1:4→1:1→1:0 EtOAc/hexanes, gradient elution) providing 6.00 mg (16.5 μmol, 32%) of ketone **II.67** as yellow oil and 8.40 mg (15.2 μmol, 31%) of amide **II.65** as a yellow oil.

(2*S*,3*R*,4*R*)-3-Hydroxy-4-isobutyl-1-((4-methoxybenzyl)oxy)-2-methylnonan-5-one (II.67).

R_f = 0.8, 1:3 EtOAc/hexanes.

[α]_D²⁴ = +2.18 (*c* = 0.28, CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ/ppm = 7.23–7.21 (m, 2H, Ar-H, H17), 6.88–6.86 (m, 2H, Ar-H, H18), 4.43 (d, ²*J* = 11.5 Hz, 1H, CH₂, H15), 4.38 (d, ²*J* = 11.5 Hz, 1H, CH₂, H15), 3.81–3.78 (m, 4H, CH and CH₃, H7 and H20), 3.49 (dd, ²*J* = 9.2 Hz, ³*J* = 3.9 Hz, 1H, CH₂, H9), 3.43 (dd, ²*J* = 9.2 Hz, ³*J* = 5.5 Hz, 1H, CH₂, H9), 3.04 (d, ³*J* = 4.9 Hz, 1H, OH), 2.79 (ddd, ³*J* = 9.4 Hz, ³*J* = 7.9 Hz, ³*J* = 5.0 Hz, 1H, CH, H6), 2.54–2.48 (m, 1H, CH₂, H4), 2.44–2.39 (m, 1H, CH₂, H4), 1.87–1.79 (m, 1H, CH, H8), 1.55–1.41 (m, 4H, CH₂ and CH, H3, H10 and H11), 1.31–1.23 (m, 2H, CH₂, H2), 1.18–1.14 (m, 1H, CH₂, H10), 0.97 (d, ³*J* = 7.0 Hz, 3H, CH₃, H14), 0.92–0.83 (m, 9H, CH₃, H1, H12 and H13).



¹³C NMR (100 MHz, CDCl₃): δ/ppm = 216.5 (CO, C5), 159.4 (Ar-C_q, C19), 130.2 (Ar-C_q, C16), 129.5 (2 x Ar-CH, C17), 114.0 (2 x Ar-CH, C18), 76.1 (CH, C7), 74.8 (CH₂, C9), 73.3 (CH₂, C15), 55.4 (OCH₃, C20), 52.4 (CH, C6), 44.5 (CH₂, C4), 38.5 (CH₂, C10), 36.0 (CH, C8), 26.1 (CH, C11), 25.3 (CH₂, C3), 23.6 (CH₃, C12 or C13), 22.4 (CH₂, C2), 22.2 (CH₃, C12 or C13), 14.1 (CH₃, C1), 10.9 (CH₃, C14).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3482 (w), 2959 (w), 1708 (w), 1612 (w), 1514 (w), 1466 (w), 1368 (w), 1265 (m), 1248 (m), 1173 (w), 1088 (w).

HRMS (ESI) calculated for C₂₂H₃₆O₄Na [M+Na]⁺ 387.2506, found 387.2508.

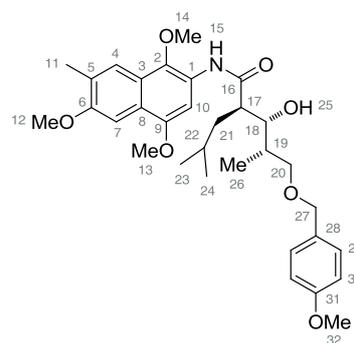
(2*R*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-*N*-(1,4,6-trimethoxy-7-methylnaphthalen-2-yl)pentanamide (II.65).

Yellow oil.

R_f = 0.24, 1:3 EtOAc/hexanes.

$[\alpha]_D^{21} = +1.5$ ($c = 1.0$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.49$ (s, 1H, NH, H15), 7.93 (s, 1H, Ar-H, H10), 7.67 (q, $^4J = 0.7$ Hz, 1H, Ar-H, H4), 7.42 (s, 1H, Ar-H, H7), 7.27–7.19 (m, 2H, Ar-H, H29), 6.88–6.81 (m, 2H, Ar-H, H30), 4.52 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H27), 4.42 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H27), 4.01 (s, 3H, OCH_3 , H13), 3.94 (s, 3H, OCH_3 , H12), 3.82 (s, 3H, OCH_3 , H14), 3.78 (s, 3H, OCH_3 , H32), 3.78–3.76 (m, 1H, CH, H18), 3.53 (dd, $^2J = 9.3$ Hz, $^3J = 3.6$ Hz, 1H, CH_2 , H20), 3.47–3.40



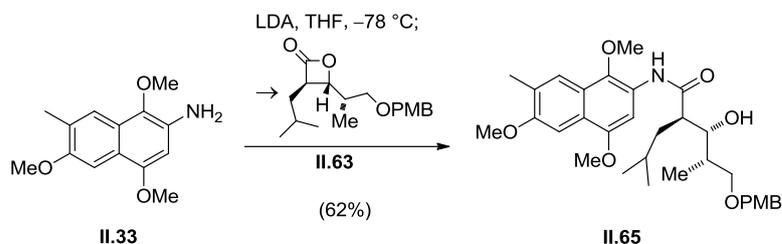
(m, 2H, CH_2 and OH, H20 and H25), 2.74–2.69 (m, 1H, CH, H17), 2.39 (s, 3H, CH_3 , H11), 2.04–1.85 (m, 2H, CH and CH_2 , H19 and H21), 1.76–1.64 (m, 1H, CH, H22), 1.37 (ddd, $^2J = 13.6$ Hz, $^3J = 9.0$ Hz, $^3J = 4.8$ Hz, 1H, CH_2 , H21), 1.03 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H26), 0.97 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H23 or H24), 0.93 (d, $^3J = 6.6$ Hz, 3H, CH_3 , H23 or H24).

^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 174.1$ (CO, C16), 159.4 (Ar- C_q , C31), 156.1 (Ar- C_q , C6), 150.9 (Ar- C_q , C9), 136.9 (Ar- C_q , C2), 129.9 (Ar- C_q , C3 or C5), 129.6 (2 x Ar-CH, C29), 129.5 (Ar- C_q , C28), 125.7 (Ar- C_q , C1), 122.9 (Ar- C_q , C3 or C5), 122.7 (Ar- C_q , C8), 122.3 (Ar-CH, C4), 113.9 (2 x Ar-CH, C30), 99.9 (Ar-CH, C7), 98.8 (Ar-CH, C10), 76.6 (CH, C18), 74.7 (CH_2 , C20), 73.4 (CH_2 , C27), 61.8 (OCH_3 , C14), 55.9 (OCH_3 , C13), 55.5 (OCH_3 , C12), 55.4 (OCH_3 , C32), 49.6 (CH, C17), 39.7 (CH_2 , C21), 37.3 (CH, C19), 26.1 (CH, C22), 23.6 (CH_3 , C23 or C24), 22.2 (CH_3 , C23 or C24), 17.3 (CH_3 , C11), 12.4 (CH_3 , C26).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3318$ (w), 2956 (w), 1658 (m), 1611 (s), 1502 (s), 1464 (m), 1410 (m), 1373 (m), 1330 (s), 1246 (s), 1209 (s).

HRMS (ESI) calculated for $\text{C}_{32}\text{H}_{44}\text{O}_7\text{N}$ $[\text{M}+\text{H}]^+$ 554.3112, found 554.3113.

Preparation of amide II.65



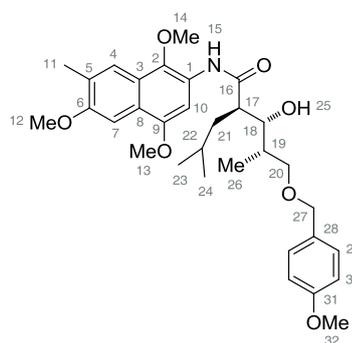
(2*R*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-*N*-(1,4,6-trimethoxy-7-methylnaphthalen-2-yl)pentanamide (II.65). To a magnetically stirred solution of freshly

distilled diisopropylamine (516 mg, 550 μL , 3.99 mmol) in dry THF (32 mL) was added *n*-BuLi (2.4M in hexanes, 1.47 mL, 3.68 mmol), and the LDA solution (0.2M) was stirred for 10 min at room temperature. To a solution of amine **II.33** (15.0 mg, 61.0 μmol) in dry THF (2 mL) was added dropwise the above prepared LDA solution (0.2M, 0.65 mL, 130 μmol) at $-78\text{ }^\circ\text{C}$. After the reaction was stirred for 30 min at $-78\text{ }^\circ\text{C}$, a solution of lactone **II.63** (28.0 mg, 91.0 μmol) in dry THF (2 mL) was added and the mixture was stirred for an additional 1 h at the same temperature. Then, the reaction was warmed to room temperature and stirred for another 1 h before it was quenched by an addition of aqueous pH-7-phosphate buffer (0.1M, 5 mL) and brine (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:5 \rightarrow 1:3 \rightarrow 1:0 EtOAc/hexanes, gradient elution) providing 21.0 mg (37.9 μmol , 62%) of amide **II.65** as a yellow oil.

$R_f = 0.24$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{21} = +1.5$ ($c = 1.0$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 8.49$ (s, 1H, NH, H15), 7.93 (s, 1H, Ar-H, H10), 7.67 (q, $^4J = 0.7$ Hz, 1H, Ar-H, H4), 7.42 (s, 1H, Ar-H, H7), 7.27–7.19 (m, 2H, Ar-H, H29), 6.88–6.81 (m, 2H, Ar-H, H30), 4.52 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H27), 4.42 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H27), 4.01 (s, 3H, OCH_3 , H13), 3.94 (s, 3H, OCH_3 , H12), 3.82 (s, 3H, OCH_3 , H14), 3.78 (s, 3H, OCH_3 , H32), 3.78–3.76 (m, 1H, CH, H18), 3.53 (dd, $^2J = 9.3$ Hz, $^3J = 3.6$ Hz, 1H, CH_2 , H20), 3.47–3.40 (m, 2H, CH_2 and OH, H20 and H25), 2.74–2.69 (m, 1H, CH, H17), 2.39 (s, 3H, CH_3 , H11), 2.04–1.85 (m, 2H, CH and CH_2 , H19 and H21), 1.76–1.64 (m, 1H, CH, H22), 1.37 (ddd, $^2J = 13.6$ Hz, $^3J = 9.0$ Hz, $^3J = 4.8$ Hz, 1H, CH_2 , H21), 1.03 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H26), 0.97 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H23 or H24), 0.93 (d, $^3J = 6.6$ Hz, 3H, CH_3 , H23 or H24).

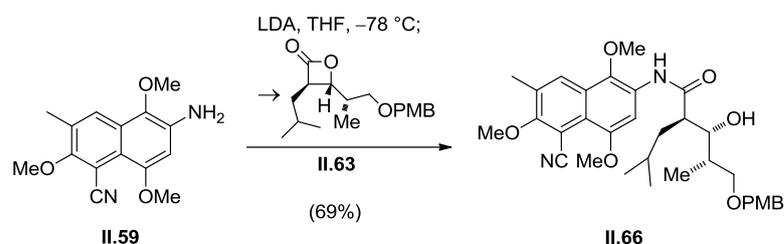


^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 174.1$ (CO, C16), 159.4 (Ar- C_q , C31), 156.1 (Ar- C_q , C6), 150.9 (Ar- C_q , C9), 136.9 (Ar- C_q , C2), 129.9 (Ar- C_q , C3 or C5), 129.6 (2 x Ar-CH, C29), 129.5 (Ar- C_q , 28), 125.7 (Ar- C_q , C1), 122.9 (Ar- C_q , C3 or C5), 122.7 (Ar- C_q , C8), 122.3 (Ar-CH, C4), 113.9 (2 x Ar-CH, C30), 99.9 (Ar-CH, C7), 98.8 (Ar-CH, C10), 76.6 (CH, C18), 74.7 (CH_2 , C20), 73.4 (CH_2 , C27), 61.8 (OCH_3 , C14), 55.9 (OCH_3 , C13), 55.5 (OCH_3 , C12), 55.4 (OCH_3 , C32), 49.6 (CH, C17), 39.7 (CH_2 , C21), 37.3 (CH, C19), 26.1 (CH, C22), 23.6 (CH_3 , C23 or C24), 22.2 (CH_3 , C23 or C24), 17.3 (CH_3 , C11), 12.4 (CH_3 , C26).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3318 (w), 2956 (w), 1658 (m), 1611 (s), 1502 (s), 1464 (m), 1410 (m), 1373 (m) 1330 (s), 1246 (s), 1209 (s).

HRMS (ESI) calculated for $\text{C}_{32}\text{H}_{44}\text{O}_7\text{N}$ $[\text{M}+\text{H}]^+$ 554.3112, found 554.3113.

Preparation of amide **II.66**

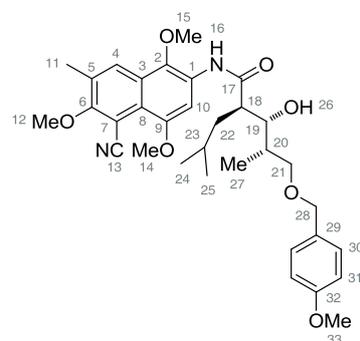


(2R,3R,4S)-3-Hydroxy-2-isobutyl-N-(5-isocyano-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)-5-((4-methoxybenzyl)oxy)-4-methylpentanamide (II.66). To a magnetically stirred solution of freshly distilled diisopropylamine (516 mg, 550 μL , 3.99 mmol) in dry THF (32 mL) was added *n*-BuLi (2.4M in hexanes, 1.47 mL, 3.68 mmol), and the LDA solution (0.2M) was stirred for 10 min at room temperature. To a solution of amine **II.59** (13.0 mg, 47.9 μmol) in dry THF (1 mL) was added dropwise the above prepared LDA solution (0.2M, 0.5 mL, 101 μmol) at -78°C . After the reaction was stirred for 30 min at -78°C , a solution of lactone **II.63** (22.0 mg, 71.9 μmol) in dry THF (1 mL) was added and the mixture was stirred for an additional 2 h at the same temperature before being warmed to room temperature and quenched by an addition of a mixture of aqueous pH-7-phosphate buffer (0.1M, 2 mL), *i*-PrOH (2 mL) and brine (5 mL). Then, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:5 \rightarrow 1:2 \rightarrow 1:0 EtOAc/hexanes, gradient elution) providing 19.0 mg (32.9 μmol , 69%) of amide **II.66** as a yellow oil.

R_f = 0.38, 1:2 EtOAc/hexanes.

$[\alpha]_D^{24} = +9.0$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (400 MHz, CDCl_3): δ/ppm = 8.62 (s, 1H, NH, H16), 8.13 (s, 1H, Ar-H, H10), 7.92 (q, $^4J = 1.0$ Hz, 1H, Ar-H, H4), 7.24–7.21 (m, 2H, Ar-H, H30), 6.85–6.83 (m, 2H, Ar-H, H31), 4.51 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H28), 4.41 (d, $^2J = 11.6$ Hz, 1H, CH_2 , H28), 4.05 (s, 3H, OCH_3 , H12), 4.03 (s, 3H, OCH_3 , H14), 3.85–3.80 (m,



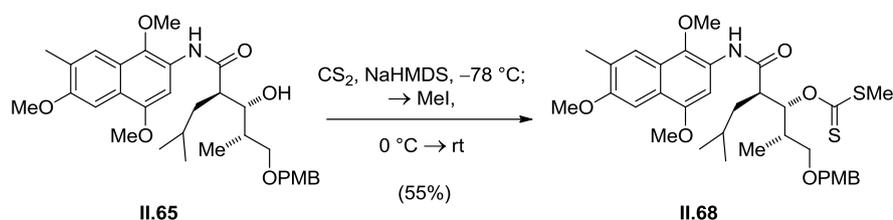
^1H , CH, H19), 3.79 (s, 3H, OCH_3 , H15 or H333), 3.79 (s, 3H, OCH_3 , H15 or H33), 3.57 (dd, $^2J = 9.3$ Hz, $^3J = 3.4$ Hz, 1H, CH_2 , H21), 3.46 (dd, $^2J = 9.3$ Hz, $^3J = 5.9$ Hz, 1H, CH_2 , H21), 3.37 (d, $^3J = 4.6$ Hz, 1H, OH, H26), 2.72–2.67 (m, 1H, CH, H18), 2.47 (d, $^4J = 0.9$ Hz, 3H, CH_3 , H11), 2.00–1.93 (m, 1H, CH, H20), 1.95–1.85 (m, 1H, CH_2 , H22), 1.74–1.65 (m, 1H, CH, H23), 1.35 (ddd, $^2J = 13.7$ Hz, $^3J = 9.1$ Hz, $^3J = 4.9$ Hz, 1H, CH_2 , H22), 1.04 (d, $^3J = 7.0$ Hz, 3H, CH_3 , H27), 0.97 (d, $^3J = 6.5$ Hz, 3H, CH_3 , H24 or H25), 0.93 (d, $^3J = 6.6$ Hz, 3H, CH_3 , H24 or H25).

^{13}C NMR (100 MHz, CDCl_3): $\delta/\text{ppm} = 174.3$ (CO, C17), 163.1 (Ar- C_q , C6), 159.5 (Ar- C_q , C32), 151.1 (Ar- C_q , C9), 136.6 (Ar- C_q , C2), 132.1 (C_q , C3 or C5 or C13), 129.8 (Ar- C_q , C29), 129.6 (2 x Ar-CH, C30), 128.7 (Ar- C_q , C1), 127.9 (Ar-CH, C4), 125.2 (C_q , C3 or C5 or C13), 120.6 (Ar- C_q , C8), 116.8 (C_q , C3 or C5 or C13), 114.0 (2 x Ar-CH, C31), 101.5 (Ar-CH, C10), 99.8 (Ar- C_q , C7), 76.6 (CH, C19), 74.9 (CH_2 , C21), 73.4 (CH_2 , C28), 62.0 (OCH_3 , C15 or C23), 61.9 (OCH_3 , C12), 56.1 (OCH_3 , C14), 55.4 (OCH_3 , C15 or C23), 49.9 (CH, C18), 39.6 (CH_2 , C22), 37.1 (CH, C20), 26.1 (CH, C23), 23.6 (CH_3 , C24 or C25), 22.2 (CH_3 , C24 or C25), 17.0 (CH_3 , C11), 12.1 (CH_3 , C27).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2984$ (w), 1737 (s), 1447 (w), 1372 (m), 1230 (s), 1098 (w), 1043 (s).

HRMS (ESI) calculated for $\text{C}_{33}\text{H}_{43}\text{O}_7\text{N}_2$ $[\text{M}+\text{H}]^+$ 579.3065, found 579.3070.

Preparation of xanthate II.68



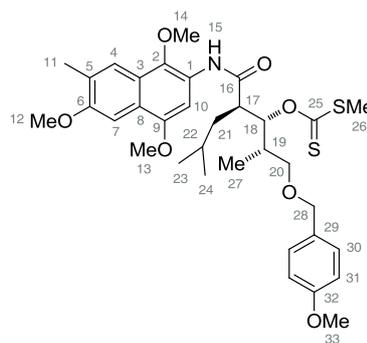
***O*-((2*S*,3*R*,4*R*)-1-((4-Methoxybenzyl)oxy)-2,6-dimethyl-4-((1,4,6-trimethoxy-7-methylnaphthalen-2-yl)carbamoyl)heptan-3-yl) *S*-methyl carbonodithioate (**II.68**). To a magnetically stirred solution of alcohol **II.65** (129 mg, 233 μmol) in carbon disulfide (5.5 mL) was added dropwise a solution of NaHMDS (1M in THF, 956 μmol , 0.960 mL) at -78 °C and the ensuing mixture was stirred at this temperature for 1 h. After dropwise addition of MeI (728 mg, 5.13 mmol, 320 μL) at -78 °C, the reaction mixture was allowed to warm to 0 °C and was stirred for 3 h before the ice bath was removed. The reaction was stirred at room temperature for 30 min before carbon disulfide was evaporated *in vacuo*. Thus obtained residue was dissolved in EtOAc (50 mL) and washed with aqueous HCl solution (1M, 30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated**

in vacuo to afford crude yellow oil. Subjection of this material to flash column chromatography (1:7→1:5→1:3→1:0 EtOAc/hexanes, gradient elution) provided 82.4 mg (128 μmol , 55%) of xanthate **II.68** as a yellow oil.

$R_f = 0.45$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{23} = +11.0$ ($c = 0.65$, CHCl_3).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 8.52$ (s, 1H, NH, H15), 7.93 (s, 1H, Ar-H, H10), 7.67 (q, $^4J = 0.9$ Hz, 1H, Ar-H, H4), 7.43 (s, 1H, Ar-H, H7), 7.15–7.13 (m, 2H, Ar-H, H30), 6.72–6.70 (m, 2H, Ar-H, H31), 6.18 (dd, $^3J = 7.4$ Hz, $^3J = 4.4$ Hz, 1H, CH, H18), 4.42 (d, $^2J = 11.4$ Hz, 1H, CH_2 , H28), 4.37 (d, $^2J = 11.4$ Hz, 1H, CH_2 , H28), 3.99 (s, 3H, OCH_3 , H13), 3.95 (s, 3H, OCH_3 , H12), 3.79 (s, 3H, OCH_3 , H14), 3.70 (s, 3H, OCH_3 , H33), 3.55 (dd, $^2J = 9.4$ Hz, $^3J = 4.4$ Hz, 1H, CH_2 , H20), 3.42 (dd, $^2J = 9.4$ Hz, $^3J = 6.0$ Hz, 1H, CH_2 , H20), 3.15–3.12 (m, 1H, CH, H17), 2.57 (s, 3H, SCH_3 , H26), 2.41–2.35 (m, 1H, CH, H19), 2.39 (d, $^4J = 0.6$ Hz, 3H, CH_3 , H11), 1.87 (ddd, $^2J = 13.6$ Hz, $^3J = 10.2$ Hz, $^3J = 5.0$ Hz, 1H, CH_2 , H21), 1.75–1.66 (m, 1H, CH, H22), 1.39–1.33 (m, 1H, CH_2 , H21), 1.05 (d, $^3J = 6.9$ Hz, 3H, CH_3 , H27), 0.94–0.88 (m, 6H, CH_3 , H23 and H24).

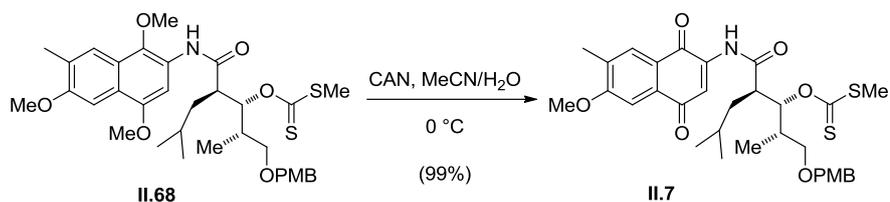


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 216.7$ (CS, C25), 170.3 (CO, C16), 159.2 (Ar- C_q , C32), 156.2 (Ar- C_q , C6), 150.9 (Ar- C_q , C9), 136.9 (Ar- C_q , C2), 130.2 (Ar- C_q , C5), 129.5 (2 x Ar-CH, C30), 129.4 (Ar- C_q , C29), 125.9 (Ar- C_q , C1), 122.9 (Ar- C_q , C3 or C8), 122.8 (Ar- C_q , C3 or C8), 122.3 (Ar- C_q , C4), 113.8 (2 x Ar-CH, C31), 99.9 (Ar-CH, C7), 98.9 (Ar-CH, C10), 85.9 (CH, C18), 73.1 (CH_2 , C28), 72.2 (CH_2 , C20), 61.8 (OCH_3 , C14), 55.9 (OCH_3 , C13), 55.5 (OCH_3 , C12), 55.3 (OCH_3 , C33), 49.1 (CH, C17), 37.5 (CH_2 , C21), 36.6 (CH, C19), 26.2 (CH, C22), 23.5 (CH_3 , C23 or C24), 22.0 (CH_3 , C23 or C24), 19.3 (SCH_3 , C26), 17.3 (CH_3 , C11), 13.9 (CH_3 , C27).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3334$ (w), 2955 (m), 1699 (m), 1612 (s), 1514 (s), 1502 (s), 1465 (m), 1410 (w), 1374 (w), 1330 (m), 1247 (s), 1200 (s), 1052 (s).

HRMS (ESI) calculated for $\text{C}_{34}\text{H}_{46}\text{O}_7\text{NS}_2$ $[\text{M}+\text{H}]^+$ 644.2710, found 644.2703.

Preparation of naphthoquinone II.7

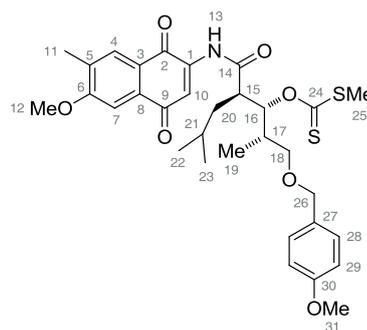


(2*R*,3*R*,4*S*)-*N*-(6-methoxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-[(4-methoxyphenyl) methoxy]-4-methyl-2-(2-methylpropyl)-3-[(methylsulfanyl)methanethioyl]oxy pentanamide (II.7). To a magnetically stirred solution of hydroquinone **II.68** (10.0 mg, 15.5 μmol) in MeCN (0.7 mL) and water (20.0 μL) was added dropwise a solution of ceric ammonium nitrate (25.0 mg, 44.9 μmol) in MeCN/water (1:1, 0.2 mL) at 0 °C. The ensuing mixture was stirred at this temperature for 25 min before EtOAc (10 mL) was added and the solution was washed with water, 10 mL), saturated aqueous NaHCO_3 solution (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford crude yellow oil. Subjection of this material to a quick flash column chromatography (1:6 \rightarrow 1:3 \rightarrow 1:1 EtOAc/hexanes, gradient elution) provided 9.5 mg (15.4 μmol , 99%) of naphthoquinone **II.7** as a yellow oil.

$R_f = 0.36$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{25} = +12.5$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (400 MHz, CDCl_3): $\delta/\text{ppm} = 9.27$ (s, 1H, NH, H13), 7.87 (q, $^4J = 0.8$ Hz, 1H, Ar-H, H4), 7.74 (s, 1H, CH, H10), 7.45 (s, 1H, Ar-H, H7), 7.26–7.23 (m, 2H, Ar-H, H28), 6.81–6.78 (m, 2H, Ar-H, H29), 6.08 (dd, $^3J = 8.0$ Hz, $^3J = 4.0$ Hz, 1H, CH, H16), 4.56 (d, $^2J = 11.7$ Hz, 1H, CH_2 , H26), 4.43 (d, $^2J = 11.7$ Hz, 1H, CH_2 , H26), 3.99 (s, 3H, OCH_3 , H12), 3.73 (s, 3H, OCH_3 , H31), 3.48 (dd, $^2J = 9.5$ Hz, $^3J = 4.1$ Hz, 1H, CH_2 , H18), 3.39 (dd, $^2J = 9.5$ Hz, $^3J = 6.7$ Hz, 1H, CH_2 , H18), 3.17 (ddd, $^3J = 9.2$ Hz, $^3J = 4.5$ Hz, $^3J = 4.5$ Hz, 1H, CH, H15), 2.58 (s, 3H, SCH_3 , H25), 2.31 (d, $^4J = 0.5$ Hz, 3H, CH_3 , H11), 2.31–2.26 (m, 1H, CH, H17), 1.77 (ddd, $^2J = 13.6$ Hz, $^3J = 9.7$ Hz, $^3J = 5.4$ Hz, 1H, CH_2 , H20), 1.62–1.54 (m, 1H, CH, H21), 1.34 (ddd, $^2J = 13.5$ Hz, $^3J = 8.5$ Hz, $^3J = 4.9$ Hz, 1H, CH_2 , H20), 0.99 (d, $^3J = 6.9$ Hz, 3H, CH_3 , H19), 0.88–0.85 (m, 6H, CH_3 , H22 and H23).

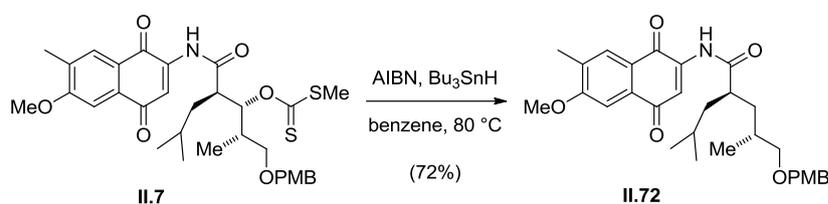


^{13}C NMR (100 MHz, CDCl_3): δ/ppm = 216.7 (CS, C24), 186.0 (CO, C9), 180.2 (CO, C2), 171.9 (CO, C14), 163.2 (Ar-C_q, C6), 159.2 (Ar-C_q, C30), 140.3 (C_q, C1), 132.9 (Ar-C_q, C8), 132.7 (Ar-C_q, C5), 130.0 (Ar-C_q, C27), 129.4(0) (2 x Ar-CH, C28), 129.3(7) (Ar-CH, C4), 123.2 (Ar-C_q, C3), 116.7 (CH, C10), 113.9 (2 x Ar-CH, C29), 106.7 (Ar-CH, C7), 85.4 (CH, C16), 73.1 (CH₂, C26), 72.0 (CH₂, C18), 56.3 (OCH₃, C12), 55.3 (OCH₃, C31), 49.1 (CH₂, C15), 37.2 (CH₂, C20), 36.8 (CH, C17), 26.2 (CH, C21), 23.2 (CH₃, C22 or C23), 22.1 (CH₃, C22 or C23), 19.2 (SCH₃, C25), 16.7 (CH₃, C11), 14.2 (CH₃, C19).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2957 (m), 1662 (m), 1594 (m), 1500 (s), 1350 (s), 1241 (m), 1208 (m), 1053 (s).

HRMS (ESI) calculated for $\text{C}_{32}\text{H}_{39}\text{O}_7\text{NS}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 636.2060, found 636.2053.

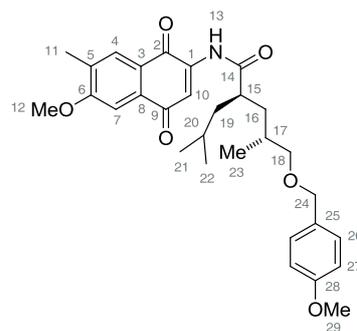
Preparation of naphthoquinone II.72



(2*R*,4*R*)-2-isobutyl-*N*-(6-methoxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-((4-methoxy benzyl)oxy)-4-methylpentanamide (II.72). To a magnetically stirred solution of azobisisobutyronitrile (3.00 mg, 16.3 μmol) and tributyltin hydride (474 mg, 1.63 mmol, 0.44 mL) in dry toluene (2 mL) was added a solution of naphthoquinone **II.7** (10.0 mg, 16.3 μmol) in dry toluene (2 mL) at 80 °C over a period of 2 h. The ensuing mixture was stirred at this temperature for 5 h and after it was cooled to room temperature, MeCN (10 mL) was added. Thus obtained solution was washed with hexanes (3 x 10 mL) and concentrated *in vacuo* to afford crude yellow oil. Subjection of this material to flash column chromatography (1:4→1:1→1:0 EtOAc/hexanes, gradient elution) provided 6.00 mg (11.8 μmol , 72%) of the Barton-McCombie product **II.72** as a yellow oil, which still showed traces of impurities in the NMR spectra.

R_f = 0.49, 1:3 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): δ/ppm = 8.97 (s, 1H NH, H13) 7.85 (d, 4J = 0.7 Hz, 1H, Ar-H, H4), 7.79 (s, 1H, CH, H10), 7.46 (s, 1H, Ar-H, H7), 7.31–7.29 (m, 2H, Ar-H, H26), 6.88–6.86 (m, 2H, Ar-H, H27), 4.68 (d, 2J = 11.9 Hz, 1H, CH₂, H24), 4.46 (d, 2J = 11.9 Hz, 1H, CH₂, H24), 3.99 (s, 3H,



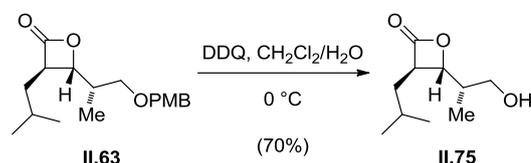
OCH₃, H12), 3.79 (s, 3H, OCH₃, H29), 3.34 (dd, ²J = 9.0 Hz, ³J = 4.0 Hz, 1H, CH₂, H18), 3.25 (dd, ²J = 8.0 Hz, ³J = 8.0 Hz, 1H, CH₂, H18), 2.83–2.78 (m, 1H, CH, H15), 2.31 (s, 3H, CH₃, H11), 1.87–1.79 (m, 1H, CH, H7), 1.71–1.60 (m, 2H, CH₂, H16 and H19), 1.54–1.50 (m, 1H, CH, H20), 1.45–1.40 (m, 1H, CH₂, H16), 1.23–1.18 (m, 1H, CH₂, H19), 0.89–0.83 (m, 9H, CH₃, H21, H22 and H23).

¹³C NMR (150 MHz, CDCl₃): δ/ppm = 186.0 (CO, C9), 180.4 (CO, C2), 176.9 (CO, C14), 163.3 (Ar-C_q, C6), 159.4 (Ar-C_q, C28), 140.3 (Ar-C_q, C1), 132.9 (Ar-C_q, C8), 132.7 (Ar-C_q, C5), 130.4 (Ar-C_q, C25), 129.8 (2 x Ar-CH, C26), 129.3 (Ar-CH, C4), 123.3 (Ar-C_q, C3), 116.5 (Ar-CH, C10), 114.0 (2 x Ar-CH, C27), 106.7 (Ar-CH, C7), 76.4 (CH₂, C18), 73.2 (CH₂, C24), 56.3 (OCH₃, C12), 55.4 (OCH₃, C29), 44.6 (CH, C15), 42.6 (CH₂, C19), 40.4 (CH₂, C16), 31.6 (CH, C17), 26.2 (CH, C20), 23.2 (CH₃, C21 or C22), 22.5 (CH₃, C21 or C22), 18.5 (CH₃, C23), 16.6 (CH₃, C11).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2956 (s), 2870 (s), 1707 (s), 1662 (m), 1594 (m), 1496 (s), 1323 (s), 1241 (s), 1167 (s), 1065 (s), 1033 (s).

HRMS (ESI) calculated for C₃₀H₃₈O₆N [M+H]⁺ 508.2694, found 508.2694.

Preparation of alcohol II.75

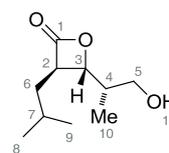


(3*R*,4*R*)-4-((*S*)-1-Hydroxypropan-2-yl)-3-isobutyloxetan-2-one (II.75). To a magnetically stirred biphasic solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (326 mg, 1.44 mmol) in CH₂Cl₂ (10 mL) and water (20 mL) was added dropwise a solution of PMB-ether **II.63** (200 mg, 653 μmol) in CH₂Cl₂ (10 mL) at 0 °C. The reaction was stirred at room temperature for 3 h before aqueous saturated NaHCO₃/Na₂SO₃ solution (1:1 mixture, 40 mL) was added and the mixture was stirred until all solid components completely dissolved. Then, the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:10→1:0 EtOAc/hexanes, gradient elution) providing 85.0 mg (456 μmol, 70%) of alcohol **II.75** as a yellow oil.

R_f = 0.67, 1:2 EtOAc/hexanes.

$[\alpha]_D^{21} = +43.0$ ($c = 1.0$, CHCl_3).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 4.22$ (dd, $^3J = 6.7$ Hz, $^3J = 4.0$ Hz, 1H, CH, H3), 3.69 (dd, $^2J = 10.7$ Hz, $^3J = 4.9$ Hz, 1H, CH_2 , H5), 3.60 (dd, $^2J = 10.7$ Hz, $^2J = 7.2$ Hz, 1H, CH_2 , H5), 3.49 (ddd, $^3J = 8.3$ Hz, $^3J = 7.2$ Hz, $^3J = 4.0$ Hz, 1H, CH, H2), 2.08–2.01 (m, 1H, CH, H4), 1.81–1.73 (m, 2H, CH and CH_2 , H6 and H7), 1.67–1.61 (m, 1H, CH_2 , H6), 1.50 (s, 1H, OH, H11), 1.05 (d, $^3J = 6.9$ Hz, 3H, CH_3 , H10), 0.95–0.93 (m, 6H, CH_3 , H8 and H9).

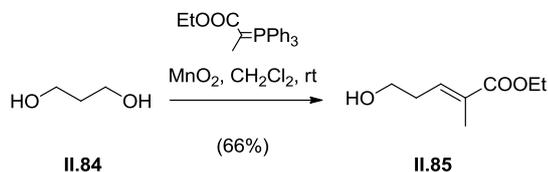


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 172.1$ (CO, C1), 80.5 (CH, C3), 64.5 (CH_2 , C5), 52.6 (CH, C2), 39.2 (CH, C4), 37.6 (CH_2 , C6), 26.3 (CH, C7), 22.7 (CH_3 , C8 or C9), 22.5 (CH_3 , C8 or C9), 11.7 (CH_3 , C10).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3464$ (w), 2960 (w), 2874 (w), 1807 (s), 1468 (w), 1388 (w), 1216 (w), 1130 (m), 1080 (w), 1041 (m).

HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{17}\text{O}_3$ $[\text{M}-\text{H}]^-$ 185.1173, found 185.1183.

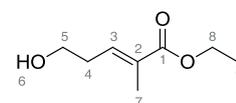
Preparation of ethyl ester **II.85**^[97]



(E)-Ethyl 5-hydroxy-2-methylpent-2-enoate (II.85). To a magnetically stirred solution of 1,3-propanediol **II.84** (2.94 g, 38.7 mmol, 280 mL) in dry CH_2Cl_2 (900 mL) was added (carbethoxyethylidene)triphenylphosphorane (25.0 g, 69.0 mmol) followed by manganese dioxide (51.7 g, 600 mmol) and the ensuing mixture was stirred at room temperature for 4 d. After being filtered over Celite, the solvent was evaporated *in vacuo* and thus obtained crude material was subjected to flash column chromatography (1:90→1:4→1:2 EtOAc/hexanes, gradient elution) providing 4.04 g (25.5 mmol, 66%) of a single diastereoisomer of ethyl ester **II.85** as colorless oil.

$R_f = 0.17$, 1:3 EtOAc/hexanes.

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.77$ (tq, $^3J = 7.4$ Hz, $^4J = 1.5$ Hz, 1H, CH, H3), 4.18 (q, $^3J = 7.1$ Hz, 2H, CH_2 , H8), 3.75 (t, $^3J = 6.5$ Hz, 2H, CH_2 , H5), 2.49–2.41 (m, 2H, CH_2 , H4), 1.86 (dt, $^4J = 1.4$ Hz, $^5J = 1.0$ Hz, 3H, CH_3 , H7), 1.77 (br s, 1H, OH, H6), 1.28 (t, $^3J = 7.1$ Hz, 3H, CH_3 , H9).

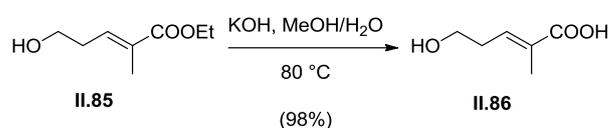


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 168.2$ (CO, C1), 137.9 (CH, C3), 130.3 (C_q , C2), 61.6 (CH_2 , C5 or C8), 60.7 (CH_2 , C5 or C8), 32.2 (CH_2 , C4), 14.4 (CH_3 , C7 or C9), 12.7 (CH_3 , C7 or C9).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3416$ (m), 2931 (m), 2361 (w), 1705 (s), 1649 (m), 1445 (w), 1367 (m), 1250 (s), 1191 (m), 1129 (s), 1039 (s).

HRMS (EI) calculated for $\text{C}_8\text{H}_{14}\text{O}_3$ $[\text{M}]^+$ 158.0943, found 158.0940.

Preparation of acid **II.86**

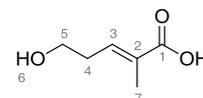


(E)-5-Hydroxy-2-methylpent-2-enoic acid (II.86). A solution of ethyl ester **II.85** (1.47 g, 9.29 mmol) and KOH (1.09 g, 19.5 mmol) in methanol/water (1:1, 88 mL) was stirred at 80 °C for 3h. After being cooled to room temperature, the mixture was washed with EtOAc (2 x 100 mL) and the organic phase was discarded. The aqueous phase was acidified with aqueous HCl solution (1M) to pH = 1 and extracted with EtOAc (4 x 150 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing 1.19 g (9.14 mmol, 98%) of acid **II.86** as a white solid.

$R_f = 0.1$, 1:1 EtOAc/hexanes.

mp: 55.3–57.0 °C (EtOAc).

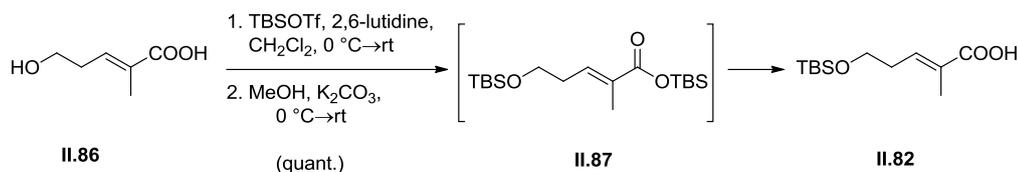
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.92$ (tq, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz, 1H, CH, H3), 3.78 (t, $^3J = 6.4$ Hz, 2H, CH_2 , H5), 2.49 (td, $^3J = 7.3$ Hz, $^3J = 0.8$ Hz, 2H, CH_2 , H4), 1.87–1.86 (m, 3H, CH_3 , H7).



^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 172.9$ (COOH, C1), 140.8 (CH, C3), 129.6 (C_q , C2), 61.4 (CH_2 , C5), 32.4 (CH_2 , C4), 12.4 (CH_3 , C7).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3450$ (m), 2953 (m), 2632 (w), 1680 (s), 1375 (m), 1241 (s), 1139 (m), 1041 (s).

HRMS (EI) calculated for $\text{C}_6\text{H}_{10}\text{O}_3$ $[\text{M}]^+$ 130.0630, found 130.0625.

Preparation of TBS ether **II.82**

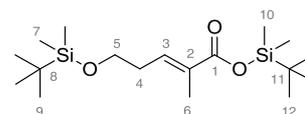
(E)-5-((Tert-butyldimethylsilyloxy)-2-methylpent-2-enoic acid (II.82). To a magnetically stirred solution of free hydroxyacid **II.86** (3.23 g, 24.7 mmol) and 2,6-lutidine (7.42 g, 69.3 mmol, 8.07 mL) in dry CH_2Cl_2 (320 mL) was added dropwise *tert*-butyldimethylsilyl triflate (15.7 g, 59.4 mmol, 13.7 mL) at 0°C . The reaction was stirred for 10 min and then warmed to room temperature. Stirring was continued for an additional 10 min. After addition of EtOAc (600 mL), the organic phase was washed with aqueous HCl solution (1M, 400 mL) and brine (300 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude TBS ester **II.87** was dissolved in MeOH (100 mL) and after being cooled to 0°C , K_2CO_3 (3.76g, 27.2 mmol) was added in one portion. Then, the mixture was stirred at 0°C for 10 min and warmed to room temperature, and stirring was continued for an additional 1 h. After addition of EtOAc, the mixture was washed with aqueous HCl solution (1M, 300 mL) and brine (300 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* providing 7.86 g (3.22 mmol, 100%) of acid **II.82** as a colorless oil.

(E)-Tert-butyldimethylsilyl 5-((tert-butyldimethylsilyloxy)-2-methylpent-2-enoate (II.87).

Colorless oil.

$R_f = 0.9$, 1:1 EtOAc/hexanes.

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 6.82$ (tq, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz, 1H, CH, H3), 3.70 (t, $^3J = 6.5$ Hz, 2H, CH_2 , H5), 2.43–2.36 (m, 2H, CH_2 , H4), 1.83 (d, $^4J = 1.3$ Hz, 3H, CH_3 , H6), 0.95 (s, 9H, CH_3 , H12), 0.88 (s, 9H, CH_3 , H9), 0.28 (s, 6H, SiCH_3 , H10), 0.05 (s, 6H, SiCH_3 , H7).



^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 168.3$ (CO, C1), 139.9 (CH, C3), 130.5 (C_q , C2), 61.8 (CH_2 , C5), 32.7 (CH_2 , C4), 26.0 (3 x CH_3 , C9), 25.8 (3 x CH_3 , C12), 18.4 (C_q , C11), 17.9 (C_q , C8), 12.8 (CH_3 , C6), -4.7 (2 x SiCH_3 , C10), -5.2 (2 x SiCH_3 , C7).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2956$ (w), 2859 (w), 1690 (m), 1472 (w), 1288 (m), 1252 (s), 1099 (s).

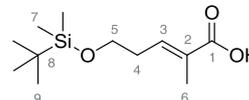
HRMS (EI) calculated for $\text{C}_{18}\text{H}_{38}\text{O}_2^{28}\text{Si}_2$ $[\text{M}-\text{O}+\text{H}]^+$ 343.2483, found 343.2410.

(E)-5-((Tert-butyldimethylsilyl)oxy)-2-methylpent-2-enoic acid (II.82).

Colorless oil.

 $R_f = 0.46$, 1:1 EtOAc/hexanes.

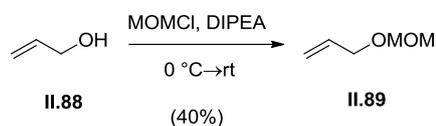
^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.93$ (tq, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz, 1H, CH, H3), 3.72 (t, $^3J = 6.6$ Hz, 2H, CH_2 , H5), 2.43–2.41 (m, 2H, CH_2 , H4), 1.86 (d, $^4J = 1.4$ Hz, 3H, CH_3 , H6), 0.89 (s, 9H, CH_3 , H9), 0.06 (s, 6H, CH_3 , H7).



^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 173.4$ (CO, C1), 141.7 (CH, C3), 128.6 (C_q , C2), 61.7 (CH_2 , C5), 32.8 (CH_2 , C4), 26.0 (3 x CH_3 , C9), 18.5 (C_q , C8), 12.4 (CH_3 , C6), -5.2 (2 x SiCH_3 , C7).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2956$ (w), 2858 (w), 1687 (m), 1421 (w), 1288 (w), 1257 (w), 1100 (m), 905 (s).

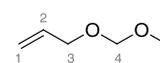
HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{23}\text{O}_3^{28}\text{Si}$ $[\text{M}-\text{H}]^-$ 243.1422, found 243.1422.

Preparation of MOM ether II.89^{198l}

3-(Methoxymethoxy)prop-1-ene (II.89). To a magnetically stirred solution of allyl alcohol (14.4 g, 248 mmol, 16.9 mL) in dry diisopropylethylamine (63 mL) was added dropwise chloromethyl methyl ether **II.88** (25.0 g, 311 mmol, 23.6 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 48 h before water (150 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with water (3 x 100 mL) and brine (100 mL), dried over Na_2SO_4 and filtered. Thus obtained solution was subjected to several fractional distillations over a 10 cm vacuum isolated Vigreux column, providing 10.1 g (98.9 mmol, 40%) of MOM ether **II.89** as a colorless liquid, which was still contaminated with traces of DIPEA. The product is sensitive to silica and could not be purified any further using flash column chromatography.

bp: 70–75 °C.

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 5.92$ –5.73 (m, 1H, CH, H2), 5.26–5.14 (m, 1H, CH, H1), 5.14–5.04 (m, 1H, CH, H1), 4.55 (s, 2H, CH_2 , H4), 3.97



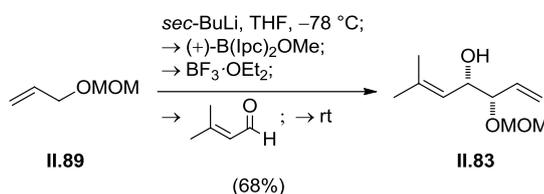
(ddd, $^3J = 5.7$ Hz, $^4J = 1.4$ Hz, $^4J = 1.4$ Hz, 2H, CH₂, H3), 3.28 (s, 3H, OCH₃, H5).

¹³C NMR (75 MHz, CDCl₃): δ /ppm = 134.5 (CH, C2), 117.3 (CH, C1), 95.8 (CH₂, C4), 68.4 (CH₂, C3), 55.4 (CH₃, C5).

IR: $\tilde{\nu}$ /cm⁻¹ = 2933 (w), 2824 (w), 1649 (w), 1453 (w), 1402 (w), 1213 (w), 1145 (m), 1105 (m), 1050 (s).

HRMS (EI) calculated for C₅H₉O₂ [M-H]⁺ 101.0597, found 101.0614.

Preparation of alcohol **II.83**



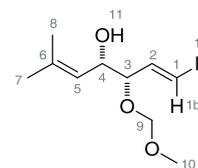
(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-ol (II.83). To a magnetically stirred solution of methoxymethyl allyl ether **II.89** (9.00 g, 88.1 mmol) in dry THF (36 mL) was added slowly *sec*-BuLi solution (1.4M in cyclohexane, 62.9 mL, 88.1 mmol) at -78°C . After the resultant orange-yellow mixture was stirred at -78°C for 1 h, (+)-*B*-methoxydiisopinocampheylborane (23.2 g, 73.4 mmol) solution in dry THF (73 mL) was added *via* a cannula. Then, the mixture was stirred at -78°C for an additional 1 h and subsequently, boron trifluoride etherate (13.6 g, 95.5 mmol, 12.1 mL) followed by 3-methylcroton aldehyde (6.17 g, 73.4 mmol, 7.10 mL) were added dropwise. The mixture was slowly warmed to room temperature over the time course of 12 h, before aqueous saturated NaHCO₃ solution (160 mL) and aqueous H₂O₂ solution (30wt%, 100 mL) were added at 0°C and the reaction was stirred for an additional 30 min at room temperature. After addition of diethyl ether (160 mL), the layers were separated and the aqueous phase was extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:10→1:7→1:3→1:1 EtOAc/hexanes, gradient elution) providing 9.31 g (50.0 mmol, 68%, er = 92 : 8; **II.83a** : **II.83b**) of alcohol **II.83** as a colorless oil.

The enantiomeric ratio (er) was measured on chiral HPLC (Nucleocel DELTA S, 250 x 4.6 mm, isocratic elution, hexanes (A)/*i*-propanol (B), 95% A, flow rate: 1 mL/min, detection at 210 nm, $t_{\text{R}}(\text{II.83a}) = 5.65$ min, $t_{\text{R}}(\text{II.83b}) = 6.48$ min).

$R_{\text{f}} = 0.31$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{21} = +102.4$ ($c = 1.25$, CHCl_3).

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 5.66$ (ddd, $^3J = 17.6$ Hz, $^3J = 10.3$ Hz, $^3J = 7.3$ Hz, 1H, CH, H2), 5.32–5.27 (m, 1H, CH, H1b), 5.26–5.24 (m, 1H, CH, H1a), 5.18–5.15 (m, 1H, CH, H5), 4.75 (d, $^2J = 6.6$ Hz, 1H, CH_2 , H9), 4.63 (d, $^2J = 6.6$ Hz, 1H, CH_2 , H9), 4.31–4.25 (m, 1H, CH, H4), 3.90 (dd, $^3J = 7.4$ Hz, $^3J = 7.3$ Hz, 1H, CH, H3), 3.41 (s, 3H, CH_3 , H10), 2.62 (d, $^3J = 2.7$ Hz, 1H, OH, H11), 1.74 (d, $^3J = 1.3$ Hz, 3H, CH_3 , H7), 1.69 (d, $^3J = 1.3$ Hz, 3H, CH_3 , H8).

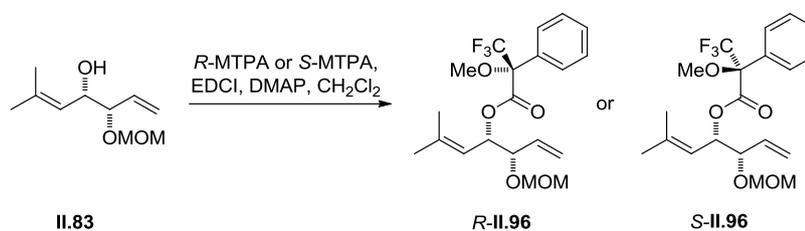


^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 138.1$ (C_q , C6), 134.6 (CH, C2), 123.1 (CH, C5), 119.3 (CH_2 , C1), 94.6 (CH_2 , C9), 81.7 (CH, C3), 70.8 (CH, C4), 55.9 (CH_3 , C10), 26.1 (CH_3 , C7), 18.9 (CH_3 , C8).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3432$ (w), 2912 (w), 1677 (w), 1443 (w), 1376 (w), 1257 (w), 1214 (w), 1150 (m), 1098 (m), 1030 (s), 920 (s).

HRMS (EI) calculated for $\text{C}_{10}\text{H}_{17}\text{O}_2$ $[\text{M}-\text{OH}]^+$ 169.1229, found 169.1250.

Proof of stereochemistry: Preparation of the *R*- and *S*-MTPA-methyl esters *R*-II.96 and *S*-II.96:



(*R*)-(3*S*,4*S*)-3-(methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (*R*-II.96). To a magnetically stirred solution of alcohol **II.83** (10.0 mg, 53.7 μmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (51.5 mg, 331 μmol) and 4-dimethylaminopyridine (19.7 mg, 161 μmol) in dry CH_2Cl_2 (1 mL) was added dropwise a solution of (*R*)- α -methoxy- α -trifluoromethylphenylacetic acid (*R*-MTPA) (25.2 mg, 108 μmol) in dry CH_2Cl_2 (0.5 mL) and the resulting mixture was stirred at room temperature overnight. After addition of water (3 mL) and EtOAc (3 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic fractions were washed with brine (6 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:10 EtOAc/hexanes) providing 6.50 mg (16.2 μmol , 30%) of *R*-MTPA-ester *R*-II.96 as a colorless oil.

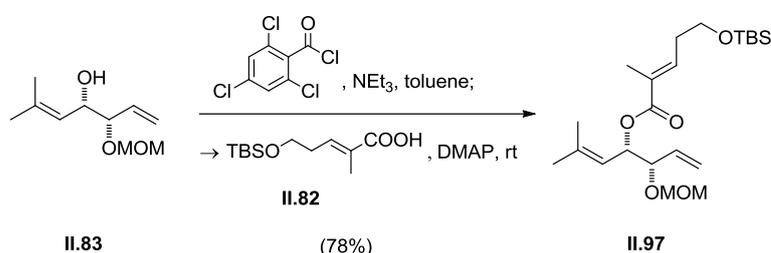
R-II.96: (R)-(3S,4S)-3-(methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate.

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.62–7.48 (m, 2H), 7.41–7.34 (m, 3H), 5.76–5.72 (m, 1H), 5.65–5.49 (m, 1H), 5.30–5.21 (m, 2H), 5.21–5.13 (m, 1H), 4.49 (d, 2J = 6.7 Hz, 1H), 4.38 (d, 2J = 6.7 Hz, 1H), 4.15–4.04 (m, 1H), 3.57 (s, 3H), 3.13 (s, 3H), 1.80 (d, 4J = 1.3 Hz, 3H), 1.76 (d, 4J = 1.3 Hz, 3H).

In entirely analogous fashion, the *S*-MTPA-ester **S-II.96** was prepared using *S*-MTPA:

S-II.96: (S)-(3S,4S)-3-(methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate.

^1H NMR (600 MHz, CDCl_3): δ/ppm = 7.56–7.49 (m, 2H), 7.40–7.35 (m, 3H), 5.72–5.67 (m, 1H), 5.64 (ddd, 3J = 17.6 Hz, 3J = 10.4 Hz, 3J = 7.3 Hz, 1H), 5.36–5.23 (m, 2H), 5.06–5.00 (m, 1H), 4.67 (d, 2J = 6.7 Hz, 1H), 4.56 (d, 2J = 6.7 Hz, 1H), 4.15 (dd, 3J = 7.4 Hz, 3J = 7.4 Hz, 1H), 3.53 (s, 3H), 3.29 (s, 3H), 1.80 (d, 4J = 1.2 Hz, 3H), 1.73 (d, 4J = 1.2 Hz, 3H).

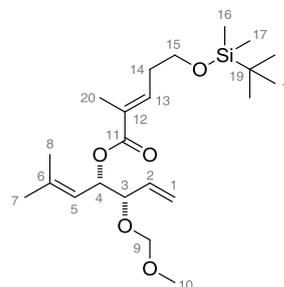
Preparation of ester II.97

(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-((tert-butyl)dimethyl silyl)oxy-2-methylpent-2-enoate (II.97). To a magnetically stirred solution of acid **II.82** (100 mg, 409 μmol) in dry toluene (12 mL) were added 2,4,6-trichlorobenzoyl chloride (149 mg, 614 μmol , 96.9 μL) and triethylamine (83.0 mg, 818 μmol , 120 μL). After the resultant mixture was stirred at room temperature for 1.5 h, a solution of alcohol **II.83** (76.0 mg, 409 μmol) in dry toluene (17 mL) was added *via* a cannula. The reaction was stirred for 6 h at room temperature before EtOAc (50 mL) and aqueous pH-7-phosphate buffer (0.1M, 30 mL) were added. Then, the layers were separated and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash column chromatography (1:20 EtOAc/hexanes) providing 132 mg (320 μmol , 78%) of ester **II.97** as a colorless oil.

$R_f = 0.65$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{21} = +2.5$ ($c = 1.0$, CHCl_3).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.79$ (ddq, $^3J = 7.4$ Hz, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz, 1H, CH, H13), 5.70 (ddd, $^3J = 17.4$ Hz, $^3J = 10.5$ Hz, $^3J = 7.1$ Hz, 1H, CH, H2), 5.64 (dd, $^3J = 9.4$ Hz, $^3J = 6.5$ Hz, 1H, CH, H4), 5.32–5.25 (m, 2H, CH_2 , H1), 5.17–5.15 (m, 1H, CH, H5), 4.68 (d, $^2J = 6.7$ Hz, 1H, CH_2 , H21), 4.59 (d, $^2J = 6.7$ Hz, 1H, CH_2 , H9), 4.17 (dd, $^3J = 6.8$ Hz, $^3J = 6.8$ Hz, 1H, CH, H3), 3.70–3.68 (m, 2H, CH_2 , H15), 3.35 (s, 3H, OCH_3 , H10), 2.41–2.37 (m, 2H, CH_2 , H14), 1.85 (d, $^4J = 1.3$ Hz, 3H, CH_3 , H20), 1.76 (d, $^4J = 1.3$ Hz, 3H, CH_3 , H8), 1.73 (d, $^4J = 1.3$ Hz, 3H, CH_3 , H7), 0.89 (s, 9H, CH_3 , H18), 0.05 (s, 6H, SiCH_3 , H16 and H17).

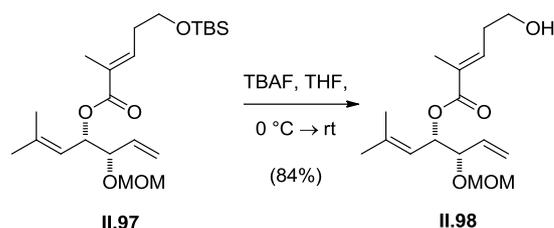


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 167.2$ (CO, C11), 139.3 (C_q , C6), 138.8 (CH, C13), 134.2 (CH, C2), 129.5 (C_q , C12), 120.1 (CH, C5), 119.1 (C_q , C1), 94.3 (CH_2 , C9), 78.4 (CH, C3), 72.6 (CH, C4), 61.9 (CH_2 , C15), 55.6 (OCH_3 , C10), 32.6 (CH_2 , C14), 26.1 (4 x CH_3 , C7 and C18), 18.9 (CH_3 , C8), 18.5 (C_q , C19), 12.8 (CH_3 , C20), -5.2 (2 x SiCH_3 , C16 and C17).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2956$ (w), 2859 (w), 1740 (s), 1710 (m), 1580 (w), 1446 (w), 1373 (m), 1230 (s), 1151 (m), 1100 (s), 1044 (s).

HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{40}\text{O}_5^{28}\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 435.2543, found 435.2545.

Preparation of alcohol II.98



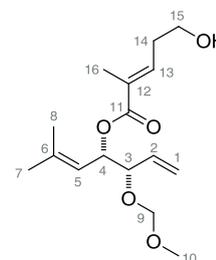
(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-hydroxy-2-methylpent-2-enoate (II.98). To a magnetically stirred solution of TBS ether II.97 (600 mg, 1.45 mmol) in dry THF (25 mL) was added *tetra-N*-butylammonium fluoride solution (1M in THF, 3.18 mmol, 3.18 mL) at 0 °C. The reaction was stirred for 1 h at room temperature before pH-7-phosphate buffer (0.1M, 30 mL) was added. Then, the mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (70 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude material was subjected to flash

column chromatography (1:4→1:1 EtOAc/hexanes, gradient elution) providing 363 mg (1.22 mmol, 84%) of alcohol **II.98** as a colorless oil.

$R_f = 0.25$, 1:3 EtOAc/hexanes.

$[\alpha]_D^{21} = +19.2$ ($c = 0.5$, CHCl_3).

^1H NMR (600 MHz, CDCl_3): $\delta/\text{ppm} = 6.79$ (ddq, $^3J = 7.4$ Hz, $^3J = 7.4$ Hz, $^4J = 1.3$ Hz, 1H, CH, H13), 5.69 (ddd, $^3J = 17.5$ Hz, $^3J = 10.4$ Hz, $^3J = 7.2$ Hz, 1H, CH, H2), 5.64 (dd, $^3J = 9.5$ Hz, $^3J = 6.7$ Hz, 1H, CH, H4), 5.32–5.26 (m, 2H, CH_2 , H1), 5.17–5.15 (m, 1H, H5), 4.68 (d, $^2J = 6.8$ Hz, 1H, CH_2 , H17), 4.59 (d, $^2J = 6.7$ Hz, 1H, CH_2 , H9), 4.17 (dd, $^3J = 6.9$ Hz, $^3J = 6.9$ Hz, 1H, CH, H3), 3.76–3.73 (m, 2H, CH_2 , H15), 3.35 (s, 3H, OCH_3 , H10), 2.47–2.44 (m, 2H, CH_2 , H14), 1.87 (s, 3H, CH_3 , H16), 1.77 (d, $^4J = 1.0$ Hz, 3H, CH_3 , H8), 1.74 (s, 3H, CH_3 , H7).

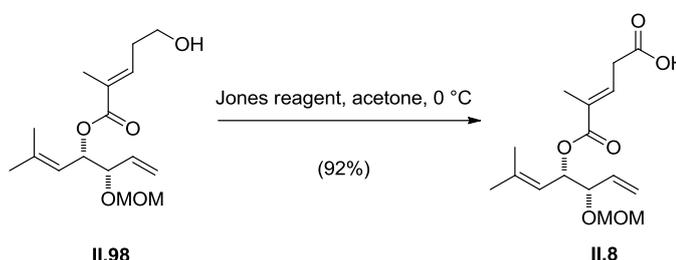


^{13}C NMR (150 MHz, CDCl_3): $\delta/\text{ppm} = 167.1$ (CO, C11), 139.5 (C_q , C6), 138.0 (CH, C13), 134.1 (CH, C2), 130.5 (C_q , C12), 120.0 (CH, C5), 119.2 (C_q , C1), 94.2 (CH_2 , C9), 78.4 (CH, C3), 72.8 (CH, C6), 61.6 (CH_2 , C15), 55.6 (OCH_3 , C10), 32.4 (CH_2 , C14), 26.1 (CH_3 , C7), 18.9 (CH_3 , C8), 12.8 (CH_3 , C16).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3454$ (w), 2933 (w), 2888 (w), 1820 (w), 1707 (m), 1649 (w), 1442 (w), 1324 (w), 1265 (m), 1150 (m), 1099 (m), 1026 (s).

HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{26}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 321.1672, found 321.1672.

Preparation of acid **II.8**



(E)-5-(((3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl)oxy)-4-methyl-5-oxopent-3-enoic acid (II.8). To a magnetically stirred solution of alcohol **II.98** (105 mg, 352 μmol) in acetone (5 mL) was added dropwise as much of freshly prepared Jones reagent (8N) at 0 °C until the reaction mixture maintained orange (ca. 1.4 mL). After the mixture was stirred at 0 °C for 30 min, water (20 mL) was added and the solution was extracted with EtOAc

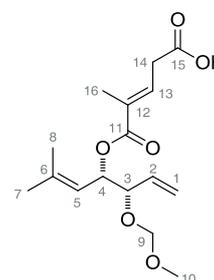
(3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* providing 101 mg (323 μmol, 92%) of the free acid **II.8** as a colorless oil. The product is sensitive to silica and could not be purified any further using flash column chromatography.

R_f = 0.33, 1:1 EtOAc/hexanes.

[α]_D²² = +18.3 (*c* = 0.5, CHCl₃).

The product exists in CDCl₃ solution as a mixture of two double bond isomers. Only the major isomer was characterized.

¹H NMR (600 MHz, CDCl₃): δ/ppm = 6.90 (dd, ³*J* = 6.6 Hz, ³*J* = 6.6 Hz, 1H, CH, H13), 5.71–5.63 (m, 2H, CH, H2 and H4), 5.33–5.26 (m, 2H, CH₂, H1), 5.18–5.15 (m, 1H, CH, H5), 4.68 (d, ²*J* = 6.8 Hz, 1H, CH₂, H9), 4.57 (d, ²*J* = 6.8 Hz, 1H, CH₂, H9), 4.18 (dd, ³*J* = 6.9 Hz, ³*J* = 6.9 Hz, 1H, CH, H3), 3.35 (s, 3H, OCH₃, H10), 3.27–3.26 (m, 2H, CH₂, H14), 1.86 (s, 3H, CH₃, H16), 1.75 (d, ⁴*J* = 1.1 Hz, 3H, CH₃, H8), 1.72 (d, ⁴*J* = 1.1 Hz, 3H, CH₃, H7).

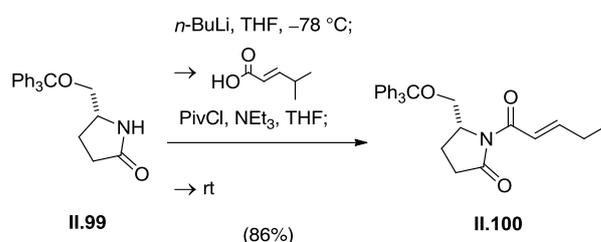


¹³C NMR (150 MHz, CDCl₃): δ/ppm = 175.7 (CO, C11), 166.6 (COOH, C15), 139.7 (C_q, C6), 134.0 (CH, C2), 131.9 (CH, C13), 131.6 (C_q, C12), 119.8 (CH, C5), 119.4 (CH₂, C1), 94.1 (CH₂, C9), 78.3 (CH, C3), 73.1 (CH, C4), 55.6 (OCH₃, C10), 33.9 (CH₂, C14), 26.1 (CH₃, C7), 18.9 (CH₃, C8), 13.0 (CH₃, C16).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2935 (w), 1708 (s), 1441 (w), 1386 (w), 1250 (s), 1118 (s), 1025 (s).

HRMS (ESI) calculated for C₁₆H₂₃O₆ [M-H]⁻ 311.1500, found 311.1502.

Preparation of imide **II.100**^[104a]



(*R,E*)-1-(Pent-2-enoyl)-5-((trityloxy)methyl)pyrrolidin-2-one (II.100). To a magnetically stirred solution of amide **II.99** (16.7 g, 46.7 mmol) in dry THF (200 mL) at -78 °C was added dropwise a solution of *n*-BuLi (2.5M in hexanes, 58.4 mmol, 23.4 mL). The ensuing mixture

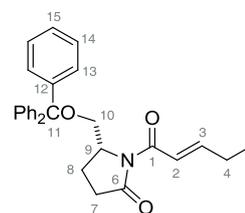
was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. In the meantime, in a separate flask, to a solution of *trans*-2-pentenoic acid (5.85 g, 58.4 mmol, 5.90 mL) in dry THF (300 mL) was added freshly distilled NEt_3 (8.27 g, 81.8 mmol, 11.3 mL) followed by pivaloyl chloride (7.75 g, 64.2 mmol, 7.90 mL) at $0\text{ }^{\circ}\text{C}$. After this mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min, thus obtained acid anhydride was added slowly to the amide anion at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was warmed to room temperature over a 2 h period, before aqueous saturated NH_4Cl solution (500 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (400 mL), water (400 mL) and brine (400 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford crude colorless oil. Subjection of this material to flash column chromatography (1:9→1:6→1:4 EtOAc/hexanes, gradient elution) provided 17.6 g (40.0 mmol, 86%) of imide **II.100** as a white solid.

$R_f = 0.5$, 1:3 EtOAc/hexanes.

mp: $107\text{--}108\text{ }^{\circ}\text{C}$ (EtOAc/hexanes).

$[\alpha]_D^{23} = +84.7$ ($c = 1.0$, CH_2Cl_2).

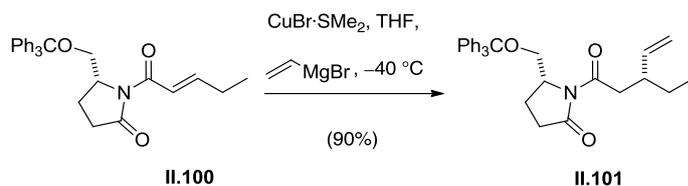
^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 7.37\text{--}7.07$ (m, 17H, Ar-H and CH, H13, H14, H15, H2 and H3), 4.56–4.50 (m, 1H, CH, H9), 3.55 (dd, $^2J = 9.7\text{ Hz}$, $^3J = 4.0\text{ Hz}$, 1H, CH_2 , H10), 3.14 (dd, $^2J = 9.7\text{ Hz}$, $^3J = 2.7\text{ Hz}$, 1H, CH_2 , H10), 2.95 (ddd, $^2J = 17.9\text{ Hz}$, $^3J = 11.0\text{ Hz}$, $^3J = 10.0\text{ Hz}$, 1H, CH_2 , H7), 2.48 (ddd, $^2J = 17.9\text{ Hz}$, $^3J = 9.7\text{ Hz}$, $^3J = 2.1\text{ Hz}$, 1H, CH_2 , H7), 2.39–2.23 (m, 2H, CH_2 , H4), 2.07–1.97 (m, 2H, CH_2 , H8), 1.12 (dd, $^3J = 7.4\text{ Hz}$, $^3J = 7.4\text{ Hz}$, 3H, CH_3 , H5).



^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 176.5$ (CO, C1 or C6), 166.2 (CO, C1 or C6), 152.0 (CH, C3), 143.8 (3 x Ar- C_q , C12), 128.7 (6 x Ar-CH, C13 or C14), 128.0 (6 x Ar-CH, C13 or C14), 127.2 (3 x Ar-CH, C15), 121.9 (CH, C2), 87.2 (C_q , C11), 64.3 (CH_2 , C10), 56.9 (CH, C9), 33.5 (CH_2 , C7), 26.0 (CH_2 , C4), 21.2 (CH_2 , C8), 12.6 (CH_3 , C5).

IR: $\tilde{\nu}/\text{cm}^{-1} = 3100$ (w), 2967 (w), 2929 (w), 1728 (s), 1675 (s), 1621 (m), 1490 (m), 1356 (m), 1291 (m), 1193 (s), 1151 (m), 1080 (m).

HRMS (ESI) calculated for $\text{C}_{29}\text{H}_{29}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 462.2040, found 462.2035.

Preparation of imide **II.101**^[104a]

(R)-1-((R)-3-Ethylpent-4-enoyl)-5-((trityloxy)methyl)pyrrolidin-2-one (II.101). To a magnetically stirred solution of copper(I) bromide dimethyl sulfide complex (933 mg, 4.54 mmol) with 3Å molecular sieves in dry THF (44 mL) was added dropwise dimethyl sulfide (11.3 g, 181 mmol, 13.3 mL) at room temperature. The ensuing mixture was cooled to $-48\text{ }^\circ\text{C}$ and vinyl Grignard solution (1M in THF, 9.08 mmol, 9.08 mL) was added dropwise. After the reaction was stirred for 20 min, a solution of imide **II.100** (1.33 g, 3.03 mmol) in dry THF (13 mL) was added and the mixture was stirred for an additional 3 h at $-40\text{ }^\circ\text{C}$, before aqueous saturated NH_4Cl solution (50 mL) was added. The biphasic mixture was warmed to room temperature, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus afforded crude product was subjected to flash column chromatography (1:8 EtOAc/hexanes) providing 1.27 g (2.72 mmol, 90%) of imide **II.101** as a white solid.

$R_f = 0.31$, 1:5 EtOAc/hexanes.

mp: $108\text{--}109\text{ }^\circ\text{C}$ (EtOAc/hexanes).

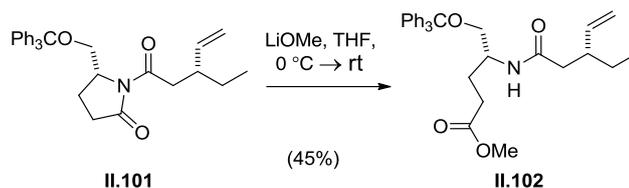
$[\alpha]_D^{24} = +64.7$ ($c = 1.0$, CH_2Cl_2).

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 7.37\text{--}7.20$ (m, 15H), 5.68 (ddd, $^3J = 17.1\text{ Hz}$, $^3J = 10.2\text{ Hz}$, $^3J = 8.3\text{ Hz}$, 1H), 5.03–4.95 (m, 2H), 4.53–4.40 (m, 1H), 3.52 (dd, $^2J = 9.7\text{ Hz}$, $^3J = 4.2\text{ Hz}$, 1H), 3.17 (dd, $^2J = 9.7\text{ Hz}$, $^3J = 2.6\text{ Hz}$, 1H), 3.11–2.82 (m, 3H), 2.56–2.38 (m, 2H), 2.14–1.84 (m, 2H), 1.53–1.23 (m, 2H), 0.87 (t, $^3J = 7.4\text{ Hz}$, 3H).

^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 176.3$, 172.9, 143.8 (3 x C), 141.5, 128.7 (6 x C), 128.0 (6 x C), 127.3 (3 x C), 115.0, 87.2, 64.1, 56.9, 42.1, 41.3, 33.4, 27.5, 21.5, 11.7.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2959$ (w), 2876 (w), 1733 (s), 1691 (s), 1489 (m), 1370 (m), 1280 (m), 1219 (m), 1198 (m), 1074 (m).

HRMS (ESI) calculated for $\text{C}_{31}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 490.2353, found 490.2348.

Preparation of ester **II.102****(R)-Methyl 4-((R)-3-ethylpent-4-enamido)-5-(trityloxy)pentanoate (II.102).**

Preparation of lithium methoxide: To a magnetically stirred solution of dry methanol (174 mg, 5.43 mmol, 0.22 mL) in dry THF (2.75 mL) was added dropwise a solution of *n*-BuLi (2.5M in hexanes, 3.68 mmol, 1.47 mL) at 0 °C and the mixture was stirred at room temperature for 10 min.

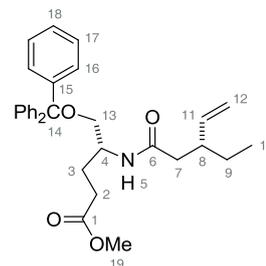
The freshly prepared lithium methoxide solution was added to a solution of imide **II.101** (250 mg, 534 μ mol) in dry THF (2.5 mL) and the mixture was stirred at room temperature for 36 h before aqueous saturated NH₄Cl solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus afforded crude product was subjected to flash column chromatography (1:6→1:0 diethyl ether/pentane, gradient elution) providing 120 mg (240 μ mol, 45%) of ester **II.102** as white solid.

R_f = 0.2, 1:5 EtOAc/hexanes.

mp: 107–109 °C (EtOAc/hexanes).

$[\alpha]_D^{23} = +84.7$ ($c = 1.0$, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ /ppm = 7.41–7.38 (m, 6H, Ar-H, H16), 7.32–7.27 (m, 6H, Ar-H, H17), 7.25–7.21 (m, 3H, Ar-H, H18), 5.68 (d, ³J = 9.0 Hz, 1H, NH, H5), 5.55 (ddd, ³J = 17.2 Hz, ³J = 10.2 Hz, ³J = 8.4 Hz, 1H, CH, H11), 4.99–4.91 (m, 2H, CH₂, H12), 4.13–4.05 (m, 1H, CH, H4), 3.66 (s, 3H, OCH₃, H19), 3.18 (dd, ²J = 9.3 Hz, ³J = 3.6 Hz, 1H, CH₂, H13), 3.10 (dd, ²J = 9.3 Hz, ³J = 4.2 Hz, 1H, CH₂, H13), 2.42–2.29 (m, 3H, CH₂ and CH, H2 and H8), 2.19 (dd, ²J = 14.2 Hz, ³J = 5.9 Hz, 1H, CH₂, H7), 2.11–2.02 (m, 1H, CH₂, H7), 1.97–1.91 (m, 2H, CH₂, H3), 1.49–1.36 (m, 1H, CH₂, H9), 1.35–1.20 (m, 1H, CH₂, H9), 0.85 (dd, ³J = 7.4 Hz, ³J = 7.4 Hz, 3H, CH₃, H10).



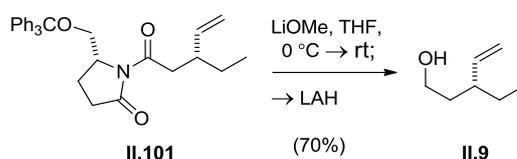
¹³C NMR (100 MHz, CDCl₃): δ /ppm = 174.1 (CO, C1), 171.5 (CO, C6), 143.8 (3 x Ar-C_q, C15), 141.1 (CH, C11), 128.7 (6 x Ar-CH, C16), 128.0 (6 x Ar-CH, C17), 127.3 (3 x Ar-CH,

C18), 115.6 (CH₂, C12), 86.7 (Ar-C_q, C14), 65.1 (CH₂, C13), 51.8 (OCH₃, C19), 48.9 (CH, C4), 42.5 (CH₂ or CH, C7 or C8), 42.4 (CH₂ or CH, C7 or C8), 31.0 (CH₂, C2), 27.6 (CH₂, C3 or C9), 27.5 (CH₂, C3 or C9), 11.6 (CH₃, C10).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3275 (w), 2924 (w), 1738 (m), 1643 (s), 1552 (m), 1448 (m), 1344 (s), 1287 (m), 1169 (m), 1070 (m).

HRMS (ESI) calculated for C₃₂H₃₇NO₄Na [M+Na]⁺ 522.2615, found 522.2608.

Preparation of alcohol **II.9**^[104]



(*R*)-3-Ethylpent-4-en-1-ol (**II.9**).

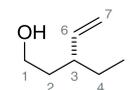
Preparation of lithium methoxide: To a magnetically stirred solution of dry methanol (174 mg, 5.43 mmol, 0.22 mL) in dry THF (2.75 mL) was added dropwise a solution of *n*-BuLi (2.5M in hexanes, 3.68 mmol, 1.47 mL) at 0 °C and the mixture was stirred at room temperature for 10 min.

To the freshly prepared lithium methoxide solution (0.8M in THF, 2.2 mL) was added a solution of imide **II.101** (200 mg, 428 μmol) in dry THF (2 mL) at 0 °C and the mixture was stirred at room temperature for 48 h before LAH (47.0 mg, 1.28 mmol) was added in one portion. The reaction was stirred for an additional 3 h before it was quenched by slow addition of water (10 mL). Then, the layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Thus afforded crude product was subjected to flash column chromatography (1:7→1:4 diethyl ether/pentane, gradient elution) to give 34.0 mg (298 μmol , 70%) of alcohol **II.9** as a colorless oil contaminated with solvent residues.

R_f = 0.7, 1:3 EtOAc/hexanes.

$[\alpha]_D^{23} = -11.1$ ($c = 0.5$, diethyl ether).

¹H NMR (400 MHz, CD₂Cl₂): δ/ppm = 5.62–5.51 (m, 1H, CH, H6), 5.00–4.99 (m, 1H, CH₂, H7), 4.96 (ddd, ³ $J = 6.0$, ² $J = 2.1$ Hz, ⁴ $J = 0.6$ Hz, 1H, CH₂, H7), 3.66–3.49 (m, 2H, CH₂, H1), 2.05–1.96 (m, 1H, CH, H3), 1.67–1.59 (m, 1H, CH₂, H2), 1.50–



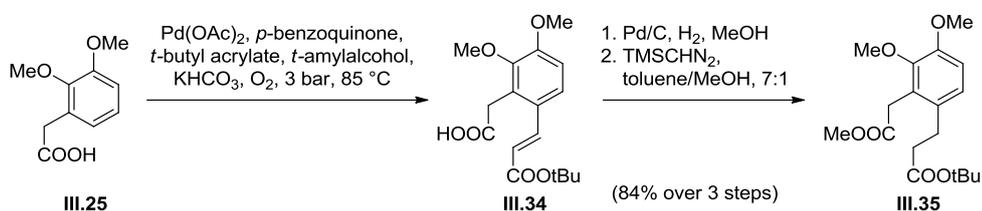
1.34 (m, 2H, CH₂, H2 and H4), 1.31–1.20 (m, 1H, CH₂, H4), 0.86 (dd, ³J = 7.4 Hz, ³J = 7.4 Hz, 3H, CH₃, H5).

¹³C NMR (100 MHz, CD₂Cl₂): δ/ppm = 143.3 (CH, C6), 114.9 (CH₂, C7), 61.5 (CH₂, C1), 43.2 (CH, C3), 38.0 (CH₂, C2), 28.3 (CH₂, C4), 11.7 (CH₃, C5).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 3319 (m), 2960 (m), 2924 (m), 1640 (w), 1463 (w), 1420 (w), 1379 (w), 1057 (s), 994 (s).

HRMS (EI) calculated for C₇H₁₄O₁ [M]⁺ 114.1045, found 114.1039.

Preparation of methyl ester **III.35**^[7]

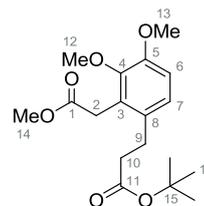


Tert-butyl 3-(3,4-dimethoxy-2-(2-methoxy-2-oxoethyl)phenyl)propanoate (III.35). An autoclave was charged with a suspension of 2,3-dimethoxyphenylacetic acid (**III.25**) (10.0 g, 51.0 mmol), *para*-benzoquinone (276 mg, 1.28 mmol), dry KHCO₃ (10.2 g, 102 mmol), *tert*-butyl acrylate (19.8 g, 153 mmol, 22.4 mL) and palladium(II) acetate (1.15 g, 5.10 mmol) in dry *tert*-amylalcohol (100 mL). The apparatus was flushed with oxygen gas five times and the reaction mixture was stirred under oxygen atmosphere (3 bar) at 85 °C for 96 h. After the reaction was cooled to room temperature, aqueous HCl solution (2M, 150 mL) was added and the mixture was extracted with diethyl ether (3 x 200 mL). The combined organic fractions were dried over MgSO₄ and the suspension was filtered through a pad of Celite to remove all solid materials. Then, the Celite plug was washed with diethyl ether (100 mL) and the combined filtrates were concentrated *in vacuo*. The crude acid **III.34** was immediately re-dissolved in MeOH (300 mL) and palladium on charcoal (10wt%, 2.00 g) was added. The reaction flask was purged with hydrogen gas five times and the mixture was then stirred under hydrogen atmosphere at room temperature for 16 h before the catalyst was removed by filtration through a pad of Celite. The Celite plug was washed with MeOH (200 mL) and the combined filtrates were concentrated *in vacuo* to afford crude saturated ester, which was immediately re-dissolved in toluene/MeOH (7:1, 314 mL). This mixture was cooled to 0 °C and a solution of (trimethylsilyl)diazomethane in hexanes (2.0M, 30.6 mL, 61.2 mmol) was added dropwise. After stirring for 15 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 40 min. Then, the reaction was quenched with acetic acid (15 mL)

and diluted with saturated aqueous NaHCO_3 solution (600 mL). The aqueous phase was extracted with EtOAc (3 x 400 mL) and the combined organic fractions were washed with brine (500 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Thus obtained crude ester **III.35** was subjected to flash column chromatography (1:19→1:9→1:6→1:4 EtOAc/hexanes, gradient elution) providing 14.5 g (42.8 mmol, 84% over three steps) of methyl ester **III.35** as a colorless oil.

$R_f = 0.27$, 1:9 EtOAc/hexanes.

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta/\text{ppm} = 6.90$ (d, $^3J = 8.5$ Hz, 1H, Ar-H, H7), 6.80 (d, $^3J = 8.5$ Hz, 1H, Ar-H, H6), 3.84 (s, 3H, OCH_3 , H13), 3.81 (s, 3H, OCH_3 , H12), 3.75 (s, 2H, CH_2 , H2), 3.69 (s, 3H, OCH_3 , H14), 2.86–2.79 (m, 2H, CH_2 , H9), 2.48–2.41 (m, 2H, CH_2 , H10), 1.43 (s, 9H, CH_3 , H16).



$^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta/\text{ppm} = 172.4$ (2 x CO, C1 and C11), 151.1 (Ar- C_q , C5), 147.8 (Ar- C_q , C4), 132.5 (Ar- C_q , C8), 127.2 (Ar- C_q , C3), 124.2 (Ar-CH, C7), 111.6 (Ar-CH, C6), 80.5 (C_q , C15), 60.6 (OCH_3 , C12), 55.9 (OCH_3 , C13), 52.1 (OCH_3 , C14), 36.6 (CH_2 , C10), 32.1 (CH_2 , C2), 28.3 (3 x CH_3 , C16), 27.9 (CH_2 , C9) ppm.

IR: $\tilde{\nu}/\text{cm}^{-1} = 2976$ (w), 1726 (s), 1492 (m), 1366 (m), 1275 (s), 1145 (s), 1083 (s).

HRMS (EI) calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_6^+$ $[\text{M}]^+$ 338.1724, found 338.1718.

To fully characterize carboxylic acid **III.34**, an analytical sample of the crude mixture, which was obtained after palladium-catalyzed C-H activation, was subjected to flash column chromatography (1:3 EtOAc/hexanes, 1% AcOH) providing **III.34** as a white solid.

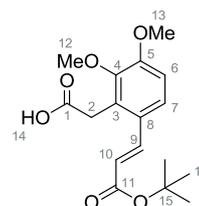
(E)-2-(6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-2,3-dimethoxyphenyl)acetic acid (III.34).

White solid.

$R_f = 0.20$, 1:3 EtOAc/hexanes + 1% AcOH.

mp: 115–117 °C (EtOAc/hexanes).

$^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta/\text{ppm} = 7.73$ (d, $^3J = 15.7$ Hz, 1H, CH_2 , H9), 7.34 (d, $^3J = 8.7$ Hz, 1H, Ar-H, H7), 6.87 (d, $^3J = 8.7$ Hz, 1H, Ar-H, H6), 6.20 (d, $^3J = 15.6$ Hz, 1H, CH, H10), 3.90–3.86 (m, 5H, OCH_3 and CH_2 , H2 and H13), 3.83 (s, 3H, OCH_3 , H12), 1.51 (s, 9H, CH_3 , H16).

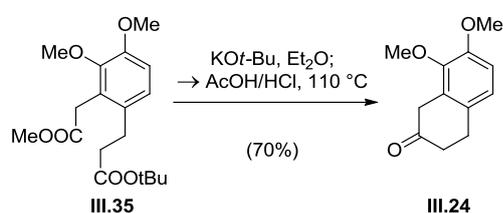


^{13}C NMR (75 MHz, CDCl_3): δ/ppm = 176.7 (COOH, C1), 166.5 (COOt-Bu, C11), 153.8 (Ar-C_q, C5), 147.7 (Ar-C_q, C4), 140.3 (CH, C9), 127.8 (Ar-C_q, C3), 127.6 (Ar-C_q, C8), 122.9 (Ar-CH, C7), 121.0 (CH, C10), 111.9 (Ar-CH, C6), 80.7 (C_q, C15), 60.8 (OCH₃, C13), 55.9 (OCH₃, C12), 31.8 (CH₂, C2), 28.3 (3 x CH₃, C16).

IR: $\tilde{\nu}/\text{cm}^{-1}$ = 2983 (w), 1734 (m), 1700 (s), 1494 (s), 1255 (m), 1145 (s), 1078 (s).

HRMS (EI) calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_6$: $[\text{M}]^+$ 322.1411, found 322.1400.

Preparation of β -tetralone **III.24**^[7]

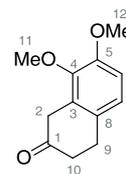


7,8-Dimethoxy-3,4-dihydronaphthalen-2(1H)-one (III.24). To a magnetically stirred solution of ester **III.35** (8.07 g, 23.8 mmol) in dry diethyl ether (300 mL) was added potassium *tert*-butoxide (3.34 g, 29.8 mmol) and the ensuing mixture was stirred at room temperature for 35 min. After the reaction mixture was cooled to 0 °C, aqueous HCl solution (1M, 300 mL) was added slowly and the resulting mixture was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Thus obtained crude product was re-dissolved in acetic acid (190 mL) and aqueous HCl (conc. 50 mL). Then, this mixture was heated to 110 °C for 3 h, and was then cooled to 0 °C before being quenched by a careful addition of NaHCO_3 (280 g). After dilution with water (700 mL), the reaction was extracted with diethyl ether (3 x 300 mL) and the combined organic layers were washed with aqueous NaHCO_3 solution (2 x 500 mL) and brine (500 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Thus obtained crude product was subjected to flash column chromatography (1:19→1:9→1:3 EtOAc/hexanes, gradient elution) providing 3.45 g (16.7 mmol, 70%) of β -tetralone **III.24** as a white solid.

R_f = 0.43, 1:3 EtOAc/hexanes.

mp: 75–76 °C (EtOAc/hexanes).

^1H NMR (300 MHz, CDCl_3): δ/ppm = 6.93 (d, 3J = 8.3 Hz, 1H, Ar-H, H7), 6.79 (d, 3J = 8.3 Hz, 1H, Ar-H, H6), 3.86 (s, 3H, OCH₃, H12), 3.81 (s, 3H, OCH₃, H11), 3.60 (s, 2H, CH₂, H2), 3.04–2.97 (m, 2H, CH₂, H9), 2.58–2.51 (m, 2H, CH₂, H10).

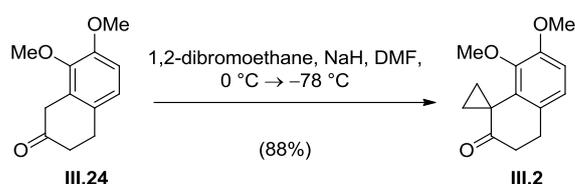


^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 210.6$ (CO, C1), 151.4 (Ar- C_q , C5), 146.5 (Ar- C_q , C4), 129.7 (Ar- C_q , C8), 127.5 (Ar- C_q , C3), 123.0 (Ar-CH, C7), 110.9 (Ar-CH, C6), 60.6 (OCH_3 , C11), 56.1 (OCH_3 , C12), 38.9 (CH_2 , C10), 38.7 (CH_2 , C2), 28.3 (CH_2 , C9).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2998$ (w), 2944 (w), 1702 (s), 1492 (s), 1350 (w), 1273 (s), 1155 (w), 1080 (s).

HRMS (EI) calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3^+ [\text{M}]^+$ 206.0937, found 206.0942.

Preparation of cyclopropane III.2

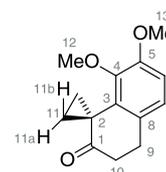


7',8'-Dimethoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-2'-one (III.2). To a magnetically stirred solution of β -tetralone **III.24** (500 mg, 2.42 mmol) and dibromoethane (682 mg, 3.63 mmol, 310 μL) in dry DMF (9 mL) was added sodium hydride (60wt% suspension in mineral oil, 240 mg, 6.00 mmol) at 0 $^\circ\text{C}$ and the ensuing mixture was stirred for 90 min before being cooled to $-78\text{ }^\circ\text{C}$. After addition of MeOH (15 mL), the reaction was allowed to warm to 0 $^\circ\text{C}$ and water (50 mL) was added. The mixture was extracted with diethyl ether (4 x 50 mL) and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Thus obtained crude product was subjected to flash column chromatography (1:4 EtOAc/hexanes) providing 497 mg (2.14 mmol, 88%) of cyclopropane **III.2** as white solid.

$R_f = 0.57$, 1:3 EtOAc/hexanes.

mp: 59–61 $^\circ\text{C}$ (EtOAc/hexanes).

^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 6.90$ (ddd, $^3J = 8.2$ Hz, $^4J = 0.8$ Hz, $^4J = 0.8$ Hz, 1H, Ar-H, H7), 6.73 (d, $^3J = 8.2$ Hz, 1H, Ar-H, H6), 3.84 (s, 3H, OCH_3 , H13), 3.74 (s, 3H, OCH_3 , H12), 3.02–2.97 (m, 2H, CH_2 , H9), 2.65 – 2.60 (m, 2H, CH_2 , H10), 1.89–1.86 (m, 2H, CH_2 , H11b), 1.67–1.65 (m, 2H, CH_2 , H11a).

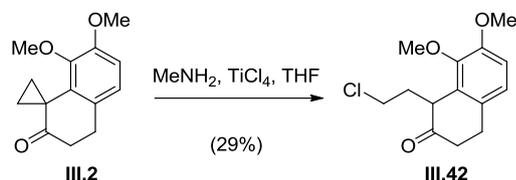


^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 210.4$ (CO, C1), 152.2 (Ar- C_q , C5), 146.9 (Ar- C_q , C4), 131.9 (Ar- C_q , C8), 130.4 (Ar- C_q , C3), 122.9 (Ar-CH, C7), 109.8 (Ar-CH, C6), 61.5 (OCH_3 , C12), 56.0 (OCH_3 , C13), 39.4 (CH_2 , C10), 31.3 (C_q , C2), 28.2 (CH_2 , C9), 21.3 (2 x CH_2 , C11).

IR: $\tilde{\nu}/\text{cm}^{-1} = 2936$ (m), 1686 (m), 1575 (w), 1478 (m), 1263 (s), 1045 (s).

HRMS (EI) calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_3^+ [\text{M}]^+$ 232.1094, found 232.1097.

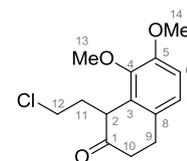
Preparation of cyclopropane **III.42**



1-(2-Chloroethyl)-7,8-dimethoxy-3,4-dihydronaphthalen-2(1H)-one (III.42). To a solution of cyclopropane **III.2** (10.0 mg, 43.0 μmol , 1 eq) in dry THF (0.5 mL) was added a solution of methylamine in THF (2M, 177 μL , 0.344 mmol, 8 eq), followed by a solution of titanium tetrachloride in toluene (1M, 21.5 μL , 21.5 μmol , 0.5 eq). The reaction mixture was stirred at room temperature for 5 d, and was then quenched with aqueous saturated NaHCO_3 solution (5 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic fractions were washed with brine (10 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. Thus provided crude material was subjected to flash column chromatography (1:19 \rightarrow 1:9 \rightarrow 1:4 EtOAc/hexanes, gradient elution) to give 3.3 mg (12.3 μmol , 29%) of chloride **III.42** as a colorless oil.

$R_f = 0.36$, 1:3 EtOAc/hexanes.

$^1\text{H-NMR}$ (600 MHz, CDCl_3): $\delta = 6.92$ (br d, $^3J = 8.3$ Hz, 1H, Ar-H, H7), 6.81 (d, $^3J = 8.3$ Hz, 1H, Ar-H, H6), 3.87 (s, 3H, OCH_3 , H14), 3.87–3.85 (m, 1H, CH, H2), 3.84 (s, 3H, OCH_3 , H13), 3.58 (ddd, $^2J = 10.9$ Hz, $^3J = 8.5$ Hz, $^3J = 5.7$ Hz, 1H, CH_2 , H12), 3.48 (ddd, $^2J = 10.9$ Hz, $^3J = 8.4$ Hz, $^3J = 7.1$ Hz, 1H, CH_2 , H12), 3.18–3.11 (m, 1H, CH_2 , H9), 2.91 (ddd, $^2J = 15.6$ Hz, $^3J = 6.4$ Hz, $^3J = 2.7$ Hz, 1H, CH_2 , H9), 2.74 (ddd, $^2J = 17.3$ Hz, $^3J = 5.0$ Hz, $^3J = 2.7$ Hz, 1H, CH_2 , H10), 2.46–2.41 (m, 1H, CH_2 , H10), 2.25–2.20 (m, 2H, CH_2 , H11) ppm.



$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 212.3$ (CO, C1), 151.5 (Ar- C_q , C5), 146.7 (Ar- C_q , C4), 130.4 (Ar- C_q , C3), 129.3 (Ar- C_q , C8), 123.4 (Ar-CH, C7), 111.4 (Ar-CH, C6), 60.9 (OCH_3 , C13), 56.0 (OCH_3 , C14), 46.3 (CH, C2), 42.5 (CH_2 , C12), 38.4 (CH_2 , C10), 36.5 (CH_2 , C11), 27.3 (CH_2 , C9) ppm.

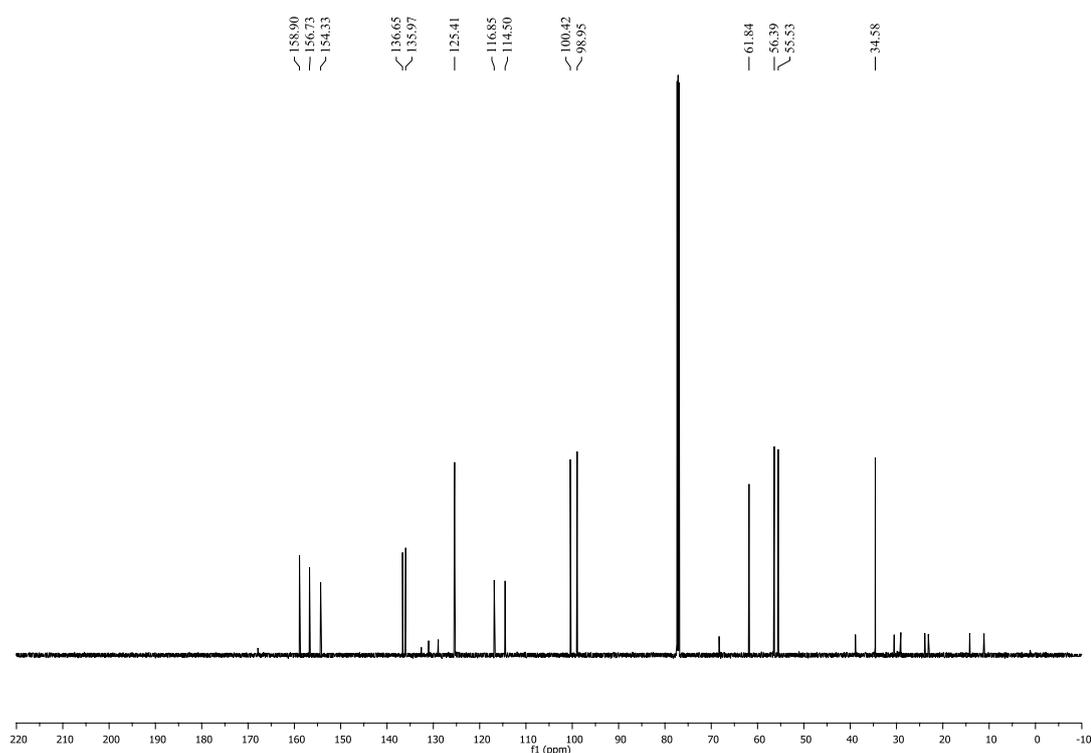
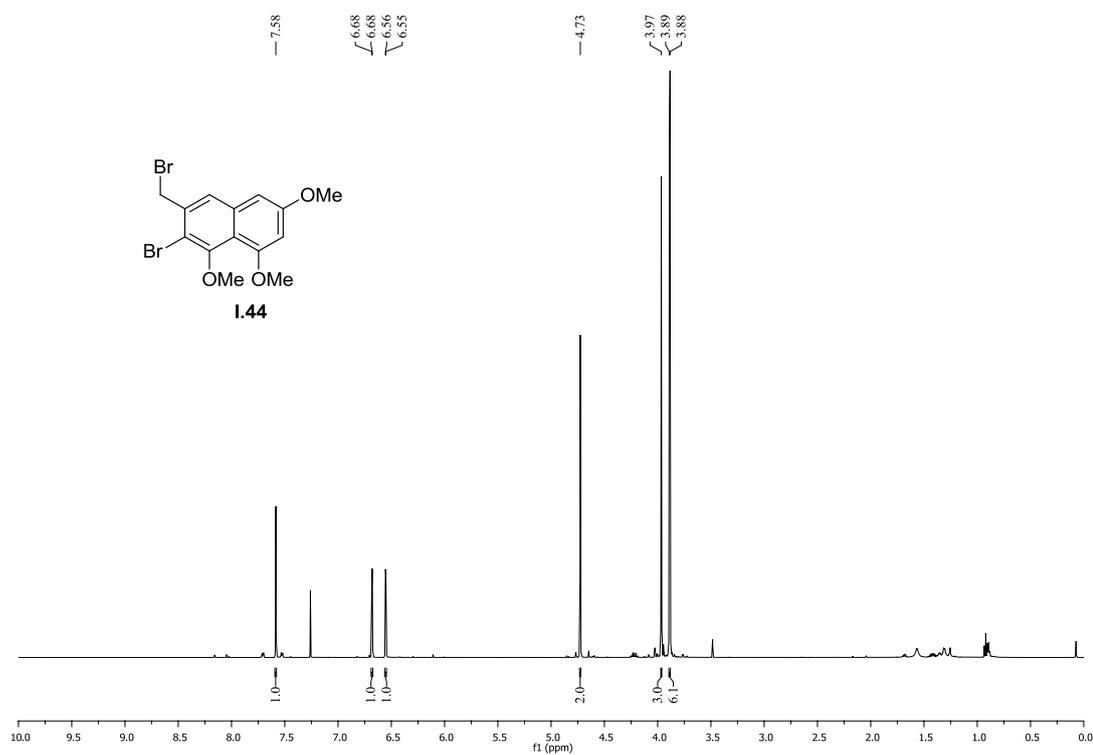
IR: $\tilde{\nu}/\text{cm}^{-1} = 2942$ (w), 1706 (s), 1606 (w), 1491 (s), 1278 (s), 1087 (s), 807 (m).

HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{16}\text{ClO}_3^+ [\text{M-H}]^+$ 267.0782, found: 267.0781.

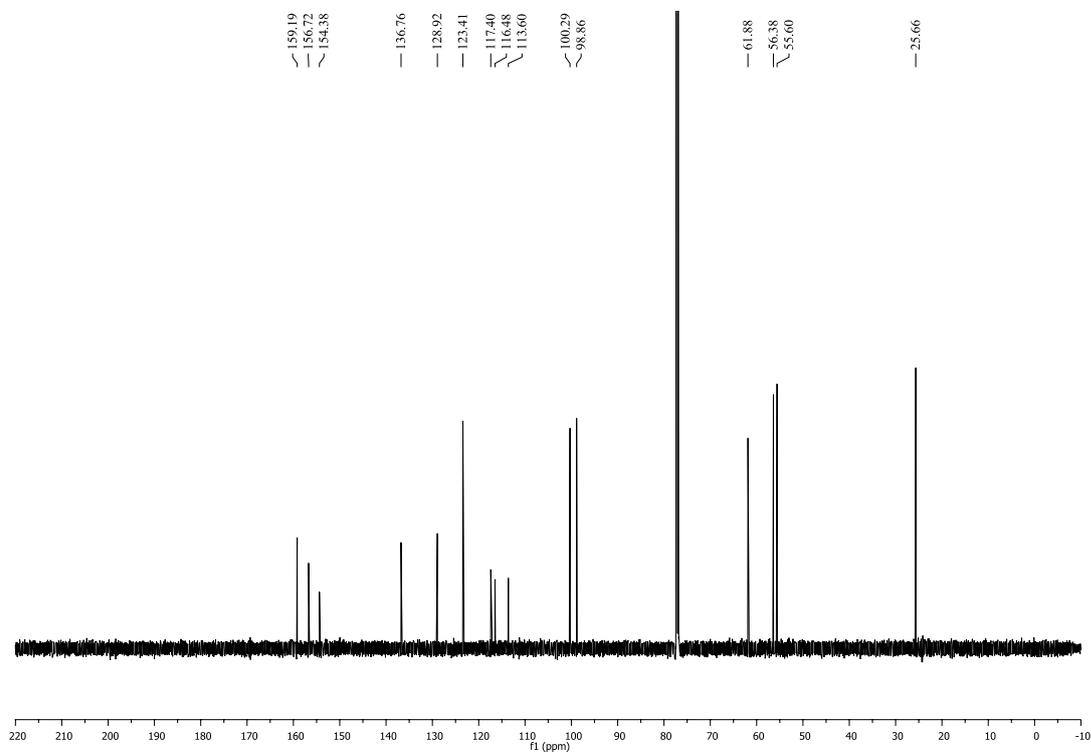
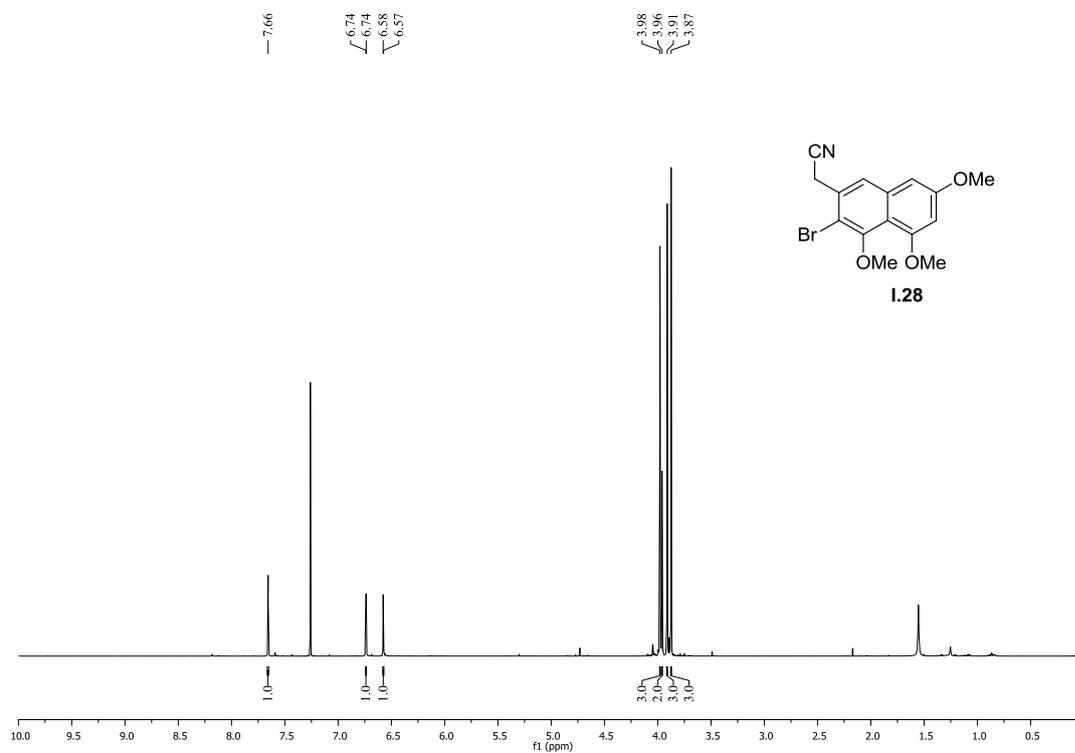
APPENDIX I

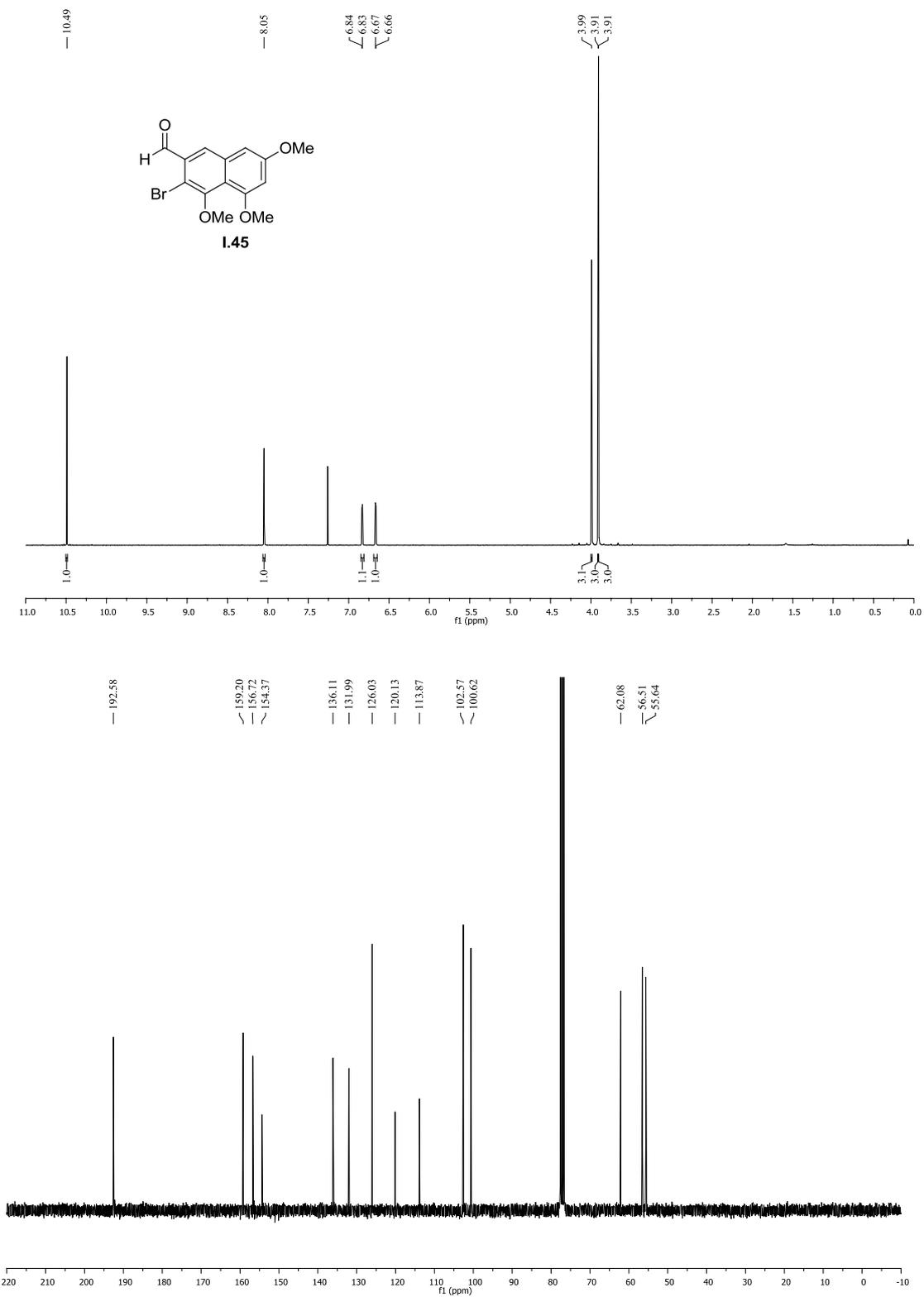
—NMR spectra—

APPENDIX I: NMR SPECTRA

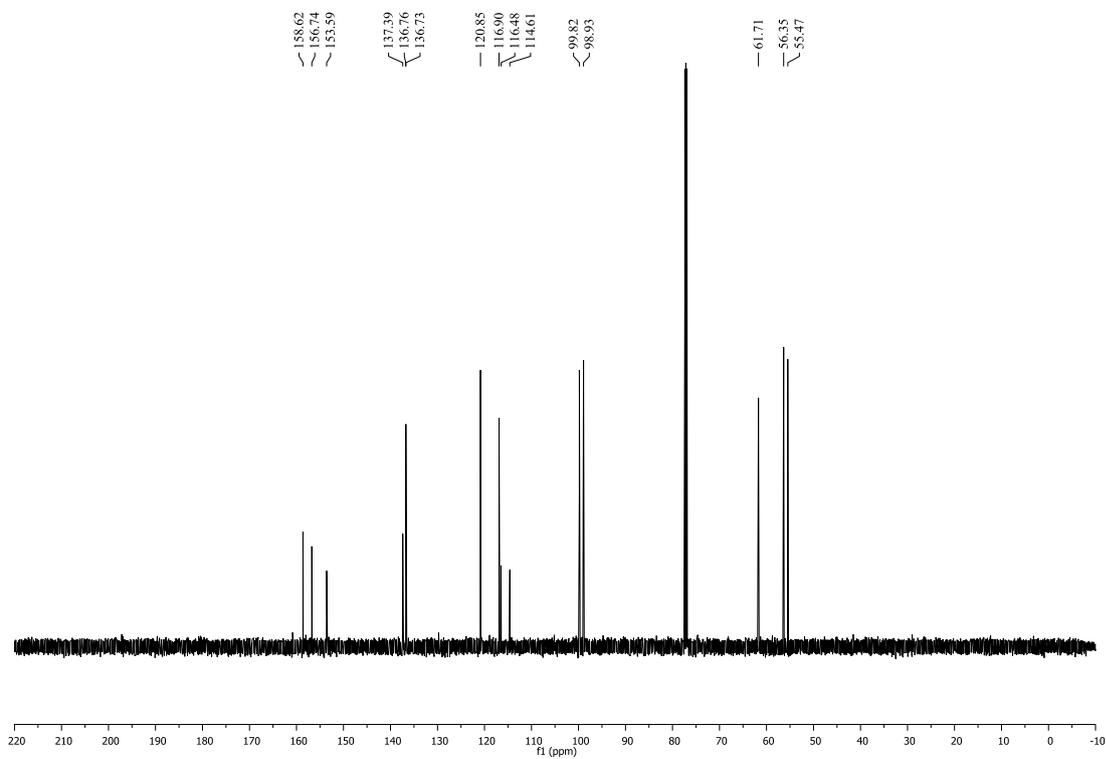
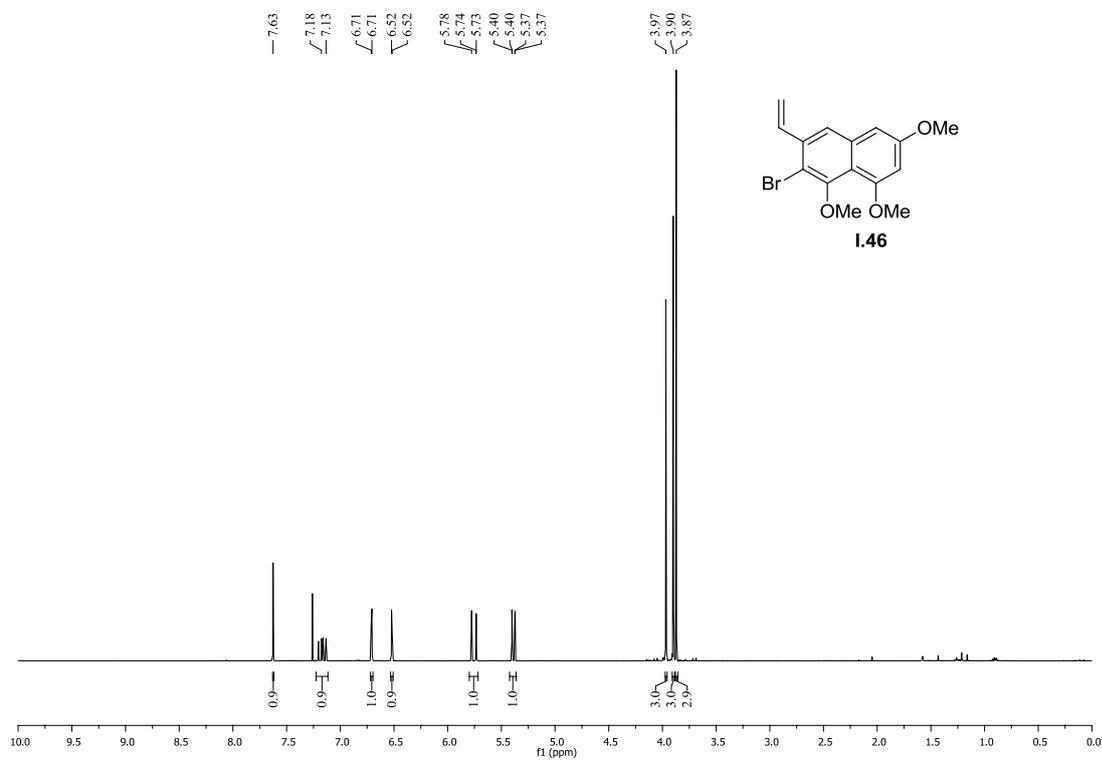
2-Bromo-3-(bromomethyl)-1,6,8-trimethoxynaphthalene (I.44) (^1H , ^{13}C)

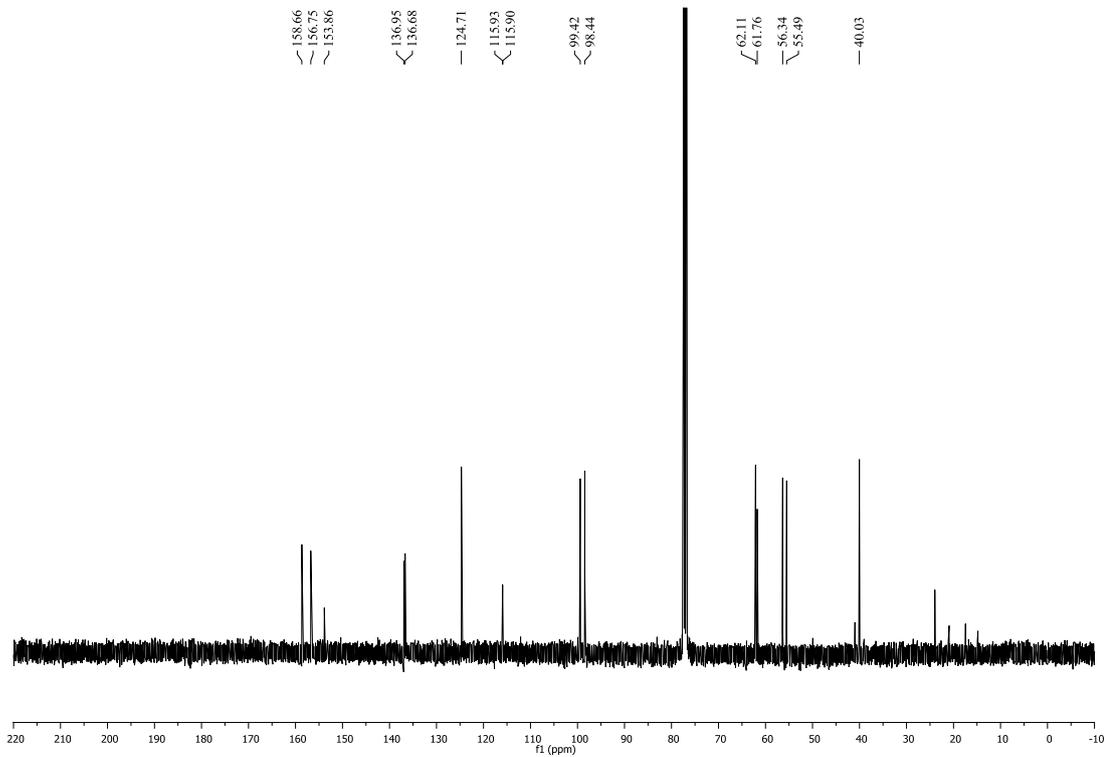
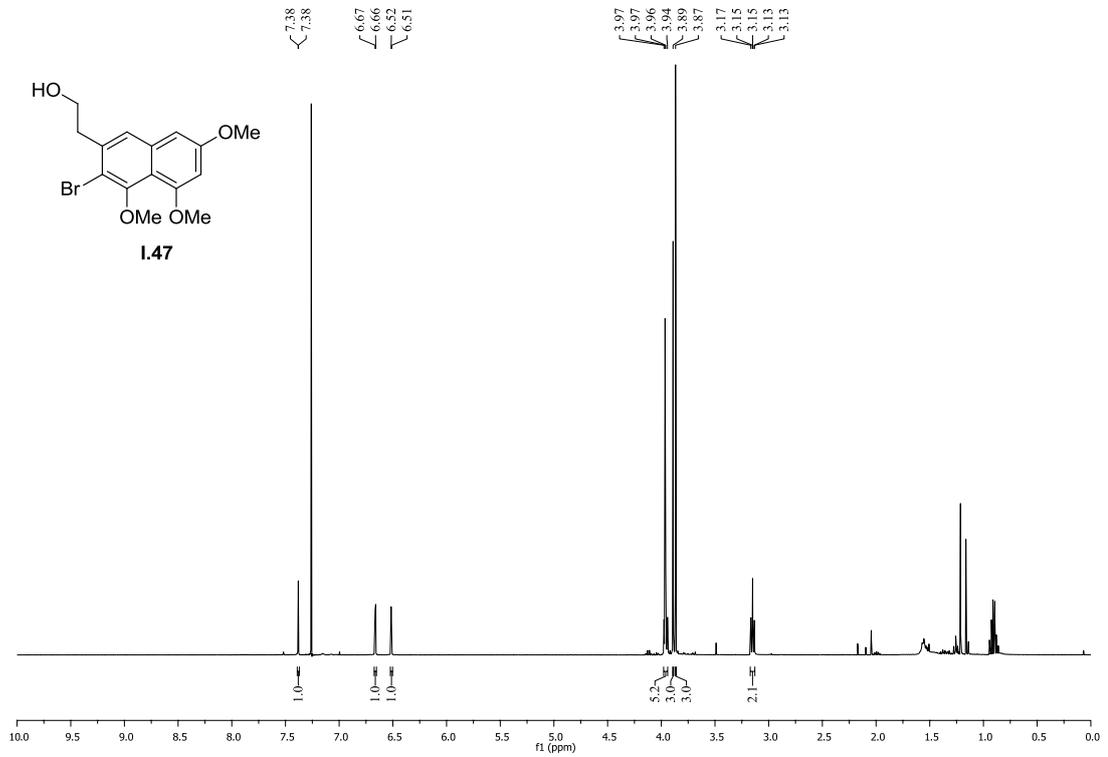
2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)acetonitrile (I.28) (^1H , ^{13}C)

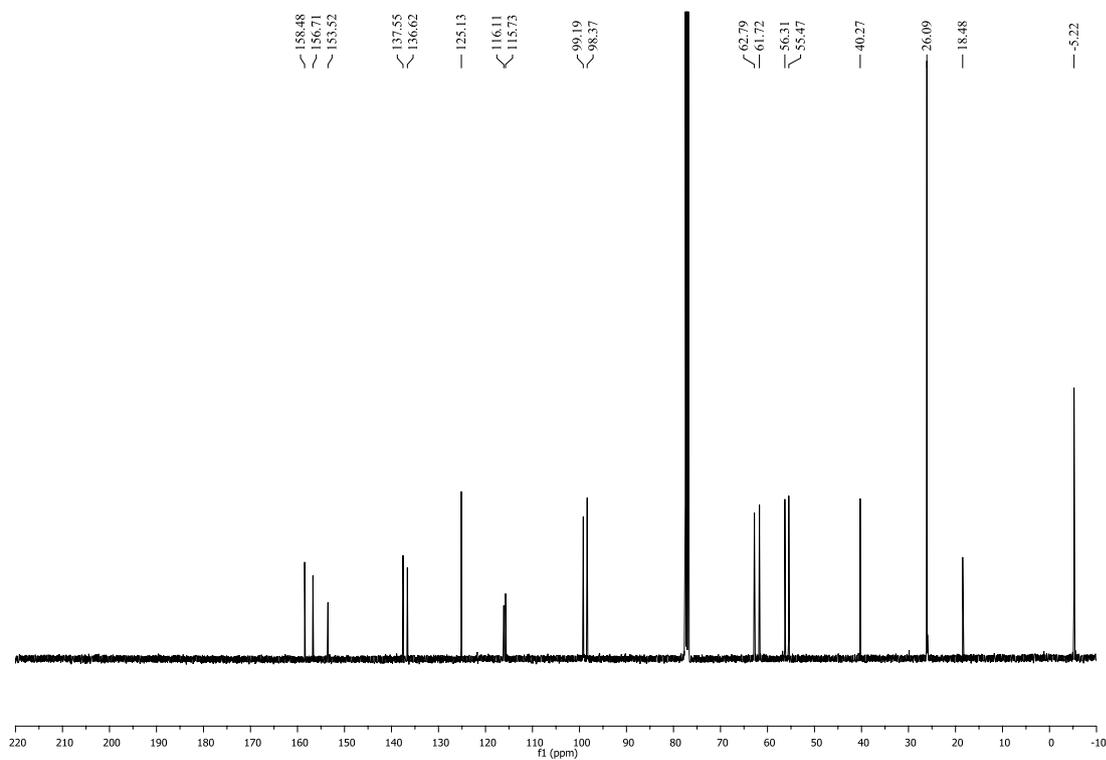
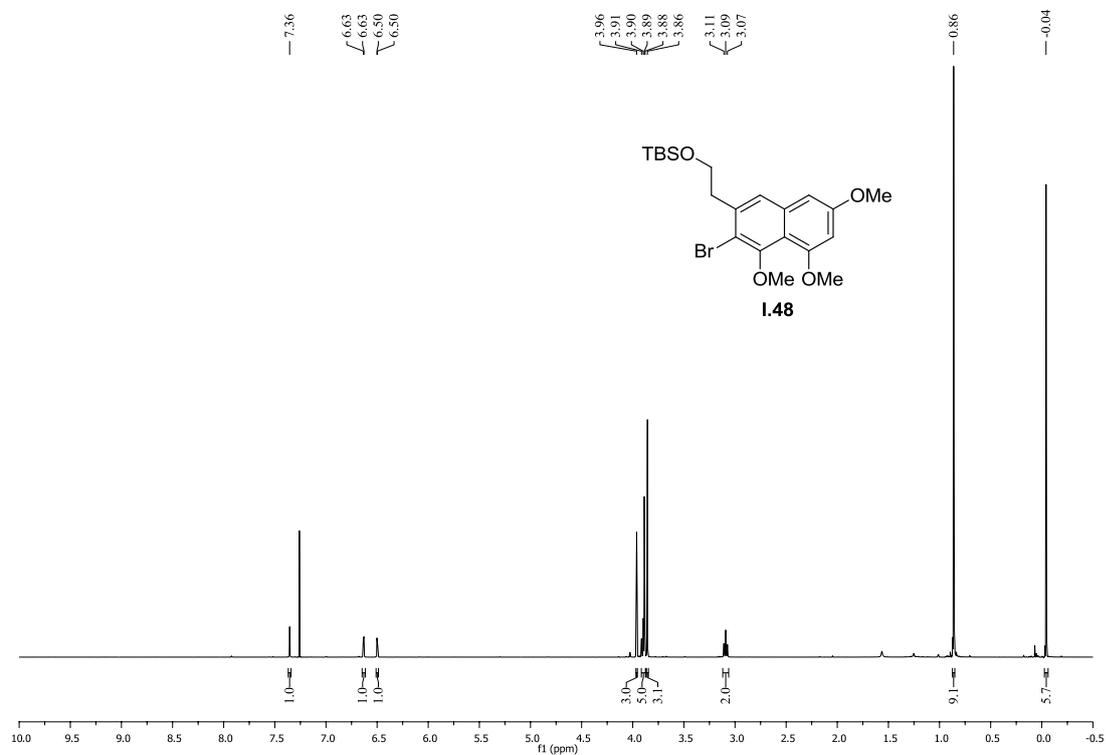


3-Bromo-4,5,7-trimethoxy-2-naphthaldehyde (1.45) (^1H , ^{13}C)

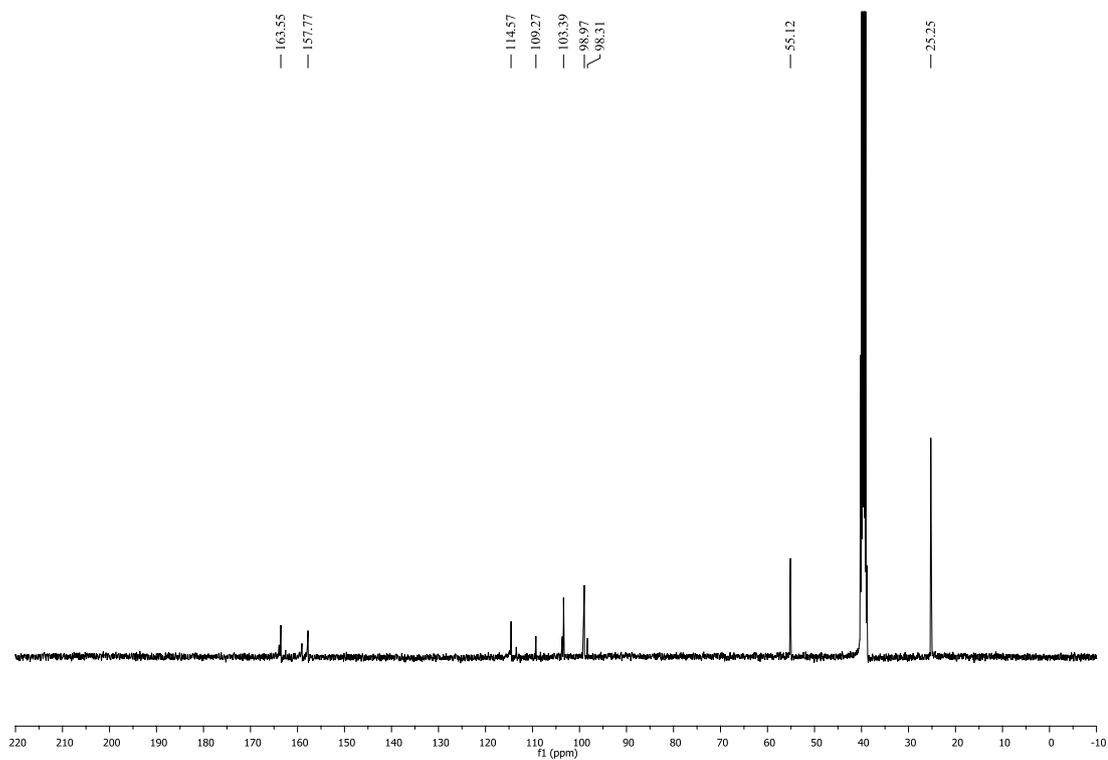
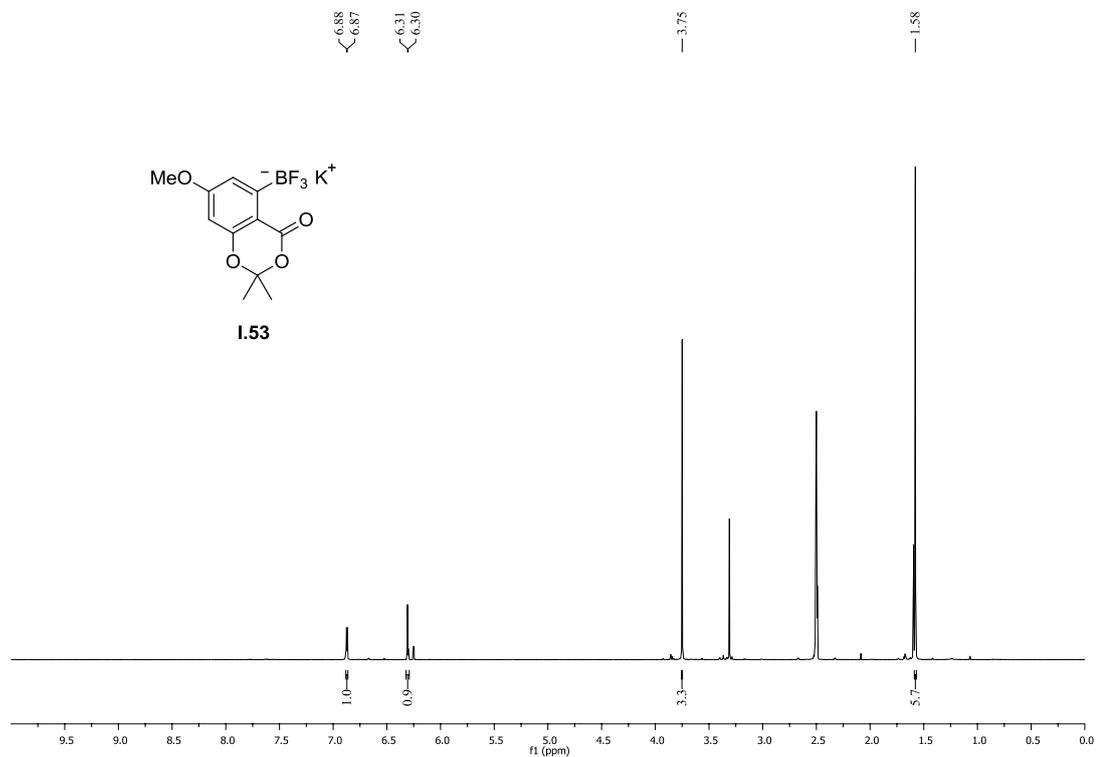
2-Bromo-1,6,8-trimethoxy-3-vinylnaphthalene (I.46) (^1H , ^{13}C)

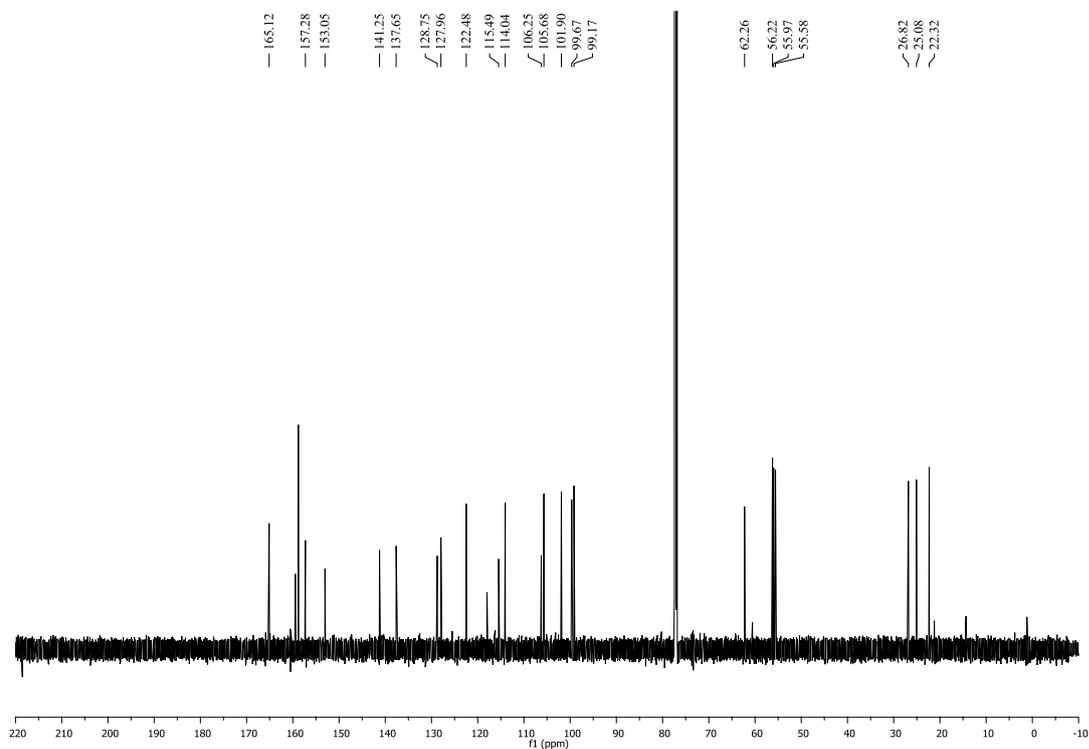
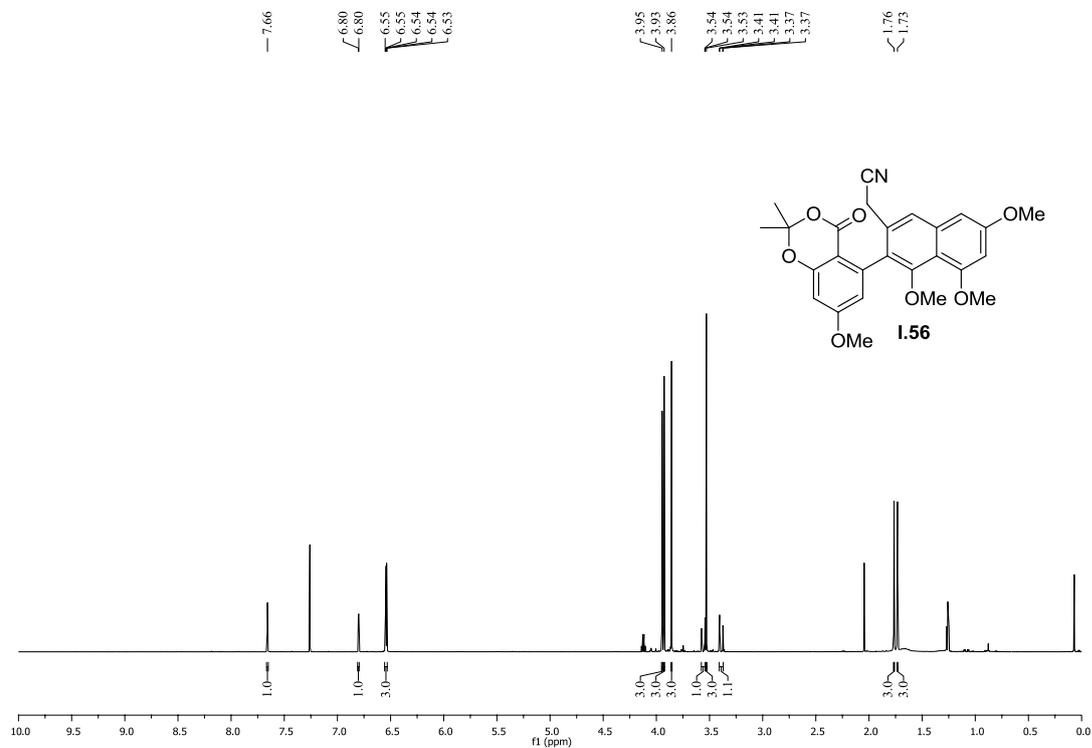


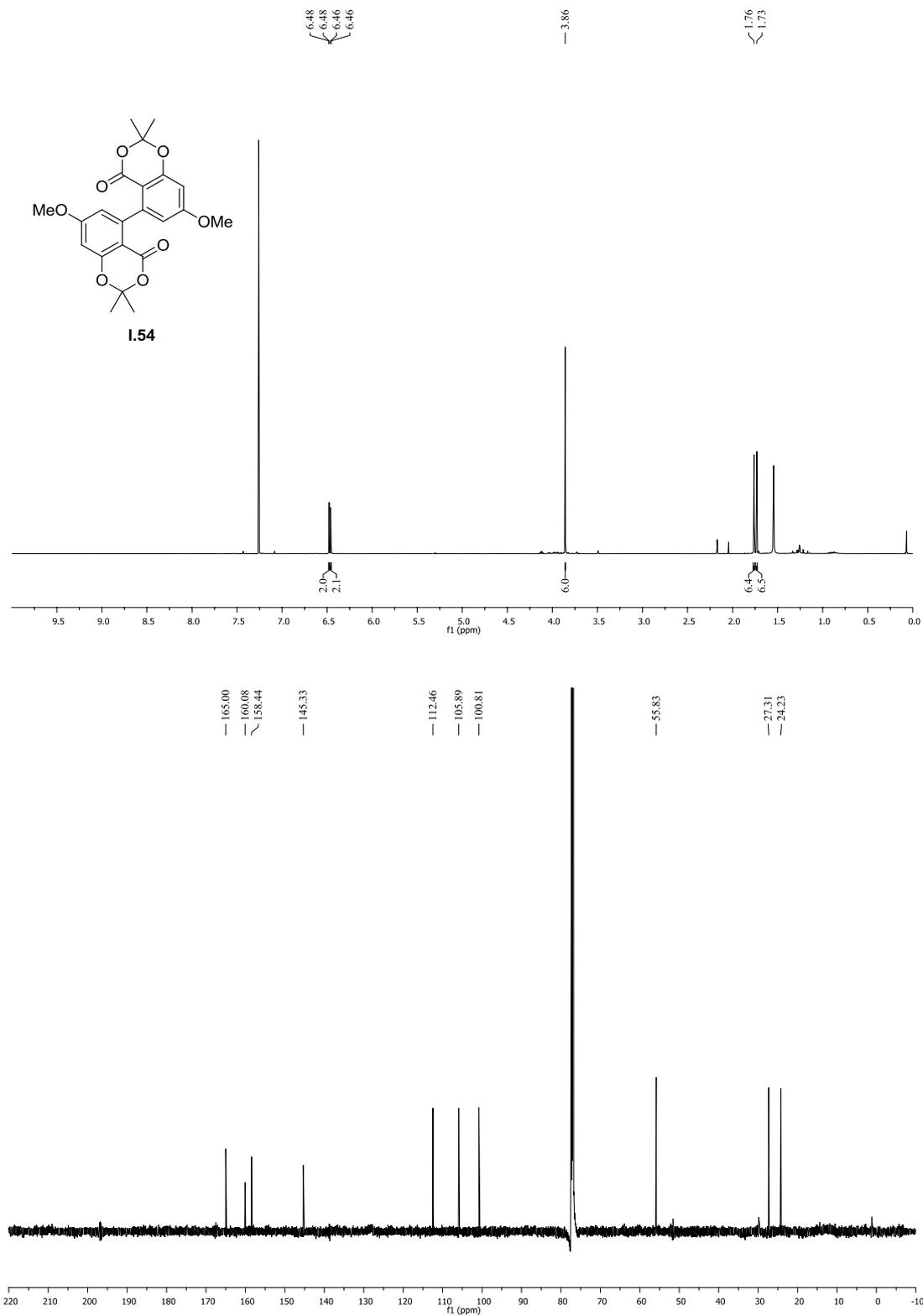
2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)ethanol (I.47) (^1H , ^{13}C)

(2-(3-Bromo-4,5,7-trimethoxynaphthalen-2-yl)ethoxy)(tert-butyl)dimethylsilane (I.48) (^1H , ^{13}C)

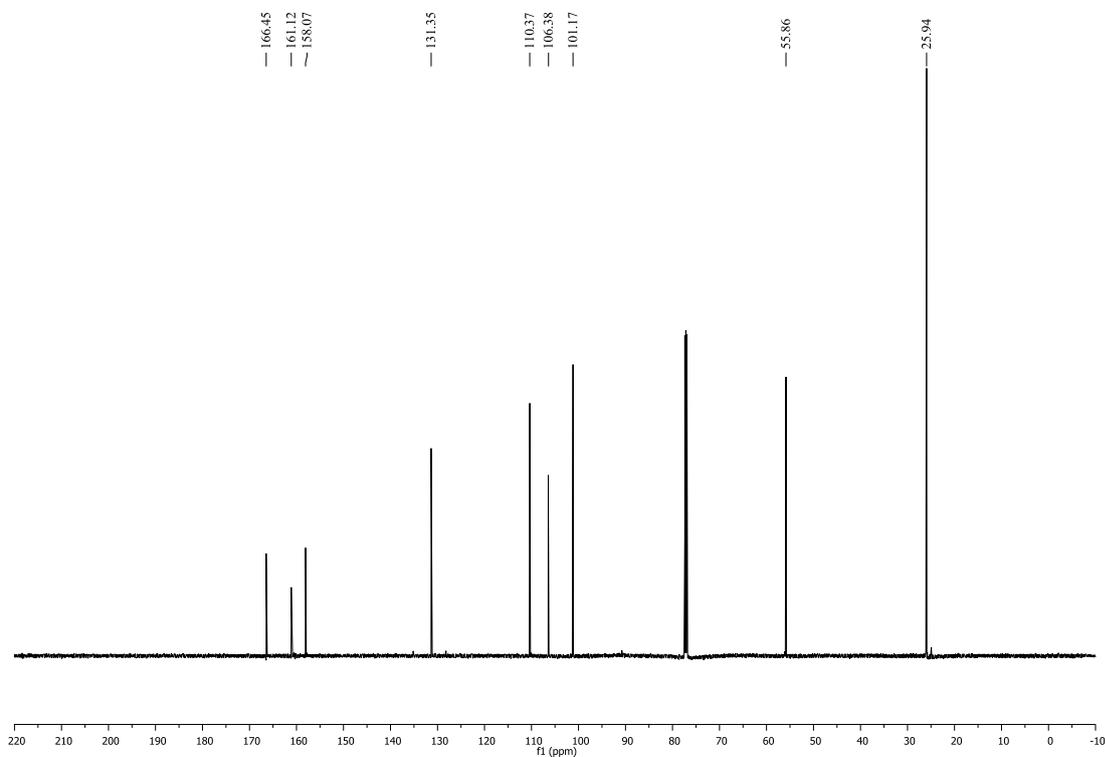
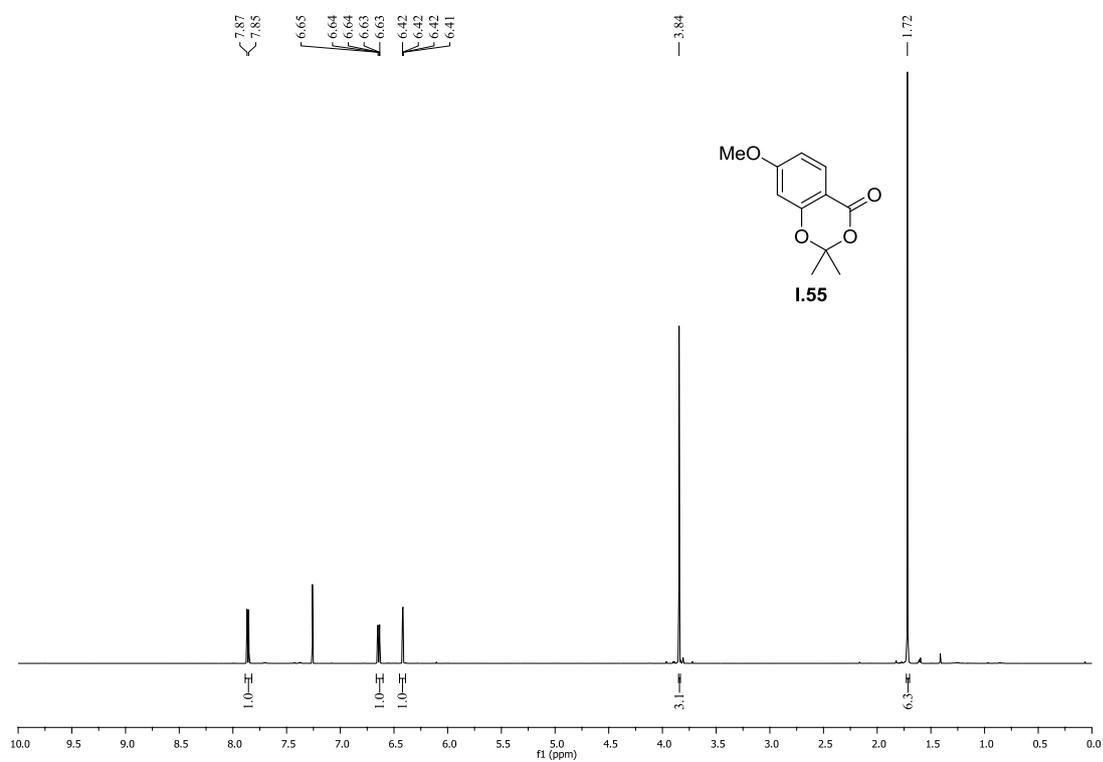
Potassium trifluoro(7-methoxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)borate (I.53) (^1H , ^{13}C)



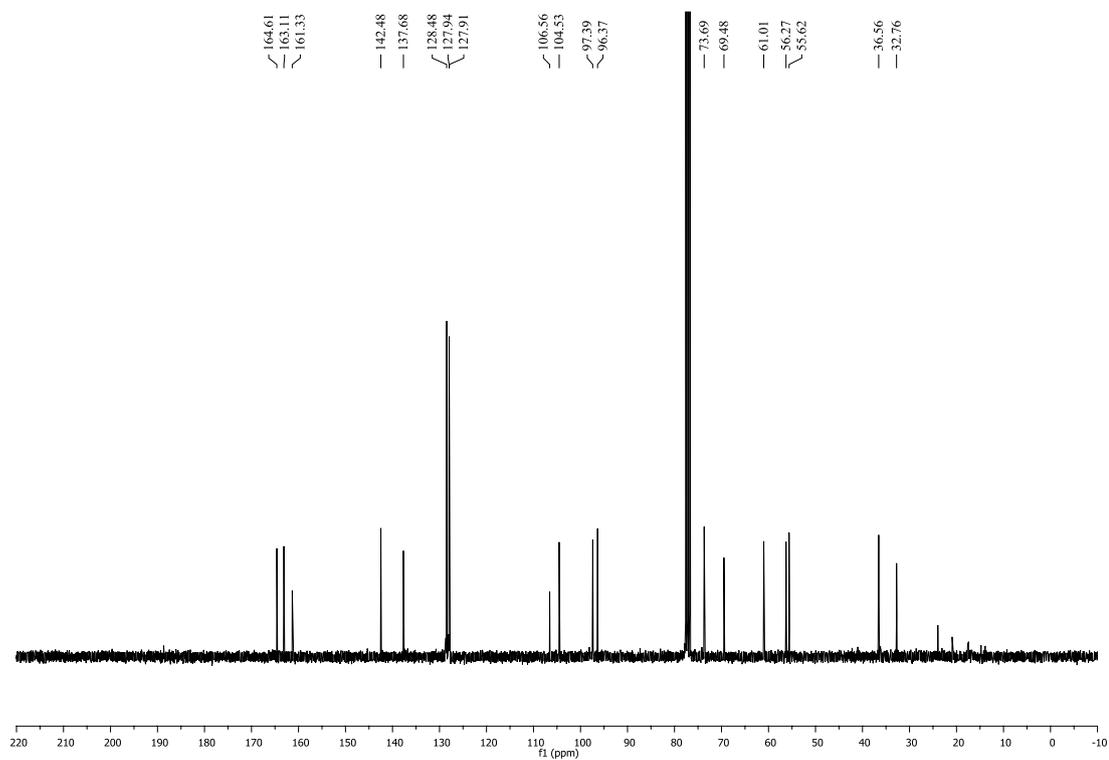
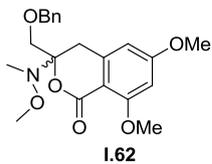
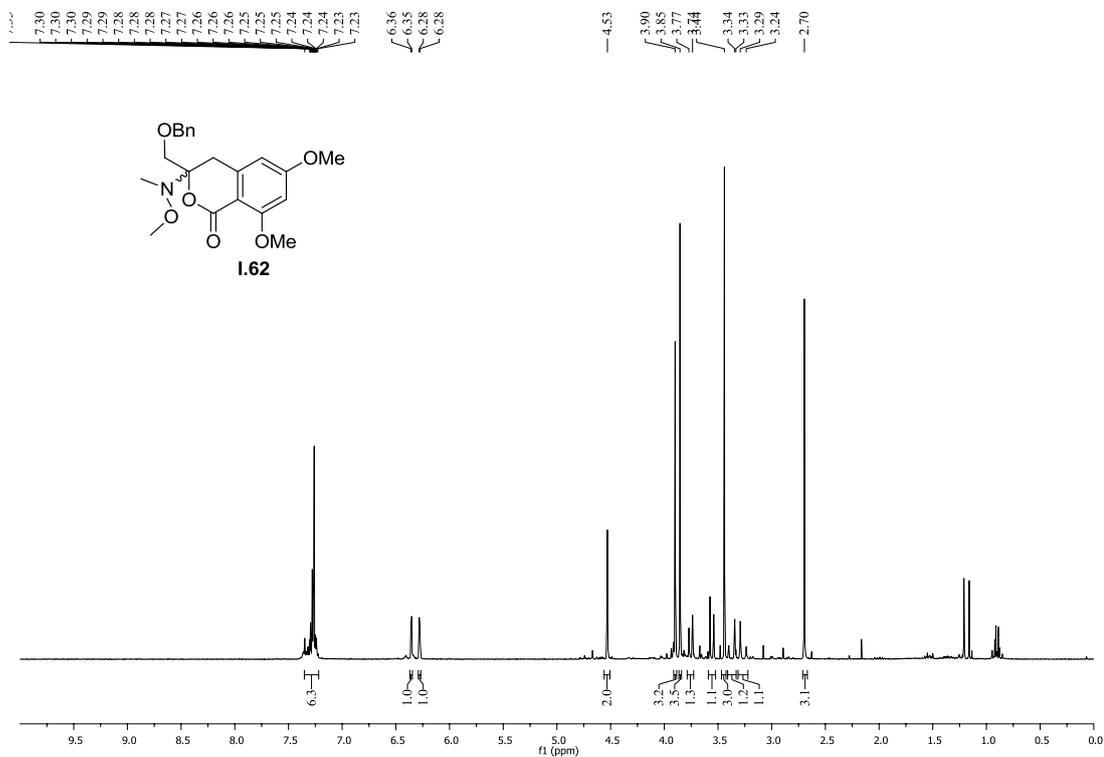
2-(4,5,7-Trimethoxy-3-(7-methoxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)naphthalen-2-yl)acetonitrile (I.56) (^1H , ^{13}C)

7,7'-Dimethoxy-2,2,2',2'-tetramethyl-4*H*,4'*H*-[5,5'-bibenzo[*d*][1,3]dioxine]-4,4'-dione (1.54)
(¹H, ¹³C)

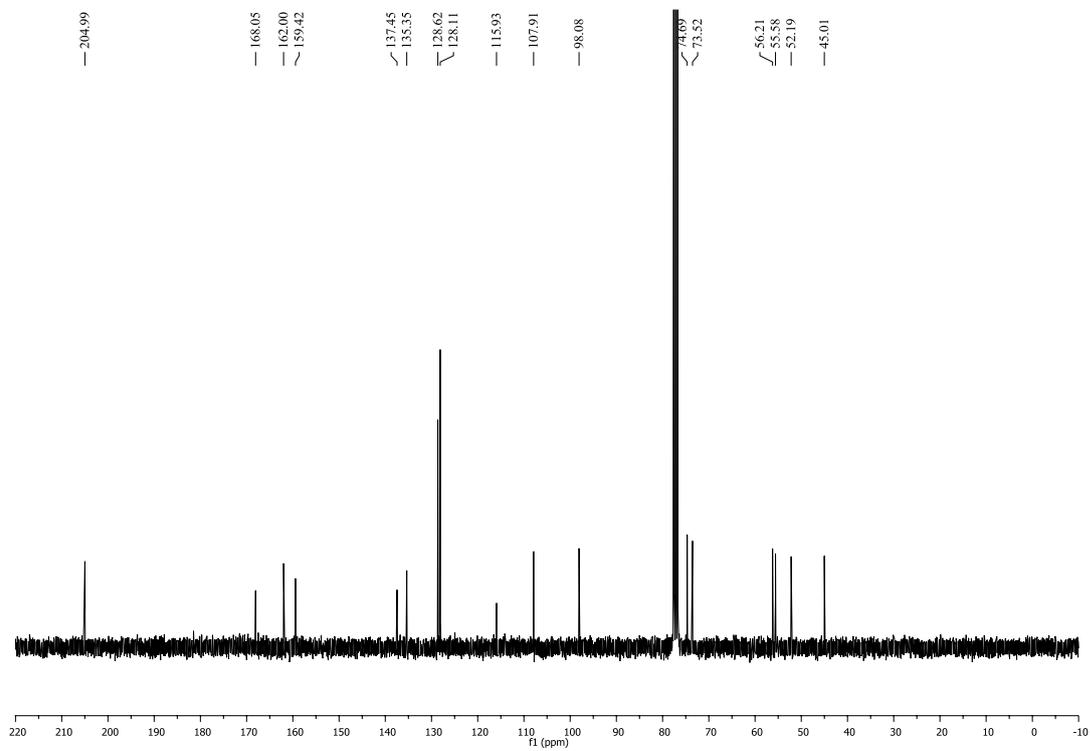
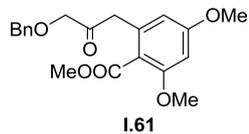
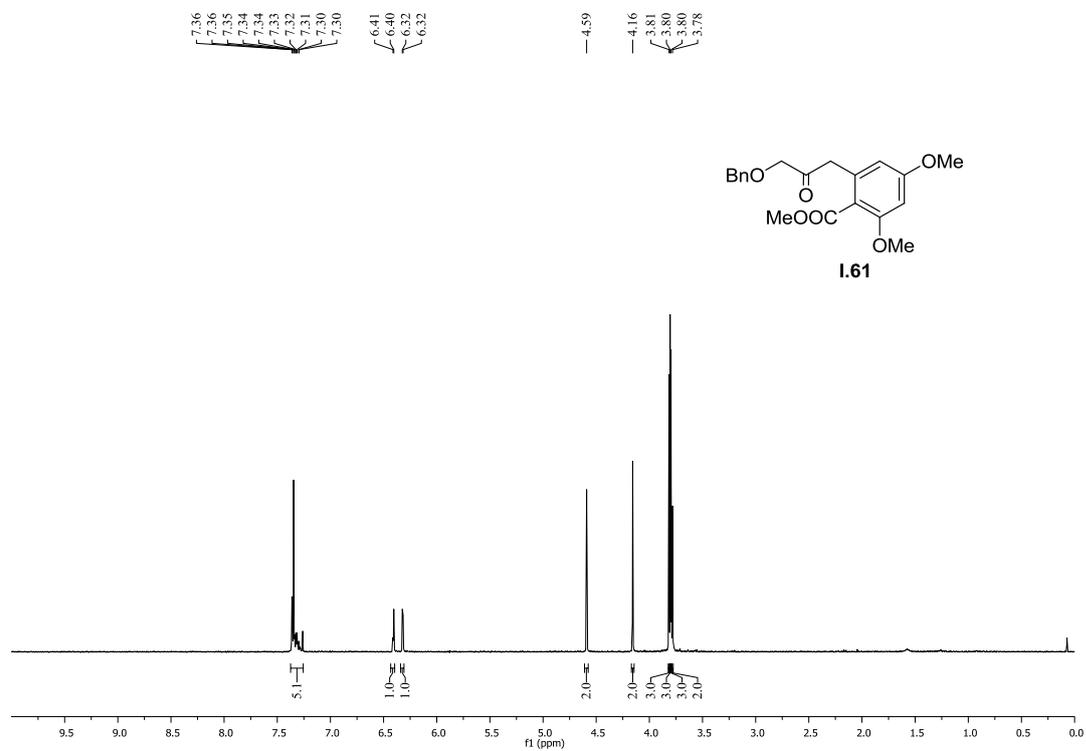
7-Methoxy-2,2-dimethyl-4H-benzo[*d*][1,3]dioxin-4-one (I.55) (^1H , ^{13}C)

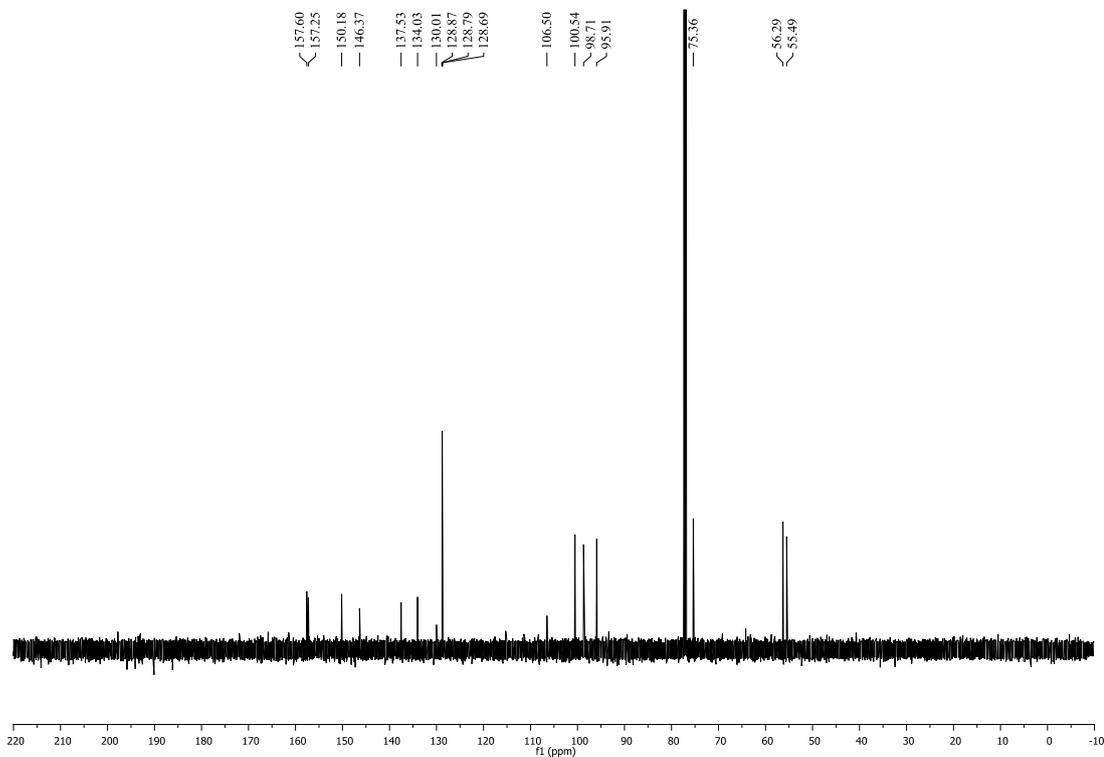
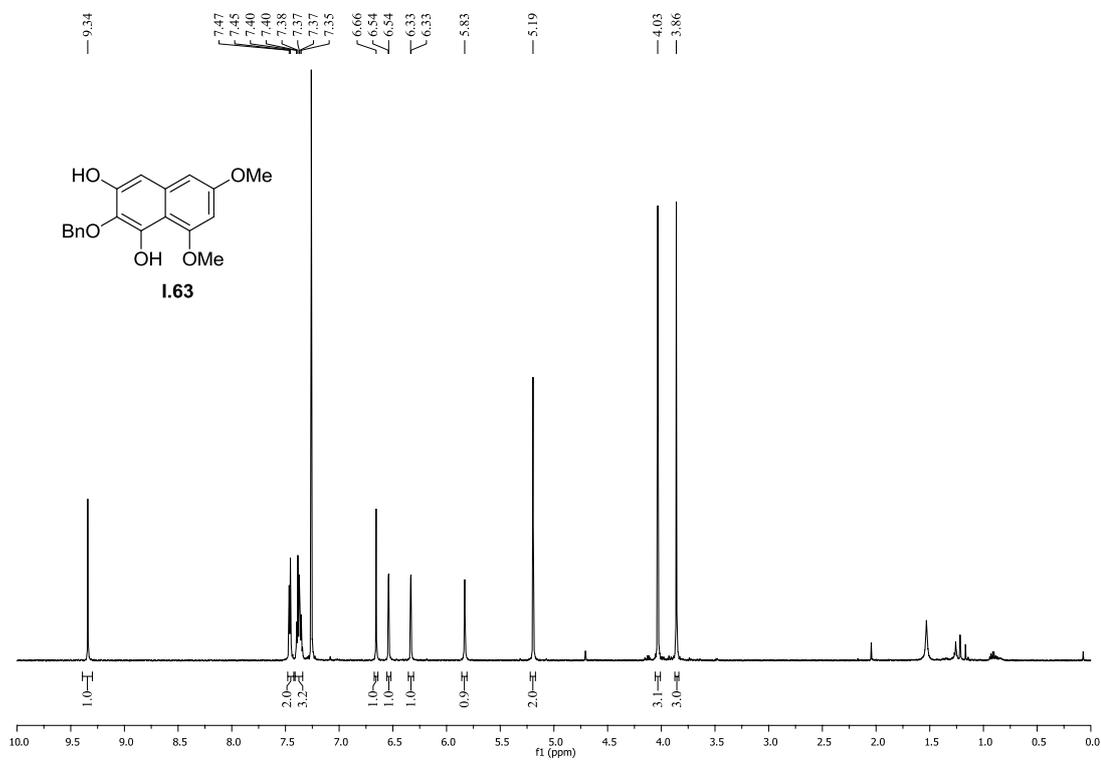


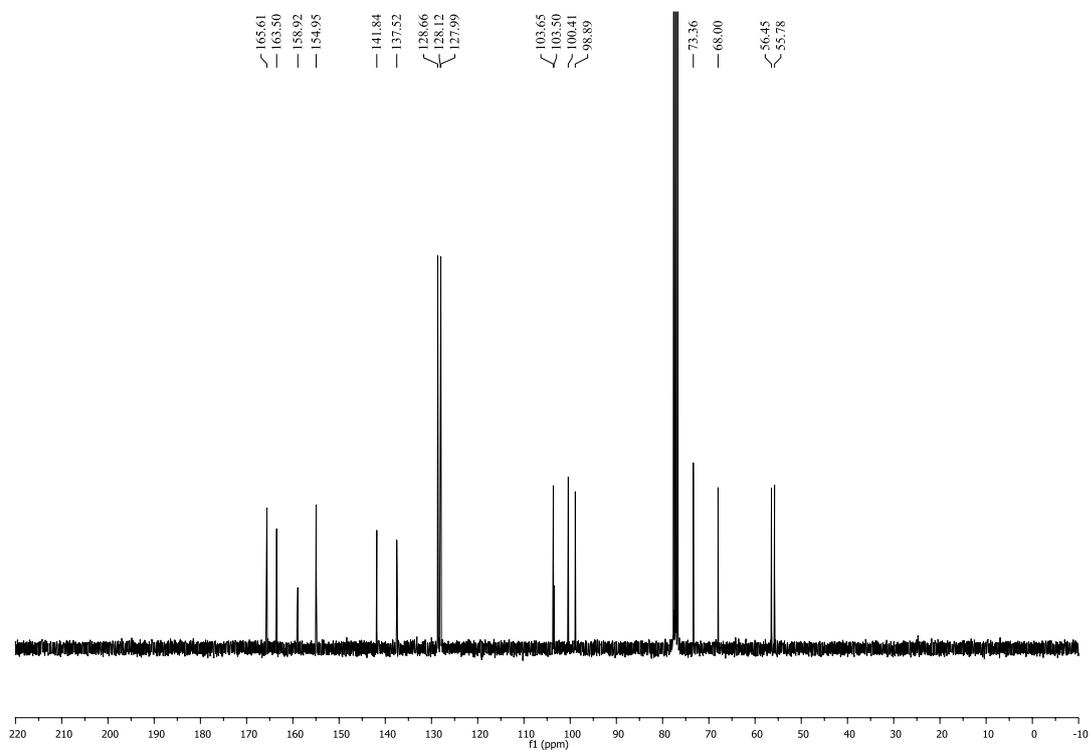
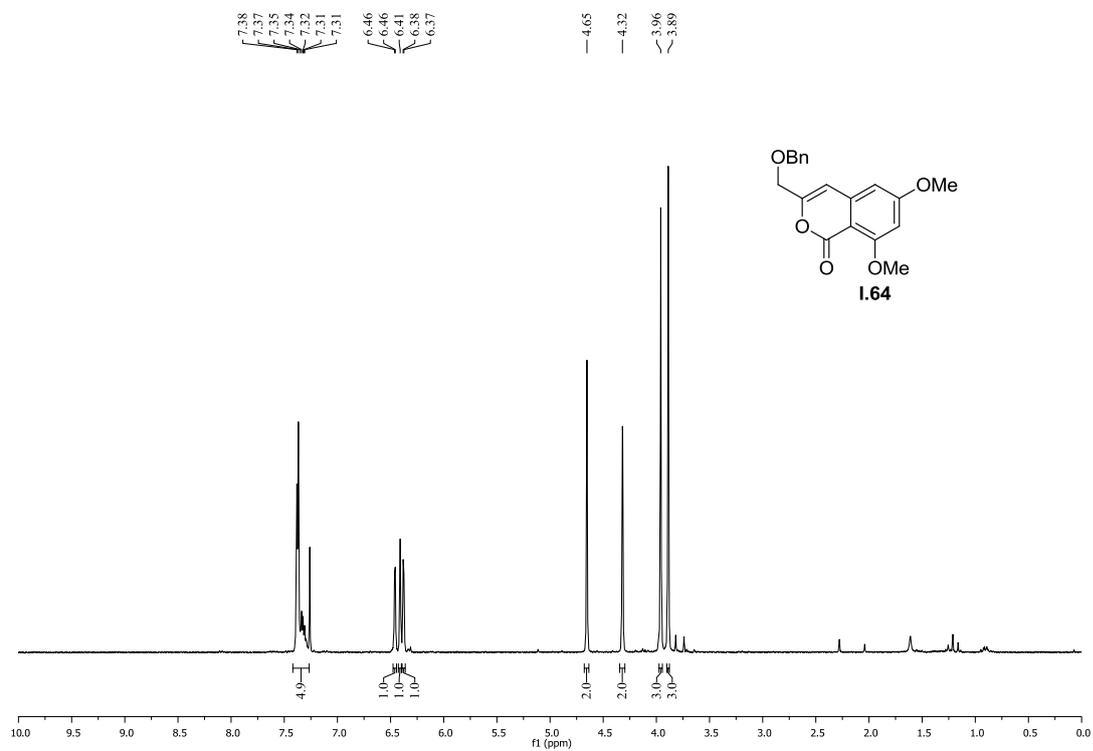
3-((Benzyloxy)methyl)-6,8-dimethoxy-3-((methoxy(methyl)amino)methyl)-3,4-dihydro naphthalen-1(2H)-one (I.62) (^1H , ^{13}C)



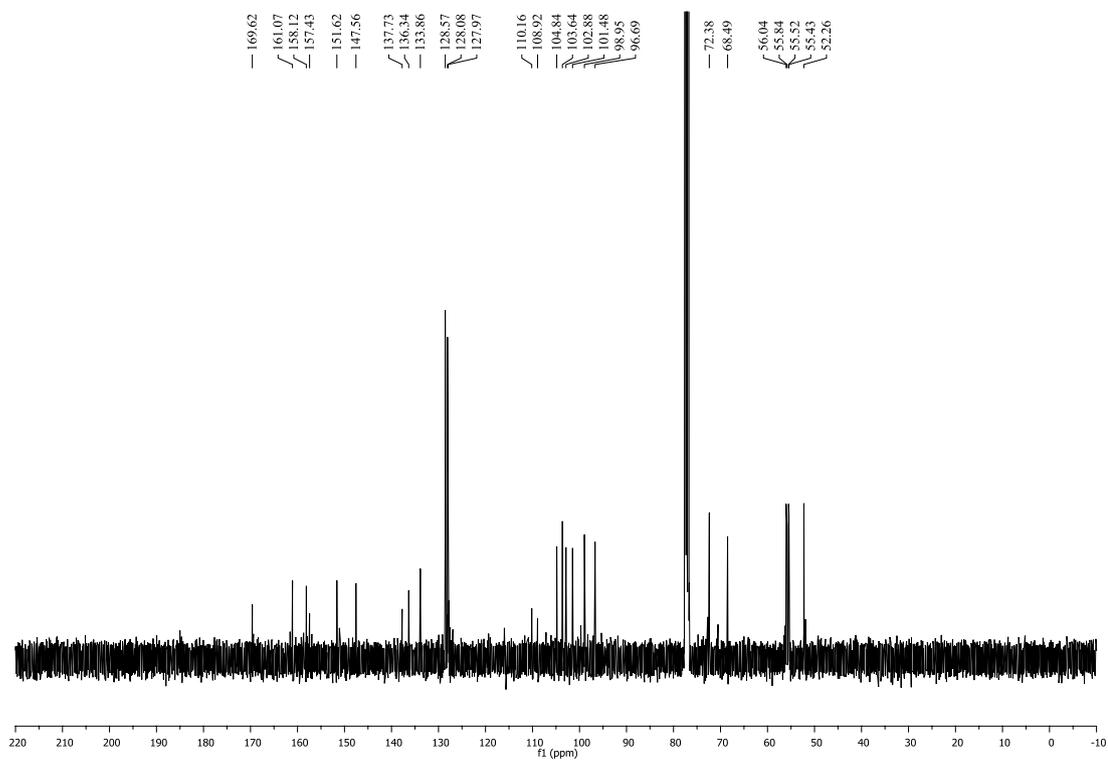
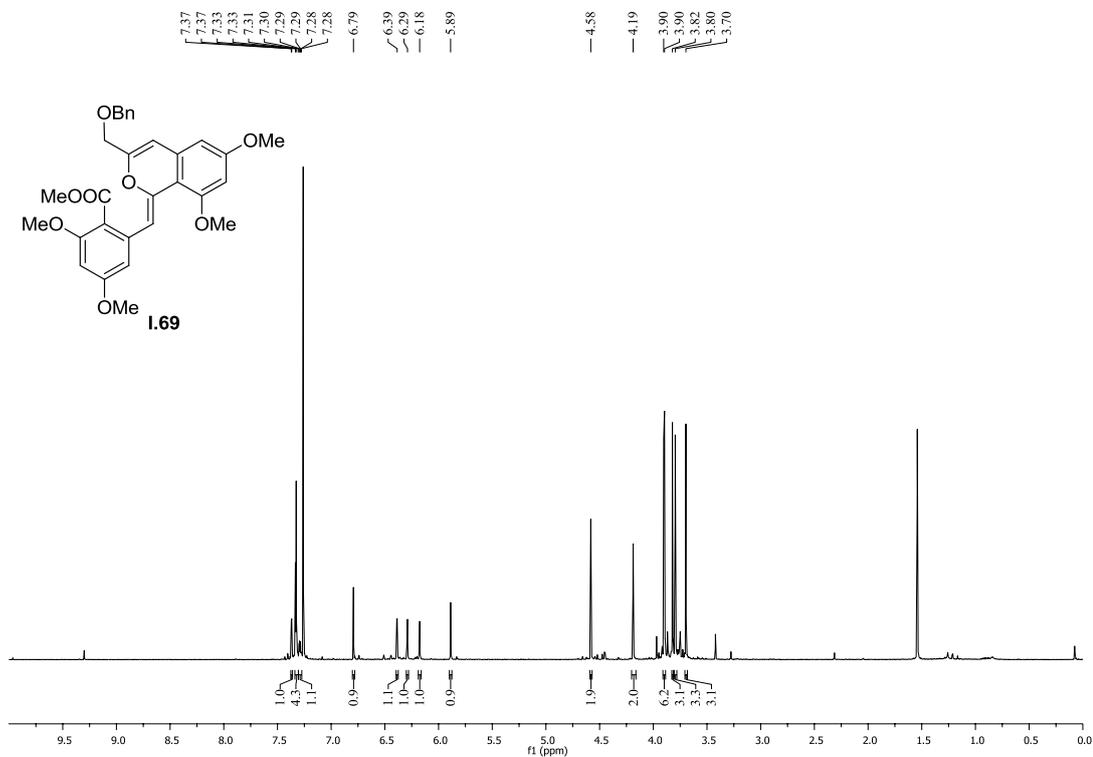
Methyl 2-(3-(benzyloxy)-2-oxopropyl)-4,6-dimethoxybenzoate (**I.61**) (^1H , ^{13}C)

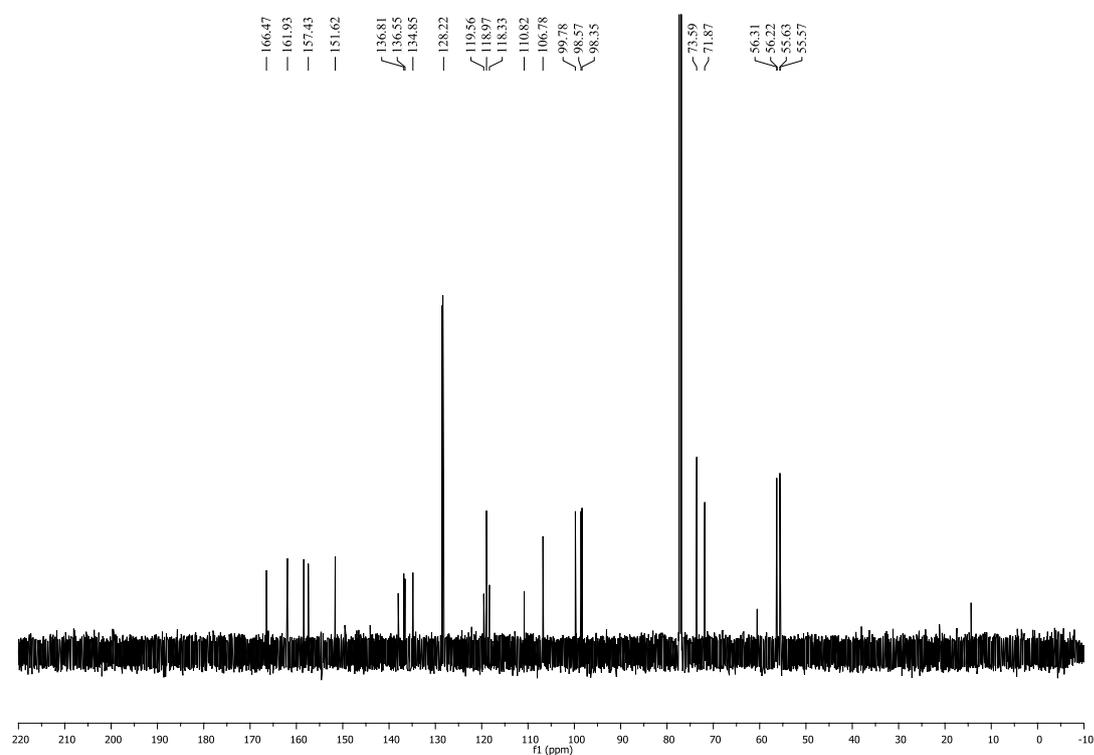
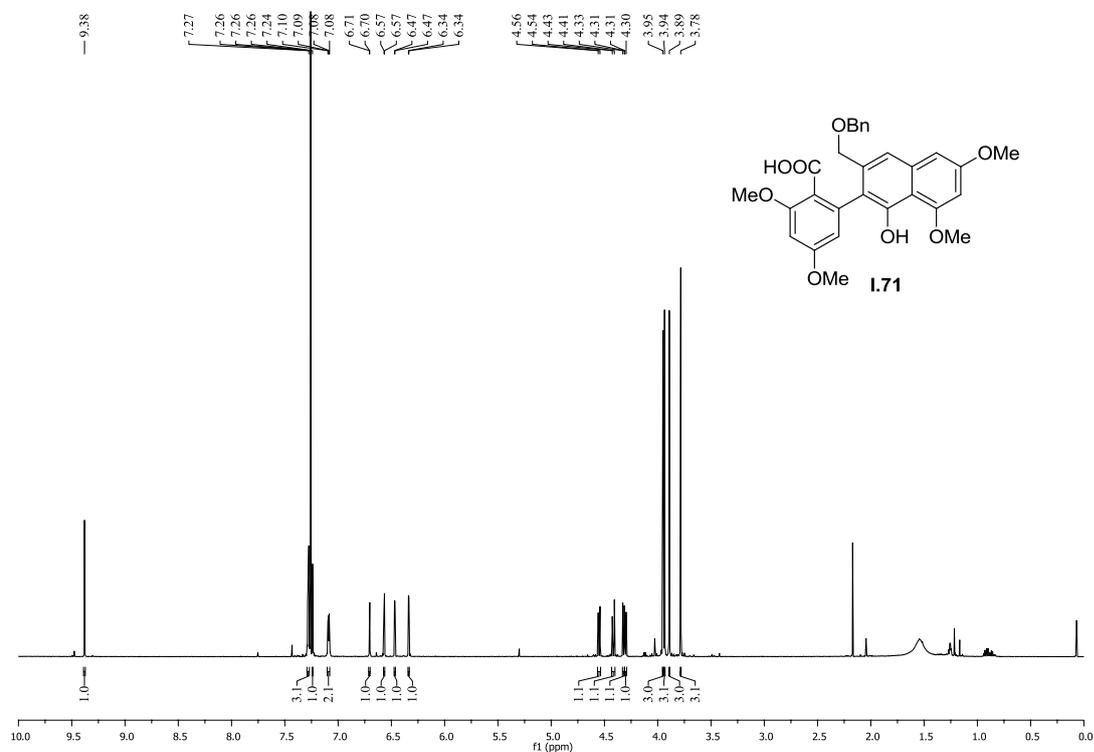


2-(Benzyloxy)-6,8-dimethoxynaphthalene-1,3-diol (I.63) (^1H , ^{13}C)

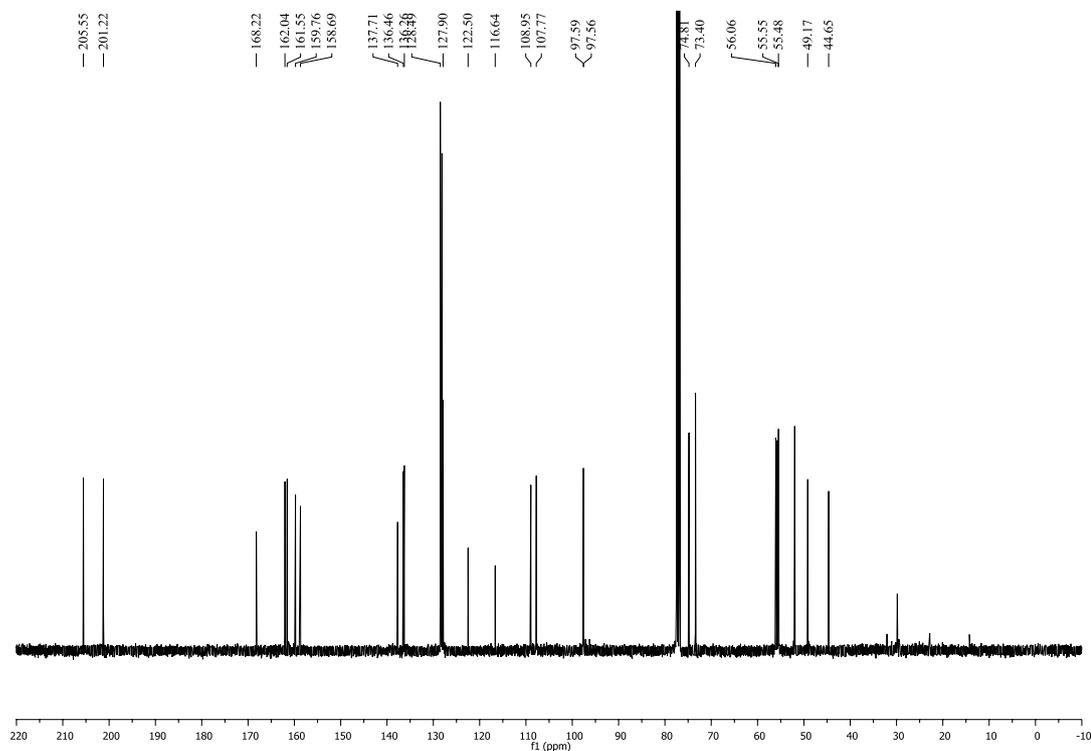
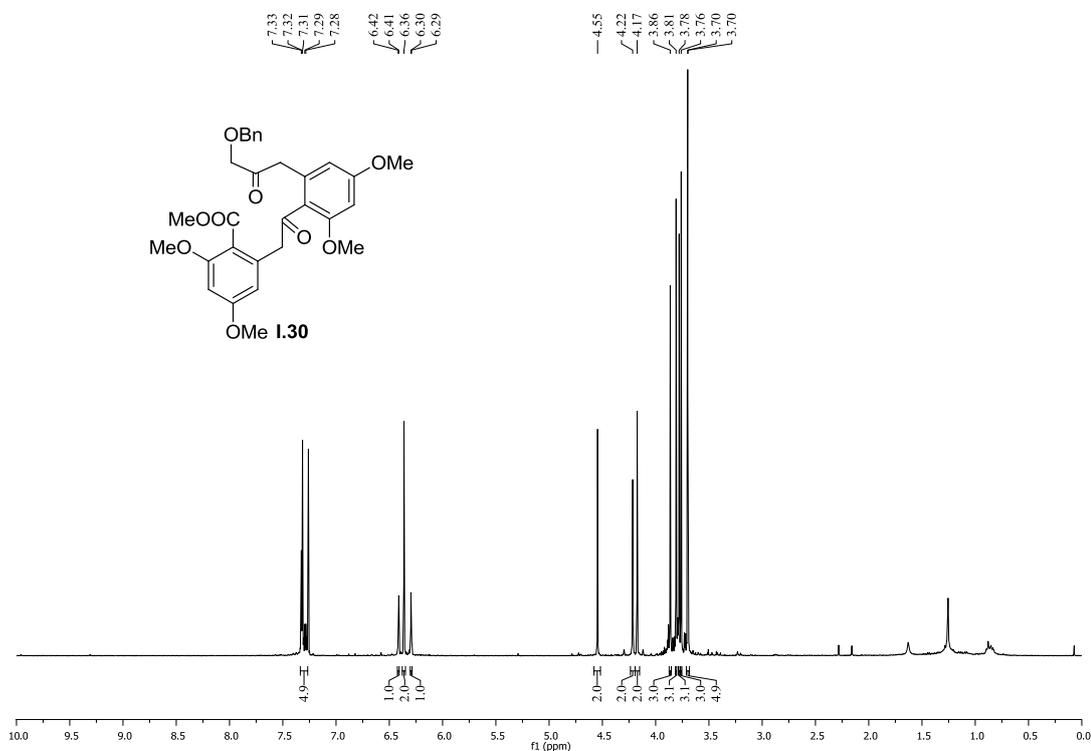
3-((Benzyloxy)methyl)-6,8-dimethoxy-1*H*-isochromen-1-one (I.64) (¹H, ¹³C)

**(Z)-3-((Benzyloxy)methyl)-1-(3,5-dimethoxy-2-methylbenzylidene)-6,8-dimethoxy-1H-
isochromene (I.69) (¹H, ¹³C)**

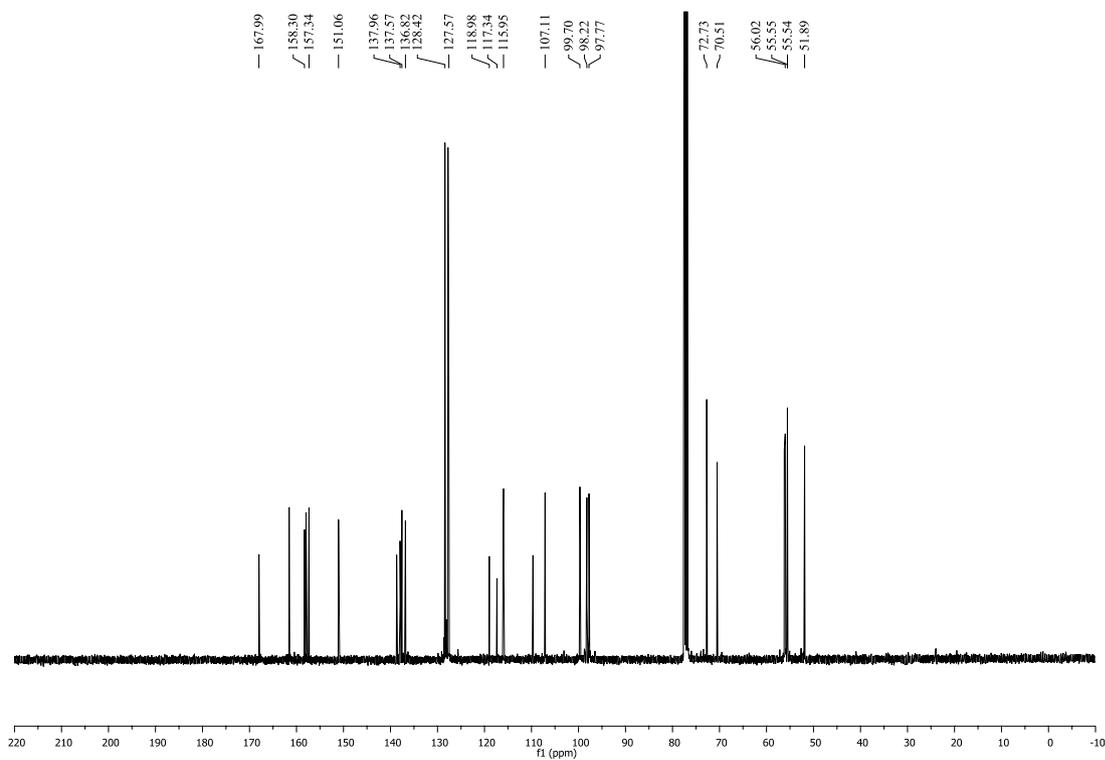
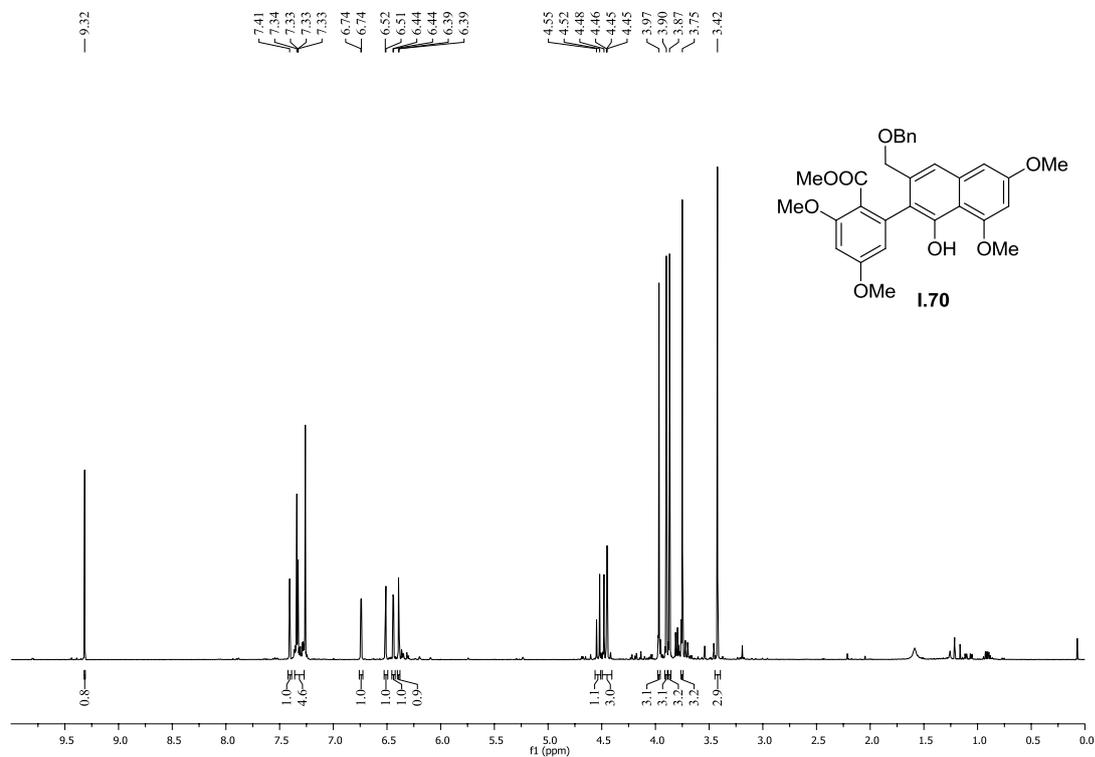


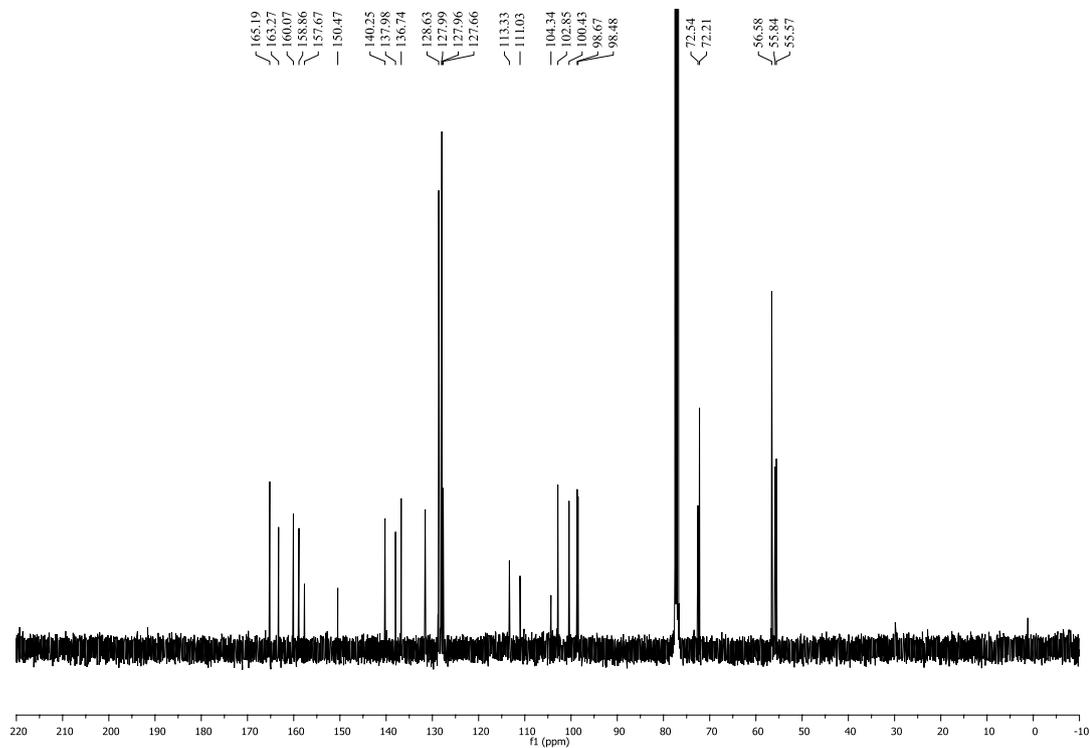
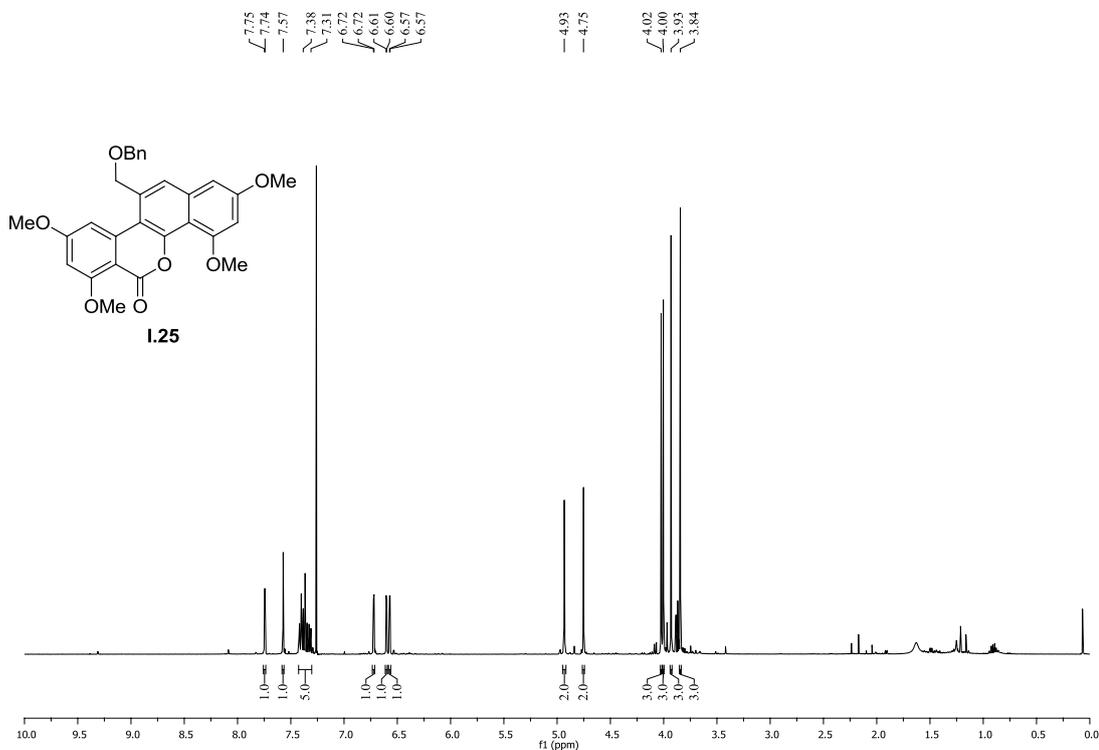
2-(3-((Benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxybenzoic acid (I.71) (^1H , ^{13}C)

**1-(benzyloxy)-3-{2-[2-(3,5-dimethoxy-2-methylphenyl)acetyl]-3,5-dimethoxyphenyl}
propan-2-one-methanedione (I.30) (^1H , ^{13}C)**

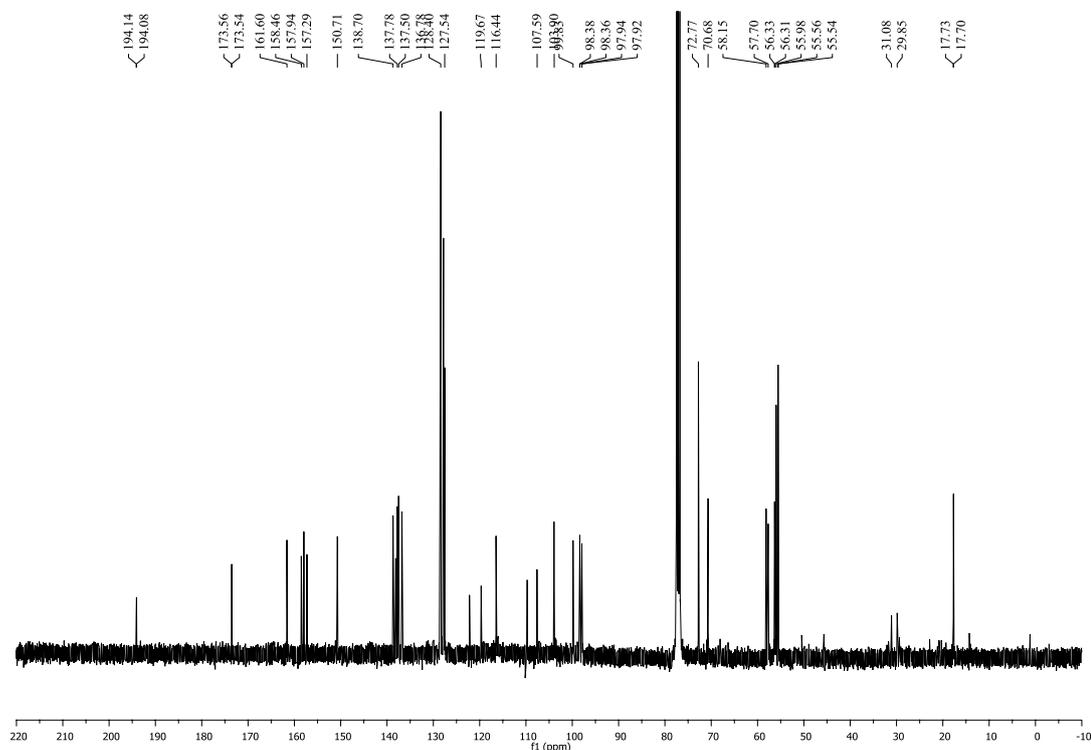
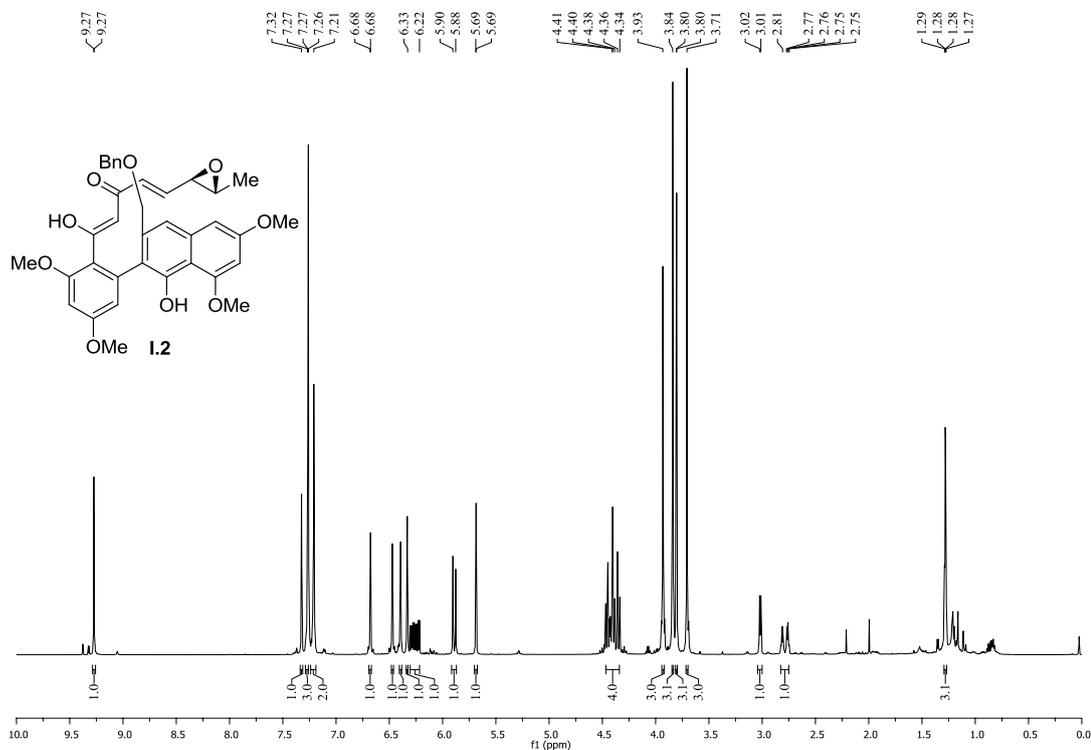


3-[(benzyloxy)methyl]-2-(3,5-dimethoxy-2-methylphenyl)-6,8-dimethoxynaphthalen-1-olmethanedione (I.70) (^1H , ^{13}C)

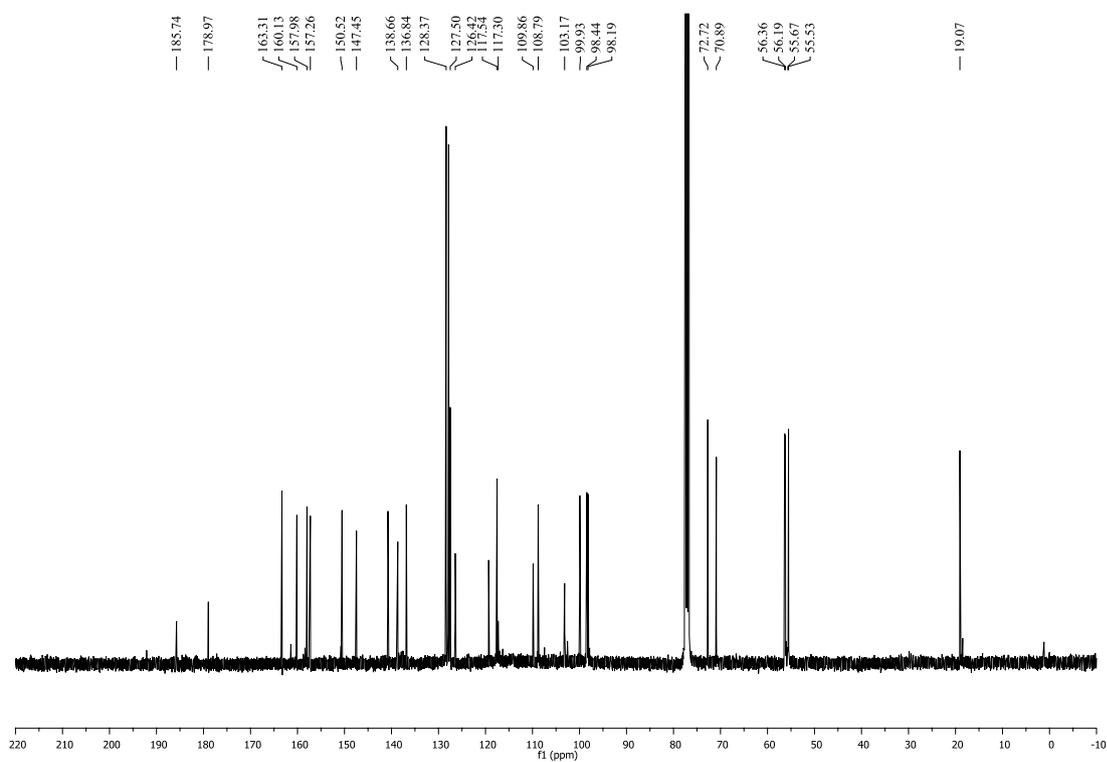
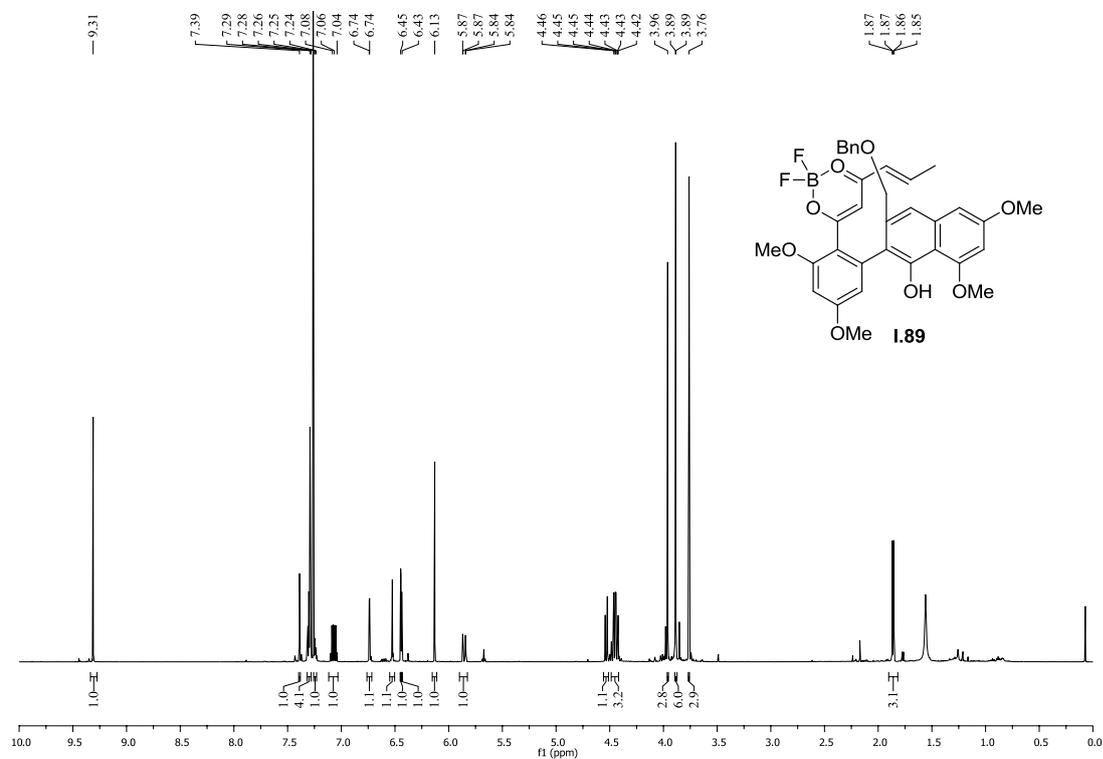


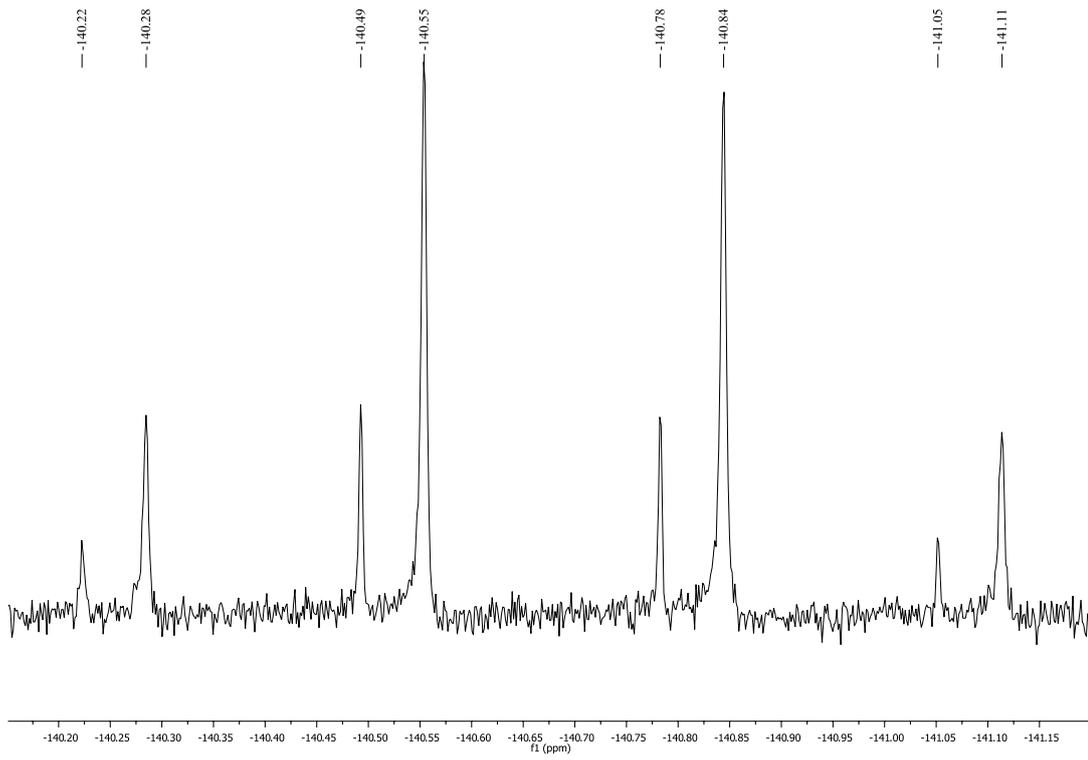
11-((Benzyloxy)methyl)-2,4,7,9-tetramethoxy-6H-dibenzo[*c,h*]chromen-6-one (I.25) (^1H , ^{13}C)

(1Z,4E)-1-(2-(3-((Benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxy phenyl)-1-hydroxyhexa-1,4-dien-3-one (I.2) (^1H , ^{13}C)

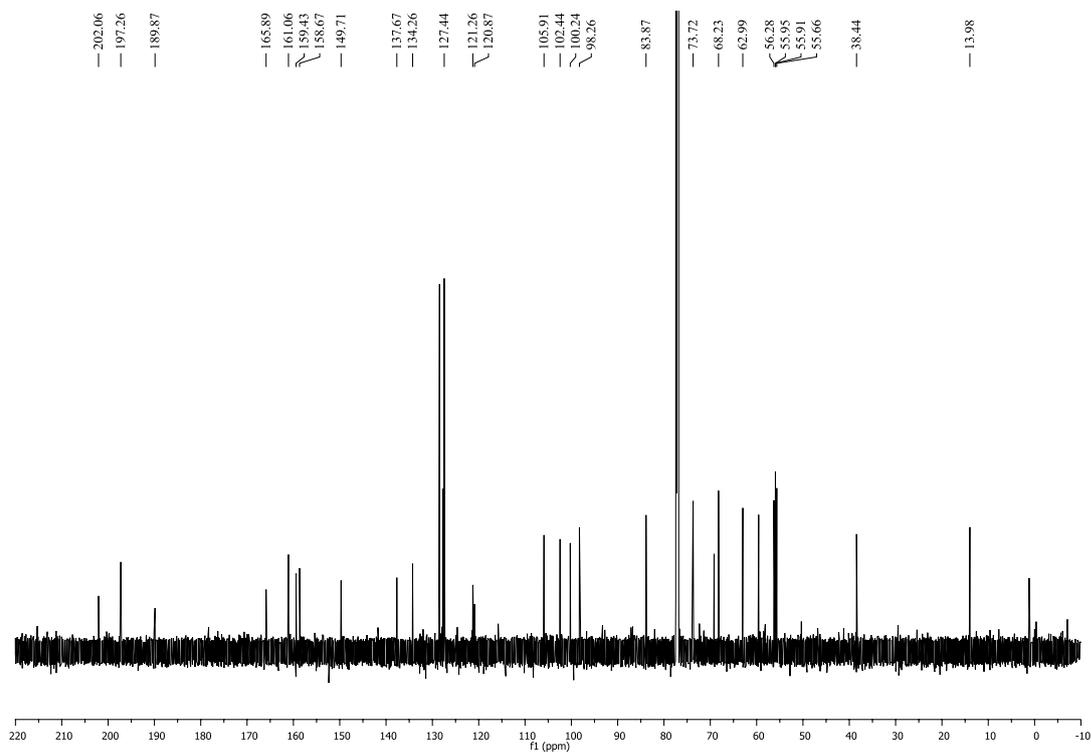
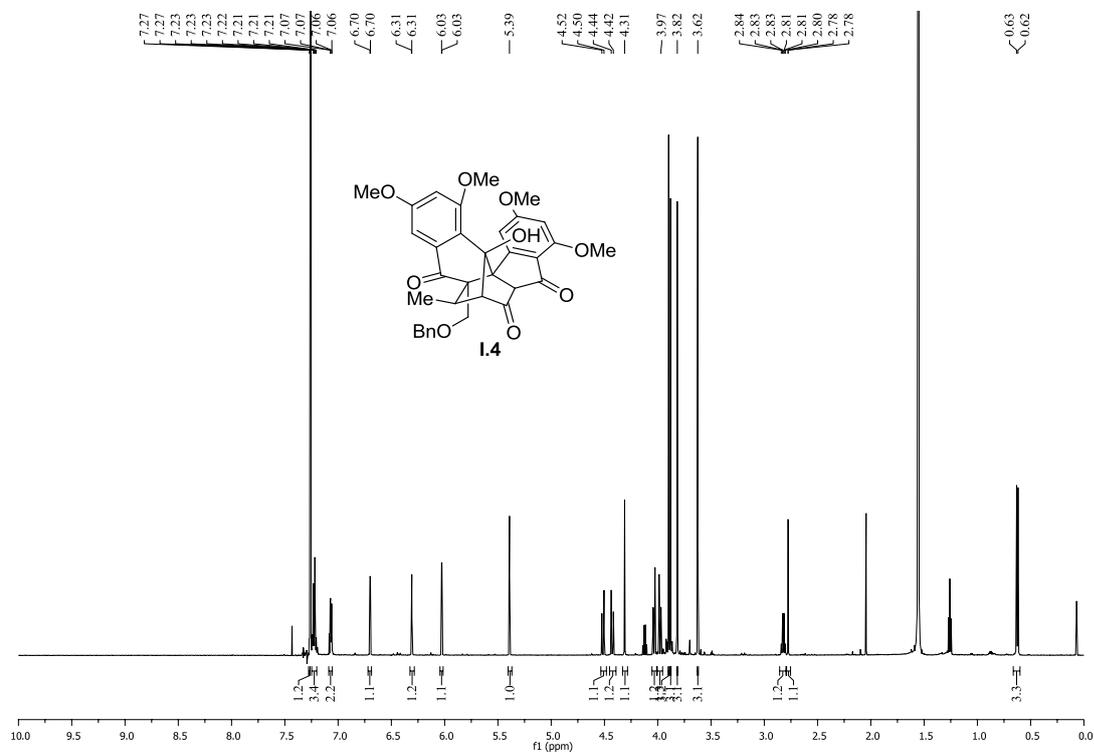


(1Z,4E)-1-(2-(3-((benzyloxy)methyl)-1-hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxyphenyl)-1-((difluoroboryl)oxy)hexa-1,4-dien-3-one (I.89) (^1H , ^{13}C , ^{19}F)

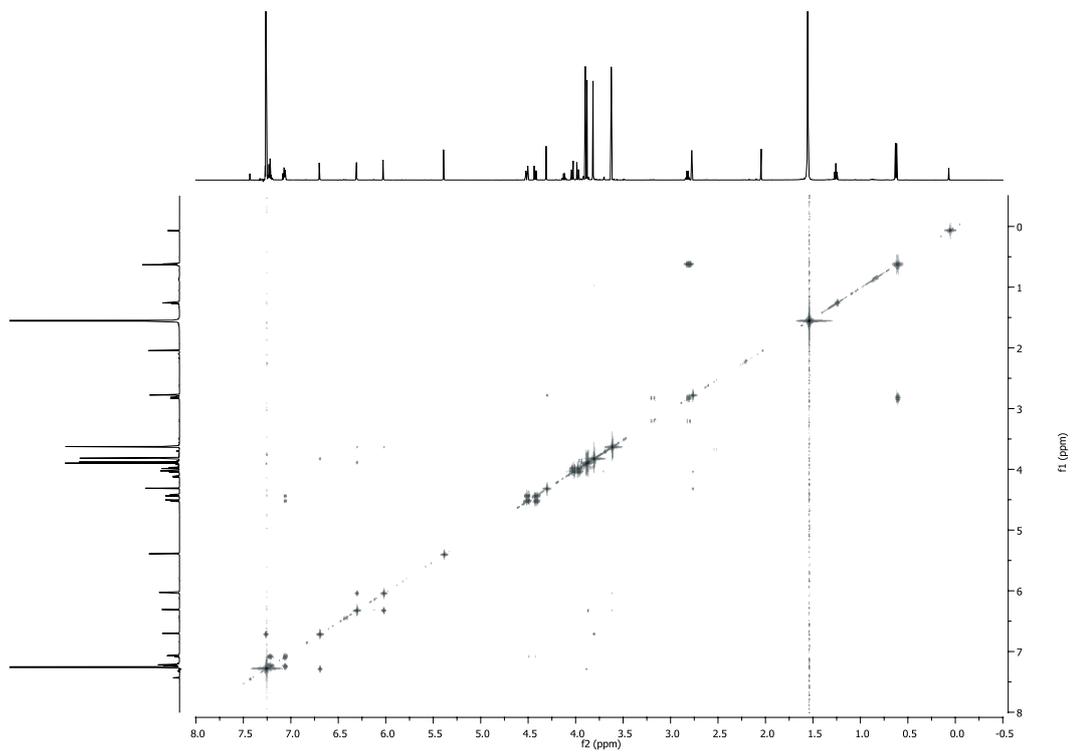




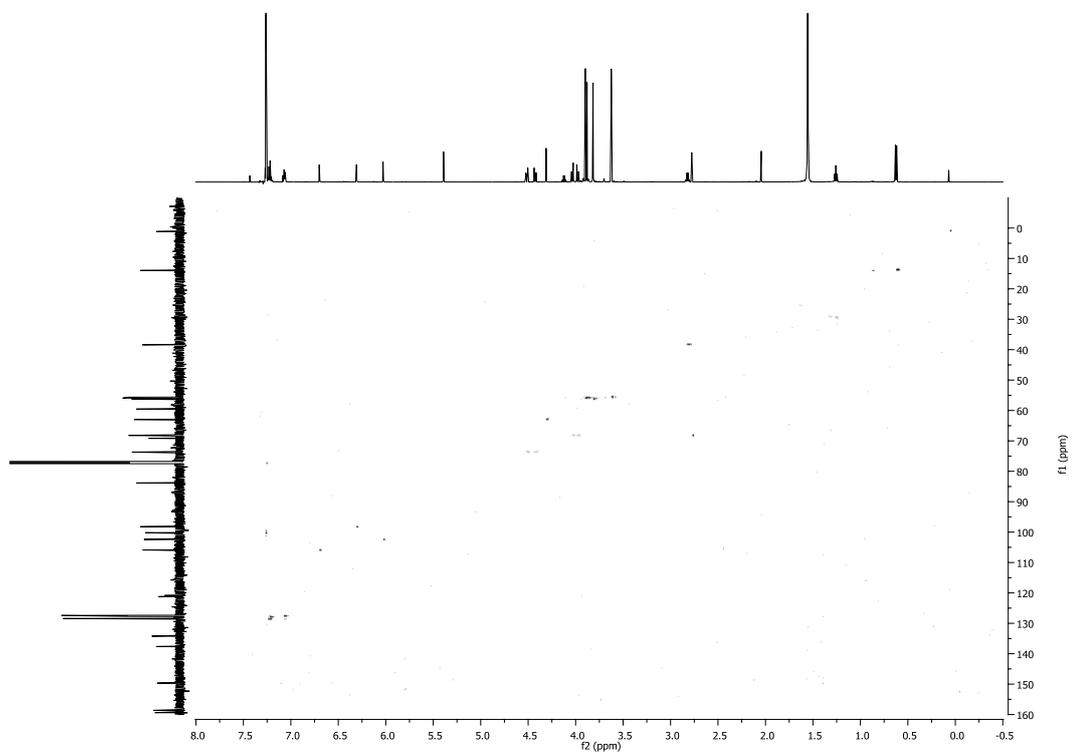
12-((Benzyloxy)methyl)-4b-hydroxy-2,4,8,10-tetramethoxy-14-methyl-4bH-5,12-methanobenzo[5,6]pentaleno[1,6a-a]naphthalene-6,7,13(5H,6aH,12H)-trione (I.4) (^1H , ^{13}C , COSY, HSQC, HMBC, NOESY)



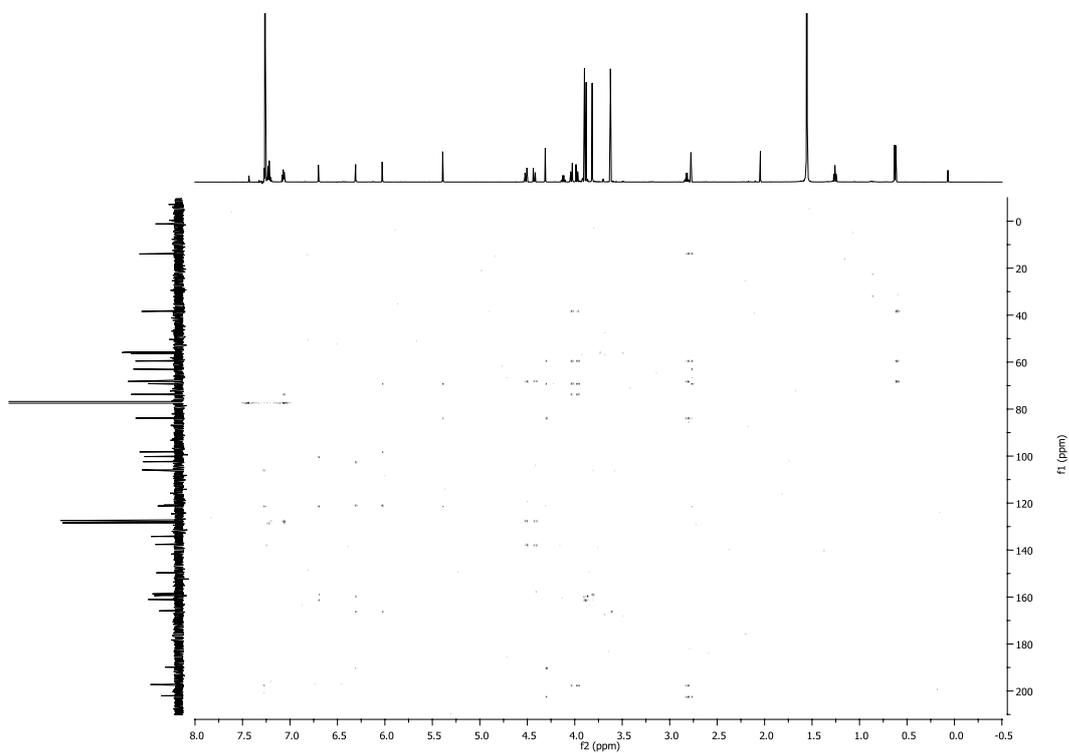
COSY



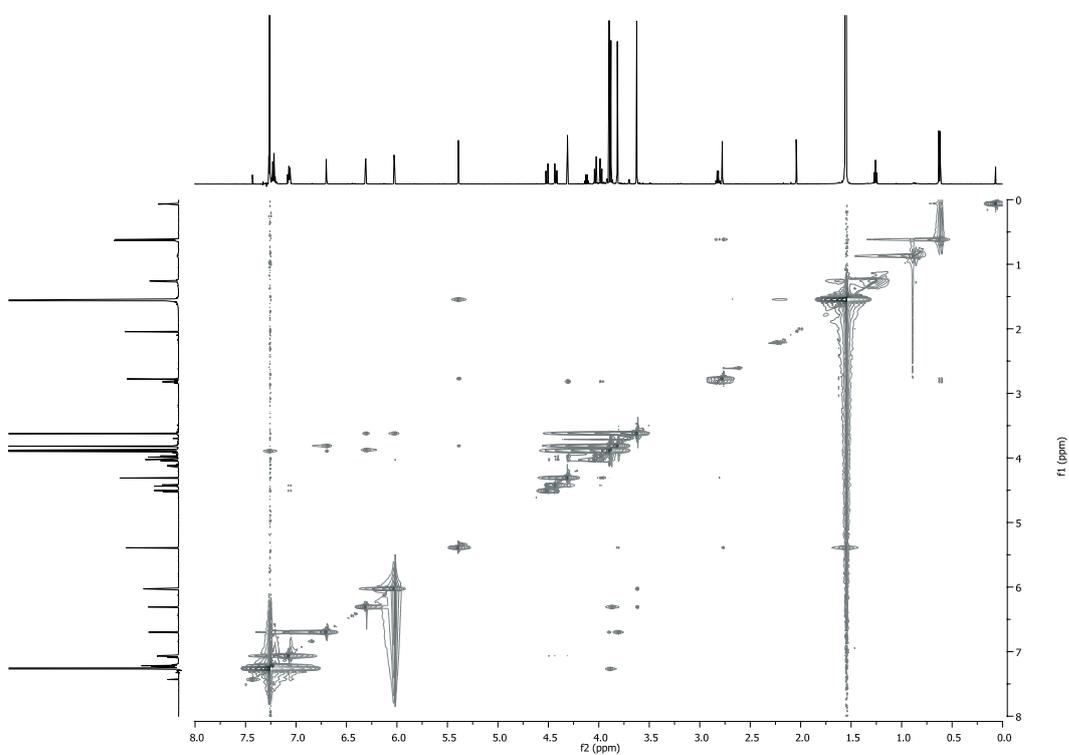
HSQC



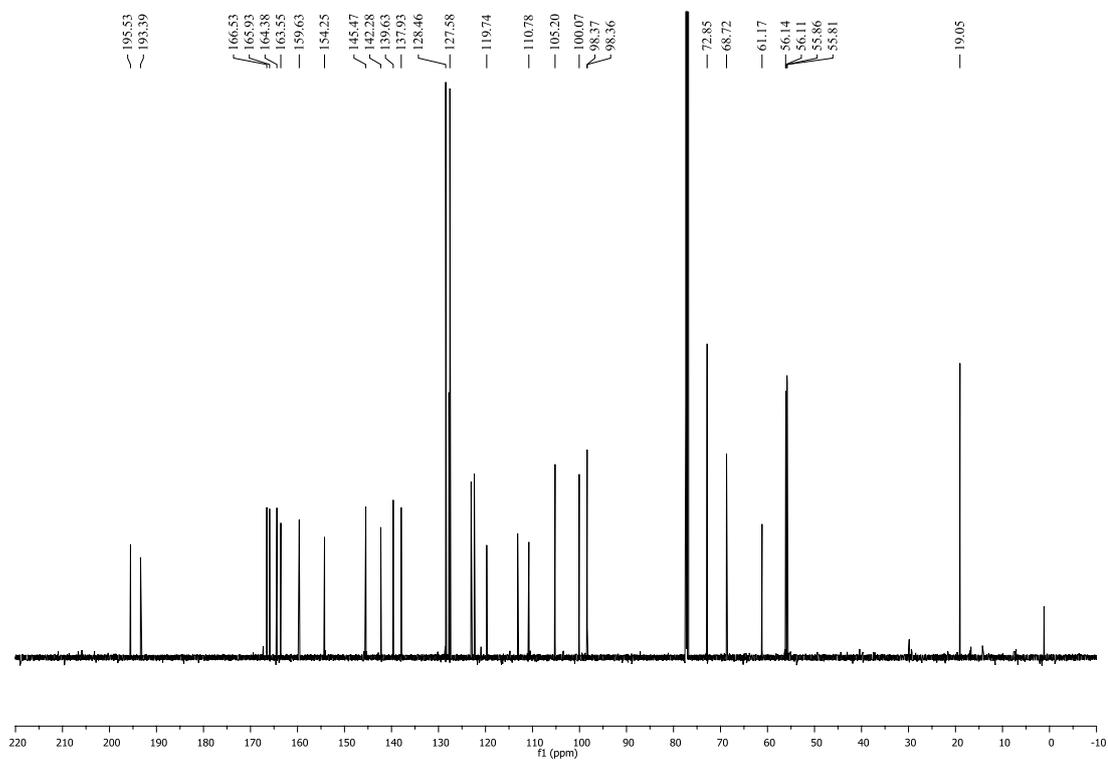
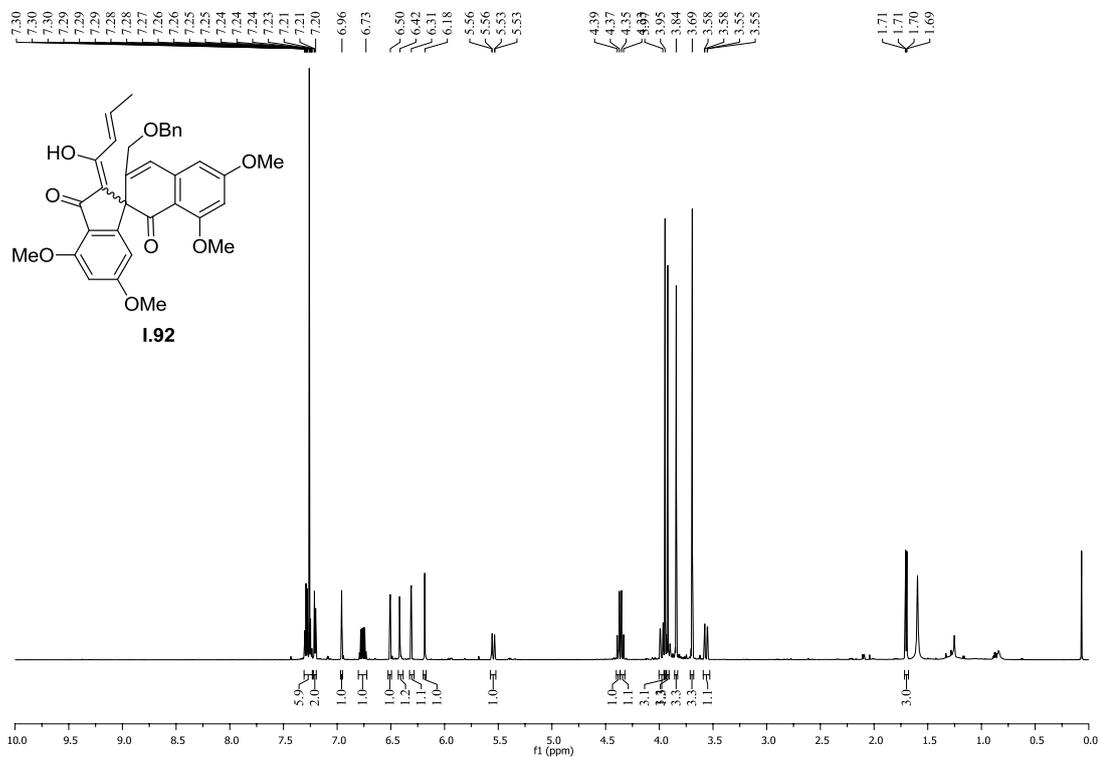
HMBC

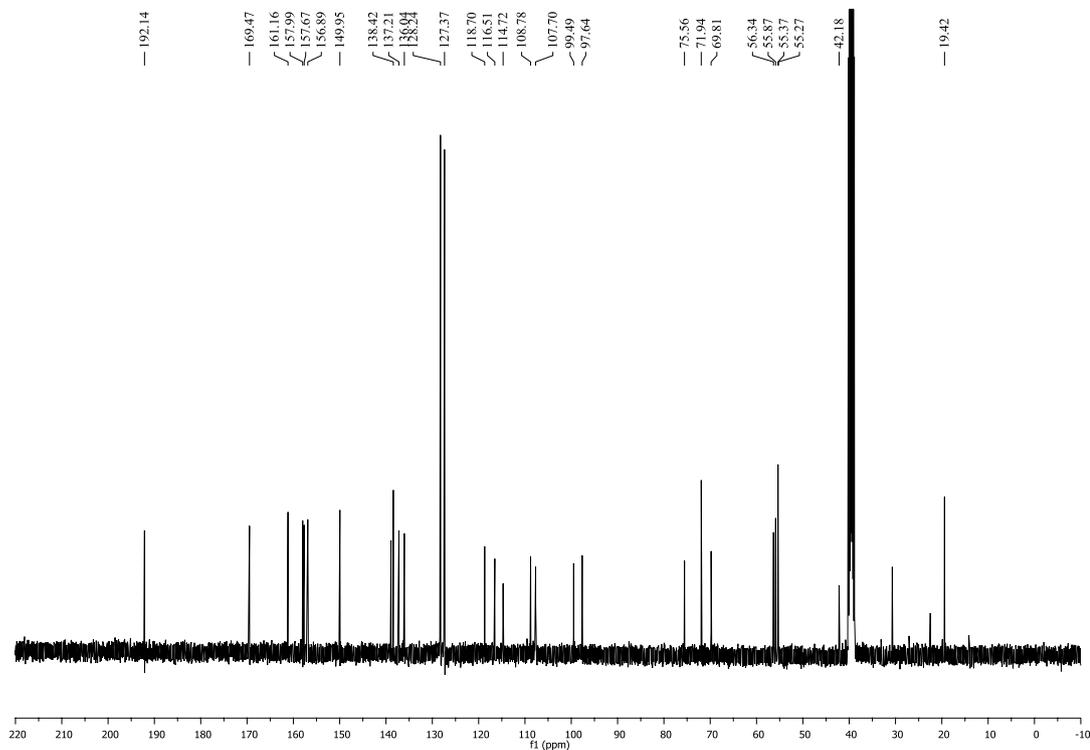
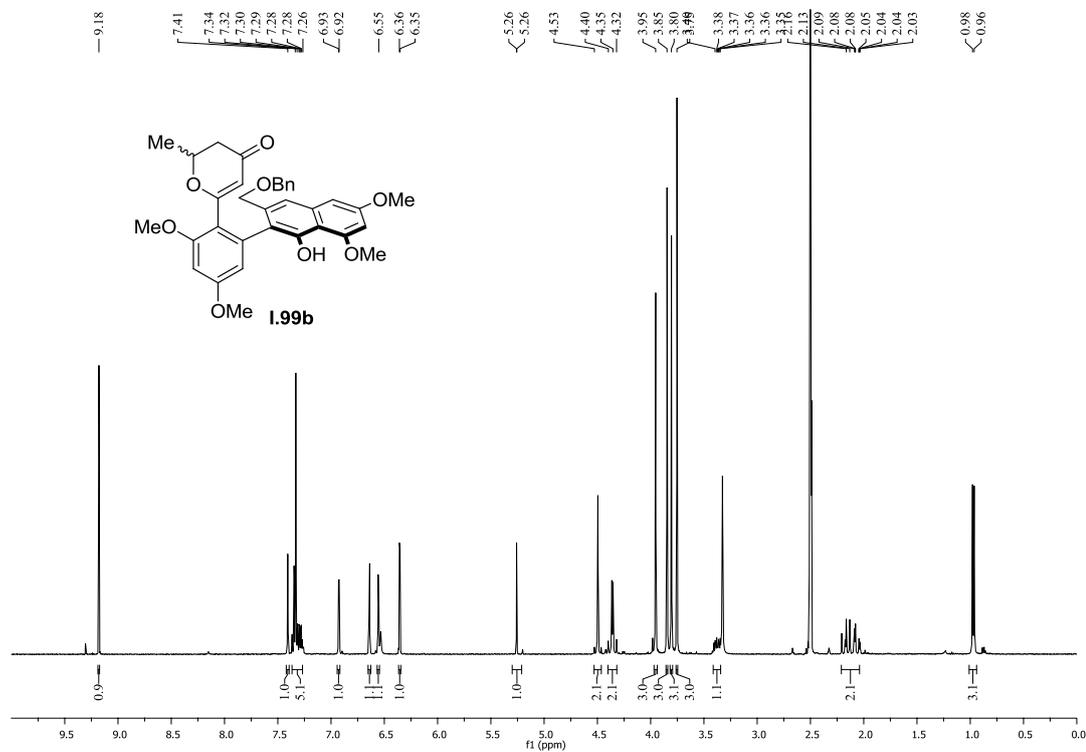


NOESY

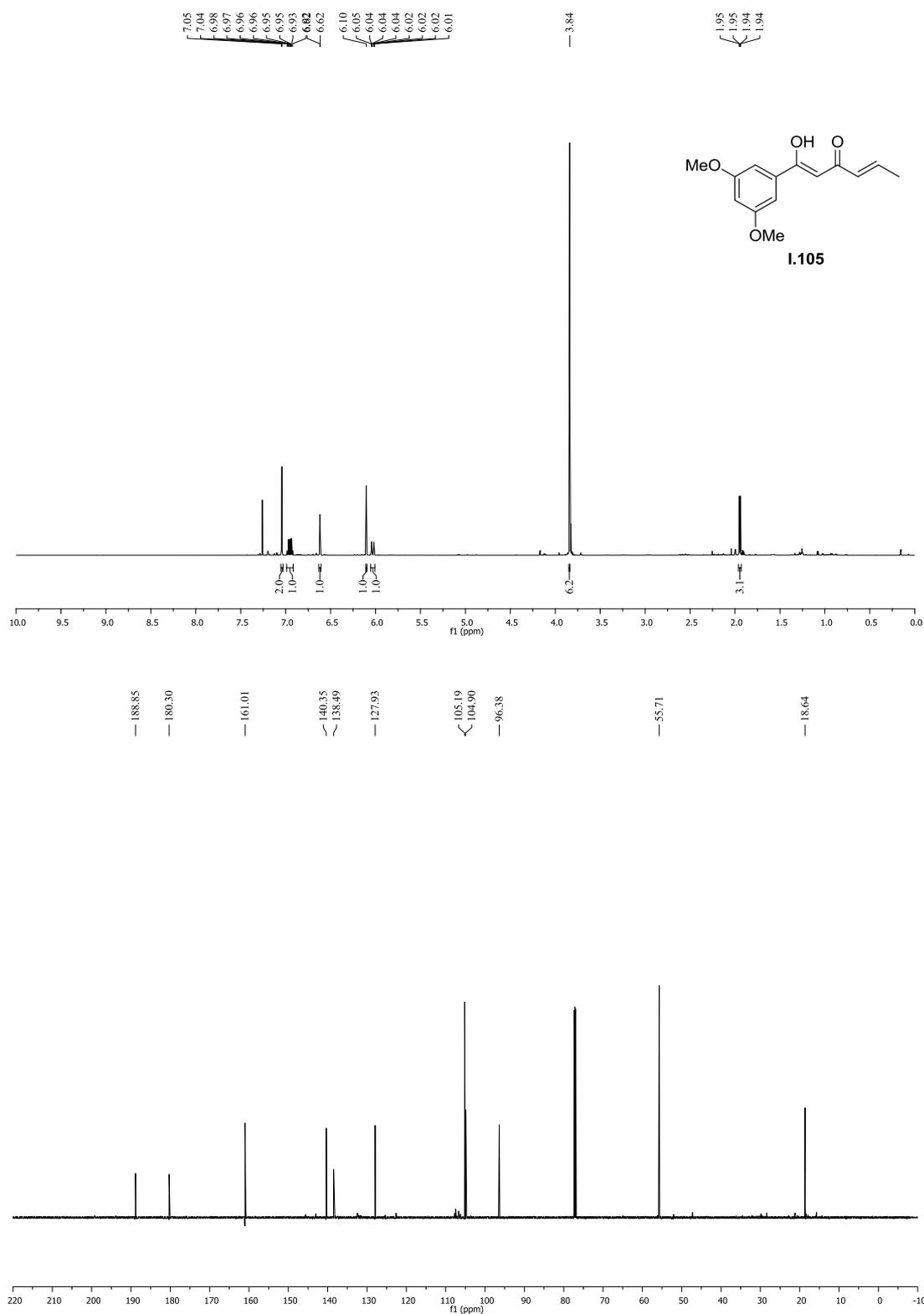


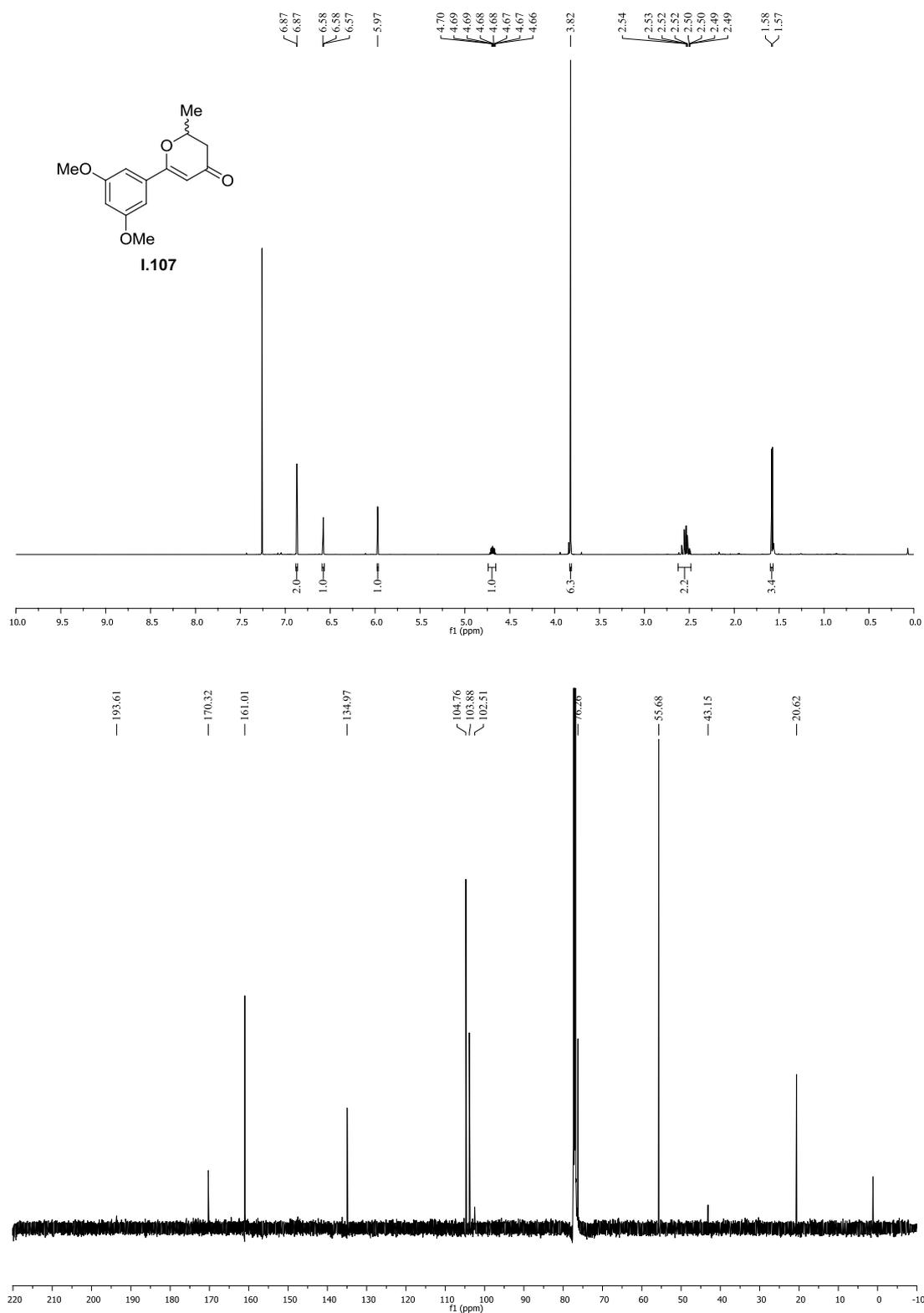
(2Z)-3'-[(benzyloxy)methyl]-2-[(2E)-1-hydroxybut-2-en-1-ylidene]-4,6,6',8'-tetramethoxy-2,3-dihydro-1'H-spiro[indene-1,2'-naphthalene]-1',3-dione (I.92) (¹H, ¹³C)



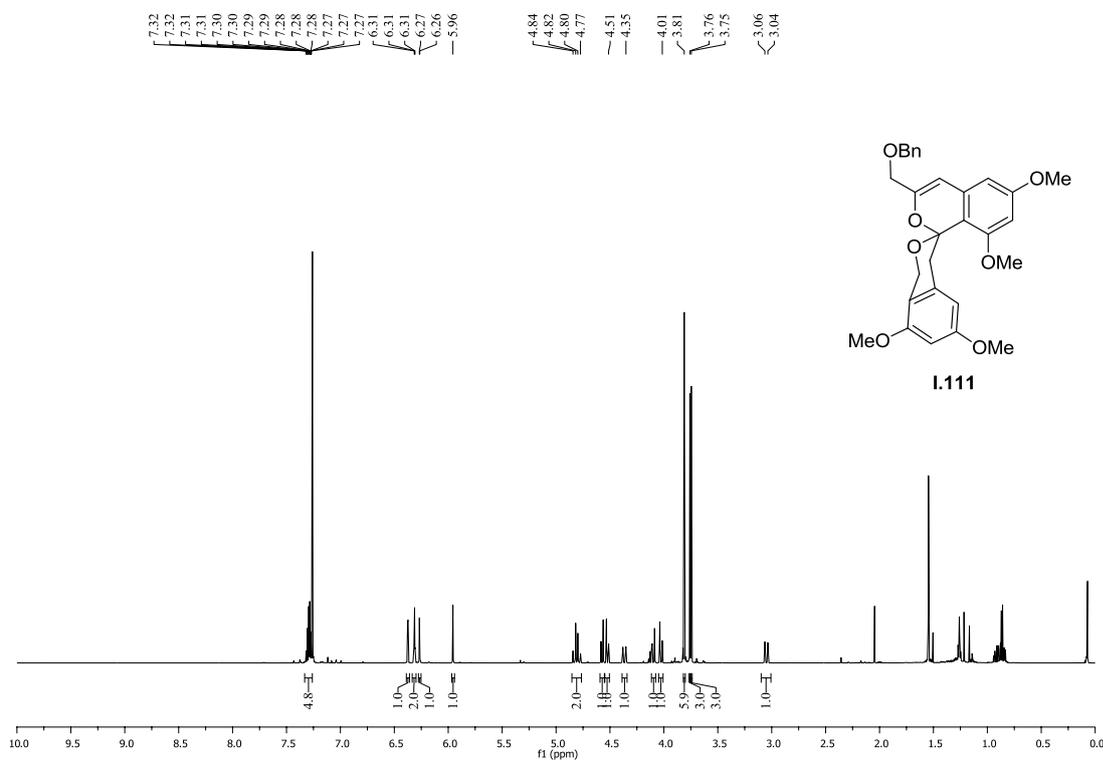
6-(2-{3-[(Benzyloxy)methyl]-1-hydroxy-6,8-dimethoxynaphthalen-2-yl}-4,6-dimethoxyphenyl)-2-methyl-3,4-dihydro-2H-pyran-4-one (1.99b) (^1H , ^{13}C)

(E)-1-(3,5-dimethoxyphenyl)hex-4-ene-1,3-dione (I.105) (¹H, ¹³C)

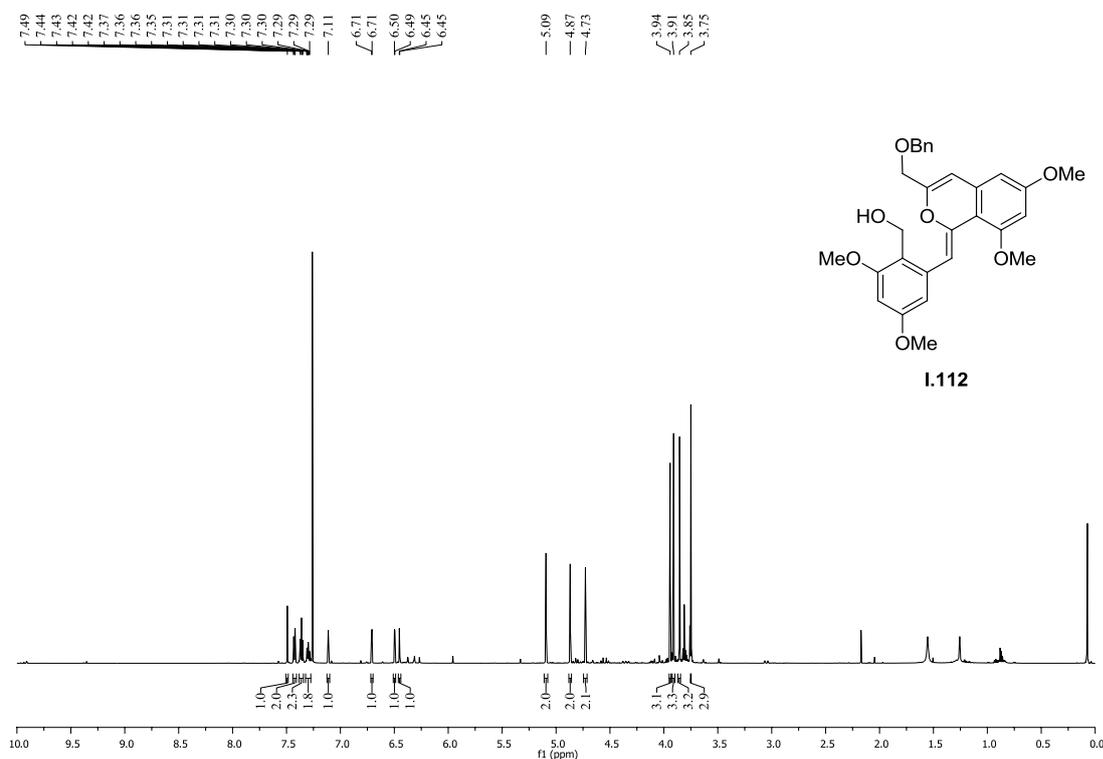


6-(3,5-dimethoxyphenyl)-2-methyl-2H-pyran-4(3H)-one (I.107) (^1H , ^{13}C)

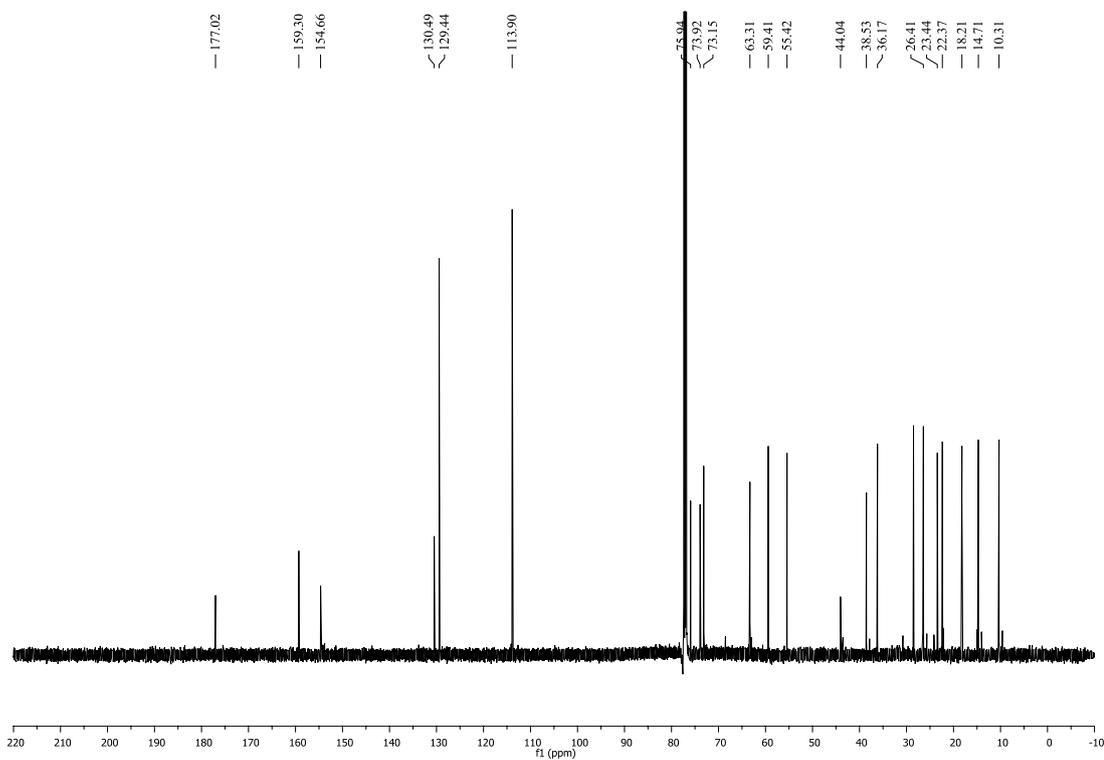
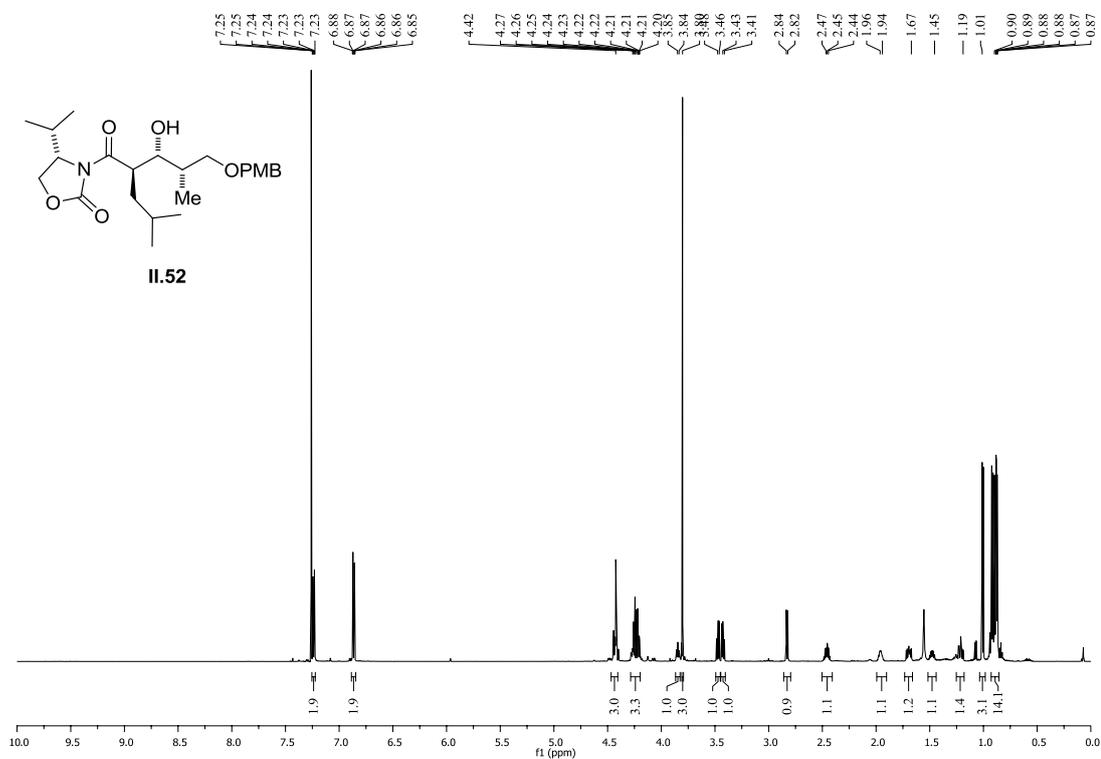
**(R)-3'-((benzyloxy)methyl)-6,6',8,8'-tetramethoxyspiro[isochroman-3,1'-isochromenel]
(I.111) (¹H)**

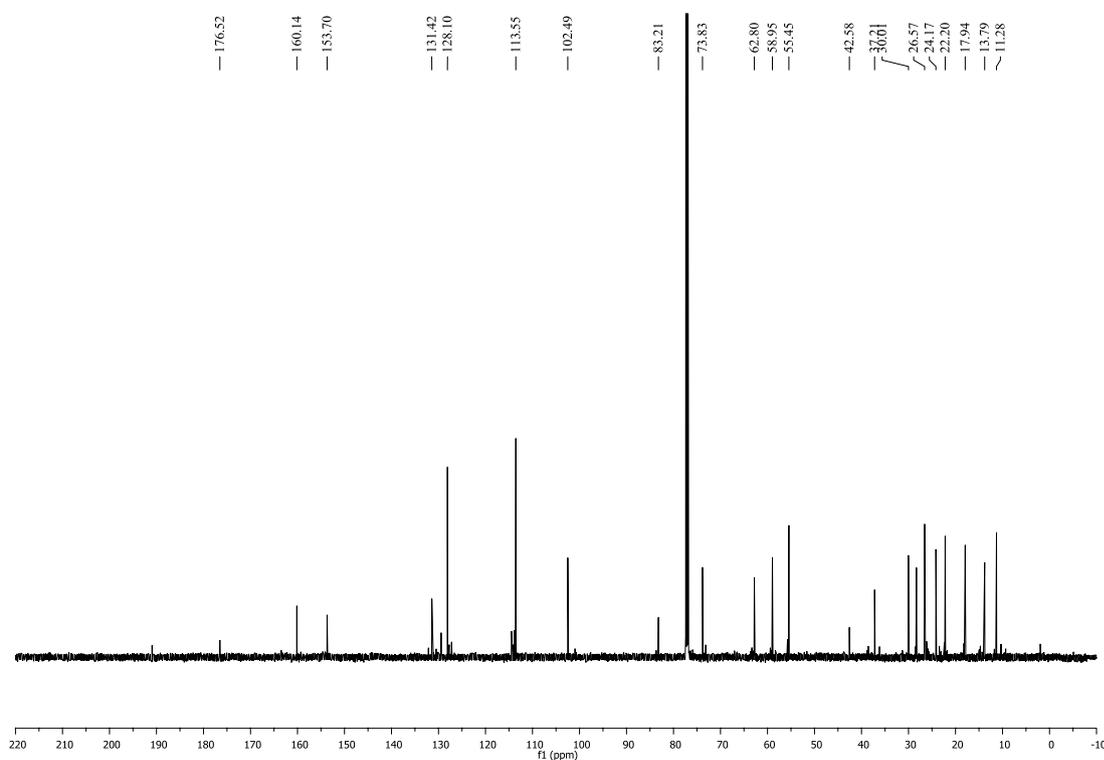
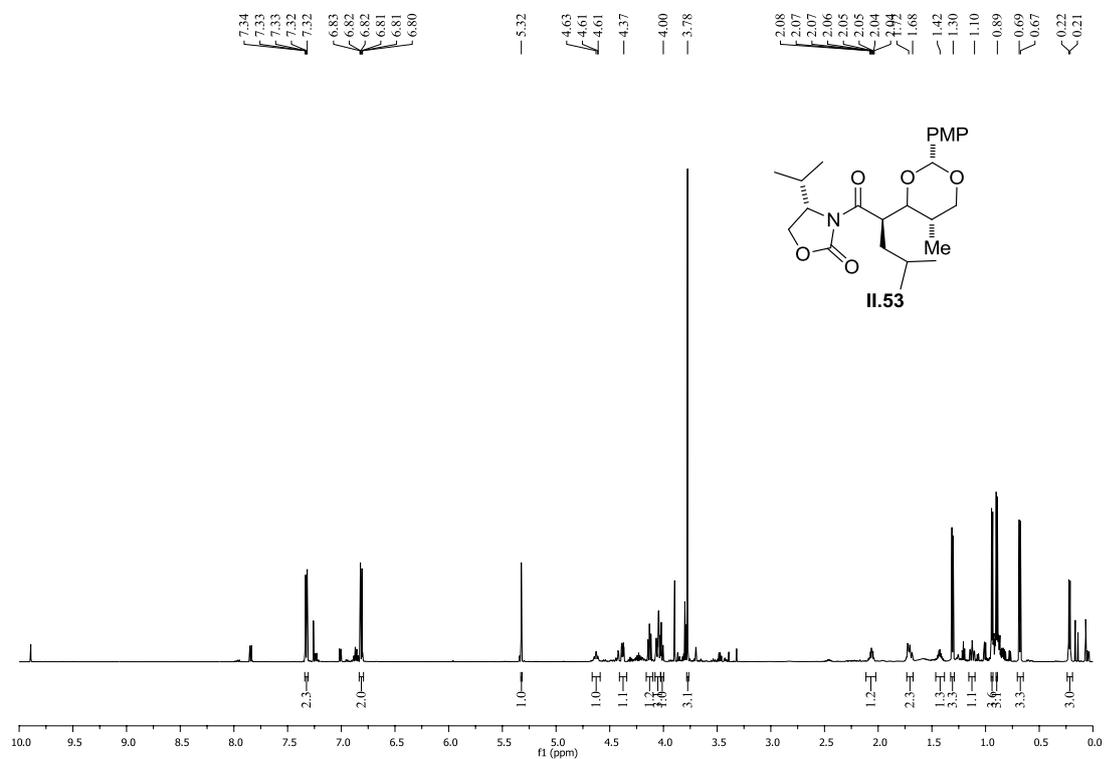


(Z)-2-((3-((benzyloxy)methyl)-6,8-dimethoxy-1H-isochromen-1-ylidene)methyl)-4,6-dimethoxy phenyl)methanol (I.112) (¹H)

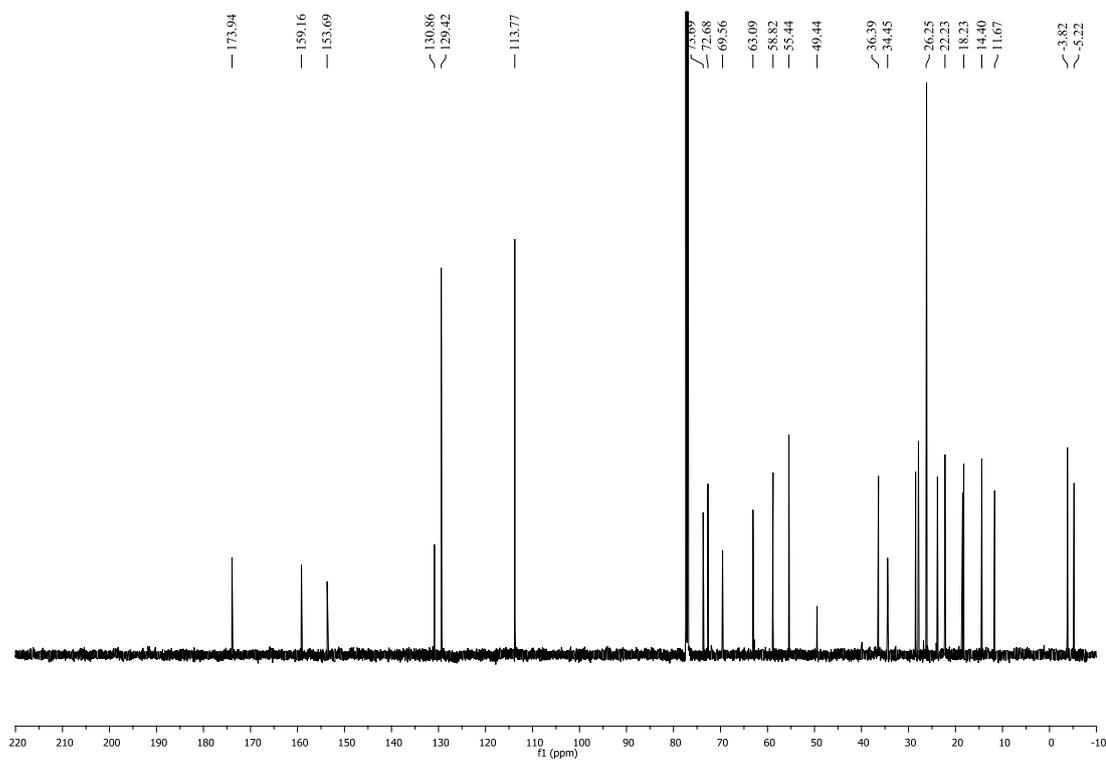
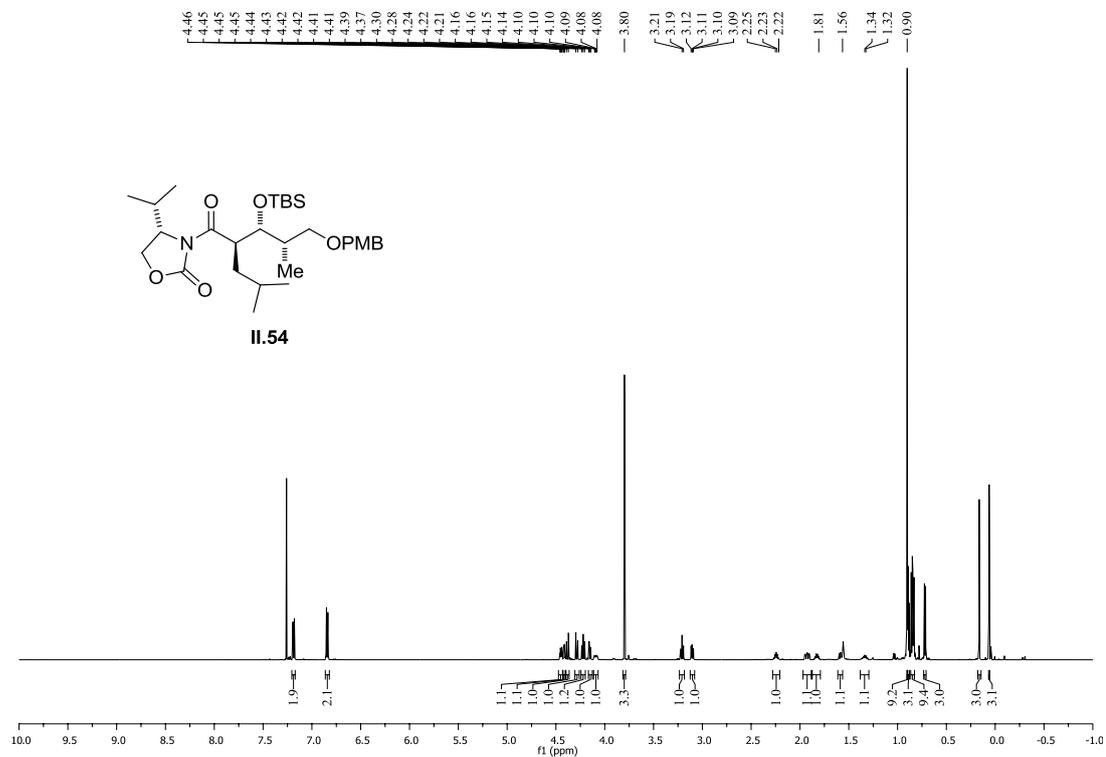


(S)-3-((2R,3R,4S)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methylpentanoyl)-4-isopropylloxazolidin-2-one (II.52) (^1H , ^{13}C)

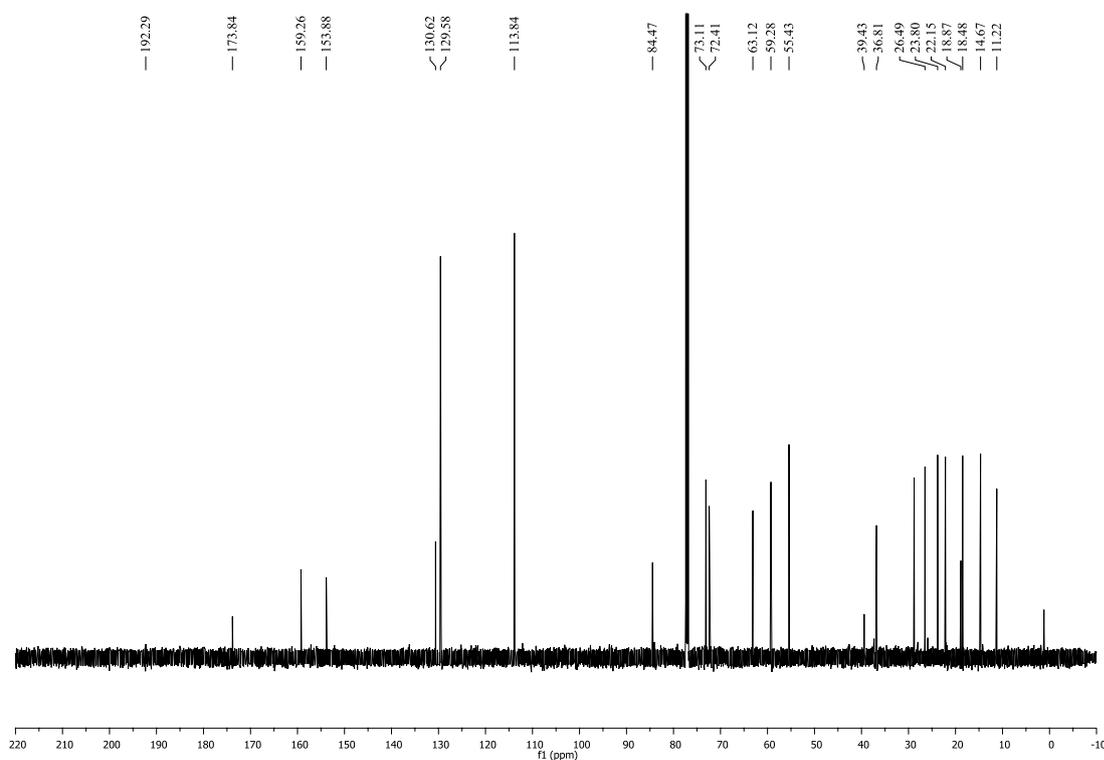
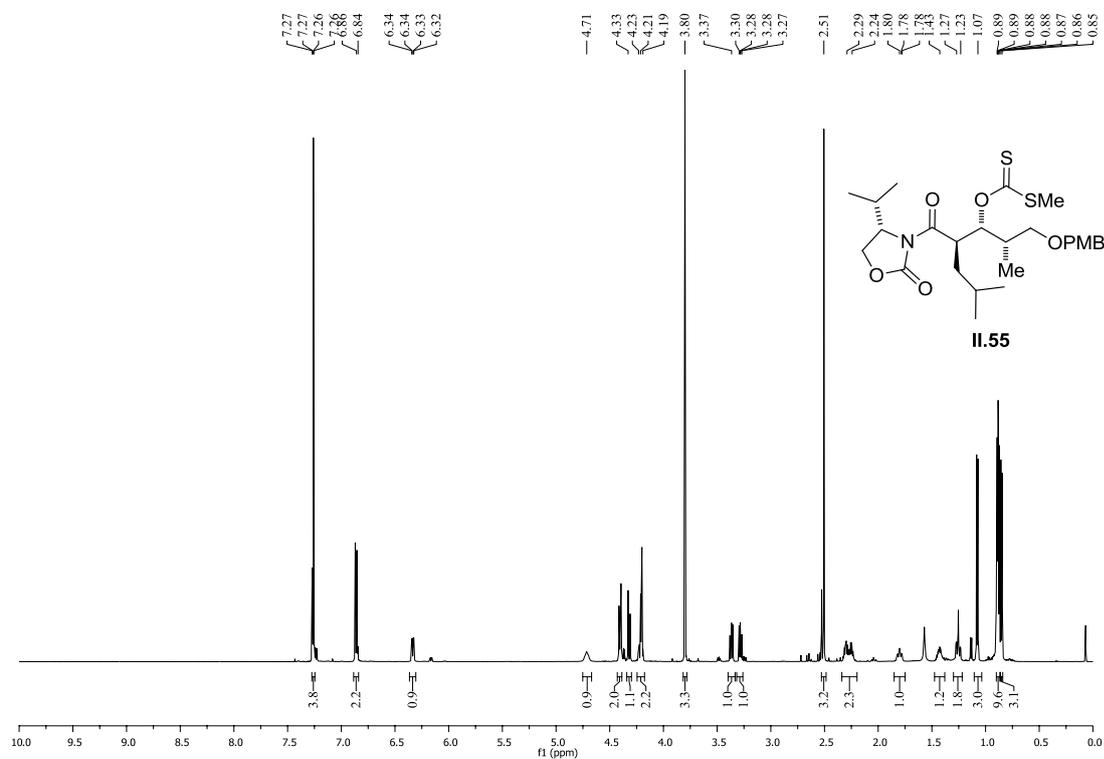


(5R)-5-Isobutyl-3-((2R)-2-((2R,5S)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyl pentanoyl)oxazolidin-2-one (II.53) (¹H, ¹³C)

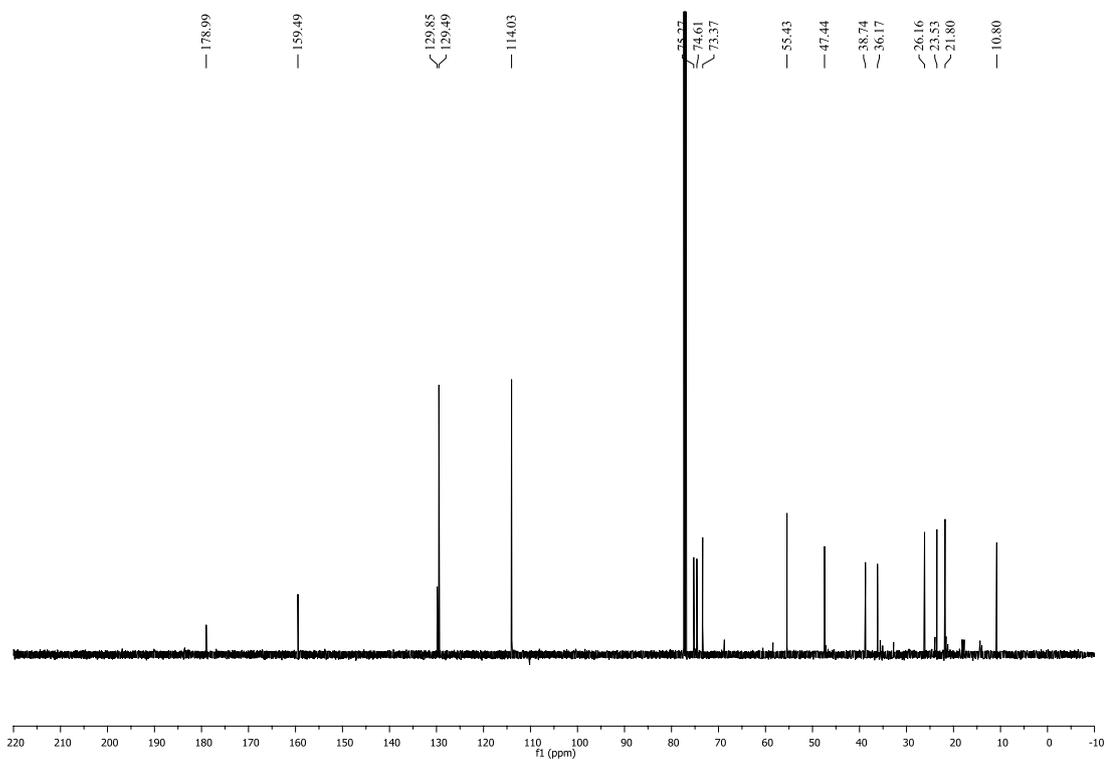
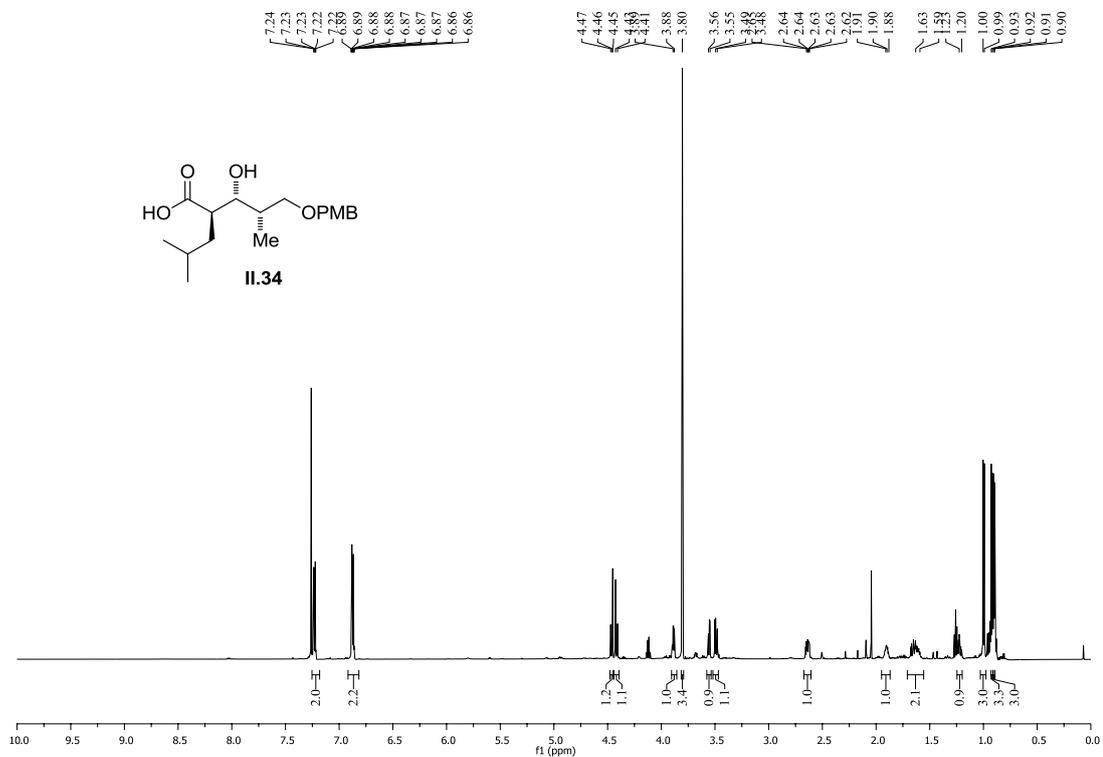
(R)-3-((2R,3R,4S)-3-((Tert-butyl dimethylsilyl)oxy)-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl pentanoyl)-5-isobutyloxazolidin-2-one (II.54) (¹H, ¹³C)

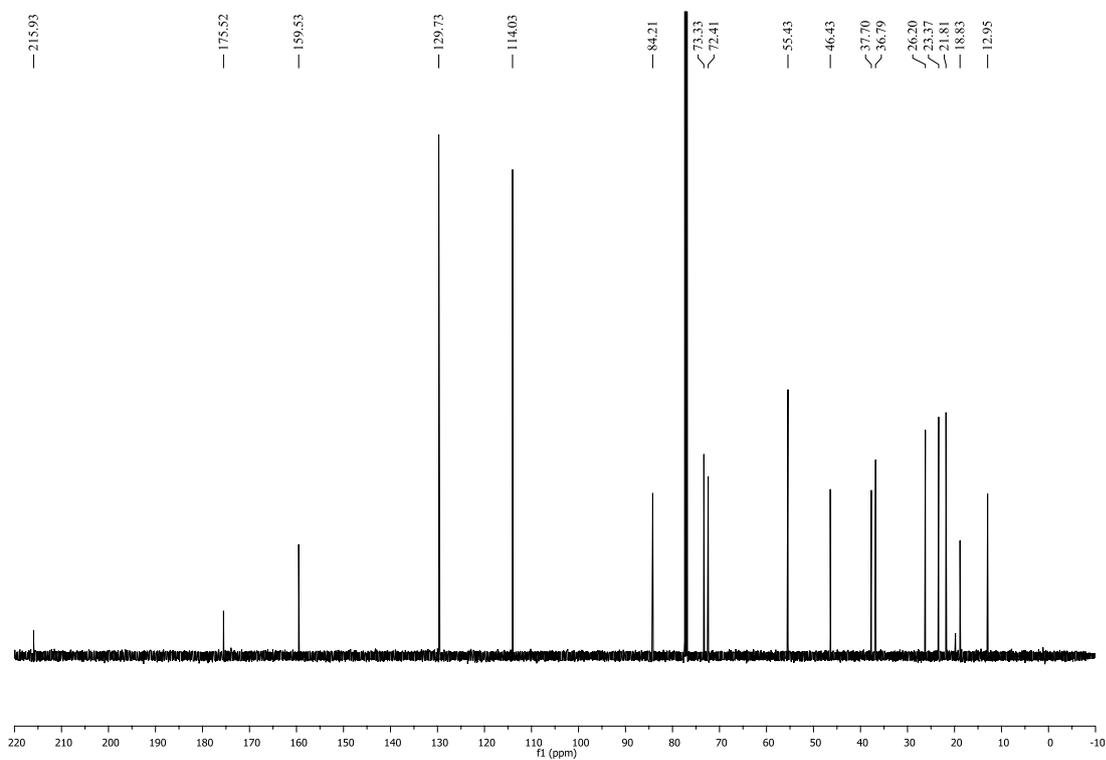
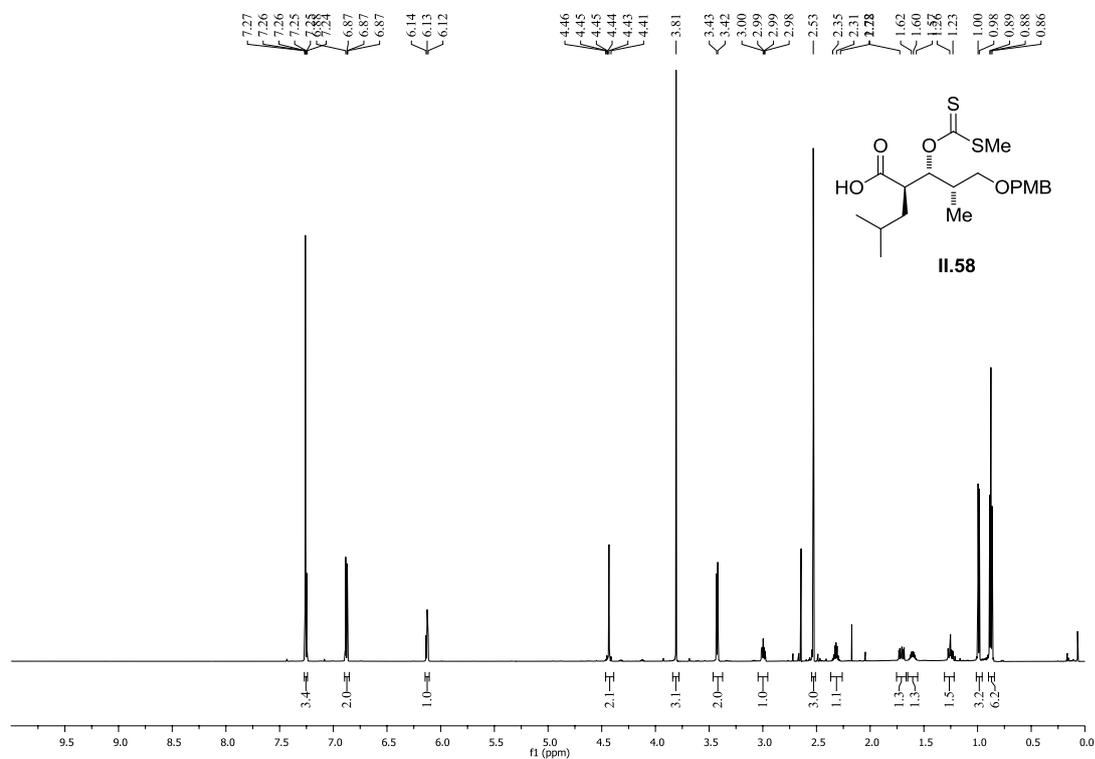


***O*-((2*S*,3*R*,4*R*)-4-((*S*)-4-Isopropyl-2-oxooxazolidine-3-carbonyl)-1-((4-methoxybenzyl)oxy)-2,6-dimethylheptan-3-yl)-*S*-methyl carbonodithioate (II.55) (¹H, ¹³C)**

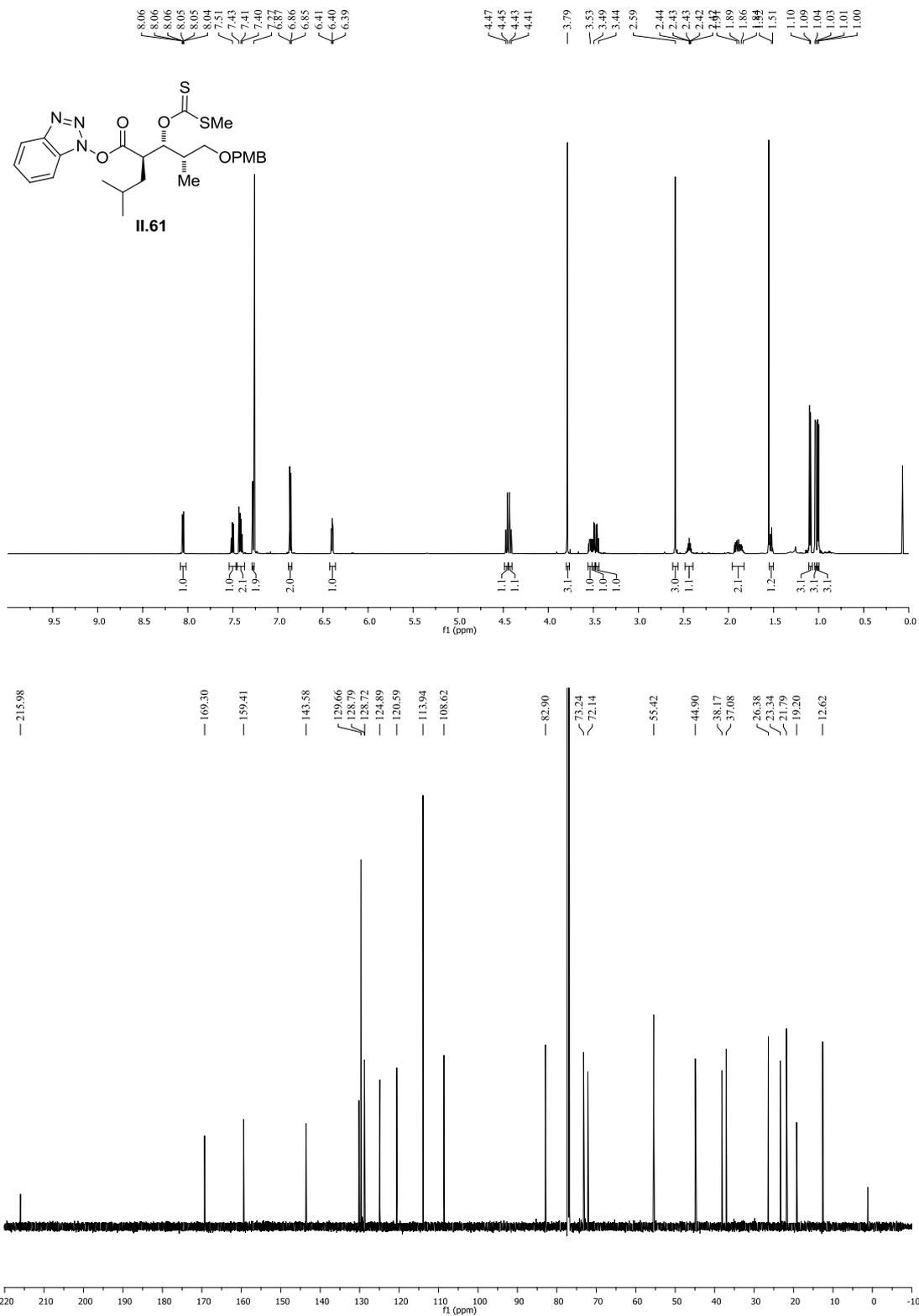


(2*R*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methylpentanoic acid (II.34)
(¹H, ¹³C)

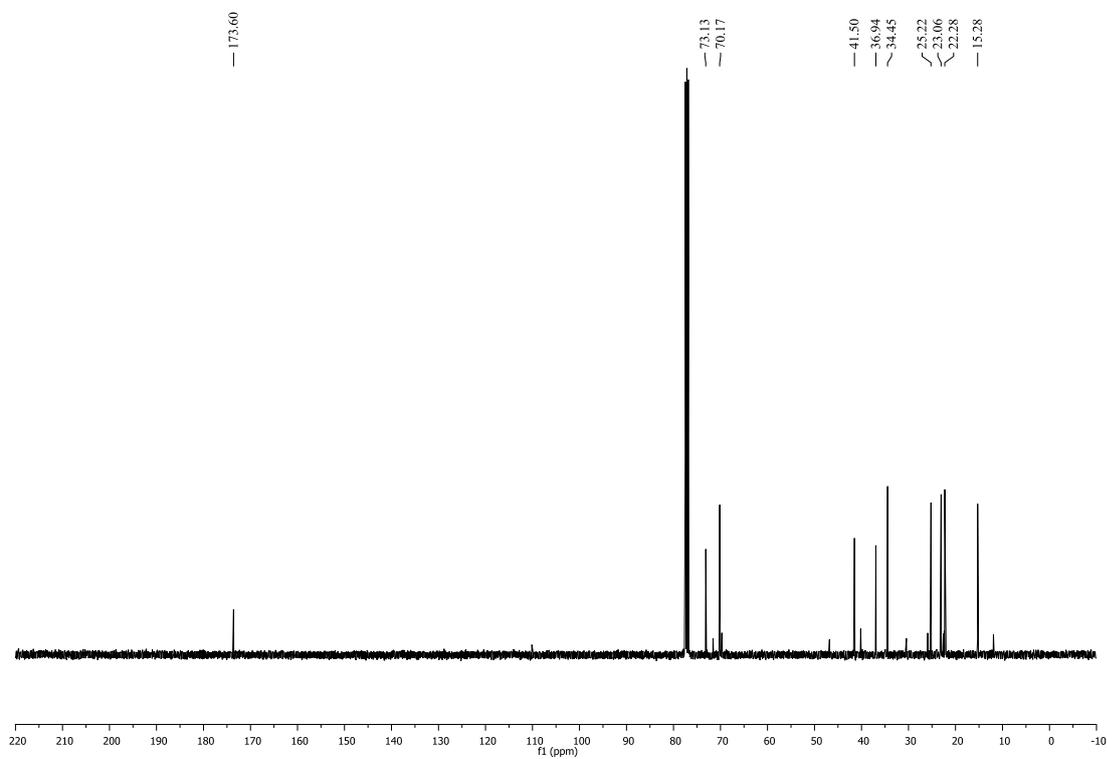
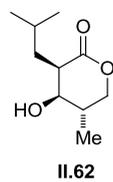
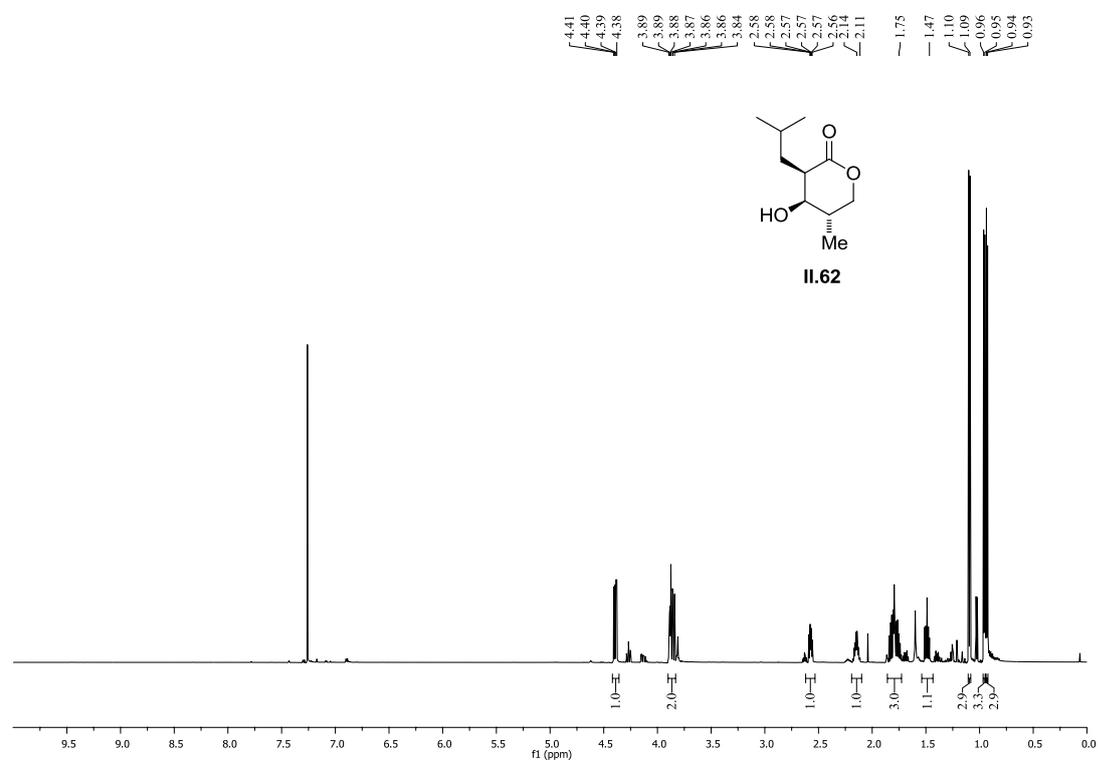


(2*R*,3*R*,4*S*)-2-Isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((methylthio)carbonothioyl)oxy)pentanoic acid (II.58) (¹H, ¹³C)

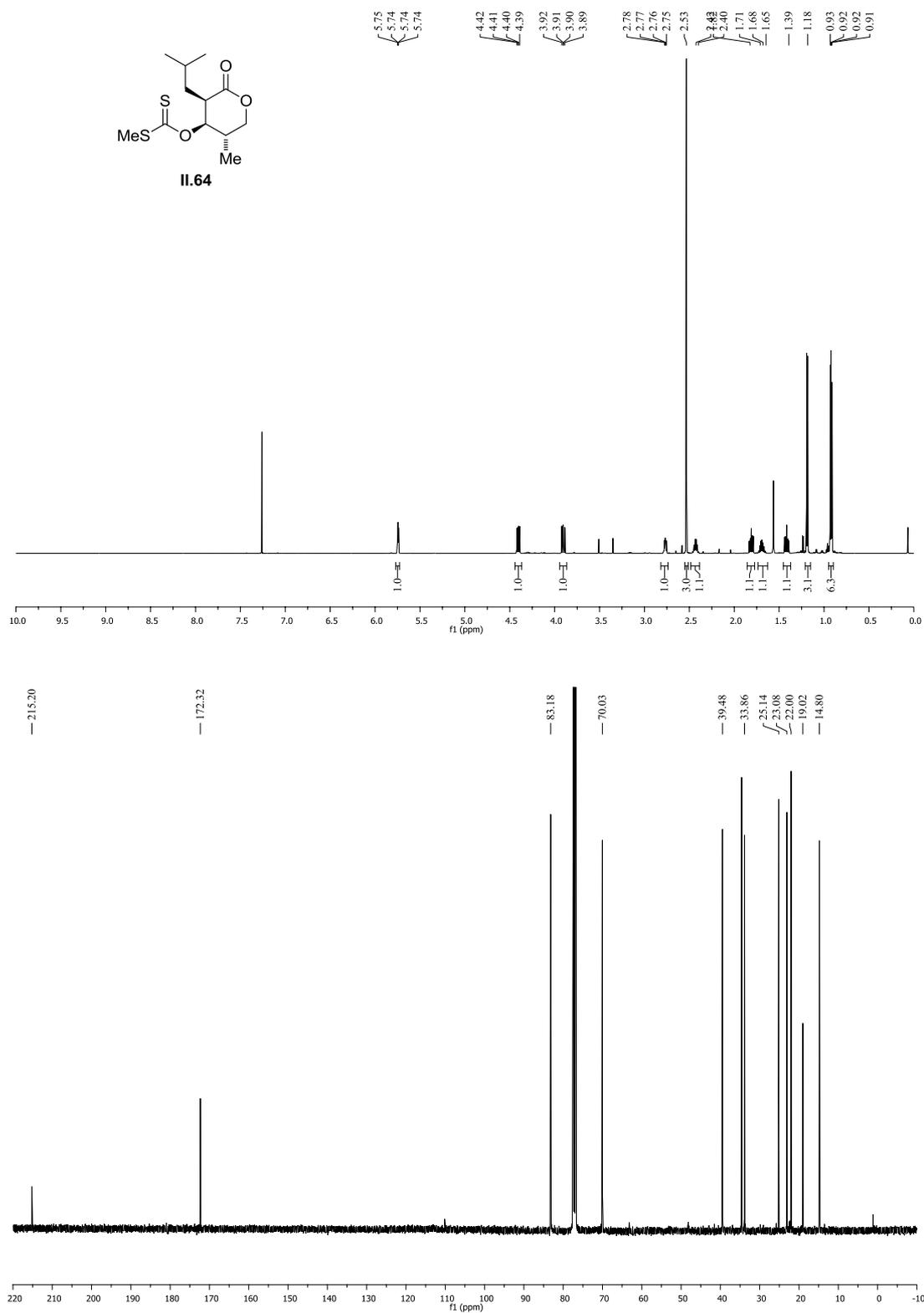
(2*R*,4*S*)-1*H*-Benzo[*d*][1,2,3]triazol-1-yl 2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((methylthio)carbonothioyl)oxy)pentanoate (II.61) (¹H, ¹³C)



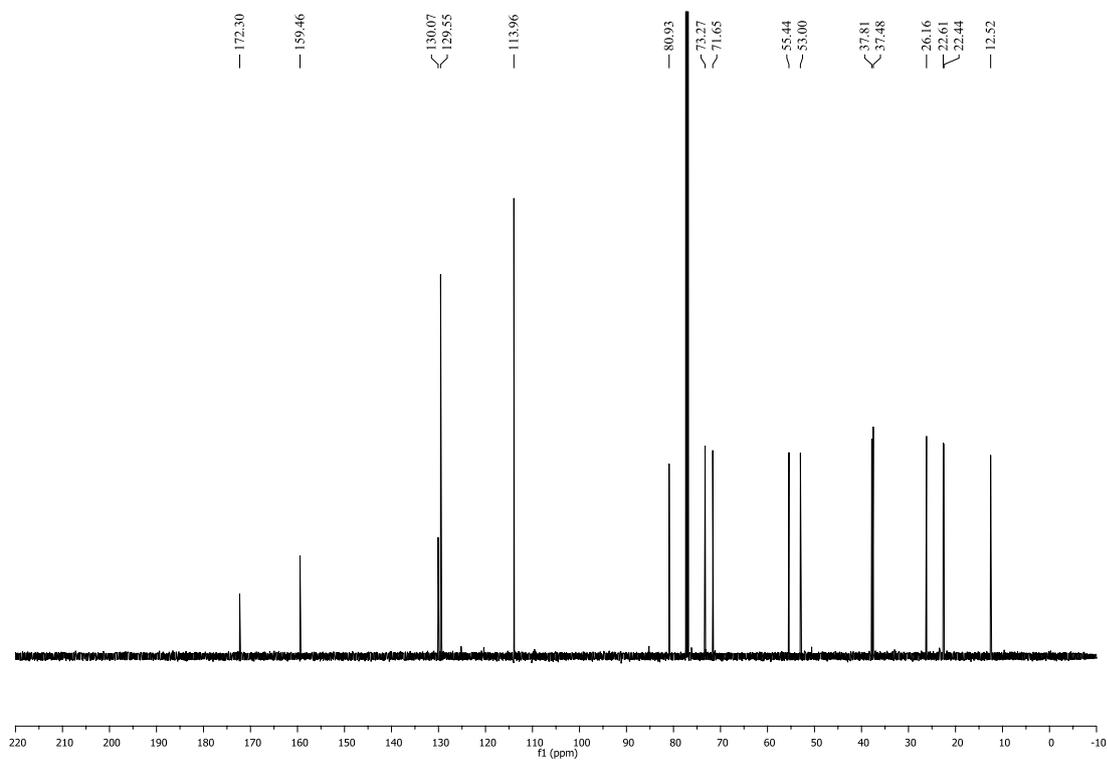
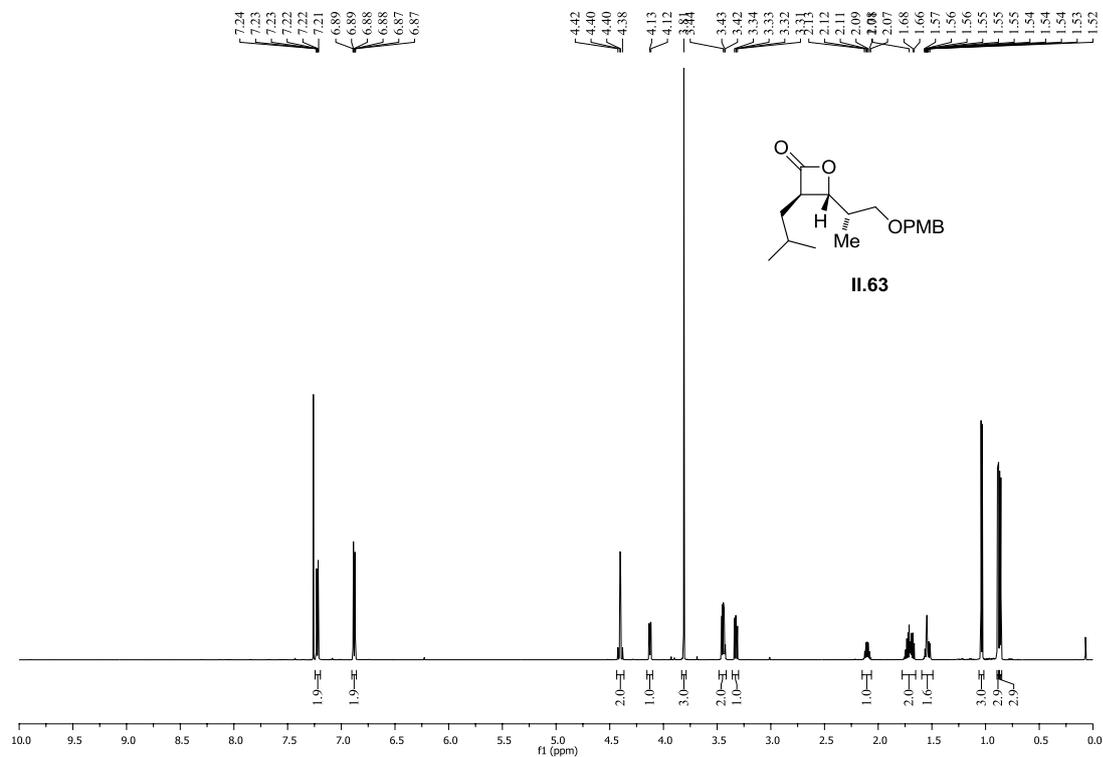
(3*R*,4*R*,5*S*)-4-hydroxy-3-isobutyl-5-methyltetrahydro-2*H*-pyran-2-one (II.62) (¹H, ¹³C)



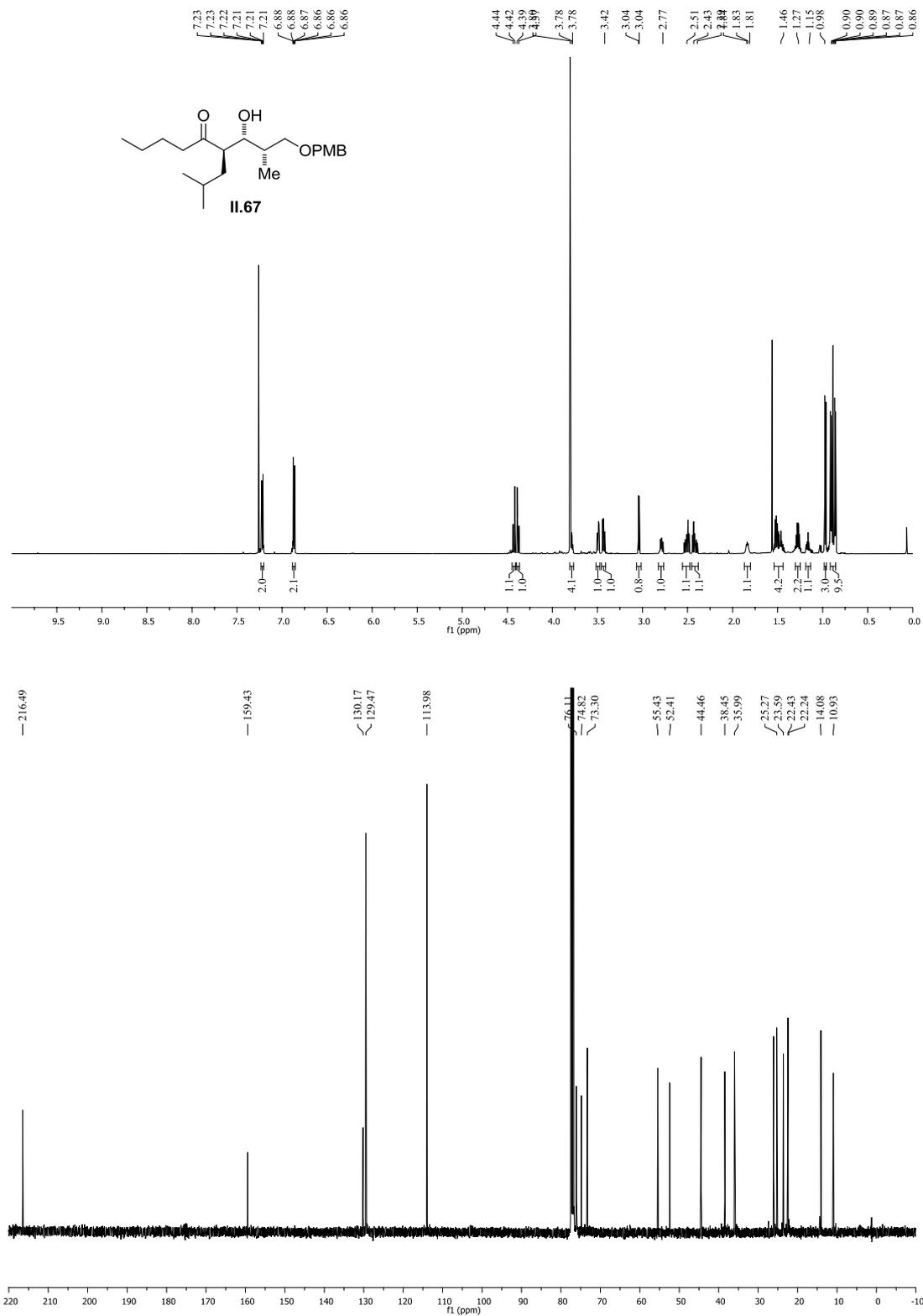
***O*-((3*R*,4*R*,5*S*)-3-Isobutyl-5-methyl-2-oxotetrahydro-2*H*-pyran-4-yl) *S*-methyl carbonyl dithioate (II.64) (¹H, ¹³C)**



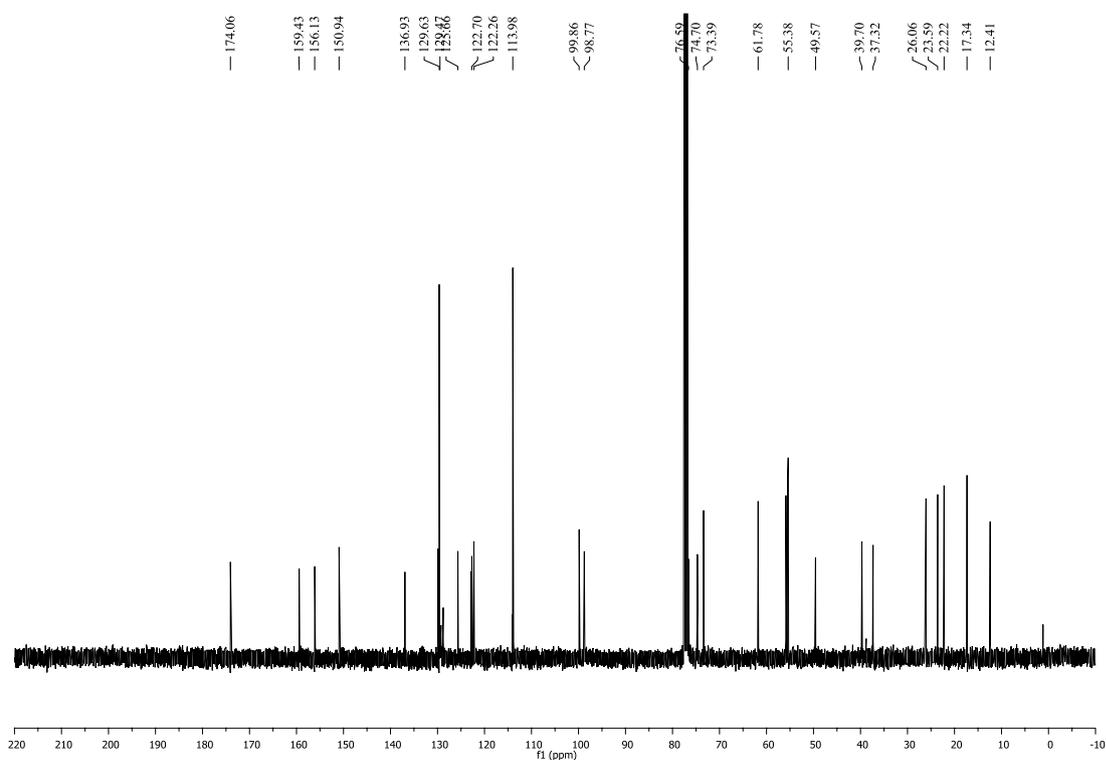
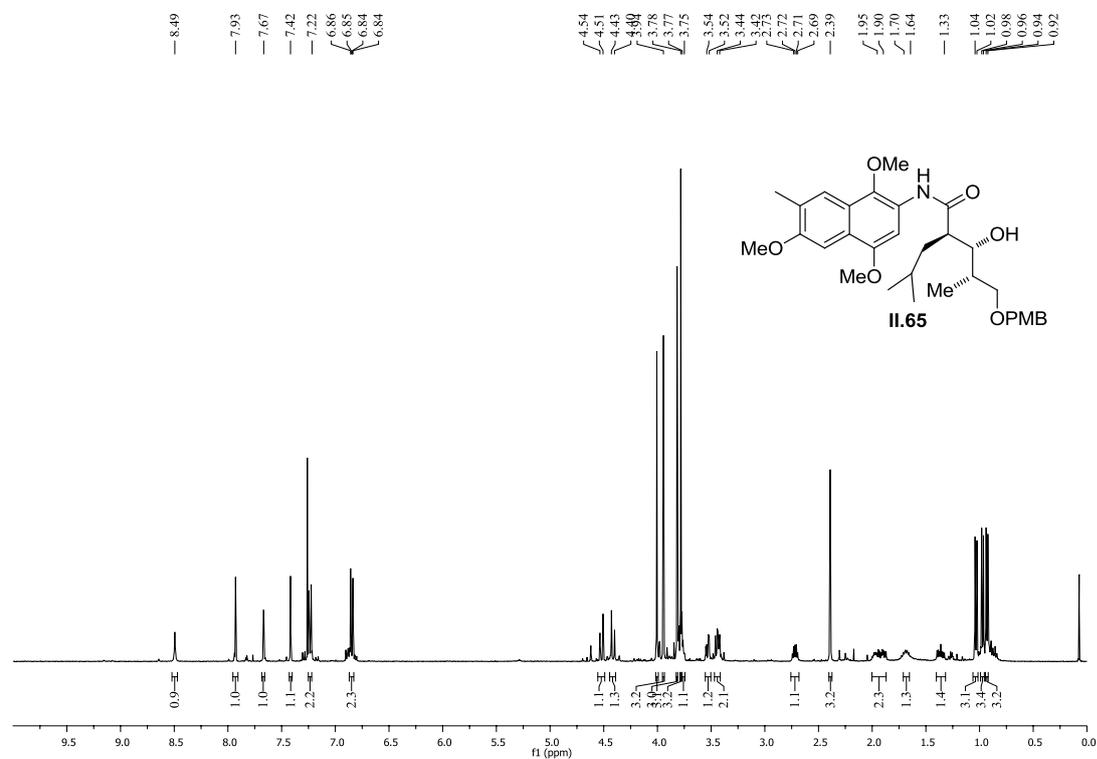
(3*R*,4*R*)-3-Isobutyl-4-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)oxetan-2-one (II.63) (¹H, ¹³C)



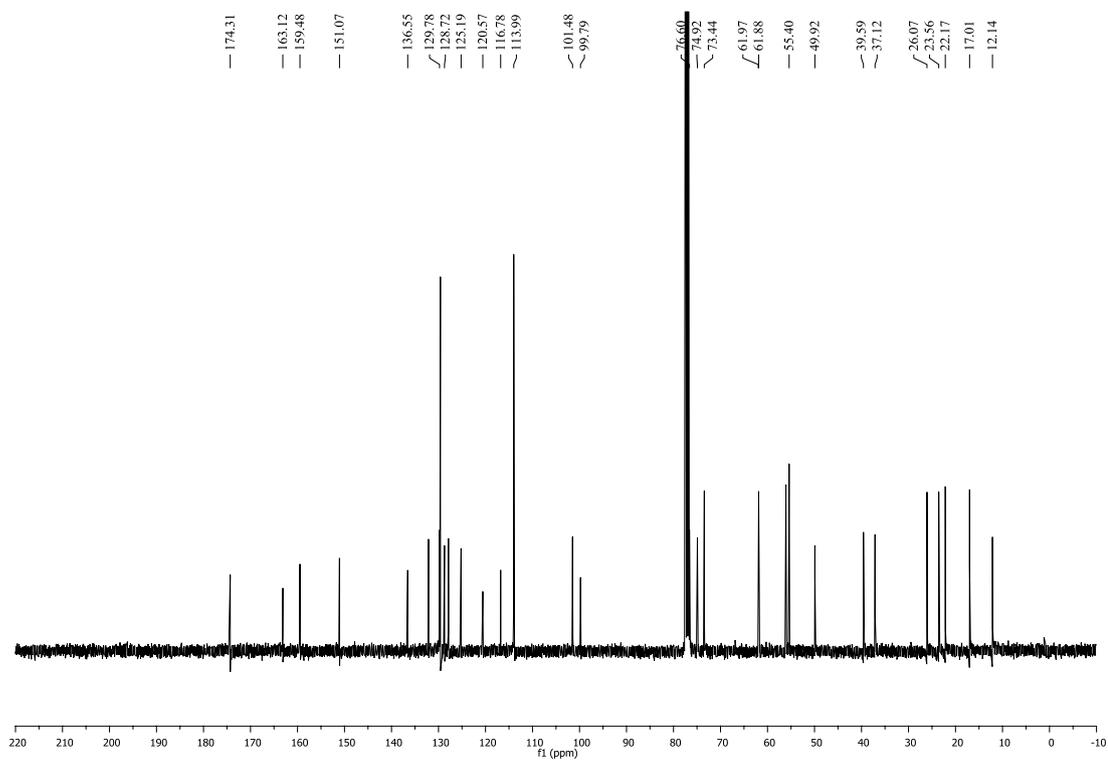
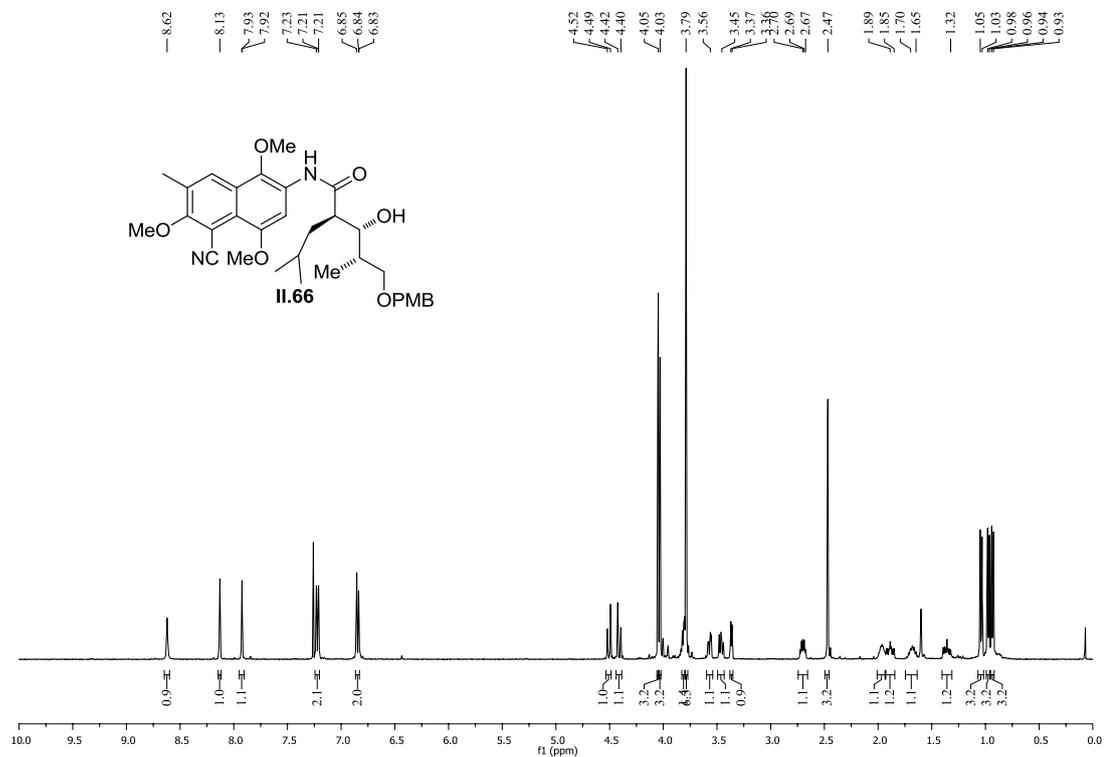
(2*S*,3*R*,4*R*)-3-Hydroxy-4-isobutyl-1-((4-methoxybenzyl)oxy)-2-methylnonan-5-one (II.67)
 (¹H, ¹³C)



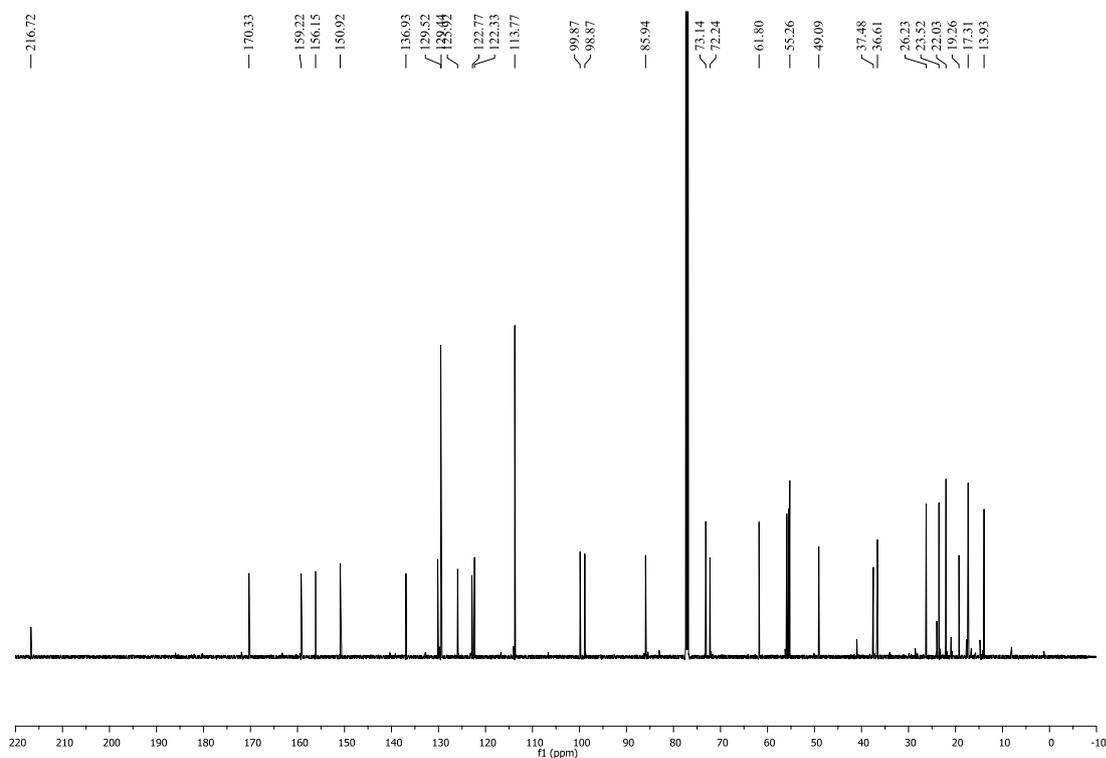
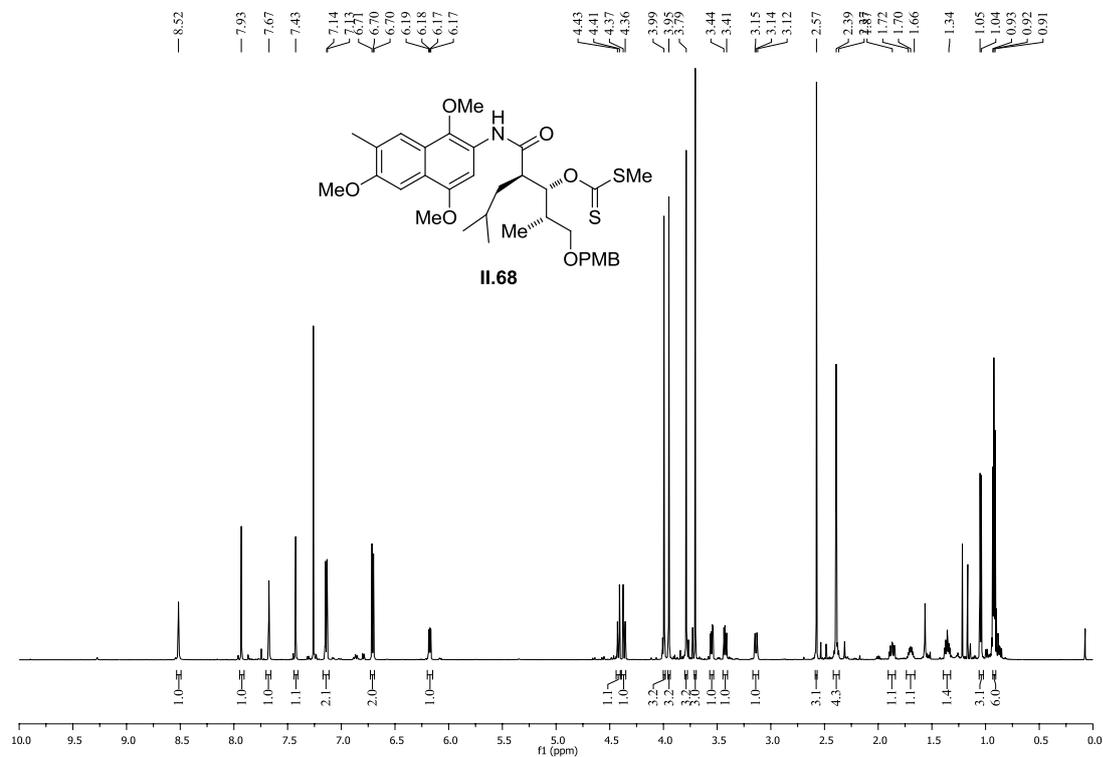
(2*R*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-5-((4-methoxybenzyl)oxy)-4-methyl-*N*-(1,4,6-trimethoxy-7-methylnaphthalen-2-yl)pentanamide (II.65) (¹H, ¹³C)



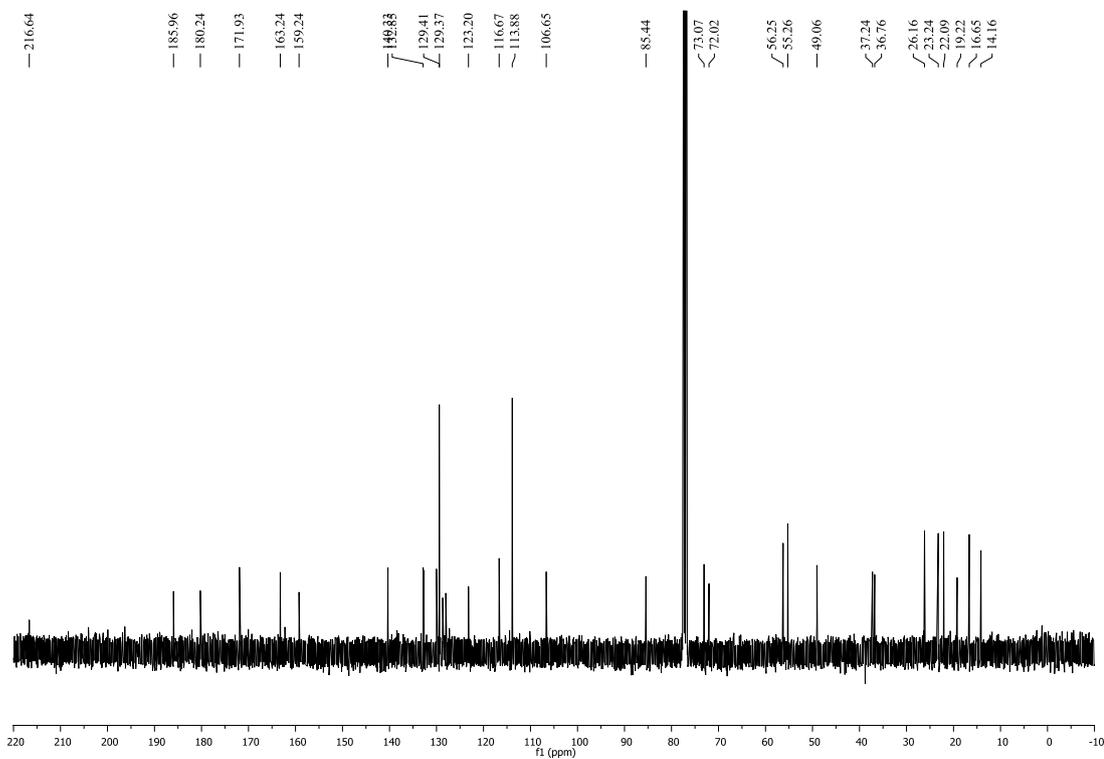
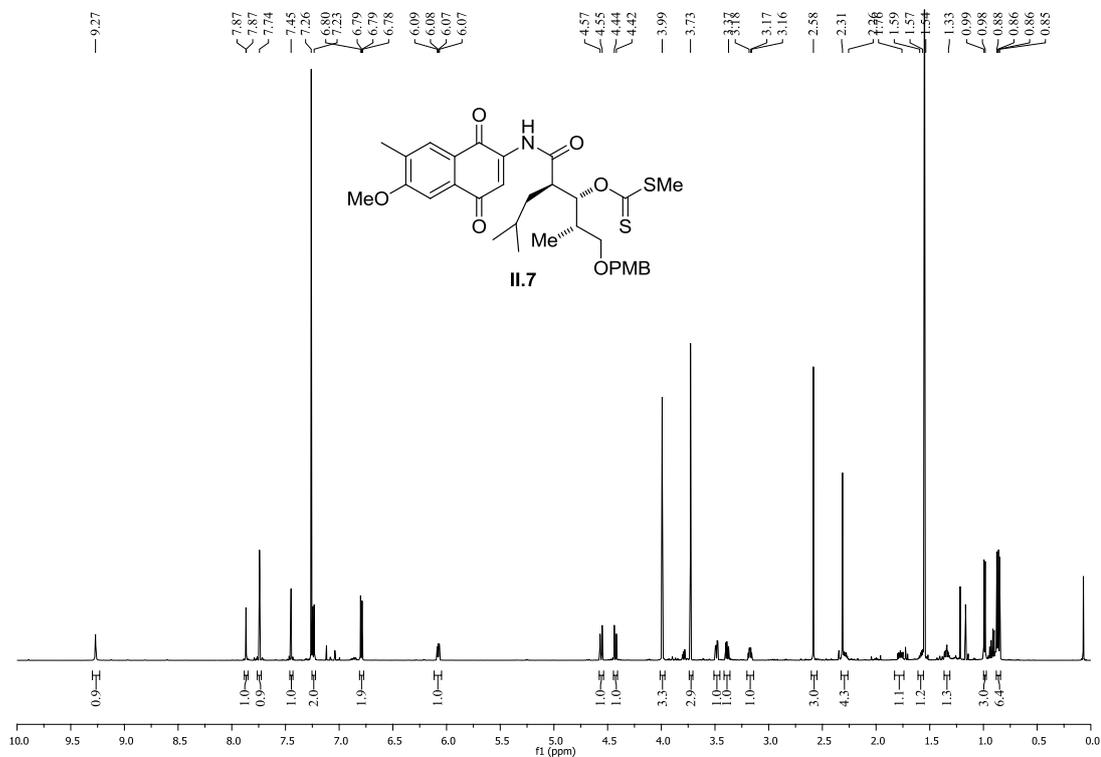
(2*R*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-*N*-(5-isocyano-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)-5-((4-methoxybenzyl)oxy)-4-methylpentanamide (II.66) (¹H, ¹³C)

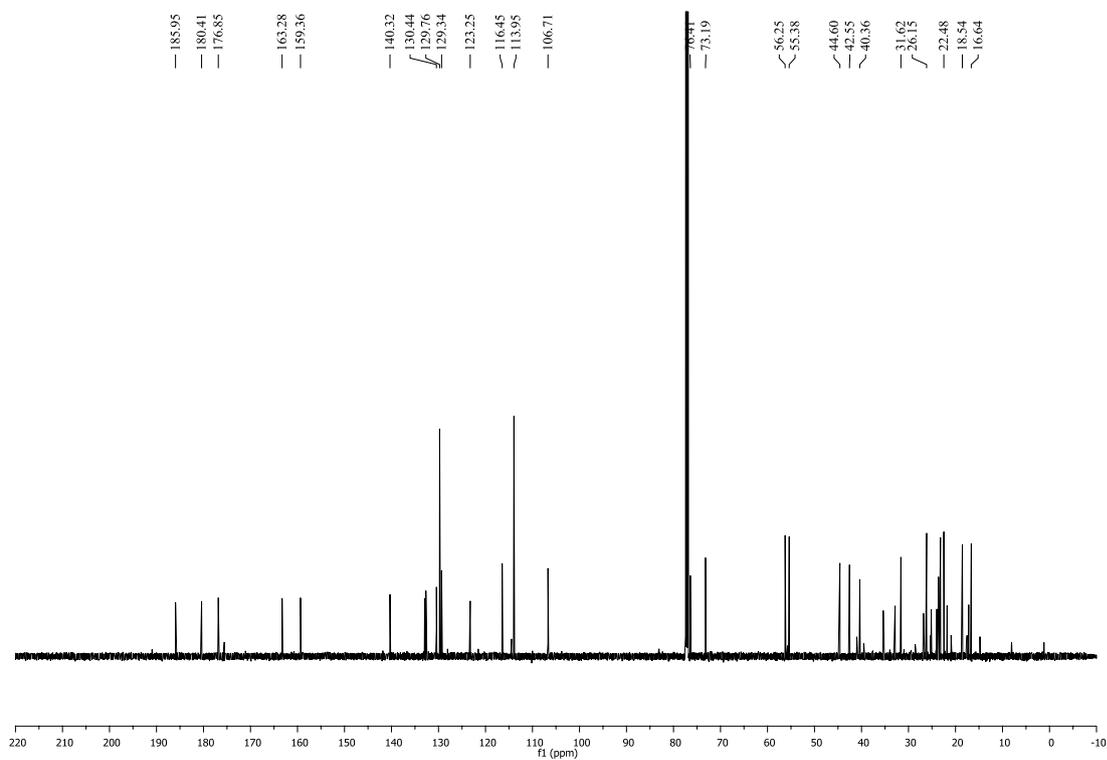
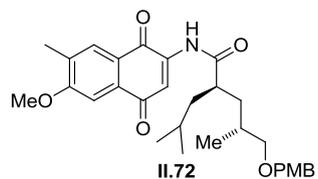
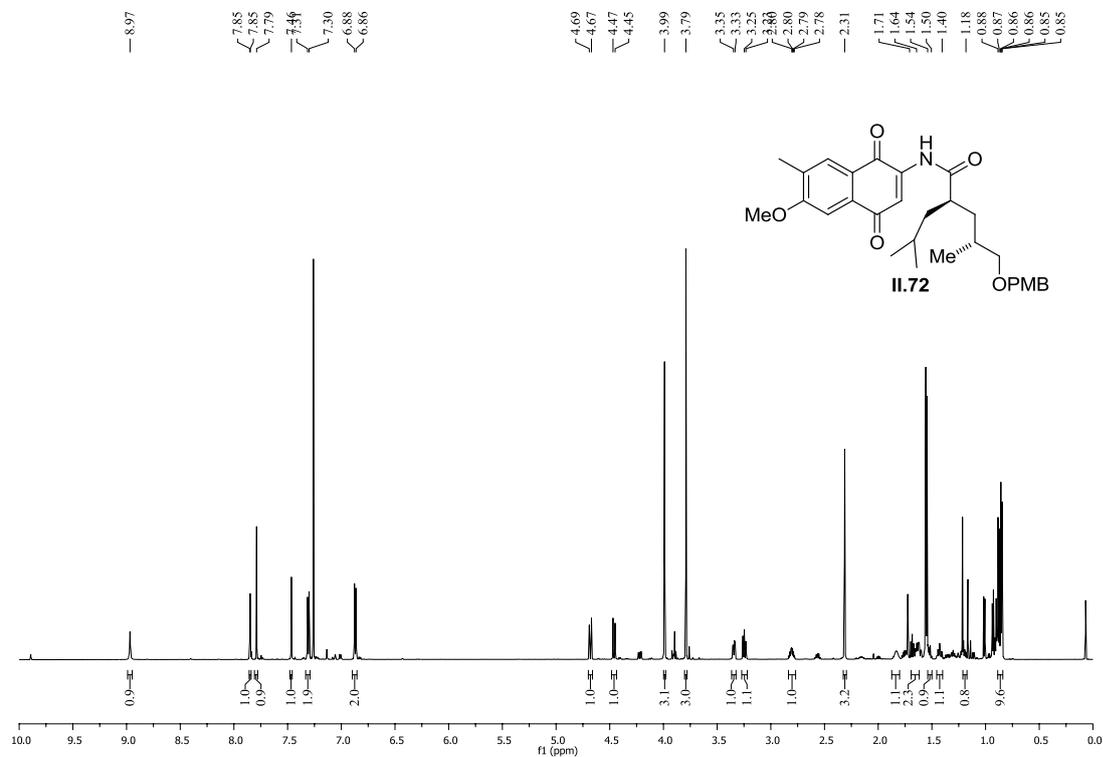


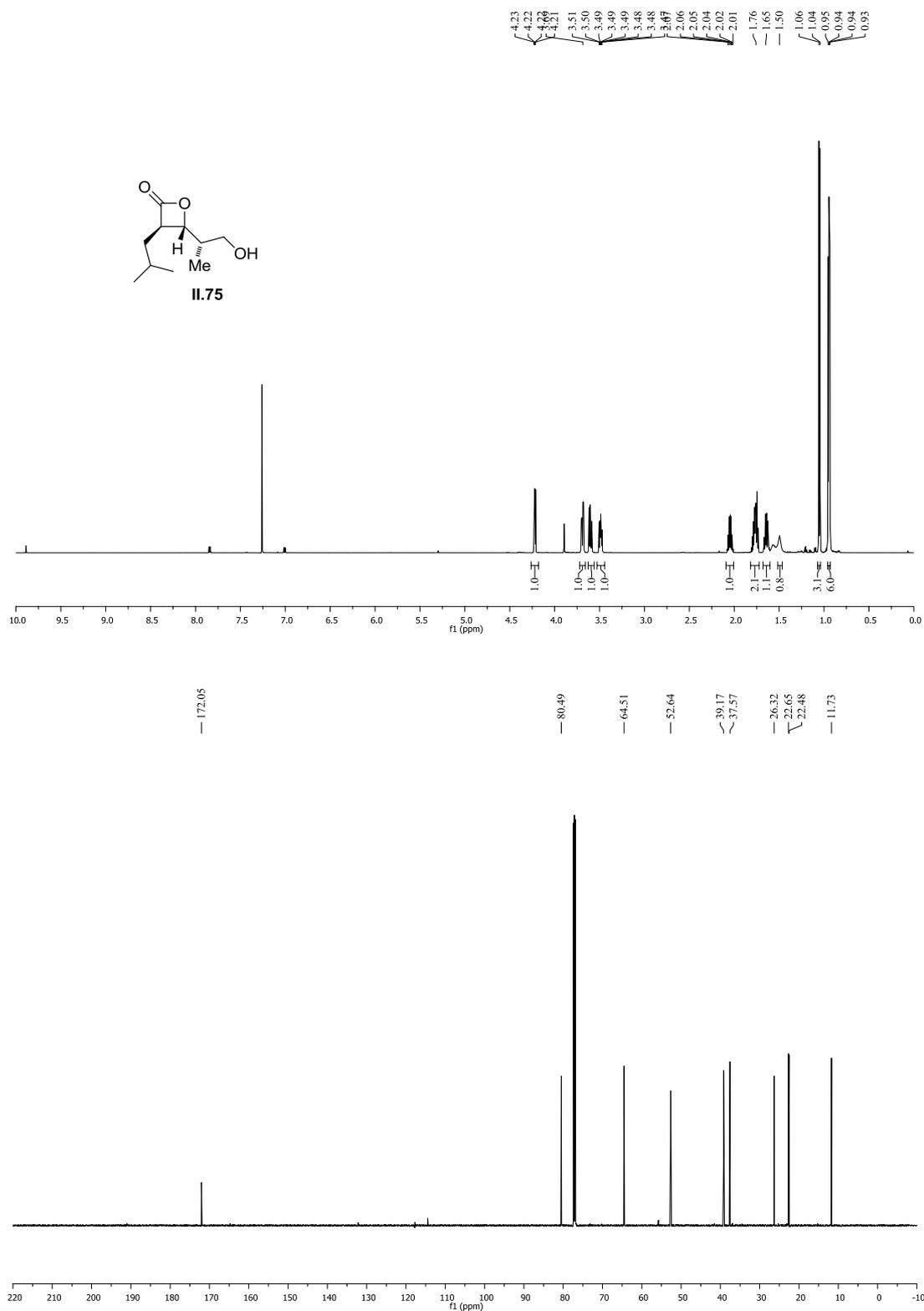
***O*-((2*S*,3*R*,4*R*)-1-((4-Methoxybenzyl)oxy)-2,6-dimethyl-4-((1,4,6-trimethoxy-7-methylnaphthalen-2-yl)carbamoyl)heptan-3-yl) *S*-methylcarbonodithioate (II.68) (¹H, ¹³C)**

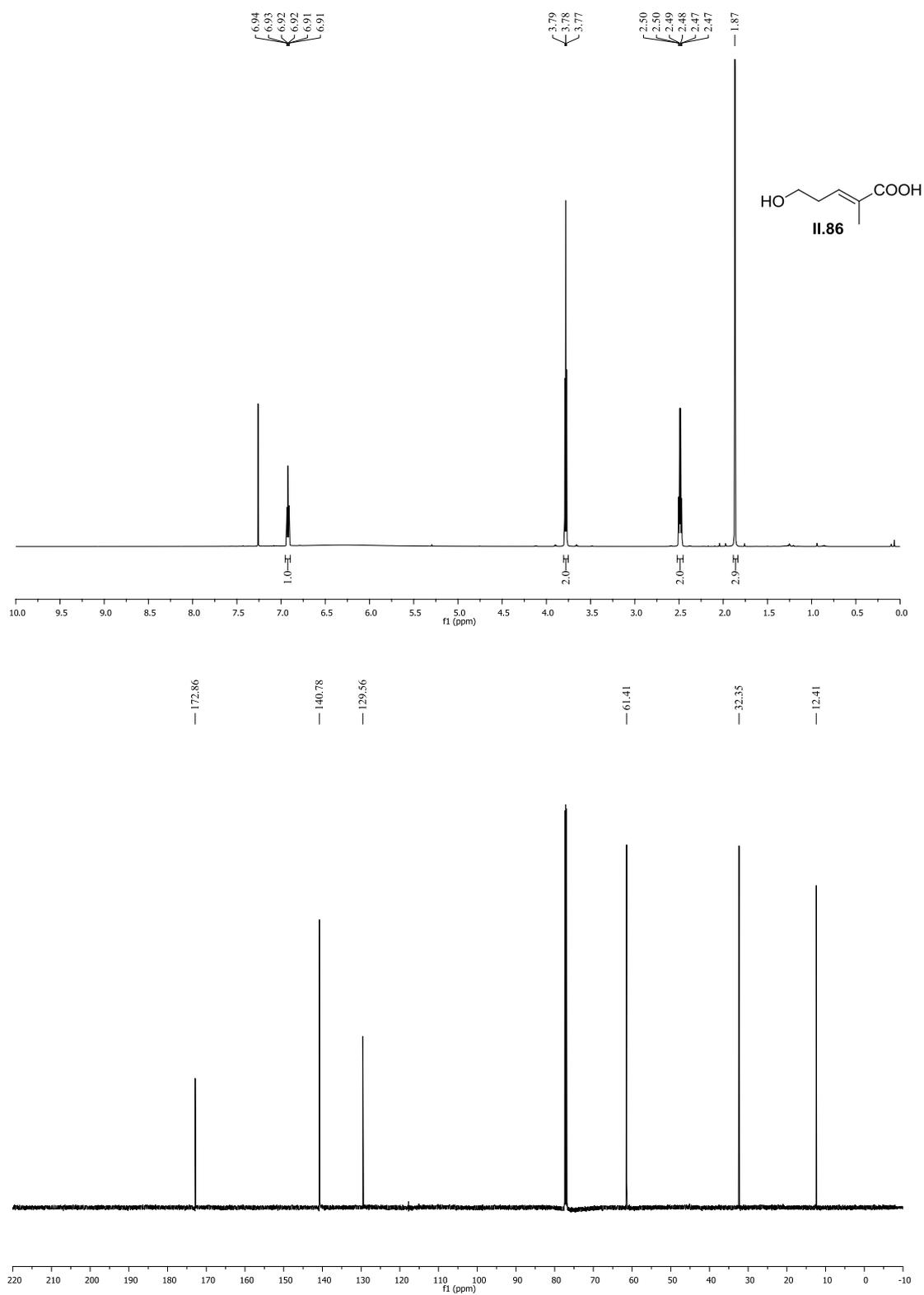


(2*R*,3*R*,4*S*)-*N*-(6-methoxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-[(4-methoxyphenyl)methoxy]-4-methyl-2-(2-methylpropyl)-3-[[methylsulfanyl)methanethioyl]oxy} pentanamide (II.7) (¹H, ¹³C)

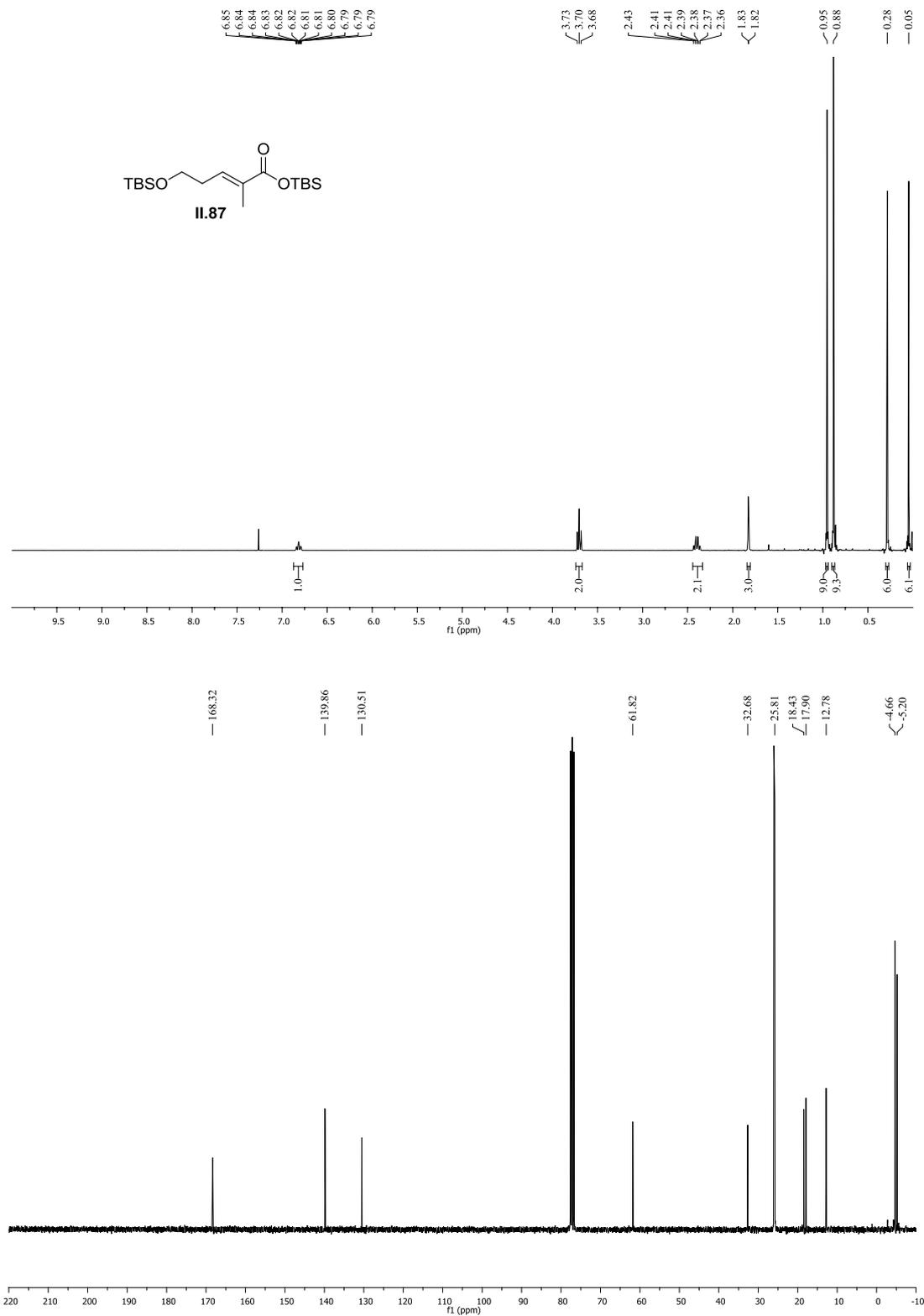


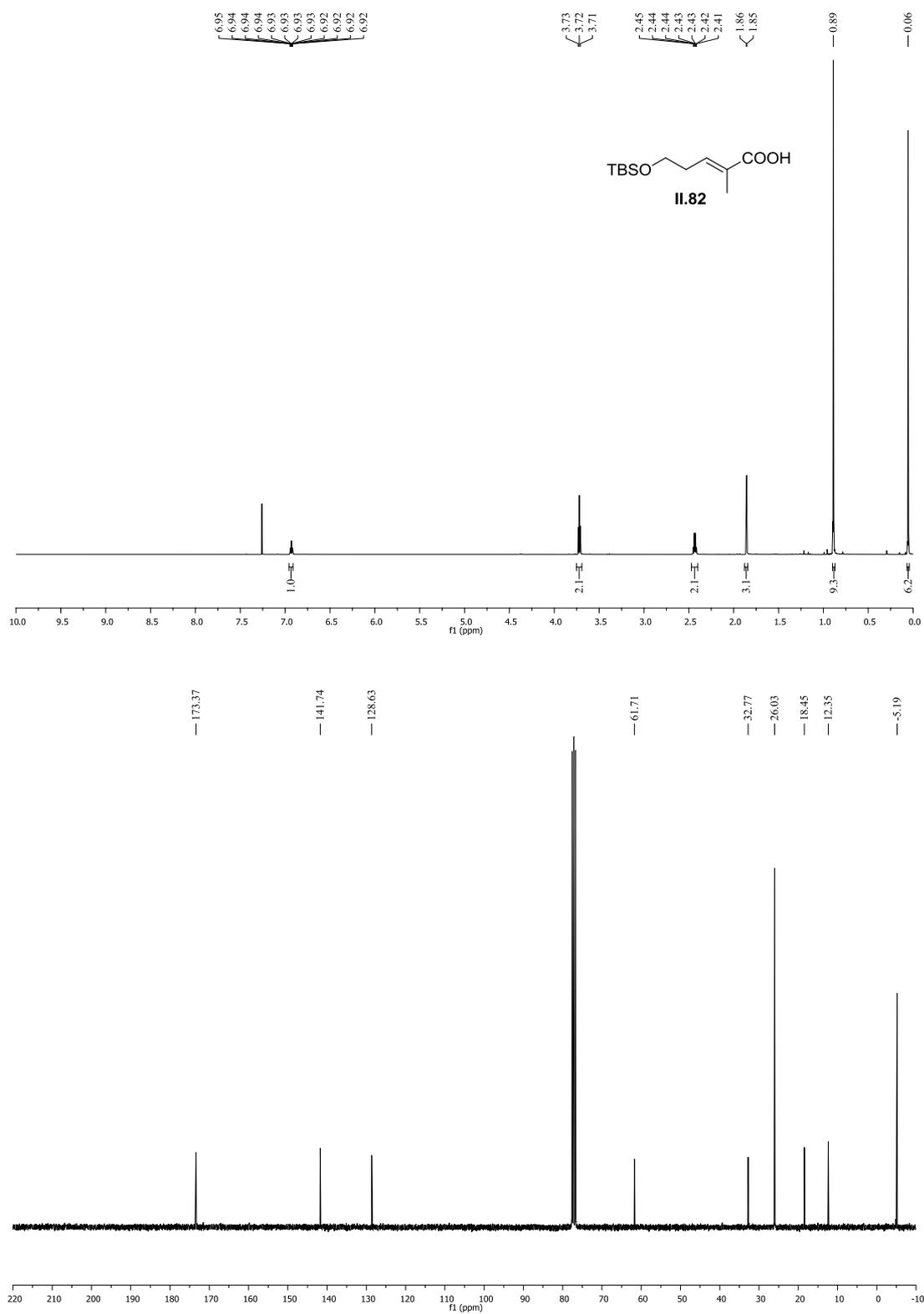
(2*R*,4*R*)-2-isobutyl-*N*-(6-methoxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-((4-methoxy benzyl)oxy)-4-methylpentanamide (II.72) (¹H, ¹³C)

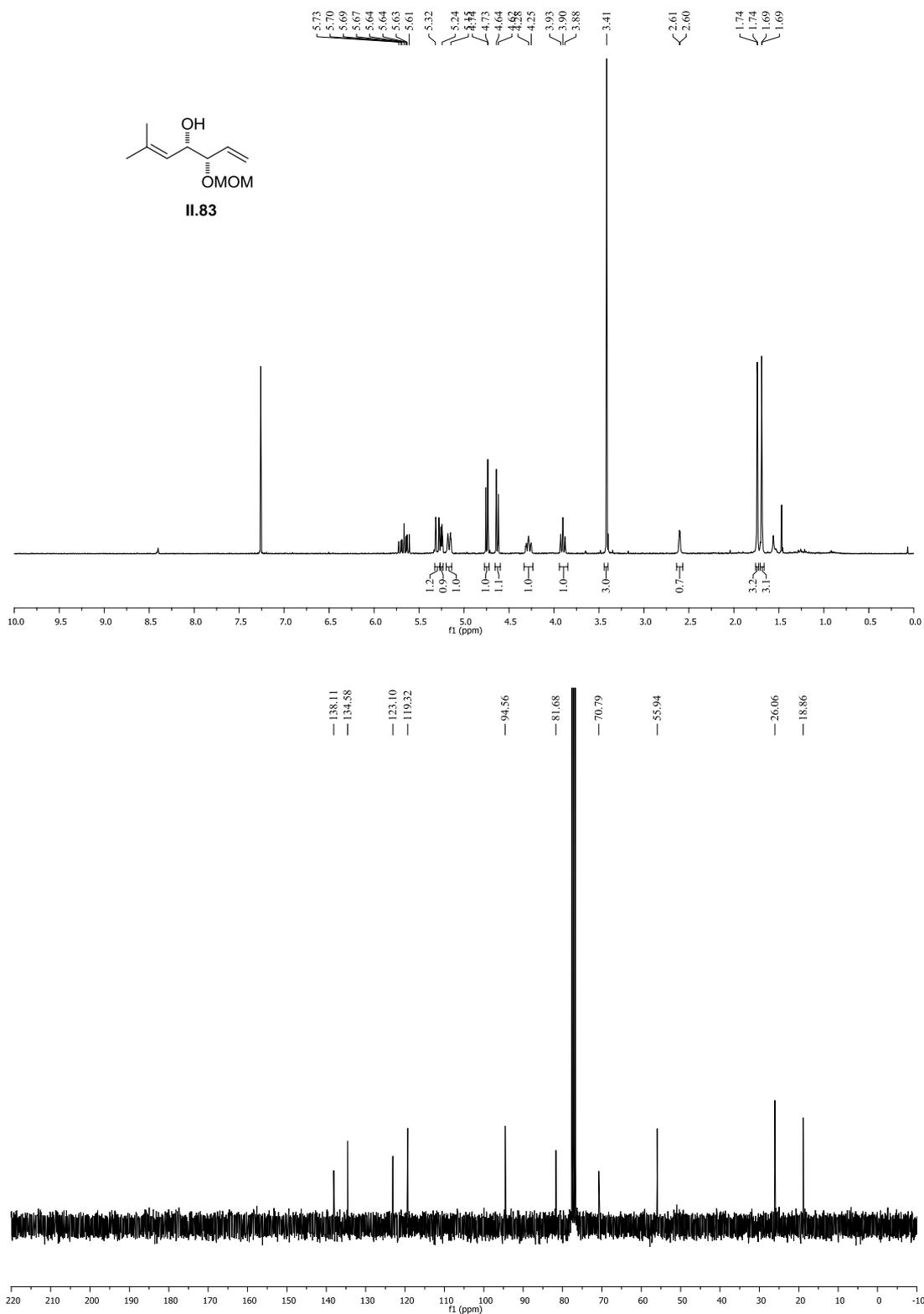
(3*R*,4*R*)-4-((*S*)-1-Hydroxypropan-2-yl)-3-isobutyloxetan-2-one (II.75) (¹H, ¹³C)

(E)-5-Hydroxy-2-methylpent-2-enoic acid (II.86) (^1H , ^{13}C)

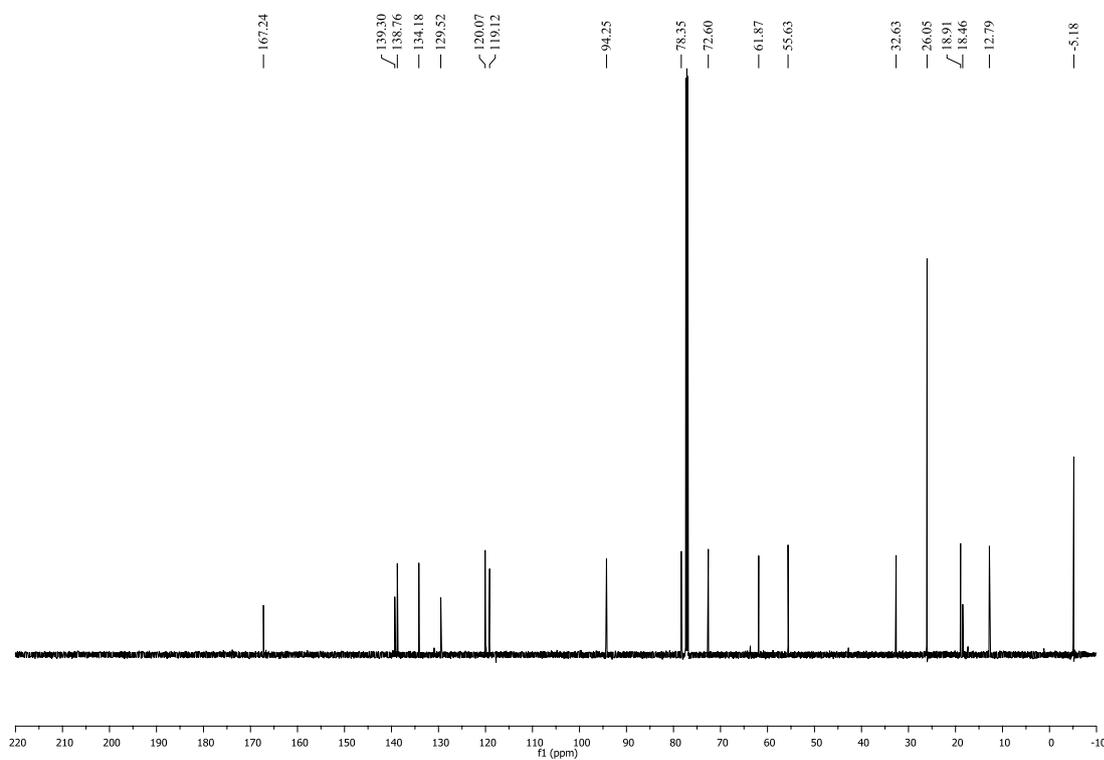
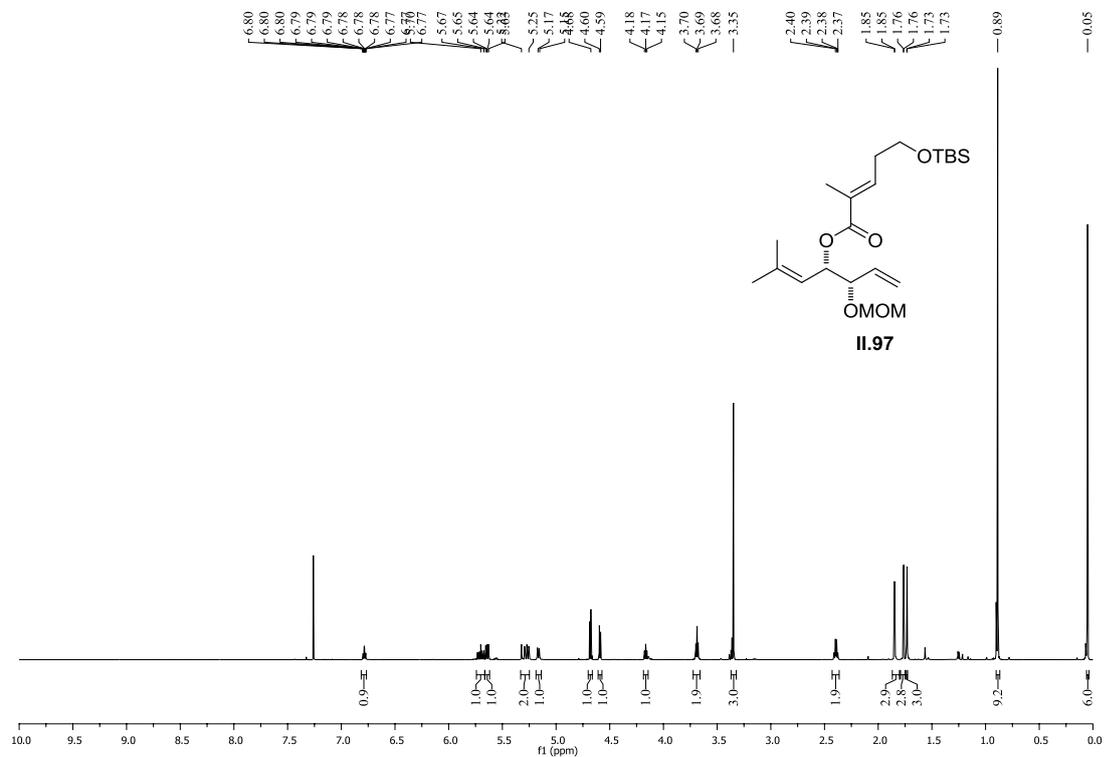
(*E*)-Tert-butyldimethylsilyl 5-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-2-enoate (II.87)
(¹H, ¹³C)



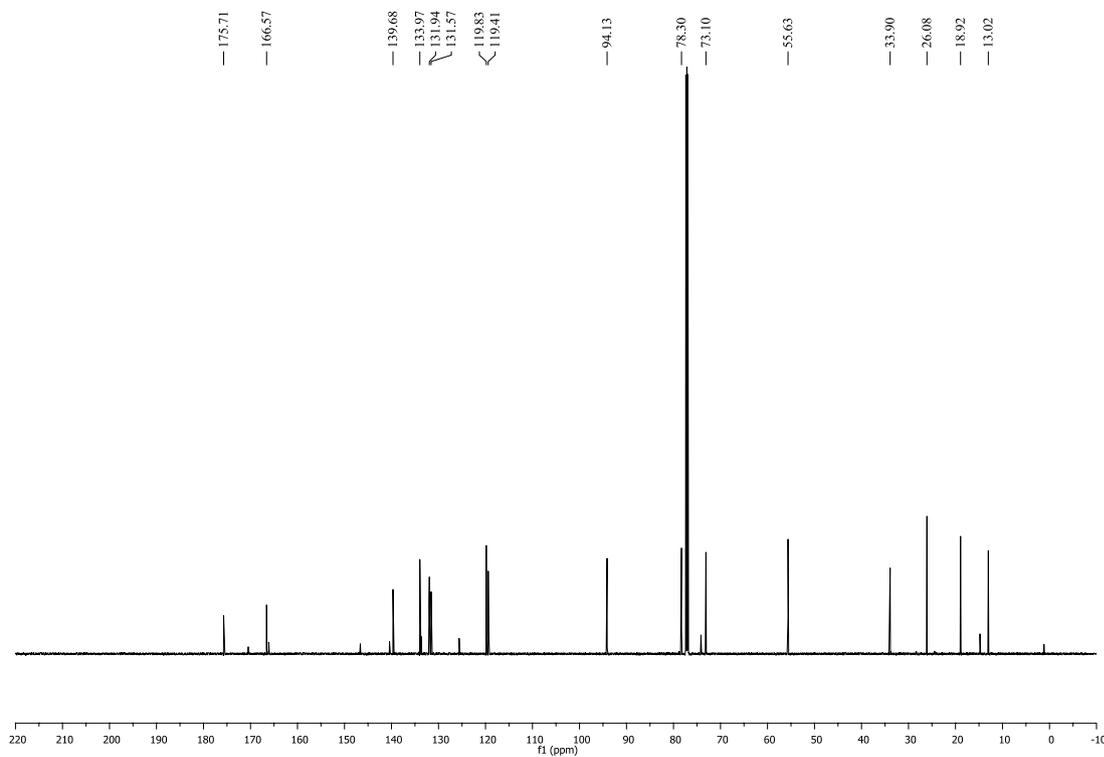
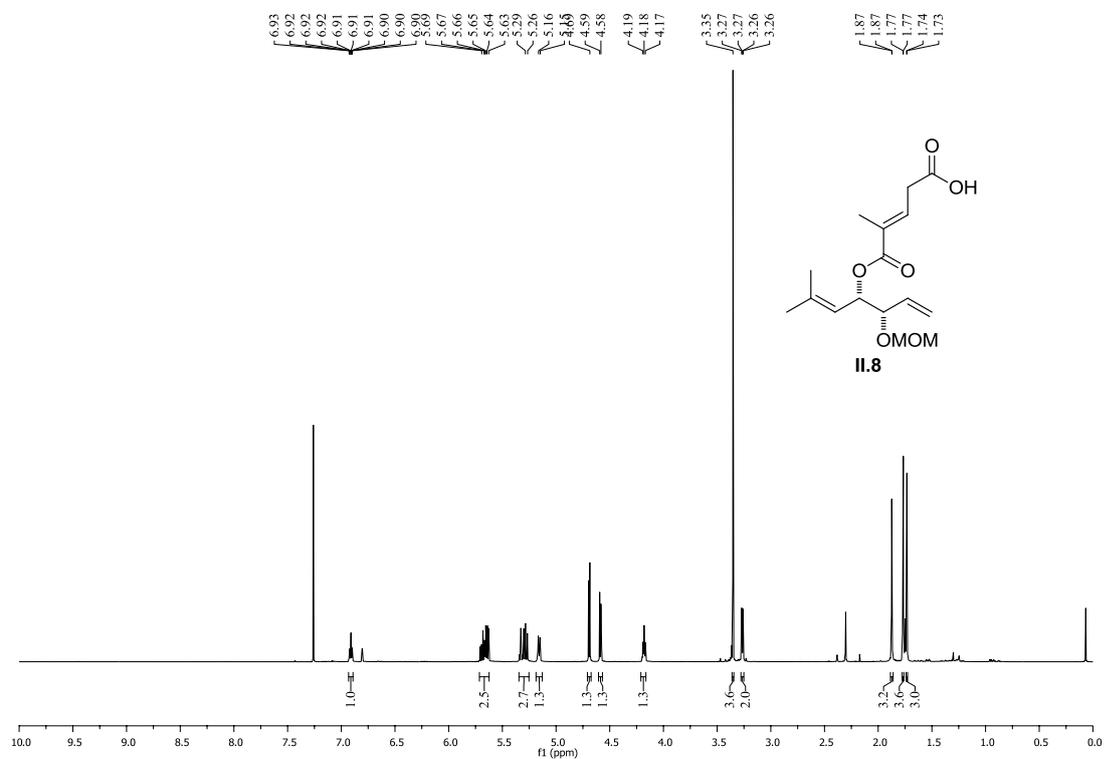
(E)-5-((Tert-butyldimethylsilyl)oxy)-2-methylpent-2-enoic acid (II.82) (¹H, ¹³C)

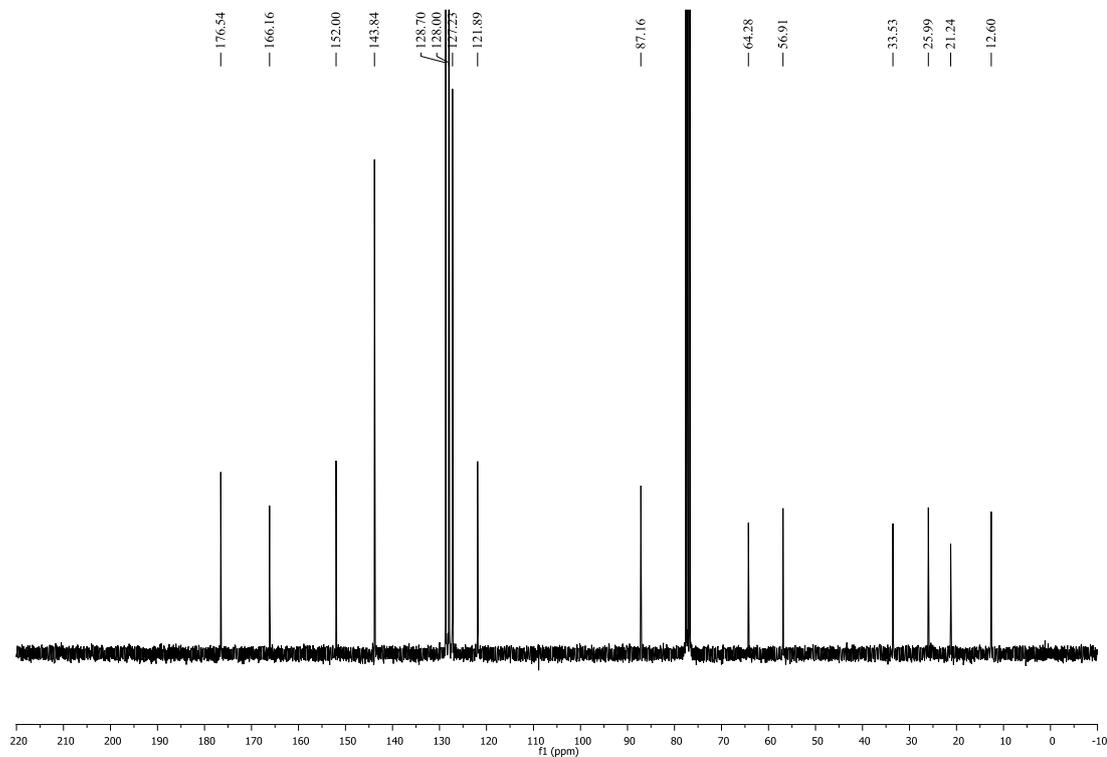
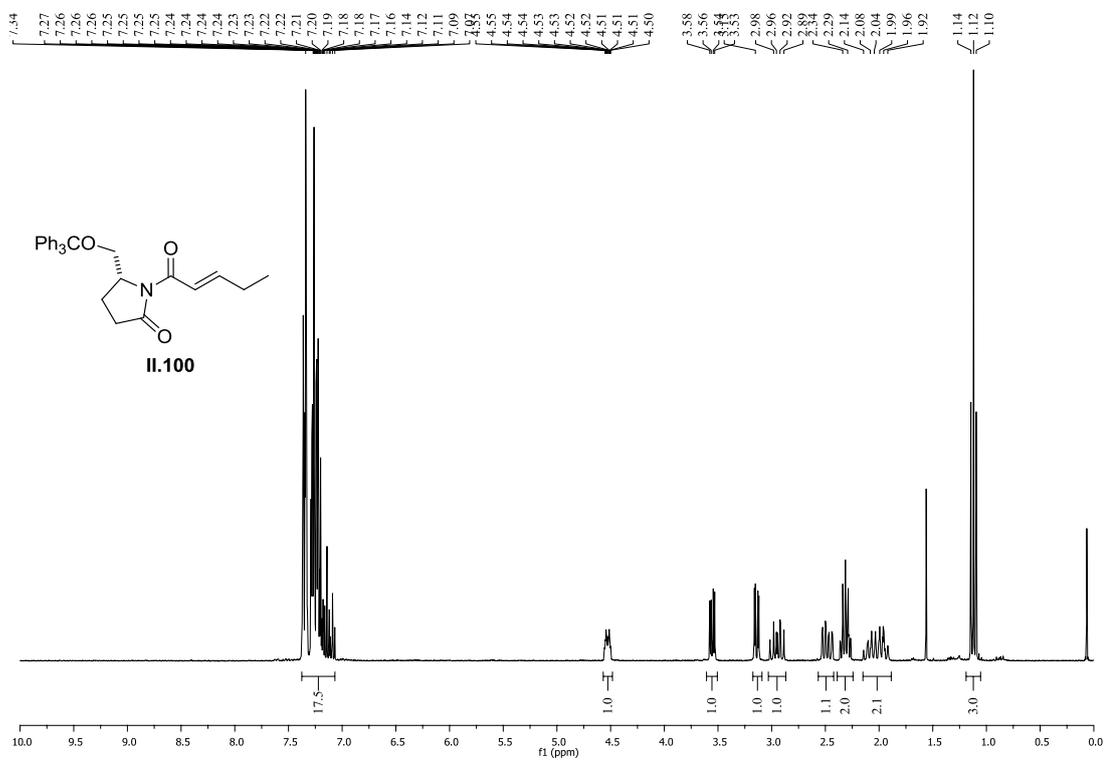
(3*S*,4*S*)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-ol (II.83) (¹H, ¹³C)

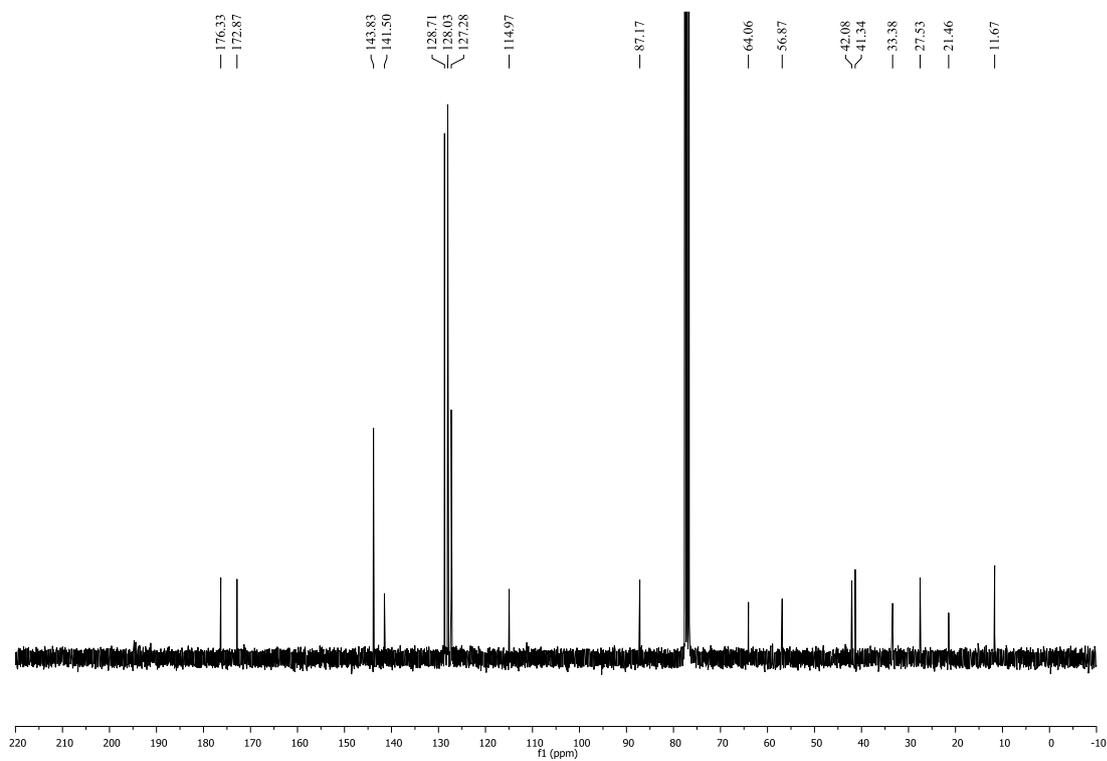
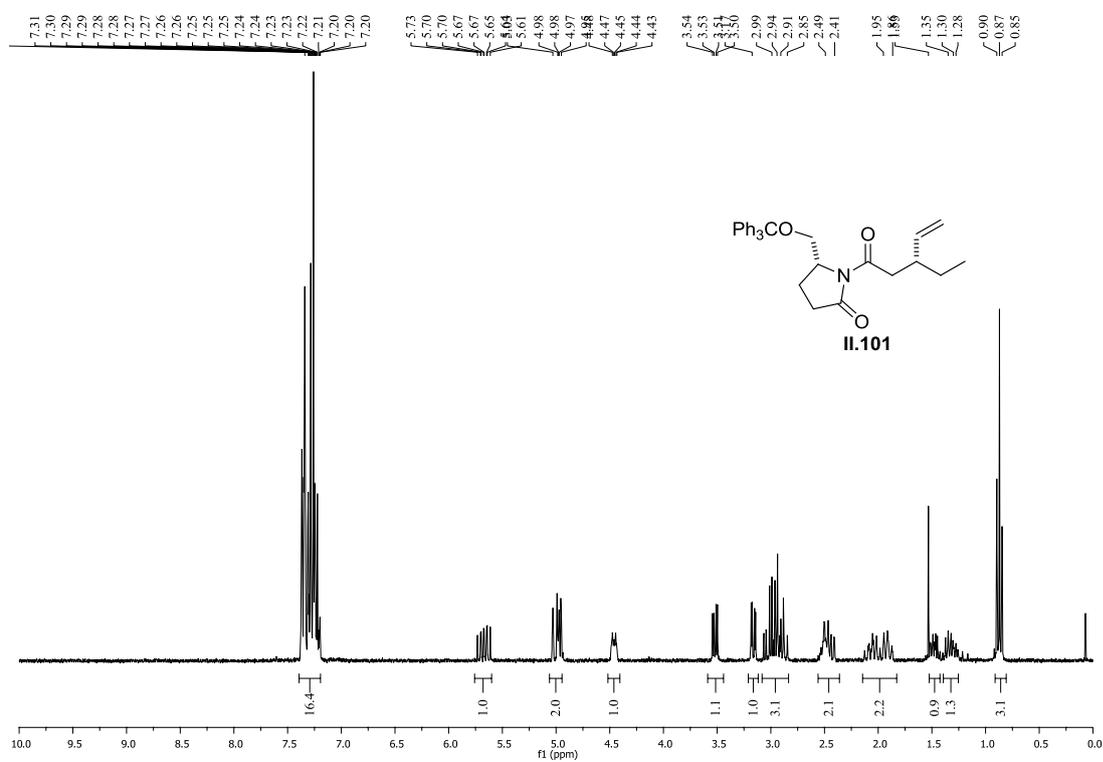
(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-((tert-butyldimethylsilyl)oxy)-2-methylpent-2-enoate (II.97) (¹H, ¹³C)

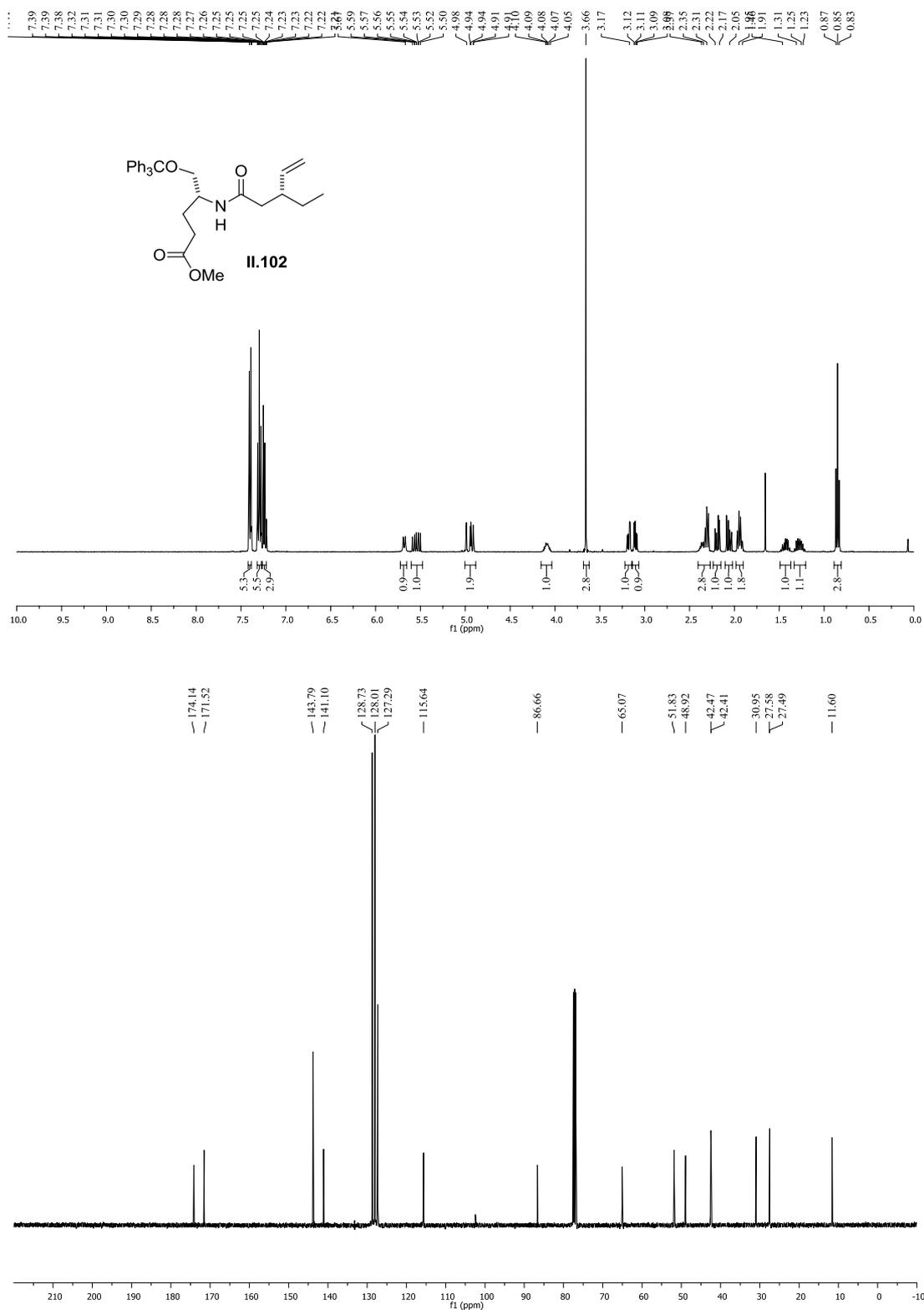


(E)-5-(((3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl)oxy)-4-methyl-5-oxopent-3-enoic acid (II.8) (^1H , ^{13}C)

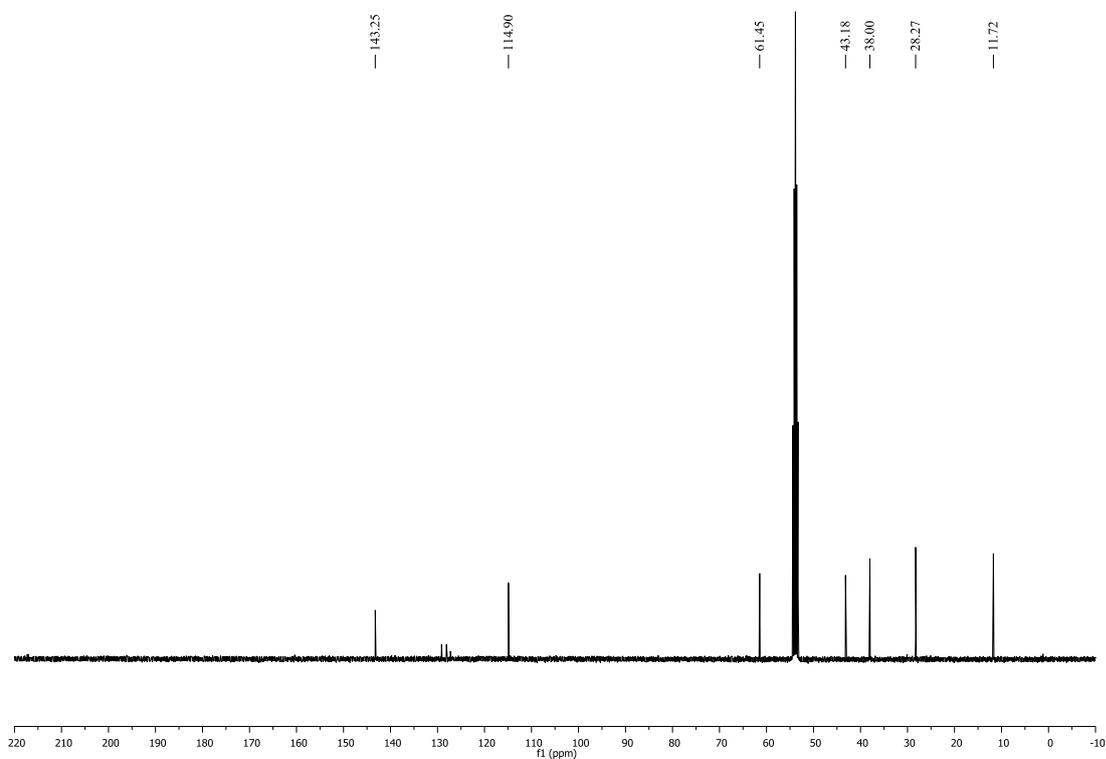
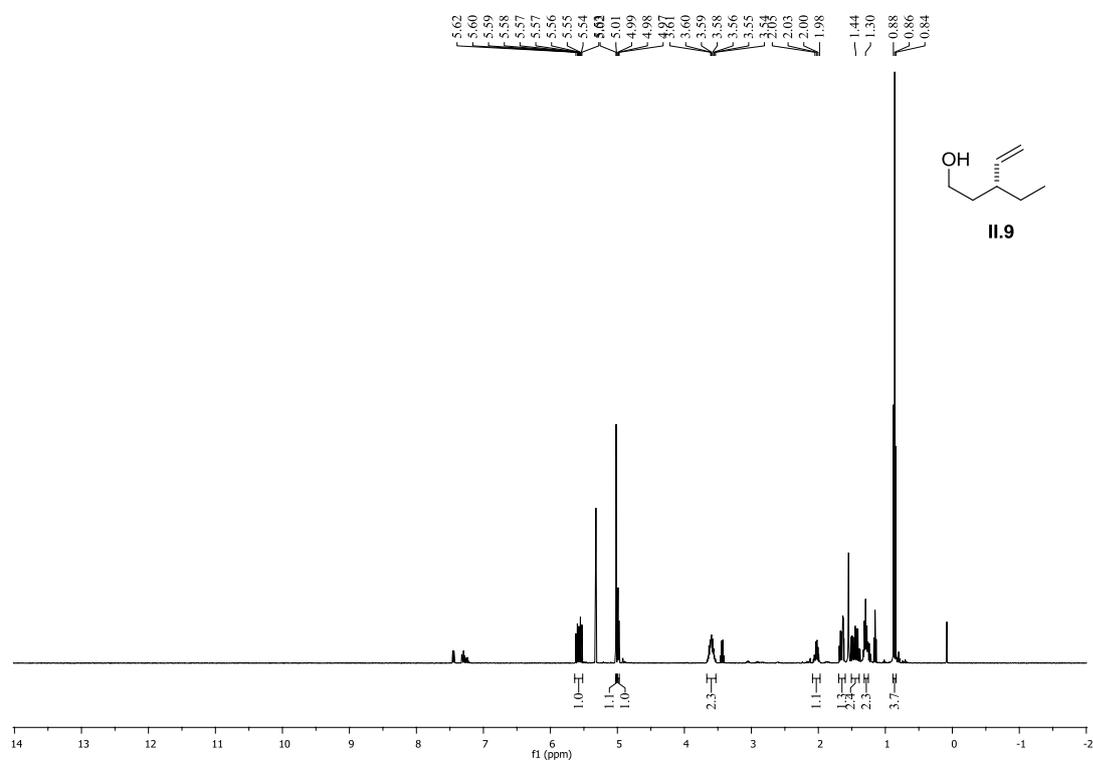


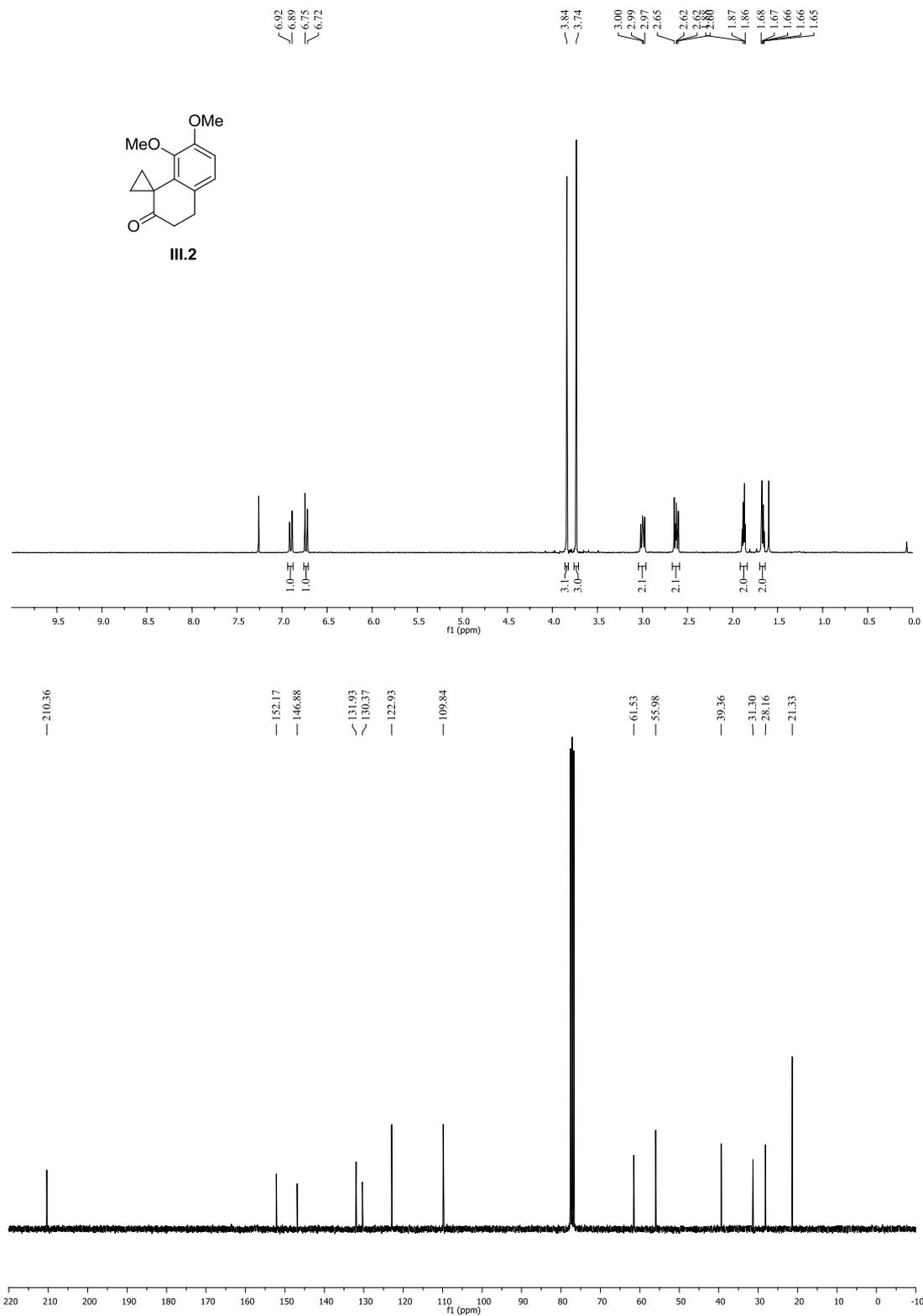
(*R,E*)-1-(Pent-2-enyl)-5-((trityloxy)methyl)pyrrolidin-2-one (II.100) (¹H, ¹³C)

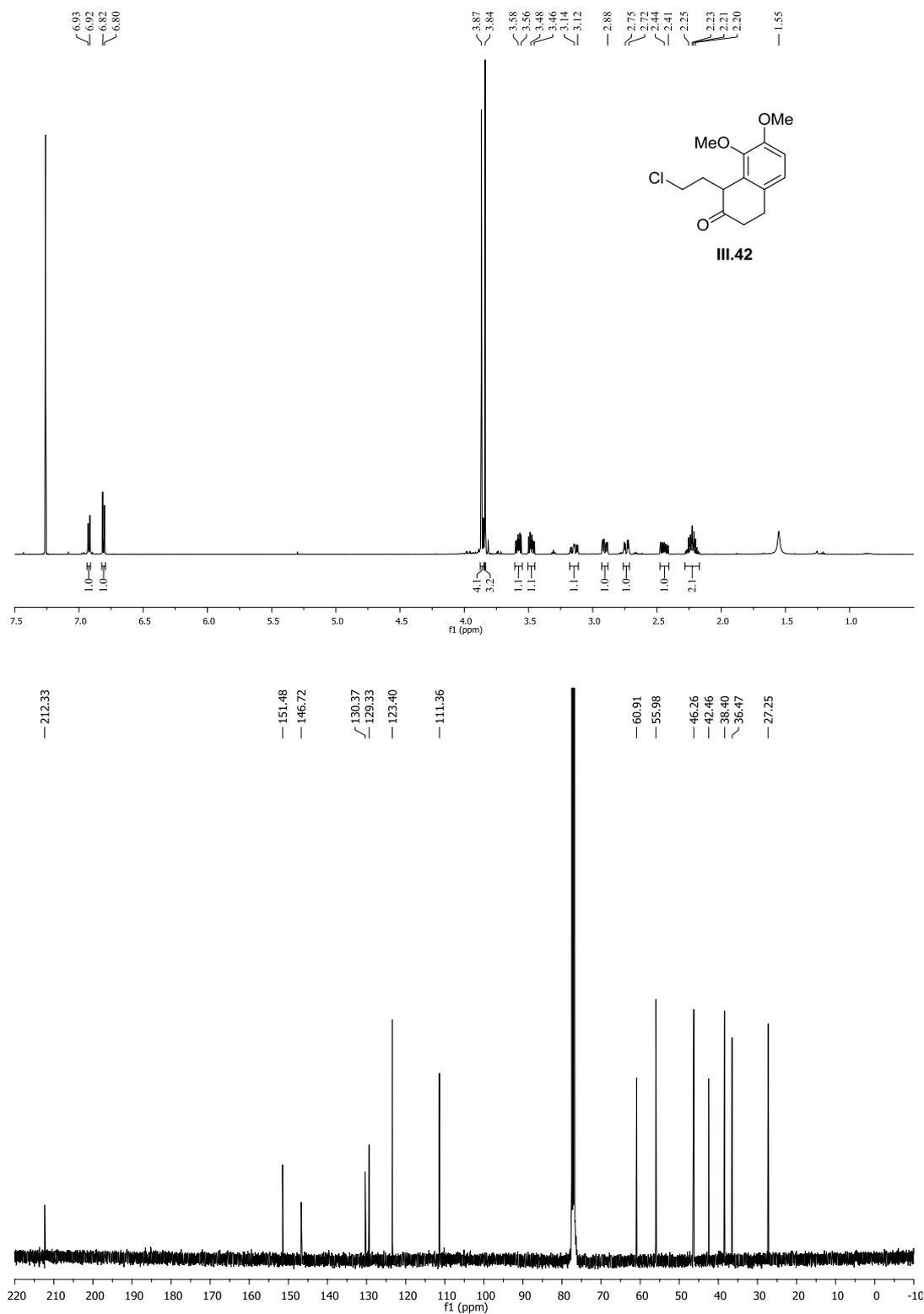
(R)-1-((R)-3-Ethylpent-4-enyl)-5-((trityloxy)methyl)pyrrolidin-2-one (II.101) (^1H , ^{13}C)

(R)-Methyl 4-((R)-3-ethylpent-4-enamido)-5-(trityloxy)pentanoate (II.102) (^1H , ^{13}C)

(R)-3-Ethylpent-4-en-1-ol (II.9) (^1H , ^{13}C)



7',8'-Dimethoxy-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-2'-one (III.2) (¹H,¹³C)

1-(2-Chloroethyl)-7,8-dimethoxy-3,4-dihydronaphthalen-2(1H)-one (III.42) (^1H , ^{13}C)

APPENDIX II

–Table A–

APPENDIX II: TABLE A

Table A. Condition screened toward the envisioned dearomatizing Michael-Michael addition.

	Reagent	Additive	Solvent	T [°C]	Observation
1	AcOH/piperidine	–	toluene	rt	sm ^a /decomposition
2	PPTS	–	CH ₂ Cl ₂	rt	sm ^a /decomposition
3	Phenylboronic acid	–	toluene	100	sm ^a /pyrone I.99
4	methanolic HCl	–	MeOH	rt	lactone I.99 /pyrone I.99
5	TFA	–	CH ₂ Cl ₂	rt	sm ^a
6	BF ₃ ·OEt ₂	–	THF	0→rt	sm ^a /unknown compound
7	TiCl ₄	–	CH ₂ Cl ₂	0→rt	s. m.
8	AlCl ₃	–	CH ₂ Cl ₂	rt	sm ^a /decomposition
9	AlCl ₃	–	CH ₂ Cl ₂	–78→rt	sm ^a
10	Sc(OTf) ₃	–	MeCN/H ₂ O	rt	lactone I.25
11	LiClO ₄	–	CH ₂ Cl ₂	rt	lactone I.25
12	TMSI	–	CH ₂ Cl ₂	0→rt	decomposition
13	-	–	benzene	70	sm ^a
14	-	–	DMSO	70	sm ^a /decomposition
15	-	–	dichlorobenzene	150	pyrone I.99
16		–	dichlorobenzene	120/μw	sm ^a /pyrone I.99
17		–	benzene	hv, rt	decomposition
18	TBAF	–	THF	0→rt	sm ^a
19	TBAF	–	THF/DMF	–78→rt	I.4 and I.92
20	TBAF	–	THF/DMF	rt→60	decomposition
21	TBAF	3 Å ms ^b	THF/DMF	rt→60	sm ^a /decomposition
22	TBAF	3 Å ms ^b	THF/DMF	–78→rt	sm ^a
23	DBU	–	CH ₂ Cl ₂	rt	pyrone I.99 /lactone I.25

24	NEt ₃	–	dichlorobenzene	150	pyrone I.99 /lactone I.25
25	DABCO	–	dichlorobenzene	120/ μw	sm ^a /pyrone I.99
26	CsF	–	MeCN	60	lactone I.25
27	K ₂ CO ₃	–	MeOH	rt	decomposition
28	piperidine	–	EtOH	rt	sm ^a /lactone I.25
29	LiOH	–	THF/H ₂ O	rt→60	decomposition
30	LDA	–	THF	–78→rt	sm ^a
31	L-proline	–	<i>i</i> -PrOH	rt	pyrone I.99
32	L-proline	–	DMF	rt	pyrone I.99
33	L-proline	–	DMSO	rt	pyrone I.99
34	MacMillan cat.	–	DMSO	rt	pyrone I.99
35	MacMillan cat./L-proline	–	DMSO	rt	pyrone I.99
36	Li-prolinate	–	DMSO	rt	pyrone I.99
37	Jørgensen cat.	–	DMSO	rt	pyrone I.99
38	Mn(OAc) ₃	NaOAc/AcOH	AcOH	70	unknown compound
39	Mn(OAc) ₃	–	AcOH	70	decomposition
40	Mn(OAc) ₃	–	AcOH	rt	decomposition
41	Mn(OAc) ₃	–	EtOH	0	unknown compound
42	Mn(OAc) ₃	–	AcOH	90	decomposition
43	K ₃ Fe(CN) ₆	KOH	H ₂ O	0	sm ^a
44	K ₃ Fe(CN) ₆	K ₂ CO ₃	toluene/H ₂ O	60	sm ^a /decomposition
45	Pb(OAc) ₄	pyridine	CH ₂ Cl ₂	–78→–30	spiro I.92
46	[Fe(DMF) ₃ Cl ₂][FeCl ₄]	LDA	THF	–78→–30	sm ^a
47	[Fe(DMF) ₃ Cl ₂][FeCl ₄]	–	EtOH/H ₂ O	rt→40	sm ^a /unknown compound
48	Cu(OAc) ₂ /Mn(OAc) ₃	–	Benzene/AcOH	70	decomposition
49	PIFAI	–	CH ₂ Cl ₂	0	decomposition
50	PIFAI	–	CF ₃ OH	0	decomposition
51	DIB	–	MeOH	0	decomposition

^asm = starting material; ^bms = molecular sieves

APPENDIX III

–Crystal Structures of I.28, I.29, I.71
and I.99–

APPENDIX III: CRYSTAL STRUCTURES OF I.28, I.29, I.71, AND I.99

Single-Crystal X-Ray Analysis for Compounds I.28, I.29, I.71 and I.99

The data collections were performed on an Oxford Diffraction Xcalibur or KappaCCD diffractometers at 173 K (I.71: 200 K) using MoK α -radiation ($\lambda = 0.71073$ Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) [ref. 1] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 [ref. 2] and refined by least-squares methods against F^2 with SHELXL-97 [ref. 3]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table B. The corresponding Cambridge Crystallographic Data Center (CCDC) storage numbers for the compounds I.28, I.29, I.71 and I.99 are 795937, 795938, 795939 and 847091, respectively.

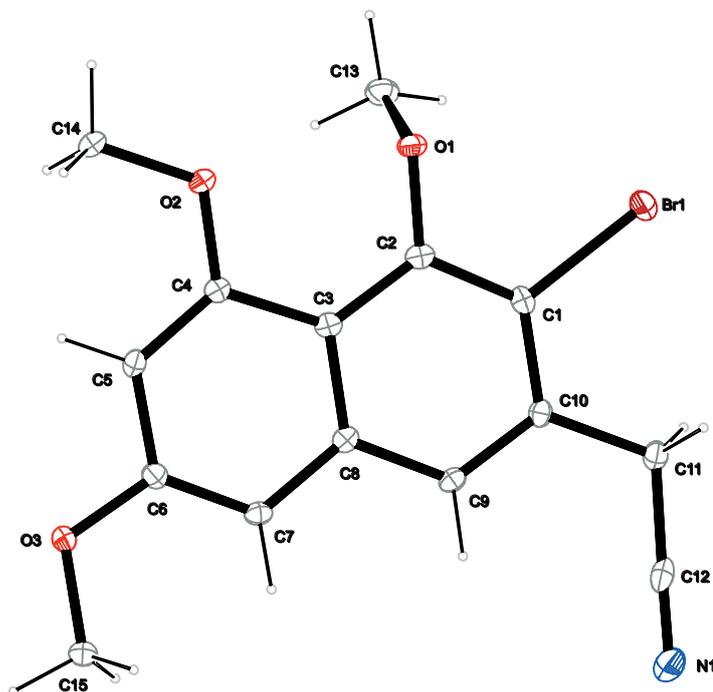


Figure A. Crystal structure of cyanide I.28.

ref. 1 CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.41 (release 06-05-2009 CrysAlis171 .NET).

ref. 2 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, 32, 115-119.

ref. 3 G. M. Sheldrick, *Acta. Crystallogr. Sect. A* **2008**, 64, 112-122.

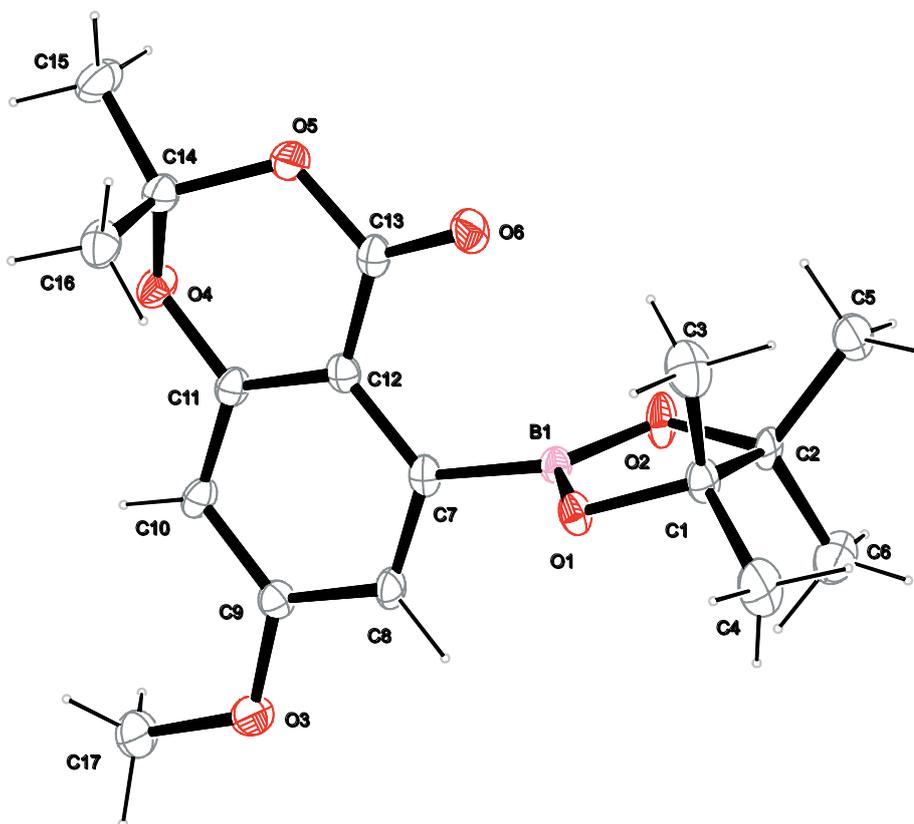


Figure B. Crystal structure of boronate ester 1.29.

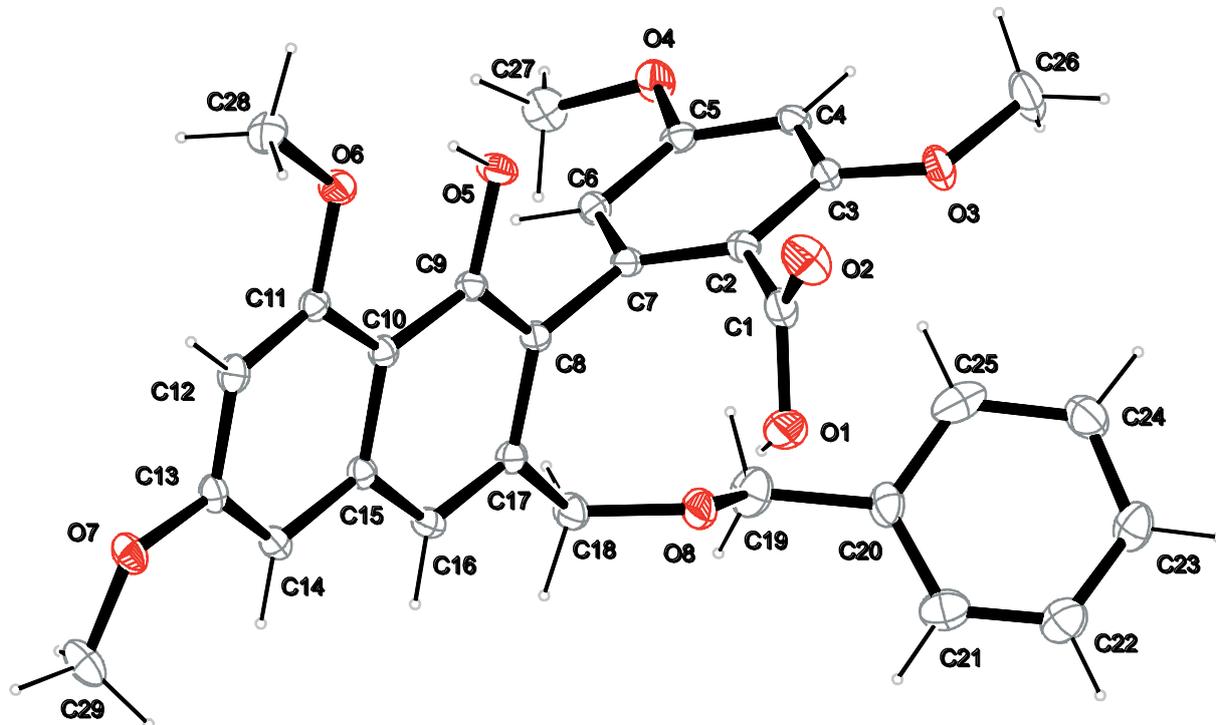


Figure C. Crystal structure of biaryl acid 1.71.

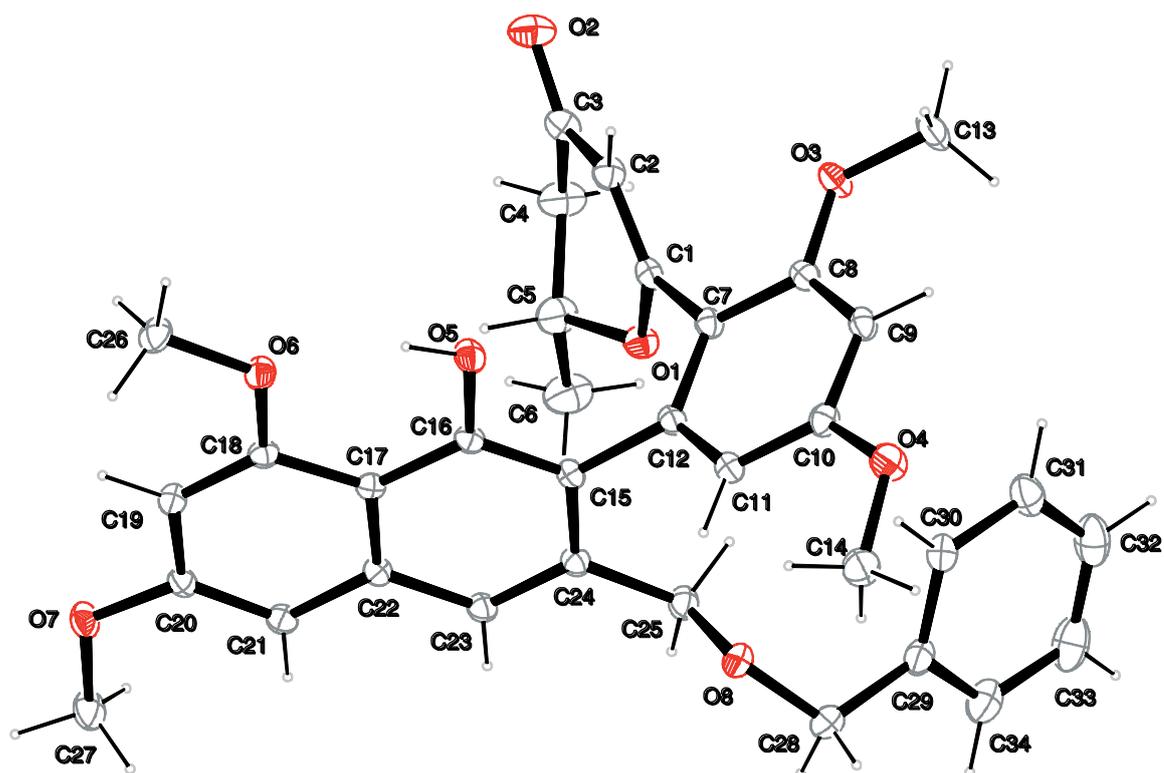


Figure D. Crystal structure of pyrone 1.99.

Table B. Crystallographic data of cyanide **I.28**, boronate ester **I.29**, biaryl acid **I.71** and pyrone **I.99**.

	I.28	I.29	I.71	I.99
net formula	C ₁₅ H ₁₄ BrNO ₃	C ₁₇ H ₂₃ BO ₆	C ₂₉ H ₂₈ O ₈	C _{35.50} H ₃₈ O _{8.50}
<i>M_r</i> /g mol ⁻¹	336.181	334.172	504.528	600.676
crystal size/mm	0.29 × 0.18 × 0.18	0.27 × 0.18 × 0.04	0.24 × 0.22 × 0.13	0.37 × 0.14 × 0.11
crystal system	triclinic	orthorhombic	monoclinic	triclinic
space group	<i>P1</i> bar	<i>P2</i> ₁ <i>2</i> ₁	<i>P2</i> ₁ / <i>c</i>	<i>P1</i> bar
<i>a</i> /Å	7.8896(3)	10.3923(8)	18.0088(8)	9.9088(4)
<i>b</i> /Å	9.0992(3)	10.6376(8)	8.1117(3)	10.1821(4)
<i>c</i> /Å	9.4428(4)	15.6535(14)	18.6667(9)	17.4815(7)
α /°	88.983(3)	90	90	78.031(2)
β /°	84.074(3)	90	113.387(5)	87.621(2)
γ /°	83.609(3)	90	90	64.401(2)
<i>V</i> /Å ³	670.06(4)	1730.5(2)	2502.8(2)	1553.73(11)
<i>Z</i>	2	4	4	2
calc. density/g cm ⁻³	1.66627(10)	1.28267(15)	1.33896(10)	1.28396(9)
μ /mm ⁻¹	3.074	0.095	0.098	0.091
absorption correction	'multi-scan'	'multi-scan'	'multi-scan'	none
transmission factor range	0.78568–1.00000	0.67012–1.00000	0.96203–1.00000	–
refls. measured	4733	7133	9844	10413
<i>R</i> _{int}	0.0218	0.0553	0.0228	0.0357
mean $\sigma(I)/I$	0.0398	0.0975	0.0544	0.0509
θ range	4.34–26.33	4.30–26.37	4.23–26.36	3.14–25.30
observed refls.	2275	1094	3021	3876
<i>x</i> , <i>y</i> (weighting scheme)	0.0328, 0	0.0454, 0	0.0810, 0	0.0664, 1.1944
hydrogen refinement	constr	constr	constr	constr
refls in refinement	2708	2003	5051	5612
parameters	184	224	340	401
restraints	0	0	0	3
<i>R</i> (<i>F</i> _{obs})	0.0256	0.0440	0.0490	0.0566
<i>R</i> _w (<i>F</i> ²)	0.0588	0.0922	0.1338	0.1589
<i>S</i>	0.974	0.803	0.908	1.026

shift/error _{max}	0.001	0.001	0.001	0.001
max electron density/e Å ⁻³	0.413	0.235	0.691	0.745
min electron density/e Å ⁻³	-0.291	-0.181	-0.318	-0.508

APPENDIX IV

–Crystal Structures of II.100, II.101
and II.102–

APPENDIX IV: CRYSTAL STRUCTURES OF II.100, II.101 AND II.102

Single-Crystal X-Ray Analysis for Compounds II.100, II.101 and II.102

The data collections were performed on an Oxford Diffraction Xcalibur or KappaCCD diffractometers at 173 K using MoK α -radiation ($\lambda = 0.71073 \text{ \AA}$, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) [ref. 1] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 [ref. 2] and refined by least-squares methods against F^2 with SHELXL-97 [ref. 3]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table C. The corresponding Cambridge Crystallographic Data Center (CCDC) storage numbers for the compounds II.100, II.101, and II.102 are 894000, 894001 and 894002, respectively.

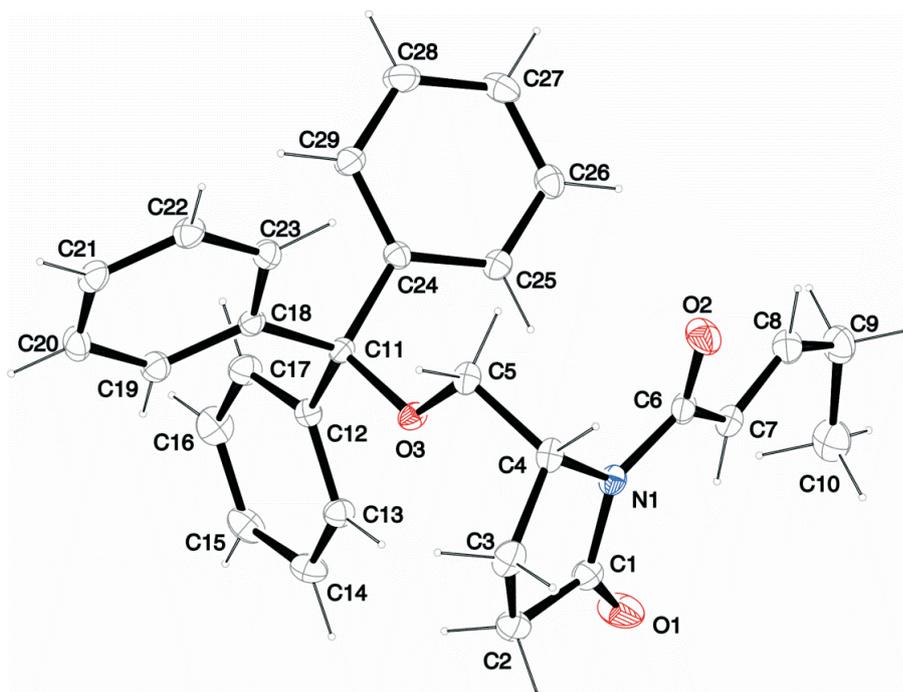


Figure E. Crystal structure of acylated auxiliary II.100.

- ref. 1** CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.41 (release 06-05-2009 CrysAlis171 .NET).
ref. 2 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, 32, 115-119.
ref. 3 G. M. Sheldrick, *Acta. Crystallogr. Sect. A* **2008**, 64, 112-122.

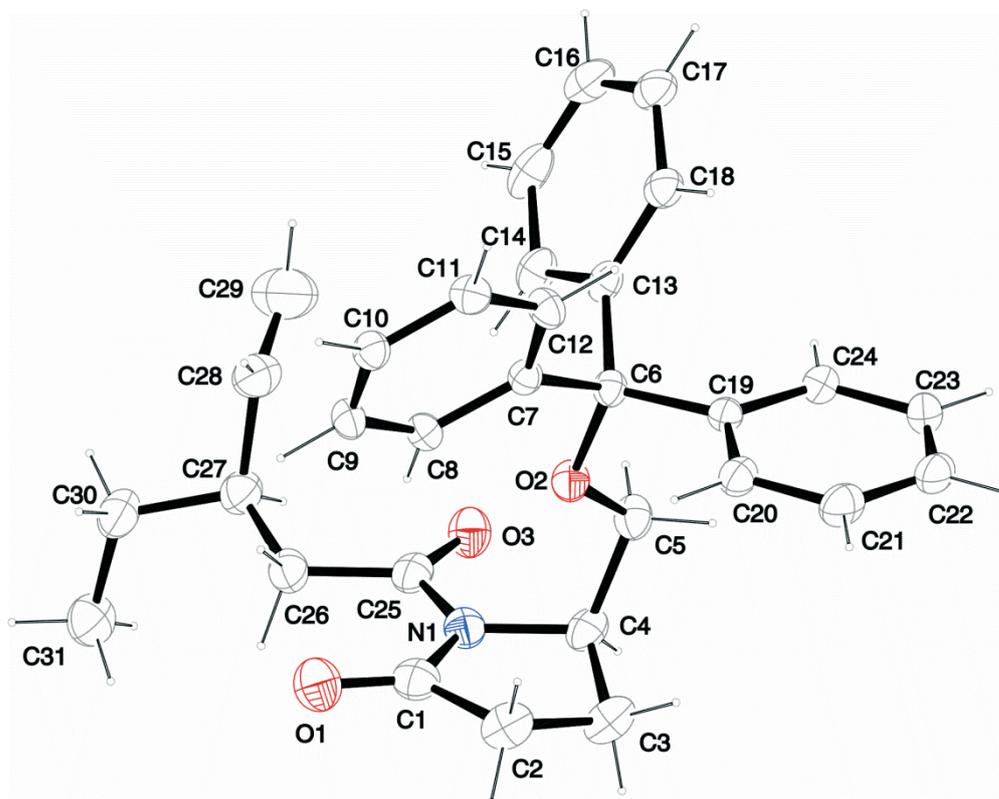


Figure F. Crystal structure of alkene II.101.

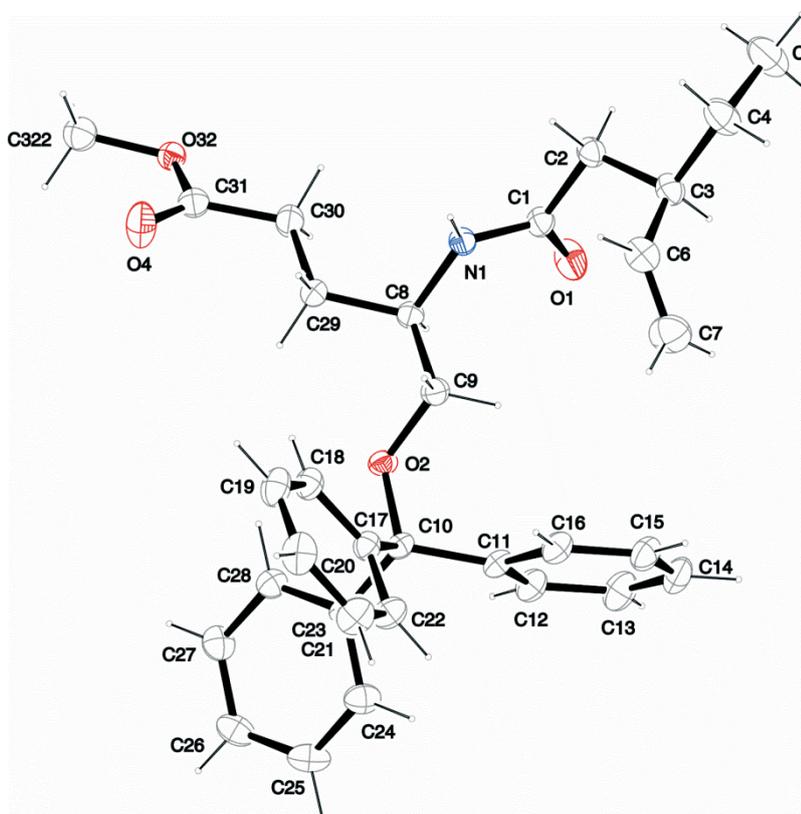


Figure G. Crystal structure of open auxiliary II.102.

Table C. Crystallographic data of auxiliary **II.100**, amide **II.101** and alkene **II.102**.

	II.100	II.101^a	II.102
net formula	C ₂₉ H ₂₉ NO ₃	C ₃₂ H ₃₇ NO ₄	C ₃₁ H ₃₃ NO ₃
<i>M_r</i> /g mol ⁻¹	439.546	499.641	467.599
crystal size/mm	0.28 × 0.19 × 0.12	0.41 × 0.20 × 0.13	0.23 × 0.07 × 0.04
<i>T</i> /K	173(2)	173(2)	173(2)
radiation	MoK α	MoK α	MoK α
diffractometer	'Oxford XCalibur'	'Oxford XCalibur'	'KappaCCD'
crystal system	triclinic	orthorhombic	monoclinic
space group	<i>P</i> 1	<i>P</i> 2 ₁ 2 ₁	<i>P</i> 2 ₁
<i>a</i> /Å	6.9353(7)	9.6228(10)	9.1381(5)
<i>b</i> /Å	9.0952(19)	13.9778(16)	14.9979(5)
<i>c</i> /Å	10.104(2)	21.478(2)	9.6298(4)
α /°	76.081(18)	90	90
β /°	77.509(13)	90	106.100(2)
γ /°	71.231(15)	90	90
<i>V</i> /Å ³	579.00(18)	2888.9(5)	1268.02(10)
<i>Z</i>	1	4	2
calc. density/g cm ⁻³	1.2606(4)	1.14879(20)	1.22471(10)
μ /mm ⁻¹	0.081	0.075	0.078
absorption correction	'multi-scan'	'multi-scan'	none
refls. measured	3203	7199	8252
<i>R</i> _{int}	0.0369	0.0262	0.0356
mean $\sigma(I)/I$	0.0433	0.0524	0.0545
θ range	4.43–26.37	4.24–26.37	3.50–25.37
observed refls.	2617	4045	3483
<i>x</i> , <i>y</i> (weighting scheme)	0.0623, 0.0058	0.0446, 0.2676	0.0614, 0.0936
hydrogen refinement	constr	mixed	constr
Flack parameter ^b	1.0(12)	1.9(13)	2.3(14)
refls in refinement	2792	5019	4486
parameters	299	350	317

APPENDIX IV: CRYSTAL STRUCTURES ANSALACTAM A AND DIVERGOLIDES C AND D

restraints	3	1	1
$R(F_{\text{obs}})$	0.0371	0.0473	0.0469
$R_w(F^2)$	0.1016	0.1111	0.1195
S	1.062	1.037	1.028
shift/error _{max}	0.001	0.001	0.001
max electron density/e \AA^{-3}	0.163	0.207	0.187
min electron density/e \AA^{-3}	-0.177	-0.189	-0.217

^aMethoxy group disordered over three sites, split model applied, sof ratio 0.36/0.40/0.24, Split atoms refined isotropically.

^bFlack parameter meaningless, correct structure derived from synthesis.

APPENDIX V

–Crystal Structure III.2–

APPENDIX V: CRYSTAL STRUCTURE OF III.2

Single-Crystal X-Ray Analysis for Cyclopropane III.2

The data collections were performed on an Oxford Diffraction Xcalibur diffractometer at 173 K (20: 200 K) using MoK α -radiation ($\lambda = 0.71073$ Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) [ref. 1] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 [ref. 2] and refined by least-squares methods against F^2 with SHELXL-97 [ref. 3]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table D. The corresponding Cambridge Crystallographic Data Center (CCDC) storage number for the compound III.2 is 893995.

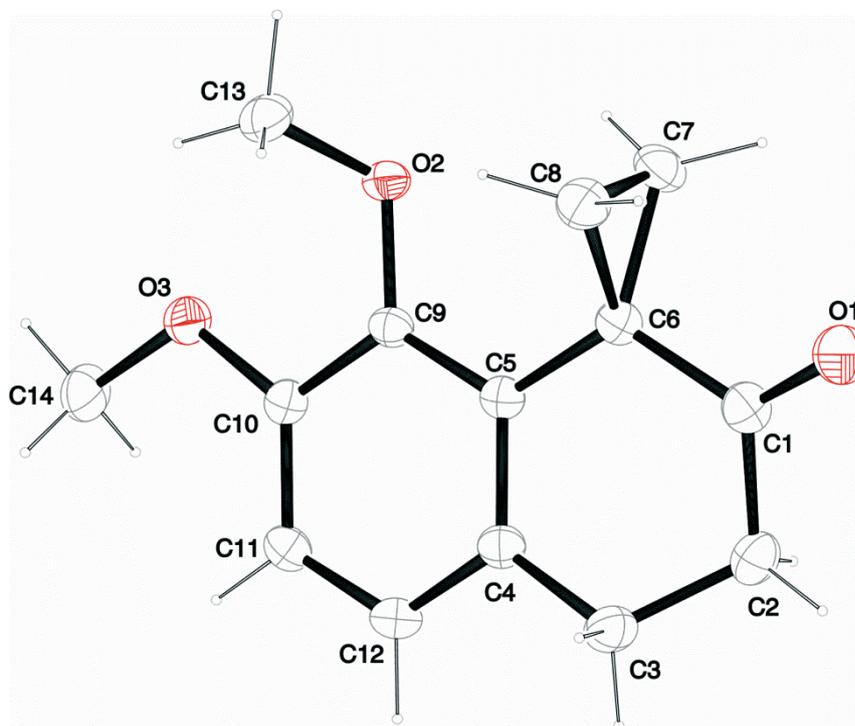


Figure H. Crystal structure of cyclopropane III.2.

ref. 1 CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.41 (release 06-05-2009 CrysAlis171 .NET).

ref. 2 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, 32, 115-119.

ref. 3 G. M. Sheldrick, *Acta. Crystallogr. Sect. A* **2008**, 64, 112-122.

Table D. Crystallographic data of cyclopropane **III.2**.

	III.2
net formula	C ₁₄ H ₁₆ O ₃
<i>M_r</i> /g mol ⁻¹	232.275
crystal size/mm	0.38 × 0.20 × 0.17
<i>T</i> /K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	<i>P</i> 1bar
<i>a</i> /Å	8.2043(10)
<i>b</i> /Å	8.9981(11)
<i>c</i> /Å	9.7491(12)
α/°	64.913(12)
β/°	70.609(11)
γ/°	66.139(12)
<i>V</i> /Å ³	584.81(13)
<i>Z</i>	2
calc. density/g cm ⁻³	1.3191(3)
μ/mm ⁻¹	0.092
absorption correction	'multi-scan'
transmission factor range	0.82941–1.00000
refls. measured	3141
<i>R</i> _{int}	0.0264
mean σ(<i>I</i>)/ <i>I</i>	0.0429
θ range	4.34–26.37
observed refls.	1931
<i>x</i> , <i>y</i> (weighting scheme)	0.0613, 0.1358
hydrogen refinement	constr
refls in refinement	2345
parameters	156
restraints	0
<i>R</i> (<i>F</i> _{obs})	0.0496
<i>R</i> _w (<i>F</i> ²)	0.1369

S	1.062
shift/error _{max}	0.001
max electron density/e \AA^{-3}	0.248
min electron density/e \AA^{-3}	-0.226

APPENDIX VI

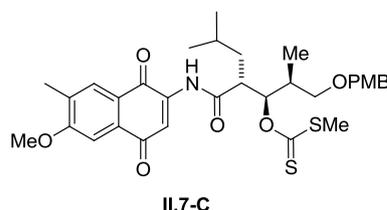
–Computational Details–

APPENDIX VI: COMPUTATIONAL DETAILS

Computational Details

The conformational search was performed with MacroModel (Version 9.0; MMFF/gas phase/PRCG/500 steps).^[47] Optimizations of MMFF structures were performed with Gaussian03.^[151] The method was B3LYP.^[152] The 6-31G(d) basis set was used for H, C, N and S.^[153] The optimized geometries were characterized as energy minima by a nonexistence of imaginary frequencies in the diagonalization of the analytically computed Hessian (vibrational frequency calculations). No solvation effects were considered.

anti-isomer II.7-C:



Free energies of optimized conformers. The Cartesian coordinates are given only for the most stable identified conformer.

II.7-1 ($E = -2620,008573$ a.u.).

II.7-2 ($E = -2620,011841$ a.u.).

II.7-3 ($E = -2620,014809$ a.u.).

II.7-4 ($E = -2620,007387$ a.u.).

II.7-5 ($E = -2620,008324$ a.u.).

II.7-6 ($E = -2620,016720$ a.u.).

II.7-7 ($E = -2620,010105$ a.u.).

II.7-8 ($E = -2620,010528$ a.u.).

II.7-9 ($E = -2620,020519$ a.u.).

II.7-10 ($E = -2620,017237$ a.u.).

II.7-11 ($E = -2620,006949$ a.u.).

II.7-12 ($E = -2620,009221$ a.u.).

II.7-13 ($E = -2620,012348$ a.u.).

II.7-14 ($E = -2620,009176$ a.u.).

II.7-15 ($E = -2620,014719$ a.u.).

II.7-16 ($E = -2620,007896$ a.u.).

II.7-17 ($E = -2620,010971$ a.u.).

II.7-18 ($E = -2620,010250$ a.u.).

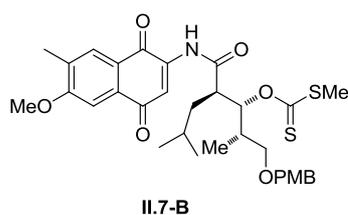
II.7-19 ($E = -2620,005709$ a.u.).

II.7-20 ($E = -2620,004854$ a.u.).

Cartesian coordinates (Å) of **II.7-9**.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	4.910731	-0.339788	0.481880
2	6	0	4.225954	0.688035	-0.173067
3	6	0	4.949279	1.729342	-0.770135
4	6	0	6.344586	1.755242	-0.725498
5	6	0	7.023309	0.710101	-0.062372
6	6	0	6.307259	-0.329191	0.537926
7	6	0	2.748782	0.689084	-0.238684
8	6	0	4.160163	-1.448679	1.123259
9	6	0	2.010171	-0.454253	0.392149
10	6	0	2.689693	-1.434017	1.028863
11	6	0	7.118121	2.878352	-1.370097
12	6	0	9.125991	-0.221086	0.578580
13	8	0	2.125159	1.598201	-0.782081
14	8	0	4.737617	-2.357364	1.713319
15	8	0	8.383488	0.808830	-0.063406
16	6	0	-0.316192	-1.244957	0.744272
17	6	0	-1.772518	-0.838137	0.453277
18	7	0	0.632872	-0.368122	0.254324
19	8	0	-0.031104	-2.262575	1.365186
20	6	0	-2.258107	-1.415429	-0.903718
21	6	0	-2.708002	-1.286154	1.603503
22	6	0	-2.757369	-0.331815	2.818104
23	6	0	-1.403116	-0.140772	3.513654
24	6	0	-3.800677	-0.838820	3.825041
25	6	0	-1.501700	-0.971877	-2.181433
26	6	0	-3.207111	-3.699705	-0.872224
27	16	0	-2.763732	-5.390705	-0.682766
28	6	0	-1.171207	-5.285415	0.194252
29	16	0	-4.781972	-3.250240	-1.164485
30	8	0	-2.154329	-2.861493	-0.827546
31	6	0	-1.613560	0.538001	-2.440588
32	6	0	-0.861478	2.699238	-1.724557
33	8	0	-0.808677	1.279167	-1.521366
34	6	0	-4.083628	4.503776	0.542542
35	6	0	-2.935167	4.025355	1.187396
36	6	0	-1.899498	3.455012	0.453015
37	6	0	-1.984284	3.345193	-0.942806
38	6	0	-3.132814	3.829146	-1.576691
39	6	0	-4.178763	4.406061	-0.847026
40	6	0	-2.036310	-1.722531	-3.414219
41	6	0	-6.218947	5.538122	0.759885
42	8	0	-5.033007	5.042078	1.364837
43	1	0	4.411566	2.526427	-1.275401
44	1	0	6.802363	-1.143310	1.055152
45	1	0	2.196173	-2.271402	1.504114
46	1	0	7.800401	2.493546	-2.135995

47	1	0	6.444358	3.595392	-1.848887
48	1	0	7.713756	3.419485	-0.626164
49	1	0	10.181013	0.038531	0.457111
50	1	0	8.899191	-0.267538	1.649533
51	1	0	8.949936	-1.194241	0.106330
52	1	0	0.294557	0.426921	-0.305585
53	1	0	-1.835888	0.249875	0.383396
54	1	0	-3.728864	-1.353755	1.206396
55	1	0	-2.438761	-2.293572	1.938726
56	1	0	-3.094713	0.651238	2.459753
57	1	0	-1.516943	0.468468	4.417922
58	1	0	-0.968476	-1.101993	3.808767
59	1	0	-0.681565	0.375587	2.871701
60	1	0	-3.899304	-0.147242	4.669854
61	1	0	-4.788623	-0.937158	3.360368
62	1	0	-3.518343	-1.819934	4.225318
63	1	0	-3.309574	-1.135975	-1.026005
64	1	0	-0.855089	-6.305683	0.429653
65	1	0	-0.404945	-4.813846	-0.422831
66	1	0	-1.280411	-4.726771	1.124783
67	1	0	-2.862510	4.106455	2.268364
68	1	0	-1.016554	3.091264	0.972644
69	1	0	-3.223817	3.762500	-2.658257
70	1	0	-5.049946	4.769133	-1.381979
71	1	0	-0.441686	-1.232115	-2.076783
72	1	0	-1.254352	0.748899	-3.456932
73	1	0	-2.661732	0.860829	-2.374132
74	1	0	0.106054	3.087862	-1.391041
75	1	0	-0.945620	2.920339	-2.796353
76	1	0	-1.502095	-1.404979	-4.316879
77	1	0	-1.892781	-2.801542	-3.314422
78	1	0	-3.104381	-1.534125	-3.569101
79	1	0	-6.766045	4.743101	0.239531
80	1	0	-6.847172	5.916235	1.570825
81	1	0	-6.002714	6.365720	0.073819

anti-isomer II.7-B:

Free energies of optimized conformers. The Cartesian coordinates are given only for the most stable identified conformer.

II.7-21 ($E = -2619,996745$ a.u.).

II.7-22 ($E = -2619,996615$ a.u.).

II.7-23 ($E = -2619,996594$ a.u.).

II.7-24 ($E = -2619,991466$ a.u.).

II.7-25 ($E = -2620,002455$ a.u.).

- II.7-26** ($E = -2619,992771$ a.u.).
II.7-27 ($E = -2619,991527$ a.u.).
II.7-28 ($E = -2620,001064$ a.u.).
II.7-29 ($E = -2619,998213$ a.u.).
II.7-30 ($E = -2619,990167$ a.u.).
II.7-31 ($E = -2619,995270$ a.u.).
II.7-32 ($E = -2620,001213$ a.u.).
II.7-33 ($E = -2619,996788$ a.u.).
II.7-34 ($E = -2619,993970$ a.u.).
II.7-35 ($E = -2620,001255$ a.u.).
II.7-36 ($E = -2619,997344$ a.u.).
II.7-37 ($E = -2619,996518$ a.u.).
II.7-38 ($E = -2619,997353$ a.u.).
II.7-39 ($E = -2620,002518$ a.u.).
II.7-40 ($E = -2619,994347$ a.u.).
II.7-41 ($E = -2619,997100$ a.u.).
II.7-42 ($E = -2619,994869$ a.u.).
II.7-43 ($E = -2619,998249$ a.u.).
II.7-44 ($E = -2620,004003$ a.u.).
II.7-45 ($E = -2619,99519$ a.u.).
II.7-46 ($E = -2619,991771$ a.u.).
II.7-47 ($E = -2620,002707$ a.u.).
II.7-48 ($E = -2619,996945$ a.u.).
II.7-49 ($E = -2619,997098$ a.u.).
II.7-50 ($E = -2619,999475$ a.u.).

Cartesian coordinates (Å) of **II.7-44**.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.305519	0.399774	-0.102851
2	6	0	3.491280	-0.061786	1.193656
3	6	0	4.742084	0.079099	1.804519
4	6	0	5.806687	0.683533	1.116673
5	6	0	5.611295	1.150525	-0.196166
6	6	0	4.360415	1.005536	-0.801185
7	6	0	2.384590	-0.700476	1.928420
8	6	0	1.996930	0.246218	-0.754510
9	6	0	1.037004	-0.810629	1.269249
10	6	0	0.896538	-0.360867	0.019807

11	6	0	7.144870	0.824281	1.793094
12	6	0	6.552119	2.221684	-2.113284
13	8	0	2.550943	-1.136851	3.064920
14	8	0	1.808445	0.597514	-1.913048
15	8	0	6.704275	1.726743	-0.788468
16	6	0	-1.236228	-1.703016	2.005966
17	7	0	0.098160	-1.433317	2.070837
18	6	0	-3.199718	-2.154905	-1.387846
19	6	0	-2.633894	-1.091586	-2.342341
20	6	0	-2.109328	1.191096	-2.605394
21	8	0	-2.656879	0.195395	-1.740581
22	6	0	-2.018107	4.944093	-0.463660
23	6	0	-3.235153	4.328953	-0.754968
24	6	0	-3.259867	3.113465	-1.448835
25	6	0	-2.071260	2.499011	-1.862031
26	6	0	-0.853151	3.124366	-1.572606
27	6	0	-0.830707	4.335855	-0.877812
28	6	0	-4.696419	-1.954216	-1.148049
29	6	0	-3.030500	6.760023	0.686375
30	8	0	-1.852744	6.123645	0.209222
31	6	0	-2.362064	-2.366009	-0.094461
32	6	0	-0.552625	-4.055395	-0.644704
33	16	0	1.148698	-4.182245	-1.077898
34	6	0	1.096093	-3.316250	-2.660879
35	16	0	-1.493502	-5.406200	-0.384613
36	8	0	-1.026290	-2.781444	-0.557461
37	6	0	-2.142068	-1.181408	0.893576
38	8	0	-1.715688	-2.415171	2.898099
39	6	0	-3.449486	-0.644423	1.522019
40	6	0	-3.277069	0.384622	2.666454
41	6	0	-4.653063	0.796520	3.196936
42	6	0	-2.502890	1.627260	2.227453
43	1	0	4.889491	-0.285715	2.821449
44	1	0	4.177599	1.353672	-1.813864
45	1	0	-0.007392	-0.436433	-0.560315
46	1	0	7.913807	0.289905	1.225278
47	1	0	7.417888	1.881051	1.873189
48	1	0	7.129081	0.406451	2.804194
49	1	0	7.511700	2.646109	-2.423796
50	1	0	6.305460	1.413278	-2.809327
51	1	0	5.805423	3.021990	-2.152902
52	1	0	0.495113	-1.793062	2.941813
53	1	0	-4.182588	4.761665	-0.453192
54	1	0	-4.215995	2.637962	-1.656474
55	1	0	0.087611	2.676988	-1.884937
56	1	0	0.121475	4.812557	-0.657406
57	1	0	-3.121675	-3.098285	-1.947671
58	1	0	-1.605379	-1.347195	-2.620176
59	1	0	-3.231888	-1.068979	-3.261189
60	1	0	-1.099690	0.895966	-2.916527
61	1	0	-2.732142	1.294181	-3.501089
62	1	0	-5.253352	-2.210852	-2.057595
63	1	0	-5.063013	-2.603805	-0.347217
64	1	0	-4.954675	-0.919302	-0.915074
65	1	0	-3.561734	6.123128	1.402074
66	1	0	-2.728600	7.670851	1.211914
67	1	0	-3.682735	7.054703	-0.142096
68	1	0	2.086178	-3.348099	-3.122618
69	1	0	0.381346	-3.796080	-3.336004
70	1	0	0.813770	-2.270254	-2.522074
71	1	0	-2.817528	-3.181450	0.478917

APPENDIX VI: COMPUTATIONAL DETAILS

72	1	0	-1.664775	-0.339613	0.406401
73	1	0	-4.037008	-0.152404	0.743114
74	1	0	-4.049293	-1.485469	1.892615
75	1	0	-2.735396	-0.077991	3.498766
76	1	0	-5.250976	1.284436	2.419121
77	1	0	-5.209504	-0.076386	3.554633
78	1	0	-4.554575	1.494431	4.035204
79	1	0	-2.994786	2.115441	1.382434
80	1	0	-2.440041	2.354262	3.044611
81	1	0	-1.478908	1.382366	1.932955

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