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DISSERTATION

Titel der Dissertation

„Toward a Total Synthesis of Bielschowskysin“

verfasst von

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angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr.rer.nat.)

Wien, 2013

Studienkennzahl lt. Studienblatt: A 091 419

Dissertationsgebiet lt. Studienblatt: Chemie

Betreuet von: Univ.-Prof. Dr. Johann Mulzer

*dedicated to Theresa and my
family*

Acknowledgement

First of all, I thank my research advisor and teacher Prof. Dr. Johann Mulzer for giving me the freedom to pursue my own ideas and for his patience when things stood still. He always provided me with fruitful ideas during our discussions about synthetic problems and offered great guidance when help was needed. Furthermore, I have to thank him for giving me the opportunity to improve my theoretical and practical chemical skills within such an interesting and challenging research topic.

I thank the members of the so called “big-“ and “Ösi-lab”, Dr. Harald Weinstabl, Dr. Peter Siengalewicz, Dr. Tanja Gaich, Dr. Kathrin Prantz, Dr. Konrad Tiefenbacher, Dr. Andreas Gollner, Dr. Thomas Magauer, Dr. Ela Rosenbeiger, Dr. Nina Tölle, Dr. Martin Ariger, MSc Johannes Preindl, MSc Christian Leitner, MSc Simon Baldauf, Martina Drescher, Martin Lux-Amon, Sabine Schneider, Fikret Nasufi as well as Dr. Harry Martin, Dr. Valentin Enev, Dr. Alexey Gromov, Dr. Stefan Marchart, Mag. Rita Fürst, Mag. Christoph Lentsch, Mag. Christian Aichinger and Dr. Uwe Rinner for providing me with great ideas, practical tips and hints and for the numerous fruitful and motivating conversations. I want to thank all of the actual and former Mulzer group members for the constructive and comfortable working atmosphere and for being good colleagues and friends.

I thank the NMR department, Dr. Lothar Brecker, Dr. Hans-Peter Kählig and Susanne Felsing, for providing accurate spectra and fast and professional help with any kind of problem as well as the whole technical staff for good infrastructure at work. Furthermore, I thank the Mass-department, Ing. Peter Unteregger, Josef Plangger and Lenka Vakermanova as well as Dr. Vladimir Arion and Alexander Roller - for X-ray analysis - for their reliable and solution-oriented work.

Special thanks go to Dr. Julien Gagnepain and DI Jean-Baptiste Farcet, my Bielschowskysin-team mates and friends, for the countless hours of productive work in the lab, great discussions and the fun we shared.

My friends, some of whom I already know for two thirds of my life, were a great support during the many days of long and hard work as they always knew how to get my mind off chemistry when I needed a rest.

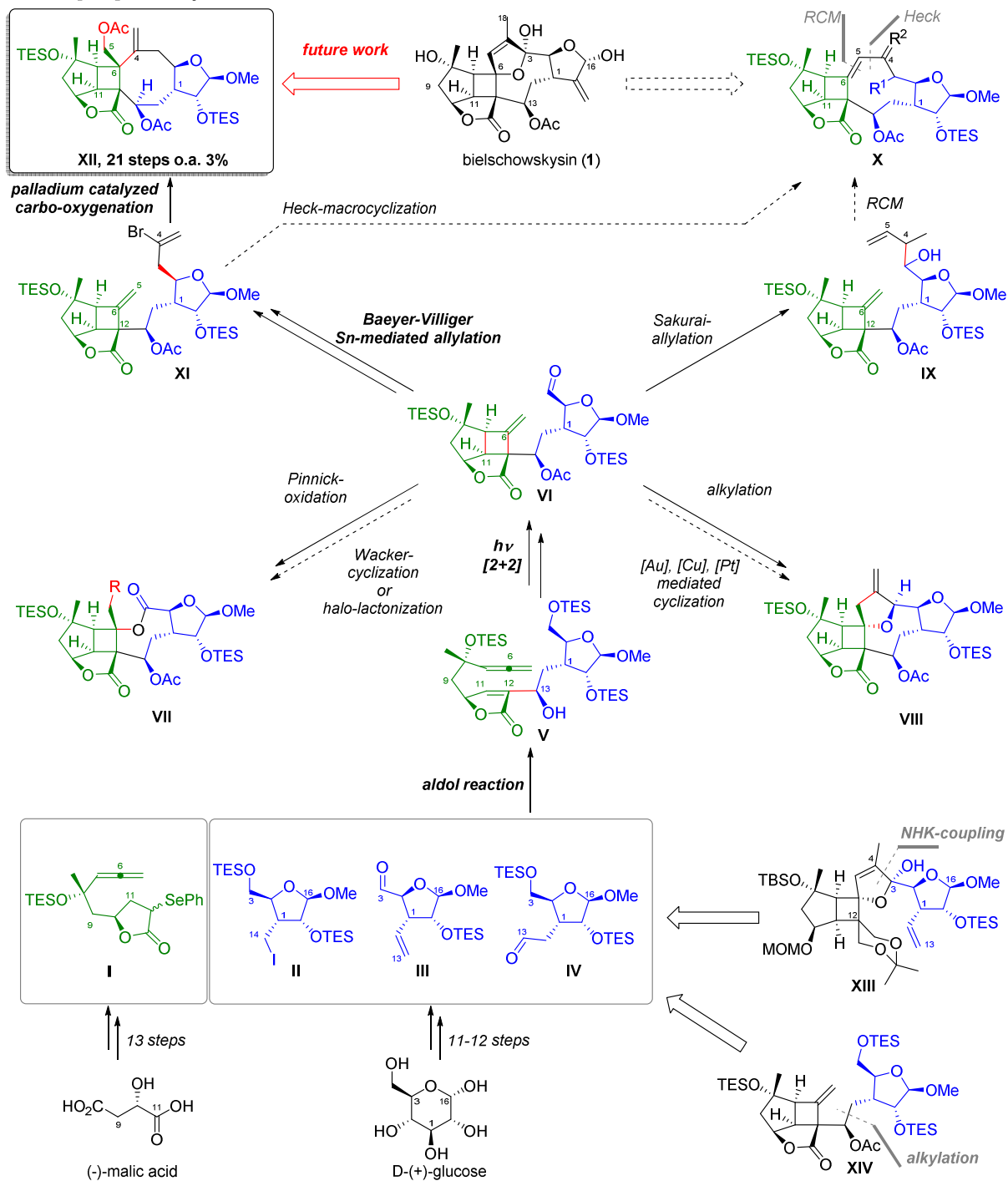
Of course I have to thank my parents, Gerda and Karl, not only for financial support, but also for their patience and confidence that I will pursue my academic education as serious as possible. I want to thank my mother for her thoroughgoing love and support until the last day of her life as well as my father for being a great guide. I also thank Renate and my brother Jakob for the countless wonderful hours and for being a great enrichment to our family life. I want to thank my brother and

friend Robert, who - as long as I can remember - was a role model for me, due to his persistence with which he manages his life and his numerous talents.

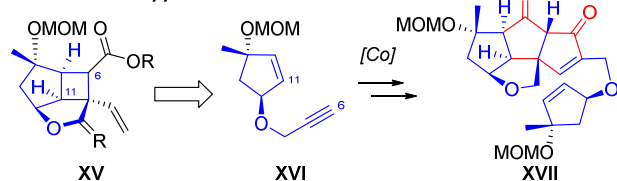
Finally, I thank Theresa, my partner, for her appreciation for the numerous working hours I invested in this project. Her support and the patience with which she listened to my problems and the empathy she felt are invaluable and for sure the corner-stones for my development.

Graphical Abstract

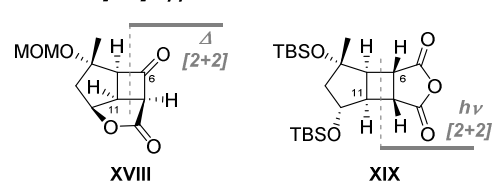
Central [2+2]-Photocycloaddition Approach



Pauson-Khand Approach



Alternative [2+2] Approach



Abstract

Bielschowskysin (**1**), a highly oxygenated furanocembranoid isolated from the gorgonian octocoral *Pseudopterogorgia kallos*, is currently one of the most pursued targets in natural product synthesis. Besides its challenging molecular structure, bearing an unprecedented tricyclo[9.3.0.0^{2,10}]tetradecane ring system and eleven stereogenic centers, it was found to exhibit interesting cytotoxic activity against human cancer cell lines and shows biological activity against *Plasmodium falciparum*, the main causative organism of malaria.

Herein, synthetic efforts towards a total synthesis of bielschowskysin, centered upon a biomimetic [2+2]-photocycloaddition to construct the western bicyclo[3.2.0]heptane core, are described. Starting from (-)-malic acid and D-(+)-glucose, a stereoselective synthetic approach was initiated.

An aldol reaction was the method of choice for coupling between western allene building block **I** and tetrasubstituted eastern tetrahydrofuran **IV**. By utilizing a custom-made photoreactor, the envisaged biomimetic [2+2]-photocycloaddition regio- and stereoselectively allowed the synthesis of common central intermediate **VI**. The ease of the crucial cycloaddition is remarkable considering the high complexity of the substrate. A scalable route to the common intermediate allowed us to test several different macrocyclization reactions. Unfortunately, cutting-edge transition metal catalysis, including Au(I) salts, failed. Adventurous, but not unpromising, we envisaged powerful ruthenium based metathesis catalysts as tools for the macrocyclization, which remained unrewarded.

Nonetheless, in regard of the numerous successful examples for palladium catalyzed cyclizations in total synthesis, we decided to tackle an *endo*-selective Heck-macrocyclization. Unexpectedly, an unprecedented reproducible palladium catalyzed carbo-oxygenation was observed under these conditions. The resulting highly advanced tricyclo[8.3.0.0^{2,8}]tridecane carbon ring system **XII** contains 8 stereogenic centers of desired configuration, including the crucial all carbon quaternary center at C12. Ring enlargement strategies to the desired tricyclo[9.3.0.0^{2,10}]tetradecane ring system of the natural product have been proposed and will be pursued in due course.

Aside this central approach, the flexible synthesis of the eastern fragment enabled us to tackle alternative approaches towards bielschowskysin. Thus, coupling with two western fragments, bearing the bicyclo[3.2.0]heptane carbon core, by either metal-halogen exchange or NHK-coupling lead to completion of the southern **XIV** and northern hemisphere **XIII** of the natural product.

Zusammenfassung

Bielschowskysin (**1**), ein hoch oxygeniertes Furanocembranolid isoliert aus der gorgonischen Oktokoralle *Pseudopterogorgia kallos*, ist zur Zeit eines der meist verfolgten Ziele in der Naturstoffsynthese. Neben seiner herausfordernden Struktur, welche ein neuartiges Tricyclo[9.3.0.0^{2,10}]tetradecan Ringsystem und elf stereogene Zentren beinhaltet, weist es interessante zytostatische Aktivität gegen menschliche Krebszelllinien und biologische Aktivität gegen *Plasmodium falciparum*, dem Haupterreger von Malaria, auf.

Unsere zentrale Retrosynthese von Bielschowskysin baut auf einer biomimetischen [2+2]-Photocycloaddition auf, welche den Cyclobutanring und drei stereogene Zentren auf einen Schlag aufbauen soll. Diese stereoselektive Synthese hat mit (-)-Äpfelsäure und D-(+)-Glucose billige und chirale Ausgangsmaterialien. Für die Verknüpfung eines westlichen Allen-Baustein **I** mit einem östlichen vierfachsubstituierten Tetrahydrofuranring **IV** war eine Aldolreaktion die Methode der Wahl. Durch Bestrahlung mit einem sonderangefertigten Photoreaktor wurde die regio- und stereoselektive Synthese des zentralen Intermediates **VI** gewährleistet. Die Einfachheit, mit der diese kritische Cycloaddition vonstattenging, ist im Hinblick auf die Komplexität des Substrates bemerkenswert. Mehrere Makrocyclisierungen konnten aufgrund der zuverlässigen Synthese des zentralen Intermediates in Angriff genommen werden. Die Anwendung von innovativer Übergangsmetallkatalyse, unter anderem mit Au(I) Salzen, und leistungsfähiger Ringschlußmetathese, war ambitioniert aber nicht utopisch und führte nicht zu dem gewünschten Ergebnis.

Im Hinblick auf die zahlreichen erfolgreichen Palladium-katalysierten Cyclisierungen in der Totalsynthese wurde eine *endo*-selektive Heck-Makrocyclisierung anvisiert. Diese Versuche führten über eine neuartige und reproduzierbare Carbo-Oxygenierung zu dem unerwarteten, hochfunktionalisierten Tricyclo[8.3.0.0^{2,8}]tridecan Kohlenstoffringsystem **XII**. Die erhaltene hochentwickelte, makrocyclische Struktur enthält acht stereogene Zentren, unter anderem den wichtigen quaternären C12 Kohlenstoff mit gewünschter Konfiguration. Strategien für eine Ringerweiterung zum gewünschten Tricyclo[9.3.0.0^{2,10}]tetradecan Ringsystem sind beschrieben und werden zu gegebener Zeit ausgeführt.

Neben diesem zentralen Ansatz befähigte uns die flexible Synthese des östlichen Fragments dazu alternative Zugänge zu Bielschowskysin zu unternehmen. Die Verknüpfung durch konventionellen Halogen-Metall-Austausch oder NHK-Kupplung mit zwei westlichen Fragmenten, welche den Bicyclo[3.2.0]heptan Kohlenstoffkern beinhalten, führte zur Ausbildung der südlichen (**XIV**) sowie nördlichen Hemisphäre (**XIII**) des gewünschten Naturstoffs.

Publications, Oral and Poster Presentations as well as Awards

Publications

“An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy”; **Himmelbauer, M.**; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Eur. J. Org. Chem.* **2013**, submitted for publication.

“An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photochemical Strategy”; Farcet, J.-B., **Himmelbauer, M.**; Mulzer, J. *Eur. J. Org. Chem.* **2013**, submitted for publication.

“Photochemical and Thermal [2 + 2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin”; Farcet, J.-B.; **Himmelbauer, M.**; Mulzer, J. *Eur. J. Org. Chem.* **2013**, 4379.

“A Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case”; **Himmelbauer, M.**; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Org. Lett.* **2013**, 15, 3098.

“A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin”; Farcet, J.-B.; **Himmelbauer, M.**; Mulzer, J. *Org. Lett.* **2012**, 14, 2195.

Oral Presentations

„Recent Developments towards the Total Synthesis of Bielschowskysin”; Himmelbauer, M.; invited speaker at VISOC 2011; Vienna, Austria; May **2011**.

„Towards a Total Synthesis of Bielschowskysin”; Himmelbauer, M.; invited speaker at institute colloquium, Technical University of Graz, Austria; January **2011**.

„Auf dem Weg zu Bielschowskysin”; Himmelbauer, M.; invited speaker at 40. Naturstofftreffen; Würzburg, Germany; November **2010**.

Poster Presentations

“Towards a Total Synthesis of Bielschowskysin”; Himmelbauer, M.; Syngenta Workshop for Talented Young Chemists 2012; Stein, Switzerland; September **2012**.

“Towards a Total Synthesis of Bielschowskysin”; Himmelbauer, M.; ICOS-18; Bergen, Norway; August **2010**.

Awards

Syngenta Workshop for Talented Young Chemists 2012; 2nd best contribution to all sessions; **Himmelbauer, M.**; Stein, Switzerland; September **2012**.

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1. Introduction

Some plants are well known for their pleasant or unpleasant smell, specific taste and/or have found application in traditional medicine for the treatment of a wide range of diseases. These properties are related to the ingredients, natural compounds, which the plant produces to fulfill a specific task. The use of such compounds may be of a wide variety reaching from protection from natural enemies or as an attractant for insects, which are indispensable for pollination. Terpenes represent one of the major families of natural compounds exhibiting such properties. In general all natural compounds with a carbon skeleton built up by a different number of isoprene units are referred to as terpenes.¹ Predominantly, these natural compounds originate from plants but some are produced by insects, for example as pheromones.

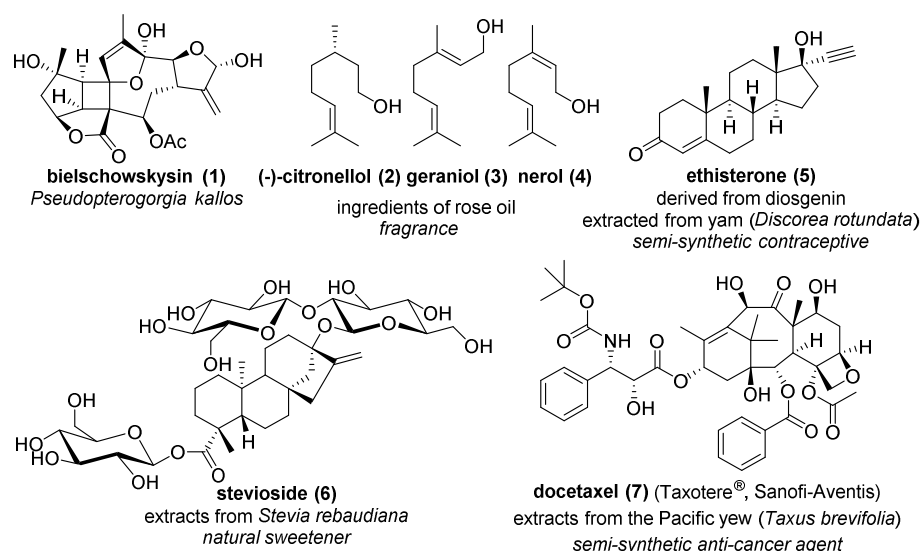


Figure 1 Various Terpenes and Terpene-derived Compounds and their Application

Steam distillation and extraction are the traditional methods to obtain large quantities of the desired terpenes as essential oils. In this way roses, lavender, thyme, citrus fruits, eucalyptus amongst many other natural sources are treated providing large quantities of fragrances and flavoring agents for the industry. In cases where the desired terpene is of little concentration in the plant or the plant itself is scarce in nature and/or a protected species the common extraction methods seem inappropriate both ethically as well as economically. At this point a demand for a synthetic access to the desired molecule arises. This need becomes even stronger, if the target substance exploits pharmacological activity and therefore is a potential drug for the treatment of a specific disease. Besides the importance of a synthetic access itself, the possibility for the derivatization of the natural compound displays a flexibility which allows the improvement of its pharmaceutical activity.

2. Structure and Biosynthesis of Terpenes¹

The basic structure of all terpenes is related to one common building block, the isoprene unit (**9**). One or more of these 2-methylbutadiene entities are linked together building up the carbon-framework of this class of natural products, which therefore are also referred to as isoprenoids. This simple but consistent finding is referred to as the isoprene-rule introduced by Ruzicka and Wallach.²

According to the number of linked isoprene units the natural products are classified as hemi- (C_5), mono- (C_{10}), sesqui- (C_{15}), di- (C_{20}), sester- (C_{25}), tri- (C_{30}), tetra- (C_{40}) and polyterpenes (C_5)_n (Figure 2). The 2-methylbutane subunits are predominantly linked in a head-to-tail fashion, with the isopropyl part of isoprene referred to as head and the ethyl part as tail. Merely, the sester-, tri- and tetraterpenes feature tail-to-tail connections.

Various degrees of oxygenation of these carbon skeletons as well as a manifold of different cyclizations during the biosynthesis of terpenes result in numerous subfamilies with about 30.000 different known congeners.

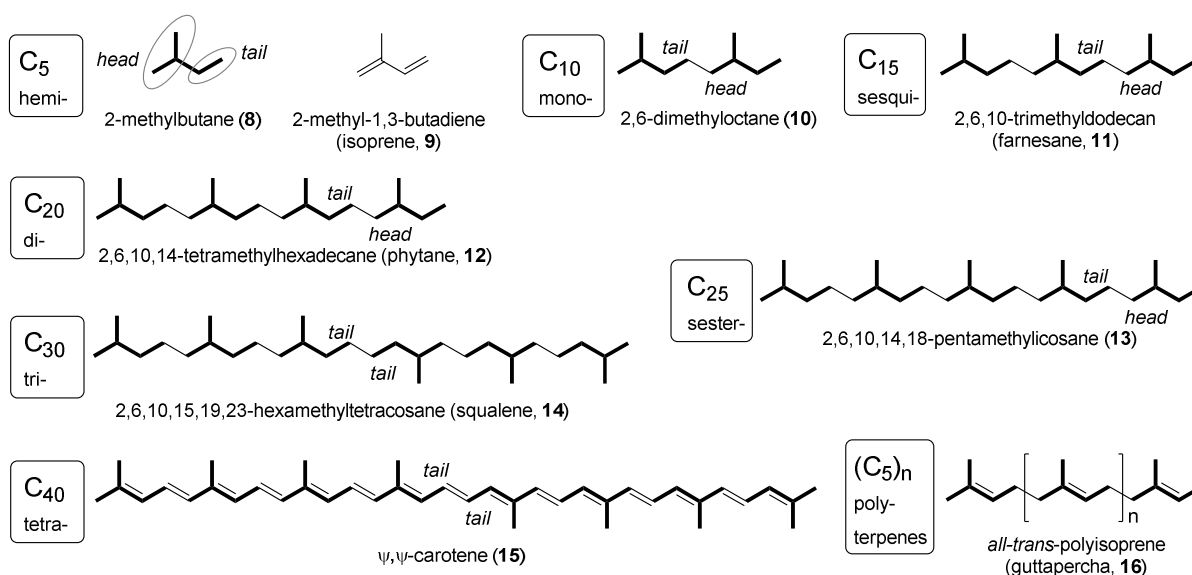
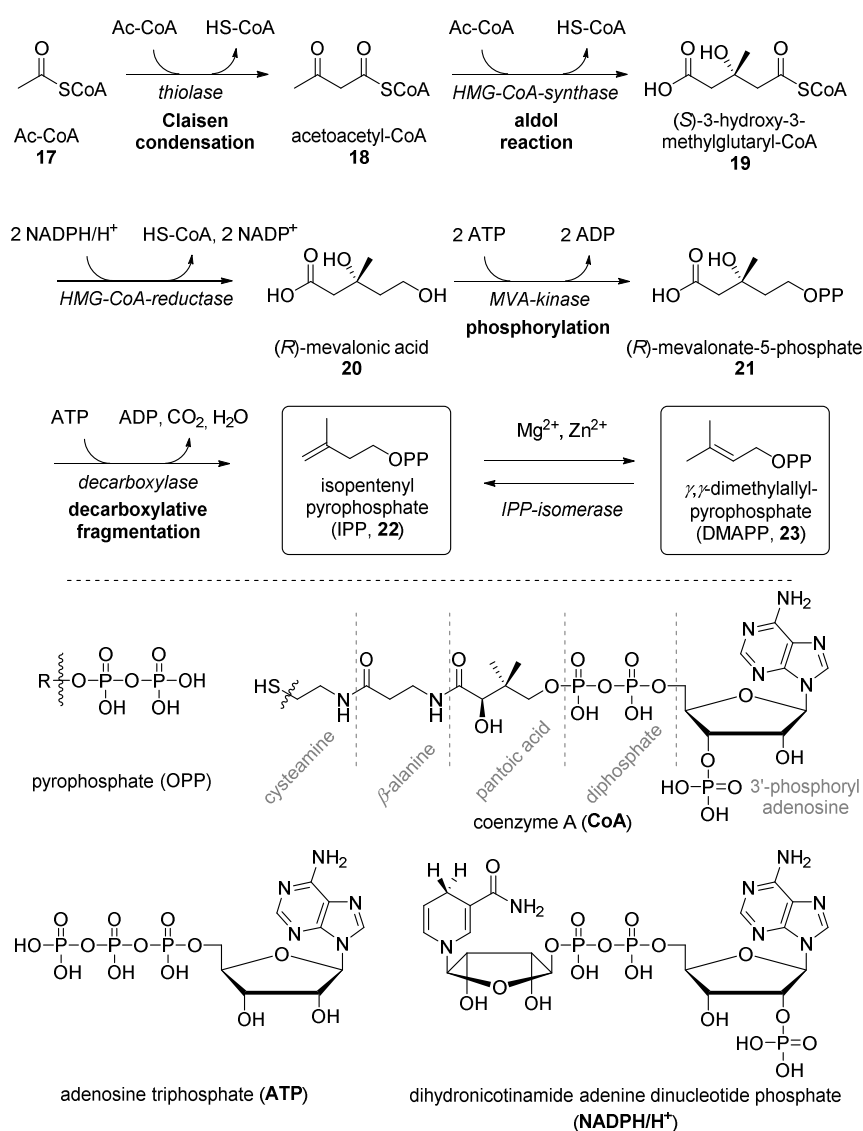


Figure 2 Basic Hydrocarbons of Terpenes

Terpenes are said to be built up along two different biogenetic pathways. Both, the acetate-mevalonate- and the Rhomer-pathway (also known as activated acetaldehyde-glyceraldehyde-3-phosphate pathway or non-mevalonate pathway), lead to the same C_5 -intermediates, namely isopentenyl pyrophosphate (IPP, **22**) and dimethylallyl pyrophosphate (DMAPP, **23**). These biogenetic building blocks are later connected to give the basic hydrocarbon skeletons of the different isoprenoids.

2.1. The Mevalonate Pathway¹

The MVA-pathway (Scheme 1) starts with the biogenetic Claisen condensation of two molecules of acetyl-coenzyme A (Ac-CoA, **17**), which is also known as activated acetic acid, forming acetoacetyl-CoA (**18**).^{1,3} This biological acetoacetate equivalent reacts as an electrophile with a third acetyl-CoA molecule in an aldol-reaction to give (*S*)-3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, **19**), which is subject to an enzymatic reduction with NADPH/H⁺. The resulting *R*-(-)-mevalonic acid (MVA, **20**) is phosphorylated twice by adenosine triphosphate (ATP) to give mevalonate-5-phosphate (**21**), which consecutively undergoes decarboxylative fragmentation leading to isopentenyl pyrophosphate (IPP, **22**). Finally, a Mg²⁺ or Zn²⁺ dependent isomerase converts IPP (**22**) to γ,γ -dimethylallyl pyrophosphate (DMAPP, **23**). Both indispensable building blocks for the first time contain the branched C₅ isoprenic skeleton in the biogenesis of terpenes.

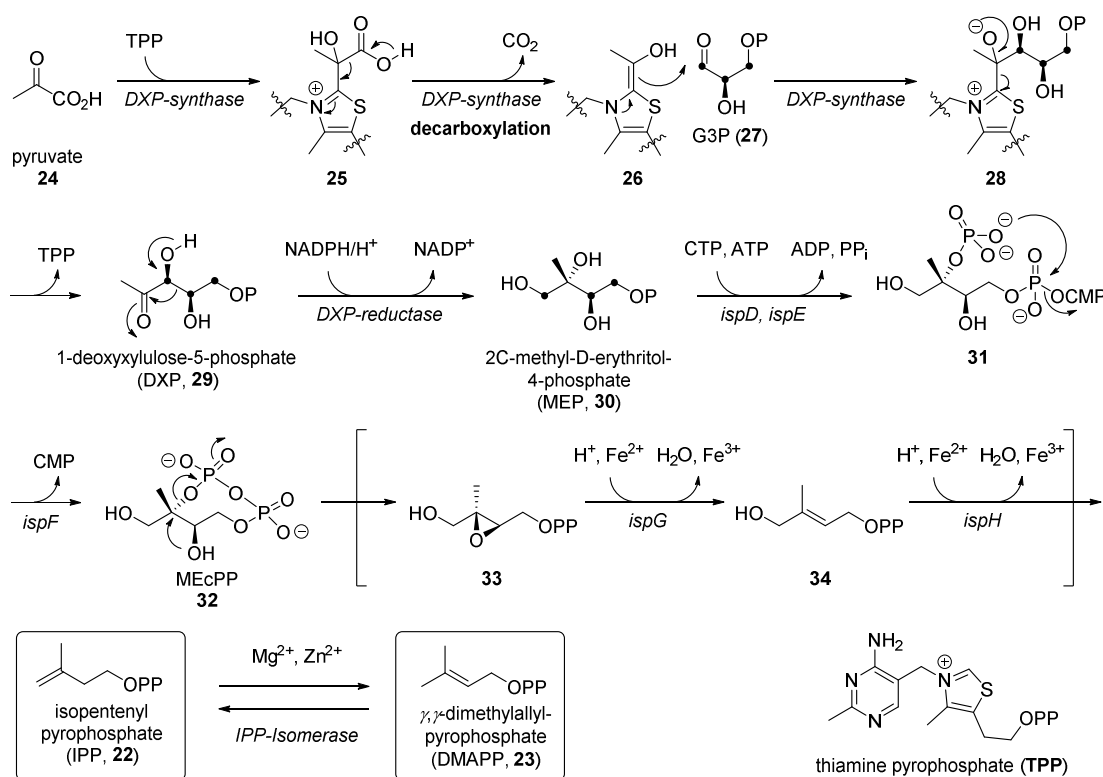


Scheme 1 Biosynthesis of IPP (22) and DMAPP (23) via the Mevalonate Pathway

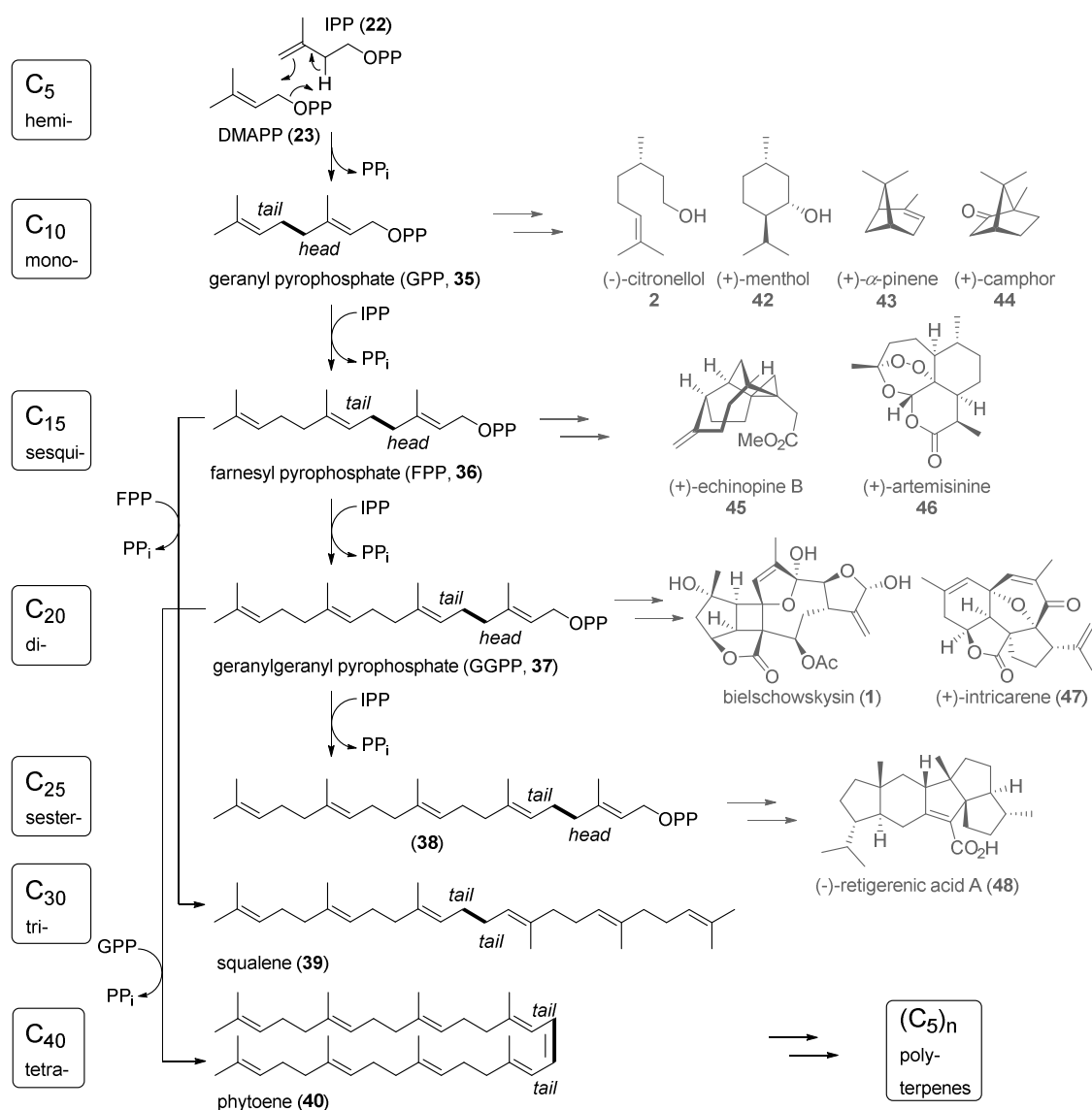
2.2. The Non-Mevalonate Pathway (Rhommer-pathway)^{1,4}

In 1996, Rhomer and coworkers reported an alternative non-mevalonate pathway for isoprenoid biosynthesis. Incorporation of ¹³C-labeled glycerol or pyruvate into ubiquinone Q8 of *Escherichia coli* mutants and into the triterpenoids of the hopane series of *Zymomonas mobilis*, whereas metabolism of ¹³C-labeled acetate failed, indicated that in some organisms IPP does not stem from the mevalonate pathway.⁴

Thus, pyruvate (**24**) forms an adduct with deprotonated TPP (vitamin B₁ or thiamine pyrophosphate), the coenzyme of the pyruvate-dehydrogenase (Scheme 2). Intermediate **25** undergoes decarboxylation accompanied by Umpolung of the carbonyl-carbon atom. Consequently, the former electrophilic carbon of the ketone attacks the second biogenetic precursor, glyceraldehyde-3-phosphate (G3P, **27**), resulting in **28**. Consecutive retro-aldol reaction liberates TPP and 1-deoxyxylulose-5-phosphate (DXP, **29**). MEP (2C-methyl-D-erythritol-4-phosphate, **30**) is generated in an acyloin rearrangement/reduction sequence with NADPH/H⁺. In multiple phosphorylations cyclic pyrophosphate MEcPP (**32**) is established, which is said to be reduced to IPP (**22**), presumably by a Fe²⁺-dependent enzyme. Again a Mg²⁺- or Zn²⁺-dependent isomerase is said to convert IPP (**22**) to γ,γ -dimethylallyl pyrophosphate (DMAPP, **23**).



Scheme 2 Biosynthesis of IPP (**22**) and DMAPP (**23**) via the Non-Mevalonate Pathway



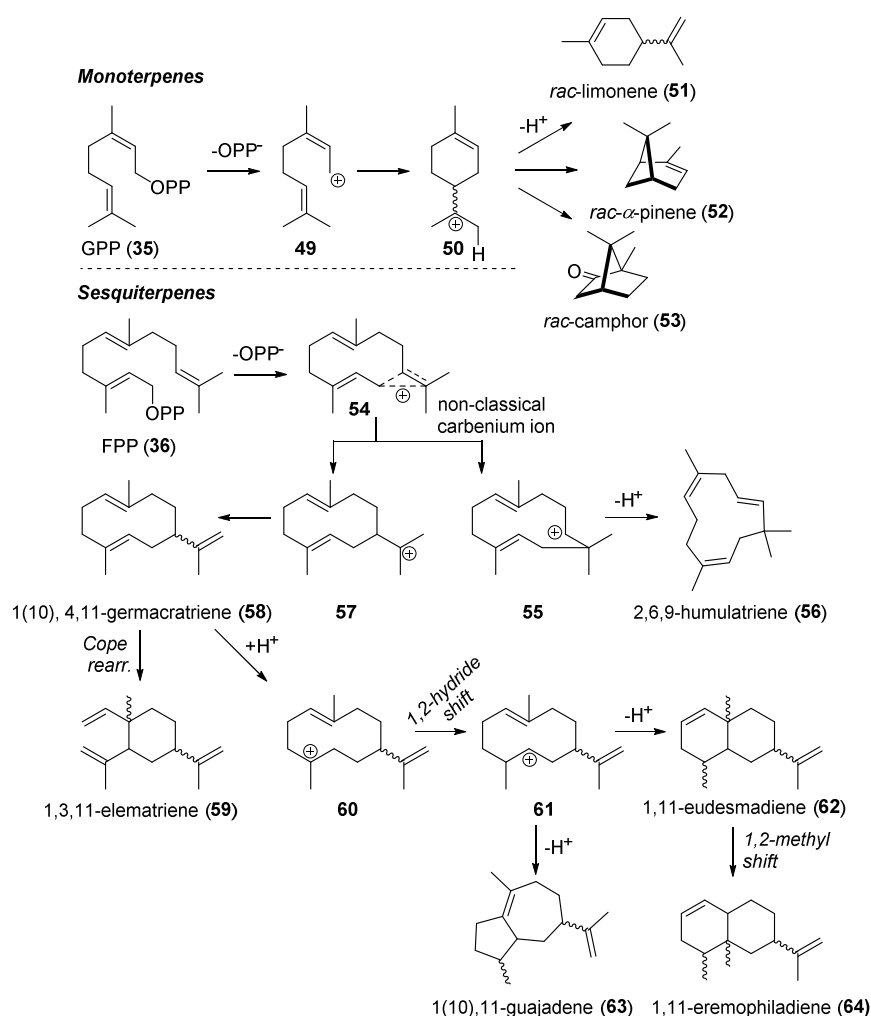
Scheme 3 Biosynthesis of the Carbon Back Bone of Terpenes

The two known biogeneses of IPP (22) and DMAPP (23) combine at this stage in the biosynthesis generating mono- to polyterpenes as follows. An Alder-Ene like reaction connects IPP (22), acting as the ene with its nucleophilic methylene group, with DMAPP (23), as the corresponding enophile, giving geranyl pyrophosphate (GPP, 35), the basic intermediate to all known monoterpenes (Scheme 3). Elongation of GPP (35) with another IPP (23) along the same reaction mechanism, building up a second tail-to-tail connection, establishes sesquiterpenoid farnesyl pyrophosphate (FPP, 36). The C₂₀ carbon backbone of diterpenes in geranylgeranyl pyrophosphate (GGPP, 37) is generated from FPP (36) via another C₅ elongation with IPP (23). Various oxygenation and cyclization steps starting from 36 generate more complex diterpenes such as bielschowskysin (1) and intricarene (47). After a consecutive C₅ elongation in a head-to-tail fashion leading to sesterterpenes,

tail-to-tail connectivities are possible for tri-, tetra- and polyterpenes by either combining FPP (**36**) molecules or GGPP (**37**) molecules.

2.3. From Open-Chain to Cyclic and Polycyclic Terpenes¹

Dissociation of the pyrophosphate anion in **35** to **38** is assumed to generate a carbocation. This leaves plenty of opportunities for the formation of new carbon-carbon bonds and one or more carbocycles. Thus, a broad variety of terpenes with mono- to polycyclic carbon cores arise from their parent open-chain precursors. Not enough, the formation of diastereomers, enantiomers as well as nonclassical carbocations, 1,2-hydride shifts, Wagner-Meerwein-rearrangements (1,2-alkyl-shifts) and sigmatropic reactions add further paths to terpenes of high diversity. Scheme 4 depicts the biogenesis of some basic mono- and sesquiterpenes including most of the aforementioned operations.



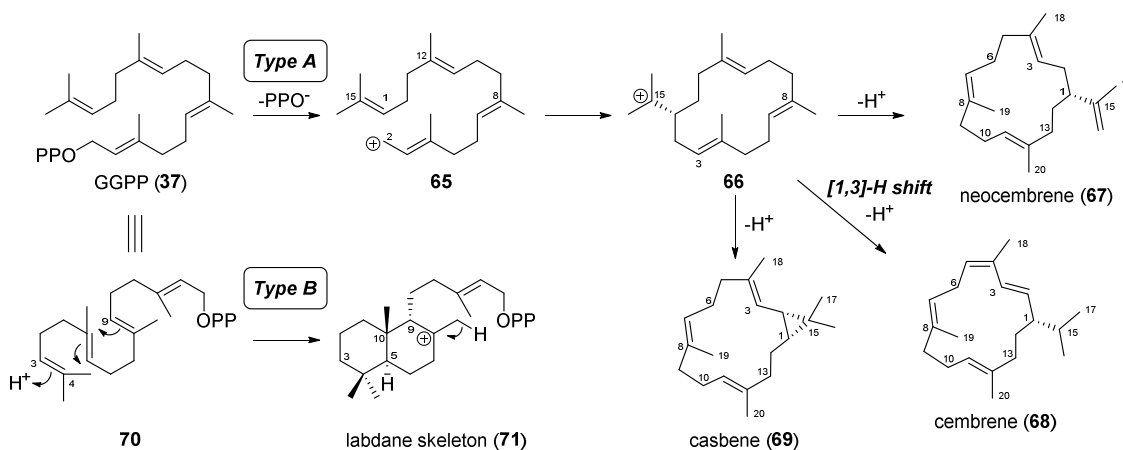
Scheme 4 Cyclization of GPP (**35**) and FPP (**36**)

2.4. Biogenetic Cyclizations of GGPP (37) Yielding Diterpenes^{1,5}

Though geranylgeranyl pyrophosphate (GGPP, **37**) is the sole cyclization precursor for all known diterpenes, the structure and connectivity of their carbon frameworks partly differ drastically due to a variety of possible cationic cyclization mechanisms (*vide infra*). The natural product family of diterpenes is divided in several subfamilies, each of which is defined by a common carbon core, which also determines the numbering of the contained carbon atoms of all its members.

2.4.1. Type A Cyclization⁵

Similar to the already discussed syntheses of cyclic mono- and sesquiterpenes, GGPP (**37**) forms an allylic carbocation (**65**) at C2 via dissociation of the pyrophosphate group, which initiates the Type A cyclization (Scheme 5). Consecutively, the $\Delta^{1,15}$ -double bond acts as a nucleophile generating a 14-membered carbon macrocycle under formation of a stabilized carbocation at C15 (**66**). The next step is a junction opening three different paths. On one hand construction of a $\Delta^{15,16}$ -double bond upon abstraction of a proton leads to neocembrene (**67**). Alternatively, 1,3-hydride shift and consecutive proton abstraction biogenetically yields cembrene (**68**). Along the third path, on the other hand, casbene (**69**) is derived by formation of a cyclopropane ring via β -proton abstraction. The 14-membered cembrene macrocycle **67** is the biogenetic precursor of the family of furanocembranoids which will be discussed in detail in the next section of this work.



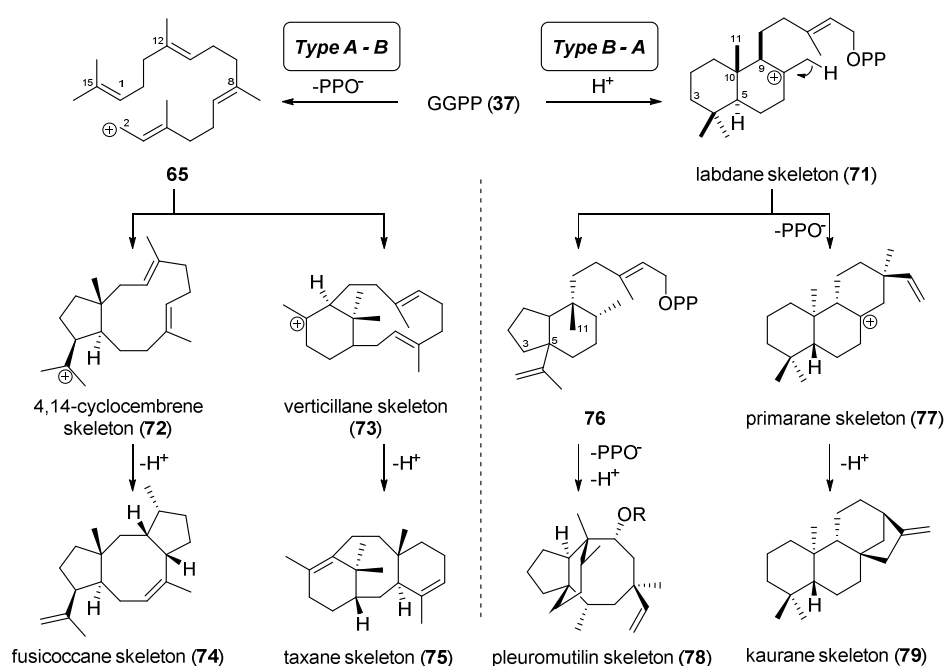
Scheme 5 Type A and Type B Cyclization of GPP (37)

2.4.2. Type B Cyclization⁵

In contrast to Type A cyclizations, Type B cyclizations are not initialized by disproportion of OPP^- , but by protonation of the $\Delta^{3,4}$ -double bond of GGPP-conformer (**70**, Scheme 5). The following cyclization cascade forms C4-C5 and C10-C11 single bonds along with a decaline system, the carbon skeleton of labdane diterpenoids (**71**).

2.4.3. Mixed Cyclization Types: Type A - B and Type B - A Cyclizations⁵

Type A – B cyclizations, as the name already indicates, is initiated as Type A by dissociation of the pyrophosphate, generating an allylic carbocation (**65**, Scheme 6). Depending on the biogenetic surrounding and therefore on the conformation of the GG-cation, the carbenium ion proceeds in the formation of either the 4,14-cyclocembrene skeleton (**72**) or the verticillane skeleton (**73**) of diterpenes. These two macrocycles are transformed in either isoprenoids of the fusicoccane-family (**74**) or of the taxane-family (**75**) by a consecutive Type B cyclization initiated by the protonation of one double bond. Consequently this pathway is referred to as Type A – B.



Scheme 6 Type A - B and Type B – A Cyclization of GPP (37)

Hence, not surprisingly, Type B – A cyclizations start with the protonation of a double bond and generation of a carbocation which forms new CC single bonds (**37** to **71**, Type B, Scheme 6). After proton abstraction this pathway proceeds in the formation of additional carbocyclic rings by disproportionation of the pyrophosphate in a Type A fashion (**76** to **78**, **77** to **79**). Basically, via this Type B – A cyclization and optional Wagner-Meerwein rearrangements the carbon skeletons of primarane- (**77**), kaurane- (**79**) and pleuromutilin-isoprenoids (**78**) are constructed.

As a rule of thumb, Type A and Type A – B cyclizations generally form large to medium sized carbocycles. On the contrary, Type B and Type B – A cyclizations result in the formation of smaller rings. In particular, a decaline system is initially formed.

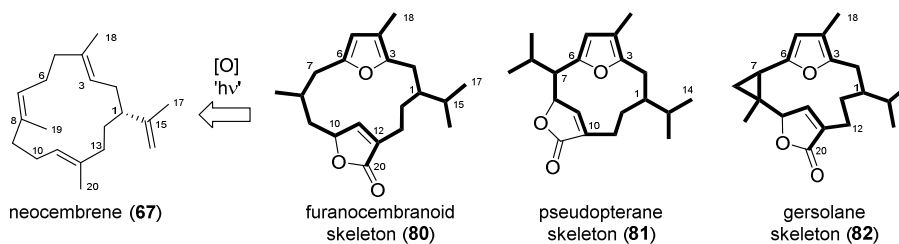
2.5. Marine Derived Diterpenes: Furanocembranoids, Pseudopteranes and Gersolanes^{6,7}

2.5.1. The Biosynthetic Correlation between Marine Derived Diterpenes

The marine environment is an immeasurable source of interesting natural products, which often possess interesting biological activities (antitumor, anti-inflammatory and antimicrobial among others) besides fascinating molecular structures. Due to these facts the scientific community developed a broad interest in the investigation of the ingredients and constituents of corals. One of the largest families found in this milieu are cembranoid macro- and polycyclic diterpenes most commonly found in gorgonian and soft corals. These isoprenoids, biogenetically stemming from GGPP (**37**) via Type A cyclization to neocembrene (**67**), are interconnected by a network of oxygenation processes as well as rearrangements, ring contractions and transannular cyclizations. According to the carbon skeletons arising from this manifold of biochemical operations, the group of marine derived diterpenes has been divided into three basic subfamilies (Scheme 7). The by far largest subfamily featuring a cembrane-skeleton is characterized by a 14-membered carbon macrocycle. Furthermore, an oxygen-bridge between C3 and C6 of the cembrane, establishing a furan ring in the northern hemisphere is another attribute, which together with the macrocycle act as eponyms of this subfamily, the "furanocembranoids" (**80**, Scheme 7). Additionally, a butenolide moiety along C10 to C12 and C20 is a common structural motive and the reason for the older name "furanocembranolides".

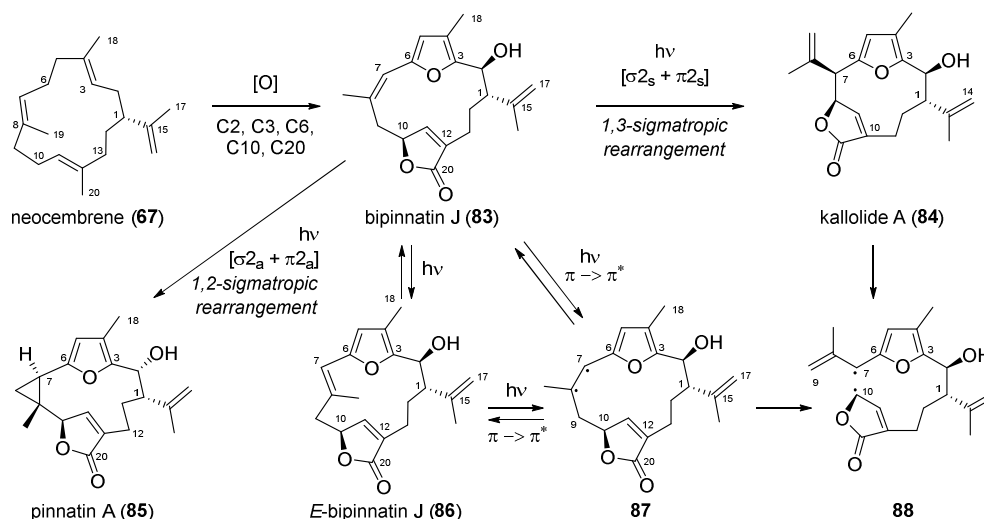
Other prevalent common structural features of furanocembranoids are:

- C1 is usually (*R*)-configured
- Oxygenated C2
- C18 can occur in the oxidation states of an aldehyde, carboxylic acid or ester. But, to date, no congener is known bearing a hydroxy functionality at C18
- No representative with C18 as CO₂Me bearing an oxygenated C2
- The furan moiety (C3 to C6) may occur as enedione
- The $\Delta^{11,12}$ -double bond often is oxygenated exclusively from the α -face (often as an epoxide)
- The $\Delta^{7,8}$ -double bond often is oxygenated almost exclusively as the (*E*)-isomer and usually from the α -face (as epoxides or diol-derivatives)
- C13 often appears with an oxygen substituent, frequently with an acetate



Scheme 7 Subfamilies of Marine Derived Cembranoids

Marine derived diterpenes of the second most abundant subfamily are referred to as “pseudopteranes” (**81**, Scheme 7). Structural motives of this pool of natural products are a rearranged 12-membered macrocycle as well as a furan ring and a butenolide. Members of the “gersolanes” (**82**), the third known subfamily, contain a characteristic bicyclo[11.1.0]tetradecane carbon macrocycle (Scheme 7). As for the other two subfamilies the furan ring and the butenolide are common structural features.

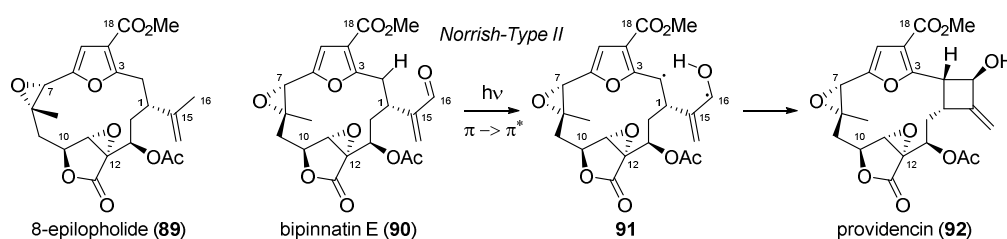


Scheme 8 Biosynthetic Photochemical Relation between Cembranoids

Several synthetic studies concerning the biosynthesis of diterpenes and two excellent reviews by Trauner⁶ and Pattenden⁷ point out, that all highly oxygenated and polycyclic diterpenes might biosynthetically arise from simpler common congeners. Thus, a series of oxygenations, presumably mediated by cytochrome P450 monooxygenases, could convert neocembrene skeleton **67** to bipinnatin J (**83**), amongst other simple congeners. As demonstrated by Rodríguez *et al.*, irradiation of bipinnatin J gave pseudopterane **84**, known as kallolide A, via photochemically allowed $[\sigma_{2s} + \pi_{2s}]$ -cycloaddition, as the main product (1,3-sigmatropic rearrangement, Scheme 8).⁸ Additionally, this was accompanied by the formation of small amounts of gersolane pinnatin A (**85**), presumably via $[\sigma_{2a} + \pi_{2a}]$ -cycloadditions (1,2-sigmatropic rearrangement). Inversion of the hydroxy group at C2 in **85** is observed, most likely via a furanoxonium intermediate. These seminal findings

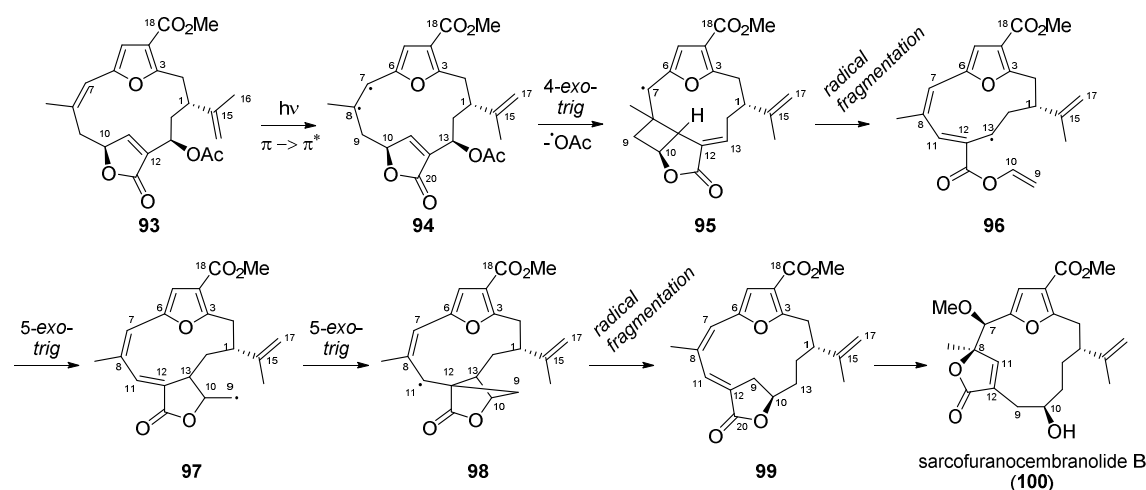
are a strong indication that pseudopteranes and gersolanes have a furanocembranoid as biogenetic origin.

Along with the rearrangement an isomerization of the (Z)- $\Delta^{7,8}$ -double bond to the (E)-diastereomer **86** is observed. Alternatively to the concerted ring-contraction, a radical mechanism has been proposed. Excitation of the $\Delta^{7,8}$ -double bond in either isomers is said to result in diradical **87**, which can undergo homolytical C9-C10 bond cleavage (Scheme 8). Intermediary formed **88** finally recombines between former C7 and C10 to give the pseudopterane skeleton in kallolide A (**84**). Interestingly, furanocembranoids featuring a (Z)- $\Delta^{7,8}$ -double bond are very rare congeners and those with an epoxide at this juncture exclusively stem from the (E)-diastereomers, with one known exception, 8-epilopholide (**89**, Scheme 9). Additionally, epoxidation of this double bond seems to occur almost exclusively from the less hindered α -face of the cembrane-skeleton, generating substitution patterns as found, for example, in providencin (**92**). As already mentioned in a previous section this natural occurring furanocembranoid is the only one besides bielschowskysin (**1**), featuring a cyclobutane core.



Scheme 9 Cembranoids with an Oxygenated $\Delta^{7,8}$ -Double Bond and the Photochemical Biosynthesis of Providencin (**92**)

Again, a photoinduced reaction has been postulated to *in vivo* generate the methylenecyclobutanol ring system from bipinnatin E (**90**) - which itself is biogenetically derived from lopholide, the C8-epimer of 8-epilopholide (**89**) - as depicted in Scheme 9.^{7,9} This Norrish-Type II reaction (Norrish-Yang reaction)¹⁰ is a formal insertion of the aldehyde functionality at C16 into the C2-H bond. The initiating step is photochemical excitation of the α,β -unsaturated aldehyde and abstraction of a hydrogen in the γ -position forming biradical **91**. Finally, radical combination closes the cyclobutane ring in **92**.

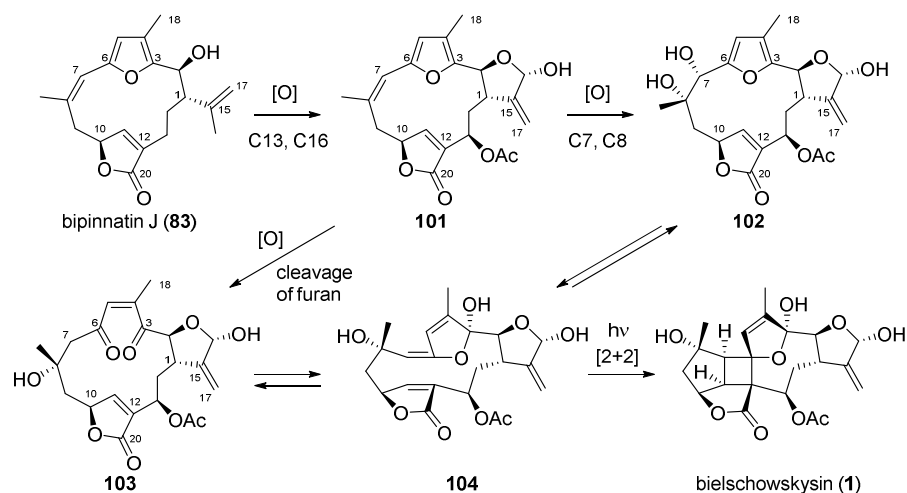


Scheme 10 Biogenesis of Rearranged Furanocembranoid Sarcofuranocembranolide B (100)

The structure of skeletal rearranged furanocembranoid sarcofuranocembranolide B (**100**) is quite remarkable and deserves some mechanistic explanation at this place (Scheme 10). Furthermore, it is another example for a photochemically induced biogenesis of a furanocembranoid. Excitation of $\Delta^{7,8}$ in **93** is presumed to generate diradical **94**, which via a radical 4-*exo-trig* cyclization expels an acetate radical giving cyclobutane **95**. Next, fragmentation of the C8-C9 σ -bond generates allylic radical **96**, which itself takes part in a 5-*exo-trig* cyclization generating the C10-C13 bond in **97**. Consecutively, via a second 5-*exo-trig* cyclization followed by fragmentation (C12-C13) and a formal H-radical quench at C13, rearranged cembranoid scaffold **99** is formed. Finally, dihydroxylation of the $\Delta^{7,8}$ -double bond and a translactonization provide sarcofuranocembranolide B (**100**).

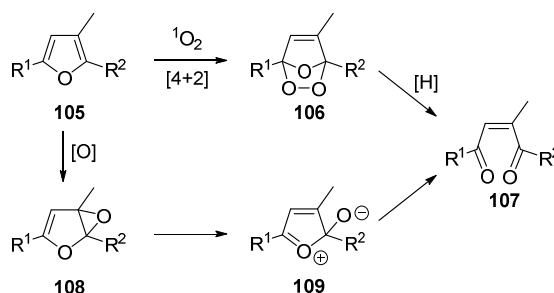
2.5.2. The Biosynthesis of Bielschowskysin (1)

Besides intricarene (**47**) and verrillin (**117**), bielschowskysin (**1**) (amongst others) is said to biosynthetically originate from bipinnatin J (**101**) as depicted in Scheme 11.¹¹ Enzymatic oxidation of C13 and C16, followed by cyclization to the hemiacetal in **101** is likely to construct the eastern part of the natural product. On one hand, face-selective dihydroxylation (**102**), of the $\Delta^{7,8}$ -double bond and consecutive S_N2' reaction could deliver enol ether cyclic hemi-ketal **104**. A photoinduced [2+2]-cycloaddition of this enol-intermediate with the $\Delta^{11,12}$ -double bond of the southern butenolide has been proposed to contract the 14-membered cembranoid macrocycle, creating the hexacyclic skeleton in bielschowskysin (**1**).



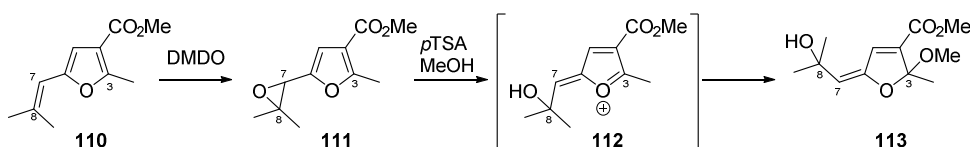
Scheme 11 Photochemical Biosynthesis of Bielschowskysin (1)

Alternatively, hydration of $\Delta^{7,8}$ and an oxidative cleavage of the furan ring should give enedione **103**, which simply is a tautomer of cyclization precursor **104**. This oxidative furan cleavage is a common functionalization among diterpenes and may proceed either via a [4+2]-cycloaddition with photochemically derived singlet oxygen via peroxide **106** or by an Achmatowicz-type oxidation via epoxide **108**, as depicted in Scheme 12.⁷



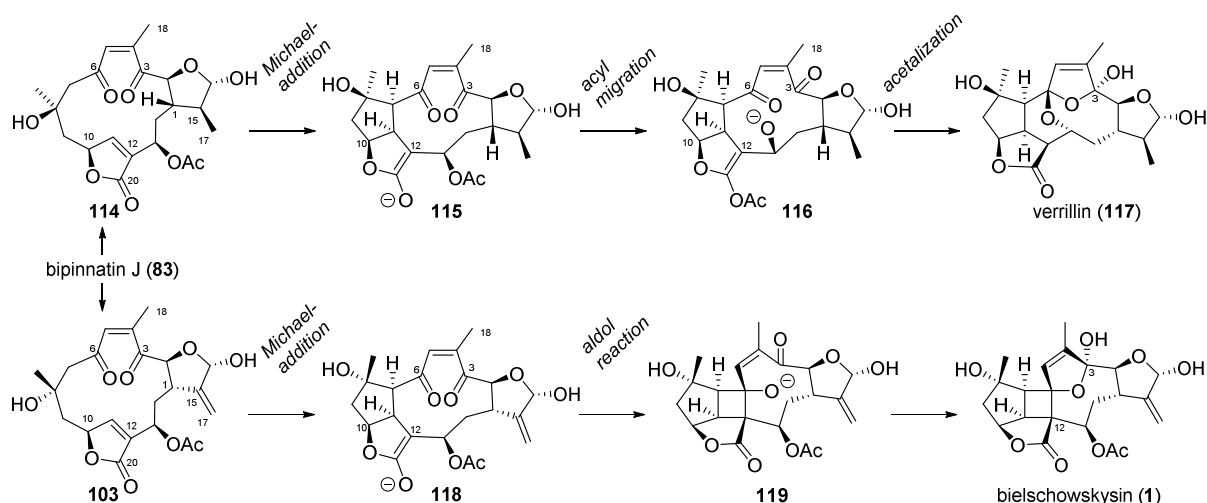
Scheme 12 Biogenetic Oxidative Furan Cleavage

Another path for the formation of enol ether cyclic hemiacetal **104** may be initiated by the enzymatic epoxidation of $\Delta^{7,8}$ according to biosynthetic studies by Pattenden and coworkers, which are outlined in Scheme 13.¹² Hence, after epoxidation of **110** to **111** an acid catalyzed opening of the epoxide presumably gave furanoxonium ion **112**, which was quenched by methanol forming (*E*)-enol ether **113**, which in analogy to the biosynthesis depicted in Scheme 12 may proceed in a [2+2]-cycloaddition.



Scheme 13 Biomimetic Enol Ether Formation Proposed by Pattenden

So far, all biosyntheses described in this work contain one or more photoinduced or photochemically allowed reactions according to the rules of orbital symmetry.¹³ This is very remarkable and deserves further discussion, as marine derived natural products have been isolated from soft and gorgonian corals which usually are found in shallow water, 15 to 50 m beyond ocean surface.¹⁴ In consideration of the habitat of these invertebrates and the amount of light available at this depth, the photochemical steps might be arguable. It is possible that at least some of the mentioned photoinduced reactions are enzyme mediated or are facilitated by a binding protein.⁶ Furthermore, the conditions under which the marine sources are harvested and prepared for investigation might be the reason for some observed structures. In particular, the common method of drying the species under sunlight might be the reason for structural rearrangements and therefore some of the isolated furanocembranoids might be artifacts rather than natural products. However, as for bielschowskysin (**1**), further investigations and comparison with the biosyntheses of related compounds might reveal plausible biosynthetic pathways, which proceed without a photoinduced step.



Scheme 14 Stepwise Related Biosyntheses of Verrillin (**117**) and Bielschowskysin (**1**)

As already mentioned earlier, verrillin (**117**) has been isolated from the same gorgonian octocoral as bielschowskysin (**1**). Thus, their skeletons might emerge from the same biogenetic precursor, namely bipinnatin J (**83**). Therefore, enediones **114** and **103** are proposed to form new C7-C11 σ -bonds via Michael-additions, giving enolates **115** and **118** respectively (Scheme 14). The biogenetic path to verrillin proceeds with an acyl migration from O13 to the enolate-O at C20 resulting in oxygen anion **116**.⁷ This specific oxygen initiates the formation of a hemiacetal at C6, which consecutively cyclizes onto C3, finalizing the biogenesis of **117**. On the other hand, the proposed non-photochemical biogenesis of bielschowskysin continues with an aldol reaction of the intermediary formed enolate

118. Thus, the cyclobutane-moiety and the 9-membered carbon macrocycle in **119** are generated by formation of the C6-C12 junction. Finally, hemiketal formation at C3 results in bielschowskysin (**1**).

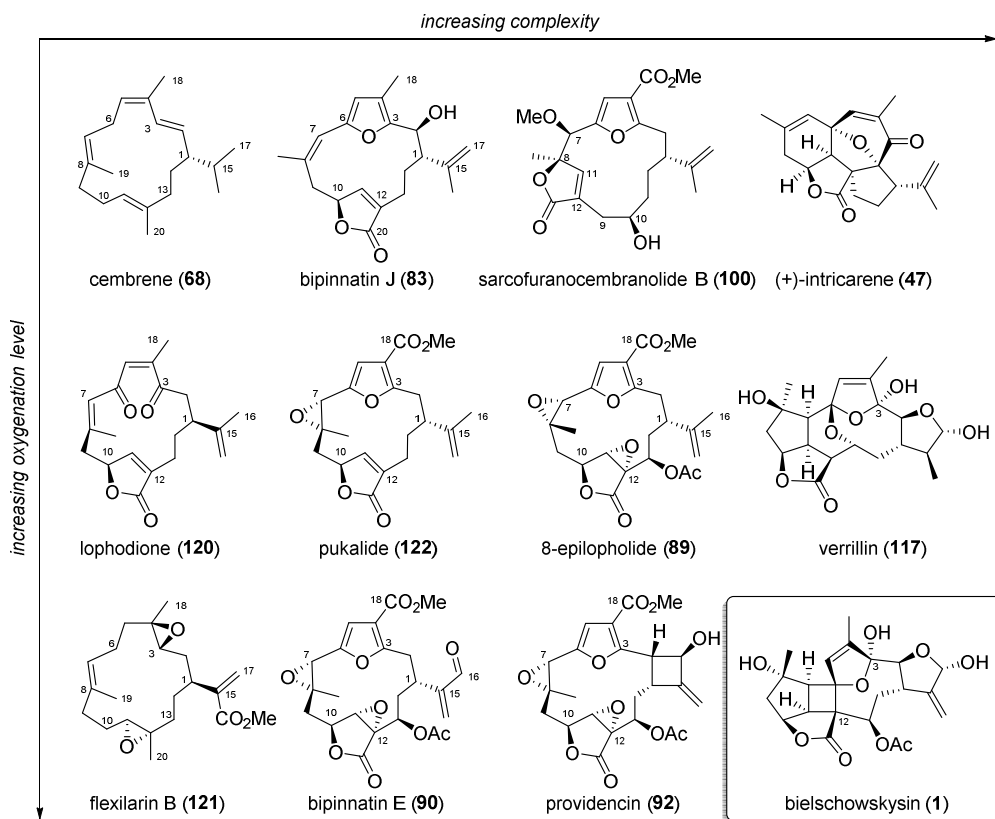


Figure 3 Increasing Complexity and Oxygenation Level of Marine Derived Cembranoids

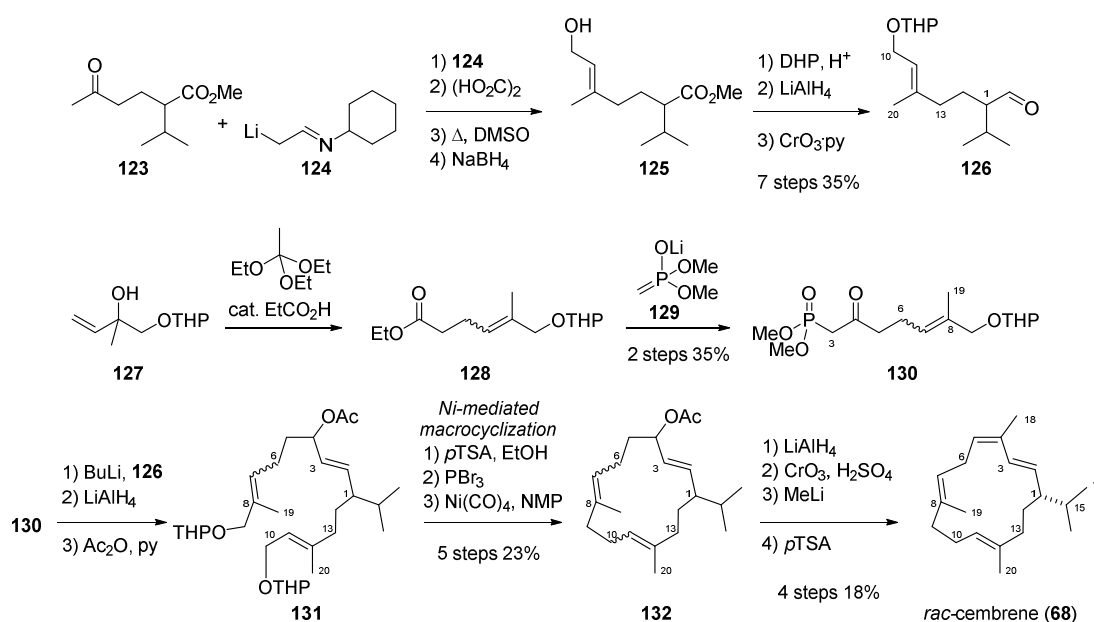
To conclude this section, Figure 3 shows a number of different cembranoids with various grades of oxygenation and increasing complexity, most of which have already appeared in this section. Bielschowskysin (**1**) likely is the most complex of all known congeners. Probably, this is one reason why this natural compound has gained such intensive attention by the scientific synthetic community, which will be discussed later in this thesis.

3. Selected Syntheses of Cembranoids

In the following section a selection of cornerstones in total synthesis of marine derived natural products of differing complexity are given. All accomplished natural products are structurally related to bielschowskysin.

3.1. Dauben's Synthesis of ($\pm$)-Cembrene (68)¹⁵

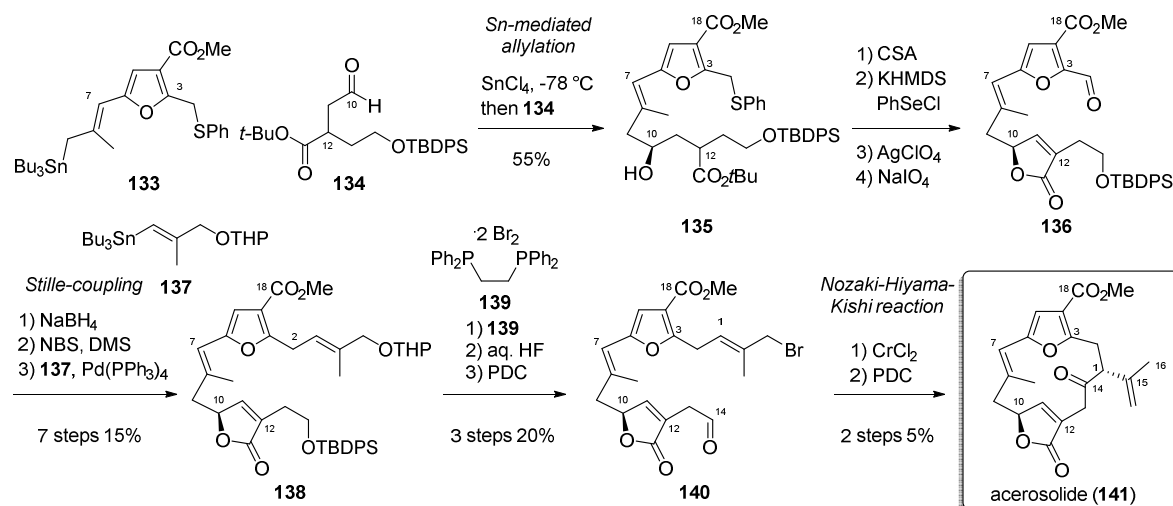
In 1974, Dauben and coworkers published a racemic synthesis of the basic macrocyclic hydrocarbon diterpene cembrene (**52**) centered upon a $\text{Ni}(\text{CO})_4$ mediated macrocyclization between two terminal allylic bromides.¹⁶ Their convergent synthetic strategy started with ketone **123** (Scheme 15). Nucleophilic addition of 2-imine-ethylolithium **124**, followed by hydrolysis, dehydration and reduction of the aldehyde led to allylic alcohol **125**. Finally, protection of the alcohol and a reduction/oxidation sequence provided aldehyde building block **126**. Second building block **130** of this convergent synthesis was obtained after Johnson-Claisen rearrangement¹⁷ of allylic alcohol **127** with triethyl orthoacetate and addition of lithium dimethyl methylphosphonate (**129**). Horner-Wadsworth-Emmons-reaction,¹⁸ to couple fragments **126** and **130**, was followed by reduction of the resulting enone and acylation yielding intermediate **131**. Before the nickel-mediated macrocyclization (**132**) was elaborated, removal of the THP-protecting groups and conversion of the diol to the corresponding dibromide was performed. To accomplish the racemic total synthesis of cembrene (**68**), the C18 methyl group was installed by 1,2-addition of MeLi to C4-ketone and consecutive acidic dehydration, regioselectively installing the labile diene in the target molecule.



Scheme 15 Dauben's Synthesis of ($\pm$)-Cembrene (68)

3.2. Paquette's Synthesis of Acerosolide (141)¹⁹

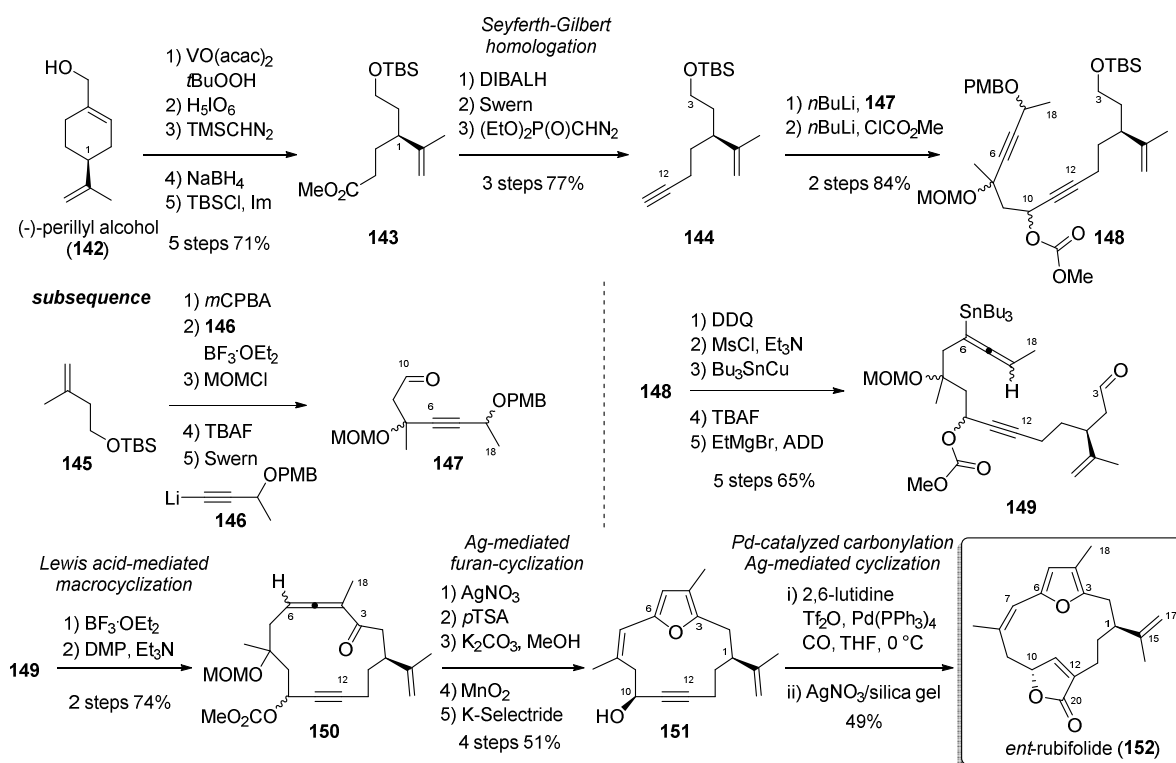
Paquette and Astles introduced one of the first routes to furanocembranoids by the publication of the total synthesis of acerosolide (**141**) in 1993. Their retrosynthetic consideration was based on the early introduction of the furan moiety, to which a butenolide moiety in the southern entity should be appended before closing the 14-membered macrocycle by a chromium mediated intramolecular Nozaki-Hiyama-Kishi reaction (NHK).²⁰ Thus, known trisubstituted furan **133**²¹ was initially coupled with aldehyde **134** via a tin-mediated allylation reaction resulting in (*E*)-isomer **135** in acceptable yield. Acid catalyzed cyclization of the lactone, double phenylselenide introduction at C2 and C12 and sequential oxidative removal of the selenide residues provided butenolide **136**. Stille-coupling at C2, via the corresponding furfuryl-bromide, with vinyl stannane **137** introduced carbons C1 and C15-17 in **138**. Suitable macrocyclization precursor **140** was obtained after conversion of the THP ether to the allylic bromide by treatment with 1,2-bis(diphenylphosphino)ethane tetrabromide (**139**) and an deprotection/oxidation sequence at C14. Nozaki-Hiyama-Kishi reaction closed the macrocycle generating an inconsequential single diastereomer at C14, presumably via a six-membered Zimmermann-Traxler transition state. This was further oxidized with PDC finalizing the total synthesis of acerosolide (**141**). A similar macrocyclization strategy will later be discussed in Trauner's total synthesis of bipinnatin J (**83**) (Section 3.5.1.), creating the C1-C2 single bond.



Scheme 16 Paquette's Synthesis of Acerosolide (**141**)

3.3. Marshall's Synthesis of *ent*-Rubifolide (**152**)²²

Marshall *et al.* reasoned the low yielding steps in Paquette's synthesis of acerosolide (**141**) due to a) the sensitivity of the early introduced trisubstituted furan moiety and to the fact that b) the macrocyclization might be energetically too high to overcome the arising ring strain as well as unfavorable enthalpic and entropic factors of the macrocyclization. To proof this assumption, Marshall's related total syntheses of rubifolide (**152**) and deoxypukalide (**164**)²³ were centered upon prior formation of a macrocycle and downstream intraannular furan cyclization. As the assignment of the absolute configuration of rubifolide was planned, enantiopure (*S*)-(-)-perillyl alcohol (**142**) was chosen as starting material for the total synthesis (Scheme 17). This terpene was transformed into intermediate **143** in five steps. After a reduction/oxidation sequence and C1 homologation, utilizing the Seyferth-Gilbert reagent (diethyl (diazomethyl)phosphonate),²⁴ alkyne **144** was derived in good yield.



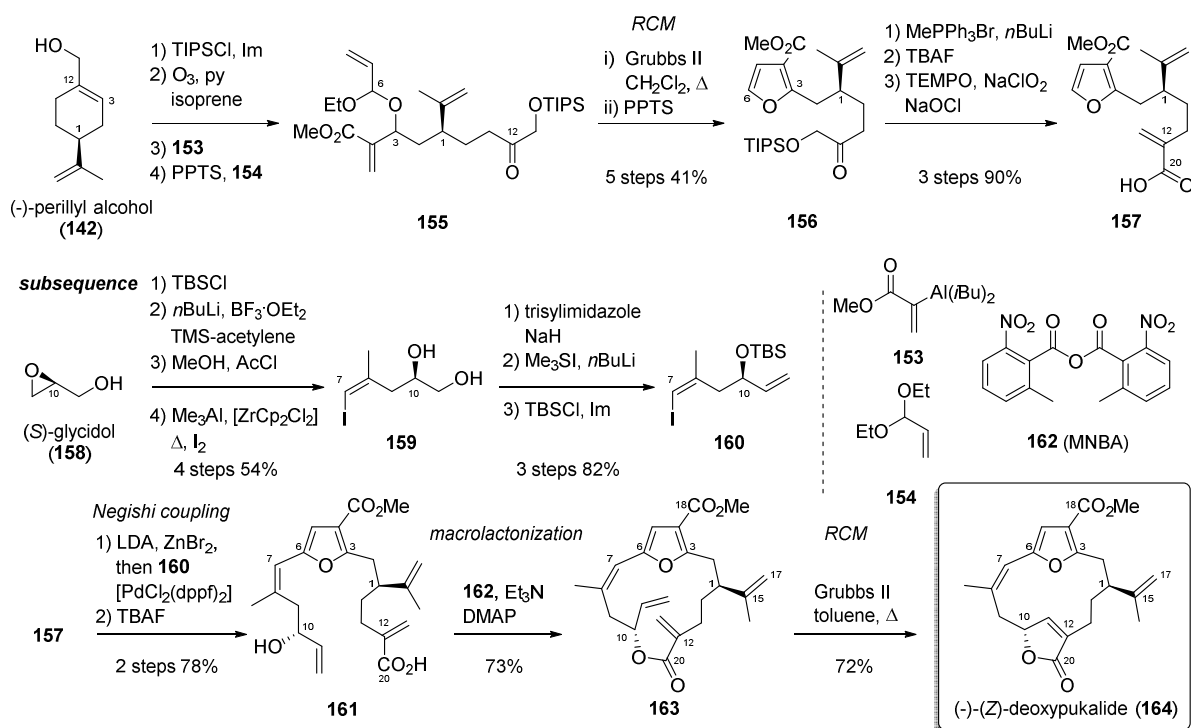
Scheme 17 Marshall's Synthesis of *ent*-Rubifolide (**152**)

Aldehyde **147** was synthesized in overall five steps from **145** containing an epoxidation, regioselective opening of the same, protecting group operations and a Swern oxidation. Fragments **144** and **147** were coupled along C10-C11 via the lithium acetylide. Protecting group operations, S_N2' reaction of a tributylstannyl cuprate onto a propargylic mesylate as well as oxidation of C3 furnished precursor **149**, suitable for the envisaged macrocyclization. Upon treatment with Lewis-acid, bond formation between C3 and C4 was accomplished followed by oxidation of the alcohol. With **150** in

hands the silver-mediated furan-cyclization was performed,²⁵ which was followed by deprotection/dehydration, stereoselectively establishing the (Z)-configured $\Delta^{7,8}$ -double bond. The propargylic alcohol was converted into a single diastereomer by a substrate controlled oxidation/reduction sequence giving intermediate **151**. A Pd(0)-catalyzed carbonylation followed by *in situ* AgNO₃ mediated butenolide-cyclization of the intermediary formed allene²⁶ finished the total synthesis of *ent*-rubifolide (**152**). All spectroscopic data was identical with that of a natural sample of the target molecule, solely the optical rotation was equal in magnitude but of opposite sign, indicating that the enantiomer was synthesized. Nonetheless, the absolute configuration of rubifolide (**174**) was thus assigned. However, by applying (*R*)-(+)-perillyl alcohol as starting material, naturally occurring rubifolide (**174**) would be accessible in 5% via this 22 steps counting sequence.

3.4. Donohoe's Synthesis of (-)-(Z)-Deoxypukalide (**164**)²⁷

Donohoe *et al.* tested a methodology developed in their own laboratories²⁸ in a total synthesis of the furanocembranoid (-)-(Z)-deoxypukalide (**164**). Thus, the retrosynthesis was based on formation of the trisubstituted furan and late-stage formation of the southern butenolide via ring-closing metathesis (RCM) with a macrolactone (**163**) as key intermediate (Scheme 18).



Scheme 18 Donohoe's Synthesis of (-)-(Z)-Deoxypukalide (**164**)

Due to economic reasons, (*S*)-(-)-perillyl alcohol (**142**) was chosen as starting material, resulting in the enantiomer of the target compound after successful synthesis. Reaction of the aldehyde intermediate from ozonolysis of **142** with vinylalane **153**, which is derived from hydroalumination of

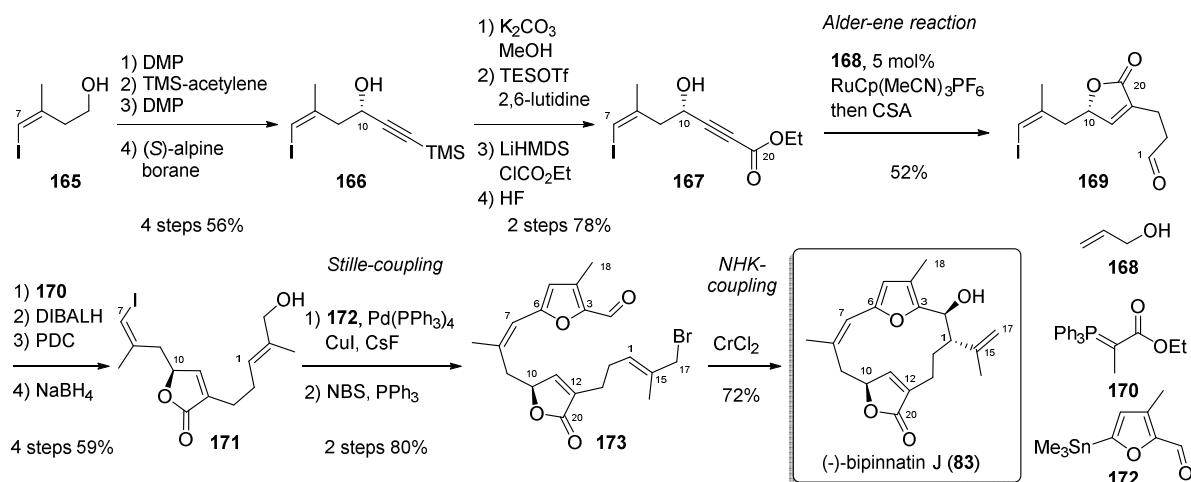
methylpropionate, and formation of the acetal with **154** under acidic conditions readily furnished **155**. RCM reaction followed by acidic workup allowed the formation of the furan moiety giving **156**.²⁸ Along three consecutive reaction steps building block **157** of this convergent synthesis was finished. Double deprotonation of **157** and formation of the zinc species was followed by Negishi cross-coupling with **160**, which itself was derived from (*S*)-glycidol (**158**), leading to macrolactonization precursor **161** after deprotection. Activation of the carboxylic acid with MNBA (**162**)²⁹ allowed the closure of macrolactone **163**. Finally, RCM reaction, generating the $\Delta^{11,12}$ -double bond, finished the total synthesis of (-)-(Z)-deoxypukalide (**164**).

3.5. Trauner's Studies on the Biosynthetic Relationship among Furanocembranoids: Relay Synthesis of Furanocembranoids^{6,11}

Members of the furanocembranoid family have been preferred synthetic targets of the research group of Trauner for a long time. Starting with bipinnatin J (**83**) in 2006,³⁰ this research group published a total of eight total syntheses of marine derived cembranoids. Based on profound understanding of the biosynthetic correlation among this family of natural products^{6,11} seven of these targets were accomplished in a biomimetic way from bipinnatin J as the common starting point.³¹

3.5.1. Total Synthesis of (-)-Bipinnatin J (**83**)^{11,30}

Shortly after the research group reported a racemic synthesis of bipinnatin J (**83**)³⁰ a stereoselective total synthesis of the target molecule via a slightly modified sequence was published.¹¹ Their synthesis started with literature known alcohol **165**,³² which was readily converted into enantiopure propargylic alcohol **166** including a stereoselective reduction with (*S*)-alpine borane (Scheme 19). C1-Elongation to intermediate **167** was accomplished via a series of protecting group operations and coupling of the corresponding lithium acetylide with ethyl chloroformate. Ruthenium catalyzed intermolecular Alder-ene reaction³³ of **167** with allylic alcohol (**168**), stereoselectively yielded the butenolide moiety in **169**. (*E*)-Selective HWE-reaction¹⁸ and a series of reduction oxidation steps set the stage for the Stille-coupling³⁴ of 2-methylfurfurylstannane **172** and vinyl iodide **171**. After Appel reaction³⁵ of the allylic alcohol to bromide **173** the macrocyclization was scheduled. Thus, similar to Paquette's synthesis of acerosolide (**141**, *vide supra*), a chromium mediated Nozaki-Hiyama-Kishi reaction³⁶ was used to diastereoselectively form (-)-bipinnatin J (**83**).

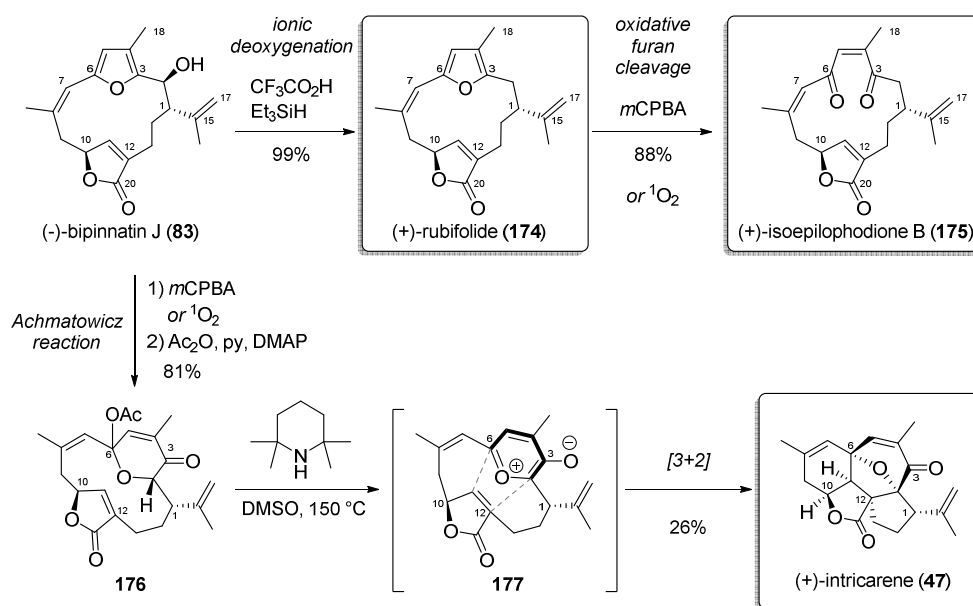


Scheme 19 Total Synthesis of (-)-Bipinnatin J (**83**)

With a viable stereoselective total synthesis of (-)-bipinnatin J (**83**) over 16 steps, starting from alcohol **165** and 8% overall yield, Trauner *et al.* were able to tackle their endeavor to access other congeners via biomimetic steps from this natural product as relay compound.

3.5.2. Total Syntheses of (+)-Rubifolide (**174**), (+)-Isoepilophodione B (**175**) and (+)-Intricarene (**47**)¹¹

Bipinnatin J (**83**) was directly converted to two more natural products by consecutive simple one step procedures (Scheme 20). Thus, ionic deoxygenation of the benzylic position by trifluoroacetic acid and triethylsilane³⁷ readily furnished (+)-rubifolide (**174**). Treatment of **174** with either *m*CPBA or singlet oxygen lead to formation of the enedione in (+)-isoepilophodione B (**175**), completing another total synthesis and confirming earlier proposed biomimetic correlations.

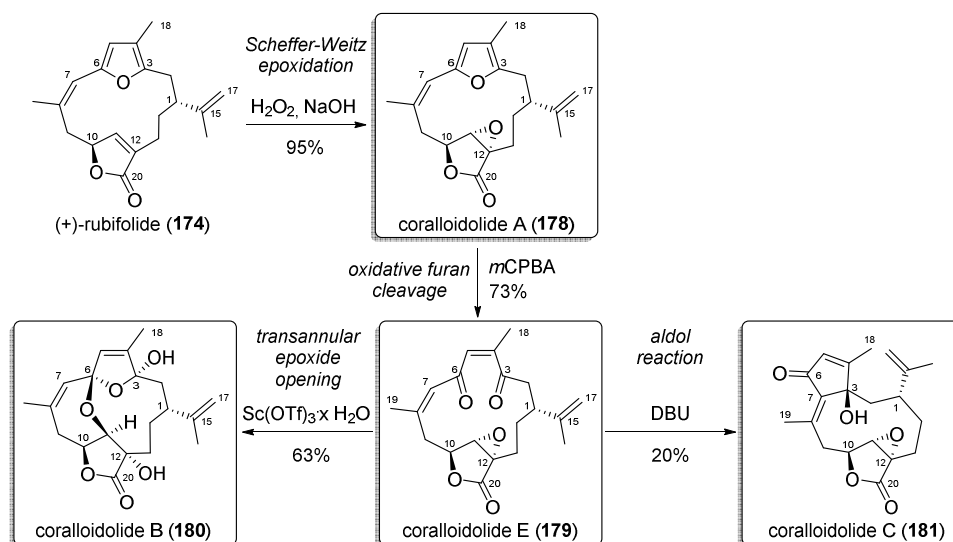


Scheme 20 Total Syntheses of (+)-Rubifolide (**174**), (+)-Isoepilophodione B (**175**) and (+)-Intricarene (**47**)

Treatment of bipinnatin J (**83**) with *m*CPBA, via an Achmatowicz reaction,³⁸ resulted in a dihydropyran which was directly converted to **176** by acylation. Various conditions were screened until heating of **176** in DMSO and 2,2,6,6-tetramethylpiperidine yielded (+)-intricarene (**47**) by an intramolecular 1,3-dipolar cycloaddition of oxidopyryliumbetaine **177** with the butenolide, stereoselectively forming $\Delta^{2,12}$ - and $\Delta^{6,11}$ - σ -bonds. A few months earlier the research group of Pattenden *et al.* published an almost identical endgame in their total synthesis of **47**, only differing in the reagents applied.³⁹

3.5.3. Total Syntheses of Coralloidolides A, B, C and E³¹

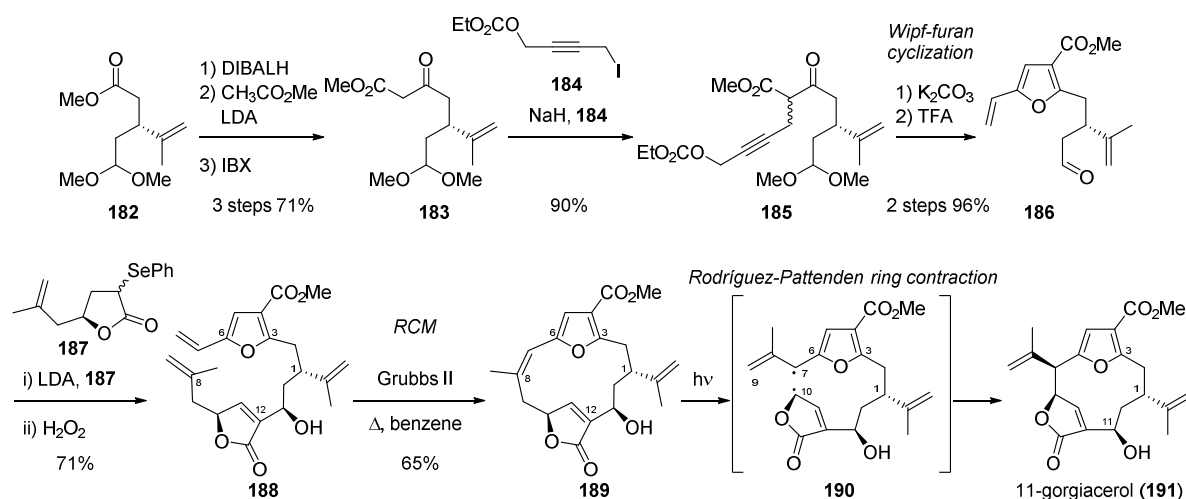
(+)-Rubifolide (**174**), which itself is available in one step from bipinnatin J (**83**), served as a precursor for another four natural products (Scheme 21). Scheffer-Weitz epoxidation⁴⁰ of the butenolide in **174** provided coralloidolide A (**178**) as a single diastereomer by attack from the less hindered α -face. Upon oxidative cleavage of the furan moiety the next furanocembranoid, coralloidolide E (**179**), was synthesized. Treatment with scandium triflate resulted in hydration of the enedione and transannular epoxide opening, which established the oxygen bridged tetracyclic coralloidolide B (**180**). The fourth and so far last furanocembranoid synthesized by Trauner *et al.* is coralloidolide C (**181**). Formation of the cyclopentenone in **181** was accomplished by treatment of **179** with DBU, presumably via γ -deprotonation at C19 and transannular aldol reaction closing the C3-C7 connection followed by migration of the resulting double bond in conjugation to the carbonyl at C6.



Scheme 21 Total Syntheses of Coralloidolides A, B, C and E

3.6. Mulzer's Synthesis of 11-Gorgiacerol (**191**)⁴¹

Our research group has been working on a number of terpenoids such as bielschowskysin (**1**), providencin (**92**)⁴² and 11-gorgiacerol (**191**). The synthesis of the latter was recently accomplished by Weinstabl and Mulzer utilizing the biomimetic Rodríguez-Pattenden ring contraction⁴³ of a 14-membered carbocyclic precursor. The synthesis of **191**, which belongs to the pseudopterane family of furanocembranoids, commenced with literature known ester **182**, derived from (*R*)-(-)-carvone in four steps.⁴⁴ Reduction of the ester, aldol reaction with methylacetate and subsequent oxidation furnished **183** (Scheme 22), which was further alkylated with propargyl iodide **184** to **185**. Furan cyclization according to a procedure reported by Wipf⁴⁵ and subsequent acidic cleavage of the dimethylacetal provided aldehyde **186**. Aldol coupling with seleno lactone **187**⁴² and oxidative elimination of the selenide ensued. By application of Grubbs II catalyst in refluxing benzene, **188** was readily converted to 14-membered carbon macrocycle **189** with the newly formed $\Delta^{7,8}$ -(*Z*)-double bond. As generally proposed for the biosynthesis of pseudopteranes (biosynthesis of kallolide A (**84**), Scheme 8) irradiation lead to contraction of the cembrane to the pseudopterane skeleton completing the total synthesis of 11-gorgiacerol (**191**), presumably via diradical **190**. Similar to the studies by Pattenden,⁴⁶ initial formation of the $\Delta^{7,8}$ -(*E*)-isomer was observed. Furthermore, the completion of this synthesis and the synthesis of the C11 epimer lead to revision of the structure of the natural compound.



Scheme 22 Mulzer's Synthesis of 11-Gorgiacerol (**191**)

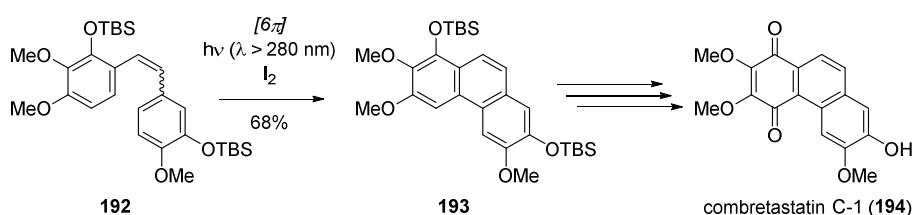
The syntheses by Trauner and Mulzer elegantly represent the application of biomimetic strategies in total synthesis. The biomimetic photoinduced ring contraction utilized in Mulzer's total synthesis of 11-gorgiacerol (**191**) displays a suitable connection to the following section of this thesis, which deals with the application of photochemical reactions as key steps in natural product synthesis.

4. Photochemical Reactions as C-C Bond Forming Strategies in Natural Product Synthesis

The design of natural product syntheses is a challenging field for synthetic organic chemists and demands a deep seated knowledge of a broad number of chemical transformations as well as certain creativity in setting the retrosynthetic cuts. Photochemical reactions add a wide range of different, often underestimated transformations to the toolbox of synthetic chemists. The following section is devoted to photochemical C-C bond forming processes with an emphasis on the [2+2]-photocycloaddition, as this transformation has the largest impact of all photochemical reactions on total synthesis and a main part of this thesis is centered upon this reaction. An insight into the role of molecular orbitals in each of these reactions is not given, as this is part of numerous excellent articles and books and would go beyond the scope of this thesis.⁴⁷

4.1. Photocyclizations⁴⁸

Conrotatory [6 π]- and disrotatory [4 π]-photocyclizations are photochemically allowed according to the Woodward-Hoffmann-rules¹³ and are among the most important light induced pericyclic ring closing reactions. Phenanthrenes are readily accessed by [6 π]-cyclizations forming the central benzene ring under oxidative conditions. For example combretastatin C-1 (**194**) was synthesized from stilbene **192** utilizing this pericyclic reaction (Scheme 23).⁴⁹ Irradiation of stilbene **192** in the presence of iodine, as oxidant of an intermediary formed cyclohexadiene, gave the desired phenanthrene scaffold **193**.

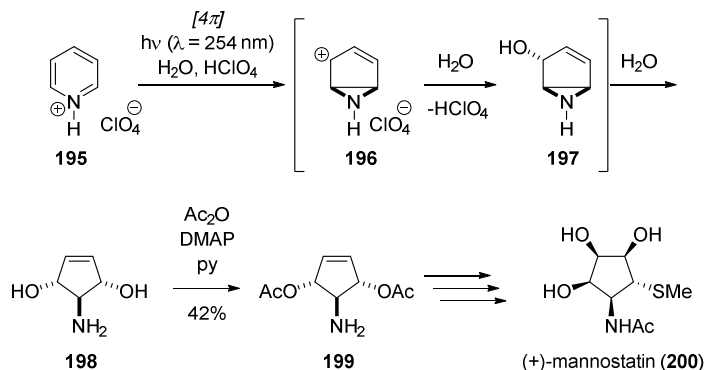


Scheme 23 Application of a [6 π]-Photocyclization in the Total Synthesis of Combretastatin C-1 (**194**)

Substrates halogenated *ortho* to the alkenyl-bridge have also been applied, leading to the rearomatization of the central benzene ring by elimination of HX under neutral conditions.⁵⁰ Amongst others, further substrates of this pericyclic process were enamides of benzoic acid giving isoquinolines and derivatives.⁵¹

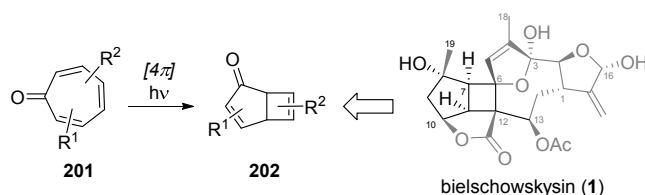
Pyridinium salts as **195** were applied in [4 π]-photocyclizations in natural product synthesis (Scheme 24). The disrotatory reaction yields carbenium ion **196**, which is saturated in the presence

of water. A consecutive S_N2 opening of aziridine **197** and acylation afforded amino cyclopentene **199**, which was proceeded to (+)-mannostatin (**200**) by Mariano *et al.*⁵²



Scheme 24 Application of a $[4\pi]$ -Photocyclization in the Total Synthesis of (+)-Mannostatin (**200**)

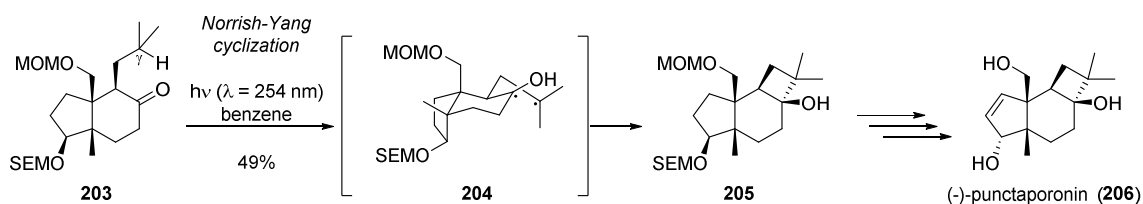
$[4\pi]$ -photocyclization of a cycloheptatrienone of general structure **201** is known to result in bicyclo[3.2.0]cycloheptane **202** (Scheme 25), which might be a suitable intermediate for the elaboration of bielschowskysin's western carbon core (*vide infra*).



Scheme 25 Proposed $[4\pi]$ -Photocyclization to Generate the Bicyclo[3.2.0]cycloheptane Core of Bielschowskysin (**1**)

4.2. Norrish-Yang Cyclization⁴⁸

Photoexcitation of a carbonyl group may result in the abstraction of a hydrogen in γ -position, leading to a short lived 1,4-diradical, which recombines closing a cyclobutane moiety. This process is referred to as Norrish-Yang cyclization (Norrish type II reaction).¹⁰ As an example (Scheme 26), the reaction was used to construct the *trans*-fused cyclobutane ring in the total synthesis of (-)-punctaporonin (**206**).⁵³ Competitive cleavage of diradical **204** (Norrish type II cleavage), giving isobutene and a ketone in the substrate, were found to be the reason for the moderate yield.

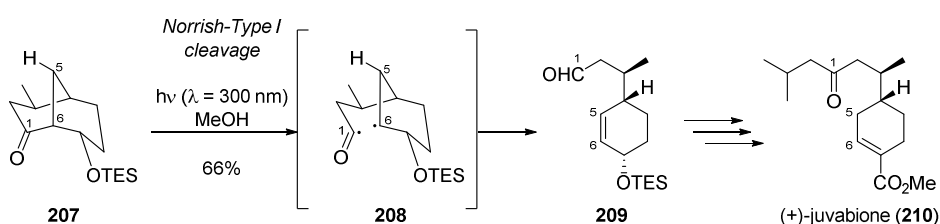


Scheme 26 Norrish-Yang Cyclization in the Total Synthesis of (-)-Punctaporonin (**206**)

Mechanistically, the excitation may result in a triplet state carbonyl, which abstracts the γ -hydrogen, where after spin-flip to the singlet state (ISC, inter-system-crossing) facilitates recombination of the 1,4-diradical. The Norrish Yang cyclization has also been reported to form cyclopentanes in cases where no γ -hydrogen but a δ -hydrogen was present.⁵⁴ Furthermore, irradiation of α,β -unsaturated carbonyl compounds was found to lead to the deconjugated β,γ -unsaturated equivalents by abstraction of a γ -hydrogen.⁵⁵

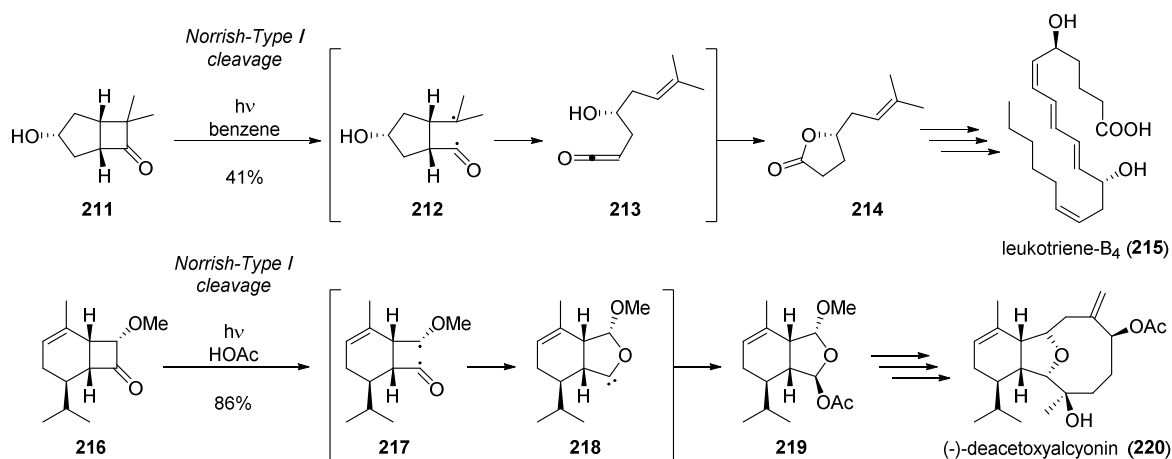
4.3. Norrish-Type I Cleavage⁴⁸

The following section deals with the Norrish-Type I reaction, which refers to the α -cleavage of photoexcited carbonyl compounds.¹⁰ Homolytic cleavage of the σ -bond next to the carbonyl results in the formation of a diradical, which offers different paths for further reactions. For example, excitation of cyclohexanone **207** led to formation of unconjugated exocyclic aldehyde **209** via diradical **208** (Scheme 27). In particular, the acyl-radical (**208**) abstracts the δ -hydrogen (C5) and the $\Delta^{5,6}$ -double bond is formed by recombination of the C5-C6 diradical. Compound **209** served as intermediate in the total synthesis of sesquiterpene (+)-juvabione (**210**).⁵⁶



Scheme 27 Norrish-Type I Cleavage in the Total Synthesis of (+)-Juvabione (**210**)

Formation of ketene **213** by Norrish-Type I reaction, which directly underwent cyclization to butyrolactone **214** was used in the total synthesis of leukotriene- B_4 (**215**, Scheme 28).⁵⁷ Irradiation of cyclobutanone **216** in acetic acid was used to establish mixed bisketal **219** in the total synthesis of (-)-deacetoxyalcyonin **220**.⁵⁸ After homolytic bond cleavage to 1,4-diradical **217**, formation of oxacarbene **218** and trapping by the solvent resulted in the desired ring-enlargement.

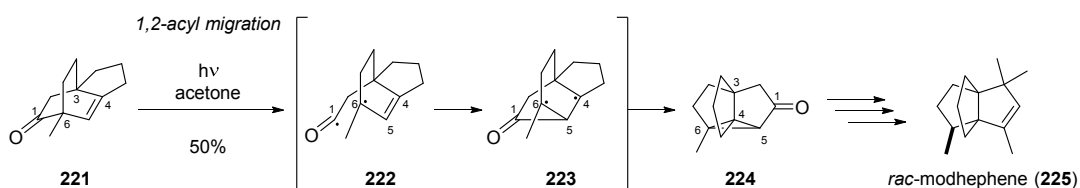


Scheme 28 Norrish-Type I Cleavage in the Total Syntheses of Leukotriene-B₄ (**215**) and (-)-Deacetoxyalcyonin (**220**)

4.4. Photochemical Rearrangements⁴⁸

4.4.1. 1,2- and 1,3-Acyl Migration

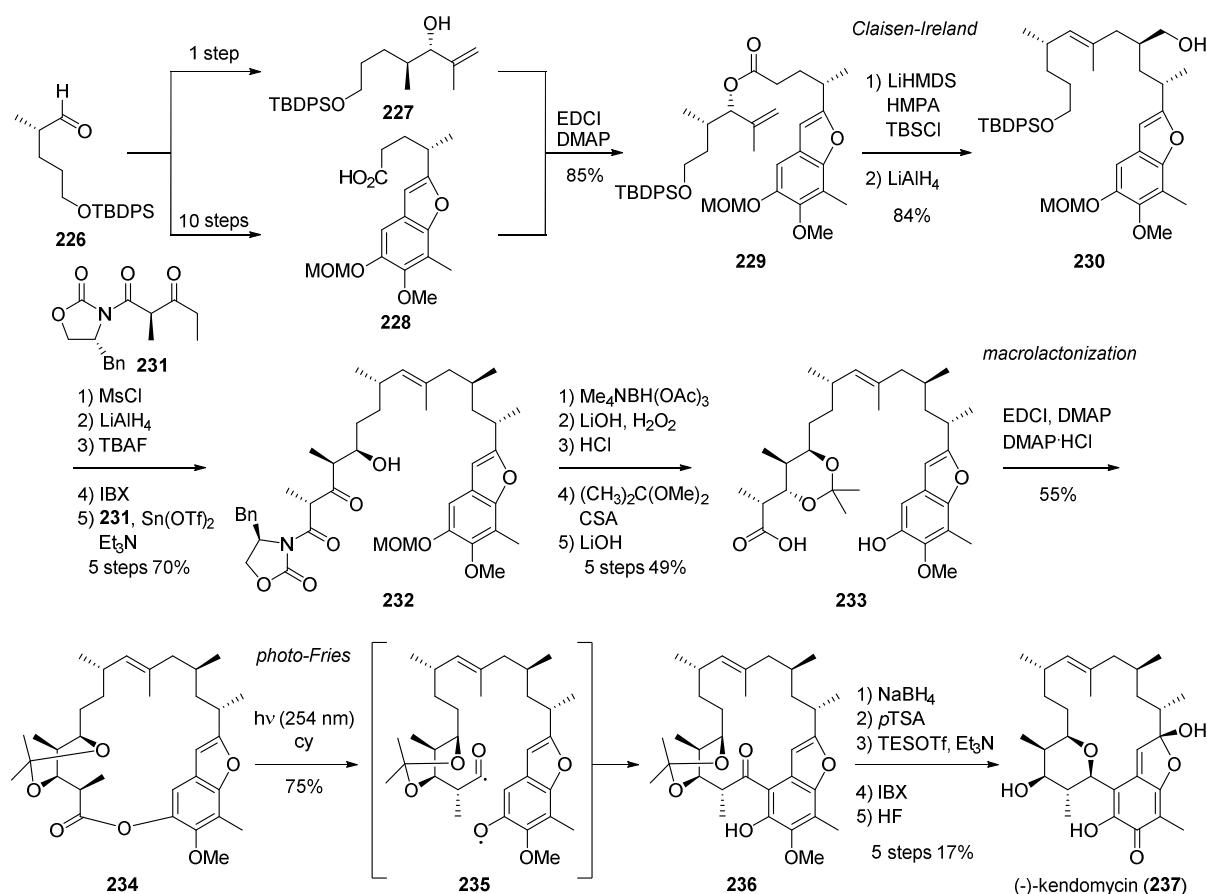
These photochemical reactions are closely related to the Norrish-Type I reaction, starting with homolytic cleavage of the bond in α -position to the photoexcited carbonyl group. The 1,3-acyl migration presumably is a singlet state process, whereas the 1,2-acyl-migration, also known as oxo-di- π -methane rearrangement, is a triplet process requiring a sensitizer. Scheme 29 gives an example for the latter. Mechanistically, the excited triplet carbonyl in β,γ -unsaturated ketone **221** - via 1,2-acyl migration - generates 1,3-diradical **223**, which recombines affording cyclopropane **224**. Three more steps, including a reductive cleavage of the cyclopropane ring under Birch conditions,⁵⁹ finalized the total synthesis of [3.3.3]propellane ($\pm$)-modhephene **225**.⁶⁰



Scheme 29 Photochemical 1,2-Acyl Migration in the Total Synthesis of the [3.3.3]Propellane ($\pm$)-Modhephene (**225**)

4.4.2. Photo-Fries Rearrangement – Mulzer’s Total Synthesis of (-)-Kendomycin (237)⁶²

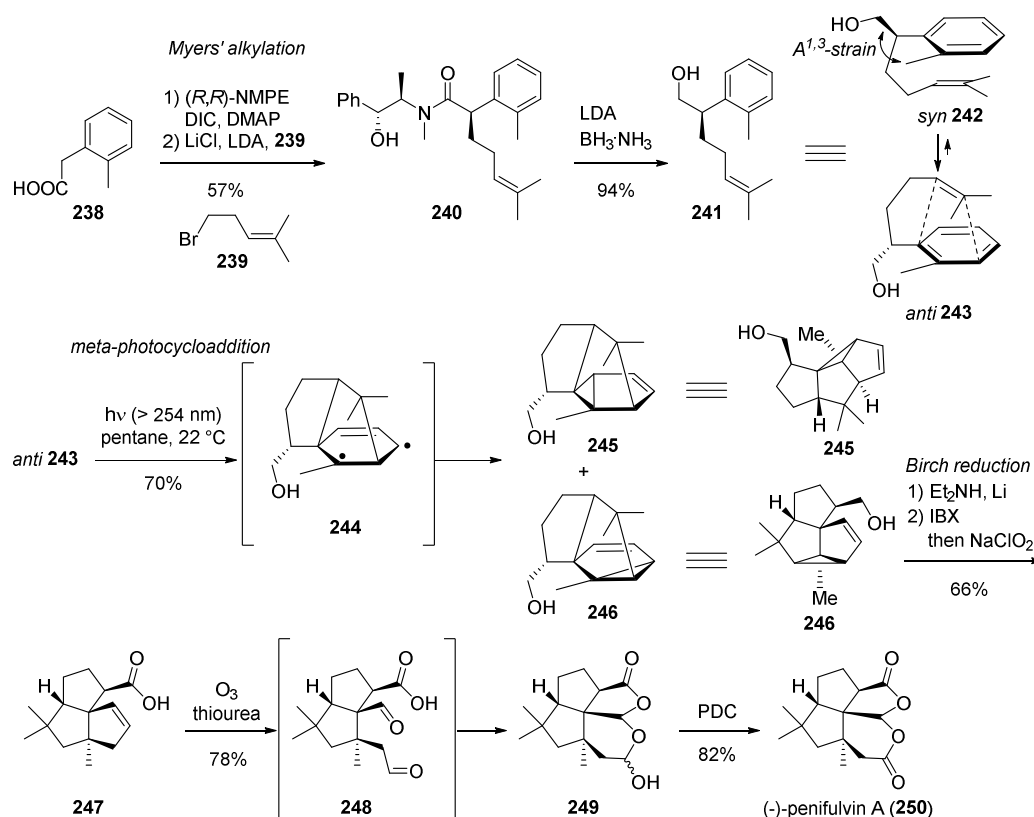
In contrast to the thermal variant of the Fries rearrangement,⁶¹ the photoinduced modification does not require strong Lewis acidic conditions, facilitating the acyl-migration by irradiation with light of short wavelengths. Magauer and Mulzer reported an application of the photo-Fries reaction for the construction of a macrocycle in their total synthesis of (-)-kendomycin (**237**).⁶² Their highly convergent synthesis was based on the connection of three building blocks **231**, **228** and **227**. The latter two were accessed from aldehyde **226** in one and ten steps, respectively (Scheme 30). Connection of these two intermediates by esterification was followed by Claisen-Ireland rearrangement⁶³ and reduction of the resulting carboxylic acid providing (*E*)-alkene **230**. Further transformations and chain elongation with Evans ketoimide **231**⁶⁴ under Lewis acidic conditions led to intermediate **232**. Diastereoselective reduction to the 1,3-*anti* diol⁶⁵ and further manipulations afforded seco acid **233**, setting the stage for the macrolactonization. After successful lactonization, irradiation of macrolactone **234** in cyclohexane resulted in intermediate **236** with the correct ring size via photo-Fries reaction. Finally, a series of protecting group operations, reductions and oxidations completed the total synthesis of (-)-kendomycin (**237**).



Scheme 30 Mulzer’s Total Synthesis of (-)-Kendomycin (**237**) Containing a Photo-Fries Rearrangement as Key Step

4.4.3. *meta*-Photocycloaddition – Mulzer’s Synthesis of (-)-Penifulvin A (**250**)^{48,66}

This singlet process usually between an electron-rich arene and a double bond is one of the most fascinating photochemical reactions applied in total synthesis. As the intermolecular case of this reaction rarely gives satisfying yields it is most often carried out in an intramolecular fashion of an arene with an alkenyl side chain. Along the path of this transformation three single bonds are formed with up to six stereogenic centers. Gaich and Mulzer’s synthesis of sesquiterpenoid (-)-penifulvin A (**250**),⁶⁷ which is outlined in Scheme 31, is a very elegant example for the application of this reaction in total synthesis.



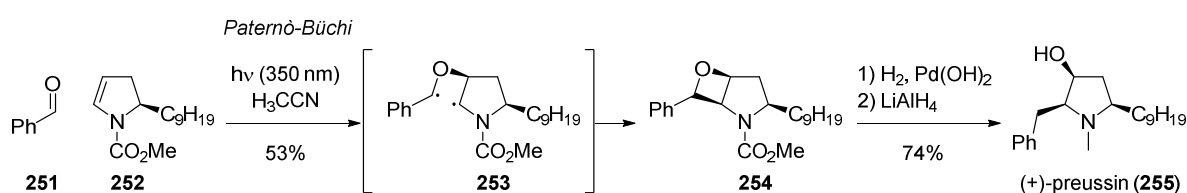
Scheme 31 Mulzer’s Total Synthesis of (-)-Penifulvin A (**250**) via *meta*-Photocycloaddition

Centered upon Wender’s previous work on this photocycloaddition,⁶⁶ the synthesis commenced with *o*-tolylacetic acid (**238**). Elongation in the benzylic position in stereoselective manner by Myers’ alkylation (**240**), utilizing pseudoephedrine ((*R,R*)-NMPE),⁶⁸ afforded **241** after reductive cleavage of the chiral auxiliary. Next, the *meta*-photocycloaddition was scheduled. On irradiation a singlet state exciplex is said to be formed which reacts in a formal [3+2]-cycloaddition, preferentially as the *anti*-conformer **243**, due to reduced 1,3-allylic strain. In two different paths diradical **244** is able to recombine, generating either linear triquinane system **245** or the angular **246**. As a rule of thumb, donor-substituents on the arene usually end up at the newly formed bridge head atom, forming a quaternary center. Tetracycle **246** was further proceeded to **247** by Birch⁵⁹ reduction cleaving the

cyclopropane ring and an oxidation sequence to the carboxylic acid. Ozonolysis of the double bond, cyclization of intermediary dialdehyde **248** to hemiketal **249** and PDC oxidation completed the total synthesis of (-)-penifulvin A (**250**) in eight steps and 8% overall yield.

4.5. Paternò-Büchi Reaction^{48,69}

The photocycloaddition of a carbonyl with an olefin, providing an oxetane, is a well established photochemical reaction referred to as Paternò-Büchi reaction.⁶⁹ Usually the reaction precedes on the triplet hypersurface, involving 1,4-diradicals, and therefore it is a stepwise rather than a concerted process. As oxetanes are rare structural motives in natural products, they are most often used as intermediates and usually cleaved. Both inter- and intramolecular cases are feasible in total synthesis. An example for the former is given in Scheme 32 in the total synthesis of (+)-preussin (**255**).⁷⁰ In the photochemical reaction enamine **252** was treated with benzaldehyde giving intermediate **254**, which is the formal *anti*-aldol product due to the inherent 1,3-functionality. Hydrogenolysis of 2-phenyloxetane **254** and reduction of the amide were the remaining steps to conclude the total synthesis of (+)-preussin (**255**).



Scheme 32 Application of the Paternò-Büchi Reaction in the Total Synthesis of (+)-Preussin (**255**)

4.6. [2+2]-Photocycloaddition⁴⁸

4.6.1. General Discussion

The [2+2]-photocycloaddition is the most utilized photochemical reaction in natural product synthesis. Even though cyclobutanes are scarce motives, they are often used as intermediates in syntheses mimicking a variety of structural features. Besides inter- and intramolecular cases the [2+2]-photocycloaddition can be classified into three different pathways.

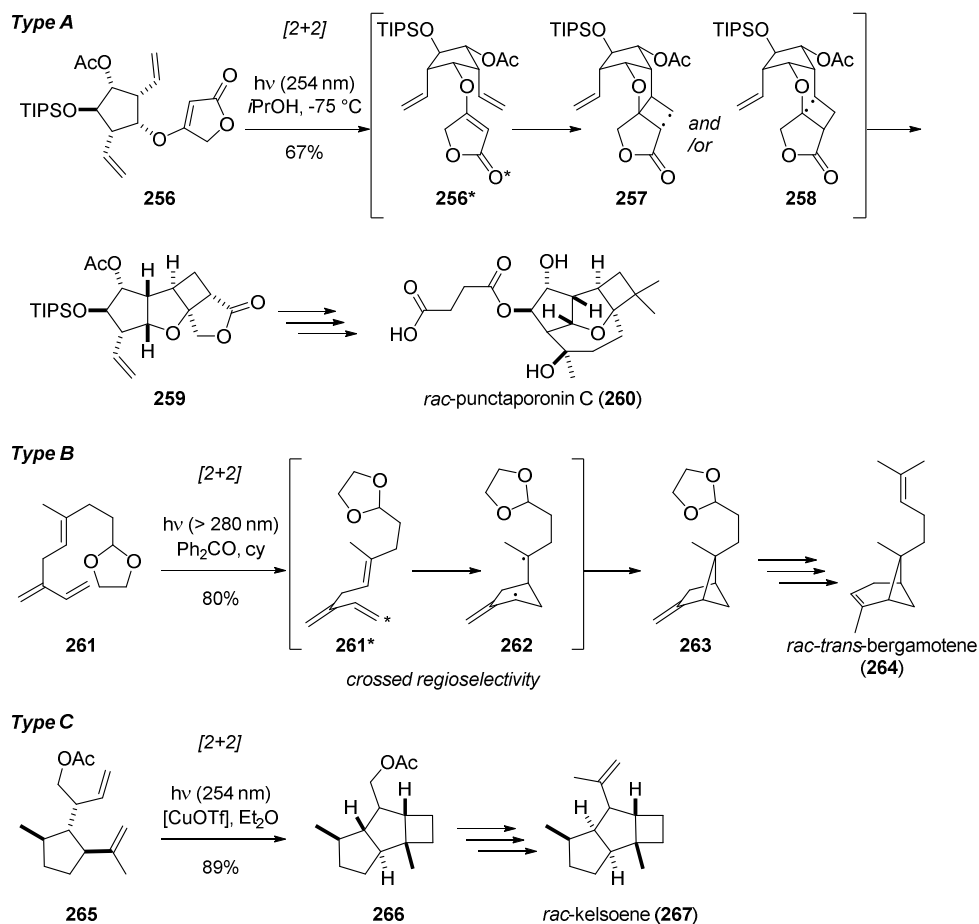
- (A) Most commonly, α,β -unsaturated usually cyclic carbonyl compounds react with olefins in a stepwise fashion via comparatively long lived $\pi\pi^*$ triplet states, similar to the Paternò-Büchi reaction via 1,4 diradicals.
- (B) [2+2]-photocycloadditions utilizing triplet sensitizers such as acetone, acetophenone or benzophenone. This pathway enables photoexcitation of olefins with rather low triplet energy, for example dienes and styrenes.
- (C) [2+2]-photocycloadditions employing copper(I) salts as catalysts. This reaction is only useful for 1,6-dienes, establishing bicyclo[3.2.0]heptanes or corresponding heterocycles. Mechanistically, the charge-transfer band of the copper-alkene complex is excited at wavelengths of about 250 nm, resulting in [2+2]-photocycloadditions.

Whether on the singlet or triplet hypersurface, the [2+2]-photocycloaddition is the direct way to cyclobutanes. Thus, whenever such a moiety is present in the scaffold of a natural product, this process can immediately be recognized as a central retrosynthetic step. Scheme 33 gives examples for the application of all three general pathways discussed above in intramolecular fashion.

In the racemic total synthesis of punctaporonin C (**260**) an intramolecular [2+2]-photocyclization was employed to construct the tetrahydrofuran moiety of an oxygen linked butenolide with excellent regio- and stereoselectivity (Scheme 33).⁷¹ Excitation of butenolide **256** and formation of 1,4-diradicals **257** and/or **258**, after spin-flip to the singlet state, results in recombination and formation of tetracycle **259**.

1,3-bridged cyclobutanes like **263** are available from [2+2]-photocyclizations of 1,5-dienes, which are said to react in crossed regioselectivity via their triplet states according to the so called rule of five⁷² - not to be confused with the Lipinski rules (RO5).⁷³ The former describes the preference for the formation of five membered rings in triplet-state reactions, whereas the latter is used to predict the druglikeness of chemical compounds. Thus, by excitation of **261** in the presence of benzophenone as sensitizer 1,4-diradical **262** is formed by closure of a cyclopentane ring. By inter-system-crossing to

the singlet state, recombination becomes feasible and the bridged cyclobutane **263** is constructed. Further transformations allowed the synthesis of *rac-trans*-bergamotene (**264**).⁷⁴



Scheme 33 [2+2]-Photocycloaddition Types and their Application in Total Syntheses

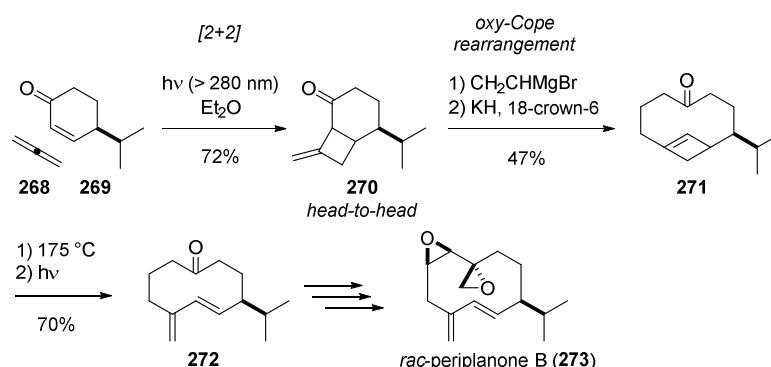
The photocyclization of **265** to **266** represents the third general case. 1,6-Diene **265** was irradiated in the presence of copper(I)triflate giving the cyclobutane in good overall yield and excellent regio- and stereoselectivity. Further steps, including an epimerization, led to the racemic synthesis of kelsoene (**267**).⁷⁵

4.6.2. [2+2]-Photocycloaddition Products as Intermediates in Total Synthesis

The following section discusses the different ways in which cyclobutanes have been used as intermediates in total synthesis. The potential of this strategy strongly depends on both reaction partners and the outcome of the [2+2]-photocycloaddition itself.

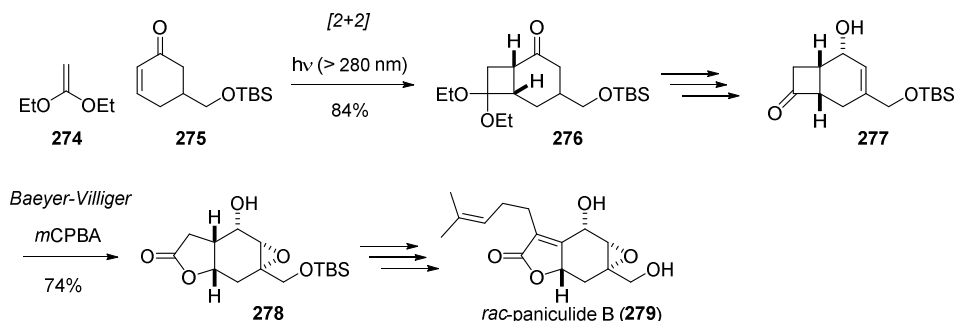
The racemic total synthesis of periplanone B (**273**) by Schreiber and Santini utilized an allene/[2+2]-photocycloaddition of cyclohexenone **269** to yield bicycle **270** in a regioselective head-to-head fashion as an inconsequential 2:1 diastereomeric mixture (Scheme 34).⁷⁶ Addition of a vinyl

appendage and consecutive oxy-Cope rearrangement⁷⁷ provided cyclobutene **271**. Thermal conrotatory ring opening followed by double-bond isomerization afforded (*E*)-cyclodecenone **272**, which could be proceeded to the desired natural compound **273**.



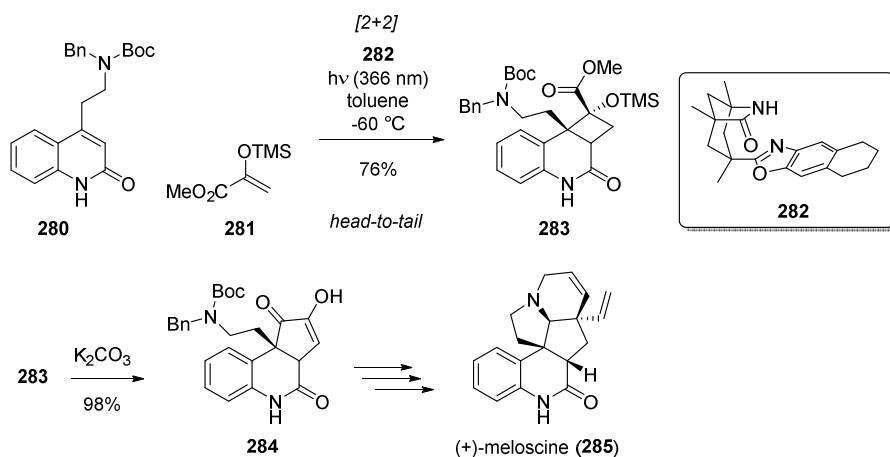
Scheme 34 Head-to-Head Allene/[2+2]-Photocycloaddition in the Total Synthesis of *rac*-Periplanone B (**273**)

Alkenes with electron-donor substituents at the double bond preferentially react in a head-to-tail fashion. Thus, [2+2]-photocycloaddition of 1,1-dialkoxyalkene **274** with cyclohexene **275** regioselectively afforded bicycle **276** as reported by Smith and Richmond (Scheme 35).⁷⁸ The latent cyclobutanone was subjected to Baeyer-Villiger oxidation⁷⁹ affording γ -butyrolactone **278**, which was converted to *rac*-paniculide B (**279**).



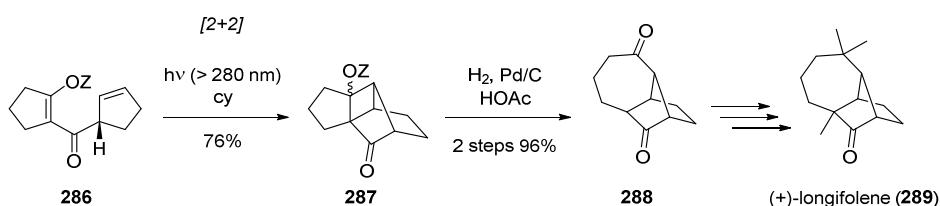
Scheme 35 Head-to-Tail [2+2] Photocycloaddition in the Total Synthesis of *rac*-Paniculide B (**279**)

So far, only racemic total syntheses containing [2+2]-photocycloadditions have been discussed. However, there are stereoselective cases utilizing chiral complexing agents or chiral auxiliaries. As an example for such an enantioselective photocycloaddition, irradiation of a mixture of quinolone **280** and silyl enol ether **281** in the presence of enantiopure **282** afforded **283** with excellent regio- and diastereoselectivity (Scheme 36). Fragmentation of the cyclobutane moiety was achieved under basic conditions providing enone **284**, which was further proceeded to (+)-meloscine (**285**) by Bach *et al.*⁸⁰



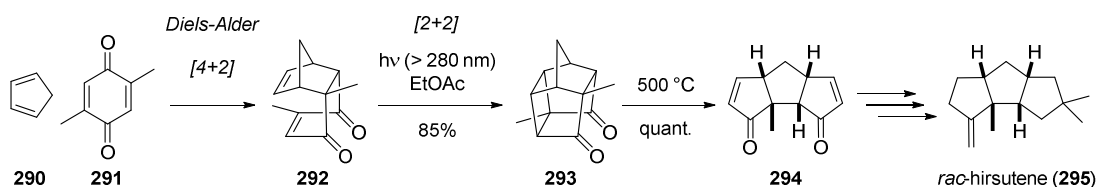
Scheme 36 Enantioselective Intermolecular Head-to-Tail [2+2]-Photocycloaddition by Bach *et al.*

Silyloxy or alkoxy substituted double bonds are frequently used in de Mayo reaction sequences.⁸¹ This strategy was applied by Oppolzer and Godel to the total synthesis of (+)-longifolene (**289**), as depicted in Scheme 37.⁸² Intramolecular [2+2]-photocycloaddition of 1,3-dicarbonyl surrogate **286** resulted in caged intermediate **287**. Upon cleavage of the benzyloxycarbonyl protecting group (Z) at the tertiary alcohol by hydrogenolysis, retro-aldol reaction (the second step in the de Mayo reaction) afforded tricyclic **288** which could be proceeded to desired natural product **289**.



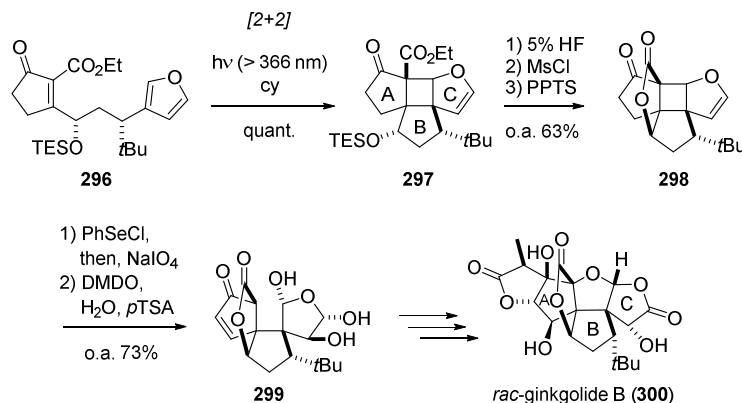
Scheme 37 Photochemical de Mayo Reaction in the Total Synthesis of (+)-Longifolene (**289**)

Another very elegant example for an intramolecular [2+2]-photocycloaddition is the racemic synthesis of (±)-hirsutene (**295**) by Mehta, outlined in Scheme 38.⁸³ Photocycloaddition precursor **292** was derived by Diels-Alder reaction of cyclopentadiene (**290**) and *para*-benzoquinone **291**. Irradiation of the [4+2]-cycloaddition product gave pentacyclic cubic intermediate **293**. Thermal cleavage of the cyclobutane resulted in the formation of the linear triquinane scaffold **294** of (±)-hirsutene (**295**). Overall, the sequence from **292** to **294** can be seen as stepwise photothermal metathesis.



Scheme 38 [2+2]-Photocycloaddition in Mehta's Synthesis of *rac*-Hirsutene (295)

Crimmins *et al.* also utilized a [2+2]-photocycloaddition/fragmentation sequence in their remarkable synthesis of ginkgolide B (**300**).⁸⁴ In their complex retrosynthetic considerations the intramolecular cycloaddition between an enone and a furan moiety was envisaged to stereoselectively form spiro-connectivity between three central rings (A, B and C). Thus, photoexcitation of **296** led to formation of tetracycle **297**, which was proceeded to **298** in three more steps (Scheme 39). After installation of the enone functionality via the α -phenylselenenyl ketone, the degradation of the cyclobutane ring was performed. Thus, epoxidation of the dihydrofuran ring in the presence of water was accompanied by a retro-aldol reaction resulting in cleavage of the cyclobutane ring in **299**, which was further converted to desired natural product **300**.



Scheme 39 [2+2]-Photocycloaddition/Fragmentation Sequence in the Total Synthesis of *rac*-Ginkgolide B (300)

A series of applications of photochemical reactions and the [2+2]-photocycloaddition has been discussed in this chapter, pointing out that these transformations are useful operations in total synthesis only requiring light as "reagent". Photochemical transformations, if designed carefully, are very selective, high yielding and atom-economic processes leaving no waste at the end of the reaction. As most of the presented syntheses were racemic, further elaboration of stereoselective versions of these reactions is desirable. The good experience with photochemical reactions in our group and the great potential of the [2+2]-photocyclization to construct cyclobutanes as intermediates in total synthesis or as structural motives of natural products, encouraged us to utilize this reaction in our efforts towards a total synthesis of bielschowskysin as outlined in the following chapters.

5. Bielschowskysin

The research group of A. Rodríguez has devoted a large part of its research to the investigation of marine invertebrates and natural products isolated from them. Trying to find new types of therapeutics and possible drug leads, the research group intensively studied extracts from specimen of soft and gorgonian corals. Starting with a publication in 2004, this research group has reported the isolation of more than 25 different cembranoid diterpenes from the gorgonian octocoral *Pseudopterogorgia kallos* (Bielschowsky, 1918). Extracts of this specimen, collected near the Old Providence Island located in the Southwestern Caribbean Sea off the coast of Colombia (Figure 4),⁸⁵ revealed the isolation of a furanocembranoid with an unprecedented carbon skeleton, bielschowskysin (**1**).⁸⁶



Figure 4 Location of Old Providence Island and a Photography of *Pseudopterogorgia kallos*

From 1.07 kg of air-dried animal specimen, 166 g of a crude dry extract were obtained by extraction with CH_2Cl_2 -MeOH (1:1). After a standardized extraction procedure and purification by flash chromatography followed by normal-phase HPLC, 39.6 mg of pure crystalline **1** were obtained, which equates 0.024 wt% of the crude extracts.

The carbon scaffold of bielschowskysin consists of a novel tricyclo[9.3.0.0^{2,10}]tetradecane ring system, which was confirmed by single-crystal X-ray diffraction analysis (Figure 5). Accompanied by 2D-NMR analysis, the relative configuration of the natural product could be assigned as depicted in Figure 5. Furthermore Rodríguez *et al.* proposed a new class of regular diterpenes, bielschowskyanes, named after the so far sole representative **1**.

The biogenesis of bielschowskysin is interrelated to the biosyntheses of its congeners and has therefore been treated in context with them in a previous section of this work.

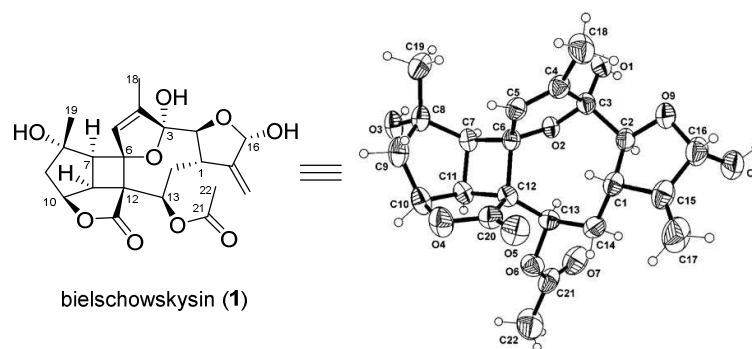


Figure 5 Crystal Structure of Bielschowskysin (1)

The unprecedented hexacyclic skeleton of **1** contains eleven stereogenic centers, seven of which are part of or contiguous to the cyclobutane ring. This cyclobutane ring is encompassed by a fused cyclopentane in the west (along C7-C11), a butyrolactone in the south (along C11-C12) and a spiro-2-oxo-dihydrofuran ring in the north-east (C6). The natural product with the molecular formula $C_{22}H_{26}O_9$ features one all-carbon quaternary center (C12) and a total of nine oxygen atoms. Thus, with a statistical carbon to oxygen ratio of 2.4:1 the level of oxygenation is remarkably high amongst diterpenes. These oxygen atoms are part of two cyclic hemiacetals at C3 and C16, an acetoxy-group at *R*-configured C13, a lactone bridging between C10 and C20, as well as a tertiary alcohol at *S*-configured C8.

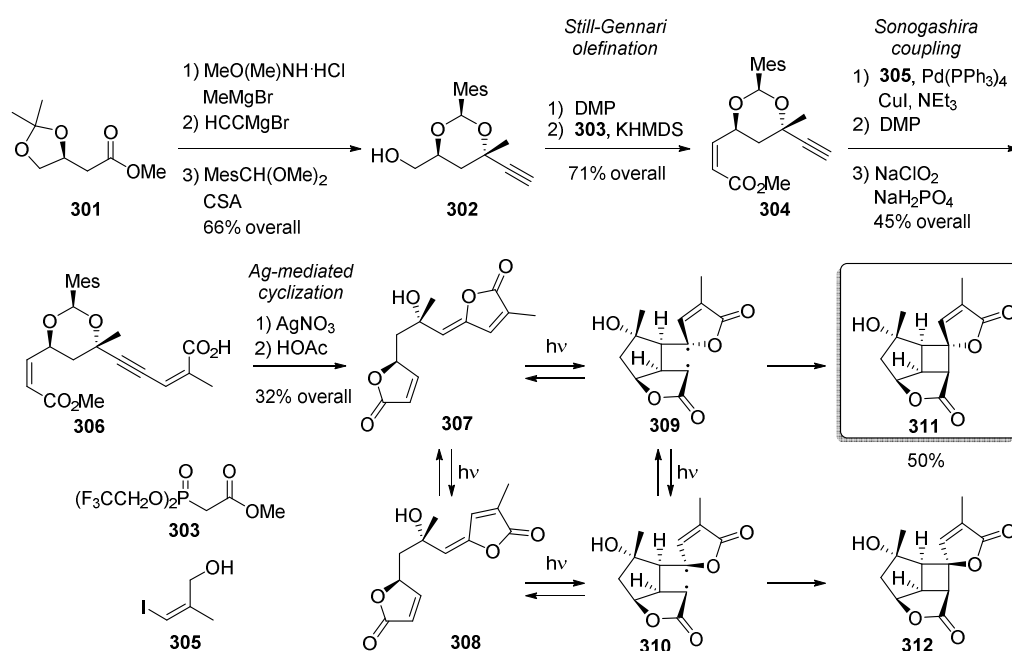
Besides the isolation and the assignment of the dense polycyclic structure, Rodríguez *et al.* reported significant biological activity of bielschowskysin (**1**). Compound **1** was found to exhibit *in vitro* cytotoxicity against two human cancer cell lines, EKVX nonsmall cell lung cancer ($GI_{50} < 50 \mu M$) and CAKI-1 renal cancer. More interestingly it showed antiparasmodial activity against *Plasmodium falciparum* ($IC_{50} = 10 \mu g/ml$), the number one malaria causing parasite. With an estimated number of 200 million global cases and an annual mortality of more than one million people according to the WHO, malaria is one of the most life-threatening diseases.⁸⁷ Additionally, the parasite, whose vector is the female anopheles fly, is well known to rapidly form resistances against common commercial drugs. Therefore, an enormous interest of the scientific community concerning the investigation of this disease and a pressing need for new therapeutics against *Plasmodium* species exists. With its remarkable antiparasmodial activity, bielschowskysin (**1**) may serve as possible drug against *P. falciparum* or at least as a promising drug lead. Thus, combined with its challenging structural features, **1** represents a very attractive target for synthetic chemists, which is reflected by the numerous contributions reported in literature. The following section is going to review all present synthetic efforts towards a total synthesis of bielschowskysin.

6. Previous Synthetic Efforts towards Bielschowskysin

In the following sections, synthetic efforts towards a total synthesis of bielschowskysin (**1**) by different research groups, including our own, are disclosed in full detail and in chronological order. To anticipate, though several approaches have been reported, no total synthesis was accomplished so far.

6.1. Sulikowski's Contribution⁸⁸

In 2006, only two years after the isolation of bielschowskysin (**1**) was reported, Sulikowski and coworker published a synthesis of a tetracyclic fragment of the natural product utilizing a biomimetic [2+2]-cycloaddition to construct the cyclobutane ring (Scheme 40). Their endeavors started with literature known ester **301**, which is readily available from malic acid. Introduction of an alkyne appendage via the Weinreb-amide⁸⁹ and transacetalization with mesitaldehyde dimethylacetal under acidic conditions furnished 1,3-dioxane **302** in good overall yield. Oxidation of the primary alcohol to the aldehyde was followed by a Still-Gennari olefination⁹⁰ with compound **303** providing (Z)-enoate **304** in good overall yield. Palladium mediated Sonogashira coupling⁹¹ with vinyl iodide **305** and a two-step oxidation sequence – DMP oxidation to the aldehyde followed by Pinnick oxidation⁹² – lead to carboxylic acid **306**. Silver-mediated cyclization of the carboxylic acid onto its conjugated triple-bond gave the alkylidene butenolide⁹³ followed by acidic cleavage of the mesitylene-acetal leading to formation of the second butenolide, providing [2+2]-photocyclization precursor **307** in low yield.

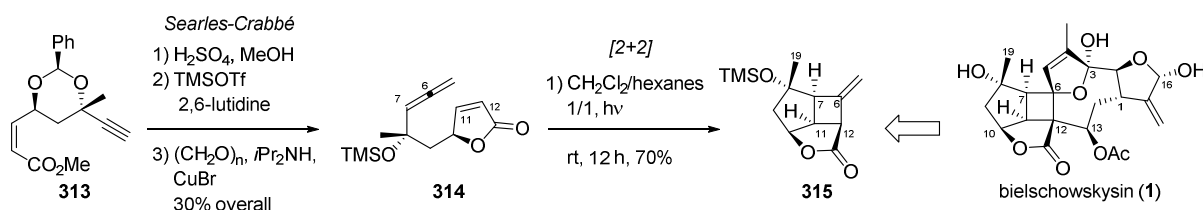


Scheme 40 Sulikowski's Efforts towards a Total Synthesis of Bielschowskysin (**1**)

After irradiation of a solution of **307** in CHCl_3 with a sun lamp for 2 h, a 3.6:1 mixture of **307** and diastereomeric **308** was observed. Prolonged irradiation resulted in a complex mixture of products. By replacing CHCl_3 with acetone as solvent the reaction was much cleaner allowing the isolation of a 5:1 diastereomeric mixture of [2+2]-photoadducts **311** and **312**. Sulikowski explained the diastereomeric outcome of the photocyclization by stereoelectronic effects and, according to the rule of five,⁷² by a two-step mechanism along with the formation of 1,4-diradical intermediates **309** and **310**, which are in equilibrium by bond rotation. Thus, with 1,4- and 1,6-dienes, as observed for **307**, parallel addition is favored, whereas 1,5-dienes are said to preferentially form the cross-adducts. This rule of five is regarded as general and applies where photosensitizers as acetone are used generating triplet-state excimers or exciplex.

6.2. Lear's Contribution⁹⁴

Three years after the publication of Sulikowski, Lear and coworkers reported a biomimetic intramolecular [2+2]-photocyclization generating the cyclobutane moiety in a north-south manner between an allene and a butenolide (Scheme 41). Their endeavors started from malic acid giving intermediate **313** via a similar reaction sequence as in the previous publication, with the only difference being a benzylidene instead of mesitylene acetal. Cyclization precursor **314** was obtained by acidic deprotection of the acetal accompanied by closure of the butenolide, protection of the tertiary alcohol and copper mediated allene-formation with formaldehyde via a protocol developed by Searles and Crabbé.⁹⁵ Irradiation of **314** in a 1:1 mixture of CH_2Cl_2 /hexanes with three conventional UV-lamps at a wavelength of 254 nm, appertaining to the UV-C range, gave the western bicyclo[3.2.0]heptane core **315** in regio- as well as diastereoselective manner and good yield.



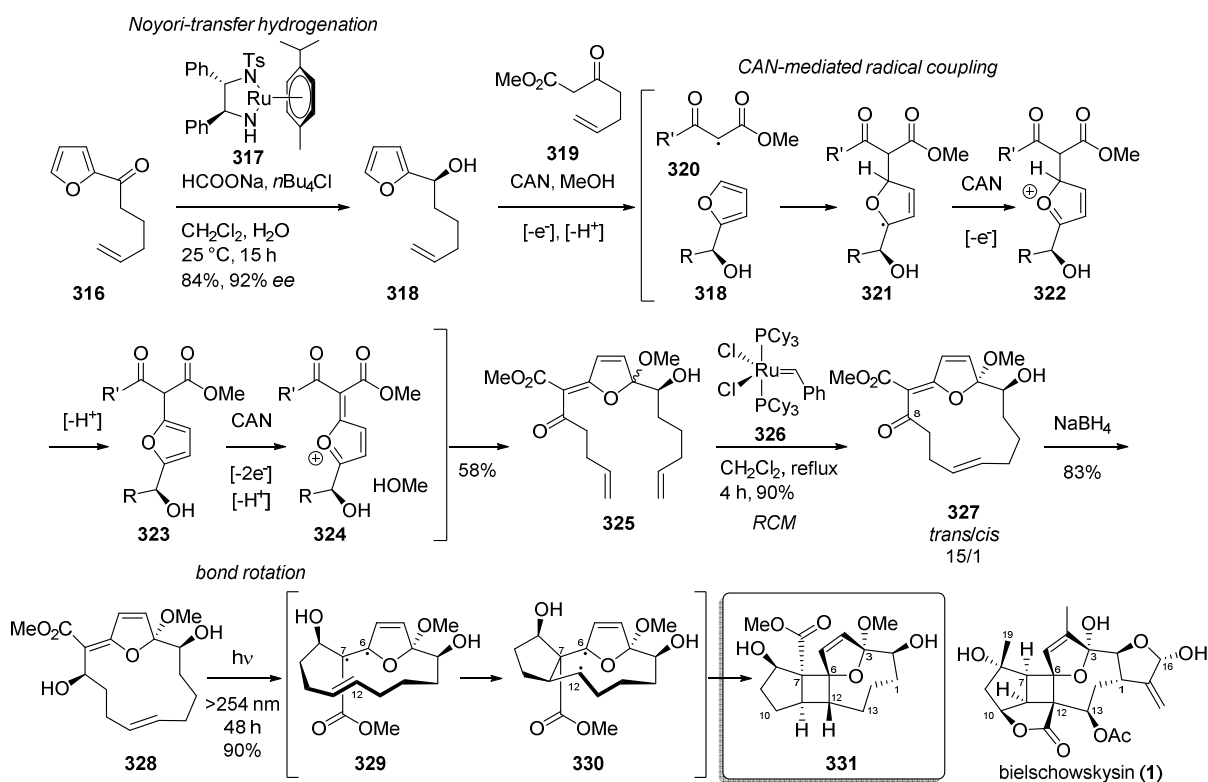
Scheme 41 Lear's Synthesis of the Bicyclo[3.2.0]heptane Core of Bielschowskysin (1)

Both so far discussed approaches formed the cyclobutane moiety via [2+2]-cycloadditions along $\Delta^{6,7}$ and $\Delta^{11,12}$. Though caged ring systems **311** and **315** contain five respectively four stereocenters with the correct configuration, both lack the crucial all-carbon quaternary at C12. Apparently, neither the research group of Sulikowski nor that of Lear was able to report an accomplished total synthesis of the target molecule so far, utilizing these advanced intermediates. Presumably, an elongation at C12

could not be carried out as deprotonation of this bridge-head atom might be unfeasible according to Bredt's rule.⁹⁶

6.3. Nicolaou's Synthetic Studies⁹⁷

Six years after the isolation of bielschowskysin (**1**), Nicolaou and coworkers published results on a biomimetic transannular [2+2]-photocycloaddition of a simplified macrocycle. Similar to the proposed biosynthesis (*vide supra*), irradiation of a macrocyclic enol ether cyclic ketal **328** should give the tricyclo[9.3.0.0^{2,10}]tetradecane ring system present in the natural product. The synthesis of the macrocyclic test system commenced with a stereoselective reduction of acyl furan **316**, utilizing Noyori's catalyst **317** and sodium formate (Scheme 42).⁹⁸ Consecutive treatment of a mixture of alcohol **318** and β -keto ester **319** with CAN resulted in diastereomeric enol ether **325** in modest yield.⁹⁹ Mechanistically, CAN initially forms radical **320**, which creates the $\Delta^{6,7}$ -bond. Thereafter, a series of SETs (Single Electron Transfers) and deprotonations give enol ether furanoxonium ion **324**, which is finally quenched by methanol, installing the ketal at C3. RCM reaction of the enantiopure α -epimer of **325** with Grubbs I catalyst **326** provided macrocycle **327** in good yield.



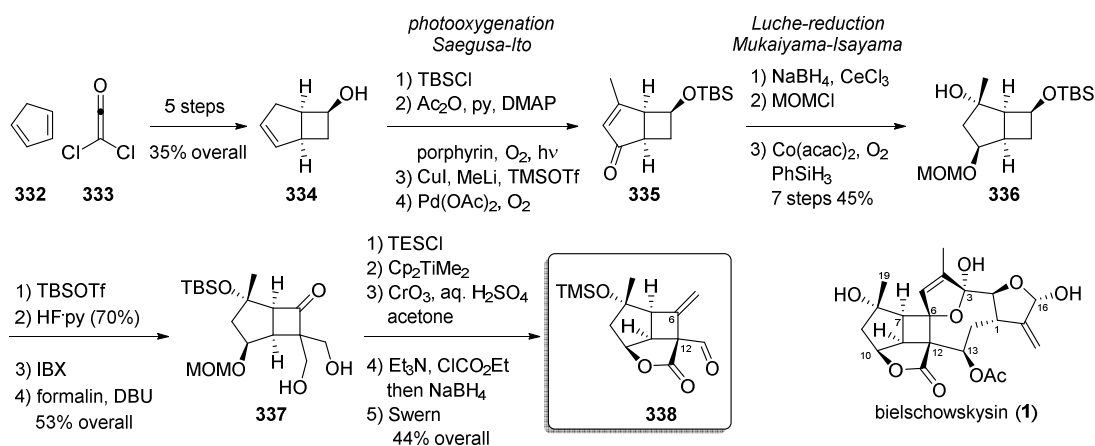
Scheme 42 Nicolaou's Synthetic Studies on Bielschowskysin (**1**)

Initial [2+2]-photocyclization attempts with **327**, bearing a carbonyl group at C8, failed, presumably because of too high ring strain imposed by the sp^2 -hybridized center. Thus, after NaBH_4 reduction to the corresponding alcohol, irradiation of **328** resulted in contraction of the macrocycle along C7-C11

and C6-C12 furnishing the carbocyclic core **331**, representing the carbon scaffold of bielschowskysin (**1**). Nicolaou proposed a stepwise mechanism for the [2+2]-photocycloaddition, explaining the stereochemical outcome of the reaction. Photoexcitation of the enol-ether ($\Delta^{6,7}$) is said to generate a diradical, which after bond rotation to **329** forms the C7-C11 σ -bond. Finally, recombination of diradical **330** between C6 and C12 forms the cyclobutane and installs the spiro-dihydrofuran. The unprecedented tricyclo[9.3.0.0^{2,10}]tetradecane ring system was accessed in only five steps from achiral acyl furan **316**, but a lot of work seems to be necessary to incorporate this fast sequence in a total synthesis of **1**. The accomplished model structure **331** lacks six carbon atoms (C15-17, C19-20) of the cembranoid carbon backbone, the all carbon quaternary C12 as well as oxygenation at C10, C13, C16 and C20. The ester-functionality at C7 is redundant, but may be necessary to stabilize the crucial enol-ether cyclic ketal **325** and to guarantee the CAN mediated C-C bond formation.

6.4. Mulzer's Non-Photochemical Approach^{100,101,102}

Very recently, our research group reported a non-photochemical approach towards bielschowskysin generating an advanced bicyclo[3.2.0]heptane fragment, which for the first time in literature contained the crucial all-carbon quaternary center at C12. This synthetic entry to the western fragment is not part of this PhD-thesis and is included in this section to complete all previous contributions towards a total synthesis of bielschowskysin (**1**).¹⁰²

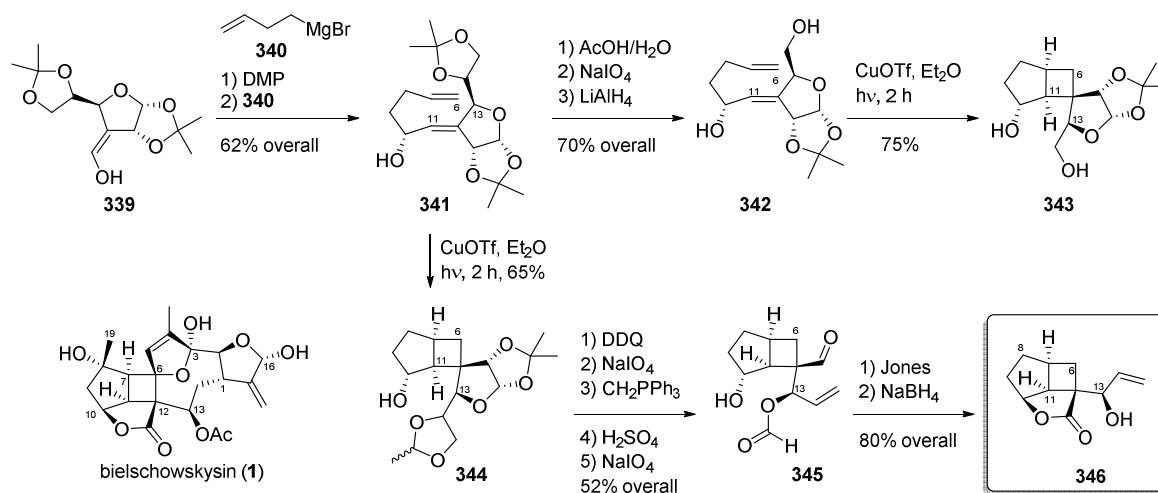


Scheme 43 Mulzer's Non-Photochemical Approach towards Bielschowskysin (**1**)

This approach, in contrast to the preliminary publications by other research groups, was not centered on a [2+2]-photocyclization to generate the cyclobutane moiety, but on the stepwise introduction of the necessary functionalities on secondary alcohol **334** (Scheme 43). This starting material - which itself is available by a thermal [2+2]-cyclization between cyclopentadiene (**332**) and 2,2-dichloroketene (**333**), reduction and enzymatic resolution (Lipase SAM-II) of the corresponding chloroacetate - is an old acquaintance in our research group and has previously been used in

synthetic efforts towards a total synthesis of providencin.⁴² However, enantiopure **334** was converted to α,β -unsaturated ketone **335** including a photooxygenation with molecular oxygen, acetic anhydride and porphyrin,¹⁰³ a 1,4-addition of a methyl-group and consecutive Saegusa-Ito oxidation.¹⁰⁴ After Luche-reduction¹⁰⁵ and protection of the secondary alcohol as a MOM-ether the stage was set for a Mukaiyama-Isayama oxidation-hydration reduction.¹⁰⁶ Thus, tertiary alcohol **336** was installed utilizing catalytic amounts of cobalt-catalyst, molecular oxygen and phenylsilane as hydrogen source. A series of protecting group operations, oxidation and double alkylation with formalin gave diol **337**. Protection of the free alcohols and olefination of the ketone with Petasis' reagent (Cp_2TiMe_2) was followed by treatment with Jones' reagent¹⁰⁷ leading to deprotection of the primary and secondary alcohols, oxidation to the diacid and *in situ* formation of the lactone. Finally, a reduction/oxidation sequence via a carbonate gave the desired bicyclo[3.2.0]heptane core **338** containing all-carbon quaternary C12 as well as an aldehyde at C13, suitable for further functionalization, in overall 16 steps and 11% yield from enantiopure **334**. Despite initial difficulties, this sequence evolved as a reliable and scalable route to the cyclobutane-moiety in our laboratory.

6.5. Ghosh's Contribution¹⁰⁸



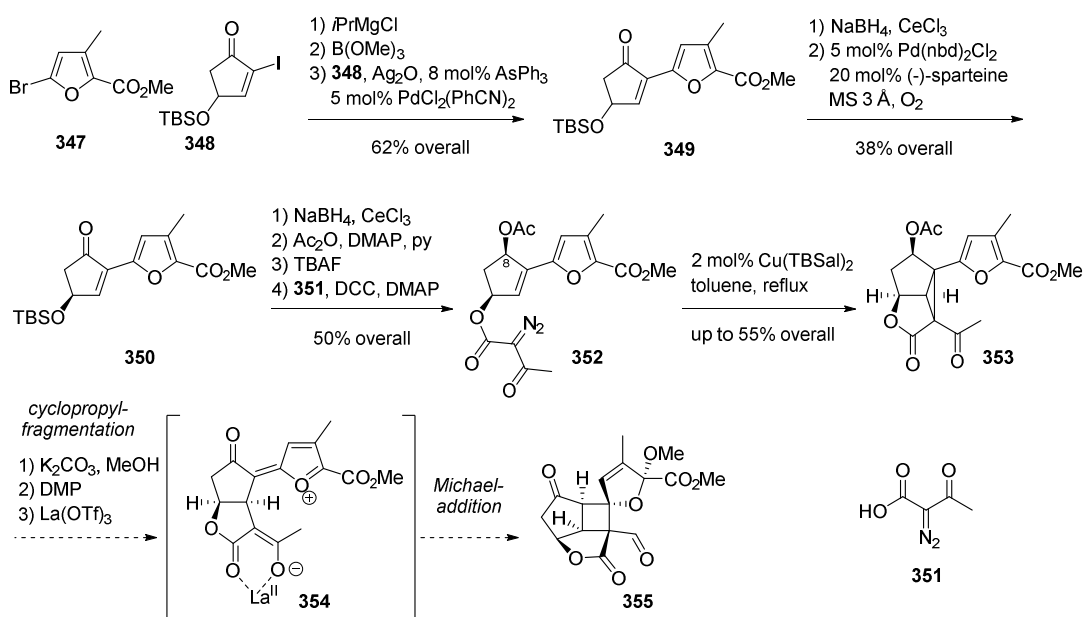
Scheme 44 Ghosh's Copper(I) Catalyzed [2+2]-Approach

While our first publication in Organic Letters¹⁰⁰ was published, the ongoing research by Gosh *et al.* was dealing with the installation of the all-carbon quaternary center and the introduction of the oxygen at C13 with the correct configuration. As depicted in Scheme 44, their synthesis started with known glucofuranose derivative **339**. Oxidation and chain elongation with homoallyl-magnesium bromide resulted in allylic alcohol **341**, which was converted to a first [2+2]-photocyclization precursor **342** within three more steps. The photocyclization to **343** was carried out with a 450 W Hanovia medium pressure mercury vapor lamp in the presence of CuOTf, proving the feasibility of the copper catalyzed [2+2]-photocyclization to install the C12 quaternary center. Alternatively, **341**

was directly subjected to irradiation, stereoselectively providing **344** in acceptable yield, accompanied by degeneration of one of the acetonides. Sequential selective degradation of one acetonide to the allylic formate and the other acetonide to an aldehyde gave intermediate **345**. Finally, Jones' oxidation¹⁰⁷ followed by substrate controlled stereoselective reduction of the C10 ketone and cleavage of the formate furnished Ghosh's bicyclo[3.2.0]heptane intermediate **346**. Though this caged fragment contains the C13 oxygen with correct configuration, it lacks crucial structural features such as the tertiary alcohol at C8 and a functionalization at C6 for the downstream introduction of any carbon appendage.

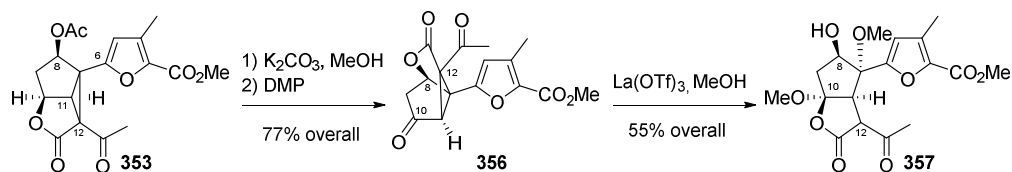
6.6. Stoltz' Attempts to form the Cyclobutane-Moiety¹⁰⁹

Early this year (2013), Stoltz and coworkers reported their endeavors to access the bicyclo[3.2.0]heptane core of bielschowskysin (**1**) via a Lewis acid mediated cyclopropane fragmentation/Michael addition sequence.¹¹⁰ Initially, furan **347** was converted to racemic α -furanyl enone **349** in four steps including a Suzuki-coupling¹¹¹ with iodide **348** (Scheme 45). Next, reduction of the enone under Luche conditions¹⁰⁵ and palladium(II) catalyzed oxidative kinetic resolution, utilizing (-)-sparteine as chiral ligand,¹¹² afforded optically active **350** in 40% yield and 93% *ee*. In the following, face-selective reduction, protecting group operations and esterification with 2-diazoacetoacetic acid (**351**) afforded diazo compound **352**. Cyclopropanation mediated by Cu²⁺ gave tetracycle **353**. Attempts to form a cyclopropane ring between $\Delta^{7,11}$ and C12 with numerous Cu and Ru catalysts with a ketone present at C8 proofed unsuccessful, presumably due to too little electron-density in the olefin.



Scheme 45 Stoltz' Attempted Construction of the Western Fragment of Bielschowskysin (**1**)

Next acetate cleavage and oxidation with DMP were scheduled. Subsequent Lewis-acid mediated cyclopropane-fragmentation to furanoxonium ion **354** was envisaged to be followed by an intramolecular Michael-addition between C6 and nucleophilic C12, forming the spiro dihydrofuran moiety and closing the cyclobutane ring in tetracycle **355**.



Scheme 46 Stoltz' Results towards a Total Synthesis of Bielschowskysin (1)

Unfortunately, the removal of the acetate protecting group in **353** resulted in a transesterification (Scheme 46). Thus by applying DMP, the alcohol at C10 in **356** was oxidized instead of C8. Finally, treatment with $\text{La}(\text{OTf})_3$ in methanol resulted in unexpected fused lactone **357**, the absolute configuration and connectivity of which was confirmed by X-ray analysis of a *p*-bromobenzoic ester analog.

7. Results

This year overall four articles concerning synthetic efforts towards a total synthesis of bielschowskysin have been submitted for publication by our research group. Two of them are still pending for publication. As substantial input was made to all of these manuscripts, they have been attached in this section with a short discussion ahead. The notation that has been used for structures, tables and schemes in the publications section is in analogy to the published articles for better understanding.

7.1. Photochemical and Thermal [2+2]-Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin^{101,102}

Farcet, J.-B.; **Himmelbauer, M.**; Mulzer, J. *Eur. J. Org. Chem.* **2013**, 4379.

Planning: Farcet, J.-B.; Himmelbauer, M.; Mulzer, J.

Experimentation: Farcet, J.-B.; Himmelbauer, M.

Manuscript preparation: Farcet, J.-B.; Himmelbauer, M.; Mulzer, J.

Discussion

Contributions have been made to the planning of the described approach. Preparation of all thermal [2+2]-precursors (Table 1, Entries 12-14) as well as the cycloaddition and the characterization of these intermediates have been carried out by Martin Himmelbauer (M. H.). Furthermore, the successful intermolecular photochemical [2+2]-cycloaddition furnishing tricycle **(-)-50** pointed out that ring strain was the reason for all unfruitful [2+2]-attempts carrying a carbonyl functionality at the later C20 of the desired natural product. At this time ongoing attempts to construct the cyclobutane moiety of the natural product by a photochemical [2+2]-cycloaddition between an allene and a butenolide¹¹³ as well as attempts utilizing a Pauson-Khand/Wolff rearrangement¹¹⁴ sequence (see section 7.3.) have been substantial for the successful cycloaddition of **(+)-52** to **(+)-53** (Table 1, Entry 17 and Scheme 5). Furthermore, significant contribution to the manuscript concerning phrasing of the article and the experimental procedures has been made by the author of this thesis.

Entries in the experimental section of the publication, which are irrelevant for this thesis and ascribed to the first author, have been omitted.

Photochemical and Thermal [2 + 2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin

Jean-Baptiste Farcet,^[a] Martin Himmelbauer,^[a] and Johann Mulzer*^[a]

Keywords: Total synthesis / Natural products / Terpenoids / Photochemistry / Oxidation

A bicyclic core fragment of the marine diterpenoid bielschowskysin has been synthesized. First, a large library of precursors for a photochemical [2 + 2] cycloaddition was prepared and tested, but with limited success. In the end, a ther-

mal [2 + 2] cycloaddition followed by appropriate regio- and stereocontrolled functionalization efficiently gave access to the desired bicyclo[3.2.0]heptane core. An optimized route to this remarkable molecular structure is presented.

Introduction

Furanocembranoids are diterpenoids that have, to date, been isolated exclusively from marine sources, in particular from gorgonian corals. The combination of significant bioactivity and interesting architectural structures has aroused the interest of the scientific community over the last decade. Notwithstanding their wide structural diversity, all members seem to be related and have biogenetic interconnections.^[1] Although bielschowskysin (**1**) has an uncommon bicyclo[3.2.0]heptane core,^[2] it probably originates from an

intramolecular [2 + 2] cycloaddition of an “ordinary” diterpenoid precursor.^[3]

It has been suggested that *exo* enol ethers or known cembranoids such as sethukarailide (**3**) or unnamed compound **4** are stable key intermediates in the biosynthesis of more complex polycyclic diterpenes.^[1] These metabolites could undergo transannular additions to form a furan-2(5*H*)-one moiety en route to more complex furanocembranoids such as bielschowskysin (**1**) and verrillin (**2**; Figure 1).

To design a biomimetic route to bielschowskysin (**1**), we investigated the suitability of a nucleophilic insertion into the furan ring of **5** as a potential precursor in the biosynthesis of bielschowskysin (Scheme 1). However, before starting with the construction of the complex and fully substituted furanocembranoid macrocycle, it seemed reasonable to test

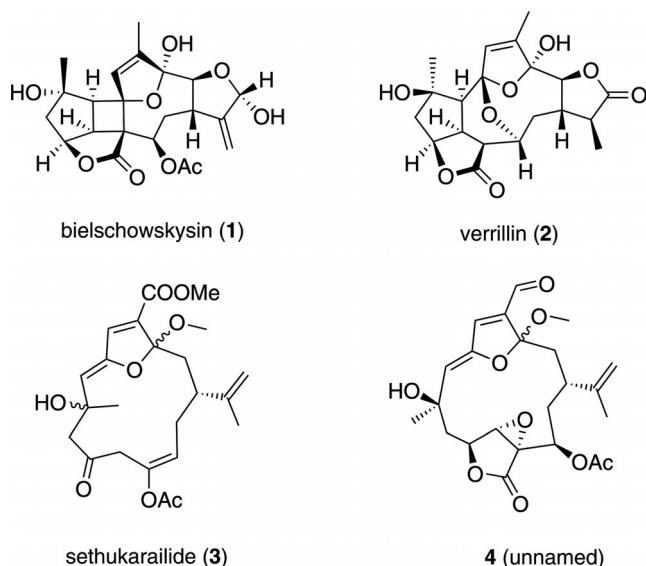
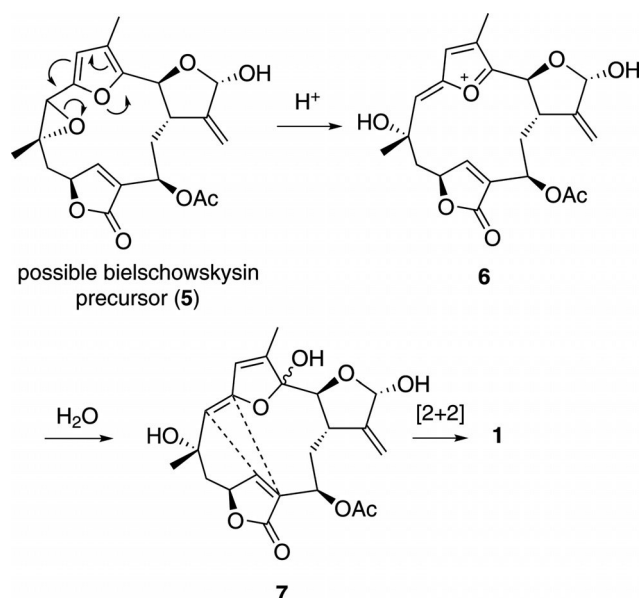


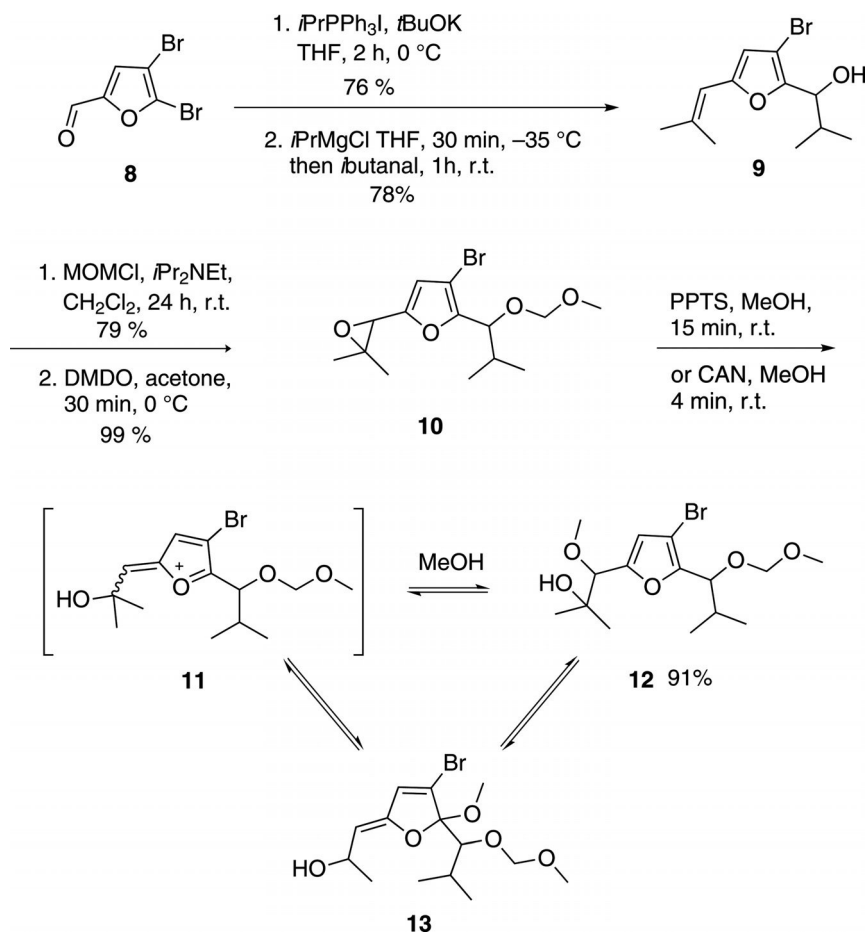
Figure 1. Furanocembranoid family members.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201300382>.



Scheme 1. Biosynthesis of bielschowskysin.



Scheme 2. Synthesis of a test system. CAN = ceric ammonium nitrate.

the cycloaddition in a model system. Epoxide **10** was chosen as a model for the reactivity of **5** (Scheme 2).

precursor (–)-**15**, readily available from furfuryl alcohol^[6] (Figure 2).

Results and Discussion

To prepare alcohol **9**, Wittig olefination of known aldehyde **8**^[4] was used to generate a trisubstituted double bond. This was followed by regioselective halogen–metal exchange with isopropylmagnesium chloride ($i\text{PrMgCl}$) and addition of the resulting intermediate to isobutyraldehyde to form secondary alcohol **9**. The hydroxy group was protected as a methoxymethyl (MOM) ether to mimic the acetal group in the target molecule. When a solution of dimethyldioxirane (DMDO) was added, oxirane **10** was the only product formed. By stirring **10** in methanol in presence of pyridinium *para*-toluenesulfonate (PPTS), compound **12** was isolated as single product after work-up and chromatographic purification (Scheme 2). This was not surprising, as Patenden and co-workers have already reported the formation of intermediate **13** and its rapid isomerization into **12**.^[5]

The lability of intermediate **13** discouraged us from pursuing this approach further. Instead, we considered the photo-[2 + 2] cycloaddition of enoate **14**, which could be accessed from known enantiomerically pure prostaglandin

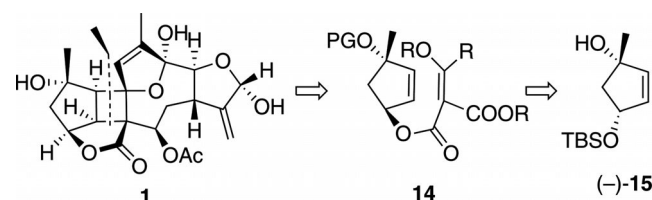


Figure 2. Retrosynthesis based on photo-[2 + 2] cycloaddition.

A protection–deprotection sequence was used to convert (–)-**15** into (+)-**16**, whose esterification with known carboxylic acid **17**^[7] under Mitsunobu conditions^[8] delivered ester (–)-**18**. However, the desired photo-cycloaddition to cyclobutane **19** was not observed under various photochemical activation conditions (Table 1, entry 3). Instead, malonate (–)-**20** was isolated in moderate yield (Scheme 3).

Next, we envisaged that compound (–)-**27**, containing a push–pull system, could be a suitable precursor for the photo-[2 + 2] reaction. Hence, mixed ester **22** was formed quantitatively from potassium malonate **21**^[9] and methyl 2-bromoacetate. Tetronic acid derivative **23** was obtained as

crystalline tetrabutyl ammonium salt from **22** upon treatment with TBAF in THF. Methylation followed by debenzoylation gave carboxylic acid **25** in an excellent overall yield

(Scheme 4). As the Mitsunobu protocol failed to deliver ester (–)-**27** directly from alcohol (+)-**16** and carboxylic acid **25**, the desired inversion was effected in a two-step pro-

Table 1. Screening of [2 + 2] cyclization substrates and conditions.

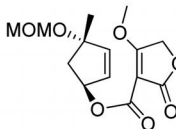
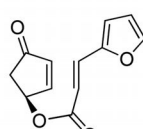
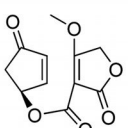
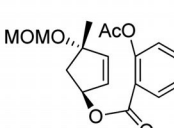
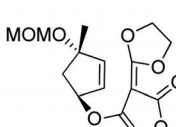
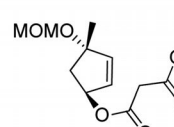
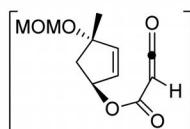
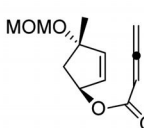
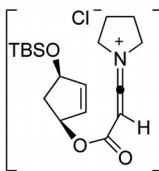
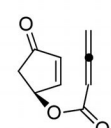
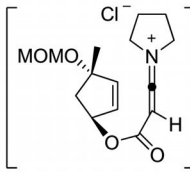
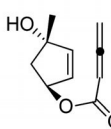
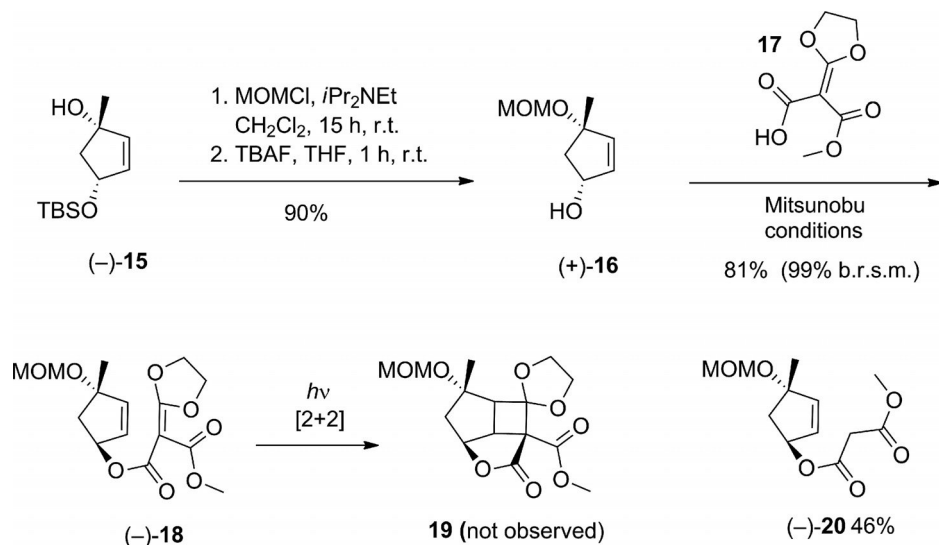
Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions ^[a]	Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions ^[a]
1	 (–)- 27 66% from (–)- 26 and 25	decomposition	A, B, C, F, G, H	10	 (–)- 41 71% from (–)- 29 ^[b] and 39 ^[b]	starting material recovered + decomposition	A, B, F
2	 (–)- 30 72% from (–)- 29 ^[b] and 25	decomposition	A, B	11	 (–)- 42 52%, 97% b.r.s.m. from (+)- 16 and aspirin	starting material recovered + decomposition	A, B, C, E
3	 (–)- 18 (81%, 99% b.r.s.m.) from (+)- 16 and 17	 (–)- 20 46%	A, B, C, F, G, H	12	 43 from (–)- 26 and suboxide	no reaction, then decomposition	J
4	 (–)- 32 87% from (+)- 16 and 31 ^[b]	decomposition	A, B, D, F, I, J	13	 46 from (–)- 45 ^[b]	no reaction, then decomposition	K
5	 (–)- 33 60% from (–)- 29 ^[b] and 31 ^[b]	decomposition	A, B, C, D, J	14	 48 from (–)- 26 and 47 ^[b]	no reaction, then decomposition	K
6	 (–)- 35 35% from (–)- 34 ^[b] and 31 ^[b]	decomposition	A, B				

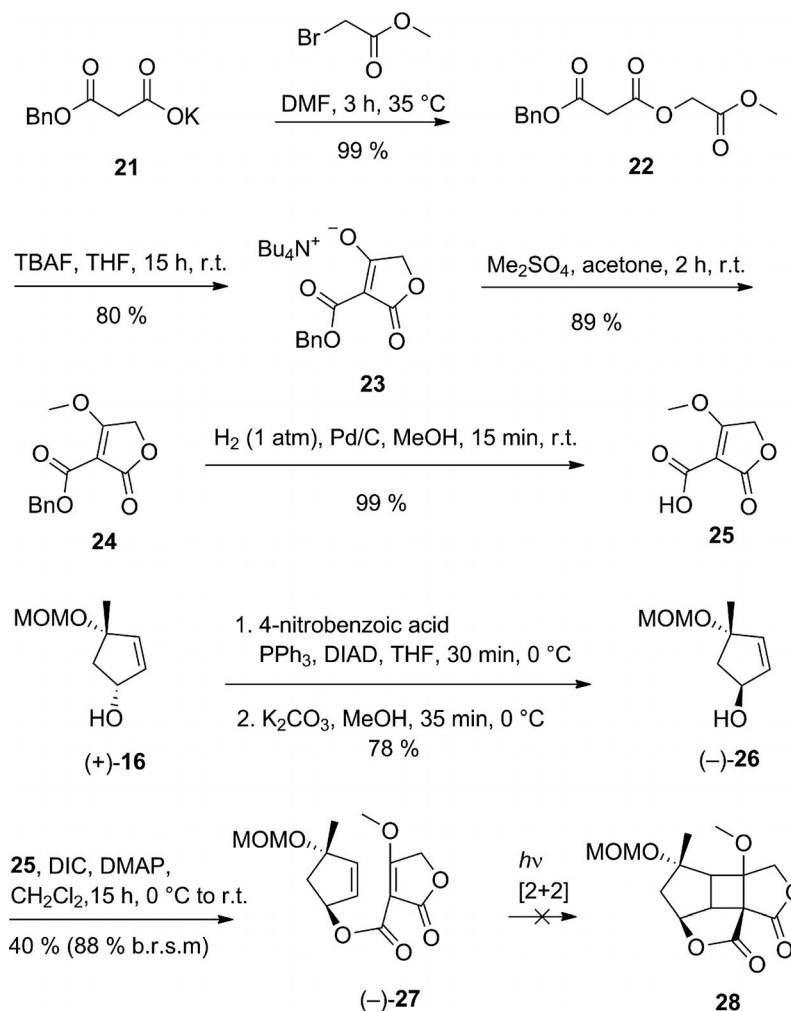
Table 1. (continued).

Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions ^[a]	Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions ^[a]
7	 (-)-36 62% from <i>para</i> - formaldehyde and (-)-32	decomposition	A, B, F, G, H	15	Intermolecular reaction from (-)-49 ^[b] and maleic anhydride	 (-)-50 58%	A
8	 (-)-38 58% from (+)-16 and 37 ^[b]	starting material recovered + decomposition	A, B, C, D, E, F, G, I	16	 (+)-51 83%, 2 steps from (+)-44 ^[b] and propargyl bromide	no reaction, then decomposition	A, B, D, F, H
9	 (-)-40 99% from (+)-16 and 39 ^[b]	starting material recovered + decomposition	A, B, F	17	 (+)-52 29%, 3 steps from (+)-44 ^[b] and propargyl bromide	 (+)-53 60%	G

[a] Irradiation conditions: A: UV-A lamps 8×16 W, acetone; B: UV-B lamps 8×16 W, acetone/ CH_2Cl_2 , 1:1; C: Sun lamp 750 W, duran filter, pentane/ CH_2Cl_2 , 1:1; D: Sun lamp 750 W, duran filter, acetone; E: Sun lamp 750 W, quartz filter, pentane/ CH_2Cl_2 , 1:1; F: Sun lamp 750 W, quartz filter, acetone; G: UV-B lamp 2×16 W, quartz filter, Et_2O ; H: UV-B lamp 2×16 W, quartz filter, Et_2O + cat. $\text{Cu}(\text{OTf})_2$; I: Sun lamp 750 W, quartz filter, Et_2O + cat. $\text{Cu}(\text{OTf})_2$; J: THF, 0°C 90 min, then room temp. 6 h; K: DCE, room temp. 6 h, then reflux 2 h. [b] For preparation and characterization, see Supporting Information. [c] Formed in situ, not isolated.



Scheme 3. Synthesis of [2 + 2] precursor (-)-18. TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; b.r.s.m. = based on recovered starting material.



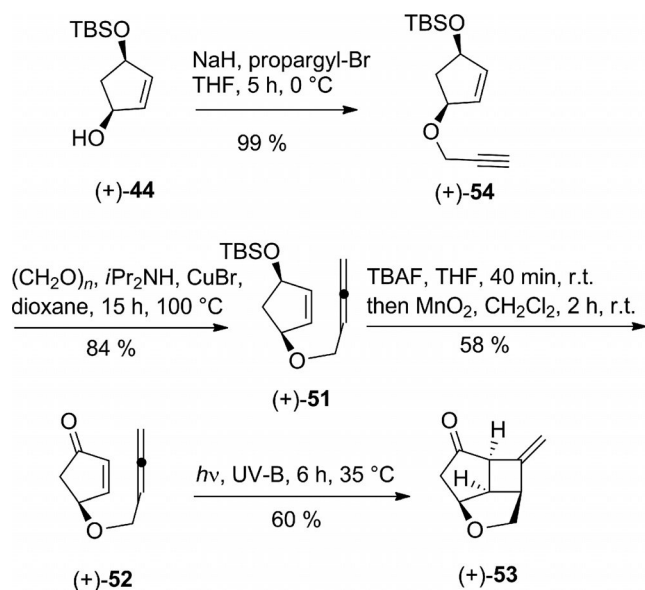
Scheme 4. Synthesis of [2 + 2] precursor (–)-27. DIAD = diisopropyl azodicarboxylate; DIC = *N,N'*-diisopropylcarbodiimide; DMAP = 4-dimethyl aminopyridine.

cedure to give (–)-26 in good yield. Carbodiimide-mediated esterification eventually gave [2 + 2] precursor (–)-27. Unfortunately, this substrate only underwent decomposition under photo-cyclization conditions, and polycycle 28 was not formed (Scheme 4 and Table 1, entry 1). Nevertheless, a broad screening of potential photo-[2 + 2] substrates under various irradiation conditions was initiated (Table 1).

When enone (–)-30 (Table 1, entry 2) was used to promote a stepwise ionic mechanism via zwitterionic intermediates, decomposition occurred after a few minutes of UV irradiation (conditions A and B). Similarly, irradiation of buta-2,3-dienoic esters (–)-32, (–)-33, (–)-35, (–)-36, and (–)-38 led to the formation of complex product mixtures, none of which contained the desired tricycle (Table 1, entries 4–8). Furylacrylic esters (–)-40 and (–)-41 (Table 1, entries 9 and 10) were more stable to irradiation, but under various conditions (conditions A, B, and F) only the starting material was recovered. Substituted phenyl ester (–)-42 (Table 1, entry 11) did not lead to cycloaddition, even after a prolonged irradiation time. Our attention turned to thermally driven [2 + 2] cycloadditions, but no product was de-

tected when ketene 43 or ketene iminium salts 46 and 48 (Table 1, entries 12–14) were stirred at room temperature or even heated to reflux.

On reviewing these results, we suspected that cycloaddition could have been prevented not only by electronic effects, but also by conformational issues. Hence, an intermolecular cycloaddition was performed between alkene (–)-49 and an excess of maleic anhydride (Table 1, entry 15) in acetone under UV-A irradiation (conditions A). Tricycle (–)-50 was formed as a single isomer in satisfactory yield. Next, the carbonyl group was exchanged for a methylene group to give more flexibility to the allenic side-chain. Thus, alcohol (+)-44^[6] was alkylated with propargyl bromide in quantitative yield. A Searles–Crabbé reaction^[10] gave desired allene (+)-51, which was unreactive to photoirradiation (conditions A, B, D, F, H, Table 1, entry 16, Scheme 5). However, when (+)-51 was converted into enone (+)-52 by TBAF deprotection and oxidation of the allylic alcohol, irradiation of (+)-52 with UV-B light led to tricycle (+)-53 as a volatile liquid in good overall yield (Table 1, entry 17, Scheme 5).



Scheme 5. Synthesis of polycycle (+)-53.

From this screening, we concluded that precursors with a carbonyl group in the position α to the reacting double bond were unsuitable for intramolecular [2 + 2] photocyclization under various conditions. Nevertheless, an intermolecular cycloaddition seemed possible. More interestingly, we showed that an intramolecular cycloaddition between homoallylic ether and enone indeed gave tricyclic core (+)-53. While further investigations to elaborate this intermediate were underway, we capitalized on the abundant non-photochemical availability of functionalized bicyclo[3.2.0] systems such as (+)-56.^[11] This compound was used in a stereocontrolled synthesis of a fully substituted western fragment (–)-55^[2d] of bielschowskysin (**1**), including its all-carbon quaternary center (Figure 3). Here, we disclose the full details of this route, as well as optimized procedures for nine steps of the sequence.

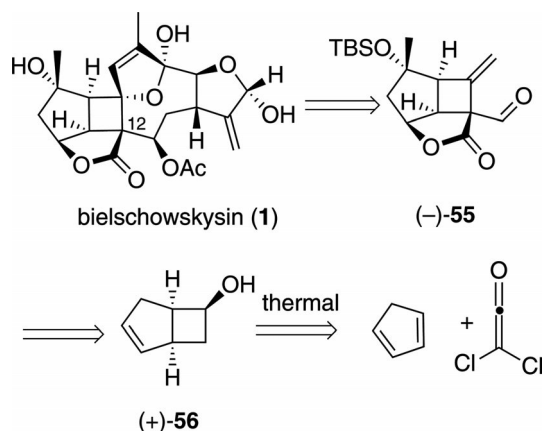
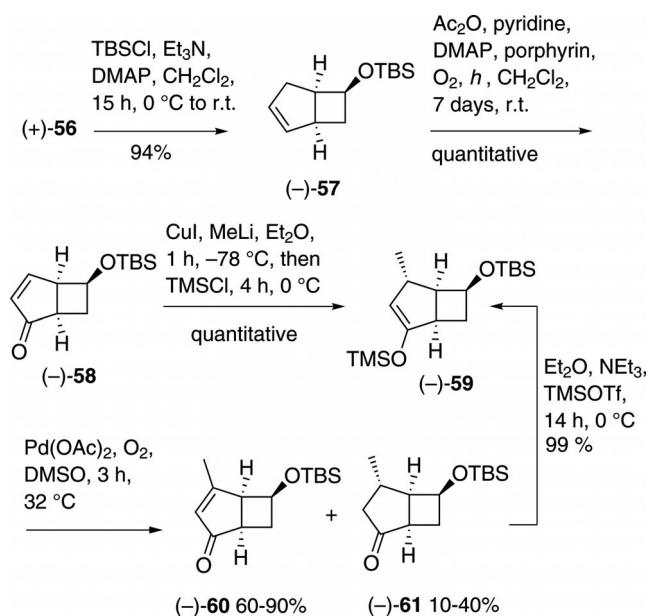


Figure 3. Retrosynthesis based on a non-photochemical approach.

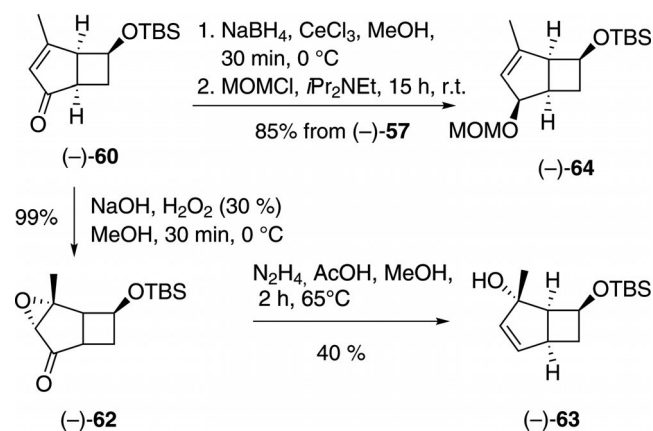
Our synthesis started with TBS protection of enantiomerically enriched (+)-56, which was obtained in a four-step sequence from commercially available racemic mate-

rial,^[11] to give (–)-57. To functionalize the five-membered ring, photooxygenation^[12] with molecular oxygen in the presence of acetic anhydride and base was chosen. This oxidation was exceptionally easy to carry out, even on a molar scale, and produced α,β -unsaturated ketone (–)-58 with high regioselectivity (isomeric ratio: 20:1). Conjugate addition of dimethyl cuprate and trapping of the enolate with trimethylsilyl chloride (TMSCl) gave enol ether (–)-59, which was used in a Saegusa–Ito oxidation^[13] to provide enone (–)-60. The success of this oxidation crucially depended on the use of dimethyl sulfoxide (DMSO) as solvent and molecular oxygen as co-oxidant. Otherwise, the reaction was difficult to scale up and suffered from inconsistent yields. Moreover, TMS enol ether (–)-59 was prone to desilylation to form undesired ketone (–)-61. It was shown that this side-reaction was highly dependent on the batch of palladium(II) acetate used and, on a larger scale, the ratio of products (–)-60 and (–)-61 was not reproducible. However, it was possible to recover (–)-61 by chromatography, and to reconvert it into (–)-59 in quantitative yield. This procedure led to a 10% increase in the overall yield (Scheme 6).



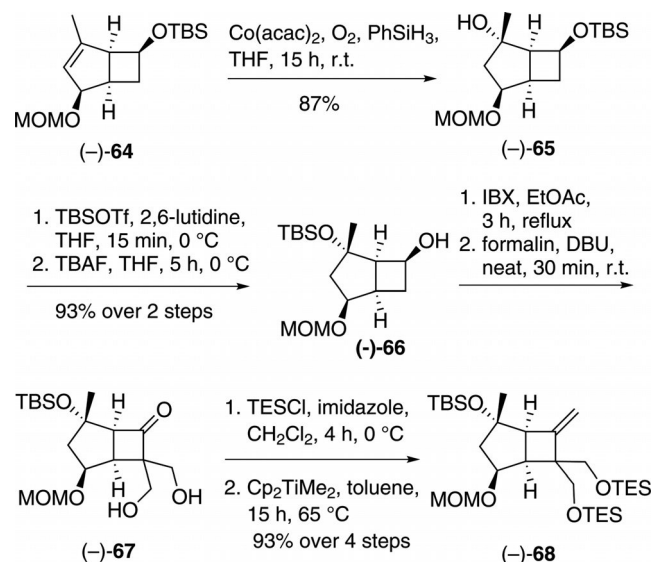
Scheme 6. Synthesis of enone (–)-60. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Taking advantage of the “open-book” geometry of bicyclic (–)-60, the enone was epoxidized diastereoselectively under Scheffer–Weitz conditions.^[14] No conditions could be found for the opening of epoxide (–)-62 to install the required tertiary alcohol. For instance, a Wharton transposition^[15] did provide allylic alcohol (–)-63, but it turned out to be highly unstable and impractical for the synthesis. Alternatively, the carbonyl group was reduced diastereoselectively under Luche conditions,^[16] and the product was protected with a MOM group to give compound (–)-64. This sequence could be carried out in 85% overall yield from (–)-57 (Scheme 7).



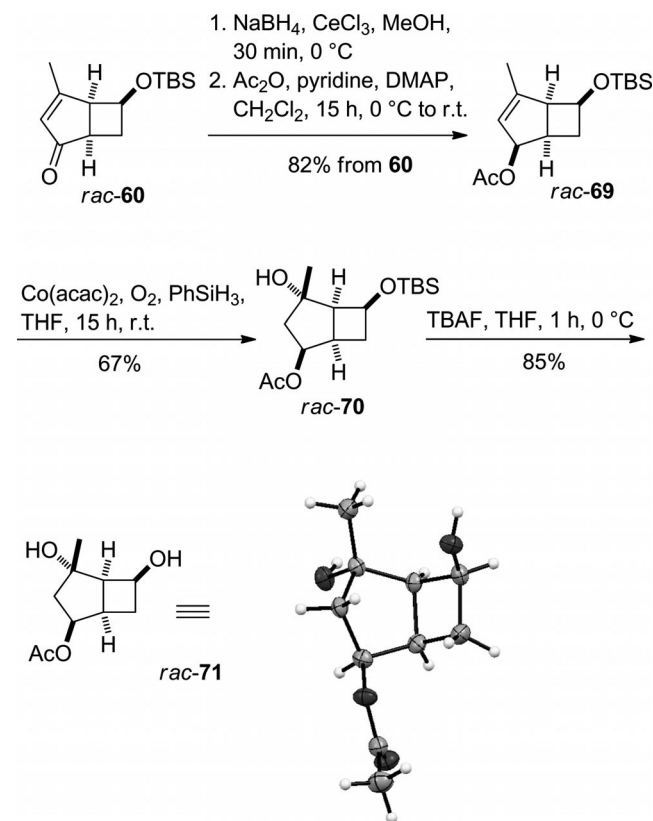
Scheme 7. Synthesis of enone (–)-63 and (–)-64.

Molecular oxygen, a catalytic amount of a cobalt complex, and phenylsilane promoted the Mukaiyama–Isayama oxidation–reduction–hydration sequence^[17] in a regio- and stereoselective manner, leading to tertiary alcohol (–)-65. The yield could be increased from 64 to 87% by using a 24 h aqueous workup, a time that presumably allowed the peroxide intermediate to rearrange and hydrolyse completely. After an optimized protection–deprotection sequence, the five-membered ring in bicycle (–)-66 was appropriately substituted, and the installation of the quaternary center could be envisaged (Scheme 8). Oxidation with 2-iodoxybenzoic acid (IBX) smoothly formed the ketone, which underwent a double aldol reaction with formalin to deliver key intermediate (–)-67. Triethylsilyl (TES) protection of the two primary alcohols and Petasis' olefination gave (–)-68 (Scheme 8). The four-step sequence from (–)-66 to (–)-68 was performed with a single final purification step, and allowed a quick and high-yielding substitution of the bicycle.



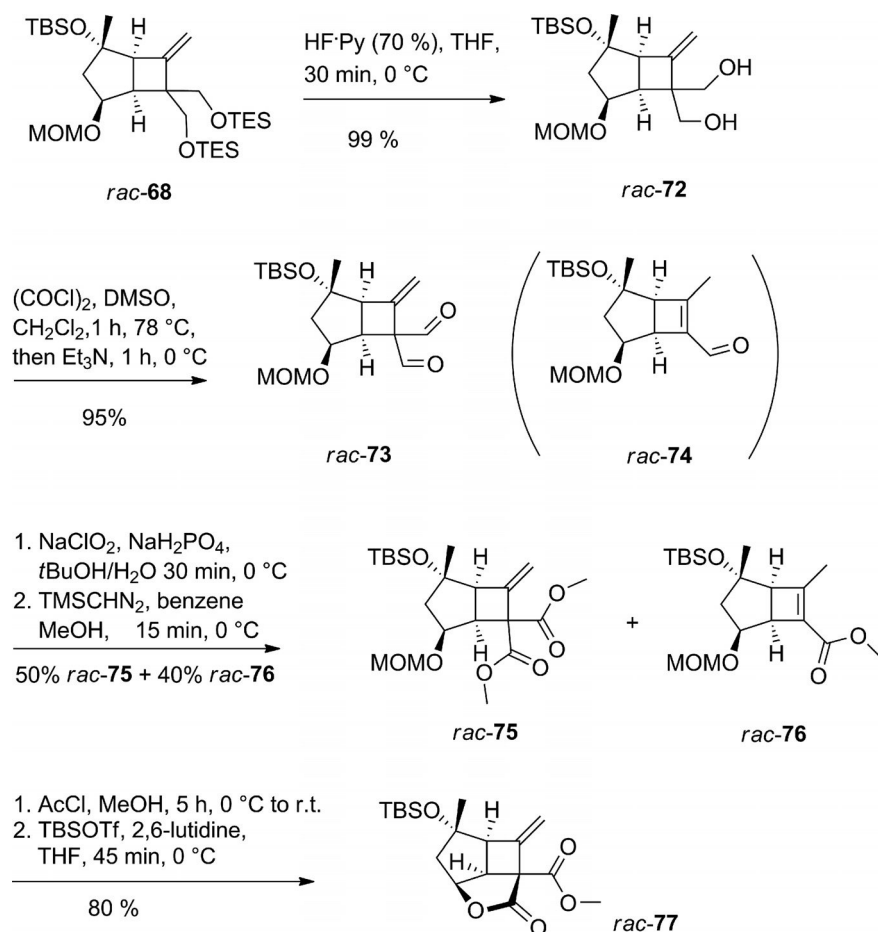
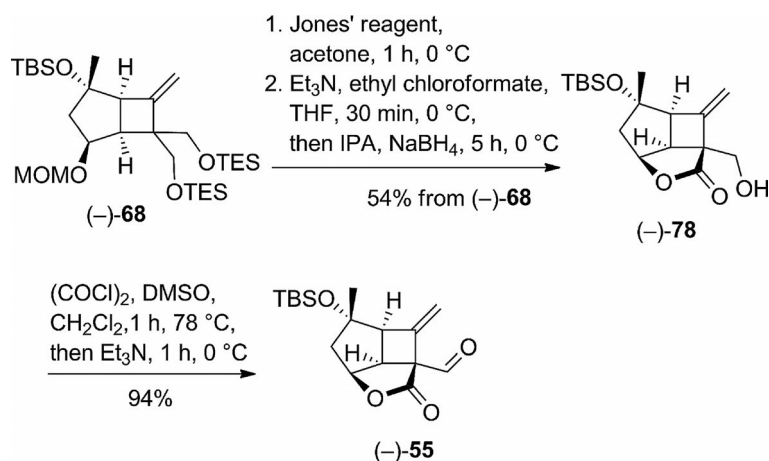
Scheme 8. Synthesis of olefin (–)-68. acac = acetylacetonate; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Cp = cyclopentadiene.

To assign the relative configuration by single crystal diffraction, racemic crystalline acetoxy diol *rac*-71 was prepared by an analogous sequence (Scheme 9).^[18]

Scheme 9. Synthesis and X-ray structure of *rac*-71.

To form lactone *rac*-77, the two TES protecting groups were removed to give diol *rac*-72. Subsequent Swern oxidation led to dialdehyde *rac*-73 in excellent yield. However, during evaporation of the volatiles at bath temperatures >30 °C, a decarbonylation with concomitant double-bond shift was observed, which led exclusively to compound *rac*-74. Similarly, Pinnick oxidation of crude dialdehyde *rac*-73 and subsequent esterification of the product with trimethylsilyl diazomethane (TMSCHN₂) gave dimethyl ester *rac*-75 and decarboxylated methyl ester *rac*-76 as a nearly 1:1 mixture. Gratifyingly, dimethyl ester *rac*-75 could be transformed into lactone *rac*-77 in good yield (Scheme 10).

After some experimentation, an optimized cascade reaction was developed to create the tricyclic core of bielschowskysin directly from (–)-68. Thus, under the acidic conditions of the Jones' reagent, deprotection of the two TES protecting groups was followed by oxidation of the resulting diol to the dicarboxylic acid. Concomitantly, the MOM protecting group was removed, and lactonization of the resulting alcohol with the *cis* carboxy group occurred spontaneously. Without purification, the free carboxylic acid was transformed into a mixed carbonate with ethyl chloroformate, and this product was reduced with NaBH₄ to give alcohol (–)-78 in 54% overall yield over eight transformations (>92% each) starting from (–)-68. Swern oxidation gave desired aldehyde (–)-55 (Scheme 11).

Scheme 10. Synthesis of bicyclo[3.2.0]heptane lactone *rac*-77.Scheme 11. Synthesis of aldehyde (–)-55. Jones' reagent = CrO₃, H₂SO₄ in water; IPA = isopropyl alcohol.

Conclusions

After screening various substrates to obtain the bicyclo[3.2.0]heptane core of bielschowskyisin by [2 + 2] photocycloaddition, we developed a stereoselective and optimized

scalable non-photochemical route to aldehyde (–)-55 [$>30\%$ overall yield from known alcohol (+)-56]. This tricyclic building block bears promising functional groups for connection with an eastern fragment and completion of the total synthesis of bielschowskyisin.

Experimental Section

General Remarks: All moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under a slight argon overpressure. All solvents (except dichloromethane and methanol) were purchased as the highest available grade from Sigma–Aldrich, Acros Organics, or Fischer Chemicals. Anhydrous dichloromethane was purified by filtration through alumina under argon immediately before use. Methanol was heated at reflux for several hours over sodium and then distilled. NEt_3 , $i\text{Pr}_2\text{NEt}$, and 2,6-lutidine were distilled from CaH_2 before use. All other reagents were used as received from Sigma–Aldrich, Acros Organics, Fischer Chemicals, TCI, or ABCR, unless otherwise stated. Preparative column chromatography was performed with silica gel 60 from Merck (0.040–0.063 μm , 240–400 mesh). NMR spectra were measured with Bruker AV400, DRX400, or DRX600 spectrometers. Chemical shifts are given in ppm and are referenced to the solvent residual peaks (CDCl_3 : ^1H , $\delta = 7.26$ ppm; ^{13}C , $\delta = 77.16$ ppm). Infrared spectra were recorded as thin films of pure products on an ATR-unit with a Bruker Vertex 70 instrument. High-resolution mass spectra were measured with a Bruker MaXis (ESI-TOF) instrument at a resolution of 10000. A P341 Perkin–Elmer polarimeter equipped with in a 10 cm cell and a Na lamp (589 nm) was used for the measurement of optical rotation.

1-[3-Bromo-5-(2-methylprop-1-en-1-yl)furan-2-yl]-2-methylpropan-1-ol (9): Potassium *tert*-butoxide (5.7 g, 51.0 mmol) was added in one portion to a solution of isopropyl(triphenyl)phosphonium iodide (2.5 g, 56.7 mmol) in THF (200 mL) at 0 °C. 4,5-Dibromofuran-2-carbaldehyde (**8**; 7.20 g, 28.4 mmol) in THF (50 mL) was added rapidly to the prepared solution. The mixture was stirred at 0 °C for 60 min, after which TLC indicated complete consumption of the starting material. Water (300 mL) was then added. The dark solution was filtered through a pad of Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (2 $\times$ 150 mL). The combined organic extracts were washed with brine (50 mL) and dried with MgSO_4 . SiO_2 (25 g) was added to the solution before it was concentrated under reduced pressure. The material was purified by column chromatography (SiO_2 , hexane) to give a light yellow oil (6.03 g, 76%) that darkened within a few hours. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.20$ (s, 1 H), 5.95 (m, $J = 1.1$ Hz, 1 H), 1.94 (s, 3 H), 1.90 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 155.6$, 138.3, 120.2, 113.1, 111.9, 102.8, 27.0, 20.2 ppm. HRMS (EI): calcd. for $\text{C}_8\text{H}_8\text{OBr}_2$ [$\text{M}]^+$ 277.8942; found 277.8940. IR: $\tilde{\nu} = 1780$, 1553, 1440, 1267, 1205, 951, 935, 925, 788, 586 cm^{-1} . R_f (hexane/EtOAc, 20:1): 0.93.

A solution of dibromoalkene (5.3 g, 19.1 mmol) in THF (200 mL) was cooled to –35 °C. A solution of isopropylmagnesium chloride (2 M in ether; 11.5 mL, 23.0 mmol) was added slowly, and the resulting solution was stirred at the same temperature for 60 min. Freshly distilled isobutanal (2.28 mL, 24.8 mmol) was added, and the reaction mixture was stirred for 4 h at –35 °C, and then it was allowed to warm to room temp. over 3 h. NH_4Cl (saturated aq.; 40 mL) was added, and the aqueous phase was extracted with EtOAc (3 $\times$ 45 mL). The combined organic extracts were washed with brine (20 mL) and dried with MgSO_4 . After removal of the solvent, the crude product was purified by flash chromatography (SiO_2 , hexane/EtOAc, 20:1) to give **9** (4.07 g, 78%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.15$ (s, 1 H), 6.00–5.97 (m, 1 H), 4.41 (dd, $J = 5.5$, $J = 8.3$ Hz, 1 H), 2.21–2.09 (m, 1 H), 1.95 (s, 3 H), 1.91 (d, $J = 4.6$ Hz, 1 H), 1.90 (s, 3 H), 1.09 (d, $J = 6.6$ Hz, 3 H), 0.82 (d, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 153.1$, 149.7, 137.6, 113.9, 110.6, 99.3, 71.7, 33.8, 27.2, 20.4, 19.1, 18.6 ppm. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{Br}$ [$\text{M}]^+$

272.0412; found 272.0413. IR: $\tilde{\nu} = 3370$, 2963, 2872, 1468, 1384, 1142, 1013, 844, 633, 537 cm^{-1} . R_f (hexane/EtOAc, 10:1): 0.21.

3-Bromo-5-(3,3-dimethyloxiran-2-yl)-2-[1-(methoxymethoxy)-2-methylpropyl]furan (10): MOMCl (3.77 mL, 41.7 mmol) was added dropwise to a solution of alcohol **9** (3.8 g, 13.9 mmol) in DIPEA (10 mL) and CH_2Cl_2 (20 mL) at 0 °C. A few crystals of NaI were added, and the solution was stirred for 1 h at 0 °C, and then for a further 20 h at room temp. Water (100 mL) and EtOAc (100 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (3 $\times$ 50 mL), and the combined organic extracts were washed with brine (30 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 , hexane/EtOAc, 20:1) to give the MOM-protected alkene (3.47 g, 79%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.15$ (s, 1 H), 6.02–5.98 (m, 1 H), 4.55 (d, $J = 6.8$ Hz, 1 H), 4.50 (d, $J = 6.9$ Hz, 1 H), 4.34 (d, $J = 8.9$ Hz, 1 H), 3.36 (s, 3 H), 2.31–2.17 (m, 1 H), 1.95 (s, 3 H), 1.90 (s, 3 H), 1.11 (d, $J = 6.6$ Hz, 3 H), 0.79 (d, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 153.5$, 147.8, 137.6, 114.0, 110.3, 101.7, 94.5, 74.8, 55.8, 32.3, 27.2, 20.4, 19.7, 18.7 ppm. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_3\text{Br}$ [$\text{M}]^+$ 316.0674; found 316.0665. IR: $\tilde{\nu} = 2959$, 1471, 1386, 1154, 1098, 1032, 971, 923, 784, 561 cm^{-1} . R_f (hexane/EtOAc, 10:1): 0.43.

A solution of dimethyldioxirane (2.8 mL, 0.13 mmol) was added to a magnetically stirred solution of the MOM-protected alkene (40 mg, 0.13 mmol) in acetone (1.3 mL) at 0 °C. After 30 min at 0 °C, the solvent was removed to give pure oxide **10** (42 mg, 99%) as a 1:1 mixture of diastereoisomers. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.25$ and 6.24 (2 d, $J = 0.5$ Hz, 1 H), 4.56–4.50 (m, 2 H), 4.33 (d, $J = 9.0$ Hz, 1 H), 3.71 and 3.70 (2 s, 1 H), 3.36 and 3.34 (2 s, 3 H), 2.28–2.17 (m, 1 H), 1.44 and 1.43 (2 s, 3 H), 1.30 (s, 3 H), 1.10 (2 d, $J = 6.5$ Hz, 3 H), 0.79 and 0.76 (2 d, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 151.3$, 150.3, 111.8 and 111.7, 100.8, 94.7 and 94.6, 74.9, 61.7 and 61.7, 58.7 and 58.6, 55.9 and 55.8, 32.3, 24.2, 19.7 and 19.6, 18.7, 18.6 ppm. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_5\text{BrNa}$ [$\text{M} + \text{MeOH} + \text{Na}]^+$ 387.0783; found 387.0796. IR: $\tilde{\nu} = 2977$, 2871, 1676, 1461, 1370, 1099, 1010, 979, 840, 653 cm^{-1} . R_f (hexane/EtOAc, 5:1): 0.34.

1-[4-Bromo-5-[1-(methoxymethoxy)-2-methylpropyl]furan-2-yl]-1-methoxy-2-methylpropan-2-ol (12)

Procedure A: PPTS (1 mg) was added to a solution of epoxide **10** (26 mg, 0.08 mmol) in MeOH (0.8 mL), and the solution was stirred at room temp. for 15 min. The reaction mixture was quenched with water (1.5 mL) and extracted with EtOAc (3 $\times$ 5 mL). The combined organic extracts were washed with brine (5 mL), dried with MgSO_4 , filtered, and concentrated. The residue was purified over a short column (SiO_2 , hexane/EtOAc, 4:1) to give undesired tertiary alcohol **12** (26 mg, 91%) as a 1:1 mixture of diastereoisomers.

Procedure B: Cerium ammonium nitrate (90 mg, 0.16 mmol) was added to a solution of epoxide **10** (13.6 mg, 0.04 mmol) in MeOH (2.7 mL). The reaction mixture was stirred for 4 min before being cautiously quenched with sodium hydrogen carbonate (saturated aq.; 2 mL). The mixture was diluted with water (5 mL) and EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2 $\times$ 20 mL). The combined organic extracts were dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (SiO_2 , hexane/EtOAc, 4:1) to give undesired tertiary alcohol **12** (13.5 mg, 91%) as a 1:1 mixture of diastereoisomers. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.36$ and 6.34 (2 s, 1 H), 4.55 (d, $J = 3.8$ Hz, 1 H), 4.52 (s, 1 H), 4.34 and 4.32 (2 d, $J = 4.0$ Hz, 1 H), 3.99 and 3.96 (2 s, 1 H), 3.35 and

3.34 (2 s, 3 H), 3.32 and 3.30 (2 s, 3 H), 2.45 (br. s, 1 H), 2.29–2.18 (m, 1 H), 1.19 and 1.18 (2 s, 3 H), 1.17 and 1.14 (2 s, 3 H), 1.11 and 1.09 (2 d, $J = 3.8$ Hz, 3 H), 0.78 and 0.76 (2 d, $J = 2.6$ Hz, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 152.8$ and 152.4 , 150.2 and 150.1 , 112.9 and 112.2 , 100.9 and 100.7 , 94.8 and 94.7 , 84.6 and 84.4 , 75.2 and 75.0 , 72.7 , 57.9 and 57.7 , 55.8 , 32.3 and 32.2 , 26.1 and 26.0 , 24.6 and 24.4 , 19.6 , 18.6 ppm. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_5\text{BrNa}$ [$\text{M} + \text{Na}$] $^+$ 387.0783; found 387.0797. IR: $\tilde{\nu} = 3466$, 2981 , 2877 , 2401 , 1370 , 1137 , 1098 , 1035 , 779 , 597 cm^{-1} . R_f (hexane/EtOAc, 1:1): 0.42.

(1*R*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-enol [(+)-16]: $i\text{Pr}_2\text{NEt}$ (757 μL , 4.33 mmol) and MOMCl (225 μL , 2.96 mmol) were added to a stirred solution of tertiary alcohol (–)-15 (450 mg, 1.97 mmol) in CH_2Cl_2 (4 mL) at 0°C . The reaction mixture was stirred at room temp. until the reaction was complete (after 24 h, only traces of starting material remained). After slow addition of NH_4Cl (saturated aq.; 0.5 mL), the mixture was diluted with water (25 mL) and EtOAc (35 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2×60 mL). The combined organic extracts were dried with MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 20:1) to give methoxy methyl ether (434 mg, 81%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.82$ (dd, $J = 1.0$, $J = 5.6$ Hz, 1 H), 5.78 (dd, $J = 1.9$, $J = 5.6$ Hz, 1 H), 4.75 (d, $J = 7.0$ Hz, 1 H), 4.71–4.66 (m, 1 H), 4.65 (d, $J = 7.0$ Hz, 1 H), 3.35 (s, 3 H), 2.28 (dd, $J = 7.1$, $J = 13.8$ Hz, 1 H), 2.92 (dd, $J = 4.5$, $J = 13.8$ Hz, 1 H), 1.33 (s, 3 H), 0.89 (s, 9 H), 0.07 (2 s, 6 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 138.2$, 135.8 , 91.9 , 86.1 , 75.0 , 55.2 , 47.9 , 27.4 , 26.0 (3 C), 18.3 , -4.5 (2 C) ppm. HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{25}\text{O}_3\text{Si}$ [$\text{M} - \text{CH}_3$] $^+$ 257.1573; found 257.1572. IR: $\tilde{\nu} = 2930$, 2858 , 1365 , 1255 , 1100 , 1039 , 836 , 632 , 534 , 504 cm^{-1} . $[\alpha]_D^{20} = +7.2$ ($c = 1.00$, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.57.

Methoxy methyl ether (381 mg, 1.40 mmol) was dissolved in THF (9 mL), and TBAF (1 M in THF; 1.82 mL, 1.82 mmol) was added at 0°C . The resulting solution was stirred at room temp. for 1 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 , hexane/EtOAc, 5:1) to give free alcohol (+)-16 (205 mg, 93%) as a colorless oil. Alternatively, the crude methoxy methyl ether could be used directly to give the product in 90% yield over two steps. ^1H NMR (400 MHz, CDCl_3): $\delta = 6.10$ (dd, $J = 2.4$, $J = 5.5$ Hz, 1 H), 5.74 (d, $J = 5.6$ Hz, 1 H), 4.91 (d, $J = 7.6$ Hz, 1 H), 4.64–4.58 (m, 1 H), 4.59 (d, $J = 7.7$ Hz, 1 H), 3.39 (s, 3 H), 3.11 (d, $J = 9.6$ Hz, 1 H), 2.24 (dd, $J = 7.4$, $J = 15.0$ Hz, 1 H), 2.00 (dd, $J = 2.3$, $J = 14.9$ Hz, 1 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 138.1$, 137.3 , 92.0 , 86.5 , 75.6 , 55.0 , 46.9 , 27.6 ppm. HRMS (EI): calcd. for $\text{C}_7\text{H}_{11}\text{O}_3$ [$\text{M} - \text{CH}_3$] $^+$ 143.0708; found 143.0712. IR: $\tilde{\nu} = 3402$, 2972 , 2891 , 1444 , 1354 , 1220 , 1144 , 1091 , 1035 , 773 cm^{-1} . $[\alpha]_D^{20} = +115.7$ ($c = 1.00$, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.11.

1-[(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl] 3-Methyl 2-(1,3-Dioxolan-2-ylidene)malonate [(–)-18]: Triphenylphosphane (318 mg, 1.2 mmol) was dissolved in THF (3 mL), and the solution was cooled to 0°C . DIAD (236 μL , 1.2 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage, a milky precipitate formed. Acid 17 (226 mg, 1.2 mmol) was added in one portion, and then a solution of alcohol (+)-16 (95 mg, 0.60 mmol) in THF (0.5 mL) was added dropwise at 0°C . The mixture was stirred at the same temperature for 20 h. Water (15 mL) was added, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (15 mL), dried with MgSO_4 , filtered, and concentrated. The residue

was purified by chromatography (SiO_2 , hexane/EtOAc, 5:1 to 0:1) to give recovered starting material (+)-16 (18 mg, 19%) and ester (–)-18 (160 mg, 81%). ^1H NMR (400 MHz, CDCl_3): $\delta = 6.00$ (s, 2 H), 5.83 (dd, $J = 2.9$, $J = 7.2$ Hz, 1 H), 4.67 (d, $J = 7.3$ Hz, 1 H), 4.60 (s, 4 H), 4.59 (d, $J = 7.3$ Hz, 1 H), 3.73 (s, 3 H), 3.35 (s, 3 H), 2.54 (dd, $J = 7.2$, $J = 14.6$ Hz, 1 H), 1.88 (dd, $J = 2.9$, $J = 14.6$ Hz, 1 H), 1.47 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 170.5$, 165.5 , 165.0 , 141.6 , 132.4 , 92.0 , 87.5 , 80.9 , 78.8 , 67.8 , 67.7 , 55.2 , 51.8 , 44.1 , 27.1 ppm. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 351.1056; found 351.1048. IR: $\tilde{\nu} = 2926$, 1724 , 1686 , 1471 , 1304 , 1270 , 1084 , 1031 , 983 , 954 cm^{-1} . $[\alpha]_D^{20} = -131.8$ ($c = 1.11$, CHCl_3). R_f (EtOAc): 0.23.

(1*R*,4*R*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl Methyl Malonate [(–)-20]: Ester (–)-18 (13 mg, 0.04 mmol) was dissolved in degassed Et_2O (4 mL) in a quartz vial. One crystal of $\text{Cu}(\text{OTf})_2$ was added, and the mixture was irradiated with two 16 W UV-B lamps (Irradiation conditions H) at room temp. for 50 min. The solution was diluted with ice (15 g) and NH_4OH (0.5 mL), and extracted with EtOAc. The organic phase was washed with brine (5 mL), dried with MgSO_4 , filtered, and concentrated. The residue was purified by chromatography (SiO_2 , hexane/EtOAc, 1:1 to 1:2) to give undesired (–)-20 (6 mg, 46%). ^1H NMR (400 MHz, CDCl_3): $\delta = 6.03$ (dd, $J = 5.7$, $J = 1.0$ Hz, 1 H), 5.96 (dd, $J = 5.7$, $J = 2.1$ Hz, 1 H), 5.83–5.77 (m, 1 H), 4.66 (d, $J = 7.4$ Hz, 1 H), 4.57 (d, $J = 7.4$ Hz, 1 H), 3.74 (s, 3 H), 3.36 (s, 2 H), 3.34 (s, 3 H), 2.56 (dd, $J = 7.3$, $J = 14.7$ Hz, 1 H), 1.85 (dd, $J = 3.1$, $J = 14.7$ Hz, 1 H), 1.47 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 167.1$, 166.5 , 142.3 , 131.7 , 92.1 , 87.3 , 80.1 , 55.3 , 52.6 , 44.1 , 41.6 , 27.2 ppm. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 281.1001; found 281.1003. IR: $\tilde{\nu} = 2920$, 2852 , 1736 , 1439 , 1349 , 1275 , 1144 , 1029 , 641 , 597 cm^{-1} . $[\alpha]_D^{20} = -95.6$ ($c = 0.09$, CHCl_3). R_f (EtOAc): 0.61.

Benzyl (2-Methoxy-2-oxoethyl) Malonate (22): Methyl bromoacetate (2.61 mL, 28.4 mmol) was added dropwise to a suspension of monopotassium carboxylate 21 (6.00 g, 25.8 mmol) in DMF (51 mL) at 35°C . The mixture was stirred for 1 h. The solvent was removed (water bath at 55°C), and the residue was partitioned between water (100 mL) and toluene (100 mL). The phases were separated, and the aqueous phase was extracted with toluene (100 mL). The organic phases were combined, washed with brine (50 mL), dried with MgSO_4 , and concentrated to give analytically pure malonate 22 (6.87 g, 99%). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.30$ – 7.38 (m, 5 H), 5.20 (s, 2 H), 4.67 (s, 2 H), 3.76 (s, 3 H), 3.54 (s, 2 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 167.6$, 165.8 , 165.7 , 135.2 , 128.6 , 128.5 , 128.3 , 67.4 , 61.3 , 52.3 , 41.0 ppm. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_6$ [M] $^+$ 266.0790; found 266.0784. IR: $\tilde{\nu} = 1755$, 1737 , 1383 , 1337 , 1274 , 1214 , 1145 , 633 , 535 , 498 cm^{-1} . R_f (hexane/EtOAc, 1:1): 0.40.

Tetrabutylammonium 4-[(Benzyloxy)carbonyl]-5-oxo-2,5-dihydrofuran-3-olate (23): TBAF (1 M in THF; 19.3 mL, 19.3 mmol) was slowly added to a solution of malonate 22 (3.43 g, 12.9 mmol) in THF (26 mL) at 0°C . The resulting solution was stirred at room temp. for 15 h. The reaction mixture was concentrated, and the residue was heated to reflux in EtOAc (50 mL). The suspension was cooled to room temp. The precipitate was filtered off and washed with cold EtOAc (20 mL). After drying under high vacuum, 23 (4.89 g, 80%) was obtained as pure white crystals. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.45$ (d, $J = 7.3$ Hz, 2 H), 7.29–7.23 (m, 2 H), 7.21–7.15 (m, 1 H), 5.24 (s, 2 H), 4.19 (s, 2 H), 3.18–3.10 (m, 8 H), 1.59–1.48 (m, 8 H), 1.40–1.19 (m, 8 H), 0.95 (t, $J = 7.4$ Hz, 12 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 193.6$, 176.5 , 164.8 , 138.9 , 128.2 (2 C), 127.2 (2 C), 126.9 , 85.0 , 70.4 , 63.4 , 58.8

(4 C), 24.0 (4 C), 19.8 (4 C), 13.7 (4 C) ppm. HRMS (ESI): calcd. for $C_{12}H_9O_5$ [$M - NBU_4$] $^-$ 233.0450; found 233.0452. IR: $\tilde{\nu}$ = 2959, 2873, 1742, 1684, 1634, 1432, 1056, 736, 698, 609 cm^{-1} , m.p. 151–153 °C. R_f (hexane/EtOAc, 1:1): 0.00.

Benzyl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate (24): Ammonium salt **23** (2.0 g, 4.20 mmol) was dissolved in THF (21 mL). Dimethyl sulfate (0.42 mL, 4.41 mmol) was added at room temp., and the mixture was stirred for 2 h before further dimethyl sulfate (1 equiv.) was added. Stirring was continued for a further 3 h, and then the mixture was concentrated under reduced pressure. The residue was filtered through a chromatography column (SiO₂, hexane/EtOAc, 1:1 to 0:1) to give methylated product **24** (928 mg, 89%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 7.47–7.40 (m, 2 H), 7.40–7.27 (m, 3 H), 5.30 (s, 2 H), 4.75 (s, 2 H), 4.06 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 182.5, 168.6, 160.8, 135.8, 128.7 (2 C), 128.3, 128.2 (2 C), 97.2, 66.7, 65.1, 59.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}O_5Na$ [$M + Na$] $^+$ 271.0582; found 271.0583. IR: $\tilde{\nu}$ = 1768, 1709, 1623, 1478, 1411, 1338, 1262, 1066, 1025, 606 cm^{-1} , m.p. 172–173 °C. R_f (EtOAc): 0.28.

4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylic Acid (25): Benzyl ester **24** (928 mg, 3.74 mmol) was dissolved in MeOH (75 mL), and Pd (5% on C; 50 mg) was added under Ar. Then a gentle flow of H₂ (1 atm) was bubbled through the solution for 60 min at room temp. The heterogeneous mixture was filtered through a Celite pad and concentrated to give carboxylic acid **25** (587 mg, 99%) as a white solid that turned pale yellow after a few days. ¹H NMR (400 MHz, [D₄]methanol): δ = 5.06 (s, 2 H), 4.15 (s, 3 H) ppm. ¹³C NMR (400 MHz, [D₄]methanol): δ = 187.7, 172.9, 163.7, 96.3, 66.7, 60.4 ppm. HRMS (EI): calcd. for $C_6H_4O_4$ [$M - H_2O$] $^+$ 140.0110; found 140.0108. IR: $\tilde{\nu}$ = 2921, 1748, 1615, 1464, 1285, 1145, 1087, 1059, 903, 701 cm^{-1} , m.p. 157–159 °C. R_f (EtOAc): 0.05.

(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-enol [(–)-26]: Secondary alcohol (+)-**16** (133 mg, 0.84 mmol), triphenylphosphane (662 mg, 2.52 mmol), and *p*-nitrobenzoic acid (821 mg, 2.52 mmol) were dissolved in THF (4 mL), and the solution was cooled to 0 °C under Ar. DIAD (480 μ L, 2.44 mmol) was added slowly, and the mixture was stirred for 40 min. The mixture was diluted with EtOAc (50 mL) and water (30 mL), and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with NaHCO₃ (15 mL) and brine (2 $\times$ 20 mL), dried with MgSO₄, filtered, and concentrated. The residue was then purified by flash chromatography (SiO₂, hexane/EtOAc, 7:1) to give the *para*-nitrobenzoic ester (218 mg, 84%) as a clear semi-solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.31–8.22 (m, 2 H), 8.22–8.14 (m, 2 H), 6.11 (dd, J = 0.7, J = 5.6 Hz, 1 H), 6.09 (dd, J = 2.0, J = 5.6 Hz, 1 H), 6.05–6.00 (m, 1 H), 4.66 (dd, J = 35.9, J = 7.4, 2 Hz), 3.37 (s, 3 H), 2.69 (dd, J = 14.7, J = 7.2 Hz, 1 H), 1.99 (dd, J = 14.8, J = 3.2 Hz, 1 H), 1.54 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 164.6, 150.7, 142.6, 135.9, 131.7, 130.8 (2 C), 123.7 (2 C), 92.1, 87.3, 80.5, 55.3, 44.3, 27.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}O_6NNa$ [$M + Na$] $^+$ 330.0954; found 330.0961. IR: $\tilde{\nu}$ = 1721, 1608, 1528, 1340, 1271, 1143, 1102, 1031, 842, 720 cm^{-1} . [α]_D²⁰ = +158.4 (c = 1.00, CHCl₃). R_f (hexane/EtOAc, 5:1): 0.14.

The *p*-nitrobenzoic ester (205 mg, 0.67 mmol) was dissolved in MeOH (13 mL), and the solution was cooled to 0 °C. K₂CO₃ (92 mg, 0.67 mmol) was added in one portion, and the mixture was stirred for 35 min before being quenched with NH₄Cl. Almost all of the organic solvent was removed under reduced pressure, and EtOAc (20 mL) was added. The aqueous phase was removed and extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (2 $\times$ 10 mL), dried with MgSO₄, filtered, and concentrated. The residue was purified by flash chromatog-

raphy (SiO₂, hexane/EtOAc, 2:1) to give alcohol (–)-**26** (86 mg, 82%) as a colorless oil. Alternatively the crude product from the Mitsunobu reaction could be used, which gave the product in 78% yield over two steps. ¹H NMR (400 MHz, CDCl₃): δ = 5.96 (dd, J = 5.6, J = 1.9 Hz, 1 H), 5.86 (dd, J = 5.6, J = 1.2 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.59 (dd, J = 31.7, J = 7.3 Hz, 2 H), 3.33 (s, 3 H), 2.53 (dd, J = 14.4, J = 7.0 Hz, 1 H), 1.68 (dd, J = 14.3, J = 3.9 Hz, 1 H), 1.67 (br. s, 1 H), 1.48 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 138.9, 137.0, 92.0, 87.8, 76.4, 55.2, 47.8, 27.8 ppm. HRMS (ESI): calcd. for $C_7H_{11}O_3$ [$M - CH_3$] $^+$ 143.0708; found 143.0712. IR: $\tilde{\nu}$ = 3371, 2932, 1449, 1356, 1143, 1091, 1030, 918, 634, 537 cm^{-1} . [α]_D²⁰ = –99.4 (c = 1.05, CHCl₃). R_f (hexane/EtOAc, 1:1): 0.45.

(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate [(–)-27]: Secondary alcohol (–)-**26** (40 mg, 0.25 mmol) and carboxylic acid **25** (96 mg, 0.61 mmol) were dissolved in CH₂Cl₂ (5.1 mL), and the mixture was cooled to 0 °C. DIC (47 μ L, 0.30 mmol) was added, followed by DMAP (6 mg, 0.05 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed, and the residue was purified by column chromatography (SiO₂, hexane/EtOAc, 1:1 to 1:2) to give starting material (–)-**26** (22 mg, 55%) and ester (–)-**27** (30 mg, 40%, 88% based on recovered starting material) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.08–6.00 (m, 2 H), 5.89 (dt, J = 7.2, J = 2.2 Hz, 1 H), 4.74 (s, 2 H), 4.64 (dd, J = 34.3, J = 7.3 Hz, 2 H), 4.11 (s, 3 H), 3.35 (s, 3 H), 2.58 (dd, J = 14.6, J = 7.2 Hz, 1 H), 1.96 (dd, J = 14.7, J = 3.0 Hz, 1 H), 1.51 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 181.7, 168.5, 160.9, 142.4, 131.8, 97.6, 92.1, 87.4, 79.7, 65.0, 59.9, 55.3, 44.1, 27.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_7Na$ [$M + Na$] $^+$ 321.0950; found 321.0951. IR: $\tilde{\nu}$ = 2931, 1771, 1709, 1626, 1413, 1264, 1143, 1028, 632, 538 cm^{-1} . [α]_D²⁰ = –140.6 (c = 0.55, CHCl₃). R_f (EtOAc): 0.22.

(S)-4-Oxocyclopent-2-en-1-yl 4-Methoxy-2-oxo-2,5-dihydrofuran-3-carboxylate [(–)-30]: Secondary alcohol (–)-**29** (40 mg, 0.41 mmol) and carboxylic acid **25** (77 mg, 0.49 mmol) were dissolved in CH₂Cl₂/MeCN (3:1; 4 mL), and the mixture was cooled to 0 °C. DIC (76 μ L, 0.49 mmol) was added, followed by DMAP (10 mg, 0.08 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed, and the residue was purified by column chromatography (SiO₂, hexane/EtOAc, 2:1 to 0:1) to give starting material (–)-**29** (4 mg, 10%) ester (–)-**30** (88 mg, 78%) as a white solid that turned yellow on contact with air. ¹H NMR (400 MHz, CDCl₃): δ = 7.64 (dd, J = 2.4, J = 5.7 Hz, 1 H), 6.36 (dd, J = 1.3, J = 5.7 Hz, 1 H), 5.99 (m, 1 H), 4.81 (s, 2 H), 4.12 (s, 3 H), 2.87 (dd, J = 6.3, J = 18.8 Hz, 1 H), 2.44 (dd, J = 2.2, J = 18.8 Hz, 1 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 204.7, 183.5, 168.1, 160.3, 158.7, 137.5, 96.6, 72.7, 64.9, 59.8, 41.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{10}O_6Na$ [$M + Na$] $^+$ 261.0375; found 261.0377. IR: $\tilde{\nu}$ = 1766, 1711, 1619, 1479, 1409, 1341, 1261, 1066, 1026, 794 cm^{-1} . [α]_D²⁰ = 106.8 (c = 0.50, CHCl₃), m.p. 148–149 °C. R_f (EtOAc): 0.25.

(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-32]: Triphenylphosphane (935 mg, 3.57 mmol) was dissolved in THF (30 mL), and the solution was cooled to 0 °C. DIAD (702 μ L, 3.57 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage, a milky precipitate formed. Allenic acid **31** (300 mg, 3.57 mmol) was added in one portion, and a solution of alcohol (+)-**16** (470 mg, 2.97 mmol) in THF (5 mL) was then added dropwise at 0 °C. The mixture was stirred at the same temperature for 2 h. Water (45 mL) was added, and the re-

sulting mixture was extracted with EtOAc (3×80 mL). The combined organic extracts were washed with brine (50 mL), dried with MgSO_4 , filtered, and concentrated. The residue was subjected to column chromatography (SiO_2 , hexane/EtOAc, 6:1) to give ester (–)-**32** (580 mg, 87%). ^1H NMR (400 MHz, CDCl_3): δ = 6.00 (dd, J = 0.8, J = 5.7 Hz, 1 H), 5.96 (dd, J = 2.1, J = 5.7 Hz, 1 H), 5.82–5.76 (m, 1 H), 5.60 (t, J = 6.5 Hz, 1 H), 5.20 (d, J = 6.6 Hz, 2 H), 4.61 (dd, J = 7.3, J = 33.4 Hz, 2 H), 3.33 (s, 3 H), 2.55 (dd, J = 7.3, J = 14.6 Hz, 1 H), 1.84 (dd, J = 3.3, J = 14.7 Hz, 1 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 216.0, 165.7, 141.7, 132.2, 92.0, 88.14, 87.3, 79.4, 79.3, 55.2, 44.2, 27.2 ppm. HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_4$ [$\text{M} - \text{CH}_3$] $^+$ 209.0814; found 209.0808. IR: $\tilde{\nu}$ = 2929, 1714, 1450, 1350, 1256, 1163, 1144, 1032, 632, 535 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ = –187.3 (c = 1.04, CHCl_3). R_f (hexane/EtOAc, 4:1): 0.22.

(S)-4-Oxocyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-33]: Alcohol (–)-**29** (100 mg, 1.02 mmol) and carboxylic acid **31** (103 mg, 1.22 mmol) were dissolved in CH_2Cl_2 (5.1 mL), and the mixture was cooled to 0 °C. DIC (189 μL , 1.22 mmol) was added, followed by DMAP (41 mg, 0.20 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp. and stirring was continued overnight. The volatiles were removed, and the residue was purified by chromatography column (SiO_2 , hexane/EtOAc, 1:1 to 1:2) to give ester (–)-**33** (100 mg, 60%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 7.58 (dd, J = 2.5, J = 5.8 Hz, 1 H), 6.33 (dd, J = 1.2, J = 5.7 Hz, 1 H), 5.92–5.89 (m, 1 H), 5.64 (t, J = 6.5 Hz, 1 H), 5.24 (d, J = 6.5 Hz, 2 H), 2.83 (dd, J = 6.3, J = 18.6 Hz, 1 H), 2.36 (dd, J = 2.3, J = 18.7 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 216.4, 204.8, 165.2, 158.9, 137.2, 87.5, 79.8, 72.5, 41.1 ppm. HRMS (ESI): calcd. for $\text{C}_9\text{H}_8\text{O}_3$ [M] $^+$ 164.0473; found 164.0475. IR: $\tilde{\nu}$ = 3451, 2927, 2856, 1713, 1659, 1442, 1362, 1231, 1184, 1102 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ = –132.54 (c = 1.00, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.48.

(1S,4S)-4-Hydroxy-4-methylcyclopent-2-en-1-yl Buta-2,3-dienoate [(–)-35]: Triphenylphosphane (172 mg, 0.66 mmol) was dissolved in THF (6.6 mL), and the solution was cooled to 0 °C. DIAD (129 μL , 0.66 mmol) was added very slowly, and the mixture was stirred for 30 min. At this stage a milky precipitate formed. Allenic acid **31** (55 mg, 0.66 mmol) was added in one portion, and a solution of alcohol (–)-**34** (75 mg, 0.66 mmol) in THF (1 mL) was then added dropwise at 0 °C. The mixture was stirred at the same temperature for 2 h. Water (25 mL) was added, and the resulting mixture was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (20 mL), dried with MgSO_4 , filtered, and concentrated. The residue was subjected to column chromatography (SiO_2 , hexane/EtOAc, 2:1) to give ester (–)-**35** (41 mg, 35%). ^1H NMR (400 MHz, CDCl_3): δ = 6.00 (dd, J = 0.9, J = 5.5 Hz, 1 H), 5.90 (dd, J = 2.3, J = 5.5 Hz, 1 H), 5.85–5.80 (m, 1 H), 5.60 (t, J = 6.6 Hz, 1 H), 5.21 (d, J = 6.6 Hz, 2 H), 2.38 (dd, J = 7.1, J = 14.6 Hz, 1 H), 1.98 (dd, J = 3.1, J = 14.6 Hz, 1 H), 1.91 (br. s, 1 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 215.9, 165.6, 143.6, 130.8, 88.0, 82.1, 79.3 (2 C), 46.6, 28.6 ppm. HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_3$ [M] $^+$ 180.0786; found 180.0783. IR: $\tilde{\nu}$ = 3407, 1970, 1942, 1707, 1348, 1256, 1164, 1086, 854, 631 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ = –130.3 (c = 0.95, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.26.

(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-(Hydroxymethyl)buta-2,3-dienoate [(–)-36]: A solution of DABCO (pre-dried under vacuum for 30 min; 5 mg, 0.04 mmol) in THF (0.5 mL) was added dropwise to a suspension of paraformaldehyde (pre-dried under vacuum at 50 °C for 30 min; 33 mg, 1.12 mmol) in THF (1 mL) at –10 °C, and then a solution of ester (–)-**32** (50 mg,

0.22 mmol) in THF (0.5 mL) was added to the mixture. The reaction mixture was allowed to warm to room temp. and stirred for 7 h. The reaction was quenched by the addition of NH_4Cl (saturated aq.; 3 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried with MgSO_4 , filtered and concentrated in vacuo. Purification by column chromatography (SiO_2 , hexane/EtOAc, 3:1) gave product (–)-**36** (35 mg, 62%) as an oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.03 (dd, J = 0.7, J = 5.6 Hz, 1 H), 5.97 (dd, J = 2.1, J = 5.7 Hz, 1 H), 5.84–5.80 (m, 1 H), 5.21 (t, J = 2.1 Hz, 1 H), 4.62 (dd, J = 7.2, J = 33.8 Hz, 2 H), 4.31 (t, J = 1.8 Hz, 2 H), 3.34 (s, 3 H), 2.55 (dd, J = 7.2, J = 14.6 Hz, 1 H), 2.48 (br. s, 1 H), 1.85 (dd, J = 3.1, J = 14.7 Hz, 1 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 213.3, 166.7, 142.1, 132.0, 100.0, 92.1, 87.3, 80.5, 79.6, 61.1, 55.3, 44.2, 27.1 ppm. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_5$ [M] $^+$ 239.0919; found 239.0906. IR: $\tilde{\nu}$ = 3220, 2930, 1713, 1449, 1361, 1214, 1142, 1091, 1030, 631 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ = –172.0 (c = 0.27, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.29.

(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-(Ethoxy Methyl)buta-2,3-dienoate [(–)-38]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (232 mg, 0.88 mmol), and carboxylic acid **37** (180 mg, 1.26 mmol) were dissolved in THF (6.3 mL), and the solution was cooled to 0 °C under Ar. DIAD (174 μL , 0.88 mmol) was slowly added, and the mixture was stirred for 30 min. The mixture was diluted with EtOAc (30 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with NaHCO_3 (15 mL) and brine (2×15 mL), dried with MgSO_4 , filtered, and concentrated. The residue was then purified by flash column chromatography (SiO_2 , hexane/EtOAc, 8:1) to give ester (–)-**38** (104 mg, 58%) as a viscous oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.01 (dd, J = 0.7, J = 5.6 Hz, 1 H), 5.98 (dd, J = 2.0, J = 5.6 Hz, 1 H), 5.82–5.78 (m, 1 H), 5.21 (t, J = 2.2 Hz, 2 H), 4.62 (dd, J = 7.4, J = 32.4 Hz, 2 H), 4.18 (t, J = 2.1 Hz, 2 H), 3.53 (q, J = 7.0 Hz, 2 H), 3.34 (s, 3 H), 2.53 (dd, J = 7.2, J = 14.6 Hz, 1 H), 1.85 (dd, J = 3.1, J = 14.6 Hz, 1 H), 1.46 (s, 3 H), 1.20 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 214.6, 165.8, 141.7, 132.0, 98.3, 91.9, 87.2, 79.5, 79.2, 67.2, 66.0, 55.1, 44.1, 27.0, 15.1 ppm. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 305.1365; found 305.1359. IR: $\tilde{\nu}$ = 2975, 2873, 1967, 1710, 1371, 1259, 1143, 1091, 1031, 535 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ = –115.9 (c = 1.00, CHCl_3). R_f (hexane/EtOAc, 3:1): 0.29.

(E)-(1S,4S)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 3-(Furan-2-yl)acrylate [(–)-40]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (249 mg, 0.95 mmol), and carboxylic acid **39** (131 mg, 0.95 mmol) were dissolved in THF (4.2 mL), and the solution was cooled to 0 °C under Ar. DIAD (187 μL , 0.95 mmol) was slowly added, and the mixture was stirred for 20 min. The mixture was diluted with EtOAc (20 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (40 mL). The combined organic extracts were washed with NaHCO_3 (10 mL) and brine (2×20 mL), dried with MgSO_4 , filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 6:1) to give ester (–)-**40** (175 mg, 99%) as a crystalline product. ^1H NMR (400 MHz, CDCl_3): δ = 7.47 (d, J = 1.6 Hz, 1 H), 7.40 (d, J = 15.7 Hz, 1 H), 6.60 (d, J = 3.5 Hz, 1 H), 6.46 (dd, J = 1.8, J = 3.4 Hz, 1 H), 6.28 (d, J = 15.7 Hz, 1 H), 6.03–5.99 (m, 2 H), 5.89–5.84 (m, 1 H), 4.63 (dd, J = 7.3, J = 32.9 Hz, 2 H), 3.35 (s, 3 H), 2.60 (dd, J = 7.3, J = 14.7 Hz, 1 H), 1.88 (dd, J = 3.3, J = 14.6 Hz, 1 H), 1.50 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 166.9, 151.1, 144.9, 141.6, 132.5, 131.3, 116.0, 114.9, 112.4, 92.1, 87.4, 78.8, 55.3, 44.3,

27.3 ppm. HRMS (EI): calcd. for $C_{15}H_{18}O_5$ $[M]^+$ 278.1154; found 278.1097. IR: $\tilde{\nu}$ = 2930, 1706, 1638, 1448, 1302, 1259, 1209, 1163, 1110, 1032 cm^{-1} . $[a]_D^{25}$ = -242.9 (c = 1.50, $CHCl_3$), m.p. 74–75 °C, R_f (hexane/EtOAc, 3:1): 0.31.

(*S,E*)-4-Oxocyclopent-2-en-1-yl 3-(Furan-2-yl)acrylate [(–)-(41)]: Secondary alcohol (–)-**29** (500 mg, 5.10 mmol) and carboxylic acid **39** (845 mg, 6.12 mmol) were dissolved in CH_2Cl_2 (25.5 mL), and the solution was cooled to 0 °C. DIC (947 μ L, 6.12 mmol) was added, followed by DMAP (201 mg, 1.02 mmol). The mixture was stirred at 0 °C for 2 h, then it was allowed to warm to room temp., and stirring was continued overnight. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography (SiO_2 , hexane/EtOAc, 6:1 to 4:1) to give ester (–)-**41** (788 mg, 71%) as a white crystalline solid. 1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, J = 2.5, J = 5.8 Hz, 1 H), 7.48 (d, J = 1.4 Hz, 1 H), 7.44 (d, J = 15.7 Hz, 1 H), 6.64 (d, J = 3.5 Hz, 1 H), 6.47 (dd, J = 1.8, J = 3.4 Hz, 1 H), 6.64 (dd, J = 1.3, J = 5.8 Hz, 1 H), 6.29 (d, J = 15.7 Hz, 1 H), 5.98–5.94 (m, 1 H), 2.86 (dd, J = 6.5, J = 18.8 Hz, 1 H), 2.39 (dd, J = 2.2, J = 18.8 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 204.9, 166.3, 159.1, 150.6, 15.1, 137.0, 132.1, 115.5, 114.5, 112.4, 71.9, 41.1 ppm. HRMS (EI): calcd. for $C_{12}H_{10}O_4$ $[M]^+$ 218.0579; found 218.0562. IR: $\tilde{\nu}$ = 2933, 1708, 1635, 1479, 1353, 1282, 1207, 1156, 1016, 753 cm^{-1} . $[a]_D^{25}$ = -243.1 (c = 4.00, $CHCl_3$), m.p. 80–81 °C, R_f (hexane/EtOAc, 3:1): 0.21.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-Acetoxycarboxylate [(–)-(42)]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (199 mg, 0.76 mmol), and 2-acetoxycarboxylic acid (137 mg, 0.76 mmol) were dissolved in THF (6.3 mL), and the solution was cooled to 0 °C under Ar. DIAD (149 μ L, 0.76 mmol) was added slowly, and the mixture was stirred for 40 min. The mixture was diluted with EtOAc (30 mL) and water (15 mL), and the aqueous phase was extracted with EtOAc (50 mL). The combined organic extracts were washed with $NaHCO_3$ (25 mL) and brine (2 $\times$ 40 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was then purified by flash column chromatography (SiO_2 , hexane/EtOAc, 6:1) to give ester (–)-**42** (106 mg, 52%) and recovered starting material (45 mg, 45%). 1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, J = 1.8, J = 7.9 Hz, 1 H), 7.54 (dt, J = 1.7, J = 7.8 Hz, 1 H), 7.29 (dt, J = 1.2, J = 7.7 Hz, 1 H), 7.08 (dd, J = 1.2, J = 8.1 Hz, 1 H), 6.07–6.02 (m, 2 H), 5.98–5.93 (m, 1 H), 4.63 (dd, J = 7.4, J = 34.5 Hz, 2 H), 3.35 (s, 3 H), 2.64 (dd, J = 7.3, J = 14.9 Hz, 1 H), 2.32 (s, 3 H), 1.92 (dd, J = 3.4, J = 14.8 Hz, 1 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.7, 164.4, 150.7, 142.0, 133.9, 132.3, 131.9, 126.1, 123.9, 123.6, 92.1, 87.3, 79.5, 55.3, 44.3, 27.3, 21.2 ppm. HRMS (EI): calcd. for $C_{17}H_{20}O_6Na$ $[M + Na]^+$ 343.1158; found 343.1184. IR: $\tilde{\nu}$ = 2932, 1770, 1717, 1607, 1368, 1289, 1191, 1029, 961, 915 cm^{-1} . $[a]_D^{20}$ = -147.5 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.32.

Ketene 43: Et_3N (14 μ L, 0.10 mmol) was added to a solution of alcohol (–)-**26** (15 mg, 0.09 mmol) in THF (0.5 mL) at 0 °C. After 15 min at this temperature, the resulting clear reaction mixture was slowly added to a pre-formed solution of suboxide at 0 °C [Ketene preparation: A solution of malonyl dichloride (18 μ L, 0.19 mmol) in THF (0.5 mL) was treated with $iPrEt_3N$ (35 μ L, 0.21 mmol) dropwise at 0 °C. The reaction mixture was kept at this temperature for 30 min, resulting in an orange suspension]. The resulting suspension was stirred at the same temperature for 90 min, and then it was allowed to warm to room temp. After 6 h, no starting material was left, as indicated by TLC. Water (5 mL) and then EtOAc (5 mL) were added to the reaction mixture. The mixture was ex-

tracted with EtOAc (3 $\times$ 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure. Column chromatography (SiO_2 , EtOAc) of the resulting yellow oil led neither to the recovery of starting material nor to the isolation of the desired cyclization product or ketene **43**.

Ketene Iminium Ion 46: A solution of amide (–)-**45** (48 mg, 0.14 mmol) and collidine (19 μ L, 0.14 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (25 μ L, 0.15 mmol) in CH_2Cl_2 (0.5 mL) at room temp. The reaction mixture was stirred at this temperature for 6 h. As no reaction was indicated by TLC, the reaction vessel was sealed with a stopper and heated to reflux for an additional 2 h. Water (5 mL) and then CH_2Cl_2 (5 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3 $\times$ 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over $MgSO_4$. After evaporation of the volatiles, flash column chromatography (SiO_2 , EtOAc) did not result in isolation of the desired cyclization product or **46**.

Ketene Iminium Ion 48: A solution of alcohol (–)-**26** (30 mg, 0.19 mmol), acid **47** (33 mg, 0.21 mmol), and DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (1.9 mL) was treated with DIC (35 μ L, 0.23 mmol) dropwise at 0 °C under an Ar atmosphere. The resulting pale beige suspension was allowed to warm to room temp. and stirred for 24 h. As TLC indicated full consumption of the starting material, ammonium chloride (saturated aq.; 5 mL) was added to the reaction mixture. After extraction with CH_2Cl_2 (3 $\times$ 10 mL), $MgSO_4$ was added to the combined organic extracts. Filtration followed by removal of the volatiles resulted in a pale yellow oil, which was purified by column chromatography (SiO_2 , EtOAc) to give the desired amide (56 mg, quant. yield) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ = 6.01 (dd, J = 5.6, J = 0.9 Hz, 1 H), 5.97 (dd, J = 5.6, J = 2.0 Hz, 1 H), 5.80 (m, 1 H), 4.65 (d, J = 7.3 Hz, 1 H), 4.57 (d, J = 7.3 Hz, 1 H), 3.49 (t, J = 6.8 Hz, 2 H), 3.43 (t, J = 6.8 Hz, 2 H), 3.36 (s, 2 H), 3.33 (s, 3 H), 2.55 (dd, J = 14.7, J = 7.2 Hz, 1 H), 1.96 (m, 2 H), 1.91–1.84 (m, 3 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.6, 164.4, 142.0, 132.0, 92.1, 87.3, 79.8, 55.3, 47.3, 46.1, 44.1, 42.7, 27.2, 26.2, 24.6 ppm. HRMS (EI): calcd. for $C_{15}H_{23}NNaO_5$ $[M + Na]^+$ 320.1474; found 320.1473. IR: $\tilde{\nu}$ = 2973, 2881, 1736, 1646, 1442, 1344, 1259, 1144, 1032, 750 cm^{-1} . $[a]_D^{20}$ = -97.7 (c = 0.60, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.19.

A solution of amide (56 mg, 0.19 mmol) and collidine (26 μ L, 0.19 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (34 μ L, 0.21 mmol) in CH_2Cl_2 (0.5 mL) at room temp. The reaction mixture was stirred at this temperature for 6 h. As no reaction was indicated by TLC, the reaction vessel was sealed with a stopper and heated to reflux for an additional 2 h. Water (5 mL) and then CH_2Cl_2 (5 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3 $\times$ 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over $MgSO_4$. After evaporation of the volatiles, flash column chromatography (SiO_2 , EtOAc) did not result in isolation of the desired cyclization product or **48**.

Anhydride (–)-50: A quartz vial of 1 cm diameter was charged with cyclopentene (–)-**49** (20 mg, 0.06 mmol), maleic anhydride (29 mg, 0.29 mmol), a magnetic stirrer bar and acetone (6.0 mL). The vial was sealed with a rubber septum and equipped with an argon balloon. The reaction vessel was placed in an ultrasound bath, and the reaction mixture was degassed by passing a gentle stream of argon through the solution. After 30 min, the quartz vial was placed 1 cm in front of 8 $\times$ 16 W UV-A lamps, and irradiated for

a period of 8 h. After full consumption of the cyclopentene, as judged by TLC, the solvent was removed under reduced pressure. The colorless semi-solid was purified by column chromatography (SiO₂, hexane/EtOAc, 10:1) to give desired tricycle (–)-**50** (15 mg, 58%) as a colorless oil, which partially crystallized upon storage in the fridge. During purification by chromatography, as well as upon dissolving and storing in CDCl₃, partial hydrolysis of the anhydride functionality was observed, resulting in a small amount of impurity in the NMR spectra. ¹H NMR (400 MHz, CDCl₃): δ = 4.26 (dt, *J* = 10.7, *J* = 7.0 Hz, 1 H), 3.56 (dd, *J* = 6.5, *J* = 2.6 Hz, 1 H), 3.51 (dd, *J* = 6.5, *J* = 3.0 Hz, 1 H), 2.87 (dt, *J* = 6.7, *J* = 2.7 Hz, 1 H), 2.62 (dd, *J* = 6.1, *J* = 3.0 Hz, 1 H), 2.00 (dd, *J* = 12.7, *J* = 6.6 Hz, 1 H), 1.86 (m, 1 H), 1.52 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 173.9, 173.4, 76.7, 70.2, 51.6, 45.7, 44.5, 38.9, 35.9, 29.8, 29.4, 26.0 (3 C), 25.9 (3 C), 18.2, –2.2, –2.3, –4.7, –4.8 ppm. HRMS (EI): calcd. for C₂₃H₄₄NaO₆Si₂ [M + MeOH + Na]⁺ 495.2574; found 495.2592. [α]_D²⁰ = –127.8 (*c* = 0.75, CHCl₃). IR: ν̄ = 2973, 2879, 1875, 1834, 1642, 1601, 1332, 1269, 1144, 834 cm^{–1}. *R*_f (hexane/EtOAc, 6:1): 0.58.

tert-Butyldimethyl[(1*R*,4*S*)-4-(prop-2-yn-1-yloxy)cyclopent-2-en-1-yl]oxy]silane [(+)-54**]:** A solution of (+)-**44** (1.00 g, 4.66 mmol) in THF (3.5 mL) was added to a suspension of NaH (450 mg, 18.66 mmol) in THF (3.5 mL) at 0 °C. The mixture was allowed to warm to room temp., and after the evolution of H₂ had subsided, the mixture was cooled again to 0 °C. Propargyl bromide (80 wt-% in toluene; 1.51 mL, 13.99 mmol) was then slowly added, and the reaction mixture was stirred overnight while it warmed to room temp. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL) and water (15 mL), and dried with MgSO₄, and the solvent was removed in vacuo. Purification by chromatography column (SiO₂, hexane/EtOAc, 15:1) gave (+)-**54** (1.38 g, 99%) as a slightly viscous liquid. ¹H NMR (400 MHz, CDCl₃): δ = 5.97–5.90 (m, 2 H), 4.67 (m, 1 H), 4.56 (m, 1 H), 4.17 (dd, *J* = 2.4, *J* = 4.1 Hz, 2 H), 2.69 (td, *J* = 7.2, *J* = 13.4 Hz, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 1.60 (td, *J* = 5.3, *J* = 13.4 Hz, 1 H), 0.98 (s, 9 H), 0.83 (s, 3 H), 0.79 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 138.0, 132.2, 81.2, 80.4, 74.8, 74.0, 55.6, 41.2, 25.9 (3 C), 18.1, –4.6 (2 C) ppm. HRMS (EI): calcd. for C₁₀H₁₅O₂Si [M – *t*Bu]⁺ 195.0841; found 195.0841. IR: ν̄ = 2955, 2931, 2857, 1372, 1253, 1081, 1059, 905, 837, 777 cm^{–1}. [α]_D²⁰ = +32.7 (*c* = 1.05, CHCl₃). *R*_f (hexane/EtOAc, 3:1): 0.48.

[(1*R*,4*S*)-4-(Buta-2,3-dien-1-yloxy)cyclopent-2-en-1-yl]oxy(tert-butyl)dimethylsilane [(+)-51**]:** Paraformaldehyde (416 mg, 13.85 mmol), DIPA (1.0 mL, 7.13 mmol), and CuBr (331 mg, 2.31 mmol) were sequentially added to a solution of alkyne (+)-**54** (1.17 g, 4.38 mmol) in dioxane (30 mL). The reaction mixture was heated at reflux overnight. After the reaction was complete (TLC monitoring), the solvent was removed in vacuo. The residue was purified by column chromatography (SiO₂, hexane/EtOAc, 1:0 to 20:1) to give (+)-**51** (1.04 g, 84%) as a slightly yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 5.94–5.87 (m, 2 H), 5.25 (d, *J* = 6.8 Hz, 1 H), 4.78 (td, *J* = 2.5, *J* = 6.6 Hz, 1 H), 4.66 (m, 1 H), 4.42 (m, 1 H), 4.05 (m, 1 H), 2.67 (td, *J* = 7.2, *J* = 13.2 Hz, 1 H), 1.58 (td, *J* = 5.6, *J* = 13.2 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 1 H), 0.08 (s, 1 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 209.2, 137.5, 132.7, 88.2, 81.1, 75.6, 74.9, 66.3, 41.5, 25.9 (3 C), 18.2, –4.6 (2 C) ppm. HRMS (ESI): calcd. for C₁₅H₂₆O₂SiNa [M + Na]⁺ 289.1600; found 289.1592. IR: ν̄ = 2955, 2931, 2857, 1368, 1253, 1079, 940, 905, 837, 777 cm^{–1}. [α]_D²⁰ = +10.4 (*c* = 0.85, CHCl₃). *R*_f (hexane/EtOAc, 15:1): 0.49.

(*S*)-4-(Buta-2,3-dien-1-yloxy)cyclopent-2-enone [(+)-52**]:** Compound (+)-**51** (500 mg, 1.88 mmol) was dissolved in THF (2 mL), and TBAF (1 M in THF; 2.40 mL, 2.40 mmol) was added at room temp. After TLC had indicated an almost complete conversion, CH₂Cl₂ (12 mL) was added. Then MnO₂ (4.89 g, 56.25 mmol) was added, and stirring was continued overnight at room temp. The mixture was filtered through Celite, and, after gentle evaporation of the solvent in vacuo, the residue was purified by column chromatography (SiO₂, pentane/Et₂O, 2:1) to give (+)-**52** (164 mg, 58%) as a volatile greenish-yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ = 7.61 (dd, *J* = 2.3, *J* = 5.7 Hz, 1 H), 6.26 (dd, *J* = 1.4, *J* = 5.7 Hz, 1 H), 5.26 (t, *J* = 6.8 Hz, 1 H), 4.83 (td, *J* = 2.4, *J* = 6.6 Hz, 2 H), 4.78 (m, 1 H), 4.16–4.09 (m, 2 H), 2.69 (dd, *J* = 5.9, *J* = 18.3 Hz, 1 H), 2.33 (dd, *J* = 2.3, *J* = 18.3 Hz, 1 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 209.5, 205.8, 161.0, 135.8, 87.5, 76.5, 76.1, 67.7, 41.8 ppm. HRMS (ESI): calcd. for C₉H₁₀O₂Na [M + Na]⁺ 150.0681; found 150.0699. IR: ν̄ = 2926, 2856, 1719, 1351, 1184, 1105, 1074, 996, 849, 792 cm^{–1}. [α]_D²⁰ = +5.14 (*c* = 1.23, CHCl₃). *R*_f (Pentane/Et₂O, 2:1): 0.20.

(3*aS*)-1-Methylenhexahydro-3-oxacyclobuta[cd]pentalen-5(1*aH*)-one [(+)-53**]:** Enone (+)-**52** (30 mg, 0.21 mmol) was dissolved in diethyl ether (6 mL). The solution was irradiated with UV-B light under 2 × 16 W lamps (Irradiation conditions G) in a quartz vial for 6 h. After TLC indicated partial conversion, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (pentane/Et₂O, 2:1) to give (+)-**53** (18 mg, 60%) as a volatile liquid. ¹H NMR (400 MHz, CDCl₃): δ = 5.16 (m, 1 H), 5.00 (m, 1 H), 4.66 (t, *J* = 5.7 Hz, 1 H), 4.00 (d, *J* = 9.1 Hz, 1 H), 3.70 (dd, *J* = 4.2, *J* = 9.1 Hz, 1 H), 3.61–3.56 (m, 1 H), 3.49–3.44 (m, 1 H), 3.38–3.34 (m, 1 H), 2.70 (d, *J* = 18.2 Hz, 1 H), 2.54 (ddd, *J* = 0.6, *J* = 5.0, *J* = 18.2 Hz, 1 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 214.1, 145.2, 111.7, 79.3, 73.9, 51.8, 48.7, 48.3, 42.7 ppm. HRMS (EI): calcd. for C₉H₁₀O₂ [M]⁺ 150.0681; found 150.0692. IR: ν̄ = 2965, 2831, 1747, 1291, 1114, 1056, 1001, 943, 819, 732 cm^{–1}. [α]_D²¹ = +12.1 (*c* = 0.90, CHCl₃). *R*_f (pentane/Et₂O, 2:1): 0.14.

[(1*S*,5*R*,6*S*)-Bicyclo[3.2.0]hept-2-en-6-yloxy](tert-butyl)dimethylsilane [(–)-57**]:** TBSCl (9.36 g, 59.0 mmol) was added to a solution of alcohol (+)-**56** (5.00 g, 45.4 mmol) in anhydrous CH₂Cl₂ (91 mL) at 0 °C under Ar, and then Et₃N (10.1 mL, 72.6 mmol) and DMAP (277 mg, 2.30 mmol) were added. The reaction mixture was allowed to warm to room temp. overnight. NH₄Cl (saturated aq.; 50 mL) was added. The mixture was diluted with CH₂Cl₂ (50 mL), washed in sequence with HCl (0.5 M; 40 mL), water (40 mL), and brine (2 × 50 mL), and dried with MgSO₄. The volatile materials were removed under reduced pressure to give a crude product. Purification by column chromatography (SiO₂, hexane) gave protected alcohol (–)-**57** (9.52 g, 94%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 5.85–5.75 (m, 2 H), 4.51–4.44 (m, 1 H), 3.14–3.04 (m, 1 H), 2.92–2.80 (m, 2 H), 2.64–2.54 (m, 1 H), 2.36–2.26 (m, 1 H), 1.64–1.56 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 134.6, 133.0, 65.6, 44.1, 40.8, 39.1, 31.5, 26.0 (3 C), 18.3, –4.7 (2 C) ppm. HRMS (EI): calcd. for C₉H₁₅OSi [M – *t*Bu]⁺ 167.0892; found 167.0890. IR: ν̄ = 2930, 2857, 1709, 1471, 1254, 1125, 1004, 879, 837, 777 cm^{–1}. [α]_D²² = –0.2 (*c* = 1.0, CHCl₃). *R*_f (hexane): 0.49.

(1*R*,5*R*,6*S*)-6-[(tert-butyl)dimethylsilyloxy]bicyclo[3.2.0]hept-3-en-2-one [(–)-58**]:** A solution of alkyne (–)-**57** (9.36 g, 41.7 mmol), acetic anhydride (4.34 mL, 45.9 mmol), pyridine (1.69 mL, 20.9 mmol), DMAP (305 mg, 2.50 mmol), and tetraphenylporphyrin (25.6 mg, 41.7 μmol) in CH₂Cl₂ (52 mL) was irradiated with a halogen lamp (500 W) for 7 d under vigorous stirring while O₂ was bubbled con-

tinuously through the solution. The mixture was diluted with CH_2Cl_2 (100 mL), washed in sequence with NaHCO_3 (saturated aq.; 50 mL), water (50 mL), CuSO_4 (saturated aq.; 50 mL), and brine (50 mL), and dried with MgSO_4 . The volatile materials were removed under reduced pressure to give crude enone (–)-**58** (10.0 g, 100%) as a dark red oil containing <5% of starting material. An aliquot was purified by column chromatography (SiO_2 , hexane/EtOAc, 5:1) for analytical purposes. ^1H NMR (400 MHz, CDCl_3): δ = 7.66 (dd, J = 2.8, J = 5.6 Hz, 1 H), 6.39 (dd, J = 1.1, J = 5.6 Hz, 1 H), 4.58 (q, J = 7.7 Hz, 1 H), 3.68–3.62 (m, 1 H), 2.84–2.74 (m, 1 H), 2.60–2.52 (m, 1 H), 1.84–1.76 (m, 1 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 212.3, 162.7, 136.8, 65.3, 49.4, 36.9, 35.4, 25.8 (3 C), 18.1, –4.7, –4.9 ppm. HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2\text{Si}$ 238.1389; found 238.1389. IR: $\tilde{\nu}$ = 2953, 2857, 1706, 1252, 1183, 1122, 949, 870, 837, 777 cm^{-1} . $[\alpha]_D^{25}$ = –179.5 (c = 1.0, CHCl_3). R_f (hexane/EtOAc, 5:1): 0.25.

Optimized Procedure for TMS Enol Ether (–)-**59**

Procedure A, From Enone (–)-58**:** MeLi (1.6 M in Et_2O ; 336 mL, 503 mmol) was slowly added to a suspension of CuI (47.9 g, 252 mmol) in anhydrous Et_2O (840 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then cooled to –78 °C. A solution of enone (–)-**58** (60.0 g, 252 mmol) in Et_2O (100 mL) was slowly added to the solution over 25 min. The mixture was stirred for 1 h at –78 °C and then warmed quickly to 0 °C. TMSCl (39.9 mL, 315 mmol) was rapidly added, followed immediately by Et_3N (43.8 mL, 315 mmol). The mixture was stirred for 16 h at 0 °C and then ether (300 mL) and water (300 mL) were slowly added. The organic phase was extracted with NH_4OH (10% aq.; 3×100 mL), water (3×150 mL), and brine (200 mL), dried with MgSO_4 , and filtered. The volatiles were removed to give pure TMS enol ether (–)-**59** (82.2 g, quantitative).

Procedure B, From Ketone (–)-61**:** TMSOTf (17.2 mL, 95.1 mmol) and Et_3N (23.2 mL, 166 mmol) were slowly added to a suspension of ketone (–)-**61** (12.1 g, 47.6 mmol) in anhydrous Et_2O (237 mL) at 0 °C. The mixture was stirred for 16 h at 0 °C and then NaHCO_3 (saturated aq.; 500 mL) was added. The aqueous phase was extracted with Et_2O (2×250 mL), and the combined organic extracts were washed with water (2×150 mL) and brine (200 mL), dried with MgSO_4 , and filtered. The volatiles were removed to give pure TMS enol ether (–)-**59** (15.4 g, 99%).

Optimized Procedure for Enone (–)-60**:** Crude TMS enol ether (–)-**59** (82.2 g, 252 mmol) was dissolved in DMSO (840 mL), and the solution was warmed to 32 °C and saturated with oxygen by bubbling gas through the solution for 10 min. Under an O_2 atmosphere, $\text{Pd}(\text{OAc})_2$ (28.2 g, 126 mmol) was added in one portion. After 3 h, the reaction mixture was filtered through Celite (10 cm thick). The filtrate was diluted with EtOAc (400 mL), and the filtration through Celite (10 cm thick) was repeated. A mixture of water (200 mL) and crushed ice (200 g) was added with vigorous agitation. After separation of the phases, the organic phase was washed with water (2×100 mL). The combined aqueous phases were extracted with EtOAc (3×200 mL). The organic extracts were combined, washed with water (3×100 mL) and brine (100 mL), dried with MgSO_4 , and concentrated under reduced pressure. NMR analysis showed a 4:1 mixture of enone (–)-**60** and ketone (–)-**61**. Compounds (–)-**60** and (–)-**61** were separated by column chromatography (hexane/EtOAc, 20:1 then 5:1) to give ketone (–)-**61** (12.1 g, 19%) and enone (–)-**60** (51.4 g, 81%). Data for enone (–)-**60**: ^1H NMR (400 MHz, CDCl_3): δ = 6.09 (s, 1 H), 4.61 (q, J = 7.7 Hz, 1 H), 3.50–3.44 (m, 1 H), 2.79–2.69 (m, 1 H), 2.59–2.52 (m, 1 H), 2.19 (s, 3 H), 1.81–1.73 (m, 1 H), 0.85 (s, 9 H), 0.04 (s, 3

H), 0.00 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 211.9, 177.4, 132.3, 65.2, 51.9, 38.2, 34.9, 25.7 (3 C), 19.9, 17.9, –4.77, –5.05 ppm. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{Si}$ [M]⁺ 252.1546; found 252.1548. IR: $\tilde{\nu}$ = 2929, 2857, 1698, 1613, 1253, 1183, 1117, 955, 838, 778 cm^{-1} . $[\alpha]_D^{20}$ = –238.0 (c = 1.0, CHCl_3). R_f (hexane/EtOAc, 3:1): 0.32.

Data for ketone (–)-**61**: ^1H NMR (400 MHz, CDCl_3): δ = 4.43 (q, J = 7.2 Hz, 1 H), 2.85–2.73 (m, 2 H), 2.73–2.55 (m, 2 H), 2.55–2.45 (m, 1 H), 2.00–1.90 (m, 2 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 220.9, 64.6, 50.9, 47.2, 39.6, 36.3, 27.3, 25.9 (3 C), 21.6, 18.1, –4.6, –4.9 ppm. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_2\text{Si}$ [M – CH_3]⁺ 239.1467; found 239.1465. IR: $\tilde{\nu}$ = 2954, 2857, 1735, 1252, 1187, 1118, 949, 887, 837, 777 cm^{-1} . $[\alpha]_D^{25}$ = –96.4 (c = 1.0, CHCl_3). R_f (hexane/EtOAc, 4:1): 0.24.

(1R,2R,4R,6R,8S)-8-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-3-oxatricyclo[4.2.0.0.2,4]octan-5-one [(–)-62**]:** Enone (–)-**60** (150 mg, 0.59 mmol) was dissolved in MeOH (6.1 mL), and the solution was cooled to –20 °C. NaOH (1 M aq.; 179 μL , 0.179 mmol) was added, followed by the dropwise addition of hydrogen peroxide (30 wt.-%; 750 μL). The reaction mixture was allowed to warm to 0 °C. After 1 h at this temperature, the reaction was quenched with HCl (0.5 M aq.; 2 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (saturated aq.; 5 mL). The solution was diluted with water (40 mL) and EtOAc (60 mL), the phases were separated, and the aqueous phase extracted with EtOAc (60 mL). The combined organic extracts were washed with brine (40 mL), dried with MgSO_4 , filtered and concentrated. The crude product (160 mg, 99%) was used without further purification. ^1H NMR (400 MHz, CDCl_3): δ = 4.49–4.40 (m, 1 H), 3.35 (s, 1 H), 3.17 (t, J = 6.8 Hz, 1 H), 2.75–2.64 (m, 1 H), 2.60–2.53 (m, 1 H), 1.77 (ddt, J = 1.1, J = 4.1, J = 12.8 Hz, 1 H), 1.63 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 211.0, 65.9, 64.2, 63.8, 47.4, 38.8, 35.2, 25.8 (3 C), 18.0, 16.8, –4.6, –5.0 ppm. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_3\text{SiNa}$ [M + Na]⁺ 291.1392; found 291.1383. IR: $\tilde{\nu}$ = 2931, 2587, 1743, 1399, 1254, 1124, 1070, 922, 834, 776 cm^{-1} . $[\alpha]_D^{22}$ = –32.8 (c = 1.00, CHCl_3). R_f (hexane/EtOAc, 5:1): 0.45.

(1R,2S,5S,7S)-7-[(*tert*-Butyldimethylsilyl)oxy]-2-methylbicyclo[3.2.0]hept-3-en-2-ol [(–)-63**]:** $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (27 μL , 0.56 mmol) and AcOH (80 μL , 1.40 mmol) were added to a solution of epoxide (–)-**62** (75 mg, 0.28 mmol) in MeOH (3 mL) at 0 °C. After 5 min at this temperature, TLC showed no remaining starting materials, and the hydrazine intermediate and a new product spot had appeared. The mixture was stirred for a further 15 min. The mixture was then heated to reflux for 2 h. Then water (5 mL) was added. The solution was neutralized with NaHCO_3 and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (15 mL) and dried with MgSO_4 . Removal of the solvent by rotary evaporation and purification by flash column chromatography (hexane/EtOAc, 6:1) gave tertiary alcohol (–)-**63** (29 mg, 40%) as an unstable colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 5.93 (dd, J = 2.4, J = 5.3 Hz, 1 H), 5.80 (d, J = 5.3 Hz, 1 H), 4.58–4.48 (m, 1 H), 3.09–3.00 (m, 1 H), 2.91–2.83 (m, 1 H), 2.59–2.49 (m, 1 H), 1.62 (s, 3 H), 1.56–1.44 (m, 2 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 140.0, 136.7, 85.4, 65.8, 54.7, 39.2, 38.6, 29.7, 25.8 (3 C), 24.1, –3.6, –4.8 ppm. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{SiNa}$ [M + Na]⁺ 277.1600; found 277.1583. IR: $\tilde{\nu}$ = 2998, 2787, 1319, 1124, 1099, 1021, 977, 902, 874, 736 cm^{-1} . $[\alpha]_D^{20}$ = –5.9 (c = 1.2, CHCl_3). R_f (hexane/EtOAc, 5:1): 0.17.

Alkene (–)-64**:** Cerium chloride heptahydrate (5.79 g, 15.6 mmol) was added to a stirred solution of enone (–)-**60** (3.27 g, 13.0 mmol)

in MeOH (65 mL) at room temp. After 5 min, the mixture was cooled to 0 °C, and NaBH₄ (539 mg, 14.3 mmol) was added portionwise. The reaction mixture was stirred at 0 °C until the starting material had been completely consumed (30 min). The reaction was quenched by the addition of acetic acid (1:1 in water; 5 mL). Water (100 mL) and EtOAc (150 mL) were added, and the heterogeneous mixture was extracted with EtOAc (4 × 80 mL). The organic phase was washed with water (2 × 75 mL) and brine (2 × 50 mL). The combined organic extracts were dried with MgSO₄, and the solvent was removed under reduced pressure to give crude allylic alcohol (3.30 g, quantitative) as a viscous oil.

The crude alcohol (3.30 g, 12.9 mmol) was dissolved in CH₂Cl₂ (43 mL), and *i*Pr₂NEt (6.78 mL, 38.9 mmol) and MOMCl (2.45 mL, 32.3 mmol) were added at 0 °C. The reaction mixture was stirred at room temp. for 15 h. After the addition of water (100 mL) and CH₂Cl₂ (150 mL), the organic phase was washed with NaHCO₃ (5% aq.; 75 mL) and brine (3 × 60 mL), then dried with MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO₂, hexane/EtOAc, 20:1) to give alkene (–)-**64** (3.29 mg, 85%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 5.41 (br. s, 1 H), 4.80 (dq, *J* = 1.7, *J* = 7.1 Hz, 1 H), 4.62 (d, *J* = 6.7 Hz, 1 H), 4.57 (d, *J* = 6.7 Hz, 1 H), 4.27 (q, *J* = 7.7 Hz, 1 H), 3.36 (s, 3 H), 3.19 (br. s, 1 H), 2.55–2.45 (m, 1 H), 2.32–2.22 (m, 1 H), 2.20–2.11 (m, 1 H), 1.83 (br. s, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 144.0, 127.4, 96.3, 85.0, 65.4, 55.6, 55.3, 32.3, 31.7, 26.0 (3 C), 18.2, 17.1, –4.5, –4.8 ppm. HRMS (ESI): calcd. for C₁₆H₃₀O₃Si Na [M + Na]⁺ 321.1862; found 321.1866. IR: ν̄ = 2929, 2857, 2361, 2342, 1375, 1254, 1122, 1042, 835, 776 cm^{–1}. [α]_D²⁴ = 81.4 (*c* = 1.1, CHCl₃). *R*_f (hexane/EtOAc, 5:1): 0.55.

Optimized Procedure for Alcohol (–)-65: Co(acac)₂ (741 mg, 2.88 mmol) was added to a solution of alkene (–)-**64** (8.60 g, 28.8 mmol) in THF (300 mL) in a 2 L flask at room temp. The reaction mixture was then saturated with O₂ (40 min), and then PhSiH₃ (14.2 mL, 115 mmol) was added over 45 min using a syringe pump, while a gentle flow of O₂ was blown 5 cm above the well-stirred solution. The O₂ flow was reduced, and stirring was maintained for 15 h at room temp. The reaction mixture was diluted with EtOAc (250 mL), water (100 mL), and saturated NaHCO₃ (100 mL), and stirred for a further 24 h. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The aqueous phase was saturated with solid NaCl and further extracted with EtOAc (2 × 200 mL). The combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane/EtOAc, 3:1) to give tertiary alcohol (–)-**65** (7.93 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ = 4.60 (d, *J* = 6.4 Hz, 1 H), 4.57 (d, *J* = 6.4 Hz, 1 H), 4.48–4.36 (m, 2 H), 3.34 (s, 3 H), 2.69–2.55 (m, 2 H), 2.29–2.20 (m, 1 H), 2.18–2.09 (m, 1 H), 2.08–1.96 (m, 2 H), 1.49 (s, 3 H), 1.24 (br. s, 1 H), 0.88 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 96.1, 79.7, 78.9, 64.7, 55.5, 55.4, 44.5, 33.5, 30.3, 26.0 (3 C), 25.5, 18.2, –4.6, –5.0 ppm. HRMS (EI): calcd. for C₁₆H₃₂O₄SiNa [M + Na]⁺ 339.3968; found 339.3964. IR: ν̄ = 3405, 2955, 2884, 2362, 1254, 1132, 1044, 869, 867, 777 cm^{–1}. [α]_D²⁴ = –1.73 (*c* = 1.1, CHCl₃). *R*_f (hexane/EtOAc, 2:1): 0.25.

Optimized Procedure for Alcohol (–)-66: Alcohol (–)-**65** (18.3 g, 57.8 mmol) was dissolved in THF (290 mL), and the solution was cooled to 0 °C. 2,6-Lutidine (26.9 mL, 231 mmol) and then TBSOTf (26.6 mL, 116 mmol) were rapidly added to the reaction vessel, and the mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of NaHCO₃ (150 mL), and the mix-

ture was diluted with water (100 mL) and diethyl ether (200 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 150 mL). The organic phases were dried with Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, hexane/EtOAc, 15:1) to give the di-TBS-protected alcohol (25.5 g, quantitative) contaminated with TBS-OH and 2,6-lutidine. ¹H NMR (400 MHz, CDCl₃): δ = 4.61 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.45–4.32 (m, 2 H), 3.34 (s, 3 H), 2.70–2.63 (m, 1 H), 2.70–2.54 (m, 1 H), 2.28–2.17 (m, 1 H), 2.07–1.97 (m, 3 H), 1.48 (s, 3 H), 0.88 (s, 9 H), 0.83 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 96.3, 82.2, 79.7, 65.0, 55.9, 55.5, 45.6, 33.7, 30.3, 26.0 (3 C), 25.9 (3 C), 24.9, 18.2, 18.1, –2.0, –2.2, –4.6, –5.0 ppm. HRMS (ESI): calcd. for C₂₂H₄₆O₄SiNa [M + Na]⁺ 453.2832; found 453.2813. IR: ν̄ = 2929, 2856, 1253, 1108, 1076, 1043, 1001, 939, 832, 772 cm^{–1}. [α]_D²⁴ = –9.3 (*c* = 1.0, CHCl₃). *R*_f (hexane/EtOAc, 5:1): 0.61.

The crude residue was dissolved in THF (116 mL), and the solution was cooled to 0 °C. Then, TBAF (1 M in THF; 69.6 mL, 69.6 mmol) was added over 15 min. The reaction mixture was allowed to warm slowly to room temp. overnight, and then the volatiles were removed under reduced pressure at 30 °C. The residue was purified by column chromatography (SiO₂, hexane/EtOAc, 3:1) to give alcohol (–)-**66** (17.1 g, 93%). ¹H NMR (400 MHz, CDCl₃): δ = 4.60 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.53–4.42 (m, 1 H), 4.40–4.31 (m, 1 H), 3.33 (s, 3 H), 2.69–2.57 (m, 2 H), 2.35–2.25 (m, 1 H), 2.11–1.97 (m, 3 H), 1.68 (d, *J* = 3.7 Hz, 1 H), 1.50 (s, 3 H), 0.82 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 96.3, 81.9, 79.6, 65.0, 55.5, 55.4, 45.9, 33.7, 28.9, 25.8 (3 C), 24.9, 18.1, –2.0, –2.2 ppm. HRMS (ESI): calcd. for C₁₆H₃₂O₄SiNa [M + Na]⁺ 339.1968; found 339.1961. IR: ν̄ = 3444, 2930, 2856, 1461, 1252, 1107, 1036, 995, 832, 772 cm^{–1}. [α]_D²⁰ = –34.8 (*c* = 1.0, CHCl₃). *R*_f (hexane/EtOAc, 3:1): 0.30.

Optimized Procedure for Diol (–)-67: Alcohol (–)-**66** (8 g, 25.3 mmol) was dissolved in EtOAc (168 mL), and IBX (14.1 g, 50.6 mmol) was added to the solution. The heterogeneous mixture was heated to reflux for 3 h and then cooled to room temp. Hexane (150 mL) was added, and stirring was continued for 15 min. The suspension was filtered through a Celite pad (3 cm), and the filtrate was concentrated to give the ketone (7.90 g, 99%). ¹H NMR (400 MHz, CDCl₃): δ = 4.65 (s, 2 H), 4.63–4.55 (m, 1 H), 4.43–4.37 (m, 1 H), 3.35 (s, 3 H), 3.19–3.11 (m, 1 H), 3.10–3.00 (m, 1 H), 2.95–2.86 (m, 1 H), 2.15 (ddd, *J* = 1.9, *J* = 6.4, *J* = 13.0 Hz, 1 H), 1.63 (dd, *J* = 11.1, *J* = 13.0 Hz, 1 H), 1.38 (s, 3 H), 0.84 (s, 9 H), 0.10 (s, 36 H), 0.08 (s, 3 H) ppm. ¹³C NMR (400 MHz, CDCl₃): δ = 209.1, 96.5, 79.5, 78.9, 76.0, 55.7, 45.3, 45.2, 31.4, 25.8 (3 C), 24.5, 18.0, –2.2, –2.5 ppm. HRMS (ESI): calcd. for C₁₆H₃₀O₄SiNa [M + Na]⁺ 337.1811; found 337.1804. IR: ν̄ = 2929, 2856, 1777, 1253, 1147, 1109, 1042, 833, 773, 696 cm^{–1}. [α]_D²⁰ = –151.6 (*c* = 1.4, CHCl₃). *R*_f (hexane/EtOAc, 2:1): 0.55.

DBU (11.2 mL, 75.4 mmol) was slowly added to a solution of crude ketone (7.90 g, 25.1 mmol) in formalin (65 mL). A cold water bath was used to avoid a slight increase of temperature. The water bath was then warmed to 30 °C, and the solution was stirred vigorously for a further 30 min. The reaction mixture was diluted with water (120 mL) and EtOAc (200 mL), and the aqueous phase was extracted with EtOAc (6 × 80 mL). The combined organic extracts were washed with brine (40 mL), dried with MgSO₄, and concentrated under reduced pressure to give diol (–)-**67** (10.1 g, quantitative) contaminated with polymethylene ether derivatives. ¹H NMR (400 MHz, CDCl₃): δ = 4.79–4.70 (m, 3 H), 4.11 (d, *J* = 12.9 Hz,

1 H), 3.92 (d, $J = 11.2$ Hz, 1 H), 3.87–3.78 (m, 2 H), 3.49 (d, $J = 9.6$ Hz, 1 H), 3.42 (dd, $J = 2.0$, $J = 7.5$ Hz, 1 H), 3.39 (s, 3 H), 3.20 (t, $J = 7.7$ Hz, 1 H), 2.83 (br. s, 1 H), 2.28 (ddd, $J = 2.0$, $J = 6.5$, $J = 12.6$ Hz, 1 H), 1.71 (t, $J = 12.3$ Hz, 1 H), 1.42 (s, 3 H), 0.85 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 210.0$, 97.3, 80.6, 80.0, 71.5, 71.4, 67.3, 61.9, 55.9, 46.9, 39.8, 25.8 (3 C), 24.5, 18.1, 0.0, -0.2 ppm. HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{34}\text{O}_6\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 397.2022; found 397.2022. IR: $\tilde{\nu} = 3416$, 2929, 2856, 1766, 1254, 1153, 1109, 1001, 835, 774 cm^{-1} . $[\alpha]_D^{25} = -91.6$ ($c = 1.05$, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.25.

Optimized Procedure for Alkene (–)-68: Imidazole (8.55 g, 126 mmol) was added to a solution of crude diol (–)-67 (10.1 g, 25.1 mmol) in CH_2Cl_2 (251 mL) at 0 °C, and then neat TESCl (9.28 mL, 55.3 mmol) was added. The resulting mixture was allowed to warm slowly to room temp. overnight before it was quenched with NaHCO_3 (saturated aq.; 120 mL). The aqueous phase was extracted with CH_2Cl_2 (2×80 mL). The combined organic extracts were washed with water (3×90 mL) and brine (50 mL), dried with MgSO_4 , and concentrated under reduced pressure to give the desired ketone (17.2 g, quantitative) contaminated with TES-OH. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.80$ – 4.72 (m, 1 H), 4.71 (d, $J = 6.6$ Hz, 1 H), 4.56 (d, $J = 6.6$ Hz, 1 H), 3.98 (d, $J = 10.5$ Hz, 1 H), 3.91 (d, $J = 10.5$ Hz, 1 H), 3.86 (d, $J = 9.3$ Hz, 1 H), 3.81 (d, $J = 9.3$ Hz, 1 H), 3.36 (s, 3 H), 3.27 (dd, $J = 2.0$, $J = 7.6$ Hz, 1 H), 3.12 (t, $J = 7.6$ Hz, 1 H), 2.11 (ddd, $J = 2.2$, $J = 6.4$, $J = 12.6$ Hz, 1 H), 1.76 (t, $J = 12.3$ Hz, 1 H), 1.41 (s, 3 H), 0.95 (t, $J = 8.0$ Hz, 9 H), 0.94 (t, $J = 8.0$ Hz, 9 H), 0.84 (s, 9 H), 0.62–0.53 (m, 12 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 212.3$, 96.0, 79.4, 78.4, 73.0, 71.3, 65.0, 60.2, 55.3, 47.7, 39.0, 25.8 (6 C), 24.7, 18.1, 6.9 (3 C), 4.5 (6 C), -2.3 , -2.6 ppm. HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{62}\text{O}_6\text{Si}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ 625.3752; found 625.3740. IR: $\tilde{\nu} = 2954$, 2877, 1772, 1461, 1085, 1046, 1003, 834, 805, 740 cm^{-1} . $[\alpha]_D^{25} = -113.6$ ($c = 1.0$, CHCl_3). R_f (hexane/EtOAc, 1:1): 0.75.

Cp_2TiMe_2 (19 wt.-% in toluene; 54.7 mL, 42.7 mmol) was mixed with the carbonyl compound (17.2 g, 25.1 mmol) and the mixture was stirred under argon at 65 °C for 3 d. The mixture was diluted with hexane (150 mL), stirred for 30 min, and then cooled in the fridge overnight. The resulting yellow-orange precipitate was removed by filtration (two or three filtrations were required), and the filtrate was concentrated. The residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 20:1) to give alkene (–)-68 (14.2 g, 94%, 93% over 4 steps) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.15$ (d, $J = 2.7$ Hz, 1 H), 4.82 (d, $J = 2.1$ Hz, 1 H), 4.69 (d, $J = 6.4$ Hz, 1 H), 4.60–4.52 (m, 1 H), 4.49 (d, $J = 6.4$ Hz, 1 H), 3.96 (d, $J = 10.1$ Hz, 1 H), 3.87 (d, $J = 9.3$ Hz, 1 H), 3.84 (d, $J = 10.2$ Hz, 1 H), 3.40 (d, $J = 9.3$ Hz, 1 H), 3.33 (s, 3 H), 3.01–2.96 (m, 1 H), 2.86 (t, $J = 7.2$ Hz, 1 H), 2.00–1.86 (m, 2 H), 1.38 (s, 3 H), 0.96 (t, $J = 7.9$ Hz, 9 H), 0.95 (t, $J = 7.9$ Hz, 9 H), 0.84 (s, 9 H), 0.54 (q, $J = 7.9$ Hz, 6 H), 0.54 (q, $J = 7.9$ Hz, 6 H), 0.09 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 155.2$, 112.1, 97.6, 83.5, 80.2, 68.5, 64.3, 57.9, 57.5, 54.9, 48.4, 45.1, 28.5 (3 C), 26.4, 20.3, 9.2 (3 C), 9.2 (3 C), 6.9 (3 C), 6.9 (3 C), 0.0, -0.1 ppm. HRMS (ESI): calcd. for $\text{C}_{31}\text{H}_{64}\text{O}_5\text{Si}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ 623.3959; found 623.3952. IR: $\tilde{\nu} = 2954$, 2878, 1461, 1253, 1072, 1046, 1004, 836, 773, 742 cm^{-1} . $[\alpha]_D^{25} = -60.5$ ($c = 1.0$, CHCl_3). R_f (hexane/EtOAc, 40:1): 0.26.

Acetate *rac*-69: Cerium chloride heptahydrate (1.24 g, 3.33 mmol) was added to a stirred solution of crude enone *rac*-60 (700 mg, 2.77 mmol) in MeOH (14 mL) at room temp. After 5 min, the mixture was cooled to 0 °C, and NaBH_4 (115 mg, 3.05 mmol) was added portionwise. The reaction mixture was stirred at 0 °C until

the starting material had been completely consumed (30 min). The reaction was quenched by the addition of a few drops of acetic acid (50% aq.) to reach neutral pH. Water (30 mL) and EtOAc (50 mL) were added, and the heterogeneous mixture was extracted with EtOAc (4×20 mL). The combined organic extracts were washed with water (2×15 mL) and brine (2×15 mL), and dried with MgSO_4 . The solvent was removed under reduced pressure to give the crude allylic alcohol as a viscous oil.

Acetic anhydride (394 μL , 4.15 mmol), pyridine (448 μL , 5.54 mmol), and 4-(dimethylamino)pyridine (34 mg, 0.28 mmol) were added to a solution of the crude alcohol (705 mg, 2.77 mmol) in CH_2Cl_2 (28 mL) at 0 °C. The solution was allowed to warm to room temp. overnight. The mixture was diluted with CH_2Cl_2 (12 mL), washed in sequence with NaHCO_3 (saturated aq.; 15 mL), water (15 mL), and brine (10 mL), and dried with MgSO_4 . The volatile materials were removed by evaporation to give the crude product. Purification over a short column (SiO_2 , hexane/EtOAc, 20:1) gave acetate *rac*-69 (673 mg, 82%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.66$ – 5.61 (m, 1 H), 5.41 (br. s, 1 H), 4.29 (q, $J = 7.7$ Hz, 1 H), 3.22 (t, $J = 6.6$ Hz, 1 H), 2.77–2.65 (m, 1 H), 2.17–2.09 (m, 2 H), 2.03 (s, 3 H), 1.88–1.84 (m, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 171.3$, 146.2, 125.4, 82.65, 65.14, 55.18, 31.99, 31.49, 26.00 (3 C), 21.11, 18.21, 17.16, -4.61 , -4.81 ppm. HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{28}\text{O}_3\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 319.1705; found 319.1678. IR: $\tilde{\nu} = 2929$, 2858, 1735, 1372, 1242, 1123, 1021, 872, 836, 777 cm^{-1} . R_f (hexane/EtOAc, 5:1): 0.54.

Alcohol *rac*-70: Co(acac) $_2$ (18 mg, 67 μmol) was added to a solution of acetate *rac*-69 (100 mg, 0.34 mmol) in THF (6 mL). The reaction mixture was then saturated with O_2 (20 min), and then PhSiH_3 (166 μL , 1.35 mmol) was added over 15 min. Stirring was continued under a static O_2 atmosphere for 15 h at room temp. The reaction mixture was then diluted with EtOAc (15 mL), washed with NaHCO_3 (10 mL), water (10 mL), and brine (10 mL), dried with MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 5:1) to give tertiary alcohol *rac*-70 (71 mg, 67%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.34$ – 5.26 (m, 1 H), 4.48–4.40 (m, 1 H), 2.85–2.77 (m, 1 H), 2.66–2.59 (m, 1 H), 2.30–2.15 (m, 2 H), 2.13–2.06 (m, 1 H), 2.03 (s, 3 H), 1.94–1.86 (m, 1 H), 1.50 (s, 3 H), 1.18 (br. s, 1 H), 0.89 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 171.0$, 79.6, 76.3, 64.7, 55.1, 43.6, 33.4, 30.2, 26.0 (3 C), 25.2, 21.2, 18.2, -4.7 , -4.9 ppm. HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{30}\text{O}_4\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 337.1811; found 337.1821. IR: $\tilde{\nu} = 3420$, 2930, 2857, 1737, 1374, 1250, 1131, 1041, 837, 778 cm^{-1} . R_f (hexane/EtOAc, 1:1): 0.48.

Diol *rac*-71: TBAF (1 M in THF; 159 μL , 0.16 mmol) was added to a stirred solution of alcohol *rac*-70 (50 mg, 0.16 mmol) in THF (2 mL) at 0 °C. The solution was allowed to warm to room temp., and after stirring for 1 h, the reaction was quenched by the addition of NaHCO_3 (saturated aq.; 10 mL). The mixture was diluted with water (30 mL) and Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2×20 mL). The organic phases were combined, dried with Na_2SO_4 , filtered, and concentrated to give a colorless oil. This residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 1:1) to give diol *rac*-71 (27 mg, 85%), which crystallized from CHCl_3 as a colorless plates. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.31$ (dt, $J = 7.1$, $J = 10.4$ Hz, 1 H), 4.53 (q, $J = 8.1$ Hz, 1 H), 2.90–2.80 (m, 1 H), 2.66–2.58 (m, 1 H), 2.38–2.27 (m, 1 H), 2.24–2.10 (m, 2 H), 2.03 (s, 3 H), 1.99–1.90 (m, 1 H), 1.64 (br. s, 1 H), 1.53 (s, 3 H), 1.33 (br. s, 1 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 171.0$, 79.4, 76.2,

64.7, 54.6, 43.7, 33.2, 28.7, 25.6, 21.2 ppm. HRMS (EI): calcd. for $C_{10}H_{16}O_4Na$ $[M + Na]^+$ 223.0946; found 223.0937. IR: $\tilde{\nu}$ = 3367, 2925, 1714, 1377, 1264, 1173, 1107, 1039, 853, 612 cm^{-1} , m.p. 117–120 °C. R_f (EtOAc): 0.40.

{(1R,2S,4S,5S)-2-[(tert-Butyldimethylsilyloxy]-4-(methoxymethoxy)-2-methyl-7-methylenebicyclo[3.2.0]heptane-6,6-diyl}dimethanol [(–)-72]: HF (70% in pyridine; 269 μ L, 9.22 mmol) was slowly added to a solution of (–)-68 (277 mg, 0.46 mmol) in THF (3 mL) in a teflon vial at 0 °C. The mixture was stirred for 30 min at the same temperature, after which time TLC analysis indicated a clean conversion. The reaction was carefully quenched with $NaHCO_3$ (saturated aq.; 10 mL) and the mixture was extracted with EtOAc (3 $\times$ 30 mL). The combined organic extracts were washed with water (30 mL) and brine (50 mL), dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (SiO_2 , hexane/EtOAc, 2:1) to give diol (–)-72 (170 mg, 99%) as a viscous colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ = 4.88 (d, J = 1.9 Hz, 1 H), 4.83 (d, J = 2.5 Hz, 1 H), 4.71 (d, J = 6.6 Hz, 1 H), 4.69 (d, J = 6.6 Hz, 1 H), 4.64–4.55 (m, 1 H), 4.05 (d, J = 11.9 Hz, 1 H), 3.80 (dd, J = 3.1, J = 11.1 Hz, 1 H), 3.77–3.63 (m, 3 H), 3.37 (s, 3 H), 3.20 (br. d, J = 7.0 Hz, 1 H), 3.07–2.98 (m, 2 H), 2.12 (ddd, J = 1.4, J = 6.4, J = 13.4 Hz, 1 H), 1.86 (t, J = 12.0 Hz, 1 H), 1.37 (s, 3 H), 0.84 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 151.0, 108.8, 97.1, 81.6, 80.8, 71.7, 65.7, 55.9, 55.1, 52.2, 45.6, 43.9, 25.8 (3 C), 24.0, 18.1, –2.2, –2.3 ppm. HRMS (ESI): calcd. for $C_{19}H_{36}O_5SiNa$ $[M + Na]^+$ 395.2230; found 395.2219. IR: $\tilde{\nu}$ = 3435, 2929, 1462, 1372, 1253, 1151, 1106, 1034, 835, 772 cm^{-1} . $[\alpha]_D^{20}$ = –64.4 (c = 1.0, $CHCl_3$). R_f (hexane/EtOAc, 2:1): 0.12.

Dialdehyde rac-73: DMSO (118 μ L, 0.166 mmol) was added to a solution of oxalyl chloride (70 μ L, 0.83 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C. The solution was stirred at –78 °C for 20 min. Compound rac-72 (50 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) was then added slowly to the reaction mixture. The solution was stirred at –78 °C for 1 h. Et_3N (290 μ L, 2.08 mmol) was added to the mixture, and stirring was continued at –78 °C for 15 min and then at 0 °C for 1 h. The reaction was quenched with NH_4Cl (5 mL), and the aqueous phase was extracted with EtOAc (2 $\times$ 25 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure (water bath temperature: 30 °C) to give pure dialdehyde rac-73 (29 mg, 95%). 1H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 9.61 (s, 1 H), 5.30 (dd, J = 1.6, J = 2.0 Hz, 1 H), 5.21 (dd, J = 1.5, J = 2.7 Hz, 1 H), 4.63 (dt, J = 6.8, J = 11.3 Hz, 1 H), 4.57 (d, J = 6.5 Hz, 1 H), 4.54 (d, J = 6.5 Hz, 1 H), 3.75 (t, J = 7.3 Hz, 1 H), 3.29 (s, 3 H), 3.07–3.03 (m, 1 H), 2.15 (ddd, J = 1.4, J = 6.7, J = 12.7 Hz, 1 H), 1.82 (dd, J = 11.6, J = 12.5 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.4, 194.6, 141.4, 115.8, 96.6, 82.0, 79.0, 71.3, 56.4, 46.2, 44.3, 25.8 (3 C), 23.6, 18.1, 8.8, –2.2, 2.3 ppm. HRMS (EI): calcd. for $C_{19}H_{32}O_5SiNa$ $[M + Na]^+$ 391.1917; found 391.1903. IR: $\tilde{\nu}$ = 2929, 2855, 1728, 1700, 1254, 1153, 1109, 1042, 835, 774 cm^{-1} . R_f (hexane/EtOAc, 2:1): 0.38.

Aldehyde rac-74: While trying to synthesize rac-73, undesired product rac-74 was formed almost quantitatively if the concentration of the organic phases was done in a water bath warmer than 30 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 4.80 (d, J = 6.8 Hz, 1 H), 4.55 (d, J = 6.8 Hz, 1 H), 4.36–4.28 (m, 1 H), 3.58–3.52 (m, 1 H), 3.34 (s, 3 H), 2.86–2.81 (m, 1 H), 2.12 (t, J = 1.4 Hz, 3 H), 2.02 (ddd, J = 1.7, J = 3.4, J = 12.9 Hz, 1 H), 1.83 (dd, J = 10.6, J = 12.8 Hz, 1 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 186.2, 162.6,

140.4, 95.8, 78.0, 74.0, 59.0, 55.4, 44.5, 43.9, 25.8 (3 C), 25.6, 18.2, 15.4, –2.1, –2.1 ppm. HRMS (EI): calcd. for $C_{18}H_{32}O_5SiNa$ $[M + Na]^+$ 363.1968; found 363.1962. IR: $\tilde{\nu}$ = 2928, 2855, 1678, 1254, 1150, 1101, 1040, 918, 860, 772 cm^{-1} . R_f (hexane/EtOAc, 2:1): 0.49.

Dimethyl Ester rac-75: A solution of dialdehyde rac-73 (40 mg, 0.11 mmol) and 2-methylbutene (300 μ L) in t BuOH (1.4 mL) was cooled to 0 °C, then a solution of $NaClO_2$ (122 mg, 1.09 mmol) and NaH_2PO_4 (180 mg, 1.30 mmol) in water (1 mL) was added. The mixture was stirred for 30 min. The solution was diluted with NH_4Cl (aq.; 15 mL) and extracted with Et_2O (2 $\times$ 30 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and concentrated. The crude dicarboxylic acid was dissolved in benzene/MeOH (3:2; 2 mL), and then $TMSCHN_2$ (2 M in Et_2O ; 200 μ L, 0.40 mmol) was added slowly at 0 °C. The solution was stirred at this temperature for 2 h, and then it was allowed to warm to room temp. overnight. After concentration, the residue was purified by column chromatography (SiO_2 , hexane/EtOAc, 15:1) to give an inseparable mixture (39 mg) containing dimethyl ester rac-75 (23 mg, 50%) and methyl ester rac-76 (16 mg, 40%). Data for rac-75: 1H NMR (400 MHz, $CDCl_3$): δ = 5.37 (dd, J = 0.8, J = 2.7 Hz, 1 H), 5.21 (dd, J = 0.9, J = 2.1 Hz, 1 H), 4.68–4.60 (m, 1 H), 4.58 (d, J = 6.6 Hz, 1 H), 4.46 (d, J = 6.6 Hz, 1 H), 3.83 (t, J = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.32 (s, 3 H), 3.10–3.04 (m, 1 H), 2.12 (t, J = 12.0 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.42 (s, 3 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.1, 169.3, 143.6, 115.4, 95.8, 81.3, 77.1, 59.2, 58.1, 56.4, 53.2, 52.3, 44.9, 44.2, 25.8 (3 C), 23.7, 18.1, –2.2, –2.3 ppm. HRMS (EI): calcd. for $C_{21}H_{36}O_7SiNa$ $[M + Na]^+$ 451.2128; found 451.2143. R_f (hexane/EtOAc, 5:1): 0.28.

Data for rac-76: 1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (d, J = 6.9 Hz, 1 H), 4.53 (d, J = 6.9 Hz, 1 H), 4.34 (dt, J = 6.7, J = 10.4 Hz, 1 H), 3.71 (s, 3 H), 3.51–3.46 (m, 1 H), 3.34 (s, 3 H), 2.76–2.73 (m, 1 H), 2.04 (t, J = 1.3 Hz, 3 H), 2.00–1.91 (m, 1 H), 1.86 (dd, J = 10.5, J = 12.8 Hz, 1 H), 1.34 (s, 3 H), 0.85 (s, 9 H), 0.10 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.3, 159.8, 131.5, 95.5, 73.6, 59.1, 55.5, 55.2, 51.0, 44.4, 43.7, 25.8 (3 C), 23.7, 18.2, 16.1, –2.0, –2.1 ppm. HRMS (EI): calcd. for $C_{19}H_{34}O_5SiNa$ $[M + Na]^+$ 391.2073; found 391.2083. R_f (hexane/EtOAc, 5:1): 0.28.

Lactone rac-77: $AcCl$ (10 drops) was added to an ice-cold solution of dimethyl ester rac-75 (54 mg, 0.12 mmol) in MeOH (6.3 mL). The resulting solution was stirred at the same temperature for 5 h, and then allowed to warm to room temp. to be stirred for a further 40 h. The mixture was concentrated and purified by column chromatography (SiO_2 , hexane/EtOAc, 2:1) to give the tricycle (30 mg, 99%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ = 5.63 (dd, J = 1.9, J = 2.8 Hz, 1 H), 5.36–5.29 (m, 2 H), 3.89 (dd, J = 6.5, J = 8.3 Hz, 1 H), 3.83 (s, 3 H), 3.31–3.26 (m, 1 H), 2.48 (ddd, J = 1.7, J = 7.8, J = 15.2 Hz, 1 H), 2.05 (dd, J = 5.0, J = 15.1 Hz, 1 H), 1.45 (s, 3 H), 1.30 (br. s, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.1, 167.1, 141.3, 117.3, 83.3, 82.4, 57.5, 53.4, 48.5, 46.9, 29.9, 24.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_5Na$ $[M + Na]^+$ 261.0739; found 261.0738. IR: $\tilde{\nu}$ = 3498, 2928, 1771, 1734, 1437, 1302, 1227, 1156, 1030, 906 cm^{-1} . R_f (EtOAc): 0.42.

The tricycle (30 mg, 0.13 mmol) was dissolved in THF (1.2 mL), and the solution was cooled to 0 °C. Lutidine (59 μ L, 0.50 mmol) and then TBSOTf (58 μ L, 0.25 mmol) were added to the reaction vessel, and the mixture was stirred for a further 45 min at 0 °C. The reaction was quenched by the addition of water (5 mL), and diluted with additional sodium hydrogen carbonate (aq.; 3 mL) and diethyl ether (30 mL). The phases were separated, and the aqueous

phase was extracted with diethyl ether (2×20 mL). The organic phases were dried with Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , hexane/EtOAc, 10:1) to give lactone **rac-77** (36 mg, 81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 5.58 (dd, J = 1.8, J = 2.8 Hz, 1 H), 5.31–5.24 (m, 2 H), 3.82 (s, 3 H), 3.79 (dd, J = 6.6, J = 8.5 Hz, 1 H), 3.31–3.26 (m, 1 H), 2.48 (ddd, J = 1.7, J = 7.8, J = 14.7 Hz, 1 H), 1.94 (dd, J = 5.5, J = 14.7 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 171.3, 167.3, 141.7, 117.0, 84.6, 83.6, 58.3, 57.9, 53.4, 49.3, 47.1, 25.7 (3 C), 23.3, 18.0, –2.3 (2 C) ppm. HRMS (EI): calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_5\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 375.1604; found 375.1613. IR: $\tilde{\nu}$ = 2954, 2857, 1779, 1734, 1254, 1151, 1038, 990, 836, 775 cm^{-1} . R_f (hexane/EtOAc, 5:1): 0.34.

Alcohol (–)-78: Cold Jones reagent (2.5 M in water; 665 μL , 1.66 mmol) was added to a stirred cooled (water/ice bath, 0°C) solution of alkene (–)-**68** (100 mg, 0.17 mmol) in acetone (3.3 mL). Stirring was continued for 40 min. The excess of the Jones reagent was quenched by the addition of IPA (1.5 mL). The suspension was stirred for 5 min at 0°C and for 10 min at room temp. The clear greenish supernatant was decanted, and the remaining green solid residue was extracted with EtOAc (5×15 mL). The combined organic extracts were washed with brine (2×5 mL) and dried with Na_2SO_4 . The volatiles were removed to give the crude carboxylic acid.

A solution of the crude carboxylic acid in THF (3.7 mL) was stirred at 0°C under Ar while Et_3N (43 μL , 0.31 mL) was added. The solution was stirred for 30 min, and then ethyl chloroformate (40 μL , 0.40 mmol) was added. The reaction mixture became cloudy as it was stirred at 0°C for 1.5 h. At this point, IPA (1 mL) was added, followed by NaBH_4 (30 mg, 0.79 mmol) 5 min later. The mixture was stirred at 0°C for 5 h, then it was diluted with Et_2O (20 mL), treated dropwise with HCl (5% aq.; 2 mL), and poured into a mixture of Et_2O (30 mL) and HCl (1% aq.; 20 mL). The aqueous phase was extracted with Et_2O (2×20 mL), and the combined organic extracts were washed with NaHCO_3 (saturated aq.; 2×20 mL) and brine (20 mL), dried with Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography (SiO_2 , hexane/EtOAc, 4:1) to give primary alcohol (–)-**78** (29 mg, 54%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 5.31 (dd, J = 1.4, J = 2.8 Hz, 1 H), 5.23 (dt, J = 5.5, J = 8.2 Hz, 1 H), 5.18 (dd, J = 1.6, J = 2.1 Hz, 1 H), 4.00 (dd, J = 7.1, J = 11.9 Hz, 1 H), 3.84 (dd, J = 5.6, J = 11.7 Hz, 1 H), 3.45 (dd, J = 6.0, J = 8.2 Hz, 1 H), 3.22–3.17 (m, 1 H), 2.47 (ddd, J = 1.9, J = 7.9, J = 14.6 Hz, 1 H), 2.23 (t, J = 6.4 Hz, 1 H), 1.94 (dd, J = 5.5, J = 14.6 Hz, 1 H), 1.42 (s, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 177.0, 144.9, 114.5, 84.9, 84.0, 63.4, 57.1, 55.6, 49.3, 44.8, 25.7 (3 C), 23.2, 18.0, –2.3, –2.3 ppm. HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{28}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 347.1655; found 347.1648. IR: $\tilde{\nu}$ = 3446, 2930, 2856, 1764, 1252, 1153, 1047, 988, 835, 774 cm^{-1} . $[\alpha]_D^{20}$ = –52.3 (c = 1.0, CHCl_3). R_f (hexane/EtOAc, 3:1): 0.20.

Aldehyde (–)-55: DMSO (16 μL , 0.22 mmol) was added to a solution of oxalyl chloride (9 μL , 0.11 mmol) in CH_2Cl_2 (0.6 mL) at -78°C . The solution was stirred for 20 min at -78°C , then alcohol (–)-**78** (18 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) was slowly added to the reaction mixture. The solution was stirred for 1 h at -78°C . Et_3N (46 μL , 0.33 mmol) was added, and stirring was continued for 15 min at -78°C and then for 1 h at 0°C . The reaction was quenched with NH_4Cl (5 mL) and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine (15 mL), dried with MgSO_4 , and concentrated under reduced pres-

sure. Purification by flash chromatography (SiO_2 , hexane/EtOAc, 3:1) gave aldehyde (–)-**55** (17 mg, 94%) as an amorphous white solid. ^1H NMR (400 MHz, CDCl_3): δ = 9.83 (s, 1 H), 5.44 (t, J = 2.5 Hz, 1 H), 5.30 (t, J = 2.3 Hz, 1 H), 5.26 (dd, J = 5.7, J = 8.0 Hz, 1 H), 3.80 (dd, J = 6.2, J = 8.1 Hz, 1 H), 3.25–3.21 (m, 1 H), 2.52 (ddd, J = 1.8, J = 7.8, J = 14.8 Hz, 1 H), 1.96 (dd, J = 5.6, J = 14.8 Hz, 1 H), 1.43 (s, 3 H), 0.83 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (400 MHz, CDCl_3): δ = 192.5, 171.8, 142.7, 116.2, 84.8, 84.2, 63.6, 57.8, 49.3, 42.7, 25.7 (3 C), 23.1, 18.0, –2.3 (2 C) ppm. HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 345.1498; found 345.1490. IR: $\tilde{\nu}$ = 2931, 2856, 1768, 1721, 1253, 1145, 1047, 987, 836, 775 cm^{-1} . $[\alpha]_D^{22}$ = –87.6 (c = 0.7, CHCl_3). R_f (hexane/EtOAc, 3:1): 0.28.

Supporting Information (see footnote on the first page of this article): Preparation/characterization of (–)-**29**, **31**, (–)-**34**, **37**, **39**, (+)-**44**, (–)-**45**, **47**, and (–)-**49**. Copies of ^1H and ^{13}C NMR spectra for compounds: **9**, **10**, **12**, (+)-**16**, (–)-**18**, (–)-**20**, **22**, **23**, **24**, **25**, (–)-**26**, (–)-**27**, (–)-**30**, (–)-**32**, (–)-**33**, (–)-**35**, (–)-**36**, (–)-**38**, (–)-**40**, (–)-**41**, (–)-**42**, (–)-**50**, (+)-**54**, (+)-**51**, (+)-**52**, (+)-**53**, (–)-**57**, (–)-**58**, (–)-**60**, (–)-**61**, (–)-**62**, (–)-**63**, (–)-**64**, (–)-**65**, (–)-**66**, (–)-**67**, (–)-**68**, *rac*-**69**, *rac*-**70**, *rac*-**71**, (–)-**72**, *rac*-**73**, *rac*-**74**, *rac*-**75**, *rac*-**76**, *rac*-**77**, (–)-**78**, (–)-**55**.

Acknowledgments

Financial support from the University of Vienna (doctoral program, Initiativkolleg Functional Molecules IK I041-N) and from the Austrian Science Fund (FWF) (project number P22180) is gratefully acknowledged. The authors thank H. P. Kählig, L. Brecker, and S. Felsinger for assistance with NMR spectroscopy, M. Drescher for experimental work, and A. Roller and V. Arion (all of the University of Vienna) for X-ray analysis.

- [1] a) P. A. Roethle, D. Trauner, *Nat. Prod. Rep.* **2008**, *25*, 298–317.
- [2] Isolation article: J. Marrero, A. D. Rodriguez, P. Baran, R. G. Raptis, J. A. Sanchez, E. Ortega-Barria, T. L. Capson, *Org. Lett.* **2004**, *6*, 1661–1664. For efforts toward a total synthesis see: a) B. Doroh, G. A. Sulikowski, *Org. Lett.* **2006**, *8*, 903–906; b) R. Miao, S. G. Gramani, M. J. Lear, *Tetrahedron Lett.* **2009**, *50*, 1731–1733; c) K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Angew. Chem.* **2011**, *123*, 5255–5258; *Angew. Chem. Int. Ed.* **2011**, *50*, 5149–5152; d) J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Org. Lett.* **2012**, *14*, 2195–2197; e) A. Jana, S. Mondal, Md. F. Hossain, S. Ghosh, *Tetrahedron Lett.* **2012**, *53*, 6830–6833.
- [3] Y. Li, G. Pattenden, *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.
- [4] J. Chiarello, M. M. Joullie, *Tetrahedron* **1988**, *44*, 41–48.
- [5] Y. Li, G. Pattenden, J. Rogers, *Tetrahedron Lett.* **2010**, *51*, 1280–1283.
- [6] a) T. T. Curran, D. A. Hay, *Tetrahedron: Asymmetry* **1996**, *7*, 2791–2792; b) A. Roy, S. W. Schneller, *J. Org. Chem.* **2003**, *68*, 9269–9273; c) M. W. Gilbert, A. Galkina, J. Mulzer, *Synlett* **2004**, *14*, 2558–2562.
- [7] A. Rutar, F. Tratar, D. Kikelj, *Synthesis* **1995**, 512–514.
- [8] O. Mitsunobu, Y. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.
- [9] P. C. B. Page, D. C. Leach, C. M. Hayman, A. S. Hamzah, S. M. Allin, V. McKee, *Synlett* **2003**, *7*, 1025–1027.
- [10] S. Searles, Y. Li, B. Nassim, M. T. Lopes, P. T. Tran, P. Crabbé, *J. Chem. Soc. Perkin Trans. 1* **1984**, 747–751.
- [11] a) T. Gaich, H. Weinstabl, J. Mulzer, *Synlett* **2009**, *9*, 1357–1366; b) PhD Thesis Harald Weinstabl, University of Vienna, **2011**.
- [12] E. D. Mihelich, D. J. Eickhoff, *J. Org. Chem.* **1983**, *48*, 4135–4137.

- [13] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.
- [14] E. Weitz, A. Scheffer, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327–2344.
- [15] a) P. S. Wharton, D. H. Bohlen, *J. Org. Chem.* **1961**, *26*, 3615–3616; b) C. Dupuy, J.-L. Luche, *Tetrahedron* **1989**, *45*, 3437–3444.
- [16] J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
- [17] S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, *18*, 1071–1074.
- [18] CCDC-884126 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: March 13, 2013

Published Online: June 7, 2013

SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201300382

Title: Photochemical and Thermal [2 + 2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin

Author(s): Jean-Baptiste Farcet, Martin Himmelbauer, Johann Mulzer*

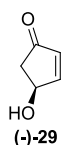
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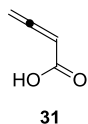
Preparation/characterization of (-)-29, 31, (-)-34, 37, 39, (+)-44, (-)-45, 47, (-)-49.

Alcohol (-)-29:



For preparation protocol and full characterization see: Ref [6] in main article.

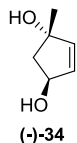
Carboxylic acid 31:



For preparation protocol of ethyl buta-2,3-dienoate see: Organic Syntheses, Coll. Vol. 7, p.232 (1990); Vol. 62, p.202 (1984).

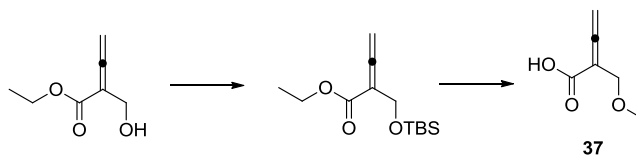
Saponification see patent: PCT Int. Appl., 2007111948, 04 Oct 2007

Diol (-)-34:



For preparation protocol and full characterization see: Ref [6b] in main article.

2-(ethoxymethyl)buta-2,3-dienoic acid (37):

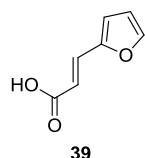


A solution of ethyl 2-(hydroxymethyl)buta-2,3-dienoate (950 mg, 6.68 mmol) (Preparation see: Eur. J. Org. Chem. **2006**, 127–137, characterization see: Org. Lett., **2008**, 10, 3359–3362) and Et₃N (1.49 mL, 10.69 mmol) in CH₂Cl₂ (16.7 mL) was treated dropwise with TBSCl (1.38 mL, 8.69 mmol) and DMAP (2 crystals) at 0 °C. The reaction was allowed to warm to rt and stirred for 36 h being diluted with Et₂O (110 mL) and quenched with water (30 mL) and sat. aq. NaHCO₃ (50 mL). The aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic phases were dried over MgSO₄, filtered and the volatiles were removed under reduced pressure. The resulting slightly yellow oil was purified by column chromatography

(SiO₂, Hex/EtOAc = 10/1) giving 1.18 g (69%) of the TBS intermediate as colorless oil. ¹H-NMR (400 MHz, CDCl₃): δ = 5.23 (t, J = 3.1 Hz, 2H), 4.37 (t, J = 3.1 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H) ppm. ¹³C-NMR (400 MHz, CDCl₃): δ = 213.5, 165.9, 101.5, 80.4, 61.0, 60.1, 26.9 (3C), 18.4, 14.2, -5.3 (2C) ppm. HRMS (EI) (m/z): [M+Na]⁺ calculated for C₁₃H₂₄O₃SiNa: 279.1392, found: 279.1398. IR (cm⁻¹): 2930, 1971, 1712, 1464, 1255, 1123, 1070, 835, 776, 633. R_f: (Hex/EtOAc 3/1) 0.55.

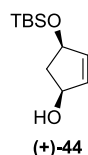
To a solution of the TBS intermediate (1.18 g, 4.60 mmol) in EtOH (9.2 mL) was added to an aqueous solution of LiOH (1 M, 30 mL, 30 mmol) at rt. After 24 h, K₂CO₃ (3.0 g, 21.7 mmol) was added. The white solution was stirred overnight and acidified with an aqueous solution of HCl (2 M, 20 mL). The reaction mixture was diluted with CH₂Cl₂ (50 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 x 60 mL). The combined organic phase was extracted with water (10 mL) and brine (10 mL) followed by the addition of MgSO₄. Filtration and evaporation of the volatiles gave 650 mg (99%) of **37** as a white semi solid. ¹H-NMR (400 MHz, CDCl₃): δ = 7.10 (br s, 1H), 5.31 (t, J = 2.1 Hz, 2H), 4.20 (t, J = 2.1 Hz, 2H), 3.55 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H) ppm. ¹³C-NMR (400 MHz, CDCl₃): δ = 215.3, 170.4, 97.7, 79.9, 67.0, 66.1, 15.0 ppm. HRMS (EI) (m/z): [M+Na]⁺ calculated for C₁₀H₇O₃Na: 165.0528, found: 165.0225. IR (cm⁻¹): 3395, 2943, 2840, 1981, 1707, 1207, 1101, 1064, 842, 791, R_f: (Hex/EtOAc 3/1) 0.00.

Furylacrylic acid (**39**):



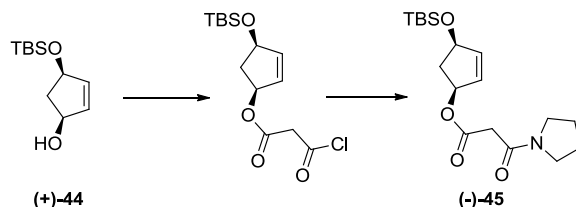
For preparation protocol see: Organic Syntheses, Coll. Vol. 3, p.425 (1955); Vol. 25, p.51 (1945).

(1S,4R)-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-enol ((+)-**44**):



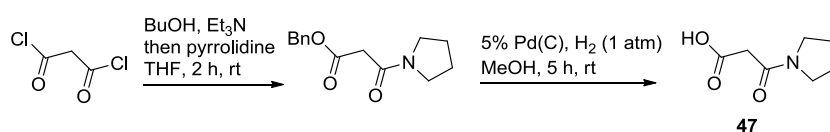
For preparation protocol and full characterization see: Ref [6] in main article.

Amide (-)-**45**:



A solution of alcohol (+)-**44** (100 mg, 0.47 mmol) in THF (3.0 mL) was treated with Et₃N (71 μL, 0.51 mmol) at rt. After 15 min the resulting colorless solution was cooled to 0 °C followed by the dropwise addition of a solution of malonyl dichloride (226 μL, 2.30 mmol) in THF (4.0 mL). The resulting reaction mixture was aged at this temperature for 1 h. Thereafter, pyrrolidine (570 μL, 7.00 mmol) in THF (3.5 mL) was added dropwise to the reaction within 5 min. The resulting white suspension was stirred at 0 °C for 3 h, filtered through a pad of Celite and the solvents were removed under reduced pressure. The resulting slightly yellow solid was subjected to column chromatography (SiO₂, Hex/EtOAc 3/1 to EtOAc) to yield 141 mg (85%) of the desired amide (-)-**45** as colorless oil. ¹H-NMR (400 MHz, CDCl₃): δ = 5.98 (d br, J = 5.6 Hz, 1H), 5.90 (d br, J = 5.6 Hz, 1H), 5.53 (t br, J = 6.5 Hz, 1H), 4.71 (t br, J = 5.9 Hz, 1H), 3.49 (t, J = 6.9 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 3.38 (s, 2H), 2.82 (ddd, J₁ = 14.5 Hz, J₂ = 7.5 Hz, J₃ = 7.5 Hz, 1H), 1.96 (m, 2H), 1.87 (m, 2H), 1.64 (ddd, J₁ = 13.9 Hz, J₂ = 5.0 Hz, J₃ = 5.0 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. ¹³C-NMR (400 MHz, CDCl₃): δ = 167.5, 164.4, 139.4, 131.0, 78.1, 75.0, 47.3, 46.1, 42.6, 41.2, 29.8, 26.2, 26.0 (3C), 24.6, -4.49, -4.55 ppm. HRMS (EI) (m/z): [M+Na]⁺ calculated for C₁₈H₃₁O₄NSiNa: 376.1920, found: 376.1937. IR (cm⁻¹): 2954, 2930, 2857, 2361, 1739, 1652, 1439, 1105, 1049, 837. [α]_D²⁰: - 5.04 (c = 0.26; CHCl₃). R_f: (EtOAc) 0.66.

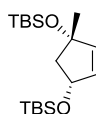
Acid **47**:



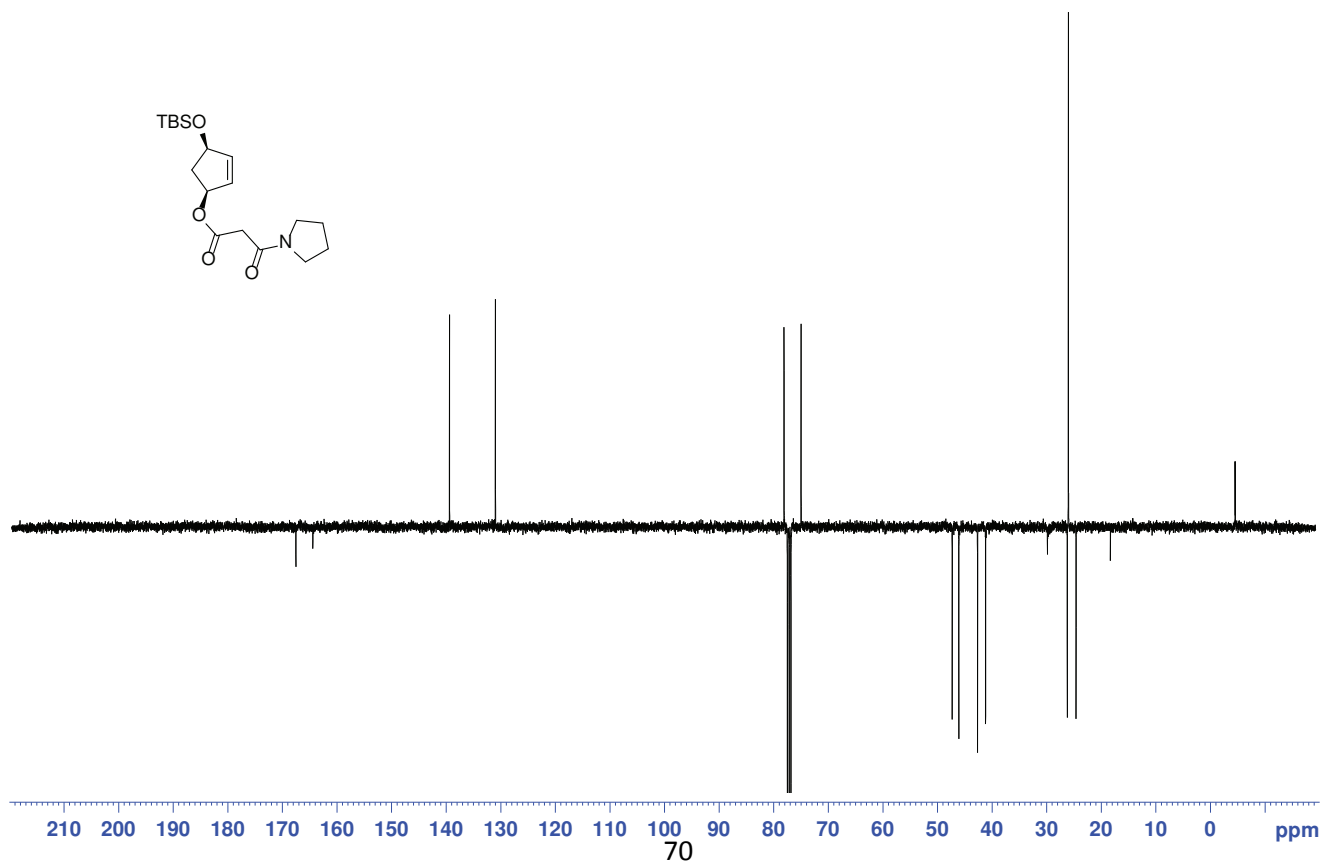
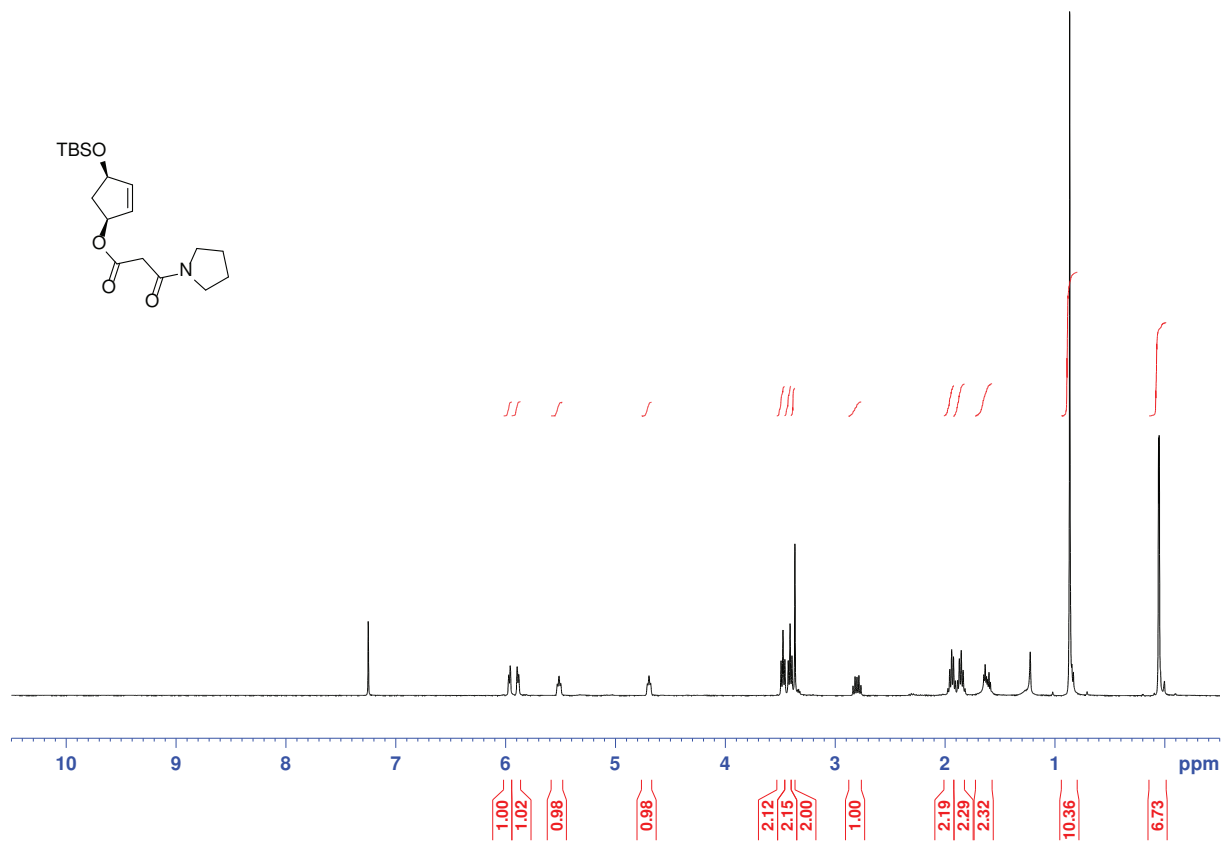
Benzylic alcohol (50 μ L, 0.48 mmol, in THF (3.0 mL) was treated at 0 °C with Et₃N (74 μ L, 0.53 mmol) and stirred for 15 min. Consecutively, the resulting solution was dropwise added to malonyl dichloride (103 μ L, 1.06 mmol) in THF (3.0 mL) within 8 min. After one hour at this temperature pyrrolidine (261 μ L, 3.19 mmol) in THF (3.0 mL) was added. After 1 h the reaction mixture was allowed to warm to rt and stirred for additional 2 h. The resulting white suspension was quenched by addition of 1N HCl (5 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phase was extracted with water (10 mL) and brine (10 mL) followed by the addition of MgSO₄. Filtration and evaporation of the volatiles was followed by column chromatography (SiO₂, Hex/EtOAc 3/1). Finally 74 mg (63%) of the desired amide were isolated as colorless oil. ¹H-NMR (400 MHz, CDCl₃): δ = 7.36-7.29 (m, 5H), 3.49 (t, J = 6.8 Hz, 2H), 3.44 (s, 3H), 3.39 (t, J = 6.8 Hz, 2H), 1.96-1.81 (m, 4H) ppm. ¹³C-NMR (400 MHz, CDCl₃): δ = 167.5, 164.3, 135.7, 128.7 (2C), 128.5, 128.4 (2C), 67.2, 47.3, 46.1, 42.7, 26.1, 24.6 ppm. HRMS (EI) (m/z): [M+Na]⁺ calculated for C₁₄H₁₇NO₃: 270.1106, found: 270.1103. IR (cm⁻¹): 2971, 2877, 1735, 1638, 1437, 1306, 1255, 1149, 984, 750. R_f: (Hex/EtOAc 3/1) 0.40.

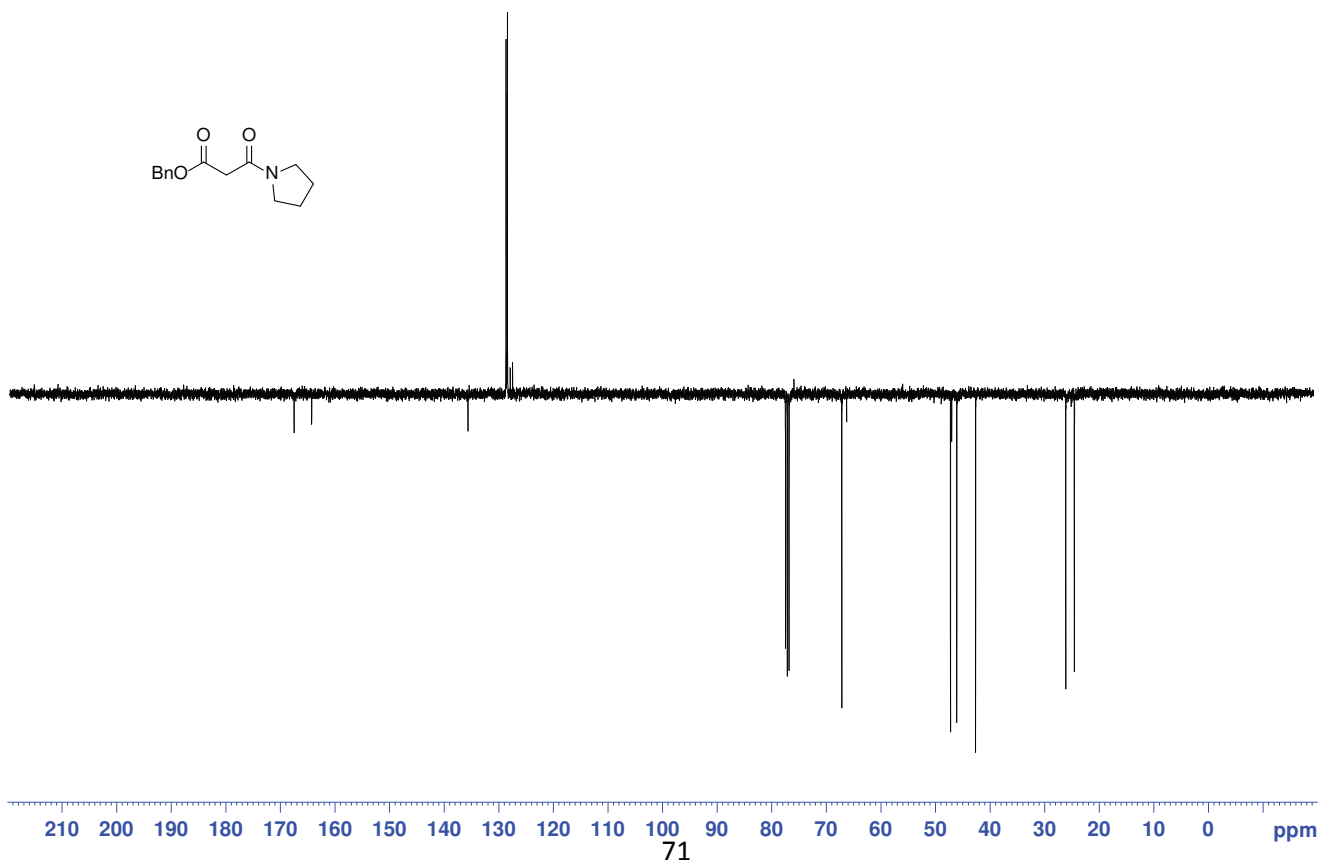
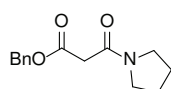
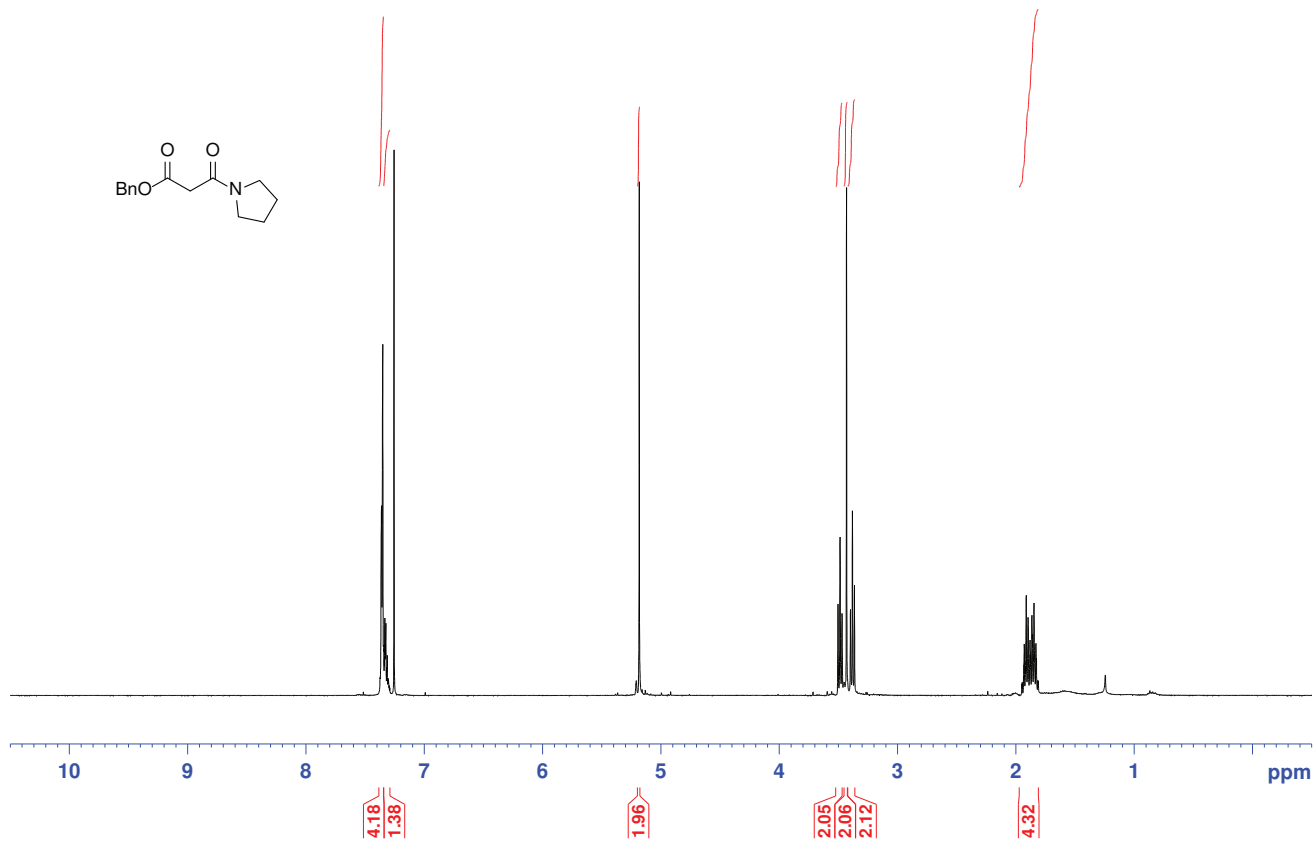
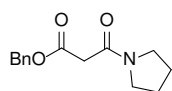
Benzyl ester (150 mg, 0.60 mmol) was dissolved in MeOH (6.0 mL) in a 25 mL round bottomed flask equipped with a magnetic stirring bar and a rubber septum. To the resulting slightly yellow solution a spatula tip of Pd/C was added. In the following, hydrogen was gently bubbled through the black suspension over a period of 5 h. Filtration through Celite and removal of the volatiles resulted in 95 mg (quantitative) of a slightly yellow oil. Crude acid **47** was used without further purification in the next reaction.

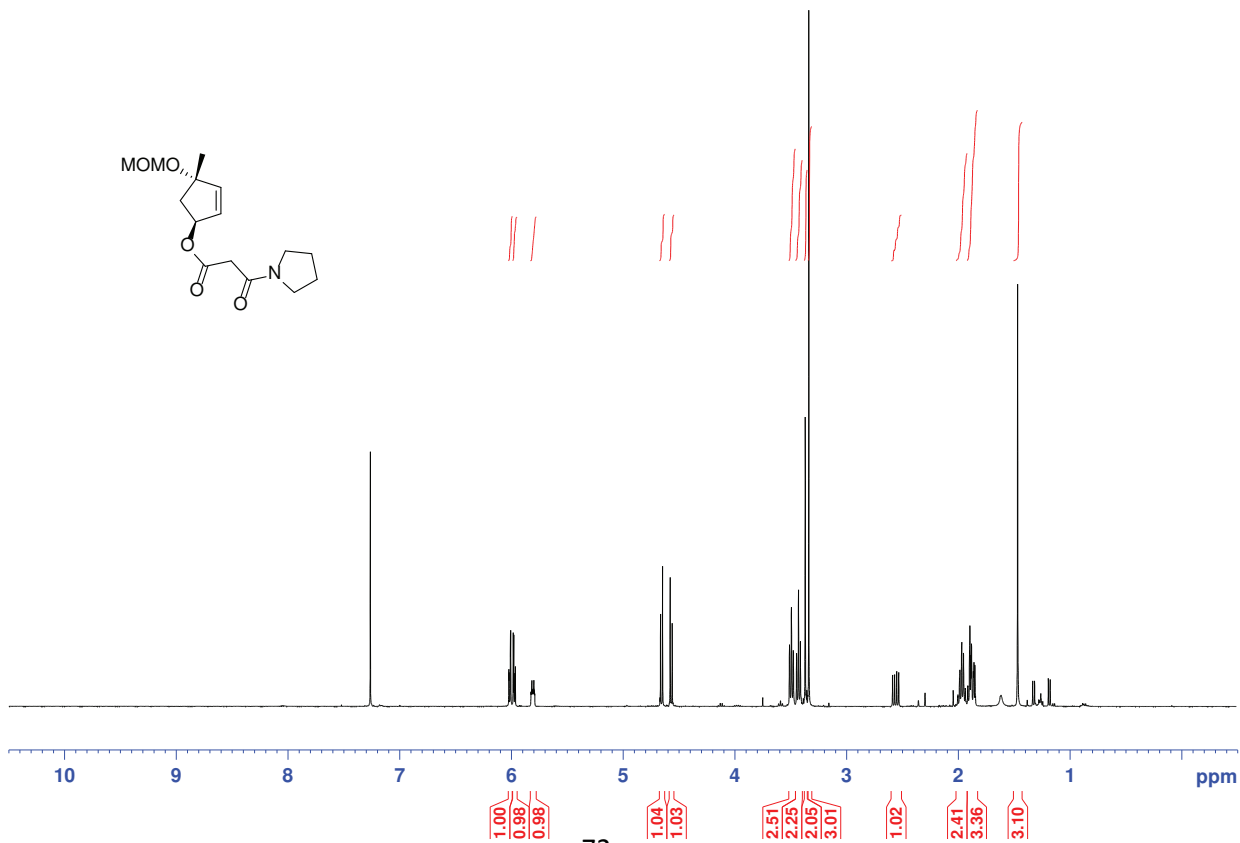
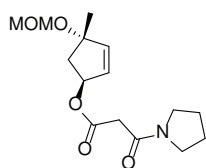
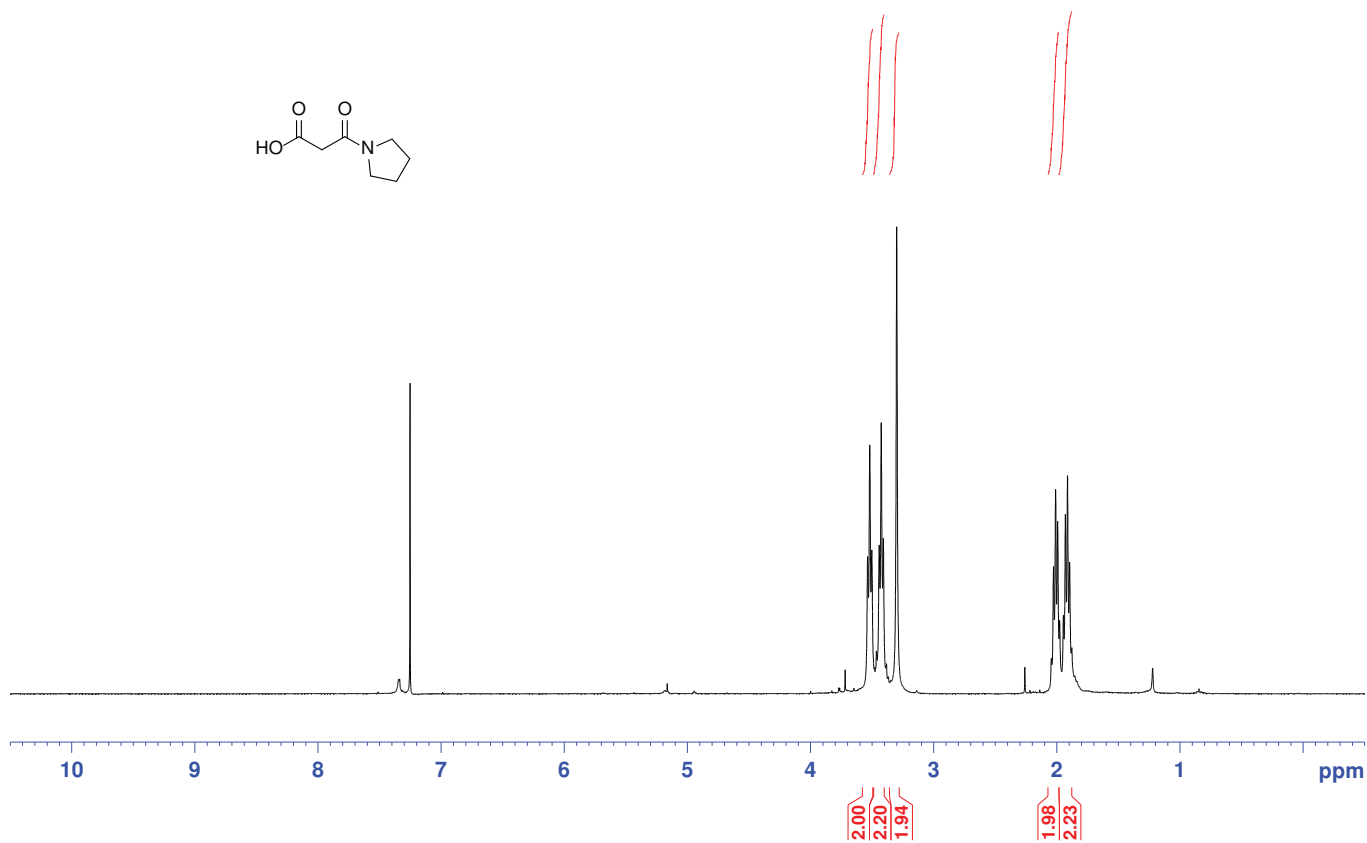
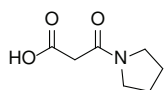
Alkene (-)-**49**:

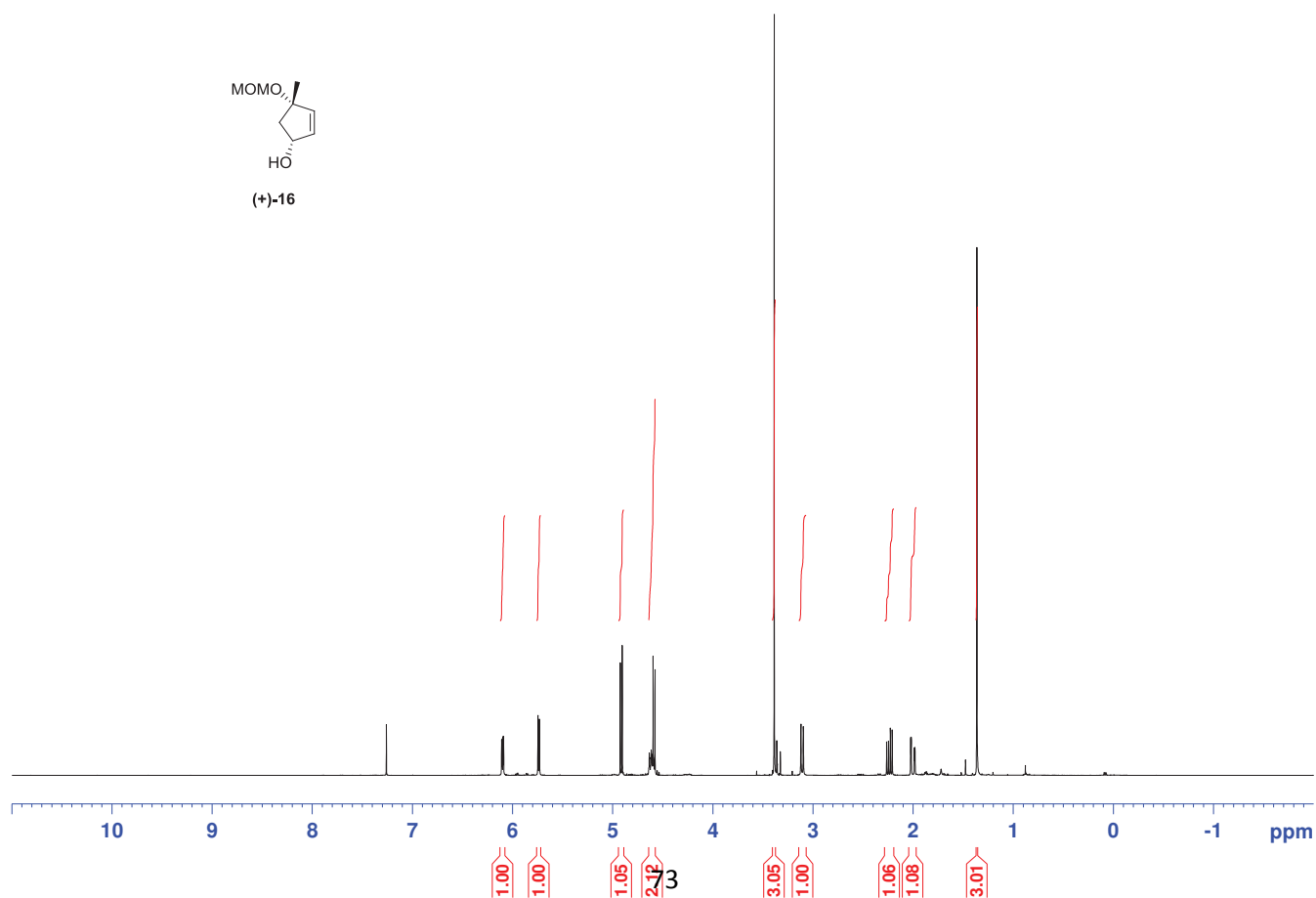
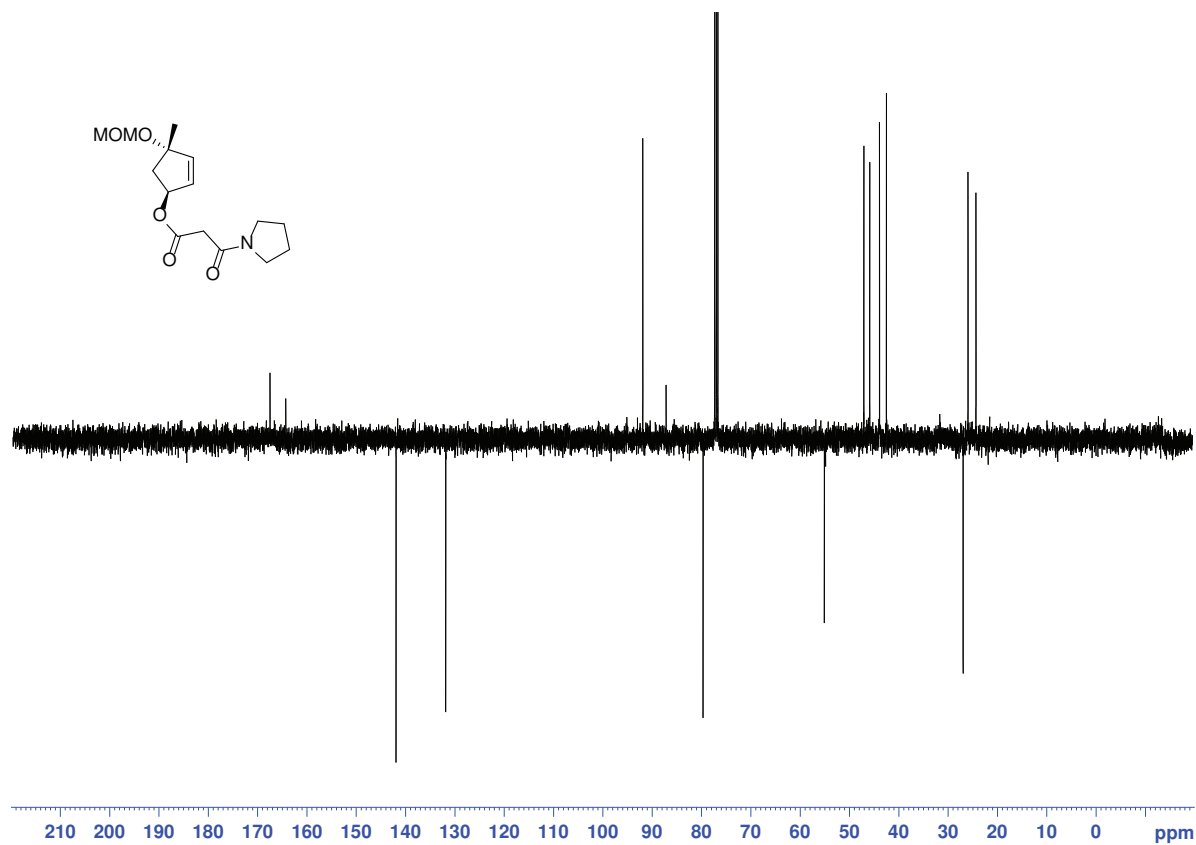


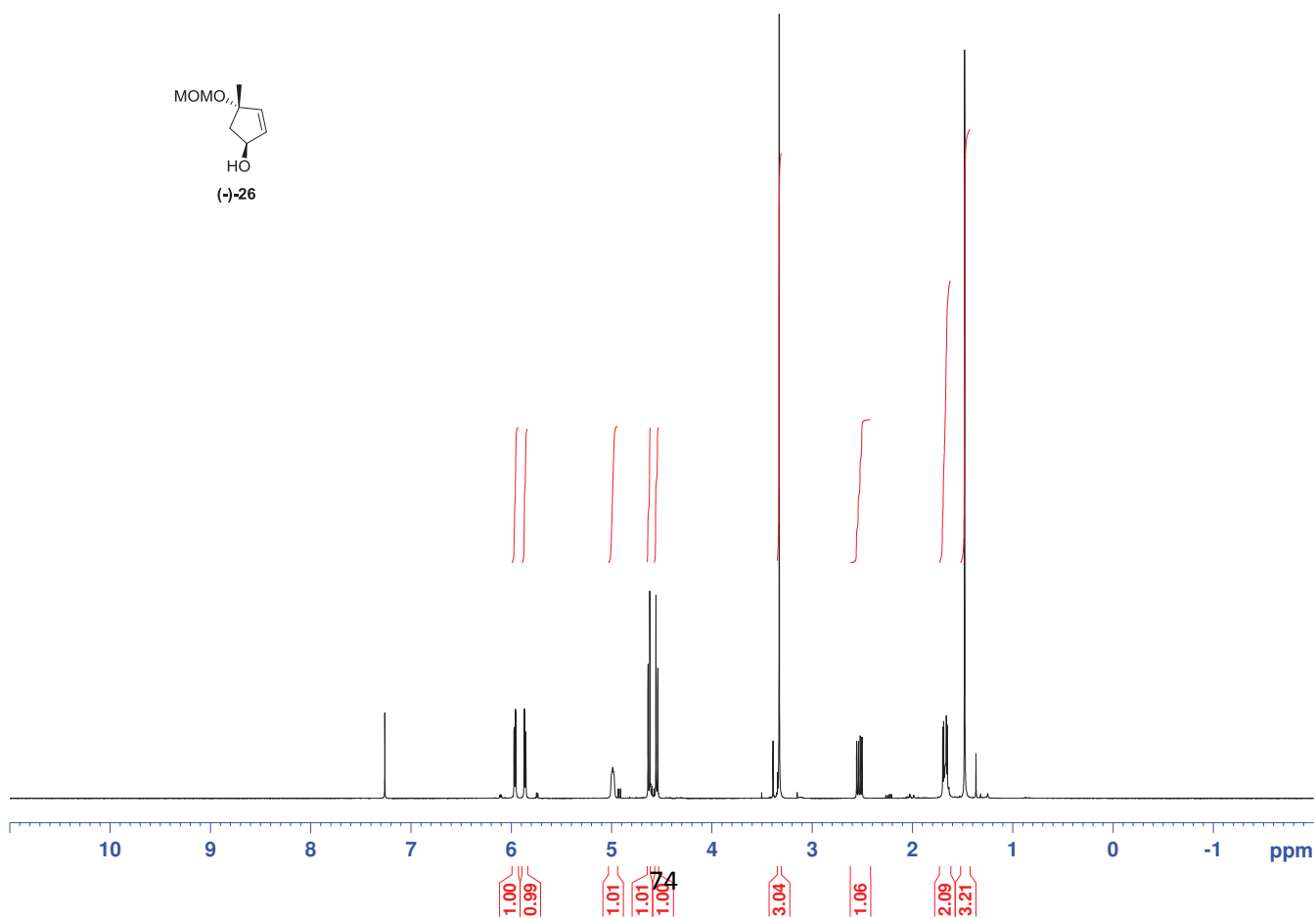
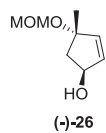
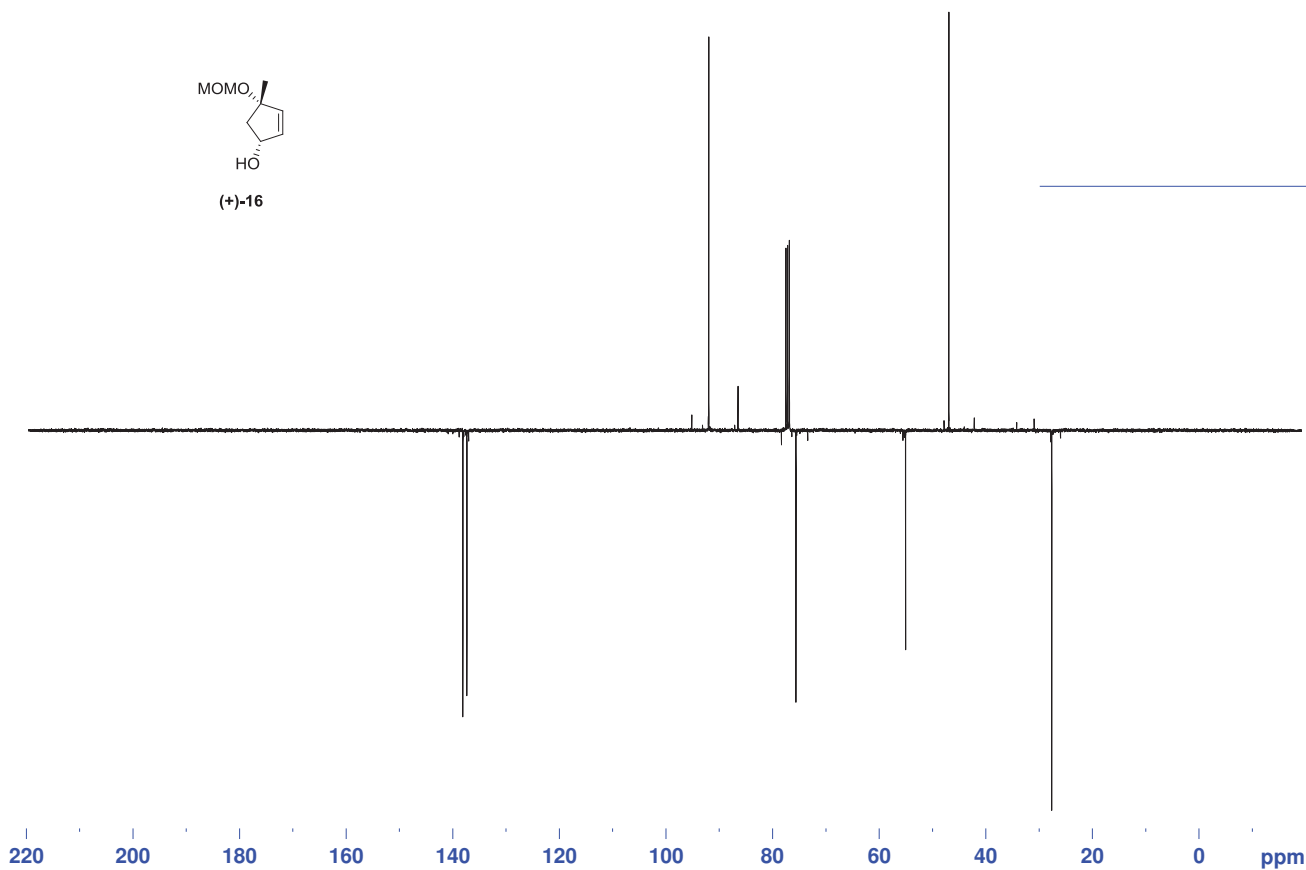
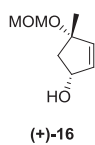
A solution of alcohol (-)-**15** (500 mg, 2.19 mmol) and 2,6-lutidine (1.02 mL, 8.76 mmol) in DMF (4.4 mL) was treated dropwise with TBSOTf (1.51 mL, 6.57 mmol) at 0 °C. The reaction was allowed to warm to rt and was finally warmed to 40 °C overnight before being diluted with Et₂O (100 mL) and quenched with water (30 mL) and sat. aq. NaHCO₃ (30 mL). The aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic phases were dried over MgSO₄, filtered and the volatiles were removed under reduced pressure. The resulting slightly yellow oil was purified by column chromatography (SiO₂, Hex/EtOAc = 20/1) giving 549 mg (73%) of the desired alkene (-)-**49** as slightly yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ = 5.78 (dd, J₁ = 1.4 Hz, J₂ = 5.6 Hz, 1H), 5.62 (dd, J₁ = 1.8 Hz, J₂ = 5.7 Hz, 1H), 4.68-4.63 (m, 1H), 2.35 (dd, J₁ = 6.9 Hz, J₂ = 12.7 Hz, 1H), 1.84 (ddd, J₁ = 0.5 Hz, J₂ = 5.5 Hz, J₃ = 12.8 Hz, 1H), 1.26 (d, J = 0.5 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. ¹³C-NMR (400 MHz, CDCl₃): δ = 146.6, 135.6, 84.6, 77.5, 54.1, 32.2, 28.1 (3C), 28.0 (3C), 20.2, 20.1, 0.0, -0.1, -2.3, -2.4 ppm. HRMS (EI) (m/z): [M+Na]⁺ calculated for C₁₈H₃₈O₂SiNa: 365.2308, found: 365.2322. IR (cm⁻¹): 2956, 2995, 2857, 1472, 1362, 1166, 1120, 1098, 836, 775. [α]_D²⁰: -15.4 (c = 1.0; CHCl₃). R_f: (Hex/EtOAc 3/1) 0.80.

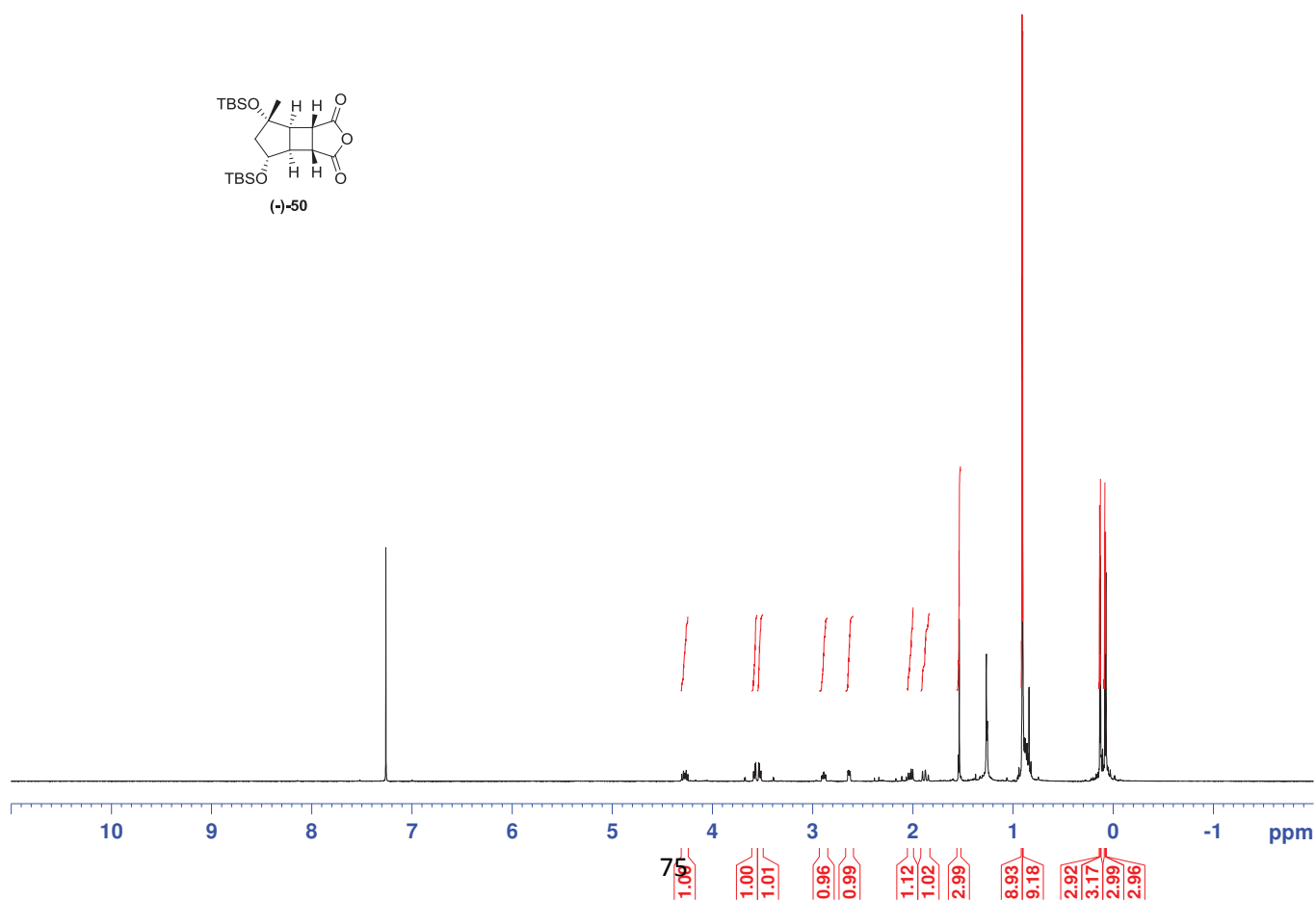
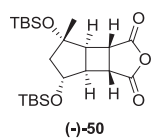
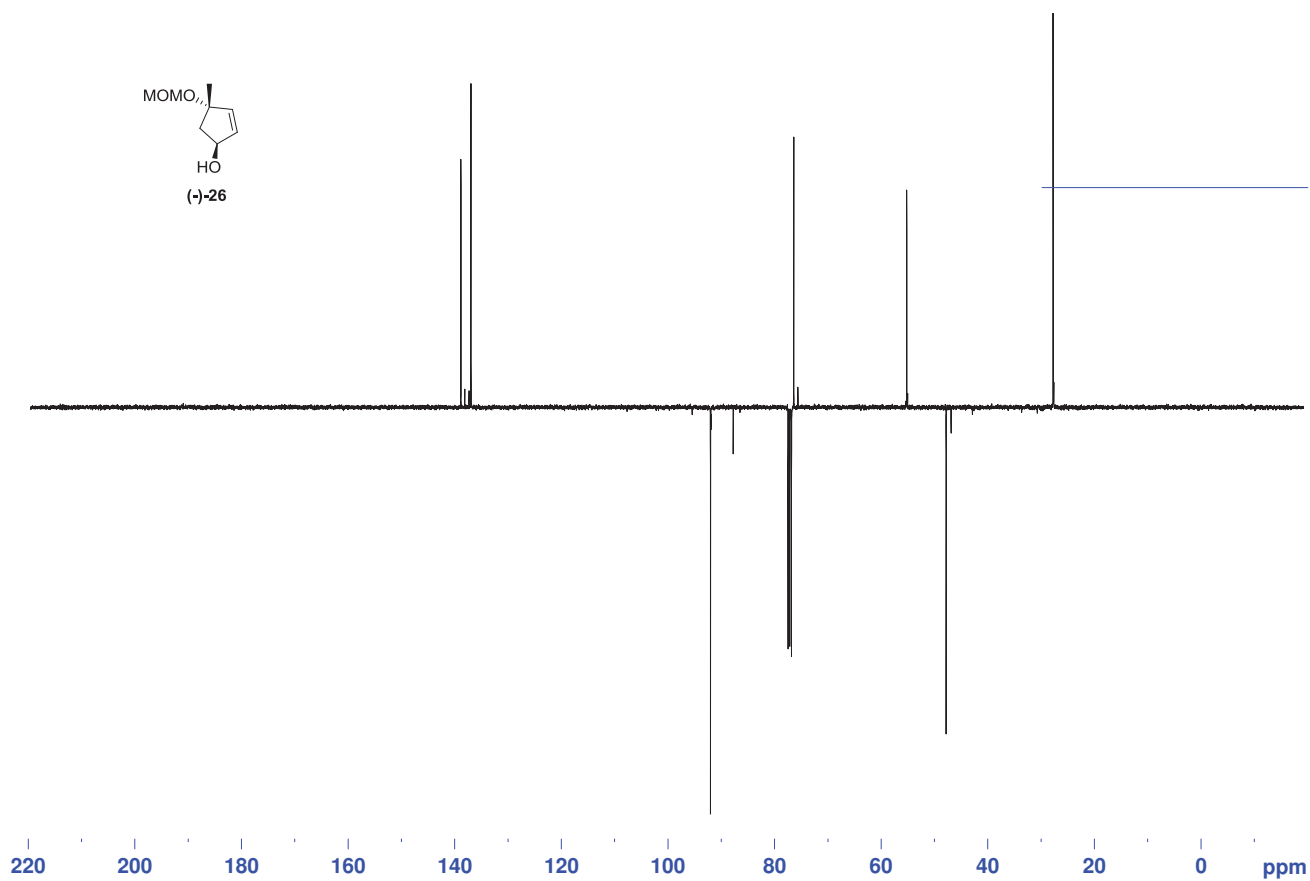
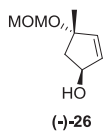


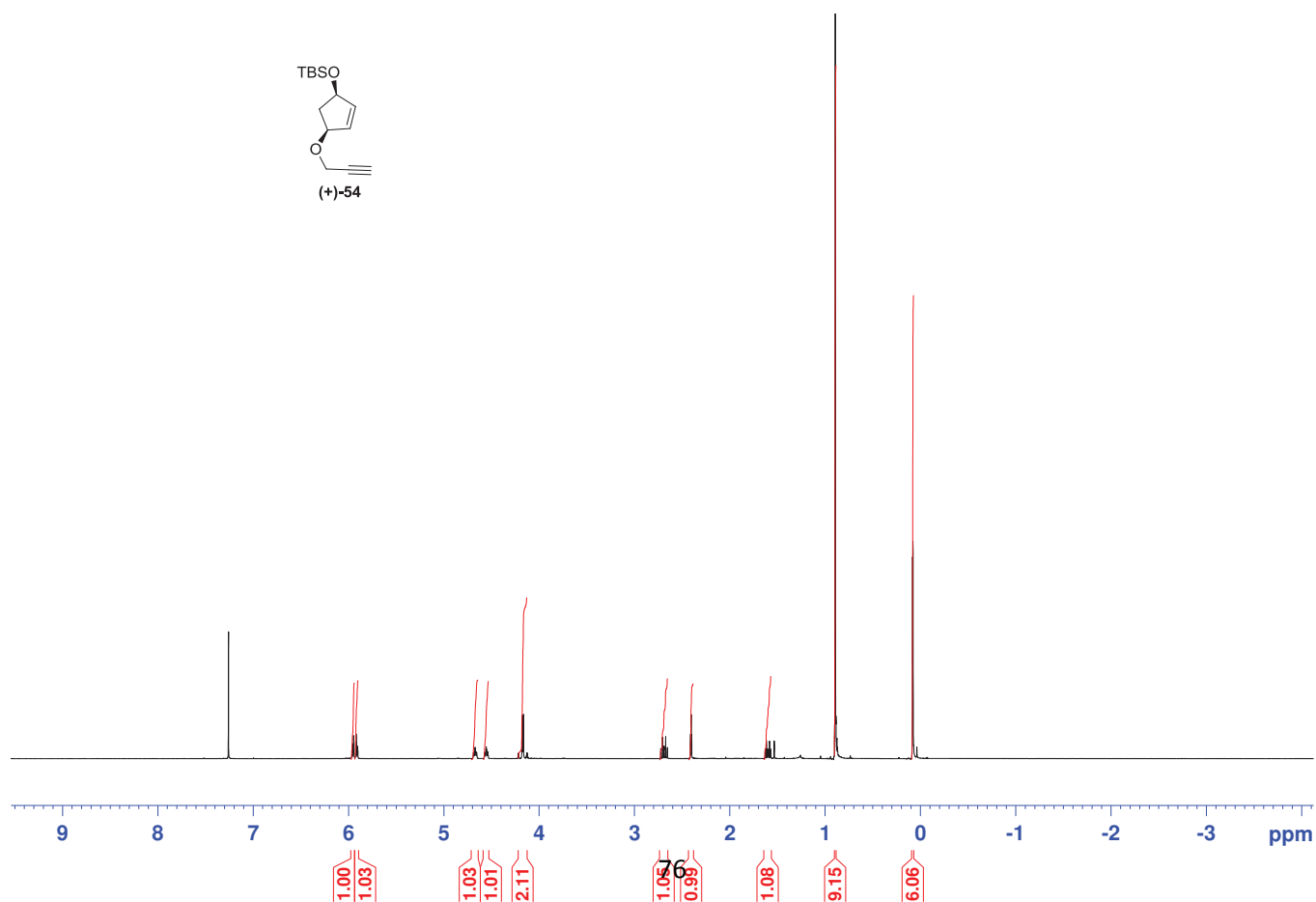
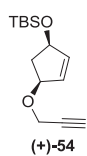
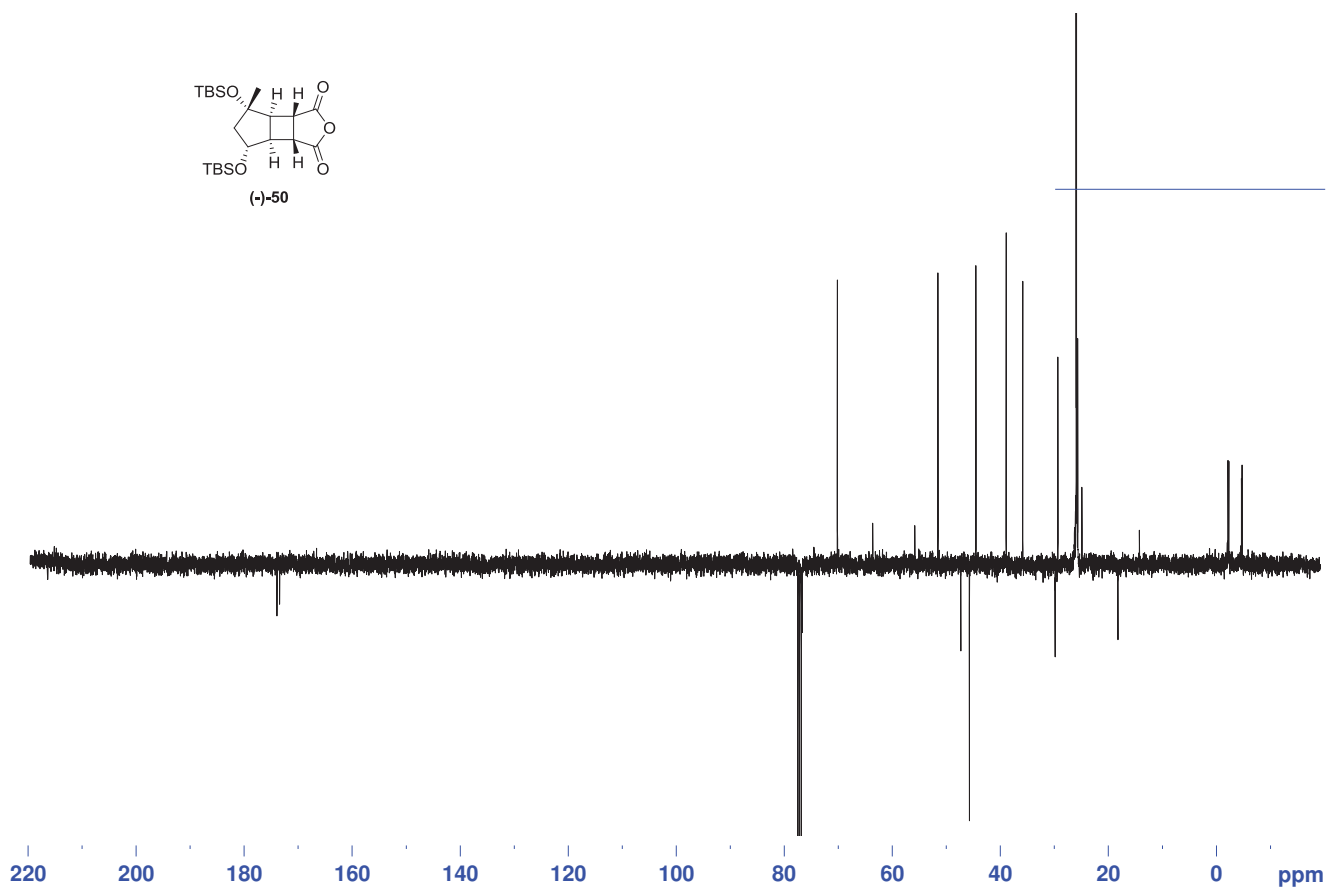
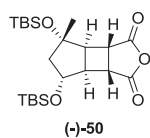


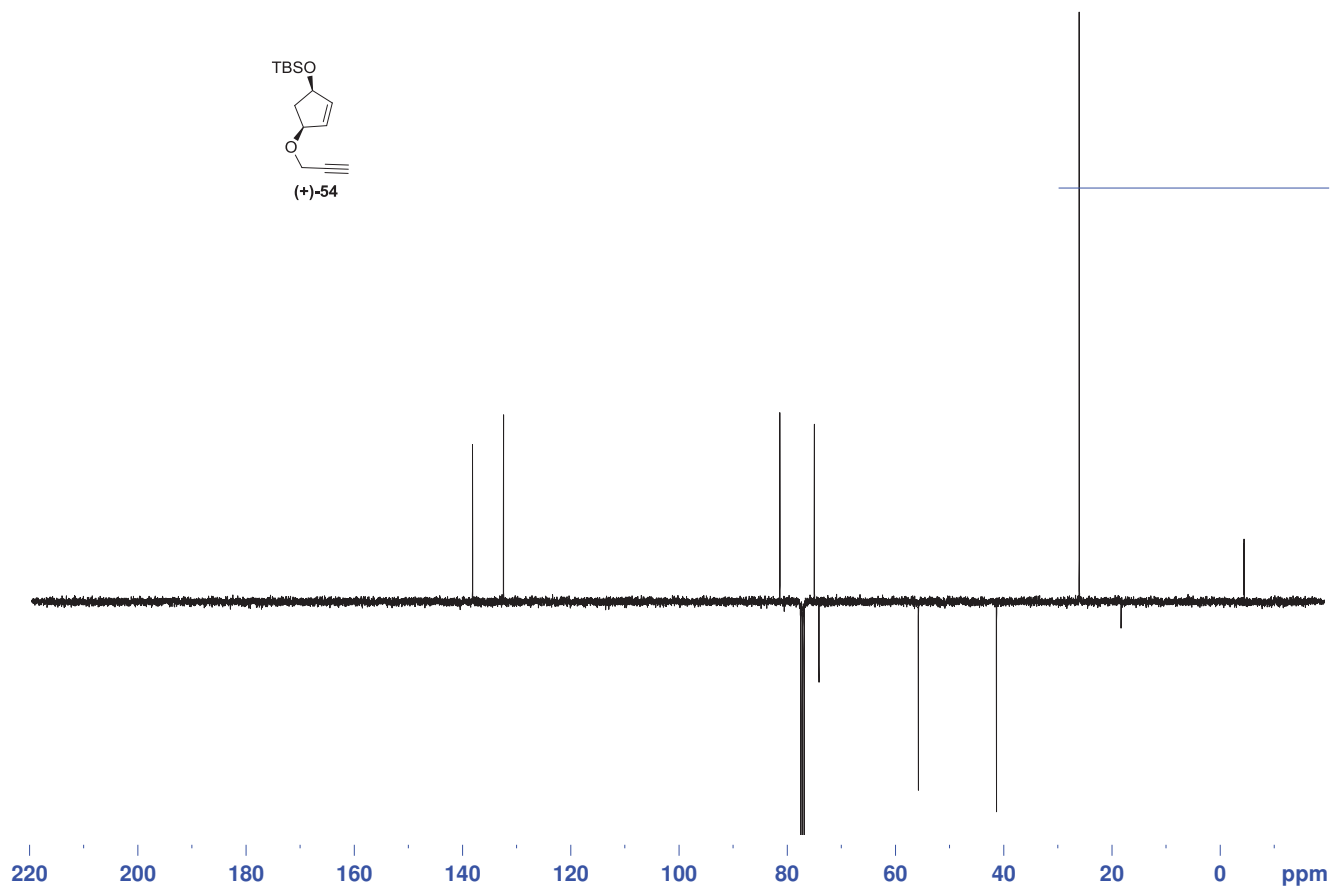
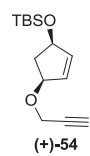












7.2. A Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case¹¹³

Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Org. Lett.* **2013**, *15*, 3098.

Planning: Himmelbauer, M.; Farcet, J.-B.; Mulzer, J.

Experimentation: Himmelbauer, M.

Manuscript preparation: Himmelbauer, M.; Farcet, J.-B.; Mulzer, J.

Discussion

All experiments, characterization of all intermediates as well as the preparation of the manuscript have been carried out by M. H. To avoid redundancy, experimental procedures have been omitted as they are also part of the full paper (see section 7.3.).¹¹⁴

A Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case

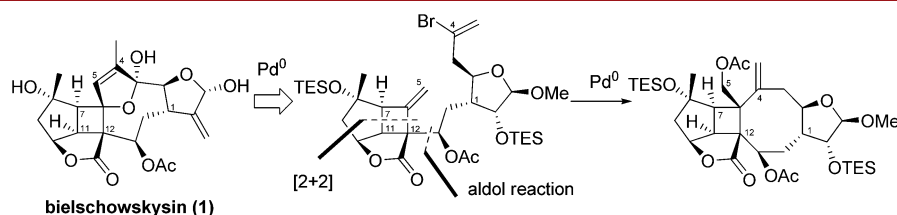
Martin Himmelbauer, Jean-Baptiste Farcet, Julien Gagnepain, and Johann Mulzer*

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Received May 10, 2013

ABSTRACT



An asymmetric synthesis of an advanced tetracyclic intermediate toward the synthesis of bielschowskysin (1) is described. A biomimetic [2 + 2]-photocyclization was used to establish the cyclobutane core of bielschowskysin. Macrocyclization under Heck conditions led to an unprecedented carbo-oxygenation of a 1,1-disubstituted double bond.

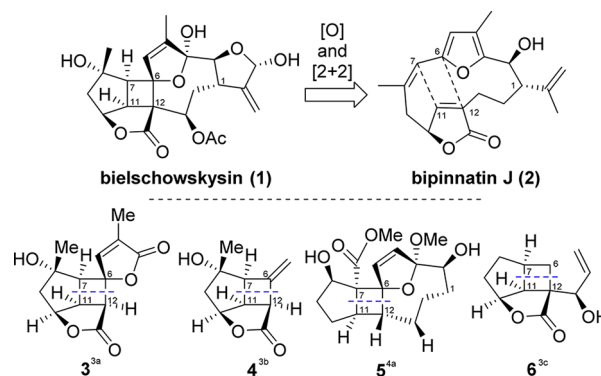
Over the past years the Rodríguez group has reported the isolation of a stunning variety of terpenoids from the Caribbean Sea plume *Pseudopterogorgia kallos*, among which bielschowskysin (1)¹ (Scheme 1) has attracted an unusual amount of interest.

Partly this is due to its significant antiparasitic activity against the malaria causing protozoan parasite *Plasmodium falciparum* and its cytotoxic activity against two human cancer cell lines. Most significantly, its densely functionalized polycyclic diterpenoid structure including an unprecedented tricyclo[9.3.0.0^{2,10}]-tetradecane ring system and 11 stereogenic centers has rendered bielschowskysin a highly competitive target in synthetic chemistry.

So far, activities from numerous research groups, including our own,² have resulted in several advanced intermediates³ and test systems.⁴

According to the studies by Roethle and Trauner the biosynthesis of different furanocembranoids could be related to bipinnatin J (2) and should therefore be accessible

Scheme 1. Biosynthesis and Reported [2 + 2]-Approaches



from this natural product within a short number of steps including oxidations, rearrangements, and cyclo-additions.^{5,6} In particular, it is proposed that epoxidation of the $\Delta^{7,8}$ double bond of bipinnatin J (2) followed by the addition of water and a consecutive formal [2 + 2]-cycloaddition could lead to bielschowskysin (Scheme 1).

To date this biomimetic [2 + 2]-photocycloaddition strategy has been pursued by four groups. However, the

(1) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, 6, 1661–1664.

(2) (a) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, 14, 2195–2197. (b) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Eur. J. Org. Chem.* **2013** accepted for publication.

(3) (a) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, 8, 903–906. (b) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, 50, 1731–1733. (c) Jana, A.; Mondal, S.; Md. Hossain, F.; Ghosh, S. *Tetrahedron Lett.* **2012**, 53, 6830–6833.

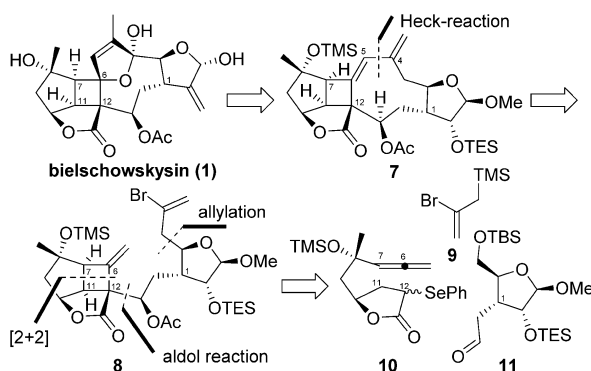
(4) (a) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, 50, 5149–5152. (b) Meyer, M. E.; Phillips, J. H.; Ferreira, E. M.; Stoltz, B. M. *Tetrahedron* **2013**, 1–9.

(5) (a) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, 8, 345–347. (b) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, 8, 5901–5904. (c) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, 8, 298–317.

(6) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, 28, 1269–1310.

intermediates advanced by Sulikowski (**3**),^{3a} Lear (**4**),^{3b} Nicolaou (**5**),^{4a} and Gosh (**6**)^{3c} are deficient in functionalization and **3–5** lack the crucial all-carbon quaternary center at C-12 (Scheme 1).

Scheme 2. Retrosynthetic Analysis



Our retrosynthetic plan (Scheme 2) is centered around key intermediate **8**, which was to be assembled from components **9** to **11**. An allylation with 2-bromo-3-trimethylsilyl propene (**9**) should lead to vinyl bromide **8** as the substrate of a palladium mediated Heck macrocyclization. Hopefully, this would furnish cyclononadiene **7** which might be carried on to the final target by allylic oxidation and formation of the dihydrofuran ring.

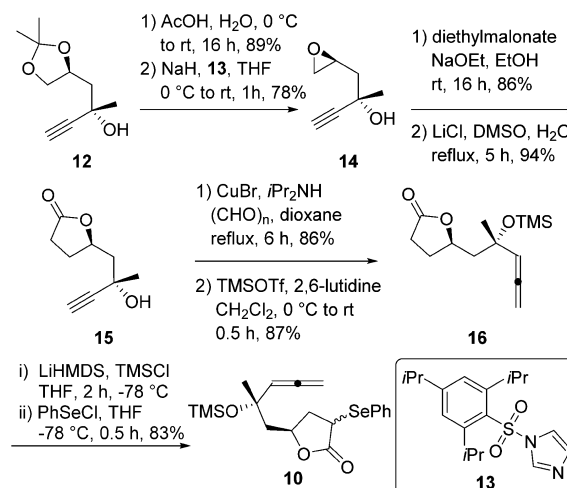
The synthesis of allene **10** (Scheme 3) started with known alkyne **12**, easily available from (–)-malic acid.^{3a,b,7} Conversion to epoxide **14** was followed by regioselective ring opening with diethylmalonate. In situ lactonization and Krapcho decarboxylation⁸ gave butyrolactone **15** in 56% yield from **12**. The Searles–Crabbé protocol⁹ was used for generating the allene. Finally, deprotonation of the lactone, treatment with chlorotrimethylsilane, and addition of phenylselenenyl chloride furnished building block **10** as a 1:1.5 mixture of diastereomers in 83% yield.

Coupling partner **11** (Scheme 4) was prepared from known α -D-ribofuranose **17**¹⁰ via lactone **18** (diastereomerically pure). On subjecting the protected diol **19** to Swern oxidation conditions, the primary triethylsilyl protecting group was selectively removed and aldehyde **11** was obtained in 97% yield.

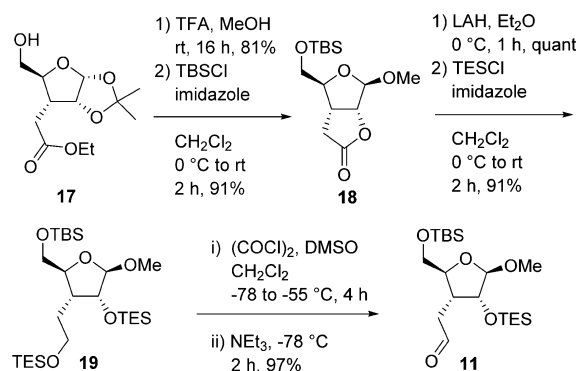
Both building blocks **10** and **11** are readily available in gram quantities and easy to couple by aldol addition. Thus, deprotonation of the seleno lactone **10** at low temperature followed by addition of aldehyde **11** resulted in a mixture of all four diastereomeric adducts which was used without separation in the next step (Scheme 5).

Regioselective oxidative elimination of the phenylselenide gave an inseparable 1:1 mixture of diastereoisomers

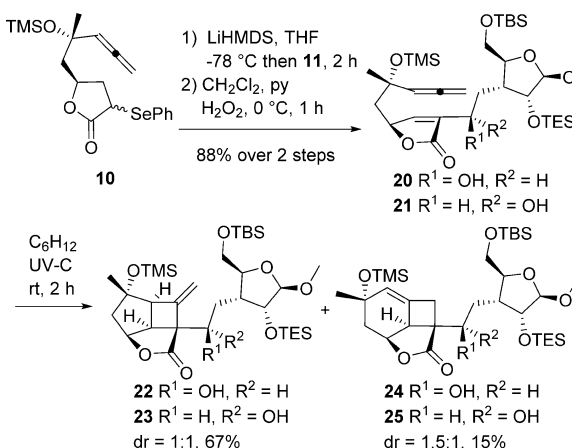
Scheme 3. Preparation of the Allene Building Block



Scheme 4. Preparation of the Coupling Partner



Scheme 5. Fragment Coupling and [2 + 2]-Photocycloaddition



(7) Saito, S.; Hasegawa, T.; Inaba, N.; Nishida, R.; Fujii, T.; Nomizu, S.; Muriwake, T. *Chem. Lett.* **1984**, 1389–1392.

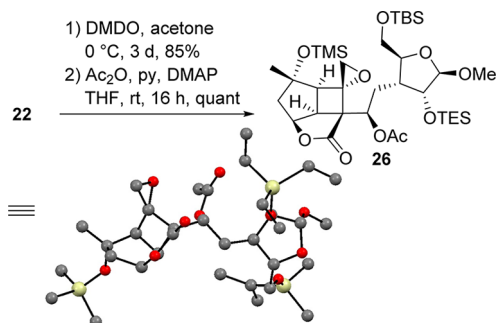
(8) Krapcho, P. A.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138–147.

(9) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

(**20** and **21**) which was irradiated in degassed cyclohexane in quartz tubes with commercially available UV-C-lamps in a homemade UV-reactor for 4 h to provide the tetra-cyclic photoadducts **22** and **23** in 67% combined yield.

Additionally regioisomers **24** and **25**, originating from the cyclization of the terminal allenic double bond, were isolated in a 15% combined yield. Flash column chromatography at this stage provided us with pure isomers **22** and **23** for the envisaged Heck macrocyclization.

Scheme 6. Preparation of Single Crystals for X-ray Analysis

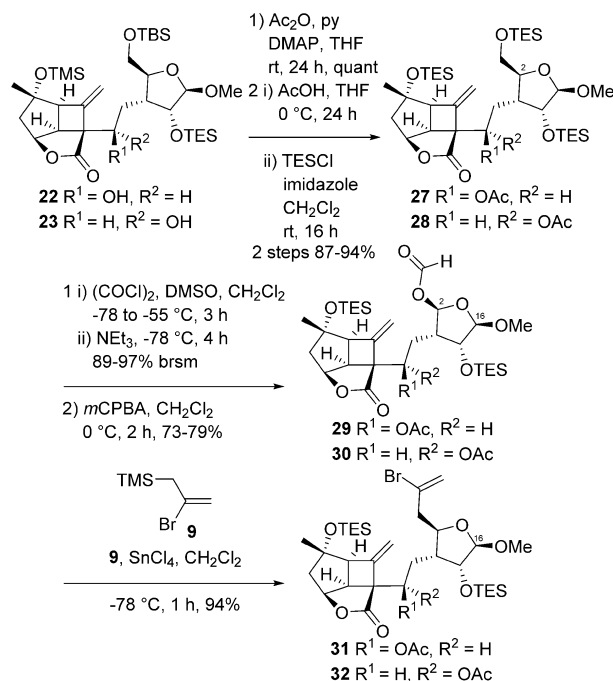


For the assignment of the newly created stereocenters, olefin **22** was epoxidized with a freshly prepared solution of dimethyldioxirane with a d.r. of 6.7:1 (Scheme 6). Standard acetylation provided **26**, suitable for single crystal diffraction.

The synthesis was separately carried on with diastereomerically pure **22** and **23**. To unify the silyl protecting groups, global deprotection with acetic acid in THF was followed by treatment with chlorotriethylsilane to give TES-derivative **27** and **28** in excellent yield (Scheme 7). Again, under the Swern oxidation conditions the primary silyl group was removed selectively. Gratifyingly, Baeyer–Villiger oxidation of the aldehyde with *meta*-chloropero-benzoic acid in dichloromethane at 0 °C was much faster than the epoxidation of the *exo*-methylene group so that formates **29** and **30** were generated in fair yield. Lewis acid mediated allylation with silane **9** gave *trans*-isomers **31** and **32** as single diastereomers, presumably via an oxonium intermediate which was attacked from the less hindered ring face.^{11,12} Obviously, the formate is such a superior leaving group that the second anomeric center at C-16 is not touched.

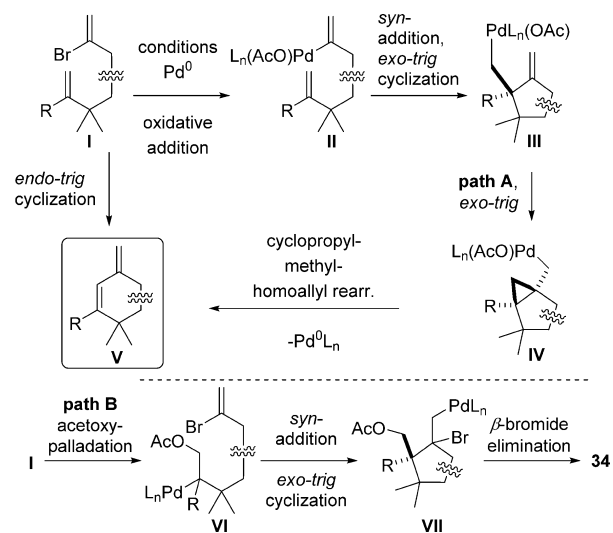
With an appropriate bromoallyl appendage in place we tackled the Heck macrocyclization. Although a preference for *exo*-mode Heck cyclizations exists,¹³ *endo*-type reactions have also been observed,^{14,15} generally when the

Scheme 7. Introduction of the Bromoallyl Appendage



exo-pathway is precluded. A general mechanistic picture (Scheme 8) suggests that the usual oxidative addition generates σ -alkenylpalladium(II) complex **II** which adds to the *exo*-methylene double bond in a *exo-trig* fashion forming neopentylpalladium intermediate **III**. As β -hydride elimination at this stage is impossible, a 3-*exo-trig* ring closure to cyclopropane **IV** should occur (Scheme 8, path A). Elimination of palladium would then give the desired diene **V** in a formal overall *endo-trig* cyclization.

Scheme 8. Mechanistic Rationalization



A wide variety of Heck conditions were applied to precursors **31** and **32** (Table 1, Supporting Information).

(10) (a) Rosenthal, A.; Nguyen, L. B. *J. Org. Chem.* **1969**, *34*, 1029–1034. (b) Xie, M.; Berges, D. A.; Robins, M. *J. Org. Chem.* **1996**, *61*, 5178–5179 and references cited therein.

(11) (a) Martinez, H. O.; Reinke, H.; Michalik, D.; Vogel, C. *Synthesis* **2009**, *11*, 1834–1840. (b) McDevitt, J.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 3818–3828.

(12) Schmitt, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893–3901.

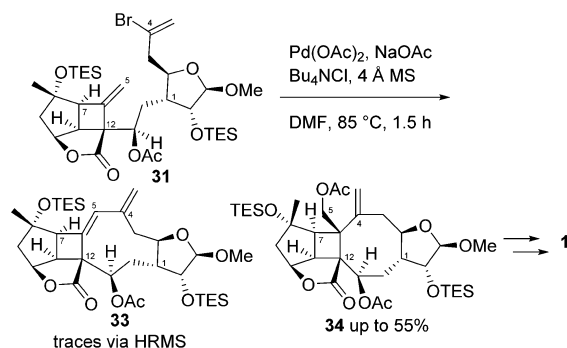
(13) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423–1430. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. Schulman, J. M.; Friedman, A. A.; Pantelev, J.; Lautens, M. *Chem. Commun.* **2012**, *48*, 55–57.

(14) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379–2411.

(15) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835 and references cited therein.

For **31**, a standard procedure¹⁶ led to a complex product mixture, in which traces of the desired diene **33** were detected by mass analysis (Scheme 9). Trying to improve this result, we used the findings by Rigby et al.,¹⁵ who have reported that electronic effects and a relatively small metal coordination sphere of the palladium tend to favor the *endo*-pathway in Heck cyclizations. On this basis, we subjected **31** to Jeffery conditions.^{17,18} To our surprise, this reaction stereoselectively led to product **34** in 55% yield. Thus, the *exo*-methylene group has been attacked from the less hindered face of the cage-shaped precursor to form a tricyclo[8.3.0.0^{2,9}]tridecane ring system instead of the desired “natural” tricyclo[9.3.0.0^{2,10}]tetradecane framework (Scheme 9). The stereochemistry and connectivity of **34** were determined by 2D NMR analysis (see Supporting Information).

Scheme 9. Macrocyclization and Carbo-oxygenation



So, obviously unlike the carbohalogenations reported by Lautens¹⁹ and Tong,²⁰ acetoxy-palladation of **I** to **VI** is followed by *syn*-addition and reductive β -bromide

(16) Pd(OAc)₂ (0.1 equiv), PPh₃ (0.2 equiv), Ag₂CO₃ (3.0 equiv), 4 Å MS, toluene (0.01 M), 80 °C, 3 d. For a detailed procedure, see Supporting Information.

(17) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289. (b) Jeffery, T. *Synthesis* **1987**, 70–71. (c) Jeffery, T. *Tetrahedron* **1996**, 52, 10113–10130.

(18) Pd(OAc)₂ (0.1 equiv), NaOAc (5.0 equiv), Bu₄NCl (2.0 equiv), 4 Å MS, DMF (0.01 M), 85 °C, 1.5 h. For a detailed procedure, see Supporting Information.

elimination leading to **34** (path B). Thus, an eight-membered macrocycle (**34**) and a newly formed carbon–oxygen bond were generated in a single step from vinyl bromide **31** in acceptable overall yield.

To our knowledge this reaction which converts a 1,1-disubstituted olefin into an allylic neopentyl acetate so far has not been described in the literature.

In conclusion, we have developed a stereocontrolled route to an advanced macrocyclization precursor **31** within a longest linear sequence of 15 steps from the literature known alkyne **12** with an overall yield of 13%. A biomimetic [2 + 2]-photocyclization was used to install the all-carbon quaternary center at C-12. In this step the western [3.2.0]-carbon core of bielschowskysin with all-carbon atoms of the cyclobutane moiety is set up correctly. Moreover, the stereocenters at C-1 and C-2 have been introduced with acetal building block **11**, which could be a suitable building block for other syntheses. The Heck macrocyclization of **31** revealed an unprecedented carbo-oxygenation reaction of a vinyl bromide onto a 1,1-disubstituted double bond. This led to the complex macrocycle **34** featuring a tricyclo[8.3.0.0^{2,8}]tridecane ring system and an allylic neopentyl acetate. Work to generalize this methodology is in progress.

Acknowledgment. Financial support from the University of Vienna (doctoral program, Initiativkolleg Functional Molecules IK I041-N) and from the Austrian Science Fund (FWF, Project No. P22180) is gratefully acknowledged. We thank H. Kählig, L. Brecker, and S. Felsinger for NMR assistance and A. Roller and V. Arion (University of Vienna) for X-ray analysis.

Supporting Information Available. Experimental procedures and full characterization including copies of ¹H and ¹³C NMR spectra and crystal structure analysis of **26** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(19) (a) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, 133, 1778–1780. (b) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, 133, 14916–14919.

(20) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, 133, 6187–6193.

The authors declare no competing financial interest.

7.3. An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy¹¹⁴

Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Eur. J. Org. Chem.* **2013**, *accepted for publication*.

Planning: Himmelbauer, M.; Farcet, J.-B.; Mulzer, J.

Experimentation: Himmelbauer, M.; Gagnepain, J.

Manuscript preparation: Himmelbauer, M.; Farcet, J.-B.; Mulzer, J.

Discussion

All experiments, characterization of all intermediates as well as the preparation of the manuscript have been carried out by M. H. The contribution of Julien Gagnepain lies in the development of the synthesis of the allene building block, in particular in the application of the Searles-Crabbé procedure installing the allene functionality.

An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy

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Keywords: bielschowskysin / terpenoids / total synthesis / asymmetric synthesis / cycloaddition /

Several macrocyclization attempts of highly advanced precursors toward a total synthesis of marine diterpene bielschowskysin are disclosed. Biomimetic [2+2]-photocyclizations were applied to

construct the cyclobutane core in these intermediates, which could be accessed along scalable high yielding reaction sequences from cheap enantiopure starting materials.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.xxxxxxxx>.



Introduction

In 2003 Rodríguez et al. reported the isolation of bielschowskysin (**1**) along with other congeners from the Caribbean Sea plume *Pseudopterogorgia kallos*,^[1] among which **1** and providencin (**2**)^[2] are the only ones bearing unusual cyclobutane moieties. Due to its densely functionalized furanocembranoid structure featuring an unprecedented tricyclo[9.3.0.0^{2,10}]tetradecane ring system and eleven stereogenic centers, bielschowskysin has attracted considerable interest from the scientific community.^[3] Furthermore, the compound shows significant biological activity against the malaria causing protozoan parasite *Plasmodium falciparum* and two human cancer cell lines.

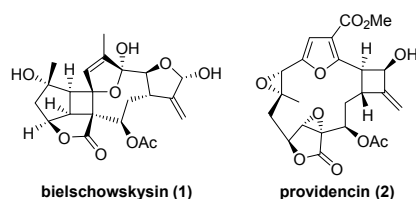
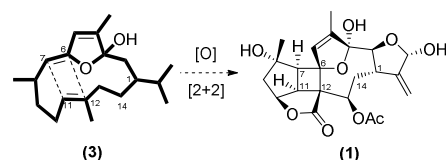


Figure 1. Structures of bielschowskysin and providencin.

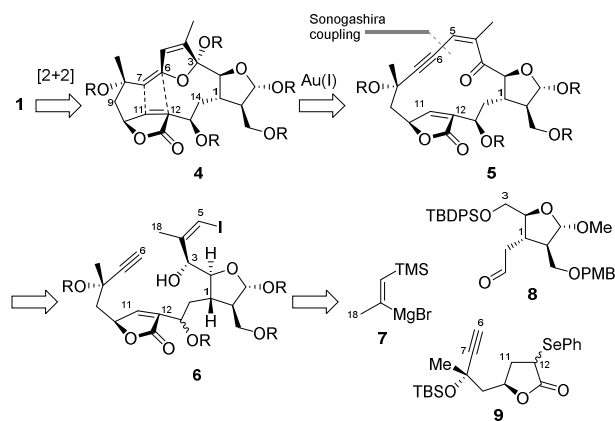
The members of the furanocembranoid family display a wide degree of functionalization. Nonetheless, they appear to be biogenetically interconnected.^[4] Thus, the cyclobutane moiety of bielschowskysin has been postulated to arise from a transannular [2+2]-cycloaddition of a much simpler macrocyclic precursor **3** (Scheme 1). We report two entirely different approaches to the full carbon backbone of bielschowskysin. The present article deals with the biomimetic [2+2]-photocyclization, whereas the following paper presents a non-photochemical access.^[5]



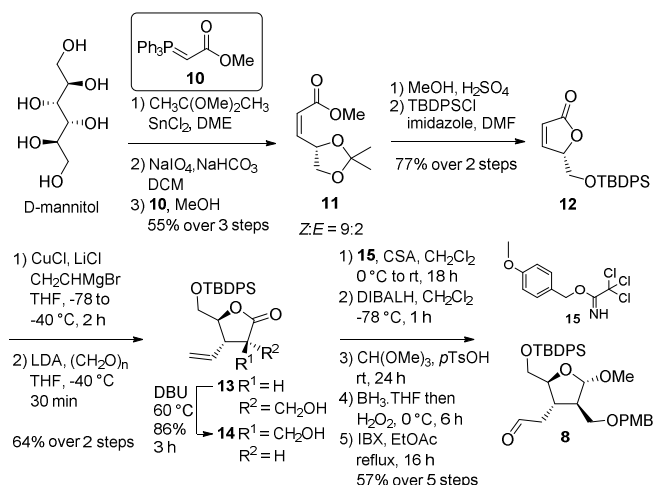
Scheme 1. Biosynthetic [2+2]-cycloaddition forming bielschowskysin.

Results and Discussion

Our retrosynthetic considerations were centered around the photochemical ring contraction^[6] of a 14-membered carbocycle **4** (Scheme 2). A gold-mediated cyclization^[7] of macrocyclic enyne **5** was envisaged to generate the required *exo*-methylene dihydrofuran ring. Palladium mediated intramolecular Sonogashira reaction^[8] of vinyl iodide **6** should close the 14-membered carbon macrocycle. As outlined in Scheme 2, precursor **6** should be assembled from three rather simple building blocks. Thus, aldol reaction of seleno lactone **9** and aldehyde **8** was planned to form the southern part and the enone functionality in **6**, which is essential for the [2+2]-cycloaddition, should be established by regioselective oxidative elimination of the selenide. After that, vinyl magnesium species **7** should introduce the vinyl moiety for the later macrocyclization.

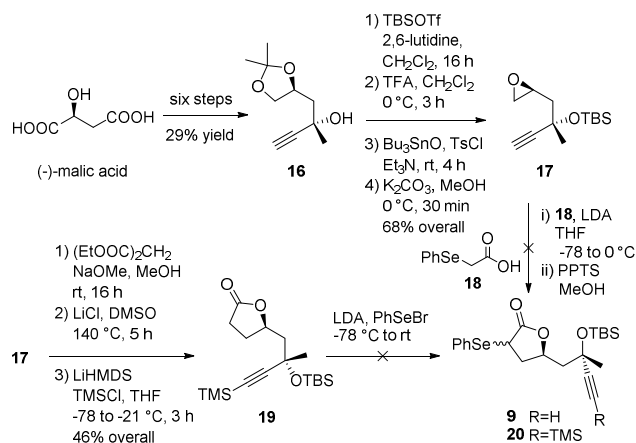


Scheme 2. Initial retrosynthesis based on a transannular [2+2]-cycloaddition.



Scheme 3. Synthesis of the eastern fragment **8**.

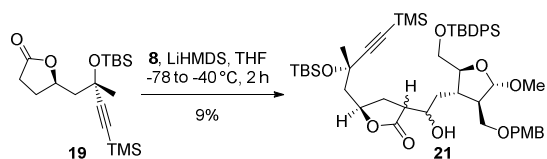
The synthesis of aldehyde **8** commenced with D-mannitol, which was converted to enantiomerically pure butenolide **12** in five steps (Scheme 3).^[9] We noticed that the bulky TBDPS-protecting group in **12** was essential for the stereochemical outcome of the copper mediated Michael addition of vinylmagnesium bromide. Unexpectedly, the introduction of the α -hydroxymethylene group met with problems. Neither in situ generation of formaldehyde^[10] nor introduction of gaseous formaldehyde gave satisfying results. However, deprotonation of the γ -butyrolactone followed by addition of a freshly prepared solution of formaldehyde in THF (see **14** in Experimental Section) resulted in a 4:1 mixture of diastereomers **13** and **14**. As expected, 2,3-*cis* lactone **13** could be epimerized to all-*trans* **14** with DBU at elevated temperature. Finally, PMB protection, reduction of the lactone, acetalization of the anomeric center and a hydroboration/oxidation sequence provided desired aldehyde **8**.



Scheme 4. Synthesis of the western alkyne **19**.

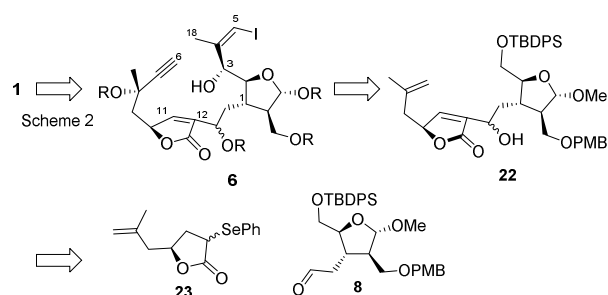
For the synthesis of the western alkyne building block **9** (Scheme 4), the known acetonide **16**^[3a,b] was converted to epoxide **17** in 68% yield over four steps. Various attempts to form α -phenylselenenyl lactone **9** in a single step by opening of the epoxide with the dianion of phenylselenenyl acetic acid failed.^[11] Thus, epoxide **17** was converted to γ -butyrolactone **19** by opening the epoxide with diethylmalonate followed by Krapcho-decarboxylation^[12] and protection of the terminal alkyne. Unfortunately, **19** could not be α -selenenylated by any means. Thus,

we coupled intermediates **19** and **8** (Scheme 5) and tried to introduce the selenide in the next step. Unfortunately, the yield of the aldol reaction was unacceptably low.



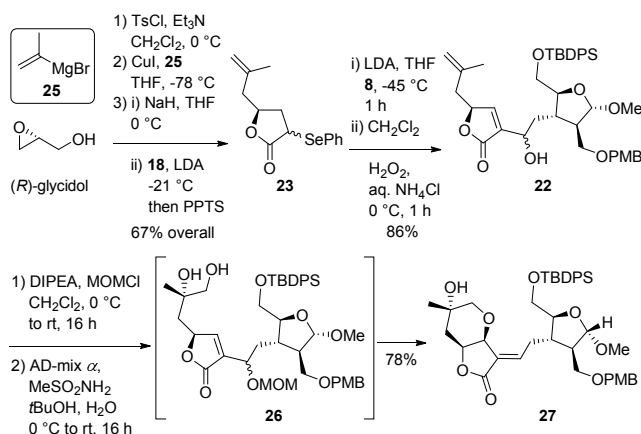
Scheme 5. Building block coupling.

In view of these failures we decided to add fragment **8** to seleno lactone **23** (Scheme 6), which is readily available from (*R*)-glycidol in three steps^[11] (Scheme 7). If the coupling indeed gave **22**, elaboration of the isopropenyl moiety (Scheme 6) might still lead to our envisaged intermediate **6**.



Scheme 6. Altered retrosynthesis.

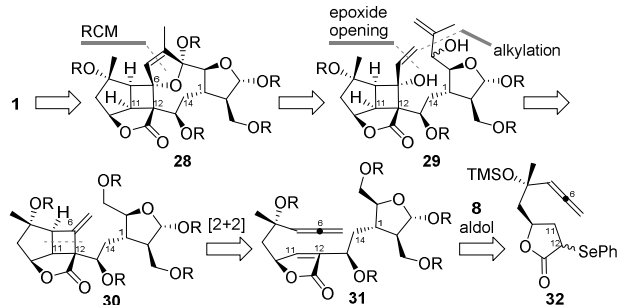
To our delight, the aldol reaction smoothly furnished the desired coupling product as a mixture of all four possible diastereomers (Scheme 7). Oxidative elimination of the phenylselenenyl group gave butenolide **22** as a mixture of two diastereomers, which was used as such in the next reaction. After protection of the free secondary alcohol a SAD-reaction was performed. Interestingly but unproductively, the primary product **26** underwent a $\text{S}_\text{N}2'$ -reaction under OMOM-elimination to generate compound **27**.



Scheme 7. Fragment coupling and formation of pyran **27**.

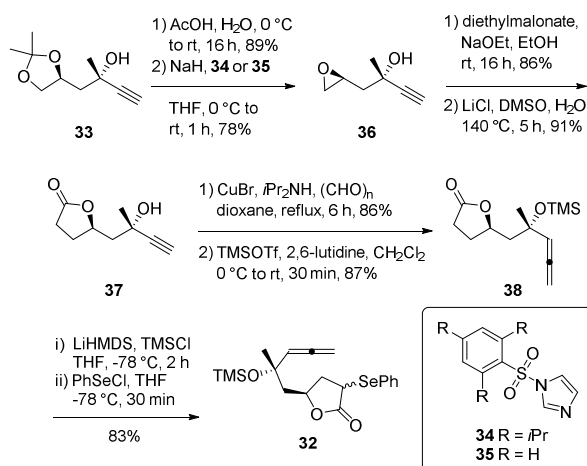
At this juncture we decided to abandon the transannular [2+2]-approach and to modify our strategy as shown in Scheme 8. Thus, aldol addition of **32** and **8** should provide precursor **31**, which in an

allene-olefin-[2+2]-photocyclization should lead to polycycle **30**. Further transformations should be directed toward **29** as the substrate of a RCM reaction to give dihydrofuran **28**.



Scheme 8. Retrosynthesis based on an allene-olefin-[2+2]-photocyclization.

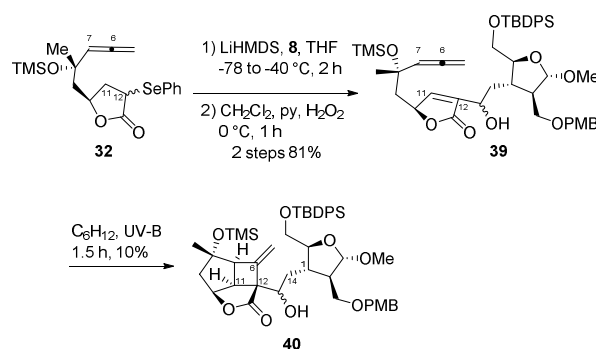
To start with, epoxide **36** was synthesized from **33** in two steps (Scheme 9). Regioselective addition of diethylmalonate, cyclization to the corresponding lactone and Krapcho decarboxylation gave γ -butyrolactone **37** in fair yield. Copper-mediated formation of the allene via the Searles-Crabbé protocol^[13] proceeded with high yield and was exceptionally easy to carry out. Protection of the tertiary alcohol and α -selenylation delivered lactone **32** in scalable seven steps with an overall yield of 35%. Interestingly, in situ formation of a trimethylsilyl enol ether and the use of phenylselenenyl chloride instead of the more reactive bromide were essential to stop the reaction after mono-selenylation.



Scheme 9. Synthesis of the western allene building block **32**.

Aldol coupling of building block **32** with **8** and regioselective oxidative elimination of the selenide uneventfully gave **39** as a mixture of diastereomers (Scheme 10). Without separation, a plethora of irradiation conditions was tested, some of which are outlined in Table 1. In many cases complex product mixtures were formed, and we found that irradiation of **39** with a sunlamp destroyed the starting material within few minutes. On narrowing the spectrum we either reisolated starting material or detected traces of presumptive product in the mass-spectrum of the reaction mixture. Eventually, irradiation of **39** with UV-B light in cyclohexane for 2.5 h allowed the isolation of 10% (Entry 13, Table 1) of the desired [3.2.0]-carbocycle **40** as a diastereomeric mixture. Purification by column chromatography allowed partial

separation of the C13-epimers. Thus, for the first time the crucial all-carbon quaternary center at C-12 of **1** was established.



Scheme 10. Fragment coupling and [2+2]-photocyclization.

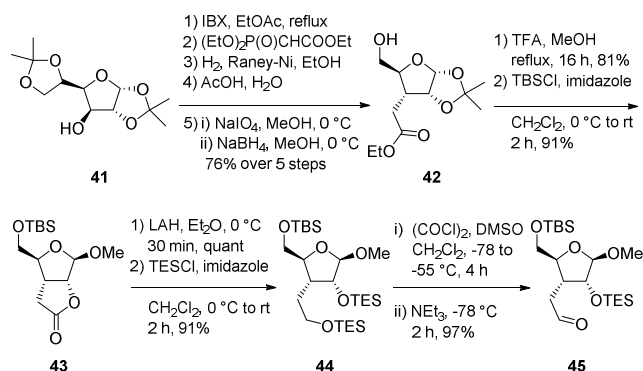
Table 1. [2+2]-photocyclization conditions of **39** to **40**.

Entry ^[a]	Solvent	Conditions ^[b]	Yield
1	EtOH	750 W, > 100 nm, 30 °C, 0.5 h	decomp.
2	acetone	750 W, > 100 nm, 30 °C, 0.5 h	decomp.
3	Hex/CH ₂ Cl ₂	750 W, > 100 nm, 30 °C, 0.5 h	decomp.
4	Hex/CH ₂ Cl ₂	6 W, > 350 nm, rt, 3 h	SM
5	EtOH	6 W, > 350 nm, rt, 3 h	SM
6	Hex	6 W, > 350 nm, rt, 9 h	SM
7	MeOH	6 W, > 350 nm, rt, 9 h	SM
8	acetone	2*6 W, > 350 nm, rt, 9 h	SM
9	cy	750 W, > 100 nm, 30 °C, 0.5 h	40 , traces
10	cy	750 W, > 350 nm, 30 °C, 0.5 h	decomp.
11	cy	2*6 W, > 350 nm, rt, 7 h	40 , traces
12	cy	8*6 W, 320-400 nm, rt, 7 h	SM
13	cy	8*6 W, 280-320 nm, rt, 1.5 h	40 , 10%

[a] All solutions were 0.001 M and freshly degassed prior to use. [b] In all entries quartz tubes were used as reaction vessels.

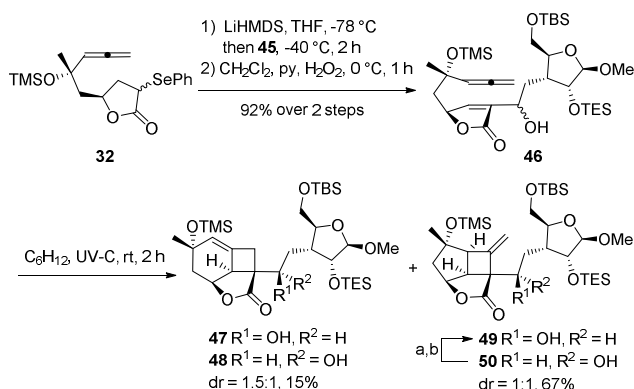
We reasoned that the formation of complex mixtures in the photoreaction might be due to the presence of the aryl chromophores in our substrate and decided to remove the PMB and the TBDPS-protecting groups in the [2+2]-cycloaddition precursor. The synthesis of the eastern tetrahydrofuran ring was redesigned accordingly (Scheme 11).

To circumvent the experimentally tedious 1,4-addition α -alkylation procedure of **12** (Scheme 3) we started from diacetone D-glucofuranose (**41**) (Scheme 11), from which known α -D-ribofuranose **42**^[14] was prepared in five steps along an optimized scalable sequence. Thus, IBX oxidation of **41** was followed by Horner-Wittig reaction giving an α,β -unsaturated ester. In contrast to the literature procedures, which either required aqueous workup, prolonged reaction times or high pressure for acquiring acceptable yields, we were able to hydrogenate the double bond with Raney-nickel in ethanol in an ultrasound bath at 1 atm of hydrogen pressure within 2 h. Removal of the acetonide, glycol cleavage and reductive workup yielded primary alcohol **42**. Acid catalyzed acetalization of the anomeric center and protection of the primary alcohol gave lactone **43**. After reduction to the diol, silyl protection and subsequent Swern-oxidation afforded the desired aldehyde **45**.



Scheme 11. Synthesis of the new eastern building block.

Deprotonation of **32**, addition of **45** and oxidative elimination of the phenylselenide furnished the [2+2]-photocyclization precursor **46** (Scheme 12) with a dr of about 1:1. Capitalizing on our earlier results a solution of **46** in freshly degassed cyclohexane was irradiated with UV-B light for 18 h to give 57% of diastereomeric cyclobutanes **49** and **50**. As the UV-spectrum of **46** revealed an absorption maximum at 235 nm, UV-light of 200 – 280 nm was applied. Gratifyingly the reaction time was reduced to 2 h and the yield of cyclization products **49/50** was increased to 67%. Additionally 15% of the undesired regioisomers **47/48** were formed. After separation of the isomers, the “wrong” diastereomer **50** was recycled to **49** by an oxidation-reduction sequence, and all ensuing reactions were carried out with enantiomerically pure **49** and **50**.

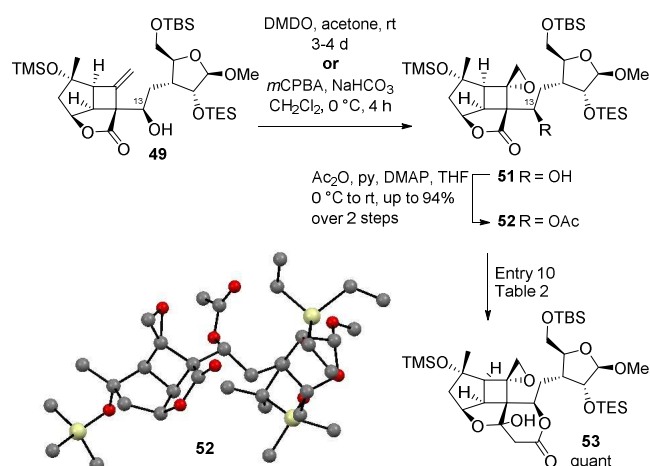


Scheme 12. Fragment coupling and improved [2+2]-photocyclization. a) TPAP, NMO, 4 Å MS, CH₂Cl₂, 0 °C; b) (S)-2-(–)-methyl-CBS oxazaborolidine, BH₃.THF, THF, -78 to -40 °C., 33% + 66% of **50**.

Next we epoxidized the *exo*-methylene group of **49** with DMDO and found that a free 13-OH group was necessary to obtain reasonable diastereoselectivity (6:1) (Scheme 13). In presence of a 13-OAc (13-OTMS) the dr dropped to 2:1 (1:1). With *m*CPBA the reaction was much faster and gave higher yields with a dr of 4:1. To assign the relative configuration, crystalline acetate **52** was prepared and subjected to single crystal diffraction.^[15]

For the opening of the epoxide, a number of nucleophiles were tested both with the free alcohol and the acetate, to no avail (Table 2). Interestingly, on **52** the lithium acetylide ethylenediamine complex acted as base and furnished pentacycle **53** in quantitative yield within 15 min at 0 °C, whereas **51** led to complex product mixtures. The *exo*-methylene group of **47** was subjected to a variety of alternative functionalizations (dihydroxylation,

ozonolysis, hydroboration, 1,3-dipolar cycloaddition) with disappointing results.

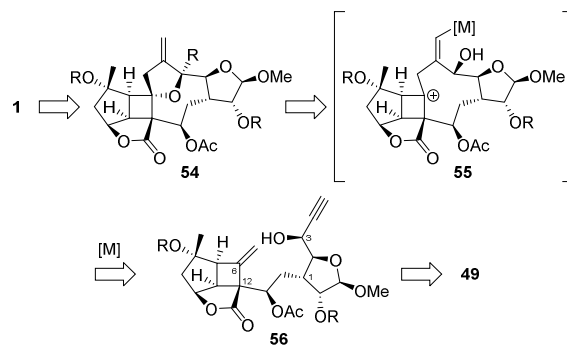


Scheme 13. Synthesis and X-ray structure of **52** and formation of pentacycle **53**.

Table 2. Conditions for the epoxide opening.

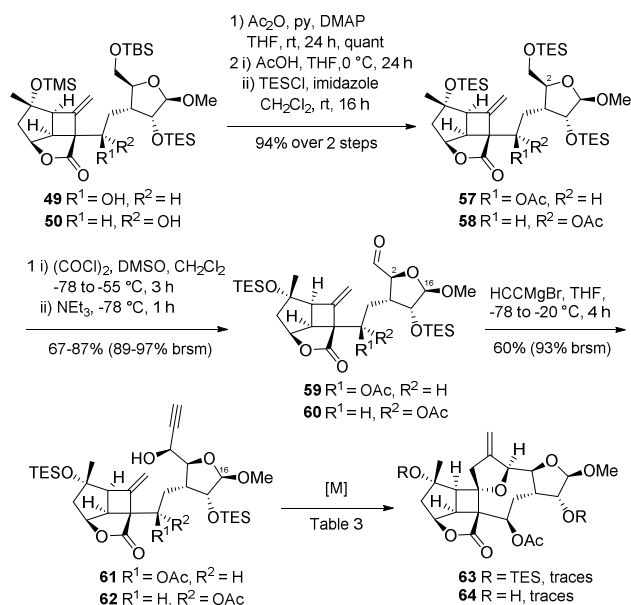
Entry	Conditions	Yield
1	52 , Me ₃ Si, <i>n</i> BuLi, THF, -78 °C, 8 h	SM
2	52 , Me ₃ Si, <i>n</i> BuLi, THF, -21 °C, 8 h	SM
3	52 , Me ₃ Si, <i>n</i> BuLi, THF, 0 °C to rt, 10 h	SM
4	52 , <i>i</i> -propenylMgBr, CuI, THF, -78 °C to 0 °C, 24 h	SM
5	52 , Me ₃ SBF ₄ , <i>n</i> BuLi, THF, -21 °C, 24 h	SM
6	52 , Me ₃ SBF ₄ , <i>n</i> BuLi, THF, -21 °C to rt, 24 h	SM
7	52 , CH ₂ CHMgBr, <i>n</i> BuLi, CuCN, THF, -78 °C to rt, 12 h	SM
8	52 , CH ₂ CHMgBr, <i>n</i> BuLi, CuCN, BF ₃ ·OEt ₂ , THF, -78 °C to rt, 12 h	SM
9	52 , PhSH, 0.5 M NaOH, dioxane, reflux, 16 h	decomp.
10	52 , Lithium acetylide ethylenediamine complex, THF, DMSO, 0 °C, 15 min	53 , quant

Being aware of the rich potential of transition metal catalyzed CC-connections between olefins and alkynes,^[7] we envisaged propargylic alcohol **56** as a suitable substrate for closing both the nine-membered carbocycle **55** and the furan moiety in **54** in a single step (Scheme 14). The introduction of the alkyne into **49/50** via aldehydes **59** and **60**^[3h] is outlined in Scheme 15.



Scheme 14. Retrosynthesis based on transition metal mediated cyclization of the carbon core of bielschowskysin.

At the end, propargylic alcohol **61** was formed in good overall yield as a single diastereomer, and subjected to macrocyclization (Table 3, Scheme 15). Though mass analysis indicated the formation of the desired product in some cases, we were not able to obtain suitable NMR-spectra.

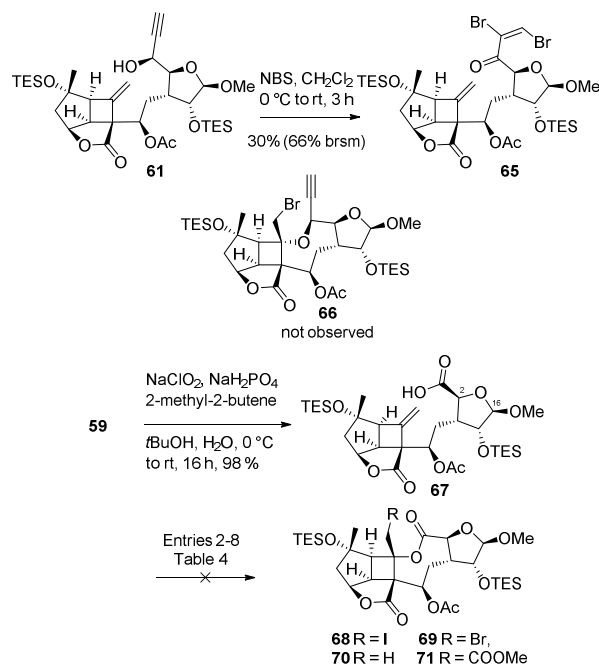


Scheme 15. Introduction of the alkyne and transition metal mediated cyclization attempts.

Table 3. Conditions for the transition metal mediated cyclization.

Entry	SM	Conditions ^[c]	Yield
1	61	$[(\text{PPh}_3)\text{Au}]\text{NTf}_2$, CH_2Cl_2 , -78 to 0 °C, 24 h	63 , traces
2	61	PtCl_2 , toluene, 75 °C, 2 d	64 , traces
3	61	$[(\text{PPh}_3)\text{Au}]\text{Cl}$, AgSbF_6 , CH_2Cl_2 , 0 °C, 1 h	61 - global TES
4	61	$[(\text{PPh}_3)\text{Au}]\text{Cl}$, AgSbF_6 , MeOH, 0 °C, 6 h	61 - global TES
5	61	$[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$, toluene, 80 °C, 5 h	63 , traces
6	61 - global TES	$[(\text{PPh}_3)\text{Au}]\text{NTf}_2$, CH_2Cl_2 , 0 °C to rt, 1 h	decomp.

Trying to close a macrocyclic ether **66** by treating enyne **61** with NBS^[16] (Scheme 16) only led to the formation of **65** (connectivity and relative configuration of the bromides were determined by 2D-NMR analysis). In another attempt, aldehyde **59** was oxidized to carboxylic acid **67** which was subjected to several halo-lactonization and Wacker cyclization conditions (Scheme 16, Table 4),^[17] but the substrate either was unreactive or decomposed without revealing any trace of products **68-71**.



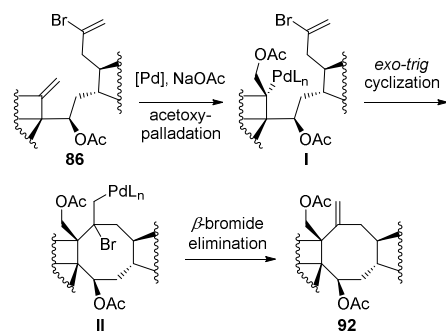
Scheme 16. Additional macrocyclization attempts.

Table 4. Conditions for alternative macrocyclizations.

Entry	SM	Conditions	Yield
1	61	NBS, CH_2Cl_2 , 50 °C, 5 h	65 , 66%
2	67	NIS, CDCl_3 , 40 °C, 2 h	SM
3	67	I_2 , NaHCO_3 , CH_2Cl_2 , 40 °C, 6 h	SM
4	67	NBS, CH_3CN , 82 °C, 3 h	decomp.
5	67	PdCl_2 , CuCl, O ₂ , DMF, rt, 16 h	decomp.
6	67	PdCl_2 , CuCl, O ₂ , NaHCO_3 , DMF, rt, 16 h	decomp.
7	67	PdCl_2 , CuCl, CO, CH_3CN , MeOH, 140 °C, 4 h	SM
8	67	$\text{Pd}(\text{OAc})_2$, CuCl, CO, CH_3CN , MeOH, 140 °C, 6 h	SM

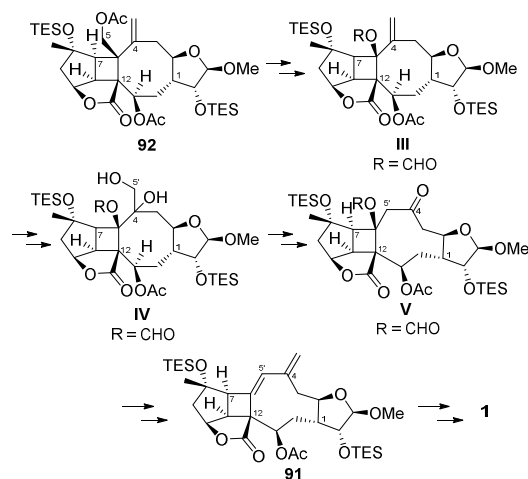
To get more flexibility in the eastern building block and to obtain a suitable protecting group pattern we decided to modify the synthesis of **46** and prepared derivatives **75**, **76** and **77** along scalable and reliable routes (Scheme 17).

Metal halogen exchange of iodide **76** and addition of the lithium derivative to aldehyde **81**, which was derived from our earlier intermediate **80**^[3f,g] in three steps, delivered **82** with a dr of 4:1 at C-13 but low yield (Scheme 18).



Scheme 22. Mechanistic explanation for the carbo-oxygenation.

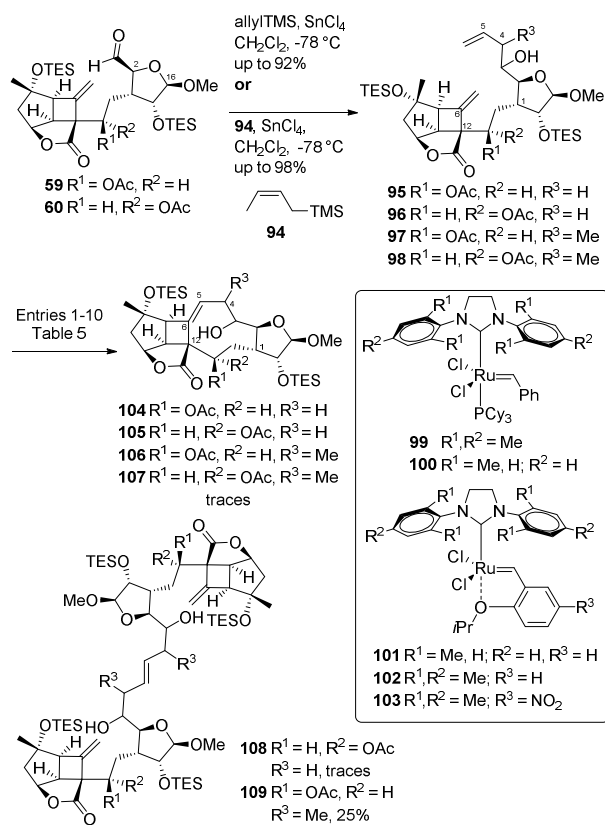
Not necessarily the formation of the wrong ring sized macrocycle **92** is to put an end to our synthesis. After all, there are a number of options to achieve a suitable ring expansion, one of which is tentatively suggested in Scheme 23.



Scheme 23. Tentative conversion of **92** to desired macrocycle **91**.

Thus, saponification of the acetate group at C-5 in **92** followed by oxidation to the aldehyde and Baeyer-Villiger oxidation should provide **III**. Dihydroxylation of the *exo*-methylene bond, mesylation of the primary alcohol at C-5' followed by Wagner-Meerwein rearrangement forming the $\Delta^{6,5'}$ bond should deliver the desired nine-membered macrocycle and the ketone at C-4 in **V**. Elimination of the formate and an olefination should give diene **91** which can be processed to the natural product within a few reactions mainly consisting of protecting group operations and oxidations.

In parallel to the Heck type cyclization we tried to set the stage for the RCM approach and various attempts to introduce an allyl appendage at aldehyde **59/60** were initiated (Scheme 24). Conventional treatment with allylmagnesium halides, allyl-zinc species, Brown-allylation^[20] and Duthaler-Hafner allyl complex^[21] all failed. Finally, reaction of **59/60** with allyltrimethylsilane or (*Z*)-crotyltrimethylsilane (**94**) and tin tetrachloride afforded **95** to **98** as inseparable mixtures of diastereomers along with some unreacted aldehyde. These mixtures were used in the RCM-experiments (Scheme 24, Table 5).



Scheme 24. Ring closing metathesis attempts.

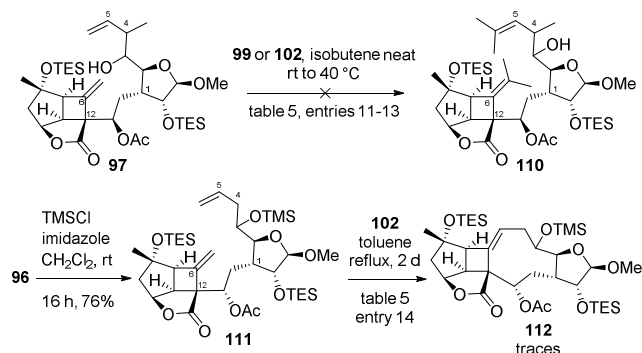
Table 5. Metathesis conditions

Entry	SM	Conditions	Yield
1 ^[a]	96	99 (0.4 eq.), benzene (0.001 M), reflux, 24 h	105 , traces
2 ^[a]	96	102 (0.4 eq.), benzene (0.001 M), reflux, 24 h	108 , traces
3 ^[a]	96	102 (0.4 eq.), toluene (0.001 M), reflux, 24 h	105 , traces.
4 ^[a]	95	102 (0.3 eq.), toluene (0.001 M), reflux, 30 h	104 , traces
5 ^[a]	97	102 (0.3 eq.), toluene (0.0005 M), reflux, 18 h	109 , 15%
6 ^[a]	97	101 (0.2 eq.), toluene (0.0005 M), reflux, 36 h	SM
7 ^[a]	97	103 (0.2 eq.), toluene (0.0005 M), reflux, 36 h	SM
8 ^[b]	97	103 (0.2 eq.), toluene (0.0005 M), reflux, 16 h	SM
9 ^[a]	97	103 (0.2 eq.), toluene (0.0005 M), reflux, 20 h	109 , 25%
10 ^[a]	97	99 (0.2 eq.), hexafluorobenzene (0.001 M), reflux, 38 h	109 , 24%
11 ^[b]	97	99 (0.1 eq.), isobutene (0.01 M), reflux, 16 h	SM
12 ^[b]	97	99 (0.1 eq.), isobutene (0.01 M), 45 °C, 24 h	SM
13 ^[b]	97	102 (0.3 eq.), isobutene (0.01 M), 45 °C, 24 h	SM
14 ^[a]	111	102 (0.4 eq.), toluene (0.001 M), reflux, 48 h	112 , traces

[a] Catalyst constantly added as 0.005 M solution via syringe pump within 8 h [b] Catalyst added in one portion as a solid.

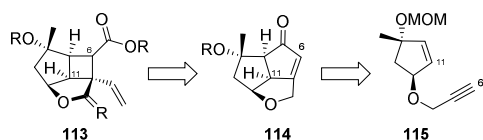
A broad spectrum of catalysts and solvents were employed (Table 5). Specifically, the conventional Grubbs 2nd generation **99**^[22], Grubbs-Hoyveda II catalyst **102**, **100**, Stevens catalyst **101**^[23], fast initiating Nitro-Grela catalyst **103**^[24] and additionally, the doping-effect of poly-fluorinated solvents on the RCM reaction were tested.^[25] In most cases complex product mixtures were obtained and indeed, in some cases traces of the desired macrocycle **104** to **107** were identified in the mass spectrum. Predominantly however, homodimers **108** and **109** were obtained.

From the dimerization products we reasoned that replacing the terminal vinyl group by an isobutene appendage would facilitate the RCM reaction with the *exo*-methylene group in *neo*-pentyl position.^[26] Therefore, cross-metathesis of **97** to **110** with isobutene was initiated (Table 5, Entries 11 – 12; Scheme 25), but no reaction occurred under these conditions. Finally, the free 3-OH in **96** was protected as the silyl ether **111**. Disappointingly, this did not improve the outcome of the RCM reaction either (Table 5, Entry 14; Scheme 25), leading only to traces of the desired macrocycle **112**.

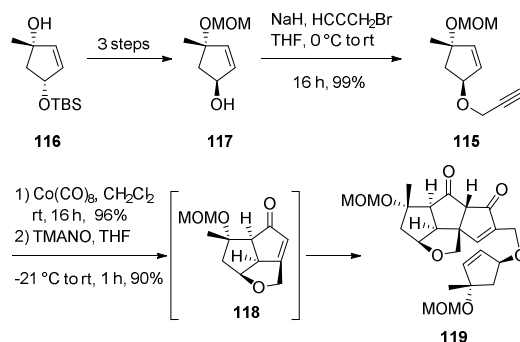


Scheme 25. Additional metathesis experiments.

Having sizeable quantities of iodide **76** in hand, we thought of accessing the western [3.2.0]-carbocyclic structure of bielschowskysin via a totally different strategy (Scheme 26). This approach was centered around a Pauson-Khand reaction^[27] of **115** to form cyclopentenone **114**, which after 1,4-addition and contraction of the five membered ring by either Favorskii-^[28] or Wolff-rearrangement^[29] should lead to cyclobutane **113**.



Scheme 26. Pauson-Khand strategy to construct the cyclobutane moiety.



Scheme 27. Pauson-Khand reaction cascade.

Thus, prostaglandin precursor **116**^[30] was readily converted to **115** (Scheme 27). After formation of the stable hexacarbonyldicobalt complex a trimethylamine-*N*-oxide (TMANO) induced Pauson-Khand reaction (PKR) was performed. Interestingly, the intra-molecular PKR to **118** was followed by an inter-molecular PKR with a second molecule of **115** to furnish the highly functionalized poly-cycle **119** in excellent yield. This remarkable cascade generated three carbocycles and three stereogenic centers, including an all carbon quaternary center, in a single step. After conducting the reaction at lower temperatures and at higher dilution intermediate **118** could be identified in an inseparable mixture with an uncharacterized side product. As pentacycle **119** features a *cis,trans,cis*-triquinane terpene type core, this serendipitous result may be useful in other synthetic ventures.

Conclusions

In conclusion, in this part of our bielschowskysin project we were able to synthesize several advanced macrocyclization precursors. Stereoselective high yielding syntheses of building blocks representing the eastern hemisphere of the target compound have led to the optically active tetrahydrofuran building blocks **8**, **45**, and **75-77** which may be also useful in other syntheses. Our initial synthetic plan was modified and optimized, so that the biomimetic [2+2]-photocyclization could be carried out on a large scale and provided the [3.2.0]-carbocyclic core of bielschowskysin in a stereoselective manner. Except for an epoxidation, the *exo*-methylene group proved exceptionally unreactive to numerous transformations. Various RCM reactions, instead of closing the desired nine-membered macrocycle, exclusively led to dimers **108** and **109**. However, macrocyclization under Jeffery-Heck-conditions was successful, and, via an unprecedented carbonylation, led to the highly functionalized macrocycle **92**, which had the wrong ring size, but eight correctly substituted stereocenters in place. At present, synthetic efforts to enlarge the eight-membered ring to the desired nine-membered one are well under way in our laboratory.

Experimental Section

General remarks: All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under a slight argon overpressure. All solvents (except dichloromethane and methanol) were purchased as the highest available grade from Sigma-Aldrich, Acros-Organics or Fischer-Chemicals. Anhydrous dichloromethane was purified by filtration through alumina under argon immediately before use. Methanol was heated at reflux for several hours over sodium before being distilled. NEt₃, iPr₂NEt and 2,6-lutidine were distilled over CaH₂ before use. All other reagents were used as received from Sigma-Aldrich, Acros-Organics, Fischer-Chemicals, TCI or ABCR unless otherwise stated. Preparative column

chromatography was performed with silica gel 60 from Merck (0.040-0.063 μm , 240-400 mesh). All NMR spectra were measured on a Bruker AV400, DRX400 or DRX600. Chemical shifts are given in ppm and referenced to the solvent residual peaks (CDCl_3 ^1H , $\delta = 7.26$ ppm, ^{13}C , $\delta = 77.16$ ppm). Infrared spectra were recorded as thin films of pure products on an ATR-unit on a Bruker Vertex 70. High-resolution mass spectra were measured on Bruker MaXis (ESI-TOF) with a resolution of 10,000. A P341 Perkin-Elmer polarimeter equipped with in a 10 cm cell and a Na-lamp (589 nm) was used for the measurement of optical rotation.

(3R,4S,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-(hydroxymethyl)-4-vinyldihydrofuran-2(3H)-one (14): In a round-bottomed flask copper chloride (35 mg, 0.35 mmol) and lithium chloride (37 mg, 0.87 mmol) were gently dried with a heat gun in vacuo. The flask was carefully purged with argon and equipped with a rubber septum. The solids were digested in THF (20 mL) at room temperature and cooled to -78°C . Vinylmagnesium bromide (5.7 mL, 5.70 mmol) was added to the vigorously stirred mixture via syringe within 10 min. After 30 min to the resulting beige milky suspension a solution of butenolide **12** (1.54 g, 4.37 mmol) was dropwise added in THF (20 mL) via cannula within 30 min at -78°C . After 1 h the resulting yellow solution was warmed to -40°C and stirred for an additional hour. The resulting dark red reaction mixture was quenched with sat. aq. NH_4Cl (40 mL) and warmed to room temperature. The aqueous phase was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (40 mL), sat. aq. NaCl (40 mL) dried with MgSO_4 , filtered and concentrated under reduced pressure. Column chromatography (SiO_2 , Hex/EtOAc 6/1) afforded the desired 1,4 adduct as slightly yellow gum (1.38g, 3.62 mmol) in 83%. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.78$ -7.65 (m, 4H), 7.47-7.38 (m, 6H), 5.76 (ddd, $J = 17.6, 9.6, 8.0$ Hz, 1H), 5.13 (d, $J = 17.6$ Hz, 1H), 5.11 (d, $J = 9.6$ Hz, 1H), 4.25 (ddd, $J = 6.8, 3.5, 2.7$ Hz, 1H), 3.93 (dd, $J = 11.6, 2.7$ Hz, 1H), 3.73 (dd, $J = 11.6, 3.5$ Hz, 1H), 3.20 (dddd, $J = 8.9, 8.4, 8.0, 6.8$ Hz, 1H), 2.82 (dd, $J = 17.6, 8.9$ Hz, 1H), 2.44 (dd, $J = 17.6, 8.4$ Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 175.9, 136.4, 136.0, 135.5, 132.9, 132.5, 129.9, 127.8, 117.3, 104.5, 84.6, 63.3, 40.7, 35.0, 26.7, 19.2$.

Preparation of the formaldehyde solution: Paraformaldehyde (3.8 g, 126 mmol) was placed in a two-necked round-bottomed flask equipped with a rubber septum and an argon inlet on one side and a glass-bridge filled with fresh calcium chloride on the other. The glass-bridge was connected to a second two-necked round bottomed flask as a water-trap which was cooled to 0°C . The second neck was equipped with a rubber septum and a thick teflon cannula which reaches into dry THF (28 mL) at -40°C in a third two necked round bottomed flask equipped with a bubbler on the remaining neck. In the following the flask containing formaldehyde was heated in an oil bath to 150°C under a constant stream of argon (one bubble per second in THF). Heating was continued for 15 min after all the formaldehyde was gone (overall 2 h). The resulting clear solution was kept at -40°C and used immediately as such in the alkylation.

A solution of diisopropylamine (1.75 mL, 12.3 mmol) in THF (16 mL) was dropwise treated with $n\text{BuLi}$ (1.6 M in hex, 7.4 mL, 11.7 mmol) at -21°C . 5 min after the addition the resulting solution was warmed to 0°C for 30 min. At -40°C a solution of the 1,4-adduct (3.9 g, 10.2 mmol) in THF (12 mL) was dropwise added within 15 min and the resulting solution was aged for 1 h. The freshly prepared cold solution of formaldehyde was added via teflon cannula within 2 min and the resulting turbid reaction mixture was allowed to stir for additional 30 min. The reaction was quenched with sat. aq. NH_4Cl (30 mL). The aqueous phase was separated and extracted with diethyl ether (2 x 40 mL). The combined organic phases were washed with sat. aq. NaCl (40 mL), dried with MgSO_4 , filtered and concentrated in vacuo resulting in a 2:1 mixture of diastereomers. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 6/1) yielded **14** (2.21g, 5.40 mmol) and **13** (1.11 g, 2.69 mmol) as single diastereomers in combined 79% yield. Analytic data for **13**: ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.67$ -7.65 (m, 4H), 7.47-7.38 (m, 6H), 5.88 (dt, $J = 17.0, 9.9$ Hz, 1H), 5.22-5.20 (m, 1H), 5.19-5.15 (m, 1H), 4.36 (dt, $J = 5.3, 3.1$ Hz, 1H), 3.94-3.84 (m, 2H), 3.92 (dd, $J = 11.7, 3.0$ Hz, 1H), 3.72 (dd, $J = 11.7, 3.3$ Hz, 1H), 3.29 (td, $J = 14.5, 5.2$ Hz, 1H), 3.04 (dt, $J = 10.2, 5.1$ Hz, 1H), 2.18 (dd, $J = 7.0, 4.8$ Hz, 1H), 1.55 (1H), 1.06 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 176.8, 135.8$ (2C), 135.7 (2C), $134.7, 133.1$ (2C), $132.9, 130.0, 128.0$ (4C), $119.9, 83.2, 62.4, 59.8, 48.8, 43.2, 26.9$ (3C), 19.4 . HRMS (ESI) (m/z): calculated for $\text{C}_{24}\text{H}_{30}\text{O}_4\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 433.1811, found 433.1815.

Epimerization of 13: Alcohol **13** (611 mg, 1.15 mmol) was dissolved in toluene (5 mL) and DBU (170 μL , 1.13 mmol). The resulting solution was heated to 60°C for 3 h. The organic phase was washed with 1 N HCl (2 x 5 mL) and water (5 mL), dried with MgSO_4 , filtered, concentrated under reduced pressure and subjected to column chromatography (SiO_2 , Hex/EtOAc 6/1). Desired alcohol **14** (529 mg, 1.0 mmol) was isolated as colorless oil in 86% yield. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.68$ -7.65 (m,

4H), 7.46-7.37 (m, 6H), 5.68 (ddd, $J = 16.9, 10.3, 8.3$ Hz, 1H), 5.21-5.16 (m, 2H), 4.22 (ddd, $J = 9.5, 4.0, 2.6$ Hz, 1H), 4.00-3.95 (m, 1H), 3.96 (dd, $J = 11.7, 2.7$ Hz, 1H), 3.78-3.72 (m, 1H), 3.74 (dd, $J = 11.9, 3.8$ Hz, 1H), 3.18 (dt, $J = 11.4, 9.1$ Hz, 1H), 2.67 (ddd, $J = 11.6, 5.8, 4.0$ Hz, 1H), 2.35 (dd, $J = 7.5, 5.6$ Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 178.3, 135.8$ (2C), 135.7 (2C), $133.9, 133.0$ (2C), $132.6, 130.1, 128.0$ (4C), $119.4, 84.2, 63.8, 60.3, 46.3, 43.9, 26.9$ (3C), 19.4 . HRMS (ESI) (m/z): calculated for $\text{C}_{24}\text{H}_{30}\text{O}_4\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 433.1811, found 433.1816. IR (cm^{-1}): 3481, 2932, 1859, 1770, 1472, 1428, 1113, 1047, 929, 703. $[\alpha]_D^{25}$: +12.7, (CHCl_3 , $c = 1.2$). R_f: (Hex/EtOAc 3/1) 0.28.

2-((2S,3S,4R,5S)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)-5-methoxy-4-((4-methoxybenzyl)oxy)methyl)tetrahydrofuran-3-yl)acetaldehyde (8):

To a solution of alcohol **14** (5.0 g, 12.2 mmol) and freshly prepared 4-methoxybenzyl-2,2,2-trichloroacetimidate (7.0 g, 24.9 mmol) in CH_2Cl_2 (80 mL) was added CSA (140 mg, 0.6 mmol) at 0°C . The resulting pale yellow solution was allowed to warm to room temperature overnight. After 18 h water (50 mL) was added and stirring was continued for an additional hour. The organic phase was separated, dried with MgSO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (SiO_2 , Hex/EtOAc 12/1) yielded the desired PMB protected alcohol (5.94 g, 11.2 mmol, 92%) as pale yellow oil. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.68$ -7.66 (m, 4H), 7.45-7.36 (m, 4H), 7.21 (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 5.66 (ddd, $J = 17.0, 10.3, 8.4$ Hz, 1H), 5.14-5.08 (m, 2H), 4.51 (d, $J = 11.8$ Hz, 1H), 4.43 (d, $J = 11.9$ Hz, 1H), 4.18 (ddd, $J = 9.5, 4.2, 2.7$ Hz, 1H), 3.93 (dd, $J = 11.8, 2.7$ Hz, 1H), 3.81-3.78 (m, 1H), 3.79 (s, 3H), 3.75 (dd, $J = 11.8, 4.3$ Hz, 1H), 3.61 (dd, $J = 9.7, 3.5$ Hz, 1H), 3.37-3.30 (m, 1H), 2.62 (dt, $J = 11.2, 3.7$ Hz, 1H), 1.04 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 175.8, 159.3, 135.8$ (2C), 135.7 (2C), $135.4, 133.3, 133.0, 130.2, 129.9, 129.9, 129.3$ (2C), 127.9 (4C), $119.1, 113.9$ (2C), $82.7, 73.1, 65.6, 62.8, 55.4, 47.7, 43.3, 26.8$ (3C), 19.4 . HRMS (ESI) (m/z): calculated for $\text{C}_{32}\text{H}_{38}\text{O}_5\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 553.2386, found 553.2388. IR (cm^{-1}): 3000, 2858, 1777, 1513, 1247, 1113, 1008, 823, 702, 504. $[\alpha]_D^{20}$: +0.63, (CHCl_3 , $c = 0.64$). R_f: (Hex/EtOAc 3/1) 0.37.

To a solution of the PMB-ether (4.34 g, 8.2 mmol) in CH_2Cl_2 (100 mL) was added DIBALH (25 wt% in toluene, 9.3 mL, 16.3 mmol) with a syringe at -78°C within 10 min. the resulting reaction mixture was allowed to stir at this temperature for 1 h before the reaction was carefully quenched with sat. aq. Na/K tartrate (100 mL). The resulting biphasic mixture was vigorously stirred for 2 h. The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with water (100 mL) and sat. aq. NaCl (100 mL), dried with MgSO_4 and filtered. Evaporation of all volatiles provided the desired lactol at a dr of 2:1 as pale yellow oil which was used without further purification in the next reaction.

The residue was dissolved in trimethylorthoformate (40 mL) and PPTS (18 mg, 0.1 mmol) was added. The reaction was stirred at room temperature for 24 h after which sat. aq. NaHCO_3 (20 mL) was added. The aqueous phase was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (40 mL) and sat. aq. NaCl (40 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 6/1) yielded the desired acetal (3.6 g, 6.6 mmol, 80%). Major diastereomer: ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.70$ -7.67 (m, 4H), 7.43-7.34 (m, 6H), 7.23 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.71 (ddd, $J = 16.9, 10.1, 8.8$, 1H), 4.95 (dd, $J = 10.1, 1.6$ Hz, 1H), 4.94-4.90 (m, 1H), 4.91 (d, $J = 2.4$ Hz, 1H), 4.46 (d, $J = 11.8$ Hz, 1H), 4.41 (d, $J = 11.8$ Hz, 1H), 3.90 (ddd, $J = 8.7, 7.9, 3.0$ Hz, 1H), 3.82 (dd, $J = 9.4, 2.9$ Hz, 1H), 3.80 (s, 3H), 3.70 (dd, $J = 11.2, 4.7$ Hz, 1H), 3.43 (dd, $J = 9.5, 5.2$ Hz, 1H), 3.38 (s, 3H), 3.38-3.35 (m, 1H), 2.40 (dd, $J = 16.6, 8.6$ Hz, 1H), 2.26-2.20 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 159.3, 138.1, 135.9$ (2C), 135.8 (2C), 133.8 (2C), $130.6, 129.7$ (2C), 129.3 (2C), 127.75 (2C), 127.73 (2), $116.7, 113.9$ (2C), $107.6, 82.8, 72.7, 69.4, 64.2, 55.4, 55.2, 52.8, 47.4, 27.0$ (3C), 19.5 . HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{42}\text{O}_5\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 569.2699, found 569.2697. IR (cm^{-1}): 2999, 2931, 2858, 1613, 1513, 1248, 1112, 1007, 823, 703. $[\alpha]_D^{23}$: +15.7, (CHCl_3 , $c = 0.42$). R_f: (Hex/EtOAc 3/1) 0.48.

To a solution of the acetal (1.3 g, 2.38 mmol) in THF (24 mL) was added $\text{BH}_3\cdot\text{THF}$ (1.0 M in THF, 7.2 mL, 7.2 mmol) at 0°C within 10 min. After 5 h of stirring at 0°C 1 M NaOH (6 mL) and hydrogen peroxide (30 wt%, 3 mL) were added sequentially and the resulting biphasic mixture was stirred for an additional hour at that temperature. Sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (15 mL) was added, the aqueous phase was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (20 mL) and sat. aq. NaCl (20 mL), dried with MgSO_4 and concentrated under reduced pressure. After column chromatography (SiO_2 , Hex/EtOAc 6/1) the desired alcohol (1.0 g, 1.7 mmol, 75%) was obtained as pale yellow oil. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.71$ -7.67 (m, 4H), 7.45-7.35 (m, 6H), 7.20 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.72 (s br, 1H), 4.43 (d, $J =$

11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.82 (ddd, J = 8.2, 4.8, 3.8 Hz, 1H), 3.79 (s, 3H), 3.77 (dd, J = 11.2, 3.6 Hz, 1H), 3.72 (dd, J = 11.2, 4.9 Hz, 1H), 3.65–3.56 (m, 2H), 3.52 (dd, J = 8.7, 6.8 Hz, 1H), 3.31 (s, 3H), 3.24 (t, J = 9.0 Hz, 1H), 2.34–2.29 (m, 1H), 1.96–1.90 (m, 1H), 1.69–1.59 (m, 1H), 1.58–1.51 (m, 1H), 1.07 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 159.5, 135.9 (2C), 135.8 (2C), 133.6, 133.5, 129.84 (2C), 129.83 (2C), 129.7, 127.83 (2C), 127.81 (2C), 114.0 (2C), 107.3, 84.3, 73.2, 71.7, 65.2, 61.2, 55.4, 54.6, 51.4, 40.0, 36.1, 27.0 (3C), 19.4. HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{44}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 587.2805, found 587.2814. IR (cm^{-1}): 3470, 2932, 2859, 1613, 1472, 1249, 1112, 1080, 823, 703. [α] $_{\text{D}}^{21}$: +20.1, (CHCl_3 , c = 0.30). R_f (Hex/EtOAc 3/1) 0.21.

A suspension of the alcohol (244 mg, 0.43 mmol) and IBX (242 mg, 0.86 mmol) in EtOAc (4.3 mL) was refluxed for 16 h. The fine suspension was cooled to room temperature and hexane (5 mL) was added. The mixture was filtered through a pad of Celite, which was rinsed with hexane (5 mL). The remaining colorless filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2 , Hex/EtOAc 8/1), which gave the desired aldehyde **8** (239 mg, 0.42 mmol, 98%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 9.65 (t, J = 1.3 Hz, 1H), 7.69–7.65 (m, 4H), 7.45–7.35 (m, 6H), 7.21 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.86 (d, J = 1.0 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 3.80 (s, 3H), 3.79–3.77 (m, 1H), 3.77–3.75 (m, 2H), 3.44–3.34 (m, 2H), 3.31 (s, 3H), 2.65 (ddd, J = 17.6, 8.4, 1.6 Hz, 1H), 2.54 (ddd, J = 17.6, 5.4, 1.2 Hz, 1H), 2.23–2.16 (m, 1H), 2.15–2.10 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 201.3, 159.1, 135.7 (2C), 135.6 (2C), 133.3, 133.3, 130.3, 129.73, 129.71, 129.2 (2C), 127.69 (2C), 127.78 (2C), 113.8 (2C), 107.2, 82.9, 72.7, 70.4, 64.9, 55.2, 54.6, 52.4, 48.1, 36.4, 26.9 (3C), 19.3. HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{42}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 585.2648, found 585.2665. IR (cm^{-1}): 2932.5, 1759.8, 1613.7, 1514.5, 1428.5, 1249.3, 1180.5, 1112.2, 823.9, 704.0. [α] $_{\text{D}}^{22}$: +0.5, (CHCl_3 , c = 1.1). R_f (Hex/EtOAc 3/1) 0.44.

tert-Butyldimethyl((S)-2-methyl-1-((S)-oxiran-2-yl)but-3-yn-2-yl)oxy)silane (17): Tertiary alcohol **16** (5.96 g, 32.3 mmol) and 2,6-lutidine (7.6 mL, 65.3 mmol) were dissolved in CH_2Cl_2 (130 mL) and cooled to 0 °C. TBSOTf (8.2 mL, 35.7 mmol) was dropwise added via syringe within 10 min. The resulting pale yellow solution was stirred at that temperature for 16 h followed by the addition of sat. aq. NH_4Cl (50 mL). The organic phase was separated, dried with MgSO_4 and concentrated under reduced pressure providing the crude TBS-ether (9.0 g, 30 mmol, 93%) which was exceptionally clean and used in the next step without further purification. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.37–4.31 (m, 1H), 4.14 (dd, J = 8.1, 5.8 Hz, 1H), 3.63 (t, J = 8.0 Hz, 1H), 2.45 (s, 1H), 2.12 (dd, J = 13.8, 4.3 Hz, 1H), 1.90 (dd, J = 13.8, 7.6 Hz, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 0.87 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 107.9, 88.1, 72.8, 72.7, 70.4, 67.3, 48.8, 31.4, 27.0, 26.0, 25.9 (3C), 18.2, -2.7, -3.06. HRMS (EI) (m/z): calculated for $\text{C}_{15}\text{H}_{27}\text{NaO}_3\text{SiNa}$ [$\text{M}-\text{CH}_3$] $^+$ 283.1729, found 183.1722.

The alkyne (50 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. TFA (85 μL , 1.1 mmol) was added. After 3 h sat. aq. KHCO_3 (10 mL) and CH_2Cl_2 (10 mL) were added. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried with MgSO_4 , filtered and concentrated under reduced pressure giving the desired vicinal diol (39 mg, 15 mmol, 90%) as colorless oil, which was clean enough to proceed without further purification. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.31–4.25 (m, 1H), 3.81 (s, 1H), 3.66–3.61 (m, 1H), 3.51–3.46 (m, 1H), 2.53 (s, 1H), 2.19–2.16 (m, 1H), 1.92 (dd, J = 14.2, 9.7 Hz, 1H), 1.69 (dd, J = 14.3, 1.6 Hz, 1H), 1.56 (s, 3H), 0.89 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 86.6, 73.7, 70.9, 70.3, 66.9, 47.3, 32.0, 25.7 (3C), 18.0, -2.6, -3.1. HRMS (ESI) (m/z): calculated for $\text{C}_{13}\text{H}_{26}\text{O}_3\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 281.1549, found 281.1555. IR (cm^{-1}): 3311, 2929, 2858, 1670, 1463, 1254, 1120, 983, 838, 778. [α] $_{\text{D}}^{20}$: -1.6, (CHCl_3 , c = 0.25). R_f (Hex/EtOAc 1/1) 0.50.

To a solution of the vicinal diol (1.2 g, 4.6 mmol) and tributyltin oxide (25 mg, 0.02 mmol) in CH_2Cl_2 (50 mL) was added tosyl chloride (970 μL , 5.1 mmol) followed by triethylamine (711 μL , 5.1 mmol) at 0 °C. The resulting mixture was warmed to room temperature after 15 min and stirred for further 4 h. Water (30 mL) was added, the aqueous phase was separated and extracted with CH_2Cl_2 (30 mL). The combined organic phases were dried with MgSO_4 , filtered and the volatiles were removed under reduced pressure. The remaining residue was subjected to column chromatography (SiO_2 , Hex/EtOAc 8/1) yielding the desired terminal tosylate (1.68 g, 4.1 mmol) as colorless oil in 87%. ^1H NMR (CDCl_3 , 400 MHz): δ = 7.80 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 4.39–4.34 (m, 1H), 3.98 (s, 1H), 3.97 (s, 1H), 3.65 (s, 1H), 2.51 (s, 1H), 2.43 (s, 3H), 1.83 (dd, J = 14.3, 9.0 Hz, 1H), 1.77 (dd, J = 14.3, 2.5 Hz, 1H), 1.52 (s, 3H), 0.84 (s, 9H, s), 0.22 (s, 3H), 0.21 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 144.9, 133.0, 129.9 (3C), 128.2 (3C), 86.1, 74.0, 73.2, 70.6, 67.7, 47.1, 31.9, 25.7 (3C),

21.7, 18.0, 17.6, -2.62, -3.16. HRMS (ESI) (m/z): calculated for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{SSiNa}$ [$\text{M}+\text{Na}$] $^+$ 435.1637, found 435.1644. IR (cm^{-1}): 3286 2984, 2921, 2887, 1463, 1409, 1298, 1164, 1126, 999. [α] $_{\text{D}}^{20}$: -21.4, (CHCl_3 , c = 1.0). R_f (Hex/EtOAc 4/1) 0.48.

At 0 °C K_2CO_3 (1.4 g, 10.3 mmol) was added to a solution of the tosylate (1.64 g, 3.97 mmol) in methanol (40 mL). After 30 min Et_2O /Hex 1/1 (30 mL) was added and the resulting solids were removed by filtration. The organic phase was washed with water (20 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Crude epoxide **17** (877 mg, 3.65 mmol, 92%) was used in the next step without further purification. ^1H NMR (CDCl_3 , 400 MHz): δ = 3.21–3.16 (m, 1H), 2.79 (t, J = 4.5 Hz, 1H), 2.54 (dd, J = 5.0, 2.7 Hz, 1H), 2.47 (1H, s), 1.97 (dd, J = 13.8, 5.7 Hz, 1H), 1.80 (dd, J = 13.8, 5.6 Hz, 1H), 1.54 (s, 3H), 0.88 (s, 9H), 0.20 (s, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 87.9, 72.7, 67.9, 49.1, 48.0, 46.9, 31.1, 25.8 (3C), 18.2, -2.7, -3.1. HRMS (EI) (m/z): calculated for $\text{C}_{12}\text{H}_{21}\text{O}_2\text{Si}$ [$\text{M}-\text{CH}_3$] $^+$ 225.1311, found 225.1306. IR (cm^{-1}): 2992, 2956, 2987, 1473, 1427, 1304, 1165, 1135, 1047, 996. [α] $_{\text{D}}^{20}$: -9.7, (CHCl_3 , c = 1.0). R_f (Hex/EtOAc 4/1) 0.81.

(R)-5-((S)-2-((tert-Butyldimethylsilyloxy)-2-methyl-4-(trimethylsilyl)but-3-yn-1-yl)dihydrofuran-2(3H)-one (19): Sodium (0.93 g, 40.5 mmol) was added to ethanol (42 mL) at rt. After the evolution of gas ceased diethylmalonate (3.8 mL, 25.2 mmol) was dropwise added. The resulting solution was stirred for 1 h at room temperature. A solution of epoxide **17** (1.22 g, 5.1 mmol) in EtOH (12 mL) was added within 10 min and the resulting mixture was stirred for 16 h. Diethyl ether (100 mL), sat. aq. NH_4Cl (50 mL) and water (100 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with water (50 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure providing the desired malonate as a mixture of diastereomers which was used as such in the next reaction.

A solution of the malonate (2.0 g, 5.6 mmol) and LiCl (480 mg, 11.3 mmol) in DMSO (12 mL) and water (0.1 mL) was heated to 140 °C and stirred at this temperature for 5 h. The resulting brown mixture was cooled to room temperature and quenched with sat. aq. NH_4Cl (10 mL) and H_2O (10 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried with MgSO_4 , filtered and evaporated to give a viscous brown oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 3/1) afforded the desired lactone (1.43 g, 5.1 mmol, 91%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.79 (ddd, J = 12.1, 8.8, 6.0 Hz, 1H), 2.53 (dd, J = 9.9, 1.1 Hz, 1H), 2.51 (d, J = 9.5 Hz, 1H), 2.48 (s, 1H), 2.45–2.39 (m, 1H), 2.20 (dd, J = 14.3, 6.0 Hz, 1H), 2.09–1.99 (m, 1H), 1.98 (dd, J = 14.2, 5.6 Hz, 1H), 1.5 (s, 3H), 0.88 (s, 9H), 0.194 (s, 3H), 0.191 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 177.2, 87.9, 77.7, 73.0, 67.1, 50.4, 31.3, 29.5, 29.0, 25.8 (3C), 18.2, -2.7, -3.0. HRMS (ESI) (m/z): calculated for $\text{C}_{15}\text{H}_{26}\text{O}_3\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 305.1549, found 305.1546. IR (cm^{-1}): 2929, 2856, 1780, 1463, 1253, 1166, 1113, 1002, 838, 778. [α] $_{\text{D}}^{20}$: -27.8, (CHCl_3 , c = 0.54). R_f (Hex/EtOAc 3/1) 0.31.

To a solution of alkyne (50 mg, 0.18 mmol) in THF (2 mL) was dropwise added LiHMDS (390 μL , 0.39 mmol) at -78 °C. TMSCl (52 μL , 0.41 mmol) was dropwise added via syringe. In the following the resulting mixture was gradually warmed to -21 °C within 3 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and diethyl ether (5 mL) was added to the biphasic mixture. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Column chromatography (SiO_2 , Hex/EtOAc 3/1) of the remaining residue gave **19** (31 mg, 0.08 mmol, 49%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.78 (dq, J = 8.4, 6.0 Hz, 1H), 2.52 (d, J = 9.8 Hz, 1H), 2.51 (d, J = 9.4 Hz, 1H), 2.41 (sext, 1H), 2.19 (dd, J = 14.1, 5.5 Hz, 1H), 2.04 (dq, J = 12.5, 9.1 Hz, 1H), 1.94 (dd, J = 14.1, 6.3 Hz, 1H), 1.50 (s, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 177.3, 109.7, 89.2, 77.9, 77.2, 67.3, 50.2, 31.5, 29.4, 29.0, 25.9 (3C), 18.2, 0.2 (3C), -2.7, -3.0. HRMS (ESI) (m/z): calculated for $\text{C}_{18}\text{H}_{34}\text{O}_3\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 377.1944, found 377.1949. IR (cm^{-1}): 2956, 2857, 1780, 1462, 1360, 1251, 1165, 1110, 1000, 838. [α] $_{\text{D}}^{23}$: -16.4, (CHCl_3 , c = 0.7). R_f (Hex/EtOAc 3/1) 0.45.

Secondary alcohol 21: To a solution of **19** (30 mg, 0.08 mmol) in THF (1 mL) was added LiHMDS (93 μL , 0.09 mmol) at -78 °C. The resulting pale yellow solution was cooled to -40 °C for 30 min, then to -78 °C and a solution of **8** (52 mg, 0.09 mmol) in THF (1 mL) was added. The reaction was warmed to -40 °C within 1 h and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and diethyl ether (5 mL) was added to the biphasic mixture. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and concentrated under

reduced pressure. Purification of the residue by column chromatography (SiO₂, Hex/EtOAc 10/1) provided **21** as inseparable mixture of all four possible diastereomers (7 mg, 0.01 mmol). ¹H NMR (CDCl₃, 400 MHz): δ = 7.71-7.66 (m, 4H), 7.44-7.35 (m, 6H), 7.22-7.17 (m, 2H), 6.88-6.84 (m, 2H), 4.86-4.81 (m, 1H), 4.69-4.63 (m, 1H), 4.47-4.36 (m, 1H), 4.23-4.10 (m, 1H), 3.84-3.68 (m, 5H), 3.54-3.39 (m, 2H), 3.34-3.28 (m, 3H), 3.23-3.17 (m, 1H), 2.63-2.39 (m, 2H), 2.33-2.15 (m, 3H), 2.11-2.02 (m, 2H), 1.99-1.84 (m, 2H), 1.49 (s, 3H), 1.07 (s, 9H), 0.86 (s, 9H), 0.18 (s, 6H), 0.16 (s, 6H), 0.13 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.6, 159.5, 150.3, 135.9 (2C), 135.7 (2C), 133.3, 133.3, 130.3, 129.9, 129.8, 129.2 (2C), 127.9 (2C), 127.8 (2C), 114.2 (2C), 107.3, 107.4, 84.6, 84.2, 78.2, 73.4, 72.8, 71.7, 66.9, 64.8, 55.4, 54.6, 52.4, 47.1, 41.0, 40.1, 38.7, 29.8, 27.9 (3C), 26.9 (3C), 19.3, 19.5, 2.4 (3C), -2.7, -3.0. HRMS (ESI) (m/z): calculated for C₅₁H₇₆O₉Si₃Na [M+Na]⁺ 939.4695, found 939.4685. IR (cm⁻¹): 3479, 2988, 2878, 1721, 1501, 1453, 1393, 1267, 1101, 992. [α]_D²⁰: -11.3, (CHCl₃, c = 0.3). R_f: (Hex/EtOAc 3/1) 0.38.

Butyrolactone 22: To a solution of diisopropylamine (150 μ L, 1.06 mmol) in THF (2.8 mL) was dropwise added *n*BuLi (1.6 M in hexane, 633 μ L, 1.0 mmol) at -21 °C. 10 min after the addition the resulting solution was put to 0 °C for 30 min and thereafter cooled to -78 °C. A solution of seleno lactone **22** (274 mg, 0.93 mmol) in THF (3.6 mL) was dropwise added within 10 min. The mixture was allowed to warm to -60 °C before aldehyde **8** (475 mg, 0.84 mmol) in THF (3.6 mL) was added within 10 min. The mixture was further warmed to -45 °C within 1 h. Sat. aq. NH₄Cl (15 mL) was added, the layers were separated and the aqueous was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with water (20 mL) and sat. aq. NaCl (20 mL), dried with MgSO₄ and concentrated under reduced pressure. The obtained yellow oil was used without purification in the next step.

The mixture of diastereomers was dissolved in CH₂Cl₂ (7.8 mL), cooled to 0 °C and sat. aq. NH₄Cl (0.8 mL) and H₂O₂ (30 wt%, 1.6 mL, 14 mmol) were added. After 1 h sat. aq. Na₂S₂O₃ (10 mL) was added and stirring was continued for additional 30 min. The separated aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with water (15 mL), sat. aq. NaCl (15 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography (SiO₂, Hex/EtOAc 3/1) gave **22** (512 mg, 0.73 mmol, 86%) as a mixture of diastereomers. Diastereomer A: ¹H NMR (CDCl₃, 400 MHz): δ = 7.71-7.66 (m, 4H), 7.44-7.35 (m, 6H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.04 (t, *J* = 1.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.96 (ddt, *J* = 7.7, 6.3, 1.4 Hz, 1H), 4.91 (br s, 1H), 4.81 (br s, 1H), 4.69 (s, 1H), 4.55-4.51 (m, 1H), 4.44 (br s, 2H), 3.90 (d, *J* = 5.7 Hz, 1H), 3.88-3.84 (m, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.71 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.58 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.30 (s, 3H), 3.28 (dd, *J* = 9.0, 1.1 Hz, 1H), 3.22 (dd, *J* = 12.5, 6.3 Hz, 1H), 2.42-2.34 (m, 2H), 2.29 (dd, *J* = 14.4, 6.1 Hz, 1H), 2.15-2.08 (m, 1H), 1.90 (ddd, *J* = 13.8, 10.7, 3.1 Hz, 1H), 1.78 (br s, 3H), 1.66 (ddd, *J* = 13.7, 9.7, 4.0 Hz, 1H), 1.06 (br s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.1, 159.6, 148.6, 140.0, 137.1, 135.9 (4C), 135.8 (2C), 133.54, 133.49, 129.8 (4C), 129.5, 127.9 (2C), 127.8 (2C), 114.3, 114.1 (2C), 107.1, 84.2, 80.1, 73.4, 71.7, 65.6, 64.7, 55.4, 54.5, 51.5, 41.5, 38.82, 38.77, 27.0 (3C), 23.1, 19.4. HRMS (ESI) (m/z): calculated for C₄₁H₅₂O₈SiNa [M+Na]⁺ 723.3329, found 723.3325. IR (cm⁻¹): 3386, 2967, 2930, 2889, 1773, 1752, 1467, 1365, 1277, 1034. [α]_D²⁰: -16.6, (CHCl₃, c = 0.8). R_f: (Hex/EtOAc 3/1) 0.29. Diastereomer B: ¹H NMR (CDCl₃, 400 MHz): δ = 7.71-7.67 (m, 4H), 7.44-7.35 (m, 6H), 7.22-7.17 (m, 3H), 6.87-6.84 (m, 2H), 5.03-4.99 (m, 1H), 4.91 (br s, 1H), 4.81 (br s, 1H), 4.70 (s, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.42-4.39 (m, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.85-3.81 (m, 2H), 3.79 (s, 3H), 3.79-3.75 (m, 2H), 3.57 (dd, *J* = 8.5, 6.3 Hz, 1H), 3.31 (s, 3H), 3.27 (t, *J* = 9.1 Hz, 1H), 2.49-2.44 (m, 1H), 2.39 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.28 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.06-2.00 (m, 1H), 1.95-1.88 (m, 1H), 1.79 (br s, 3H), 1.65-1.60 (m, 1H), 1.07 (br s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 171.6, 159.1, 148.6, 139.9, 137.0, 135.9 (2C), 135.8 (2C), 133.6, 133.5, 129.9, 129.8, 129.7 (2C), 129.4, 127.91 (2C), 127.85 (2C), 114.4, 114.1 (2C), 107.3, 84.5, 80.1, 73.3, 71.6, 67.1, 64.8, 55.4, 54.6, 52.4, 41.6, 40.9, 39.9, 27.1 (3C), 23.1, 19.5. HRMS (ESI) (m/z): calculated for C₄₁H₅₂O₈SiNa [M+Na]⁺ 723.3329, found 723.3334. IR (cm⁻¹): 3407, 2975, 2904, 2904, 1779, 1746, 1467, 1392, 1292, 1015. [α]_D²⁰: -11.2, (CHCl₃, c = 0.65). R_f: (Hex/EtOAc 3/1) 0.28.

Pyran 27: To a solution of **22** (1.27 g, 1.8 mmol) as a mixture of diastereomers in diisopropylethylamine (3.0 mL) was dropwise added MOMCl (410 μ L, 5.4 mmol). The resulting solution was stirred at room temperature for 16 h. Sat. aq. NH₄Cl (10 mL) and diethyl ether (20 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the crude oil gave the desired MOM-protected

secondary alcohol (1.05 g, 1.4 mmol, 78%) as pale yellow oil. Diastereomer A: ¹H NMR (CDCl₃, 400 MHz): δ = 7.72-7.66 (s, 4H), 7.42-7.35 (s, 6H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.13 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.97 (t, *J* = 6.8 Hz, 1H), 4.91 (br s, 1H), 4.89 (s, 1H), 4.79 (br s, 1H), 4.51 (s, 2H), 4.42-4.40 (m, 3H), 3.79 (s, 3H), 3.76 (s, 1H), 3.70 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.36-3.34 (m, 2H), 3.32 (s, 3H), 3.24 (s, 3H), 2.40 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.34-2.26 (m, 2H), 1.99-1.93 (m, 1H), 1.86 (t, *J* = 6.4 Hz, 2H), 1.78 (s, 3H), 1.73 (d, *J* = 15.3 Hz, 1H), 1.05 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 171.6, 159.3, 149.7, 139.9, 135.9 (2C), 135.8 (2C), 135.6, 133.69, 133.66, 130.5, 129.8 (2C), 129.5 (2C), 127.80 (2C), 127.78 (2C), 114.5, 113.9 (2C), 107.7, 96.0, 83.8, 79.9, 72.7, 71.1, 70.8, 64.8, 56.1, 55.4, 54.6, 52.2, 41.6, 38.7, 38.2, 27.0 (3C), 23.1, 19.43. HRMS (ESI) (m/z): calculated for C₄₃H₅₆O₉SiNa [M+Na]⁺ 767.3591, found 767.3582. IR (cm⁻¹): 2954, 2928, 2888, 1756, 1749, 1421, 1383, 1227, 1117, 987. [α]_D²⁰: -26.1, (CHCl₃, c = 0.5). R_f: (Hex/EtOAc 3/1) 0.48. Diastereomer B: ¹H NMR (CDCl₃, 400 MHz): δ = 7.72-7.67 (m, 4H), 7.44-7.36 (m, 6H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.02 (s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.95-4.91 (m, 1H), 4.88 (s, 1H), 4.87 (br s, 1H), 4.76 (br s, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 4.45 (d, *J* = 6.7 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.31 (t, *J* = 6.5 Hz, 1H), 3.91-3.87 (m, 1H), 3.82 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.79 (s, 3H), 3.69 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.34 (s, 3H), 3.34-3.30 (m, 2H), 3.23 (s, 3H), 2.33-2.20 (m, 3H), 1.99-1.94 (m, 2H), 1.74 (s, 3H), 1.31-1.27 (m, 1H), 1.06 (s, 9H). ¹³C NMR (CDCl₃, 400 MHz): δ = 171.4, 159.3, 150.4, 139.8, 135.9 (2C), 135.8 (2C), 134.8, 133.8, 133.6, 130.5, 129.8, 129.7, 129.4 (2C), 127.81 (2C), 127.78 (2C), 114.4, 113.9 (2C), 107.4, 95.6, 84.3, 79.8, 72.8, 71.0, 70.8, 65.3, 55.9, 55.4, 54.6, 52.6, 41.4, 38.6, 38.5, 27.01 (3C), 23.1, 19.4. HRMS (ESI) (m/z): calculated for C₄₃H₅₆O₉SiNa [M+Na]⁺ 767.3591, found 767.3596. IR (cm⁻¹): 2954, 2928, 2888, 1756, 1749, 1421, 1383, 1227, 1117, 987. [α]_D²⁰: -23.4, (CHCl₃, c = 0.6). R_f: (Hex/EtOAc 3/1) 0.41.

The MOM-protected mixture of diastereomers (100 mg, 0.13 mmol) was dissolved in *t*BuOH/H₂O 1/1 (1.4 mL), methylsulfonamide (12 mg, 0.28 mmol) and AD-mix- α (190 mg, 0.27 mmol) were added. The resulting mixture was stirred for 16 h, diethyl ether (10 mL) and sat. aq. NaHS₂O₃ (5 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the oil by column chromatography (SiO₂, Hex/EtOAc 3/1) gave pyran **27** (80 mg, 0.11 mmol) in 83% yield. ¹H NMR (CDCl₃, 400 MHz): δ = 7.69-7.66 (m, 4H), 7.44-7.36 (m, 6H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.87-6.85 (m, 3H), 5.15 (d, *J* = 5.5 Hz, 1H), 5.04 (t, *J* = 6.1 Hz, 1H), 4.84 (br s, 1H), 4.38 (br s, 2H), 3.90-3.86 (m, 1H), 3.80 (br s, 3H), 3.76 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.72 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.47 (d, *J* = 11.3 Hz, 1H), 3.36-3.22 (m, 3H), 3.33 (s, 3H), 2.63-2.48 (m, 2H), 2.42 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.10-2.03 (m, 2H), 1.98-1.91 (m, 1H), 1.88 (br s, 1H), 1.12 (s, 3H), 1.06 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 169.6, 159.4, 145.1, 135.82 (2C), 135.77 (2C), 133.51, 133.46, 130.4, 130.2, 129.90, 129.87, 129.4 (2C), 127.9 (2C), 127.8 (2C), 114.0 (2C), 107.4, 85.9, 83.4, 83.2, 77.4, 72.9, 70.5, 68.2, 64.9, 55.4, 54.8, 51.9, 41.3, 39.3, 34.0, 27.0 (3C), 24.4, 19.4. HRMS (ESI) (m/z): calculated for C₄₁H₅₂O₉SiNa [M+Na]⁺ 739.3278, found 739.3287. IR (cm⁻¹): 3461, 2943, 2917, 2875, 1763, 1741, 1453, 1399, 1202, 1016. [α]_D²²: -41.1, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.63.

(S)-2-Methyl-1-((S)-oxiran-2-yl)but-3-yn-2-ol (36): Alkyne **33** (2.40 g, 13.0 mmol) was dissolved in a mixture of acetic acid (27 mL) and H₂O (1.4 mL) at room temperature. The clear colorless solution was stirred for 24 h and concentrated under reduced pressure. The remaining pale yellow residue was evaporated with toluene (3 x 10 mL) till the smell of AcOH was gone. Purification by flash column chromatography (SiO₂, Hex/EtOAc 2/1) afforded the corresponding triol as colorless gum (1.67 g, 89%). ¹H NMR (CDCl₃, 400 MHz): δ = 4.42-4.38 (m, 1H), 4.05 (br s, 1H), 3.68 (dd, *J* = 11.1, 2.9 Hz, 1H), 3.51 (dd, *J* = 10.7, 6.9 Hz, 1H), 3.33 (br s, 1H), 2.51 (s, 1H), 2.11 (br s, 1H), 1.85 (dd, *J* = 14.4, 10.6 Hz, 1H), 1.70 (dd, *J* = 14.4, 2.1 Hz, 1H), 1.55 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 87.0, 72.3, 71.3, 68.3, 66.8, 43.9, 31.2. HRMS (ESI) (m/z): calculated for C₇H₁₂O₃ [M]⁺ 144.0786, found 144.0791. IR (cm⁻¹): 3298, 2983, 2359, 1418, 1133, 1109, 1058, 1036, 1016, 908. [α]_D²⁰: -7.9, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 1/2) 0.19.

A solution of aforementioned triol (3.8 g, 26.4 mmol) in THF (40 mL) was added to a suspension of NaH (5.2 g, 132 mmol) in THF (100 mL) at 0 °C. The resulting heterogeneous mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and aged for 30 min before being cooled to 0 °C again. Solid trisylimidazole **34** (11.5 g, 34.3 mmol) was added in three portions under a constant stream of argon. The resulting reaction mixture was vigorously stirred at 0 °C for 1 h before it was quenched with H₂O (50 mL) and brine (20 mL). The aqueous phase was extracted with CH₂Cl₂ (4 x 20 mL), the combined organic phases were

dried with MgSO_4 , filtered and evaporated to give a brown oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 1/1) afforded epoxide **36** as colorless oil (2.36 g, 78%). ^1H NMR (CDCl_3 , 400 MHz): δ = 3.34–3.29 (m, 1H), 3.07 (s, 1H), 2.81 (dd, J = 4.8, 4.2 Hz, 1H), 2.53 (dd, J = 4.9, 2.8 Hz, 1H), 2.50 (s, 1H), 2.02 (dd, J = 4.2, 14.2 Hz, 1H), 1.71 (dd, J = 14.2, 7.6 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 87.0, 72.1, 67.2, 49.5, 46.7, 45.5, 30.2. HRMS (EI) (m/z): calculated for $\text{C}_6\text{H}_7\text{O}_2$ [$\text{M}-\text{CH}_3$] $^+$ 111.0446, found 111.0441. IR (cm^{-1}): 3408, 3283, 2985, 2926, 1450, 1410, 1304, 1165, 1135, 1047. $[\alpha]_{\text{D}}^{20}$: –20.5, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 1/2) 0.58.

(R)-5-((S)-2-Hydroxy-2-methylbut-3-ynyl)dihydrofuran-2(3H)-one

(37): Sodium (1.08 g, 46.8 mmol) was added as small pieces under a constant stream of argon to EtOH (100 mL). After all solids were dissolved, diethylmalonate (14.2 mL, 94 mmol) was added dropwise. A solution of epoxide **36** (2.36 g, 18.7 mmol) in EtOH (100 mL) was added after stirring at room temperature for 15 min. The reaction mixture was aged at this temperature for 16 h and quenched with sat. aq. NH_4Cl (50 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic phases were dried with MgSO_4 , filtered and evaporated to give a pale yellow oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 4/1) afforded a (1:1.45) diastereoisomeric mixture of the desired malonate as colorless oil (3.86 g, 86%). Major diastereomer: ^1H NMR (CDCl_3 , 400 MHz): δ = 4.98–4.91 (m, 1H), 4.28 (dd, J = 7.12, 1.3 Hz, 1H), 4.24 (dd, J = 7.1, 1.2 Hz, 1H), 3.61 (dd, J = 11.2, 9.1 Hz, 1H), 2.68 (dd, J = 9.1, 6.1 Hz, 1H), 2.65 (dd, J = 9.1, 6.1 Hz, 1H), 2.52 (s, 1H), 2.43 (dd, J = 11.2, 9.8 Hz, 1H), 2.18 (dd, J = 14.8, 8.7 Hz, 1H), 2.07–2.03 (m, 1H), 1.56 (s, 3H), 1.31 (t, J = 1.4 Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 171.2, 167.7, 86.5, 76.9, 72.8, 66.6, 62.4, 48.0, 46.8, 32.9, 30.5, 14.2. Minor diastereomer: ^1H NMR (CDCl_3 , 400 MHz): δ = 5.19–5.12 (m, 1H), 4.27 (d, J = 7.1 Hz, 1H), 4.23 (d, J = 7.1 Hz, 1H), 3.57 (dd, J = 9.6, 4.1 Hz, 1H), 2.80 (dd, J = 6.7, 4.1 Hz, 1H), 2.77 (dd, J = 6.7, 4.1 Hz, 1H), 2.54 (s, 1H), 2.39 (dd, J = 11.2, 9.8 Hz, 1H), 2.20 (m, 1H), 2.05–2.02 (m, 1H), 1.55 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 171.2, 167.7, 86.4, 77.9, 72.9, 66.6, 62.5, 48.1, 46.5, 32.9, 30.5, 14.2. HRMS (ESI) (m/z): calculated for $\text{C}_{11}\text{H}_{13}\text{O}_5$ [$\text{M}-\text{CH}_3$] $^+$ 225.0763, found 225.0765. IR (cm^{-1}): 3473, 2984, 1767, 1450, 1371, 1260, 1156, 1095, 1035, 1008. $[\alpha]_{\text{D}}^{20}$ = –33.5, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 1/1) 0.51.

Aforementioned malonate (3.8 g, 15.83 mmol) was heated to 140 °C in the presence of LiCl (1.33 g, 31.66 mmol) in a mixture of DMSO (32 mL) and water (1 mL) and stirred for 5 h. The resulting brown mixture was cooled to room temperature and quenched with sat. aq. NH_4Cl (10 mL) and H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (7 × 10 mL) and the combined organic phases were dried with MgSO_4 , filtered and evaporated to give a viscous brown oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 3/1) afforded alcohol **37** as colorless oil (2.5 g, 94%). ^1H NMR (CDCl_3 , 400 MHz): δ = 5.03–4.97 (m, 1H), 2.72 (br s, 1H), 2.54 (dd, J = 9.9, 1.7 Hz, 1H), 2.53 (d, J = 9.6 Hz, 1H), 2.52 (s, 1H), 2.47–2.39 (m, 1H), 2.09–1.89 (m, 3H), 1.55 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 176.3, 86.6, 78.5, 72.7, 66.9, 48.2, 30.5, 28.9, 28.3. HRMS (ESI) (m/z): calculated for $\text{C}_9\text{H}_{10}\text{O}_3$ [$\text{M}-\text{CH}_3$] $^+$ 153.0552, found 153.0557. IR (cm^{-1}): 3430, 3280, 2985, 2934, 1760, 1357, 1173, 1124, 1035, 1008. $[\alpha]_{\text{D}}^{20}$ = –67.2, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 1/2) 0.41.

(R)-5-((S)-2-Methyl-2-(trimethylsilyloxy)penta-3,4-dienyl)dihydrofuran-2(3H)-one

(38): A heterogeneous mixture of alcohol **37** (2.5 g, 14.9 mmol), paraformaldehyde (1.29 g, 44.6 mmol), $i\text{Pr}_2\text{NH}$ (3.2 mL, 22.32 mmol) and CuBr (1.07 g, 7.45 mmol) in 1,4-dioxane (30 mL) was stirred at 125 °C for 6 h. The resulting greenish reaction mixture was cooled to room temperature, filtered through a pad of Celite followed by the addition of sat. aq. NH_4Cl (10 mL) and H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL) and the combined organic phases were washed with sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and evaporated to give a brown oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc, 2/1) afforded the desired allene as colorless oil (1.9 g, 86%). ^1H NMR (CDCl_3 , 400 MHz): δ = 5.31 (t, J = 6.6 Hz, 1H), 4.90 (d, J = 6.6 Hz, 2H), 4.83–4.76 (m, 1H), 2.51 (d, J = 9.7 Hz, 1H), 2.49 (d, J = 9.7 Hz, 1H), 2.40–2.32 (m, 1H), 2.24 (br s, 1H), 2.02 (dd, J = 14.7, 8.5 Hz, 1H), 1.94–1.82 (m, 2H), 1.38 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 205.5, 176.9, 99.4, 79.1, 78.1, 70.4, 47.7, 29.4, 28.9, 28.7. HRMS (EI) (m/z): calculated for $\text{C}_{10}\text{H}_{12}\text{O}_2$ [M] $^+$ 164.0839, found 164.0837. IR (cm^{-1}): 3423, 2978, 2934, 1956, 1760, 1727, 1457, 1419, 1357, 1289, 1223, 1179, 1114, 1075, 1012, 986, 917, 850. $[\alpha]_{\text{D}}^{20}$: –49.3, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 1/1) 0.18.

2,6-Lutidine (8.0 mL, 69.1 mmol) and TMSOTf (6.3 mL, 34.6 mmol) were sequentially added to a solution of the tertiary allenic alcohol (4.2 g, 23.0

mmol) in THF (50 mL) at 0 °C. After removal of the cooling bath and additional 30 min the reaction was quenched with sat. aq. NH_4Cl (50 mL). The aqueous phase was extracted with hexanes (10 mL) and the combined organic phases were washed with sat. aq. NaCl (20 mL), dried with MgSO_4 , filtered and evaporated to give a crude colorless oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 4/1) afforded lactone **38** as colorless oil (5.1 g, 87%). ^1H NMR (CDCl_3 , 400 MHz): δ = 5.25 (t, J = 6.6 Hz, 1H), 4.82 (d, J = 6.6 Hz, 2H), 4.76–4.70 (m, 1H), 2.50 (dd, J = 8.4, 2.5 Hz, 1H), 2.48 (d, J = 9.7 Hz, 1H), 2.36 (sext., J = 6.5 Hz, 1H), 1.99–1.84 (m, 3H), 1.39 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 206.3, 177.4, 99.8, 78.1, 77.9, 72.8, 49.4, 29.8, 29.0, 27.7, 2.4 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{13}\text{H}_{22}\text{O}_3\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 277.1233, found 277.1236. IR (cm^{-1}): 2955, 1956, 1773, 1249, 1154, 1110, 1078, 1001, 982, 916, 836. $[\alpha]_{\text{D}}^{20}$: –42.3, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 1/1) 0.64.

2-Phenylselenenyl- γ -butyrolactone 32: LiHMDS (1.0 M in toluene, 6.5 mL, 64.9 mmol) and TMSCl (0.83 mL, 64.9 mmol) were sequentially added to a solution of lactone **39** (1.50 g, 5.9 mmol) in THF (30 mL) at –78 °C. After 2 h at –78 °C a solution of PhSeCl (1.24 g, 64.9 mmol) in THF (30 mL) was added within 10 min. After 30 min at –78 °C, the reaction was quenched with sat. aq. NH_4Cl (40 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with sat. aq. NaCl (40 mL), dried with MgSO_4 , filtered and evaporated to give a colorless oil. Purification by flash column chromatography (SiO_2 , Hex/EtOAc 20/1) afforded a 1:1.5 diastereoisomeric mixture of lactone **32** as colorless oil (2.0 g, 83%). ^1H NMR (CDCl_3 , 400 MHz): δ = 7.71–7.63 (m, 3H), 7.41–7.29 (m, 4.6H), 5.20 (t, J = 6.6 Hz, 1H), 5.19 (t, J = 6.6 Hz, 0.5H), 4.81 (d, J = 6.6 Hz, 3H), 4.70–4.62 (m, 0.5H), 4.57–4.48 (m, 1H), 4.02 (dd, J = 10.1, 9.1 Hz, 0.5H), 3.91 (dd, J = 6.4, 4.0 Hz, 1H), 2.79–2.69 (m, 0.5H), 2.41–2.35 (m, 2H), 2.01 (dt, J = 13.3, 10.0 Hz, 0.5H), 1.92 (dd, J = 14.3, 6.3 Hz, 1H), 1.86–1.76 (m, 1.5H), 1.70 (dd, J = 14.4, 5.1 Hz, 1H), 1.35 (s, 1.5H), 1.32 (s, 3H), 0.09 (s, 9H), 0.08 (s, 4.5H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 206.1, 175.8, 136.0, 135.9, 135.6, 128.7, 127.1, 126.8, 99.6, 99.6, 77.8, 76.6, 76.4, 72.6, 49.2, 48.9, 38.3, 37.0, 27.5, 2.2 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{19}\text{H}_{26}\text{O}_3\text{SeSiNa}$ [$\text{M}+\text{Na}$] $^+$ 433.0709, found 433.0715. IR (cm^{-1}): 2956, 1956, 1769, 1483, 1251, 1112, 1022, 840, 740. $[\alpha]_{\text{D}}^{20}$: –53.5, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 8/1) 0.27 (major), 0.32 (minor).

Butenolide 39: A freshly prepared solution of LDA (810 μL , 0.5 M THF, 0.40 mmol; see 22) was dropwise added to a solution of **32** (153 mg, 0.37 mmol) in THF (1.5 mL) at –78 °C. The resulting pale yellow solution was stirred for 30 min before **8** (190 mg, 0.34 mmol) in THF (2 mL) was added within 10 min. The reaction mixture was gradually warmed to –40 °C within 2 h. Sat. aq. NH_4Cl (10 mL) and diethyl ether (10 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (15 mL) and sat. aq. NaCl (15 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. NMR-analysis of the crude mixture of four diastereomers indicated full consumption of **32**. The crude mixture was used as such in the next step.

The crude oil was dissolved in a mixture of CH_2Cl_2 (3.5 mL) and pyridine (350 μL) and cooled to 0 °C. Hydrogen peroxide (230 μL , 2.0 mmol) was added and the resulting biphasic mixture was stirred at that temperature for 1 h. Sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and diethyl ether (20 mL) were added and the resulting biphasic mixture was stirred for another hour. The aqueous phase was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with sat. aq. CuSO_4 (2 × 15 mL) water (15 mL) and water (15 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2 , Hex/EtOAc 6/1) afforded desired butyrolactone **39** (224 mg, 0.28 mmol) as inseparable mixture of diastereomers. ^1H NMR (CDCl_3 , 400 MHz): δ = 7.74–7.67 (m, 4H), 7.44–7.37 (m, 6H), 7.25–7.20 (m, 3H), 7.07–7.02 (m, 0.4H), 6.89–6.85 (m, 2H), 5.27 (t, J = 6.6 Hz, 1H), 5.21–5.15 (m, 1H), 4.86–4.84 (m, 1H), 4.72 (d, J = 8.0 Hz, 1H), 4.57–4.51 (m, 0.5H), 4.48–4.40 (m, 2.5H), 4.06 (d, J = 4.2 Hz, 0.5H), 3.90–3.84 (m, 1.5H), 3.80–3.68 (m, 4H), 3.62–3.56 (m, 1H), 3.31–3.27 (m, 4H), 3.24–3.21 (m, 0.5H), 2.49–2.40 (m, 1H), 2.19–2.14 (m, 0.5H), 2.07–2.01 (m, 0.5H), 1.95–1.88 (m, 2H), 1.82–1.61 (m, 2H), 1.47 (s, 3H), 1.09 (s, 4H), 1.08 (s, 5H), 0.15 (s, 5H), 0.14 (s, 4H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 206.3, 172.5, 172.4, 159.6, 159.5, 150.4, 150.2, 136.0, 135.9, 135.8, 135.8, 135.7, 133.6, 133.5, 133.42, 133.38, 133.3, 129.82, 129.80, 129.78, 129.6, 127.9, 127.83, 127.80, 127.77, 114.1, 114.0, 107.3, 107.1, 99., 84.5, 84.2, 78.8, 78.7, 78.2, 78.1, 73.3, 73.2, 72.82, 72.77, 71.7, 71.5, 66.9, 65.7, 64.7, 64.5, 55.3, 54.5, 54.4, 52.4, 51.5, 47.1, 47.0, 40.7, 40.0, 38.8, 38.6, 27.78, 27.76, 27.02, 26.98, 19.41, 19.39, 2.39. HRMS (ESI) (m/z): calculated for $\text{C}_{46}\text{H}_{62}\text{O}_9\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 837.3830, found 837.3823.

IR (cm⁻¹): 3433, 2971, 2921, 2879, 1776, 1429, 1227, 1164, 1023, 973. [α]_D²⁰: -13.7, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 2/1) 0.51.

Cage-shaped cyclobutane 40: A 1:1 diastereomeric mixture of **39** (25 mg, 0.03 mmol) was dissolved in freshly degassed cyclohexane (13 mL) and placed 1 cm in front of UV-B lamps. The resulting colorless solution was irradiated for 1.5 h. The volatiles were removed under reduced pressure and the resulting yellow oil was subjected to column chromatography (SiO₂, Hex/EtOAc 8/1) leading to the isolation of a diastereomeric mixture of **40** (3 mg, 0.003 mmol, 10%). ¹H NMR (CDCl₃, 400 MHz): δ = 7.71-7.66 (m, 4H), 7.44-7.35 (m, 6H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.31 (dd, *J* = 2.6, 1.2 Hz, 1H), 5.17-5.11 (m, 2H), 4.75 (br s, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.01-3.99 (m, 1H), 3.90-3.83 (m, 1H), 3.80 (s, 3H), 3.76-3.74 (m, 2H), 3.49 (d, *J* = 2.9 Hz, 1H), 3.46-3.41 (m, 1H), 3.30 (s, 3H), 3.30-3.25 (m, 2H), 3.09-3.06 (m, 1H), 2.45 (qd, *J* = 12.4, 1.8 Hz, 1H), 2.26-2.20 (m, 1H), 2.06-1.99 (m, 1H), 1.92 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.65 (td, *J* = 19.0, 4.2 Hz, 1H), 1.42-1.38 (m, 4H), 1.06 (s, 9H), 0.12 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 177.2, 159.5, 144.8, 135.91 (2C), 135.86 (2C), 133.7, 133.5, 130.0, 129.80, 129.78, 129.5 (2C), 127.82 (2C), 127.79 (2C), 114.5, 114.0 (2C), 107.4, 84.9, 83.9, 83.7, 73.0, 71.5, 69.7, 65.5, 57.90, 57.88, 55.4, 54.6, 51.7, 49.5, 44.4, 39.6, 35.2, 27.0 (3C), 23.5, 19.4, 2.44 (3C). HRMS (ESI) (*m/z*): calculated for C₄₆H₆₀O₉Si₂Na [M+Na]⁺ 837.3830, found 837.3809. IR (cm⁻¹): 3433, 2971, 2921, 2879, 1776, 1429, 1227, 1164, 1023, 973. [α]_D²⁰: -33.9, (CHCl₃, c = 0.08). R_f: (Hex/EtOAc 2/1) 0.60.

Ethyl 2-((3aR,5S,6R,6aR)-5-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)acetate (42): A mixture of diacetone-(D)-glucofuranose (34.4 g, 127.3 mmol) and IBX (82 g, 292.8 mmol) in EtOAc (1 L) was heated to reflux for 26 h. After the thick suspension reached room temperature, hexane (500 mL) were added and the resulting suspension was filtered through a pad of Celite. The volatiles were removed under reduced pressure and the crude ketone (35.4 g) was used as such in the olefination. R_f: (Hex/EtOAc 1/1) 0.25.

To a solution of PPh₃ (55 g, 209.6 mmol) in EtOAc (360 mL) was added a solution of methyl bromoacetate (32.3 g, 211 mmol) in EtOAc (90 mL) via dropping funnel within 45 min at 0 °C. The resulting thick white suspension was allowed to warm to room temperature and stirred for 20 h. The solids were collected by filtration, digested in CH₂Cl₂ (400 mL) in a separatory funnel and vigorously shaken with 1 M NaOH (300 mL) for 30 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The organic phases were washed with sat. aq. NaCl (200 mL), dried with MgSO₄, filtered and concentrated under reduced pressure yielding the Wittig-ylide (70 g, 209.3 mmol) as white solid after extensive drying under high vacuum for 2 h.

A solution of the ylide (50.4 g, 150.7 mmol) in CHCl₃ (500 mL) was added via cannula to a solution of the ketone (35.4 g, 137.1 mmol) in CHCl₃ (500 mL) at 0 °C within 30 min. After the addition the reaction mixture was warmed to room temperature and stirred for 16 h resulting in a dark red solution. The volatiles were evaporated and the dark gum was subjected to filtration through a short pad of silica (Hex/EtOAc 2/1). After evaporation the orange gum (40 g, 127.3 mmol, 93%) was used as such in the next step. R_f: (Hex/EtOAc 1/1) 0.70.

To a solution of the α,β -unsaturated ester (20 g, 63.6 mmol) in EtOH (250 mL) was added Raney-Nickel 2400 (10 g). The round-bottomed flask was sealed with a rubber-septum. A rubber-balloon charged with H₂ was connected to a needle which reached into the solution. A gas outlet was installed and the flow of the gas was regulated with a hose clamp to about 4 bubbles per second. The round-bottomed flask was placed in an ultra sound bath and treated for 2 h in a well fumed hood. The balloon was replaced by a balloon filled with argon and the reaction mixture was purged in the ultra sound bath for 30 min. The nickel catalyst was filtered off through a pad of Celite, which was washed with EtOH (2 x 100 mL). Removal of the solvent under reduced pressure gave the desired product as a clean single diastereomer (20.0 g, 63.2 mmol, 99%) and colorless gum, which was used as such in the next reaction. ¹H NMR (CDCl₃, 400 MHz): δ = 5.77 (d, *J* = 3.8 Hz, 1H), 4.81 (t, *J* = 4.2 Hz, 1H), 4.19-4.13 (m, 2H), 4.12-4.09 (m, 1H), 4.00-3.97 (m, 1H), 3.96-3.92 (m, 1H), 3.69 (dd, *J* = 9.9, 7.5 Hz, 1H), 2.81 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.65 (dd, *J* = 17.4, 10.4 Hz, 1H), 2.36-2.29 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.26 (t, *J* = 7.15 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.5, 112.0, 109.8, 105.2, 81.7, 81.1, 78.0, 68.0, 60.7, 44.7, 30.2, 26.9, 26.8, 26.5, 25.4, 14.4. HRMS (ESI) (*m/z*): calculated for C₁₆H₂₆O₇Na [M+Na]⁺ 353.1576, found 353.1586. IR (cm⁻¹): 2986, 2938, 1734, 1381, 1333, 1241, 1213, 1065, 1016, 847. [α]_D²²: +69.0, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.70.

The crude diacetone (20.0 g 63.2 mmol) was digested in AcOH/H₂O 2/1 (60 mL). After all of the crude gum was dissolved the solution was stirred at room temperature for 18 h. The volatiles were removed under reduced

pressure and the resulting slightly yellow residue was co-evaporated with toluene (5 x 50 mL) till the smell of acetic acid was gone. The desired vicinal diol (17.7 g, 63.2 mmol, 100%) was used in the next reaction without further purification. ¹H NMR (CDCl₃, 400 MHz): δ = 5.78 (d, *J* = 3.7 Hz, 1H), 4.78 (dd, *J* = 4.6, 4.1 Hz, 1H), 4.20-4.12 (m, 2H), 3.84 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.80-3.76 (m, 1H), 3.73-3.68 (m, 2H), 2.78 (br s, 1H), 2.72 (d, *J* = 6.9 Hz, 2H), 2.42-2.35 (m, 1H), 2.25 (br s, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 173.1, 112.1, 104.9, 81.9, 81.6, 73.6, 64.1, 61.0, 43.3, 30.6, 26.9, 26.6, 14.4. HRMS (ESI) (*m/z*): calculated for C₁₃H₂₂O₇Na [M+Na]⁺ 313.1263, found 313.1256. IR (cm⁻¹): 3438, 2924, 2854, 1732, 1460, 1377, 1218, 1168, 1016, 772. [α]_D²⁰ = +10.0, (CHCl₃, c = 0.35). R_f: (Hex/EtOAc 1/1) 0.18.

The gum (17.7 g, 63.2 mmol, 100%) was dissolved in MeOH (160 mL) and H₂O (20 mL). The solution was cooled to 0 °C and NaIO₄ (13.6 g, 63.6 mmol) was added under vigorous stirring at once. After 1 h at that temperature glucose (0.5 g, 2.77 mmol) was added to the thick suspension. After 15 min the solids were removed by filtration through a pad of Celite. The residue was washed with MeOH (50 mL). The combined liquids were cooled to 0 °C followed by the careful addition of NaBH₄ (3.50 g, 92.5 mmol) in three portions. After an additional hour acetic acid was added carefully till pH 6 of the solution was reached. The volatiles were removed and the residue was subjected to column chromatography (SiO₂, Hex/EtOAc 1/1) yielding the desired α -D-ribofuranose **42** (13.5 g, 51.8 mmol, 82%). ¹H NMR (CDCl₃, 400 MHz): δ = 5.82 (d, *J* = 3.6 Hz, 1H), 4.78 (dd, *J* = 4.3, 3.8 Hz, 1H), 4.22-4.11 (m, 2H), 3.90-3.85 (m, 2H), 3.59-3.54 (m, 1H), 2.70 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.48-2.41 (m, 1H), 2.38 (dd, *J* = 16.5, 5.4 Hz, 1H), 2.04 (br s, OH), 1.50 (s, 3H), 1.32 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.4, 111.9, 104.9, 81.8, 81.5, 61.6, 61.0, 39.8, 30.0, 26.8, 26.5, 14.3. HRMS (ESI) (*m/z*): calculated for C₁₂H₂₀O₆Na [M+Na]⁺ 283.1158, found 283.1153. IR (cm⁻¹): 3474, 2985, 2937, 1731, 1374, 1214, 1167, 1112, 1013, 874. [α]_D²⁰: +62.9, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.33.

(3aR,4S,6R,6aR)-4-(((tert-Butyldimethylsilyl)oxy)methyl)-6-methoxytetrahydrofuro[3,4-b]furan-2(3H)-one (43): A mixture of trifluoroacetic acid (60 mL) and α -D-ribofuranose **42** (9.8 g, 37.7 mmol) in MeOH (370 mL) was heated to reflux for 16 h. The resulting pale yellow solution was concentrated in vacuo and the remaining oil was co-evaporated with toluene (3 x 50 mL). Purification by flash column chromatography (SiO₂, Hex/EtOAc 1/1 $\rightarrow$ 1/2) afforded the desired lactone as pale yellow oil (5.7 g, 81%). ¹H NMR (CDCl₃, 400 MHz): δ = 5.08 (s, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 4.23 (dd, *J* = 3.8 Hz, 1H), 3.73 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.57 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.46 (s, 3H), 3.25-3.19 (m, 1H), 2.86 (dd, *J* = 18.4, 9.9 Hz, 1H), 2.52 (dd, *J* = 18.4, 3.9 Hz, 1H), 1.25 (br s, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 175.5, 107.8, 89.6, 87.7, 64.7, 55.9, 38.1, 34.1. HRMS (ESI) (*m/z*): calculated for C₈H₁₂O₅Na [M+Na]⁺ 211.0582, found 211.0582. IR (cm⁻¹): 3412, 2923, 1776, 1454, 1377, 1161, 1106, 1049, 959, 813. [α]_D²⁵: -40.3, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 1/4) 0.29.

To a solution of the primary alcohol (4.1 g, 21.8 mmol) and imidazole (3.6 g, 52.3 mmol) in CH₂Cl₂ (200 mL) was added *tert*-butyldimethylsilyl chloride (3.9 g, 26.1 mmol) as a solid in three portions under an argon stream at room temperature. After stirring for 2 h the resulting pale yellow reaction mixture was quenched by the addition of water (100 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were washed with water (100 mL) and aq. sat. NaCl (100 mL), dried with MgSO₄ and filtered. After evaporation of all volatiles flash column chromatography (SiO₂, Hex/EtOAc 3/1) of the residue gave lactone **43** (6.0 g, 91%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.06 (s, 1H), 4.81 (d, *J* = 6.4 Hz, 1H), 4.00 (ddd, *J* = 8.3, 5.1, 4.7 Hz, 1H), 3.74 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.52 (dd, *J* = 9.8, 8.3 Hz, 1H), 3.34 (s, 3H), 3.05-3.00 (m, 1H), 2.82 (dd, *J* = 18.1, 9.3 Hz, 1H), 2.48 (dd, *J* = 18.1, 2.0 Hz, 1H), 0.88 (s, 9H), 0.59 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 175.8, 107.4, 88.1, 87.3, 65.8, 55.0, 40.3, 34.5, 25.9 (3C), 18.3, -5.2, -5.3. HRMS (ESI) (*m/z*): calculated for C₁₄H₂₆O₅SiNa [M+Na]⁺ 325.1447, found 325.1448. IR (cm⁻¹): 2953.6, 2930.1, 2857.2, 1787.9, 1471.8, 1254.4, 1154.0, 1106.7, 1004.4, 837.7. [α]_D²⁰: -88.3, (CHCl₃, c = 0.6). R_f: (Hex/EtOAc 1/2) 0.73.

***tert*-Butyl(((2S,3R,4R,5R)-5-methoxy-4-((triethylsilyl)oxy)-3-(2-((triethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)methoxy)dimethylsilane (44):** A solution of lactone **43** (11.7 g, 38.8 mmol) in diethyl ether (200 mL) was added to a suspension of freshly powdered lithium aluminium hydride pellets (2.5 g, 66.1 mmol) in anhydrous diethyl ether (100 mL) at 0 °C within 30 min under vigorous stirring in a 1 L round-bottomed flask. After 1 h sat. aq. NH₄Cl (200 mL) was carefully added at 0 °C followed by the addition of sat. aq. Na/K tartrate (200 mL). The resulting turbid biphasic system was stirred for 2 h and warmed to room temperature. The aqueous

phase was separated and extracted with diethyl ether (5 x 100 mL). The combined organic phases were washed with sat. aq. NaCl (200 mL) and dried with MgSO₄. After evaporation of all volatiles under reduced pressure the desired diol was isolated as colorless sticky oil (11.9 g, quant.) which was used without further purification in the next reaction. ¹H NMR (CDCl₃, 400 MHz): δ = 4.83 (s, 1H), 4.18 (d, *J* = 4.6 Hz, 1H), 3.95 (dt, *J* = 8.6, 5.5 Hz, 1H), 3.86-3.81 (m, 1H), 3.74 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.73-3.67 (m, 1H), 3.62 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.33 (s, 3H), 3.00 (br s, 1H), 2.29 (br s, 1H), 2.23-2.17 (m, 1H), 1.92-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 109.0, 84.3, 77.2, 66.8, 62.0, 54.6, 43.9, 28.9, 26.1 (3C), 18.5, -5.24, -5.26. HRMS (ESI) (*m/z*): calculated for C₁₄H₃₀O₅SiNa [M+Na]⁺ 329.1760, found 329.1749. IR (cm⁻¹): 3394, 2929, 2857, 1471, 1254, 1103, 1061, 1036, 951, 837. [α]_D²⁰: -28.2, (CHCl₃, *c* = 1.1). R_f: (Hex/EtOAc 1/1) 0.19.

To a solution of the crude diol (10.9 g, 35.6 mmol) in CH₂Cl₂ (150 mL) and imidazole (9.7 g, 142.5 mmol) was added triethylsilyl chloride (13.1 mL, 78.2 mmol) via syringe within 15 min. The resulting pale yellow solution was aged at room temperature for 2 h during which a white precipitate formed. Sat. aq. NH₄Cl (100 mL) was added and stirring was continued for another 30 min. The aqueous layer was separated and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with water (100 mL), sat. aq. NaCl (100 mL) and dried with MgSO₄. After removal of all volatiles a pale yellow oil was obtained which yielded tetrahydrofuran **44** (17.3 g, 91%) as colorless oil after flash column chromatography (SiO₂, Hex/EtOAc 20/1). ¹H NMR (CDCl₃, 400 MHz): δ = 4.67 (s, 1H), 4.04 (d, *J* = 4.4 Hz, 1H), 3.93 (ddd, *J* = 9.3, 5.4, 3.9 Hz, 1H), 3.71 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.67-3.55 (m, 3H), 3.32 (s, 3H), 2.16-2.09 (m, 1H), 1.89-1.80 (m, 1H), 1.61-1.53 (m, 1H), 0.96 (dt, *J* = 8.1, 4.3 Hz, 18H), 0.91 (s, 9H), 0.65-0.58 (m, 12H), 0.07 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 109.3, 84.8, 77.3, 66.3, 61.8, 54.5, 40.2, 28.9, 26.1 (3C), 18.6, 6.9 (6C), 5.1 (3C), 4.6 (3C), -5.2 (2C). HRMS (ESI) (*m/z*): calculated for C₂₆H₅₈O₅Si₃Na [M+Na]⁺ 557.3490, found 557.3477. IR (cm⁻¹): 2953, 2877, 1461, 1251, 1102, 1041, 1003, 958, 834, 775. [α]_D²⁰: +6.9, (CHCl₃, *c* = 1.2). R_f: (Hex/EtOAc 10/1) 0.36.

2-((2S,3R,4R,5R)-2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-methoxy-4-((triethylsilyl)oxy)tetrahydrofuran-3-yl)acetaldehyde (45): To a solution of oxalyl chloride (2.0 mL, 23.4 mmol) in CH₂Cl₂ (20 mL) in flame dried 50 mL round-bottomed flask equipped with a bubbler was dropwise added dimethylsulfoxide (3.4 mL, 48.1 mmol) within 5 min at -78 °C. After the evolution of gas had ceased the bubbler was removed and stirring was continued for further 10 min at -78 °C. Tetrahydrofuran **44** (2.5 g, 4.7 mmol) dissolved in CH₂Cl₂ (20 mL) was added to the resulting reaction mixture via syringe within 10 min. After 3 h at -78 °C an intermediate formed (TLC, Hex/EtOAc 3/1, R_f = 0.18). The reaction mixture was dropwise treated with Et₃N (6.5 mL, 46.7 mmol). The turbid solution was quenched by the addition of sat. aq. NaHCO₃ (20 mL) after 4 h and warmed to room temperature. The aqueous layer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (30 mL) and sat. aq. NaCl (30 mL) and dried with MgSO₄. Removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 20/1) of the remaining residue gave aldehyde **45** (1.9 g, 97%) as pale yellow oil. ¹H NMR (CDCl₃, 400 MHz): δ = 9.79 (s, 1H), 4.69 (s, 1H), 4.22 (d, *J* = 4.4 Hz, 1H), 3.94 (ddd, *J* = 8.4, 5.5, 0.7 Hz, 1H), 3.74 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.59 (dd, *J* = 10.3, 6.1 Hz, 1H), 3.32 (s, 3H), 2.79 (ddd, *J* = 17.3, 8.6, 1.0 Hz, 1H), 2.64-2.76 (m, 1H), 2.58-2.53 (m, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.58 (ddd, *J* = 17.3, 7.5, 0.9 Hz, 6H), 0.06 (s, 3H), 0.06 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 201.2, 109.5, 83.3, 77.1, 66.4, 54.7, 41.0, 39.4, 26.1 (3C), 18.5, 6.9 (3C), 4.9 (3C), -5.3 (2C). HRMS (ESI) (*m/z*): calculated for C₂₀H₄₂O₅Si₂Na [M+Na]⁺ 441.2468, found 441.2476. IR (cm⁻¹): 2955, 2929, 2879, 1728, 1462, 1254, 1127, 1108, 1039, 837. [α]_D²⁰: +1.4, (CHCl₃, *c* = 1.2). R_f: (Hex/EtOAc 8/1) 0.68.

Butenolide 46: LiHMDS (720 μL, 1.0 M in toluene, 5.6 mmol) was added to a solution of butyrolactone **32** (2.0 g, 4.9 mmol) in THF (22 mL) at -40 °C within 10 min. After 30 min a solution of aldehyde **45** (2.05 mg, 4.9 mmol) in THF (25 mL) was dropwise added within 20 min. After 2 h at -40 °C the reaction mixture was quenched by the addition of sat. aq. NH₄Cl (30 mL) and CH₂Cl₂ (30 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (3 x 40 mL). The combined organic phases were washed with water (40 mL) and sat. aq. NaCl (40 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. NMR analysis of the crude pale yellow oil indicated consumption of butyrolactone **32** and showed a complex mixture of four diastereomers (4.5 g, 4.9 mmol) and traces of aldehyde **45**.

H₂O₂ (3.7 mL, 32.6 mmol) was added under vigorous stirring to the aforementioned complex mixture in CH₂Cl₂ (50 mL) and pyridine (5 mL) at 0 °C. The resulting biphasic mixture was aged at this temperature for 1 h,

quenched by the addition of sat. aq. Na₂S₂O₃ (30 mL) and stirred for additional 30 min. The aqueous phase was separated and extracted with CH₂Cl₂ (3 x 30 mL). After the combined organic phases were washed with water (50 mL) and sat. aq. NaCl (50 mL), MgSO₄ was added followed by filtration. Evaporation of the volatiles and flash column chromatography (SiO₂, Hex/EtOAc 12/1) of the remaining oil yielded desired butenolide **46** as inseparable 1:1 mixture as pale yellow oil (3.01 g, 4.5 mmol, 92%). Diastereomer A: ¹H NMR (CDCl₃, 400 MHz): δ = 7.30 (t, *J* = 1.5 Hz, 1H), 5.26 (t, *J* = 6.7 Hz, 1H), 5.24-5.20 (m, 1H), 4.84 (d, *J* = 6.5 Hz, 1H), 4.69 (s, 1H), 4.51-4.47 (m, 1H), 4.16 (d, *J* = 4.6 Hz, 1H), 4.12 (d, *J* = 7.1 Hz, 1H), 4.06 (dt, *J* = 8.7, 5.3 Hz, 1H), 3.77 (t, *J* = 4.7 Hz, 1H), 3.72-3.69 (m, 1H), 3.69-3.65 (m, 1H), 3.31 (s, 3H), 2.42-2.35 (m, 1H), 1.98-1.90 (m, 2H), 1.81 (dd, *J* = 14.3, 7.3 Hz, 1H), 1.69-1.61 (m, 1H), 1.47 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.91 (s, 9H), 0.73 (q, *J* = 7.7 Hz, 6H), 0.14 (s, 9H), 0.1 (br s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.7, 150.1, 136.0, 109.0, 99.7, 83.9, 79.0, 78.6, 78.2, 78.0, 72.8, 66.7, 66.2, 54.7, 47.1, 41.7, 32.1, 27.8, 26.1 (3C), 18.6, 6.9 (3C), 5.0 (3C), 2.4 (3C), -5.3 (2C). Diastereomer B: ¹H NMR (CDCl₃, 400 MHz): δ = 7.31 (t, *J* = 1.4 Hz, 1H), 5.26 (t, *J* = 6.7 Hz, 1H), 5.24-5.20 (m, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.67 (s, 1H), 4.51-4.46 (m, 1H), 4.13 (d, *J* = 12.6 Hz, 1H), 4.10 (d, *J* = 4.4 Hz, 1H), 4.00 (dt, *J* = 9.0, 4.8 Hz, 1H), 3.79 (t, *J* = 4.8 Hz, 1H), 3.72-3.68 (m, 1H), 3.40 (d, *J* = 5.2 Hz, 1H), 3.31 (s, 3H), 2.35-2.29 (m, 1H), 2.20 (dd, *J* = 7.9, 2.6 Hz, 1H), 2.17 (dd, *J* = 7.9 Hz, 2.5 Hz, 1H), 1.96-1.90 (m, 1H), 1.79 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.47 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 9H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.14 (s, 9H), 0.1 (br s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 172.8, 150.2, 135.9, 109.2, 99.7, 83.9, 78.9, 78.6, 78.2, 78.0, 72.8, 66.5, 66.1, 54.8, 47.2, 41.1, 32.3, 27.8, 26.1 (3C), 18.6, 6.9 (3C), 5.0 (3C), 2.4 (3C), -5.3 (2C). HRMS (ESI) (*m/z*): calculated for C₃₃H₆₂O₈Si₃Na [M+Na]⁺ 693.3650, found 693.3650. R_f: (Hex/EtOAc 3/1) 0.57.

Cage-shaped lactones 49 and 50 (+ 47 and 48): A solution of a diastereomeric mixture of **46** (dr = 1:1, 490 mg, 0.7 mmol) in freshly degassed cyclohexane (four pump-freeze-thaw cycles, 80 mL) was split in 8 equal parts and transferred to quartz tubes of a diameter of 1 cm and a total height of 16 cm, which were equipped with a magnetic stirring bar. These charged quartz vials were placed 0.5 cm in front of a UV-C lamp (SYLVANIA G8W T5, 8W) in a custom-made reactor and irradiated for 2 h while stirring. The contents of all vials were combined and the volatiles were removed under reduced pressure. The remaining slightly yellow oil was subjected to flash column chromatography (SiO₂, Hex/EtOAc 20/1) yielding undesired [4.2.0]ring systems **47** and **48** (76 mg, 15% combined yield) as well as the desired caged [2+2]-photocyclization products **49** (170 mg, 35%) and **50** (169 mg, 34%) as colorless oils. Analytic data for **49**: ¹H NMR (CDCl₃, 400 MHz): δ = 5.40 (dd, *J* = 2.7, 1.2 Hz, 1H), 5.20 (dd, *J* = 2.1, 1.1 Hz, 1H), 5.16 (td, *J* = 7.9, 5.2 Hz, 1H), 4.69 (s, 1H), 4.14 (d, *J* = 4.5 Hz, 1H), 4.02 (dt, *J* = 9.0, 5.5 Hz, 1H), 3.98 (dt, *J* = 9.7, 2.9 Hz, 1H), 3.75 (dd, *J* = 10.4, 5.3 Hz, 1H), 3.71 (d, *J* = 2.2 Hz, 1H), 3.66 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.33-3.29 (m, 4H), 3.14-3.11 (m, 1H), 2.45 (qd, *J* = 12.4, 1.7 Hz, 1H), 2.43-2.46 (m, 1H), 1.94 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.79-1.67 (m, 2H), 1.43 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.91 (s, 9H), 0.62 (q, *J* = 8.2 Hz, 6H), 0.11 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 177.7, 144.0, 115.1, 109.0, 84.9, 84.1, 83.7, 77.5, 70.4, 67.0, 57.8, 57.7, 54.6, 49.6, 44.8, 41.4, 27.9, 26.2 (3C), 23.4, 18.6, 7.0 (3C), 5.1 (3C), 2.4 (3C), -5.2, -5.3. HRMS (ESI) (*m/z*): calculated for C₃₃H₆₂O₈Si₃Na [M+Na]⁺ 693.3650, found 693.3629. IR (cm⁻¹): 3500, 2954, 1767, 1462, 1375, 1301, 1251, 1186, 1104, 988. [α]_D²⁰: -38.7, (CHCl₃, *c* = 1.1). R_f: (Hex/EtOAc 4/1) 0.45. Analytical data for **50**: ¹H NMR (CDCl₃, 400 MHz): δ = 5.27 (dd, *J* = 2.7, 1.4 Hz, 1H), 5.19 (td, *J* = 8.0, 5.3 Hz, 1H), 5.15 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.66 (s, 1H), 4.17 (d, *J* = 4.8 Hz, 1H), 4.12 (ddd, *J* = 11.7, 5.7, 2.2 Hz, 1H), 3.96 (ddd, *J* = 8.1, 5.9, 4.7 Hz, 1H), 3.79 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.66 (dd, *J* = 10.6, 6.1 Hz, 1H), 3.43 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.31 (s, 3H), 3.13-3.09 (m, 1H), 3.05 (d, *J* = 5.7 Hz, 1H), 2.45 (qd, *J* = 12.4, 1.6 Hz, 1H), 2.44-2.38 (m, 1H), 1.93 (dd, *J* = 14.8, 5.3 Hz, 1H), 1.87 (ddd, *J* = 14.1, 8.7, 2.3 Hz, 1H), 1.67 (ddd, *J* = 14.0, 11.7, 5.7 Hz, 1H), 1.42 (s, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.91 (s, 9H), 0.63 (q, *J* = 8.2 Hz, 6H), 0.12 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 176.8, 145.4, 114.5, 109.2, 85.0, 84.0, 83.6, 79.1, 70.2, 67.1, 59.6, 57.7, 54.7, 49.8, 43.5, 41.6, 28.9, 26.2 (3C), 23.6, 18.7, 6.9 (3C), 5.1 (3C), 2.4 (3C), -5.3 (2C). HRMS (ESI) (*m/z*): calculated for C₃₃H₆₂O₈Si₃Na [M+Na]⁺ 693.3650, found 693.3647. IR (cm⁻¹): 3484, 2954, 1768, 1462, 1348, 1251, 1187, 1106, 1040, 991. [α]_D²⁰: -26.7, (CHCl₃, *c* = 0.6). R_f: (Hex/EtOAc 4/1) 0.39.

Analytic data for **47**: ¹H NMR (CDCl₃, 400 MHz): δ = 5.76-5.74 (m, 1H), 4.75 (dt, *J* = 8.7, 1.8 Hz, 1H), 4.66 (s, 1H), 4.13 (m, 1H), 4.09 (d, *J* = 4.9 Hz, 1H), 3.93-3.90 (m, 2H), 3.84 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.61 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.51-3.49 (m, 1H), 3.29 (s, 3H), 3.28-3.24 (m, 1H), 2.74 (dd, *J* = 13.4, 1.1 Hz, 1H), 2.35-2.27 (m, 1H), 2.53 (dd, *J* = 15.4, 5.9 Hz, 1H), 1.95 (dd, *J* = 15.4, 1.8 Hz, 1H), 1.77 (dd, *J* = 6.0, 4.1 Hz, 2H), 1.36 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.91 (s, 9H), 0.62 (q, *J* = 7.7 Hz, 6H), 0.10 (s,

6H), 0.06 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 179.1, 137.9, 127.9, 108.8, 83.1, 78.3, 76.6, 71.1, 70.1, 67.0, 55.6, 54.5, 47.9, 44.8, 42.8, 38.8, 31.2, 29.2, 25.9 (3C), 18.4, 6.7 (3C), 4.8 (3C), 2.2 (3C), -5.5 (2C). HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{62}\text{O}_8\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 693.3650, found 693.3650. IR (cm^{-1}): 3476, 2955, 2930, 1768, 1462, 1251, 1111, 1042, 1005, 839. $[\alpha]_{\text{D}}^{20}$: -44.1, (CHCl_3 , c = 2.0). R_f: (Hex/EtOAc 4/1) 0.28.

Oxidation/reduction sequence of 50 to 49: At 0 °C crushed 4 Å molecular sieves (100 mg), NMO (52 mg, 0.45 mmol) and tetrapropylammonium perruthenate (5 mg, 0.05 mmol) were added sequentially to a solution of **50** (100 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Diethyl ether (10 mL) was added and the resulting mixture was filtered through a pad of Celite. Removal of the volatiles and column chromatography (SiO_2 , Hex/EtOAc 6/1) gave the desired ketone (74 mg, 0.11 mmol, 74%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.52 (t, J = 2.4 Hz, 1H), 5.30 (t, J = 2.2 Hz, 1H), 5.22 (dt, J = 8.0, 5.3 Hz, 1H), 4.69 (s, 1H), 4.32 (d, J = 4.5 Hz, 1H), 3.93 (dt, J = 10.1, 5.2 Hz, 1H), 3.87 (dd, J = 8.2, 6.5 Hz, 1H), 3.69 (dd, J = 10.6, 5.4 Hz, 1H), 3.64 (dd, J = 10.5, 5.1 Hz, 1H), 3.33 (s, 3H), 3.22 (dd, J = 19.4, 3.4 Hz, 1H), 3.17-3.13 (m, 1H), 3.04 (dd, J = 19.4, 9.9 Hz, 1H), 2.54-2.46 (m, 2H), 1.94 (dd, J = 14.8, 5.3 Hz, 1H), 1.44 (s, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.90 (s, 9H), 0.58 (dd, J = 8.0, 2.4 Hz, 3H), 0.54 (dd, J = 8.0, 3.2 Hz, 3H), 0.11 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 200.0, 171.7, 144.0, 115.7, 109.5, 84.8, 83.7, 83.4, 76.9, 66.5, 65.1, 57.5, 54.6, 49.5, 44.6, 39.5, 34.9, 26.1 (3C), 23.5, 18.6, 6.9 (3C), 5.0 (3C), 2.4 (3C), -5.2, -5.3. HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{60}\text{O}_8\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 691.3494, found 691.3495. IR (cm^{-1}): 2955, 2929, 1769, 1714, 1464, 1252, 1149, 1108, 1039, 840. $[\alpha]_{\text{D}}^{20}$: -77.3, (CHCl_3 , c = 0.3). R_f: (Hex/EtOAc 6/1) 0.66.

To a solution of the ketone (15 mg, 0.02 mmol) and (*S*)-2-methyl-CBS-oxazaborolidine (45 μL , 0.05 mmol, 1.0 M in toluene) in THF (500 μL) was added $\text{BH}_3\cdot\text{THF}$ (45 μL , 0.05 mmol, 1.0 M in THF) at -78 °C. No reaction was observed monitored by TLC (Hex/EtOAc 4/1) till reaching 0 °C. The reaction mixture was stirred at 0 °C for 6 h. Sat. aq. NH_4Cl (5 mL) and diethyl ether (5 mL) were added. The aqueous layer was separated and washed with diethyl ether (2 x 5 mL). The combined organic phases were washed with sat. aq. NaCl (5 mL), dried with MgSO_4 , filtered and concentrated in vacuo giving a 1:2 mixture of **49** and **50** (15 mg) in quantitative yield. For analytic data see above.

Cage shaped epoxide 52: At 0 °C alcohol **49** (10 mg, 0.07 mmol) was dissolved in a freshly prepared solution of DMDO (0.4 mL, 0.08 M, 0.03 mmol) in acetone. The resulting colorless reaction mixture was allowed to warm to room temperature overnight. Additional DMDO (0.4 mL, 0.08 M, 0.03 mmol) was added and the reaction was stirred for additional 24 h. As TLC-analysis (Hex/EtOAc 4/1) still indicated remaining starting material DMDO (0.4 mL, 0.08 M, 0.03 mmol) was added again and the reaction was stirred for another 24 h. The volatiles were removed under reduced pressure in a cold water bath (15 °C). The resulting colorless residue was purified by flash column chromatography (SiO_2 , Hex/EtOAc 12/1) yielding desired epoxide **51** (9 mg, 85%) as colorless oil.

Alternatively: To a solution of **49** (32 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added NaHCO_3 (12 mg, 0.14 mmol) and *m*CPBA (25 mg, 0.14 mmol) at 0 °C. Prior to use, the commercially available *m*CPBA was purified by extraction of solution in diethyl ether (mL/g) with pH 7.5 buffer (3 x mL/g) and evaporation of the organic solvent in a water bath at 20 °C. After 4 h at 0 °C, sat. aq. NaHCO_3 (5 mL) and diethyl ether (5 mL) were added, the aqueous phase was separated and extracted with diethyl ether (2 x 5 mL). The combined organic phases were washed with sat. aq. NaCl (5 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2 , Hex/EtOAc 8/1) yielding desired epoxide **51** (30 mg, 94%) as a 4:1 diastereomeric mixture. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.21-5.15 (m, 1H), 4.68 (s, 1H), 4.11 (d, J = 4.5 Hz, 1H), 4.03 (dt, J = 8.6, 5.4 Hz, 1H), 3.95 (t, J = 6.6 Hz, 1H), 3.76 (dd, J = 10.3, 5.2 Hz, 1H), 3.67 (dd, J = 10.3, 5.7 Hz, 1H), 3.56 (t, J = 7.7 Hz, 1H), 3.31 (s, 3H), 3.25 (sbr, OH), 3.07 (dd, J = 7.3, 1.8 Hz, 1H), 2.97 (d, J = 4.4 Hz, 1H), 2.78 (d, J = 4.4 Hz, 1H), 2.57 (ddd, J = 14.7, 7.5, 1.9 Hz, 1H), 2.40-2.33 (m, 1H), 1.93 (dd, J = 14.7, 5.1 Hz, 1H), 1.66 (t, J = 6.7 Hz, 2H), 1.32 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.92 (s, 9H), 0.63 (q, J = 7.8 Hz, 6H), 0.11-0.09 (m, 15H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 176.2, 109.1, 83.9, 83.5, 82.9, 77.6, 67.5, 67.0, 62.9, 58.0, 56.9, 54.6, 50.7, 47.7, 42.1, 41.7, 27.9, 26.2 (3C), 23.4, 18.9, 6.9 (3C), 5.0 (3C), 2.4 (3C), -5.2, -5.3. HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{62}\text{O}_9\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 709.3555, found 709.3598. IR (cm^{-1}): 2955, 2930, 1768, 1462, 1376, 1252, 1143, 1040, 991, 840. $[\alpha]_{\text{D}}^{20}$: -32.0, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 4/1) 0.53.

A solution of epoxide (21 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C and pyridine (7 μL , 0.09 mmol), acetic anhydride (6 μL , 0.06 mmol) and DMAP (1 mg, 0.01 mmol) were sequentially added. The round-

bottomed flask was sealed with a stopper and the reaction mixture was warmed to room temperature overnight. Diethyl ether (5 mL) and sat. aq. NH_4Cl (5 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with sat. aq. CuSO_4 (10 mL), water (10 mL) and sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (SiO_2 , Hex/EtOAc 12/1) of the residue gave desired acylated epoxide **52** (22 mg, quant.) as needle-shaped crystals which were subjected to X-ray analysis. ^1H NMR (CDCl_3 , 600 MHz): δ = 5.31 (dd, J = 11.1, 3.2 Hz, 1H), 5.19 (dt, J = 7.9, 5.3 Hz, 1H), 4.65 (s, 1H), 4.23 (d, J = 4.2 Hz, 1H), 3.83 (dt, J = 9.4, 5.1 Hz, 1H), 3.71 (dd, J = 10.3, 4.9 Hz, 1H), 3.57 (dd, J = 10.3, 5.8 Hz, 1H), 3.54 (dd, J = 8.7, 7.4 Hz, 1H), 3.27 (s, 3H), 3.02 (dd, J = 7.1, 1.8 Hz, 1H), 2.88 (d, J = 4.6 Hz, 1H), 2.70 (d, J = 4.6 Hz, 1H), 2.58 (dq, J = 2.5, 2.0 Hz, 1H), 2.14 (s, 3H), 2.03-1.94 (m, 1H), 1.91 (dd, J = 14.7, 5.3 Hz, 1H), 1.84-1.75 (m, 2H), 1.31 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.92 (s, 9H), 0.69 (q, J = 8 Hz, 6H), 0.12 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (CDCl_3 , 150 MHz): δ = 174.9, 170.3, 109.5, 83.5, 83.4, 82.6, 76.4, 68.2, 66.3, 62.2, 57.9, 55.8, 54.6, 50.2, 47.0, 42.4, 40.7, 26.1 (3C), 25.7, 23.1, 21.3, 18.5, 7.0 (3C), 4.9 (3C), 2.4 (3C), -5.3 (2C). HRMS (ESI) (m/z): calculated for $\text{C}_{35}\text{H}_{64}\text{O}_{10}\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 751.3705, found 751.3704. mp = 93 - 95 °C. IR (cm^{-1}): 2955, 2928, 1768, 1744, 1231, 1124, 1041, 991, 843, 776. $[\alpha]_{\text{D}}^{20}$: -23.1, (CHCl_3 , c = 0.4). R_f: (Hex/EtOAc 4/1) 0.53.

Hemiacetal 53: To a solution of **51b** (5 mg, 0.01 mmol) in THF/DMSO 2/1 (450 μL) was added lithium acetylide ethylenediamine complex (50 mg, 0.54 mmol) at 0 °C. After 15 min diethyl ether (5 mL) and sat. aq. NH_4Cl (5 mL) were added. The aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with water (10 mL) and sat. aq. NaCl (5 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2 , Hex/EtOAc 6/1) gave hemiacetal **53** (5 mg, 0.01 mmol) in quantitative yield. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.96 (dd, J = 14.9, 7.5 Hz, 1H), 4.71 (s, 1H), 4.53 (dd, J = 10.7, 3.7 Hz, 1H), 4.19 (d, J = 4.3 Hz, 1H), 3.93 (dt, J = 8.86, 5.13 Hz, 1H), 3.72 (dd, J = 10.5, 5.4 Hz, 1H), 3.62 (dd, J = 10.5, 5.4 Hz, 1H), 3.40 (t, J = 7.5 Hz, 1H), 3.29 (s, 3H), 3.02 (d, J = 4.8 Hz, 1H), 3.00 (d, J = 4.8 Hz, 1H), 2.87 (d, J = 15.3 Hz, 1H), 2.77 (d, J = 15.3 Hz, 1H), 2.73 (s, OH), 2.70 (dd, J = 7.2, 1.9 Hz, 1H), 2.36 (dd, J = 13.9, 7.0 Hz, 1H), 2.32-2.07 (m, 4H), 1.34 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.89 (s, 9H), 0.68 (q, J = 7.9 Hz, 6H), 0.08 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 169.1, 109.1, 108.0, 86.1, 85.7, 84.1, 79.6, 76.9, 66.5, 60.6, 57.7, 54.6, 54.2, 50.6, 49.5, 48.0, 45.4, 41.2, 26.2, 26.1 (3C), 24.0, 18.4, 7.0 (3C), 5.2 (3C), 2.4 (3C), -5.2 (2C). HRMS (ESI) (m/z): calculated for $\text{C}_{35}\text{H}_{64}\text{O}_{10}\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 751.3705, found 751.3694. IR (cm^{-1}): 2955, 2929, 1760, 1413, 1375, 1252, 1146, 1121, 1021, 838. $[\alpha]_{\text{D}}^{20}$: +28.4, (CHCl_3 , c = 0.25). R_f: (Hex/EtOAc 3/1) 0.31.

Acetate 57: To a solution of alcohol **49** (250 mg, 0.37 mmol) in CH_2Cl_2 (4.0 mL), pyridine (90 μL , 1.12 mmol), acetic anhydride (70 μL , 0.70 mmol) and DMAP (5 mg, 0.04 mmol) were sequentially added at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. Diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with sat. aq. CuSO_4 (20 mL), water (20 mL) and sat. aq. NaCl (20 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. The desired acetylated product (266 mg, quant.) was isolated as colorless amorphous solid, which was used without further purification in the next reaction. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.48 (dd, J = 11.0, 3.1 Hz, 1H), 5.34 (dd, J = 2.6, 1.6 Hz, 1H), 5.20 (dd, J = 2.2, 1.6 Hz, 1H), 5.13 (dt, J = 8.0, 5.3 Hz, 1H), 4.66 (s, 1H), 4.14 (d, J = 4.1 Hz, 1H), 3.87 (dt, J = 9.1, 5.1 Hz, 1H), 3.69 (dd, J = 10.4, 4.8 Hz, 1H), 3.60 (dd, J = 10.4, 5.4 Hz, 1H), 3.40 (dd, J = 8.2, 6.5 Hz, 1H), 3.27 (s, 3H), 3.14-3.11 (m, 1H), 2.47 (ddd, J = 14.8, 7.7, 1.7 Hz, 1H), 2.08 (s, 3H), 2.01-1.88 (m, 4H), 1.41 (s, 3H), 0.99 (t, J = 7.9 Hz, 9H), 0.92 (s, 9H), 0.69 (q, J = 7.8 Hz, 6H), 0.12 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.2, 170.7, 144.1, 115.8, 109.4, 84.8, 83.7, 82.9, 76.5, 71.0, 66.1, 57.6, 57.2, 54.6, 49.6, 44.7, 40.5, 26.1 (3C), 25.5, 23.6, 21.0, 18.5, 7.0 (3C), 5.0 (3C), 2.4 (3C), -5.3 (2C). HRMS (ESI) (m/z): calculated for $\text{C}_{35}\text{H}_{64}\text{O}_9\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 735.3756, found 735.3769. IR (cm^{-1}): 2954, 1772, 1747, 1462, 1372, 1251, 1150, 1040, 991, 840. $[\alpha]_{\text{D}}^{20}$: -15.8, (CHCl_3 , c = 0.7). R_f: (Hex/EtOAc 5/1) 0.52.

The acylated substrate was taken up in an AcOH/THF/ H_2O 2/1/1 mixture (2.8 mL) and aged at room temperature for 24 h. All volatiles were removed under reduced pressure and the remaining pale yellow residue was subsequently co-evaporated with toluene (3 x 20 mL) till the smell of acetic acid was gone.

To a solution of the resulting crude colorless amorphous solid (144 mg) and imidazole (600 mg, 8.75 mmol) in CH_2Cl_2 (4.0 mL) was added

chlorotriethylsilane (650 μ L, 3.85 mmol) via syringe under vigorous stirring within 5 min. After 16 h, diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL) were added to the resulting suspension. The aqueous layer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (20 mL) and sat. aq. NaCl (20 mL) before being dried with MgSO_4 . The solids were removed by filtration and the filtrate was concentrated under reduced pressure. Flash column chromatography (SiO_2 , Hex/EtOAc 10/1) gave desired globally TES-protected acetate **57** (265 mg, 94%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.48 (dd, J = 10.2, 3.6 Hz, 1H), 5.34 (dd, J = 2.6, 1.6 Hz, 1H), 5.19 (dd, J = 2.1, 1.6 Hz, 1H), 5.14 (dt, J = 8.0, 5.3 Hz, 1H), 4.64 (s, 1H), 4.14 (d, J = 3.8 Hz, 1H), 3.89 (dt, J = 8.6, 5.2 Hz, 1H), 3.69 (dd, J = 10.3, 5.2 Hz, 1H), 3.60 (dd, J = 10.3, 5.4 Hz, 1H), 3.39 (dd, J = 8.2, 6.5 Hz, 1H), 3.28 (s, 3H), 3.11-3.08 (m, 1H), 2.44 (ddd, J = 14.7, 7.8, 1.6 Hz, 1H), 2.08 (s, 3H), 1.97-1.87 (m, 4H), 1.41 (s, 3H), 1.01-0.90 (m, 27H), 0.69 (q, J = 8.0 Hz, 6H), 0.65-0.55 (m, 12H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.3, 170.6, 144.3, 115.7, 109.4, 84.4, 83.7, 83.0, 76.5, 71.0, 66.1, 57.8, 57.2, 54.6, 49.7, 44.8, 40.8, 25.5, 23.4, 21.0, 7.1 (3C), 7.0 (3C), 6.9 (3C), 6.6 (3C), 5.1 (3C), 4.5 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{38}\text{H}_{70}\text{O}_9\text{Si}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 777.4225, found 777.4195. IR (cm^{-1}): 2954, 2877, 1772, 1371, 1230, 1150, 1040, 991, 807, 743. $[\alpha]_{\text{D}}^{22}$: -17.8, (CHCl_3 , c = 0.7). R_f: (Hex/EtOAc 3/1) 0.59.

Acetate 58: Alcohol **50** (284 mg, 0.42 mmol) was subjected to the identical procedure as alcohol **49** (see above, **57**) giving the corresponding globally TES-protected acetate **58** (278 mg, 87%) as a colorless oil.

Analytic data for the intermediate: ^1H NMR (CDCl_3 , 400 MHz): δ = 5.48 (dd, J = 11.1, 2.4 Hz, 1H), 5.32 (dd, J = 2.7, 1.6 Hz, 1H), 5.22 (dd, J = 2.1, 1.7 Hz, 1H), 5.18 (dt, J = 8.1, 5.4 Hz, 1H), 4.67 (s, 1H), 3.96 (d, J = 4.5 Hz, 1H), 3.93-3.89 (m, 1H), 3.73 (dd, J = 10.9, 3.7 Hz, 1H), 3.62 (dd, J = 10.9, 6.0 Hz, 1H), 3.42 (dd, J = 8.3, 6.4 Hz, 1H), 3.30 (s, 3H), 3.16-3.13 (m, 1H), 2.47 (ddd, J = 14.7, 7.8, 1.7 Hz, 1H), 2.11 (dd, J = 14.2, 6.0 Hz, 1H), 2.07 (m, 1H), 2.03 (s, 3H), 1.92 (dd, J = 14.7, 5.4 Hz, 1H), 1.84 (m, 1H), 1.42 (s, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.91 (s, 9H), 0.63 (q, J = 8.13 Hz, 6H), 0.11 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.7, 170.1, 144.4, 115.6, 109.2, 85.1, 84.9, 83.1, 77.9, 71.9, 66.8, 58.1, 58.0, 54.8, 49.4, 44.2, 40.9, 26.2 (3C), 26.1, 23.4, 21.2, 18.6, 6.9 (3C), 5.1 (3C), 2.4 (3C), -5.1, -5.2. HRMS (ESI) (m/z): calculated for $\text{C}_{35}\text{H}_{64}\text{O}_9\text{Si}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 735.3756, found 735.3759. IR (cm^{-1}): 2954, 2878, 1774, 1748, 1461, 1372, 1250, 1149, 1040, 991. $[\alpha]_{\text{D}}^{20}$: -46.6, (CHCl_3 , c = 1.5). R_f: (Hex/EtOAc 5/1) 0.48.

Analytic data for acetate **58**: ^1H NMR (CDCl_3 , 400 MHz): δ = 5.49 (dd, J = 11.2, 2.2 Hz, 1H), 5.32 (dd, J = 2.6, 1.6 Hz, 1H), 5.22 (dd, J = 2.1, 1.6 Hz, 1H), 5.19 (dt, J = 8.1, 5.4 Hz, 1H), 4.67 (s, 1H), 3.95 (d, J = 4.4 Hz, 1H), 3.93-3.89 (m, 1H), 3.73 (dd, J = 10.8, 3.7 Hz, 1H), 3.60 (dd, J = 10.8, 6.4 Hz, 1H), 3.42 (dd, J = 8.2, 6.4 Hz, 1H), 3.30 (s, 3H), 3.12 (m, 1H), 2.45 (ddd, J = 14.7, 7.9, 1.6 Hz, 1H), 2.12-2.05 (m, 1H), 2.03 (s, 3H), 2.05-2.01 (m, 1H), 1.92 (dd, J = 14.7, 5.4 Hz, 1H), 1.85 (ddd, J = 14.4, 5.4, 2.4 Hz, 1H), 1.42 (s, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.97 (t, J = 7.8 Hz, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.9 Hz, 12 H), 0.58 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.7, 170.1, 144.5, 115.5, 109.2, 85.2, 84.6, 83.2, 76.9, 72.0, 66.6, 58.19, 58.16, 54.7, 49.5, 44.2, 41.1, 26.1, 23.3, 21.2, 7.1 (3C), 6.9 (3C), 6.9 (3C), 6.6 (3C), 5.1 (3C), 4.5 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{38}\text{H}_{70}\text{O}_9\text{Si}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 777.4225, found 777.4232. IR (cm^{-1}): 2955, 2877, 1775, 1749, 1229, 1150, 1108, 1077, 1042, 1001. $[\alpha]_{\text{D}}^{23}$: -45.9, (CHCl_3 , c = 0.7). R_f: (Hex/EtOAc 3/1) 0.52.

Aldehyde 59: To a solution of oxalyl chloride (660 μ L, 7.7 mmol) in CH_2Cl_2 (8 mL) in flame dried 50 mL round-bottomed flask equipped with a bubbler was dropwise added dimethylsulfoxide (1.1 mL, 15.5 mmol) within 5 min at -78 °C. After the evolution of gas had ceased the bubbler was removed and stirring was continued for further 10 min at -78 °C. Acetate **57** (1.16 g, 1.5 mmol) dissolved in CH_2Cl_2 (8 mL) was added to the resulting reaction mixture via syringe within 10 min. After 3 h at -78 °C an intermediate formed (TLC, Hex/EtOAc 2/1, R_f = 0.23). The reaction mixture was dropwise treated with Et_3N (2.2 mL, 15.5 mmol). The turbid solution was quenched by the addition of sat. aq. NaHCO_3 (15 mL) after 4 h and warmed to room temperature. The aqueous layer was separated and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with water (20 mL) and sat. aq. NaCl (20 mL) and dried with MgSO_4 . Removal of the volatiles under reduced pressure and flash column chromatography (SiO_2 , Hex/EtOAc 8/1) of the remaining residue gave aldehyde **59** (666 mg, 67%, 89% brsm) as pale yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 9.57 (d, J = 3.1 Hz, 1H), 5.50 (dd, J = 11.6, 2.4 Hz, 1H), 5.31 (dd, J = 2.7, 1.7 Hz, 1H), 5.19 (dd, J = 3.8, 2.0 Hz, 1H), 5.17 (dt, J = 7.9, 5.4 Hz, 1H), 4.81 (s, 1H), 4.21 (d, J = 4.2 Hz, 1H), 4.05 (dd, J = 9.7, 3.0 Hz, 1H), 3.43 (dd, J = 8.2, 6.4 Hz, 1H), 3.39 (s, 3H), 3.10-3.07 (m, 1H), 2.45 (ddd, J = 14.7, 7.8, 1.7 Hz, 1H), 2.20-2.13 (m, 1H), 2.07 (s, 3H), 1.98-

1.79 (m, 3H), 1.41 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.71 (q, J = 7.8 Hz, 6H), 0.58 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 202.4, 174.2, 170.7, 144.3, 115.6, 110.6, 86.5, 84.4, 83.2, 75.7, 70.6, 58.0, 57.4, 55.2, 49.7, 44.5, 40.4, 25.2, 23.5, 21.0, 7.1 (3C), 6.9 (3C), 6.6 (3C), 5.0 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{53}\text{O}_{10}\text{Si}_2\text{Na}$ [$\text{M}+\text{MeOH}+\text{Na}$] $^+$ 693.3466, found 693.3467. IR (cm^{-1}): 2955, 2877, 1770, 1745, 1459, 1373, 1231, 1151, 1038, 808. $[\alpha]_{\text{D}}^{20}$: -39.3, (CHCl_3 , c = 0.6). R_f: (Hex/EtOAc 2/1) 0.50.

Aldehyde 60: Aldehyde **60** (310 mg, 87%, 97% brsm) was prepared according to the procedure for **59**. ^1H NMR (CDCl_3 , 400 MHz): δ = 9.57 (d, J = 3.1 Hz, 1H), 5.38 (t, J = 6.4 Hz, 1H), 5.36 (dd, J = 2.7, 1.7 Hz, 1H), 5.26 (t, J = 2.0 Hz, 1H), 5.20 (td, J = 8.1, 5.4 Hz, 1H), 4.80 (s, 1H), 4.11 (dd, J = 8.7, 3.0 Hz, 1H), 4.00 (d, J = 4.6 Hz, 1H), 3.42 (dd, J = 8.3, 6.3 Hz, 1H), 3.39 (s, 3H), 3.15-3.11 (m, 1H), 2.50-2.42 (m, 2H), 2.04 (s, 3H), 2.03 (t, J = 6.6 Hz, 2H), 1.92 (dd, J = 14.7, 5.4 Hz, 1H), 1.42 (s, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.94 (t, J = 8.2 Hz, 9H), 0.64 (q, J = 8.2 Hz, 6H), 0.58 (q, J = 8.3 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 201.4, 174.6, 170.3, 144.1, 116.0, 110.3, 87.2, 84.7, 83.3, 77.6, 71.4, 58.2, 58.1, 55.2, 49.5, 44.1, 40.6, 26.5, 23.3, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 5.02 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{33}\text{H}_{53}\text{O}_{10}\text{Si}_2\text{Na}$ [$\text{M}+\text{MeOH}+\text{Na}$] $^+$ 693.3466, found 693.3458. IR (cm^{-1}): 2955, 2912, 2877, 1773, 1748, 1231, 1150, 1106, 1040, 1017. $[\alpha]_{\text{D}}^{23}$: -50.0, (CHCl_3 , c = 0.6). R_f: (Hex/EtOAc 3/1) 0.43.

Alkyne 61: A solution of **59** (72 mg, 0.11 mmol) in THF (1 mL) was treated with a 0.5 M solution of ethynylmagnesium bromide (340 μ L, 0.17 mmol) in THF at -78 °C. The resulting solution was allowed to warm to -20 °C within 4 h and aged at this temperature for 16 h. Sat. aq. NH_4Cl (5 mL) and diethyl ether (5 mL) were added. The aqueous phase was separated and extracted with diethyl ether (2 x 5 mL). The combined organic phases were washed with sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2 , Hex/EtOAc 8/1) gave the desired propargylic alcohol **61** (45 mg, 0.07 mmol, 93% brsm) as single diastereomer. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.47 (dd, J = 11.7, 2.4 Hz, 1H), 5.34 (dd, J = 2.7, 1.7 Hz, 1H), 5.20 (dd, J = 2.2, 1.7 Hz, 1H), 5.16 (dt, J = 8.0, 5.3 Hz, 1H), 4.68 (s, 1H), 4.51 (dt, J = 3.7, 2.3 Hz, 1H), 4.20 (d, J = 4.4 Hz, 1H), 4.07 (dd, J = 9.0, 3.4 Hz, 1H), 3.39 (dd, J = 6.3, 2.0 Hz, 1H), 3.36 (s, 3H), 3.12-3.09 (m, 1H), 2.69 (d, J = 4.1 Hz, 1H, 1H), 2.50-2.42 (m, 1H), 2.48 (d, J = 2.2 Hz, 1H, 1H), 2.34-2.27 (m, 1H), 2.17-2.13 (m, 1H), 2.11 (s, 3H), 2.03-1.97 (m, 1H), 1.90 (dd, J = 14.7, 5.3 Hz, 1H), 1.41 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.70 (q, J = 8.0 Hz, 6H), 0.58 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.2, 170.9, 144.3, 115.6, 109.7, 85.9, 84.5, 83.1, 81.4, 76.5, 74.8, 71.0, 63.4, 57.7, 57.2, 55.5, 49.7, 44.8, 38.1, 26.1, 23.5, 21.1, 7.1 (3C), 7.0 (3C), 6.6 (3C), 5.0 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{34}\text{H}_{56}\text{O}_9\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 687.3361, found 687.3366. IR (cm^{-1}): 3484, 2955, 2877, 1770, 1745, 1459, 1231, 1151, 1039, 991. $[\alpha]_{\text{D}}^{20}$: -9.04, (CHCl_3 , c = 0.37). R_f: (Hex/EtOAc 3/1) 0.28.

Dibromide 65: NBS (4 mg, 0.02) was added as solid to a solution of **61** (11 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL). the round-bottomed flask was sealed with a stopper and heated to 50 °C for 5 h. The volatiles were removed under reduced pressure and the remaining residue was subjected to column chromatography (SiO_2 , Hex/EtOAc 12/1). *trans*-dibromo compound **65** (4 mg, 0.01 mmol, 30%, 66% brsm) was obtained as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 8.66 (s, 1H), 5.50 (dd, J = 11.4, 2.4 Hz, 1H), 5.31 (dd, J = 2.5, 1.8 Hz, 1H), 5.19 (t, J = 1.8 Hz, 1H), 5.16 (dt, J = 8.0, 5.3 Hz, 1H), 4.75 (s, 1H), 4.61 (d, J = 8.9 Hz, 1H), 4.21 (d, J = 4.32 Hz, 1H), 3.45 (dd, J = 8.1, 6.5 Hz, 1H), 3.25 (s, 3H), 3.11-3.08 (m, 1H), 2.61-2.54 (m, 1H), 2.45 (ddd, J = 14.7, 7.8, 1.6 Hz, 1H), 2.09 (s, 3H), 1.96-1.87 (m, 2H), 1.83-1.76 (m, 1H), 1.40 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.72 (q, J = 7.9 Hz, 6H), 0.58 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 189.9, 174.3, 170.8, 144.4, 131.6, 130.8, 115.5, 110.6, 84.6, 84.4, 83.3, 75.9, 70.6, 57.9, 57.5, 55.5, 49.7, 44.5, 40.9, 25.9, 23.5, 21.0, 7.2 (3C), 7.0 (3C), 6.6 (3C), 4.9 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{34}\text{H}_{54}\text{Br}_2\text{O}_9\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 845.1550, found 845.1547. IR (cm^{-1}): 2955, 2877, 2349, 1770, 1702, 1460, 1373, 1232, 1151, 1042. $[\alpha]_{\text{D}}^{20}$: -11.1, (CHCl_3 , c = 0.02). R_f: (Hex/EtOAc 4/1) 0.48.

Carboxylic acid 67: A solution of NaClO_2 (34 mg, 0.37 mmol) and NaH_2PO_4 (62 mg, 0.45 mmol) in water (450 μ L) were added via Pasteur pipette to a solution of aldehyde **59** (24 mg, 0.04 mmol) in 2-methyl-2-butene (300 μ L) and *t*BuOH (800 μ L) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 h. Sat. aq. NH_4Cl (5 mL) and diethyl ether (10 mL) were added. The aqueous phase was separated and extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with water (10 mL) and sat. aq. NaCl (10 mL),

dried with MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (SiO₂, Hex/EtOAc 1/1) afforded desired acid **67** (24 mg, 0.37 mmol, 98%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 9.6 (br s, 1H), 5.50 (dd, J = 11.6, 2.5 Hz, 1H), 5.30 (dd, J = 2.6, 1.8 Hz, 1H), 5.22-5.17 (m, 2H), 4.82 (s, 1H), 4.30 (d, J = 10.1 Hz, 1H), 4.27 (d, J = 4.0 Hz, 1H), 3.49 (dd, J = 8.2, 6.5 Hz, 1H), 3.44 (s, 3H), 3.40-3.30 (m, 1H), 3.10-3.08 (m, 1H), 2.44 (qd, J = 12.4, 1.7 Hz, 1H), 2.28-2.20 (m, 1H), 2.10-1.88 (m, 4H), 2.08 (1H, s), 1.41 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.73 (q, J = 8.2 Hz, 6H), 0.58 (q, J = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.3, 173.4, 170.9, 144.5, 115.4, 111.0, 84.4, 83.3, 80.7, 75.6, 70.4, 58.1, 57.5, 49.7, 44.4, 42.9, 29.9, 25.6, 23.5, 21.0, 7.15 (3C), 6.89 (3C), 6.62 (3C), 4.95 (3C). HRMS (ESI) (m/z): calculated for C₃₂H₅₄NaO₁₀Si₂ [M+Na]⁺ 677.3153, found 677.3135. IR (cm⁻¹): 3218, 2922, 2853, 1769, 1743, 1460, 1374, 1231, 1137, 990. [α]_D²⁰: -14.7, (CHCl₃, c = 0.5). R_f: (Hex/EtOAc 1/1) 0.14.

(3aR,5S,6R,6aR)-5-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-d][1,3]dioxole (73): To a suspension of freshly powdered LAH (911 mg, 24 mmol) in diethyl ether (150 mL) was added a solution of ester **72** (7.6 g, 24 mmol) in diethyl ether (100 mL) at 0 °C within 15 min. After 1 h at that temperature, sat. aq. NH₄Cl (100 mL) was carefully added followed by sat. aq. Na/K tartrate (100 mL). The resulting biphasic mixture was stirred at room temperature for 1 h. The aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (100 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. The alcohol was isolated as colorless gum (6.31 g, 21.9 mmol, 91%) and used without purification in the next reaction.

To a solution of the alcohol (6.3 g, 21.9 mmol), triphenylphosphine (17.2 g, 65.7 mmol) and imidazole (4.5 g, 65.7 mmol) in CH₃CN/benzene 1/2 (210 mL) was added iodine (16.7 g, 65.6 mmol) in 6 portions within 30 min at 0 °C. The resulting mixture was stirred for 1 h where after sat. aq. Na₂S₂O₃ (50 mL) was added. The organic phase was separated, washed with water (50 mL) and sat. aq. NaCl (50 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Filtration (Hex/EtOAc 3/1) through a short pad of silica gave the desired iodide (8.5 g, 21.3 mmol, 97%) as slightly yellow oil, which was used without further purification in the next step. ¹H NMR (CDCl₃, 400 MHz): δ = 5.77 (d, J = 3.7 Hz, 1H), 4.66 (t, J = 3.9 Hz, 1H), 4.09 (dd, J = 8.2, 6.3 Hz, 1H), 4.02 (dd, J = 6.7, 5.3 Hz, 1H), 3.91 (dd, J = 8.2, 5.3 Hz, 1H), 3.79 (dd, J = 9.1, 7.0 Hz, 1H), 3.43-3.38 (m, 1H), 3.25 (dt, J = 9.4, 6.3 Hz, 1H), 2.31 (dt, J = 9.5, 7.3 Hz, 1H), 2.15-2.04 (m, 2H), 1.50 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 112.1, 109.8, 105.1, 81.5, 80.8, 77.7, 67.6, 49.0, 29.2, 26.9, 26.8, 26.6, 25.4, 4.9. HRMS (ESI) (m/z): calculated for C₁₄H₂₃IO₅Na [M+Na]⁺ 421.0488, found 421.0485. IR (cm⁻¹): 2986, 2934, 1454, 1380, 1256, 1214, 1171, 1065, 1017, 847. [α]_D²⁰: +76.5, (CHCl₃, c = 0.9). R_f: (Hex/EtOAc 1/1) 0.67.

To a solution of the iodide (11.7 g, 29 mmol) in THF (300 mL) was added *t*BuOK (9.9 g, 88 mmol) in three portions at 0 °C within 30 min. The resulting mixture was stirred at that temperature for 2 h. Sat. aq. NH₄Cl (100 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (100 mL) and sat. aq. NaCl (100 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography (SiO₂, Hex/EtOAc 6/1) gave desired diacetone **73** (7.7 g, 28.5 mmol, 97%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.87 (dd, J = 10.3, 8.8 Hz, 1H), 5.82 (d, J = 3.6 Hz, 1H), 5.28 (ddd, J = 17.3, 1.6, 0.7 Hz, 1H), 5.22 (dd, J = 10.3, 1.6 Hz, 1H), 4.62 (dd, J = 4.5, 3.8 Hz, 1H), 4.26 (dt, J = 4.0, 6.7 Hz, 1H), 4.10 (dd, J = 10.1, 3.9 Hz, 1H), 3.99 (dd, J = 8.2, 6.8 Hz, 1H), 3.89 (dd, J = 8.2, 6.6 Hz, 1H), 2.62 (dt, J = 4.8, 9.5 Hz, 1H), 1.54 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 132.5, 119.2, 112.0, 109.7, 104.9, 83.9, 80.0, 76.3, 65.5, 50.7, 26.9, 26.6, 26.4, 25.4. HRMS (ESI) (m/z): calculated for C₁₄H₂₂O₅Na [M+Na]⁺ 293.1365, found 293.1362. IR (cm⁻¹): 2986, 2935, 1372, 1251, 1214, 1167, 1102, 1065, 1015, 848. [α]_D²²: +94.5, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 2/1) 0.38.

Triethyl(((2S,3R,4R,5R)-5-methoxy-4-((triethylsilyloxy)-3-vinyltetrahydrofuran-2-yl)methoxy)silane (74): To a solution of diacetone **73** (330 mg, 1.22 mmol) in MeOH (13 mL) was added acetyl chloride (260 μ L, 3.66 mmol) at 0 °C. The resulting solution was warmed to room temperature and stirred for 3 h. Et₃N (1 mL) was added and the volatiles were removed under reduced pressure. The remaining white residue was subjected to column chromatography (SiO₂, EtOAc) giving the desired triol (170 mg, 0.83 mmol, 68%) as colorless gum. ¹H NMR (CDCl₃, 400 MHz): δ = 5.91 (ddd, J = 17.9, 9.9, 8.1 Hz, 1H), 5.35-5.32 (m, 1H), 5.30 (d, J = 0.8 Hz, 1H), 4.83 (s, 1H), 4.24 (dd, J = 9.0, 4.5 Hz, 1H), 4.10 (t, J = 4.3 Hz, 1H), 3.87-3.83 (m, 1H), 3.67 (t, J = 4.8 Hz, 1H), 3.40 (s, 3H),

3.08 (td, J = 8.6, 4.5 Hz, 1H), 2.71 (d, J = 3.7 Hz, 1H), 2.28 (t, J = 5.6 Hz, 1H), 2.09 (d, J = 4.3 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 133.2, 120.2, 109.2, 83.0, 78.4, 73.8, 63.6, 55.5, 47.0. HRMS (ESI) (m/z): calculated for C₉H₁₆O₅Na [M+Na]⁺ 227.0895, found 227.0891. IR (cm⁻¹): 3363, 2926, 1438, 1420, 1306, 1195, 1154, 1103, 1033, 943. [α]_D²²: +10.5, (CHCl₃, c = 0.6). R_f: (EtOAc) 0.29.

Glycol cleavage of the vicinal diol (11.0 g, 53 mmol) was done according to the procedure for **42** giving the desired diol (8.1 g, 46.5 mmol, 86%) as colorless gum. ¹H NMR (CDCl₃, 400 MHz): δ = 5.89 (1H, ddd, J = 17.2, 10.5, 8.1 Hz), 5.30-5.28 (m, 1H), 5.27-5.24 (m, 1H), 4.84 (s, 1H), 4.24 (ddd, J = 9.3, 4.2, 2.7 Hz, 1H), 4.11 (t, J = 4.4 Hz, 1H), 3.79 (ddd, J = 11.9, 4.3, 2.7 Hz, 1H), 3.53-3.46 (m, 1H), 3.41 (s, 3H), 2.97 (td, J = 8.8, 4.4 Hz, 1H), 2.10 (dd, J = 7.8, 4.6 Hz, 1H), 2.03 (d, J = 4.6 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 132.3, 120.1, 109.2, 83.1, 78.2, 63.2, 55.8, 46.3. HRMS (ESI) (m/z): calculated for C₈H₁₄O₄Na [M+Na]⁺ 197.0790, found 197.0783. IR (cm⁻¹): 3397, 2924, 1640, 1451, 1352, 1305, 1248, 1092, 1035, 970. [α]_D²²: +14.6, (CHCl₃, c = 0.7). R_f: (EtOAc) 0.5.

To a solution of the crude diol (8.1 g, 46.5 mmol) in CH₂Cl₂ (500 mL) was added imidazole (19.0 g, 279.0 mmol). Triethylsilyl chloride (19.5 mL, 117.5 mmol) was added via syringe within 10 min. The resulting suspension was stirred for 6 h. Water (100 mL) was added and the separated aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (100 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (SiO₂, Hex/EtOAc 30/1) afforded **74** (17.8 g, 44.2 mmol, 96%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.86 (1H, dt, J = 18.0, 9.3 Hz), 5.15 (dd, J = 5.1, 2.0 Hz, 1H), 5.12-5.11 (m, 1H), 4.70 (br s, 1H), 4.11 (ddd, J = 9.7, 6.0, 2.8 Hz, 1H), 4.04 (d, J = 4.2 Hz, 1H), 3.73 (dd, J = 10.9, 2.9 Hz, 1H), 3.55 (dd, J = 10.9, 6.1 Hz, 1H), 3.34 (s, 3H), 2.67 (td, J = 9.4, 4.2 Hz, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H), 0.60 (q, J = 7.8 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 134.3, 118.4, 109.5, 83.8, 79.4, 65.0, 54.5, 48.6, 6.89 (3C), 6.87 (3C), 4.9 (3C), 4.5 (3C). HRMS (ESI) (m/z): calculated for C₂₀H₄₂O₄Si₂Na [M+Na]⁺ 425.2519, found 425.2518. IR (cm⁻¹): 2954, 2912, 2877, 1459, 1415, 1239, 1120, 1042, 1004, 917. [α]_D²⁰: +12.1, (CHCl₃, c = 1.2). R_f: (Hex/EtOAc 2/1) 0.89.

(2S,3R,4R,5R)-5-Methoxy-4-((triethylsilyloxy)-3-vinyltetrahydrofuran-2-carbaldehyde (75): **74** (5.0 g, 12.4 mmol) was subjected to the same Swern-oxidation procedure as **57** (to **59**) giving desired aldehyde **75** (3.3 g, 11.4 mmol, 92%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 9.56 (d, J = 2.9 Hz, 1H), 5.88 (ddd, J = 17.1, 10.3, 8.8 Hz, 1H), 5.23-5.21 (m, 1H), 5.20-5.17 (m, 1H), 4.82 (s, 1H), 4.30 (dd, J = 9.7, 2.8 Hz, 1H), 4.10 (d, J = 4.2 Hz, 1H), 3.43 (s, 3H), 2.93 (dt, J = 9.2, 4.2 Hz, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.61 (q, J = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 201.0, 131.9, 119.9, 110.6, 85.9, 78.6, 55.1, 48.8, 6.8 (3C), 4.9 (3C). HRMS (ESI) (m/z): calculated for C₁₄H₂₆O₄SiNa [M+Na]⁺ 309.1498, found 309.1479. IR (cm⁻¹): 2955, 2832, 1737, 1460, 1415, 1314, 1239, 1120, 1002, 836. [α]_D²⁰: +10.8, (CHCl₃, c = 0.65). R_f: (Hex/EtOAc 3/1) 0.45.

Triethyl(((2R,3R,4R,5S)-4-(iodomethyl)-2-methoxy-5-(((triethylsilyloxy)methyl)tetrahydrofuran-3-yl)oxy)silane (76):

Through a solution of **74** (1.3 g, 3.2 mmol) in CH₂Cl₂/MeOH 3/1 (40 mL) was bubbled an ozone/air mixture at -78 °C till the color of the solution turned blue (10 min). The resulting solution was degassed with a stream of air till colorless and NaBH₄ (490 mg, 12.9 mmol) was added. The reaction mixture was warmed to 0 °C and stirred for 1 h. Water (30 mL) and diethyl ether (30 mL) were added and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO₂, Hex/EtOAc 10/1) gave the desired alcohol (1.0 g, 2.5 mmol, 76%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 4.64 (s, 1H), 4.21 (d, J = 4.8 Hz, 1H), 4.20 (dt, J = 8.3, 4.7 Hz, 1H), 3.86 (dd, J = 9.6, 4.8 Hz, 1H), 3.78 (t, J = 5.7 Hz, 2H), 3.46 (dd, J = 9.3, 8.5 Hz, 1H), 3.30 (s, 3H), 3.23 (t, J = 5.72, 1H), 2.30-2.24 (m, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.9 Hz, 6H), 0.61 (q, J = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 109.3, 82.8, 79.0, 66.2, 61.0, 54.6, 48.9, 6.8 (3), 6.7 (3C), 4.8 (3C), 4.3 (3C). HRMS (ESI) (m/z): calculated for C₁₉H₄₂O₅Si₂Na [M+Na]⁺ 465.3180, found 465.3172. IR (cm⁻¹): 3471, 2954, 2912, 2877, 1460, 1240, 1113, 1006, 957, 810. [α]_D²⁰: -27.9, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 6/1) 0.43.

At 0 °C, to a solution of the alcohol (112 mg, 0.28 mmol), triphenylphosphine polymer-bound (1.6 mmol/g, 344 mg, 0.55 mmol) and imidazole (56 mg, 0.83 mmol) in CH₂Cl₂ (5.5 mL) was added a solution of freshly sublimated and crushed iodine (140 mg, 0.55 mmol) in CH₂Cl₂ (2 mL). The reaction mixture was warmed to rt and stirred for 6 h. Sat. aq. NH₄Cl solution (10 mL) and sat. aq. Na₂S₂O₃ solution (5 mL) were added

and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (20 mL) and dried over MgSO_4 . After removal of the solvent the crude product was purified by flash chromatography (SiO_2 , Hex/EtOAc 20/1) delivering iodide **76** (115 mg, 0.20 mmol, 81%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 4.68 (s, 1H), 4.17 (d, J = 4.0 Hz, 1H), 3.84 (dt, J = 9.0, 5.7 Hz, 1H), 3.74 (dd, J = 10.1, 5.3 Hz, 1H), 3.59 (dd, J = 10.1, 6.2 Hz, 1H), 3.31 (s, 3H), 3.32-3.23 (m, 2H), 2.57-2.50 (m, 1H), 0.99 (t, J = 8.0 Hz, 9H), 0.97 (t, J = 8.0 Hz, 9H), 0.69 (q, J = 8.1 Hz, 6H), 0.62 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 108.5, 82.6, 77.8, 66.3, 54.6, 49.8, 7.0 (3C), 6.9 (3C), 5.2 (3C), 4.50 (3C), 0.64. HRMS (ESI) (m/z): calculated for $\text{C}_{19}\text{H}_{44}\text{O}_4\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 539.1486, found 539.1487. IR (cm^{-1}): 2954, 2876, 1459, 1415, 1237, 1186, 1119, 1071, 1005, 888. $[\alpha]_{\text{D}}^{20}$: +21.9, (CHCl_3 , c = 0.75). R_f: (Hex/EtOAc 5/1) 0.84.

2-((2S,3R,4R,5R)-5-Methoxy-4-((triethylsilyloxy)-2-(((triethylsilyloxy)methyl)tetrahydrofuran-3-yl)acetaldehyde (77):

To a solution of **74** (250 mg, 0.62 mmol) in THF (6 mL) was added $\text{BH}_3\cdot\text{THF}$ (1.9 mL, 1.9 mmol) within 10 min at 0 °C. After 4 h sat. aq. NaHCO_3 (6 mL) and H_2O_2 (170 μL , 1.49 mmol) were added. The resulting biphasic mixture was vigorously stirred for 1 h at 0 °C before sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) was added. The aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with water (10 mL) and sat. aq. NaCl (10 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Column chromatography (SiO_2 , Hex/EtOAc 12/1) yielded the desired alcohol (200 mg, 0.48 mmol, 76%). ^1H NMR (CDCl_3 , 400 MHz): δ = 4.66 (s, 1H), 4.08 (d, J = 4.6 Hz, 1H), 4.03-3.99 (m, 1H), 3.72 (ddd, J = 10.4, 5.2, 1.1 Hz, 1H), 3.68-3.60 (m, 3H), 3.30 (s, 3H), 2.30-2.17 (m, 2H), 1.90-1.81 (m, 1H), 1.70-1.61 (m, 1H), 0.96 (t, J = 7.9 Hz, 9H), 0.96 (t, J = 8.0 Hz, 9H), 0.66-0.58 (m, 12H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 109.2, 84.0, 78.1, 66.6, 61.6, 54.5, 41.6, 29.5, 6.9 (3C), 6.8 (3C), 5.0 (3C), 4.4 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{20}\text{H}_{44}\text{O}_5\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 443.2625, found 443.2622. IR (cm^{-1}): 3458, 2954, 2912, 2877, 1459, 1415, 1239, 1128, 1041, 1005. $[\alpha]_{\text{D}}^{20}$: -9.7, (CHCl_3 , c = 1.50). R_f: (Hex/EtOAc 6/1) 0.33.

At 0 °C $\text{SO}_3\cdot\text{py}$ (170 mg, 1.07 mmol) was added in one portion to a solution of the alcohol (150 mg, 0.36 mmol) and Et_3N (250 μL , 1.78 mmol) in $\text{CH}_2\text{Cl}_2/\text{DMSO}$ 4/1 (4.0 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for further 16 h. Sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and diethyl ether (5 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with water (5 mL) and sat. aq. NaCl (5 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Column chromatography (SiO_2 , Hex/EtOAc 6/1) gave the desired aldehyde **77** (139 mg, 0.33 mmol, 93%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 9.78 (br s, 1H), 4.68 (s, 1H), 4.21 (d, J = 4.2 Hz, 1H), 3.94 (t, J = 8.7, 5.7 Hz, 1H), 3.74 (dd, J = 10.2, 5.3 Hz, 1H), 3.57 (dd, J = 10.2, 6.1 Hz, 1H), 3.32 (s, 3H), 2.82-2.74 (m, 1H), 2.61-2.53 (m, 2H), 0.95 (t, J = 8.0 Hz, 9H), 0.93 (t, J = 7.9 Hz, 9H), 0.63-0.54 (m, 12H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 201.2, 109.5, 83.3, 77.1, 66.3, 54.6, 41.1, 39.6, 6.84 (6C), 4.9 (3C), 4.5 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{20}\text{H}_{42}\text{O}_5\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 441.2468, found 441.2469. IR (cm^{-1}): 2955, 2912, 2877, 1728, 1458, 1386, 1239, 1107, 1007, 958. $[\alpha]_{\text{D}}^{20}$: +7.0, (CHCl_3 , c = 1.45). R_f: (Hex/EtOAc 6/1) 0.67.

Aldehyde 81: To a solution of alcohol **80** (40 mg, 0.12 mmol) in MeOH (4.1 mL) was added AcCl (35 μL , 0.49 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for further 4 h, the volatiles were removed under reduced pressure and the residue was dried under high vacuum for 2 h to yield 23 mg (89%) of the diol as slightly pink solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.36 (br s, 1H), 5.32-5.25 (m, 1H), 5.22 (br s, 1H), 4.01 (d, J = 11.6 Hz, 1H), 3.87 (d, J = 11.6 Hz, 1H), 3.53 (t, J = 6.2 Hz, 1H), 3.21 (br s, 1H), 2.48 (dd, J = 7.7 Hz, 15.1 Hz, 1H), 2.04 (dd, J = 4.7 Hz, 15.0 Hz, 1H), 1.73 (br s, 2H), 1.45 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 176.8, 144.4, 115.0, 83.7, 82.7, 63.3, 56.8, 55.9, 48.6, 44.8, 24.1. HRMS (ESI) (m/z): calculated for $\text{C}_{11}\text{H}_{14}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 233.0790, found: 233.0781. IR (cm^{-1}): 3370, 2925, 1743, 1352, 1158, 1056, 995, 906, 729, 647. $[\alpha]_{\text{D}}^{21}$: -26.7 (CHCl_3 , c = 1.1). R_f: (Hex/EtOAc 1/1) 0.15. mp.: 110-112 °C.

The crude diol (15 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (1.4 mL) and cooled to 0 °C. 2,6-lutidine (50 μL , 0.43 mmol), followed by TESOTf (64 μL , 0.29 mmol) were rapidly added to the reaction vessel and the mixture was stirred at 0 °C for 45 min. The reaction was quenched by addition of NaHCO_3 (10 mL), diluted with water (10 mL) and diethyl ether (30 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 15 mL). The organic layers were washed with sat. aq. NaCl (15 mL), dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , Hex/EtOAc 15/1) furnishing 30 mg (96%) of the desired TES protected diol as colorless

oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.22-5.16 (m, 2H), 5.12 (dd, J = 1.5, 2.2 Hz, 1H), 4.01 (d, J = 10.6 Hz, 1H), 3.77 (d, J = 10.5 Hz, 1H), 3.47 (dd, J = 6.2, 8.3 Hz, 1H), 3.18-3.14 (m, 1H), 2.45 (ddd, J = 1.8, 7.8, 14.7 Hz, 1H), 1.92 (dd, J = 5.5, 14.6 Hz, 1H), 1.41 (s, 3H), 0.95 (t, J = 8.0 Hz, 9 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.63-0.54 (m, 12H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 176.3, 145.7, 113.6, 84.7, 83.5, 62.9, 57.4, 56.4, 49.9, 44.8, 23.6, 7.1 (3C), 6.8 (3C), 6.6 (3C), 4.5 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{23}\text{H}_{42}\text{O}_4\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 461.2519, found: 461.2517. IR (cm^{-1}): 2954, 2876, 1773, 1458, 1239, 1146, 1107, 991, 805, 742. $[\alpha]_{\text{D}}^{24}$: -12.7 (CHCl_3 , c = 1.5). R_f: (Hex/EtOAc 10/1) 0.54.

The TES protected diol (18 mg, 0.04 mmol) was subjected to the same Swern-oxidation procedure as for **59**. Purification by flash chromatography (SiO_2 , Hex/EtOAc 3/1) furnished 11 mg (83%) of aldehyde **81** as amorphous white solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 9.83 (s, 1H), 5.44 (t, J = 2.5 Hz, 1H), 5.30 (t, J = 2.3 Hz, 1H), 5.26 (dd, J = 5.7, 8.0 Hz, 1H), 3.80 (dd, J = 6.2, 8.1 Hz, 1H), 3.25-3.21 (m, 1H), 2.52 (ddd, J = 1.8, 7.8, 14.8 Hz, 1H), 1.96 (dd, J = 5.6, 14.8 Hz, 1H), 1.43 (s, 3H), 0.93 (t, J = 7.9 Hz, 9 H), 0.61 (q, J = 7.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 192.5, 171.8, 142.7, 116.2, 84.8, 84.2, 63.6, 57.8, 49.3, 42.7, 7.1 (3C), 23.1, 6.6 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{17}\text{H}_{26}\text{O}_4\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 345.1498, found: 345.1490. IR (cm^{-1}): 2931, 2856, 1768, 1721, 1253, 1145, 1047, 987, 836, 775. $[\alpha]_{\text{D}}^{22}$: -87.6 (CHCl_3 , c = 0.7). R_f: (Hex/EtOAc 3/1) 0.28.

Cage-shaped cyclobutane 82: To a solution of **76** (48 mg, 0.09 mmol) in THF (700 μL) was dropwise added $t\text{BuLi}$ (120 μL , 1.7 M in THF, 0.20 mmol) at -78 °C. After 30 min a solution of crude aldehyde **81** (30 mg, 0.09 mmol) in THF (700 μL) was added within 5 min. The resulting mixture was allowed to warm to 0 °C within 3 h. Sat. aq. NH_4Cl (5 mL) and diethyl ether (5 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with water (5 mL) and sat. aq. NaCl (5 mL), dried with MgSO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2 , Hex/EtOAc 6/1) provided **82** with a dr of 4:1 (8 mg, 0.01 mmol, 12%) as colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 5.39 (dd, J = 2.7, 1.2 Hz, 1H), 5.20 (dd, J = 1.9, 1.4 Hz, 1H), 5.17 (td, J = 8.1, 5.6 Hz, 1H), 4.69 (s, 1H), 4.13 (d, J = 4.5 Hz, 1H), 4.05 (dt, J = 8.8, 5.7 Hz, 1H), 3.98 (dt, J = 9.8, 2.9 Hz, 1H), 3.83 (d, J = 2.4 Hz, 1H), 3.74 (dd, J = 10.3, 5.7 Hz, 1H), 3.64 (dd, J = 10.3, 5.8 Hz, 1H), 3.32 (dd, J = 8.2, 6.2 Hz, 1H), 3.31 (s, 3H), 3.12-3.09 (m, 1H), 2.45 (ddd, J = 14.6, 7.9, 1.7 Hz, 1H), 2.39-2.32 (m, 1H), 1.94 (dd, J = 14.6, 5.4 Hz, 1H), 1.79-1.67 (m, 2H), 1.42 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.96 (t, J = 8.0 Hz, 9H), 0.93 (t, J = 7.7 Hz, 9H), 0.63 (q, J = 8.0 Hz, 12H), 0.57 (q, J = 8.8 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 177.6, 144.3, 114.9, 109.1, 84.6, 84.1, 83.8, 77.6, 70.5, 67.0, 58.0, 57.8, 54.6, 49.6, 44.8, 41.7, 28.2, 23.3, 7.1 (3C), 6.93 (3C), 6.88 (3C), 6.6 (3C), 5.1 (3C), 4.4 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{36}\text{H}_{66}\text{O}_5\text{Si}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 735.4125, found 735.4125. IR (cm^{-1}): 2954, 2876, 1767, 1460, 1376, 1300, 1240, 1104, 990, 906. $[\alpha]_{\text{D}}^{20}$: -38.7, (CHCl_3 , c = 0.55). R_f: (Hex/EtOAc 4/1) 0.42.

(5S)-5-((S)-2-Methyl-2-((triethylsilyloxy)penta-3,4-dien-1-yl)-3-(phenylselenanyl)dihydrofuran-2(3H)-one (83):

Alcohol **37** was subjected to the same procedure as for **32** using TESOTf for the protection instead of TMSOTf. Protection: Allenic alcohol (5.4 g, 29.6 mmol), 2,6-lutidine (10 mL, 88.9 mmol), TESOTf (10 mL, 44.5 mmol), CH_2Cl_2 (150 mL). TES-protected allenic alcohol (8.2 g, 27.6 mmol, 93%). ^1H NMR (CDCl_3 , 400 MHz): δ = 5.26 (t, J = 6.6 Hz, 1H), 4.83 (d, J = 0.6 Hz, 1H), 4.82 (br s, 1H), 4.80-4.74 (m, 1H), 2.51 (br d, J = 10.1 Hz, 1H), 2.49 (d, J = 9.8 Hz, 1H), 2.39-2.31 (m, 1H), 2.00-1.85 (m, 3H), 1.40 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 206.4, 177.4, 99.9, 78.1, 77.9, 72.4, 49.7, 29.9, 29.1, 27.7, 7.1 (3C), 6.6 (3C). HRMS (ESI) (m/z): calculated for $\text{C}_{16}\text{H}_{28}\text{O}_3\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$ 319.1705, found 319.1708. IR (cm^{-1}): 2953, 2876, 1957, 1777, 1459, 1379, 1155, 1110, 1003, 917. $[\alpha]_{\text{D}}^{20}$: -36.1, (CHCl_3 , c = 1.0). R_f: (Hex/EtOAc 2/1) 0.21.

The phenylselenyl group was introduced according to the procedure for **32**. TES-protected allenic alcohol (2.5 g, 8.4 mmol), LiHMDS (8.9 mL, 1.0 M in toluene, 8.9 mmol), TMSCl (1.2 mL, 9.3 mmol), PhSeCl (1.9 g, 9.7 mmol). Phenylseleno lactone **83** (3.31 g, 7.3 mmol, 87%) with a dr of 1:1 as pale yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 7.69-7.65 (m, 4H), 7.40-7.29 (m, 6H), 5.21 (dt, J = 8.8, 6.7 Hz, 2H), 4.82-4.80 (m, 4H), 4.72-4.62 (m, 2H), 4.02 (dd, J = 10.2, 9.1 Hz, 1H), 3.93 (dd, J = 6.3, 4.0 Hz, 1H), 2.75 (ddd, J = 13.6, 9.1, 6.4 Hz, 1H), 2.39-2.36 (m, 2H), 2.06-1.93 (m, 2H), 1.87-1.79 (m, 2H), 1.74-1.69 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.91 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.5 Hz, 6H), 0.55 (q, J = 7.6 Hz, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 206.3, 136.0, 135.8, 129.5, 129.5, 129.2, 128.9, 127.3, 127.1, 99.8, 78.0, 77.2, 76.8, 76.5, 72.4, 72.3, 49.6, 49.3, 38.5, 37.9, 37.3, 27.6, 7.18 (3C), 7.15 (3C), 6.62 (3CH), 6.59 (3CH). HRMS (ESI) (m/z): calculated for $\text{C}_{22}\text{H}_{32}\text{O}_3\text{SeSiNa}$ [$\text{M}+\text{Na}$] $^+$ 475.1184, found 475.1190. IR (cm^{-1}): 2954, 2875, 1956, 1770, 1458, 1414,

1354, 1180, 1112, 1003. $[\alpha]_D^{20}$: -23.7, (CHCl₃, c = 1.0). R_f: (Hex/EtOAc 6/1) 0.36.

Butenolide 84: Phenylseleno lactone **83** (842 mg, 1.86 mmol) was coupled with aldehyde **77** (820 mg, 1.96 mmol) according to the procedure for **46**. A mixture of four diastereomers (1.63 g) was obtained as colorless oil which was used without further purification in the next reaction. The oxidative elimination of the phenylselenide was carried out according to the procedure for **22**. A mixture of four diastereomers (1.63 g) gave the desired butenolide **84** (1.1 g, 1.54 mmol, 83% over 2 steps) with a dr of 3:1 as colorless gum which was used as such in the next reaction. ¹H NMR (CDCl₃, 400 MHz): δ = 7.30 (t, *J* = 1.5 Hz, 1H), 7.29 (t, *J* = 1.5 Hz, 3H), 5.28-5.23 (m, 8H), 4.84-4.83 (m, 8H), 4.68-4.66 (m, 4H), 4.52-4.46 (m, 4H), 4.16 (d, *J* = 4.6 Hz, 3H), 4.12-4.07 (m, 4H), 3.90 (d, *J* = 4.3 Hz, 3H), 3.81-3.76 (m, 4H), 3.66-3.61 (m, 4H), 3.53 (d, *J* = 5.1 Hz, 1H), 3.31 (s, 9H), 3.30 (s, 3H), 2.39-2.28 (m, 4H), 2.23-2.17 (m, 3H), 1.99-1.85 (m, 6H), 1.83-1.75 (m, 4H), 1.67-1.60 (m, 4H), 1.46 (br s, 12H), 0.99-0.93 (m, 108H), 0.67-0.58 (m, 72H). ¹³C NMR (CDCl₃, 100 MHz): δ = 206.42, 206.41, 172.7, 172.6, 150.1, 150.0, 136.2, 136.1, 109.2, 109.0, 99.7, 83.8, 83.7, 78.94, 78.87, 78.7, 78.17, 78.15, 77.2, 72.39, 72.37, 66.8, 66.5, 66.4, 66.0, 54.7, 54.6, 47.4, 47.2, 42.5, 41.5, 32.5, 32.5, 27.9, 27.8, 7.1, 6.9, 6.8, 6.6, 5.0, 4.4, 4.3. HRMS (ESI) (*m/z*): calculated for C₃₆H₆₈O₈Si₃Na [M+Na]⁺ 735.4120, found 735.4128. R_f: (Hex/EtOAc 6/1) 0.30.

Cage-shaped cyclobutanes 82 and 85: A diastereomeric mixture of **84** (153 mg, 0.21 mmol) was treated with UV-C light according to the procedure for **47/48** giving **82** (78 mg, 0.11 mmol) and **85** (38 mg, 0.05 mmol) as colorless gums. For analytic data of **82** see above. Analytic data for **85**: ¹H NMR (CDCl₃, 400 MHz): δ = 5.26 (dd, *J* = 2.7, 1.3 Hz, 1H), 5.20 (td, *J* = 8.0, 5.3 Hz, 1H), 5.14 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.66 (s, 1H), 4.18-4.12 (m, 2H), 4.02-3.96 (m, 1H), 3.78 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.59 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.54-3.49 (m, 1H), 3.45 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.31 (s, 3H), 3.22 (d, *J* = 5.6 Hz, 1H), 3.09-3.06 (m, 1H), 2.48-2.38 (m, 2H), 1.95-1.87 (m, 1H), 1.71-1.61 (m, 1H), 1.54 (s, 3H), 0.99-0.91 (m, 27H), 0.68-0.53 (m, 18H). ¹³C NMR (CDCl₃, 100 MHz): δ = 176.8, 145.5, 114.4, 109.3, 84.7, 83.9, 83.7, 79.1, 69.9, 66.9, 59.6, 58.0, 54.6, 49.8, 43.4, 41.9, 29.2, 23.5, 7.1 (3C), 6.92 (3C), 6.86 (3C), 6.6 (3C), 5.0 (3C), 4.3 (3C). HRMS (ESI) (*m/z*): calculated for C₃₆H₆₈O₈Si₃Na [M+Na]⁺ 735.4120, found 735.4123. IR (cm⁻¹): 2955, 2912, 2877, 1769, 1459, 1414, 1240, 1107, 1042, 1006. $[\alpha]_D^{20}$ -107.1, (CHCl₃, c = 0.2). R_f: (Hex/EtOAc 4/1) 0.35.

Formate 89: The acylation of **82** (246 mg, 0.34 mmol) was performed according to the procedure for **57** giving the desired acetate (260 mg, quant) as colorless oil. For the preparation of aldehyde **59** and for analytic data see above.

To a suspension of aldehyde **59** (207 mg, 0.3 mmol) and NaHCO₃ (82 mg, 0.1 mmol) in CH₂Cl₂ (3.5 mL) was added mCPBA (111 mg, 0.7 mmol), which was purified by extraction of a solution in diethyl ether with pH 7.5 buffer prior to use, in one portion under vigorous stirring at 0 °C. After 2 h the reaction was quenched by the addition of dimethyl sulfide (300 μ L, 4 mmol). After additional 30 min diethyl ether (10 mL) and sat. aq. NH₄Cl (10 mL) were added at 0 °C. The aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (15 mL), water (15 mL) and sat. aq. NaCl (15 mL). After drying with MgSO₄ and filtration, the volatiles were removed under reduced pressure. Purification of the remaining residue by flash column chromatography (SiO₂, Hex/EtOAc 8/1) gave desired formate **89** (169 mg, 79%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 8.11 (s, 1H), 6.14 (d, *J* = 4.6 Hz, 1H), 5.49 (dd, *J* = 10.5, 3.1 Hz, 1H), 5.33 (dd, *J* = 2.6, 1.8 Hz, 1H), 5.21 (dd, *J* = 2.1, 1.8 Hz, 1H), 5.17 (dt, *J* = 8.0, 5.4 Hz, 1H), 4.79 (s, 1H), 4.26 (dd, *J* = 5.0, 0.3 Hz, 1H), 3.40 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.35 (s, 3H), 3.11-3.09 (m, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.7 Hz, 1H), 2.39-2.33 (m, 1H), 2.08 (s, 3H), 2.04-1.94 (m, 2H), 1.90 (dd, *J* = 14.6, 5.3 Hz, 1H), 1.41 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.3, 170.7, 160.7, 144.1, 115.9, 110.9, 102.4, 84.5, 83.2, 76.2, 71.2, 57.8, 57.4, 55.6, 49.6, 44.9, 44.7, 25.0, 23.4, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 4.9 (3C). HRMS (ESI) (*m/z*): calculated for C₃₂H₅₄O₁₀Si₂Na [M+Na]⁺ 677.3153, found 677.3136. IR (cm⁻¹): 2955, 2877, 1769, 1740, 1227, 1152, 1111, 1039, 1017, 990. $[\alpha]_D^{25}$ = -9.3, (CHCl₃, c = 0.8). R_f: (Hex/EtOAc 3/1) 0.55.

Aldehyde 60: Secondary alcohol **85** (284 mg, 0.42 mmol) was subjected to the identical acylation procedure as **57** (see above) giving acetate **58** (300 mg, quant) as colorless oil (for analytical data see there). For the preparation of aldehyde **60** and for analytical data see there.

Vinyl bromide 86: To a slightly turbid mixture of formate **89** (186 mg, 0.28 mmol) and bromoallylsilane **90** (112 μ L, 0.65 mmol) in CH₂Cl₂ (5.6 mL) was dropwise added SnCl₄ (454 μ L, 0.45 mmol) via syringe at -78 °C. The reaction was stirred till TLC-analysis (Hex/EtOAc 6/1) indicated full consumption of the starting aldehyde. Thereafter, a mixture of MeOH and sat. aq. NaHCO₃ 2/1 (6 mL) and diethyl ether (6 mL) were sequentially added. The resulting heterogenic mixture was warmed to room temperature and water was added till all solids were dissolved. The resulting clear aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with Na/K tartrate (15 mL), water (15 mL) and sat. aq. NaCl (15 mL). After drying with MgSO₄ the solids were removed by filtration and the filtrate was concentrated under reduced pressure giving a colorless oil. The residue was taken up in a minimum amount of Hex/EtOAc 6/1 and purified by filtration over a short pad of silica (Hex/EtOAc, 6/1) yielding desired vinyl bromide **86** (194 mg, 94%) after removal of the volatiles as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.64 (s, 1H), 5.52 (dd, *J* = 11.5, 2.7 Hz, 1H), 5.50 (s, 1H), 5.33 (dd, *J* = 2.5, 1.8 Hz, 1H), 5.21 (dd, *J* = 1.9, 1.8 Hz, 1H), 5.17 (dt, *J* = 8.0, 5.4 Hz, 1H), 4.72 (s, 1H), 4.40 (ddd, *J* = 10.3, 8.5, 2.6 Hz, 1H), 4.07 (d, *J* = 4.2 Hz, 1H), 3.39 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.31 (s, 3H), 3.12-3.09 (m, 1H), 2.79 (dd, *J* = 14.6, 10.5 Hz, 1H), 2.48-2.36 (m, 3H), 2.11 (s, 3H), 1.90 (dd, *J* = 14.8, 5.3 Hz, 1H), 1.89-1.77 (m, 2H), 1.41 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.66 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.4, 170.7, 144.2, 131.8, 118.7, 115.8, 108.5, 84.4, 83.2, 77.9, 77.1, 71.5, 57.7, 57.3, 55.0, 49.6, 45.5, 44.8, 40.0, 23.8, 23.4, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 4.9 (3C). HRMS (ESI) (*m/z*): calculated for C₃₆H₆₄BrN₂O₈Si₂ [M+H₃CCN+NH₄]⁺ 789.3364, found 789.3349. IR (cm⁻¹): 2954, 2877, 1770, 1747, 1459, 1372, 1226, 1151, 1049, 990. $[\alpha]_D^{25}$: -50.1, (CHCl₃, c = 1.5). R_f: (Hex/EtOAc 3/1) 0.55.

Macrocycle 91: To a solution of vinyl bromide **86** (14 mg, 0.02 mmol) in freshly degassed toluene (0.8 mL) were added Pd(OAc)₂ (0.5 mg, 0.002 mmol), triphenylphosphine (1 mg, 0.004 mmol), Ag₂CO₃ (16 mg, 0.058 mmol) and crushed 4 Å molecular sieve (100 mg). After stirring at 80 °C for 3 days the reaction mixture was cooled to room temperature at which diethyl ether (5 mL) and water (5 mL) were added. The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with water (5 mL) and sat. aq. NaCl (5 mL) followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue and mass analysis of the collected fractions indicated the formation of desired macrocycle **91**. HRMS (ESI) (*m/z*): calculated for C₃₆H₆₃N₂O₈Si₂ [M+CH₃CN+NH₄]⁺ 707.4117, found 707.4108.

Macrocycle 92: A suspension of vinyl bromide **86** (20 mg, 0.027 mmol), NaOAc (11 mg, 0.13 mmol), Bu₄NCl (15 mg, 0.053 mmol) and crushed 4 Å molecular sieve (150 mg) in freshly degassed DMF (2.7 mL) was added Pd(OAc)₂ (0.6 mg, 0.003 mmol) as a solid at room temperature. The flask was sealed and immediately heated to 85 °C in an oil bath under vigorous stirring. After 1.5 h the starting material was consumed. The reaction mixture was cooled to room temperature followed by the addition of diethyl ether (5 mL) and water (5 mL). The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with water (5 mL) and sat. aq. NaCl (5 mL) followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue resulted in isolation of carbo-oxygenation product **92** (10 mg, 55%) and vinyl nitrile **93** (4 mg, 22%). Analytic data for **92**: ¹H NMR (CDCl₃, 600 MHz): δ = 5.50 (dd, *J* = 11.3, 2.6 Hz, 1H), 5.33 (dd, *J* = 2.7, 1.8 Hz, 1H), 5.21 (t, *J* = 1.92 Hz, 1H), 5.18 (dt, *J* = 5.4, 8.0 Hz, 1H), 4.83 (s, 2H), 4.73 (s, 1H), 4.25 (ddd, *J* = 10.8, 8.3, 2.7 Hz, 1H), 4.09 (d, *J* = 4.3 Hz, 1H), 3.40 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.31 (s, 3H), 3.11-3.09 (m, 1H), 2.55 (dd, *J* = 15.1, 10.8 Hz, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.7 Hz, 1H), 2.36-2.34 (m, 1H), 2.34-2.32 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 1.90 (dd, *J* = 14.6, 5.4 Hz, 1H), 1.88-1.79 (m, 2H), 1.41 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.67 (q, *J* = 8.0 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 150 MHz): δ = 174.4, 170.6, 169.3, 154.0, 144.2, 115.8, 108.8, 103.4, 84.4, 83.2, 77.6, 76.8, 71.4, 57.7, 57.3, 55.1, 49.6, 44.8, 40.1, 37.7, 23.7, 23.4, 21.3, 21.0, 7.2 (3C), 6.9 (3C), 6.6 (3C), 6.4 (3C). HRMS (ESI) (*m/z*): calculated for C₃₆H₆₀NaO₁₀Si₂ [M+H₃CCN+NH₄]⁺ 731.3623, found 731.3628. IR (cm⁻¹): 2955, 2915, 1769,

1371, 1226, 1207, 1101, 1051, 1018, 990. $[\alpha]_D^{15}$ = -50.8, (CHCl₃, c = 0.4). R_f: (Hex/EtOAc 4/1) 0.27.

Vinyl nitrile 93: A round bottomed flask was charged with vinyl bromide **86** (15 mg, 0.021 mmol) in freshly degassed DMF (5.3 mL). Pd(OAc)₂ (2.0 mg, 0.009 mmol), triphenylphosphine (5 mg, 0.021 mmol), K₂CO₃ (28 mg, 0.21 mmol) and crushed 4 Å molecular sieve (100 mg) were added. The reaction was stirred at 125 °C for 3 h and allowed to cool to room temperature at which diethyl ether (10 mL) and water (10 mL) were added. The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with water (10 mL) and sat. aq. NaCl (10 mL) followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue gave vinyl nitrile **93** (7 mg, 50%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.92 (s, 1H), 5.76 (s, 1H), 5.52 (dd, *J* = 11.4, 2.6 Hz, 1H), 5.33 (br s, 1H), 5.22 (s br, 1H), 5.18 (dt, *J* = 5.5, 7.9 Hz, 1H), 4.72 (s, 1H), 4.29 (ddd, *J* = 10.8, 8.6, 2.2 Hz, 1H), 4.08 (d, *J* = 4.1 Hz, 1H), 3.40 (dd, *J* = 7.9, 6.7 Hz, 1H), 3.30 (s, 3H), 3.13-3.10 (m, 1H), 2.58 (dd, *J* = 14.1, 11.2 Hz, 1H), 2.46 (ddd, *J* = 14.8, 7.9, 0.8 Hz, 1H), 2.41-2.37 (m, 1H), 2.34 (br d, *J* = 14.8 Hz, 1H), 2.12 (s, 3H), 1.91 (dd, *J* = 14.3, 5.3 Hz, 1H), 1.88-1.79 (m, 2H), 1.42 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.4, 170.7, 144.2, 132.4, 120.8, 118.9, 115.8, 108.6, 84.5, 83.2, 78.1, 77.0, 71.4, 57.7, 57.3, 55.0, 49.6, 44.8, 40.2, 39.1, 23.7, 23.4, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 4.9 (3C). HRMS (ESI) (*m/z*): calculated for C₃₇H₆₄N₃O₉Si₂ [M+H₃CCN+NH₄]⁺ 734.4226, found 734.4215. IR (cm⁻¹): 2955, 2914, 2877, 2259, 1769, 1747, 1373, 1227, 1152, 1050. $[\alpha]_D^{18}$ = -69.4, (CHCl₃, c = 0.35). R_f: (Hex/EtOAc 4/1) 0.58.

General procedure for the tin mediated allylation; Homoallylic alcohol 97: To a solution of the aldehyde **59** (25 mg, 0.04 mmol) and (Z)-crotylsilane (**94**) (41 μ L, 0.23 mmol) in CH₂Cl₂ (800 μ L) was dropwise added SnCl₄ (120 μ L, 1.0 M in CH₂Cl₂, 0.12 mmol) at -78 °C. The reaction mixture was stirred at his temperature for 4 h. A suspension of sat. aq. NaHCO₃/MeOH 1/2 (3 mL) was rapidly added at -78 °C. The cooling bath was removed and diethyl ether (5 mL) and water (2 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with sat. aq. Na/K tartrate (5 mL) and sat. aq. NaCl (5 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (SiO₂, Hex/EtOAc 8/1) gave homoallylic alcohol **97** (27 mg, 0.039 mmol, 98%) as a mixture of diastereomers, which was used as such in the next reaction. Major diastereomer: ¹H NMR (CDCl₃, 400 MHz): δ = 5.75 (ddd, *J* = 17.2, 10.3, 8.3 Hz, 1H), 5.47 (dt, *J* = 11.7, 2.1 Hz, 1H), 5.34 (dd, *J* = 4.3, 2.3 Hz, 1H), 5.20 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.17 (td, *J* = 8.0, 5.4 Hz, 1H), 5.11 (ddd, *J* = 17.3, 1.8, 1.0 Hz, 1H), 5.04 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.67 (d, *J* = 1.4 Hz, 1H), 4.14 (d, *J* = 4.2 Hz, 1H), 4.02 (t, *J* = 10.2 Hz, 1H), 3.40-3.32 (m, 2H), 3.36 (s, 3H), 3.18-3.09 (m, 2H), 2.48-2.42 (m, 1H), 2.25-2.13 (m, 2H), 2.09 (s, 3H), 1.92-1.87 (m, 2H), 1.75-1.65 (m, 1H), 1.41 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.01-0.92 (m, 18H), 0.73-0.67 (m, 6H), 0.61-0.55 (m, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.3, 170.9, 144.3, 141.2, 116.0, 109.9, 84.4, 84.3, 83.1, 76.1, 73.5, 73.1, 70.9, 57.7, 57.2, 55.6, 49.7, 44.8, 43.1, 38.4, 24.9, 23.4, 21.9, 17.0, 7.2 (3C), 6.9 (3C), 6.6 (3C), 5.0 (3C). HRMS (ESI) (*m/z*): calculated for C₃₆H₆₂O₉Si₂Na [M+Na]⁺ 717.3830, found 717.3833. IR (cm⁻¹): 2958, 2933, 2909, 1775, 1752, 1238, 1147, 1101, 1015, 988. $[\alpha]_D^{20}$ = -43.3, (CHCl₃, c = 0.4). R_f: (Hex/EtOAc 2/1) 0.48.

Homoallylic alcohol 95: Aldehyde **59** (26 mg, 0.04 mmol) and allyltrimethylsilane (26 μ L, 0.16 mmol) were treated with SnCl₄ (81 μ L, 0.08 mmol) according to the general procedure for the tin mediated allylation giving **95** (25 mg, 0.04 mmol, 93%) as a mixture of diastereomers. Major diastereomer: ¹H NMR (CDCl₃, 400 MHz): δ = 5.96-5.82 (m, 1H), 5.50-5.44 (m, 1H), 5.35-5.29 (m, 1H), 5.21-5.20 (m, 1H), 5.19-5.08 (m, 3H), 4.68-4.66 (m, 1H), 4.21-4.15 (m, 1H), 3.89-3.85 (m, 1H), 3.50-3.43 (m, 1H), 3.41-3.27 (m, 4H), 3.10 (br d, *J* = 5.4 Hz, 1H), 2.47-2.29 (m, 3H), 2.27-2.14 (m, 1H), 2.10-1.96 (m, 5H), 1.94-1.87 (m, 2H), 1.41 (br s, 3H), 1.01-0.92 (m, 18H), 0.73-0.67 (m, 6H), 0.61-0.55 (m, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 175.2, 171.0, 144.8, 135.2, 117.2, 115.7, 110.3, 87.1, 84.8, 83.6, 78.2, 71.6 (2C), 58.3, 58.2, 55.9, 49.6, 44.0, 39.6, 39.5, 27.7, 22.9, 20.8, 7.2 (3C), 6.9 (3C), 6.5 (3C), 5.0 (3C). HRMS (ESI) (*m/z*): calculated for C₃₇H₆₇N₂O₉Si₂ [M+CH₃CN+NH₄Cl]⁺ 739.4385, found 739.4388. IR (cm⁻¹): 2962, 2946, 2928, 1781, 1741, 1243, 1178, 1119, 1024, 998. $[\alpha]_D^{20}$ = -11.7, (CHCl₃, c = 0.2). R_f: (Hex/EtOAc 2/1) 0.50.

Homoallylic alcohol 96: Aldehyde **60** (30 mg, 0.05 mmol) and allyltrimethylsilane (26 μ L, 0.16 mmol) were treated with SnCl₄ (71 μ L,

0.07 mmol) according to the general procedure for the tin mediated allylation giving **96** (30 mg, 0.04 mmol, 94%) as a mixture of diastereomers. Major diastereomer: ¹H NMR (CDCl₃, 400 MHz): δ = 5.91 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.45 (dd, *J* = 11.1, 2.1 Hz, 1H), 5.32 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.24 (t, *J* = 1.9 Hz, 1H), 5.21 (td, *J* = 8.0, 5.4 Hz, 1H), 5.14 (ddd, *J* = 17.1, 3.4, 1.4 Hz, 1H), 5.09 (br d, *J* = 10.2 Hz, 1H), 4.69 (s, 1H), 4.13 (d, *J* = 5.5 Hz, 1H), 3.98 (dd, *J* = 6.6, 2.1 Hz, 1H), 3.62-3.56 (m, 1H), 3.43 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.39 (s, 3H), 3.15-3.11 (m, 1H), 2.50 (d, *J* = 8.8 Hz, 1H), 2.45 (ddd, *J* = 14.7, 7.9, 1.7 Hz, 1H), 2.38-2.28 (m, 3H), 2.04 (s, 3H), 2.09-2.01 (m, 1H), 1.92 (dd, *J* = 14.7, 5.4 Hz, 1H), 1.85 (ddd, *J* = 14.8, 8.6, 2.2 Hz, 1H), 1.42 (s, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.7 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.8, 170.4, 144.5, 135.4, 117.2, 115.6, 110.1, 87.3, 84.7, 83.4, 78.5, 71.3 (2C), 58.23, 58.17, 55.7, 49.5, 44.2, 39.6, 39.5, 27.1, 23.3, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 5.0 (3C). HRMS (ESI) (*m/z*): calculated for C₃₇H₆₇N₂O₉Si₂ [M+CH₃CN+NH₄Cl]⁺ 739.4385, found 739.4388. IR (cm⁻¹): 2955, 2935, 2912, 1773, 1748, 1231, 1153, 1105, 1040, 1017. $[\alpha]_D^{20}$ = -44.0, (CHCl₃, c = 0.2). R_f: (Hex/EtOAc 2/1) 0.37.

Homoallylic alcohol 98: Aldehyde **60** (30 mg, 0.05 mmol) and (Z)-crotylsilane (**94**) (26 μ L, 0.16 mmol) were treated with SnCl₄ (71 μ L, 0.07 mmol) according to the general procedure for the tin mediated allylation giving **98** (30 mg, 0.04 mmol, 94%) as a mixture of diastereomers. Major diastereomer: ¹H NMR (CDCl₃, 400 MHz): δ = 5.94-5.88 (1H, s), 5.67 (d, *J* = 11.0 Hz, 1H), 5.35 (br d, *J* = 1.4 Hz, 1H), 5.25-5.19 (m, 2H), 5.15 (br d, *J* = 3.3 Hz, 1H), 5.12 (br s, 1H), 4.67 (br s, 1H), 4.08 (d, *J* = 5.6 Hz, 1H), 3.82 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.43 (t, *J* = 7.3 Hz, 1H), 3.39-3.35 (m, 1H), 3.32 (s, 3H), 3.12 (br d, *J* = 4.1 Hz, 1H), 2.71 (d, *J* = 6.4 Hz, 1H), 2.63 (td, *J* = 10.7, 3.1 Hz, 1H), 2.45 (dd, *J* = 14.7, 7.9 Hz, 1H), 2.28-2.24 (m, 1H), 2.07-2.02 (m, 4H), 1.92 (dd, *J* = 14.7, 5.4 Hz, 1H), 1.87 (dd, *J* = 14.9, 8.6 Hz, 1H), 1.41 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.57 (q, *J* = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 175.0, 171.6, 144.2, 139.2, 116.3, 115.8, 109.7, 85.6, 84.6, 83.4, 78.8, 77.7, 72.1, 58.3, 58.2, 55.2, 49.5, 44.0, 41.7, 40.0, 27.8, 23.3, 21.3, 17.5, 7.1 (3C), 6.9 (3C), 6.6 (3C), 4.9 (3C). HRMS (ESI) (*m/z*): calculated for C₃₆H₆₂O₉Si₂Na [M+Na]⁺ 717.3830, found 717.3836. IR (cm⁻¹): 3490, 2956, 2877, 1774, 1459, 1373, 1236, 1150, 1106, 997. $[\alpha]_D^{24}$ = -35.6, (CHCl₃, c = 0.25). R_f: (Hex/EtOAc 3/1) 0.57.

Dimer 109: To a degassed solution of **97** (42 mg, 0.06 mmol) in toluene (120 mL) at reflux was added catalyst **103** (8mg, 0.01 mmol) as a solid in one portion. After 20 h, air was bubbled through the solution for 15 min to destroy the active catalyst. The volatiles were removed and the residue was subjected to column chromatography, where after, dimer **109** (10 mg, 0.02 mmol, 25%) was isolated as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.58-5.54 (m, 1H), 5.43 (dd, *J* = 11.7, 2.1 Hz, 1H), 5.33 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.20 (t, *J* = 1.8 Hz, 1H), 5.16 (td, *J* = 8.0, 5.4 Hz, 1H), 4.69 (s, 1H), 4.16 (d, *J* = 4.2 Hz, 1H), 3.89 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.77 (t, *J* = 4.7 Hz, 1H), 3.39-3.32 (m, 4H), 3.11-3.08 (m, 1H), 2.57 (d, *J* = 5.1 Hz, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.6 Hz, 1H), 2.09 (s, 3H), 2.04-1.98 (m, 1H), 1.94-1.87 (m, 2H), 1.76-1.70 (m, 1H), 1.66 (br s, 4H), 1.41 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.69 (q, *J* = 7.8 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.2, 170.8, 144.2, 135.2, 122.1, 115.8, 109.7, 85.4, 84.5, 83.0, 78.6, 76.2, 70.9, 57.7, 57.0, 55.3, 49.7, 44.8, 39.6, 25.0, 23.4, 21.0, 13.2, 7.12 (3C), 6.98 (3C), 6.60 (3C), 5.01 (3C). HRMS (ESI) (*m/z*): calculated for C₇₀H₁₂₀O₁₈Si₄Na [M+Na]⁺ 1383.7449, found 1383.7454. IR (cm⁻¹): 2956, 2914, 2877, 2369, 1771, 1746, 1373, 1222, 1151, 1043. $[\alpha]_D^{20}$ = -5.0, (CHCl₃, c = 0.2). R_f: (Hex/EtOAc 3/1) 0.29.

Diene 111: A solution of **96** (32 mg, 0.05 mmol) and 2,6-lutidine (27 μ L, 0.23 mmol) in CH₂Cl₂ (700 μ L) was treated with TMSOTf (27 μ L, 0.15 mmol) at 0 °C. The resulting mixture was stirred for 3 h, sat. aq. NH₄Cl (5 mL) and diethyl ether (5mL) were added. The separated aqueous layer was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with sat. aq. NaCl (5 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO₂, Hex/EtOAc 6/1) gave TMS protected allylic alcohol **111** (27 mg, 0.04 mmol, 76%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 5.87-5.77 (m, 1H), 5.56 (dd, *J* = 11.3, 2.7 Hz, 1H), 5.33 (dd, *J* = 2.6, 1.6 Hz, 1H), 5.22-5.17 (m, 1H), 5.10 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.06-5.03 (m, 1H), 4.64 (s, 1H), 3.94 (d, *J* = 4.0 Hz, 1H), 3.82 (dd, *J* = 8.1, 3.1 Hz, 1H), 3.76-3.72 (m, 1H), 3.43 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.31 (s, 3H), 3.15-3.12 (m, 1H), 2.45 (ddd, *J* = 14.7, 7.9, 1.7 Hz, 1H), 2.40-2.33 (m, 1H), 2.25-2.15 (m, 2H), 2.14-2.07 (m, 1H), 2.04 (s, 3H), 1.92 (dd, *J* = 14.7, 5.5 Hz, 1H), 1.84 (dt, *J* = 14.3, 3.1 Hz, 1H), 1.58 (br d, *J* = 3.1 Hz, 1H), 1.42 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.11 (s, 9H). ¹³C NMR (CDCl₃, 100 MHz): δ = 174.8, 170.1, 144.5, 135.9, 117.1, 115.5, 108.7, 85.5, 84.7, 83.3,

77.4, 73.2, 72.2, 58.23, 58.1, 54.7, 49.4, 44.2, 39.7, 38.1, 24.9, 23.3, 21.2, 7.10 (3C), 6.91 (3C), 6.61 (3C), 5.16 (3C), 0.62 (3C). HRMS (ESI) (m/z): calculated for $C_{38}H_{68}O_9Si_3$ [M+Na]⁺ 775.4069, found 775.4050. IR (cm⁻¹): 2955, 2877, 1775, 1747, 1372, 1229, 1150, 1107, 1041, 993. [α]_D²⁰: -51.8, (CHCl₃, c = 0.8). R_f: (Hex/EtOAc 3/1) 0.56.

(3S,5S)-3-(Methoxymethoxy)-3-methyl-5-(prop-2-yn-1-yloxy)cyclopent-1-ene (115): A solution of alcohol **117** (150 mg, 0.95 mmol) in THF (6 mL) was dropwise added to a suspension of NaH (164 mg, 3.80 mmol) in THF (9 mL) at 0 °C. After 1 h propargyl bromide (310 μ L, 2.80 mmol) was added via syringe and the resulting mixture was warmed to room temperature. After 16 h sat. aq. NH₄Cl (10 mL) was added and the aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with sat. aq. NaCl (10 mL), dried with MgSO₄, filtered and concentrated under reduced pressure. Column chromatography (SiO₂, Hex/EtOAc 3/1) of the residue afforded desired propargyl ether **115** (184 mg, 0.94 mmol, 99%) as colorless oil. ¹H NMR (d⁶-DMSO, 400 MHz): δ = 6.05 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.89 (*J* = 5.6, 1.2 Hz, 1H), 4.72-4.69 (m, 1H), 4.54 (d, *J* = 7.2 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 4.15 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.11 (dd, *J* = 13.7, 2.4 Hz, 1H), 3.39 (t, *J* = 2.4 Hz, 1H), 3.21 (s, 3H), 2.33 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.66 (dd, *J* = 14.1, 3.7 Hz, 1H), 1.36 (s, 3H). ¹³C NMR (d⁶-DMSO, 100 MHz): δ = 139.3, 133.7, 91.2, 86.6, 82.1, 80.8, 76.8, 55.8, 54.4, 43.9, 27.1. HRMS (EI) (m/z): calculated for $C_{10}H_{13}O_3$ [M-CH₃]⁺ 181.0865, found 181.0862. IR (cm⁻¹): 3290, 2930, 1632, 1444, 1361, 1270, 1142, 1095, 1031, 916. [α]_D²⁰: -88.7, (CHCl₃, c = 0.54). R_f: (Hex/EtOAc 3/1) 0.42.

Poly-cycle 119: To a solution of propargyl ether **115** (66 mg, 0.34 mmol) in CH₂Cl₂ (3.5 mL) was added Co₂(CO)₈ (133 mg, 0.37 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirring was continued for 16 h. The volatiles were removed under reduced pressure and the crude residue was used without purification in the next reaction.

To a solution of the crude cobalt complex (12 mg, 0.03 mmol) in THF (0.5 mL) was added TMANO (6 mg, 0.08 mmol) at -21 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The precipitate was removed by filtration through a short pad of Celite which was rinsed with diethyl ether (5 mL). The volatiles were removed and the remaining residue was subjected to column chromatography (SiO₂, Hex/EtOAc 3/1) leading to the isolation of dimer **119** (10 mg, 0.02 mmol, 90%) as colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 7.47 (t, *J* = 1.6 Hz, 1H), 6.03 (dd, *J* = 5.7, 1.9 Hz, 1H), 5.94 (dd, *J* = 5.5, 1.2 Hz, 1H), 4.88-4.83 (m, 1H), 4.72-4.69 (m, 1H), 4.67-4.63 (m, 3H), 4.55 (d, *J* = 7.3 Hz, 1H), 4.19-4.11 (m, 2H), 4.00 (d, *J* = 9.6 Hz, 1H), 3.98 (d, *J* = 9.5 Hz, 1H), 3.50-3.45 (m, 1H), 3.34 (s, 3H), 3.34 (s, 3H), 3.26 (s, 1H), 3.04 (1H, d, *J* = 8.4 Hz, 1H), 2.46 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.41 (ddd, *J* = 14.3, 6.6, 1.5 Hz, 1H), 1.77 (dd, *J* = 14.2, 3.8 Hz, 1H), 1.68 (dd, *J* = 14.3, 5.2 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ = 205.5, 196.1, 158.1, 143.8, 139.9, 133.8, 91.9, 91.4, 90.4, 85.8, 84.2, 77.9, 68.9, 63.04, 62.95, 60.38, 58.0, 55.74, 55.68, 55.1, 46.7, 44.3, 27.2, 20.5. HRMS (ESI) (m/z): calculated for $C_{24}H_{32}O_8Na$ [M+Na]⁺ 471.1995, found 471.2006. IR (cm⁻¹): 2923, 2852, 1747, 1700, 1466, 1366, 1270, 1145, 1081, 1030. [α]_D²²: -75.9, (CHCl₃, c = 0.25). R_f: (Hex/EtOAc 1/1) 0.17.

Supporting Information (see footnote on the first page of this article): Details on the Heck-macrocyclization conditions

Acknowledgments

Financial support from the University of Vienna (doctoral programm, Initiativkolleg Functional Molecules IK I041-N) and from the Austrian Science Fund (FWF, Project No. P22180) is gratefully acknowledged. We thank H. Kählig, L. Brecker, and S. Felsinger for NMR assistance and A. Roller and V. Arion (University of Vienna) for X-ray analysis.

- [1] J. Marrero, A. D. Rodríguez, P. Baran, R. G. Raptis, J. A. Sanchez, E. Ortega-Barria, T. L. Capson, *Org. Lett.* **2004**, 6, 1661-1664.
- [2] J. Marrero, A. D. Rodríguez, P. Baran, R. G. Raptis, *Org. Lett.* **2003**, 5, 2551-2554.
- [3] a) B. Doroh, G. A. Sulikowski, *Org. Lett.* **2006**, 8, 903-906; b) R. Miao, S. G. Gramani, M. J. Lear, *Tetrahedron Lett.* **2009**, 50, 1731-1733; c) K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Angew. Chem. Int. Ed.* **2011**, 50, 5149-5152; d) A. Jana, S. Mondal, Md. F. Hossain, S. Ghosh, *Tetrahedron Lett.* **2012**, 53, 6830-6833; e) M. E. Meyer, J. H. Phillips, E. M. Ferreira, B. M. Stoltz, *Tetrahedron* **2013**, 69, 7627-7635; f) A. P. G. Macabeo, C. W. Lehmann, O. Reiser *Synlett*

- 2012**, 23, 2909-2912; g) A. Saitman, S. D. E. Sullivan, E. A. Theodorakis *Tetrahedron Lett.* **2013**, 54, 1612-1615; h) J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Org. Lett.* **2012**, 14, 2195-2197; i) J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Eur. J. Org. Chem.* **2013**, 4379-4398; j) M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *Org. Lett.* **2013**, 12, 3098-3101.
- [4] a) P. A. Roethle, D. Trauner, *Org. Lett.* **2006**, 8, 345-347; b) P. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, 8, 5901-5904; c) P. A. Roethle, D. Trauner, *Nat. Prod. Rep.* **2008**, 8, 298-317; d) Y. Li, G. Pattenden, *Nat. Prod. Rep.* **2011**, 28, 1269-1310.
- [5] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Eur. J. Org. Chem.* **2013**, following paper.
- [6] a) T. Bach, *Synthesis* **1998**, 683-703; b) For a review on photochemical reactions in total syntheses see T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, 50, 1000-1054.
- [7] a) A. Stephen, K. Hashmi, M. Rudolph *Chem. Soc. Rev.* **2008**, 37, 1766-1775; b) V. Belting, N. Krause, *Org. Biomol. Chem.* **2009**, 7, 1221-1225; c) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, 7, 3925-3927; d) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chemistry Eur. J.* **2006**, 12, 1677-1693; e) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, 43, 2402-2406; f) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, 348, 2271-2296.
- [8] K. Sonogashira, *J. Organomet. Chem.* **2002**, 653, 46-49.
- [9] a) C. R. Schmid, J. D. Bryant, *Org. Synth.* **1995**, 72, 6; b) J. Mann, A. C. Weymouth-Wilson, *Org. Synth.* **1998**, 75, 139; c) W. Felzmann, V. B. Arion, J. L. Mieusset, J. Mulzer, *Org. Lett.* **2006**, 8, 3849-3851.
- [10] a) G. Deguest, L. Bischoff, C. Fruit, F. Marsais, *Org. Lett.* **2007**, 9, 1165-1167; b) K. Maruoka, A. B. Concepcion, N. Murase, M. Oishi, N. Hirayama, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, 115, 3943-3949.
- [11] T. Gaich, H. Weinstabl, J. Mulzer, *Synlett* **2009**, 9, 1357-1366.
- [12] P. A. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jr. Jahngen, A. J. Lovey, W. P. Stephens, *J. Org. Chem.* **1978**, 43, 138-147.
- [13] S. Searles, Y. Li, B. Nassim, M.-T. R. Lopes, P. T. Tran, P. Crabbé, *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.
- [14] a) A. Rosenthal, L. B. Nguyen, *J. Org. Chem.* **1969**, 34, 1029-1034; b) M. Xie, D. A. Berges, M. Robins, *J. Org. Chem.* **1996**, 61, 5178-5179 and references cited therein.
- [15] CCDC-943950 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [16] J.-P. Dulcère, J. Crandall, R. Faure, M. Santelli, V. Agati, M. N. Mihoubi, *J. Org. Chem.* **1993**, 58, 5702-5708.
- [17] For a review see: E. M. Becalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, 107, 5318-5365.
- [18] a) L. E. Overman, *Pure & Appl. Chem.* **1994**, 66, 1423-1430; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, 103, 2945-2963.
- [19] For a review see: K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, 44, 4490-4527.
- [20] U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, 56, 401-404.
- [21] A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, 114, 2321-2336.
- [22] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, 34, 18-29 and references cited therein.
- [23] I. C. Stewart, T. Ung, A. A. Pletnev, J. M. Berlin, R. H. Grubbs, Y. Schrodi, *Org. Lett.* **2007**, 9, 1589-1592.
- [24] K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem. Int. Ed.* **2002**, 41, 4038-4040.
- [25] C. Samojłowicz, M. Bieniek, A. Zarecki, R. Kadyrov, K. Grela, *Chem. Comm.* **2008**, 47, 6282-6284.

- [26] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
- [27] a) I. Khand, G. R. Knox, P. L. Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, 977-981; b) P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855-5860.
- [28] For a review see: A. S. Kende, *Org. React.* **1960**, *11*, 261-316.
- [29] For a review see: H. Meier, K. P. Zeller, *Angew. Chem.* **1975**, *87*, 52-63.
- [30] a) T. T. Curran, D. A. Hay, *Tetrahedron: Asymmetry* **1996**, *7*, 2791-2792; b) A. Roy, S. W. Schneller, *J. Org. Chem.* **2003**, *68*, 9269-9273; c) M. W. Gilbert, A. Galkina, J. Mulzer, *Synlett* **2004**, *14*, 2558-2562.

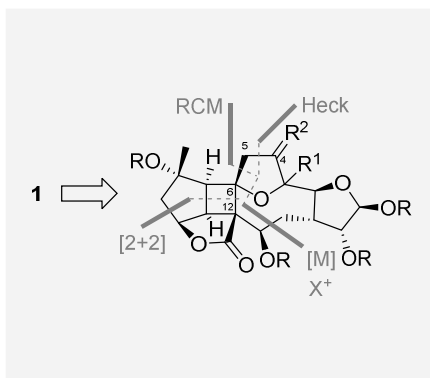
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Entry for the Table of Contents ((Please choose one layout.))

Layout 1:

Total Synthesis

Asymmetric syntheses of various highly functionalized intermediates toward the total synthesis of bielschowskysin (1) are described. In particular a biomimetic [2+2]-photocycloaddition strategy, forming the cyclobutane core, was followed by various macrocyclizations attempts.



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An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy

Keywords: bielschowskysin / terpenoids / total synthesis / cycloaddition / macrocyclization /

An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy

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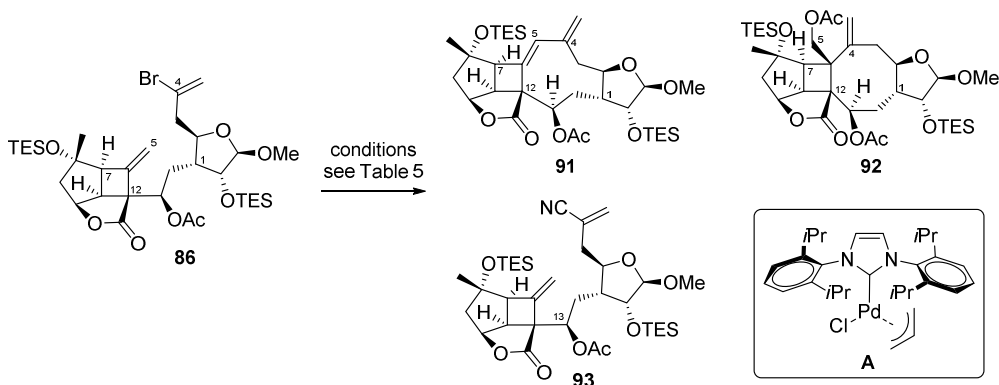


Table 1 Heck macrocyclization attempts.

Entry	Conditions	Product	Yield
1	Pd(PPh ₃) ₄ (0.5 eq.), Ag ₂ CO ₃ (3.0 eq.), CH ₃ CN (0.01 M), 4 Å MS, 90 °C, 24 h	Starting material recovered	-
2	Pd(OAc) ₂ (0.1 eq.), PPh ₃ (0.2 eq.), Ag ₂ CO ₃ (3.0 eq.), 4 Å MS, toluene (0.01 M), 80 °C, 3 d	91	traces
3	Pd(OAc) ₂ (0.5 eq.), DIPEA (15.0 eq.), Bu ₄ NCl (10.0 eq.), 4 Å MS, DMF (0.02 M), 110 °C, 1 h	92	41%
4	Pd(OAc) ₂ (0.5 eq.), PPh ₃ (1.0 eq.), K ₂ CO ₃ (10.0 eq.), 4 Å MS, DMF (0.004 M), 125 °C, 3 h	93	50%
5	[PdCl ₂ (PPh ₃) ₂] (0.1 eq.), Et ₂ NH (0.4 eq.), Et ₃ N (5.0 eq.), DMF (0.004 M), 100 °C, 4 h	93	37%

6	Pd(OAc) ₂ (0.1 eq.), Bu ₄ NCl (2.0 eq.), Ag ₂ CO ₃ (3.0 eq.), 4 Å MS, DMF (0.004 M), 80 °C, 5 d	93	35% ^b
7^a	Pd(OAc) ₂ (0.2 eq.), KOAc (1.5 eq.), K ₂ CO ₃ (5.0 eq.), Bu ₄ NCl (2.5 eq.), CH ₃ CN (0.01 M), 140 °C, 1h	92	16%
8^a	Pd(OAc) ₂ (0.2 eq.), K ₂ CO ₃ (5.0 eq.), Bu ₄ NCl (2.5 eq.), CH ₃ CN (0.01 M), 120 °C, 0.5 h	92	traces
9^a	Pd(PPh ₃) ₄ (0.2 eq.), Et ₃ N (0.1 eq.), CH ₃ CN (0.01 M), 120 °C, 0.5 h	Complex mixture	-
10	Pd(OAc) ₂ (0.3 eq.), PPh ₃ (0.6 eq.), Cs ₂ CO ₃ (3.0 eq.), DMF (0.01 M), 130 °C, 1.5 h	92	traces
11	Pd(OAc) ₂ (0.1 eq.), KOAc (5.0 eq.), Bu ₄ NCl (2.0 eq.), 4 Å MS, DMF (0.01 M), 85 °C, 4 h	92	54%
12	Pd(OAc) ₂ (0.1 eq.), NaOAc (5.0 eq.), Bu ₄ NCl (2.0 eq.), 4 Å MS, DMF (0.01 M), 85 °C, 1.5 h	92, 93	55%, 22%
13	[Pd(dppf) ₂ Cl ₂] (0.4 eq.), Cs ₂ CO ₃ (3.0 eq.), nBu ₄ NCl (3.0 eq.), 4 Å MS, DMF (0.01 M), 90 °C, 2 h	Complex mixture	-
14	[Pd(dppf) ₂ Cl ₂] (0.4 eq.), PBu ₃ (0.8 eq.), Cs ₂ CO ₃ (3.0 eq.), 4 Å MS, DMF (0.01 M), 90 °C, 16 h	Complex mixture	-
15	[Pd(dppf) ₂ Cl ₂] (0.4 eq.), Cs ₂ CO ₃ (3.0 eq.), PPh ₃ (0.8 eq.), 4 Å MS, DMF (0.01 M), 90 °C, 24 h	Complex mixture	-
16	A (0.4 eq.), Cs ₂ CO ₃ (3.0 eq.), toluene (0.01 M), 90 °C, 24 h	Complex mixture	-

a) Microwave assisted heating was used instead of conventional heating in an oil bath, b) based on recovered starting material

General procedure A: “standard” Heck reaction: Freshly degassed solvent was added at room temperature under an argon atmosphere to a mixture of the vinyl bromide, a phosphine ligand, base and crushed 4 Å molecular sieves (where stated). Subsequently, the palladium species was added to the reaction mixture as a solid, the flask was sealed with a plastic stopper and immediately heated in an oil bath under vigorous stirring. The reaction was monitored by TLC-analysis (Hex/EtOAc 3/1). The reaction mixture was allowed to cool to room temperature at which diethyl ether and water were added. The resulting heterogeneous mixture was filtered through a short pad of

Celite. The aqueous phase was separated and extracted with diethyl ether three times. The combined organic phases were washed with water and sat. aq. NaCl followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue gave the depicted product.

General procedure B: phosphine free Heck reaction: Freshly degassed solvent was added at room temperature under an argon atmosphere to a mixture of the vinyl bromide, base and crushed 4 Å molecular sieves (where stated). Freshly degassed solvent was added at room temperature under an argon atmosphere. The palladium species was added to the reaction mixture as a solid and the flask was sealed with a plastic stopper and immediately heated in an oil bath under vigorous stirring. The reaction was monitored by TLC-analysis (Hex/EtOAc 3/1). The reaction mixture was allowed to cool to room temperature at which diethyl ether and water were added. The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether three times. The combined organic phases were washed with water and sat. aq. NaCl followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue gave the depicted product.

General procedure C: Jeffery-Heck reaction: Freshly degassed solvent was added at room temperature under an argon atmosphere to a mixture of the vinyl bromide, base, tetrabutylammonium chloride and crushed 4 Å molecular sieves (where stated). The palladium species was added to the reaction mixture as a solid and the flask was sealed with a plastic stopper and immediately heated in an oil bath under vigorous stirring. The reaction was monitored by TLC-analysis (Hex/EtOAc 3/1). The reaction mixture was allowed to cool to room temperature at which diethyl ether and water were added. The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether three times. The combined organic phases were washed with water and sat. aq. NaCl followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8: 1) of the residue gave the depicted product.

General procedure D: microwave assisted Heck reaction: A microwave tube was charged with the vinyl bromide, base, tetrabutylammonium chloride (where stated) and freshly degassed solvent under an argon atmosphere. The palladium species was added to the reaction mixture as a solid and the tube was sealed with a plastic stopper and immediately heated with a Biotage InitiatorTM Microwave Synthesizer under stirring. The reaction was monitored by TLC-analysis (Hex/EtOAc 3/1). At room temperature diethyl ether and water were added. The resulting heterogeneous mixture was filtered through a short pad of Celite. The aqueous phase was separated and extracted with diethyl ether three times. The combined organic phases were washed with water and sat. aq. NaCl followed by drying with MgSO₄. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO₂, Hex/EtOAc 8:1) of the residue gave the depicted product.

Table 1, Entry 1

Vinyl bromide **99** (20 mg, 0.03 mmol) was subjected to **general procedure B** using Pd(PPh₃)₄ (16 mg, 0.01 mmol) and Ag₂CO₃ (23 mg, 0.8 mmol) in acetonitrile (4.0 mL) as solvent. After 24 h at 90 °C no reaction was observed and starting material was recovered.

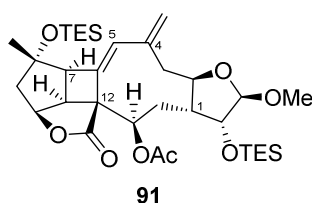
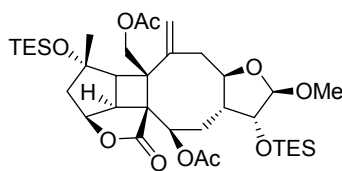


Table 1, Entry 2

Vinyl bromide **86** (14 mg, 0.02 mmol) was subjected to **general procedure A** using Pd(OAc)₂ (0.5 mg, 0.002 mmol), triphenylphosphine (1 mg, 0.004 mmol), Ag₂CO₃ (16 mg, 0.058 mmol) and crushed 4 Å molecular sieve (100 mg) in toluene (0.8 mL) as solvent. After 3 d at 80 °C no starting material was left. Purification of the residue and mass analysis of the collected fractions indicated the formation of desired macrocycle **91**.

HRMS (ESI) (m/z): calculated for C₃₆H₆₃N₂O₈Si₂ [M+H₃CN+NH₄]⁺ 707.4117, found 707.4108.



92

Table 1, Entry 3: tricyclo[8.2.0.0^{2,9}]tridecane ring system 92

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure C** using Pd(OAc)₂ (3.0 mg, 0.014 mmol), DIPEA (70 μ L, 0.41 mmol), Bu₄NCl (78 mg, 0.27 mmol) and crushed 4 Å molecular sieve (70 mg) in DMF (0.8 mL) as solvent. After 1 h at 110 °C no starting material was left. Purification of the residue resulted in isolation of carbo-oxygenation product **92** (8 mg, 41%) as a single diastereomer.

¹H NMR (CDCl₃, 600 MHz): δ = 5.50 (dd, J = 11.3, 2.6 Hz, 1H), 5.33 (dd, J = 2.7, 1.8 Hz, 1H), 5.21 (t, J = 1.92 Hz, 1H), 5.18 (dt, J = 5.4, 8.0 Hz, 1H), 4.83 (s, 2H), 4.73 (s, 1H), 4.25 (ddd, J = 10.8, 8.3, 2.7 Hz, 1H), 4.09 (d, J = 4.3 Hz, 1H), 3.40 (dd, J = 8.2, 6.5 Hz, 1H), 3.31 (s, 3H), 3.11-3.09 (m, 1H), 2.55 (dd, J = 15.1, 10.8 Hz, 1H), 2.45 (ddd, J = 14.7, 7.8, 1.7 Hz, 1H), 2.36-2.34 (m, 1H), 2.34-2.32 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 1.90 (dd, J = 14.6, 5.4 Hz, 1H), 1.88-1.79 (m, 2H), 1.41 (s, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.94 (t, J = 7.9 Hz, 9H), 0.67 (q, J = 8.0 Hz, 6H), 0.58 (q, J = 7.9 Hz, 6H).

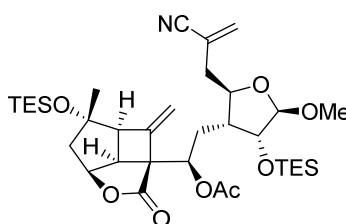
¹³C NMR (CDCl₃, 150 MHz): δ = 174.4, 170.6, 169.3, 154.0, 144.2, 115.8, 108.8, 103.4, 84.4, 83.2, 77.6, 76.8, 71.4, 57.7, 57.3, 55.1, 49.6, 44.8, 40.1, 37.7, 23.7, 23.4, 21.3, 21.0, 7.2 (3C), 6.9 (3C), 6.6 (3C), 6.4 (3C).

HRMS (ESI) (m/z): calculated for C₃₆H₆₀NaO₁₀Si₂ [M+H₃CCN+NH₄]⁺ 731.3623, found 731.3628.

IR (cm⁻¹): $\tilde{\nu}$ = 2955, 2915, 1769, 1371, 1226, 1207, 1101, 1051, 1018, 990.

[α]_D¹⁵ = -50.8, (CHCl₃, c = 0.4).

R_f: (Hex/EtOAc 4/1) 0.27.



93

Table 1 Entry 4: Vinyl nitrile 93

Vinyl bromide **86** (15 mg, 0.021 mmol) was subjected to **general procedure A** using Pd(OAc)₂ (2.0 mg, 0.009 mmol), triphenylphosphine (5 mg, 0.021 mmol), K₂CO₃ (28 mg, 0.21 mmol) and crushed 4 Å molecular sieve (100 mg) in DMF (5.3 mL) as solvent. After 3 h at 125 °C no starting material was left. Purification of the residue gave vinyl nitrile **93** (7 mg, 50%) as colorless oil.

¹H NMR (CDCl₃, 400 MHz): δ = 5.92 (s, 1H), 5.76 (s, 1H), 5.52 (dd, J = 11.4, 2.6 Hz, 1H), 5.33 (br s, 1H), 5.22 (s br, 1H), 5.18 (dt, J = 5.5, 7.9 Hz, 1H), 4.72 (s, 1H), 4.29 (ddd, J = 10.8, 8.6, 2.2 Hz, 1H), 4.08 (d, J = 4.1 Hz, 1H), 3.40 (dd, J = 7.9, 6.7 Hz, 1H), 3.30 (s, 3H), 3.13-3.10 (m, 1H), 2.58 (dd, J = 14.1, 11.2 Hz, 1H), 2.46 (ddd, J = 14.8, 7.9, 0.8 Hz, 1H), 2.41-2.37 (m, 1H), 2.34 (br d, J = 14.8 Hz, 1H), 2.12 (s, 3H), 1.91 (dd, J = 14.3, 5.3 Hz, 1H), 1.88-1.79 (m, 2H), 1.42 (s, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.95 (t, J = 7.8 Hz, 9H), 0.67 (q, J = 7.9 Hz, 6H), 0.58 (q, J = 7.8 Hz, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ = 174.4, 170.7, 144.2, 132.4, 120.8, 118.9, 115.8, 108.6, 84.5, 83.2, 78.1, 77.0, 71.4, 57.7, 57.3, 55.0, 49.6, 44.8, 40.2, 39.1, 23.7, 23.4, 21.1, 7.1 (3C), 6.9 (3C), 6.6 (3C), 4.9 (3C).

HRMS (ESI) (m/z): calculated for C₃₇H₆₄N₃O₈Si₂ [M+H₃CCN+NH₄]⁺ 734.4226, found 734.4215.

IR (cm⁻¹): $\tilde{\nu}$ = 2955, 2914, 2877, 1769, 1747, 1373, 1227, 1152, 1050, 990.

[α]_D¹⁸ = -69.4, (CHCl₃, c = 0.35).

R_f: (Hex/EtOAc 4/1) 0.58.

Table 1 Entry 5: Vinyl nitrile 93

Vinyl bromide **86** (15 mg, 0.021 mmol) was subjected to **general procedure B** using [PdCl₂(PPh₃)₂] (1.5 mg, 0.002 mmol), Et₂NH (1 μ L, 0.008 mmol) and Et₃N (28 mg, 0.21 mmol) in DMF (5.0 mL) as solvent. After 4 h at 100 °C no starting material was left. Purification of the residue gave vinyl nitrile **93** (5 mg, 37%) as colorless oil.

Table 1 Entry 6: Vinyl nitrile 93

Vinyl bromide **86** (14 mg, 0.020 mmol) was subjected to **general procedure C** using Pd(OAc)₂ (0.5 mg, 0.002 mmol), Ag₂CO₃ (16 mg, 0.57 mmol), Bu₄NCl (11 mg, 0.38 mmol) and crushed 4 Å molecular sieve (70 mg) in DMF (5.0 mL) as solvent. After 5 d at 80 °C the reaction was quenched. Purification of the residue resulted in isolation of vinyl cyanide **93** (3 mg, 23%, 35% brsm) as colorless oil.

Table 1, Entry 7: tricyclo[8.2.0.0^{2,9}]tridecane ring system 92

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure D** using Pd(OAc)₂ (1.0 mg, 0.005 mmol), KOAc (4 mg, 0.041 mmol), K₂CO₃ (19 mg, 0.137 mmol) and Bu₄NCl (19 mg, 0.068 mmol) in acetonitrile (2.7 mL) as solvent. After 1 h at 140 °C no starting material was left. Purification of the residue resulted in isolation of carbo-oxygenation product **92** (3 mg, 16%) as colorless oil.

Table 1, Entry 8: tricyclo[8.2.0.0^{2,9}]tridecane ring system 92

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure D** using Pd(OAc)₂ (1.0 mg, 0.005 mmol), K₂CO₃ (19 mg, 0.137 mmol) and Bu₄NCl (19 mg, 0.068 mmol) in acetonitrile (2.7 mL) as solvent. After 30 min at 120 °C no starting material was left. Purification of the residue and mass- as well as NMR-analysis of the collected fractions indicated the formation of carbo-oxygenation product **92**.

Table 1, Entry 9

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure D** using Pd(PPh₃)₄ (6.3 mg, 0.005 mmol), Et₃N (38 µL, 0.273 mmol) in acetonitrile (2.7 mL) as solvent. After 30 min at 120 °C no starting material was left. Purification of the residue did not lead to isolation of any previously described products.

Table 1, Entry 10

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure A** using Pd(OAc)₂ (2 mg, 0.008 mmol), triphenylphosphine (4 mg, 0.016 mmol) and Cs₂CO₃ (27 mg, 0.082 mmol) in DMF (3.0 mL) as solvent. After 1.5 h at 130 °C no starting material was left. Purification of the residue and mass- as well as NMR-analysis of the collected fractions indicated the formation of carbo-oxygenation product **92**.

Table 1, Entry 11: tricyclo[8.2.0.0^{2,9}]tridecane ring system 92

Vinyl bromide **86** (32 mg, 0.044 mmol) was subjected to **general procedure C** using Pd(OAc)₂ (1.0 mg, 0.004 mmol), KOAc (22 mg, 0.22 mmol), Bu₄NCl (25 mg, 0.088 mmol) and crushed 4 Å molecular sieve (150 mg) in DMF (1.8 mL) as solvent. After 4 h at 85 °C no starting material was left. Purification of the residue resulted in isolation of carbo-oxygenation product **92** (16 mg, 54%) as a single diastereomer.

Table 1, Entry 12: tricyclo[8.2.0.0^{2,9}]tridecane ring system 92 and vinyl nitrile 93

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure C** using Pd(OAc)₂ (0.6 mg, 0.003 mmol), NaOAc (11 mg, 0.13 mmol), Bu₄NCl (15 mg, 0.053 mmol) and crushed 4 Å molecular sieve (150 mg) in DMF (2.7 mL) as solvent. After 1.5 h at 85 °C no starting material was left. Purification of the residue resulted in isolation of vinyl nitrile **93** (4 mg, 22%) and carbo-oxygenation product **92** (10 mg, 55%).

Table 1, Entry 13

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure C** using [Pd(dppf)₂Cl₂] (7 mg, 0.011 mmol), Cs₂CO₃ (27 mg, 0.082 mmol), Bu₄NCl (15 mg, 0.053 mmol) and crushed 4 Å molecular sieve (100 mg) in DMF (2.7 mL) as solvent. After 2 h at 90 °C no starting material was left. Purification of the residue lead to a complex mixture of products.

Table 1, Entry 14

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure A** using [Pd(dppf)₂Cl₂] (7 mg, 0.011 mmol), tributylphosphine (5.5 µL, 0.022 mmol), Cs₂CO₃ (27 mg, 0.082 mmol) in DMF (2.7 mL) as solvent. After 16 h at 90 °C no starting material was left. Purification of the residue lead to a complex mixture of products.

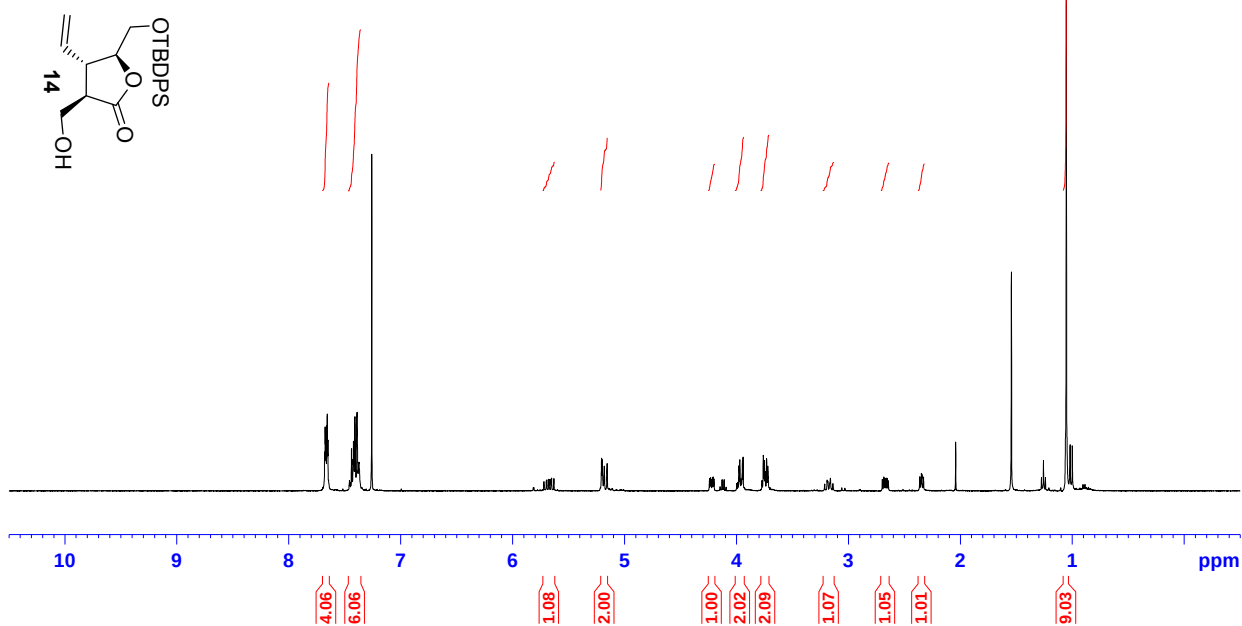
Table 1, Entry 15

Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure A** using [Pd(dppf)₂Cl₂] (7 mg, 0.011 mmol), triphenylphosphine (6 mg, 0.022 mmol), Cs₂CO₃ (27 mg, 0.082 mmol) and crushed 4 Å molecular sieve (100 mg) in DMF (2.7 mL) as solvent. After 24 h at 90 °C no starting material was left. Purification of the residue lead to a complex mixture of products.

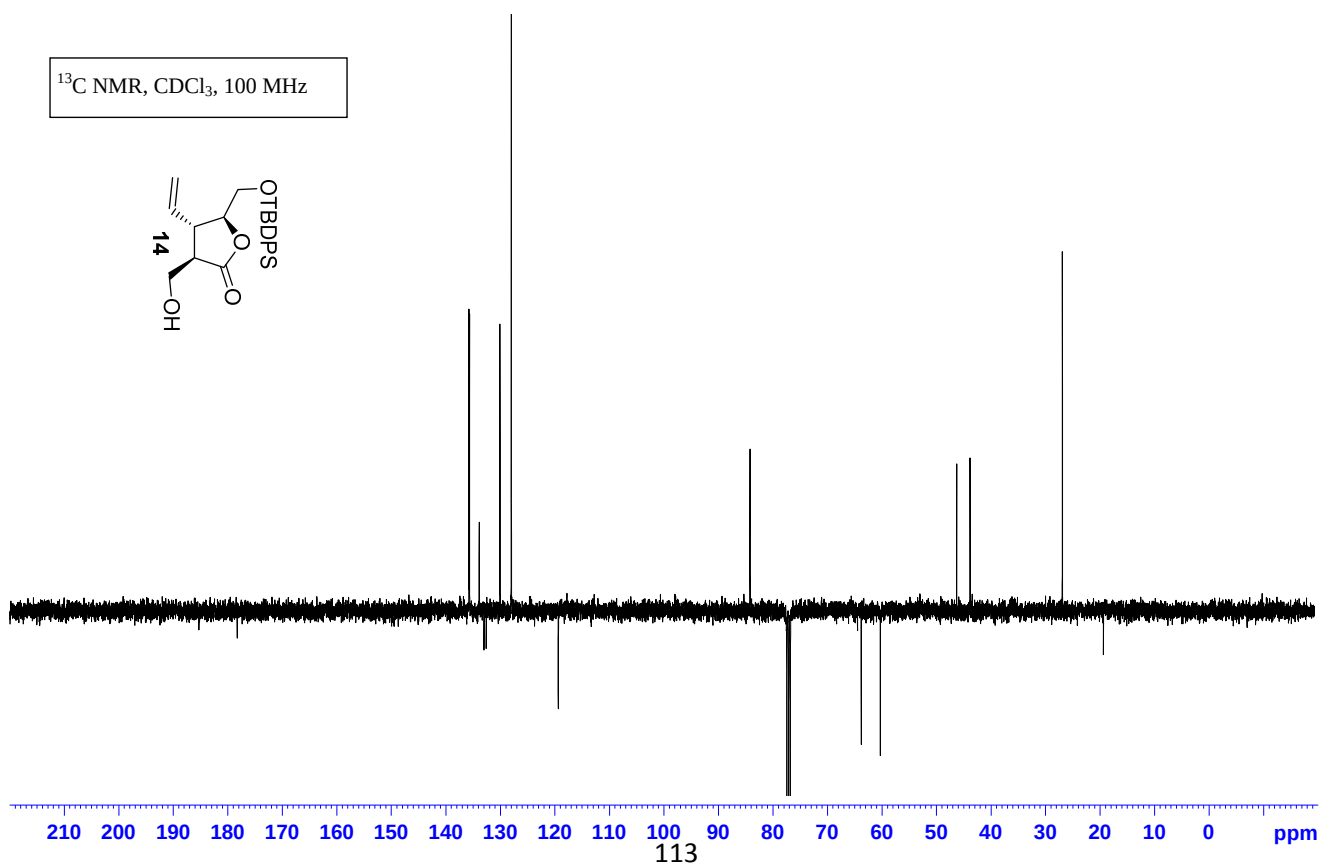
Table 1, Entry 16

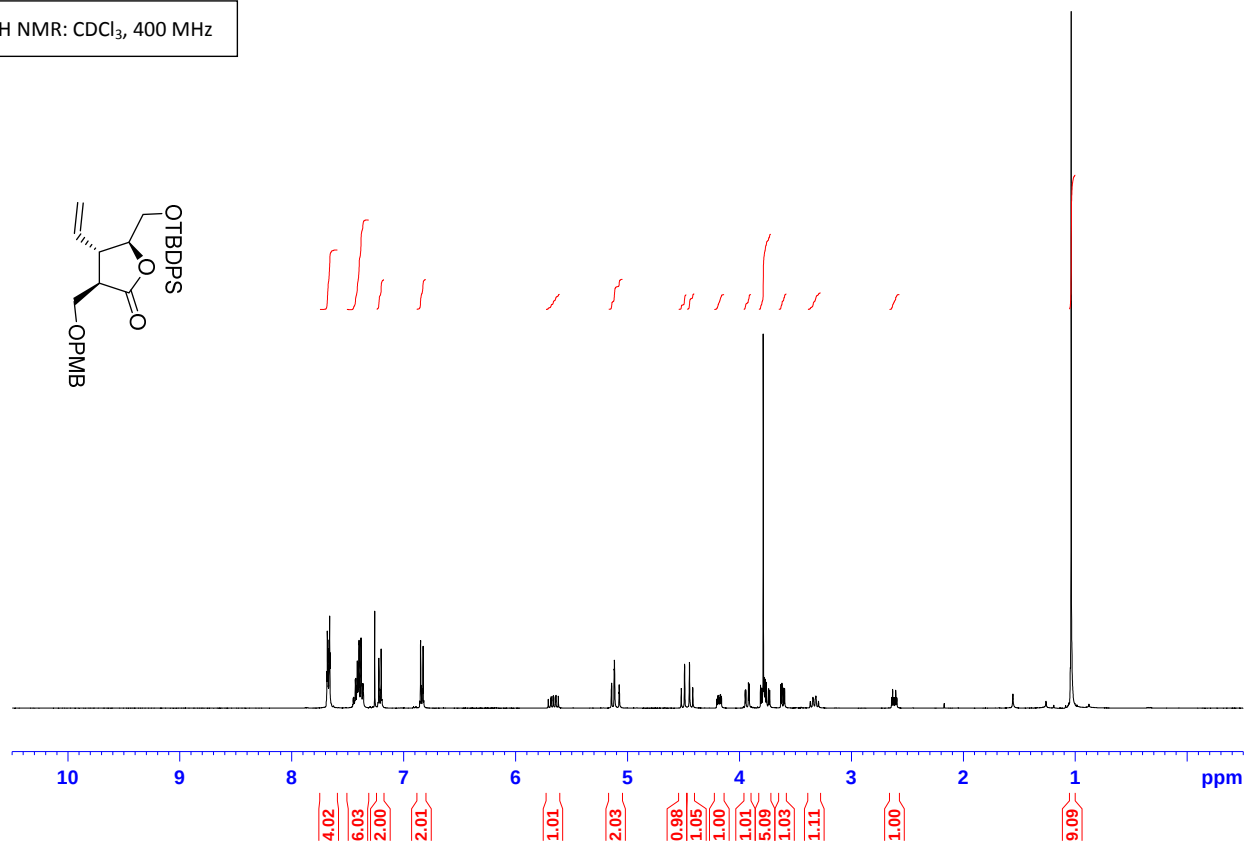
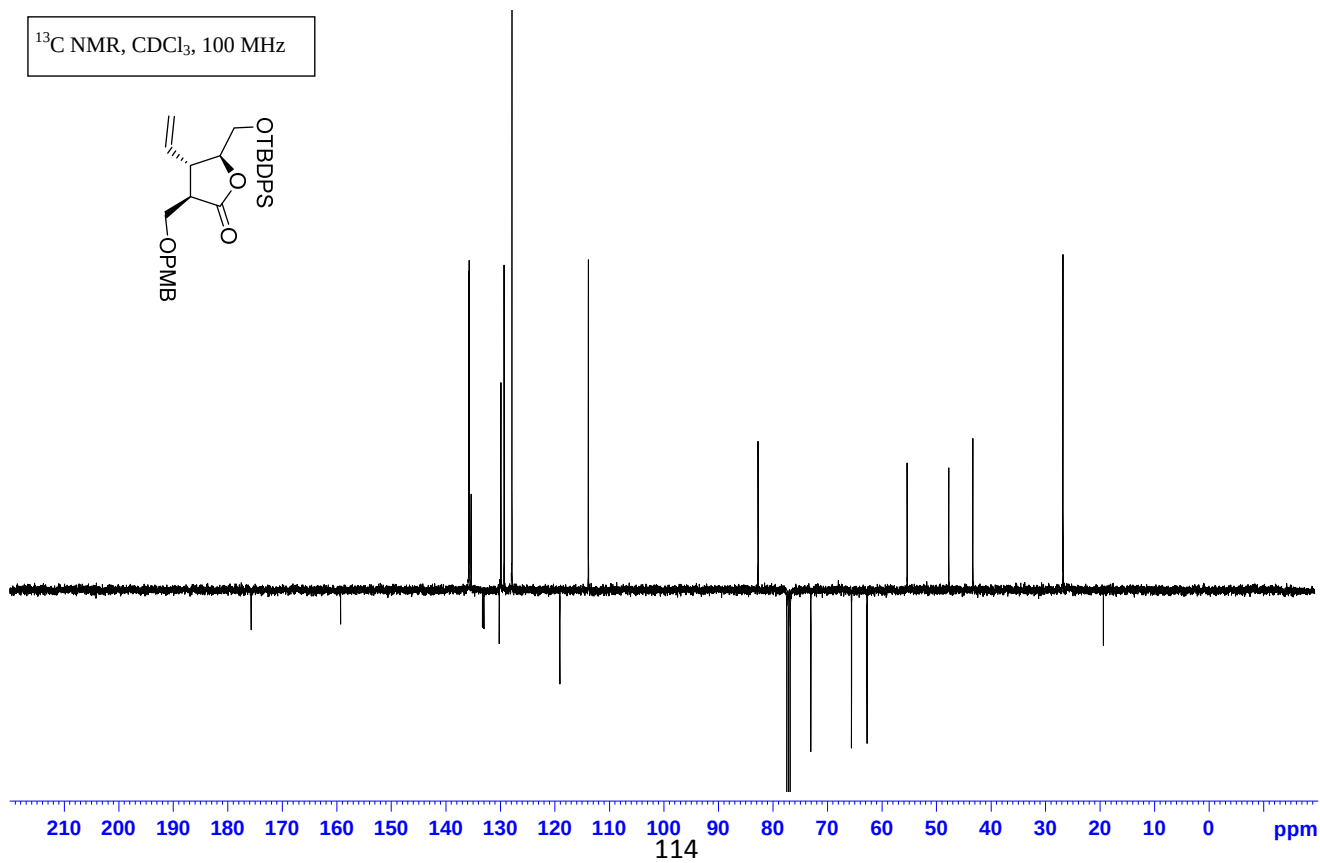
Vinyl bromide **86** (20 mg, 0.027 mmol) was subjected to **general procedure B** using allyl palladium catalyst **A** (6 mg, 0.011 mmol) and Cs₂CO₃ (27 mg, 0.082 mmol) in toluene (2.7 mL) as solvent. After 24 h at 90 °C no starting material was left. Purification of the residue lead to a complex mixture of products.

¹H NMR: CDCl₃, 400 MHz

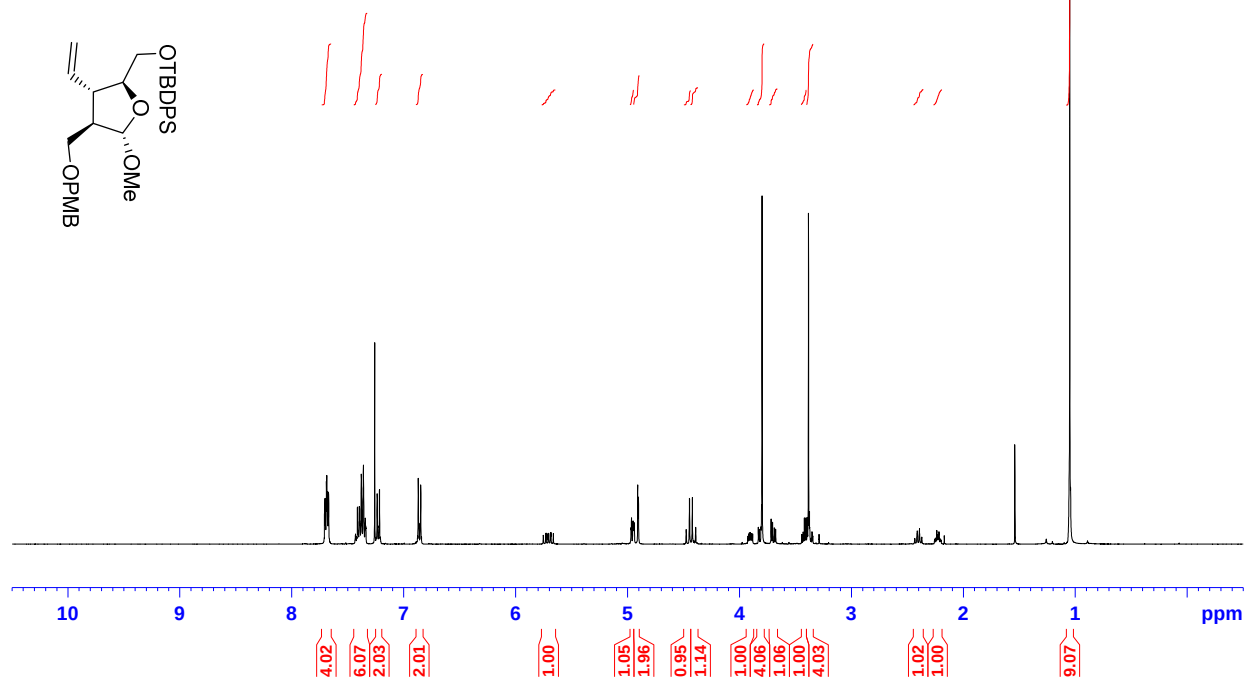


¹³C NMR: CDCl₃, 100 MHz

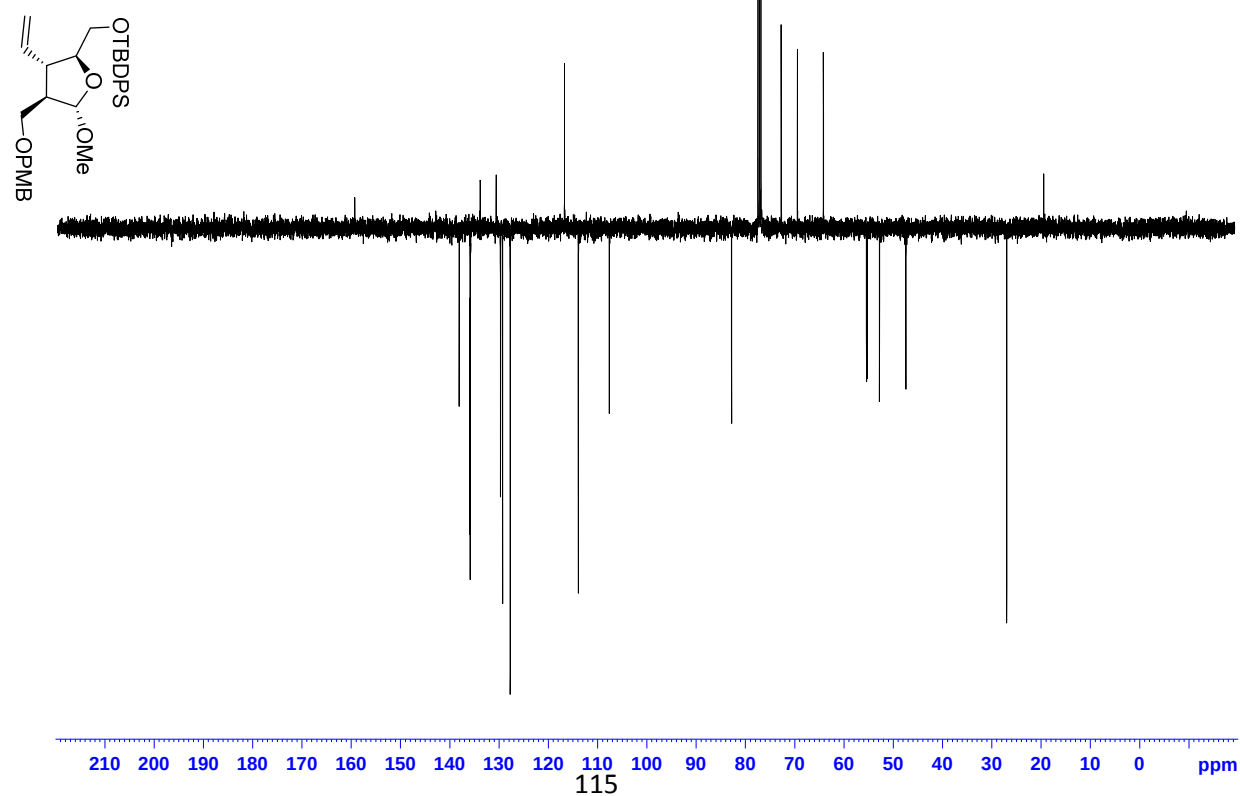


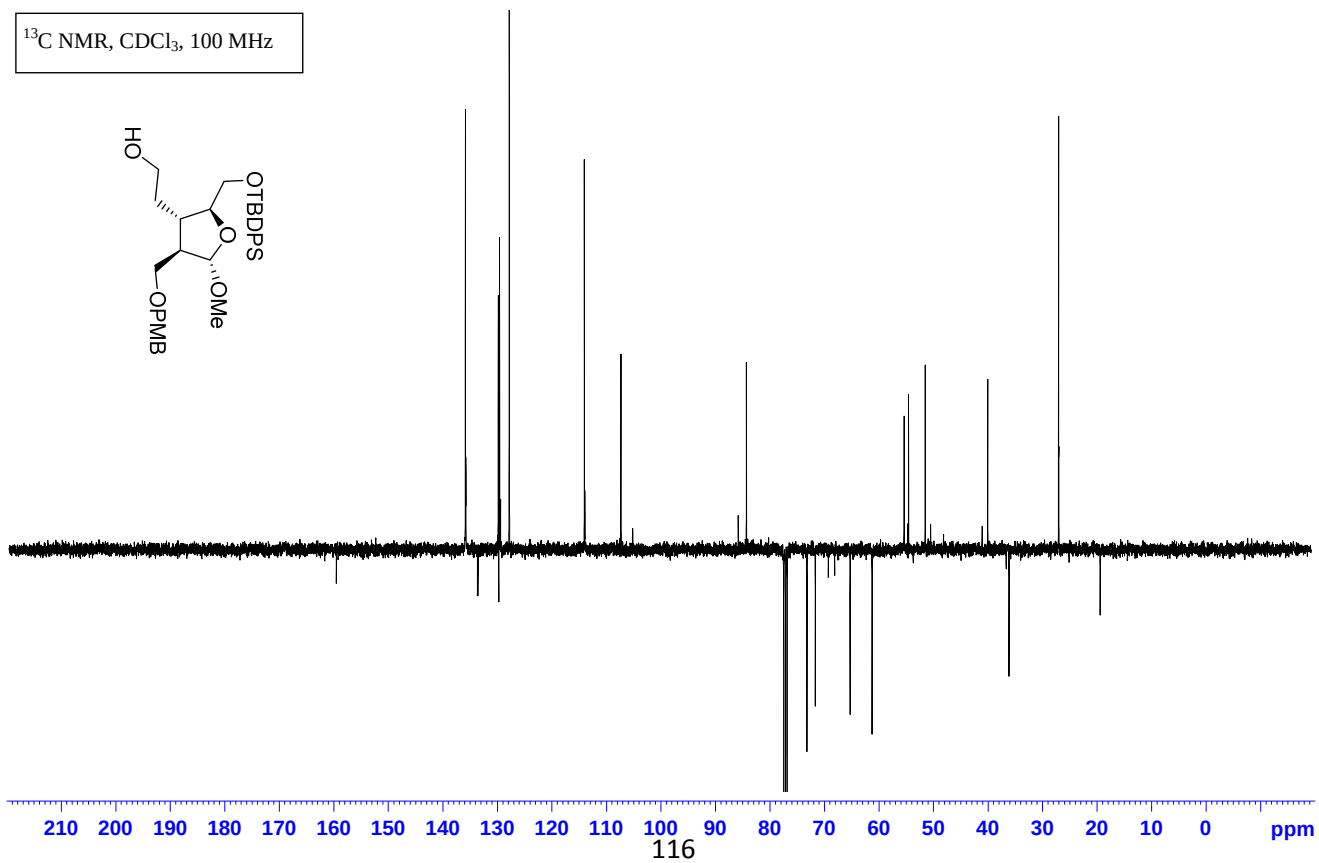
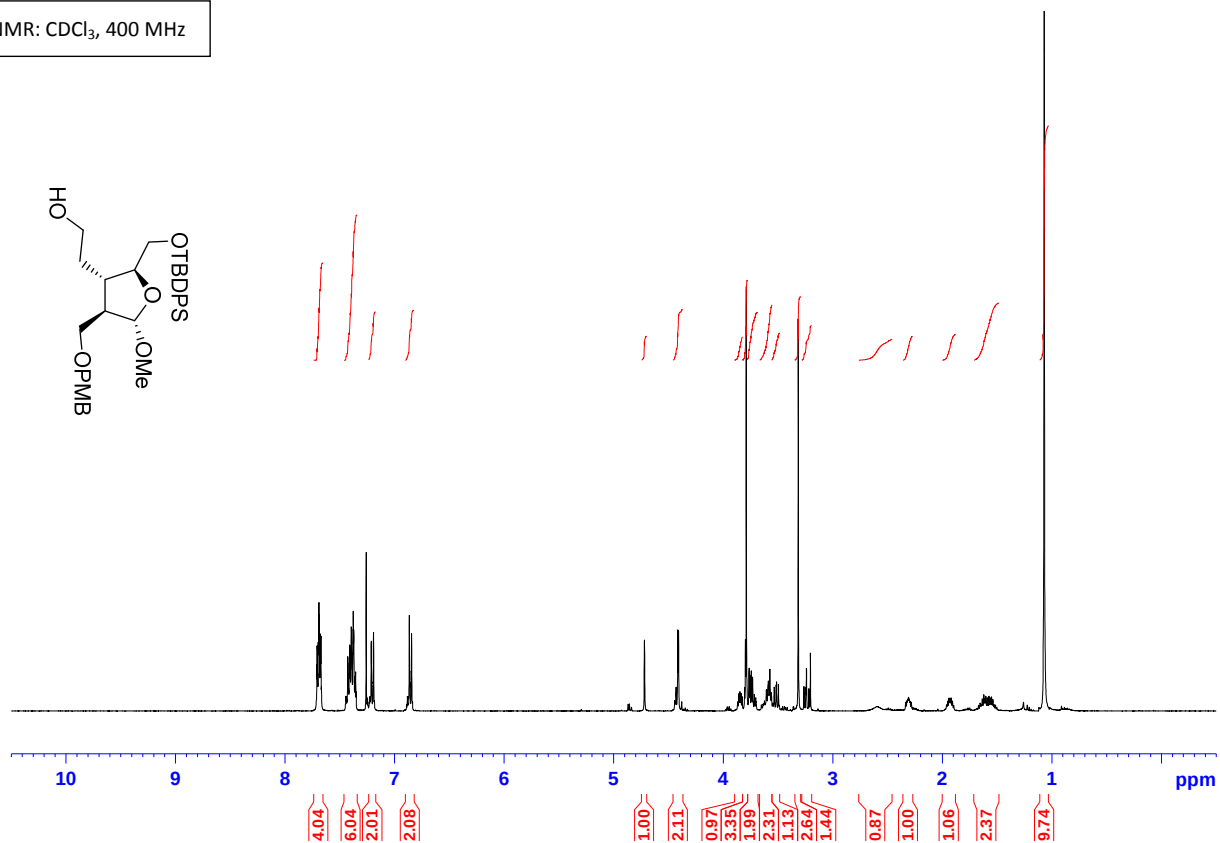
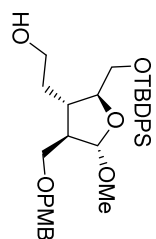
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^1H NMR: CDCl_3 , 400 MHz

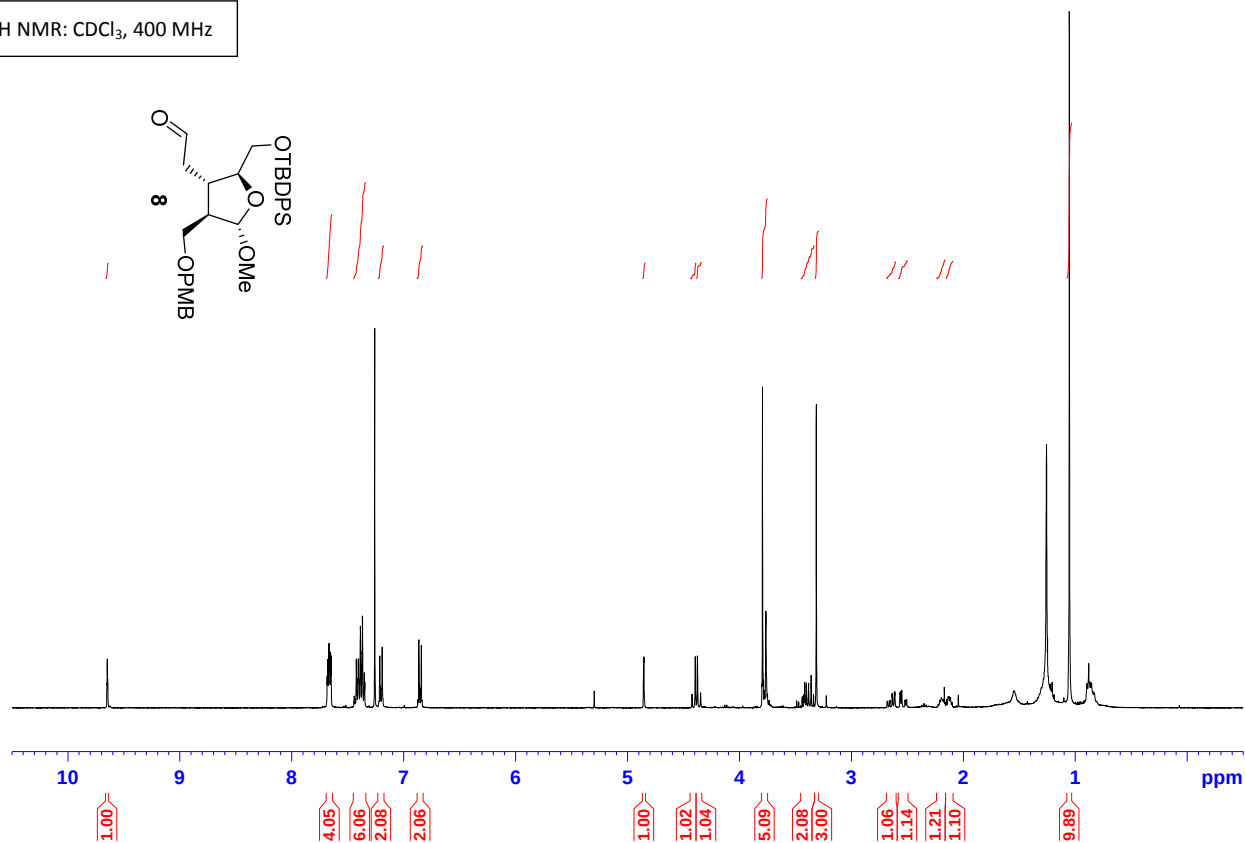


^{13}C NMR, CDCl_3 , 100 MHz

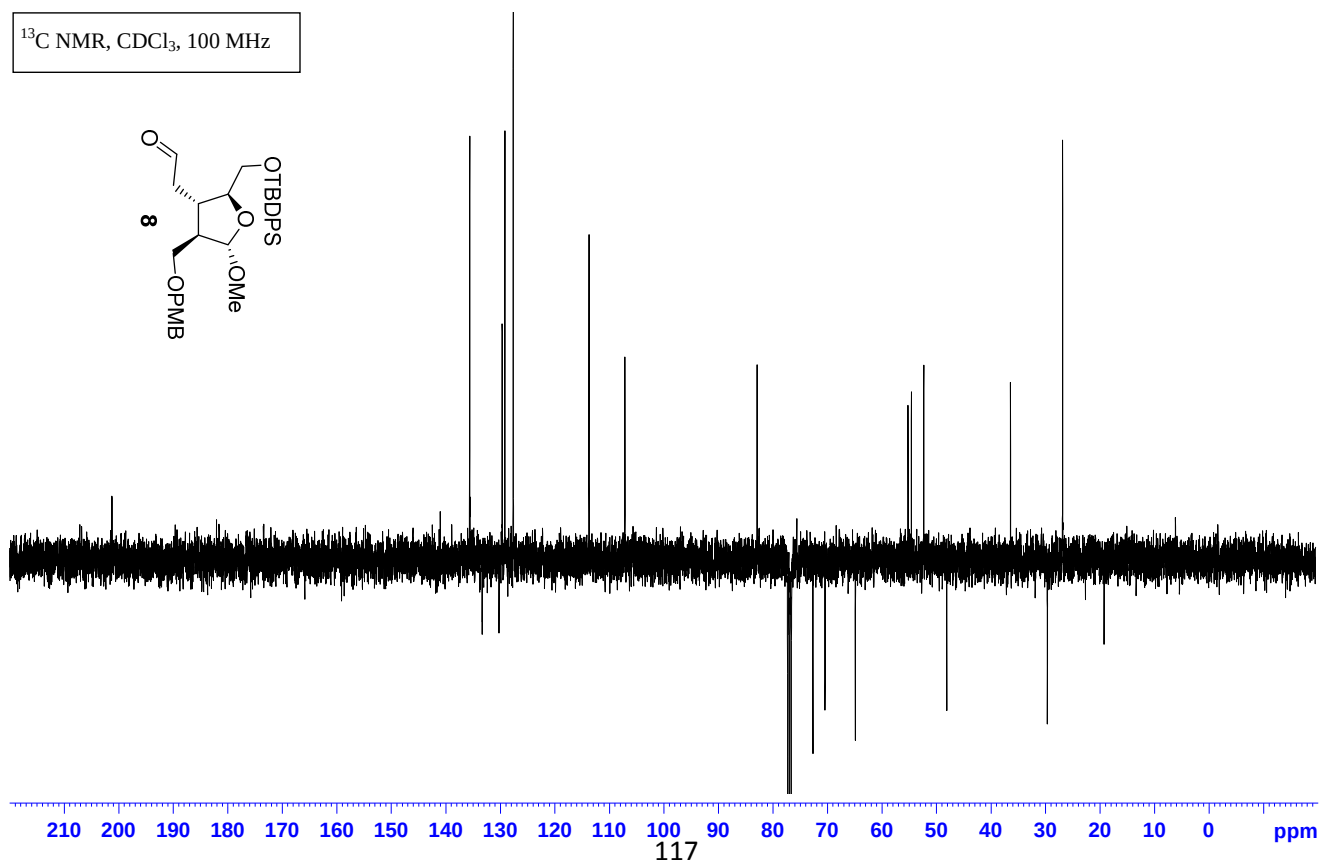




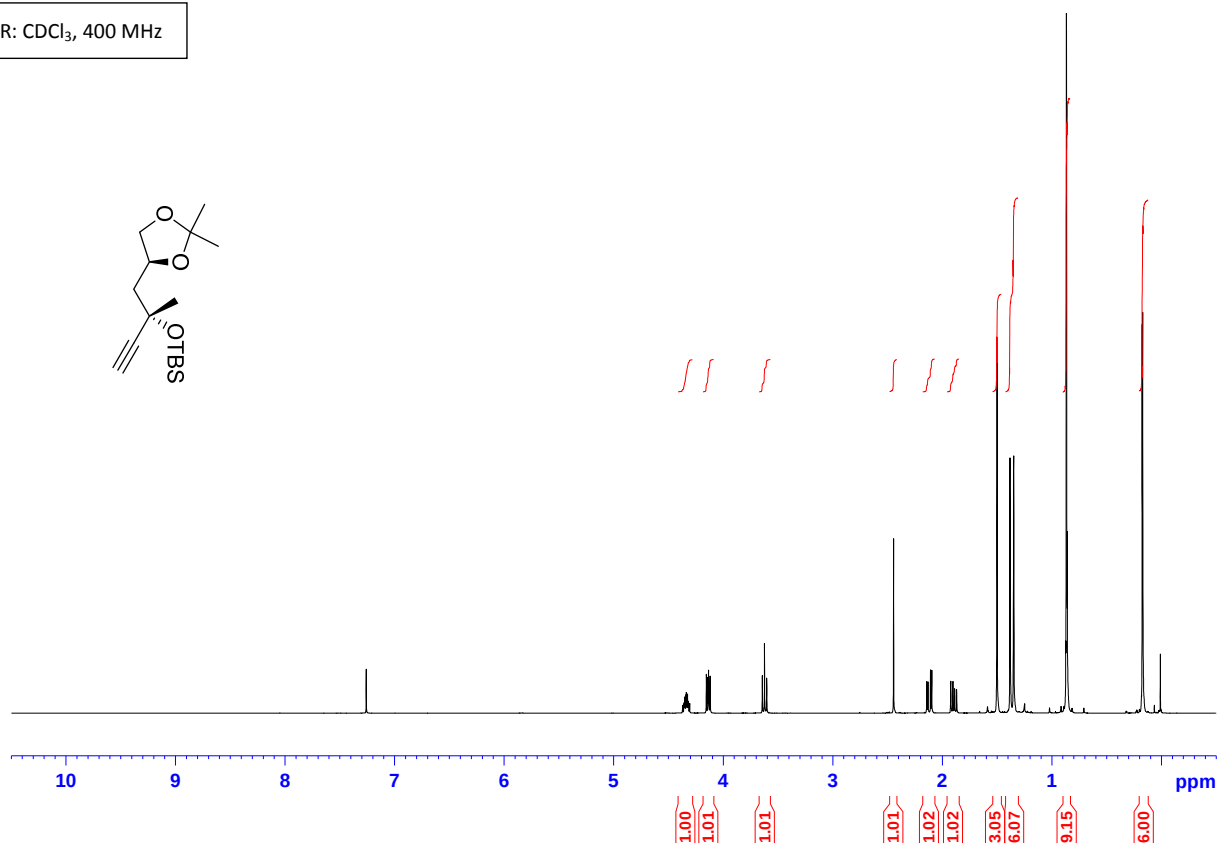
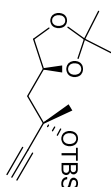
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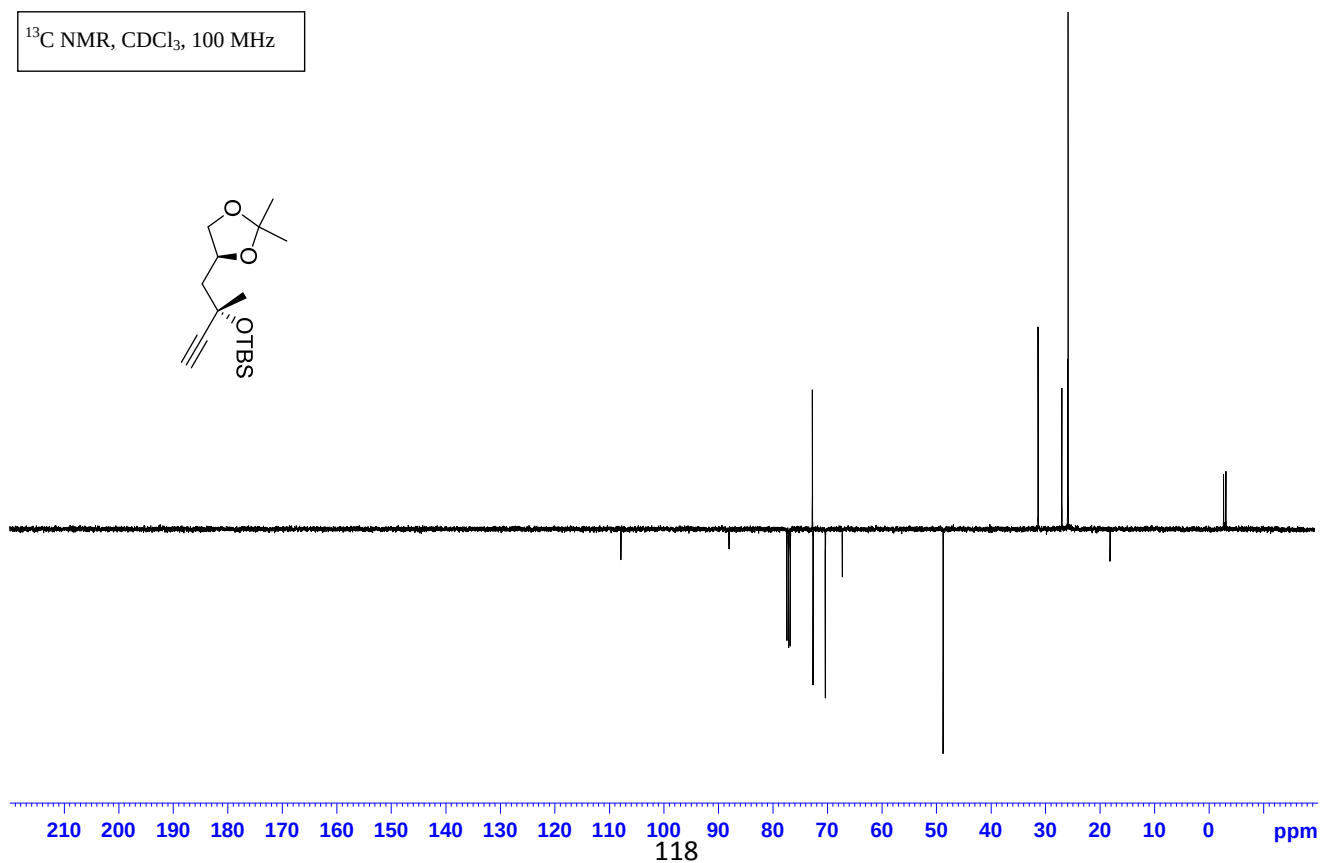
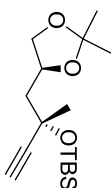
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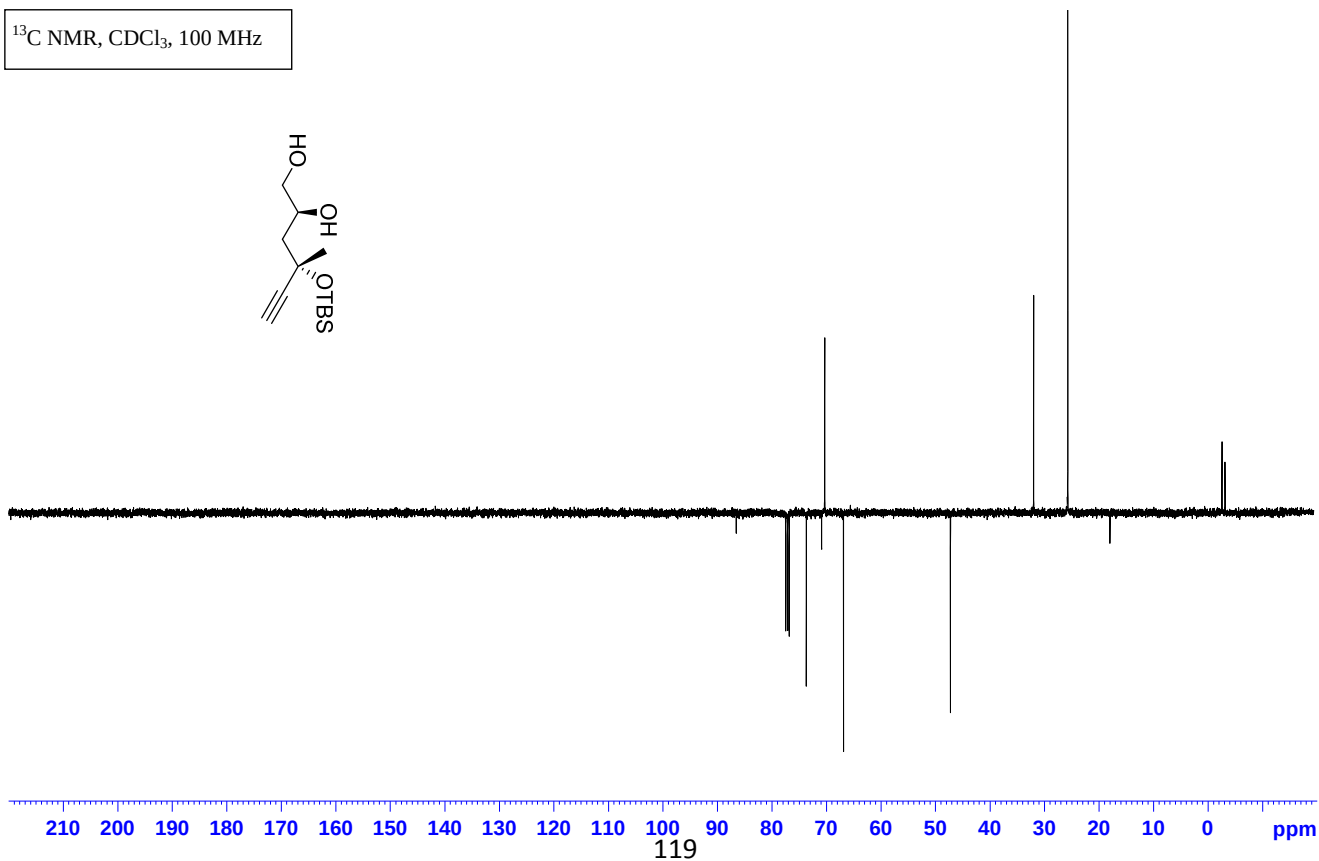
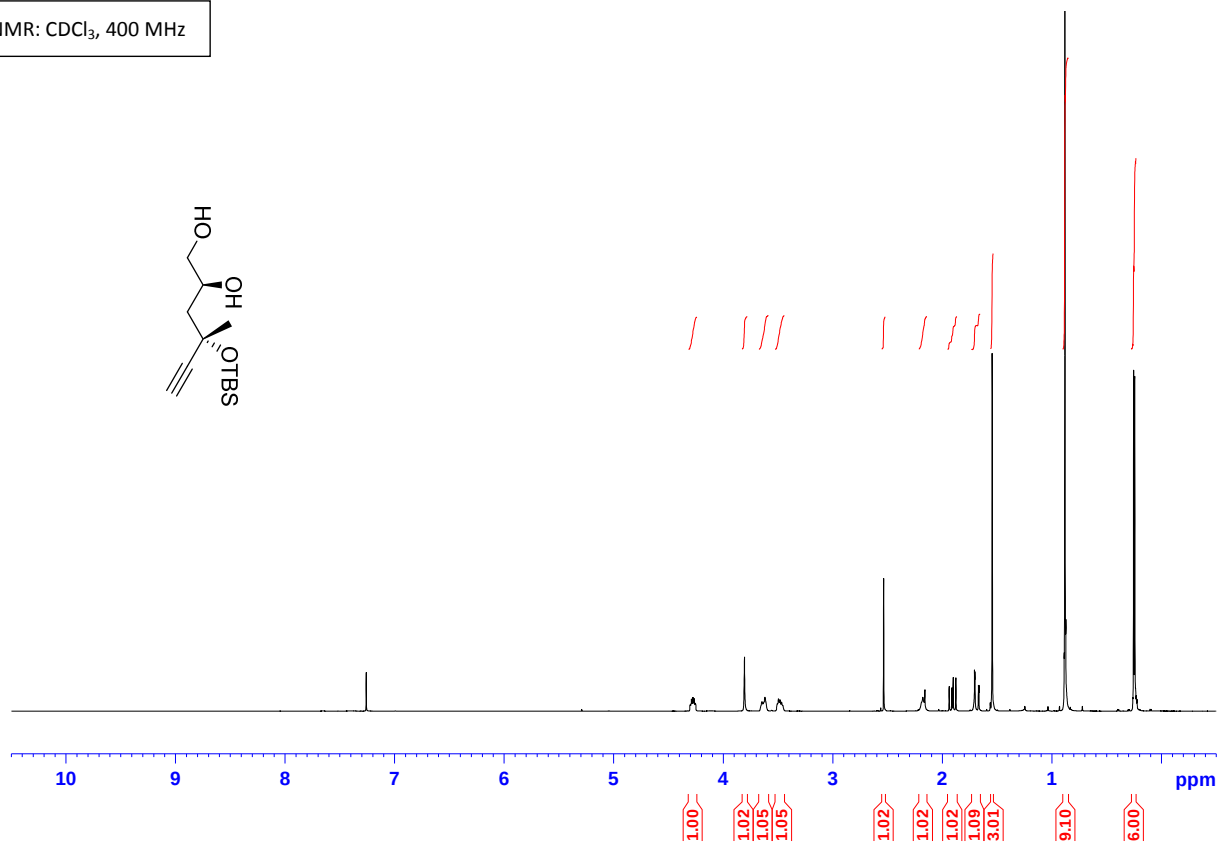


¹H NMR: CDCl₃, 400 MHz

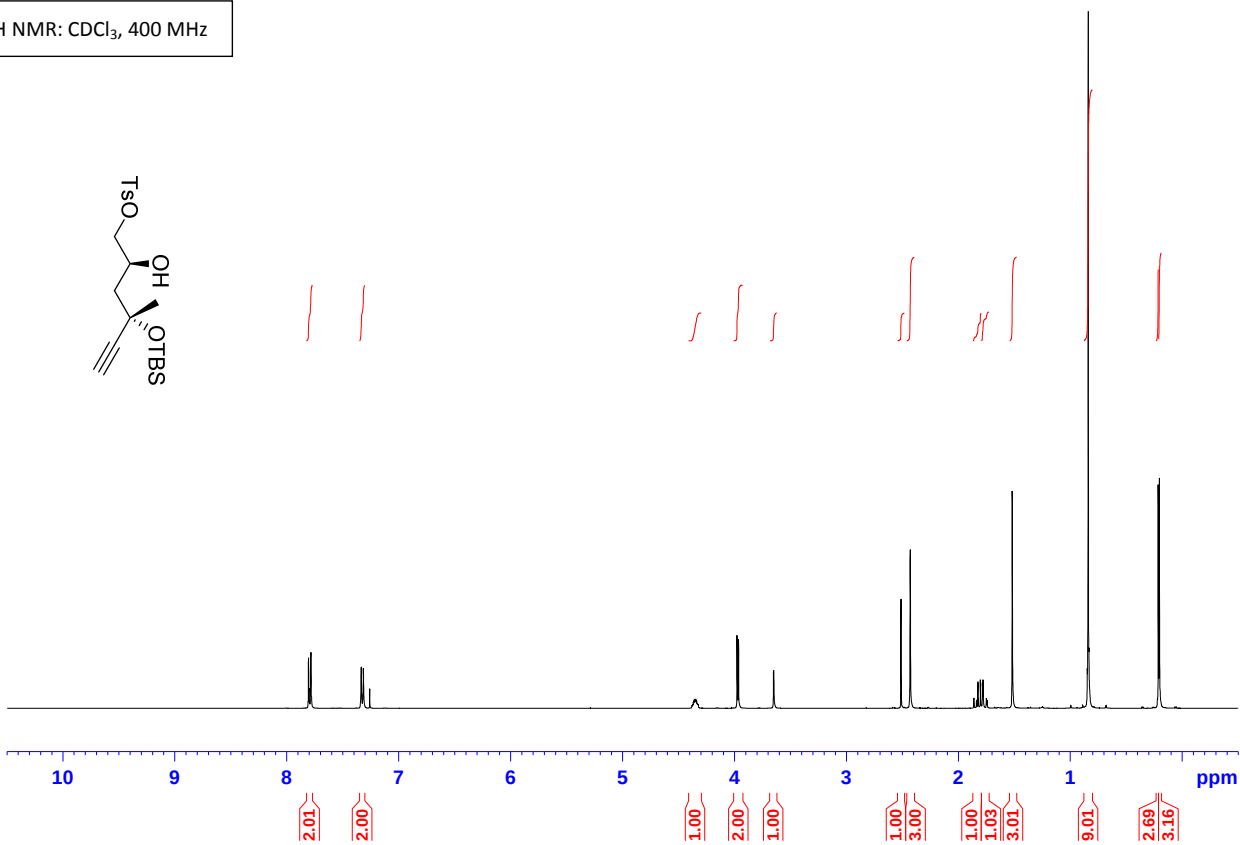


¹³C NMR, CDCl₃, 100 MHz

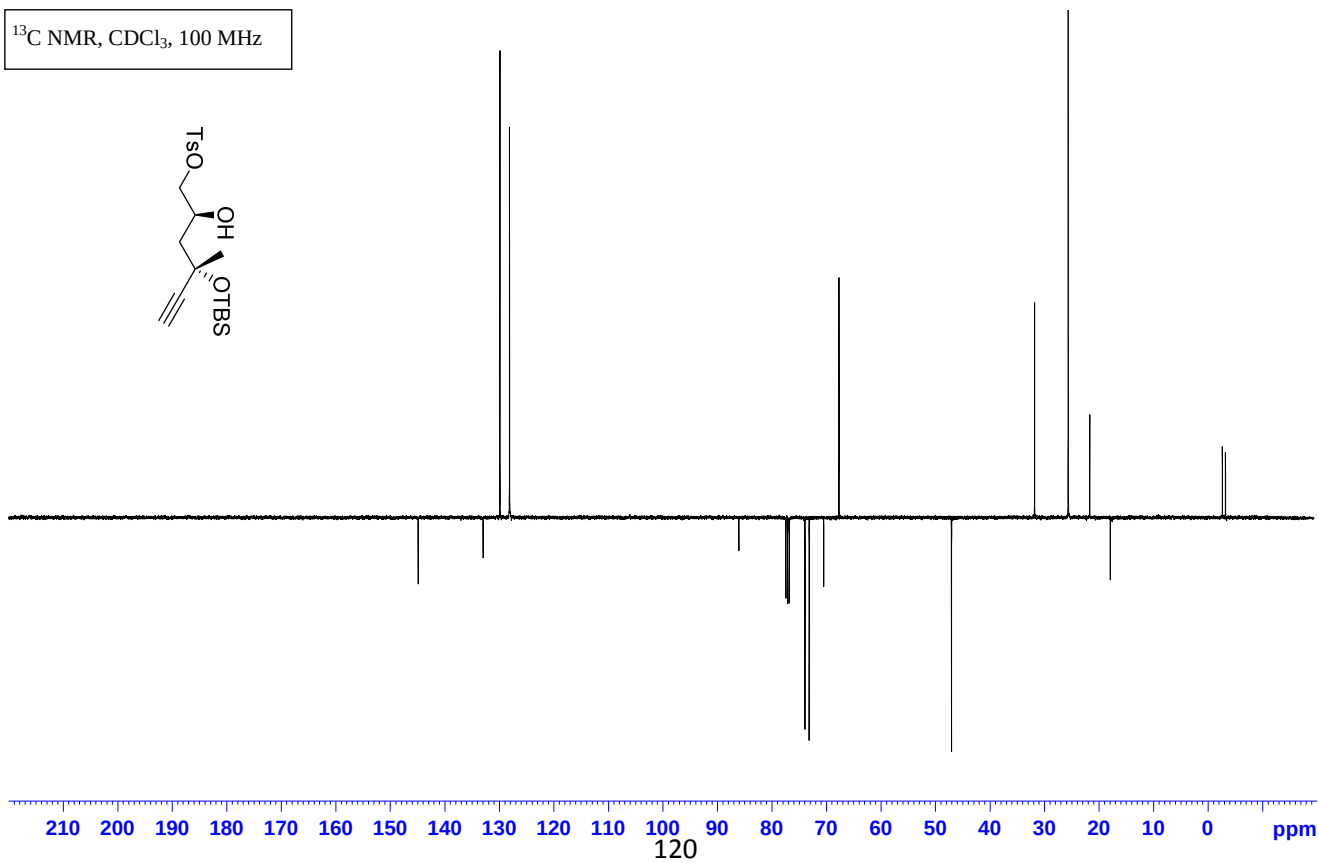




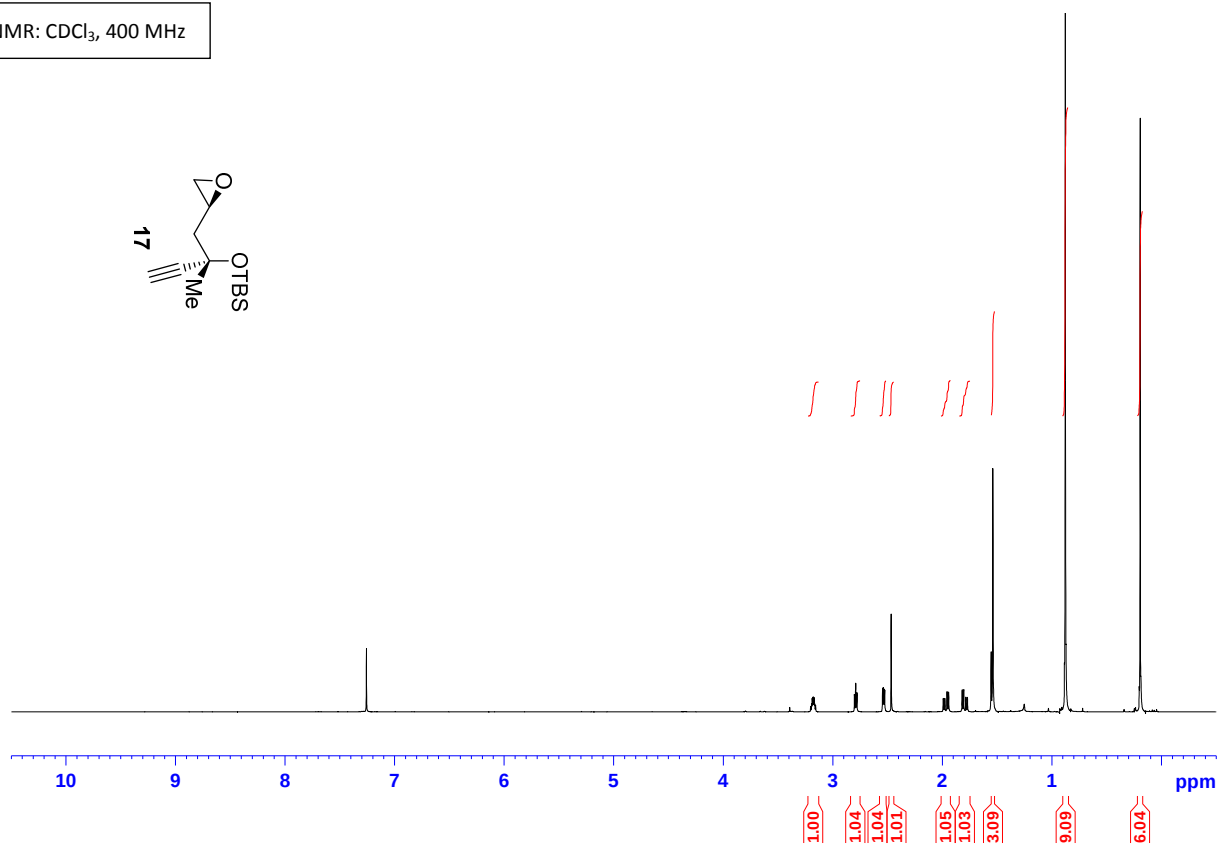
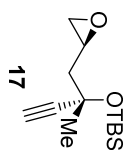
¹H NMR: CDCl₃, 400 MHz



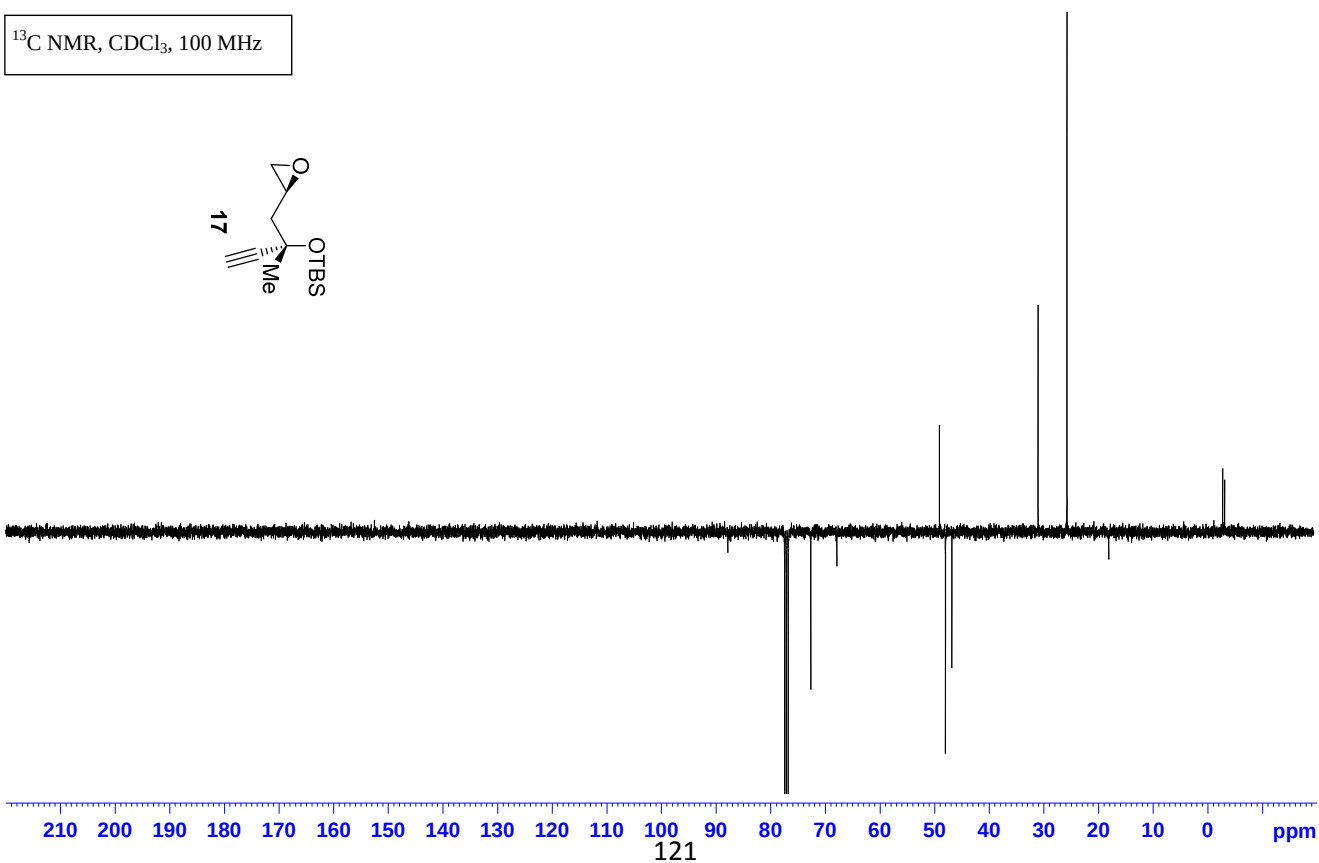
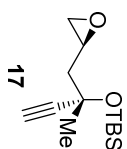
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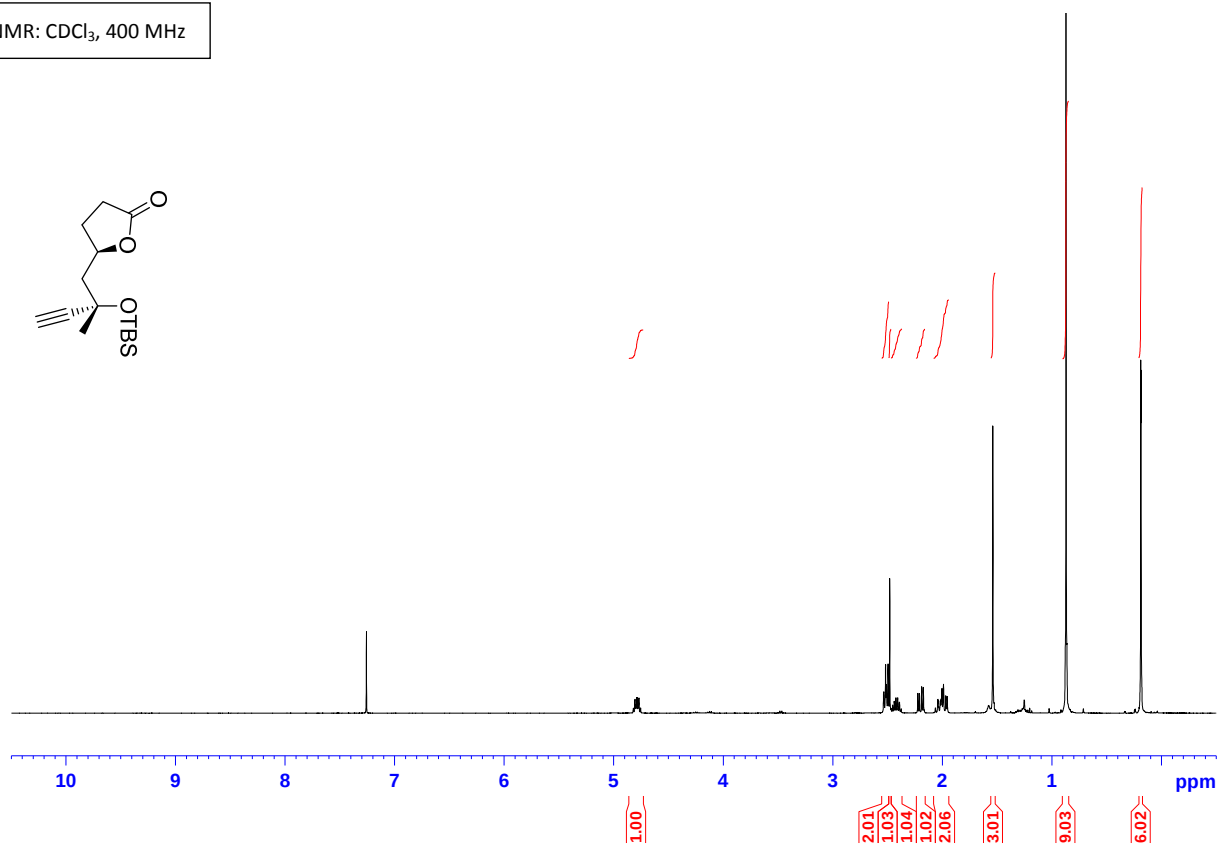
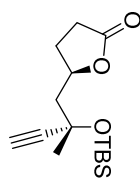
^1H NMR: CDCl_3 , 400 MHz



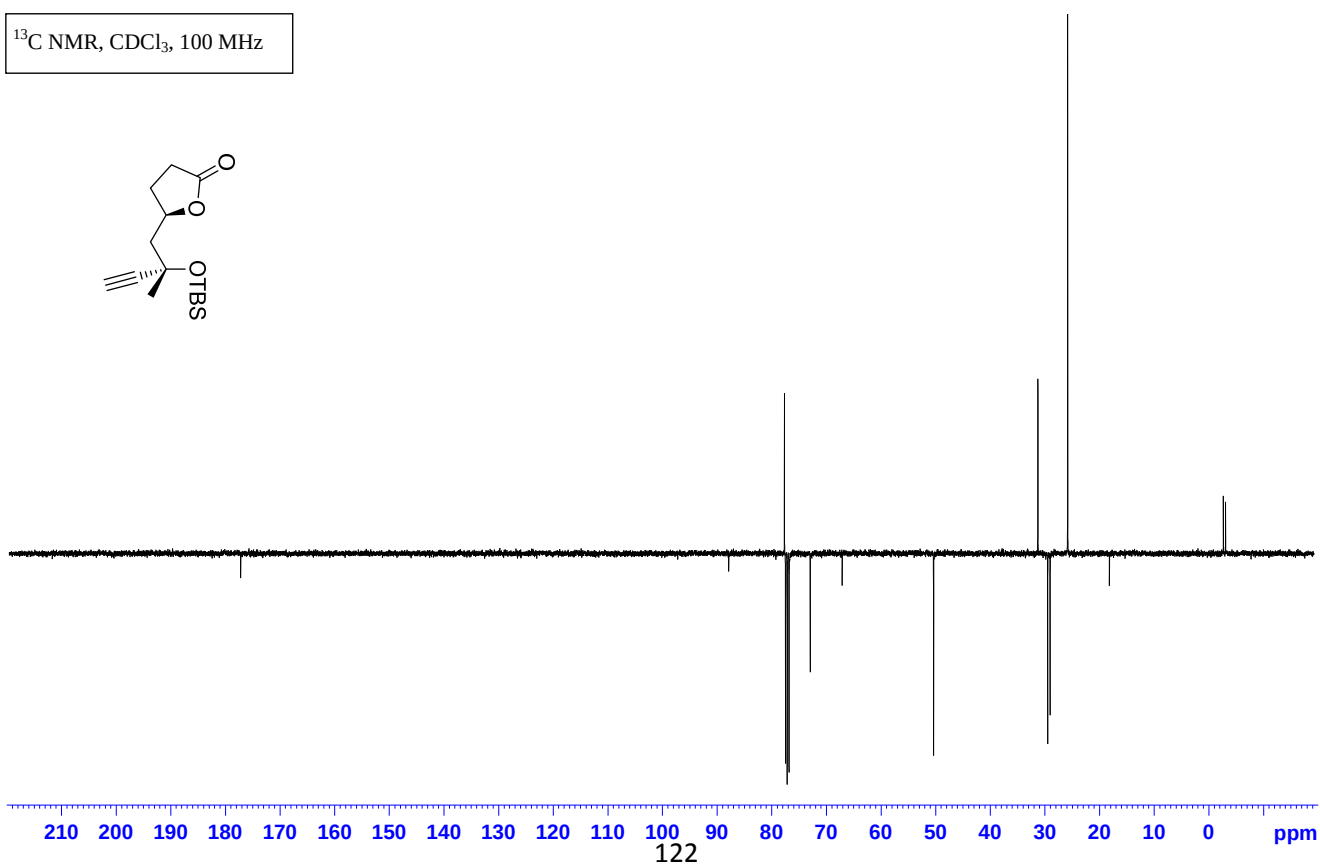
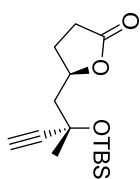
^{13}C NMR, CDCl_3 , 100 MHz



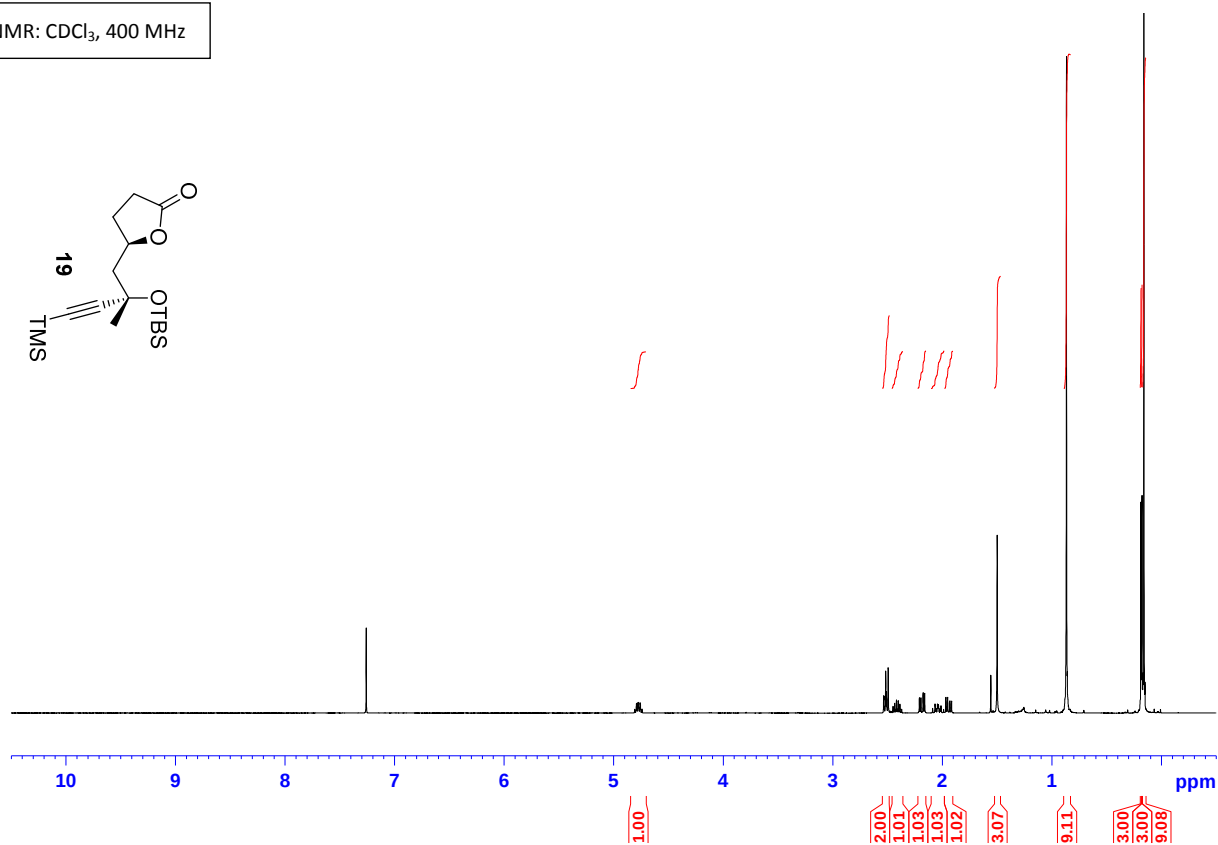
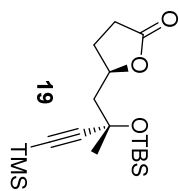
^1H NMR: CDCl_3 , 400 MHz



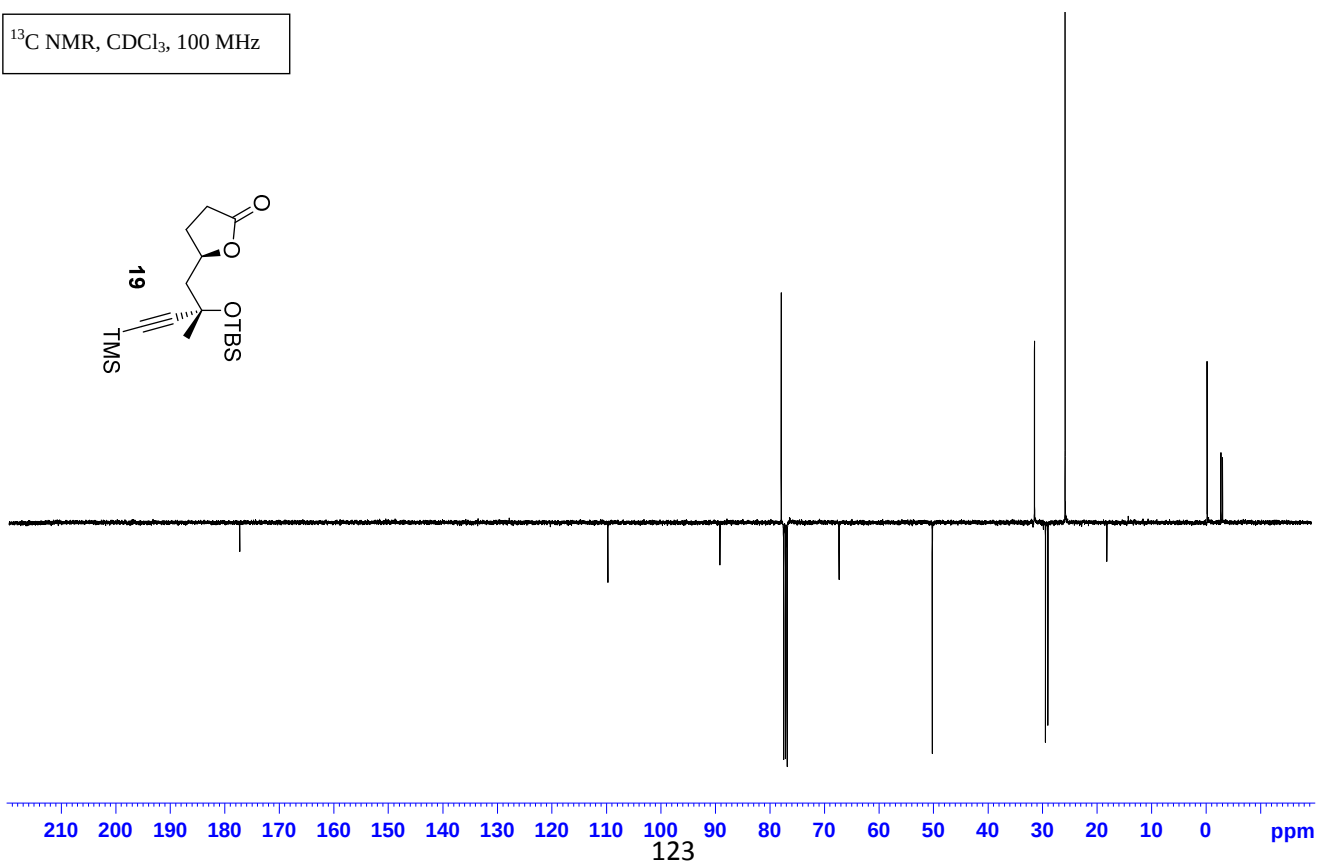
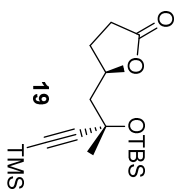
^{13}C NMR, CDCl_3 , 100 MHz

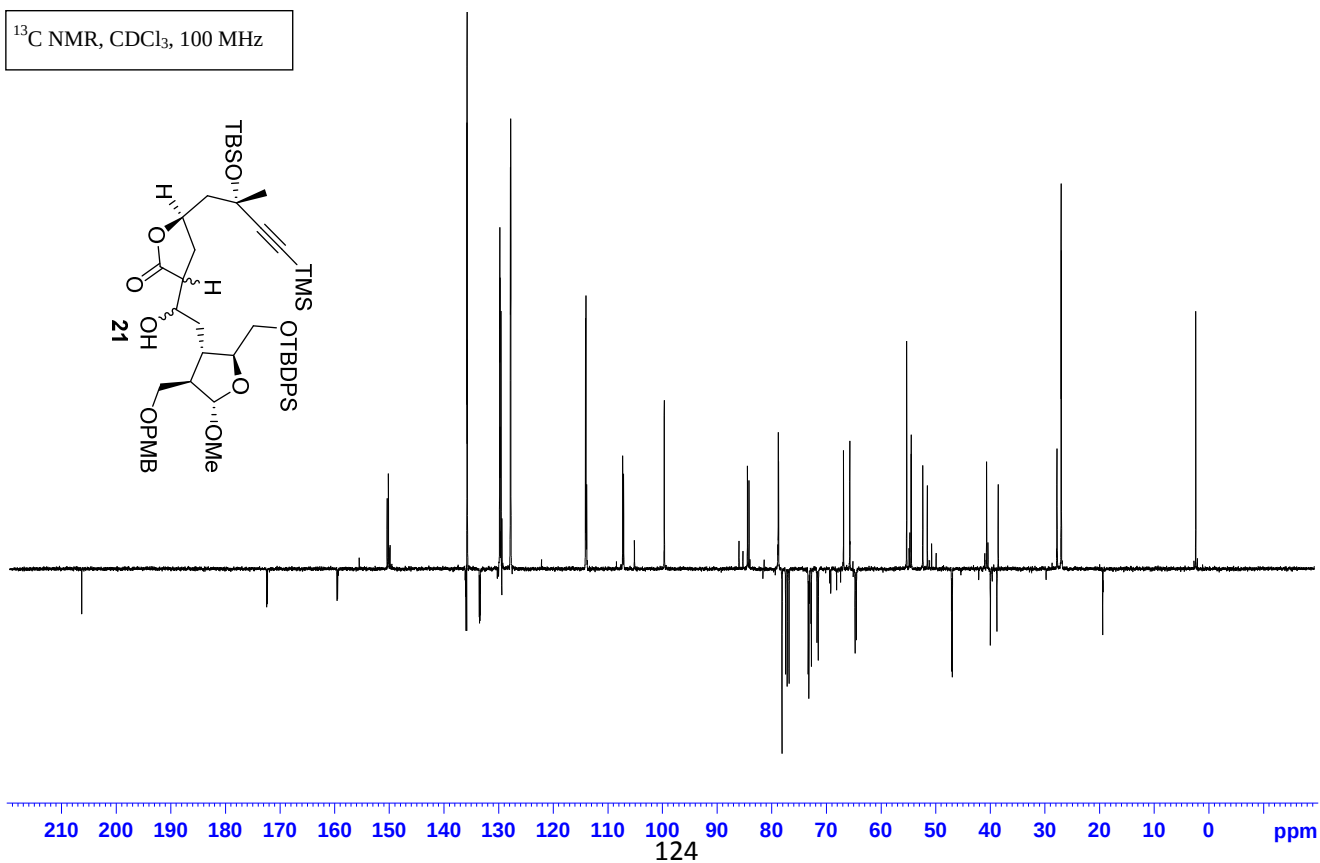
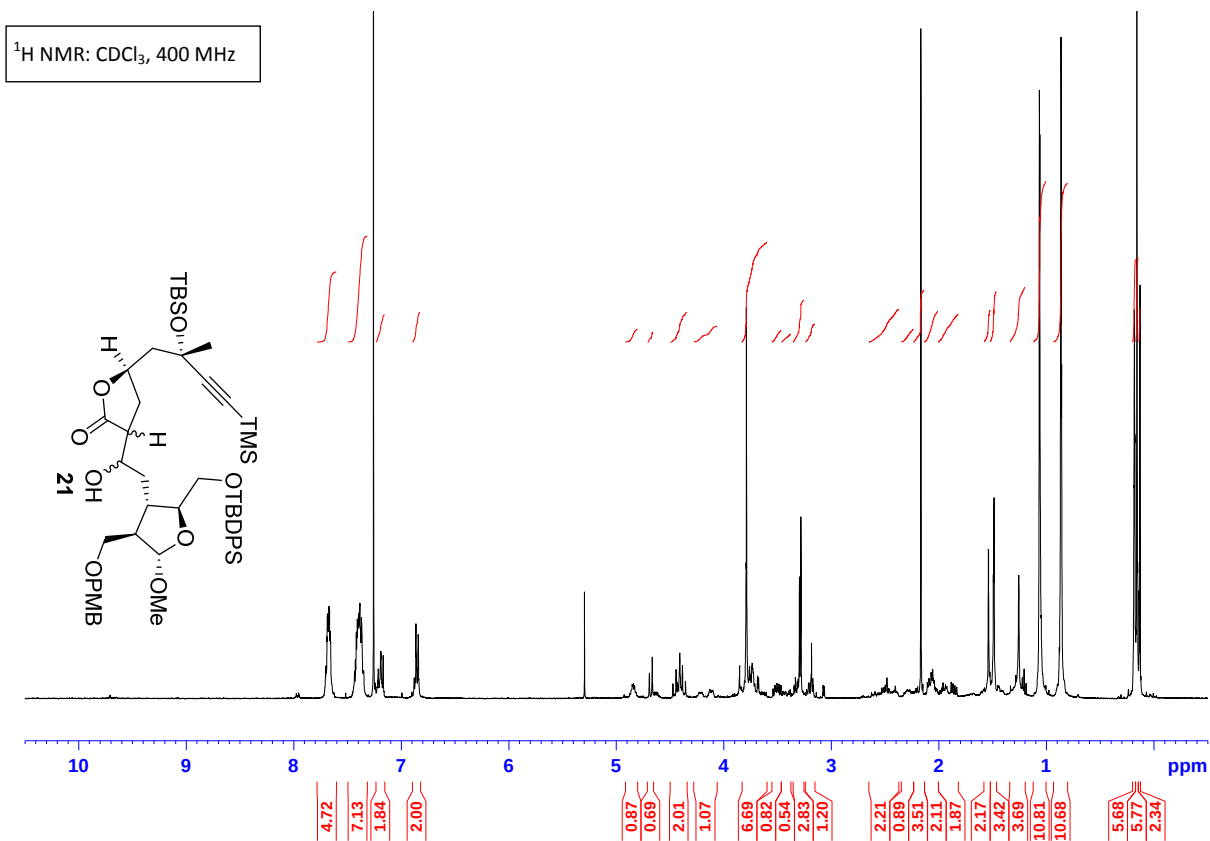


¹H NMR: CDCl₃, 400 MHz

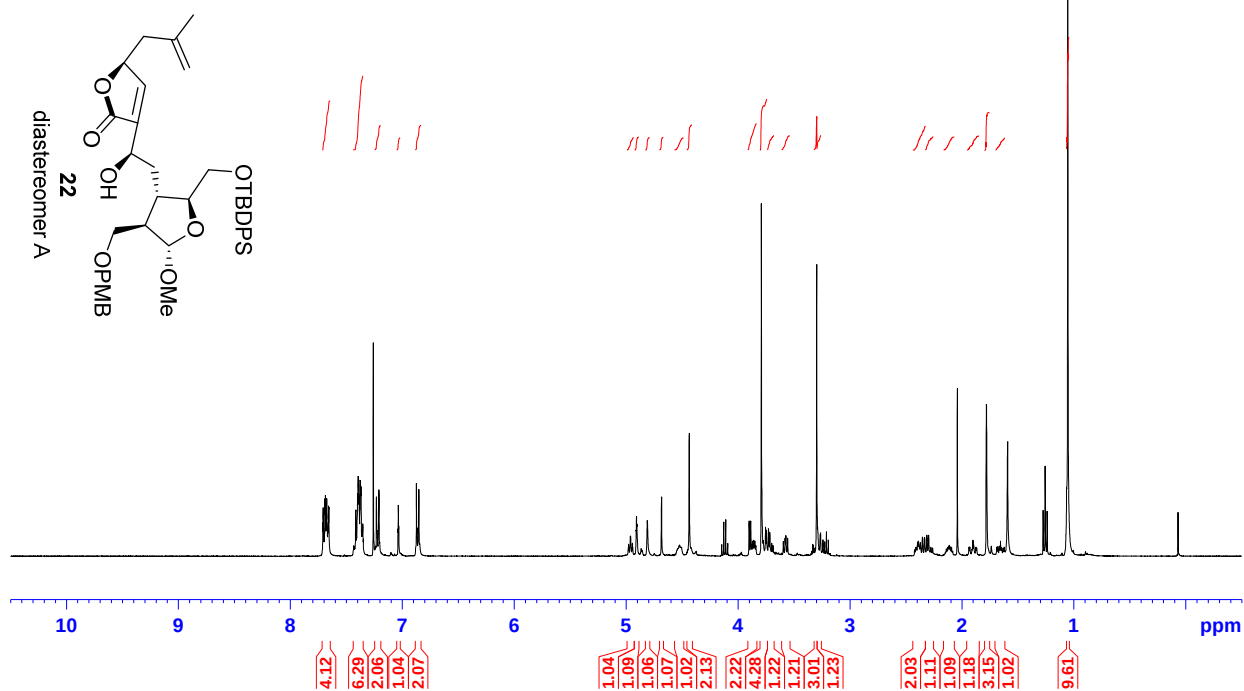


¹³C NMR, CDCl₃, 100 MHz

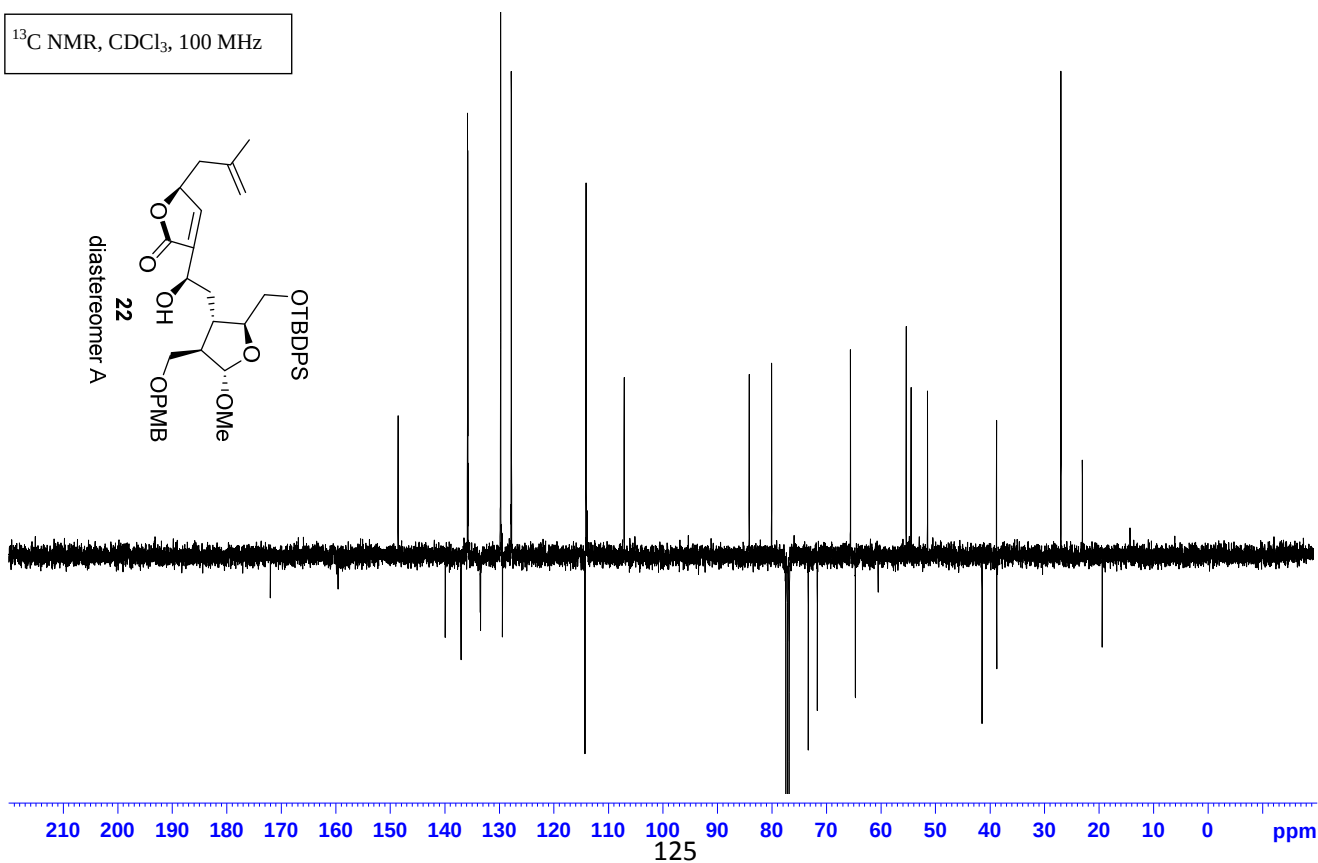


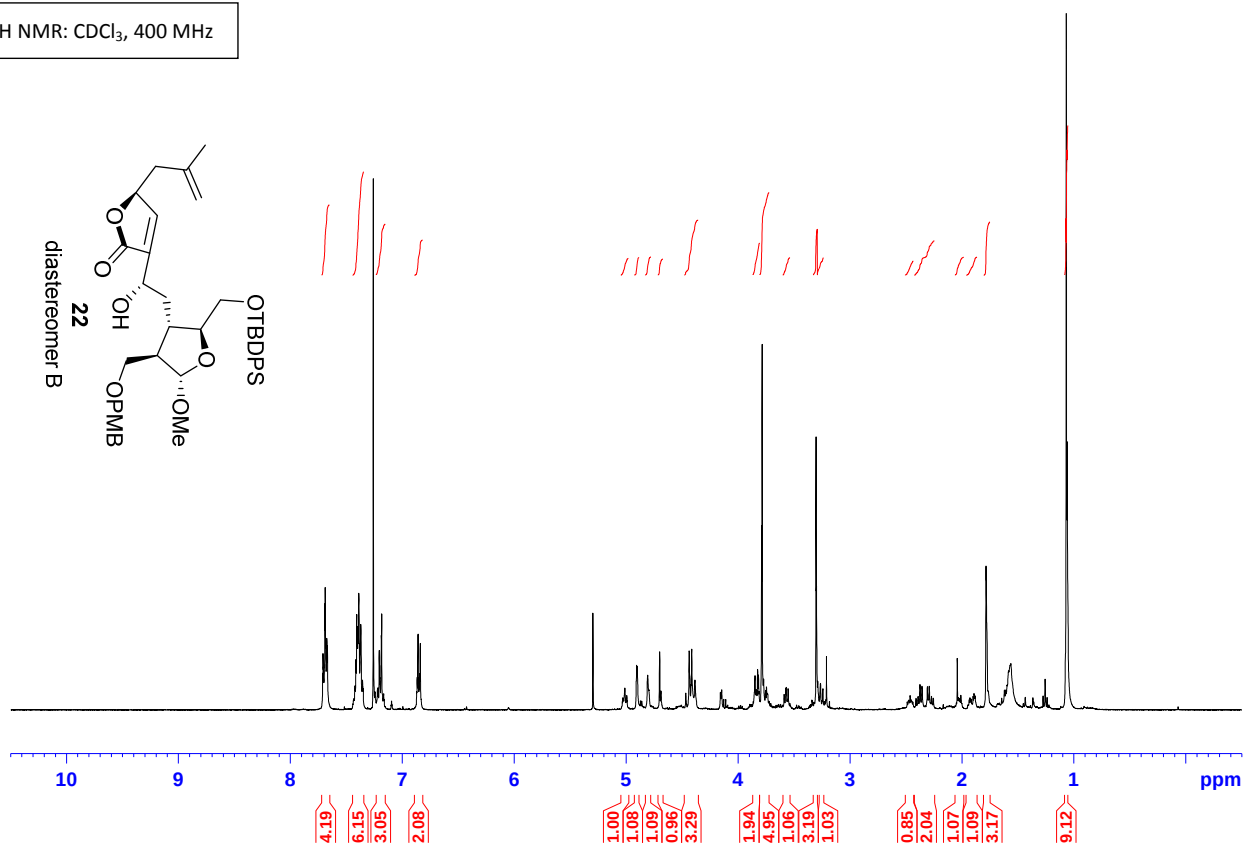
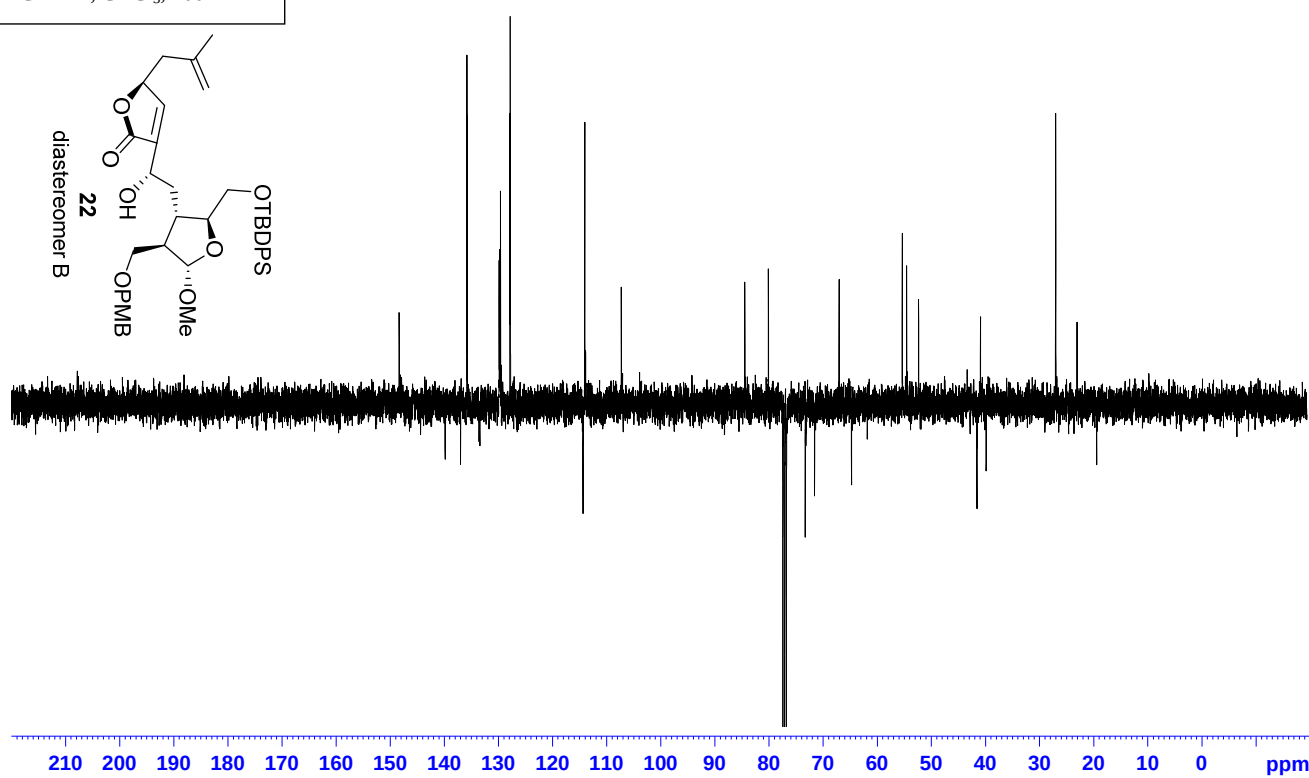


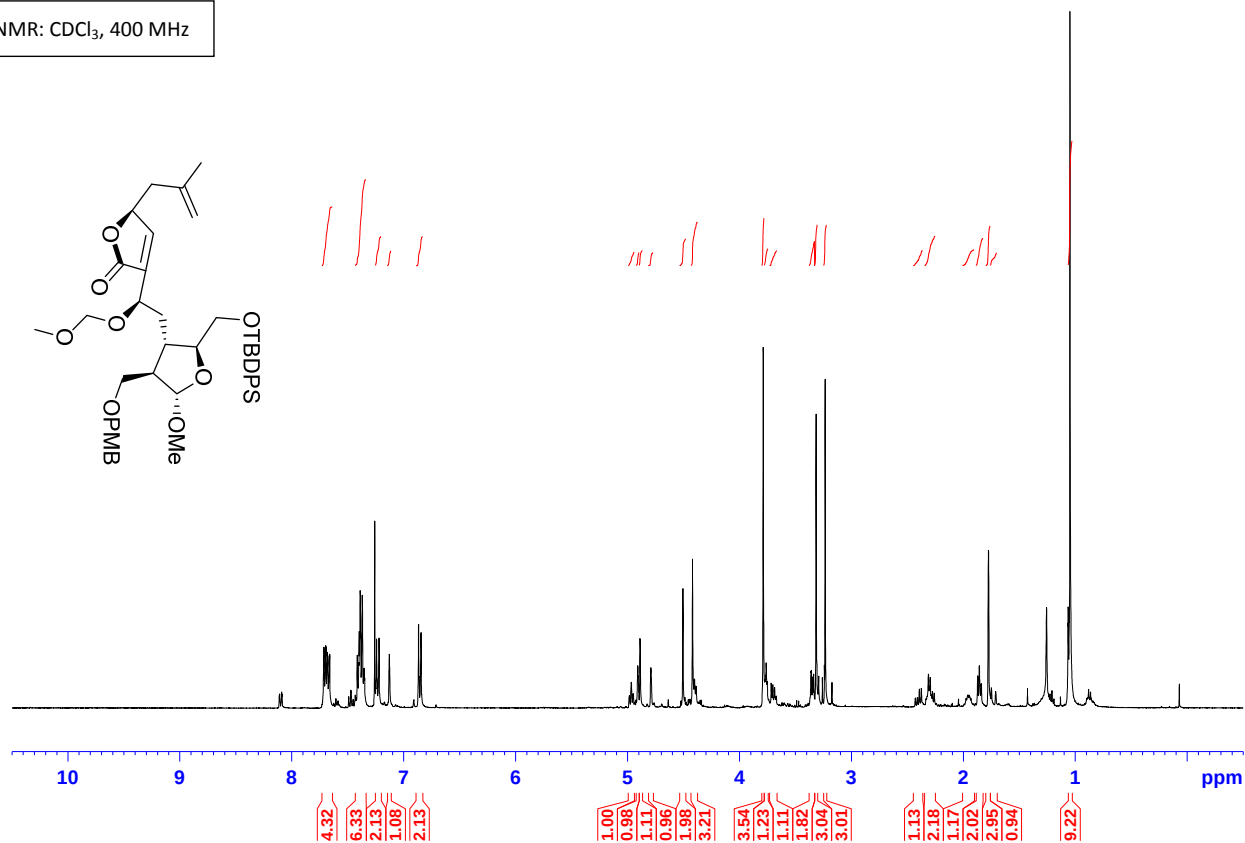
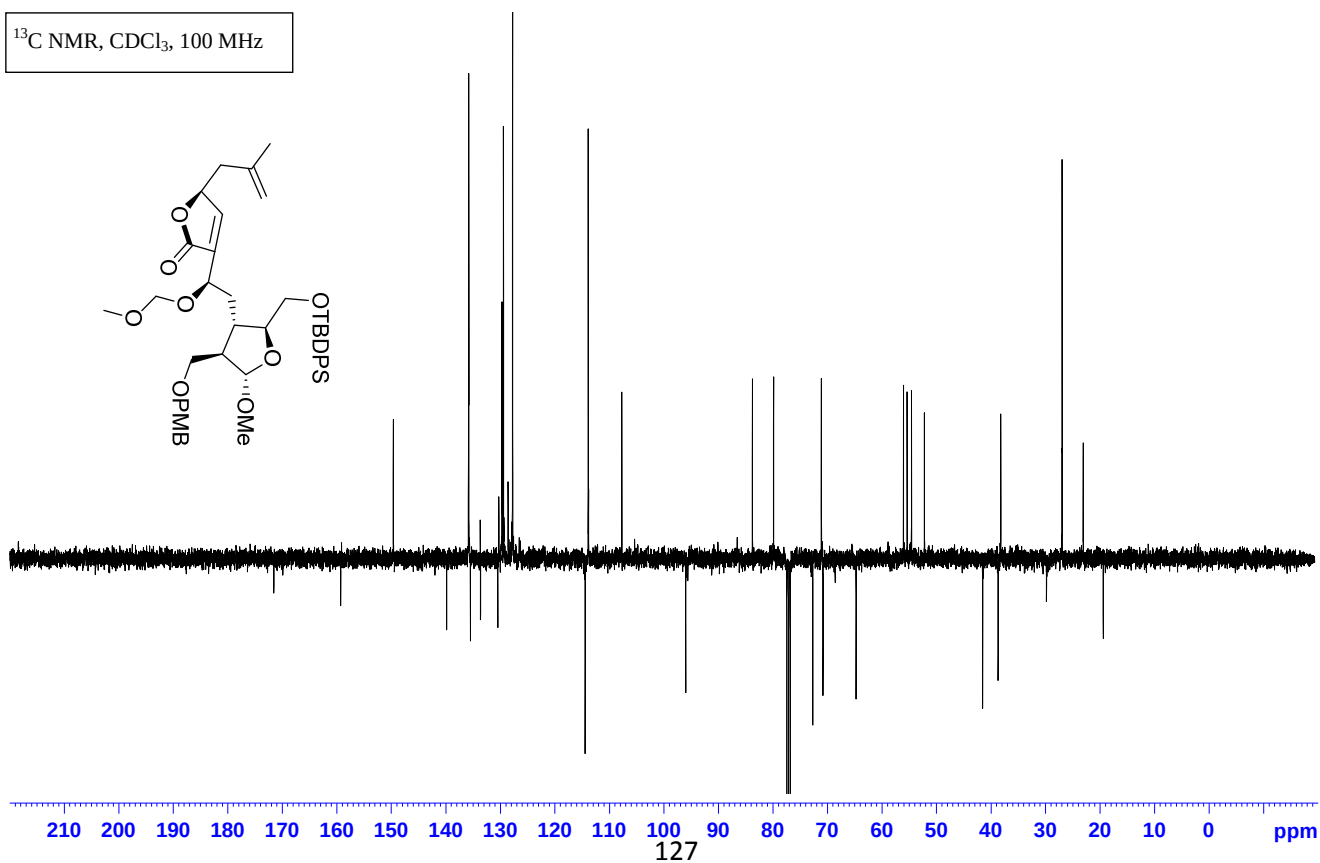
^1H NMR: CDCl_3 , 400 MHz



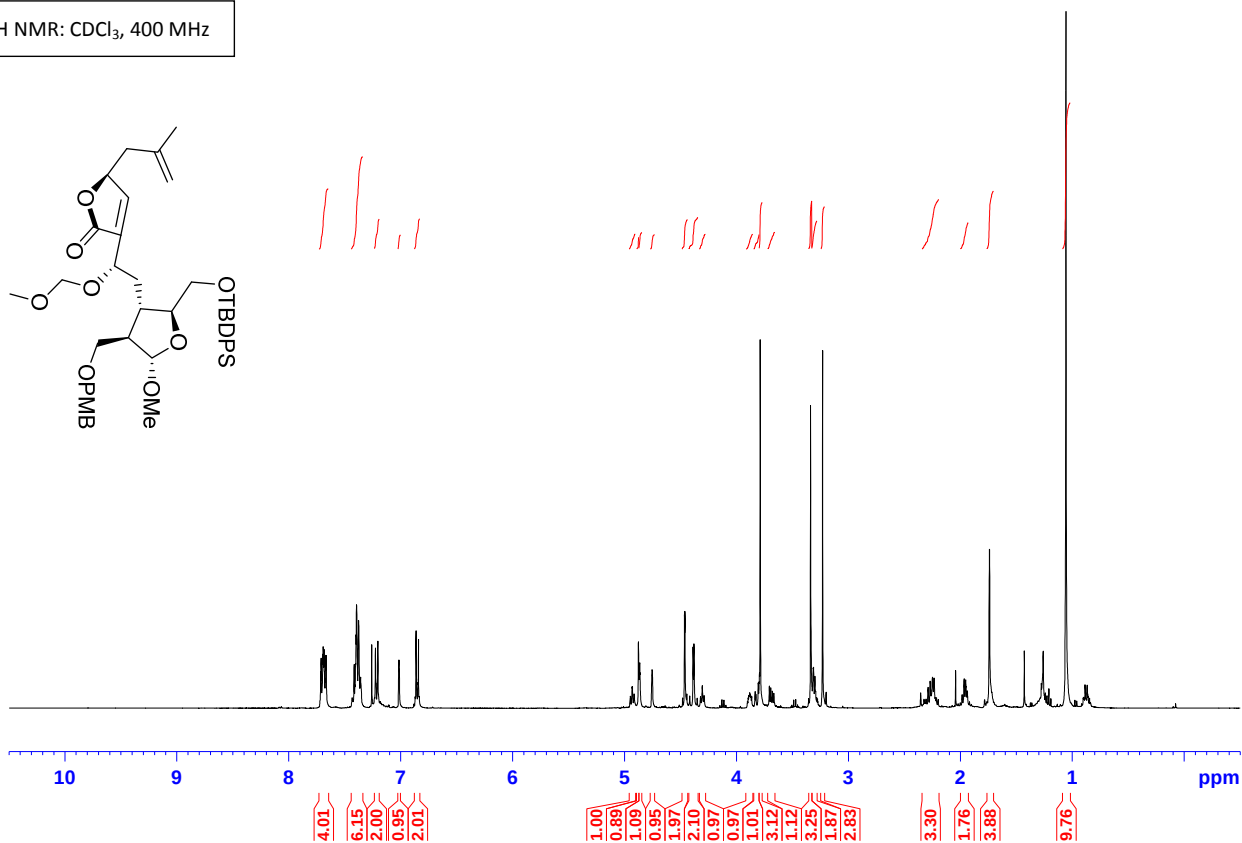
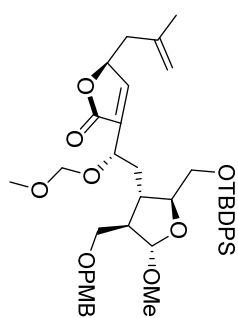
^{13}C NMR: CDCl_3 , 100 MHz



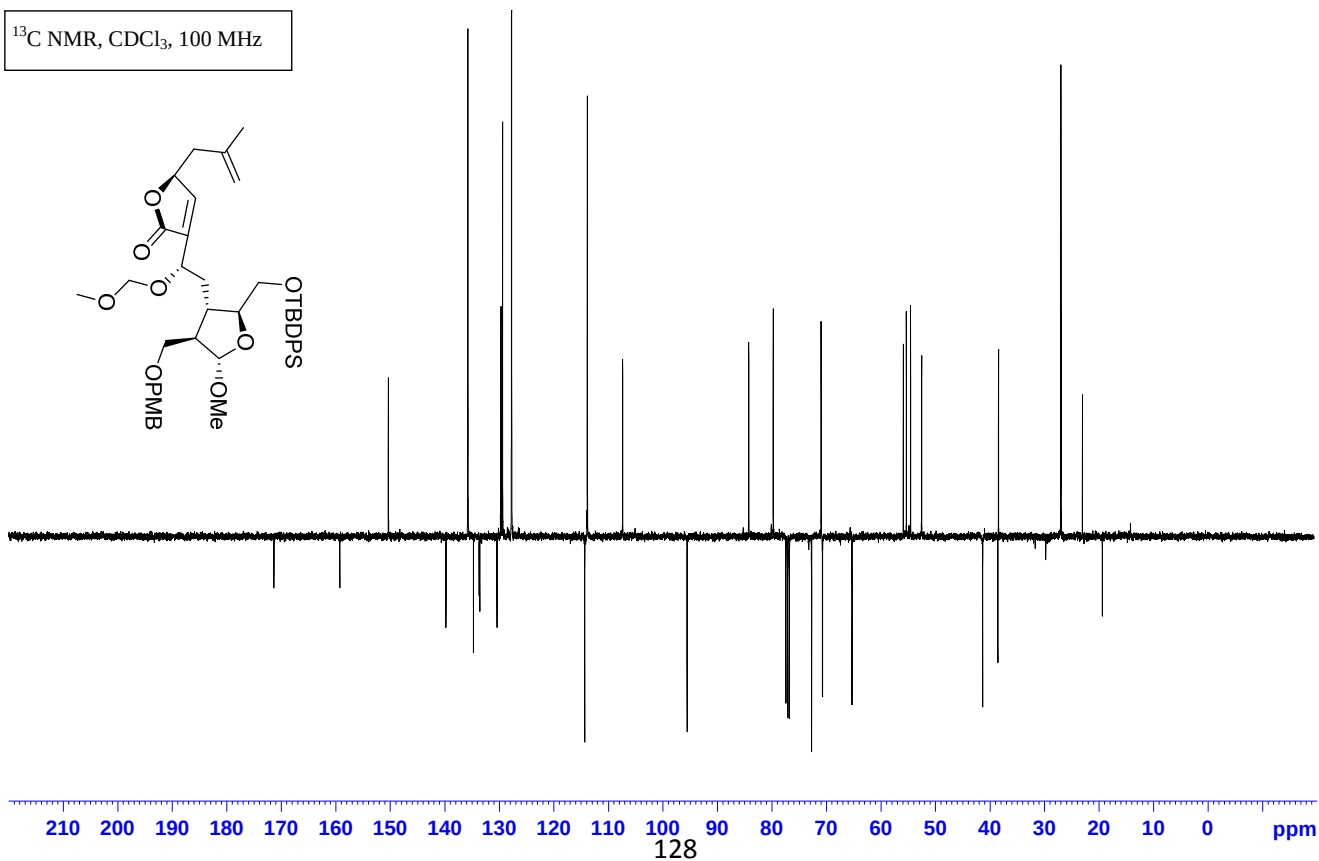
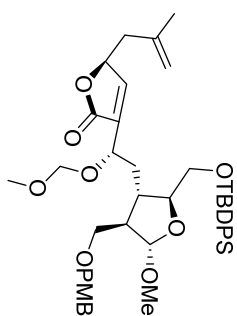
^1H NMR, CDCl_3 , 400 MHz ^{13}C NMR, CDCl_3 , 100 MHz

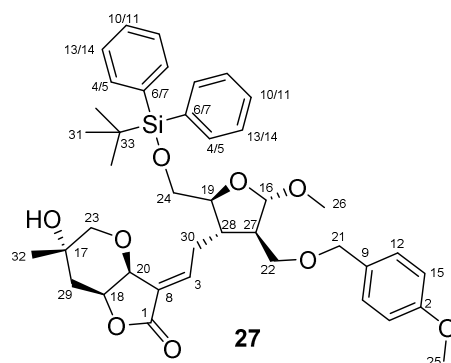
^1H NMR: CDCl_3 , 400 MHz ^{13}C NMR, CDCl_3 , 100 MHz

^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR, CDCl_3 , 100 MHz





No.	¹³ C [ppm]	¹ H [ppm]
1	169.6	-
2	159.4	-
3	145.1	6.87-6.85
4	135.82	7.69-7.66
5	135.77	7.69-7.66
6	133.51	-
7	133.46	-
8	130.4	-
9	130.2	-
10	129.90	7.44-7.36
11	129.87	7.44-7.36
12	129.4	7.20
13	127.9	7.44-7.36
14	127.8	7.44-7.36
15	114.0	6.87-6.85
16	107.4	4.84
17	85.9	-
18	83.4	5.04
19	83.2	3.90-3.86
20	77.4	5.15
21	72.9	4.38
22	70.5	3.32-3.22
23	68.2	3.47, 3.32
24	64.9	3.76, 3.72
25	55.4	3.80
26	54.8	3.33
27	51.9	2.10-2.03
28	41.3	1.95
29	39.3	2.42, 2.08
30	34.0	2.63-2.48
31	27.0	1.06
32	24.4	1.12
33	19.4	-
OH	-	1.88

HMBC-Correlation:

20 ↔ 3 ↔ 1; 3 ↔ 8

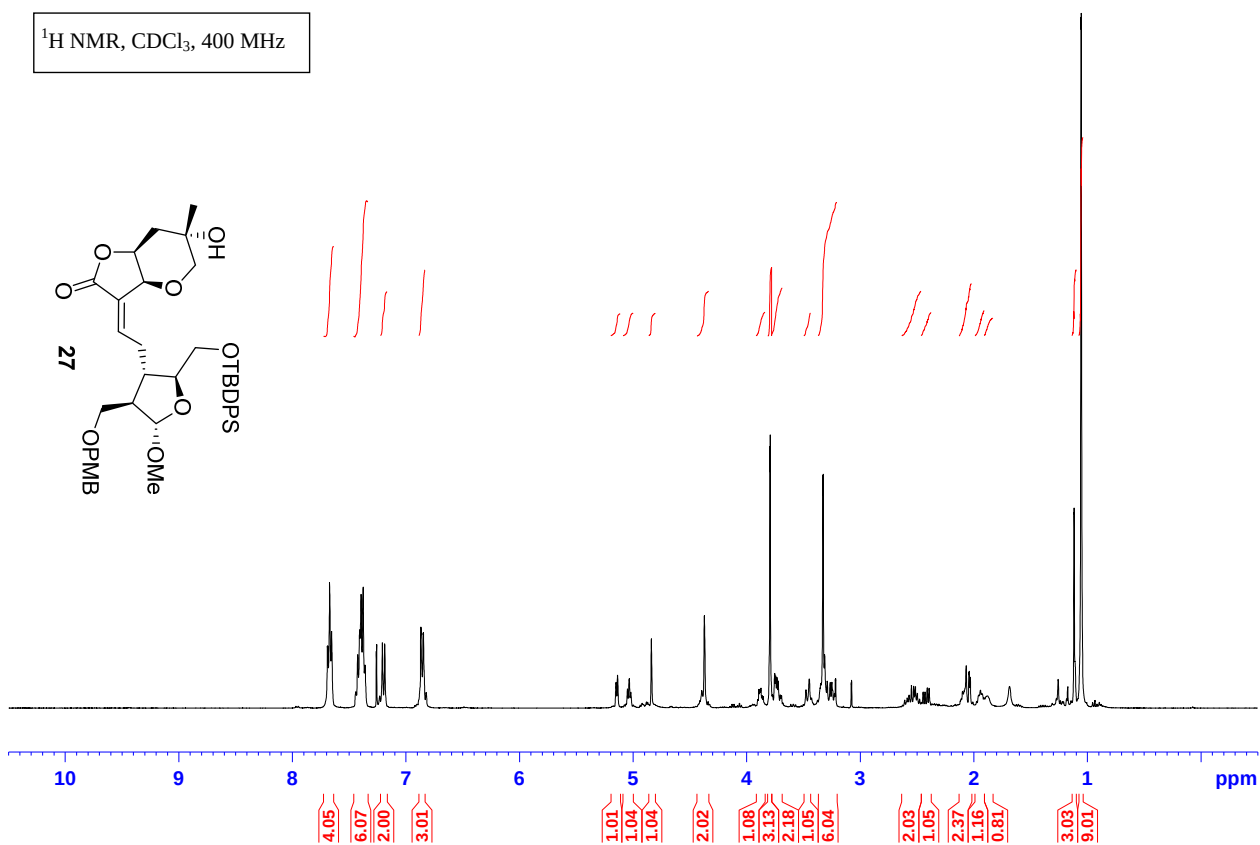
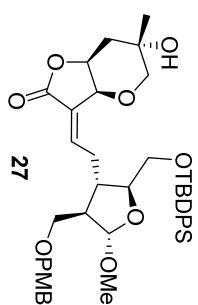
32 ↔ 17, 32 ↔ 29, 32 ↔ 23

20 ↔ 18 ↔ 17

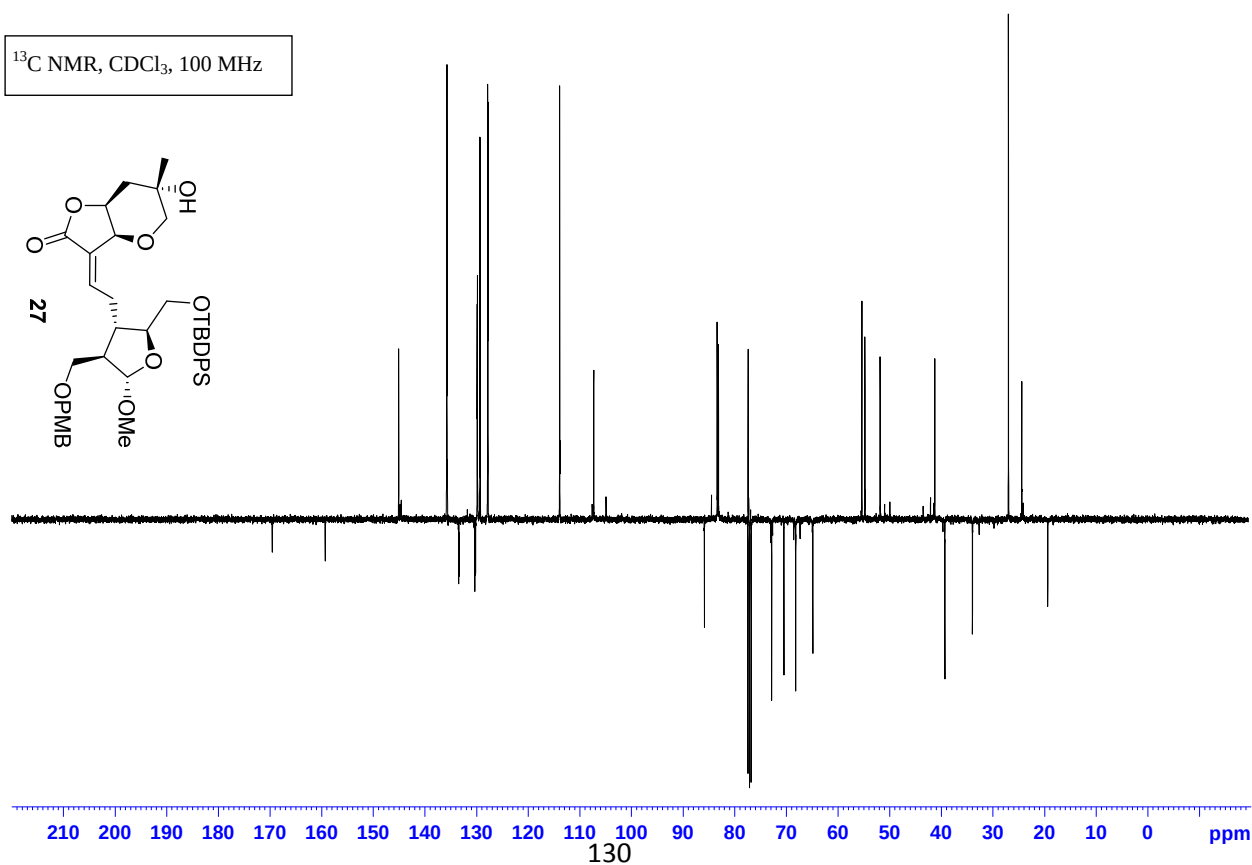
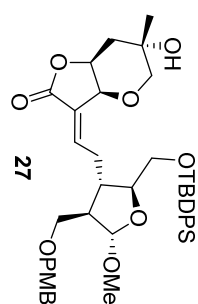
COSY-Correlation:

3 ↔ 30,

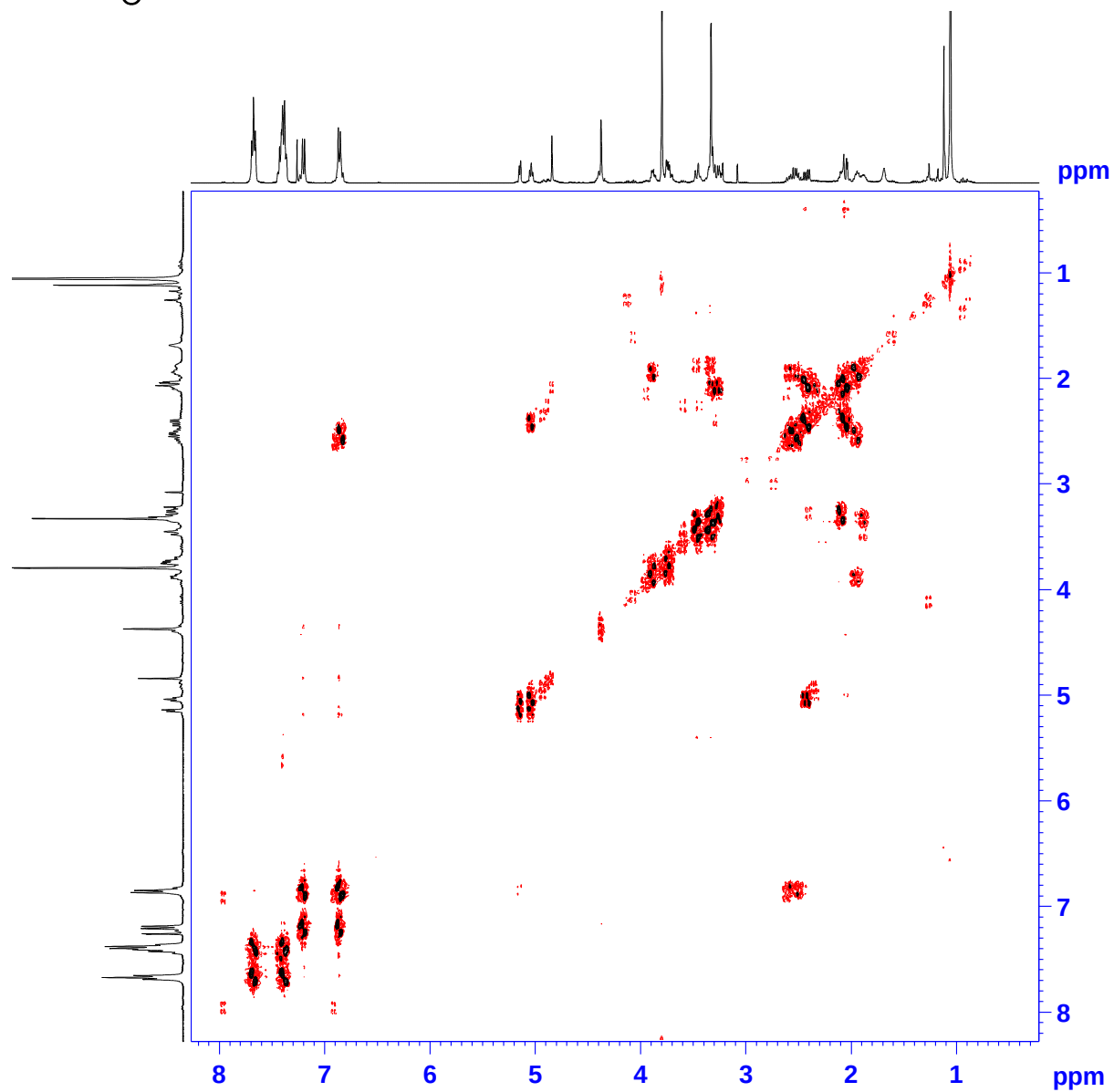
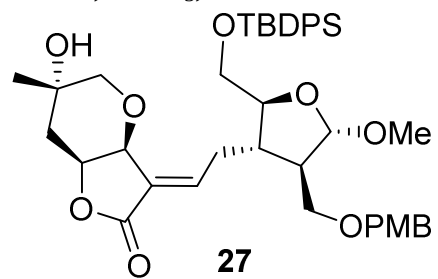
¹H NMR, CDCl₃, 400 MHz



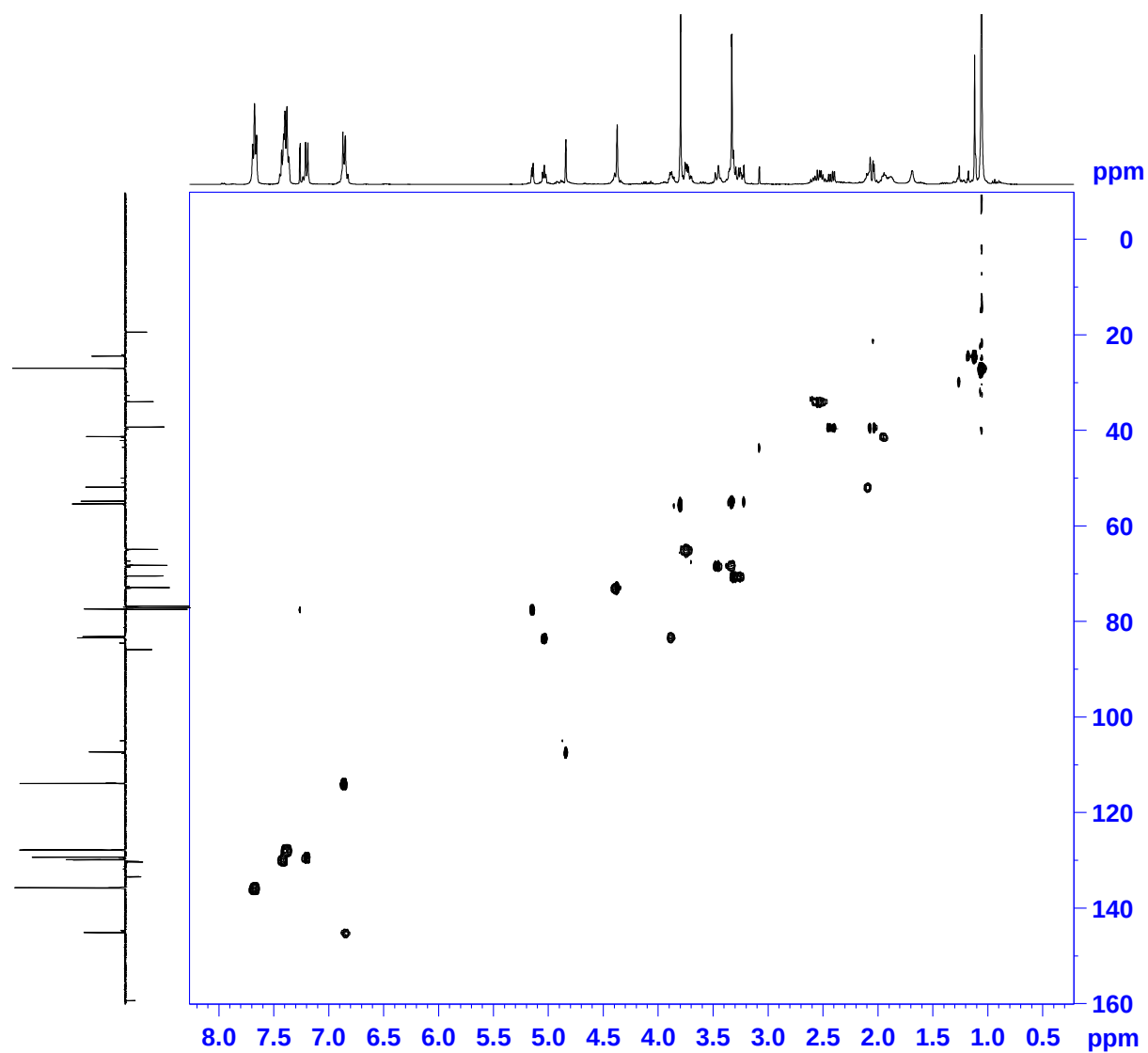
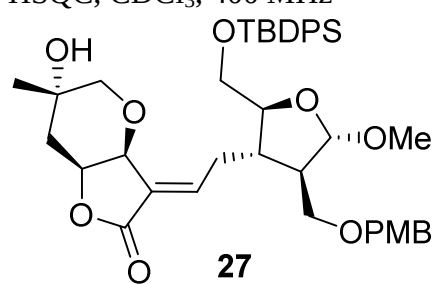
¹³C NMR, CDCl₃, 100 MHz



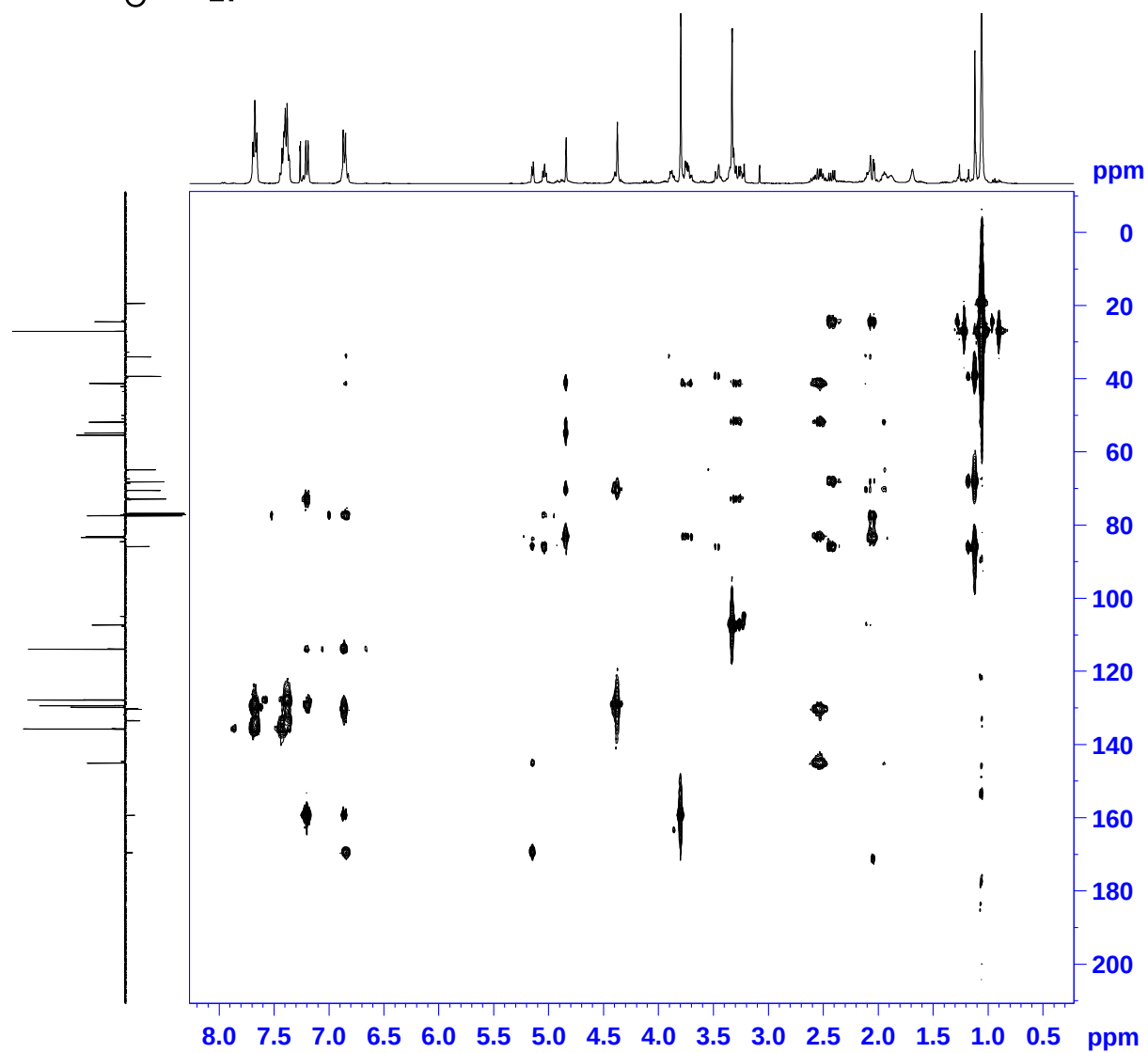
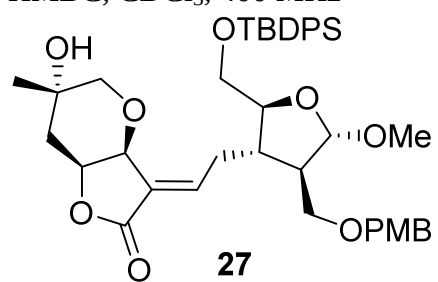
COSY, CDCl₃, 400 MHz



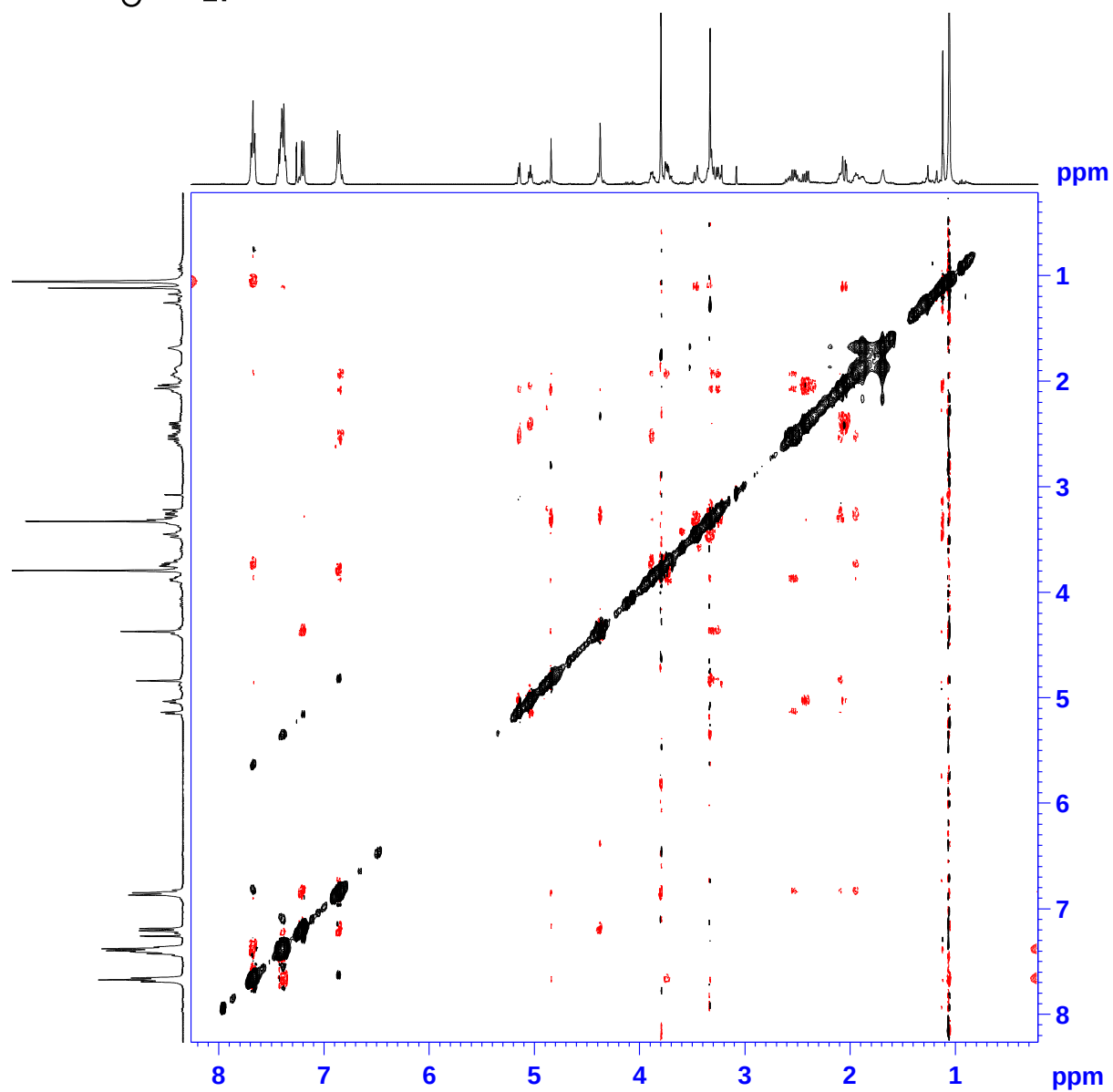
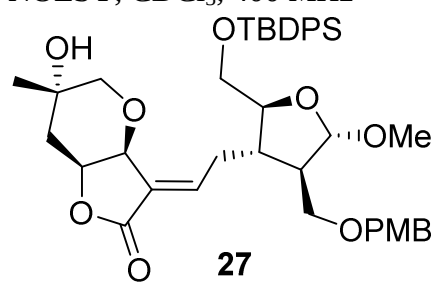
HSQC, CDCl₃, 400 MHz



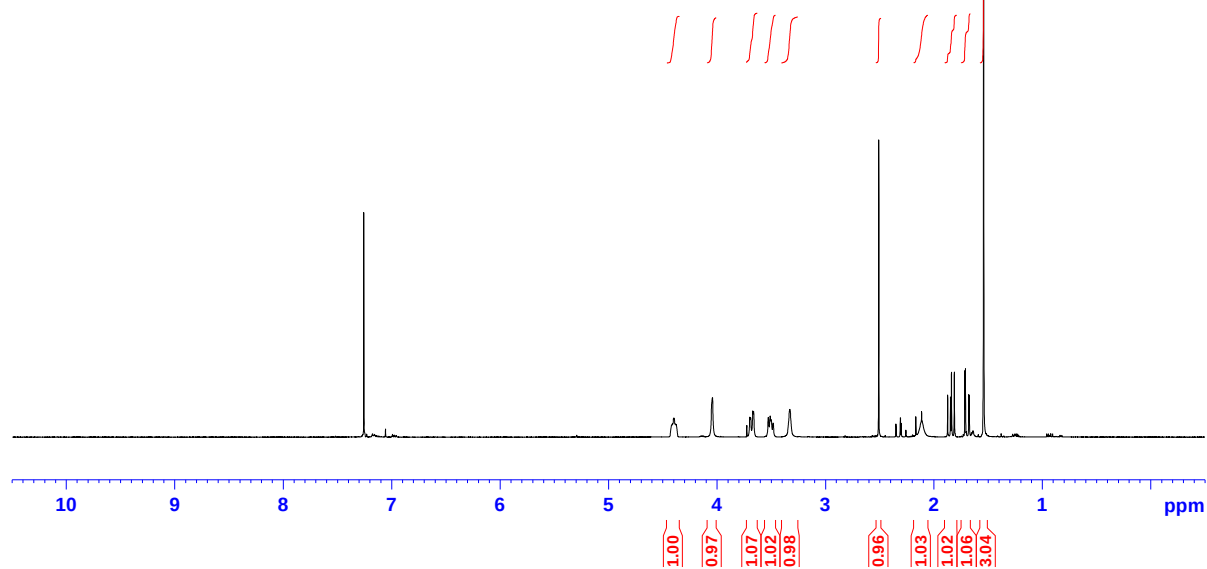
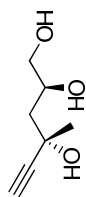
HMBC, CDCl₃, 400 MHz



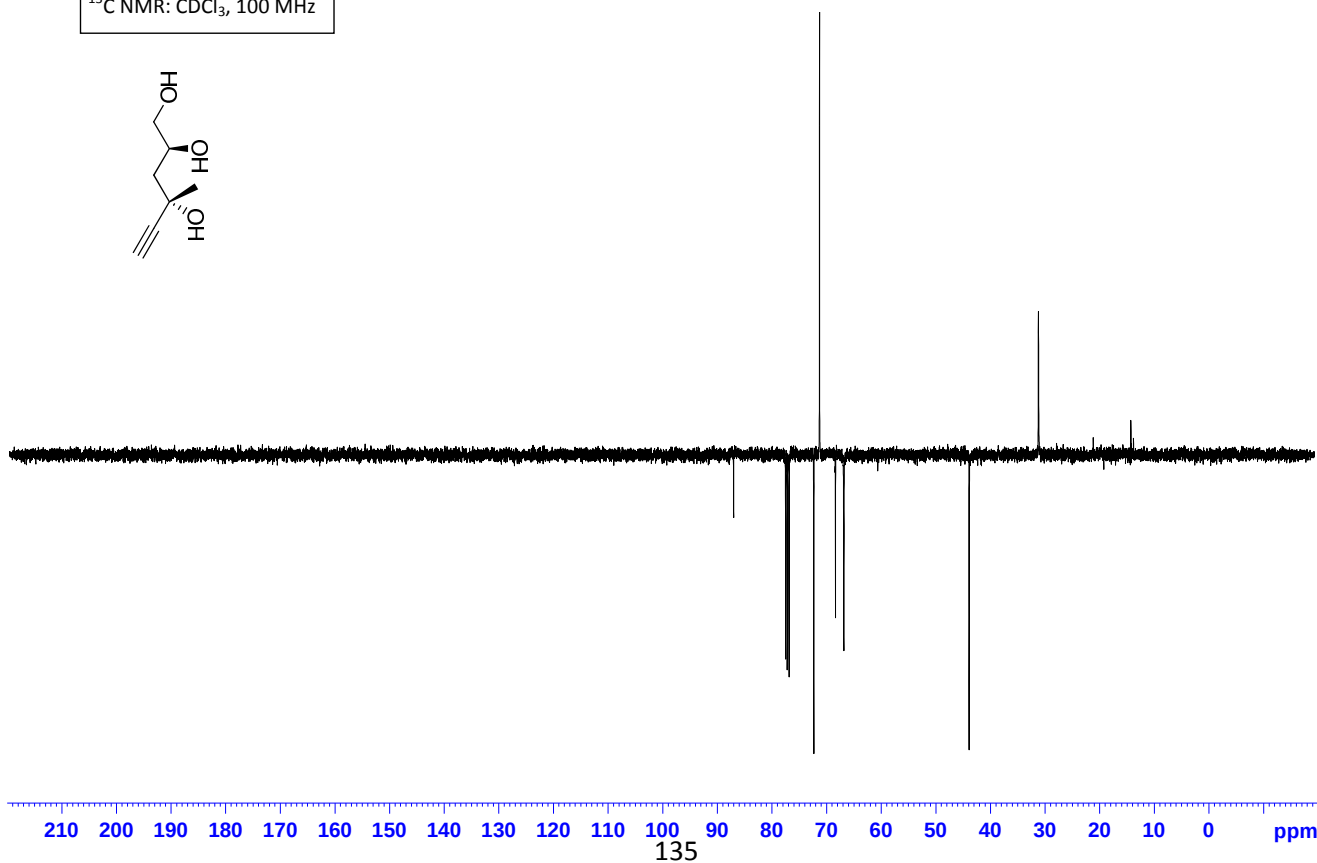
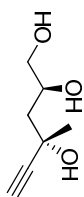
NOESY, CDCl₃, 400 MHz



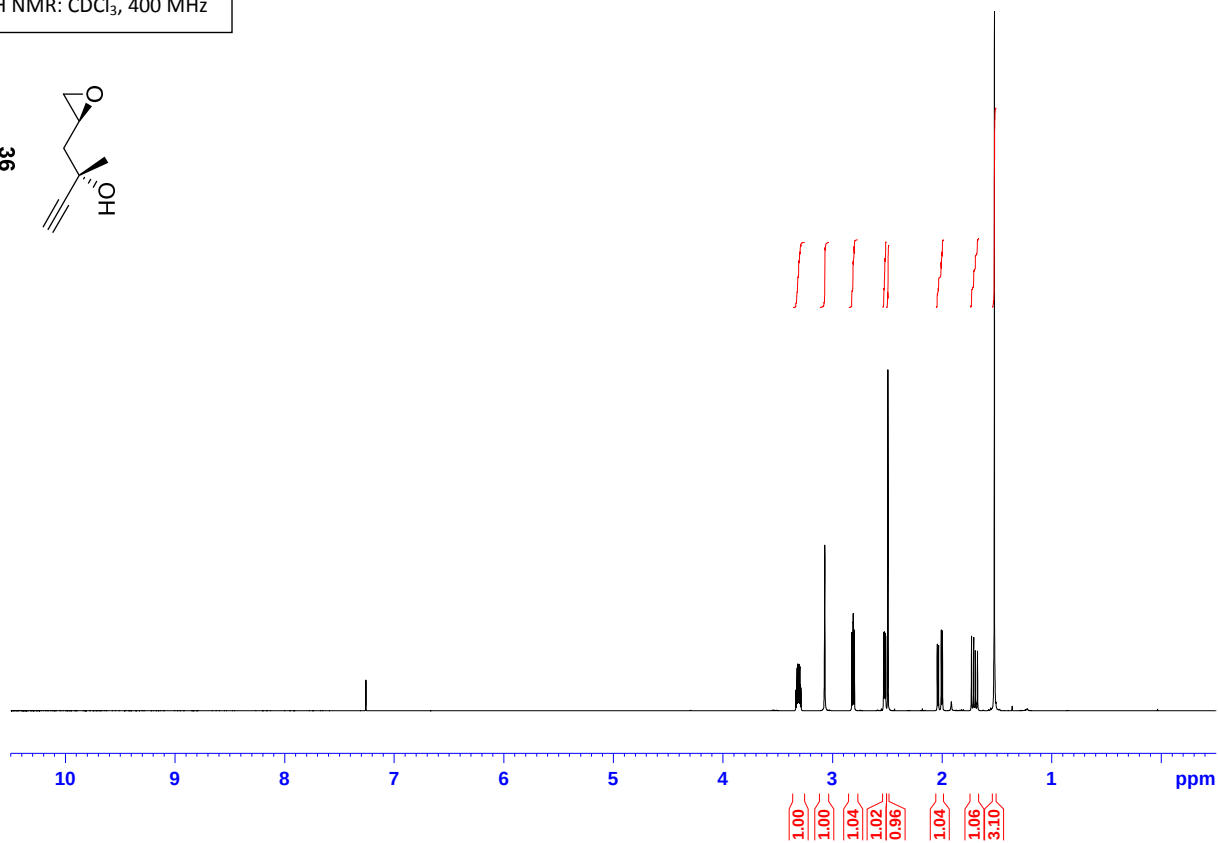
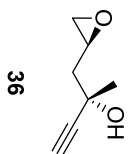
¹H NMR: CDCl₃, 400 MHz



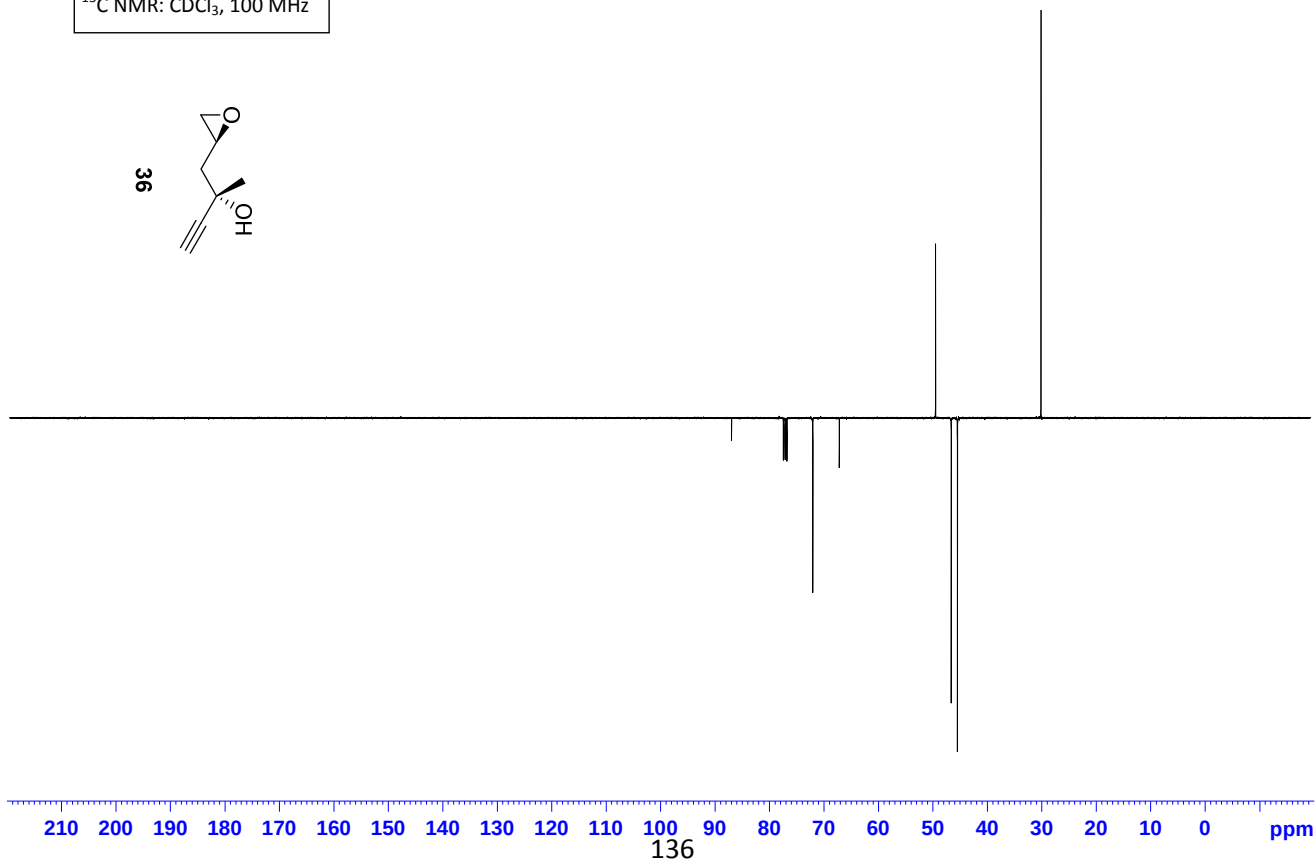
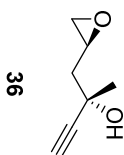
¹³C NMR: CDCl₃, 100 MHz



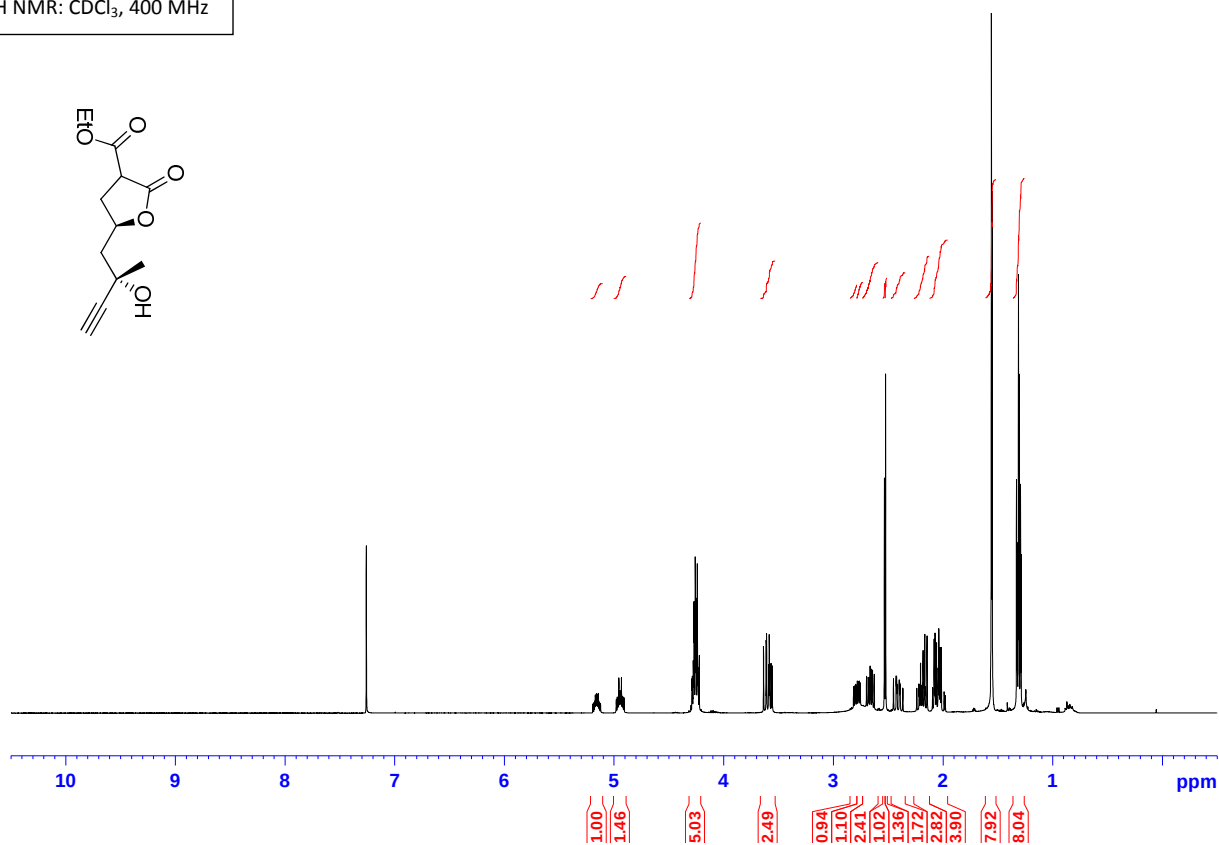
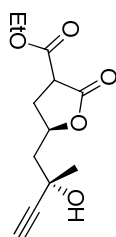
¹H NMR: CDCl₃, 400 MHz



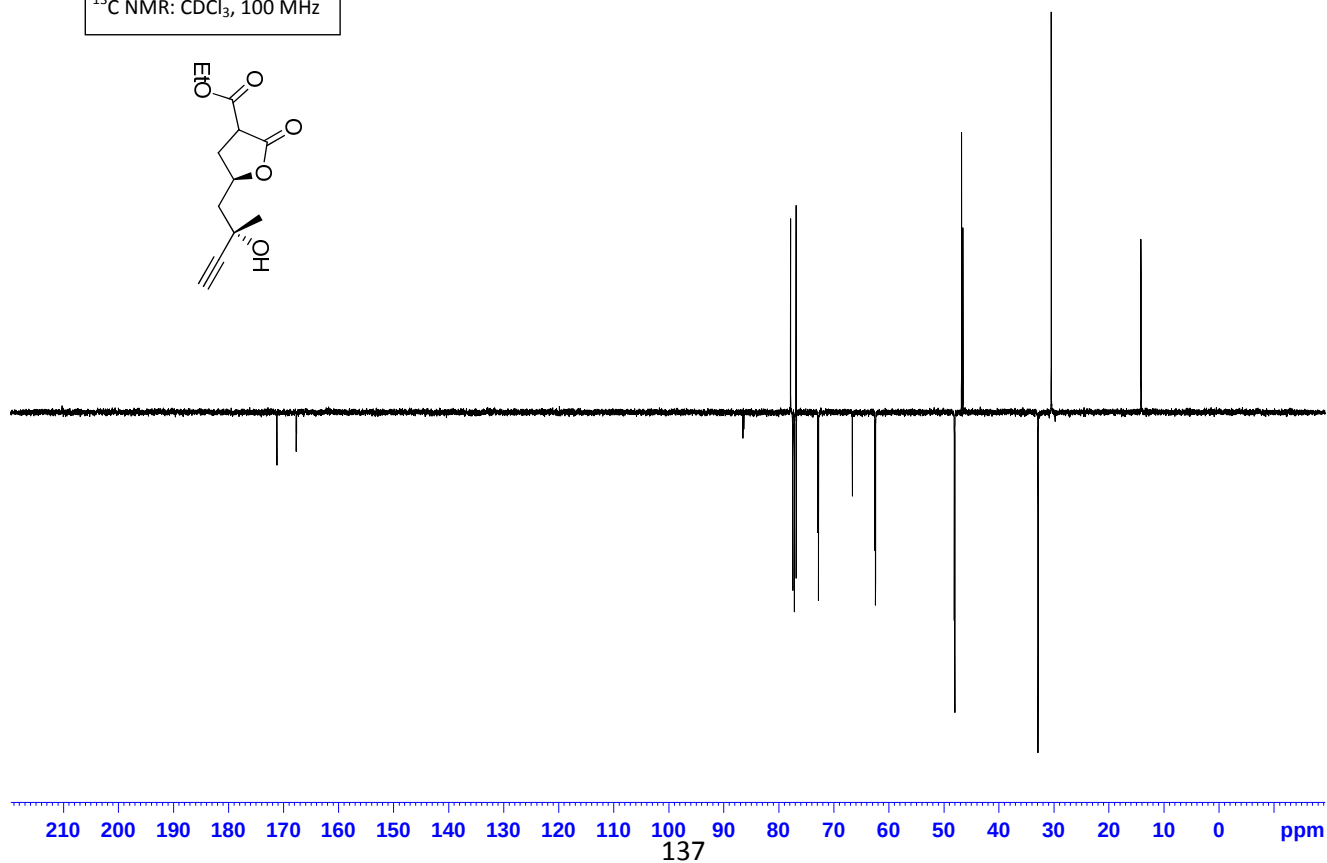
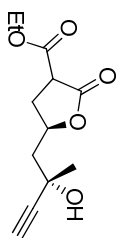
¹³C NMR: CDCl₃, 100 MHz



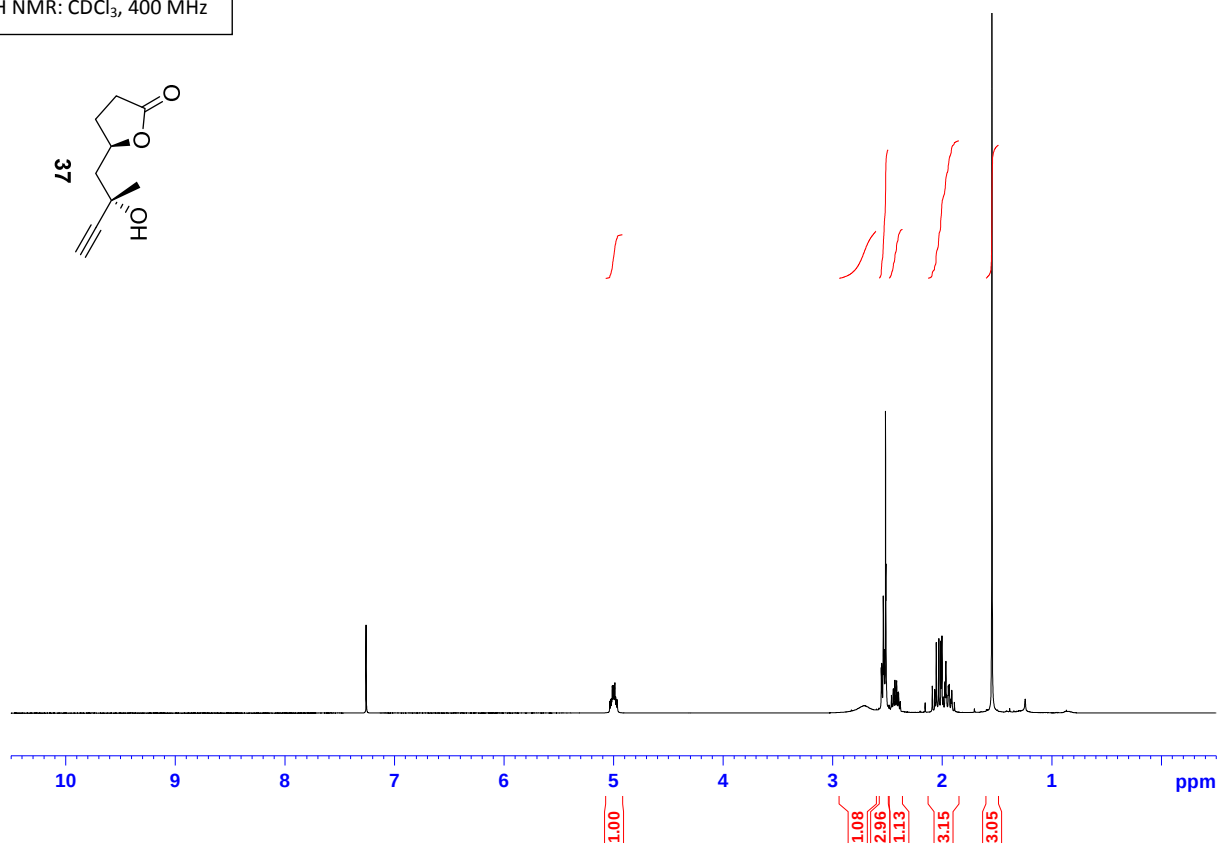
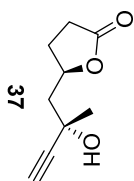
¹H NMR: CDCl₃, 400 MHz



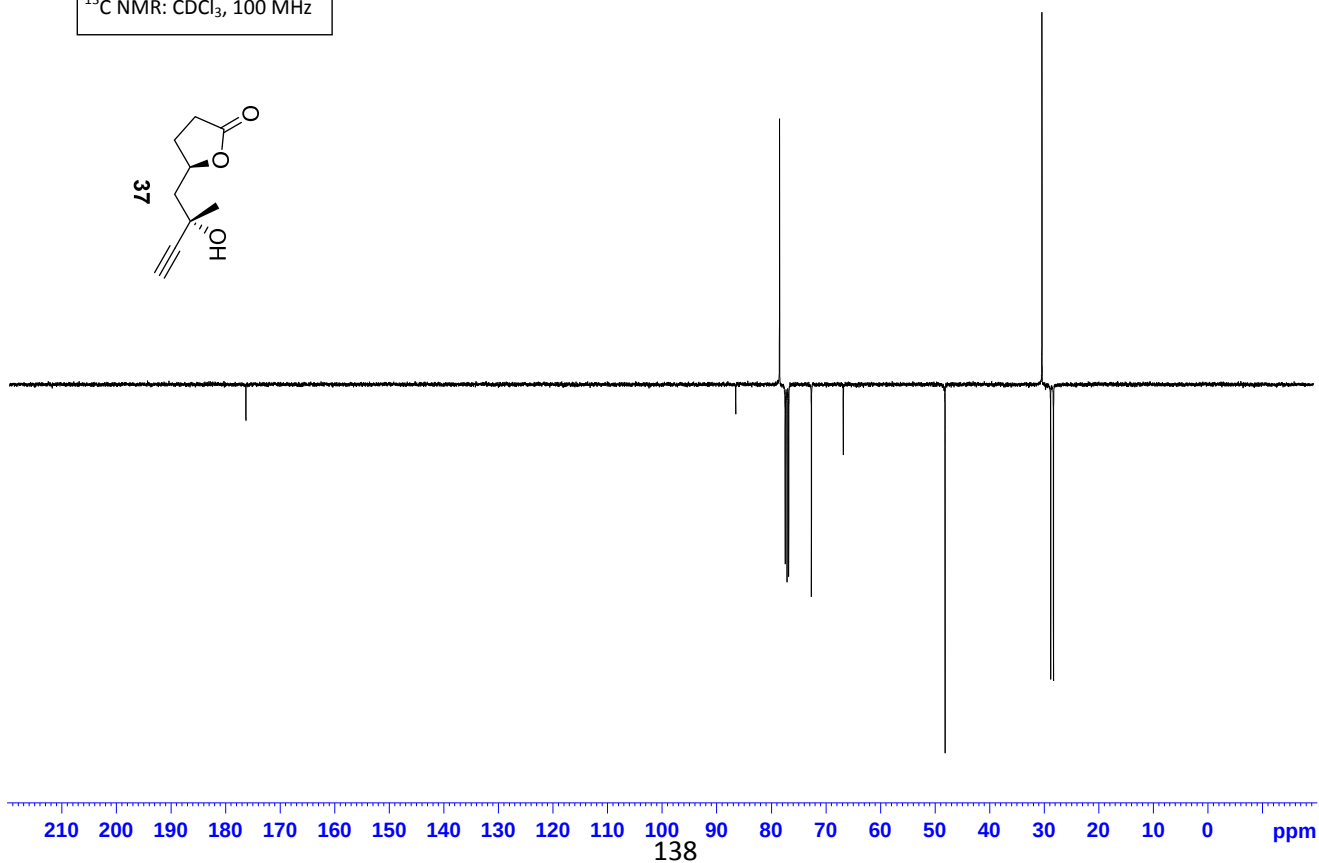
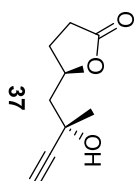
¹³C NMR: CDCl₃, 100 MHz

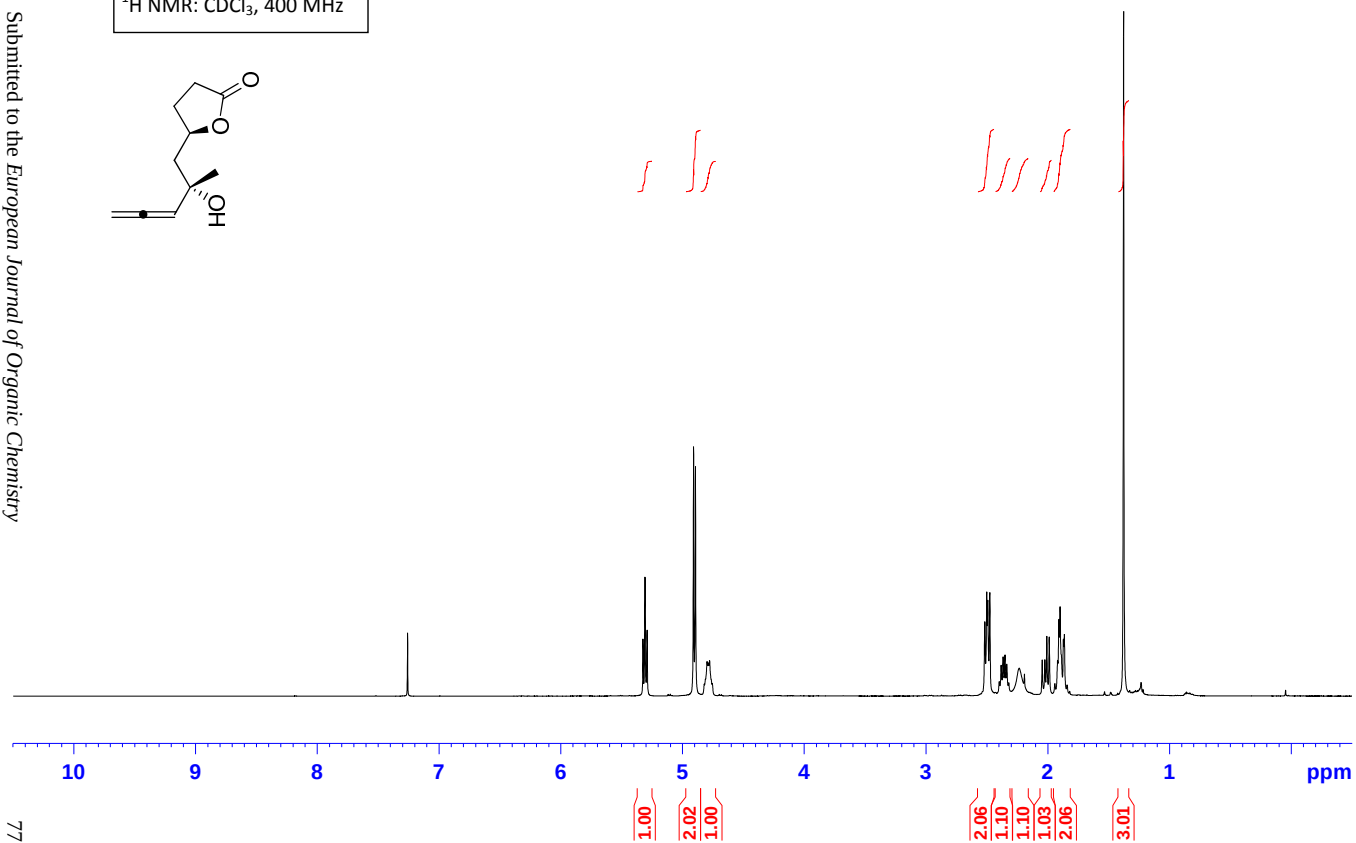
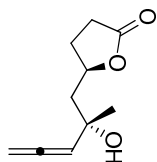
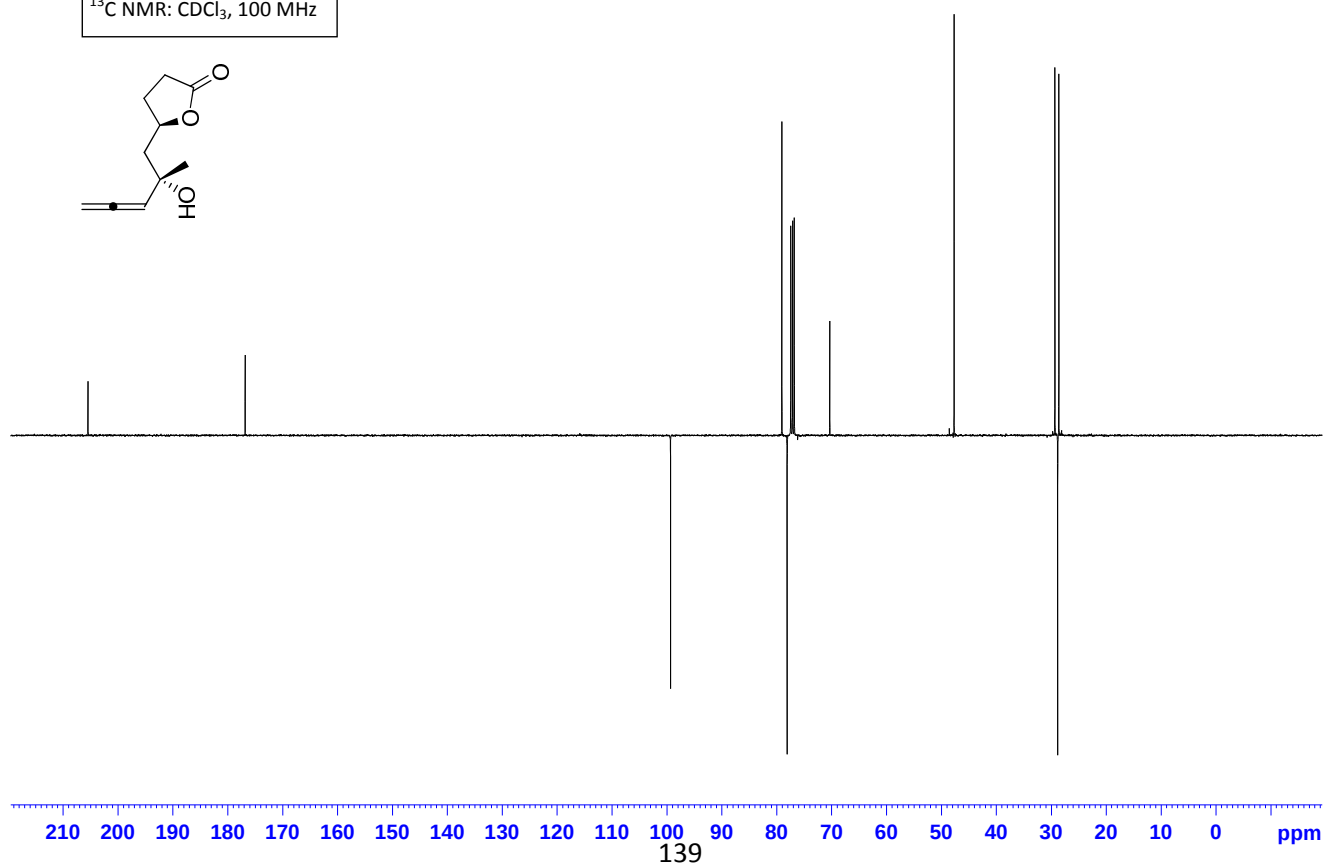
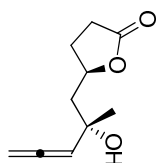


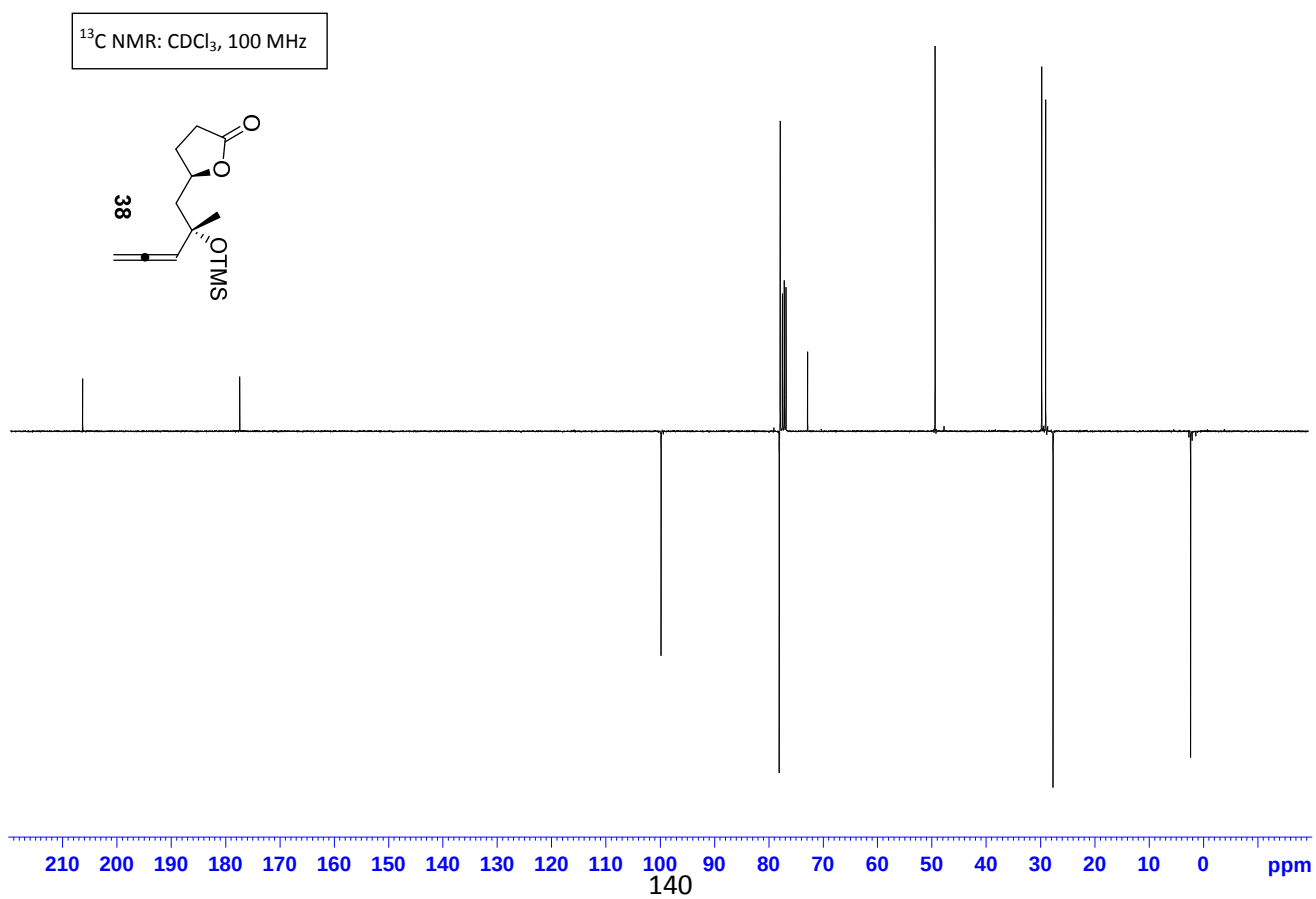
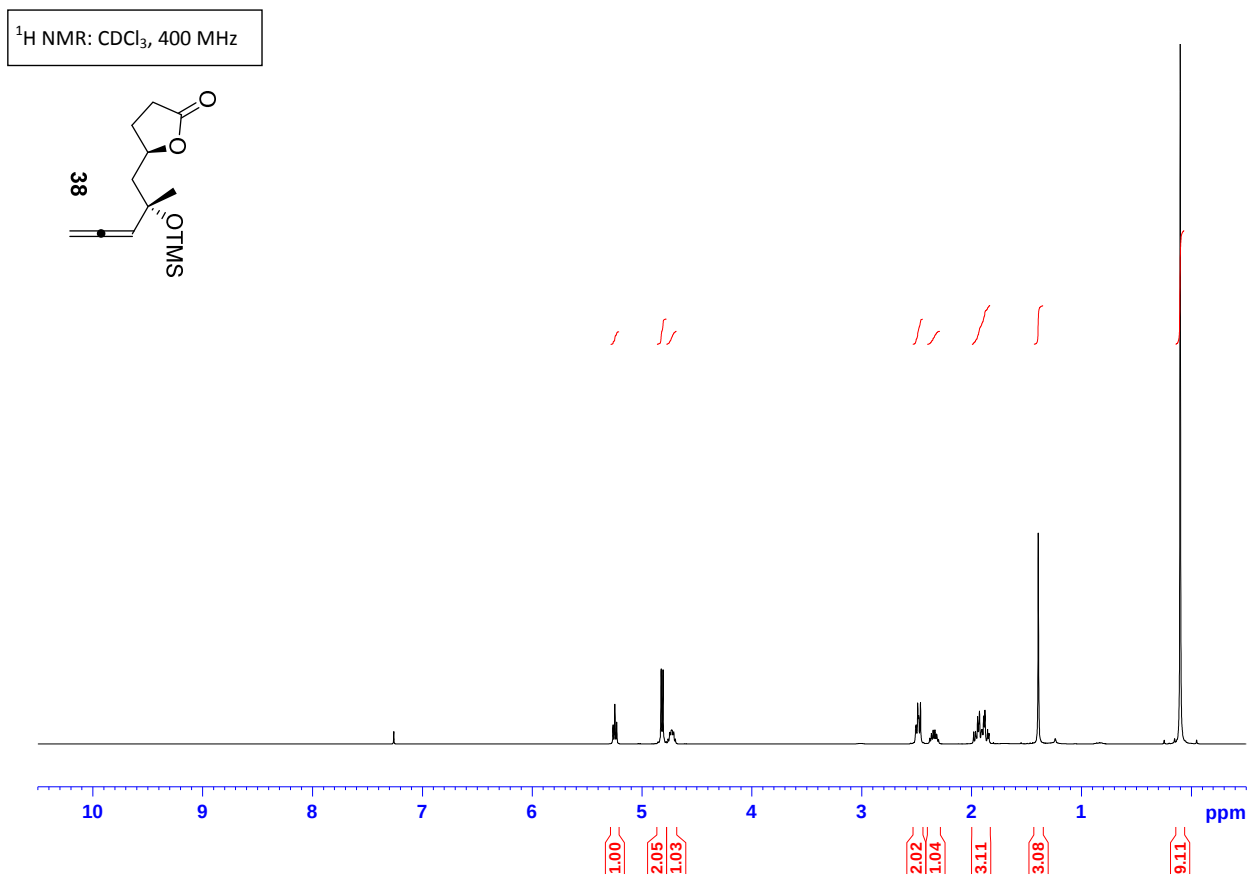
^1H NMR: CDCl_3 , 400 MHz



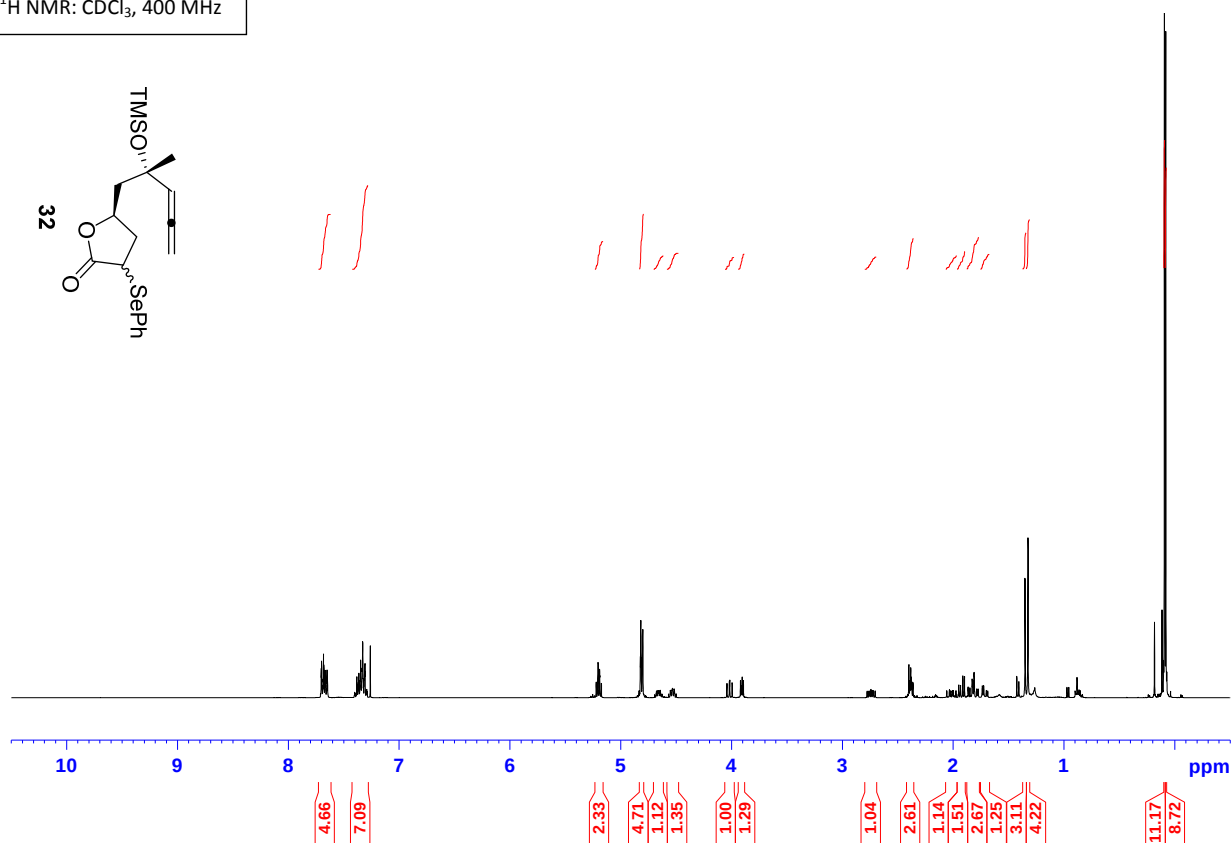
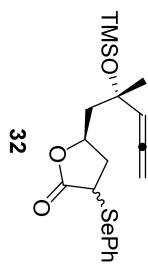
^{13}C NMR: CDCl_3 , 100 MHz



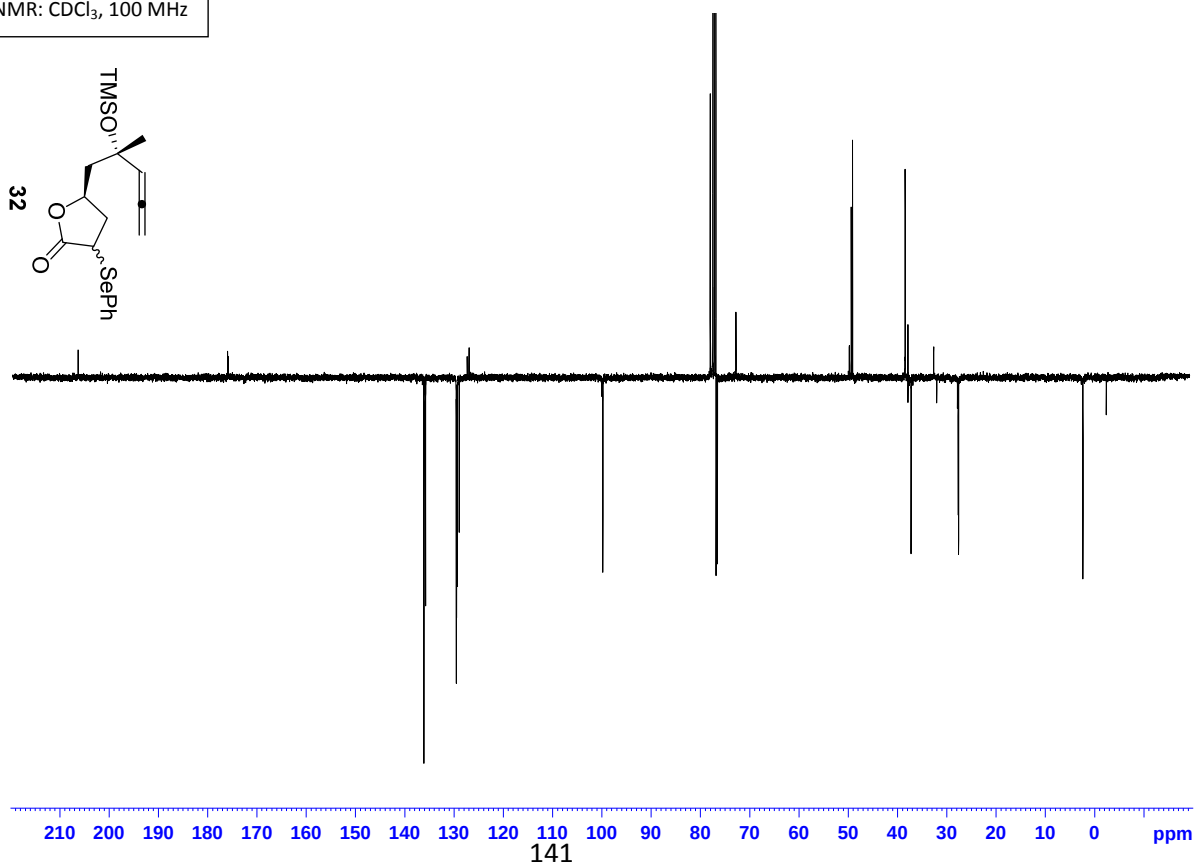
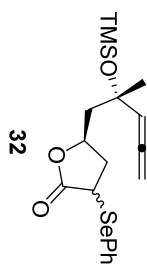
^1H NMR: CDCl_3 , 400 MHz ^{13}C NMR: CDCl_3 , 100 MHz



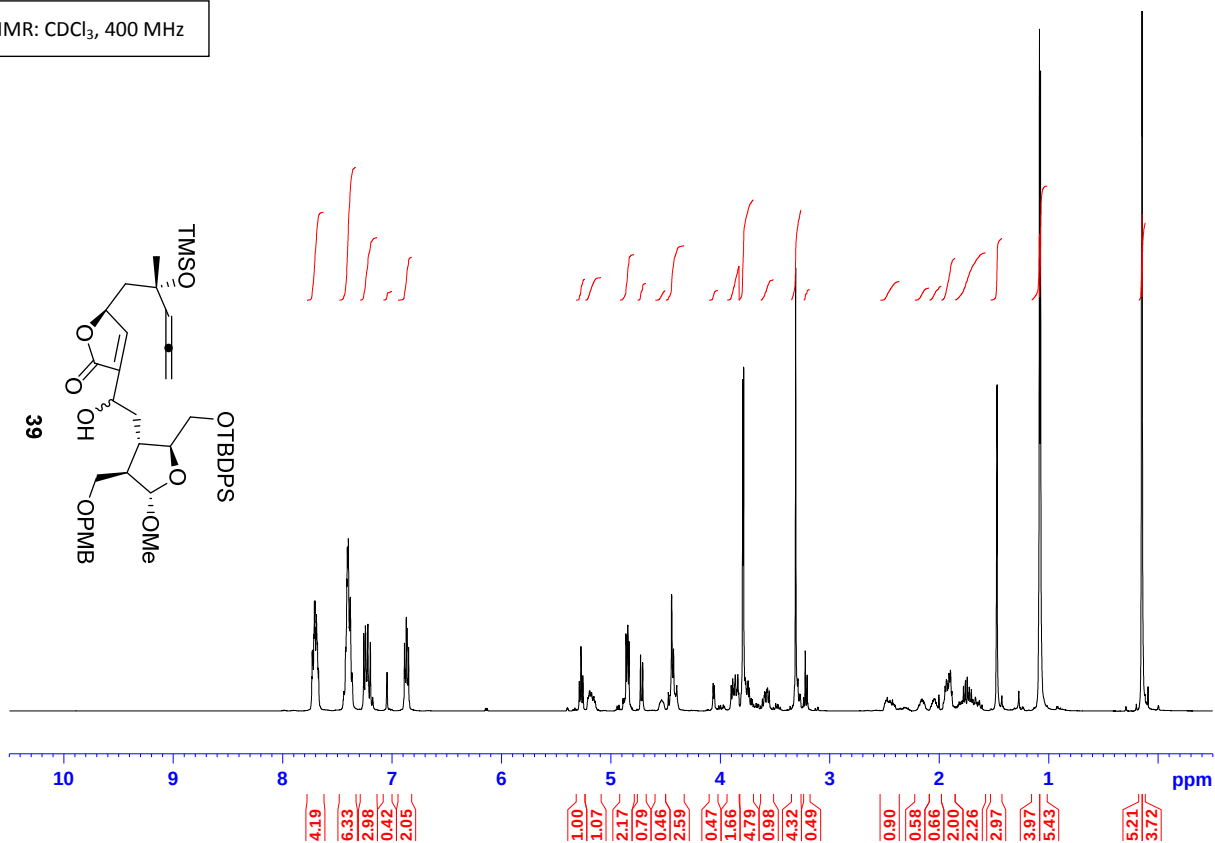
^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR: CDCl_3 , 100 MHz

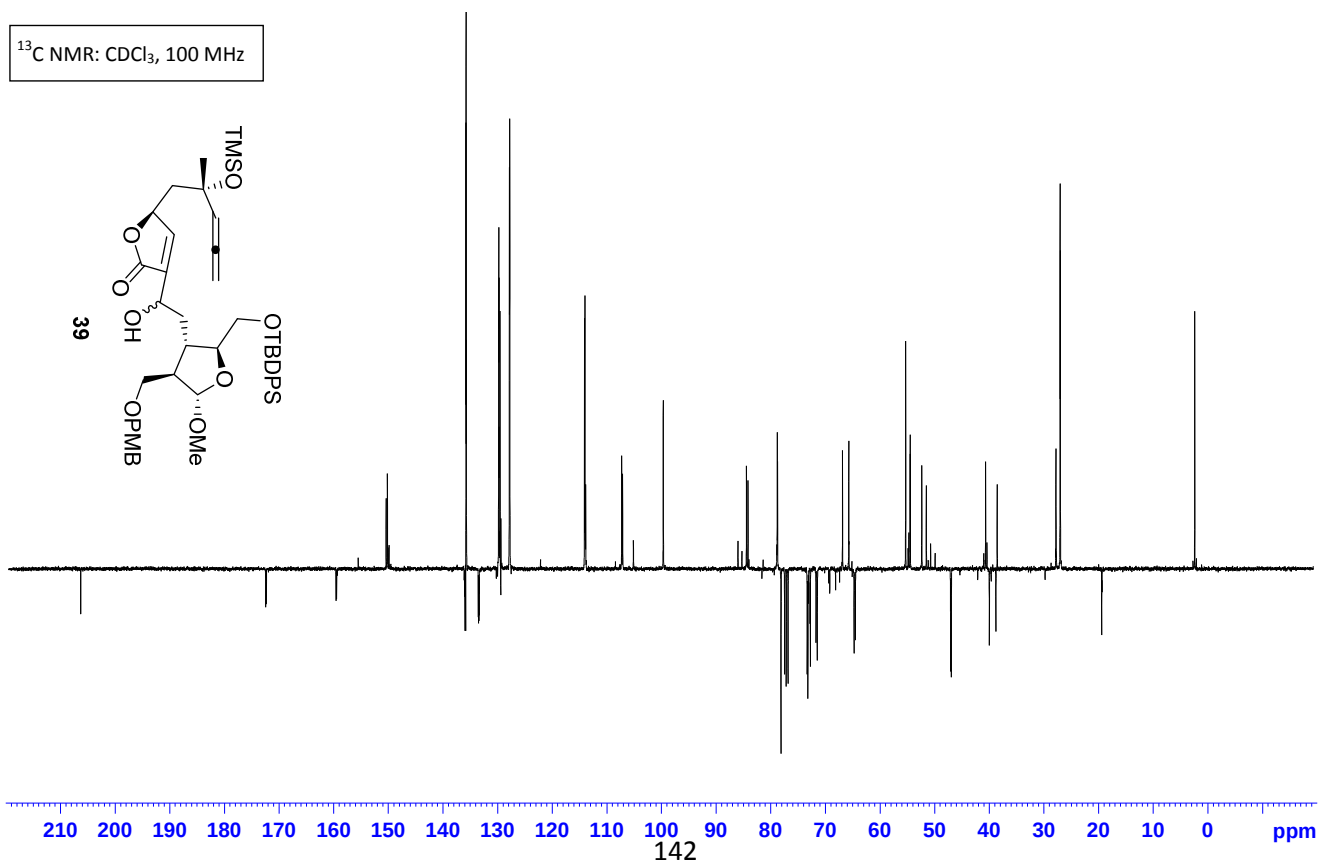


^1H NMR: CDCl_3 , 400 MHz

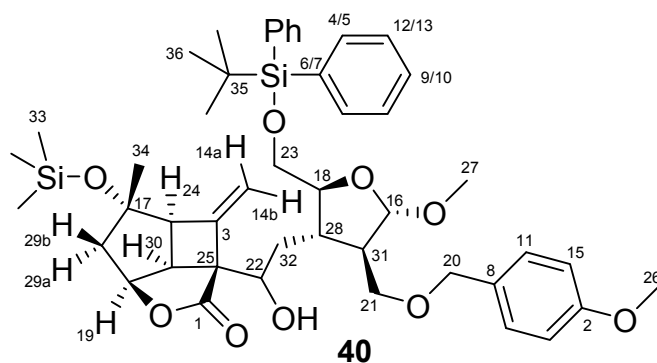


83

^{13}C NMR: CDCl_3 , 100 MHz



84



No.	¹³ C [ppm]	¹ H [ppm]
1	177.2	-
2	159.5	-
3	144.8	-
4	135.91	7.71-7.66
5	135.86	7.71-7.66
6	133.7	-
7	133.5	-
8	130.0	-
9	129.80	7.44-7.35
10	129.78	7.44-7.35
11	129.5	7.21
12	127.82	7.44-7.35
13	127.79	7.44-7.35
14	114.5	5.31 ^a ; 5.17-5.11 ^b
15	114.0	6.85
16	107.4	4.75
17	84.9	-
18	83.9	3.84
19	83.7	5.17-5.11
20	73.0	4.45; 4.40
21	71.5	3.46-3.41; 3.30-3.25
22	69.7	4.01-3.99
23	65.5	3.76-3.74
24	57.90	3.09
25	57.88	-
26	55.4	3.80
27	54.6	3.30
28	51.7	2.26-2.20
29	49.5	2.45 ^a , 1.92 ^b
30	44.4	3.30-3.25
31	39.6	2.06-1.99
32	35.2	1.65; 1.42-1.38
33	27.0	1.06
34	23.5	1.42-1.38
35	19.4	-
36	2.44	0.12
OH	-	3.49

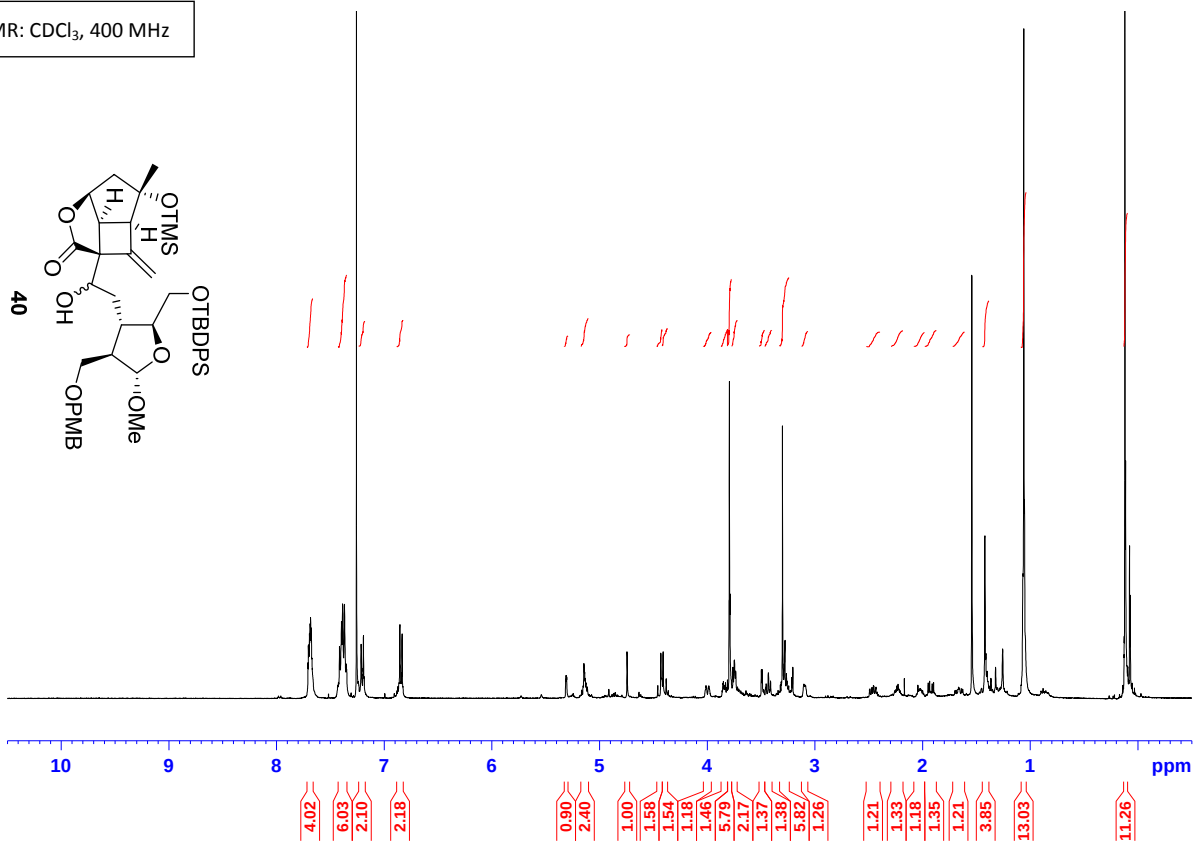
NOE- correlation:

14a ↔ 24, 29a ↔ 19

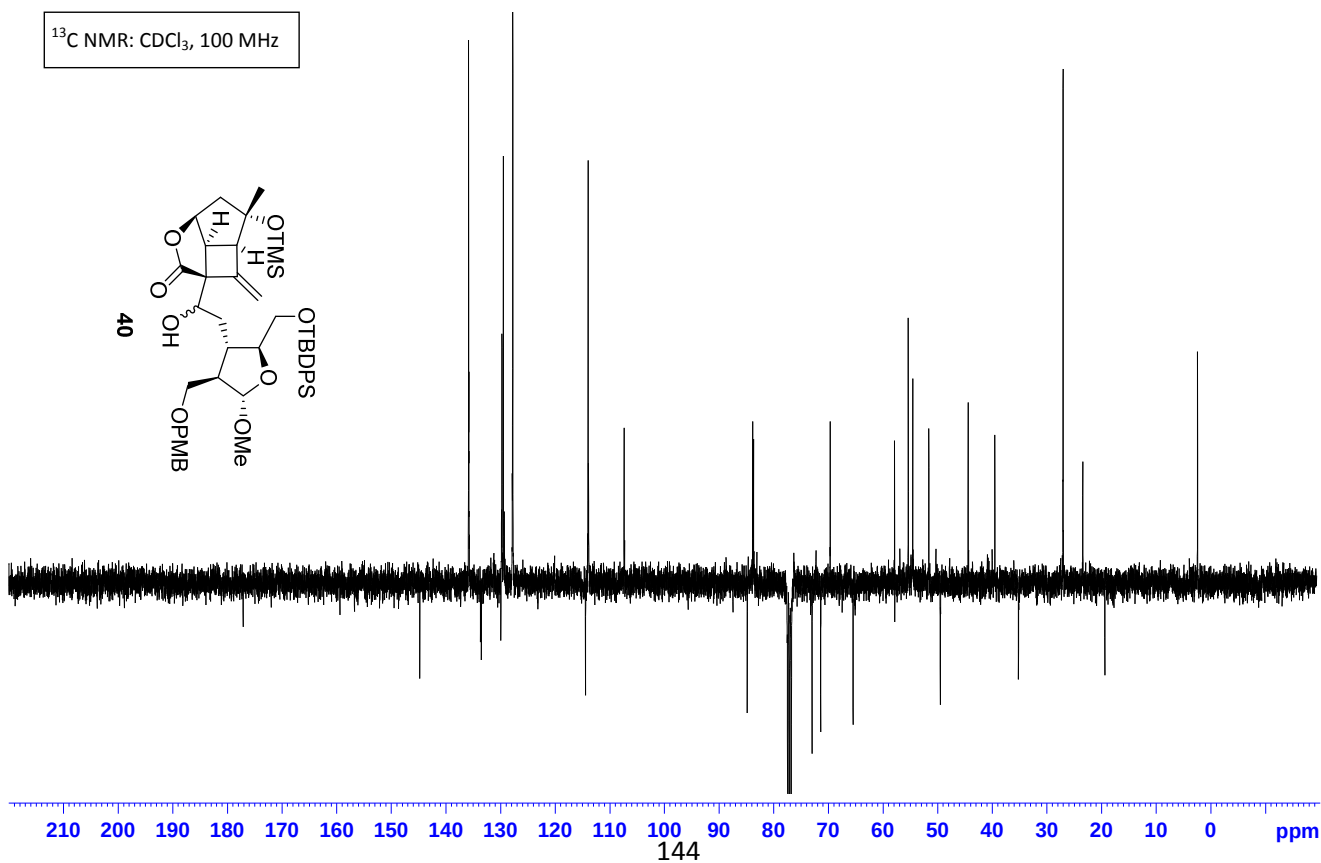
HMBC-correlation:

30 ↔ 3 ↔ 14a ↔ 24

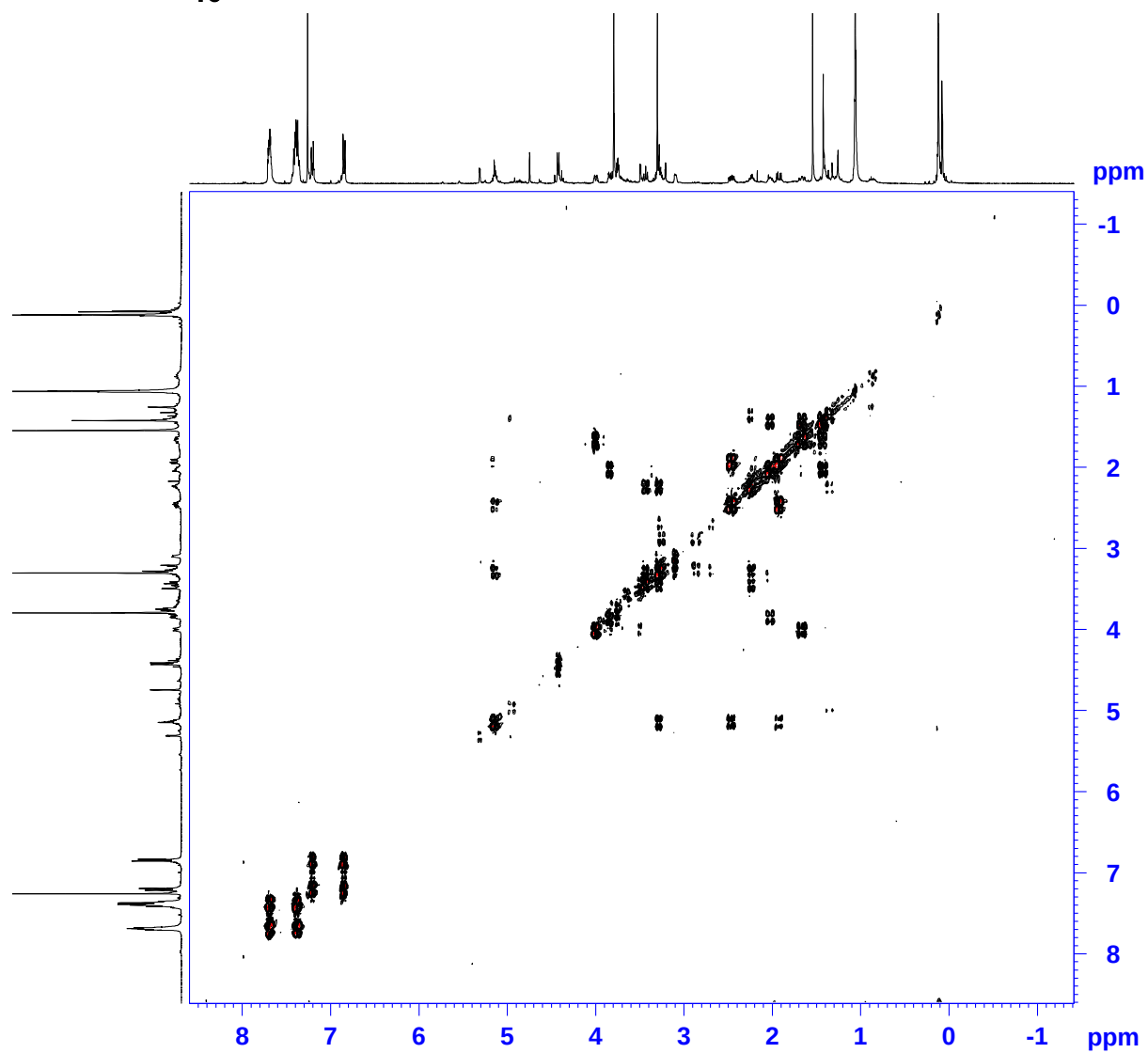
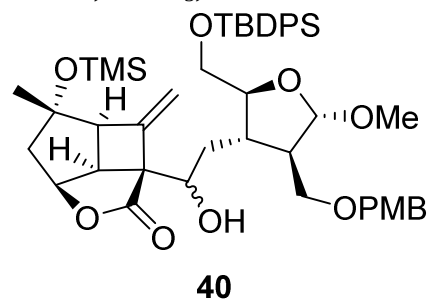
¹H NMR: CDCl₃, 400 MHz



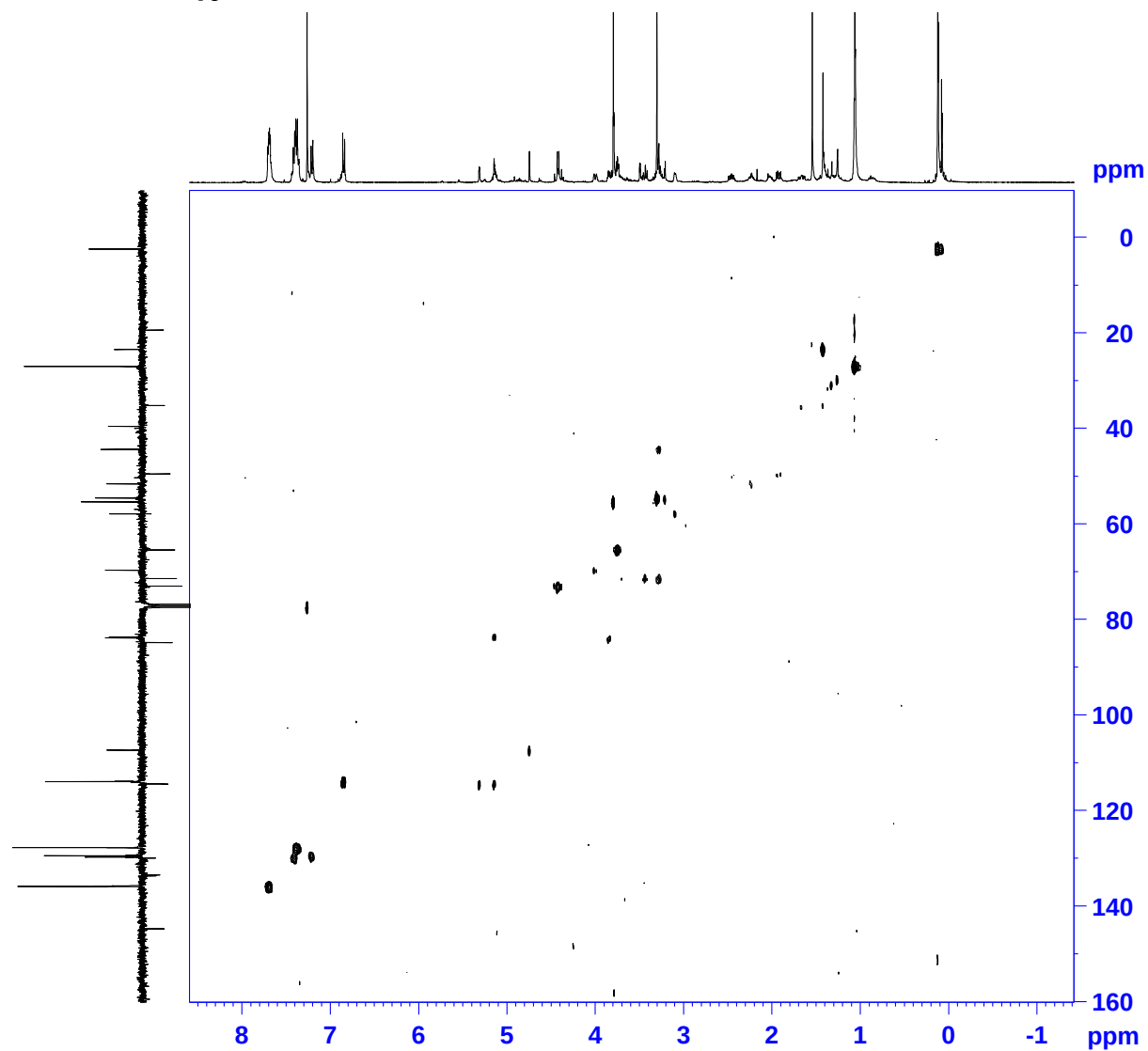
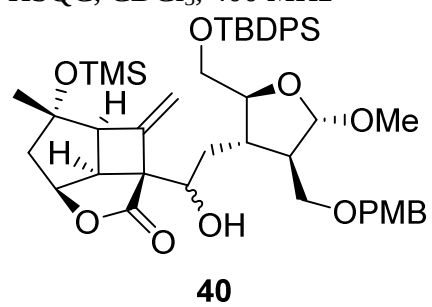
¹³C NMR: CDCl₃, 100 MHz



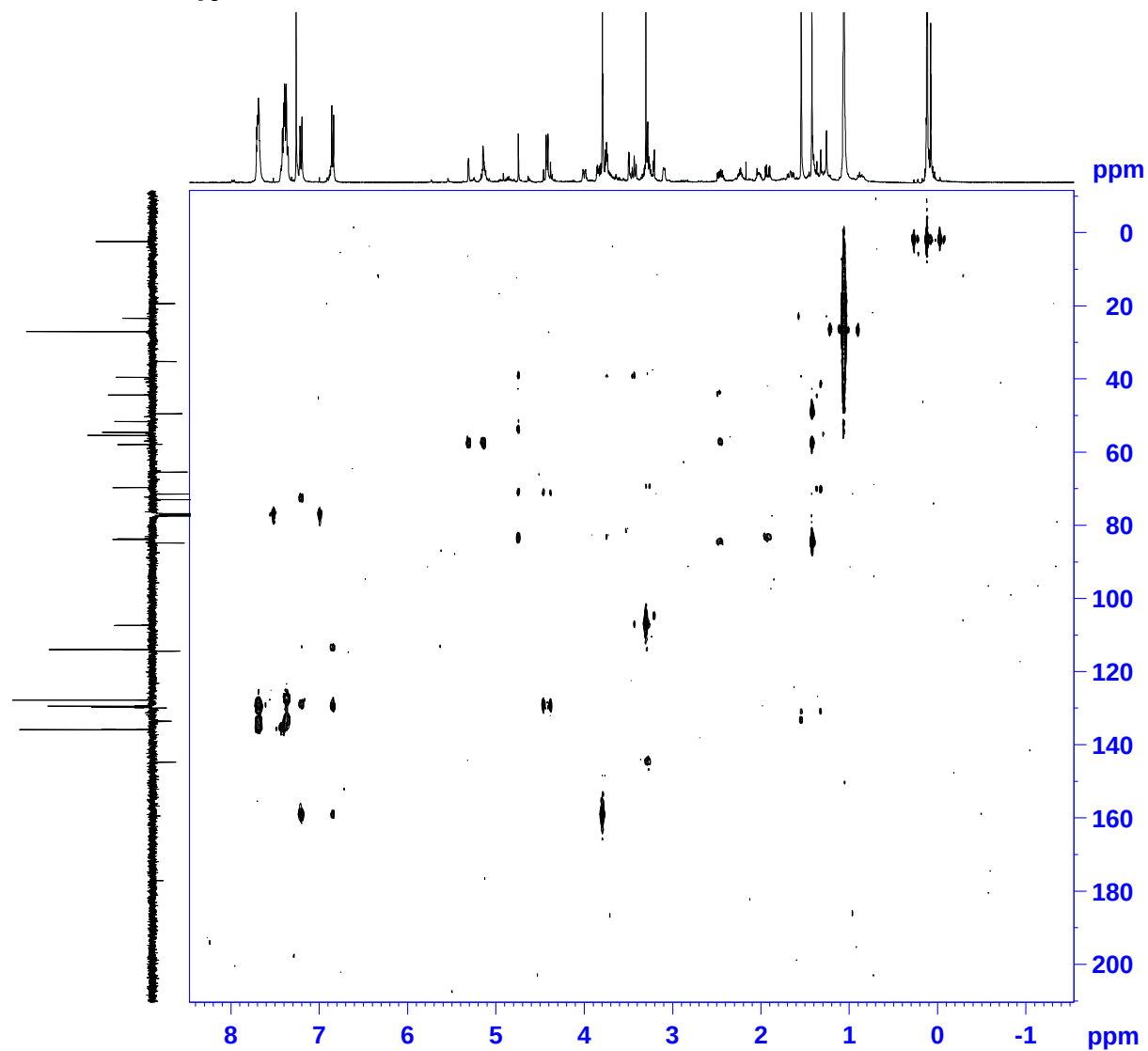
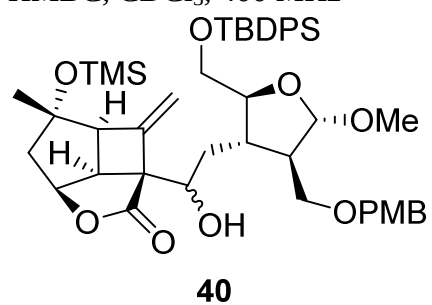
COSY, CDCl₃, 400 MHz



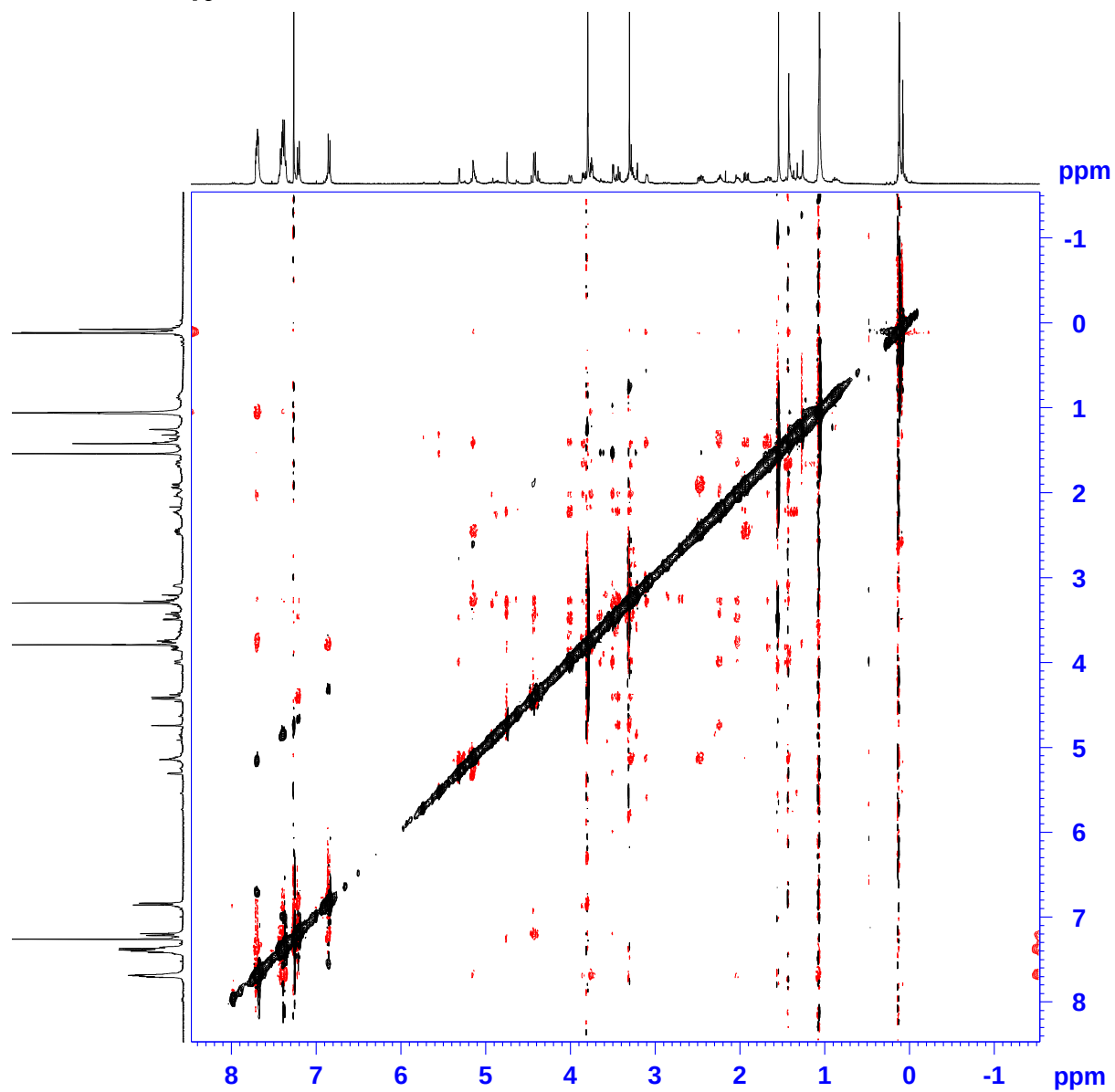
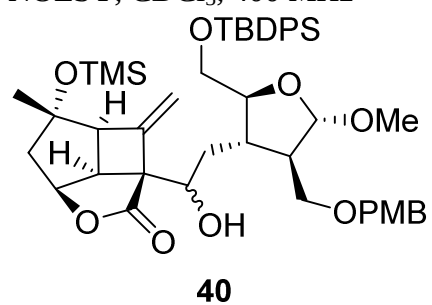
HSQC, CDCl₃, 400 MHz

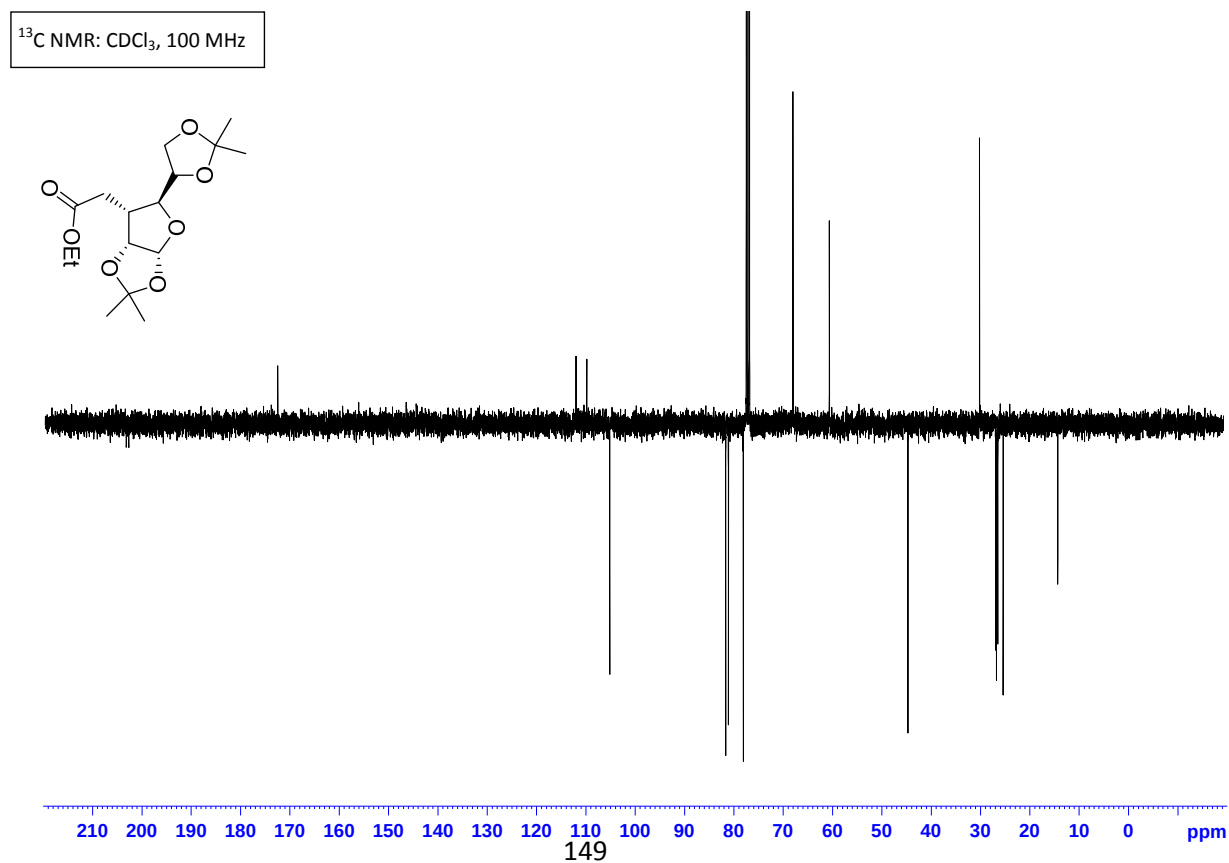
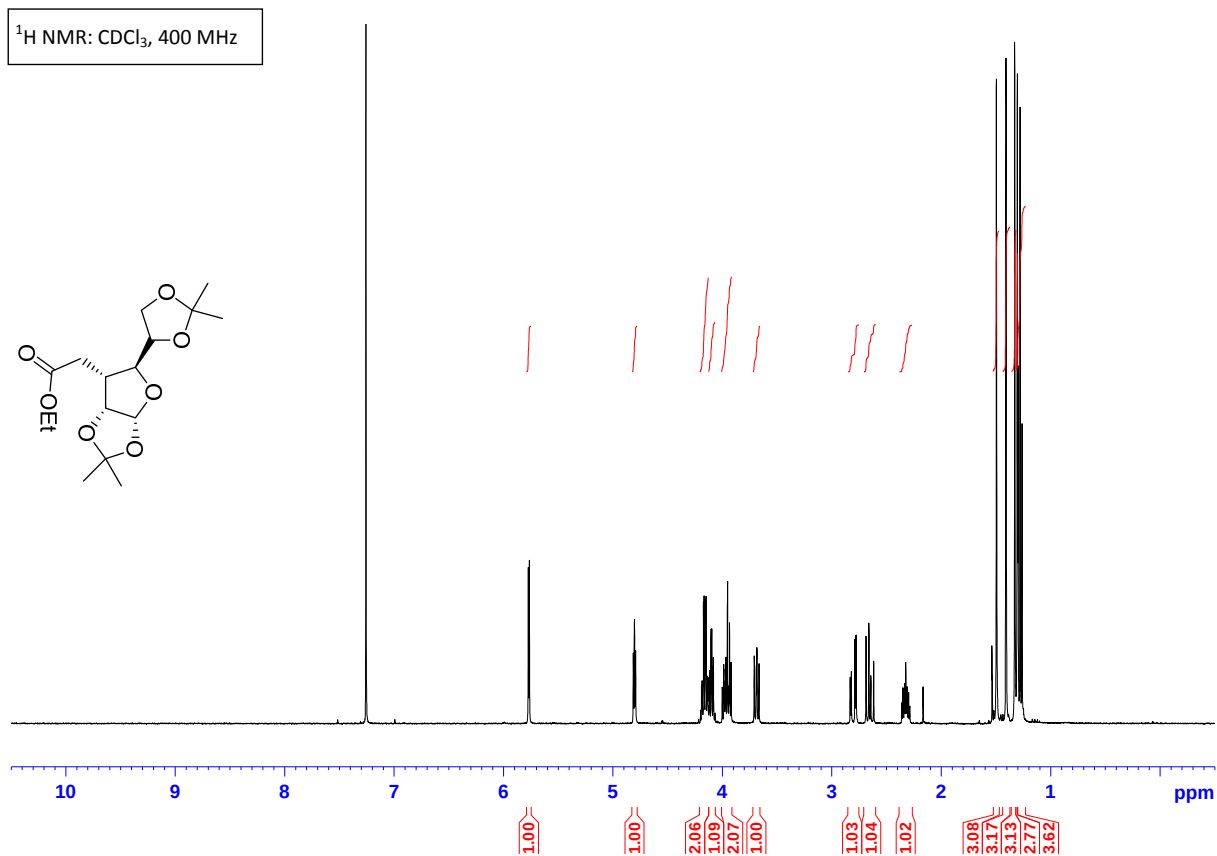


HMBC, CDCl₃, 400 MHz

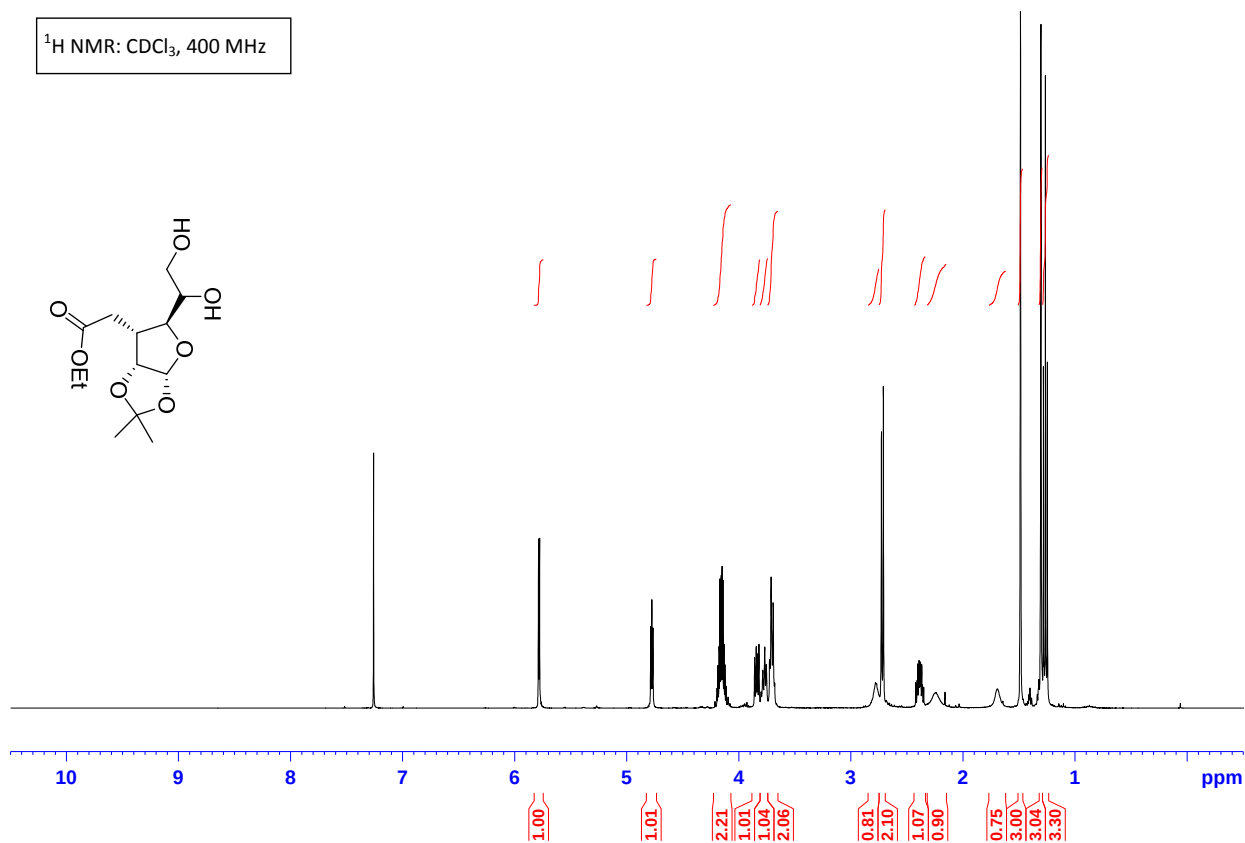


NOESY, CDCl₃, 400 MHz

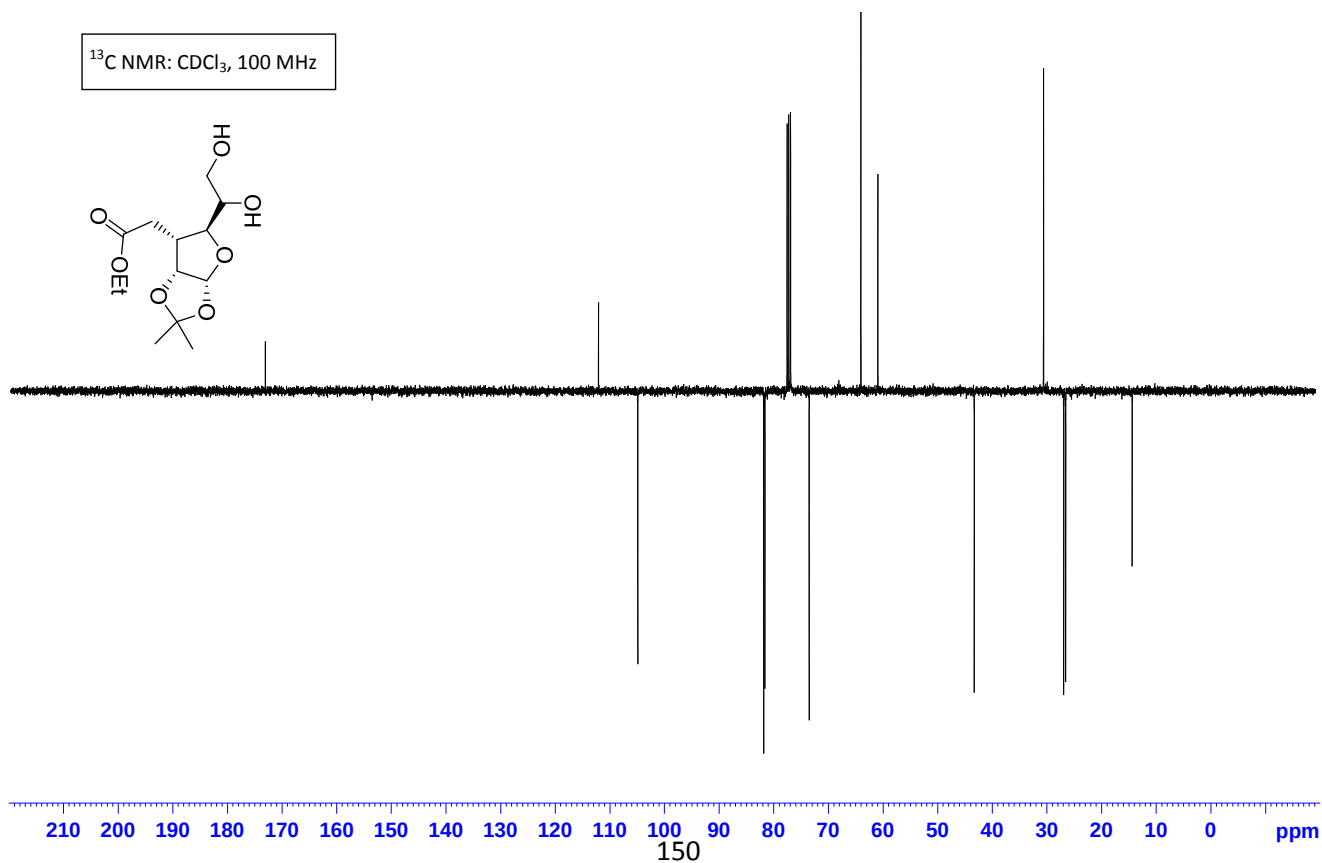


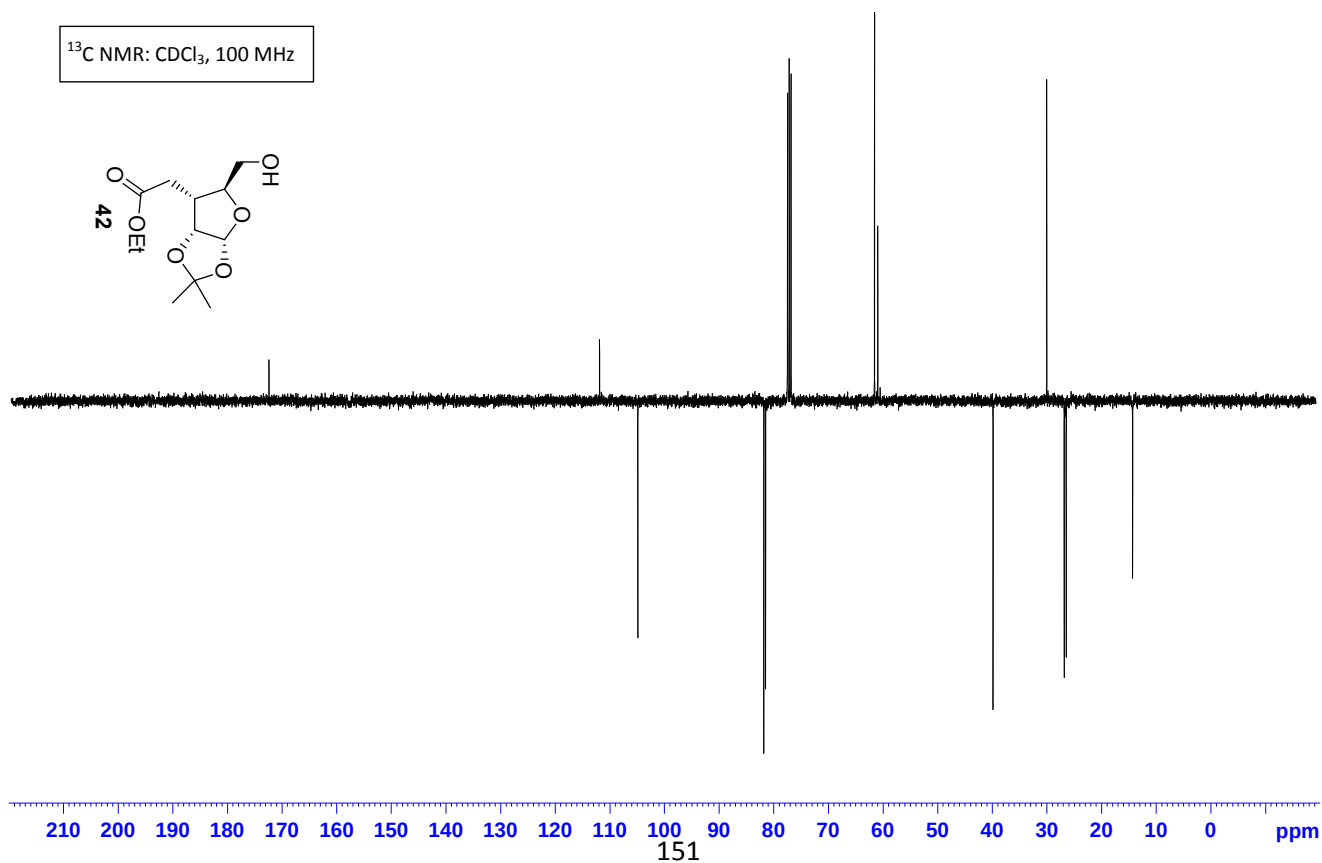
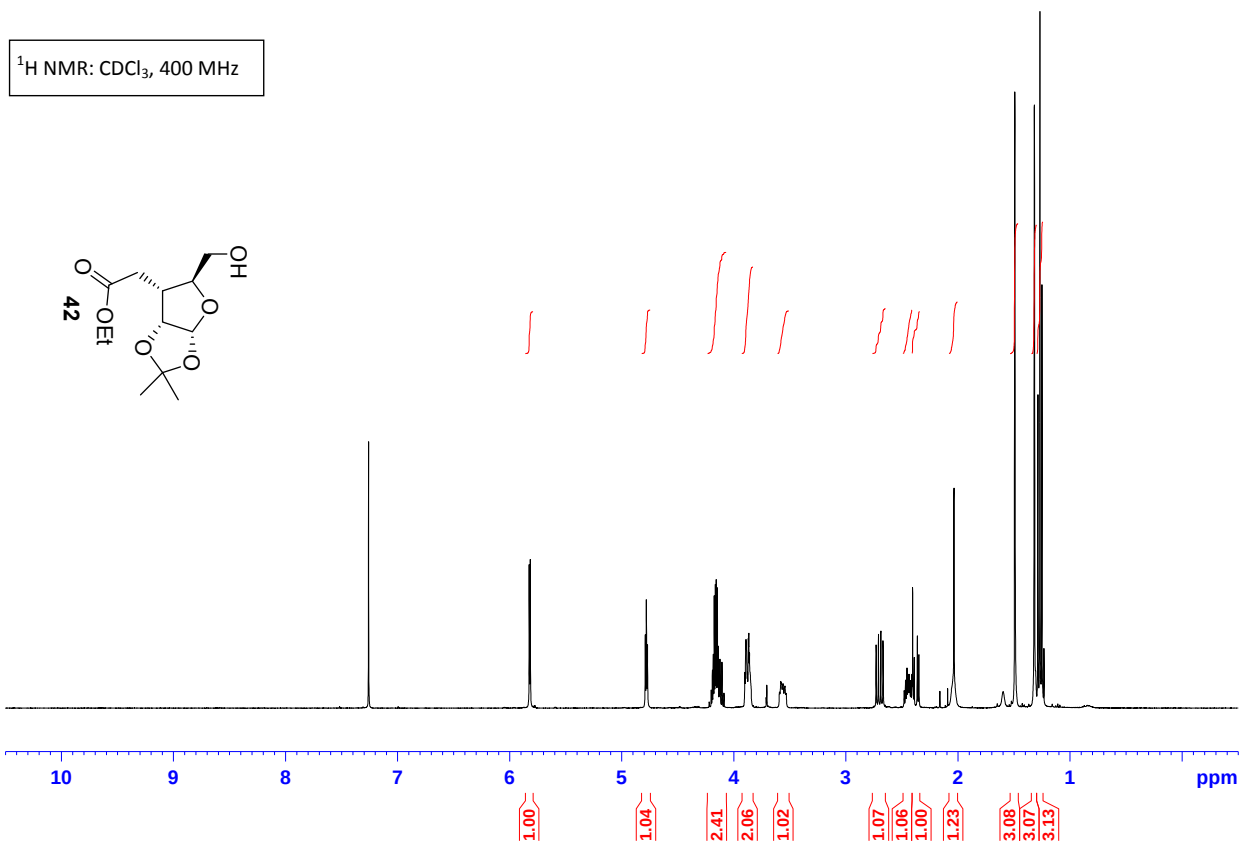


^1H NMR: CDCl_3 , 400 MHz

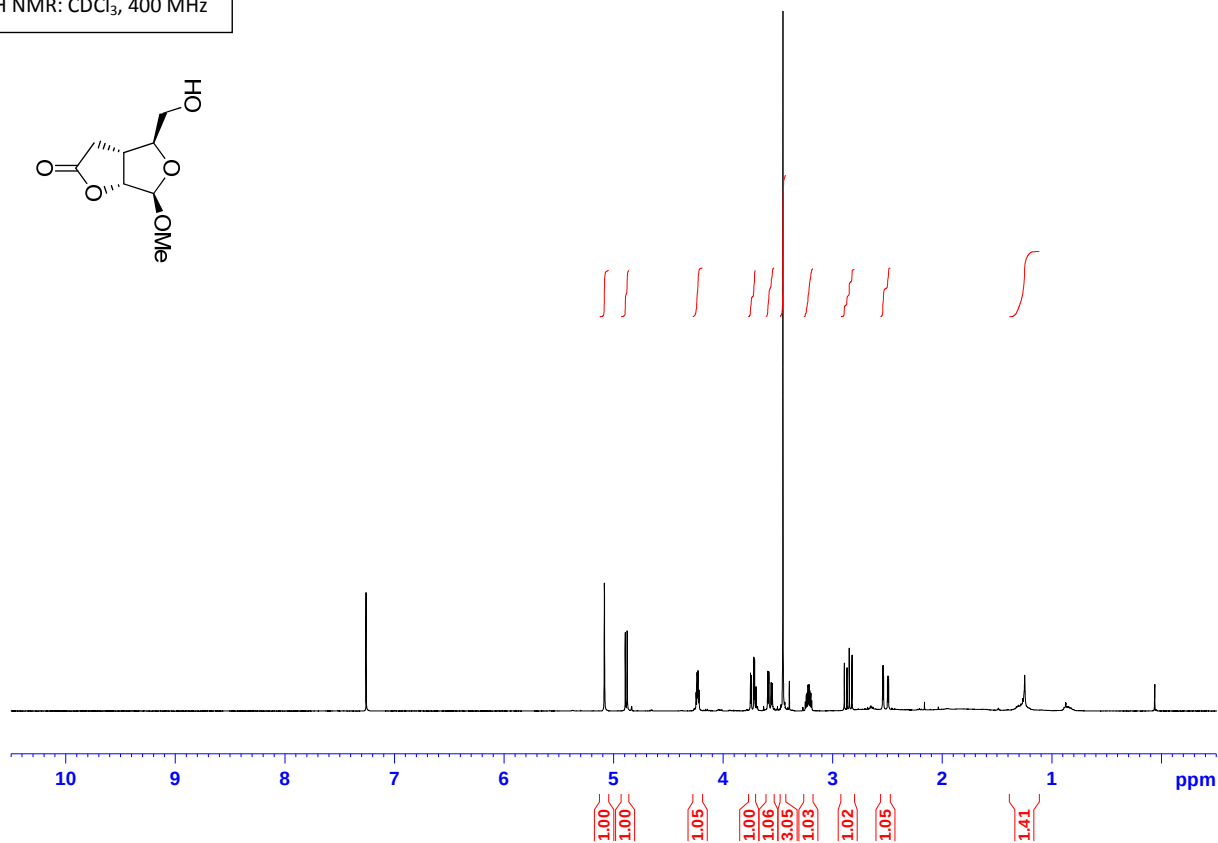
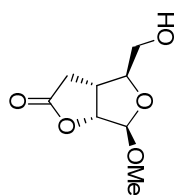


^{13}C NMR: CDCl_3 , 100 MHz

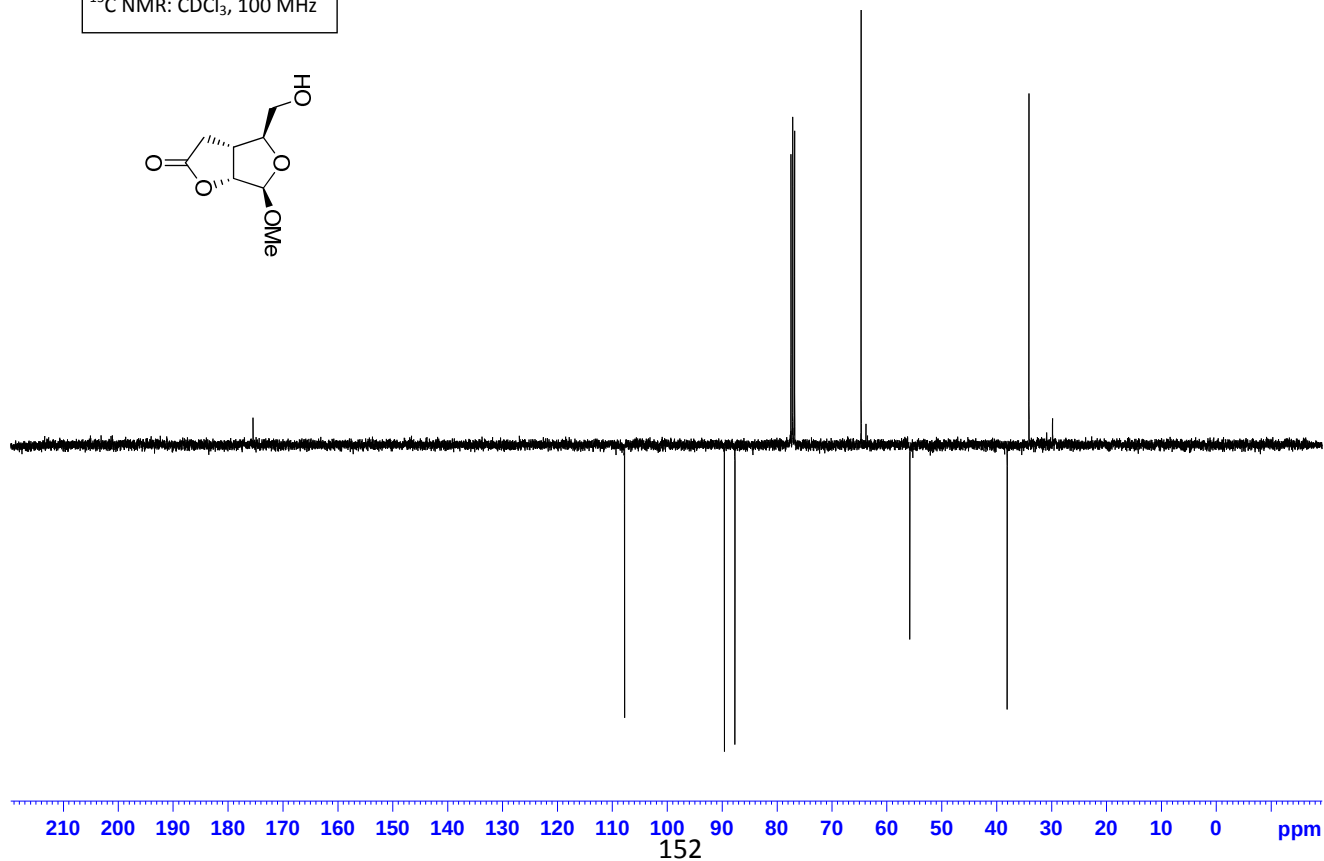
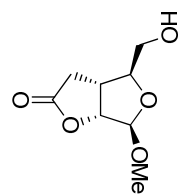




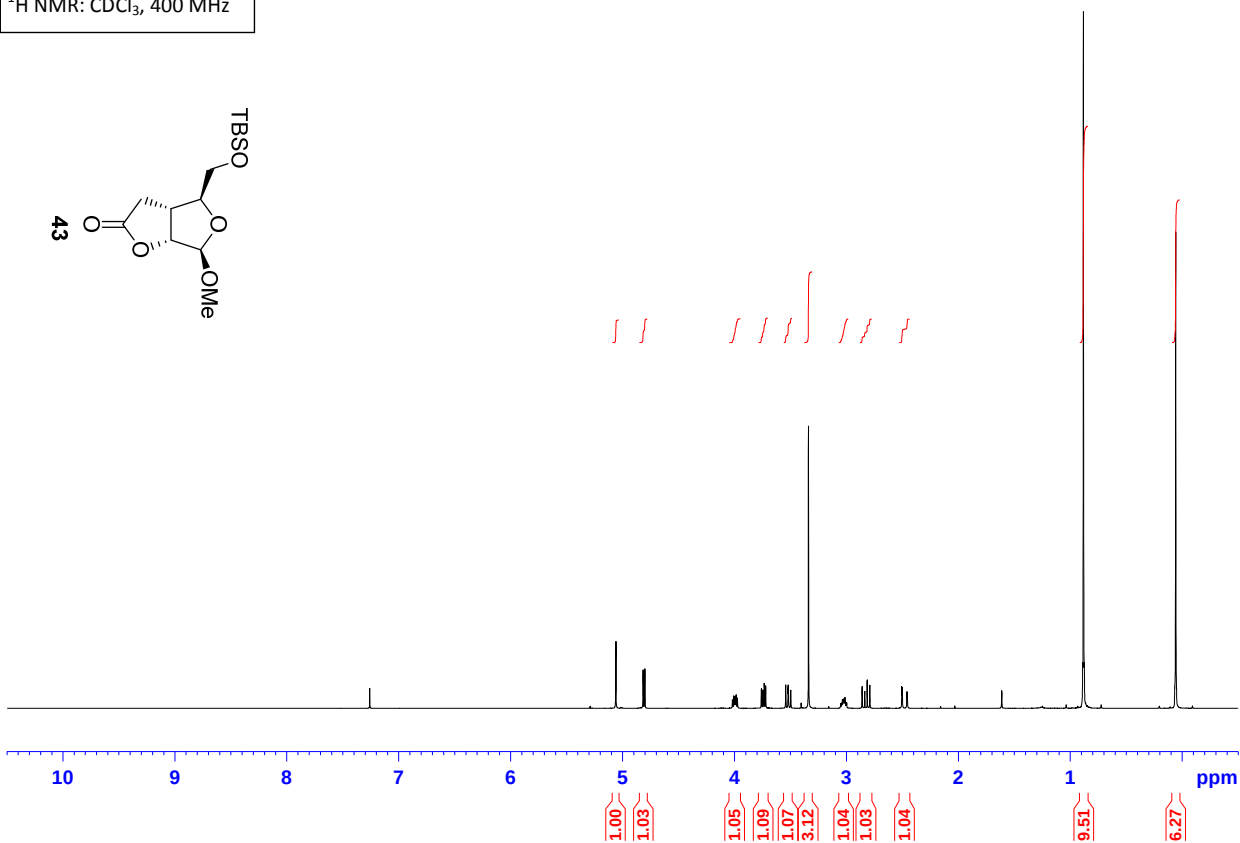
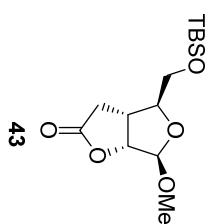
¹H NMR: CDCl₃, 400 MHz



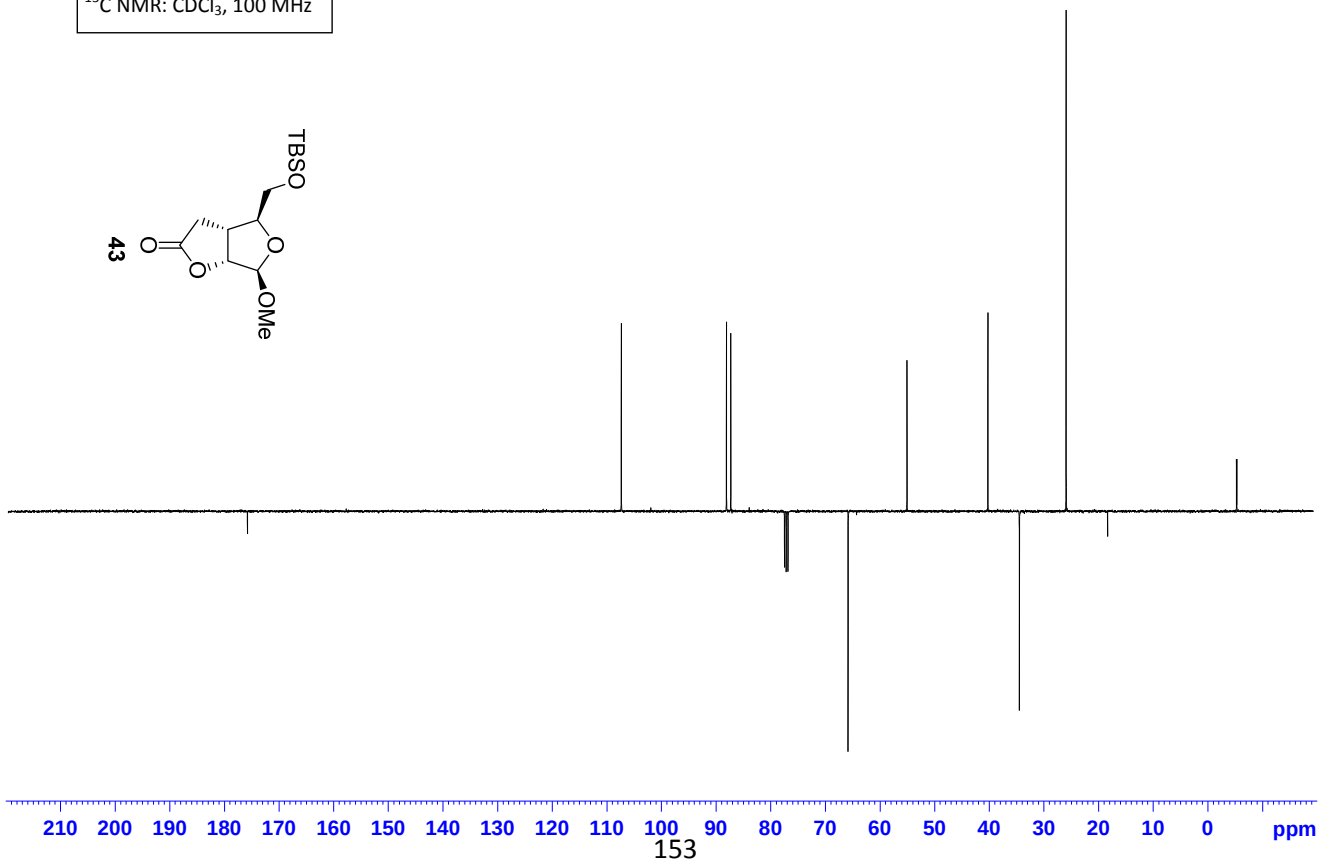
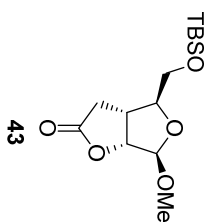
¹³C NMR: CDCl₃, 100 MHz



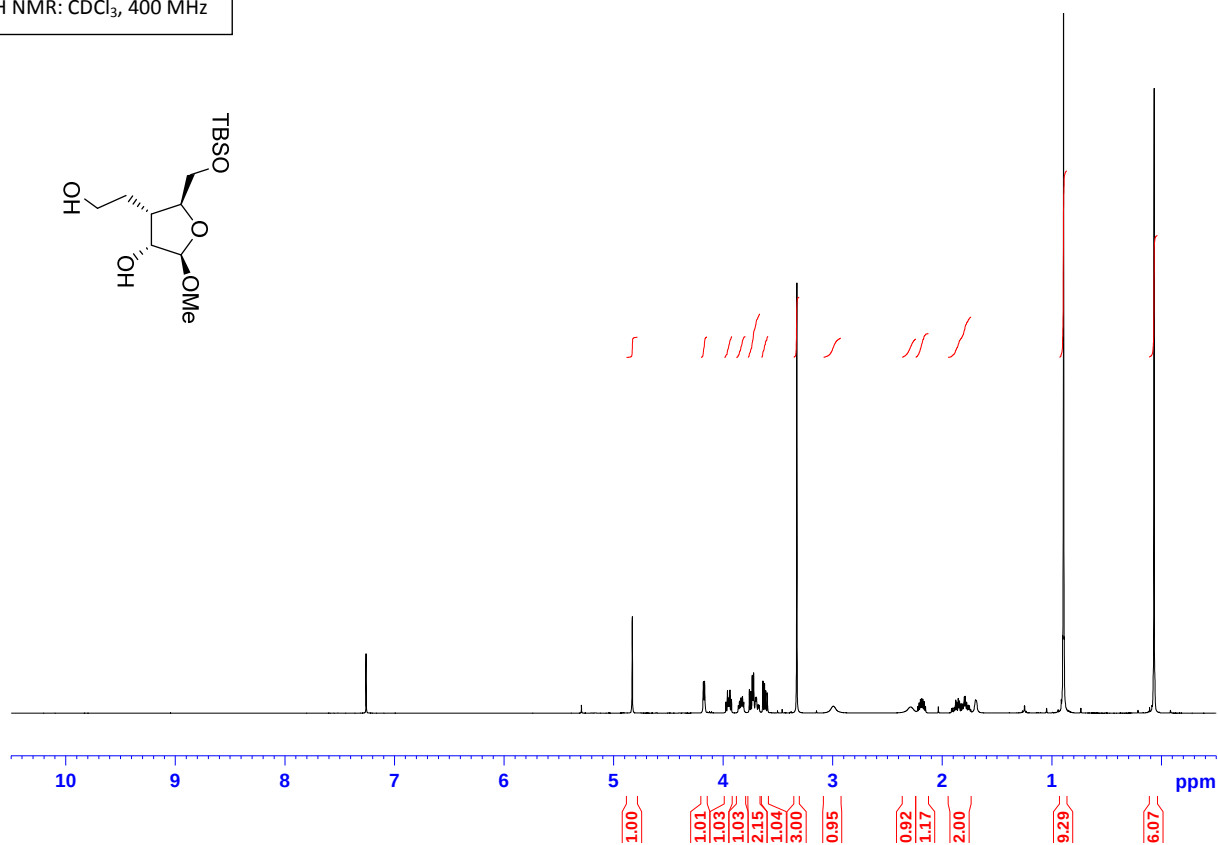
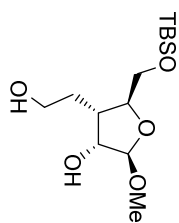
¹H NMR: CDCl₃, 400 MHz



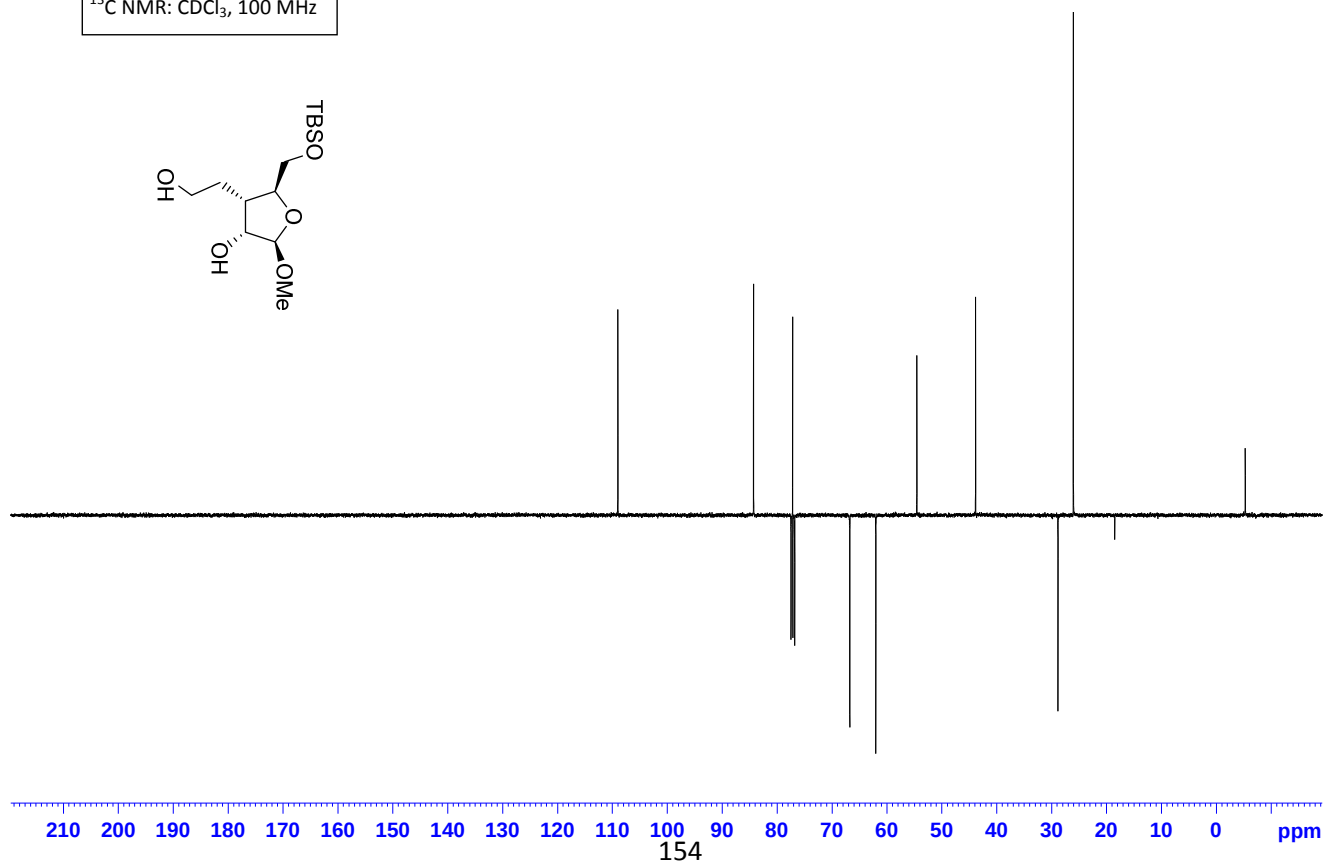
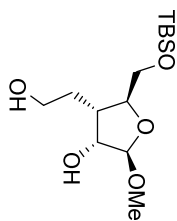
¹³C NMR: CDCl₃, 100 MHz



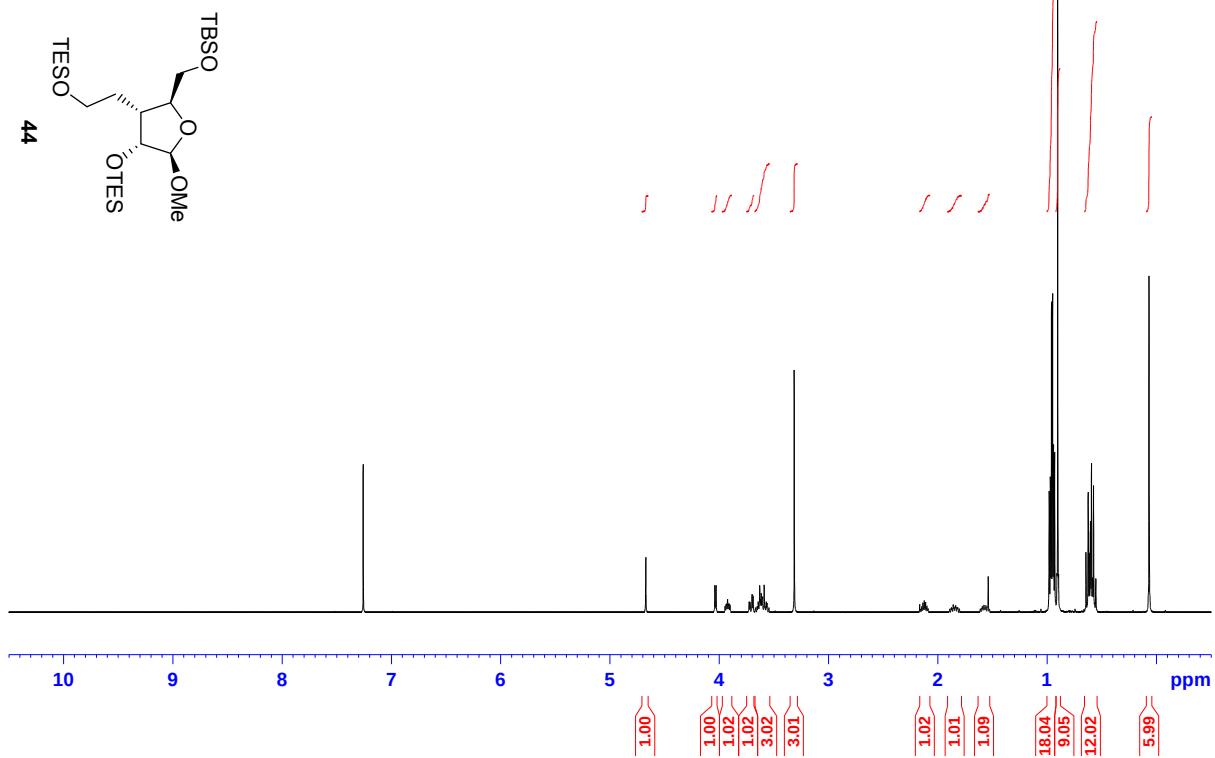
¹H NMR: CDCl₃, 400 MHz



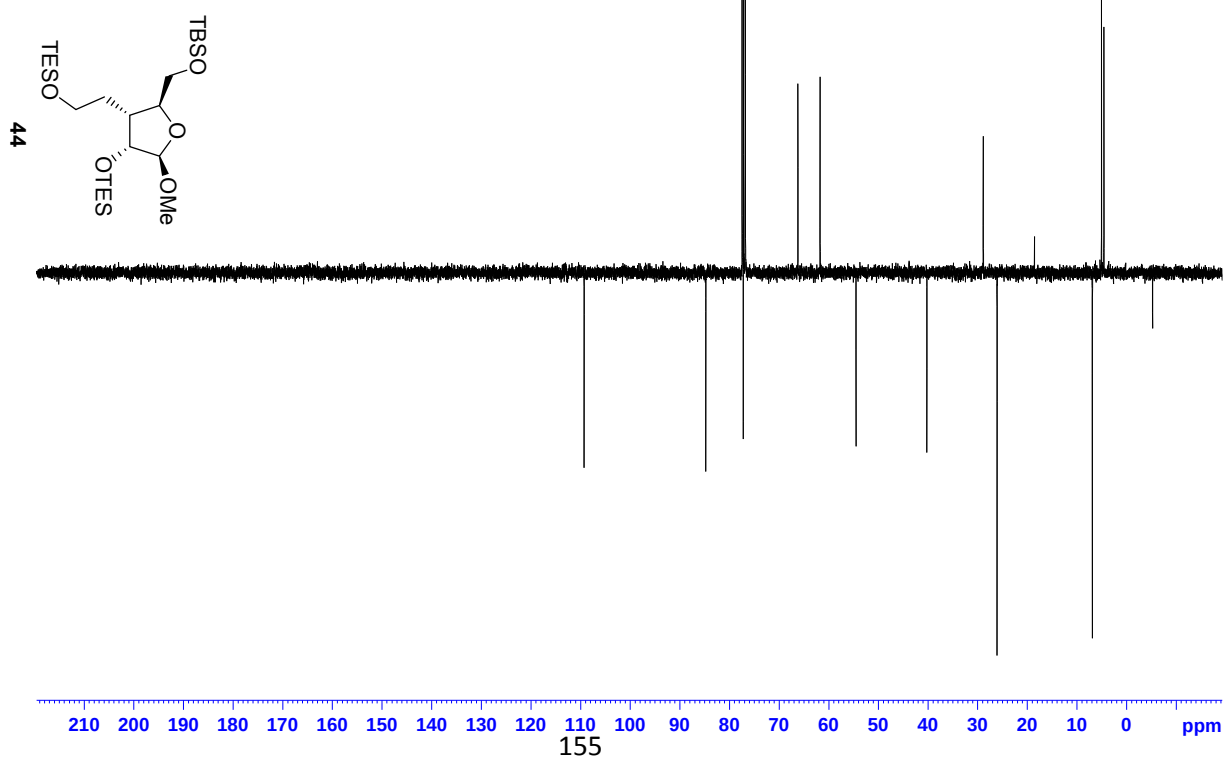
¹³C NMR: CDCl₃, 100 MHz



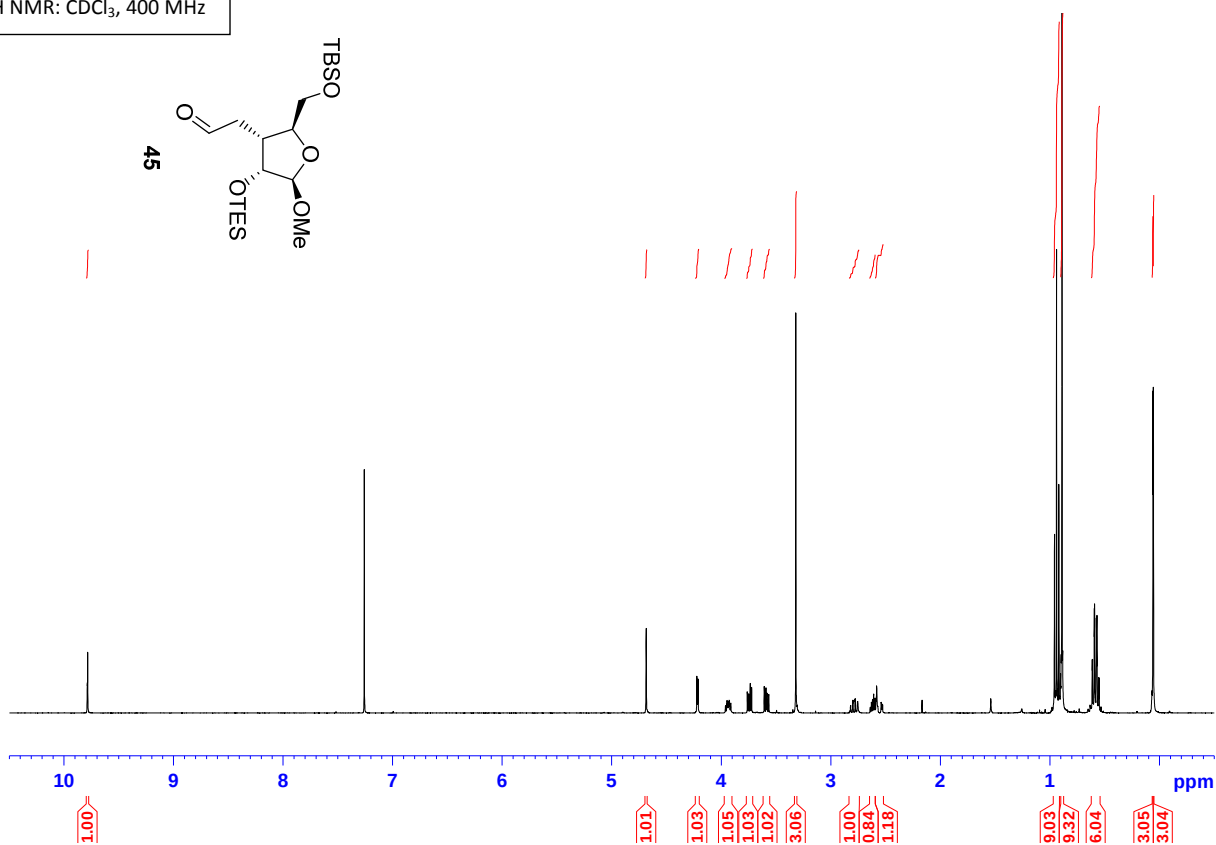
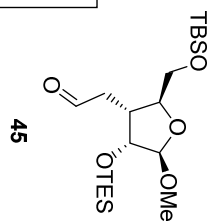
^1H NMR: CDCl_3 , 400 MHz



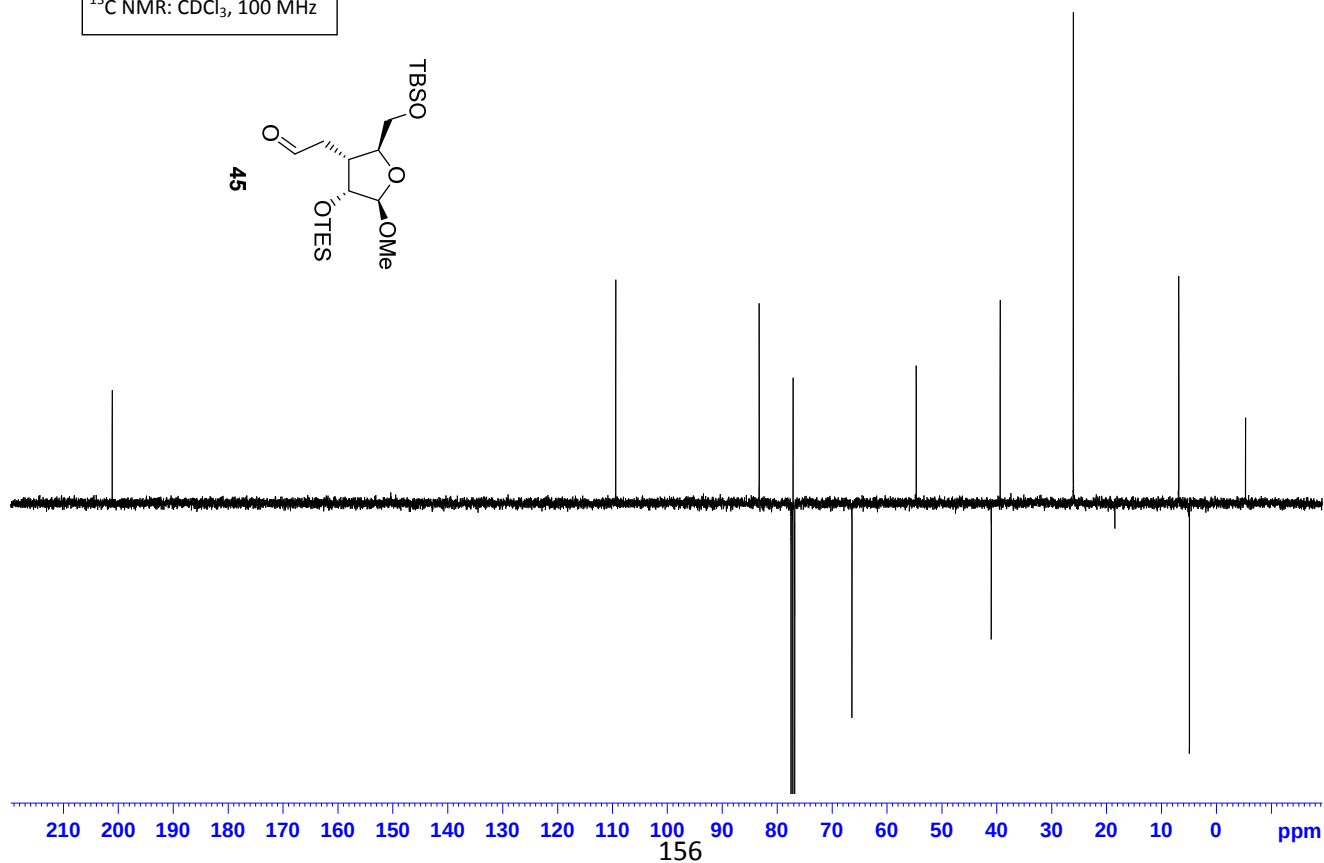
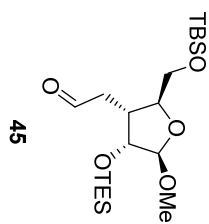
^{13}C NMR: CDCl_3 , 100 MHz



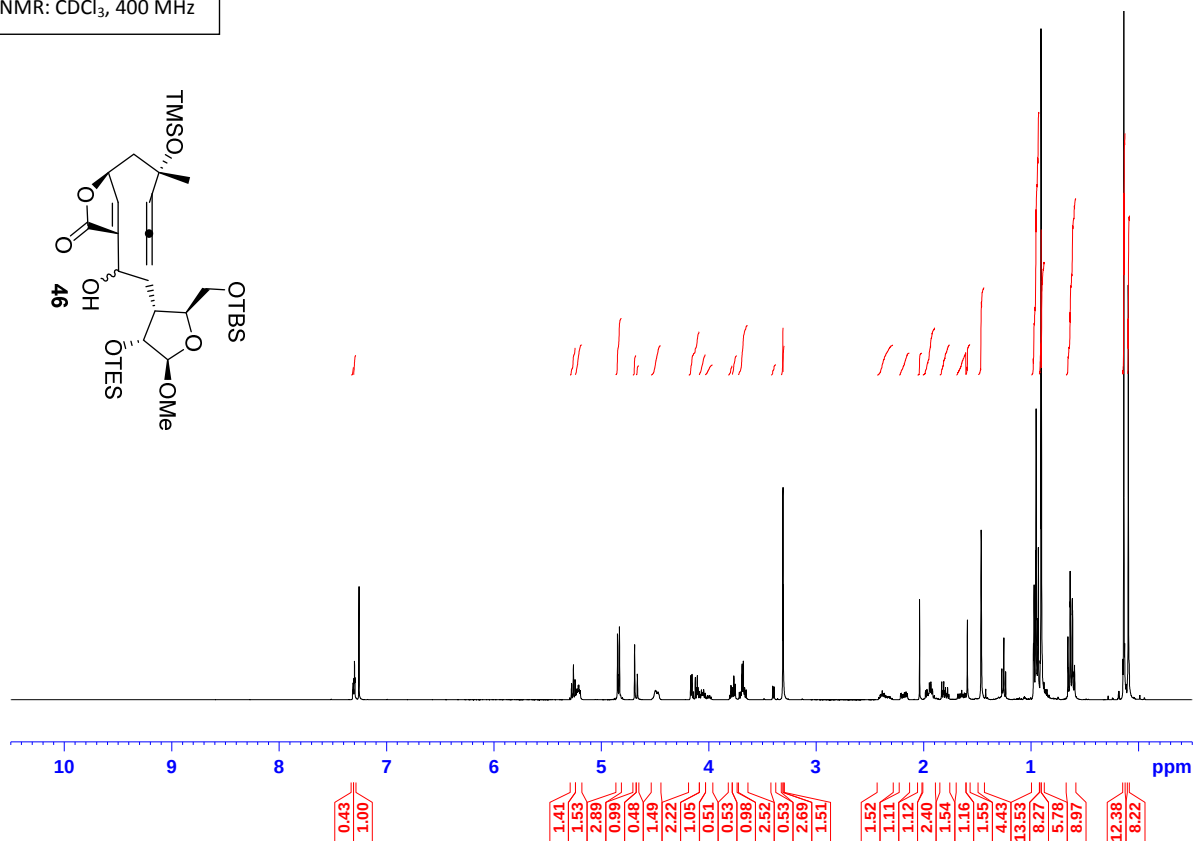
^1H NMR: CDCl_3 , 400 MHz



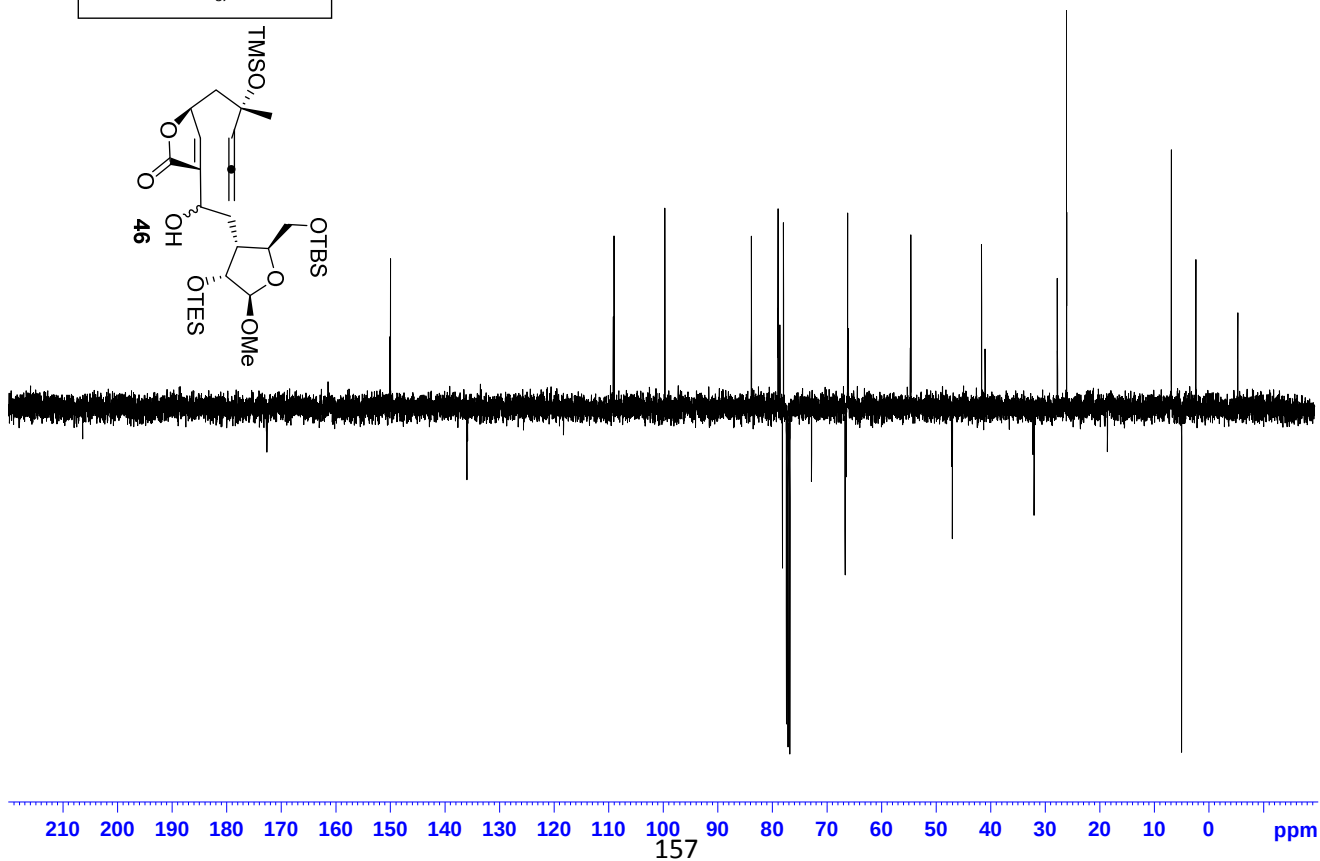
^{13}C NMR: CDCl_3 , 100 MHz

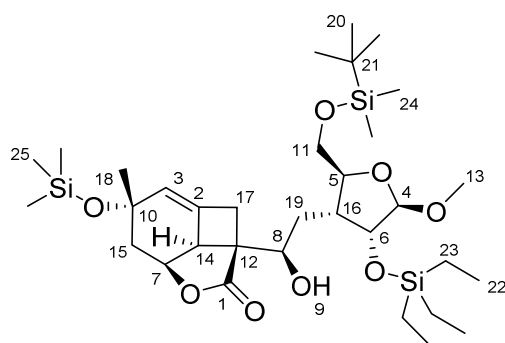


^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR: CDCl_3 , 100 MHz

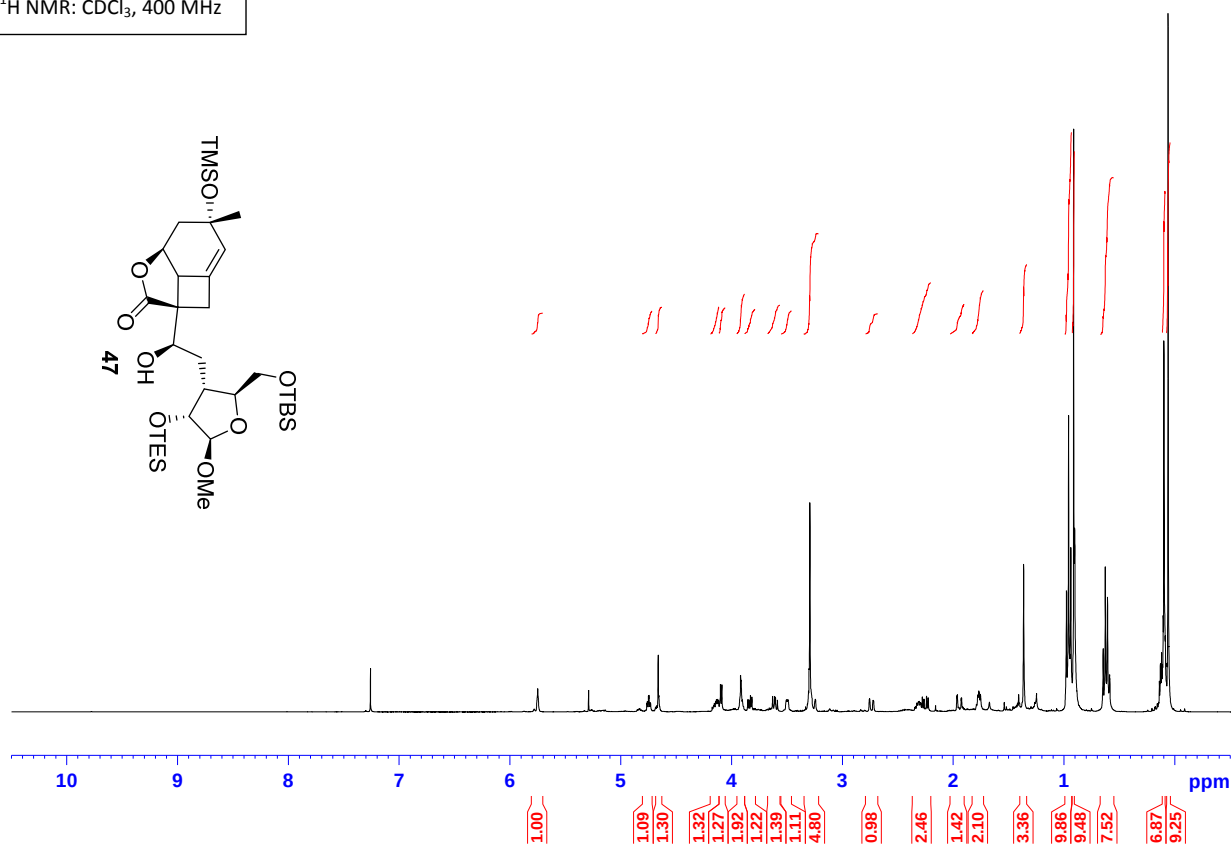




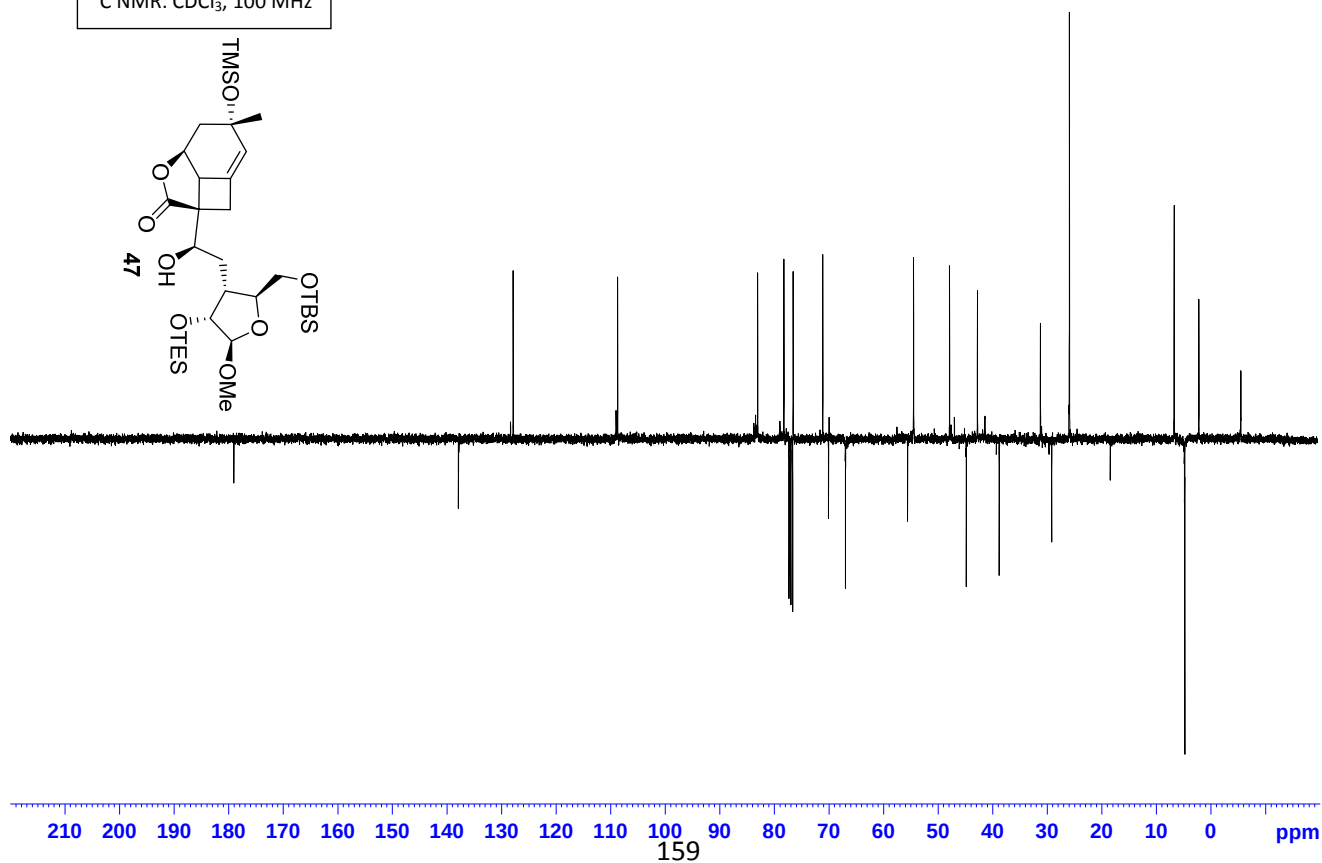
47

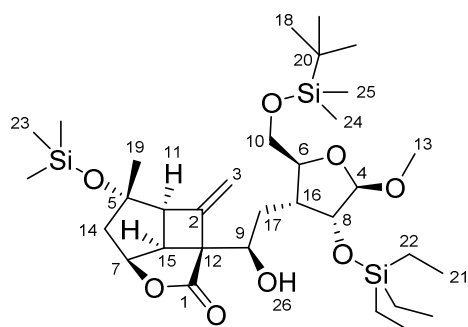
No.	¹³ C [ppm]	¹ H [ppm]
1	179.1	-
2	137.9	-
3	127.9	5.75
4	108.8	4.66
5	83.1	4.13
6	78.3	4.09
7	76.6	4.75
8	71.1	3.91
9	-	3.91 (OH)
10	70.1	-
11	67.0	3.84, 3.61
12	55.6	-
13	54.5	3.29
14	47.9	3.50
15	44.8	2.53, 1.95
16	42.8	2.31
17	38.8	3.26, 2.74
18	31.2	1.36
19	29.2	1.77
20	25.9	0.91
21	18.4	-
22	6.7	0.96
23	4.8	0.62
24	2.2	0.10
25	-5.5	0.06

^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR: CDCl_3 , 100 MHz

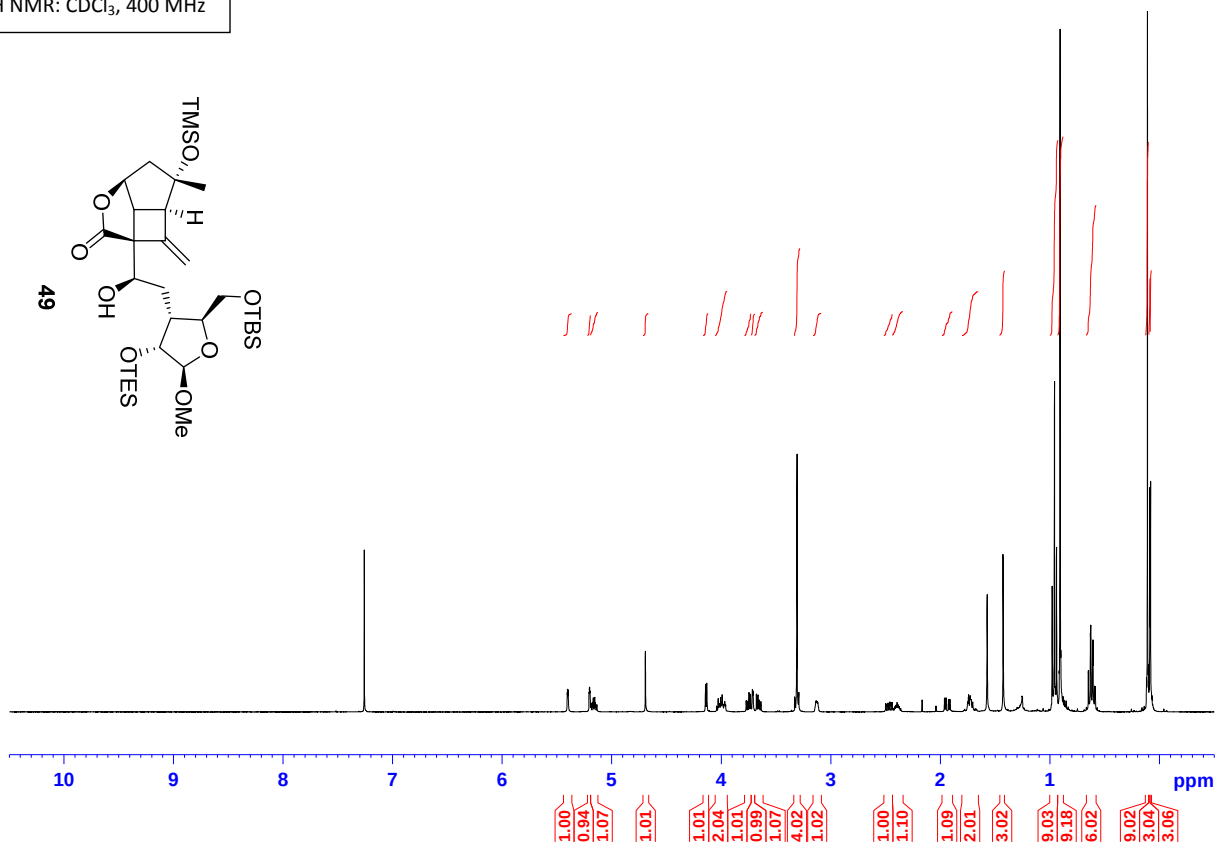




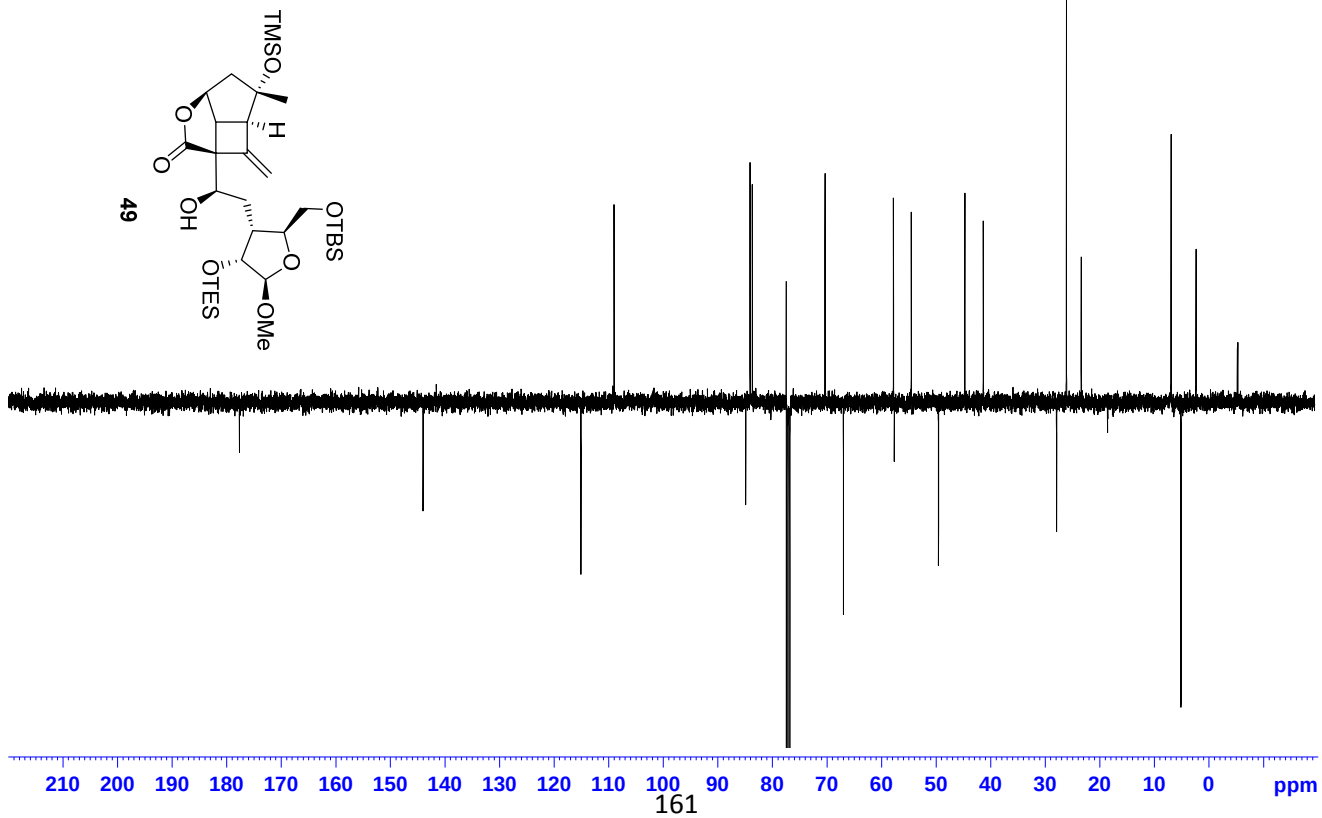
49

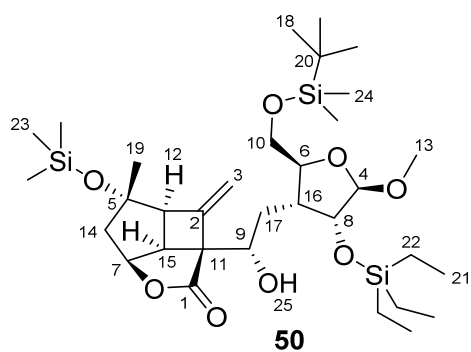
No.	¹³ C [ppm]	¹ H [ppm]
1	177.7	-
2	144.0	-
3	115.1	5.40, 5.20
4	109.0	4.69
5	84.9	-
6	84.1	4.02
7	83.7	5.16
8	77.5	4.14
9	70.4	3.98
10	67.0	3.75, 3.66
11	57.8	3.13
12	57.7	-
13	54.6	3.33-3.29
14	49.6	2.45, 1.94
15	44.8	3.33-3.29
16	41.4	2.40
17	27.9	1.79-1.67
18	26.2	0.91
19	23.4	1.43
20	18.6	-
21	7.0	0.96
22	5.1	0.62
23	2.4	0.11
24	-5.2	0.08
25	-5.3	0.09
26	-	3.71 (OH)

^1H NMR: CDCl_3 , 400 MHz



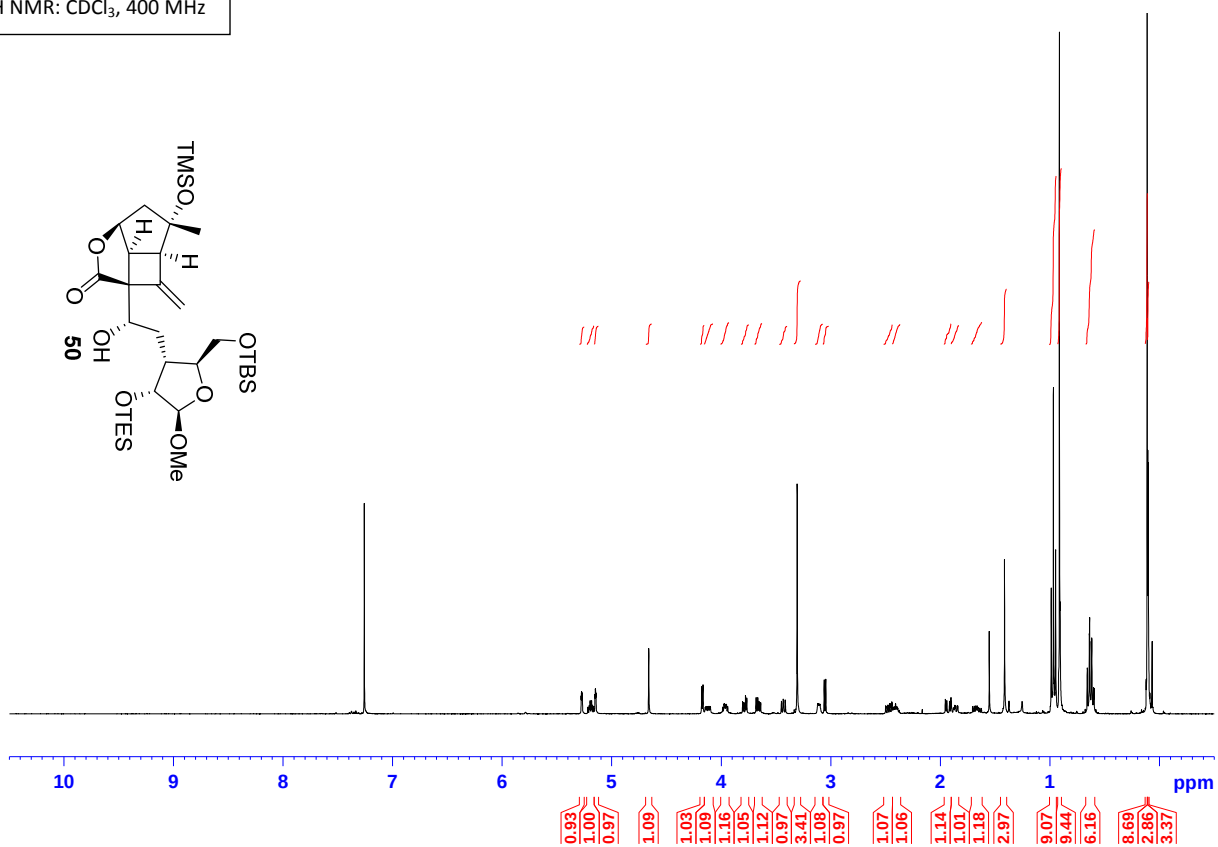
^{13}C NMR: CDCl_3 , 100 MHz



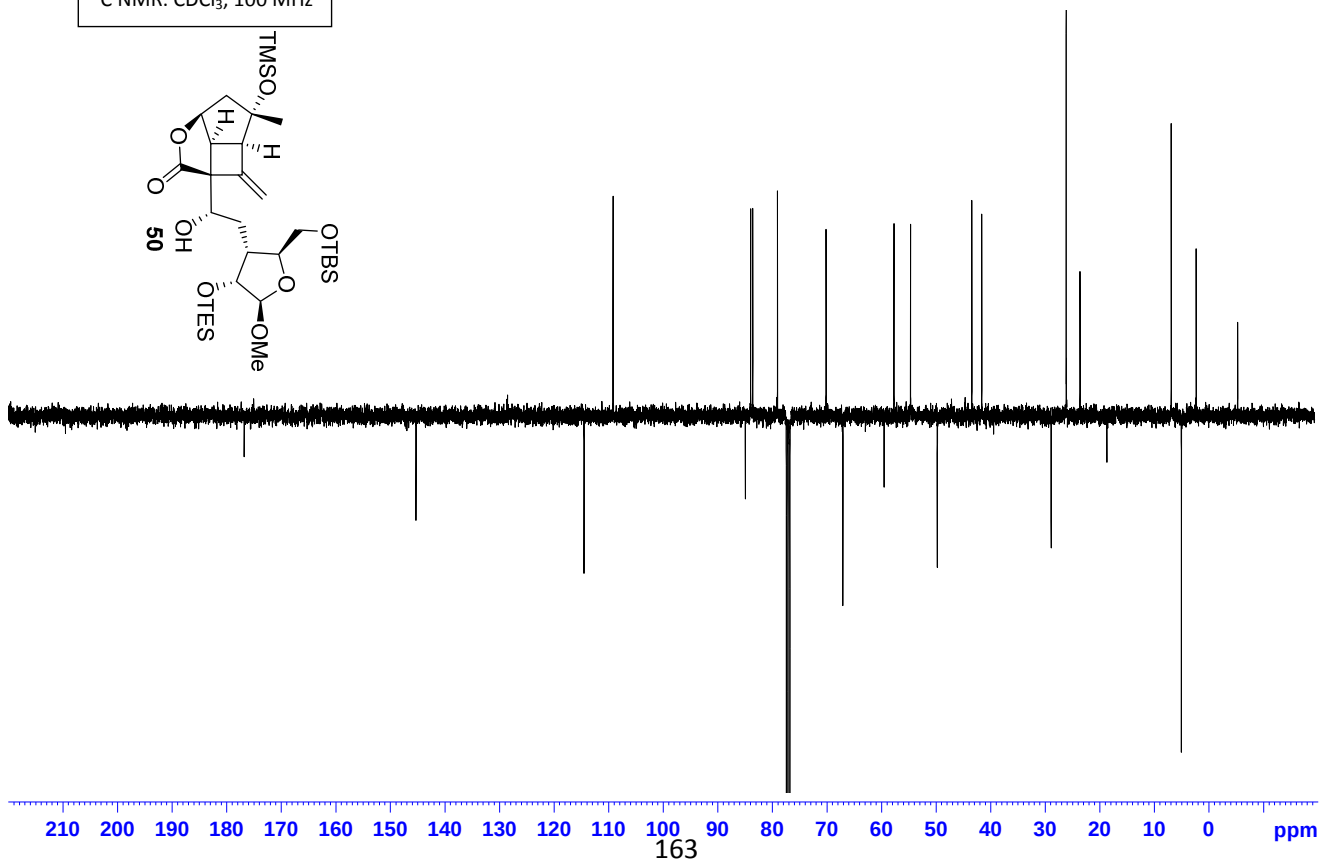


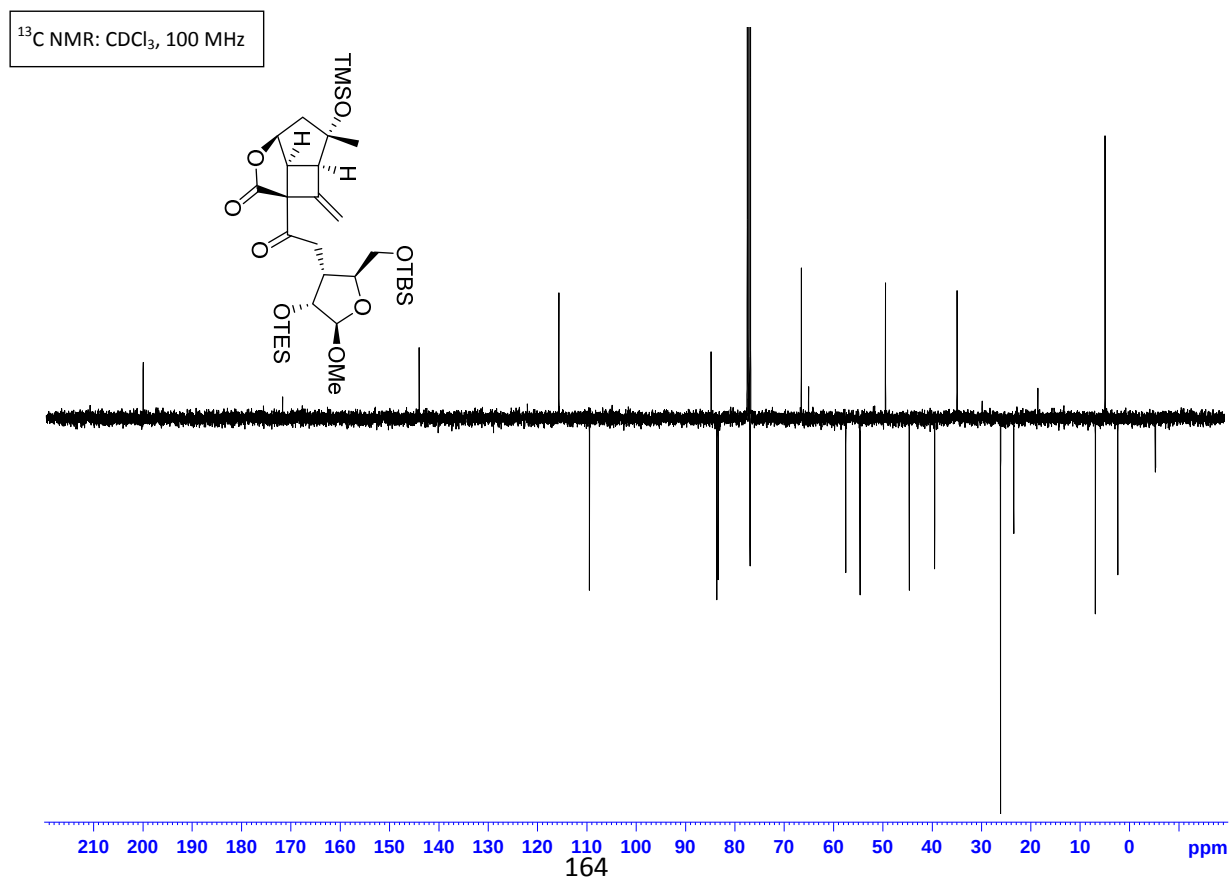
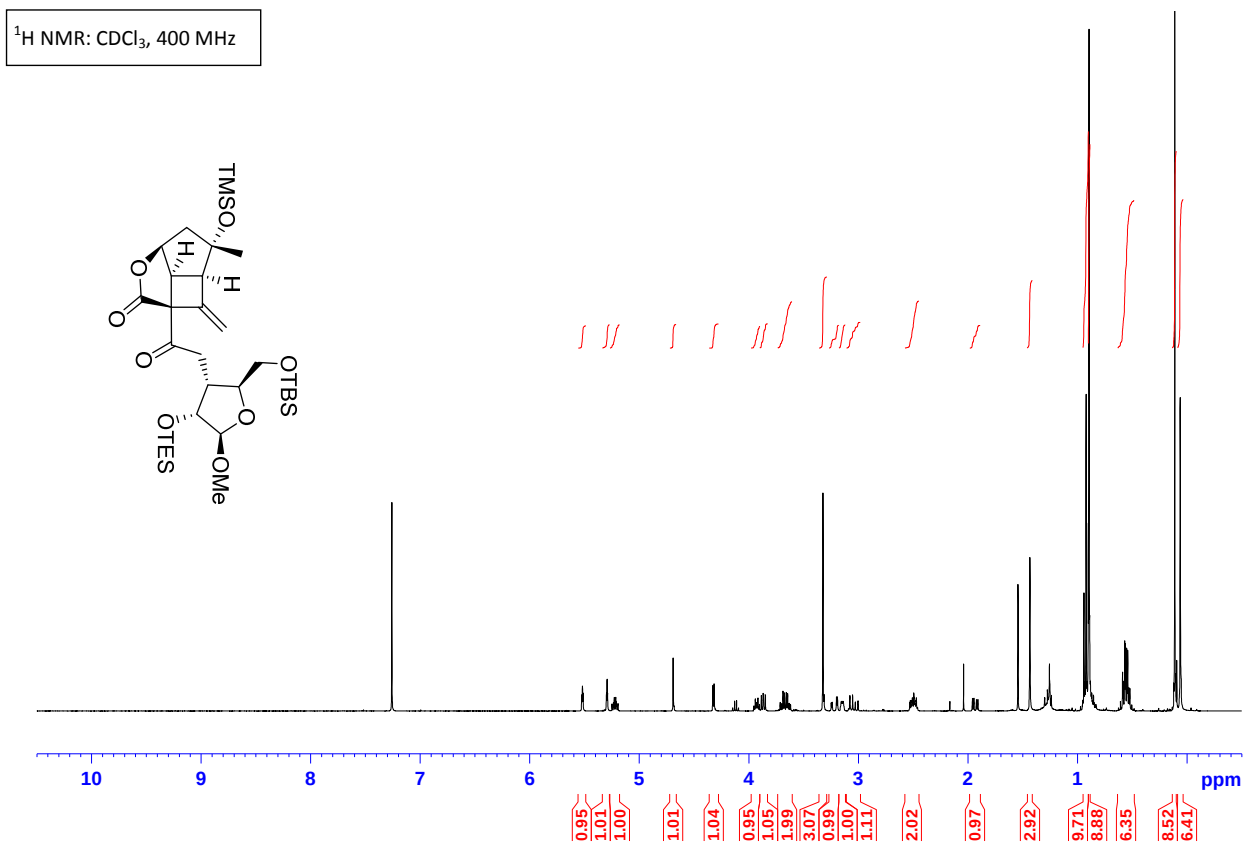
No.	¹³ C [ppm]	¹ H [ppm]
1	176.8	-
2	145.4	-
3	114.5	5.27, 5.15
4	109.2	4.69
5	85.0	-
6	84.0	3.96
7	83.6	5.19
8	79.1	4.17
9	70.2	4.12
10	67.1	3.79, 3.65
11	59.6	-
12	57.7	3.11
13	54.7	3.31
14	49.8	2.45, 1.93
15	43.5	3.43
16	41.6	2.41
17	28.9	1.87, 1.67
18	26.2	0.91
19	23.6	1.42
20	18.7	-
21	6.9	0.97
22	5.1	0.63
23	2.4	0.12
24	-5.3	0.11, 0.12
25	-	3.05 (OH)

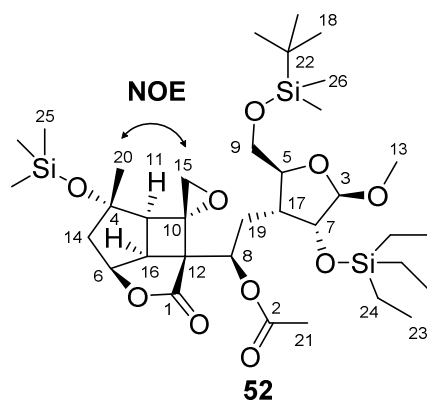
^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR: CDCl_3 , 100 MHz

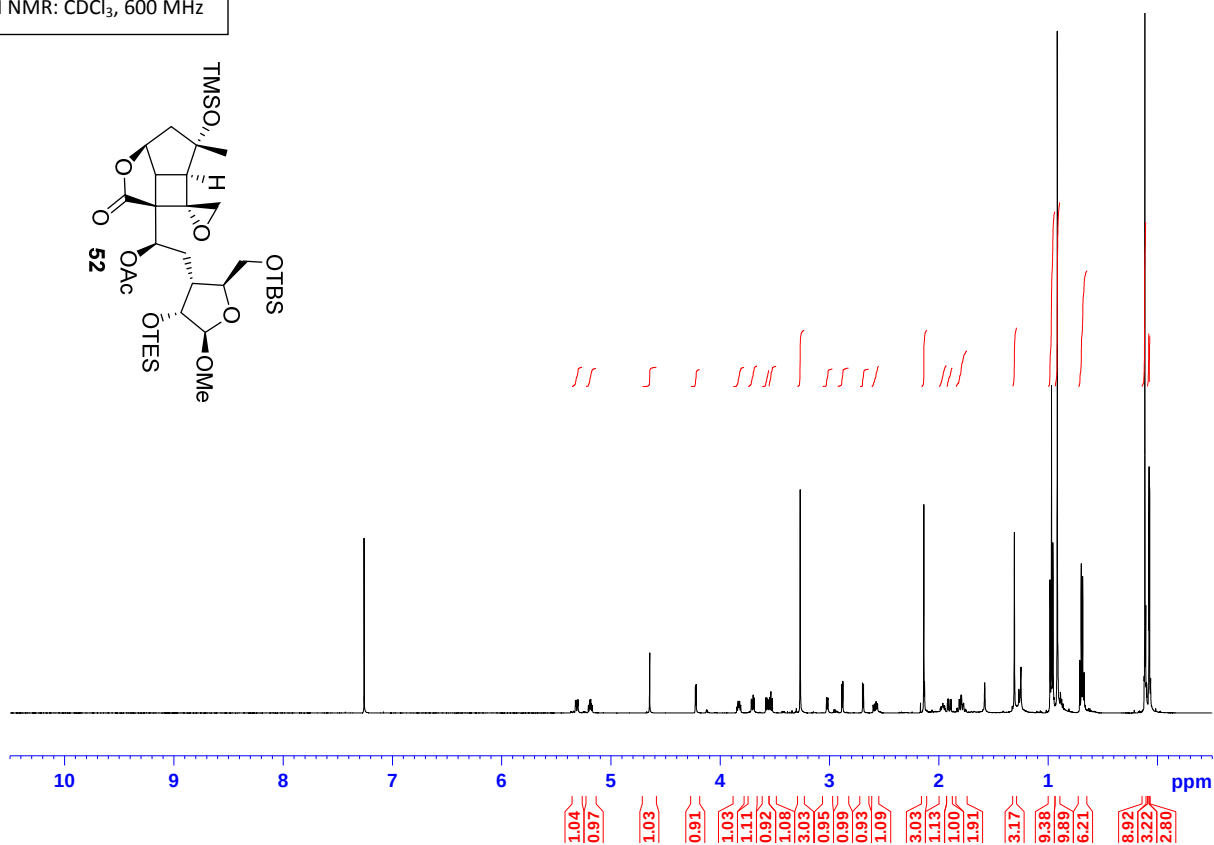




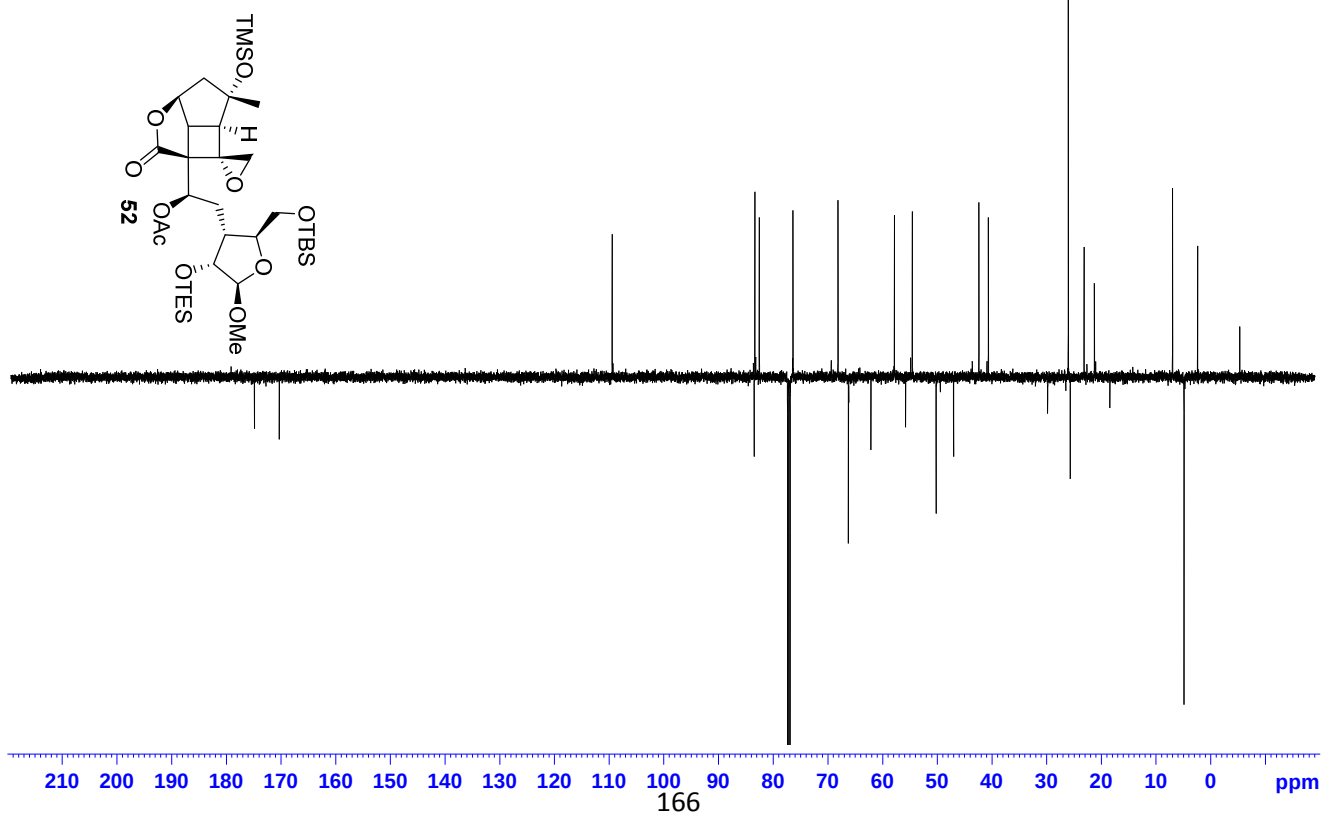


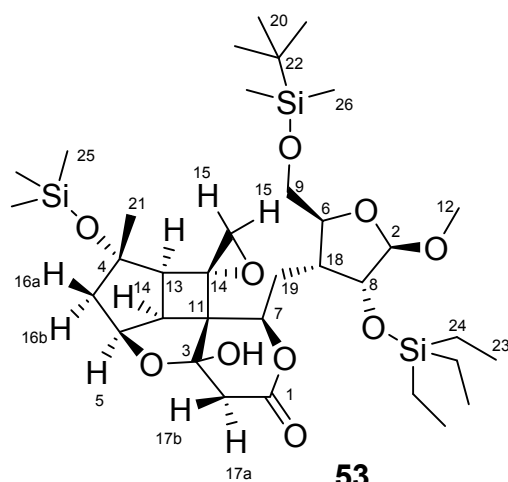
No.	¹³ C [ppm]	¹ H [ppm]
1	174.9	-
2	170.3	-
3	109.5	4.65
4	83.5	-
5	83.4	3.83
6	82.6	5.19
7	76.4	4.23
8	68.2	5.31
9	66.3	3.71, 3.57
10	62.2	-
11	57.9	3.02
12	55.8	-
13	54.6	3.27
14	50.2	2.58, 1.91
15	47.0	2.88, 2.70
16	42.4	3.54
17	40.7	2.00
18	26.1	0.92
19	25.7	1.84-1.75
20	23.1	1.31
21	21.3	2.14
22	18.5	-
23	7.0	0.97
24	4.9	0.69
25	2.4	0.12
26	-5.3	0.08

^1H NMR: CDCl_3 , 600 MHz



^{13}C NMR: CDCl_3 , 150 MHz





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NOE- correlation:

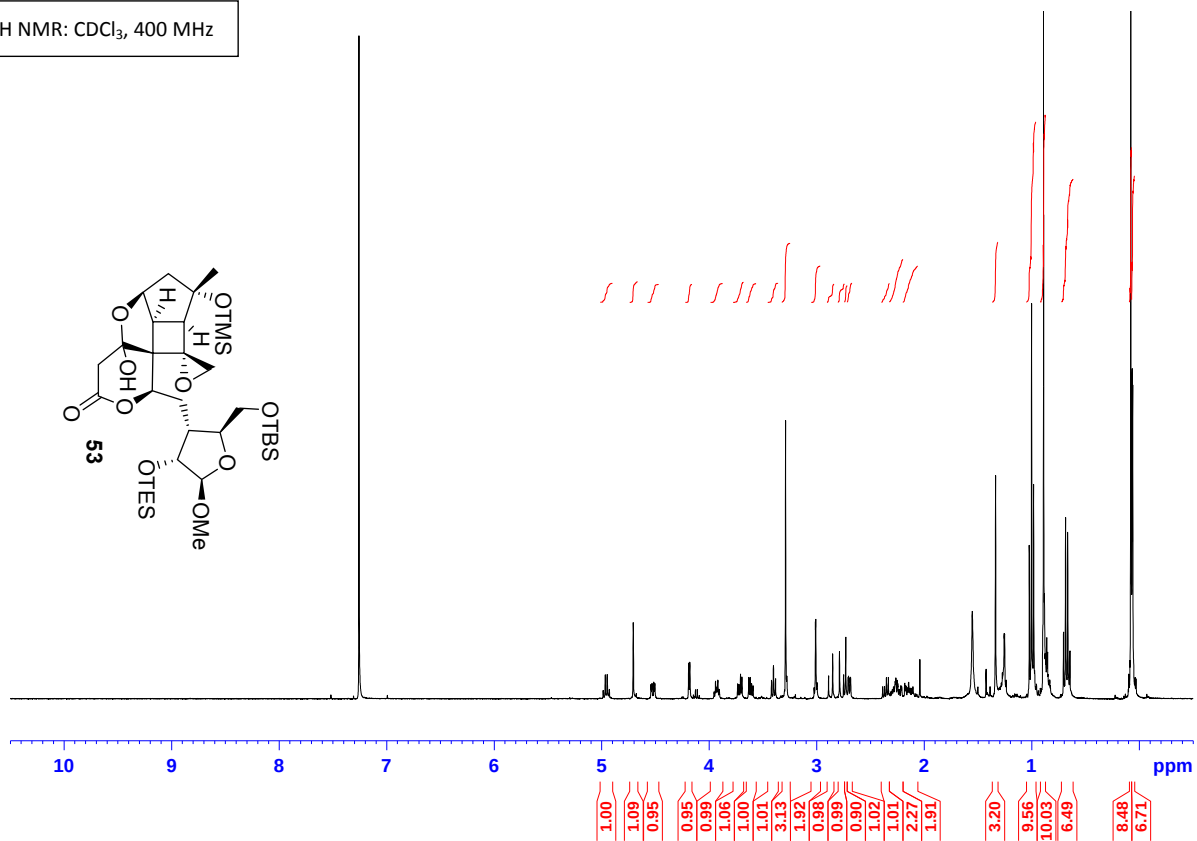
5 ↔ 14 ↔ 13; 14 ↔ 7 ↔ 17a, 15 ↔ 21 ↔ 16a

HMBC-correlation:

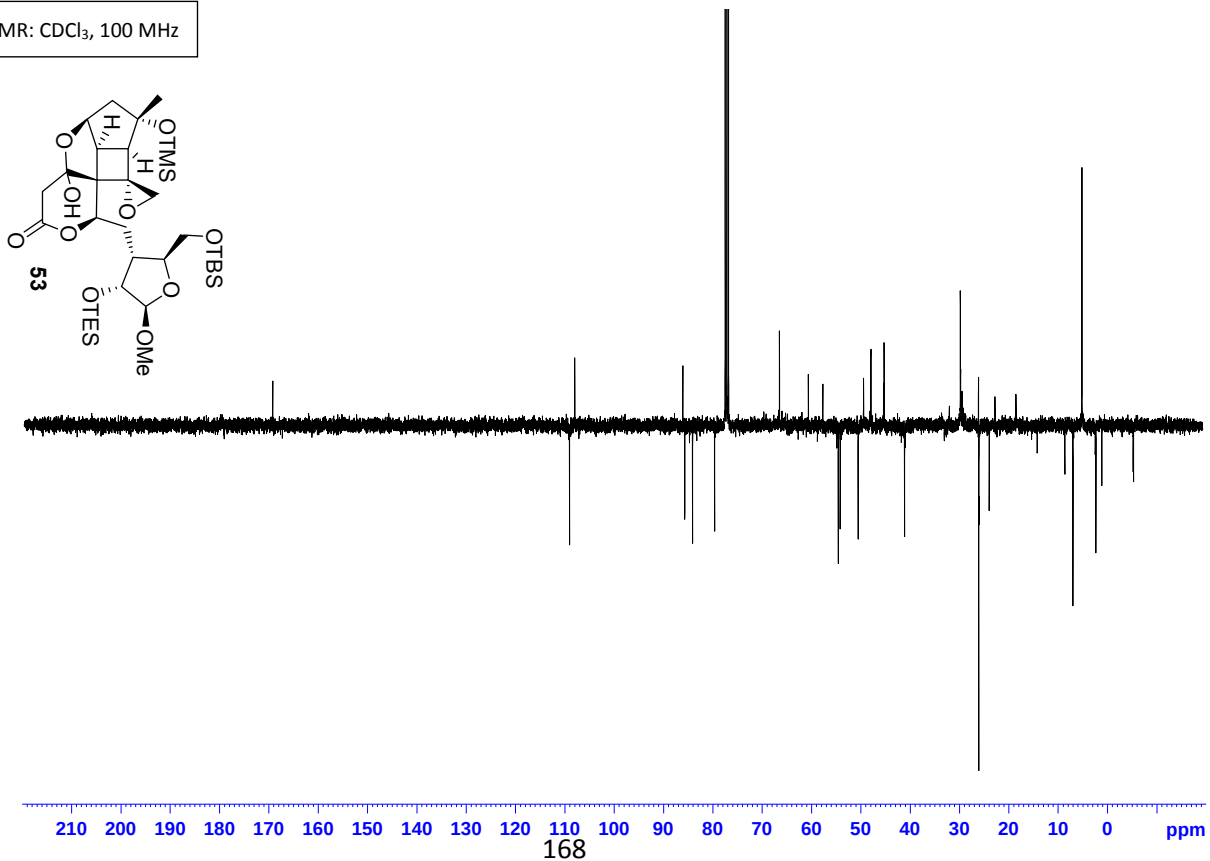
1 ↔ 17 ↔ 11; 17 ↔ 3

No.	¹³ C [ppm]	¹ H [ppm]
1	169.1	-
2	109.1	4.71
3	108.0	-
4	86.1	-
5	85.7	4.96
6	84.1	3.93
7	79.6	4.53
8	76.9	4.19
9	66.5	3.72 ^a ; 3.62 ^b
10	60.6	-
11	57.7	-
12	54.6	3.29
13	54.2	2.70
14	50.6	3.40
15	49.5	3.02 ^a ; 3.00 ^b
16	48.0	2.36 ^a ; 2.25 ^b
17	45.4	2.87 ^a ; 2.77 ^b
18	41.2	2.29
19	26.2	2.19-2.07
20	26.1	0.89
21	24.0	1.34
22	18.4	-
23	7.0	1.0
24	5.2	0.68
25	2.4	0.08
26	-5.2	0.07; 0.06
27	OH	2.73

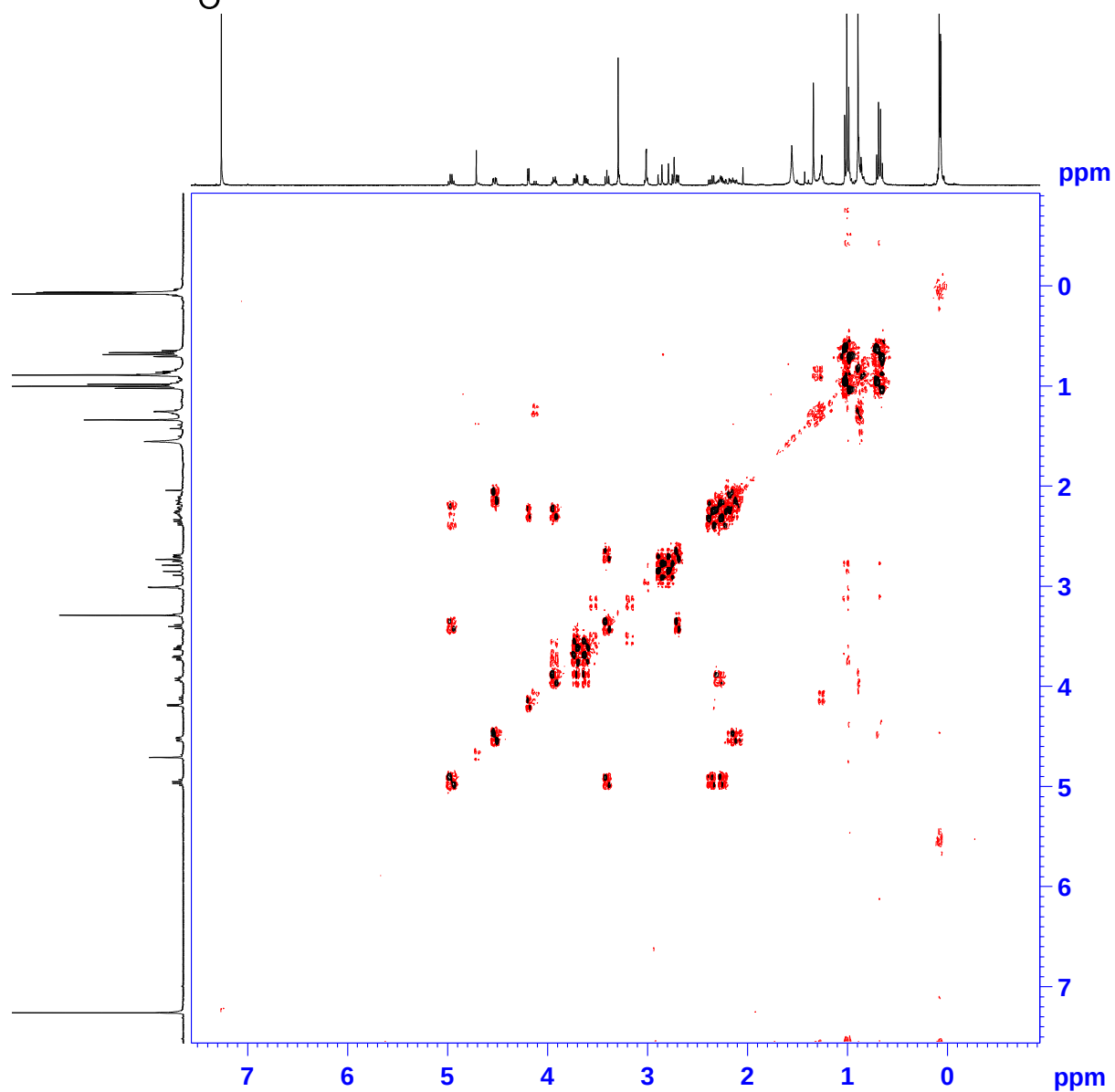
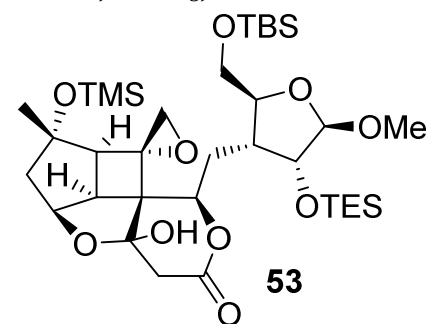
¹H NMR: CDCl₃, 400 MHz



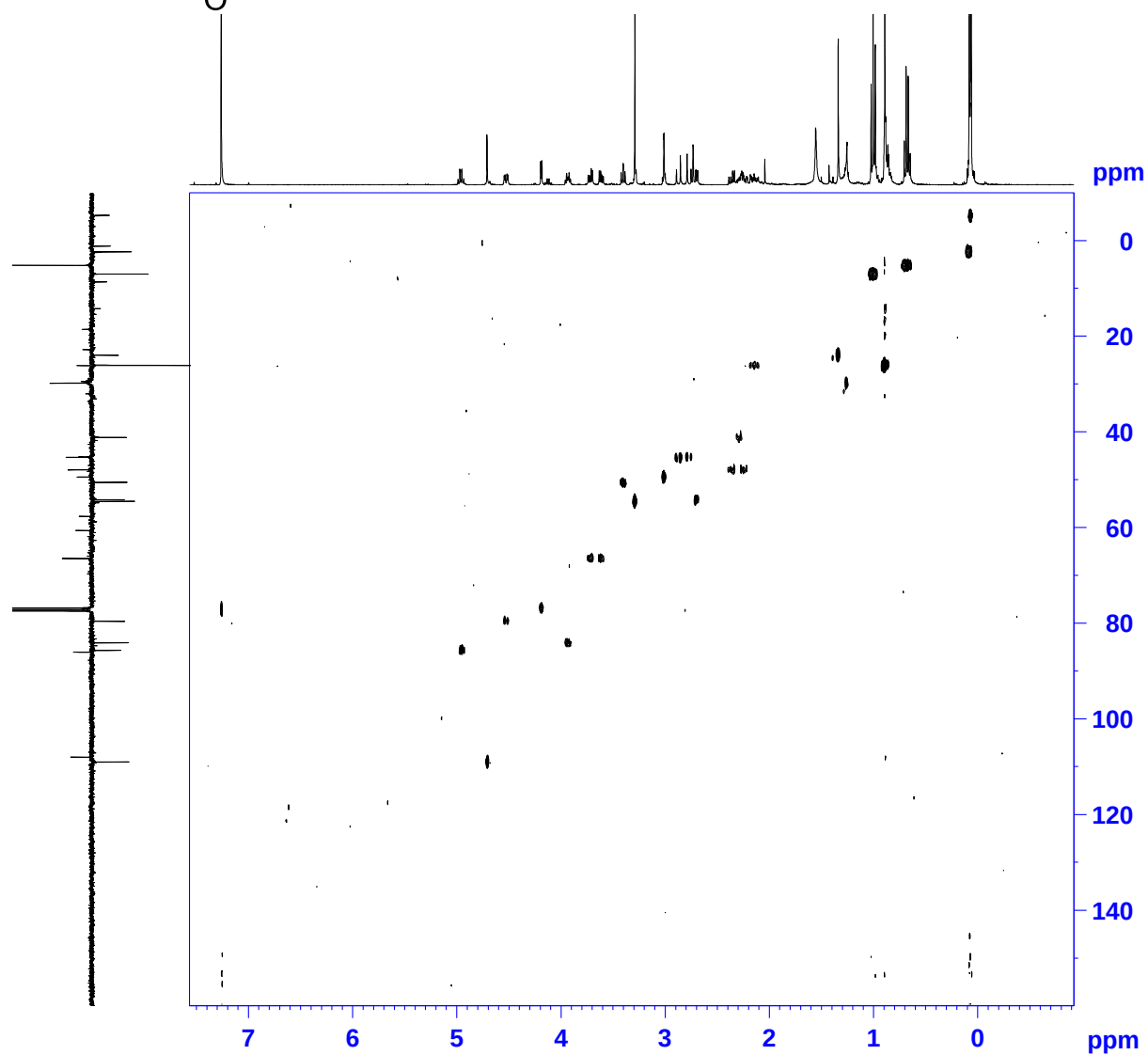
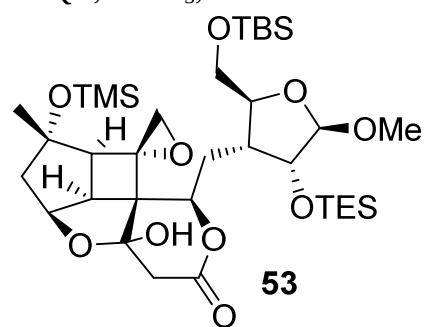
¹³C NMR: CDCl₃, 100 MHz



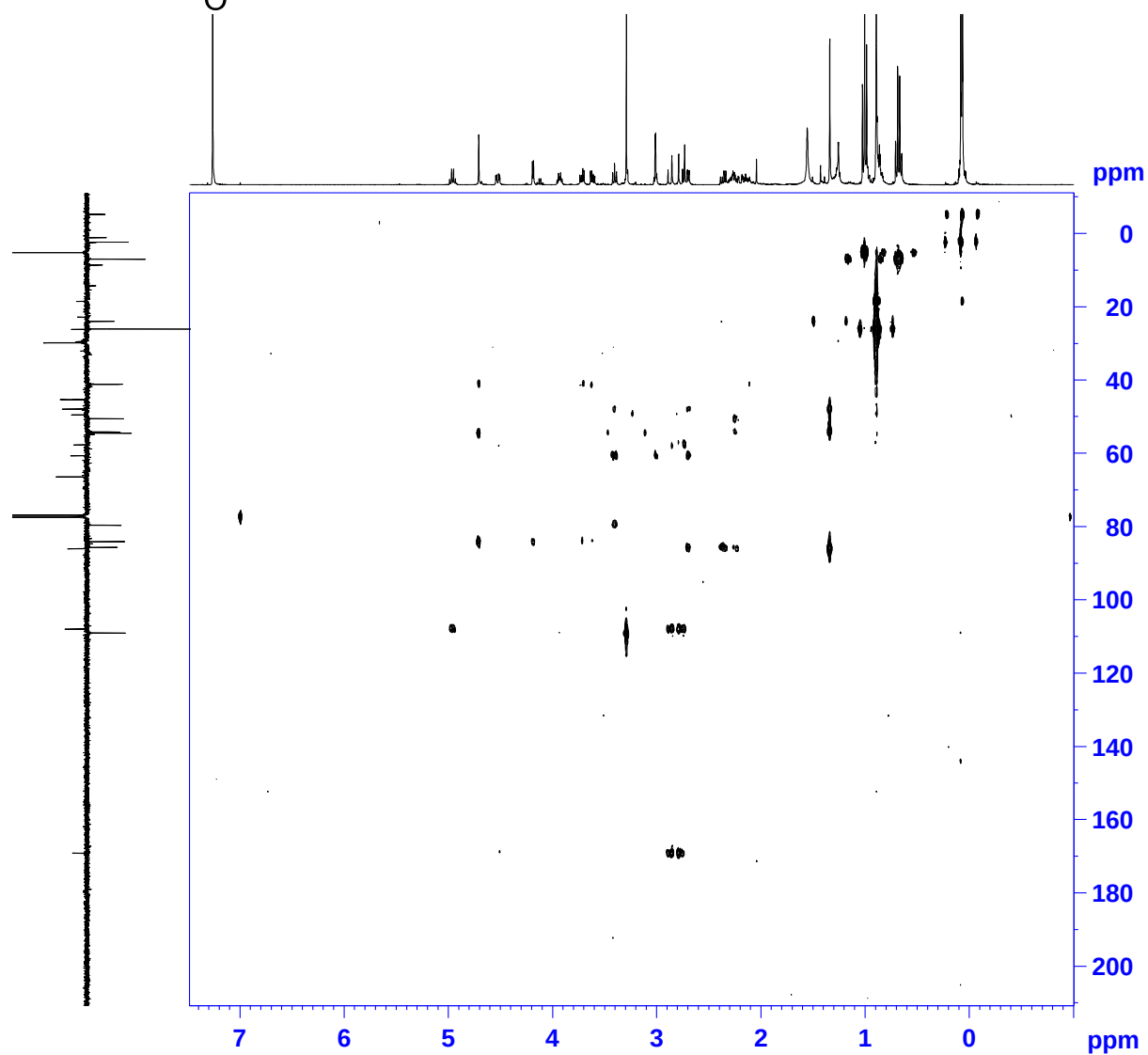
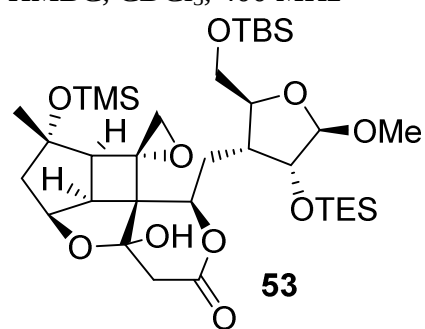
COSY, CDCl₃, 400 MHz



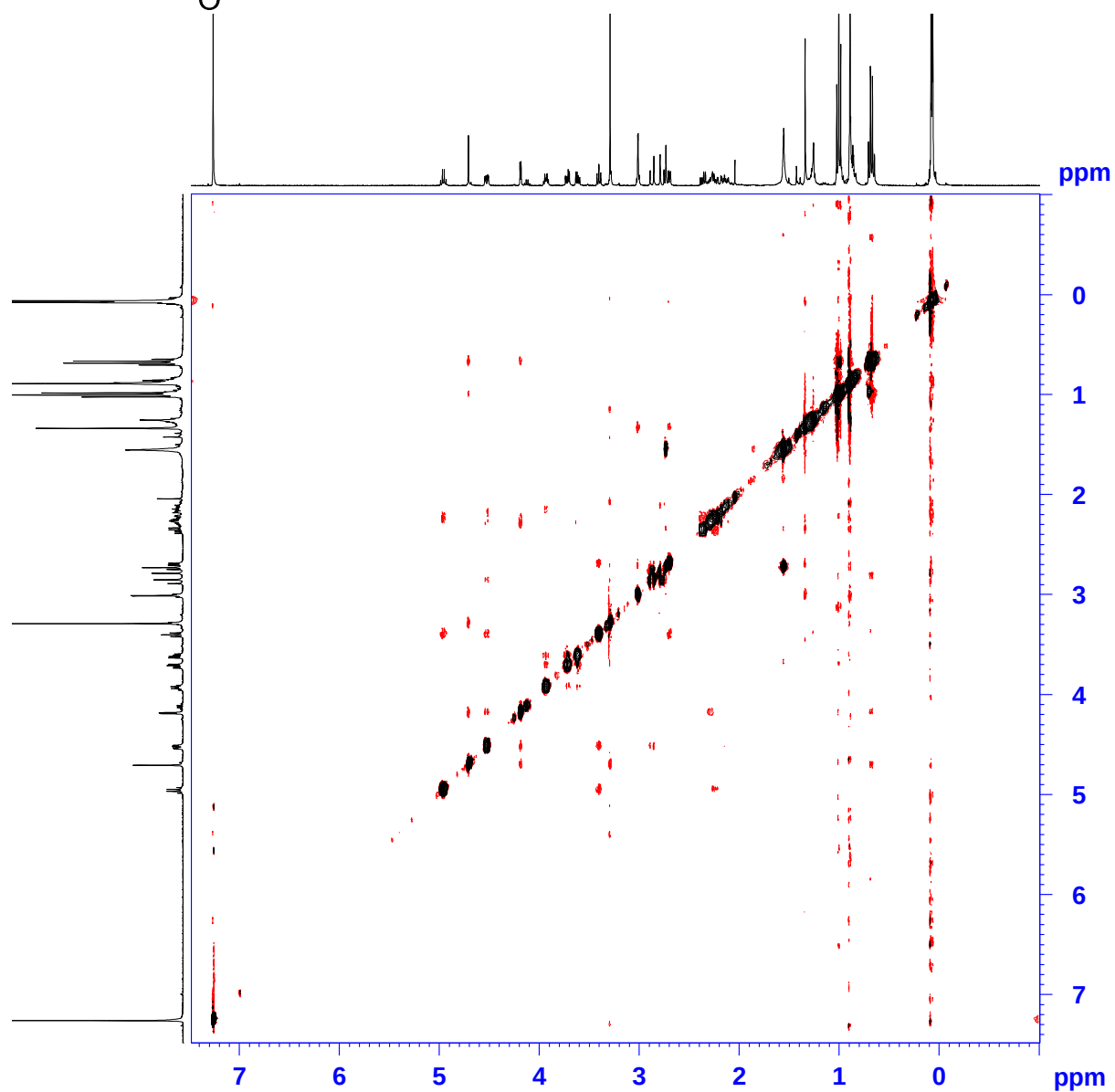
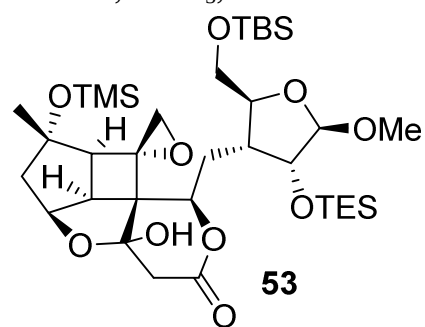
HSQC, CDCl₃, 400 MHz

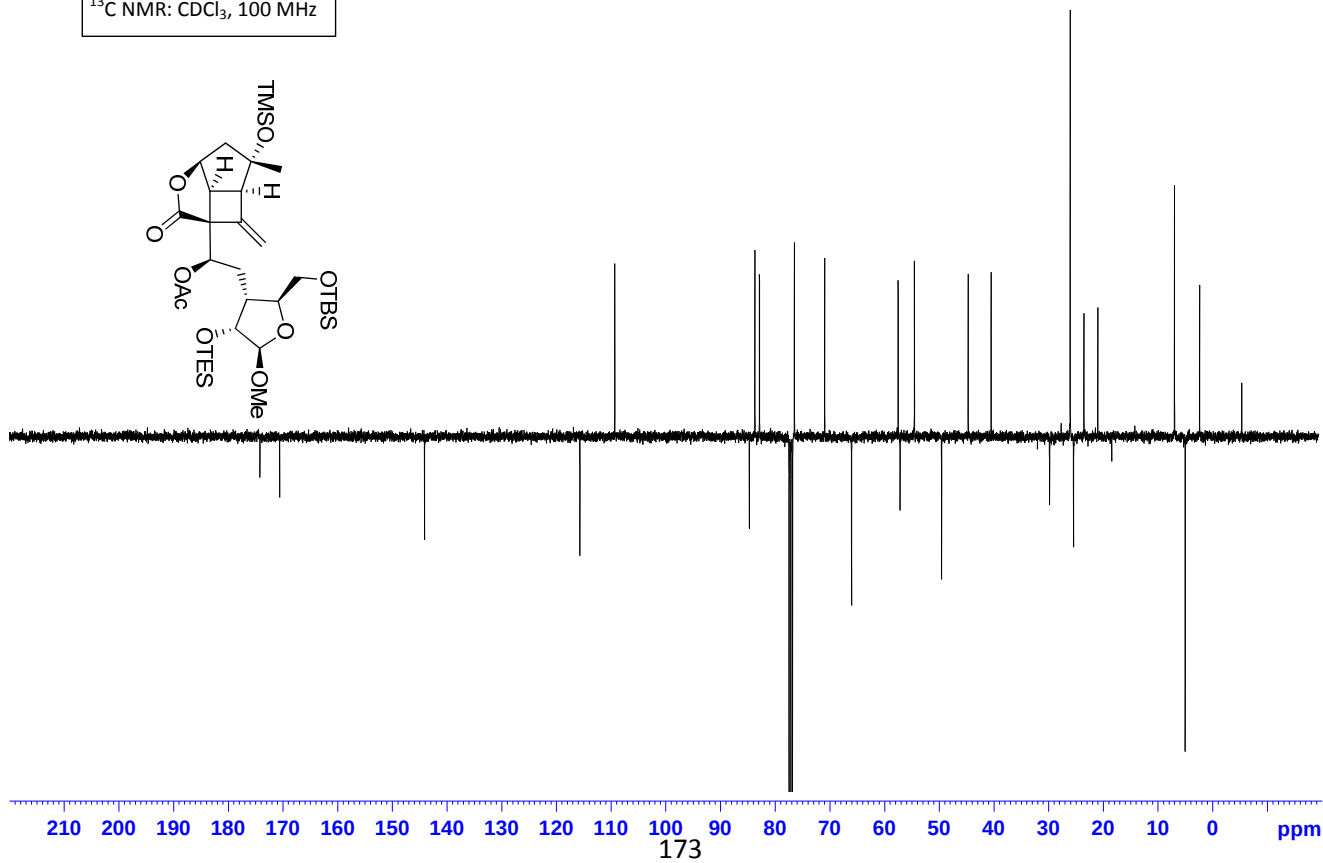
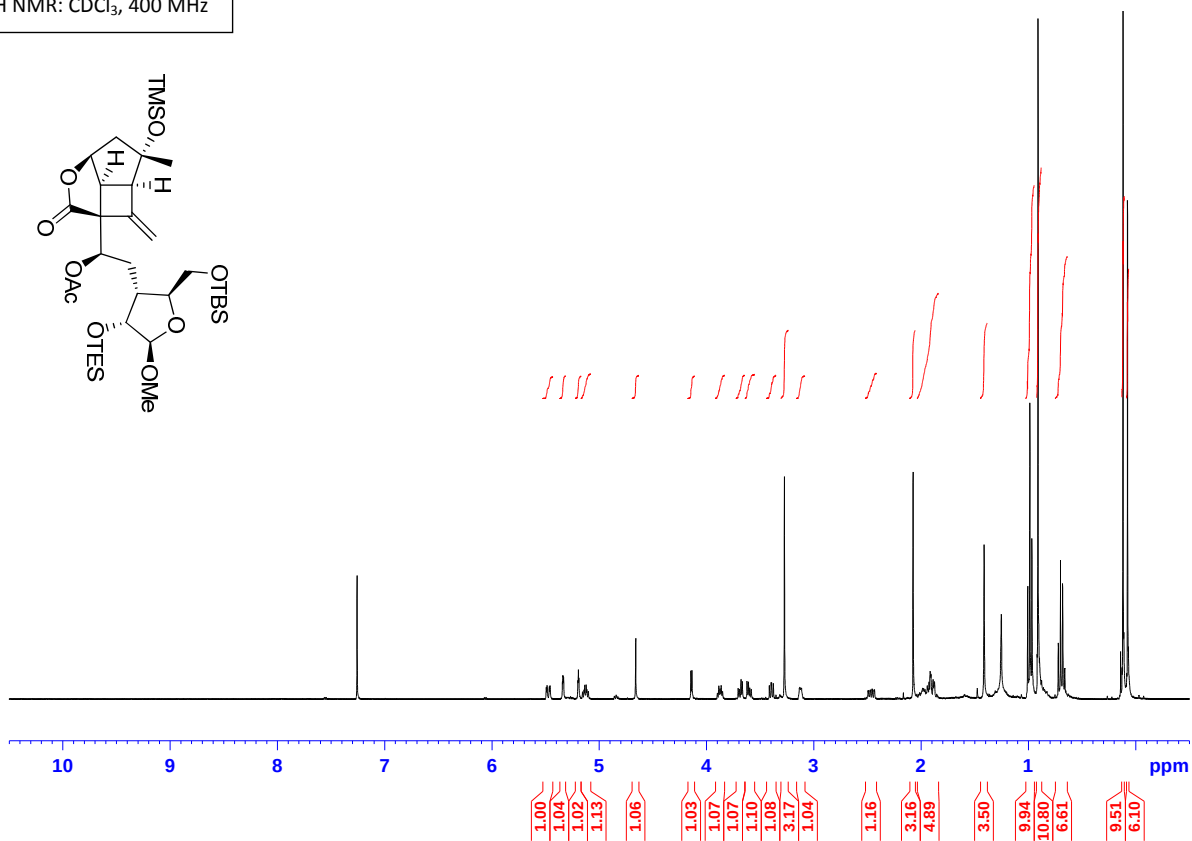


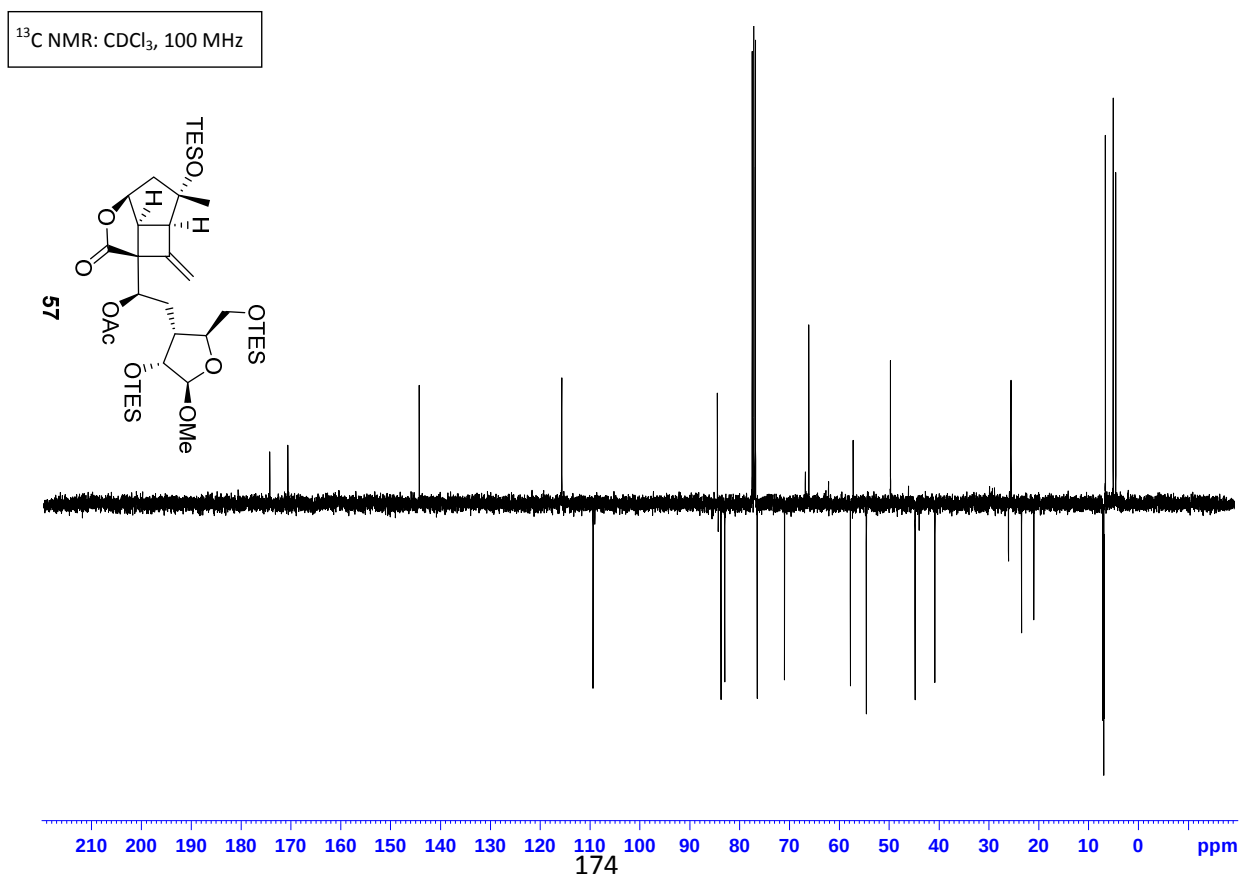
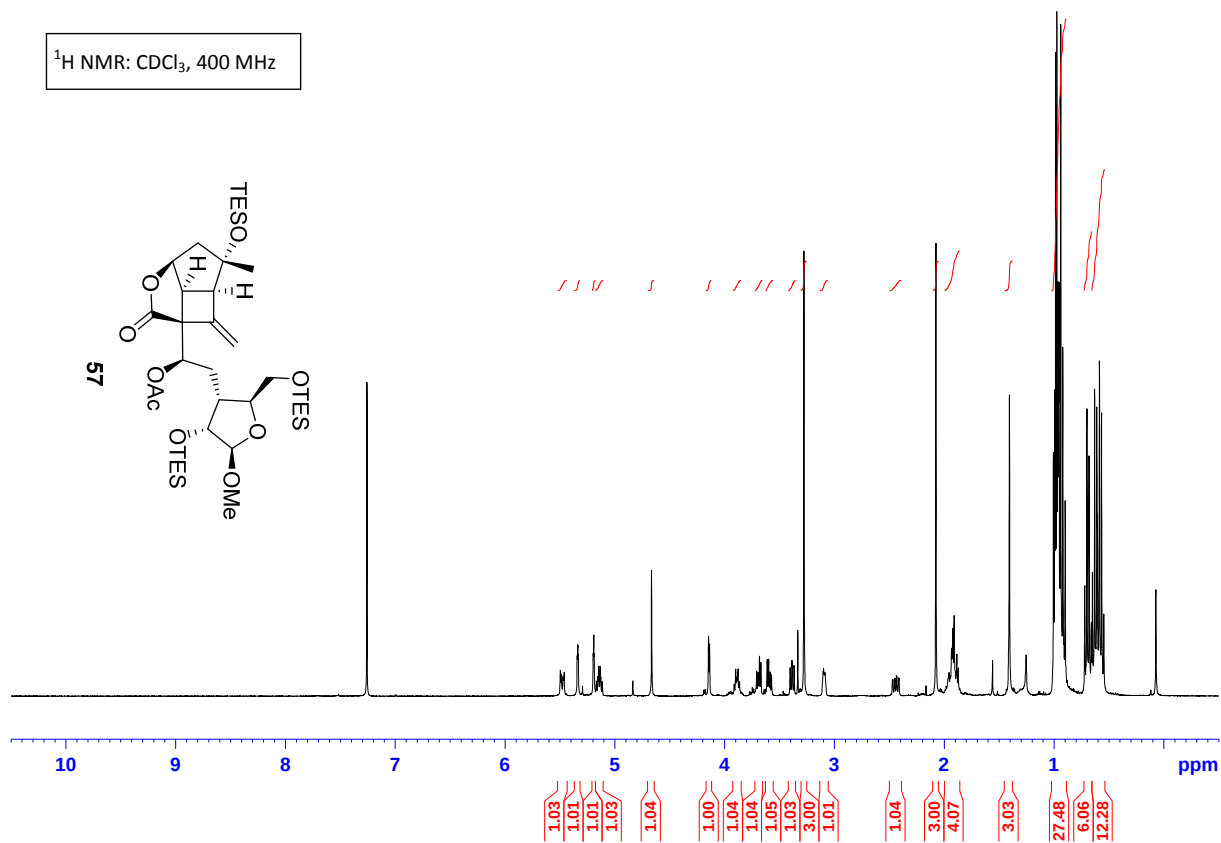
HMBC, CDCl₃, 400 MHz

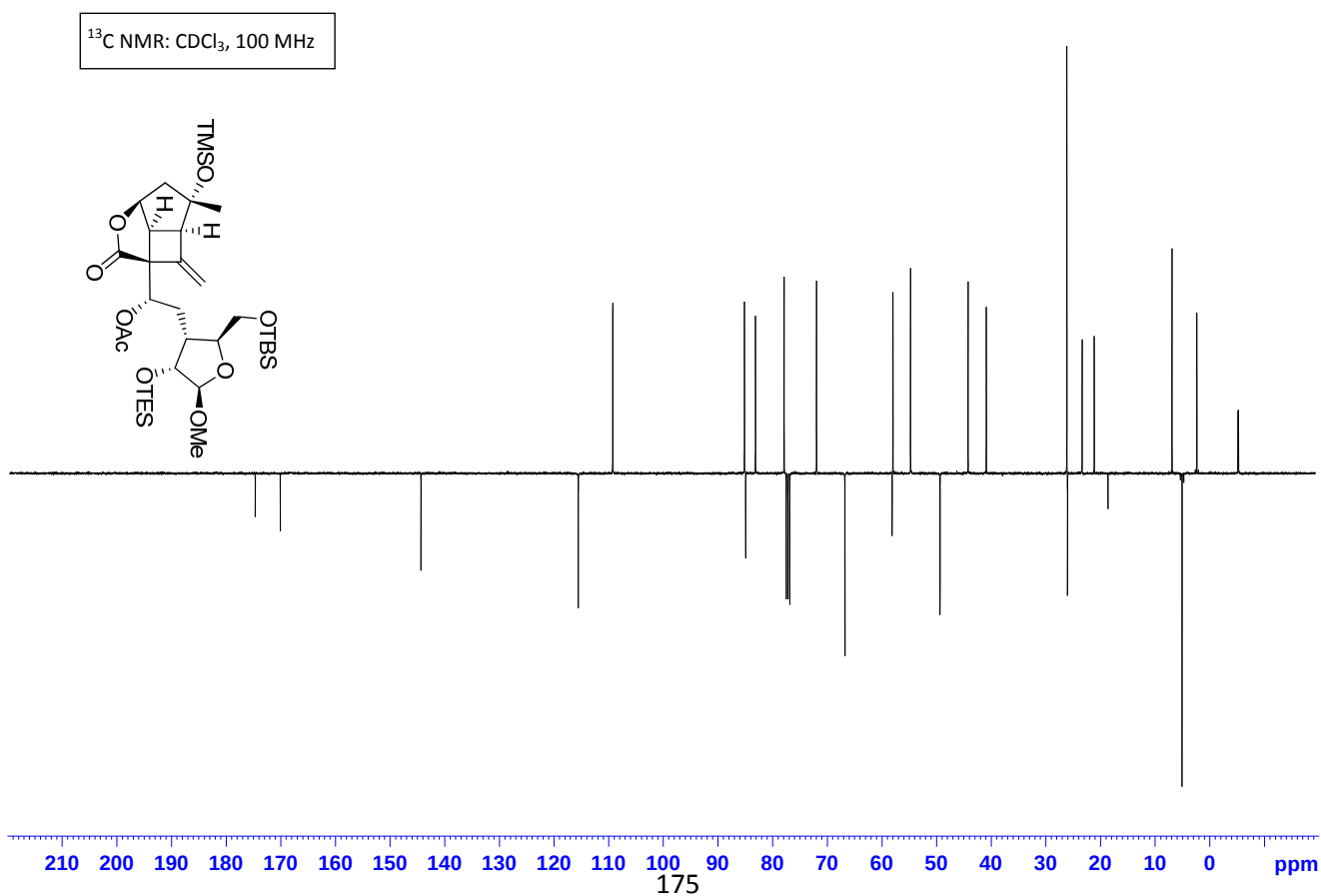
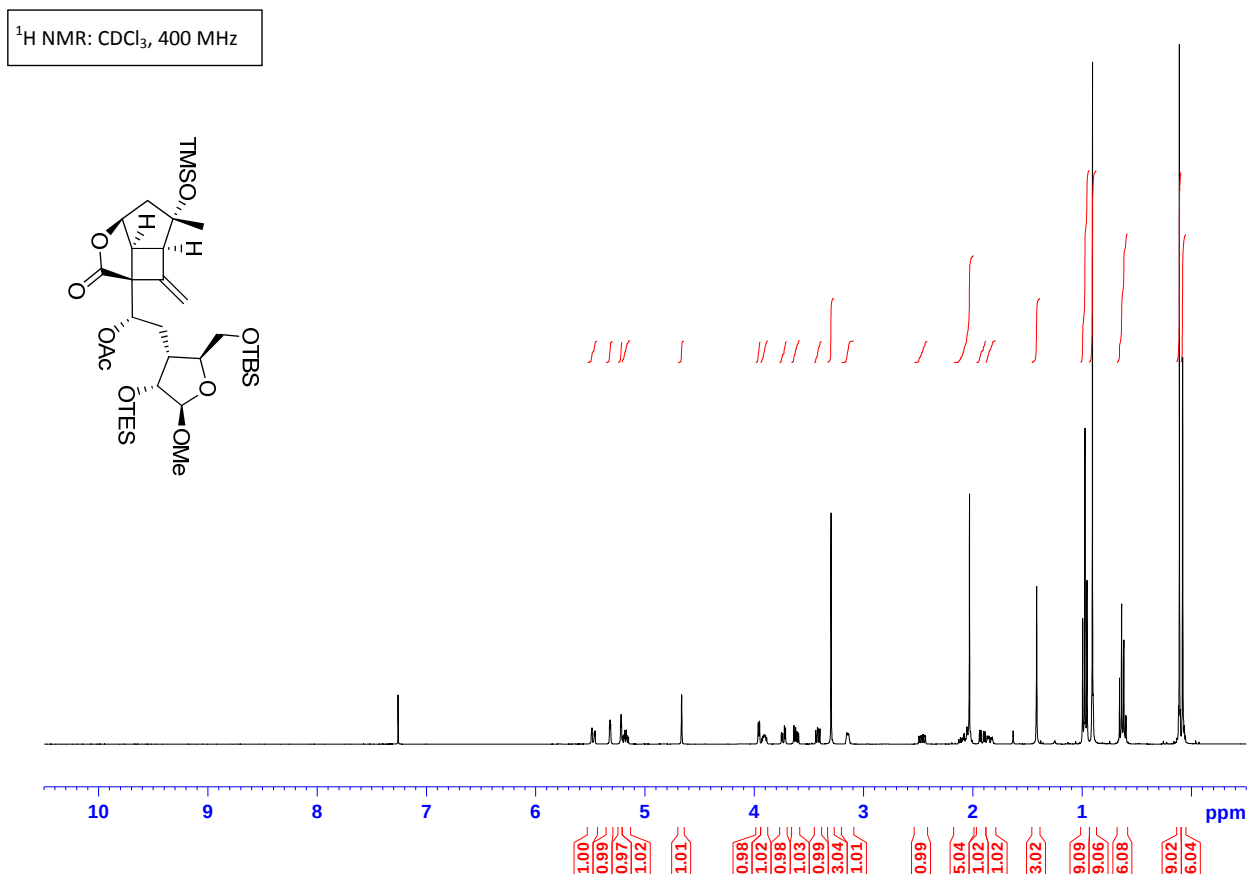


NOESY, CDCl₃, 400 MHz

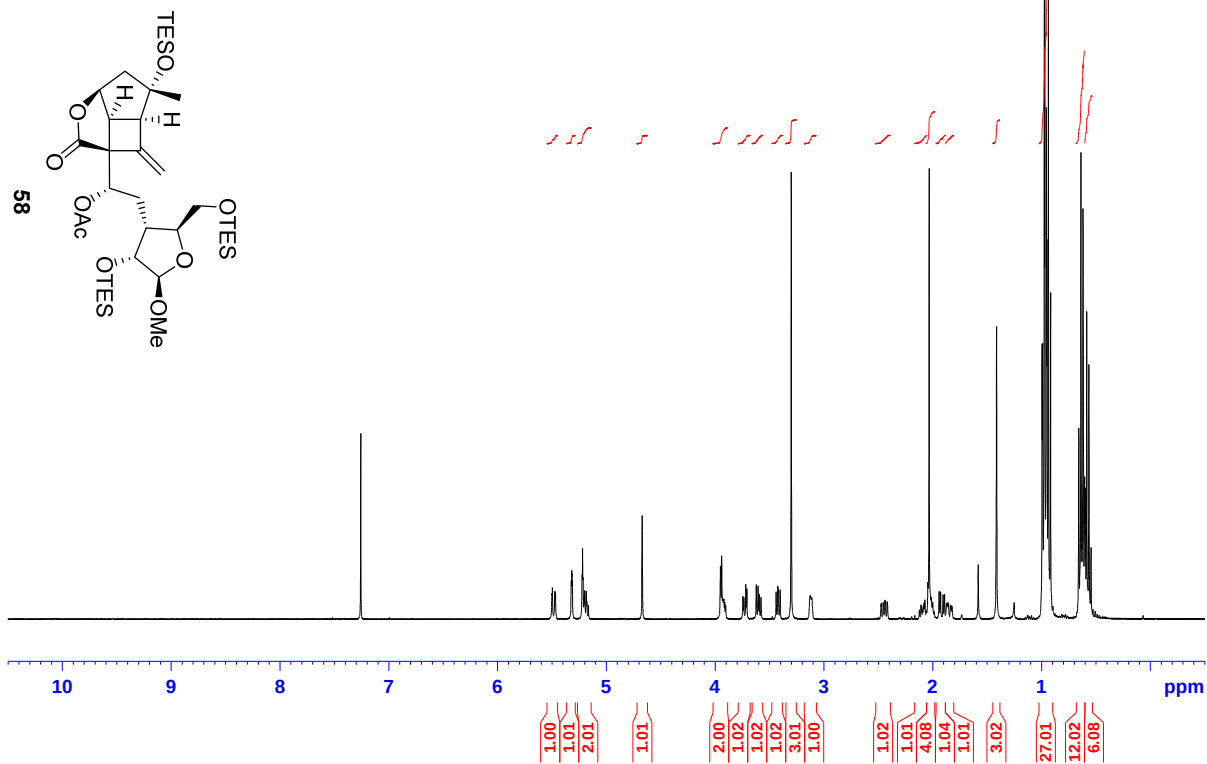




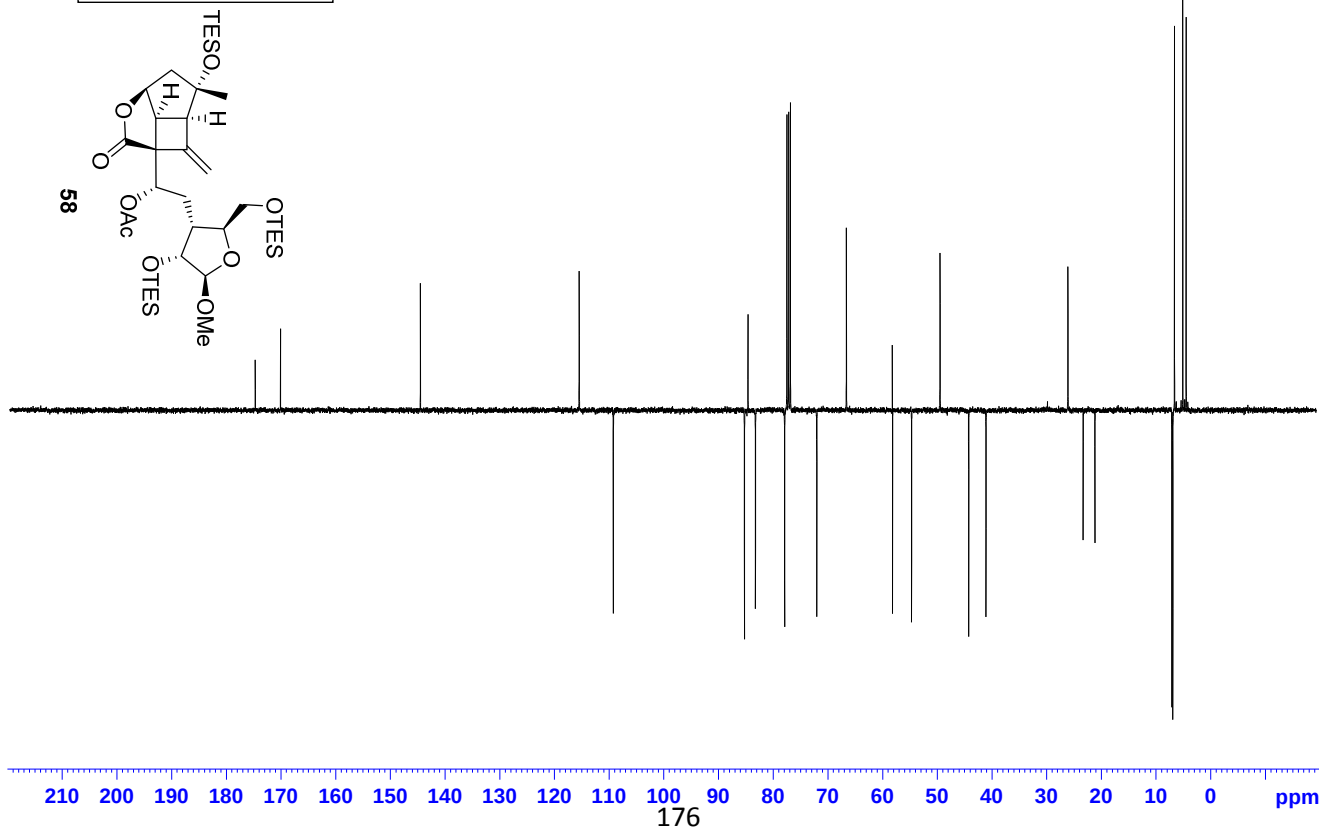




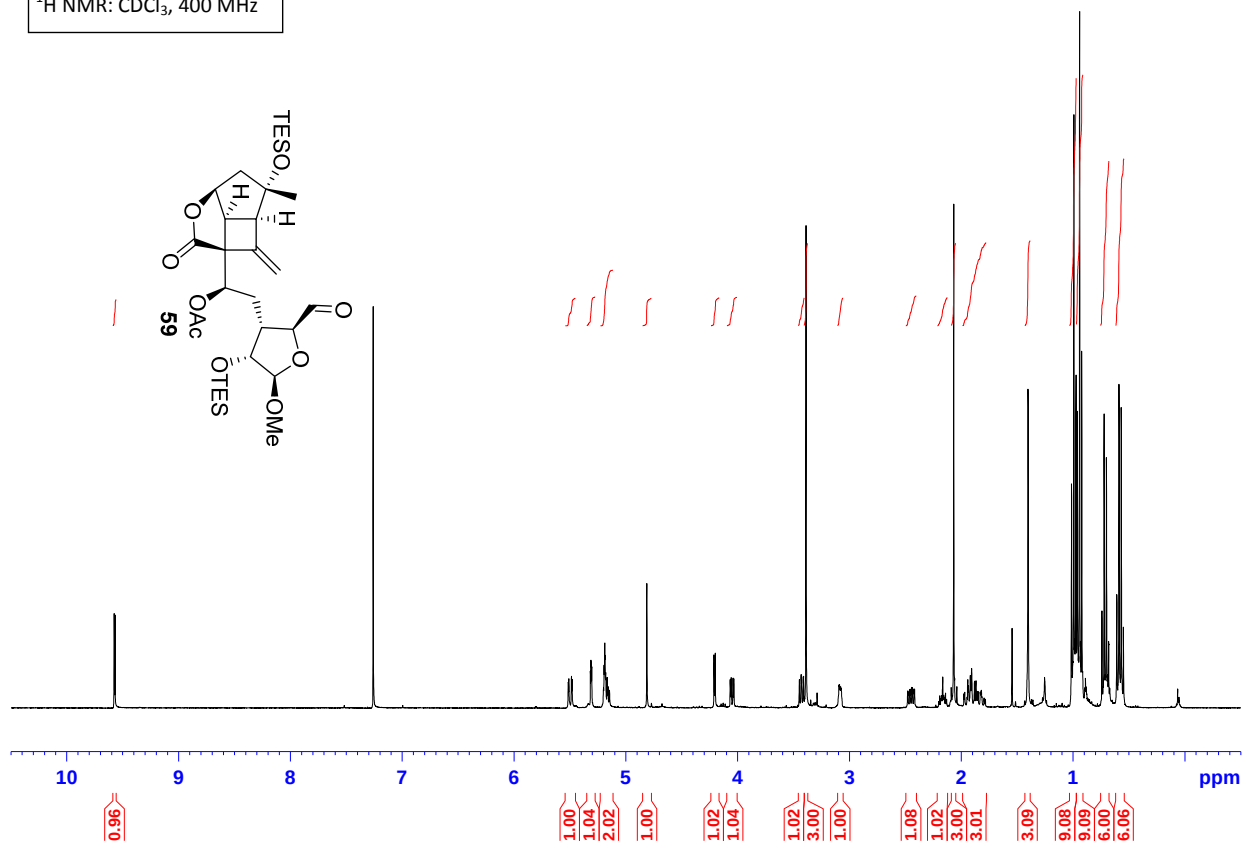
^1H NMR: CDCl_3 , 400 MHz



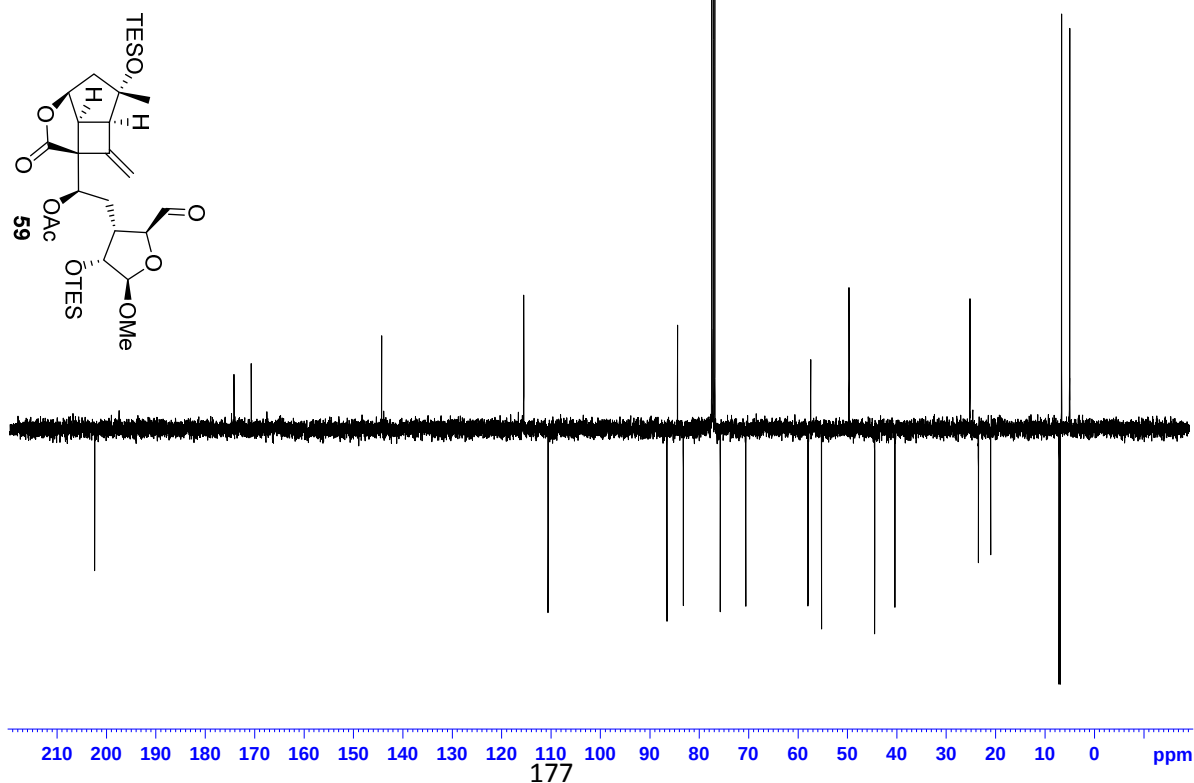
^{13}C NMR: CDCl_3 , 100 MHz

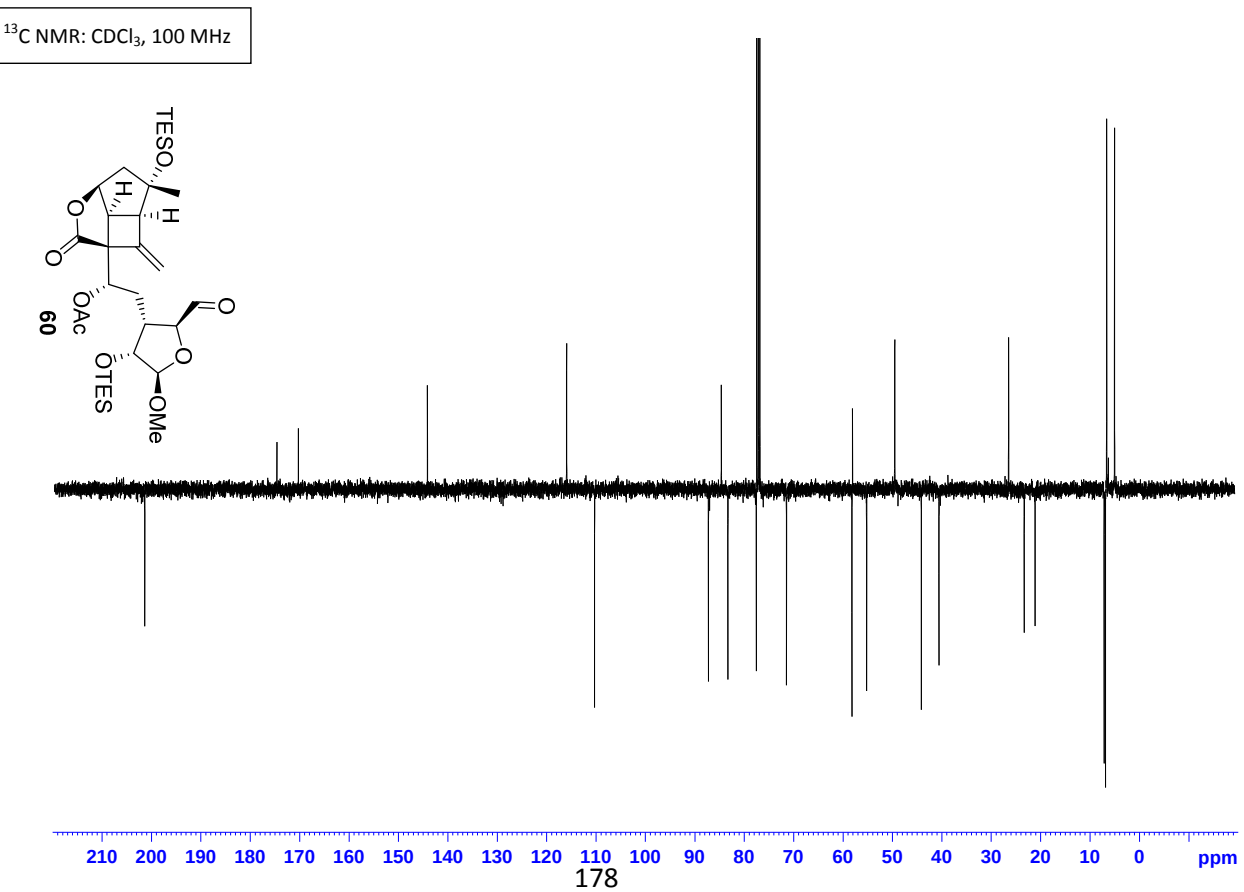


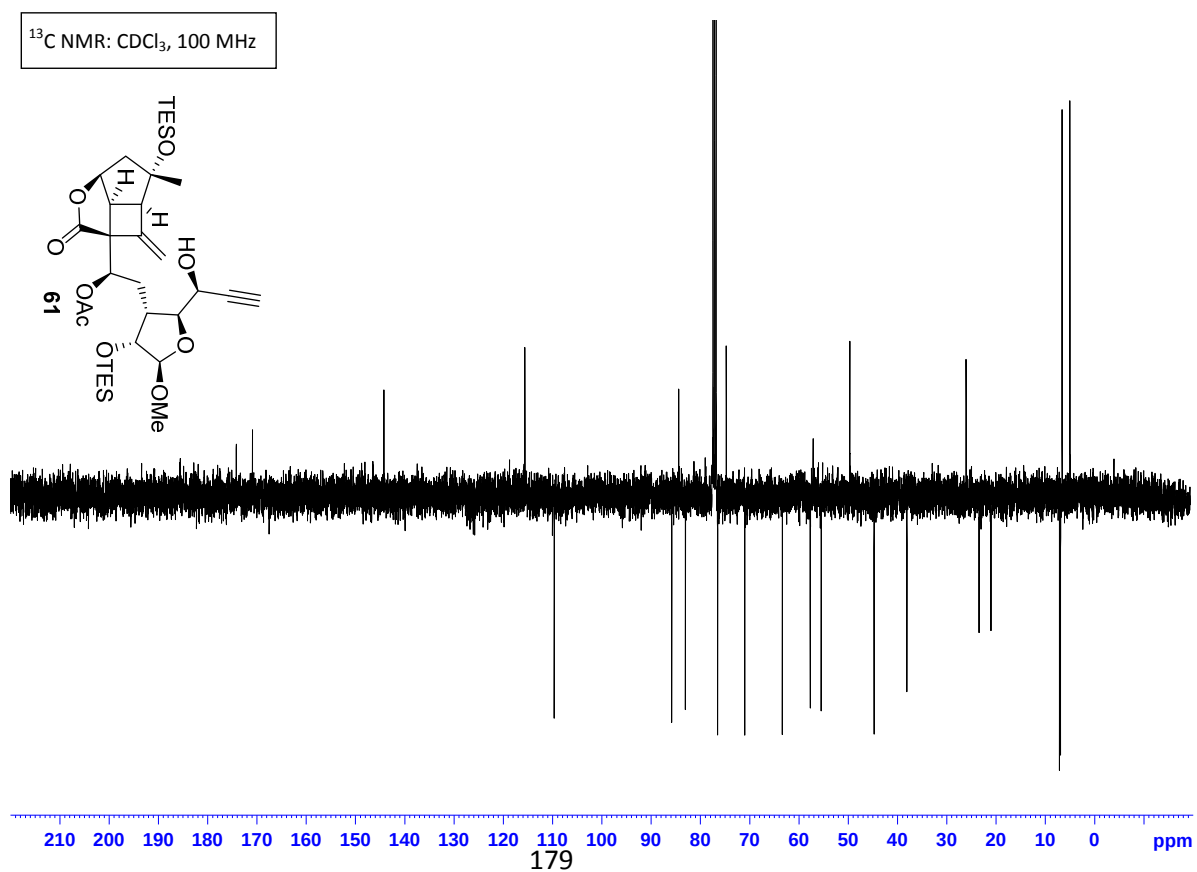
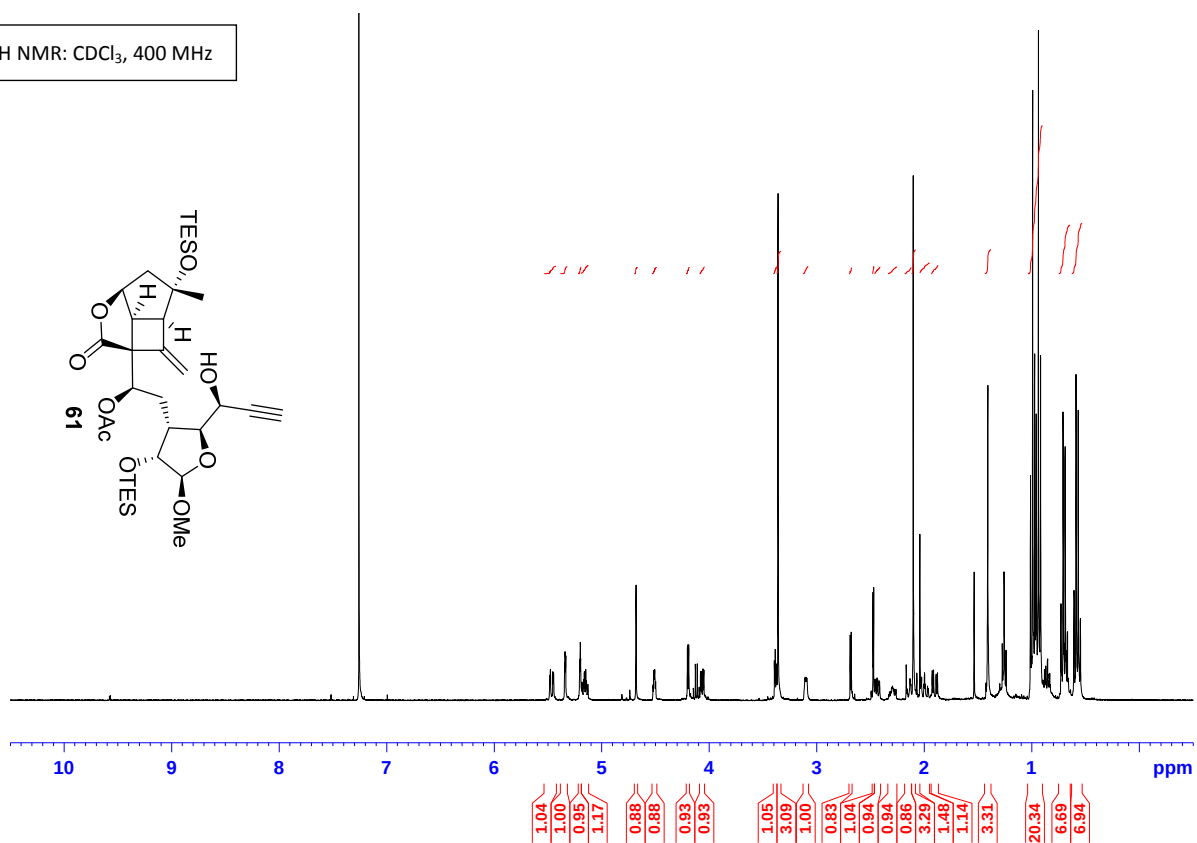
^1H NMR: CDCl_3 , 400 MHz

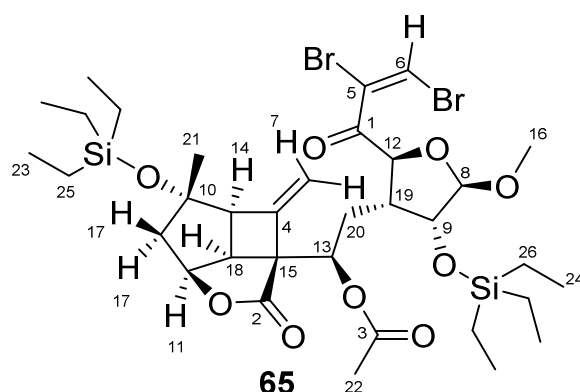


^{13}C NMR: CDCl_3 , 100 MHz





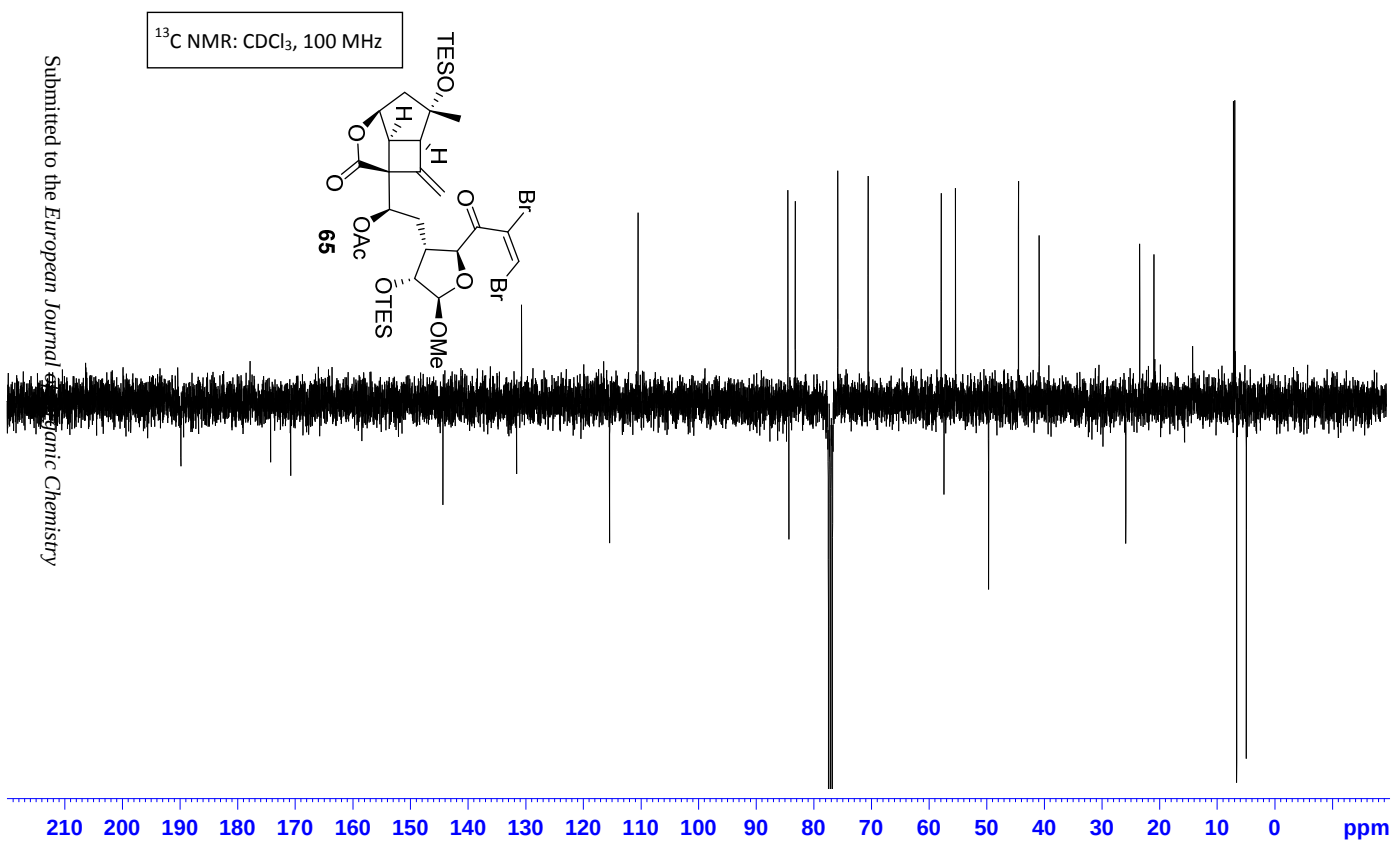
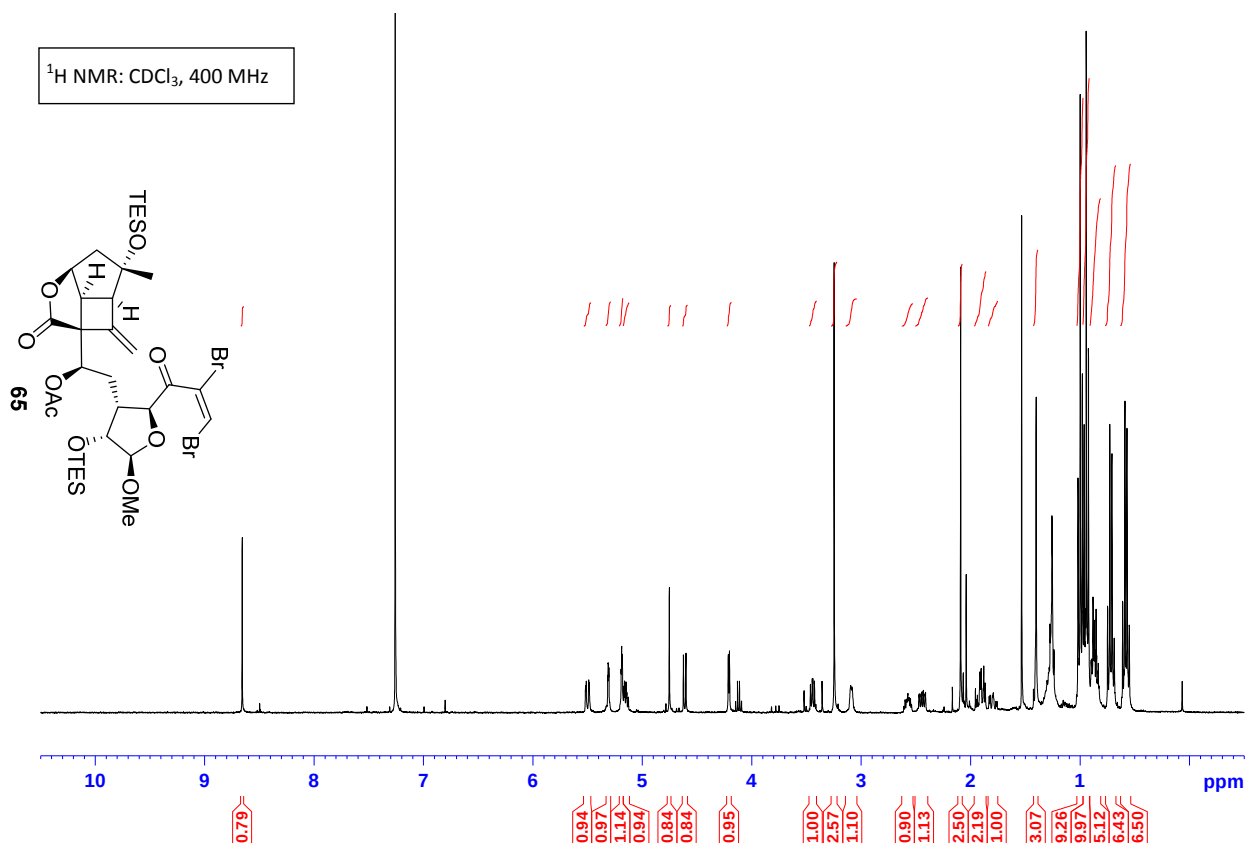




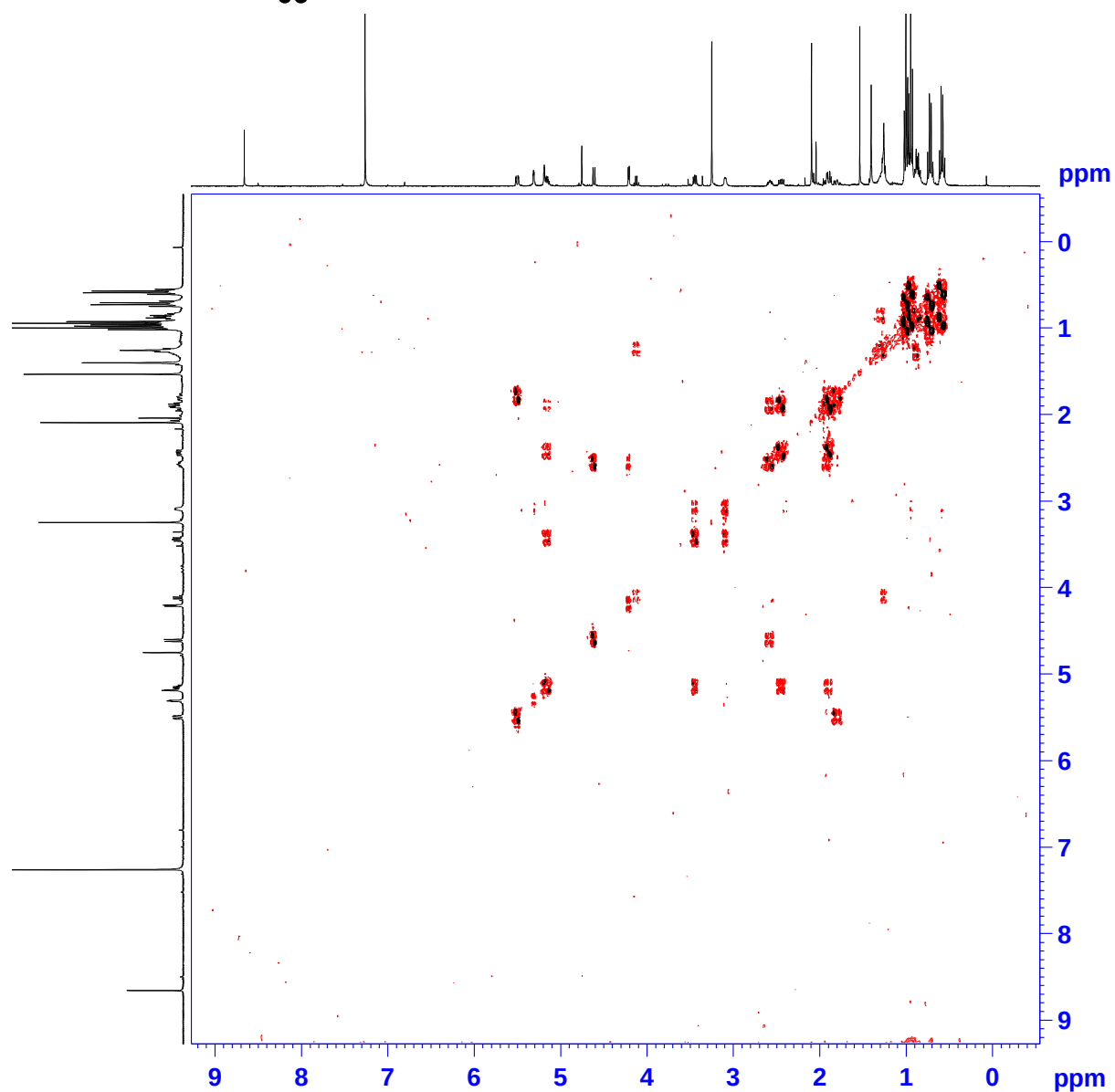
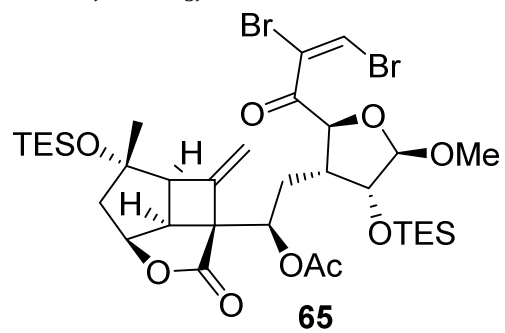
NOE- correlation: 16 ↔ 6 ↔ 9; 6 ↔ 19

HMBC-correlation: 19 ↔ 1 ↔ 6 ↔ 5

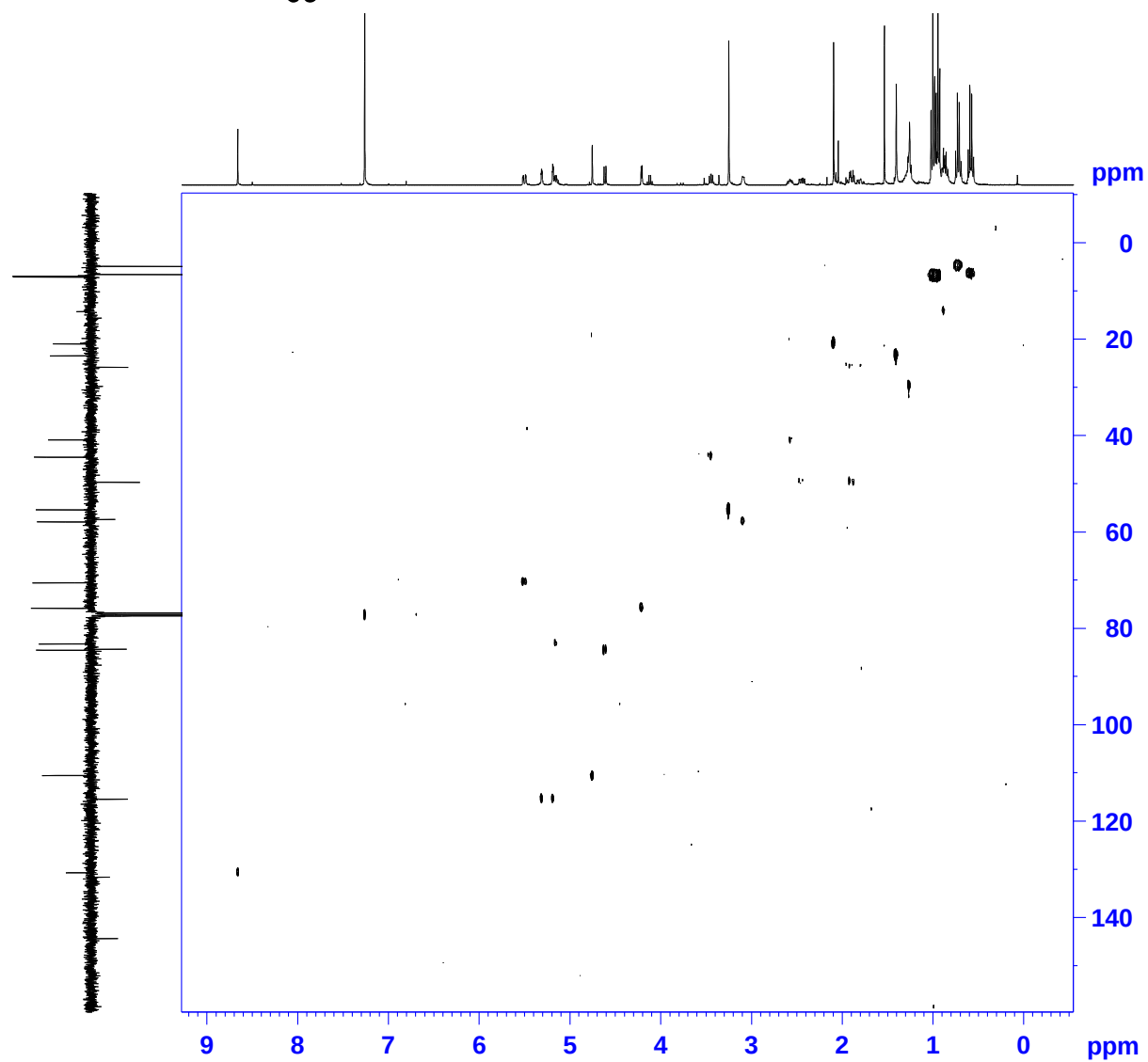
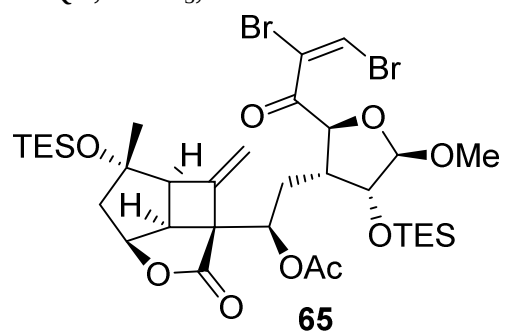
No.	¹³ C [ppm]	¹ H [ppm]
1	189.9	-
2	174.3	-
3	170.8	-
4	144.4	-
5	131.6	-
6	130.8	8.66
7	115.5	5.31 ^a ; 5.19 ^b
8	110.6	4.75
9	84.6	4.61
10	84.4	-
11	83.3	5.16
12	75.9	4.21
13	70.6	5.50
14	57.9	3.09
15	57.5	-
16	55.5	3.25
17	49.7	2.45 ^a ; 1.90 ^b
18	44.5	3.45
19	40.9	2.58
20	25.9	1.90 ^a , 1.80 ^b
21	23.5	1.40
22	21.0	2.09
23	7.2	0.95
24	7.0	1.00
25	6.6	0.58
26	4.9	0.72



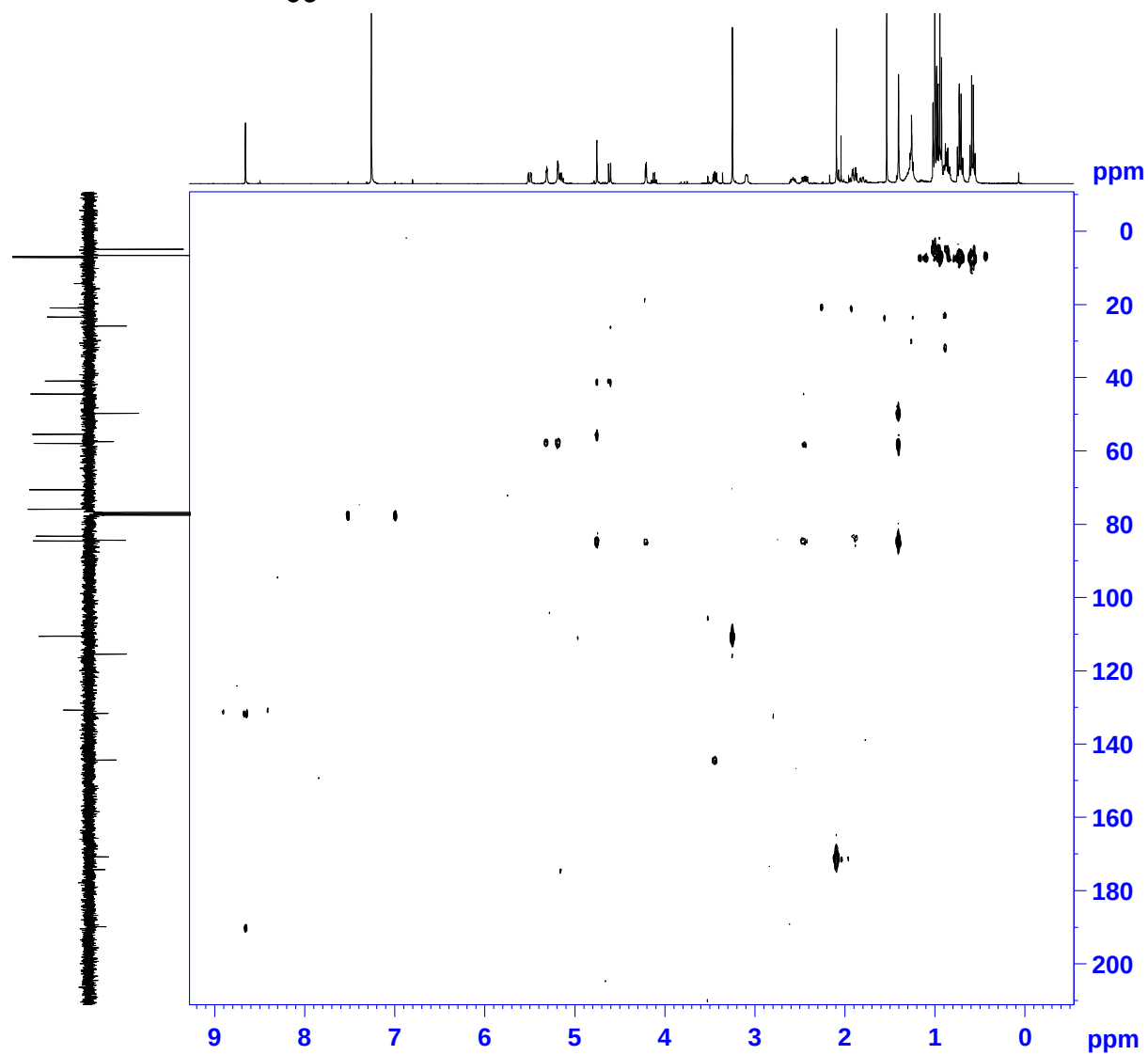
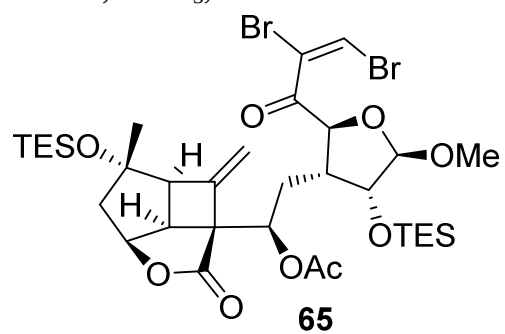
COSY, CDCl₃, 400 MHz



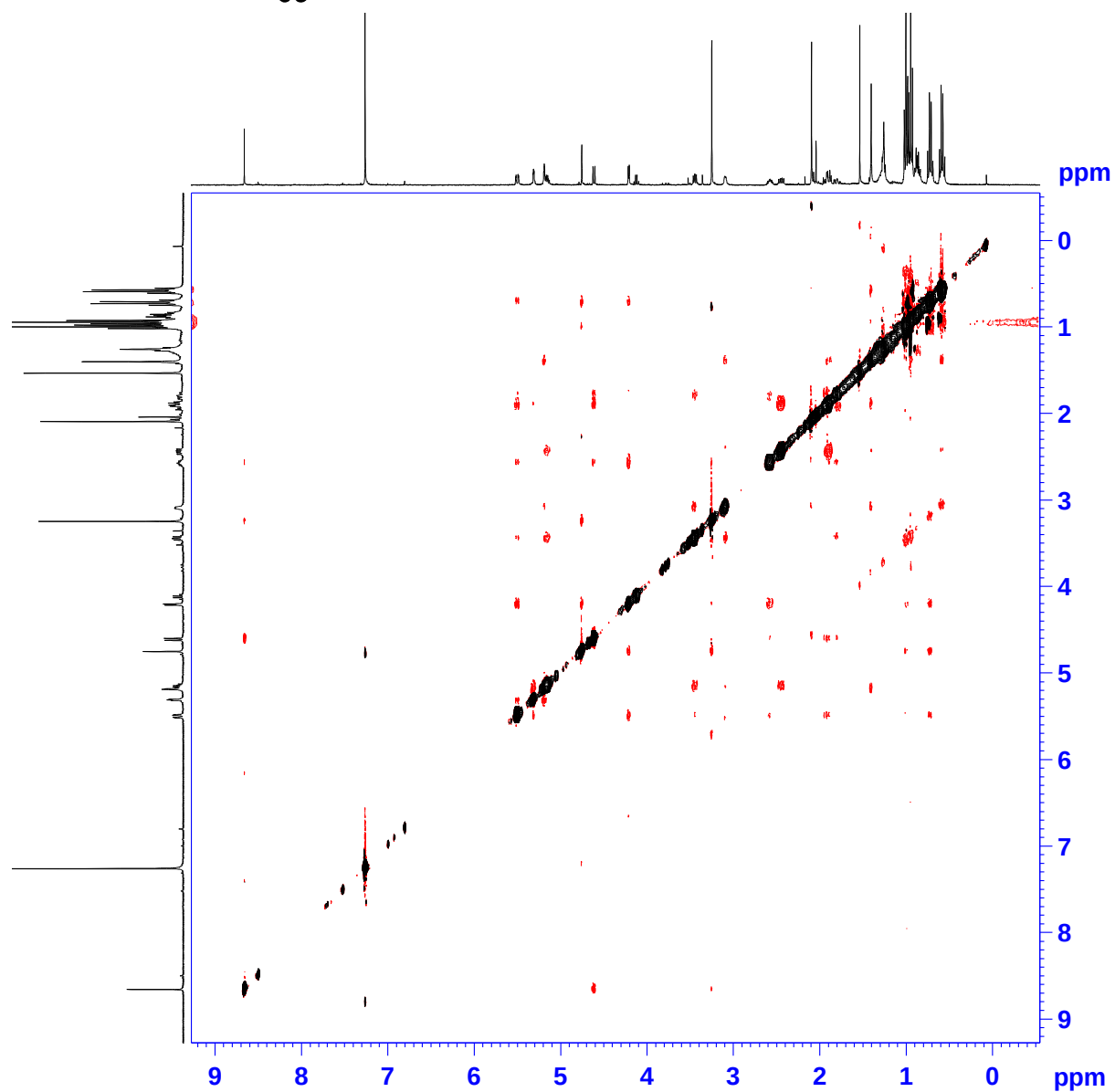
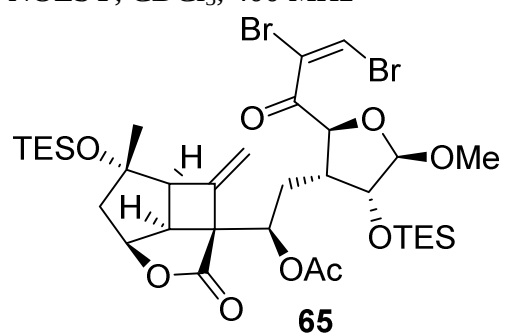
HSQC, CDCl₃, 400 MHz



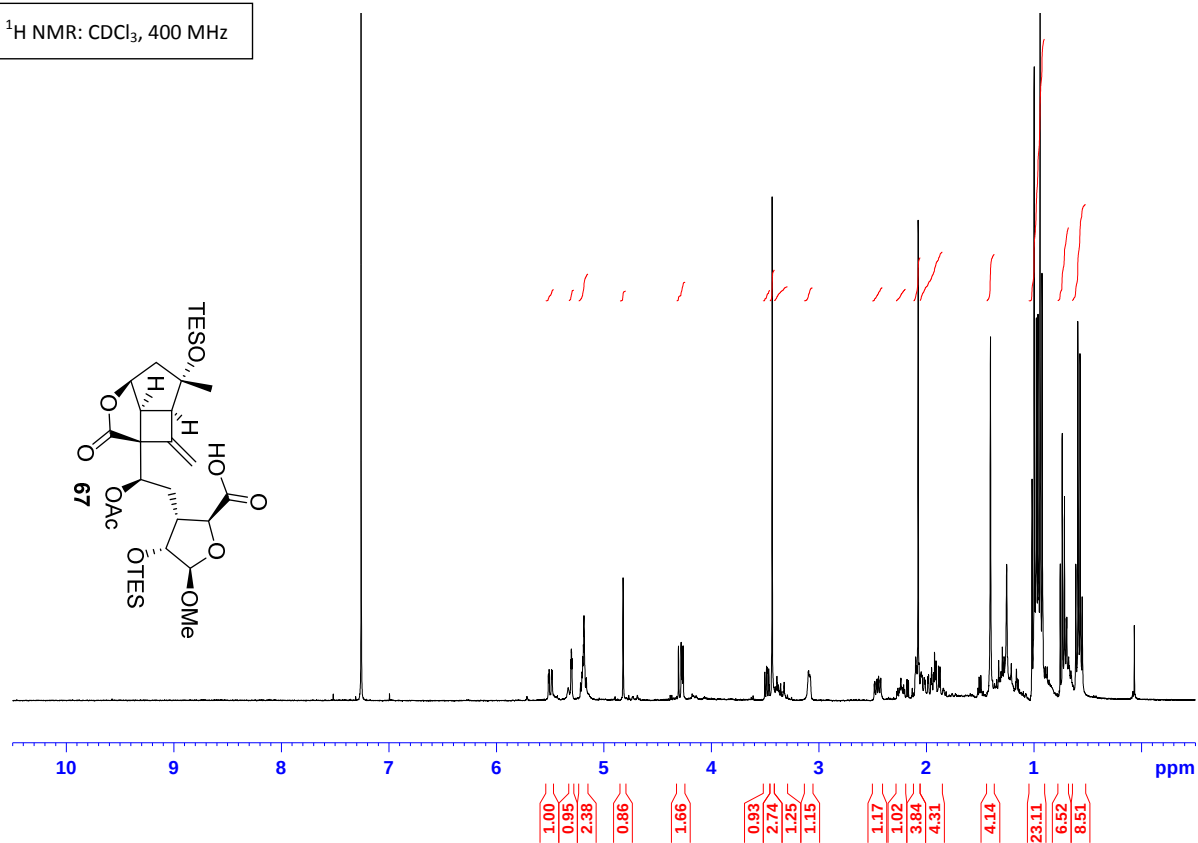
HMBC, CDCl₃, 400 MHz



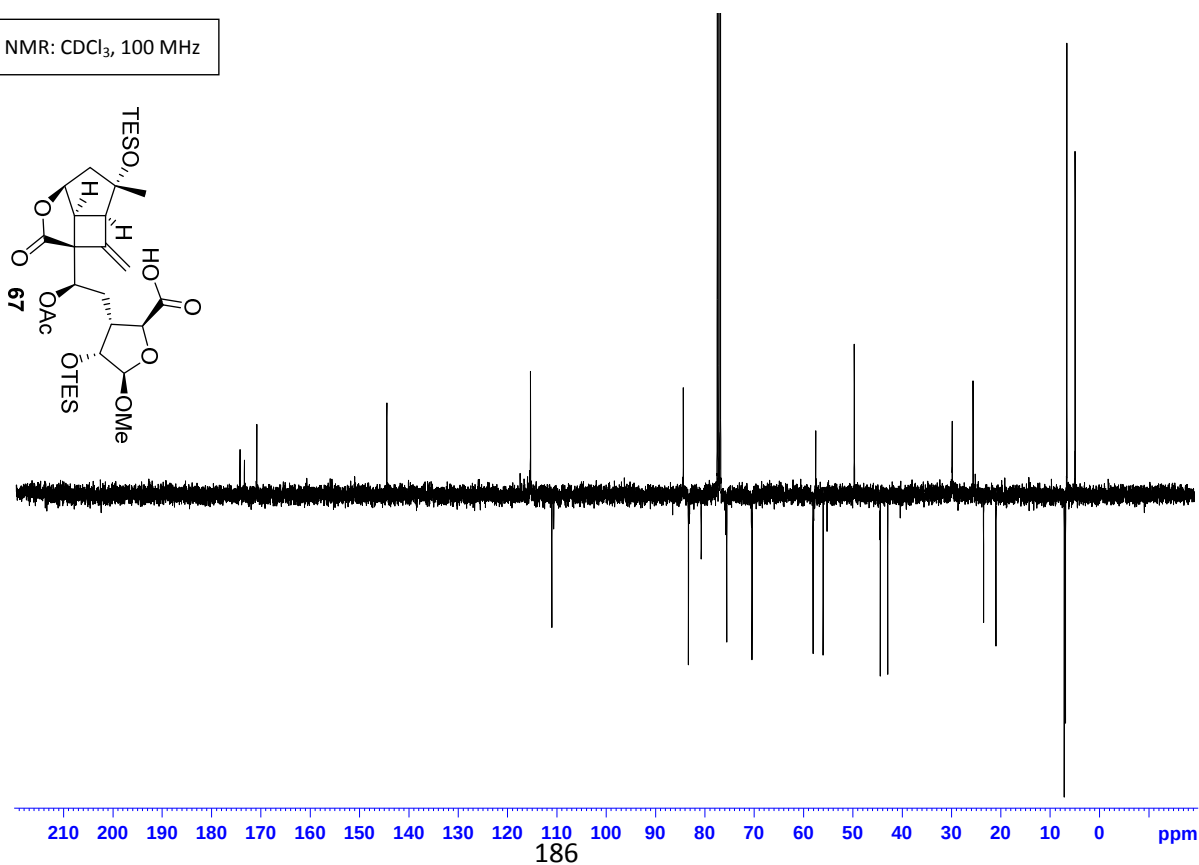
NOESY, CDCl₃, 400 MHz



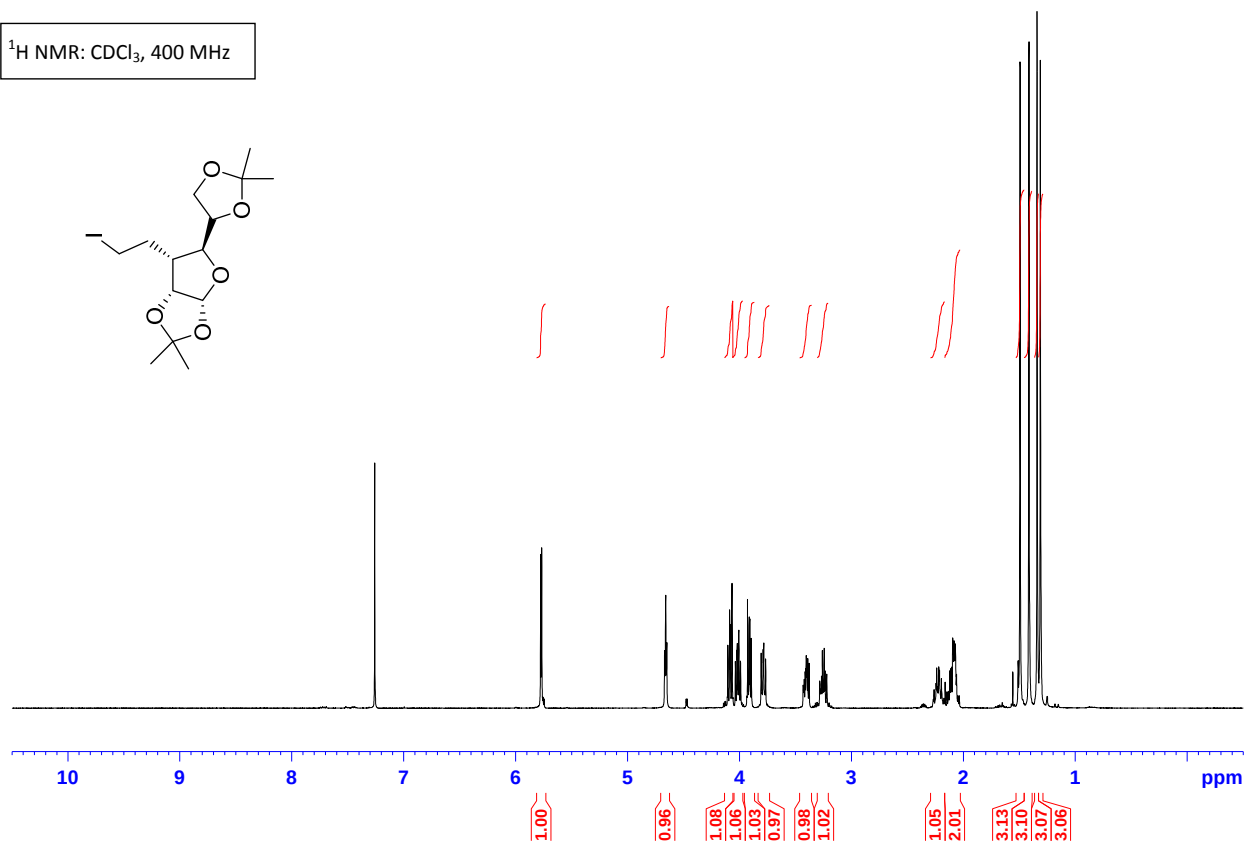
¹H NMR: CDCl₃, 400 MHz



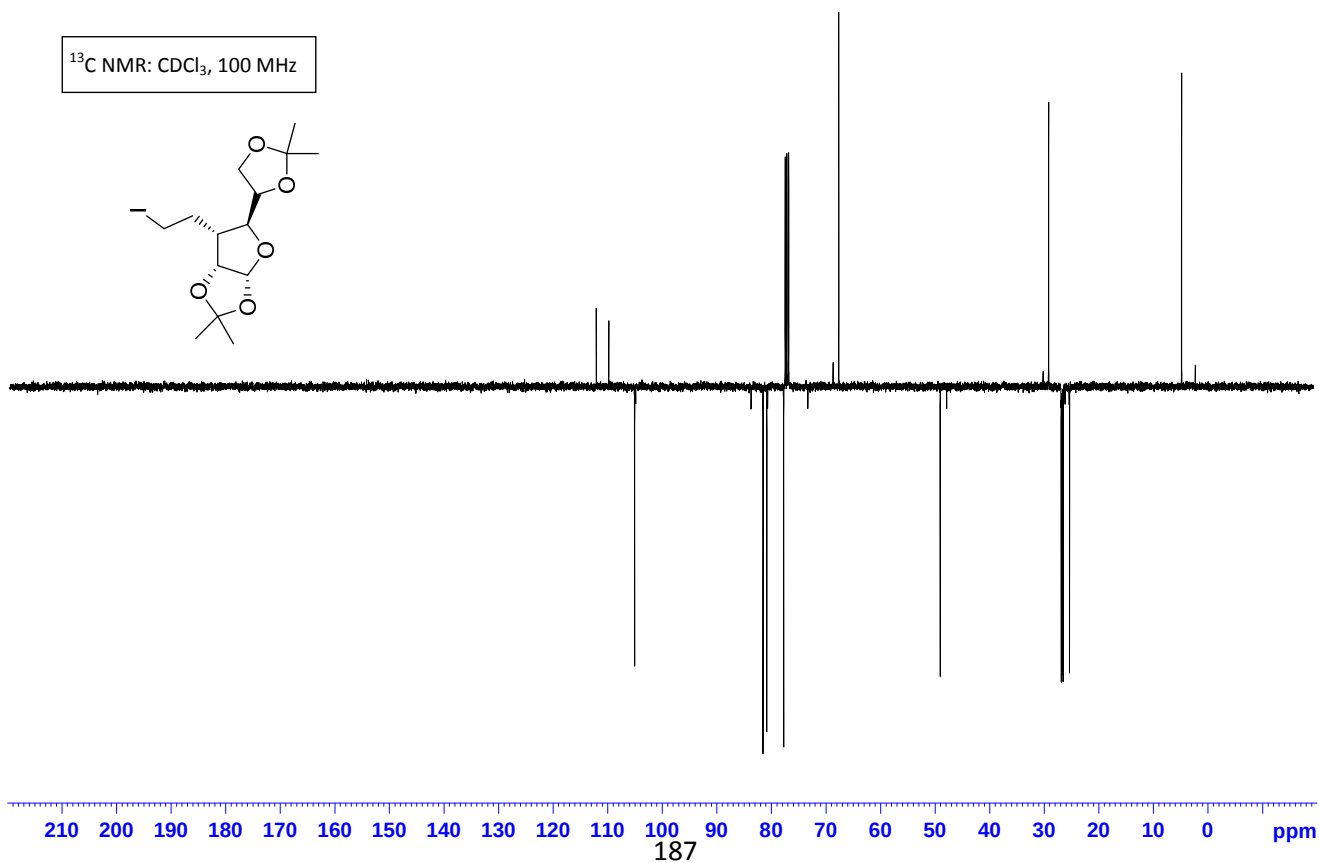
¹³C NMR: CDCl₃, 100 MHz



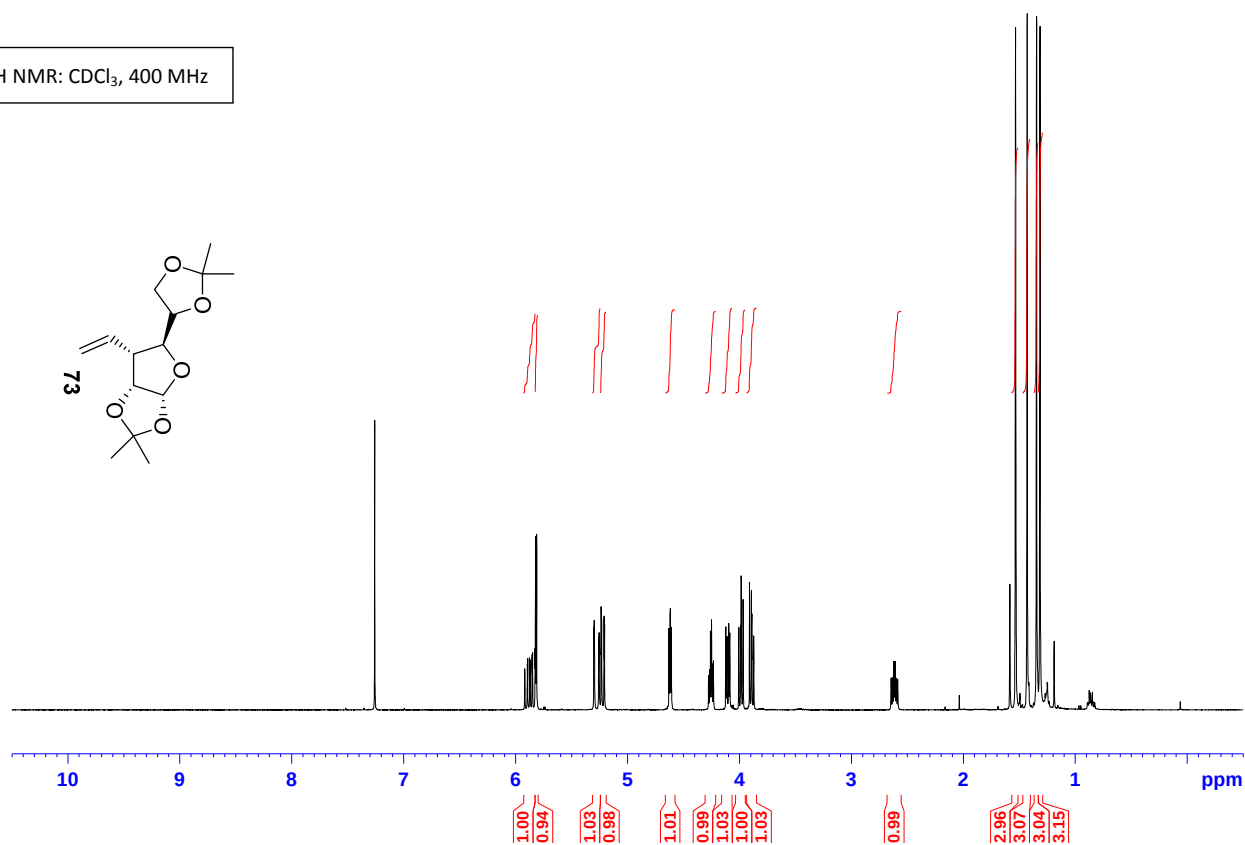
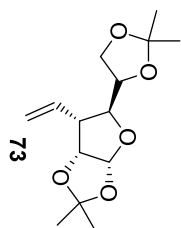
¹H NMR: CDCl₃, 400 MHz



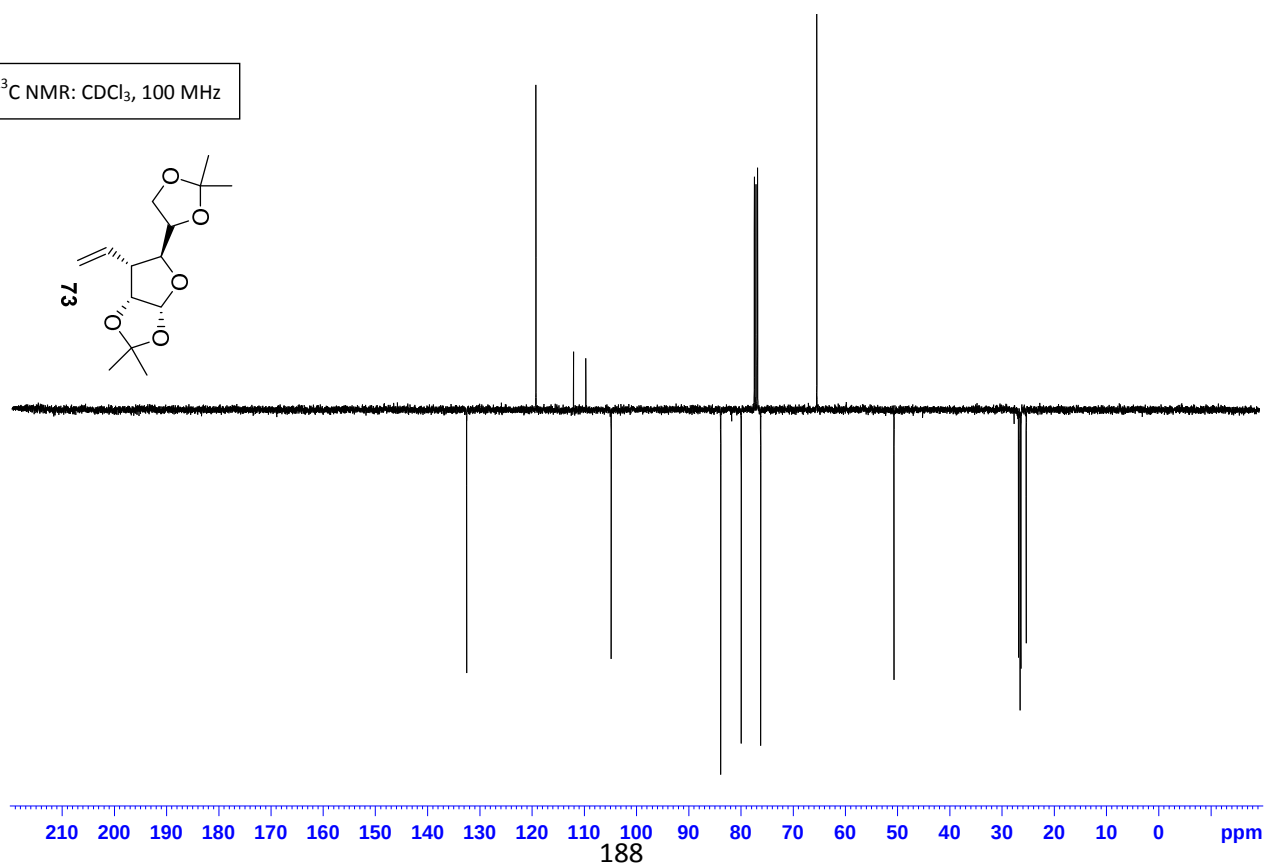
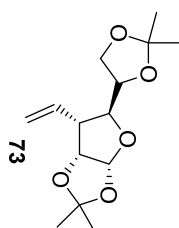
¹³C NMR: CDCl₃, 100 MHz



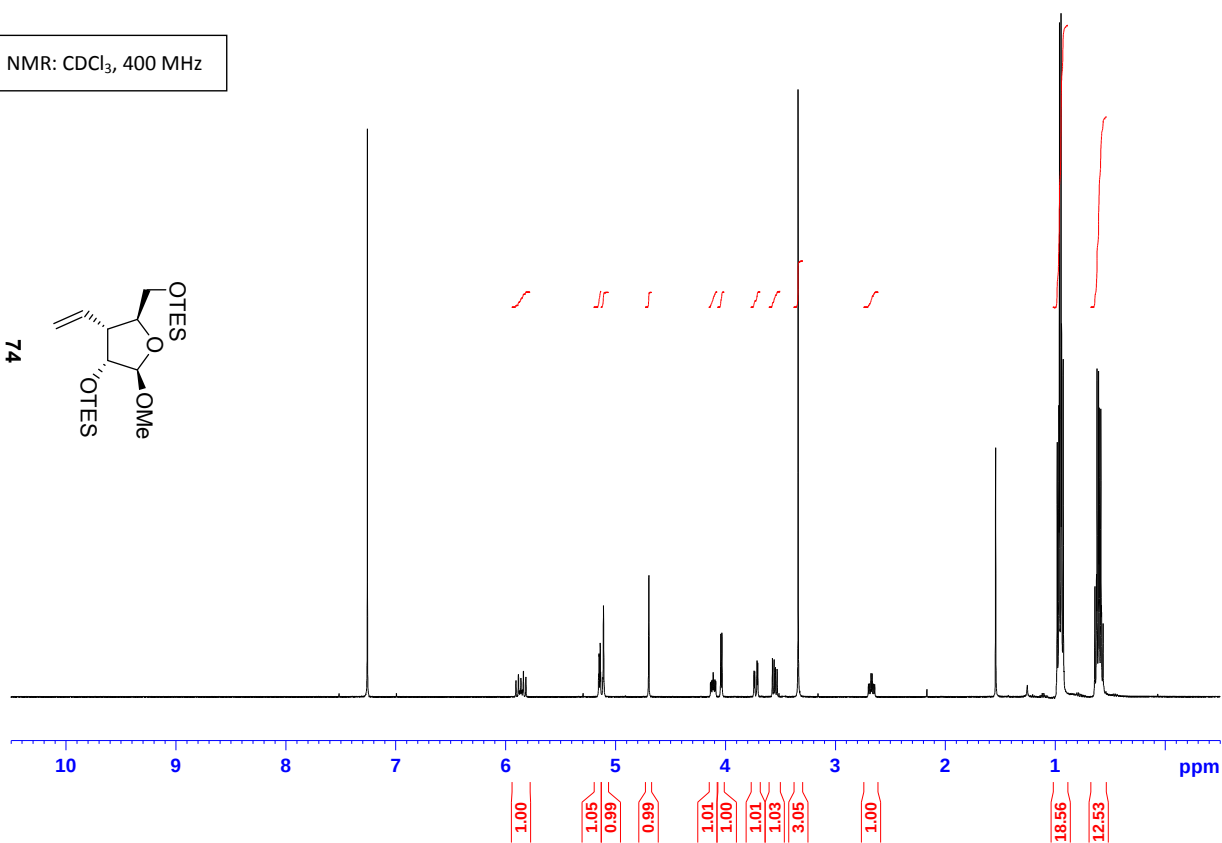
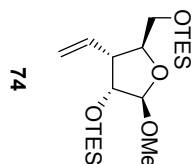
^1H NMR: CDCl_3 , 400 MHz



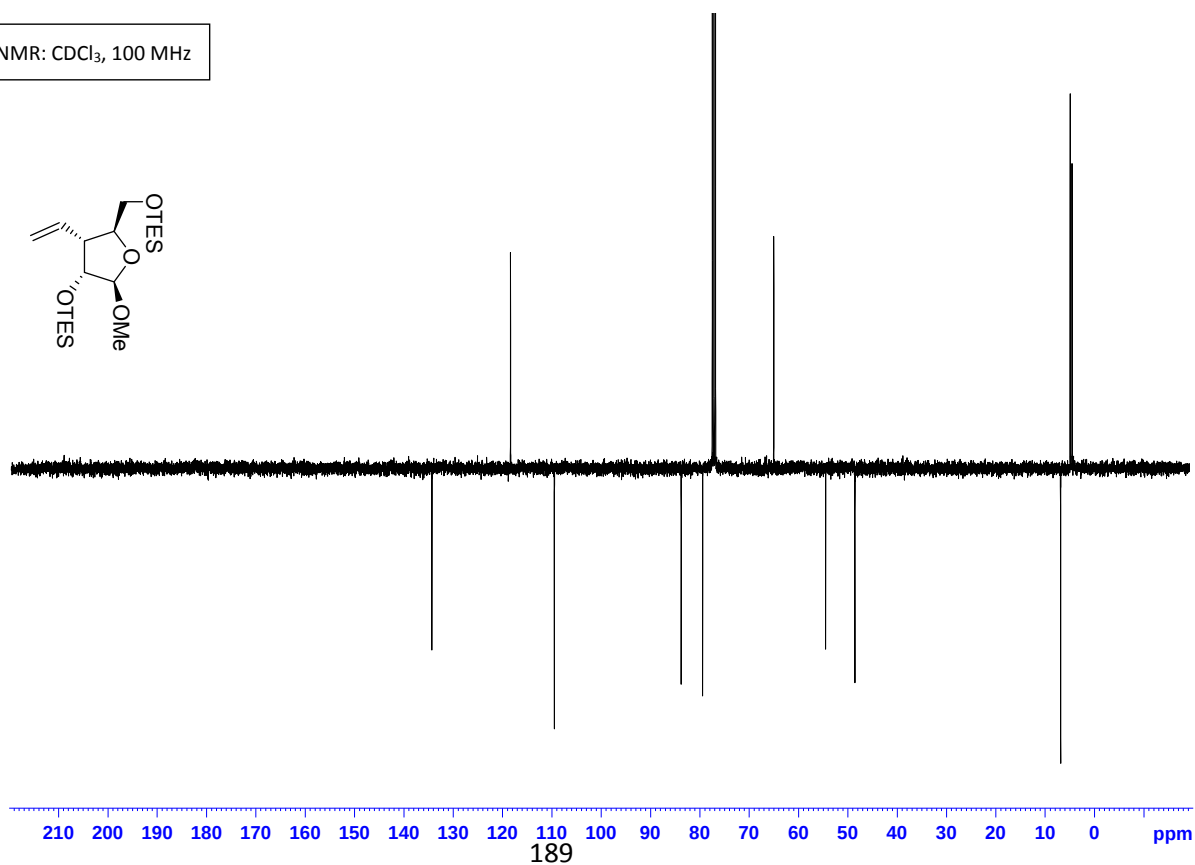
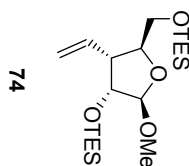
^{13}C NMR: CDCl_3 , 100 MHz

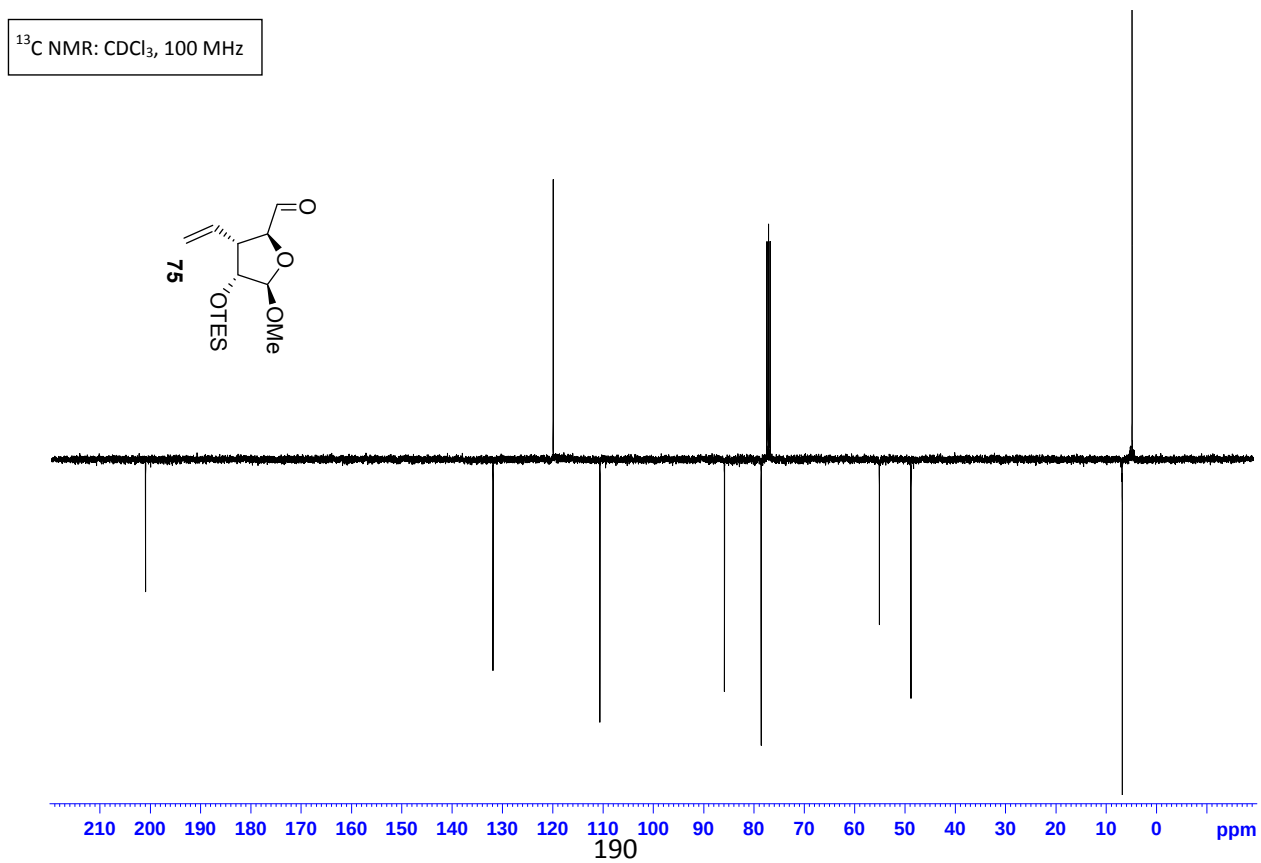
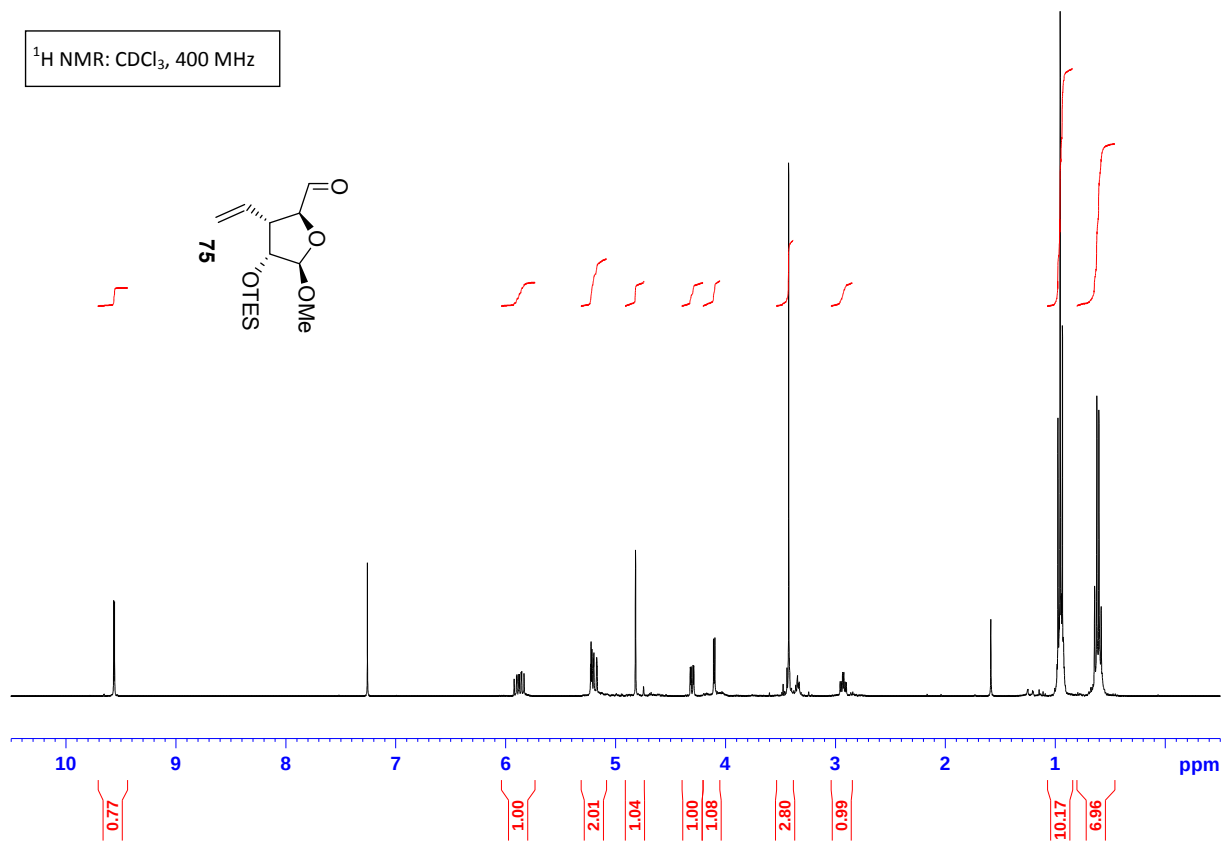


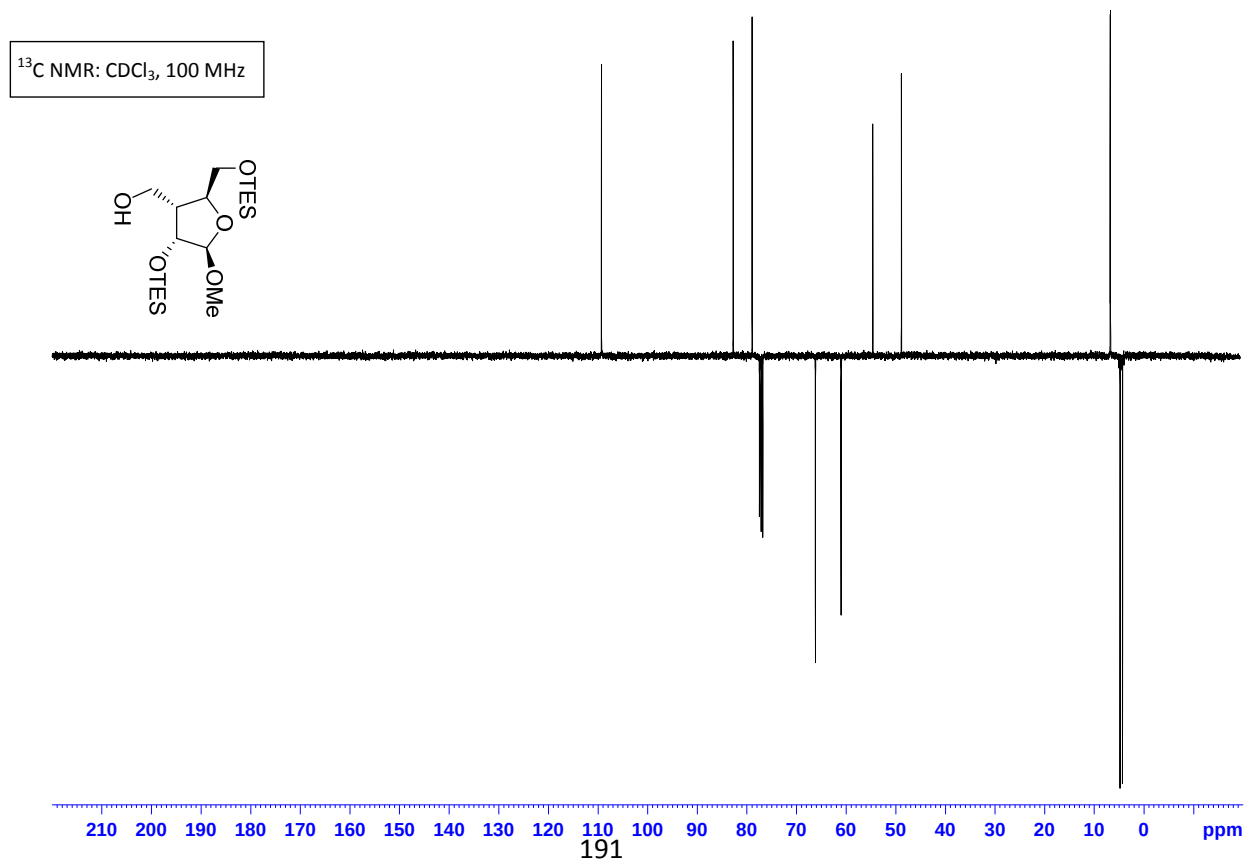
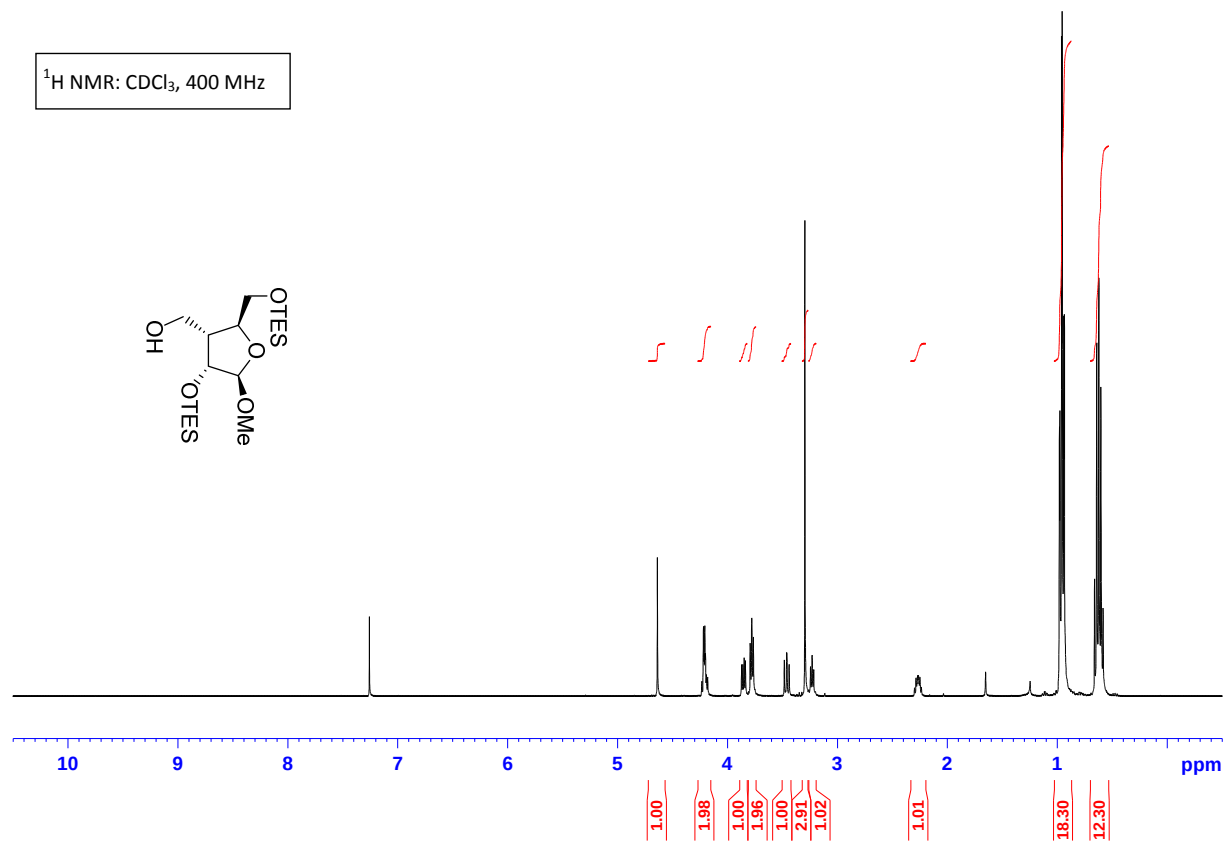
^1H NMR: CDCl_3 , 400 MHz

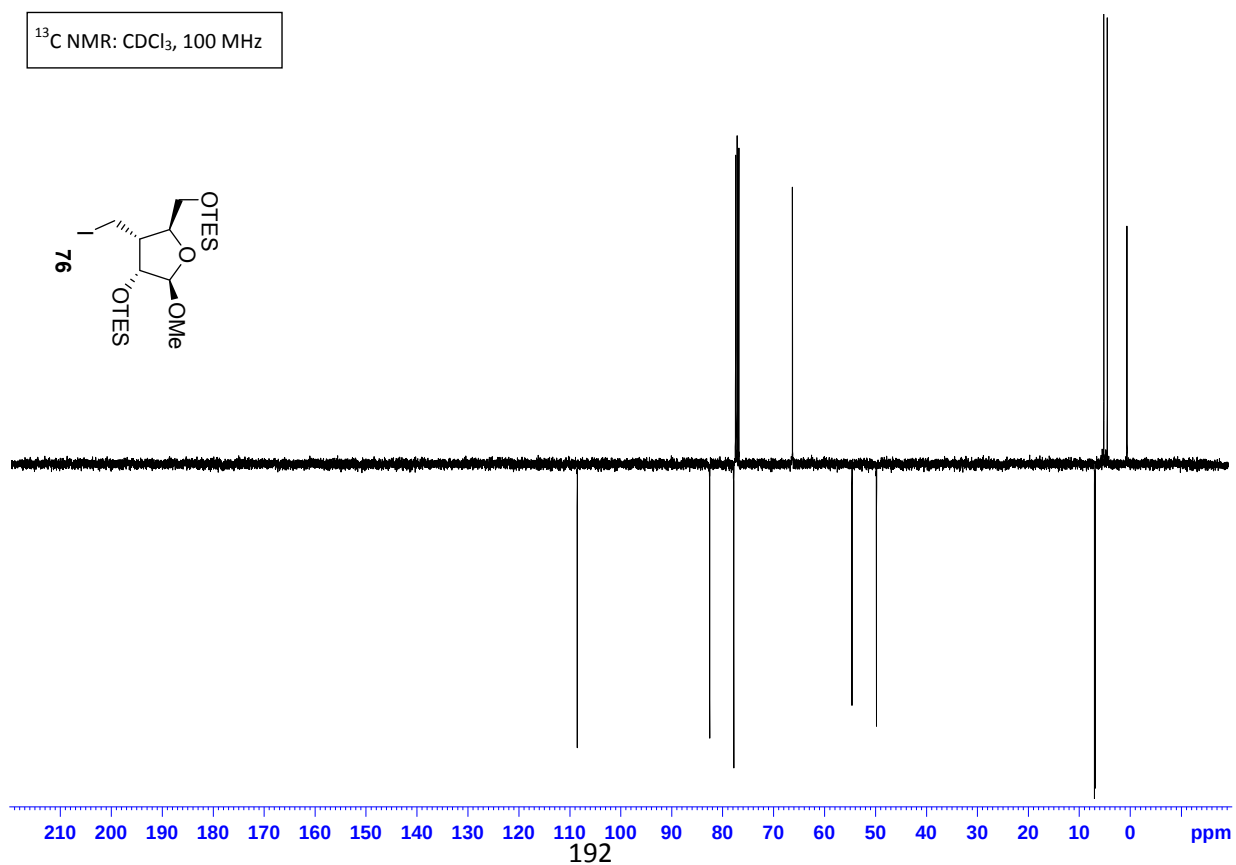
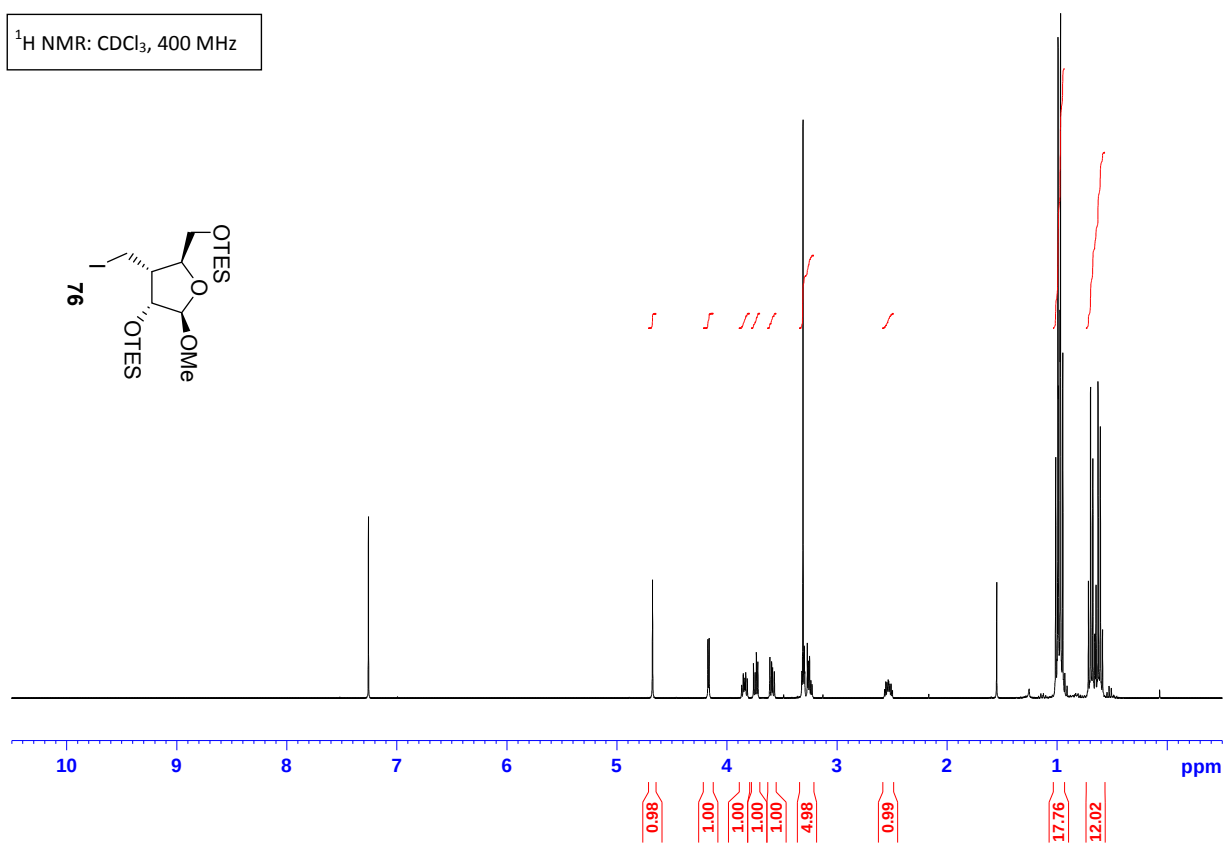


^{13}C NMR: CDCl_3 , 100 MHz

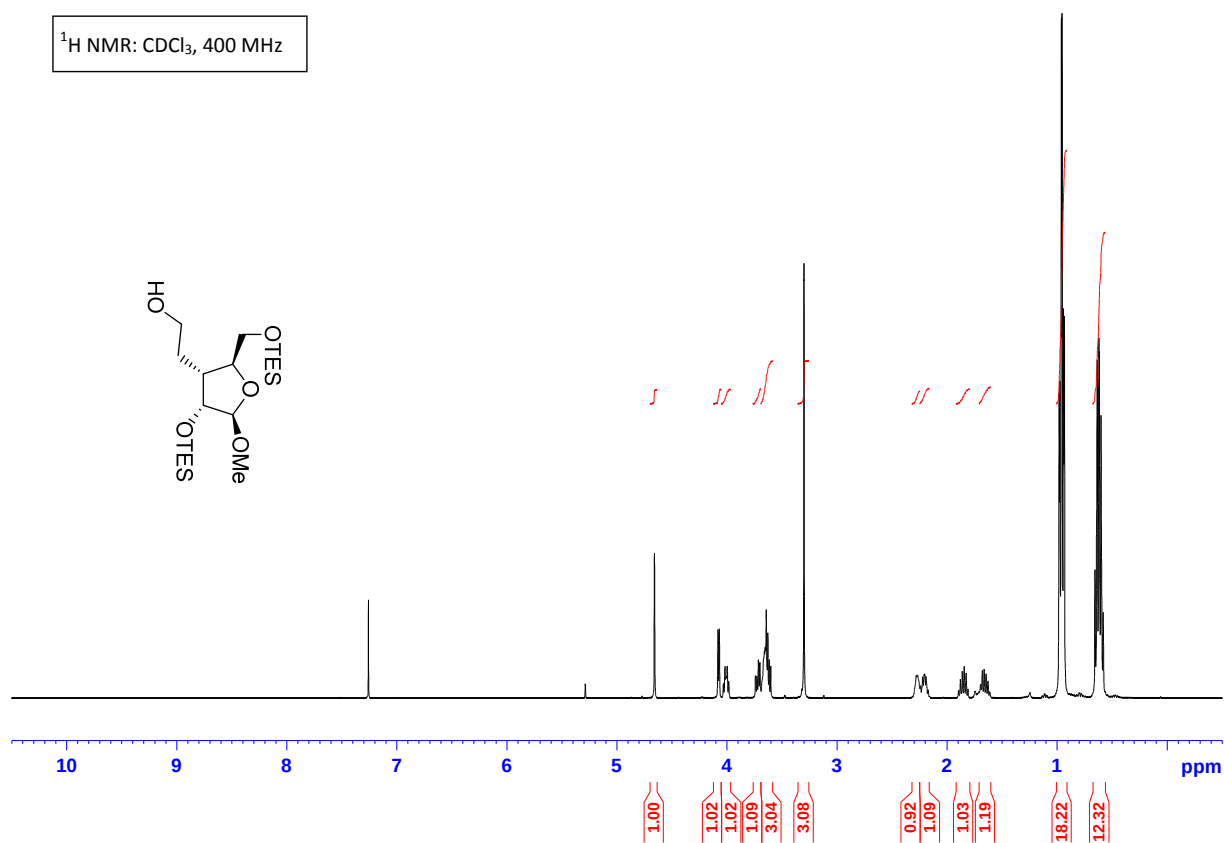




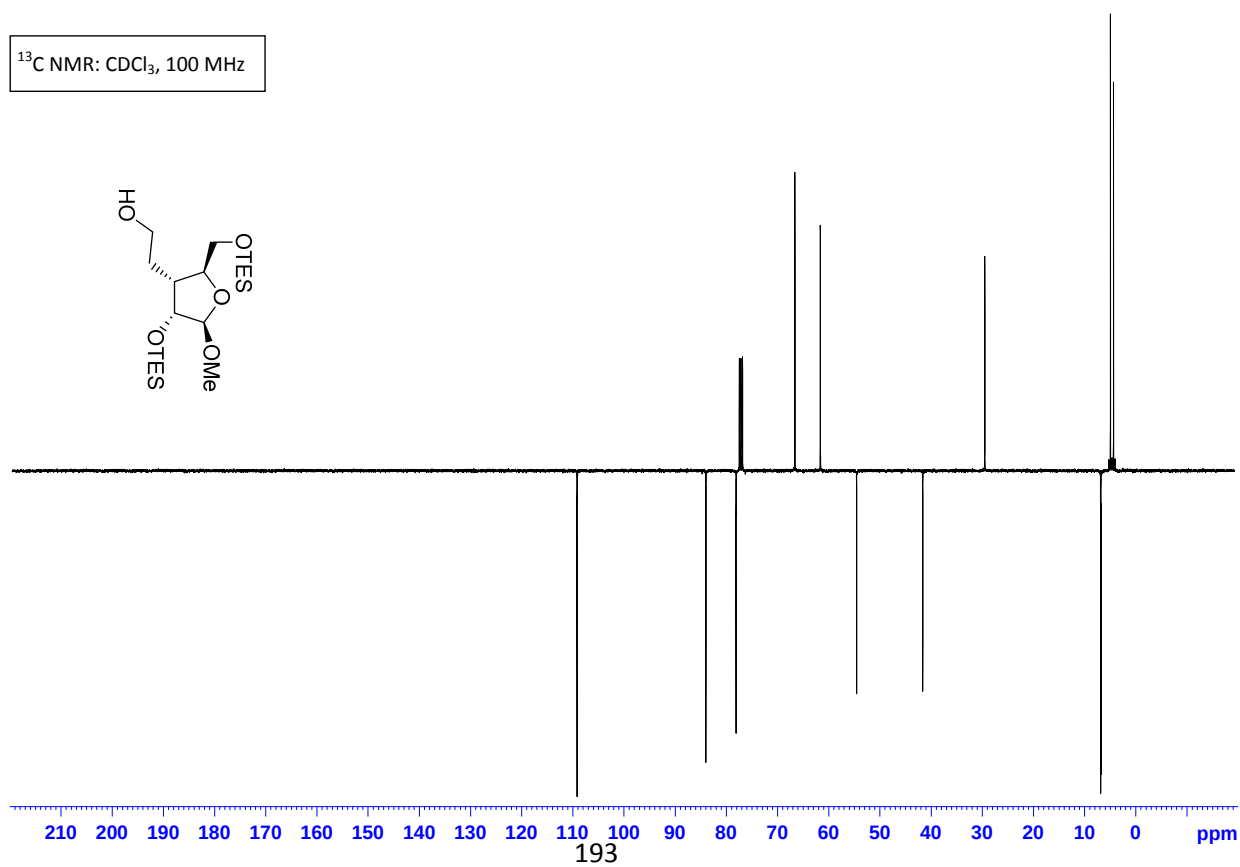




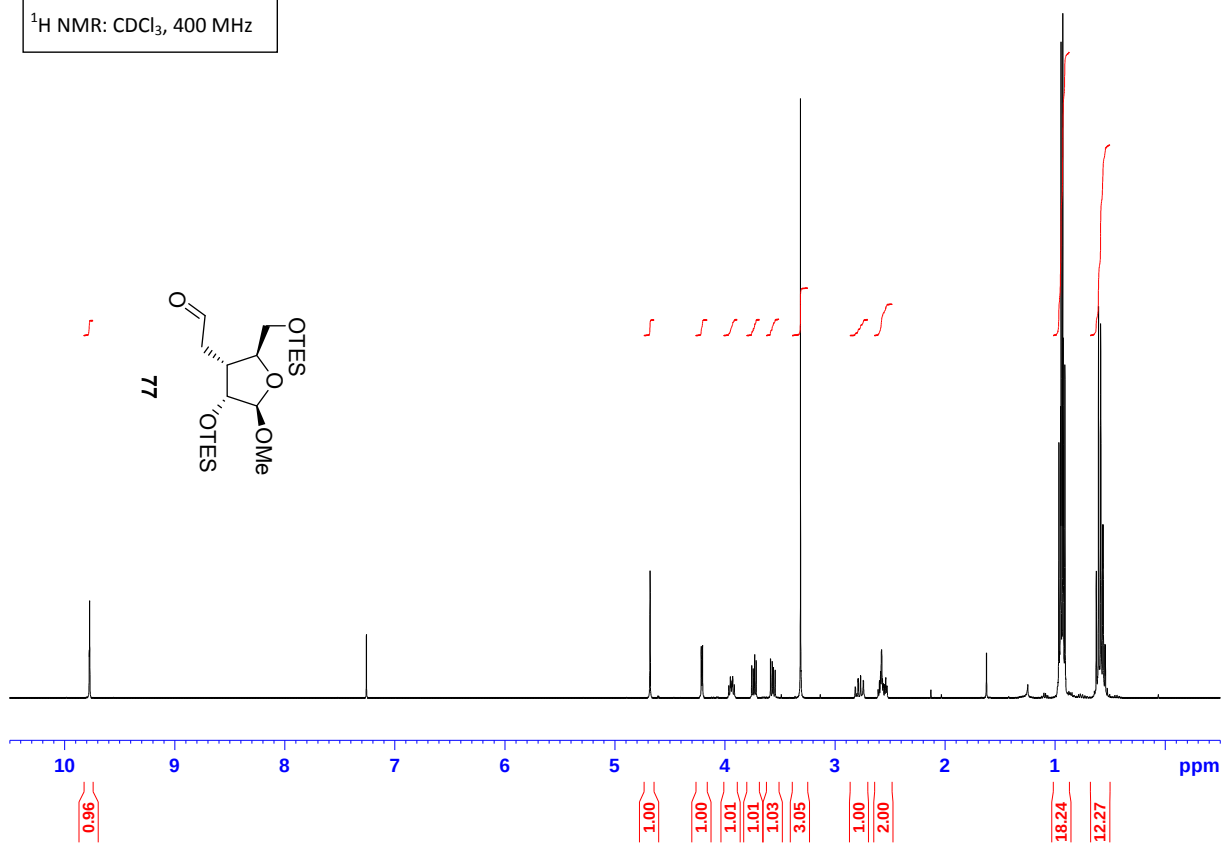
^1H NMR: CDCl_3 , 400 MHz



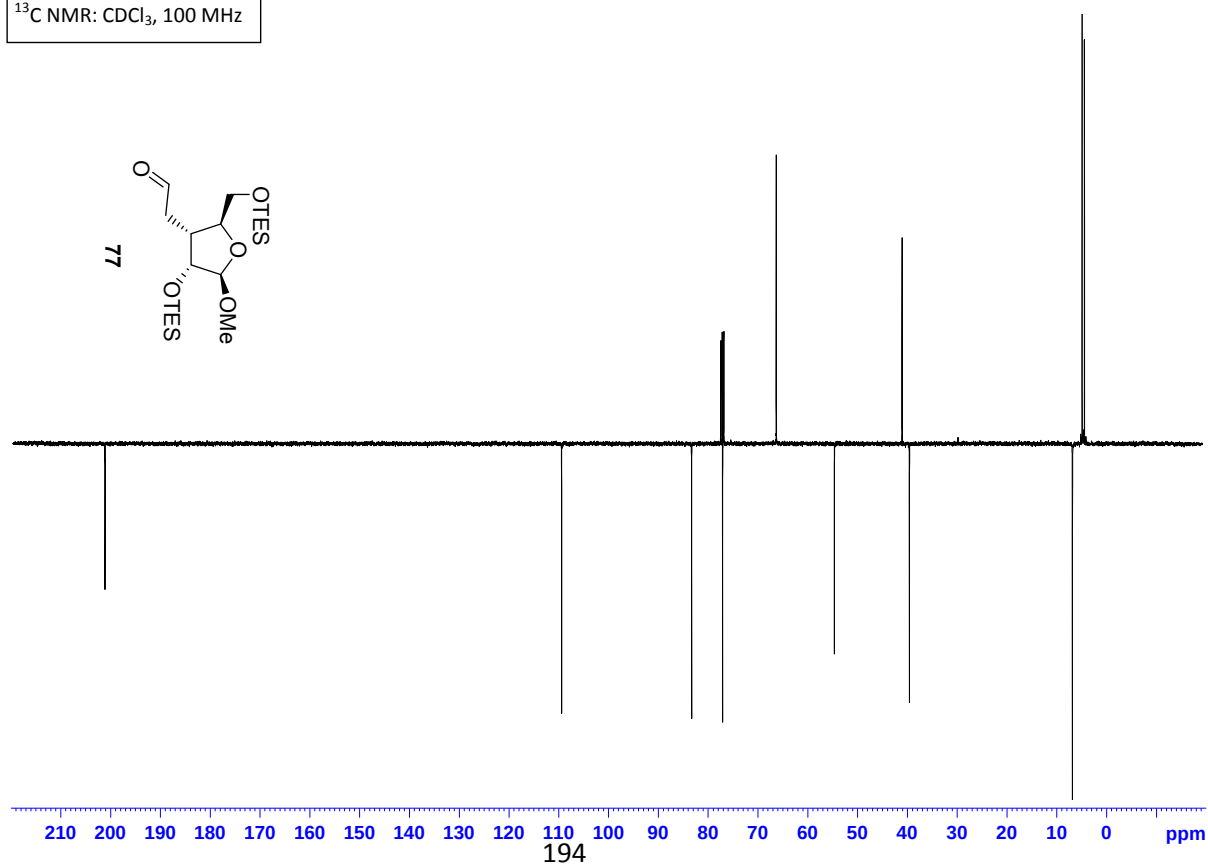
^{13}C NMR: CDCl_3 , 100 MHz

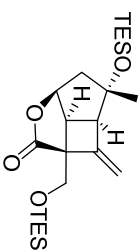
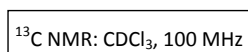


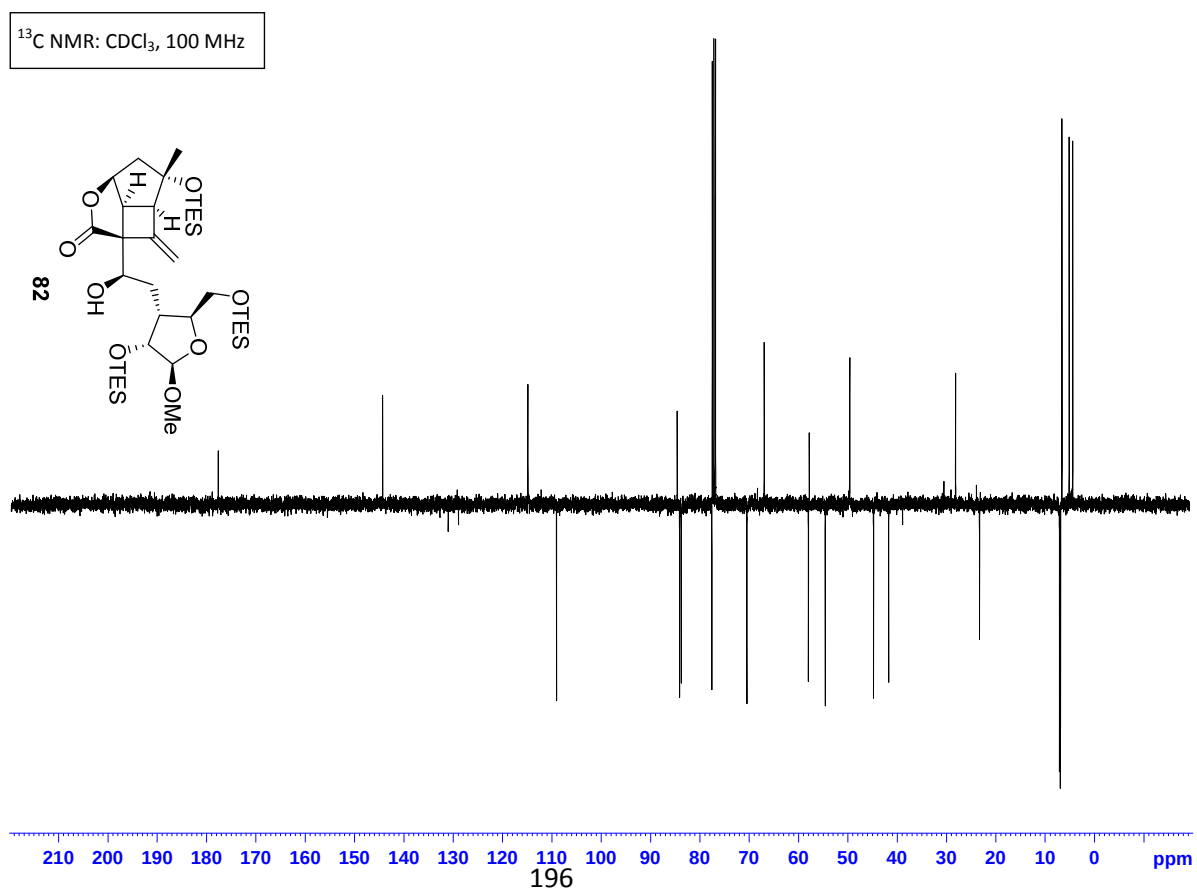
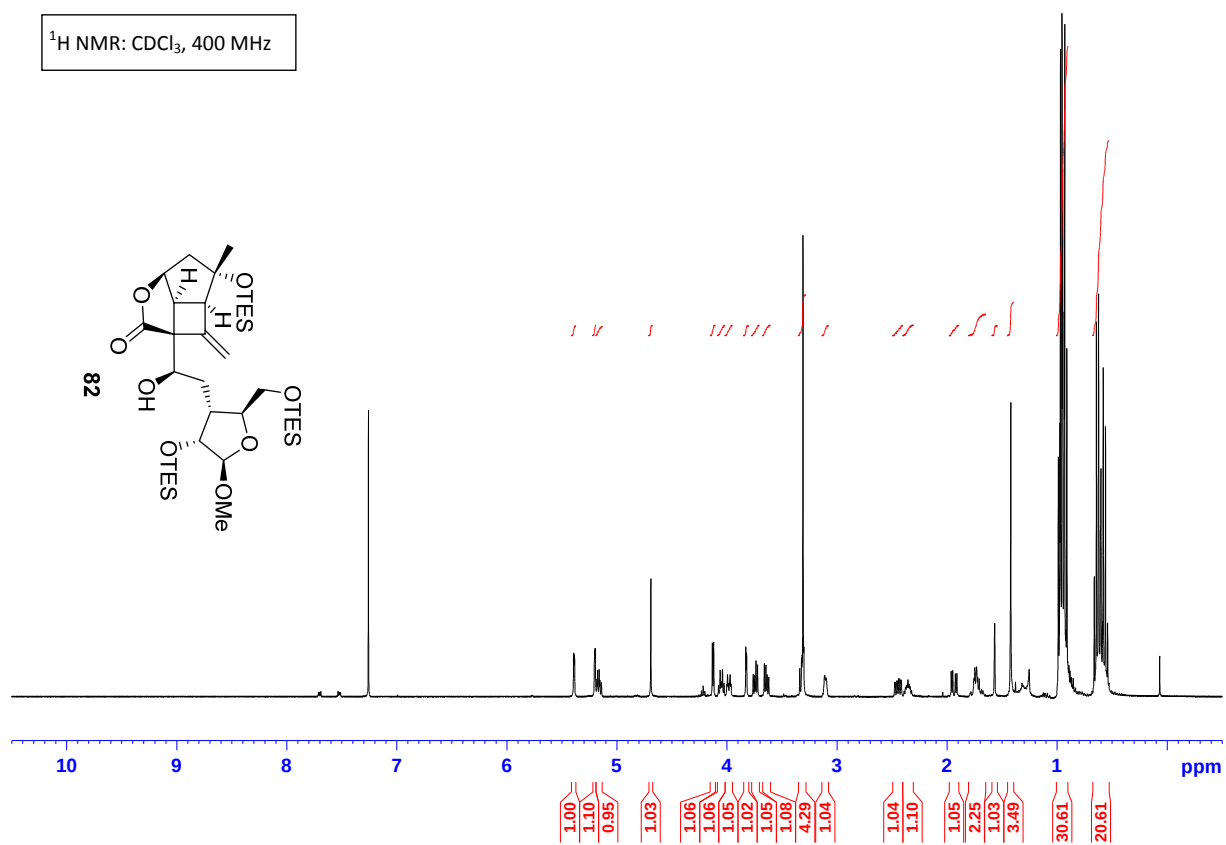
¹H NMR: CDCl₃, 400 MHz

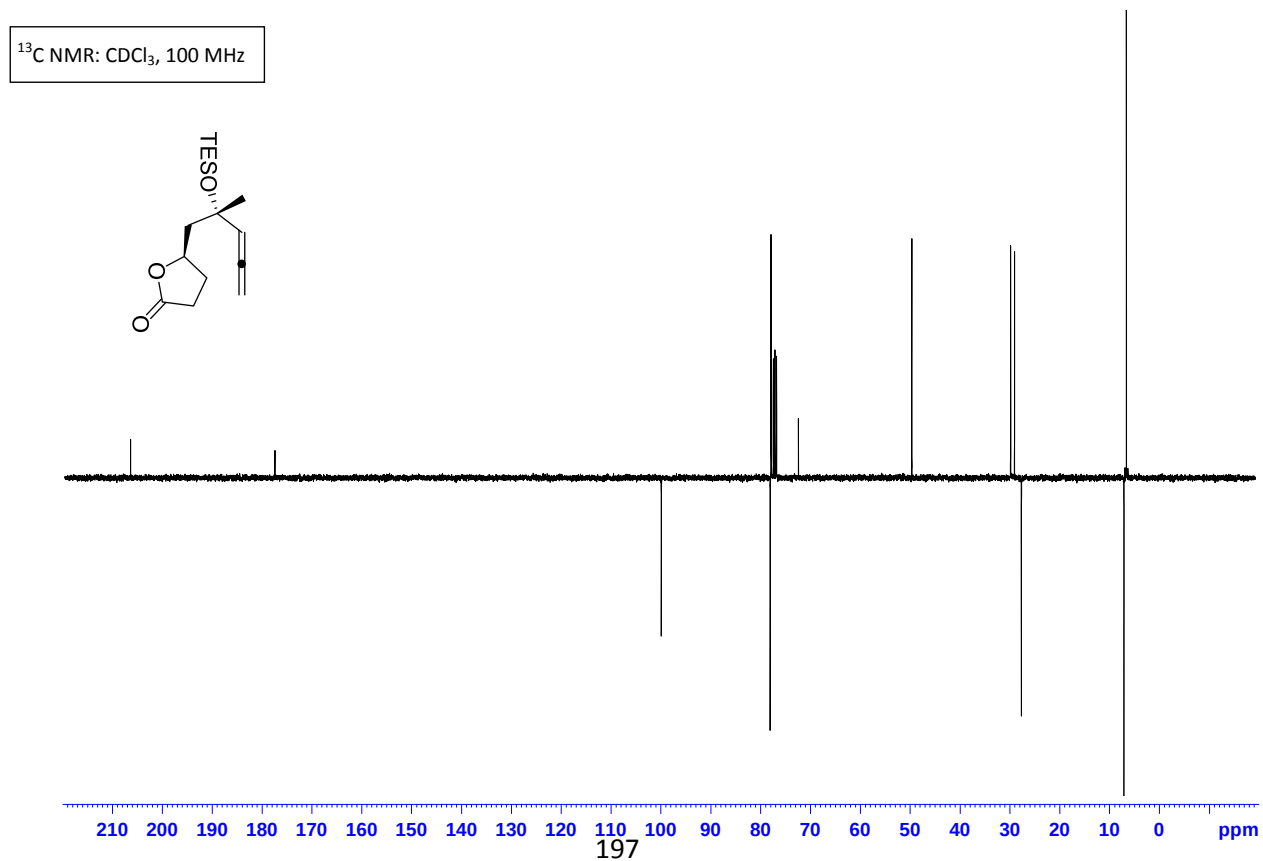
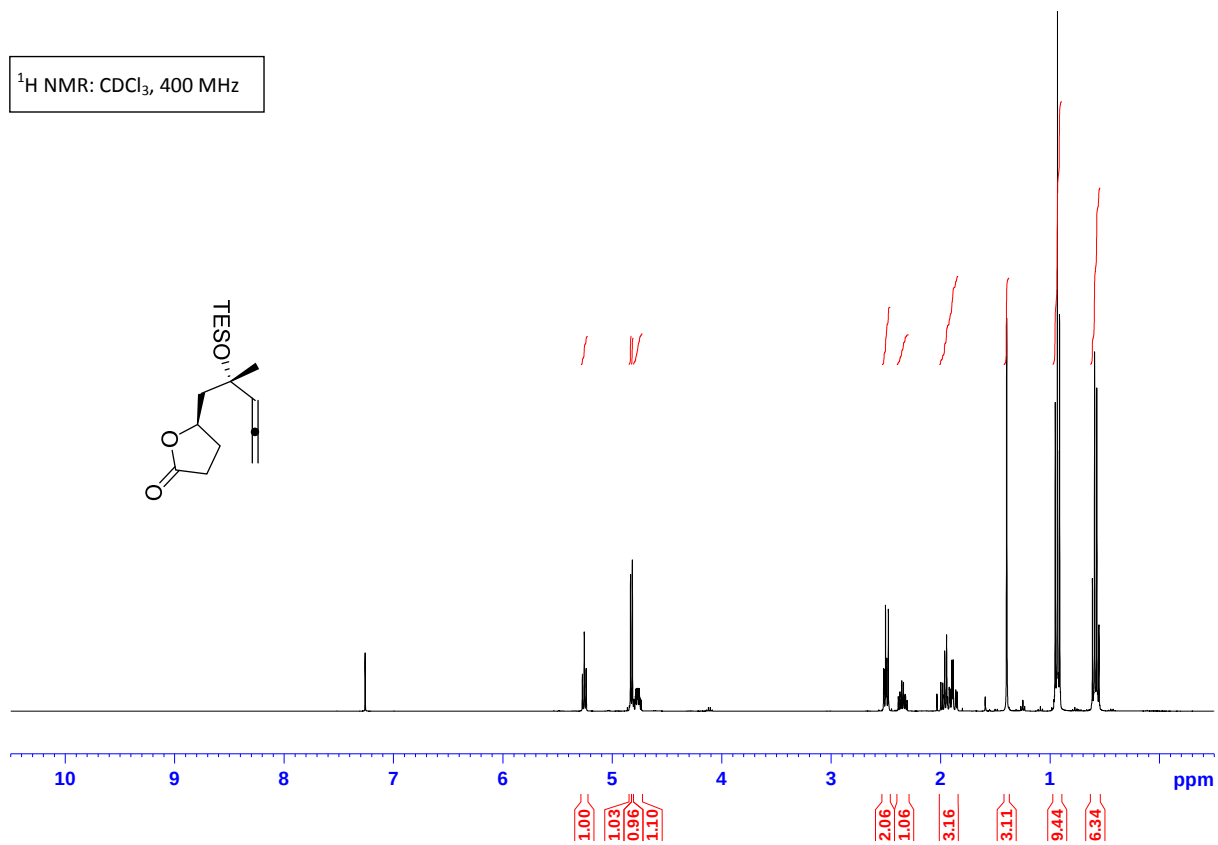


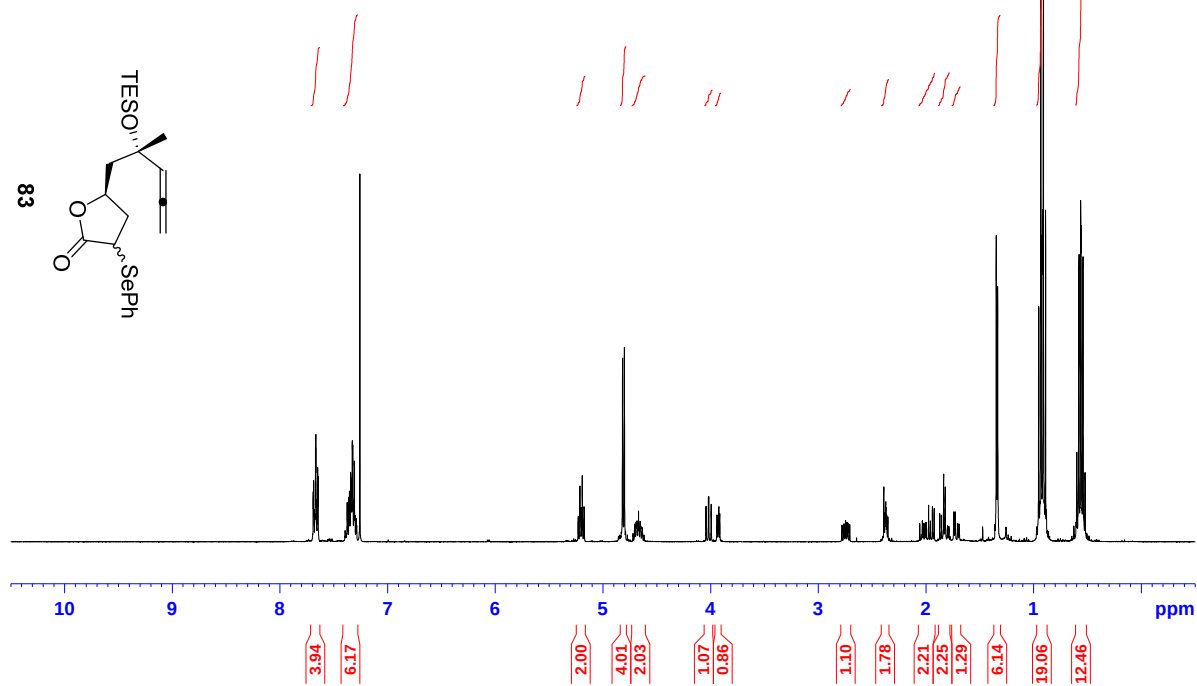
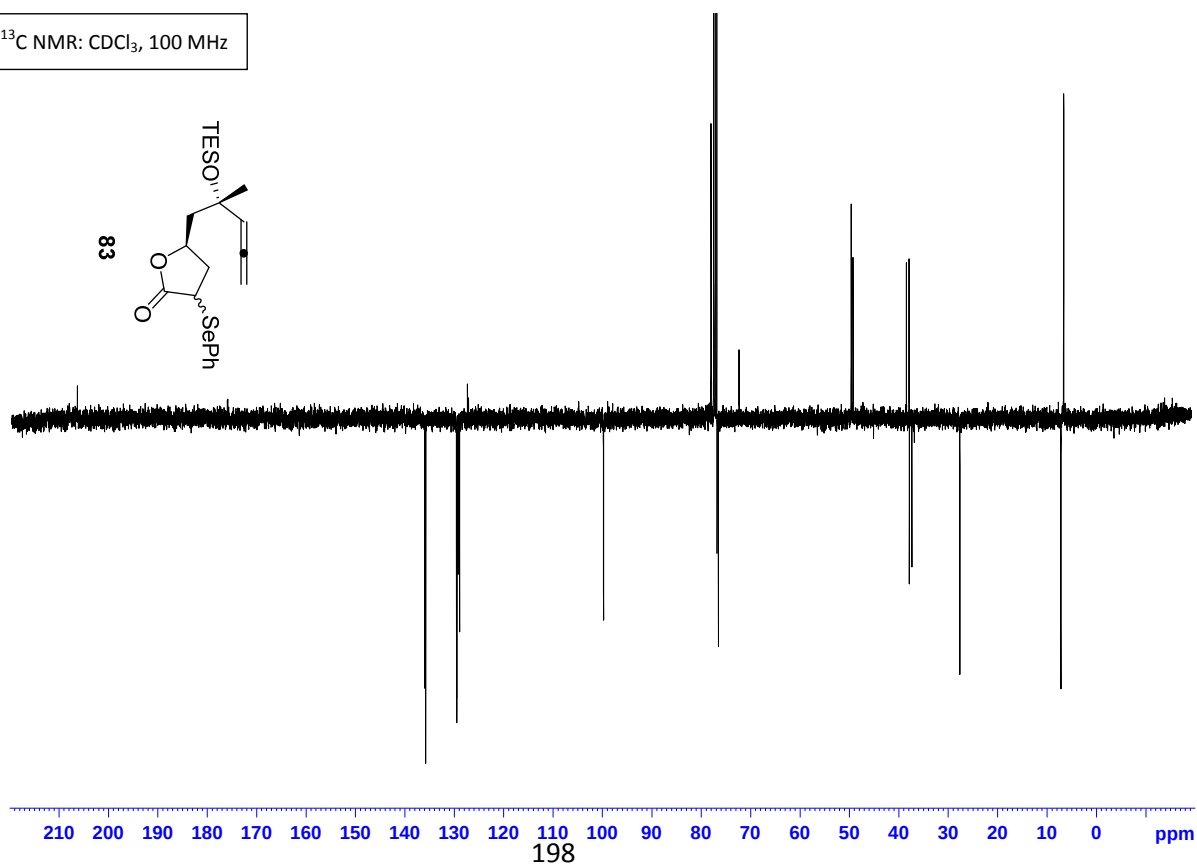
¹³C NMR: CDCl₃, 100 MHz



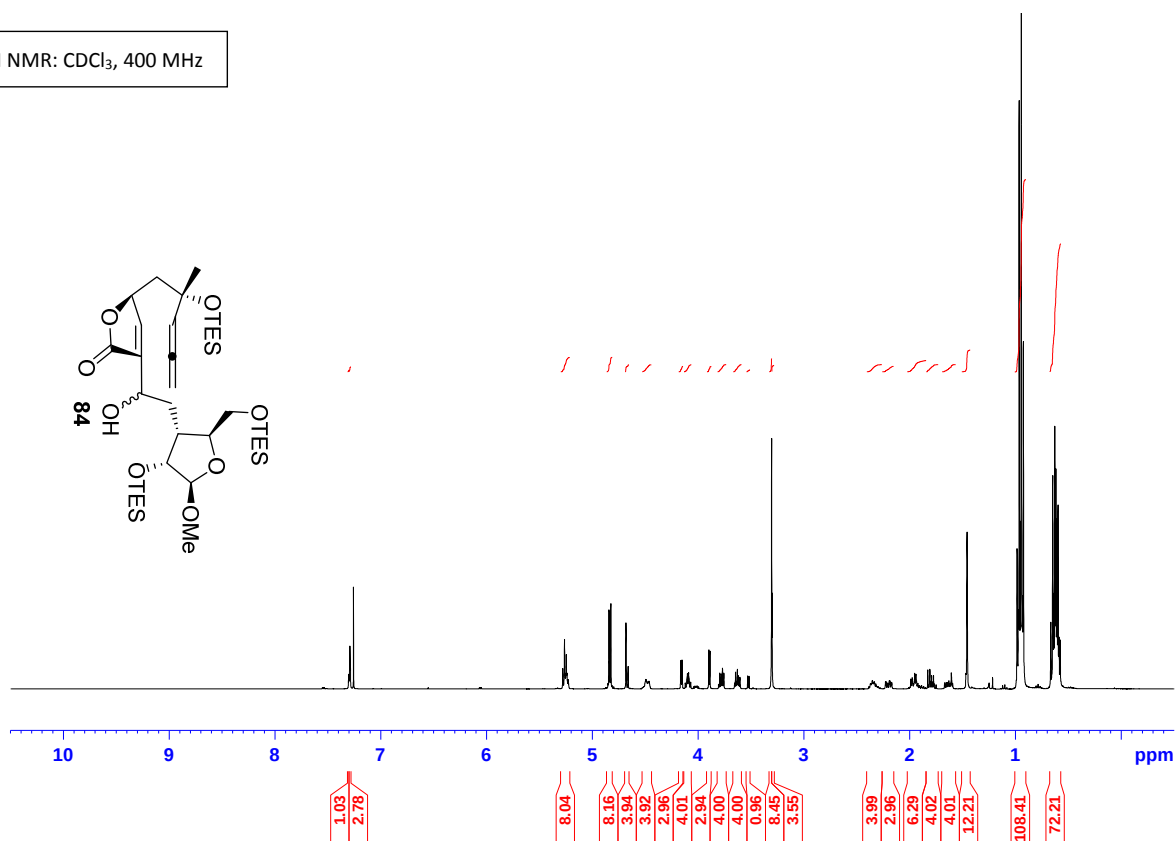




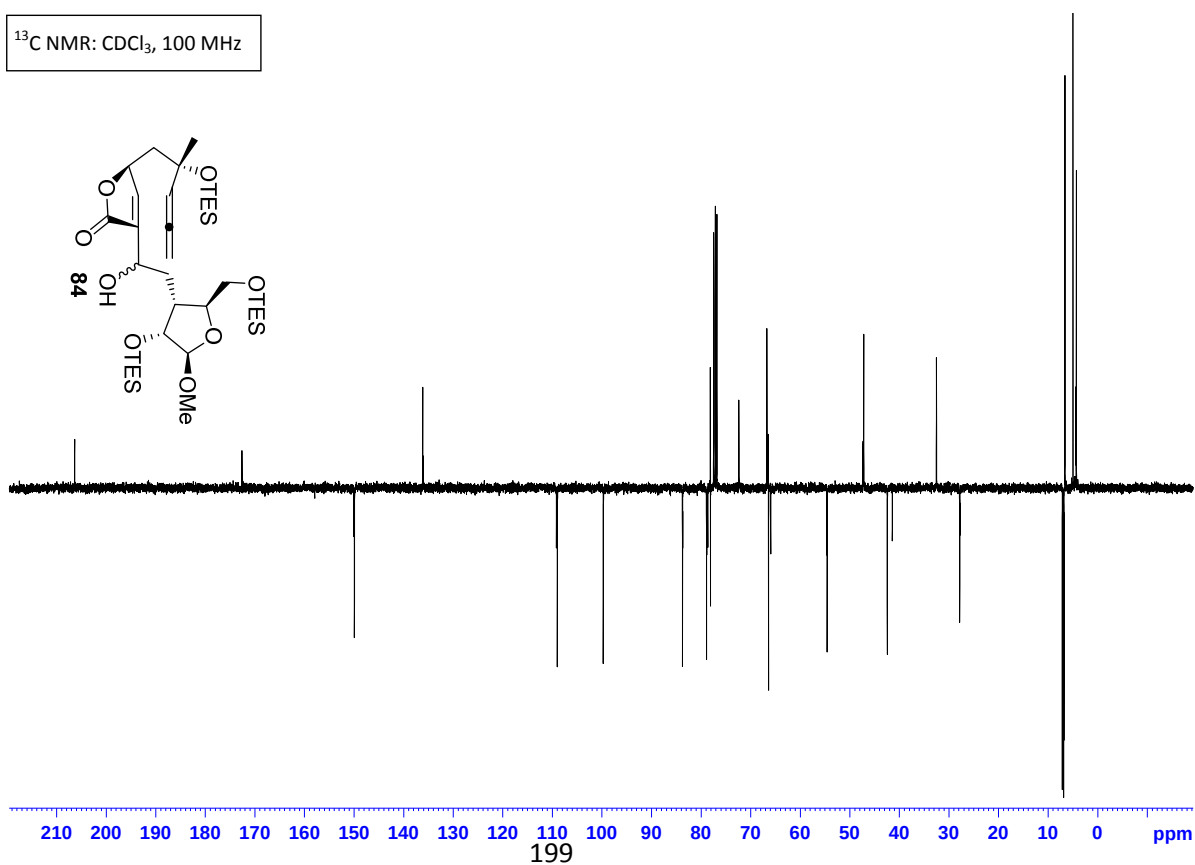


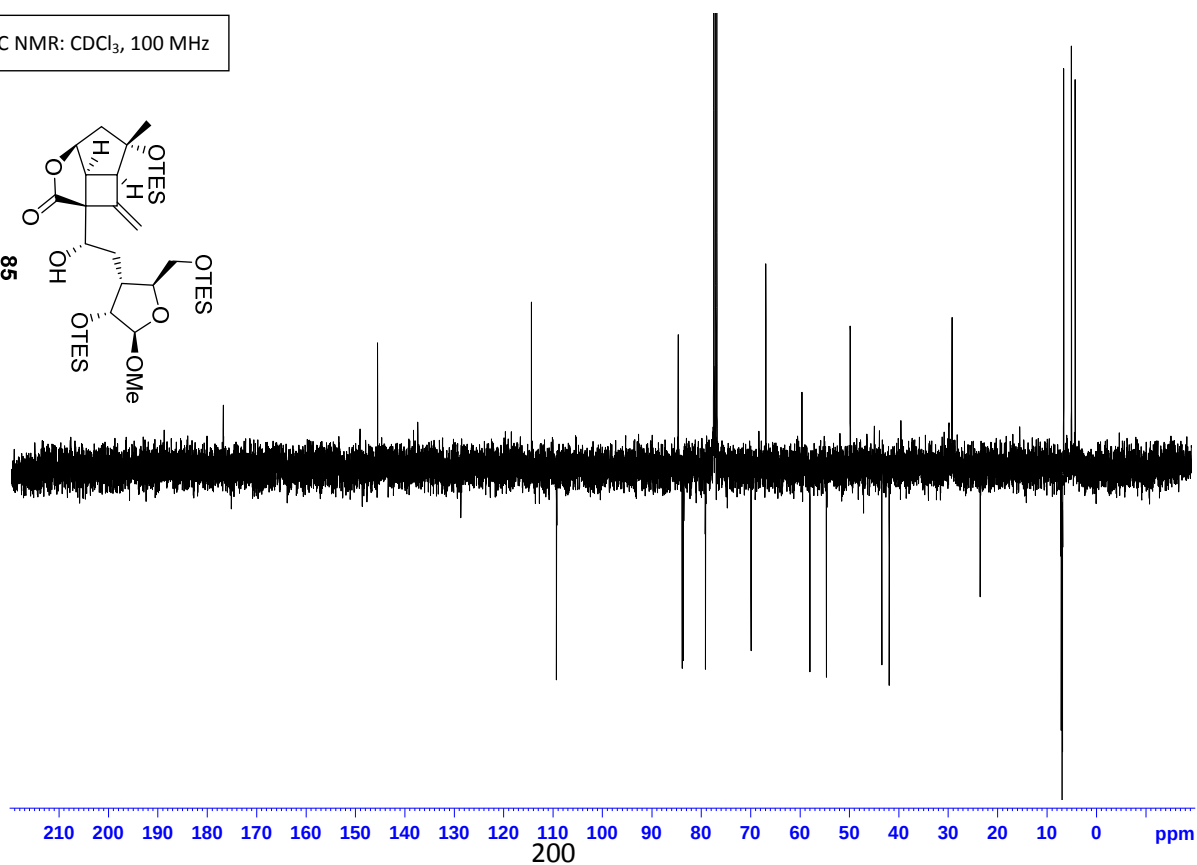
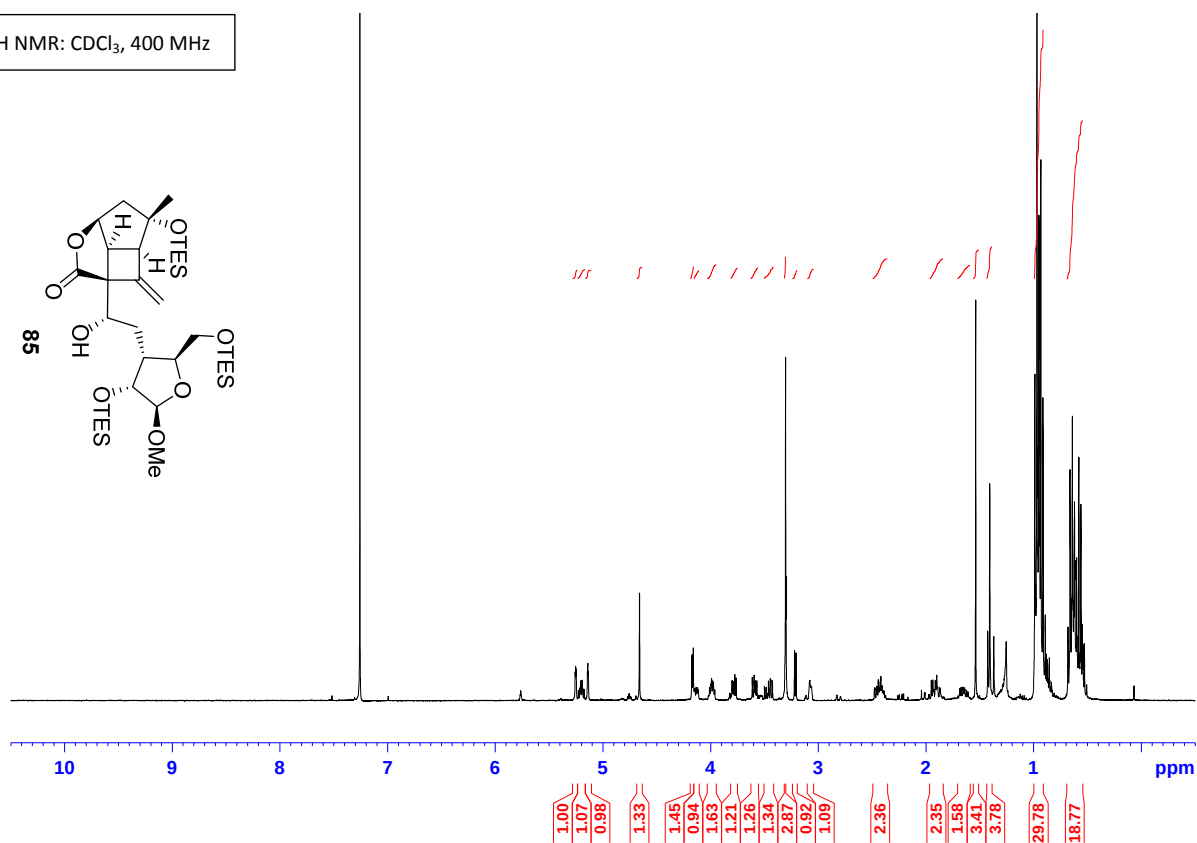
^1H NMR: CDCl_3 , 400 MHz ^{13}C NMR: CDCl_3 , 100 MHz

^1H NMR: CDCl_3 , 400 MHz

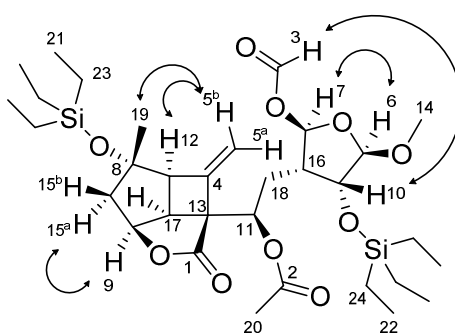


^{13}C NMR: CDCl_3 , 100 MHz





NOE-Correlation



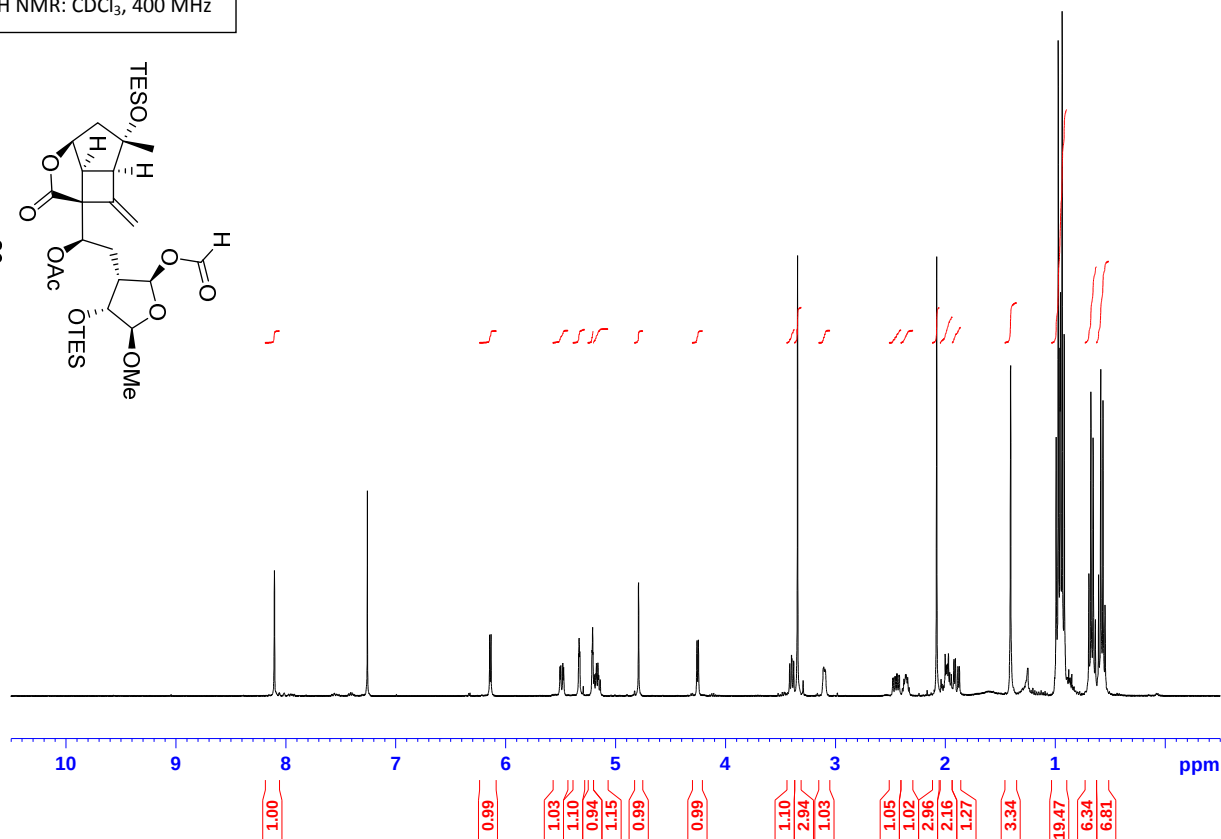
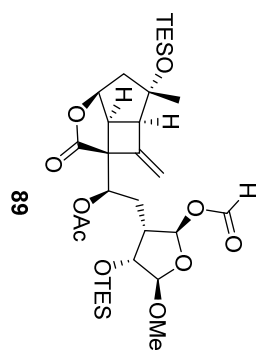
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NOE
5^a ↔ 18

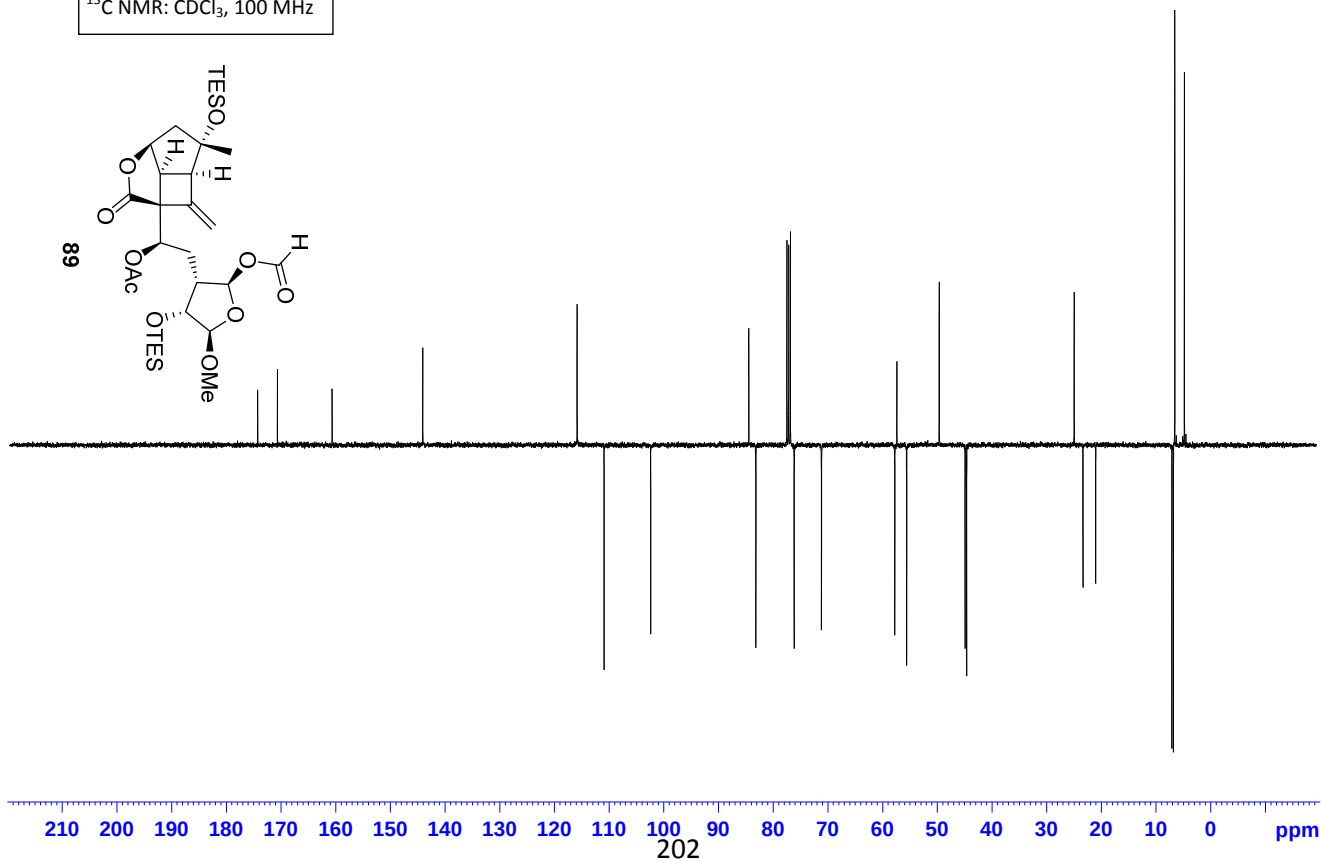
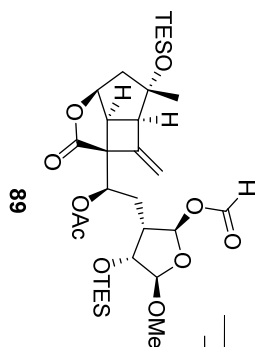
NOE
12 ↔ 17

No.	¹³ C [ppm]	¹ H [ppm]
1	174.3	-
2	170.7	-
3	160.7	8,11
4	144.1	-
5	115.9	5.33 ^a , 5.21 ^b
6	110.9	4,79
7	102.4	6,14
8	84.5	-
9	83.2	5,17
10	76.2	4,26
11	71.2	5,49
12	57.8	3,1
13	57.4	-
14	55.6	3,35
15	49.6	2.45 ^a , 1.90 ^b
16	44.9	2,36
17	44.7	3,4
18	25.0	2.04-1.94
19	23.4	1,41
20	21.1	2,08
21	7.1	0,94
22	6.9	0,98
23	6.6	0,58
24	4.9	0,67

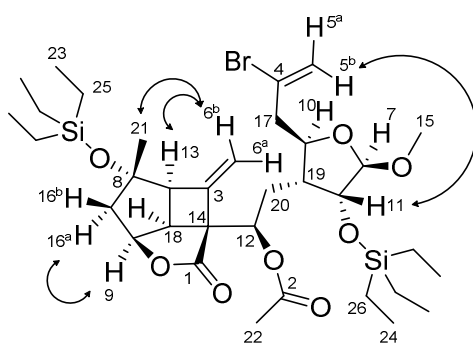
¹H NMR: CDCl₃, 400 MHz



¹³C NMR: CDCl₃, 100 MHz



NOE-Correlation

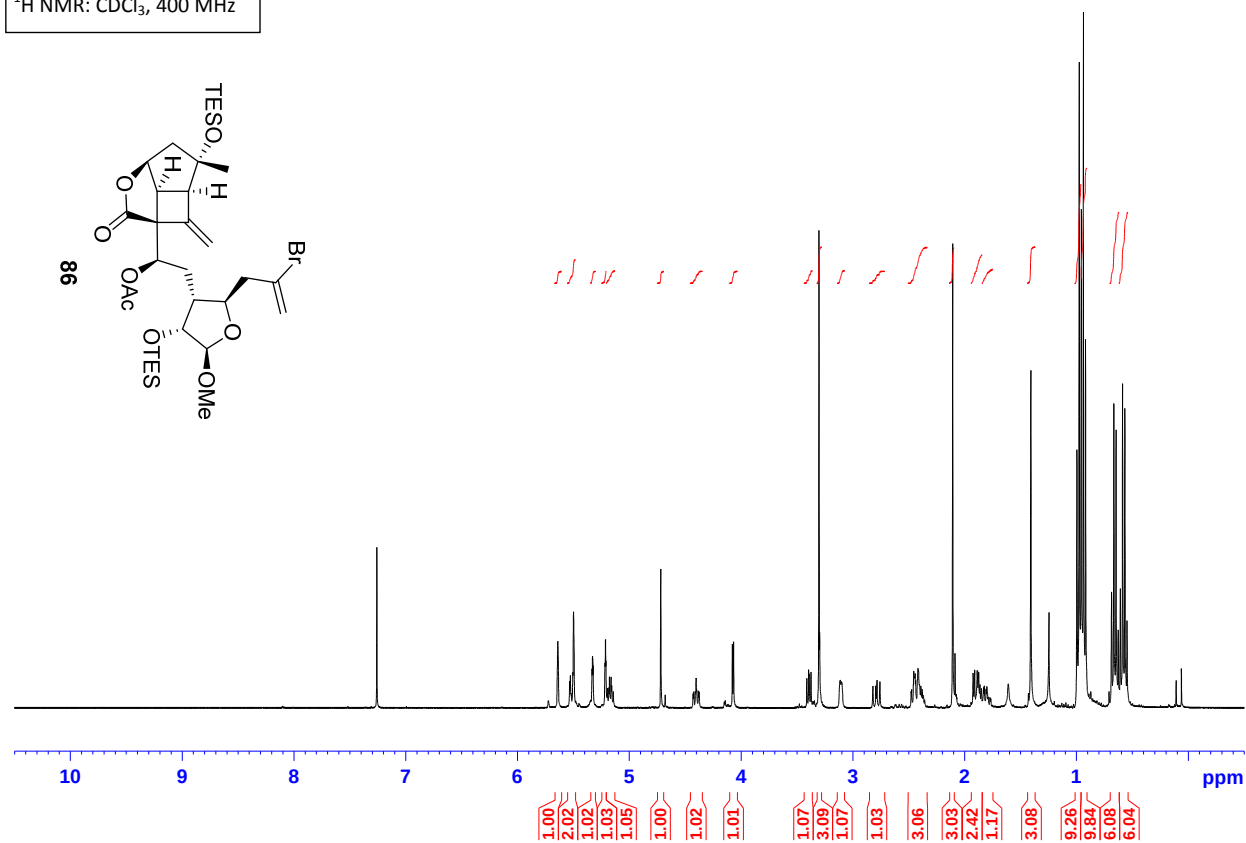


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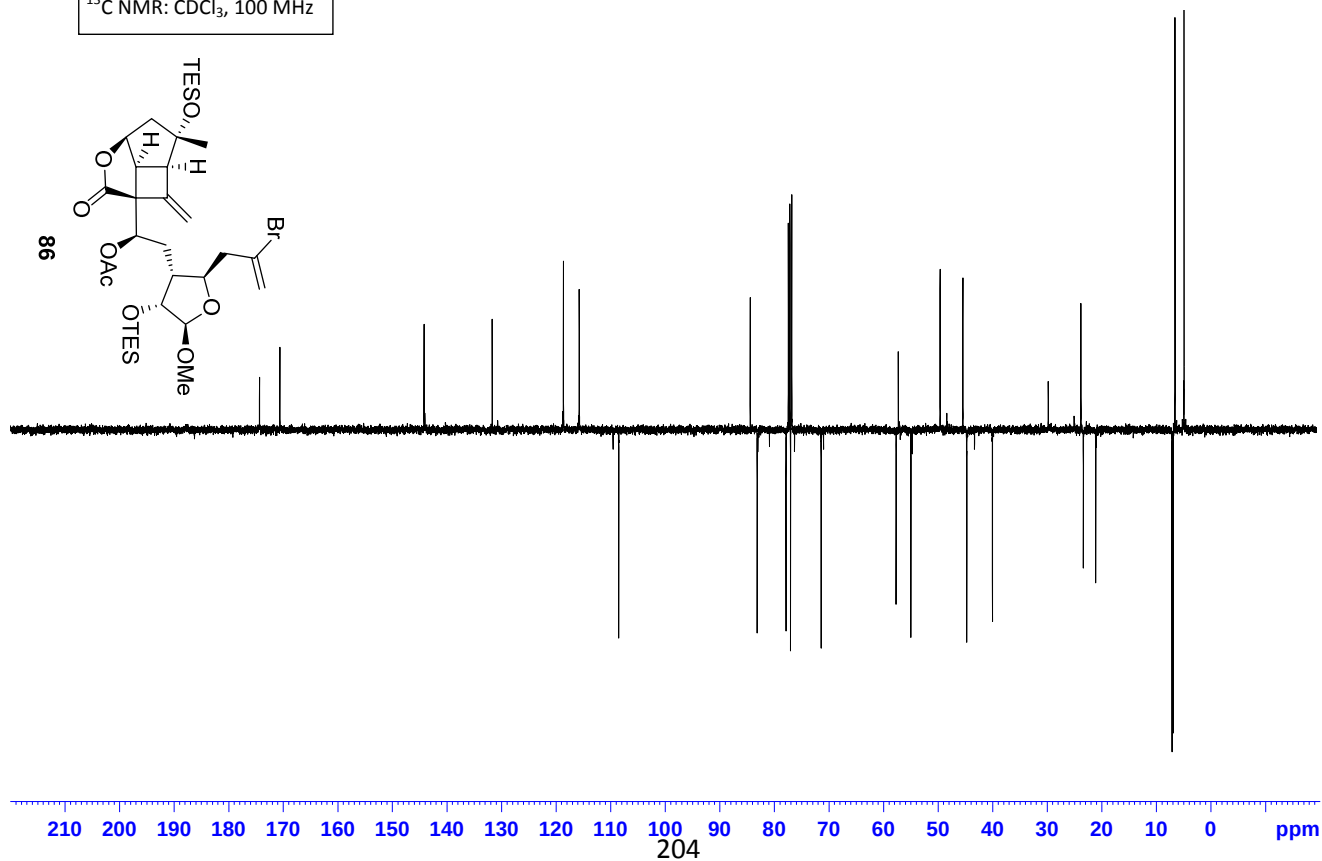
NOE NOE NOE
 $5^b \longleftrightarrow 19$ $19 \longleftrightarrow 11$ $7 \longleftrightarrow 10$

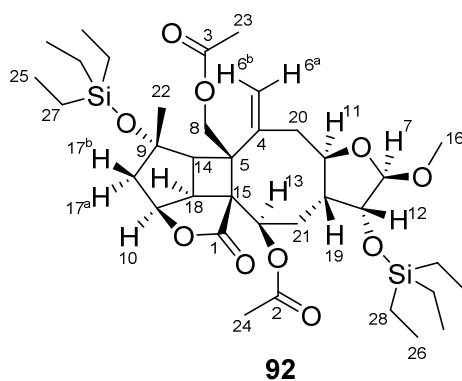
No.	^{13}C [ppm]	^1H [ppm]
1	174.4	-
2	170.7	-
3	144.2	-
4	131.8	-
5	118.7	5.64 ^a , 5.50 ^b
6	115.8	5.33, 5.21
7	108.5	4.72
8	84.4	-
9	83.2	5.17
10	77.9	4.40
11	77.1	4.07
12	71.5	5.52
13	57.7	3.11
14	57.3	-
15	55.0	3.31
16	49.6	2.45 ^a , 1.90 ^b
17	45.5	2.79, 2.44
18	44.8	3.39
19	40.0	2.4
20	23.8	1.89, 1.82
21	23.4	1.41
22	21.1	2.11
23	7.1	0.94
24	6.9	0.98
25	6.6	0.58
26	4.9	0.66

^1H NMR: CDCl_3 , 400 MHz



^{13}C NMR: CDCl_3 , 100 MHz





NOE-Correlation

6^b ↔ 14 ↔ 18 ↔ 10 ↔ 17^a

21 ↔ 20 ↔ 8

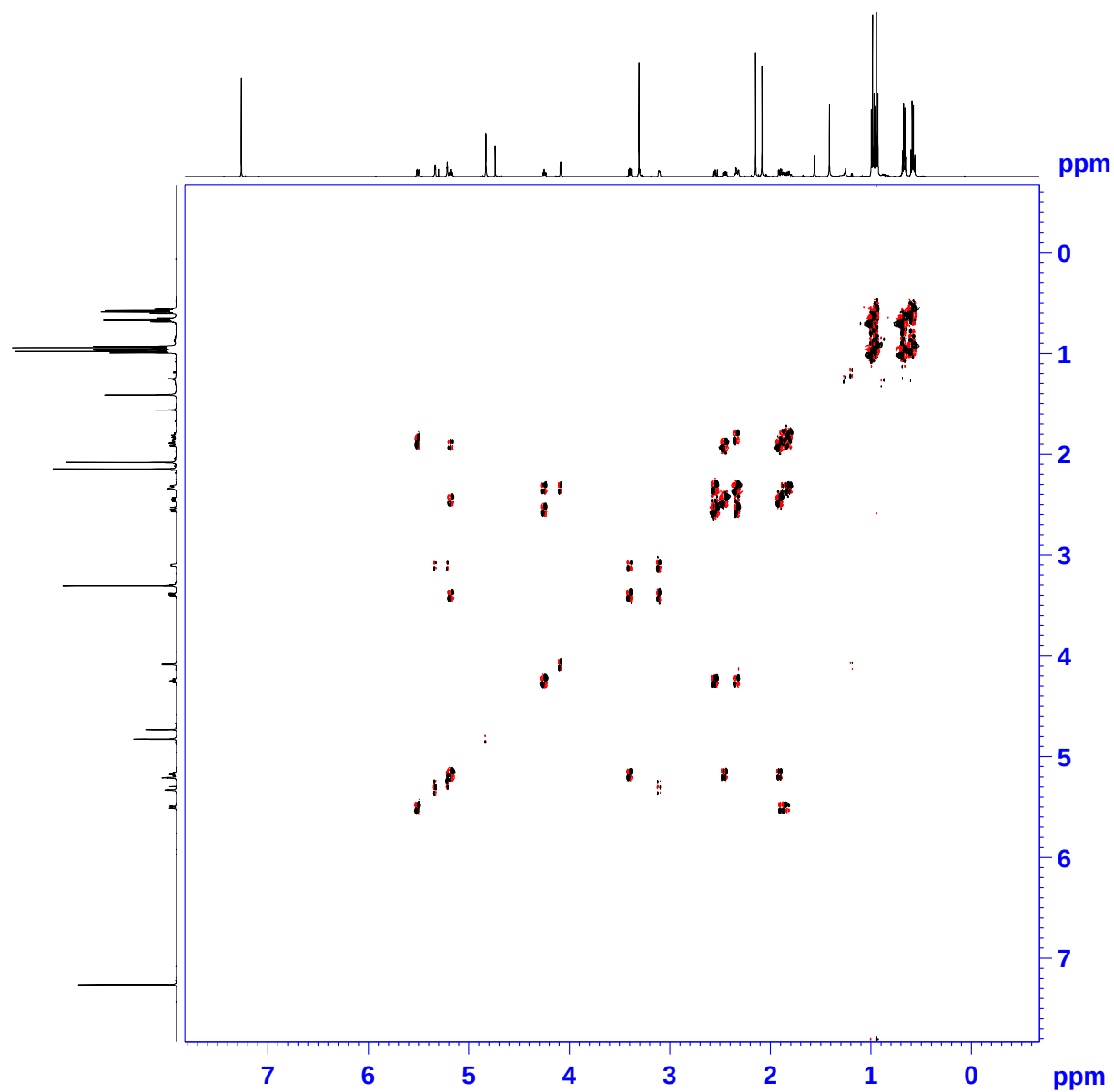
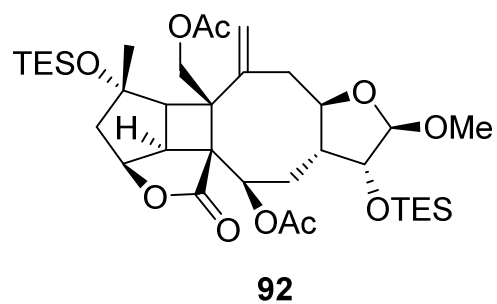
HMBC-Correlation

8 ↔ 4 8 ↔ 20 8 ↔ 3

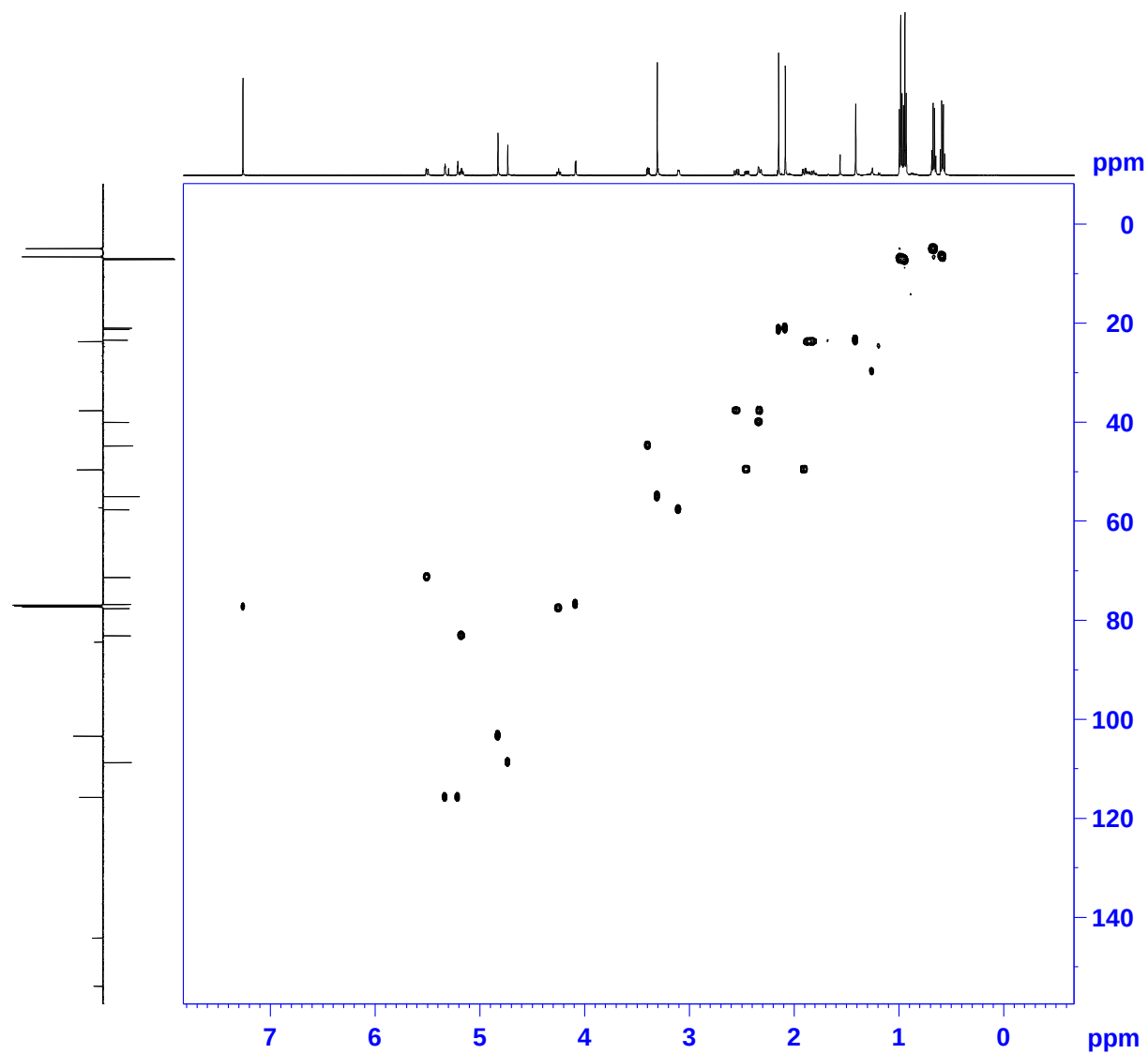
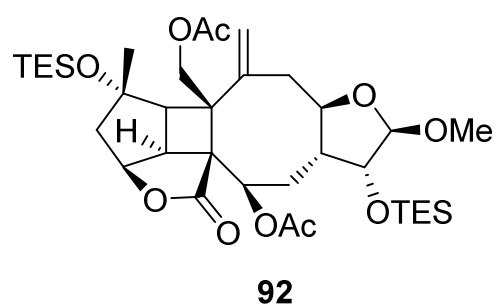
6 ↔ 15 6^a ↔ 5 5 ↔ 13

No.	¹³ C [ppm]	¹ H [ppm]
1	174.4	-
2	170.6	-
3	169.3	-
4	154.0	-
5	144.2	-
6	115.8	5.33 ^a , 5.21 ^b
7	108.8	4.73
8	103.4	4.83
9	84.4	-
10	83.2	5.18
11	77.6	4.25
12	76.8	4.09
13	71.4	5.50
14	57.7	3.10
15	57.3	-
16	55.1	3.31
17	49.6	2.45 ^a , 1.90 ^b
18	44.8	3.40
19	40.1	2.34
20	37.7	2.55 ^a , 2.33 ^b
21	23.7	1.84
22	23.4	1.41
23	21.3	2.15
24	21.0	2.08
25	7.2	0.94
26	6.9	0.98
27	6.6	0.58
28	6.4	0.67

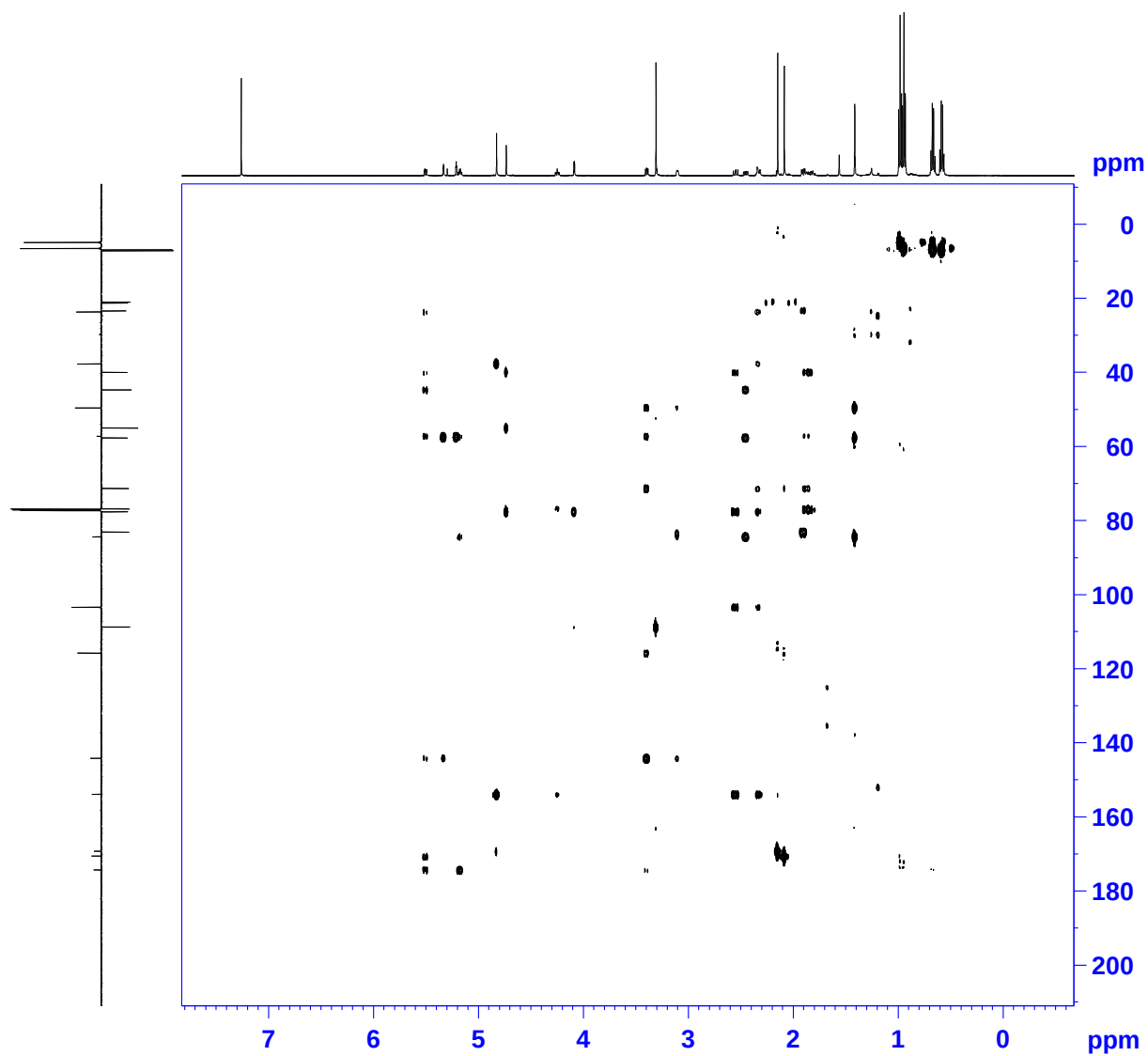
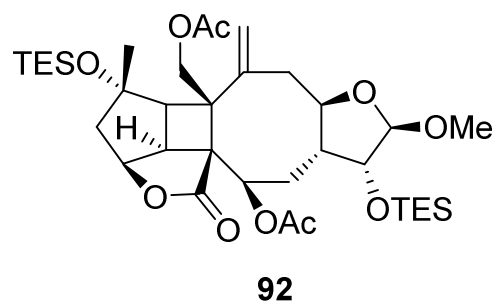
COSY, CDCl₃, 600 MHz



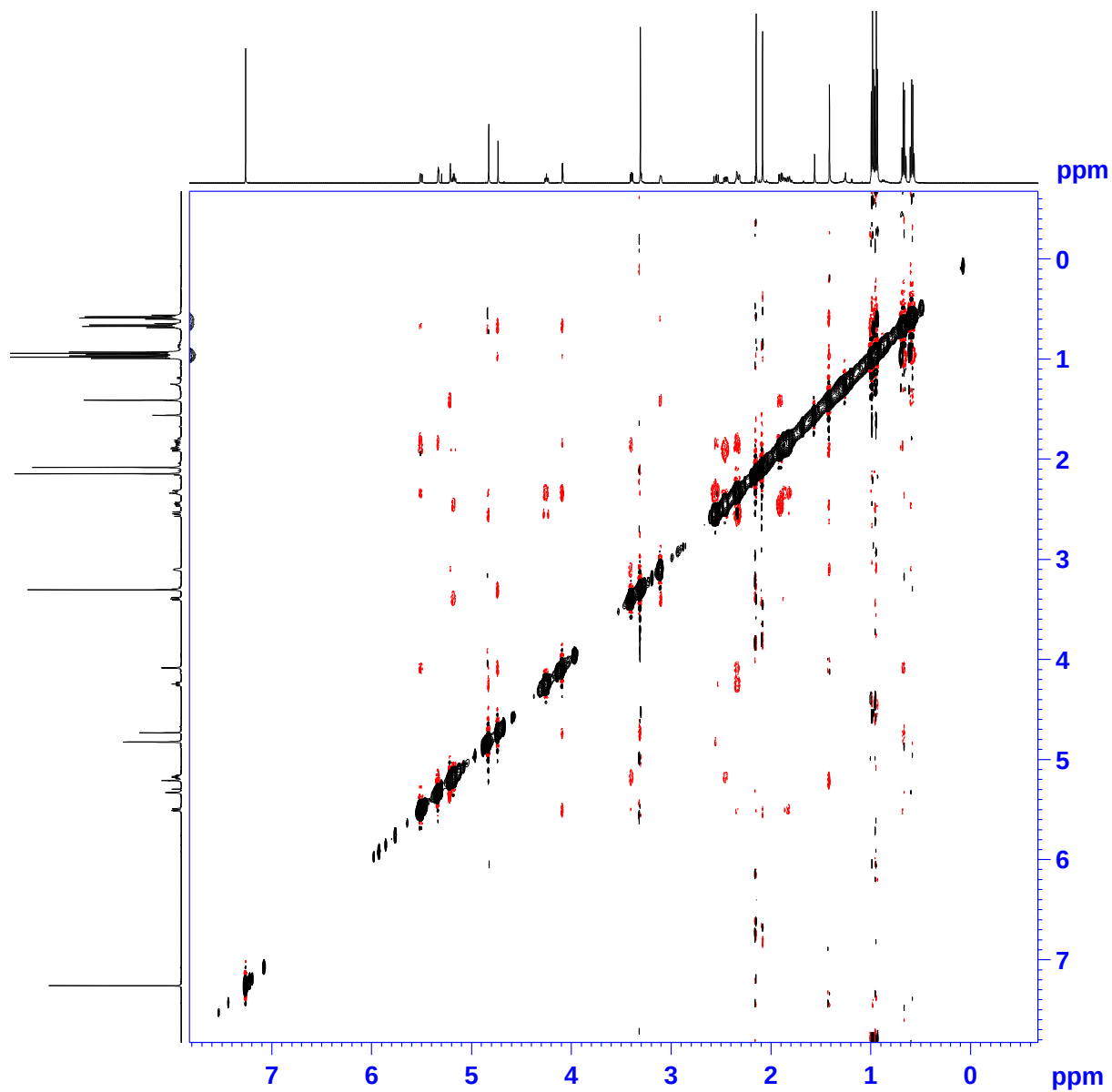
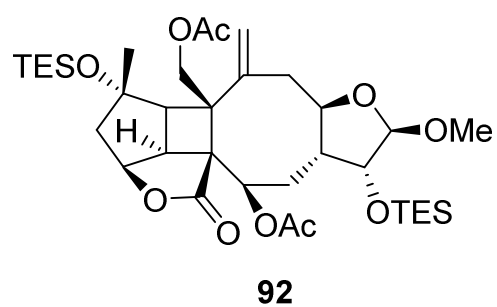
HSQC, CDCl₃, 600 MHz

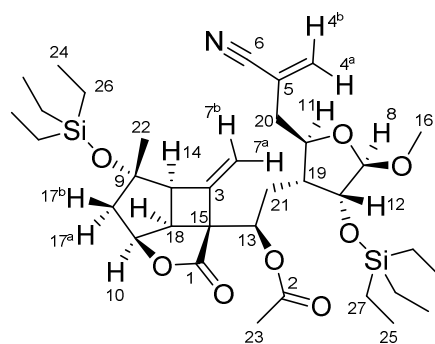


HMBC, CDCl₃, 600 MHz



NOESY, CDCl₃, 600 MHz





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NOE-Correlation

11 $\longleftrightarrow$ 4^b $\longleftrightarrow$ 20^b $\longleftrightarrow$ 12 $\longleftrightarrow$ 13

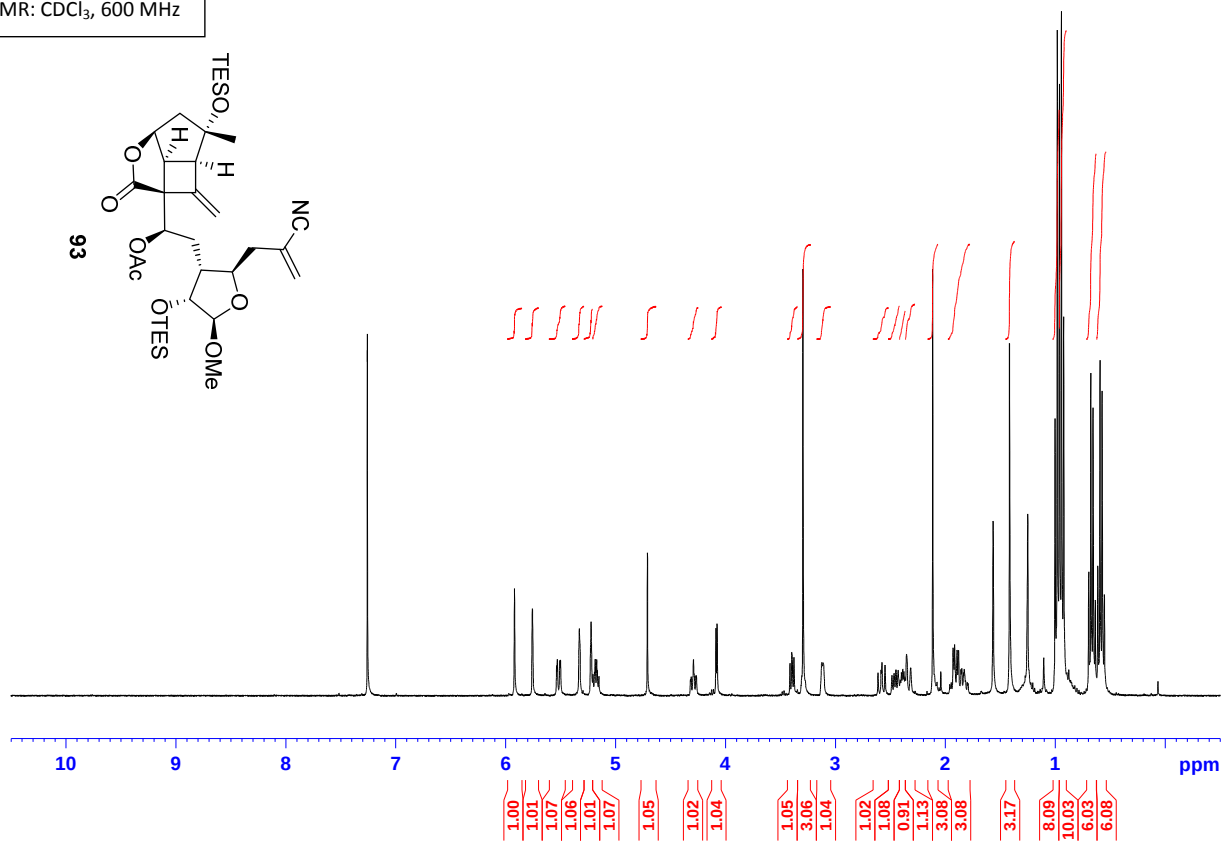
HMBC-Correlation

4^b $\longleftrightarrow$ 20 $\longleftrightarrow$ 4^a $\longleftrightarrow$ 6 $\longleftrightarrow$ 20^a

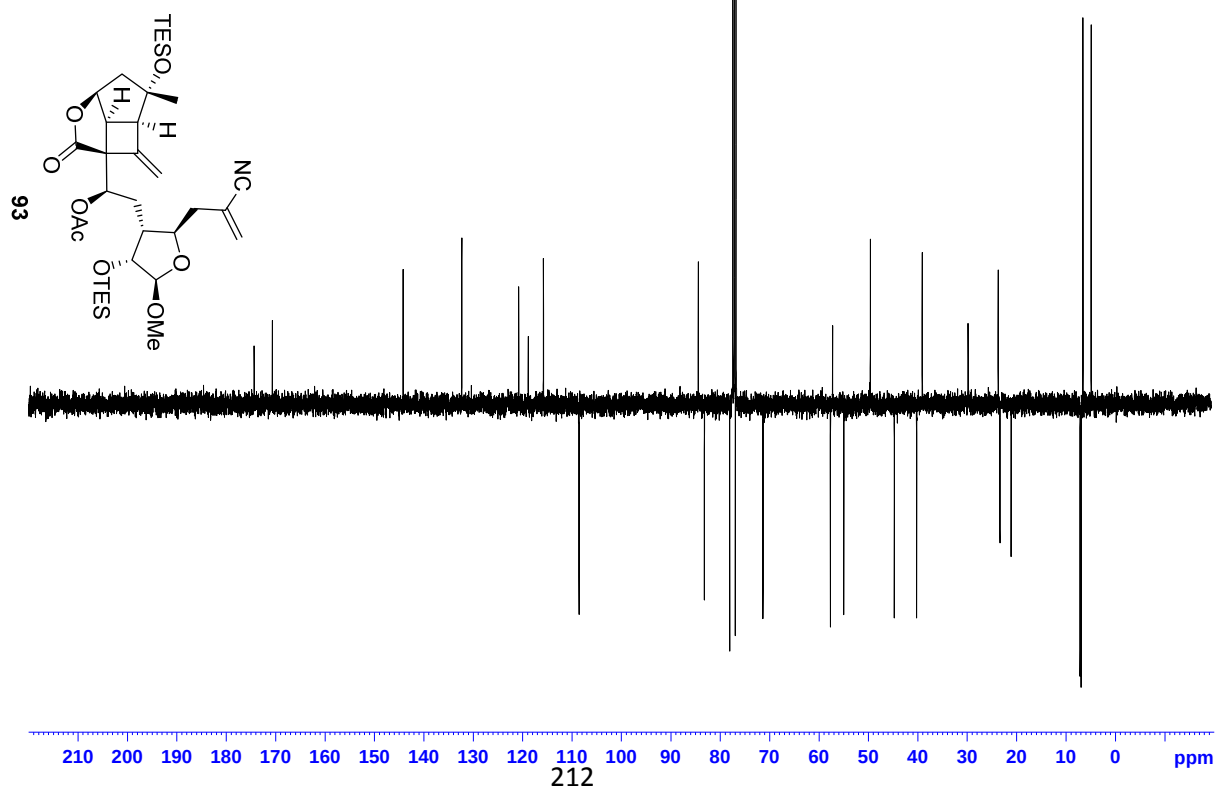
7 $\longleftrightarrow$ 15 $\longleftrightarrow$ 18 $\longleftrightarrow$ 3 $\longleftrightarrow$ 7

No.	¹³ C [ppm]	¹ H [ppm]
1	174.4	-
2	170.7	-
3	144.2	-
4	132.4	5.92 ^a , 5.76 ^b
5	120.8	-
6	118.9	-
7	115.8	5.33 ^a , 5.22 ^b
8	108.6	4.72
9	84.5	-
10	83.2	5.18
11	78.1	4.29
12	77.0	4.08
13	71.4	5.52
14	57.7	3.12
15	57.3	-
16	55.0	3.30
17	49.6	2.46 ^a , 1.91 ^b
18	44.8	3.40
19	40.2	2.39
20	39.1	2.58 ^a , 2.34 ^b
21	23.7	1.87
22	23.4	1.42
23	21.1	2.12
24	7.1	0.58
25	6.9	0.67
26	6.6	0.95
27	4.9	0.98

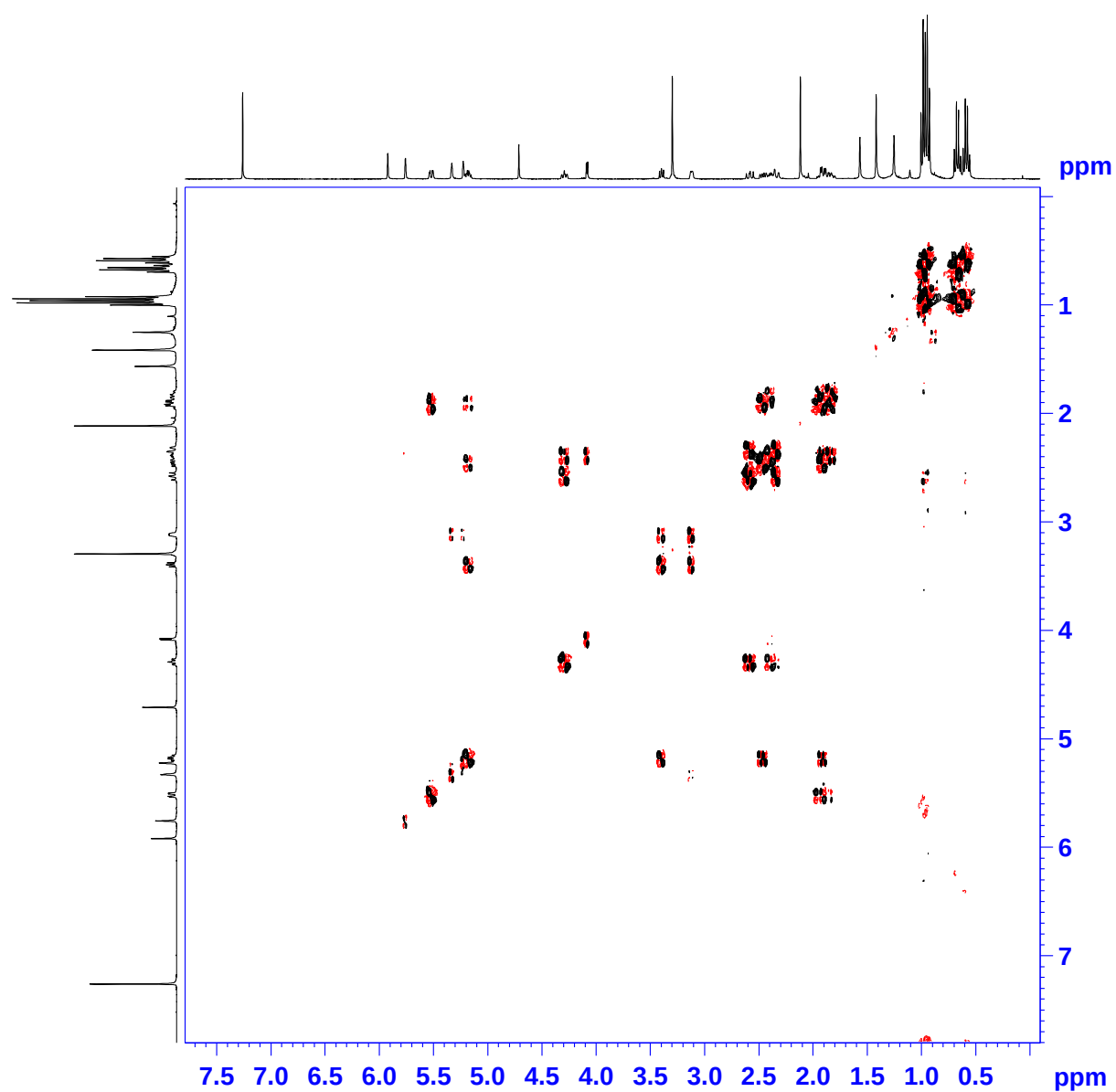
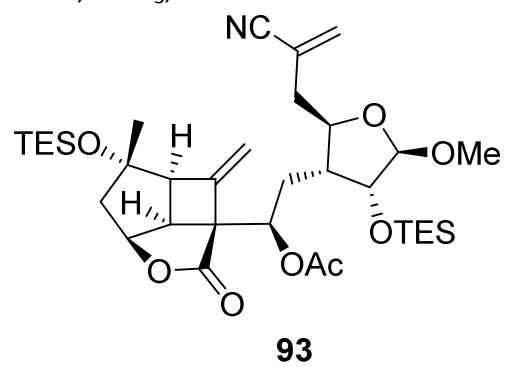
^1H NMR: CDCl_3 , 600 MHz



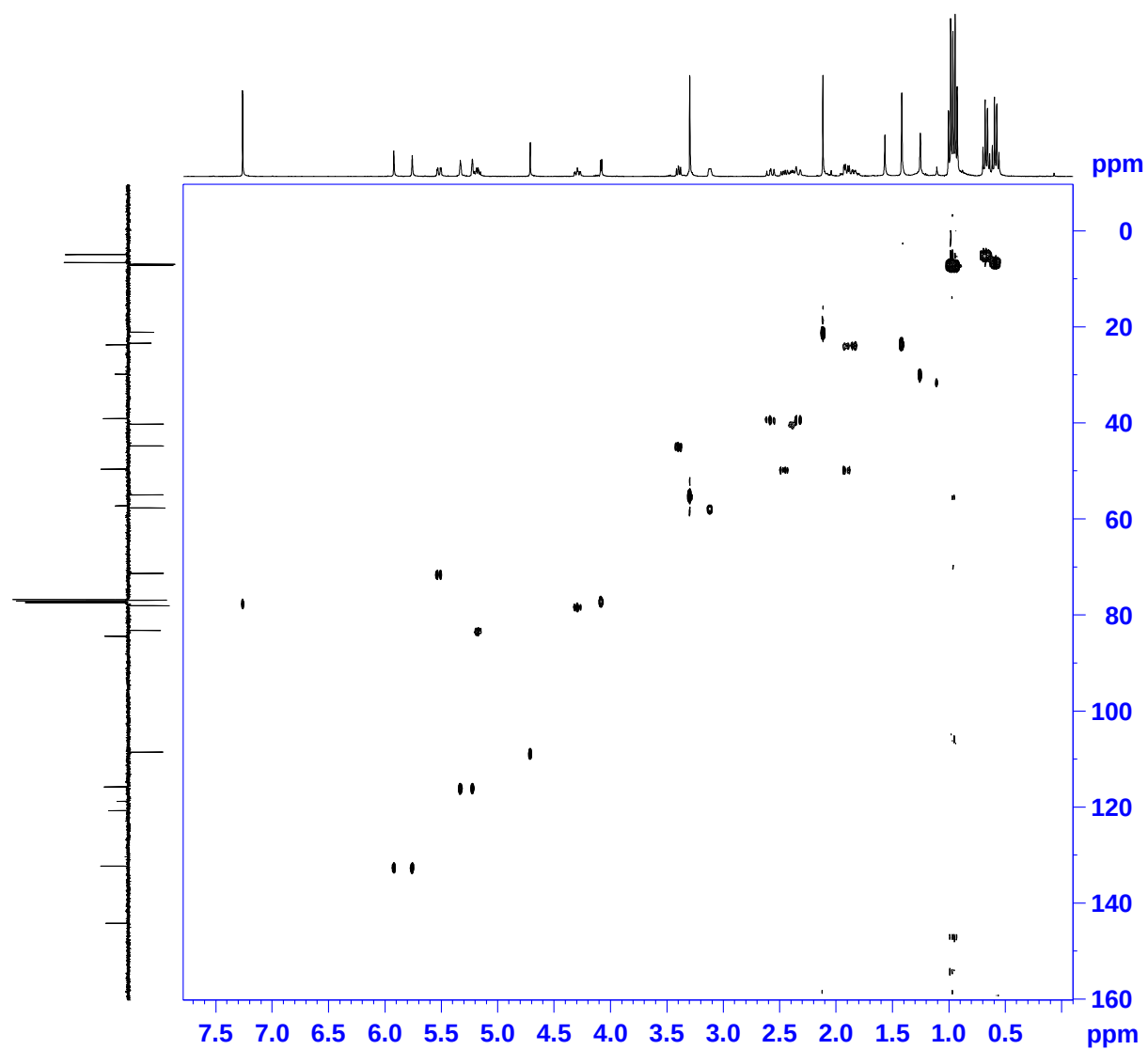
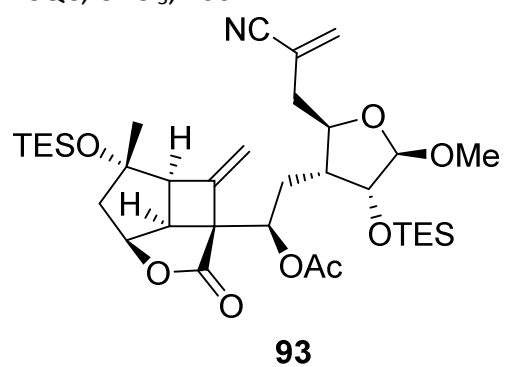
^{13}C NMR: CDCl_3 , 150 MHz



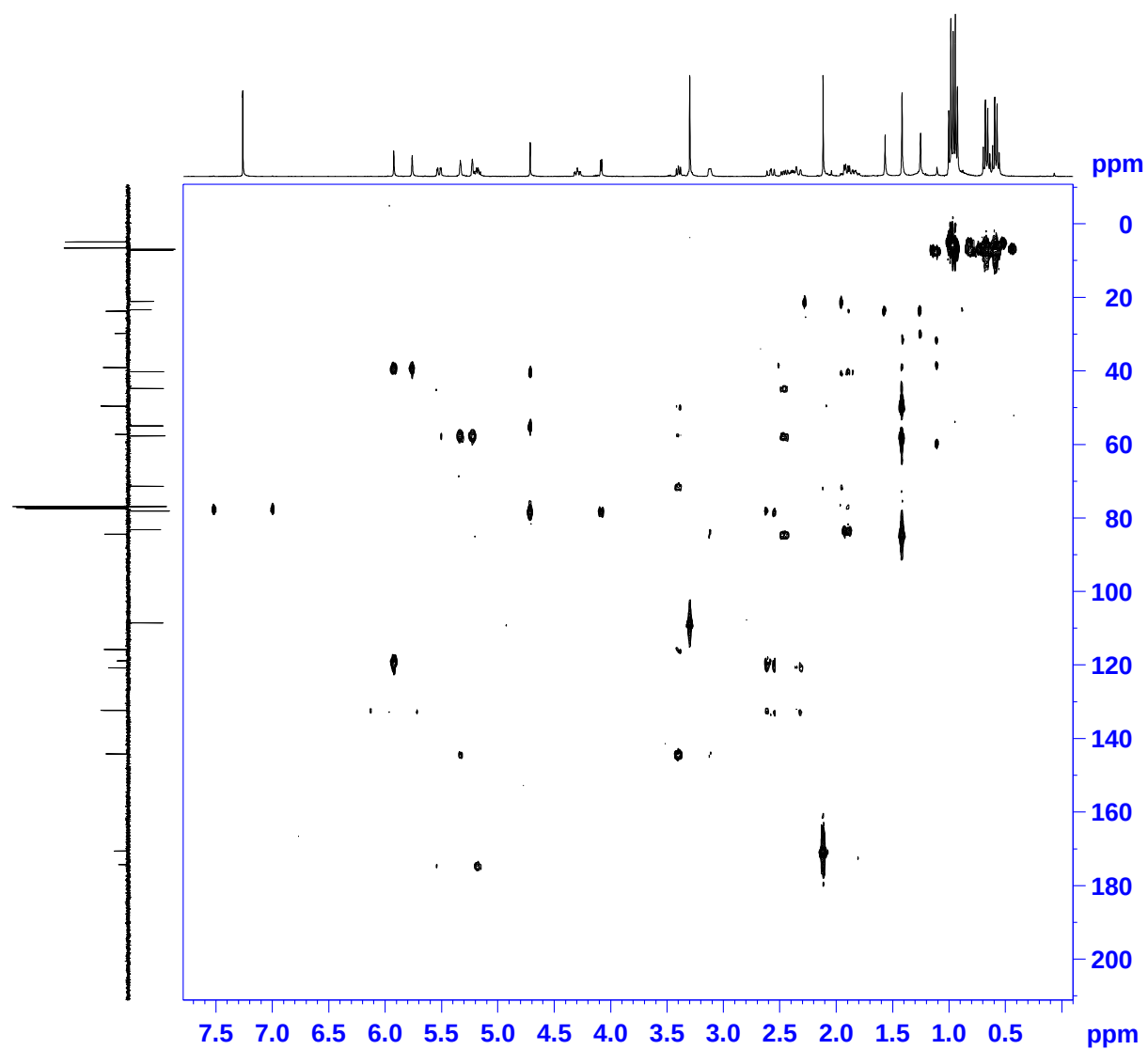
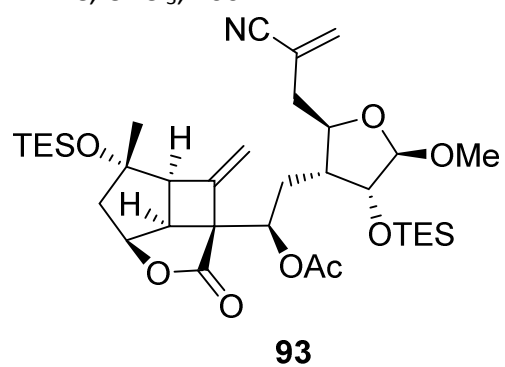
COSY, CDCl₃, 400 MHz



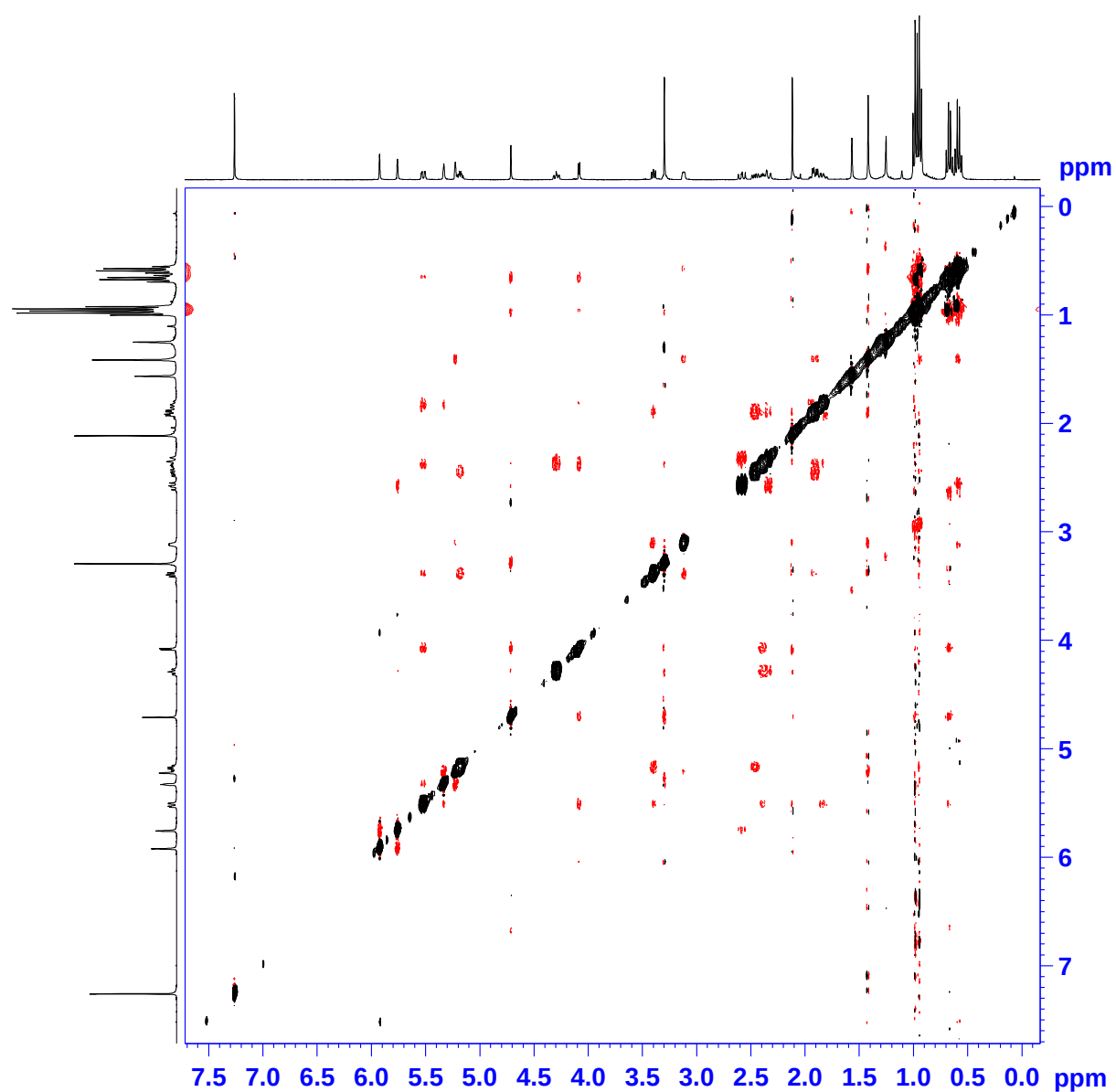
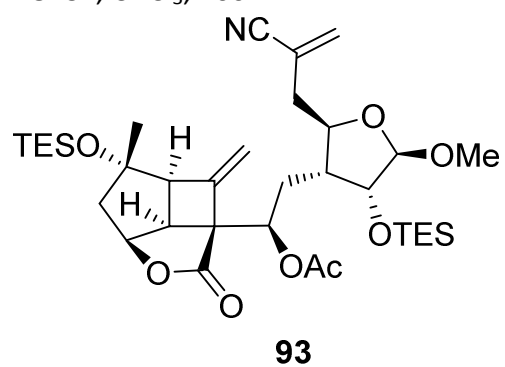
HSQC, CDCl₃, 400 MHz

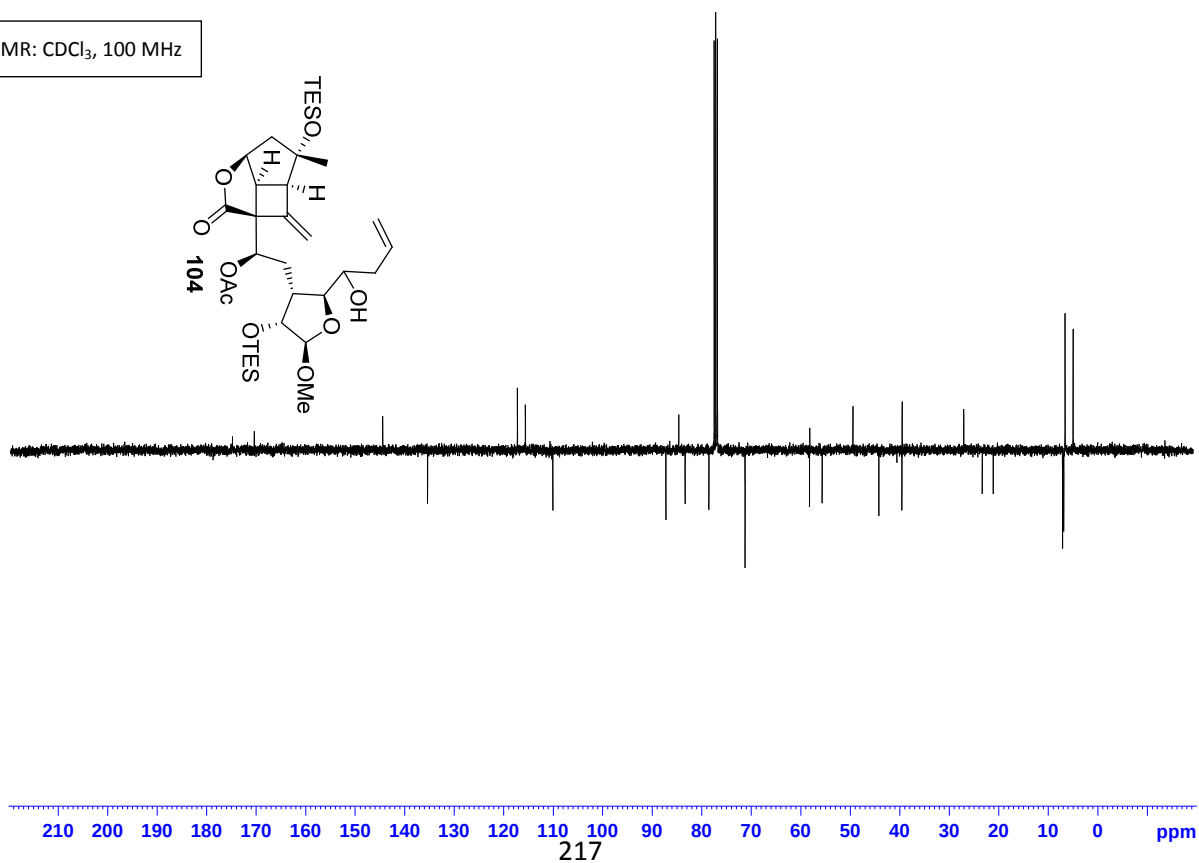
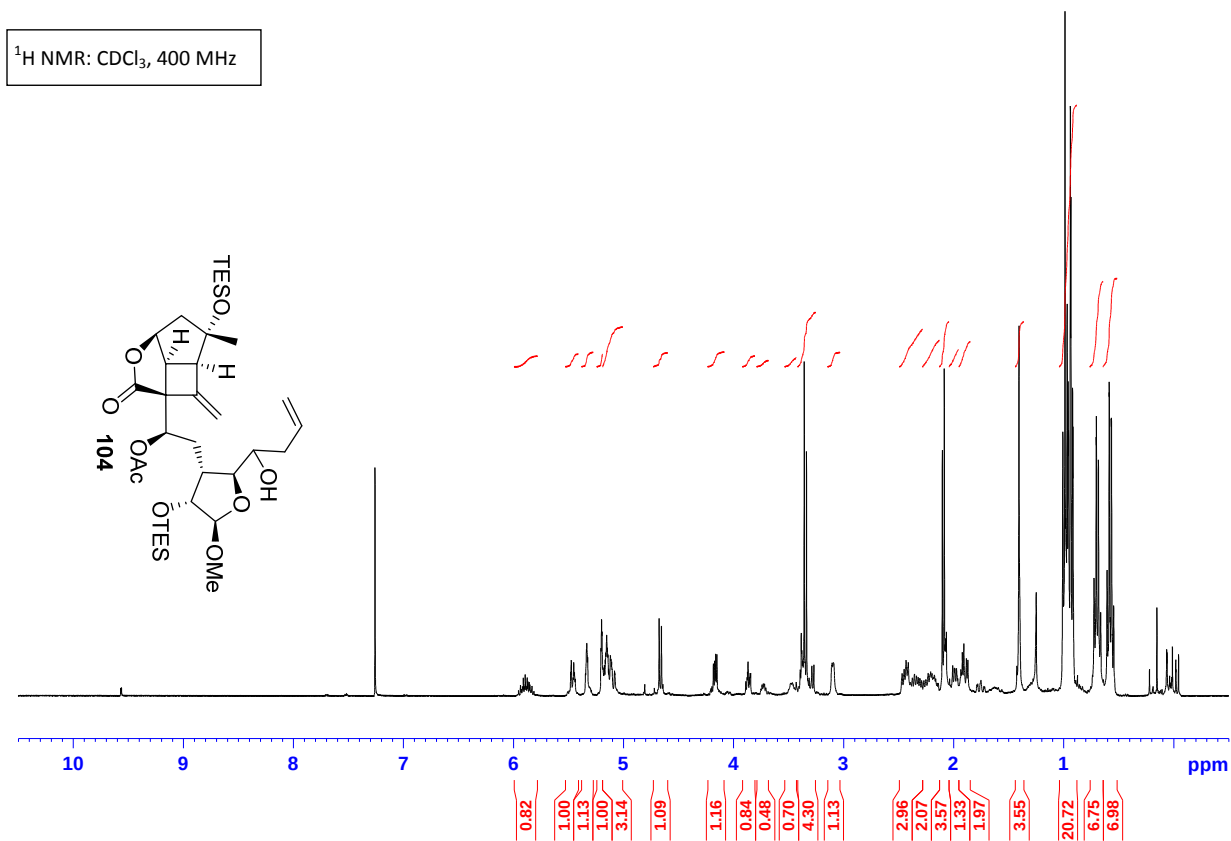


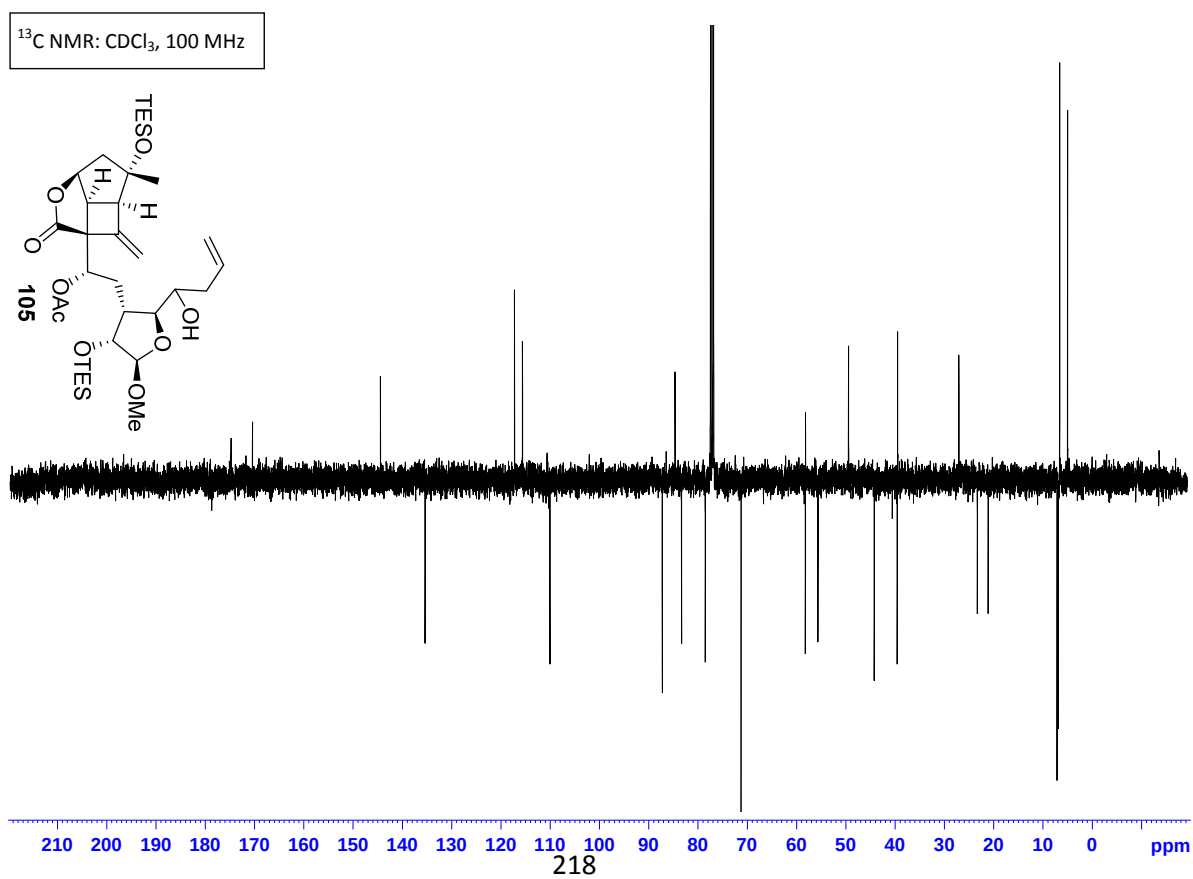
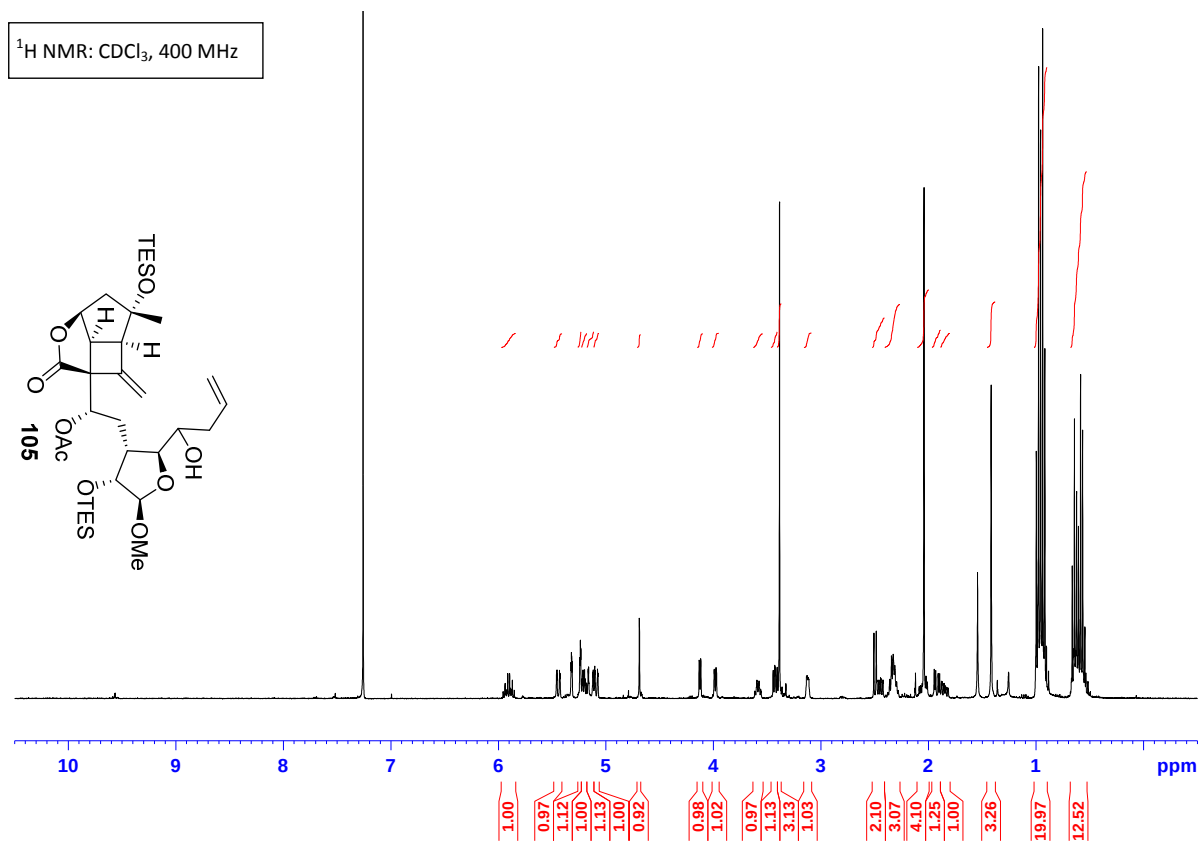
HMBC, CDCl₃, 400 MHz



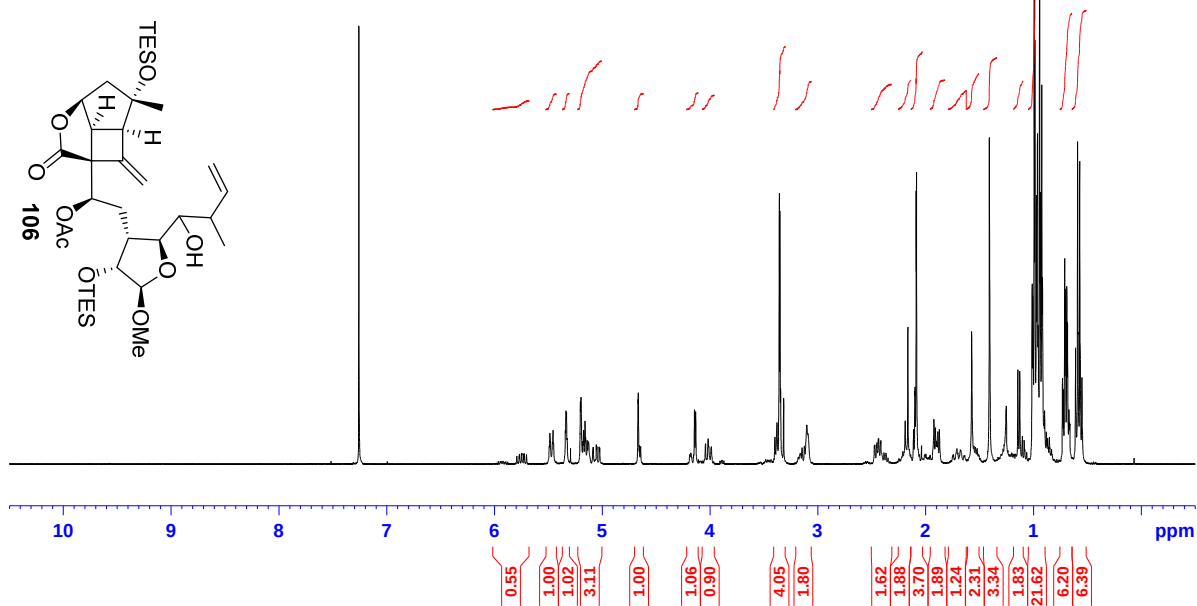
NOESY, CDCl₃, 400 MHz



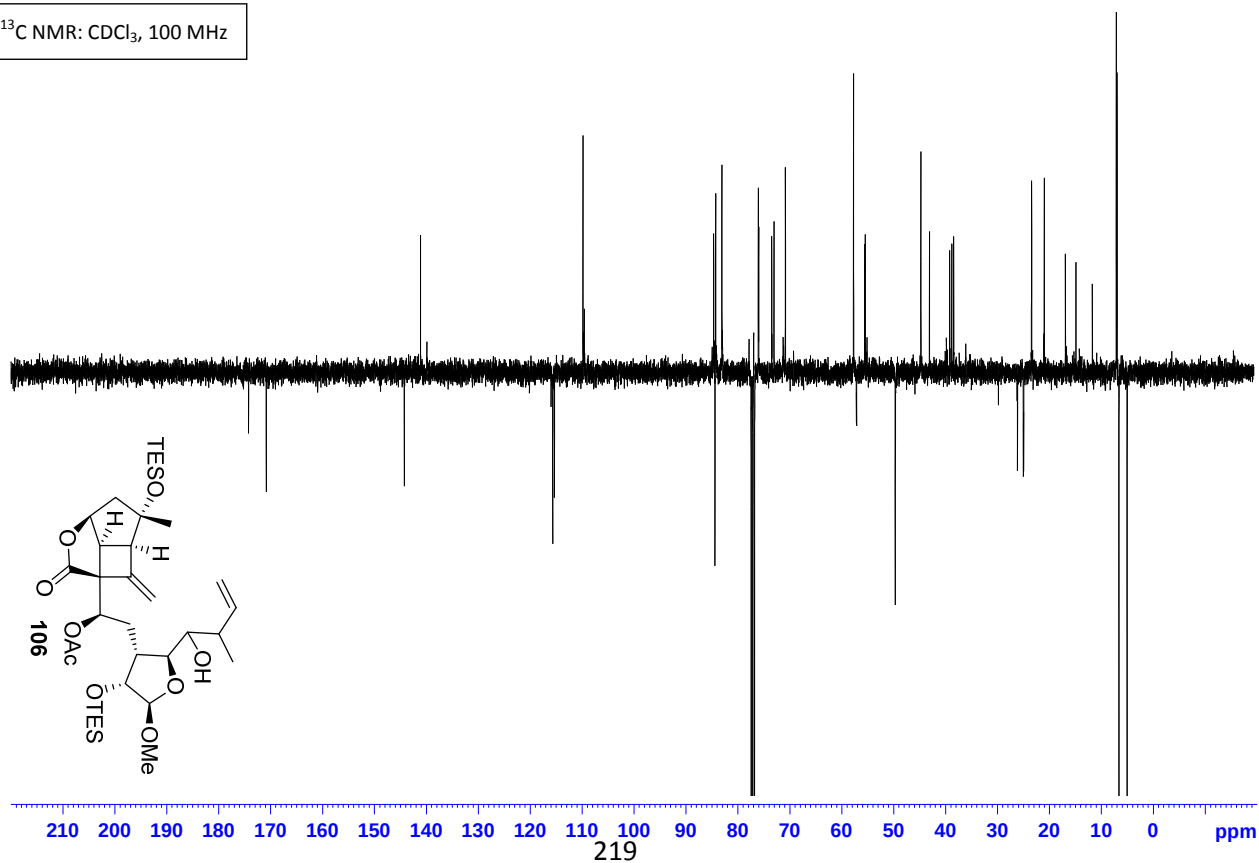


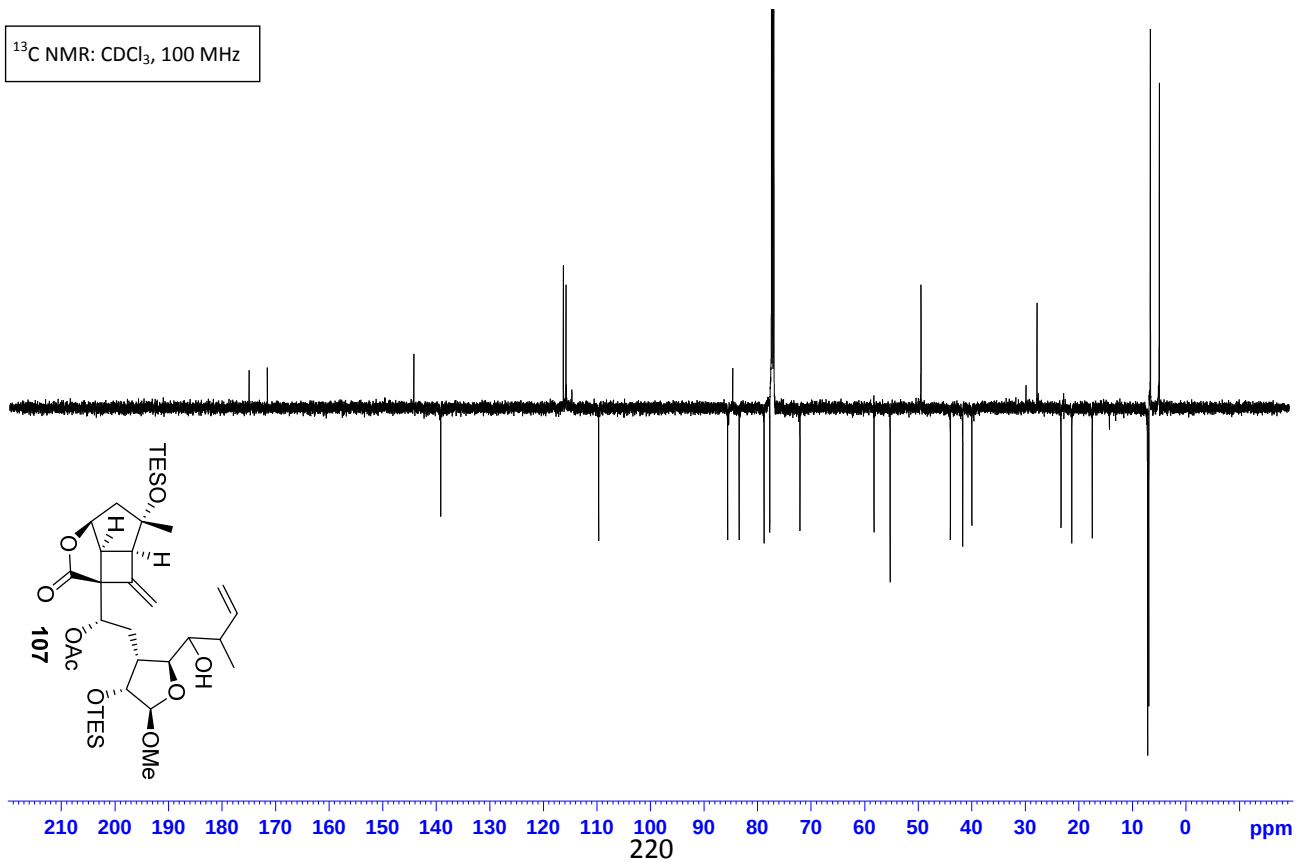
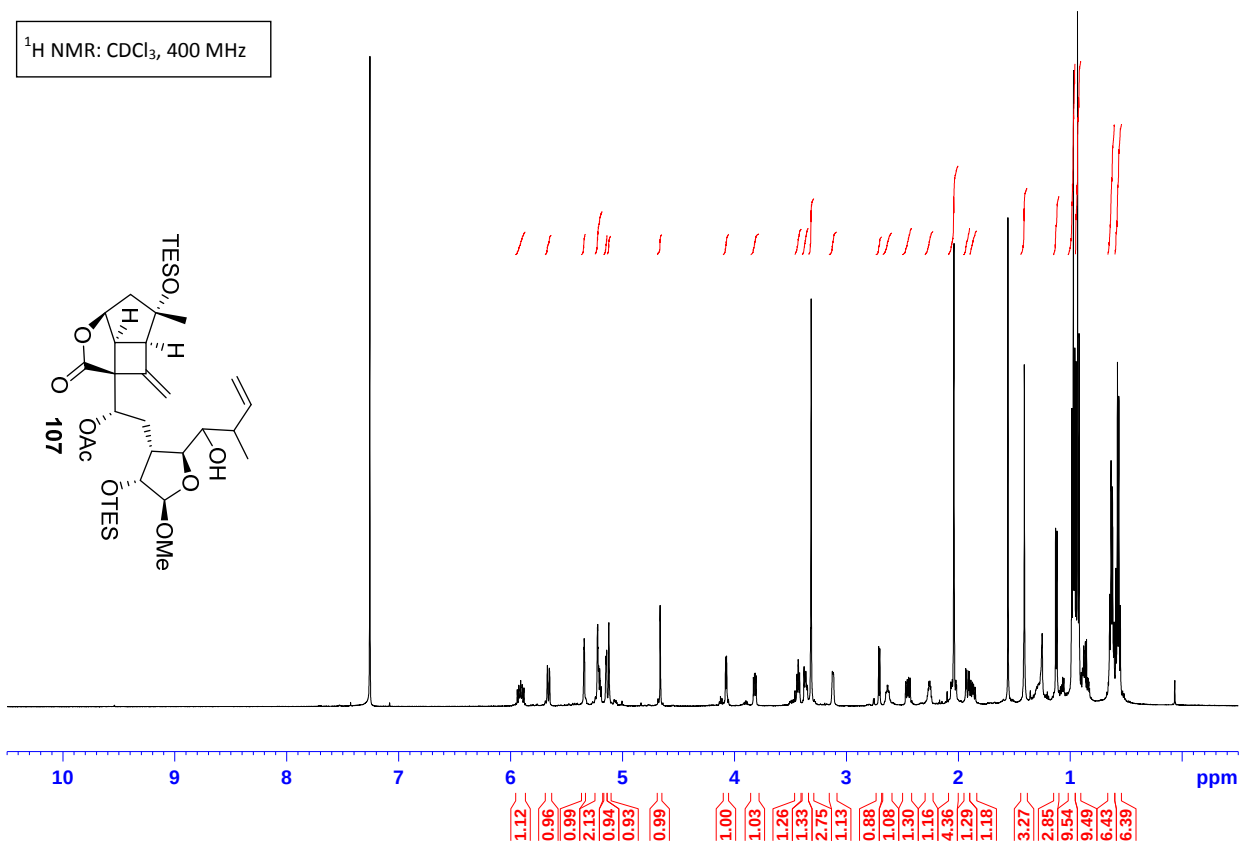


^1H NMR: CDCl_3 , 400 MHz

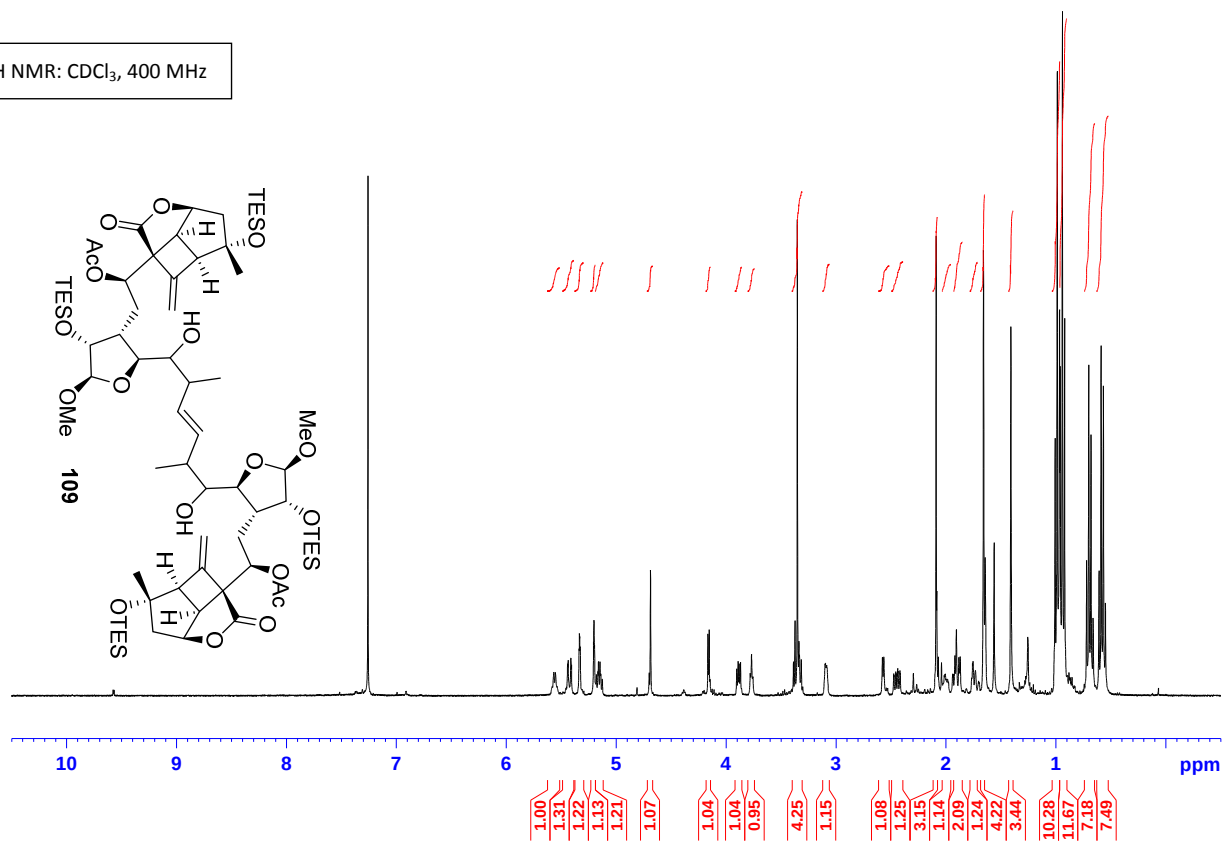


^{13}C NMR: CDCl_3 , 100 MHz

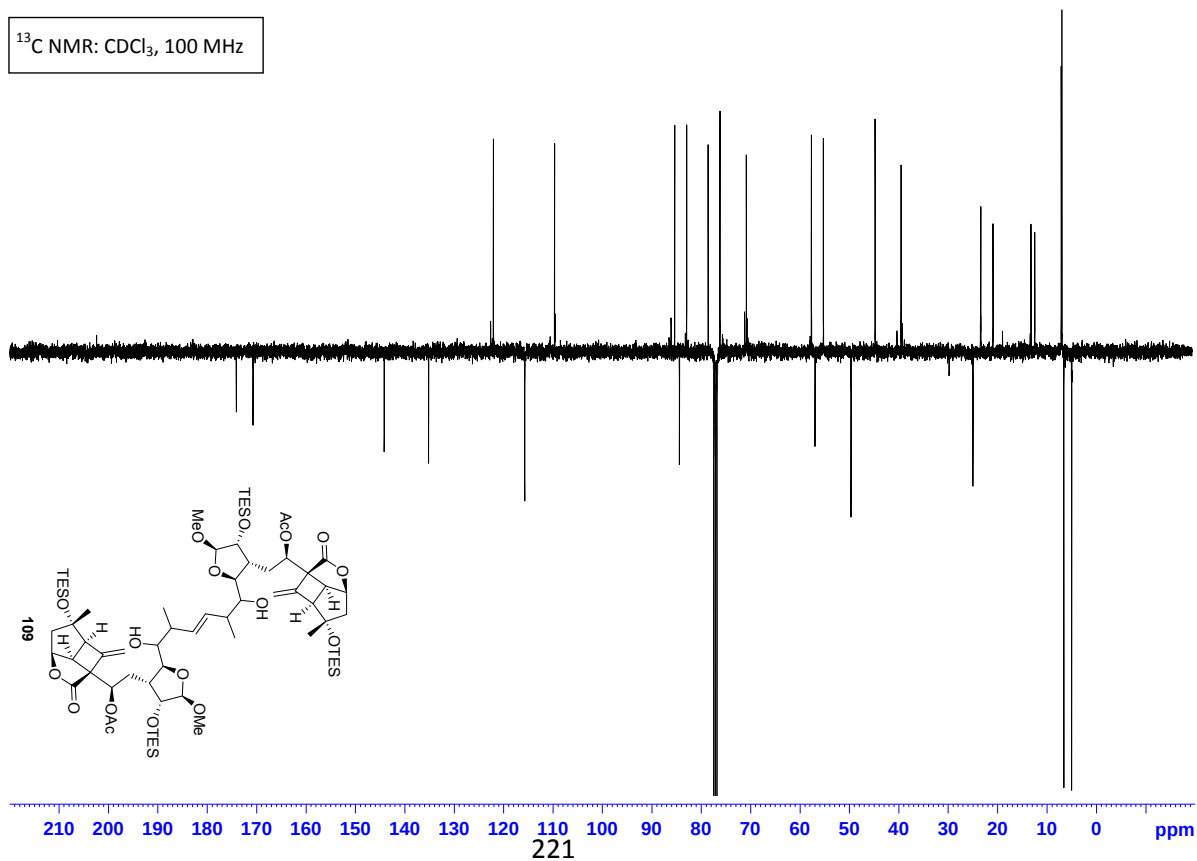




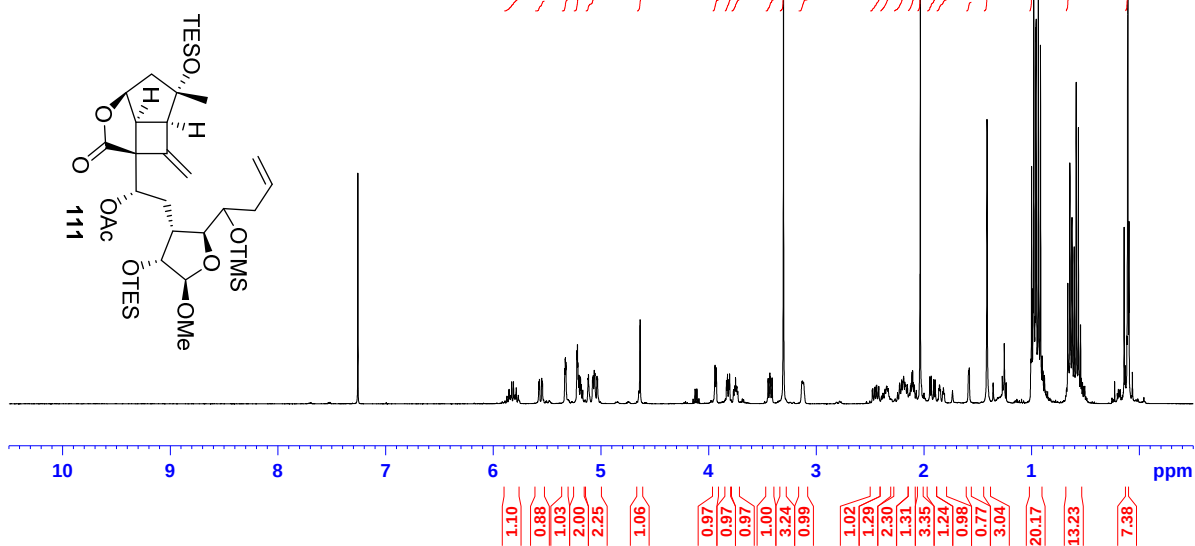
¹H NMR: CDCl₃, 400 MHz



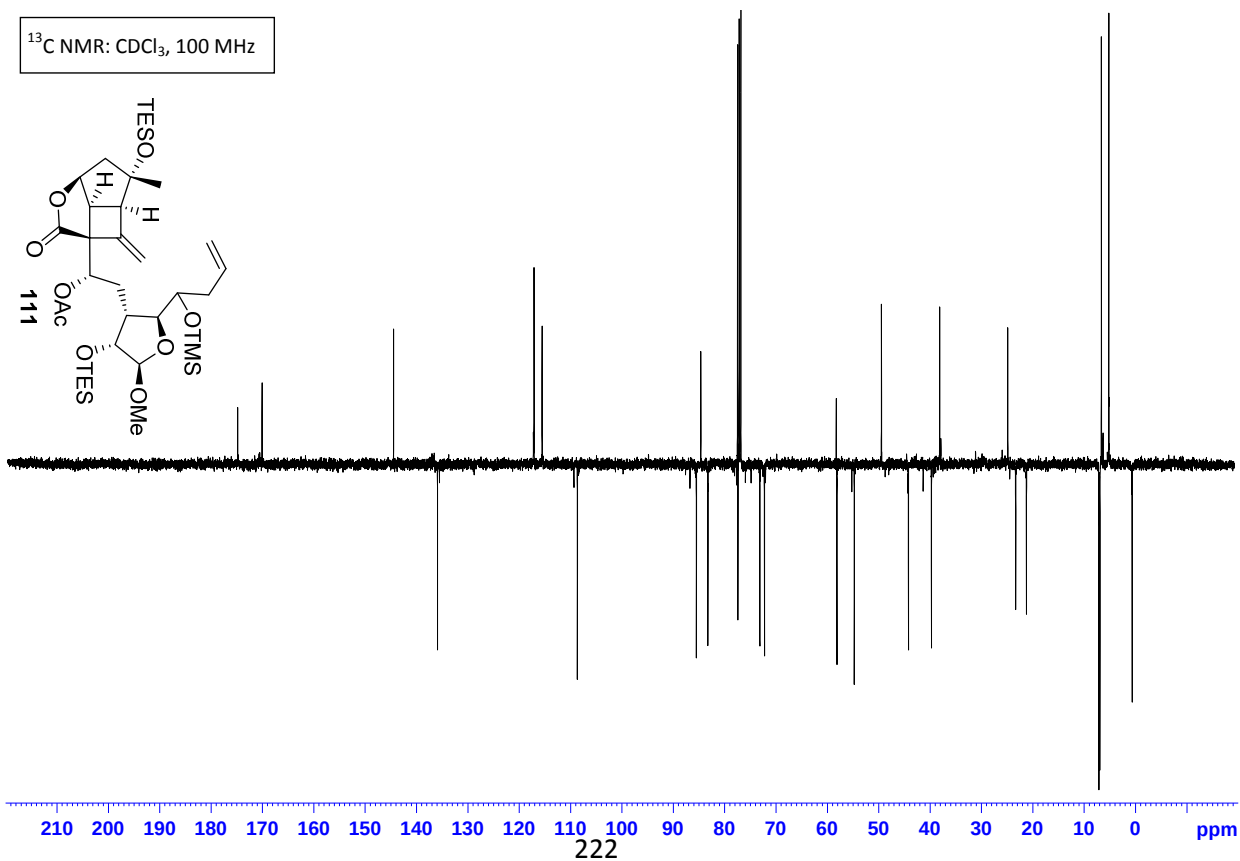
¹³C NMR: CDCl₃, 100 MHz

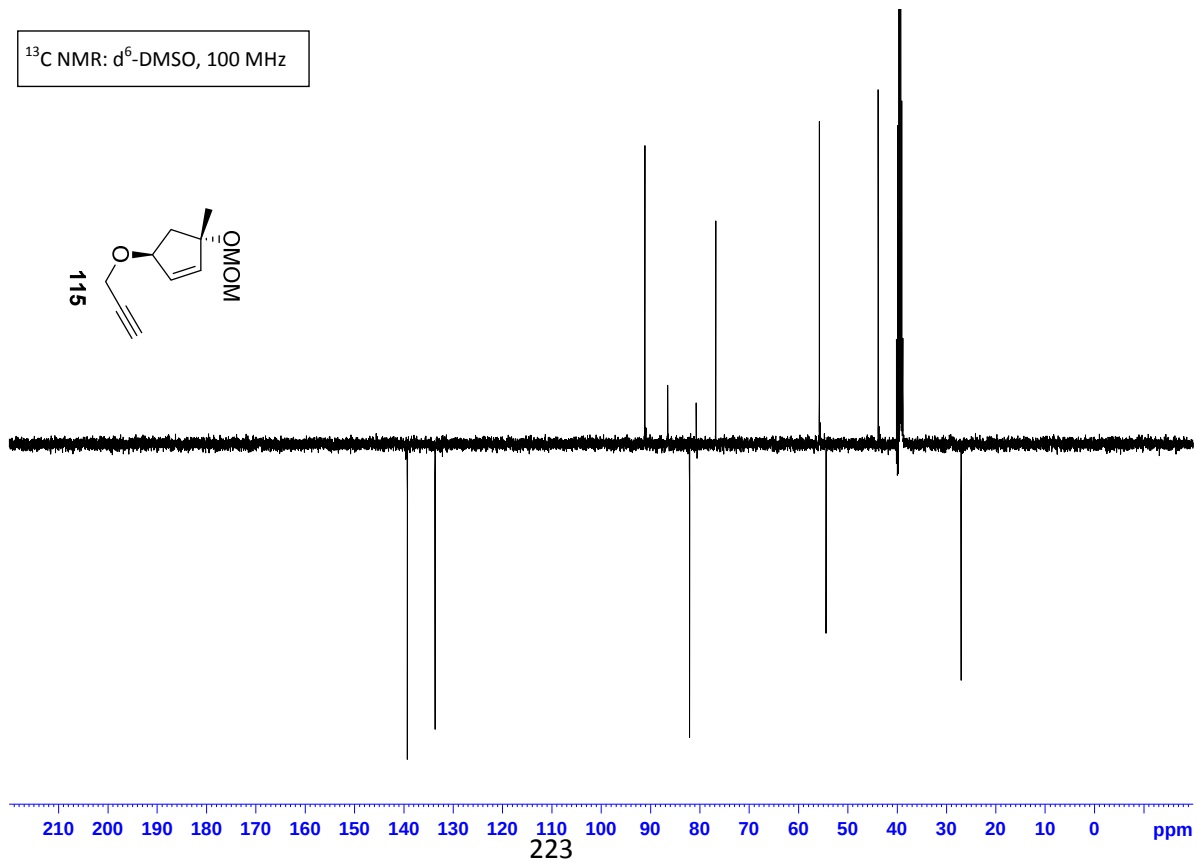
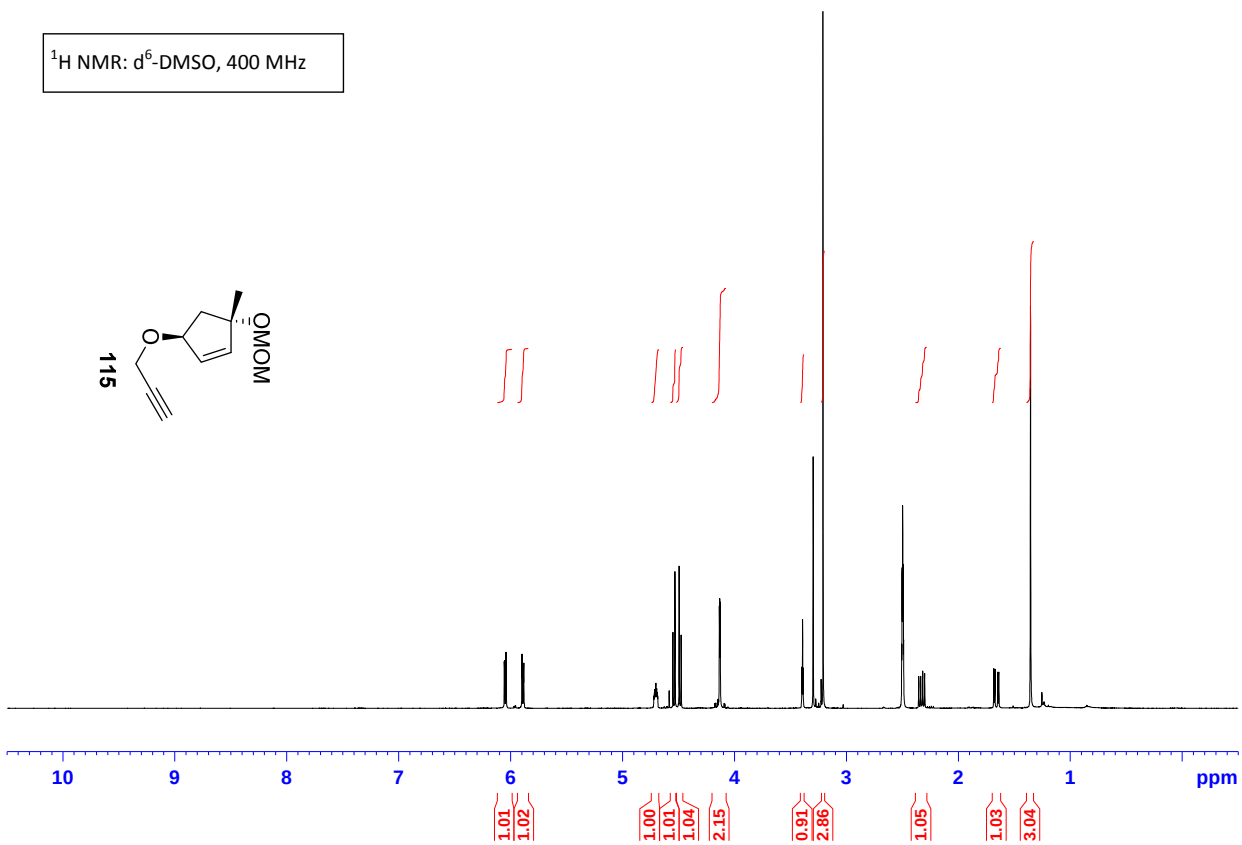


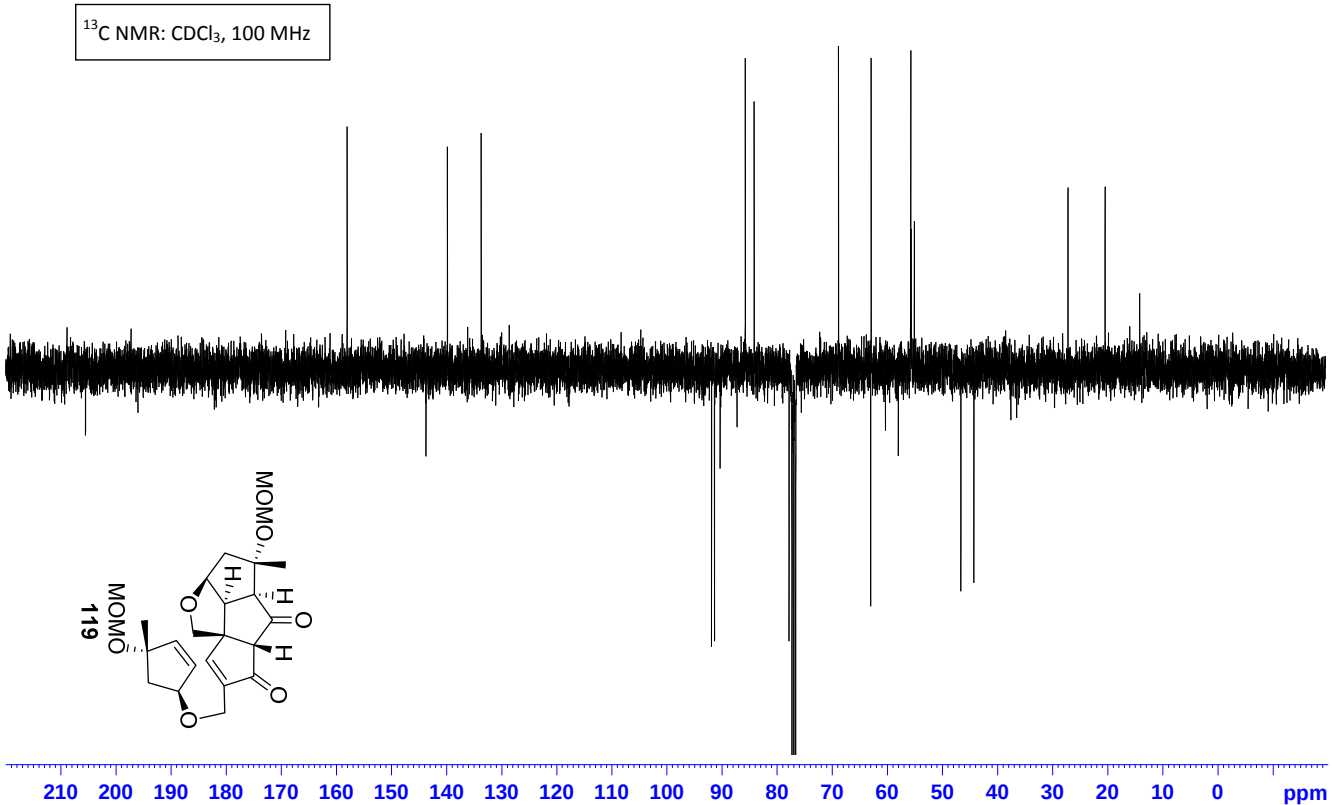
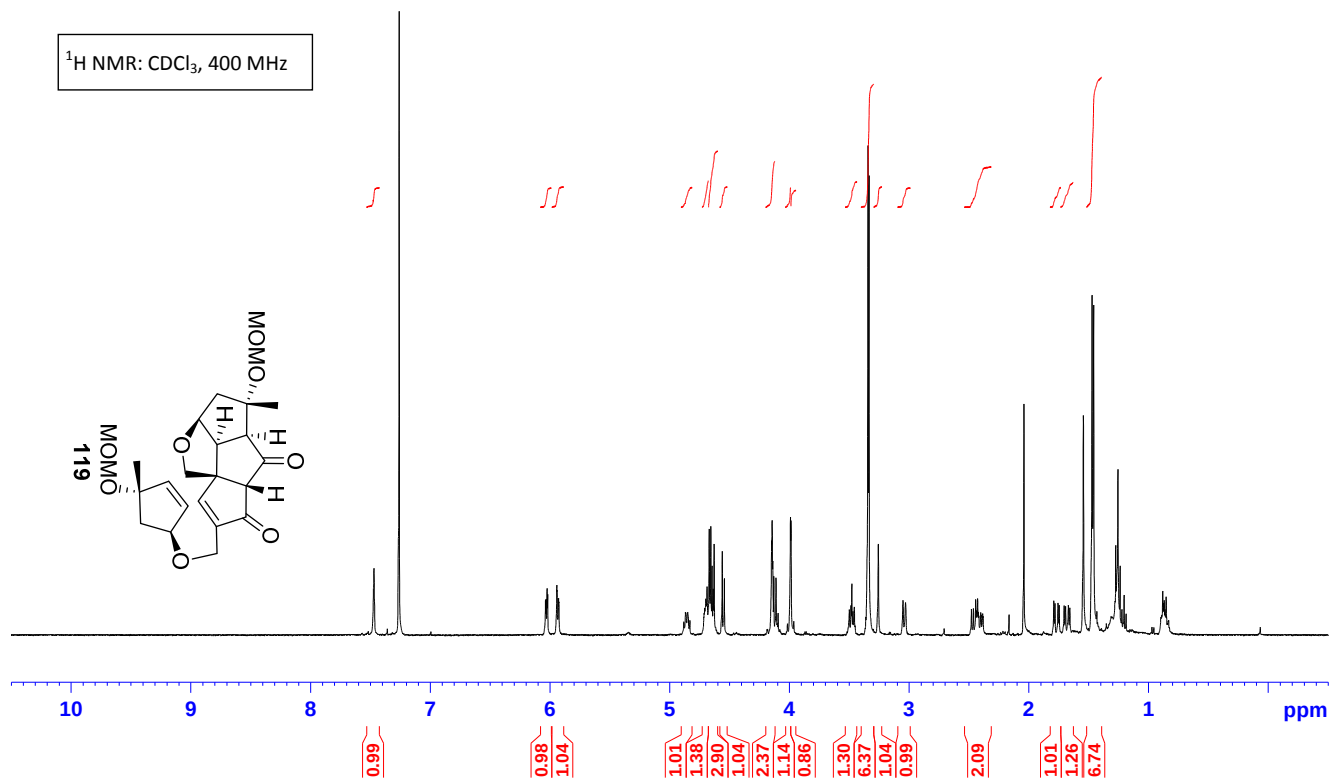
¹H NMR: CDCl₃, 400 MHz

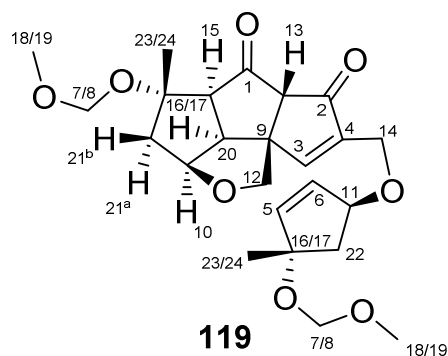


¹³C NMR: CDCl₃, 100 MHz









NOE- correlation:

21a ↔ 10 ↔ 20 ↔ 15; 12 ↔ 13; 23/24 ↔ 5

HMBC-correlation:

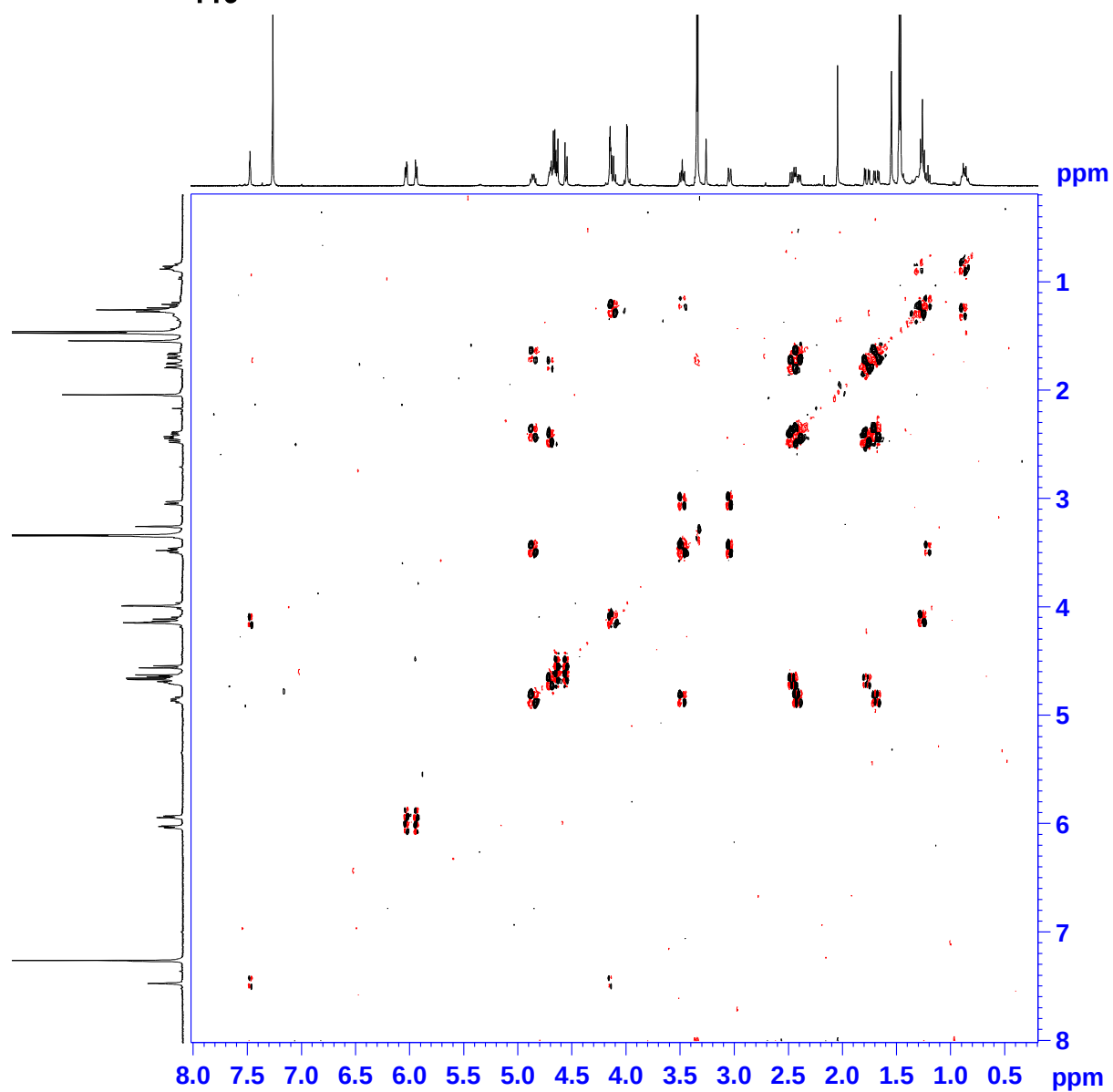
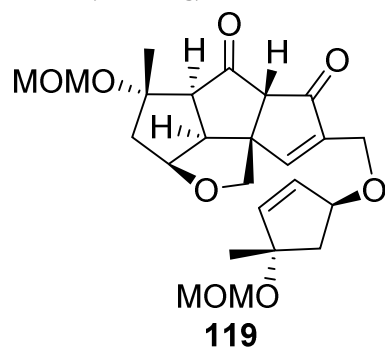
20 ↔ 1 ↔ 14; 17 ↔ 3 ↔ 2; 3 ↔ 15 ↔ 4; 10 ↔ 12 ↔ 13

COSY-correlation:

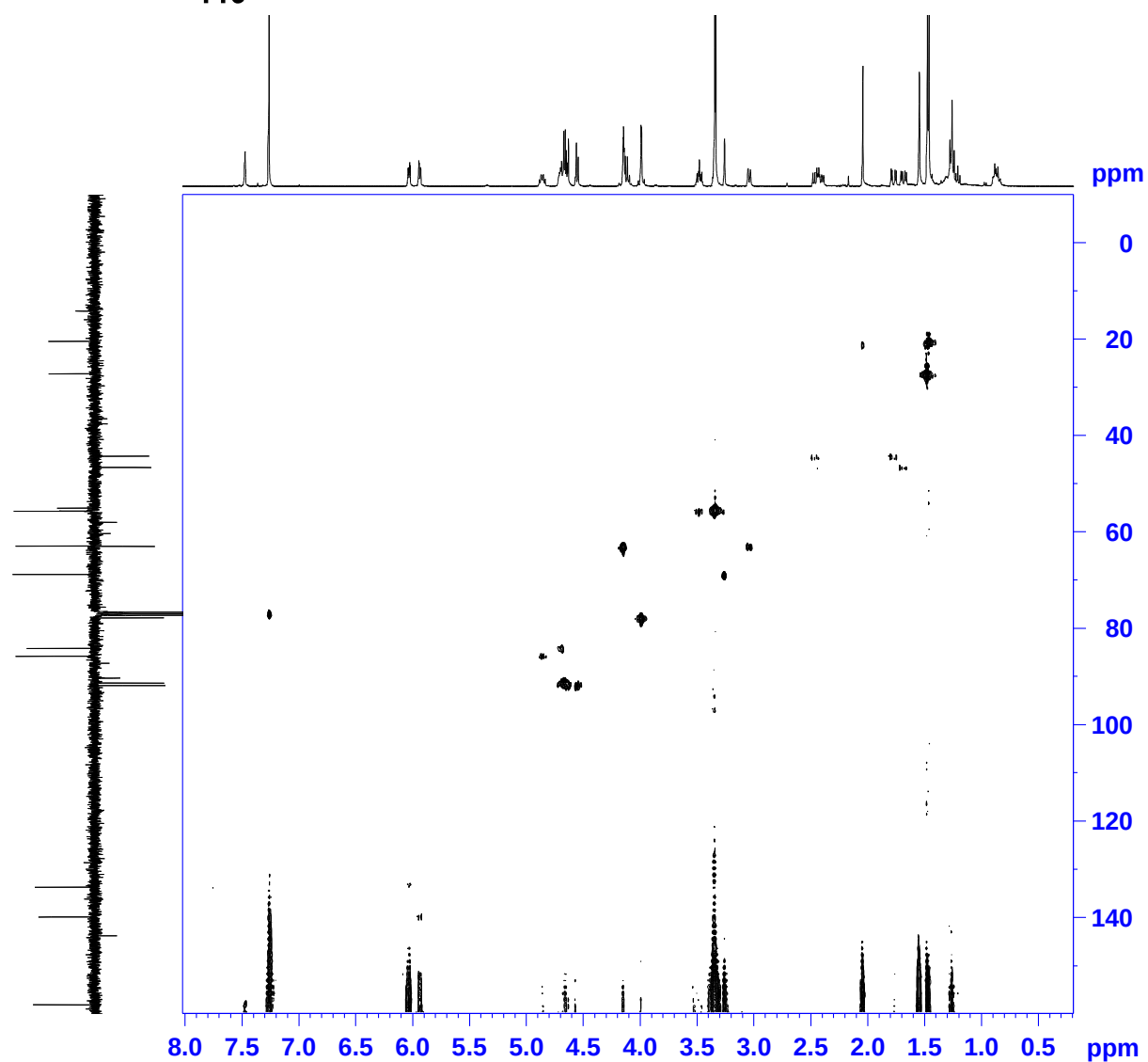
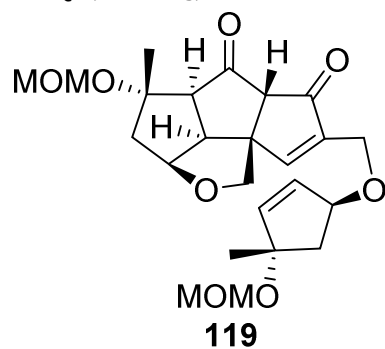
21 ↔ 10 ↔ 20 ↔ 14

No.	¹³ C [ppm]	¹ H [ppm]
1	205.5	-
2	196.1	-
3	158.1	7.47
4	143.8	-
5	139.9	5.94
6	133.8	6.03
7	91.9	4.67-4.55
8	91.4	4.67-4.55
9	90.4	-
10	85.8	4.86
11	84.2	4.70
12	77.9	4.00; 3.98
13	68.9	3.26
14	63.04	3.04
15	62.95	4.15
16	60.38	-
17	58.0	-
18	55.74	3.34
19	55.68	3.33
20	55.1	3.48
21	46.7	2.41; 1.68
22	44.3	2.46; 1.77
23	27.2	1.48
24	20.5	1.46

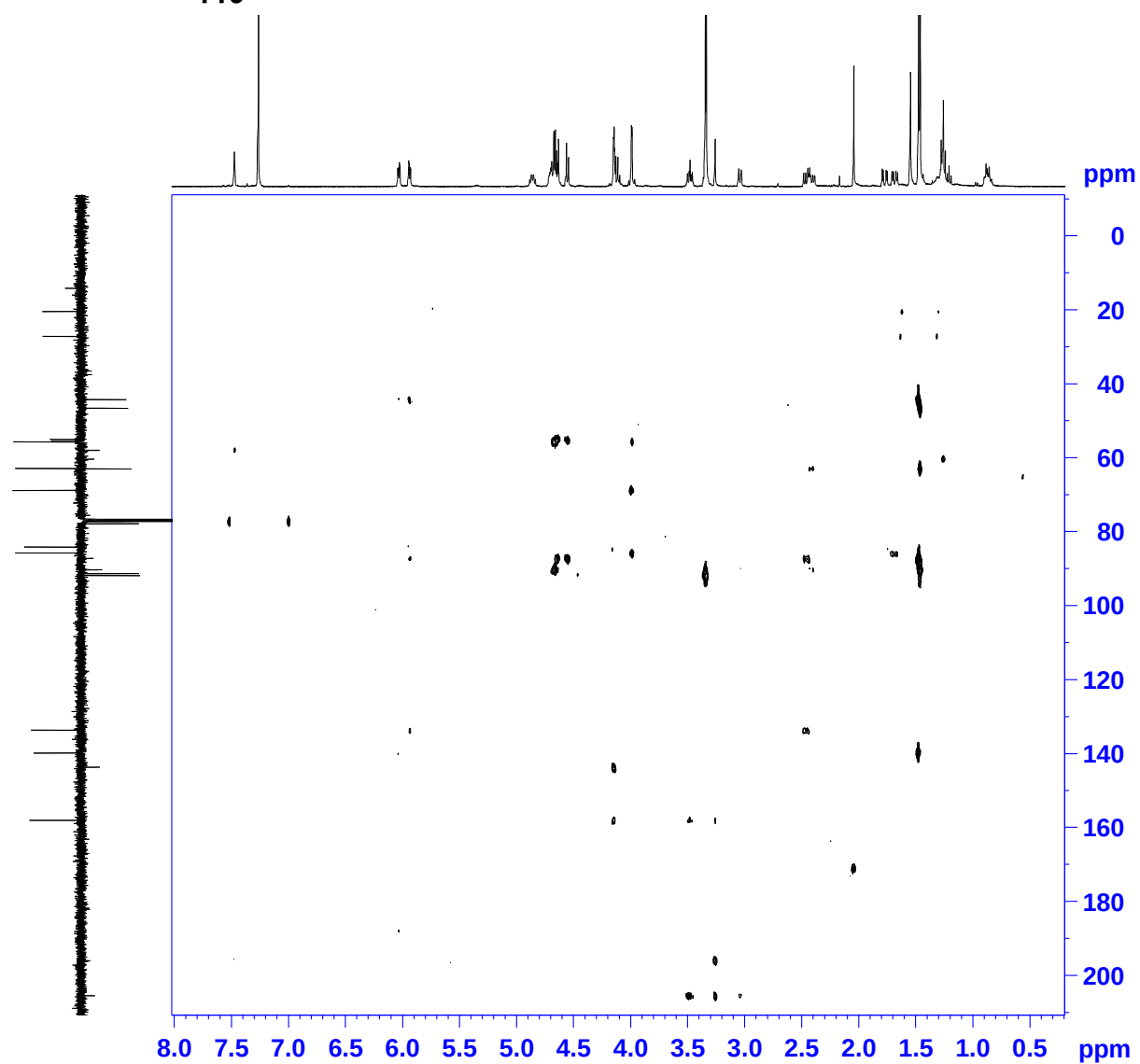
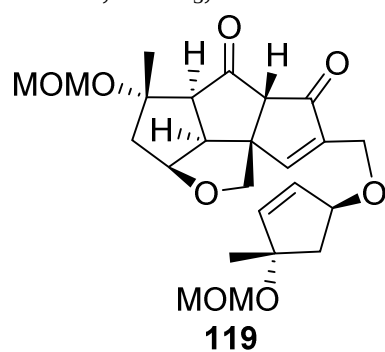
COSY, CDCl₃, 400 MHz



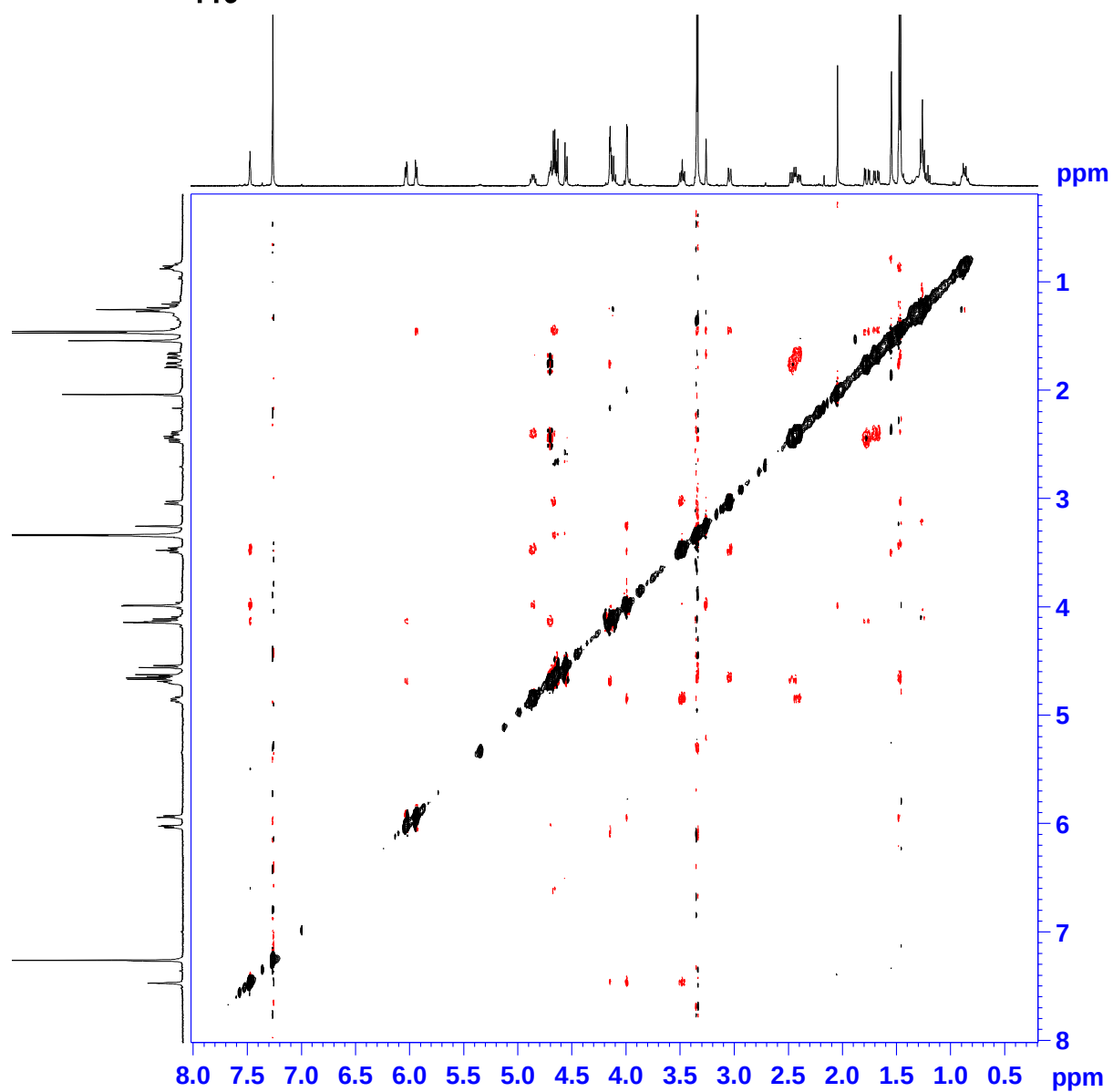
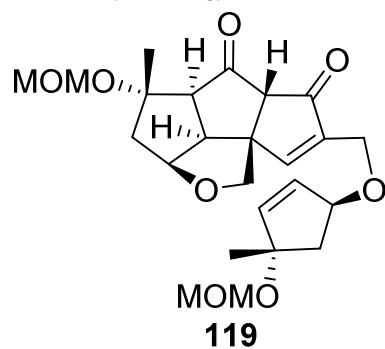
HSQC, CDCl₃, 400 MHz



HMBC, CDCl₃, 400 MHz



NOESY, CDCl₃, 400 MHz



7.4. An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photocyclization Strategy^{102,115}

Farcet, J.-B.; **Himmelbauer, M.**; Mulzer, J. *Eur. J. Org. Chem.* **2013**, *accepted for publication*.

Planning: Farcet, J.-B.; Himmelbauer, M.; Mulzer, J.

Experimentation: Farcet, J.-B.; Himmelbauer, M.

Manuscript preparation: Farcet, J.-B.; Himmelbauer, M.; Mulzer, J.

Discussion

Substantial contribution to this publication has been made in planning the approach as well as by the synthesis of the indispensable eastern building block **6**. Furthermore, contribution as an author of the manuscript concerning phrasing has been made by M. H.

As the experimental work mainly results from the first author, the supporting information was omitted.

An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photochemical Strategy

Jean-Baptiste Farcet,^[a] Martin Himmelbauer,^[a] and Johann Mulzer*^[a]

Keywords: Total synthesis / Natural products / Terpenoids / Chromium / Hydroalumination

The stereocontrolled synthesis of a complex and highly substituted polycyclic synthetic precursor **2** of the diterpene bielschowskysin is presented. Key steps include a regio- and stereoselective

hydroalumination as well as an optimized Cr/Ni mediated carbon-carbon bond formation between two complex fragments to establish the northern hemisphere of the natural product.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.xxxxxxxx>.

Introduction

The diterpene bielschowskysin, isolated in 2003 from the gorgonian octocoral *Pseudopterogorgia kallos*,^[1] is probably the most complex natural product from the furanocembranoid group.^[2] Over the past few years, the attractive molecular architecture has created a challenge for many synthetic groups,^{[3]-[9]} including ours.^{[10]-[11]} In the preceding paper^[12] we have described a photochemical access to tetracycle **1** (Figure 1), which contains the full carbon skeleton of bielschowskysin, though with a wrong ring size. In this article, a non-photochemical alternative to a similarly advanced intermediate **2** is presented. The functionalization is basically different in both compounds: **1** was prepared by a ring closure in the northern part and has a correct substitution pattern in the southern region, whereas **2** has a fully developed northern hemisphere and waits for a southern CC-connection.

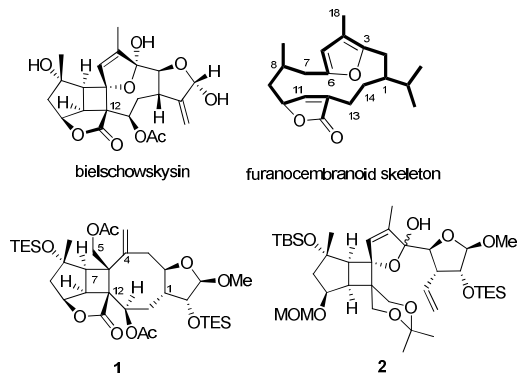
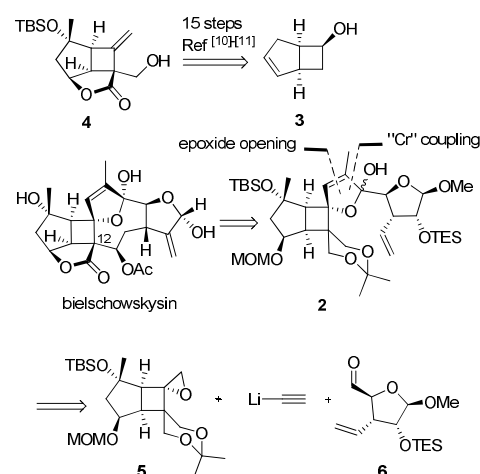


Figure 1. Bielschowskysin and the furanocembranoid skeleton, as well as two advanced synthetic intermediates **1** and **2**.

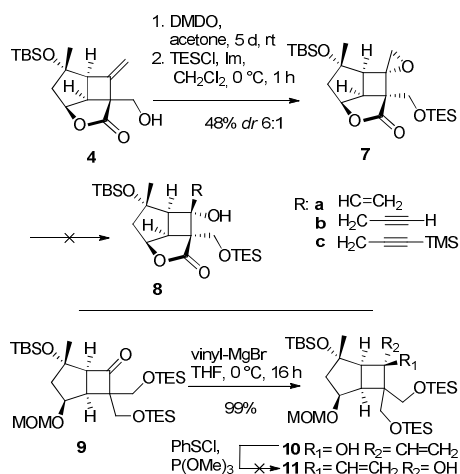
Results and Discussion

We recently published a stereoselective and optimized scalable synthesis of the tricyclic alcohol **4** from known alcohol **3**.^{[10]-[11]} For further elaboration, we reasoned that after formation of oxirane **5**, an epoxide opening with acetylide and subsequent formation of a vinyl halide would set the stage for chromium mediated coupling with aldehyde **6** (Scheme 1).



Scheme 1. Previous work and retrosynthetic considerations.

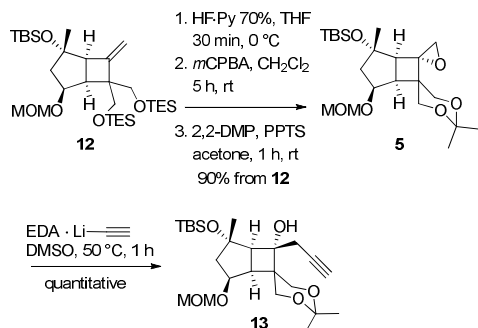
Hence, **4** was epoxidized with a *dr* of 6:1 from the convex side of the tricycle. TES protection furnished precursor **7**, which failed to deliver the allylic alcohol **8a** with Alcaraz protocol^[13] (trimethylsulfonium iodide and *n*BuLi) or the homopropargylic alcohols **8b-c** with acetylides. A similar epoxide inertness towards nucleophiles has been observed in our previous approach.^[12]



Scheme 2. Investigations to open the epoxide **7** and invert the stereochemistry of the tertiary alcohol **10**.

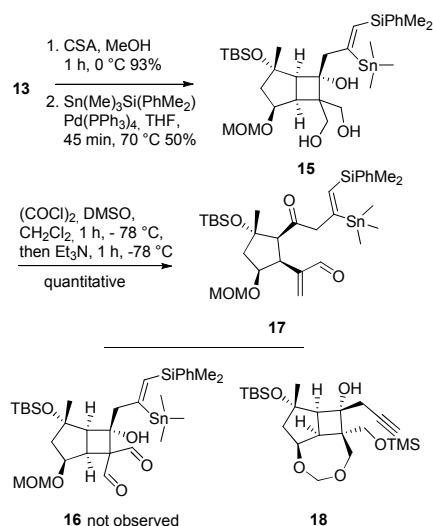
Finally, allylic alcohol **10** was readily formed from ketone **9**,^{[10]-[11]} but the undesired configuration of the tertiary alcohol could not be inverted via the Mislow-Evans rearrangement protocol (Scheme 2).^[14]

Reasoning that the presence of the lactone bridge strongly interferes with epoxide openings at the vicinal position, we returned to our previous intermediate **12**,^{[10]-[11]} which was converted to epoxide **5** as a single diastereomer (Scheme 3). Now, the addition of commercially available lithium acetylide ethylenediamine complex provided pure homopropargylic alcohol **13** in excellent yield (Scheme 3).



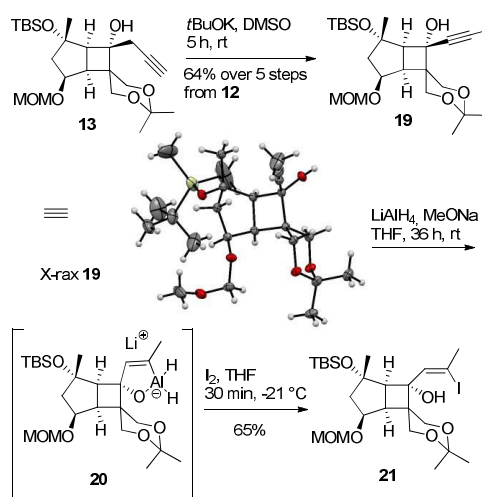
Scheme 3. Epoxide opening and formation of **13**.

In parallel, diastereomerically and enantiomerically pure aldehyde **6** was prepared in 11 steps from D-(+)-glucose.^[12] A number of procedures for coupling of fragments **6** and **13** were tested. As Takai conditions^[15] failed, (CrCl₂, NiCl₂, H₂O, PPh₃, DMF) we converted the alkyne into a suitably metalated vinyl derivative (Scheme 4). In fact, trimethyltin derivative **15** could be obtained in moderate yield, though with excellent regio- and stereoselectivity. However, to our disappointment, its Swern oxidation did not furnish dialdehyde **16**. Instead, enone **17** was obtained as the single product (Scheme 4), presumably via base induced Grob-type fragmentation^[16] of the activated alcohol intermediate followed by oxidation of the allylic alcohol. This reaction could be extended to several other substrates and may be an interesting access to highly functionalized cyclopentanes.



Scheme 4. Grob-type rearrangement under Swern conditions and formation of product **18** during the protection attempt of **13**.

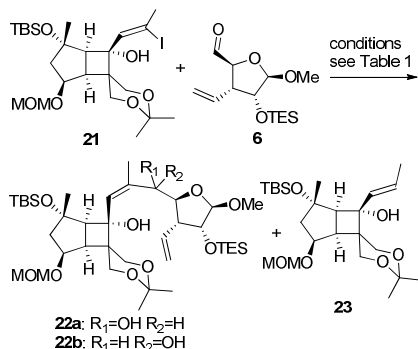
To avoid fragmentation, tertiary alcohol **13** was protected with TMSOTf and 2,6-lutidine. Unfortunately, yet not unexpectedly, this afforded **18** as sole product (Scheme 4).^[17] Hence, we decided to carry on without protection and to use the tertiary alcohol as an anchor for the formation of the envisaged vinyl halide. First, according to an established protocol^[18] (cat *t*BuOK, DMSO), the homopropargylic alcohol **13** was isomerized to crystalline propargylic alcohol **19** (Scheme 5), whose structure was confirmed by single crystal diffraction.^[19] Hydroalumination of **19** led to intermediate **20**, which was quenched with iodine to give (*Z*)-vinyl iodide **21** with excellent regio- and stereocontrol (Scheme 5).^[20]



Scheme 5. Synthesis of vinyl iodide **21**.

First coupling experiments of vinyl iodide **21** and aldehyde **6** were attempted via iodine-lithium exchange. With equimolar amounts of both partners, dehalogenated starting material **23** was formed as the single product of the reaction. Obviously, the vinyl lithium species once formed is immediately quenched by proton transfer from the tertiary alcohol. Indeed, when alcohol **21** was first deprotonated with LiHMDS and then the iodine-lithium exchange was performed with *t*BuLi/LiCl, the coupling product **22** was isolated in 10% yield along with 80% of **23** (Scheme 6). As vinyl lithium is too basic for our purposes, we turned to the Nozaki-

Hiyama-Kishi (NHK) reaction^{[21]-[22]} as a prime option for adding vinyl iodides to aldehydes. We carefully screened conditions to optimize the coupling of fragments **21** and **6** (Scheme 6, Table 1).



Scheme 6. Coupling of vinyl iodide **21** and aldehyde **6**.

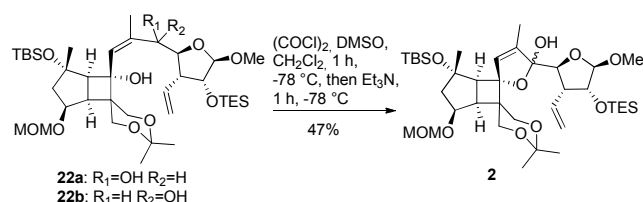
Table 1. Optimization of the NHK coupling reaction.

Entry	Conditions	%Yield ^[a] of 22 (dr)	%Yield ^[a] of 23
1	CrCl ₂ + NiCl ₂ (0.1) in DMSO 10 °C	49 (1.7:1)	33
2	CrCl ₂ + NiCl ₂ (0.1) in DMSO rt	50 (3.6:1)	31
3	CrCl ₂ + NiCl ₂ (0.1) in DMSO 40 °C	30 (4.5:1)	30
4	CrCl ₂ /LiAlH ₄ + NiCl ₂ (0.1) in DMSO rt	52 (3.4:1)	36
5	CrCl ₂ + NiCl ₂ (0.1) in DMF rt	30 (3.8:1)	54
6	CrCl ₂ + NiCl ₂ (0.1) in DMA rt	16 (8.0:1)	74
7	CrCl ₂ + NiCl ₂ (0.1) in DME/DMSO (10:1) 60 °C	0 (n.d.)	64
8	CrCl ₂ + NiCl ₂ (0.1) in DMSO/HMPA (2:1) rt	52 (2.1:1)	28
9	CrCl ₂ + NiCl ₂ (0.1) in DMSO rt ^[b]	17 (3.7:1)	76
10	CrCl ₂ + NiCl ₂ (0.1) in DMSO rt ^[c]	24 (2.8:1)	38
11	CrCl ₂ + Pd(OAc) ₂ (0.1) in DMSO rt	15 (n.d.)	69
12	CrCl ₂ + Ni(acac) ₂ (0.1) in DMSO rt	57 (3.8:1)	29
13	CrCl ₂ + Ni(acac) ₂ (3) in DMSO rt	54 (3.0:1)	39
14	CrCl ₂ + NiCl ₂ (3) in DMSO rt	64 (2.4:1)	25

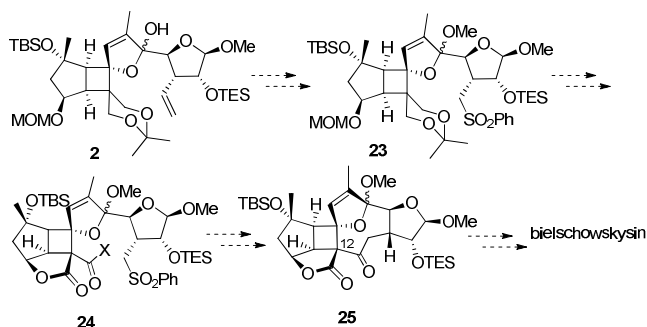
Standard conditions: 0.05 M, 50 mg of **21**, 2 equiv. of **6**, 7 equiv. of [Cr] + co-catalyst. [a] isolated yield, [b] addition of **21** by syringe pump over 1 h, [c] in ultra sound bath. n.d. not determined.

Using standard conditions (Table 1, entry 2) alcohol **22** was formed in 50% isolated yield together with 31% of side product **23**. Varying the reaction temperature (Table 1, entries 1-3) mainly altered the diastereoisomeric ratio. Similarly, changing the source of chromium and generating CrCl₂ in situ (Table 1, entry 4) did not reduce the amount of side product **23**. Changing the solvent from DMSO to DMA significantly increased the diastereoselectivity, but not the yield (Table 1, entry 6). Slow addition of **21** or performing the reaction in an ultra sound bath (Table 1, entries 9 and 10) or the use of Pd(OAc)₂ as co-catalyst (Table 1, entry 11) gave unsatisfactory results. However, using Ni(acac)₂ (Table 1, entry 12) instead of NiCl₂, or administering the Ni-reagent in excess (Table 1, entries 13 and 14) both helped to promote CC-connection vs. proton transfer, so that **22** was formed in 54-64% yield.

In all cases alcohol **22** was obtained as an inconsequential diastereomeric mixture, which was oxidized to furnish hemiacetal **2** in a 5:1 anomeric ratio (Scheme 7).



Scheme 7. Formation of hemiacetal **2**.



Scheme 8. Hypothetical endgame.

A hypothetical endgame is suggested in Scheme 8. Introduction of a sulfone would be followed by acid promoted removal of the acetonide, oxidation and formation of dicarbonyl intermediate **24**. This has already been performed with a simpler analogue.^{[10]-[11]} Base induced cyclization and reductive removal of the sulfone^[23] would lead to **25**, which is about five steps away from the target.

Conclusions

A synthesis of an advanced precursor of bielschowskysin has been presented in 21 steps and 7.4% overall yield starting from known alcohol **3**. Formation of the properly substituted vinyl halide by regio- and stereoselective hydroalumination was followed by an optimized NHK coupling, which furnished pentacycle **2** after oxidation. On evaluating intermediates **1** and **2**, we tend to favor the route leading to **1**. So this will be our preferred line, and **2** will remain as back-up.

Experimental Section

General Experimental Details: Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant *J*, integration. Infrared spectra were recorded as thin films of pure product on an ATR-unit. High-resolution mass spectra were measured as ESI-TOF with a resolution of 10,000. **Standard work up:** The reaction was then diluted with Et₂O (10 mL/0.1 mmol) and NH₄Cl (7 mL/0.1 mmol), the phases were separated and the aqueous phase was extracted with Et₂O (2 x 5 mL/0.1 mmol). The combined organic phases were washed with water (5 mL/0.1 mmol), brine (5 mL/0.1 mmol), dried over MgSO₄ and concentrated under reduced pressure.

(1S,1aR,3aS,5S,5aR)-5-[[tert-butyl(dimethyl)silyl]oxy]-5-methyl-1a-[[triethylsilyl]oxy]methyl]hexahydro-2H-spiro[3-oxacyclobuta[cd]pentalene-1,2'-oxiran]-2-one (7): A solution of DMDO (0.07 M in acetone, 0.55 mmol) was added to primary alcohol **4** (30 mg, 0.09 mmol). The resulting mixture was stirred at rt for 5 days and was evaporated to yield 31 mg (quantitative) of the epoxide intermediate. To a solution of free alcohol (31 mg, 0.09 mmol) in CH₂Cl₂ (1.8 mL) was added Im (15 mg, 0.23 mmol) followed by TESCl (20 µL, 0.12 mmol) at 0 °C. The mixture was stirred for 1 h at rt. Standard work up was followed by column chromatography of the residue (SiO₂, Hex/EtOAc 30/1) furnishing

20 mg (48% over 2 steps) of the TES protected **7** as colorless oil in a *dr* of 6:1. Main diastereoisomer : $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 5.23 (dt, J_1 = 5.5 Hz, J_2 = 7.9 Hz, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.81 (d, J = 10.8 Hz, 1H), 3.56 (dd, J_1 = 7.2 Hz, J_2 = 8.4 Hz, 1H), 3.06 (dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 1H), 2.90 (d, J = 4.7 Hz, 1H), 2.70 (d, J = 4.6 Hz, 1H), 2.56 (ddd, J_1 = 2.1 Hz, J_2 = 7.9 Hz, J_3 = 14.7 Hz, 1H), 1.94 (dd, J_1 = 5.5 Hz, J_2 = 14.6 Hz, 1H), 1.31 (s, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.84 (s, 9H), 0.62 (q, J = 8.0 Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 177.1, 83.7, 83.0, 61.0, 59.2, 57.3, 50.4, 47.1, 42.7, 29.8, 25.7(3C), 23.1, 18.0, 6.8(3C), 4.5(3C), -2.3, -2.4 ppm. HRMS (EI) (*m/z*): calculated for $\text{C}_{23}\text{H}_{42}\text{O}_5\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 477.2468, found: 477.2454. IR(cm^{-1}): 2954, 2877, 1770, 1461, 1254, 1142, 1103, 990, 834, 729. $[\alpha]_{\text{D}}^{22}$ -41.8 (*c* = 0.55; CHCl_3). R_f: (Hex/EtOAc 5/1) 0.44.

(1S,2S,4S,5R,6R)-4-[[tert-butyl(dimethyl)silyl]oxy]-6-ethenyl-2-(methoxymethoxy)-4-methyl-7,7-bis[[triethylsilyl]oxy]methyl]bicyclo[3.2.0]heptan-6-ol (10): At 0 °C vinylMgBr (1 M in Et₂O, 564 μL , 0.56 mmol) was added to a solution of ketone **9** (200 mg, 0.28 mmol) dissolved in Et₂O (2.8 mL). The reaction vessel was stirred overnight at rt. Standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 20/1 then 10/1) furnishing 207 mg (99 %) of alcohol **10** as colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 5.94 (dd, J_1 = 10.4 Hz, J_2 = 17.0 Hz, 1H), 5.17 (dd, J_1 = 1.3 Hz, J_2 = 17.0 Hz, 1H), 5.04 (dd, J_1 = 1.4 Hz, J_2 = 10.8 Hz, 1H), 4.64 (d, J = 6.4 Hz, 1H), 4.60-4.52 (m, 1H), 4.48 (d, J = 10 Hz, 1H), 4.47 (d, J = 6.2 Hz, 1H), 3.79 (d, J = 10.2 Hz, 1H), 3.70 (d, J = 9.1 Hz, 1H), 3.37-3.31 (m, 5H), 2.64 (t, J = 8 Hz, 1H), 2.58 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H), 2.52 (t, J = 11.8 Hz, 1H), 1.98 (ddd, J_1 = 1.7 Hz, J_2 = 7.0 Hz, J_3 = 12.0 Hz, 1H), 1.48 (s, 3H), 1.00-0.90 (m, 18H), 0.83 (s, 9H), 0.64-0.54 (m, 12H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 142.9, 112.4, 95.4, 82.4, 78.9, 75.3, 64.5, 60.9, 55.3, 52.1, 51.4, 47.3, 40.8, 25.9(3C), 24.3, 18.1, 7.0(3C), 6.9(3C), 4.6(6C), -2.0, -2.2 ppm. HRMS (EI) (*m/z*): calculated for $\text{C}_{32}\text{H}_{66}\text{O}_6\text{Si}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 653.4065, found 653.4068. IR(cm^{-1}): 2954, 2878, 1461, 1253, 1100, 1046, 1004, 834, 806, 742. $[\alpha]_{\text{D}}^{22}$ -59.2 (*c* = 1.0; CHCl_3). R_f: (Hex/EtOAc 10/1) 0.69.

tert-butyl{[(1'R,2'S,4'S,5'S,7'S)-4'-(methoxymethoxy)-2,2,2'-trimethylspiro[1,3-dioxane-5,6'-bicyclo[3.2.0]heptane-7',2''-oxiran]-2'-yl]oxy}dimethylsilane (5): To a solution of **12** (277 mg, 0.46 mmol) in THF (3 mL) in a teflon vial was slowly added a 70% HF solution in pyridine (269 μL , 9.22 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature while tlc analysis indicated clean conversion. Standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 2/1) furnishing 170 mg (99%) of the diol intermediate as viscous colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.88 (d, J = 1.9 Hz, 1H), 4.83 (d, J = 2.5 Hz, 1H), 4.71 (d, J = 6.6 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.64-4.55 (m, 1H), 4.05 (d, J = 11.9 Hz, 1H), 3.80 (dd, J_1 = 3.1 Hz, J_2 = 11.1 Hz, 1H), 3.77-3.63 (m, 3H), 3.37 (s, 3H), 3.20 (br d, J = 7.0 Hz, 1H), 3.07-2.98 (m, 2H), 2.12 (ddd, J_1 = 1.4 Hz, J_2 = 6.4 Hz, J_3 = 13.4 Hz, 1H), 1.86 (t, J = 12.0 Hz, 1H), 1.37 (s, 3H), 0.84 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 151.0, 108.8, 97.1, 81.6, 80.8, 71.7, 65.7, 55.9, 55.1, 52.2, 45.6, 43.9, 25.8(3C), 24.0, 18.1, -2.2, -2.3 ppm. HRMS (ESI) (*m/z*): [$\text{M}+\text{Na}$] $^+$ calculated for $\text{C}_{19}\text{H}_{36}\text{O}_5\text{SiNa}$: 395.2230, found: 395.2219. IR(cm^{-1}): 3435, 2929, 1462, 1372, 1253, 1151, 1106, 1034, 835, 772. $[\alpha]_{\text{D}}^{20}$: -64.4 (*c* = 1.0; CHCl_3). R_f: (Hex/EtOAc 2/1) 0.12.

To a solution of the diol (1.15 g, 3.09 mmol) in CH_2Cl_2 (61 mL) was added purified *m*CPBA (1.60 g, 9.26 mmol) at rt. After 5 h the mixture was diluted with CH_2Cl_2 (100 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) were added. The organic phase was washed with aq. KOH (1 M, 2 x 30 mL) and brine (30 mL) and dried over MgSO_4 , filtered, and concentrated to yield 1.20 g (quantitative) of the epoxide intermediate as colorless viscous oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.71 (d, J = 6.5 Hz, 1H), 6.69 (d, J = 6.5 Hz, 1H), 4.64-4.56 (m, 1H), 3.94-3.87 (m, 2H), 3.80-3.68 (m, 2H), 3.53 (dd, J_1 = 10.0, J_2 = 12.2 Hz, 1H), 3.38 (s, 3H), 3.04 (d, J = 4.1 Hz, 1H), 2.87 (dd, J_1 = 2.2 Hz, J_2 = 7.9 Hz, 1H), 2.77 (d, J = 8.2 Hz, 1H), 2.74 (d, J = 4.1 Hz, 1H), 2.68 (dd, J_1 = 3.0 Hz, J_2 = 9.8 Hz, 1H), 2.22 (ddd, J_1 = 2.1 Hz, J_2 = 6.3 Hz, J_3 = 12.4 Hz, 1H), 1.92 (dd, J_1 = 11.3, J_2 = 12.0 Hz, 1H), 1.31 (s, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 97.1, 80.7, 80.1, 68.0, 63.7, 62.1, 55.9, 54.6, 48.4, 47.6, 46.8, 40.6, 25.8(3C), 24.4, 18.1, -2.2, -2.4 ppm. HRMS (EI) (*m/z*): calculated for $\text{C}_{19}\text{H}_{36}\text{O}_6\text{Si}$ [M]: 388.2276, found: 388.2263. IR(cm^{-1}): 3470, 2928, 2855, 1254, 1152, 1103, 1036, 979, 832, 773. $[\alpha]_{\text{D}}^{20}$ -19.7 (*c* = 1.0; CHCl_3). R_f: (Hex/EtOAc 2/1) 0.14.

At 0 °C, PPTS (71 mg, 0.28 mmol) was added to a solution of the diol (2.20 g, 5.66 mmol) and 2,2-dimethoxypropane (6.96 mL, 56.6 mmol) in acetone (57 mL). After 10 min at 0 °C the reaction was warmed to rt and stirring was continued for 30 min. Standard work up gave acetone **5** 2.18 g (90%)

as colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.67 (d, J = 6.4 Hz, 1H), 4.59 (d, J = 6.3 Hz, 1H), 4.57-4.49 (m, 1H), 4.34 (d, J = 12.1 Hz, 1H), 4.00 (dd, J_1 = 2.0, J_2 = 11.7 Hz, 1H), 3.86 (dd, J_1 = 2.0, J_2 = 11.3 Hz, 1H), 3.83 (d, J = 11.9 Hz, 1H), 3.36 (s, 3H), 3.14 (d, J = 5.2, 1H), 3.01 (d, J = 5.2 Hz, 1H), 2.77 (dd, J_1 = 2.1 Hz, J_2 = 8.2 Hz, 1H), 2.49 (t, J = 8.0 Hz, 1H), 2.16 (ddd, J_1 = 2.1 Hz, J_2 = 6.0 Hz, J_3 = 12.6 Hz, 1H), 1.81 (d, J = 12.0 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 0.81 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 97.4, 96.6, 80.7, 79.4, 66.5, 65.2, 63.7, 55.5, 54.8, 47.5, 47.3, 41.3, 40.7, 27.2, 25.8(3C), 24.4, 20.4, 18.0, -2.2, -2.3 ppm. HRMS (ESI) (*m/z*): calculated for $\text{C}_{22}\text{H}_{40}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 451.2492, found: 451.2500. IR(cm^{-1}): 2933, 2856, 1467, 1371, 1256, 1152, 1080, 1045, 834, 774. $[\alpha]_{\text{D}}^{25}$ -59.7 (*c* = 0.3; CHCl_3). R_f: (Hex/EtOAc 2/1) 0.36.

(1R,2S,4S,5S,7S)-2-[[tert-butyl(dimethyl)silyl]oxy]-4-(methoxymethoxy)-2,2',2'-trimethyl-7-(prop-2-yn-1-yl)spiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (13): To a solution of crude epoxide **5** (595 mg, 1.39 mmol) in DMSO (13.9 mL) was added lithium acetylide ethylenediamine complex (1.02 g, 11.1 mmol) in one portion at rt. Next, the mixture was warmed to 50 °C and stirred for 1 h. Standard work up yielded 630 mg (quantitative) of crude and pure tertiary alcohol **13** as light brown viscous oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.60 (d, J = 6.3 Hz, 1H), 4.54 (d, J = 6.4 Hz, 1H), 4.45-4.37 (m, 1H), 4.30 (d, J = 13.1 Hz, 1H), 4.24 (dd, J_1 = 2.7, J_2 = 11.6 Hz, 1H), 3.98 (dd, J_1 = 2.8, J_2 = 11.1 Hz, 1H), 3.68 (d, J = 11.6 Hz, 1H), 3.34 (s, 3H), 3.14 (dd, J_1 = 2.7, J_2 = 17.2 Hz, 1H), 2.88 (br s, 1H), 2.81 (dd, J_1 = 2.7, J_2 = 17.5 Hz, 1H), 2.52 (dd, J_1 = 1.7 Hz, J_2 = 8.6 Hz, 1H), 2.32 (t, J = 8.2 Hz, 1H), 2.12 (ddd, J_1 = 1.9 Hz, J_2 = 6.7 Hz, J_3 = 12.3 Hz, 1H), 2.13 (t, J = 2.5 Hz, 1H), 1.66 (dd, J_1 = 11.1 Hz, J_2 = 12.6 Hz, 1H), 1.56 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 0.81 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 98.1, 96.7, 81.6, 81.4, 80.1, 75.8, 72.4, 66.5, 63.4, 58.5, 55.5, 47.9, 43.3, 39.9, 28.8, 25.8(3C), 25.7, 24.6, 19.1, 18.1, -2.1, -2.9 ppm. HRMS (ESI) (*m/z*): calculated for $\text{C}_{24}\text{H}_{42}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 477.2648, found: 477.2643. IR(cm^{-1}): 3464, 2928, 2855, 1200, 1151, 1107, 1073, 1042, 834, 773. $[\alpha]_{\text{D}}^{20}$ -31.3 (*c* = 1.0; CHCl_3). R_f: (Hex/EtOAc 4/1) 0.20.

(1S,2S,4S,5R,6S)-4-[[tert-butyl(dimethyl)silyl]oxy]-6-[(2Z)-3-[dimethyl(phenyl)silyl]-2-(trimethylstannanyl)prop-2-en-1-yl]-7,7-bis(hydroxymethyl)-2-(methoxymethoxy)-4-methylbicyclo[3.2.0]heptan-6-ol (15): To a solution of acetone **13** (120 mg, 0.25 mmol) in MeOH (2.6 mL) was added CSA (6.1 mg, 0.03 mmol) at 0 °C. After 1 h tlc analysis showed an almost completed reaction. Standard work up was followed by column chromatography of the residue (SiO_2 , EtOAc/Hex 2/1 to 1/1) furnishing the diol intermediate 102 mg (93%) as amorphous white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.66 (s, 1H), 4.66 (s, 1H), 4.55-4.47 (m, 1H), 4.06-3.86 (m, 4H), 3.75 (dd, J_1 = 4.6 Hz, J_2 = 9.9 Hz, 1H), 3.51 (br s, 1H), 3.36 (s, 3H), 2.84 (br s, 1H), 2.75-2.55 (m, 4H), 2.21 (dd, J_1 = 1.8 Hz, J_2 = 6.7 Hz, J_3 = 12.6 Hz, 1H), 2.16 (t, J = 2.6 Hz, 1H), 1.78 (dd, J_1 = 11.5 Hz, J_2 = 12.3 Hz, 1H), 1.45 (s, 3H), 0.82 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 97.1, 81.2, 80.6, 80.5, 76.2, 73.2, 66.5, 60.7, 59.3, 55.9, 50.6, 47.4, 39.7, 25.8(3C), 25.5, 24.8, 18.1, -2.2, -2.3 ppm. HRMS (ESI) (*m/z*): calculated for $\text{C}_{21}\text{H}_{38}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 437.2335, found: 437.2322. IR(cm^{-1}): 3413, 2952, 2856, 1254, 1157, 1104, 1037, 976, 836, 774. $[\alpha]_{\text{D}}^{25}$ +4.0 (*c* = 0.7; CHCl_3). R_f: (Hex/EtOAc 2/1) 0.19.

To a solution of the alkyne diol (27 mg, 0.07 mmol) in THF (0.2 mL) was added trimethylstannyltrimethylphenyl silane (29 μL , 0.07 mmol) followed by Pd(PPh₃)₄ (4 mg, 0.01 mmol). This mixture was stirred at 70 °C for 45 min. The crude reaction mixture was concentrated and directly applied onto a column chromatography (SiO_2 , Hex/EtOAc 5/1 to 2/1) to afford 23 mg (50%) of the desired diol **15** as a single regio- and stereoisomer. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.54-7.50 (m, 2H), 7.36-7.31 (m, 3H), 6.77 (s, 1H), 4.67 (s, 2H), 4.57-4.48 (m, 1H), 4.02-3.84 (m, 5H), 3.64 (dd, J_1 = 3.9 Hz, J_2 = 17.0 Hz, 1H), 3.37 (s, 3H), 2.97 (dd, J_1 = 1.6 Hz, J_2 = 14.1 Hz, 1H), 2.71 (d, J = 14.3 Hz, 1H), 2.69 (t, J = 8.6 Hz, 1H), 2.59 (t, J = 5.4 Hz, 1H), 2.48 (dd, J_1 = 1.7 Hz, J_2 = 8.8 Hz, 1H), 2.20 (ddd, J_1 = 1.6 Hz, J_2 = 6.3 Hz, J_3 = 12.3 Hz, 1H), 1.89 (dd, J_1 = 11.3 Hz, J_2 = 11.6 Hz, 1H), 1.49 (s, 3H), 0.83 (s, 9H), 0.38 (s, 3H), 0.37 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.01 (s, 9H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 166.8, 146.4, 139.1, 134.3(2C), 129.2, 128.0(2C), 97.0, 81.6, 80.7, 79.8, 66.9, 62.5, 61.6, 55.9, 52.7, 49.3, 47.5, 39.6, 25.9, 25.8(3C), 18.1, -0.6, -0.7, -2.1, -2.3, -4.9(3C) ppm. HRMS (ESI) (*m/z*): calculated for $\text{C}_{32}\text{H}_{58}\text{O}_6\text{Si}_2\text{SnNa}$ [$\text{M}+\text{Na}$] $^+$: 737.2692, found: 737.2693. IR(cm^{-1}): 3390, 2953, 2856, 1253, 1157, 1110, 1036, 836, 731, 702. $[\alpha]_{\text{D}}^{23}$ -15.0 (*c* = 0.6; CHCl_3). R_f: (Hex/EtOAc 3/1) 0.23.

2-[(1S,2S,3S,5S)-3-[[tert-butyl(dimethyl)silyl]oxy]-2-[(3Z)-4-[dimethyl(phenyl)silyl]-3-(trimethylstannanyl)but-3-en-1-yl]-5-(methoxymethoxy)-3-methylcyclopentyl]prop-2-enal (17): To a solution

of oxalyl chloride (9 μ L, 0.11 mmol) in CH_2Cl_2 (0.6 mL) at -78°C was added DMSO (14 μ L, 0.20 mmol). The solution was stirred 20 min at -78°C then alcohol **15** (12 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) was slowly added to the reaction mixture. The solution was stirred at -78°C for 1 h. Et_3N (46 μ L, 0.33 mmol) was introduced and stirring was continued at -78°C for 1 h, then the reaction was warmed to -40°C within 2 h. Standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 3/1) furnishing 12 mg (quantitative) of aldehyde **17** as amorphous white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 9.37 (s, 1H), 7.51-7.47 (m, 2H), 7.35-7.32 (m, 3H), 6.47 (t, J = 0.8 Hz, 1H), 6.41 (t, J = 0.9 Hz, 1H), 6.06 (d, J = 0.9 Hz, 1H), 4.51 (d, J = 6.4 Hz, 1H), 4.46-4.40 (m, 2H), 3.97 (dt, J_1 = 0.7 Hz, J_2 = 8.3 Hz, 1H), 3.46 (dd, J_1 = 1.1 Hz, J_2 = 16.2 Hz, 1H), 3.29 (s, 3H), 3.30 (dd, J_1 = 1.3 Hz, J_2 = 16.3 Hz, 1H), 3.24 (dd, J_1 = 0.9 Hz, J_2 = 8.3 Hz, 1H), 2.28 (ddd, J_1 = 1.1 Hz, J_2 = 7.1 Hz, J_3 = 13.5 Hz, 1H), 2.19 (dd, J_1 = 6.9 Hz, J_2 = 13.2 Hz, 1H), 1.33 (s, 3H), 0.89 (s, 9H), 0.36 (s, 3H), 0.36 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.06 (s, 9H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 209.4, 194.9, 160.5, 146.8, 145.8, 139.9, 134.1(2C), 129.1, 127.9(2C), 96.3, 82.2, 78.0, 66.7, 64.0, 55.6, 48.8, 40.8, 29.8, 25.9(3C), 25.2, 18.1, 0.8, 0.8, -2.1, -2.1, -6.0(3C) ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{32}\text{H}_{54}\text{O}_5\text{Si}_2\text{SnNa}$ [$\text{M}+\text{Na}$] $^+$: 717.2429, found: 717.2433. IR(cm^{-1}): 2927, 2853, 2358, 1695, 1252, 1150, 1111, 1043, 835, 773. [α] $_{\text{D}}^{20}$ -23.1 (c = 0.33; CHCl_3). R_f: (Hex/EtOAc 10/1) 0.36.

(1S,1aR,2S,3aS,7aR,7bS)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-methyl-1-(prop-2-yn-1-yl)-7a-[[trimethylsilyl]oxy]methyloctahydro-4,6-dioxacyclobuta[cd]azulen-1-ol (18): To a solution of acetone **13** (192 mg, 0.42 mmol) in CH_2Cl_2 was sequentially added 2,6-lutidine (221 μ L, 1.90 mmol) and TMSOTf (229 μ L, mmol) at 0°C . After 1 h standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 10/1) to yield 100 mg (52%) of ether **18** as colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.91 (d, J = 5.3 Hz, 1H), 4.75 (d, J = 5.5 Hz, 1H), 4.63 (q, J = 8.3 Hz, 1H), 4.49 (d, J = 12.8 Hz, 1H), 3.98 (d, J = 12.8 Hz, 1H), 3.96 (dd, J_1 = 2.0, J_2 = 11.0 Hz, 1H), 3.42 (t, J = 11.5 Hz, 1H), 3.31 (dd, J_1 = 2.6, J_2 = 16.4 Hz, 1H), 2.72 (dd, J_1 = 1.9 Hz, J_2 = 11.5 Hz, 1H), 2.62 (dd, J_1 = 1.6 Hz, J_2 = 9.2 Hz, 1H), 2.58 (dd, J_1 = 2.7 Hz, J_2 = 16.3 Hz, 1H), 2.38 (t, J = 8.9 Hz, 1H), 2.20 (dd, J_1 = 8.9 Hz, J_2 = 13.4 Hz, 1H), 2.08 (ddd, J_1 = 1.5 Hz, J_2 = 7.5 Hz, J_3 = 13.3 Hz, 1H), 2.04 (t, J = 2.4 Hz, 1H), 1.48 (s, 3H), 0.81 (s, 9H), 0.25 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 93.5, 83.7, 81.5, 81.3, 80.3, 71.5, 68.0, 66.2, 59.3, 54.3, 46.4, 41.9, 25.7(3C), 25.5, 25.1, 18.0, 2.1(3C), -2.1, -2.2 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{23}\text{H}_{42}\text{O}_5\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 477.2468, found: 477.2473. IR(cm^{-1}): 2953, 2928, 2854, 1253, 1168, 1102, 1073, 1014, 838, 773. [α] $_{\text{D}}^{20}$ -7.0 (c = 0.5; CHCl_3). R_f: (Hex/EtOAc 4/1) 0.57.

(1R,2S,4S,5S,7R)-2-[[tert-butyl(dimethyl)silyl]oxy]-4-(methoxymethoxy)-2,2',2'-trimethyl-7-(prop-1-yn-1-yl)spiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (19): To a solution of terminal alkyne **13** (200 mg, 0.44 mmol) in DMSO (4.4 mL) was added *t*BuOK (25 mg, 0.22 mmol) in one portion. The mixture was stirred at rt for 5 h. Standard work up was followed by column chromatography of the residue to yield 128 mg (64% from **12**) of internal alkyne **19** as crystalline light yellow solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 4.58 (d, J = 6.3 Hz, 1H), 6.54 (d, J = 6.3 Hz, 1H), 4.47-4.39 (m, 1H), 4.31 (dd, J_1 = 2.4 Hz, J_2 = 12.4 Hz, 1H), 4.14 (dd, J_1 = 2.4 Hz, J_2 = 11.5 Hz, 1H), 4.11 (d, J = 12.7 Hz, 1H), 3.79 (d, J = 11.9 Hz, 1H), 3.34 (s, 3H), 3.18 (br s, 1H), 2.45 (dd, J_1 = 2.0 Hz, J_2 = 8.2 Hz, 1H), 2.28 (dd, J_1 = 11.1 Hz, J_2 = 12.4 Hz, 1H), 2.22 (t, J = 8.6 Hz, 1H), 1.98 (ddd, J_1 = 1.8 Hz, J_2 = 6.8 Hz, J_3 = 12.5 Hz, 1H), 1.93 (s, 3H), 1.61 (s, 3H), 1.46 (s, 3H), 1.37 (s, 6H), 0.81 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 98.1, 96.7, 86.1, 81.8, 80.3, 79.0, 72.6, 66.5, 64.8, 58.0, 55.6, 46.1, 44.0, 39.3, 29.1, 26.0(3C), 22.6, 19.1, 18.2, 4.1, -2.0, -2.1 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{24}\text{H}_{42}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 477.2648, found: 477.2637. IR(cm^{-1}): 3448, 2928, 2855, 1372, 1257, 1151, 1078, 1044, 835, 773. mp: 124-125 $^\circ\text{C}$. [α] $_{\text{D}}^{22}$ -45.9 (c = 1.2; CHCl_3). R_f: (Hex/EtOAc 4/1) 0.13. X-ray: see ref^[17]

(1R,2S,4S,5S,7R)-2-[[tert-butyl(dimethyl)silyl]oxy]-7-[(1Z)-2-iodoprop-1-en-1-yl]-4-(methoxymethoxy)-2,2',2'-trimethylspiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (21): A solution of alkyne **19** (2.15 g, 4.73 mmol) dissolved in THF (20 mL) was added to a suspension of MeONa (1.12 g, 20.8 mmol) in LiAlH_4 (0.15 M in THF, 69.3 mL, 10.4 mmol) at -20°C . The mixture was slowly warmed to rt and stirred for 36 h. The solution was cooled to 0°C and EtOAc (924 μ L, 9.46 mmol) was added. After 10 min the solution was further cooled to -21°C and treated with a solution of I_2 (3.59 g, 14.2 mmol) in THF (12 mL). The reaction was stirred at this temperature for 30 min and warmed to 0°C within 1 h. Standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 10/1) furnishing 1.78 g (65%) of vinyl iodide **21** as viscous colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.49 (s, 1H), 4.59 (d, J = 6.5 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H),

4.46-4.38 (m, 1H), 4.23 (dd, J_1 = 2.9 Hz, J_2 = 11.1 Hz, 1H), 4.20 (d, J = 13.0 Hz, 1H), 4.07 (dd, J_1 = 2.8 Hz, J_2 = 13.1 Hz, 1H), 3.71 (d, J = 11.5 Hz, 1H), 3.35 (s, 3H), 2.83 (br s, 1H), 2.66 (d, J = 0.9 Hz, 3H), 2.62 (dd, J_1 = 1.8 Hz, J_2 = 8.6 Hz, 1H), 2.32 (t, J = 8.3 Hz, 1H), 2.10 (ddd, J_1 = 1.8 Hz, J_2 = 6.9 Hz, J_3 = 12.9 Hz, 1H), 1.65 (dd, J_1 = 10.6 Hz, J_2 = 12.8 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 0.81 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 124.5, 98.2, 96.8, 96.7, 81.6, 80.3, 76.2, 67.0, 63.7, 59.3, 55.6, 47.9, 45.3, 39.8, 37.3, 29.2, 25.8(3C), 23.8, 19.0, 18.1, -2.1, -2.3 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{24}\text{H}_{43}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 605.1771, found: 605.1751. IR(cm^{-1}): 2929, 2856, 1255, 1200, 1152, 1098, 1072, 1045, 835, 774. [α] $_{\text{D}}^{22}$ -25.1 (c = 0.45; CHCl_3). R_f: (Hex/EtOAc 3/1) 0.37.

(1R,2S,4S,5S,7S)-2-[[tert-butyl(dimethyl)silyl]oxy]-7-[(1Z)-3-((2S,3R,4R,5R)-3-ethenyl-5-methoxy-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-3-hydroxy-2-methylprop-1-en-1-yl]-4-(methoxymethoxy)-2,2',2'-trimethylspiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (22a/22b): A mixture of vinyl iodide **21** (50 mg, 85.8 μ mol) and aldehyde **6** (49 mg, 172 μ mol) was dried by azeotropic distillation in benzene. The dried starting materials were dissolved in degassed DMSO (1.8 mL) and CrCl_2 (74 mg, 601 μ mol) and NiCl_2 (33 mg, 257 μ mol) were sequentially added at rt. The resulting mixture was stirred at rt for 20 h. Standard work up was followed by column chromatography of the residue (SiO_2 , Hex/EtOAc 8/1) giving 12 mg (19%) of **22b** as minor diastereoisomer, 10 mg (25%) of **23**, and 29 mg (45%) of **22a** as major diastereoisomer.

Major diastereoisomer **22a**: (2D NMR analysis: see supporting information) $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 5.94 (ddd, J_1 = 9.0 Hz, J_2 = 10.0 Hz, J_3 = 17.3 Hz, 1H), 5.91 (br s, 1H), 5.28 (dd, J_1 = 1.7 Hz, J_2 = 17.4 Hz, 1H), 5.20-5.15 (m, 2H), 4.65 (s, 1H), 4.65 (d, J = 6.3 Hz, 1H), 4.56 (d, J = 6.5 Hz, 1H), 4.54-4.50 (m, 1H), 4.25 (d, J = 7.8 Hz, 1H), 4.21 (s, 1H), 4.20 (dd, J_1 = 1.7 Hz, J_2 = 15.6 Hz, 1H), 4.10 (d, J = 12.5 Hz, 1H), 4.07 (d, J = 4.4 Hz, 1H), 4.06 (s, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.43 (s, 3H), 3.35 (s, 3H), 2.91 (dt, J_1 = 4.3 Hz, J_2 = 9.1 Hz, 1H), 2.62 (dd, J_1 = 1.9 Hz, J_2 = 8.7 Hz, 1H), 2.38 (d, J = 8.4 Hz, 1H), 2.29 (d, J = 2.5 Hz, 1H), 2.06 (ddd, J_1 = 2.2 Hz, J_2 = 7.0 Hz, J_3 = 13.0 Hz, 1H), 1.84 (d, J = 1.1 Hz, 3H), 1.77 (dd, J_1 = 11.1 Hz, J_2 = 13.2 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.81 (s, 9H), 0.59 (q, J = 8.0 Hz, 6H), 0.06 (s, 3H), 0.06 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 137.9, 135.3, 128.1, 118.6, 110.8, 97.8, 96.6, 83.3, 81.8, 80.3, 80.2, 76.7, 74.0, 67.0, 63.6, 60.3, 56.5, 55.5, 50.2, 48.0, 45.7, 39.7, 26.7, 25.9(3C), 23.3, 21.2, 20.3, 18.1, 6.9(3C), 4.9(3C), -2.1, -2.2 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{38}\text{H}_{70}\text{O}_{10}\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 765.4405, found: 765.4427. IR(cm^{-1}): 3452, 2953, 2358, 1372, 1256, 1199, 1077, 1044, 1002, 835. [α] $_{\text{D}}^{20}$ -31.2 (c = 0.25; CHCl_3). R_f: (Hex/EtOAc 5/1) 0.16.

Minor diastereoisomer **22b** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.11 (d, J = 11.4 Hz, 1H), 5.93 (br s, 1H), 5.79 (ddd, J_1 = 9.2 Hz, J_2 = 10.1 Hz, J_3 = 17.4 Hz, 1H), 5.37 (s, 1H), 5.28 (dd, J_1 = 1.9 Hz, J_2 = 17.3 Hz, 1H), 5.19 (dd, J_1 = 2.1 Hz, J_2 = 10.3 Hz, 1H), 4.67 (s, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 6.4 Hz, 1H), 4.49-4.43 (m, 1H), 4.23-4.17 (m, 2H), 4.15 (d, J = 13.1 Hz, 1H), 4.09 (d, J = 10.7 Hz, 1H), 4.06 (d, J = 4.2 Hz, 1H), 3.84 (d, J = 11.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 3.46 (s, 3H), 3.35 (s, 3H), 3.07 (dt, J_1 = 3.9 Hz, J_2 = 9.6 Hz, 1H), 2.51 (dd, J_1 = 2.1 Hz, J_2 = 8.6 Hz, 1H), 2.25 (dd, J_1 = 8.6 Hz, J_2 = 9.4 Hz, 1H), 2.06 (ddd, J_1 = 2.0 Hz, J_2 = 6.7 Hz, J_3 = 12.7 Hz, 1H), 1.83 (d, J = 1.0 Hz, 3H), 1.71 (dd, J_1 = 10.9 Hz, J_2 = 12.4 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.80 (s, 9H), 0.59 (q, J = 8.0 Hz, 6H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 137.8, 133.3, 126.5, 119.9, 111.0, 97.9, 96.8, 83.3, 81.8, 80.7, 79.3, 76.0, 71.3, 67.2, 64.0, 59.1, 56.9, 55.6, 47.8, 47.4, 45.9, 39.4, 26.3, 25.8(3C), 25.8, 23.8, 19.2, 18.1, 6.8(3C), 4.8(3C), -2.1, -2.3 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{38}\text{H}_{70}\text{O}_{10}\text{Si}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 765.4405, found: 765.4396. IR(cm^{-1}): 3464, 2973, 2339, 1381, 1261, 1190, 1065, 1041, 1023, 834. [α] $_{\text{D}}^{22}$ -30.0 (c = 0.5; CHCl_3). R_f: (Hex/EtOAc 5/1) 0.30.

(1R,2S,4S,5S,7S)-2-[[tert-butyl(dimethyl)silyl]oxy]-4-(methoxymethoxy)-2,2',2'-trimethyl-7-[(1E)-prop-1-en-1-yl]spiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (23): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 6.11 (dq, J_1 = 1.4 Hz, J_2 = 15.3 Hz, 1H), 5.87 (dq, J_1 = 6.6 Hz, J_2 = 15.0 Hz, 1H), 4.60 (d, J = 6.4 Hz, 1H), 4.56 (d, J = 6.3 Hz, 1H), 4.50-4.42 (m, 1H), 4.24 (dt, J_1 = 1.1 Hz, J_2 = 11.5 Hz, 1H), 4.12-4.10 (m, 2H), 3.73 (d, J = 11.3 Hz, 1H), 3.35 (s, 3H), 2.76 (s, 1H), 2.50 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 2.29 (t, J = 8.6 Hz, 1H), 2.10 (ddd, J_1 = 1.9 Hz, J_2 = 6.9 Hz, J_3 = 12.8 Hz, 1H), 1.83-1.75 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H), 0.81 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 131.5, 124.4, 98.0, 96.7, 81.8, 80.6, 67.6, 64.1, 59.1, 55.6, 48.0, 44.9, 39.3, 29.8, 28.9, 25.8(3C), 23.9, 18.9, 18.2, 18.1, -2.1, -2.2 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{24}\text{H}_{44}\text{O}_6\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 479.2805, found: 479.2796. IR(cm^{-1}): 2930, 2856, 1372, 1255, 119, 1106, 1073, 1043, 835, 773. [α] $_{\text{D}}^{21}$ -39.1 (c = 0.5; CHCl_3). R_f: (Hex/EtOAc 5/1) 0.22.

(1'*R*,2'*S*,4'*S*,5'*S*,5'*S*,7'*S*)-2'-[*tert*-butyl(dimethyl)silyl]oxy]-5''-
{(2*S*,3*R*,4*R*,5*R*)-3-ethenyl-5-methoxy-4-
[(triethylsilyl)oxy]tetrahydrofuran-2-yl)-4'-(methoxymethoxy)-
2,2,2',4''-tetramethyl-5''*H*-dispiro[1,3-dioxane-5,6'-

bicyclo[3.2.0]heptane-7',2''-furan]-5''-ol (2): To a solution of oxalylchloride (2.5 μ L, 30 μ mol) in CH_2Cl_2 (0.3 mL) at -78°C was added DMSO (4.2 μ L, 59 μ mol). The solution was stirred at -78°C for 20 min. Alcohol **22** (11 mg, 15 μ mol) in CH_2Cl_2 (0.3 mL) was slowly added to the reaction mixture. The solution was stirred at -78°C for 1 h. Et_3N (12 μ L, 89 μ mol) was added to the mixture and stirring was continued at -78°C for 15 min and warmed to -60°C . Standard work up furnish the crude ketone (Hex/EtOAc 5/1 R_f = 0.20). After 24 h in the fridge (4°C) the residue no longer contained the former product. Purification by column chromatography (SiO_2 , Hex/EtOAc 5/1) delivered 5 mg (47%) of half acetal **2** as a 5/1 anomeric mixture. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 5.85 (ddd, J_1 = 9.2 Hz, J_2 = 10.3 Hz, J_3 = 19.6 Hz, 1H), 5.83 (br s, 1H), 5.12-5.04 (m, 2H), 4.74 (s, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.60 (s, 1H), 4.57 (d, J = 6.5 Hz, 1H), 4.49-4.43 (m, 1H), 4.31 (d, J = 12.8 Hz, 1H), 4.26 (dd, J_1 = 1.8 Hz, J_2 = 11.6 Hz, 1H), 4.21 (d, J = 9.0 Hz, 1H), 4.03 (d, J = 4.61 Hz, 1H), 3.88 (J_1 = 1.6 Hz, J_2 = 12.5 Hz, 1H), 3.67 (d, J = 11.5 Hz, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 2.89 (dt, J_1 = 4.4 Hz, J_2 = 9.1 Hz, 1H), 2.76 (dd, J_1 = 1.9 Hz, J_2 = 8.5 Hz, 1H), 2.31 (d, J = 8.1 Hz, 1H), 2.11 (ddd, J_1 = 2.2 Hz, J_2 = 6.5 Hz, J_3 = 12.5 Hz, 1H), 1.80 (d, J = 1.2 Hz, 3H), 1.72 (t, J = 12.0 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 0.95 (t, J = 7.4 Hz, 9H), 0.82 (s, 9H), 0.60 (q, J = 7.9 Hz, 6H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 140.5, 135.9, 124.6, 117.6, 108.9, 108.6, 98.0, 96.8, 90.0, 85.3, 80.5, 80.5, 80.3, 66.0, 63.2, 58.4, 55.5, 54.3, 47.8, 47.5, 45.5, 39.3, 25.9, 25.9(3C), 24.8, 20.6, 18.1, 13.0, 6.9(3C), 4.9(3C), -2.3, -2.6 ppm. HRMS (ESI) (m/z): calculated for $\text{C}_{38}\text{H}_{68}\text{O}_{10}\text{Si}_2\text{Na}$ [$M+\text{Na}$] $^+$: 763.4249, found: 763.4247. IR(cm^{-1}): 3469, 2927, 1409, 1256, 1205, 1111, 1046, 1001, 834, 773. [α] $_{\text{D}}^{22}$ +22.4 (c = 0.25; CHCl_3). R_f : (Hex/EtOAc 5/1) 0.11.

Supporting Information (see footnote on the first page of this article):

Copies of ^1H NMR and ^{13}C NMR spectra of all products as well as COSY, HMBC, HSQC and NOESY spectra of **22a**.

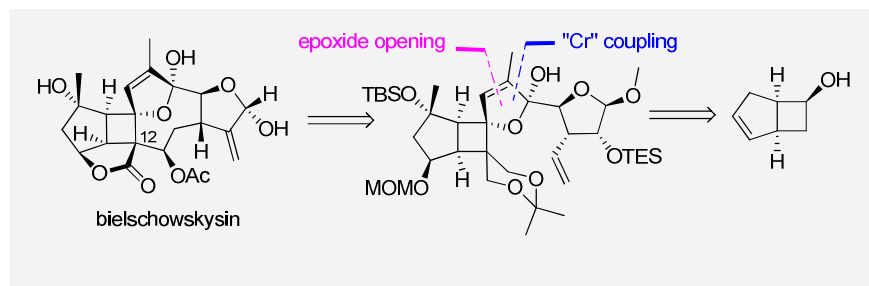
Acknowledgments

Financial support from the University of Vienna (doctoral program, Initiativkolleg Functional Molecules IK I041-N) and from the Austrian Science Fund (FWF) (Project P22180) is gratefully acknowledged. We thank H.P. Kählig, L. Brecker, and S. Felsinger for NMR assistance, M. Drescher for experimental work and A. Roller and V. Arion (all University of Vienna) for X-ray analysis.

- [1] J. Marrero, A. D. Rodriguez, P. Baran, R. G. Raptis, J. A. Sanchez, E. Ortega-Barria, T. L. Capson, *Org. Lett.* **2004**, 6, 1661–1664.
- [2] Y. Li, G. Pattenden, J. Rogers, *Tetrahedron Lett.*, **2010**, 51, 1280-1283.
- [3] B. Doroh, G. A. Sulikowski, *Org. Lett.* **2006**, 8, 903-906.

- [4] R. Miao, S. G. Gramani, M. J. Lear, *Tetrahedron Lett.* **2009**, 50, 1731-1733.
- [5] K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Angew. Chem. Int. Ed.*, **2011**, 50, 5149-5152
- [6] A. Jana, S. Mondal, Md. F. Hossain, S. Ghosh, *Tetrahedron Lett.* **2012**, 53, 6830-6833.
- [7] M. E. Meyer, J. H. Phillips, E. M. Ferreira, B. M. Stoltz, *Tetrahedron* **2013**, 69, 7627-7635.
- [8] A. P. G. Macabeo, C. W. Lehmann, O. Reiser, *Synlett* **2012**, 23, 2909–2912.
- [9] A. Saitman, S. D. E. Sullivan, E. A. Theodorakis, *Tetrahedron Lett.* **2013** 12, 1612-1615.
- [10] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Org. Lett.* **2012**, 14, 2195-2197.
- [11] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Eur. J. Org. Chem.* **2013**, 20, 4379-4398.
- [12] M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *Org. Lett.* **2013**, 12, 3098-3101; M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *Eur. J. Org. Chem.* **2013**, submitted (preceding paper).
- [13] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, 35, 5449-5452.
- [14] D. A. Evans, G. C. Andrew, *Acc. Chem. Res.* **1974**, 7, 147-155 and references cited therein.
- [15] K. Takai, S. Sakamoto, T. Isshiki, *Org. Lett.* **2003**, 5, 653–655.
- [16] K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, 110, 3741–3766.
- [17] N. A. Powell, W. R. Roush, *Org. Lett.* **2001**, 3, 453–456.
- [18] S. Takano, Y. Sekiguchi, N. Sato, K. Ogasawara, *Synthesis* **1987**, 2, 139-141.
- [19] CCDC-943957 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] E. J. Corey, J. A. Katzenellenbogen, G. A. Posner, *J. Am. Chem. Soc.* **1967**, 89, 4245–4247.
- [21] H. Jin, J.-I. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, 108, 5644-5646.
- [22] K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, 108, 6048-6050.
- [23] B. M. Trost, H. C. Arndt, P. E. Strege, T. R. Verhoeven, *Tetrahedron Lett.* **1976**, 39, 3477-3478 and references therein.

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Published online: ((will be filled in by the editorial staff))



An approach to the northern part of the complex diterpenoid bielschowskysin is described. Formation of the dihydrofuran ring moiety was achieved by stereoselective epoxidation, followed

by alkyne opening and stereoselective formation of a vinyl halide suitable for a chromium mediated coupling. A final oxidation step furnished the hemiacetal.

Jean-Baptiste Farcet, Martin Himmelbauer, Johann Mulzer*.....
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An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photochemical Strategy

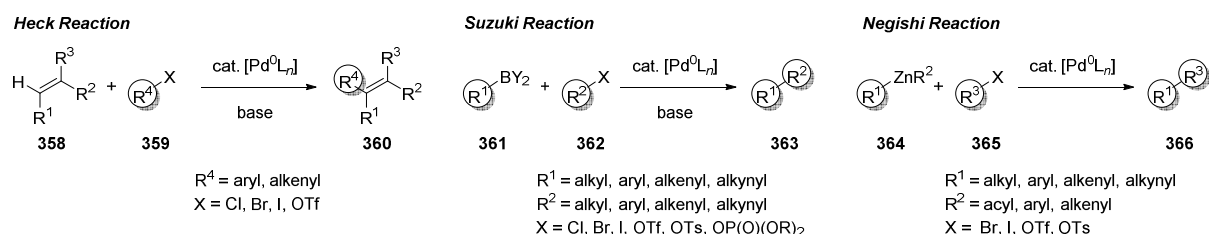
Keywords: Total synthesis / Natural products / Terpenoids / Chromium / Hydroalumination

8. On the Carbo-Oxygenation

8.1. General Introduction¹¹⁶

Carbon-carbon bond formation is one of the most important and challenging transformation in organic chemistry. Ample methods to forge carbons have been developed including the well studied and frequently used classic examples like the Diels-Alder reaction,¹¹⁷ the aldol reaction¹¹⁸ and all sorts of olefinations like the Wittig reaction¹¹⁹ in all its variations. Moreover, the use of organo metal reagents for alkylation from Grignard reagents to zinc-organyls is undoubtedly a must-have in the tool box of every organic chemist. The fields of application of these reactions are numerous and their use in organic chemistry and natural product synthesis are of utmost importance.

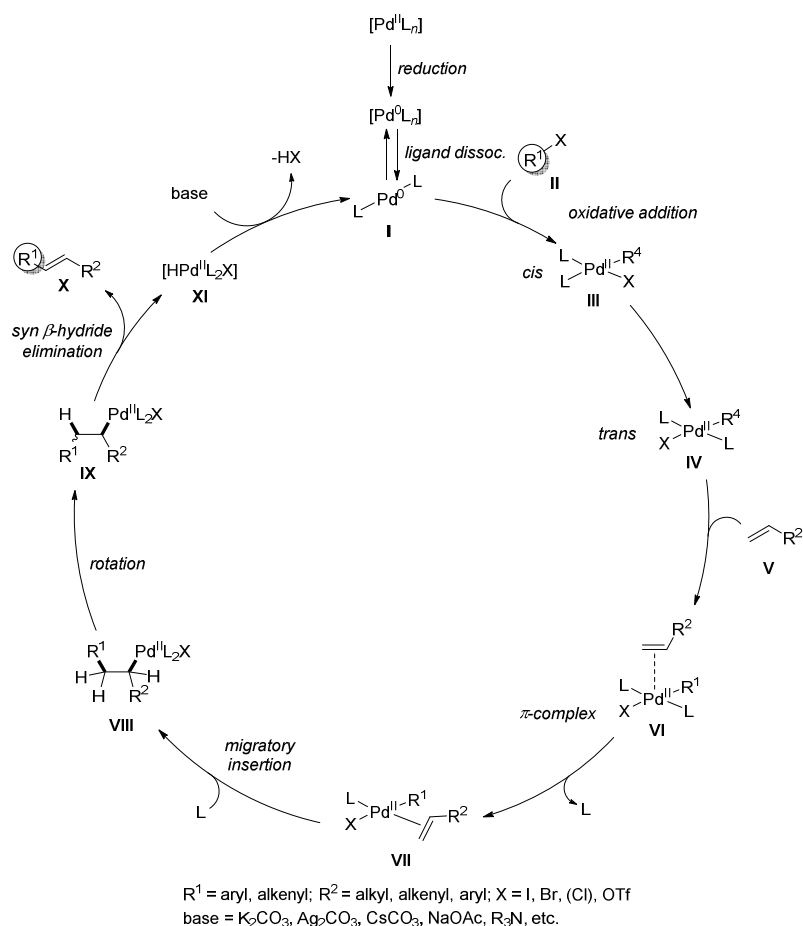
A new paradigm of carbon-carbon bond formation has emerged in the last quarter of the 20th century by the use of transition metals. The development of tungsten and ruthenium based metathesis¹²⁰ on one hand and the manifold of palladium catalyzed reactions are undoubtedly most astonishing and useful. Not surprisingly, these fields of research have been honored with two Nobel prizes in Chemistry during the last 10 years. Schrock, Chauvin and Grubbs received this honor for their work on transition metal based metathesis reactions in 2005.¹²¹ Five years later, on the development of C-C bond formation under palladium catalysis, Suzuki, Negishi and Heck were awarded the Nobel Prize in Chemistry in 2010, which was only a question of time considering the immense impact their research has had on the field of synthetic chemistry.



Scheme 47 Nobel Prize Winning Palladium-Catalyzed C-C Bond Forming Reactions

8.2. The Heck Reaction

The coupling of alkenyl or aryl halides (sp² hybridized) and triflates (359) with alkenes (358) by palladium catalysis are generally referred to as Heck reaction (Scheme 47).¹¹⁶ From today's point of view, first examples of this reaction have been independently published by Mizoroki (1971)¹²² and Heck (1972).¹²³ Till now various variations, including stereoselective, inter- and intramolecular examples have found acceptance and application by the broader scientific community.^{124,125} Cascade reactions, formations of quaternary carbon centers¹²⁶ as well as carbonylation reactions¹²⁷ are just a few indispensable examples for the further development of the general reaction.



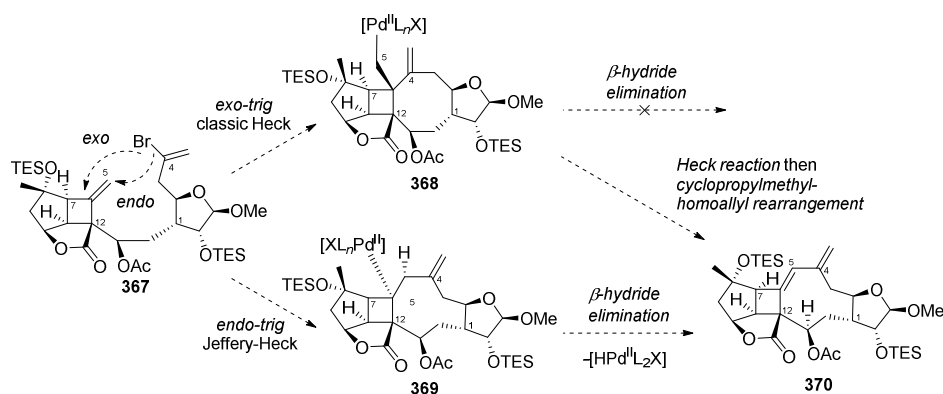
Scheme 48 General Mechanism for the Heck Reaction

Mechanistically, the Heck reaction is said to proceed via three related catalytic cycles determined by the formal charge of the first formed palladium(II)-alkene complex, namely cationic, neutral or anionic pathway.^{124,125,128} In general 14-electron palladium(0) species **I**, usually derived from neutral $Pd(PPh_3)_4$ by ligand dissociation or from *in situ* reduction of Pd(II)-precatalysts as $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$, is the active catalytic species (Scheme 48). As depicted in the general catalytic cycle in Scheme 48, haloalkenes or haloarenes (**II**) oxidatively add to the active catalyst, generating a *cis*- σ -alkenyl or *cis*- σ -arylpalladium(II) complex **III**. After adoption of the thermodynamically favored *trans*-orientation of the halide and the alkenyl rest (**IV**) the Pd(II) species forms a π -complex (**VI**) with alkene **V**. Presumably, after dissociation of another ligand, the alkene and the alkenyl substituent adopt the crucial *cis*-configuration in η^2 -complex **VII** which is necessary for the migratory insertion in *syn*-manner providing σ -alkylpalladium species **VIII**. Finally, rotation around the newly formed carbon-carbon bond and consecutive *syn* β -hydride elimination liberates desired alkene **X** and closes the catalytic cycle by formation of active catalyst **I** after deprotonation of hydridopalladium complex **XI**.

8.3. Discussion of the Carbo-Oxygenation and its Mechanism

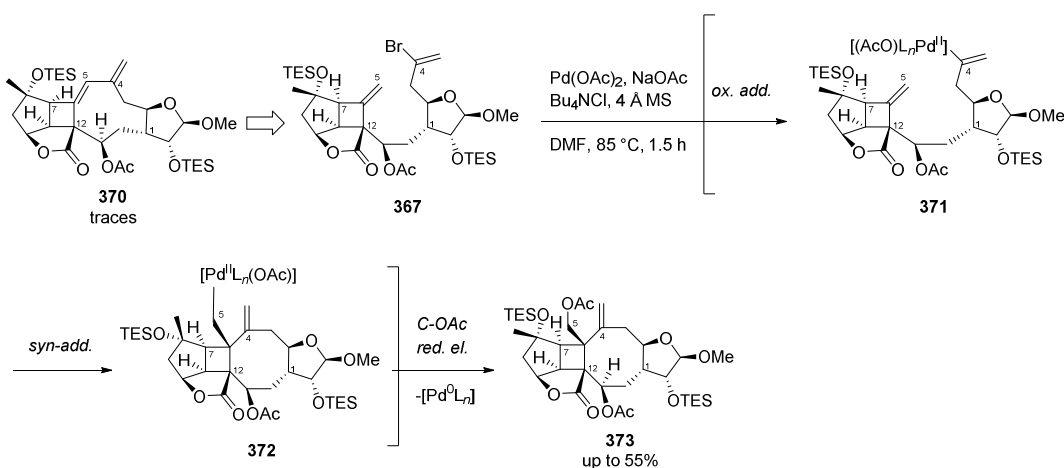
The general mechanism of Scheme 48 also applies for intramolecular Heck reactions, which are said to proceed with an overwhelming preference for the *exo*- over the *endo*-mode cyclization. According to findings by Rigby *et al.*,¹²⁹ it should be possible to invert this preference by applying Heck conditions with reduced coordination sphere on the palladium. Additionally, substrates in which the *exo*-pathway seems to be precluded - for example when no β -hydrides for reductive elimination are available - should preferentially lead to the *endo-trig* cyclization product.

We realized that these findings would ideally apply to the envisaged *endo*-selective Heck macrocyclization of substrate **367** (Scheme 49). An *exo*-selective Heck reaction would lead to σ -alkylpalladium(II) species **368**, which is unable to undergo β -hydride elimination with a newly formed C4-C6 single bond. As described in our publication, cyclopropyl formation via a consecutive Heck-reaction of **368** and cyclopropylmethyl-homoallyl rearrangement could result in formal *endo-trig* cyclization product **370**.¹²⁵ Alternatively, by application of Jeffery's conditions,¹³⁰ *endo*-cyclization to intermediate **369**, which after β -hydride elimination provides macrocycle **370** of desired ring size, should be possible.



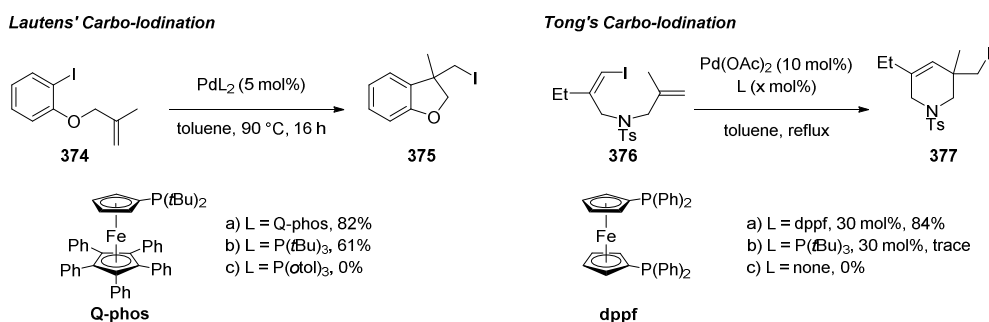
Scheme 49 Consideration of the *endo*-Selective Heck Reaction

Instead of diene **370**, formation of unexpected **373** via a palladium catalyzed carbo-oxygenation was observed.¹¹³ Our initially proposed mechanism, outlined in Scheme 50, was based on findings of Tong¹³¹ and Lautens,¹³² who independently reported palladium catalyzed carbo-halogenations (Scheme 51). We assumed that this unprecedented reaction takes place along a Heck-like path. Oxidative addition of the vinyl halide to a Pd(0) catalyst should give σ -alkenyl palladium(II) species **371**, which proceeds in *syn*-addition to the *exo*-methylene bond along an *exo-trig* reaction trajectory, resulting in σ -alkylpalladium(II) species **372**. Unable to perform β -hydride elimination we suggested a C-OAc reductive elimination – according to the C-I reductive elimination proposed for the literature known carbo-iodination – to form the observed product **373**.



Scheme 50 Initially Proposed Mechanism for the Carbo-Oxygenation

Upon discussion of this reaction mechanism with one of the reviewers of our publication in Organic Letters¹¹³ we reasoned, that the carbo-oxygenation might take place via a different mechanism. In fact, Lautens and Tong only observed the carbo-iodination reaction by the use of exceptionally bulky and electron rich phosphine ligands (Q-phos and dppf), as outlined in Scheme 51.



Scheme 51 Literature Known Carbo-Iodinations

Furthermore, Pd(OAc)₂ was used as precatalyst in the reaction from **376** to **377** and no formation of a similar carbo-oxygenation product was observed or reported. As Jeffery-Heck conditions are ligand-less and not at all bulky, we were prompted to propose another mechanism. Hence, the path starting with acetoxy-palladation of the *exo*-methylene group, followed by *syn*-addition of the resulting σ -alkylpalladium(II) species to the vinyl-bromide and β -bromide elimination (Section 7.2. and 7.3.), was elaborated.¹¹³ If this mechanism is the case, it is quite surprising that all attempts to functionalize the *exo*-methylene double bond on the cyclobutane ring by Pd(II)-catalyzed reactions, similar to the Wacker reaction (Section 7.3.),¹³³ did not result in any related cyclization product. Yet, both proposed mechanisms are speculative and will be investigated along with experiments to generalize this methodology in due course.

9. Conclusion and Outlook

An evolutionary approach towards the total synthesis of bielschowskysin has been described. A variety of different complex building blocks were synthesized along feasible and scalable routes starting from the chiral pool.

Initial attempts to generate the complex carbon skeleton according to a biomimetic transannular [2+2]-photocycloaddition had to be abandoned due to incompatibility of the building blocks. The synthetic strategy was altered in a way, to first form the cyclobutane-moiety with an appropriate appendage and to later close the oxygen-bridged nine membered macrocycle. In this second generation approach, fragment coupling between a western allene-building block and an eastern tetrahydrofuran by aldol addition was effortless. Problems arose when the crucial intramolecular [2+2]-photocycloaddition between a butenolide and an allene was tackled.

By redesign of the eastern fragment and replacement of the phenyl containing protecting groups by trialkylsilyl groups to remove all dispensable chromophores, we hoped to improve the key cycloaddition. As a matter of fact, after fragment coupling the hypothesis was proven, as the [2+2]-photocycloaddition regio- and stereoselectively delivered the desired bicyclo[3.2.0]heptane core with remarkable 67% yield. Unfortunately, the *exo*-methylene appendage at the newly formed cyclobutane ring turned out to be exceptionally sluggish towards functionalization, which should prove troublesome in later macrocyclization attempts. Cutting-edge transition metal catalyzed cyclizations as well as RCM conditions to close the macrocycle in the northern part of the molecule remained unrewarded. Our strategy to first form the spirofused furan ring and to close the macrocycle in the southern part of the molecule seems to be a plausible alternative and will be enhanced in due course.

As initial attempts of a Heck-macrocyclization led to promising results, we hypothesized to improve the outcome of the reaction by reducing the ligand sphere at the palladium catalyst. Thus, Jeffery's conditions were tested, which reproducibly resulted in the unexpected formation of a tricyclo[8.3.0.0^{2,8}]tridecane carbon macrocycle by an unprecedented palladium catalyzed carbo-oxygenation.

Though the ambitious and adventurous goal to complete a total synthesis could not be reached so far, the presented synthetic efforts led to the most advanced intermediates toward bielschowskysin reported so far. Moreover, for the first time serious attempts to form the unprecedented tricyclo[9.3.0.0^{2,10}]tetradecane carbon core of the target molecule with suitable substitution pattern

have been undertaken utilizing various strategies. Observation of a novel palladium catalyzed carbo-oxygenation reaction by application of Jeffery's Heck-reaction conditions led to a pleasant outcome of this thesis.

The venture to access the desired tricyclo[9.3.0.0^{2,10}]tetradecane ring system and to complete the first total synthesis of bielschowskysin (**1**) is still ongoing. Thus, a first reasonable ring enlargement strategy has already been proposed (Section 7.3.) and will be conducted in due course. Furthermore, studies to generalize the observed carbo-oxygenation are pending and will be part of our future research.

10. List of Abbreviations

Ac	acyl
acac	acetylacetone
Ac-CoA	acetyl-coenzyme A
ADD	1,1'-(azodicarbonyl)dipiperidine
ADP	adenosine diphosphate
aq.	aqueous
ATP	adenosine triphosphate
Bu	butyl
CAN	cerium(IV) ammonium nitrate
cat.	catalytic
CoA	coenzyme A
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
cy	cyclohexane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano- <i>para</i> -benzoquinone
DHP	dihydropyranyl
DIBALH	diisobutylaluminium hydride
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DMAPP	dimethylallyl pyrophosphate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMP	Dess-Martin-periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DXP	1-deoxyxylulose-5-phosphate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
FPP	farnesyl pyrophosphate
GGPP	geranylgeranyl pyrophosphate
GI ₅₀	half maximal inhibition of cell proliferation
G3P	glyceraldehyde-3-phosphate
HMPA	hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
<i>i</i>	<i>iso</i>
IBX	2-iodoxybenzoic acid
IC ₅₀	half maximal inhibitory concentration
Im	imidazole
IPP	isopentyl pyrophosphate
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MEP	2C-methyl-D-erythritol-4-phosphate
Mes	mesitylene
M. H.	Martin Himmelbauer

MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
MVA	mevalonic acid
NADPH	dihydronicotinamide adenine dinucleotide phosphate
nbd	norbornadiene (bicyclo[2.2.1]hepta-2,5-dien)
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMPE	pseudoephedrine
<i>p</i>	<i>para</i>
PDC	pyridinium dichromate
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PP	pyrophosphate
Pr	propyl
PPTS	pyridinium <i>para</i> -toluenesulfonate
<i>p</i> TSA	<i>para</i> -toluenesulfonic acid
py	pyridine
Q-phos	1,2,3,4,5-Pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
quant.	quantitative
R	rest
RCM	ring closing metathesis
(<i>R,R</i>)-NMPE	(1 <i>R</i> ,2 <i>R</i>)-(-)-pseudoephedrinepropionamide
rt	room temperature
rearr.	Rearrangement
SEM	2-(Trimethylsilyl)ethoxymethyl
SET	single electron transfer
<i>t</i>	<i>tert</i>
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TBSal	<i>tert</i> -butyl salicimine
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPP	thiamine pyrophosphate
WHO	World Health Organization
Z	benzyloxycarbonyl

11. References

- ¹ Breitmeier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*. Wiley-VCH Verlag GmbH & Co, Weinheim, **2006**.
- ² Ruzicka, L. *Proc. Chem. Soc.* **1959**, 341.
- ³ (a) Bloch, K. *Steroids* **1992**, *57*, 378; (b) Horbach, S.; Sahm, H.; Welle, R. *FEMS Microbiol. Lett.* **1993**, *115*, 135.
- ⁴ Rohmer, M.; Seemann, M.; Horbach, S.; Bringer-Meyer, S.; Sahm, H. *J. Am. Chem. Soc.* **1996**, *118*, 2564.
- ⁵ (a) Tomonobu, T.; Takeshi, S.; Editors-in-Chief: Mander, L.; Liu, H.-W. *Comprehensive Natural Products II: 1.17 – Diterpenes*. Elsevier, Amsterdam, **2010**; (b) Editors-in-Chief: Cane, D. E.; Barton, Sir D. *Comprehensive Natural Product Chemistry. 2. Isoprenoids including carotenoids and steroids*. Elsevier, Amsterdam, **1999**.
- ⁶ Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298 and reference cited herein.
- ⁷ Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269 and reference cited herein.
- ⁸ Rodríguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425.
- ⁹ Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 3937.
- ¹⁰ Paulson, S. E.; Liu, D.-L.; Orzechowska, G. E.; Campos, L. M.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 6403.
- ¹¹ Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *25*, 5901.
- ¹² Li, Y.; Pattenden, G.; Rogers, J. *Tetrahedron Lett.* **2010**, *51*, 1280.
- ¹³ (a) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17; (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781.
- ¹⁴ Sánchez, J. A.; Aguilar, C.; Dorado, D.; Manrique, N. *BMC Evolutionary Biology* **2007**, *7*, 1.
- ¹⁵ (a) Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. J. *Am. Chem. Soc.* **1974**, *96*, 4724; (b) Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. J. *Am. Chem. Soc.* **1975**, *97*, 4973.
- ¹⁶ Corey, E. J.; Wat, E. K. W. *J. Am. Chem. Soc.* **1967**, *89*, 2757.
- ¹⁷ Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
- ¹⁸ Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61.
- ¹⁹ Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165.
- ²⁰ Okude, Y.; Hirano, S.; Hiyama, T.; Kimura, K.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.
- ²¹ Paquette, L. A.; Doherty, A. M.; Rayner, C. M. **1992**, *114*, 3910.
- ²² Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313.
- ²³ Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037.
- ²⁴ (a) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. H. *J. Org. Chem.* **1996**, *61*, 2540; (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
- ²⁵ Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
- ²⁶ Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.
- ²⁷ Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7314.
- ²⁸ (a) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.* **2005**, 1969; (b) Donohoe, T. J.; Kershaw, M. N.; Orr, A. J.; Wheelhouse, K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, A. R. *Tetrahedron* **2008**, *64*, 809; (c) Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, A. R. *Org. Lett.* **2007**, *9*, 953.
- ²⁹ Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.
- ³⁰ Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345.
- ³¹ Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 2619.
- ³² Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.
- ³³ Trost, B. M.; Müller, T. J. J.; Martinez, J. J. *Am. Chem. Soc.* **1995**, *117*, 1888.
- ³⁴ Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
- ³⁵ Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801.
- ³⁶ Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.
- ³⁷ Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, *9*, 633.
- ³⁸ Achmatowicz, O. Jr.; Bukowski, P.; Szechner, B.; Zwierzkowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973.
- ³⁹ Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401.
- ⁴⁰ Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327.
- ⁴¹ Weinstabl, H.; Gaich, T.; Mulzer, J. *Org. Lett.* **2012**, *14*, 2834.

- ⁴² (a) Gaich, T.; Weinstabl, H.; Mulzer, J. *Synlett* **2009**, 1357; (b) Weinstabl, H. *PhD-Thesis* **2011**, University of Vienna, Vienna.
- ⁴³ Rodríguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425.
- ⁴⁴ González, M. A.; Ghosh, S.; Rivas, F.; Fischer, D.; Theodorakis, E. A. *Tetrahedron Lett.* **2004**, *45*, 5039.
- ⁴⁵ Wipf, R.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132.
- ⁴⁶ (a) Yang, Z.; Li, Y.; Pattenden, G. *Tetrahedron*, **2010**, *66*, 6546; (b) Li, Y.; Pattenden, G. *Tetrahedron Lett.* **2011**, *52*, 3315.
- ⁴⁷ Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*, John Wiley Sons Ltd, West Sussex, **2009**.
- ⁴⁸ Hehn, J. P. *Angew. Chem. Int. Ed.*, **2011**, *50*, 1000 and references cited therein.
- ⁴⁹ Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1989**, *54*, 4105.
- ⁵⁰ Cava, M. P.; Stern, P.; Wakisaka, K. *Tetrahedron* **1973**, *29*, 2245.
- ⁵¹ Ninomiya, I.; Takasugi, H.; Naito, T. *J. Chem. Soc. Chem. Commun.* **1973**, 732.
- ⁵² Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072.
- ⁵³ Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017.
- ⁵⁴ Krais, G. A.; Chen, L. *J. Am. Chem. Soc.* **1990**, *112*, 3463.
- ⁵⁵ Piva, O. *J. Org. Chem.* **1995**, *60*, 7879.
- ⁵⁶ Itagaki, N.; Iwabuchi, Y. *Chem. Commun.* **2007**, 1175.
- ⁵⁷ Cotterill, I. C.; Jaouhari, R.; Dorman, G.; Roberts, S. M.; Scheinmann, F.; Wakefield, B. J. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1543.
- ⁵⁸ Molander, G. A.; Jean, D. J. St.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642.
- ⁵⁹ Birch, A. J. *J. Chem. Soc.* **1944**, 430.
- ⁶⁰ Mehta, S.; Subrahmanyam, D. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 395.
- ⁶¹ Fries, K.; Finck, G. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4271.
- ⁶² Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6032.
- ⁶³ Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271.
- ⁶⁴ Evans, D. A.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.
- ⁶⁵ Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.*, **1988**, *110*, 3578.
- ⁶⁶ Wender, P. A.; Ternansky, R. J.; DeLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* **1990**, *62*, 1597.
- ⁶⁷ Gaich, T.; Mulzer, J. *J. Am. Chem. Soc.* **2009**, *131*, 452.
- ⁶⁸ Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
- ⁶⁹ (a) Paternò, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, *39*, 341; (b) Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327.
- ⁷⁰ Bach, T.; Brummerhop, H. **1998**, *37*, 3400.
- ⁷¹ Fleck, M.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 6189.
- ⁷² (a) Srinivasan, R.; Hill Carlough, K. *J. Am. Chem. Soc.* **1967**, *89*, 4932; (b) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4932.
- ⁷³ (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3; (b) Lipinski, C. A. *Drug Discov. Today* **2004**, *1*, 337.
- ⁷⁴ Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016.
- ⁷⁵ Bach, T.; Spiegel, A. *Synlett* **2002**, 1305.
- ⁷⁶ Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.
- ⁷⁷ Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441.
- ⁷⁸ Richmond, R. E.; Smith III, A. B. *J. Am. Chem. Soc.* **1983**, *105*, 575.
- ⁷⁹ Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.
- ⁸⁰ Selig, P.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5082.
- ⁸¹ De Mayo, P.; Takeshita, H.; Sattar, A. B. M. A. *Proc. Chem. Soc.* **1962**, 119.
- ⁸² (a) Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583; (b) Oppolzer, W.; Godel, T. *Helv. Chim. Acta* **1984**, *67*, 1154.
- ⁸³ Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443.
- ⁸⁴ Crimmins, M. T.; Pace, M. J.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453.
- ⁸⁵ Etnoyer, P. J.; Wirshing, H. H.; Sánchez, J. A. *PLoS ONE* **2010**, *5*, e10668; doi:10.1371/journal.pone.0010668.
- ⁸⁶ Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661.

- ⁸⁷ (a) Greenwood, B. M.; Bojang, K.; Whitty, C. J.; Targett, G. A. *Lancet* **2005**, 365, 1487; (b) Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, 434, 214.
- ⁸⁸ Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, 8, 903.
- ⁸⁹ Nahm, S.; Weinreb, S. M. *Tetrahedron* **1981**, 22, 3815.
- ⁹⁰ Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405.
- ⁹¹ Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 16, 4467.
- ⁹² (a) Lindgren, B. O.; Nilsson, T. *Acta Chim. Scand.* **1973**, 27, 888; (b) Balkrishna, S. B.; Wayne, E. C. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091.
- ⁹³ Negishi, E.; Kotori, M. *Tetrahedron* **1997**, 53, 6707.
- ⁹⁴ Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, 50, 1731.
- ⁹⁵ Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc. Perkin Trans. 1* **1984**, 747.
- ⁹⁶ Bredt, J. *Justus Liebigs Ann. Chem.* **1924**, 437, 1.
- ⁹⁷ Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem. Int. Ed.* **2011**, 50, 5149.
- ⁹⁸ Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, 118, 2521.
- ⁹⁹ Weinstock, L. M.; Corley, E.; Abramson, N. L.; King, A. O.; Karady, S. *Heterocycles* **1988**, 27, 2627.
- ¹⁰⁰ Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, 14, 2195.
- ¹⁰¹ Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Eur. J. Org. Chem.* **2013**, 4379.
- ¹⁰² Farcet, J.-B. *PhD-Thesis* **2013**, University of Vienna, Vienna.
- ¹⁰³ Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, 48, 4135.
- ¹⁰⁴ Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, 43, 1011.
- ¹⁰⁵ Luche, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 2226.
- ¹⁰⁶ Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071.
- ¹⁰⁷ Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
- ¹⁰⁸ Jana, A.; Mondal, S.; Hossain, F. Md.; Ghosh, S. *Tetrahedron Lett.* **2012**, 53, 6830.
- ¹⁰⁹ Meyer, M. E.; Phillips, J. H.; Ferreira, E. M.; Stoltz, B. M. *Tetrahedron* **2013**, in press.
- ¹¹⁰ Ihara, M.; Ohnishi, M.; Takano, M. *J. Am. Chem. Soc.* **1992**, 114, 4408.
- ¹¹¹ Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 20, 3437.
- ¹¹² Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, 123, 7725.
- ¹¹³ Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Org. Lett.* **2013**, 15, 3098.
- ¹¹⁴ Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Eur. J. Org. Chem.* **2013**, August 21st 2013 accepted for publication.
- ¹¹⁵ Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Eur. J. Org. Chem.* **2013**, August 21st 2013 accepted for publication.
- ¹¹⁶ For a review on palladium-catalyzed cross-coupling reactions in total synthesis see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, 44, 4442.
- ¹¹⁷ Diels, O.; Alder, K. *Justus Liebig's Ann. Chem.* **1928**, 460, 98.
- ¹¹⁸ Wurtz, M. A. *Bull. Soc. Chim. Fr.* **1872**, 17, 436.
- ¹¹⁹ Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, 87, 1318.
- ¹²⁰ For a review on metathesis in total synthesis see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, G. *Angew. Chem. Int. Ed.* **2005**, 44, 4490.
- ¹²¹ Casey, C. P. *J. Chem. Educ.* **2006**, 83, 192.
- ¹²² Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, 44, 581.
- ¹²³ Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, 37, 2320.
- ¹²⁴ For a review on asymmetric intramolecular Heck reactions in total synthesis see: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, 103, 2945.
- ¹²⁵ For a general review on the Heck reaction see: de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1994**, 33, 2379.
- ¹²⁶ Overman, L. E. *Pure App., Chem.* **1994**, 66, 1423.
- ¹²⁷ Ashfield, L.; Barnard, C. F. J. *Org. Process Res. Dev.* **2007**, 11, 39.
- ¹²⁸ Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, 33, 314.
- ¹²⁹ Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, 117, 7834.
- ¹³⁰ Jeffery, T. *Tetrahedron* **1996**, 52, 10113.
- ¹³¹ Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, 133, 6187.
- ¹³² (a) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, 133, 1778; (b) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, 133, 14916.
- ¹³³ Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sotoocornola, S. *Chem. Rev.* **2007**, 107, 5318.

CURRICULUM VITAE

Martin Himmelbauer, MSc



Education

May 2009 – present	PhD in Chemistry expected (Summer 2013), University of Vienna, Supervisor: Univ. Prof. Dr. Johann Mulzer, Focus: natural product synthesis with emphasis on the total synthesis of Bielschowskysin
2002 – April 2009	MSc in Chemistry, University of Vienna, Focus: organic synthesis and spectroscopy Diploma Thesis: “Synthetic Efforts Towards a Synthesis of the Tetracyclic Core of (-)-Lemonomycin” at the Department of Organic Chemistry under the supervision of Univ. Prof. Dr. Johann Mulzer
2002	Military Service at Austrian Guards Division
1993 – 2001	High school at the BRG 1 Linz (Fadingerstraße), with emphasis on natural science and mathematics

Relevant Employments

2008 – present	Tutor and lector of graduate and undergraduate students; University of Vienna
2004 – 2007	Industrial Internship, Division: Process Development and Optimization; Nycomed Austria GmbH; Linz, Austria

Publications

2013	“An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photocyclization Strategy” Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. <i>Eur. J. Org. Chem</i> 2013 , <i>accepted</i> .
2013	“An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photochemical Strategy” Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. <i>Eur. J. Org. Chem</i> 2013 , <i>accepted</i> .
2013	“Photochemical and Thermal [2+2]-Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin” Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. <i>Eur. J. Org. Chem.</i> 2013 , 4379.

2013	“A Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case” Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J; Mulzer, J. <i>Org. Lett.</i>, 2013, 15, 3098.
2012	“A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin” Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. <i>Org. Lett.</i> 2012, 14, 2195.

Prizes and Awards

September 2012	2 nd best Contribution to all sessions at “Syngenta Workshop for Talented Young Chemists 2012”; Stein, Switzerland
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Oral Presentations

May 2011	„Recent Developments Towards the Total Synthesis of Bielschowskysin”; VISOC 2011; Vienna, Austria
January 2011	„Towards a Total Synthesis of Bielschowskysin”; Institute colloquium, Technical University of Graz, Austria
November 2010	„Towards a Total Synthesis of Bielschowskysin”; 40. Naturstofftreffen; Würzburg, Germany

Poster Presentations

September 2012	“Towards a Total Synthesis of Bielschowskysin”; Syngenta workshop 2012 for talented PhD chemistry students; Stein, Switzerland
August 2010	“Towards a Total Synthesis of Bielschowskysin”; ICOS-18; Bergen, Norway
March 2009	“Towards a Synthesis of (-)-Lemonomycin”; Synthesefest 2009; Munich, Germany
February 2009	“Towards a Synthesis of Lemonomycin”; ESPCI workshop; Paris, France
September 2008	“Towards the Stereocontrolled Synthesis of the Tetracyclic Core Framework of (-)-Lemonomycin”; EuCheMS 2008; Turin, Italy

Other Skills and Interests

Languages	German (native), English (fluent), Italian (basic)
IT-skills	Windows, MS-Office, Linux, TYPO3 webpage, as well as numerous chemistry oriented programs
Chemical Analysis	NMR, IR, UV-VIS, HPLC