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DISSERTATION

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„Synthetic Studies Toward the Total Syntheses of the
Jatrophane Diterpenes PI-3 and PI-4“

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LIST OF ABBREVIATIONS

(R)-HYTRA	(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate
2,2-DMP	2,2-Dimethoxypropane
9-BBN	9-Borabicyclo[3.3.1]nonane
ABC	ATP-Binding cassette
AcOH	Acetic acid
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BnCl	Benzyl chloride
BSA	Bis(trimethylsilyl)acetamide
CSA	Camphorsulfonic acid
Da	Dalton
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMP	Dess-Martin periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DTPS	Diterpene synthase
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>ent</i>	enantiomeric
GGPP	Geranylgeranyl diphosphate
HMPA	Hexamethylphosphoramide
HWE	Horner Wadsworth Emmons reaction
IBX	2-Iodoxybenzoic acid
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
liq.	Liquid
MDR	Multi drug resistance
MeLi	Methylolithium

MEM	2-Methoxyethoxymethyl
MOM	Methyl chloromethyl
Ms	Mesyl (methanesulfonyl group)
MsCl	Methansulfonyl chloride
<i>n</i> -Bu ₂ BOTf	Dibutylborontriflate
<i>n</i> -BuLi	<i>n</i> -Butyllithium
NADPH	Nicotinamide adenine dinucleotide phosphate
NaHMDS	Sodium hexamethyldisilazide
NBD	Nucleotide binding domain
NCS	<i>N</i> -Chlorsuccinimide
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
ox.	Oxidation
PDC	Pyridinium chlorochromate
Pgp	P-glycoprotein
PhNTf ₂	<i>N</i> -Phenyl-bis(trifluoromethanesulfonimide)
P _i	Inorganic phosphate
PMB	<i>para</i> -Methoxybenzyl
PP	Diphosphate (pyrophosphate)
PPTS	Pyridinium <i>p</i> -toluenesulfonate
pyr, Py	Pyridine
RCM	Ring closing metathesis
rfx	Reflux
<i>t</i> -BuLi	<i>tert</i> -Butyllithium
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflate (trifluoromethanesulfonate group)
TMD	Transmembrane domain
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
Ts	Tosyl (<i>p</i> -toluenesulfonyl group)
TsOH	<i>para</i> -Toluenesulfonic acid
UDP	Uridine diphosphate

ABSTRACT

The jatrophone diterpenes Pl-3 and Pl-4, two highly oxygenated and stereochemically demanding natural products were isolated in 2003 from *Euphorbia platyphyllos* by Hohmann *et al.* Jatrophone diterpenes show a wide range of pharmacologically promising properties, including the selective inhibition of the ATP-dependent efflux pump P-glycoprotein (Pgp), which is responsible for multi-drug resistance (MDR) in cancer.

Jatrophone diterpenes are characterized by a bicyclo[10.3.0]pentadecane framework; a highly functionalized five-membered ring is annulated to a twelve-membered macrocycle. In most of these terpene-based natural products the two rings are *trans*-fused, as in Pl-3. However, a few compounds were isolated, including Pl-4, which possess a double bond at the ring junction.

The synthetic goal of the first part of this doctoral thesis is the development of a general, diastereoselective synthesis of the eastern part of the jatrophone skeleton (C7-12, jatrophone numbering). Due to the recurring stereochemical substitution pattern of this part of the macrocycle the route is suitable for the preparation of Pl-3, Pl-4 and other jatrophones. Key step in the synthesis for the eastern segment of both compounds is a samarium diiodide mediated Reformatsky reaction.

The second part of the thesis is devoted to the investigation of an enantioselective route toward Pl-4. The aim of the proposed strategy was to close both rings, present in the natural product, at a very late stage of the synthesis. While the 12-membered macrocycle was envisaged to be elaborated through an RCM-reaction, an internal vinyl halide should serve as key intermediate for the closure of the five-membered ring *via* a nucleophilic, or radical reaction.

The focus of the second part rests on the preparation of an advanced internal vinyl-halide as precursor for the five-membered ring closing reaction. Three strategically different routes were investigated: The initial approach for the preparation of the advanced internal vinyl-halide relied on a late stage, regioselective *syn*-hydrometalation of a sterically demanding ynone. Alternatively, in a more concise manner, the alkyne of the requisite ynone could also be directly employed in a five-*exo*-dig ring closure reaction *via* a ketyl radical as intermediate. A conceptually different strategy for the synthesis of an internal vinyl halide takes advantage of a chelation controlled regioselective lithiation/alkylation reaction of an unsymmetrical terminal vinyl dibromide and the appropriate aldehyde. The method is suitable for the facile access of sterically hindered internal vinyl halides and constitutes a valuable alternative to hydrometalation reactions, as these often give unsatisfying results with sterically demanding substrates.

The mechanistic considerations and synthetic attempts proposing the preparation of highly advanced intermediates toward the natural product Pl-4 are described in detail within this thesis.

ZUSAMMENFASSUNG

Die beiden hochoxygenierten Jatrophan Diterpene PI-3 und PI-4 wurden erstmals 2003 von Hohmann *et al.* aus *Euphorbia platyphyllos* isoliert. Jatrophan Diterpene zeigen unterschiedliche pharmakologische Eigenschaften. Die selektive Hemmung von P-Glycoprotein (Pgp) stellt wohl die interessanteste biologische Wirkung dar. Das Transmembranprotein schleust unter ATP-Verbrauch toxische Substanzen aus der Zelle und ist somit für die Entwicklung von Resistenzen gegen Chemotherapeutika in der Krebstherapie verantwortlich.

Auf Grund des immer wieder kehrenden Substitutionsmusters im östlichen Teil (C7-C12, Jatrophan-Nummerierung) von Jatrophan Diterpenen, wie auch in PI-3 und PI-4, wurde im ersten Teil der Disstertation eine allgemein anwendbare, diastereoselektive Synthese des besagten Teils des Makrozyklus erarbeitet. Schlüsselschritt in der durchgeführten Synthese, die von D-Ribose ausgeht, ist eine Samariumdiiodid-induzierte Reformatsky Reaktion.

Der zweite Teil der Doktorarbeit umfasst die Ausarbeitung einer enantioselektiven Totalsynthese des Diterpenes PI-4. Das Ziel der verfolgten Route ist die Bildung sowohl des fünf-gliedrigen als auch des zwölf-gliedrigen Rings auf einer bereits sehr weit fortgeschrittenen Stufe der Synthese. Der zwölf-gliedrige Makrozyklus soll durch eine RCM-Reaktion verknüpft werden. Als ein möglicher Vorläufer für einen späten Ringschluss durch einen nucleophilen Angriff bzw. eine radikalische Reaktion, sollte ein sterisch anspruchsvolles Vinylhalogenid dienen.

Der Schwerpunkt im zweiten Teil liegt vor allem auf der Herstellung des internen Vinylhalogenids als Vorstufe für die Ringschlussreaktion zur Formierung des fünf-gliedrigen Rings. Es wurden drei Herangehensweisen detailliert betrachtet: Unsere ursprüngliche Strategie für die Synthese eines internen Vinylhalogenids basiert auf einer regioselektiven syn-Hydrometallierung eines entsprechenden internen Alkins. Als Alternative dazu wird versucht den fünf-gliedrigen Ring direkt über eine 5-*exo*-dig radikalische Ringschlussreaktion zu schließen. Einen vollkommen unterschiedlichen Zugang zur Synthese von internen Vinylbromiden stellt eine regioselektive Lithiierungs-Alkylierungs-Reaktionsequenz zwischen Vinyldibromiden und entsprechenden Aldehyden dar. Die Reaktion verläuft über eine chelierende Zwischenstufe. Die Reaktionssequenz ist als Methode zur Herstellung von internen Vinylhalogeniden hervorragend geeignet und stellt eine Alternative zur Hydrometallierungsreaktion dar, die, bei sterisch gehinderten Verbindungen oftmals nicht zufriedenstellend abläuft.

Die Synthese und mechanistische Betrachtungen von anspruchsvollen Intermediaten auf dem Weg zur Totalsynthese von PI-4 ist Inhalt der vorliegenden Dissertation.

1. GENERAL PART

1.1. INTRODUCTION

The genus *Euphorbia*, member of the Euphorbiaceae plant family, is one of the largest and most diverse genera among flowering plants with more than 2000 species, which are endemic in different climate zones worldwide. The common characteristic of *Euphorbia* species, also known as spurges, is the existence of a milky sap (latex), which has a very high content of mainly terpene-based, biologically active ingredients.¹ These structurally diverse plant metabolites are responsible for the application of spurges in traditional phytotherapy, preferentially used as anticancer agents and for the treatment of swellings and warts.²

Although predominantly known as poisonous plants, some members of the genus *Euphorbia* are of great economic importance. To name just a few examples – the latex of *Hevea brasiliensis* (Para rubber tree) is the major source of natural rubber, the starch tapioca is obtained from the roots of *Manihot esculenta* (cassava) or *Ricinus communis*, which is the commercial source of castor oil. The latter has a wide field of application ranging from the use as laxative right up to the utilization as a naturally occurring polyol for the preparation of polyurethane plastic.³

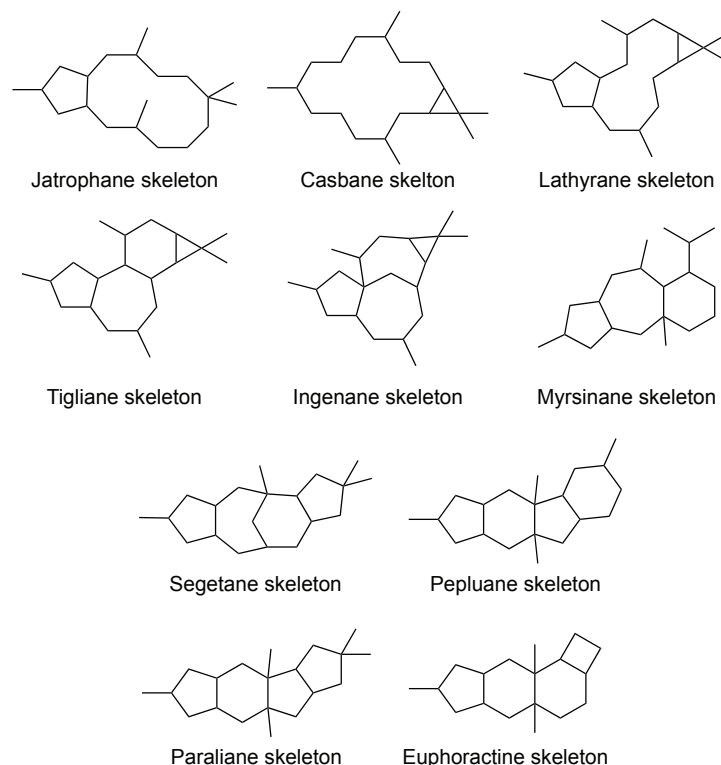


Figure 1. Core structures of Euphorbiaceae diterpenes.

Natural products isolated from plants of the Euphorbiaceae plant family show a fascinating diversity in their isoprenoid structures. Diterpenes with different, partially closely related, core frameworks such as jatrophanes, casbanes, lathyranes, tiglanes, ingenanes, myrsinanes, segetanes, pepluanes, paralianes and euphoractines, summarized as Euphorbiaceae diterpenes, were identified

as major constituents (Figure 1). In addition, tetra- and pentacyclic triterpenes as well as sesquiterpenoids, phloracetophenones, glycerols, cerebrosides, flavonoids and steroids were isolated.¹

Jatrophone (**1**), the first jatrophane-type diterpene, was isolated by Kupchan and co-workers in 1970 from an alcoholic extract of *Jatropha gossypifolia* L. The mentioned *Euphorbia* species was used for the treatment of neuroplasms in traditional herbal folk medicine. When **1** was identified as a natural product with significant antiproliferative effects against human tumor cell lines, the biological and chemical interest in active ingredients of the jatrophane skeleton increased.^{4, 5} As a result, a huge number of diterpenes, characterized by the jatrophane framework, was isolated from plant extracts of members of the genus *Euphorbia* in the past decades and biologically evaluated.

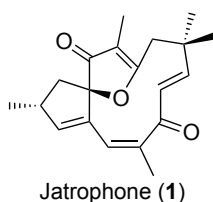


Figure 2

The two title compounds PI-3 (**2**) and PI-4 (**3**), two highly oxygenated and stereochemically complex diterpenes were isolated from *Euphorbia platyphyllos* L., a glabrous or pubescent annual plant which occurs mainly in southern Europe, by Hohman *et al* in 2003.⁶

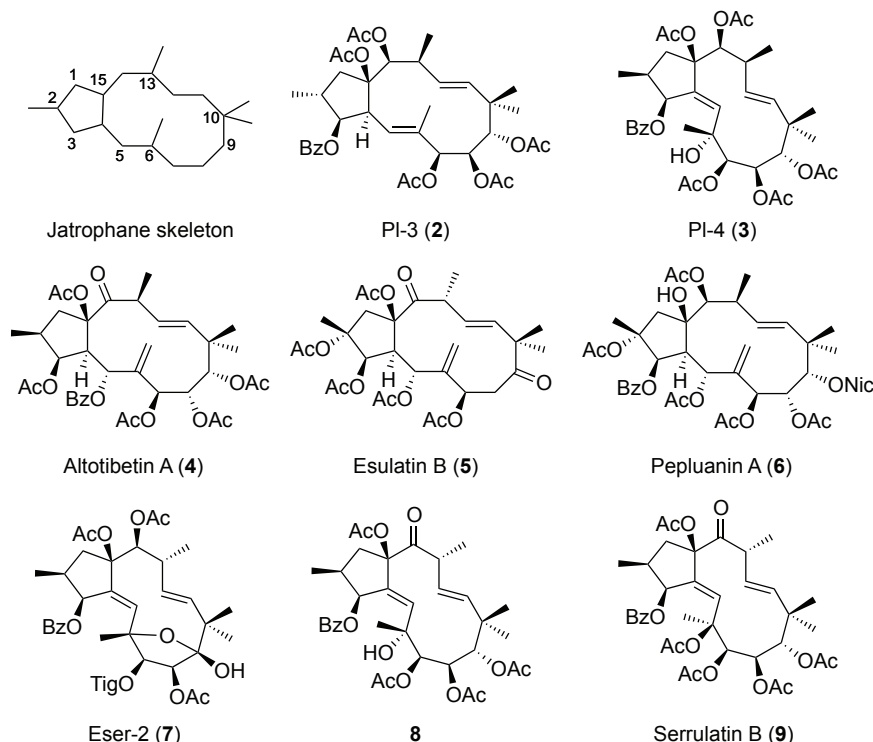


Figure 3. Representative jatrophane diterpenes.

Jatrophane diterpenes are characterized by a *trans*-bicyclo[10.3.0]pentadecane framework. A highly functionalized five-membered ring is annulated to a twelve-membered macrocycle. In most diterpenes the two rings are *trans*-fused as in PI-3. However, a few compounds were isolated,

including Pl-4, which possess a double bond at the ring junction. Individual members of this class of natural products often only differ in the stereochemical pattern of methyl- and hydroxyl groups, while the regiochemical substitution pattern remains highly similar.^{7, 8} The structurally elucidated compounds are substituted with various acyl groups, including acetyl, propanoyl, butanoyl, benzoyl, tigloyl, nicotinoyl, angeloyl, etc. which is why they are often called jatrophone polyesters.¹ A few representative jatrophone diterpenes (**2–9**) are outlined in Figure 3.

Numerous jatrophone diterpenes were analyzed in detail within different biological studies, demonstrating a wide range of pharmacologically promising properties including antiproliferation, cytotoxic, antimicrobial, anti-inflammatory as well as antiviral activities.^{1, 9} Several of these diterpenes were also identified as highly active inhibitors of the ATP-dependent efflux pump P-glycoprotein (Pgp), which is responsible for multi drug resistance (MDR) in cancer.¹⁰⁻¹⁴

Summarizing, jatrophone diterpenes represent an interesting target for different scientific areas. Probably, the most important aspect is that these diterpenes could provide potential lead structures for drug development. As the overexpression of Pgp in cancer cells of malignant tumors is a serious problem in cancer therapy the examination of potential novel anticancer drugs that could address this problem is of great importance in modern cancer research. At this point the synthetic influence becomes more and more important. Since natural sources afford insufficient quantities of diterpenes required for biological studies, a synthetic access to target compounds will be inevitable. Simplified unnatural derivatives could play an important role in the elucidation of the physiological mode of action of natural products. The synthesis of simplified substrates for structure-activity relationship (SAR) studies needs the expertise of synthetic chemists and combines the scientific ambitions of biology and chemistry. Nevertheless, the fundamental idea behind this thesis is that jatrophone diterpenes represent stereochemically challenging and fascinating natural products yielding excellent targets in the field of total synthesis.

1.2. BIOSYNTHESIS OF JATROPHONE DITERPENES^{15, 16}

The biosynthesis of diterpenes arises from geranylgeranyl diphosphate (GGPP, **10**). Carbocation mediated cyclization reactions combined with Wagner-Meerwein rearrangements allow the synthesis of numerous structural variants of compounds belonging to this important class of natural products.

As demonstrated in Figure 4, two mechanistically different biogenetic pathways are possible for the biosynthesis of polycyclic diterpenes, leading either to the phytanes¹⁶ such as abietanes, kauranes, atisanes, etc. or to the casbene derived diterpenes including casbanes, jatrophanes, tiglanes, etc.¹⁷

While most of the biosynthesis of polycyclic phytanes has been elucidated in detail, including the enzymes that are catalyzing the formation of intermediates, only little is known about the biogenetic routes toward the synthesis of the casbene derived diterpenes.¹⁵

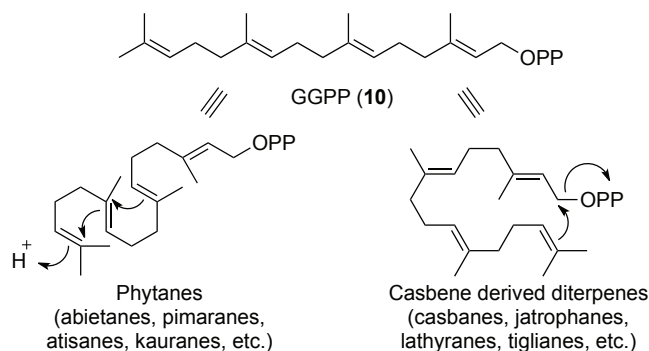
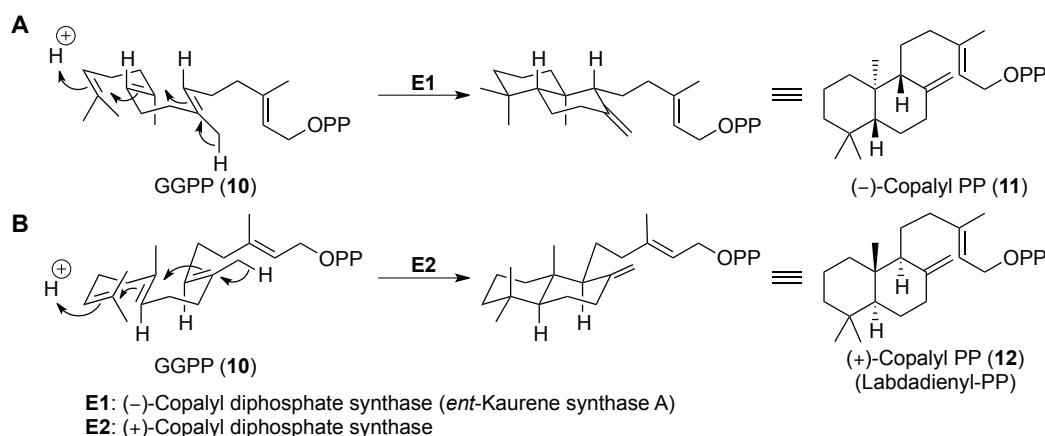


Figure 4. Biogenetic route from GGPP to phytanes and casbene derived diterpenes.

1.2.1. Biosynthesis of polycyclic phytanes

The cyclization sequence is initiated by the protonation of the double bond at the end of the chain of GGPP (**10**), affording a tertiary carbocation. The concerted process is terminated by the proton loss of a methyl group, leading to (–)-copalyl PP (**11**), outlined in Scheme 1A.¹⁵



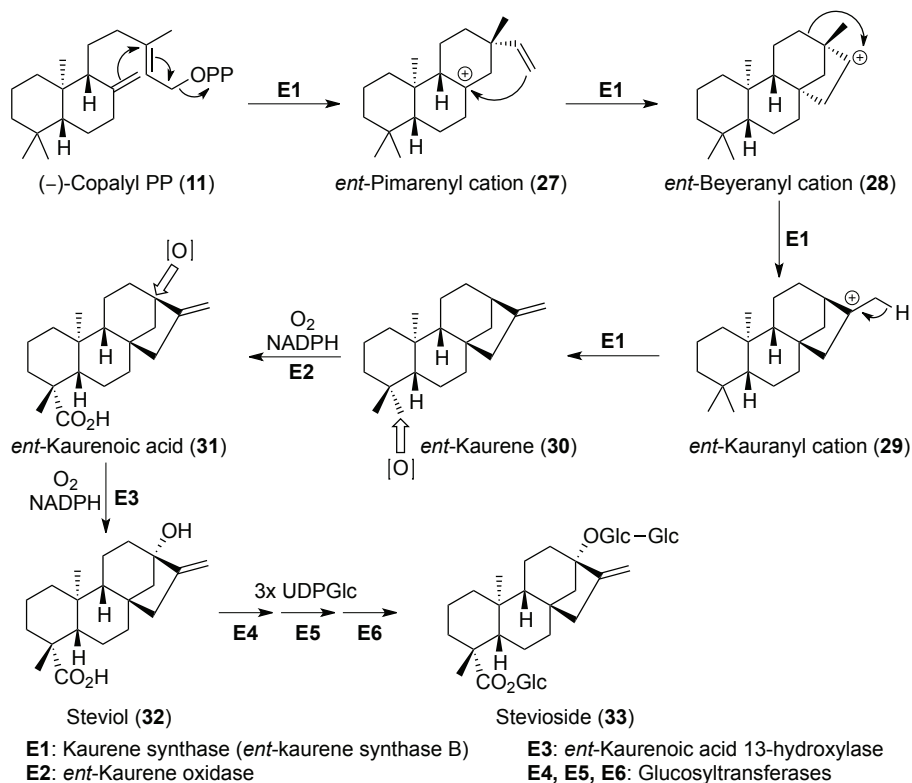
Scheme 1. Biosynthetic pathway leading to (–) and (+)- copalyl PP.

The cyclization-cascade is catalyzed by a single enzyme, called (–)-copalyl diphosphate synthase or *ent*-karene synthase A (**E1**). The stereochemistry of the product is dependent on the folding of the substrate and its interaction with the enzyme surface. The enantiomeric product, (+)-copalyl PP (**12**, labdadienyl-PP), is formed by an alternative folding of GGPP (Scheme 1B) catalyzed by (+)-copalyl diphosphate synthase (**E2**). In natural products the stereochemistry is most often derived from (+)-copalyl diphosphate and derivatives thereof. Natural products that can be deduced from (–)-copalyl diphosphate are often referred to as the enantiomeric (*ent*-) series.¹⁵

The starting point for the cyclization cascades leading to natural products of the abietane-, pimarane-, atisane-, kaurane-, etc., frameworks is the loss of the diphosphate leaving group of (+)- or (–)-copalyl diphosphate. Associated carbocation formation and additional Wagner-Meerwein rearrangements create numerous possibilities leading to structural variants of diterpenes. Scheme 2 demonstrates a representative, but small cutout, of the diversity of possible frameworks and attributed natural products (**13–26**).

The cyclization sequence of the kaurane skeleton is outlined in Scheme 3 on the example of the biosynthesis of the tetracyclic diterpene stevioside (**33**), an important non-calorific sugar substitute, starting from (–)-copalyl PP (**11**).

The third six-membered ring within the kaurane framework is built by an allylic-cation-mediated cyclization reaction resulting in the formation of the tertiary *ent*-pimarenyl cation (**27**), which is further attacked by the terminal double bond. The resulting secondary cation, namely *ent*-beyeranyl cation (**28**) is again converted into the more stable tertiary *ent*-kauranyl cation (**29**), by a Wagner-Meerwein 1,2-alkyl migration, affording the ring system present in the natural product. A final proton loss delivers the exocyclic double bond of *ent*-kaurene (**30**). All described cyclization reactions as well as the Wagner-Meerwein shift are catalyzed by the same enzyme, the kaurene synthase (**E1**). The final transformations, stereoselective oxidation followed by hydroxylation and three glycosylation reactions complete the biosynthetic route of the natural product **33**.¹⁸

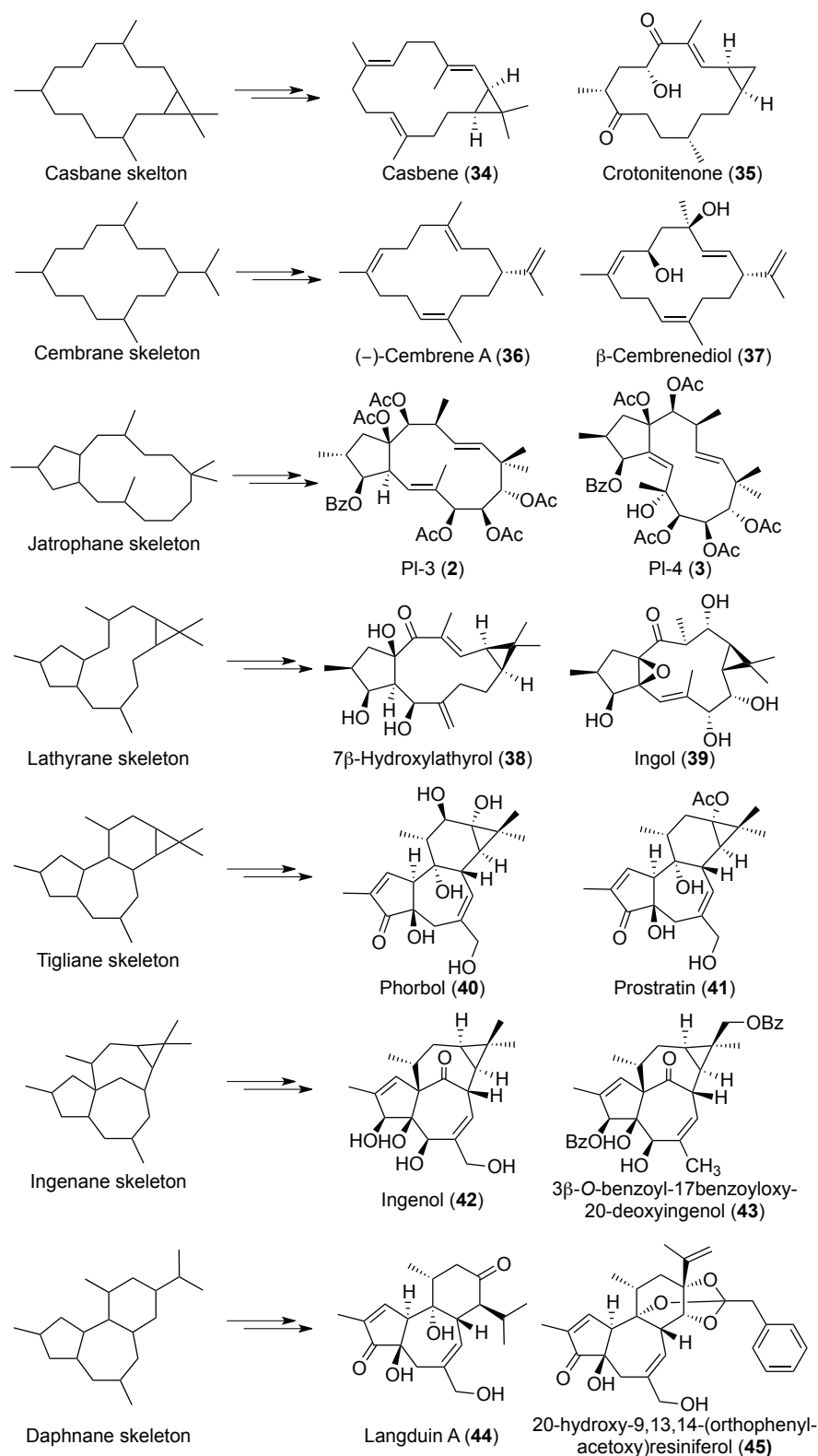


Scheme 3. Biosynthetic pathway of stevioside.

1.2.2. Biosynthesis of casbene derived diterpenes

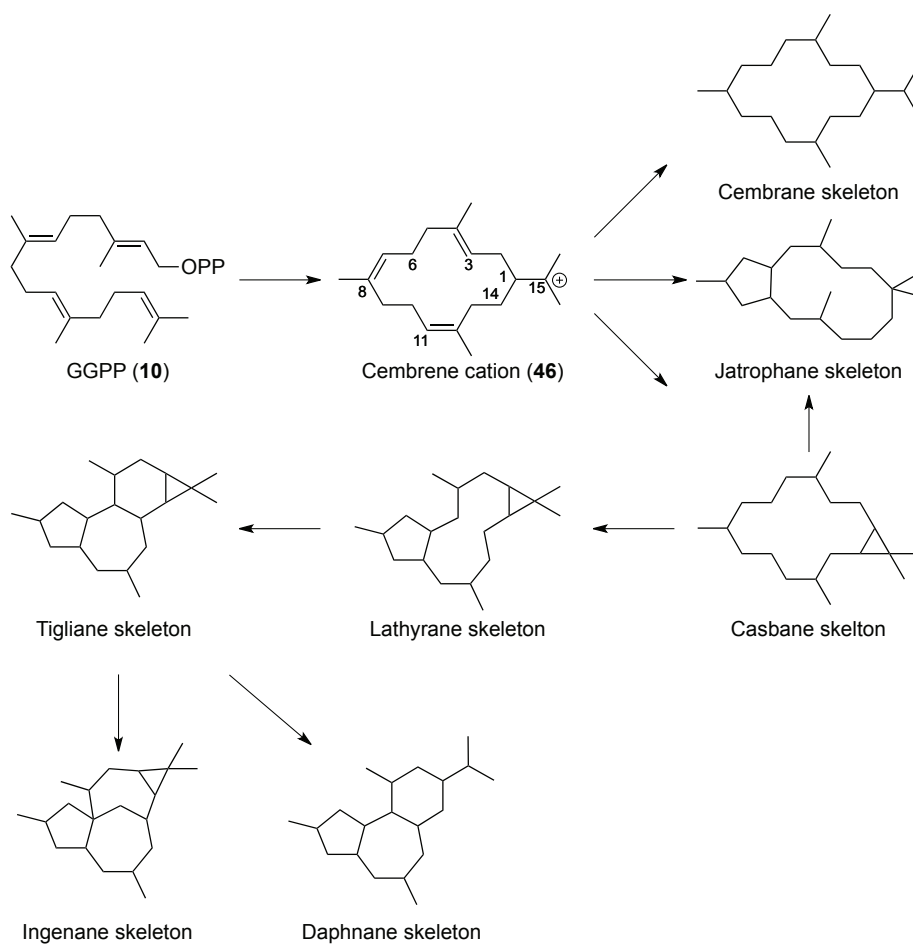
Already in 1970, Robinson *et al.* demonstrated through intense experimentation in a cell free medium, derived from *Ricinus communis* (castor bean, Euphorbiaceae), that the biosynthesis of casbene (**34**) starts from geranylgeranyl pyrophosphate (**10**).¹⁹

Casbene is considered as a precursor for different macrocyclic and polycyclic diterpenes including those of the jatrophone-, casbane-, lathyrane-, tiglane-, ingenane- and daphnane- type.²⁰ An overview of representative examples of natural products consisting of the mentioned skeletons is shown in Scheme 4 (**34–45**).



Scheme 4. An overview of casbene derived natural products.

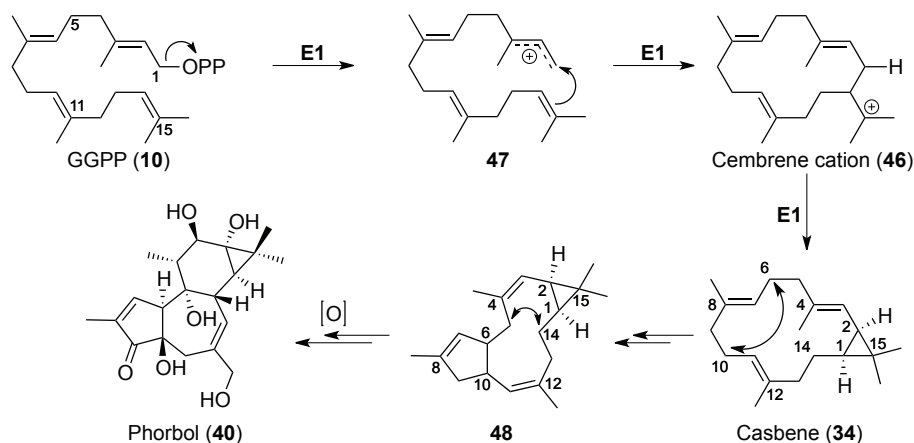
A proposed biogenetic route for the formation of the structurally related diterpenoid skeletons that represent the frameworks of the casbene derived natural products is outlined in Scheme 5. The cembrene cation (**46**) is considered as their common intermediate. Based on this reactive species all other frameworks are established through different enzymatic sequences.²⁰



Scheme 5. Possible biogenetic routes to related diterpenoid skeletons.

As mentioned above, only a few details are known about the biosynthetic pathways leading to the casbene derived natural products. The biogenetic pathway toward casbene (**34**) and the proposed formation of the tigliane skeleton, by the example of phorbol (**40**), is outlined in Scheme 6. Especially the phorbol esters show important biological properties. The identification of these compounds as tumor promoters through the activation of protein kinase C had a major impact on the investigation of central regulatory pathways within cells.²¹ Therefore, it is not surprising that the elucidation of the biogenetic route toward the natural products of the tigliane skeleton was of particular scientific interest in the past years.¹⁵

First, the diphosphate group is cleaved, affording delocalized cation **47**, which interacts with the C-(14,15) terminal double bond under the formation of the macrocyclic cembrene cation (**46**).²²⁻²⁴ Finally, the cyclopropane ring is formed *via* proton loss, delivering casbene (**34**). The whole sequence is catalyzed by a single enzyme, called casbene synthase (**E1**). A second ring closure between C-6 and C-10 delivers the precursor of natural products of the lathyrane family (**48**) and a third ring closure between C-5 and C-14 affords the tigliane skeleton, an intermediate in the hypothetical biogenetic route toward phorbol (**40**). The enzymes involved in the formation of **40** are not identified yet, except for the above-mentioned casbene synthase.



E1:Casbene Synthase

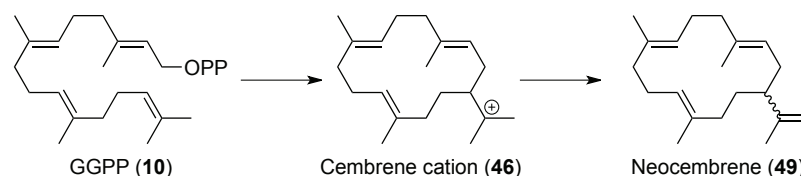
Scheme 6. Biosynthesis of casbene (34) and phorbol (40).

The casbene synthase was first isolated from *Ricinis communis* (Euphorbiaceae) in 1985 by West *et al.* and could be identified as the enzyme catalyzing the biosynthesis of casbene starting from GGPP.²⁵⁻²⁷ A divalent cation is probably of crucial importance in the enzymatic cleavage of the allylic pyrophosphate at the beginning of the catalytic cycle but the mechanism could not be elucidated so far.^{25, 28, 29} That was the only reported successful isolation and characterization of a diterpene synthase (DTPS) from a plant of the Euphorbiaceae plant family for a long time. (DTPSs catalyze the cyclization reactions leading to the hydrocarbon backbone of diterpenes. Further functionalization typically occurs through oxidation of cytochrome P450 monooxygenases to finalize the biosynthesis of oxygenated diterpenoid natural products.) Only recently Demura and co-workers have succeeded in the isolation of a casbene synthase homolog from *Jatropha curcas* L., also suggesting that the enzyme is involved in the casbene biosynthesis.³⁰

Furthermore, Keasling *et al.* reported the isolation and cloning of casbene synthases from five representative Euphorbia species (*H. nutans*, *E. resinifera*, *S. sebiferum*, *E. esula*, *R. communis*).³¹ As the authors could not isolate other diterpene synthases, they suggest that the casbene synthase must indeed be a crucial catalyst in the biosynthetic pathway of casbene-derived natural products, an assumption that also confirms the findings of the above-mentioned groups. Nonetheless, Keasling *et al.* indicated that despite the isolation of the casbene synthases, not a single functionalized diterpene comprising the unaltered casbene backbone was identified among the analyzed natural products isolated from the above-mentioned Euphorbia species. Therefore, the authors suggest that they could not completely rule out that possibly other DTPSs, which remained undiscovered within their investigations, are involved in the biosynthesis of plant metabolites belonging to the class of casbene derived diterpenes.

However, several compounds possessing a functionalized lathyrane skeleton were isolated from the five Euphorbia species, which in turn could imply that the five-membered ring, present also in the tiglane skeleton, is closed first on the proposed way to the phorbols. Additionally, they were able to characterize a neocembrene synthase in *R. communis*, which catalyzes the biogenetic sequence

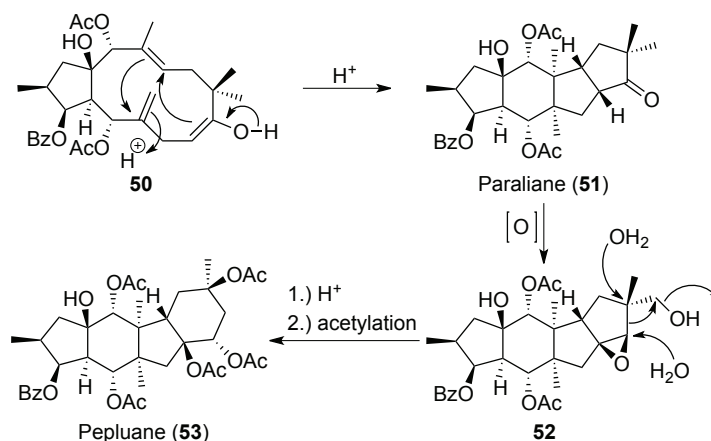
outlined in Scheme 7. This was the first report of the evidence of a neocembrene synthase gene but its role in the biosynthesis of Euphorbia diterpenes has not yet been clarified.³¹



Scheme 7. Biosynthesis of neocembrene (49).

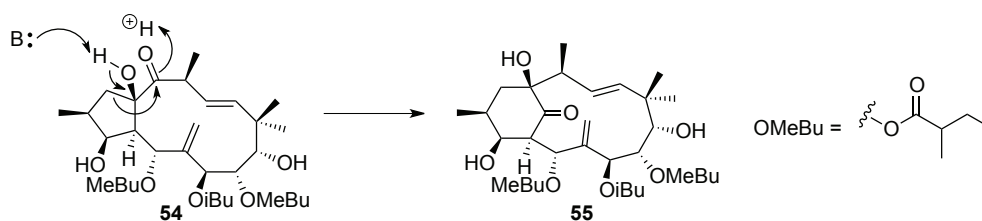
Jatrophone diterpenes, isolated from Euphorbia species, are lacking the cyclopropane ring, which is present in the lathyrane skeleton. Two different biogenetic mechanisms for the formation of the jatrophone framework are mentioned and are already indicated in Scheme 5. The macrocycle could either be formed directly from the cembrene cation (46) *via* a Wagner-Meerwein shift or, alternatively but more likely, the casbene precursor is formed first, followed by the opening of the cyclopropane ring.²⁰ Final closure of the five-membered ring between C-6 and C-10 would accomplish the biogenetic route toward the jatrophone skeleton. Further functionalization leads to a huge class of natural products with different oxygenation states and stereochemical features.

Only a few explanations concerning the biosynthesis of natural products, which are considered to arise from the jatrophone skeleton, have been reported. A proposed biogenetic pathway for the synthesis of the tetracyclic natural product pepluane (53) is shown in Scheme 8. Paraliane (51) is formed through a transannular ring closing reaction of the jatrophone diterpene 50 resulting in a 5/6/5/5-ring system. Introduction of a primary alcohol and an epoxide by enzymatic oxidation, followed by a ring expansion and further acetylation complete the biosynthesis of 53.^{32, 33}



Scheme 8. Proposed biosynthesis of pepluane (53).

The 1(15 $\rightarrow$ 14) *abeo*jatrophone-type skeleton 55 could be formed by a base-induced pinacol rearrangement of 54, demonstrated in Scheme 9. The possibility of 55 being an artifact, generated during the isolation process, could be excluded. Thus, the proposed biosynthetic precursor (54) was treated with acetic acid and sodium acetate which did not alter its structure, suggesting that 55 was formed by means of enzymatic transformations.³⁴



Scheme 9. Pinacol-type rearrangement of **54** to the *abeo*jatrophone **55**.

1.3. BIOLOGICAL ACTIVITY OF JATROPHANE DITERPENES

Jatrophone diterpenes, isolated from plants of the genus *Euphorbia* show a wide range of biological and pharmacological properties, including skin-irritant and tumor-promoting effects, antimicrobial, anti-inflammatory, antiproliferative, antiviral and cytotoxic activity.⁹ Furthermore, several structurally diverse diterpenes of the jatrophone skeleton were identified as highly active multidrug resistant reversal (MDR) candidates, by binding to Pgp. This is probably the most interesting biological activity of this class of natural products and, therefore, subject of numerous scientific investigations in the past years.¹⁰⁻¹⁴ The ability to inhibit the MDR effect turns those compounds to very promising candidates for the investigation of new chemotherapeutics.

1.3.1. Multidrug resistant reversal effect

The development of resistance mechanisms in cancer cells to drugs that combat the growth of tumors is a common reason why chemotherapy can fail. MDR can have different causes but the most important mechanism is the overexpression of active drug efflux pumps in the membrane of cancer cells caused by mutations during chemotherapy. As a result, these transport proteins discharge cytotoxic molecules from the cancer cell and the intracellular drug concentration is always held below a cell-killing threshold.³⁵

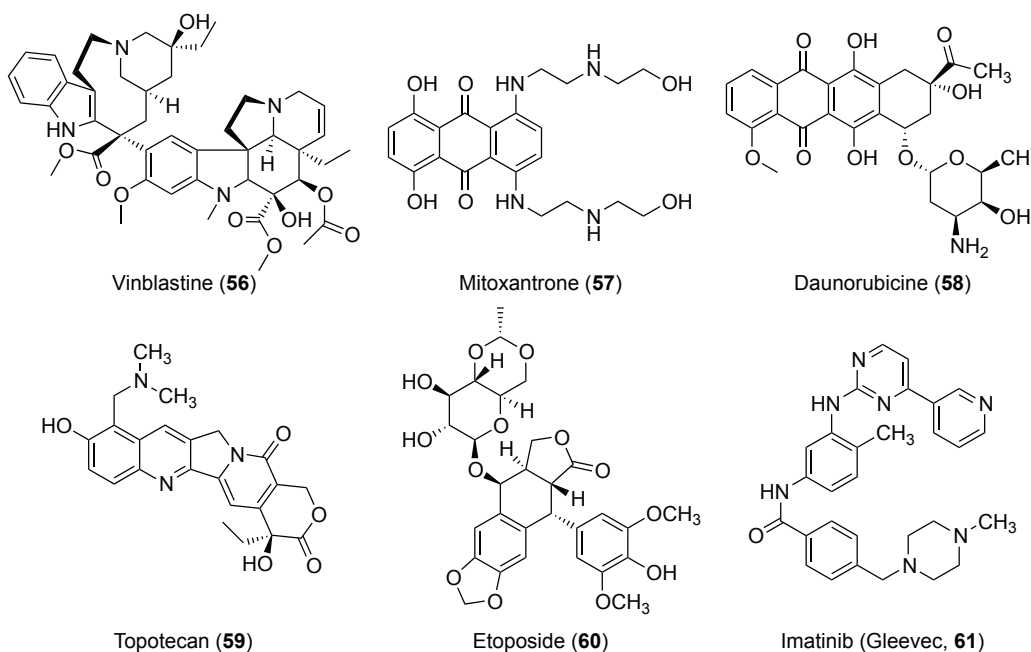


Figure 5. Chemotherapeutics that are substrates for Pgp, MRP1 and ABCG2.

The efflux pump proteins belong to the ATP-Binding Cassette (ABC) superfamily of proteins that utilize the energy of ATP-hydrolysis to carry out certain transport processes. The 49 members of this protein family, identified in the human genome, organize a variety of transport processes in healthy prokaryotic and eukaryotic cells.³⁶ The efflux processes include the transport of phospholipids, sterols, bile salts and amphiphatic drugs. 15 ABC proteins were identified to export chemotherapeutics in *in vitro* experiments³⁷ but only three transporters have been found as major contributors to MDR in human cancer. These are the transmembrane proteins, P-glycoprotein (Pgp also termed as MDR1 or ABCB1), multidrug resistance-associated protein 1 (MRP1 or ABCC1) and ABCG2 (also known as breast cancer resistance protein, BCRP, or mitoxantrone resistance protein, MXR). These drug efflux pumps are “polyspecific” which means that they are able to bind and transport a wide range of structurally diverse compounds. The substrate spectra of the three mentioned transport proteins comprise hundreds of different molecules and are not identical although a partial overlap is observed. Figure 5 shows six structures of current chemotherapeutics (**56–61**) that are substrates for all three termed transport proteins active in human cancer cells.³⁵

In the following, the spectrum of substrates and the mechanism of binding and transport of Pgp are discussed. Pgp is the transport protein for which the most structural information is available and additionally it is the target efflux protein of jatrophone diterpenes.

Pgp-substrates show different chemical characteristics, some of them are amphiphatic or lipophilic, also uncharged binding partners are observed and others possess a positively charged nitrogen atom under physiological conditions. Basically, the interacting substrates are large (200-1900 Da) organic molecules. Among others, Pgp-binding partners are classic chemotherapeutics (such as the *Vinca* alkaloids and taxols), tyrosine kinase inhibitors, HIV protease inhibitors, ionophores, peptides, steroids and cardiac glycosides. It is very difficult to make a generalization of structural features and no common pharmacophore has been found until today.³⁵

Through different biochemical and biophysical methods including mutagenesis, cross-linking experiments or electron microscopy, the topology of Pgp could be proposed in the past years as follows: Pgp is a pseudosymmetrical heterodimer in which each monomer comprises a nucleotide binding domain (NBD) as well as a transmembrane domain (TMD). The cytoplasmatically localized NBDs are responsible for the ATP-binding and hydrolysis, and their sequence is highly conserved within the ABC-transporter family. On the other hand, the membrane-embedded TMDs contain the substrate-binding site and they show only low sequence similarity within the protein family. Furthermore, a large and flexible binding region is more likely than one or several discrete binding sites within the substrate-binding domain. This could also explain the broad and polyspecific substrate spectrum.³⁵

Cryo-electron microscopy and diverse biochemical experiments demonstrated that Pgp undergoes large conformational changes during its catalytic cycle. The different models used to describe the catalytic cycle share the same feature of an ATP-binding dependent dimerization of the NBDs,

which induces the trans-membrane transport of a substrate: In the ATP switch model the transport cycle is initiated by binding of the substrate to its high affinity site on the TMDs at the inner leaflet of the membrane. The model further proposes that the dimerization of the two NBDs through ATP-binding induces a conformational change in the TMDs. As a result, the drug-binding site is exposed extracellularly and its affinity is reduced, leading to the release of the bound drug. Further ATP-hydrolysis and sequential release of inorganic phosphate (P_i) and ADP restores the transporter to its basal configuration (Figure 6).³⁸

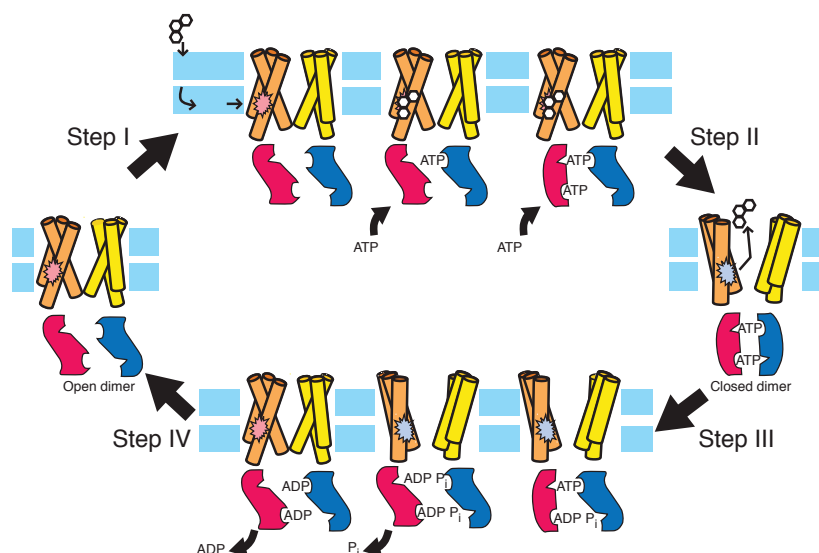


Figure 6. ATP-switch model.³⁹

An alternative theory, based on the ATP switch model, hypothesizes that an additional, asymmetric occlusion of one ATP molecule within the dimerized NBDs is responsible for the conformational change in the TMD and the associated substrate release.^{40, 41} Although our knowledge of substrate binding and understanding of the mechanism of the catalytic cycle is increasing, so far we can only speculate about these processes within biological systems.

The availability of high-resolution X-ray structures of transmembrane transport proteins is essential to understand their function on a molecular basis and additionally, their structure elucidation will offer striking possibilities toward structure-based drug design. While bacterial ABC importers and exporters have already been investigated in detail and X-ray structures are available,⁴²⁻⁴⁷ crystallization of mammalian transporters has proven to be more difficult. Only in 2009, Aller *et al.* succeeded in describing the X-ray structure (3.8 Å crystal structure) of murine Pgp, which is the highest-resolution structure of a mammalian drug transporter to date.⁴⁸ The murine transport protein shows 87% sequence identity to human Pgp. The publication describes the structures of apo-Pgp (nucleotide-free structure) and, for the very first time, co-crystal structures of Pgp with cyclic peptide inhibitors providing a deeper understanding of substrate binding. It is remarkable that their results reinforce most of the structural features that were proposed based on biochemical and biophysical experiments in the past years as already mentioned above. Most importantly, Aller and co-workers were able to characterize the substrate-binding region, which is a large cavity of

approximately 6000 Å³. This flexible binding site comprises mostly hydrophobic and aromatic amino acids and only a small number of polar and potentially charged amino acid residues where drugs can bind in different orientations.^{48, 49} Although the published murine Pgp crystal structure is just a single snapshot of the protein within its catalytic cycle and lacks the high resolution needed to elucidate the uncertainty about the broad substrate recognition spectrum, it provided useful new insights into the molecular function of mammalian Pgp.⁴⁹

1.3.2. Jatrophone diterpenes as Pgp-inhibitors

Numerous jatrophone diterpenes isolated over the past years were identified as inhibitors or modulators that reverse MDR in intact cancer cells in *in vitro* experiments. In 2001 Hohmann *et al.* reported the isolation of the diterpene euphosalicin (**62**), from *Euphorbia salicifolia*. They could identify **62** to be more than twice as active as the reference substance verapamil in inhibiting multidrug resistance in mouse lymphoma cells. By contrast, two additional jatrophone diterpenes (**63**, **64**), isolated from the same *Euphorbia* species as **62**, were found to be inactive in reversing MDR. The cells, incubated with the assumed MDR modulators, were analyzed using flow cytometry for their ability to efflux the fluorescent dye Rhodamine 123. Verapamil was used as positive control for those exclusion experiments.¹⁰

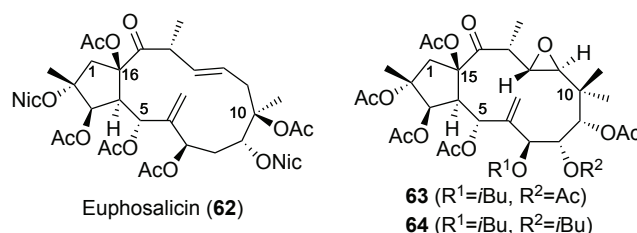


Figure 7. MDR modulators I.

In 2002, again Hohmann *et al.* published detailed biological investigations of additional 15 jatrophone polyesters isolated from *E. serrulata*, *E. esula*, *E. salicifolia*, and *E. peplus* concerning their MDR reversing activity.⁵⁰ These diterpenes, although structurally closely related, differ significantly in their inhibiting effect of Pgp in tumor cells. Unfortunately, a consistent structure-activity relationship trend could not be observed.

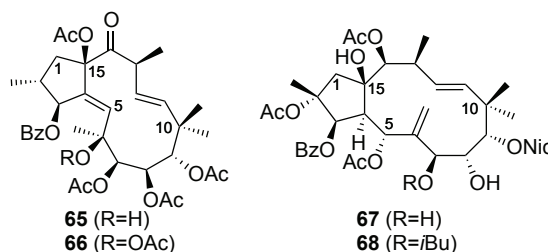


Figure 8. MDR modulators II.

However, a few similarities could be demonstrated: comparison of the pairs **65** and **66** as well as **67** and **68** which vary only in the lipophilicity of one substituent, shows an increase of MDR reversing activity. This link between lipophilicity and the increase of the inhibiting effect is consistent with

the assumption that the effect of drug accumulation in drug-resistant cells is proportional to their hydrophobicity.⁵⁰

Surprisingly, regarding other pairs such as **68** and **69** where also an increase in the overall lipophilicity can be observed the above-mentioned trend could not be confirmed, because **69**, the more hydrophilic compound, shows higher inhibition of Pgp. The authors mention that this phenomenon could be explained by the high flexibility of the macrocyclic ring and its alignment of different conformers.⁵⁰ These early observations demonstrate that the analysis of the three-dimensional structure of related jatrophone diterpenes will be the crucial point for a more detailed understanding of their structure-activity relationship.

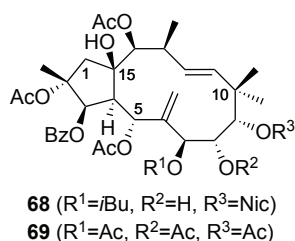


Figure 9. MDR modulators III.

Lanzotti and co-workers published the isolation of ten closely related jatrophone diterpenes from the latex of *E. dendroides*. For the first time, the authors tried to elaborate a definite structure-activity relationship based on the substitution pattern of the south-western fragment (C-2 to C-5) of the newly isolated diterpenes. Finally they identified euphodendroidin D (**70**) as the most potent inhibitor of MDR within their test series. Euphodendroidin D shows almost double efficiency compared to the internal standard cyclosporine A. They hypothesized that the free hydroxyl group at C-3 as well as the lack of a quaternary center at C-2 possess a crucial role in the MDR inhibiting properties of the jatrophone diterpenes compared in this study.¹²

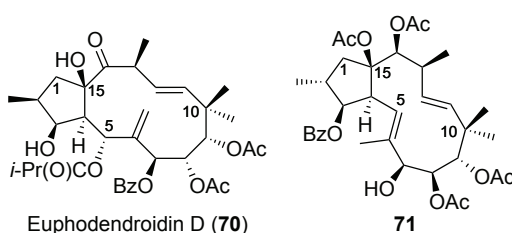


Figure 10. MDR modulators IV.

In the following years Hohmann *et al.* as well as Lanzotti and co-workers isolated numerous jatrophone diterpenes from different *Euphorbia* species and evaluated those structurally complex natural products in respect to their MDR modulating effect.^{13, 51-53} Different jatrophone diterpenes from *E. esula*, *E. peplus*, *E. villosa* and *E. serrulata* were tested for their MDR reversing activity on human colon cancer cell lines. Unfortunately, compared to the results received from mouse lymphoma cell assays, the inhibiting effect of Pgp decreased for all tested compounds. Thus, compound **71**, isolated from *E. serrulata*, showed highly potent properties as a MDR-inhibitor on mouse lymphoma cells with an almost three fold activity compared to the reference substance

verapamil. Otherwise, in the human colon cancer assay the activity decreased and reached not even the value of the internal standard.⁹

Ferreira *et al.* published the isolation of related jatrophane diterpenes from *E. mellifera* and tested their activity as Pgp modulators. Euphomelliferine (**72**) and euphomelliferine A (**73**), two jatrophane diterpenes, which are structurally very similar to **71**, displayed a significant MDR reversing activity on mouse lymphoma cells in a dose-dependent manner (again about twice as active compared to verapamil). They could also confirm the decrease of activity on human colon cancer cells.¹⁴

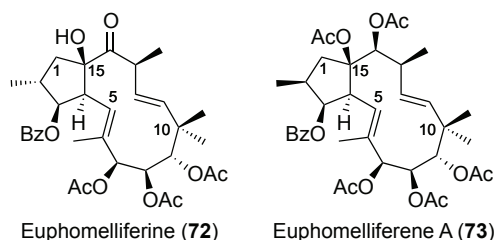


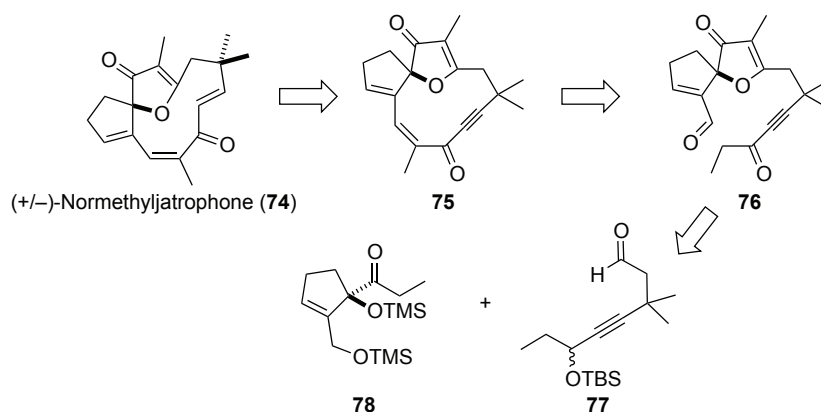
Figure 11. MDR modulators VI.

Summarizing, a large number of jatrophane diterpenes could be isolated in the past years and evaluated in respect to their MDR-reversing activity. Numerous, partially structurally closely related natural products were identified as highly promising MDR-modulators showing a higher activity than different reference substances such as verapamil or cyclosporine A. Although a vast number of compounds was investigated no definite trend within their substitution pattern, which could explain their structure-activity relationship, was observed. As already mentioned, the conformation of the macrocycle probably plays a crucial role in the interaction of the diterpene within the binding pocket of Pgp. X-ray structures of the substrates combined with the synthesis of systematic compound libraries and expanding knowledge of the Pgp-substrate binding process will be essential for the identification of lead structures as foundation for structure-based drug design.

1.4. TOTAL SYNTHESSES OF JATROPHANE DITERPENES

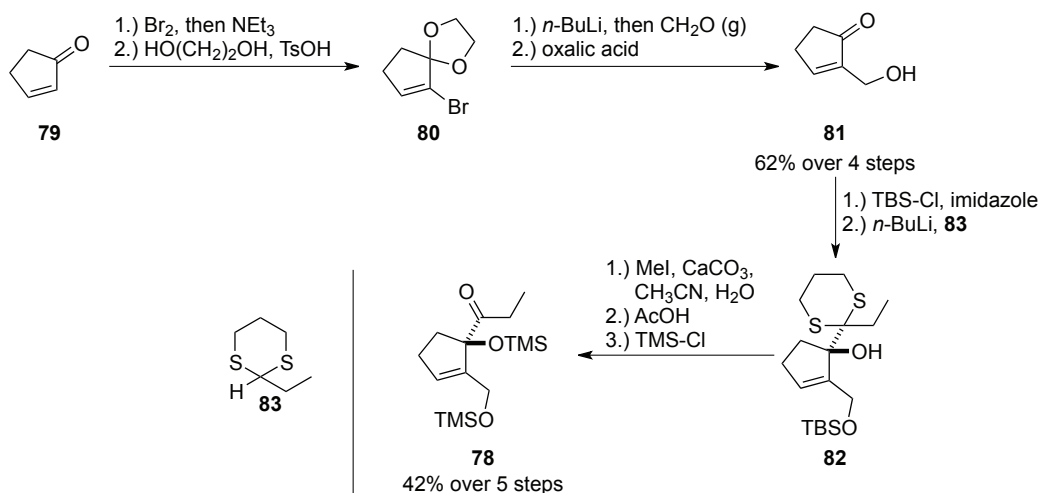
1.4.1. Total synthesis of $\pm$ -normethyljatrophone by Smith *et al.*⁵⁴

In 1981 A. B. Smith *et al.* reported the racemic total synthesis of normethyljatrophone (**74**).⁵⁴ The retrosynthetic analysis is shown in Scheme 10. The macrocyclization should be achieved *via* a Mukaiyama-aldol reaction^{55, 56} and the conversion of the acetylene functionality to the corresponding *trans*-double bond would complete the synthesis of **74**. The key part of the molecule, the spiro-3(2*H*)-furanone-moiety, was envisaged to be formed through an acid catalyzed cyclization-dehydration sequence after the connection of ketone **78** and TBS-protected aldehyde **77** through an aldol reaction.



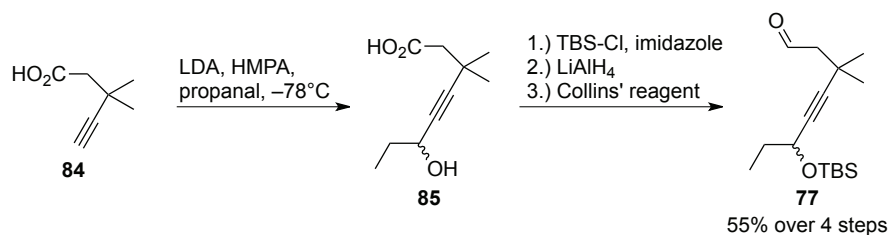
Scheme 10. Retrosynthetic analysis of $\pm$ -normethyljatrophone (**74**).

Cyclopentenone **79** was converted to acetal-protected bromide **80** through a two-step procedure. A bromination-elimination sequence was followed by an acid catalyzed protection of the keto-functionality with ethylene glycol. In the next step, first a vinyl anion was formed which was captured with formaldehyde.^{57, 58} Further treatment with oxalic acid resulted in deprotection of the acetal group to afford α -(hydroxymethyl)cyclopentenone **81** in 62% yield over four steps. The formation of the silyl-ether was followed by the treatment with lithioethyldithiane **83**, delivering racemic tertiary alcohol **82**. Next, the dithiane moiety was hydrolyzed and after the cleavage of the TBS-group, both free hydroxyl functionalities were TMS-protected to give ketone **78** in 42% yield over 5 steps (Scheme 11).⁵⁴



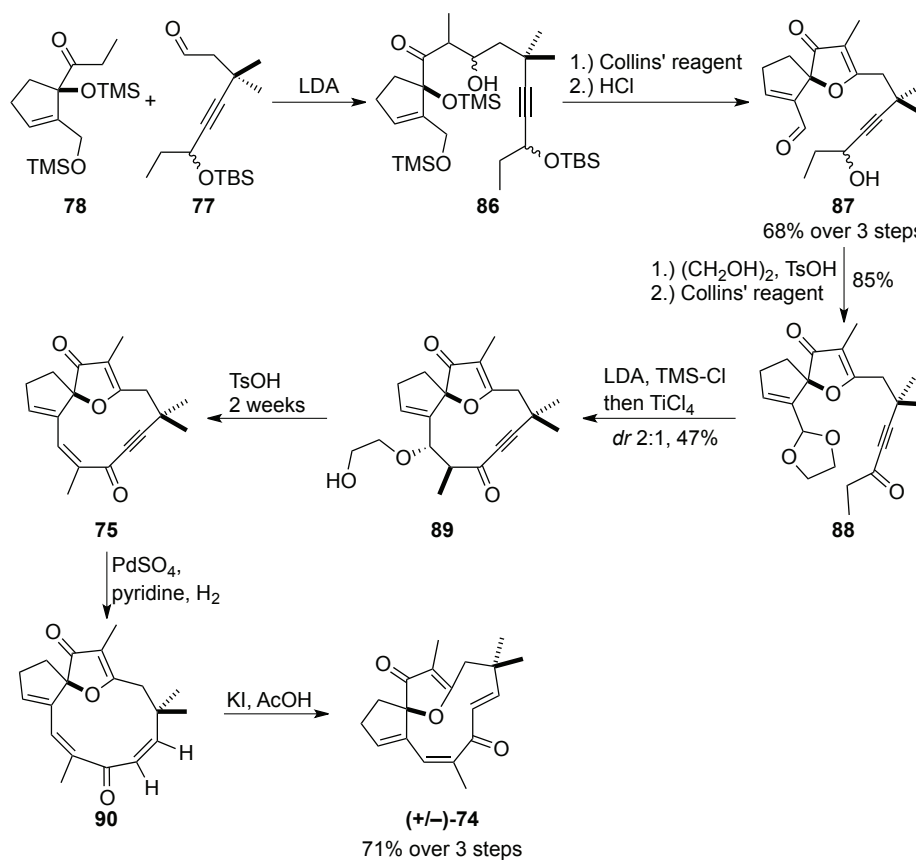
Scheme 11. Preparation of ketone **78**.

The preparation of aldehyde **77** is outlined in Scheme 12. The dianion, derived from 3,3-dimethyl-4-pentynoic acid (**84**) under exposure to LDA/HMPA, was treated with an excess of propanal to afford elongated hydroxy-acid **85**. The secondary alcohol was protected as a TBS-ether and a reduction-oxidation sequence completed the synthesis of the desired aldehyde **77** in 55% yield over 4 steps.



Scheme 12. Synthesis of aldehyde **77**.

Next, aldehyde **77** and ketone **78** were coupled *via* an aldol reaction to give β -hydroxy ketone **86**. Exposure of **86** to an excess of the Collins' reagent⁵⁹ resulted in oxidation of the secondary alcohol and concomitant cleavage of the primary TMS-group. The resulting primary alcohol was immediately oxidized within the same step to deliver the corresponding aldehyde. Finally, acid catalyzed deprotection of the remaining silyl-groups followed by an acid induced cyclization-dehydration reaction sequence afforded spirofuranone **87** as a mixture of diastereomers in 68% overall yield. Unfortunately, the direct closure of the macrocycle through an aldol reaction after the oxidation of the free alcohol functionality in **87** was met with failure. An alternative route was found by aspiring a TiCl_4 -promoted Mukaiyama condensation of an acetal with a silyl-enol ether.⁶⁰ Therefore, the aldehyde functionality in **87** was protected as an acetal with ethylene glycol and the secondary hydroxyl group was oxidized by using the Collins' reagent to yield ketone **88**.



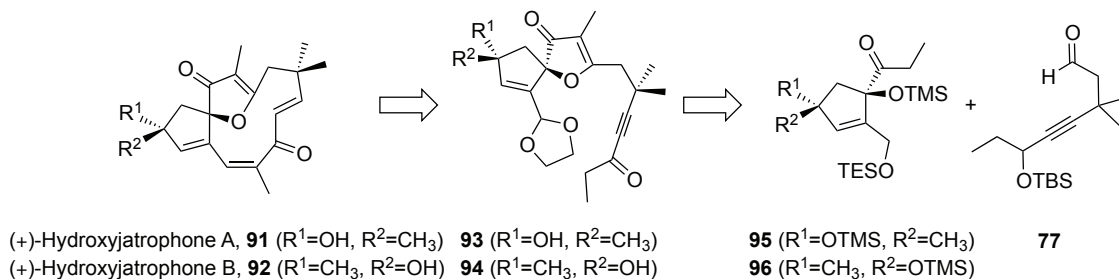
Scheme 13. Final sequence toward the total synthesis of ± 74 .

The formation of the macrocycle succeeded under Mukaiyama-aldol reaction conditions and the formation of two diastereomeric products (47%, 2:1). The stereochemistry of the major product **89**

was identified by X-ray analysis. Elimination of ethylene glycol initially afforded the *trans*-fused double bond, but it could be demonstrated that the undesired *E*-isomer undergoes slow isomerization to the desired *cis*-double bond (**75**) after extended exposure (2 weeks) to toluenesulfonic acid. Final *cis*-hydrogenation of the acetylene moiety followed by isomerization of the double bond completed the total synthesis of $\pm$ -normethyljatrophone **74** (Scheme 13).⁵⁴ Summarizing, the total synthesis of **74** has been achieved in a convergent manner in 5.6% overall yield, starting from cyclopentenone (**79**).

1.4.2. Total synthesis of (+)-hydroxyjatrophone A and (+)-hydroxyjatrophone B by Smith *et al.*⁶¹

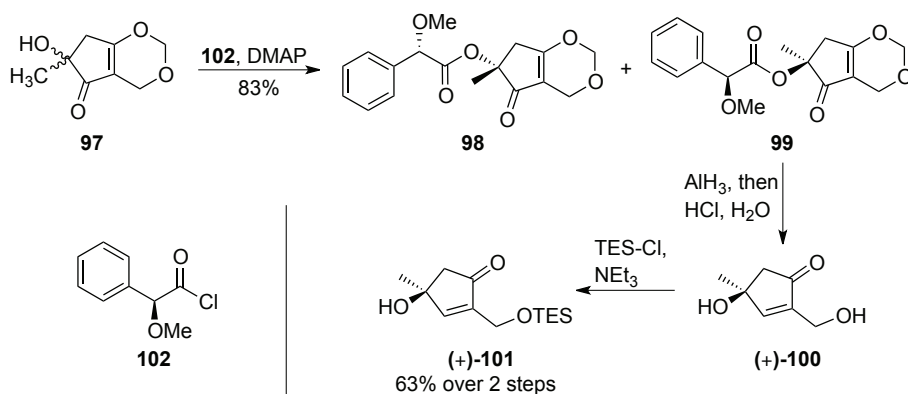
In 1989 again A. B. Smith *et al.* published the first non-racemic total syntheses of (+)-hydroxyjatrophone A (**91**) and (+)-hydroxyjatrophone B (**92**).⁶¹ The synthetic strategy (Scheme 14) is in close analogy to the synthesis of normethyljatrophone (**74**) discussed above. The spirofuranone-part should again be constructed by an acid-promoted cyclization sequence and closure of the macrocycle should be achieved through a Mukaiyama aldol-reaction, as already elaborated for the synthesis of **74**.⁵⁴ The intermediates **93** and **94** can be attributed to aldehyde **77** and highly substituted five-membered ring fragments **95** and **96**, respectively. Aldehyde **77** should be coupled with the respective ketone (**95** or **96**) *via* an aldol reaction to give the precursors for the spirofuranone formation reaction.



Scheme 14. Retrosynthetic analysis of (+)-hydroxyjatrophone A (**91**) and B (**92**)

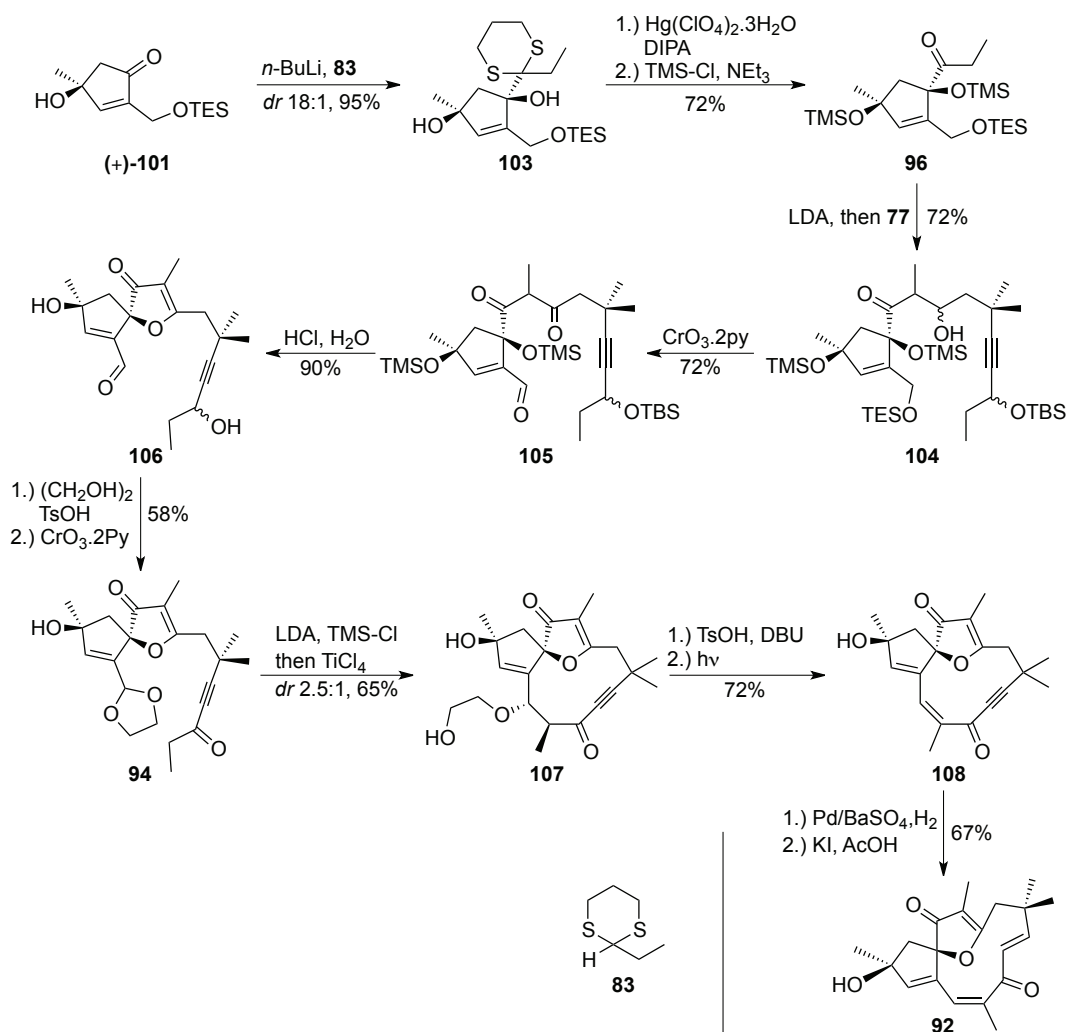
The synthesis of chiral cyclopentenone **101** started with the esterification of racemic tertiary alcohol **97**⁶² with (+)-*O*-methylmendeloyl chloride (**102**) to afford the diastereomeric esters **98** and **99**. In the following, the total synthesis of (+)-hydroxyjatrophone B (**92**) is discussed, as the synthesis of (+)-hydroxyjatrophone A (**91**) essentially differs only in the choice of the diastereomeric ester **98** at the beginning of the synthetic route.

After separation of the two esters **98** and **99** by column chromatography, reduction of **99** was followed by an acid-promoted-hydrolysis rearrangement to give diol **100**, before selective protection of the primary alcohol as a silyl-ether completed the sequence with the isolation of cyclopentenone **101** (Scheme 15).



Scheme 15. Preparation of the five-membered ring intermediate **101**.

Subsequent reaction of **101** with the lithiated dithiane species **83** afforded intermediate **103** in an 18:1 diastereomeric ratio, favoring the desired isomer (Scheme 16). The resulting *syn*-diol was TMS-protected after hydrolysis of the thioacetal moiety, delivering **96**. Subsequent deprotonation with LDA generated the corresponding enolate, the reactive coupling partner for aldehyde **77**. Oxidation of the diastereomeric aldol product **104** using the Collins' reagent resulted in additional deprotection of the primary TES-group and oxidation of the resulting alcohol to provide enal-dione **105**.

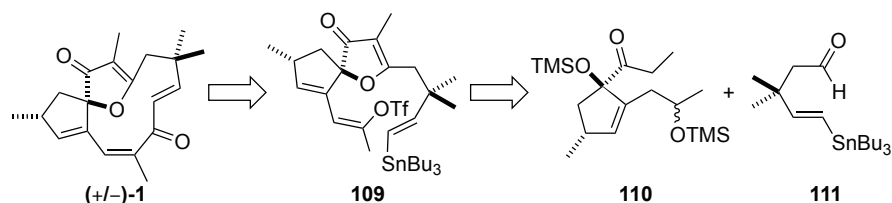


Scheme 16. Total synthesis of (+)-hydroxyjatrophone B (**92**).

Thus, the stage was set for the crucial acid-promoted cyclization of the spirofuranone part. Exposure of **105** to hydrochloric acid promoted the cleavage of all silyl-ethers and concomitant formation of furanone **106** in excellent 90% yield. Conversion of the aldehyde functionality to the acetal and oxidation of the free secondary alcohol in **106** was required as preparation for the Mukaiyama aldol reaction to close the macrocyclic ring. Initial transformation of **94** to the TMS-enolate and following treatment with titanium tetrachloride delivered the macrocyclic intermediate **107** in a 2.5:1 mixture of diastereomers with respect to the α -methyl group. Next, the *cis*-alkene **108** could be isolated after elimination of ethylene glycol with p-toluenesulfonic acid and DBU and subsequent photoisomerization of the formed undesired *trans*-double bond. Final palladium catalyzed *syn*-hydrogenation and isomerization of the double bond to provide the *trans*-linked product completed the total synthesis of (+)-hydroxyjatrophone B (**92**).⁶¹

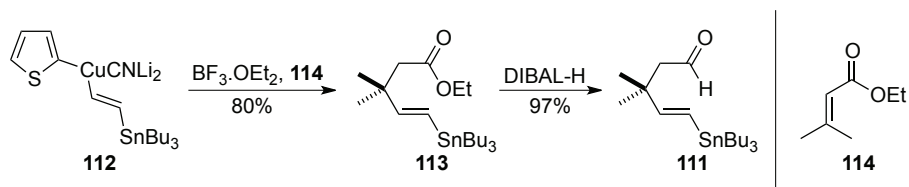
1.4.3. Total synthesis of $\pm$ -jatrophone and $\pm$ -*epi*-jatrophone by Hegedus *et al.*⁶³

Racemic syntheses of jatrophone (**1**) and C2-*epi*-jatrophone were published by Hegedus *et al.* in 1990.⁶³ They intended to close the macrocycle *via* a palladium catalyzed carbonylative Stille coupling reaction^{64, 65} of advanced intermediate **109**, while the construction of the spirofuranone part was intended to be elaborated in close analogy to the synthesis published by Smith, described above, through a Lewis acid-catalyzed cyclization-dehydration reaction sequence (Scheme 17). The proposed aldol reaction of ketone **110** and aldehyde **111** has already been employed in the syntheses discussed earlier.



Scheme 17. Retrosynthesis of $\pm$ -jatrophone.

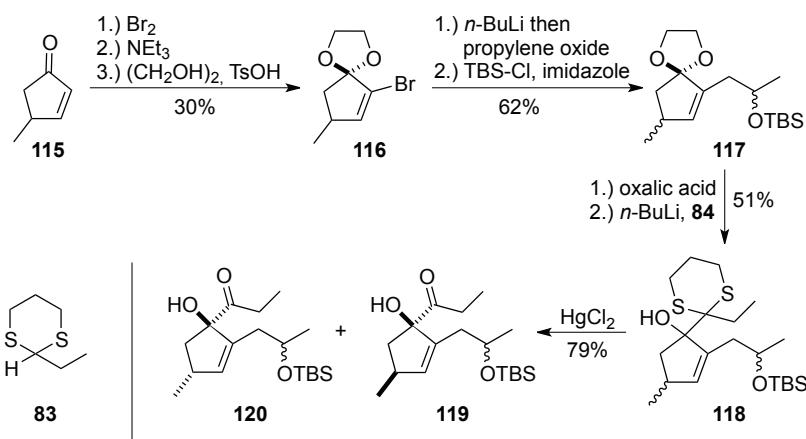
The thiophene derived cuprate **112**⁶⁶ was allowed to react with ethyl-3,3-dimethylacrylate **114** in the presence of boron trifluoride etherate in a 1,4-addition. The following reduction afforded aldehyde **111** in overall 78% yield over two steps.



Scheme 18. Synthesis of vinyl-stannane **111**.

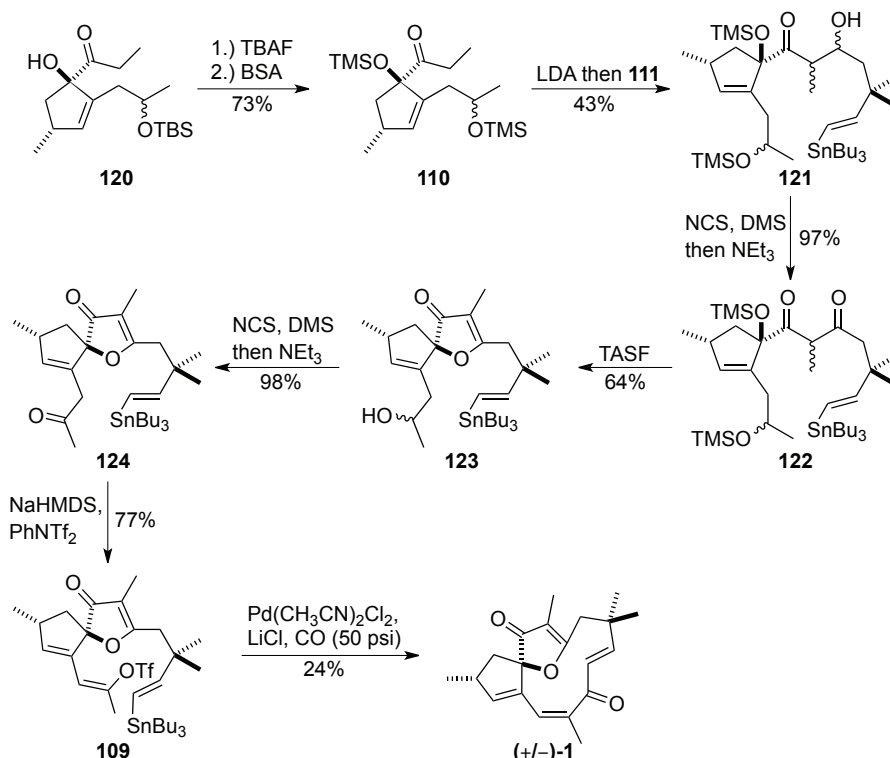
Starting from racemic cyclopentenone **115**, α -bromo-ketal **116** was isolated after an initial bromination/dehydrobromination sequence followed by ketalization with ethylene glycol. Halogen-metal exchange of the vinylic bromide with *n*-BuLi and further addition of propylene oxide afforded the corresponding secondary alcohol, which was protected as a TBS-ether, to provide **117**

as a mixture of diastereomers. Deprotection of the ketal moiety gave the intermediate α,β -unsaturated ketone, precursor for the dithiane addition. The attack of lithiated **83** resulted in the formation of **118** as an unseparable mixture of diastereomers. After cleavage of the thioketal with mercury chloride ketones **119** and **120** were obtained as a 9:1 diastereomeric mixture. Thus, the initial dithiane addition proceeded mainly from the opposite side of the methyl group.



Scheme 19. Preparation of cyclopentene fragments **119** and **120**.

Next, the secondary TBS-group was cleaved and the resulting diol was protected with *bis*(trimethylsilyl)acetamide (BSA), delivering **110**. Enolate formation was followed by the addition of aldehyde **111** to afford highly advanced intermediate **121**. After oxidation, following the Corey-Kim protocol⁶⁷, diketone **122** was obtained.



Scheme 20. Completion of the total synthesis of $\pm$ -jatrophone.

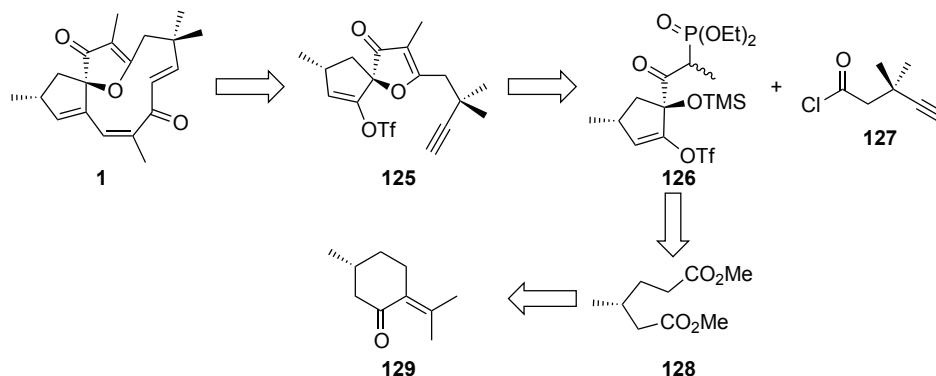
The spirofuranone part could be formed by the exposure to TASF, which served as a weak Lewis acid. Additional deprotection of the secondary TMS-group resulted in the isolation of **123** in

acceptable 64% yield. Oxidation of the free hydroxyl group to the corresponding ketone **124** and installation of the vinyl-triflate (**109**) paved the way for the final carbonylative Stille coupling to complete the racemic total synthesis of jatrophone (**1**).

C2-*epi*-jatrophone was prepared following exactly the same route using **119**, the major diastereomer after the dithiane addition (Scheme 19), as the cyclopentene fragment within the natural product.

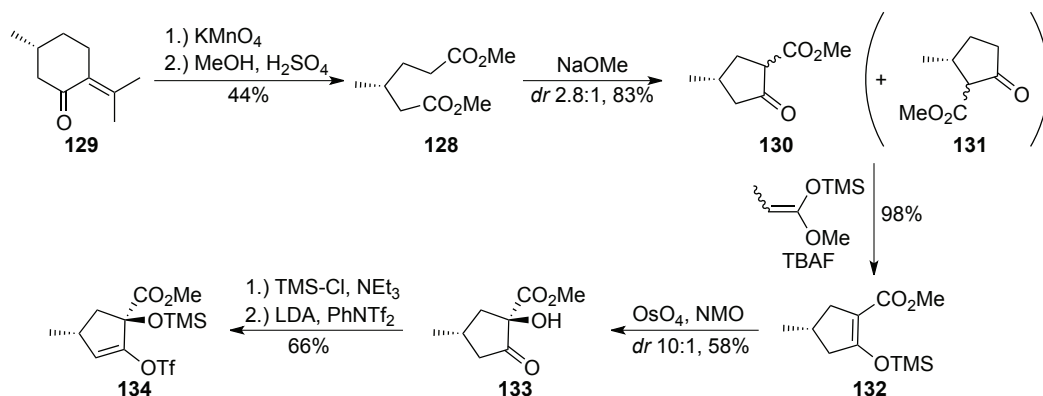
1.4.4. Total synthesis of (+)-jatrophone by Wiemer *et al.*⁶⁸

The first nonracemic total synthesis of (+)-jatrophone (**1**) was published by Wiemer *et al.* in 1992.⁶⁸ The construction of the core of the molecule, the cyclofuranone part, was envisioned to proceed *via* an intramolecular Horner-Wadsworth-Emmons reaction⁶⁹, leading to intermediate **125**. Cyclopentene fragment **126** and acetylenic acid chloride **127** should be connected *via* direct esterification to afford the precursor for the HWE reaction. Commercially available (+)-pulegone (**129**) was chosen as starting material from the chiral pool, which should initially be converted to diester **128** (Scheme 21).



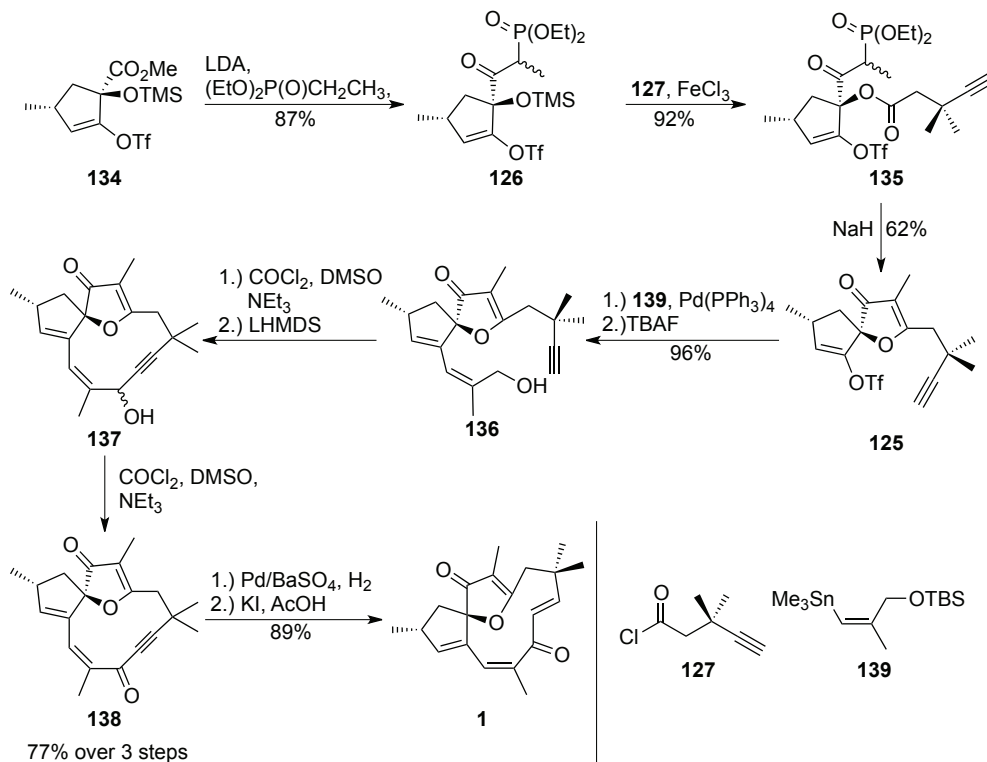
Scheme 21. Retrosynthetic analysis of (+)-jatrophone (**1**).

The monoterpene (+)-pulegone (**129**) was oxidized to the corresponding dicarboxylic acid, which was esterified with methanol to yield chiral diester **128**.⁷⁰ The following Dieckmann condensation⁷¹ resulted in the formation of a 2.8:1 mixture of the regioisomers **130** and **131** favoring desired cyclopentanone **130**. The introduction of a TMS-enol ether (**132**) was followed by dihydroxylation with OsO₄/NMO, delivering preferentially R-configured cyclopentanone **133** (in respect to the newly introduced stereocenter) *via* a substrate-controlled reaction mechanism. TMS-protection of the tertiary alcohol and final triflate-formation concluded the sequence toward the highly substituted cyclopentene fragment **134**, the chiral key intermediate in the synthesis of (+)-jatrophone (**1**, Scheme 22).⁷²



Scheme 22. Synthesis of the cyclopentene fragment **134**.

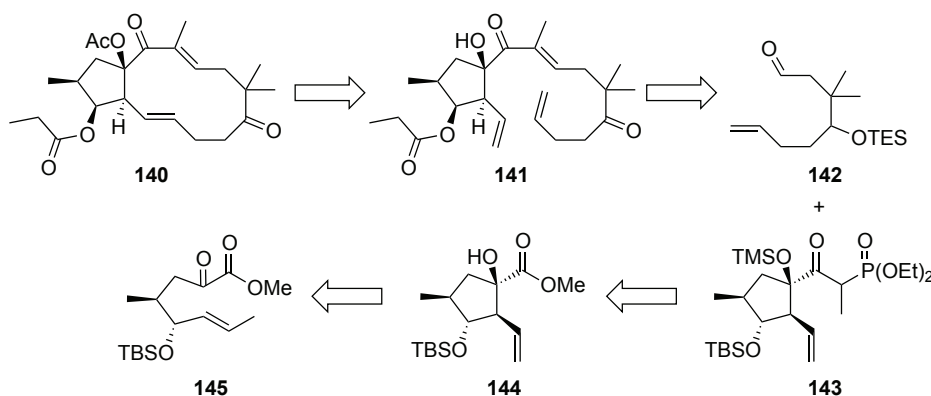
Reaction of TMS-protected triflate **134** with diethyl-ethyl phosphonate provided β -keto phosphonate **127**, which was directly esterified with acid chloride **127** under the influence of FeCl_3 to afford **135**, the precursor for the spirofuranone constructing HWE-reaction. Treatment with sodium hydride gave **125**, which was converted to primary alcohol **136** *via* palladium catalyzed Stille coupling with vinyl stannane **139**, followed by deprotection of the silyl-ether with TBAF. Macrocyclic intermediate **137** was obtained after Swern-oxidation⁷³ to give the corresponding acetylenic aldehyde and deprotonation of the acetylene moiety with LHMDS. Oxidation of the propargylic alcohol in **137**, again under Swern conditions, delivered ynone **138** and final palladium catalyzed hydrogenation followed by isomerization of the undesired *cis*-double bond completed the total synthesis of optically active (+)-jatrophone (**1**, Scheme 23).⁶⁸



Scheme 23. Total synthesis of (+)-jatrophone (**1**).

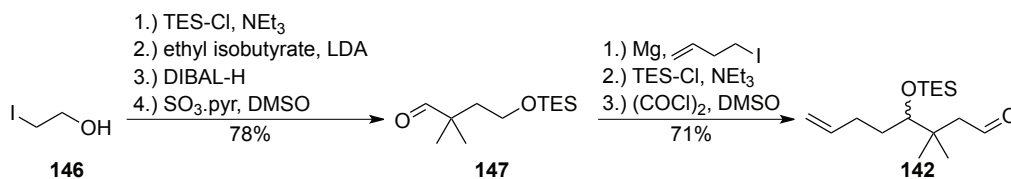
1.4.5. Total synthesis of the norjatrophone diterpene (–)-15-acetyl-3-propionyl-17-norcharaciol by Hiersemann *et al.*⁷⁴

Hiersemann *et al.* published the total synthesis of the unnatural norjatrophone diterpene, (–)-15-acetyl-3-propionyl-17-norcharaciol (**140**).^{74, 75} The retrosynthetic analysis of the target compound is outlined in Scheme 24. The twelve-membered macrocycle was intended to be closed *via* a ring closing metathesis (RCM) reaction of diene **141**, which could be established from aldehyde **142** and phosphonate **143** through a HWE reaction. The preparation of the highly functionalized five-membered ring fragment **144** was envisioned to proceed *via* an intramolecular thermal ene-reaction of α -keto ester **145**.



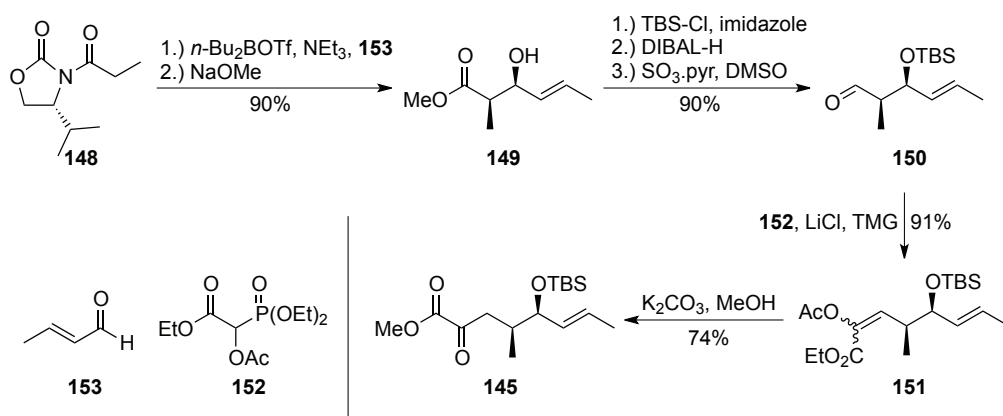
Scheme 24. Retrosynthetic analysis of (–)-15-acetyl-3-propionyl-17-norcharaciol (**140**).

2-Iodo-ethanol (**146**) was protected as a TES-ether, alkylated with ethyl isobutyrate and a subsequent reduction/oxidation sequence delivered aldehyde **147** in 78% overall yield. Silylation of the intermediate secondary alcohol, obtained after Grignard reaction with homoallyl iodide, was followed by the exposure to Swern oxidation conditions, which resulted in the isolation of aldehyde **142** *via* cleavage of the primary TES-group and subsequent oxidation of the alcohol.



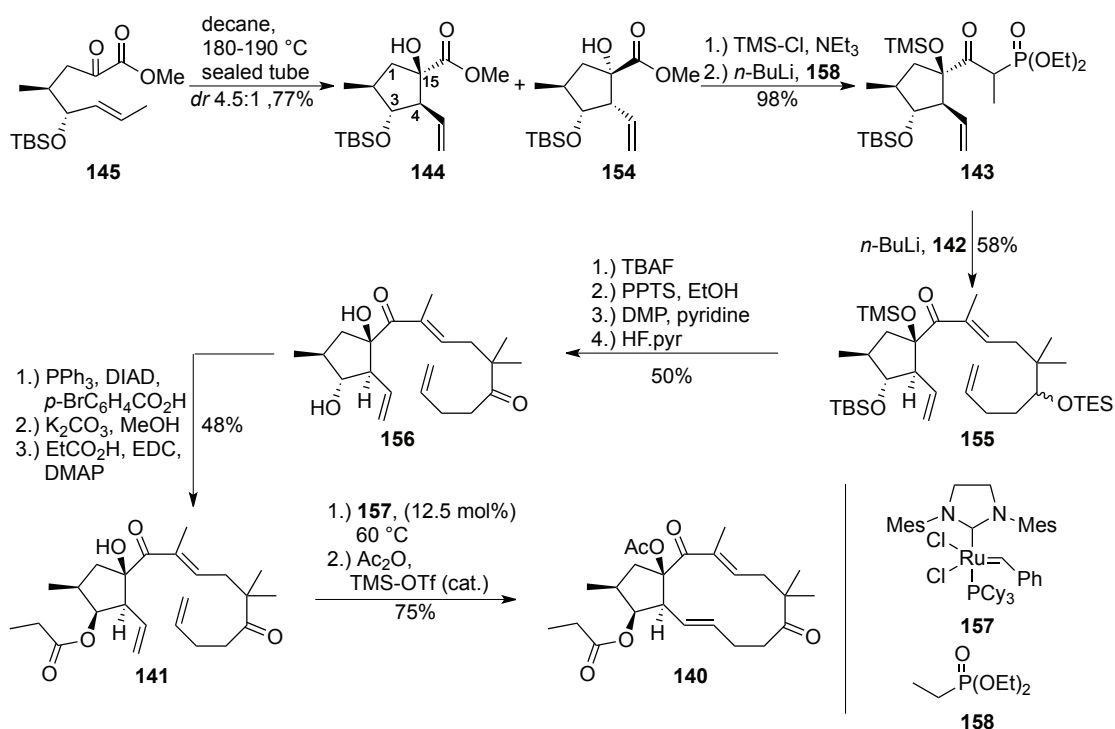
Scheme 25. Synthesis of aldehyde (**142**).

The preparation of α -keto ester **145**, started with an Evans aldol reaction⁷⁶ of chiral oxazolidinone **148** and aldehyde **153**. Removal of the auxiliary allowed the isolation of methyl ester **149**. Next, TBS-protection of the free hydroxyl group was followed by a reduction/oxidation sequence, which resulted in the formation of aldehyde **150**. A HWE-reaction using phosphonate **152** and 1,1,3,3-tetramethylguanidin (TMG) as base afforded intermediate **151**, which was subsequently converted to the desired α -keto ester **145** *via* cleavage of the acetate group.⁷⁵



Scheme 26. Synthesis of α -keto ester **145**.

The thermal intramolecular ene-reaction provided the corresponding cyclopentanes **144** and **154** in a 4.5:1 diastereomeric ratio, favoring the desired isomer **144**. The exclusive formation of the 4,15-*cis* configuration (jatrophone numbering) was observed.⁷⁷ Protection of the tertiary alcohol with TMS-chloride was followed by a Claisen-type condensation with diethyl ethylphosphonate (**158**) delivering β -keto ester **143**, which was further deprotonated with $n\text{BuLi}$ and allowed to react with aldehyde **142** to give α,β -unsaturated ketone **155**.



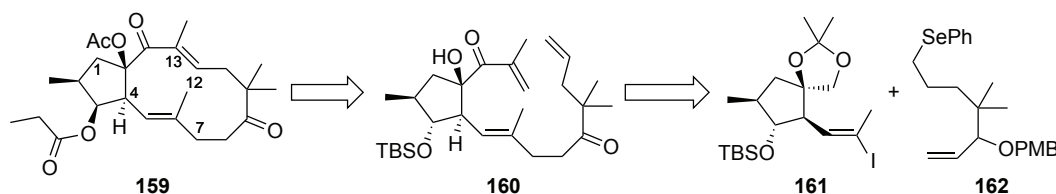
Scheme 27. Total synthesis of **140**.

Next, the tertiary TMS- and the secondary TES-ethers were cleaved consecutively followed by oxidation of the resulting secondary alcohol with Dess-Martin periodinane and deprotection of the remaining silyl-ether employing $\text{HF}\cdot\text{pyridine}$, to afford diene **156**. The synthesis was continued by inversion of the C-3 stereocenter *via* a Mitsunobu reaction^{78, 79}, delivering the corresponding benzoate, which was subsequently saponified to the free alcohol. A final regioselective acylation completed the sequence toward the RCM-precursor **141**. The RCM-reaction, using the second

generation Grubbs catalyst⁸⁰ (**157**), proceeded successfully and supplied exclusively the *E*-configured double bond isomer. Finally, acetate protection of the free tertiary alcohol functionality completed the synthesis of (–)-15-acetyl-3-propionyl-17-norcharaciol (**140**).⁷⁵

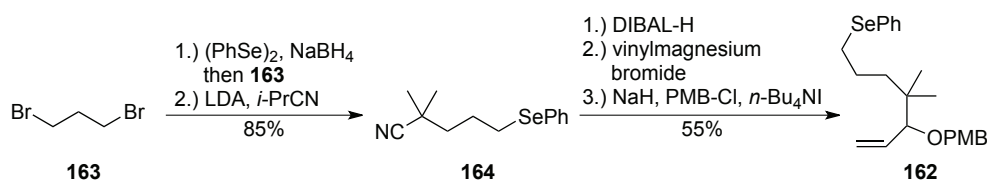
1.4.6. Total synthesis of (–)-15-*O*-acetyl-3-*O*-propionylcharaciol by Hiersemann *et al.*⁸¹

In close analogy to the synthesis of the unnatural norjatrophone **140**, described above, Hiersemann *et al.* reported the first enantioselective total synthesis of (–)-15-*O*-acetyl-3-*O*-propionylcharaciol (**159**), a jatrophone diterpene isolated from *Euphorbia characias*.⁸¹ As outlined in the retrosynthetic analysis given in Scheme 28, the twelve-membered macrocycle will be dissected between C-12 and C-13 and again constructed *via* an RCM-reaction from diene **160**. One of the key operations of the synthesis, the fusion of vinyl iodide **161** and alkene **162**, will be established through a palladium catalyzed Suzuki-Miyaura cross coupling⁸² reaction.



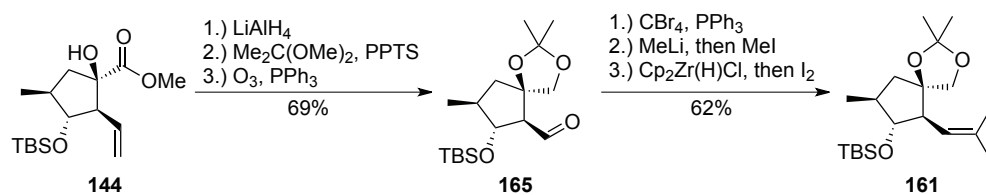
Scheme 28. Retrosynthetic analysis of (–)-15-*O*-acetyl-*O*-propionylcharaciol (**159**).

An *in situ* generated phenylselenide anion equivalent was allowed to react with dibromide **163**, followed by alkylation with deprotonated isobutyronitrile to afford intermediate **164**. Subsequent reduction of the nitrile moiety to give the corresponding aldehyde, a Grignard reaction with vinylmagnesium bromide and PMB-protection of the resulting secondary alcohol provided alkene **162** in 55% overall yield (Scheme 29).



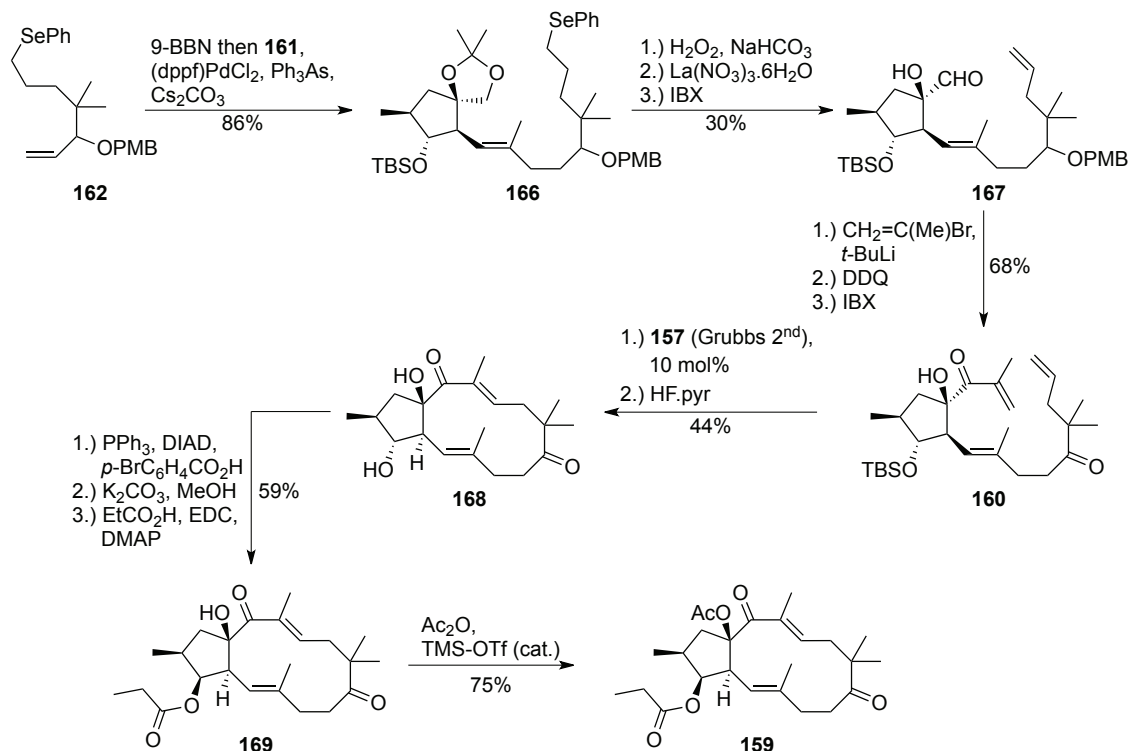
Scheme 29. Synthesis of alkene **162**.

The five-membered ring intermediate **144** (the synthesis thereof is described in section 1.4.5) was reduced using lithium aluminum hydride to give the corresponding diol, which was protected as acetonide with 2,2-dimethoxypropane and further oxidative cleavage of the double bond resulted in the formation of aldehyde **165**. Following the Corey-Fuchs protocol^{83, 84}, **165** was first converted to the corresponding dibromoolefin with CBr_4 and PPh_3 followed by the treatment with methyl lithium to form the terminal alkyne, which was *in situ* alkylated with methyl iodide. Finally, vinyl iodide **161** was synthesized *via* hydrozirconation using the Schwartz reagent^{85, 86} and exposure of the intermediate vinyl zirconium species to iodide.



Scheme 30. Preparation of vinyl iodide **161**.

Alkene **162** and vinyl iodide **161** were connected *via* a Suzuki-Miyaura cross coupling to afford highly advanced intermediate **166** in excellent yield. The synthesis was continued by oxidation of the selenide with hydrogen peroxide and elimination of the resulting selenoxide. Deprotection of the acetonide protection group under mild Lewis acidic conditions to avoid additional cleavage of the TBS-group and additional oxidation using IBX allowed the isolation of α -hydroxy-aldehyde **167**. Ketone **160**, precursor for the RCM-reaction, was obtained through nucleophilic attack of **167** with isopropenyl lithium followed by the cleavage of the PMB group and oxidation of the free secondary alcohol. The twelve-membered macrocycle was closed *via* an RCM reaction, mediated by Grubbs' 2nd generation catalyst, exclusively affording the *trans*-connected double-bond isomer. Deprotection of the remaining TBS-group delivered diol **168**, which already features the complete jatrophane framework. Mitsunobu reaction to introduce the desired stereocenter at C-3, subsequent transesterification and final acylation provided tertiary alcohol **169**, which was finally converted to (–)-15-*O*-acetyl-3-*O*-propionylcharaciol (**159**) through the introduction of the missing acetate group.

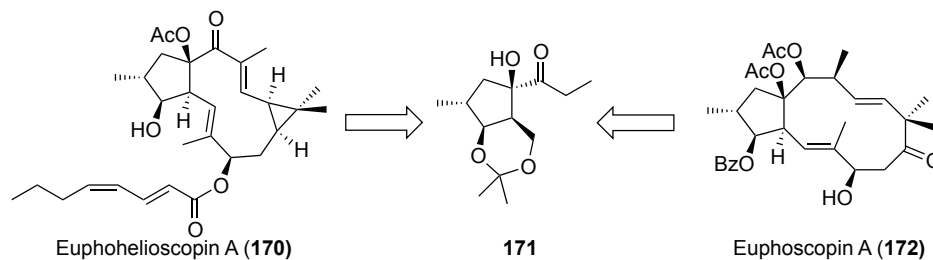


Scheme 31. Completion of the total synthesis of (–)-15-*O*-acetyl-3-*O*-propionylcharaciol (**159**).

1.5. PARTIAL SYNTHESISES – SYNTHESIS OF FIVE-MEMBERED RING INTERMEDIATES

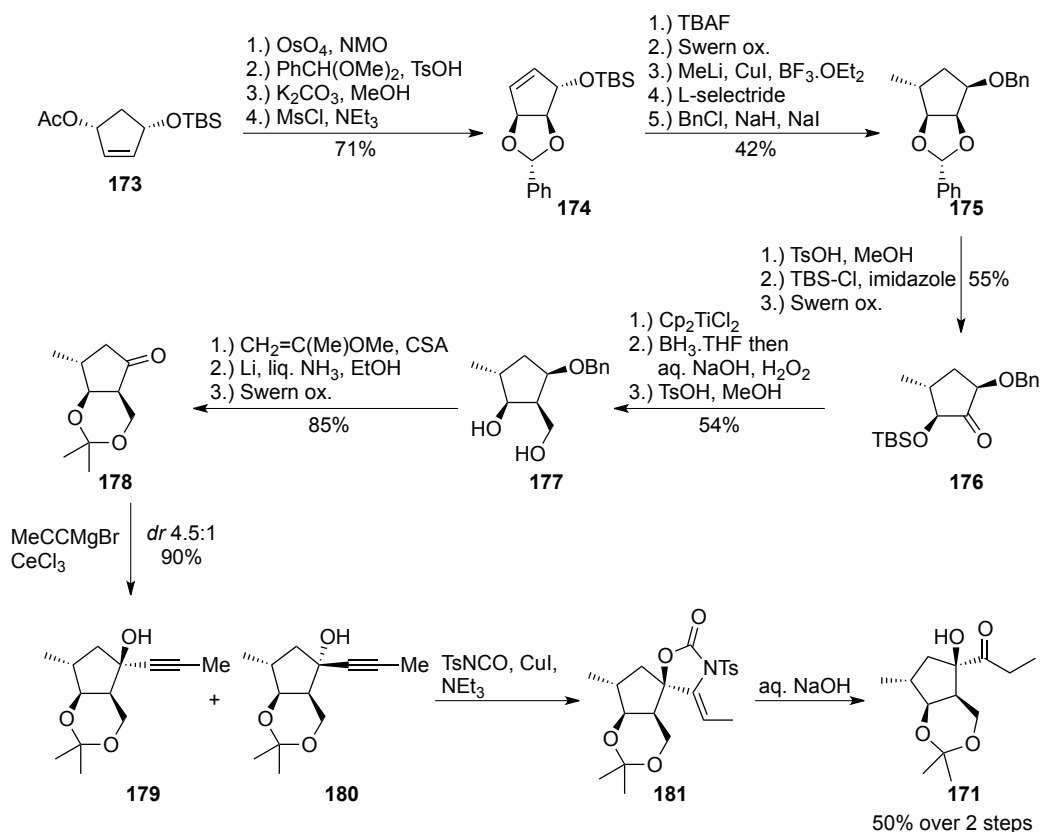
1.5.1. Synthesis of a cyclopentane fragment by Yamamura *et al.*⁸⁷

The synthesis of the cyclopentane core (**171**), as found in euphohelioscopin A (**170**) and euphoscopin A (**172**), was published by Yamamura *et al.* in 1993 (Scheme 32).⁸⁷



Scheme 32. Retrosynthetic analysis of the cyclopentane fragment **171**.

Cyclopentene **173** was oxidized using OsO_4 and the resulting diol was protected as a benzylidene acetal. Cleavage of the acetate group was followed by a mesylation/elimination sequence resulting in the isolation of intermediate **174**. The secondary alcohol, obtained after TBS-deprotection with TBAF, was oxidized under Swern oxidation conditions. The synthesis was continued by 1,4-addition of a methyl-cuprate species, substrate-controlled reduction with L-selectride and benzyl-protection of the intermediate secondary alcohol to afford **175**.

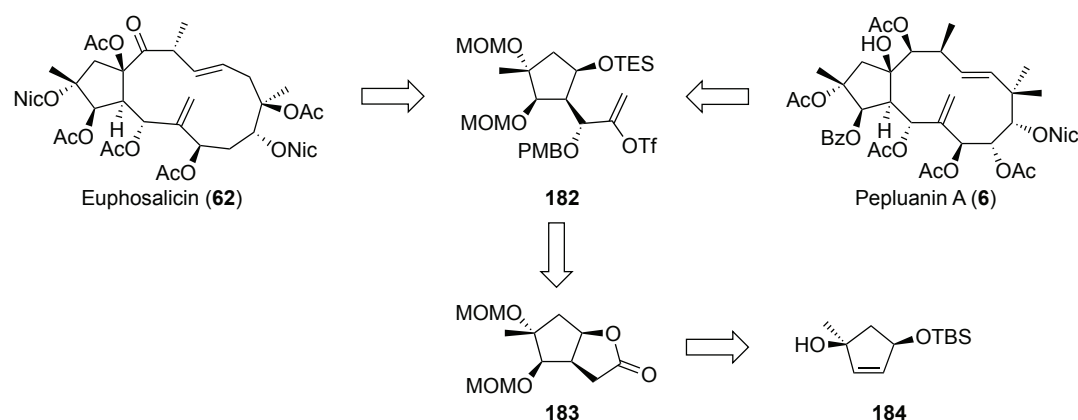


Scheme 33. Synthesis of the cyclopentane fragment **171**.

Next, deprotection of the benzylidene acetal, regioselective TBS-protection of the sterically less hindered hydroxyl group and Swern oxidation allowed the isolation of ketone **176**. Petasis methylenation⁸⁸ of **176**, subsequent hydroboration and additional deprotection of the remaining TBS-group delivered diol **177**, which was protected as an isopropylidene acetal in the next step. Cleavage of the benzyl group and oxidation of the corresponding secondary alcohol under Swern conditions furnished ketone **178**. Substrate controlled addition of propynylmagnesium bromide provided the propynyl-adducts **179** and **180** as a 4.5:1 mixture of diastereomers, in favor of the desired isomer **179**. Finally, the introduction of the ethyl-ketone moiety was accomplished *via* the cyclic carbamate **181**, which was subsequently hydrolyzed to the desired five-membered ring fragment **171**.

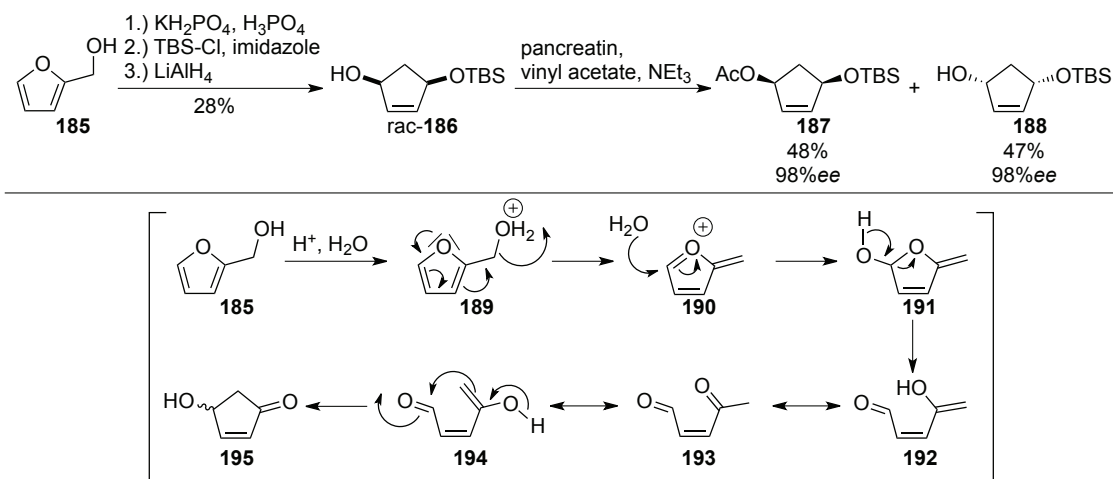
1.5.2. Synthesis of the cyclopentane fragment of euphosalicin and pepluanin A by Mulzer *et al.*⁸⁹

Mulzer *et al.* published a highly substrate-controlled synthesis of the cyclopentanyl vinyl triflate **182**, an advanced synthetic target toward the total synthesis of euphosalicin and pepluanin A.^{89, 90} The authors intended to prepare vinyl triflate **182** from intermediate **183** *via* stereoselective α -hydroxylation and opening of the lactone. Cyclopentene **184** was elaborated as a suitable precursor for bicyclic lactone **183** (Scheme 34).



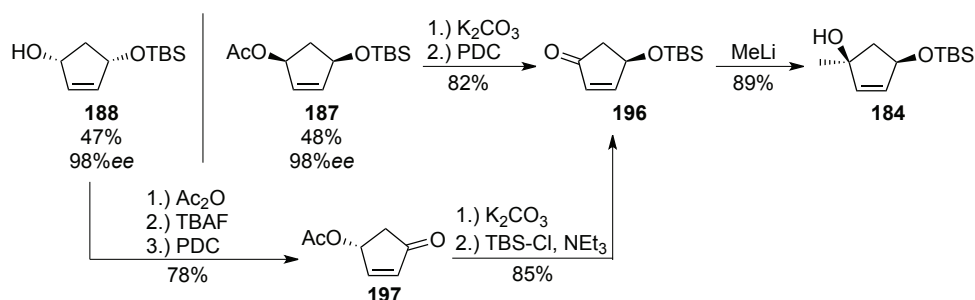
Scheme 34. Retrosynthetic analysis of cyclopentane fragment **182**.

The synthesis started with the conversion of furfuryl alcohol (**185**) to the racemic secondary alcohol **186** through a three-step procedure. The initial acid mediated furfuryl alcohol rearrangement affording alcohol **195** proceeds through the mechanism outlined in Scheme 35. Protection of the hydroxyl group as a TBS-ether and reduction with lithium aluminum hydride allowed the isolation of the racemic intermediate **186**. The kinetic resolution of rac-**186** using the enzyme pancreatin and vinyl acetate as the acylating agent delivered acetate **187** and secondary alcohol **188** with excellent enantiomeric purity.⁹¹



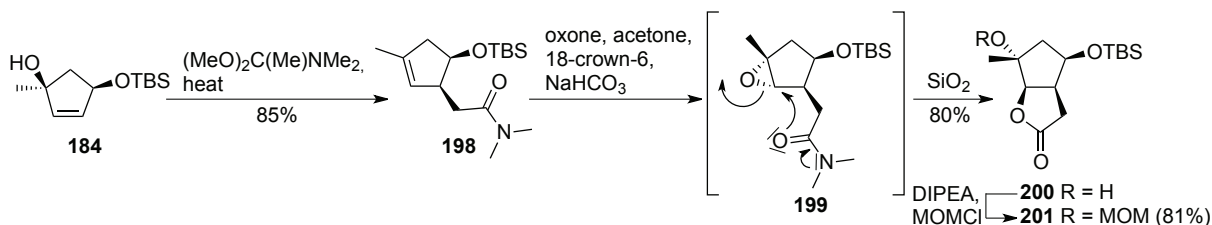
Scheme 35. Synthesis of the cyclopentene fragments **187** and **188**.

Deprotection of the acetate group in **187** and oxidation of the intermediate secondary alcohol resulted in the isolation of ketone **196**. Transformation of alcohol **188**, obtained as second product after the kinetic resolution, to ketone **196** was accomplished *via* intermediate **197** in five steps. Finally, substrate-controlled addition of methyllithium, attacking from the opposite side of the TBS-group provided tertiary alcohol **184** (Scheme 36).



Scheme 36. Preparation of enantiomerically pure cyclopentene **184**.

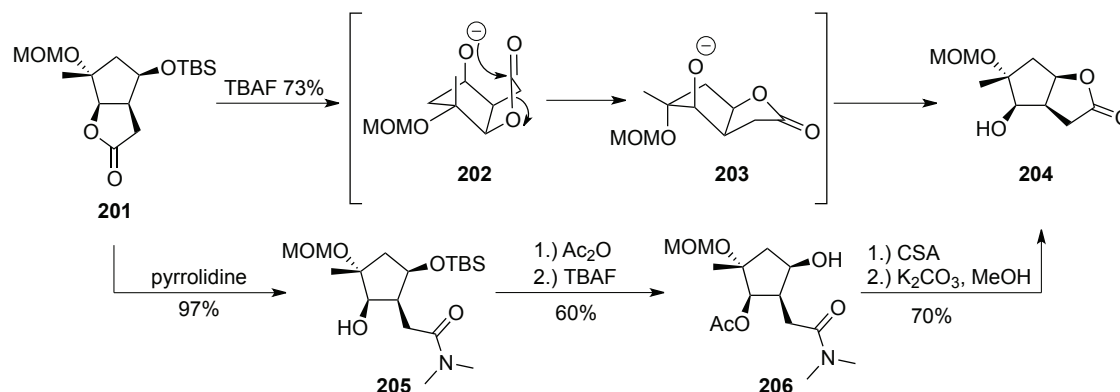
In the following step, an Eschenmoser-Claisen rearrangement⁹² provided amide **198** in excellent yield. The treatment with dimethyldioxirane (DMDO) delivered epoxide **199**, which was subsequently converted to intermediate **200** *via* flash chromatography mediated intramolecular epoxide-opening lactonization. Subsequent MOM-protection of the resulting tertiary alcohol afforded lactone **201**.



Scheme 37. Preparation of bicyclic lactone **201**.

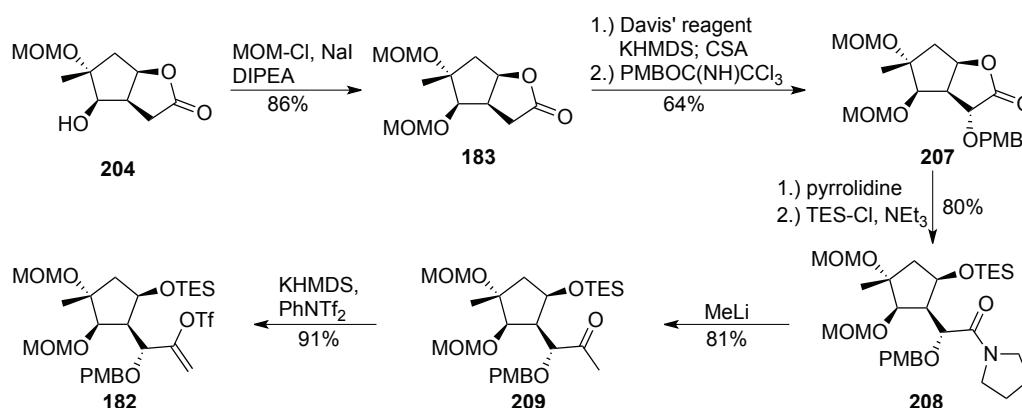
Initially, a five-step sequence was elaborated for the synthesis of secondary alcohol **204** (Scheme 38). The conversion to amide **205** through opening of the lactone with pyrrolidine, was followed by acetate protection of the free hydroxyl functionality and deprotection of the TBS-group with

TBAF. Amide **206** was subsequently utilized in an intramolecular lactonization reaction and final cleavage of the acetate protecting group afforded secondary alcohol **204**. The authors could impressively optimize the described sequence by the application of a single-step transformation. The treatment of lactone **201** with TBAF at room temperature induced TBS-deprotection and translactonization in one step. Mechanistically, alkoxide **202**, which is formed in the desilylation reaction, adopts the appropriate conformation for the intramolecular lactonization reaction.



Scheme 38. Synthesis of lactone **204**.

The final sequence toward the highly substituted five-membered ring fragment **182** commenced with the protection of the free alcohol functionality in lactone **204** as a MOM-ether. The last missing hydroxyl functionality was introduced from the convex face of the *cis*-fused bicyclic lactone by α -hydroxylation using the Davis' reagent (2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine)⁹³. Further PMB-protection provided intermediate **207** and methyl ketone **209** could be prepared *via* amide **208** in a three-step sequence. The lactone moiety was opened with pyrrolidine and TES-protection of the resulting secondary alcohol was carried out before addition of methyl lithium completed the sequence. Finally, kinetically controlled formation of a vinyl triflate concluded the highly substrate-controlled synthesis of the cyclopentane fragment **182**.⁹⁰

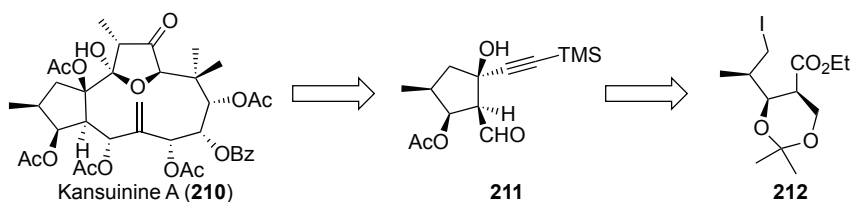


Scheme 39. Total synthesis of cyclopentanyl vinyl triflate **182**.

1.5.3. Synthesis of the cyclopentane fragment of Kansuine A by Uemura *et al.*⁹⁴

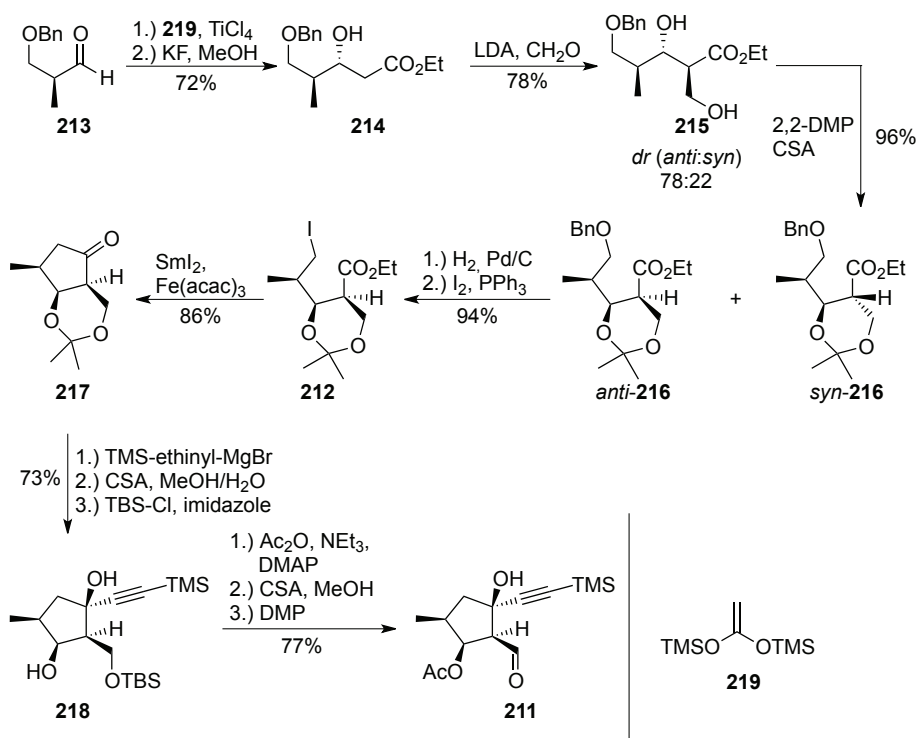
Uemura *et al.* published the synthesis of the highly functionalized cyclopentane fragment **211** on their route toward the total synthesis of kansuine A (**210**).⁹⁴ They envisaged a samarium diiodide

mediated intramolecular nucleophilic acyl substitution of δ -halo ester **212** as their ring closing reaction (Scheme 40).



Scheme 40. Retrosynthetic analysis of Uemura's cyclopentane fragment (211**).**

The sequence was initiated with a Mukaiyama aldol reaction of ethyl-*C,O*-bis(trimethylsilyl)ketene acetal (**219**) and benzyl-protected aldehyde **213**, followed by TMS-deprotection to give β -hydroxy ester **214**. A second aldol reaction using formaldehyde and LDA afforded diol **215** in a 78:22 mixture of diastereomers and further acetal protection provided *anti*- and *syn*-**216** in excellent yield. Reductive cleavage of the benzyl group and conversion of the resulting primary alcohol to iodide **212** under Appel reaction conditions⁹⁵ was followed by the crucial samarium diiodide induced ring closing reaction, delivering ketone **217**. The next sequence, substrate controlled addition of TMS-ethynylmagnesium bromide, deprotection of the isopropylidene group and protection of the primary alcohol allowed the isolation of intermediate **218**. Finally, acetate protection of the remaining free secondary hydroxyl group, cleavage of the TBS-ether and subsequent oxidation with Dess-Martin periodinane concluded the synthesis of the advanced cyclopentane fragment **211**.

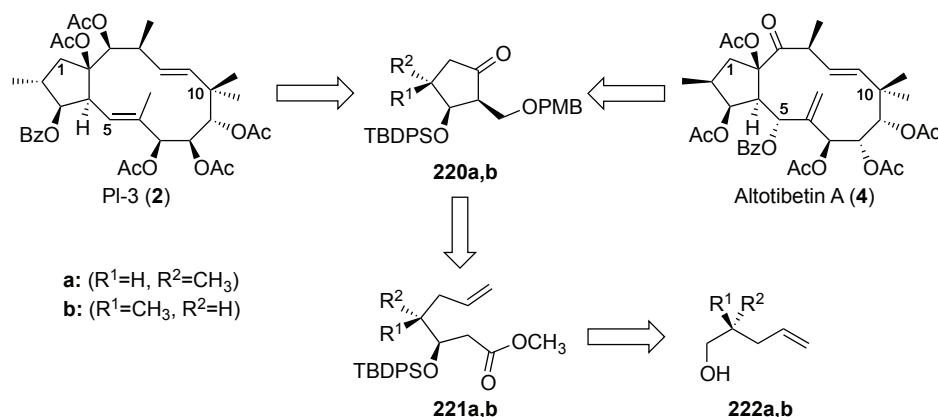


Scheme 41. Synthesis of cyclopentane fragment **211.**

1.5.4. A general access to cyclopentane fragments of jatrophone diterpenes by Rinner *et al.*⁹⁶

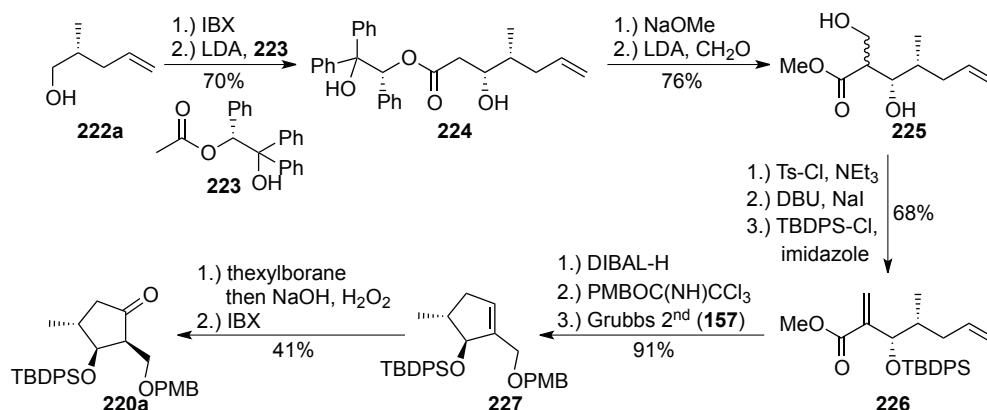
A general approach for the synthesis of the five-membered ring part of jatrophone diterpenes giving access to various natural products such as Pl-3 (**2**) or altotibetin A (**4**) was reported by our group in 2009.⁹⁶ Cyclopentanones **220a** and **220b** were established as advanced intermediates for further application in the total synthesis of different jatrophone diterpenes (Scheme 42). The approach allows the flexible introduction of the stereocenters at C-2 and C-3 (jatrophone numbering) of the jatrophone skeleton. The decisive idea behind this variable access is, that a methyl group at C-2, present in an either *R* or *S* configuration, as well as an oxygen functionality at C-3 are common structural motifs of the cyclopentane fragment of jatrophone diterpenes.

The intended key-step in the synthesis is an RCM-reaction to close the five-membered ring. The intermediates **220a** and **220b** could be synthesized starting from primary alcohols **222a** or **222b** via a C-2 elongation.



Scheme 42. Retrosynthetic analysis of cyclopentanones **220a** and **220b**.

The synthesis of cyclopentanone **220a** is outlined in Scheme 43. Stereoselective C-2 elongation using (*R*)-HYTRA (**223**) as chiral auxiliary^{97, 98} was achieved after oxidation of primary alcohol **222a**. The cleavage of the auxiliary in **224** and an aldol reaction with formaldehyde delivered diol **225**, which was converted to α,β -unsaturated ester **226** through a tosylation/elimination sequence followed by TBDPS-protection.



Scheme 43. Synthesis of cyclopentanone **220a**.

Reduction of the methyl ester and subsequent PMB-protection gave the precursor for the RCM reaction using Grubbs 2nd generation catalyst (**157**). Cyclopentene containing intermediate **227**, formed in excellent yield, was further converted to the corresponding secondary alcohol by a hydroboration/oxidation sequence and, finally, cyclopentanone **220a** was provided after IBX oxidation in 12 steps starting from chiral **222a**.

2. AIM OF THE SYNTHETIC WORK

The present Ph.D. thesis is divided into two parts. The first part is dealing with a general synthetic access to the eastern part of jatrophone diterpenes while in the second part the synthetic efforts toward the total synthesis of PI-4 are described.

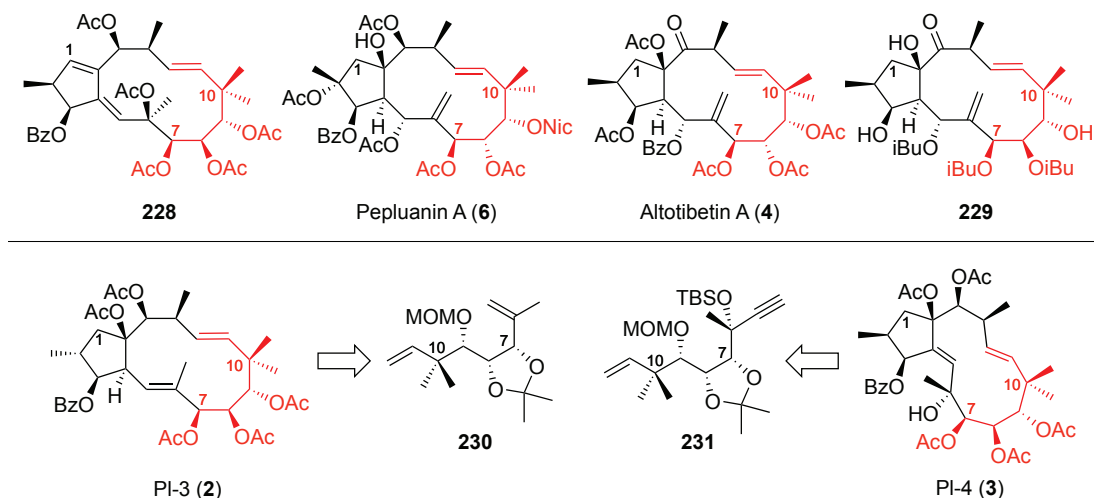
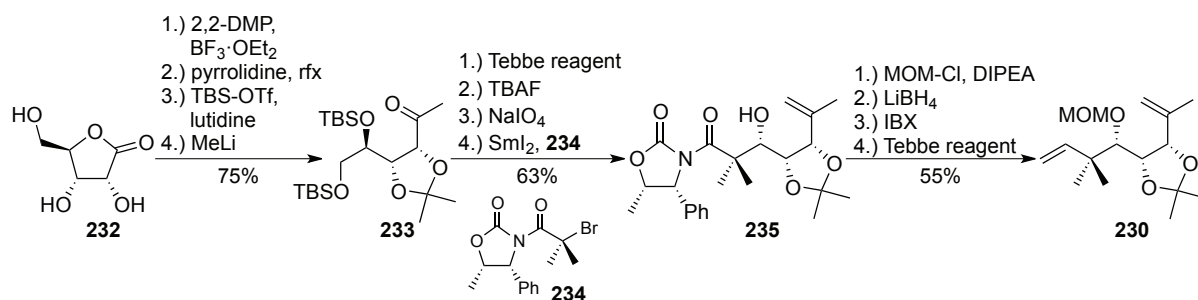


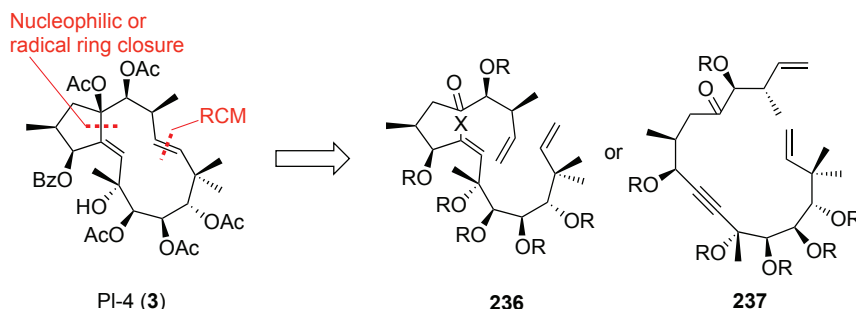
Figure 12. Recurring substitution pattern of the eastern fragment of different jatrophone diterpenes.

Due to the recurring stereochemical substitution pattern of the eastern fragment (C7–12) in various jatrophone diterpenes, including PI-3 and PI-4 (Figure 12), we have established a general sequence for the synthesis of this part of the macrocycle. The intermediates **230** and **231**, precursors within our retrosynthetic considerations, were both synthesized in a diastereoselective manner. The sequence for the preparation of the eastern fragment of PI-3 is outlined in Scheme 44. Key step in the preparation of **230** is a samarium diiodide mediated Reformatsky reaction, which works exclusively *via* stereochemical control of the chiral auxiliary. The application of D-ribose (**232**) as starting material for the preparation of **230** offers the advantage of acquiring stereochemical information from the chiral pool. Individual jatrophone diterpenes often only differ in the stereochemistry of the methyl and hydroxyl groups while the substitution pattern remains highly similar. Therefore, the utilization of different sugars as starting materials and the application of the enantiomeric chiral auxiliary (*ent*-**236**) in the Reformatsky reaction grants access to different stereochemical substitution patterns within the eastern fragment of jatrophone diterpenes.⁷



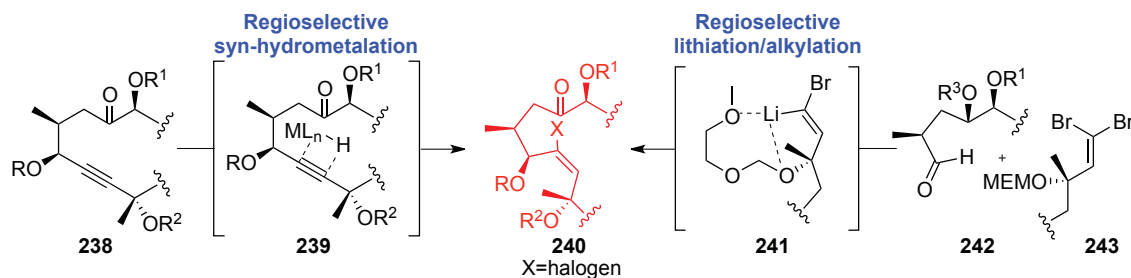
Scheme 44. Synthesis of the eastern fragment of PI-3.

As already mentioned above, the second part of this thesis is focusing on synthetic studies toward the total synthesis of the jatrophone diterpene PI-4. The aim of our strategies is a late stage closure of both rings, present in the natural product (Scheme 45). The 12-membered macrocycle should be closed *via* an RCM-reaction in all our approaches. Different ring closing reactions would be conceivable, for the preparation of the cyclopentane ring, leading to highly advanced intermediates **236** and **237**. On the one hand, starting from vinyl halide **236** the closure of the five-membered ring could be achieved either by a nucleophilic reaction *via* lithiation of the vinyl halide, an NHK-coupling reaction or a SmI_2 -induced radical ring closing reaction. On the other hand, regarding ynone **237** as the cyclization precursor, the five-membered ring could be directly formed through the generation of a ketyl-radical, using SmI_2 , which attacks the internal alkyne in a five-*exo-dig* ring closing reaction.⁸



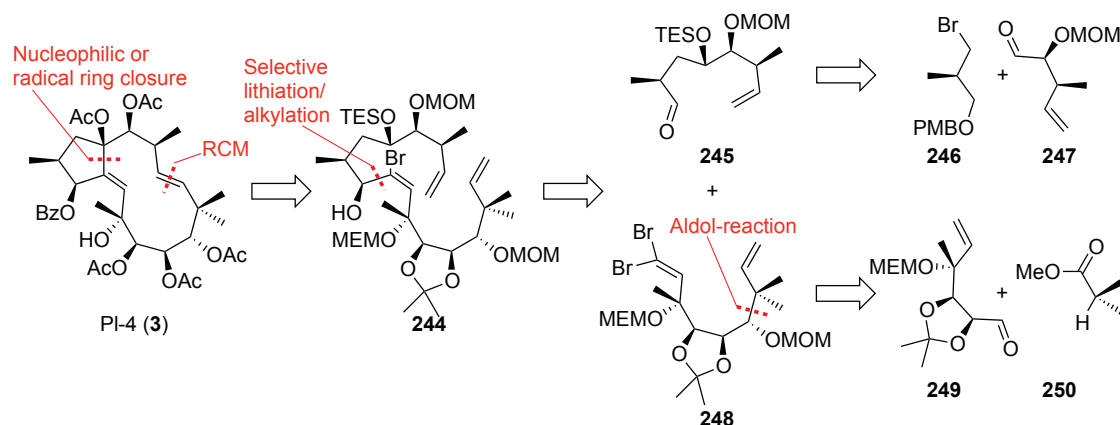
Scheme 45. Retrosynthetic analysis of PI-4.

Two general strategies for the preparation of vinyl-bromide **236** were pursued and are outlined in Scheme 46. Either a regioselective *syn*-hydrometalation of ynone **238** or a lithiation/alkylation sequence of aldehyde **242** and dibromide **243** *via* a chelating, regioselective transition state, were considered.⁸



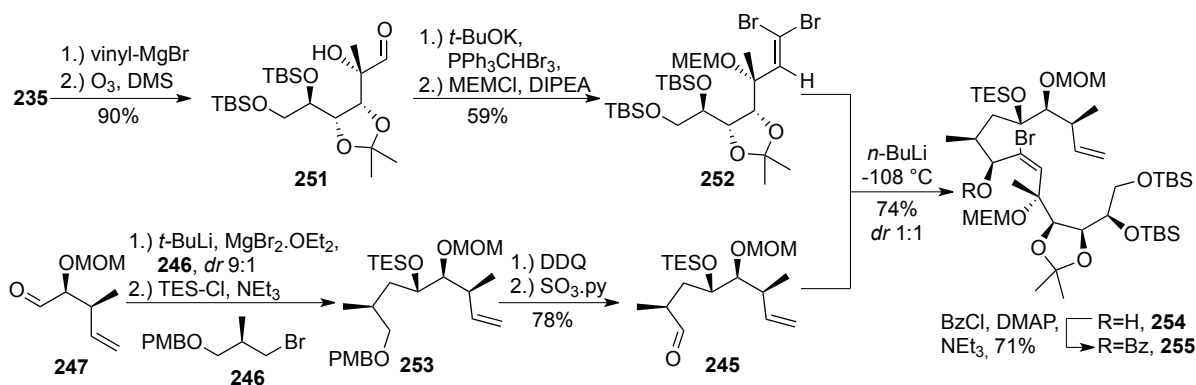
Scheme 46. General considerations for the synthesis of internal vinyl halide **240**.

Unfortunately, despite intense experimentation the hydrometalation as well as the direct cyclization approach *via* a ketyl species (from **237**) were not brought to an end. Therefore, we turned our attention on the dibromide coupling approach.⁹⁹ As outlined in Scheme 47, the northern fragment (aldehyde **245**) should become accessible *via* coupling of Roche-ester derived bromide **246** and aldehyde **247**. Dibromide **248** was intended to be elaborated from aldehyde **249** and methylisobutyrate (**250**). Again, D-ribose could be employed as an ideal and inexpensive starting material from the chiral pool for the preparation of intermediate **249**.



Scheme 47. Retrosynthesis dibromide coupling approach.

Following the route outlined in Scheme 48, the desired coupling partners, dibromide **252** and aldehyde **245**, could be obtained in good overall yield on a multigram scale. The regioselective lithiation/alkylation reaction, key step in the synthesis of **255**, is based on a report by Braun and co-workers.¹⁰⁰ They demonstrated that regioselective alkylation of the more hindered position of a vinyl dibromide could be achieved through coordination of the intermediary formed organolithium species to a chelating MEM-group in α -position to the double bond. We were pleased to find that the lithiation of dibromide **252** proceeded exclusively *via* the anticipated, chelate-controlled transition state and advanced intermediate **254** could be isolated in excellent yield. Unfortunately, the chiral information of the chelating MEM-group in the lithiated species was not transferred to the reaction partner and **254** was obtained in a 1:1 mixture of diastereomers.⁹⁹



Scheme 48. Preparation of vinylbromide **255**.

Summarizing, we could demonstrate that the application of the regioselective lithiation/alkylation reaction of the more hindered bromide in geminal vinyl dibromides is a valuable alternative for the preparation of internal vinyl halides. The protocol allows the selective, stepwise introduction of functionalities, and the preparation of highly substituted alkenes. The remaining bromide constitutes an anchor for further functionalization and closure of the cyclopentane moiety. In future studies, strategies toward the closure of the five-membered ring, as well as the completion of the synthesis, will be elaborated.

Our synthetic efforts toward the total synthesis of Pl-4 can be divided into three related approaches:

- The direct alkyne cyclization approach
- The hydrometalation approach
- The dibromide coupling approach.

Detailed discussion of our retrosynthetic analyses, synthetic achievements and setbacks are content of the following three manuscripts, published in the course of this Ph.D. thesis.

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4. LIST OF PUBLICATIONS

Peer-reviewed Publications

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- Towards the First Total Synthesis of Pl-4 – A Jatrophone Diterpene with Remarkable Multidrug Resistant Reversal (MDR) Effect. 240th National Meeting of the American Chemical Society, Boston, MA, USA, August 22-26, **2010**.
- Synthesis and Biological Evaluation of Novel Combretastatin Analogs. Graz University of Technology, Austria, December 4, **2008**.
- Synthesis of Novel Combretastatin A-4 Analogs. University of Szeged, Hungary, September 16, **2008**.

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5. APPENDIX I

Fürst, R.; Lentsch, C.; Rinner, U., Towards the Total Synthesis of Pl-3: Preparation of the Eastern Fragment through a Diastereoselective SmI_2 -Mediated Reformatsky Reaction. *Eur J Org Chem* **2013**, (12), 2293-2297. DOI: 10.1002/Ejoc.201300148.

Towards the Total Synthesis of PI-3: Preparation of the Eastern Fragment through a Diastereoselective SmI_2 -Mediated Reformatsky Reaction

Rita Fürst,^[a] Christoph Lentsch,^[a] and Uwe Rinner*^[a]

Keywords: Natural products / Terpenoids / Samarium / Diastereoselectivity / Multidrug resistance

The jatrophone diterpene PI-3, isolated in 2003 from *Euphorbia platyphyllos*, is a structurally complex natural product with highly promising biological properties that include pronounced antiproliferative activity and the inhibition of the efflux-pump activity of multidrug resistance p-glycoprotein. Herein, the synthesis of the eastern fragment of PI-3 is outlined. The target compound is synthesized in nine synthetic

operations in good overall yield, starting from readily available D-ribose. The key step in the preparation of the eastern part of PI-3 is a diastereoselective SmI_2 -mediated Reformatsky reaction. The proposed route is highly flexible and could also be applied to the synthesis of structurally related jatrophone diterpenes.

Introduction

The genus *Euphorbia*, a member of the Euphorbiaceae plant family, is one of the largest genera among flowering plants comprising more than 2000 species. *Euphorbia* plants, also known as spurges, are endemic in tropical and subtropical regions as well as in temperate climate zones. Several members are in cultivation and are of great economic importance. For example, the Pará rubber tree (*Hevea brasiliensis*) serves as a source of natural rubber, whereas Cassava (*Manihot esculenta*) is an important annual crop that is rich in carbohydrates. Other members, such as poinsettia (*Euphorbia pulcherrima*), are cultivated for their appealing nature.

Because of their pronounced biological activities, spurges have been common ingredients in traditional herbal folk medicine, and they are mainly used in the treatment of cancerous conditions, swellings, and warts.^[1] The milky sap (latex) is a common attribute of members of the Euphorbiaceae plant family. It contains a large number of structurally diverse diterpenes, which are responsible for the application of spurges in traditional phytotherapy.^[2] Several of these diterpenes were also identified as highly active inhibitors of the adenosine-5'-triphosphate (ATP)-dependent efflux pump p-glycoprotein, which is responsible for multidrug resistance in cancer.^[3] Given that resistance to prevalent drugs is one of the major drawbacks in the development of cancer therapeutics, progress in the synthetic prepa-

ration of *Euphorbia* diterpenes is also of medicinal importance.

Chemical interest in the biologically active ingredients of the genus *Euphorbia* started with the isolation of jatrophone by Kupchan in 1970.^[4] Since then, numerous diterpenes of the jatrophone, tiglane, ingenane, and lathyrane frameworks have been isolated and, to some extent, evaluated for their biological activity.^[2] Despite their challenging structural features, only few synthetic efforts towards these fascinating natural products have been reported to date.^[5]

PI-3 (**1**) was isolated by Hohmann and co-workers from *Euphorbia platyphyllos* in 2003.^[6] As outlined in Figure 1, jatrophone diterpenes are characterized by a highly functionalized *trans*-bicyclo[10.3.0]pentadecane framework. Individual diterpenes often only differ in the stereochemical pattern of the methyl and hydroxy groups, whereas the substitution pattern remains highly similar.

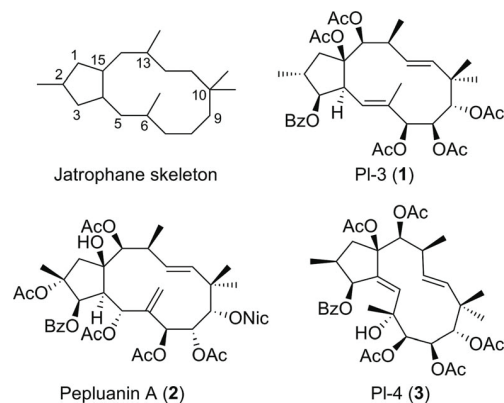


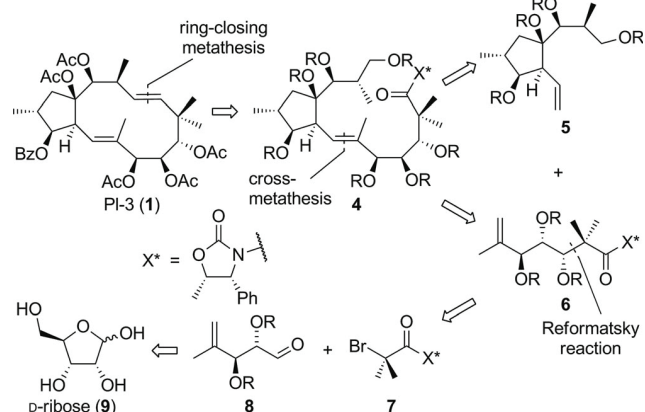
Figure 1. Jatrophone skeleton and representative jatrophone diterpenes.

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The retrosynthetic analysis is shown in Scheme 1. The final operation in the synthesis of PI-3 is a metathesis reaction to close the macrocyclic ring, whereas advanced intermediate **4** should become available from cyclopentane **5** and alkene **6** through cross-metathesis. The key step in the preparation of the eastern part of PI-3 is a diastereoselective SmI_2 -mediated Reformatsky reaction.^[7] In an attempt to take advantage of the chiral pool, D-ribose was identified as an ideal starting material to access alkene **6**. The utilization of different sugars and the application of an enantiomeric chiral auxiliary in the Reformatsky reaction should furthermore allow the facile preparation of related fragments for the synthesis of other jatrophone diterpenes.

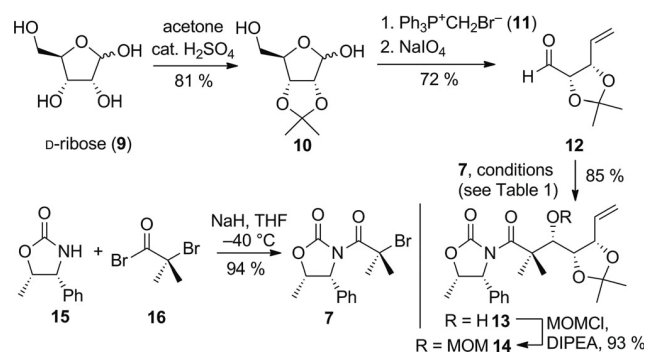


Scheme 1. Retrosynthetic analysis.

Recently, we reported the synthesis of the cyclopentane moiety of PI-3 (**1**).^[5h] Herein, we will discuss the preparation of the eastern fragment (i.e., **6**).

Results and Discussion

The first approach towards alkene **6** started with acetone protection of D-ribose (**9**) as outlined in Scheme 2. Initially, we intended to install the alkene moiety required for the cross-metathesis reaction by Tebbe olefination of the corresponding methyl ketone, which should be accessible from terminal alkene **14** after Wacker oxidation. Thus, acetone **10** was allowed to react with Wittig salt **11** before



Scheme 2. Preparation of alkene **14** (DIPEA = *N,N*-diisopropylethylamine).

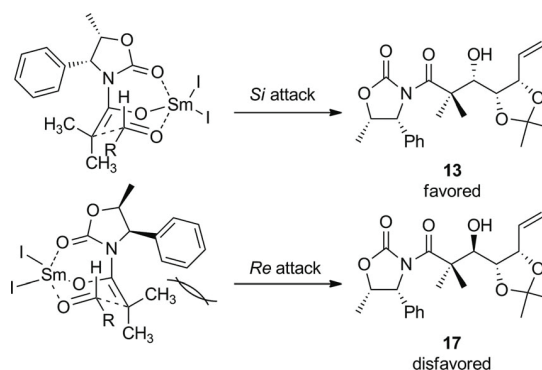
periodate cleavage of the formed diol afforded unsaturated aldehyde **12** in excellent yield.^[8]

With **12** in hand, the crucial diastereoselective Reformatsky reaction could be attempted. According to literature precedents, the *S* configuration at the newly generated stereocenter is expected when bromoacetyl oxazolidinone **7**, readily available on multigram scale upon acylation of oxazolidinone **15** and 2-bromoisobutyryl bromide (**16**), is allowed to react with aldehyde **12**.^[7a,9] Unfortunately, as shown in Table 1, initial attempts with the use of tin^[9,10] and zinc^[11] for the generation of the nucleophile in the Reformatsky reaction resulted in reisololation of the starting material. The desired product, although only in low yield, was first obtained when chromium salts were employed (Table 1, entries 3–6).^[12] Cp_2TiCl (Cp = cyclopentadienyl) has been described to promote Reformatsky reactions,^[13] but we chose to utilize SmI_2 next and were able to isolate oxazolidinone **13** in excellent yield as a single diastereomer (the opposite diastereomer was not observed by NMR spectroscopy), which was further converted into methoxymethyl (MOM)-protected intermediate **14**. The high level of selectivity can be explained by the exclusive formation of a pentacoordinate transition state, as described by Thornton and Pridgen.^[7a,14] Steric repulsion of the auxiliary and presumably the bulky geminal dimethyl group efficiently prevents *Re* attack and forces the system to undergo the desired *Si* attack. The *S*-configured hydroxy group in **13** (Scheme 3) is formed through exclusive stereochemical control of the chiral auxiliary.

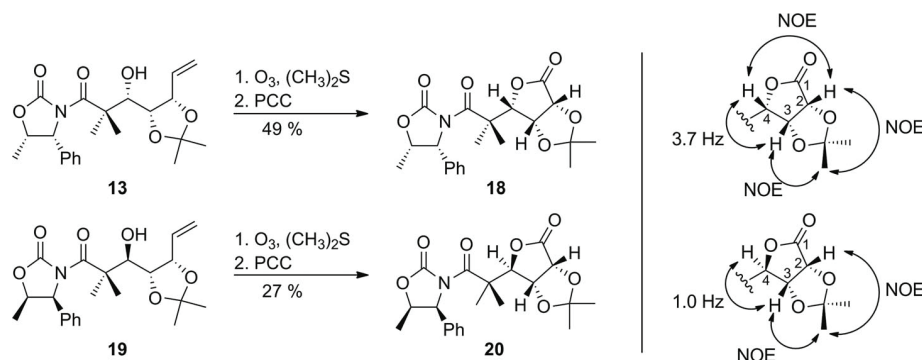
Table 1. Reaction conditions in the diastereoselective Reformatsky reaction.

Entry	Metal and solvents	Temp. [°C]	% Yield of 13
1	SnCl_2 , LiAlH_4 , THF	0 to r.t.	0
2	Zn , THF	0 to r.t.	0
3	CrCl_2 , LiI , THF	r.t.	7
4	CrCl_2 , THF	r.t.	23
5	CrCl_2 , NiCl_2 , THF	r.t.	<10 ^[a]
6	CrCl_3 , LiAlH_4 , THF	r.t.	<10 ^[a]
7	SmI_2 , THF	–78	85

[a] Yield was determined by analysis of the crude product by ^1H NMR spectroscopy.



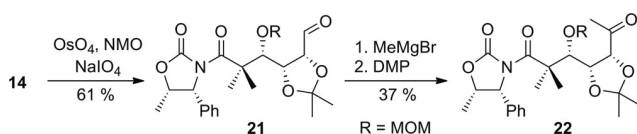
Scheme 3. Transition-state model for the diastereoselective Reformatsky reaction.



Scheme 4. Determination of the stereochemistry.

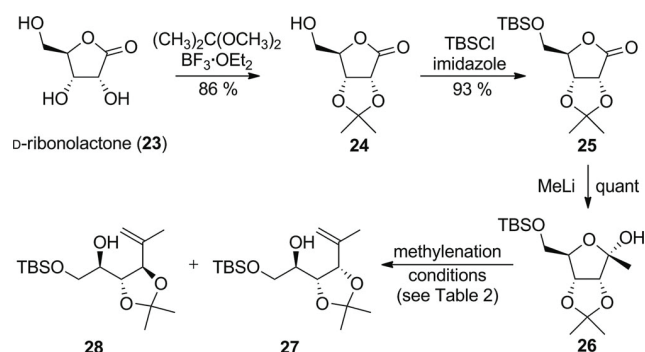
The proposed configuration of the newly installed hydroxy moiety in **13** was unambiguously confirmed by comparison of the coupling constants between H-4 and H-3 in cyclic intermediates **18** and **20**, according to the Karplus correlation and NOESY experiments (Scheme 4). Cleavage of the terminal double bond in **13** and **19**, available upon Reformatsky reaction of **12** with *ent*-**7**, by ozonolysis was followed by pyridinium chlorochromate (PCC) oxidation of the resulting lactol. Whereas the H-4–H-3 coupling constant in **20**, which originated from the alcohol with the *R* configuration, was 1.0 Hz, a value of 3.7 Hz was measured for cyclic intermediate **18**, and thus, the stereochemical configuration of alcohol **13** could be confirmed.

All attempts to convert alkene **14** into methyl ketone **22** through Wacker oxidation failed and only resulted in re-isolation of the starting material. As outlined in Scheme 5, dihydroxylation of the terminal double bond with OsO₄ and periodate cleavage of the resulting diol allowed the isolation of highly unstable aldehyde **21**. However, the conversion of **21** into methyl ketone **22** proved to be troublesome, as addition of the methyl Grignard reagent and subsequent oxidation of the secondary alcohol delivered the desired compound in low and irreproducible yield.

Scheme 5. Preparation of methyl ketone **22** (NMO = *N*-methylmorpholine-*N*-oxide; DMP = Dess–Martin periodinane).

In a modified approach, we intended to install the methyl ketone at an early stage to circumvent the problems discussed above. As shown in Scheme 6, the route started with Lewis acid promoted conversion of D-ribonolactone (**23**) into acetone **24**. Silylation of the primary hydroxy group delivered lactone **25**, which was treated with methyllithium to afford lactol **26** as a masked methyl ketone in quantitative yield as a single diastereomer.^[15] Next, we intended to install the terminal double bond. Methylation of **26** with Tebbe's reagent was unsuccessful, and even at elevated temperature no conversion could be detected (Table 2, entries 1 and 2). Surprisingly, when allowed to react with the methyl Wittig reagent (**11**) under standard reaction conditions in

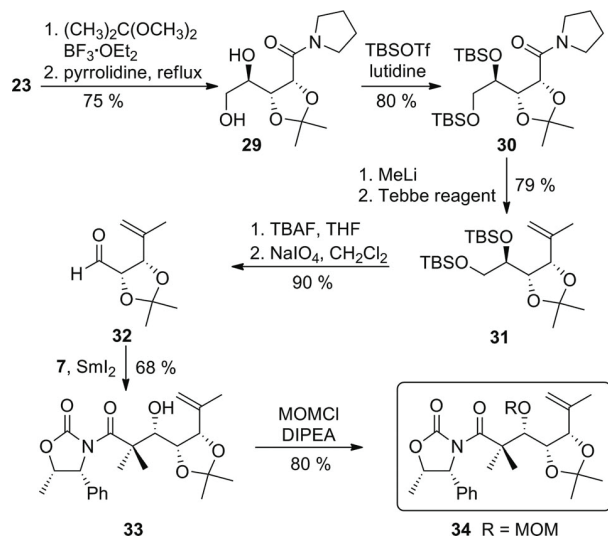
THF with *t*BuOK as the base, α -racemization occurred and a diastereomeric mixture of **27/28** in a 5:1 ratio was isolated in moderate 34% yield. When toluene was used as the solvent, the exclusive formation of desired alkene **27** was observed; however, the isolated yield did not exceed 30%. Several other protocols were investigated: potassium hexamethyldisilazane (KHMDs) in THF afforded exclusively undesired diastereomer **28** (Table 2, entry 7), whereas other bases such as NaH and BuLi resulted in re-isolation of the starting material. As the yield in the methylation reaction could not be further improved, another approach was elaborated.

Scheme 6. Second approach – preparation of alkenes **27** and **28** (TBS = *tert*-butyldimethylsilyl).Table 2. Methylation of lactol **26**.

Entry	Reagent/solvent	Temp. [°C]	Time [h]	% Yield (27/28)
1	Tebbe reagent/THF	0	3	0
2	Tebbe reagent/THF	r.t. to 80	3	0
3	<i>t</i> BuOK/THF ^[a]	0 to r.t.	4	34 (5:1)
4	NaH/DMSO ^[b]	r.t. to 50	12	0
5	NaH/THF ^[c]	–20 to r.t.	12	0
6	<i>n</i> BuLi/THF ^[d]	–78 to r.t.	12	0
7	KHMDs/THF ^[a]	–78 to r.t.	14	13 (<1:99)
8	<i>t</i> BuOK/toluene ^[a]	–78 to r.t.	4	30 (>99:1)

[a] The Wittig salt was deprotonated at 0 °C over 20 min and at r.t. over 1.5 h before **26** was added. [b] NaH was heated in DMSO to 75 °C for 45 min before the Wittig salt was added at 0 °C, and deprotonation was accomplished at r.t. over 20 min. [c] The Wittig salt was deprotonated at r.t. over 2 h. [d] The Wittig salt was deprotonated at –78 °C over 1 h.

In our third approach, protection of D-ribonolactone (**23**) as its acetonide was followed by exposure of the lactone to pyrrolidine at elevated temperature to obtain amide **29** in excellent yield (Scheme 7). Next, silylation of both hydroxy functionalities was followed by addition of methyllithium to deliver the corresponding methyl ketone, which could be smoothly converted into alkene **31** upon reaction with Tebbe's reagent. Removal of both silyl ethers and subsequent oxidative cleavage of the vicinal diol with NaIO₄ delivered aldehyde **32**, the precursor for the crucial diastereoselective Reformatsky reaction. Again, as discussed for the first approach, the desired secondary alcohol was obtained in good yield as a single isomer when a degassed, precooled THF solution of bromide **7** and aldehyde **32** was added to a SmI₂ solution at –78 °C. Final MOM protection delivered advanced intermediate **34** and completed the preparation of the eastern part of PI-3 (**1**).



Scheme 7. Preparation of alkene **34** (TBAF = tetrabutylammonium fluoride).

Conclusions

We have established a general nine-step sequence for the synthesis of the eastern fragment of PI-3. The Reformatsky reaction, described in detail within this manuscript, can be employed in the synthesis of jatrophone diterpenes to establish recurring structural motifs within the eastern part. The application of different carbohydrate derivatives as the starting material in combination with the highly diastereoselective SmI₂-mediated Reformatsky reaction grants access to a variety of structurally related Euphorbiaceae diterpenes. Owing to the diastereoselective control of the chiral auxiliary within the SmI₂-mediated Reformatsky reaction, the utilization of this reaction will be of interest for other synthetic applications. The scope of the synthetic route and the completion of the preparation of PI-3 are currently under investigation in our group.

Experimental Section

Preparation of **33:** To a solution of SmI₂ (0.1 M in THF, 100 mL, 10 mmol, 2.5 equiv.) in a 250 mL round bottom Schlenk flask was added a solution of bromide **7** (1.44 g, 4.41 mmol, 1.1 equiv.) and aldehyde **32** (683 mg, 4.01 mmol, 1.0 equiv.) in degassed THF (60 mL, 3 pump–freeze–thaw cycles) at –78 °C by cannula. The reaction mixture was stirred for 1 h at –78 °C before it was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium hydrogen carbonate (50 mL) at –78 °C, and the biphasic system was warmed to room temperature. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic extract was dried with sodium sulfate and filtered, and the organic solvents were removed under reduced pressure to deliver alcohol **33** as a light-yellow oil, which was further purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to provide **33** (1.14 g, 68%).

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ¹H NMR and ¹³C NMR spectra of all compounds described in this communication.

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Supporting Information

Towards the Total Synthesis of Pl-3 – Preparation of the Eastern Fragment via a diastereoselective SmI_2 induced Reformatsky Reaction

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General methods

Synthetic methods: All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum) unless noted otherwise.

Solvents and chemical purification: THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, benzene and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DMSO and *N,N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral, activity. Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å). Triethylamine, diethylisopropylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/ethyl acetate or toluene/ethyl acetate. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [H_2SO_4 (conc., 22 mL), phosphormolybdic acid (20 g), $\text{Ce}(\text{SO}_4)_2$ (0.5 g), 378 mL H_2O)] or silica gel impregnated with iodine.

Chromatography: Preparative column chromatography and flash chromatography were performed with silica gel 60 from Merck (0.040-0.063 μm , 240-400 mesh).

For HPLC separations on analytical scale module systems from Jasco (PU-980, UV- 975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was Superphere Si 60 (40 μm , Merck) or Nucleosil 50 (4 μm , Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

Solvents were removed by rotary evaporation at 30 °C at the appropriate pressure, unless stated otherwise. Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise.

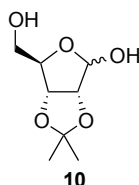
Optical rotations: Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent.

NMR spectra: NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl_3 solutions and referenced to the residual CDCl_3 signal (^1H , $\delta = 7.26$, ^{13}C , $\delta = 77.16$). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy

(COSY, HSQC, HMBC, TOCSY, NOESY).

IR spectra: IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR spectrometer and are reported in wave numbers (cm^{-1}). All compounds were measured as a thin film on silicon single crystal plate.

Experimental part

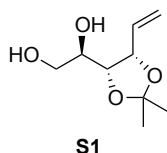


(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (10). To a suspension of D-ribose (5 g, 33.3 mmol, 1 eq) in acetone (62.5 mL) was added dropwise at room temperature a catalytic amount of concentrated sulfuric acid (150 μL , 0.1 eq). The reaction mixture was stirred for twelve hours at ambient temperature before it was neutralized with solid sodium bicarbonate. The suspension was stirred for additional five hours before the precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 2:1) providing lactole **10** (5.2 g, 81%) as colorless oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.32 (s, 3H), 1.49 (s, 3H), 3.47 (bs, 1H), 3.62-3.83 (m, 2H), 4.40 (bs, 1H), 4.58 (d, J = 5.83 Hz, 1H), 4.84 (d, J = 5.83 Hz, 1H), 5.42 (bs, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 24.9 (CH_3), 26.5 (CH_3), 63.9 (CH_2), 81.9 (CH), 87.0 (CH), 88.0 (CH), 103.2 (CH), 112.3 (C) ppm.

These spectral characteristics are identical to those previously reported.^[1]



(R)-1-((4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethane-1,2-diol (S1). To a stirred suspension of methyltriphenylphosphonium bromide (3.5 g, 9.8 mmol, 3.5 eq) in THF (10 mL) was added potassium *tert*-butoxide (1.1 g, 9.8 mmol, 3.5 eq) at 0 °C. The reaction mixture was kept at that temperature for 20 min before it was warmed to room temperature and stirred for one additional hour. After recooling to 0 °C, lactole **10** (530 mg, 2.8 mmol, 1.0 eq) was dissolved in 2.5 mL THF and added *via* syringe. The resulting yellow mixture was stirred for 14 hours at room temperature. The reaction was then quenched by the addition of saturated ammonium chloride solution. The aqueous phase was extracted three times with ethyl acetate, the combined organic extracts were dried over solid sodium sulfate and the solvent was removed under reduced pressure. Afterwards, the crude material was purified by flash chromatography (hexanes/ethyl acetate 1:2) affording the Wittig-product (**S1**, 470 mg, 89%) as light yellow oil.^[2]

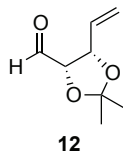
^1H NMR (400 MHz, CDCl_3): δ = 1.37 (s, 3H), 1.48 (s, 3H, CH_3), 2.0-2.08 (bs, 1H), 2.19-2.42 (m, 1H), 3.67-3.87 (m, 3H), 4.11 (dd, J = 6.6, 8.4 Hz, 1H), 4.71 (bt, J = 6.58 Hz, 1H), 5.33 (dt, J = 1.2, 10.4 Hz, 1H), 5.47 (dt, J = 1.2, 17.3 Hz, 1H), 6.01 (ddd, J = 6.6, 10.4, 17.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 25.4 (CH_3), 27.9 (CH_3), 64.5 (CH_2), 70.0 (CH), 78.4 (CH), 78.7 (CH), 109.2 (C), 118.8 (CH_2), 133.9 (CH) ppm.

IR (thin film) ν 3384, 2987, 2937, 1372, 1216, 1055, 928, 872, 798 cm^{-1} .

HRMS (EI) calcd for $\text{C}_9\text{H}_{16}\text{O}_4$ $[\text{M}+\text{Na}]^+$, 211.0947; found 211.0940 $\pm$ 5ppm.

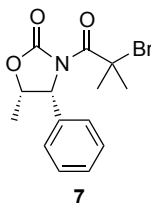
Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = +25.9°.



(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (12). Diol **S1** (3.3 g, 17.5 mmol, 1.0 eq) was dissolved in methylene chloride (60 mL) before sodium periodate (5.6 g, 26.3 mmol, 1.5 eq) dissolved in 40 mL water was added dropwise *via* syringe. The cooling bath was removed and the reaction mixture was stirred at room temperature for two hours before it was diluted with water. The layers were separated and the aqueous phase was extracted three times with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvent was removed in vacuum (180-250 mbar, 30 °C water bath temperature). The resulting very labile product was filtered through a short plug of silica gel (pentanes/diethyl ether 3:1) delivering aldehyde **12** (2.2 g, 81%) as colorless oil which was immediately used for the next step.

^1H NMR (400 MHz, CDCl_3): δ = 1.44 (s, 3H), 1.62 (s, 3H), 4.41 (dd, J = 3.0, 7.5 Hz, 1H), 4.86 (bt, J = 7.5 Hz, 1H), 5.33 (dt, J = 1.3, 10.5 Hz, 1H), 5.47 (dt, J = 1.3, 17.1 Hz, 1H), 5.74 (ddd, J = 6.8, 10.3, 17.3 Hz, 1H), 9.56 (d, J = 3.0 Hz, 1H) ppm.

These spectral characteristics are identical to those previously reported.^[1a]



(4R,5S)-3-(2-Bromo-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (7). To a solution of (4R,5S)-5-methyl-4-phenyloxazolidin-2-one (3.0 g, 16.9 mmol, 1.0 eq) in dry THF (30 mL) was added sodium hydride (608 mg, 23.4 mmol, 1.5 eq) in one portion at room temperature. After the addition, the resulting suspension was cooled to -40 °C and a solution of 2-bromoisobutyryl bromide in 80 mL THF was added. The reaction mixture was stirred for one hour at -40 °C and one additional hour at 0 °C before TLC control showed total consumption of the starting material. The reaction was terminated by addition of saturated ammonium chloride solution. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined

organic extracts were dried over solid sodium sulfate and afterwards the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 5:1) giving bromide **7** (5.15 g) in 94% yield.

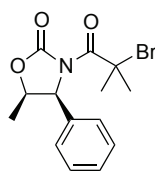
^1H NMR (400 MHz, CDCl_3): δ = 0.94 (d, J = 6.6 Hz, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 4.81 (quint, J = 6.7 Hz, 1H), 5.73 (d, J = 7.1 Hz, 1H), 7.29-7.46 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 14.2 (CH_3), 30.6 (CH_3), 31.7 (CH_3), 57.1 (C), 57.6 (CH), 79.1 (CH), 125.8 (CH) 128.9 (CH), 129.0 (CH), 133.6 (C), 151.2 (C), 171.57 (C) ppm.

IR (thin film) ν 1788, 1682, 1455, 1339, 1284, 1191, 1122, 1068, 966, 699 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{14}\text{H}_{16}\text{BrNO}_3$ $[\text{M}+\text{Na}]^+$, 325.0314; found 325.0318 $\pm$ 5 ppm.

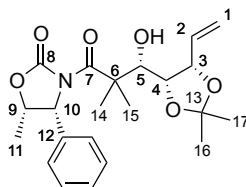
Optical Rotation: $[\alpha]_D^{20}$ (c 0.1, CHCl_3) = +28.4°.



S2

(4*S*,5*R*)-3-(2-Bromo-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (S2). Bromide **S2** was synthesized following the same procedure as described for bromide **7**, starting from (4*S*,5*R*)-5-methyl-4-phenyloxazolidin-2-one (3 g, 23.4 mmol) in 94% yield.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.1, CHCl_3) = -28.4°.



13

(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (13).

SmI₂ methode: A solution of SmI₂ (100 mL, 0.1 M in THF, 10.0 mmol, 2.5 eq) was cannulated in a 250 mL round bottom Schlenk flask which was precooled to -78 °C. A solution of bromide **7** (1.44 g, 4.4 mmol, 1.1 eq) and aldehyde **12** (624 mg, 4 mmol, 1.0 eq) in 60 mL degassed THF (3 pump freeze thaw cycles) was added to the SmI₂ solution *via* cannula. The reaction mixture was stirred for one hour at -78 °C before the reaction was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium bicarbonate (50 mL) at -78 °C and the biphasic mixture was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure delivering alcohol **13** as light oil which was further purified by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) in 85% yield (1.37 g).

Chromium method I: Chromium dichloride (157 mg, 128 mmol, 4.0 eq) and lithium chloride (21 mg, 0.16 mmol, 0.5 eq) were suspended in freshly distilled THF (2 mL) and vigorously stirred at room temperature. Aldehyde **12** was added, followed by bromide **7**, each dissolved in THF (1.0 mL). The reaction mixture was stirred for 1.5 h at room temperature, 1 h 20 min at 40 °C and 3 h at 60 °C before it was quenched with brine. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 9/1) delivering alcohol **13** (8.5 mg) in 7% yield.

Chromium method II: Chromium dichloride (98 mg, 0.8 mmol, 2.5 eq) was suspended in freshly distilled THF (1.5 mL). Aldehyde **12** (50 mg, 0.32 mmol, 1.0 eq) and bromide **7** (114 mg, 0.35 mmol, 1.1 eq), dissolved in 1.0 mL THF each, were added consecutively within five minutes at room temperature. The resulting mixture was stirred for seven hours at room temperature before the reaction was quenched with brine. The two layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) delivering alcohol **13** (30 mg) in 23% yield.

Chromium method III: Chromium trichloride (136 mg, 0.86 mmol, 2.7 eq) was suspended in 1.3 mL THF and a solution of lithium aluminum hydride (4.0 M in diethyl ether, 0.113 mL, 0.45 mmol, 1.4 eq) was added at 0 °C under vigorous stirring. The resulting black suspension was stirred for 45 min at 0 °C before aldehyde **12** (50 mg, 0.32 mmol, 1.0 eq) was added, followed by the addition of bromide **7** (147 mg, 0.45 mmol, 1.4 eq) at 0 °C; both dissolved in 0.5 mL THF, respectively. The reaction mixture was allowed to warm to room temperature over a period of 3.5 hours. The reaction was terminated by the addition of brine, the two layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9/1) delivering alcohol **13** (12.5 mg, 10%) as light yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.92 (d, *J* = 6.6 Hz, 3H, CH₃-11), 1.35 (s, 3H, CH₃-14 or 15), 1.36 (s, 3H, CH₃-16 or 17), 1.44 (s, 3H, CH₃-14 or 15), 1.51 (s, 3H, CH₃-16 or 17), 3.44 (d, *J* = 10.1 Hz, 1H, OH), 4.28 (d, *J* = 7.6 Hz, 1H, H-4), 4.35 (d, *J* = 10.1 Hz, 1H, H-5), 4.67 (dd, *J* = 7.6, 8.0 Hz, 1H, H-3), 4.78 (quint, *J* = 6.6 Hz, 1H, H-9), 5.33-5.42 (m, 2H, H-1a,b), 5.66 (d, *J* = 6.8, 1H, H-10), 6.14 (ddd, *J* = 8.1, 10.1, 17.5 Hz, 1H, H-2), 7.28-7.33 (m, 2H, CH-phenyl), 7.34-7.45 (m, 3H, CH-phenyl) ppm.

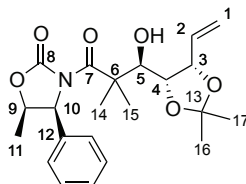
¹³C NMR (100 MHz, CDCl₃): δ = 14.0 (CH₃-11), 20.0 (CH₃-14 or 15), 23.3 (CH₃-14 or 15), 24.9 (CH₃-16 or 17), 27.0 (CH₃-16 or 17), 50.7 (C-6), 57.8 (CH-9), 71.5 (CH-5), 76.1 (CH-4), 79.3

(CH-10), 80.4 (CH-3), 108.8 (C-13), 119.8 (CH₂-1), 125.8 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.6 (C-12), 152.7 (C-8), 177.0 (C-7) ppm.

IR (thin film) ν 3424, 2987, 2937, 1773, 1687, 1456, 1341, 1255, 1150, 1119, 1045, 939, 889, 768, 701, 657 cm⁻¹.

HRMS (EI) calcd for C₂₂H₂₉NO₆ [M+Na]⁺, 426.1893; found 426.1890 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl₃) = +52.8°.



19

(4*R*,5*S*)-3-((*R*)-3-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (19).

Diastereomer **19** was prepared following the same procedures as described above for alcohol **13**.

	Aldehyde (12)	Bromide (S2)	Yield (19)
SmI ₂ (4.9 eq)	50 mg, 0.32 mmol, 1.0 eq	111 mg, 0.34 mmol, 1.06 eq	56 mg (43%)
CrCl ₂ (2.5 eq), LiI (0.1 eq)	50 mg, 0.32 mmol, 1.0 eq	115 mg, 0.35 mmol, 1.1 eq	50 mg (39%)

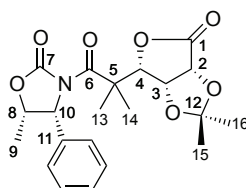
¹H NMR (400 MHz, CDCl₃): δ = 0.93 (d, J = 6.6 Hz, 3H, CH₃-11), 1.35 (s, 3H, CH₃-16 or 17), 1.38 (s, 3H, CH₃-14 or 15), 1.48 (s, 3H, CH₃-16 or 17), 1.49 (s, 3H, CH₃-14 or 15), 2.21 (d, J = 6.1 Hz, 1H, OH), 4.18 (dd, J = 6.3, 9.9 Hz, 1H, H-4), 4.64 (dd, J = 6.3, 7.5 Hz, 1H, H-3), 4.70-4.80 (m, 2H, H-5, H-9), 5.29-5.42 (m, 2H, H-1a,b), 5.62 (d, J = 7.1 Hz, 1H, H-10), 5.99 (ddd, J = 7.5, 10.2, 17.1 Hz, 1H, H-2), 7.27-7.32 (m, 2H, CH-phenyl), 7.33-7.44 (m, 3H, CH-phenyl) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 14.6 (CH₃-11), 20.0 (CH₃-14 or 15), 20.8 (CH₃-14 or 15), 25.2 (CH₃-16 or 17), 28.0 (CH₃-16 or 17), 49.6 (C-6), 57.6 (CH-9), 69.5 (CH-5), 77.9 (CH-4), 79.2 (CH-10), 79.8 (CH-3), 109.1 (C-13), 118.9 (CH₂-1), 125.7 (CH-phenyl), 128.8 (CH-phenyl), 133.6 (C-12), 135.0 (CH-2), 152.5 (C-8), 175.9 (C-7) ppm.

IR (thin film) ν 3424, 2987, 2937, 1773, 1687, 1456, 1341, 1255, 1150, 1119, 1045, 939, 889, 768, 701, 657 cm⁻¹.

HRMS (EI) calcd for C₂₂H₂₉NO₆ [M+Na]⁺, 426.1893; found 426.1890 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl₃) = +8.3°.



18

(4*R*,5*S*)-3-(2-((3*aR*,4*S*,6*aR*)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (18). Alkene **13** (58 mg, 0.14 mmol, 1.0 eq) was dissolved in 5 mL methylene chloride and cooled to $-78\text{ }^{\circ}\text{C}$. A stream of ozone was bubbled through the reaction mixture (for approximately 2 min) until the solution turned characteristically blue. In order to remove excess of ozone from the reaction mixture, oxygen was bubbled through the solution and the reaction mixture turned colorless. Next, the solution was purged with argon for approximately two minutes before the reaction mixture was allowed to warm to room temperature over a period of 14 hours. The solvent was removed under reduced pressure delivering an inseparable mixture of diastereomers of the corresponding lactol (43 mg, 75%) as colorless oil, which was used for the next step without any purification.

To a solution of the crude mixture of lactols from above (20 mg, 0.05 mmol, 1.0 eq) in methylene chloride (1.0 mL) was added sodium acetate (8 mg, 0.1 mmol, 2.0 eq) and PCC (22 mg, 0.1 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at room temperature for twelve hours. The resulting suspension was filtered through a short plug of silica gel and the solvent was removed under reduced pressure delivering the crude lactone as yellow oil. Further purification by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) delivered lactone **18** (13 mg) in 65% yield.

^1H NMR (400 MHz, CDCl_3): δ = 0.91 (d, J = 6.6 Hz, 3H, CH_3 -9), 1.35 (s, 3H, CH_3 -15), 1.47 (s, 3H, CH_3 -16), 1.60 (s, 3H, CH_3 -13 or 14), 1.65 (s, 3H, CH_3 -13 or 14), 4.82 (d, J = 5.6 Hz, 1H, H-2), 4.83 (quint, J = 4.8 Hz, 1H, H-8) 4.99 (dd, J = 3.7, 5.5 Hz, 1H, H-3), 5.24 (d, J = 3.7 Hz, 1H, H-4), 5.68 (d, J = 7.3 Hz, 1H, H-10), 7.28-7.32 (m, 2H, CH-phenyl), 7.36-7.46 (m, 3H, CH-phenyl) ppm.

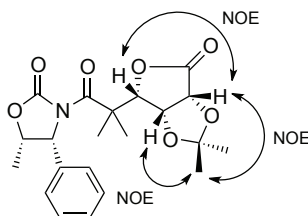
^{13}C NMR (100 MHz, CDCl_3): δ = 14.5 (CH_3 -9), 18.6 (CH_3 -15), 21.0 (CH_3 -16), 25.7 (CH_3 -13 or 14), 26.7 (CH_3 -13 or 14), 48.3 (C-5), 76.6 (CH-2), 77.5 (CH-3), 79.6 (CH-10), 80.3 (CH-4), 114.7 (C-12), 125.9 (CH-phenyl), 128.9 (CH-phenyl), 129.1 (CH-phenyl), 133.5 (C-11), 125.5 (C-7), 173.5 (C-1), 175.8 (C-6) ppm.

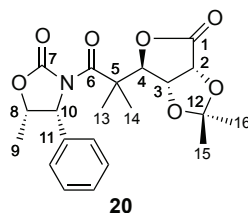
IR (thin film): ν 2990, 2929, 1780, 1675, 1457, 1341, 1191, 1069, 1014, 953, 733, 701 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_7$ $[\text{M}+\text{Na}]^+$, 426.1529; found 426.1527 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}$ (c 1.0, CHCl_3) = -1.9° .

NOE-analysis:





(4*R*,5*S*)-3-(2-((3*aR*,4*R*,6*aR*)-2,2-Dimethyl-6-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-methylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (20). For the preparation of intermediate **20** the same procedure as described above was used starting from diastereomeric alcohol **19** (60 mg, 0.13 mmol). Lactone **20** (14 mg, 27%) was isolated after the two step procedure.

^1H NMR (400 MHz, CDCl_3): δ = 0.83 (d, J = 6.7 Hz 3H, CH_3 -9), 1.40 (s, 3H, CH_3 -15), 1.49 (s, 3H, CH_3 -16), 1.57 (s, 3H, CH_3 -13 or 14), 1.67 (s, 3H, CH_3 -13 or 14), 4.36 (d, J = 1.0 Hz, 1H, H-4), 4.74-4.82 (m, 2H, H-3, H-8), 4.99 (d, J = 6.6 Hz, 1H, H-2), 5.67 (d, J = 7.6 Hz, 1H, H-10), 7.24-7.45 (m, 5H, CH-phenyl) ppm.

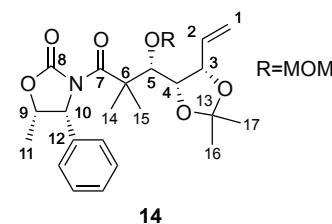
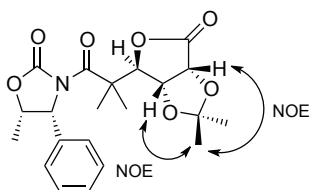
^{13}C NMR (100 MHz, CDCl_3): δ = 14.5 (CH_3 -9), 19.0 (CH_3 -13 or 14), 20.7 (CH_3 -13 or 14), 25.4 (CH_3 -15), 26.6 (CH_3 -16), 47.9 (C-5), 56.6 (CH-3), 76.9 (CH-2), 78.1 (CH-8), 79.3 (CH-10), 92.4 (CH-4), 113.9 (C-12), 125.8 (CH-phenyl), 129.0 (CH-phenyl), 129.1 (CH-phenyl), 133.3 (C-11), 151.6 (C-7), 174.0 (C-1), 175.5 (C-6) ppm.

IR (thin film) ν 2990, 2929, 1780, 1675, 1457, 1341, 1191, 1069, 1014, 953, 733, 701 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_7$ $[\text{M}+\text{Na}]^+$, 426.1529; found 426.1527 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.5, CHCl_3) = -3.8° .

NOE-analysis:



(4*R*,5*S*)-3-((*S*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (14). To a cooled solution (0 $^\circ\text{C}$) of alcohol **13** (230 mg, 0.57 mmol, 1.0 eq) in methylene chloride (3.0 mL) was added DIPEA (0.49 mL, 2.85 mmol, 5.0 eq), followed by the slow dropwise addition of MOM-Cl (0.13 mL, 1.71 mmol, 3.0 eq). Next, the cooling bath was removed and the reaction mixture was stirred for twelve hours at room temperature and additional 2.5 hours at 50 $^\circ\text{C}$ until no more starting material could be detected by TLC. The reaction mixture was quenched with water and diluted with methylene chloride. The layers were separated and the aqueous phase was extracted three times

with methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The resulting crude MOM-protected product was purified by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) providing intermediate **14** (237 mg, 93%) as colorless oil.

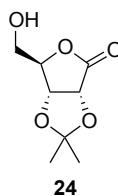
^1H NMR (400 MHz, CDCl_3): δ = 0.90 (d, J = 6.6 Hz, 3H, CH_3 -13), 1.38 (s, 3H, CH_3 -14 or 15), 1.44 (s, 3H, CH_3 -16 or 17), 1.48 (s, 3H, CH_3 -16 or 17), 1.53 (s, 3H, CH_3 -14 or 15), 3.36 (s, 3H, OCH_3 -MOM), 4.32 (dd, J = 3.7, 6.2 Hz, 1H, H-4), 4.57 (dd, J = 6.2, 7.5 Hz, 1H, H-3), 4.62 (d, J = 6.6 Hz, 1H, CH_2 -MOM), 4.68 (d, J = 6.6 Hz, 1H, CH_2 -MOM), 4.77 (quint, J = 6.7 Hz, 1H, H-9), 4.78 (d, J = 3.7 Hz, 1H, H-5), 5.28-5.39 (m, 2H, CH_2 -1), 5.63 (d, J = 7.1 Hz, 1H, H-10), 6.09 (ddd, J = 7.5, 10.1, 17.4 Hz, 1H, H-2), 7.27-7.32 (m, 2H, CH-phenyl), 7.34-7.44 (m, 3H, CH-phenyl) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 14.4 (CH_3 -13) 21.3 (CH_3 -14 or 15), 21.9 (CH_3 -14 or 15), 25.8 (CH_3 -16 or 17), 27.5 (CH_3 -16 or 17), 50.5 (C-6), 56.7 (OCH_3 -MOM), 57.3 (CH-5), 76.6 (CH-9), 78.3 (CH-4), 79.3 (CH-10), 79.9 (CH-3), 98.5 (CH_2 -MOM), 108.5 (C-12), 118.8 (CH_2 -1), 125.9 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.7 (C-11), 134.9 (CH-2), 152.6 (C-8), 176.6 (C-7) ppm.

IR (thin film) ν 2985, 2937, 1776, 1690, 1456, 1369, 1339, 1247, 1191, 1121, 1068, 1032, 882, 769, 700 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{24}\text{H}_{33}\text{NO}_7$ $[\text{M}+\text{Na}]^+$, 470.2155; found 470.2160 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}$ (c 1.0, CHCl_3) = -11.5° .



(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (24).

D-Ribonolactone (10.0 g, 67.5 mmol) was dissolved in acetone (50 mL) and boron trifluoride etherate (0.855 mL, 6.75 mmol, 0.1 eq) was added to the solution at room temperature, followed by 2,2-dimethoxypropane (10.0 mL). The reaction mixture was stirred for one hour before the solvent was removed under reduced pressure to afford a light brown solid, which was dissolved in ethyl acetate. The resulting solution was extracted with water twice, with brine once, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure delivering crude lactone **24** (10.93 g, 86%) as light yellow crystals. The product was used without any further purification for the following step.

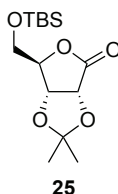
^1H NMR (400 MHz, CDCl_3): δ = 1.38 (s, 3H), 1.48 (s, 3H), 2.29 (t, J = 5.4 Hz, 1H, OH), 3.81 (ddd, J = 1.8, 5.6, 12.1 Hz, 1H), 4.0 (ddd, J = 2.5, 5.6, 12.1 Hz, 1H), 4.63 (bt, J = 2.0 Hz, 1H), 4.78 (d, J = 5.8 Hz, 1H), 4.83 (d, J = 5.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 25.6 (CH_3), 26.9 (CH_3), 62.2 (CH_2), 75.8 (CH), 78.4 (CH), 82.7 (CH), 113.3 (C), 174.9 (C) ppm.

IR (thin film) ν 3469, 2991, 1767, 1379, 1273, 1222, 1200, 1154, 1093, 975, 856, 810, 774 cm^{-1} .

HRMS (EI) calcd for $\text{C}_8\text{H}_{12}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 211.0583; found 211.0583 $\pm$ 5 ppm.

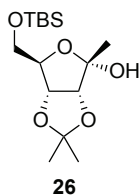
Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = -66.9° .



(3aR,6R,6aR)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (25). Imidazole (2.17 g, 31.9 mmol, 1.2 eq) and TBS-Cl (4.08 g, 27.1 mmol, 1.02 eq) were added to a solution of lactone **24** (5.0 g, 26.6 mmol, 1.0 eq) in DMF (20 mL) at 0 $^\circ\text{C}$. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours before the reaction was quenched by the addition of water. After separating the two layers the aqueous phase was extracted with diethyl ether three times. The combined organic extracts were dried over magnesium sulfate, filtered and the organic solvents were removed under reduced pressure to afford the crude fully protected ribonolactone (**25**), which was further purified by flash chromatography (hexanes/ethyl acetate 5:1) to give **25** in 93% yield (7.5 g).

^1H NMR (400 MHz, CDCl_3): δ = 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.39 (s, 3H), 1.47 (s, 3H), 3.80 (dd, J = 1.5, 11.3 Hz, 1H), 3.90 (dd, J = 1.5, 11.3 Hz, 1H), 4.58-4.61 (m, 1H), 4.70 (d, J = 5.8 Hz, 1H), 4.73 (d, J = 5.8 Hz, 1H) ppm.

These spectral characteristics are identical to those previously reported.^[3]



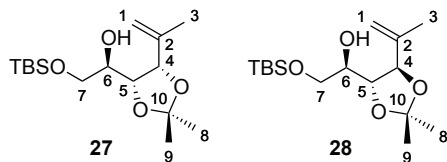
(3aR,4S,6R,6aR)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (26). A solution of methyllithium (0.68 mL, 1.6 M in Et_2O , 1.1 mmol, 1.1 eq) was added dropwise to a solution of lactone **25** (300 mg, 0.99 mmol, 1.0 eq) in dry THF (3.5 mL). The reaction mixture was stirred for 3.5 hours at -78°C before it was quenched with water at -78°C and warmed to room temperature. The product was extracted with ethyl acetate, the combined organic extracts were washed with brine and dried over sodium sulfate. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude lactole **26** (312 mg, 99%) was used for the following step without any further purification.

^1H NMR (400 MHz, CDCl_3): δ = 0.14 (s, 3H), 0.15 (s, 3H), 0.93 (s, 9H), 1.34 (s, 3H), 1.50 (s, 3H), 1.52 (d, 3H, J = 1.0 Hz), 3.75 (dd, J = 2.0, 11.1 Hz, 1H), 3.78 (dd, J = 2.0, 11.1 Hz, 1H), 4.25 (dd,

$J = 2.0, 3.5$ Hz, 1H), 4.43 (d, $J = 5.8$ Hz, 1H), 4.80 (dd, $J = 1.5, 5.8$ Hz, 1H), 5.11 (bd, $J = 1.0$ Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.6$ (CH_3), -5.5 (CH_3), 18.4 (C), 21.4 (CH_3), 25.3 (CH_3), 25.9 (CH_3), 26.8 (CH_3), 65.1 (CH_2), 82.2 (CH), 86.0 (CH), 88.2 (CH), 106.7 (C), 112.6 (C) ppm.

These spectral characteristics are identical to those reported.^[4]



Most conditions applied for the installation of the double bond resulted in α -racemization. Depending on reaction conditions, mixtures containing diastereomeric alkenes **27** and **28** were obtained.

The following procedure allowed the isolation of pure diastereomer **27** in moderate yield.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-((*4R,5S*)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)ethanol (27**).** Methyltriphenylphosphonium bromide (789 mg, 2.2 mmol, 2.2 eq) was dissolved in toluene (6.5 mL) and cooled to 0 °C. *t*-BuOK (248 mg, 2.2 mmol, 2.2 eq) was added in one portion and the resulting yellow reaction mixture was stirred for 30 min at 0 °C and additional three hours at room temperature. The yellow suspension was cooled to -78 °C, lactole **26** (200 mg, 1.0 mmol, 1.0 eq) was added and the reaction mixture was allowed to come to room temperature over twelve hours. The reaction was terminated by the addition of saturated ammonium chloride solution, the layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (hexanes/ethyl acetate 19:1) delivering alcohol **27** (58 mg) in 30% yield.

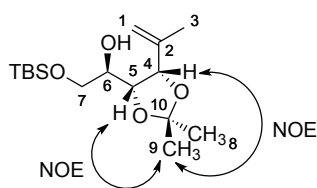
^1H NMR (400 MHz, CDCl_3): $\delta = 0.08$ (s, 3H, Si- CH_3), 0.081 (s, 3H, Si- CH_3), 0.90 (s, 9H, CH_3 -*t*Bu), 1.36 (s, 3H, CH_3 -9), 1.47 (s, 3H, CH_3 -8), 1.85 (s, 3H, CH_3 -3), 2.47 (d, $J = 4.8$ Hz, 1H, OH), 3.56-3.64 (m, 1H, H-6), 3.67 (dd, $J = 6.3, 9.9$ Hz, 1H, H-7), 3.80 (dd, $J = 3.0, 9.9$ Hz, 1H, H-7), 4.07 (dd, $J = 6.3, 8.8$ Hz, 1H, H-5), 6.06 (d, $J = 6.3$ Hz, 1H, H-4), 5.0-5.04 (m, 1H, H-1a), 5.16-5.19 (m, 1H, H-1b) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.2$ (Si- CH_3), -5.24 (Si- CH_3), 18.5 (C-*t*Bu), 20.8 (CH_3 -3), 25.3 (CH_3 -9), 26.1 (CH_3 -*t*Bu), 27.4 (CH_3 -8), 64.6 (CH_2 -7), 69.7 (CH-6), 77.9 (CH-5), 80.4 (CH-4), 108.2 (C-10), 112.5 (CH_2 -1), 141.5 (C-2) ppm.

IR (thin film) ν 3565, 2929, 2857, 1463, 1380, 1253, 1165, 1115, 1078, 1057, 899, 833 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{16}\text{H}_{32}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$, 339.1968; found 339.1970 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +40.8^\circ$.

NOE-analysis:**Experimental data for diastereomer 28 (undesired):**

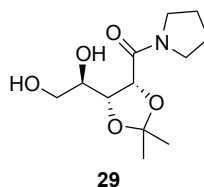
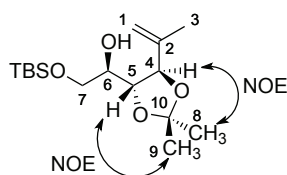
^1H NMR (400 MHz, CDCl_3): δ = 0.08 (s, 3H, Si- CH_3), 0.081 (s, 3H, Si- CH_3), 0.90 (s, 9H, CH_3 -*t*Bu), 1.41 (s, 3H, CH_3 -8), 1.43 (s, 3H, CH_3 -9), 1.81 (s, 3H, CH_3 -3), 3.63-3.71 (m, 1H, H-7), 3.71-3.80 (m, 2H, H-7, H-6), 3.83-3.89 (m, 1H, H-5), 4.48 (d, J = 7.8 Hz, 1H, H-4), 4.98-5.02 (m, 1H, H-1a), 5.13-5.16 (m, 1H, H-1b) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.29 (Si- CH_3), -5.23 (Si- CH_3), 17.7 (CH_3 -3), 18.4 (C-*t*Bu), 26.0 (CH_3 -*t*Bu), 27.2 (CH_3 -9), 27.3 (CH_3 -8), 64.1 (CH_2 -7), 73.0 (CH-5), 78.3 (CH-6), 82.9 (CH-4), 109.2 (C-10), 115.1 (CH_2 -1), 142.6 (C-2) ppm.

IR (thin film) ν 3487, 2930, 2859, 1463, 1370, 1253, 1167, 1060, 902, 836, 778 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{16}\text{H}_{32}\text{O}_4\text{Si}$ [$\text{M}+\text{Na}$] $^+$, 339.1968; found 339.1967 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.5, CHCl_3) = -3.4°.

NOE-analysis:**29****((4*R*,5*R*)-5-((*R*)-1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-**

yl)methanone (29). Protected ribonolactone **24** (500 mg, 2.7 mmol, 1.0 eq) was dissolved in toluene (11 mL). After the addition of pyrrolidine (1.1 mL, 13.5 mmol, 5.0 eq) the reaction mixture was heated to reflux for twelve hours. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (methylene chloride/methanol 19/1) to give amide **29** (610 mg) in 87% yield.

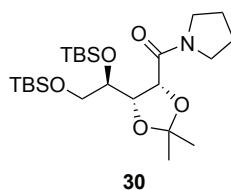
^1H NMR (400 MHz, CDCl_3): δ = 1.37 (s, 3H), 1.52 (s, 3H), 1.79-2.03 (m, 4H), 2.35 (bs, 1H, OH), 3.43-3.59 (m, 2H), 3.60-3.72 (m, 3H), 3.77-3.89 (m, 2H), 4.27 (dd, J = 6.3, 8.8 Hz, 1H), 4.59 (bs, 1H, OH), 4.84 (d, J = 6.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 23.8 (CH_2), 25.3 (CH_3), 26.5 (CH_2), 27.2 (CH_3), 47.02 (CH_2), 47.14 (CH_2), 64.5 (CH_2), 70.0 (CH), 76.7 (CH), 78.3 (CH), 109.9 (C), 167.8 (C) ppm.

IR (thin film) ν 3335, 2981, 2876, 1781, 1630, 1454, 1372, 1214, 1164, 1053, 907, 726 cm^{-1} .

HRMS (EI) calcd for $C_{12}H_{21}O_5NH [M+H]^+$, 260.1498; found 260.1492 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(c\ 1.0, CHCl_3) = +16.2^\circ$.



((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (30**).** To a solution of diol **29** (250 mg, 0.96 mmol, 1.0 eq) in methylene chloride (2 mL) were sequentially added 2,6-lutidine (0.335 mL, 2.88 mmol, 3.0 eq) and TBS-triflate (0.706 mL, 3.07 mmol, 3.2 eq) at 0 °C. The cooling bath was removed after the addition and the reaction mixture was allowed to stir at room temperature for 15 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over solid sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) delivering **30** (375 mg) in 80% yield.

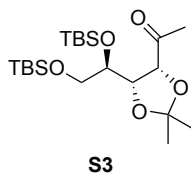
1H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.74-2.0 (m, 4H), 3.36-3.55 (m, 3H), 3.60-3.69 (m, 1H), 3.74-3.77 (m, 2H), 4.37-4.41 (m, 2H), 4.67-4.70 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.4 (CH_3), -5.2 (CH_3), -4.5 (CH_3), -3.7 (CH_3), 18.3 (C), 18.6 (C), 24.2 (CH_2), 26.0 (CH_3), 26.05 (CH_3), 26.1 (CH_3), 26.4 (CH_2), 27.0 (CH_3), 46.1 (CH_2), 46.6 (CH_2), 64.7 (CH_2), 72.4 (CH), 74.6 (CH), 77.6 (CH), 110.4 (C), 167.3 (C) ppm.

IR (thin film) ν 2953, 2929, 2856, 1655, 1442, 1368, 1342, 1250, 1223, 1090, 992, 938, 831, 774, 675 cm^{-1} .

HRMS (EI) calcd for $C_{24}H_{49}NO_5Si_2 [M+Na]^+$, 510.3047; found 510.3048 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(c\ 1.0, CHCl_3) = -46.7^\circ$.



1-((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)ethanone (S3**).** A solution of methyllithium (1.6 M, 12.8 mL, 20.4 mmol, 2.0 eq) was added to amide **30** (5 g, 10.2 mmol, 1.0 eq) in THF (50 mL) at -78 °C. The reaction mixture was stirred for 15 min when TLC-control showed total consumption of the starting material. The reaction was then terminated by the addition of water. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. Further purification of crude

S3 by flash chromatography (hexanes/ethyl acetate 40:1) delivered ketone **S3** (4.23 g) in 95% yield.

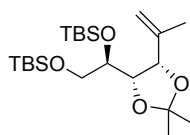
^1H NMR (400 MHz, CDCl_3): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.36 (s, 3H), 1.60 (s, 3H), 2.31 (s, 3H), 3.57 (dd, J = 5.1, 10.4 Hz, 1H), 3.74 (dd, J = 7.3, 10.4 Hz, 1H), 4.05 (ddd, J = 3.4, 5.1, 7.3 Hz, 1H), 4.38 (d, J = 7.8 Hz, 1H), 4.57 (dd, J = 3.4, 7.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), -4.8 (CH_3), -4.1 (CH_3), 18.4 (C), 18.6 (C), 24.7 (CH_3), 26.1 (CH_3), 26.15 (CH_3), 26.7 (CH_3), 29.2 (CH_3), 63.9 (CH_2), 72.6 (CH), 79.8 (CH), 80.6 (CH), 109.1 (C), 209.3 (C) ppm.

IR (thin film) ν 2930, 2887, 2858, 1717, 1473, 1361, 1253, 1214, 1150, 1082, 939, 832, 776, 669 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{21}\text{H}_{44}\text{O}_5\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 455.2625; found 455.2620 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c 1.0, CHCl}_3) = -20.2^\circ$.



31

(R)-5-((4S,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (31). Ketone **S3** (2.8 g, 6.5 mmol, 1.0 eq) was dissolved in freshly distilled THF (40 mL) and cooled to 0 °C. A solution of Tebbe-reagent (15.6 mL, 0.5 M in toluene, 7.8 mmol, 1.2 eq) was slowly added *via* syringe. The reaction mixture was stirred for one hour at 0 °C before it was quenched by the addition of a saturated sodium bicarbonate solution. After the separation of the two layers, the aqueous phase was extracted with ethyl acetate three times. The combined organic extracts were dried over solid sodium sulfate, filtered and the solvent was removed under reduced pressure. Crude alkene **31** was further purified by flash chromatography (hexanes/ethyl acetate 40:1) delivering 2.32 g (83%) of the desired intermediate as light yellow oil.

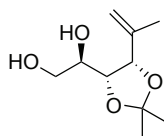
^1H NMR (400 MHz, CDCl_3): δ = 0.04 (s, 6H), 0.041 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.78 (s, 3H), 3.64-3.75 (m, 3H), 4.28 (dd, J = 4.8, 7.1 Hz, 1H), 4.61 (d, J = 7.1 Hz, 1H), 4.95-4.98 (m, 1H), 5.07-5.10 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), -4.3 (CH_3), -3.7 (CH_3), 18.50 (C), 18.59 (C), 20.4 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.6 (CH_3), 65.4 (CH_2), 73.2 (CH), 79.4 (CH), 80.5 (CH), 107.9 (C), 113.9 (CH_2), 141.0 (C) ppm.

IR (thin film) ν 2954, 2857, 1492, 1463, 1368, 1252, 1211, 1143, 1087, 1040, 1002, 986, 965, 947, 830, 773, 665 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{22}\text{H}_{46}\text{O}_4\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 453.2833; found 453.2834 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c 1.0, CHCl}_3) = +30.1^\circ$.

**S4**

(R)-1-((4R,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)ethane-1,2-diol (S4). TBAF (1.59 mL, 1 M in THF, 1.59 mmol, 3.0 eq) was added to a solution of TBS-protected diol **31** (230 mg, 0.53 mmol, 1.0 eq) in THF (3 mL) at 0 °C. After the addition the cooling bath was removed and the reaction mixture was stirred for 3.5 hours at room temperature. The reaction was then quenched by the addition of saturated ammonium chloride solution. The two layers were separated and the aqueous layer was extracted with ethyl acetate three times. The organic extracts were dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude diol was purified by flash chromatography (hexanes/ethyl acetate 5:1 to 1:1) providing **S4** (107 mg) in quantitative yield.

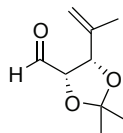
^1H NMR (400 MHz, CDCl_3): δ = 1.37 (s, 3H), 1.49 (s, 3H), 1.87 (s, 3H), 2.06 (dd, J = 5.3, 6.8 Hz, OH), 2.14 (d, J = 4.8 Hz, OH), 3.65-3.74 (m, 2H), 3.76-3.86 (m, 1H), 4.08-4.16 (m, 1H), 4.66 (d, J = 6.1 Hz, 1H), 5.06-5.09 (m, 1H), 5.24-5.27 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 20.9 (CH_3), 25.4 (CH_3), 27.5 (CH_3), 64.5 (CH_2), 69.9 (CH), 78.2 (CH), 80.0 (CH), 108.4 (C), 112.9 (CH_2), 141.7 (C) ppm.

IR (thin film) ν 3369, 2986, 2935, 1652, 1380, 1234, 1212, 1164, 1038, 900, 875, 799 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{10}\text{H}_{18}\text{O}_4$ $[\text{M}+\text{Na}]^+$, 225.1103; found 225.1100 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +80.4^\circ$.

**32**

(4S,5S)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane-4-carbaldehyde (32). To a solution of diol **S4** (900 mg, 4.44 mmol, 1.0 eq) in methylene chloride (24 mL) was added a solution of sodium periodate (1.42 g, 6.66 mmol, 1.5 eq) in water (12 mL) at 0 °C. The reaction was stirred for two hours at 0 °C before it was diluted with methylene chloride and water. The layers were separated and the aqueous phase was extracted with methylene chloride three times. The combined organic extracts were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The crude aldehyde was further purified by flash chromatography (pentanes/diethyl ether 5:1) giving **32** (683 mg) in 90% yield.

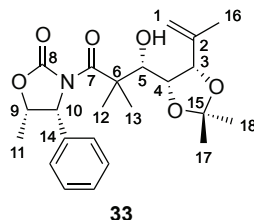
^1H NMR (400 MHz, CDCl_3): δ = 1.44 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 4.37 (dd, J = 3.5, 7.6 Hz, 1H), 4.79 (d, J = 7.6 Hz, 1H), 4.98-5.01 (m, 1H), 5.19-5.22 (m, 1H), 9.44 (d, J = 3.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 19.7 (CH_3), 25.3 (CH_3), 27.2 (CH_3), 80.9 (CH), 81.6 (CH), 111.3 (C), 113.7 (CH_2), 138.1 (C), 199.9 (CHO) ppm.

IR (thin film) ν 2989, 2939, 1732, 1655, 1450, 1381, 1255, 1215, 1159, 1078, 907, 858, 795, 744 cm^{-1} .

HRMS (EI) calcd for $\text{C}_9\text{H}_{14}\text{O}_3$ $[\text{M}+\text{Na}]^+$, 193.0841; found 193.0848 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +55.0^\circ$.



(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*S*)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (33). A solution of SmI_2 (100 mL, 0.1 M in THF, 10 mmol, 2.5 eq) was cannulated into a 250 mL round bottom Schlenk flask which was precooled to -78°C . A solution of bromide **7** (1.44 g, 4.41 mmol, 1.1 eq) and aldehyde **32** (683 mg, 4.01 mmol, 1.0 eq) in 60 mL degassed THF (3 pump freeze thaw cycles) was added to the SmI_2 solution *via* cannula. The reaction mixture was stirred for one hour at -78°C before it was quenched by the addition of aqueous saturated solutions of sodium thiosulfate (50 mL) and sodium bicarbonate (50 mL) at -78°C . The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were dried over sodium sulfate, filtered and the organic solvents were removed under reduced pressure delivering alcohol **33** as light yellow oil which was further purified by flash chromatography (hexanes/ethyl acetate 9:1) providing **33** (1.14 g) in 68% yield.

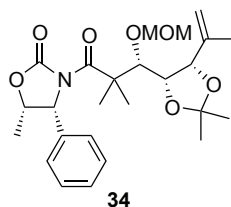
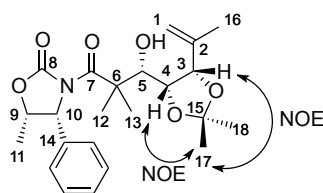
^1H NMR (400 MHz, CDCl_3): δ = 0.91 (d, J = 6.6 Hz, 3H, CH_3 -11), 1.36 (s, 3H, CH_3 -12 or 13), 1.39 (s, 3H, CH_3 -17), 1.43 (s, 3H, CH_3 -12 or 13), 1.56 (s, 3H, CH_3 -18), 1.87 (s, 3H, CH_3 -16), 2.93 (d, J = 8.6 Hz, 1H, OH), 4.29 (d, J = 7.6 Hz, 1H, H-4), 4.42 (d, J = 8.6 Hz, 1H, H-5), 4.71 (d, J = 7.6 Hz, 1H, H-3), 4.79 (quint, J = 6.6 Hz, 1H, H-9), 5.08-5.12 (m, 1H, H-1a), 5.16-5.20 (m, 1H, H-1b), 5.64 (d, J = 7.1 Hz, 1H, H-10), 7.28-7.33 (m, 2H, phenyl), 7.33-7.46 (m, 3H, phenyl) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 14.2 (CH_3 -11), 19.9 (CH_3 -12 or 13), 20.0 (CH_3 -16), 22.4 (CH_3 -12 or 13), 25.0 (CH_3 -17), 26.4 (CH_3 -18), 50.8 (C-6), 57.6 (CH-9), 70.5 (CH-5), 76.0 (CH-4), 79.3 (CH-10), 81.2 (CH-3), 108.8 (C-15), 112.9 (CH_2 -1), 125.9 (CH-phenyl), 128.8 (CH-phenyl), 128.9 (CH-phenyl), 133.7 (C-14), 141.3 (C-2), 152.6 (C-8), 176.7 (C-7) ppm.

IR (thin film) ν 3330, 2987, 2937, 1777, 1689, 1456, 1340, 1254, 1214, 1191, 1152, 1120, 972, 950, 905, 768, 700 cm^{-1} .

HRMS (EI) calcd for $\text{C}_{23}\text{H}_{31}\text{O}_6\text{N}$ $[\text{M}+\text{Na}]^+$, 440.2049; found 440.2039 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +55.6^\circ$.

NOE-analysis:**(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*S*)-2,2-Dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolan-4-yl)-3-**

(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (34). Alcohol **33** (1.0 g, 2.4 mmol, 1.0 eq) was dissolved in methylene chloride (8 mL) and cooled to 0 °C. DIPEA (2.1 mL, 12.0 mmol, 5.0 eq) and MOM-Cl (0.54 mL, 7.2 mmol, 3.0 eq) were added sequentially. After the addition, the ice bath was removed, the reaction mixture was heated to 50 °C and the yellow solution was stirred for 48 hours. The reaction was quenched by the addition of water. After separating the two layers the aqueous phase was extracted with methylene chloride three times. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (hexanes/ethyl acetate 9:1 to 5:1) 879 mg (79%) of the MOM protected alkene (**34**) could be isolated as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.91 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.86 (s, 3H), 3.26 (s, 3H), 4.46 (dd, *J* = 1.5, 6.8 Hz, 1H), 4.48 (d, *J* = 6.4 Hz, 1H), 4.57 (d, *J* = 6.4 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 1.5 Hz, 1H), 4.77 (quint, *J* = 6.8 Hz, 1H), 5.0-5.02 (m, 1H), 5.15-5.17 (m, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 7.28-7.33 (m, 2H), 7.34-7.44 (m, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 14.3 (CH₃), 20.4 (CH₃), 21.9 (CH₃), 22.2 (CH₃), 26.0 (CH₃), 26.3 (CH₃), 50.8 (C), 56.3 (OCH₃), 57.7 (CH), 77.5 (CH), 77.9 (CH), 79.4 (CH), 81.0 (CH), 99.3 (CH₂), 108.2 (C), 112.6 (CH₂), 125.8 (CH), 128.8 (CH), 128.82 (CH), 133.7 (C), 140.6 (C), 152.6 (C), 176.6 (C) ppm.

IR (thin film) ν 2985, 2939, 1776, 1693, 1455, 1367, 1340, 1247, 1192, 1158, 1121, 1083, 1033, 948, 904 cm⁻¹.

HRMS (EI) calcd for C₂₅H₃₅O₇N [M+Na]⁺, 484.2311; found 484.2309 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = -0.9°.

References

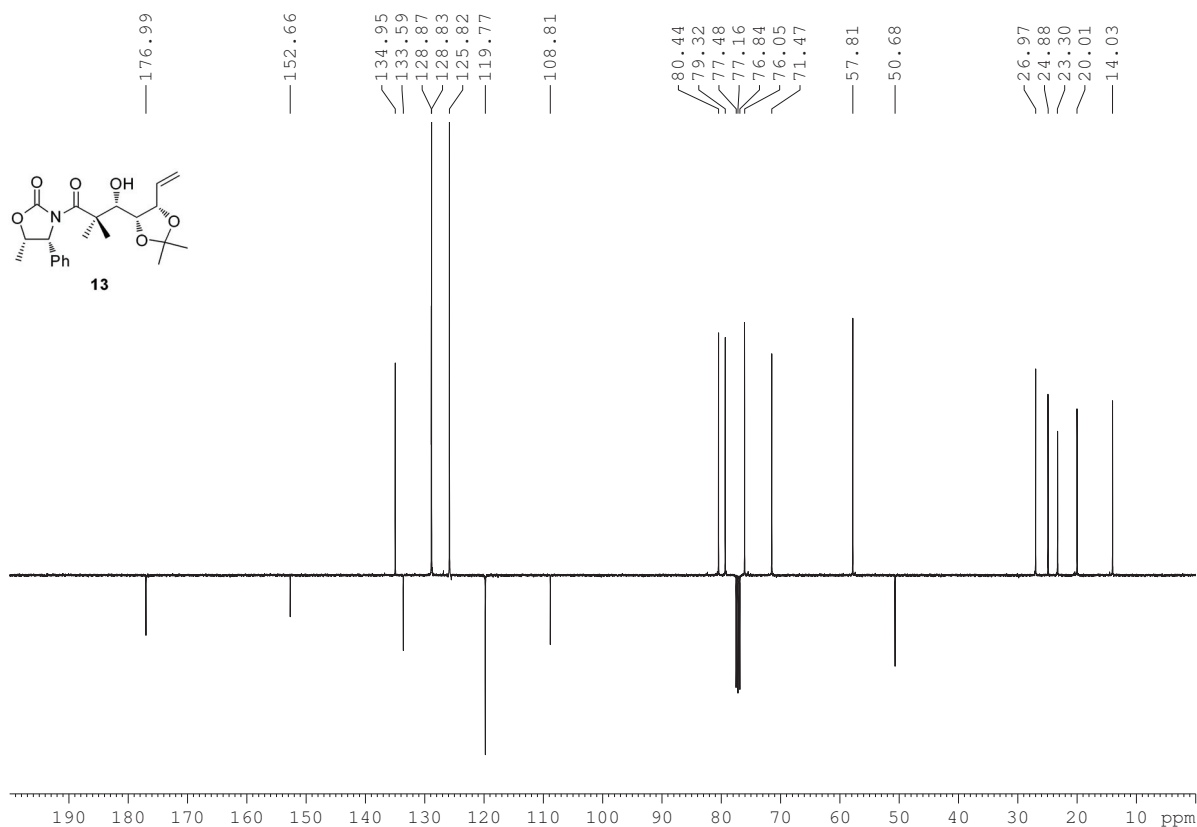
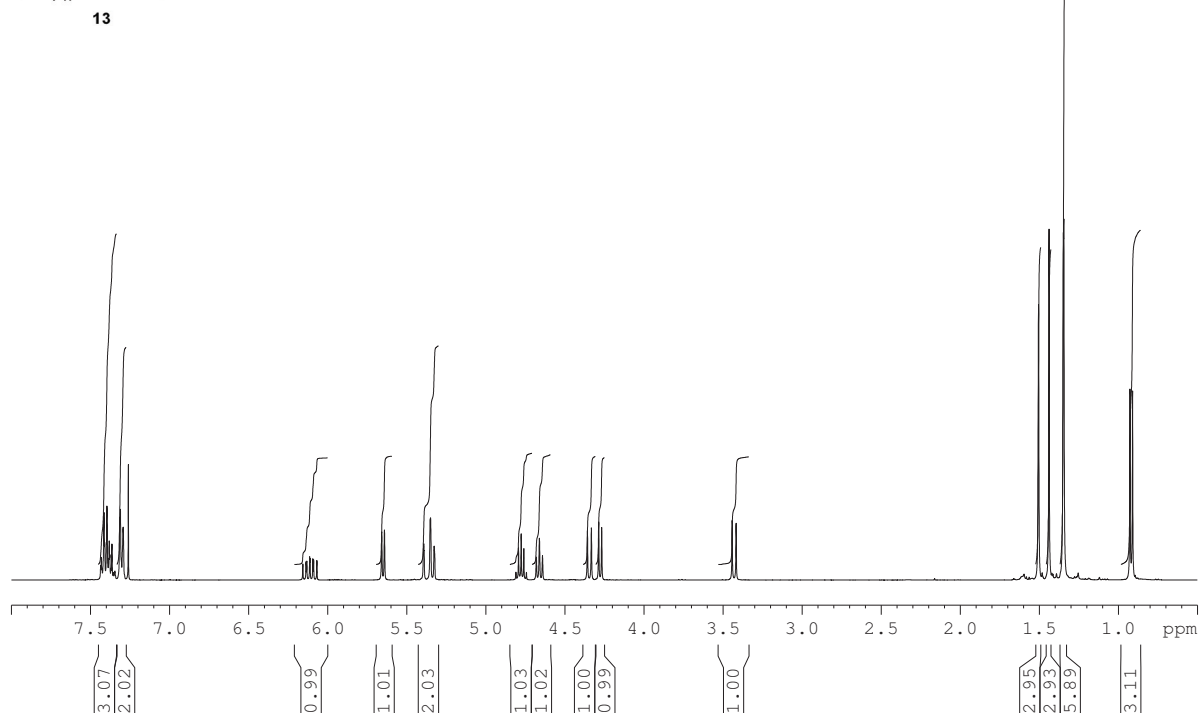
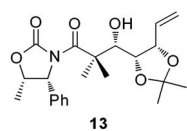
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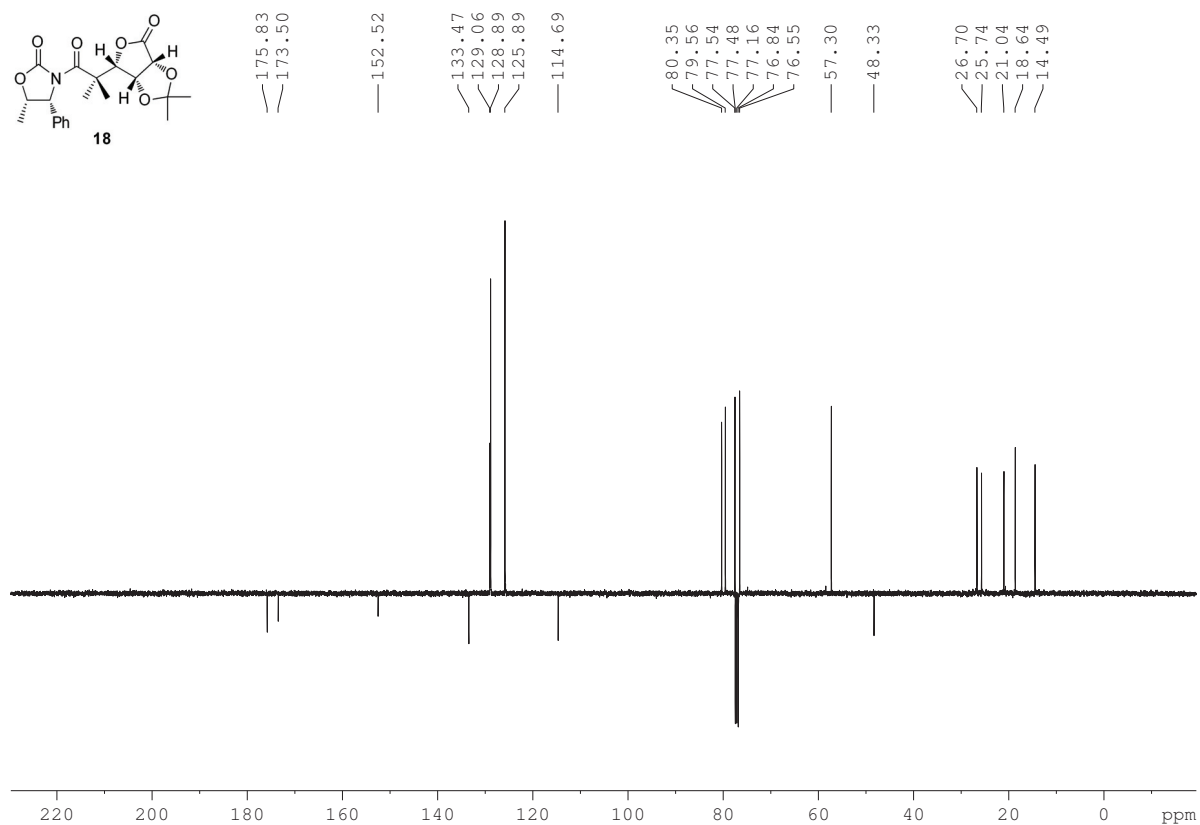
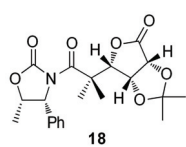
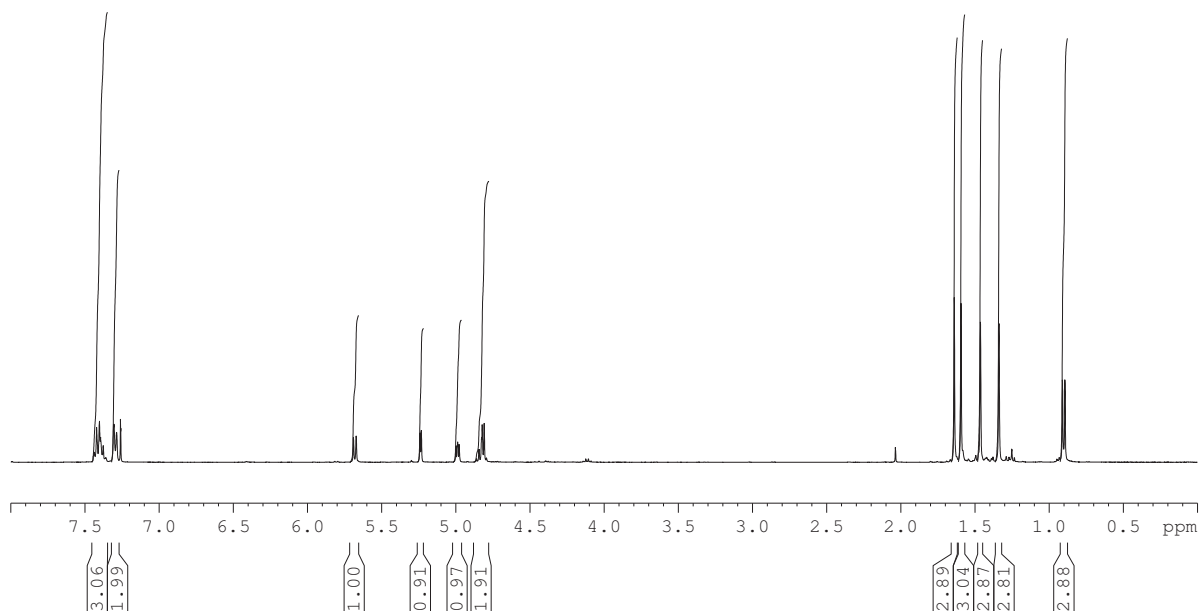
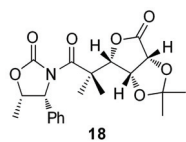
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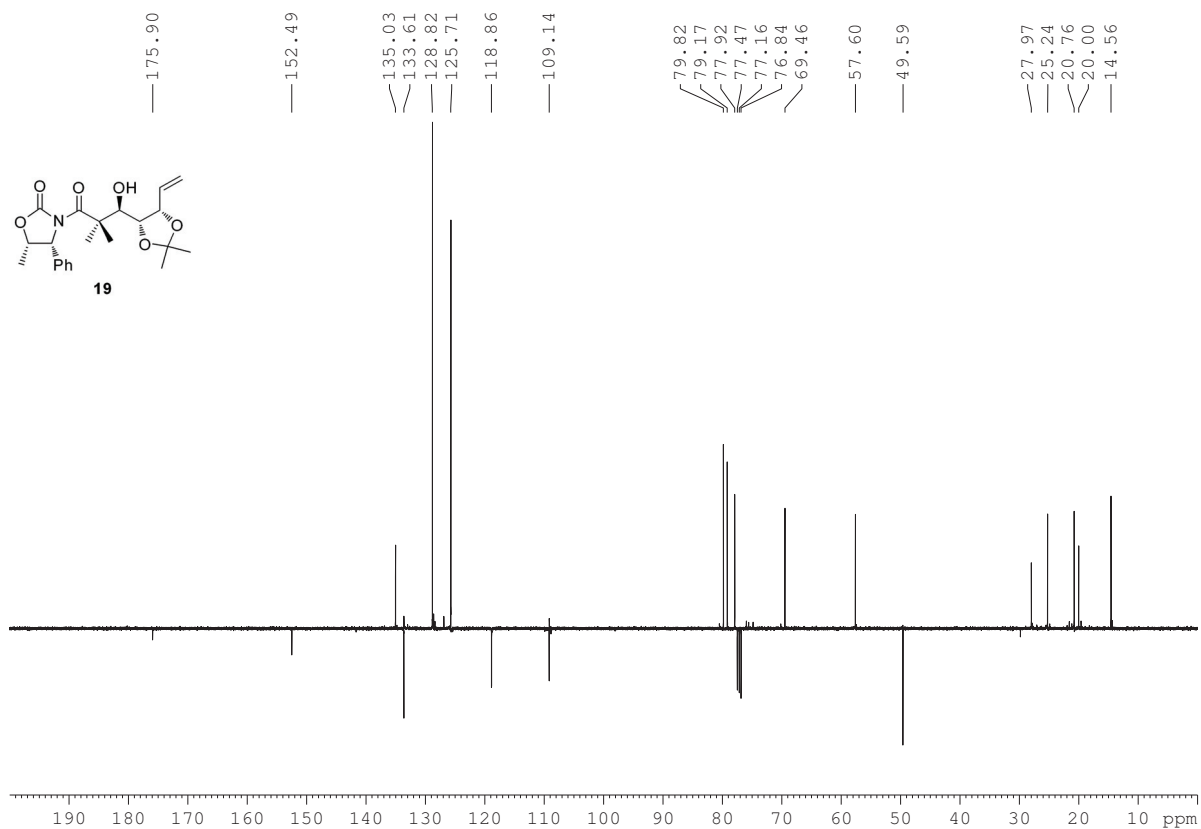
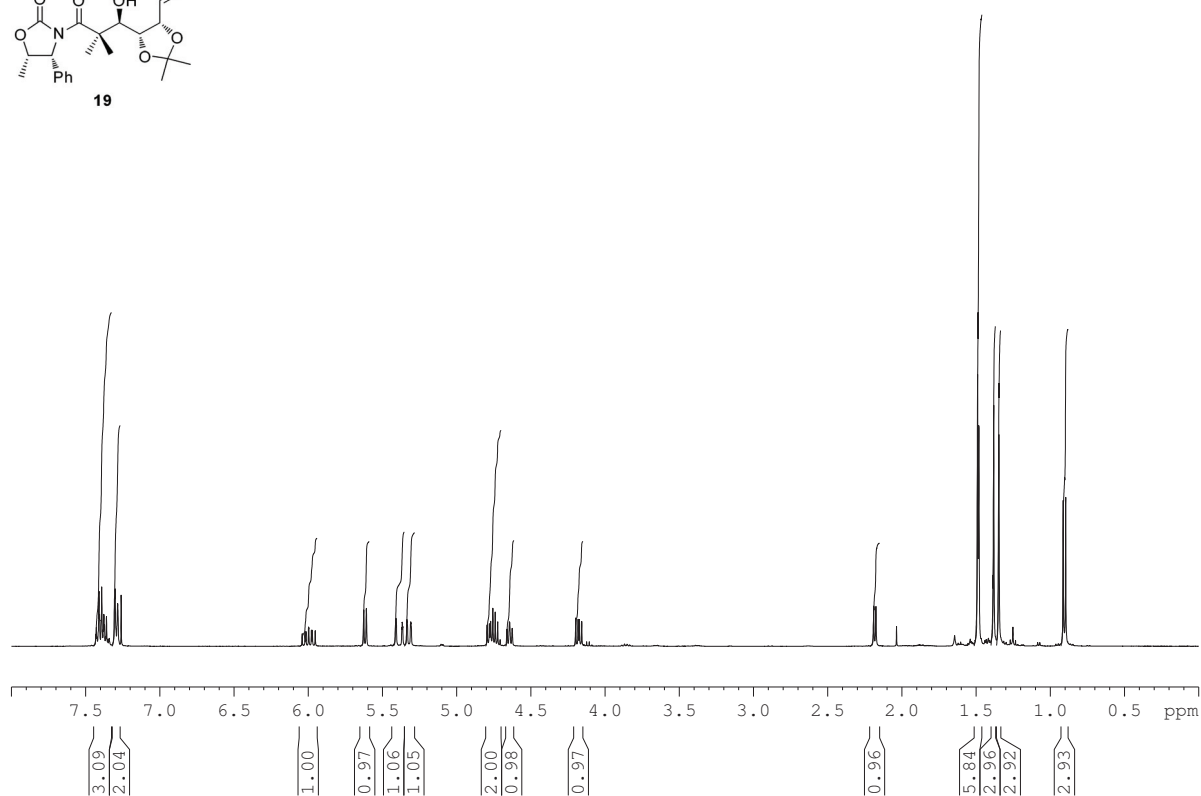
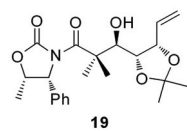
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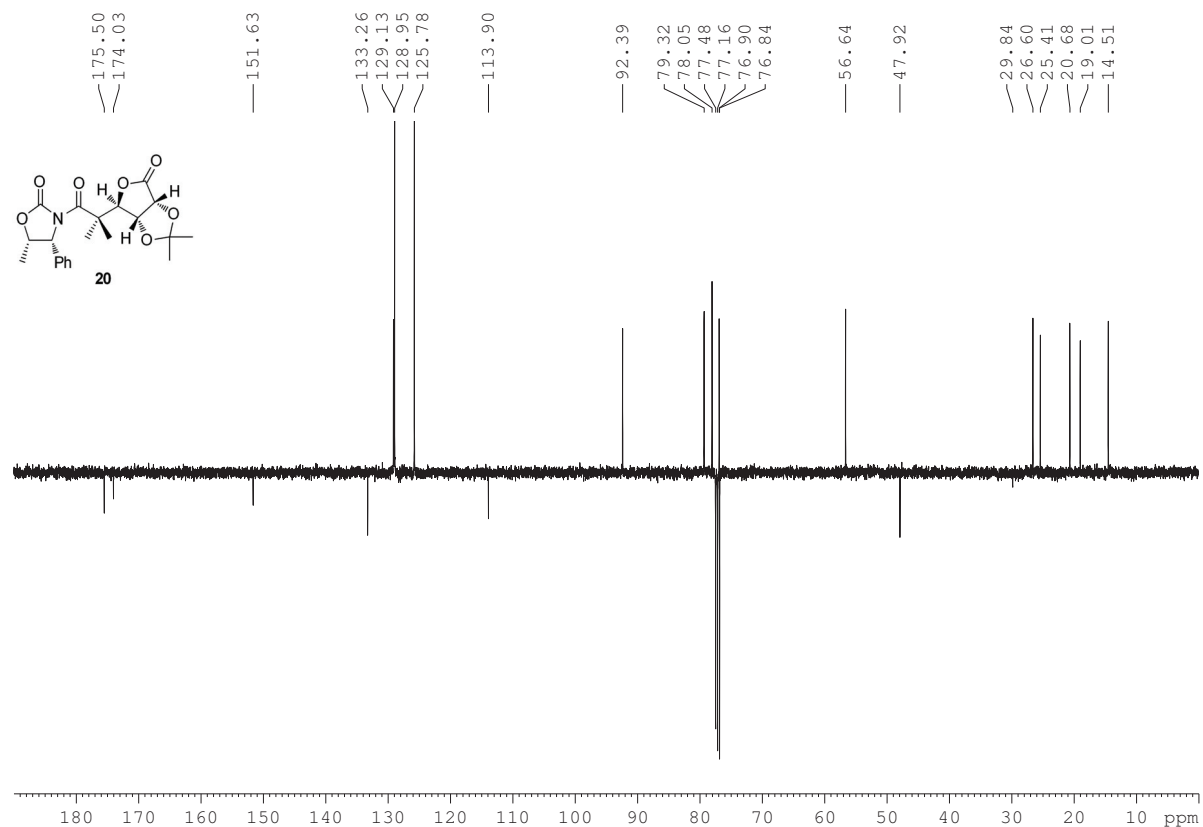
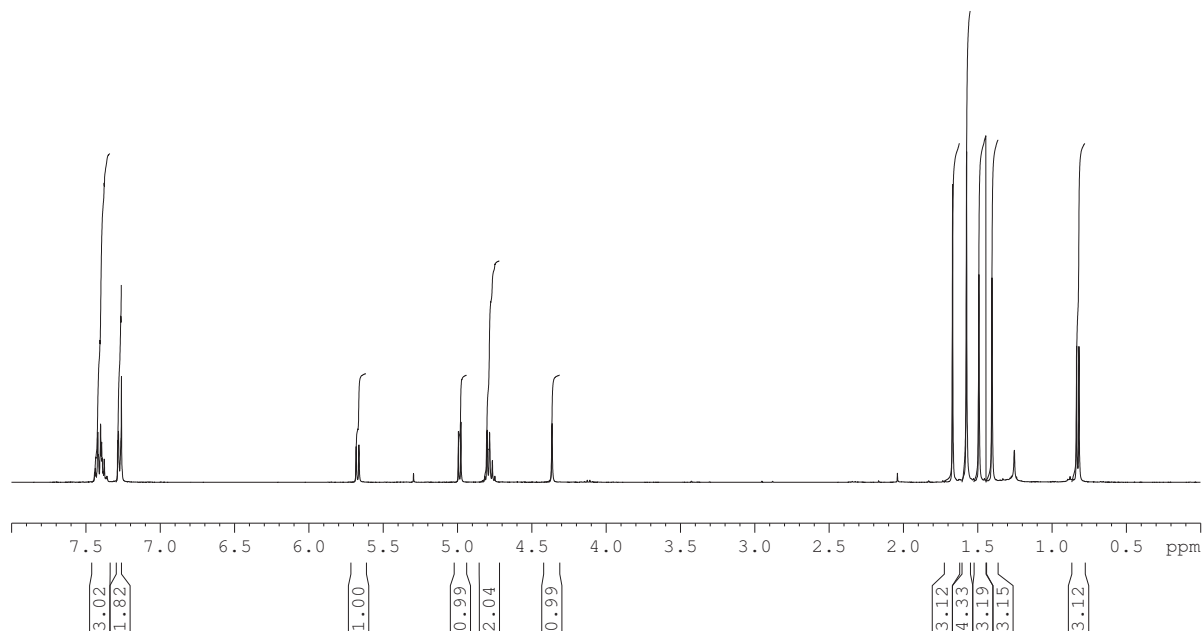
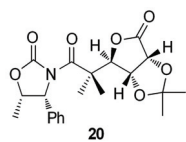
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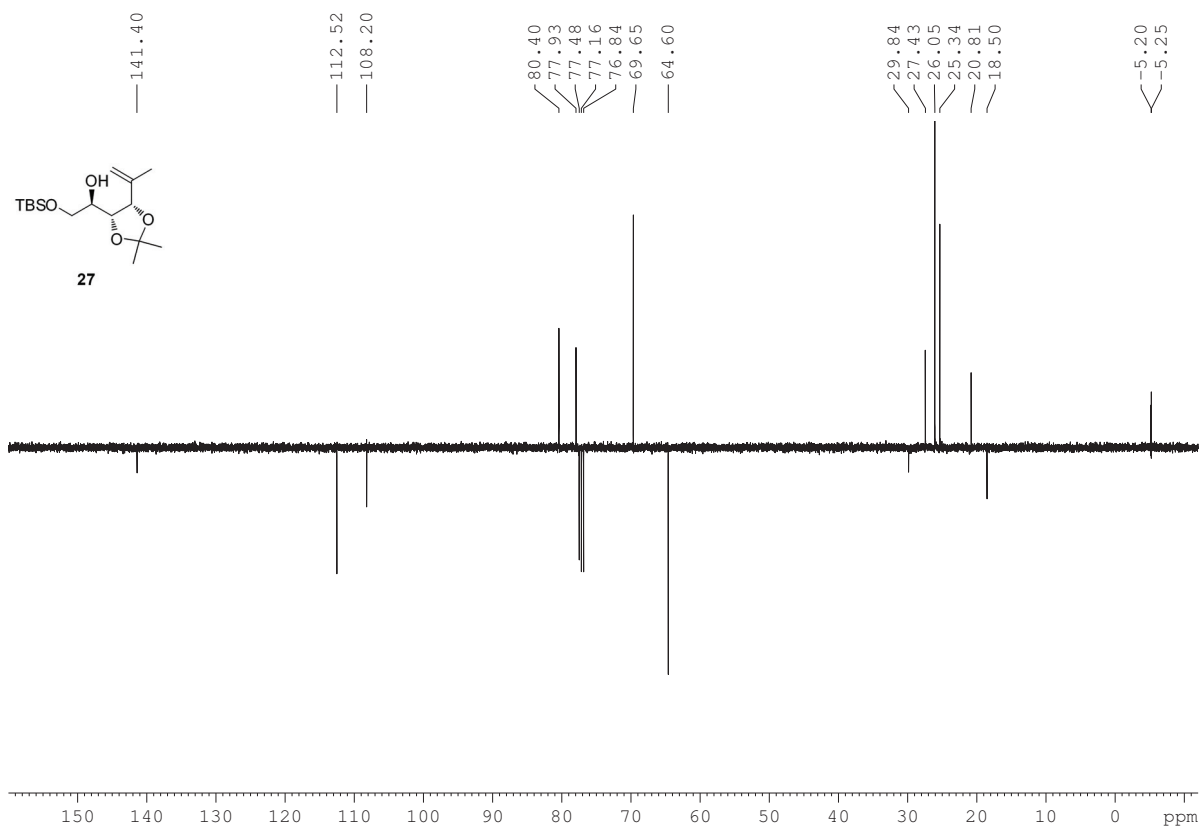
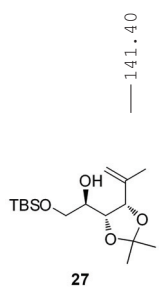
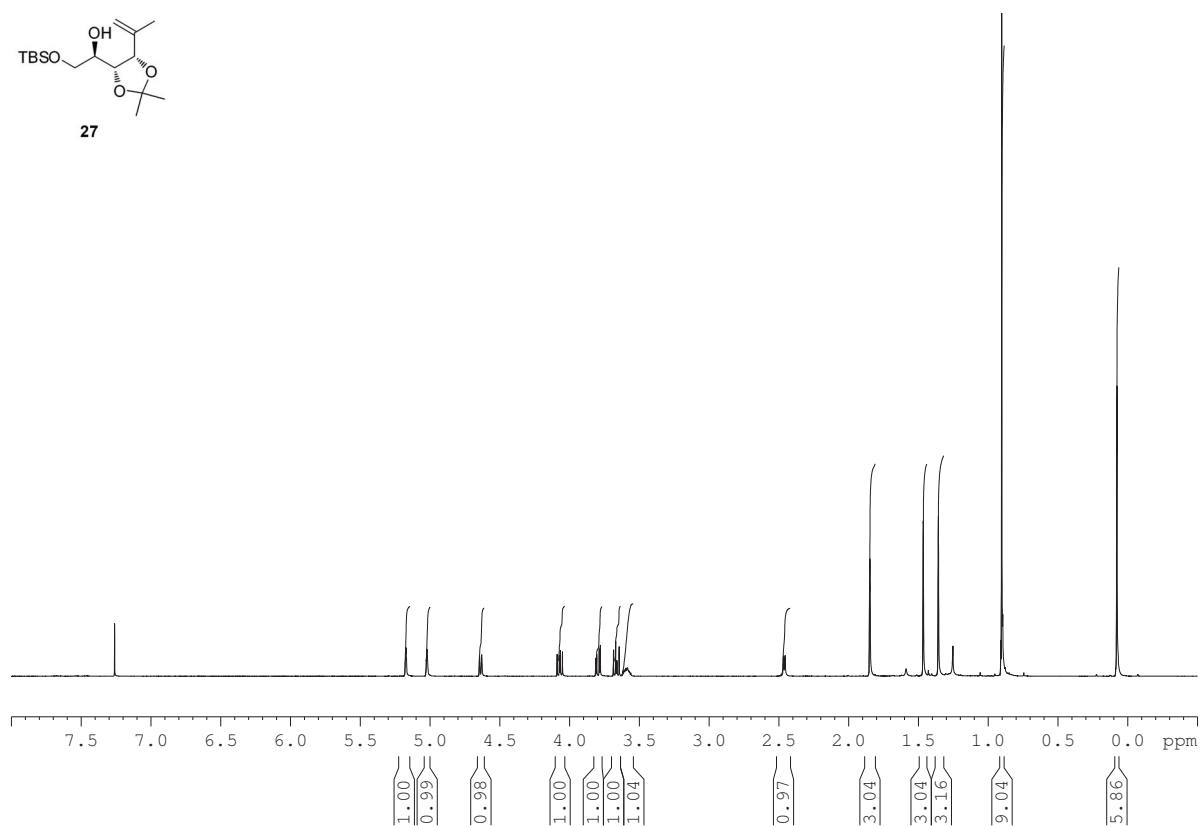
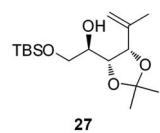
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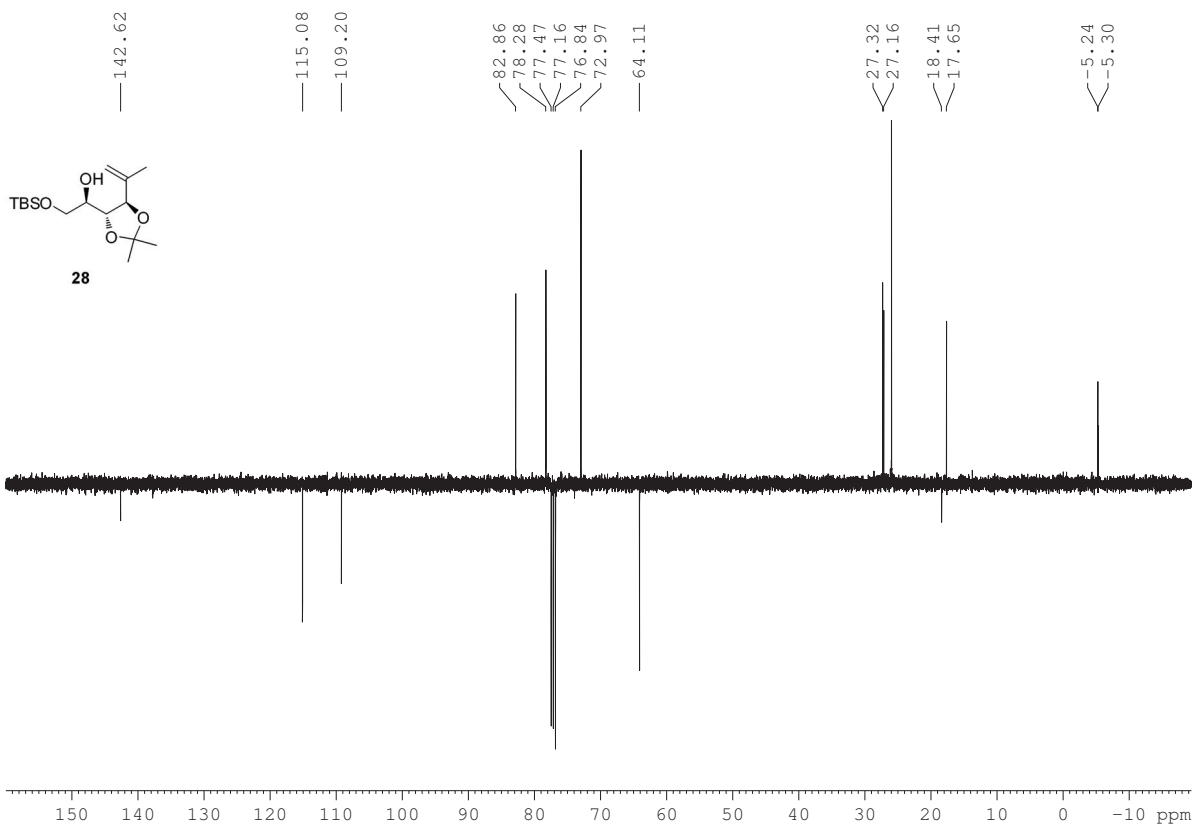
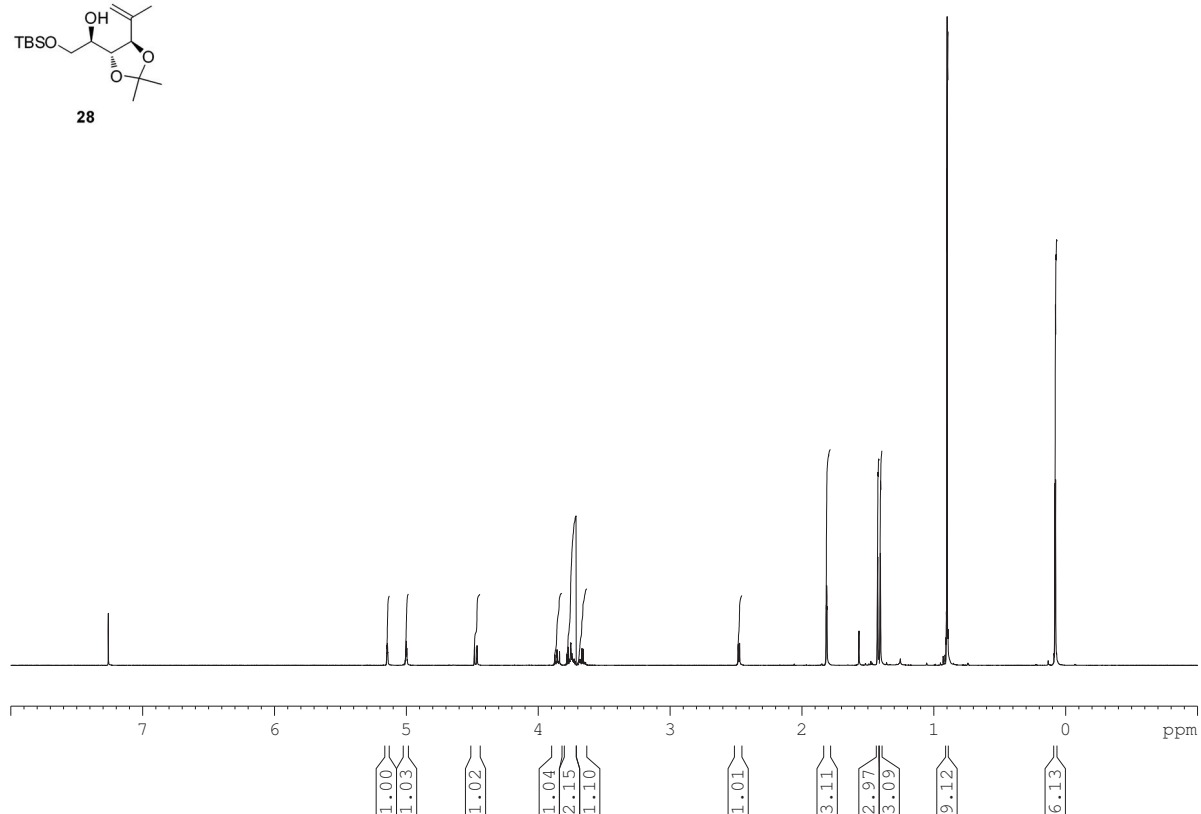
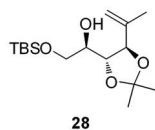


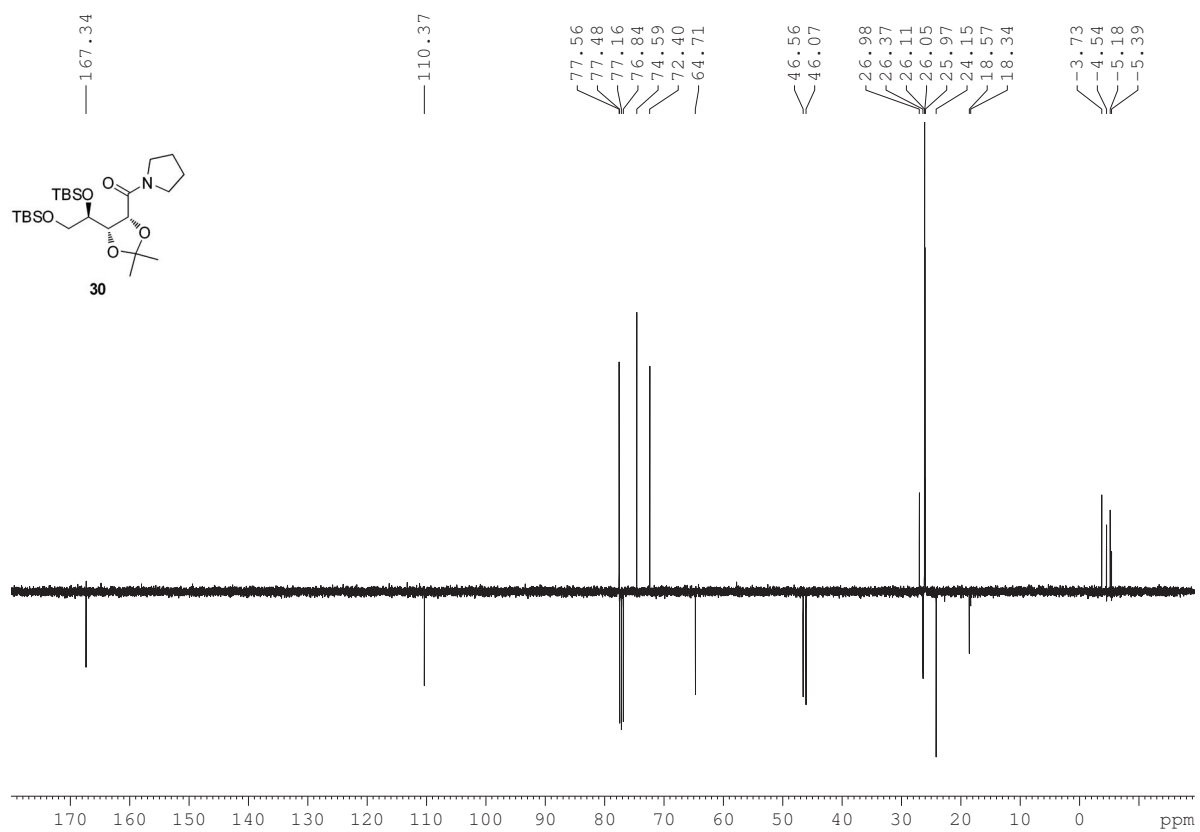
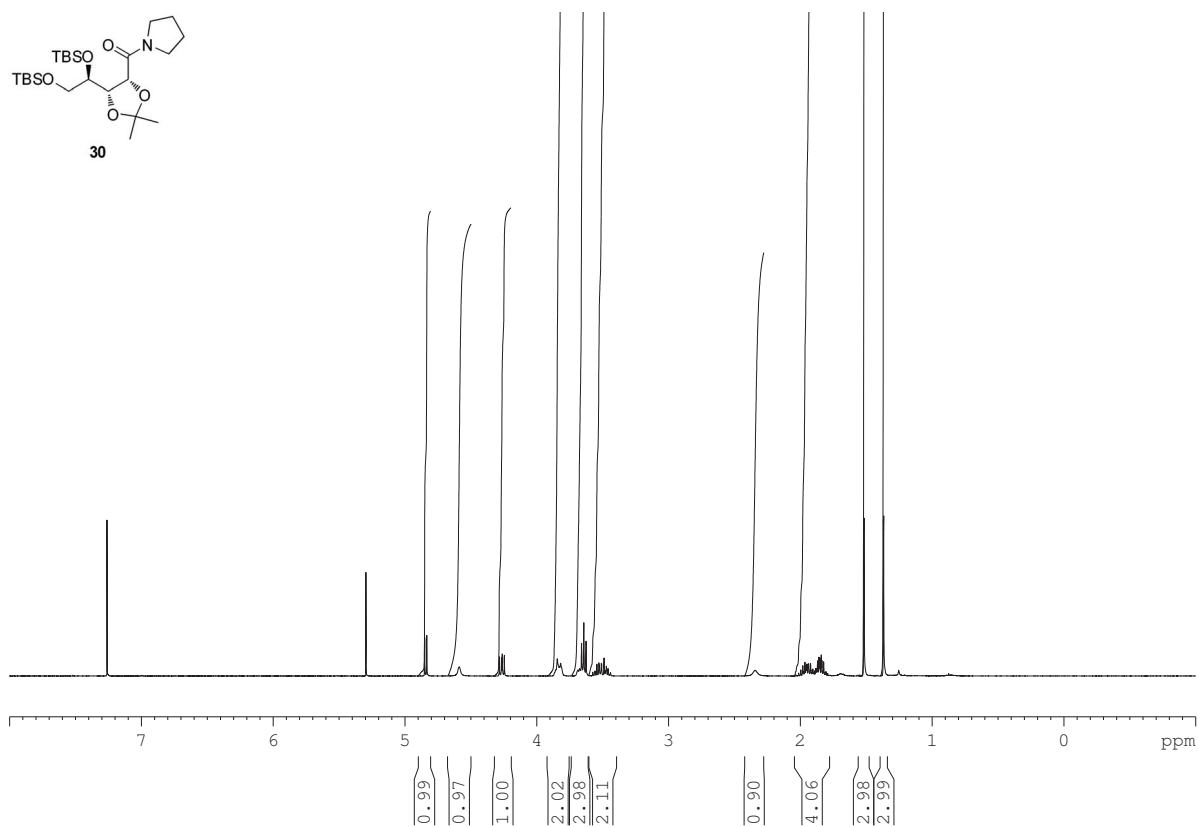


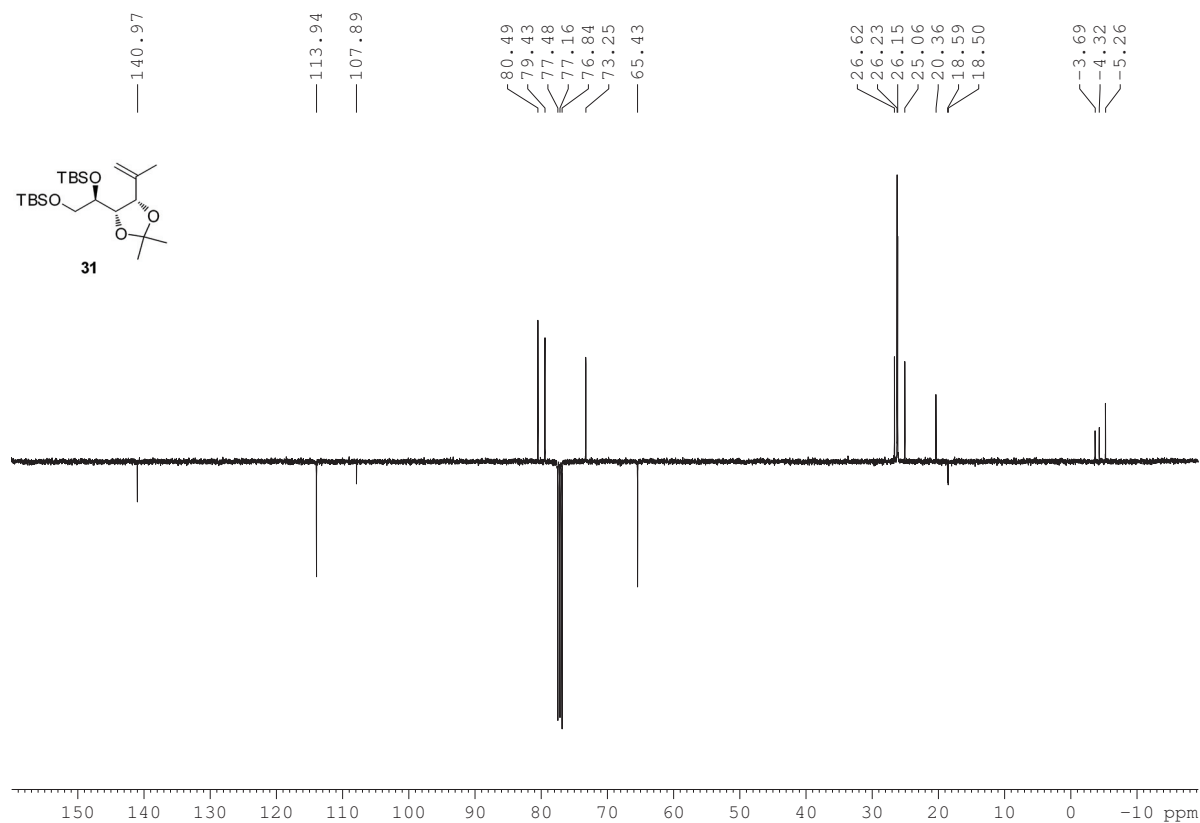
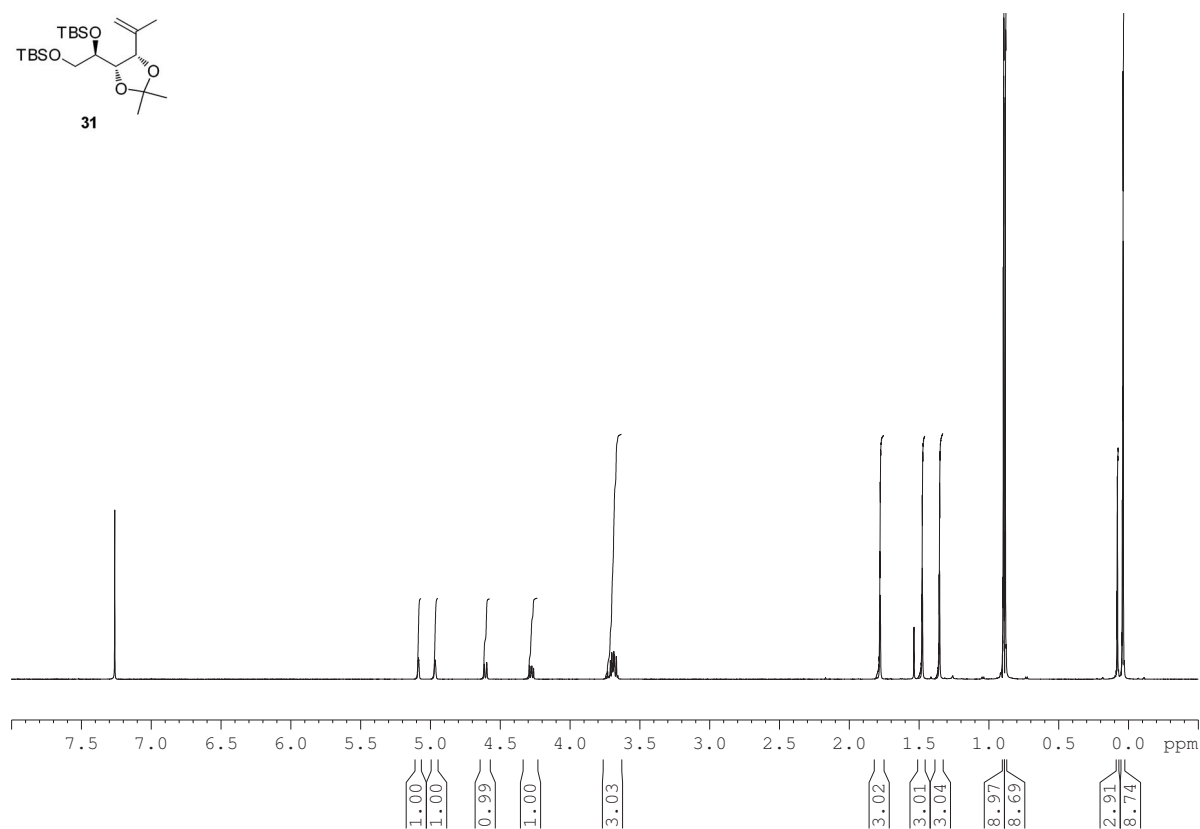
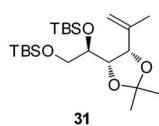


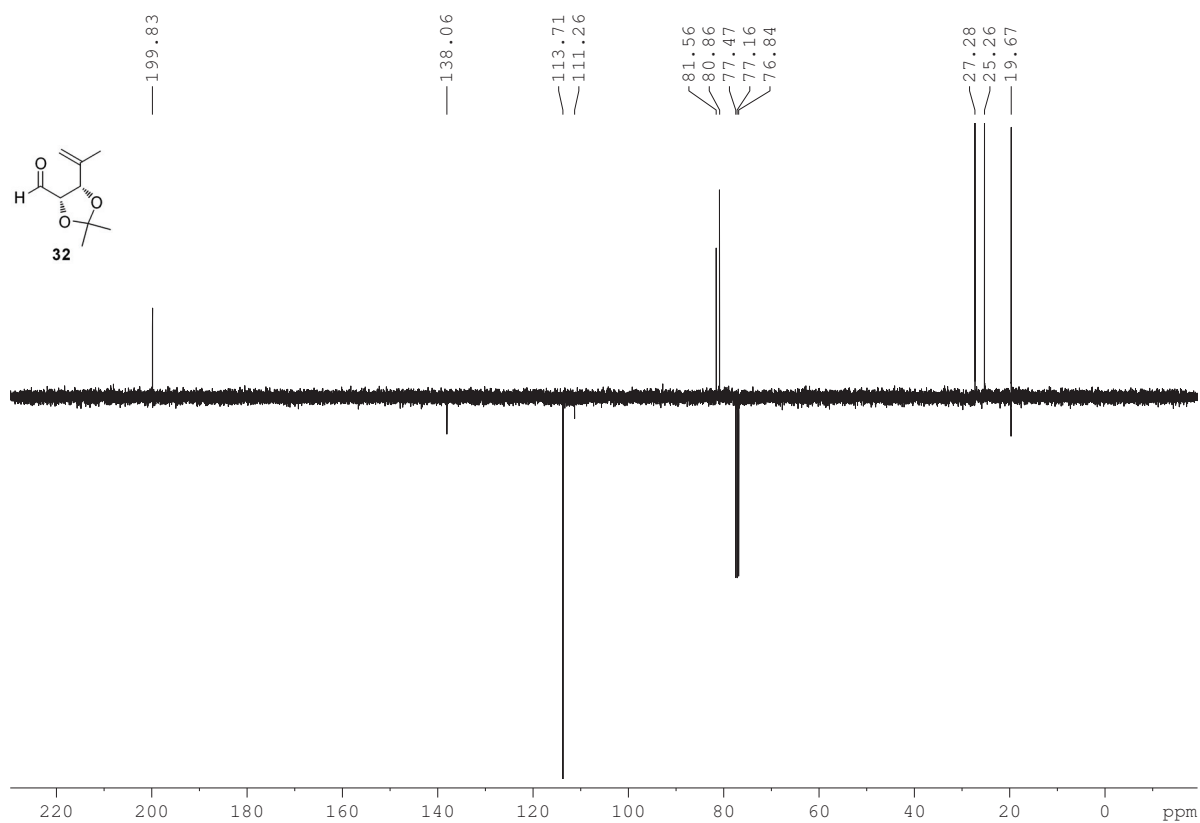
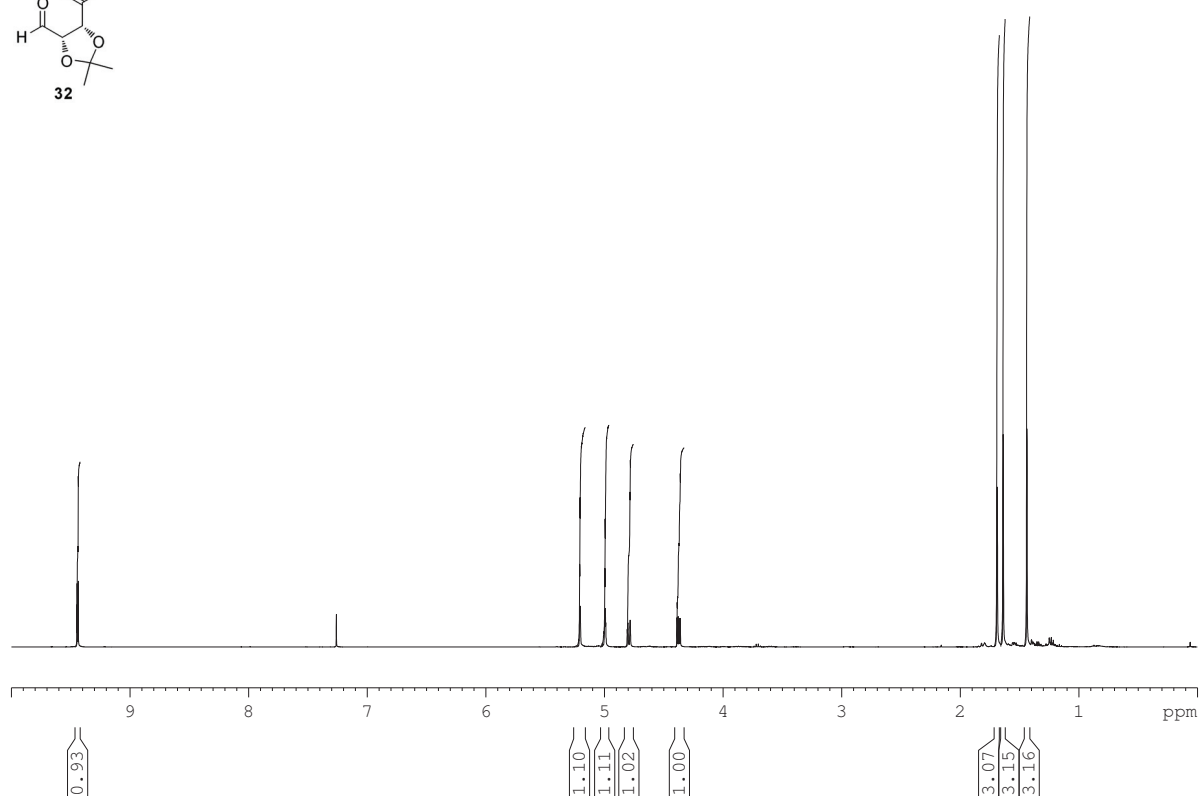
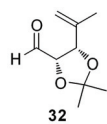


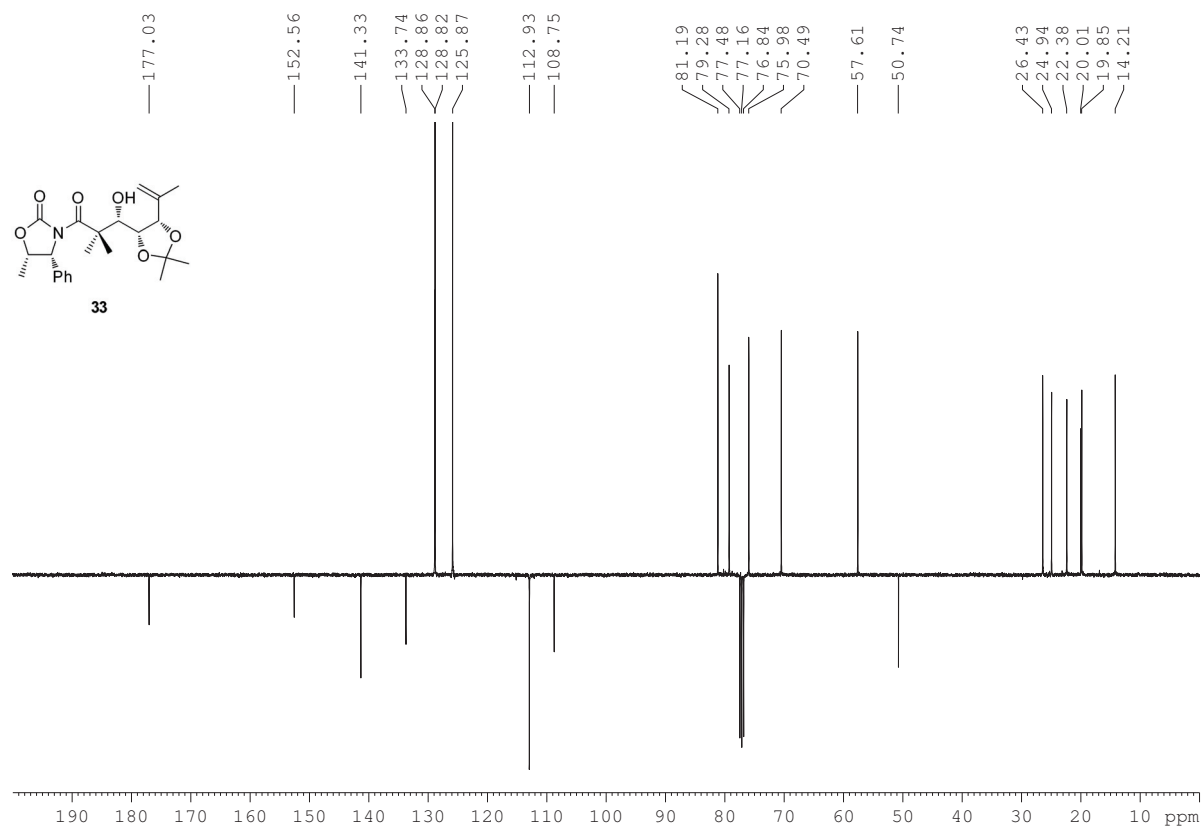
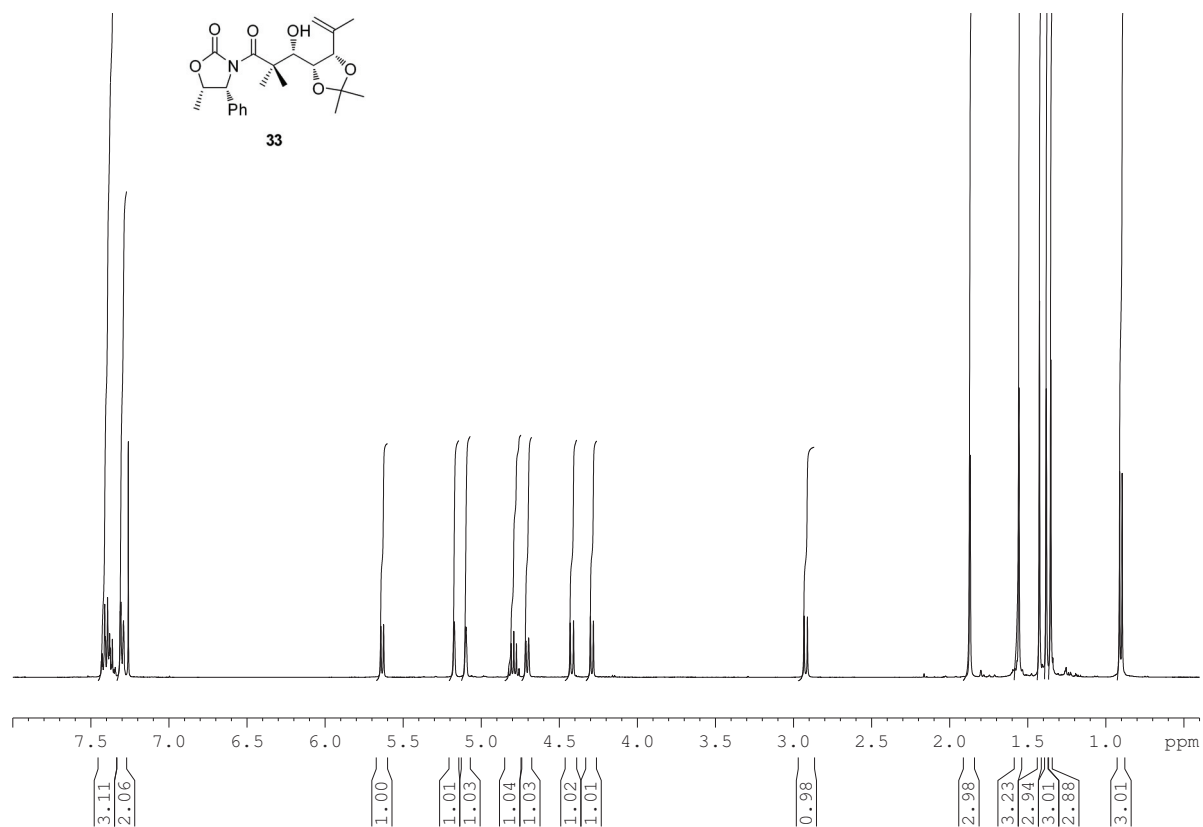


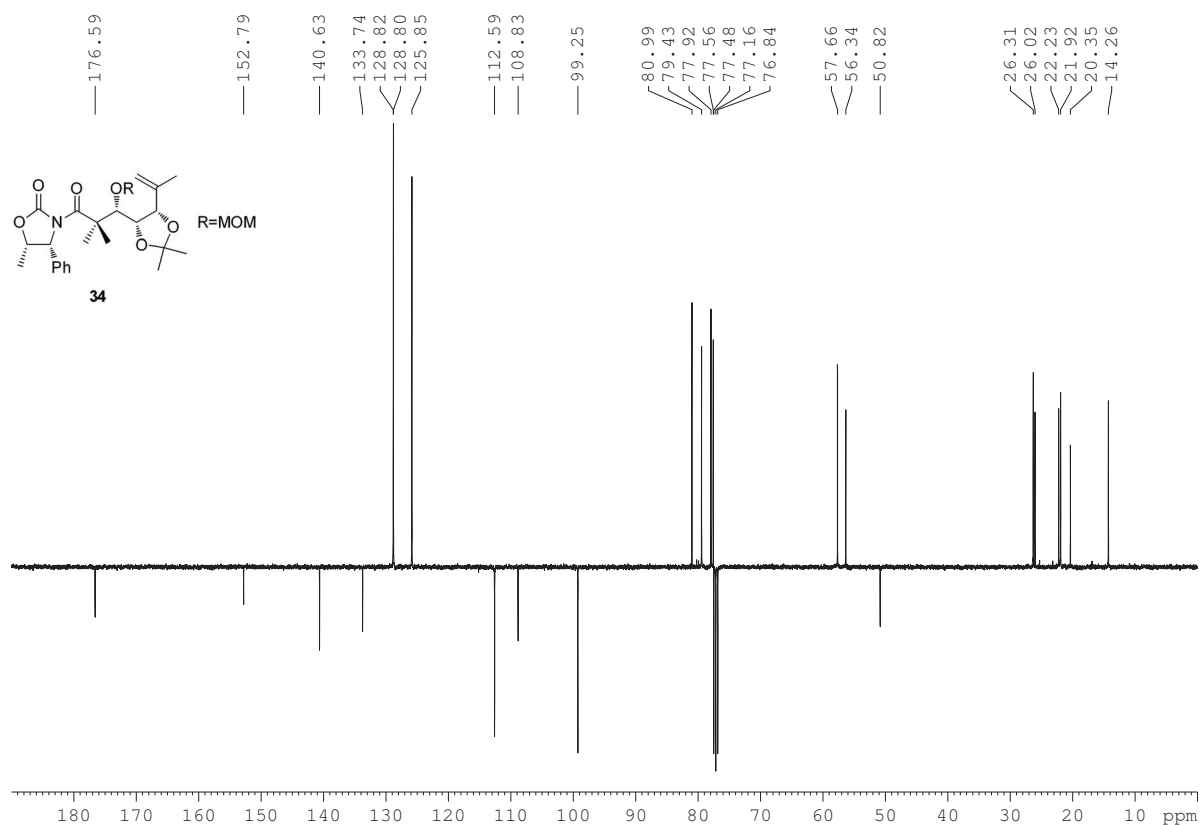
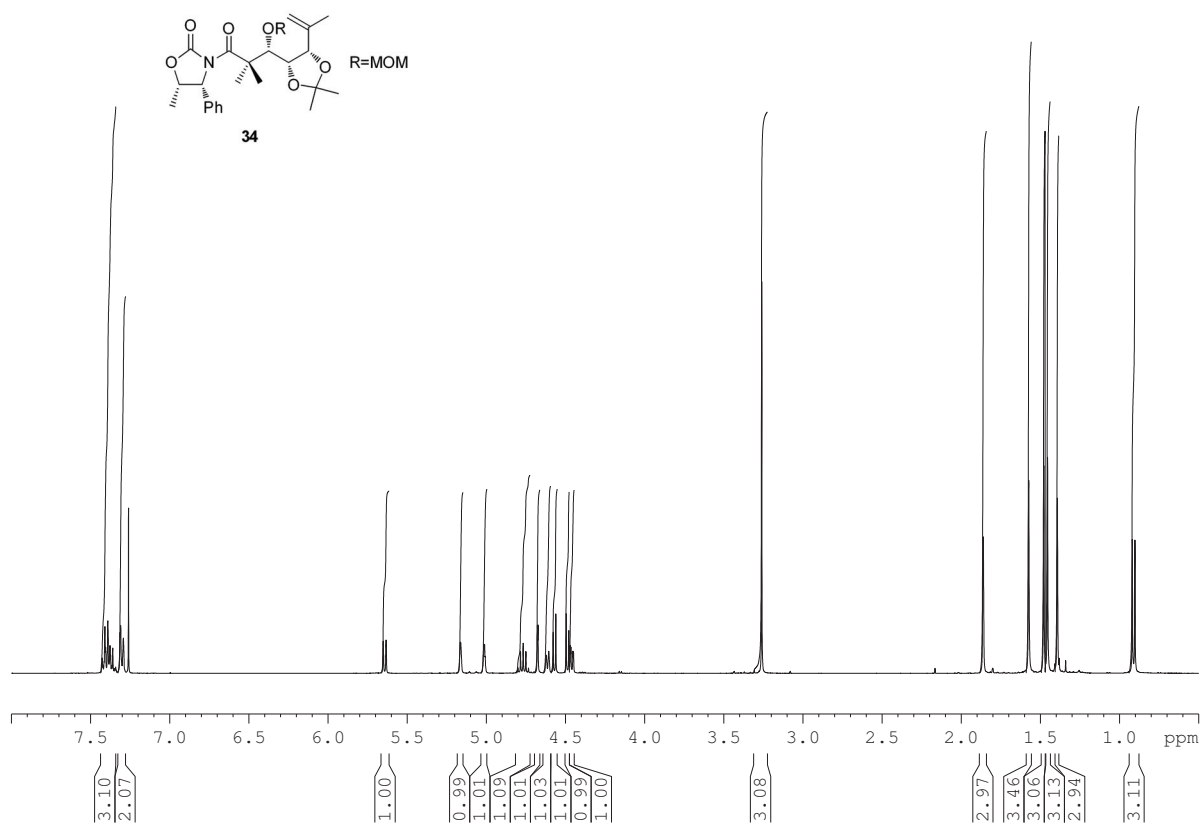












6. APPENDIX II

Fürst, R.; Rinner, U., Synthesis of an Advanced Intermediate of the Jatrophone Diterpene Pl-4: A Dibromide Coupling Approach. *The Journal of Organic Chemistry* **2013**, 78 (17), 8748-8758. DOI: 10.1021/jo401480t.

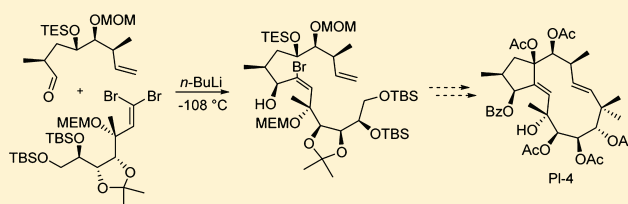
Synthesis of an Advanced Intermediate of the Jatrophone Diterpene PI-4: A Dibromide Coupling Approach

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Supporting Information

ABSTRACT: The preparation of an advanced intermediate toward the synthesis of the jatrophone diterpene PI-4 is described. The key step is a regioselective chelation-controlled lithiation of the (Z)-configured bromide in the corresponding vinyl dibromide precursor. The method outlined within this Article is suitable for the facile access of sterically hindered internal vinyl halides for further coupling reactions.



INTRODUCTION

A general characteristic of members of the Euphorbiaceae plant family, commonly referred to as spurges, is the milky latex that has been identified as a rich source of structurally complex and intriguing terpene-based natural products. Over the past decades, phytochemists have shown great interest in the active ingredients of the Euphorbia species, and a vast number of diterpenes of the jatrophone, tiglane, ingenane, and lathyrane frameworks have been isolated.¹

Some of these complex natural products show promising biological properties, including cytotoxic, antiviral, multidrug-resistance reversing (MDR), and antitumor activities,^{2–5} and recently, an ingenol ester has been approved for the topical treatment of precancerous skin conditions.^{6,7} Thus, it is not surprising that several Euphorbia species have been employed in traditional herbal folk medicines, mainly to treat cancerous conditions, swellings, and warts.⁸ In particular, the MDR-reversing properties, more precisely, the selective inhibition of the ATP-dependent efflux pump p-glycoprotein, are of great interest to modern cancer research. The overexpression of p-glycoprotein in the cancer cells of malignant tumors is a serious problem in chemotherapy. The elaboration of synthetic routes to jatrophone diterpenes is of importance for the development of novel anticancer drugs that could potentially address this problem.

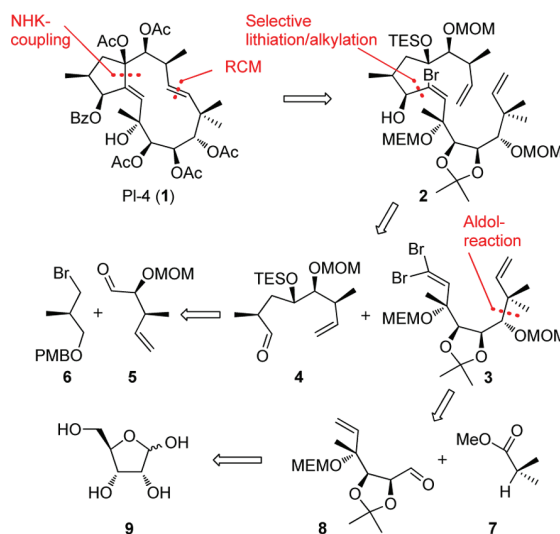
In 2003, PI-4 (1) was isolated by Hohmann et al. from *Euphorbia platyphyllos*, an annual herbaceous plant that is found in different climate regions.⁹ PI-4 belongs to the family of jatrophone diterpenes and is characterized by a highly functionalized five-membered ring that is annulated to a 12-membered macrocycle. Despite the challenging structural properties, only a few approaches to jatrophone diterpenes have been reported.^{10–24}

RESULTS AND DISCUSSION

Herein, we present a concise route to a highly advanced intermediate of PI-4 via a regioselective lithiation/alkylation sequence of geminal dibromide 3 as a key step, which is

retrosynthetically outlined in Scheme 1. The synthetic approach is based on a report by Braun and co-workers who

Scheme 1. Retrosynthetic Analysis of PI-4 (1)



showed that selective alkylation of the more hindered bromide can be achieved through coordination of the intermediate organolithium species to a chelating functionality in the α -position to the vinyl dibromide.²⁵ Furthermore, Braun demonstrated that the chiral information of the chelating MEM group in the lithium species is transferred to the reaction partner to deliver the corresponding secondary alcohol in a diastereoselective manner.

Surprisingly, this protocol has not yet been applied to total synthesis, especially because this reaction sequence provides access to sterically hindered vinyl halides that could serve as

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useful building blocks for further coupling reactions. The absence of applications is even more striking because other procedures to hindered vinyl halides, for example, via hydrometalation reactions using substituted alkynes, are not reliable on structurally complex substrates.^{26,27}

As outlined in Scheme 1, a ring-closing metathesis (RCM) reaction was envisaged to be the final operation to establish the jatrophone framework. The cyclopentane ring would be closed via an NHK-coupling reaction of key intermediate **2**, which is available through the previously mentioned selective lithiation/alkylation sequence of dibromide **3** and aldehyde **4**. The northern fragment (aldehyde **4**) should become accessible via the coupling of Roche ester-derived bromide **6** and aldehyde **5**. Dibromide **3** would be elaborated from aldehyde **8** and methyl isobutyrate (**7**). D-Ribose could be employed as an ideal and inexpensive starting material from the chiral pool for the preparation of intermediate **8**.

The first approach toward dibromide **3** started with methyl ketone **10**, readily available from D-ribose in 60% yield, via a five-step procedure.²⁰ The addition of vinylmagnesium bromide to methyl ketone **10** afforded terminal alkene **11** in excellent yield as the only detectable isomer after MEM protection of the newly formed tertiary alcohol.^{28,29} Deprotection of the vicinal silyl ethers and subsequent periodate cleavage delivered aldehyde **8**, which served as a substrate for the aldol reaction with methyl isobutyrate to give alcohol **12** in 78% yield as a 3:1 mixture of diastereomers.³⁰ Protection of the hydroxy group and subsequent ozonolysis delivered aldehyde **13**, the precursor for the installation of the dibromide, in good overall yield.

With aldehyde **13** in hand, the installation of the dibromoolefin was pursued. As outlined in Table 1, the

Table 1. Reagents and Conditions for the Formation of Dibromide 14

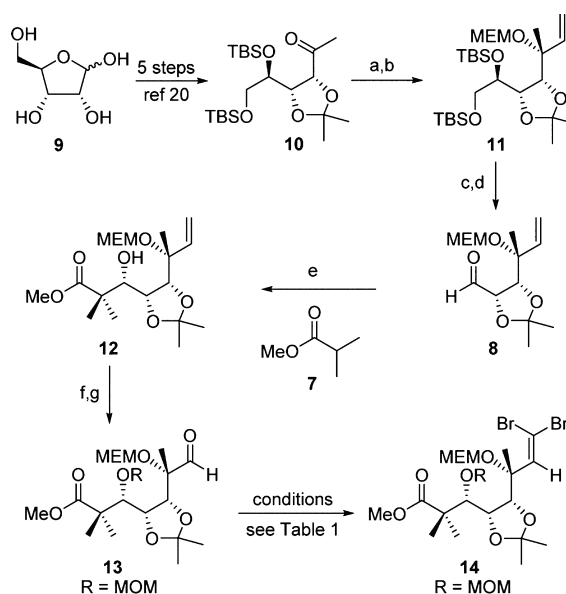
reagents	temperature	solvent	yield (%)
PPh ₃ , CBr ₄	0 °C to rt	CH ₂ Cl ₂	0
PPh ₃ , CBr ₄ , 2,6-lutidine	0 to 50 °C	CH ₂ Cl ₂	0
PPh ₃ , CBr ₄ , Zn	0 °C to rt	CH ₂ Cl ₂	0
PPh ₃ CHBr ₃ , <i>t</i> -BuOK, Zn	reflux	dioxane	0
PPh ₃ CHBr ₃ , <i>t</i> -BuOK	0 °C to rt	THF	12
PPh ₃ CHBr ₃ , <i>t</i> -BuOK	0 °C to rt	toluene	17

reaction of PPh₃ and CBr₄ for the in situ generation of the ylide resulted in no reaction. Also, the addition of activated zinc dust³¹ or 2,6-lutidine³² did not lead to any detectable amounts of **14**. Reaction of aldehyde **13** with the preformed Wittig salt and *t*-BuOK as base allowed the isolation of **14** in low yield (Scheme 2).³³ Presumably, the steric hindrance of the MEM group as well as chelating effects in close proximity to the aldehyde is responsible for the observed results. Because of the inability to improve the yield of the Wittig transformation at this stage, the sequence was abandoned.

In a slightly modified approach, outlined in Scheme 3, we decided to introduce the dibromide segment prior to introducing the bulky MEM group. Thus, ozonolysis of the terminal alkene in **15** was followed by Wittig olefination and MEM protection of the resulting tertiary alcohol to afford **16** in 59% overall yield.

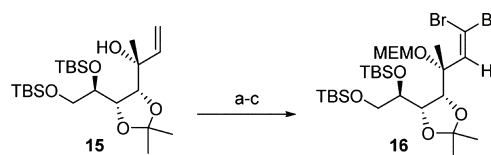
We decided to employ dibromide **16** earlier than originally planned in the key lithiation/alkylation sequence to keep the substrate as structurally simple as possible for this novel transformation. Further elaboration of the alkyl chain and the

Scheme 2. Preparation of Dibromide 14^a



^aReagents and conditions: (a) vinyl-MgBr, THF, 0 °C to rt, 92%; (b) MEMCl, DIPEA, DCM, 0 to 50 °C, 97%; (c) TBAF, THF, 0 °C to rt, quant.; (d) NaIO₄, DCM, 0 °C to rt, 90%; (e) **7**, LDA, THF, −20 °C; then **8**, 78%, dr 3:1; (f) MOMCl, DIPEA, DCM, 0 to 50 °C, 67%; and (g) O₃, DCM, −78 °C; PPh₃, 90%.

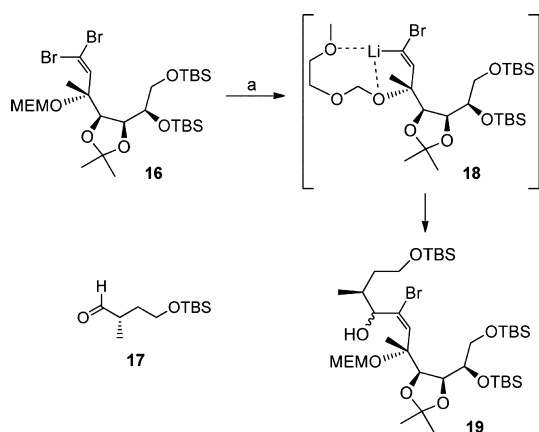
Scheme 3. Preparation of Dibromide 16^a



^aReagents and conditions: (a) O₃, DCM, −78 °C; DMS, 84%; (b) *t*-BuOK, THF, PPh₃CH₃Br, −20 to 0 °C, 85%; and (c) MEMCl, DIPEA, DCE, 100 °C, 87%.

installation of the geminal dimethyl group were postponed until after the closure of the cyclopentane ring.

Conditions for the crucial, regioselective lithiation/alkylation of dibromide **16** were first elaborated using known aldehyde **17** (Scheme 4).³⁴ In accordance with Braun's publication, we found that the temperature is of crucial importance for the selective lithiation and the reaction mixture has to be kept between −105 and −110 °C to prevent the formation of the terminal alkyne, the product of the competing Corey–Fuchs reaction.³¹ We were pleased to learn that lithiation of dibromide **16** and subsequent addition of aldehyde **17** at −110 °C delivered the desired adduct **19**. Although the product was obtained as a 1:1 diastereomeric mixture with respect to the newly formed hydroxy moiety, we showed that lithiation of the (*Z*)-configured bromide occurs preferentially, which can be explained via the formation of chelated intermediate **18**.²⁵ The selective attack and formation of the *trans* double bond in vinyl halide **19** was confirmed by termination of the lithiation reaction after 30 min at −108 °C with methanol. The resulting ¹H NMR spectroscopic analysis showed unreacted starting material, the terminal alkyne, and the exclusive formation of the *trans*-vinyl bromide. The double-bond geometry could be easily identified by the assignment of the ³J coupling constant, which

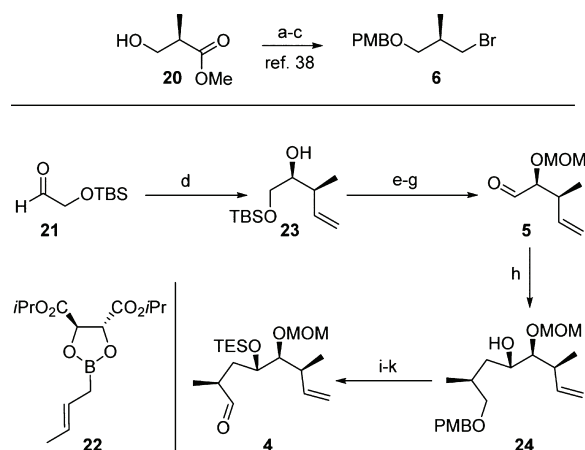
Scheme 4. Coupling Reaction with Dibromide 16^a

^aReagents and conditions: (a) *n*-BuLi, Et₂O, −116 to −108 °C; then 17, 40%, dr 1:1.

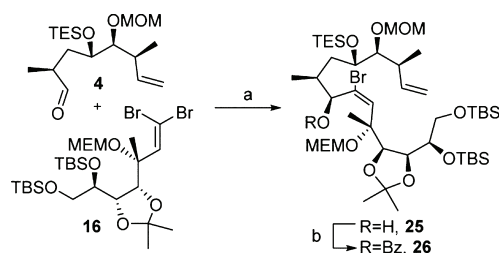
amounts to 14 Hz. As a consequence, the electrophile was introduced at the more hindered position, and the diastereomeric mixture of alcohol 19 was isolated in 40% overall yield.

With these promising results in hand, the synthesis of the northern fragment of Pl-4 was launched. The sequence started with Roush crotylation³⁵ of aldehyde 21,³⁶ which is readily available from ethylene glycol following a known two-step procedure.³⁷ Next, MOM protection of the secondary alcohol followed by deprotection of the primary TBS group with TBAF and oxidation of the resulting alcohol under Parikh–Doering reaction conditions resulted in the isolation of aldehyde 5. Bromide 6, the coupling partner for aldehyde 5, was synthesized from a commercially available Roche ester (20) via protection of the hydroxy moiety, reduction of the methyl ester, and subsequent bromination of the resulting alcohol.³⁸ Lithiation of the bromide followed by in situ formation of the corresponding Grignard reagent^{39,40} and addition of aldehyde 5 allowed the isolation of secondary alcohol 24 in a 9:1 diastereomeric ratio and in excellent yield (96%).³⁰ The formation of two diastereomeric secondary alcohols does not decrease the overall efficiency of the synthesis, as the position will be oxidized at a later point. The preparation of the northern part 4 was concluded after TES protection, cleavage of the PMB group, and oxidation of the primary alcohol (Scheme 5).

With aldehyde 4 in hand, the selective lithiation and coupling reaction of dibromide 16 was accomplished under the carefully controlled conditions described above. We were pleased to isolate desired vinyl bromide 25 in excellent yield, which was ultimately protected as benzoate 26 (Scheme 6). The diastereomers of unprotected bromide 25 were easily separated by silica gel chromatography, and the respective stereochemistries were determined by the modified Mosher ester analysis.^{41,42} Advanced intermediate 25 was obtained as a 1:1 mixture of diastereomers, which is in contrast to Braun's findings, who reported excellent diastereoselectivity with structurally simple substrates. We were hoping to observe similar preferences and, in accordance with Braun's results, the predominant formation of the desired diastereomer. However, with two structurally complex chiral substrates, the reaction of a mismatched pair is possible. Inversion of the undesired stereoisomer is envisaged to increase the overall efficiency of the route.

Scheme 5. Preparation of Northern Fragment 4^a

^aReagents and conditions: (a) PMB-trichloroacetimidate, CSA, rt; (b) DIBAL-H, THF, −78 °C; (c) CBr₄, PPh₃, 70% (over three steps); (d) 22, toluene, −78 °C, 71% (70% ee); (e) MOMCl, DIPEA, DCM, 0 °C to rt, 95%; (f) TBAF, THF, 0 °C to rt, 80%; (g) NMO, TPAP, DCM, 78%; (h) 6, *t*-BuLi, Et₂O, −78 °C; MgBr₂; 5, 96%, dr 9:1; (i) TESCl, imidazole, DMAP, DCM, 93%; (j) DDQ, DCM, phosphate buffer pH 7 to 8, 90%; and (k) SO₃py, NEt₃, DMSO, DCM, 0 °C, 93%.

Scheme 6. Coupling of Dibromide 16 and Completion of Advanced Fragment 26^a

^aReagents and conditions: (a) 16, *n*-BuLi, −112 to −108 °C, Et₂O; then 4, 74%, dr 1:1 and (b) BzCl, DMAP, NEt₃, DCM, 71%.

CONCLUSIONS

We have established a concise route to a highly advanced intermediate toward the synthesis of Pl-4. Strategies toward the closure of the cyclopentane moiety of the diterpene have to be elaborated, which will take place at a later point because we are currently experiencing extenuating circumstances and the project is on hold until the relocation of the group.

The route features a regioselective lithiation of the more hindered side of an unsymmetrical vinyl dibromide; thus, generating a species that can be used in a further coupling reaction to establish the cyclopentane motif in the jatrophone diterpene. This method constitutes a valuable alternative to the preparation of internal vinyl halides via hydrometalation reactions and allows the selective, stepwise introduction of functionalities and the preparation of highly substituted alkenes.

EXPERIMENTAL SECTION

General Methods. All nonaqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum), unless noted otherwise.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon.

DMSO and *N,N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide (neutral activity). Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Unless indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/EtOAc or toluene/EtOAc. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM (H_2SO_4 (concd, 22 mL), phosphormolybdic acid (20 g), $\text{Ce}(\text{SO}_4)_2$ (0.5 g), and 378 mL H_2O) or silica gel impregnated with iodine.

Flash column chromatography was performed with silica gel 60 (0.040–0.063 μm , 240–400 mesh).

Optical rotations were measured at the sodium D line with a 100 mm path length cell and are reported as follows: $[\alpha]_D^{25}$, concentration (g/100 mL), and solvent.

NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl_3 solutions and referenced to the residual CDCl_3 signal (1H, δ = 7.26, 13C, δ = 77.16). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, and br = broadened signal). Coupling constants *J* are given in Hz. The assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, and NOESY).

IR spectra are reported in wave numbers (cm^{-1}). All compounds were measured using a single reflection monolithic diamond ATR module.

High-resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Q_q-TOF) mass analyzer (acetonitrile/MeOH 1:1, +1% H_2O).

(*R*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-en-2-ol (**15**). To a solution of methyl ketone **10** (5.5 g, 12.7 mmol, 1.0 equiv) in THF (180 mL) was added a solution of vinylmagnesium bromide (1.0 M in THF, 38.1 mL, 38.1 mmol, 3.0 equiv) at 0 °C via a syringe. The reaction mixture was stirred for 1 h at 0 °C and then for 90 min at room temperature. After TLC analysis indicated the complete consumption of the starting material, the reaction was quenched by the addition of water (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. After purification of the crude material by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), tertiary alcohol **15** (5.39 g) was isolated in 92% yield as a light-yellow oil. $[\alpha]_D^{20}$ –7.7 (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.06 (s, 6H), 0.18 (s, 3H), 0.19 (s, 3H), 0.90 (s, 9H), 0.92 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 1.46 (s, 3H), 3.75 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.84 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.04 (s, 1H), 4.08 (d, *J* = 6.5 Hz, 1H), 4.32 (dd, *J* = 8.0, 6.5 Hz, 1H), 4.41–4.46 (m, 1H), 5.09 (dd, *J* = 10.8, 2.0 Hz, 1H), 5.44 (dd, *J* = 17.6, 2.0 Hz, 1H), 6.25 (dd, *J* = 17.6, 10.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ –5.4 (CH_3), –5.2 (CH_3), –3.6 (CH_3), –3.1 (CH_3), 18.58 (C), 18.60 (C), 24.7 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 26.9 (CH_3), 28.4 (CH_3), 64.2 (CH_2), 72.8 (CH), 73.9 (C), 77.3 (CH), 82.8 (CH), 107.4 (C), 112.7 (CH_2), 143.0 (CH). IR (ATR) ν 3450, 2955, 2930, 2886, 2359, 2342, 1472, 1463, 1381, 1254, 1213, 1193, 1141, 1083, 1059, 930, 834, 779 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{48}\text{O}_3\text{Si}_2\text{Na}$ [*M* + *Na*]⁺, 483.2938; found, 483.2939.

(*R*)-5-((4*S*,5*R*)-5-((*R*)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (**11**). Alcohol **15** (3.0 g, 6.5 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and cooled to 0 °C. DIPEA (5.5 mL,

32.5 mmol, 5.0 equiv) was added to the solution followed by the dropwise addition of MEMCl (3.7 mL, 32.5 mmol, 5.0 equiv) over 5 min. The cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature followed by 3 h at 50 °C before it was quenched by the addition of water (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were dried over MgSO_4 and filtered, and the solvent was removed under vacuum. Further purification by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) afforded alkene **11** (3.46 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ –3.1 (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.09 (s, 6H), 0.90 (s, 18H), 1.31 (s, 3H), 1.44 (s, 3H), 1.49 (s, 3H), 3.38 (s, 3H), 3.51–3.55 (m, 2H), 3.56–3.67 (m, 2H), 3.79–3.89 (m, 2H), 4.06 (d, *J* = 7.0 Hz, 1H), 4.20 (dd, *J* = 7.0, 2.5 Hz, 1H), 4.23–4.28 (m, 1H), 4.73 (d, *J* = 7.8 Hz, 1H), 4.89 (d, *J* = 7.8 Hz, 1H), 5.25–5.28 (m, 1H), 5.31 (s, 1H), 5.98–6.07 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ –5.3 (CH_3), –5.1 (CH_3), –4.5 (CH_3), –3.7 (CH_3), 18.5 (C), 18.6 (C), 21.7 (CH_3), 25.0 (CH_3), 26.22 (CH_3), 26.25 (CH_3), 26.3 (CH_3), 59.1 (CH_3), 66.9 (CH_2), 67.4 (CH_2), 72.0 (CH_2), 73.8 (CH), 79.1 (C), 82.2 (CH), 82.8 (CH), 91.0 (CH_2), 107.6 (C), 117.1 (CH_2), 139.6 (CH). IR (ATR) ν 2930, 2885, 2857, 2363, 2343, 1462, 1380, 1253, 1213, 1086, 1005, 988, 938, 834, 777 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{56}\text{O}_7\text{Si}_2\text{Na}$ [*M* + *Na*]⁺, 571.3463; found, 571.3461.

(*R*)-1-((4*R*,5*R*)-5-((*R*)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**S1**). A solution of TBS protected diol **11** (2.5 g, 4.55 mmol, 1.0 equiv) in THF (23 mL) was treated with a solution of TBAF (1.0 M in THF, 18.2 mL, 18.2 mmol, 4.0 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. As TLC analysis of the reaction mixture indicated unreacted starting material, the reaction mixture was cooled to 0 °C before one additional equiv (4.55 mL) of the TBAF solution was added. The resulting solution was warmed to room temperature and stirred for 2 h. The reaction was terminated by the addition of a saturated NH_4Cl solution (50 mL), the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/EtOAc 1:1 to pure EtOAc) to afford diol **S1** (1.45 g) in quantitative yield as a colorless oil. $[\alpha]_D^{20}$ –51.3 (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.32 (s, 3H), 1.41 (s, 3H), 1.51 (s, 3H), 2.19–2.29 (m, 1H), 3.38 (s, 3H), 3.52–3.56 (m, 2H), 3.60–3.70 (m, 2H), 3.76–3.87 (m, 2H), 4.08–4.19 (m, 3H), 4.38 (bs, 1H), 4.82 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 5.31 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.33 (dd, *J* = 17.6, 1.0 Hz, 1H), 6.15 (dd, *J* = 17.6, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 23.0 (CH_3), 25.2 (CH_3), 27.2 (CH_3), 59.2 (CH_3), 65.1 (CH_2), 68.1 (CH_2), 68.8 (CH), 71.9 (CH_2), 78.9 (CH), 81.0 (C), 82.6 (CH), 91.1 (CH_2), 108.4 (C), 117.4 (CH_2), 138.5 (CH). IR (ATR) ν 3433, 2985, 2930, 2364, 1458, 1371, 1253, 1216, 1053, 1003, 932, 871, 782 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{28}\text{O}_7\text{Na}$ [*M* + *Na*]⁺, 343.1733; found, 343.1728.

(4*S*,5*R*)-5-((*R*)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**8**). Diol **S1** (1.45 g, 4.5 mmol, 1.0 equiv) was dissolved in DCM (22 mL) and cooled to 0 °C, and a solution of NaIO_4 (1.44 g, 6.75 mmol, 1.5 equiv) in water (15 mL) was added. The solution was warmed to room temperature and stirred for 2 h 15 min. The biphasic mixture was diluted with water (15 mL) and DCM (15 mL), the phases were separated, and the aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over MgSO_4 and filtered, and the solvent was removed in vacuo. Further purification by flash column chromatography (hexanes/EtOAc 1:1) delivered aldehyde **8** (1.16 g) as a colorless oil in 90% yield. $[\alpha]_D^{20}$ –44.1 (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.38 (s, 3H), 1.42 (s, 3H), 1.59 (s, 3H), 3.37 (s, 3H), 3.50–3.55 (m, 2H), 3.56–3.62 (m, 1H), 3.70–3.76 (m, 1H), 4.29 (d, *J* = 7.0 Hz, 1H), 4.41 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.67 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 5.29 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.32 (dd, *J* = 11.0, 1.0 Hz, 1H), 6.03 (dd, *J* = 17.6, 11.0 Hz, 1H), 9.61 (d, *J* = 3.5 Hz,

1H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.1 (CH_3), 25.4 (CH_3), 27.4 (CH_3), 59.1 (CH_3), 67.7 (CH_2), 71.9 (CH_2), 78.4 (C), 81.8 (CH), 86.2 (CH), 91.3 (CH_2), 110.8 (C), 117.7 (CH_2), 138.9 (CH), 197.8 (CH). IR (ATR) ν 2987, 2938, 2880, 1730, 1457, 1415, 1377, 1249, 1216, 1162, 1077, 1020, 933 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{24}\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$, 311.1471; found, 311.1468.

Methyl-3-((4R,5R)-5-((R)-2-((2-methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (S2). A solution of DIPA (1.4 mL, 10.0 mmol) in dry THF (6 mL) was treated with *n*-BuLi (2.5 M in hexanes, 4.0 mL, 10.0 mmol) at -20°C , and the resulting reaction mixture was stirred for 15 min at that temperature. To 5.3 mL of the LDA solution (4.62 mmol, 3.3 equiv), neat methylisobutyrate (0.48 mL, 4.2 mmol, 3.0 equiv) was added at -20°C . The reaction mixture was stirred for 2 h 30 min before a solution of aldehyde **8** (400 mg, 1.4 mmol, 1.0 equiv) in THF (1.5 mL) was added. The resulting light-yellow solution was warmed to 5°C over 3 h until TLC showed the total consumption of the starting material. The reaction was quenched by the addition of a saturated NH_4Cl solution (15 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), delivering an inseparable 3:1 diastereomeric mixture of secondary alcohols **12** and **12a** (424 mg) as a colorless oil in 78% yield, which was directly used for the next reaction.

The 3:1 diastereomeric mixture of the secondary alcohols from above (**12**, **12a**, 424 mg, 1.09 mmol, 1.0 equiv) was dissolved in DCM (2 mL) and cooled to 0°C . The resulting solution was treated with DIPEA (0.57 mL, 3.27 mmol, 3.0 equiv) followed by the dropwise addition of MOMCl (0.41 mL, 5.45 mmol, 5.0 equiv) over 5 min. The reaction mixture was allowed to warm to room temperature and was heated to 50°C for 12 h. The reaction was terminated by the addition of water (10 mL), the layers were separated, and the aqueous phase was extracted with DCM (3×20 mL). The organic extracts were dried over MgSO_4 and filtered, and the solvent was removed under reduced pressure. The crude diastereomeric mixture was separated by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), delivering 97 mg (21%) of the minor and 315 mg (67%) of the major desired diastereomer, methyl ester **S2**, as colorless oils. Major diastereomer (**S2**): $[\alpha]_{\text{D}}^{20} -50.0$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.19 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.43 (s, 3H), 3.37 (s, 3H), 3.39 (s, 3H), 3.50–3.59 (m, 3H), 3.62 (s, 3H), 3.76–3.83 (m, 1H), 4.03 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 8.9, 5.8 Hz, 1H), 4.64 (d, J = 8.9 Hz, 1H), 4.642 (d, J = 7.8 Hz, 1H), 4.78 (d, J = 6.0 Hz, 1H), 4.80 (d, J = 6.0 Hz, 1H), 4.88 (d, J = 7.8 Hz, 1H), 5.24–5.35 (m, 2H), 6.17 (dd, J = 17.4, 11.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.4 (CH_3), 21.5 (CH_3), 24.7 (CH_3), 25.3 (CH_3), 26.7 (CH_3), 46.9 (C), 51.3 (CH_3), 56.3 (CH_3), 59.1 (CH_3), 67.1 (CH_2), 71.9 (CH_2), 78.9 (CH), 79.3 (CH), 80.4 (C), 82.3 (CH), 90.4 (CH_2), 99.0 (CH_2), 107.2 (C), 118.7 (CH_2), 138.7 (CH), 176.9 (C). IR (ATR) ν 2986, 2878, 2855, 2366, 1746, 1724, 1472, 1415, 368, 1295, 1217, 1193, 1101, 1036, 945, 873, 833 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{38}\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$, 457.2416; found, 457.2416. Minor diastereomer: $[\alpha]_{\text{D}}^{22} -97.6$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.23 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.45 (s, 6H), 3.35 (s, 3H), 3.37 (s, 3H), 3.51–3.56 (m, 2H), 3.58–3.64 (m, 1H), 3.67 (s, 3H), 3.79–3.85 (m, 1H), 3.88 (d, J = 5.8 Hz, 1H), 4.37 (dd, J = 6.1, 5.8 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 7.3 Hz, 1H), 4.72 (d, J = 6.1 Hz, 1H), 4.87 (d, J = 6.6 Hz, 1H), 4.89 (d, J = 7.3 Hz, 1H), 5.24–5.34 (m, 2H), 6.17 (dd, J = 17.6, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 20.5 (CH_3), 22.1 (CH_3), 22.7 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 47.8 (C), 51.9 (CH_3), 56.3 (CH_3), 59.1 (CH_3), 67.4 (CH_2), 71.9 (CH_2), 76.2 (CH), 76.8 (CH), 79.7 (C), 83.8 (CH), 90.8 (CH_2), 97.6 (CH_2), 107.6 (C), 117.9 (CH_2), 139.2 (CH). IR (ATR) ν 2986, 2878, 2855, 2366, 1746, 1724, 1472, 1415, 368, 1295, 1217, 1193, 1101, 1036, 945, 873, 833 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{38}\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$, 457.2416; found, 457.2414.

Methyl-2-((3aR,4S,7S,7aR)-7-((2-methoxyethoxy)methoxy)-2,2,7-trimethyl-6-oxotetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-

methylpropanoate (S3). For proof of the stereochemistry of alcohol **12**. Alkene **S2** (the major diastereomer from above, 78 mg, 0.18 mmol, 1.0 equiv) was dissolved in DCM (7.0 mL) and cooled to -78°C before a stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of dimethylsulfide (15 μL , 0.23 mmol, 1.3 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the crude product was purified by filtration over a short plug of silica gel (hexanes/EtOAc 5:1), affording a diastereomeric, inseparable mixture of the corresponding lactols (24 mg) in 34% yield. The diastereomeric mixture of lactols was dissolved in DCM (1 mL) and cooled to 0°C . NaHCO_3 (11 mg, 0.134 mmol, 2.2 equiv) and Dess–Martin periodinane (52 mg, 0.122 mmol, 2.0 equiv) were added sequentially. The cooling bath was removed, and the resulting reaction mixture was stirred for 2 h at room temperature before it was quenched by the addition of a saturated, aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). The two layers were separated and the aqueous phase was extracted with DCM (3×10 mL). The organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude lactone was further purified by flash column chromatography (hexanes/EtOAc 3:1 to 2:1) to afford **S3** (16 mg) in 67% yield as a colorless oil. $[\alpha]_{\text{D}}^{20} -30.3$ (c 0.8, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.30 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.57 (s, 3H), 3.36 (s, 3H), 3.49–3.54 (m, 2H), 3.65–3.74 (m, 2H), 3.69 (s, 3H), 4.33 (d, J = 7.6 Hz, 1H), 4.62 (dd, J = 7.6, 1.8 Hz, 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.86 (d, J = 6.8 Hz, 1H), 5.27 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.3 (CH_3), 21.7 (CH_3), 21.9 (CH_3), 24.3 (CH_3), 26.2 (CH_3 -15), 45.9 (C), 52.4 (OCH_3), 59.2 (OCH_3), 68.4 (CH_2), 71.8 (CH_2), 73.1 (CH), 76.9 (C), 78.4 (CH), 79.1 (CH), 91.5 (CH_2), 110.1 (C), 169.5 (C), 176.5 (C). IR (ATR) ν 2993, 2954, 2877, 2356, 1758, 1724, 1473, 1459, 1379, 1348, 1298, 1268, 1216, 1142, 1126, 1069, 1015, 978, 775 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{30}\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$, 413.1788; found, 413.1788.

(S)-Methyl-3-((4R,5R)-5-((S)-2-((2-methoxyethoxy)methoxy)-1-oxopropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (13). Alkene **S2** (200 mg, 0.46 mmol, 1.0 equiv) was dissolved in DCM (12 mL) and cooled to -78°C , and a stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of PPh_3 (181 mg, 0.69 mmol, 1.5 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (hexanes/EtOAc 3:1), delivering aldehyde **13** (180 mg, 90%) as a colorless oil. $[\alpha]_{\text{D}}^{21} -81.5^\circ$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.24 (s, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 3.34 (s, 3H), 3.37 (s, 3H), 3.50–3.56 (m, 2H), 3.68 (s, 3H), 3.72–3.79 (m, 1H), 3.80–3.88 (m, 1H), 4.05 (d, J = 5.8 Hz, 1H), 4.45 (bt, J = 5.6 Hz, 1H), 4.53 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 5.5 Hz, 1H), 4.72 (d, J = 6.8 Hz, 1H), 4.87 (d, J = 7.5 Hz, 1H), 4.92 (d, J = 7.5 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.4 (CH_3), 20.5 (CH_3), 23.1 (CH_3), 25.0 (CH_3), 26.3 (CH_3), 47.7 (C), 52.0 (CH_3), 56.5 (CH_3), 59.2 (CH_3), 68.1 (CH_2), 71.1 (CH_2), 76.4 (CH), 77.3 (CH), 82.7 (CH), 82.8 (C), 91.3 (CH_2), 97.8 (CH_2), 108.2 (C), 177.2 (C), 202.0 (CH). IR (ATR) ν 2985, 2951, 1733, 1470, 1435, 1368, 1254, 1194, 1155, 1098, 1078, 1050, 1032, 987, 884 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{36}\text{O}_{10}$ $[\text{M}]^+$, 436.2308; found, 436.2316.

(S)-Methyl-3-((4R,5R)-5-((R)-4,4-dibromo-2-((2-methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (14). For the preparation of the Wittig salt (dibromomethyl)triphenylphosphonium bromide (**S4**), tetrabromomethane (16.4 g, 49.4 mmol, 1.0 equiv) was added to a solution of triphenylphosphine (26 g, 99.1 mmol, 2.0 equiv) in 240 mL of methylene chloride at 0°C . The resulting red reaction mixture was stirred for 30 min. Water (8 mL) was added, and the resulting yellow mixture was stirred vigorously for 15 min at 0°C . The two

phases were separated, the organic layer was dried, and the solvent was evaporated. The crude Wittig-salt was precipitated by the addition of acetonitrile (150 mL). The yellow solid was filtered, acetonitrile (150 mL) was added, and the suspension was heated to reflux (110 °C) for 20 h. The suspension was filtered, and the solid was washed once with 20 mL of acetonitrile and dried under vacuum, affording 18.7 g (74%) of the Wittig-salt (**S4**).⁴³

To a suspension of Wittig-salt **S4** (180 mg, 0.35 mmol, 5.0 equiv) in THF (2.5 mL) was added *t*-BuOK (39 mg, 0.35 mmol, 5.0 equiv) in one portion at 0 °C. The resulting brown suspension was stirred for 30 min before a solution of aldehyde **13** (30 mg, 0.07 mmol, 1.0 equiv) in THF (0.5 mL) was added. The resulting reaction mixture was then stirred for 1 h at 0 °C followed by 12 h at room temperature. The reaction was terminated by the addition of brine (5 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and filtered, and the solvent was removed under vacuum. After purification of the crude product by flash column chromatography (hexanes/EtOAc 5:1), dibromide **14** was isolated as a colorless oil (5 mg, 17%). [α]_D²⁰ −77.6 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 1.21 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.52 (s, 3H), 1.67 (s, 3H), 3.37 (s, 3H), 3.39 (s, 3H), 3.53–3.57 (m, 2H), 3.66–3.72 (m, 1H), 3.68 (s, 3H), 3.78–3.84 (m, 1H), 4.03 (d, *J* = 6.5 Hz, 1H), 4.37 (dd, *J* = 6.5, 3.9 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.81 (d, *J* = 7.8 Hz, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 7.04 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 20.4 (CH₃), 21.9 (CH₃), 23.3 (CH₃), 25.0 (CH₃), 26.6 (CH₃), 48.2 (C), 52.0 (CH₃), 56.5 (CH₃), 59.2 (CH₃), 68.0 (CH₂), 72.0 (CH₂), 76.1 (CH), 78.2 (CH), 80.8 (C), 83.3 (CH), 88.9 (C), 91.5 (CH₂), 98.8 (CH₂), 108.0 (C), 139.9 (CH), 177.4 (C). IR (ATR) ν 2930, 2888, 2855, 2361, 2341, 1724, 1613, 1514, 1463, 1379, 1369, 1250, 1216, 1136, 1090, 1031, 941, 873, 810, 776 cm^{−1}. HRMS (ESI) calcd for C₂₁H₃₆⁷⁹Br⁸¹BrO₉Na [M + Na]⁺, 615.0604; found, 615.0599.

(*S*)-2-((*4R*,5*S*)-2,2-dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)-2-hydroxypropanal (**S5**). Alkene **15** (500 mg, 1.09 mmol, 1.0 equiv) was dissolved in DCM (28 mL) and cooled to −78 °C. A stream of ozone was bubbled through the reaction mixture (4 min) until the blue color persisted followed by a stream of argon to displace the excess ozone. After the addition of DMS (0.83 mL, 10.9 mmol, 10.0 equiv), the colorless solution was allowed to warm to room temperature over a period of 12 h. The reaction mixture was washed with brine (30 mL), the layers were separated, the organic phase was dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. Further purification by flash column chromatography (hexanes/EtOAc 9:1) delivered aldehyde **S5** (522 mg) in 84% yield as a colorless oil. [α]_D²⁰ −34.4 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.07 (s, 6H), 0.18 (s, 6H), 0.90 (s, 9H), 0.92 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 3.73 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.82 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.22–4.27 (m, 1H), 4.26 (d, *J* = 6.0 Hz, 1H), 4.29 (bs, 1H), 4.39 (dd, *J* = 6.0, 5.8 Hz, 1H), 9.72 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ −5.35 (CH₃), −5.30 (CH₃), −4.0 (CH₃), −3.8 (CH₃), 18.5 (C), 18.6 (C), 21.6 (CH₃), 25.1 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 26.6 (CH₃), 64.3 (CH₂), 72.8 (CH), 77.7 (CH), 78.5 (C), 81.1 (CH), 108.0 (C), 203.4 (CH). IR (ATR) ν 3473, 2930, 2858, 2362, 1737, 1463, 1381, 1253, 1216, 1147, 1082, 1046, 939, 832, 777 cm^{−1}. HRMS (ESI) calcd for C₂₂H₄₆O₆Si₂Na [M + Na]⁺, 485.2731; found, 485.2733.

(*R*)-4,4-Dibromo-2-((*4R*,5*S*)-2,2-dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-en-2-ol (**S6**). To a suspension of Wittig-salt **S4** (9.3 g, 18.1 mmol, 5.0 equiv) in THF (135 mL) was added *t*-BuOK (2.03 g, 18.1 mmol, 5.0 equiv) in three portions at 0 °C. The resulting brown suspension was stirred for 2 min at 0 °C before it was cooled to −20 °C and a solution of aldehyde **S5** (1.67 g, 3.61 mmol, 1.0 equiv) in THF (12 mL) was added. The reaction mixture was stirred for 1 h 30 min at −20 °C and 15 min at 0 °C. The reaction was terminated by the addition of a saturated NH₄Cl solution (50 mL). After separation of the two layers, the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na₂SO₄ and filtered, and

the solvent was removed under vacuum. After purification of the crude product by flash column chromatography (hexanes/EtOAc 19:1), 1.89 g (85%) of dibromide **S6** were isolated as a slightly yellow oil. [α]_D²⁰ −9.9 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.08 (s, 3H), 0.081 (s, 3H), 0.22 (s, 3H), 0.23 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 3.80 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.91 (dd, *J* = 11.3, 3.4 Hz, 1H), 4.01 (d, *J* = 6.5 Hz, 1H), 4.25–4.31 (m, 1H), 4.38 (dd, *J* = 7.9, 6.5 Hz, 1H), 4.46 (bs, 1H), 6.97 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ −5.4 (CH₃), −5.2 (CH₃), −3.5 (CH₃), −3.3 (CH₃), 18.56 (C), 18.65 (C), 24.5 (CH₃), 25.5 (CH₃), 26.1 (CH₃), 26.3 (CH₃), 27.0 (CH₃), 64.1 (CH₂), 73.4 (CH), 75.0 (C), 76.6 (CH), 83.2 (CH), 88.0 (C), 107.6 (C), 140.5 (CH). IR (ATR) ν 3415, 2930, 2858, 1598, 1471, 1383, 1256, 1213, 1142, 1062, 980, 935, 885, 835, 812, 780 cm^{−1}. HRMS (ESI) calcd for C₂₃H₄₆⁷⁹Br⁸¹BrO₅Si₂Na [M + Na]⁺, 641.1128; found, 641.1133.

(*R*)-5-((*4S*,5*R*)-2-((*R*)-4,4-Dibromo-2-((2-methoxyethoxy)-methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (**16**). To a solution of alcohol **S6** (188 mg, 0.3 mmol, 1.0 equiv) in 1,2-dichloroethane (1.0 mL) was added DIPEA (0.26 mL, 1.5 mmol, 5.0 equiv) followed by the dropwise addition of MEMCl (0.171 mL, 1.5 mmol, 5.0 equiv) at 0 °C over 5 min. The reaction mixture was allowed to warm to room temperature before it was heated at 100 °C (sealed round-bottomed flask) for 12 h. The reaction was quenched by the addition of water (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and filtered, and the solvent was removed under vacuum. Further purification by flash column chromatography (hexanes/EtOAc 19:1) afforded dibromide **16** (183 mg, 87%) as a light-yellow oil. [α]_D²⁰ −17.0 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.065 (s, 3H), 0.12 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.34 (s, 3H), 1.47 (s, 3H), 1.65 (s, 3H), 3.39 (s, 3H), 3.51–3.58 (m, 2H), 3.60–3.74 (m, 2H), 3.78–3.86 (m, 2H), 4.15–4.21 (m, 1H), 4.26 (dd, *J* = 6.8, 3.0 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 6.85 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ −5.2 (CH₃), −5.1 (CH₃), −4.3 (CH₃), −3.8 (CH₃), 18.5 (C), 18.6 (C), 21.8 (CH₃), 25.0 (CH₃), 26.25 (CH₃), 26.30 (CH₃), 26.4 (CH₃), 59.2 (CH₃), 66.3 (CH₂), 67.8 (CH₂), 71.9 (CH₂), 73.5 (CH), 80.7 (C), 80.9 (CH), 81.4 (CH), 89.1 (C), 91.6 (CH₂), 107.7 (C), 140.3 (CH). IR (ATR) ν 2930, 2886, 2858, 2359, 2342, 1471, 1381, 1254, 1215, 1088, 987, 939, 835, 750 cm^{−1}. HRMS (ESI) calcd for C₂₇H₅₄⁷⁹Br⁸¹BrO₇Si₂Na [M + Na]⁺, 729.1652; found, 729.1665.

(*S*)-4-((*tert*-Butyldimethylsilyloxy)-2-methylbutan-1-ol (**S7**). Alcohol **S7** was prepared by Myers alkylation and subsequent reductive cleavage of the chiral auxiliary following the published protocol.³⁴ ¹H NMR (400 MHz, CDCl₃): δ 0.08 (s, 6H), 0.90 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.52–1.59 (m, 2H), 1.75–1.85 (m, 2H), 2.93 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.42 (ddd, *J* = 10.9, 7.0, 5.2 Hz, 1H), 3.51 (ddd, *J* = 10.9, 7.5, 4.8 Hz, 1H), 3.62–3.69 (m, 1H), 3.73–3.80 (m, 1H). These spectral characteristics are identical to those previously reported.⁴⁴

(*S*)-4-((*tert*-Butyldimethylsilyloxy)-2-methylbutanal (**17**). To a solution of IBX (1.92 g, 6.87 mmol, 1.5 equiv) in DMSO (15 mL) was added alcohol **S7** (1.0 g, 4.58 mmol, 1.0 equiv) in DMSO (1.5 mL), and the reaction mixture was stirred for 90 min at room temperature. As TLC showed the total consumption of the starting material, the reaction was terminated by the addition of water (15 mL) at 0 °C. The resulting suspension was filtered over a plug of Celite, and the filtrate was diluted with Et₂O (20 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic fractions were washed with water (50 mL) and brine (50 mL) and dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), delivering aldehyde **17** (619 mg) in 62% yield as a colorless oil. [α]_D²⁰ +19.1 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.58–1.68 (m, 1H), 1.90–2.01 (m, 1H), 2.44–2.56 (m, 1H), 3.62–3.74 (m, 2H), 9.65 (d, *J* = 1.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ −5.32 (CH₃), −5.31 (CH₃), 13.3 (CH₃), 18.4 (C), 26.0 (CH₃), 33.9 (CH₂), 43.7 (CH),

60.4 (CH₂), 205.0 (CH). IR (ATR) ν 2954, 2929, 2857, 1728, 1472, 1462, 1388, 1254, 1097, 1005, 881, 834, 776 cm⁻¹. HRMS (ESI) calcd for C₁₁H₂₄O₂SiNa [M + Na]⁺, 239.1443; found, 239.1440. These spectral characteristics are identical to those previously reported.⁴⁵

(8*R*, 12*S*, *E*)-10-Bromo-8-((4*R*, 5*S*)-2,2-dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)-8,12,16,16,17,17-hexamethyl-2,5,7,15-tetraoxa-16-silaoctadec-9-en-11-ol (**19**). To a solution of dibromide **16** (75 mg, 0.107 mmol, 1.0 equiv) in dry Et₂O (0.53 mL) was added *n*-BuLi (2.01 M in hexanes, 48 μ L, 0.103 mmol, 0.96 equiv) at -108 °C (liquid nitrogen/ethanol cooling bath) dropwise over 3 min. The reaction mixture was stirred for 1 h with the temperature kept between -116 and -108 °C. A solution of aldehyde **17** (46 mg, 0.214 mmol, 2.0 equiv) in Et₂O (0.5 mL) was added over 5 min, and the colorless solution was stirred for 2 h in the same temperature range. The reaction was terminated by the addition of a saturated NH₄Cl solution (2 mL) at -108 °C. After warming to room temperature, the layers were separated, and the organic phase was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude 1.25:1 mixture of the corresponding diastereomeric secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), affording both diastereomers as colorless oils (**19a**, less polar, 20 mg; **19b**, more polar, 16 mg) in 40% overall yield. **19a**: [α]_D²⁰ -12.0 (c 0.3, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.05 (s, 6H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS), 0.08 (s, 3H, CH₃-TBS), 0.11 (s, 6H, CH₃-TBS), 0.89 (s, 9H, CH₃-*t*Bu-TBS), 0.91 (s, 9H, CH₃-*t*Bu-TBS), 0.913 (s, 9H, CH₃-*t*Bu-TBS), 1.07 (d, *J* = 6.6 Hz, 3H, CH₃-12), 1.07–1.10 (m, 1H, CH₂-2b), 1.33 (s, 3H, CH₃-21), 1.46 (s, 3H, CH₃-20), 1.55 (s, 3H, CH₃-14), 1.58–1.67 (m, 1H, CH₂-2a), 1.81–1.90 (m, 1H, CH-3), 3.37 (s, 3H, OCH₃-18), 3.47 (bd, *J* = 3.3 Hz, 1H, OH-13), 3.51–3.54 (m, 2H, CH₂-17a,b), 3.61–3.67 (m, 3H, CH₂-16b, 1b, 11b), 3.68–3.73 (m, 1H, CH₂-1a), 3.81–3.85 (m, 1H, CH₂-11a), 3.89–3.93 (m, 1H, CH₂-16a), 4.11 (d, *J* = 7.0 Hz, 1H, CH-8), 4.17–4.22 (m, 1H, CH-10), 4.25 (dd, *J* = 7.0, 2.3 Hz, CH-9), 4.42 (dd, *J* = 9.3, 3.3 Hz, 1H, CH-4), 4.73 (d, *J* = 7.3 Hz, 1H, CH₂-15b), 5.03 (d, *J* = 7.3 Hz, 1H, CH₂-15a), 6.13 (s, 1H, CH-6). ¹³C NMR (100 MHz, CDCl₃): δ -5.2 (CH₃-TBS), -5.13 (CH₃-TBS), -5.12 (CH₃-TBS), -5.0 (CH₃-TBS), -4.3 (CH₃-TBS), -3.6 (CH₃-TBS), 16.1 (CH₃-12), 18.4 (C-TBS), 18.5 (C-TBS), 18.8 (C-TBS), 24.9 (CH₃-21), 25.4 (CH₃-14), 26.1 (CH₃-*t*Bu-TBS), 26.2 (CH₃-20), 26.23 (CH₃-*t*Bu-TBS), 26.4 (CH₃-*t*Bu-TBS), 34.8 (CH-3), 36.1 (CH₂-2), 59.2 (OCH₃-18), 61.6 (CH₂-1), 67.0 (CH₂-11), 68.4 (CH₂-16), 71.8 (CH₂-17), 73.7 (CH-10), 74.1 (CH-4), 80.0 (C-7), 81.8 (CH-9), 82.1 (CH-8), 92.1 (CH₂-15), 107.8 (C-19), 135.8 (CH-6), 136.6 (C-5). IR (ATR) ν 3470, 2953, 2929, 2857, 2363, 2342, 1472, 1462, 1380, 1253, 1211, 1088, 1006, 989, 939, 834, 776, 735 cm⁻¹. HRMS (ESI) calcd for C₃₈H₇₉⁸¹BrO₉Si₃Na [M + Na]⁺, 867.4093; found, 867.4099. **19b**: [α]_D²⁰ +3.4 (c 0.75, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 3H, CH₃-TBS), 0.05 (s, 3H, CH₃-TBS), 0.07 (s, 6H, CH₃-TBS), 0.10 (s, 3H, CH₃-TBS), 0.11 (s, 3H, CH₃-TBS), 0.88–0.91 (m, 30H, CH₃-*t*Bu-TBS, CH₃-12), 1.33 (s, 3H, CH₃-21), 1.42–1.46 (m, 1H, CH₂-2b), 1.47 (s, 3H, CH₃-20), 1.53 (s, 3H, CH₃-14), 1.84–1.93 (m, 1H, CH-3), 1.95–2.02 (m, 1H, CH₂-2a), 3.37 (s, 3H, OCH₃-18), 3.52–3.55 (m, 2H, CH₂-17a, b), 3.62 (dd, *J* = 6.8, 10.5 Hz, 1H, CH₂-11b), 3.64–3.83 (m, 6H, CH₂-16a,b, 11a,b, 1a,b, OH-13), 4.01–4.05 (m, 1H, CH-10), 4.17 (d, *J* = 7.0 Hz, 1H, CH-8), 4.19 (dd, *J* = 7.0, 1.9 Hz, 1H, CH-9), 4.48 (dd, *J* = 9.2, 5.3 Hz, 1H, CH-4), 4.86 (d, *J* = 7.2 Hz, 1H, CH₂-15b), 4.95 (d, *J* = 7.2 Hz, 1H, CH₂-15a), 6.16 (s, 1H, CH-6). ¹³C NMR (100 MHz, CDCl₃): δ -5.3 (CH₃-TBS), -5.2 (CH₃-TBS), -5.17 (CH₃-TBS), -5.1 (CH₃-TBS), -4.3 (CH₃-TBS), -3.8 (CH₃-TBS), 17.5 (CH₃-12), 18.4 (C-TBS), 18.5 (C-TBS), 23.1 (CH₃-14), 25.0 (CH₃-21), 26.1 (CH₃-*t*Bu-TBS), 26.2 (CH₃-*t*Bu-TBS), 26.25 (CH₃-*t*Bu-TBS), 26.3 (CH₃-20), 36.6 (CH-3), 36.7 (CH₂-2), 59.2 (OCH₃-18), 61.2 (CH₂-1), 66.7 (CH₂-11), 68.0 (CH₂-16), 71.9 (CH₂-17), 72.2 (CH-10), 74.4 (CH-4), 80.0 (C-7), 81.3 (CH-9), 82.3 (CH-8), 91.6 (CH₂-15), 107.7 (C-19), 135.9 (CH-6), 136.7 (C-5). IR (ATR) ν 3470, 2953, 2929, 2857, 2363, 2342, 1472, 1462, 1380, 1253, 1211, 1088, 1006, 989, 939, 834, 776, 735 cm⁻¹. HRMS (ESI) calcd for C₃₈H₇₉⁸¹BrO₉Si₃Na [M + Na]⁺, 867.4093; found, 867.4087.

(*R,R*)-Diisopropyl Tartrate (*E*)-Crotylboronate (**22**).³⁵ To a mixture of *t*-BuOK (16.4 g, 146 mmol, 1.0 equiv) in THF (120 mL) was added *trans*-2-butene (14.2 mL, 153.3 mmol, 1.05 equiv, *trans*-2-butene was condensed from a gas lecture bottle into a rubber-stoppered 25 mL graduated Schlenk flask immersed in liquid nitrogen) via a cannula at -78 °C. Although the subsequent, dropwise addition of a solution of *n*-BuLi (2.5 M in hexanes, 58.4 mL, 146 mmol, 1.0 equiv) occurred over 20 min, the internal temperature of the (*E*)-crotylboronate solution did not rise above -65 °C. After complete addition, the reaction mixture was warmed to -50 °C and was maintained at that temperature for 25 min until it was recooled to -78 °C. Triisopropylborate (34 mL, 146 mmol, 1.0 equiv) was added slowly over 15 min, and the internal temperature did not rise above -65 °C. After complete addition, the resulting mixture was stirred for 10 min at -78 °C. The reaction was quenched by pouring the mixture into a separatory funnel containing HCl (300 mL, 1 M). The phases were separated, and the aqueous layer was extracted with EtOAc (3 $\times$ 200 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and treated with diethanolamine (11.2 mL, 116.8 mmol, 0.8 equiv). The solution was stirred over 4 Å molecular sieves (25 g) in an argon atmosphere for 3 h. The suspension was filtered, the solvent was removed under reduced pressure, and the resulting white solid was recrystallized from a mixture of Et₂O and DCM (the solid was suspended and heated to reflux in Et₂O (20 mL) and DCM was added dropwise until the solid was dissolved), affording **S8** (14.0 g) in 57% yield as a white crystalline solid. mp 121–123 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.37 (d, *J* = 7.8 Hz, 2H), 1.63 (dd, *J* = 6.3, 1.5 Hz, 3H), 2.73–2.86 (m, 2H), 3.14–3.30 (m, 2H), 3.82–3.95 (m, 2H), 3.96–4.08 (m, 2H), 4.29 (bs, 1H), 5.22–5.34 (m, 1H), 5.62–5.74 (m, 1H).

A suspension of **S8** and (*R,R*)-diisopropyl tartrate (5.37 g, 63.5 mmol, 1.0 equiv) in Et₂O (150 mL) was treated with brine (150 mL) and stirred for 5 min at room temperature. The phases were separated, and the aqueous layer was extracted with Et₂O (3 $\times$ 100 mL). The combined fractions were dried over MgSO₄ and filtered, and the solvent was removed under vacuum, delivering 9.4 g (quant.) of **22** as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.28 (s, 6H), 1.30 (s, 6H), 1.62–1.67 (m, 3H), 1.80–1.86 (m, 2H), 4.76 (s, 2H), 5.07–5.17 (m, 2H), 5.45–5.51 (m, 2H). These spectral characteristics are identical to those previously reported.³⁵

(2*S*,3*S*)-1-((*tert*-Butyldimethylsilyloxy)-3-methylpent-4-en-2-ol) (**23**). A solution of crude (*E*)-crotylboronate (**22**, 9.41 g, 31.6 mmol, 1.2 equiv) in toluene (165 mL) was cooled to -78 °C, and aldehyde **21** (4.58 g, 26.3 mmol, 1.0 equiv) dissolved in toluene (20 mL) was added dropwise over 5 min. The reaction mixture was stirred for 4 h at -78 °C before it was quenched by the addition of an aqueous NaOH solution (30 mL, 2 M) at -78 °C. The mixture was allowed to warm to 0 °C and was stirred at that temperature for 20 min before it was filtered over a pad of Celite. The aqueous layer was extracted with EtOAc (3 $\times$ 150 mL). The combined organic fractions were dried over K₂CO₃ and filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/EtOAc 40:1 to 19:1) to give secondary alcohol **23** (4.28 g) in 71% yield as a colorless oil. The enantiomeric excess (70% ee) of the product was determined by Mosher ester analysis. [α]_D²⁰ -1.4 (c 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 2.25–2.36 (m, 1H), 3.37 (d, *J* = 3.0 Hz, 1H), 3.48–3.54 (m, 2H), 3.61–3.69 (m, 1H), 5.03–5.07 (m, 1H), 5.07–5.10 (m, 1H), 5.81–5.92 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ -5.24 (CH₃), -5.18 (CH₃), 16.3 (CH₃), 18.4 (C), 26.0 (CH₃), 40.6 (CH), 65.4 (CH₂), 75.0 (CH), 115.2 (CH₂), 140.5 (CH). IR (ATR) ν 3630, 3076, 2882, 2360, 2342, 1471, 1389, 1254, 1103, 1036, 1005, 913, 836 cm⁻¹. HRMS (ESI) calcd for C₁₂H₂₆O₂SiNa [M + Na]⁺, 253.1600; found, 253.1607.

(*S*)-5-((*S*)-But-3-en-2-yl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane (**59**). A solution of secondary alcohol **23** (2.46 g, 10.7 mmol, 1.0 equiv) in DCM (3 mL) was treated consecutively with DIPEA (5.57 mL, 32.1 mmol, 3.0 equiv) and MOMCl (2.44 mL, 32.1 mmol, 1.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at room temperature before it was quenched by the addition of water (10 mL).

The layers were separated, and the aqueous phase was extracted with DCM (3×15 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexanes/EtOAc 19:1), affording **S9** (2.79 g) in 95% yield as a colorless oil. $[\alpha]_{\text{D}}^{20} -17.7$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.07 (d, $J = 7.0$ Hz, 3H), 2.45–2.55 (m, 1H), 3.39 (s, 3H), 3.48–3.54 (m, 1H), 3.58–3.64 (m, 2H), 4.65 (d, $J = 6.7$ Hz, 1H), 4.79 (d, $J = 6.7$ Hz, 1H), 5.01–5.03 (m, 1H), 5.04–5.08 (m, 1H), 5.77–5.89 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ -5.29 (CH_3), -5.26 (CH_3), 16.6 (CH_3), 18.4 (C), 26.0 (CH_3), 39.5 (CH), 55.7 (CH_3), 64.1 (CH_2), 82.0 (CH), 97.1 (CH_2), 115.0 (CH_2), 140.3 (CH). IR (ATR) ν 2952, 2855, 2360, 2341, 1513, 1462, 1372, 1249, 1148, 1095, 1036, 836 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{30}\text{O}_3\text{SiNa}$ $[\text{M} + \text{Na}]^+$, 297.1862; found, 297.1851.

(2*S*,3*S*)-2-(Methoxymethoxy)-3-methylpent-4-en-1-ol (**S10**). To a solution of alkene **S9** (4.62 g, 16.8 mmol, 1.0 equiv) in THF (85 mL) was added a solution of TBAF (1.0 M in THF, 25.2 mL, 25.2 mmol, 1.5 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. TLC showed the total consumption of the starting material, and the reaction was quenched by the addition of a saturated, aqueous NH_4Cl solution (30 mL). The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvents were removed in vacuo. The crude material was purified by flash column chromatography (hexanes/EtOAc 9:1 to 3:1), delivering **S10** (2.15 g, 80%) as a colorless oil. $[\alpha]_{\text{D}}^{20} +46.8$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.05 (s, 3H), 2.38–2.49 (m, 1H), 2.95 (dd, $J = 8.7, 4.0$ Hz, 1H), 3.43 (s, 3H), 3.43–3.47 (m, 1H), 3.52–3.64 (m, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 5.0–5.03 (m, 1H), 5.03–5.08 (m, 1H), 5.81 (ddd, $J = 17.3, 10.5, 7.7$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 16.3 (CH_3), 40.4 (CH), 55.9 (CH_3), 64.1 (CH_2), 86.1 (CH), 97.8 (CH_2), 115.2 (CH_2), 140.0 (CH). IR (ATR) ν 3424, 2360, 2340, 1514, 1462, 1418, 1372, 1251, 1213, 1149, 1102, 1036, 915 cm^{-1} . HRMS (ESI) calcd for $\text{C}_8\text{H}_{16}\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$, 183.0997; found, 183.0992.

(2*S*,3*S*)-2-(Methoxymethoxy)-3-methylpent-4-enal (**5**). To a solution of alcohol **S10** (2.0 g, 12.5 mmol, 1.0 equiv) in DCM (125 mL) were added *N*-methylmorpholine-*N*-oxide (2.2 g, 18.8 mmol, 1.5 equiv) and 4 Å molecular sieves (8 g) at room temperature. After the addition of tetrapropylammonium perruthenate (220 mg, 0.63 mmol, 0.05 equiv), the reaction mixture was stirred for 2 h at room temperature. The suspension was filtered through a plug of silica (silica packed with DCM), and the product was eluted with a mixture of pentane and Et_2O (9:1). The solvents were removed under reduced pressure. Because of the volatility of the product, the pressure was maintained at 200 mbar, and aldehyde **5** (1.54 g) was isolated in 78% yield as a colorless oil. $[\alpha]_{\text{D}}^{20} -31.6$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.13 (d, $J = 7.0$ Hz, 3H), 2.65–2.75 (m, 1H), 3.41 (s, 3H), 3.81 (dd, $J = 5.0, 2.3$ Hz, 1H), 4.69 (d, $J = 6.5$ Hz, 1H), 4.74 (d, $J = 6.5$ Hz, 1H), 5.06–5.12 (m, 2H), 5.77–5.89 (m, 1H), 9.61 (d, $J = 2.3$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 16.3 (CH_3), 39.8 (CH), 56.2 (CH_3), 85.7 (CH), 97.2 (CH_2), 116.4 (CH_2), 138.1 (CH), 203.2 (CH). IR (ATR) ν 2970, 2896, 2827, 1733, 1456, 1378, 1216, 1152, 1103, 1038, 920 cm^{-1} . HRMS (ESI) calcd for $\text{C}_8\text{H}_{14}\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$, 181.0841; found, 181.0837.

(2*S*,5*S*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (**24**). A solution of bromide **6** (590 mg, 2.16 mmol, 2.0 equiv) in Et_2O (17 mL) was cooled to -78 °C, and a solution of *t*-BuLi (1.6 M in pentane, 2.84 mL, 4.54 mmol, 4.2 equiv) was added dropwise over 3 min. The reaction mixture was stirred for 10 min at that temperature before a freshly prepared solution of magnesium bromide (1.0 M, 2.48 mL, 2.48 mmol, 2.3 equiv) was added. After 10 min at -78 °C, a solution of aldehyde **5** (171 mg, 1.08 mmol, 1.0 equiv) in Et_2O (6.8 mL) was added dropwise over 3 min. The reaction mixture was allowed to stir at -78 °C for 90 min until TLC control showed total consumption of aldehyde **5**. The reaction was terminated by the addition of saturated, aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts

were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting crude 9:1 mixture of secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), providing **24** (342 mg) and **24a** (38 mg) as colorless oils in 96% overall yield. Major diastereomer (**24**): $[\alpha]_{\text{D}}^{20} +6.3$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.93 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.22–1.31 (m, 1H), 1.52 (ddd, $J = 13.8, 10.5, 4.3$ Hz, 1H), 2.08–2.16 (m, 1H), 2.43–2.56 (m, 1H), 3.18 (dd, $J = 5.9, 3.9$ Hz, 1H), 3.23 (d, $J = 3.9$ Hz, 1H), 3.27–3.31 (m, 2H), 3.42 (s, 3H), 3.62–3.69 (m, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.99–5.02 (m, 1H), 5.02–5.06 (m, 1H), 5.76–5.88 (m, 1H), 6.84–6.90 (m, 2H), 7.22–7.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 16.9 (CH_3), 17.7 (CH_3), 30.4 (CH), 37.9 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.8 (CH), 72.6 (CH_2), 76.3 (CH_2), 88.7 (CH), 98.9 (CH_2), 113.6 (CH), 115.3 (CH_2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C). IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914, 821 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$, 375.2148; found, 375.2141. Minor diastereomer (**24a**): $[\alpha]_{\text{D}}^{20} +0.9$ (c 0.6, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.98 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 7.1$ Hz, 3H), 1.29–1.37 (m, 1H), 1.50–1.59 (m, 1H), 1.99–2.13 (m, 1H), 2.41–2.55 (m, 1H), 3.07 (d, $J = 4.5$ Hz, 1H), 3.18 (dd, $J = 5.9, 3.9$ Hz, 1H), 3.28–3.37 (m, 2H), 3.41 (s, 3H), 3.62–3.72 (m, 1H), 3.80 (s, 3H), 4.42 (s, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.98–5.05 (m, 2H), 5.76–5.87 (m, 1H), 6.83–6.90 (m, 2H), 7.21–7.27 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.5 (CH_3), 18.7 (CH_3), 30.3 (CH), 38.1 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.9 (CH), 72.9 (CH_2), 75.0 (CH_2), 88.0 (CH), 98.8 (CH_2), 113.8 (CH), 115.3 (CH_2), 129.3 (CH), 130.9 (C), 139.9 (CH), 159.1 (C). IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914, 821 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$, 375.2148; found, 375.2145.

(5*S*)-5-((*S*)-But-3-en-2-yl)-8,8-diethyl-6-((*S*)-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,4,7-trioxo-8-siladecane (**S11**). To a solution of secondary alcohol **24** (660 mg, 1.9 mmol, 1.0 equiv), imidazole (259 mg, 3.8 mmol, 2.0 equiv), and 4-dimethylaminopyridine (4 mg, 0.03 mmol, 0.02 equiv) in DCM (9.5 mL) was added chlorotriethylsilane (0.64 mL, 3.8 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of NaHCO_3 (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3×20 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (hexanes/EtOAc 9:1), affording **S11** (0.82 g) in 93% yield as a colorless oil. $[\alpha]_{\text{D}}^{20} -21.1$ (c 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 0.61 (quart, $J = 7.9$ Hz, 6H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 1.08 (d, $J = 7.1$ Hz, 3H), 1.29 (ddd, $J = 13.7, 9.7, 3.2$ Hz, 1H), 1.58 (ddd, $J = 13.7, 8.9, 3.2$ Hz, 1H), 1.88–2.01 (m, 1H), 2.44–2.56 (m, 1H), 3.22 (dd, $J = 9.3, 7.0$ Hz, 1H), 3.27–3.32 (m, 2H), 3.38 (s, 3H), 3.81 (s, 3H), 3.86–3.92 (m, 1H), 4.42 (s, 2H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.69 (d, $J = 6.8$ Hz, 1H), 4.95–5.03 (m, 2H), 5.87 (ddd, $J = 17.3, 10.3, 8.2$ Hz, 1H), 6.84–6.90 (m, 2H), 7.22–7.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 5.4 (CH_2), 7.1 (CH_3), 17.2 (CH_3), 18.9 (CH_3), 29.8 (CH), 36.8 (CH_2), 39.0 (CH), 55.4 (CH_3), 56.0 (CH_3), 72.1 (CH), 72.6 (CH_2), 76.4 (CH_2), 84.9 (CH), 98.1 (CH_2), 113.9 (CH), 114.3 (CH_2), 129.2 (CH), 131.1 (C), 141.8 (CH), 159.2 (C). IR (ATR) ν 2953, 2930, 2876, 2362, 2341, 1513, 1461, 1302, 1249, 1147, 1099, 1037, 1004, 912, 837 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{46}\text{O}_5\text{SiNa}$ $[\text{M} + \text{Na}]^+$, 489.3013; found, 489.3008.

(2*S*,5*S*,6*S*)-5-(Methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)oxy)oct-7-en-1-ol (**S12**). To a solution of alkene **S11** (722 mg, 1.55 mmol, 1.0 equiv) in DCM (77 mL) were added phosphate-buffer (pH 7 to 8, 1 M, 8 mL) and DDQ (529 mg, 2.33 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 1 h 30 min at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of NaHCO_3 (30 mL). The layers were separated, and the aqueous phase was extracted with DCM (3×100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The

crude product was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford primary alcohol **S12** (481 mg) in 90% yield as a colorless oil. $[\alpha]_D^{20}$ –27.9 (*c* 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.63 (quart, *J* = 7.9 Hz, 6H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.35 (ddd, *J* = 13.9, 9.0, 2.7 Hz, 1H), 1.50–1.62 (m, 2H), 1.74–1.85 (m, 1H), 2.46–2.58 (m, 1H), 3.31 (bt, *J* = 5.1 Hz, 1H), 3.38 (s, 3H), 3.46 (bt, *J* = 5.9 Hz, 2H), 3.91 (ddd, *J* = 9.0, 5.1, 2.7 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.95–5.06 (m, 2H), 5.88 (ddd, *J* = 17.3, 10.3, 8.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 5.4 (CH₂), 7.1 (CH₃), 16.9 (CH₃), 19.0 (CH₃), 32.6 (CH), 36.3 (CH₂), 38.9 (CH), 56.0 (CH₃), 69.2 (CH₂), 72.5 (CH), 84.9 (CH), 98.1 (CH₂), 114.4 (CH₂), 141.8 (CH). IR (ATR) ν 3449, 2953, 2876, 2359, 2340, 1790, 1513, 1458, 1415, 1377, 1301, 1245, 1147, 1098, 1034, 913, 725 cm^{–1}. HRMS (ESI) calcd for C₁₈H₃₈O₄SiNa [M + Na]⁺, 369.2437; found, 369.2430.

(2*S*,5*S*,6*S*)-5-(Methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)oxy)oct-7-enal (**4**). To a mixture of alcohol **S12** (911 mg, 2.6 mmol, 1.0 equiv) and DMSO (2.01 mL, 31.2 mmol, 12.0 equiv) in DCM (13 mL) were added triethylamine (2.16 mL, 15.6 mmol, 6.0 equiv) and SO₃·pyridine (1.24 g, 7.8 mmol, 3.0 equiv) at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. The reaction was terminated by the addition of water (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extracts were dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc 19:1), delivering aldehyde **4** (830 mg) in 93% yield as a colorless oil. $[\alpha]_D^{20}$ –8.3 (*c* 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.62 (quart, *J* = 7.9 Hz, 6H), 0.97 (t, *J* = 7.9 Hz, 9H), 1.09 (d, *J* = 4.3 Hz, 3H), 1.10 (d, *J* = 4.3 Hz, 3H), 1.49 (ddd, *J* = 14.1, 7.9, 3.3 Hz, 1H), 1.98 (ddd, *J* = 14.1, 8.8, 5.5 Hz, 1H), 2.45–2.60 (m, 2H), 3.32 (bt, *J* = 4.9 Hz, 1H), 3.37 (s, 3H), 3.92 (ddd, *J* = 8.8, 5.2, 3.7 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.97–5.07 (m, 2H), 5.88 (ddd, *J* = 17.3, 10.2, 8.3 Hz, 1H), 9.61 (d, *J* = 1.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 5.3 (CH₂), 7.1 (CH₃), 13.8 (CH₃), 19.1 (CH₃), 33.4 (CH₂), 38.8 (CH), 43.5 (CH), 56.0 (CH₃), 72.0 (CH), 84.6 (CH), 98.1 (CH₂), 114.6 (CH₂), 141.6 (CH), 205.1 (CH). IR (ATR) ν 2954, 2931, 2359, 2341, 1727, 1460, 1380, 1251, 1218, 1145, 1098, 1056, 1036, 1005, 947, 877, 725 cm^{–1}. HRMS (ESI) calcd for C₁₈H₃₆O₄SiNa [M + Na]⁺, 367.2281; found, 367.2276.

(3*R*,4*S*,5*S*)-5-((*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl)-4-(methoxymethoxy)-3-methyldihydrofuran-2(3*H*)-one (**S13**). For proof of the stereochemistry of alcohol **24**. The major diastereomer of secondary alcohol **24** (80 mg, 0.23 mmol, 1.0 equiv) was dissolved in a 1:1 solvent mixture of DCM (2.3 mL) and methanol (2.3 mL). Pyridine (185 μ L, 2.3 mmol, 10.0 equiv) and Sudan III (less than 0.1 mg, just enough to get a slightly red-colored reaction mixture) were added at room temperature. A stream of ozone was bubbled through the reaction mixture at –78 °C until the solution turned colorless (2 min). Excess ozone was removed by purging the reaction mixture with argon. After the addition of PPh₃ (72 mg, 0.28 mmol, 1.2 equiv), the colorless solution was allowed to warm to room temperature over a period of 12 h. The reaction mixture was diluted with DCM (10 mL) and washed with a saturated, aqueous solution of NH₄Cl (10 mL). The phases were separated, the organic layer was dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude material was purified by filtration over a short plug of silica delivering an inseparable mixture of the corresponding diastereomeric lactols (44 mg, 54%) as a colorless oil, which was immediately used for the next reaction.

To a solution of the mixture of lactols (30 mg, 0.085 mmol, 1.0 equiv) in DCM (1.3 mL) was added PCC (37 mg, 0.17 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred at that temperature for 12 h. To the resulting suspension was added one spatula of silica gel, and the solvent was removed under reduced pressure. The absorbed product was purified by flash column chromatography (hexanes/EtOAc 3:1), and lactone **S13** (27 mg) was obtained in 90% yield as a light-yellow oil. $[\alpha]_D^{20}$ –25.6 (*c* 0.75, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 1.0 (d, *J* = 6.6 Hz, 3H, CH₃-

15), 1.26 (d, *J* = 7.1 Hz, 3H, CH₃-14), 1.47 (ddd, *J* = 14.1, 8.5, 4.0 Hz, 1H, CH₂-5b), 1.94–2.15 (m, 2H, CH₂-5a, CH-6), 2.71 (dd, *J* = 7.1, 5.3 Hz, 1H, CH-2), 3.32 (dd, *J* = 9.2, 5.7 Hz, 1H, CH₂-7b), 3.36 (dd, *J* = 9.2, 6.2 Hz, 1H, CH₂-7a), 3.39 (s, 3H, OCH₃-17), 3.80 (s, 3H, OCH₃-13), 4.22 (dd, *J* = 5.3, 3.3 Hz, 1H, CH-3), 4.43 (s, 2H, CH₂-8a, b), 4.43–4.48 (m, 1H, CH-4), 4.63 (s, 2H, CH₂-16a, b), 6.84–6.89 (m, 2H, CH-11, 11a), 7.21–7.26 (m, 2H, CH-10, 10a). ¹³C NMR (100 MHz, CDCl₃): δ 9.3 (CH₃-14), 17.2 (CH₃-15), 30.5 (CH-6), 33.7 (CH₂-5) 42.0 (CH-2), 55.7 (OCH₃-13), 56.8 (OCH₃-17), 72.9 (CH₂-8), 75.8 (CH₂-7), 78.8 (CH-3), 80.7 (CH-4), 97.7 (CH₂-16), 114.1 (CH-11, 11a), 129.5 (CH-10, 10a), 131.1 (C-9), 159.2 (C-12), 178.2 (C-1). IR (ATR) ν 2937, 2853, 2365, 2339, 1773, 1513, 1462, 1376, 1302, 1247, 1211, 1174, 1154, 1125, 1089, 997, 964, 882, 820 cm^{–1}. HRMS (ESI) calcd for C₁₉H₂₈O₆Na [M + Na]⁺, 375.1784; found, 375.1784.

Bromide (25). Dibromide **16** (80 mg, 0.114 mmol, 2.0 equiv) was dissolved in dry Et₂O (0.57 mL) and cooled to –115 °C (liquid nitrogen/ethanol cooling bath), and a solution of *n*-BuLi (2.0 M in hexanes, 60 μ L, 0.114 mmol, 2.0 equiv) was added dropwise over 3 min. The reaction mixture was stirred for 1 h 15 min with the temperature kept between –112 and –108 °C. Aldehyde **4** (20 mg, 0.057 mmol, 1.0 equiv) in Et₂O (0.25 mL) was added over a period of 20 min via syringe pump, and the colorless solution was stirred for 1 h between –112 and –108 °C and for 90 min between –100 and –105 °C. The reaction was terminated by the addition of saturated, aqueous NH₄Cl solution (1.5 mL) at –100 °C. After warming to room temperature, the layers were separated, and the organic phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude 1:1 mixture of the corresponding diastereomeric secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), and diastereomers **25** (20 mg, less polar) and **25a** (21 mg, more polar) were obtained in 74% overall yield as colorless oils. Diastereomer **25**: $[\alpha]_D^{20}$ –21.1 (*c* 0.9, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H, CH₃-TBS), 0.08 (s, 3H, CH₃-TBS), 0.11 (s, 6H, CH₃-TBS), 0.58–0.66 (m, 6H, CH₂-TES), 0.90 (s, 9H, CH₃-*t*Bu-TBS), 0.91 (s, 9H, CH₃-*t*Bu-TBS), 0.97 (t, *J* = 8.0 Hz, 9H, CH₂-TES), 1.02–1.09 (m, 1H, CH₂-6b), 1.07 (d, *J* = 6.6 Hz, 3H, CH₃-17), 1.10 (d, *J* = 6.6 Hz, 3H, CH₃-16), 1.32 (s, 3H, CH₃-21 or 22), 1.46 (s, 3H, CH₃-21 or 22), 1.47–1.54 (m, 1H, CH₂-6a), 1.55 (s, 3H, CH₃-19), 1.92–2.0 (m, 1H, CH-7), 2.45–2.52 (m, 1H, CH-3), 3.31 (dd, *J* = 5.3, 5.1 Hz, 1H, CH-4), 3.36 (s, 3H, OCH₃-MEM), 3.38 (s, 3H, OCH₃-MOM), 3.48–3.55 (m, 3H, CH₂-MEM, OH-18), 3.62–3.68 (m, 2H, CH₂-MEM, CH₂-15b), 3.83 (dd, *J* = 10.5, 1.5 Hz, 1H, CH₂-15a), 3.88–3.92 (m, 2H, CH₂-MEM, CH-5), 4.09 (d, *J* = 7.2 Hz, 1H, CH-12), 4.19–4.22 (m, 1H, CH-14), 4.24 (dd, *J* = 7.2, 2.6 Hz, 1H, CH-13), 4.41 (dd, *J* = 9.2, 3.0 Hz, 1H, CH-8), 4.61 (d, *J* = 6.8 Hz, 1H, CH₂-MOM), 4.70 (d, *J* = 6.8 Hz, 1H, CH₂-MOM), 4.73 (d, *J* = 7.5 Hz, 1H, CH₂-MEM), 4.96 (dd, *J* = 10.3, 2.0 Hz, 1H, CH₂-1b), 4.98–5.02 (m, 1H, CH₂-1a), 5.03 (d, *J* = 7.5 Hz, 1H, CH₂-MEM), 5.82–5.90 (m, 1H, CH-2), 6.14 (s, 1H, CH-10). ¹³C NMR (100 MHz, CDCl₃): δ –5.2 (CH₃-TBS), –5.0 (CH₃-TBS), –4.2 (CH₃-TBS), –3.6 (CH₃-TBS), 5.3 (CH₂-TES), 7.2 (CH₃-TES), 16.0 (CH₃-17), 18.4 (C-*t*Bu-TBS), 18.8 (C-*t*Bu-TBS), 19.2 (CH₃-16), 24.9 (CH₃-21 or 22), 25.5 (CH₃-19), 26.2 (CH₃-21 or 22), 26.22 (CH₃-*t*Bu-TBS), 26.4 (CH₃-*t*Bu-TBS), 34.0 (CH-7), 35.1 (CH₂-6), 39.0 (CH-3), 56.0 (OCH₃-MOM), 59.2 (OCH₃-MEM), 66.9 (CH₂-15), 68.3 (CH₂-MEM), 71.6 (CH-5), 71.8 (CH₂-MEM), 73.6 (CH-14), 74.4 (CH-8), 79.8 (C-11), 81.7 (CH-13), 82.2 (CH-12), 84.7 (CH-4), 92.2 (CH₂-MEM), 98.1 (CH₂-MOM), 107.7 (C-20), 114.3 (CH₂-1), 135.8 (CH-10), 136.3 (C-9), 141.8 (CH-2). IR (ATR) ν 3462, 2954, 2929, 2856, 1461, 1380, 1252, 1211, 1101, 1067, 1036, 1005, 911, 834, 776 cm^{–1}. HRMS (ESI) calcd for C₄₅H₈₁⁸¹BrO₁₁Si₃Na [M + Na]⁺, 995.4930; found, 995.4933. Diastereomer **25a**: $[\alpha]_D^{20}$ –12.7 (*c* 1.15, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.046 (s, 3H, CH₃-TBS), 0.051 (s, 3H, CH₃-TBS), 0.10 (s, 3H, CH₃-TBS), 0.11 (s, 3H, CH₃-TBS), 0.64 (quart, *J* = 7.7 Hz, 6H, CH₂-TES), 0.87 (d, *J* = 6.8 Hz, 3H, CH₃-17), 0.89 (s, 9H, CH₃-*t*Bu-TBS), 0.90 (s, 9H, CH₃-*t*Bu-TBS), 0.98 (t, *J* = 7.7 Hz, 9H, CH₂-TES), 1.11 (d, *J* = 7.0 Hz, 3H, CH₃-16), 1.26–1.30 (m, 1H, CH₂-6b), 1.32 (s, 3H, CH₃-21 or 22), 1.46 (s, 3H,

CH₃-21 or 22), 1.54 (s, 3H, CH₃-19), 1.85–1.93 (m, 1H, CH₂-6a), 2.03–2.10 (m, 1H, CH-7), 2.47–2.55 (m, 1H, CH-3), 2.79–2.91 (bs, 1H, OH-18), 3.32 (dd, *J* = 5.5, 5.3 Hz, 1H, CH-4), 3.37 (s, 3H, OCH₃-MEM), 3.38 (s, 3H, OCH₃-MOM), 3.52–3.54 (m, 2H, CH₂-MEM), 3.62 (dd, *J* = 10.9, 7.2 Hz, 1H, CH₂-15b), 3.69–3.74 (m, 1H, CH₂-MEM), 3.77–3.82 (m, 2H, CH₂-MEM, CH₂-15a), 3.88–3.92 (m, 1H, CH-5), 4.03–4.07 (m, 1H, CH-14), 4.17 (d, *J* = 7.0 Hz, 1H, CH-12), 4.20 (dd, *J* = 7.0, 2.0 Hz, 1H, CH-13), 4.41 (dd, *J* = 9.4, 6.6 Hz, 1H, CH-8), 4.62 (d, *J* = 7.0 Hz, 1H, CH₂-MOM), 4.71 (d, *J* = 7.0 Hz, 1H, CH₂-MOM), 4.87 (d, *J* = 7.2 Hz, 1H, CH₂-MEM), 4.94 (d, *J* = 7.2 Hz, 1H, CH₂-MEM), 4.96–5.0 (m, 2H, CH₂-1a, b), 5.83–5.91 (m, 1H, CH-2), 6.18 (s, 1H, CH-10). ¹³C NMR (100 MHz, CDCl₃): δ –5.3 (CH₃-TBS), –5.1 (CH₃-TBS), –4.3 (CH₂-TBS), –3.8 (CH₃-TBS), 5.32 (CH₂-TES), 7.2 (CH₃-TES), 16.7 (CH₃-17), 18.4 (C-*t*Bu-TBS), 18.5 (C-*t*Bu-TBS), 18.9 (CH₃-16), 23.2 (CH₃-19), 25.0 (CH₃-21 or 22), 26.2 (CH₃-*t*Bu-TBS), 26.25 (CH₃-*t*Bu-TBS), 26.3 (CH₃-21 or 22), 35.2 (CH-7), 35.4 (CH₂-6), 39.0 (CH-3), 56.0 (OCH₃-MOM), 59.2 (OCH₃-MEM), 66.7 (CH₂-15), 68.0 (CH₂-MEM), 71.9 (CH₂-MEM), 72.5 (CH-5), 74.3 (CH-14), 74.6 (CH-8), 79.9 (C-11), 81.3 (CH-13), 82.3 (CH-12), 85.1 (CH-4), 91.6 (CH₂-MEM), 98.2 (CH₂-MOM), 107.7 (C-20), 114.4 (CH₂-1), 135.9 (CH-10), 136.7 (C-9), 141.7 (CH-2). IR (ATR) ν 3462, 2954, 2929, 2856, 1461, 1380, 1252, 1211, 1101, 1067, 1036, 1005, 911, 834, 776 cm^{–1}. HRMS (ESI) calcd for C₄₅H₉₁⁸¹BrO₁₁Si₃Na [M + Na]⁺, 995.4930; found, 995.4936.

Mosher Ester S14. To a solution of secondary alcohol **25a** (5 mg, 0.005 mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt₃ (9 μL, 0.06 mmol, 12.0 equiv), DMAP (0.6 mg, 0.005 mmol, 1.0 equiv), and S-(+)-Mosher's acid chloride (2 μL, 0.01 mmol, 2.0 equiv) sequentially at room temperature. The reaction mixture was stirred for 14 h at room temperature. As TLC control showed total consumption of the starting material, the reaction was terminated by the addition of a saturated, aqueous solution of NH₄Cl (1 mL), and the resulting mixture was diluted with DCM (3 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic fractions were dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) to afford Mosher ester **S14** (5 mg) in 85% yield as a colorless oil. [α]_D²⁰ +2.0 (c 0.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.60 (quart, *J* = 7.9 Hz, 6H), 0.90 (s, 18H), 0.95 (t, *J* = 7.9 Hz, 9H), 1.0 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.22–1.29 (m, 1H), 1.31 (s, 3H), 1.46 (s, 3H), 1.70 (s, 3H), 1.66–1.74 (m, 1H), 2.21–2.30 (m, 1H), 2.41–2.49 (m, 1H), 3.27 (t, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.49–3.58 (m, 5H), 3.64 (dd, *J* = 10.5, 7.3 Hz, 1H), 3.70–3.75 (m, 1H), 3.77 (dd, *J* = 10.5, 1.9 Hz, 1H), 3.80–3.85 (m, 1H), 3.87–3.91 (m, 1H), 4.16–4.19 (m, 1H), 4.26 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.30 (d, *J* = 7.3 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.88–4.96 (m, 3H), 5.06 (d, *J* = 7.3 Hz, 1H), 5.83 (ddd, *J* = 17.3, 10.3, 8.3 Hz, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 6.54 (s, 1H), 7.36–7.42 (m, 3H), 7.51–7.55 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ –5.1 (CH₃), –5.0 (CH₃), –4.2 (CH₃), –3.6 (CH₃), 5.2 (CH₂), 7.1 (CH₃), 15.7 (CH₃), 18.4 (C), 18.6 (C), 19.2 (CH₃), 23.8 (CH₃), 24.8 (CH₃), 26.2 (CH₃), 26.3 (CH₃), 26.4 (CH₃), 32.8 (CH), 35.0 (CH₂), 38.8 (CH), 55.9 (CH₃), 56.0 (CH₃), 59.2 (CH₃), 66.9 (CH₂), 68.1 (CH₂), 71.7 (CH), 72.0 (CH₂), 73.6 (CH), 78.1 (CH), 80.1 (C), 82.0 (CH), 82.5 (CH), 85.2 (CH), 91.6 (CH₂), 98.2 (CH₂), 107.7 (C), 114.5 (CH₂), 122.5 (C), 124.4 (C), 125.3 (C), 127.8 (CH), 128.5 (CH), 129.7 (CH), 131.8 (C), 140.1 (CH), 141.5 (CH), 166.3 (C). ¹⁹F NMR (565 MHz, CDCl₃): δ –72.13 (s). IR (ATR) ν 2956, 2929, 2855, 2366, 1746, 1707, 1472, 1461, 1415, 1386, 1293, 1252, 1170, 1100, 1065, 1004, 916, 859, 811, 743 cm^{–1}. HRMS (ESI) calcd for C₅₅H₉₈⁸¹BrF₃O₁₃Si₃Na [M + Na]⁺, 1211.5328; found, 1211.5350.

Mosher Ester S15. Mosher ester **S15** was prepared following the same procedure as described above. Using enantiomeric R-(–)-Mosher's acid chloride, **S15** (5 mg) was afforded in 85% yield as a colorless oil. [α]_D²⁰ –31.0 (c 0.3, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.065 (s, 3H), 0.07 (s, 3H), 0.072 (s, 3H), 0.56 (quart, *J* = 8.0 Hz, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.99 (d, *J* = 4.5 Hz, 3H), 1.0 (d, *J* = 4.5 Hz, 3H), 1.18 (dd, *J*

= 12.0, 12.0 Hz, 1H), 1.25 (s, 3H), 1.45 (s, 3H), 1.43–1.49 (m, 1H), 1.62 (s, 3H), 2.20–2.27 (m, 1H), 2.27–2.33 (m, 1H), 3.17 (t, *J* = 5.6 Hz, 1H), 3.37 (s, 3H), 3.371 (s, 3H), 3.49–3.57 (m, 2H), 3.58 (s, 3H), 3.64 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.67–3.72 (m, 1H), 3.76 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.79–3.85 (m, 2H), 4.15–4.19 (m, 1H), 4.23–4.27 (m, 2H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.92–4.94 (m, 1H), 4.95 (bs, 1H), 5.07 (d, *J* = 7.2 Hz, 1H), 5.80 (ddd, *J* = 16.7, 10.8, 8.1 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 6.58 (s, 1H), 7.36–7.40 (m, 3H), 7.56–7.60 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ –5.1 (CH₃), –5.0 (CH₃), –4.3 (CH₃), –3.6 (CH₃), 5.2 (CH₂), 7.0 (CH₃), 15.6 (CH₃), 18.4 (C), 18.5 (CH₃), 18.7 (C), 23.8 (CH₃), 24.7 (CH₃), 26.2 (CH₃), 26.3 (CH₃), 26.4 (CH₃), 32.8 (CH), 34.7 (CH₂), 39.1 (CH), 55.8 (CH₃), 56.0 (CH₃), 59.2 (CH₃), 67.0 (CH₂), 68.0 (CH₂), 71.5 (CH), 71.9 (CH₂), 73.6 (CH), 77.9 (CH), 80.2 (C), 82.0 (CH), 82.5 (CH), 85.0 (CH), 91.6 (CH₂), 98.1 (CH₂), 107.7 (C), 114.3 (CH₂), 122.5 (C), 124.4 (C), 125.3 (C), 127.5 (CH), 128.5 (CH), 129.7 (CH), 132.3 (C), 140.4 (CH), 141.7 (CH), 166.4 (C). ¹⁹F NMR (565 MHz, CDCl₃): δ –70.93 (s). IR (ATR) ν 2956, 2929, 2855, 2366, 1746, 1707, 1472, 1461, 1415, 1386, 1293, 1252, 1170, 1100, 1065, 1004, 916, 859, 811, 743 cm^{–1}. HRMS (ESI) calcd for C₅₅H₉₈⁸¹BrF₃O₁₃Si₃Na [M + Na]⁺, 1211.5328; found, 1211.5338.

Bromide 26. To a solution of secondary alcohol **25** (12 mg, 0.012 mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt₃ (22 μL, 0.144 mmol, 12.0 equiv), DMAP (1.5 mg, 0.012 mmol, 1.0 equiv), and benzoyl chloride (2.8 μL, 0.024 mmol, 2.0 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 5 h. As TLC control showed remaining starting material, 2 equiv of benzoyl chloride (2.8 μL, 0.024 mmol) were added at room temperature, and the reaction mixture was stirred for 5 h. The reaction was quenched by the addition of a saturated, aqueous solution of NH₄Cl (1 mL), and the resulting mixture was diluted with DCM (5 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic fractions were dried over Na₂SO₄ and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford bromide **26** (9 mg) in 71% yield as a colorless oil. [α]_D²⁰ –15.8 (c 0.46, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ –0.01 (s, 3H), 0.00 (s, 6H), 0.01 (s, 3H), 0.64 (q, *J* = 7.9 Hz, 6H), 0.77 (s, 9H), 0.86 (s, 9H), 0.99 (t, *J* = 7.9 Hz, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.27–1.36 (m, 1H), 1.41 (s, 3H), 1.44 (s, 3H), 1.58 (s, 3H), 1.64–1.75 (m, 1H), 2.26–2.39 (m, 1H), 2.47–2.56 (m, 1H), 3.33 (bt, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.52–3.60 (m, 3H), 3.67–3.71 (m, 1H), 3.73–3.81 (m, 2H), 3.82–3.86 (m, 1H), 3.88–3.95 (m, 1H), 4.00 (dd, *J* = 6.8, 1.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.93–5.04 (m, 3H), 5.11 (d, *J* = 7.3 Hz, 1H), 5.87 (ddd, *J* = 17.5, 10.2, 8.4 Hz, 1H), 6.18 (d, *J* = 9.3 Hz, 1H), 6.35 (s, 1H), 7.41–7.48 (m, 2H), 7.53–7.60 (m, 1H), 8.04–8.11 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ –5.4 (CH₃), –5.2 (CH₃), –4.5 (CH₃), –3.9 (CH₃), 5.4 (CH₂), 7.2 (CH₃), 15.6 (CH₃), 18.4 (C), 18.5 (C), 19.1 (CH₃), 22.4 (CH₃), 25.1 (CH₃), 26.2 (CH₃), 33.6 (CH), 34.6 (CH₂), 39.1 (CH), 56.0 (CH₃), 59.1 (CH₃), 67.1 (CH₂), 67.7 (CH₂), 71.6 (CH), 72.0 (CH₂), 74.9 (CH), 76.9 (CH), 79.6 (C), 81.6 (CH), 82.4 (CH), 84.7 (CH), 91.7 (CH₂), 98.2 (CH₂), 107.9 (C), 114.4 (CH₂), 128.5 (CH), 129.2 (C), 130.1 (CH), 130.2 (C), 133.2 (CH), 139.5 (CH), 141.7 (CH), 165.5 (C). IR (ATR) ν 2957, 2927, 2877, 2854, 1718, 1471, 1452, 1381, 1300, 1250, 1213, 1176, 1111, 1067, 1006, 989, 968, 889, 834, 777, 711 cm^{–1}. HRMS (ESI) calcd for C₅₂H₉₅⁸¹BrO₁₂Si₃Na [M + Na]⁺, 1099.5192; found, 1099.5210.

■ ASSOCIATED CONTENT

● Supporting Information

NMR spectra of all compounds, NOE analysis of **S3** and **S13**, and Mosher ester analysis of **S14** and **S15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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Supporting Information

Synthesis of an Advanced Intermediate of the Jatrophone Diterpene Pl-4 – A Dibromide Coupling Approach

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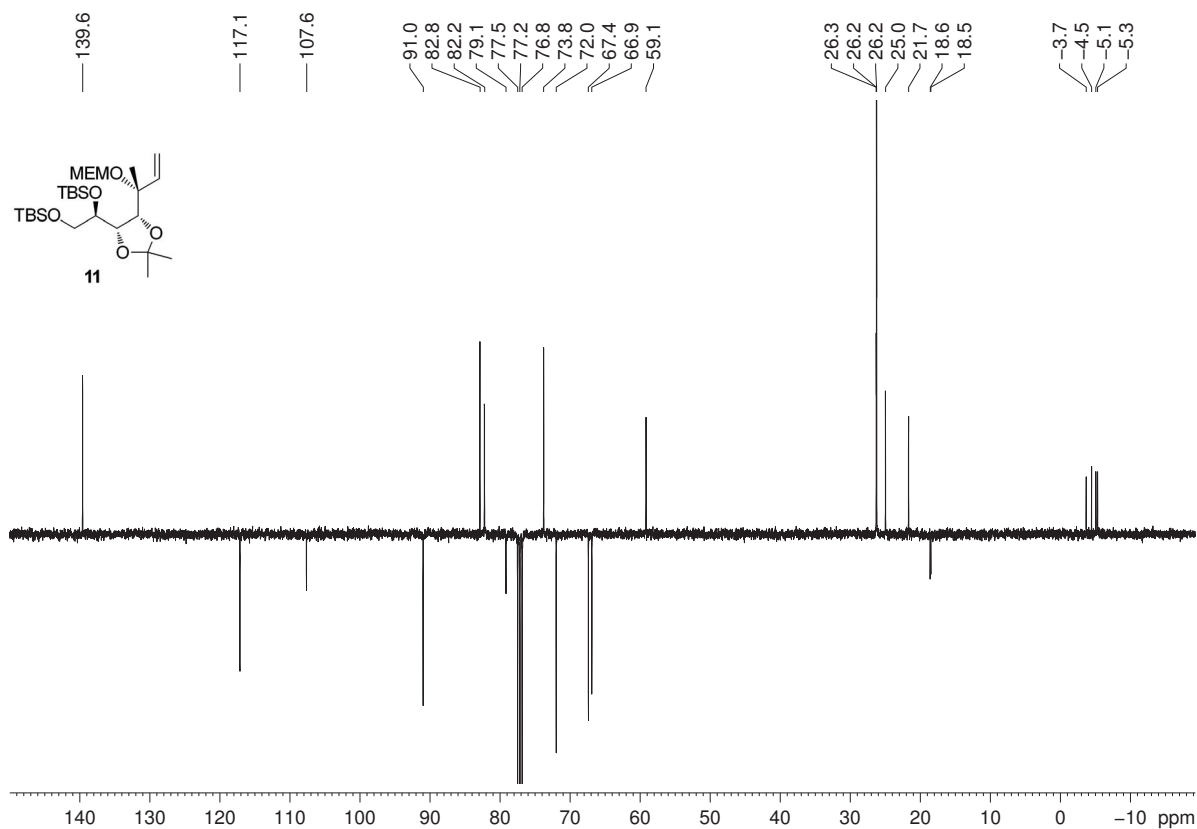
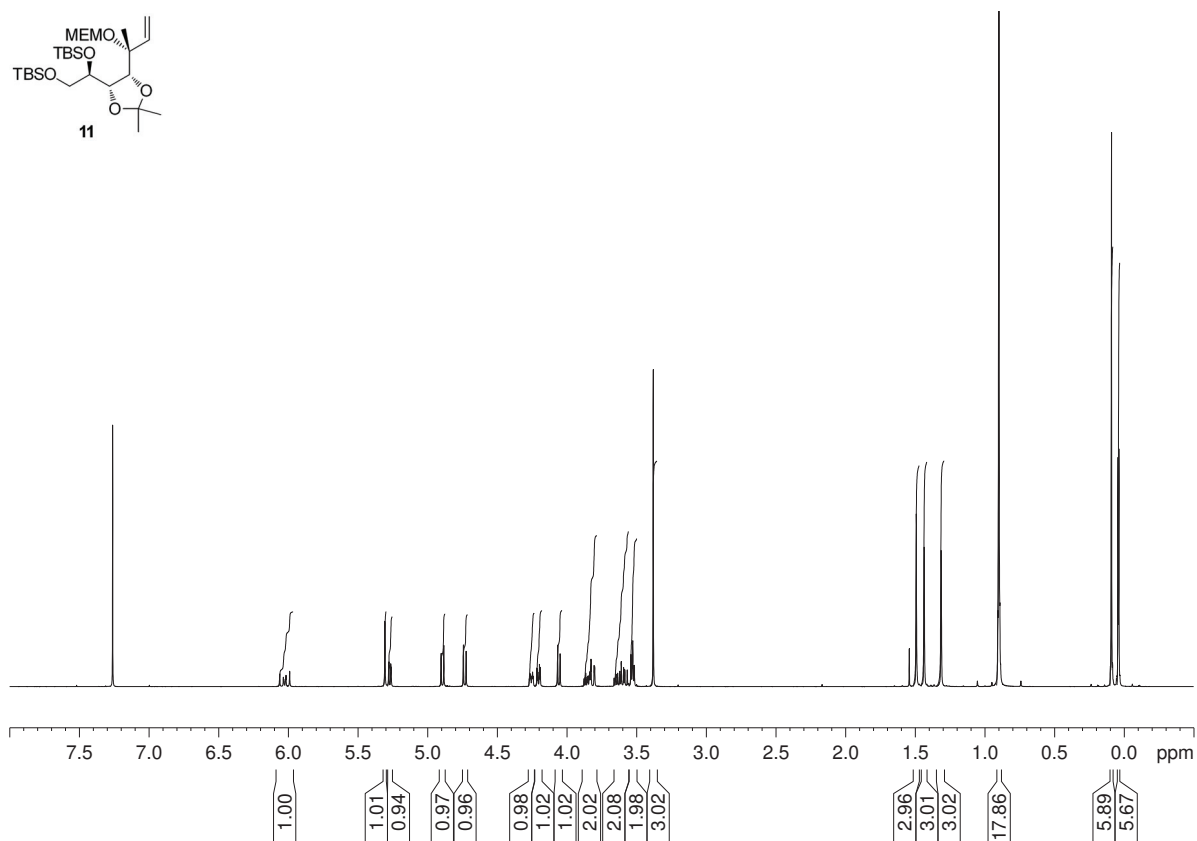
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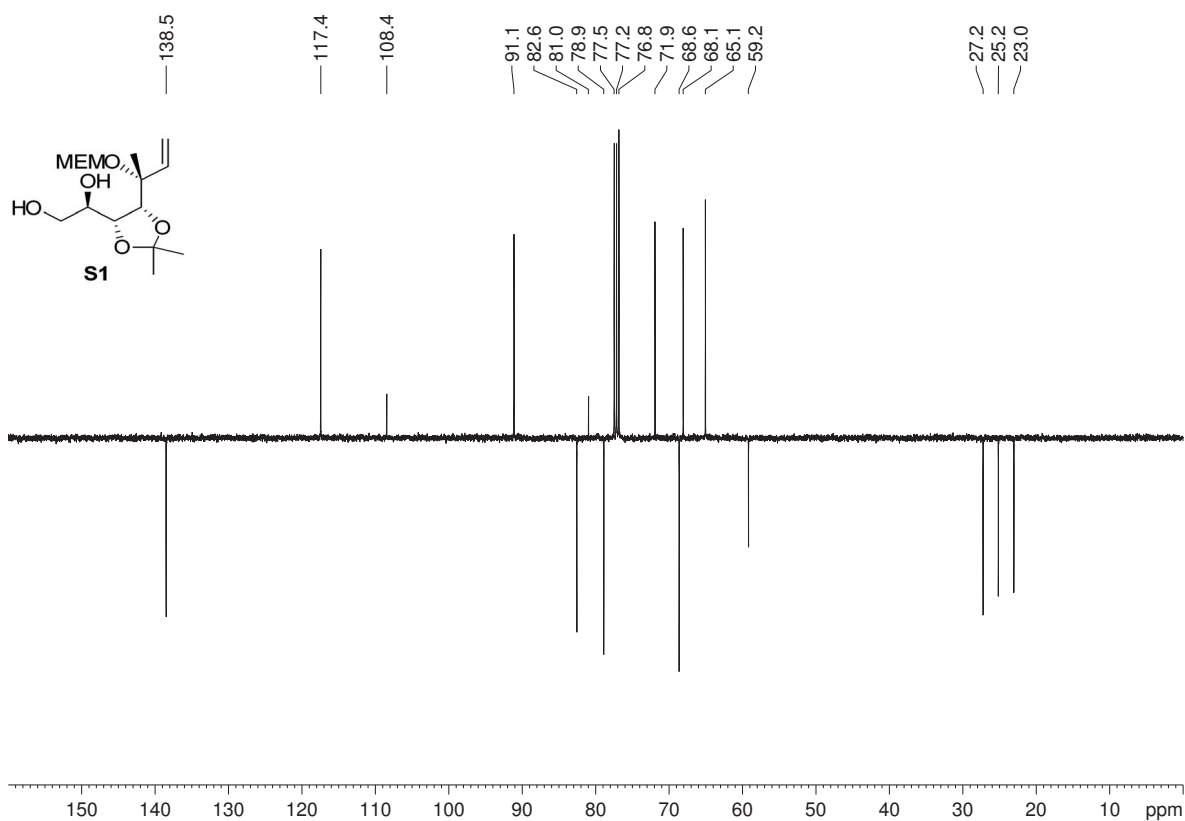
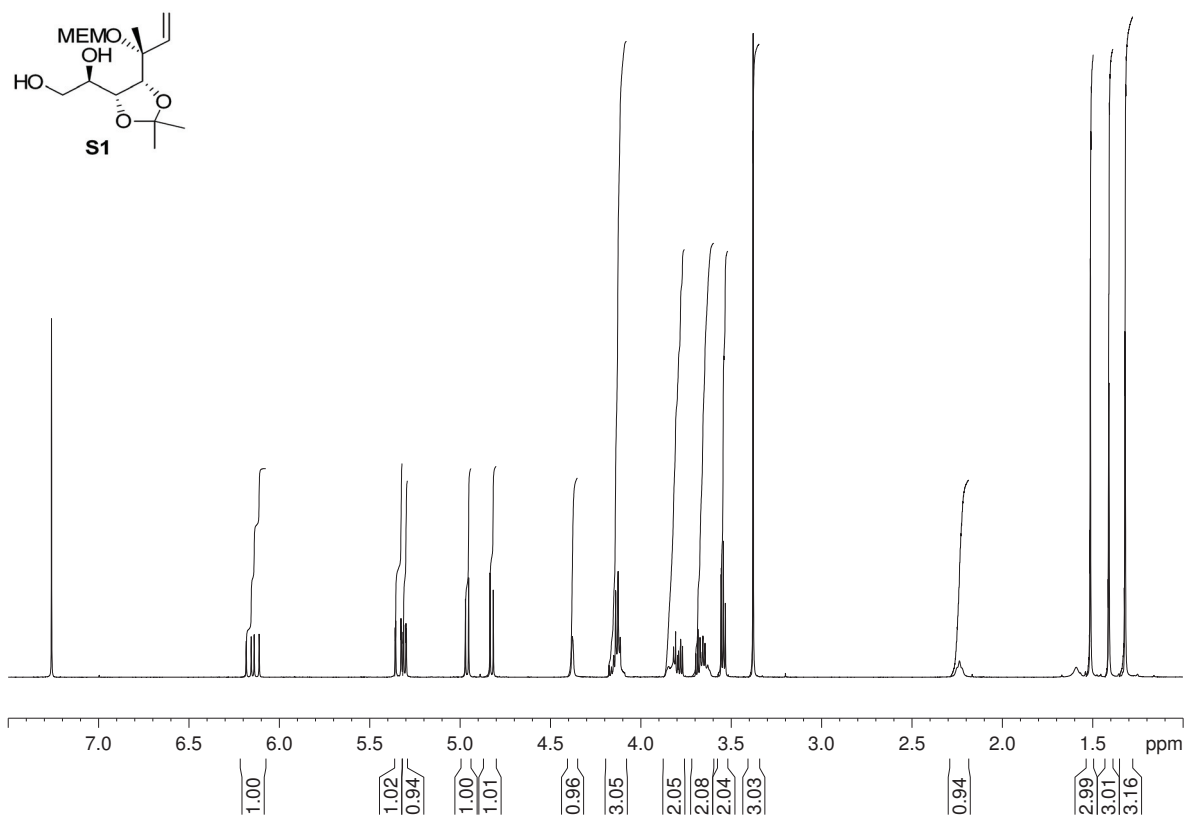
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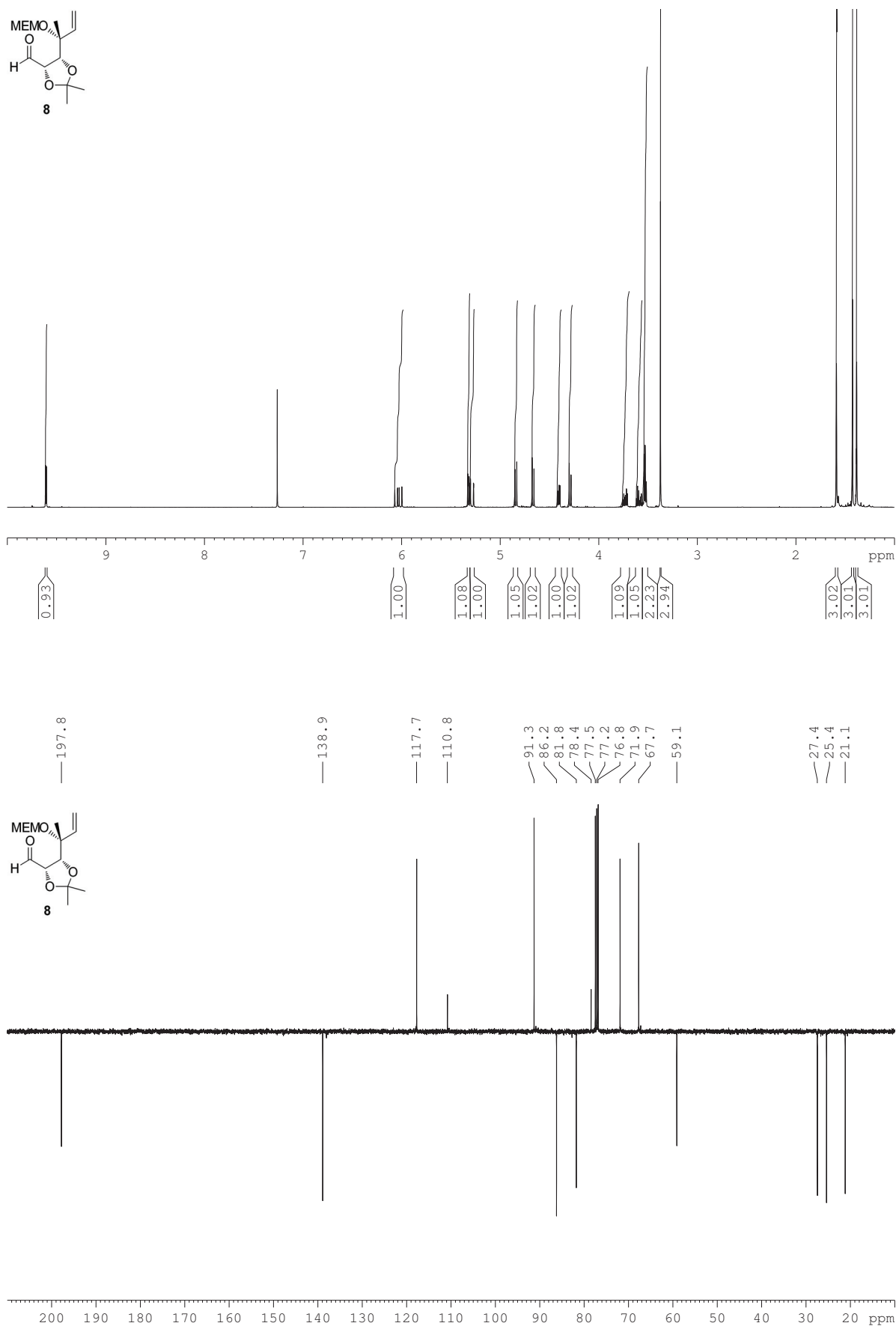
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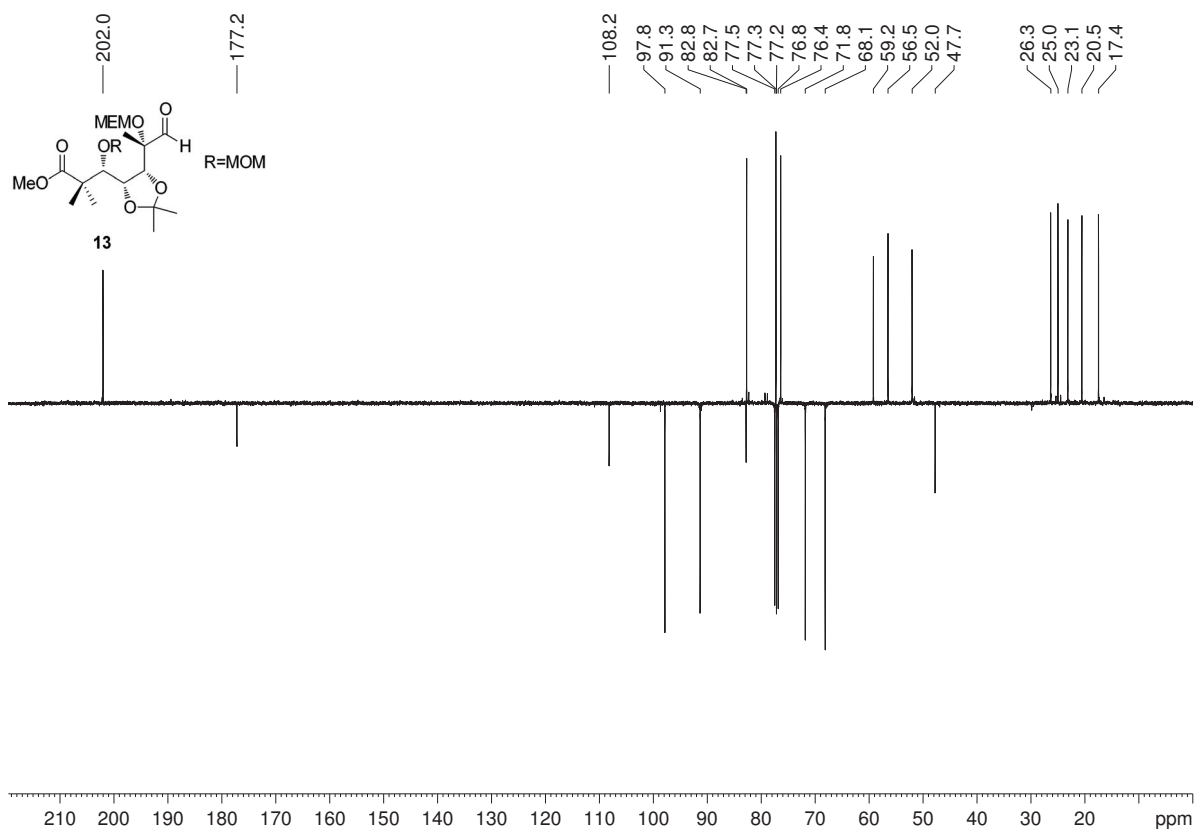
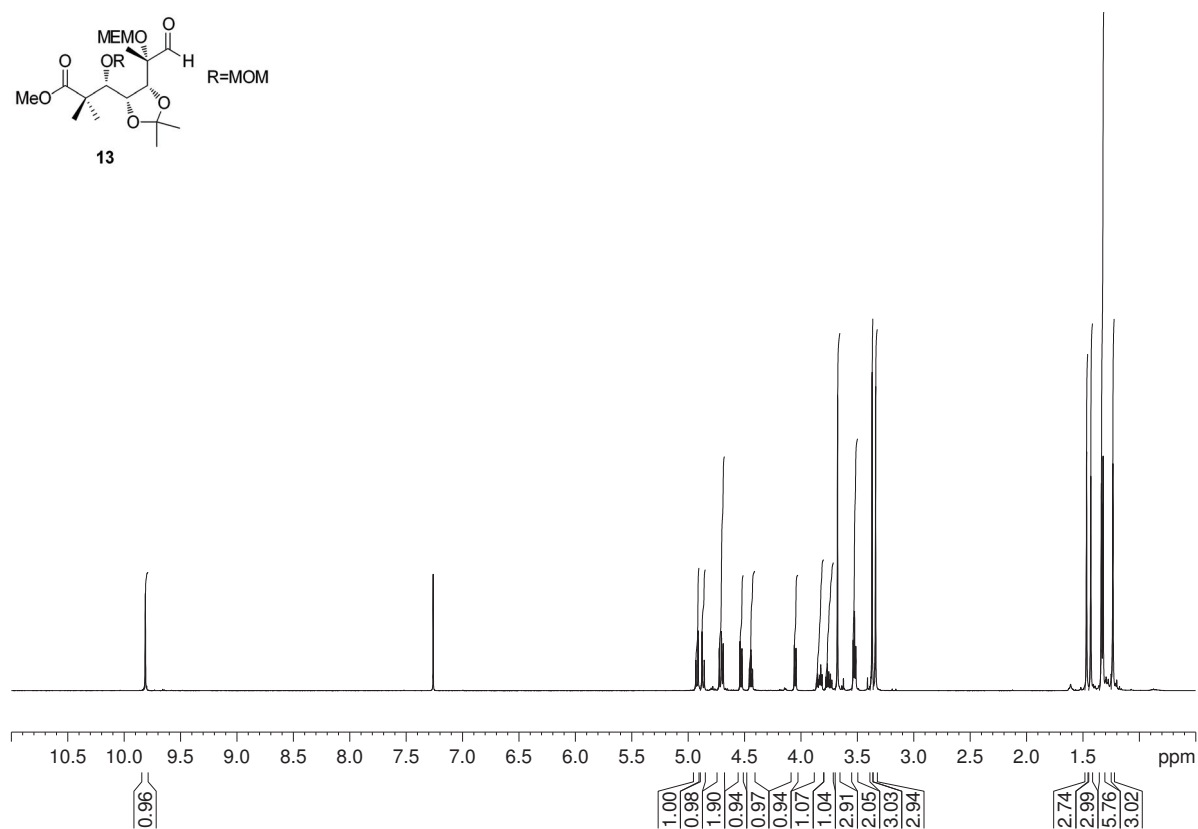
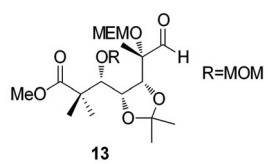
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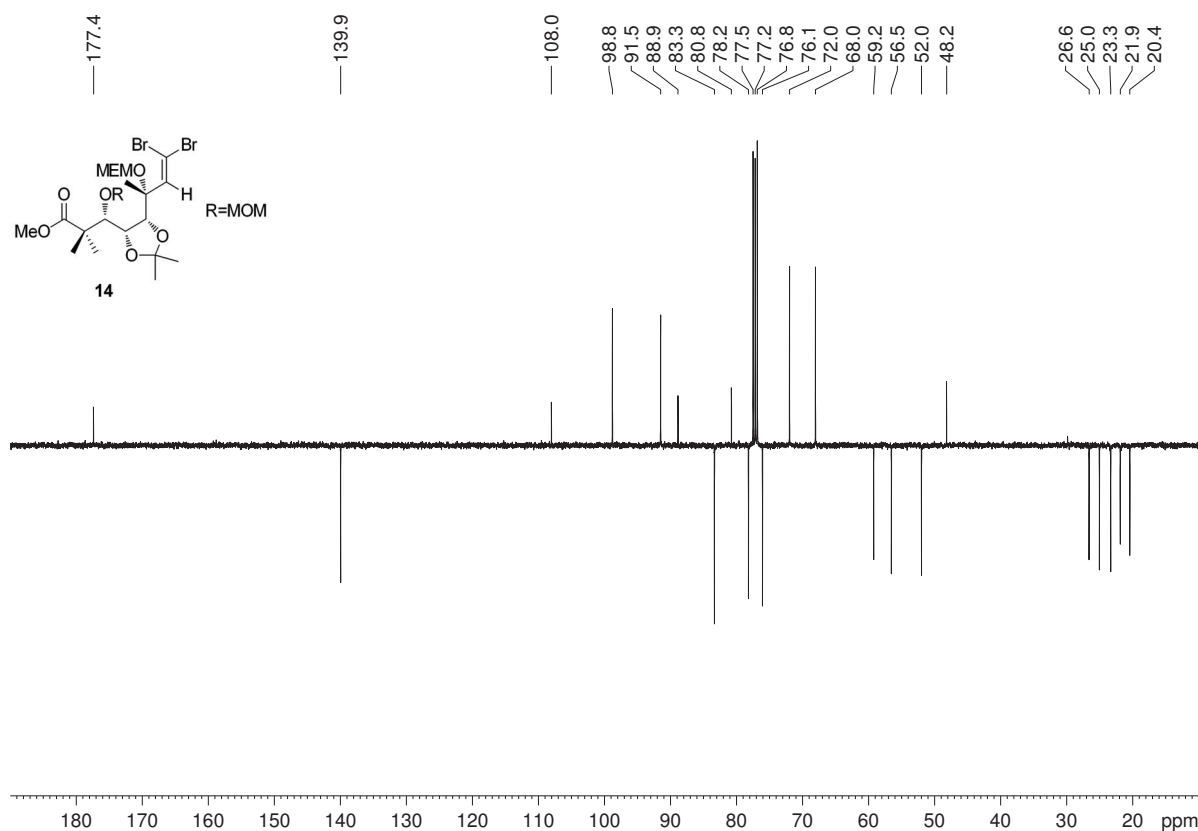
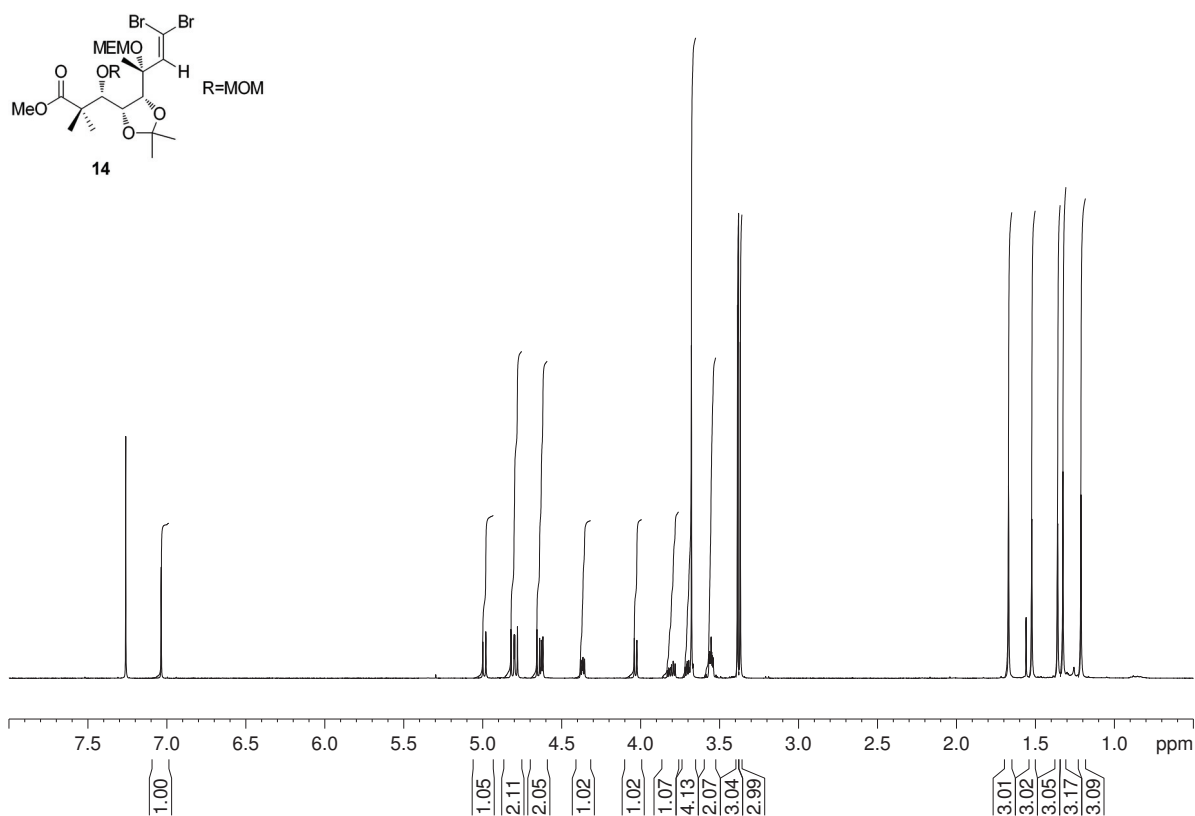
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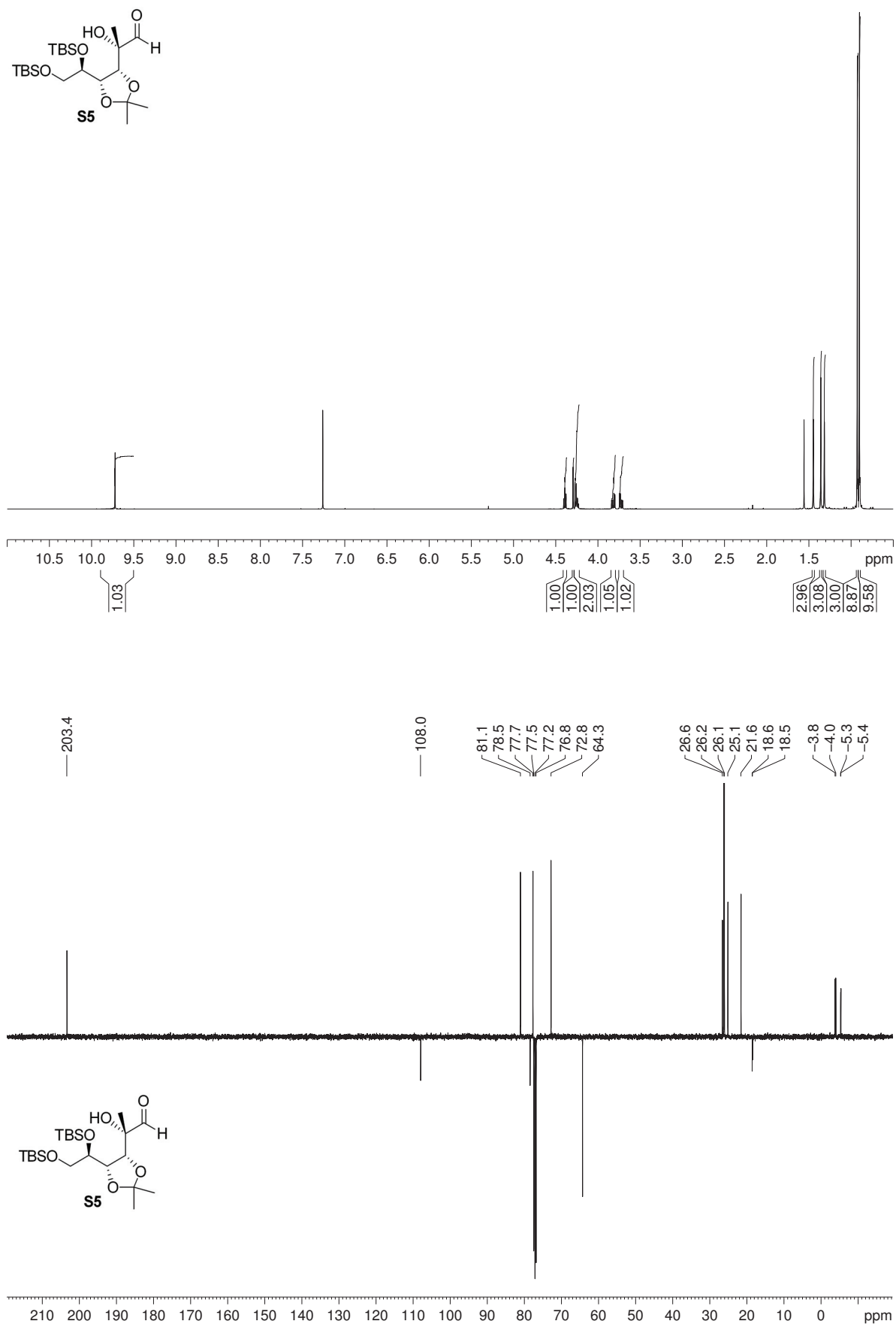


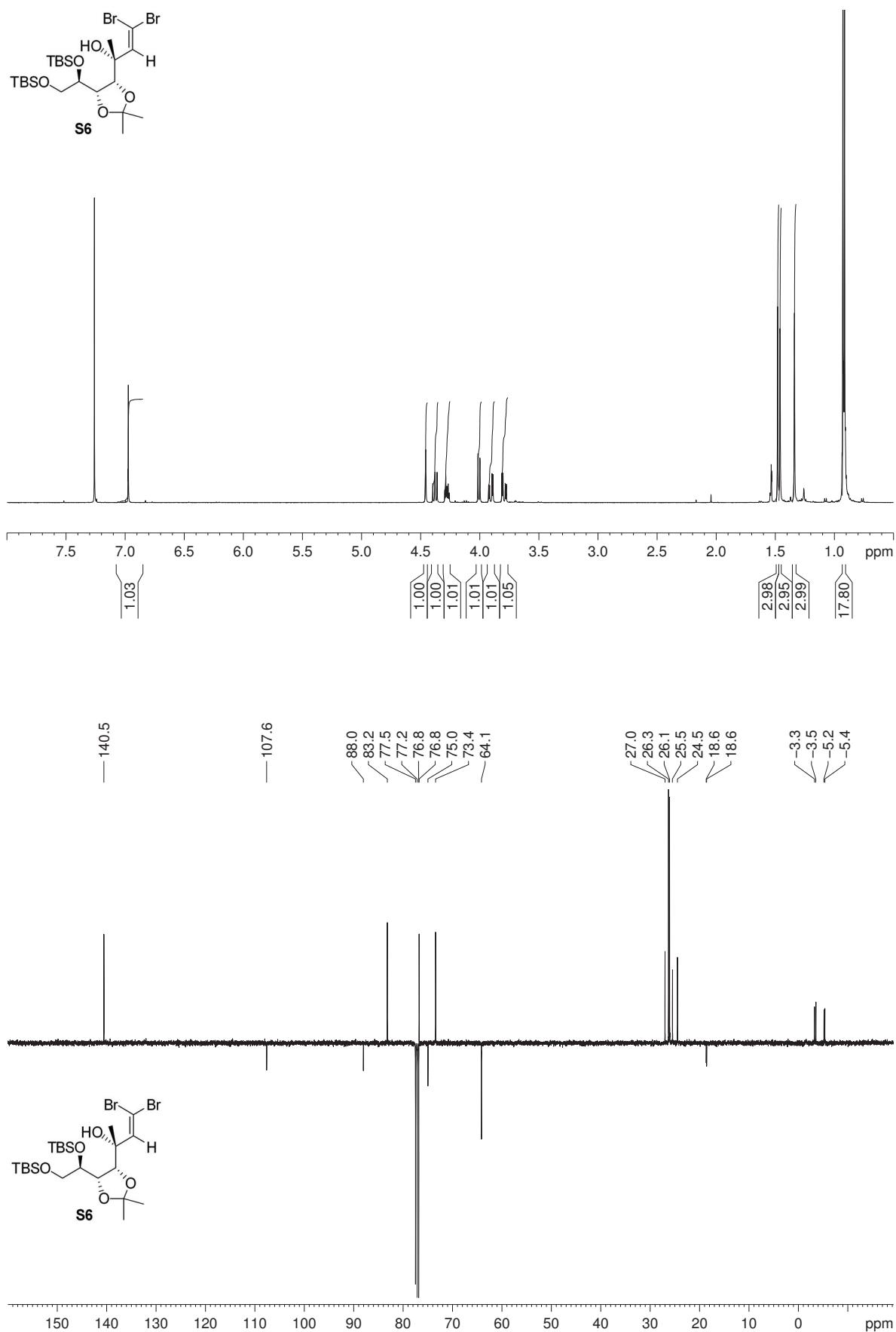


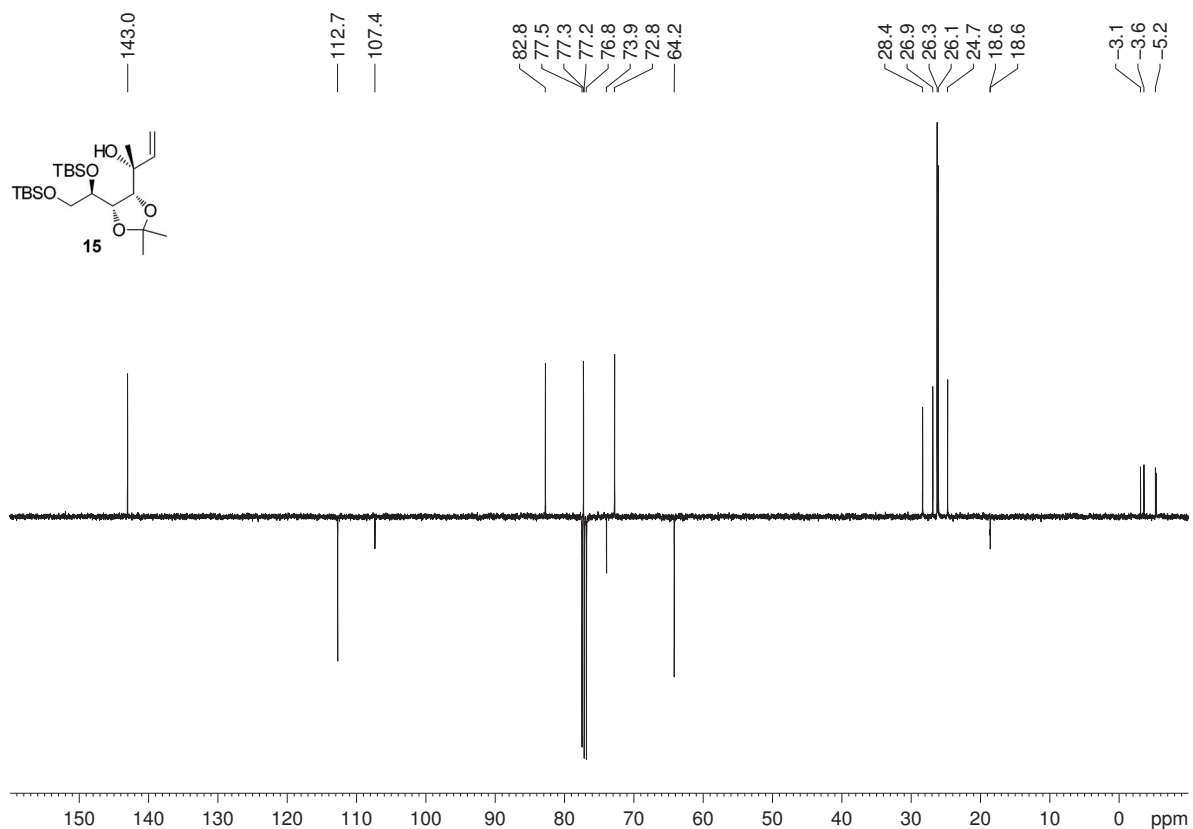
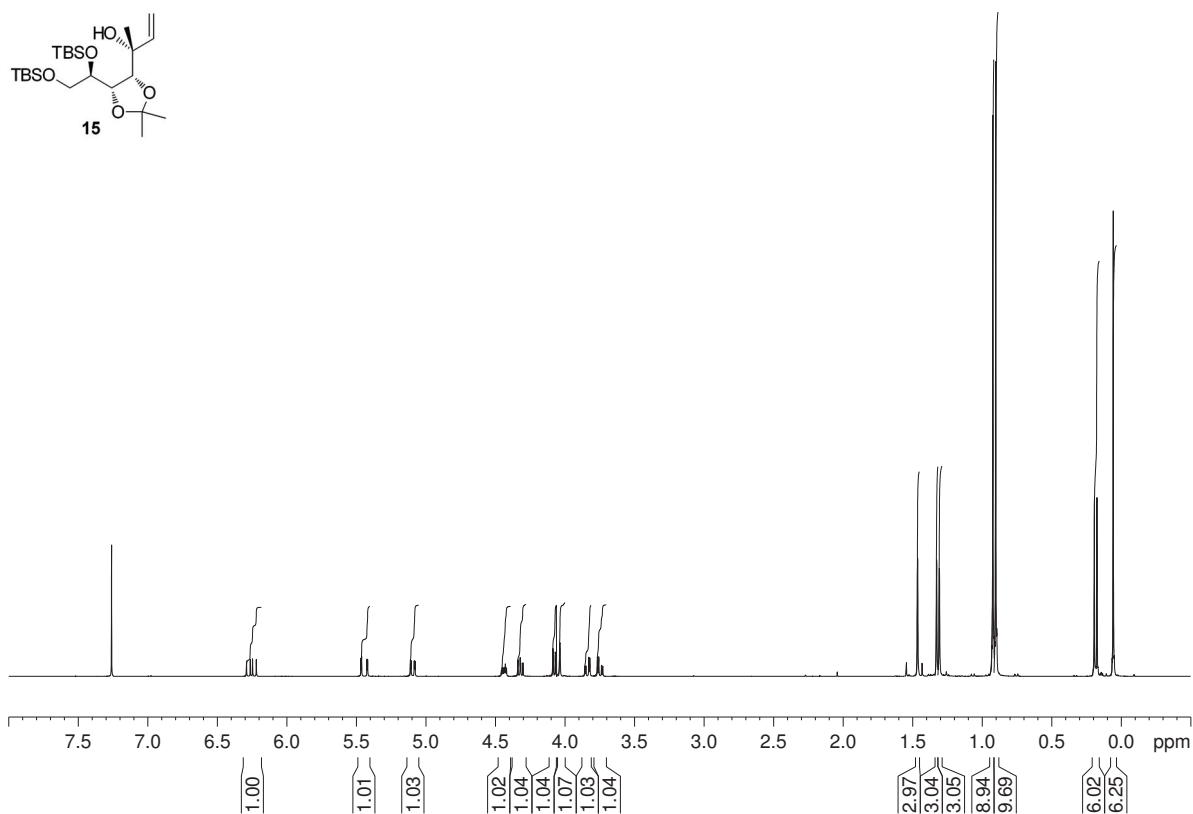


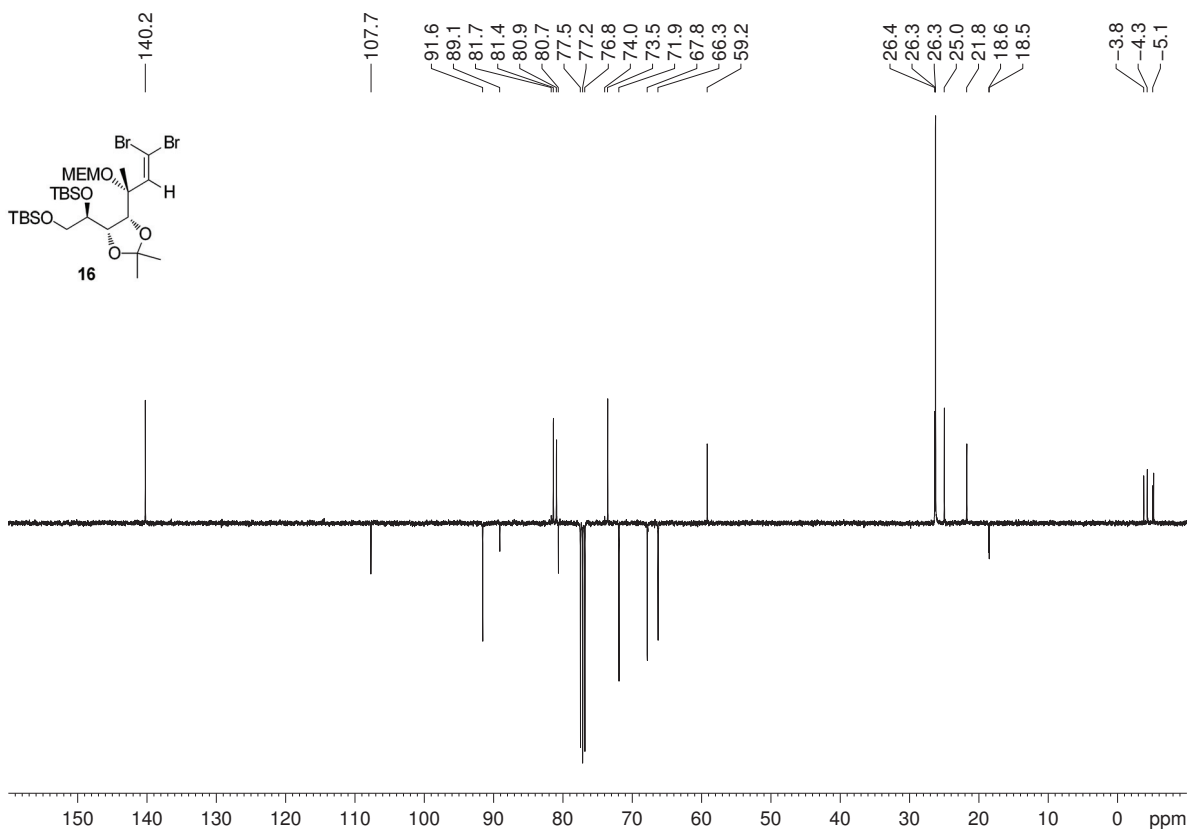
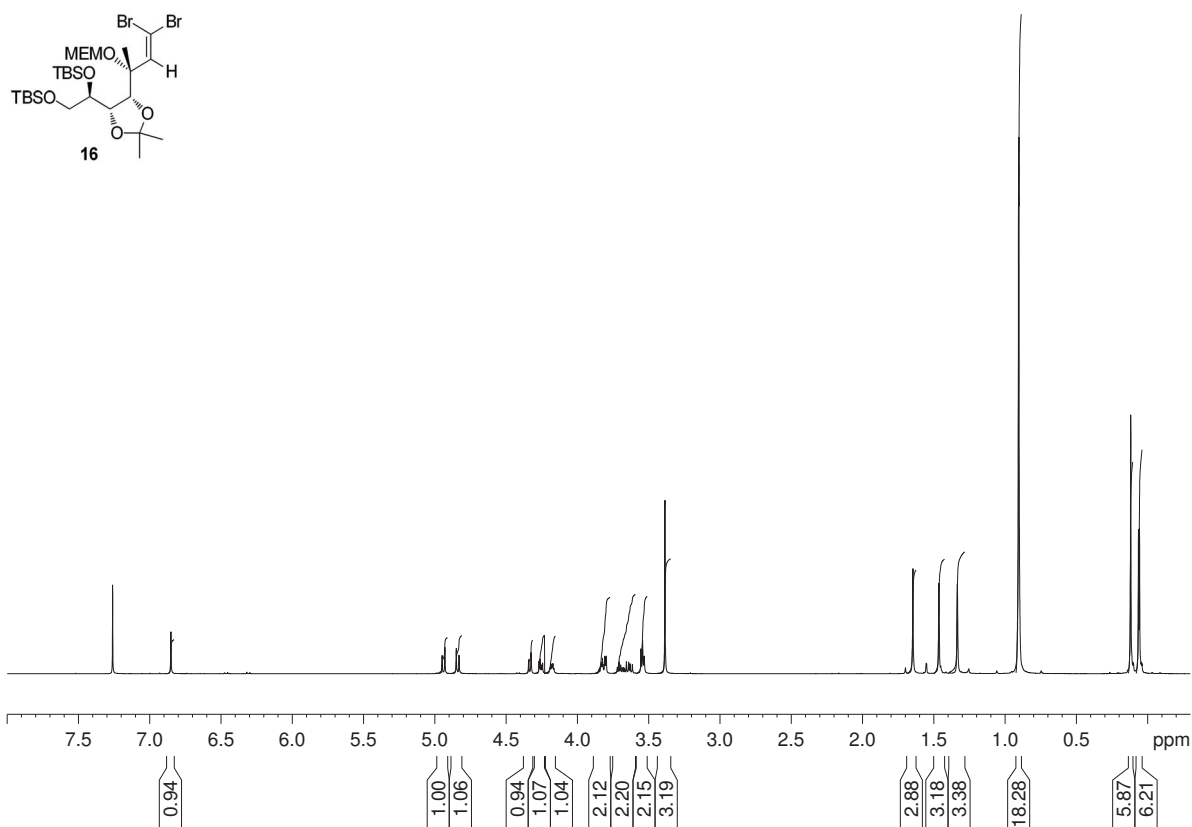


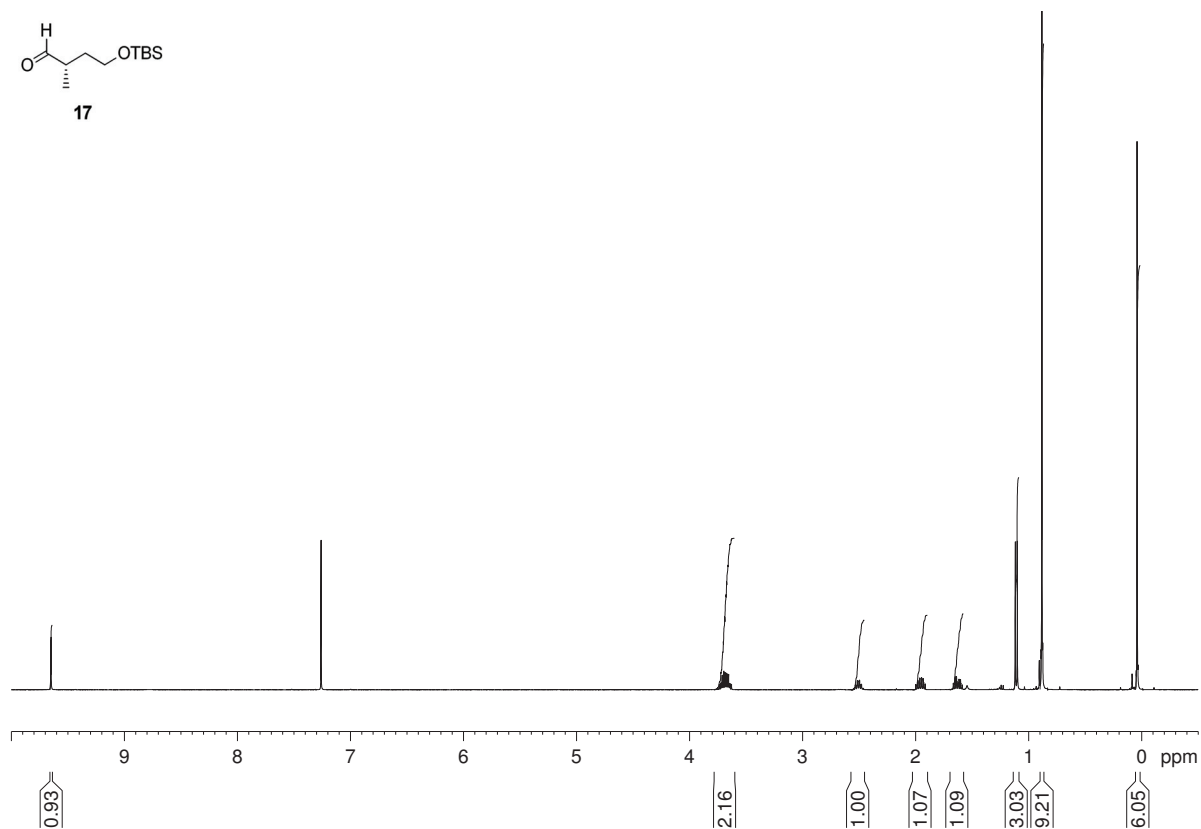
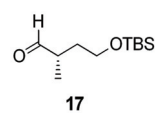
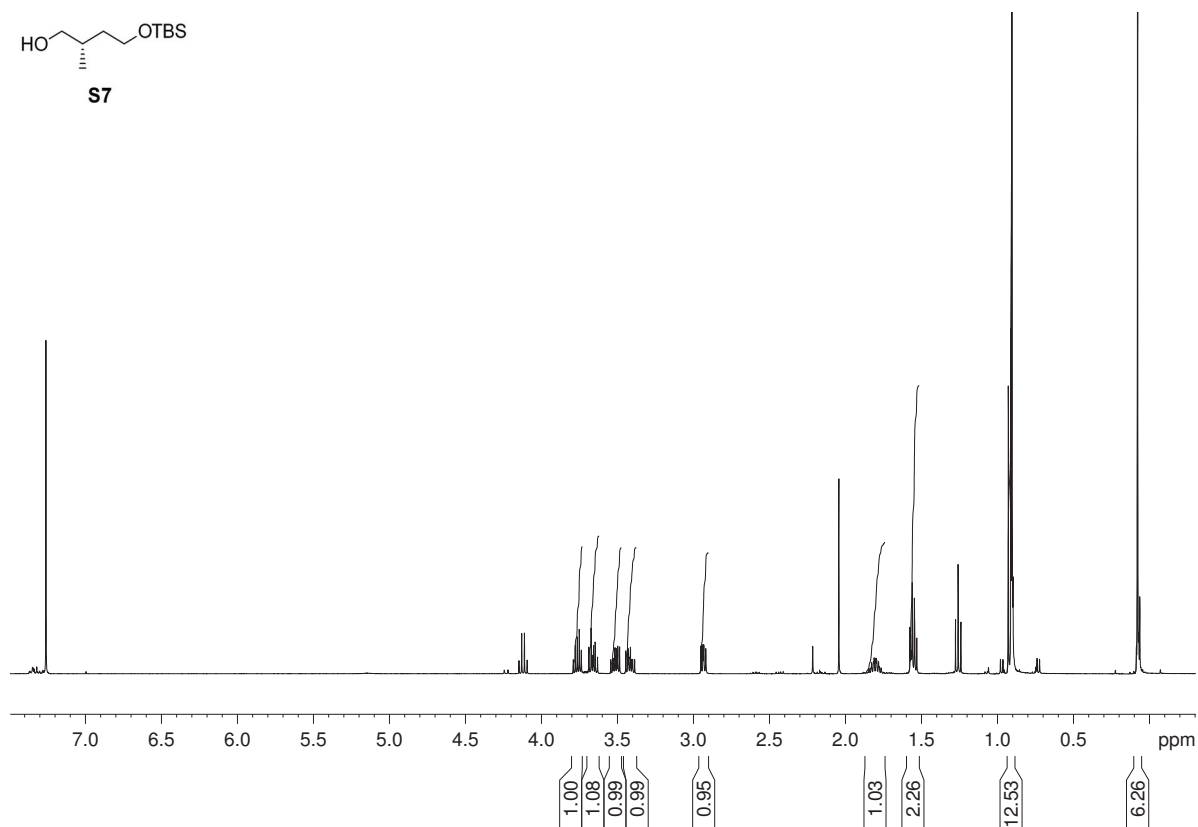
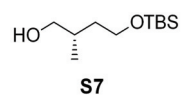


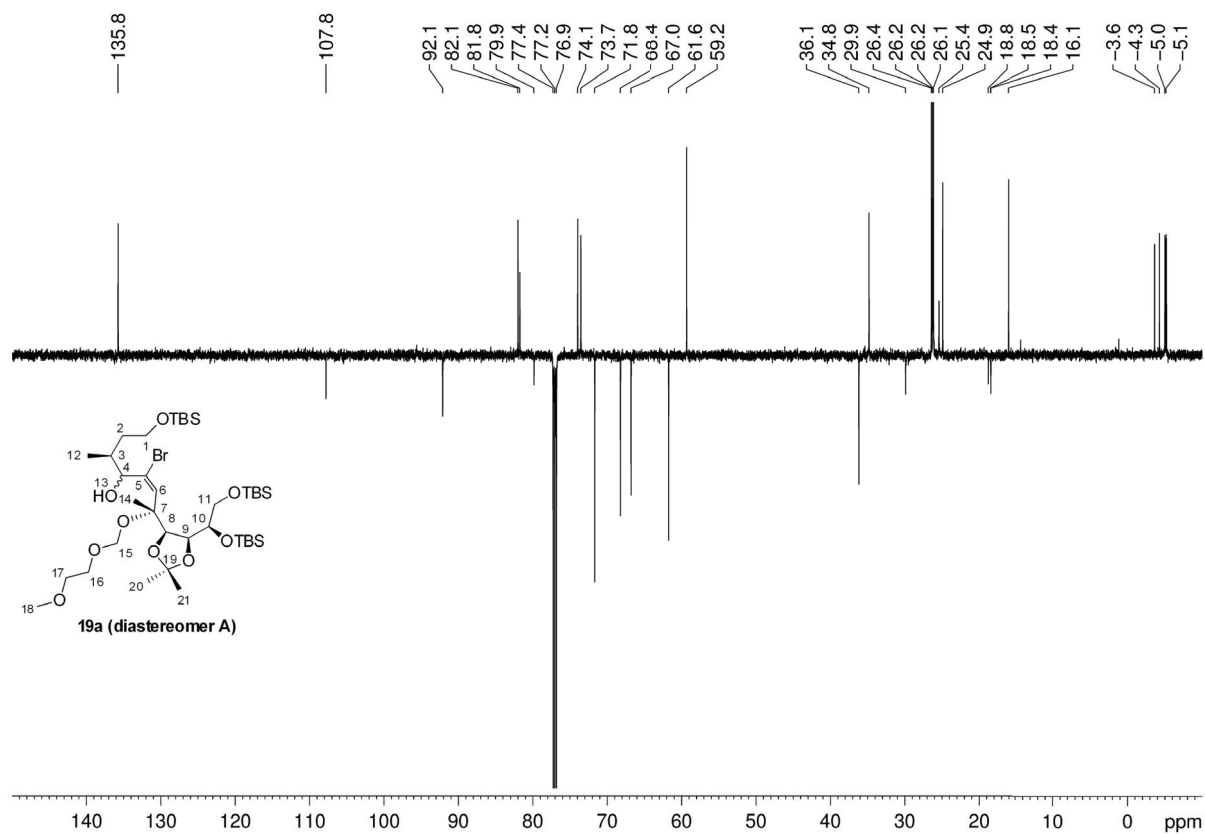
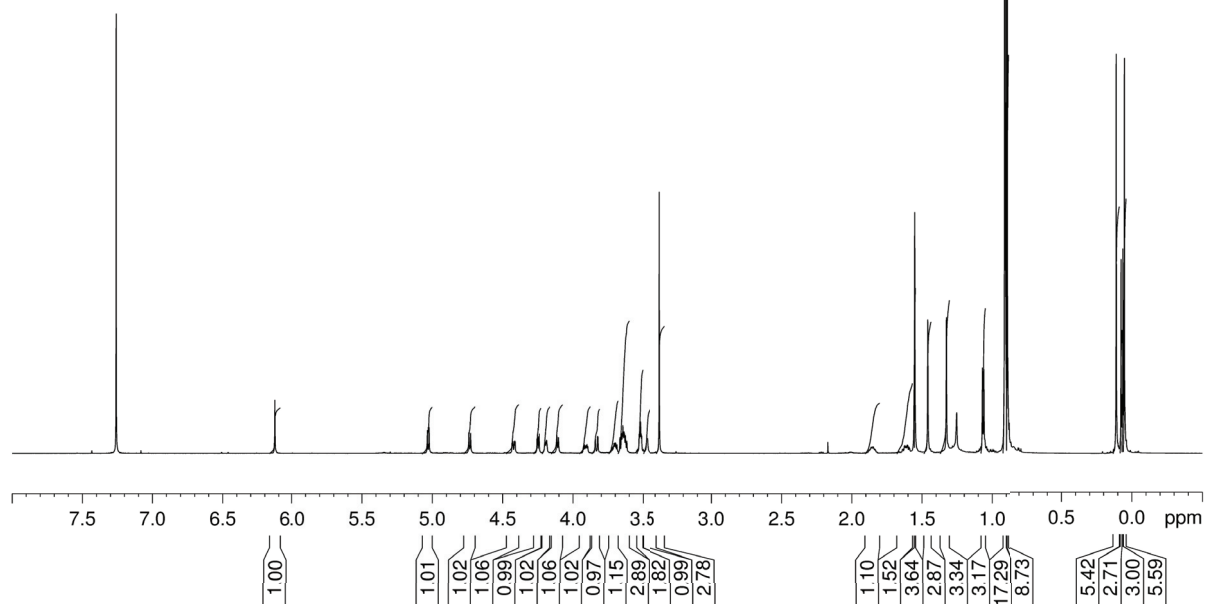
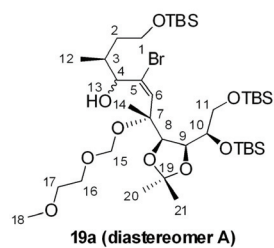


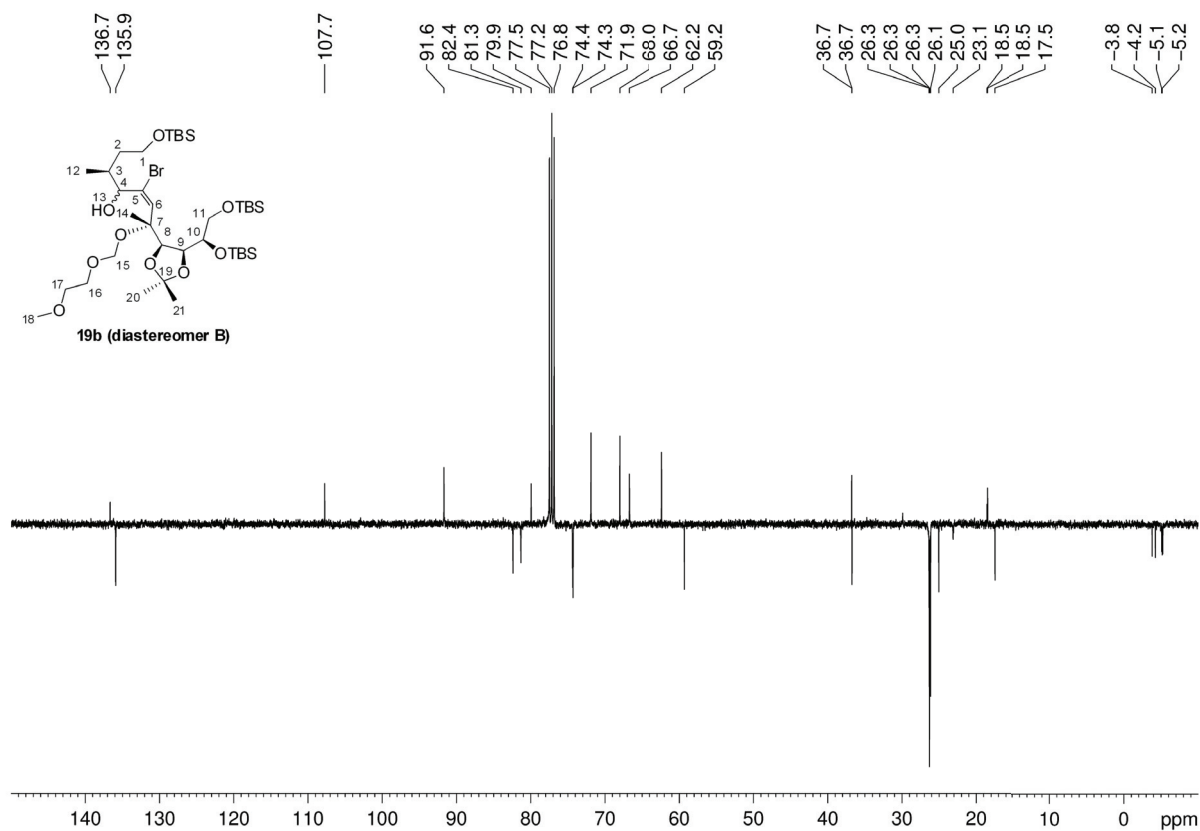
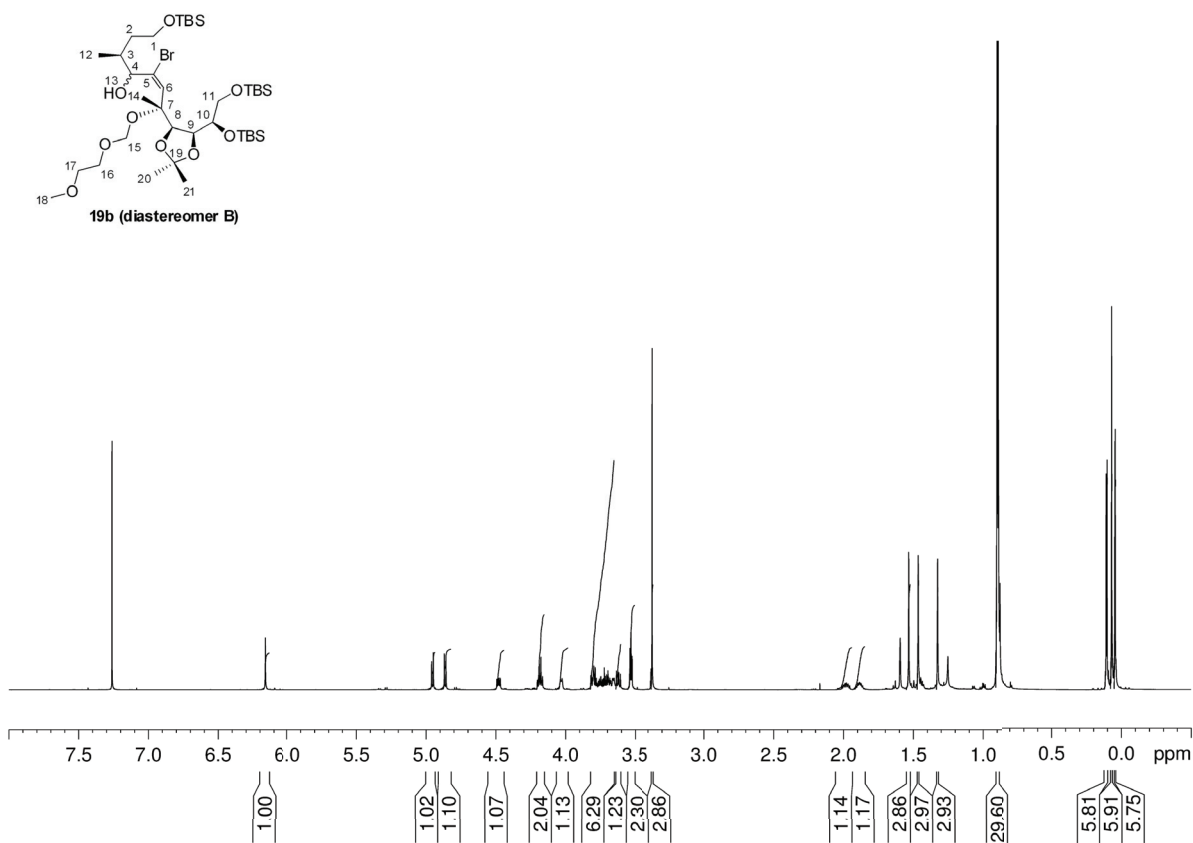


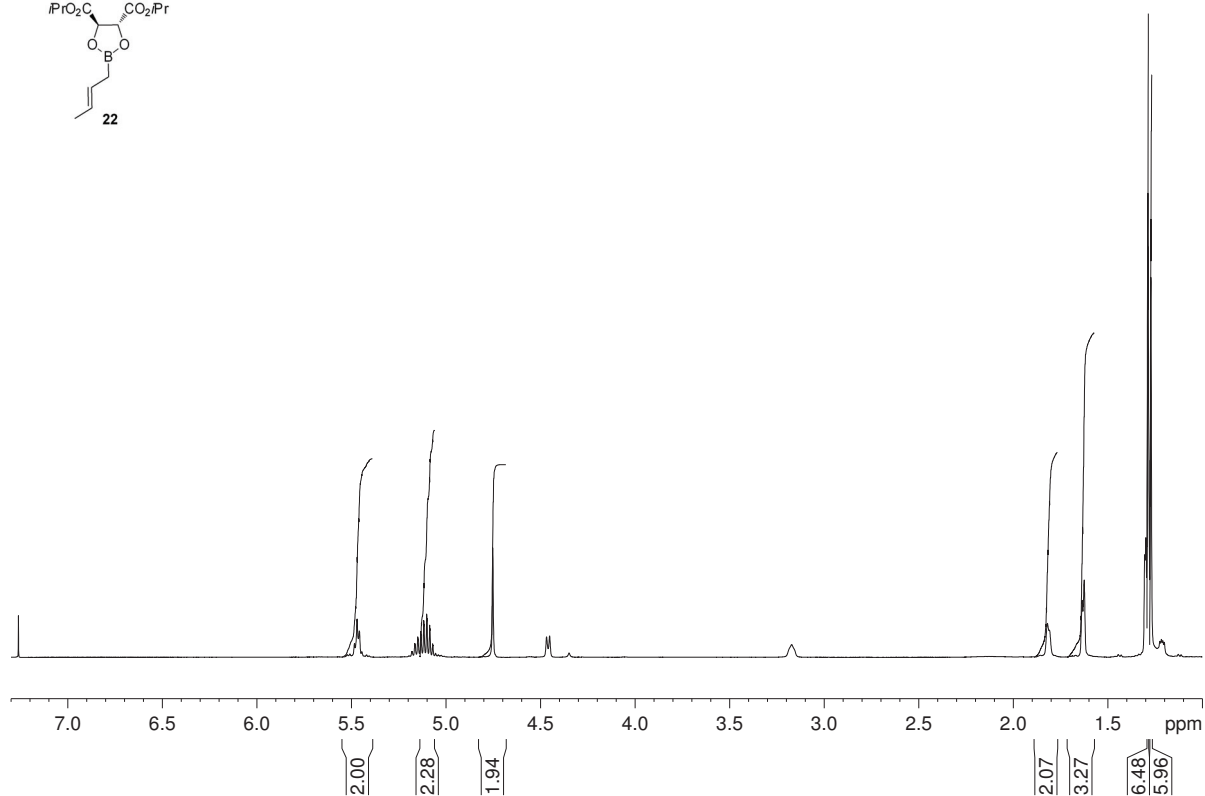
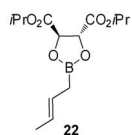
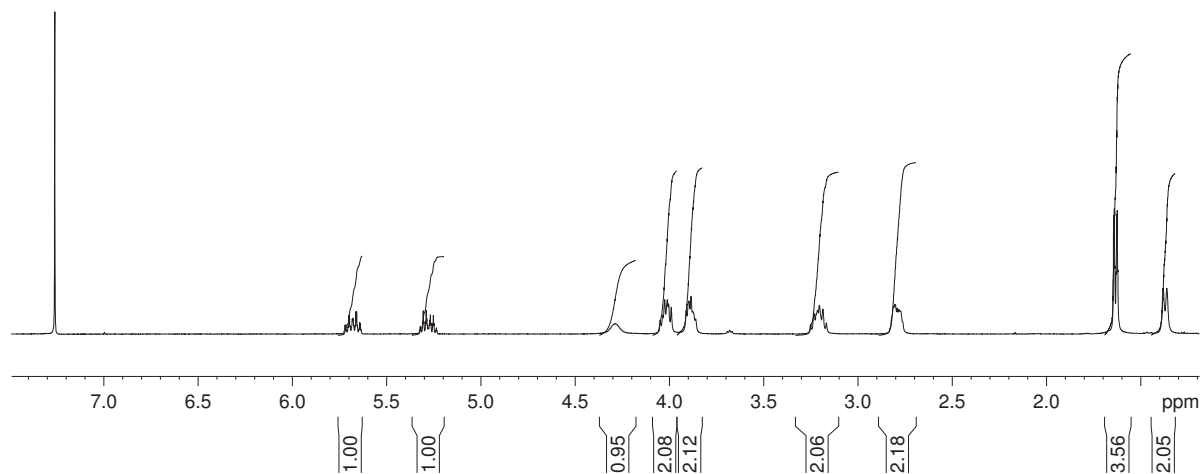
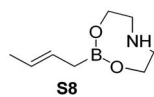


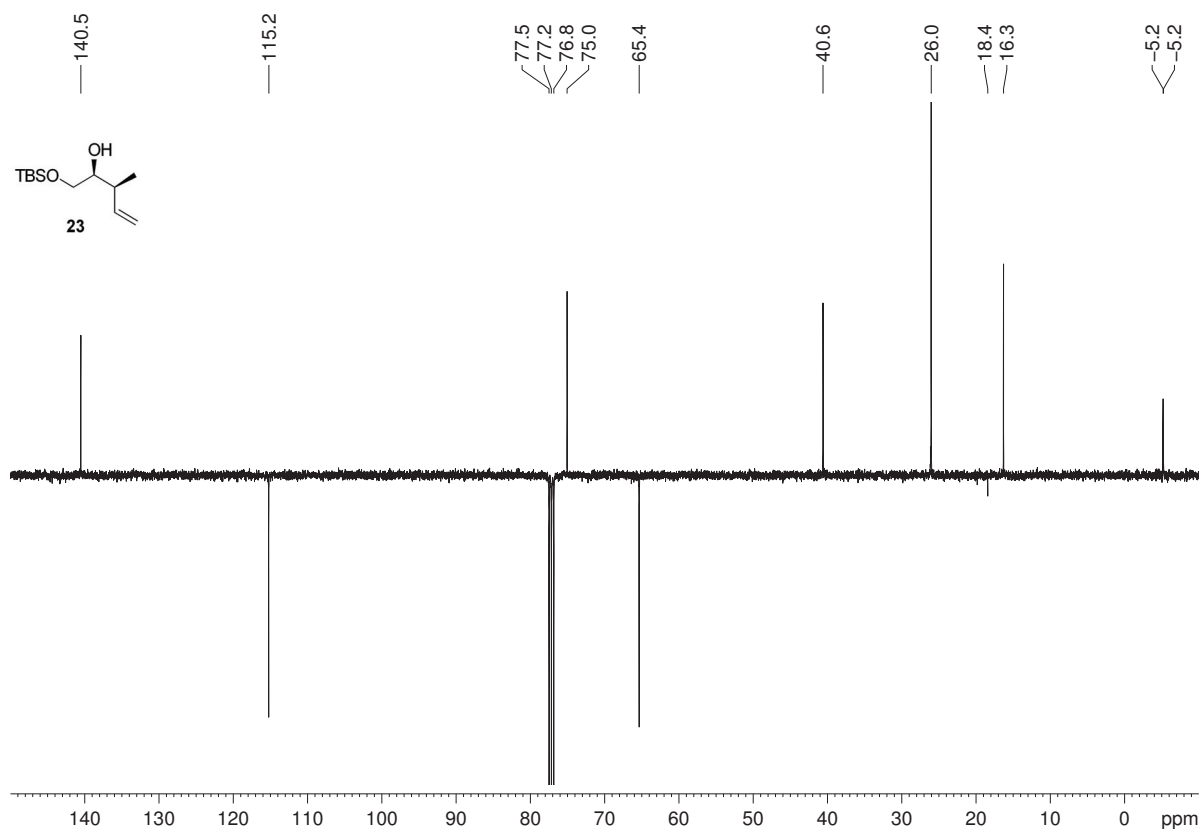
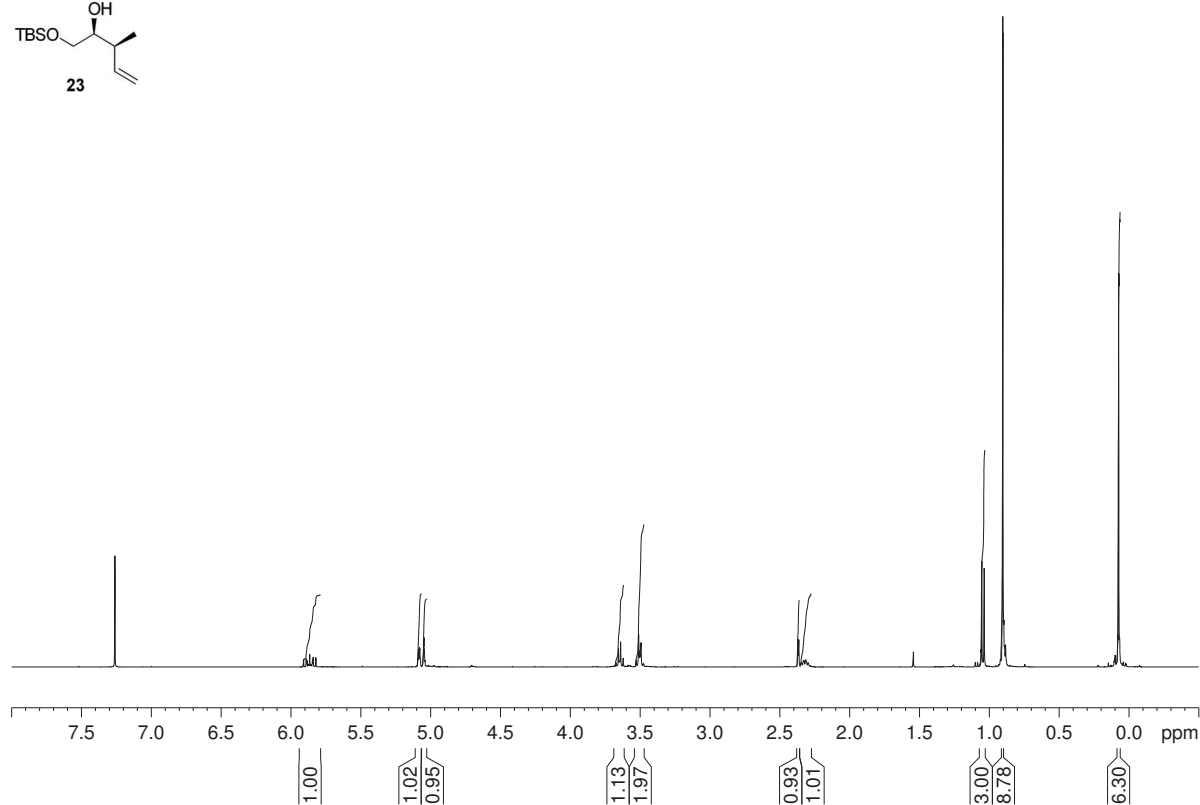
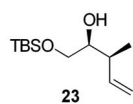


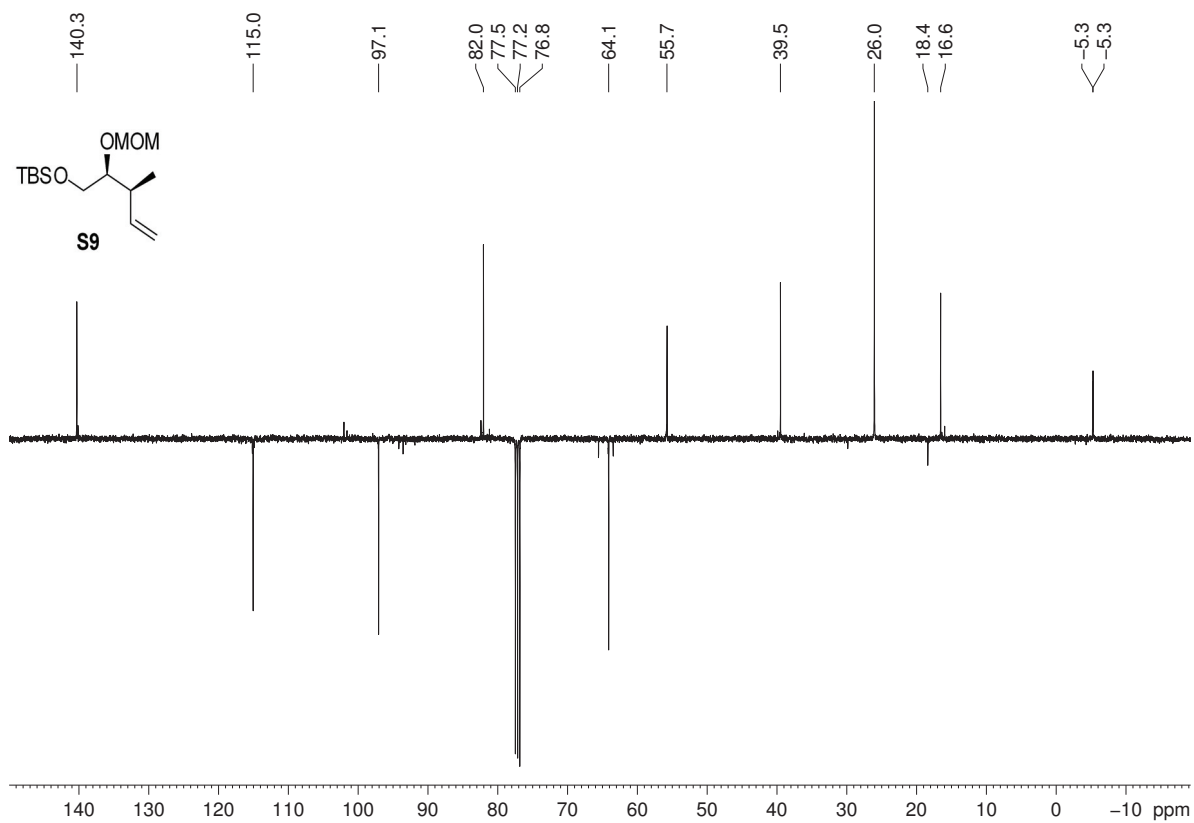
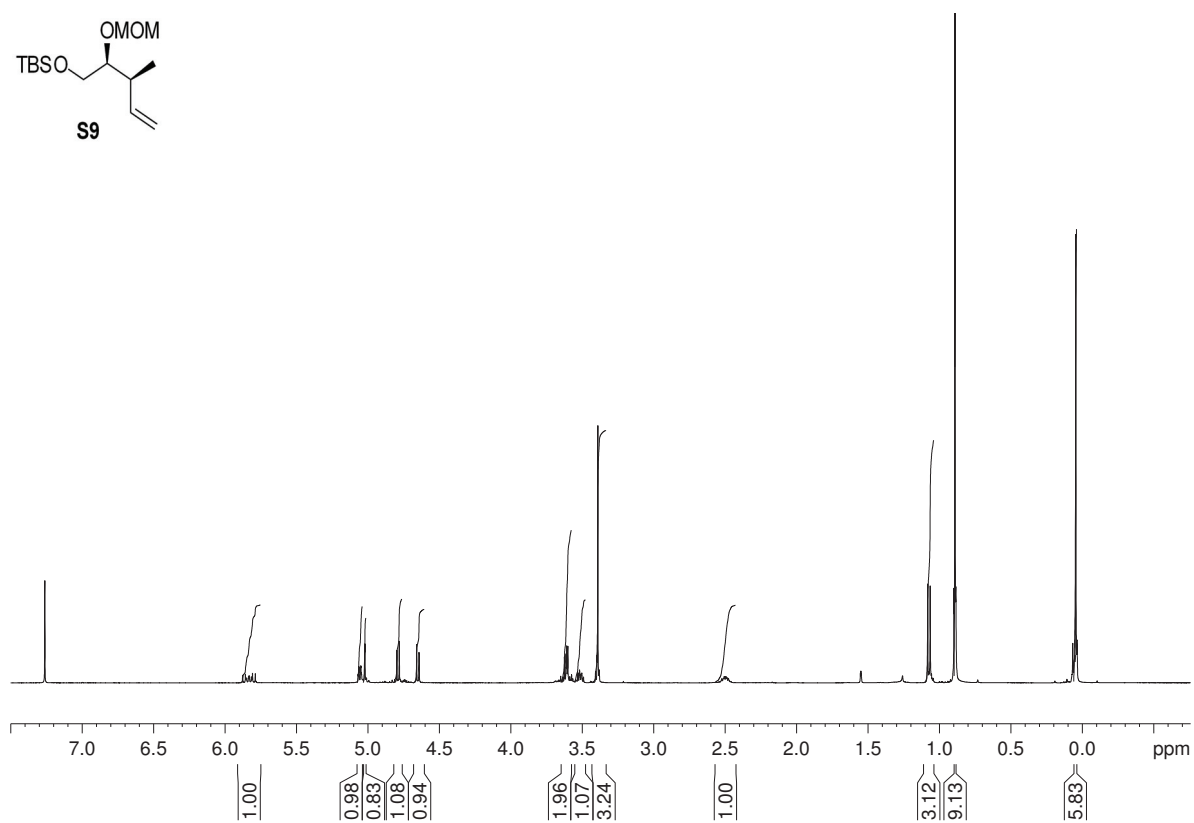
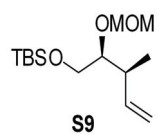


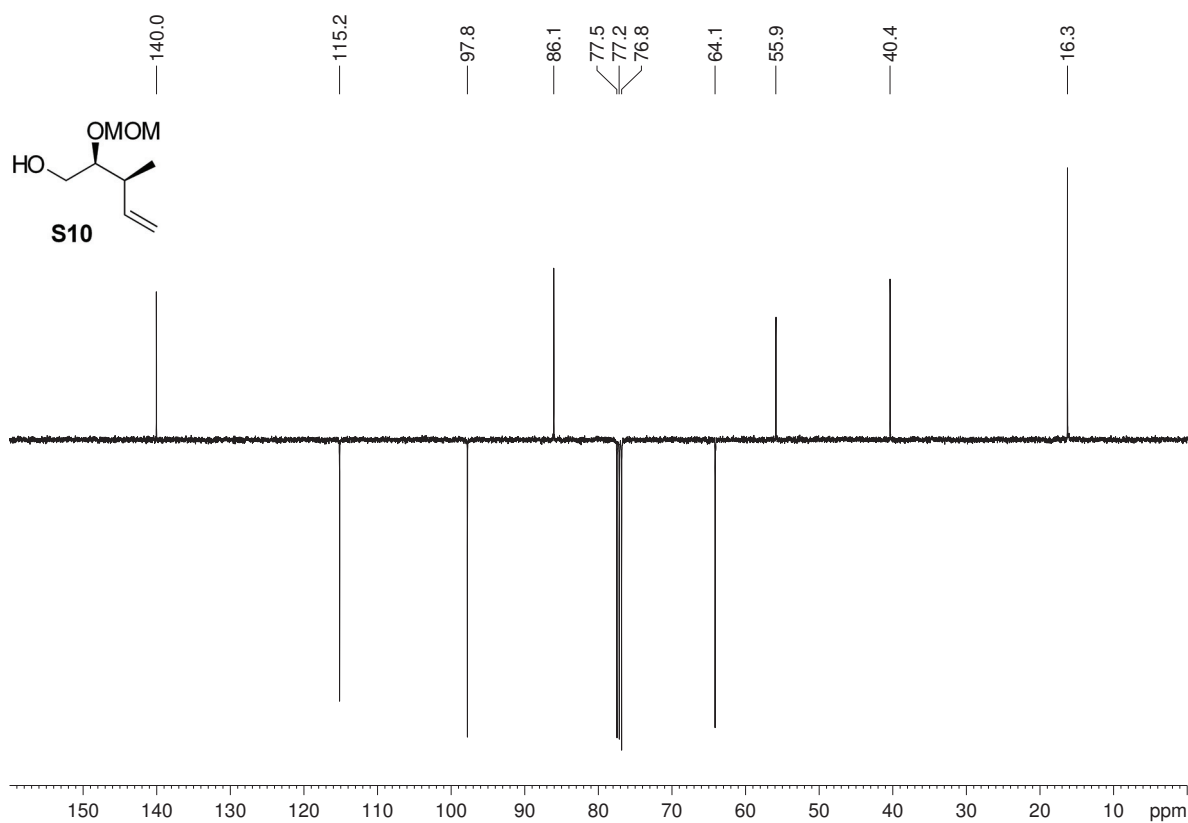
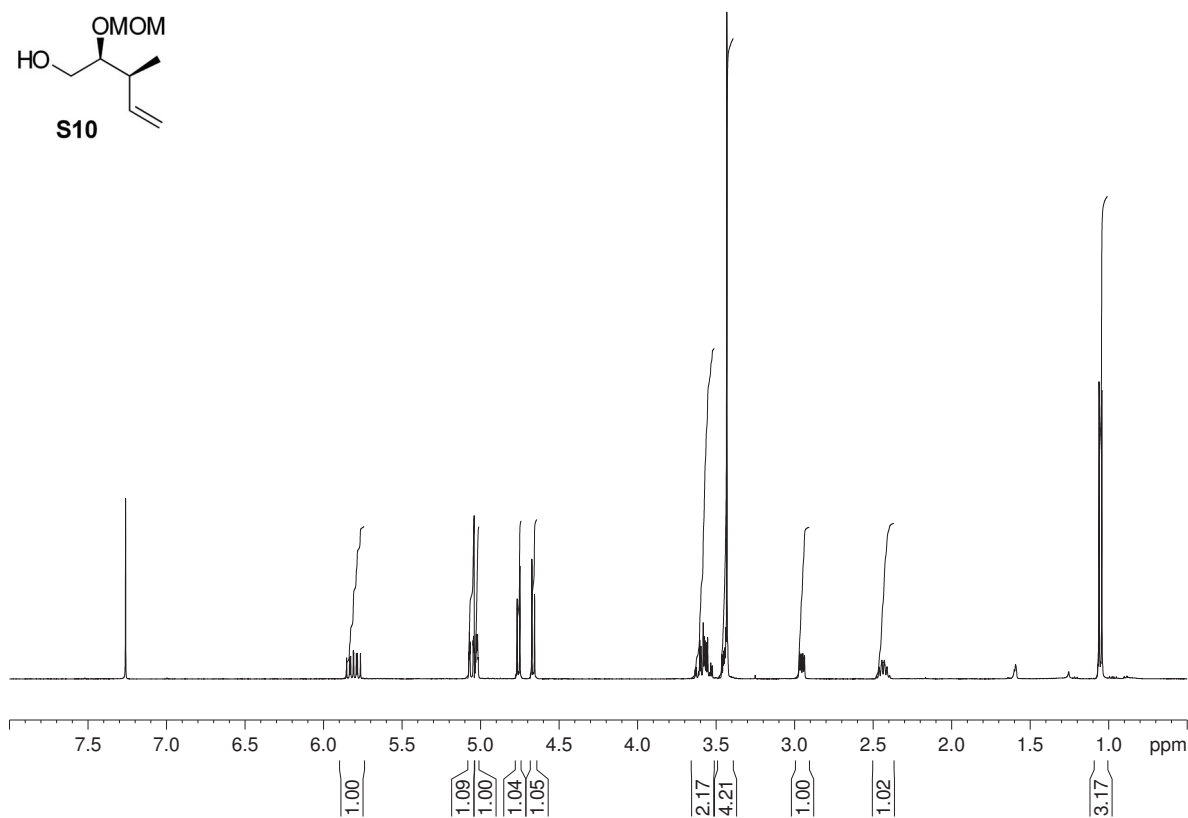


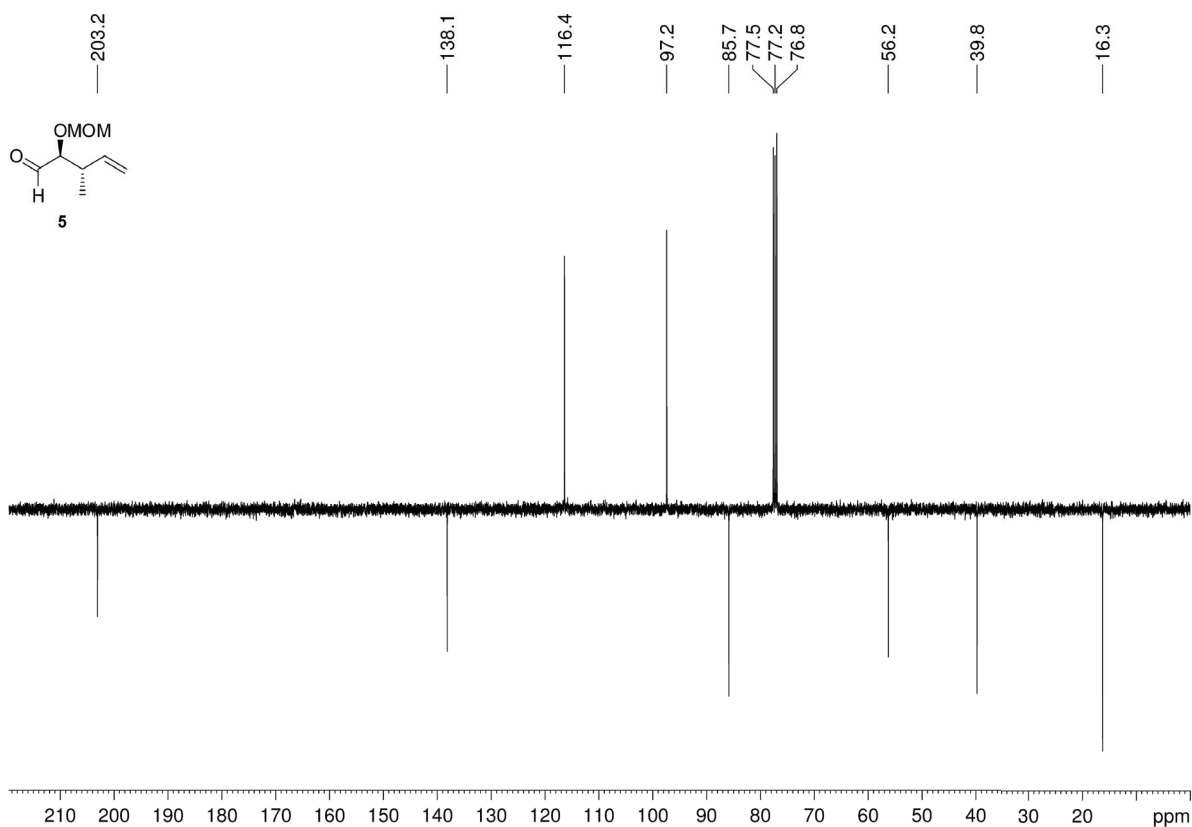
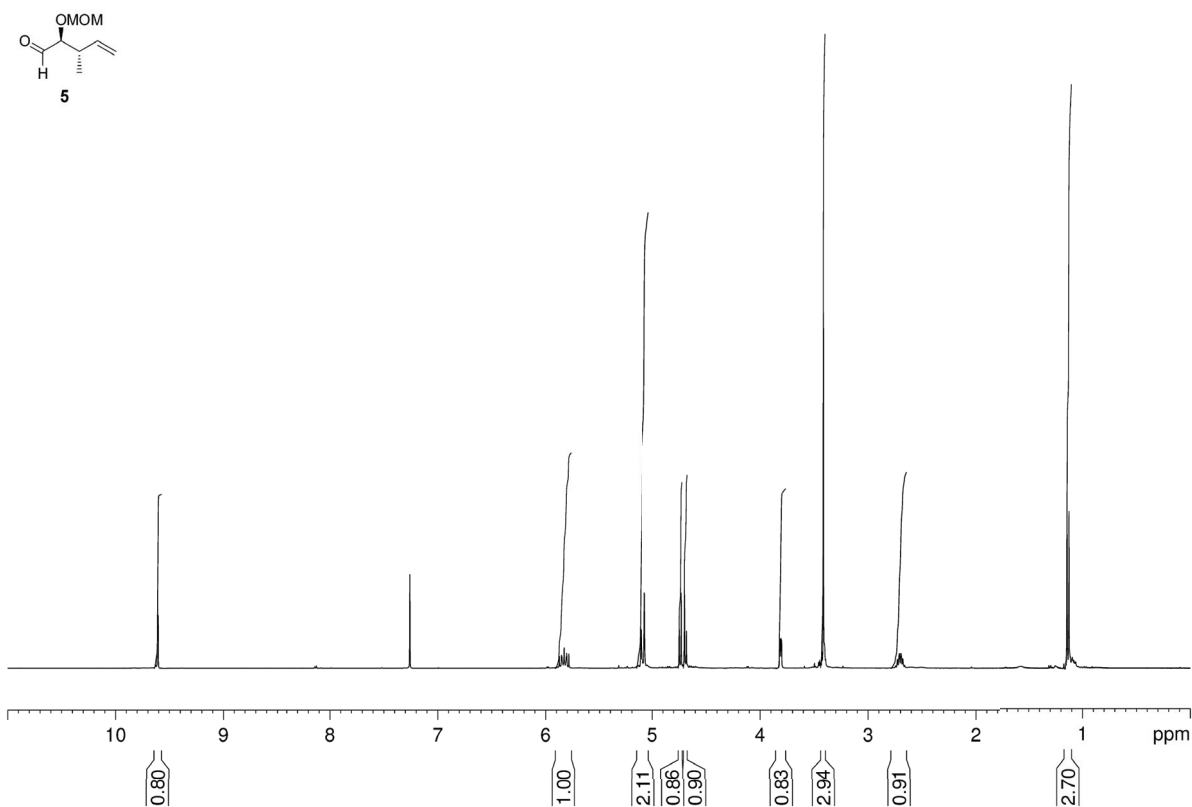


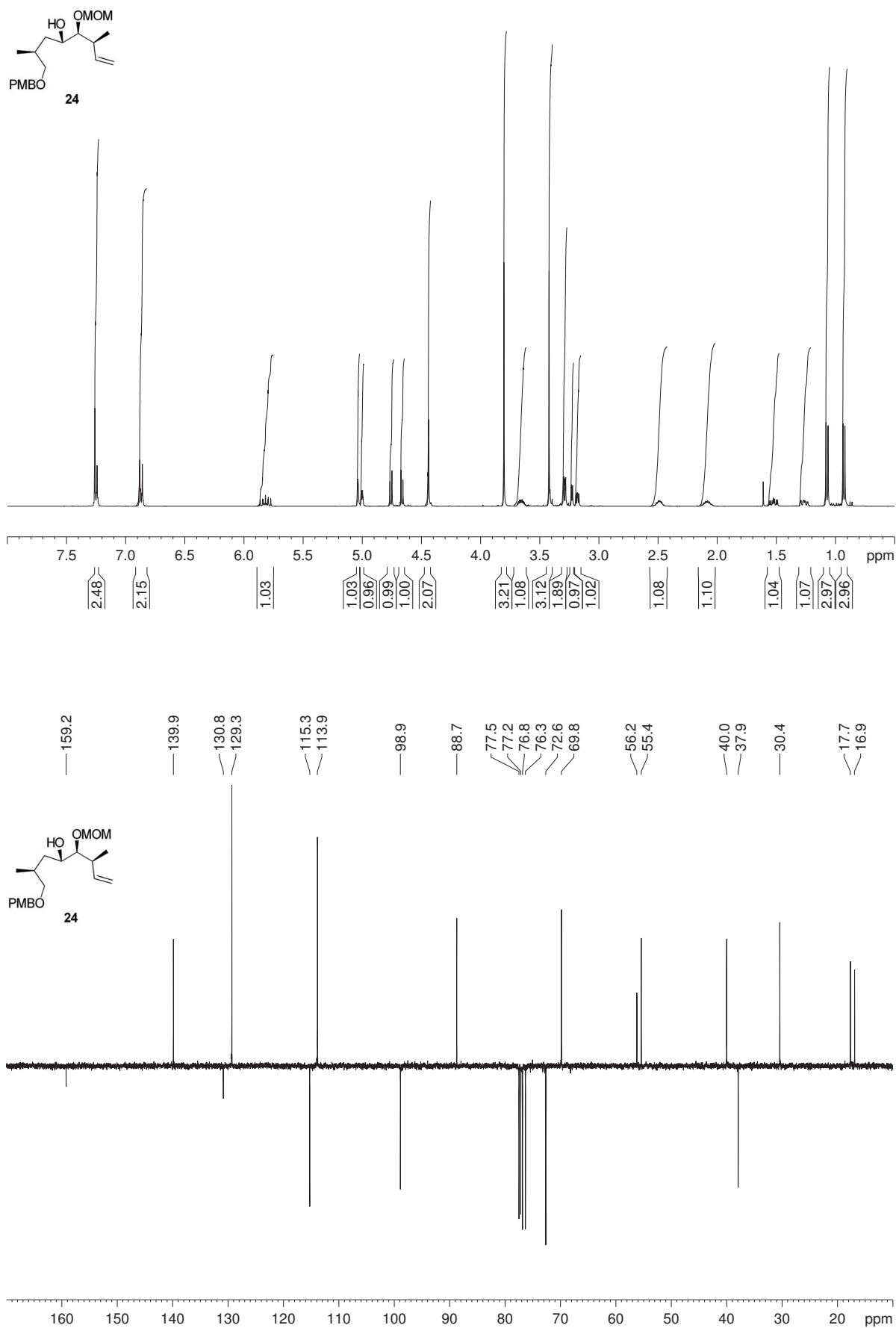


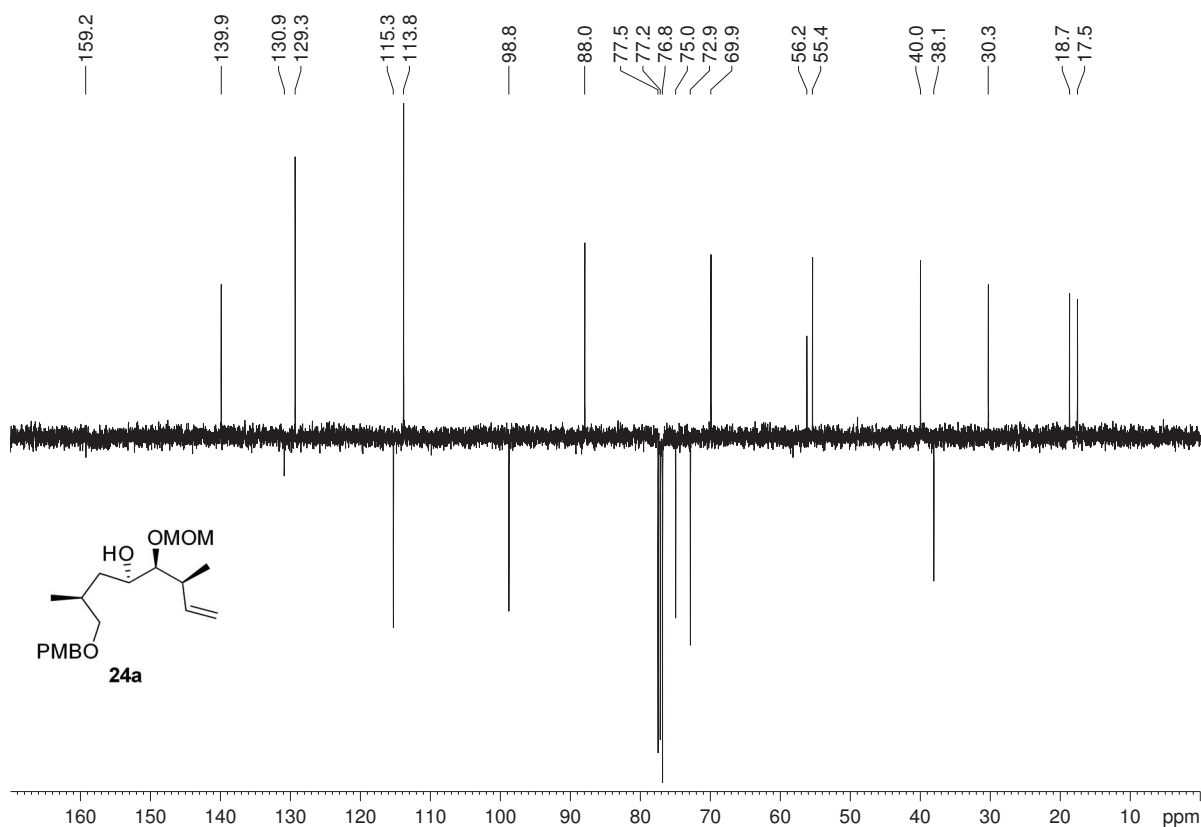
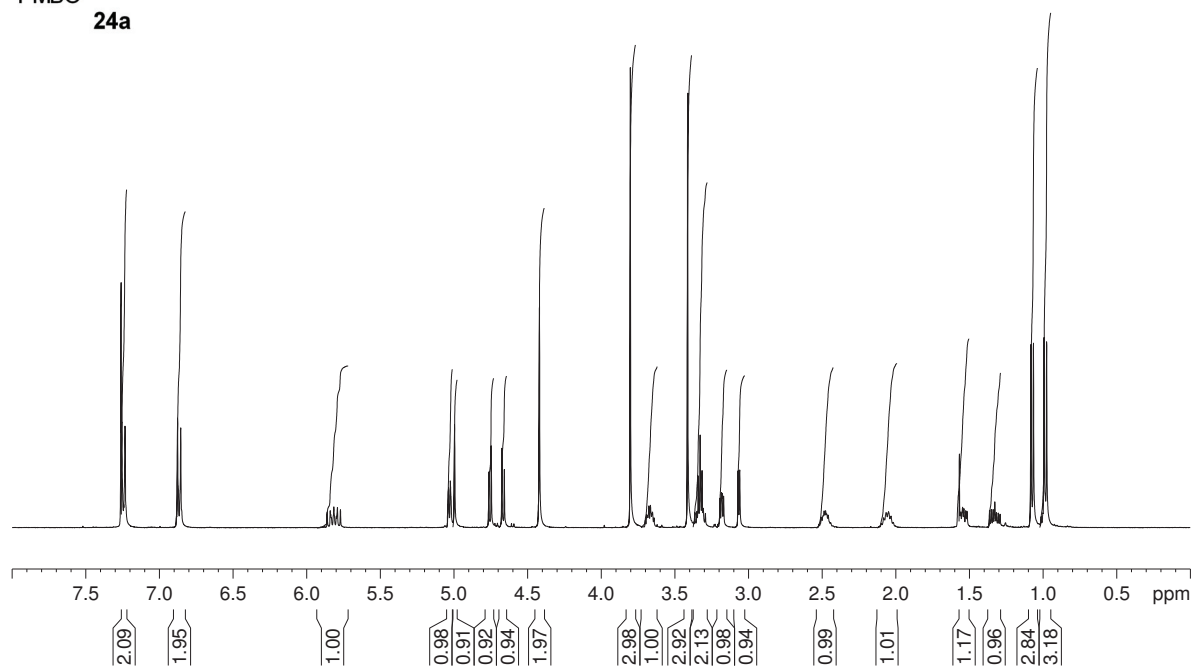
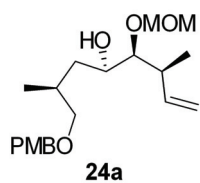


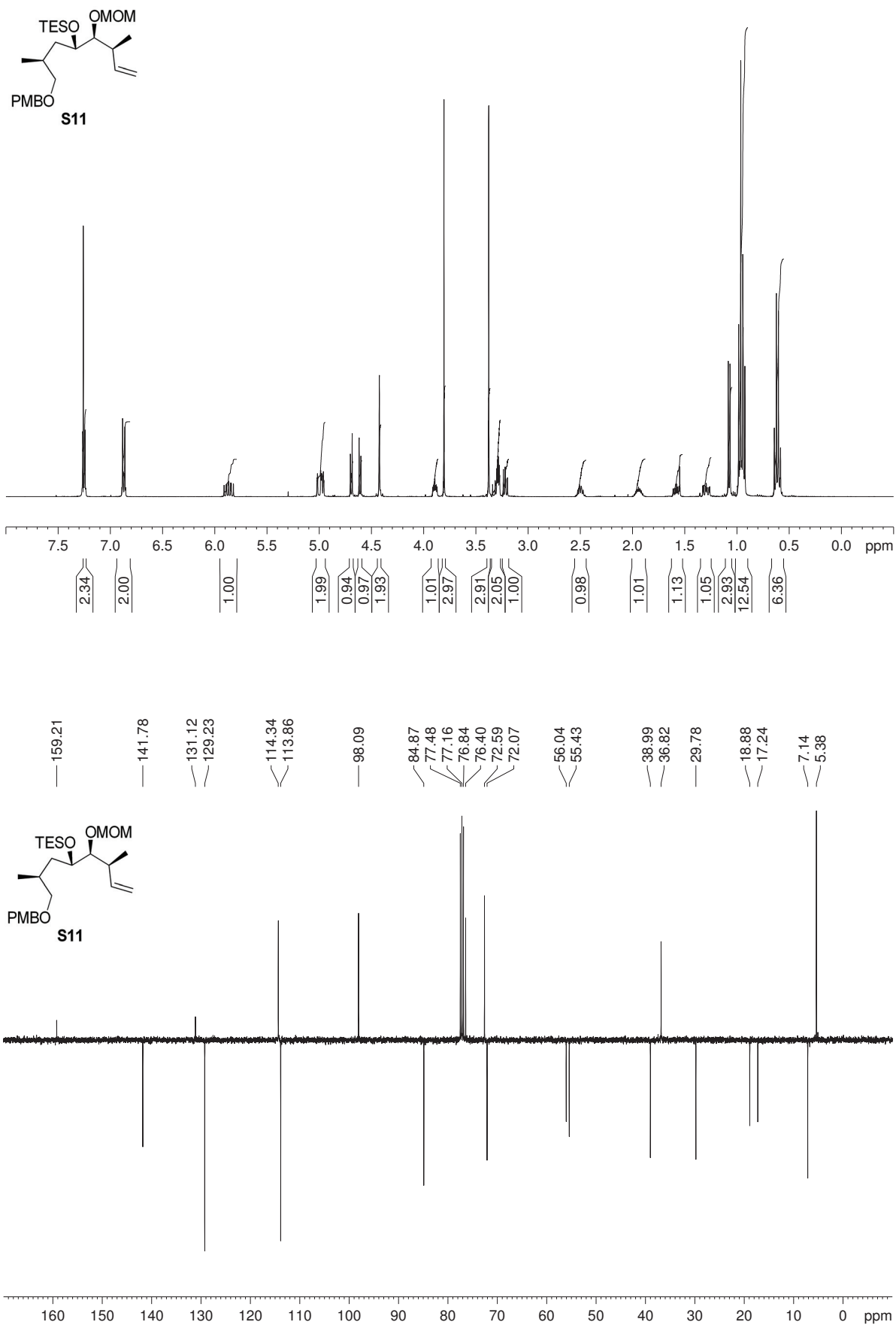


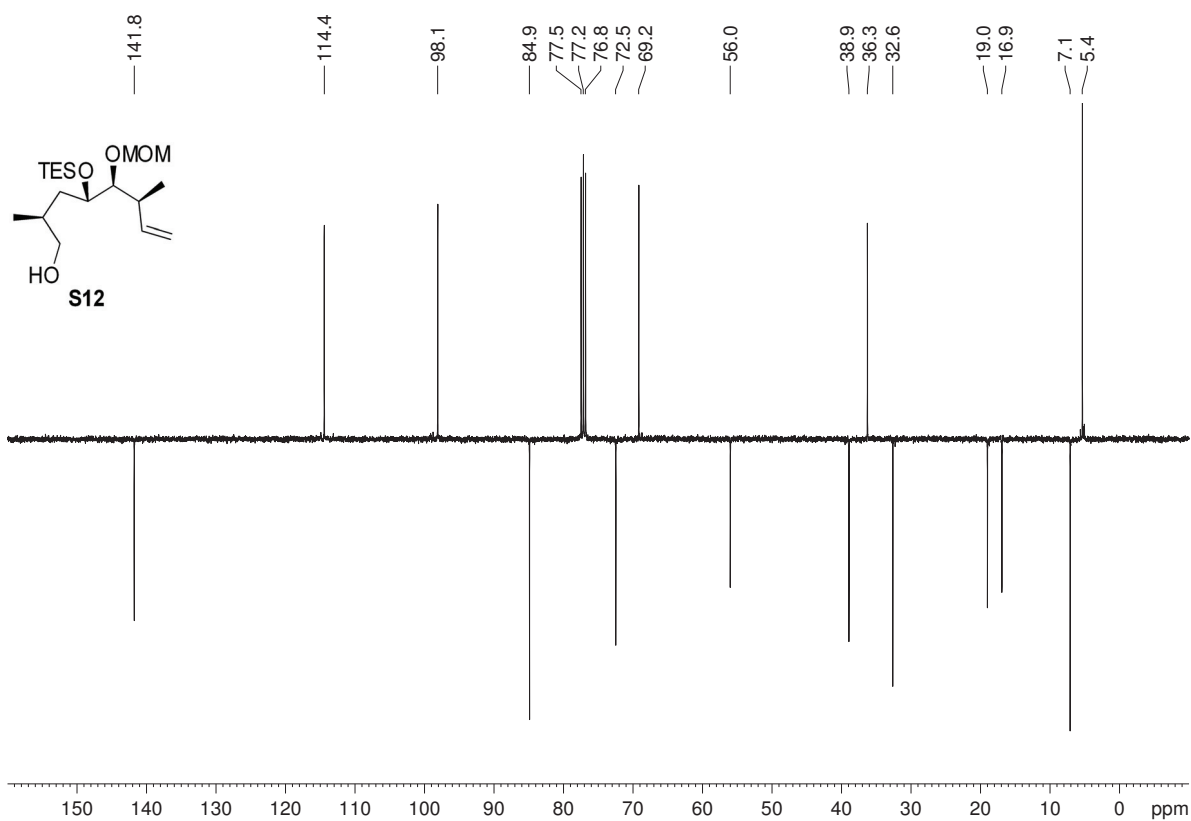
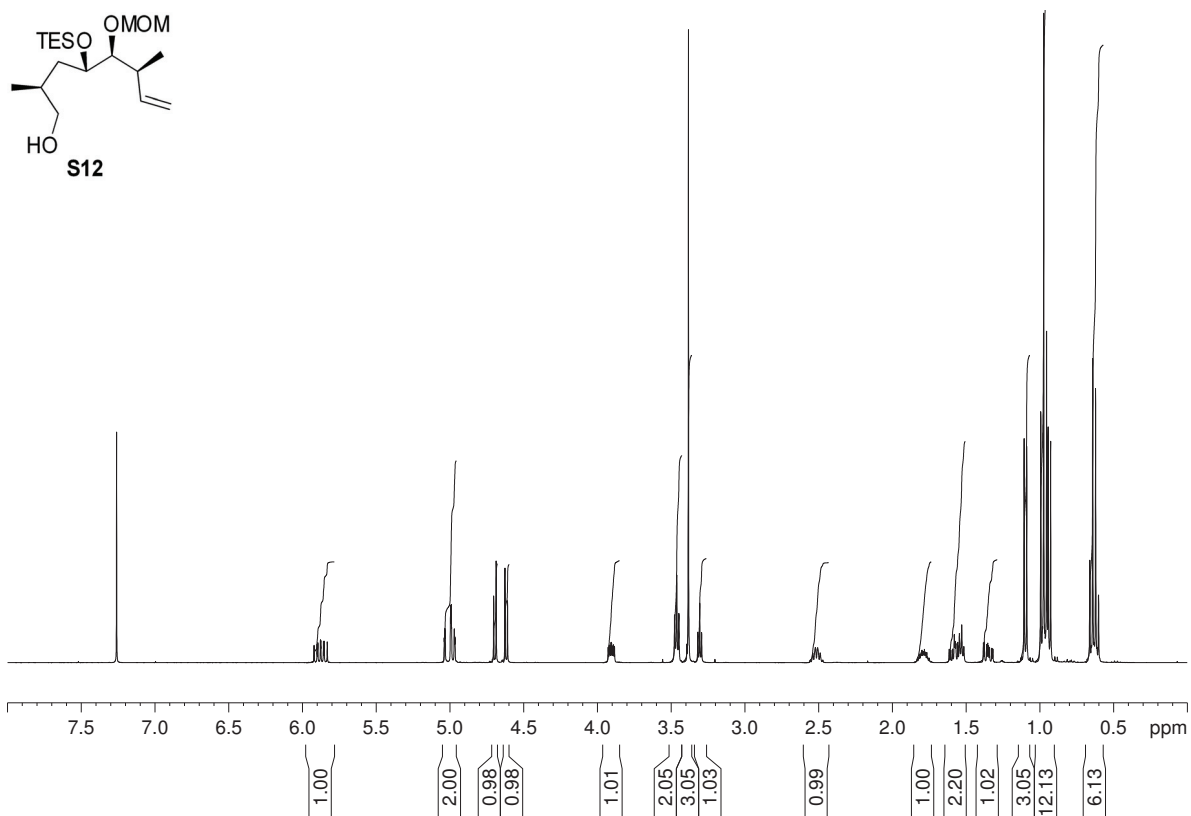


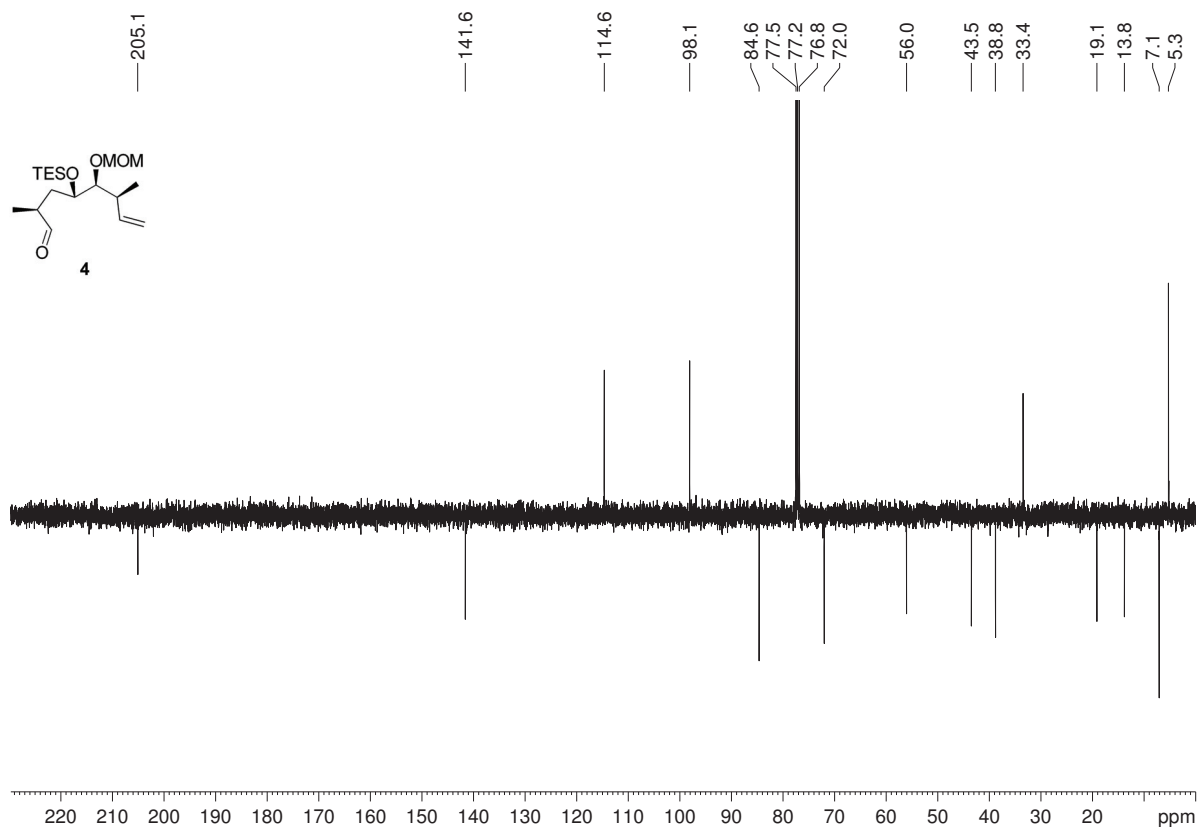
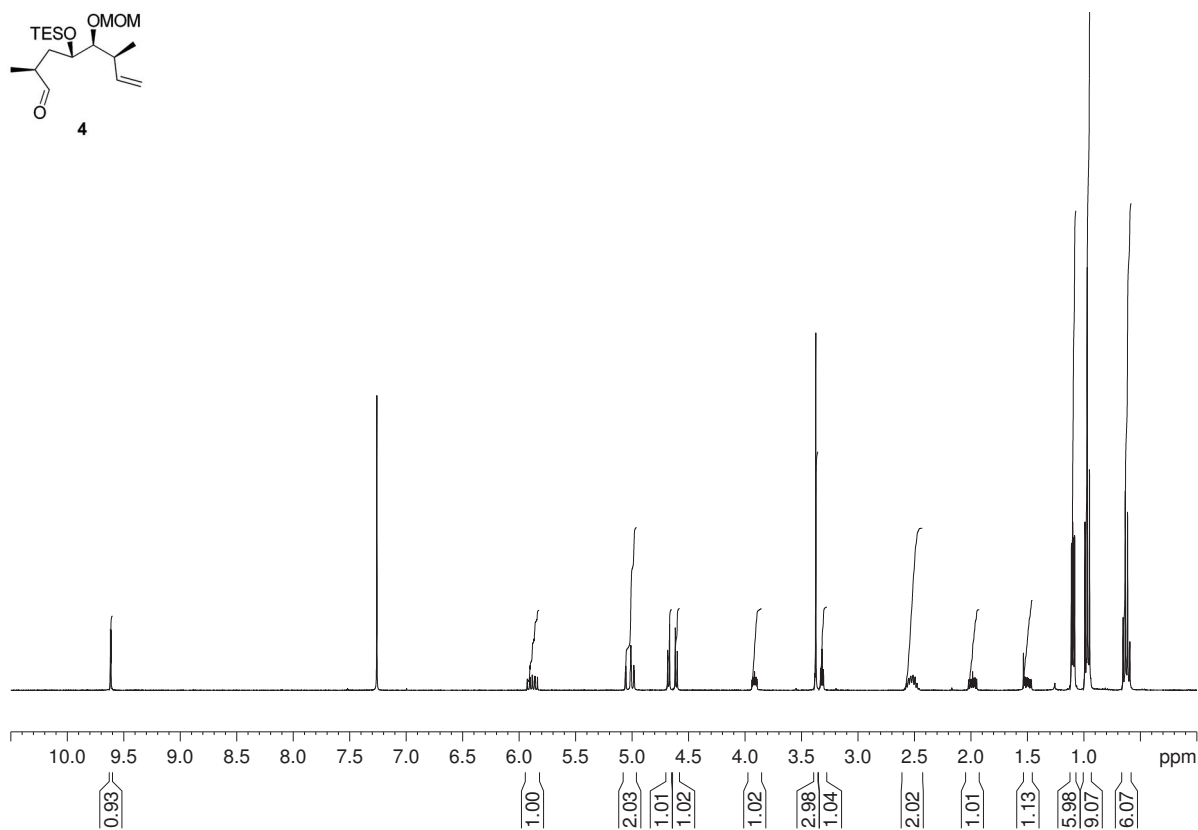


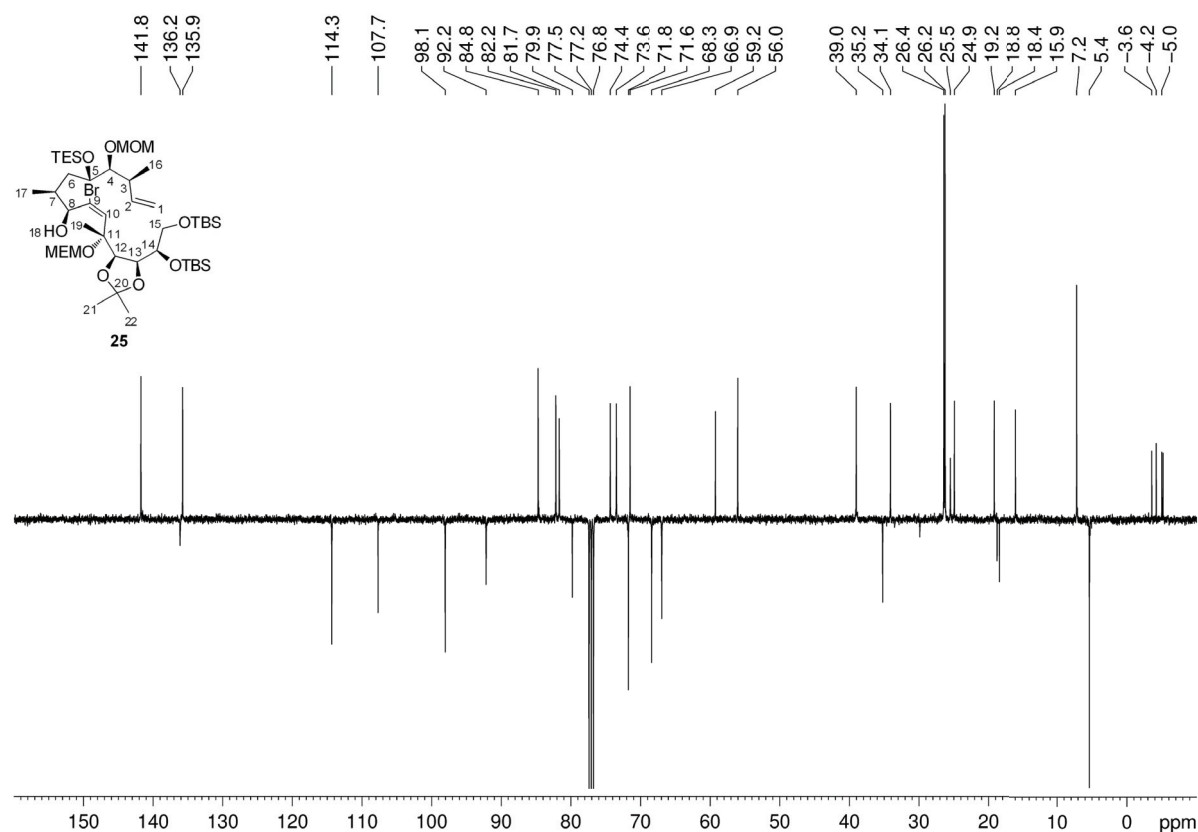
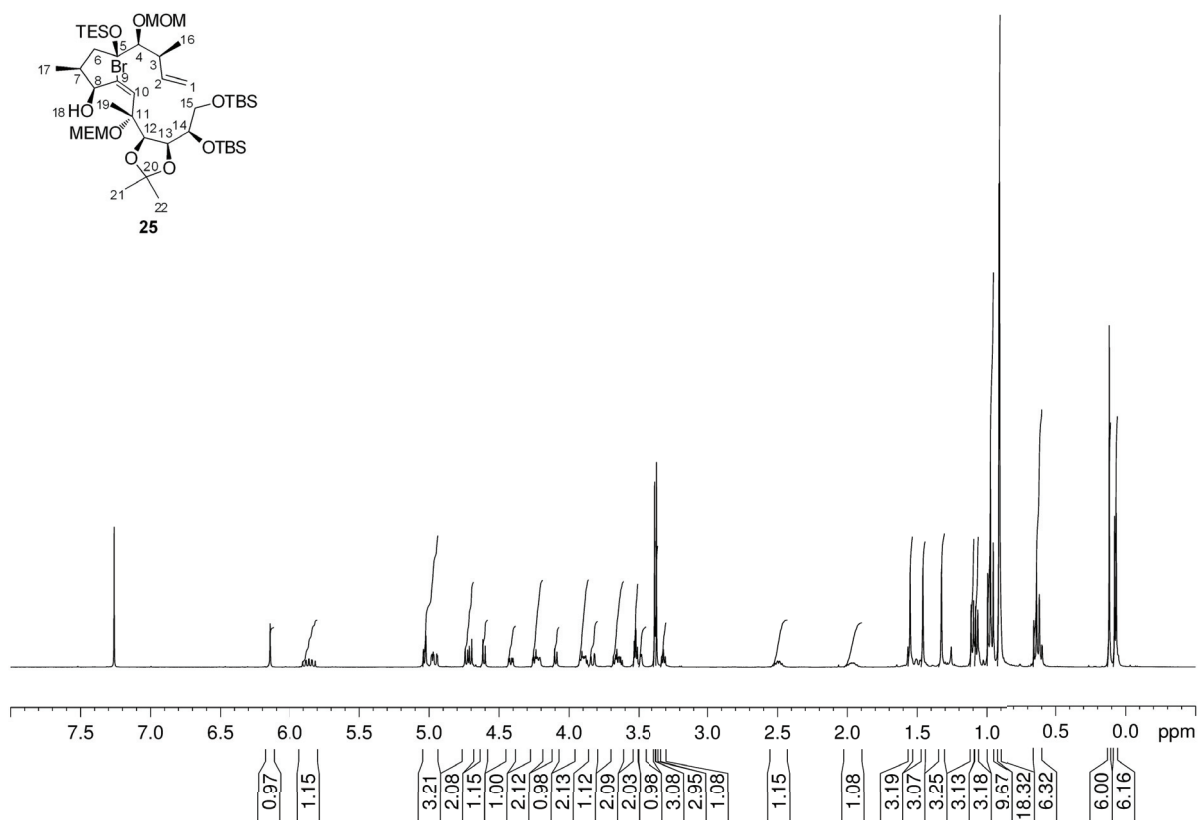


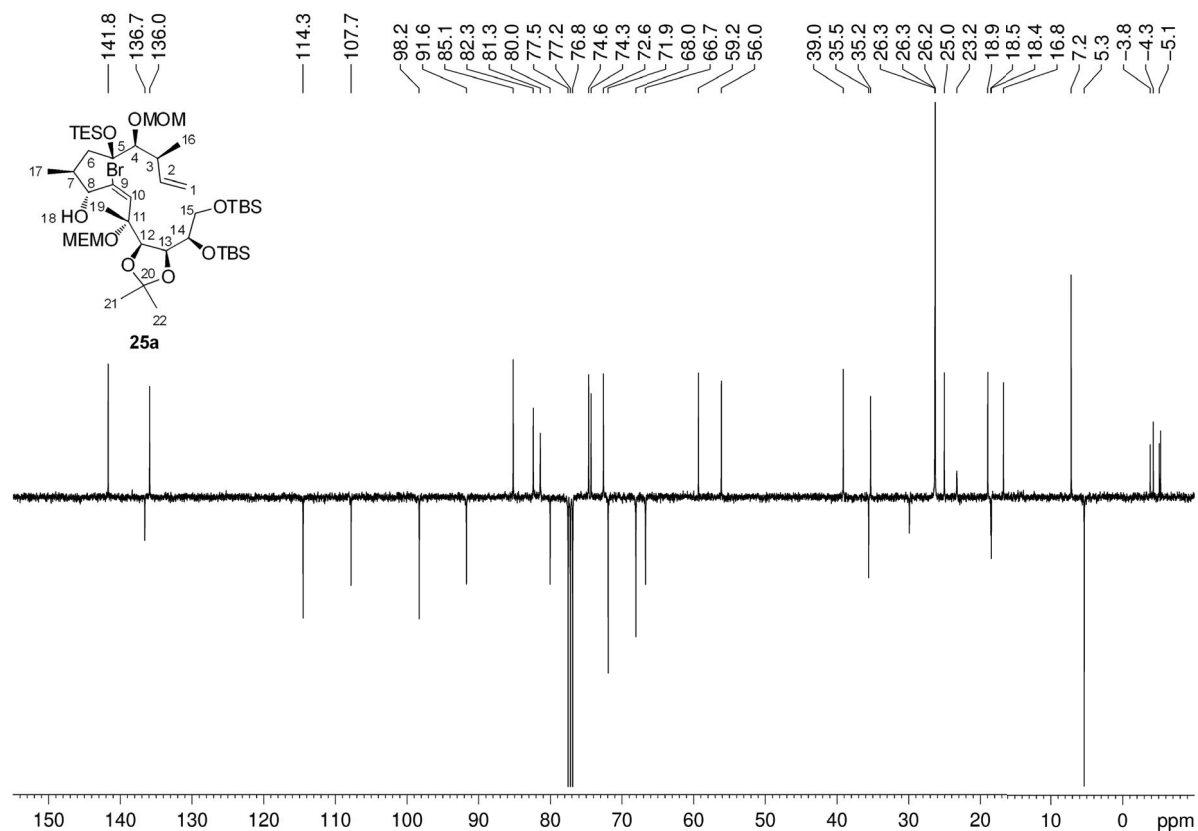
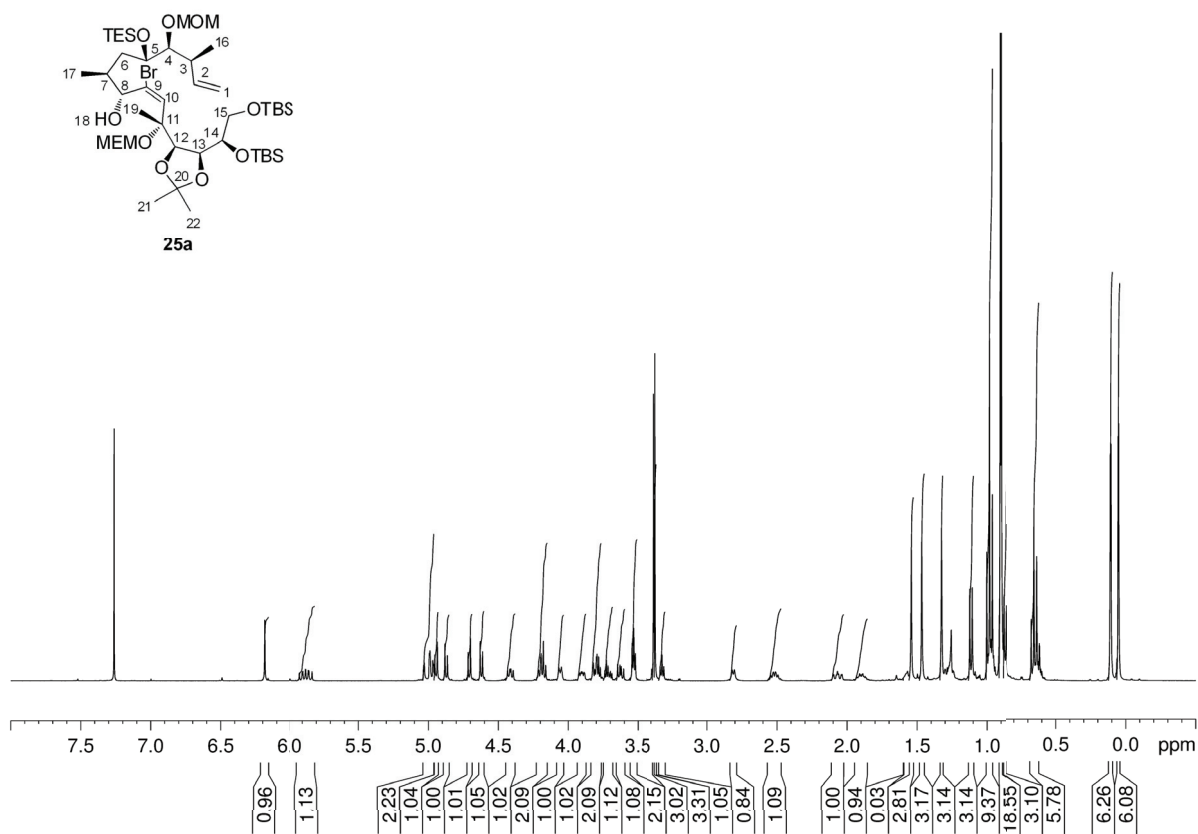


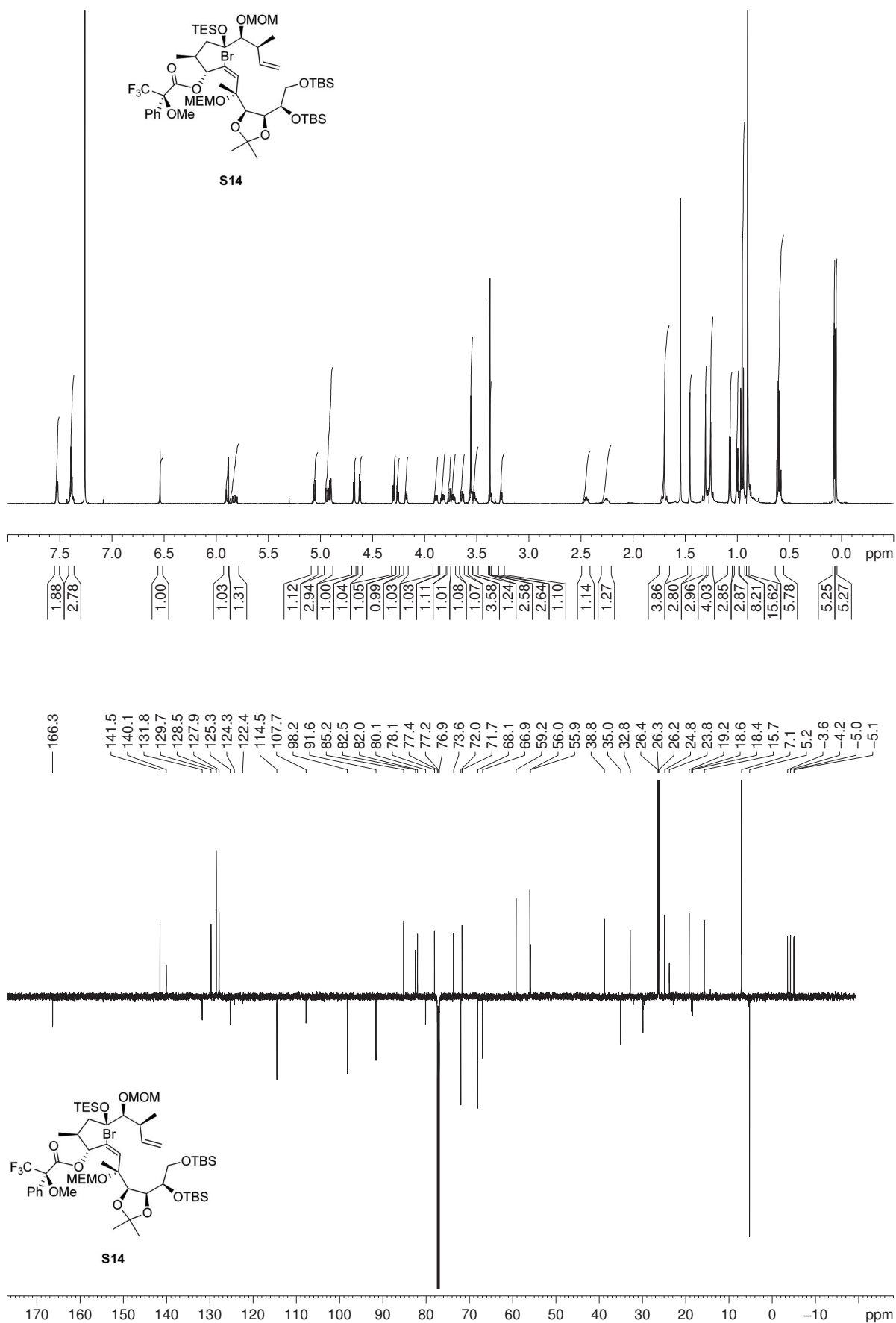


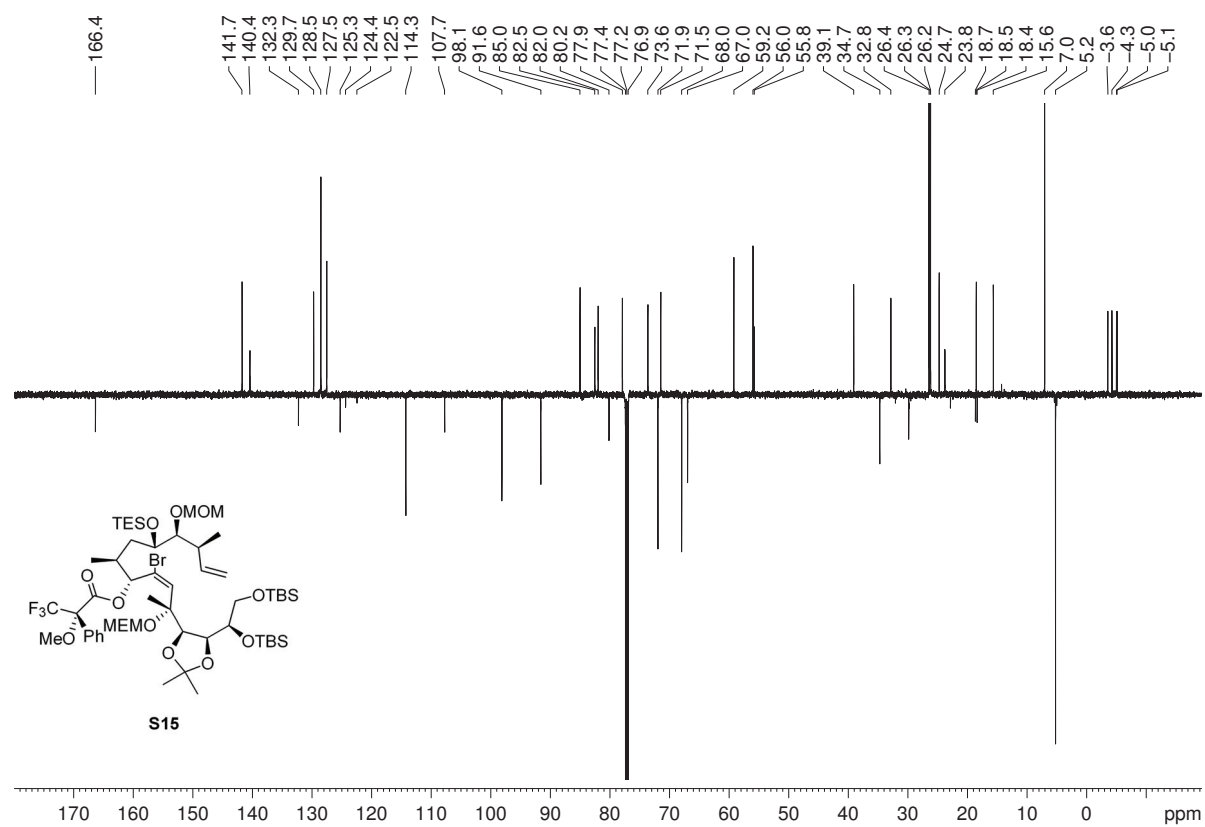
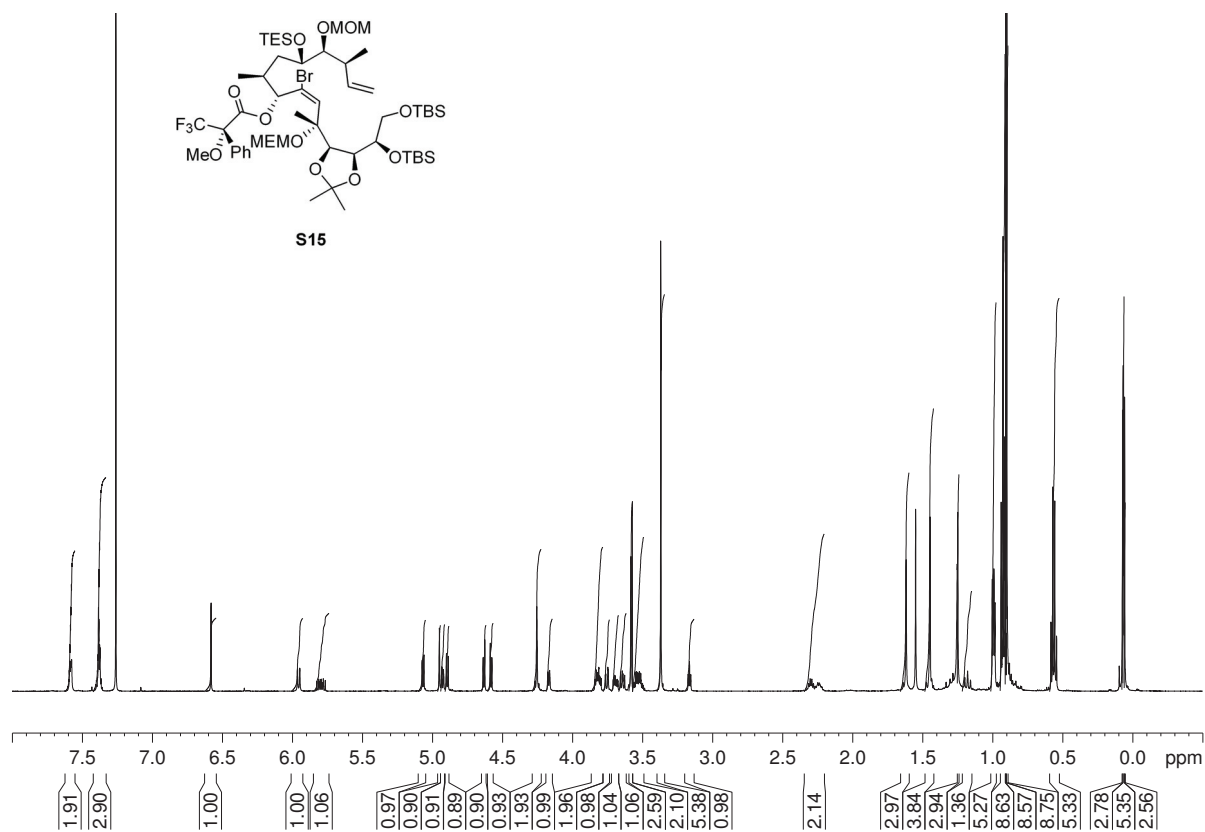


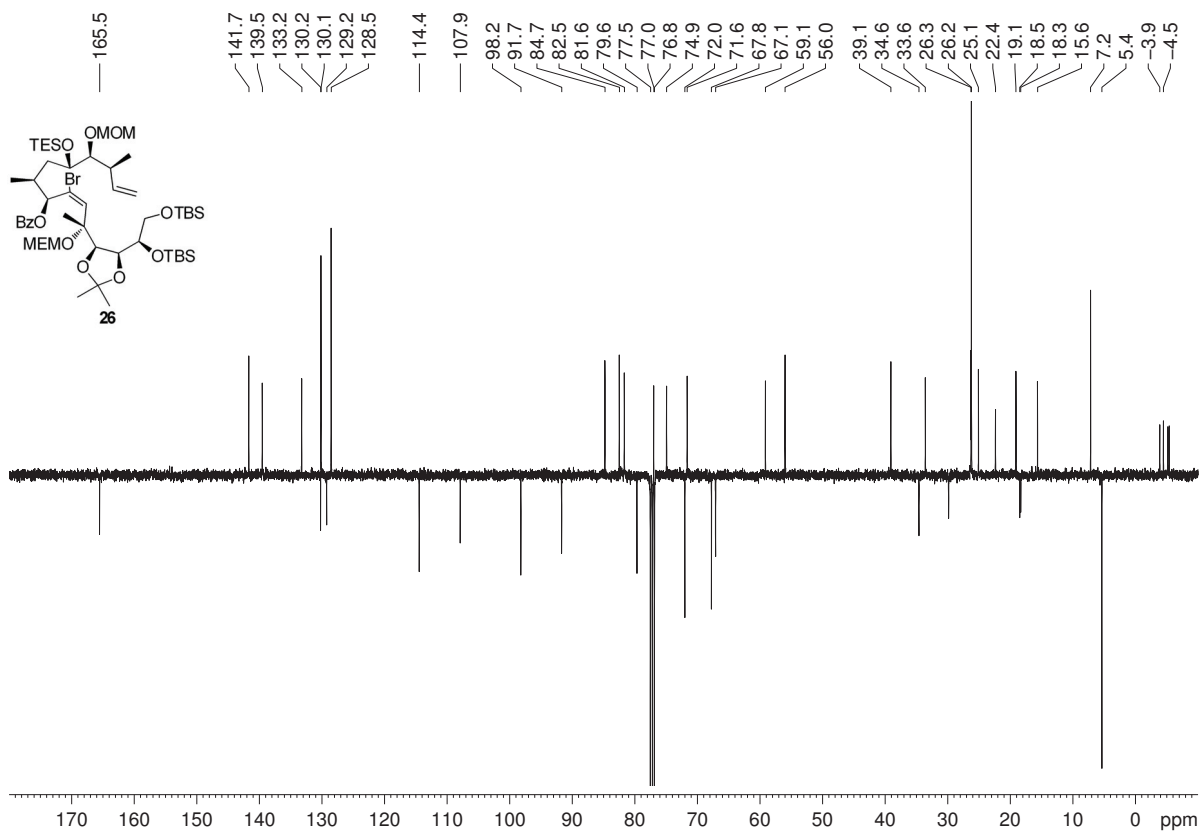
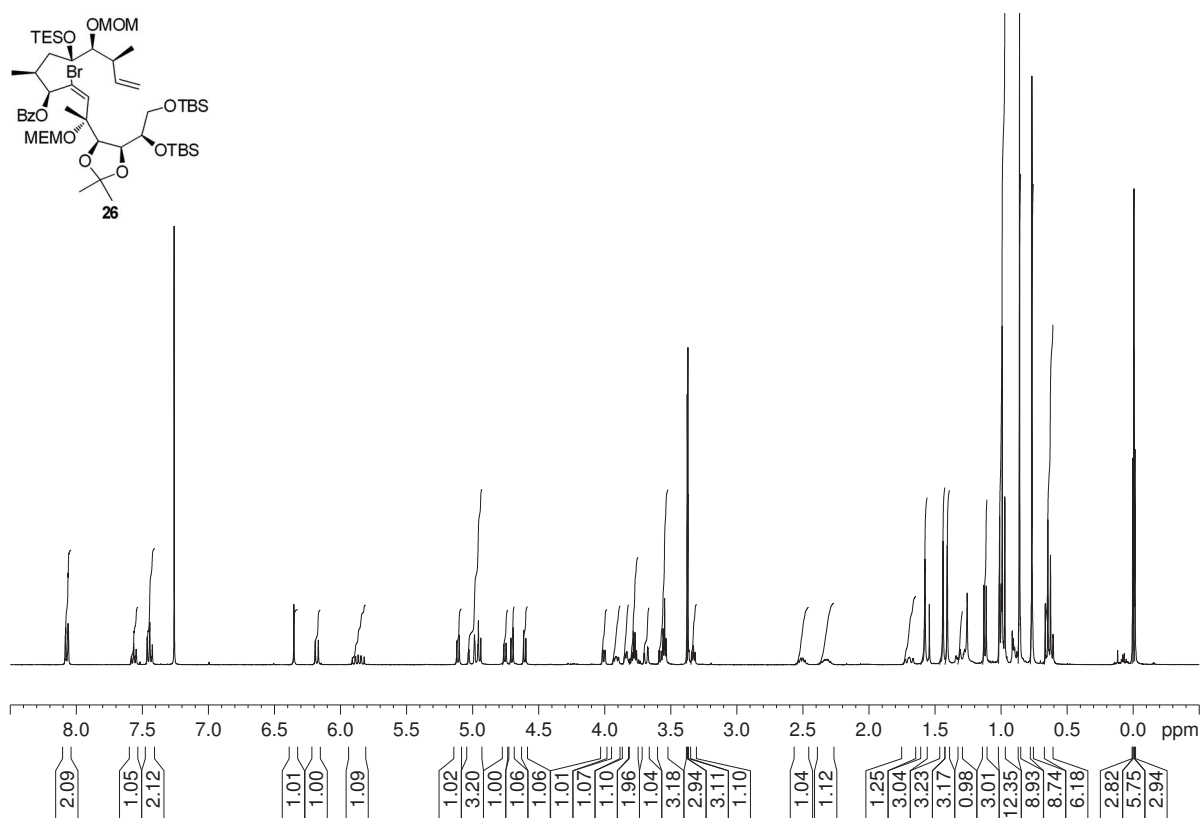


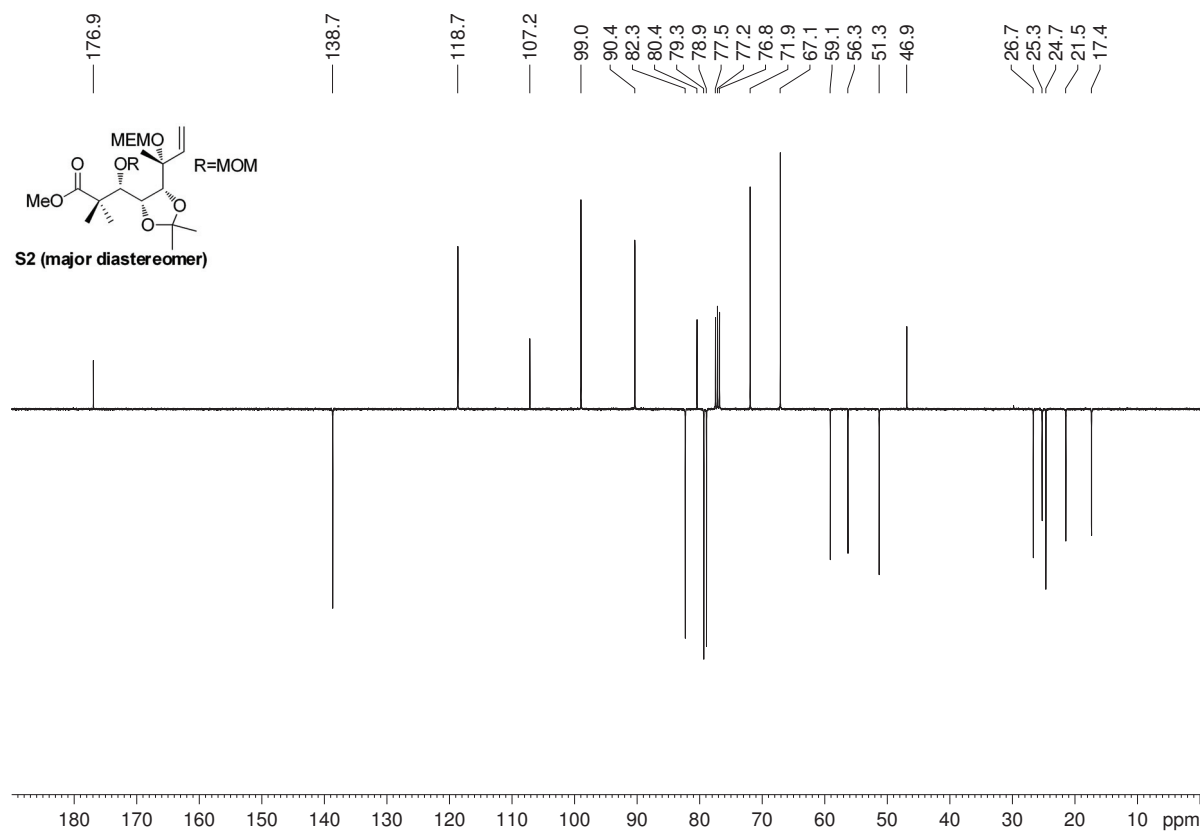
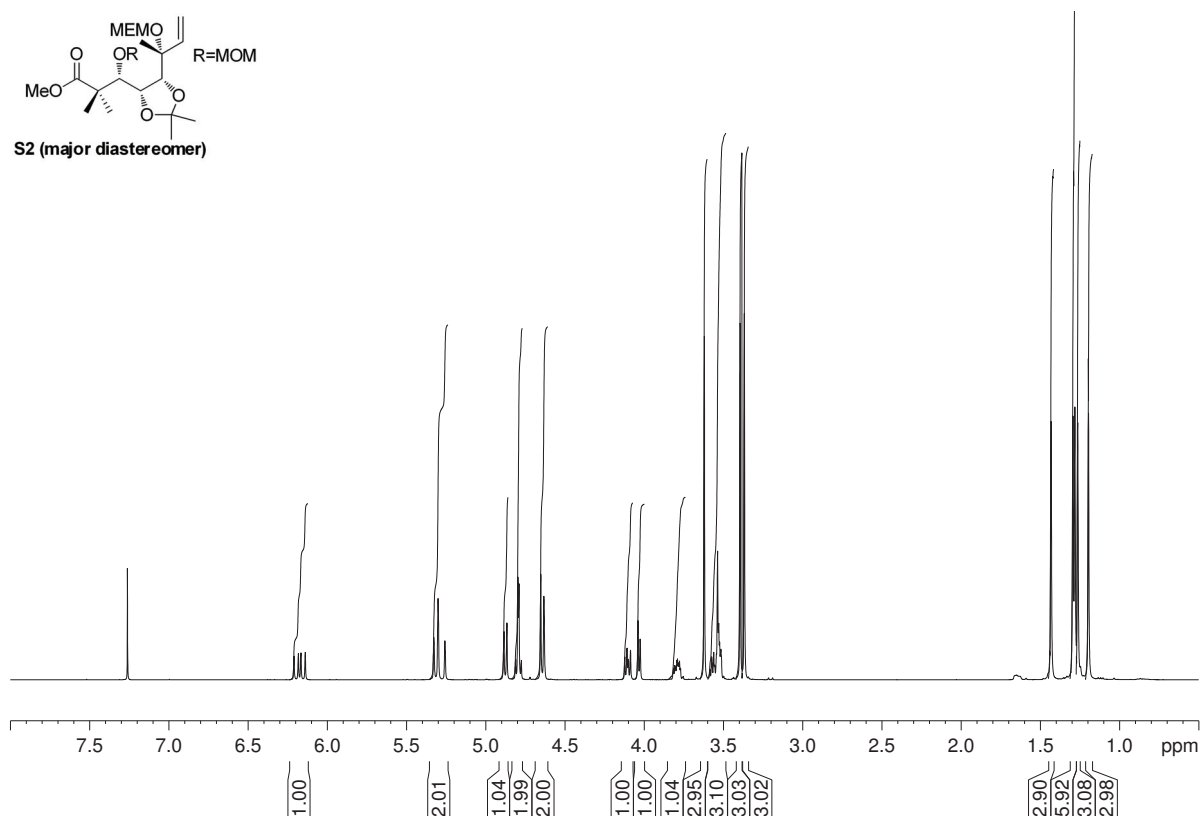
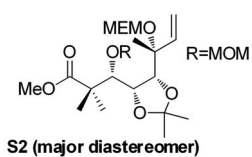


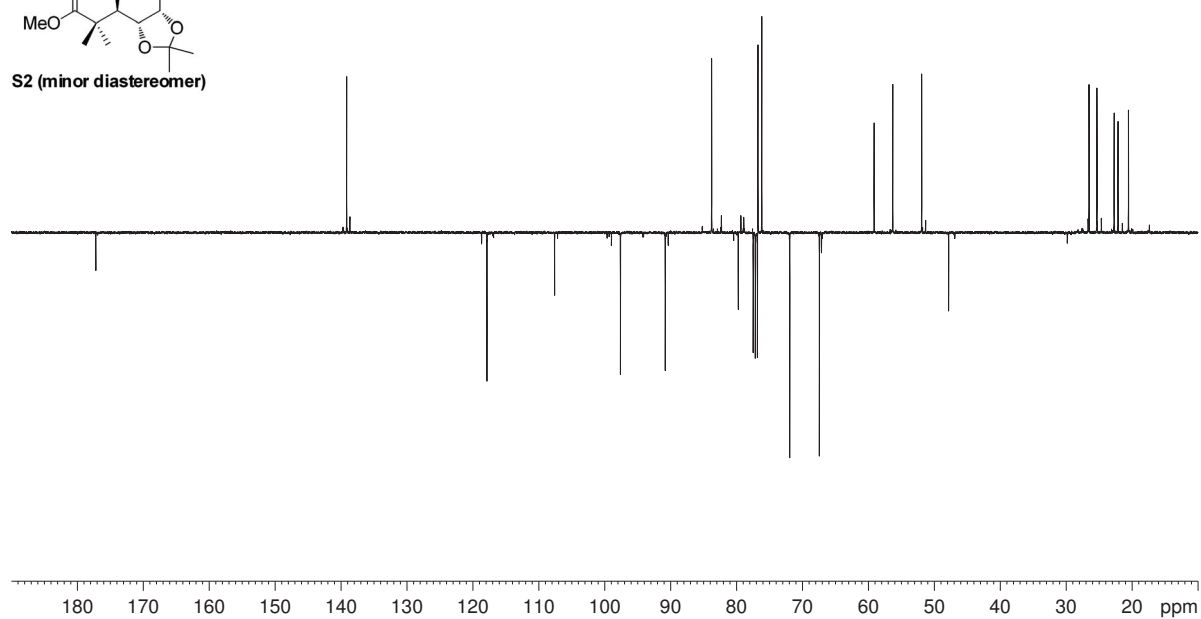
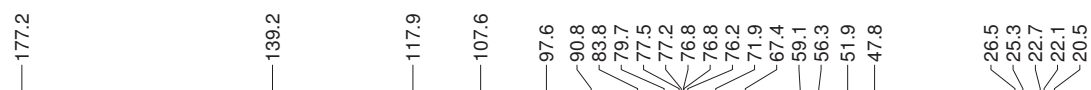
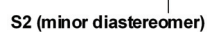


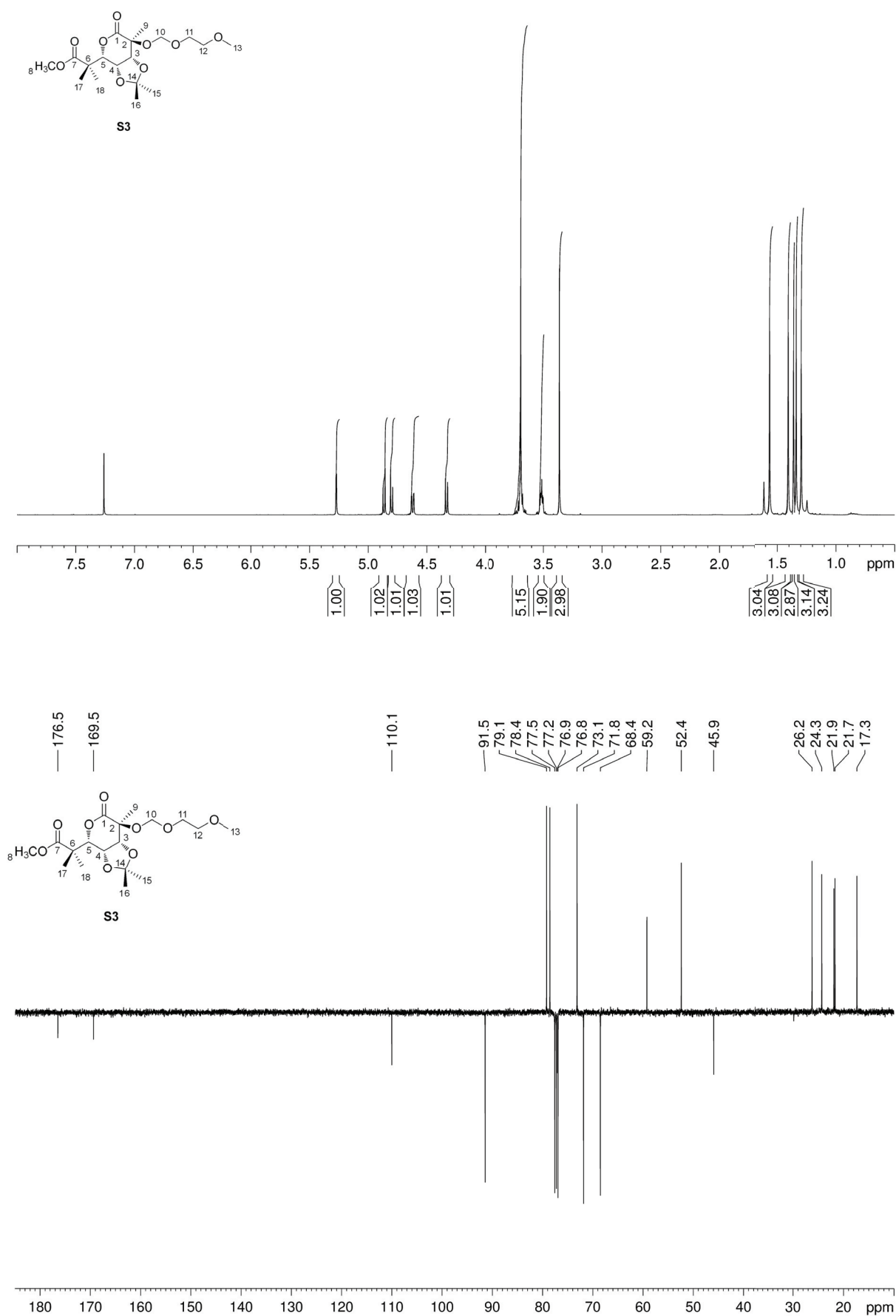


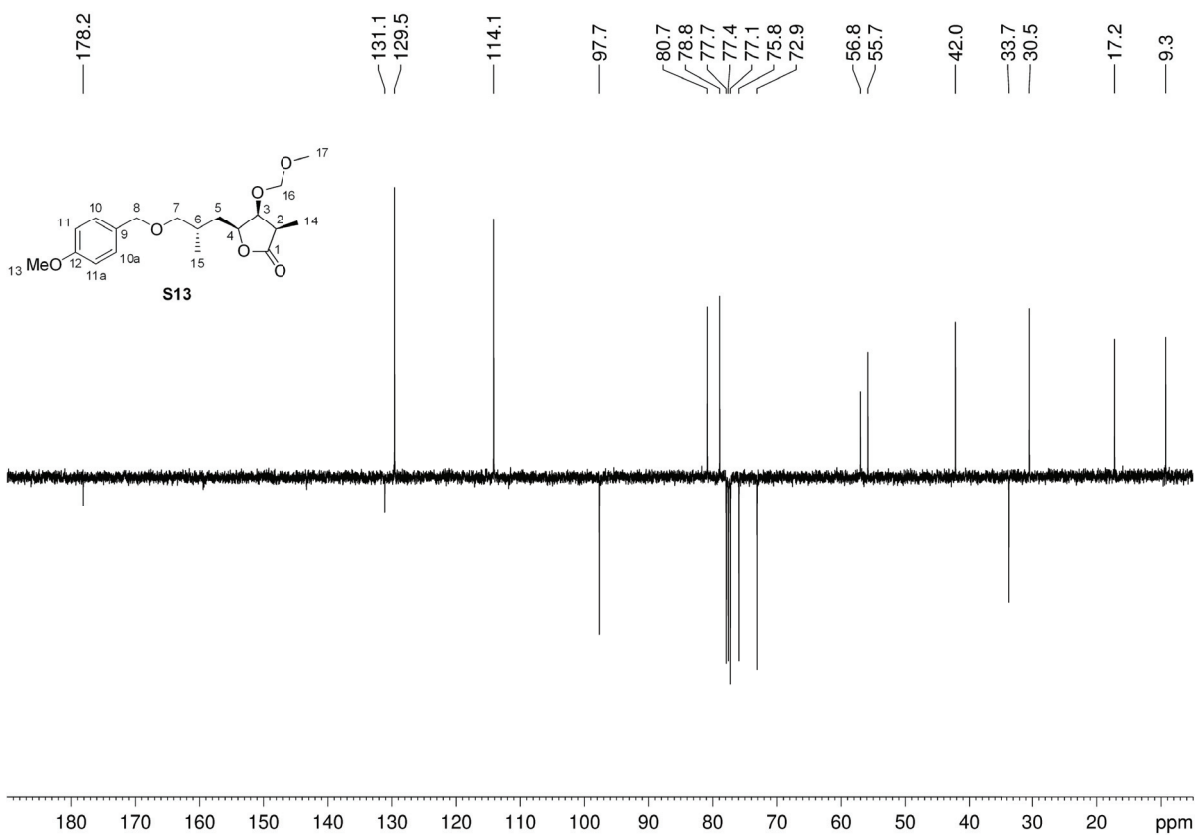
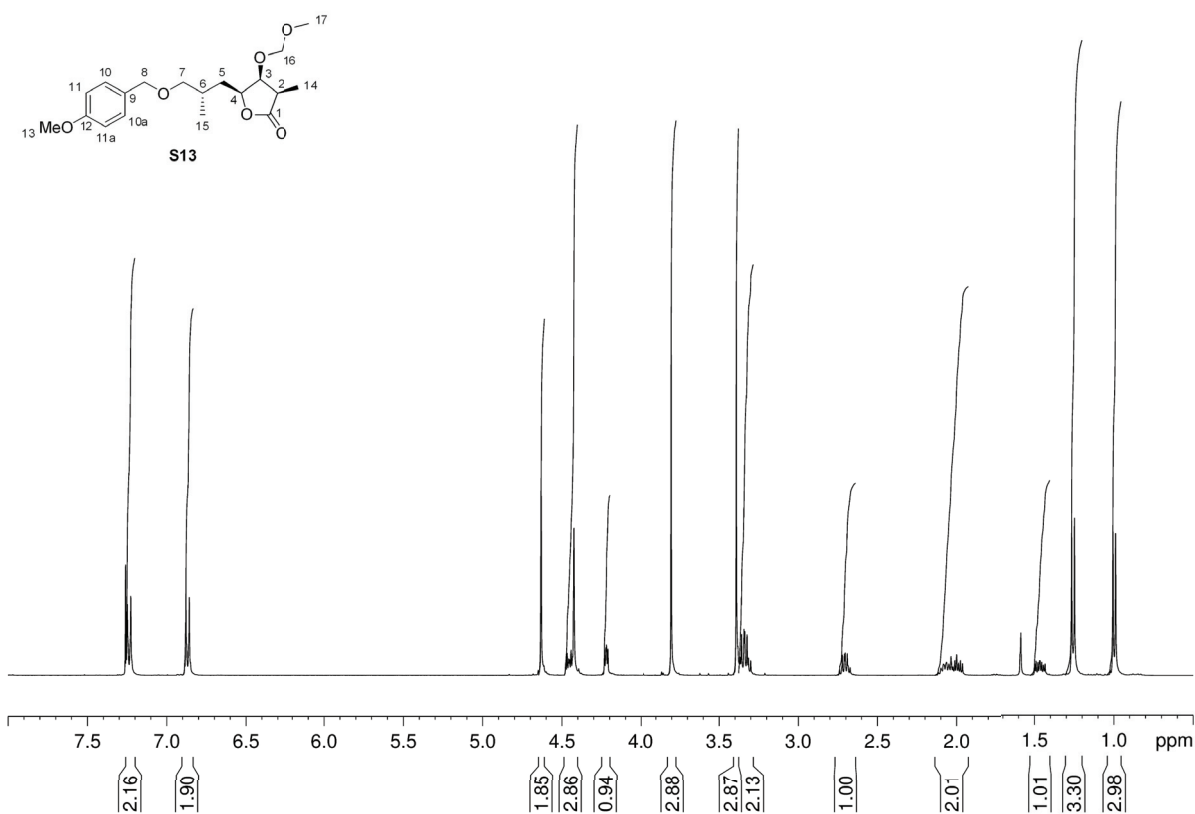






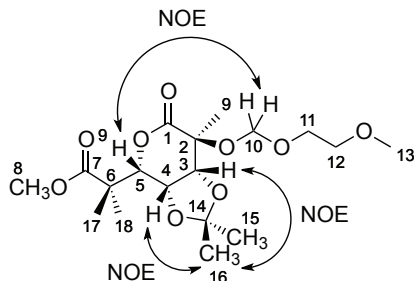




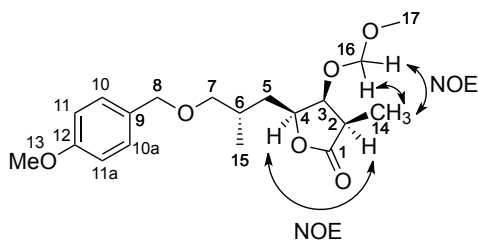


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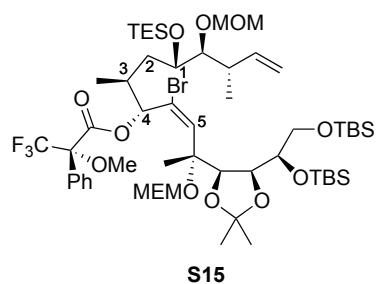
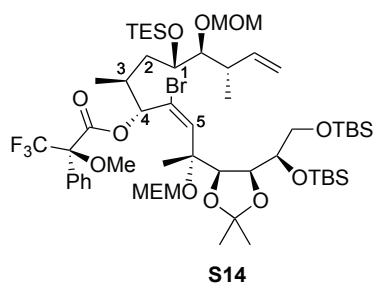
NOE-analysis S3:



NOE-analysis S13:



Mosher-ester Analysis



Mosher-ester Analysis:

Proton	S15 (<i>S</i> -configured) ppm	S14 (<i>R</i> -configured) ppm	Diff. (d _S -d _R)	S15-S14
1	3.83	3.89	-0.06	
2a	1.46	1.70	-0.24	
2b	1.18	1.25	-0.07	
3	2.24	2.26	-0.02	
4	5.96	5.90	+0.06	
5	6.58	6.54	+0.04	

7. APPENDIX III

Fürst, R.; Lentsch, C.; Rinner, U., Synthetic Studies towards an Advanced Precursor of the Jatrophone Diterpene Pl-4. *Synthesis*. In Press. DOI: 10.1055/s-0033-1338565.

Synthetic Studies Towards an Advanced Precursor of the Jatrophone Diterpene PI-4

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Received: The date will be inserted once the manuscript is accepted.

Abstract: Jatrophone diterpenes, isolated from members of the Euphorbiaceae plant family, constitute a class of biologically and structurally intriguing natural products. Herein, different strategies for the preparation of an advanced intermediate towards the total synthesis of the jatrophone diterpene PI-4 are described. Key strategies for the elaboration of the jatrophone precursors include hydrometalation, and radical reactions.

Key words: Euphorbiaceae, jatrophone diterpene, hydrometalation, samarium diiodide, Reformatsky reaction.

When Juba II of Mauretania, one of the most loyal client kings of the Roman Empire and contemporary of Emperor Augustus, was troubled by a swollen belly, Euphorbus applied herbal remedies to cure his ailments. In appreciation of his healing and relief, and in honor of his Greek physician, Juba named the succulent and strongly laxative plant, which helped to improve his conditions, Euphorbia. Much later, Carl Linnaeus, one of the most important botanists in the 18th century, assigned the name Euphorbia to the entire genus.

The application of spurge, as members of the Euphorbiaceae plant family are commonly referred to, in the treatment of cancerous conditions, swellings and warts in traditional herbal folk medicine is historically documented from different cultures around the globe.¹ Since the isolation of jatrophone by Kupchan in 1970,² phytochemists showed increasing interest in the isolation of active ingredients from plants of the Euphorbiaceae family. To date, numerous natural products, possessing different core frameworks, such as the tiglane, ingenane, daphnane, and jatrophone skeleton were isolated. These terpene-based natural products were explored within extensive biological studies demonstrating a wide range of pharmacologically promising properties, including antiproliferation, cytotoxic, antimicrobial,³ anti-inflammatory as well as antiviral activities.³ Additionally, jatrophone diterpenes were identified to bind and selectively inhibit the ATP-dependent efflux pump P-glycoprotein (Pgp).⁴ This is probably the most interesting biological activity of this class of natural products, as overexpression of Pgp and the resulting multi-drug resistance (MDR) are commonly

observed in cancer cells. Therefore, jatrophone diterpenes might serve as lead compounds in the development of co-therapeutics for cancer chemotherapy. Despite these promising biological properties and the challenging structural features, only few synthetic routes to jatrophone diterpenes have been reported.⁵

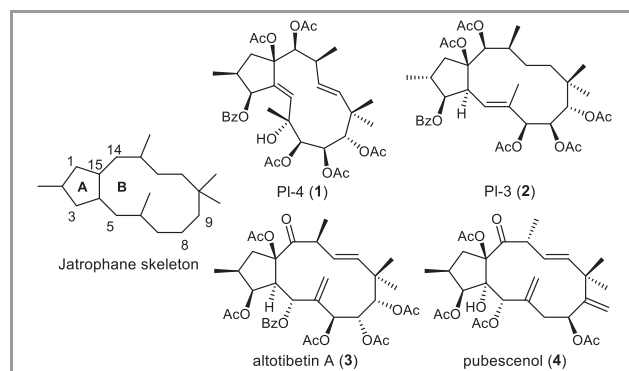


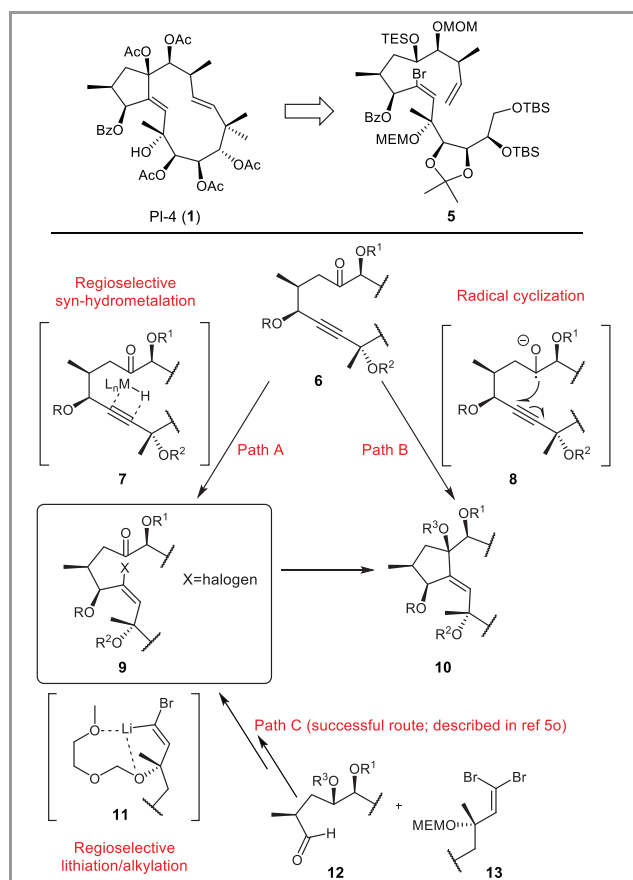
Figure 1. Jatrophone skeleton and representative jatrophone diterpenes.

PI-4 (1) was isolated in 2003 from a Hungarian sample of *Euphorbia platyphyllos*, an annual herbaceous plant.⁶ The natural product belongs to the jatrophone-type family of diterpenes. As shown in Figure 1, jatrophanes are characterized by a highly functionalized cyclopentane ring, which is annulated to a twelve-membered macrocycle. In most jatrophanes, the two rings are trans-fused, however, a few derivatives, such as PI-4, were isolated which possess a double bond at the ring junction. In addition to its promising biological properties, PI-4 represents an exciting target for a synthetic chemist, which inspired us to develop a strategy towards this terpenoid natural product.

Recently, we reported the preparation of an advanced intermediate towards the synthesis of PI-4 (1).⁵⁰ The key strategy of this approach relied on a regioselective chelation-controlled lithiation/alkylation sequence of the more hindered bromide in the requisite vinyl dibromide as outlined in Scheme 1.⁷ However, before the preparation of vinyl bromide 5 was achieved via the

aforementioned dibromide coupling approach, several routes were investigated. With the intrinsic potential of jatrophone diterpene as co-therapeutics for modern cancer chemotherapy, we also wish to describe unsuccessful approaches to accelerate the development of future synthetic routes towards members of the jatrophone family. The following section summarizes unsuccessful attempts to access **5** via different strategies, such as hydrometalation reactions and radical protocols.

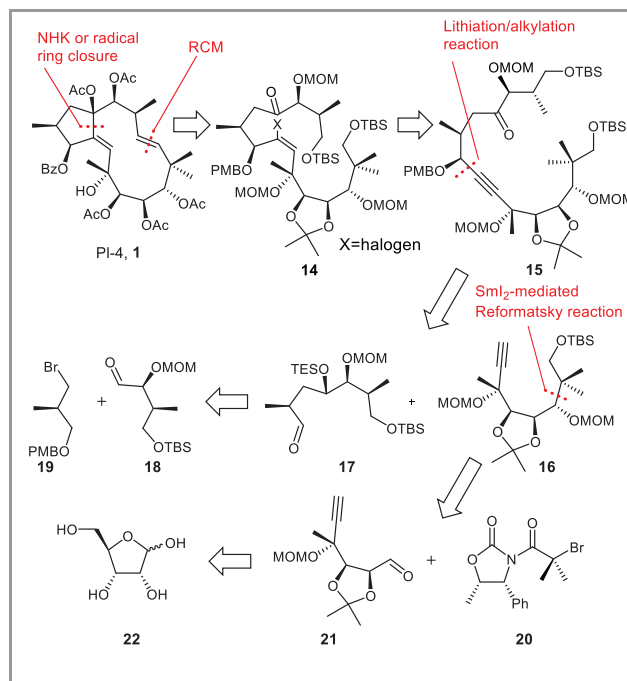
The initial retrosynthetic considerations towards the jatrophone diterpene PI-4 are outlined in Scheme 1. We envisaged a late stage closure of the cyclopentane ring and intended the preparation of vinyl halide **5** as a precursor for the key cyclization reaction. The initial strategy (Path A) relied on a regioselective syn-hydrometalation of ynone **6**. Alternatively, in a more concise manner, the alkyne in intermediate **6** could also be directly employed in a five-*exo*-dig ring closure reaction via an initially formed ketyl radical (Path B). Attempts towards the preparation of the highly advanced intermediate **5** via Path A and Path B are described in detail. The eventually successful regioselective lithiation/alkylation sequence (Path C) has already been described as pointed out above.⁵⁰



Scheme 1. General considerations.

Results and Discussion

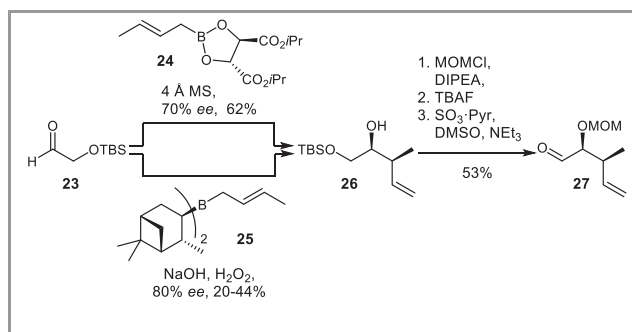
Hydrometalation Approach: The initial retrosynthetic analysis towards PI-4 (**1**) is outlined in Scheme 2. As mentioned above, we intended to close the twelve-membered macrocycle as well as the cyclopentane ring at a very late stage of the synthesis *via* a ring-closing-metathesis (RCM), and a Nozaki-Hiyama-Kishi (NHK) or a radical reaction, respectively. The precursor for the ring closing reactions, intermediate **14**, should become accessible from alkyne **15** through a syn-selective hydrometalation reaction. The sterical influence of the quaternary center adjacent to the alkyne should govern the metal to the more accessible, desired position. Alkyne **15** was envisaged to be elaborated from aldehyde **17** and terminal alkyne **16** by a lithiation/alkylation sequence. While **17** can be prepared from aldehyde **18** and literature known bromide **19**, alkyne **16** is accessible *via* a route featuring a diastereoselective SmI_2 -mediated Reformatsky reaction as key step.^{5k,8} D-Ribose was chosen as inexpensive and readily available starting material for aldehyde **21**.



Scheme 2. Retrosynthetic analysis – hydrometalation approach.

The preparation of the northern fragment of the natural product commenced with TBS-protected aldehyde **23** (Scheme 3), readily available from ethylene glycol *via* a literature known two-step procedure.⁹ While Brown crotylation¹⁰ delivered the chiral homoallylic alcohol **26** in low and irreproducible yield, the compound was obtained in satisfying yield and enantiomeric excess under Roush crotylation conditions.¹¹ Next, MOM-

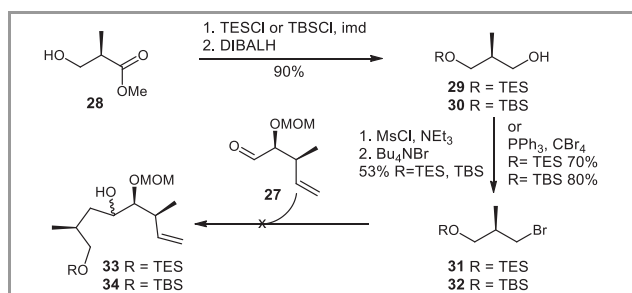
protection of the secondary alcohol and a desilylation/oxidation sequence allowed the isolation of aldehyde **27**.



Scheme 3. First attempt for the synthesis of the northern fragment of PI-4.

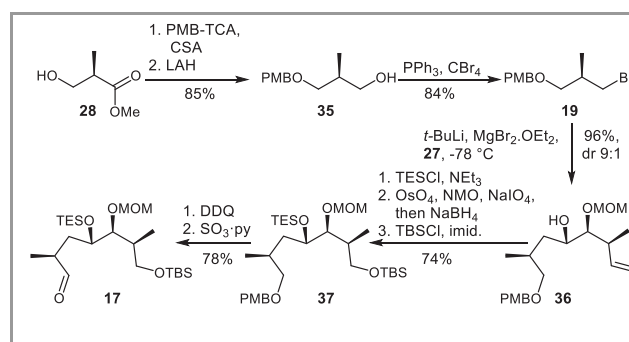
The synthesis of the coupling partners for aldehyde **27**, bromides **31** and **32**, is outlined in Scheme 4. Protection of the hydroxyl moiety in commercially available *R*-(–)-Roche ester (**28**) as TES- or TBS-ether was followed by DIBALH reduction of the methyl ester. Then, the bromide was introduced either by mesylation of the primary alcohol, followed by nucleophilic displacement with tetrabutyl-ammonium bromide¹², or alternatively under Appel conditions.

All attempts to accomplish the coupling of bromide **31** or **32** with aldehyde **27** failed. Lithiation of **31** with *n*-BuLi or *t*-BuLi in different solvents resulted in decomposition of the lithiated species. The instability of silyl ethers towards organolithium species is well documented¹³ and we hoped to solve the problem by exchanging the labile TES-ether for a more stable TBS-group (**32**). Unfortunately, lithiation of halide **32** using *n*-BuLi or *t*-BuLi also failed to deliver the desired product. Addition of $\text{MgBr}_2\cdot\text{OEt}_2$ and LiBr to the lithiated species for the *in situ* formation of the transmetalated Grignard species¹⁴ resulted in decomposition of the starting material. Direct formation of the Grignard species, reaction with indium (activated under sonication), or NHK coupling conditions only allowed the re-isolation of **32**.



Scheme 4. Completion of the northern fragment of PI-4.

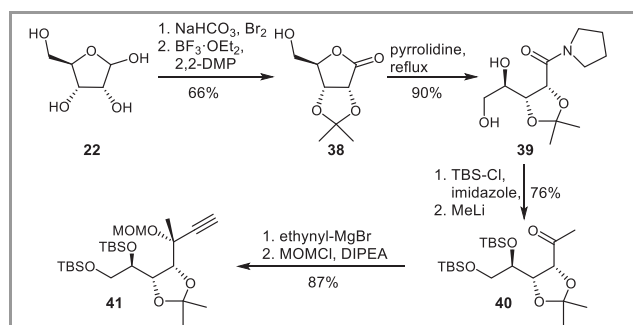
Because of the instability of the silyl-ethers, we decided to introduce a PMB protecting group. Reaction of Roche ester (**28**) with PMB-trichloroacetimidate followed by LAH reduction allowed the isolation of alcohol **35** (Scheme 5). The bromide was installed applying the Appel protocol and **19** could be obtained in good overall yield. With bromide **19** in hand, the crucial coupling reaction could be approached. Lithiation of **19** with *t*-BuLi at -78°C and subsequent addition of $\text{MgBr}_2\cdot\text{OEt}_2$ afforded the intermediate Grignard species, which readily reacted with aldehyde **27** to deliver the desired adduct **36** in excellent 96% yield, as a 9:1 diastereomeric mixture. The expected, predominant formation of the *S*-configured alcohol through this chelation-controlled addition reaction^{14c} could be confirmed by NMR studies.⁵⁰ However, as the hydroxyl moiety is oxidized at a later stage of the synthesis, the stereochemical outcome of the reaction is inconsequential to the overall efficiency and both diastereomers could be employed for all successive steps.¹⁵ Next, the corresponding secondary hydroxyl group was protected as TES-ether. The following steps were devoted to mask the terminal alkene as a primary TBS-ether to prevent potential side reactions in the hydrometalation reaction later in the synthesis. Dihydroxylation of the terminal alkene with catalytic amounts of OsO_4 and NMO, was followed by addition of sodium periodate to deliver the desired aldehyde in a one-pot-procedure, which was instantly reduced with NaBH_4 to give the corresponding alcohol. Next, the primary hydroxyl group was TBS-protected to afford fully protected intermediate **37** which was then converted to aldehyde **17** via a DDQ-mediated debenzoylation and oxidation of the primary alcohol under Parikh-Doehring conditions.¹⁶



Scheme 5. Second attempt towards the northern fragment of PI-4.

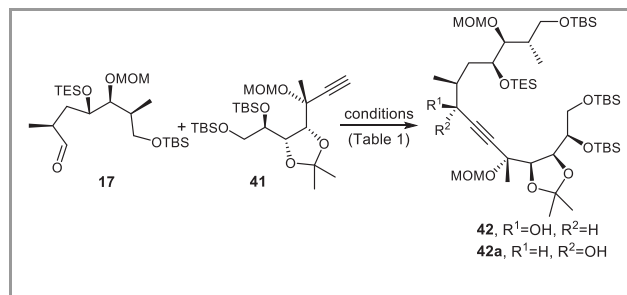
For the preparation of the southern part of the natural product D-ribose (**22**) was selected as inexpensive and readily available starting material (Scheme 6).^{5k} Oxidation of the lactol with bromine and sodium bicarbonate delivered D-ribonolactone, which was converted to acetonide **38**.¹⁷ Exposure of the lactone

to pyrrolidine at elevated temperature afforded amide **39** in excellent yield. Both hydroxyl functionalities in **39** were silylated before addition of methyllithium at $-78\text{ }^{\circ}\text{C}$ allowed the isolation of methyl ketone **40**. The synthesis of alkyne **41** was accomplished after Grignard reaction with ethynylmagnesium bromide,¹⁸ which afforded the terminal alkyne as single isomer,¹⁹ and MOM-protection of the newly generated tertiary alcohol. Alkyne **41** was used in the further course of the synthesis as a simplified model-system for the southern fragment of PI-4.



Scheme 6. Preparation of the southern fragment of PI-4.

As summarized in Table 1, various conditions for the coupling of alkyne **41** and aldehyde **17** (Scheme 7) were evaluated. Unfortunately, a chiral alkylation reaction, following the Carreira protocol,²⁰ with (–)-*N*-methylephedrine, $\text{Zn}(\text{OTf})_2$ and NEt_3 only resulted in reisolatation of the starting materials. When *n*-BuLi was used for the lithiation of alkyne **41**, the desired coupling products **42** and **42a** could be obtained, however, the yield of the reaction was non-reproducible on a larger scale. Unfortunately, further addition of HMPA or CeCl_3 resulted in decreasing yield.²¹ Non-nucleophilic bases proved to be advantageous for the coupling reaction and the desired products **42** and **42a** could be isolated in 71% yield when LHMDs was employed in THF at $-78\text{ }^{\circ}\text{C}$. In this case, transmetalation using CeCl_3 helped to further improve the overall yield of the coupling reaction to excellent 84%. The only drawback was the stereochemical outcome of the alkyne/aldehyde coupling reaction as under all reaction conditions, the desired intermediates **42** and **42a** were isolated as a 1:2 mixture of diastereomers, favoring the undesired isomer.²² However, at this point we decided to proceed with the synthesis before improving the diastereoselectivity or developing methods for the inversion of the stereocenter in the undesired isomer.



Scheme 7. Alkyne/aldehyde coupling.

Table 1 Alkyne/aldehyde coupling conditions.

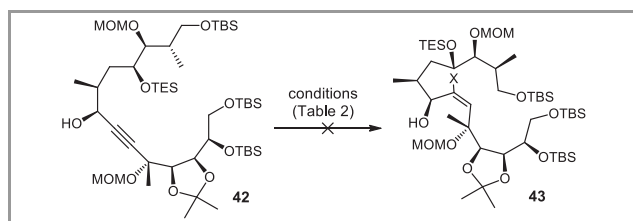
Reagents	Temperature	Solvent	Yield
(–)- <i>N</i> -Methylephedrine, $\text{Zn}(\text{OTf})_2$, NEt_3	rt	toluene	0% ^[a]
<i>n</i> -BuLi	$-78\text{ }^{\circ}\text{C}$ to rt	THF	26–47% ^[b]
<i>n</i> -BuLi, CeCl_3	$-78\text{ }^{\circ}\text{C}$ to rt	THF	5% ^[b]
<i>n</i> -BuLi, HMPA	$-78\text{ }^{\circ}\text{C}$ to rt	THF	10% ^[b]
LHMDs	$-78\text{ }^{\circ}\text{C}$ to rt	THF	71% ^[b]
KHMDs	$-78\text{ }^{\circ}\text{C}$	THF	53% ^[b]
LHMDs, CeCl_3	$-78\text{ }^{\circ}\text{C}$	THF	84% ^[b]
(–)- <i>N</i> -Methylephedrine, $\text{Zn}(\text{OTf})_2$, NEt_3	rt	THF	0% ^[a]

[a] No reaction was observed, reisolatation of the starting materials.

[b] dr 1:2 (**42**:**42a**)

With internal alkyne **42** in hand, the stage was set to explore the key hydrometalation reaction. We expected that reaction of alkyne **42** with an organometallic species should result in an attack of the metal at the less hindered position with concomitant syn-hydrogenation which should establish the desired double bond geometry. Subsequent metal-halogen exchange would further provide a synthetic anchor for the closure of the cyclopentane ring, either *via* a radical process, or a NHK coupling reaction.

As outlined in Table 2, reaction of alkyne **42** with tributyltin hydride and a catalytic amount of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (Table 2, entry 1)²³ or palladium acetate and tricyclohexylphosphine (entry 2)²⁴ only resulted in isolation of the starting material, even when the reaction was carried out at elevated temperatures. Next, we decided to apply hydrozirconation conditions.²⁵ However, no product formation was observed when the Schwartz reagent²⁶ was added to a solution of alkyne **42** in toluene (entry 3),^{5m} the same outcome was observed after addition of MeLi and ZnCl_2 (entry 4).²⁷ Our final attempt was a nickel mediated hydrometalation reaction,²⁸ which resulted in decomposition of the starting material (entry 5).



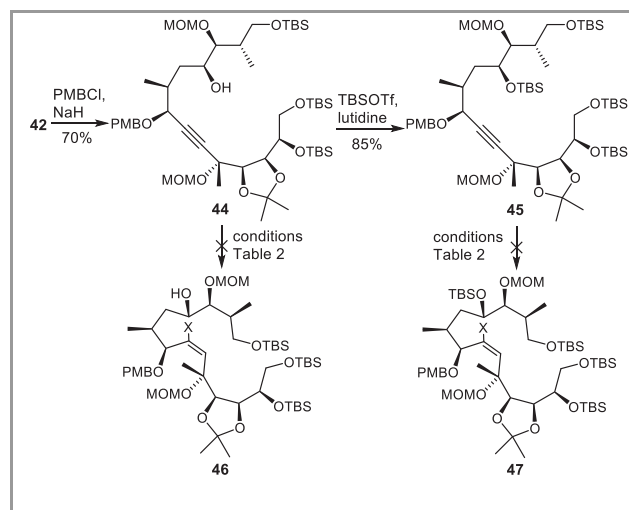
Scheme 8. Hydrometalation reaction I.

Table 2 Hydrometalation reaction conditions.

Entry	Alkynes	Reagents	Temp.	
1	42, 44, 45	Pd(PPh ₃) ₂ Cl ₂ , SnBu ₃ H, H ₂ O quench	rt to 60 °C	reisolation of s.m.
2	42, 44, 45	Pd(OAc) ₂ , PCy ₃ , Bu ₃ SnH, H ₂ O quench	rt to 60 °C	reisolation of s.m.
3	42, 44, 45	Cp ₂ Zr(HCl), I ₂ quench	60 °C	reisolation of s.m.
4	42	Cp ₂ Zr(HCl), MeLi, ZnCl ₂ , I ₂ quench	–78 °C to rt	reisolation of s.m.
5	42, 45	Ni(PPh ₃) ₂ Cl ₂ , DIBAL-H, NBS quench	0 °C to rt	decomp.

Either sterical hindrance, or the free hydroxyl moiety in alkyne **42** might be responsible for the unsatisfying outcome of the hydrometalation reaction. Thus, secondary alcohol **42** was allowed to react with NaH and PMBCl, which resulted in PMB-protection of the secondary hydroxyl moiety adjacent to the alkyne, with concomitant cleavage of the TES-group. The fully protected substrate was obtained after exposure of PMB-ether **44** to TBS-triflate and 2,6-lutidine, as shown in Scheme 9. With alkyne **45** in hand, the hydrometalation conditions, outlined in Table 2, were re-evaluated. Also, since PMB-ether **44** was available, this compound was included in this study. Unfortunately, all experiments carried out with either **44** or **45**, confirmed our previous results and the desired vinyl halide was not obtained.

We could rule out that the free hydroxyl moiety in **42** was responsible for the unfavorable outcome of the intended hydrometalation reaction and we concluded that the sterical hindrance of the internal alkyne might be the limiting factor. These results are in agreement with literature examples, as in most cases, hydrometalation reactions are carried out on unsubstituted or sterically less demanding substrates.²⁹ As the only remaining option, the cleavage of the MOM-group on the quaternary center next to the internal alkyne, seemed unfeasible with respect to the protecting group strategy and overall efficiency of the synthesis, the hydrometalation route was abandoned.

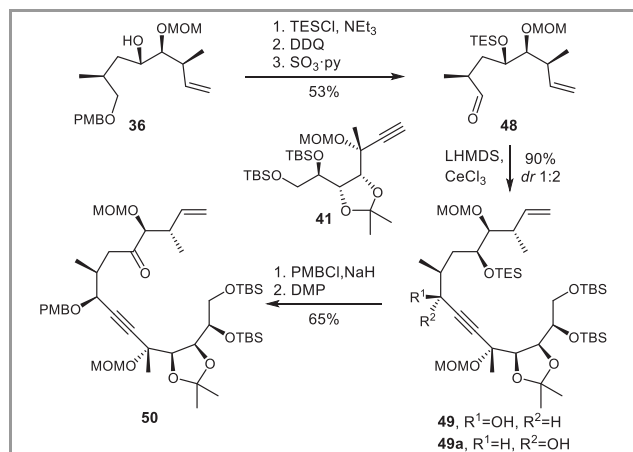


Scheme 9. Hydrometalation reaction II.

Alkyne cyclization approach: Several methods describing the direct intramolecular cyclization reaction of aldehydes or ketones with internal or terminal alkynes have been published: Nickel-mediated intramolecular ring-closing reactions between internal alkynes and ketones³⁰ as well as cyclization reactions *via* low-valent titanium complexes³¹ can be used for the preparation of five-membered cycloalkanols. Samarium diiodide is a useful reagent for the formation of ketyl radicals, which triggers cyclization reactions of alkynes.³² According to these promising literature precedents, an alternative approach was launched, based on the direct utilization of internal alkynes without the foregoing installation of a vinyl halide, as pursued in the hydrometalation approach. Additionally, this idea seemed even more appealing, as the protection of the terminal double bond within the northern fragment, originating from the enantioselective crotylation reaction, is not required, and can be directly employed in the final RCM reaction later.

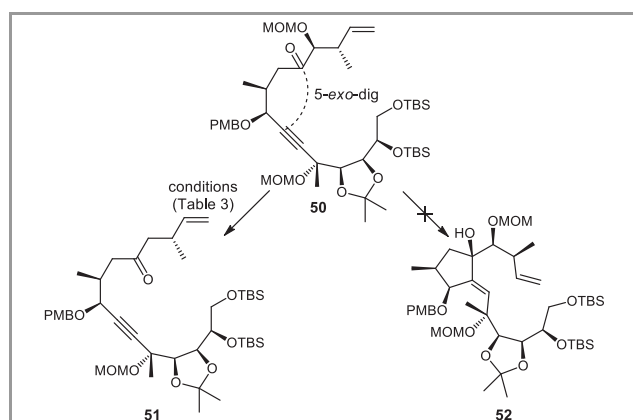
As outlined in Scheme 10, we started our endeavors from previously prepared alkene **36**. Silylation of the secondary alcohol was followed by cleavage of the benzyl ether and Parikh-Doehring oxidation of the primary hydroxyl group (**48**).⁵⁰ Next, the lithiation/alkylation reaction of aldehyde **48** and alkyne **41** was pursued. We were pleased to find that the previously established cerium-mediated coupling reaction delivered the desired diastereomeric adducts **49** and **49a** in excellent 90% overall yield. Again, the stereochemical outcome of the coupling reaction was not perfectly satisfying, as a 1:2 mixture of diastereomers, favoring the undesired isomer, was obtained.³³ We again decided to proceed with the synthesis using the desired diastereomer **49** without any optimization or correction of the stereocenter in **49a**. PMB-protection of the secondary alcohol resulted in simultaneous cleavage of the TES-group. Exposure of the resulting alcohol to Dess-Martin

periodinane allowed the isolation of the substrate for the crucial radical ring closure reaction (**50**).



Scheme 10. Preparation of the cyclization precursor.

With alkynone **50** in hand, conditions for the cyclopentane formation were investigated. As pointed out above, addition of SmI_2 to the cyclization precursor (**50**) should initiate the formation of a ketyl radical which should further attack the internal alkyne and establish the five-membered ring *via* a five-*exo-dig* ring closing reaction (Scheme 11). Unfortunately, the SmI_2 -mediated reaction only resulted in the reisolation of the starting material when carried out at -78°C , and partial formation of the reduced intermediate **51** at elevated temperature. The isolation of the reduced species (**51**) gives evidence that a ketyl radical is formed during the course of the reaction. However, the second step, the formation of the cyclopentane ring system, did not occur. We hoped that the addition of *t*-BuOH, MeOH, HMPA, LiCl, or NiI_2 would facilitate the ring closure, but the desired cyclized product could not be isolated.



Scheme 11. Cyclization reaction.

Next, we explored an intramolecular nickel-catalyzed coupling reaction in the presence of

Et_3SiH and various types of ligands, including PBU_3 and IPr [1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene] as N-heterocyclic carbene ligand (NHC), to form the five-membered ring.^{30a} Unfortunately, all experiments resulted in isolation of the starting material. The results and conditions applied for the intended cyclization reaction are summarized in Table 3.

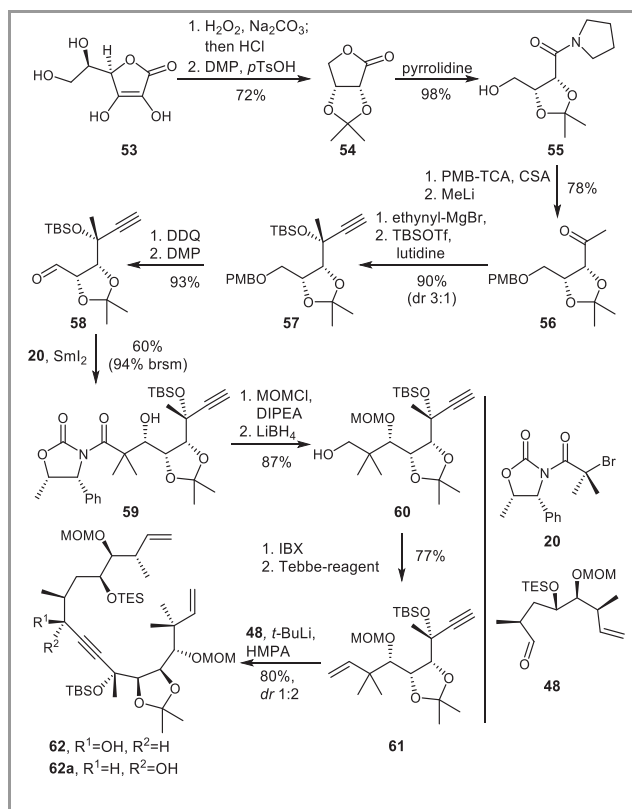
Table 3 Cyclization reaction conditions.^[a]

Entry	Reagents	Temp.	
1	SmI_2	-78°C	reisolation of s.m.
2	SmI_2	rt	51 + s.m.
3	SmI_2 , <i>t</i> -BuOH	-78°C	51 + s.m.
4	SmI_2 , <i>t</i> -BuOH, HMPA	-78°C	51 + s.m.
5	SmI_2 , <i>t</i> -BuOH, HMPA	0°C	51 ^[b]
6	SmI_2 , HMPA	rt	51 ^[b]
7	SmI_2 , MeOH	0°C to rt	51 ^[b]
8	SmI_2 , NiI_2	rt	51 ^[b]
9	SmI_2 , LiCl	rt	51 ^[b]
10	$\text{Ni}(\text{cod})_2$, IPr.HCl, Et_3SiH , <i>t</i> -BuOK	0°C to rt	reisolation of s.m.
11	$\text{Ni}(\text{cod})_2$, PBU_3 , Et_3SiH	0°C to rt	reisolation of s.m.
12	$\text{Ni}(\text{cod})_2$, PBU_3 , BEt_3	rt	reisolation of s.m.

[a] **51** was isolated in less than 10% yield under all given reaction conditions. [b] Slow decomposition of the starting material.

At this point we reasoned that again the sterical hindrance of the internal alkyne might be responsible for the lack of reactivity, as the ketyl formation was observed under the SmI_2 -mediated cyclization conditions. We expected that a closer spatial arrangement of the two reacting functionalities would enhance the reactivity and trigger the formation of the cyclopentane ring. Thus, we decided to slightly modify the route towards the natural product and intended to close the macrocycle *via* a RCM reaction prior to establishing the five-membered ring.

The synthesis of the RCM-precursor is outlined in Scheme 12. The modified sequence started with readily available D-isoascorbic acid (**53**) which was converted to acetonide protected lactone **54** via a literature known two-step procedure.³⁴ Alcohol **55** became available after reaction of lactone **54** with pyrrolidine. The resulting primary hydroxyl group was protected as PMB-ether before treatment with methyllithium allowed the isolation of methyl ketone **56** in excellent yield. Next, C2-elongation with ethynylmagnesium bromide delivered the corresponding tertiary alcohols in a 3:1 diastereomeric ratio, favoring the desired R-configured isomer, which was protected as its TBS-ether (**57**).³⁵

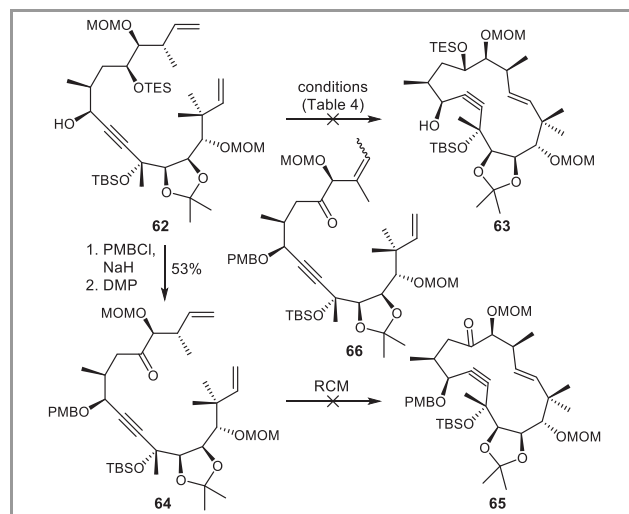


Scheme 12. Preparation of the RCM-precursor.

Then, the PMB group was removed with DDQ and the primary alcohol was oxidized with Dess-Martin periodinane to give aldehyde **58**. The installation of the geminal dimethyl group was accomplished via a diastereo-selective Sml_2 -mediated Reformatsky reaction of aldehyde **58** and chiral bromide **20**, and advanced alcohol **59** was obtained as single isomer.^{5k,8} MOM-protection of the secondary alcohol was followed by reductive cleavage of the chiral auxiliary with LiBH_4 and primary alcohol **60** was isolated in good yield. Alkene **61** was obtained after IBX-oxidation of the primary alcohol functionality, followed by installation of the terminal alkene with Tebbe's reagent. Lithiation of the terminal alkyne moiety in **61** with $t\text{-BuLi}$, and subsequent reaction with aldehyde **48** afforded the RCM precursor in 80% yield, again as a 1:2 (**62**:**62a**) mixture of diastereomers.

With diene **62** in hand, the closure of the 15-membered ring was attempted. As outlined in Table 4 (Entry 1-6), different reaction conditions and RCM catalysts were evaluated.³⁶ Unfortunately, we were not able to achieve the desired macrocyclization using either diene **62** or fully protected substrate **64**, available after PBM-protection of the hydroxyl group with concomitant cleavage of the TES-ether and subsequent oxidation of the secondary alcohol, were met with failure (Scheme 13). All attempts resulted in re-isolation of the starting material, along with minor amounts (up to 10%) of the thermodynamically more stable double bond isomer (**66**,

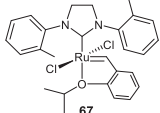
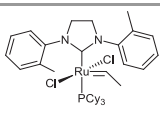
exemplarily shown for the reaction starting from diene **64**).



Scheme 13. Ring closing metathesis reaction.

As the outcome of RCM reactions strongly depends on the steric environment of the double bonds, we reasoned that the geminal dimethyl moiety in **62** and **64** prevents the formation of the 15-membered macrocycle. The influence of the sterical effects might even be more pronounced as the alkyne functionality adds additional rigidity to the system. We decided to prepare a structurally simplified model compound lacking the geminal dimethyl group. As only little information on the structural requirements for MDR-reversal activity of jatrophanes is available, the synthesis and biological evaluation of derivatives is of essential importance.

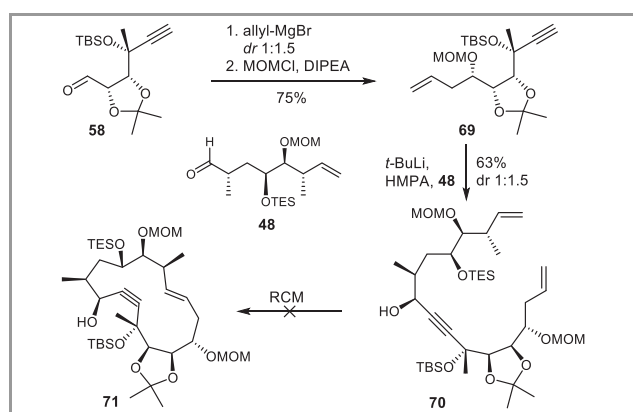
Table 4 RCM conditions.

Entry	Catalyst	Solvent	Temperature
1	Grubbs 2 nd gen ^{36a}	DCM	40 °C
2	Grubbs 2 nd gen	toluene ^[a]	80 °C to 110 °C
3	Grubbs 2 nd gen	DCE	80 °C
4	Hoveyda-Grubbs 2 nd gen ^{36b}	toluene ^[a]	80 °C to 110 °C
5 ^{36c}		toluene ^[a]	80 °C to 110 °C
6 ^{36c}		toluene ^[a]	80 °C to 110 °C

[a] Double bond isomerisation was observed with **62** and **64**.

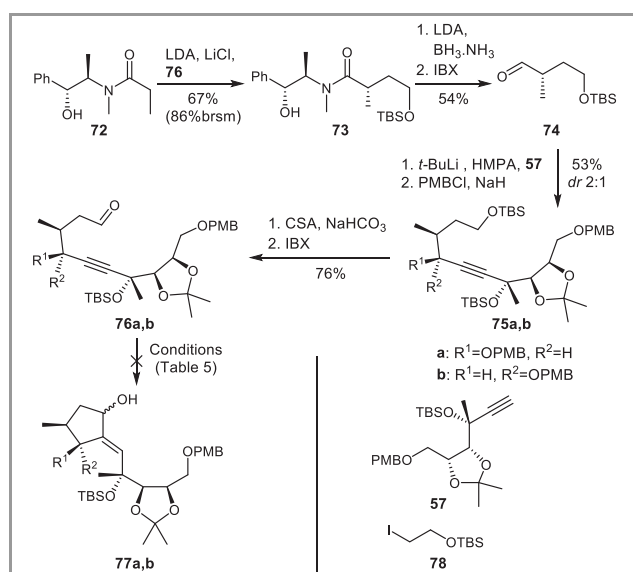
The synthesis of the sterically less demanding RCM-precursor is outlined in Scheme 14. The addition of allylmagnesium bromide to aldehyde **58** allowed the isolation of the corresponding allylic alcohols in a 1:1.5 diastereomeric ratio, favoring the undesired

isomer.³⁷ Although we were not concerned with the stereochemical outcome of the Grignard reaction, we decided to alter the reaction conditions only after successful closure of the macrocycle. The diastereomers were separated and the desired compound converted to MOM-ether **69** in 82% yield. With **69** in hand, the RCM-precursor (**70**) became accessible after lithiation of the alkyne and subsequent reaction with aldehyde **48**. Unfortunately, all attempts to close the macrocycle via a RCM-reaction (conditions as described in Table 4, Entry 1-6) remained unsuccessful and the desired product **71** could not be isolated.



Scheme 14. Synthesis of a sterically less demanding RCM-precursor.

At this point it became obvious that the rigidity provoked by the internal alkyne, was obstructive for the formation of the desired macrocycle. We decided to further investigate our initial idea which envisaged the closure of the cyclopentane ring prior to the macrocyclization.



Scheme 15. Alkyne/aldehyde cyclization - shortened chain length.

As outlined in Scheme 15, we intended to prepare aldehyde **76** as precursor for a SmI_2 - or Ni-mediated ring closure reaction. Thus, we could take advantage of the higher reactivity of aldehydes versus ketones. Additionally, the undesired reductive removal of the MOM-ether as observed in the SmI_2 -mediated reaction of **62** and **64** would be avoided. The resulting cyclopentanol could later be oxidized to the corresponding ketone and used for further functionalization.

The sequence started with Myer's alkylation using TBS-protected iodide **78** and pseudoephedrine propionamide **72** (Scheme 15).³⁸ Cleavage of the chiral auxiliary with $\text{BH}_3\cdot\text{NH}_3$, and oxidation of the primary alcohol with IBX resulted in the isolation of aldehyde **74**. The following reaction of aldehyde **74** with deprotonated alkyne **57** delivered the corresponding secondary alcohols as an inseparable 1:2 mixture of diastereomers (as previously observed for similar substrates but the stereochemistry was not proven at this point). The alcohol functionality was protected as a PMB-ether before the compound was treated with camphorsulfonic acid (CSA) to cleave the primary TBS-group (**75a,b**). Final oxidation of the primary alcohol with IBX afforded aldehydes **76a** and **76b** which served as substrates for the intended ring closing reaction.

Unfortunately, neither reaction of aldehyde **76a** nor **76b**, afforded the desired products. An overview of different reaction conditions applied to aldehydes **76a** and **76b** is presented in Table 5. Because of these disappointing findings the approach was abandoned. The inability to access the desired intermediate led to the development of the ultimately successful dibromide coupling approach (Path C in Scheme 1) which has been published elsewhere.⁵⁰

Table 5 Cyclization reaction conditions.

Entry	Reagents	Temperature	
1	SmI_2	-78 to -40 °C	reisolation of s.m.
2	SmI_2	0 to 50 °C	decomposition [a]
3	SmI_2 , HMPA	-78 °C	mixture of undefined products
4	SmI_2 , HMPA, <i>t</i> -BuOH	-78 °C	decomposition
5	SmI_2 , HMPA, MeOH	-78 to 0 °C	decomposition [a]
6	$\text{Ni}(\text{cod})_2$, IPr-HCl, Et_3SiH , <i>t</i> -BuOK	rt to 50 °C	reisolation of s.m. [a]
7	$\text{Ni}(\text{cod})_2$, PBu_3 , BEt_3 , Et_3SiH	rt	reisolation of s.m.

[a] Partial reduction of the aldehyde to the corresponding alcohol.

Conclusions

Herein, we describe two approaches towards a highly advanced intermediate in the synthesis of the jatrophane diterpene PI-4 (**1**). These routes feature a syn-selective hydrometalation reaction, and a radical approach, respectively. Although the desired advanced intermediate (**5**) could not be accessed, we

were able to elaborate efficient protocols for the preparation of structural motifs present in this fascinating class of natural products. Jatrophone diterpenes are synthetically challenging targets, mainly because of the complex stereochemical substitution pattern. Additionally, the high level of oxygenation necessitates sophisticated protecting group strategies and facilitates undesired side reactions and modified reactivity. We are positive that results and strategies discussed within this manuscript, as well as problems and synthetic drawbacks will be of importance for the design of future routes to structurally related jatrophone diterpenes.

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware. Solvents were purified and dried by standard procedures. The reactions were monitored by thin layer chromatography using silica gel 60-F254 glass plates. Flash column chromatography was performed with silica gel 60 (0.040-0.063 μm , 240-400 mesh). Optical rotations were measured at the sodium D line with a 100 mm path length cell. NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl_3 solutions and referenced to the residual CDCl_3 signal (1H, $\delta = 7.26$, 13C, $\delta = 77.16$). IR spectra are reported in wave numbers (cm^{-1}). All compounds were measured using a single reflection monolithic diamond ATR module. High resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer.

(2*S*,5*S*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (36).

A solution of bromide **19** (590 mg, 2.16 mmol, 2.0 eq) in Et_2O (17 mL) was cooled to -78°C and a solution of *t*-BuLi (1.6 M, 2.84 mL, 4.54 mmol, 4.2 eq) was added dropwise over 3 minutes. The reaction mixture was stirred for 10 minutes at that temperature before a freshly prepared MgBr_2 solution (1 M, 2.48 mL, 2.48 mmol, 2.3 eq) was added. After 10 minutes at -78°C aldehyde **27** (171 mg, 1.08 mmol, 1.0 eq), dissolved in Et_2O (6.8 mL) was added dropwise *via* syringe over 3 minutes. The reaction mixture was allowed to stir at -78°C for 90 minutes until TLC-control showed total consumption of aldehyde **5**. The reaction was terminated by the addition of a saturated, aqueous solution of NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The resulting crude mixture of secondary alcohols was purified by flash column chromatography (hexane/ EtOAc 9:1 to 5:1) providing **36** (342 mg) and **36a** (38 mg) as colorless oils, in a 9:1 diastereomeric ratio and 96% overall yield.

Major diastereomer (**36**):

$[\alpha]_{\text{D}}^{20} +6.3$ (c 1.0, CHCl_3).

IR (ATR): 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 0.93$ (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.22-1.31 (m, 1H), 1.52 (ddd, $J = 4.3, 10.5, 13.8$ Hz, 1H), 2.08-2.16 (m, 1H), 2.43-2.56 (m, 1H), 3.18 (dd, $J = 3.9, 5.9$ Hz, 1H), 3.23 (d, $J = 3.9$ Hz, 1H), 3.27-3.31 (m, 2H), 3.42 (s, 3H), 3.62-3.69 (m, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.99-5.02 (m, 1H), 5.02-5.06 (m, 1H), 5.76-5.88 (m, 1H), 6.84-6.90 (m, 2H), 7.22-7.28 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = 16.9$ (CH_3), 17.7 (CH_3), 30.4 (CH), 37.9 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.8 (CH), 72.6 (CH_2), 76.3 (CH_2), 88.7 (CH), 98.9 (CH_2), 113.6 (CH), 115.3 (CH_2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C) ppm.

HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5$: 375.2148; found: 375.2141.

(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*R*)-5-((*R*)-2-((*Tert*-butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-

phenyloxazolidin-2-one (59). A solution of SmI_2 (0.1 M in THF, 31.3 mL, 3.13 mmol, 2.5 eq) was transferred into a 250 mL round bottom Schlenk flask which was precooled to -78°C . A solution of bromide **20** (449 mg, 1.38 mmol, 1.1 eq) and aldehyde **58** (390 mg, 1.25 mmol, 1.0 eq) in 20 mL degassed THF (3 pump-freeze-thaw cycles) was added to the SmI_2 solution *via* a cannula over a period of 5 minutes. The reaction mixture was stirred for 1 hour at -78°C before it was quenched by the addition of aqueous saturated solutions of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and NaHCO_3 (20 mL) at -78°C . The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the organic solvents were removed under reduced pressure delivering the crude secondary alcohol as a light yellow oil which was purified by flash chromatography (hexane/ EtOAc 9:1) providing **59** (420 mg) as single diastereomer in 60% (94% brsm) yield.

$[\alpha]_{\text{D}}^{20} +34.4$ (c 1.0, CHCl_3).

IR (ATR): 3511, 3264, 2933, 2858, 2361, 2341, 1773, 1688, 1457, 1338, 1248, 1151, 1086, 1028, 987, 835, 768cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 0.23$ (s, 3H), 0.30 (s, 3H), 0.90 (s, 9H), 0.91 (d, $J = 6.6$ Hz, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.71 (s, 3H), 2.58 (s, 1H), 3.32 (d, $J = 4.8$ Hz, 1H), 4.08 (d, $J = 6.3$ Hz, 1H), 4.27 (d, $J = 6.3$ Hz, 1H), 4.81

(m, 1H), 4.93 (d, $J = 4.8$ Hz, 1H), 5.66 (d, $J = 6.8$ Hz, 1H), 7.27–7.31 (m, 2H), 7.33–7.44 (m, 3H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -2.9$ (CH_3), -2.2 (CH_3), 14.4 (CH_3), 18.5 (C), 20.2 (CH_3), 22.4 (CH_3), 25.7 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 28.2 (CH_3), 50.6 (C), 57.7 (CH_3), 69.1 (CH), 69.5 (C), 74.0 (CH), 75.7 (CH), 79.2 (CH), 84.5 (CH), 86.9 (C), 108.5 (C), 125.8 (CH), 128.8 (CH), 128.9 (CH), 133.8 (C), 152.6 (C), 177.0 (C) ppm.

HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{45}\text{NO}_7\text{Si}$: 582.2863; found: 582.2859 $\pm$ 5 ppm.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>. The experimental procedures and analytical data of all intermediates, described within this manuscript, can be found in the supporting information.

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Supporting Information

Synthetic Studies Towards an Advanced Precursor of the Jatrophone Diterpene Pl-4

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General methods

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum), unless noted otherwise.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DMSO and N,N-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphorus pentoxide and passage over aluminum oxide, neutral activity. Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diisopropylethylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/EtOAc or toluene/EtOAc. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [H_2SO_4 (conc., 22 mL), phosphormolybdic acid (20 g), $\text{Ce}(\text{SO}_4)_2$ (0.5 g), 378 mL H_2O] or silica gel impregnated with iodine.

Flash column chromatography was performed with silica gel 60 (0.040-0.063 μm , 240-400 mesh).

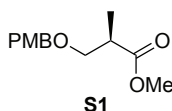
Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent.

NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in CDCl_3 solutions and referenced to the residual CDCl_3 signal (1H, $\delta = 7.26$, 13C, $\delta = 77.16$). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY).

IR spectra are reported in wave numbers (cm^{-1}). All compounds were measured using a single reflection monolithic diamond ATR module.

High resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer (acetonitrile/MeOH 1:1, +1% H_2O).

Experimental part

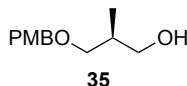


(*R*)-Methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (S1). To a solution of *R*-(-)-Roche ester (2.0 g, 16.9 mmol, 1.0 eq) in DCM (10 mL) were added a solution of *p*-methoxybenzyl trichloroacetimidate (1.1 M in hexanes, 23 mL, 23.35 mmol, 1.5 eq) and camphorsulfonic acid (314 mg, 1.35 mmol, 0.08 eq) successively. The reaction mixture was stirred for 12 hours at room temperature until TLC-control showed total consumption of the starting material. The reaction was quenched by the addition of saturated NaHCO₃ solution (15 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After flash column chromatography (hexane/EtOAc 19:1) **S1** (3.86 g) was isolated in 96% yield as a light yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 1.17 (d, *J* = 7.0 Hz, 3H), 2.72-2.81 (m, 1H), 3.46 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.63 (dd, *J* = 7.3, 9.0 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 6.84-6.90 (m, 2H), 7.21-7.25 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 14.2 (CH₃), 40.4 (CH), 51.9 (CH₃), 55.4 (CH₃), 71.8 (CH₂), 72.9 (CH₂), 113.9 (CH), 129.4 (CH), 130.4 (C), 159.4 (C), 175.5 (C) ppm.

These spectral characteristics are identical to those previously reported.^[1]

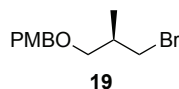


(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol (35). To a suspension of LiAlH₄ (603 mg, 15.9 mmol, 1.0 eq) in Et₂O (16 mL) was added a solution of **S1** (3.8 g, 15.9 mmol, 1.0 eq) in Et₂O (11 mL) at 0 °C. The reaction mixture was allowed to stir for 1 hour at 0 °C and additional 90 minutes at room temperature before it was quenched by the addition of H₂O (3 mL) and aqueous 15% NaOH (1.5 mL). After stirring for 15 min, MgSO₄ (heaped spoon) was added and the mixture was stirred for 30 minutes at room temperature. Afterwards the suspension was filtered over a plug of Celite and the filtrate was concentrated in vacuo. The crude material was purified by flash column chromatography (hexanes/EtOAc 5:1) delivering **35** (2.94 g) in 88% yield as a light yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.87 (d, *J* = 7.0 Hz, 3H), 1.99-2.12 (m, 1H), 2.51 (dd, *J* = 4.5, 6.8 Hz, 1H), 3.39 (dd, *J* = 8.3, 9.0 Hz, 1H), 3.53 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.56-3.67 (m, 2H), 3.81 (s, 3H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 6.85-6.90 (m, 2H), 7.22-7.27 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 13.6 (CH₃), 35.7 (CH), 55.4 (CH₃), 68.2 (CH₂), 73.2 (CH₂), 75.4 (CH₂), 114.0 (CH), 129.4 (CH), 130.3 (C), 159.4 (C) ppm.

These spectral characteristics are identical to those previously reported.^[1]

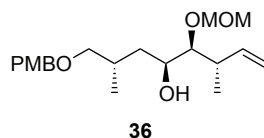


(R)-1-((3-Bromo-2-methylpropoxy)methyl)-4-methoxybenzene (19). A mixture of alcohol **35** (2.9 g, 14.2 mmol, 1.0 eq), CBr₄ (10.36 g, 31.24 mmol, 2.2 eq), pyridine (4.6 mL, 56.8 mmol, 4.0 eq) and PPh₃ (8.57 g, 32.66 mmol, 2.3 eq) in DCM (44 mL) was stirred at room temperature for 3 hours. The reaction mixture was transferred to a separatory funnel and washed once with aqueous 10% CuSO₄ solution (30 mL), saturated NaHCO₃ solution (30 mL) and H₂O (30 mL). Silica gel was added to the organic fraction and the solvent was removed under reduced pressure. The crude bromide, applicated on silica gel, was transferred to a chromatography column and eluted with hexane/EtOAc 40:1 affording **19** (3.27 g) in 84% yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 1.02 (d, *J* = 6.8 Hz, 3H), 2.07-2.18 (m, 1H), 3.34-3.42 (m, 2H), 3.44-3.53 (m, 2H), 3.81 (s, 3H), 4.45 (s, 2H), 6.86-6.91 (m, 2H), 7.23-7.28 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 16.0 (CH₃), 35.8 (CH), 38.4 (CH₂), 55.4 (CH₃), 72.7 (CH₂), 73.0 (CH₂), 114.0 (CH), 129.3 (CH), 130.6 (C), 159.4 (C) ppm.

These spectral characteristics are identical to those previously reported.^[1]



(2S,5S,6S)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (36). A solution of bromide **19** (590 mg, 2.16 mmol, 2.0 eq) in Et₂O (17 mL) was cooled to −78 °C and a solution of *t*-BuLi (1.6 M, 2.84 mL, 4.54 mmol, 4.2 eq) was added dropwise over 3 minutes. The reaction mixture was stirred for 10 minutes at that temperature before a freshly prepared MgBr₂ solution (1 M, 2.48 mL, 2.48 mmol, 2.3 eq) was added. After 10 minutes of stirring at −78 °C aldehyde **27** (171 mg, 1.08 mmol, 1.0 eq), dissolved in Et₂O (6.8 mL) was added dropwise *via* syringe over 3 minutes. The reaction mixture was allowed to stir at −78 °C for 90 minutes until TLC-control showed total consumption of aldehyde **5**. The reaction was terminated by the addition of a saturated, aqueous solution of NH₄Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting crude mixture of secondary alcohols was purified by flash column chromatography (hexane/EtOAc 9:1 to 5:1) providing **36** (342 mg) and **36a** (38 mg) as colorless oils, in a 9:1 diastereomeric ratio and 96% overall yield.

Major diastereomer (36):

¹H NMR (400 MHz, CDCl₃): δ = 0.93 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.22-1.31 (m, 1H), 1.52 (ddd, *J* = 4.3, 10.5, 13.8 Hz, 1H), 2.08-2.16 (m, 1H), 2.43-2.56 (m, 1H), 3.18 (dd, *J* = 3.9, 5.9 Hz, 1H), 3.23 (d, *J* = 3.9 Hz, 1H), 3.27-3.31 (m, 2H), 3.42 (s, 3H), 3.62-3.69 (m, 1H), 3.80

(s, 3H), 4.44 (s, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.99-5.02 (m, 1H), 5.02-5.06 (m, 1H), 5.76-5.88 (m, 1H), 6.84-6.90 (m, 2H), 7.22-7.28 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = 16.9$ (CH_3), 17.7 (CH_3), 30.4 (CH), 37.9 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.8 (CH), 72.6 (CH_2), 76.3 (CH_2), 88.7 (CH), 98.9 (CH_2), 113.6 (CH), 115.3 (CH_2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C) ppm.

IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 375.2148; found 375.2141 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}$ (c 1.0, CHCl_3) = $+6.3^\circ$.

Minor diastereomer (**36a**):

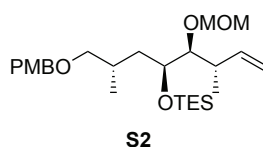
^1H NMR (400 MHz, CDCl_3): $\delta = 0.98$ (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 7.1$ Hz, 3H), 1.29-1.37 (m, 1H), 1.50-1.59 (m, 1H), 1.99-2.13 (m, 1H), 2.41-2.55 (m, 1H), 3.07 (d, $J = 4.5$ Hz, 1H), 3.18 (dd, $J = 3.9, 5.9$ Hz, 1H), 3.28-3.37 (m, 2H), 3.41 (s, 3H), 3.62-3.72 (m, 1H), 3.80 (s, 3H), 4.42 (s, 2H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.98-5.05 (m, 2H), 5.76-5.87 (m, 1H), 6.83-6.90 (m, 2H), 7.21-7.27 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = 17.5$ (CH_3), 18.7 (CH_3), 30.3 (CH), 38.1 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.9 (CH), 72.9 (CH_2), 75.0 (CH_2), 88.0 (CH), 98.8 (CH_2), 113.8 (CH), 115.3 (CH_2), 129.3 (CH), 130.9 (C), 139.9 (CH), 159.1 (C) ppm.

IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 375.2148; found 375.2145 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}$ (c 0.6, CHCl_3) = $+0.9^\circ$.



(5S)-5-((S)-But-3-en-2-yl)-8,8-diethyl-6-((S)-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,4,7-trioxa-8-siladecane (S2). To a solution of secondary alcohol **36** (660 mg, 1.9 mmol, 1.0 eq), imidazole (259 mg, 3.8 mmol, 2.0 eq) and DMAP (4 mg, 0.03 mmol, 0.02 eq) in DCM (9.5 mL) was added chlorotriethylsilane (0.64 mL, 3.8 mmol, 2.0 eq) at 0 °C. The mixture was stirred for 12 hours at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of NaHCO_3 (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 9:1) affording **S2** (0.82 g) in 93% yield as a colorless oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 0.61$ (quart, $J = 7.9$ Hz, 6H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 1.08 (d, $J = 7.1$ Hz, 3H), 1.29 (ddd, $J = 3.2, 9.7, 13.7$ Hz, 1H), 1.58 (ddd, $J = 3.2, 8.9, 13.7$ Hz, 1H), 1.88-2.01 (m, 1H), 2.44-2.56 (m, 1H), 3.22 (dd, $J = 7.0, 9.3$ Hz, 1H), 3.27-3.32 (m,

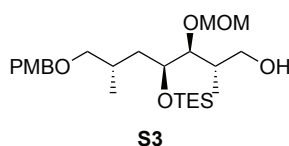
2H), 3.38 (s, 3H), 3.81 (s, 3H), 3.86-3.92 (m, 1H), 4.42 (s, 2H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.69 (d, $J = 6.8$ Hz, 1H), 4.95-5.03 (m, 2H), 5.87 (ddd, $J = 8.2, 10.3, 17.3$ Hz, 1H), 6.84-6.90 (m, 2H), 7.22-7.29 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = 5.4$ (CH_2), 7.1 (CH_3), 17.2 (CH_3), 18.9 (CH_3), 29.8 (CH), 36.8 (CH_2), 39.0 (CH), 55.4 (CH_3), 56.0 (CH_3), 72.1 (CH), 72.6 (CH_2), 76.4 (CH_2), 84.9 (CH), 98.1 (CH_2), 113.9 (CH), 114.3 (CH_2), 129.2 (CH), 131.1 (C), 141.8 (CH), 159.2 (C) ppm.

IR (ATR) ν 2953, 2930, 2876, 2362, 2341, 1513, 1461, 1302, 1249, 1147, 1099, 1037, 1004, 912 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{46}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$, 489.3013; found 489.3008 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = -21.1° .



(2S,3S,4S,6S)-7-((4-Methoxybenzyl)oxy)-3-(methoxymethoxy)-2,6-dimethyl-4-

((triethylsilyl)oxy)heptan-1-ol (S3). To a solution of *N*-methylmorpholine-*N*-oxide (376 mg, 3.21 mmol, 3.0 eq) in acetone/ H_2O 2:1 (7.5 mL) were added a solution of OsO_4 (0.16 M in H_2O , 338 μL , 0.05 mmol, 0.05 eq) and alkene **S2** (500 mg, 1.07 mmol, 1.0 eq) dissolved in acetone (1.25 mL) at room temperature. The reaction mixture was stirred for 3 hours until TLC-control showed total conversion of the starting material. After the addition of NaIO_4 (687 mg, 3.21 mmol, 3.0 eq), stirring was continued for additional 45 minutes before the mixture was filtered over a plug of Celite. The filtrate was extracted with DCM (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The resulting crude aldehyde was dissolved in MeOH (7.5 mL) and NaBH_4 (202 mg, 5.35 mmol, 5.0 eq) was added at 0°C . The reaction was allowed to stir for 45 minutes at that temperature before it was diluted with Et_2O (10 mL) and quenched by the addition of a saturated solution of NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude primary alcohol was further purified by flash column chromatography (hexane/ EtOAc 9:1 to 5:1) affording **S3** (439 mg) in 87% yield as a colorless oil.

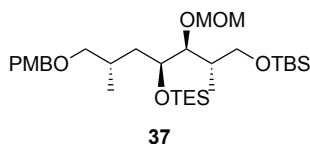
^1H NMR (400 MHz, CDCl_3): $\delta = 0.62$ (quart, $J = 7.9$ Hz, 6H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 1.03 (d, $J = 7.0$ Hz, 3H), 1.35 (ddd, $J = 3.8, 9.1, 13.6$ Hz, 1H), 1.53-1.62 (m, 1H), 1.88-2.0 (m, 2H), 2.73 (bt, $J = 6.4$ Hz, 1H), 3.23 (dd, $J = 6.7, 9.1$ Hz, 1H), 3.31 (dd, $J = 5.7, 9.1$ Hz, 1H), 3.41 (s, 3H), 3.43 (dd, $J = 7.6, 3.9$ Hz, 1H), 3.49-3.57 (m, 1H), 3.71-3.78 (m, 1H), 3.93-4.0 (m, 1H), 4.42 (s, 2H), 4.66 (d, $J = 6.7$ Hz, 1H), 4.70 (d, $J = 6.7$ Hz, 1H), 6.84-6.91 (m, 2H), 7.21-7.28 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 5.3 (CH_2), 7.1 (CH_3), 15.2 (CH_3), 17.3 (CH_3), 29.9 (CH), 36.0 (CH), 37.0 (CH_2), 55.4 (CH_3), 56.3 (CH_3), 66.3 (CH_2), 71.3 (CH), 72.7 (CH_2), 76.2 (CH_2), 85.0 (CH), 97.9 (CH_2), 113.9 (CH), 129.3 (CH), 131.0 (C), 159.2 (C) ppm.

IR (ATR) ν 3525, 2954, 2876, 1785, 1612, 1586, 1513, 1458, 1415, 1376, 1301, 1243, 1148, 1093, 1031, 938, 822, 725 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{46}\text{O}_6\text{Si}$ $[\text{M}+\text{Na}]^+$, 493.2962; found 493.2954 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = -32.7° .



(6S,7S,8S)-10,10-Diethyl-8-((S)-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-7-(methoxymethoxy)-2,2,3,3,6-pentamethyl-4,9-dioxo-3,10-disiladodecane (37). To a solution of alcohol **S3** (390 mg, 0.83 mmol, 1.0 eq) in DMF (3.5 mL) were added imidazole (68 mg, 1 mmol, 1.2 eq) and TBS-chloride (128 mg, 0.85 mmol, 1.02 eq) at room temperature. The mixture was stirred for 14 hours before the reaction was quenched by the addition of a saturated solution of NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under vacuum. Purification of the crude material by flash column chromatography (hexane/ EtOAc 19:1) delivered **37** (444 mg) in 91% yield as a colorless oil.

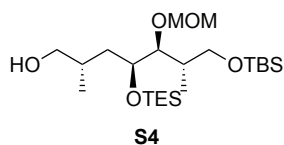
^1H NMR (400 MHz, CDCl_3): δ = 0.03 (s, 3H), 0.032 (s, 3H), 0.61 (quart, J = 7.8 Hz, 6H), 0.89 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.8 Hz, 9H), 1.01 (d, J = 7.0 Hz, 3H), 1.33 (ddd, J = 3.3, 9.4, 13.5 Hz, 1H), 1.54-1.61 (m, 1H), 1.76-1.87 (m, 1H), 1.92-2.03 (m, 1H), 3.23 (dd, J = 6.9, 9.2 Hz, 1H), 3.33 (dd, J = 5.7, 9.2 Hz, 1H), 3.37 (s, 3H), 3.39-3.44 (m, 1H), 3.56 (dd, J = 3.1, 9.4 Hz, 1H), 3.64 (dd, J = 5.1, 9.4 Hz, 1H), 3.81 (s, 3H), 3.96-4.01 (m, 1H), 4.43 (s, 2H), 4.64 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 6.84-6.89 (m, 2H), 7.23-7.29 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), 5.3 (CH_2), 7.2 (CH_3), 15.0 (CH_3), 17.3 (CH_3), 18.4 (C), 26.1 (CH_3), 29.7 (CH), 36.2 (CH_2), 36.9 (CH), 55.4 (CH_3), 55.9 (CH_3), 65.3 (CH_2), 71.7 (CH), 72.6 (CH_2), 76.4 (CH_2), 82.8 (CH), 98.3 (CH_2), 113.9 (CH), 129.3 (CH), 131.1 (C), 159.2 (C) ppm.

IR (ATR) ν 2954, 2877, 2361, 1789, 1513, 1416, 1247, 1148, 1095, 1033, 836 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{60}\text{O}_6\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 607.3826; found 607.3810 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = $+0.3^\circ$.



(2S,4S,5S,6S)-7-((tert-Butyldimethylsilyl)oxy)-5-(methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)oxy)heptan-1-ol (S4). To a solution of **37** (870 mg, 1.49 mmol, 1.0 eq) in DCM (74 mL) were added phosphate buffer (pH 7, 0.87 mL) and DDQ (507 mg, 2.24 mmol, 1.5 eq) at

0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and for 2 hours at room temperature when TLC-control showed total conversion of the starting material. The reaction was terminated by the addition of a saturated solution of NaHCO₃ (30 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was concentrated under vacuum. After purification by flash column chromatography (hexane/EtOAc 9:1), primary alcohol **S4** (596 mg) was isolated in 86% yield as a colorless oil.

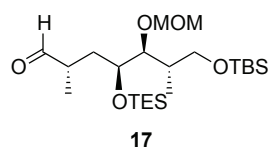
¹H NMR (400 MHz, CDCl₃): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.64 (quart, *J* = 8.0 Hz, 6H), 0.90 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.40 (ddd, *J* = 2.9, 8.5, 13.8 Hz, 1H), 1.53-1.64 (m, 2H), 1.76-1.88 (m, 2H), 3.37 (s, 3H), 3.42-3.51 (m, 3H), 3.55 (dd, *J* = 3.1, 9.5 Hz, 1H), 3.66 (dd, *J* = 4.9, 9.5 Hz, 1H), 3.97-4.04 (m, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -5.3 (CH₃), 5.3 (CH₂), 7.1 (CH₃), 15.0 (CH₃), 17.1 (CH₃), 18.4 (C), 26.1 (CH₃), 32.7 (CH), 35.7 (CH₂), 36.9 (CH), 55.9 (CH₃), 65.3 (CH₂), 69.2 (CH₂), 72.4 (CH), 82.6 (CH), 98.3 (CH₂) ppm.

IR (ATR) ν 2953, 2929, 2879, 2360, 2341, 1462, 1252, 1215, 1149, 1102, 1036, 940, 915 cm⁻¹.

HRMS (ESI) calcd for C₂₃H₅₂O₅Si₂ [M+Na]⁺, 487.3251; found 487.3252 +/- 5ppm.

Optical Rotation: [α]_D²⁰ (c 1.2, CHCl₃) = -3.9°.



(2*S*,4*S*,5*S*,6*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-(methoxymethoxy)-2,6-dimethyl-4-

((triethylsilyl)oxy)heptanal (17**).** To a mixture of alcohol **S4** (150 mg, 0.32 mmol, 1.0 eq) and DMSO (250 μL, 3.9 mmol, 12.0 eq) in DCM (2 mL) were added triethylamine (270 μL, 1.94 mmol, 6.0 eq) and SO₃·pyridine (155 mg, 0.97 mmol, 3.0 eq) at 0 °C. After the addition the cooling bath was removed and the reaction mixture was stirred for 3 hours at room temperature. The reaction was terminated by the addition of H₂O (2 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexane/EtOAc 19:1) delivering aldehyde **17** (137 mg) in 91% yield as a colorless oil.

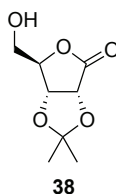
¹H NMR (400 MHz, CDCl₃): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.63 (quart, *J* = 7.7 Hz, 6H), 0.90 (s, 9H), 0.97 (t, *J* = 7.7 Hz, 9H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.50-1.57 (m, 1H), 1.76-1.88 (m, 1H), 1.96 (ddd, *J* = 6.0, 9.3, 14.0 Hz, 1H), 2.46-2.57 (m, 1H), 3.36 (s, 3H), 3.46 (dd, *J* = 3.8, 8.8 Hz, 1H), 3.55 (dd, *J* = 3.0, 9.6 Hz, 1H), 3.68 (dd, *J* = 4.7, 9.6 Hz, 1H), 3.98-4.03 (m, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 9.64 (d, *J* = 2.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.3$ (CH_3), 5.2 (CH_2), 7.1 (CH_3), 13.9 (CH_3), 14.9 (CH_3), 18.4 (C), 26.0 (CH_3), 33.0 (CH_2), 36.9 (CH), 43.5 (CH), 55.9 (CH), 65.2 (CH_2), 72.0 (CH), 82.3 (CH), 98.4 (CH_2), 205.2 (CH) ppm.

IR (ATR) ν 2955, 2930, 2856, 1728, 1707, 1472, 1460, 1415, 1252, 1148, 1100, 1066, 1032, 1004, 946, 916, 834, 775 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{50}\text{O}_5\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 485.3095; found 485.3102 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = +13.2°.



(3aR,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one

(38).^[2] A vigorously stirred solution of D-ribose (15 g, 100 mmol, 1.0 eq) and NaHCO_3 (16.8 g, 200 mmol, 2.0 eq) in H_2O (90 mL) was cooled to 0 °C and bromine (5.4 mL, 104 mmol, 1.04 eq) was added slowly (20 min) *via* an additional funnel. During the addition the temperature of the reaction mixture was controlled by an internal thermometer and did not exceed 5 °C. When the addition was completed the orange solution was stirred for an additional hour. Solid NaHSO_3 (1.26 g, 10 mmol, 0.1 eq) was added to destroy the excess of bromine. The water in the colorless reaction mixture was removed on a rotary evaporator (bath temperature 60 °C) until a yellow wet slurry remained. Afterwards EtOH (60 mL) and toluene (30 mL) were added to give a cloudy suspension and the solvent was removed under reduced pressure to give a damp solid. Again EtOH (60 mL) was added and the crude product mixture was heated to reflux on an oil bath for 30 minutes. The hot ethanolic suspension was filtered and the solids were rinsed once with hot EtOH (15 mL). The filtrate was cooled and stored in the refrigerator for 16 hours. The crystalline product was filtered, washed first with cold EtOH (10 mL), then with Et_2O (10 mL) and dried under vacuum to yield 20 g of crude product (the major contaminant is NaBr) The crude material was used without any further purification for the acetonide protection.

To a suspension of crude D-ribonolactone (20 g) in acetone (120 mL) was added boron trifluoride etherate (1.71 mL, 13.5 mmol, 0.1 eq) followed by 2,2-dimethoxypropane (24 mL, 19.6 mmol, 1.3 eq) at room temperature and the reaction mixture was stirred for 3 hours. The resulting yellow suspension was filtered through a pad of Celite, the solids were washed with acetone (15 mL) and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (50 mL), extracted with H_2O (40 mL) and brine (40 mL), respectively. The organic extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure delivering protected D-ribonolactone (**38**, 12.4 g) in 66% yield over two steps as a light yellow oil, which was used without any further purification for the next step.

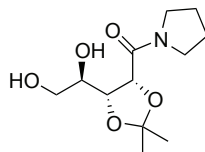
^1H NMR (400 MHz, CDCl_3): δ = 1.38 (s, 3H), 1.48 (s, 3H), 2.29 (t, J = 5.4 Hz, 1H, OH), 3.81 (ddd, J = 1.8, 5.6, 12.1 Hz, 1H), 4.0 (ddd, J = 2.5, 5.6, 12.1 Hz, 1H), 4.63 (bt, J = 2.0 Hz, 1H), 4.78 (d, J = 5.8 Hz, 1H), 4.83 (d, J = 5.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 25.6 (CH_3), 26.9 (CH_3), 62.2 (CH_2), 75.8 (CH), 78.4 (CH), 82.7 (CH), 113.3 (C), 174.9 (C) ppm.

IR (ATR) ν 3469, 2991, 1767, 1379, 1273, 1222, 1200, 1154, 1093, 975, 856, 810, 774 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_8\text{H}_{12}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 211.0583; found 211.0585 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -66.9^\circ$.



39

((4R,5R)-5-((R)-1,2-Dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (39). Protected D-ribonolactone **38** (500 mg, 2.7 mmol, 1.0 eq) was dissolved in toluene (11 mL). After the addition of pyrrolidine (1.1 mL, 13.5 mmol, 5.0 eq) the mixture was heated to reflux for 12 hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (DCM/MeOH 19:1) to afford amide **39** (610 mg) in 87% yield as a light yellow oil.

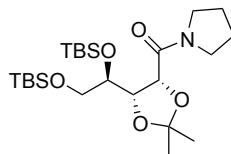
^1H NMR (400 MHz, CDCl_3): δ = 1.37 (s, 3H), 1.52 (s, 3H), 1.79-2.03 (m, 4H), 2.35 (bs, 1H, OH), 3.43-3.59 (m, 2H), 3.60-3.72 (m, 3H), 3.77-3.89 (m, 2H), 4.27 (dd, J = 6.3, 8.8 Hz, 1H), 4.59 (bs, 1H, OH), 4.84 (d, J = 6.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 23.8 (CH_2), 25.3 (CH_3), 26.5 (CH_2), 27.2 (CH_3), 47.02 (CH_2), 47.14 (CH_2), 64.5 (CH), 70.0 (CH), 76.7 (CH), 78.3 (CH), 109.9 (C), 167.8 (C) ppm.

IR (ATR) ν 3335, 2981, 2876, 1781, 1630, 1454, 1372, 1214, 1164, 1053, 907, 726 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_5$ $[\text{M}+\text{Na}]^+$, 282.1318; found 282.1321 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +16.2^\circ$.



S5

((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (S5). To a solution of diol **39** (250 mg, 0.96 mmol, 1.0 eq) in DCM (2 mL) were added 2,6-lutidine (0.335 mL, 2.88 mmol, 3.0eq) and TBS-triflate (0.706 mL, 3.07 mmol, 3.2 eq) at 0 $^\circ\text{C}$. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 15 hours. The reaction was quenched by the addition of a saturated solution of NaHCO_3 (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 , filtered

and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) to deliver **S5** (375 mg) in 80% yield as a slightly yellow oil.

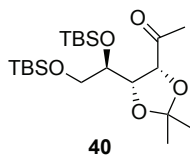
^1H NMR (400 MHz, CDCl_3): δ = 0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.35 (s, 3H), 1.48 (s, 3H), 1.74-2.0 (m, 4H), 3.36-3.55 (m, 3H), 3.60-3.69 (m, 1H), 3.74-3.77 (m, 2H), 4.37-4.41 (m, 2H), 4.67-4.70 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.4 (CH₃), -5.2 (CH₃), -4.5 (CH₃), -3.7 (CH₃), 18.3 (C), 18.6 (C), 24.2 (CH₂), 26.0 (CH₃), 26.05 (CH₃), 26.1 (CH₃), 26.4 (CH₂), 27.0 (CH₃), 46.1 (CH₂), 46.6 (CH₂), 64.7 (CH₂), 72.4 (CH), 74.6 (CH), 77.6 (CH), 110.4 (C), 167.3 (C) ppm.

IR (ATR) ν 2953, 2929, 2856, 1655, 1442, 1368, 1342, 1250, 1223, 1090, 992, 938, 831, 774 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{49}\text{NO}_5\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 510.3047; found 510.3048 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -46.7^\circ$.



1-((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)ethanone (40). A solution of MeLi (1.6 M in Et₂O, 6.4 mL, 20.5 mmol, 2.0 eq) was added to amide **S5** dissolved in THF (50 mL) at -78 °C. The reaction mixture was stirred for 15 minutes when TLC-control showed total consumption of the starting material. The reaction was terminated by the addition of H₂O (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). Further purification of crude ketone by flash column chromatography (hexane/EtOAc 40:1) delivered **40** (4.23 g) in 95% yield as a colorless oil.

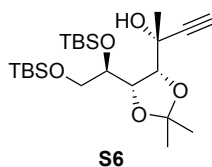
^1H NMR (400 MHz, CDCl_3): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.36 (s, 3H), 1.60 (s, 3H), 2.31 (s, 3H), 3.57 (dd, J = 5.1, 10.4 Hz, 1H), 3.74 (dd, J = 7.3 Hz, 10.4, 1H), 4.05 (ddd, J = 3.4, 5.1, 7.3 Hz, 1H), 4.38 (d, J = 7.8 Hz, 1H), 4.57 (dd, J = 3.4, 7.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH₃), -4.8 (CH₃), -4.1 (CH₃), 18.4 (CH₃), 18.6 (CH₃), 24.7 (CH₃), 26.1 (CH₃), 26.15 (CH₃), 26.7 (CH₃), 29.2 (CH₃), 63.9 (CH₂), 72.6 (CH), 79.8 (CH), 80.6 (CH), 109.1 (C), 209.3 (C) ppm.

IR (ATR) ν 2930, 2887, 2858, 1717, 1473, 1361, 1253, 1214, 1150, 1082, 939, 832, 776, 669 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{44}\text{O}_5\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 455.2625; found 455.2620 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -20.2^\circ$.



(R)-2-((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-yn-2-ol (S6). To a solution of methyl ketone **40** (5.0 g, 11.6 mmol, 1.0 eq) in THF (220 mL) was added a solution of ethynylmagnesium bromide (0.5 M in THF, 69 mL, 34.7 mmol, 3.0 eq) at 0 °C *via* a syringe. The reaction mixture was stirred for 2 hours at 0 °C and 90 minutes at room temperature. After TLC-analysis indicated complete consumption of the starting material, the reaction was quenched by the addition of H₂O (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification of the crude material by flash column chromatography (hexane/EtOAc 19:1 to 9:1) tertiary alcohol **S6** (5.13 g) was isolated as single diastereomer in 97% yield as a colorless oil.

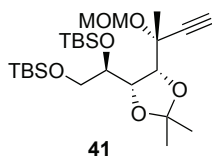
¹H NMR (400 MHz, CDCl₃): δ = 0.08 (s, 6H), 0.22 (s, 3H), 0.23 (s, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 1.34 (s, 3H), 1.52 (s, 3H), 1.56 (d, *J* = 0.98 Hz, 3H), 2.41 (s, 1H), 3.86 (dd, *J* = 3.4, 11.6 Hz, 1H), 3.92 (dd, *J* = 2.9, 11.6 Hz, 1H), 3.97 (d, *J* = 6.2 Hz, 1H), 4.37 (dd, *J* = 6.2, 8.5 Hz, 1H), 4.76-4.81 (m, 1H), 4.98 (d, *J* = 0.98 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -5.4 (CH₃), -5.2 (CH₃), -3.4 (CH₃), -3.2 (CH₃), 18.6 (C), 18.7 (C), 25.4 (CH₃), 26.1 (CH₃), 26.3 (CH₃), 27.3 (CH₃), 29.6 (CH₃), 64.0 (CH₂), 67.8 (C), 73.1 (CH), 73.3 (CH), 76.6 (CH), 82.9 (CH), 87.4 (C), 108.4 (C) ppm.

IR (ATR) ν 3312, 2986, 2930, 2885, 1472, 1410, 1254, 1172, 1084, 1053, 980, 895, 834, 779 cm⁻¹.

HRMS (ESI) calcd for C₂₃H₄₆O₅Si₂ [M+Na]⁺, 481.2782; found 481.2793 ± 5 ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = -1.6°.



(R)-5-((4S,5R)-5-((R)-2-(Methoxymethoxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (41). To a solution of tertiary alcohol **S6** (2.5 g, 5.46 mmol, 1.0 eq) in DCM (27 mL) were added DIPEA (5.68 mL, 32.8 mmol, 6.0 eq) and MOM-Cl (1.25 mL, 16.4 mmol, 3.0 eq) at 0 °C. The reaction mixture was warmed to 50 °C and was stirred for 24 hours before it was quenched by the addition of H₂O (15 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane/EtOAc 19:1) affording **41** (2.47 g) in 90% yield as a colorless oil.

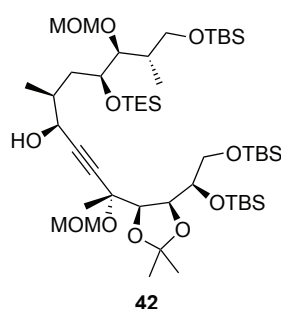
^1H NMR (400 MHz, CDCl_3): δ = 0.04 (s, 6H), 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.34 (s, 3H), 1.50 (s, 3H), 1.64 (s, 3H), 2.57 (s, 1H), 3.38 (s, 3H), 3.64 (dd, J = 6.8, 10.7 Hz, 1H), 3.94 (dd, J = 1.8, 10.7 Hz, 1H), 4.09 (d, J = 6.6 Hz, 1H), 4.24 (dd, J = 4.2, 6.6 Hz, 1H), 4.44 (ddd, J = 1.8, 4.3, 6.8 Hz, 1H), 4.71 (d, J = 7.5 Hz, 1H), 5.22 (d, J = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.2 (CH_3), -5.1 (CH_3), -4.6 (CH_3), -3.7 (CH_3), 18.5 (C), 18.6 (C), 25.1 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 55.9 (CH_3), 66.4 (CH_2), 72.3 (CH), 74.6 (C), 77.2 (CH), 81.7 (CH), 81.8 (CH), 82.7 (C), 92.8 (CH_2), 108.1 (C) ppm.

IR (ATR) ν 2929, 2887, 2856, 1463, 1380, 1371, 1251, 1135, 1092, 1056, 1021, 991, 833 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{50}\text{O}_6\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 525.3044; found 525.3033 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c 1.0, CHCl}_3) = -35.3^\circ$.



Alcohol 42.

LHMDS-method:

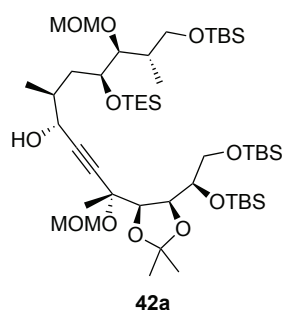
Preparation of a 0.5 M solution of LHMDS: To a solution of freshly distilled hexamethyldisilazane (0.22 mL, 1.04 mmol, 1.04 eq) in THF (1.4 mL) was added a solution of *n*-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol, 1.0 eq) at 0 °C. After the addition the reaction mixture was allowed to warm to room temperature and was stirred for 20 minutes.

A solution of freshly prepared LHMDS (0.5 M in THF, 0.73 mL, 0.36 mmol, 1.1 eq) was added to a solution of alkyne **41** (166 mg, 0.33 mmol, 1.0 eq) in dry THF (2.5 mL) at -78 °C. The reaction mixture was stirred for 2 h 30 min before it was warmed to -40 °C and dry CeCl_3 (81 mg, 0.33 mmol, 1.0 eq) was added. After stirring for an additional hour at 40 °C a solution of aldehyde **17** (91 mg, 0.2 mmol, 0.6 eq) in THF (1.3 mL) was added and the colorless solution was warmed to 0 °C and stirred for 20 minutes when TLC-analysis indicated total conversion of the aldehyde. The reaction was terminated by the addition of a saturated, aqueous solution of NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude secondary alcohols were purified by flash column chromatography (hexane/EtOAc 19:1) to obtain **42** (60 mg, less polar, minor diastereomer) and **42a** (100 mg, more polar, major diastereomer) in a 2:1 diastereomeric ratio and 84% overall yield as a colorless oils.

t-BuLi method:

To a solution of alkyne **41** (171 mg, 0.34 mmol, 2.0 eq) and HMPA (106 μL , 0.612 mmol, 3.6 eq) in THF (2.8 mL) was added *t*-BuLi (1.7 M in pentane, 200 μL , 0.34 mmol, 2.0 eq) at -78 °C. After

stirring for 30 minutes at that temperature, 30 μL of the reaction mixture were removed *via* a syringe and quenched by the addition of D_2O (mini-quench). According to the following ^1H -NMR-experiment, which indicated a 50% lithiation of the alkyne, two additional equivalents of *t*-BuLi (200 μL) were added. After 25 minutes, complete lithiation was indicated by another mini-quench experiment, and a solution of aldehyde **17** (80 mg, 0.17 mmol, 1.0 eq) in THF (1.0 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 2:1 diastereomeric ratio (**42**, less polar, minor diastereomer, 54 mg, and **42a**, more polar, major diastereomer, 108 mg) and 80% overall yield as colorless oils.



Alcohol 42a (major diastereomer):

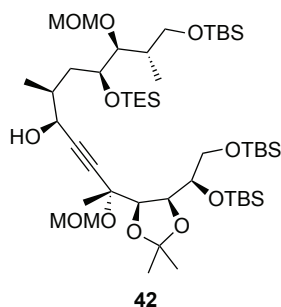
^1H NMR (400 MHz, CDCl_3): δ = 0.03 (s, 3H), 0.031 (s, 3H), 0.06 (s, 3H), 0.08 (s, 6H), 0.10 (s, 3H), 0.63 (quart, J = 7.8 Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.96 (t, J = 7.8 Hz, 6H), 1.02 (d, J = 5.1 Hz, 3H), 1.04 (d, J = 5.3 Hz, 3H), 1.33 (s, 3H), 1.37-1.46 (m, 1H), 1.50 (s, 3H), 1.62 (s, 3H), 1.73-1.83 (m, 2H), 1.85-1.93 (m, 1H), 2.75 (bd, J = 5.3 Hz, OH), 3.36 (s, 3H), 3.37 (s, 3H), 3.45 (dd, J = 3.8, 8.8 Hz, 1H), 3.53 (dd, J = 3.2, 9.7 Hz, 1H), 3.67 (dd, J = 4.6, 9.7 Hz, 1H), 3.71 (dd, J = 6.3, 10.8 Hz, 1H), 3.92 (dd, J = 1.8, 10.8 Hz, 1H), 3.96-4.01 (m, 1H), 4.05 (d, J = 6.3 Hz, 1H), 4.21-4.28 (m, 2H), 4.42-4.48 (m, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 6.6 Hz, 1H), 5.21 (d, J = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), -5.1 (CH_3), -5.0 (CH_3), -4.5 (CH_3), -3.6 (CH_3), 5.3 (CH_2), 7.1 (CH_3), 14.9 (CH_3), 15.5 (CH_3), 18.4 (C), 18.5 (C), 18.7 (C), 25.2 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 27.4 (CH_3), 34.5 (CH_2), 36.2 (CH), 37.0 (CH), 55.81 (OCH_3), 55.84 (OCH_3), 65.3 (CH_2), 66.4 (CH_2), 67.3 (CH), 72.0 (CH), 72.2 (CH), 74.7 (C), 81.3 (CH), 81.9 (CH), 82.5 (CH), 84.6 (C), 89.4 (C), 92.6 (C), 98.3 (C), 108.0 (C) ppm.

IR (ATR) ν 3409, 2953, 2929, 2856, 1462, 1380, 1252, 1216, 1144, 1097, 1032, 986, 919, 833, 775, 667 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{48}\text{H}_{100}\text{O}_{11}\text{Si}_4$ $[\text{M}+\text{Na}]^+$, 987.6241; found 987.6235 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -27.9^\circ$.

**Alcohol 42 (minor diastereomer):**

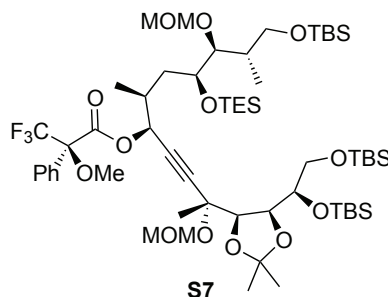
^1H NMR (400 MHz, CDCl_3): δ = 0.03 (s, 3H), 0.032 (s, 3H), 0.08 (s, 3H), 0.084 (s, 6H), 0.13 (s, 3H), 0.62 (quart, J = 7.9 Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.03 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.40-1.48 (m, 1H), 1.50 (s, 3H), 1.63 (s, 3H), 1.64-1.70 (m, 1H), 1.76-1.87 (m, 1H), 1.90-2.0 (m, 1H), 3.35 (s, 3H), 3.37 (s, 3H), 3.42 (dd, J = 3.8, 8.6 Hz, 1H), 3.53-3.58 (m, 2H), 3.66 (dd, J = 5.1, 9.6 Hz, 1H), 3.73 (dd, J = 7.1, 10.9 Hz, 1H), 3.94-4.04 (m, 2H), 4.08 (d, J = 6.6 Hz, 1H), 4.25-4.31 (m, 2H), 4.43-4.48 (m, 1H), 4.63 (d, J = 7.3 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.70 (d, J = 6.6 Hz, 1H), 5.27 (d, J = 7.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), -5.2 (CH_3), -4.6 (CH_3), -3.7 (CH_3), 5.3 (CH_2), 7.2 (CH_3), 15.0 (CH_3), 15.1 (CH_3), 18.41 (C), 18.43 (C), 19.0 (C), 25.2 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 27.9 (CH_3), 35.2 (CH), 35.3 (CH_2), 36.9 (CH), 55.87 (CH_3), 55.90 (CH_3), 65.3 (CH_2), 67.0 (CH), 67.5 (CH_2), 71.9 (CH), 72.3 (CH), 74.3 (C), 82.0 (CH), 82.2 (CH), 82.7 (CH), 84.4 (C), 89.8 (C), 92.5 (CH_2), 98.3 (CH_2), 108.2 (C) ppm.

IR (ATR) ν 3409, 2953, 2929, 2856, 1462, 1380, 1252, 1216, 1144, 1097, 1032, 986, 919, 833, 775, 667 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{48}\text{H}_{100}\text{O}_{11}\text{Si}_4$ $[\text{M}+\text{Na}]^+$, 987.6241; found 987.6260 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -19.9^\circ$.



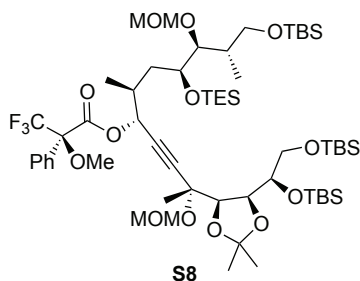
Mosher ester S7. To a solution of secondary alcohol **42** (minor diastereomer, 10 mg, 0.01 mmol, 1.0 eq) in DCM (0.3 mL) were added NEt_3 (17 μL , 0.12 mmol, 12.0 eq), DMAP (1.2 mg, 0.01 mmol, 1.0 eq) and *S*-(+)-Mosher's acid chloride (3.7 μL , 0.02 mmol, 2.0 eq) sequentially at room temperature. The reaction mixture was stirred for 4 hours at room temperature. As TLC-control showed total conversion of the starting material the reaction was terminated by the addition of a saturated, aqueous solution of NH_4Cl (5 mL) and the resulting mixture was diluted with DCM

(5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic fractions were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1) to afford Mosher-ester **S7** (12 mg) in quantitative yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.041 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.57-0.63 (m, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.30 (s, 3H), 1.36-1.40 (m, 1H), 1.41 (s, 3H), 1.58 (s, 3H), 1.62-1.73 (m, 2H), 2.08-2.16 (m, 1H), 3.34 (s, 3H), 3.342 (s, 3H), 3.43 (dd, *J* = 3.6, 9.2 Hz, 1H), 3.50 (dd, *J* = 3.0, 9.4 Hz, 1H), 3.53 (s, 3H), 3.67 (dd, *J* = 4.5, 9.4 Hz, 1H), 3.76 (dd, *J* = 4.2, 10.6 Hz, 1H), 3.79 (dd, *J* = 2.0, 10.6 Hz, 1H), 3.94-3.98 (m, 1H), 3.98 (d, *J* = 5.3 Hz, 1H), 4.23 (dd, *J* = 6.1, 5.9 Hz, 1H), 4.35-4.39 (m, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 5.17 (d, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 5.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -5.37 (CH₃), -5.36 (CH₃), -5.30 (CH₃), -5.28 (CH₃), -4.2 (CH₃), -3.6 (CH₃), 5.2 (CH₂), 7.0 (CH₃), 14.7 (CH₃), 14.8 (CH₃), 18.4 (C), 18.48 (C), 18.5 (C), 25.3 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 26.8 (CH₃), 26.9 (CH₃), 33.8 (CH), 34.5 (CH₂), 36.9 (CH), 55.5 (CH₃), 55.8 (CH₃), 55.81 (CH₃), 65.2 (CH₂), 65.5 (CH₂), 71.3 (CH), 71.7 (CH), 71.8 (CH), 74.9 (C), 79.6 (CH), 81.9 (CH), 82.3 (CH), 83.2 (C), 87.0 (C), 92.9 (CH₂), 98.3 (CH₂), 107.7 (C), 122.0 (C), 124.8 (C), 127.7 (CH), 128.5 (CH), 129.7 (CH), 132.2 (C), 165.5 (C) ppm.

HRMS (ESI) calcd for C₅₈H₁₀₇F₃O₁₃Si₄ [M+Na]⁺, 1203.6639; found 1203.6633 +/- 5ppm.



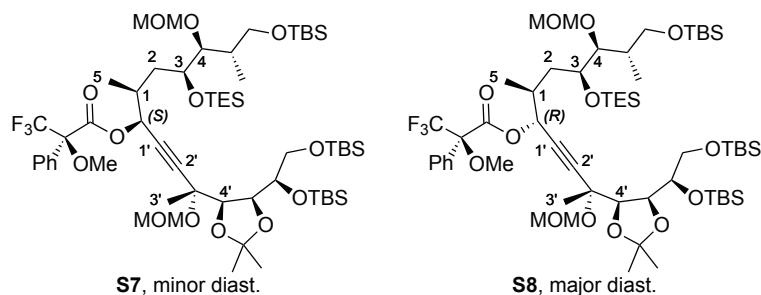
Mosher-ester S8. Mosher-ester **S8** was prepared following the same procedure as described above. Starting from diastereomeric alcohol **42a** (major diastereomer, 10 mg, 0.01 mmol, 1.0 eq) and *S*-(+)-Mosher's acid chloride, **S8** (12 mg) was afforded in quantitative yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.02 (s, 3H), 0.024 (s, 3H), 0.027 (s, 3H), 0.03 (s, 3H), 0.08 (s, 3H), 0.1 (s, 3H), 0.55-0.63 (m, 6H), 0.88 (s, 9H), 0.89 (s, 18H), 0.94 (t, *J* = 8.1 Hz, 9H), 0.97 (d, *J* = 7.3 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 3H), 1.34-1.42 (m, 1H), 1.46 (s, 3H), 1.57-1.61 (m, 1H), 1.62 (s, 3H), 1.63-.68 (m, 1H), 2.06-2.13 (m, 1H), 3.31 (s, 3H), 3.34 (s, 3H), 3.38 (dd, *J* = 4.0, 8.8 Hz, 1H), 3.49 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.56 (s, 3H), 3.64 (dd, *J* = 4.6, 9.6 Hz, 1H), 3.74 (dd, *J* = 4.3, 10.7 Hz, 1H), 3.81 (dd, *J* = 2.0, 10.7 Hz, 1H), 3.91-3.96 (m, 1H), 4.0 (d, *J* = 5.8 Hz, 1H), 4.24 (dd, *J* = 5.8, 6.3 Hz, 1H), 4.38-4.42 (m, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 7.5 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 7.5 Hz, 1H), 5.60 (d, *J* = 4.0 Hz, 1H) ppm.

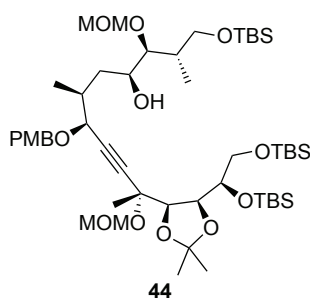
^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.4$ (CH_3), -5.28 (CH_3), -5.27 (CH_3), -4.2 (CH_3), -3.5 (CH_3), 5.2 (CH_2), 7.1 (CH_3), 14.4 (CH_3), 14.7 (CH_3), 18.4 (C), 18.5 (C), 18.6 (C), 25.4 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 33.9 (CH_2), 34.2 (CH), 36.8 (CH), 55.6 (CH_3), 55.7 (CH_3), 55.8 (CH_3), 65.2 (CH_2), 65.4 (CH_2), 71.0 (CH), 71.6 (CH), 71.9 (CH), 75.1 (C), 79.6 (CH), 81.9 (CH), 82.5 (CH), 84.1 (C), 87.0 (C), 92.8 (CH_2), 98.3 (CH_2), 107.9 (C), 122.0 (C), 124.8 (C), 127.6 (CH), 128.6 (CH), 129.7 (CH), 132.5 (C), 165.6 (C) ppm.

HRMS (ESI) calcd for $\text{C}_{58}\text{H}_{107}\text{F}_3\text{O}_{13}\text{Si}_4$ $[\text{M}+\text{Na}]^+$, 1203.6639; found 1203.6638 $\pm$ 5 ppm.

Mosher-ester Analysis:



Proton	S7 (S-configured) ppm	S8 (R-configured) ppm	Diff. S7-S8 ($d_S d_R$) ppm
CH-1	2.12	2.10	+0.02
CH ₂ -2a	1.65	1.59	+0.06
CH ₂ -2b	1.38	1.36	+0.02
CH-3	3.97	3.93	+0.04
CH-4	3.43	3.38	+0.05
CH ₃ -5	1.05	1.03	+0.02
CH ₃ -4'	3.98	4.00	-0.02
CH ₃ -5'	1.58	1.62	-0.04



Alcohol 44. To a solution of alcohol **42** (110 mg, 0.11 mmol, 1.0 eq) in DMF (2 mL) was added NaH (60% dispersion in mineral oil, 9.1 mg, 0.22 mmol, 2 eq) at 0 °C. After 30 minutes, PMB-Cl (28 μL , 0.21 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for 2 hours at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO_3 (3 mL). After dilution with Et_2O (5 mL) the layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with H_2O once (10 mL), dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The

crude product was further purified by flash column chromatography (hexane/EtOAc 19:1 to 5:1) to provide **44** (65 mg) in 59% yield as a colorless oil.

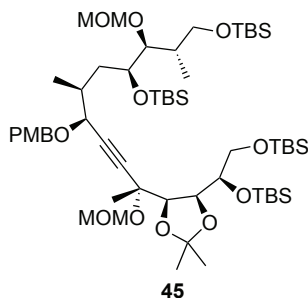
^1H NMR (400 MHz, CDCl_3): δ = 0.00 (s, 6H), 0.04 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 0.96 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H), 1.20-1.29 (m, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 1.64 (s, 3H), 1.79 (ddd, J = 4.0, 10.9, 13.6 Hz, 1H), 1.90-2.01 (m, 1H), 2.11-2.22 (m, 1H), 2.82 (d, J = 6.6 Hz, 1H), 3.26 (dd, J = 3.5, 5.6 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.54 (dd, J = 5.8, 9.9 Hz, 1H), 3.63 (dd, J = 5.6, 9.9 Hz, 1H), 3.68-3.76 (m, 1H), 3.73 (dd, J = 4.2, 10.5 Hz, 1H), 3.76-3.81 (m, 4H), 3.99 (d, J = 6.1 Hz, 1H), 4.05 (d, J = 6.1 Hz, 1H), 4.26 (dd, J = 6.1, 5.9 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.42-4.47 (m, 1H), 4.66 (d, J = 7.5 Hz, 1H), 4.67 (d, J = 6.5 Hz, 1H), 4.70 (d, J = 6.5 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 5.30 (d, J = 7.3 Hz, 1H), 6.83-6.88 (m, 2H), 7.22-7.28 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.3 (CH_3), -4.2 (CH_3), -3.5 (CH_3), 14.7 (CH_3), 15.8 (CH_3), 18.45 (C), 18.50 (CH), 18.54 (C), 25.5 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 35.0 (CH), 38.0 (CH_2), 38.1 (CH), 55.4 (CH_3), 55.8 (CH_3), 56.2 (CH_3), 64.4 (CH_2), 65.6 (CH_2), 69.2 (CH), 70.2 (CH_2), 71.7 (CH), 73.7 (CH), 75.1 (C), 79.8 (CH), 82.1 (CH), 85.7 (CH), 85.9 (C), 87.3 (C), 92.8 (CH_2), 98.6 (CH_2), 107.8 (C), 113.9 (CH), 129.5 (CH), 130.4 (C), 159.3 (C) ppm.

IR (ATR) ν 3467, 2929, 2856, 2360, 2340, 1614, 1514, 1463, 1379, 1250, 1142, 1054, 833, 775 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{94}\text{O}_{12}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 993.5951; found 993.5960 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -100.1^\circ$.



Alkyne 45. To a solution of secondary alcohol **44** (60 mg, 0.062 mmol, 1.0 eq) and 2,6-lutidine (44 μL , 0.372 mmol, 6.0 eq) in DCM (1.0 mL) was added TBS-triflate (42 μL , 0.186 mmol, 3.0 eq) at 0°C . The reaction mixture was allowed to stir for 48 hours at room temperature before it was quenched by the addition of a saturated, aqueous solution of NaHCO_3 (5 mL). After dilution with DCM (5 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) **45** (30 mg) was isolated in 45% yield (85% brsm) as a light yellow oil.

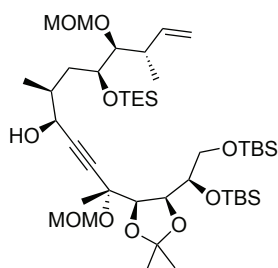
^1H NMR (400 MHz, CDCl_3): δ = 0.02 (s, 9H), 0.03 (s, 3H), 0.05 (s, 3H), 0.09 (s, 6H), 0.11 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 1.00 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.33 (s, 3H), 1.39-1.49 (m, 1H), 1.50 (s, 3H), 1.64 (s, 3H), 1.71-1.81 (m, 2H), 1.94-2.07 (m, 1H), 3.36 (s, 6H), 3.43 (dd, J = 3.5, 9.1 Hz, 1H), 3.53 (dd, J = 3.0, 9.3 Hz, 1H), 3.66 (dd, J = 4.7, 9.3 Hz, 1H), 3.76 (dd, J = 4.5, 10.6 Hz, 1H), 3.80 (s, 3H), 3.84 (dd, J = 2.0, 10.6 Hz, 1H), 3.92-3.97 (m, 1H), 3.98 (d, J = 4.8 Hz, 1H), 4.04 (d, J = 6.1 Hz, 1H), 4.26 (dd, J = 6.1, 6.3 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 4.44-4.49 (m, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.65 (d, J = 7.3 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 5.24 (d, J = 7.3 Hz, 1H), 6.83-6.88 (m, 2H), 7.22-7.26 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.1 (CH_3), -5.0 (CH_3), -4.5 (CH_3), -4.0 (CH_3), -3.4 (CH_3), -3.3 (CH_3), 15.2 (CH_3), 15.5 (CH_3), 18.4 (C), 18.6 (C), 18.7 (C), 18.8 (C), 25.7 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 26.45 (CH_3), 27.3 (CH_3), 27.7 (CH_3), 34.7 (CH), 34.9 (CH_2), 37.2 (CH), 55.6 (CH_3), 56.01 (CH_3), 56.03 (CH_3), 65.5 (CH_2), 65.9 (CH_2), 70.5 (CH_2), 71.9 (CH), 72.3 (CH), 74.0 (CH), 75.3 (C), 80.2 (CH), 82.2 (CH), 82.6 (CH), 86.0 (C), 87.5 (C), 93.0 (CH_2), 98.5 (CH_2), 108.0 (C), 114.0 (CH), 129.7 (CH), 130.8 (C), 159.5 (C) ppm.

IR (ATR) ν 2927, 2856, 2365, 1614, 1519, 1475, 1379, 1250, 1140, 1078, 1035, 837, 779 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{56}\text{H}_{108}\text{O}_{12}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 1107.6816; found 1107.6810 $\pm$ 5 ppm.

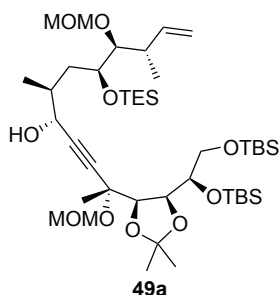
Optical Rotation: $[\alpha]_D^{20}(\text{c } 0.88, \text{CHCl}_3) = -6.3^\circ$.



49

Alcohol 49. Alcohol **49** was prepared following the same procedures as described for alcohol **42** above.

Method	Alkyne (41)	Aldehyde (48)	Yield	<i>dr</i> 49:49a
LHMDS (0.5 M in THF), 1.1 eq CeCl ₃ , 1 eq	241 mg, 0.48 mmol, 1.0 eq	100 mg, 0.29 mmol, 0.6 eq	90%	1:2
t-BuLi (1.7 M in pentane), 2.0 eq, HMPA, 3.6 eq	231 mg, 0.46 mmol, 2.0 eq	80 mg, 0.23 mmol, 1.0 eq	60%	1:2

**Alcohol 49a (major diastereomer):**

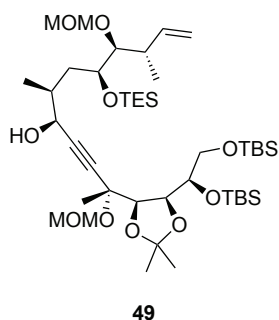
^1H NMR (400 MHz, CDCl_3): δ = 0.07 (s, 3H), 0.09 (s, 6H), 0.10 (s, 3H), 0.62 (quart, J = 7.9 Hz, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 0.97 (t, J = 7.9 Hz, 9H), 1.00 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.34 (s, 3H), 1.36-1.44 (m, 1H), 1.50 (s, 3H), 1.62 (s, 3H), 1.72-1.81 (m, 1H), 1.82-1.92 (m, 1H), 2.41-2.56 (m, 1H), 2.70 (d, J = 5.8 Hz, 1H), 3.29 (dd, J = 5.1, 5.3 Hz, 1H), 3.36 (s, 3H), 3.38 (s, 3H), 3.70 (dd, J = 6.4, 11.0 Hz, 1H), 3.84-3.90 (m, 1H), 3.92 (dd, J = 1.5, 11.0 Hz, 1H), 4.05 (d, J = 6.3 Hz, 1H), 4.21-4.27 (m, 2H), 4.42-4.48 (m, 1H), 4.61 (d, J = 7.1 Hz, 1H), 4.65 (d, J = 7.3 Hz, 1H), 4.70 (d, J = 7.1 Hz, 1H), 4.95-5.04 (m, 2H), 5.22 (d, J = 7.3 Hz, 1H), 5.87 (ddd, J = 8.2, 10.0, 17.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -5.1 (CH_3), -4.9 (CH_3), -4.5 (CH_3), -3.6 (CH_3), 5.3 (CH_2), 7.1 (CH_3), 15.5 (CH_3), 18.5 (C), 18.7 (C), 19.0 (CH_3), 25.2 (CH_3), 26.2 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 27.5 (CH_3), 35.2 (CH_2), 36.1 (CH), 39.0 (CH), 55.8 (CH_3), 56.0 (CH_3), 66.4 (CH_2), 67.2 (CH), 72.0 (CH), 72.4 (CH), 74.7 (C), 81.4 (CH), 81.9 (CH), 84.6 (C), 84.9 (CH), 89.2 (C), 92.6 (CH_2), 98.2 (CH_2), 108.0 (C), 114.5 (CH_2), 141.6 (CH) ppm.

IR (ATR) ν 3372, 2954, 2883, 2363, 2340, 1462, 1379, 1251, 1141, 1096, 1036, 833, 775 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{43}\text{H}_{86}\text{O}_{10}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 869.5427; found 869.5428 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.15, \text{CHCl}_3) = -50.1^\circ$.

**Alcohol 49 (minor diastereomer):**

^1H NMR (400 MHz, CDCl_3): δ = 0.08 (s, 3H), 0.09 (s, 6H), 0.13 (s, 3H), 0.62 (quart, J = 8.0 Hz, 6H), 0.91 (s, 9H), 0.92 (s, 9H), 0.97 (t, J = 8.0 Hz, 9H), 1.03 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.36-1.44 (m, 1H), 1.50 (s, 3H), 1.64 (s, 3H), 1.64-1.70 (m, 1H), 1.86-1.98 (m, 1H), 2.44-2.56 (m, 1H), 3.29 (dd, J = 5.3, 5.3 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.57 (d, J = 3.0 Hz, 1H), 3.73 (dd, J = 7.2, 11.0 Hz, 1H), 3.86 (ddd, J = 2.9, 5.3, 8.7 Hz, 1H), 4.01 (dd, J = 1.8, 11.0 Hz, 1H), 4.08 (d, J = 6.8 Hz, 1H), 4.24 (dd, J = 3.0, 5.2 Hz, 1H), 4.28 (dd, J = 6.8, 2.8 Hz,

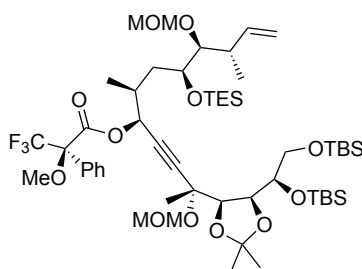
1H), 4.42-4.48 (m, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.63 (d, $J = 7.4$ Hz, 1H), 4.70 (d, $J = 6.6$ Hz, 1H), 4.95-5.05 (m, 2H), 5.28 (d, $J = 7.4$ Hz, 1H), 5.87 (ddd, $J = 8.3, 10.2, 17.3$ Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.2$ (CH_3), -4.7 (CH_3), -4.6 (CH_3), -3.7 (CH_3), 5.4 (CH_2), 7.1 (CH_3), 15.2 (CH_3), 18.4 (C), 18.8 (CH_3), 19.0 (C), 25.2 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 28.0 (CH_3), 35.2 (CH), 36.0 (CH_2), 39.0 (CH), 55.9 (CH_3), 56.0 (CH_3), 67.0 (CH), 67.4 (CH_2), 72.2 (CH), 72.3 (CH), 74.3 (C), 82.0 (CH), 82.2 (CH), 84.3 (C), 85.0 (CH), 90.0 (C), 92.5 (CH_2), 98.2 (CH_2), 108.2 (C), 114.4 (CH_2), 141.6 (CH) ppm.

IR (ATR) ν 3372, 2954, 2883, 2363, 2340, 1462, 1379, 1251, 1141, 1096, 1036, 833, 775 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{43}\text{H}_{86}\text{O}_{10}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 869.5427; found 869.5416 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 0.8, \text{CHCl}_3) = -31.0^\circ$.



S9

Mosher-ester S9. To a solution of secondary alcohol **49** (minor diastereomer, 10 mg, 0.012 mmol, 1.0 eq) in DCM (0.15 mL) were added NEt_3 (22 μL , 0.144 mmol, 12.0 eq), DMAP (1.5 mg, 0.012 mmol, 1.0 eq) and *S*-(+)-Mosher's acid chloride (4.7 μL , 0.024 mmol, 2.0 eq) sequentially at room temperature. The reaction mixture was stirred for 14 hours at room temperature. As TLC-control showed total consumption of the starting material the reaction was terminated by the addition of a saturated, aqueous solution of NH_4Cl (5 mL) and the resulting mixture was diluted with DCM (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexane/EtOAc 19:1) to afford Mosher-ester **S9** (12.8 mg) in quantitative yield as a colorless oil.

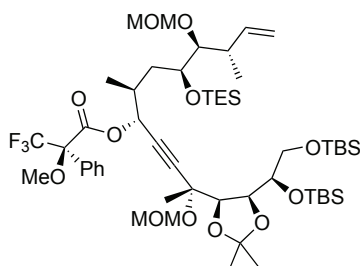
^1H NMR (400 MHz, CDCl_3): $\delta = 0.04$ (s, 6H), 0.08 (s, 3H), 0.11 (s, 3H), 0.59 (quart, $J = 7.6$ Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.96 (t, $J = 7.6$ Hz, 9H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.30 (s, 3H), 1.32-1.41 (m, 1H), 1.42 (s, 3H), 1.58 (s, 3H), 1.60-1.69 (m, 1H), 2.02-2.15 (m, 1H), 2.39-2.49 (m, 1H), 3.27 (dd, $J = 5.1, 5.3$ Hz, 1H), 3.34 (s, 3H), 3.36 (s, 3H), 3.53 (s, 3H), 3.76 (dd, $J = 4.0, 10.6$ Hz, 1H), 3.80 (dd, $J = 2.3, 10.6$ Hz, 1H), 3.85 (ddd, $J = 1.8, 5.3, 9.6$ Hz, 1H), 3.99 (d, $J = 5.8$ Hz, 1H), 4.23 (dd, $J = 5.8, 6.2$ Hz, 1H), 4.34-4.40 (m, 1H), 4.59 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 7.6$ Hz, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 4.92-5.01 (m, 2H), 5.17 (d, $J = 7.6$ Hz, 1H), 5.48 (d, $J = 5.6$ Hz, 1H), 5.85 (ddd, $J = 8.4, 10.2, 17.3$ Hz, 1H), 7.37-7.42 (m, 3H), 7.51-7.55 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.3$ (CH_3), -5.2 (CH_3), -4.2 (CH_3), -3.5 (CH_3), 5.3 (CH_2), 7.1 (CH_3), 14.8 (CH_3), 18.4 (C), 18.5 (C), 19.1 (CH_3), 25.3 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 33.9 (CH), 35.3 (CH_2), 38.8 (CH), 55.4 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 65.5 (CH_2), 71.2 (CH), 71.7 (CH), 71.9 (CH), 74.9 (C), 79.7 (CH), 81.9 (CH), 83.2 (C), 84.9 (CH), 87.1 (C), 92.9 (CH_2), 98.1 (CH_2), 107.8 (C), 114.5 (CH_2), 122.0 (C), 124.8 (C), 127.8 (CH), 128.5 (CH), 129.7 (CH), 132.2 (C), 141.5 (CH), 165.5 (C) ppm.

IR (ATR) ν 2956, 2878, 2361, 1754, 1719, 1462, 1251, 1171, 1106, 1015, 834, 777 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{53}\text{H}_{93}\text{F}_3\text{O}_{12}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 1085.5825; found 1085.5832 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 0.63, \text{CHCl}_3) = -44.3^\circ$.



S10

Mosher-ester S10. Mosher-ester **S10** was prepared following the same procedure as described above. Starting from diastereomeric alcohol **49a** (major diastereomer, 10 mg, 0.01 mmol, 1.0 eq) and *S*-(+)-Mosher's acid chloride, **S10** (12.4 mg) was afforded in 97% yield as a colorless oil.

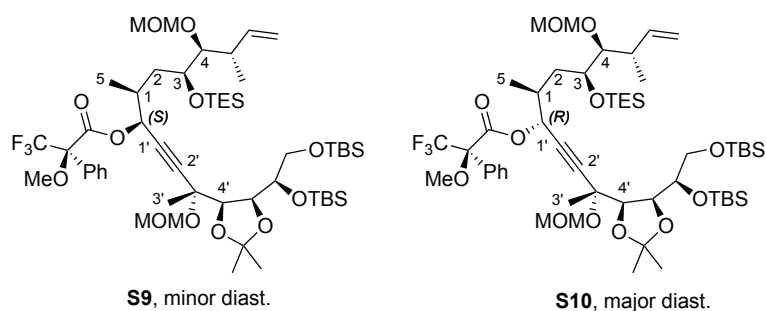
^1H NMR (400 MHz, CDCl_3): $\delta = 0.03$ (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 1.58 (quart, $J = 8.0$ Hz, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.95 (t, $J = 8.0$ Hz, 9H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 7.1$ Hz, 3H), 1.31 (s, 3H), 1.31 - 1.38 (m, 1H), 1.45 (s, 3H), 1.56 - 1.64 (m, 1H), 1.62 (s, 3H), 1.99 - 2.11 (m, 1H), 2.28 - 2.41 (m, 1H), 3.22 (dd, $J = 5.1, 5.1$ Hz, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 3.57 (s, 3H), 3.74 (dd, $J = 4.6, 10.6$ Hz, 1H), 3.78 - 3.82 (m, 1H), 3.82 (dd, $J = 2.0, 10.6$ Hz, 1H), 4.0 (d, $J = 5.8$ Hz, 1H), 4.24 (dd, $J = 5.8, 6.4$ Hz, 1H), 4.40 (ddd, $J = 2.0, 4.5, 6.4$ Hz, 1H), 4.58 (d, $J = 6.8$ Hz, 1H), 4.61 (d, $J = 7.6$ Hz, 1H), 4.65 (d, $J = 6.8$ Hz, 1H), 4.58 - 4.91 (m, 1H), 4.91 - 4.94 (m, 1H), 5.19 (d, $J = 7.6$ Hz, 1H), 5.56 (d, $J = 4.0$ Hz, 1H), 5.81 (ddd, $J = 8.3, 10.4, 17.2$ Hz, 1H), 7.37 - 7.42 (m, 3H), 7.52 - 7.57 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.3$ (CH_3), -4.2 (CH_3), -3.4 (CH_3), 5.3 (CH_2), 7.07 (CH_3), 14.4 (CH_3), 18.5 (C), 18.6 (C), 19.3 (CH_3), 25.4 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 27.1 (CH_3), 34.1 (CH_3), 34.9 (CH_2), 38.7 (CH_3), 55.6 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 65.5 (CH_2), 71.0 (CH), 71.7 (CH), 72.0 (CH), 75.1 (C), 79.7 (CH), 81.9 (CH), 84.0 (C), 85.0 (CH), 87.0 (C), 92.8 (CH_2), 98.2 (CH_2), 107.9 (C), 114.5 (CH_2), 122.0 (C), 124.9 (C), 127.6 (CH), 128.6 (CH), 129.7 (CH), 132.5 (C), 141.3 (CH), 165.6 (C) ppm.

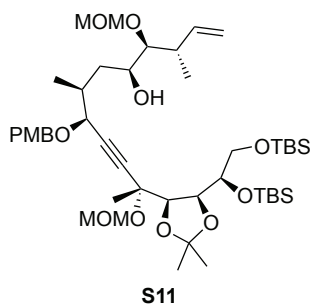
IR (ATR) ν 2956, 2878, 2361, 1754, 1719, 1462, 1251, 1171, 1106, 1015, 834, 777 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{53}\text{H}_{93}\text{F}_3\text{O}_{12}\text{Si}_3$ $[\text{M}+\text{Na}]^+$, 1085.5825; found 1085.5834 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 0.62, \text{CHCl}_3) = -22.9^\circ$.

Mosher-ester analysis:

Proton	S9 (<i>S</i> -configured) ppm	S10 (<i>R</i> -configured) ppm	Diff. S9S10 (d _S -d _R) Ppm
CH-1	2.09	2.06	+0.03
CH ₂ -2a	1.65	1.60	+0.05
CH ₂ -2b	1.37	1.35	+0.02
CH-3	3.85	3.80	+0.05
CH-4	3.27	3.22	+0.05
CH ₃ -5	1.03	1.01	+0.02
CH ₃ -3'	1.58	1.62	-0.04
CH-4'	3.99	4.00	-0.01



Alcohol S11. To a solution of alcohol **49** (268 mg, 0.32 mmol, 1.0 eq) in DMF (5.7 mL) was added NaH (60% dispersion in mineral oil, 26 mg, 0.64 mmol, 2 eq) at 0 °C. After 30 minutes PMB-Cl (78 µL, 0.58 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for 90 minutes at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO₃ (5 mL). After dilution with Et₂O (10 mL) the layers were separated and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed once with H₂O (10 mL) and brine (10 mL), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) to provide **S11** (178 mg) in 65% yield as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.00 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.23-1.32 (m, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 1.54-1.62 (m, 1H), 1.64 (s, 3H), 2.13-2.24 (m, 1H), 2.40-2.50 (m, 1H), 3.02 (d, *J* = 4.5 Hz, 1H), 3.14 (dd, *J* = 3.8, 6.3 Hz, 1H), 3.37 (s, 3H), 3.41 (s, 3H), 3.56-3.65 (m, 1H), 3.73 (dd, *J* = 4.3, 10.6 Hz, 1H), 3.76-3.81 (m, 4H), 3.97 (d, *J* = 5.8 Hz, 1H), 4.05 (d, *J* = 6.1 Hz, 1H), 4.27 (dd, *J* = 6.1, 6.1 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.42-4.46 (m, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 7.6 Hz,

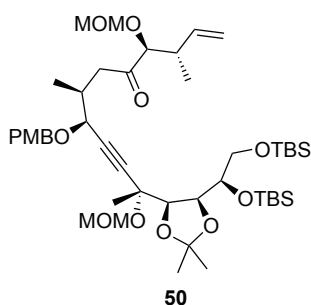
¹H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.98-5.04 (m, 2H), 5.29 (d, *J* = 7.6 Hz, 1H), 5.74-5.85 (m, 1H), 6.83-6.89 (m, 2H), 7.22-7.28 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -5.3 (CH₃), -4.2 (CH₃), -3.5 (CH₃), 15.3 (CH₃), 17.7 (CH₃), 18.4 (C), 18.5 (C), 25.5 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 27.1 (CH₃), 27.5 (CH₃), 34.7 (CH), 36.6 (CH₂), 40.0 (CH), 55.4 (CH₃), 55.8 (CH₃), 56.2 (CH₃), 65.6 (CH₂), 69.5 (CH), 70.2 (CH₂), 71.7 (CH), 73.7 (CH), 75.1 (C), 79.8 (CH), 82.0 (CH), 85.8 (C), 87.2 (C), 89.0 (CH), 92.8 (CH₂), 98.9 (CH₂), 107.8 (C), 113.9 (CH), 115.4 (CH₂), 129.5 (CH), 130.4 (C), 139.6 (CH), 159.3 (C) ppm.

IR (ATR) ν 3415, 2952, 2856, 2357, 2341, 1780, 1613, 1514, 1463, 1301, 1173, 1142, 1089, 1034, 874 811, 776 cm⁻¹.

HRMS (ESI) calcd for C₄₅H₈₀O₁₁Si₂ [M+Na]⁺, 875.5137; found 875.5129 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = -74.9°.



Ketone 50. To a solution of secondary alcohol **S11** (158 mg, 0.19 mmol, 1.0 eq) and pyridine (92 μL, 1.14 mmol, 6.0 eq) in DCM (6.0 mL), was added Dess-Martin periodinane (161 mg, 0.38 mmol, 2.0 eq) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2 hours before the reaction was quenched by the addition of saturated, aqueous solutions of Na₂S₂O₃ (5 mL) and NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) delivering **50** (126 mg) in 78% yield as a colorless oil.

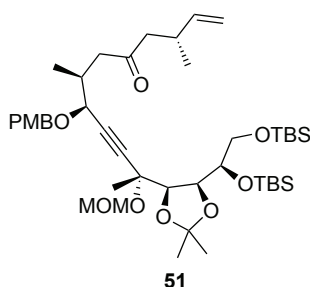
¹H NMR (400 MHz, CDCl₃): δ = -0.02 (s, 3H, CH₃-TBS), 0.00 (s, 3H, CH₃-TBS), 0.09 (s, 3H, CH₃-TBS), 0.11 (s, 3H, CH₃-TBS), 0.88 (s, 9H, *t*Bu-TBS), 0.89 (s, 9H, *t*Bu-TBS), 1.01 (d, *J* = 6.6 Hz, 3H, CH₃-IX), 1.06 (d, *J* = 7.1 Hz, 3H, CH₃-VIII), 1.34 (s, 3H, CH₃-VI), 1.51 (s, 3H, CH₃-III), 1.64 (s, 3H, CH₃-II), 2.37-2.49 (m, 2H, CH₂-X₂, CH-Z), 2.55-2.72 (m, 2H, CH₂-X₁, CH-Y), 3.34 (s, 3H, OCH₃-U), 3.37 (s, 3H, OCH₃-V), 3.72 (dd, *J* = 4.5, 10.6 Hz, 1H, CH₂-T₂), 3.77-3.82 (m, 4H, CH₂-T₁, OCH₃-W), 3.88 (d, *J* = 5.1 Hz, 1H, CH-M), 3.98 (d, *J* = 5.8 Hz, 1H, CH-Q), 4.04 (d, *J* = 5.8 Hz, 1H, CH-N), 4.26 (dd, *J* = 5.8, 6.2 Hz, 1H, CH-O), 4.38 (d, *J* = 11.4 Hz, 1H, CH₂-S₂), 4.43 (ddd, *J* = 2.0, 4.5, 6.2 Hz, 1H, CH-R), 4.56 (d, *J* = 6.8 Hz, 1H, CH₂-I₂), 4.60 (d, *J* = 6.8 Hz, 1H, CH₂-I₁), 4.66 (d, *J* = 7.3 Hz, 1H, CH₂-J₂), 4.71 (d, *J* = 11.4 Hz, 1H, CH₂-S₁), 4.97-5.01 (m, 1H, CH₂-F₂), 5.02-5.04 (m, 1H, CH₂-F₁), 5.27 (d, *J* = 7.3 Hz, 1H, CH₂-J₁), 5.76 (ddd, *J* = 8.0, 10.9, 16.6 Hz, 1H, CH-C), 6.84-6.89 (m, 2H, CH-phenyl), 7.22-7.27 (m, 2H, CH-phenyl) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.3$ (CH_3 -TBS), -5.2 (CH_3 -TBS), -4.2 (CH_3 -TBS), -3.5 (CH_3 -TBS), 16.3 (CH_3 -IX), 17.0 (CH_3 -VIII), 18.50 (C-TBS), 18.53 (C-TBS), 25.4 (CH_3 -VI), 26.1 (CH_3 -*t*Bu-TBS), 26.2 (CH_3 -*t*Bu-TBS), 27.1 (CH_3 -III), 27.4 (CH_3 -II), 33.7 (CH-Z), 40.6 (CH-Y), 42.7 (CH_2 -X), 55.4 (CH_3 -W), 55.8 (CH_3 -V), 56.2 (CH_3 -U), 65.6 (CH_2 -T), 70.4 (CH_2 -S), 71.7 (CH-R), 72.4 (CH-Q), 75.1 (C-P), 79.9 (CH-O), 82.0 (CH-N), 86.2 (CH-M), 86.3 (C-L), 86.6 (C-K), 92.8 (CH_2 -J), 96.8 (CH_2 -I), 107.8 (C-H), 113.9 (CH-G), 115.9 (CH_2 -F), 129.6 (CH-E), 130.1 (C-D), 138.9 (CH-C), 159.4 (C-B), 209.6 (C-A) ppm.

IR (ATR) ν 2929, 2855, 2363, 2341, 1794, 1719, 1612, 1514, 1462, 1248, 1139, 1090, 1054, 1033, 873, 777 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{78}\text{O}_{11}\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 873.4981; found 873.4974 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -107^\circ$.



Ketone 51:

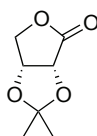
^1H NMR (400 MHz, CDCl_3): $\delta = 0.02$ (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 1.34 (s, 3H), 1.50 (s, 3H), 1.66 (s, 3H), 2.22 - 2.33 (m, 2H), 2.35 - 2.45 (m, 2H), 2.64 - 2.74 (m, 2H), 3.37 (s, 3H), 3.75 (dd, $J = 4.5, 10.6$ Hz, 1H), 3.80 (s, 3H), 3.83 (dd, $J = 2.0, 10.6$ Hz, 1H), 4.04 (d, $J = 6.1$ Hz, 1H), 4.05 (d, $J = 4.0$ Hz, 1H), 4.26 (dd, $J = 6.1, 6.3$ Hz, 1H), 4.35 (d, $J = 11.4$ Hz, 1H), 4.46 (ddd, $J = 2.0, 4.5, 6.3$ Hz, 1H), 4.68 (d, $J = 7.3$ Hz, 1H), 4.69 (d, $J = 11.4$ Hz, 1H), 4.88 - 4.93 (m, 1H), 4.93 - 4.99 (m, 1H), 5.25 (d, $J = 7.3$ Hz, 1H), 5.71 (ddd, $J = 6.8, 10.4, 17.2$ Hz, 1H), 6.83 - 6.89 (m, 2H), 7.19 - 7.26 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -5.2$ (CH_3), -4.2 (CH_3), -3.5 (CH_3), 16.1 (CH_3), 18.5 (C), 18.6 (C), 19.9 (CH_3), 25.4 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 33.3 (CH_3), 34.0 (CH_3), 45.9 (CH_2), 50.2 (CH_2), 55.4 (CH_3), 55.8 (CH_3), 65.6 (CH_2), 70.4 (CH_2), 71.6 (CH), 72.1 (CH), 75.2 (C), 79.9 (CH), 82.0 (CH), 86.3 (C), 86.4 (C), 92.8 (CH_2), 107.8 (C), 113.1 (CH_2), 113.9 (CH), 129.6 (CH), 130.2 (C), 143.7 (CH), 159.4 (C), 209.1 (C) ppm.

IR (ATR) ν 2928, 2855, 1715, 1514, 1463, 1370, 1251, 1150, 1041, 834, 778 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{43}\text{H}_{74}\text{O}_9\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 813.4769; found 813.4770 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 0.5, \text{CHCl}_3) = -9.3^\circ$.

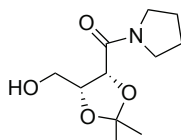
**54**

(3aR,6aR)-2,2-Dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3aH)-one (54). A 250 mL, three necked, round bottom flask equipped with an internal thermometer and an addition funnel was charged with erythorbic acid (3.52 g, 20.0 mmol) and 50 mL H₂O. The solution was cooled to 0 °C and Na₂CO₃ (4.24 g, 40.0 mmol) was added slowly in small portions because vigorous evolution of CO₂ was observed. The resulting yellow reaction mixture was stirred with ice-bath cooling while a solution of H₂O₂ (4.6 mL, 30%) was added over a period of 10 minutes during that, the internal temperature has risen to 10 °C. Stirring was continued for 5 minutes at 0 °C and then for 30 minutes at 42 °C. Active charcoal (1 g) was added in portions to decompose the excess of peroxide and the mixture was heated to 75 °C for 30 minutes while gas evolution has stopped and a negative starch-iodide test was observed. The hot reaction mixture was filtered over a pad of Celite and the solids were washed with H₂O (30 mL). The combined filtrates were acidified to pH 1 by the cautious addition of HCl (6 M, 15 mL). The acidic solution was evaporated under reduced pressure and was dried for further three hours at 50 °C on the vacuum pump (0.2 mm) to give a pale yellow solid containing D-erythrone, oxalic acid and NaCl. To this crude mixture were added first acetone (17.5 mL) and anhydrous MgSO₄ (5 g) followed by the addition of 2,2-dimethoxypropane (35 mL, 0.285 mol) and *p*-toluenesulfonic acid monohydrate (42 mg, 0.22 mmol) at room temperature. The suspension was stirred for 18 hours at room temperature before it was poured into a 5 °C cooled mixture of Et₂O (50 mL) and NEt₃ (6 mL). After being stirred for 5 minutes the mixture was filtered and the solids were washed thoroughly with Et₂O. The combined filtrates were concentrated in vacuo and the resulting solid material was purified by flash chromatography (hexane/EtOAc 1:1) delivering protected lactone **54** (2.28 g) in 72% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.40 (s, 3H), 1.49 (s, 3H), 4.40 (dd, *J* = 3.8, 11.0 Hz, 1H), 4.47 (bd, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.88 (ddd, *J* = 0.6, 3.8, 5.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 26.8 (CH₃), 26.9 (CH₃), 70.4 (CH₂), 74.8 (CH), 75.6 (CH), 114.2 (C), 174.1 (C) ppm.

These spectral characteristics are identical to those previously reported.^[3]

**55**

((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (55). Protected lactone **54** (22.1 g, 140 mmol, 1.0 eq) was dissolved in toluene (750 mL). After the addition of pyrrolidine (57.4 mL, 698 mmol, 5.0 eq) the reaction mixture was heated to reflux for 18 hours. The resulting brown solution was cooled to room temperature and the solvent was

removed under reduced pressure. The crude material was purified by flash column chromatography (DCM/MeOH 19:1 to 9:1) to give amide **55** (31.4g) in 98% yield as a light yellow oil.

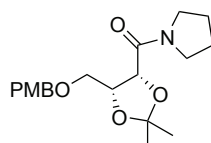
^1H NMR (400 MHz, CDCl_3): δ = 1.38 (s, 3H), 1.55 (s, 3H), 1.81-2.03 (m, 4H), 3.38-3.44 (m, 1H), 3.44-3.75 (m, 6H), 4.41 (ddd, J = 6.4, 6.4, 4.3 Hz, 1H), 4.83 (d, J = 6.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 23.8 (CH_2), 25.3 (CH_3), 26.5 (CH_2), 27.1 (CH_3), 46.8 (CH_2), 47.0 (CH_2), 62.5 (CH_2), 76.5 (CH), 78.0 (CH), 109.9 (C), 167.2 (C) ppm.

IR (ATR) ν 3348, 2977, 2877, 2361, 2342, 1637, 1456, 1371, 1242, 1164, 1093, 1052 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_4$ $[\text{M}+\text{Na}]^+$, 252.1212; found 252.1206 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +21.7^\circ$.



S12

((4R,5R)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(pyrrolidin-1-yl)methanone (S12). To a solution of alcohol **55** (15.7 g, 68.5 mmol, 1.0 eq) in DCM (115 mL) were added *p*-methoxybenzyl trichloroacetimidate (29.7 g, 105 mmol, 1.53 eq), dissolved in DCM (30 mL), and camphorsulfonic acid (1.27 g, 5.48 mmol, 0.08 eq) at room temperature. The reaction mixture was stirred for 12 hours at room temperature and 3 hours at 50 $^\circ\text{C}$ when TLC-control showed total conversion of the starting material. The reaction was quenched by the addition of saturated NaHCO_3 solution, the layers were separated and the aqueous phase was extracted with DCM (3 x 80 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. After flash column chromatography (hexane/EtOAc 1:1) **S12** (20.4 g) was isolated in 85% yield as a colorless oil.

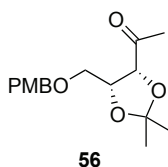
^1H NMR (400 MHz, CDCl_3): δ = 1.38 (s, 3H), 1.58 (s, 3H), 1.60-1.85 (m, 4H), 3.30-3.50 (m, 4H), 3.55 (d, J = 6.7 Hz, 1H), 3.56 (d, J = 5.5 Hz, 1H), 3.80 (s, 3H), 4.38 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.53 (ddd, J = 5.5, 6.7, 6.7 Hz, 1H), 4.82 (d, J = 6.7 Hz, 1H), 6.83-6.87 (m, 2H), 7.18-7.23 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 23.8 (CH_2), 25.5 (CH_3), 26.2 (CH_2), 27.3 (CH_3), 46.1 (CH_2), 46.4 (CH_2), 55.4 (CH_3), 69.2 (CH_2), 73.3 (CH_2), 75.9 (CH), 76.1 (CH), 110.3 (C), 113.9 (CH), 129.5 (CH), 130.2 (C), 159.4 (C), 169.5 (C) ppm.

IR (ATR) ν 2980, 2874, 2361, 2341, 1655, 1514, 1449, 1302, 1248, 1091, 1034, 822 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_5$ $[\text{M}+\text{Na}]^+$, 372.1787; found 372.1782 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +24.7^\circ$.



1-((4*R*,5*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (56**).**

A solution of MeLi (1.6 M in Et₂O, 33.2 mL, 53.1 mmol, 2.0 eq) was added to amide **S12** (9.3 g, 26.6 mmol, 1.0 eq), dissolved in THF (133 mL), at -78 °C. The reaction mixture was stirred for 10 minutes when TLC-control showed total consumption of the starting material. The reaction was terminated by the addition of H₂O (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under vacuum. Further purification of crude ketone by flash column chromatography (hexane/EtOAc 9:1 to 5:1) delivered **56** (7.3 g) in 94% yield as a colorless oil.

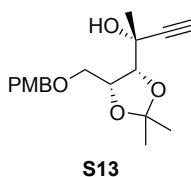
¹H NMR (400 MHz, CDCl₃): δ = 1.37 (s, 3H), 1.59 (s, 3H), 2.16 (s, 3H), 3.40 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.57 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.80 (s, 3H), 4.36 (s, 2H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.50-4.55 (m, 1H), 6.83-6.89 (m, 2H), 7.19-7.25 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 25.0 (CH₃), 27.0 (CH₃), 28.4 (CH₃), 55.4 (CH₃), 67.9 (CH₂), 73.2 (CH₂), 77.6 (CH), 81.1 (CH), 110.3 (C), 113.9 (CH), 129.6 (CH), 129.9 (C), 159.4 (C), 208.6 (C) ppm.

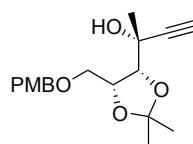
IR (ATR) ν 2935, 2360, 1711, 1613, 1514, 1459, 1380, 1302, 1245, 1211, 1135, 1060, 1034, 858, 820 cm⁻¹.

HRMS (ESI) calcd for C₁₆H₂₂O₅ [M+Na]⁺, 317.1365; found 317.1360 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = +43.2°.



(*R*)-2-((4*R*,5*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S13**).** To a solution of methyl ketone **56** (14.7 g, 50.0 mmol, 1.0 eq) in THF (880 mL) was added a solution of ethynylmagnesium bromide (0.5 M in THF, 300 mL, 150.0 mmol, 3.0 eq) at 0 °C *via* a cannula. The reaction mixture was stirred for 1 hour at 0 °C and 90 minutes at room temperature. After TLC-analysis indicated complete conversion of the starting material the reaction was quenched by the addition of H₂O (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude mixture of the corresponding tertiary alcohols was purified by flash column chromatography (hexane/EtOAc 9:1 to 3:1) affording **S13** (11.6 g) and **S13a** (3.9 g) as colorless oils in a 3:1 diastereomeric ratio and 97% overall yield.

**S13**

Major diastereomer **S13**:

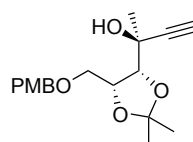
^1H NMR (400 MHz, CDCl_3): δ = 1.36 (s, 3H), 1.48 (s, 3H), 1.60 (d, J = 1.0 Hz, 3H), 2.49 (s, 1H), 3.56 (dd, J = 4.3, 8.8 Hz, 1H), 3.80 (s, 3H), 4.03 (d, J = 5.8 Hz, 1H), 4.32 (dd, J = 8.8, 10.3 Hz, 1H), 4.38-4.45 (m, 1H), 4.42 (d, J = 11.0 Hz, 1H), 4.60 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 1.0 Hz, 1H), 6.85-6.91 (m, 2H), 7.27-7.31 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 25.4 (CH_3), 27.8 (CH_3), 29.8 (CH_3), 55.4 (CH_3), 67.3 (C), 67.7 (CH_2), 72.8 (CH), 73.4 (CH_2), 75.7 (CH), 82.9 (CH), 86.5 (C), 109.1 (C), 114.1 (CH), 128.8 (C), 130.2 (CH), 159.8 (C) ppm.

IR (ATR) ν 3399, 3285, 2968, 2936, 2360, 2342, 1613, 1514, 1457, 1371, 1303, 1248, 1060 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 343.1522; found 343.1520 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = +0.4°.

**S13a**

Minor diastereomer **S13a**:

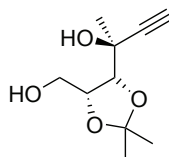
^1H NMR (400 MHz, CDCl_3): δ = 1.37 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.43 (s, 1H), 3.79 (s, 3H), 3.97 (dd, J = 4.0, 11.1 Hz, 1H), 4.03 (dd, J = 3.2, 11.1 Hz, 1H), 4.09 (d, J = 6.6 Hz, 1H), 4.36 (ddd, J = 3.2, 4.0, 6.6 Hz, 1H), 4.50 (d, J = 11.1 Hz, 1H), 4.59 (d, J = 11.1 Hz, 1H), 4.60 (s, 1H), 6.84-6.90 (m, 2H), 7.27-7.33 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = 25.4 (CH_3), 26.9 (CH_3), 27.8 (CH_3), 55.4 (CH_3), 67.0 (C), 67.5 (CH_2), 72.4 (CH), 73.5 (CH_2), 76.5 (CH), 82.5 (CH), 86.5 (C), 108.5 (C), 114.0 (CH), 129.1 (C), 130.1 (CH), 159.6 (C) ppm.

IR (ATR) ν 3399, 3285, 2968, 2936, 2360, 2342, 1613, 1514, 1457, 1371, 1303, 1248, 1060 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$ $[\text{M}+\text{Na}]^+$, 343.1522; found 343.1523 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl_3) = +26.6°.

**S14**

(S)-2-((4R,5R)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S14). To a solution of tertiary alcohol **S13a** (300 mg, 0.94 mmol, 1.0 eq) in acetonitrile (23.5 mL) was added phosphate buffer (1.0 M, pH 7-8, 2.3 mL) at room temperature. The reaction mixture was cooled to

0 °C and ceric ammonium nitrate (1.03 g, 1.88 mmol, 2.0 eq) was added in 3 portions. After stirring for 90 minutes at 0 °C TLC-control showed only partial deprotection of the starting material. 2 equivalents of ceric ammonium nitrate (1.03 g) were added and the reaction mixture was stirred for additional 30 minutes at 0°C. TLC-analysis showed total conversion of the starting material and the reaction was terminated by the addition of a saturated solution of NaHCO₃ (15 mL). The resulting suspension was filtered through a plug of Celite. The filtrate was transferred to a separatory funnel and diluted with DCM (20 mL). The layers were separated and the aqueous phase was extracted with DCM (10 mL). The combined organic fractions were dried over Na₂SO₄, filtered and the solvents were removed under reduced pressure. The crude diol was further purified by flash column chromatography (hexane/EtOAc 3:1 to 1:1) affording **S14** (145 mg) in 77% yield as a colorless oil.

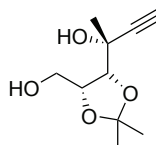
¹H NMR (400 MHz, CDCl₃): δ = 1.40 (s, 3H), 1.54 (s, 3H), 1.61 (s, 3H), 2.51 (s, 1H), 4.02 (dd, *J* = 4.0, 12.3 Hz, 1H), 4.15 (d, *J* = 7.0 Hz, 1H), 4.27 (dd, *J* = 3.6, 12.3 Hz, 1H), 4.32 (ddd, *J* = 3.6, 4.0, 7.0 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 25.1 (CH₃), 27.0 (CH₃), 28.5 (CH₃), 60.7 (CH₂), 66.9 (C), 73.4 (CH), 77.6 (CH), 82.2 (CH), 85.6 (C), 108.4 (C) ppm.

IR (ATR) ν 3280, 2987, 2361, 2341, 1380, 1218, 1063 cm⁻¹.

HRMS (ESI) calcd for C₁₀H₁₆O₄ [M+Na]⁺, 223.0947; found 223.0950 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = +16.9°.



S15

(*R*)-2-((4*R*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (S15**).** Diol **S15** was prepared following the same procedure as described above for diol **S14**. Starting from tertiary alcohol **S13** (300 mg, 0.94 mmol), diol **S15** (116 mg) was isolated in 62% yield as a colorless oil.

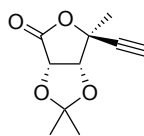
¹H NMR (400 MHz, CDCl₃): δ = 1.38 (s, 3H), 1.53 (s, 3H), 1.62 (s, 3H), 2.53 (s, 1H), 2.68 (bs, 1H), 3.61 (bs, 1H), 3.87 (dd, *J* = 3.6, 9.9 Hz, 1H), 4.04 (d, *J* = 5.8 Hz, 1H), 4.30-4.41 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = 25.4 (CH₃), 27.5 (CH₃), 29.4 (CH₃), 60.7 (CH₂), 68.1 (C), 73.7 (CH), 77.7 (CH), 82.5 (CH), 86.1 (C), 109.0 (C) ppm.

IR (ATR) ν 3280, 2987, 2361, 2341, 1380, 1218, 1063 cm⁻¹.

HRMS (ESI) calcd for C₁₀H₁₆O₄ [M+Na]⁺, 223.0947; found 223.0948 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = +3.6°.

**S16**

(3a*S*,6*S*,6a*R*)-6-Ethynyl-2,2,6-trimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (S16). A solution of diol **S14** (115 mg, 0.57 mmol, 1.0 eq) in DCM (8.8 mL) was treated with PCC (638 mg, 2.30 mmol, 4.0 eq) at room temperature. The reaction mixture was warmed to 40 °C (stoppered round bottom flask) and stirred for 12 hours at that temperature. As TLC-control indicated total conversion of the starting material silica gel was added and the solvent was removed under reduced pressure. The absorbed product was transferred to a chromatography column and was eluted with hexane/EtOAc 5:1 to afford lactone **S16** (60 mg) in 54% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.41 (s, 3H), 1.47 (s, 3H), 1.73 (s, 3H), 2.70 (s, 1H), 4.71 (d, J = 5.1 Hz, 1H), 4.97 (d, J = 5.1 Hz, 1H) ppm.

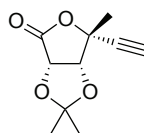
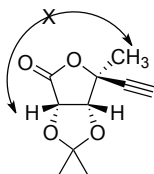
^{13}C NMR (100 MHz, CDCl_3): δ = 21.8 (CH_3), 26.4 (CH_3), 27.0 (CH_3), 76.6 (CH), 76.8 (CH), 80.6 (C), 81.4 (C), 81.8 (CH), 115.0 (C), 173.3 (C) ppm.

IR (ATR) ν 3282, 3244, 2999, 2360, 1787, 1375, 1230, 1107, 1091, 981, 835 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$ $[\text{M}+\text{Na}]^+$, 219.0634; found 219.0628 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +50.8^\circ$.

NOE-analysis:

**S17**

(3a*S*,6*R*,6a*R*)-6-Ethynyl-2,2,6-trimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (S17).

Lactone **S17** was prepared following the same procedure as described above for lactone **S16**. Starting from diol **S15** (90 mg, 0.45 mmol), lactone **S17** (45 mg) was isolated in 51% yield as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.44 (s, 3H), 1.53 (s, 3H), 1.66 (s, 3H), 2.77 (s, 1H), 4.58 (d, J = 5.6 Hz, 1H), 4.85 (d, J = 5.6 Hz, 1H) ppm.

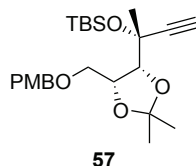
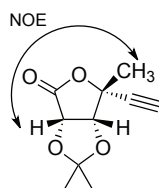
^{13}C NMR (100 MHz, CDCl_3): δ = 26.3 (CH_3), 27.0 (CH_3), 27.9 (CH_3), 75.7 (CH), 77.1 (CH), 78.8 (C), 78.9 (C), 81.5 (CH), 115.2 (C), 172.4 (C) ppm.

IR (ATR) ν 3282, 3244, 2999, 2360, 1787, 1375, 1230, 1107, 1091, 981, 835 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$ $[\text{M}+\text{Na}]^+$, 219.0634; found 219.0629 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +53.8^\circ$.

NOE analysis:



***tert*-Butyl(((*R*)-2-(((4*R*,5*R*)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (**57**).** To a solution of tertiary alcohol **S13** (3.0 g, 9.36 mmol, 1.0 eq) and 2,6-lutidine (2.17 mL, 18.7 mmol, 2.0 eq) in DCM (18 mL) was added TBS-triflate (2.15 mL, 9.36 mmol, 1.0 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature before it was stirred for 5 hours at 50 °C (stoppered round bottom flask). TLC-analysis showed partial conversion of the starting material and additional 0.2 eq (0.43 mL) of TBS-triflate and 0.4 eq (0.43 mL) of 2,6-lutidine were added. The reaction mixture was stirred for 90 minutes before it was quenched by the addition of a saturated, aqueous solution of NaHCO₃ (15 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic fractions were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1) alkyne **57** (3.8 g) was isolated in 93% yield as a colorless oil.

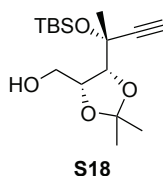
¹H NMR (400 MHz, CDCl₃): δ = 0.10 (s, 3H), 0.17 (s, 3H), 0.77 (s, 9H), 1.38 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.48 (s, 1H), 3.80 (s, 3H), 3.81 (d, J = 6.5 Hz, 1H), 3.93 (dd, J = 2.3, 10.5 Hz, 1H), 4.06 (dd, J = 9.7, 10.5 Hz, 1H), 4.44-4.50 (m, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 6.84-6.88 (m, 2H), 7.27-7.31 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -3.0 (CH₃), -2.3 (CH₃), 18.1 (C), 25.4 (CH₃), 25.8 (CH₃), 27.5 (CH₃), 30.3 (CH₃), 55.5 (CH₃), 68.6 (CH₂), 69.9 (C), 73.0 (CH₂), 74.9 (CH), 77.8 (CH), 83.2 (CH), 85.9 (C), 109.0 (C), 113.9 (CH), 129.4 (CH), 130.8 (C), 159.3 (C) ppm.

IR (ATR) ν 2934, 2857, 2361, 2341, 1514, 1463, 1249, 1171, 1091, 838, 778 cm⁻¹.

HRMS (ESI) calcd for C₂₄H₃₈O₅Si [M+Na]⁺, 457.2387; found 457.2383 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -35.4^\circ$.



((4*R*,5*R*)-5-(((*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (S18**).** To a solution of **57** (4.05 g, 9.32 mmol, 1.0 eq) in DCM (450 mL) were added

phosphate buffer (1.0 M, pH 7-8, 5.5 mL) and DDQ (3.17 g, 14.0 mmol, 1.5 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 14 hours when TLC-control showed total conversion of the starting material. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO₃ (150 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was concentrated under vacuum. After purification by flash column chromatography (hexane/EtOAc 9:1) primary alcohol **S18** (5.59 g) was isolated in 95% yield as a colorless oil.

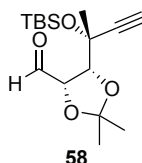
¹H NMR (400 MHz, CDCl₃): δ = 0.24 (s, 3H), 0.25 (s, 3H), 0.88 (s, 9H), 1.38 (s, 3H), 1.54 (s, 3H), 1.58 (s, 3H), 2.19 (dd, *J* = 5.8, 7.8 Hz, 1H), 2.55 (s, 1H), 3.91 (d, *J* = 6.3 Hz, 1H), 4.03-4.15 (m, 2H), 4.38 (ddd, *J* = 5.5, 6.3, 7.5 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -3.0 (CH₃), -2.2 (CH₃), 18.2 (C), 25.6 (CH₃), 25.9 (CH₃), 27.5 (CH₃), 30.4 (CH₃), 61.4 (CH₂), 70.2 (C), 75.1 (CH), 78.9 (CH), 83.3 (CH), 85.8 (C), 108.9 (C) ppm.

IR (ATR) ν 3503, 3310, 2932, 2858, 2362, 2341, 1463, 1371, 1253, 1216, 1143, 1085, 1060, 991, 836, 778 cm⁻¹.

HRMS (ESI) calcd for C₁₆H₃₀O₄Si [M+Na]⁺, 337.1811; found 337.1806 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = +0.5°.



(4S,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (58). To a solution of primary alcohol **S18** (500 mg, 1.59 mmol, 1.0 eq) and pyridine (755 μL, 9.36 mmol, 6.0 eq) in DCM (10.6 mL), was added Dess-Martin periodinane (1.01 g, 2.39 mmol, 1.5 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solutions of Na₂S₂O₃ (5 mL) and NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) delivering **58** (486 mg) in 98% yield as a colorless oil.

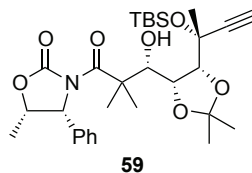
¹H NMR (400 MHz, CDCl₃): δ = 0.21 (s, 3H), 0.22 (s, 3H), 0.87 (s, 9H), 1.41 (s, 3H), 1.59 (s, 3H), 1.62 (s, 3H), 2.57 (s, 1H), 4.27 (d, *J* = 7.3 Hz, 1H), 4.44 (dd, *J* = 3.0, 7.3 Hz, 1H), 9.84 (d, *J* = 3.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -3.1$ (CH_3), -2.4 (CH_3), 18.2 (C), 25.6 (CH_3), 25.8 (CH_3), 27.2 (CH_3), 29.4 (CH_3), 69.8 (C), 75.4 (CH), 81.8 (CH), 85.4 (C), 86.2 (CH), 111.4 (C), 197.9 (CH) ppm.

IR (ATR) ν 2932, 2858, 1734, 1473, 1374, 1253, 1217, 1151, 1083, 995, 837, 780 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{28}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$, 335.1655; found 335.1658 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +0.2^\circ$.



(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*R*)-5-((*R*)-2-((Tert-butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one

(59). A solution of SmI_2 (0.1 M in THF, 31.3 mL, 3.13 mmol, 2.5 eq) was transferred into a 250 mL round bottom Schlenk flask which was precooled to -78°C . A solution of bromide **20** (449 mg, 1.38 mmol, 1.1 eq) and aldehyde **58** (390 mg, 1.25 mmol, 1.0 eq) in 20 mL degassed THF (3 pump-freeze-thaw cycles) was added to the SmI_2 solution *via* a cannula over a period of 5 minutes. The reaction mixture was stirred for 1 hour at -78°C before it was quenched by the addition of aqueous saturated solutions of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and NaHCO_3 (20 mL) at -78°C . The biphasic system was allowed to warm to room temperature. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the organic solvents were removed under reduced pressure delivering the crude secondary alcohol as a light yellow oil which was purified by flash chromatography (hexane/EtOAc 9:1) providing **59** (420 mg) as single diastereomer in 60% (94% brsm) yield.

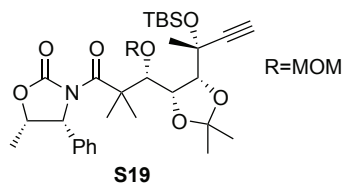
^1H NMR (400 MHz, CDCl_3): $\delta = 0.23$ (s, 3H), 0.30 (s, 3H), 0.90 (s, 9H), 0.91 (d, $J = 6.6$ Hz, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 1.58 (s, 3H), 1.71 (s, 3H), 2.58 (s, 1H), 3.32 (d, $J = 4.8$ Hz, 1H), 4.08 (d, $J = 6.3$ Hz, 1H), 4.27 (d, $J = 6.3$ Hz, 1H), 4.81 (m, 1H), 4.93 (d, $J = 4.8$ Hz, 1H), 5.66 (d, $J = 6.8$ Hz, 1H), 7.27 - 7.31 (m, 2H), 7.33 - 7.44 (m, 3H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -2.9$ (CH_3), -2.2 (CH_3), 14.4 (CH_3), 18.5 (C), 20.2 (CH_3), 22.4 (CH_3), 25.7 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 28.2 (CH_3), 50.6 (C), 57.7 (CH_3), 69.1 (CH), 69.5 (C), 74.0 (CH), 75.7 (CH), 79.2 (CH), 84.5 (CH), 86.9 (C), 108.5 (C), 125.8 (CH), 128.8 (CH), 128.9 (CH), 133.8 (C), 152.6 (C), 177.0 (C) ppm.

IR (ATR) ν 3511, 3264, 2933, 2858, 2361, 2341, 1773, 1688, 1457, 1338, 1248, 1151, 1086, 1028, 987, 835, 768 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{45}\text{NO}_7\text{Si}$ $[\text{M}+\text{Na}]^+$, 582.2863; found 582.2859 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +34.4^\circ$.



(4*R*,5*S*)-3-((*S*)-3-((4*R*,5*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (S19). Alcohol **59** (540 mg, 0.97 mmol, 1.0 eq) was dissolved in 1,2-dichloroethane (4.5 mL) and cooled to 0 °C. DIPEA (3 mL, 17.4 mmol, 18.0 eq) and MOM-Cl (0.88 mL, 11.6 mmol, 12.0 eq) were added sequentially. After the addition, the ice bath was removed, the reaction mixture was heated to 100 °C (sealed round bottom flask) and the yellow solution was stirred for 14 hours. The reaction was quenched by the addition of H₂O (5 mL). After separation of the two layers the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. After purification by flash chromatography (hexane/EtOAc 9:1) 500 mg (86%) of the MOM protected alkyne (**S19**) could be isolated as colorless oil.

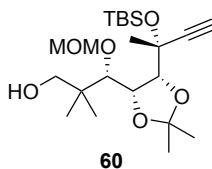
¹H NMR (400 MHz, CDCl₃): δ = 0.25 (s, 3H), 0.29 (s, 3H), 0.85 (s, 9H), 0.94 (d, *J* = 6.3 Hz, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.58 (s, 6H), 1.64 (s, 3H), 2.58 (s, 1H), 3.39 (s, 3H), 3.88 (d, *J* = 5.8 Hz, 1H), 4.40 (dd, *J* = 5.3, 5.8 Hz, 1H), 4.65-4.74 (m, 1H), 4.87 (d, *J* = 5.6 Hz, 1H), 5.0 (d, *J* = 5.6 Hz, 1H), 5.02 (d, *J* = 5.3 Hz, 1H), 5.64 (d, *J* = 6.8 Hz, 1H), 7.29-7.33 (m, 2H), 7.35-7.44 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -2.2 (CH₃), -1.9 (CH₃), 14.4 (CH₃), 17.8 (CH₃), 18.4 (C), 20.5 (CH₃), 25.5 (CH₃), 26.2 (CH₃), 26.9 (CH₃), 30.7 (CH₃), 50.3 (C), 56.7 (CH₃), 58.1 (CH), 70.2 (C), 75.8 (CH), 76.3 (CH), 76.5 (CH), 79.4 (CH), 84.6 (CH), 86.6 (C), 98.5 (CH₂), 107.8 (C), 125.8 (CH), 128.7 (CH), 128.8 (CH), 133.7 (C), 152.3 (C), 177.0 (C) ppm.

IR (ATR) ν 2936, 2361, 2341, 1782, 1689, 1458, 1340, 1255, 1216, 1189, 1069, 986, 836 cm⁻¹.

HRMS (ESI) calcd for C₃₂H₄₉NO₈Si [M+Na]⁺, 626.3125; found 626.3137 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = -44.4°.



(*S*)-3-((4*R*,5*R*)-5-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropan-1-ol (60). To a solution of **S19** (107 mg, 0.18 mmol, 1.0 eq) in THF (4.5 mL) were added MeOH (7 μL, 0.18 mmol, 1.0 eq) and a solution of lithium borohydride (2.0 M in THF, 0.35 mL, 0.71 mmol, 4.0 eq) at 0 °C. After the addition the reaction mixture was allowed to warm to room temperature and stirring was continued for 3 hours before the reaction was terminated by the addition of a saturated aqueous solution of NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL).

The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexane/EtOAc 5:1 to 3:1) afforded primary alcohol **60** (66 mg) in 87% yield as a colorless oil.

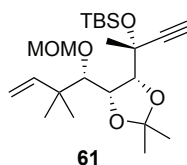
^1H NMR (400 MHz, CDCl_3): δ = 0.25 (s, 3H), 0.33 (s, 3H), 0.88 (s, 9H), 0.92 (s, 3H), 1.05 (s, 3H), 1.38 (s, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 2.59 (s, 1H), 3.13 (dd, J = 5.8, 7.8 Hz, 1H), 3.34 (dd, J = 7.8, 11.4 Hz, 1H), 3.44 (s, 3H), 3.64 (dd, J = 5.8, 11.4 Hz, 1H), 3.76-3.81 (m, 1H), 4.38-4.41 (m, 2H), 4.71 (d, J = 6.5 Hz, 1H), 5.30 (d, J = 6.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -2.0 (CH_3), -1.8 (CH_3), 18.5 (C), 19.7 (CH_3), 23.1 (CH_3), 25.4 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 31.3 (CH_3), 39.9 (C), 56.5 (CH_3), 69.9 (CH_2), 70.3 (C), 76.2 (CH), 76.3 (CH), 77.6 (CH), 84.3 (CH), 86.7 (C), 98.2 (CH_2), 107.7 (C) ppm.

IR (ATR) ν 3512, 3241, 2932, 2858, 2360, 2342, 1473, 1370, 1252, 1218, 1097, 1068, 979, 835, 779 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{42}\text{O}_6\text{Si}$ $[\text{M}+\text{Na}]^+$, 453.2649; found 453.2652 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -78.2^\circ$.



***tert*-Butyl(((*R*)-2-((4*R*,5*R*)-5-((*S*)-1-(methoxymethoxy)-2,2-dimethylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (**61**).** To a solution of IBX (162 mg, 0.58 mmol, 1.5 eq) in DMSO (10 mL) was added alcohol **60** (166 mg, 0.39 mmol, 1.0 eq) in DMSO (1.5 mL) and the reaction mixture was stirred for 3 hours at room temperature. As TLC-control indicated total consumption of the starting material the reaction was terminated by the addition of H_2O (5 mL) at 0 $^\circ\text{C}$. The resulting suspension was filtered over a plug of Celite and the filtrate was diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with H_2O (15 mL) and brine (15 mL) and dried over MgSO_4 . After filtration the solvent was removed under reduced pressure (25 $^\circ\text{C}$ bath temperature). The crude material was purified by flash column chromatography (hexane/EtOAc 40:1 to 19:1) delivering the corresponding instable aldehyde (143 mg) in 87% yield, which was used immediately for the next step.

^1H NMR (400 MHz, CDCl_3): δ = 0.25 (s, 3H), 0.35 (s, 3H), 0.87 (s, 9H), 1.13 (s, 3H), 1.20 (s, 3H), 1.36 (s, 3H), 1.56 (s, 3H), 1.62 (s, 3H), 2.61 (s, 1H), 3.35 (s, 3H), 3.77 (d, J = 5.8 Hz, 1H), 4.33 (dd, J = 5.8, 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 5.24 (d, J = 6.8 Hz, 1H), 9.71 (s, 1H) ppm.

The aldehyde from above (143 mg, 0.33 mmol, 1.0 eq) was dissolved in freshly distilled THF (2.4 mL) and cooled to 0 $^\circ\text{C}$. A solution of Tebbe-reagent (0.5 M in toluene, 0.8 mL, 0.4 mmol, 1.2 eq) was slowly added *via* a syringe. The reaction mixture was stirred for 15 minutes at 0 $^\circ\text{C}$ before it was quenched by the addition of a saturated solution of NaHCO_3 (3 mL). After the

separation of the two layers, the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. Crude alkene **61** was purified by flash column chromatography (hexane/EtOAc 40:1 to 19:1) delivering 125 mg (88%) of the desired intermediate as a light yellow oil.

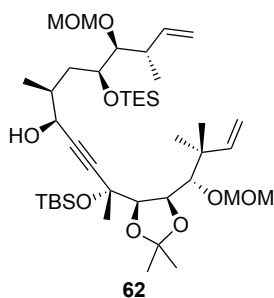
¹H NMR (400 MHz, CDCl₃): δ = 0.26 (s, 3H), 0.37 (s, 3H), 0.89 (s, 9H), 1.11 (s, 3H), 1.13 (s, 3H), 1.33 (s, 3H), 1.54 (s, 3H), 1.58 (s, 3H), 2.58 (s, 1H), 3.44 (s, 3H), 3.68 (d, *J* = 5.6 Hz, 1H), 4.18 (dd, *J* = 5.6, 8.1 Hz, 1H), 4.36 (d, *J* = 8.1 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 5.0-5.03 (m, 1H), 5.04-5.06 (m, 1H), 5.32 (d, *J* = 6.6 Hz, 1H), 6.13 (dd, *J* = 10.4, 18.0 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -1.9 (CH₃), -1.8 (CH₃), 18.5 (C), 21.9 (CH₃), 24.2 (CH₃), 25.3 (CH₃), 26.4 (CH₃), 27.2 (CH₃), 31.2 (CH₃), 41.9 (C), 56.4 (CH₃), 70.5 (C), 76.0 (CH), 76.3 (CH), 77.3 (CH), 84.2 (CH), 86.6 (C), 97.3 (CH₂), 107.2 (C), 112.5 (CH₂), 145.0 (CH) ppm.

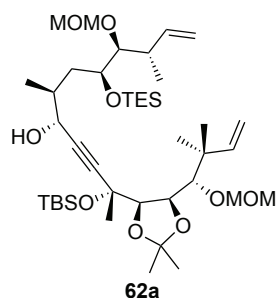
IR (ATR) ν 3241, 2930, 2858, 2361, 2342, 1463, 1369, 1252, 1134, 1069, 1035, 938, 835 cm⁻¹.

HRMS (ESI) calcd for C₂₃H₄₂O₅Si [M+Na]⁺, 449.2700; found 449.2703 +/- 5ppm.

Optical Rotation: [α]_D¹⁷(c 1.0, CHCl₃) = -92.2°.



Alcohol 62. To a solution of alkyne **61** (82 mg, 0.192 mmol, 2.0 eq) and HMPA (60 μL, 0.346 mmol, 3.6 eq) in THF (1.5 mL) was added *t*-BuLi (1.9 M in pentane, 101 μL, 0.192 mmol, 2.0 eq) at -78 °C. After stirring for 30 minutes at that temperature 30 μL of the reaction mixture were removed *via* a syringe and quenched by the addition of D₂O (mini-quench). After ¹H-NMR analysis, which indicated a 50% lithiation of the alkyne, two additional equivalents of *t*-BuLi (101 μL) were added. After 25 minutes another sample for an NMR was taken and the analysis indicated complete lithiation of the alkyne. A solution of aldehyde **48** (33 mg, 0.096 mmol, 1.0 eq) in THF (0.5 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 2:1 diastereomeric ratio (**62a**, less polar diastereomer, 41 mg, and **62**, more polar diastereomer, 21 mg) in 80% overall yield as colorless oils.

**Alcohol 62a (major diastereomer):**

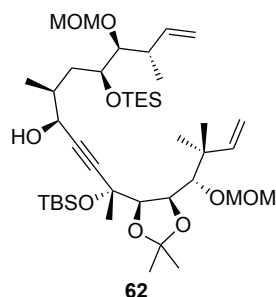
^1H NMR (400 MHz, CDCl_3): δ = 0.26 (s, 3H), 0.40 (s, 3H), 0.61 (quart, J = 7.9 Hz, 6H), 0.90 (s, 9H), 0.97 (t, J = 7.9 Hz, 9H), 1.03 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.27-1.36 (m, 1H), 1.33 (s, 3H), 1.49 (s, 3H), 1.55 (s, 3H), 1.65-1.74 (m, 1H), 1.87-1.99 (m, 1H), 2.41-2.53 (m, 1H), 3.27 (dd, J = 5.1, 5.6 Hz, 1H), 3.38 (s, 3H), 3.48 (s, 3H), 3.69 (d, J = 5.6 Hz, 1H), 3.88 (ddd, J = 1.8, 5.6, 9.7 Hz, 1H), 4.11 (dd, J = 1.8, 6.1 Hz, 1H), 4.21 (dd, J = 5.6, 8.3 Hz, 1H), 4.26 (d, J = 1.8 Hz, 1H), 4.51 (d, J = 8.3 Hz, 1H), 4.56 (d, J = 7.3 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.93-5.08 (m, 4H), 5.71 (d, J = 7.3 Hz, 1H), 5.86 (ddd, J = 8.2, 10.2, 17.3 Hz, 1H), 6.15 (dd, J = 10.2, 18.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -1.9 (CH_3), -1.6 (CH_3), 5.4 (CH_2), 7.2 (CH_3), 15.3 (CH_3), 18.5 (C), 19.0 (CH_3), 22.2 (CH_3), 24.2 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 27.1 (CH_3), 31.1 (CH_3), 35.0 (CH), 35.8 (CH_2), 39.0 (CH), 41.7 (C), 56.0 (CH_3), 56.4 (CH_3), 67.4 (CH), 70.6 (C), 72.2 (CH), 72.7 (CH), 77.5 (CH), 84.5 (CH), 85.2 (CH), 87.1 (C), 87.5 (C), 95.5 (CH_2), 98.2 (CH_2), 107.2 (C), 112.7 (CH_2), 114.3 (CH_2), 141.6 (CH), 144.9 (CH) ppm.

IR (ATR) ν 3442, 2956, 2879, 2360, 2339, 1719, 1638, 1462, 1416, 1369, 1218, 1251, 1037, 910, 835 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{41}\text{H}_{78}\text{O}_9\text{Si}_2$ $[\text{M}+\text{Na}]^+$, 793.5082; found 793.5075 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -79.5^\circ$.

**Alcohol 62 (minor diastereomer):**

^1H NMR (400 MHz, CDCl_3): δ = 0.25 (s, 3H, CH_3 -TBS), 0.34 (s, 3H, CH_3 -TBS), 0.60 (quart, J = 7.9 Hz, 6H, TES- CH_2 -VIII), 0.89 (s, 9H, $t\text{Bu}$ -TBS), 0.96 (t, J = 7.9 Hz, 9H, TES- CH_3 -VII), 0.99 (d, J = 6.6 Hz, 3H, CH_3 -VI), 1.09 (d, J = 7.6 Hz, 3H, CH_3 -IV), 1.11 (s, 3H, CH_3 -II), 1.13 (s, 3H, CH_3 -III), 1.31-1.40 (m, 1H, CH_2 -U₂), 1.32 (s, 3H, CH_3 -Z), 1.54 (s, 3H, CH_3 -X), 1.57 (s, 3H, CH_3 -V), 1.171-1.81 (m, 1H, CH_2 -U₁), 1.82-1.94 (m, 1H, CH-T), 2.41-2.52 (m, 1H, CH-S), 3.26 (dd, J = 5.3, 5.3 Hz, 1H, CH-J), 3.37 (s, 3H, OCH_3 -Q), 3.48 (s, 3H, OCH_3 -P), 3.70 (d, J = 5.6 Hz, 1H, CH-

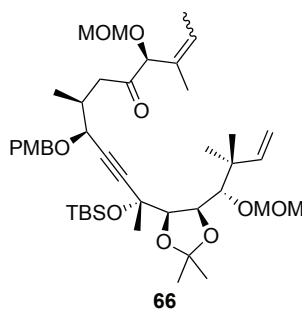
K), 3.86 (ddd, $J = 1.8, 5.3, 9.6$ Hz, 1H, CH-M), 4.19 (dd, $J = 5.6, 8.5$ Hz, 1H, CH-XII), 4.25 (d, $J = 4.3$ Hz, 1H, OH), 4.28-4.32 (m, 1H, CH-O), 4.41 (d, $J = 8.2$ Hz, 1H, CH-L), 4.53 (d, $J = 7.3$ Hz, 1H, CH₂-G₂), 4.60 (d, $J = 7.1$ Hz, 1H, CH₂-F₂), 4.69 (d, $J = 7.1$ Hz, 1H, CH₂-F₁), 4.94-5.08 (m, 4H, CH₂-D_{1,2}, CH₂-C_{1,2}), 5.68 (d, $J = 7.3$ Hz, 1H, CH₂-G₁), 5.86 (ddd, $J = 8.1, 10.2, 17.3$ Hz, 1H, CH-B), 6.14 (dd, $J = 10.4, 17.9$ Hz, 1H, CH-A) ppm.

¹³C NMR (100 MHz, CDCl₃): $\delta = -1.9$ (CH₃-TBS), 5.4 (CH₂-VIII), 7.1 (CH₃-VII), 15.0 (CH₃-VI), 18.4 (C-V), 18.9 (CH₃-IV), 22.2 (CH₃-III), 24.2 (CH₃-II), 25.0 (CH₃-Z), 26.4 (CH₃-Y), 27.6 (CH₃-X), 31.7 (CH₃-V), 35.4 (CH₂-U), 35.5 (CH-T), 38.9 (CH-S), 41.7 (C-R), 56.0 (CH₃-Q), 56.3 (CH₃-P), 67.3 (CH-O), 71.0 (C-N), 72.2 (CH-M), 73.6 (CH-L), 76.8 (CH-XII), 84.1 (CH-K), 85.1 (CH-J), 87.8 (C-I), 89.3 (C-H), 95.6 (CH₂-G), 98.2 (CH₂-H), 107.1 (C-E), 112.7 (CH₂-D), 114.4 (CH₂-C), 141.6 (C-B), 144.9 (C-A) ppm.

IR (ATR) ν 3442, 2956, 2879, 2360, 2339, 1719, 1638, 1462, 1416, 1369, 1218, 1251, 910 cm⁻¹.

HRMS (ESI) calcd for C₄₁H₇₈O₉Si₂ [M+Na]⁺, 793.5082; found 793.5076 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.35, CHCl₃) = -78.2°.



Ketone 66:

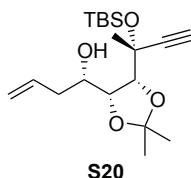
¹H NMR (400 MHz, CDCl₃): $\delta = 0.25$ (s, 3H), 0.36 (s, 3H), 0.90 (s, 9H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.34 (s, 3H), 1.50 (m, 3H), 1.55 (s, 3H), 1.63 (s, 3H), 1.67 (d, $J = 6.8$ Hz, 3H), 2.43 (dd, $J = 8.1, 17.1$ Hz, 1H), 2.47-2.55 (m, 1H), 2.69 (dd, $J = 5.0, 17.1$ Hz, 1H), 3.31 (s, 3H), 3.40 (s, 3H), 3.71 (d, $J = 5.6$ Hz, 1H), 3.80 (s, 3H), 4.07 (d, $J = 4.3$ Hz, 1H), 4.18 (dd, $J = 5.6, 7.9$ Hz, 1H), 4.32 (d, $J = 11.3$ Hz, 1H), 4.34 (d, $J = 7.9$ Hz, 1H), 4.47 (s, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.64-4.68 (m, 2H), 5.01-5.06 (m, 2H), 5.30 (d, $J = 6.8$ Hz, 1H), 5.65-5.72 (m, 1H), 6.12 (dd, $J = 10.4, 18.0$ Hz, 1H), 6.83-6.87 (m, 2H), 7.19-7.23 (m, 2H) ppm.

¹³C NMR (100 MHz, CDCl₃): $\delta = -1.7$ (CH₃), -1.8 (CH₃), 11.6 (CH₃), 13.7 (CH₃), 15.8 (CH₃), 18.5 (C), 21.9 (CH₃), 24.3 (CH₃), 25.2 (CH₃), 26.4 (CH₃), 27.4 (CH₃), 31.9 (CH₃), 33.4 (CH₃), 41.7 (C), 55.4 (CH₃), 55.8 (CH₃), 56.4 (CH₃), 70.8 (CH₂), 71.0 (C), 72.6 (CH), 76.3 (CH), 77.1 (CH), 84.5 (CH), 85.5 (C), 86.6 (CH), 89.5 (C), 93.8 (CH₂), 97.6 (CH₂), 107.2 (C), 112.6 (CH₂), 113.8 (CH), 128.0 (CH), 129.4 (CH), 130.3 (C), 130.6 (C), 145.0 (CH), 159.3 (C), 207.1 (C) ppm.

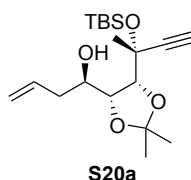
IR (ATR) ν 2928, 2856, 1724, 1370, 1252, 1150, 1103, 1039, 835, 779 cm⁻¹.

HRMS (ESI) calcd for C₄₃H₇₀O₁₀Si [M+Na]⁺, 797.4636; found 797.4641 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl₃) = +15.1°.



(S)-1-((4R,5R)-5-((R)-2-((tert-Butyldimethylsilyl)oxy)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (S20). A solution of aldehyde **58** (921 mg, 2.95 mmol, 1.0 eq) in Et₂O (100 mL) was treated with a solution of allylmagnesium bromide (1.0 M in Et₂O, 8.85 mL, 8.85 mmol, 3.0 eq) at -78 °C. The mixture was allowed to stir for 90 minutes before the reaction was terminated by the addition of a saturated, aqueous solution of NH₄Cl (50 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 30 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent was removed under vacuum. The crude material was further purified by flash column chromatography (hexane/EtOAc 19:1) affording a 1:1.5 diastereomeric mixture of the corresponding secondary alcohols (**S20**, desired, minor diastereomer, 329 mg and **S20a**, undesired, major diastereomer, 521 mg) in 82% overall yield.



Major diastereomer **S20a**:

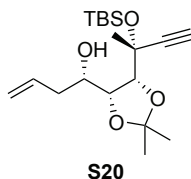
¹H NMR (400 MHz, CDCl₃): δ = 0.27 (s, 3H), 0.35 (s, 3H), 0.90 (s, 9H), 1.33 (s, 3H), 1.53 (s, 3H), 1.61 (s, 3H), 2.21-2.32 (m, 1H), 2.54-2.62 (m, 1H), 2.59 (s, 1H), 3.49-3.54 (m, 1H), 3.90 (d, *J* = 5.8 Hz, 1H), 4.10 (dd, *J* = 5.8, 9.7 Hz, 1H), 4.46-4.58 (m, 1H), 5.06-5.11 (m, 1H), 5.12-5.20 (m, 1H), 5.98 (dddd, *J* = 6.9, 6.9, 10.2, 17.1 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -3.1 (CH₃), -2.3 (CH₃), 18.3 (C), 25.3 (CH₃), 25.9 (CH₃), 27.3 (CH₃), 29.9 (CH₃), 38.0 (CH₂), 67.2 (CH), 71.2 (C), 75.8 (CH), 80.8 (CH), 83.4 (CH), 85.7 (C), 108.8 (C), 117.0 (CH₂), 134.8 (CH) ppm.

IR (ATR) ν 3489, 3254, 2930, 2858, 2360, 1463, 1368, 1304, 1254, 1133, 1065, 967, 830, 784 cm⁻¹.

HRMS (ESI) calcd for C₁₉H₃₄O₄Si [M+Na]⁺, 377.2124; found 377.2127 +/- 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = -13.8°.



Minor diastereomer **S20**:

¹H NMR (400 MHz, CDCl₃): δ = 0.24 (s, 3H), 0.25 (s, 3H), 0.88 (s, 9H), 1.39 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 2.35-2.42 (m, 2H), 2.67 (s, 1H), 2.82 (d, *J* = 2.5 Hz, 1H), 3.97 (d, *J* = 6.0 Hz, 1H),

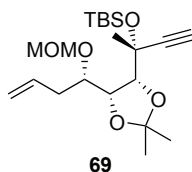
4.04 (dd, $J = 2.8, 6.0$ Hz, 1H), 4.19-4.24 (m, 1H), 5.04-5.18 (m, 2H), 5.88 (dddd, $J = 7.0, 7.0, 10.2, 17.2$ Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -2.8$ (CH_3), -2.2 (CH_3), 18.3 (C), 25.8 (CH_3), 25.9 (CH_3), 26.7 (CH_3), 30.7 (CH_3), 38.8 (CH_2), 68.0 (CH), 69.5 (C), 75.4 (CH), 79.2 (CH), 83.8 (CH), 86.0 (C), 108.9 (C), 117.2 (CH_2), 135.5 (CH) ppm.

IR (ATR) ν 3489, 3254, 2930, 2858, 2360, 1463, 1368, 1304, 1254, 1133, 1065, 967, 830 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{34}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$, 377.2124; found 377.2128 ± 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = +12.3^\circ$.



***tert*-Butyl(((*R*)-2-(((*4R,5R*)-5-((*S*)-1-(methoxymethoxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-2-yl)oxy)dimethylsilane (**69**).** To a solution of secondary alcohol **S20** (329 mg, 0.93 mmol, 1.0 eq) in 1,2-dichloroethane (4.6 mL) were added DIPEA (807 μL , 4.65 mmol, 5.0 eq) and MOM-Cl (212 μL , 2.79 mmol, 3.0 eq) at 0 $^\circ\text{C}$. The mixture was warmed to 50 $^\circ\text{C}$ (stoppered round bottom flask) and was stirred for 14 hours before the reaction was quenched by the addition of H_2O (5 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) affording **69** (336 mg) in 91% yield.

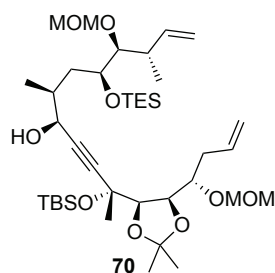
^1H NMR (400 MHz, CDCl_3): $\delta = 0.20$ (s, 3H), 0.32 (s, 3H), 0.88 (s, 9H), 1.34 (s, 3H), 1.54 (s, 3H), 1.55 (s, 3H), 2.39-2.48 (m, 1H), 2.59 (s, 1H), 2.60-2.69 (m, 1H), 3.41 (s, 3H), 3.72 (d, $J = 5.5$ Hz, 1H), 4.27 (dd, $J = 5.5, 10.0$ Hz, 1H), 4.65-4.72 (m, 1H), 4.70 (d, $J = 6.8$ Hz, 1H), 5.0 (d, $J = 6.8$ Hz, 1H), 5.05-5.10 (m, 1H), 5.10-5.13 (m, 1H), 5.98 (dddd, $J = 4.9, 9.0, 10.9, 16.4$ Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -2.7$ (CH_3), -2.1 (CH_3), 18.3 (C), 25.5 (CH_3), 26.1 (CH_3), 27.4 (CH_3), 30.1 (CH_3), 37.5 (CH_2), 55.7 (CH_3), 70.3 (C), 71.5 (CH), 75.8 (CH), 80.0 (CH), 82.8 (CH), 86.2 (C), 96.6 (CH_2), 108.2 (C), 117.6 (CH_2), 134.6 (CH) ppm.

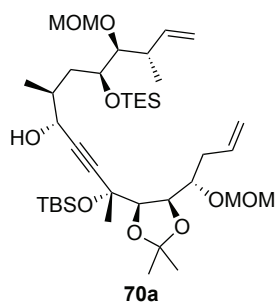
IR (ATR) ν 2931, 2858, 2361, 2341, 1473, 1380, 1252, 1211, 1141, 1092, 1038, 916, 836 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{38}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$, 421.2387; found 421.2392 ± 5 ppm.

Optical Rotation: $[\alpha]_D^{20}(\text{c } 1.0, \text{CHCl}_3) = -34.1^\circ$.



Alcohol 70. To a solution of alkyne **69** (207 mg, 0.52 mmol, 2.0 eq) and HMPA (163 μ L, 0.94 mmol, 3.6 eq) in THF (4.3 mL) was added *t*-BuLi (1.7 M in pentane, 306 μ L, 0.52 mmol, 2.0 eq) at -78 °C. After 30 minutes at this temperature 30 μ L of the reaction mixture were removed *via* a syringe and quenched by the addition of D₂O (mini-quench). ¹H-NMR-analysis indicated complete lithiation of the alkyne and a solution of aldehyde **48** (90 mg, 0.26 mmol, 1.0 eq) in THF (1 mL) was added to the reaction mixture. The mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH₄Cl (3 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 19:1 to 9:1) the secondary alcohols were isolated in a 1.5:1 diastereomeric ratio (**70a**, less polar diastereomer, 75 mg, and **70**, more polar diastereomer, 46 mg) in 63% overall yield as colorless oils.



Alcohol 70a (major diastereomer):

¹H NMR (400 MHz, CDCl₃): δ = 0.23 (s, 3H), 0.33 (s, 3H), 0.62 (quart, J = 7.9 Hz, 6H), 0.87 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.04 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.33 (s, 3H), 1.33-1.39 (m, 1H), 1.50 (s, 3H), 1.51 (s, 3H), 1.67 (ddd, J = 3.0, 9.6, 13.9 Hz, 1H), 1.87-1.99 (m, 1H), 2.34-2.62 (m, 3H), 3.27 (dd, J = 4.9, 5.7 Hz, 1H), 3.38 (s, 3H), 3.44 (s, 3H), 3.73 (d, J = 5.6 Hz, 1H), 3.88 (ddd, J = 2.0, 5.7, 9.6 Hz, 1H), 4.17 (d, J = 3.0 Hz, 1H), 4.21 (dd, J = 3.0, 5.6 Hz, 1H), 4.30 (dd, J = 5.6, 10.4 Hz, 1H), 4.58 (d, J = 7.1 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.85 (ddd, J = 4.3, 5.4, 10.4 Hz, 1H), 4.93-5.02 (m, 2H), 5.05-5.13 (m, 2H), 5.24 (d, J = 7.1 Hz, 1H), 5.87 (ddd, J = 8.1, 10.4, 17.2 Hz, 1H), 5.91-6.02 (m, 1H) ppm.

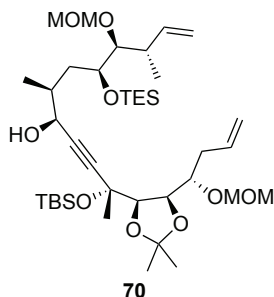
¹³C NMR (100 MHz, CDCl₃): δ = -2.7 (CH₃), -1.9 (CH₃), 5.4 (CH₂), 7.1 (CH₃), 15.1 (CH₃), 18.3 (C), 19.0 (CH₃), 25.5 (CH₃), 26.1 (CH₃), 27.3 (CH₃), 29.4 (CH₃), 35.2 (CH), 36.0 (CH₂), 38.0 (CH₂), 39.0 (CH), 55.6 (CH₃), 56.0 (CH₃), 67.3 (CH), 68.9 (CH), 70.3 (C), 72.2 (CH), 80.4 (CH),

83.3 (CH), 85.2 (CH), 87.3 (C), 87.4 (C), 95.7 (CH₂), 98.2 (CH₂), 108.2 (C), 114.4 (CH₂), 117.9 (CH₂), 134.4 (CH), 141.6 (CH) ppm.

IR (ATR) ν 3447, 2956, 2878, 1639, 1369, 1253, 1217, 1146, 1038, 1003, 908, 834, 779 cm⁻¹.

HRMS (ESI) calcd for C₃₉H₇₄O₉Si₂ [M+Na]⁺, 765.4769; found 765.4771 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 1.0, CHCl₃) = -31.1°.



Alcohol 70 (minor diastereomer):

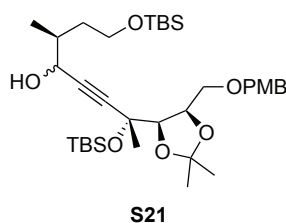
¹H NMR (400 MHz, CDCl₃): δ = 0.20 (s, 3H), 0.29 (s, 3H), 0.61 (quart, J = 7.9 Hz, 6H), 0.88 (s, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.00 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.39 (ddd, J = 2.0, 10.9, 13.6 Hz, 1H), 1.51 (s, 3H), 1.56 (s, 3H), 1.78 (ddd, J = 2.8, 9.6, 13.6 Hz, 1H), 1.83-1.94 (m, 1H), 2.36-2.53 (m, 2H), 2.54-2.63 (m, 1H), 3.27 (dd, J = 5.3, 5.6 Hz, 1H), 3.38 (s, 3H), 3.43 (s, 3H), 3.72 (d, J = 5.6 Hz, 1H), 3.83-3.92 (m, 2H), 4.25-4.31 (m, 2H), 4.55 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.84 (ddd, J = 4.3, 5.6, 10.1 Hz, 1H), 4.95-5.03 (m, 2H), 5.06-5.13 (m, 2H), 5.29 (d, J = 7.1 Hz, 1H), 5.86 (ddd, J = 8.1, 10.2, 17.3 Hz, 1H), 5.91-6.03 (m, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -2.7 (CH₃), -2.1 (CH₃), 5.3 (CH₂), 7.1 (CH₃), 15.1 (CH₃), 18.3 (C), 18.8 (CH₃), 25.4 (CH₃), 26.1 (CH₃), 27.8 (CH₃), 29.7 (CH₃), 35.3 (CH₂), 35.5 (CH), 38.0 (CH₂), 39.1 (CH), 55.6 (CH₃), 56.0 (CH₃), 67.4 (CH), 68.7 (CH), 70.6 (C), 72.3 (CH), 80.6 (CH), 82.9 (CH), 85.0 (CH), 87.7 (C), 88.6 (C), 95.7 (CH₂), 98.1 (CH₂), 108.2 (C), 114.4 (CH₂), 117.8 (CH₂), 134.4 (CH), 141.7 (CH) ppm.

IR (ATR) ν 3447, 2956, 2878, 1639, 1369, 1253, 1217, 1146, 1038, 1003, 908, 834, 779 cm⁻¹.

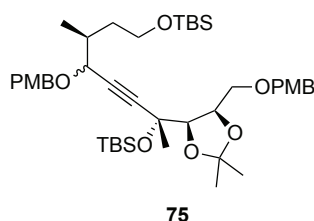
HRMS (ESI) calcd for C₃₉H₇₄O₉Si₂ [M+Na]⁺, 765.4769; found 765.4758 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_D^{20}$ (c 0.7, CHCl₃) = -44.4°.

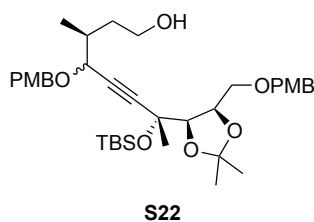


Alcohol S21. To a solution of alkyne **57** (565 mg, 1.3 mmol, 2.0 eq) and HMPA (407 μ L, 2.34 mmol, 3.6 eq) in THF (11 mL) was added *t*-BuLi (1.7 M in pentane, 0.75 mL, 1.3 mmol, 2.0 eq) at -78 °C. After stirring for 30 minutes at that temperature 30 μ L of the reaction mixture were removed *via* a syringe and quenched by the addition of D₂O (mini-quench). ¹H-NMR-analysis

indicated a 40% lithiation of the alkyne, and 1 equivalent of *t*-BuLi (375 μ L) was added. After 25 minutes another mini-quench showed complete lithiation of the alkyne and a solution of aldehyde **74** (150 mg, 0.65 mmol, 1.0 eq) in THF (1.5 mL) was added. The reaction mixture was stirred for 1 hour before it was quenched by the addition of a saturated, aqueous solution of NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (hexane/EtOAc 9:1 to 5:1) the secondary alcohol **S21** (323 mg) was isolated as an inseparable 2:1 diastereomeric mixture in 76% overall yield.



Alkyne 75. To a solution of the diastereomeric mixture of alcohol **S21** (380 mg, 0.58 mmol, 1.0 eq) in DMF (5.8 mL) was added NaH (60% dispersion in mineral oil, 46 mg, 1.16 mmol, 2.0 eq) at 0 °C. After 30 minutes PMB-Cl (141 μ L, 1.04 mmol, 1.8 eq) was added and the reaction mixture was allowed to stir for additional 8 hours at 0 °C. The reaction was terminated by the addition of a saturated, aqueous solution of NaHCO_3 (5 mL). After dilution with Et_2O the layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL) once, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude products were further purified by flash column chromatography (hexane/EtOAc 19:1 to 9:1) to provide the inseparable mixture of diastereomers **75** (311 mg) in 70% yield.



Alcohol S22. A solution of **75** (456 mg, 0.59 mmol, 1.0 eq) dissolved in MeOH (12.8 mL) was treated with camphorsulfonic acid (27 mg, 0.12 mmol, 0.2 eq) at 0 °C and was allowed to stir for 90 minutes before it was quenched by the addition of a saturated, aqueous solution of NaHCO_3 (8 mL). After dilution with EtOAc (10 mL), the layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude mixture of primary alcohols was purified by HPLC (hexane/EtOAc 7:1) affording **S22a** (less polar diastereomer, 238 mg) and **S22b** (more polar diastereomer, 119 mg) as colorless oils in a 2:1 diastereomeric ratio and 92% overall yield.

S22a (major diastereomer):

^1H NMR (400 MHz, CDCl_3): δ = 0.13 (s, 3H), 0.19 (s, 3H), 0.79 (s, 9H), 1.02 (d, J = 7.1 Hz, 3H), 1.38 (s, 3H), 1.48-1.54 (m, 1H), 1.53 (s, 3H), 1.57 (s, 3H), 1.90 (ddd, J = 6.5, 13.1, 13.4 Hz, 1H), 2.0 (ddd, J = 5.2, 6.7, 13.1 Hz, 1H), 2.12 (bs, 1H), 3.54-3.64 (m, 1H), 3.68-3.76 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.85 (d, J = 6.6 Hz, 1H), 3.96 (dd, J = 1.9, 10.2 Hz, 1H), 3.98 (d, J = 5.2 Hz, 1H), 4.11 (dd, J = 10.2, 10.2 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.48-4.53 (m, 1H), 4.64 (d, J = 12.1 Hz, 1H), 4.77 (d, J = 11.4 Hz, 1H), 6.80-6.85 (m, 2H), 6.85-6.90 (m, 2H), 7.22-7.30 (m, 4H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -2.8 (CH_3), -2.1 (CH_3), 16.8 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3), 27.5 (CH_3), 30.7 (CH_3), 35.6 (CH_3), 36.2 (CH_2), 55.4 (CH_3), 55.43 (CH_3), 61.0 (CH_2), 68.7 (CH_2), 70.1 (C), 70.7 (CH_2), 73.1 (CH_2), 73.4 (CH), 77.7 (CH), 83.3 (CH), 83.8 (C), 89.2 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.8 (CH), 129.9 (C), 130.6 (C), 159.3 (C), 159.4 (C) ppm.

IR (ATR) ν 3437, 2929, 2856, 1514, 1302, 1249, 1090, 1037, 836, 779 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{56}\text{O}_8\text{Si}$ $[\text{M}+\text{Na}]^+$, 679.3642; found 679.3641 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = +14.8^\circ$.

S22b (minor diastereomer):

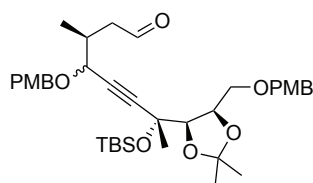
^1H NMR (400 MHz, CDCl_3): δ = 0.12 (s, 3H), 0.19 (s, 3H), 0.78 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H), 1.39 (s, 3H), 1.50-1.54 (m, 1H), 1.54 (s, 3H), 1.56 (s, 3H), 1.76-1.87 (m, 2H), 1.93-2.02 (m, 1H), 3.55-3.65 (m, 1H), 3.66-3.74 (m, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.85 (d, J = 6.6 Hz, 1H), 3.92 (d, J = 6.1 Hz, 1H), 3.94 (dd, J = 2.3, 10.4 Hz, 1H), 4.08 (dd, J = 10.1, 10.4 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 12.1 Hz, 1H), 4.49 (ddd, J = 2.3, 6.6, 10.1 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.77 (d, J = 11.4 Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.20-7.25 (m, 2H), 7.27-7.32 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ = -2.8 (CH_3), -2.1 (CH_3), 16.4 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3), 27.5 (CH_3), 30.6 (CH_3), 35.5 (CH), 36.2 (CH_2), 55.4 (CH_3 , 2x), 60.9 (CH_2), 68.8 (CH_2), 70.1 (C), 70.7 (CH_2), 73.1 (CH_2), 73.3 (CH), 77.7 (CH), 83.3 (CH), 84.4 (C), 88.6 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.8 (CH), 130.0 (C), 130.7 (C), 159.3 (C), 159.4 (C) ppm.

IR (ATR) ν 3437, 2929, 2856, 1514, 1302, 1249, 1090, 1037, 836, 779 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{56}\text{O}_8\text{Si}$ $[\text{M}+\text{Na}]^+$, 679.3642; found 679.3644 $\pm$ 5 ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -83.5^\circ$.

**76a/b****Aldehydes 76a and 76b:**

To a solution of IBX (126 mg, 0.45 mmol, 1.5 eq) in DMSO (1.5 mL) was added alcohol **S22a** (less polar diastereomer, 197 mg, 0.30 mmol, 1.0 eq) in DMSO (1.5 mL) and the reaction mixture was stirred for 3 hours at room temperature. As TLC-control showed total consumption of the starting material the reaction was terminated by the addition of H₂O (3 mL) at 0 °C. The resulting suspension was filtered through a plug of Celite and the filtrate was diluted with Et₂O (10 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic fractions were washed with H₂O (10 mL) and brine (10 mL) and dried over MgSO₄. After filtration the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexane/EtOAc 5:1 to 3:1) delivering aldehyde **76a** (163 mg) in 83% yield.

Aldehyde 76a:

¹H NMR (400 MHz, CDCl₃): δ = 0.12 (s, 3H), 0.18 (s, 3H), 0.80 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 1H), 1.38 (s, 3H), 1.52 (s, 3H), 1.57 (s, 3H), 2.30 (ddd, *J* = 2.3, 7.9, 16.7 Hz, 1H), 2.37-2.48 (m, 1H), 2.74 (ddd, *J* = 1.5, 5.1, 16.7 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.86 (d, *J* = 6.8 Hz, 1H), 3.97 (dd, *J* = 2.3, 10.5 Hz, 1H), 4.01 (d, *J* = 4.5 Hz, 1H), 4.06 (dd, *J* = 9.7, 10.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.48-4.53 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.22-7.27 (m, 4H), 9.72 (dd, *J* = 1.5, 2.3 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ = -2.7 (CH₃), -2.1 (CH₃), 16.4 (CH₃), 18.1 (C), 25.3 (CH₃), 25.8 (CH₃), 27.5 (CH₃), 30.7 (CH₃), 33.5 (CH), 46.9 (CH₂), 55.4 (CH₃, 2x), 68.9 (CH₂), 70.1 (C), 70.6 (CH₂), 72.1 (CH), 73.2 (CH₂), 77.8 (CH), 83.3 (CH), 87.1 (C), 89.5 (C), 108.9 (C), 113.9 (CH), 114.0 (CH), 129.3 (CH), 129.7 (CH), 130.0 (C), 130.7 (C), 159.3 (C), 159.4 (C), 202.0 (CH) ppm.

IR (ATR) ν 2956, 2931, 2856, 1727, 1612, 1513, 1462, 1302, 1248, 1092, 836 cm⁻¹.

HRMS (ESI) calcd for C₃₇H₅₄O₈Si [M+Na]⁺, 677.3486; found 677.3485 ± 5ppm.

Optical Rotation: [α]_D²⁰(c 1.0, CHCl₃) = +18.9°.

Starting from polar diastereomer **S22b** (150 mg, 0.23 mmol, 1.0 eq), diastereomeric aldehyde **76b**, was isolated in 82% yield (122 mg).

Aldehyde 76b:

¹H NMR (400 MHz, CDCl₃): δ = 0.11 (s, 3H), 0.19 (s, 3H), 0.79 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 2.32 (ddd, *J* = 1.8, 7.5, 16.3 Hz, 1H), 2.36-2.44 (m, 1H), 2.61 (ddd, *J* = 2.0, 5.3, 16.3 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.84 (d, *J* = 6.5 Hz, 1H), 3.85 (d, *J*

= 6.8 Hz, 1H), 3.95 (dd, $J = 2.3, 10.5$ Hz, 1H), 4.03 (dd, $J = 9.8, 10.5$ Hz, 1H), 4.36 (d, $J = 11.3$ Hz, 1H), 4.41 (d, $J = 12.0$ Hz, 1H), 4.49 (ddd, $J = 2.3, 6.5, 9.5$ Hz, 1H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.73 (d, $J = 11.3$ Hz, 1H), 6.79-6.84 (m, 2H), 6.85-6.90 (m, 2H), 7.20-7.25 (m, 2H), 7.25-7.29 (m, 2H), 9.70 (dd, $J = 1.8, 2.0$ Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = -2.8$ (CH_3), -2.1 (CH_3), 16.8 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3), 27.6 (CH_3), 30.5 (CH_3), 34.0 (CH), 47.6 (CH_2), 55.4 (CH_3 , 2x), 68.8 (CH_2), 70.1 (C), 70.7 (CH_2), 72.7 (CH), 73.1 (CH_2), 77.8 (CH), 83.3 (CH), 83.9 (C), 89.0 (C), 108.9 (C), 113.9 (CH, 2x), 129.3 (CH), 129.8 (C), 129.9 (CH), 130.7 (C), 159.3 (C), 159.5 (C), 201.9 (CH) ppm.

IR (ATR) ν 2956, 2931, 2856, 1727, 1612, 1513, 1462, 1302, 1248, 1092, 836 cm^{-1} .

HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{54}\text{O}_8\text{Si}$ $[\text{M}+\text{Na}]^+$, 677.3486; found 677.3479 $\pm$ 5ppm.

Optical Rotation: $[\alpha]_{\text{D}}^{20}(\text{c } 1.0, \text{CHCl}_3) = -67.8^\circ$.

References

- [1] M. Lorenz, M. Kalesse, *Org. Lett.* **2008**, *10*, 4371-4374.
- [2] J. D. Williams, V. P. Kamath, P. E. Morris, L. B. Townsend, *Org. Synth.* **2005**, *82*, 75-79.
- [3] N. Cohen, B. L. Banner, A. J. Laurenzano, L. Carozza, *Org. Synth.* **1985**, *63*, 127.

NMR-spectra

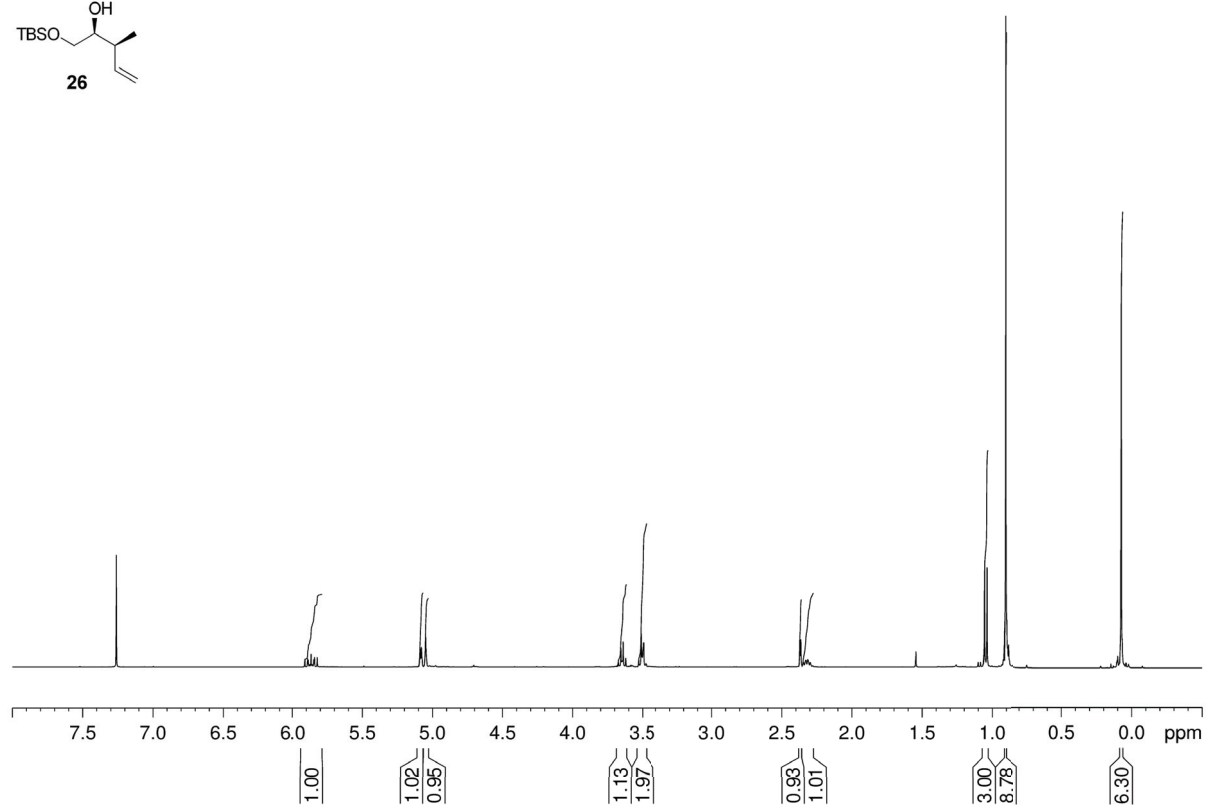
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Instrument frequency: ^1H : 400 MHz

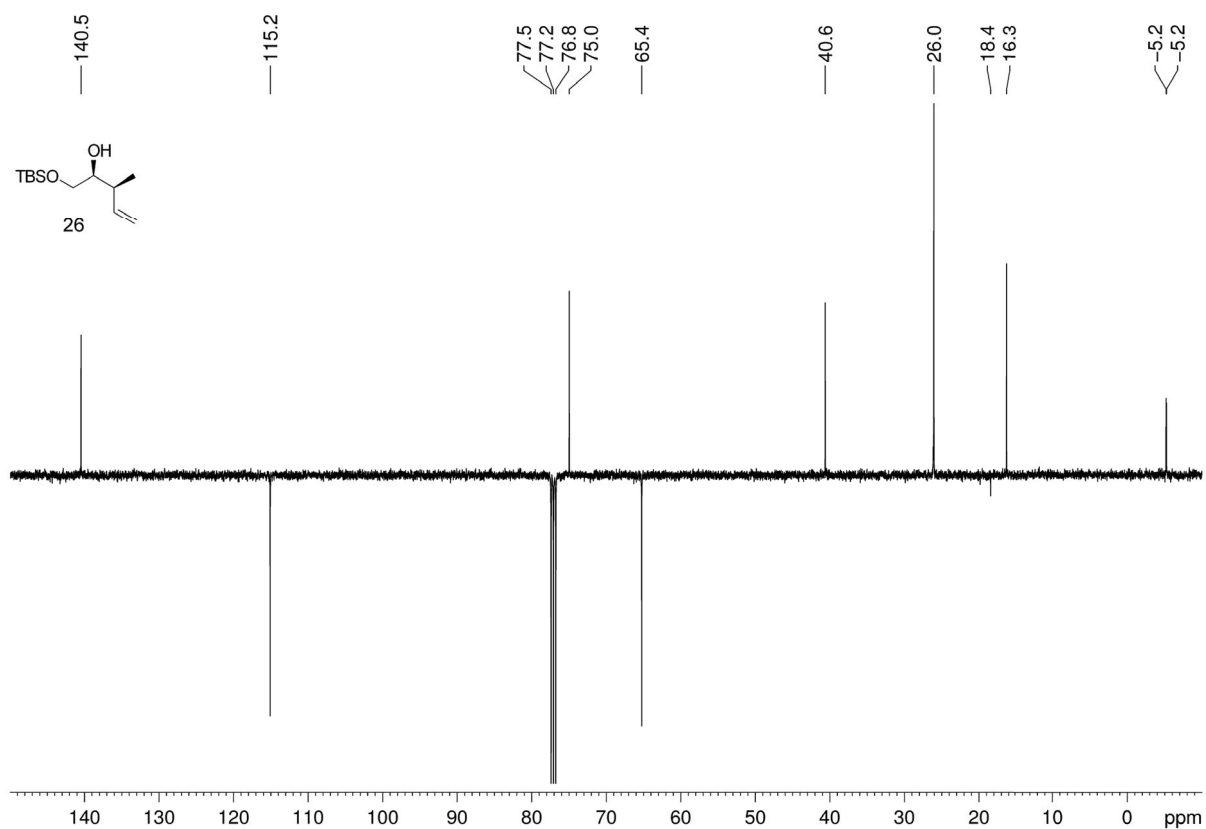
^{13}C : 100 MHz

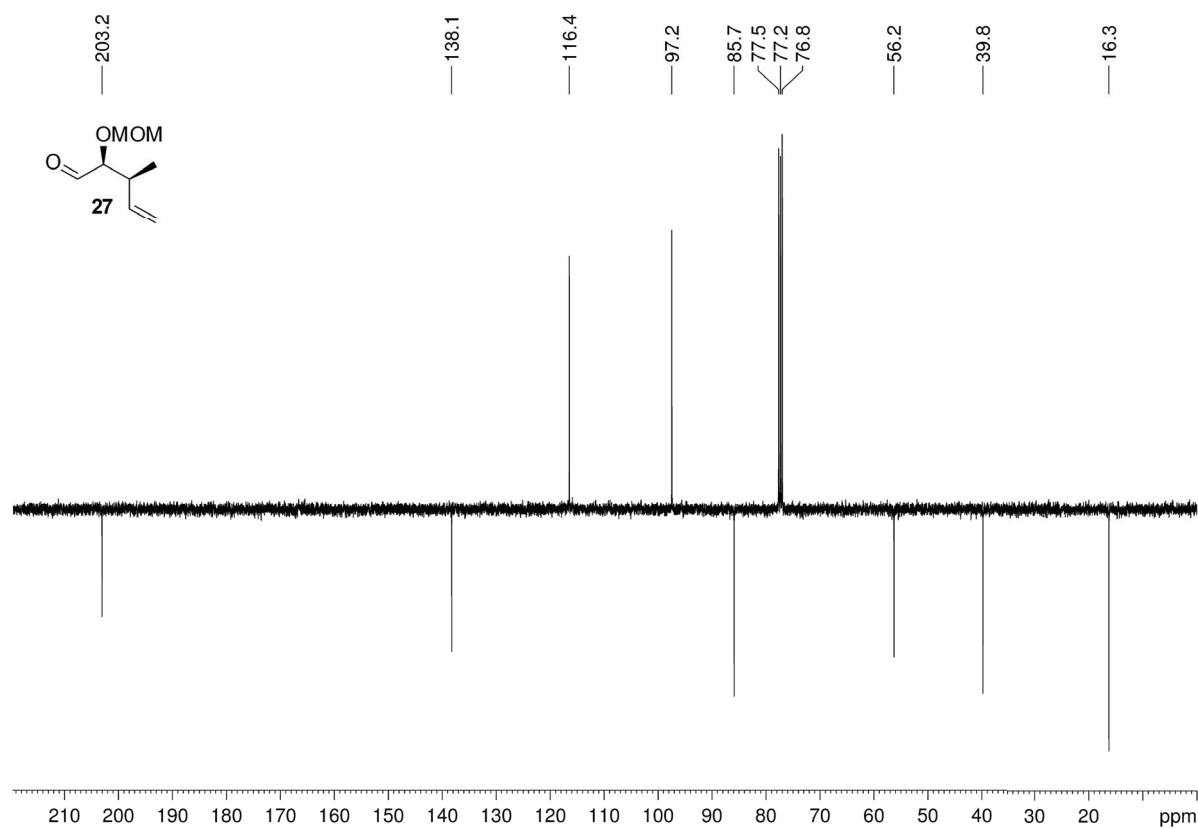
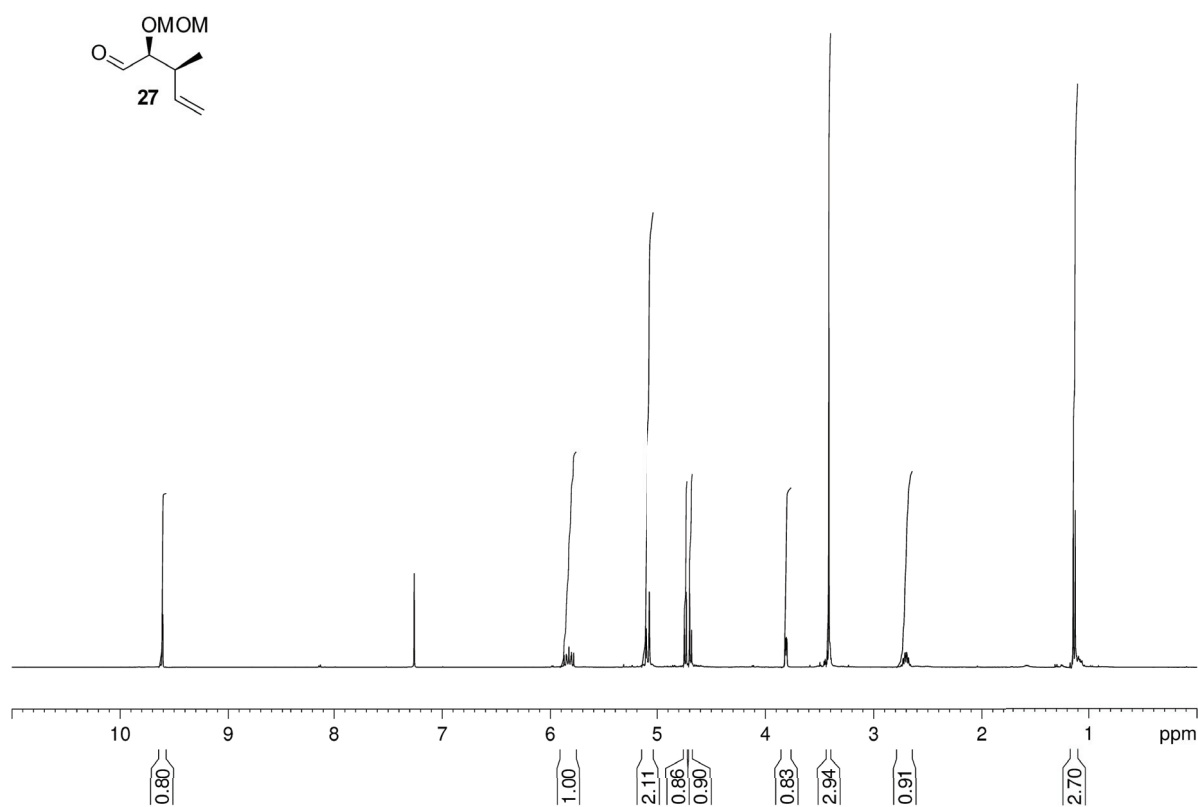
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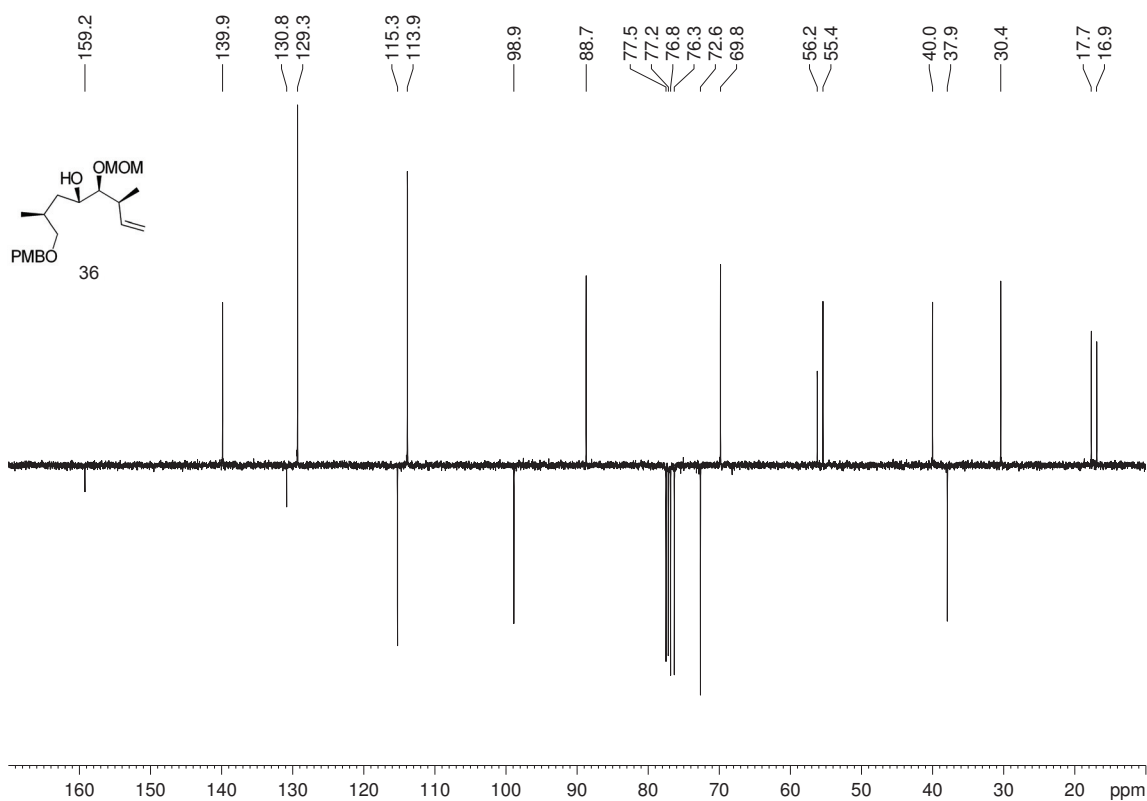
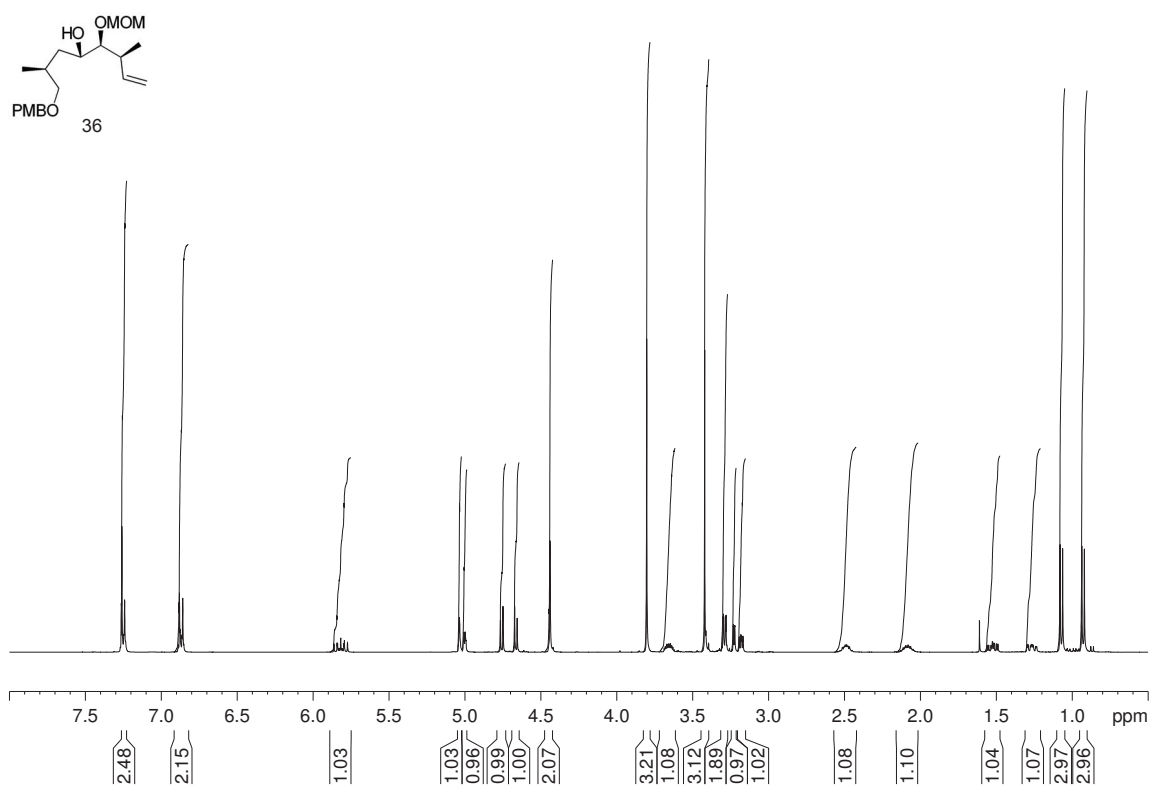
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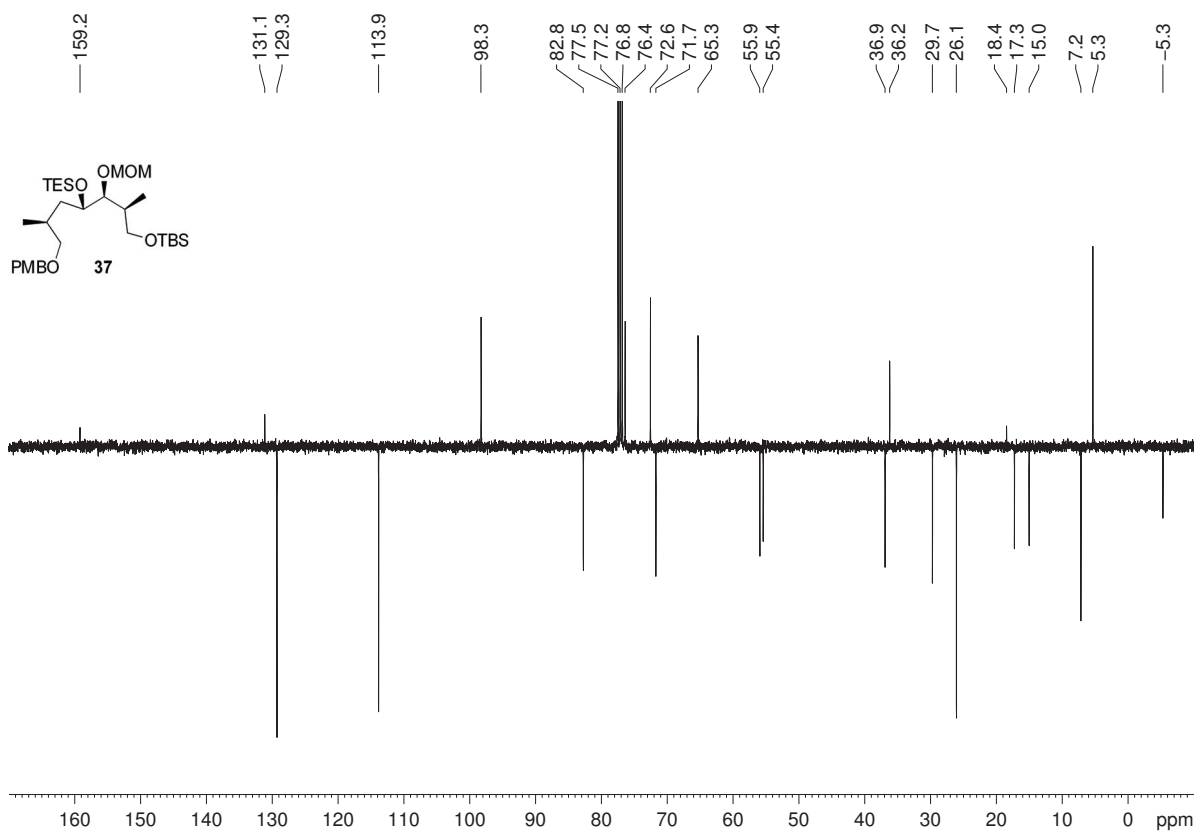
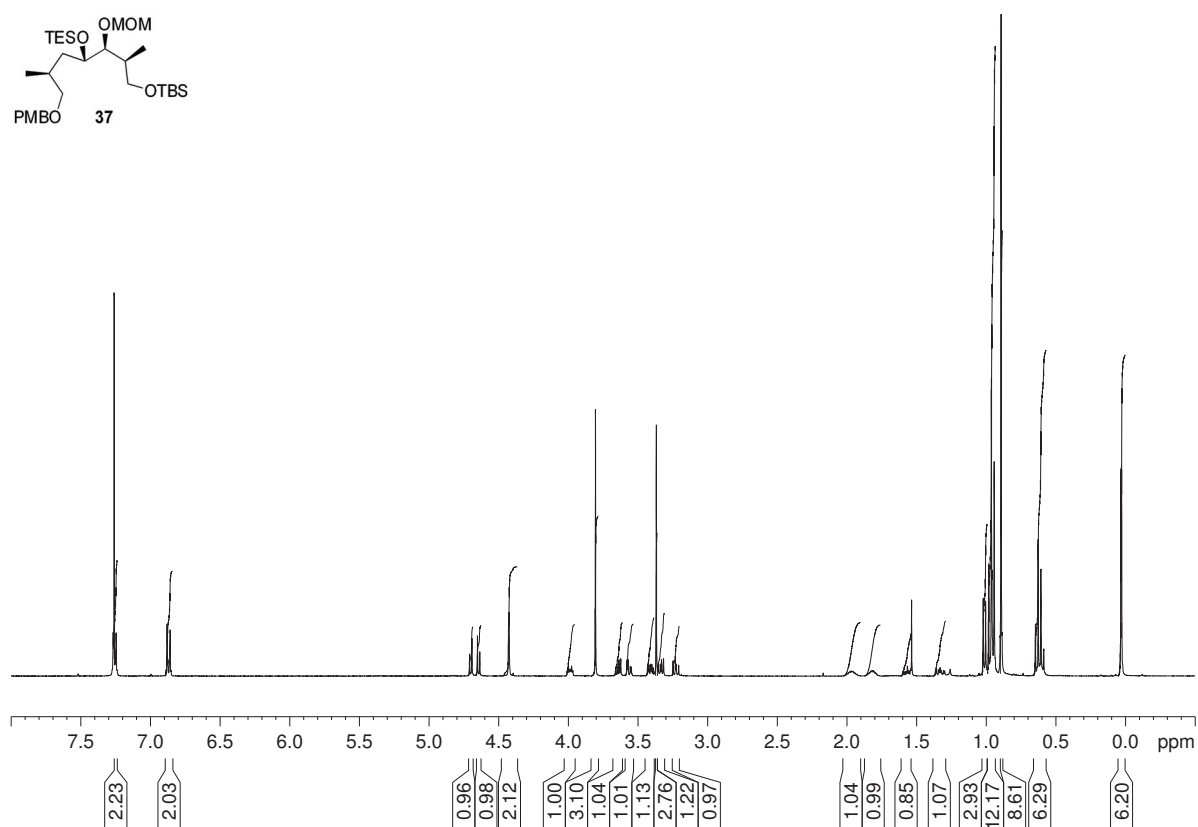
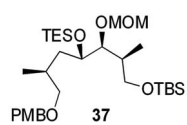
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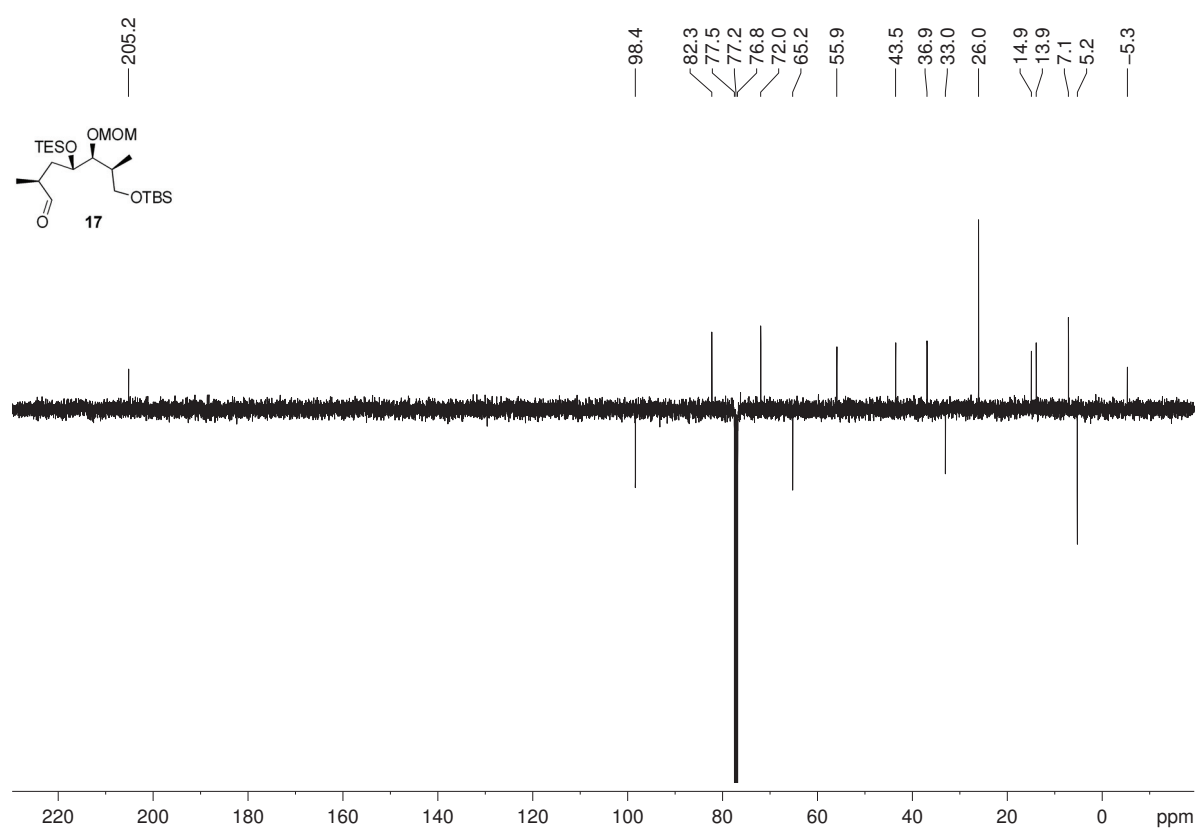
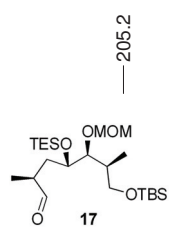
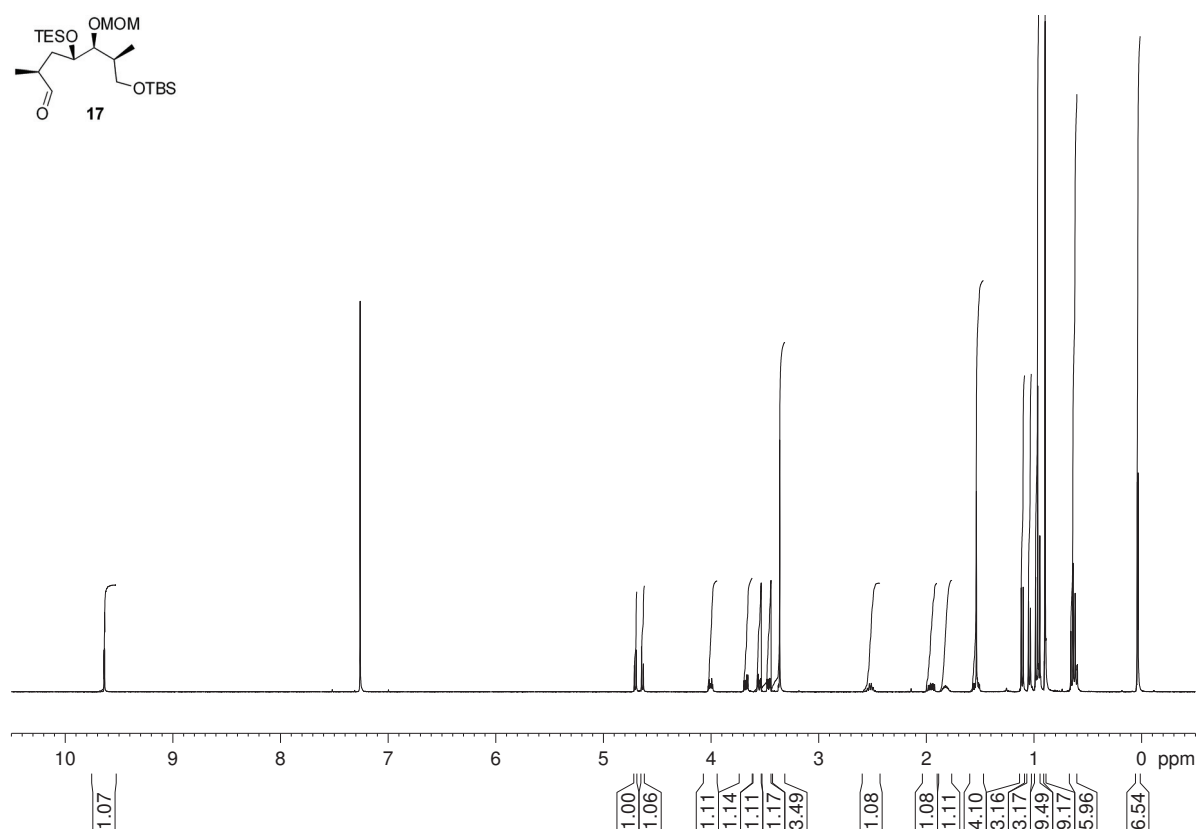
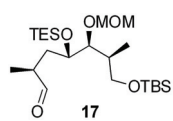
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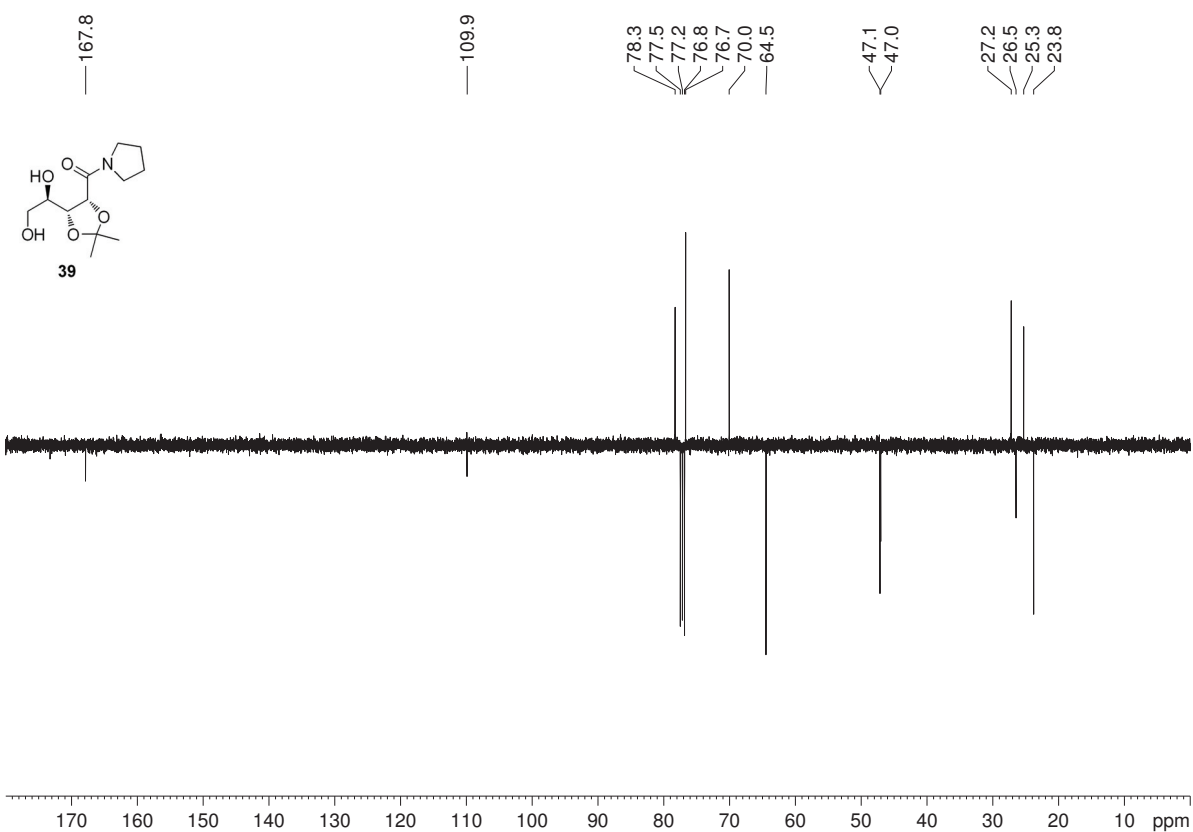
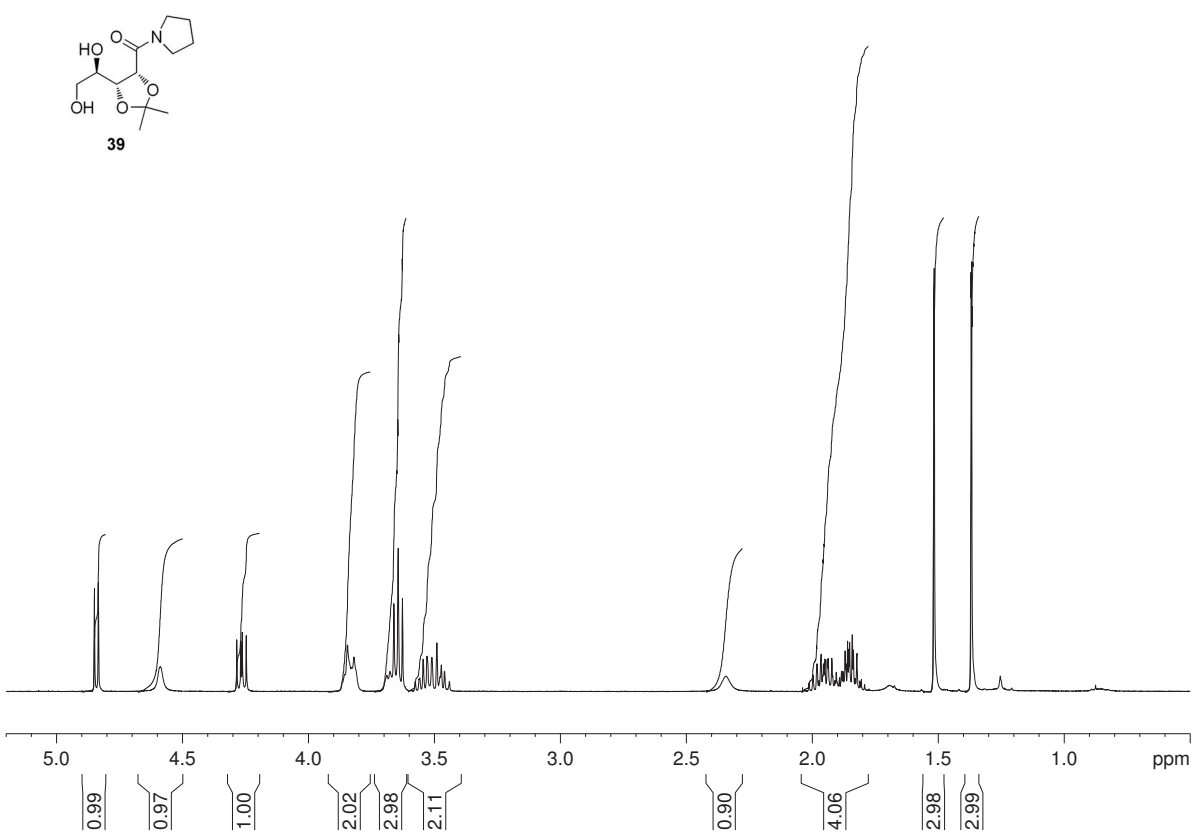


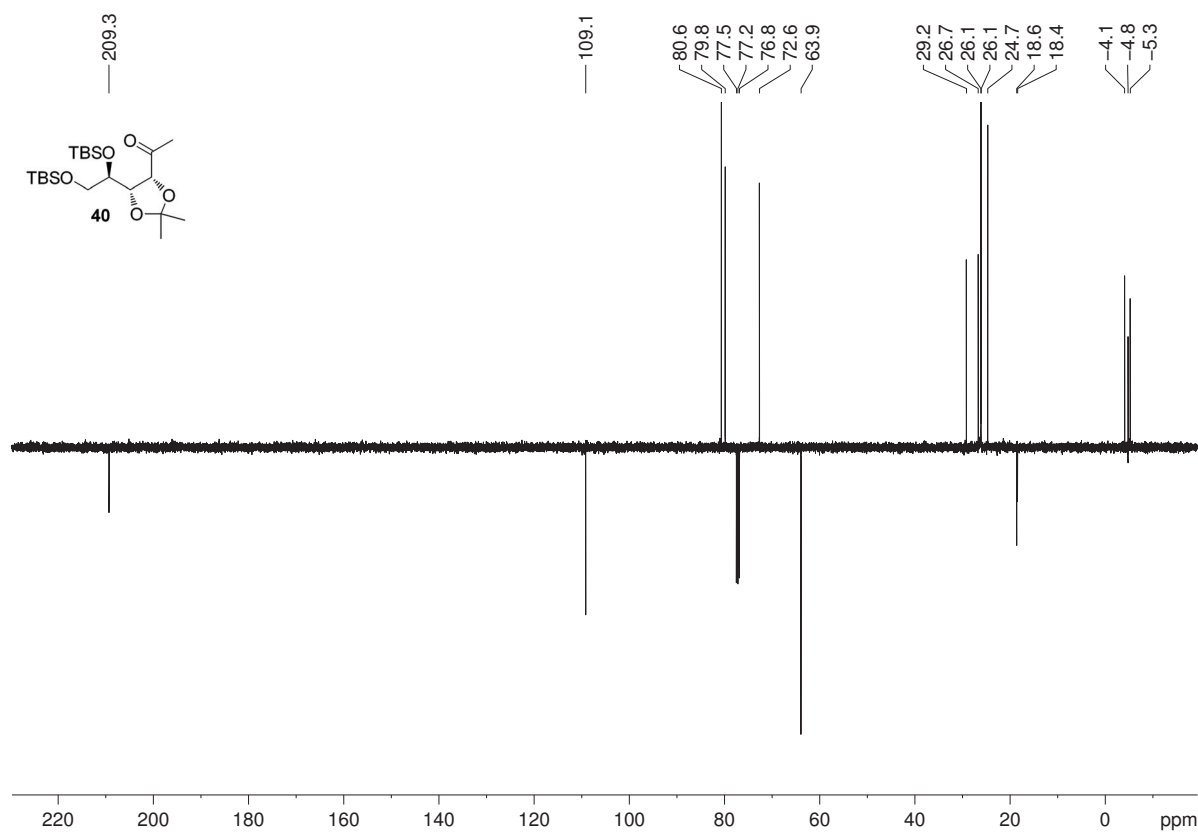
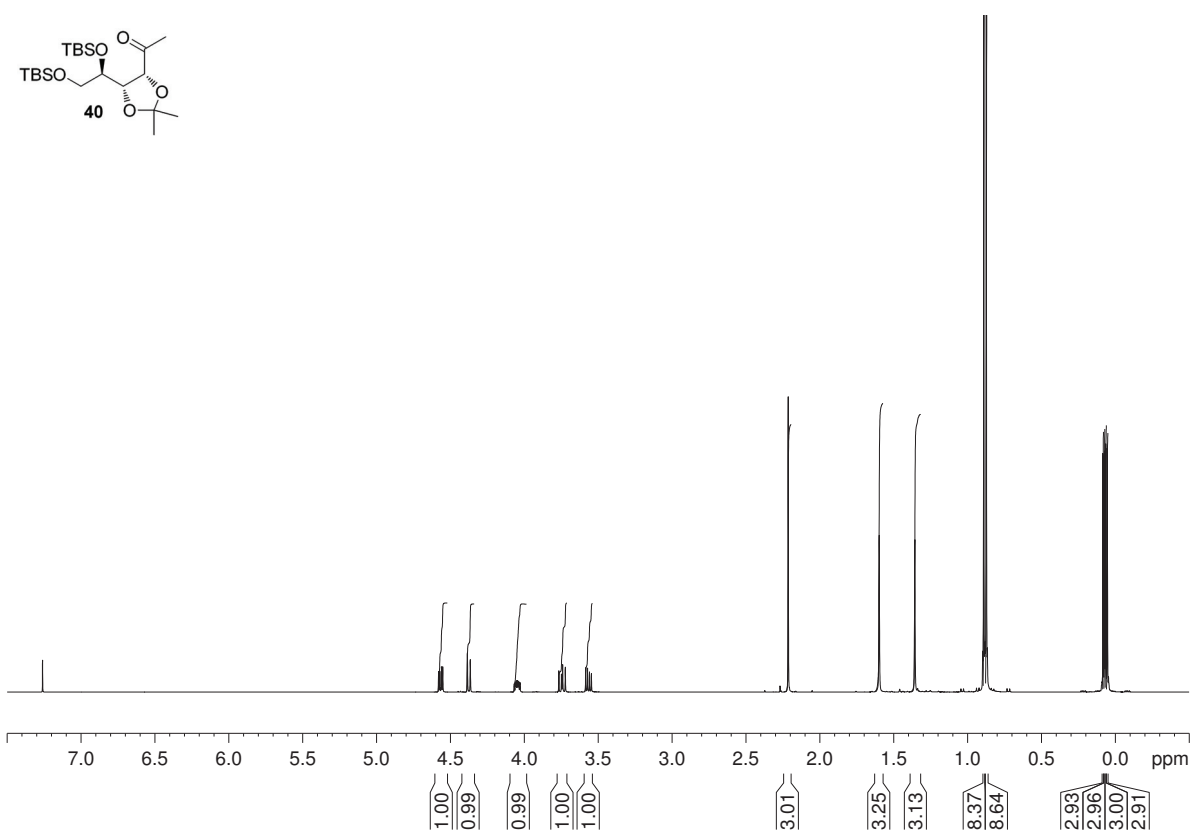


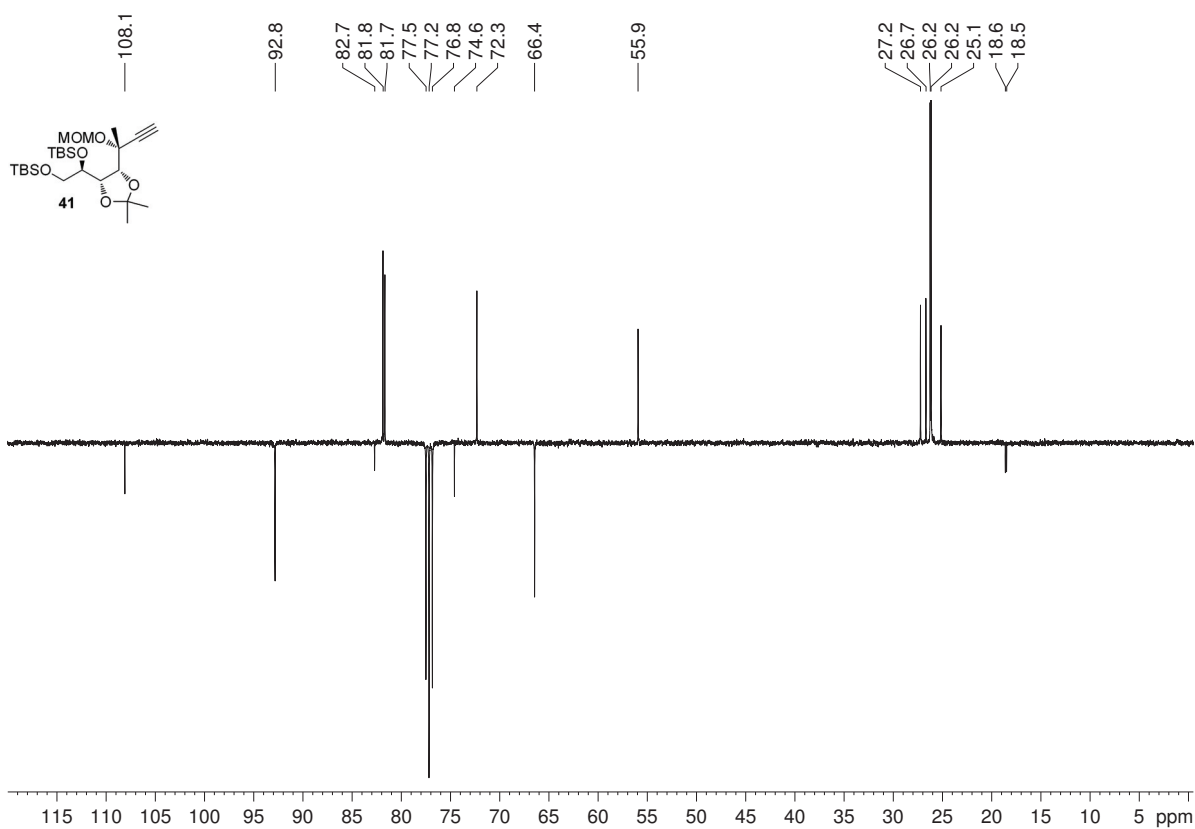
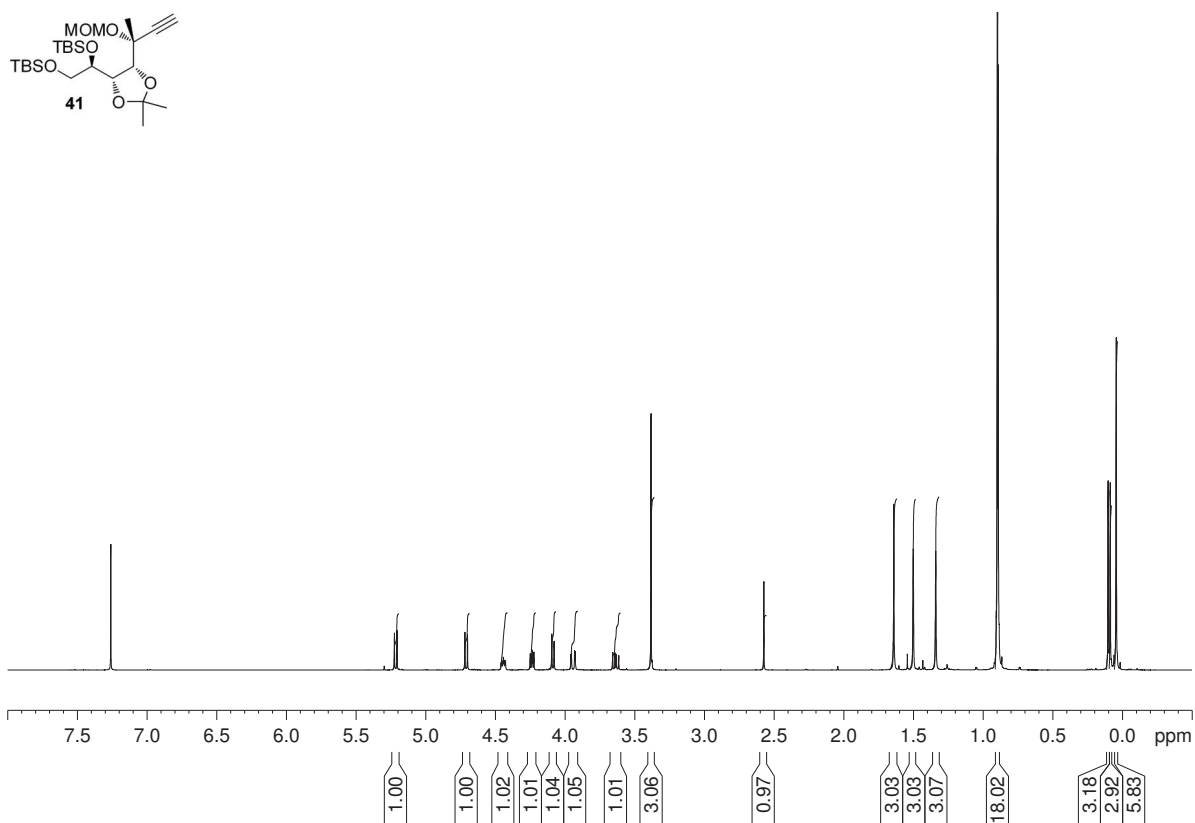


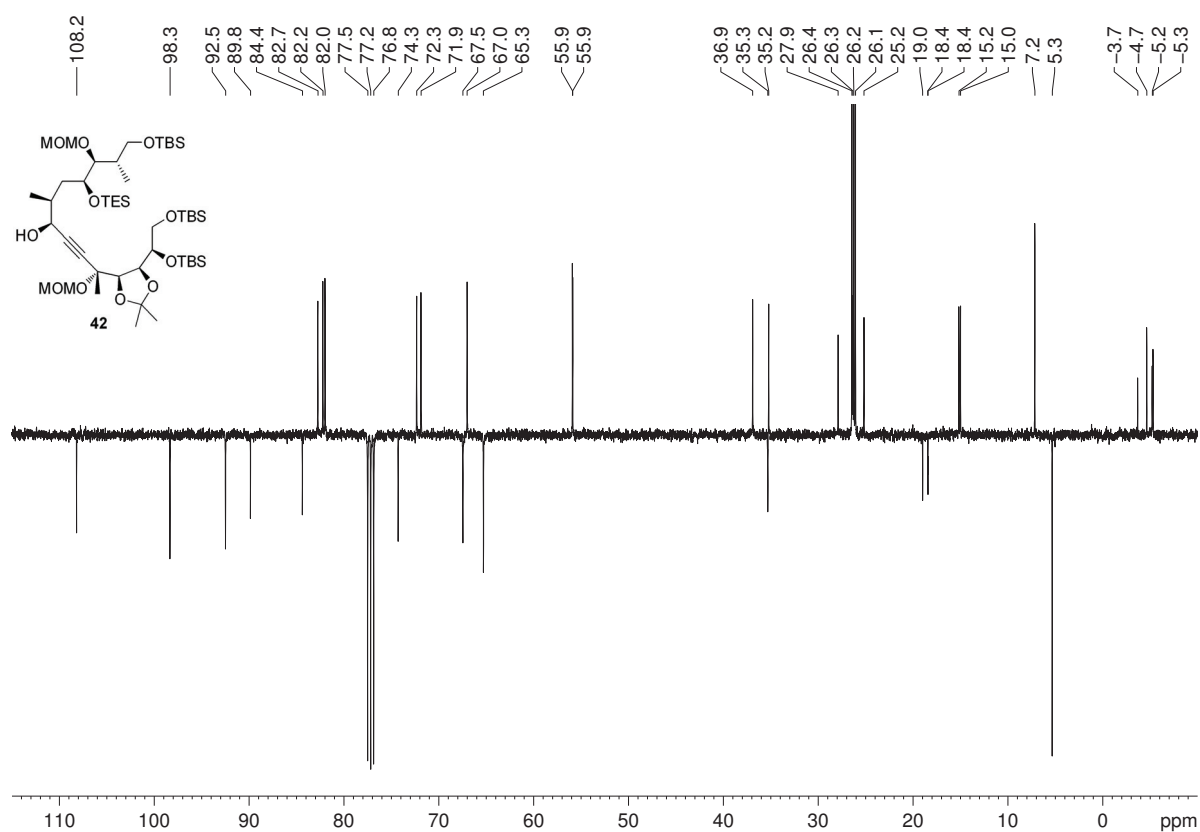
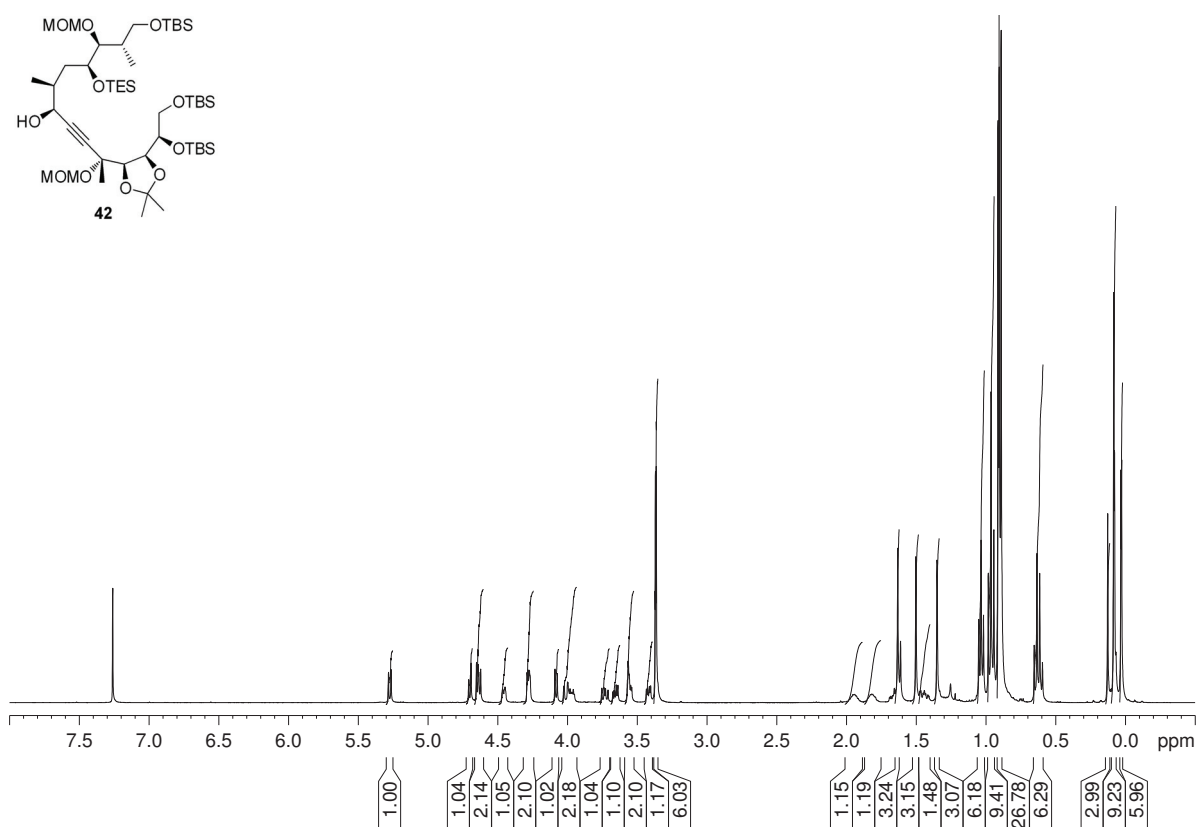


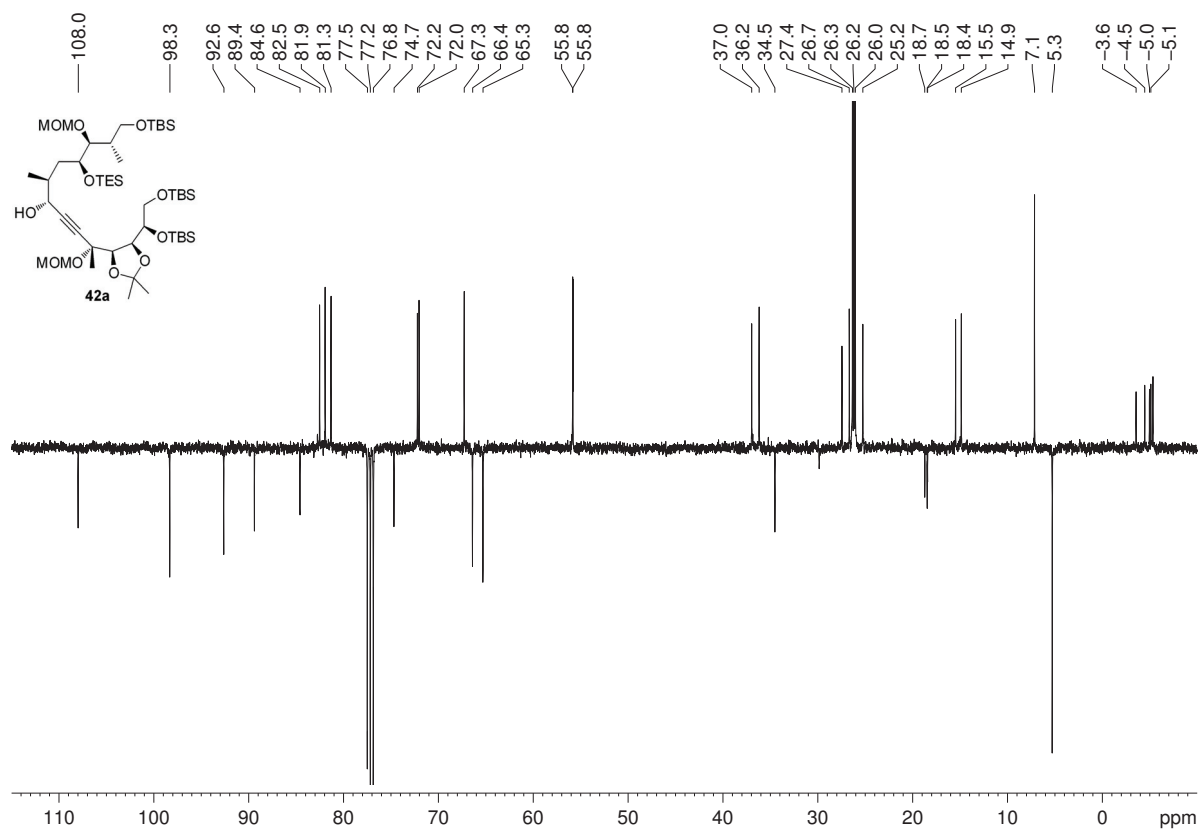
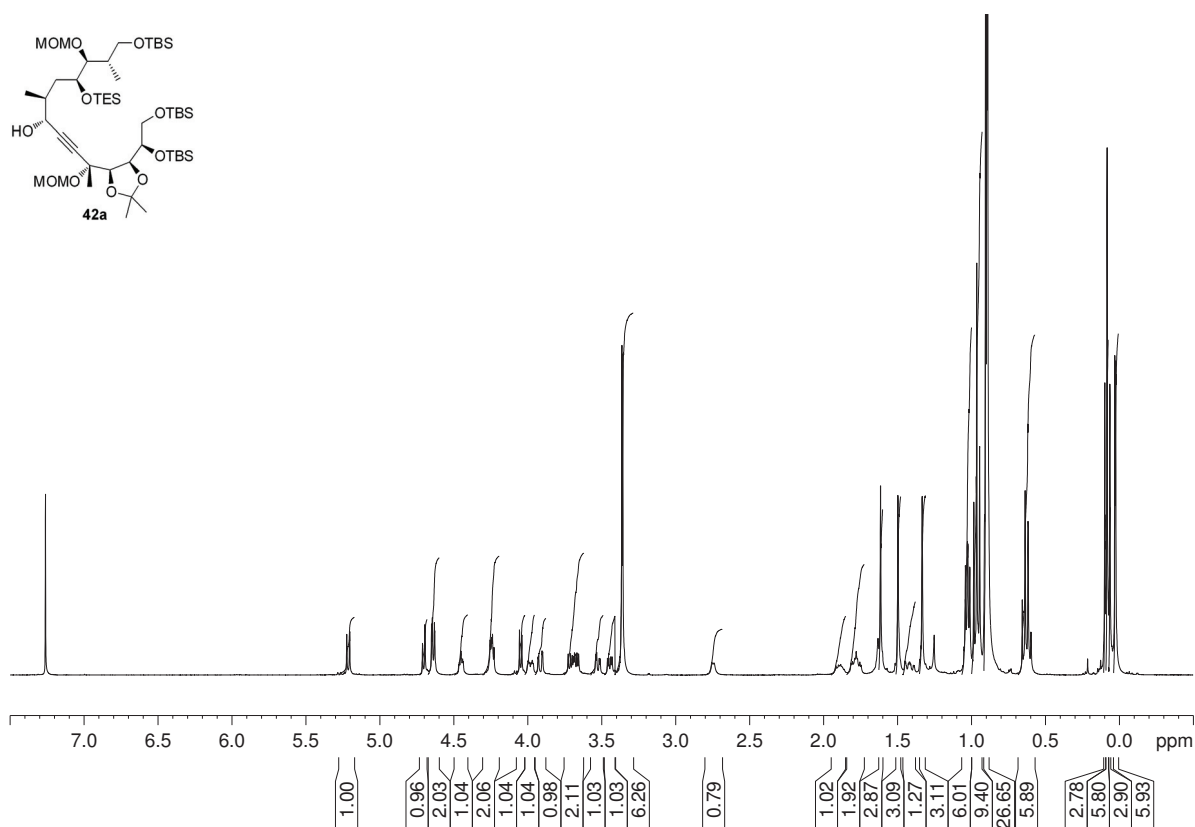


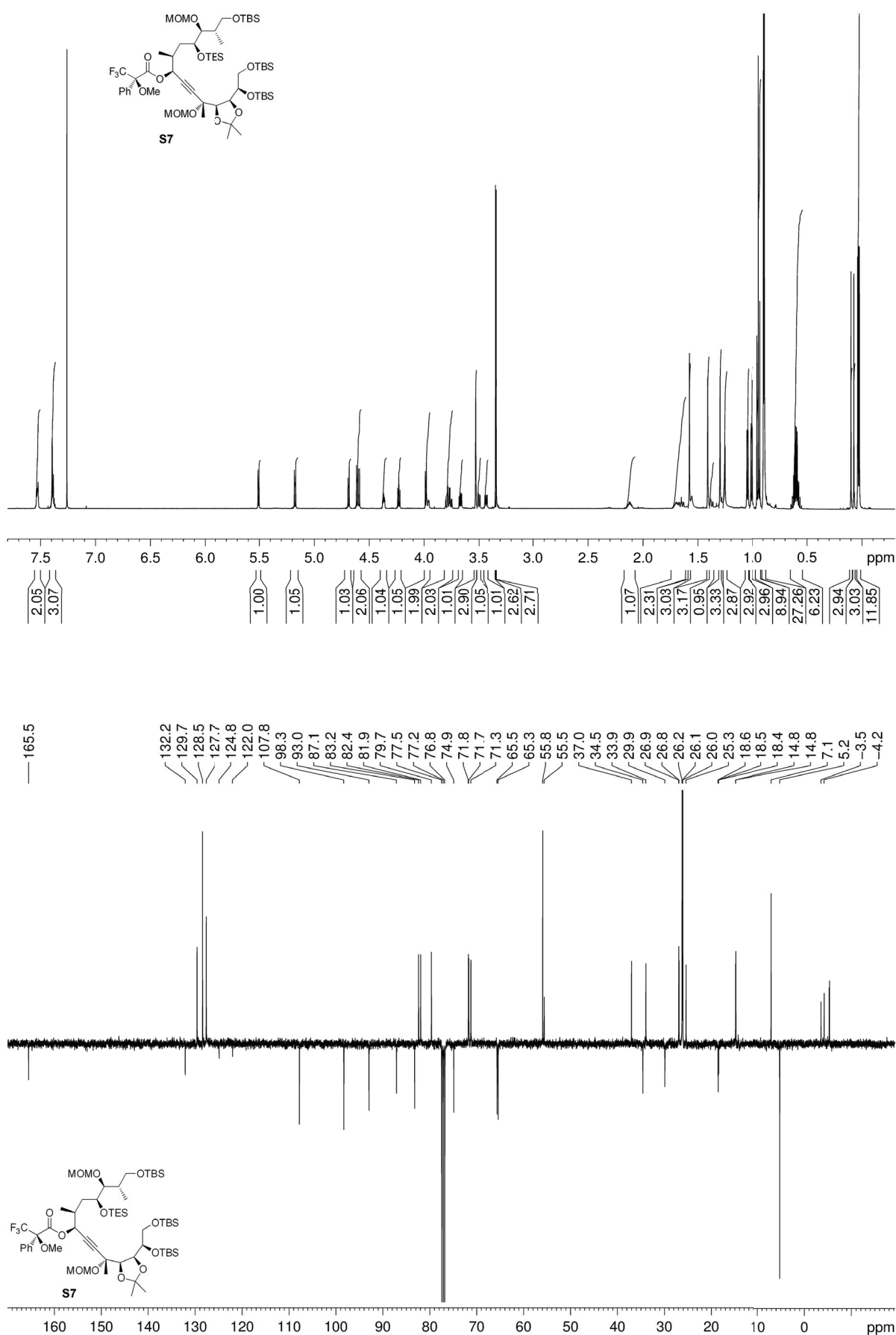


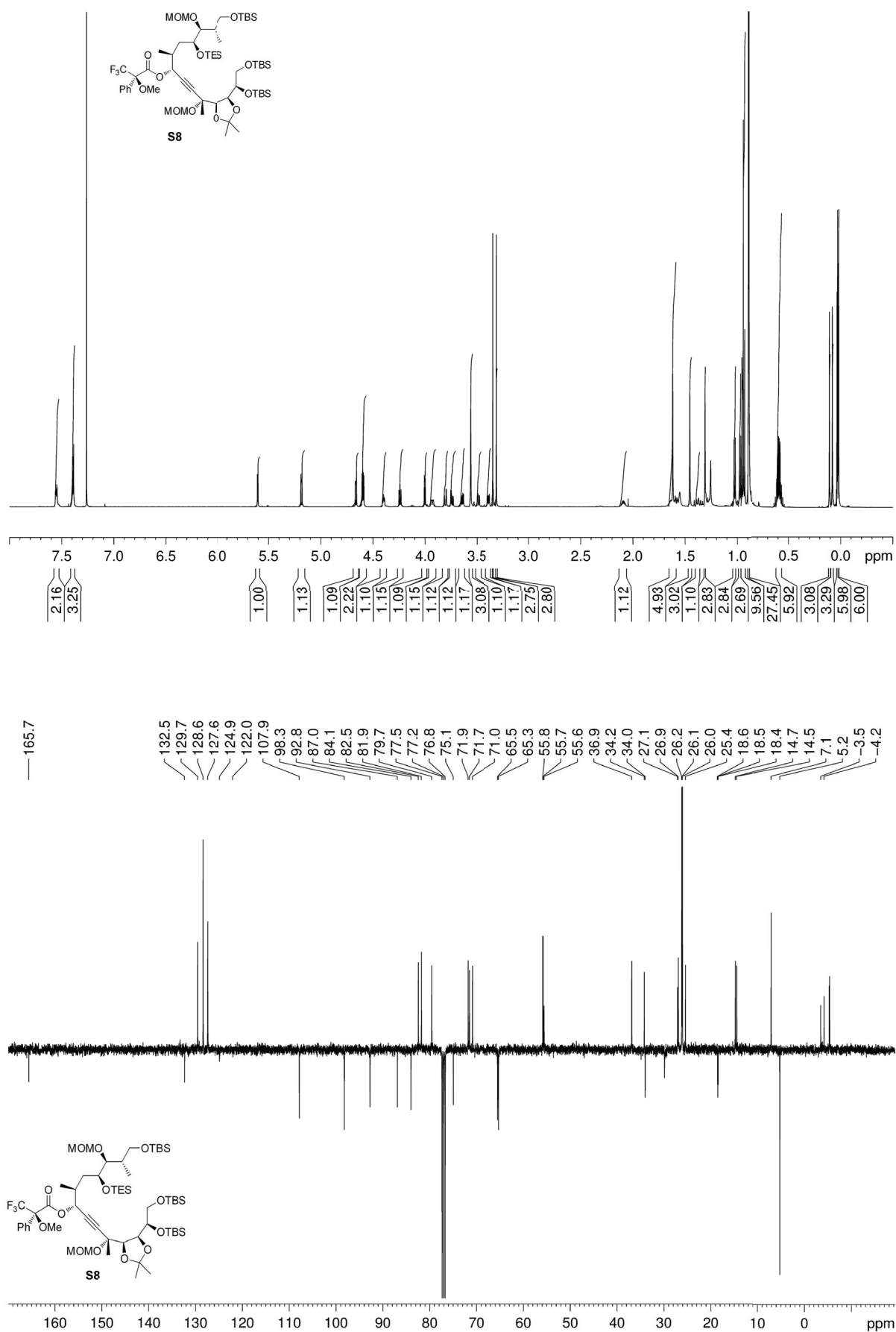


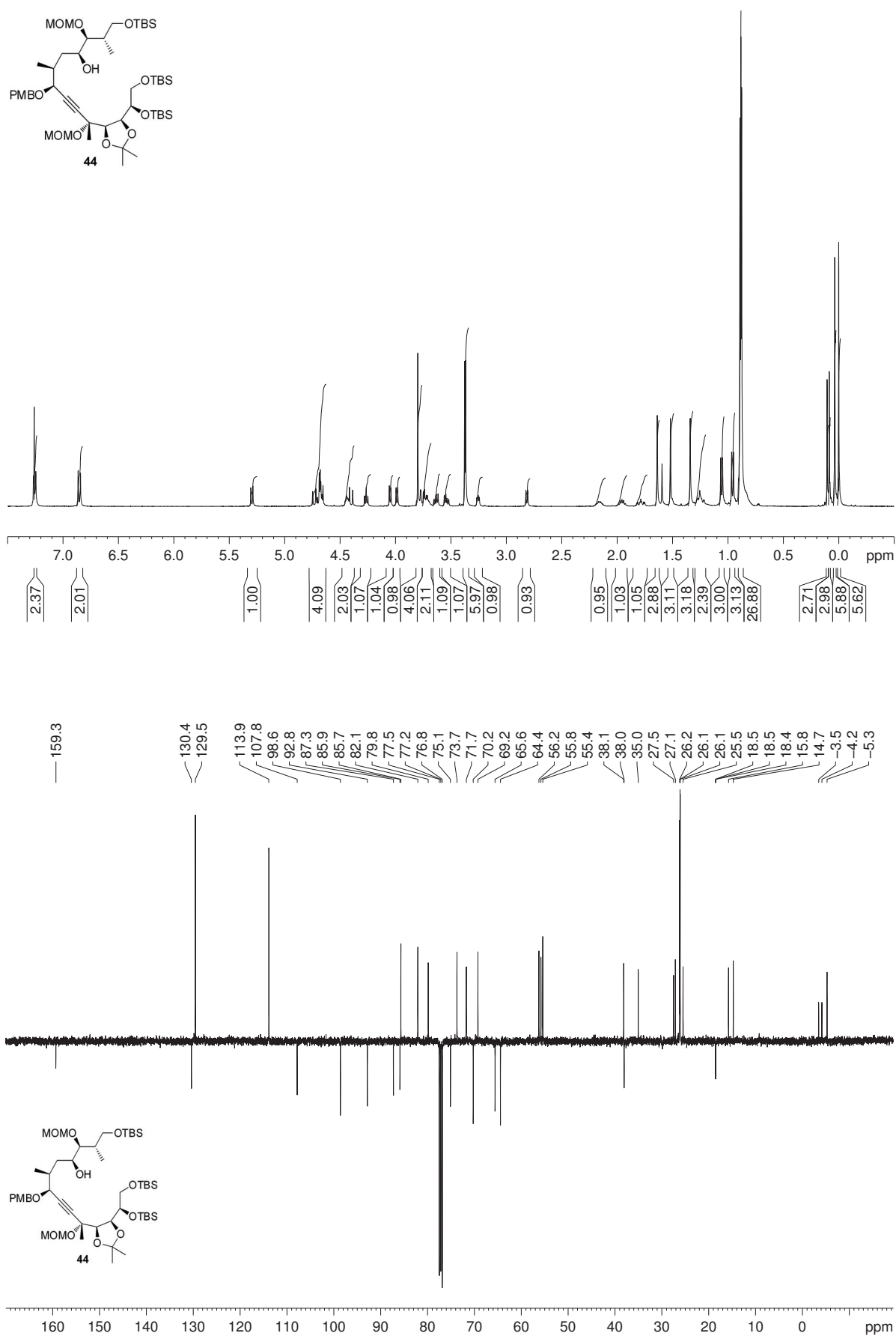


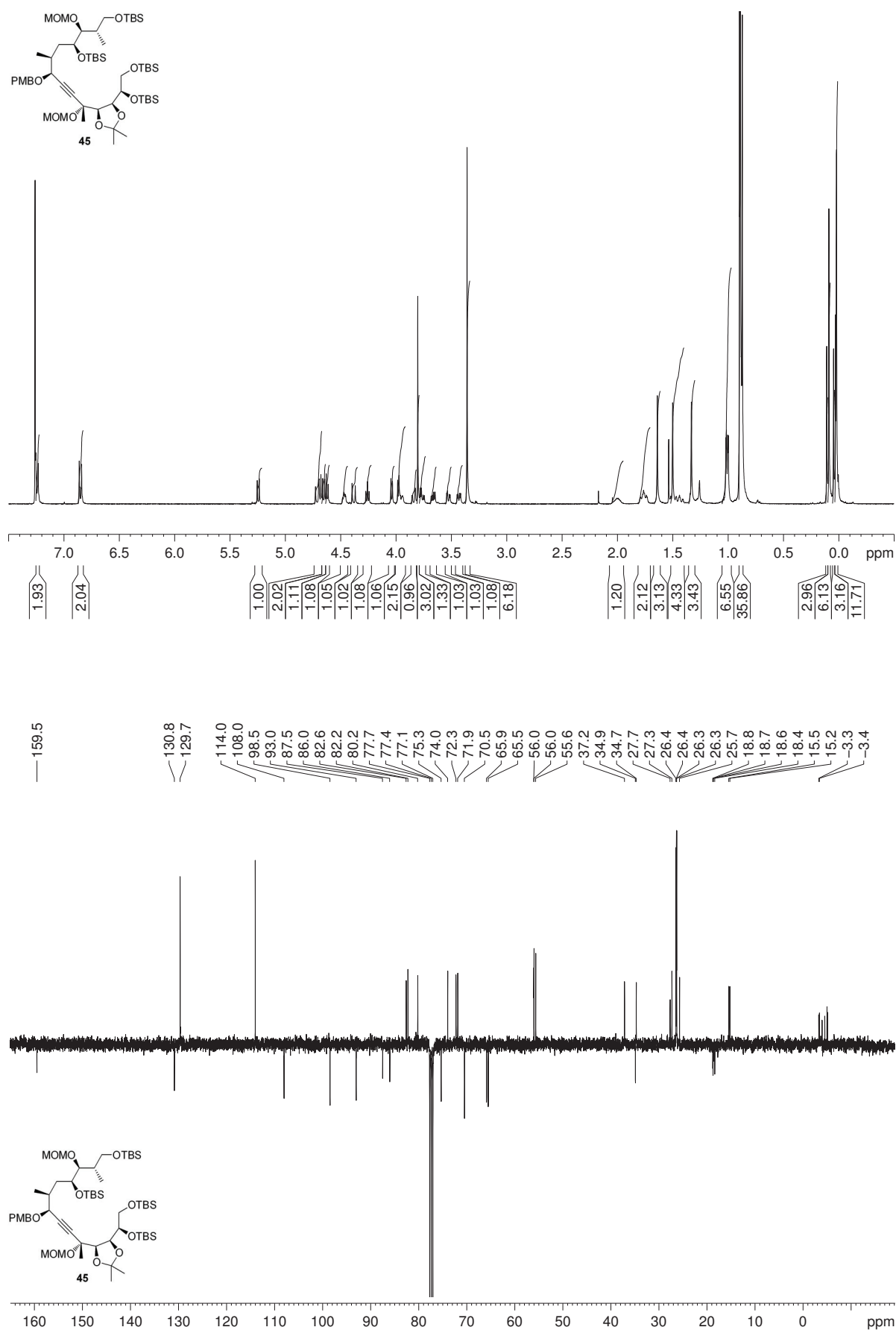


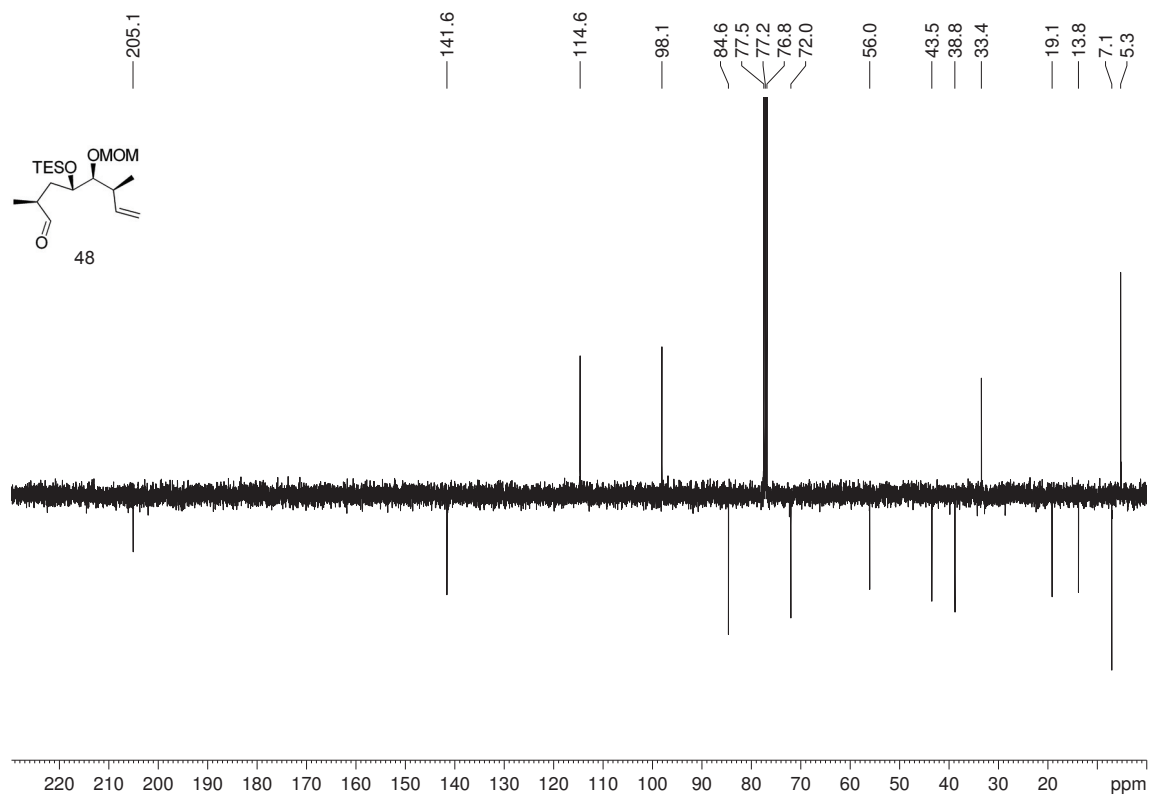
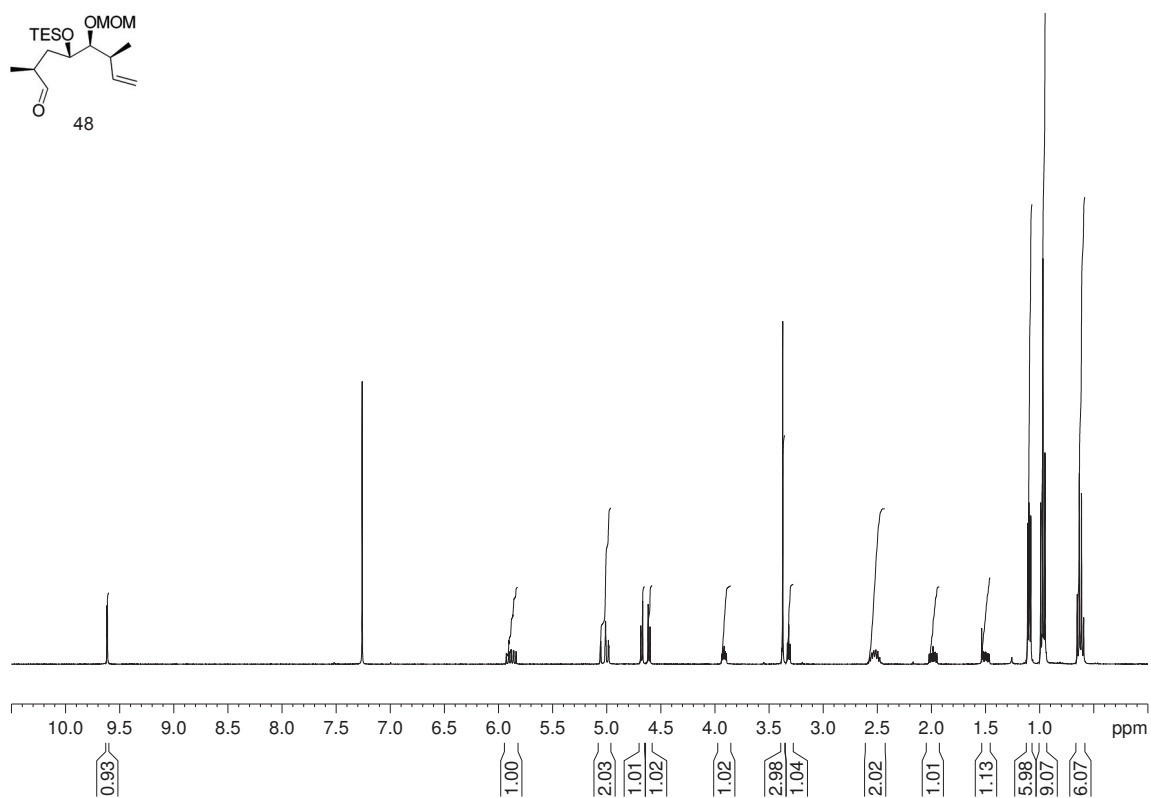


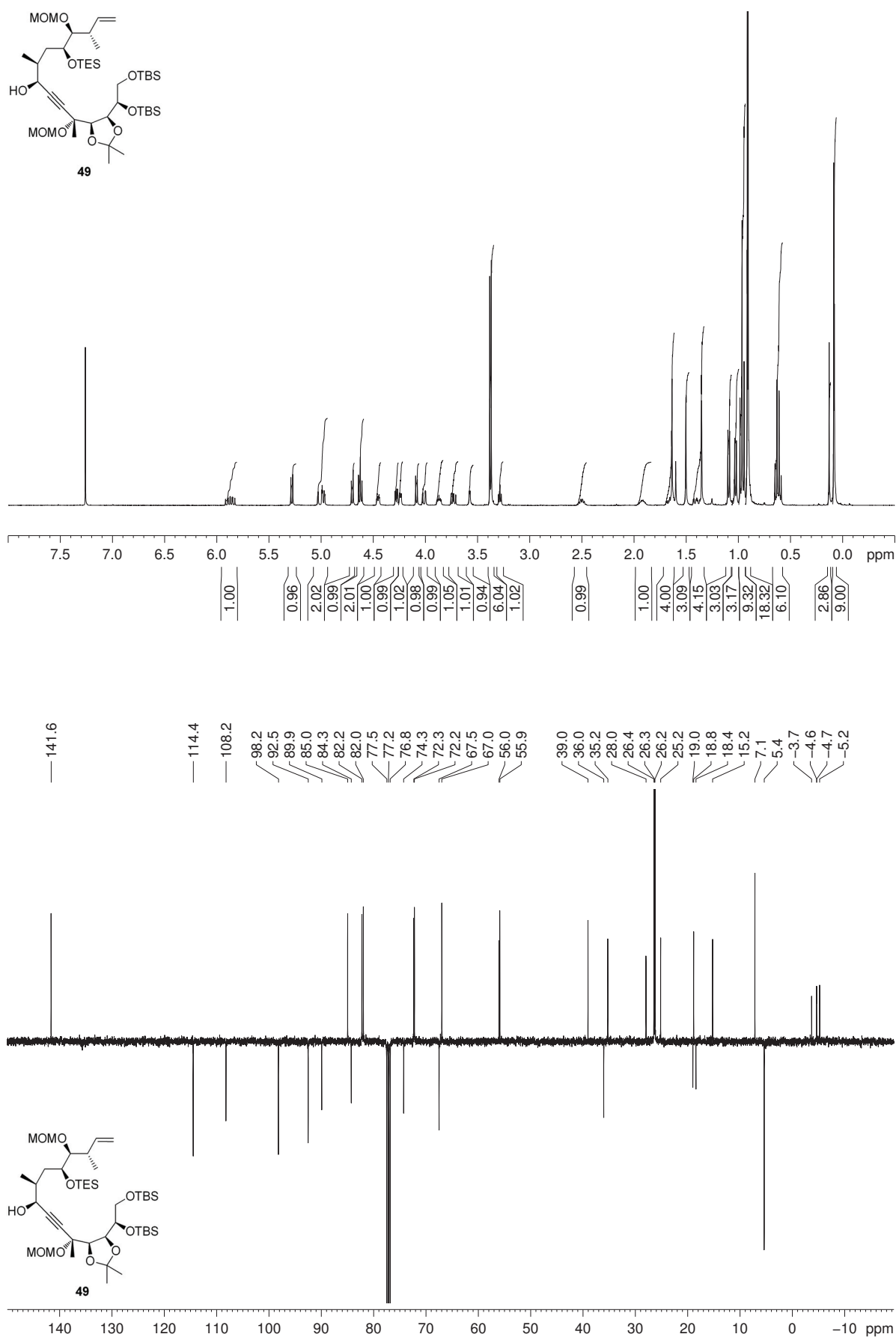


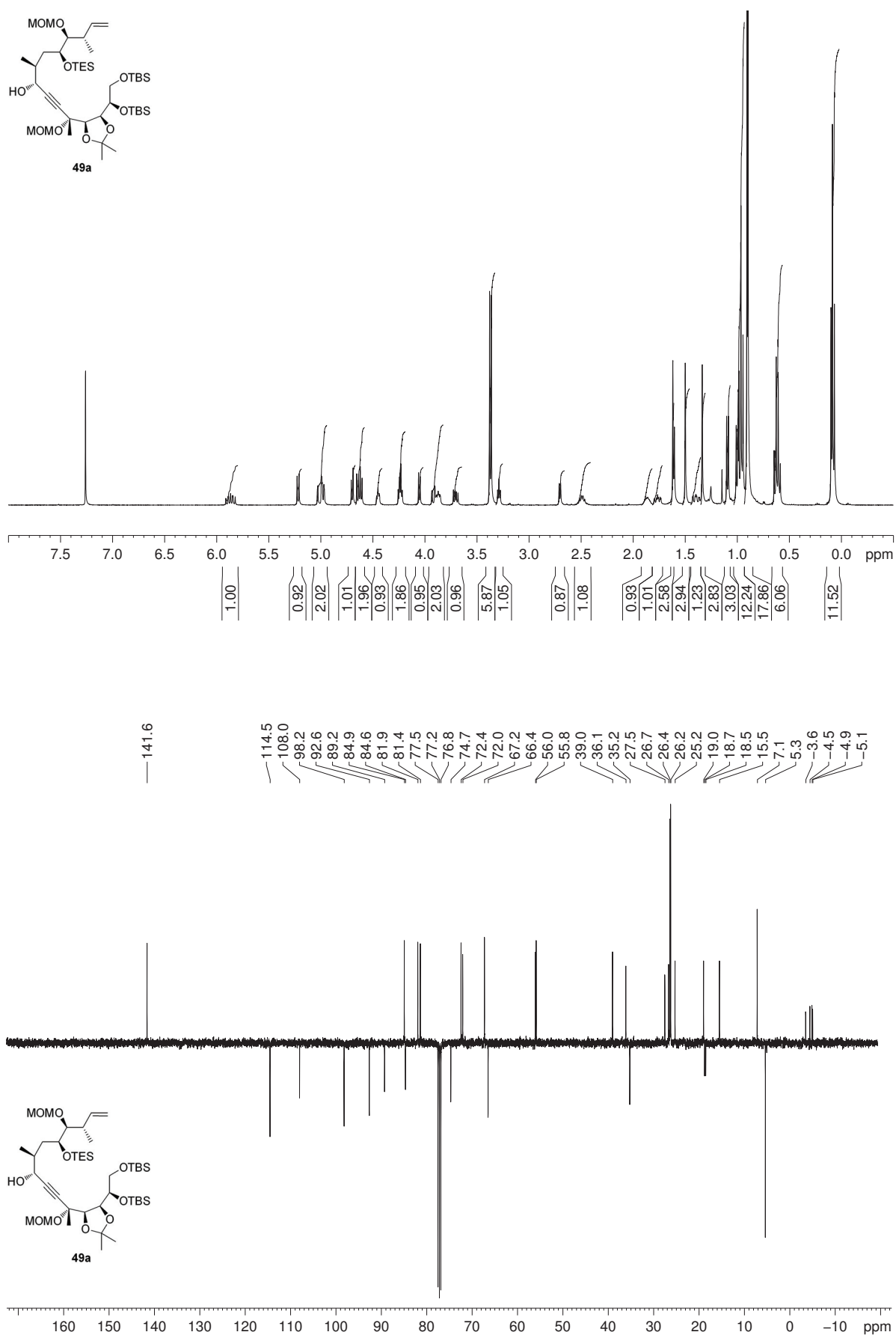


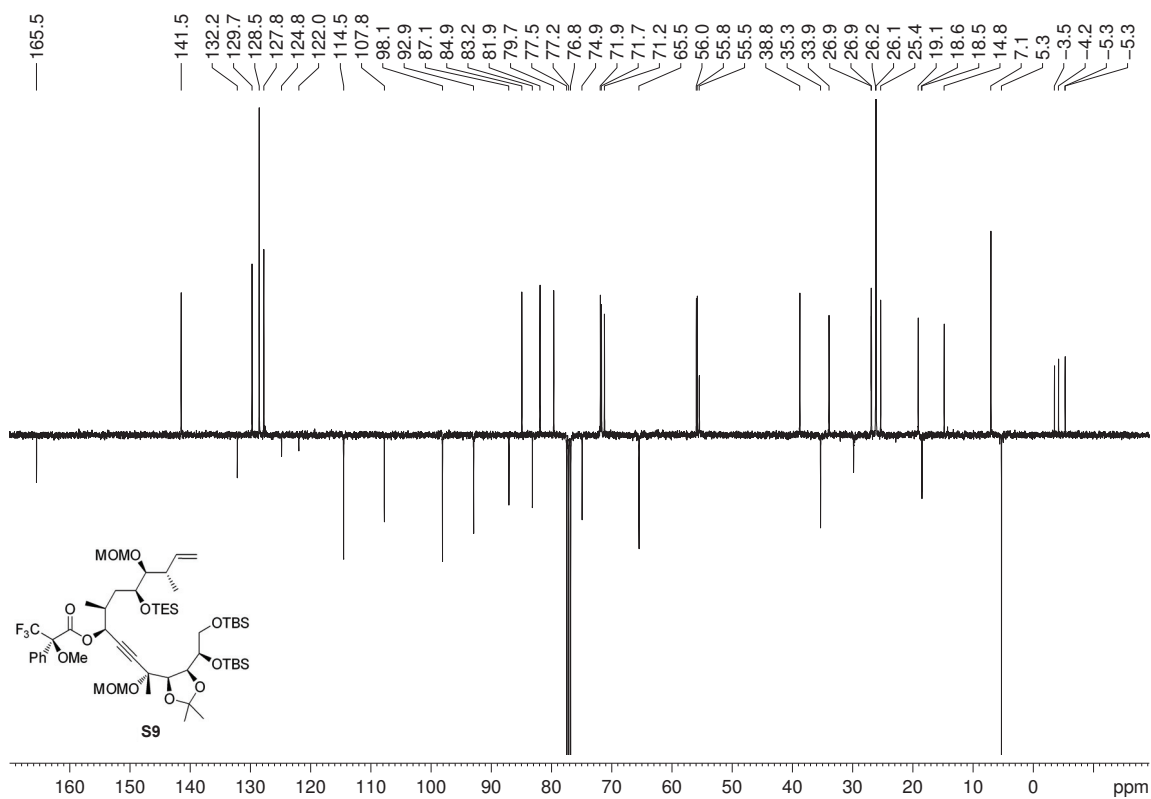
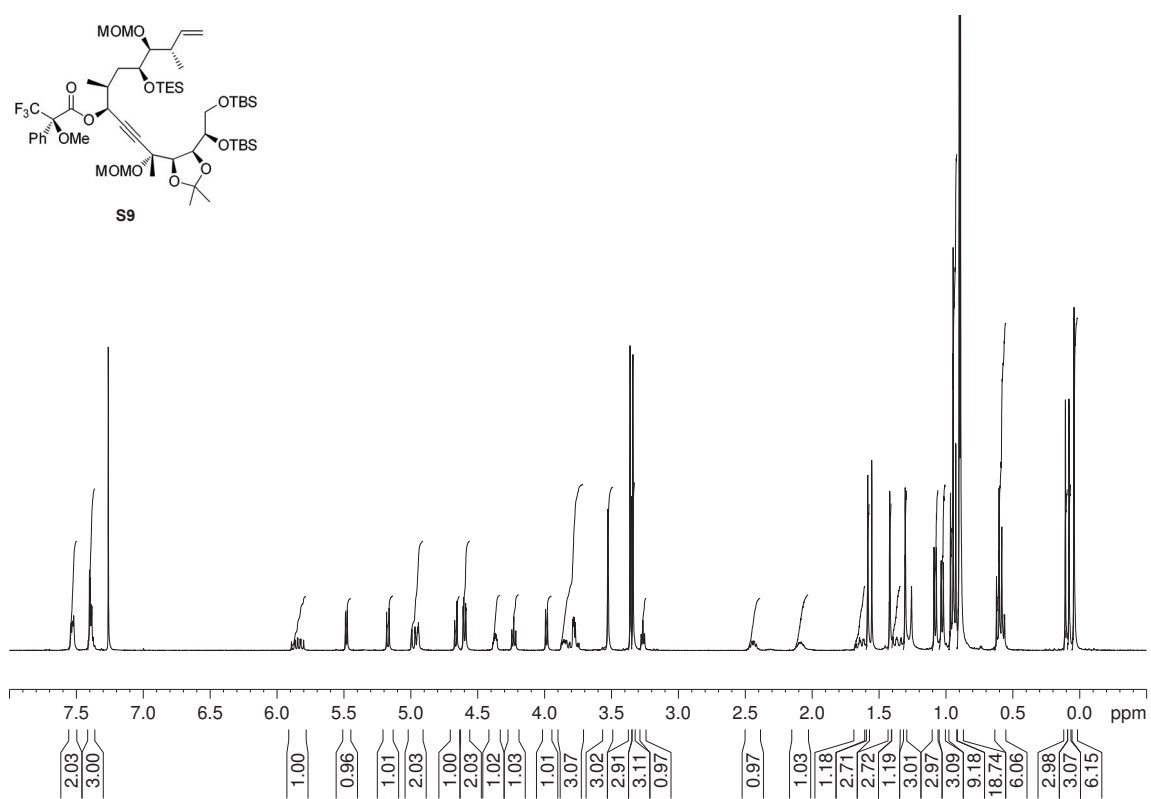


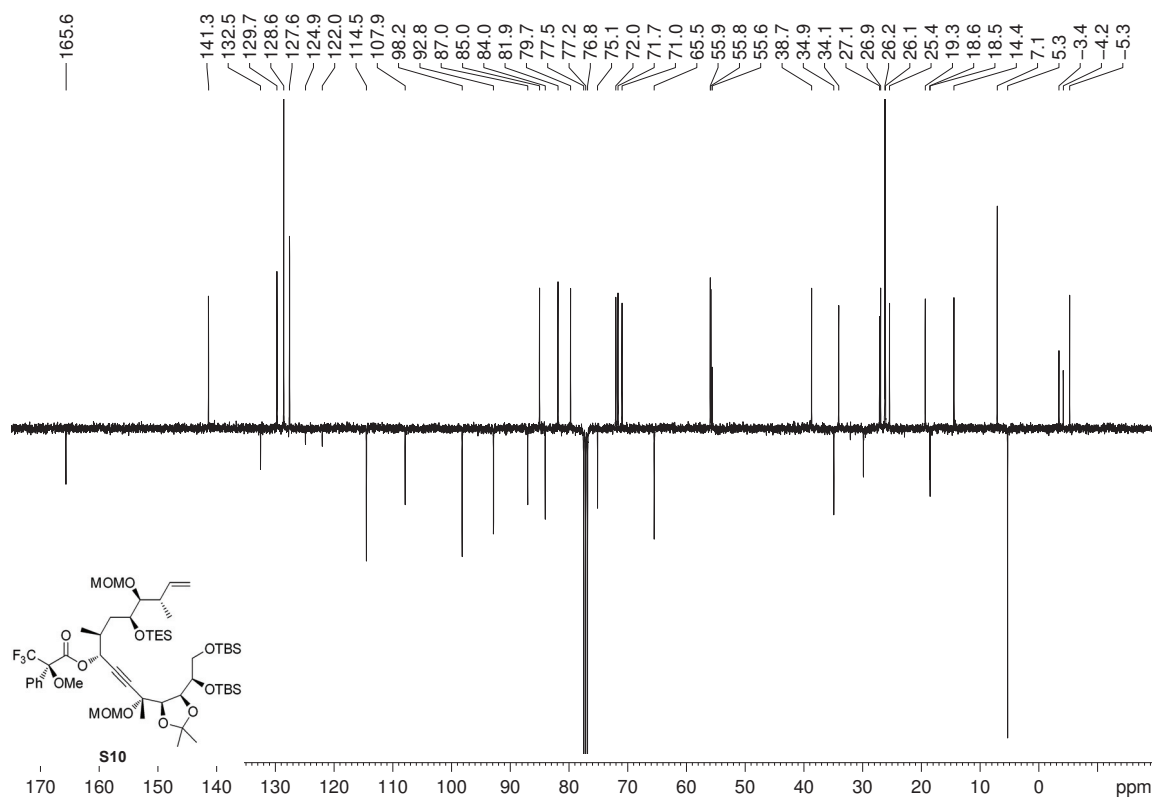
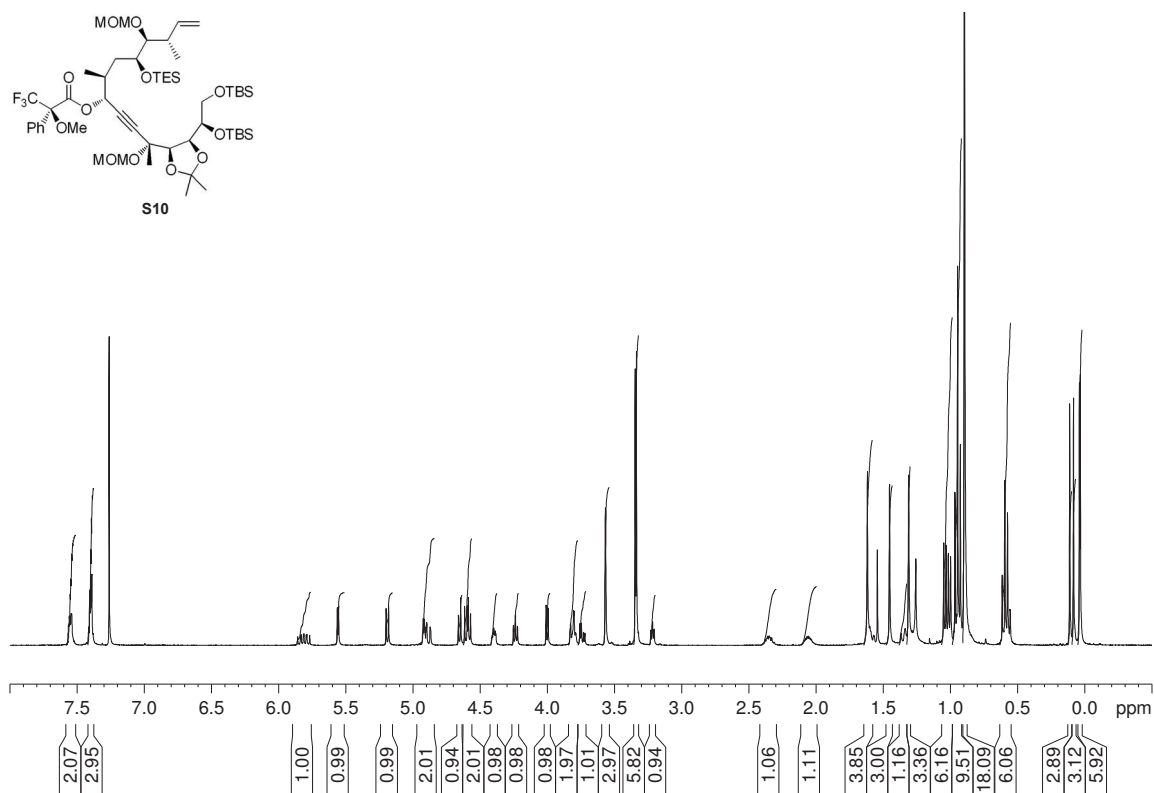


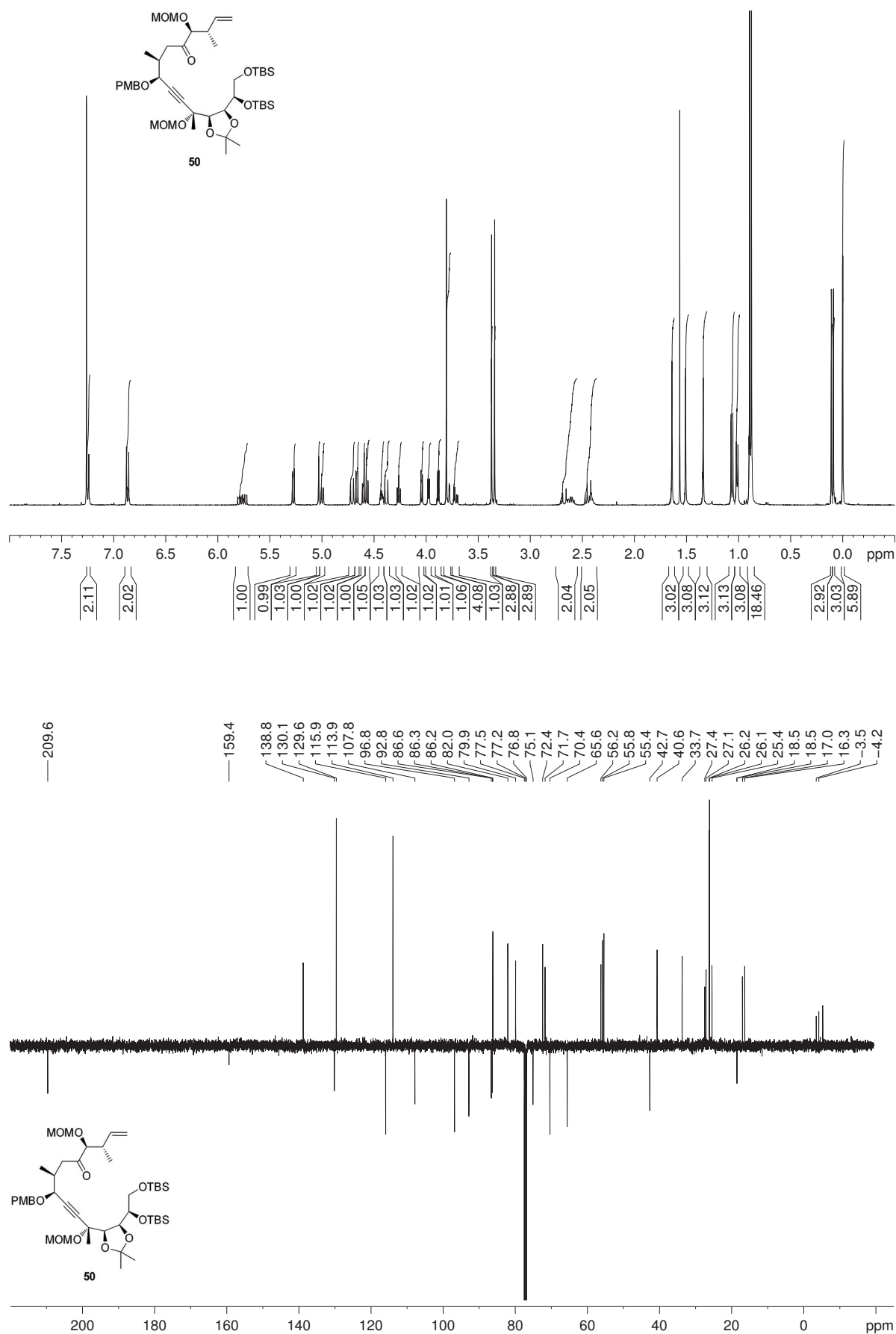


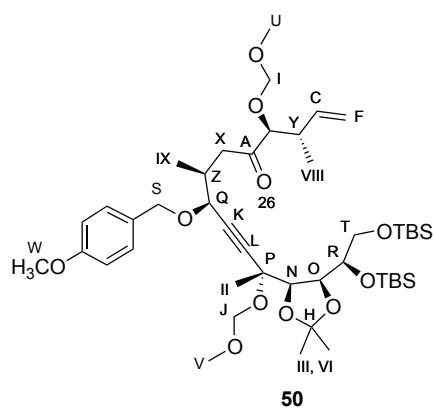




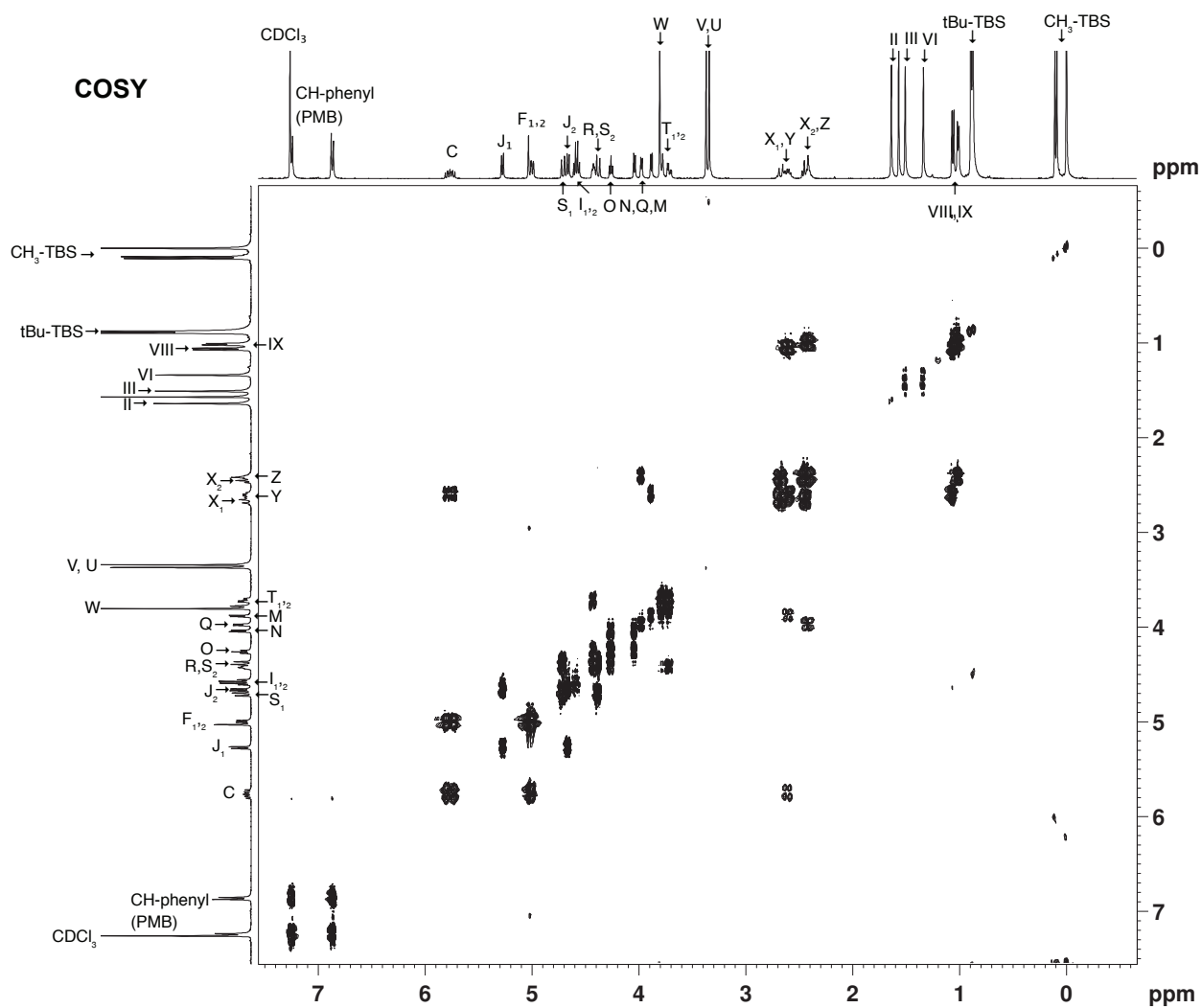


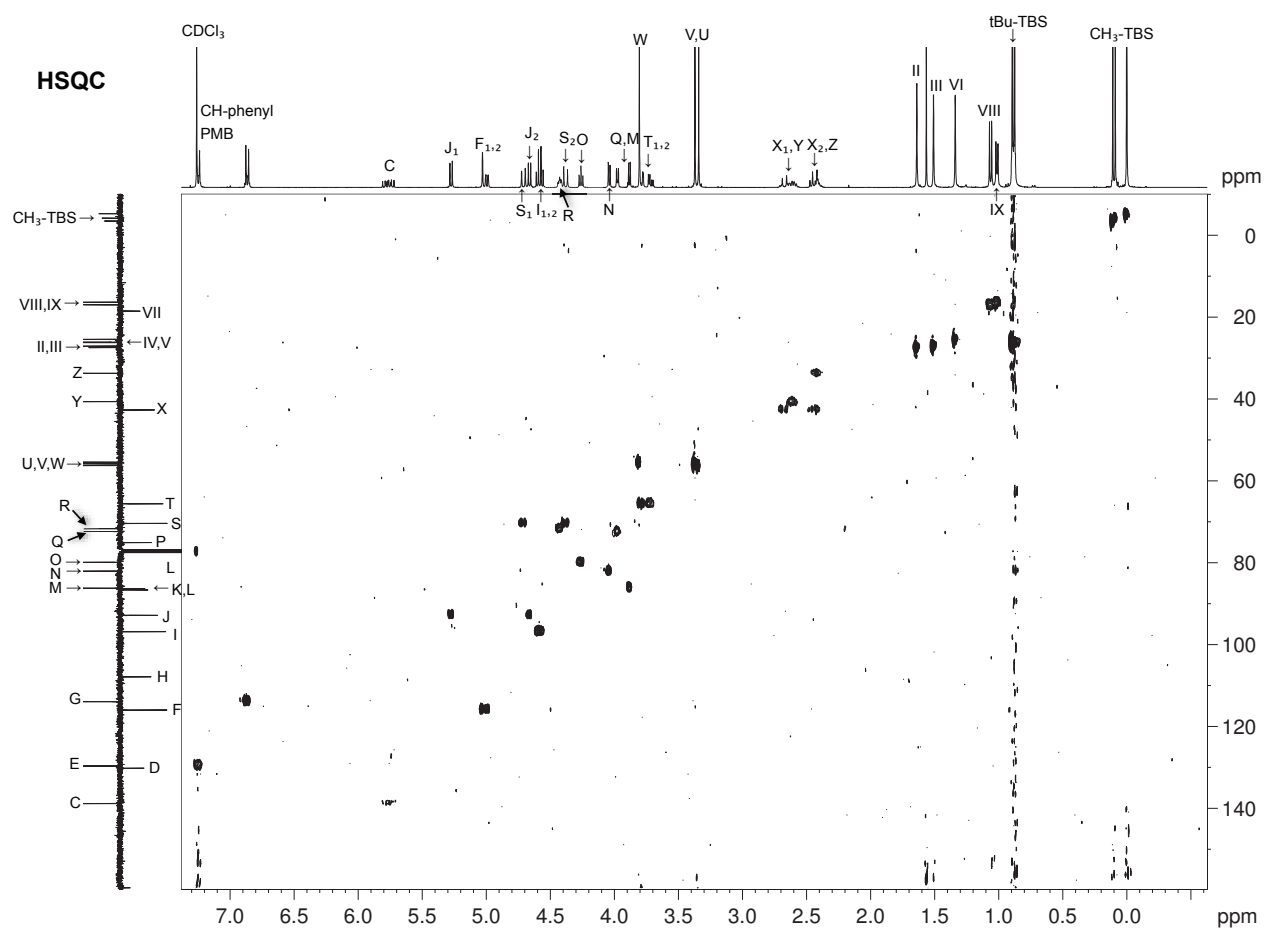


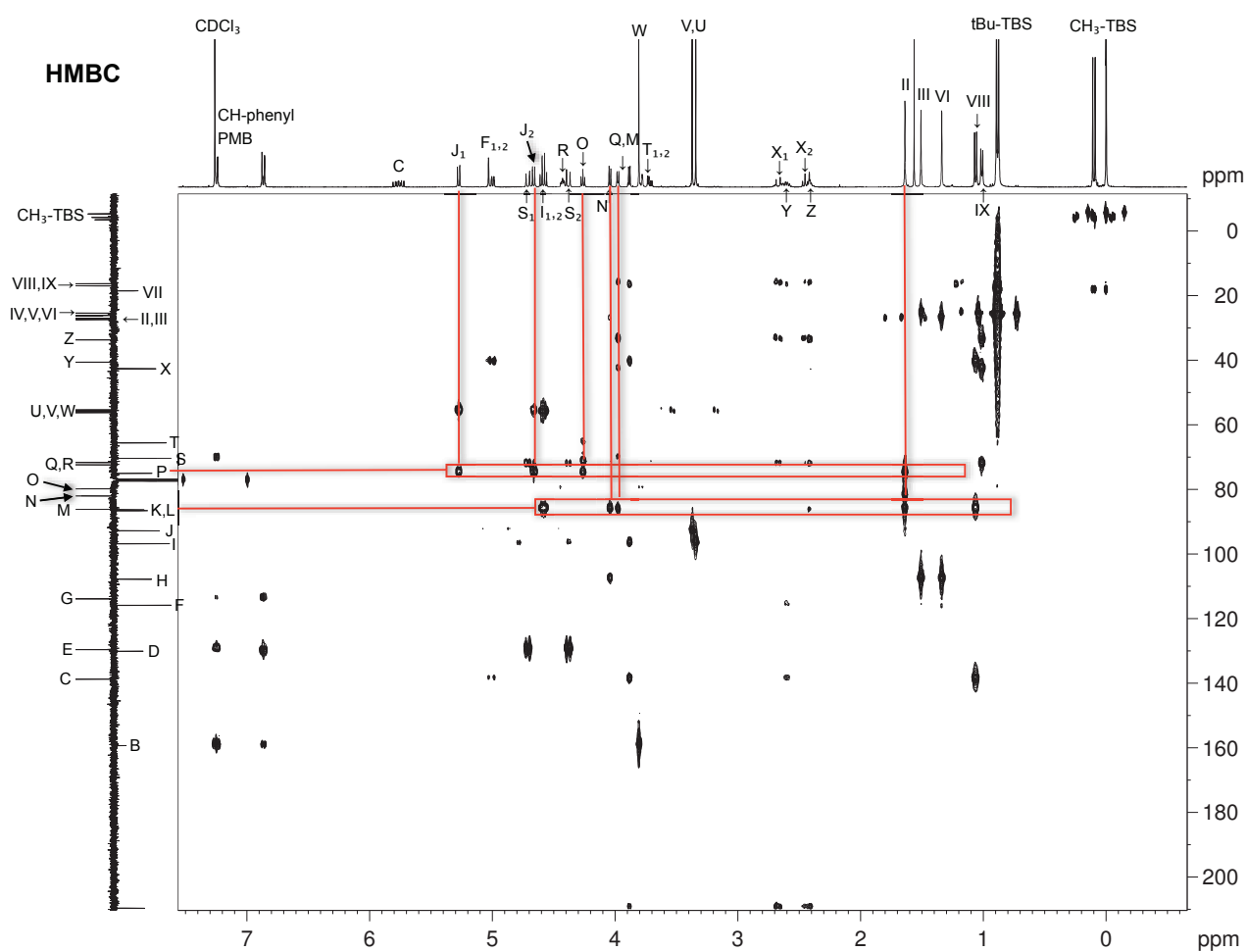


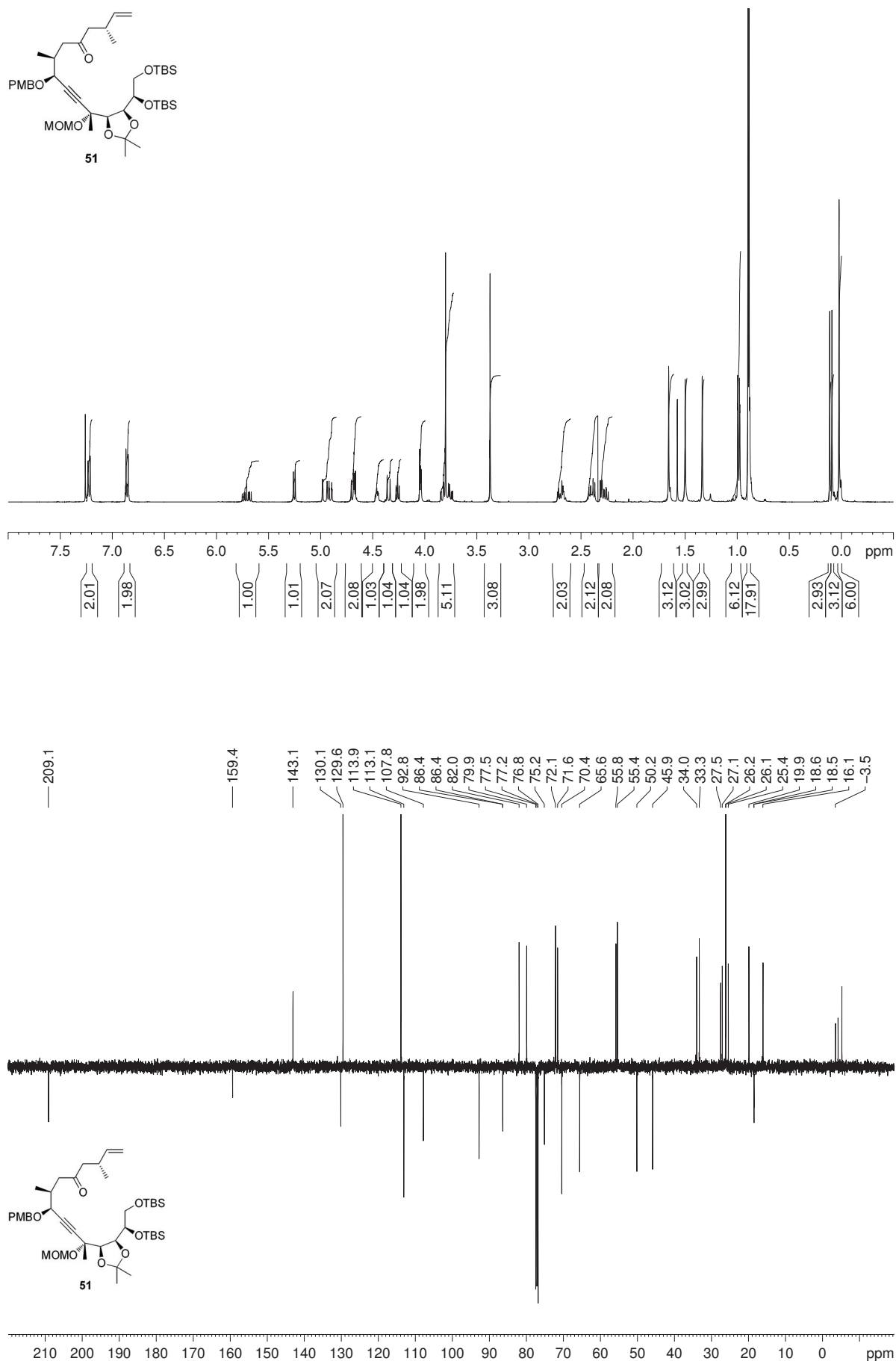


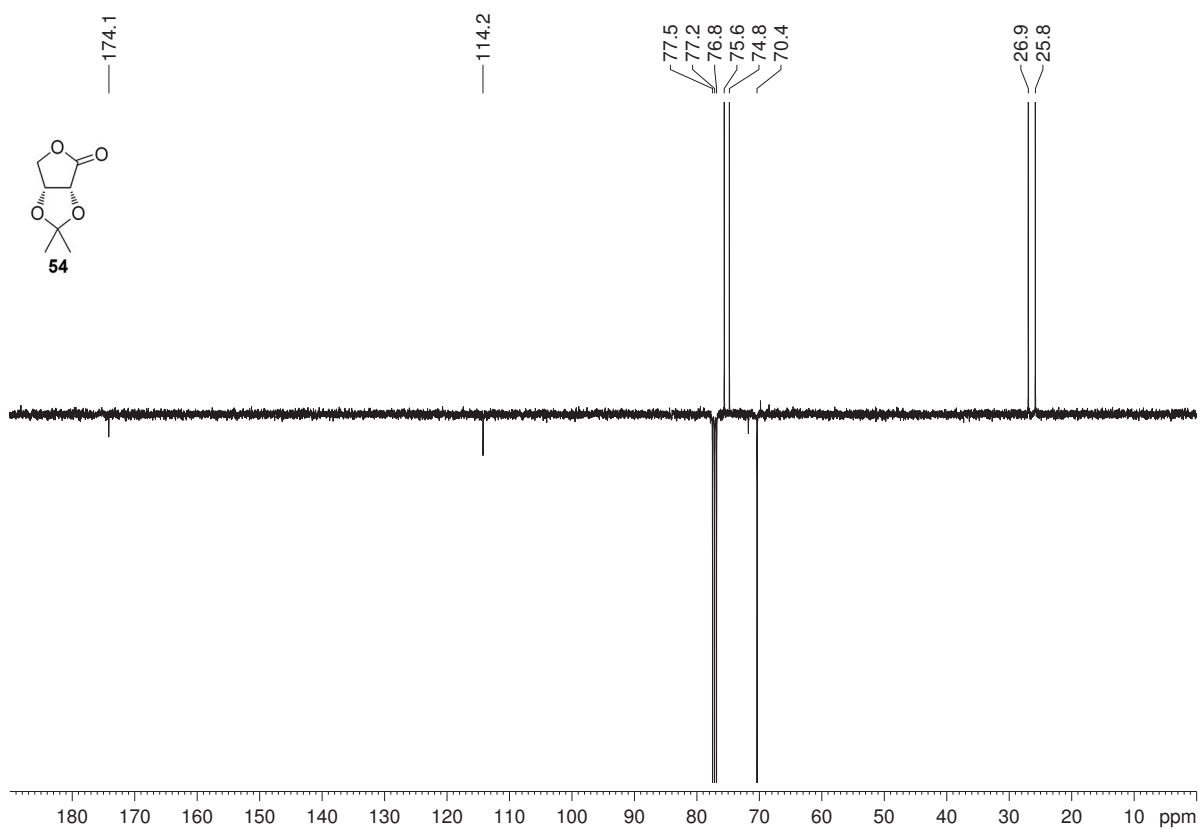
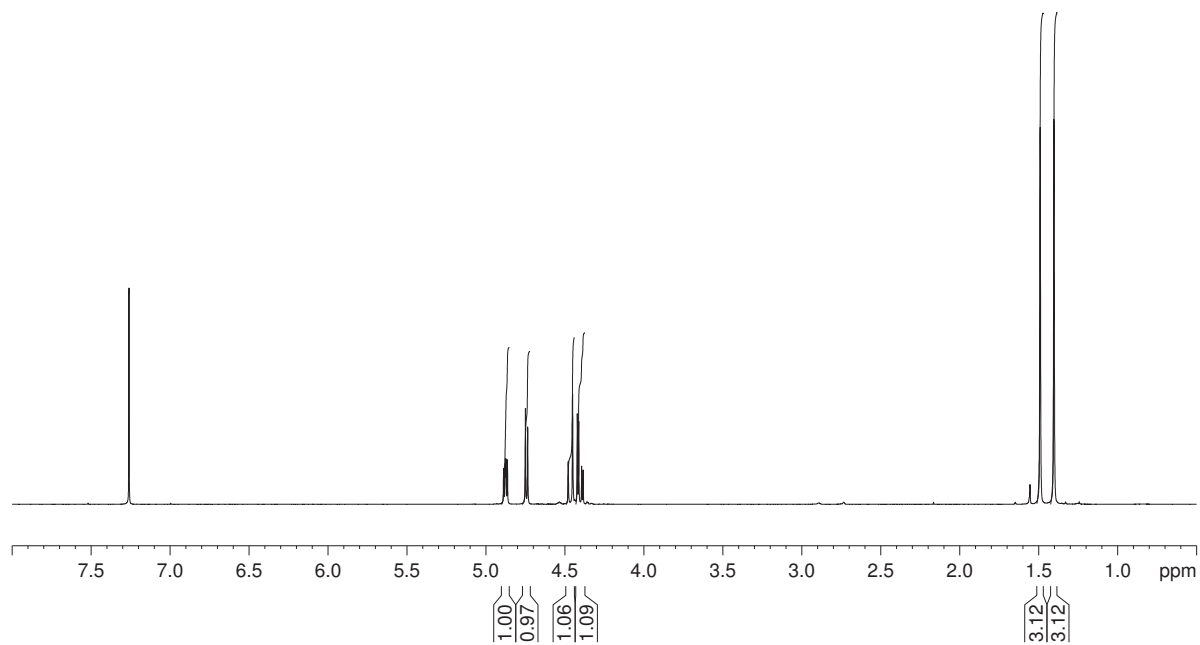
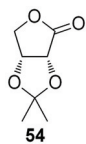
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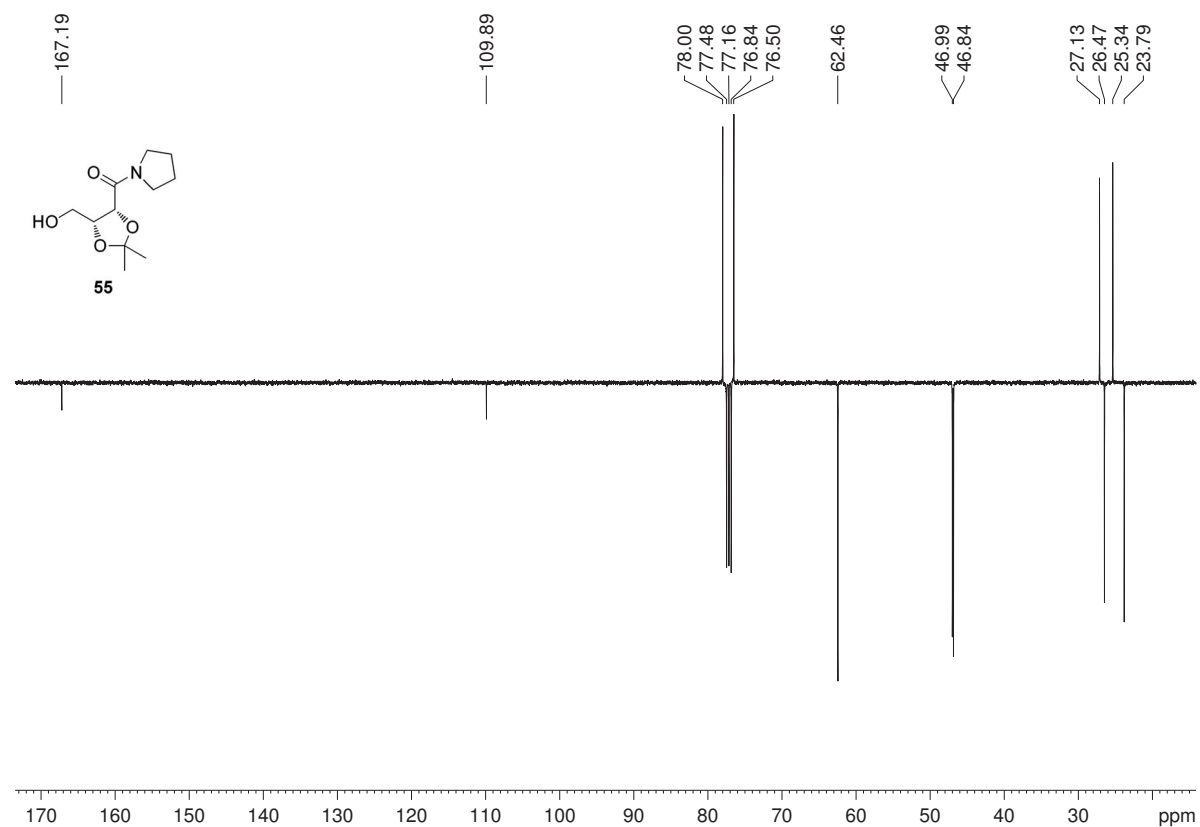
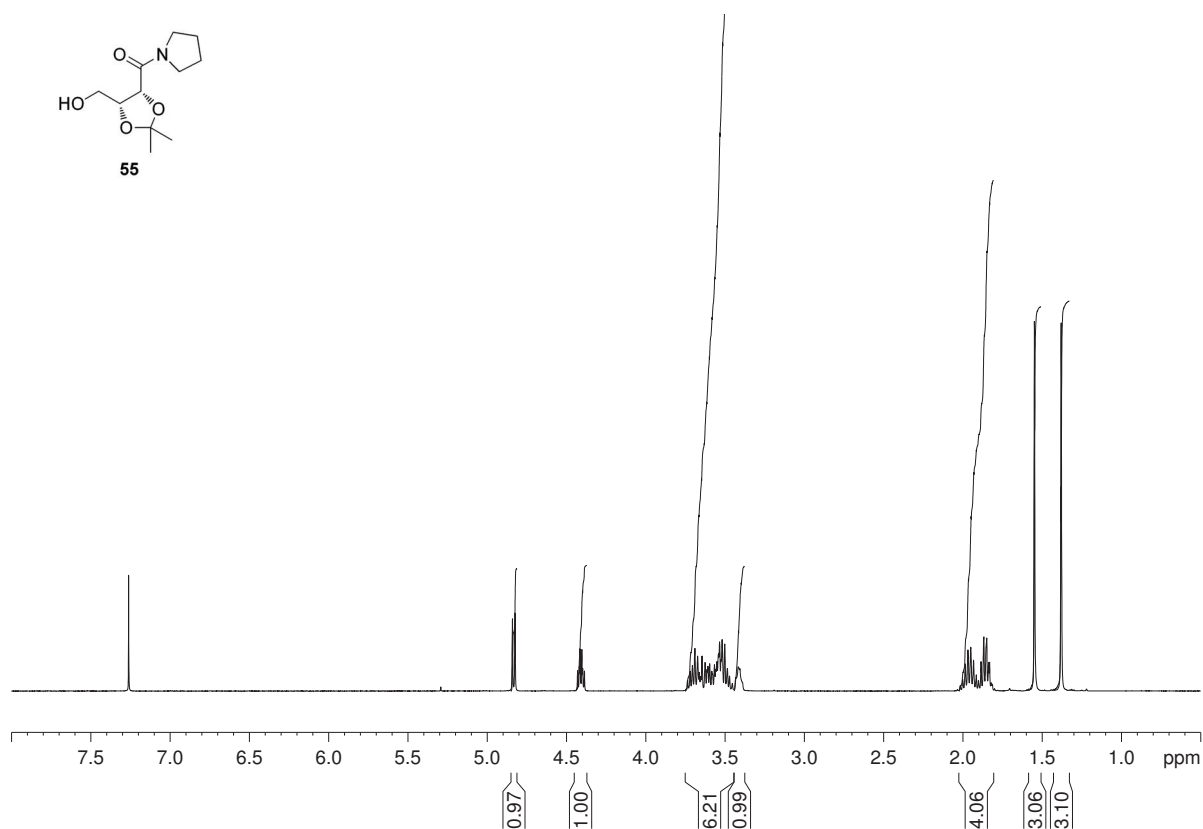


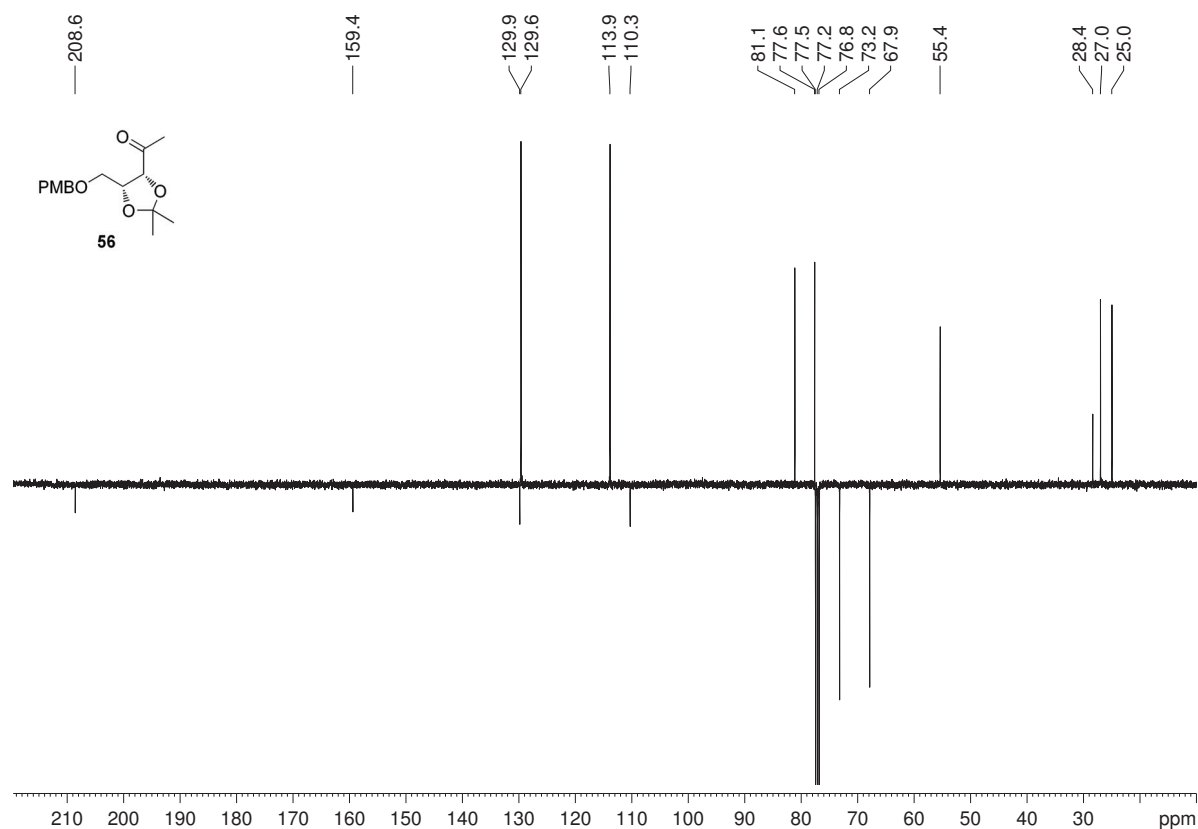
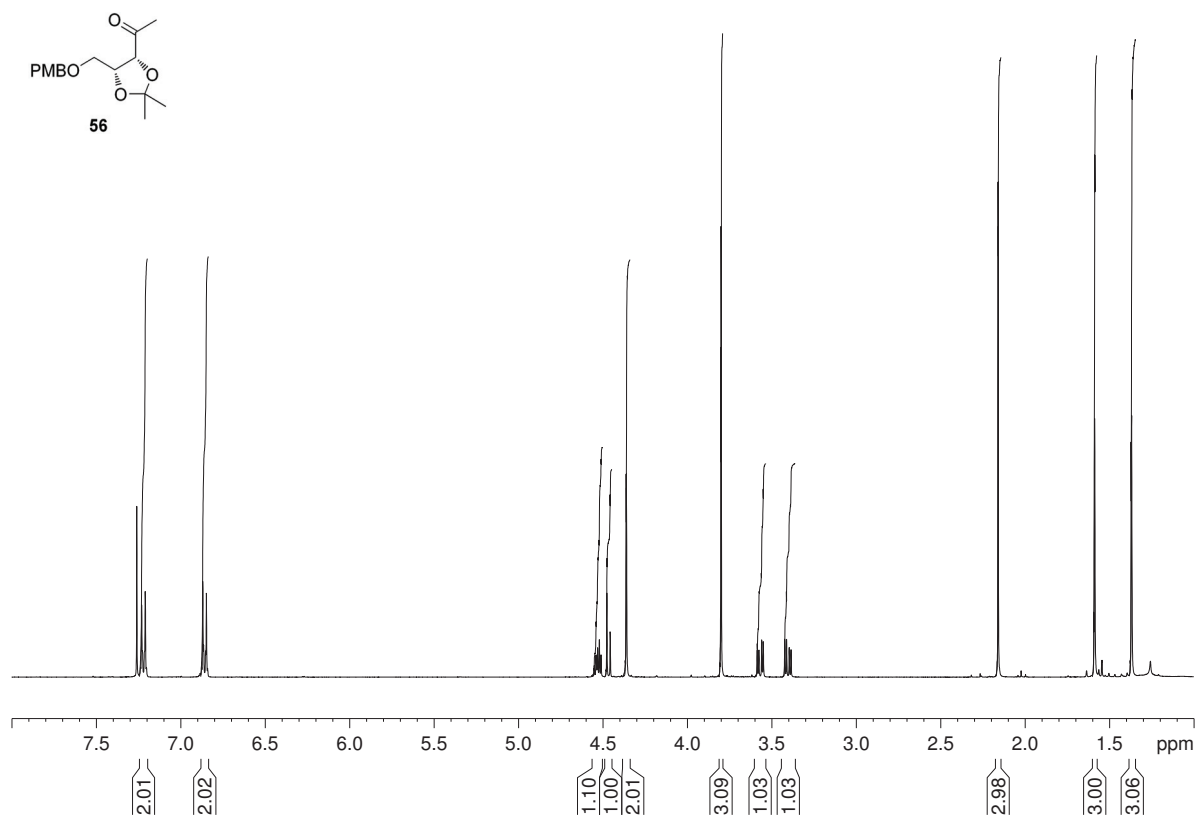
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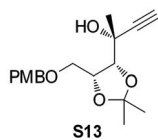
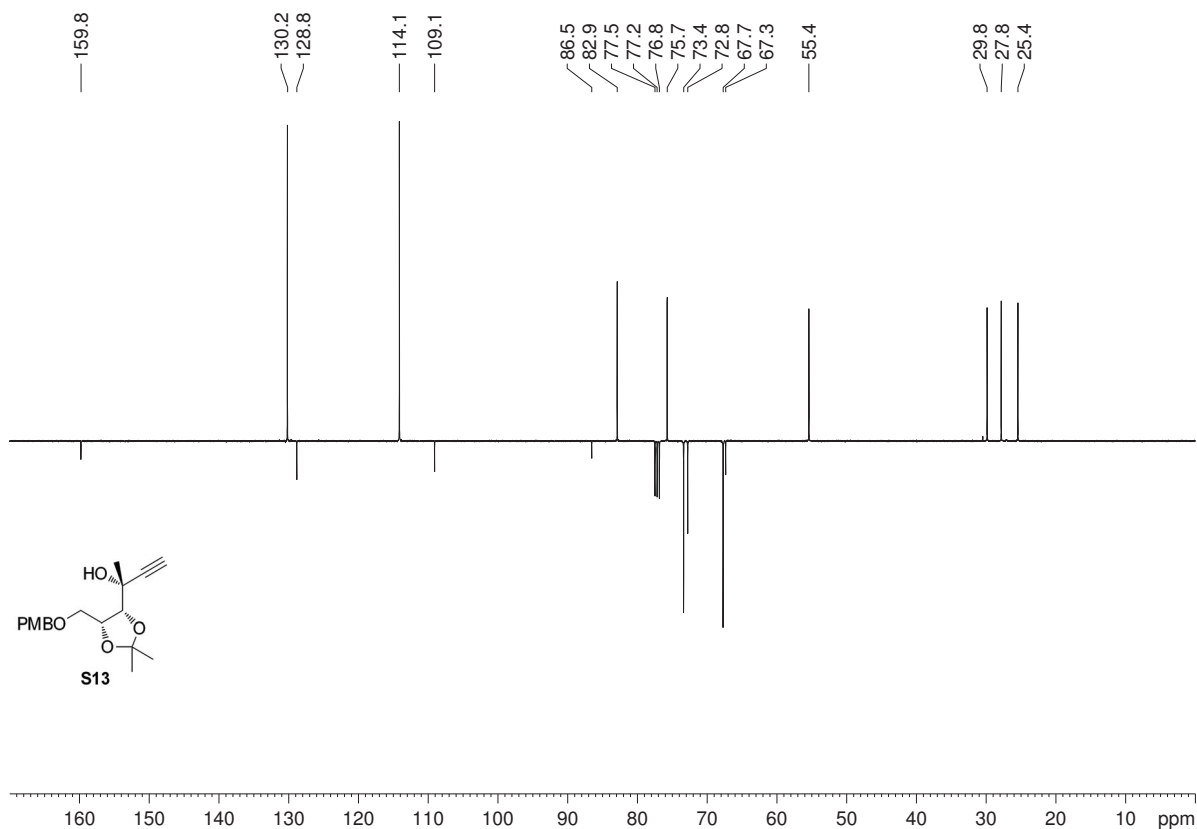
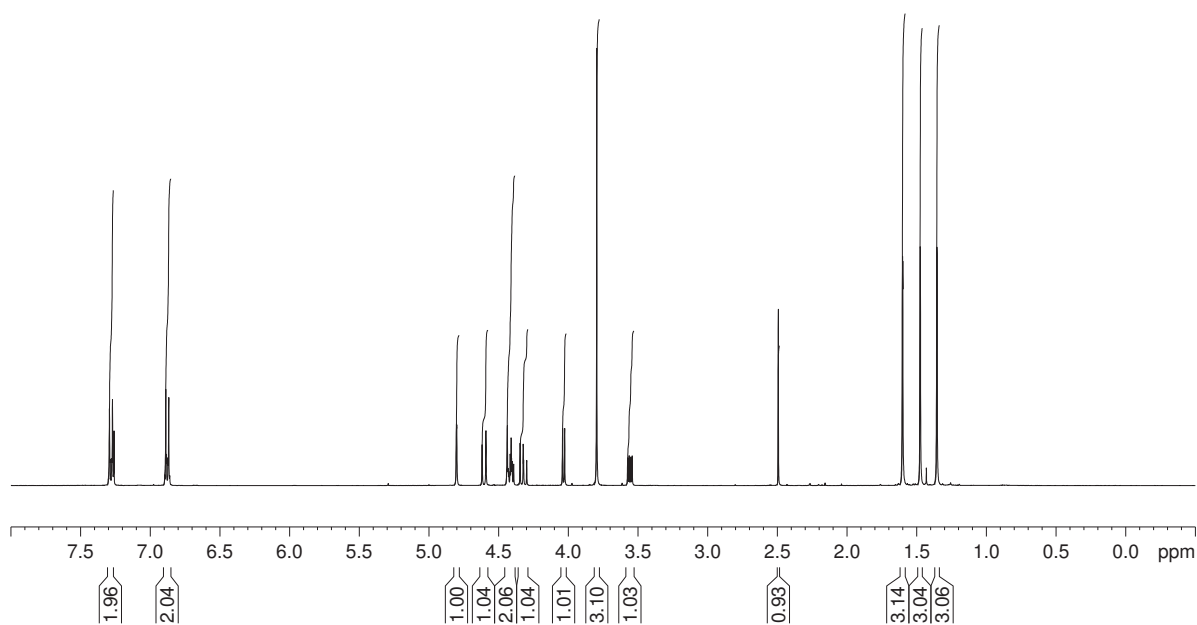
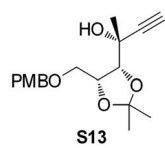
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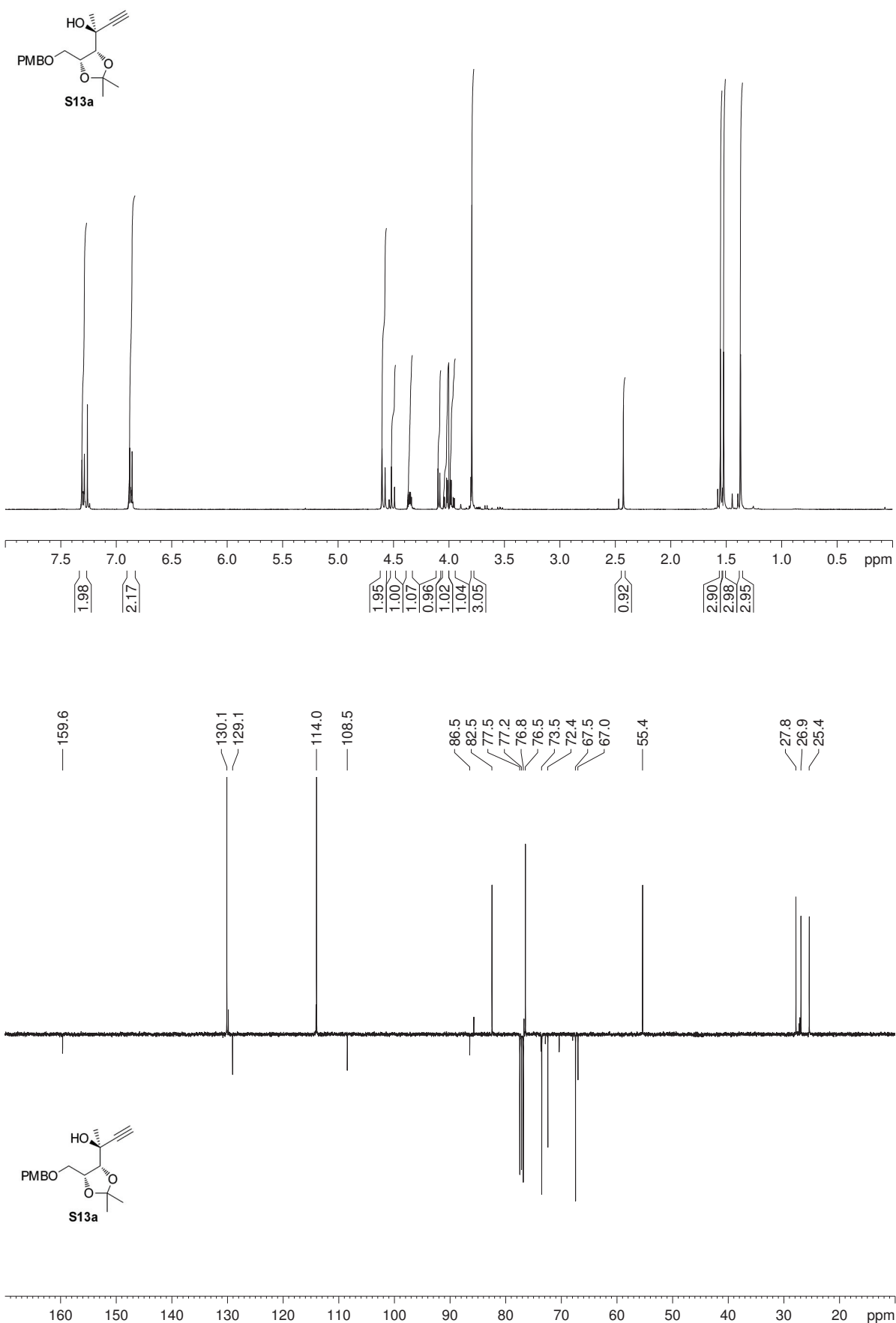


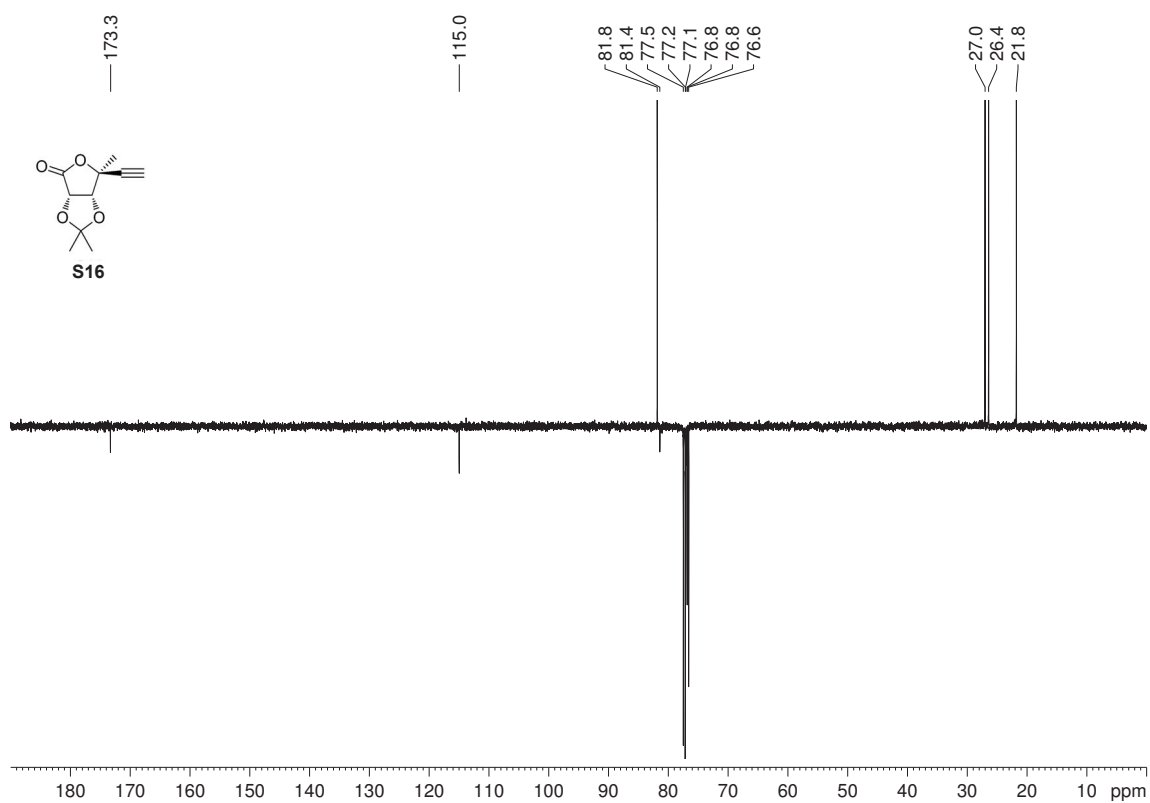
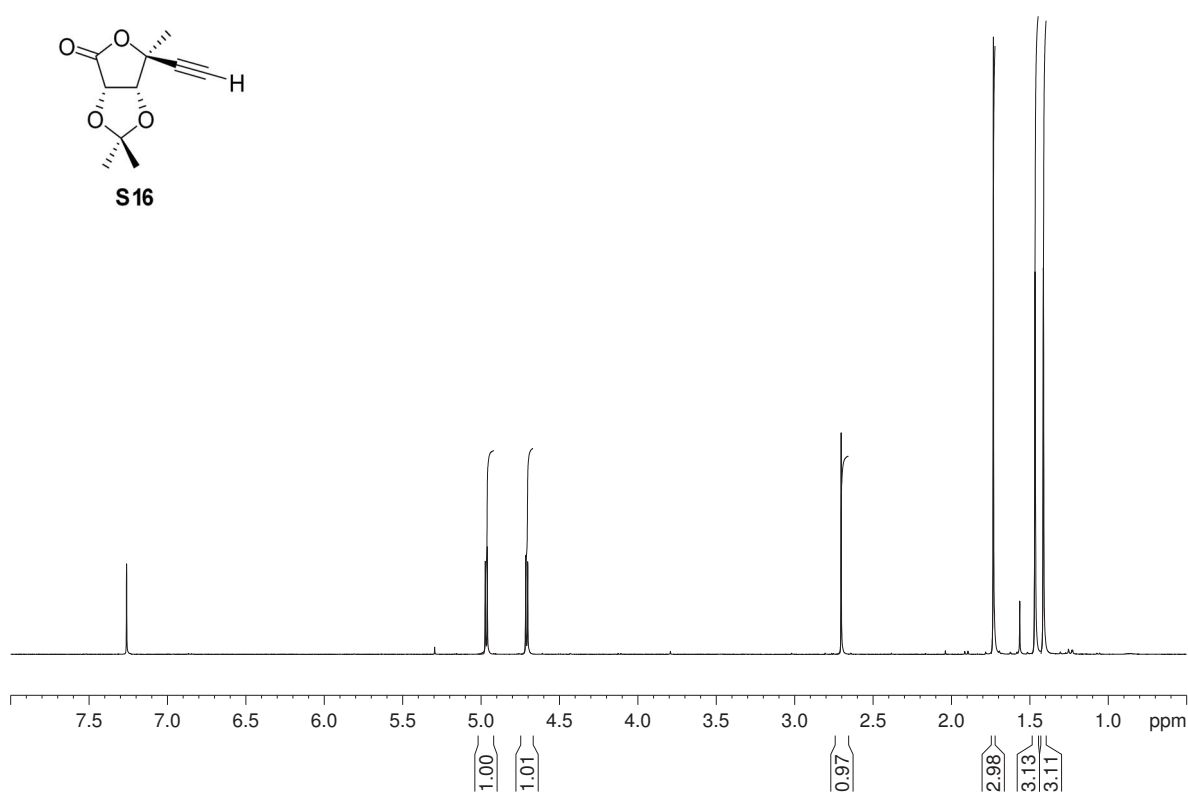


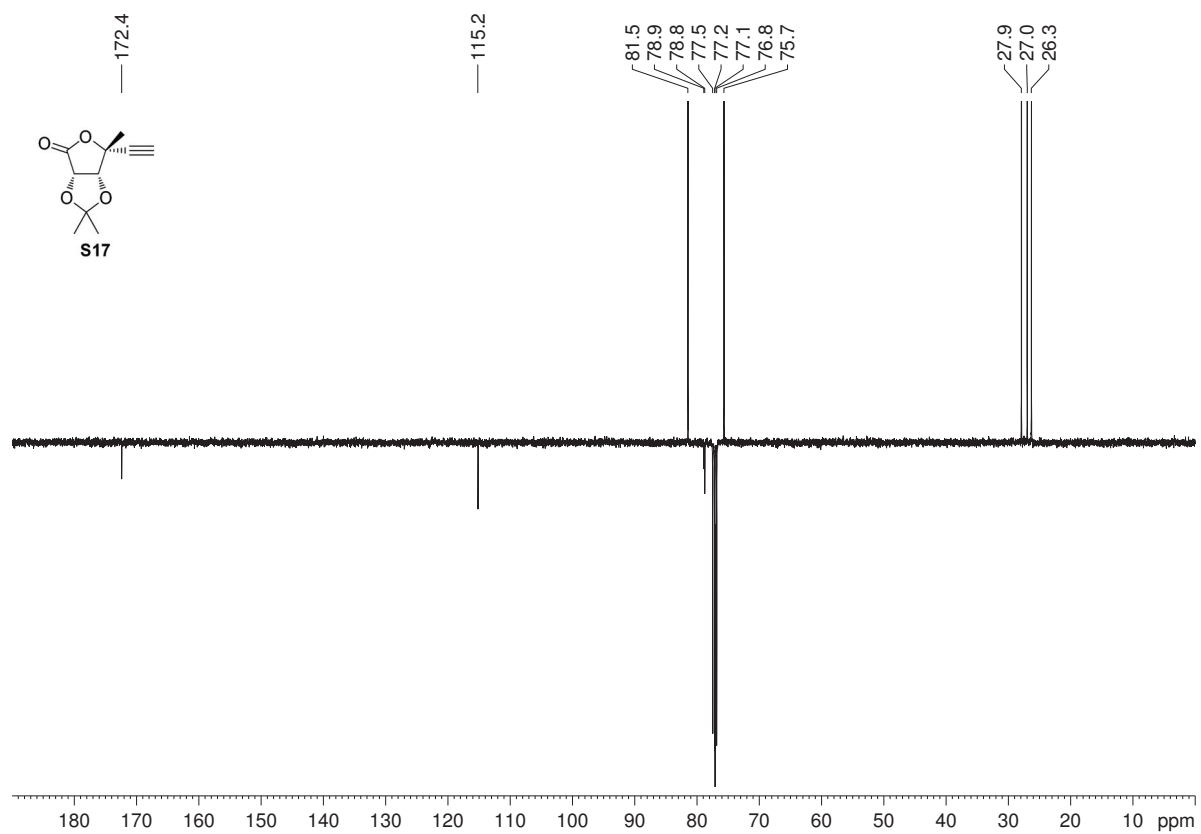
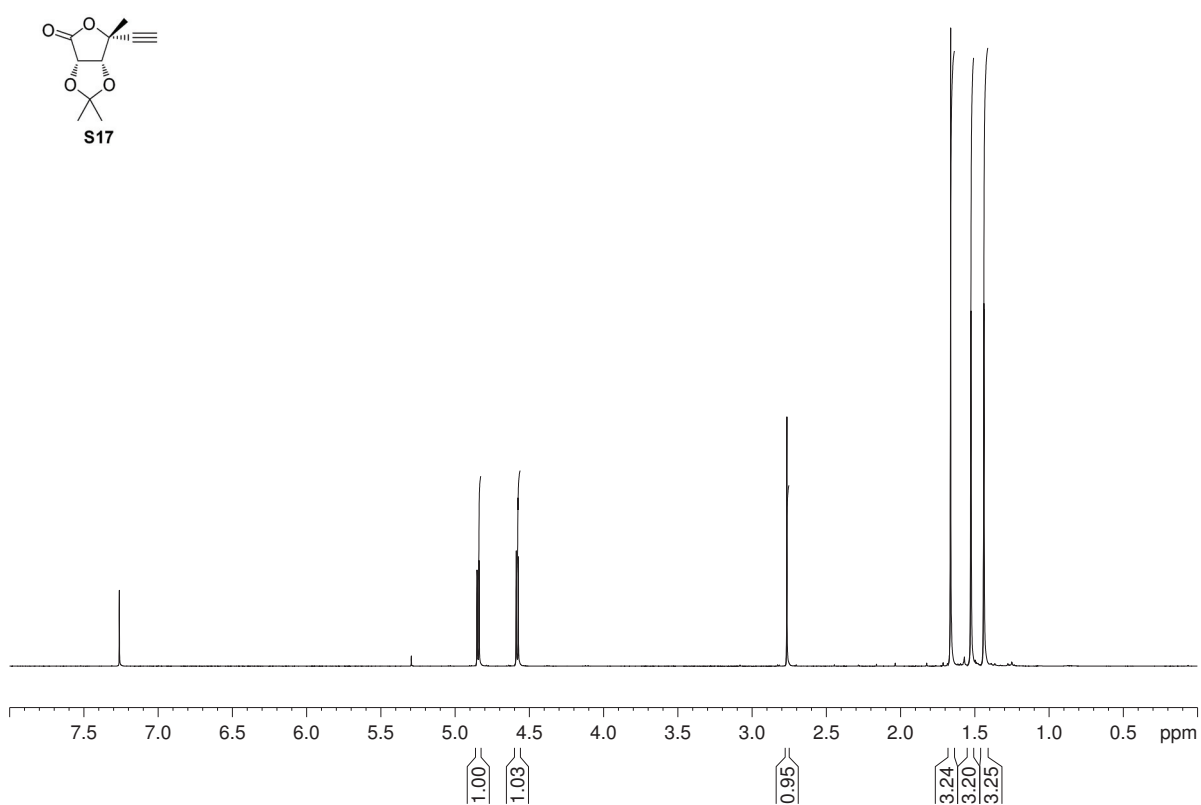


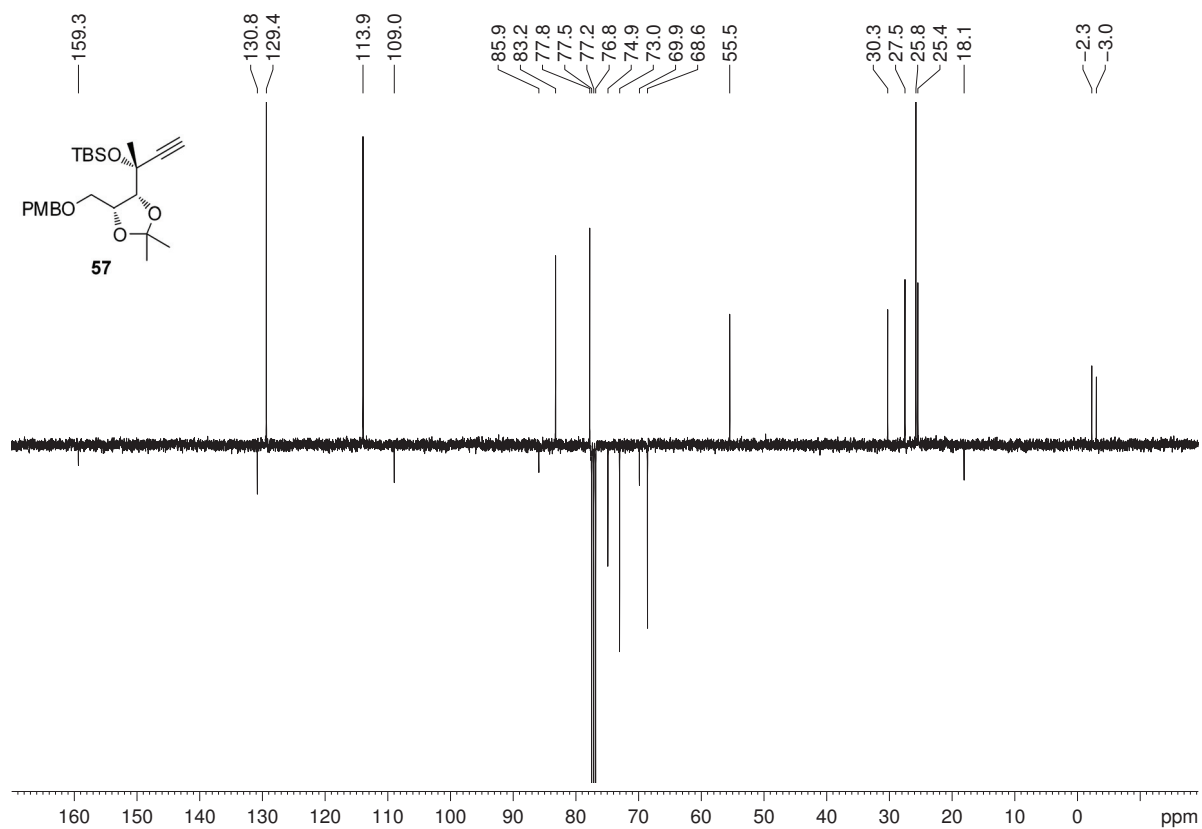
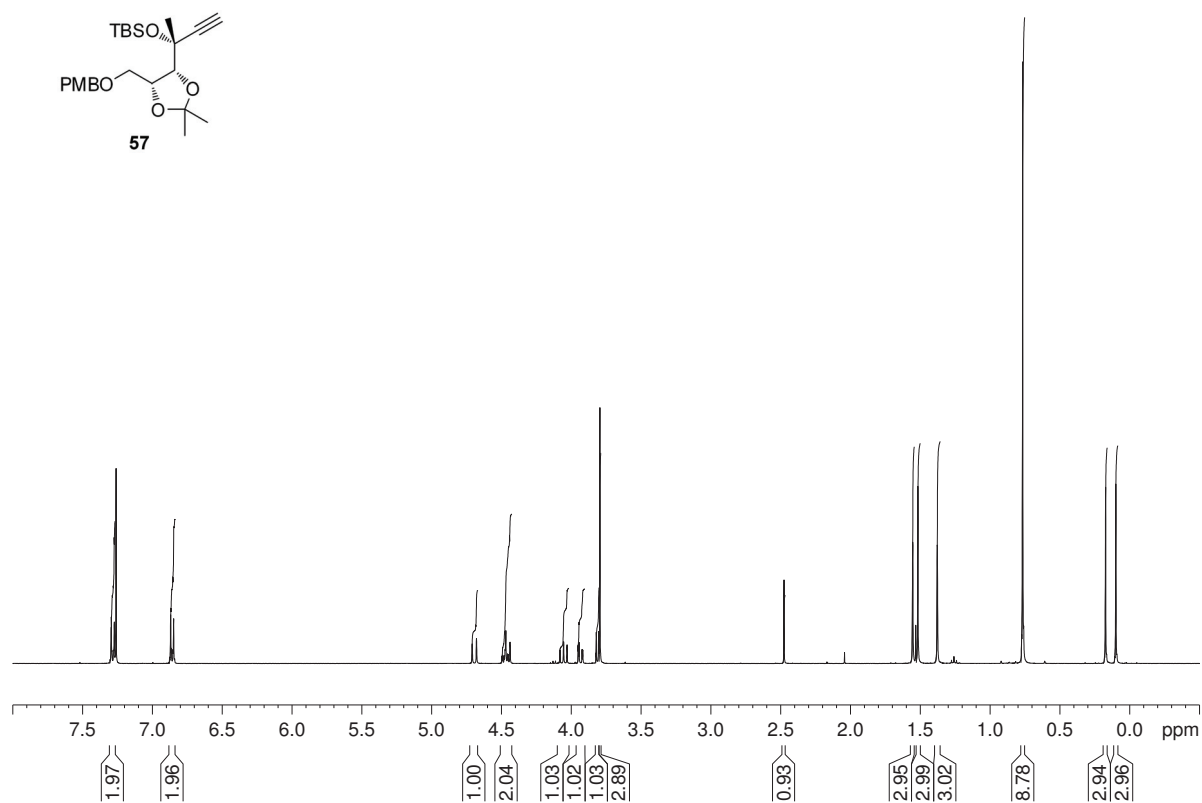


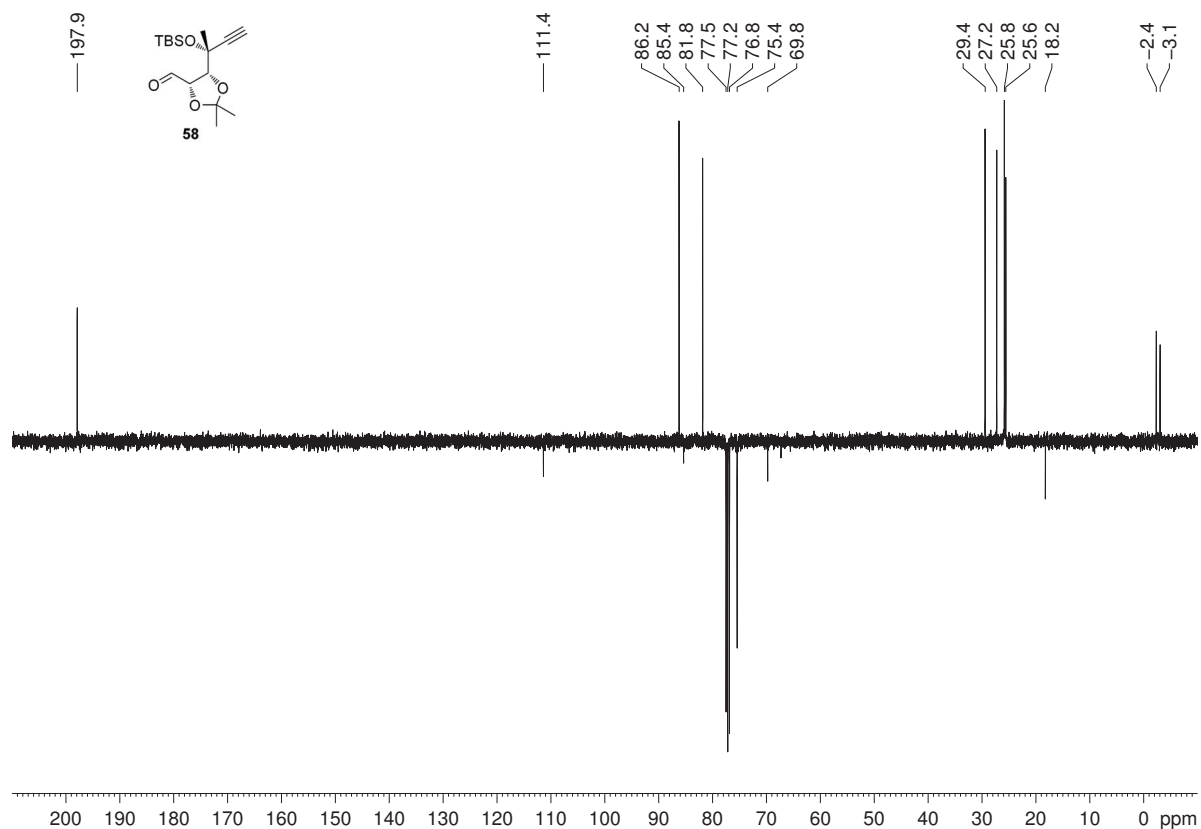
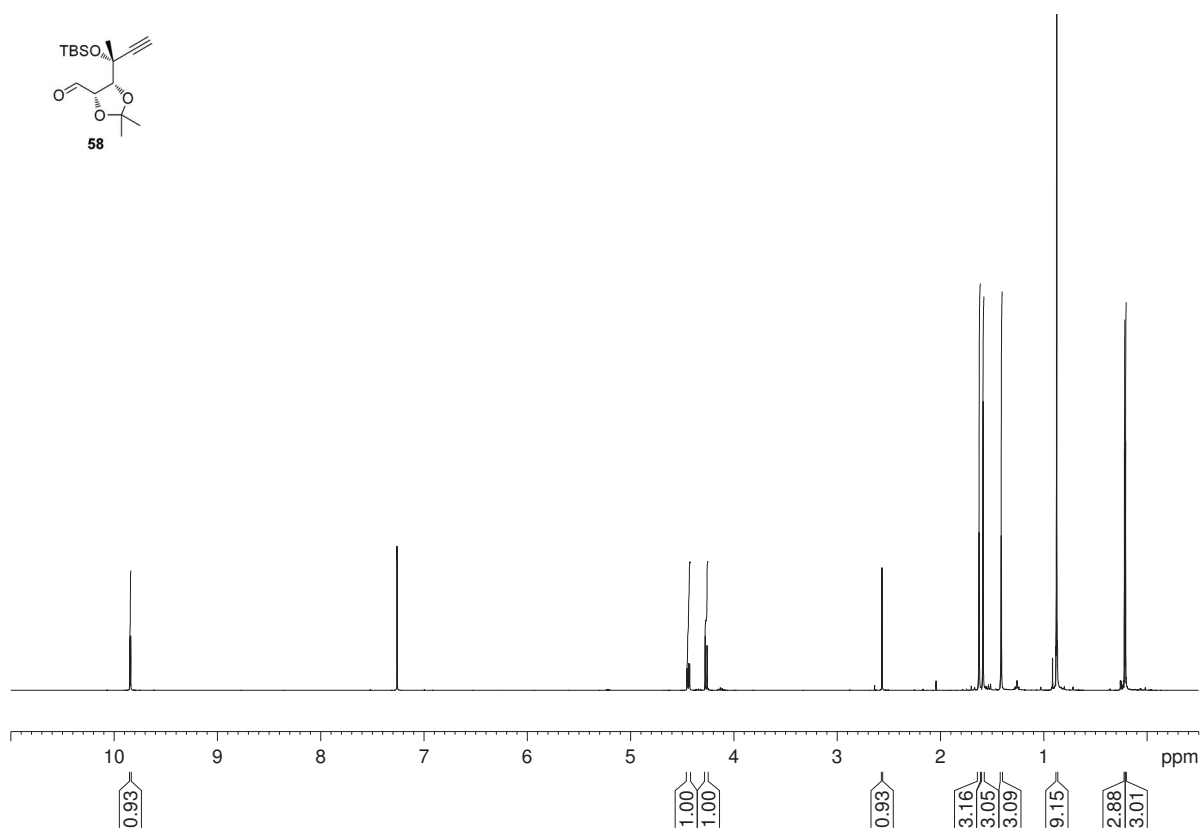


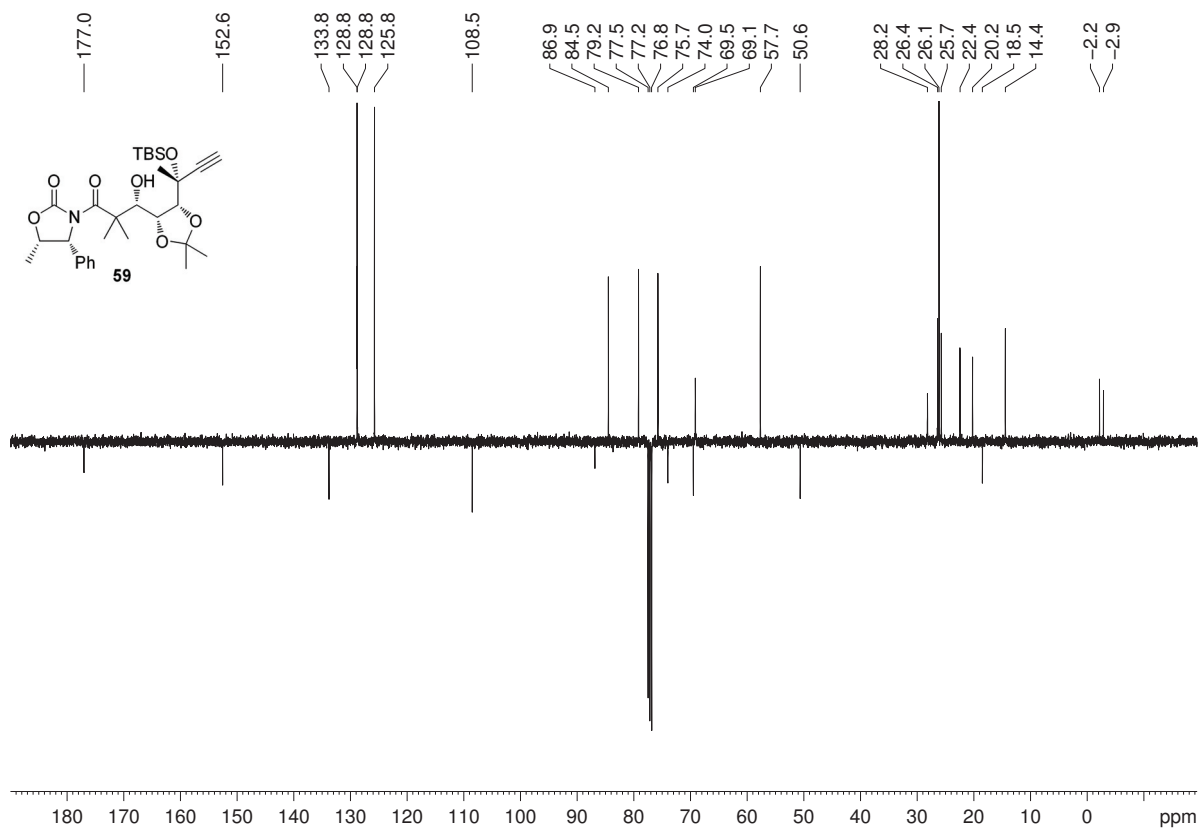
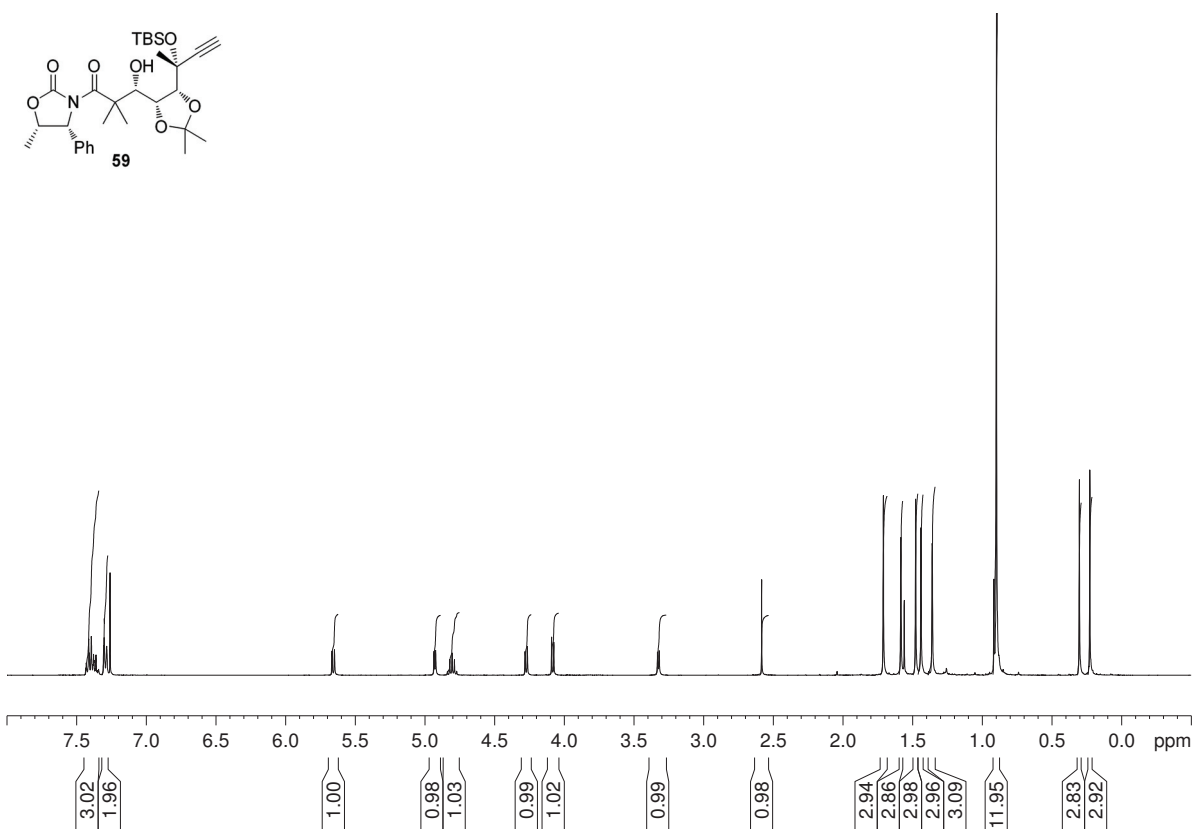


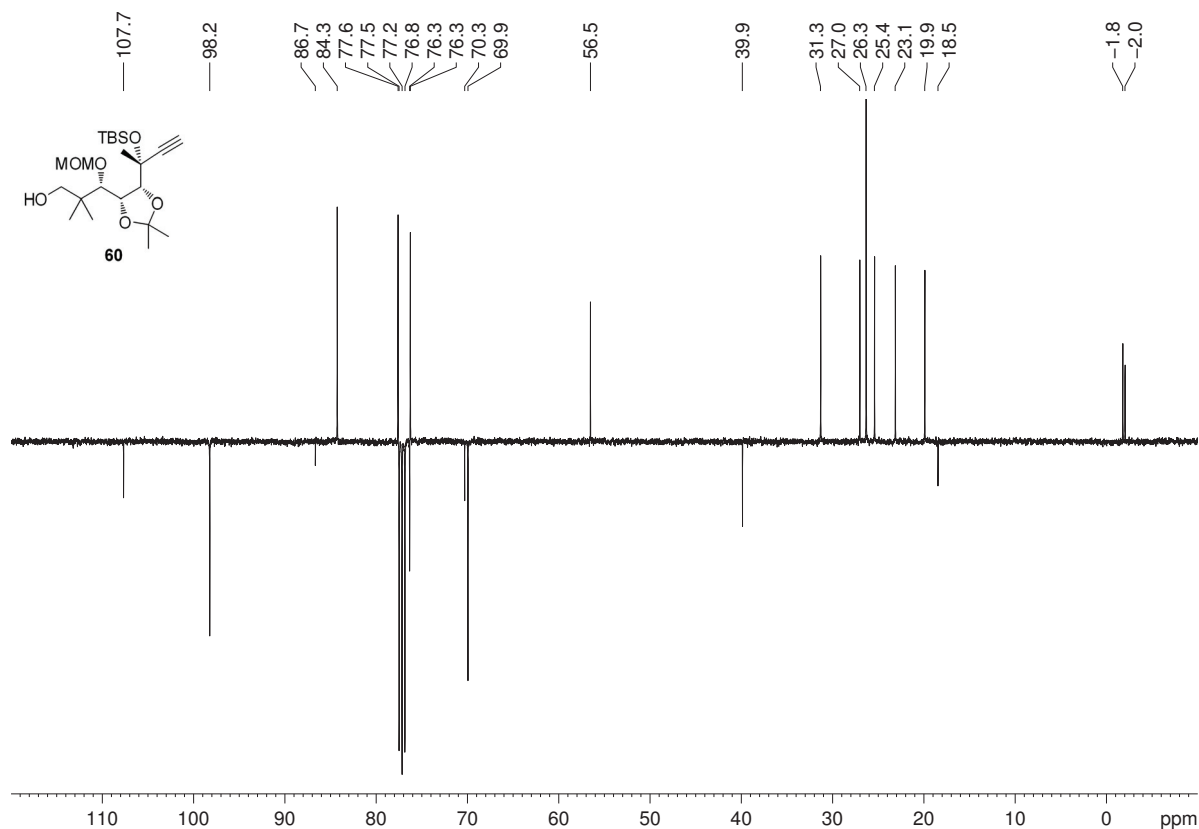
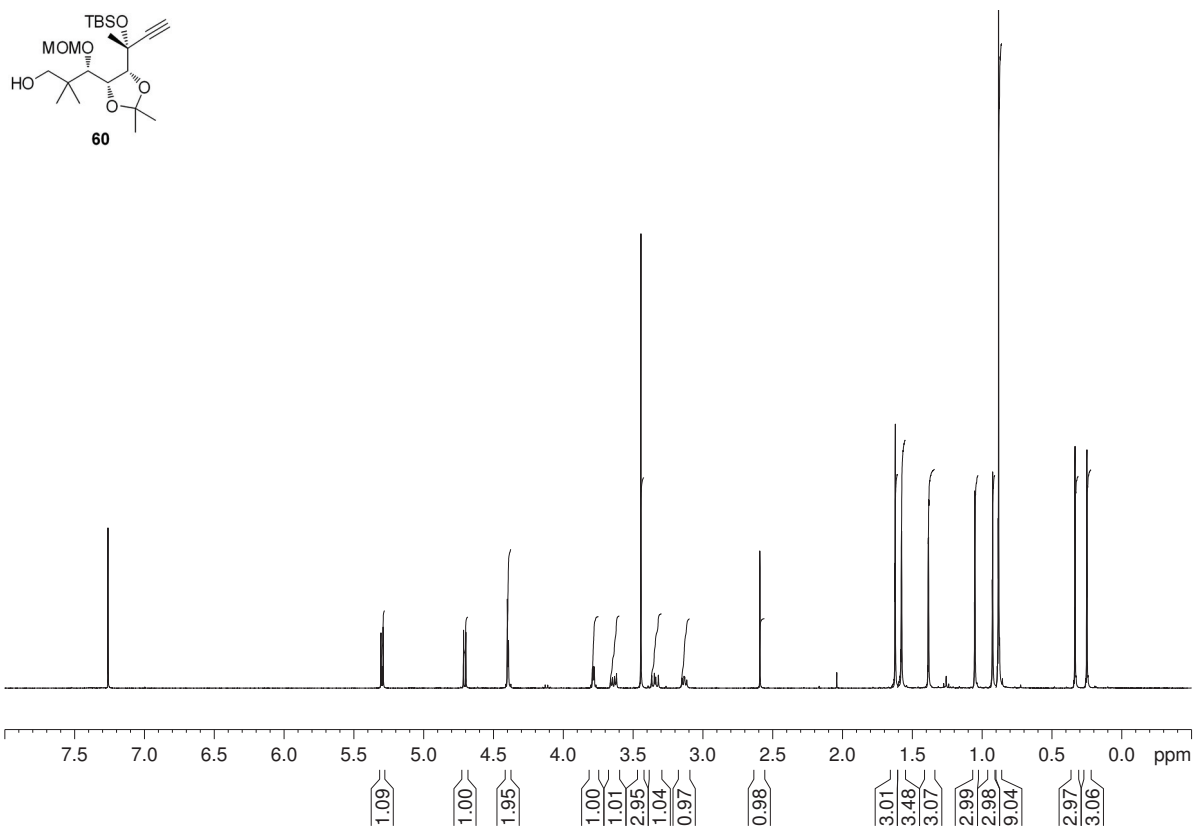


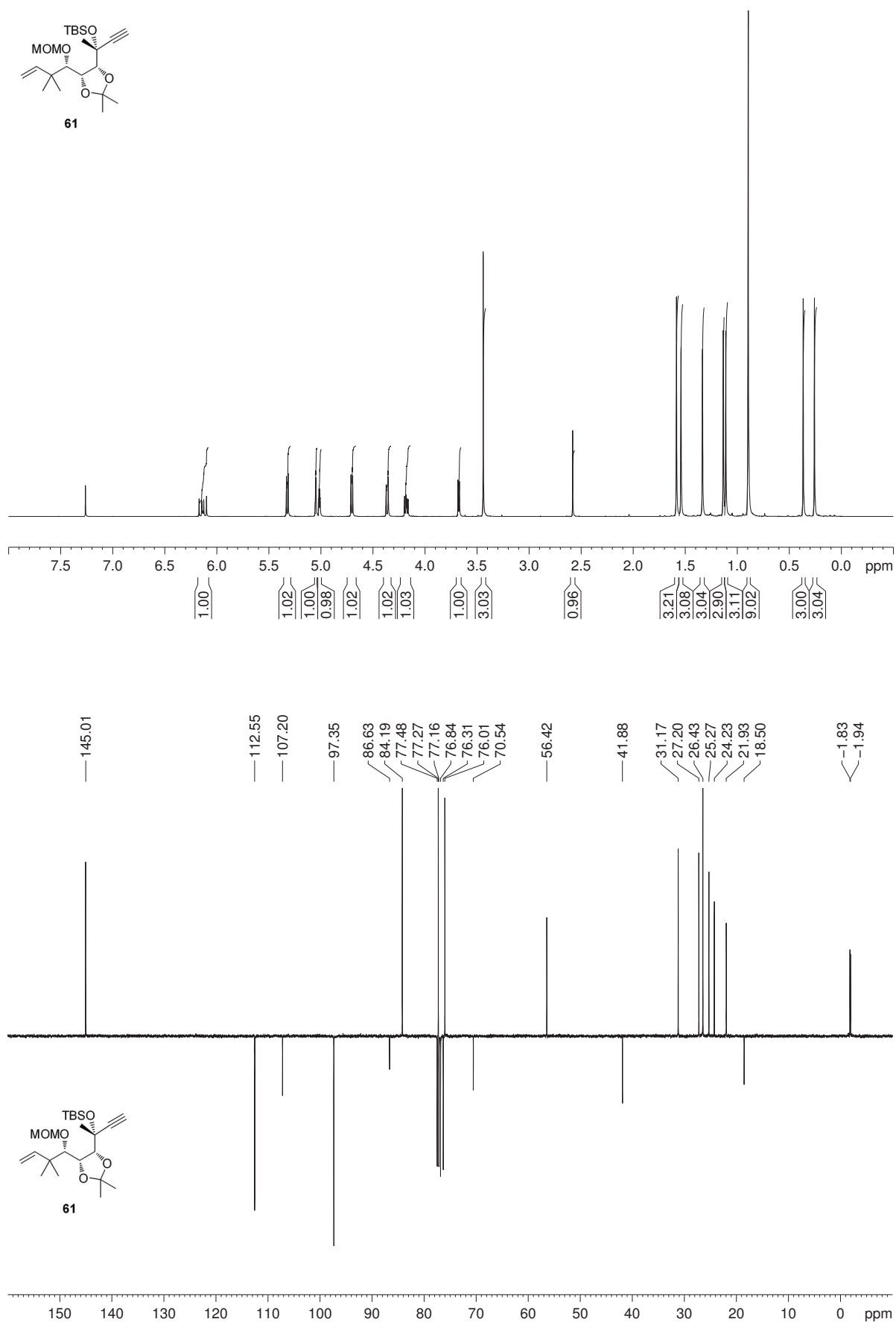


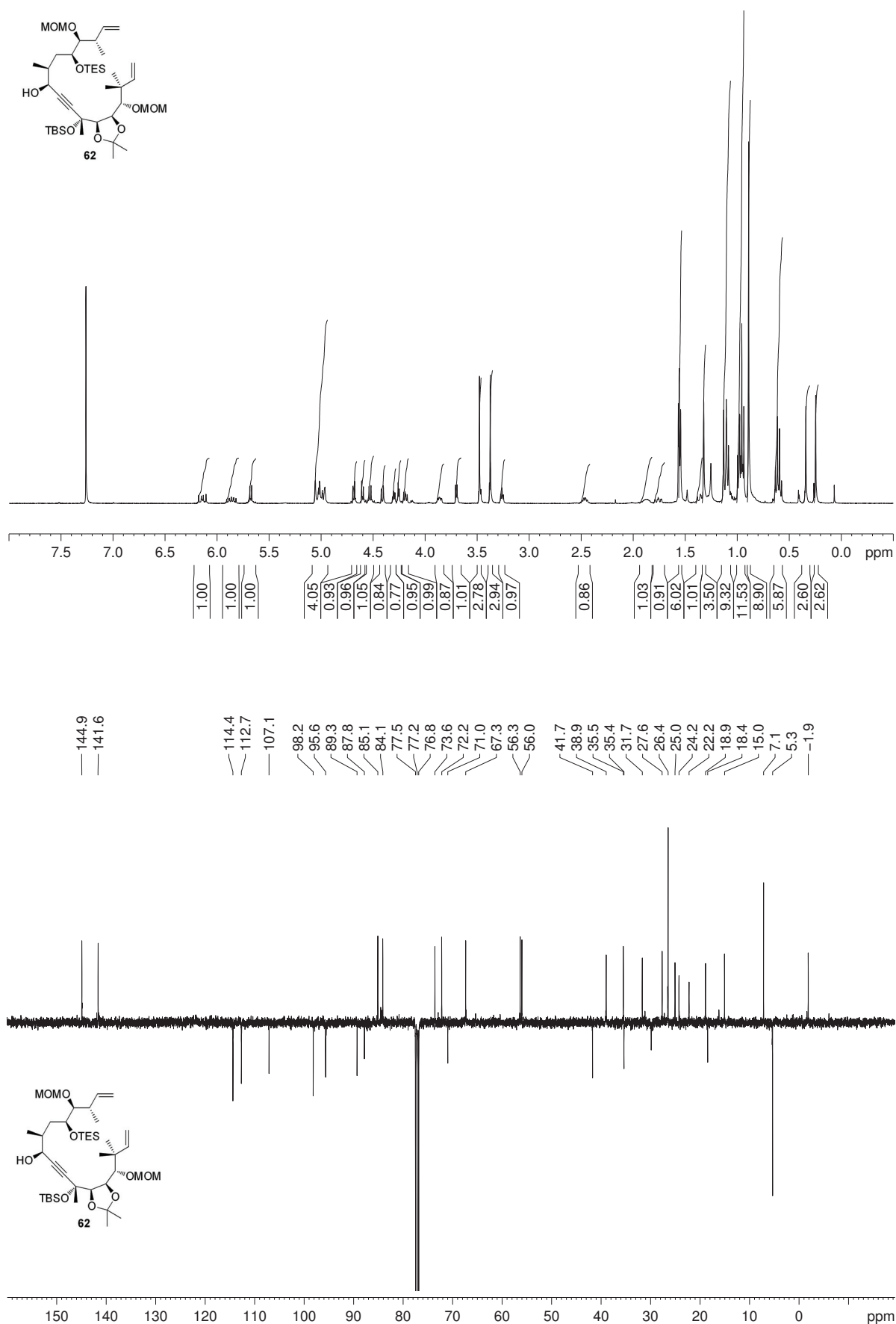


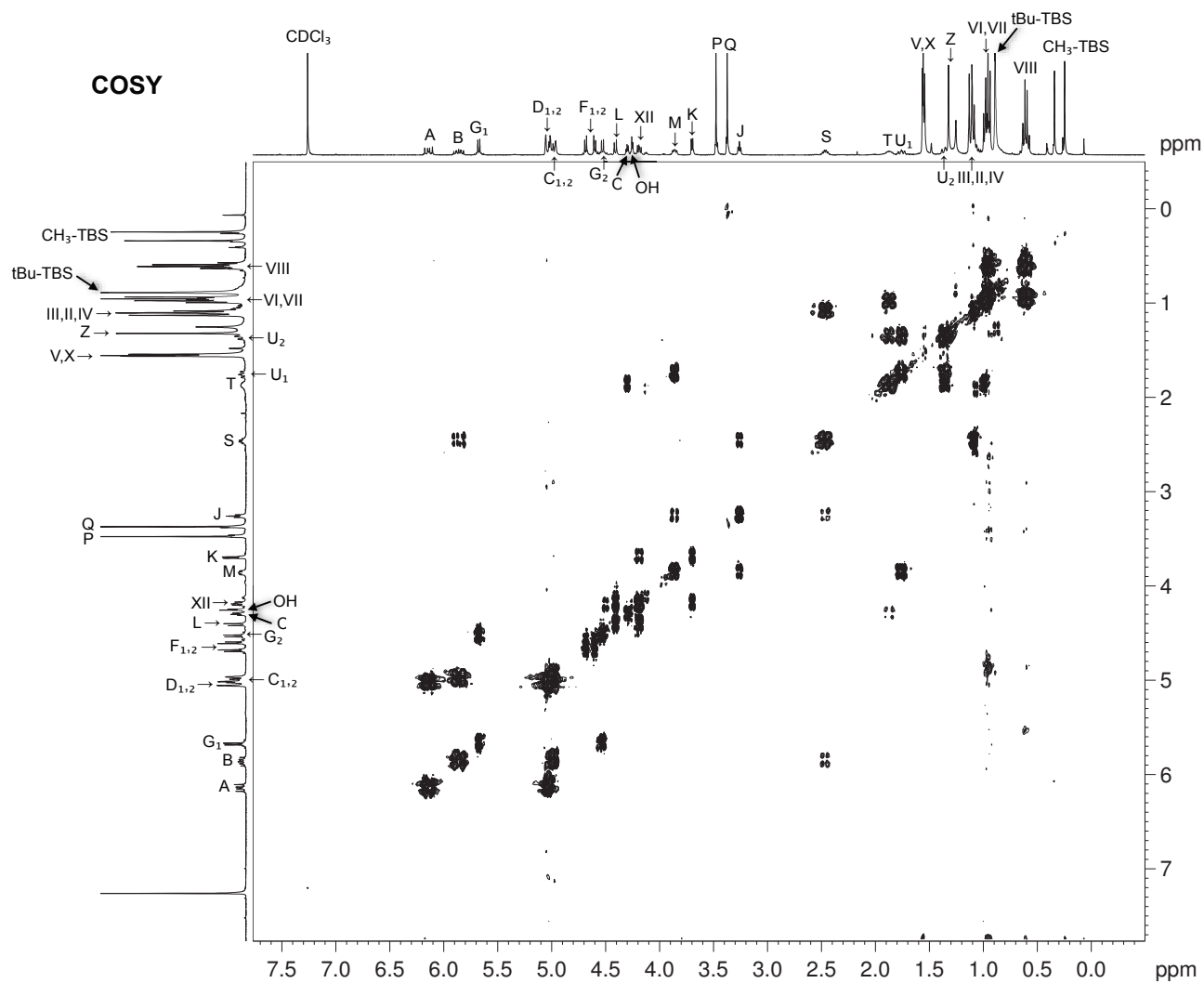
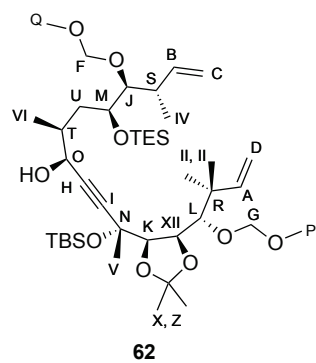


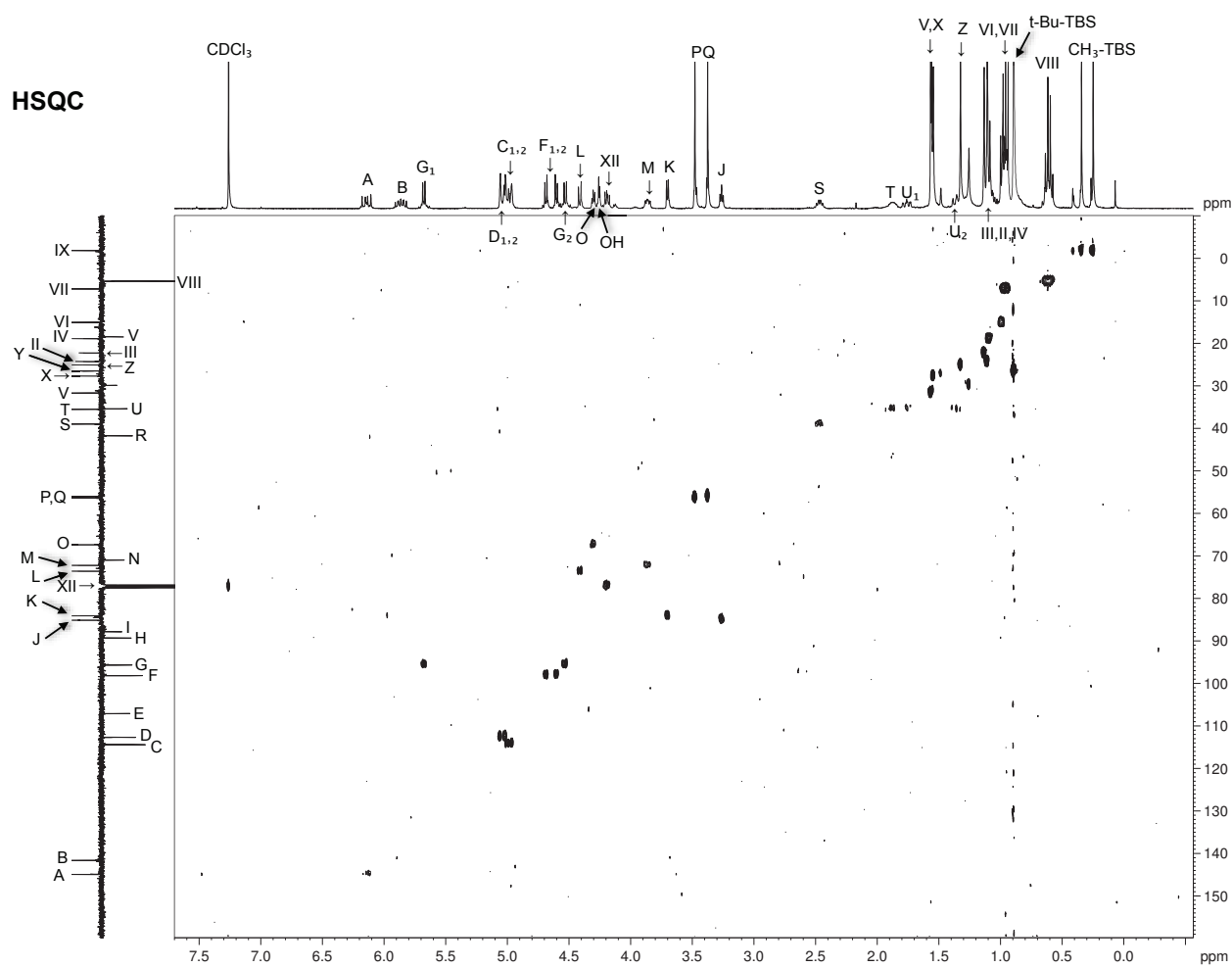


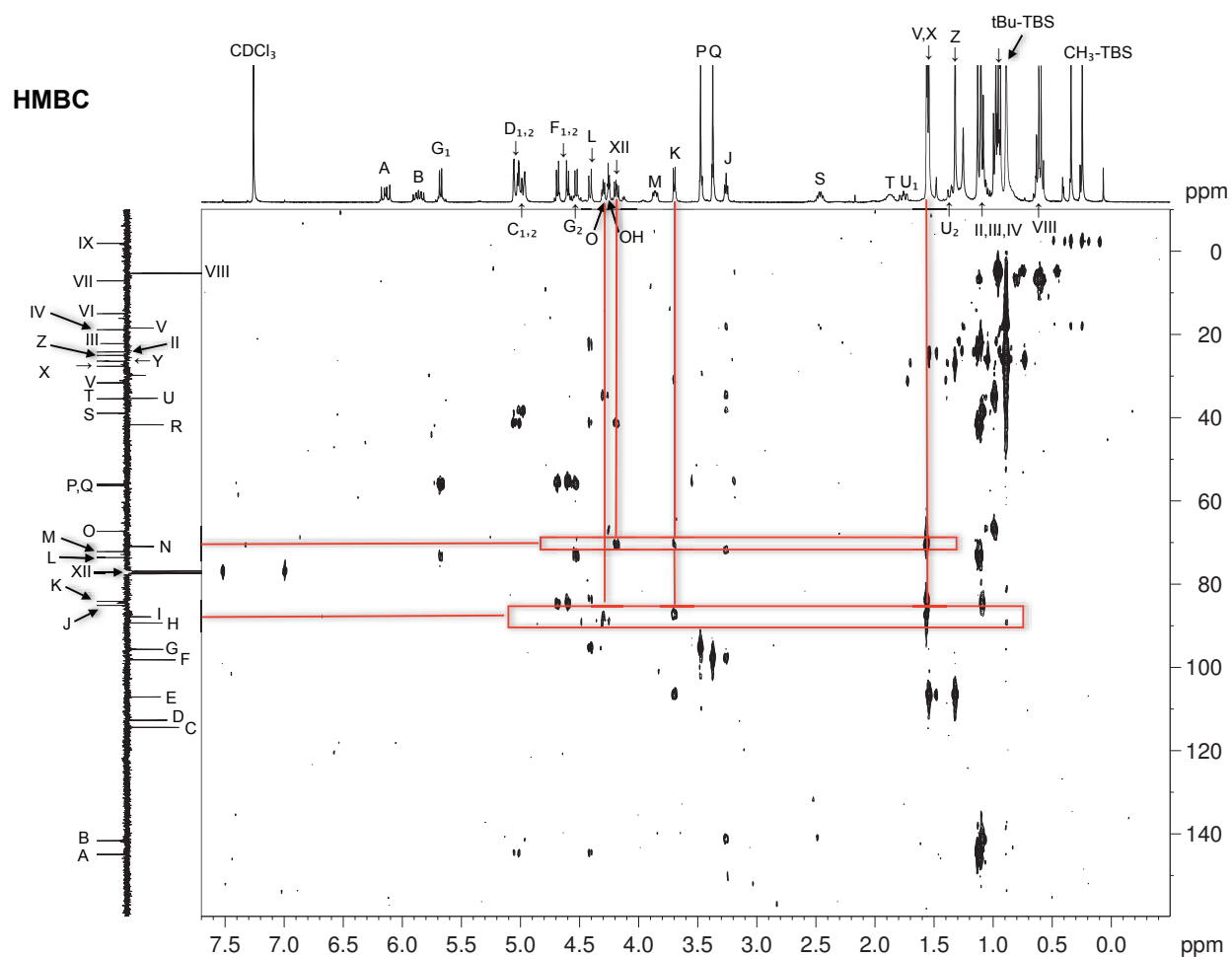


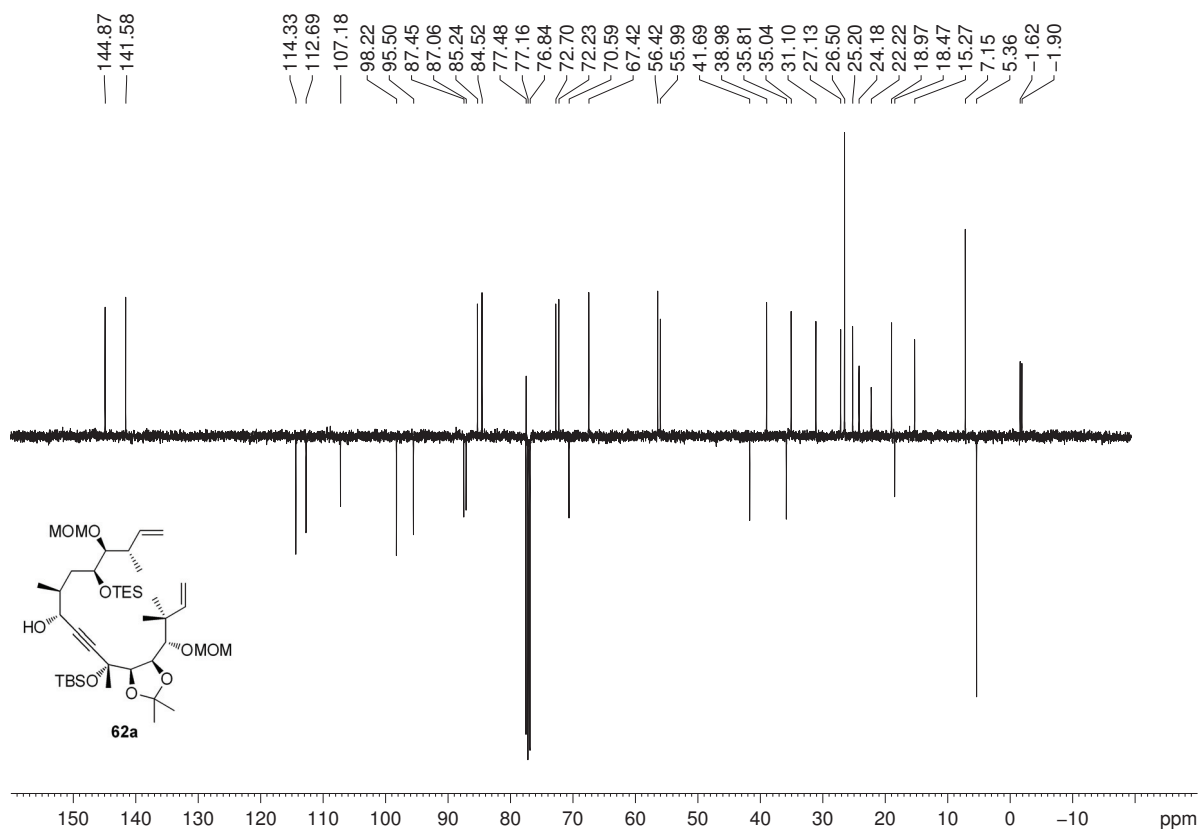
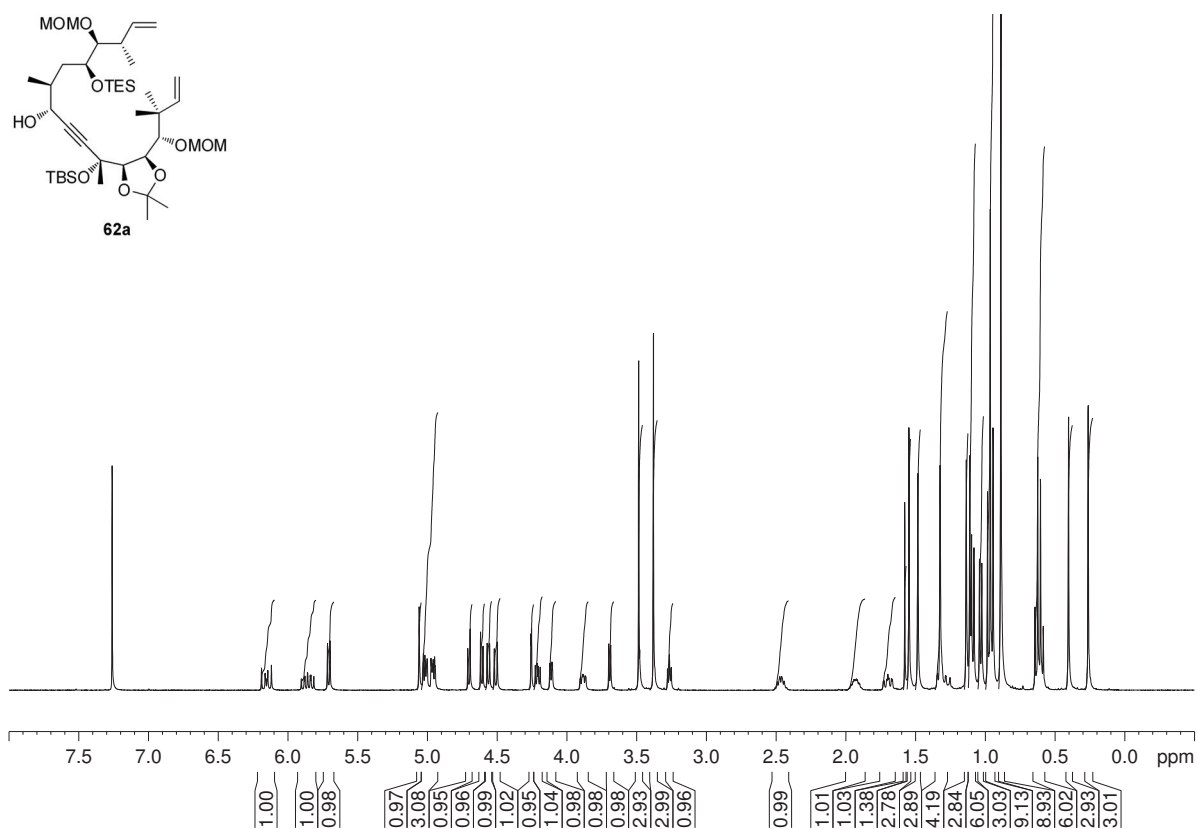


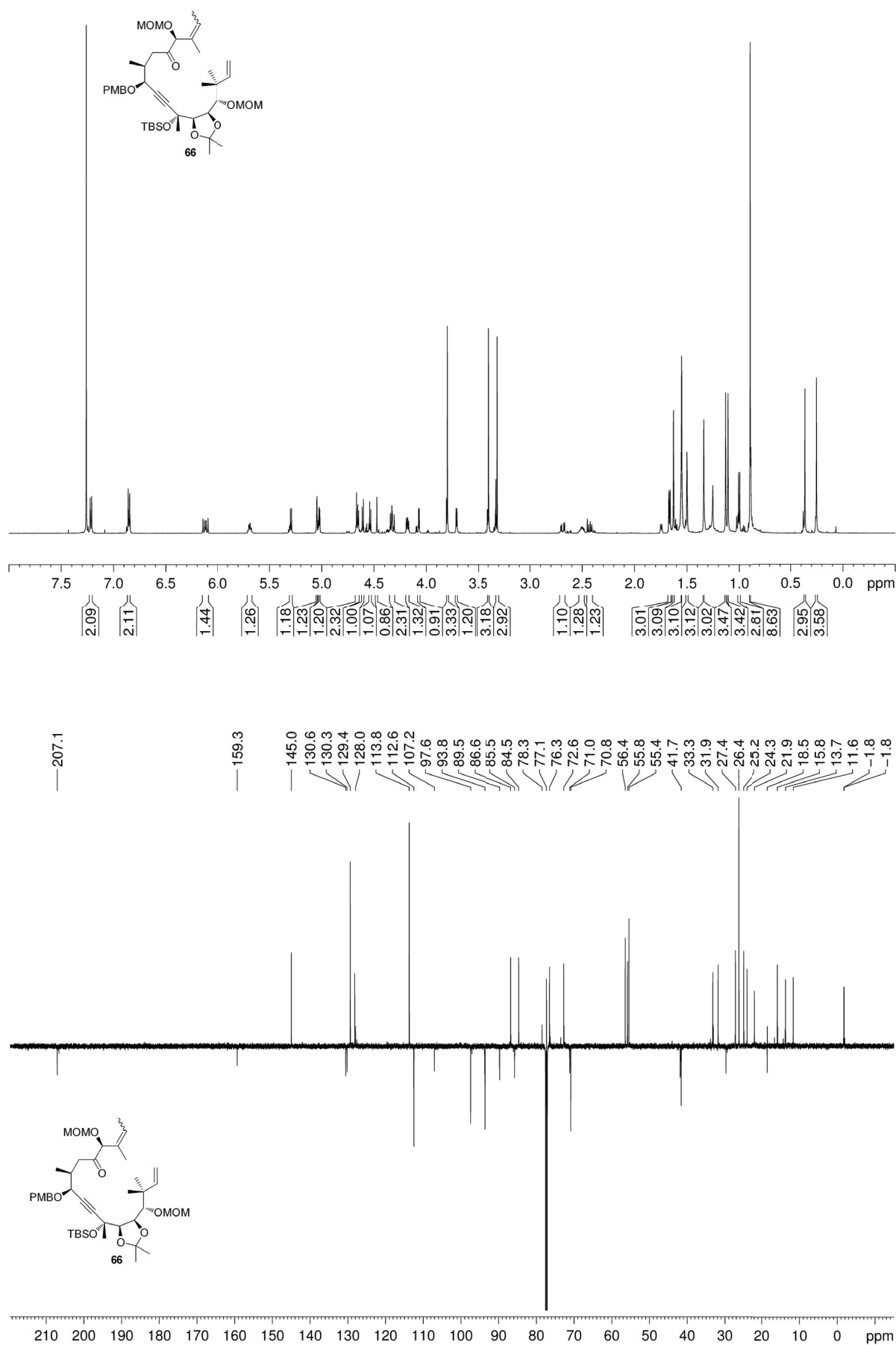


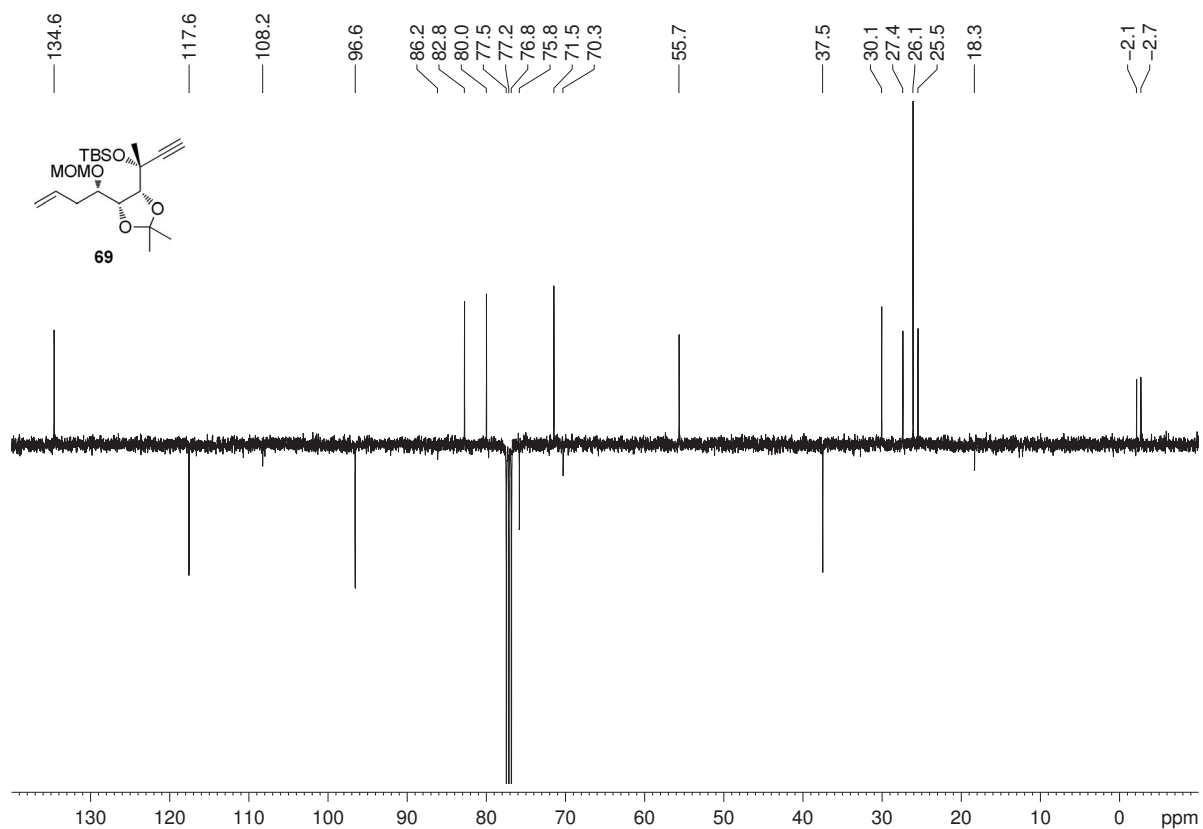
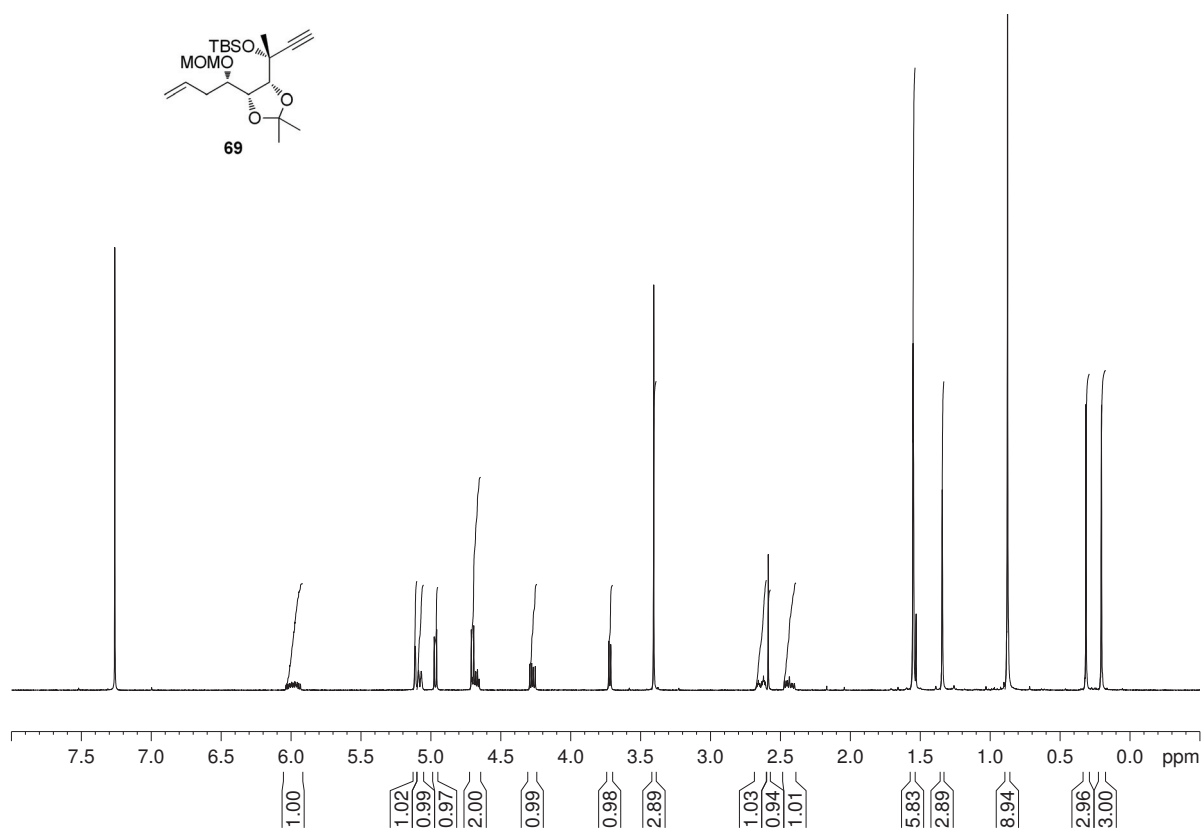


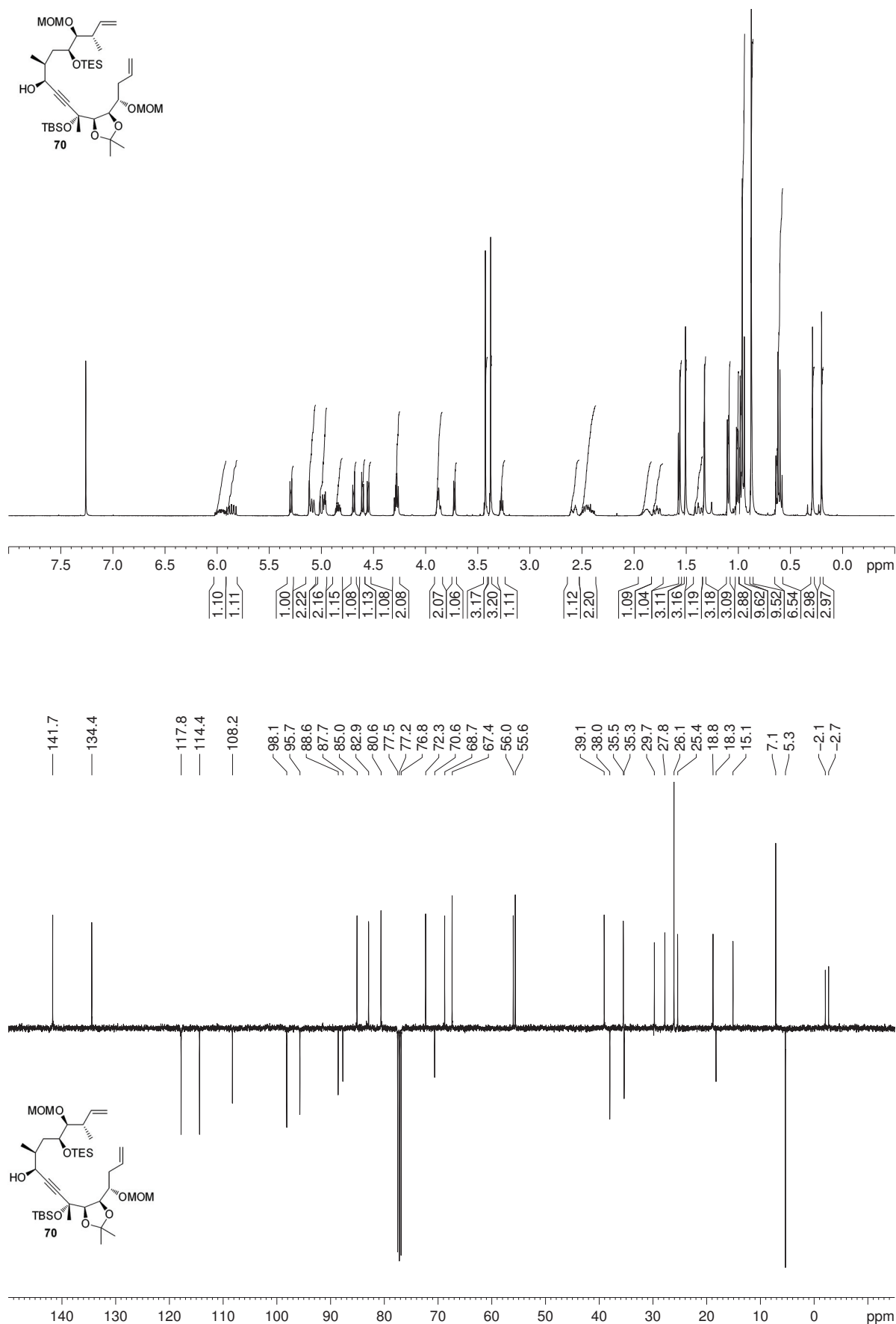
Compound **62**

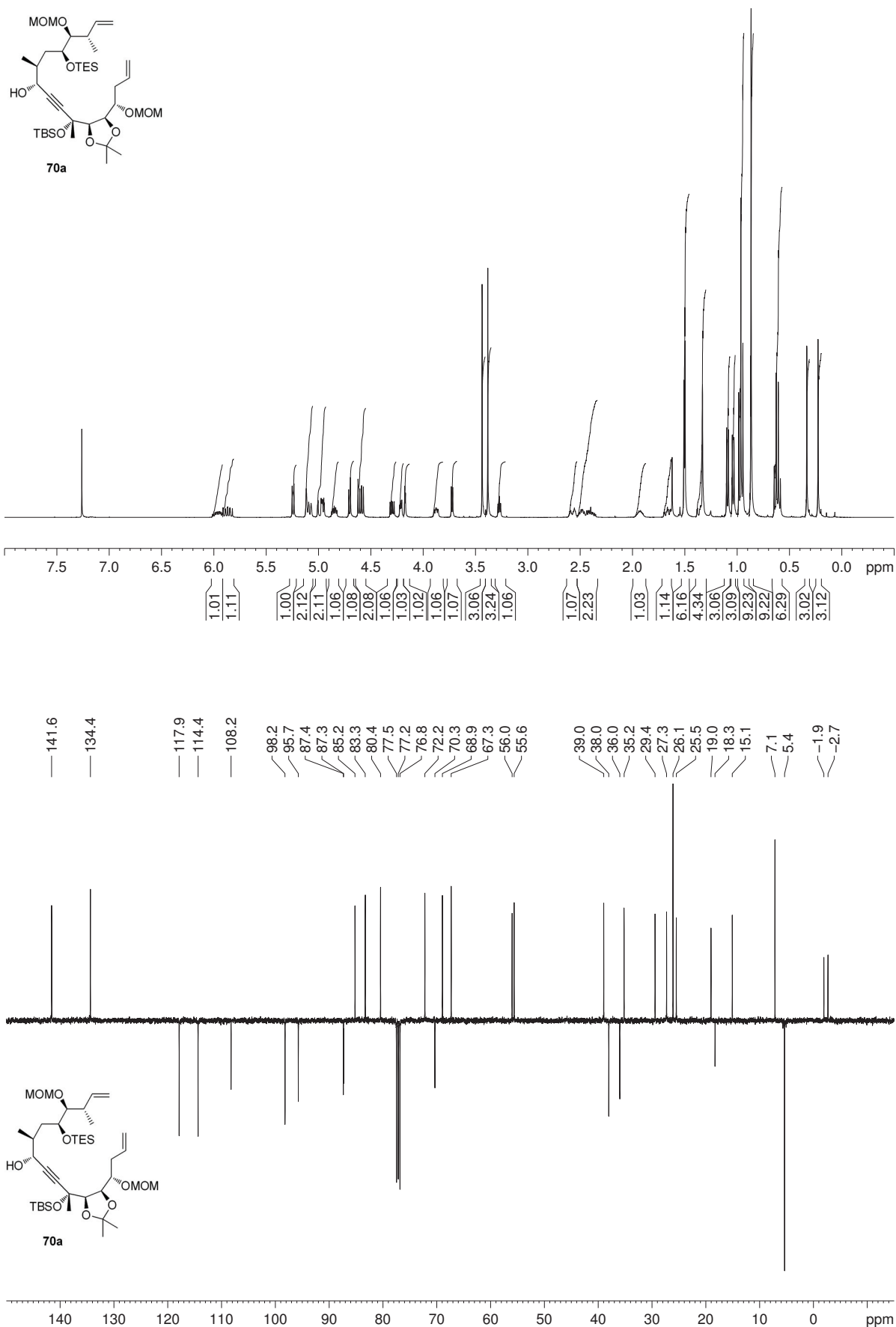
Compound **62**

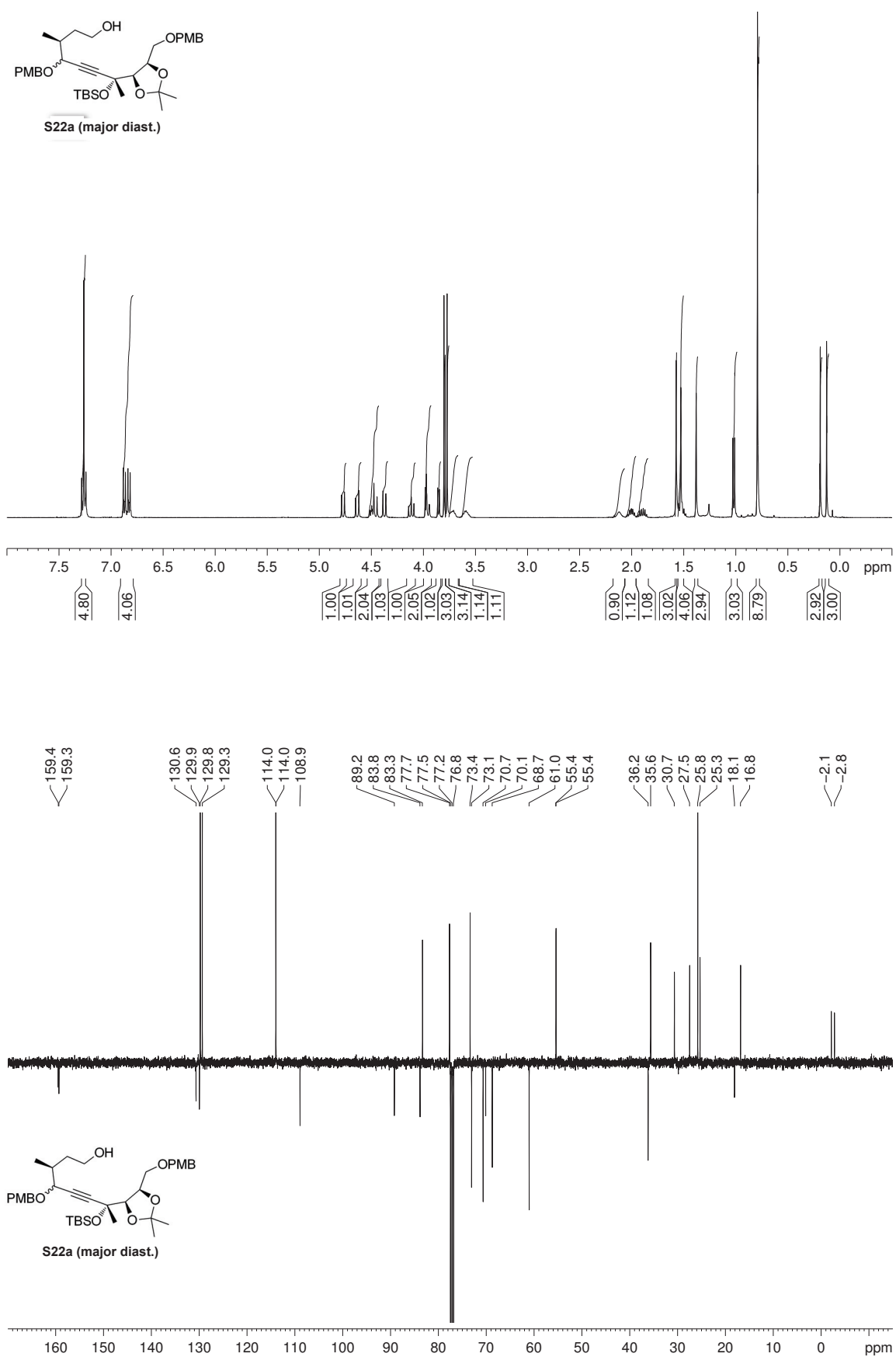


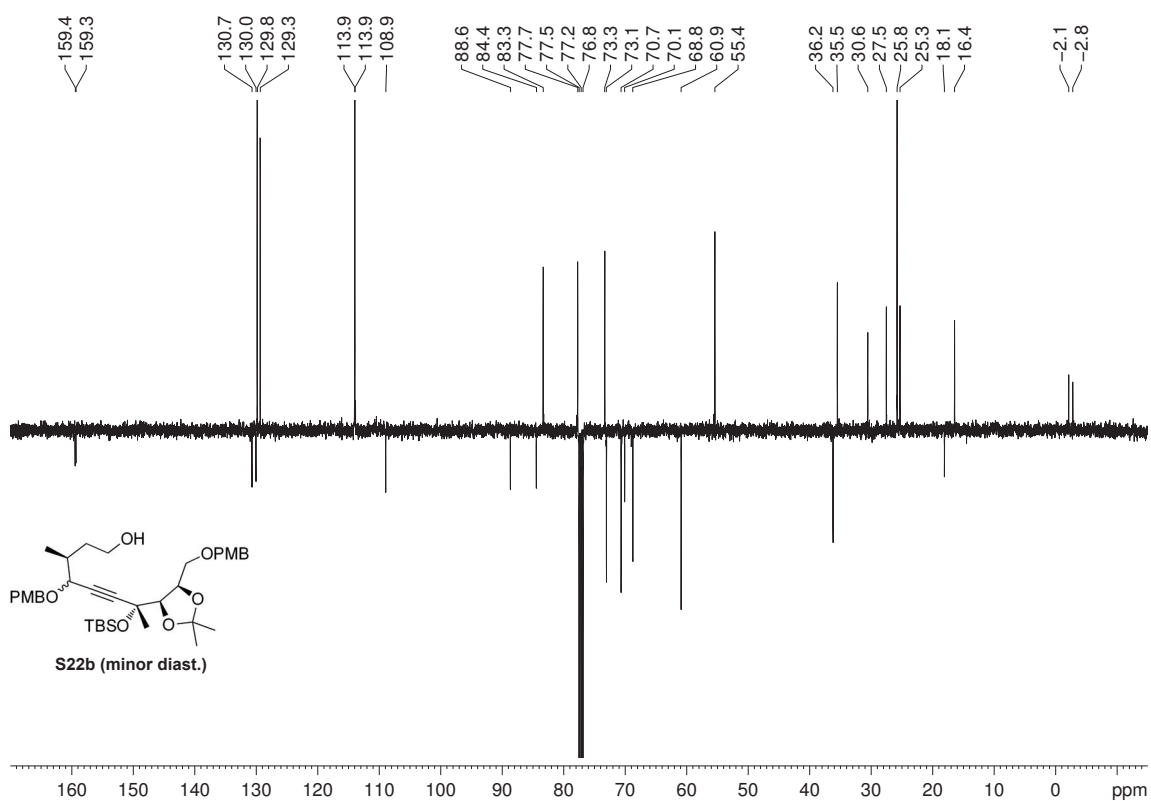
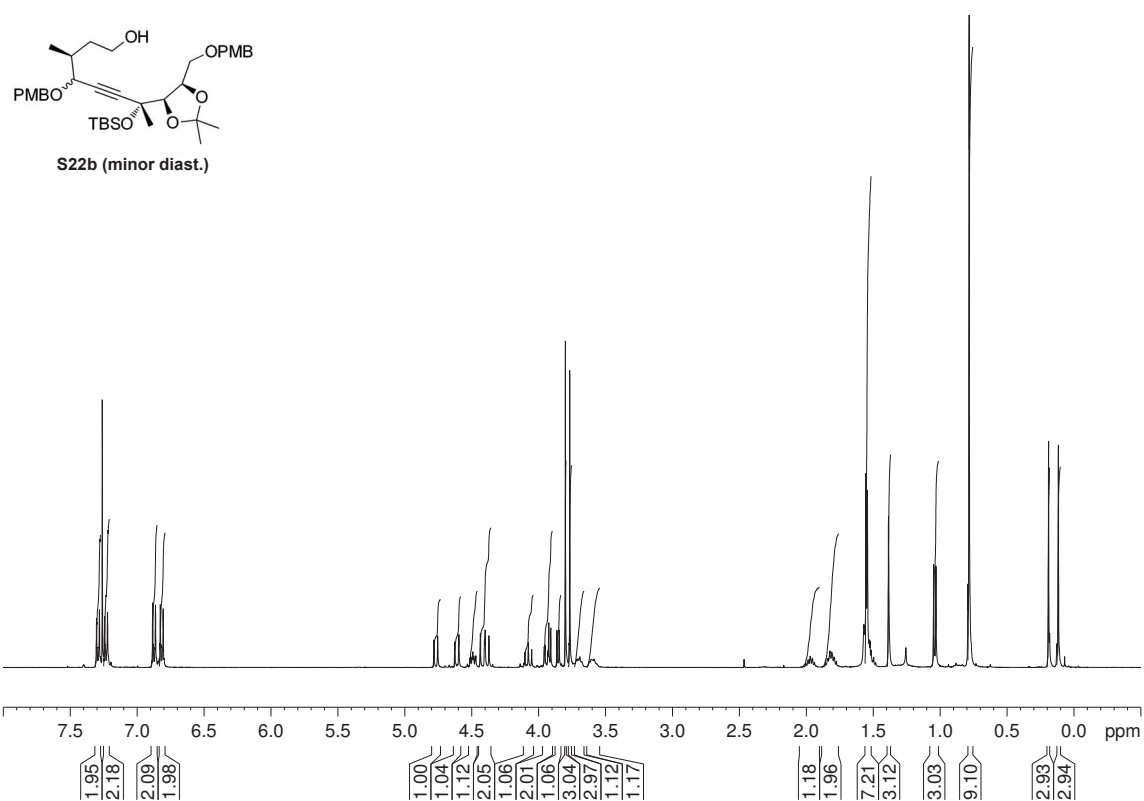


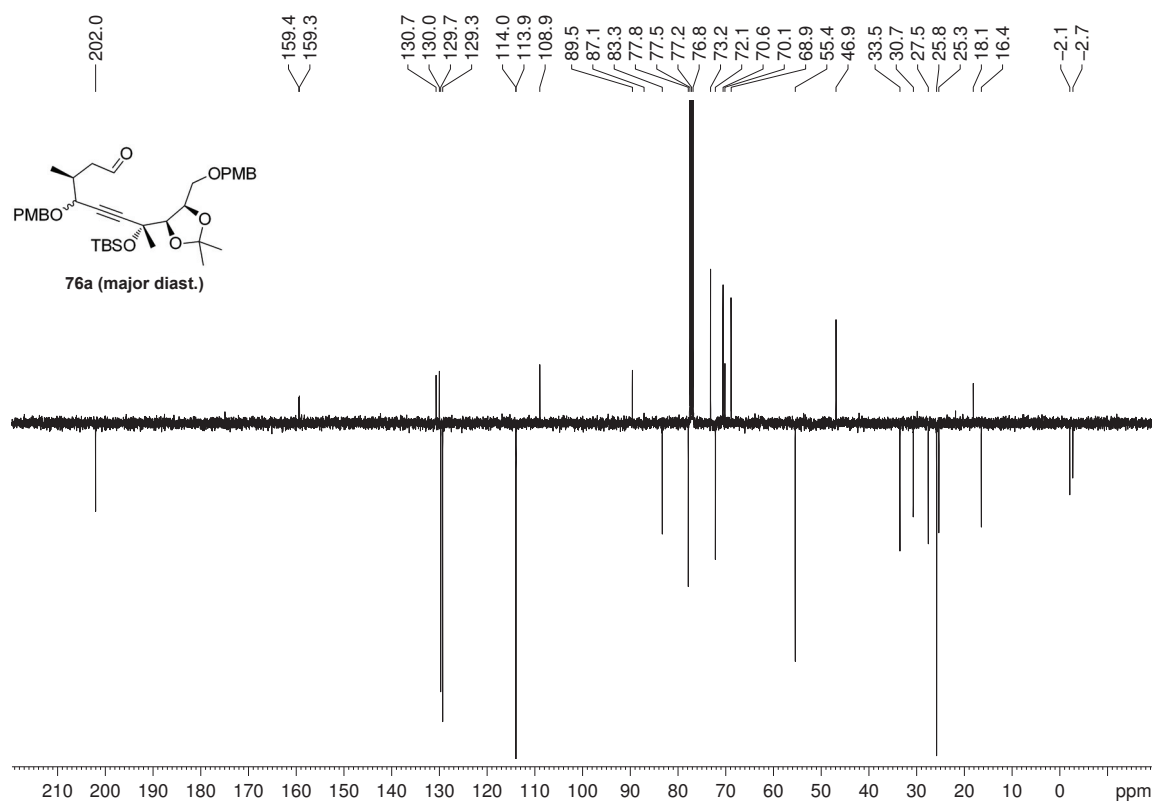
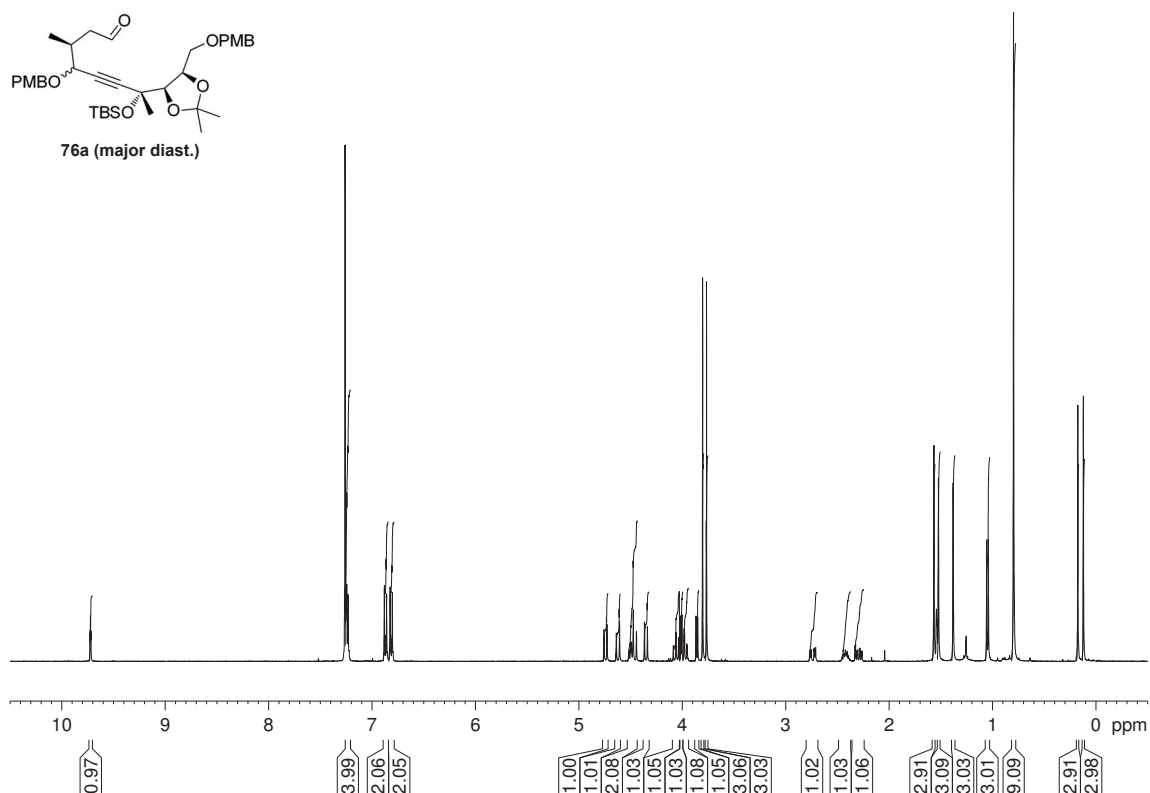


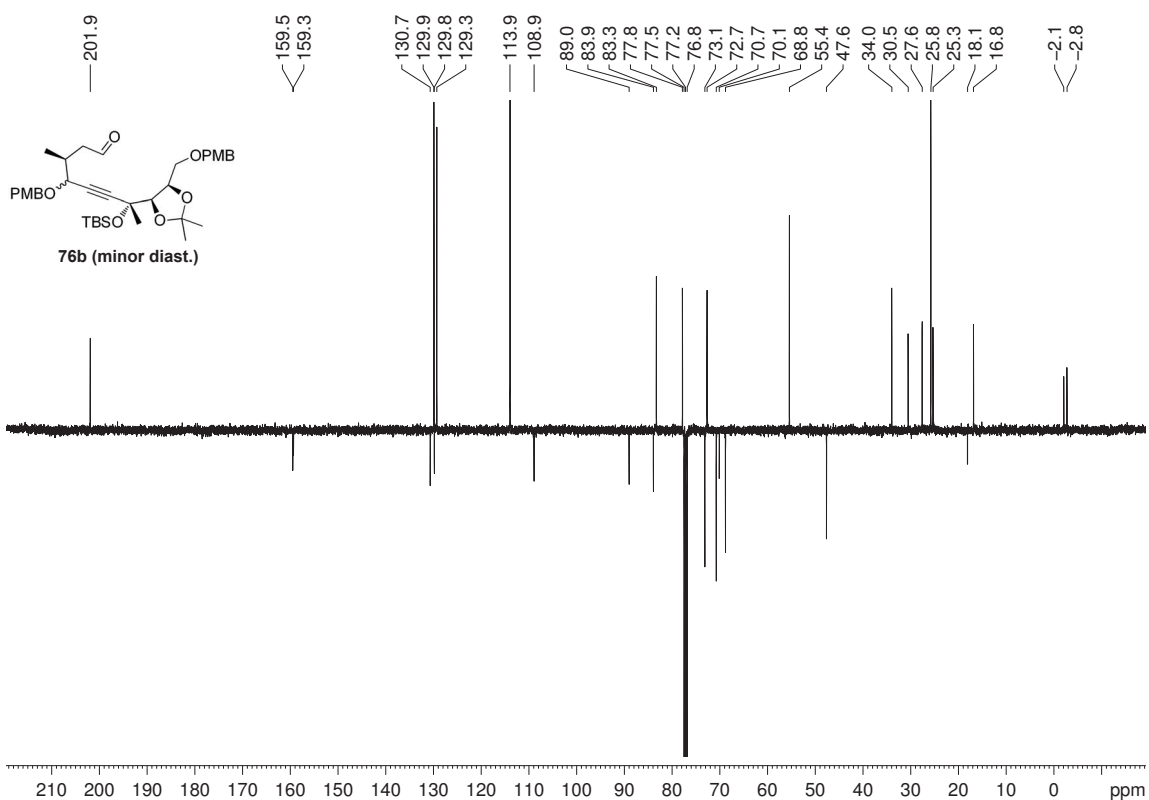
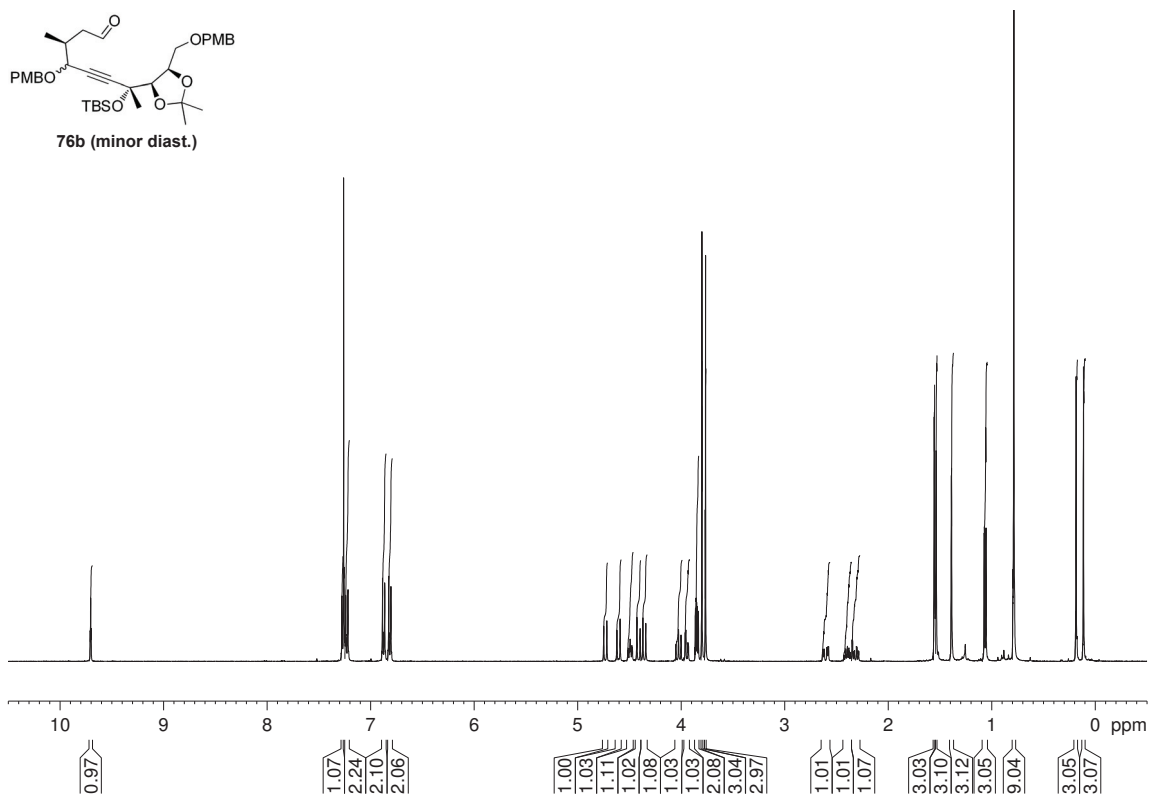












8. CURRICULUM VITAE

RITA FÜRST, MAG.

Department of Organic Chemistry
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Währinger Straße 38
1090 Vienna, Austria

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Personal Data

Date of birth: May 12, 1984 in Oberpullendorf, Austria
Citizenship: Austria

Education and Qualifications

05/2009 – present	Ph.D. Thesis, University of Vienna “Synthetic Studies Toward the Total Syntheses of the Jatrophone Diterpenes Pl-3 and Pl-4” Supervisor: Univ.-Prof. Dr. Johann Mulzer
03/2009	Graduation with honors, University of Vienna
03/2008 – 03/2009	Diploma Thesis, University of Vienna “Synthesis and Biological Evaluation of Novel Combretastatin A-4 Analogs” Supervisor: Univ.-Prof. Dr. Johann Mulzer
10/2003 – 03/2009	Studies of Chemistry, University of Vienna Focus: Organic Chemistry, Biochemistry and Analytical Chemistry
06/2003	Matura (Graduation) with honors
09/1998 – 06/2003	Gymnasium für Studierende der Musik Oberschützen , Austria (Secondary school with emphasis on music, upper grade)

Research Experience

Natural product synthesis (jatrophone diterpenes, combretastatin analogs) and supporting analytical methods (NMR, mass spectrometry, HPLC, IR).

Scholarships and Awards

01/2010 – 06/2012	DOC-fORTE [Women in Research and Technology]; Ph.D. grant, financed by the Austrian Academy of Sciences.
2009	Leistungsstipendium (excellence scholarship), University of Vienna.

Employment History

10/2007 – present	Teaching assistant, University of Vienna Tutor and lecturer in different chemistry laboratory courses of graduate and undergraduate students.
08/2006	Montanuniversität Leoben (University of Leoben), Austria, University internship at the Department of Polymer Engineering and Science.
08/2004 + 2005	Ökolab (Subsidiary company of Austria Tabak, Vienna), Internship at the Department of Tobacco Analysis.

Language, Special Skills

Languages	German: Native language English: spoken – excellent; comprehension – excellent; written – excellent Latin: high school level
Technical	Profound experience with a variety of chemistry software, such as Topspin, Beilstein, Scifinder, ChemOffice and most common office tools (Excel, Word, Power Point). Experience with advanced NMR techniques, IR, and other analysis methods (HPLC, mass-spectrometry).