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DISSERTATION

Titel der Dissertation

„Toward a Total Synthesis of

the Diterpenoid Bielschowskysin“

Verfasser

Dipl.-Ing. Jean-Baptiste Farcet

angestrebter akademischer Grad

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Pour Mathilde et Daniel

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Publications, Conference Contributions and Awards resulting from this Thesis

Publications

- ”A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin”
  Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann
  Organic Letters **2012**, *9*, 2195-2197.

- ”Photochemical and Thermal [2+2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin”
  Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann
  European Journal of Organic Chemistry **2013**, *20*, 4379-4398.

- ”A Palladium-Catalyzed Carbo-Oxygenation: the Bielschowskysin Case”
  Himmelbauer, Martin; **Farcet, Jean-Baptiste**; Gagnepain, Julien; Mulzer, Johann
  Organic Letters **2013**, *12*, 3098-3101.

- ”An Approach to the Carbon Backbone of Bielschowskysin, Part 1: the Photochemical Strategy”
  Himmelbauer, Martin; **Farcet, Jean-Baptiste**; Gagnepain, Julien; Mulzer, Johann
  European Journal of Organic Chemistry **2013**, submitted (June 13th, 2013).

- ”An Approach to the Carbon Backbone of Bielschowskysin, Part 2: the Non-Photochemical Strategy”
  Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann
  European Journal of Organic Chemistry **2013**, submitted (June 13th, 2013).

Oral contributions

- ”Toward a Total Synthesis of Bielschowskysin, an Antiplasmodial Diterpene”
  Guest lecture at Boehringer-Ingelheim (June 2013, Vienna, Austria).

- ”Photochemische [2+2]-Cycloadditionen als Schlüsselschritt auf dem Weg zum Bielschowskysin“
  Doktorandenworkshop Naturstoffchemie 2011 (May 2011, Bonn, Germany).

- ”Recent Developments toward the Total Synthesis of Bielschowskysin“
  Vienna International Symposium on Organic Chemistry 2011 (May 2011, Vienna, Austria).

Poster presentations

- ”Towards the Total Synthesis of the Antimalarial Drug Bielschowskysin”
  Balticum Organicum Syntheticum 2010 (June 2010, Riga, Latvia).

- ”Towards the Total Synthesis of the Anti-Malarial Drug Bielschowskysin”
  Belgian Organic Synthesis Symposium BOSS XII (July 2010, Namur, Belgium).

- ”Towards the Total Synthesis of Bielschowskysin”
  Advances in Synthetic and Medicinal Chemistry (August 2011, St. Petersburg, Russia).

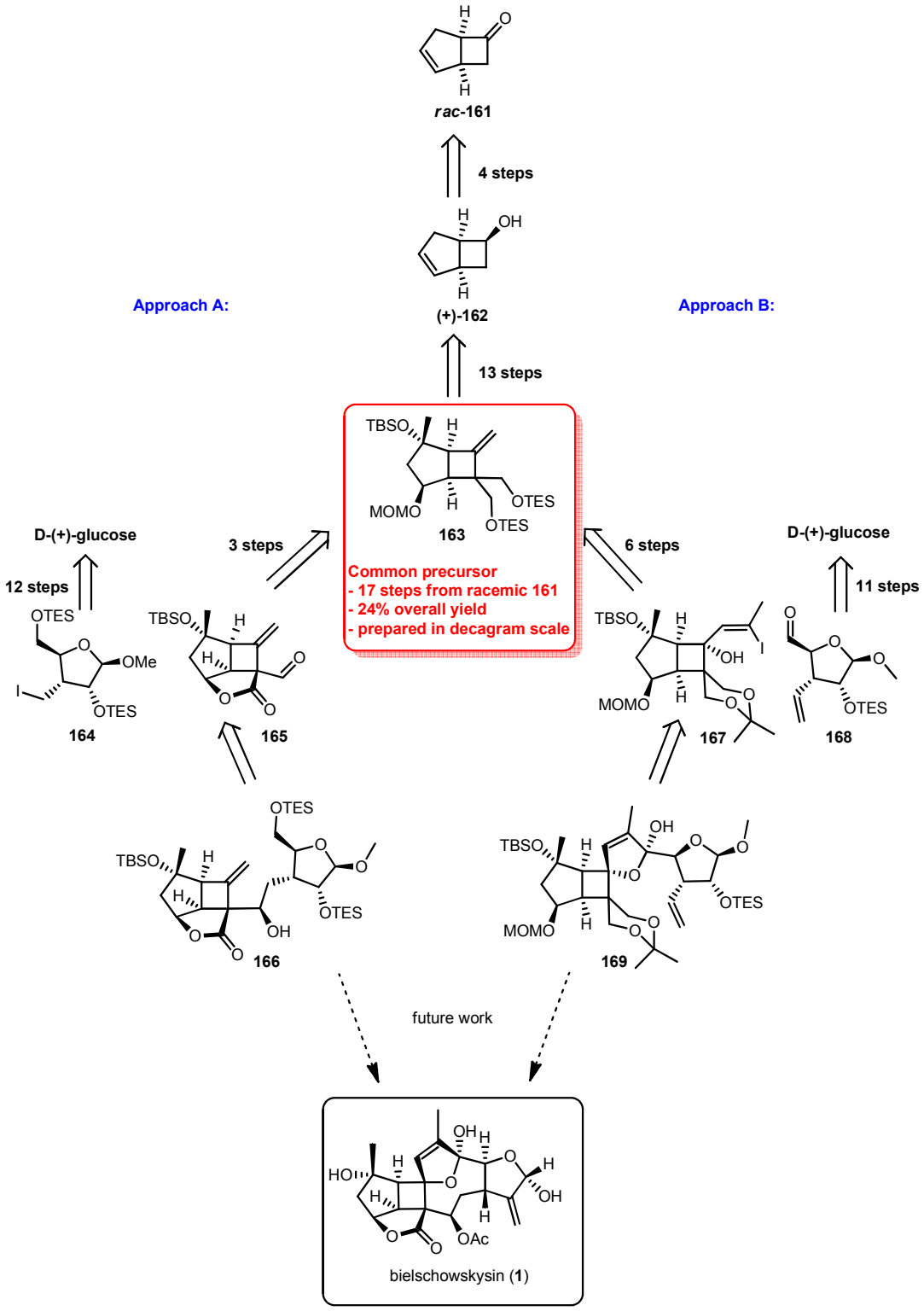
- ”Recent Developments toward the Total Synthesis of Bielschowskysin”
  Syngenta workshop for talented PhD chemistry students (September 2012, Stein, Switzerland).

Awards

- **Ph.D. Scholarship** from the University of Vienna; Initiativkolleg “Functional Molecules”, January 2010.

- **“Syngenta workshop for talented PhD chemistry students” award**, Stein, Switzerland, September 2012.

Graphical Abstract



Abstract

This PhD thesis describes the efforts toward a total synthesis of bielschowskysin.

Bielschowskysin (**1**) is a highly oxygenated diterpene, which was isolated from the gorgonian octocoral *Pseudopterogorgia kallos* found in the southwestern Caribbean Sea in 2003. Its promising cytotoxic activity against two human cancer cell lines as well as its antiplasmoidal activity, and its unprecedented hexacyclic structure containing 11 stereogenic centers, make bielschowskysin a highly challenging target for total synthesis. To date, no total synthesis of the natural product has been reported.

Herein, several approaches to access the 14-membered carbocyclic framework are described. Each fragment was synthesized in a stereoselective manner and on large scale. Starting from racemic *cis*-bicyclo[3.2.0]hept-2-en-6-one (**161**), an enzyme catalyzed kinetic resolution allowed to secure optically active *cis*-(+)-bicyclo[3.2.0]hept-2-en-6-ol (**162**) in sufficient quantities. Proper substitution of the bicyclic structure was achieved in 13 steps taking advantage of the *cis* configuration of the bicycle to yield common precursor **163**. Using Jones' reagent, a cascade reaction was developed and optimized to create the tricyclic core of bielschowskysin. A further two steps yielded western fragment **165**, suitable to couple with glucose derivate **164** to form coupling product **166**. Hence, the southern half of the natural product could be obtained.

In addition, vinyl iodide **167** was formed in a regio- and stereoselective manner, ready to couple with aldehyde **168**. Thus, the northern half of the natural product could be obtained after an oxidation step (**169**).

Both fragments **166** and **169** are highly advanced intermediates and have the potential to lead to the natural product.

Zusammenfassung

Diese Dissertation beschreibt die Arbeit an der Totalsynthese von Bielschowskysin.

Bielschowskysin (**1**) ist ein hochoxidiertes Diterpen, welches im Jahr 2003 aus der in der südwestlichen Karibik vorkommenden gorgonienartigen Octocorallia *Pseudopterogorgia kallos* isoliert wurde. Die zytotoxische Aktivität gegen zwei menschliche Zelllinien, sowie antiplasmodiale Wirkung und die beispiellose hexacyclische Struktur mit 11 stereogenen Zentren macht Bielschowskysin zu einem anspruchsvollen Ziel für die Totalsynthese. Bis heute wurde von keiner Totalsynthese des Naturstoffes berichtet.

Hier werden mehrere Strategien um das 14-gliedrige carbocyclische Grundgerüst dieses Moleküls aufzubauen beschrieben. Jedes Fragment wurde in einer stereoselektiven Weise und in großem Maßstab synthetisiert. Ausgehend von racemischen *cis*-Bicyclo[3.2.0]hept-2-en-6-on (**161**) wurde eine katalysierte enzymatische Racematspaltung verwendet, um ausreichende Mengen von optisch aktivem *cis*-(+)-Bicyclo[3.2.0-hept-2-en-6-ol (**162**) zu erzeugen. Die gewünschte Substitution der bicyclischen Struktur wurde in 13 Stufen unter Ausnutzung der *cis*-Konfiguration des Bicycluses erreicht, wobei das Intermediär **163** erhalten wurde. Mit dem Jones Reagenz wurde eine Kaskadenreaktion entwickelt und optimiert, um das tricyclische Gerüst von Bielschowskysin zu bilden. In zwei weiteren Schritten wurde Aldehyd **165** hergestellt, welches zur Kopplung mit dem Glucosederivat **164** geeignet ist, um Kopplungsprodukt **166** zu bilden. Somit wurde die südliche Hälfte des Naturstoffes erzeugt.

Ausserdem wurde Vinyliodid **167**, welches mit dem Aldehyd **168** gekoppelt werden konnte, in einer regio- und stereoselektiven Weise synthetisiert. Somit wurde die nördliche Hälfte des Naturproduktes nach einem Oxidationsschritt hergestellt (**169**).

Die beiden Fragmente **166** und **169** sind hochentwickelte Intermediare und haben das Potential zum Naturstoff zu führen.

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1 Introduction and Background

1.1 General Introduction

Natural products are a formidable source of inspiration for chemists and play a crucial role in drug development. Yet, limited availability restricts their use in the pharmaceutical industry. Total synthesis is a significant step toward the development of a medicine, when a natural product has been identified to have significant biological activity. Not only is it a great way to try out new methodology on complex substrates or even invent new chemistry, total synthesis also provides more material for biological evaluation of an active compound. It is also a valuable tool for biological verification, *i.e.* if a compound contains ambiguous stereochemistry. Furthermore, it can be applied to create analogs in order to improve the biological activity or identify the pharmacophore, which will ideally lead to a simplified, biologically highly active compound accessible in a limited number of steps, suitable for production of industrial quantities.

1.2 Isolation & Structure Elucidation

Bielschowskysin (**1**), a highly oxygenated diterpene, was isolated from the gorgonian octocoral *Pseudopterogorgia kallos*[1] (Figure 1) that was found in the southwestern Caribbean Sea in 2003, together with other furanocembranoids such as kallosin A (**2**) and providencin (**3**) (Figure 2).[2,3,4] Structurally, these marine derived natural products feature a 12- or 14-membered carbocyclic framework. Due to their challenging novel and highly functionalized structures and diverse biological activities, these furanocembranoids are the research topic of numerous groups of synthetic chemists.

Figure 1. *Pseudopterogorgia kallos*.[1]

For the isolation of the molecule 1.07 kg of the partially air-dried animal were frozen, lyophilized and the homogenized mixture was exhaustively extracted using a 1:1 mixture of MeOH/CH_2Cl_2. The resulting dried extract (166 g) was subjected to a second extraction protocol (Hexane, $CHCl_3$ then EtOAc) and the

[1] J. A. Sánchez, C. Aguilar, D. Dorado, N. Manrique, *BMC Evolutionary Biology* **2007**, *7*, 122-130.
[2] J. Marrero, A. D. Rodriguez, P. Baran, R. G. Raptis, J. A. Sanchez, E. Ortega-Barria, T. L. Capson, *Organic Letters* **2004**, *6*, 1661-1664.
[3] J. Marrero, A. D. Rodriguez, P. Baran, R. G. Raptis, *Journal of Organic Chemistry* **2003**, *68*, 4977-4979.
[4] J. Marrero, A. D. Rodriguez, P. Baran, R. G. Raptis, *Organic Letters* **2003**, *5*, 2551-2554.

EtOAc fraction was concentrated to yield 1.5 g of crude extract, which was purified first by silica gel flash chromatography followed by normal phase HPLC to yield pure bielschowskysin (**1**) (39.6 mg; 0.024% based on the crude extract dry wt.) as a colorless crystalline solid ($[\alpha]^{20}_{D}$ -17.3 (c = 1.1, MeOH)).[2]

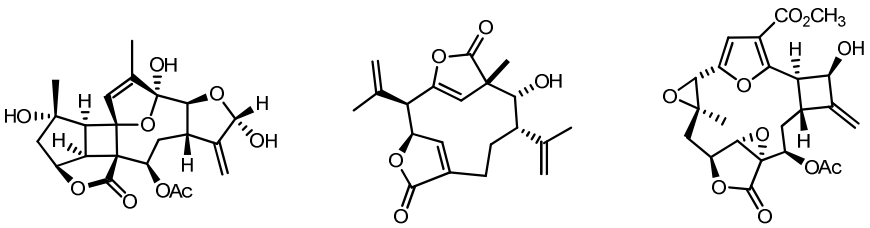

Figure 2. Cembranoids found in *Pseudopterogorgia kallos.*

Structure elucidation was performed using first HRMS (EI), ^{1}H-NMR, ^{13}C-NMR followed by HMQC, DEPT-135 and COSY experiments. However, due to a limited number of key connectivities, the isolation team elected to continue the structure determination using single crystal X-ray diffraction, after successful recrystallization by slow evaporation of a mixture of EtOAc/MeOH and formation of cubic colorless crystals. Verification of the structure and assignment of the NMR signals were conducted under standard 2D-NMR experiments. Thus, HMBC correlations were conducted in CD_3OD and relative configuration of the stereocenters were confirmed on the basis of the NOESY correlations and NMR coupling constant data (See NMR spectra and X-ray structure of **1** in Annex Section 8.3).

Bielschowskysin consists of a hexacyclic ring-system with the molecular formula $C_{22}H_{26}O_9$, a highly oxygenated structure with an oxygen/carbon ratio of 0.41, which bears two cyclic hemiacetals, two isolated carbon-carbon double bonds, one lactone, one tertiary alcohol and one acetate as functional groups. The sole all-carbon quaternary stereocenter is contained in a highly substituted cyclobutane ring fused to two five membered rings, which results in a highly strained cage-like structure. Moreover, the furanocembranoid contains 11 stereogenic centers, whose absolute configurations have yet to be assigned. Ten of these stereogenic centers are located in the novel [9.3.0.0^{2,10}] tetradecane carbocyclic framework, whereas seven of them are contiguous to or part of the highly substituted cyclobutane ring. No information is known about its absolute stereochemistry.

1.3 Biological Activity

Within the National Cancer Institute's *in vitro* antitumor screening program, bielschowskysin was found to have moderate but specific cytotoxicity against EKVX nonsmall cell lung cancer (GI_{50} < 0.01 µM) and CAKI-1 renal cancer (GI_{50} = 0.51 µM).[2] Bielschowskysin also exhibits significant antiplasmoidal activity (IC_{50} = 10 µg.mL^{-1}) as it inhibits two chloroquine-sensitive strains and one chloroquine resistant strain of *Plasmodium falciparum*,[2] which causes the most severe form of malaria. With about 300 million clinical cases and about one to two million casualties each year,[5] malaria is one of the most life-threatening diseases worldwide. Furthermore, the increasing resistance of the mosquito vector against established insecticides as well as the increasing resistance of the parasite against common medications contributes to the need for new anti-malaria agents.

1.4 Terpenes and their Biosynthesis

1.4.1 Overview [6]

Terpenes are a large and diverse class of organic compounds, produced mainly by plants but also by some animals such as insects or corals. Moreover squalene (**15**), a triterpene, is the precursor of steroids, a class of organic compounds of great significance.

Terpenes play an important role as fragrances in perfumery, flavor additives in food or environment-friendly luring compounds to trap damaging insects, but most importantly as drugs, due to one of their primary use in nature as chemical weapons. In fact, some cytotoxic terpenoids are used against predators or during the settlement area conflicts to fight away rival species. Tiglic acid (**31**) for instance, found in croton oil, is found in the defensive secretion of certain beetles.

Even though their numbers are continuously increasing, about 30 000 different terpenes are currently registered.[6] Terpenes are derived biosynthetically from units of isoprene, which make their molecular formulae multiples of $(C_5H_8)_n$, where n is the number of linked isoprene units, also called the isoprene rule or the C5 rule.[7] The isoprene units are mainly linked "head to tail" to form linear chains or are intramolecularly connected to form rings. Those rings are referred to as terpenoids, when their molecular structures have been oxidized during biogenesis.

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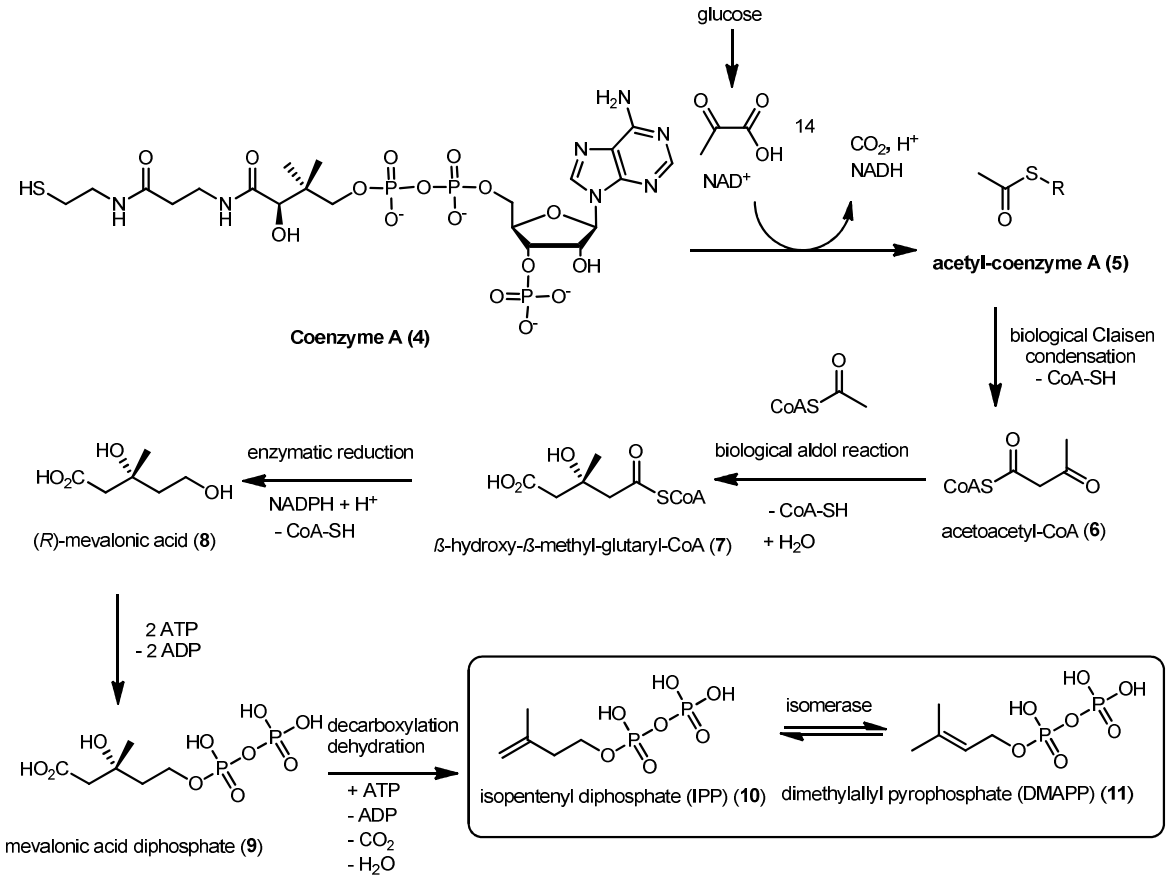
[5] Y. Corbett, L. Herrera, J. Gonzalez, L. Cubilla, T. L. Capson, P. D, Coley, T. A. Kursar, L. I. Romero, E. Ortega- Barria, *American Journal of Tropical Medicine and Hygiene* **2004**, *70*, 119-124.

[6] E. Breitmaier, *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*, WILEY-VCH Verlag GmbH & Co. Weinheim, **2006**.

[7] L. Ruzicka, Proceeding of the Chemical Society (London) **1959**, 341.

1.4.2 Biosynthesis

Coenzyme A (**4**) is the biogenetic precursor of all terpenoids, acetylation of **4** forms acetyl-coenzyme A (**5**), which is also known for its role in the synthesis and oxidation of fatty acids as well as for its role in the citric acid cycle. A biological Claisen condensation between two molecules of acetyl-CoA (**5**) forms **6**, followed by a biological aldol type reaction to give *ß*-hydroxy-*ß*-methyl-glutaryl-CoA (**7**), which is enzymatically reduced providing the C6 fragment (*R*)-mevalonic acid (**8**) (Scheme 1).

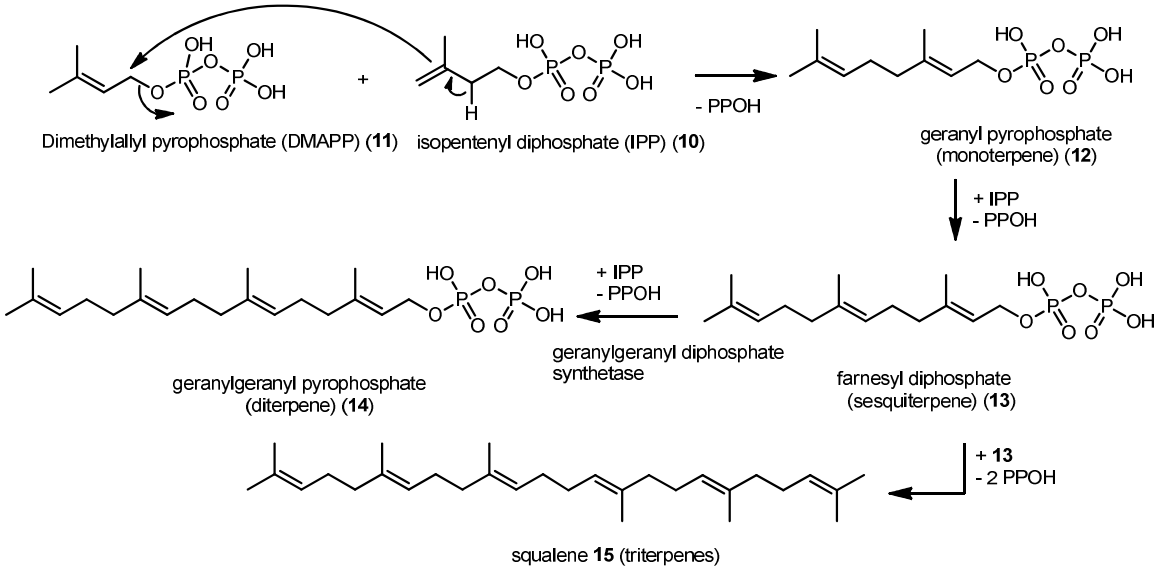


Scheme 1. The mevalonic pathway, biogenesis of IPP and DMAPP.

Phosphorylation by 2 adenosine triphosphates (ATP) generates mevalonic acid diphosphate (**9**) followed by enzymatic decarboxylation and dehydration to yield isopentenyl diphosphate (IPP, **10**). Isomerization by IPP isomerase delivers dimethylallyl pyrophosphate (DMAPP, **11**) (Scheme 1).

The former and latter activated hemiterpenes react in a nucleophilic substitution (Alder-Ene-like reaction) between the electrophilic methylene group of IPP (**10**) and the nucleophilic double bond of DMAPP (**11**), to form geranyl pyrophosphate (**12**), a linear monoterpene (Scheme 2). Enzymatic induced substitution gives likewise farnesyl diphosphate (**13**), a sesquiterpene, followed by elongation with IPP

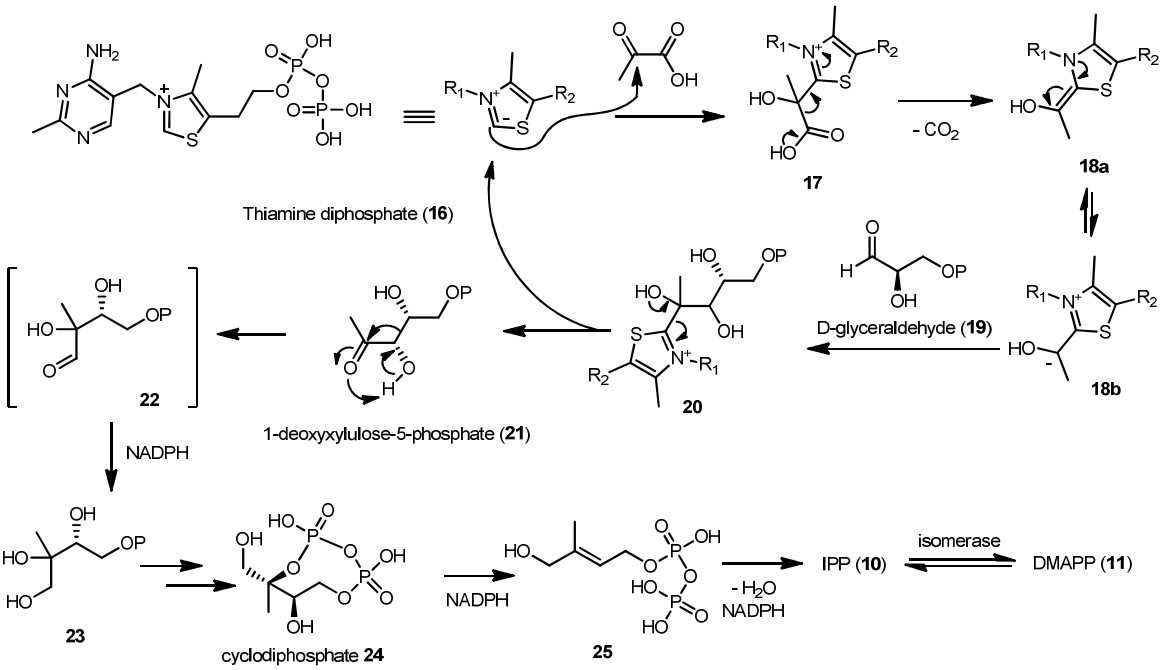
(**10**) to geranylgeranyl pyrophosphate (GGP, **14**), a diterpene. Similar head-to-tail linkages produce sesterterpenes; however, a tail-to-tail connection between two molecules of farnesyl diphosphate (**13**) is responsible for formation of the triterpene precursor squalene (**15**) (Scheme 2).



Scheme 2. Biosynthesis of GGP from IPP.

Alternatively, in some plants and bacteria, IPP (**10**) and DMAPP (**11**) are produced following the Rohmer pathway.[8,9] After deprotonation of thiamine diphosphate (**16**) at the C2 position of the thiazol ring and attack on pyruvate with concomitant decarboxylative fragmentation, an activated nucleophilic (umpolung) acetaldehyde-3-phosphate (**18**) is formed and gives 1-deoxyxylulose-5-phosphate (**20**) after attack on the electrophilic D-glyceraldehyde (**19**), a C5 building block. A retroaldol reaction gives acyloin **21**, which undergoes a 1,2-rearrangment to **22** before being reduced to **23** by NADPH. Phosphorylation leads to cyclic diphosphate **24**, which is reduced eventually to deliver IPP (**10**) (Scheme 3).

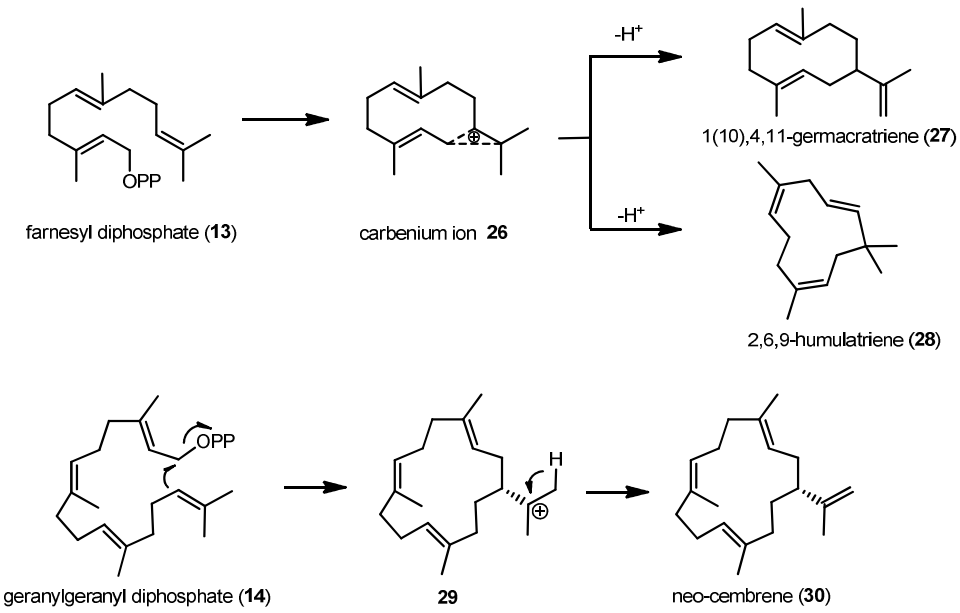
[8] M. Rohmer, M. Seemann, S. Horbach, S. Bringer-Meyer, H. Sahm, *Journal of the American Chemical Society* **1996**, *118*, 2564–2566.
[9] M. Rohmer, M. Knani, P. Simonin, B. Sutter and H. Sahm *Biochemical Journal* **1993**, *295*, 517-524.



Scheme 3. The Rohmer pathway, biogenesis of IPP and DMAPP.

Cyclic and polycyclic terpenes are assumed to have their origin from a carbenium ion intermediate of the type of cation **26** or **29**. At this point, the pathways diverge depending on how the carbocation is trapped. Additionally, cyclic diversity may arise from Wagner-Meerwein rearrangements (1,2-hydride and alkyl shifts) and sigmatropic reactions such as Cope rearrangements. In the biogenesis of furanocembranoids, it has been reported that a so-called 'type A cyclization' of geranylgeranyl pyrophosphate (**14**) produces cation **29**.[10] In the case of cembranoids, a simple loss of a proton results in the formation of the isopropenyl side chain of the 14-membered ring macrocycle neo-cembrane (**30**) (Scheme 4).

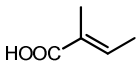
[10] J. MacMillan, M. H. Beale, in *Comprehensive Natural Products Chemistry*, vol. 2, ed. D. H. R. Barton and K. Nakanishi, Pergamon, **1999**, 217.



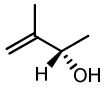
Scheme 4. Origins of some cyclic terpenes and formation of neo-cembrane (**30**).

Figure 3 shows examples of selected terpenes. Their structural diversity as well as the broad application range makes this class of molecule unique.

Hemiterpenes: C_5

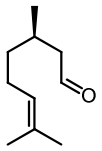


Tiglic acid (**31**), found in croton oil and defensive secretions of certain beetles

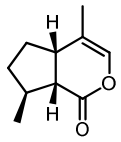


(***S***)**-3-methyl-3-buten-2-ol** (**32**), in essential oil of oranges, grapefruits and hops

Monoterpenes: C_{10}

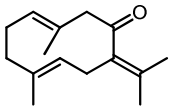


(***R***)**-(+)-citronellal** (**33**), main component of leaf oil from kaffir lime, with distinctive lemon scent

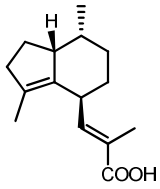


(+)-Nepetalactone (**34**), found in *Nepeta cataria* (catnip) and some leaf louses, strongly attracts cats

Sesquiterpenes: C_{15}

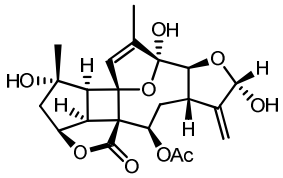


Germacrone (**35**), a herby smelling component from the essential oil of *Geranium macrorhyzum* (*Geraniaceae*)

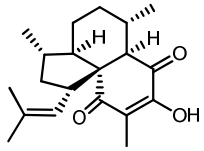


Valerenic acid (**36**), acts as a subunit specificallosteric modulator of $GABA_A$ subtype receptors

Diterpenes: C_{20}

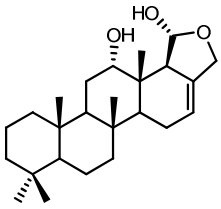


Bielschowskysin (**1**), isolated from the gorgonian octocoral *Pseudopterogorgia kallos*. Cytotoxic activity against two human cancer cell lines as well as antiplasmoidal activity

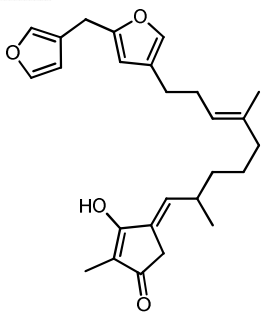


Elisabethin A (**37**), isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia elisabethae* in the late 1990s

Sesterterpenes: C_{25}

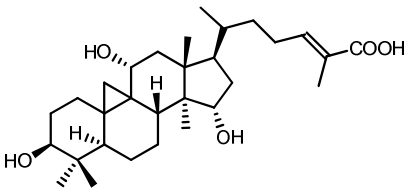


(+)-Desoxyscalarin (**38**), found in *Spongia officinalis* with antiinflamatory activity

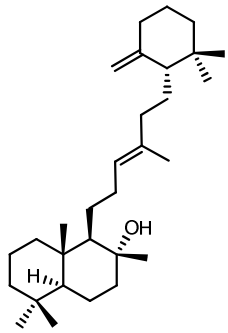


(-)-Ircinin I (**39**), isolated from *Ircinia oros* with antibacterial activity

Triterpenes: C_{30}

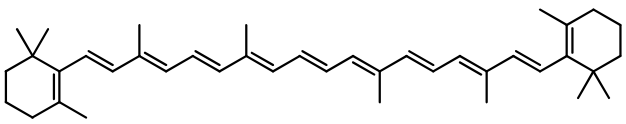


(+)-Ananas acid (**40**), from wood pineapple *Ananas comosus*, used as sedativ and analgesics



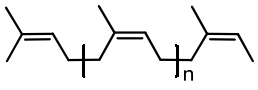
(-)-Ambrein (**41**), concretion from the intestinal tract of sperm whale, used in perfumery

Tetraterpenes: C_{40}

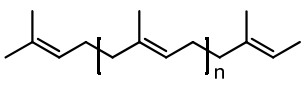


***Beta*-carotene** (**42**), strongly-colored red-orange pigment abundant in plants such as carrots, pumpkins and sweet potatoes, precursor (inactive form) of Vitamin A

Polyterpenes: $(C_5)_n$



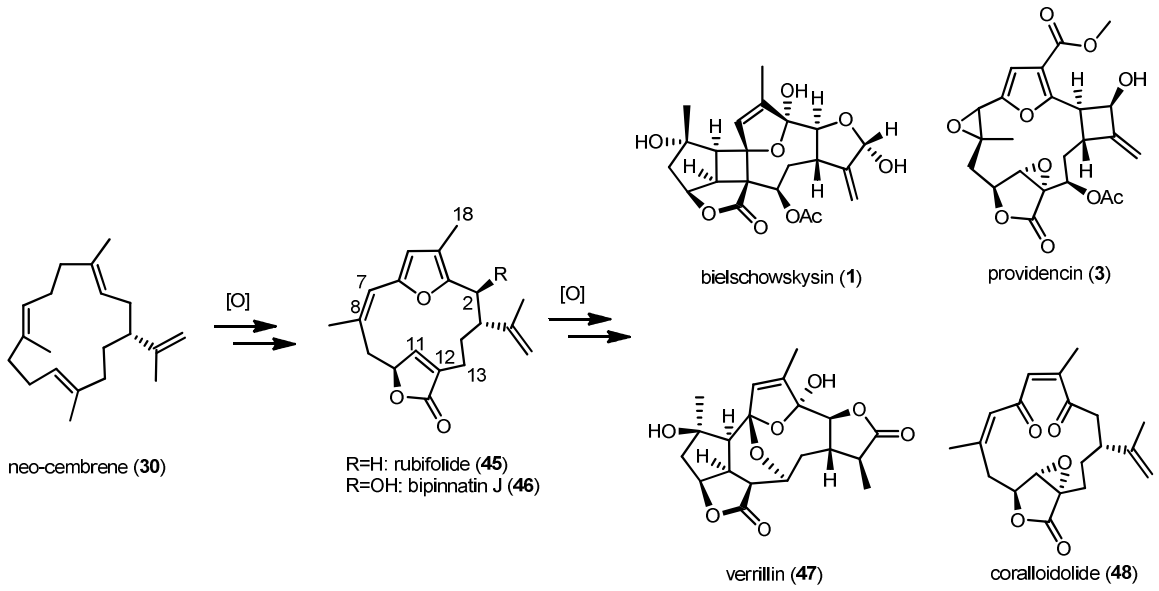
cis-polyisoprene (**43**) natural caoutchouc



***trans*-polyisoprene** (**44**), present in gutta-percha trees, chemical resistant, used as an insulator, dental cement and for covering golf balls

Figure 3. Selected terpenes with their applications/origins.[6]

Starting from neo-cembrene (**30**), a series of site selective oxidations followed by closure of the furan ring and butenolide afford rubifolide (**45**) and bipinnatin J (**46**) after double bond isomerization.[11] All members of the furanocembranoid family such as providencin (**3**), verrillin (**47**) and coralloidolide (**48**) seem to derive from this simple precursor after further site selective oxidation/isomerization (Scheme 5).[12]



Scheme 5. Biosynthesic speculations of furanocembranoids.

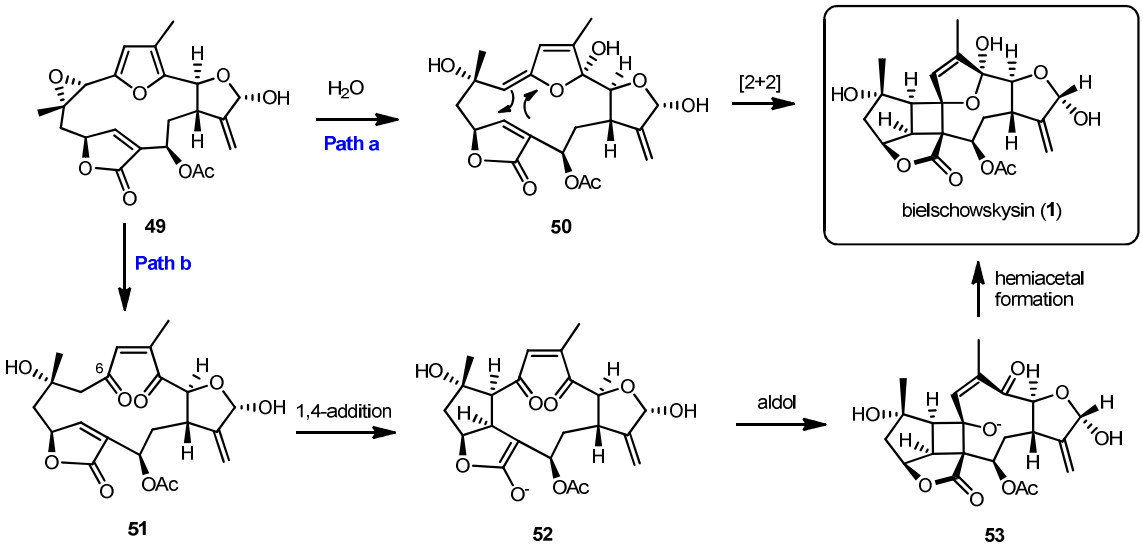
Furanocembranoids are 14 membered carbon macrocycles containing a furan and butenolide moiety. General features include:

- Frequent oxidation of C2 as a secondary alcohol
- Oxidation of C18 can take all possible oxidation states
- $\Delta^{7,8}$ is often oxidized and can be involved in further transformations
- $\Delta^{11,12}$ is in many cases epoxidized and/or is involved in subsequent transformations
- Frequent oxidation of C13 as a secondary alcohol, masked as acetate
- Diversity of the oxidation state of the furan ring

All those structural elements provide the furanocembranoid family with an immense structural diversity, which can reach high molecular complexity such as providencin (**3**), verrillin (**47**) and bielschowskysin

[11] P. A. Roethle, D. Trauner, *Natural Product Reports* **2008**, *25*, 298–317.
[12] Y. Li, G. Pattenden, *Natural Product Reports* **2011**, *28*, 1269–1310.

(**1**). However, little is known about the exact oxidation process and the involved enzyme (cytochrome-P450- mono-oxygenase type enzymes) leading to each particular member of the family. In the case of bielschowskysin, a series of oxidation events is assumed to lead to cembranoid **49**. Formal transannular [2+2] cycloaddition after hydration of **49** forming **50** is believed to lead to the natural product.[11] This assumption has been successfully modeled on a test system using sunlamp irradiation (Path a, Scheme 6).[13] On the other hand, a stepwise mechanism could be considered involving an enol (derived from C6 ketone in **51**) attacking in a nucleophilic manner (5-*exo* trig) the Michael system of the butenolide, providing intermediate **52**. Enolate **52** could thereafter be the precursor for an intramolecular aldol reaction forming cyclobutane **53**. Final and presumably spontaneous hemiacetal formation could lead to bielschowskysin (**1**) (Path b, Scheme 6).



Scheme 6. Biosynthetic speculations on bielschowskysin (**1**).

The latter mechanism could explain the formation of the closely related verrillin (**47**), as assumed in the review from Pattenden and his team.[12]

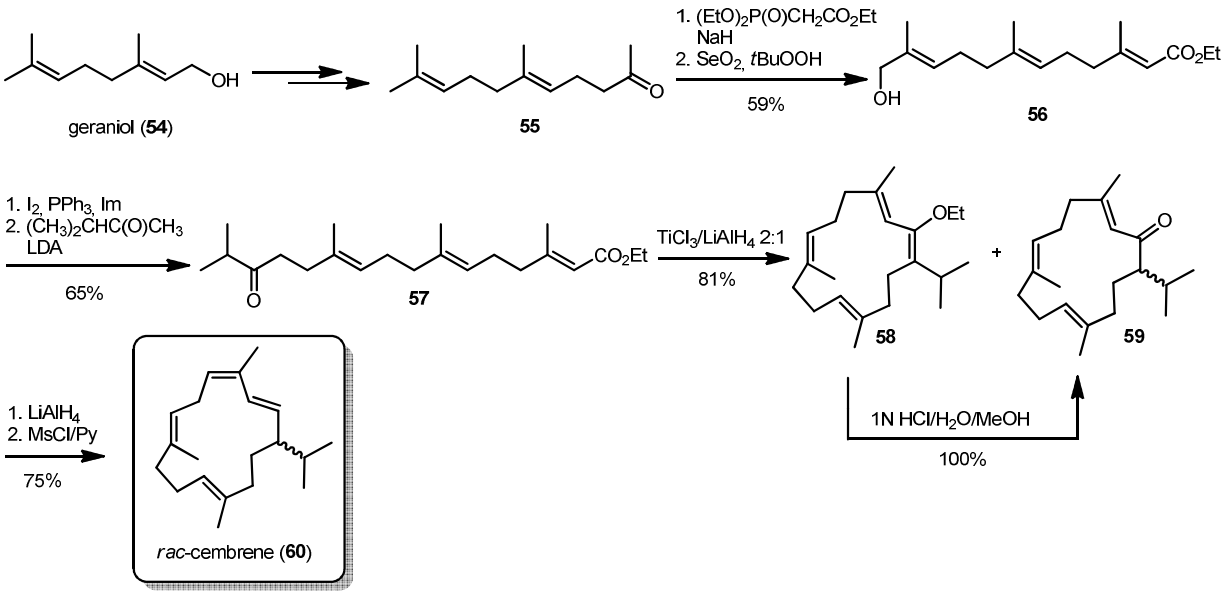
[13] B. Doroh, G. A. Sulikowski, *Organic Letters* **2006**, *8*, 903-906.

2 Selected Synthesis of Diterpenes

In this chapter, relevant syntheses of diterpenoids were selected and are briefly presented. Despite the large size of the furanocembranoids family, relatively little synthetic work has achieved its goal. The syntheses were selected according to their relevance, as bio-precursor of bielschowskysin or to illustrate the methodologies and strategies used so far to access the molecular scaffold of cembranoids.

2.1 Li's Synthesis of *rac*-Cembrene (60) [14]

In 1994, the research group of Yulin Li presented a methodology to close 14-membered ring macrocycles using titanium-induced cyclization. The target compound was cembrene (**60**) found in pine resins, the first naturally occurring cembrane hydrocarbon to be characterized.[15] Its synthesis was first achieved by Dauben.[16] The route started from geranylacetone (**55**) obtained from geraniol (**54**). In the first step conjugated ester was installed by Horner-Wadsworth-Emmons reaction to afford the *E* isomer in excellent yield. Exposure of the formed ester in the presence of catalytic amount of selenium dioxide gave regioselectively the corresponding allylic alcohol **56**. Conversion to the iodide and alkylation of the lithium enolate of 3-methylbutan-2-one afforded keto ester **57** in satisfactory yield (Scheme 7).



Scheme 7. Li's synthesis of *rac*-cembrene.

[14] W. Li, Y. Li, Y. Li, *Synthesis* **1994**, 678-680.
[15] H. Kobayashi, S. Akiyoshi *Bulletin of the Chemical Society of Japan* **1962**, *6*, 1044-1045.
[16] W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, C. Suter, *Journal of the American Chemical Society* **1975**, *17*, 4973–4980.

Macrocyclization was carried out by addition of **57** in refluxing low valent titanium slurry over 24 h followed by acidic cleavage of the remaining enol ether **58** to afford **59**. Finally, reduction to mukulol, a cembrane alcohol isolated from the gum-resin of an Indian plant (*Commiphora mukul*)[17] and elimination of the secondary hydroxy group yielded *rac*-cembrene (**60**) in good yield (Scheme 7).

This methodology was used for the syntheses of further natural cembranoids[18] and was efficient to build large and even sterically hindered macrocycles.

2.2 Paquette's Synthesis of Gorgiacerone (76) [19,20]

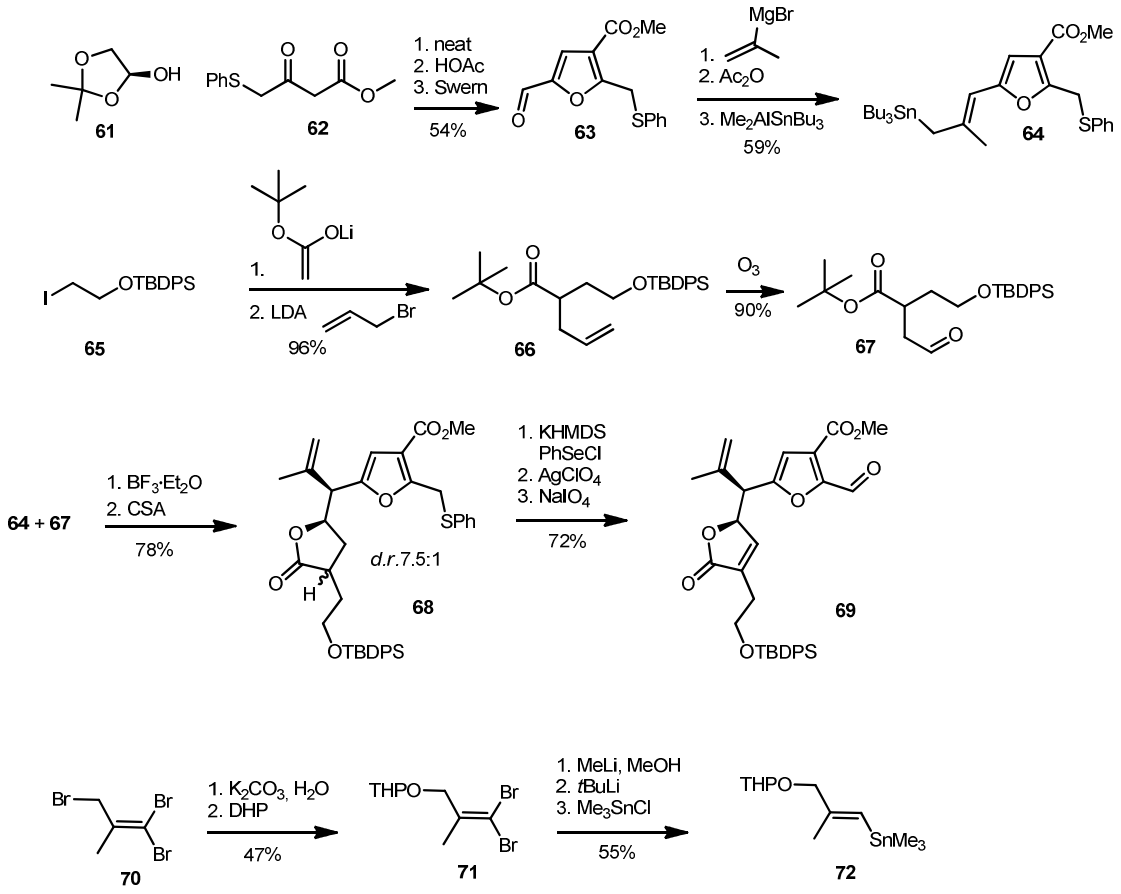
One of the earliest cembranoid syntheses was reported by Paquette and his research group in 1992,[19,20] who focused on the elaboration of the pseudopterane gorgiacerone (**76**).

Pseudopteranes are structurally related to furanocembranoids and generally found in the same organisms,[11] for example kallosin A (**2**) and bielschowskysin (**1**) were isolated from the same coral *Pseudopterogorgia kallos*. Their 12-membered carbocyclic frameworks derive most likely from a light induced ring contraction rearrangement of a furanocembranoid derivative.[21,22,33]

The synthetic route started with the elaboration of the furan moiety after condensation of **61** and **62** by treatment with acetic acid. Swern oxidation yielded aldehyde **63**. Reaction of **63** with 2-propenyl magnesium bromide afforded an allylic alcohol, which was acetylated and converted to the allylstannane **64** according to the Trost method.[23] In parallel, aldehyde **67** was accessed by a sequential double alkylation from **65** to give **66** followed by oxidative cleavage (Scheme 8).

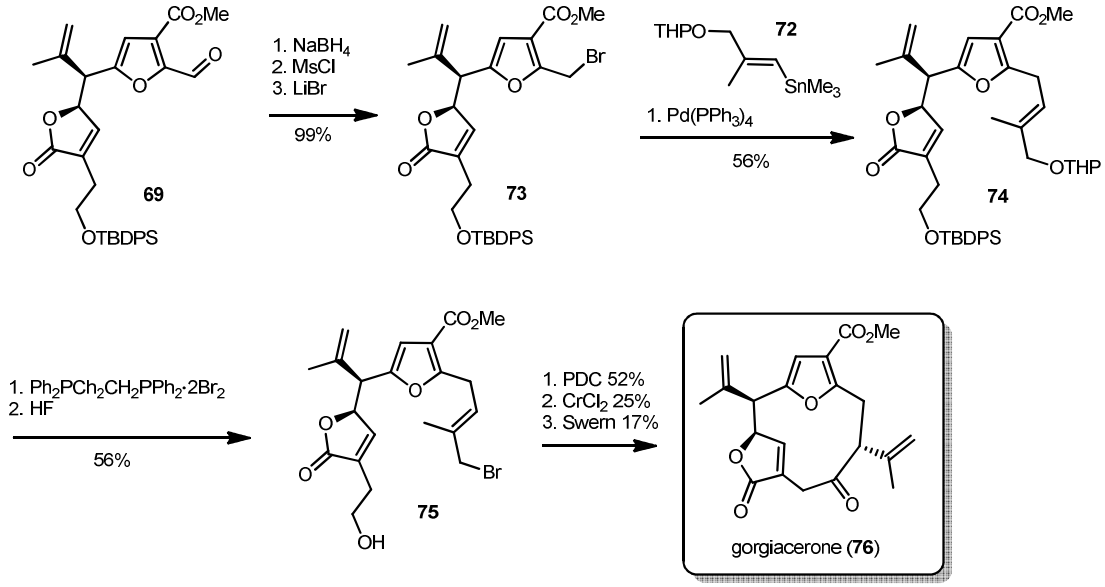
[17] V.D. Patil, U.R. Nayak, S. Dev, *Tetrahedron* **1973**, *29*, 341-348.
[18] J. E. McMurry, *Chemical Reviews* **1989**, *7*, 1513–1524.
[19] L. A. Paquette, A. M. Doherty, C. M. Rayner, *Journal of the American Chemical Society* **1992**, *10*, 3910–3926.
[20] C. M. Rayner, P. C. Astles, L. A. Paquette, *Journal of the American Chemical Society* **1992**, *10*, 3926–3936.
[21] A. D. Rodríguez, J.-G. Shi, S. D. Huang, *Journal of Organic Chemistry* **1998**, *63*, 4425-4432.
[22] Z. Yang, Y. Li, G. Pattenden *Tetrahedron* **2010**, *66*, 6546-6549.
[23] B. M. Trost , J. W. Herndon *Journal of the American Chemical Society* **1984**, *106*, 6835–6837.

Upon treatment with BF_3 and subsequent exposure to CSA building blocks **64** and **67** provided lactone **68** predominantly as the anti diastereoisomer. Double deprotonation and double selenylation furnished aldehyde **69** after oxidation and elimination. Meanwhile, **71** was formed from **70** and by using the stabilization effect of the THP group, selective metal-halogen exchange was carried out followed by a second metal-halogen exchange to yield **72** (Scheme 8).



Scheme 8. Paquette's synthesis of **69** and **72**.

After transformation of the aldehyde functionality in **69** to bromide **73**, palladium catalyzed Stille coupling with **72** afforded **74** in good yield. Conversion of allylic alcohol derivative **74** to the bromide followed by deprotonation gave intermediate **75**, which could then be easily oxidized to the aldehyde and set the stage for the chromium mediated macrocyclization (Scheme 9).



Scheme 9. Paquette's synthesis of gorgiacerone (**76**).

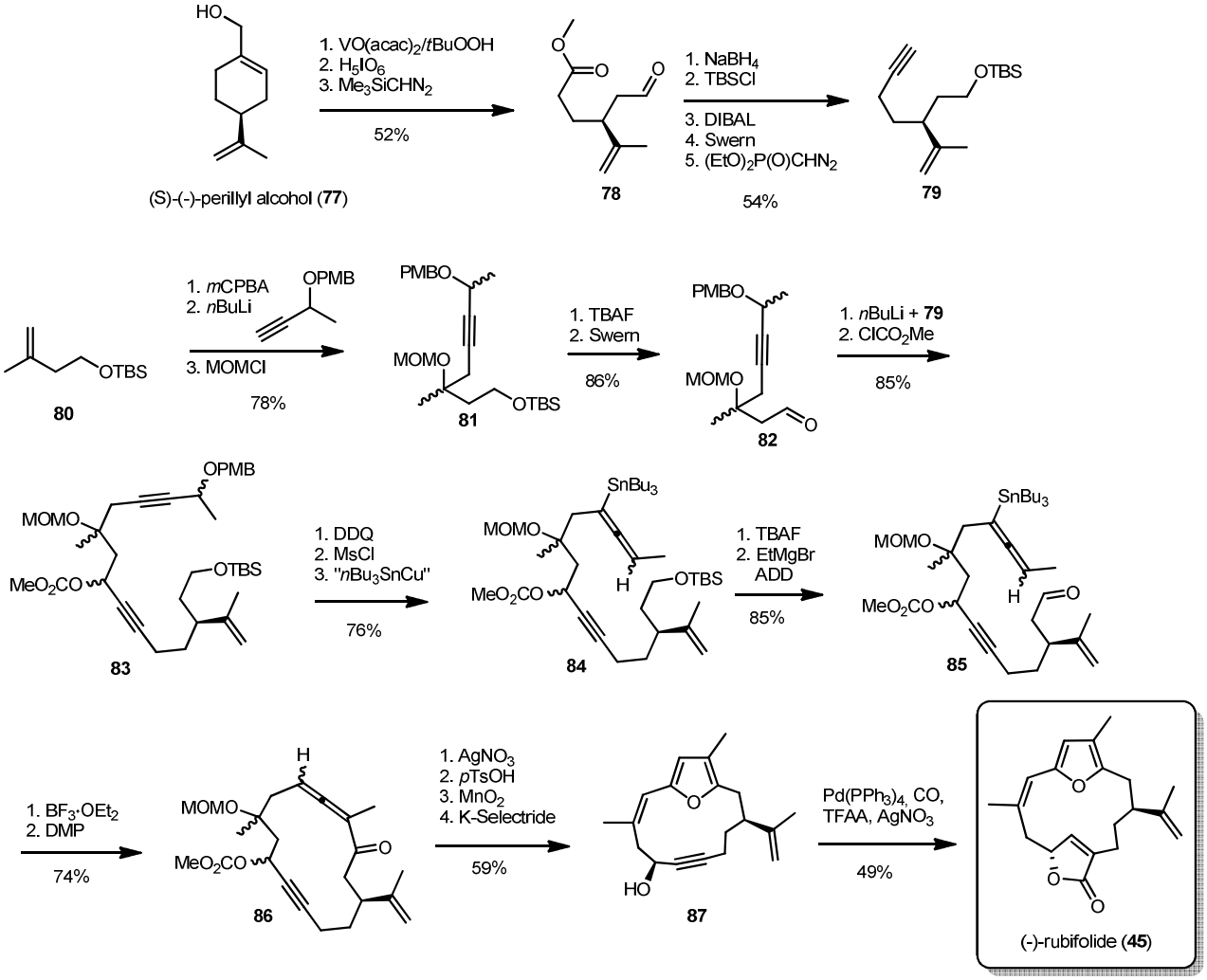
With large excess of chromium(II) chloride, the cyclization occurred in a stereoselective manner to form a single diastereoisomer in low yield. X-ray structure analysis identified the newly formed isopropenyl group to have the same orientation as the other isopropenyl side chain. After extensive investigations, the team could find conditions to oxidize the secondary alcohol with concomitant isomerization of the isopropenyl side chain to form the natural product gorgiacerone (**76**), albeit with only 17% yield (Scheme 9). The diastereoisomer outcome of the Hiyama coupling as well as the isomerization and the difficulties encountered during the final oxidation could be explained by computer simulation and steric hindrance of the macrocycle. Hence, the team completed the synthesis of gorgiacerone in a racemic way and also revealed in their publication the first attempts to synthetically interconvert gorgiacerone to other cembranoids.

2.3 Marshall's Synthesis of Rubifolide (45) [24]

Rubifolide (**45**) is believed to be at the source of biogenesis of many furanocembranoids.[11] An efficient synthetic route to access this diterpene could open the door to the synthesis of many cembranoid derivatives (see Trauner's syntheses, Section 2.4). Moreover, Marshall has previously used his methodology to close other cembranoid rings.[25]

[24] J. A. Marshall, C. A. Sehon, *Journal of Organic Chemistry* **1997**, *13*, 4313–4320.
[25] J. A. Marshall, X. J. Wang, *Journal of Organic Chemistry* **1992**, *12*, 3387–3396.

(*S*)-(−)-Perillyl alcohol (**77**) is a naturally occurring monoterpene with promising anti-tumor activity. Only small quantities can be extracted from plants but it can be produced cheaply by a bio-catalytic oxidation process from limonene.[26] The synthesis started with a hydroxyl directed epoxidation followed by a double periodate cleavage. Methylation of the resulting carboxylic acid then delivered aldehyde **78** in fair yield. Reduction followed by a protection of the primary alcohol and subsequent reduction/oxidation sequence of the methyl ester delivered the aldehyde intermediate, which was converted to alkyne **79** by Seyferth-Gilbert homologation. The second substructure was assembled starting from protected isopentenyl alcohol **80**. Epoxidation and addition of the lithium acetylide was followed by MOM protection to give **81** (Scheme 10).



Scheme 10. Marshall's synthesis of rubilolide (**45**).

[26] J. B. van Beilen, R. Holtackers, D. Lüscher, U. Bauer, B. Witholt, W. A. Duetzm, *Applied and Environmental Microbiology* **2005**, *4*, 1737-1744.

Next, silyl deprotection and Swern oxidation produced aldehyde **82**. Coupling between both fragments **79** and **82** was best achieved by deprotonation of acetylene **79** and addition to aldehyde **82** to give **83** after carbonate protection as a complex mixture of diastereoisomers. Removal of the PMB protecting group followed by mesylate formation and addition of a cuprate afforded allenylstannane **84** in excellent yield. Installation of the aldehyde group in **85** was followed by the key macrolactonization reaction. Lewis acid induced the cyclization with concomitant oxidation and isomerization to form macrocycle **86**. Intra-annular furan formation was performed by exposure of **86** to $AgNO_3$ on silica gel. Acid catalyzed elimination produced a 1:1 mixture of diastereoisomers of propargylic alcohols followed by adjustment of the stereochemistry of the secondary alcohol to yield **87** (Scheme 10).

Finally, the trifluoro-acetylated propargylic alcohol was converted to butenolide with inversion of configuration through Pd(0) catalyzed hydro-carbonylation and $AgNO_3$ catalyzed cyclization of the intermediate allenic acid to yield rubifolide (**45**). The team also confirmed the absolute configuration of the natural product after having synthesized its enantiomer (Scheme 10).

2.4 Trauner's Syntheses of Bipinnatin J (46), Rubifolide (45), Isoepilophodione B (100), Intricarene (102), Coralloidolides A, B, C and E (103-106) [27,28,29]

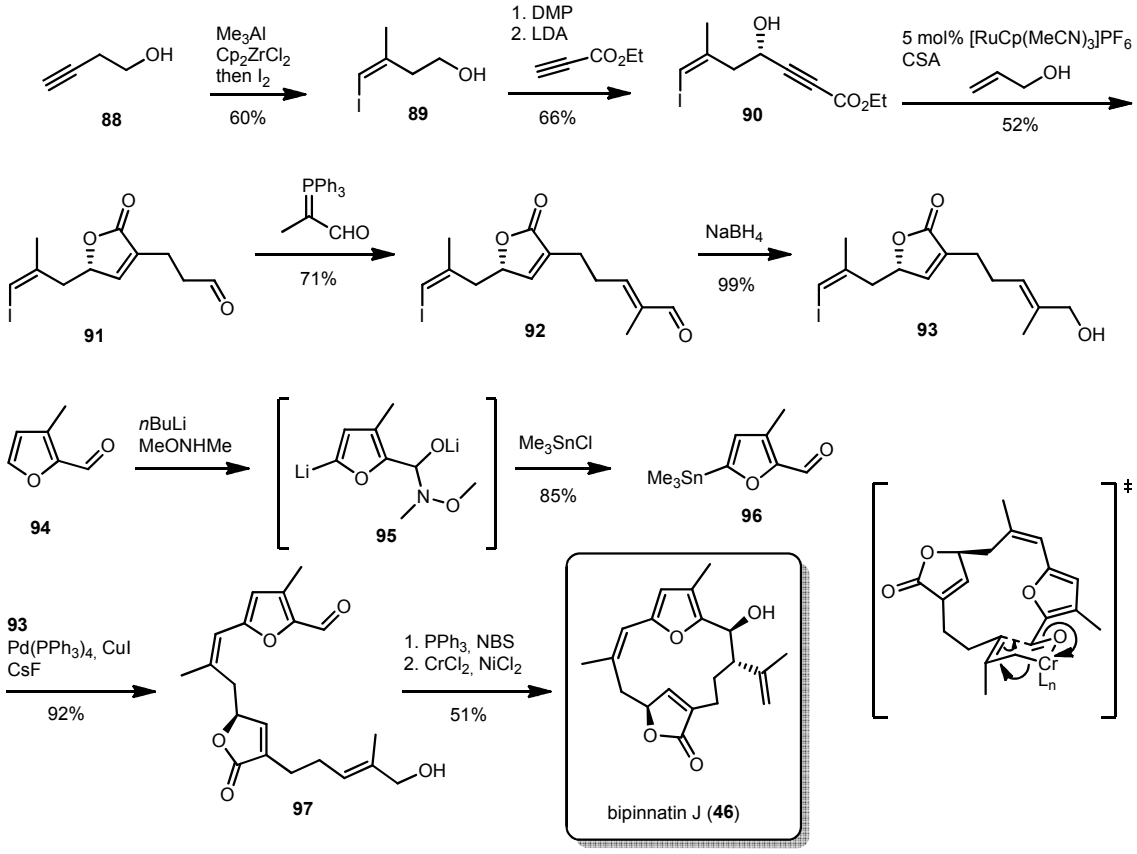
In order to confirm the interconnectivity and biosynthetic relationships between the members of the furanocembranoid family, Trauner and his research group initiated a series of syntheses in 2006. They reported the first synthesis of bipinnatin J (**46**),[27] a diterpene, which is believed to be like rubifolide (**45**) at the biosynthetic origin of hundreds of other more complex cembranoids such as bielschowskysin (**1**).

2.4.1 Bipinnatin J (46)

Trauner reported the first, protecting-group free and highly stereoselective (though racemic) synthesis of bipinnatin J (**46**) in nine step.[27] The synthetic route started with commercially available 3-buthynol (**88**), which was converted to vinyl iodide **89** in excellent regio- and stereoselectivity. Next, Dess-Martin oxidation followed by addition of acetylide gave **90** in good yield. As a key step of the sequence a ruthenium(II)-catalyzed Trost enyne reaction gave aldehyde **91** in a regio- and stereoselective manner.

[27] P. A. Roethle, D. Trauner, *Organic Letters* **2006**, *2*, 345–347.
[28] P. A. Roethle, P. T. Hernandez, D. Trauner, *Organic Letters* **2006**, *25*, 5901–5904.
[29] T. J. Kimbrough, P. A. Roethle, P. Mayer, D. Trauner, *Angewandte Chemie International Edition* **2010**, *49*, 2619 – 2621.

Wittig olefination furnished **92** followed by chemoselective reduction to give subunit **93**. In the meanwhile, furan moiety **96** was prepared in a single step from 3-methylfurfural (**94**) by *in situ* protection of the aldehyde and deprotonation to form **95** followed by lithium-tin exchange to give Stille reaction partner **96**. Palladium catalyzed coupling reaction was achieved in excellent yield to build **97**. Conversion of the allylic alcohol to the allylic bromide set the stage for the Nozaki-Hiyama-Kishi reaction,[30,31] which resulted in the formation of bipinnatin J (**46**) as a single diastereoisomer, explained by the inflexibility of the six-membered ring transition state (Scheme 11).

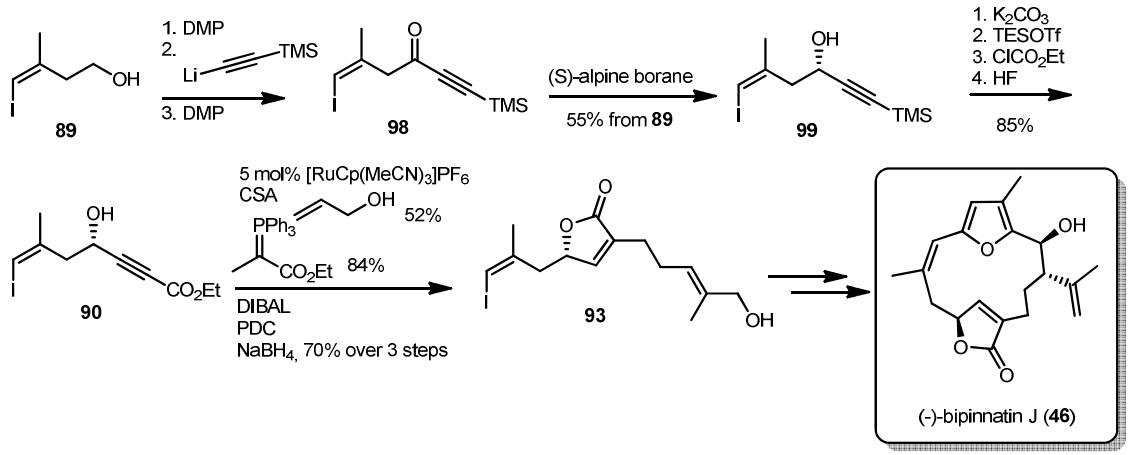


Scheme 11. Trauner's synthesis of *rac*-bipinnatin J (**46**).

A few months later, the team was able to optimize the synthesis and presented the first asymmetric route to (-)-bipinnatin J (**46**).[28] In the asymmetric approach, oxidation of **90** and asymmetric reduction did not afford enantiomerically enriched **90**, for this reason the team had to explore other substitutions.

[30] H. Jin, J.-I. Uenishi, W. J. Christ, Y. Kishi, *Journal of the American Chemical Society* **1986**, *108*, 5644-5646.
[31] K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *Journal of the American Chemical Society* **1986**, *108*, 6048-6050.

Hence, TMS alkyne **98** was synthesized, which upon Midland's (*S*)-Alpine borane reduction furnished **99** in 92% ee. Four high yielding steps afforded **90** followed by the enyne reaction. The previous steps retained the optical information, however the Wittig olefination (**91→92**) proceeded with complete racemization. After a synthetic detour by using the more reactive reagent Ph_3P=C(Me)COOEt the team obtained **(+)-93** after a reduction/oxidation sequence. Following the previously reported racemic synthesis (Scheme 11), (-)-bipinnatin J (**46**) was obtained in good yield after Stille coupling and an optimized NHK reaction (72% compared to the previously reported 59%) (Scheme 12).



Scheme 12. Trauner's synthesis of (-)-bipinnatin J (**46**).

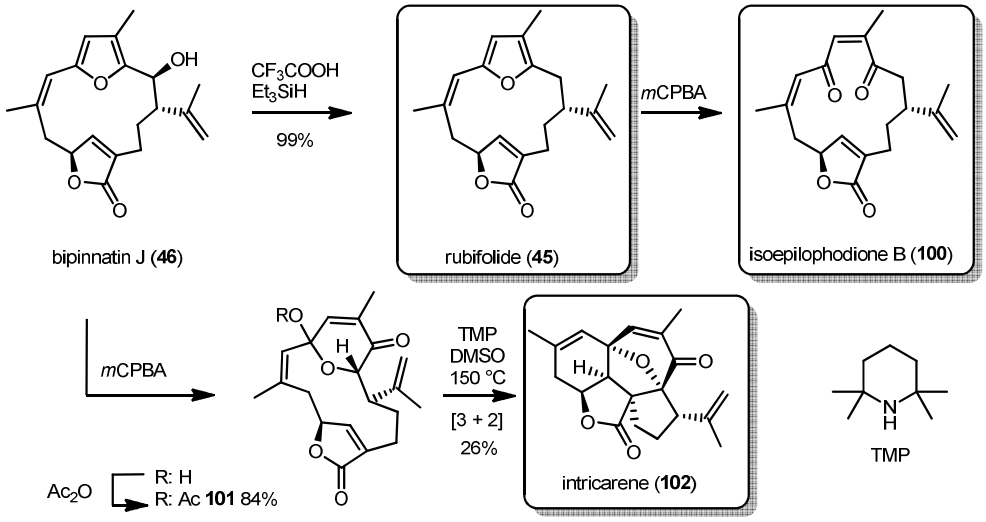
The original route contains nine steps (6.7% overall yield) but due to the troublesome asymmetric reduction and racemization of the allylic secondary alcohol in some intermediates, the final asymmetric route contains almost twice the number of steps (17 steps, 4.9% overall yield). However, this did not stop the team to produce enough supplies to explore (bio)synthetic relationships among furanocembranoids.

2.4.2 Rubifolide (45), Isoepilophodione B (100), Intricarene (102)

The series of investigations started with retro-biomimetic deoxygenation of bipinnatin J (**46**), to give rubifolide (**45**) in quantitative yield. Oxidation of the former product yielded isoepilophodione (**100**) in excellent yield.

Biosynthetic origins of intricarene (**102**) from bipinnatin J (**45**) were also investigated. Achmatowicz's protocol gave best results to produce **101**. Extensive reaction conditions were investigated to perform

the 1,3-dipolar cycloaddition to eventually furnish intricarene (**102**). The best conditions were the combination of a hindered secondary amine base with high temperature in a polar solvent (Scheme 13).



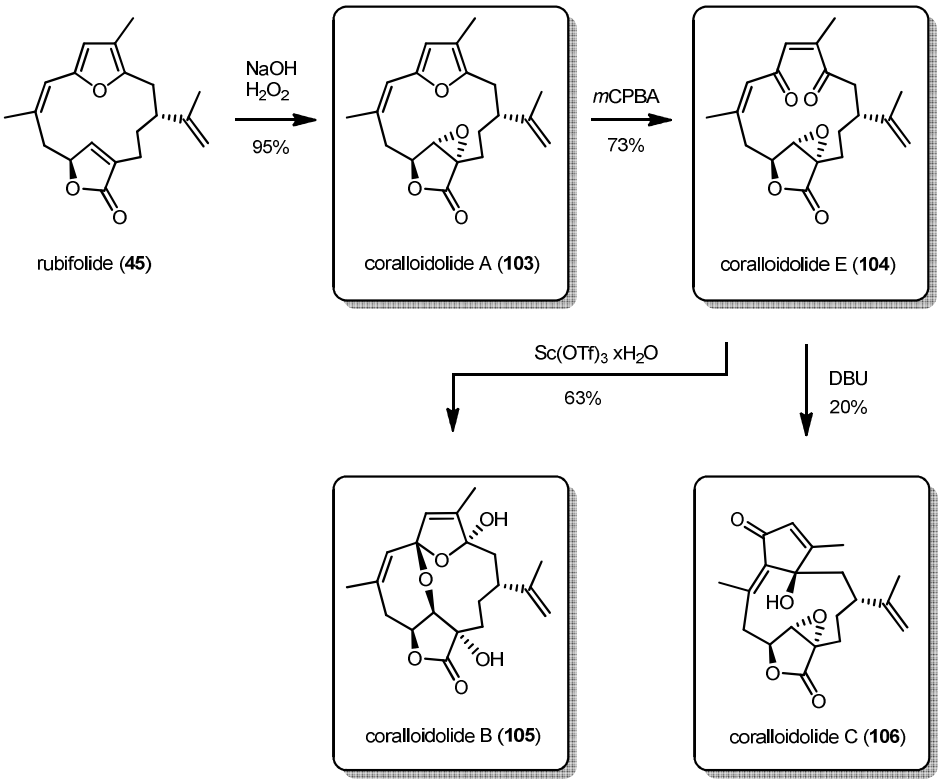
Scheme 13. Trauner's syntheses of rubifolide (**45**), isoepilophodione B (**100**) and intricarene (**102**).

As high temperatures had to be used to perform the cycloaddition, Trauner suggested a biogenesis of intricarene (**102**) catalyzed by an enzyme.

2.4.3 Coralloidolides A, B, C and E (103-106) [29]

The research group expended its biosynthetic investigation to the coralloidolides, the first family of furanocembranoids found in a Mediterranean organism.[29]

Starting from rubifolide (**45**), the alkene could be epoxidized to form coralloidolide A (**103**) in near quantitative yield. Oxidative cleavage of the furan ring using *m*CPBA gave coralloidolide E (**104**) in good yield. It is believed that coralloidolide E (**104**) is at the biogenesis origin of several other coralloidolides with prominent 2,5-diene-1,4-dione moiety, capable of being involved in many different reactive pathways. From this skeleton, transannular opening of the epoxide using scandium triflate hydrate gave tetracyclic coralloidolide B (**105**). Interestingly, this transformation seemed to be exclusively possible in dioxane as solvent. Further experiments starting from coralloidolide E (**104**) revealed that another reaction pathway could lead to the formation of more members of this family. Tautomerization and double bond isomerization could set the stage for a transannular aldol reaction, followed by double bond shift to the more thermodynamic stable position. Following the "one step, one natural product" principle, Trauner was able to access coralloidolide C (**106**) by using an excess of DBU (Scheme 14).



Scheme 14. Trauner's syntheses of coralloidolides A, B, C and E (**103**-**106**)

Thus, the team was able to proceed from bipinnatin J (**46**) to the selective interconversions of many and structurally challenging natural products and gave important insights into the bioconnectivity between all the members of the furanocembranoid family.

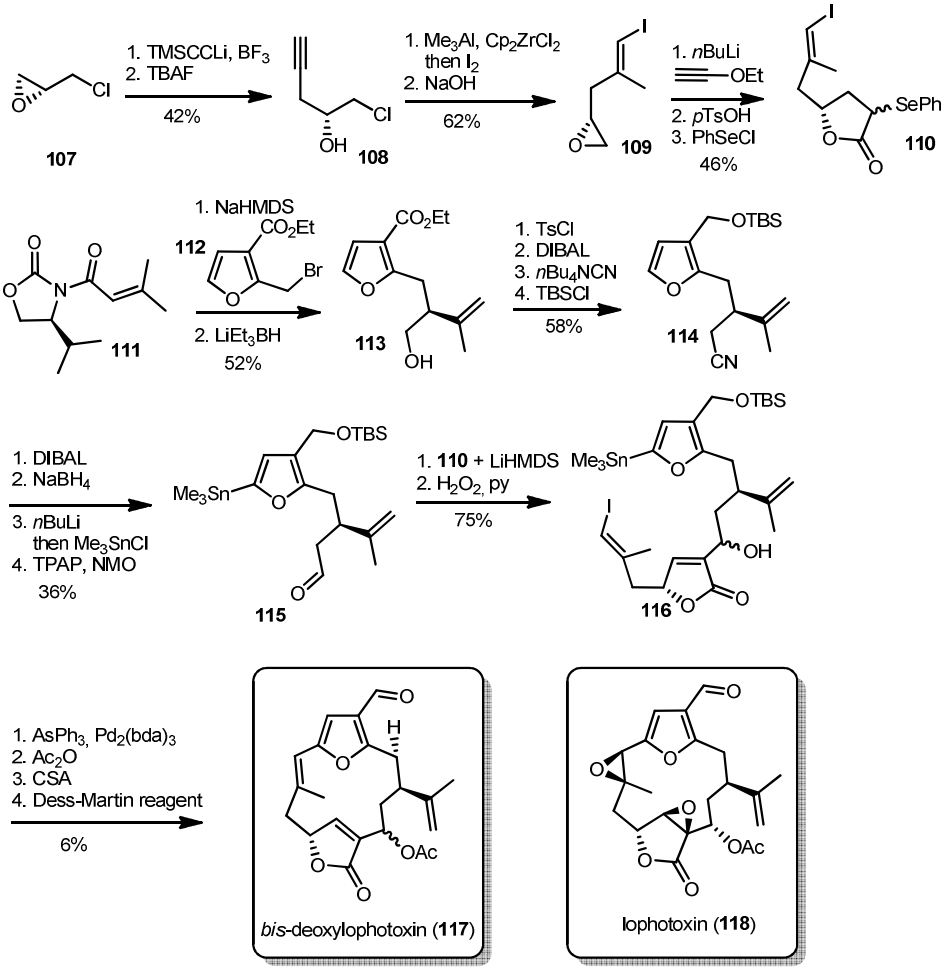
2.5 Pattenden's Synthesis of *bis*-Deoxylophotoxin (117) [32]

In 2001, the Pattenden group presented efforts toward the highly biologically active furanocembranoid lophotoxin (**118**), a potent neurotoxin, by completing the synthesis of *bis*-deoxylophotoxin (**117**), which might be a possible bioprecursor of the natural product (Scheme 15).

Lactone **110** was synthesized from (*R*)-(-)-epichlorohydrin (**107**), in which the oxiran was opened, following deprotection to yield **108**. Carbometalation-iodination of **108** gave the *E*-vinyl iodide, which was converted to epoxide **109** in the presence of a base. Lactone formation was achieved by treatment with 1-ethoxyacetylene followed by an acidic treatment and selenylation to give **110**. The second building block **115** was formed by allylic deprotonation of **111** and alkylation with furan derivate **112**.

[32] M. Cases, F. González-López de Turiso, G. Pattenden, *Synlett* **2001**, *12*, 1869-1872.

Auxiliary cleavage led to **113**, which was converted to **115** through **114** by deprotonation of the furan moiety and trimethylstannyl furan quench. Deprotonation of **110** using LiHMDS followed by addition of aldehyde **115** gave intermediate **116** in good yield after oxidative elimination. An intermolecular Stille coupling led to macrocycle **117** in low yield after acetylation and adjustment of the oxidation state of the furan substituent. The mixture of epimers at the carbon bearing the acetate group could be separated by HPLC before the final oxidation. Unfortunately, due to the low yield of the reaction sequence, the group has to date not been able to carry out the final double epoxidation, an indication of a certain chemo- and stereoselective challenge at the final step (Scheme 15).

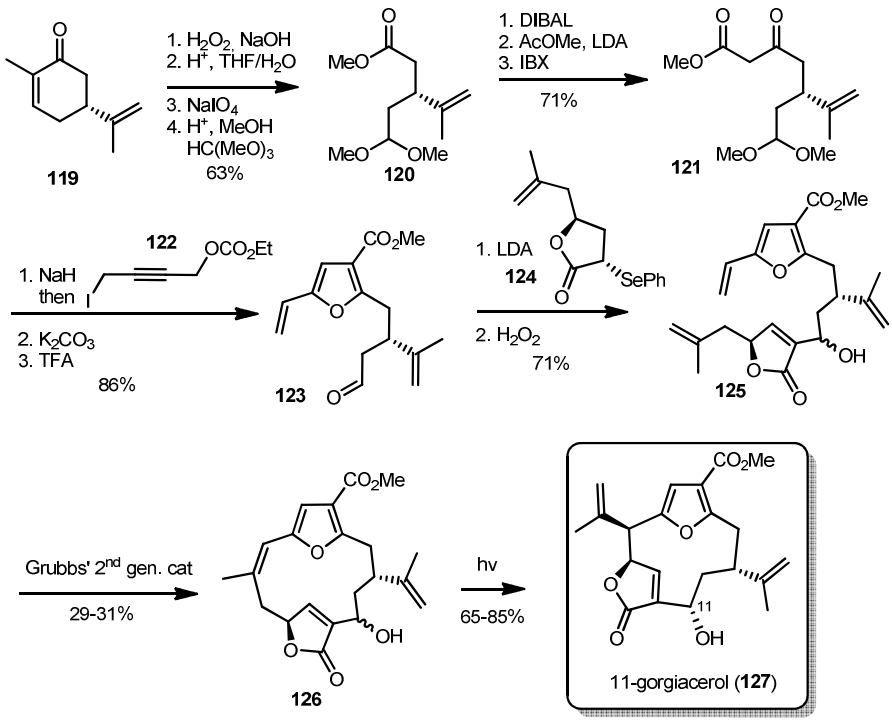


Scheme 15. Pattenden's synthesis of *bis*-deoxylophotoxin (**117**).

2.6 Mulzer's Synthesis of 11-Gorgiacerol (127) [33]

Recently, the Mulzer group presented a stereospecific biomimetic photochemical ring contraction of a furanocembranoid to the pseudopterane 11-gorgiacerol (**127**). Moreover, X-ray structure analysis was used to reassign the correct stereochemistry of the natural product, more specifically the configuration of the carbinol at C-11 (as shown in Scheme 16), misassigned by ^{1}H-NMR coupling constants only.

The synthesis started with the known 4 step sequence from (*R*)-(-)-carvone (**119**) to methylester **120**.[34] In fact, epoxidation followed by epoxide opening and glycol cleavage delivered **120** after treatment in anhydrous acidic methanol. Ketoester **121** was obtained after reduction to the aldehyde, aldol addition of methy acetate and oxidation (Scheme 16).

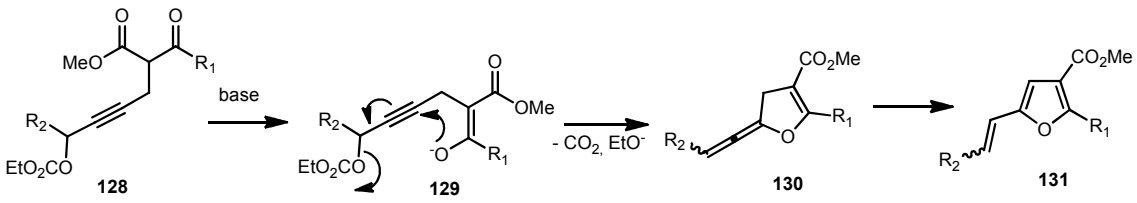


Scheme 16. Mulzer's synthesis of 11-gorgiacerol (**127**).

Deprotonation and alkylation with iodine **122** gave keto acetylide, which cyclized to furan **123** upon treatment with K_2CO_3 according to Wipf's protocol (Scheme 17) and release of the aldehyde group.[35]

[33] H. Weinstabl, T. Gaich, J. Mulzer, *Organic Letters* **2012**, *11*, 2834–2837.
[34] M. A. González, S. Ghosh, F. Rivas, D. Fischer, E. A. Theodorakis, *Tetrahedron Letters* **2004**, *45*, 5039–5041.
[35] P. Wipf, L. T. Rahman, S. R. Rector, *Journal of Organic Chemistry* **1998**, *63*, 7132-7133.

Aldol addition by deprotonation of **124** gave butanolide **125** after oxidative elimination. At this stage both diastereoisomers at C-11, resulting from the non-substrate controlled aldol addition, could be separated by column chromatography. The sequence was carried out with both epimers in parallel in order to confirm/reassign the structure of the natural product.



Scheme 17. Base mediated Wipf cyclization.

RCM with Grubb's second generation catalyst gave (*Z*)-olefin **126** in moderate yield. Completion of the syntheses of 11-gorgiacerol (**127**) and 11-epigorgiacerol (C11-epi-**127**) was achieved by irradiation with UVB light, which furnished both pseudopterane epimers, one of which was crystalline, allowing the unambiguous reassignment. In addition to the short and stereoselective synthesis, Mulzer presented access to several pseudopterane derivatives.

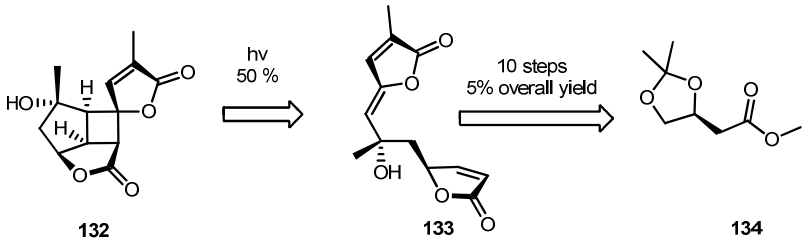
3 Previous and Present Synthetic Work

3.1 Overview

Approximately 10 academic groups are currently working worldwide on the total synthesis of bielschowskysin. It is quite surprising that since its isolation and characterization 10 years ago only a few publications from different research groups[41,43,45,48-50] including our own[36,37,38,39,40] relate synthetic efforts of advanced fragments and test systems. A PhD thesis dealing with the elaboration of this extremely dense and complex molecule appears therefore of great synthetic interest. In this chapter an overview of the published efforts toward the synthesis of the natural product is given.

3.2 The Sulikowski Approach [41]

In 2006, the group of G. Sulikowski was the first to publish a concise synthesis of the polycyclic western part of bielschowskysin resulting in the preparation of tetracycle **132**. The group reported the preparation of a tetracyclic core employing a stereoselective intramolecular [2+2] photocycloaddition of the 5-alkylidene-2(5*H*)-furanone **133**, which was prepared in 10 steps from the literature known **134** (Scheme 18).



Scheme 18. Sulikowski's retrosynthesis of tetracycle **132**.

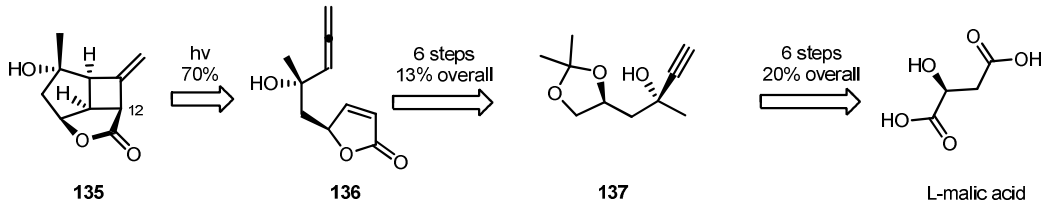
The main difficulty seems to be the generation of the correct *exo*- double bond geometry, crucial for the stereoselective outcome of the final product. During the synthesis only adduct with the wrong geometry was produced (Scheme 18). Luckily, during the [2+2] biomimetic key step reaction the geometry was

[36] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Organic Letters* **2012**, *9*, 2195-2197.
[37] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *European Journal of Organic Chemistry* **2013**, *20*, 4379-4398.
[38] M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *Organic Letters* **2013**, *12*, 3098-3101.
[39] J.-B. Farcet, M. Himmelbauer, J. Mulzer, *European Journal of Organic Chemistry* **2013**, submitted (June 13th, 2013).
[40] M. Himmelbauer, J.-B. Farcet, J. Gagnepain, J. Mulzer, *European Journal of Organic Chemistry* **2013**, submitted (June 13th, 2013).
[41] B. Doroh, G. A. Sulikowski, *Organic Letters* **2006**, *8*, 903-906.

inverted almost completely. Since this article nothing further has been published from the Sulikowski group, an indication maybe that this western fragment could not be further extended. Deprotonation in order to form the quaternary center seems difficult as the tricyclic core is already very strained and cannot be relaxed to build the necessary enolate (Bredt's rule[42]).

3.3 The Lear Approach [43]

Three years later, in 2009, Lear and his group succeeded in the elaboration of the tricyclic intermediate **135**. They proposed to build the bielschowskyane ring system through a formal [2+2] cycloaddition of an allene-butenolide functionalized furanocembrane macrocycle. Although biosynthetic considerations of cembranoid natural products involve a 5-methylenefuran intermediate, like in **133**, the group succeeded and built the tricyclic western fragment **135** in a non-biomimetic fashion (Scheme 19).



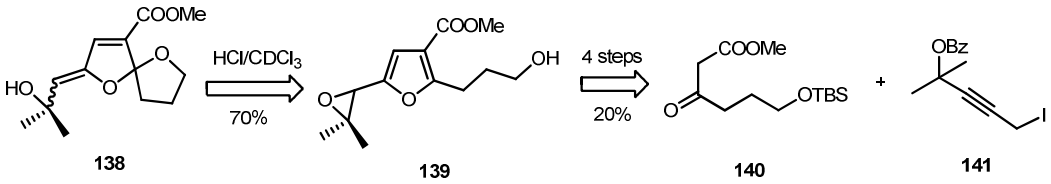
Scheme 19. Lear's retrosynthesis of tricycle **135**.

Starting from L-malic acid the team first formed **134**, followed by the introduction of an ethynyl rest in a diastereoselective manner in a separable 4:1 ratio to build **137**. Next, the butenolide moiety was formed in five steps in good yield to set the stage for a Searles-Crabbé allene formation[44] on the previously installed alkyne moiety, which delivered allene **136**. By using simple UV lamps irradiating at 254 nm, the team could perform the [2+2] cyclo-photoaddition to the tricyclic core **135** (Scheme 19). However, based on the lack of further publications, we can assume that the Lear group was not able to install the quaternary center at C-12, neither prior to the cycloaddition nor by deprotonation of the cyclobutane **135**.

[42] J. Bredt, *Justus Liebig's Annalen der Chemie* **1924**, *437*, 1–13.
[43] R. Miao, S. G. Gramani, M. J. Lear, *Tetrahedron Letters* **2009**, *50*, 1731-1733.
[44] S. Searles, Y. Li, B. Nassim, M. T. Robert Lopes, P. T. Tran, P. J. Crabbé, *Journal of the Chemical Society, Perkin Transactions 1* **1984**, 747-751.

3.4 The Pattenden Test System [45]

The following year, Pattenden and co-workers reported the synthesis of the furan derivate **138**, produced in four steps including an elegant palladium catalyzed Wipf furan cyclization[46] from literature known **140**[47] and **141**[45] (Scheme 20). They additionally attempted to confirm the biosynthesis of bielschowskysin by isolating *exo*-methylene intermediates such as **138** (Scheme 20).

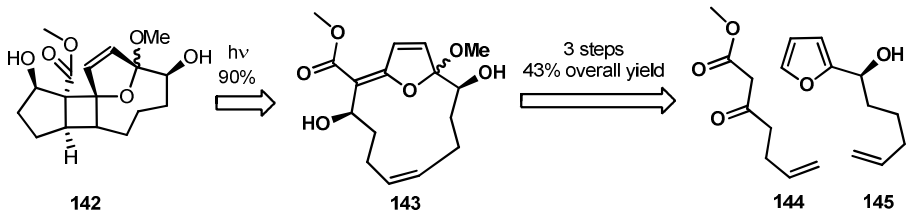


Scheme 20. Pattenden's test system **60**.

When a solution of epoxide **139** in $CDCl_3$ containing traces of HCl was left at room temperature for two hours ^{1}H-NMR showed formation of a mixture of *Z* and *E* isomers of **138**. Eventually, only the corresponding diene product resulting from water loss in **138** could be isolated.

3.5 The Nicolaou Test System [48]

In April 2011, two students of the Nicolaou group conceived a test system leading to the tetracycle **142** containing the largest 14-membered ring of the target molecule (Scheme 21).



Scheme 21. Nicolaou's test system **142**.

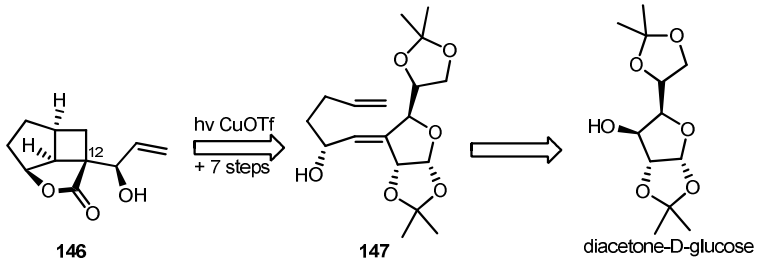
In order to verify a postulated transannular biosynthesis,[11] a ring system was designed, in which the macrocyclic precursor **143** is generated by a ring closing metathesis (RCM) reaction after oxidative CAN

[45] Y. Li, G. Pattenden, J. Rogers, *Tetrahedron Letters* **2010**, *51*, 1280–1283.
[46] P. Wipf, M. J. Soth, *Organic Letters* **2002**, 1787-1790.
[47] A. H. Davidson, C. D. Floyd, C. N. Lewis, P. L. Myers, *Journal of the Chemical Society, Chemical Communications* **1988**, 1417-1418.
[48] K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Angewandte Chemie International Edition* **2011**, *50*, 5149-5152.

mediated coupling of the fragments **144** and **145**. Indeed, CAN in MeOH afforded a conjugated ketoester, strongly stabilized by two carbonyl functionalities of the malonate derivate **144**. This allowed the dearomatisation of the furan ring **145** as well as the formation of the cyclic ketal. The rest of the synthesis was very concise with Grubb's metathesis to form the macrocycle and a reduction of the ketone to form the [2+2] precursor **143** (Scheme 21). The formation of the tetracycle as a single diastereoisomer could be obtained by UV light irradiation in good yield. The presence of the stabilizing methyl ester seems crucial and the idea may require substantial synthetic detour to be applicable for a synthesis toward bielschowskysin (**1**). Indeed, in bielschowskysin's precursor of the [2+2] cycloaddition the electron poor alkene is the γ-butenolide and not a methylester stabilized alkene as in **143**. A synthesis leading to bielschowskysin (**1**) or a similar substituted furanocembranoid is also unlikely following Nicolaou's strategy.

3.6 The Ghosh Approach [49]

Starting from diacetone-D-glucose, diene **147** was easily accessed in a few steps. Irradiation with a sun lamp using a Copper catalyzed [2+2] photocycloaddition delivered the cyclobutane intermediate in 65% yield. A further seven steps to invert the stereocenter of the secondary alcohol and to oxidize the eastern part of the molecule to the correct oxidation state was used to access **146** (Scheme 22).



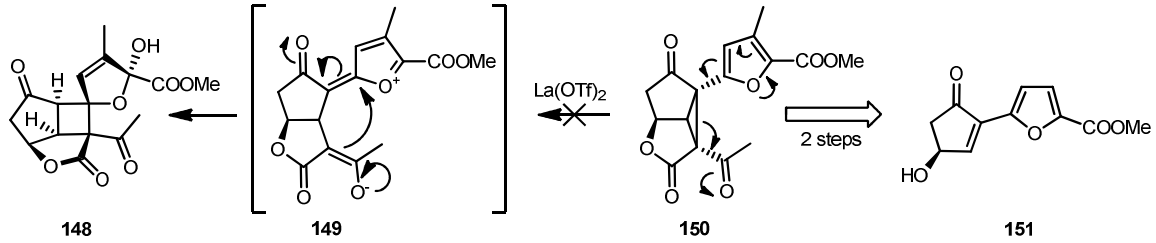
Scheme 22. Ghosh's retrosynthesis of **146**.

The attractive feature of this route is the rapid preparation of the bicyclo[3.2.0]heptane moiety with control of the stereoselectivity of the new quaternary center at C-12. Yet, extensive work needs to be done for the correct functionalization of the cyclopentane as well as the cyclobutane ring systems.

[49] A. Jana, S. Mondal, Md. F. Hossain, S. Ghosh, *Tetrahedron Letters* **2012**, *53*, 6830-6833.

3.7 The Stoltz Test System [50]

In an attempt to form the very advanced test system **148**, cyclopropane intermediate **150** was synthesized. A Lewis acid furan-mediated cyclopropane fragmentation was planned to deliver enolate **149**, followed by an enolate 1,4-Michael addition on the newly formed enone was envisaged to form the cyclobutane core **148** (Scheme 23). The synthesis started with a Suzuki coupling to form racemic **151**. Esterification with 2-diazoacetoacetic acid and a copper catalyzed cyclopropanation furnished the precursor **150** after extensive reaction optimization.



Scheme 23. Stoltz's test system **150**.

Although the key step of this route did not achieve its goal, it is noteworthy that optically enriched starting material **151** could be obtained by a successful and efficient palladium(II)-catalyzed oxidative kinetic resolution.

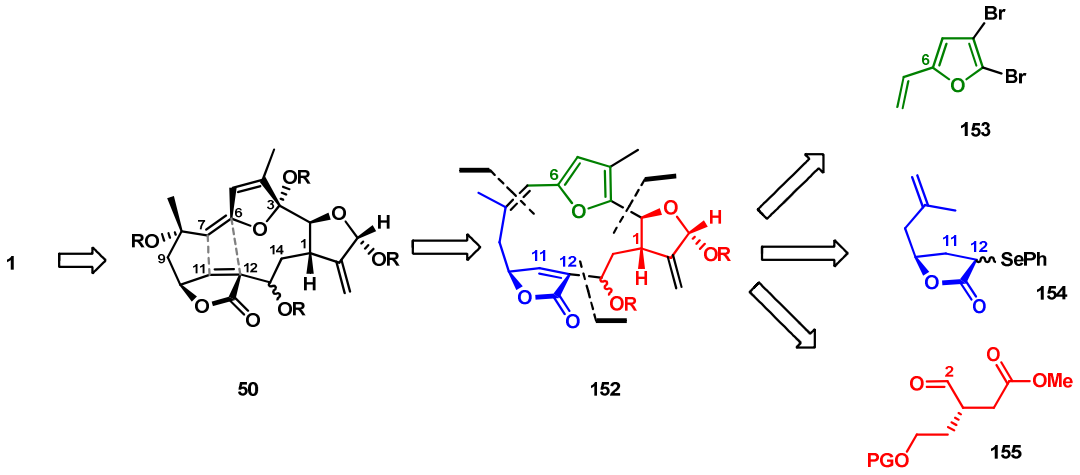
3.8 The Mulzer Approaches

From the first two published syntheses,[41,43] it can be assumed that both teams could not form the all-carbon quaternary center in the cyclobutane ring. The strained and dense cage formed with the lactone does not allow deprotonation. Moreover, an allene seems to be a good substrate to close the cyclobutane ring. These elements were taken into account while planning our syntheses. Since the beginning of the project many routes have been developed, however three main paths were followed:

3.8.1 Biomimetic Approaches

Based on the biomimetic route,[11,12] it was intended to first create the macrocycle **152**, the likely precursor of bielschowskysin (**1**), in a convergent way from the three building blocks **153**, **154** and **155**. Then, under irradiation in an aqueous medium it was envisaged that **50** could be formed, followed by generation of the natural product (Scheme 24).

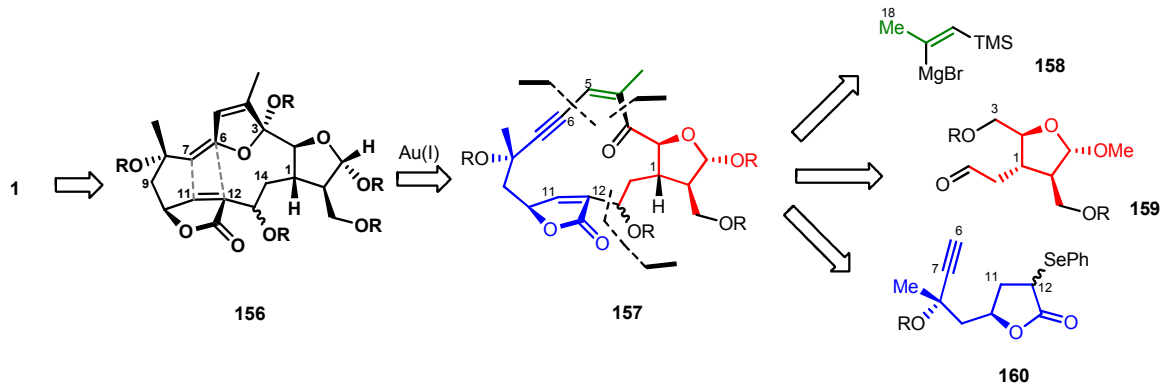
[50] M. E. Meyer, J. H. Phillips, E. M. Ferreira, B. M. Stoltz, *Tetrahedron* **2013**, 1-9.



Scheme 24. Mulzer's first retrosynthesis of bielschowskysin.

During this project, **153** could be synthesized and literature known **154**[51] was accessible in large amounts. However, the synthesis of optically active aldehyde **155** turned out to be more challenging than expected. Moreover, our early results (see Section 4.2) corroborated the results from Pattenden,[45] therefore we abandoned this approach due to the difficulties in obtaining *exo*-methylene intermediates.

In a similar fashion, macrocycle **156** was planned to be formed after gold mediated furan cyclization of **157** from building blocks **158**, **159** and **160** (Scheme 25).



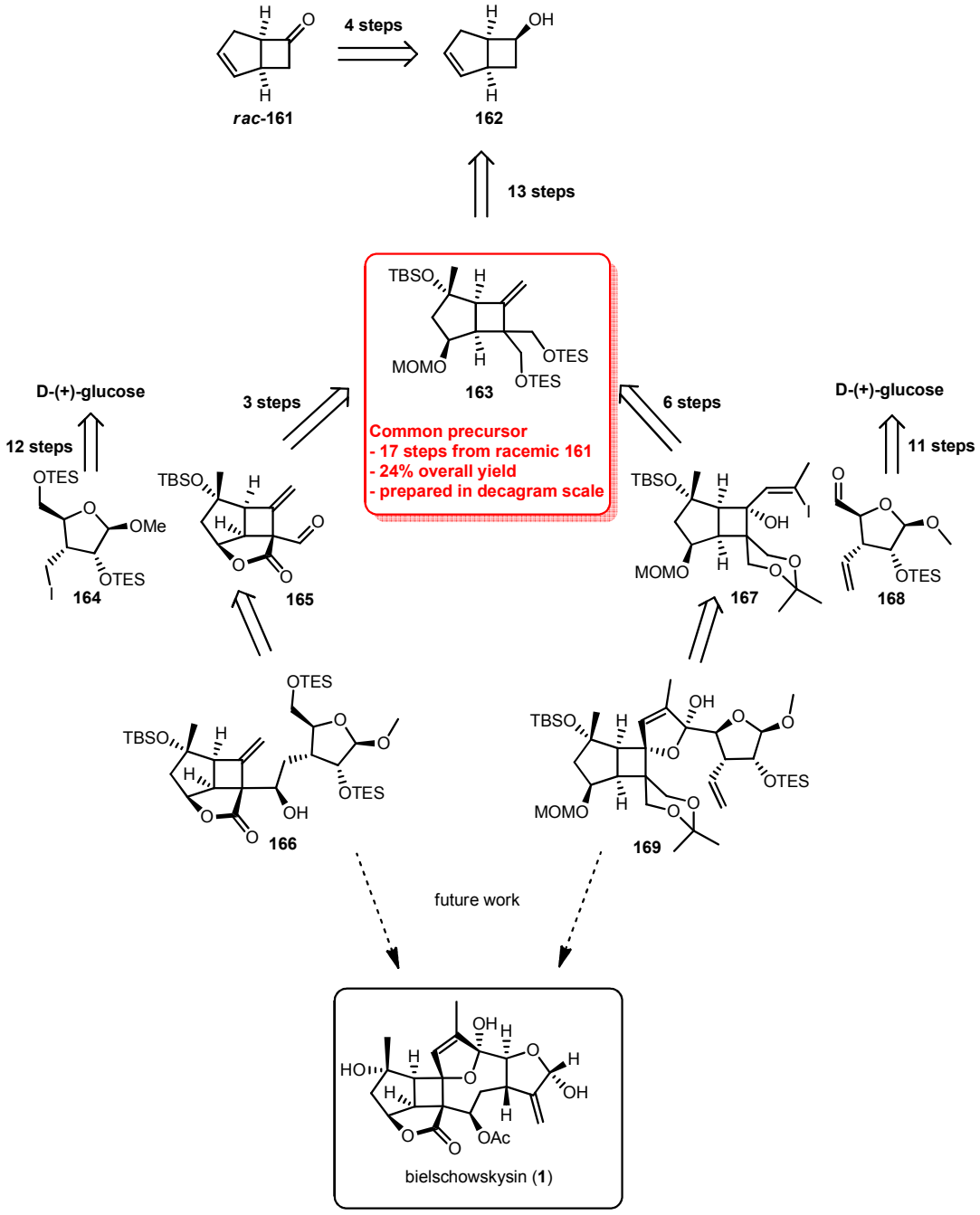
Scheme 25. Mulzer's second retrosynthesis of bielschowskysin.

Results and discussion of the synthesis of an advanced intermediate of this route can be found in the PhD thesis of Martin Himmelbauer and in Section 4.3.[40,52]

[51] T. Gaich, H. Weinstabl, J. Mulzer, *Synlett* **2009**, *9*, 1357-1366.
[52] M. Himmelbauer, Ph.D. Thesis, University of Vienna, 2013.

3.8.2 A Non-Photochemical Approach

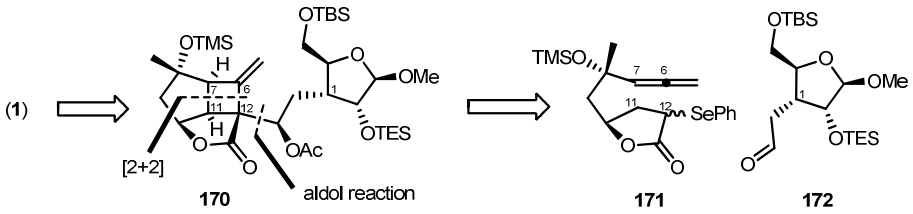
This approach is the focus of this thesis and resulted in four publications toward advanced precursors of bielschowskysin (**1**).[36,37,39] See Sections 4.1, 4.2, 4.3 and 4.4 for details (Scheme 26).



Scheme 26. Mulzer's retrosynthesis of **166** and **169**.

3.8.3 A Convergent Photochemical Approach

Starting from cheap D-(+)-glucose and L-(-)-malic acid, building blocks **171** and **172** could be synthesized in a few steps followed by their coupling by aldol reaction (Scheme 27). Next, photo cycloaddition furnished, after acetylation, **170** in a convergent manner. This synthesis represents an alternative to the synthesis of **166** (see Section 4.3)



Scheme 27. Mulzer's retrosynthesis of **170**.

Furthermore, a macrocyclization was performed successfully. Results and presentation of the synthesis of the advanced intermediate **170** and macrocycle of this route can be found in the PhD thesis of Martin Himmelbauer[38,40,52] and in Section 4.3.

4 Publications

The aim of this project was to develop the first synthetic route to bielschowskysin (**1**), with a minimum number of steps, high overall yield and to apply new methodologies, when possible. Learning from other syntheses of furanocembranoids (Section 2) and previous work on bielschowskysin (Section 3) aided in the development of a route more likely to succeed. The assignment of the absolute configuration as well as the possibility to provide diverse derivatives of the natural product were also a main objective of the outlined work.

In this Section, the results are presented in form of a collection of articles published in international reviewed journals. They also reflect, in a chronological manner, the development of the project. We aimed to synthesize a highly substituted western fragment of the target molecule. As a photochemical approach failed to deliver the desired cyclobutane ring, a non-photochemical approach was successfully developed (articles 4.1 and 4.2). However, it emerged from further investigations that the *exo*-methylene functionality was unsuitable for further macrocyclization (article 4.3). In addition, a letter was published to which I contributed in the concept developments and project discussions (not included in this thesis):

”A Palladium-Catalyzed Carbo-Oxygenation: the Bielschowskysin Case”
Himmelbauer, Martin; Farcet, Jean-Baptiste; Gagnepain, Julien; Mulzer, Johann
Organic Letters **2013**, *12*, 3098-3101.

An alternative route based on an early formation of the dihydrofuran ring and the synthesis of a fully developed northern hemisphere was successfully designed (article 4.4 submitted back-to-back with article 4.3).

Although the synthesis could not be completed within this project, a stereoselective pathway to access two advanced fragments of the natural products is presented. The first fragment is the fully developed southern hemisphere, while the second fragment processes a completed northern hemisphere. Efforts concentrate now on the last steps of the synthesis.

4.1 A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin

Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann

Organic Letters **2012**, *9*, 2195-2197.

The supporting information (SI) was omitted in order to avoid redundancy. For detailed experimental procedures and NMR data see SI of the full paper (Section 4.2).

Contribution: Concept development: Jean-Baptiste Farcet, Martin Himmelbauer and Johann Mulzer
Experimental work: Jean-Baptiste Farcet
Product characterization and analytic work: Jean-Baptiste Farcet
Preparation of the manuscript: Jean-Baptiste Farcet and Johann Mulzer

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A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin

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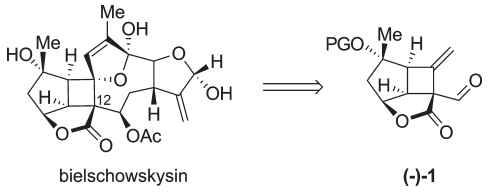
Received March 13, 2012

ABSTRACT



An asymmetric synthesis of the tricyclic core (−)-1 of the marine diterpene bielschowskysin is described. In particular, a methodology was developed to introduce the crucial quaternary center at C-12.

In 2004, Rodriguez et al.[1] reported the isolation of the highly oxygenated diterpene bielschowskysin (Figure 1) from the gorgonian octacoral *Pseudopterogorgia kallos*, found in the Southwestern Caribbean Sea. Its strong antimalarial activity and significant cytotoxicity against lung and renal cancer cell lines as well as its unique *cis*-fused tricyclo[9.3.0.0^{2,10}]tetradecane ring system including 11 stereocenters immediately caught the attention of the scientific community.

Since its structural elucidation, three efforts toward the total synthesis of the diterpenoid have been reported, all of which are centered around a biomimetic intramolecular [2 + 2]-photocycloaddition to create the crucial [4,5]-core fragment (Scheme 1).[2−4] In none of these approaches, however, could the quaternary center at C-12 be established. This appears to be a major drawback, as due to Bredt's rule, this position is deactivated in a structure such as **I** toward the formation of the enolate **II** required for the addition of an appendage, for instance via aldol addition (Scheme 2).

An obvious way to generate the appropriate functionality is the intramolecular [2 + 2]-photocyclization of **III** to **IV**.

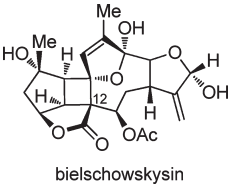


Figure 1. Structure of bielschowskysin.

However, despite extensive variation of substituents and conditions, the desired product was not obtained.

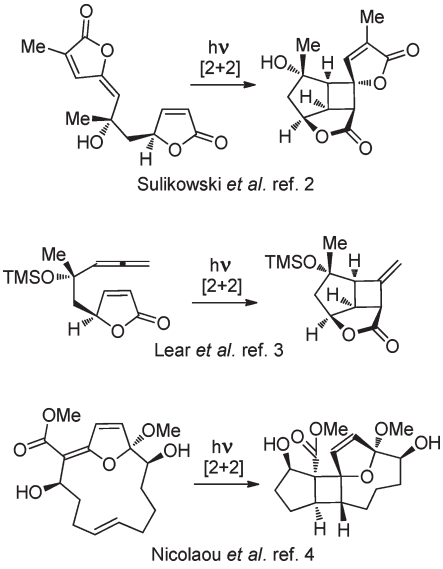
Hence, we report a stereoselective nonphotochemical synthesis of the fully substituted core fragment **(−)-1** of bielschowskysin including its all-carbon quaternary center from the known optically active alcohol **(+)-4**, which was obtained in a four-step sequence starting from commercially available **rac-2** (Scheme 3).[5]

Our synthesis started with a TBS-protection of **(+)-4** to furnish **(−)-5**. To functionalize the five-membered ring, photooxygenation[6] 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,

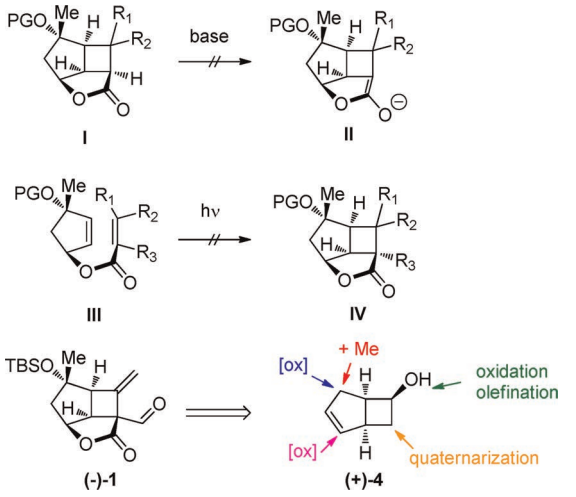
(1) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661–1664.
(2) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906.
(3) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733.
(4) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149–5152.
(5) (a) Gaich, T; Weinstabl, H; Mulzer, J. *Synlett* **2009**, *9*, 1357–1366. (b) Weinstabl, H. Ph.D. Thesis, University of Vienna, 2011.
(6) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135–4137.

10.1021/ol3006419
Published on Web 04/16/2012

Scheme 1. Previously Reported [2 + 2] Photocycloadditions



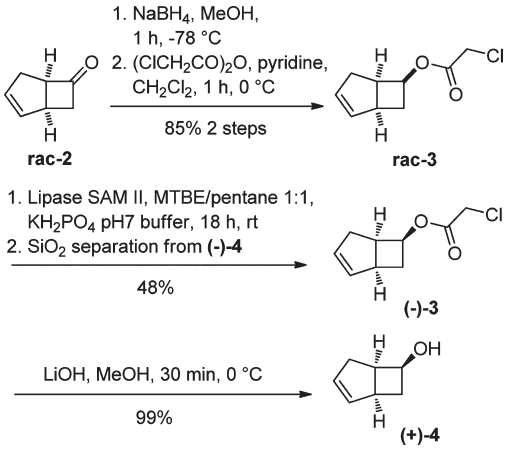
Scheme 2. Retrosynthetic Analysis



and produced the α,β-unsaturated ketone **(−)-6** with high regioselectivity (dr = 20:1). Conjugate addition with dimethyl cuprate, trapping of the enolate with TMSOTf to give enol ether **(−)-7**, and Saegusa−Ito oxidation[7] provided ketone **(−)-9**. The success of the Saegusa oxidation crucially depended on the use of DMSO as solvent and molecular oxygen as cooxidant. Otherwise, the reaction was difficult to scale up, suffered from inconsistent yields, and TMS-enol ether **(−)-7** was prone to desilylation to form undesired ketone **(−)-8** (Scheme 4).

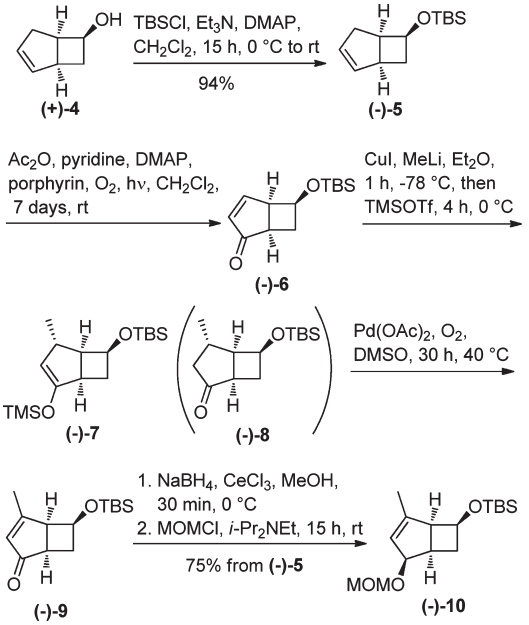
Taking advantage of the "open-book" geometry of bicycle **(−)-9**, the carbonyl group was reduced diastereoselectively under Luche conditions.[8] MOM-protection yielded diol

Scheme 3. Preparation of Optically Pure Starting Material



derivative **(−)-10**. The sequence could be carried out in 75% overall yield from **(−)-5** without purification of intermediates. Molecular oxygen, a catalytic amount of cobalt complex, and phenylsilane promoted the Mukaiyama−Isayama oxidation−reduction−hydration[9] in a regio- and stereoselective manner, leading to tertiary alcohol **(−)-11**.

Scheme 4. Functionalization of the Five-Membered Ring

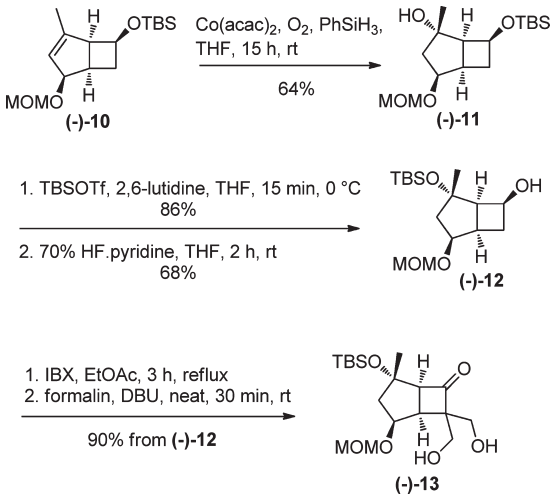


After a protection−deprotection sequence, the five-membered ring in bicycle **(−)-12** was appropriately substituted, and the installation of the quaternary center could be envisaged (Scheme 5). In effect, IBX oxidation smoothly established the ketone, which underwent double aldol reaction with formalin to deliver key intermediate **(−)-13**.

(7) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.
(8) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

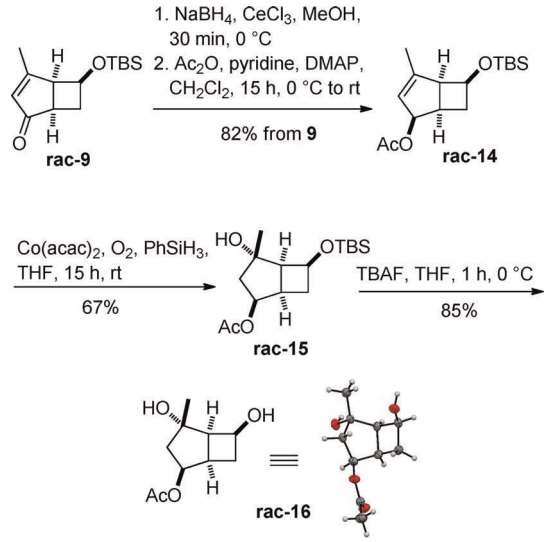
(9) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071–1074.

Scheme 5. Quaternarization of the Bicycle



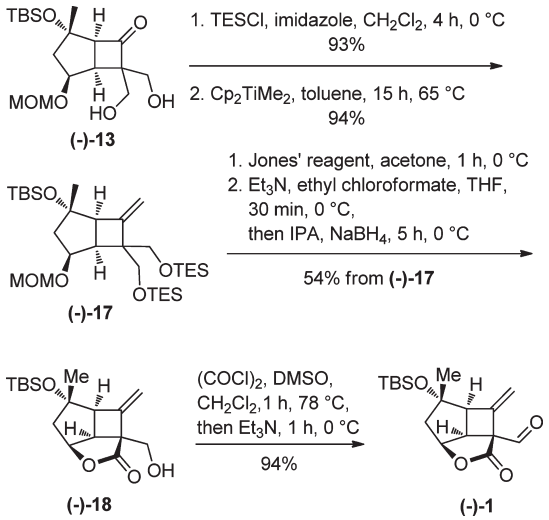
To establish the stereochemical course of the hydration, crystalline diol **16** was prepared via an analogous sequence and subjected to single crystal X-ray diffraction. In this way, it was confirmed that the oxygen indeed attacks the bicyclic olefin from the less hindered convex face, as expected (Scheme 6).

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



Our synthesis was continued with the TES-protection of the two primary alcohols (Scheme 7). Ketone olefination using Petasis' reagent generated **(−)-17** in excellent yield. Next, a cascade reaction was used to create the tricyclic core of bielschowskysin. Under the acidic conditions of Jones' reagent, the diol was formed in situ and oxidized to

Scheme 7. Formation of the Tricycle



the dicarboxylic acid. Concomitantly, the MOM protecting group was removed, whereupon lactonization occurred spontaneously. Without purification, the crude carboxylic acid was selectively reduced via a mixed carbonate formed from ethyl chloroformate. Final purification delivered alcohol **(−)-18** in 54% overall yield after a total of eight transformations (> 92% each) from **(−)-17**. Swern oxidation eventually furnished the targeted aldehyde **(−)-1**.

In conclusion, we have developed a fully stereoselective scalable route (11% overall yield from known alcohol **(+)-4**) to a tricyclic core fragment of bielschowskysin which, for the first time, contains the all-carbon quaternary center at C-12. The aldehyde function in **(−)-1** is well suited for attaching the eastern part of the molecule and this is well underway in our laboratory. Apart from this, the regio- and stereocontrolled functionalization of the versatile and readily available precursor **4** may be of interest in other synthetic projects.

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Supporting Information Available. Experimental procedure and full characterization including copies of ^{1}H and ^{13}C NMR spectra and crystal structure analysis of **rac-16** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

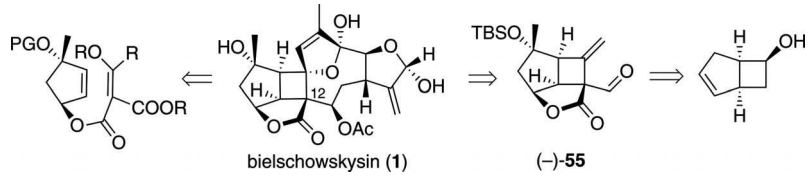
4.2 Photochemical and Thermal [2+2] Cycloaddition to Generate the Bicyclo[3.2.0]heptane Core of Bielschowskysin

Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann

European Journal of Organic Chemistry **2013**, *20*, 4379-4398.

Contribution: Concept development: Jean-Baptiste Farcet, Martin Himmelbauer and Johann Mulzer
Experimental work: Jean-Baptiste Farcet and Martin Himmelbauer
Product characterization and analytic work: Jean-Baptiste Farcet and Martin Himmelbauer
Preparation of the manuscript: Jean-Baptiste Farcet and Johann Mulzer

EurJOC European Journal of Organic Chemistry



Various photocycloaddition precursors have been designed to study both biomimetic and non-biomimetic [2 + 2] cycloadditions to form the bicyclo[3.2.0]heptane core of the marine diterpenoid bielschowskysin. Additionally, an optimized thermal approach to aldehyde (–)-**55** is described.

J.-B. Farcet, M. Himmelbauer, J. Mulzer* **1–21**

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

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

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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 thermal [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

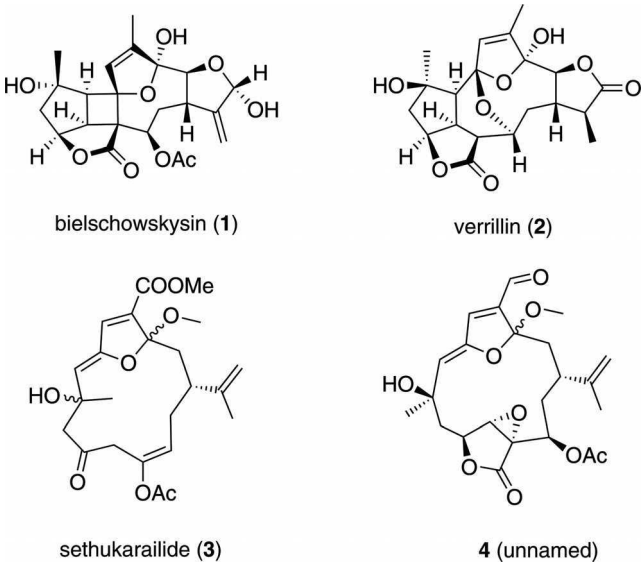
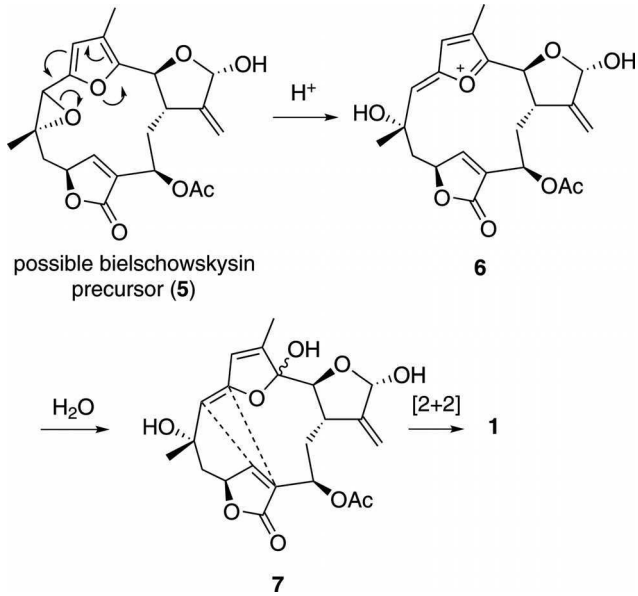


Figure 1. Furanocembranoid family members.



Scheme 1. Biosynthesis of bielschowskysin.

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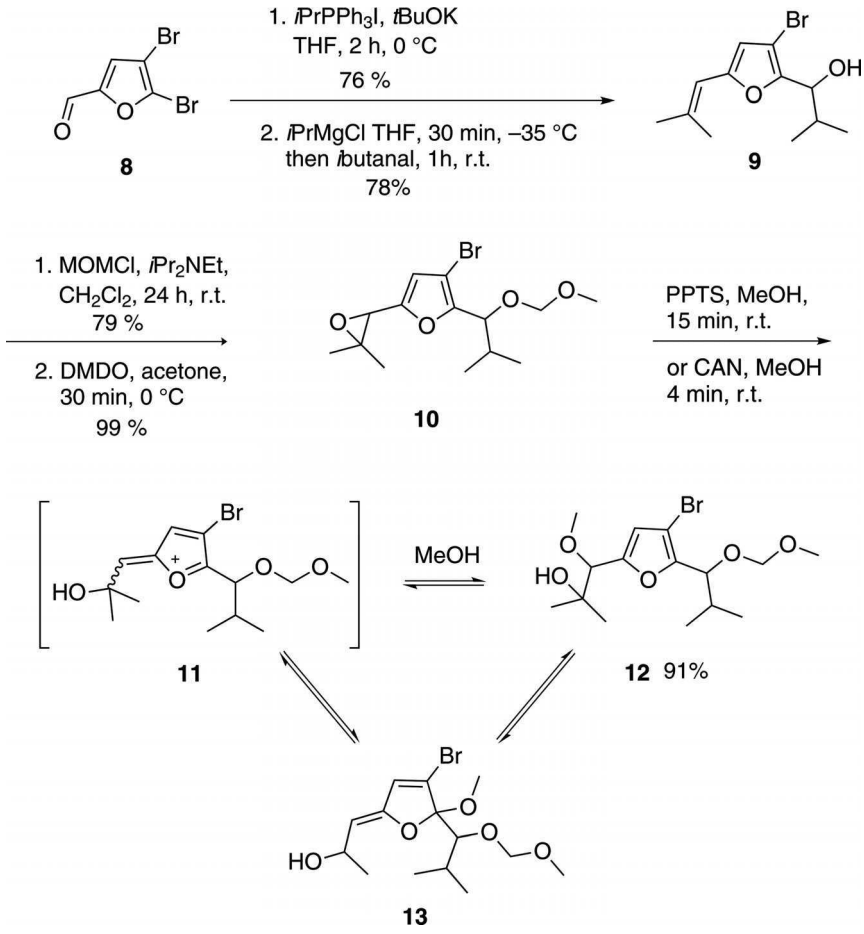
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300382.



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).

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

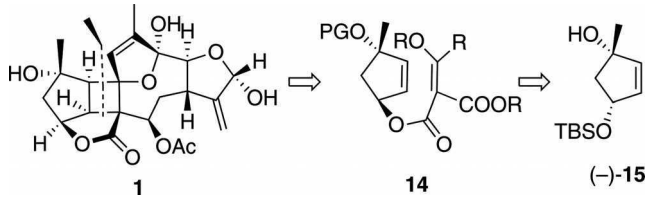


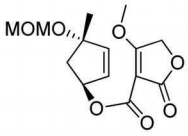
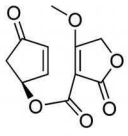
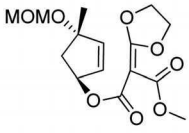
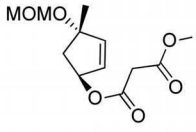
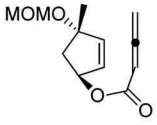
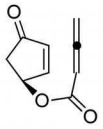
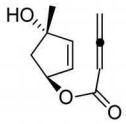
Figure 2. Retrosynthesis based on photo-[2 + 2] cycloaddition.

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-cyclization 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 debenzylation 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]
1	 **(-)-27** 66% from **(–)-26** and **25**	decomposition	**A**, **B**, **C**, **F**, **G**, **H**
2	 **(-)-30** 72% from **(–)-29**[b] and **25**	decomposition	**A**, **B**
3	 **(-)-18** (81%, 99% b.r.s.m.) from **(+)-16** and **17**	 **(-)-20** 46%	**A**, **B**, **C**, **F**, **G**. **H**
4	 **(-)-32** 87% from **(+)-16** and **31**[b]	decomposition	**A**, **B**, **D**, **F**, **I**, **J**
5	 **(-)-33** 60% from **(–)-29**[b] and **31**[b]	decomposition	**A**, **B**, **C**, **D**, **J**
6	 **(-)-35** 35% from **(–)-34**[b] and **31**[b]	decomposition	**A**, **B**

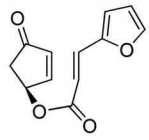
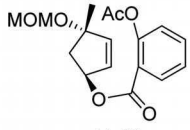
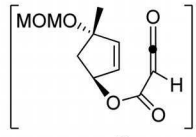
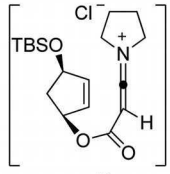
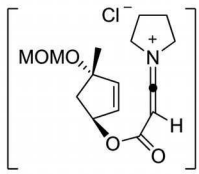
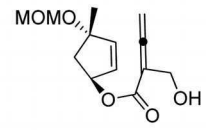
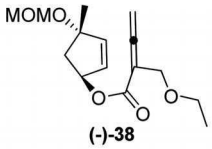
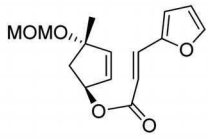
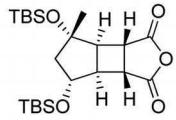
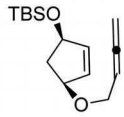
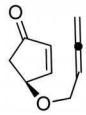
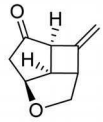
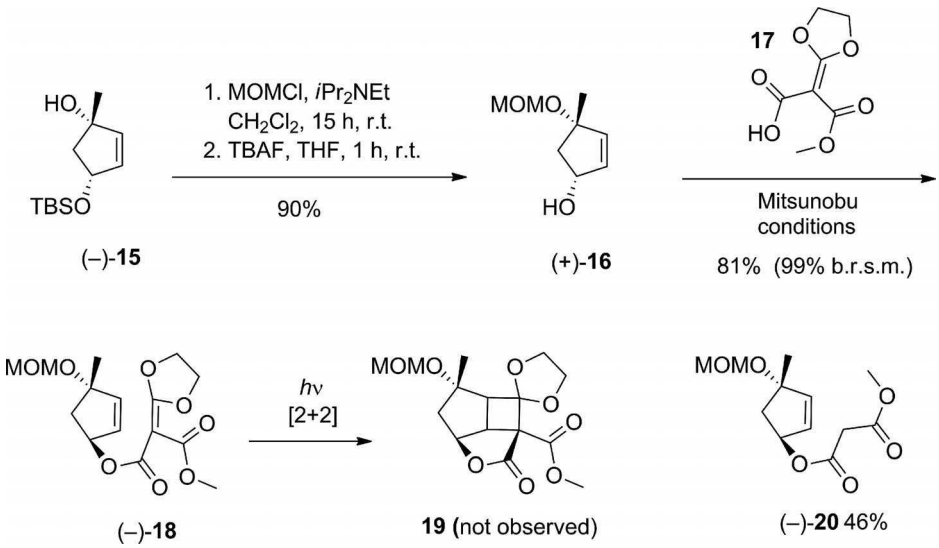
Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions[a]
10	 **(-)-41** 71% from **(–)-29**[b] and **39**[b]	starting material recovered + decomposition	**A**, **B**, **F**
11	 **(-)-42** 52%, 97% b.r.s.m. from **(+)-16** and aspirin	starting material recovered + decomposition	**A**, **B**, **C**, **E**
12	 **43** [c] from **(–)-26** and suboxide	no reaction, then decomposition	**J**
13	 **46** [c] from **(–)-45**[b]	no reaction, then decomposition	**K**
14	 **48** [c] from **(–)-26** and **47**[b]	no reaction, then decomposition	**K**

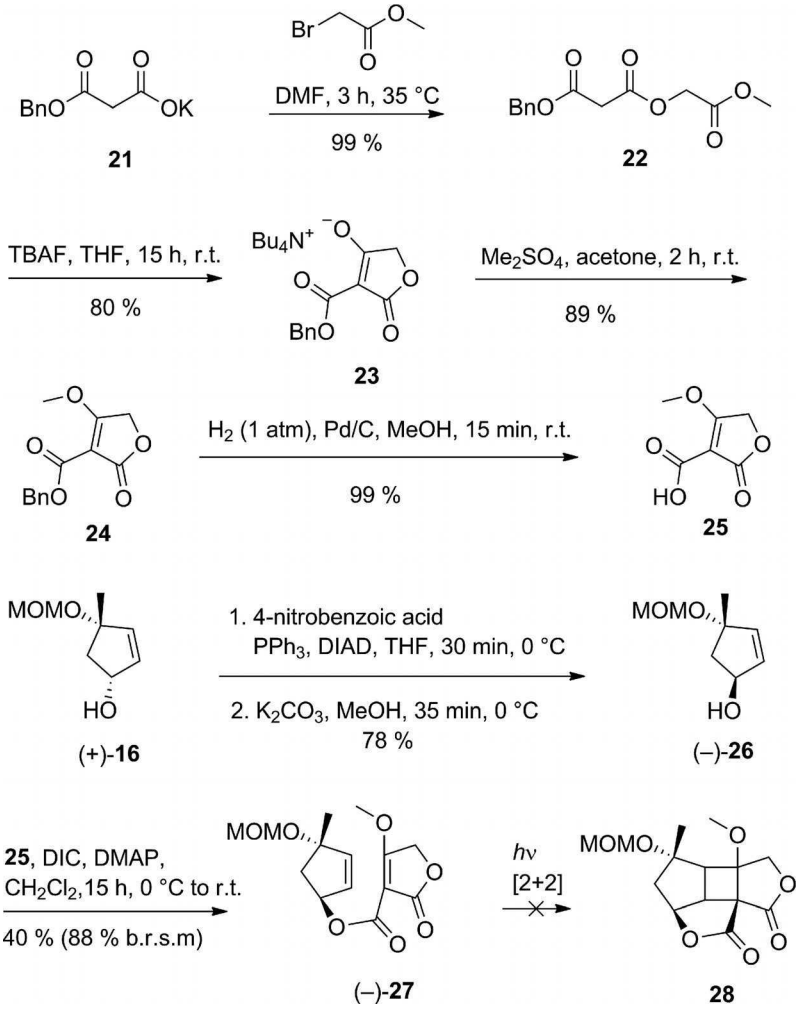
Table 1. *(continued)*.

Entry	[2+2] Precursor Yield	Outcome, yield	Irradiation conditions[a]
7	 **(-)-36** 62% from *para*-formaldehyde and **(–)-32**	decomposition	**A, B, F, G, H**
8	 **(-)-38** 58% from **(+)-16** and **37**[b]	starting material recovered + decomposition	**A, B, C, D, E, F, G, I**
9	 **(-)-40** 99% from **(+)-16** and **39**[b]	starting material recovered + decomposition	**A, B, F**
15	Intermolecular reaction from **(–)-49**[b] and maleic anhydride	 **(-)-50** 58%	**A**
16	 **(+)-51** 83%, 2 steps from **(+)-44**[b] and propargyl bromide	no reaction, then decomposition	**A, B, D, F, H**
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. $Cu(OTf)_2$, I: Sun lamp 750 W, quartz filter, Et_2O + cat. $Cu(OTf)_2$, 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.

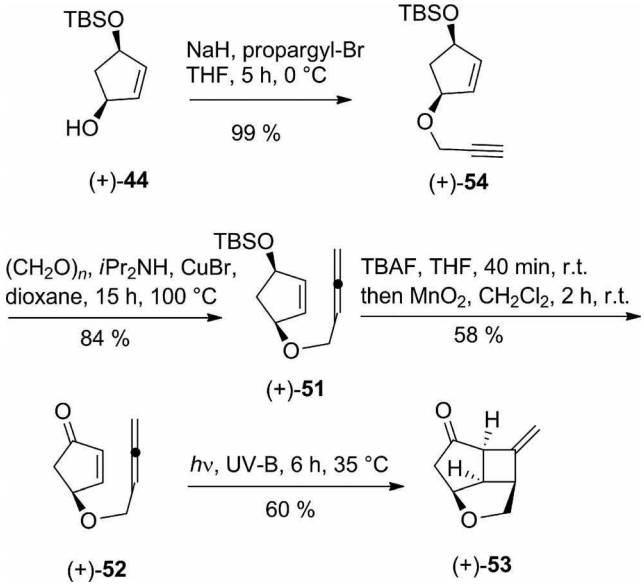


Scheme 4. Synthesis of [2 + 2] precursor (–)-**27**. DIAD = diisopropyl azodicarboxylate; DIC = *N*,*N*′-diisopropylcarbodiimide; DMAP = 4-dimethyl aminopyridine.

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 detected 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 homoallenic 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.

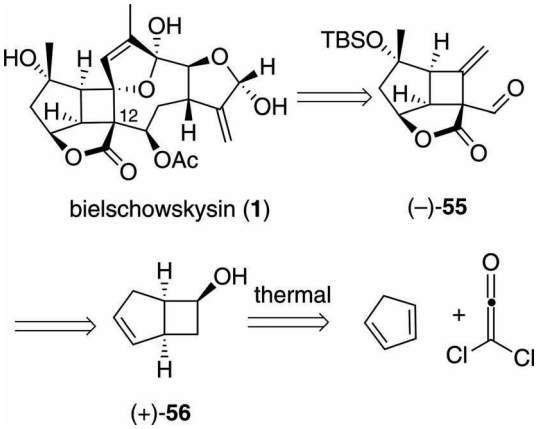
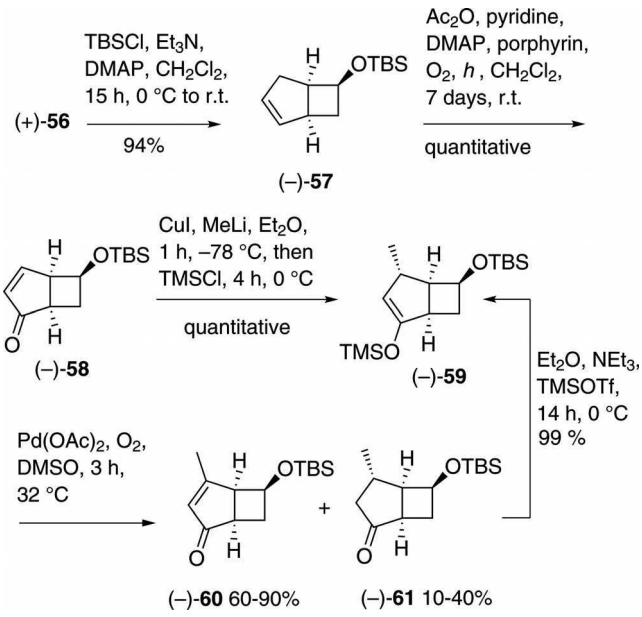


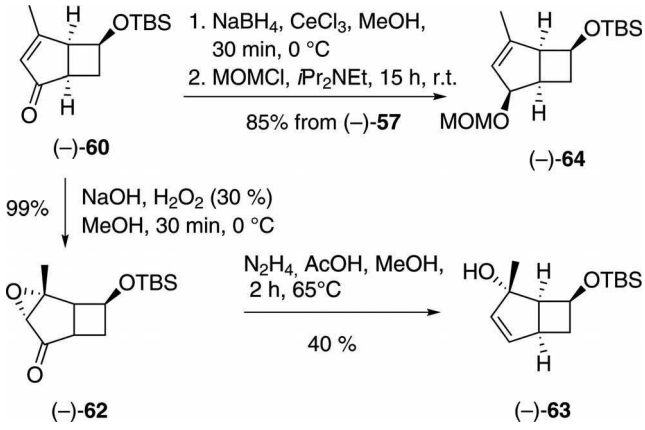
Figure 3. Retrosynthesis based on a non-photochemical approach.

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



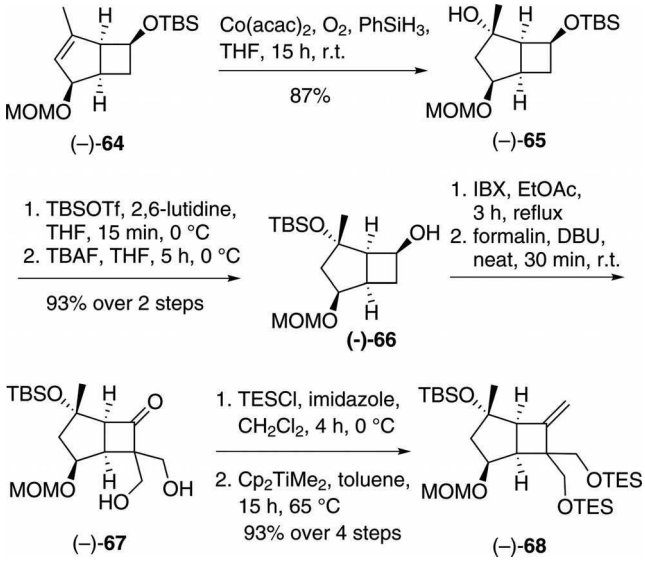
Scheme 6. Synthesis of enone (–)-**60**. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Taking advantage of the "open-book" geometry of bicycle (–)-**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).



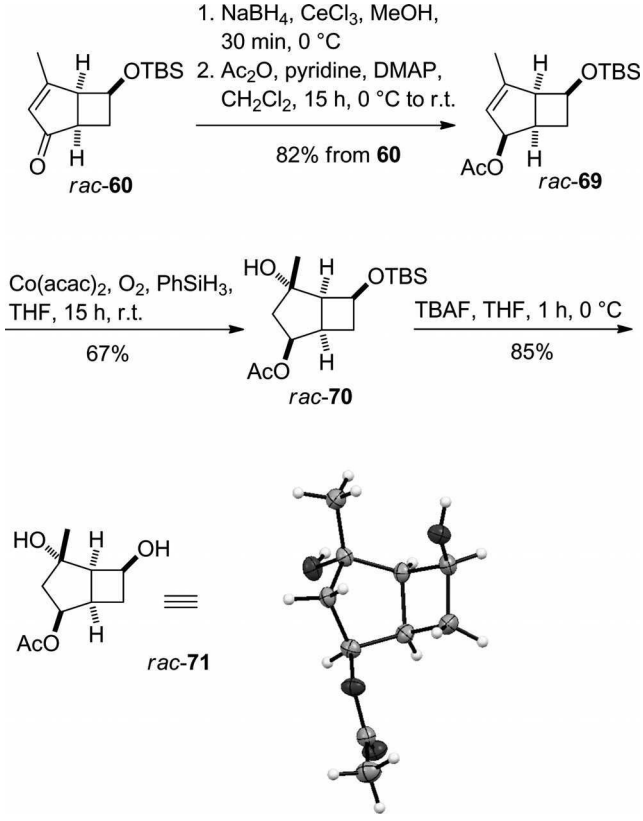
Scheme 7. Synthesis of enone (–)-**63** and (–)-**64**.

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.

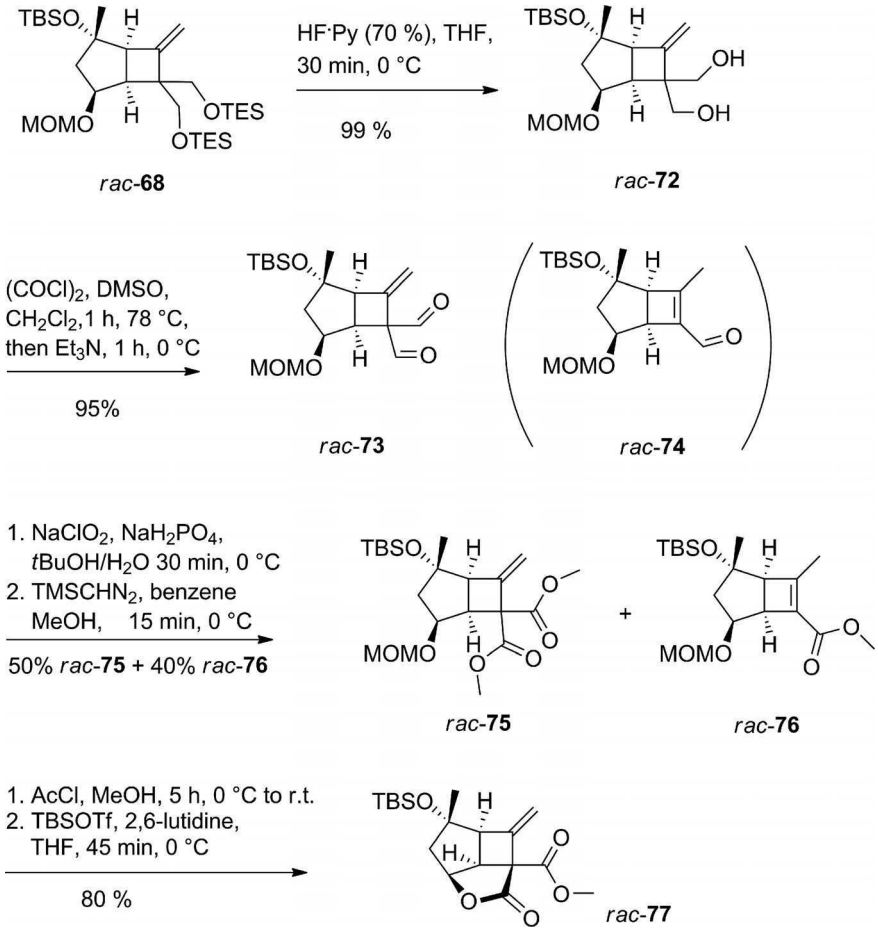
To assign the relative configuration by single crystal diffraction, racemic crystalline acetoxy diol *rac*-**71** was prepared by an analogous sequence (Scheme 9).[18]



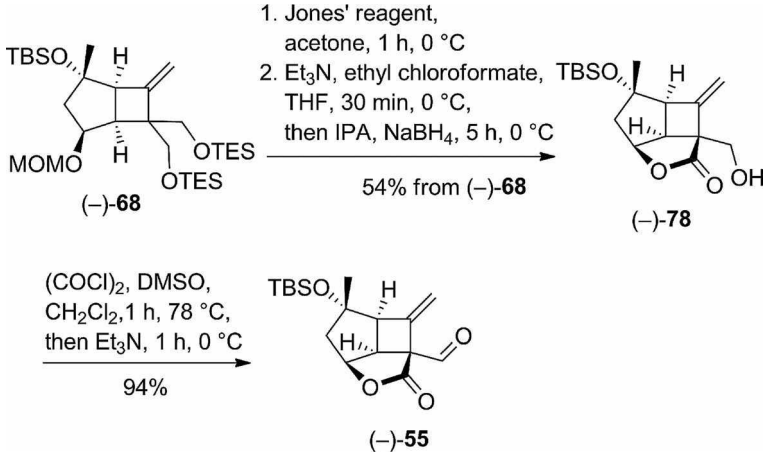
Scheme 9. Synthesis and X-ray structure of *rac*-**71**.

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 ($TMSCHN_2$) 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 $NaBH_4$ 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 = CrO_3, H_2SO_4 in water; IPA = isopropyl alcohol.

Conclusions

After screening various substrates to obtain the bicyclo[3.2.0]heptane core of bielschowskysin 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 bielschowskysin.

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, iPr_2NEt, 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, δ = 7.26 ppm; ^{13}C, δ = 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× 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 155.6, 138.3, 120.2, 113.1, 111.9, 102.8, 27.0, 20.2 ppm. HRMS (EI): calcd. for $C_8H_8OBr_2$ $[M]^+$ 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× 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{12}H_{17}O_2Br$ $[M]^+$ 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× 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{14}H_{21}O_3Br$ $[M]^+$ 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{15}H_{25}O_5BrNa$ $[M + MeOH + Na]^+$ 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× 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: Ceric 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× 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{15}H_{25}O_5BrNa$ $[M + Na]^+$ 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]: iPr$_2$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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{13}H_{25}O_3Si$ $[M – CH_3]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 138.1, 137.3, 92.0, 86.5, 75.6, 55.0, 46.9, 27.6 ppm. HRMS (EI): calcd. for $C_7H_{11}O_3$ $[M – CH_3]^+$ 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%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{15}H_{20}O_8Na$ $[M + Na]^+$ 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 $Cu(OTf)_2$ 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%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{12}H_{18}O_6Na$ $[M + Na]^+$ 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%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{13}H_{14}O_6$ $[M]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 (SiO_2, hexane/EtOAc, 1:1 to 0:1) to give methylated product **24** (928 mg, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 H_2 (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. ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 5.06 (s, 2 H), 4.15 (s, 3 H) ppm. ^{13}C NMR (400 MHz, [D$_4$]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.

(1*S*,4*S*)-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 μL, 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 $NaHCO_3$ (15 mL) and brine (2× 20 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was then purified by flash chromatography (SiO_2, hexane/EtOAc, 7:1) to give the *para*-nitrobenzoic ester (218 mg, 84%) as a clear semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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}. $[\alpha]_D^{20}$ = +158.4 (*c* = 1.00, $CHCl_3$). 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. K_2CO_3 (92 mg, 0.67 mmol) was added in one portion, and the mixture was stirred for 35 min before being quenched with NH_4Cl. 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× 10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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}. $[\alpha]_D^{20}$ = –99.4 (*c* = 1.05, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.45.

(1*S*,4*S*)-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 CH_2Cl_2 (5.1 mL), and the mixture was cooled to 0 °C. DIC (47 μL, 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 (SiO_2, 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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}. $[\alpha]_D^{20}$ = –140.6 (*c* = 0.55, $CHCl_3$). 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 CH_2Cl_2/MeCN (3:1; 4 mL), and the mixture was cooled to 0 °C. DIC (76 μL, 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 (SiO_2, 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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}. $[\alpha]_D^{20}$ = 106.8 (*c* = 0.50, $CHCl_3$), m.p. 148–149 °C. R_f (EtOAc): 0.25.

(1*S*,4*S*)-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 μL, 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%). ^{1}H 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 $C_{11}H_{13}O_4$ $[M - CH_3]^+$ 209.0814; found 209.0808. IR: $\tilde{\nu}$ = 2929, 1714, 1450, 1350, 1256, 1163, 1144, 1032, 632, 535 cm^{-1}. $[\alpha]_D^{20}$ = –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. ^{1}H 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 $C_9H_8O_3$ $[M]^+$ 164.0473; found 164.0475. IR: $\tilde{\nu}$ = 3451, 2927, 2856, 1713, 1659, 1442, 1362, 1231, 1184, 1102 cm^{-1}. $[\alpha]_D^{20}$ = –132.54 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.48.

(1*S*,4*S*)-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%). ^{1}H 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 $C_{10}H_{12}O_3$ $[M]^+$ 180.0786; found 180.0783. IR: $\tilde{\nu}$ = 3407, 1970, 1942, 1707, 1348, 1256, 1164, 1086, 854, 631 cm^{-1}. $[\alpha]_D^{20}$ = –130.3 (c = 0.95, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.26.

(1*S*,4*S*)-4-(Methoxymethoxy)-4-methylcyclopent-2-en-1-yl 2-(Hydroxymethyl)buta-2,3-dienoate [(–)-36]: A solution of DABCO (predried under vacuum for 30 min; 5 mg, 0.04 mmol) in THF (0.5 mL) was added dropwise to a suspension of paraformaldehyde (predried 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. ^{1}H 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 $C_{12}H_{15}O_5$ $[M]^+$ 239.0919; found 239.0906. IR: $\tilde{\nu}$ = 3220, 2930, 1713, 1449, 1361, 1214, 1142, 1091, 1030, 631 cm^{-1}. $[\alpha]_D^{20}$ = –172.0 (c = 0.27, $CHCl_3$). R_f (hexane/EtOAc, 1:1): 0.29.

(1*S*,4*S*)-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. ^{1}H 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 $C_{15}H_{22}O_5Na$ $[M + Na]^+$ 305.1365; found 305.1359. IR: $\tilde{\nu}$ = 2975, 2873, 1967, 1710, 1371, 1259, 1143, 1091, 1031, 535 cm^{-1}. $[\alpha]_D^{20}$ = –115.9 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.29.

(*E*)-(1*S*,4*S*)-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. ^{1}H 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}. $[\alpha]_D^{21}$ = –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 μL, 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. ^{1}H 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}. $[\alpha]_D^{21}$ = –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-Acetoxybenzoate [(–)-42]: Secondary alcohol (+)-**16** (100 mg, 0.63 mmol), triphenylphosphane (199 mg, 0.76 mmol), and 2-acetoxybenzoic 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 μL, 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 × 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%). ^{1}H 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}. $[\alpha]_D^{20}$ = –147.5 (c = 1.00, $CHCl_3$). R_f (hexane/EtOAc, 3:1): 0.32.

Ketene 43: Et_3N (14 μL, 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 μL, 0.19 mmol) in THF (0.5 mL) was treated with *i*PrEt_2N (35 μL, 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 extracted with EtOAc (3 × 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 μL, 0.14 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (25 μL, 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 × 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 cylization 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 μL, 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 × 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. ^{1}H 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}. $[\alpha]_D^{20}$ = –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 μL, 0.19 mmol) in DCE (2.0 mL) was treated with a solution of triflic anhydride (34 μL, 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 × 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 × 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 (SiO_2, 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 $CDCl_3$, partial hydrolysis of the anhydride functionality was observed, resulting in a small amount of impurity in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{23}H_{44}NaO_6Si_2$ [M + MeOH + Na]$^+$ 495.2574; found 495.2592. $[\alpha]_D^{20}$ = –127.8 (c = 0.75, $CHCl_3$). IR: $\tilde{\nu}$ = 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 H_2 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 $MgSO_4$, and the solvent was removed in vacuo. Purification by chromatography column (SiO_2, hexane/EtOAc, 15:1) gave (+)-**54** (1.38 g, 99%) as a slightly viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{10}H_{15}O_2Si$ [M – tBu]$^+$ 195.0841; found 195.0841. IR: $\tilde{\nu}$ = 2955, 2931, 2857, 1372, 1253, 1081, 1059, 905, 837, 777 cm^{-1}. $[\alpha]_D^{20}$ = +32.7 (c = 1.05, $CHCl_3$). 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 (SiO_2, hexane/EtOAc, 1:0 to 20:1) to give (+)-**51** (1.04 g, 84%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{15}H_{26}O_2SiNa$ [M + Na]$^+$ 289.1600; found 289.1592. IR: $\tilde{\nu}$ = 2955, 2931, 2857, 1368, 1253, 1079, 940, 905, 837, 777 cm^{-1}. $[\alpha]_D^{20}$ = +10.4 (c = 0.85, $CHCl_3$). 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, CH_2Cl_2 (12 mL) was added. Then MnO_2 (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 (SiO_2, pentane/Et_2O, 2:1) to give (+)-**52** (164 mg, 58%) as a volatile greenish-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 209.5, 205.8, 161.0, 135.8, 87.5, 76.5, 76.1, 67.7, 41.8 ppm. HRMS (ESI): calcd. for $C_9H_{10}O_2Na$ [M + Na]$^+$ 150.0681; found 150.0699. IR: $\tilde{\nu}$ = 2926, 2856, 1719, 1351, 1184, 1105, 1074, 996, 849, 792 cm^{-1}. $[\alpha]_D^{20}$ = +5.14 (c = 1.23, $CHCl_3$). R_f (Pentane/Et_2O, 2:1) : 0.20.

(3a*S*)-1-Methylenehexahydro-3-oxacyclobuta[cd]pentalen-5(1a1*H*)-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/Et_2O, 2:1) to give (+)-**53** (18 mg, 60%) as a volatile liquid. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 214.1, 145.2, 111.7, 79.3, 73.9, 51.8, 48.7, 48.3, 42.7 ppm. HRMS (EI): calcd. for $C_9H_{10}O_2$ [M]$^+$ 150.0681; found 150.0692. IR: $\tilde{\nu}$ = 2965, 2831, 1747, 1291, 1114, 1056, 1001, 943, 819, 732 cm^{-1}. $[\alpha]_D^{21}$ = +12.1 (c = 0.90, $CHCl_3$). R_f (pentane/Et_2O, 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 CH_2Cl_2 (91 mL) at 0 °C under Ar, and then Et_3N (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. NH_4Cl (saturated aq.; 50 mL) was added. The mixture was diluted with CH_2Cl_2 (50 mL), washed in sequence with HCl (0.5 M; 40 mL), water (40 mL), and brine (2× 50 mL), and dried with $MgSO_4$. The volatile materials were removed under reduced pressure to give a crude product. Purification by column chromatography (SiO_2, hexane) gave protected alcohol (–)-**57** (9.52 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_9H_{15}OSi$ [M – tBu]$^+$ 167.0892; found 167.0890. IR: $\tilde{\nu}$ = 2930, 2857, 1709, 1471, 1254, 1125, 1004, 879, 837, 777 cm^{-1}. $[\alpha]_D^{22}$ = –0.2 (c = 1.0, $CHCl_3$). R_f (hexane): 0.49.

(1*R*,5*R*,6*S*)-6-[(*tert*-butyldimethylsilyl)oxy]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 CH_2Cl_2 (52 mL) was irradiated with a halogen lamp (500 W) for 7 d under vigorous stirring while O_2 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. ^{1}H 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 $C_{13}H_{22}O_2Si$ 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, $Pd(OAc)_2$ (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**: ^{1}H 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 $C_{14}H_{24}O_2Si$ $[M]^+$ 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**: ^{1}H 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 $C_{13}H_{23}O_2Si$ $[M – CH_3]^+$ 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.

(1*R*,2*R*,4*R*,6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-3-oxatricyclo[4.2.0.02,4]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 $Na_2S_2O_3$ (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. ^{1}H 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 $C_{14}H_{24}O_3SiNa$ $[M + Na]^+$ 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.

(1*R*,2*S*,5*S*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2-methylbicyclo-[3.2.0]hept-3-en-2-ol [(–)-63]: $N_2H_4{\cdot}H_2O$ (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. ^{1}H 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 $C_{14}H_{26}O_2SiNa$ $[M + Na]^+$ 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 $NaBH_4$ (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 $MgSO_4$, 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 CH_2Cl_2 (43 mL), and *i*Pr_2NEt (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 CH_2Cl_2 (150 mL), the organic phase was washed with $NaHCO_3$ (5% aq.; 75 mL) and brine (3× 60 mL), then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 20:1) to give alkene (–)-**64** (3.29 mg, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{16}H_{30}O_3Si$ Na $[M + Na]^+$ 321.1862; found 321.1866. IR: $\tilde{\nu}$ = 2929, 2857, 2361, 2342, 1375, 1254, 1122, 1042, 835, 776 cm^{-1}. $[\alpha]_D^{24}$ = 81.4 (*c* = 1.1, $CHCl_3$). 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 O_2 (40 min), and then $PhSiH_3$ (14.2 mL, 115 mmol) was added over 45 min using a syringe pump, while a gentle flow of O_2 was blown 5 cm above the well-stirred solution. The O_2 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 $NaHCO_3$ (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 $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 3:1) to give tertiary alcohol (–)-**65** (7.93 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.3968; found 339.3964. IR: $\tilde{\nu}$ = 3405, 2955, 2884, 2362, 1254, 1132, 1044, 869, 867, 777 cm^{-1}. $[\alpha]_D^{24}$ = –1.73 (*c* = 1.1, $CHCl_3$). 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 $NaHCO_3$ (150 mL), and the mixture 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 Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 15:1) to give the di-TBS-protected alcohol (25.5 g, quantitative) contaminated with TBS-OH and 2,6-lutidine. ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{22}H_{46}O_4$-SiNa $[M + Na]^+$ 453.2832; found 453.2813. IR: $\tilde{\nu}$ = 2929, 2856, 1253, 1108, 1076, 1043, 1001, 939, 832, 772 cm^{-1}. $[\alpha]_D^{24}$ = –9.3 (*c* = 1.0, $CHCl_3$). 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 (SiO_2, hexane/EtOAc, 3:1) to give alcohol (–)-**66** (17.1 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.1968; found 339.1961. IR: $\tilde{\nu}$ = 3444, 2930, 2856, 1461, 1252, 1107, 1036, 995, 832, 772 cm^{-1}. $[\alpha]_D^{20}$ = –34.8 (*c* = 1.0, $CHCl_3$). 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%). ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (400 MHz, $CDCl_3$): 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 $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 337.1811; found 337.1804. IR: $\tilde{\nu}$ = 2929, 2856, 1777, 1253, 1147, 1109, 1042, 833, 773, 696 cm^{-1}. $[\alpha]_D^{20}$ = –151.6 (*c* = 1.4, $CHCl_3$). 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 $MgSO_4$, and concentrated under reduced pressure to give diol (–)-**67** (10.1 g, quantitative) contaminated with polymethylene ether derivatives. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): δ = 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 $C_{18}H_{34}O_6SiNa$ $[M + Na]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{30}H_{62}O_6Si_3Na$ $[M + Na]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{31}H_{64}O_5Si_3Na$ $[M + Na]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{16}H_{28}O_3Si$ Na $[M + Na]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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.

{(1*R*,2*S*,4*S*,5*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-2-methyl-7-methylenebicyclo[3.2.0]heptane-6,6-diyl}dimethanol [(–)-72]: HF (70% in pyridine; 269 μL, 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 × 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. ^{1}H 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 μL, 0.1.66 mmol) was added to a solution of oxalyl chloride (70 μL, 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 μL, 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 × 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%). ^{1}H 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. ^{1}H 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 $C_{18}H_{32}O_4SiNa$ [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 μL) 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 × 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 μL, 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**: ^{1}H 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**: ^{1}H 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. ^{1}H 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 μL, 0.50 mmol) and then TBSOTf (58 μL, 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. ^{1}H 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 $C_{18}H_{28}O_5SiNa$ [M + 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. ^{1}H 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 $C_{17}H_{28}O_4SiNa$ [M + 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 pressure. Purification by flash chromatography (SiO_2, hexane/EtOAc, 3:1) gave aldehyde (–)-**55** (17 mg, 94%) as an amorphous white solid. ^{1}H 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 $C_{17}H_{26}O_4SiNa$ [M + 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 ^{1}H 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**.

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[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.

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SUPPORTING INFORMATION

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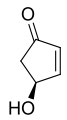
Preparation/characterization of **(-)-29**, **31**, **(-)-34**, **37**, **39**, **(+)-44**, (-)-**45**, **47**, **(-)-49**.

Alcohol (-)-29:



(-)-29

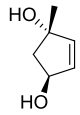
For preparation protocol and full characterization see: Ref [6] in main article.

Carboxylic acid 31:

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

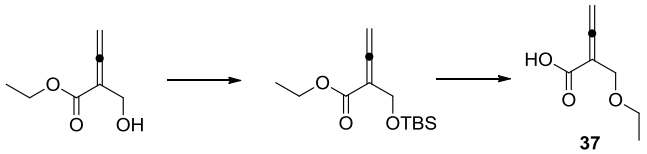
Diol (-)-34:



(-)-34

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

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

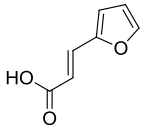


37

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 Et_3N (1.49 mL, 10.69 mmol) in CH_2Cl_2 (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 Et_2O (110 mL) and quenched with water (30 mL) and sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The resulting slightly yellow oil was purified by column chromatography

(SiO_2, Hex/EtOAc = 10/1) giving 1.18 g (69%) of the TBS intermediate as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 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. ^{13}C-NMR (400 MHz, $CDCl_3$): 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 $C_{13}H_{24}O_3SiNa$: 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, K_2CO_3 (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 CH_2Cl_2 (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic phase was extracted with water (10 mL) and brine (10 mL) followed by the addition of $MgSO_4$. Filtration and evaporation of the volatiles gave 650 mg (99%) of **37** as a white semi solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 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. ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 215.3, 170.4, 97.7, 79.9, 67.0, 66.1, 15.0 ppm. HRMS (EI) (m/z): $[M+Na]^+$ calculated for $C_{10}H_7O_3Na$: 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.

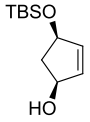
Furylacrylic acid (39):



39

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

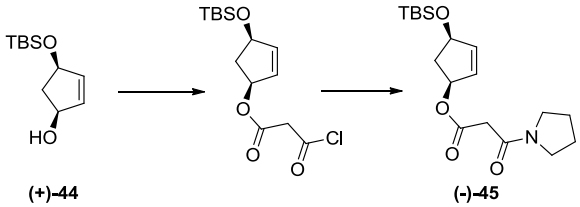
(1S,4R)-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-enol ((+)-44):



(+)-44

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

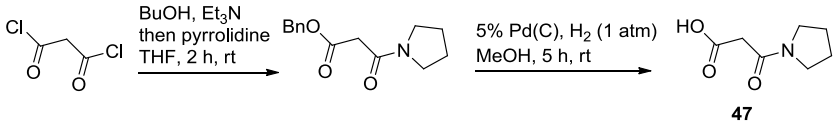
Amide (-)-45:



(+)-44 **(-)-45**

A solution of alcohol **(+)-44** (100 mg, 0.47 mmol) in THF (3.0 mL) was treated with Et_3N (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 (SiO_2, Hex/EtOAc 3/1 to EtOAc) to yield 141 mg (85%) of the desired amide **(-)-45** as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, J_1 = 14.5 Hz, J_2 = 7.5 Hz, J_3 = 7.5 Hz, 1H), 1.96 (m, 2H), 1.87 (m, 2H), 1.64 (ddd, J_1 = 13.9 Hz, J_2 = 5.0 Hz, J_3 = 5.0 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$): 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 $C_{18}H_{31}O_4NSiNa$: 376.1920, found: 376.1937. IR (cm^{-1}): 2954, 2930, 2857, 2361, 1739, 1652, 1439, 1105, 1049, 837. $[\alpha]_D^{20}$: - 5.04 (c = 0.26; $CHCl_3$). R_f: (EtOAc) 0.66.

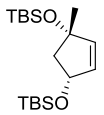
Acid 47:



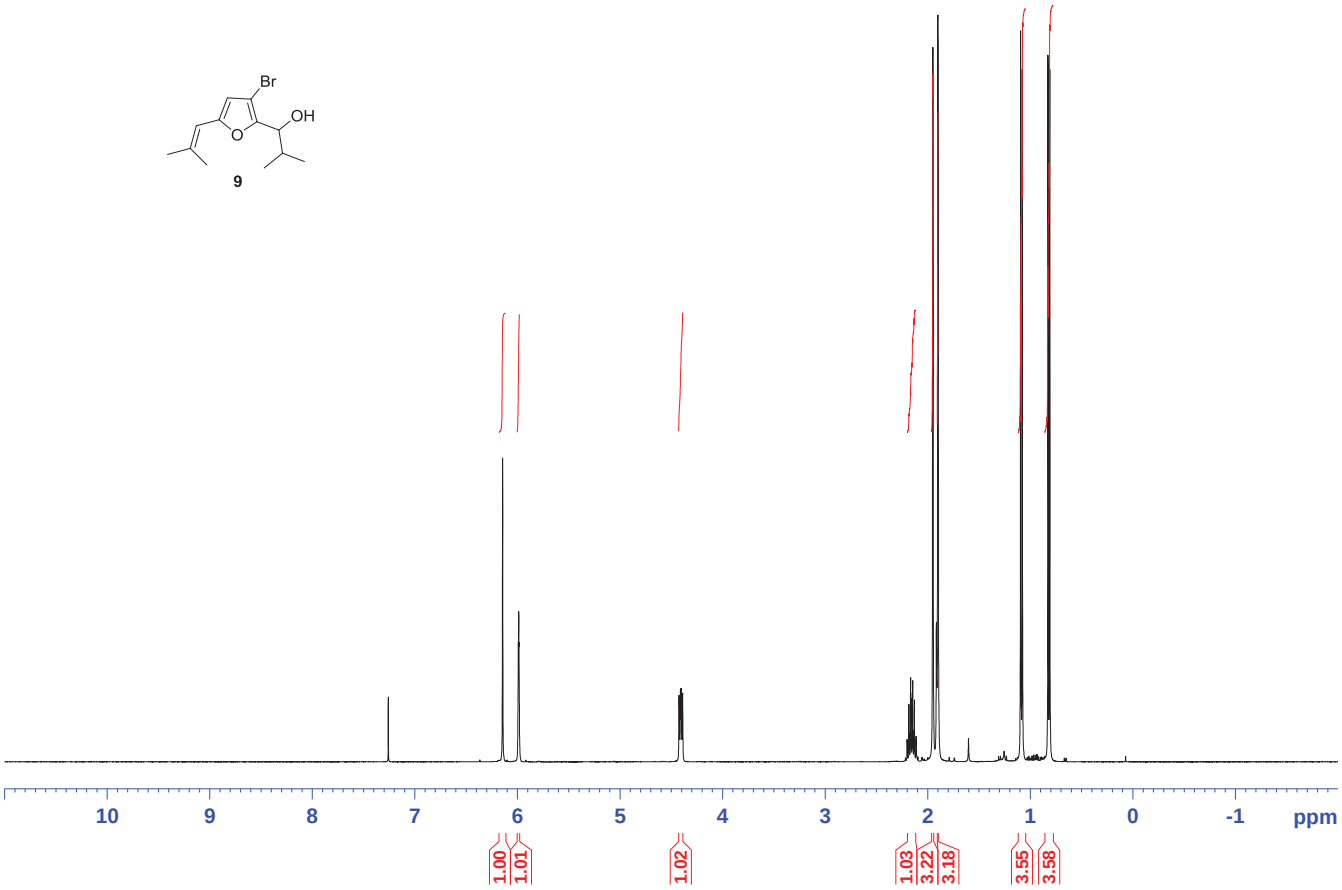
47

Benzylic alcohol (50 µL, 0.48 mmol, in THF (3.0 mL) was treated at 0 °C with Et_3N (74 µL, 0.53 mmol) and stirred for 15 min. Consecutively, the resulting solution was dropwise added to malonyl dichloride (103 µL, 1.06 mmol) in THF (3.0 mL) within 8 min. After one hour at this temperature pyrrolidine (261 µL, 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 $MgSO_4$. Filtration and evaporation of the volatiles was followed by column chromatography (SiO_2, Hex/EtOAc 3/1). Finally 74 mg (63%) of the desired amide were isolated as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 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. ^{13}C-NMR (400 MHz, $CDCl_3$): 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 $C_{14}H_{17}NO_3$: 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-lutindine (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 Et_2O (100 mL) and quenched with water (30 mL) and sat. aq. $NaHCO_3$ (30 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The resulting slightly yellow oil was purified by column chromatography (SiO_2, Hex/EtOAc = 20/1) giving 549 mg (73%) of the desired alkene **(-)-49** as slightly yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.78 (dd, J_1 = 1.4 Hz, J_2 = 5.6 Hz, 1H), 5.62 (dd, J_1 = 1.8 Hz, J_2 = 5.7 Hz, 1H), 4.68-4.63 (m, 1H), 2.35 (dd, J_1 = 6.9 Hz, J_2 = 12.7 Hz, 1H), 1.84 (ddd, J_1 = 0.5 Hz, J_2 = 5.5 Hz, J_3 = 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. ^{13}C-NMR (400 MHz, $CDCl_3$): 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 $C_{18}H_{38}O_2SiNa$: 365.2308, found: 365.2322. IR (cm^{-1}): 2956, 2995, 2857, 1472, 1362, 1166, 1120, 1098, 836, 775. $[\alpha]_D^{20}$: - 15.4 (c = 1.0; $CHCl_3$). R_f: (Hex/EtOAc 3/1) 0.80.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9
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5
4
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1.03
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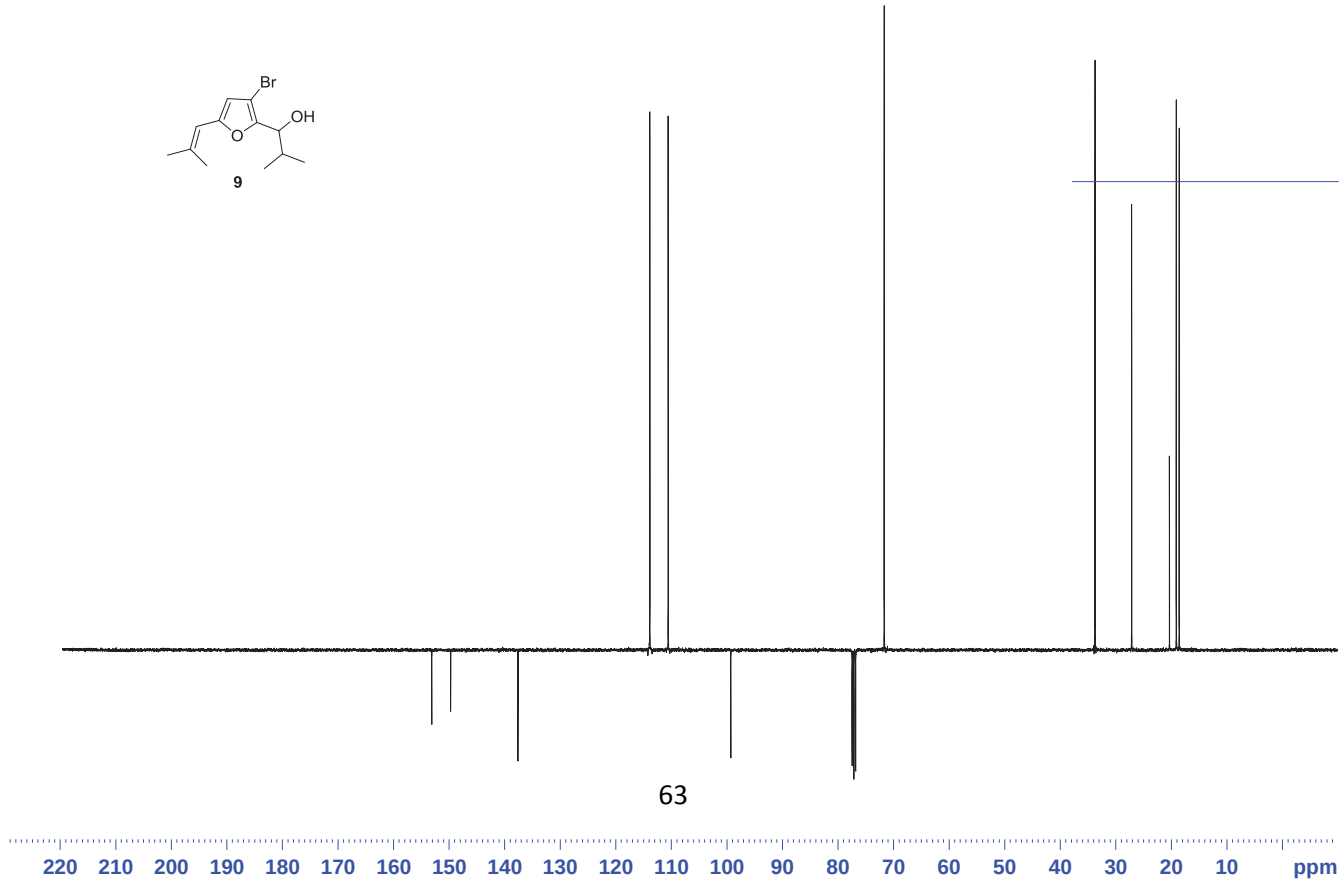
3.55
3.58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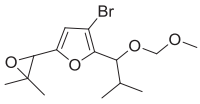
10
ppm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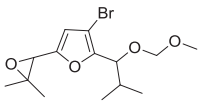
3.03
3.19
3.09
3.08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O

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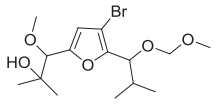
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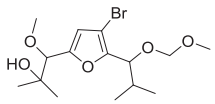
3.08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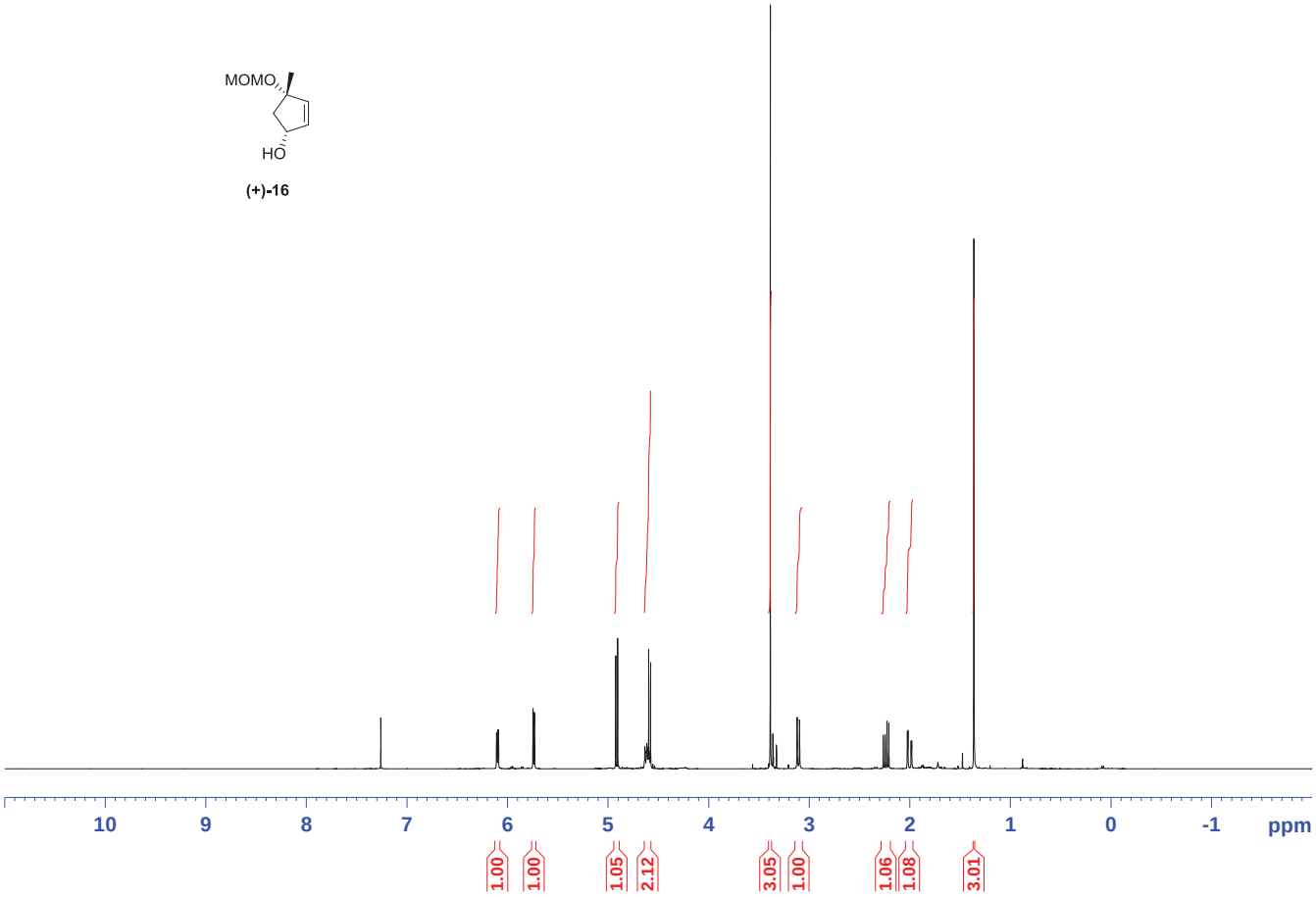
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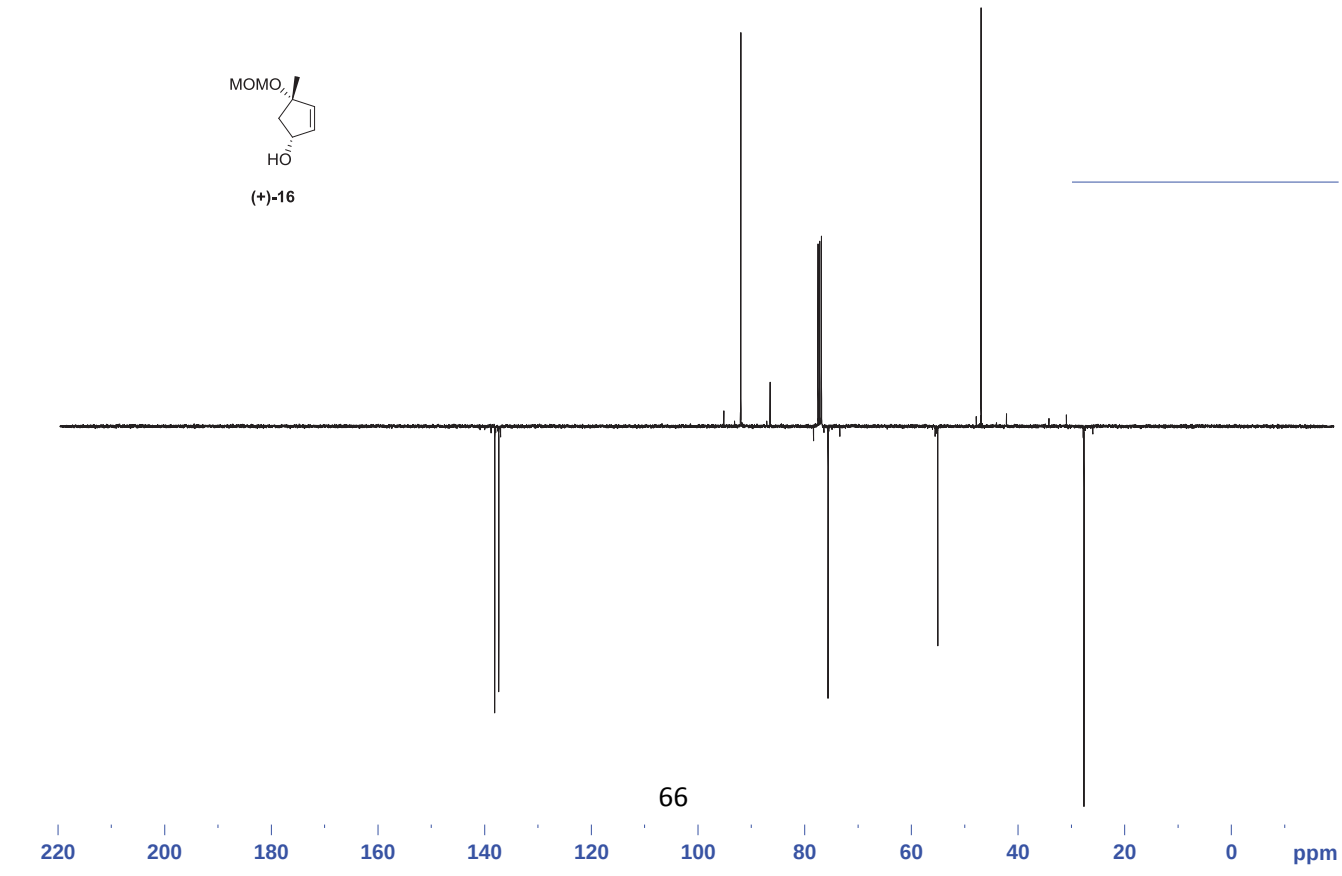
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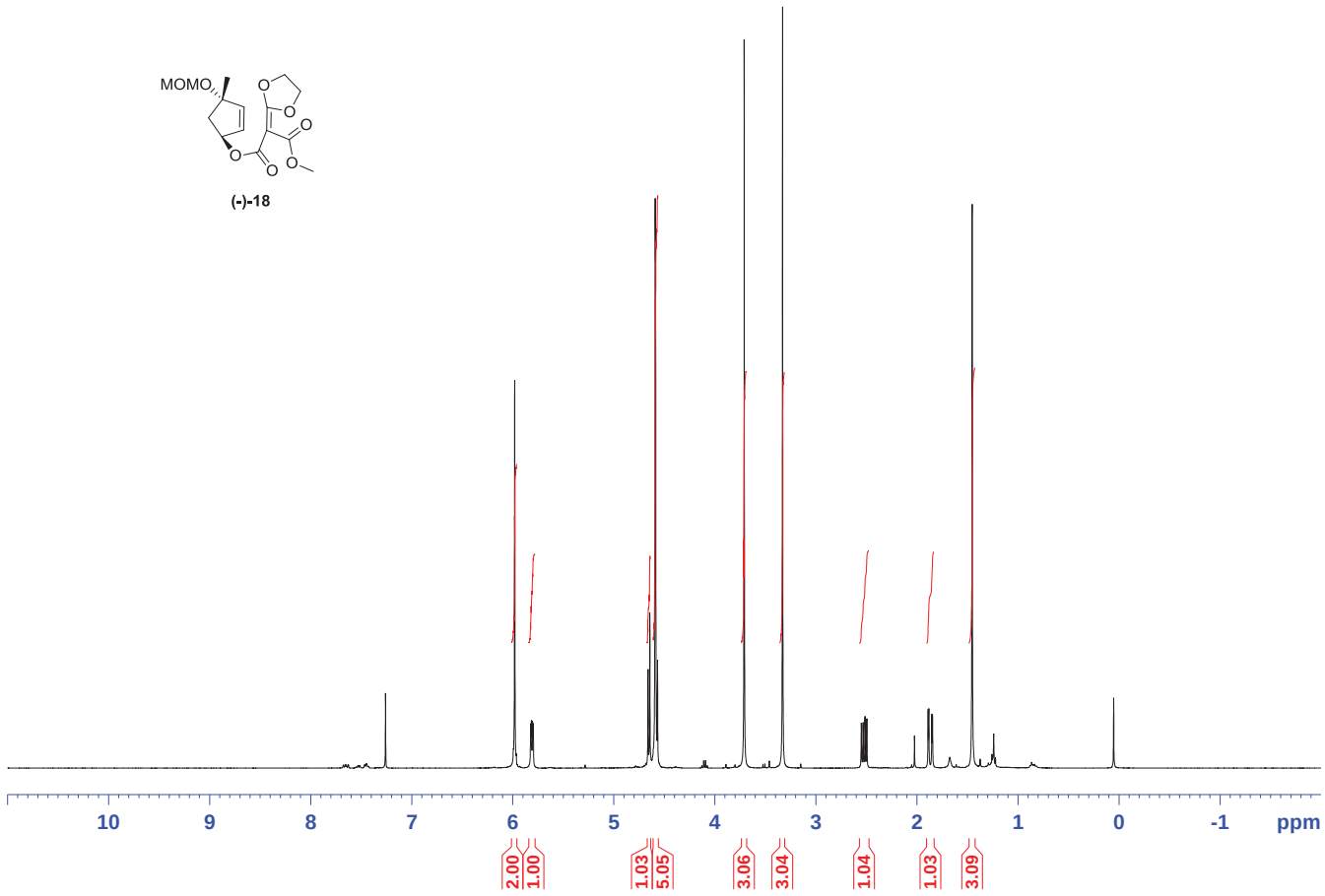
ppm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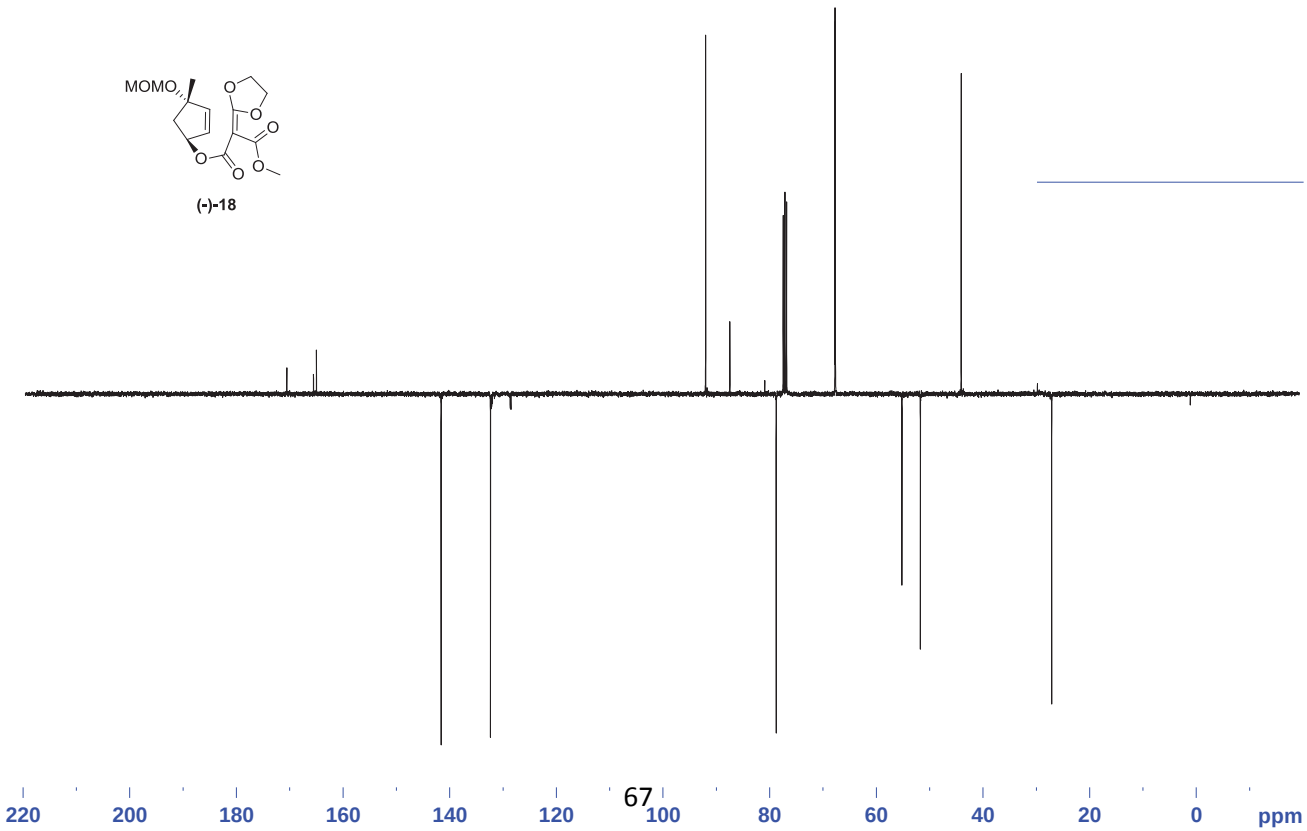
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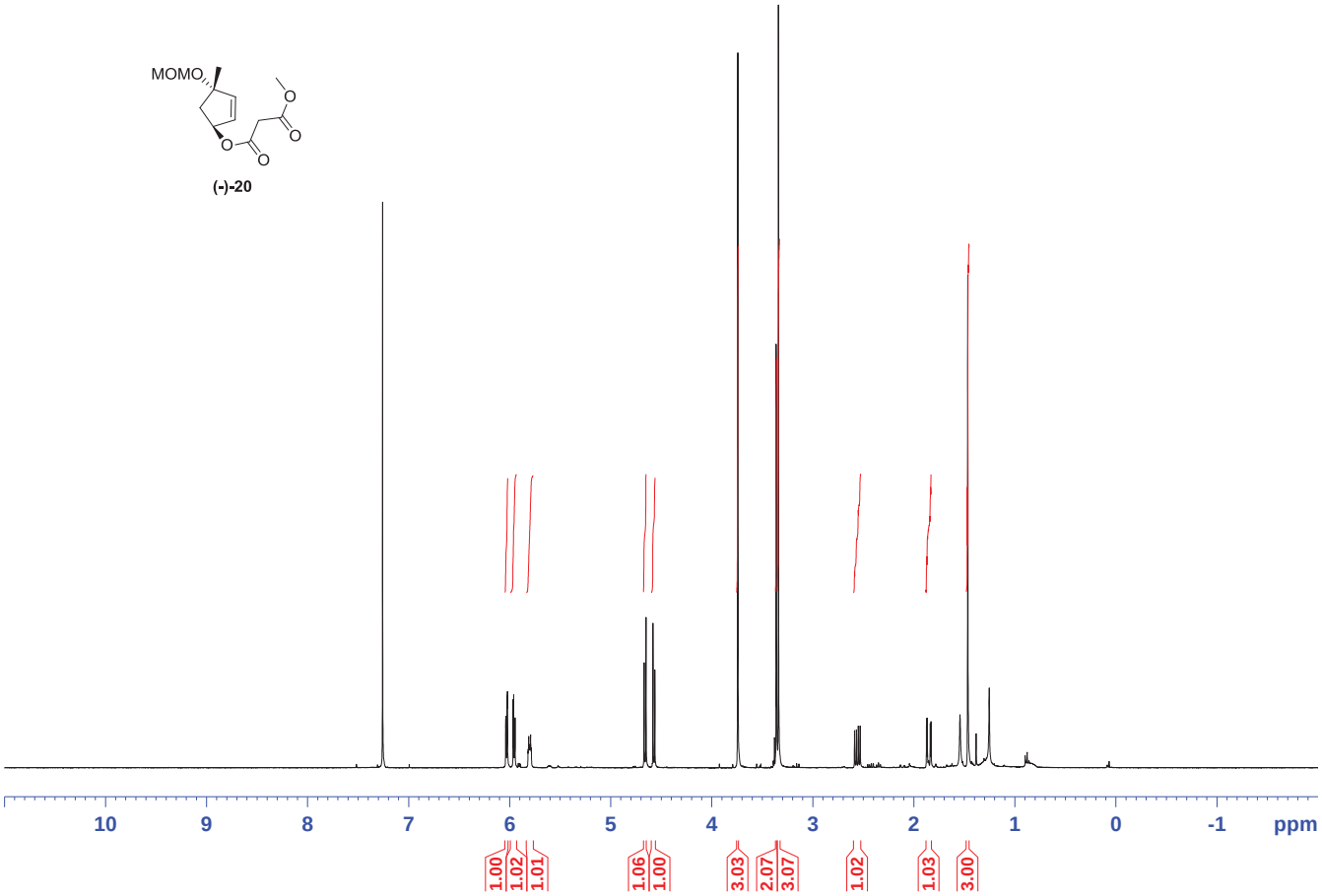
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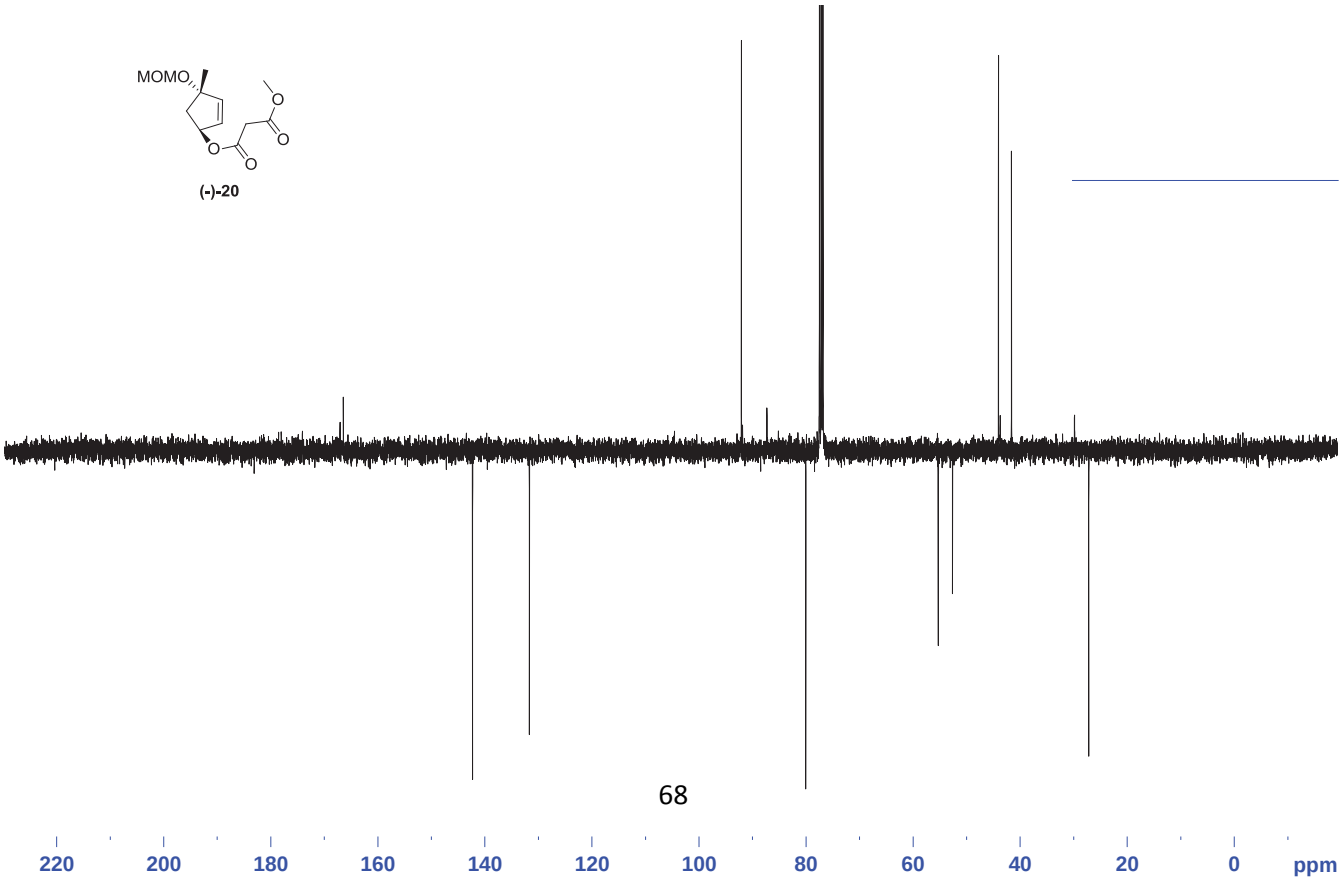
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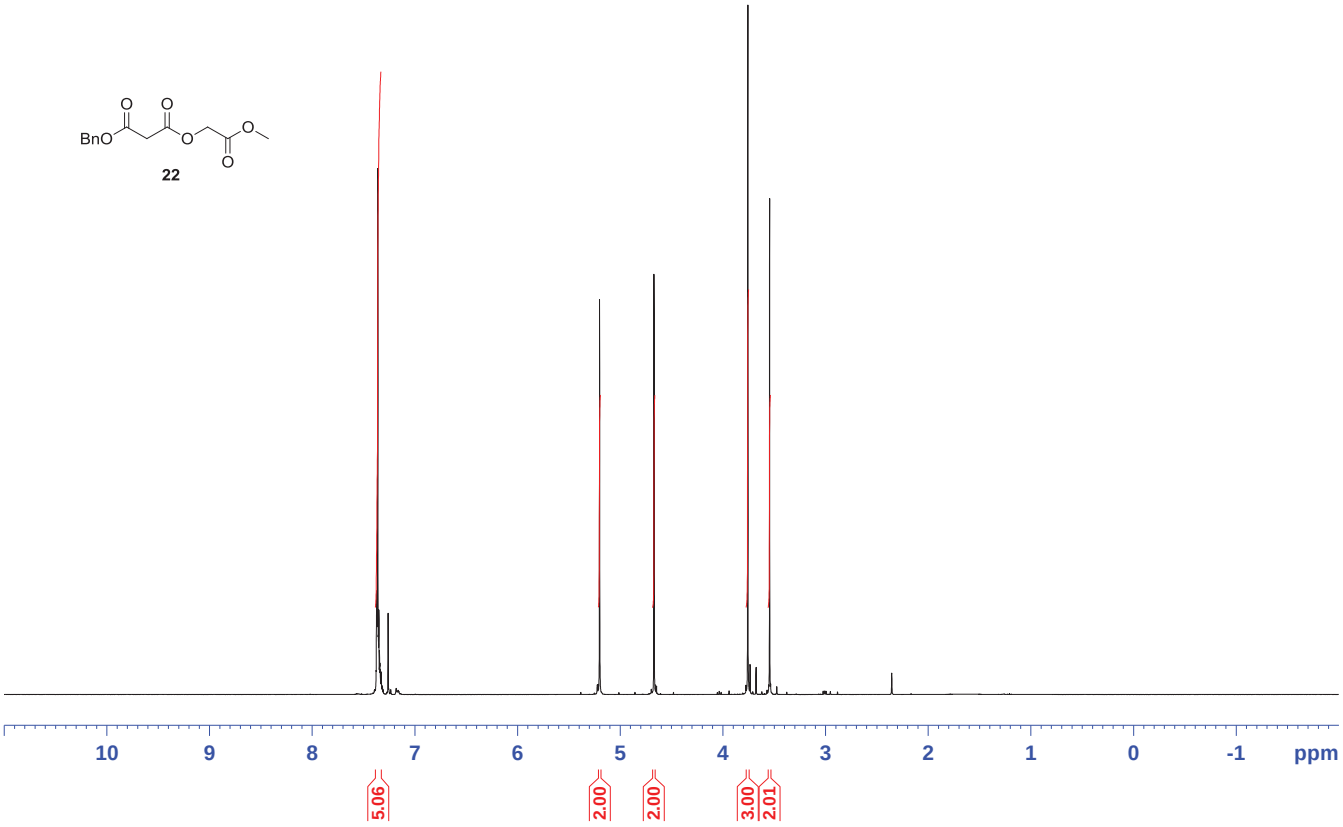
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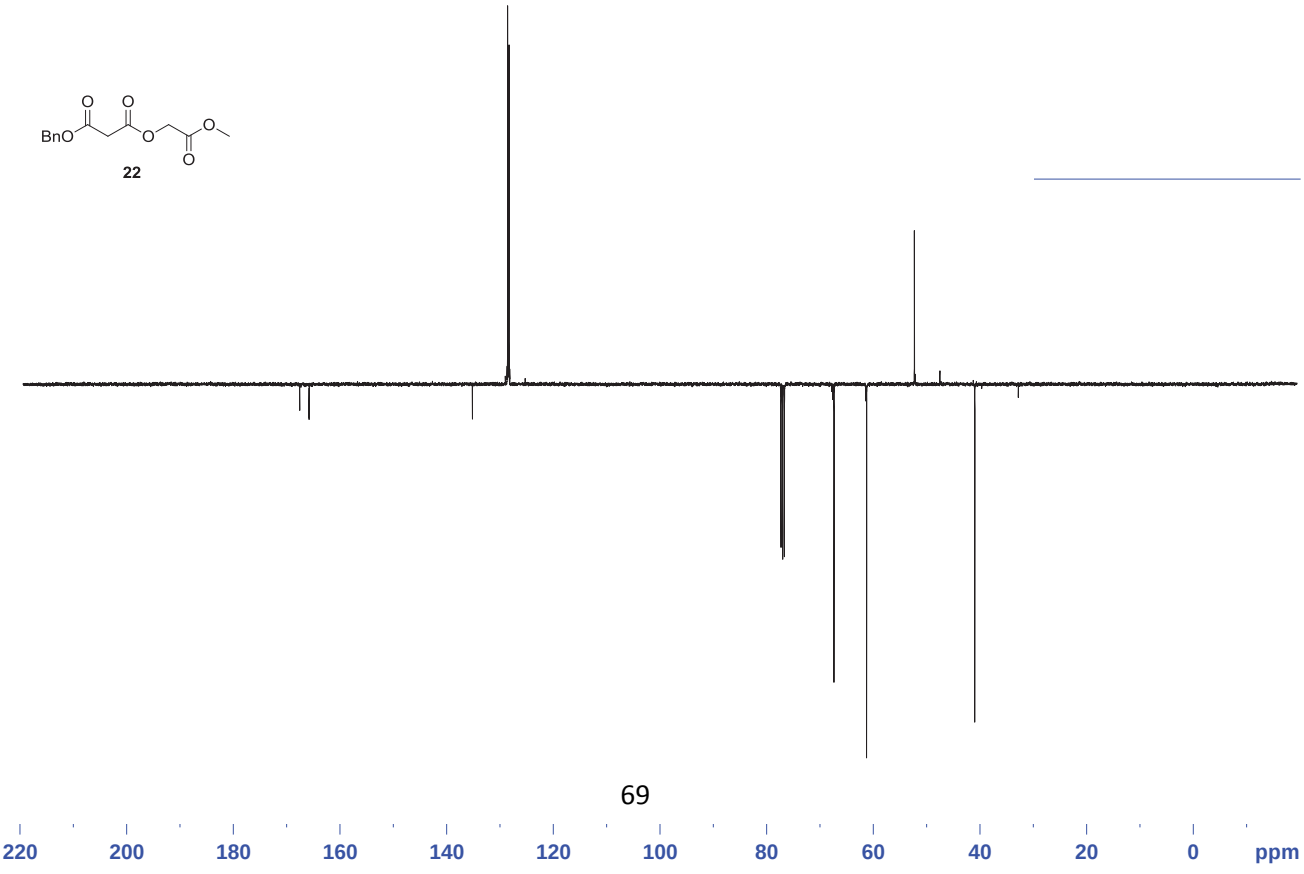
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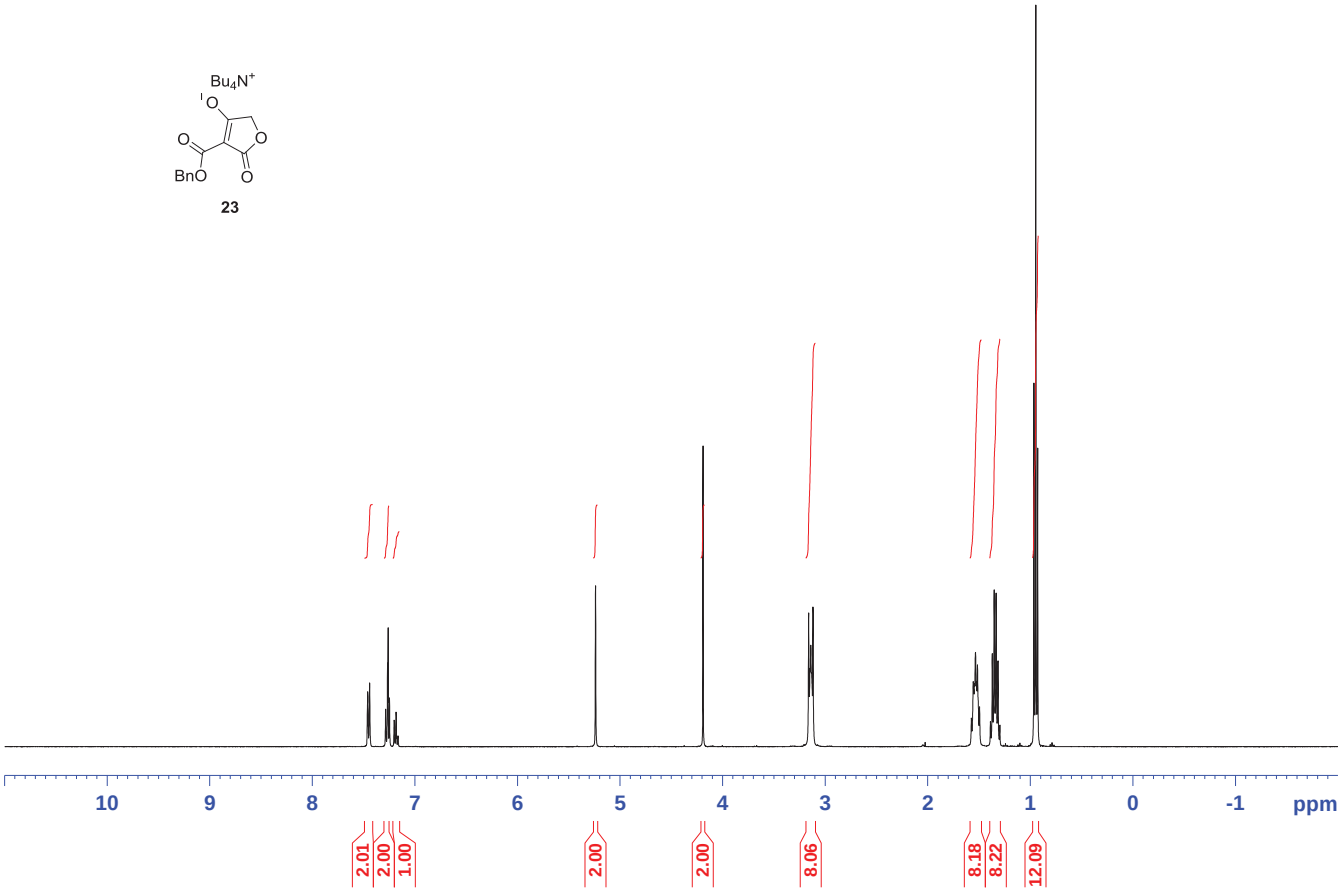
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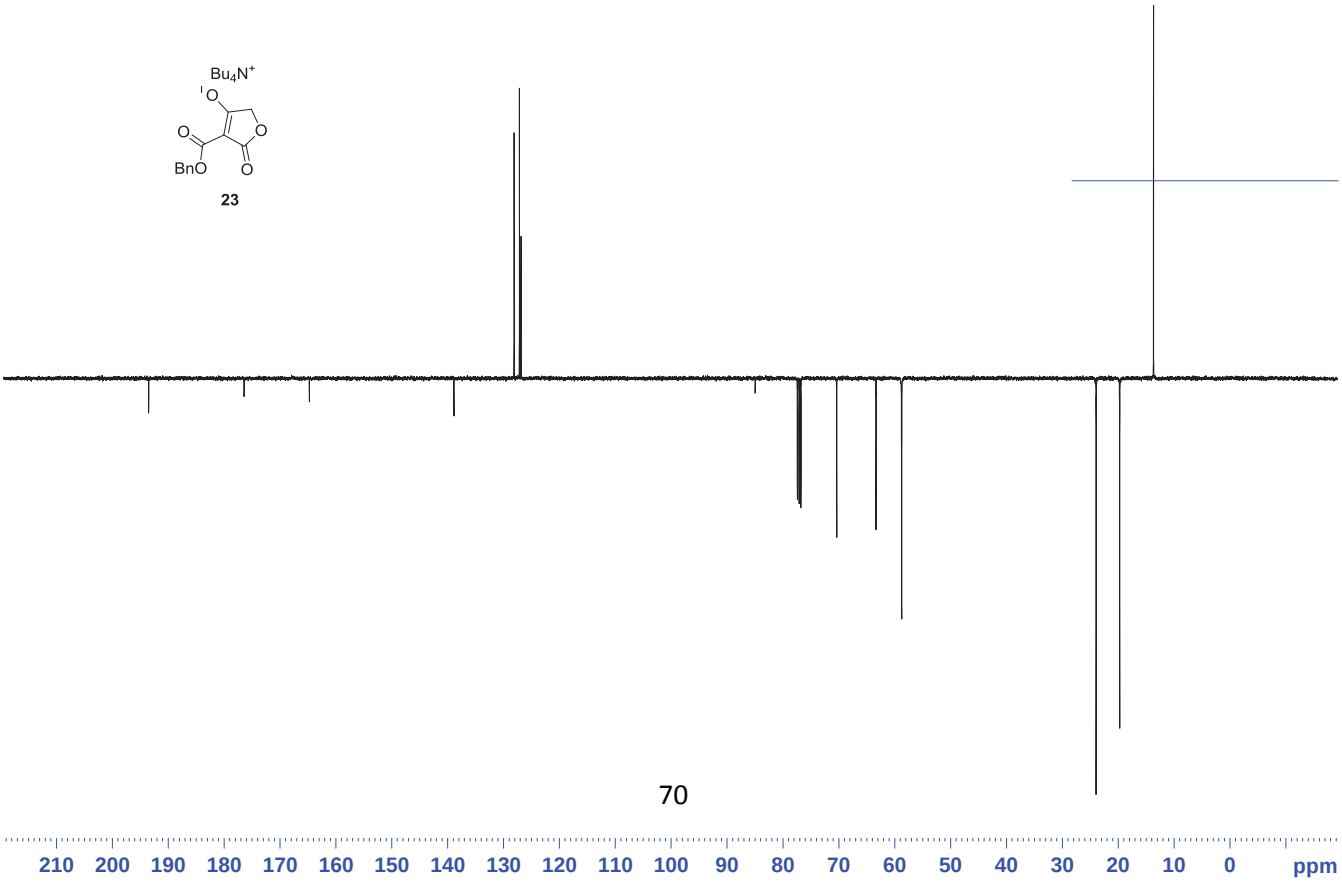
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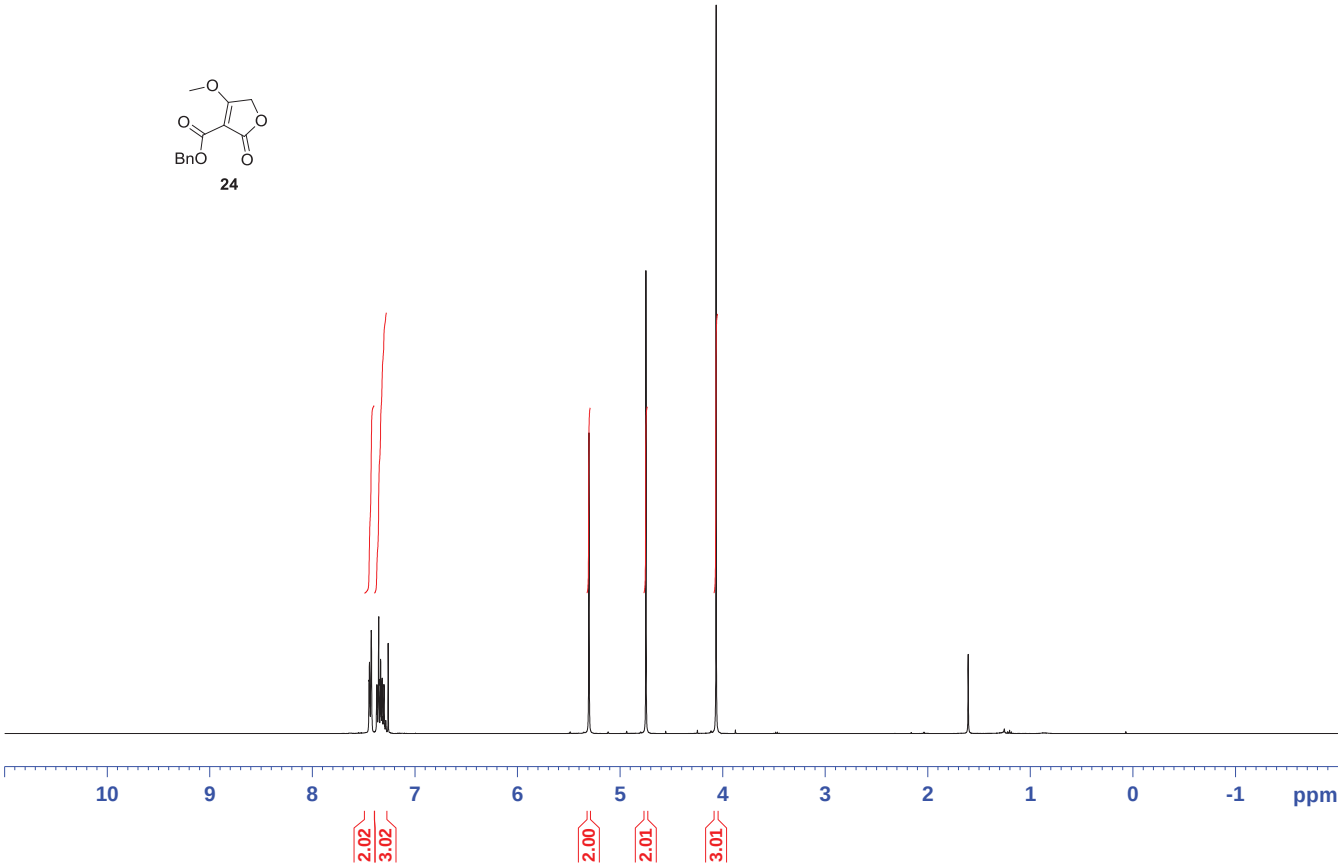
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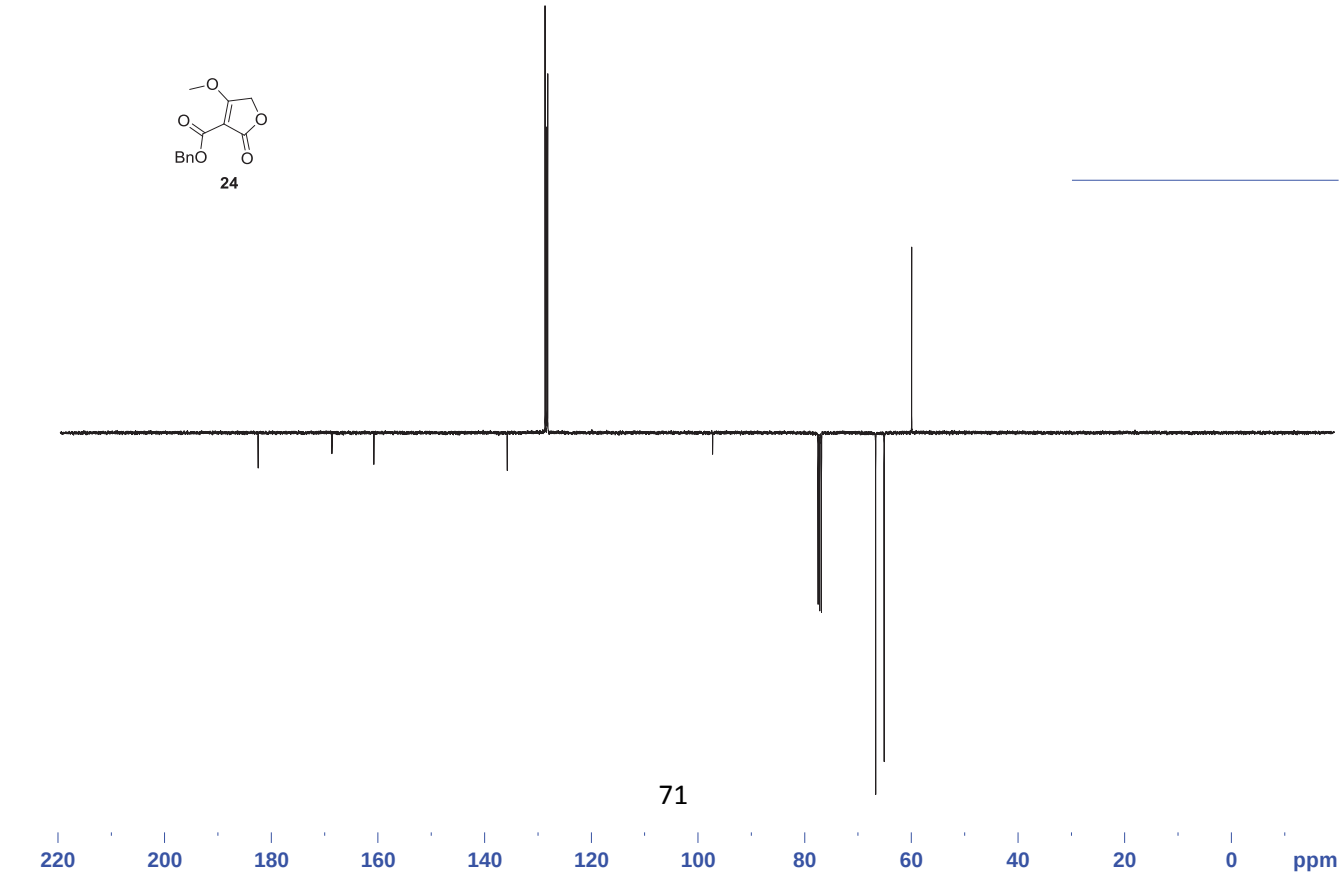
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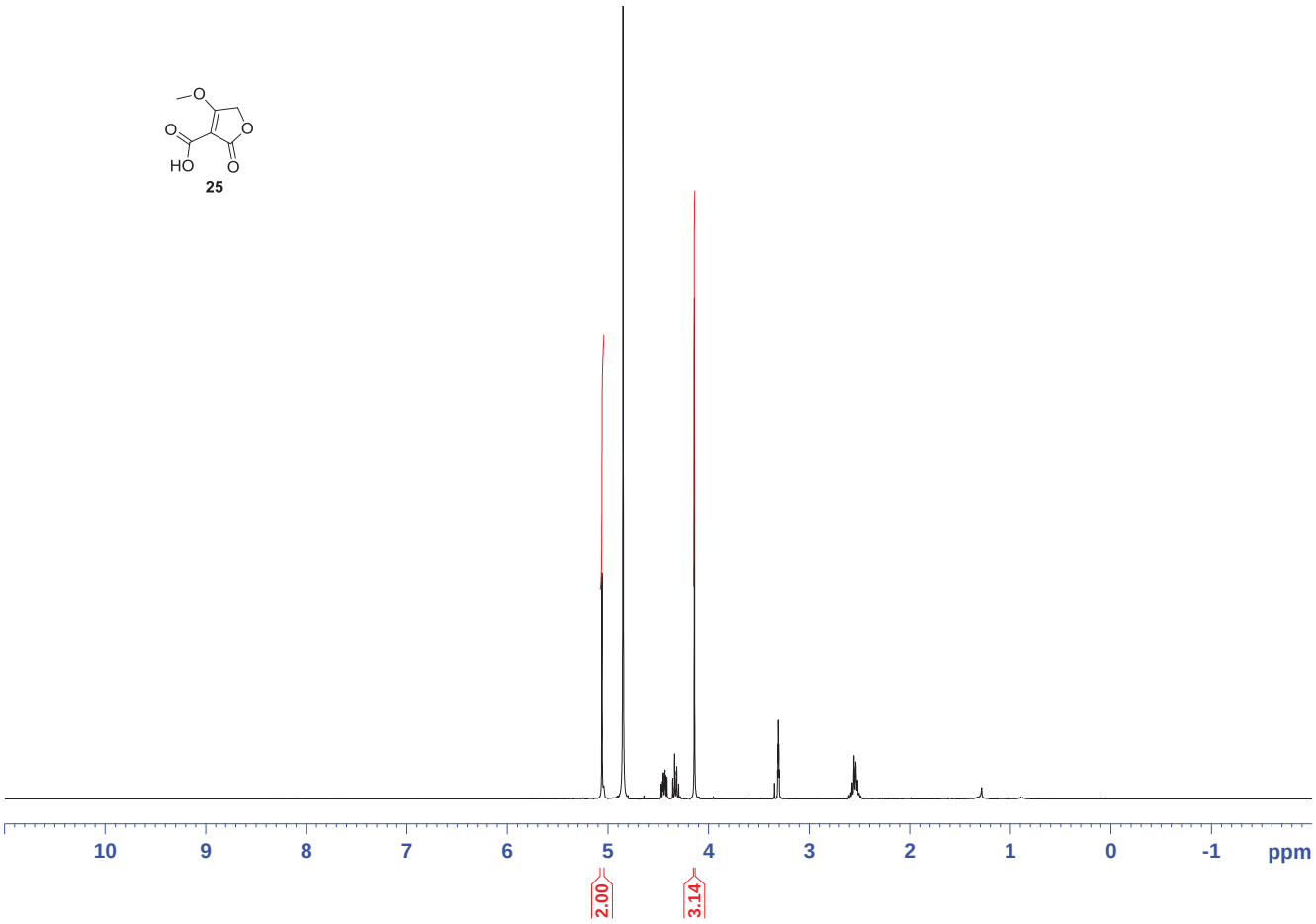
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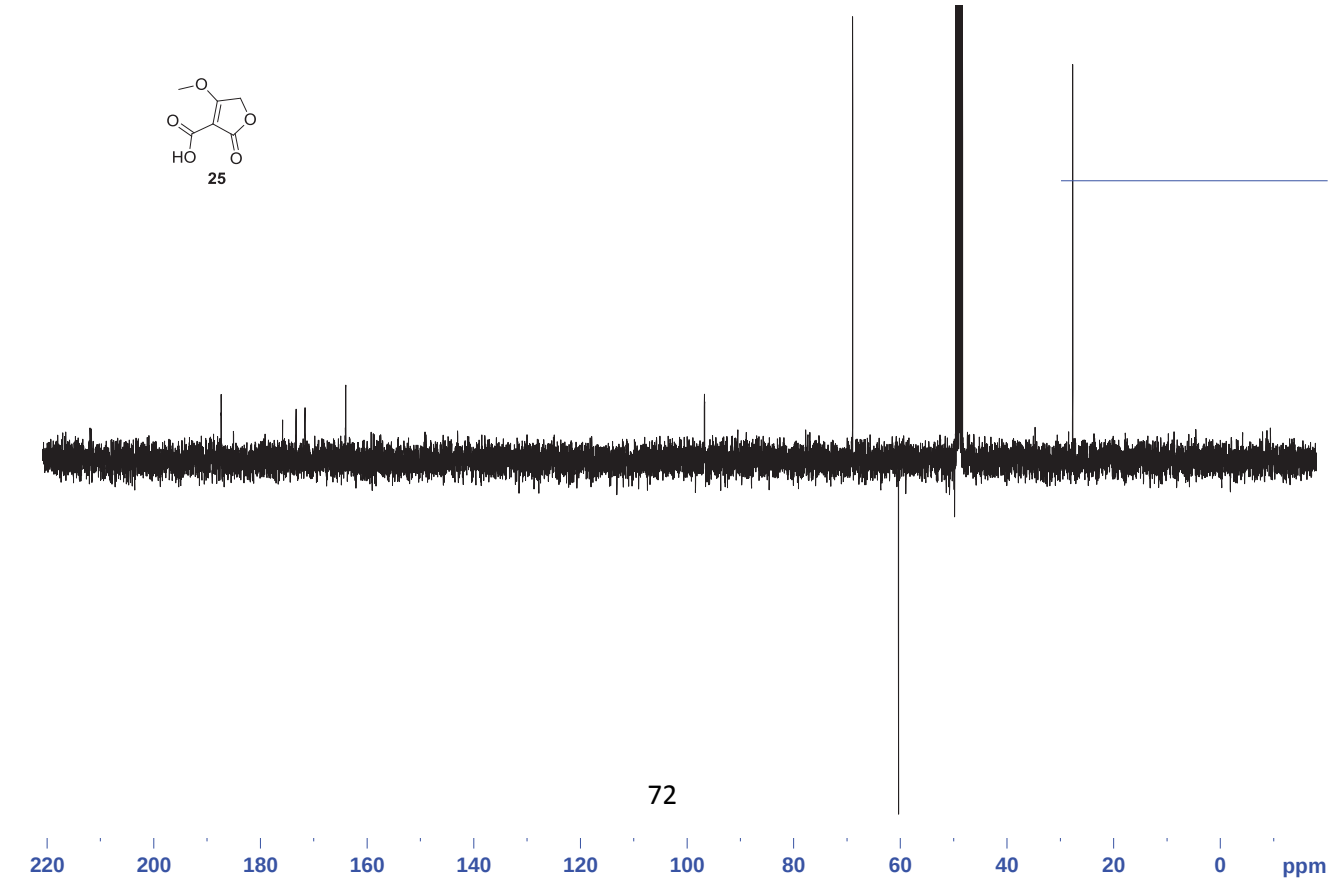
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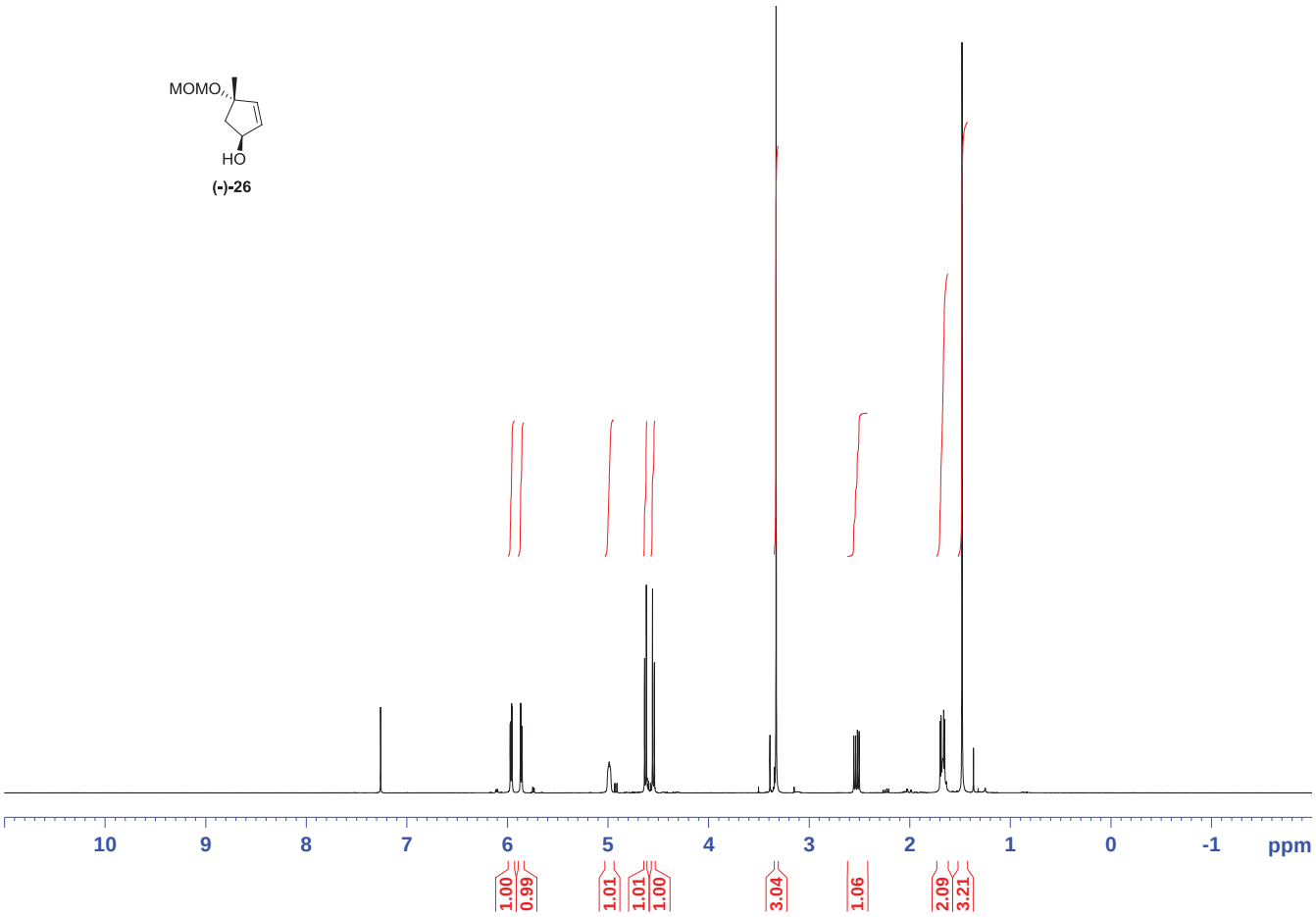
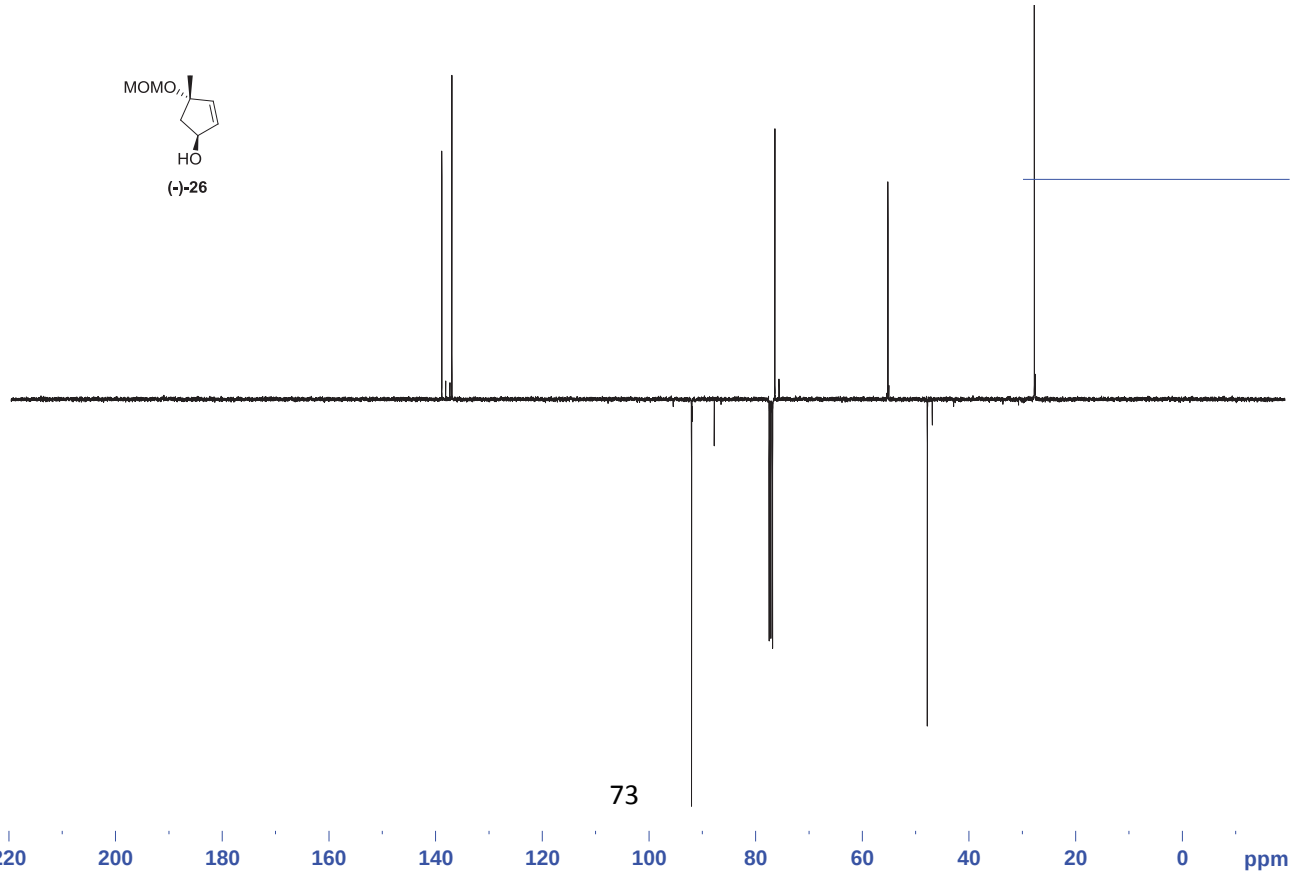
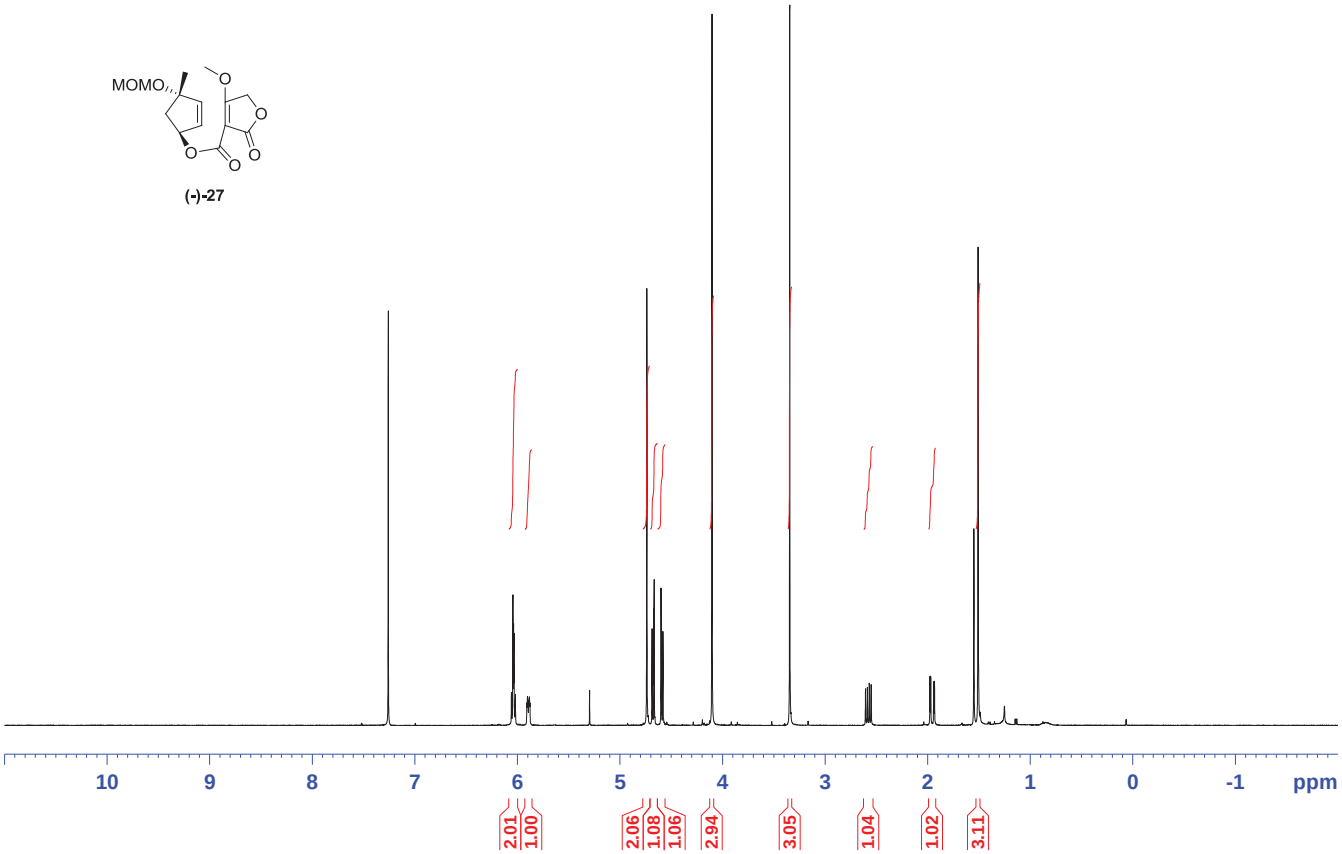
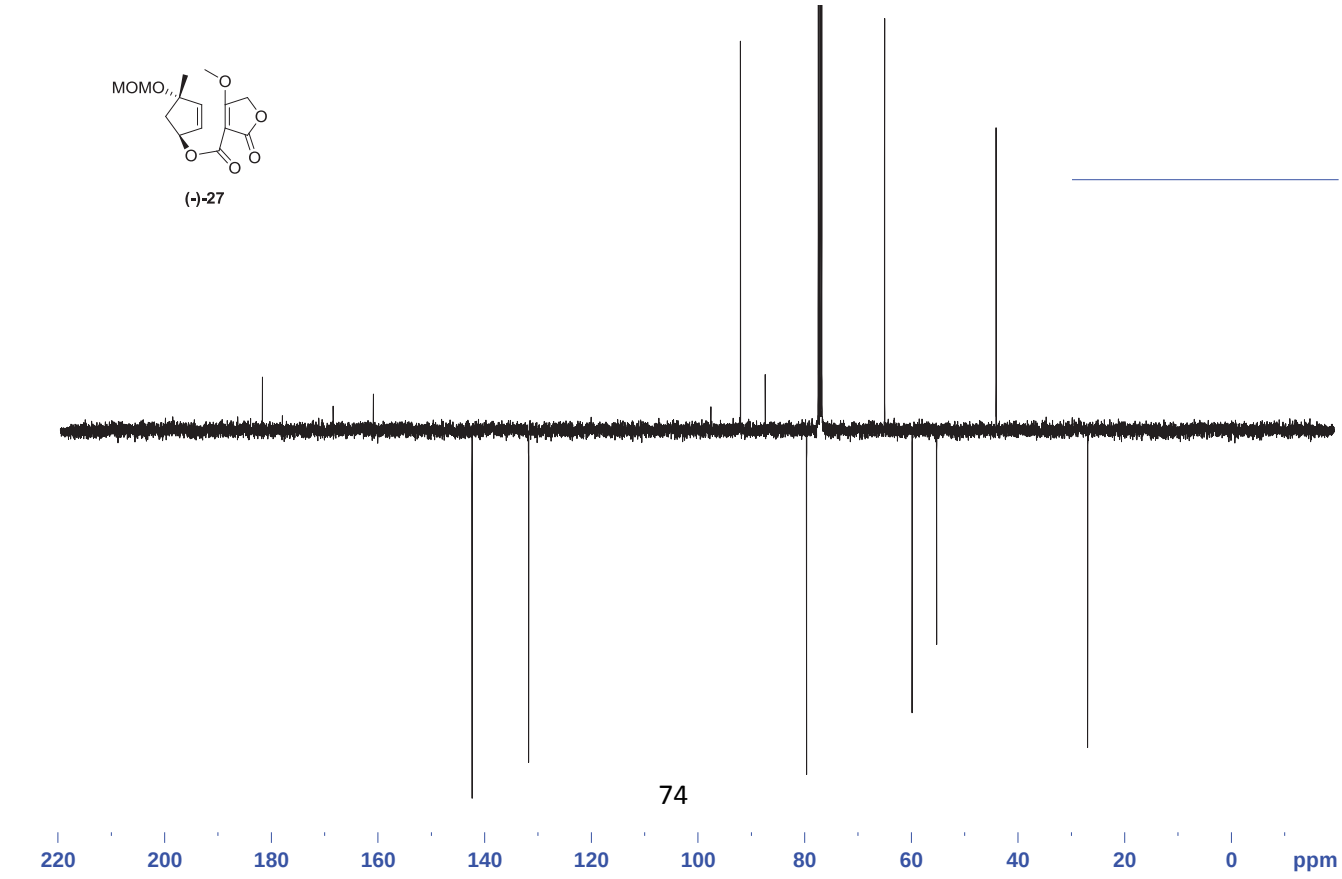
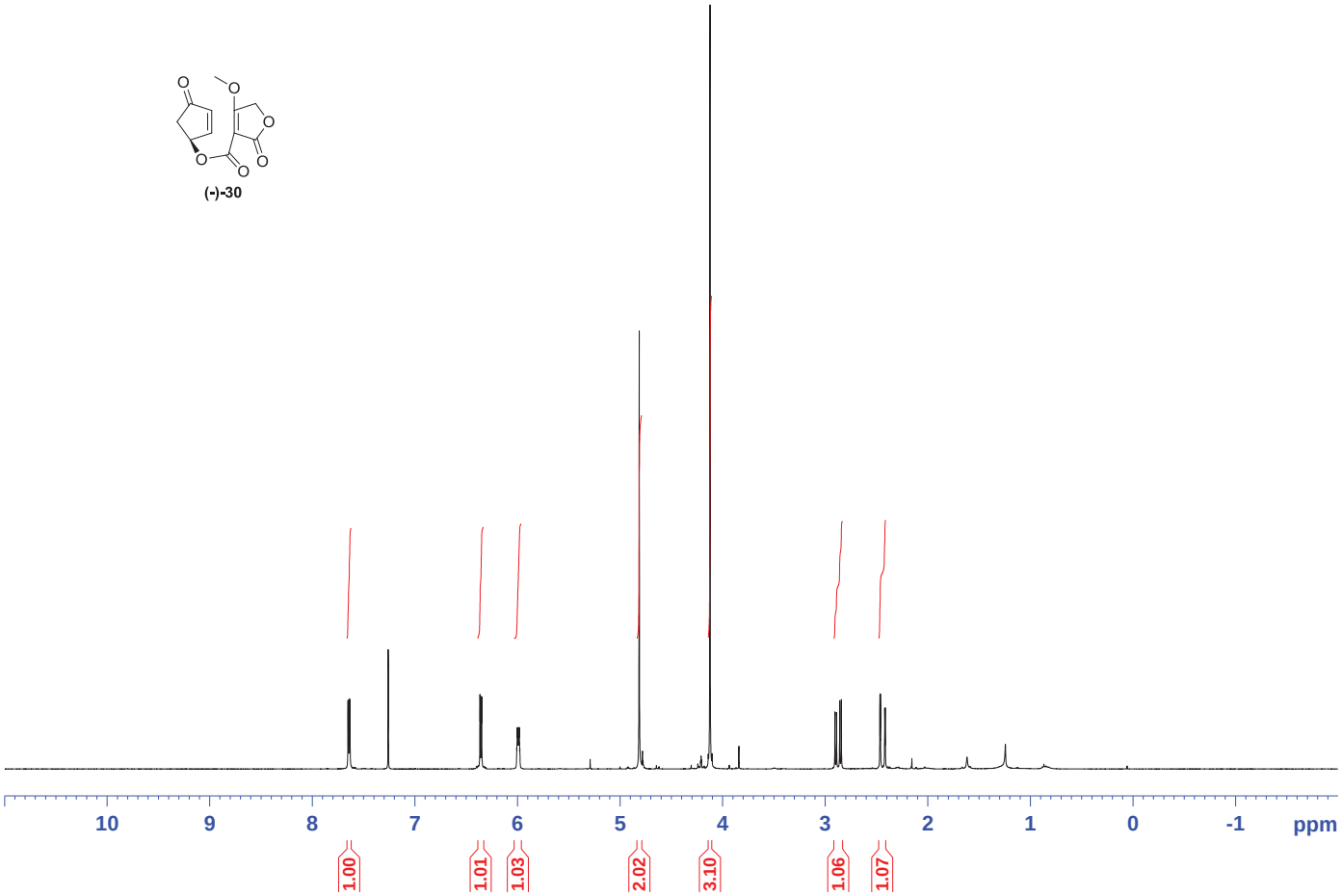
0
ppm

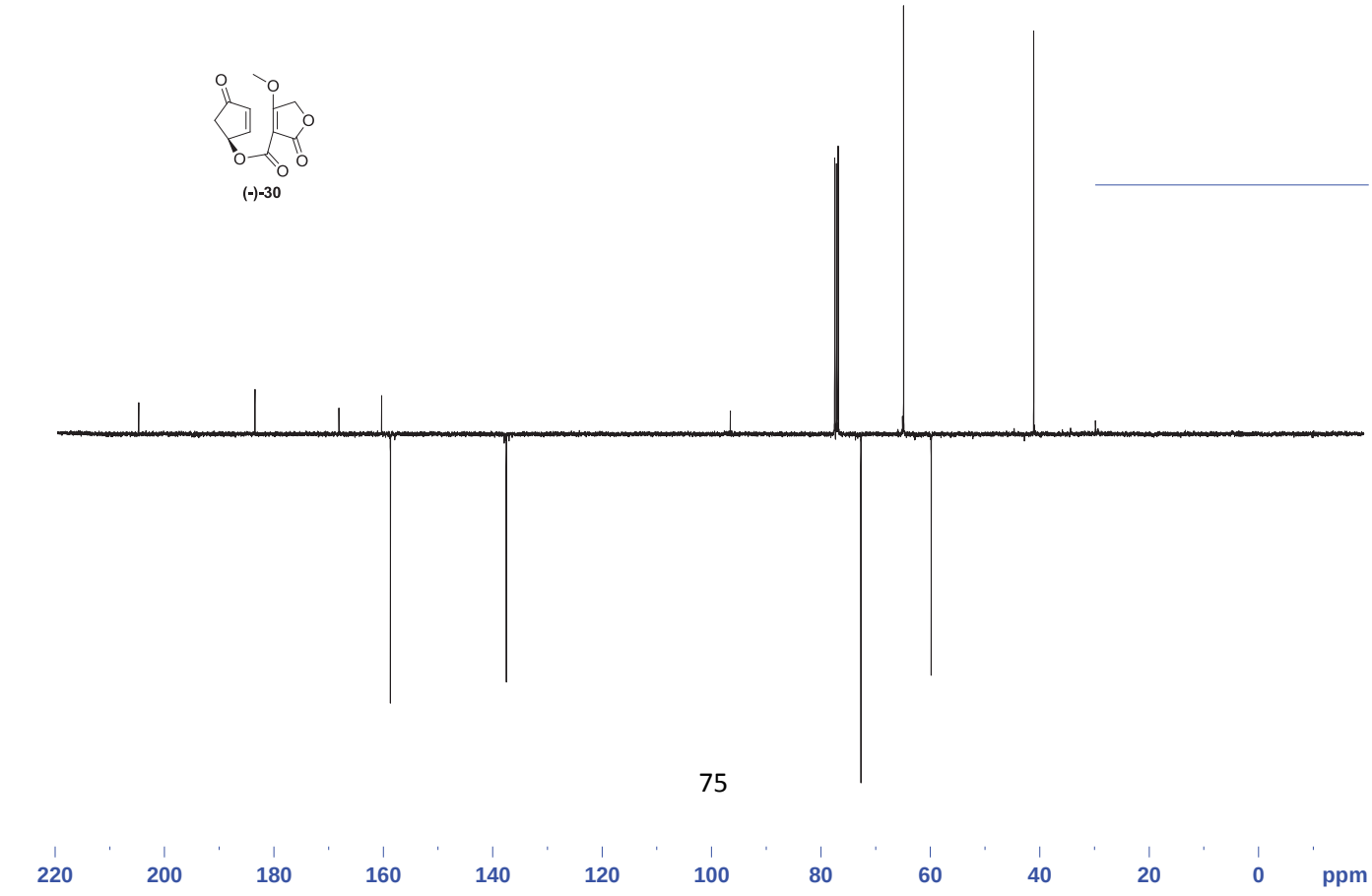

MOMO
HO
(-)-26
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.99
1.01
1.01
1.00
3.04
1.06
2.09
3.21

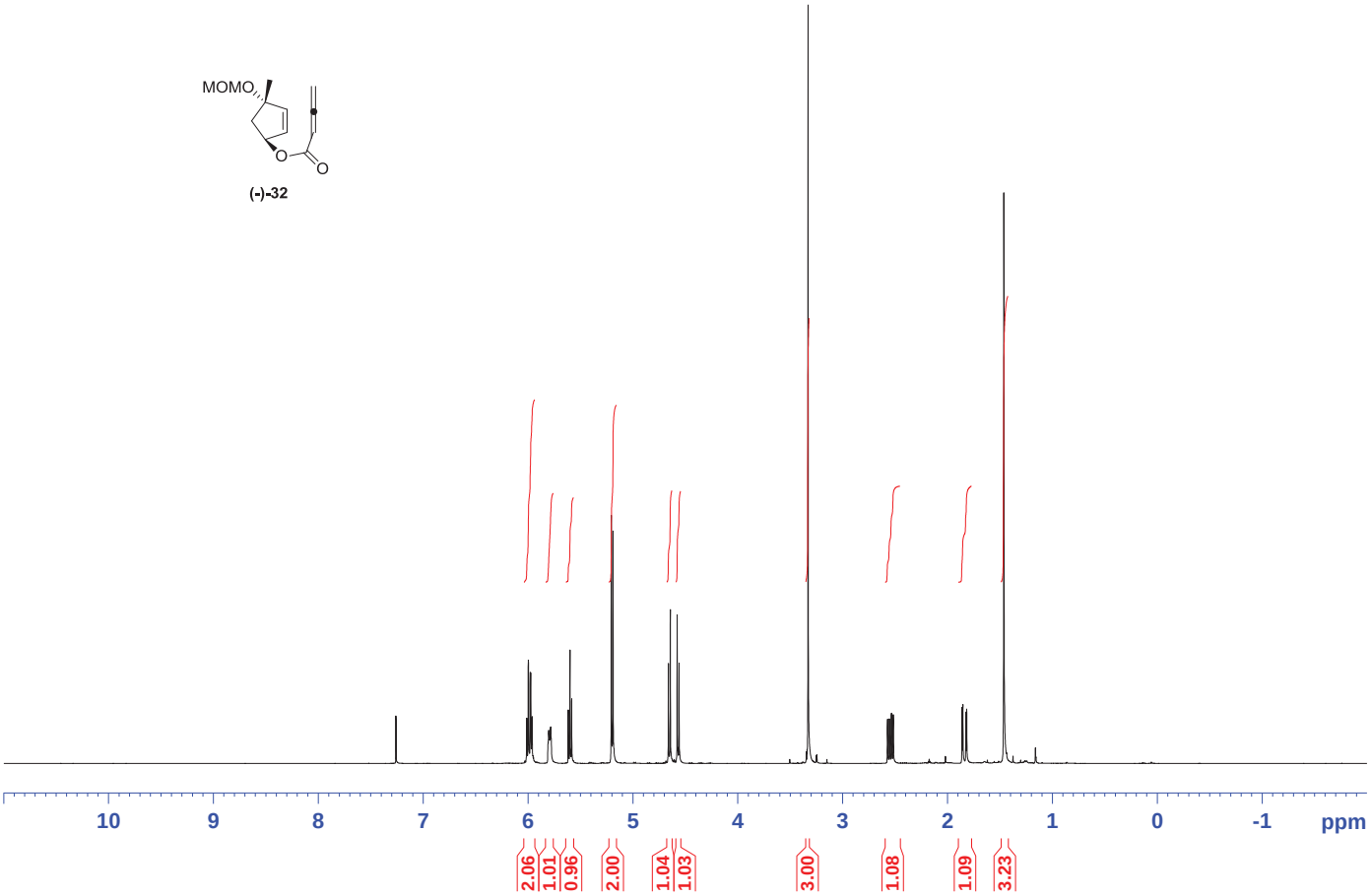

MOMO
HO
(-)-26
220
200
180
160
140
120
100
80
60
40
20
0
ppm

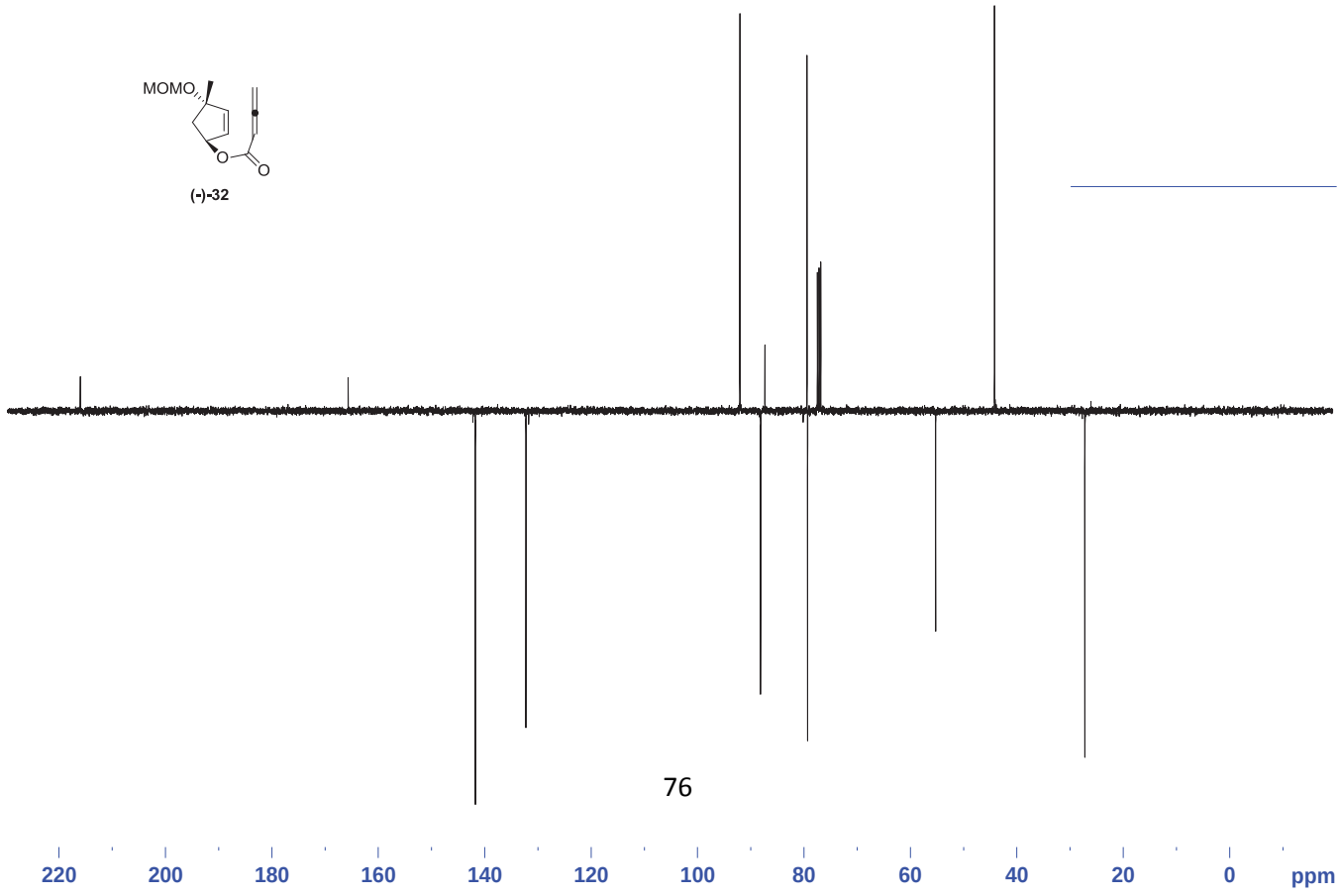

MOMO
O
O
O
O
O
(-)-27
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.01
1.00
2.06
1.08
1.06
2.94
3.05
1.04
1.02
3.11

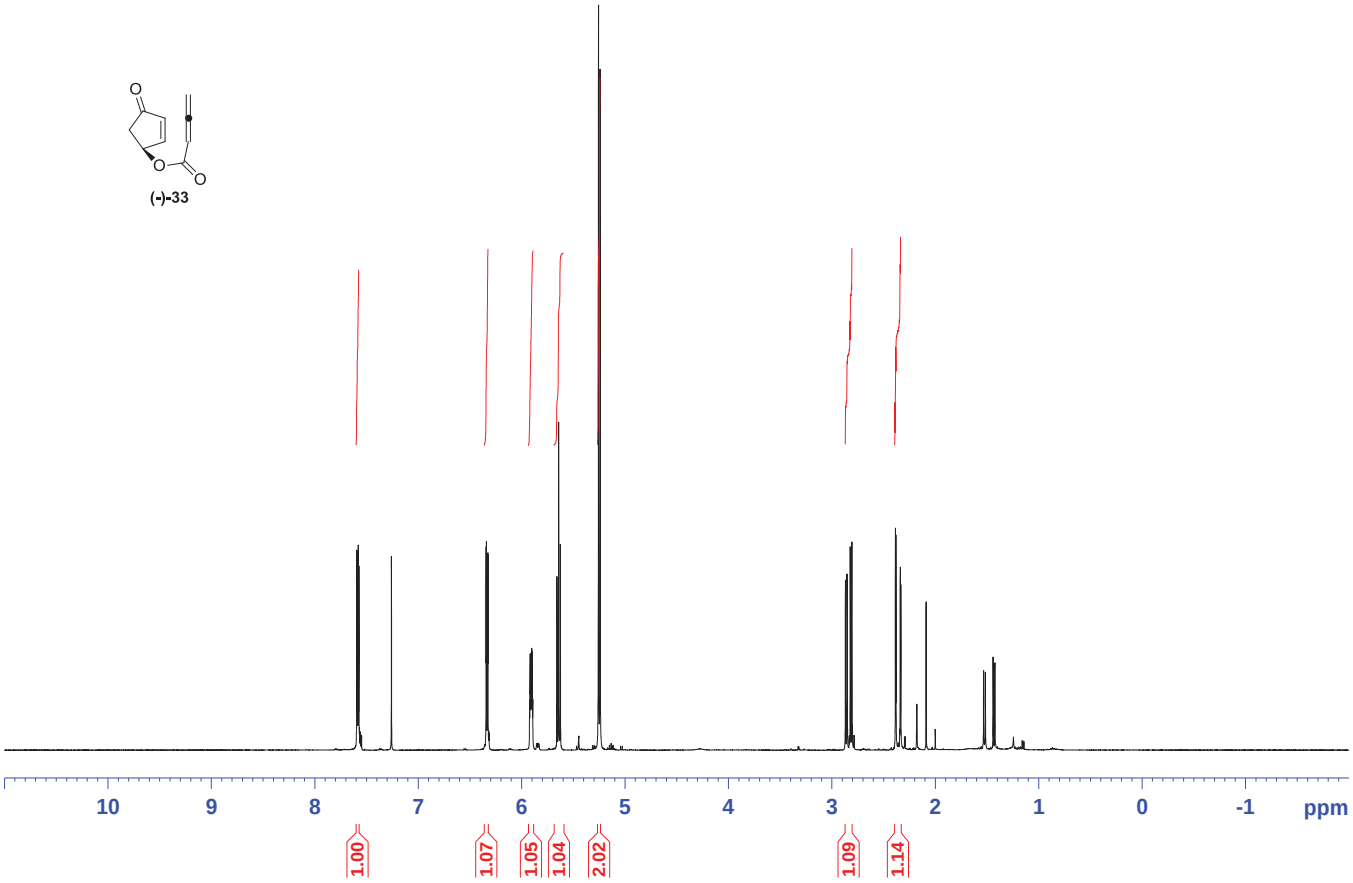

MOMO
O
O
O
O
O
(-)-27
220
200
180
160
140
120
100
80
60
40
20
0
ppm

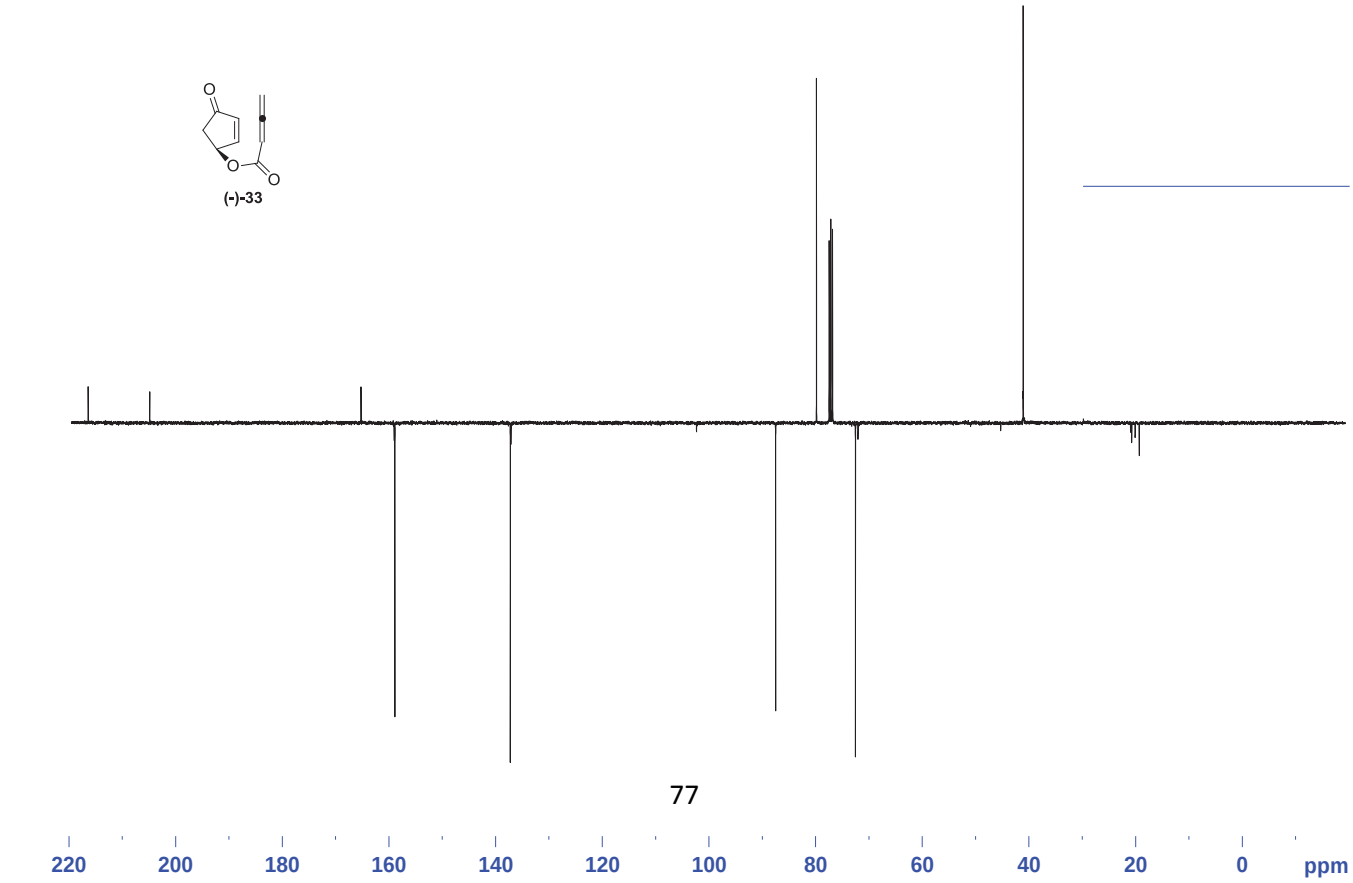

(-)-30
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.01
1.03
2.02
3.10
1.06
1.07

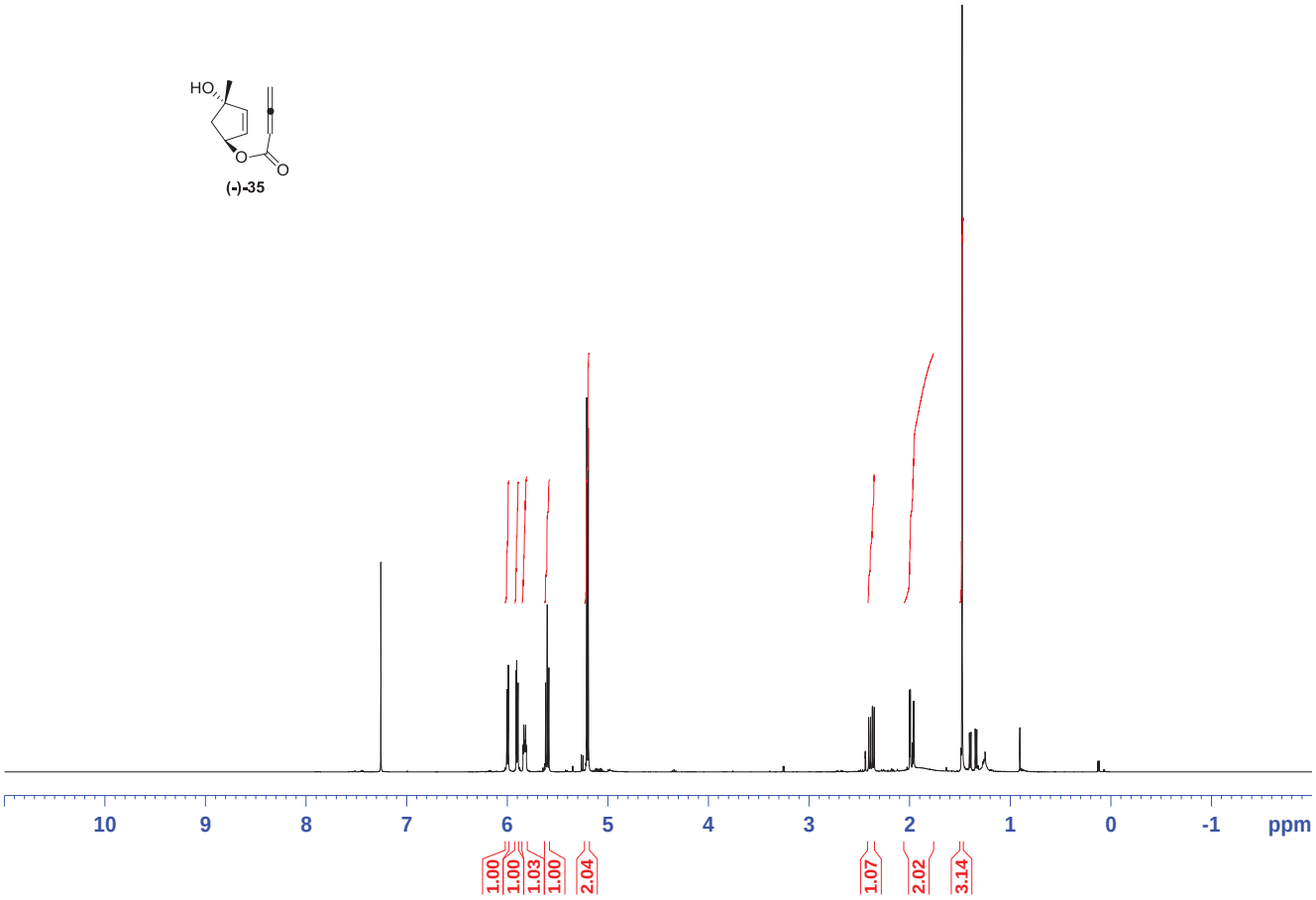

(-)-30
220
200
180
160
140
120
100
80
60
40
20
0
ppm

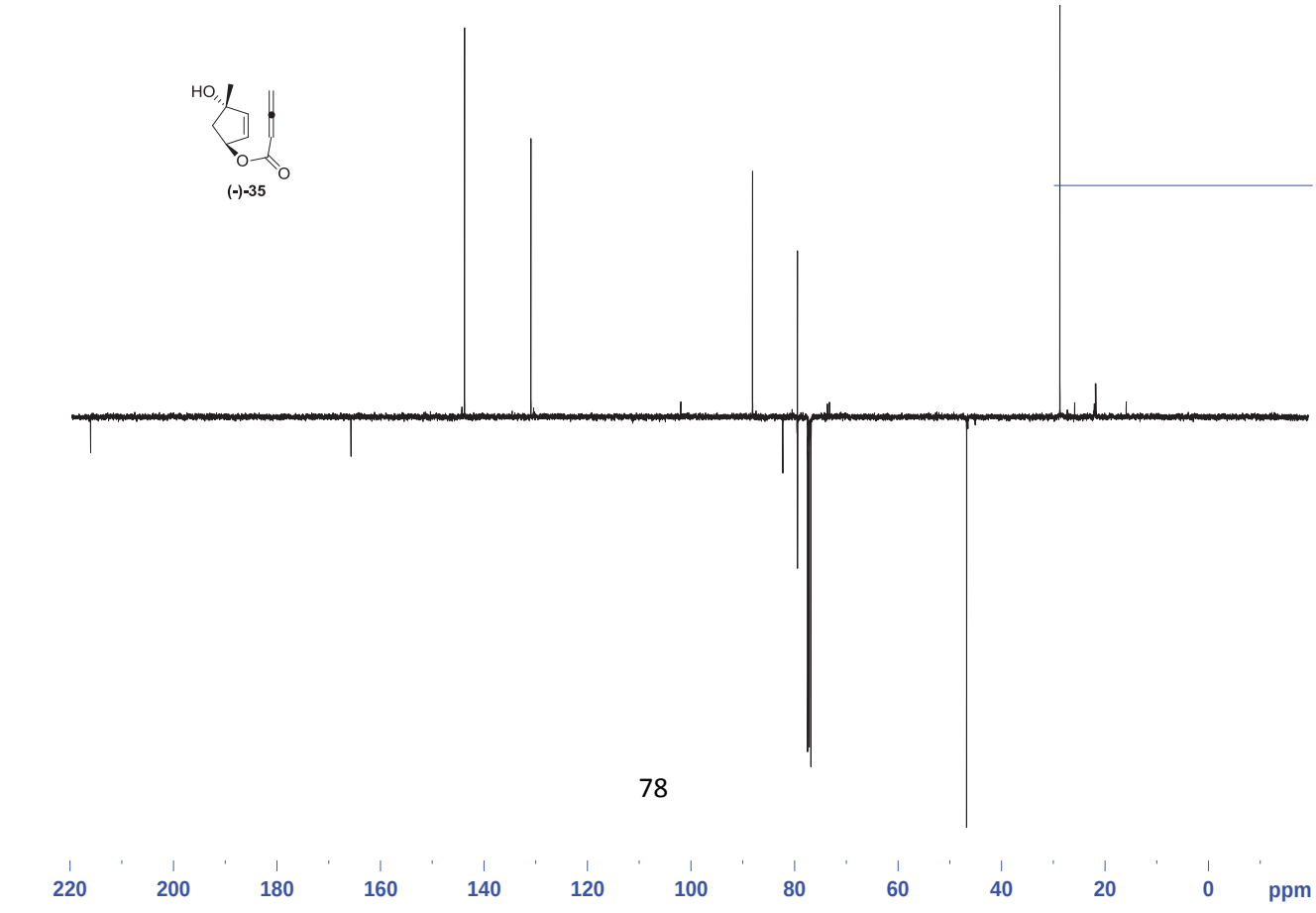

MOMO
O
O
(-)-32
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.06
1.01
0.96
2.00
1.04
1.03
3.00
1.08
1.09
3.23

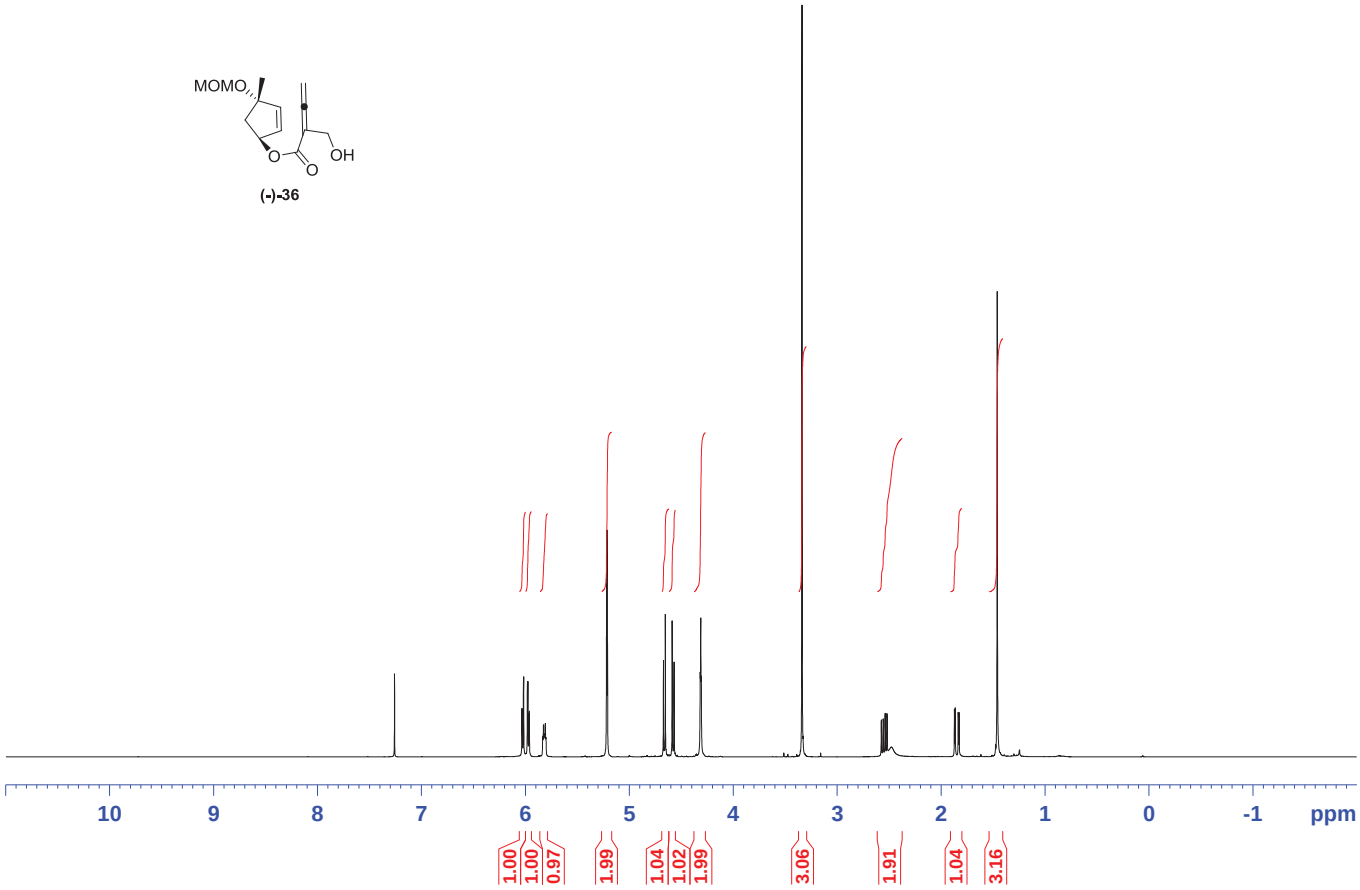

MOMO
O
O
(-)-32
220
200
180
160
140
120
100
80
60
40
20
0
ppm

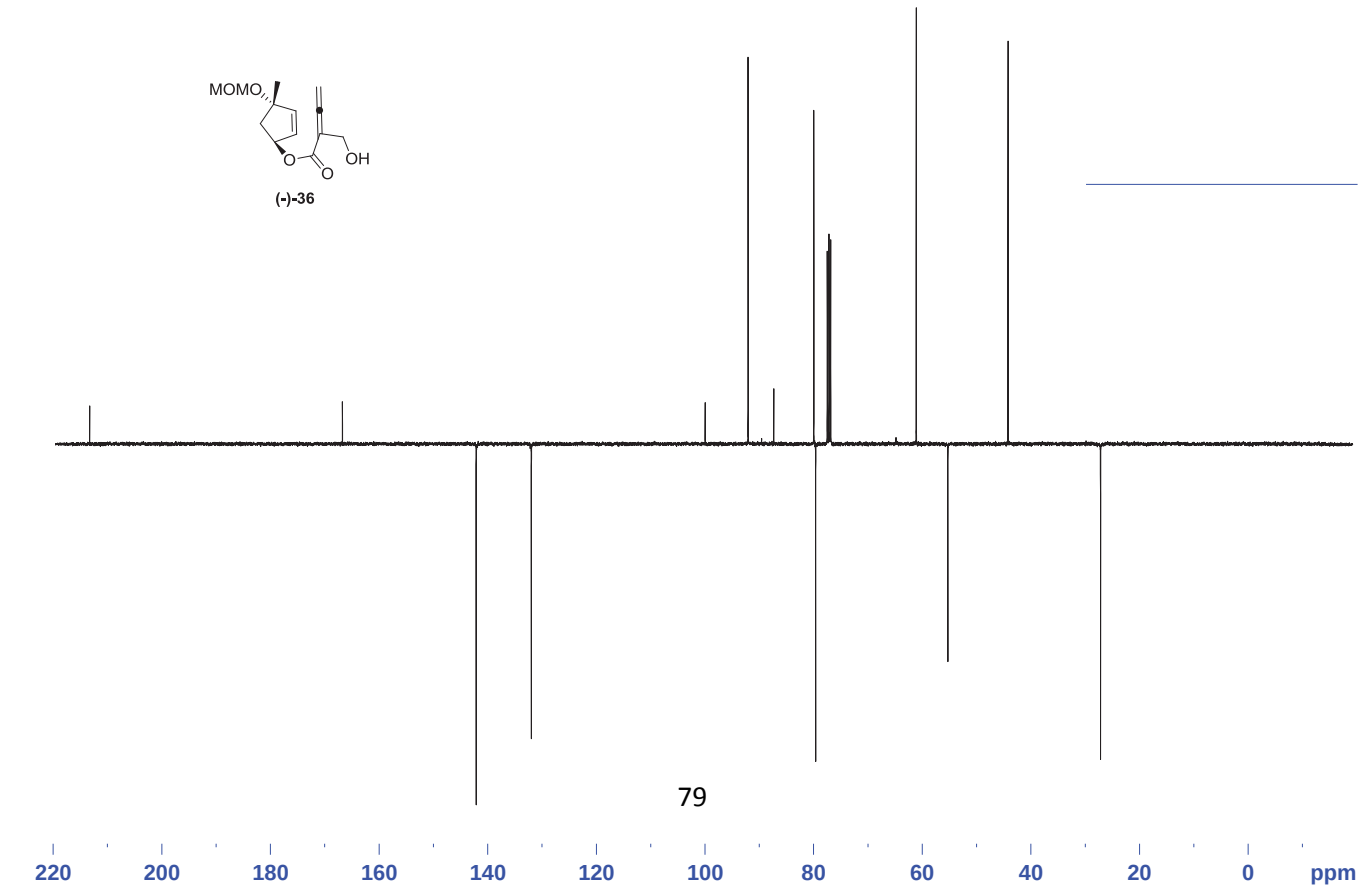

(-)-33
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.07
1.05
1.04
2.02
1.09
1.14

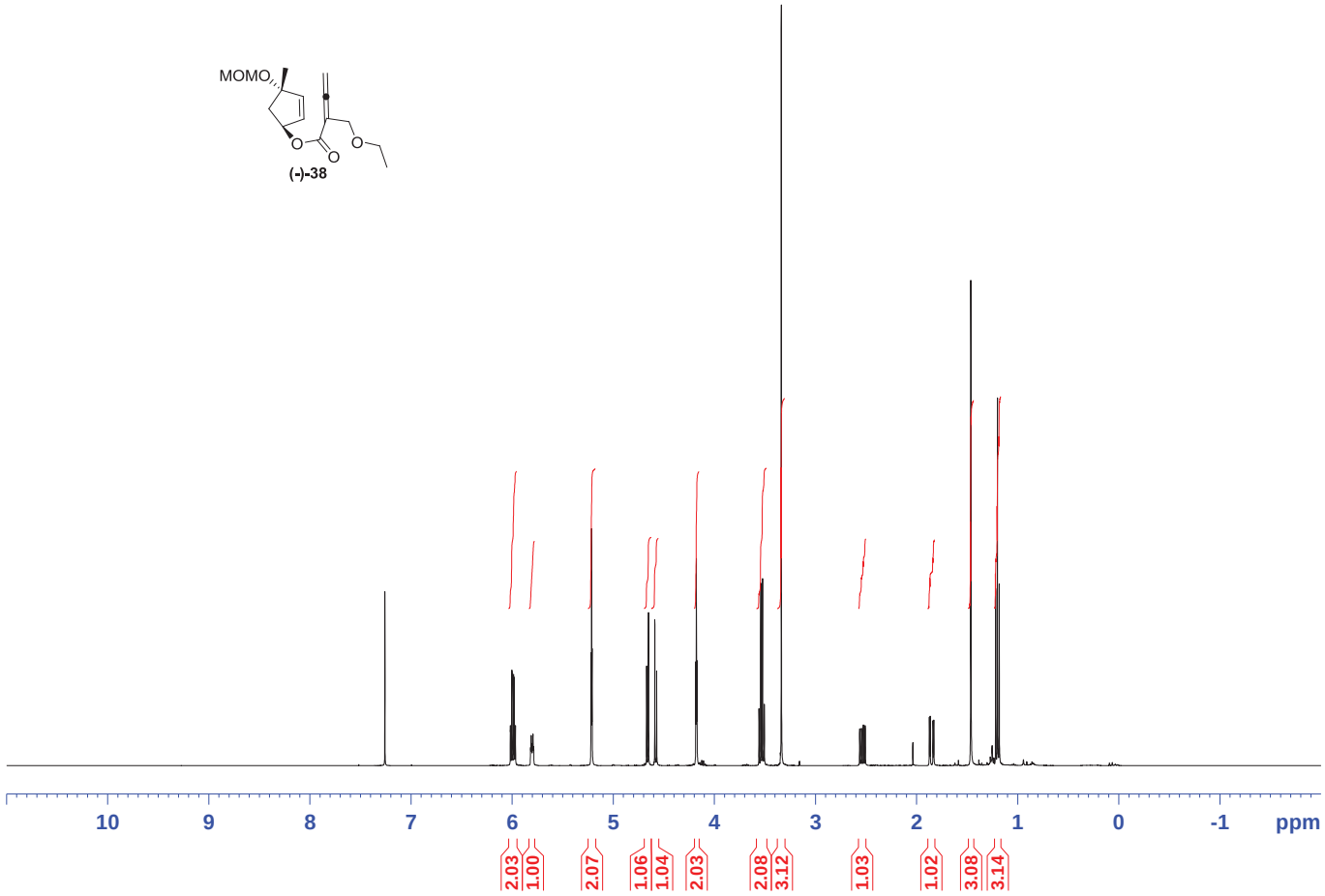

(-)-33
220
200
180
160
140
120
100
80
60
40
20
0
ppm

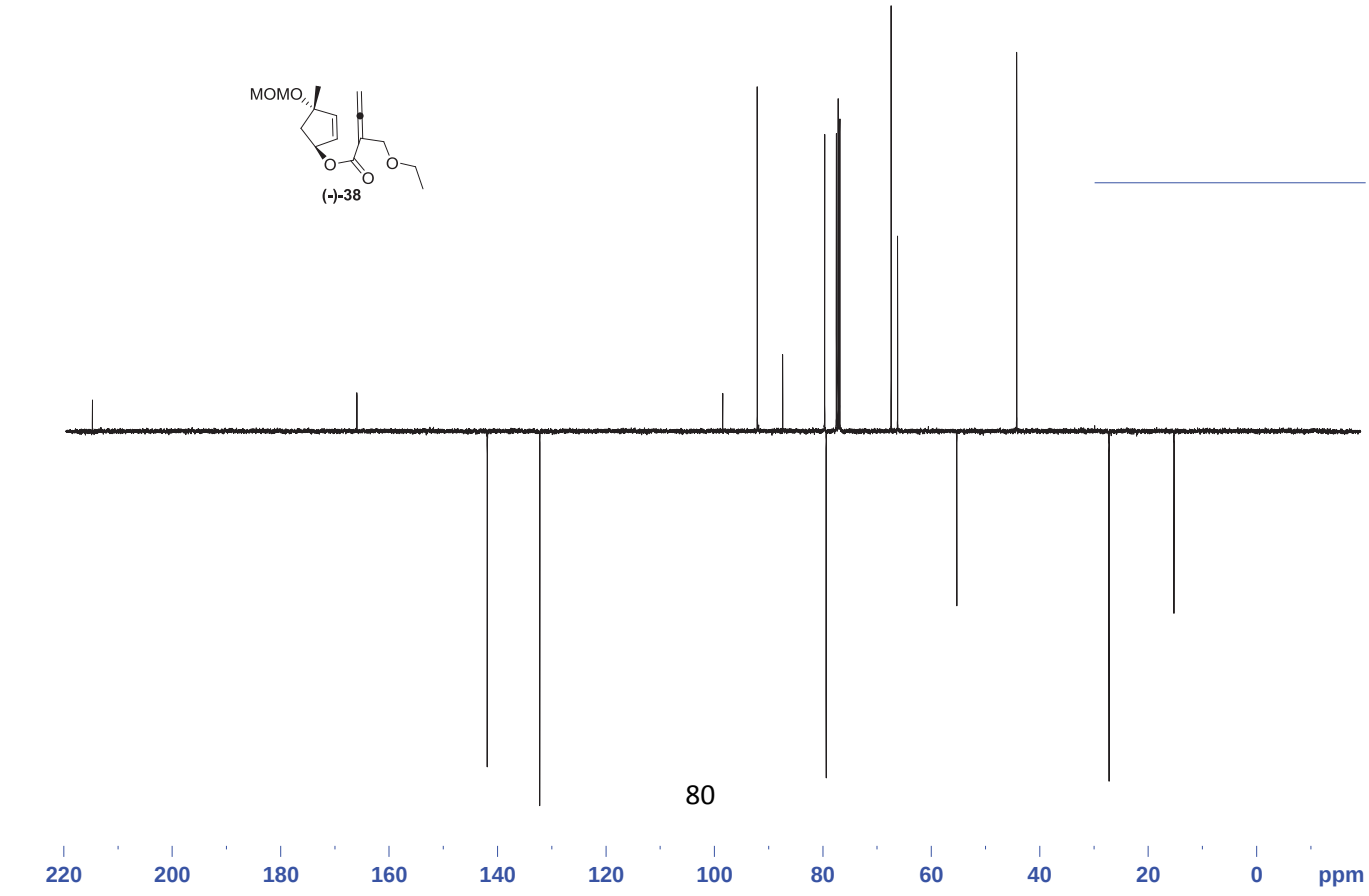

HO
O
O
(-)-35
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.00
1.03
1.00
2.04
1.07
2.02
3.14

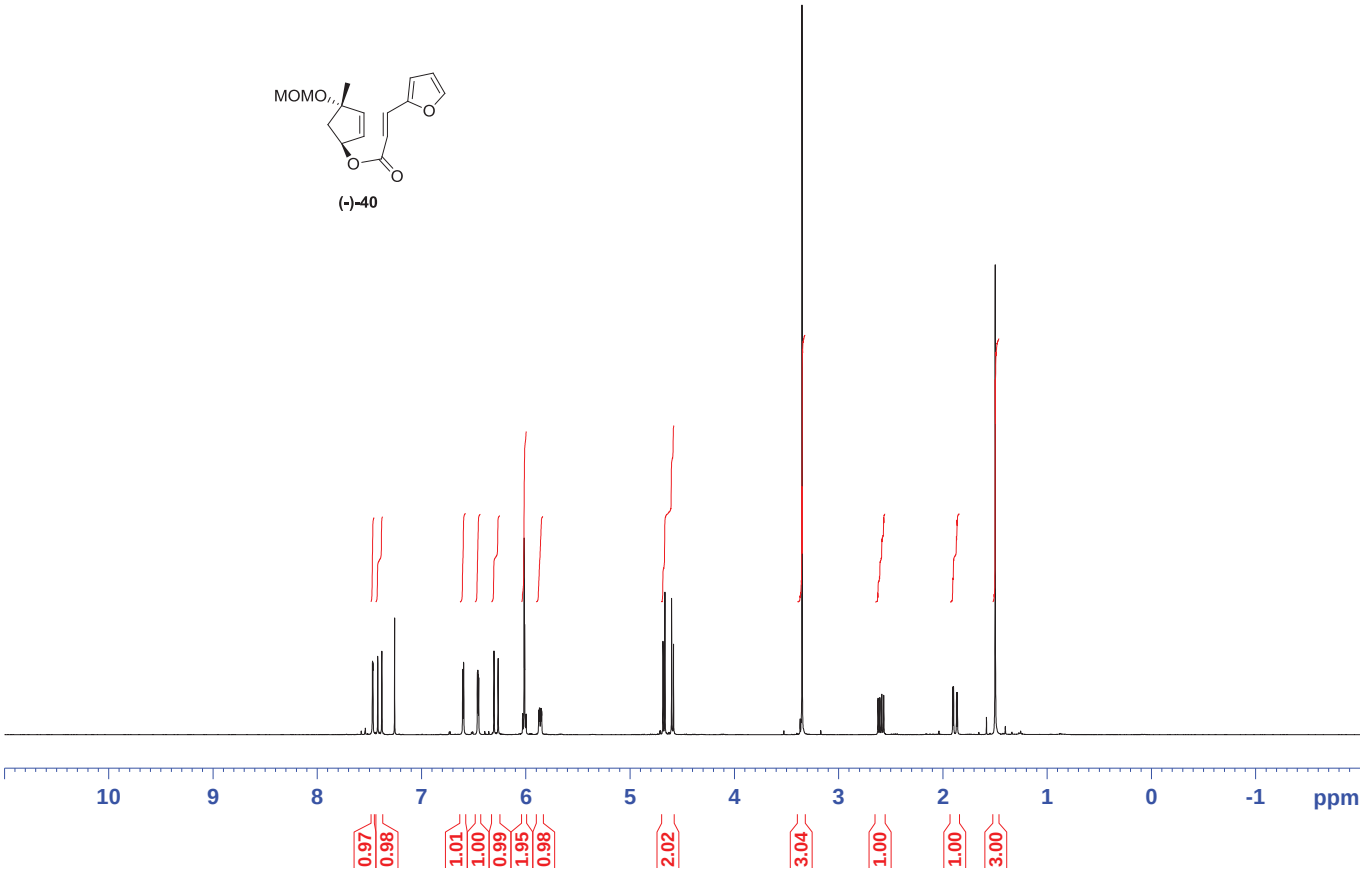

HO
O
O
(-)-35
220
200
180
160
140
120
100
80
60
40
20
0
ppm

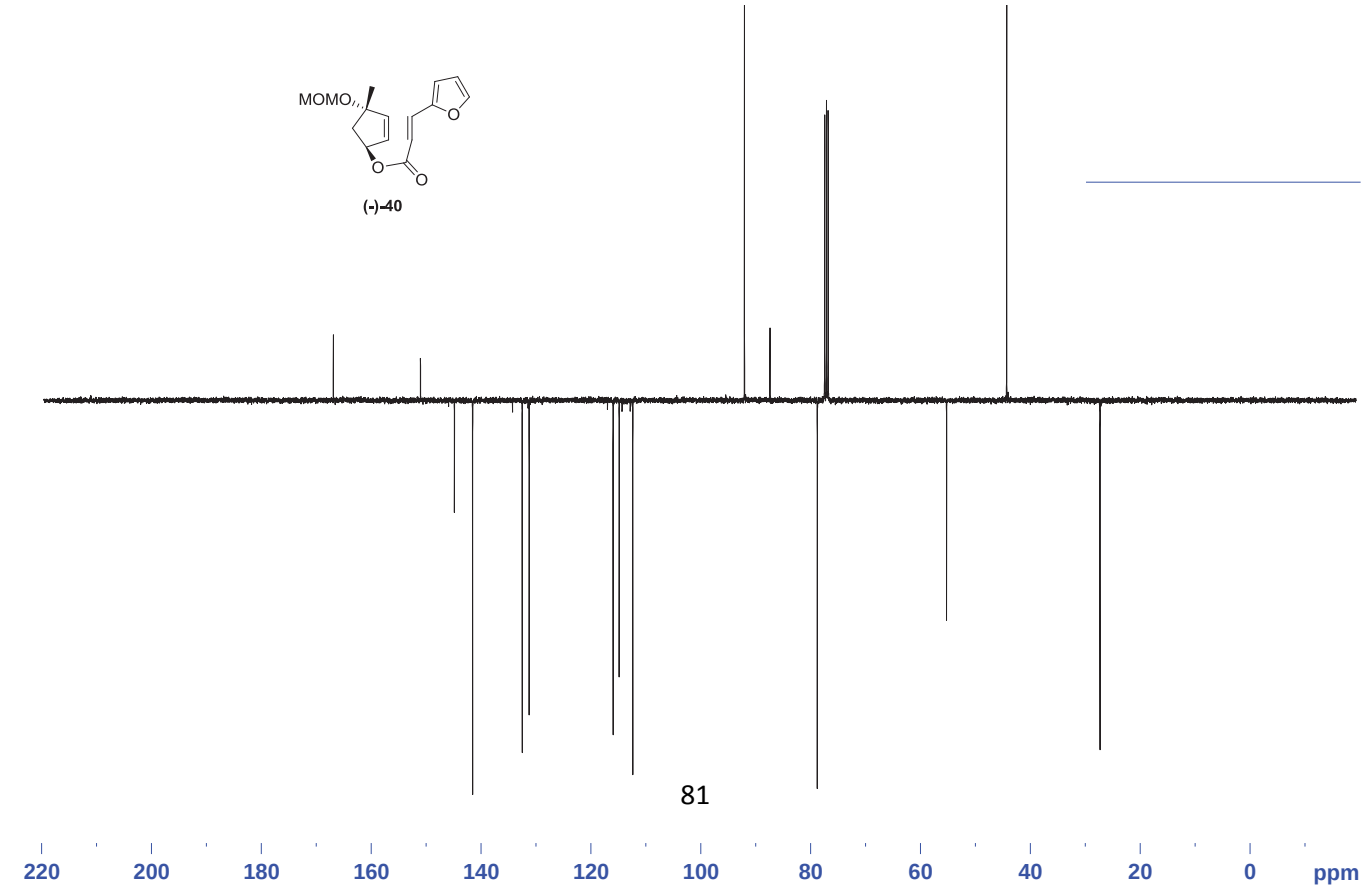

MOMO
O
O
OH
(-)-36
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.00
0.97
1.99
1.04
1.02
1.99
3.06
1.91
1.04
3.16

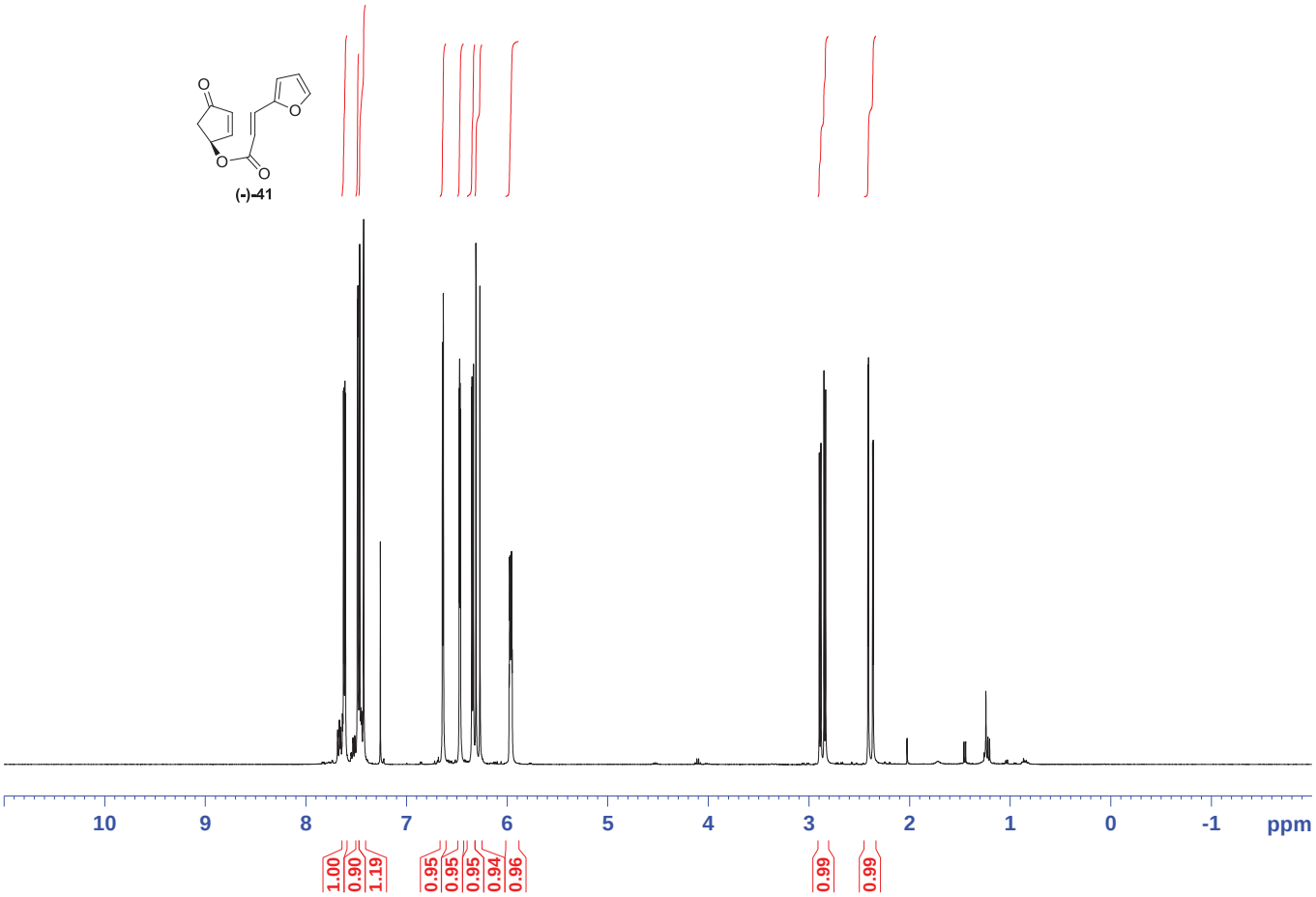

MOMO
O
O
OH
(-)-36
220
200
180
160
140
120
100
80
60
40
20
0
ppm

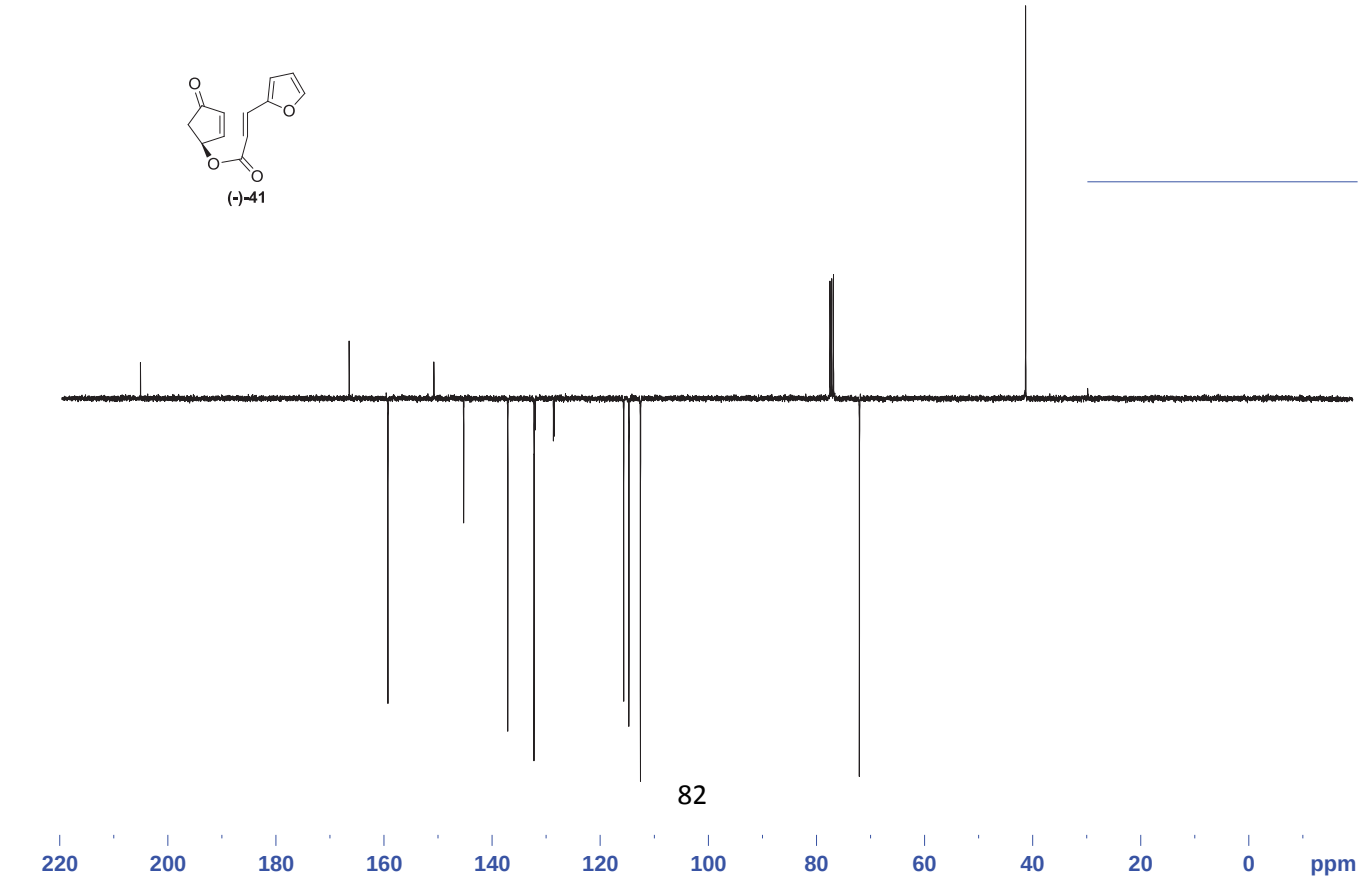

MOMO
O
O
O
(-)-38
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.03
1.00
2.07
1.06
1.04
2.03
2.08
3.12
1.03
1.02
3.08
3.14

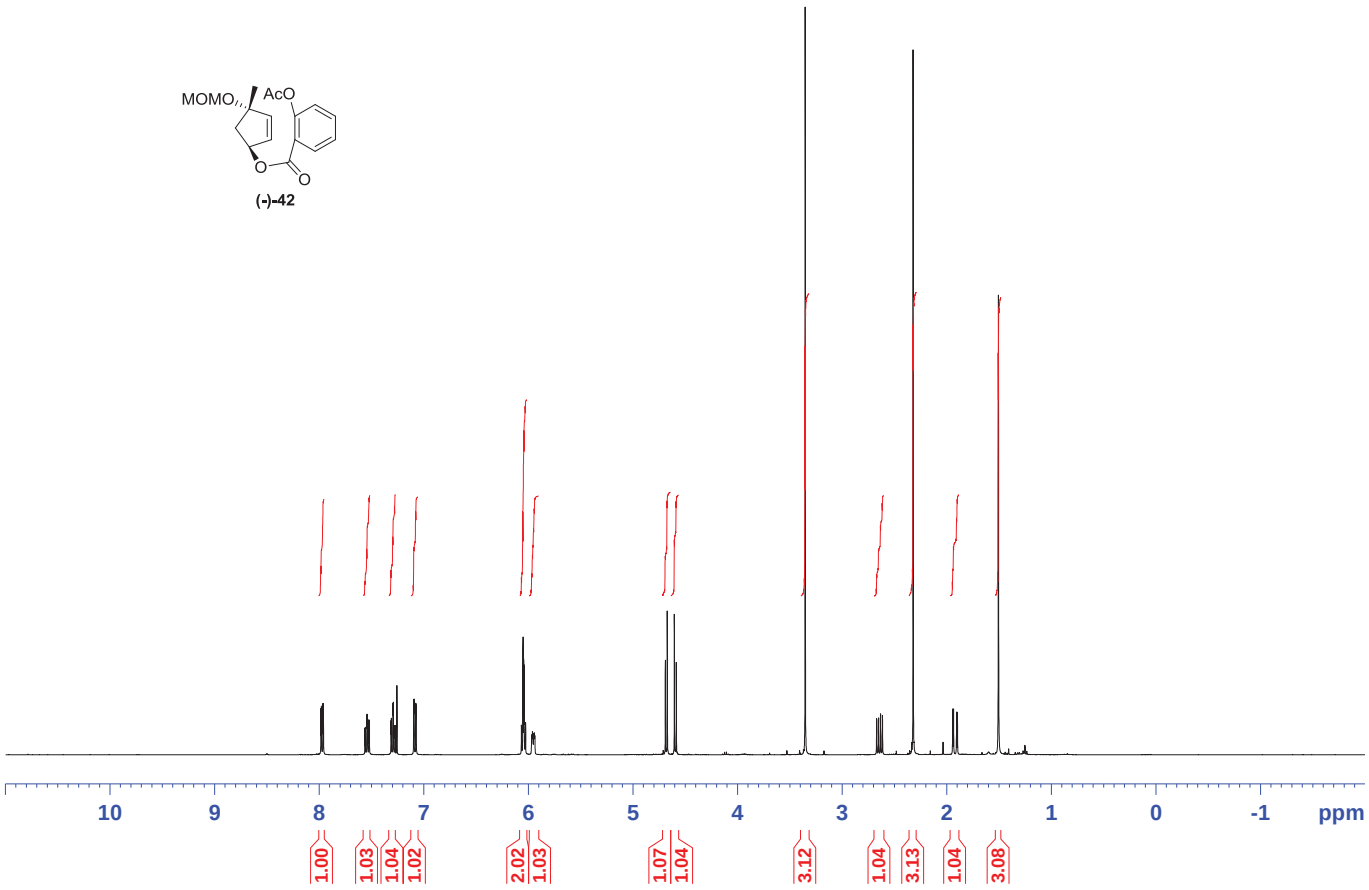

MOMO
O
O
O
(-)-38
220
200
180
160
140
120
100
80
60
40
20
0
ppm

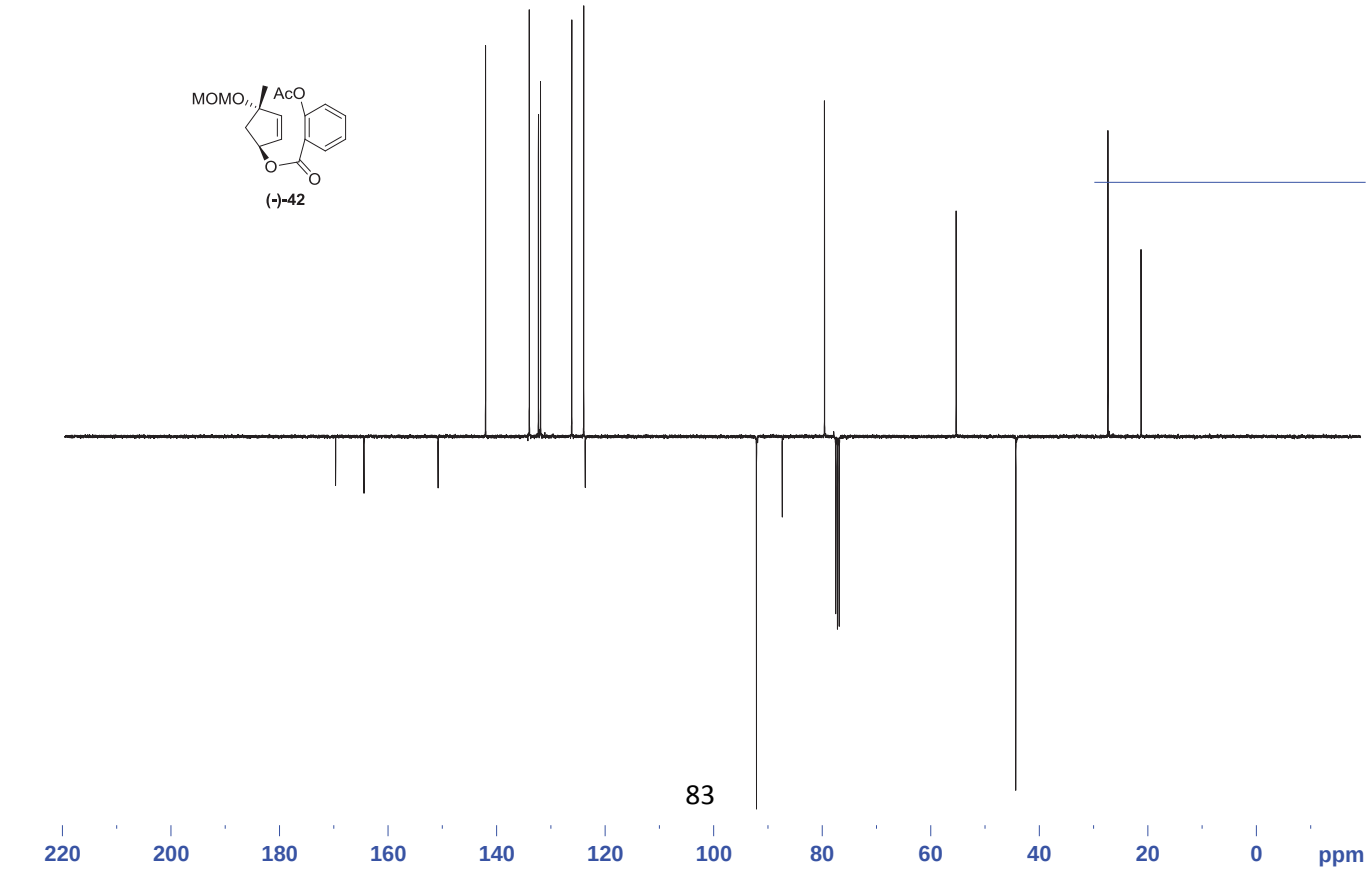

MOMO
O
O
O
(-)-40
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.97
0.98
1.01
1.00
0.99
1.95
0.98
2.02
3.04
1.00
1.00
3.00

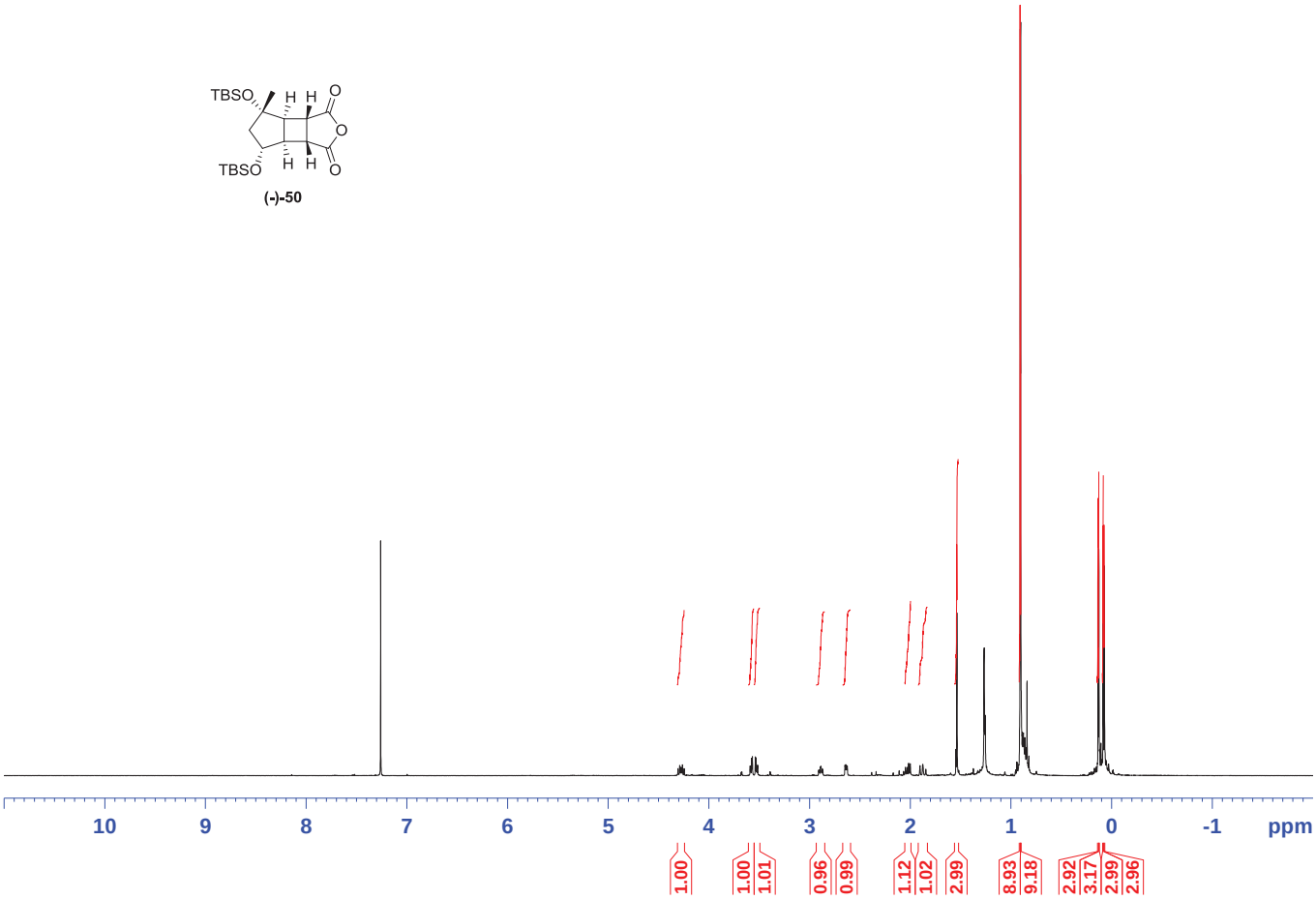

MOMO
O
O
O
(-)-40
220
200
180
160
140
120
100
80
60
40
20
0
ppm

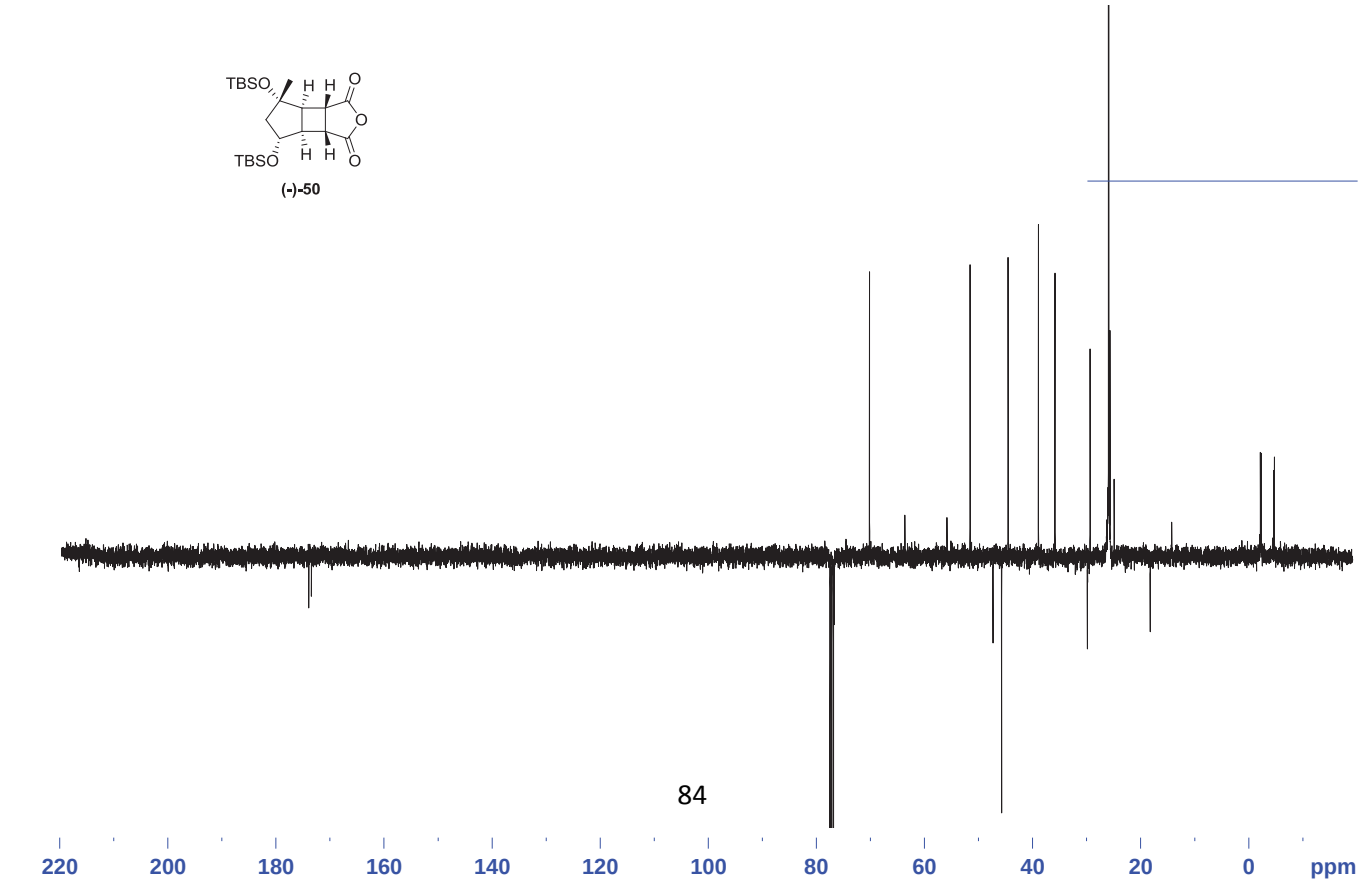

(-)-41
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.90
1.19
0.95
0.95
0.95
0.94
0.96
0.99
0.99

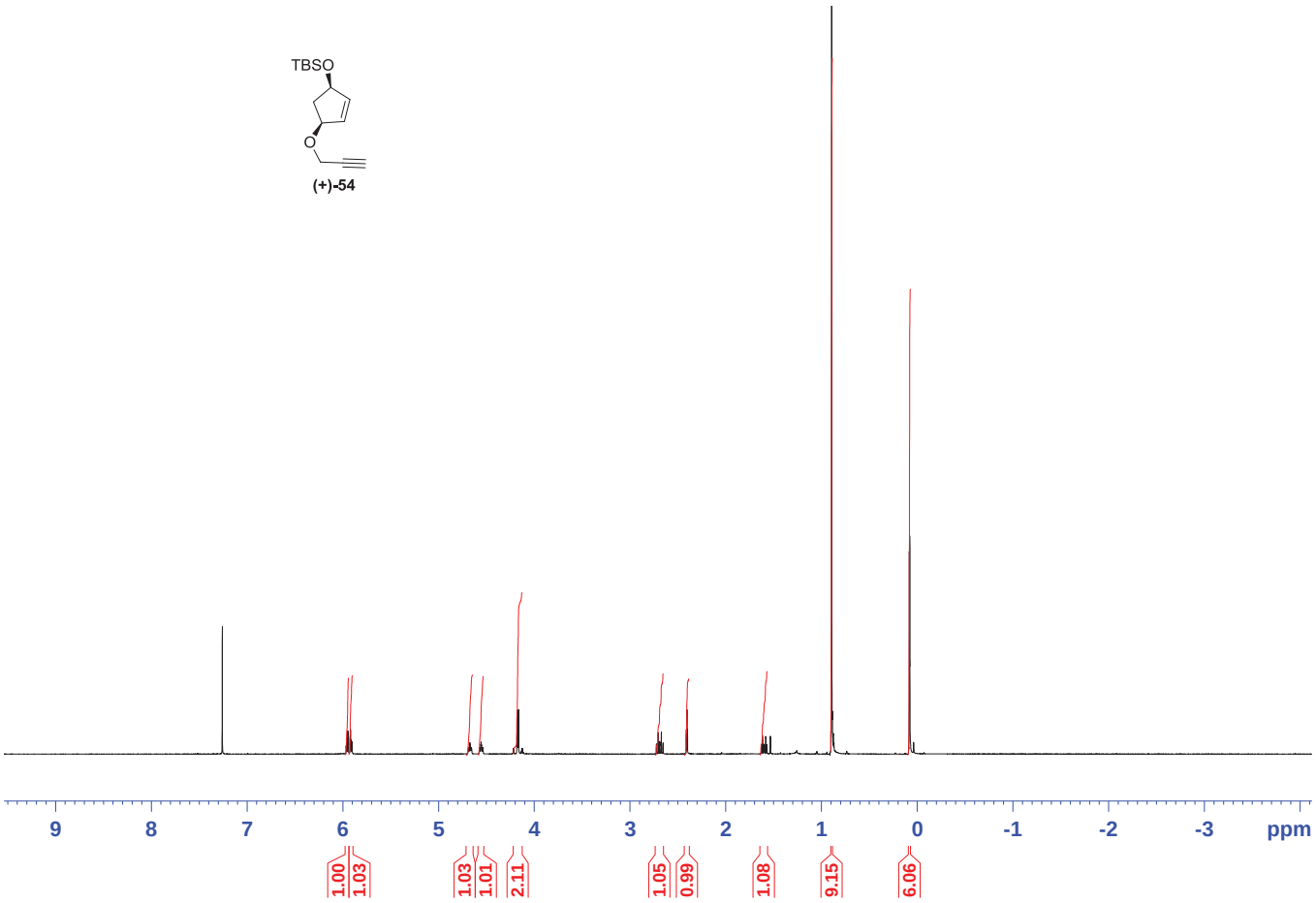

(-)-41
220
200
180
160
140
120
100
80
60
40
20
0
ppm

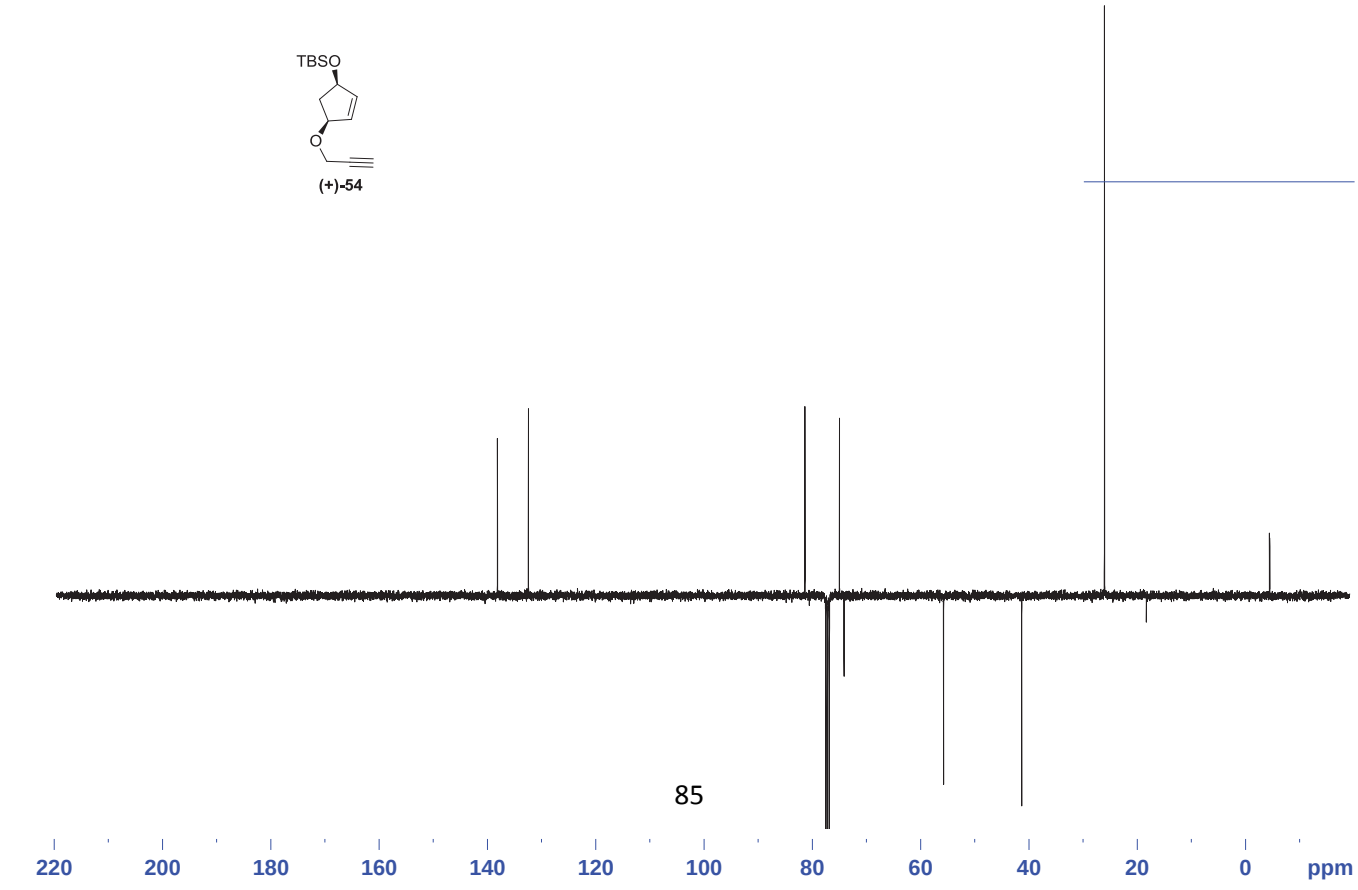

MOMO
AcO
O
O
(-)-42
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.03
1.04
1.02
2.02
1.03
1.07
1.04
3.12
1.04
3.13
1.04
3.08

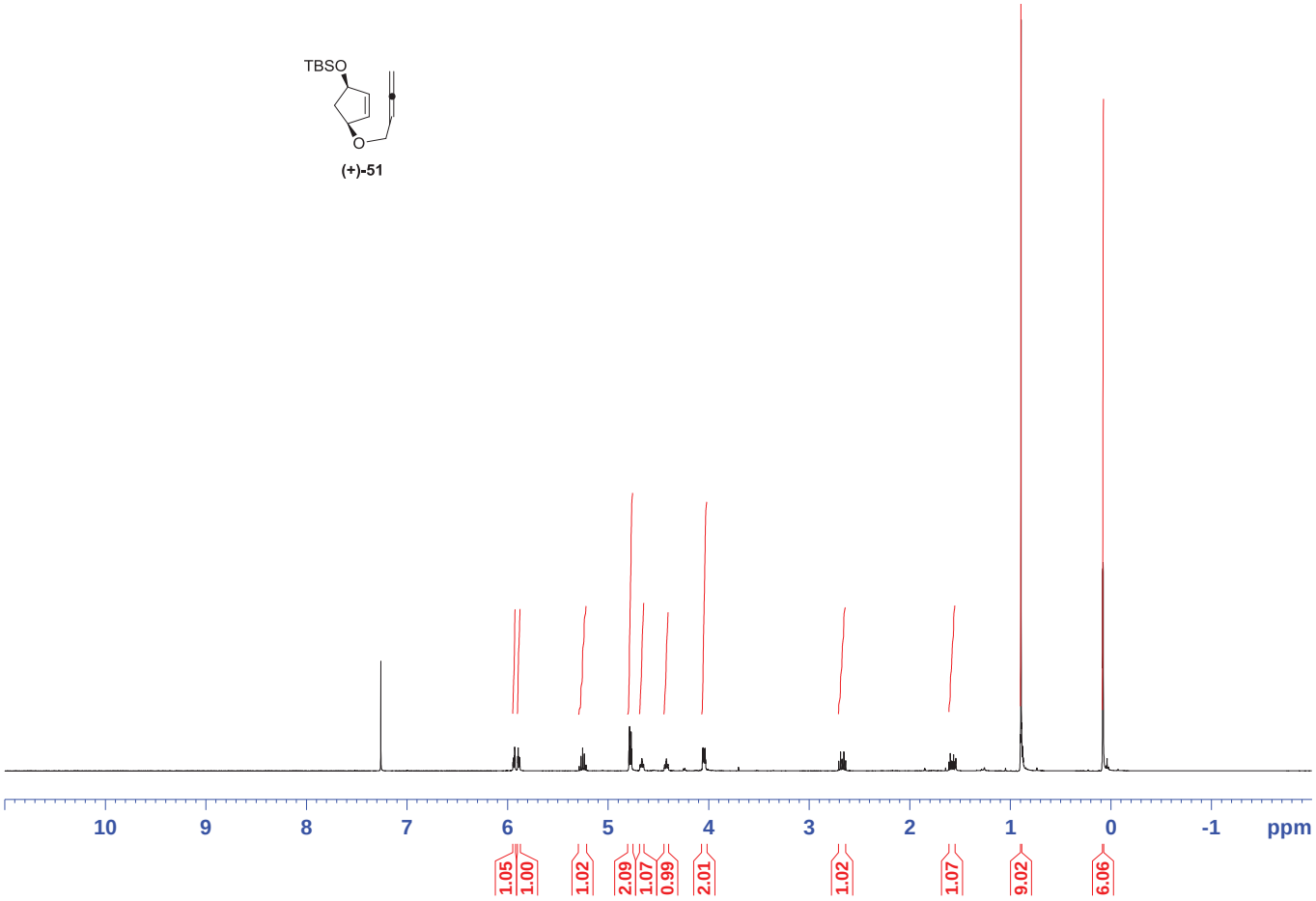

MOMO
AcO
O
O
(-)-42
220
200
180
160
140
120
100
80
60
40
20
0
ppm

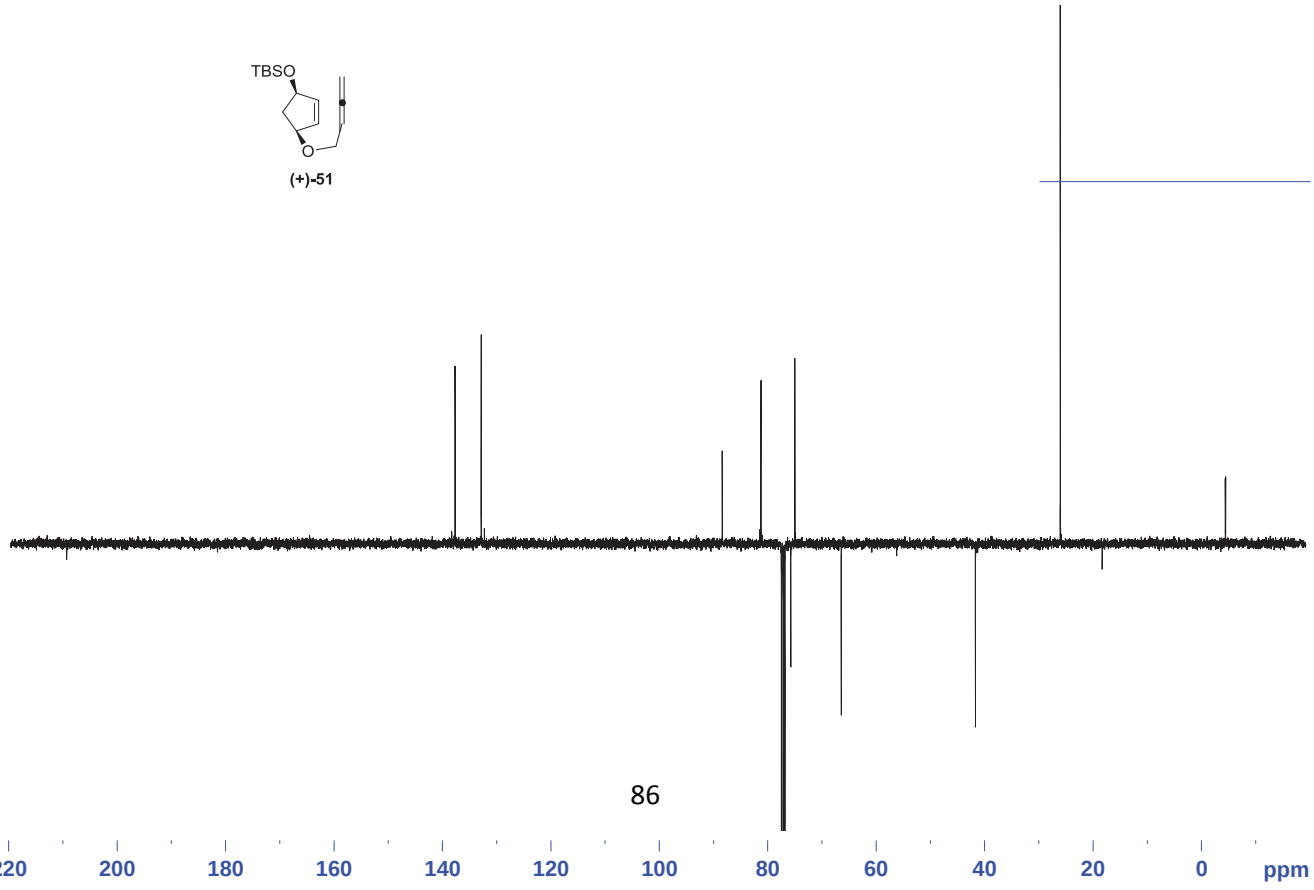

TBSO
H H
O
O
TBSO
H H
O
(-)-50
10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00 1.00 1.01 0.96 0.99 1.12 1.02 2.99 8.93 9.18 2.92 3.17 2.99 2.96

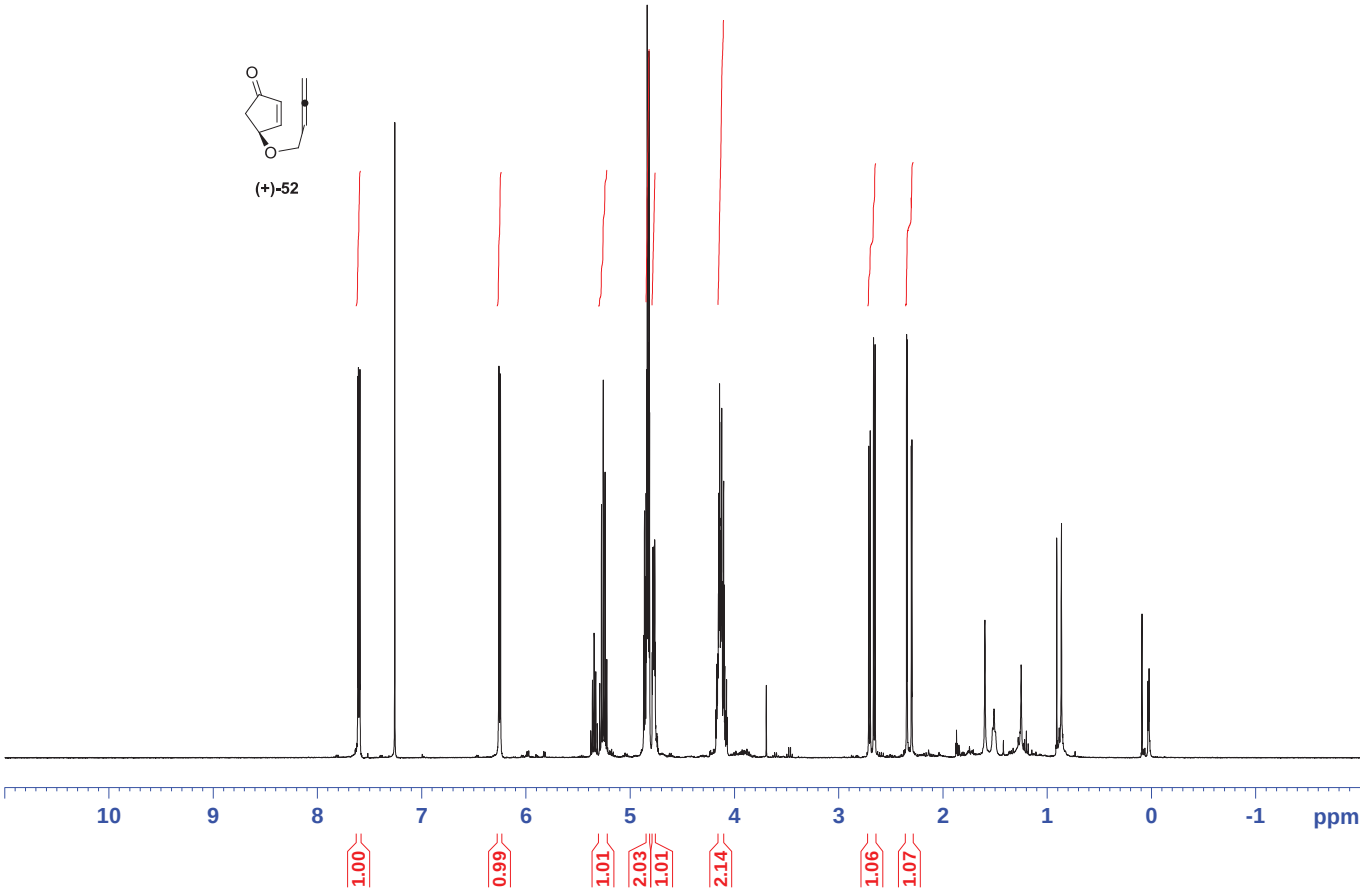

TBSO
H H
O
O
TBSO
H H
O
(-)-50
220 200 180 160 140 120 100 80 60 40 20 0 ppm

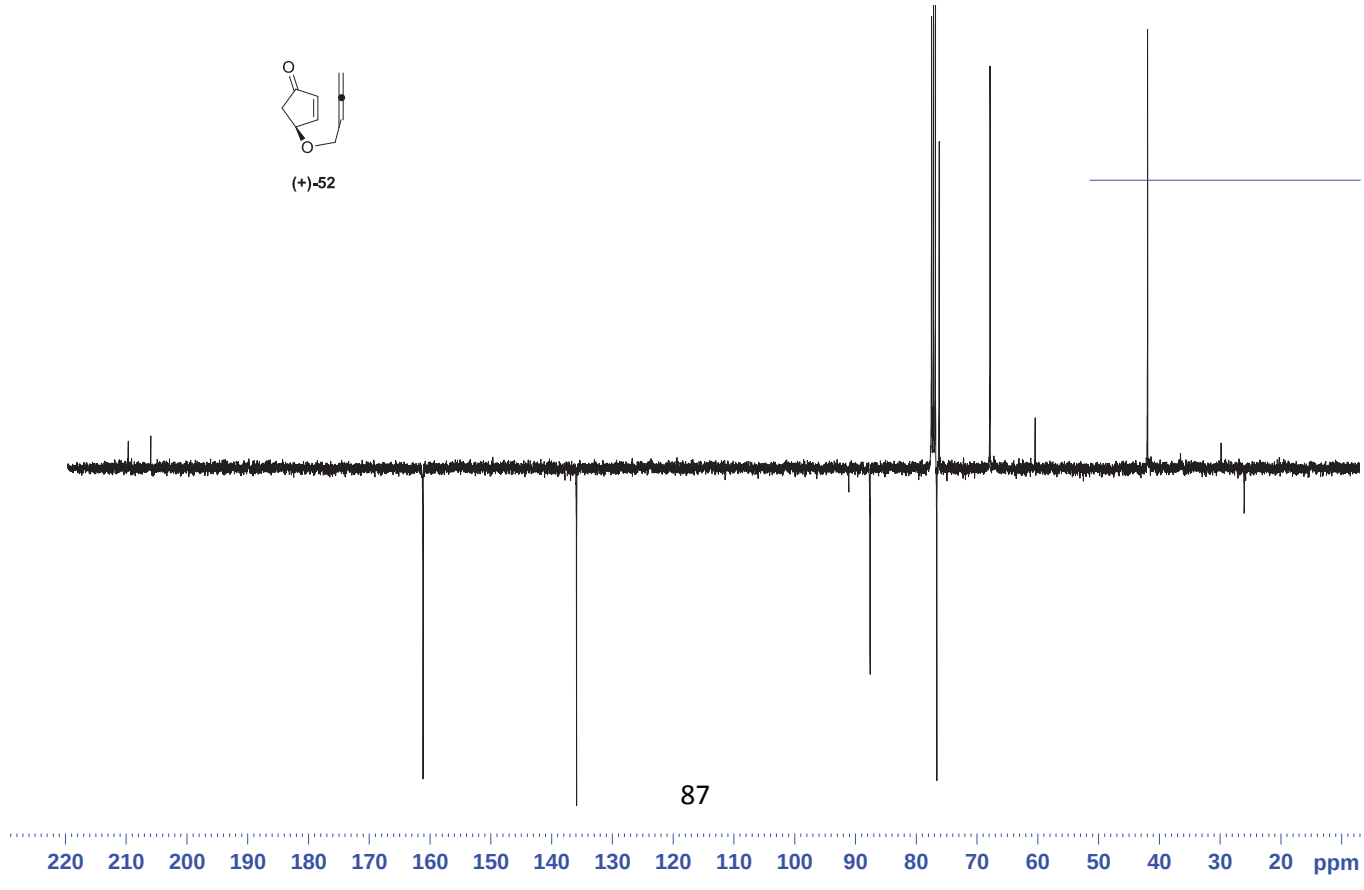

TBSO
O
(+)-54
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
ppm
1.00
1.03
1.03
1.01
2.11
1.05
0.99
1.08
9.15
6.06

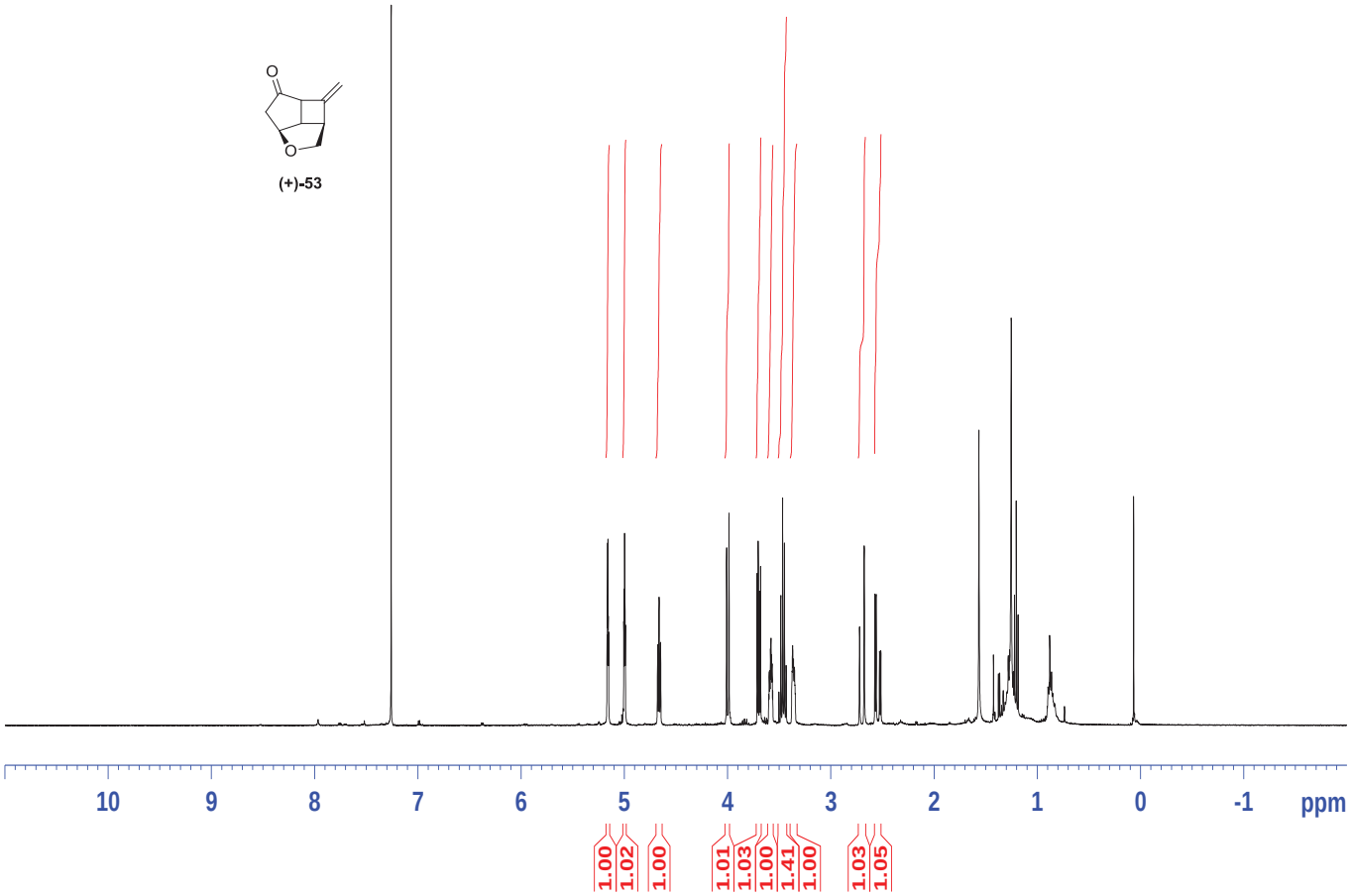

TBSO
O
(+)-54
220
200
180
160
140
120
100
80
60
40
20
0
ppm

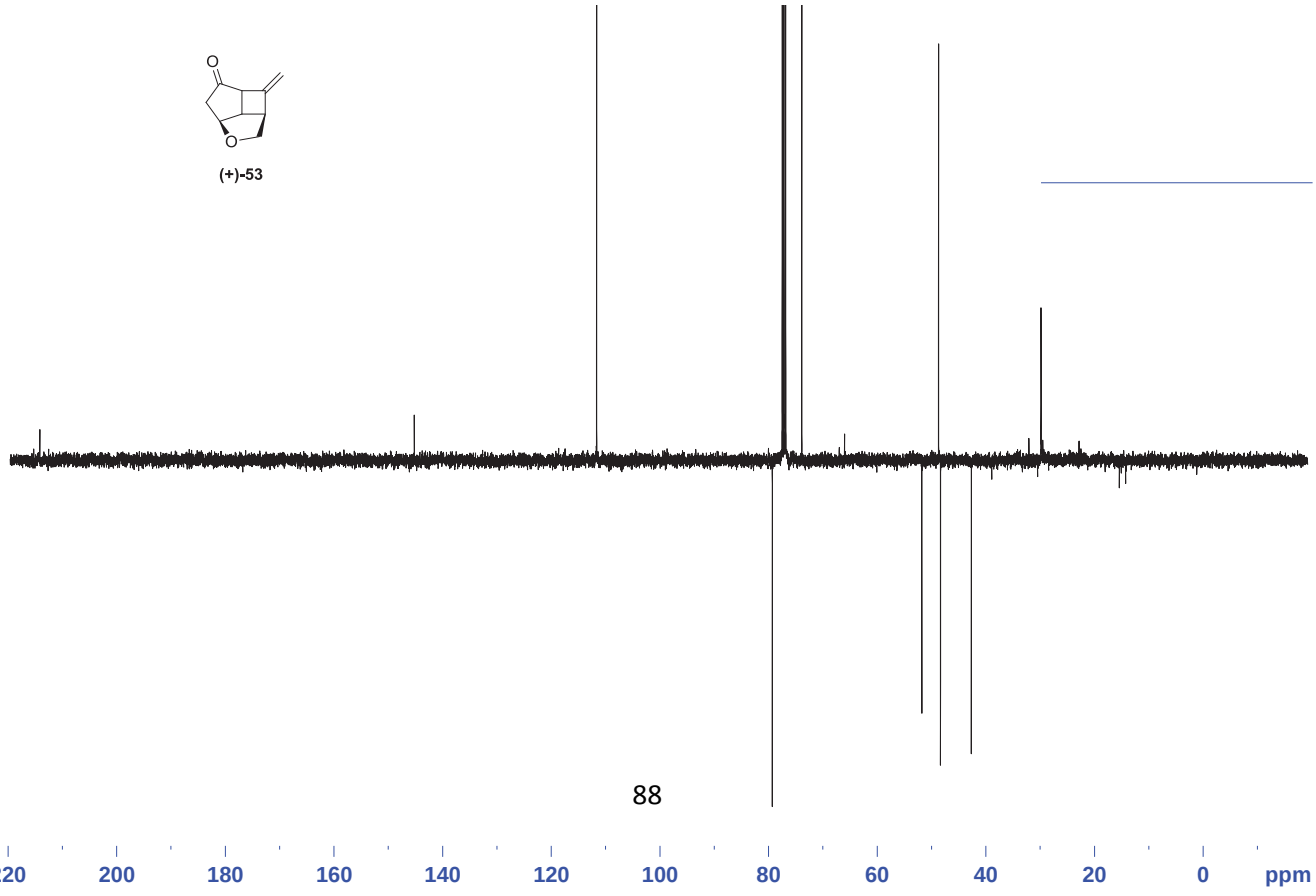

TBSO
O
(+)-51
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.05
1.00
1.02
2.09
1.07
0.99
2.01
1.02
1.07
9.02
6.06

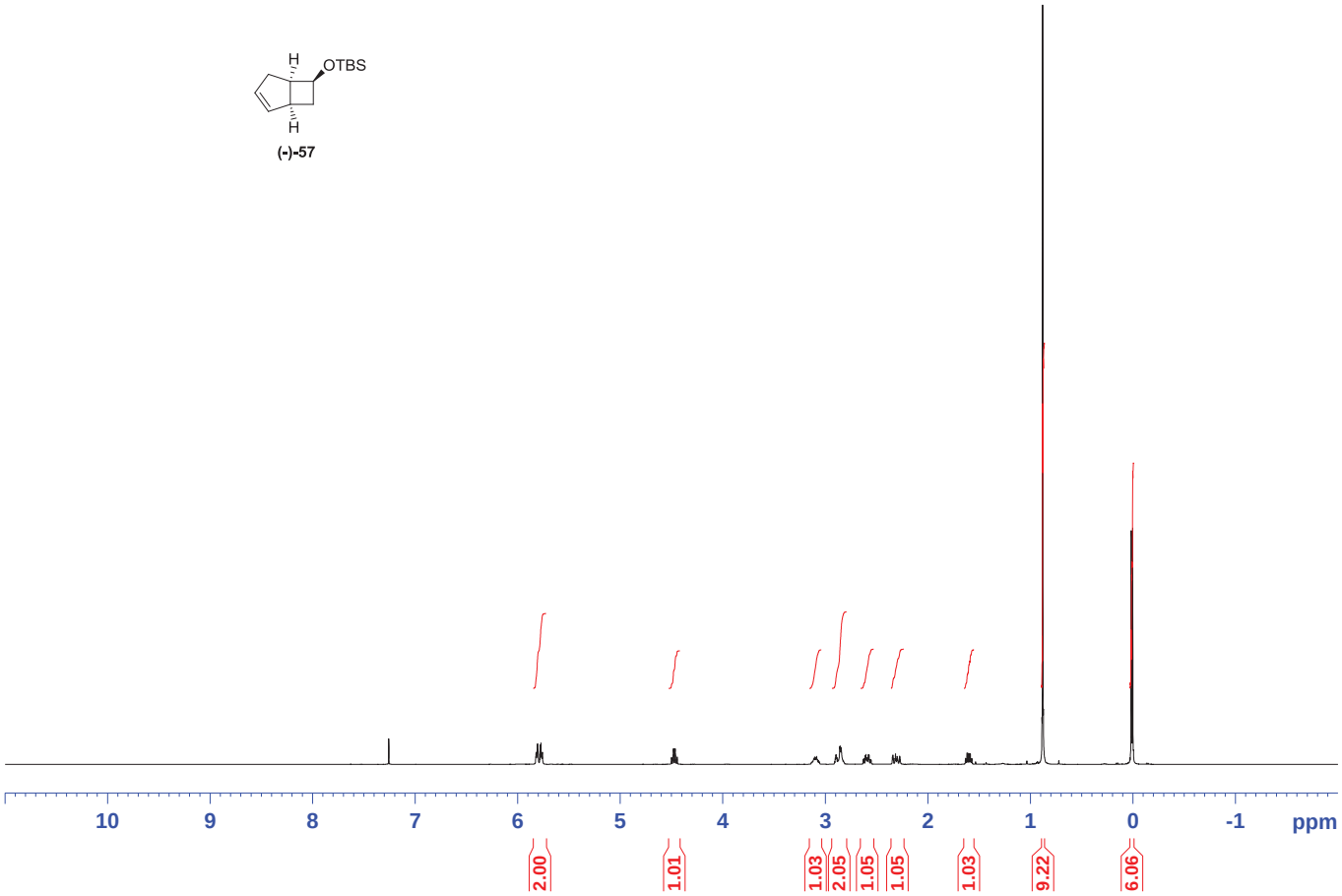

TBSO
O
(+)-51
220
200
180
160
140
120
100
80
60
40
20
0
ppm

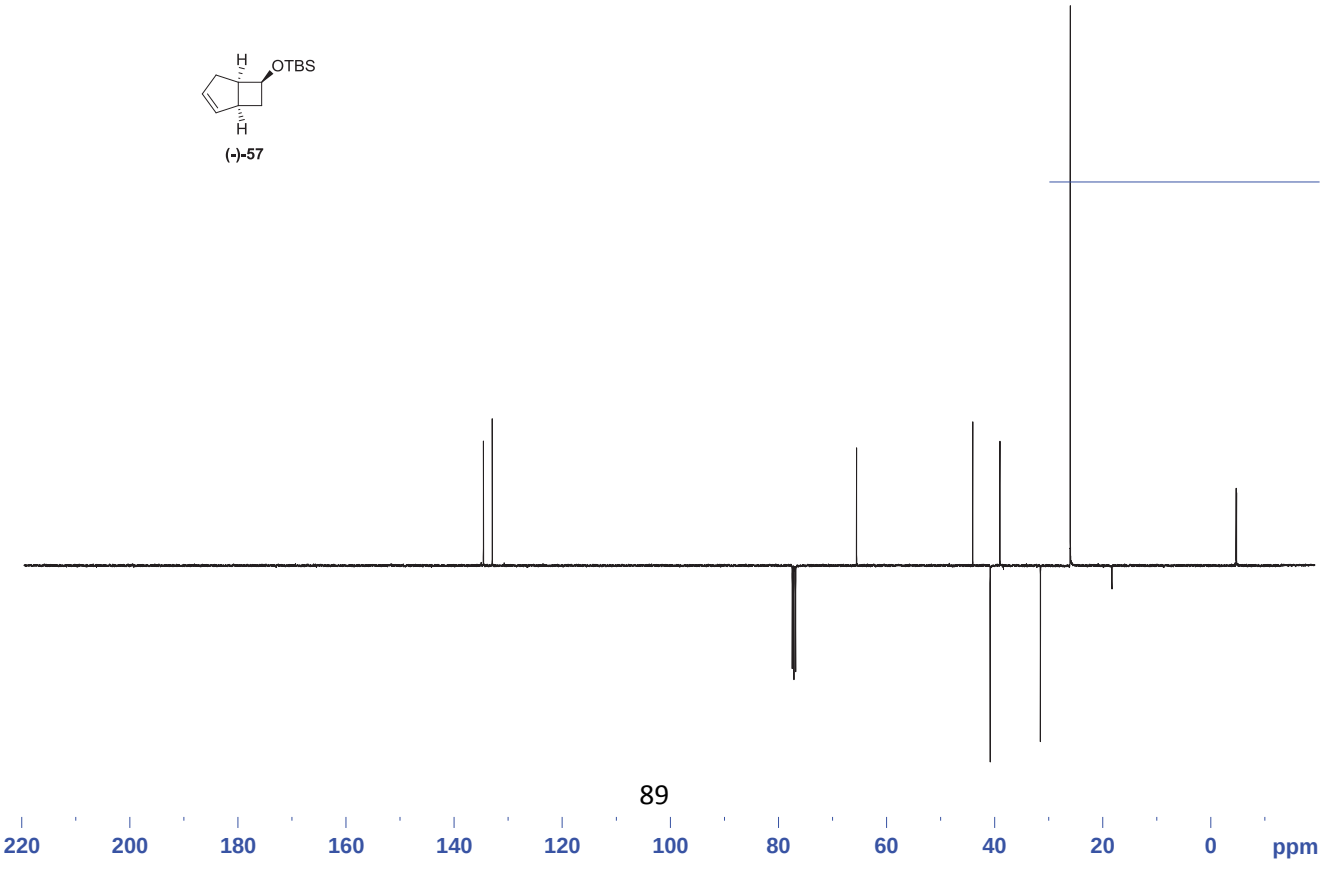

(+)-52
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.99
1.01
2.03
1.01
2.14
1.06
1.07

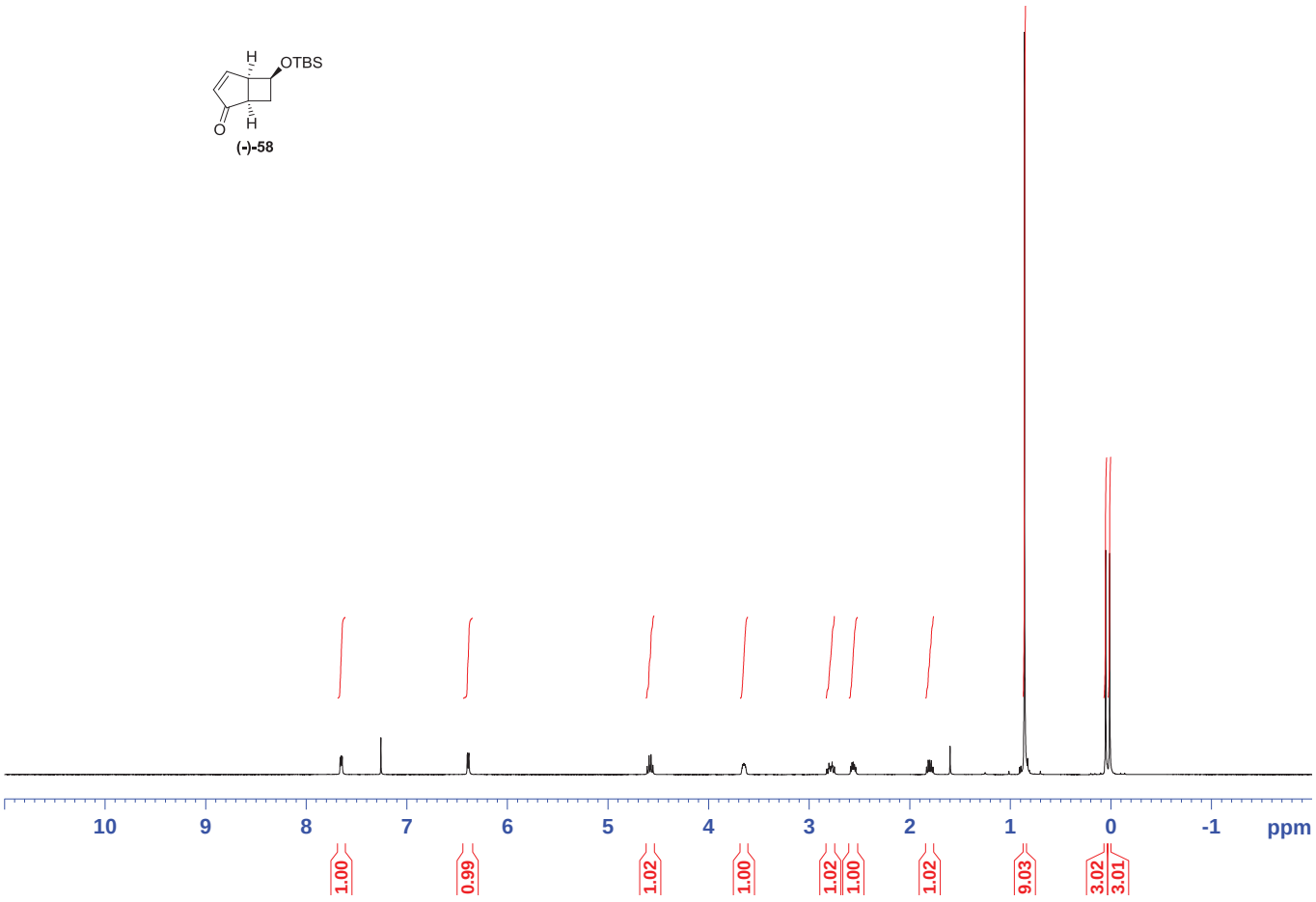

(+)-52
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

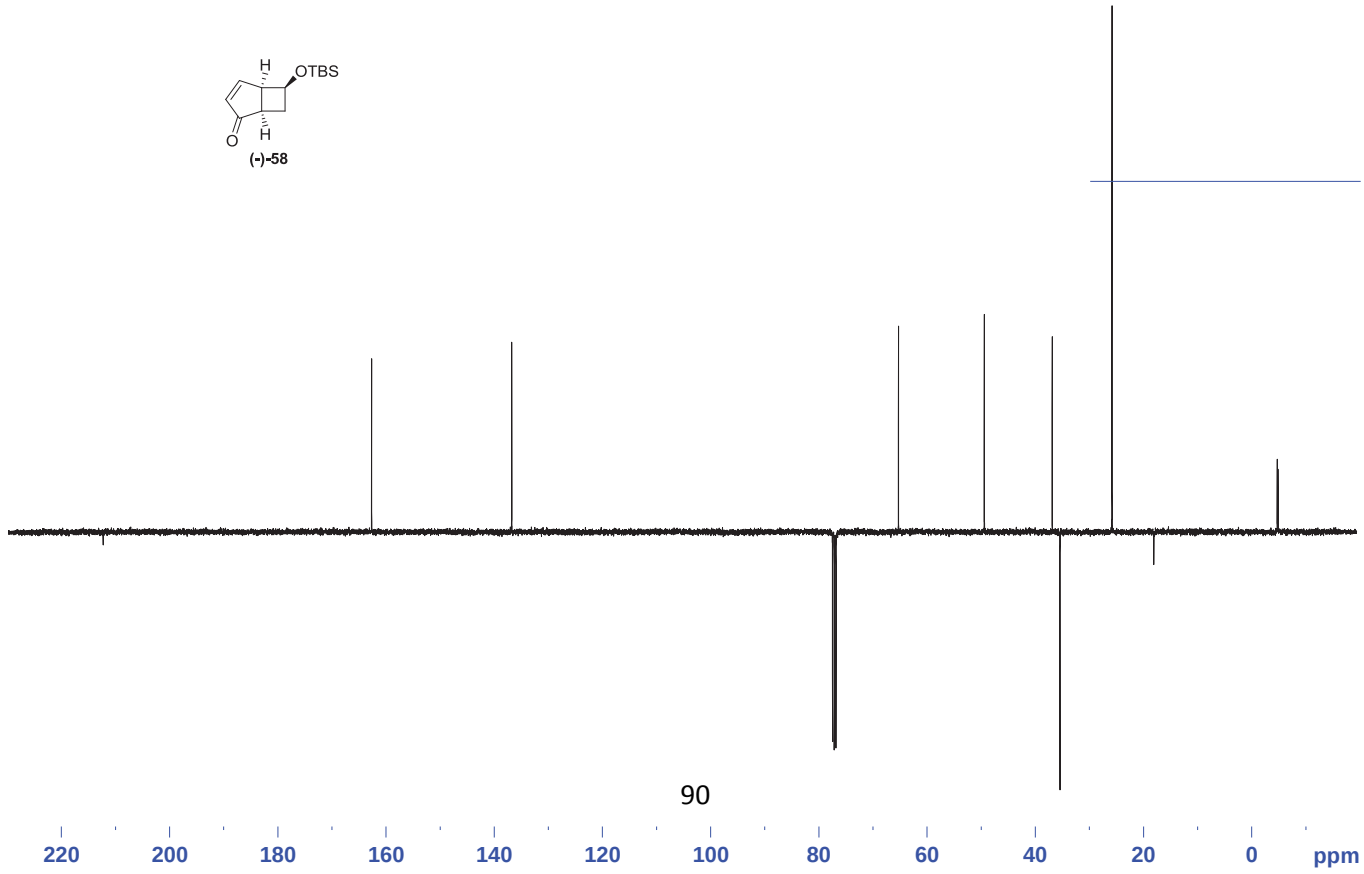

(+)-53
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.02
1.00
1.01
1.03
1.00
1.41
1.00
1.03
1.05

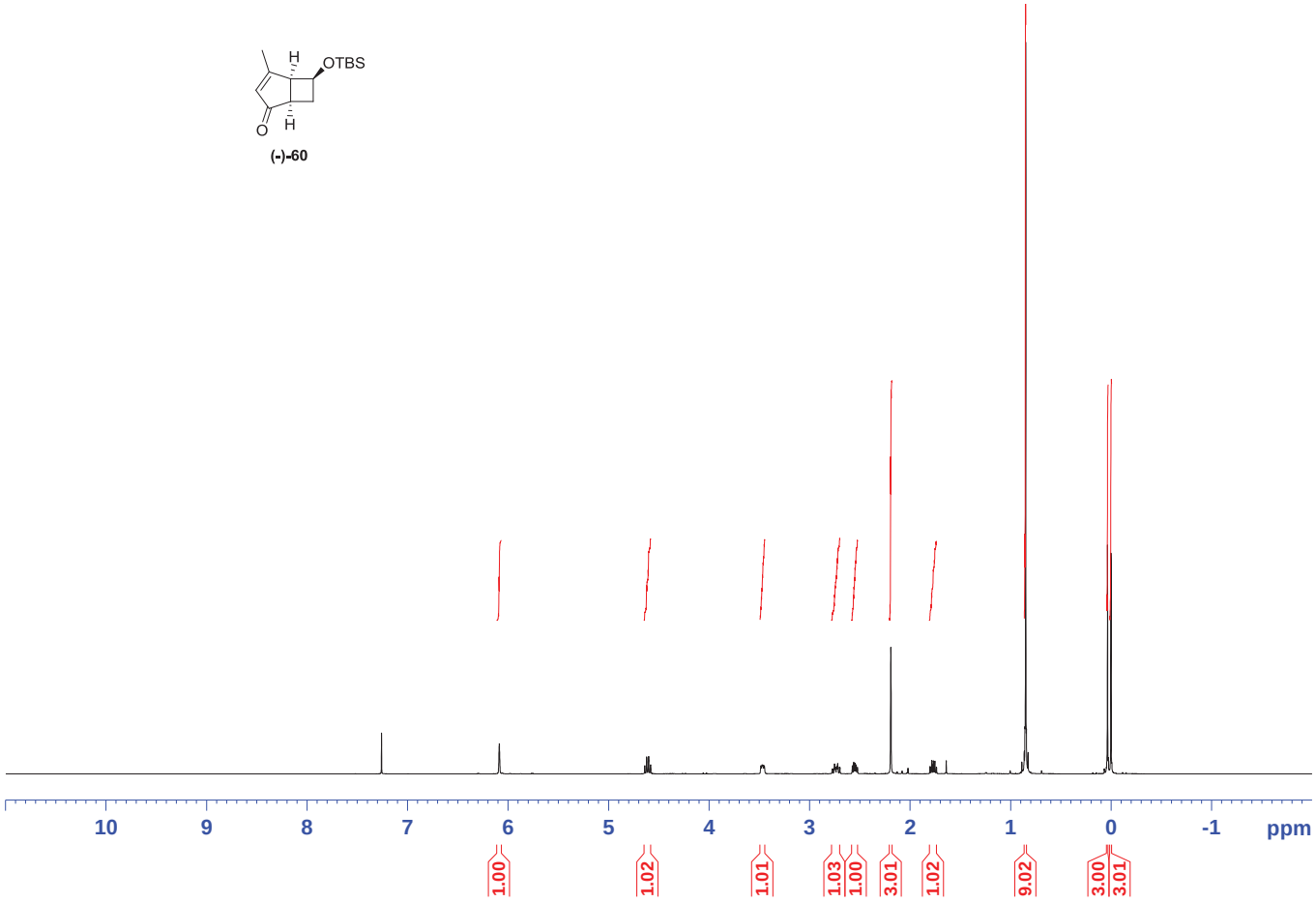

(+)-53
220
200
180
160
140
120
100
80
60
40
20
0
ppm

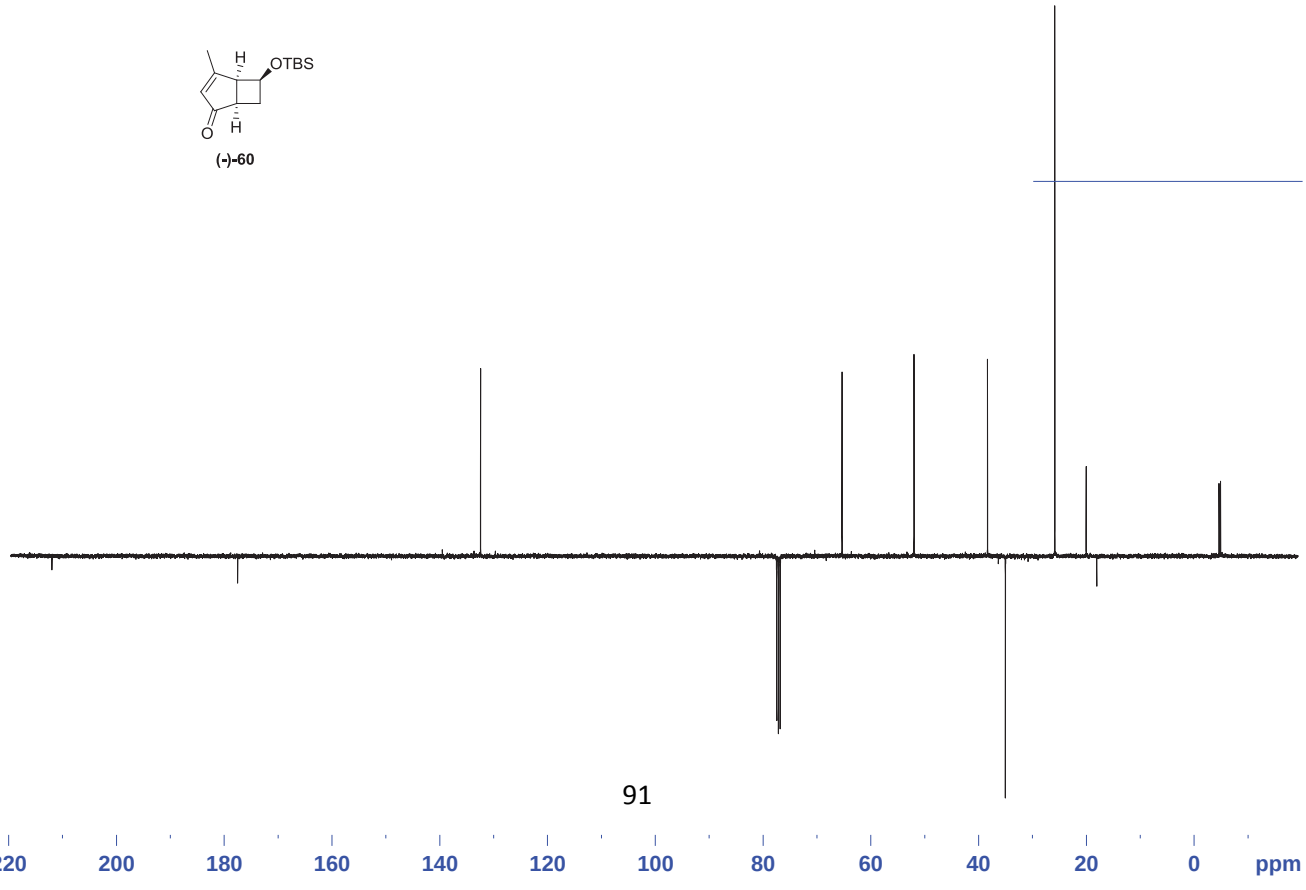

H
OTBS
H
(-)-57
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.00
1.01
1.03
2.05
1.05
1.05
1.03
9.22
6.06

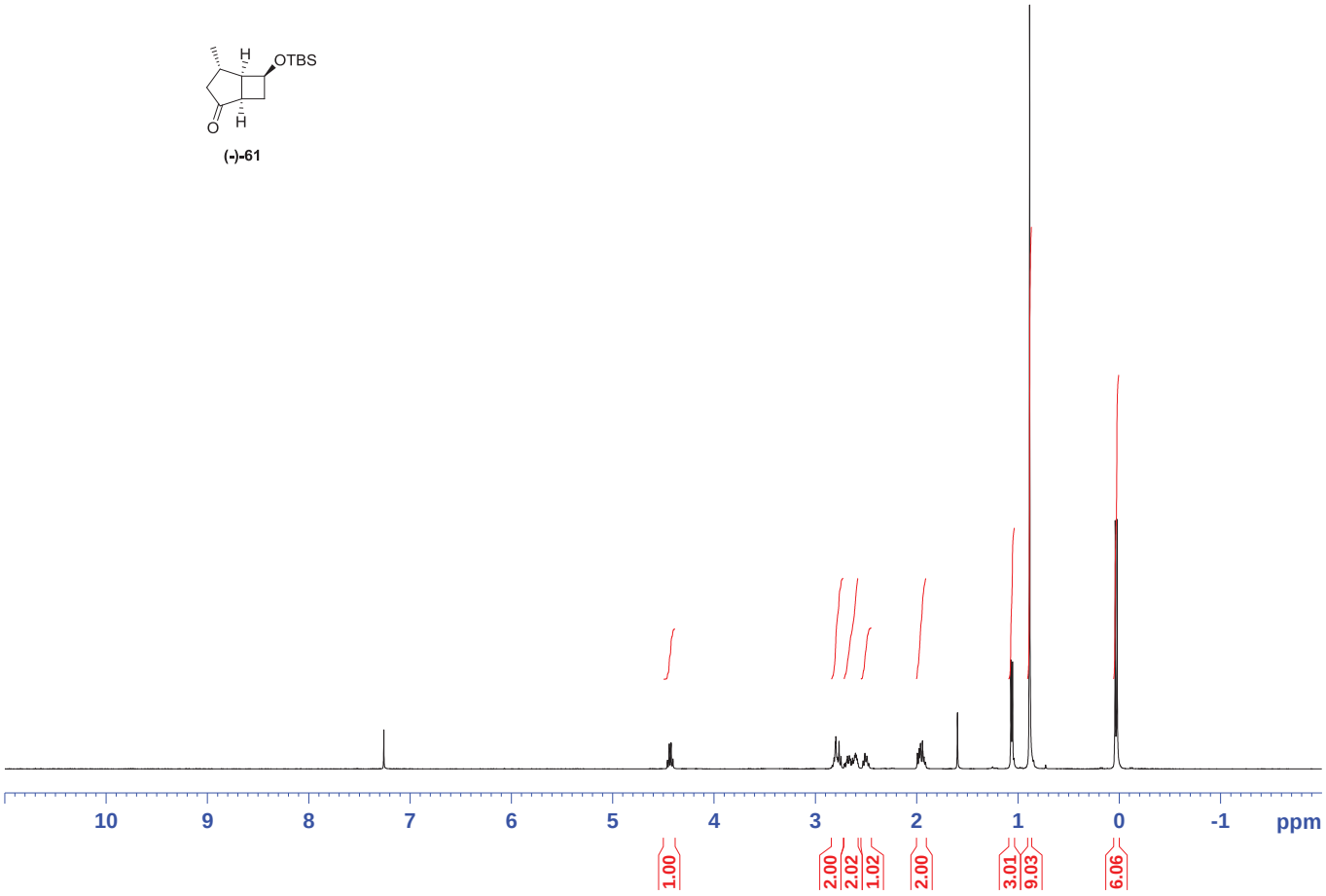

H
OTBS
H
(-)-57
220
200
180
160
140
120
100
80
60
40
20
0
ppm

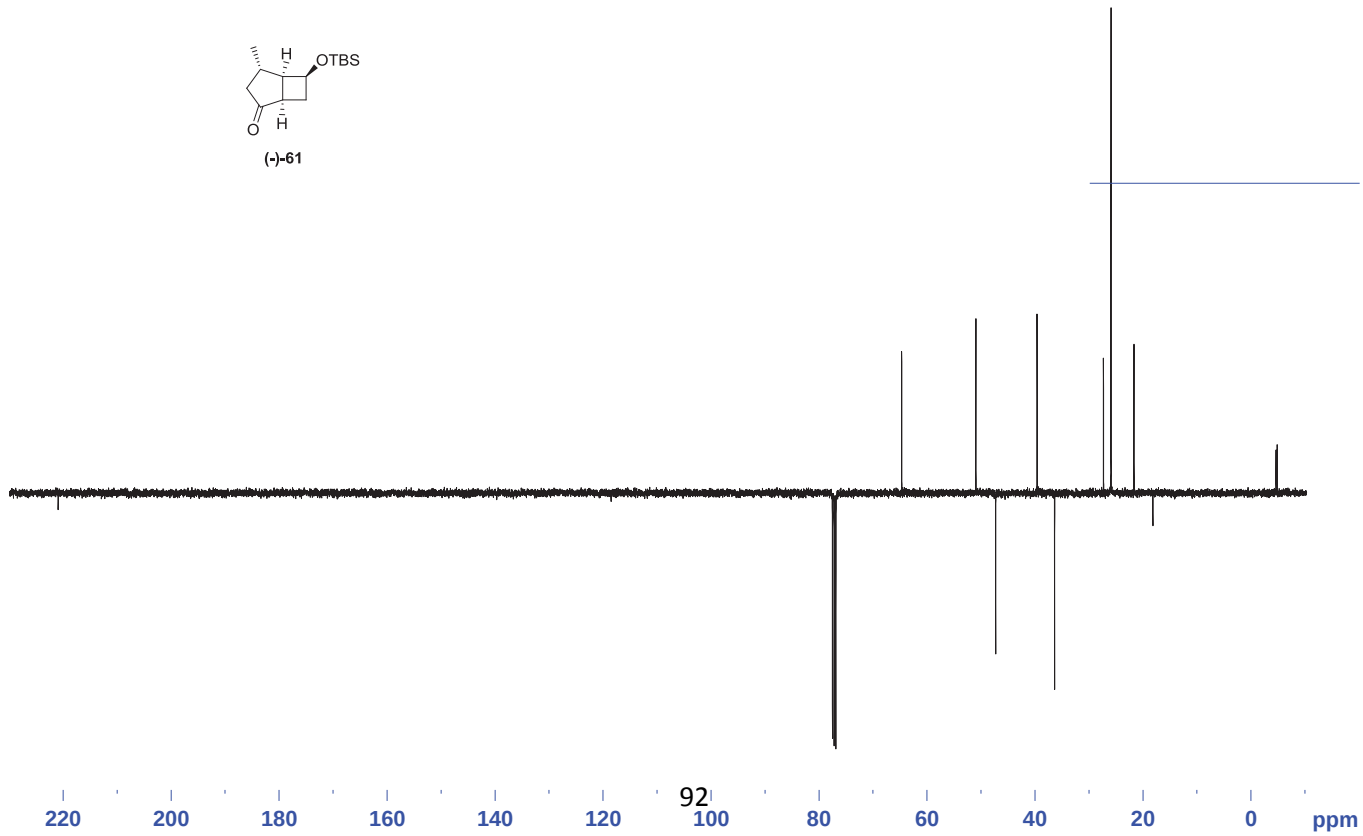

H
OTBS
O
H
(-)-58
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.99
1.02
1.00
1.02
1.00
1.02
9.03
3.02
3.01

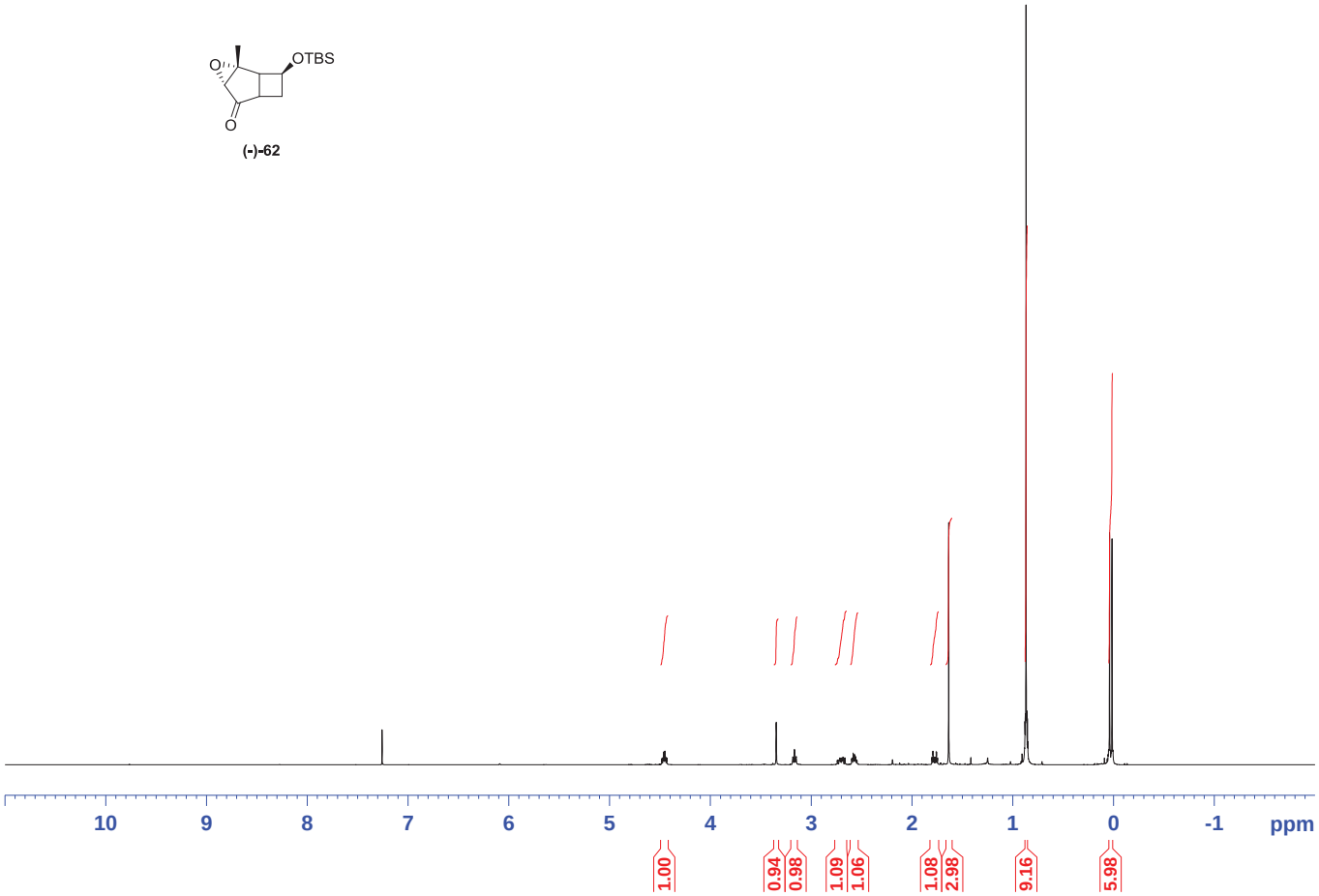

H
OTBS
O
H
(-)-58
220
200
180
160
140
120
100
80
60
40
20
0
ppm

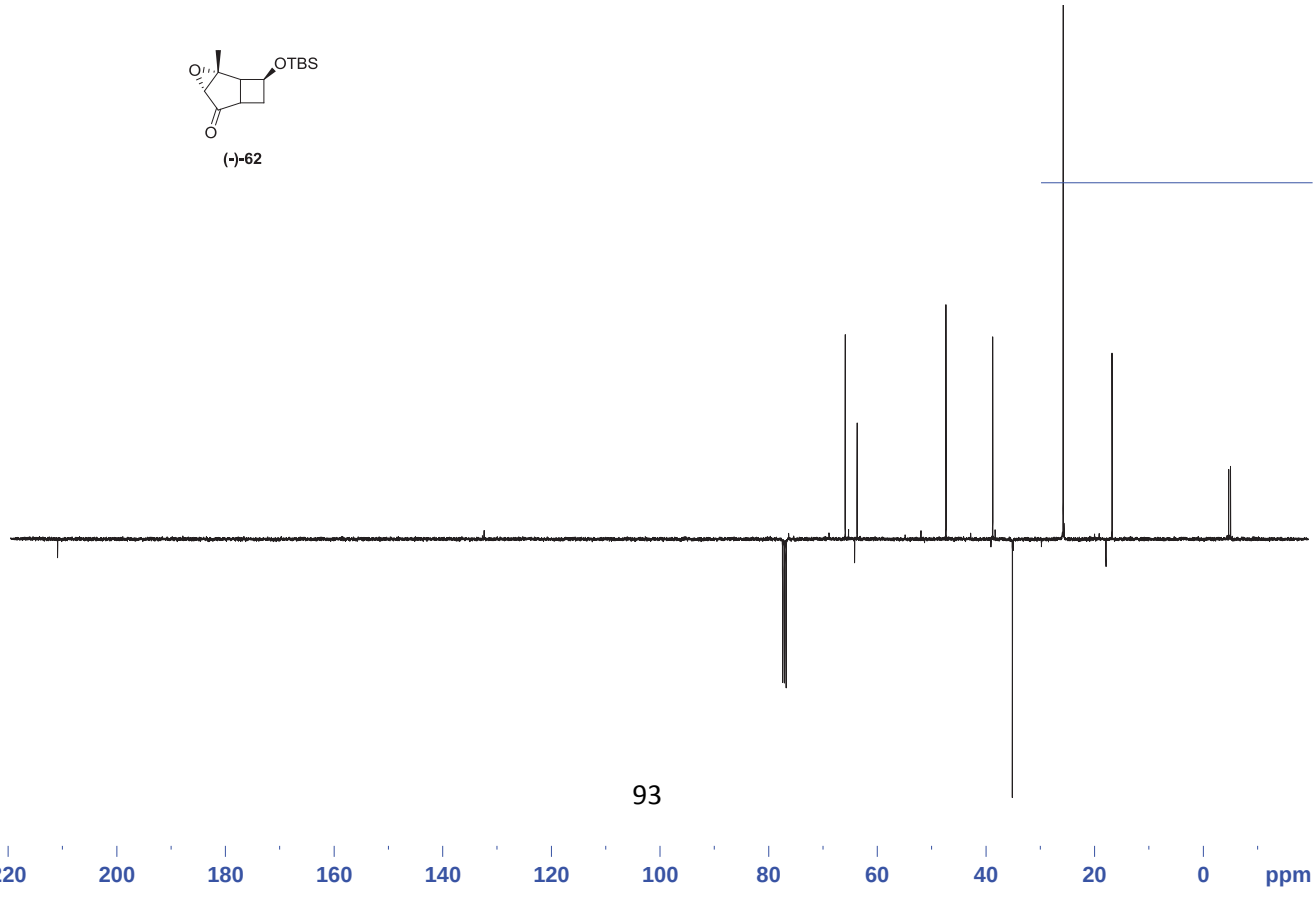

H
OTBS
O
H
(-)-60
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.02
1.01
1.03
1.00
3.01
1.02
9.02
3.00
3.01

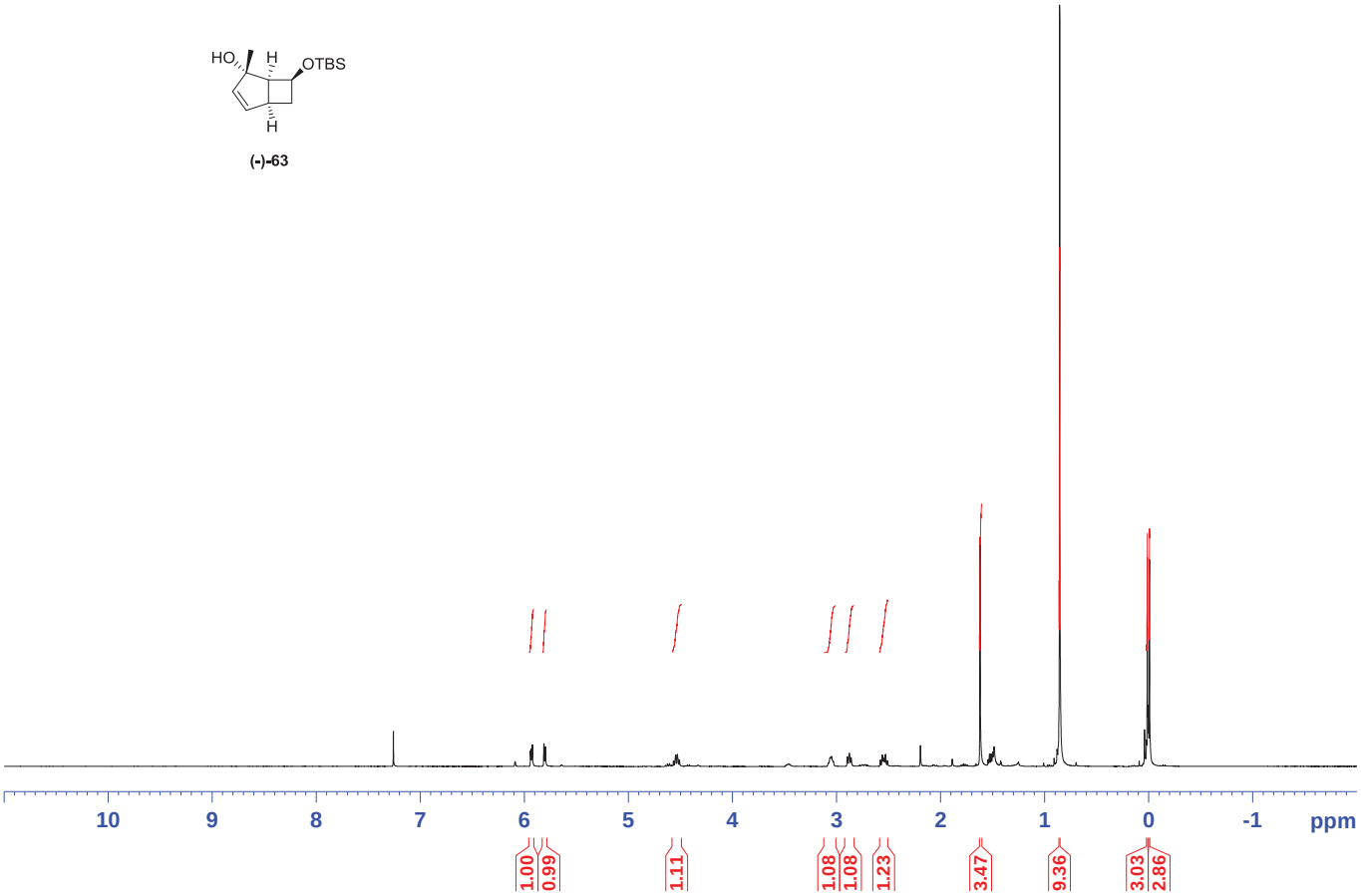

H
OTBS
O
H
(-)-60
220
200
180
160
140
120
100
80
60
40
20
0
ppm

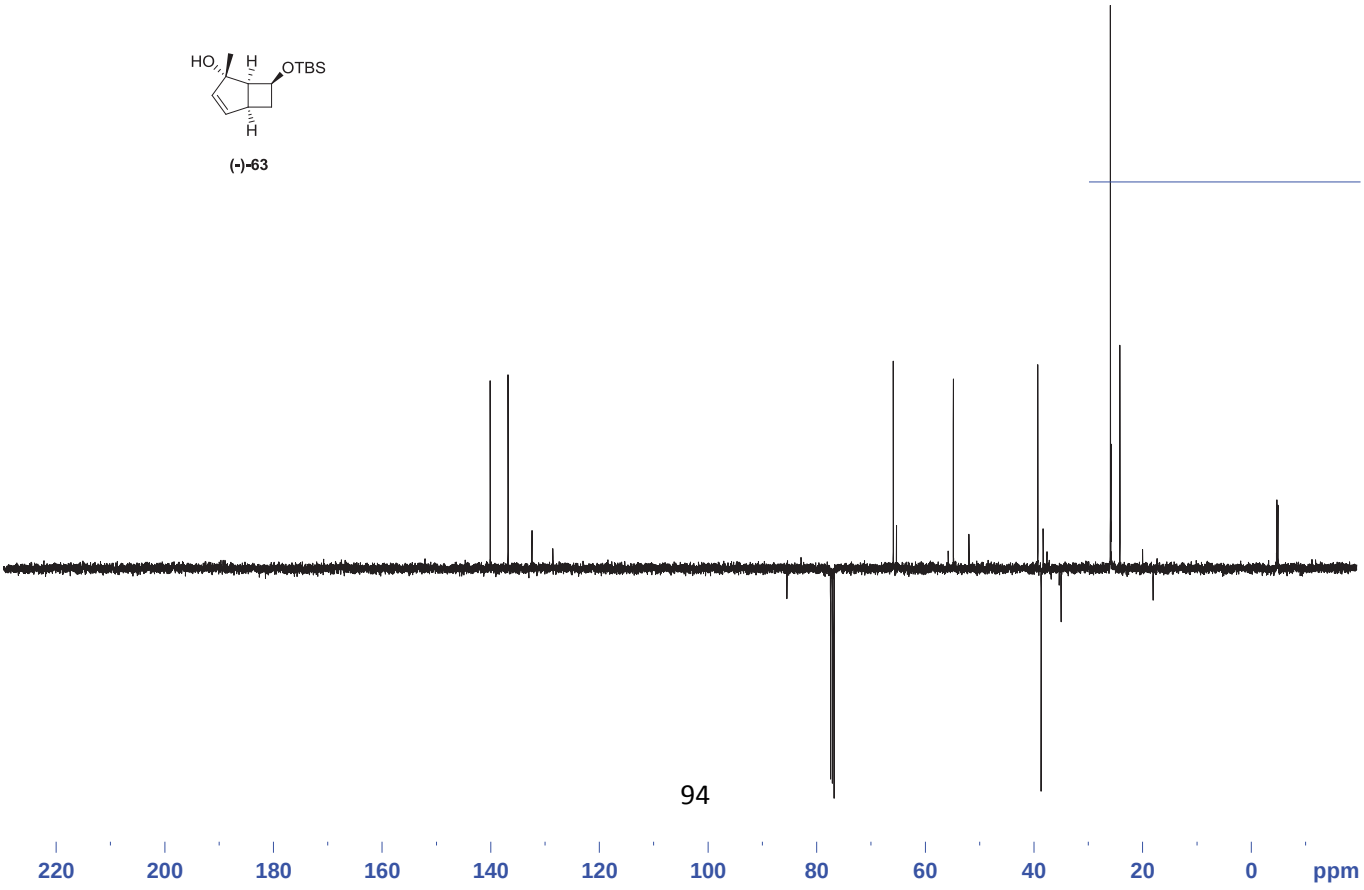

H
OTBS
O
H
(-)-61
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
2.00
2.02
1.02
2.00
3.01
9.03
6.06

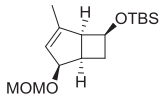

H
OTBS
O
H
(-)-61
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
O
O
(-)-62
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.94
0.98
1.09
1.06
1.08
2.98
9.16
5.98


OTBS
O
O
(-)-62
220
200
180
160
140
120
100
80
60
40
20
0
ppm

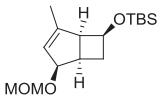

HO
H
OTBS
H
(-)-63
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.99
1.11
1.08
1.08
1.23
3.47
9.36
3.03
2.86


HO
H
OTBS
H
(-)-63
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H
OTBS
MOMO
H

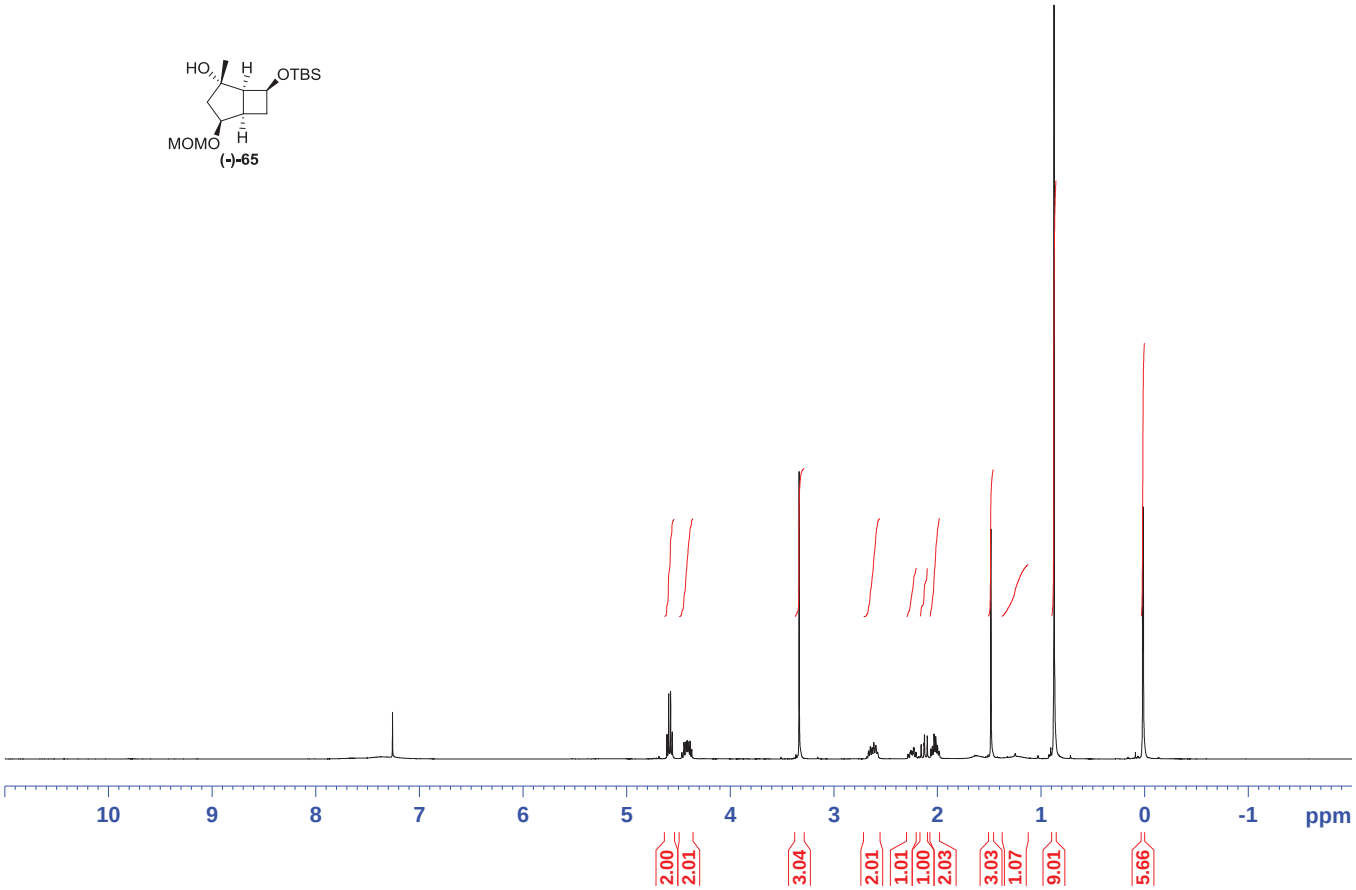
(-)-64

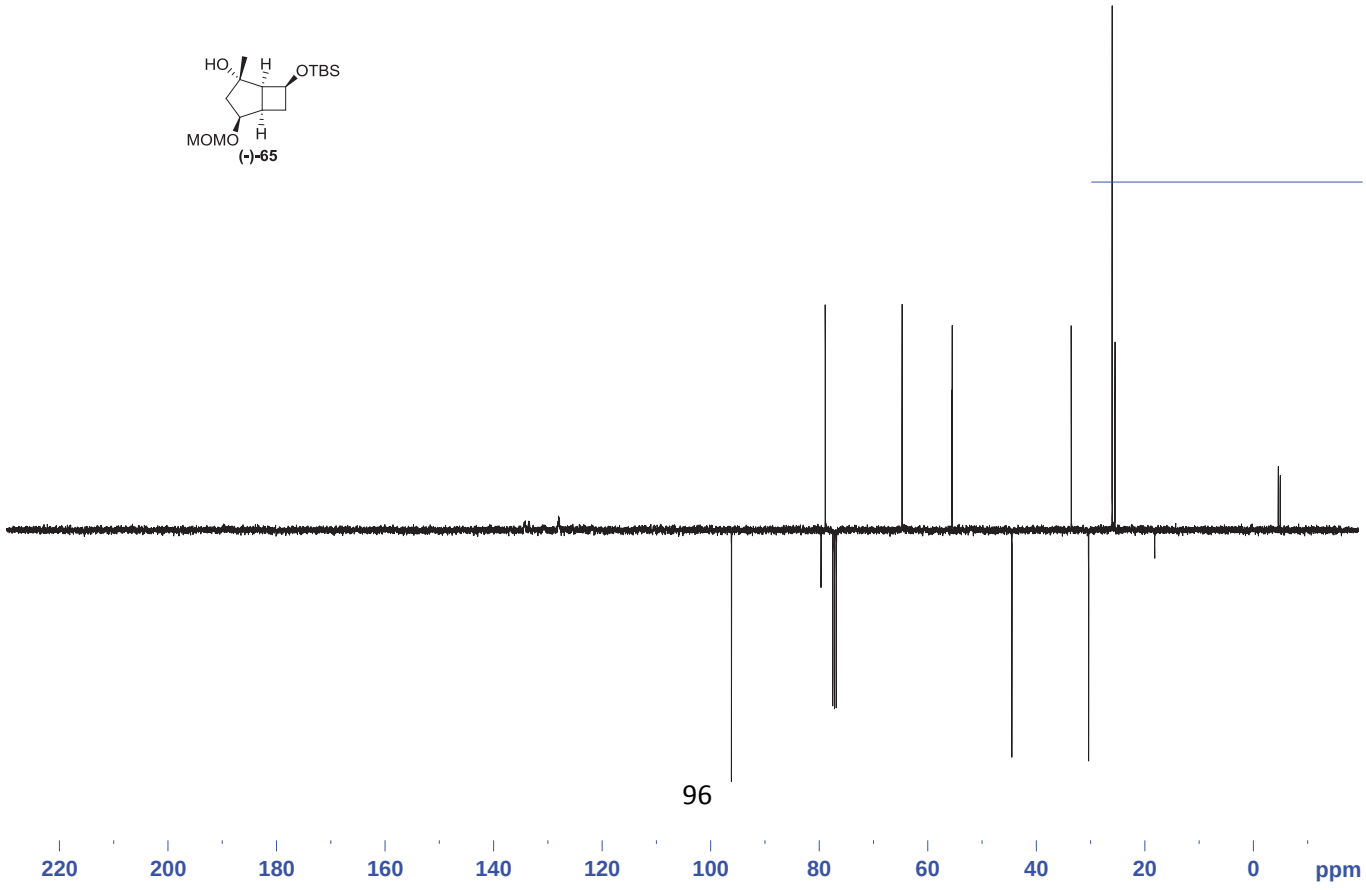
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.03
1.03
1.06
1.04
3.09
1.05
1.08
1.06
0.98
3.07
9.07
6.12

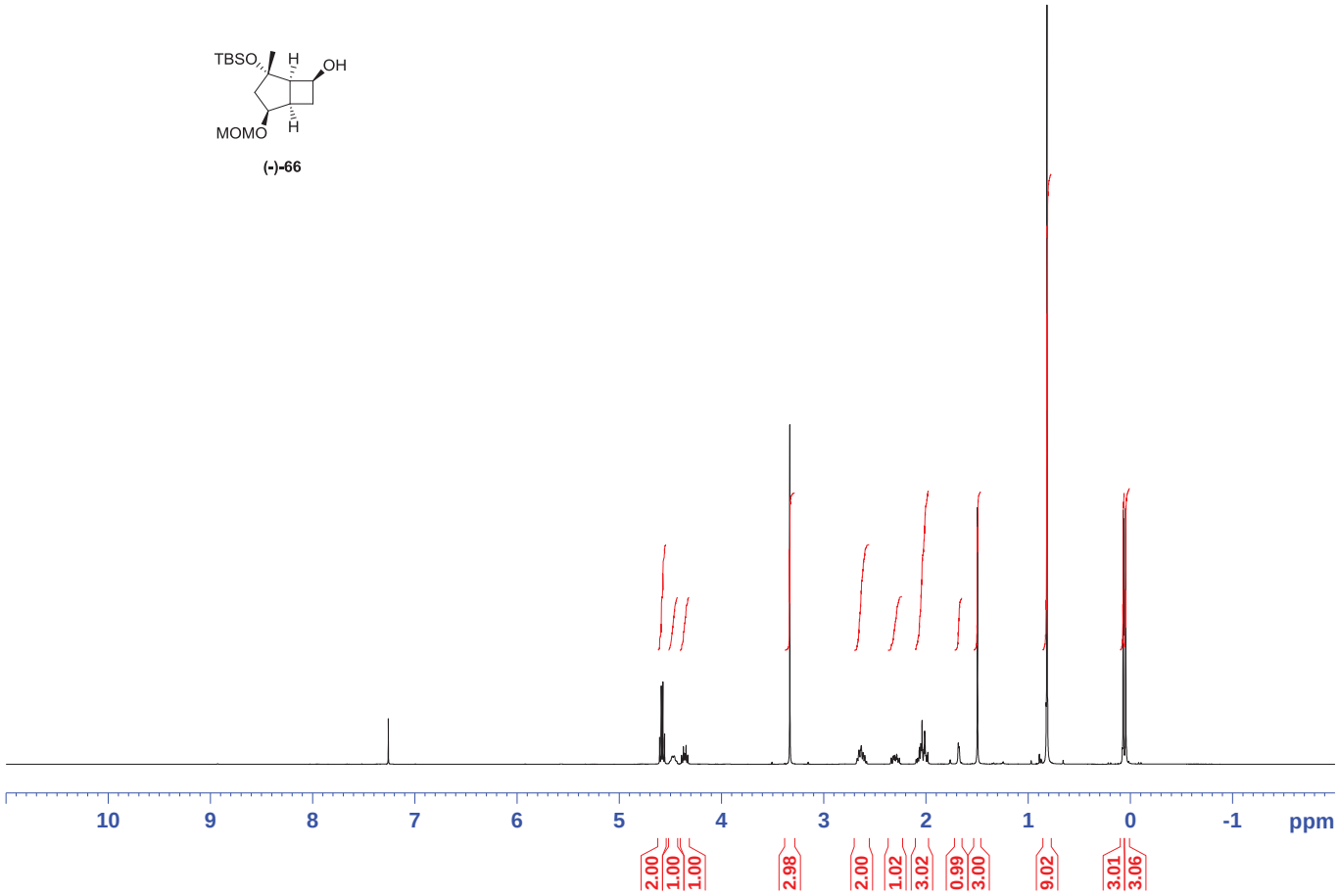

H
OTBS
MOMO
H

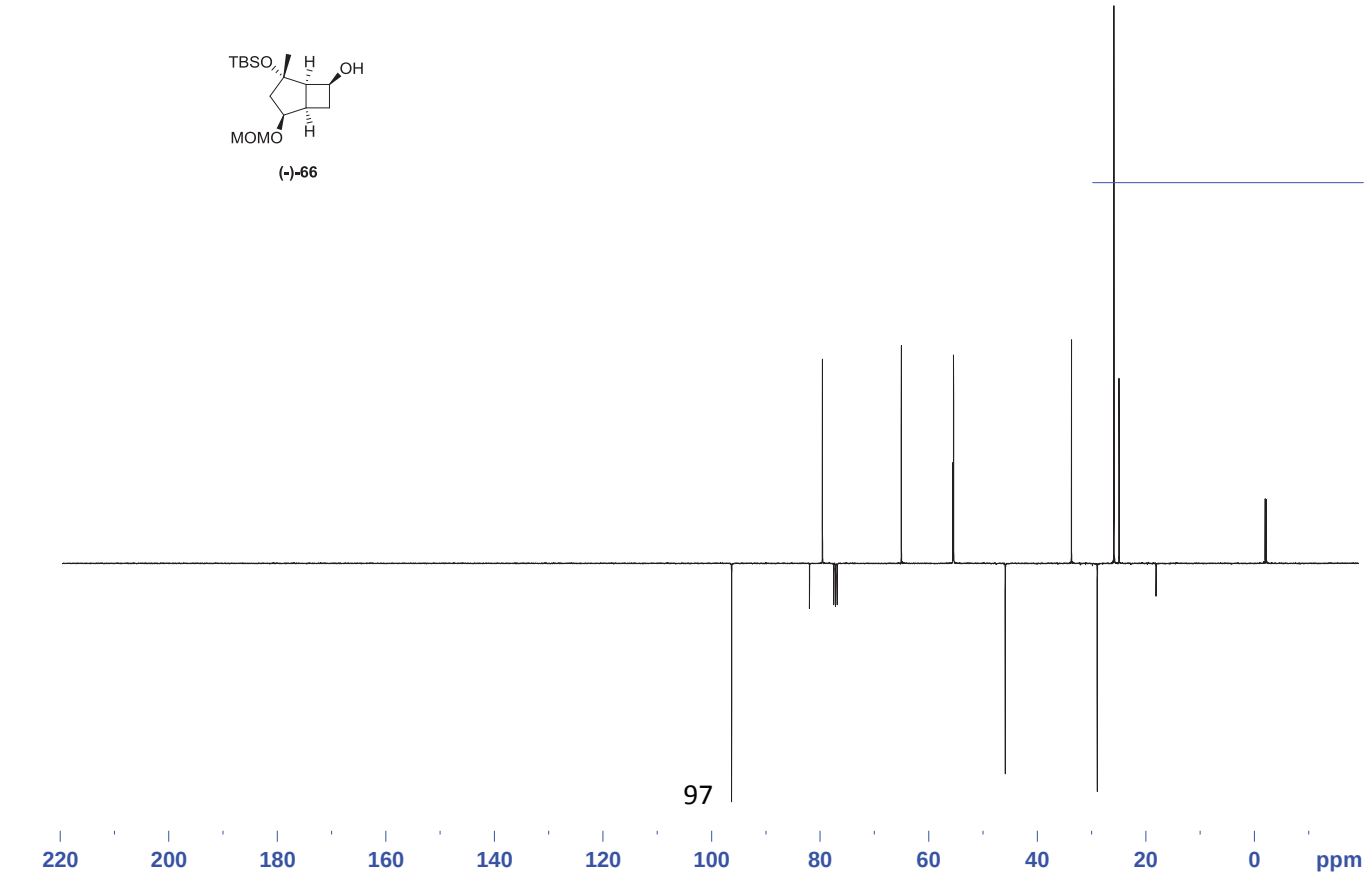
(-)-64

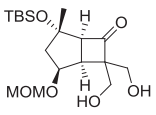
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
H
OTBS
MOMO
H
(-)-65
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.00
2.01
3.04
2.01
1.01
1.00
2.03
3.03
1.07
9.01
5.66


HO
H
OTBS
MOMO
H
(-)-65
220
200
180
160
140
120
100
80
60
40
20
0
ppm

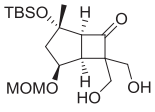

TBSO
H
OH
MOMO
H
(-)-66
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.00
1.00
1.00
2.98
2.00
1.02
3.02
0.99
3.00
9.02
3.01
3.06


TBSO
H
OH
MOMO
H
(-)-66
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
O
MOMO
H
HO
OH

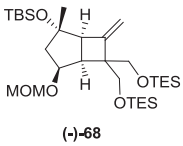
(-)-67

10
9
8
7
6
5
4
3
2
1
0
-1
ppm
3.02
1.00
0.99
2.02
0.96
1.02
3.02
0.99
0.96
1.01
1.06
3.03
9.02
2.87
3.08


TBSO
H
O
MOMO
H
HO
OH

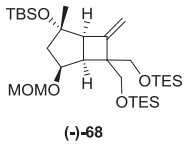
(-)-67

220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
MOMO
H
OTES
OTES

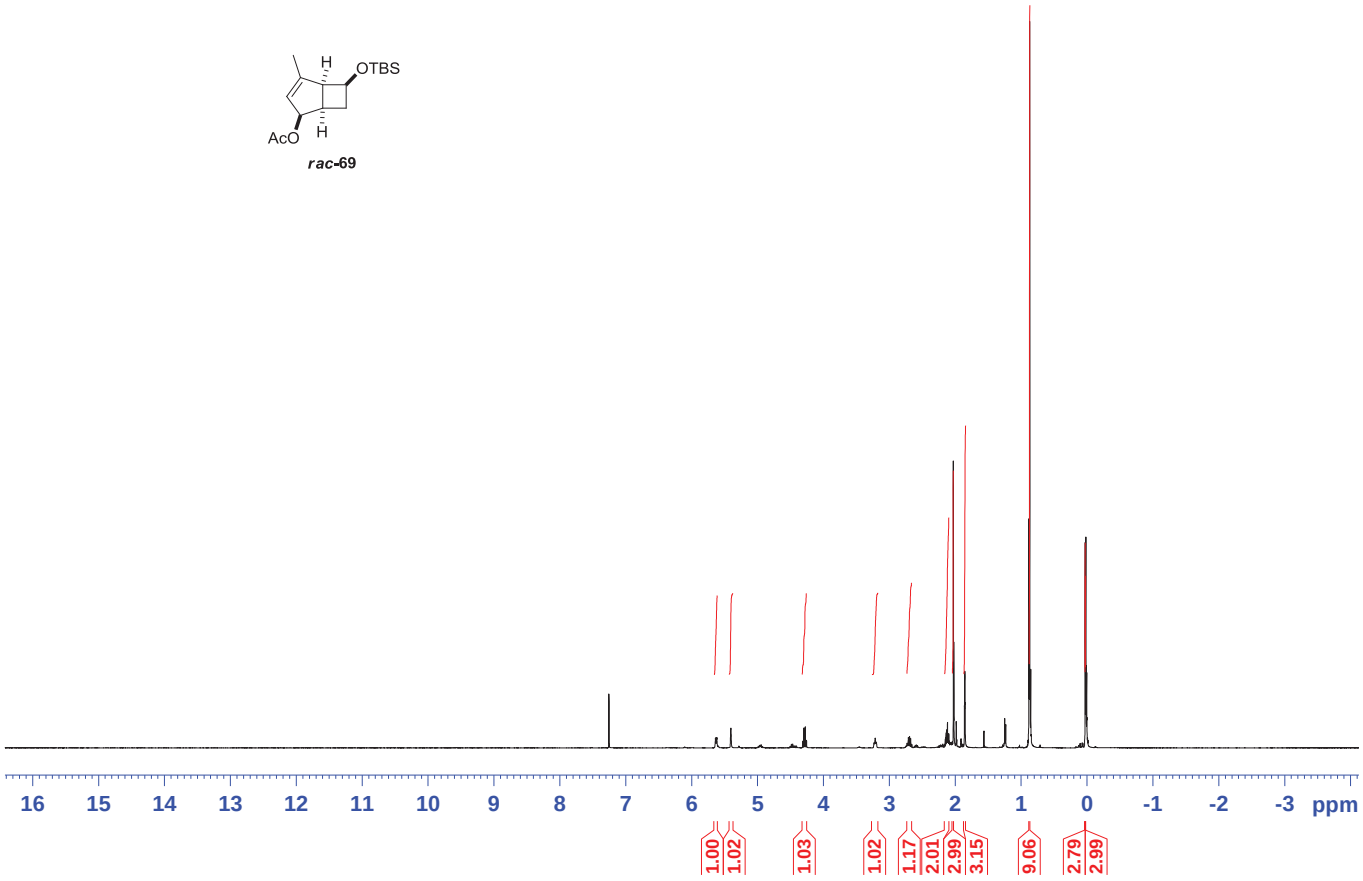
(-)-68

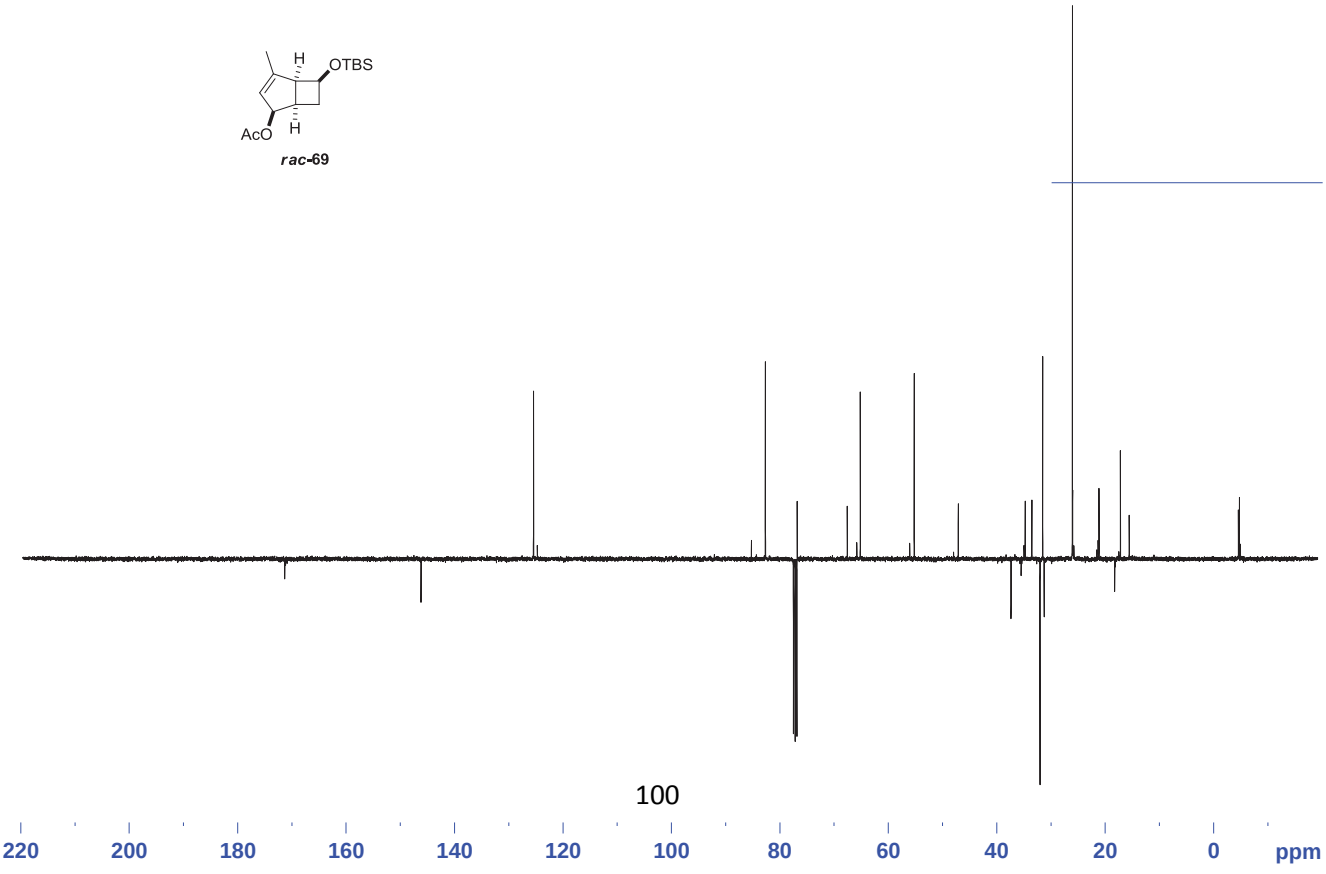
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.00
1.00
1.05
1.03
1.02
1.02
1.02
1.01
3.01
1.03
1.03
2.03
3.03
18.06
9.03
12.09
3.00
3.10

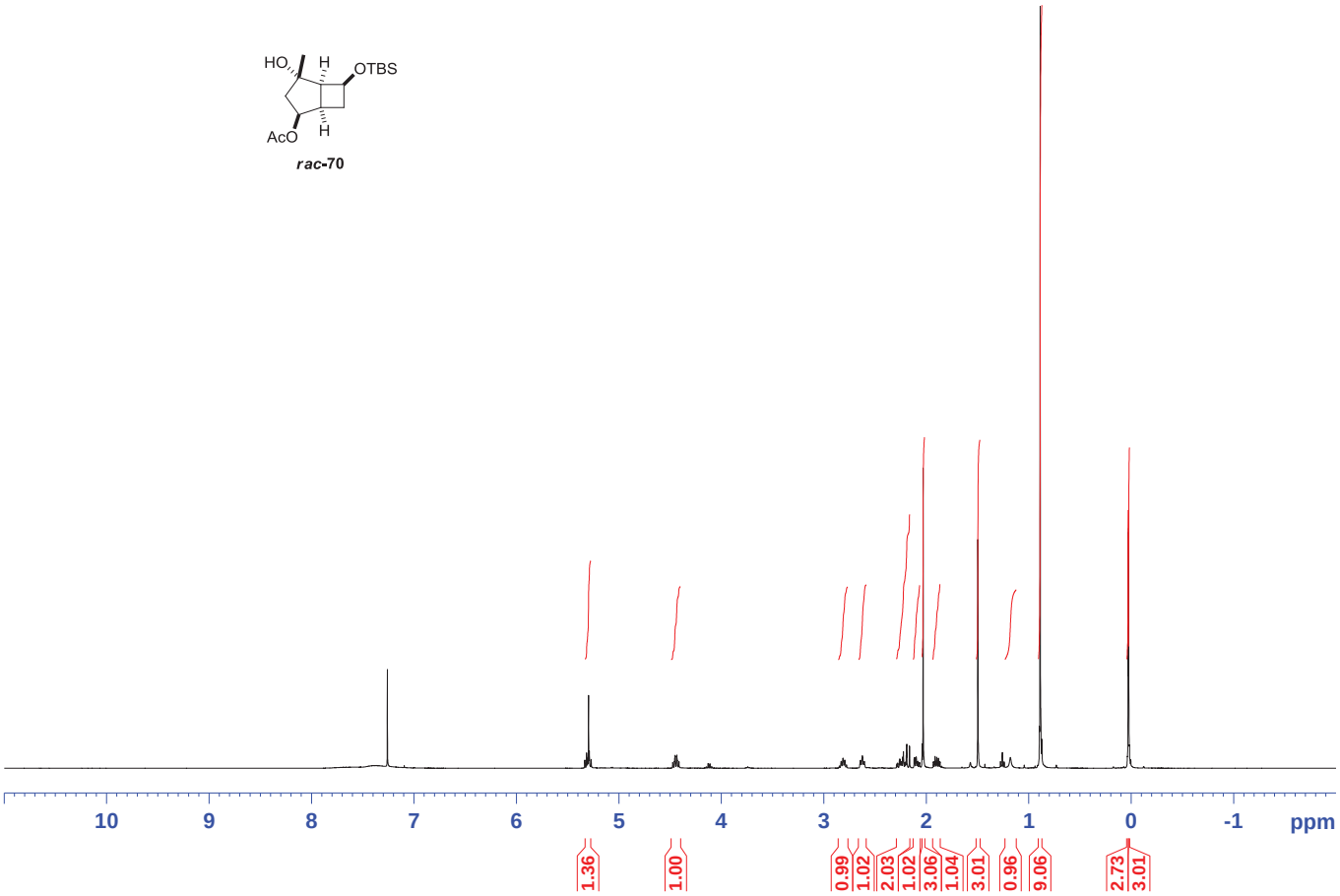

TBSO
H
MOMO
H
OTES
OTES

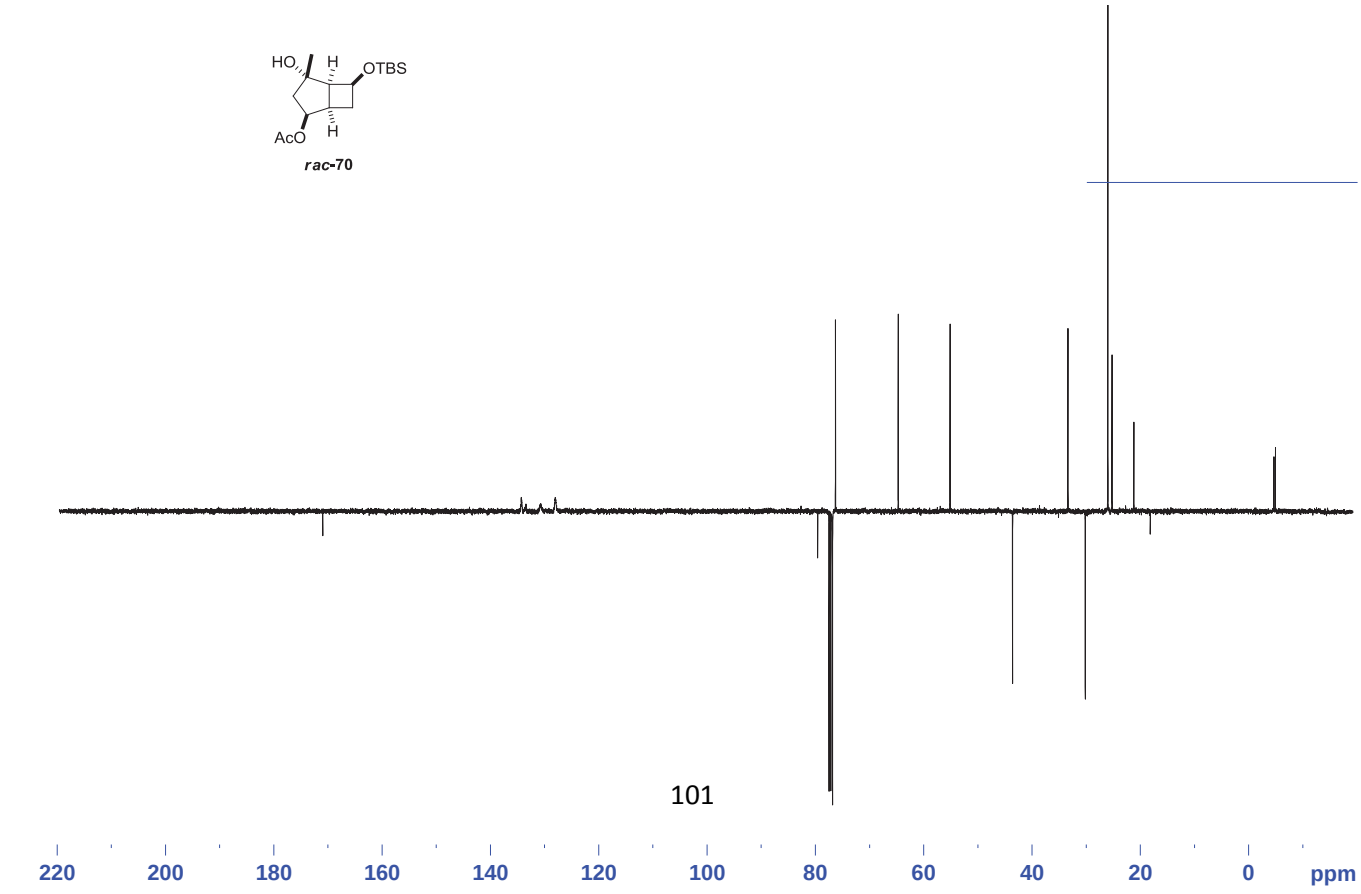
(-)-68

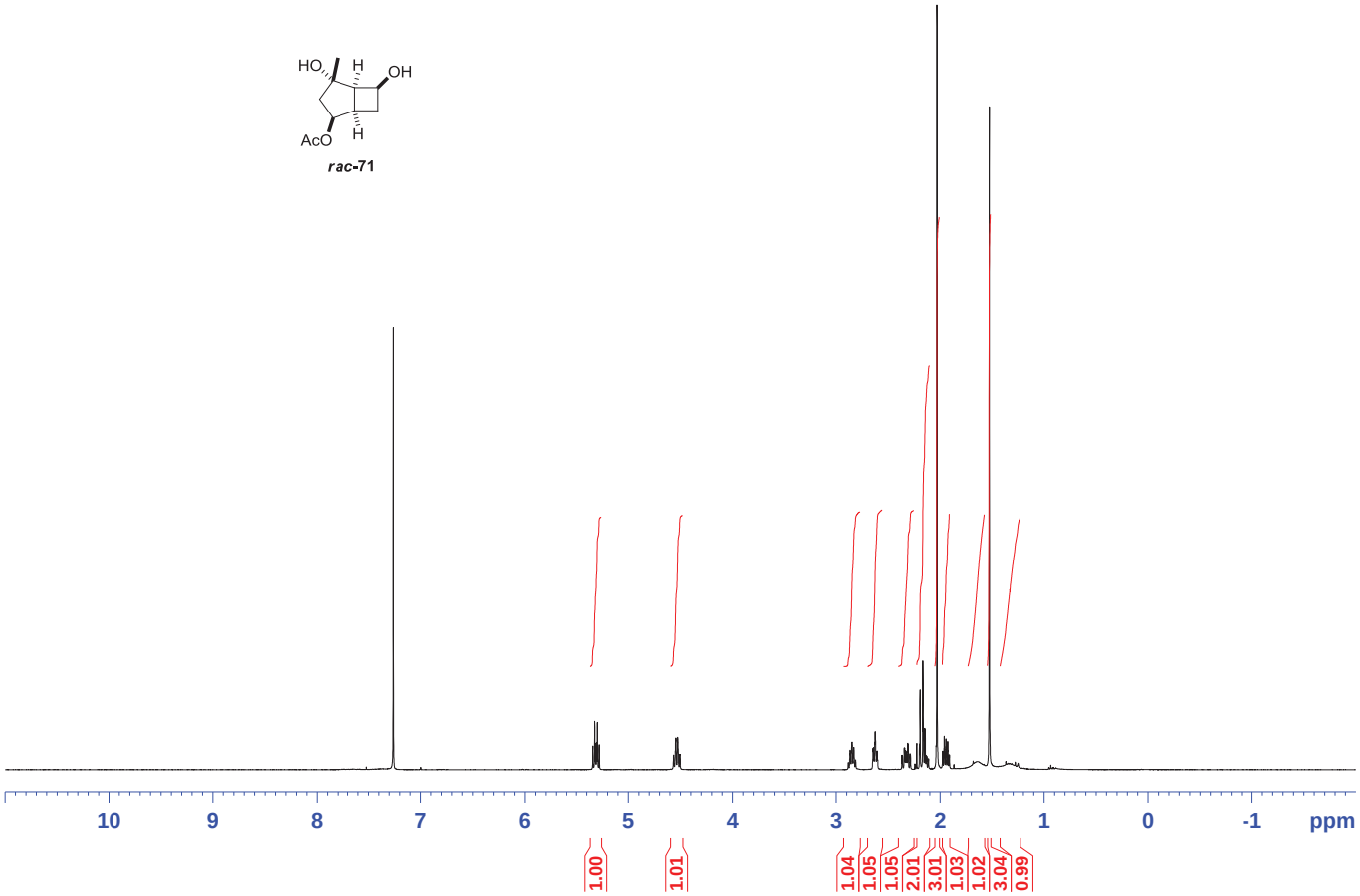
220
200
180
160
140
120
100
80
60
40
20
0
ppm

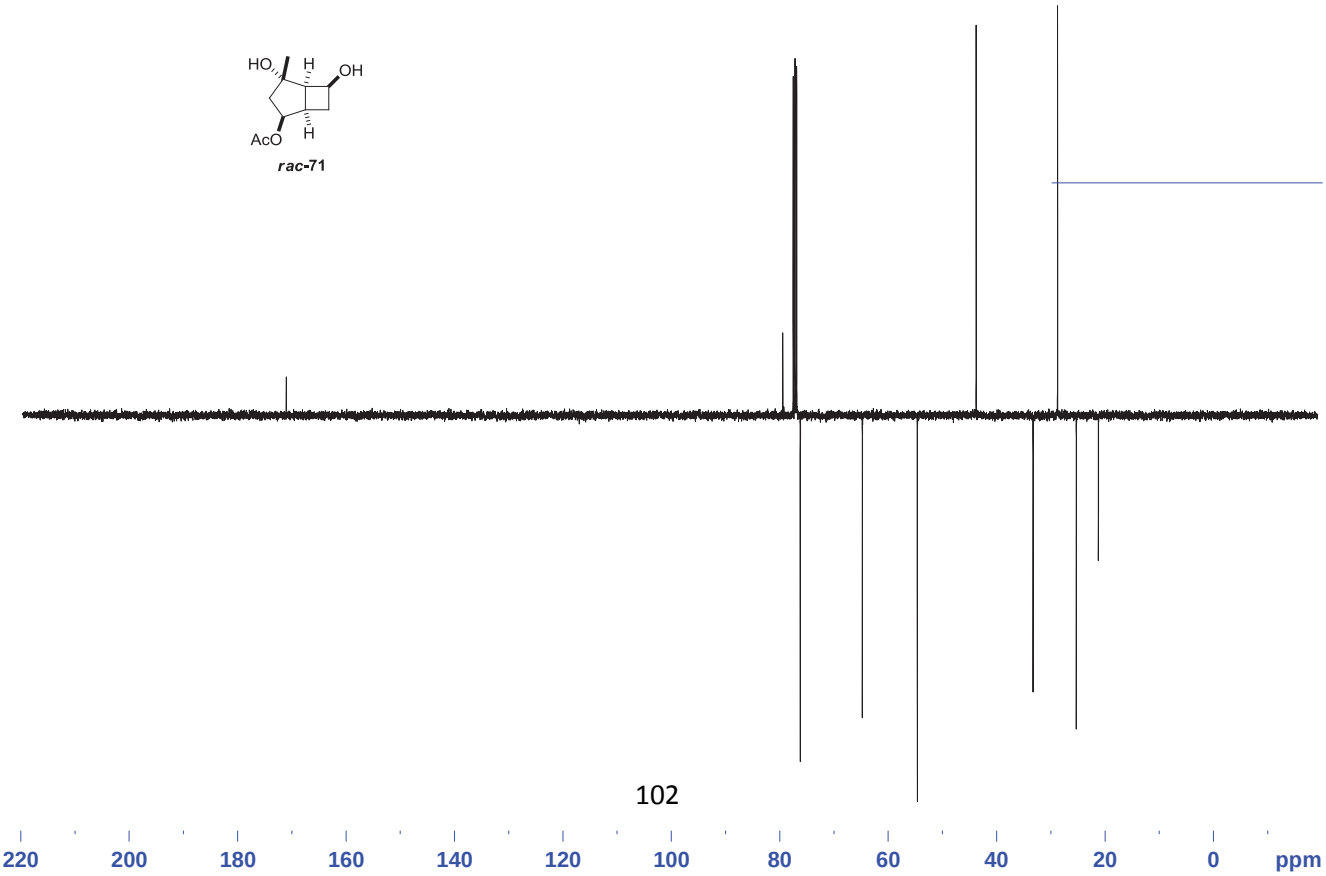

H
OTBS
AcO
H
rac-69
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
1.00 1.02 1.03 1.02 1.17 2.01 2.99 3.15 9.06 2.79 2.99

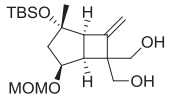

H
OTBS
AcO
H
rac-69
220 200 180 160 140 120 100 80 60 40 20 0 ppm


HO
H
OTBS
AcO
H
rac-70
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.36
1.00
0.99
1.02
2.03
1.02
3.06
1.04
3.01
0.96
9.06
2.73
3.01


HO
H
OTBS
AcO
H
rac-70
220
200
180
160
140
120
100
80
60
40
20
0
ppm

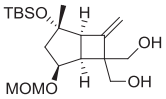

HO
H
OH
AcO
H
rac-71
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.01
1.04
1.05
1.05
2.01
3.01
1.03
1.02
3.04
0.99


HO
H
OH
AcO
H
rac-71
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
OH
MOMO
H
OH

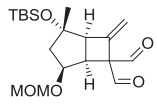
(-)-72

10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.07
2.05
1.06
1.02
4.16
3.08
1.02
2.09
1.05
1.05
3.14
9.13
6.00


TBSO
H
OH
MOMO
H
OH

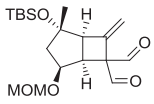
(-)-72

220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
O
MOMO
H
O

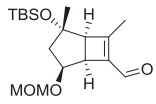
rac-73

10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.98
0.94
1.00
1.01
1.03
2.15
1.02
2.99
1.12
1.11
1.16
3.11
9.06
3.02
3.00


TBSO
H
O
MOMO
H
O

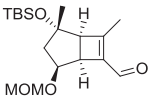
rac-73


220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
MOMO
H
O

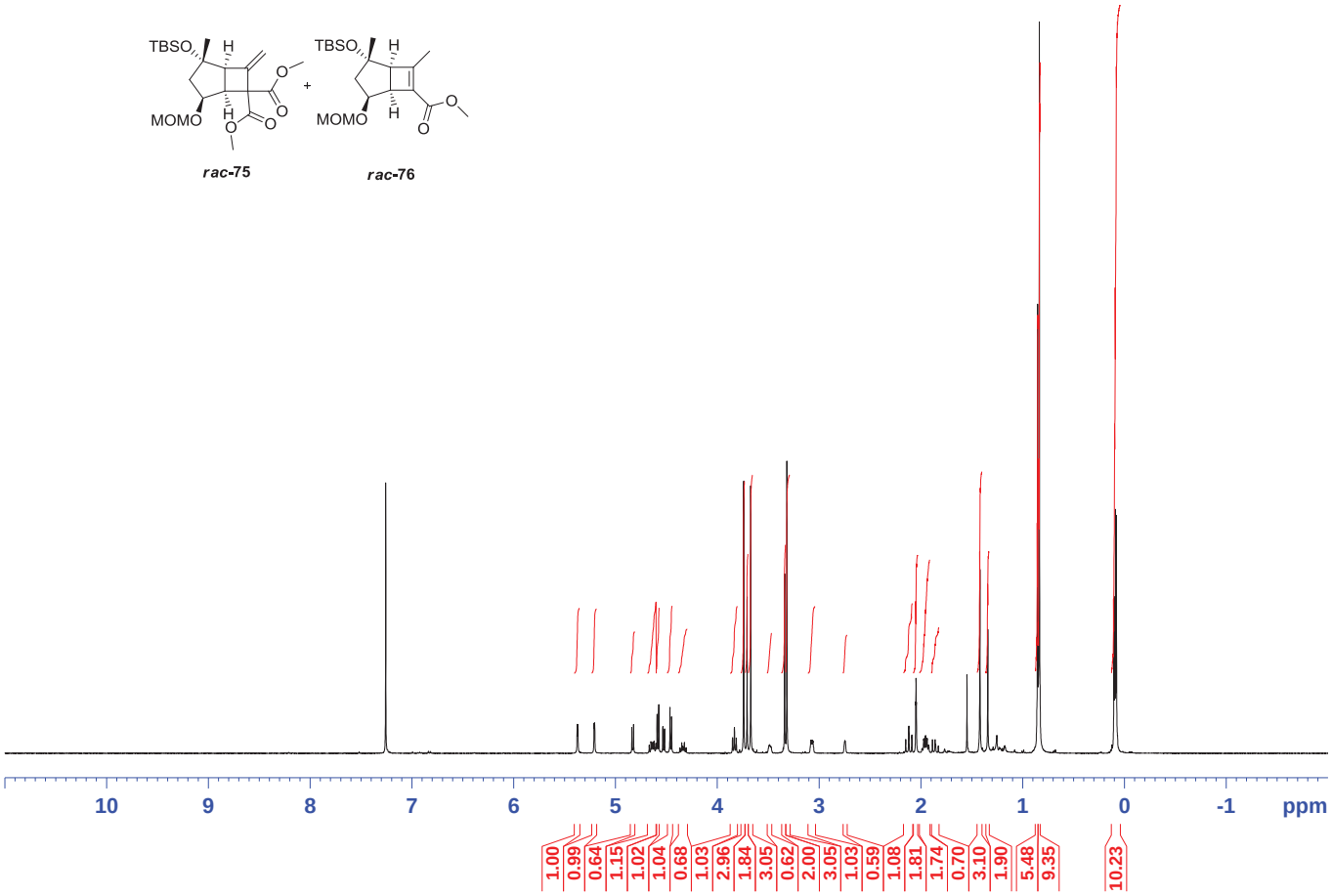
rac-74

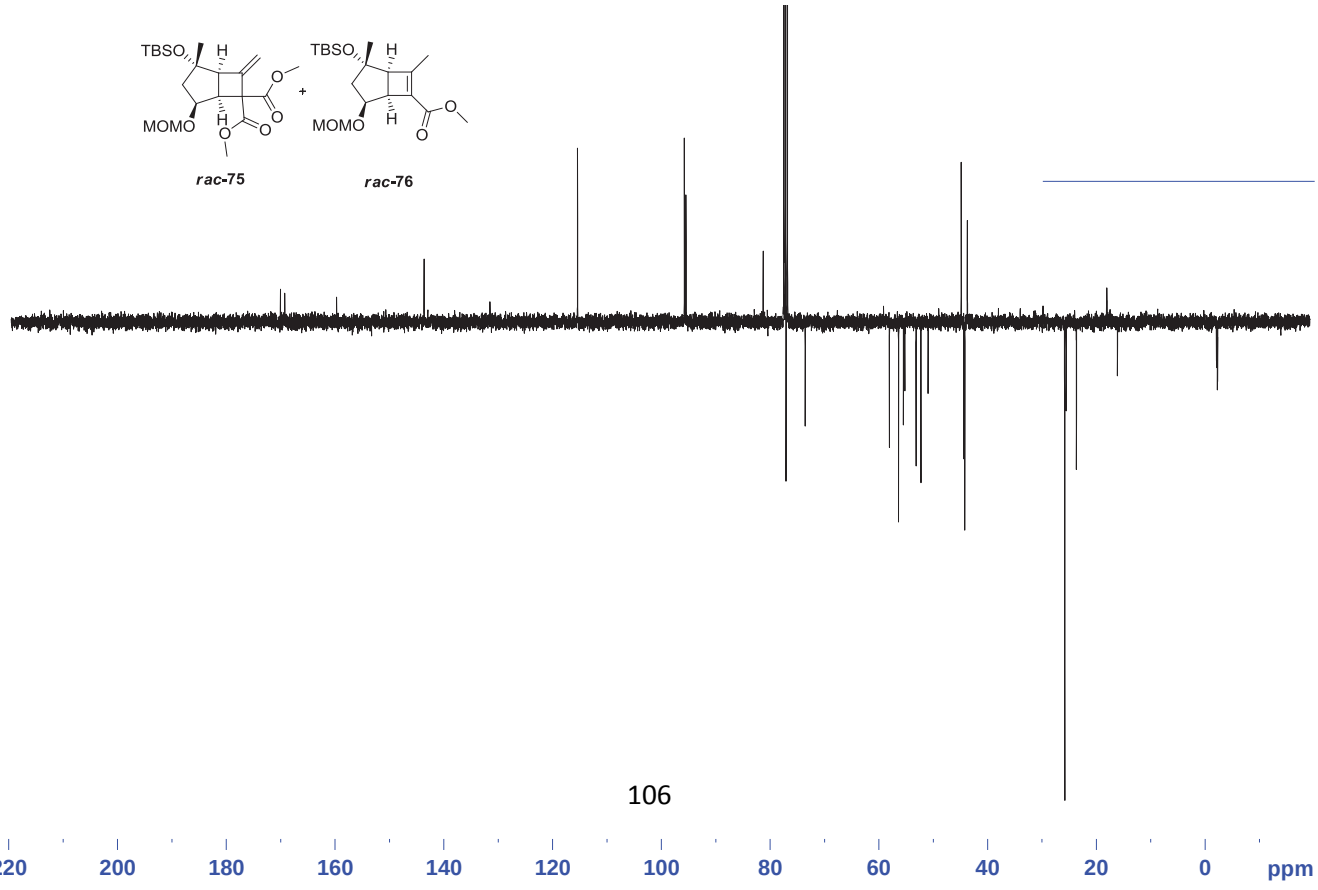
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.09
1.05
1.08
1.11
3.00
1.05
3.01
1.02
1.10
3.10
9.08
6.05

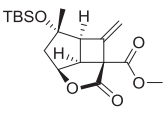

TBSO
H
MOMO
H
O

rac-74

220
200
180
160
140
120
100
80
60
40
20
0
ppm

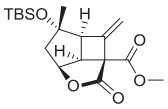

TBSO
H
MOMO
O
O
O
O
rac-75
rac-76
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
0.99
0.64
1.15
1.02
1.04
0.68
1.03
2.96
1.84
3.05
0.62
2.00
3.05
1.03
0.59
1.08
1.81
1.74
0.70
3.10
1.90
5.48
9.35
10.23


TBSO
H
MOMO
O
O
O
O
rac-75
rac-76
220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
H
O
O
O
O—

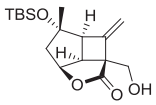
rac-77

10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
2.04
3.03
1.07
1.03
1.03
1.02
3.21
9.10
6.26


TBSO
H
H
O
O
O
O—

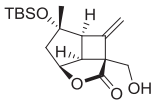
rac-77

220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
H
O
O
OH

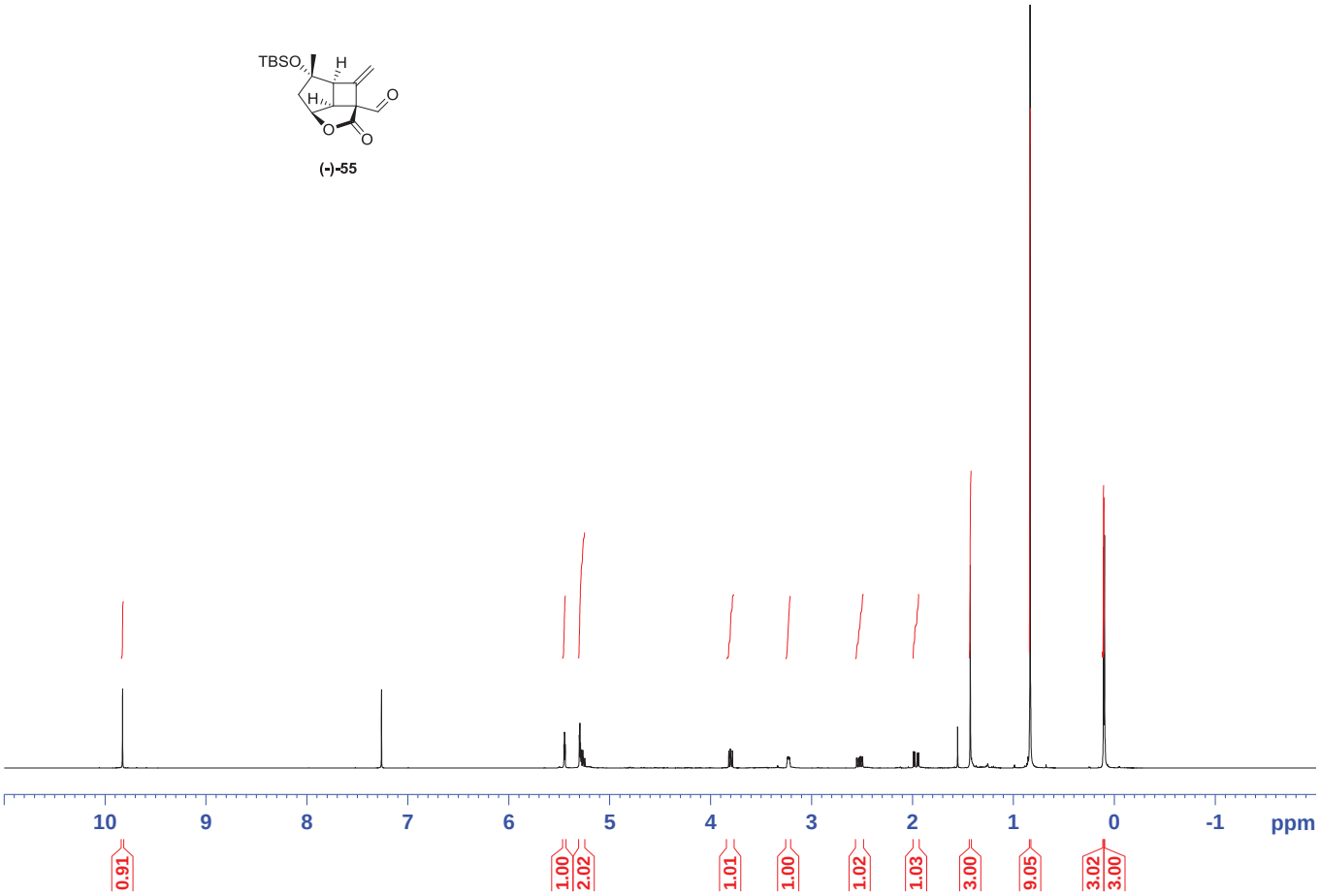
(-)-78

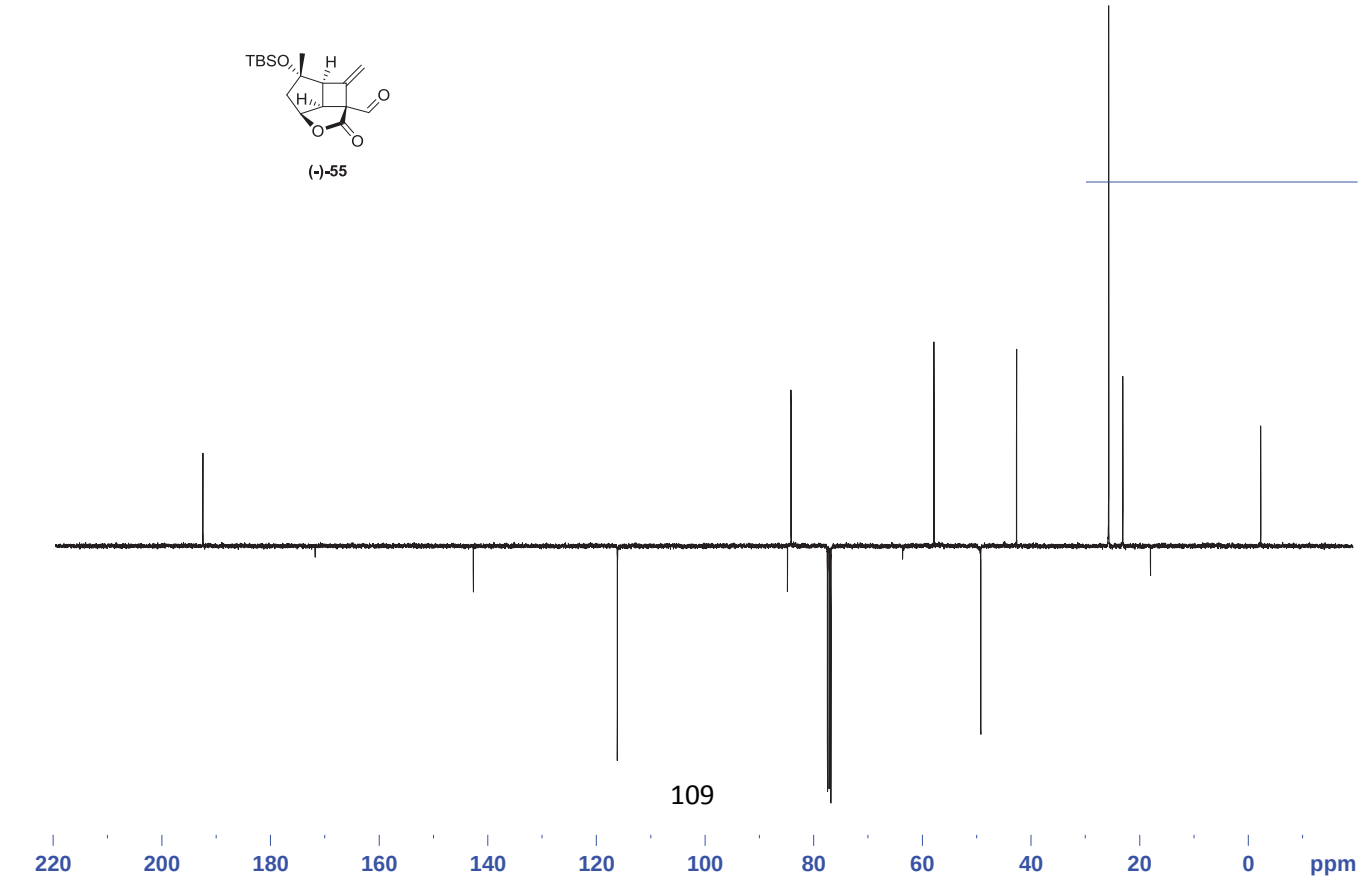
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.02
0.99
1.01
1.00
1.00
0.98
1.01
0.96
1.01
3.02
9.04
2.77
3.07


TBSO
H
H
O
O
OH

(-)-78

220
200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
H
H
O
O
O
(-)-55
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.91
1.00
2.02
1.01
1.00
1.02
1.03
3.00
9.05
3.02
3.00


TBSO
H
H
O
O
O
(-)-55
220
200
180
160
140
120
100
80
60
40
20
0
ppm

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

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

European Journal of Organic Chemistry **2013**, submitted (June 13th, 2013).

The supporting information (SI) was omitted as this work resulted mainly from the efforts of the first author. SI to this article can be found on the home page of the journal.

Contribution: Concept development: Martin Himmelbauer, Jean-Baptiste Farcet, Julien Gagnepain and Johann Mulzer
Experimental work: Martin Himmelbauer, Julien Gagnepain and Jean-Baptiste Farcet
Product characterization and analytic work: Martin Himmelbauer, Julien Gagnepain and Jean-Baptiste Farcet
Preparation of the manuscript: Martin Himmelbauer and Johann Mulzer

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

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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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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.

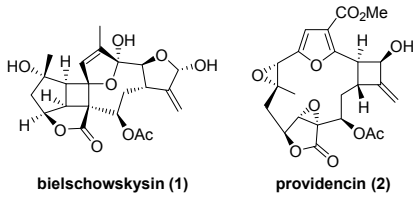
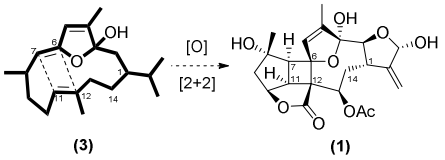


Figure 1. Structures of bielschowskysin and providencin.

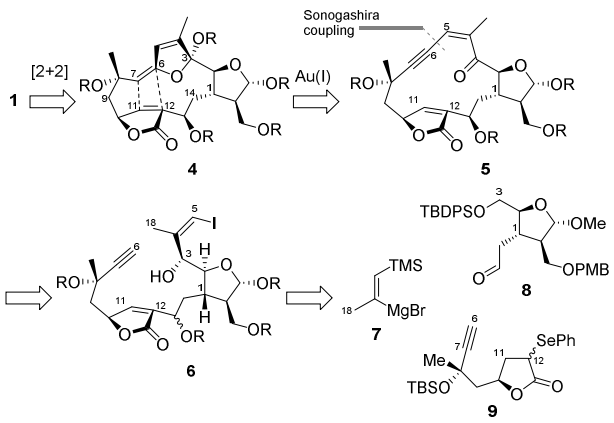
The members of the furanocembranoid family display a wide degree of functionalization. Nonetheless, they appear to be biogenetically interconnected.[4] Thus, the cyclobutane moiety of bielschowskysin has been postulated to arise from a transannular [2+2]-cycloaddition of a much simpler macrocyclic precursor **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]



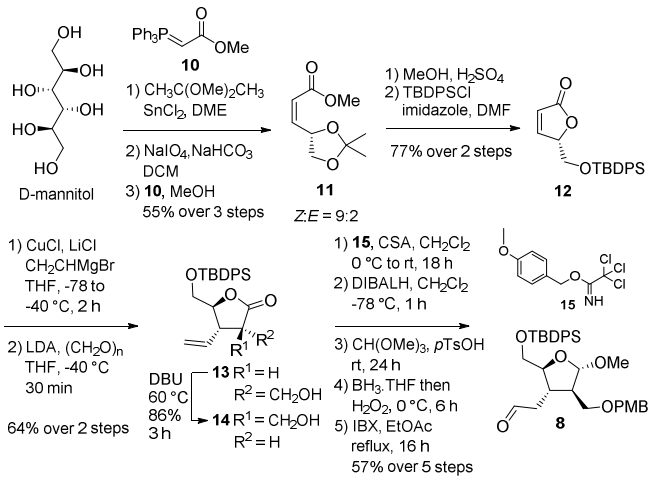
Scheme 1. Biosynthetic [2+2]-cycloaddition forming bielschowskysin.

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.

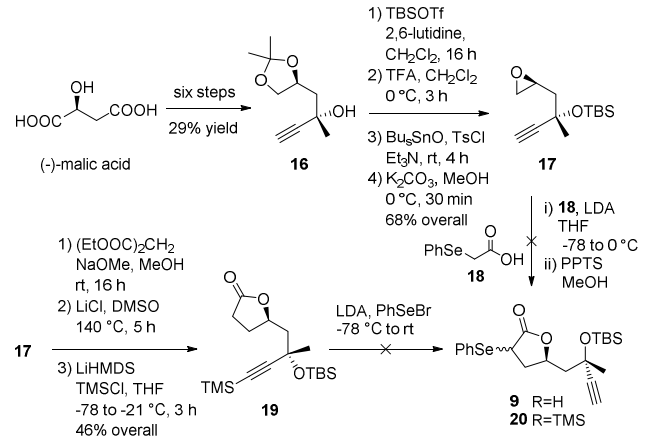


Scheme 2. Initial retrosynthesis based on a transannular [2+2]-cycloaddition.



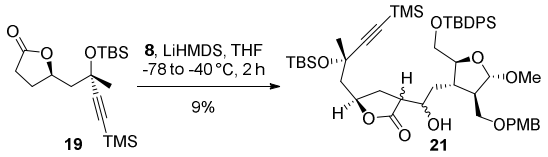
Scheme 3. Synthesis of the eastern fragment **8**.

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 immission of gaseous formaldehyde gave satisfying results. However, deprotonation of the γ-butyrolactone followed by addition of a freshly prepared solution of formaldehyde in THF 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**.



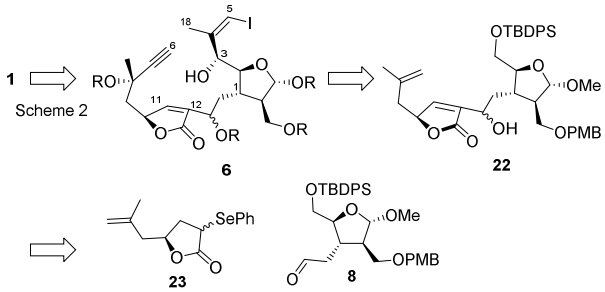
Scheme 4. Synthesis of the western alkyne **19**.

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-phenylselenyl lactone **9** in a single step by opening of the epoxide with the dianion of phenylselenyl 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-selenylated 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.



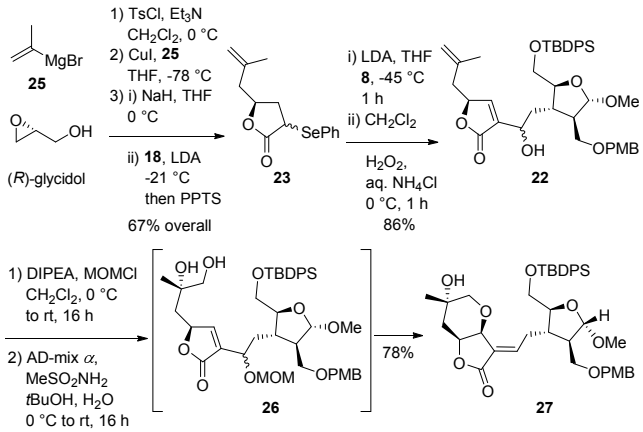
Scheme 5. Building block coupling.

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.

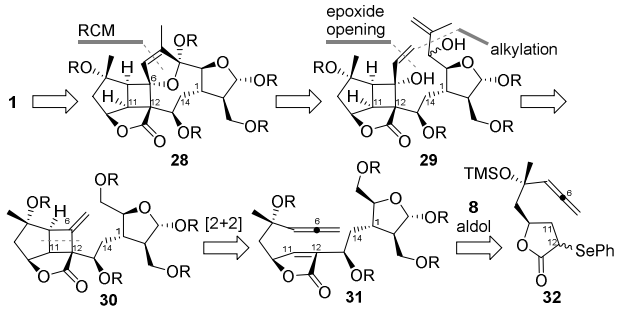
To our delight, the aldol reaction smoothly furnished the desired coupling product as a mixture of all four possible diastereomers (Scheme 7). Oxidative elimination of the phenylselenyl group gave butenolide **22** as a mixture of two diastereomers, which was used as such in the next reaction. After protection of the free secondary alcohol a SAD-reaction was performed. Interestingly but unproductively, the primary product **26** underwent a S_N2'-reaction under OMOM-elimination to generate compound **27**.



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

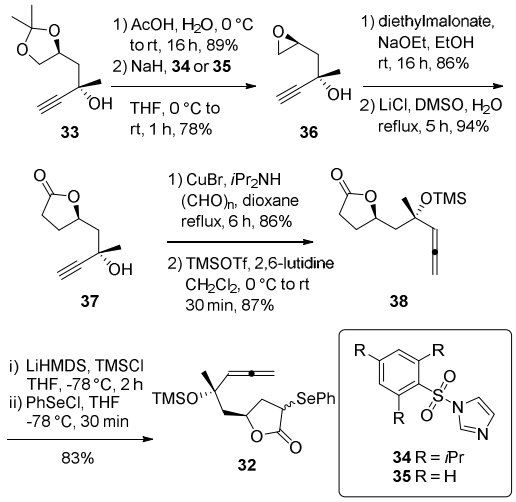
At this juncture we decided to abandon the transannular [2+2]-approach and to modify our strategy as shown in Scheme 8. Thus, aldol addition of **32** and **8** should provide precursor **31**, which in an allene-olefin-[2+2]-photocyclization should lead to polycycle **30**.

Further transformations should be directed toward **29** as the substrate of a RCM reaction to give dihydrofuran **28**.



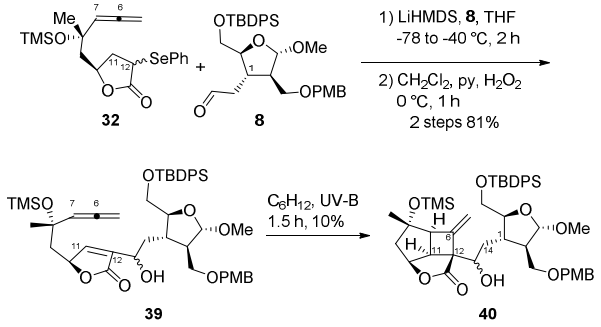
Scheme 8. Retrosynthesis based on an allene-olefin-[2+2]-photocyclization.

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 phenylselenyl 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.

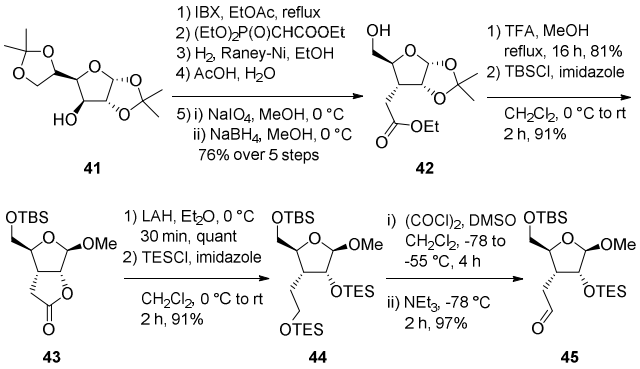
Table 1. [2+2]-photocyclization conditions of **39** to **40**.

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_2Cl_2	750 W, > 100 nm, 30 °C, 0.5 h	decomp.
4	Hex/CH_2Cl_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.

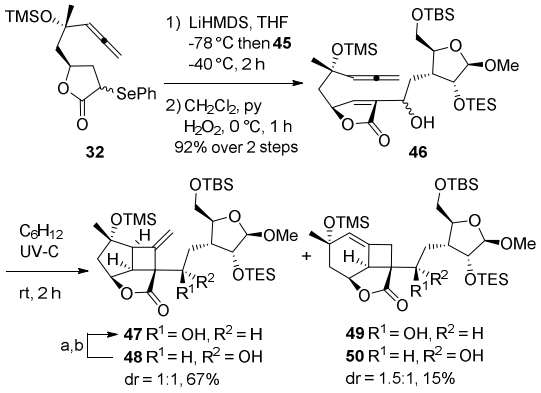
We reasoned that the formation of complex mixtures in the photoreaction might be due to the presence of the aryl chromophores in our substrate and decided to remove the PMB and the TBDPS-protecting groups in the [2+2]-cycloaddition precursor. The synthesis of the eastern tetrahydrofuran ring was redesigned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

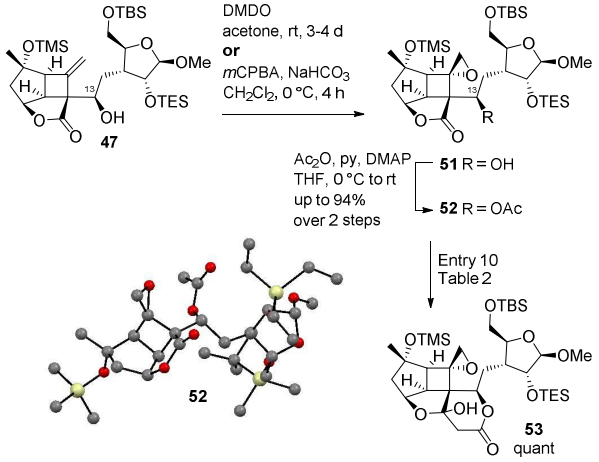
Deprotonation of **32**, addition of **45** and oxidative elimination of the phenylselenide furnished the [2+2]-photocyclization precursor **46** (Scheme 12) with a dr of about 1:1. Capitalizing on our earlier results a solution of **46** in freshly degassed cyclohexane was irradiated with UV-B light for 18 h to give 57% of diastereomeric cyclobutanes **47** and **48**. 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 **47**/**48** was increased to 67%. Additionally 15% of the undesired regioisomers **49**/**50** were formed. After separation of the isomers, the "wrong" diastereomer **48** was recycled to **47** by an oxidation-reduction sequence, and all ensuing reactions were carried out with enantiomerically pure **47** and **48**.



Scheme 12. Synthesis of the new eastern building block. a) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C; b) (S)-2(-)-methyl-CBS oxazaborolidine, BH_3.THF, THF, -78 to -40 °C., 33% + 66% of **49**.

Next we epoxidized the *exo*-methylene group of **47** 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 ethylendiamine 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.

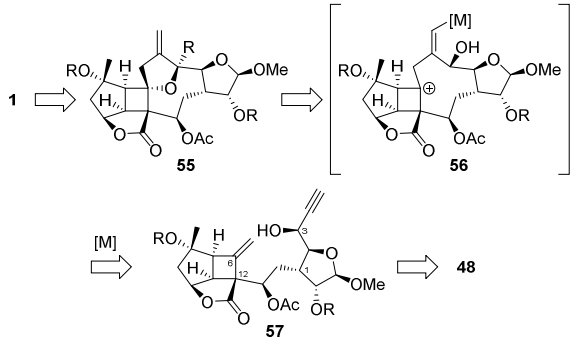


Scheme 13. Synthesis and X-ray structure of **52** and formation of pentacycle **53**.

Table 2. Conditions for the epoxide opening.

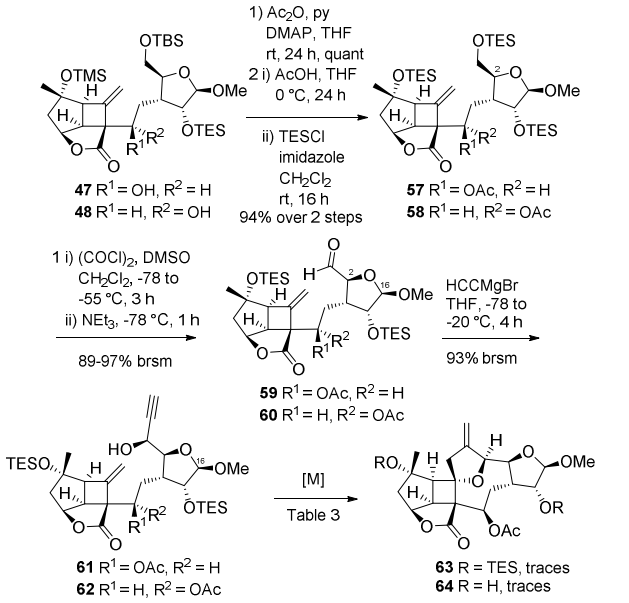
Entry	Conditions	Yield
1	**52**, Me_3SI, *n*BuLi, THF, -78 °C, 8 h	SM
2	**52**, Me_3SI, *n*BuLi, THF, -21 °C, 8 h	SM
3	**52**, Me_3SI, *n*BuLi, THF, 0 °C to rt, 10 h	SM
4	**52**, *i*-propenylMgBr, CuI, THF -78 °C to 0 °C, 24 h	SM
5	**52**, Me_3SBF_4, *n*BuLi, THF, -21 °C, 24 h	SM
6	**52**, Me_3SBF_4, *n*BuLi, THF, -21 °C to rt, 24 h	SM
7	**52**, $CH_2CHMgBr$, *n*BuLi, CuCN, THF -78 °C to rt, 12 h	SM
8	**52**, $CH_2CHMgBr$, *n*BuLi, CuCN, $BF_3{\cdot}OEt_2$ 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,[6] 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 **47**/**48** 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.

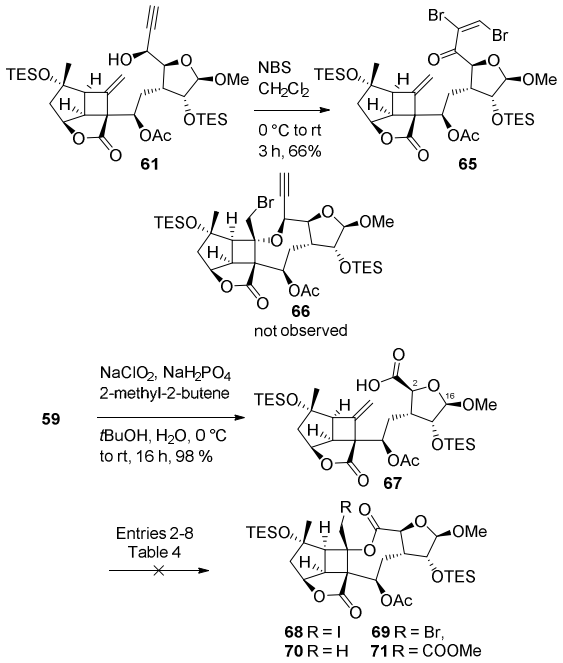


Scheme 15. Introduction of the alkyne and transition metal mediated cyclization attempts.

Table 3. Conditions for the transition metal mediated cyclization.

Entry	SM	Conditions[c]	Yield
1	**61**	$[(PPh_3)Au]NTf_2$, CH_2Cl_2, -78 to 0 °C, 24 h	**63**, traces
2	**61**	$PtCl_2$, toluene, 75 °C, 2 d	**64**, traces
3	**61**	$[(PPh_3)Au]Cl$, $AgSbF_6$, CH_2Cl_2, 0 °C, 1 h	**61** - global TES
4	**61**	$[(PPh_3)Au]Cl$, $AgSbF_6$, MeOH, 0 °C, 6 h	**61** - global TES
5	**61**	$[(CH_3CN)_4Cu]PF_6$, toluene, 80 °C, 5 h	**63**, traces
6	**61** - global TES	$[(PPh_3)Au]NTf_2$, 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**.



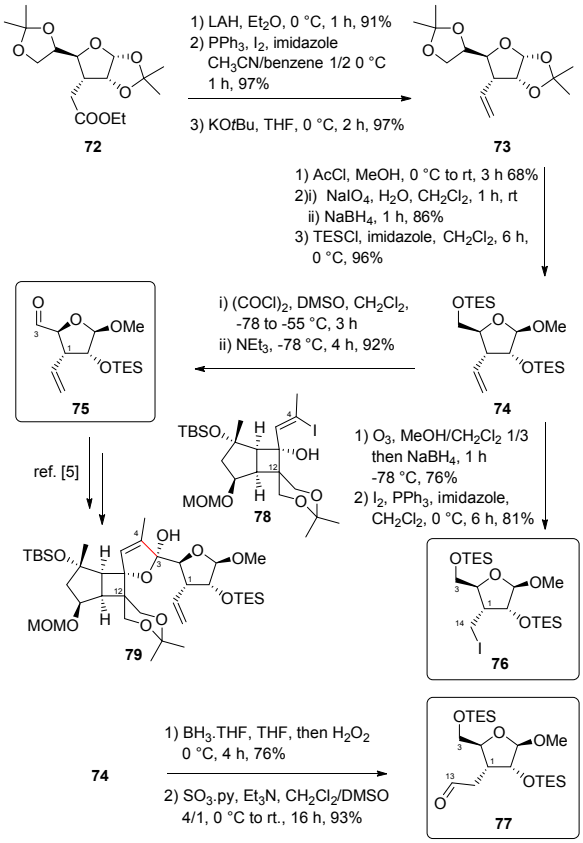
Scheme 16. Additional macrocyclization attempts.

Table 4. Conditions for alternative macrocyclizations.

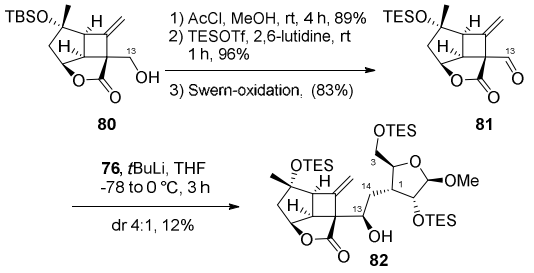
Entry	SM	Conditions	Yield
1	**61**	NBS, CH_2Cl_2, 50 °C, 5 h	**65**, 66%
2	**67**	NIS, $CDCl_3$, 40 °C, 2 h	SM
3	**67**	I_2, $NaHCO_3$, CH_2Cl_2, 40 °C, 6 h	SM
4	**67**	NBS. CH_3CN, 82 °C, 3 h	decomp.
5	**67**	$PdCl_2$, CuCl, O_2, DMF, rt, 16 h	decomp.
6	**67**	$PdCl_2$, CuCl, O_2,$NaHCO_3$ DMF, rt, 16 h	decomp.
7	**67**	$PdCl_2$, CuCl, CO, CH_3CN, MeOH, 140 °C, 4 h	SM
8	**67**	$Pd(OAc)_2$, 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).

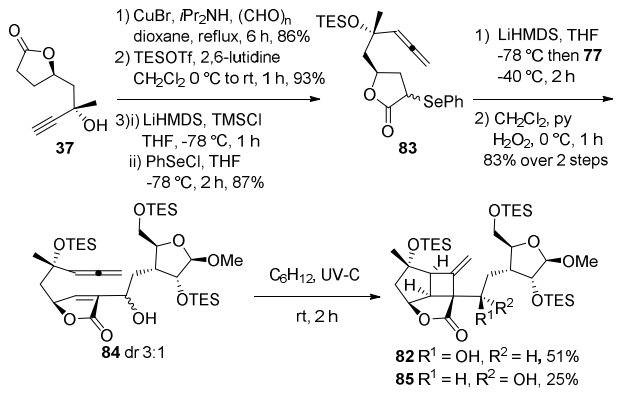


Scheme 17. New flexible route to the eastern tetrahydrofuran moiety.



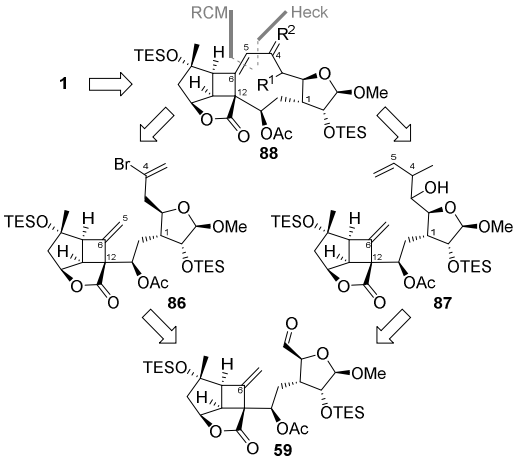
Scheme 18. Non-photochemical introduction of the cyclobutan moiety.

In parallel, we repeated the aldol coupling by using partners **83** and **77** and now adduct **84** was formed in high yield and a dr of 3:1. The [2+2]-photocycloaddition of the diastereomeric mixture gave pure **82** in 51% yield after separation (Scheme 19).



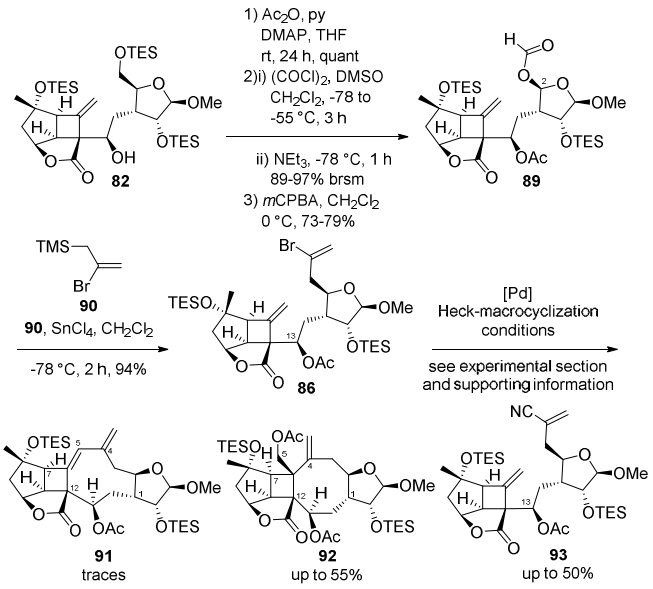
Scheme 19. Improved [2+2]-photocyclization to **82**.

With a straightforward synthesis of **82** in hand we started out to close the macrocycle. On one hand we envisaged an *endo*-selective Heck-reaction[18] of **86** to form a suitable nine-membered carbon macrocycle (Scheme 20). Alternatively a ring-closing-metathesis reaction[19] of **87** was tried to construct the tricyclo[9.3.0.0^{2,10}]tetradecane framework of bielschowskysin.



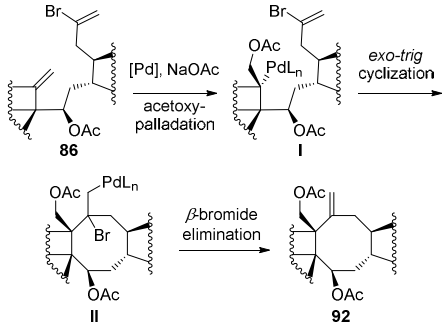
Scheme 20. Heck- and RCM-macrocyclization strategies.

The results of the Heck-reaction have already been described in detail (for experimental data see supporting information).[3h] Suffice it to say here that instead of the desired diene **91** the acetate **92** was obtained (Scheme 21), presumably along an unprecedented mechanistic pathway as outlined in Scheme 22.



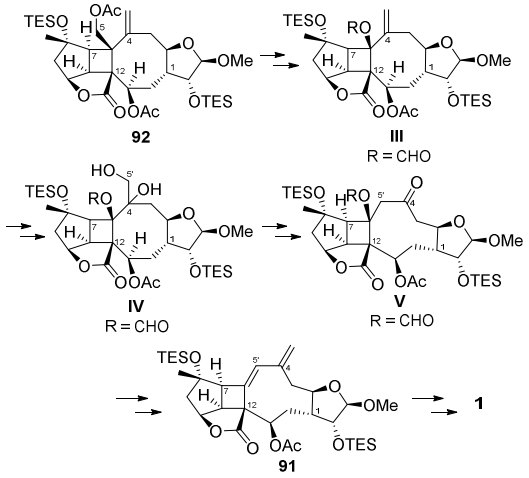
Scheme 21 Results from the palladium catalyzed macrocyclization attempts.

An interesting detail is the formation of vinyl cyanide **93**. Though we have no plausible explanation yet, in all experiments leading to **93** $Pd(OAc)_2$ has been used as catalyst and dimethylformamide as solvent and plausible "CN" source.



Scheme 22. Mechanistic explanation for the carbo-oxygenation.

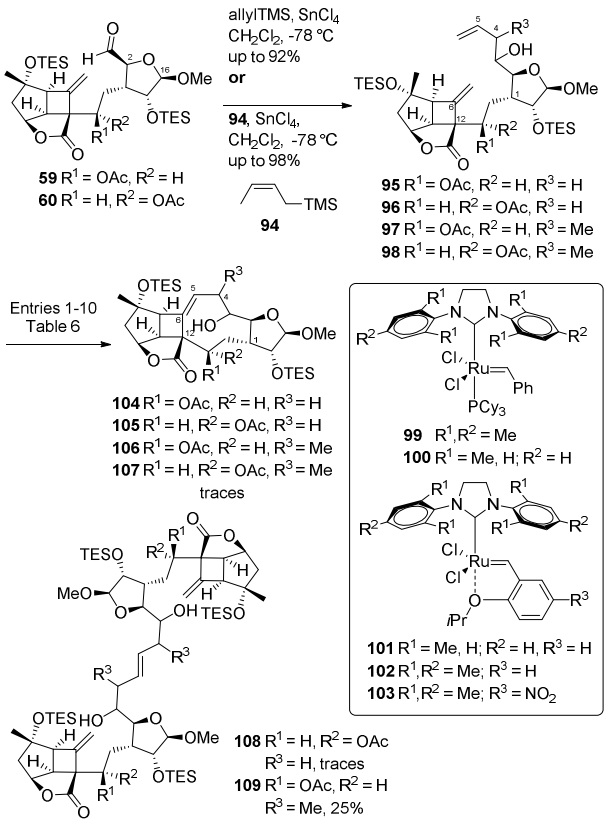
Not necessarily the formation of the wrong ring sized macrocycle **92** is to put an end to our synthesis. After all, there are a number of options to achieve a suitable ring expansion, one of which is tentatively suggested in Scheme 23.



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

Thus, saponification of the acetate group at C-5 in **86** 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.

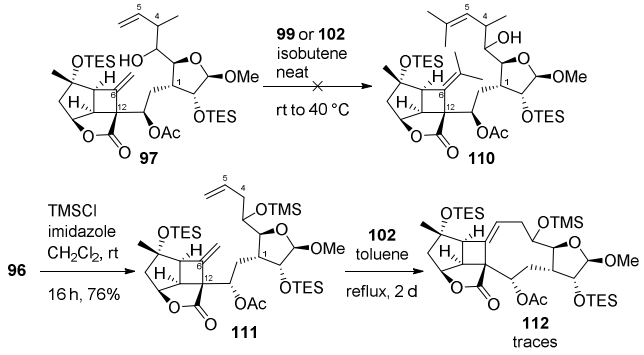
Table 5. Metathesis conditions

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.), isoprene (0.01 M), reflux, 16 h	SM
12[b]	**97**	**99** (0.1 eq.), isoprene (0.01 M), 45 °C, 24 h	SM
13[b]	**97**	**102** (0.3 eq.), isoprene (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.

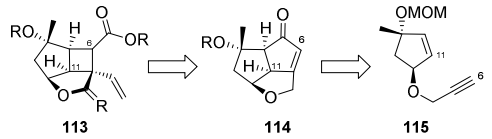
A broad spectrum of catalysts and solvents were employed (Table 5). Specifically, the conventional Grubbs 2nd generation **99**[22], Grubbs-Hoyveda II catalyst **102**, **100**, Stevens catalyst **101**[23], fast initiating Nitro-Grela catalyst **103**[24] and additionally, the doping-effect of poly-fluorinated 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**.

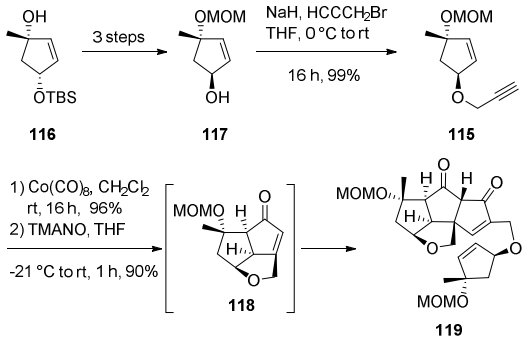


Scheme 25. Additional metathesis experiments.

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 carbo-oxygenation, 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. NEt_3, iPr_2NEt and 2,6-lutidine were distilled over 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). 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, δ = 7.26 ppm, ^{13}C, δ = 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.

(3*R*,4*S*,5*S*)-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): δ = 6.67 (m, 4H), 7.42 (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, 2.82 (dd, *J* = 17.6, 8.9 Hz, 1H), 2.44 (dd, *J* = 17.6, 8.4 Hz, 1H).^{13}C NMR ($CDCl_3$, 400 MHz): δ = 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: Formaldehyde (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*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): δ = 7.66 (m, 4H), 7.47-7.38 (m, 6H), 5.88 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.20 (m, 1H), 5.17 (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 ($CDCl_3$, 400 MHz): δ = 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 $C_{24}H_{30}O_4SiNa$ $[M+Na]^+$ 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): δ = 7.67 (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 ($CDCl_3$, 400 MHz): δ = 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 $C_{24}H_{30}O_4SiNa$ $[M+Na]^+$ 433.1811, found 433.1816. IR (cm^{-1}): 3481, 2932, 1859, 1770, 1472, 1428, 1113, 1047, 929, 703. $[\alpha]_D^{23}$: +12.7, ($CHCl_3$, c = 1.2). R_f: (Hex/EtOAc 3/1) 0.28.

2-((2*S*,3*S*,4*R*,5*S*)-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): δ = 7.68 (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), 3.33 (m, 1H), 2.62 (dt, *J* = 11.2, 3.7 Hz, 1H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 175.8, 159.3, 135.8 (2C), 135.7 (2C), 135.4, 133.3, 133.0, 130.2, 129.93, 129.92 , 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 $C_{32}H_{38}O_5SiNa$ $[M+Na]^+$ 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): δ = 7.69 (m, 4H), 7.39 (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), 4.93 (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), 3.37 (m, 1H), 2.40 (dd, *J* = 16.6, 8.6 Hz, 1H), 2.23 (m, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 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 $C_{33}H_{42}O_5SiNa$ $[M+Na]^+$ 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 BH_3·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. $Na_2S_2O_3$ (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): δ = 7.69 (m, 4H), 7.43 (m, 2H), 7.38 (m, 4H), 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, 3.6Hz, 1H), 3.72 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.59 (m, 2H), 3.52 (dd, *J* = 8.7, 6.8 Hz, 1H), 3.31 (s, 3H), 3.24 (t, *J* = 9.0Hz, 1H), 2.31 (m, 1H), 1.93 (m, 1H), 1.62 (m, 1H), 1.53 (m, 1H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{44}O_6SiNa$ $[M+Na]^+$ 587.2805, found 587.2814. IR (cm^{-1}): 3470, 2932, 2859, 1613, 1472, 1249, 1112, 1080, 823, 703. $[\alpha]_D^{21}$: +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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 9.65 (t, *J* = 1.3 Hz, 1H), 7.67 (m, 4H), 7.40 (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), 3.77 (m, 1H), 3.76 (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), 2.20 (m, 1H), 2.13 (m, 1H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{42}O_6SiNa$ $[M+Na]^+$ 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. $[\alpha]_D^{22}$: +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. ^{1}H 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 ($CDCl_3$, 400 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 $C_{15}H_{27}NaO_3SiNa$ $[M-CH_3]^+$ 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.28 (m, 1H), 3.81 (s, 1H), 3.62 (m, 1H), 3.48 (m, 1H), 2.53 (s, 1H), 2.04 (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 ($CDCl_3$, 400 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 $C_{13}H_{26}O_3SiNa$ $[M+Na]^+$ 281.1549, found 281.1555. IR (cm^{-1}): 3311, 2929, 2858, 1670, 1463, 1254, 1120, 983, 838, 778. $[\alpha]_D^{20}$= -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%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.80 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.35 (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 ($CDCl_3$, 400 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 $C_{20}H_{32}O_5SSiNa$ $[M+Na]^+$ 435.1637, found 435.1644. IR (cm^{-1}): 3286 2984, 2921, 2887, 1463, 1409, 1298, 1164, 1126, 999. $[\alpha]_D^{20}$: -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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.18 (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 ($CDCl_3$, 400 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 $C_{12}H_{21}O_2Si$ $[M-CH_3]^+$ 225.1311, found 225.1306. IR (cm^{-1}): 2992, 2956, 2987, 1473, 1427, 1304, 1165, 1135, 1047, 996. $[\alpha]_D^{20}$: -9.7, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 4/1) 0.81.

(*R*)-5-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-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 155 °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 × 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, 94%) as colorless oil. ^{1}H 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), 2.4 (m, 1H), 2.20 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.02 (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 ($CDCl_3$, 400 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 $C_{15}H_{26}O_3SiNa$ $[M+Na]^+$ 305.1549, found 305.1546. IR (cm^{-1}): 2929, 2856, 1780, 1463, 1253, 1166, 1113, 1002, 838, 778. $[\alpha]_D^{20}$: -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. ^{1}H 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 ($CDCl_3$, 400 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 $C_{18}H_{34}O_3Si_2Na$ $[M+Na]^+$ 377.1944, found 377.1949. IR (cm^{-1}): 2956, 2857, 1780, 1462, 1360, 1251, 1165, 1110, 1000, 838. $[\alpha]_D^{23}$: -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

(SiO_2, Hex/EtOAc 10/1) provided **21** as inseparable mixture of all four possible diastereomers (7 mg, 0.01 mmol). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{51}H_{76}O_9Si_3Na$ $[M+Na]^+$ 939.4695, found 939.4685. IR (cm^{-1}): 3479, 2988, 2878, 1721, 1501, 1453, 1393, 1267, 1101, 992. $[\alpha]_D^{20}$: -11.3, ($CHCl_3$, c = 0.3). R_f: (Hex/EtOAc 3/1) 0.38.

Butyrolactone 22: To a solution of diisopropylamine (150 µL, 1.06 mmol) in THF (2.8 mL) was dropwise added *n*BuLi (1.6 M in hexane, 633 µL, 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. NH_4Cl (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 $MgSO_4$ and concentrated under reduced pressure. The obtained yellow oil was used without purification in the next step.

The mixture of diastereomers was dissolved in CH_2Cl_2 (7.8 mL), cooled to 0 °C and sat. aq. NH_4Cl (0.8 mL) and H_2O_2 (30 wt%, 1.6 mL, 14 mmol) were added. After 1 h sat. aq. $Na_2S_2O_3$ (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 $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography (SiO_2, Hex/EtOAc 3/1) gave **22** (512 mg, 0.73 mmol, 86%) as a mixture of diastereomers. Diastereomer A: ^{1}H NMR ($CDCl_3$, 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), 4.53 (m, 1H), 4.44 (br s, 2H), 3.90 (d, *J* = 5.7 Hz, 1H), 3.86 (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,), 2.12 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{41}H_{52}O_8SiNa$ $[M+Na]^+$ 723.3329, found 723.3325. IR (cm^{-1}): 3386, 2967, 2930, 2889, 1773, 1752, 1467, 1365, 1277, 1034. $[\alpha]_D^{20}$: -16.6, ($CHCl_3$, c = 0.8). R_f: (Hex/EtOAc 3/1) 0.29. Diastereomer B: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 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), 5.01 (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 (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), 2.47 (m, 1H), 2.39 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.28 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.03 (m, 1H), 1.91 (m, 1H), 1.79 (br s, 3H),1.61 (m, 1H) 1.07 (br s, 9H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{41}H_{52}O_8SiNa$ $[M+Na]^+$ 723.3329, found 723.3334. IR (cm^{-1}): 3407, 2975, 2936, 2904, 1779, 1746, 1467, 1392, 1292, 1015. $[\alpha]_D^{20}$: -11.2, ($CHCl_3$, 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 µL, 5.4 mmol). The resulting solution was stirred at room temperature for 16 h. Sat. aq. NH_4Cl (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 $MgSO_4$, 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: ^{1}H NMR ($CDCl_3$, 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), 1.96 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{43}H_{56}O_9SiNa$ $[M+Na]^+$ 767.3591, found 767.3582. IR (cm^{-1}): 2954, 2928, 2888, 1756, 1749, 1421, 1383, 1227, 1117, 987. $[\alpha]_D^{20}$: -26.1, ($CHCl_3$, c = 0.5). R_f: (Hex/EtOAc 3/1) 0.48. Diastereomer B: ^{1}H NMR ($CDCl_3$, 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), 4.93 (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), 3.88 (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), 3.32 (m, 2H), 3.23 (s, 3H), 2.33-2.20 (m, 3H), 1.99-1.94 (m, 2H), 1.74 (s, 3H), 1.28 (m, 1H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 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 $C_{43}H_{56}O_9SiNa$ $[M+Na]^+$ 767.3591, found 767.3596. IR (cm^{-1}): 2954, 2928, 2888, 1756, 1749, 1421, 1383, 1227, 1117, 987. $[\alpha]_D^{20}$: -23.4, ($CHCl_3$, 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/H_2O 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. $NaHS_2O_3$ (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 $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the oil by column chromatography (SiO_2, Hex/EtOAc 3/1) gave pyran **27** (80 mg, 0.11 mmol) in 83% yield. ^{1}H NMR ($CDCl_3$, 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), 1.95 (m, 1H), 1.88 (br s, 1H), 1.12 (s, 3H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{41}H_{52}O_9SiNa$ $[M+Na]^+$ 739.3278, found 739.3287. IR (cm^{-1}): 3461, 2943, 2917, 2875, 1763, 1741, 1453, 1399, 1202, 1016. $[\alpha]_D^{22}$: -41.1, ($CHCl_3$, 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 digested in AcOH (27 mL) and H_2O (1.4 mL) at room temperature. The resulting colorless solution was stirred overnight and concentrated under reduced pressure. The remaining pale yellow gum was evaporated with toluene (3 x 10 mL) till the smell of acetic acid was gone. Purification by flash column chromatography (SiO_2, Hex/EtOAc 2/1) afforded the corresponding triol as colorless gum (1.67 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.40 (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). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 87.0, 72.3, 71.3, 68.3, 66.8, 43.9, 31.2. HRMS (ESI) (m/z): calculated for $C_7H_{12}O_3$ $[M]^+$ 144.0786, found 144.0791. IR (cm^{-1}): 3298, 2983, 2359, 1418, 1133, 1109, 1058, 1036, 1016, 908. $[\alpha]_D^{20}$: –7.9, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/2) 0.19.

To a suspension of NaH (5.2 g, 132 mmol) in THF (100 mL) at 0 °C was added a solution of the aforementioned triol (3.8 g, 26.4 mmol) in THF (40 mL). The resulting suspension was stirred at 0 °C for 30 min, warmed to room temperature and stirred for 30 min before being re-cooled to 0 °C. Trisylimidazole **34** (11.5 g, 34.3 mmol) was then added as a solid in three portions under a constant stream of argon and the resulting reaction mixture was vigorously stirred at 0 °C for 1 h. The resulting thick suspension was quenched with H_2O (50 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 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%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.31 (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 ($CDCl_3$, 400 MHz): δ = 87.0, 72.1, 67.2, 49.5, 46.7, 45.5, 30.2. HRMS (EI) (m/z): calculated for $C_6H_7O_2$ $[M–CH_3]^+$ 111.0446, found 111.0441. IR (cm^{-1}): 3408, 3283, 2985, 2926, 1450, 1410, 1304, 1165, 1135, 1047. $[\alpha]_D^{20}$: –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(3*H*)-one (37): Under a constant stream of argon Na (1.08 g, 46.8 mmol) was added to EtOH (100 mL). After the disappearance of all solids, diethylmalonate (14.2 mL, 94 mmol) was added dropwise. After stirring at room temperature for 15 min, a solution of epoxide **36** (2.36 g, 18.7 mmol) in EtOH (100 mL) was added. The reaction mixture was stirred at room 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: ^{1}H 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), 2.05 (m, 1H), 1.56 (s, 3H), 1.31 (t, *J* = 1.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 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: ^{1}H 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), 2.03 (m, 1H), 1.55 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 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 (EI): (m/z): calculated for $C_{11}H_{13}O_5$ $[M\text{-}CH_3]^+$ 225.0763, found 225.0765. IR (cm^{-1}): 3473, 2984, 1767, 1450, 1371, 1260, 1156, 1095, 1035, 1008. $[\alpha]_D^{20}$= –33.5, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.51.

A solution of the malonate (3.8 g, 15.83 mmol) and LiCl (1.33 g, 31.66 mmol) in DMSO (32 mL) and water (1 mL) was heated to 155 °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 (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%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.0 (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), 2.43 (m, 1H), 2.09–1.89 (m, 3H), 1.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 400 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 $C_8H_9O_3$ $[M\text{-}CH_3]^+$ 153.0552, found 153.0557. IR (cm^{-1}): 3430, 3280, 2985, 2934, 1760, 1357, 1173, 1124, 1035, 1008. $[\alpha]_D^{20}$= –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(3*H*)-one (38): A solution of alcohol **37** (2.5 g, 14.9 mmol), paraformaldehyde (1.29 g, 44.6 mmol), *i*Pr_2NH (3.2 mL, 22.32 mmol) and CuBr (1.07 g, 7.45 mmol) in 1,4-dioxane (30 mL) was heated to 125 °C and stirred at this temperature for 6 h. The resulting greenish suspension was cooled to room temperature, filtered through a pad of Celite and sat. aq. NH_4Cl (10 mL) and H_2O (30 mL) were added. 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%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.31 (t, *J* = 6.6 Hz, 1H), 4.90 (d, *J* = 6.6 Hz, 2H), 4.79 (m, 1H), 2.51 (d, *J* = 9.7 Hz, 1H), 2.49 (d, *J* = 9.7 Hz, 1H), 2.36 (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 ($CDCl_3$, 400 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 $C_{10}H_{12}O_2$ $[M]^+$ 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. $[\alpha]_D^{20}$: –49.3, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.18.

To a solution of the tertiary allenic alcohol (4.2 g, 23.0 mmol) in THF (50 mL) were sequentially added 2,6-lutidine (8.0 mL, 69.1 mmol) and TMSOTf (6.3 mL, 34.6 mmol) at 0 °C. The cooling bath was removed and the reaction was quenched after 30 min 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%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.25 (t, *J* = 6.6 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 2H), 4.73 (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 ($CDCl_3$, 400 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 $C_{13}H_{22}O_3SiNa$ $[M+Na]^+$ 277.1233, found 277.1236. IR (cm^{-1}): 2955, 1956, 1773, 1249, 1154, 1110, 1078, 1001, 982, 916, 836. $[\alpha]_D^{20}$: –42.3, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.64.

2-Phenylselenyl-γ-butyrolactone 32: To a solution of lactone **39** (1.50 g, 5.9 mmol) in THF (30 mL) at −78 °C was added LiHMDS (1.0 M in toluene, 6.5 mL, 64.9 mmol) and TMSCl (0.83 mL, 64.9 mmol). The resulting mixture was stirred at −78 °C for 2 h before a solution of PhSeCl (1.24 g, 64.9 mmol) in THF (30 mL) was added within 10 min. After 30 min of stirring at −78 °C, the reaction was quenched with sat. aq. NH_4Cl (40 mL). The aqueous phase was extracted with diethyl ether (3 x 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%). ^{1}H 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 ($CDCl_3$, 400 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 $C_{19}H_{26}O_3SeSiNa$ $[M+Na]^+$ 433.0709, found 433.0715. IR (cm^{-1}): 2956, 1956, 1769, 1483, 1251, 1112, 1022, 840, 740. $[\alpha]_D^{20}$: –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 x 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. $Na_2S_2O_3$ (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 x 10 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (2 x 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74-7.67 (m, 4H), 7.44-7.37 (m, 6H), 7.25-7.20 (m, 3H), 7.05 (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), 4.54 (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 ($CDCl_3$, 400 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 $C_{46}H_{62}O_9Si_2Na$ $[M+Na]^+$ 837.3830, found 837.3823. IR (cm^{-1}): 3433, 2971, 2921, 2879, 1776, 1429, 1227, 1164, 1023, 973. $[\alpha]_D^{20}$: -13.7, ($CHCl_3$, 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 (SiO_2, Hex/EtOAc 8/1) leading to the isolation of a diastereomeric mixture of **40** (3 mg, 0.003 mmol, 10%). ^{1}H NMR ($CDCl_3$, 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), 3.84 (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 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{46}H_{62}O_9Si_2Na$ $[M+Na]^+$ 837.3830, found 837.3809. IR (cm^{-1}): 3433, 2971, 2921, 2879, 1776, 1429, 1227, 1164, 1023, 973. $[\alpha]_D^{20}$: -33.9, ($CHCl_3$, c = 0.08). R_f: (Hex/EtOAc 2/1) 0.60.

Ethyl 2-((3a*R*,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 PPh_3 (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 CH_2Cl_2 (400 mL) in a separatory funnel and vigorously shaken with 1 M NaOH (300 mL) for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were washed with sat. aq. NaCl (200 mL), dried with $MgSO_4$, 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 $CHCl_3$ (500 mL) was added via cannula to a solution of the ketone (35.4 g, 137.1 mmol) in $CHCl_3$ (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 H_2 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.77 (d, *J* = 3.8 Hz, 1H), 4.81 (t, *J* = 4.2 Hz, 1H), 4.16 (m, 2H), 4.10 (m, 1H), 3.98 (m, 1H), 3.95 (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), 2.33 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{16}H_{26}O_7Na$ $[M+Na]^+$ 353.1576, found 353.1586. IR (cm^{-1}): 2986, 2938, 1734, 1381, 1333, 1241, 1213, 1065, 1016, 847. $[\alpha]_D^{22}$: +69.0, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.70.

The crude diacetonide (20.0 g 63.2 mmol) was digested in AcOH/H_2O 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (d, *J* = 3.7 Hz, 1H), 4.78 (dd, *J* =4.6, 4.1 Hz, 1H), 4.16 (m, 2H), 3.84 (dd, *J* =10.0, 5.7 Hz, 1H), 3.77 (m, 1H), 3.7 (m, 2H), 2.78 (br s, 1H), 2.72 (d, *J* = 6.9 Hz, 2H), 2.39 (m, 1H), 2.25 (br s, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{13}H_{22}O_7Na$ $[M+Na]^+$ 313.1263, found 313.1256. IR (cm^{-1}): 3438, 2924, 2854, 1732, 1460, 1377, 1218, 1168, 1016, 772. $[\alpha]_D^{20}$= +10.0, ($CHCl_3$, 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 H_2O (20 mL). The solution was cooled to 0 °C and $NaIO_4$ (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 $NaBH_4$ (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 (SiO_2, Hex/EtOAc 1/1) yielding the desired α-D-ribofuranose **42** (13.5 g, 51.8 mmol, 82%). ^{1}H NMR ($CDCl_3$, 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, 5.4Hz, 1H), 2.04 (br s, OH), 1.50 (s, 3H), 1.32 (s, 3H), 1.27 (t, J= 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{12}H_{20}O_6Na$ $[M+Na]^+$ 283.1158, found 283.1153. IR (cm^{-1}): 3474, 2985, 2937, 1731, 1374, 1214, 1167, 1112, 1013, 874. $[\alpha]_D^{20}$: +62.9, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/1) 0.33.

(3a*R*,4*S*,6*R*,6a*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-methoxytetrahydrofuro[3,4-b]furan-2(3H)-one (43): A solution of α-D-ribofuranose **42** (9.8 g, 37.7 mmol) in MeOH (370 mL) and trifluoroacetic acid (60 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 (SiO_2, Hex/EtOAc 1/1 → 1/2) afforded the desired lactone as pale yellow oil (5.7 g, 81%). ^{1}H NMR ($CDCl_3$, 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), 3.22 (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). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 175.5, 107.8, 89.6, 87.7, 64.7, 55.9, 38.1, 34.1. HRMS (ESI) (m/z): calculated for $C_8H_{12}O_5Na$ $[M+Na]^+$ 211.0582, found 211.0582. IR (cm^{-1}): 3412, 2923, 1776, 1454, 1377, 1161, 1106, 1049, 959, 813. $[\alpha]_D^{25}$: -40.3, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 1/4) 0.29.

To a solution of the primary alcohol (4.1 g, 21.8 mmol) in CH_2Cl_2 (200 mL) was added imidazole (3.6 g, 52.3 mmol) as a solid in one portion under a stream of argon at room temperature. As the solids were dissolved, *tert*-butyldimethylsilyl chloride (3.9 g, 26.1 mmol) was added as a solid in three portions under an argon stream. After stirring at room temperature 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 CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with water (100 mL) and aq. sat. NaCl (100 mL), dried with $MgSO_4$ and filtered. After evaporation of all volatiles flash column chromatography (SiO_2, Hex/EtOAc 3/1) of the residue gave lactone **43** (6.0 g, 91%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 3.03 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{14}H_{26}O_5SiNa$ $[M+Na]^+$ 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. $[\alpha]_D^{20}$: -88.3, ($CHCl_3$, c = 0.6). R_f: (Hex/EtOAc 1/2) 0.73.

***tert*-Butyl(((2*S*,3*R*,4*R*,5*R*)-5-methoxy-4-((triethylsilyl)oxy)-3-(2-((triethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)methoxy)dimethylsilane (44):** 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 was added a solution of lactone **43** (11.7 g, 38.8 mmol) in diethyl ether (200 mL) within 30 min under vigorous stirring in a 1 L round-bottomed flask. After 1 h sat. aq. NH_4Cl (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 allowed to warm 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 $MgSO_4$. 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. ^{1}H NMR ($CDCl_3$, 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), 3.84 (m, 1H), 3.74 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.70 (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), 2.19 (m, 1H), 1.92-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{14}H_{30}O_5SiNa$ $[M+Na]^+$ 329.1760, found 329.1749. IR (cm^{-1}): 3394, 2929, 2857, 1471, 1254, 1103, 1061, 1036, 951, 837. $[\alpha]_D^{20}$: -28.2, ($CHCl_3$, 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 CH_2Cl_2 (150 mL) was added imidazole (9.7 g, 142.5 mmol) as a solid in one portion under a stream of argon at room temperature. As the solids were dissolved triethylsilyl chloride (13.1 mL, 78.2 mmol) was added within 15 min via syringe. The resulting pale yellow solution was aged at room temperature for 2 h during which a white precipitate formed. Sat. aq. NH_4Cl (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 $MgSO_4$. 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 (SiO_2, Hex/EtOAc 20/1). ^{1}H NMR ($CDCl_3$, 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), 2.13 (m, 1H), 1.85 (m, 1H), 1.57 (m, 1H), 0.96 (dt, J = 8.1, 4.3Hz, 18H), 0.91 (s, 9H), 0.61 (m, 12H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{26}H_{58}O_5Si_3Na$ $[M+Na]^+$ 557.3490, found 557.3477. IR (cm^{-1}): 2953, 2877, 1461, 1251, 1102, 1041, 1003, 958, 834, 775. $[\alpha]_D^{20}$: +6.9, ($CHCl_3$, c = 1.2).R_f: (Hex/EtOAc 10/1) 0.36.

2-((2*S*,3*R*,4*R*,5*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-methoxy-4-((triethylsilyl)oxy)tetrahydrofuran-3-yl)acetaldehyde (45): A flame dried 100 mL round-bottomed flask with a rubber septum was charged with CH_2Cl_2 (20 mL) and oxalyl chloride (2.0 mL, 23.4 mmol) and cooled to -78 °C under argon atmosphere. A bubbler was installed and dimethylsulfoxide (3.4 mL, 48.1 mmol) was added to the above solution within 5 min. After the evolution of gas had ceased the bubbler was removed and stirring was continued for further 10 min at -78 °C. To the resulting reaction mixture was dropwise added tetrahydrofuran **44** (2.5 g, 4.7 mmol) dissolved in CH_2Cl_2 (20 mL) via syringe within 10 min. The resulting solution was allowed to warm to -50 °C within 4 h. As TLC-analysis indicated full consumption of the starting material and formation of an intermediate (Hex/EtOAc 3/1, R_f = 0.18) the reaction mixture was cooled to -78 °C, followed by the dropwise addition of Et_3N (6.5 mL, 46.7 mmol). After stirring for 2 h, the reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (20 mL) 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 $MgSO_4$. Removal of the volatiles under reduced pressure and flash column chromatography (SiO_2, Hex/EtOAc 20/1) of the remaining residue gave aldehyde **45** (1.9 g, 97%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 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), 2.60 (m, 1H), 2.56 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{20}H_{42}O_5Si_2Na$ $[M+Na]^+$ 441.2468, found 441.2476. IR (cm^{-1}): 2955, 2929, 2879, 1728, 1462, 1254, 1127, 1108, 1039, 837. $[\alpha]_D^{20}$: +1.4, ($CHCl_3$, c = 1.2). R_f: (Hex/EtOAc 8/1) 0.68.

Butenolide 46: To a solution of butyrolactone **32** (2.0 g, 4.9 mmol) in THF (22 mL) was added LiHMDS (720 µL, 1.0 M in toluene, 5.6 mmol) at -40 °C within 10 min. After 30 min of stirring at that temperature 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. NH_4Cl (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 40 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. 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**.

The complex mixture was digested in a mixture of CH_2Cl_2 (50 mL) and pyridine (5 mL) in a round-bottomed and cooled to 0 °C. Under vigorous stirring H_2O_2 (3.7 mL, 32.6 mmol) was added and the resulting biphasic mixture was aged at this temperature for 1 h. The reaction was quenched by the addition of sat. aq. NaS_2O_3 (30 mL) and stirring was continued for additional 30 min. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 30 mL). After the combined organic phases were washed with water (50 mL) and sat. aq. NaCl (50 mL), $MgSO_4$ was added followed by filtration. Evaporation of the volatiles and flash column chromatography (SiO_2, 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: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30 (t, *J* = 1.5 Hz, 1H), 5.26 (t, *J* = 6.7 Hz, 1H), 5.21 (m, 1H), 4.84 (d, *J* = 6.5 Hz, 1H), 4.69 (s, 1H), 4.49 (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), 3.68 (m, 1H), 3.67 (m, 1H), 3.31 (s, 3H), 2.39 (m, 1H), 1.98-1.90 (m, 2H), 1.81 (dd, J = 14.3, 7.3 Hz, 1H), 1.65 (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). ^{13}C NMR ($CDCl_3$, 400 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: ^{1}H NMR ($CDCl_3$, 400 MHz): δ =7.31 (t, *J* = 1.4 Hz, 1H), 5.26 (t, *J* = 6.7 Hz, 1H), 5.21 (m, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.67 (s, 1H), 4.49 (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), 3.69 (m, 1H), 3.40 (d, *J* = 5.2 Hz, 1H), 3.31 (s, 3H), 2.33 (m, 1H), 2.20 (dd, *J* = 7.9, 2.6 Hz, 1H), 2.17 (dd, *J* = 7.9 Hz, 2.5 Hz, 1H), 1.94 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{62}O_8Si_3Na$ $[M+Na]^+$ 693.3650, found 693.3650. R_f: (Hex/EtOAc 3/1) 0.57.

Cage-shaped lactones 47 and 48 (+ 49 and 50): A diastereomeric mixture of **46** (dr = 1:1, 490 mg, 0.7 mmol) was dissolved in freshly degassed cyclohexane (four pump-freeze-thaw cycles, 80 mL). The resulting solution 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. Each of the charged quartz vials was placed 0.5 cm in front of a UV-C lamp (*SYLVANIA* G8W T5, 8W) in a home-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 (SiO_2, Hex/EtOAc 20/1) yielding undesired [4.2.0]ring systems **49** and **50** (76 mg, 15% combined yield) as well as the desired caged [2+2]-photocyclization products **47** (170 mg, 35%) and **48** (169 mg, 34%) as colorless oils. Analytic data for **47**: ^{1}H NMR ($CDCl_3$, 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), 3.13 (m, 1H), 2.45 (qd, *J* = 12.4, 1.7 Hz, 1H), 2.40 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{62}O_8Si_3Na$ $[M+Na]^+$ 693.3650, found 693.3629. IR (cm^{-1}): 3500, 2954, 1767, 1462, 1375, 1301, 1251, 1186, 1104, 988. $[\alpha]_D^{20}$: -38.7, ($CHCl_3$, c = 1.1). R_f: (Hex/EtOAc 4/1) 0.45. Analytical data for **48**: ^{1}H NMR ($CDCl_3$, 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), 3.11 (m, 1H), 3.05 (d, *J* = 5.7 Hz, 1H), 2.45 (qd, *J* = 12.4, 1.6 Hz, 1H), 2.41 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{62}O_8Si_3Na$ $[M+Na]^+$ 693.3650, found 693.3647. IR (cm^{-1}): 3484, 2954, 1768, 1462, 1348, 1251, 1187, 1106, 1040, 991. $[\alpha]_D^{20}$: -26.7, ($CHCl_3$, C = 0.6).R_f: (Hex/EtOAc 4/1) 0.39. Analytic data for **49:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.75 (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), 3.91 (m, 2H), 3.84 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.61 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.50 (m, 1H), 3.29 (s, 3H), 3.26 (m, 1H), 2.74 (dd, *J* = 13.4, 1.1

Hz, 1H), 2.31 (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 ($CDCl_3$, 400 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 $C_{33}H_{62}O_8Si_3Na$ $[M+Na]^+$ 693.3650, found 693.3650. IR (cm^{-1}): 3476, 2955, 2930, 1768, 1462, 1251, 1111, 1042, 1005, 839. $[\alpha]_D^{20}$: -44.1, ($CHCl_3$, c = 2.0). R_f: (Hex/EtOAc 4/1) 0.28.

Oxidation/reduction sequence of 48 to 47: 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 **48** (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. ^{1}H 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), 3.15 (m, 1H), 3.04 (dd, *J* = 19.4, 9.9Hz, 1H), 2.50 (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 ($CDCl_3$, 400 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 $C_{33}H_{60}O_8Si_3Na$ $[M+Na]^+$ 691.3494, found 691.3495. IR (cm^{-1}): 2955, 2929, 1769, 1714, 1464, 1252, 1149, 1108, 1039, 840. $[\alpha]_D^{20}$: -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 BH_3·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 misture 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 **47** and **48** (15 mg) in quantitative yield. For analytic data see above.

Cage shaped epoxide 52: A round-bottomed flask was charged with alcohol **47** (10 mg, 0.07 mmol) and a magnetic stirring bar and cooled to 0 °C. A freshly prepared solution of DMDO (0.4 mL, 0.08 M, 0.03 mmol) was added and 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 aged at room temperature for 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 additional 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 **47** (32 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (12mg, 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.19 (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), 2.37 (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), 0.10 (m, 15H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{62}O_9Si_3Na$ $[M+Na]^+$ 709,3555, found 709.3598. IR (cm^{-1}): 2955, 2930, 1768, 1462, 1376, 1252, 1143, 1040, 991, 840. $[\alpha]_D^{20}$: -32.0, ($CHCl_3$, c = 1.0).R_f: (Hex/EtOAc 4/1) 0.53.

The epoxide (21 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0 °C. Pyridine (7 µL, 0.09 mmol), acetic anhydride (6 µL, 0.06 mmol) and DMAP (1 mg, 0.01 mmol) were sequentially added to the reaction mixture. The round-bottomed flask was sealed with a stopper and the reaction mixture was allowed to warm 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. ^{1}H 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), 2.00 (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* = 8.0Hz, 9H), 0.92 (s, 9H), 0.69 (q, *J* = 8 Hz, 6H), 0.12 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 600 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 $C_{35}H_{64}O_{10}Si_3Na$ $[M+Na]^+$ 751.3705, found 751.3704. mp = 93 - 95 °C. IR (cm^{-1}): 2955, 2928, 1768, 1744, 1231, 1124, 1041, 991, 843, 776. $[\alpha]_D^{20}$: -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. ^{1}H 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 ($CDCl_3$, 400 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 $C_{35}H_{64}O_{10}Si_3Na$ $[M+Na]^+$ 751.3705, found 751.3694. IR (cm^{-1}): 2955, 2929, 1760, 1413, 1375, 1252, 1146, 1121, 1021, 838. $[\alpha]_D^{20}$: +28.4, ($CHCl_3$, c = 0.25). R_f: (Hex/EtOAc 3/1) 0.31.

Acetate 57: Alcohol **47** (250 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and cooled to 0 °C. Pyridine (90 µL, 1.12 mmol), acetic anhydride (70 µL, 0.70 mmol) and DMAP (5 mg, 0.04 mmol) were sequentially added to the reaction mixture. The round-bottomed flask was sealed with a stopper and 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. ^{1}H 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), 3.13 (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 ($CDCl_3$, 400 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 $C_{35}H_{64}O_9Si_3Na$ $[M+Na]^+$ 735.3756, found 735.3769. IR (cm^{-1}): 2954, 1772, 1747, 1462, 1372, 1251, 1150, 1040, 991, 840. $[\alpha]_D^{20}$: -15.8, ($CHCl_3$, c = 0.7). R_f: (Hex/EtOAc 5/1) 0.52.
The acylated substrate was digested in an AcOH/THF/H_2O 2/1/1 mixture (2.8 mL) and stirred at room temperature for 24 h. The resulting pale yellow solution was concentrated under reduced pressure and subsequently

co-evaporated with toluene (3 x 20 mL) till the smell of acetic acid was gone.
To the resulting crude colorless amorphous solid (144 mg) was added CH_2Cl_2 (4.0 mL) at room temperature. Under vigorous stirring imidazole (600 mg, 8.75 mmol) was added and the mixture was stirred till all solids were dissolved. Chlorotriethylsilane (650 µL, 3.85 mmol) was added to the resulting pale yellow solution 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. ^{1}H 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), 3.09 (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 ($CDCl_3$, 400 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 $C_{38}H_{70}O_9Si_3Na$ $[M+Na]^+$ 777.4225, found 777.4195. IR (cm^{-1}): 2954, 2877, 1772, 1371, 1230, 1150, 1040, 991, 807, 743. $[\alpha]_D^{22}$: -17.8, ($CHCl_3$, c = 0.7). R_f: (Hex/EtOAc 3/1) 0.59.

Acetate 58: Alcohol **48** (284 mg, 0.42 mmol) was subjected to the identical procedure as alcohol **47** (see above, **57**) giving the corresponding globally TES-protected acetate **58** (278 mg, 87%) as a colorless oil.
Analytic data for the intermediate: ^{1}H 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), 3.91 (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), 3.15 (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 ($CDCl_3$, 400 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 $C_{35}H_{64}O_9Si_3Na$ $[M+Na]^+$ 735.3756, found 735.3759. IR (cm^{-1}): 2954, 2878, 1774, 1748, 1461, 1372, 1250, 1149, 1040, 991. $[\alpha]_D^{20}$: -46.6, ($CHCl_3$, c = 1.5). R_f: (Hex/EtOAc 5/1) 0.48.
Analytic data for acetate **58**: ^{1}H 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 (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), 2.09 (m, 1H), 2.03 (s, 3H), 2.02 (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 ($CDCl_3$, 400 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 $C_{38}H_{70}O_9Si_3Na$ $[M+Na]^+$ 777.4225, found 777.4232. IR (cm^{-1}): 2955, 2877, 1775, 1749, 1229, 1150, 1108, 1077, 1042, 1001. $[\alpha]_D^{23}$: -45.9, ($CHCl_3$, c = 0.7). R_f: (Hex/EtOAc 3/1) 0.52.

Aldehyde 59: A flame dried 50 mL round-bottomed flask with a rubber septum was charged with CH_2Cl_2 (8 mL) and oxalyl chloride (660 µL, 7.7 mmol) and cooled to -78 °C in a dry ice/acetone cooling bath under argon atmosphere. A bubbler was installed and dimethylsulfoxide (1.1 mL, 15.5 mmol) was added within 5 min. After the evolution of gas had ceased the bubbler was removed and stirring was continued for further 10 min at -78 °C. To the resulting reaction mixture was dropwise added acetate **57** (1.16 g, 1.5 mmol) dissolved in CH_2Cl_2 (8 mL) via syringe within 10 min. The resulting solution was stirred at -78 °C for 3 h whereupon an intermediate formed (TLC, Hex/EtOAc 2/1, R_f = 0.23). Et_3N (2.2 mL, 15.5 mmol) was dropwise added to the reaction mixture. After 4 h the turbid solution was quenched by the addition of sat. aq. $NaHCO_3$ (15 mL) 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. ^{1}H 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), 3.08 (m, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.7 Hz, 1H), 2.17 (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* = 7.8Hz, 6H), 0.58 (q, *J* = 7.9Hz, 6H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{33}H_{53}O_{10}Si_2Na$ $[M+MeOH+Na]^+$ 693.3466, found 693.3467. IR (cm^{-1}): 2955, 2877, 1770, 1745, 1459, 1373, 1231, 1151, 1038, 808. $[\alpha]_D^{20}$: -39.3, ($CHCl_3$, c = 0.6). R_f: (Hex/EtOAc 2/1) 0.50.

Aldehyde 60: Aldehyde **60** (310 mg, 97%) was prepared according to the procedure for **59**. ^{1}H 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), 3.13 (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 ($CDCl_3$, 400 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 $C_{33}H_{53}O_{10}Si_2Na$ $[M+MeOH+Na]^+$ 693.3466, found 693.3458. IR (cm^{-1}): 2955, 2912, 2877, 1773, 1748, 1231, 1150, 1106, 1040, 1017. $[\alpha]_D^{23}$: -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 µL, 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. ^{1}H 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), 3.10 (m, 1H), 2.69 (d, *J* = 4.1 Hz, 1H, 1H), 2.48 (d, *J* = 2.2 Hz, 1H, 1H), 2.45 (m, 1H), 2.3 (m, 1H), 2.13 (m, 1H), 2.11 (s, 3H), 2.0 (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 ($CDCl_3$, 400 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 $C_{34}H_{56}O_9Si_2Na$ $[M+Na]^+$ 687.3361, found 687.3366. IR (cm^{-1}): 3484, 2955, 2877, 1770, 1745, 1459, 1231, 1151, 1039, 991. $[\alpha]_D^{20}$: -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, 66% brsm) was obtained as colorless oil. ^{1}H 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), 3.09 (m, 1H), 2.58 (m, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.6 Hz, 1H), 2.09 (s, 3H), 1.96-1.87 (m, 2H), 1.80 (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 ($CDCl_3$, 400 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 $C_{34}H_{54}Br_2O_9Si_2Na$ $[M+Na]^+$ 845.1550, found 845.1547. IR (cm^{-1}): 2955, 2877, 2349, 1770, 1702, 1460, 1373, 1232, 1151, 1042. $[\alpha]_D^{20}$: -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 µL) were added via Pasteur

pipette to a solution of aldehyde **59** (24 mg, 0.04mmol) in 2-methyl-2-butene (300 µL) and *t*BuOH (800 µL) 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 $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, Hex/EtOAc 1/1) afforded desired acid **67** (24 mg, 0.37 mmol, 98%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 3.4-3.3 (m, 1H), 3.10-3.08 (m, 1H), 2.44 (qd, *J* = 12.4, 1.7 Hz, 1H), 2.24 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{32}H_{54}NaO_{10}Si_2$ $[M+Na]^+$ 677.3153, found 677.3135. IR (cm^{-1}): 3218, 2922, 2853, 1769, 1743, 1460, 1374, 1231, 1137, 990. $[\alpha]_D^{20}$: -14.7, ($CHCl_3$, c = 0.5). R_f: (Hex/EtOAc 1/1) 0.14.

(3a*R*,5*S*,6*R*,6a*R*)-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. NH_4Cl (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 $MgSO_4$, 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 CH_3CN/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. $Na_2S_2O_3$ (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.^{1}H NMR ($CDCl_3$, 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), 3.41 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{14}H_{23}IO_5Na$ $[M+Na]^+$ 421.0488, found 421.0485. IR (cm^{-1}): 2986, 2934, 1454, 1380, 1256, 1214, 1171, 1065, 1017, 847. $[\alpha]_D^{20}$: +76.5, ($CHCl_3$, 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. NH_4Cl (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 $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography (SiO_2, Hex/EtOAc 6/1) gave desired diacetonide **73** (7.7 g, 28.5 mmol, 97%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{14}H_{22}O_5Na$ $[M+Na]^+$ 293.1365, found 293.1362. IR (cm^{-1}): 2986, 2935, 1372, 1251, 1214, 1167, 1102, 1065, 1015, 848. $[\alpha]_D^{22}$: +94.5, ($CHCl_3$, c = 1.0). R_f: (Hex/EtOAc 2/1) 0.38.

Triethyl(((2*S*,3*R*,4*R*,5*R*)-5-methoxy-4-((triethylsilyl)oxy)-3-vinyltetrahydrofuran-2-yl)methoxy)silane (74): To a solution of diacetonide **73** (330 mg, 1.22 mmol) in MeOH (13 mL) was added acetyl chloride (260 µL, 3.66 mmol) at 0 °C. The resulting solution was warmed to room temperature and stirred for 3 h. Et_3N (1 mL) was added and the volatiles were removed under reduced pressure. The remaining white residue was subjected to column chromatography (SiO_2, EtOAc) giving the desired triol (170 mg, 0.83 mmol, 68%) as colorless gum. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_9H_{16}O_5Na$ $[M+Na]^+$ 227.0895, found 227.0891. IR (cm^{-1}): 3363, 2926, 1438, 1420, 1306, 1195, 1154, 1103, 1033, 943. $[\alpha]_D^{22}$: +10.5, ($CHCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 132.3, 120.1, 109.2, 83.1, 78.2, 63.2, 55.8, 46.3. HRMS (ESI) (m/z): calculated for $C_8H_{14}O_4Na$ $[M+Na]^+$ 197.0790, found 197.0783. IR (cm^{-1}): 3397, 2924, 1640, 1451, 1352, 1305, 1248, 1092, 1035, 970. $[\alpha]_D^{22}$: +14.6, ($CHCl_3$, c = 0.7). R_f: (EtOAc) 0.5.

To a solution of the crude diol (8.1 g, 46.5 mmol) in CH_2Cl_2 (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 $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, Hex/EtOAc 30/1) afforded **74** (17.8 g, 44.2 mmol, 96%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{20}H_{42}O_4Si_2Na$ $[M+Na]^+$ 425.2519, found 425.2518. IR (cm^{-1}): 2954, 2912, 2877, 1459, 1415, 1239, 1120, 1042, 1004, 917. $[\alpha]_D^{20}$: +12.1, ($CHCl_3$, c = 1.2). R_f: (Hex/EtOAc 2/1) 0.89.

(2*S*,3*R*,4*R*,5*R*)-5-Methoxy-4-((triethylsilyl)oxy)-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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.56 (d, *J* = 2.9 Hz, 1H), 5.88 (ddd, *J* = 17.1, 10.3, 8.8 Hz, 1H), 5.22 (m, 1H), 5.19 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{14}H_{26}O_4SiNa$ $[M+Na]^+$ 309.1498, found 309.1479. IR (cm^{-1}): 2955, 2832, 1737, 1460, 1415, 1314, 1239, 1120, 1002, 836. $[\alpha]_D^{20}$: +10.8, ($CHCl_3$, c = 0.65). R_f: (Hex/EtOAc 3/1) 0.45.

Triethyl(((2*R*,3*R*,4*R*,5*S*)-4-(iodomethyl)-2-methoxy-5-(((triethylsilyl)oxy)methyl)tetrahydrofuran-3-yl)oxy)silane (76): Through a solution of **74** (1.3 g, 3.2 mmol) in CH_2Cl_2/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 $NaBH_4$ (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 $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, Hex/EtOAc 10/1) gave the desired alcohol (1.0 g, 2.5 mmol, 76%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 2.27 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{19}H_{42}O_5Si_2Na$ $[M+Na]^+$ 465.3180, found 465.3172. IR (cm^{-1}): 3471, 2954, 2912, 2877, 1460, 1240, 1113, 1006, 957, 810. $[\alpha]_D^{20}$: -27.9, ($CHCl_3$, 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 CH_2Cl_2 (5.5 mL) was added a solution of freshly sublimated and crushed iodine (140 mg, 0.55 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was warmed to rt and stirred for 6 h. Sat. aq. NH_4Cl solution (10 mL) and sat. aq. $Na_2S_2O_3$ 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, 0.18mmol, 0.22 mmol, 81%) as colorless oil. ^{1}H 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 ($CDCl_3$, 400 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 $C_{19}H_{41}O_4Si_2Na$ $[M+Na]^+$ 539.1486, found 539.1487. IR (cm^{-1}): 2954, 2876, 1459, 1415, 1237, 1186, 1119, 1071, 1005, 888. $[\alpha]_D^{20}$: +21.9, ($CHCl_3$, c = 0.75). R_f: (Hex/EtOAc 5/1) 0.84.

2-((2S,3R,4R,5R)-5-Methoxy-4-((triethylsilyl)oxy)-2-(((triethylsilyl)oxy)methyl)tetrahydrofuran-3-yl)acetaldehyde (77): To a solution of **74** (250 mg, 0.62 mmol) in THF (6 mL) was added BH_3·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. $Na_2S_2O_3$ (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%). ^{1}H 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 ($CDCl_3$, 400 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 $C_{20}H_{44}O_5Si_2Na$ $[M+Na]^+$ 443.2625, found 443.2622. IR (cm^{-1}): 3458, 2954, 2912, 2877, 1459, 1415, 1239, 1128, 1041, 1005. $[\alpha]_D^{20}$: -9.7, ($CHCl_3$, c = 1.50). R_f: (Hex/EtOAc 6/1) 0.33.
At 0 °C SO_3·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 CH_2Cl_2/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. $Na_2S_2O_3$ (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. ^{1}H 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 ($CDCl_3$, 400 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 $C_{20}H_{42}O_5Si_2Na$ $[M+Na]^+$ 441.2468, found 441.2469. IR (cm^{-1}): 2955, 2912, 2877, 1728, 1458, 1386, 1239, 1107, 1007, 958. $[\alpha]_D^{20}$: +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. ^{1}H NMR (400 MHz, $CDCl_3$): 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 (400 MHz, $CDCl_3$): 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 $C_{11}H_{14}O_4Na$ $[M+Na]^+$: 233.0790, found: 233.0781. IR (cm^{-1}): 3370, 2925, 1743, 1352, 1158, 1056, 995, 906, 729, 647. $[\alpha]_D^{21}$: - 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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 (400 MHz, $CDCl_3$): 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 $C_{23}H_{42}O_4Si_2Na$ $[M+Na]^+$ 461.2519: , found: 461.2517. IR (cm^{-1}): 2954, 2876, 1773, 1458, 1239, 1146, 1107, 991, 805, 742. $[\alpha]_D^{24}$: - 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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 (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, 7.1 (3C), 23.1, 6.6 (3C). HRMS (ESI) (m/z): calculated for $C_{17}H_{26}O_4SiNa$ $[M+Na]^+$: 345.1498, found: 345.1490. IR (cm^{-1}): 2931, 2856, 1768, 1721, 1253, 1145, 1047, 987, 836, 775. $[\alpha]_D^{22}$: - 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*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 (5mL), 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. ^{1}H 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 ($CDCl_3$, 400 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 $C_{36}H_{68}O_8Si_3Na$ $[M+Na]^+$ 735.4120, found 735.4125. IR (cm^{-1}): 2954, 2876, 1767, 1460, 1376, 1300, 1240, 1104, 990, 906. $[\alpha]_D^{20}$: -38.7, ($CHCl_3$, c = 0.55). R_f: (Hex/EtOAc 4/1) 0.42.

(5S)-5-((S)-2-Methyl-2-((triethylsilyl)oxy)penta-3,4-dien-1-yl)-3-(phenylselanyl)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%). ^{1}H 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 ($CDCl_3$, 400 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 $C_{16}H_{28}O_3SiNa$ $[M+Na]^+$ 319.1705, found 319.1708. IR (cm^{-1}): 2953, 2876, 1957, 1777, 1459, 1379, 1155, 1110, 1003, 917. $[\alpha]_D^{20}$= -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. ^{1}H 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 ($CDCl_3$, 400 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, 37.9, 37.3, 27.6, 7.18 (3C), 7.15 (3C), 6.62 (3CH), 6.59 (3CH). HRMS (ESI) (m/z): calculated for $C_{22}H_{32}O_3SeSiNa$ $[M+Na]^+$ 475.1184, found 475.1190. IR (cm^{-1}): 2954, 2875, 1956, 1770, 1458, 1414, 1354, 1180, 1112, 1003. $[\alpha]_D^{20}$: -23.7, ($CHCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{36}H_{68}O_8Si_3Na$ $[M+Na]^+$ 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**: ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{36}H_{68}O_8Si_3Na$ $[M+Na]^+$ 735.4120, found 735.4123. IR (cm^{-1}): 2955, 2912, 2877, 1769, 1459, 1414, 1240, 1107, 1042, 1006. $[\alpha]_D^{20}$ -107.1, ($CHCl_3$, 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 solution of the aldehyde **59** (207 mg, 0.3 mmol) in CH_2Cl_2 (3.5 mL) was added $NaHCO_3$ (82 mg, 0.1 mmol) at 0 °C. *m*CPBA (111 mg, 0.7 mmol), which was purified by extraction of a solution in diethyl ether with pH 7.5 buffer, was added as a solid in one portion to the vigorously stirred suspension. The resulting heterogeneous mixture was stirred at 0 °C for 2 h after which dimethyl sulfide (300 µL, 4 mmol) was added. After additional 30 min diethyl ether (10 mL) and sat. aq. NH_4Cl (10 mL) were added. The aqueous phase was separated and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and sat. aq. NaCl (15 mL). After drying with $MgSO_4$ and filtration, the volatiles were removed under reduced pressure. Purification of the remaining residue by flash column chromatography (SiO_2, Hex/EtOAc 8/1) gave desired formate **89** (169 mg, 79%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 3.10 (m, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.7 Hz, 1H), 2.36 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{32}H_{54}O_{10}Si_2Na$ $[M+Na]^+$ 677.3153, found 677.3136. IR (cm^{-1}): 2955, 2877, 1769, 1740, 1227, 1152, 1111, 1039, 1017, 990. $[\alpha]_D^{25}$= -9.3, ($CHCl_3$, 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: Formate **89** (186 mg, 0.28 mmol) and bromoallylsilane **90** (112 µL, 0.65 mmol) were dissolved in CH_2Cl_2 (5.6 mL) and cooled to -78 °C. To the resulting slightly turbid mixture was dropwise added $SnCl_4$ (454 µL, 0.45 mmol) via syringe at -78 °C. After complete addition the reaction was stirred till TLC-analysis (Hex/EtOAc 6/1) indicated full consumption of the starting aldehyde). In the following, MeOH/sat. aq. $NaHCO_3$ 2/1 (4 mL) and diethyl ether (6 mL) were sequentially added. The resulting heterogenic mixture was allowed to warm 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 $MgSO_4$ 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. ^{1}H NMR ($CDCl_3$, 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), 3.11 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{36}H_{64}BrN_2O_8Si_2$ $[M+H_3CCN+NH_4]^+$ 789.3364, found 789.3349. IR (cm^{-1}): 2954, 2877, 1770, 1747, 1459, 1372, 1226, 1151, 1049, 990. $[\alpha]_D^{25}$: -50.1, ($CHCl_3$, c = 1.5). R_f: (Hex/EtOAc 3/1) 0.55.

Macrocycle 91: A round bottomed flask was charged with vinyl bromide **86** (14 mg, 0.02 mmol) in freshly degassed toluene (0.8 mL). $Pd(OAc)_2$ (0.5 mg, 0.002 mmol), triphenylphosphine (1 mg, 0.004 mmol), Ag_2CO_3 (16 mg, 0.058 mmol) and crushed 4 Å molecular sieve (100 mg) were added. The reaction was stirred at 80 °C for 3 d and allowed to cool 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 $MgSO_4$. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO_2, 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 $C_{36}H_{63}N_2O_8Si_2$ $[M+CH_3CN+NH_4]^+$ 707.4117, found 707.4108.

Macrocycle 92: A round bottomed flask was charged with vinyl bromide **86** (20 mg, 0.027 mmol), NaOAc (11 mg, 0.13 mmol), Bu_4NCl (15 mg, 0.053 mmol) and crushed 4 Å molecular sieve (150 mg). Freshly degased in DMF (2.7 mL) was added at room temperature under an argon atmosphere. $Pd(OAc)_2$ (0.6 mg, 0.003 mmol) 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. After 1.5 h at 85 °C no starting material was left. The reaction mixture was allowed to cool 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 $MgSO_4$. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO_2, 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**: ^{1}H NMR ($CDCl_3$, 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), 3.10 (m, 1H), 2.55 (dd, *J* = 15.1, 10.8 Hz, 1H), 2.45 (ddd, *J* = 14.7, 7.8, 1.7 Hz, 1H), 2.34 (m, 1H), 2.33 (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). ^{13}C NMR ($CDCl_3$, 600 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 $C_{36}H_{60}NaO_{10}Si_2$ $[M+H_3CCN+NH_4]^+$ 731.3623, found 731.3628. IR (cm^{-1}): 2955, 2915, 1769, 1371, 1226, 1207, 1101, 1051, 1018, 990. $[\alpha]_D^{15}$= -50.8, ($CHCl_3$, 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), K_2CO_3 (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 $MgSO_4$. Filtration of the solids, removal of the volatiles under reduced pressure and flash column chromatography (SiO_2, Hex/EtOAc 8:1) of the residue gave vinyl nitrile **93** (7 mg, 50%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 3.12 (m, 1H), 2.58 (dd, *J* = 14.1, 11.2 Hz, 1H), 2.46 (ddd, *J* = 14.8, 7.9, 0.8 Hz, 1H), 2.39 (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), 1.87 (m, 2H), 1.42 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9 H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 400 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 $C_{37}H_{64}N_3O_8Si_2$ $[M+H_3CCN+NH_4]^+$ 734.4226, found 734.4215. IR (cm^{-1}): 2955, 2914, 2877, 1769, 1747, 1373, 1227, 1152, 1050, 990. $[\alpha]_D^{18}$: -69.4, ($CHCl_3$, 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 µL, 0.23 mmol) in CH_2Cl_2 (800 µL) was dropwise added $SnCl_4$ (120 µL, 1.0 M in CH_2Cl_2, 0.12 mmol) at -78 °C. The reaction mixture was stirred at his temperature for 4 h. A suspension of sat. aq. $NaHCO_3$/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 $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, 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: ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{36}H_{62}O_9Si_2Na$ $[M+Na]^+$ 717.3830, found 717.3833. IR (cm^{-1}): 2958, 2933, 2909, 1775, 1752, 1238, 1147, 1101, 1015, 988. $[\alpha]_D^{20}$: -43.3, ($CHCl_3$, c = 0.4). R_f: (Hex/EtOAc 2/1) 0.48.

Homoallylic alcohol 95: Aldehyde **59** (26 mg, 0.04 mmol) and allyltrimethylsilane (26 µL, 0.16 mmol) were treated with $SnCl_4$ (81 µL, 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: ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{37}H_{67}N_2O_9Si_2$ $[M+CH_3CN+NH_4Cl]^+$ 739.4385, found 739.4388. IR (cm^{-1}): 2962, 2946, 2928, 1781, 1741, 1243, 1178, 1119, 1024, 998. $[\alpha]_D^{20}$: -11.7, ($CHCl_3$, c = 0.2). R_f: (Hex/EtOAc 2/1) 0.50.

Homoallylic alcohol 96: Aldehyde **60** (30 mg, 0.05 mmol) and allyltrimethylsilane (26 µL, 0.16 mmol) were treated with $SnCl_4$ (71 µL, 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: ^{1}H NMR ($CDCl_3$, 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), 3.13 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{37}H_{67}N_2O_9Si_2$ $[M+CH_3CN+NH_4Cl]^+$ 739.4385, found 739.4388. IR (cm^{-1}): 2955, 2935, 2912, 1773, 1748, 1231, 1153, 1105, 1040, 1017. $[\alpha]_D^{20}$: -44.0, ($CHCl_3$, 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 µL, 0.16 mmol) were treated with $SnCl_4$ (71 µL, 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: ^{1}H NMR ($CDCl_3$, 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), 3.37 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{36}H_{62}O_9Si_2Na$ $[M+Na]^+$ 717.3830, found 717.3836. IR (cm^{-1}): 3490, 2956, 2877, 1774, 1459, 1373, 1236, 1150, 1106, 997. $[\alpha]_D^{24}$: -35.6, ($CHCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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), 3.09 (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). ^{13}C NMR ($CDCl_3$, 400 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 $C_{70}H_{120}O_{18}Si_4Na$ $[M+Na]^+$ 1383.7449, found 1383.7454. IR (cm^{-1}): 2956, 2914, 2877, 2369, 1771, 1746, 1373, 1222, 1151, 1043. $[\alpha]_D^{20}$= -5.0, ($CHCl_3$, 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 µL, 0.23 mmol) in CH_2Cl_2 (700 µL) was treated with TMSOTf (27 µL, 0.15 mmol) at 0 °C. The resulting mixture was stirred for 3 h, sat. aq. NH_4Cl (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 $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, Hex/EtOAc 6/1) gave TMS protected allylic alcohol **111** (27 mg, 0.04 mmol, 76%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 5.22-517 (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), 3.75 (m, 1H), 3.43 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.31 (s, 3H), 3.13 (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). ^{13}C NMR ($CDCl_3$, 400 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. $[\alpha]_D^{20}$: -51-8, ($CHCl_3$, 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 µL, 2.80 mmol) was added via syringe and the resulting mixture was warmed to room temperature. After 16 h sat. aq. NH_4Cl (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 $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, Hex/EtOAc 3/1) of the residue afforded desired propargyl ether **115** (184 mg, 0.94 mmol, 99%) as colorless oil. ^{1}H NMR (d^6-DMSO, 400 MHz): δ = 6.05 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.89 (*J* = 5.6, 1.2 Hz, 1H), 4.70 (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). ^{13}C NMR (d^6-DMSO, 400 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 $C_{10}H_{13}O_3$ $[M-CH_3]^+$ 181.0865, found 181.0862. IR (cm^{-1}): 3290, 2930, 1632, 1444, 1361, 1270, 1142, 1095, 1031, 916. $[\alpha]_D^{20}$: -88.7, ($CHCl_3$, c = 0.54). R_f: (Hex/EtOAc 3/1) 0.42.

Poly-cycle 119: To a solution of propargyl ether **91** (66 mg, 0.34 mmol) in CH_2Cl_2 (3.5 mL) was added $Co_2(CO)_8$ (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 (SiO_2, Hex/EtOAc 3/1) leading to the isolation of dimer **119** (10 mg, 0.02 mmol, 90%) as colorless oil. ^{1}H NMR ($CDCl_3$, 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), 3.48 (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). ^{13}C NMR ($CDCl_3$, 400 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. $[\alpha]_D^{22}$: -75.9, ($CHCl_3$, 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

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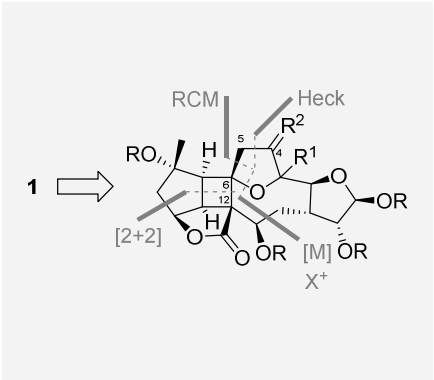
Entry for the Table of Contents ((Please choose one layout.))

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 /

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

Farcet, Jean-Baptiste; Himmelbauer, Martin; Mulzer, Johann

European Journal of Organic Chemistry **2013**, submitted (June 13th, 2013).

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Product characterization and analytic work: Jean-Baptiste Farcet
Preparation of the manuscript: Jean-Baptiste Farcet and Johann Mulzer

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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.xxxxxxxxx.

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]-[7] including ours.[8]-[9] In the preceding paper[10] 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.

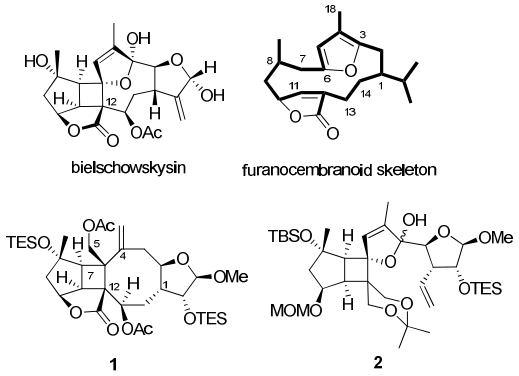
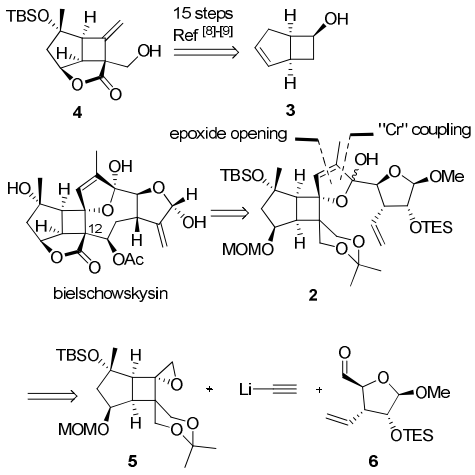


Figure 1. Bielschowskysin and the furanocembranoid skeleton, as well as two advanced synthetic intermediates **1** and **2**.

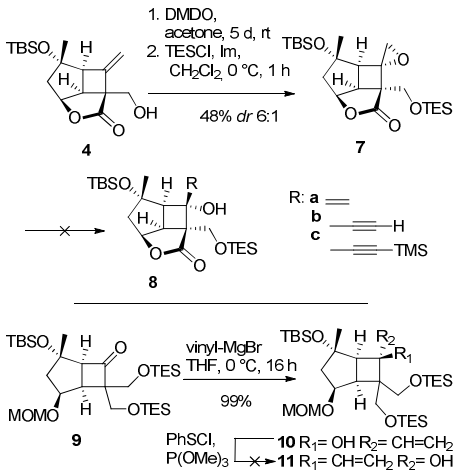
Results and Discussion

We recently published a stereoselective and optimized scalable synthesis of the tricyclic alcohol **4** from known alcohol **3**.[8]-[9] 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.

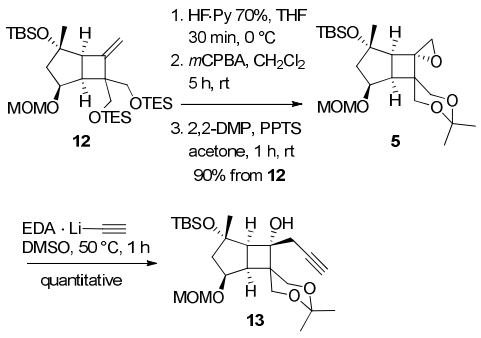
Hence, **4** was epoxidized with a *dr* of 6:1 from the convex side of the tricycle. TES protection furnished precursor **7**, which failed to deliver the allylic alcohol **8a** with Alcaraz protocol[11] (trimethylsulfonium iodide and *n*BuLi) or the homopropargylic alcohols **8b-c** with acetylides. A similar epoxide inertness towards nucleophiles has been observed in our previous approach.[10]



Scheme 2. Unfruitful formation of the tertiary alcohol.

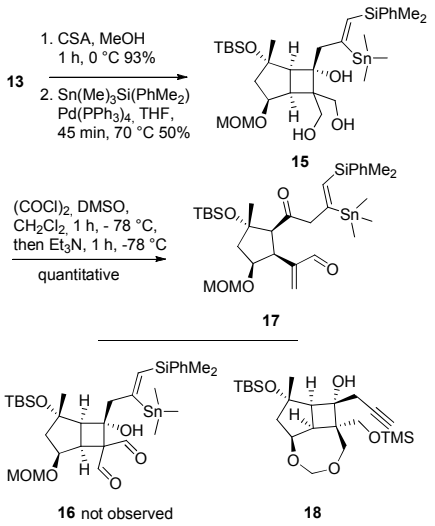
Finally, allylic alcohol **10** was readily formed from ketone **9**,[8]-[9] but the undesired configuration of the tertiary alcohol could not be inverted via the Mislow-Evans rearrangement protocol (Scheme 2).[12]

Reasoning that the presence of the lactone bridge strongly interferes with epoxide openings at the vicinal position, we returned to our previous intermediate **12**,[8]-[9] 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).



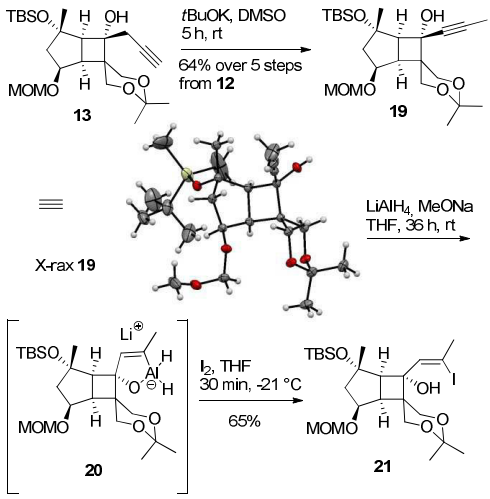
Scheme 3. Epoxide opening and formation of **13**.

In parallel, diastereomerically and enantiomerically pure aldehyde **6** was prepared in 11 steps from D-(+)-glucose.[10] A number of procedures for coupling of fragments **6** and **13** were tested. As Takai conditions[13] failed, ($CrCl_2$, $NiCl_2$, H_2O, PPh_3, 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 furnished dialdehyde **16**. Instead, enone **17** was obtained as the single product (Scheme 4), presumably via base induced Grob-type fragmentation[14] 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**.

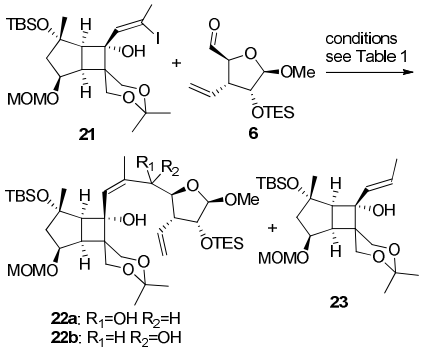
To avoid fragmentation, tertiary alcohol **13** was protected with TMSOTf and 2,6-lutidine. Unfortunately, yet not unexpectedly, this afforded **18** as sole product (Scheme 4).[15] Hence, we decided to carry on without protection and to use the tertiary alcohol as an anchor for the formation of the envisaged vinyl halide. First, according to an established protocol [16] (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.[17] 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).[18]



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[19]-[20] 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**.

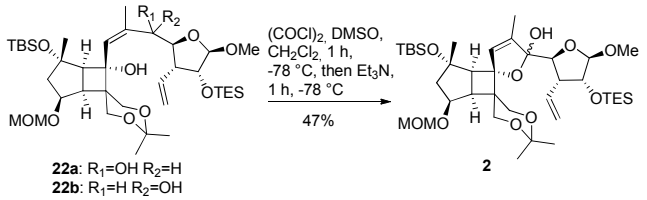
Table 1. Optimization of the NHK coupling reaction.

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	$CrCl_3$/$LiAlH_4$ + $NiCl_2$ (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	$CrCl_2$ + $Ni(acac)_2$ (2) in DMSO rt	54 (3.0:1)	39
14	$CrCl_2$ + $NiCl_2$ (2) in DMSO rt	**64** (2.4:1)	25

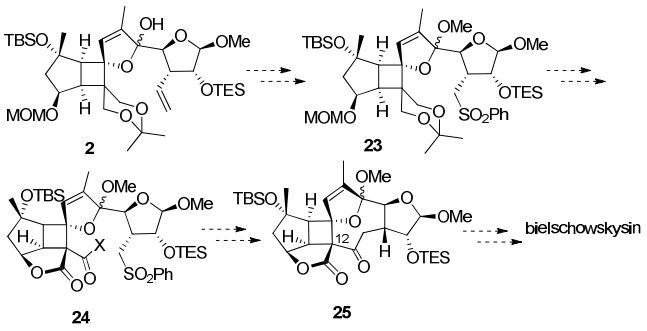
Standard conditions: 0.05 M, 50 mg of **21**, 2 equiv. of **6**, 5 equiv. of [Cr] + co-catalyst.[a] isolated yield, [b] addition of **21** by syringe pump over 1 h, [c] in ultra sound bath. n.d. not determined.

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 $CrCl_2$ 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 $NiCl_2$, 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.[8]-[9] Base induced cyclization and reductive removal of the sulfone[21] 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 **1**. So this will be our preferred line, and **2** will remain in evidence 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 Et_2O (10 mL/0.1 mmol) and NH_4Cl (7 mL/0.1 mmol), the phases were separated and the aqueous phase was extracted with Et_2O (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 $MgSO_4$ and concentrated under reduced pressure.

(1*S*,1a*R*,3a*S*,5*S*,5a*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-5-methyl-1a-{[(triethylsilyl)oxy]methyl}hexahydro-2*H*-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 CH_2Cl_2 (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 (SiO_2, 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}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}C-NMR (400 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 $C_{23}H_{42}O_5Si_2$ Na $[M+Na]^+$: 477.2468, found: 477.2454. IR(cm^{-1}): 2954, 2877, 1770, 1461, 1254, 1142, 1103, 990, 834, 729. $[\alpha]_D^{22}$ -41.8 (c = 0.55; $CHCl_3$). R_f: (Hex/EtOAc 5/1) 0.44.

(1*S*,2*S*,4*S*,5*R*,6*R*)-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 Et_2O, 564 µL, 0.56 mmol) was added to a solution of ketone **9** (200 mg, 0.28 mmol) dissolved in Et_2O (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 172 mg (99 %) of alcohol **10** as colorless oil. ^{1}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}C-NMR (400 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 $C_{32}H_{66}O_6Si_3Na$ $[M+Na]^+$: 653.4065, found 653.4068. IR(cm^{-1}): 2954, 2878, 1461, 1253, 1100, 1046, 1004, 834, 806, 742. $[\alpha]_D^{22}$ -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'-trimethyldispiro[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}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}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(3C), 24.0, 18.1, -2.2, -2.3 ppm. HRMS (ESI) (m/z): $[M+Na]^+$ calculated for $C_{19}H_{36}O_5SiNa$: 395.2230, found: 395.2219. IR(cm^{-1}): 3435, 2929, 1462, 1372, 1253, 1151, 1106, 1034, 835, 772. $[\alpha]_D^{20}$: - 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. $Na_2S_2O_3$ (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}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, 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}C-NMR (400 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 $C_{19}H_{36}O_6Si$ [M]: 388.2276, found: 388.2263. IR(cm^{-1}): 3470, 2928, 2855, 1254, 1152, 1103, 1036, 979, 832, 773. $[\alpha]_D^{20}$ -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 1,1-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 acetonide **5** 2.18 g (90%) as colorless oil. ^{1}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}C-NMR (400 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 $C_{22}H_{40}O_6SiNa$ $[M+Na]^+$: 451.2492, found: 451.2500. IR(cm^{-1}): 2933, 2856, 1467, 1371, 1256, 1152, 1080, 1045, 834, 774. $[\alpha]_D^{25}$ -59.7 (c = 0.3; $CHCl_3$). R_f: (Hex/EtOAc 2/1) 0.36.

(1*R*,2*S*,4*S*,5*S*,7*S*)-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}H-NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, *J* = 6.3 Hz, 1H), 6.54 (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}C-NMR (400 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 $C_{24}H_{42}O_6SiNa$ $[M+Na]^+$: 477.2648, found: 477.2643. IR(cm^{-1}): 3464, 2928, 2855, 1200, 1151, 1107, 1073, 1042, 834, 773. $[\alpha]_D^{20}$ -31.3 (c = 1.0; $CHCl_3$). R_f: (Hex/EtOAc 4/1) 0.20.

(1*S*,2*S*,4*S*,5*R*,6*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-6-[(2*Z*)-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 acetonide **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}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 (ddd, 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}C-NMR (400 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 $C_{21}H_{38}O_6SiNa$ $[M+Na]^+$: 437.2335, found: 437.2322. IR(cm^{-1}): 3413, 2952, 2856, 1254, 1157, 1104, 1037, 976, 836, 774. $[\alpha]_D^{25}$ +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 trimethylstannyldimethylphenyl silane (29 µL, 0.07 mmol) followed by $Pd(PPh_3)_4$ (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}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), 4.02-3.8 (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}C-NMR (400 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 $C_{32}H_{58}O_6Si_2SnNa$ $[M+Na]^+$: 737.2692, found: 737.2693. IR(cm^{-1}): 3390, 2953, 2856, 1253, 1157, 1110, 1036, 836, 731, 702. $[\alpha]_D^{23}$ -15.0 (c = 0.6; $CHCl_3$). R_f: (Hex/EtOAc 3/1) 0.23.

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

of oxalyl chloride (9 µL, 0.11 mmol) in CH_2Cl_2 (0.6 mL) at -78 °C was added DMSO (14 µL, 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 µL, 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}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}C-NMR (400 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 $C_{32}H_{54}O_5Si_2SnNa$ $[M+Na]^+$: 717.2429, found: 717.2433. IR(cm^{-1}): 2927, 2853, 2358, 1695, 1252, 1150, 1111, 1043, 835, 773. $[\alpha]_D^{20}$ –23.1 (c = 0.33; $CHCl_3$). R_f: (Hex/EtOAc 10/1) 0.36.

(1*S*,1a*R*,2*S*,3a*S*,7a*R*,7b*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methyl-1-(prop-2-yn-1-yl)-7a-{[(trimethylsilyl)oxy]methyl}octahydro-4,6-dioxacyclobuta[*cd*]azulen-1-ol (**18**): To a solution of acetonide **13** (192 mg, 0.42 mmol) in CH_2Cl_2 was sequentially added 2,6-lutidine (221 µL, 1.90 mmol) and TMSOTf (229 µL, 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}H-NMR (400 MHz, $CDCl_3$): δ = 4.91 (d, *J* = 5.3 Hz, 1H), 6.75 (d, *J* = 5.5 Hz, 1H), 4.63 (q, *J* = 8.3 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 9.98 (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}C-NMR (400 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 $C_{23}H_{42}O_5Si_2Na$ $[M+Na]^+$: 477.2468, found: 477.2473. IR(cm^{-1}): 2953, 2928, 2854, 1253, 1168, 1102, 1073, 1014, 838, 773. $[\alpha]_D^{20}$ -7.0 (c = 0.5; $CHCl_3$). R_f: (Hex/EtOAc 4/1) 0.57.

(1*R*,2*S*,4*S*,5*S*,7*R*)-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}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, 3H), 0.81 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. ^{13}C-NMR (400 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 $C_{24}H_{42}O_6SiNa$ $[M+Na]^+$: 477.2648, found: 477.2637. IR(cm^{-1}): 3448, 2928, 2855, 1372, 1257, 1151, 1078, 1044, 835, 773. mp: 124-125 °C. $[\alpha]_D^{22}$ -45.9 (c = 1.2; $CHCl_3$). R_f: (Hex/EtOAc 4/1) 0.13. X-ray: see ref [17]

(1*R*,2*S*,4*S*,5*S*,7*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-7-[(1*Z*)-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 µL, 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}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}C-NMR (400 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 $C_{24}H_{43}O_6SiINa$ $[M+Na]^+$: 605.1771, found: 605.1751. IR(cm^{-1}): 2929, 2856, 1255, 1200, 1152, 1098, 1072, 1045, 835, 774. $[\alpha]_D^{22}$ -25.1 (c = 0.45; $CHCl_3$). R_f: (Hex/EtOAc 3/1) 0.37.

(1*R*,2*S*,4*S*,5*S*,7*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-7-[(1*Z*)-3-{(2*S*,3*R*,4*R*,5*R*)-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 µmol) and aldehyde **6** (49 mg, 172 µmol) was dried by azeotrope distillation in benzene. The dried starting materials were dissolved in degassed DMSO (1.8 mL) and $CrCl_2$ (74 mg, 601 µmol) and $NiCl_2$ (33 mg, 257 µmol) 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}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}C-NMR (400 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 $C_{38}H_{70}O_{10}Si_2Na$ $[M+Na]^+$: 765.4405, found: 765.4427. IR(cm^{-1}): 3452, 2953, 2358, 1372, 1256, 1199, 1077, 1044, 1002, 835. $[\alpha]_D^{20}$ -31.2 (c = 0.25; $CHCl_3$). R_f: (Hex/EtOAc 5/1) 0.16.

Minor diastereoisomer **22b** ^{1}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}C-NMR (400 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 $C_{38}H_{70}O_{10}Si_2Na$ $[M+Na]^+$: 765.4405, found: 765.4396. IR(cm^{-1}): 3464, 2973, 2339, 1381, 1261, 1190, 1065, 1041, 1023, 834. $[\alpha]_D^{22}$ -30.0 (c = 0.5; $CHCl_3$). R_f: (Hex/EtOAc 5/1) 0.30.

(1*R*,2*S*,4*S*,5*S*,7*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-4-(methoxymethoxy)-2,2',2'-trimethyl-7-[(1*E*)-prop-1-en-1-yl]spiro[bicyclo[3.2.0]heptane-6,5'-[1,3]dioxan]-7-ol (**23**): ^{1}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}C-NMR (400 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 $C_{24}H_{44}O_6SiNa$ $[M+Na]^+$: 479.2805, found: 479.2796. IR(cm^{-1}): 2930, 2856, 1372, 1255, 119, 1106, 1073, 1043, 835, 773. $[\alpha]_D^{21}$ -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 µL, 30 µmol) in CH_2Cl_2 (0.3 mL) at -78 °C was added DMSO (4.2 µL, 59 µmol). The solution was stirred at -78 °C for 20 min. Alcohol **22** (11 mg, 15 µmol) 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 µL, 89 µmol) 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}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}C-NMR (400 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 $C_{38}H_{68}O_{10}Si_2Na$ $[M+Na]^+$: 763.4249, found: 763.4247. IR(cm^{-1}): 3469, 2927, 1409, 1256, 1205, 1111, 1046, 1001, 834, 773. $[\alpha]_D^{22}$ +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 ^{1}H NMR and ^{13}C NMR spectra of all products as well as COSY, HMBC, HSQC and NOESY spectra of **22a**.

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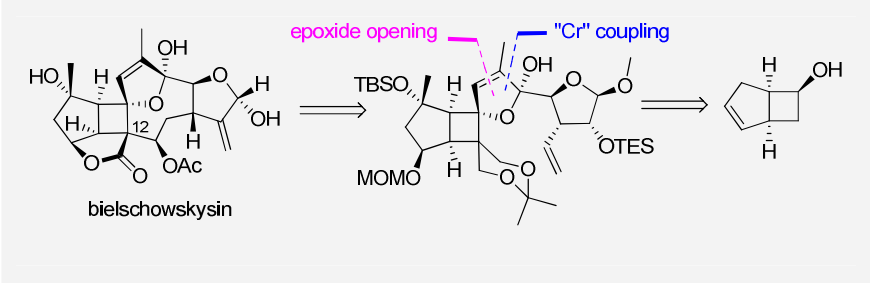

An approach to the northern part of the complex diterpenoid bielschowskysin is described. Formation of the dihydrofuran ring moiety was achieved by stereoselective epoxidation, followed by alkyne opening and stereoselective formation of a vinyl halide suitable for a chromium mediated coupling. A final oxidation step furnished the hemiacetal.

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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

Supporting Information

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

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SUPPORTING INFORMATION

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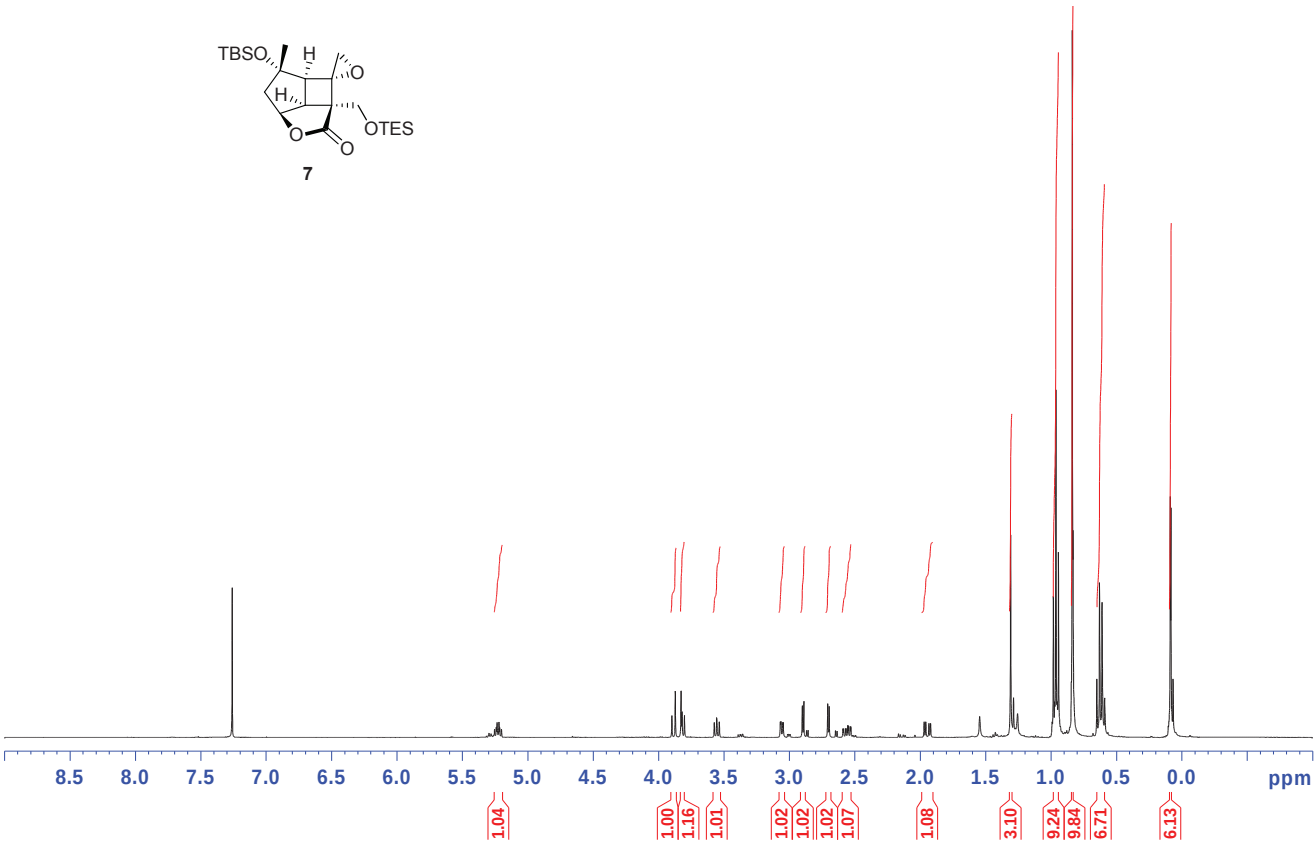
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1.04
1.00
1.16
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1.02
1.02
1.02
1.07
1.08
3.10
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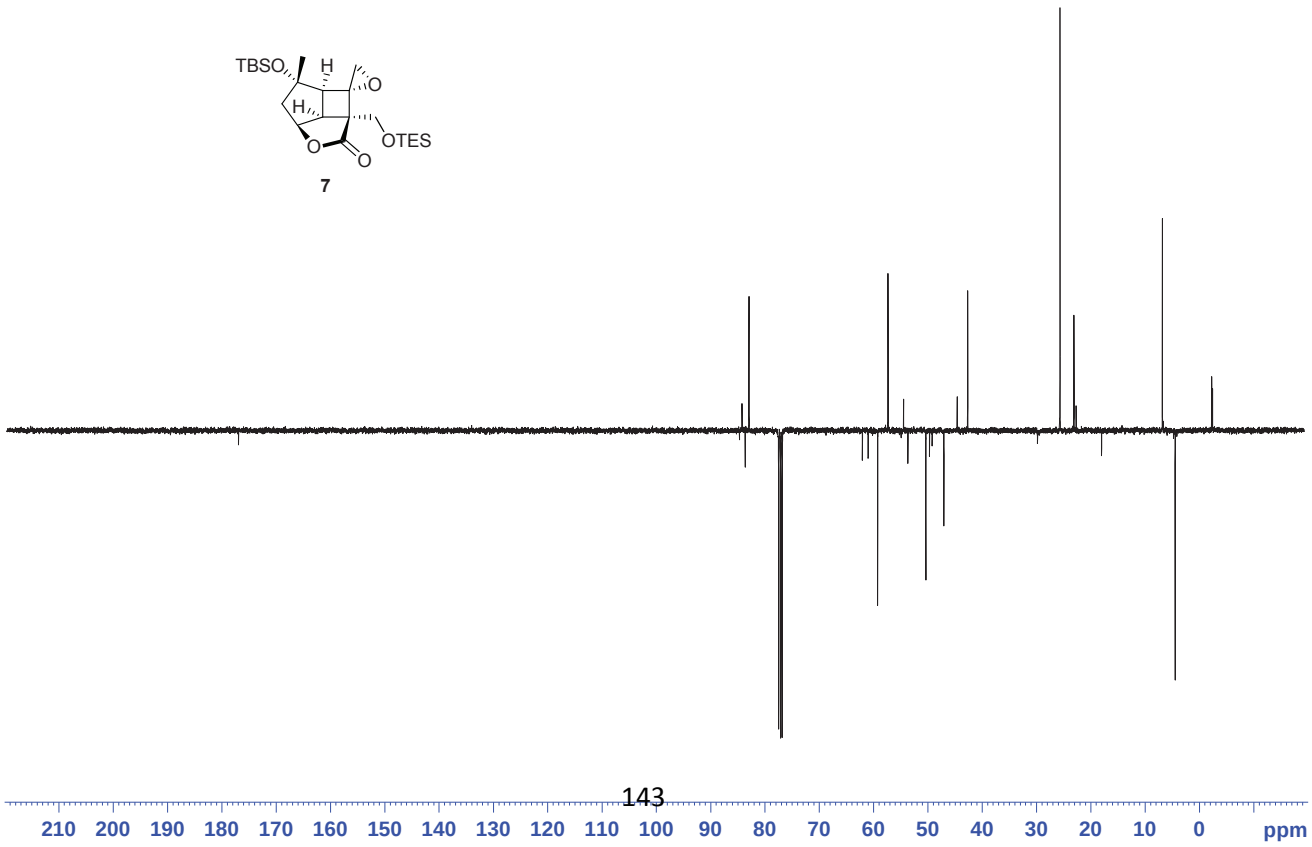
6.71
6.13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O
OTES
O
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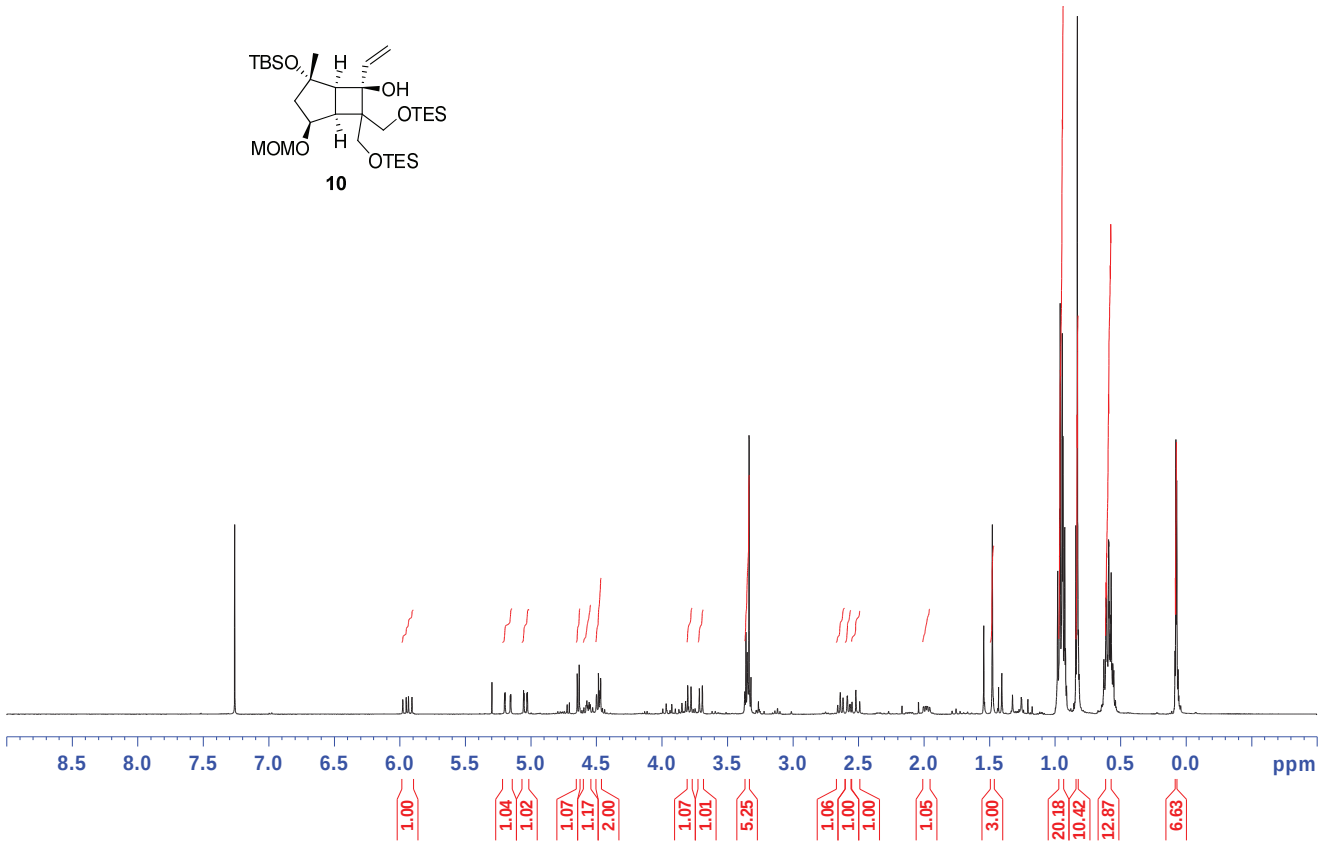
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H
OTES
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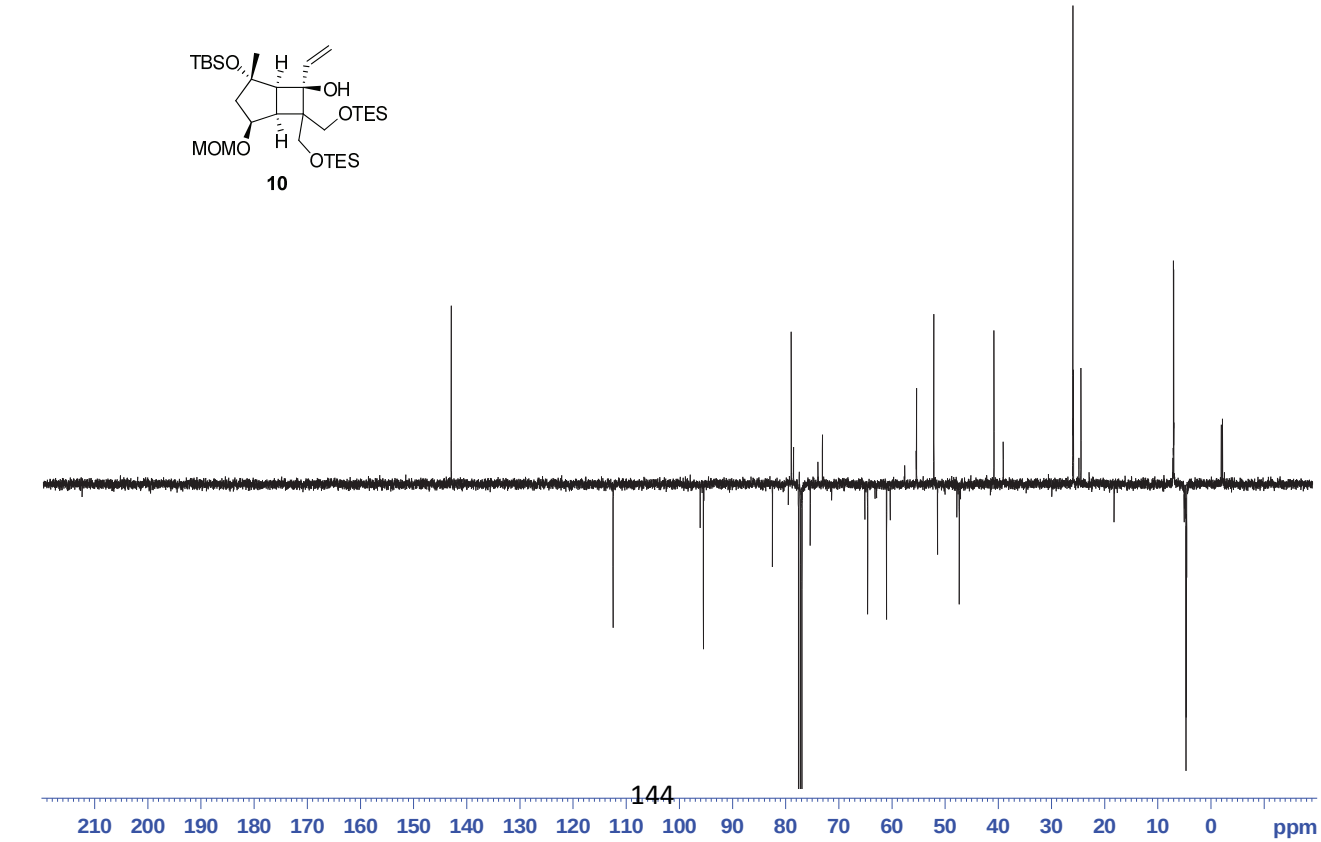
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OTES
MOMO
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OTES
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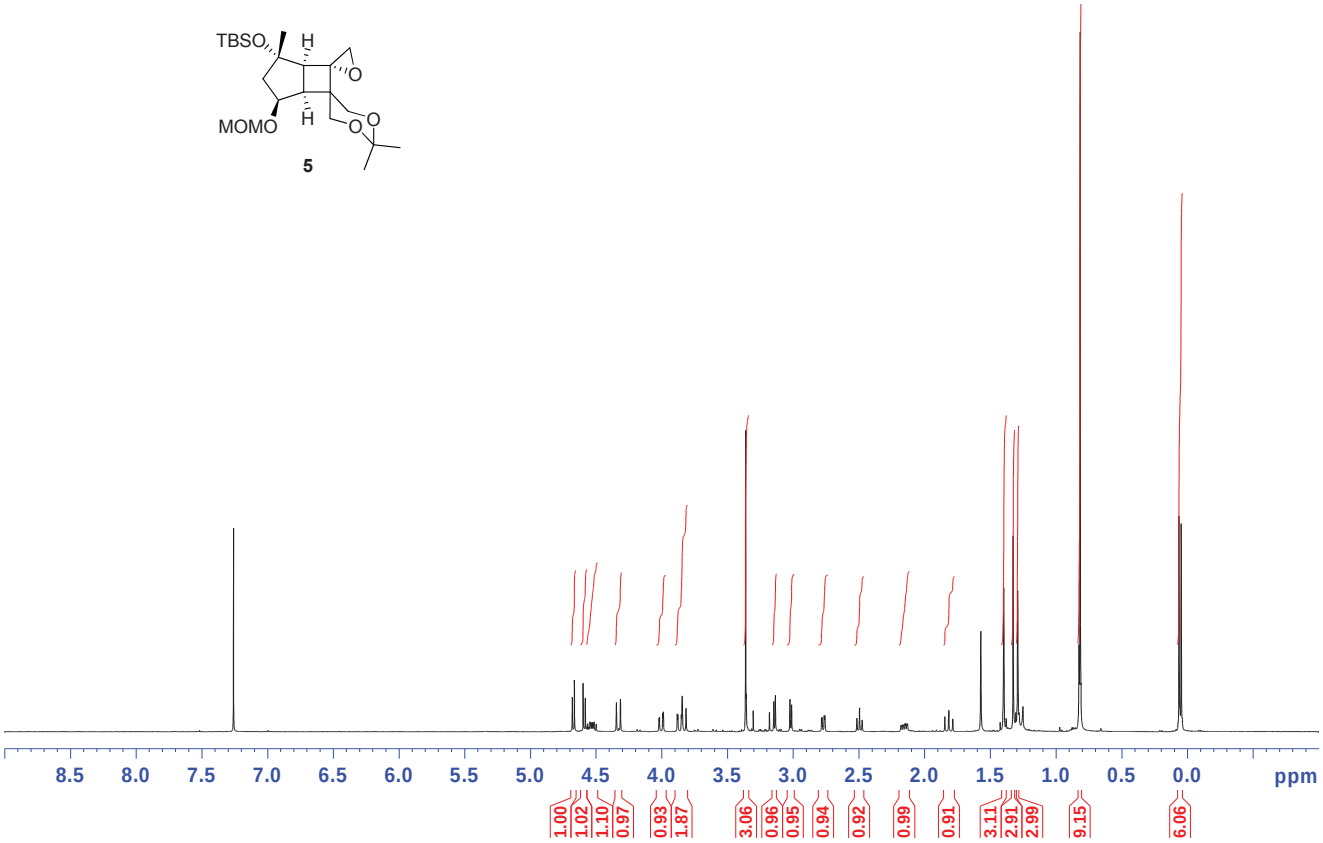
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MOMO
H
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O
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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
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0.93
1.87
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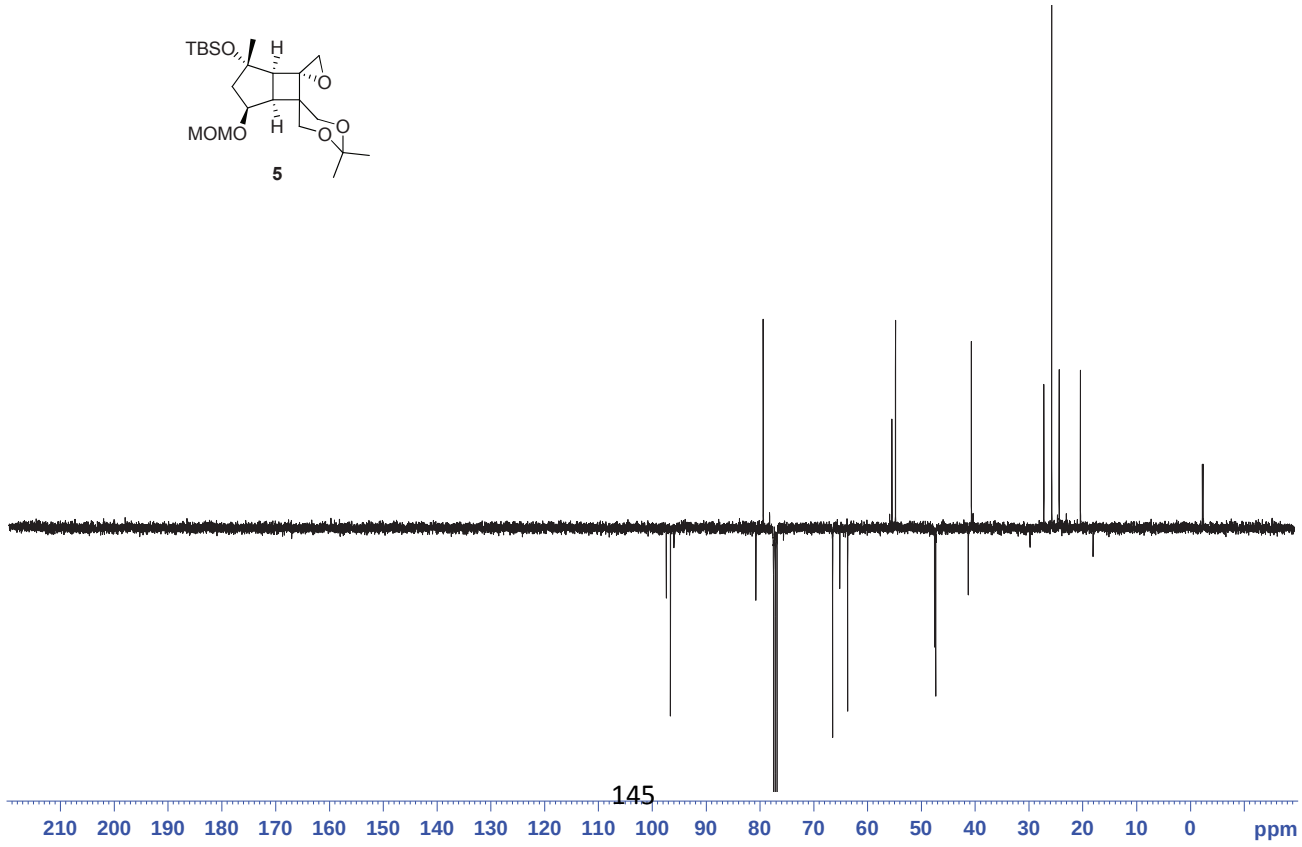
6.06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O
O
5
210
200
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180
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150
140
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100
90
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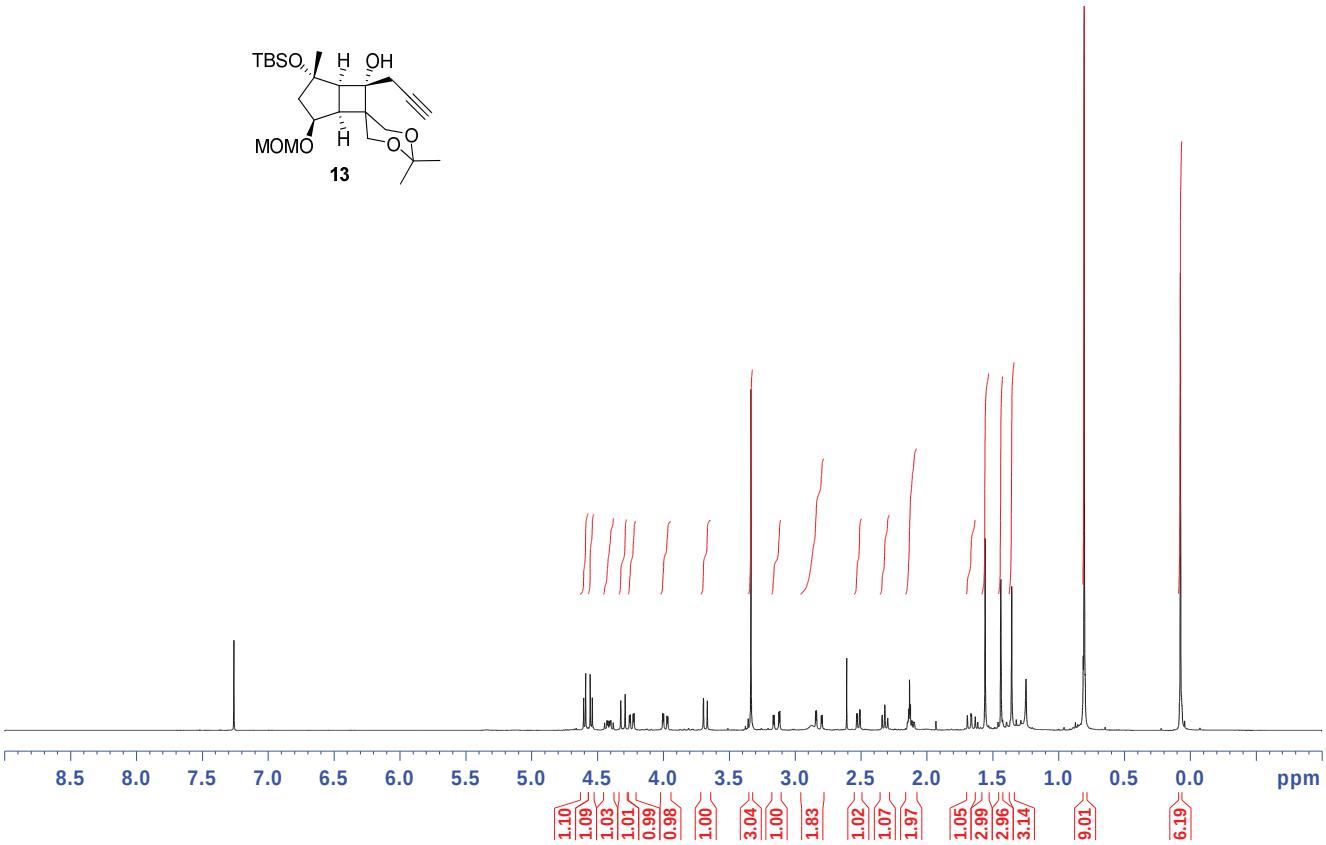
60
50
40
30
20
10
0
ppm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MOMO
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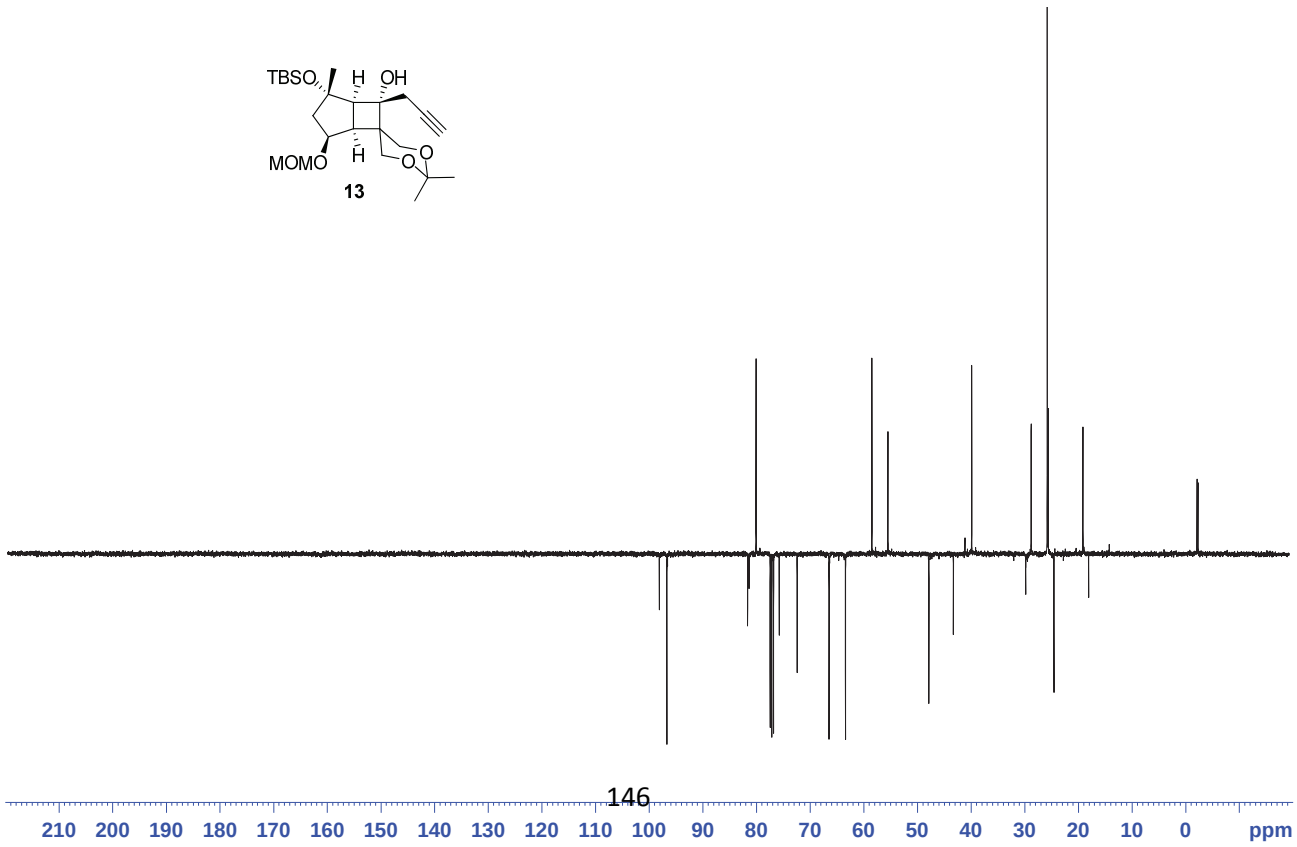
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MOMO
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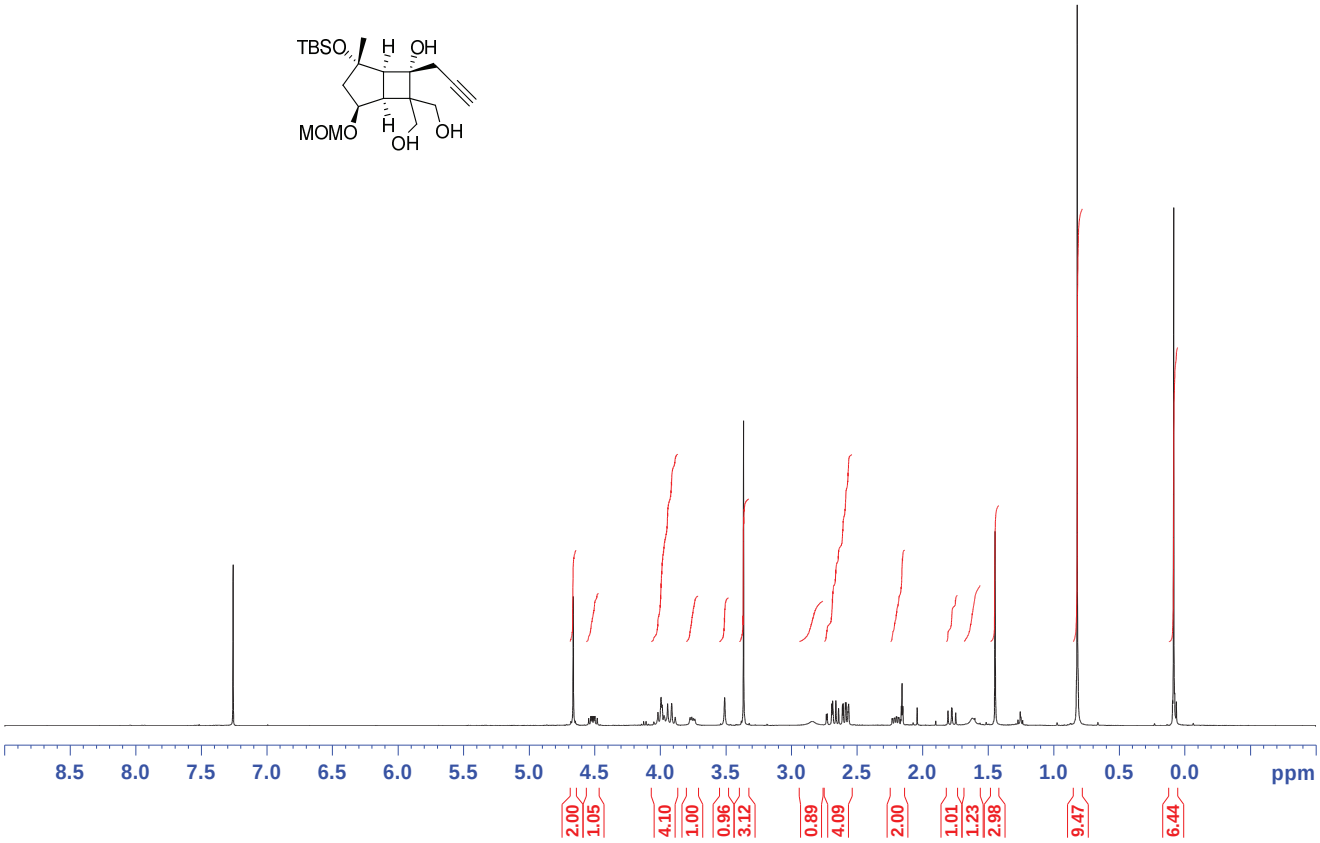
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MOMO
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OH
OH
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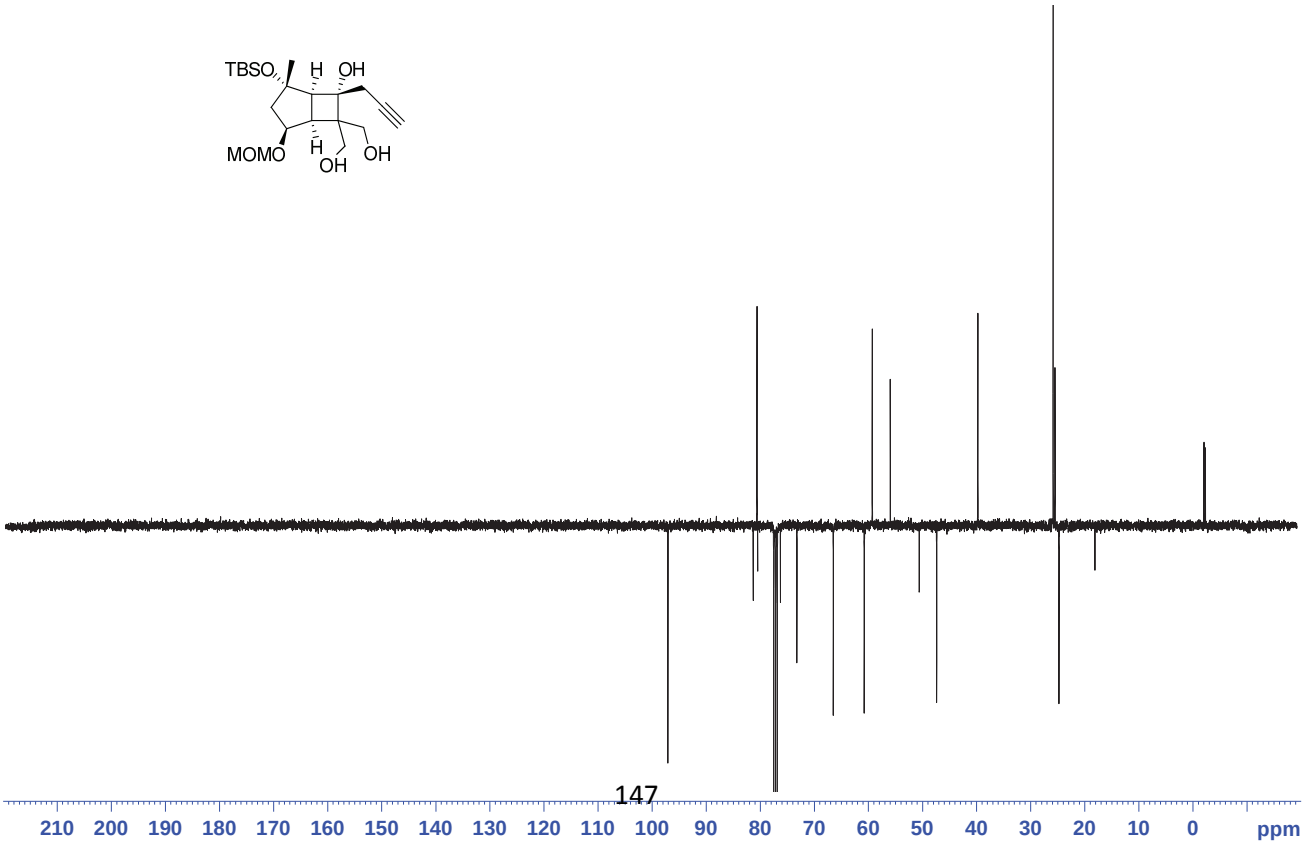
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H
OH
MOMO
H
OH
OH
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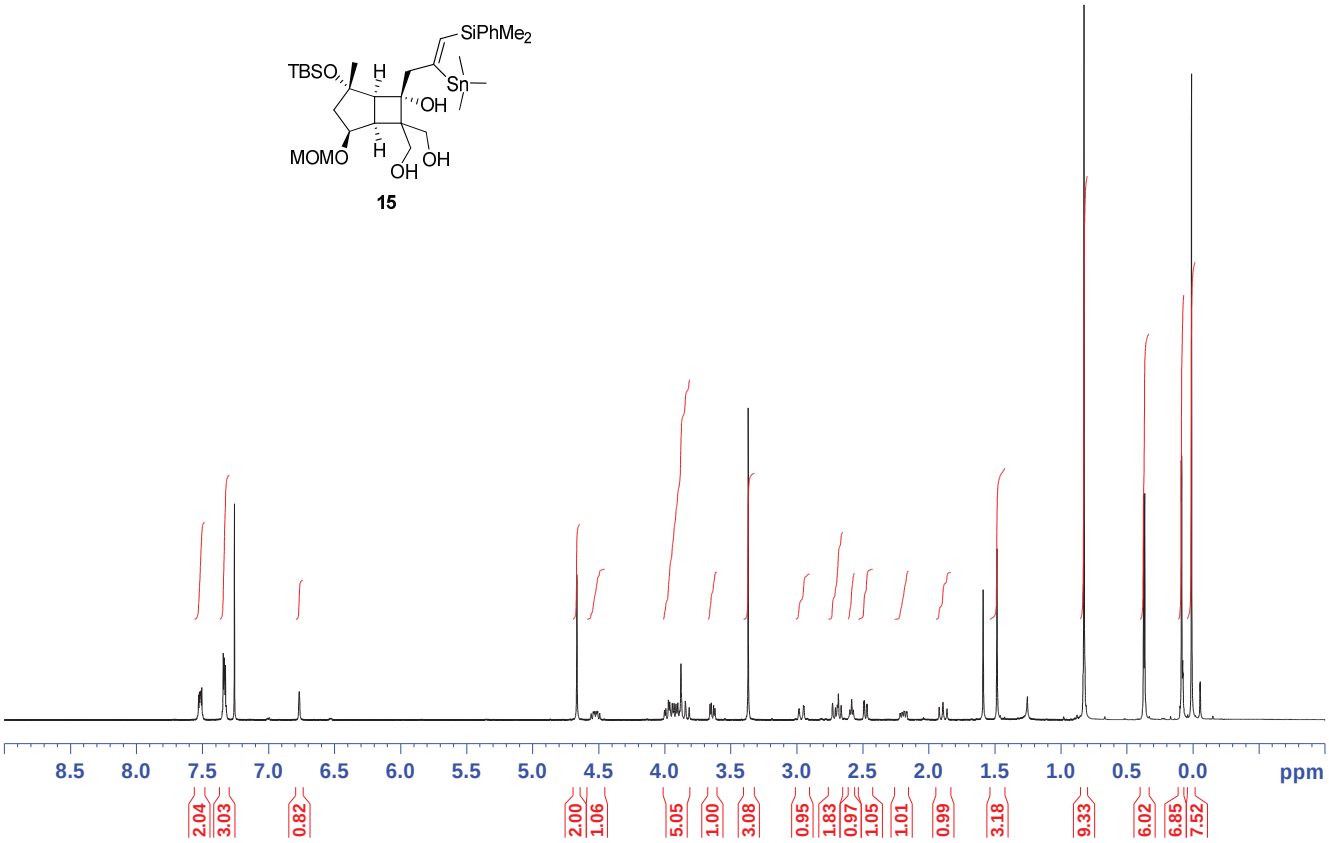
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Sn
OH
MOMO
H
OH
OH
15
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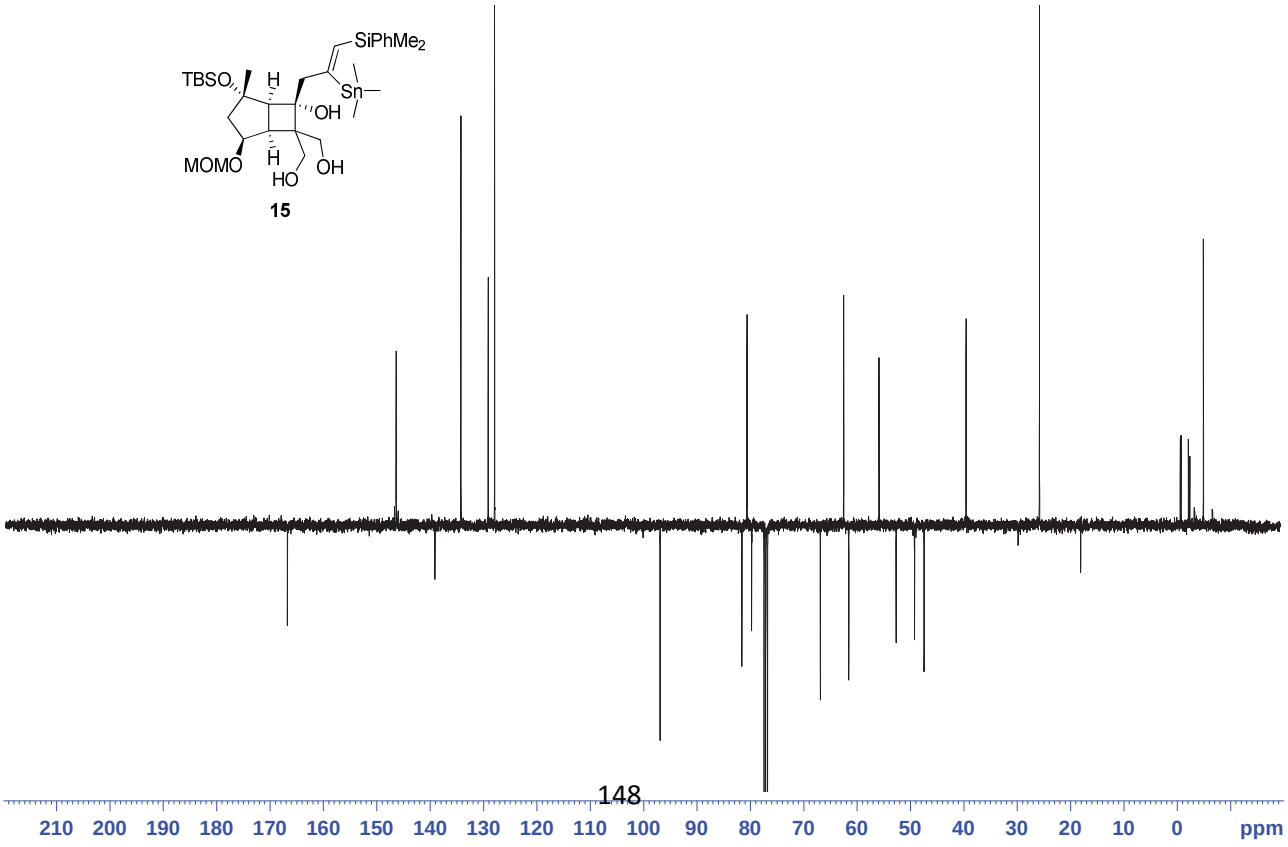
2.04 3.03 0.82 2.00 1.06 5.05 1.00 3.08 0.95 1.83 0.97 1.05 1.01 0.99 3.18 9.33 6.02 6.85 7.52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Sn
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MOMO
H
HO
OH
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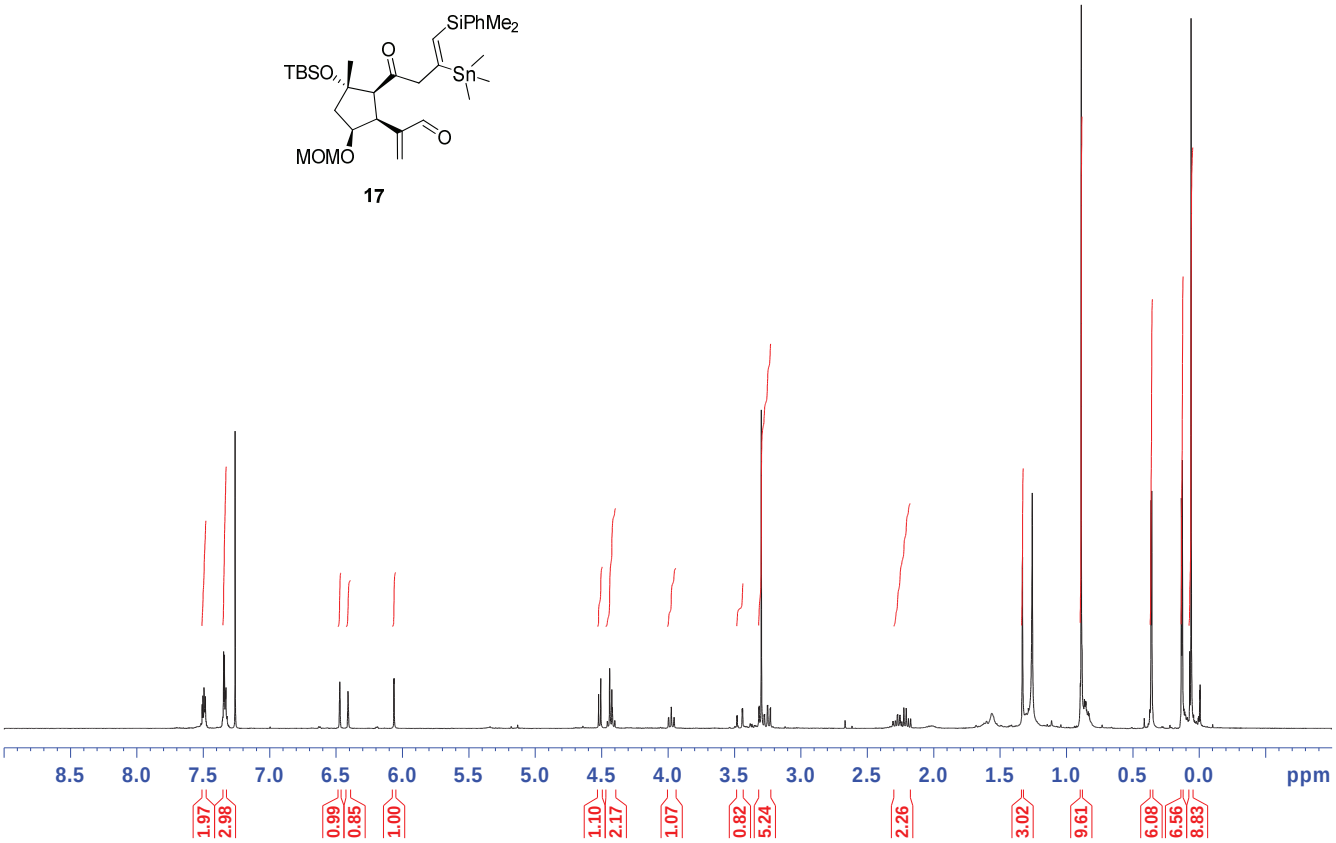
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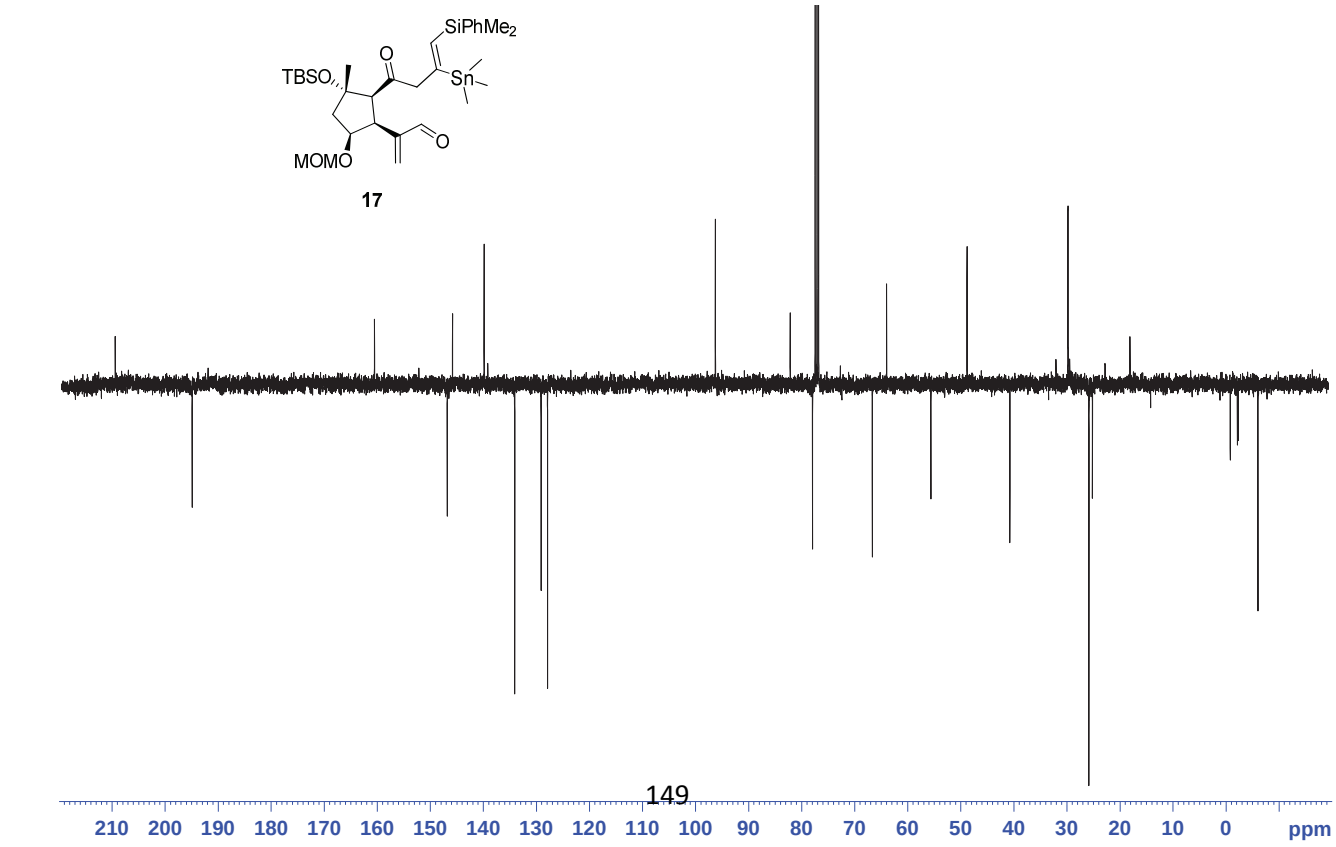
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TBSO
O
Sn
MOMO
O
17
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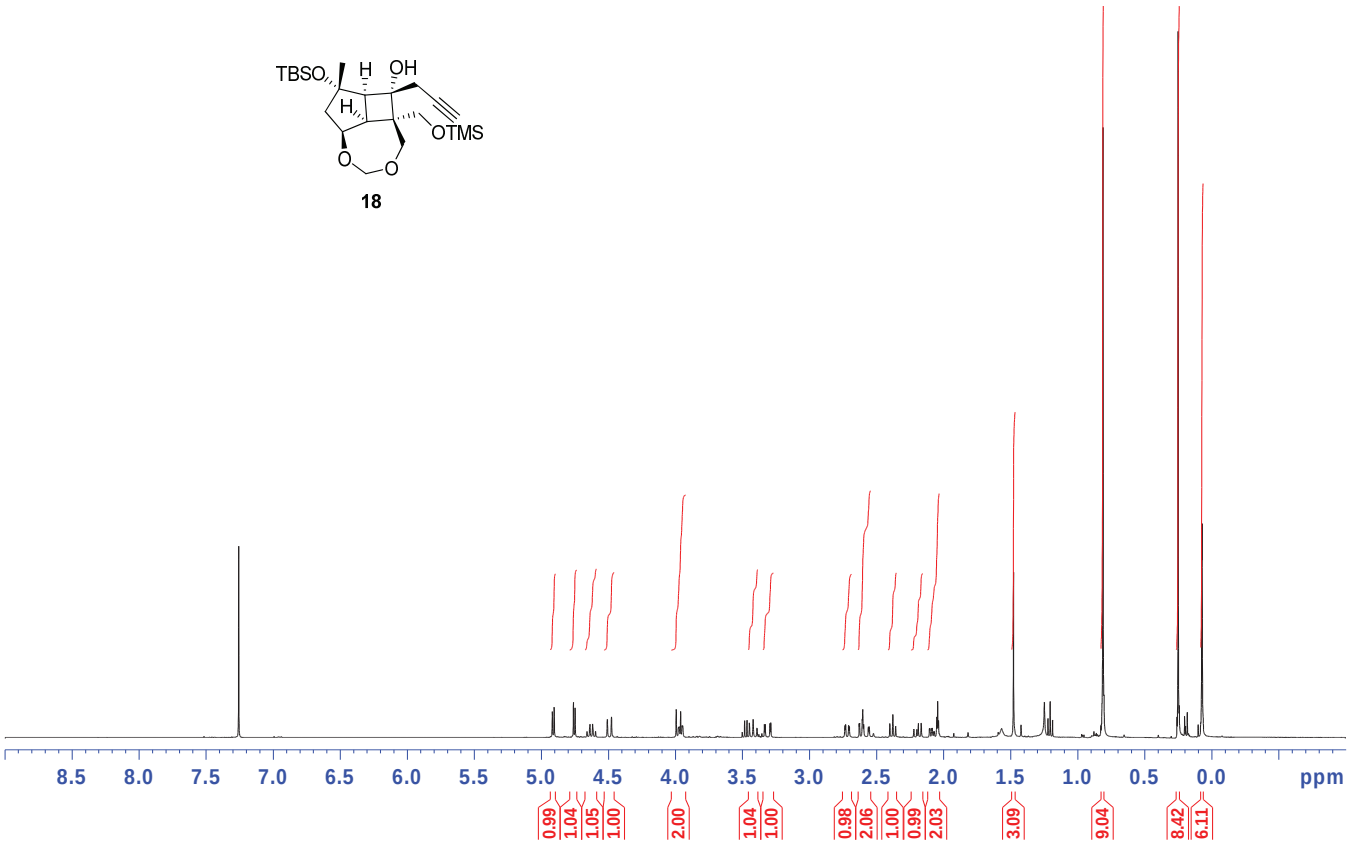
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OTMS
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.99
1.04
1.05
1.00
2.00
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3.09
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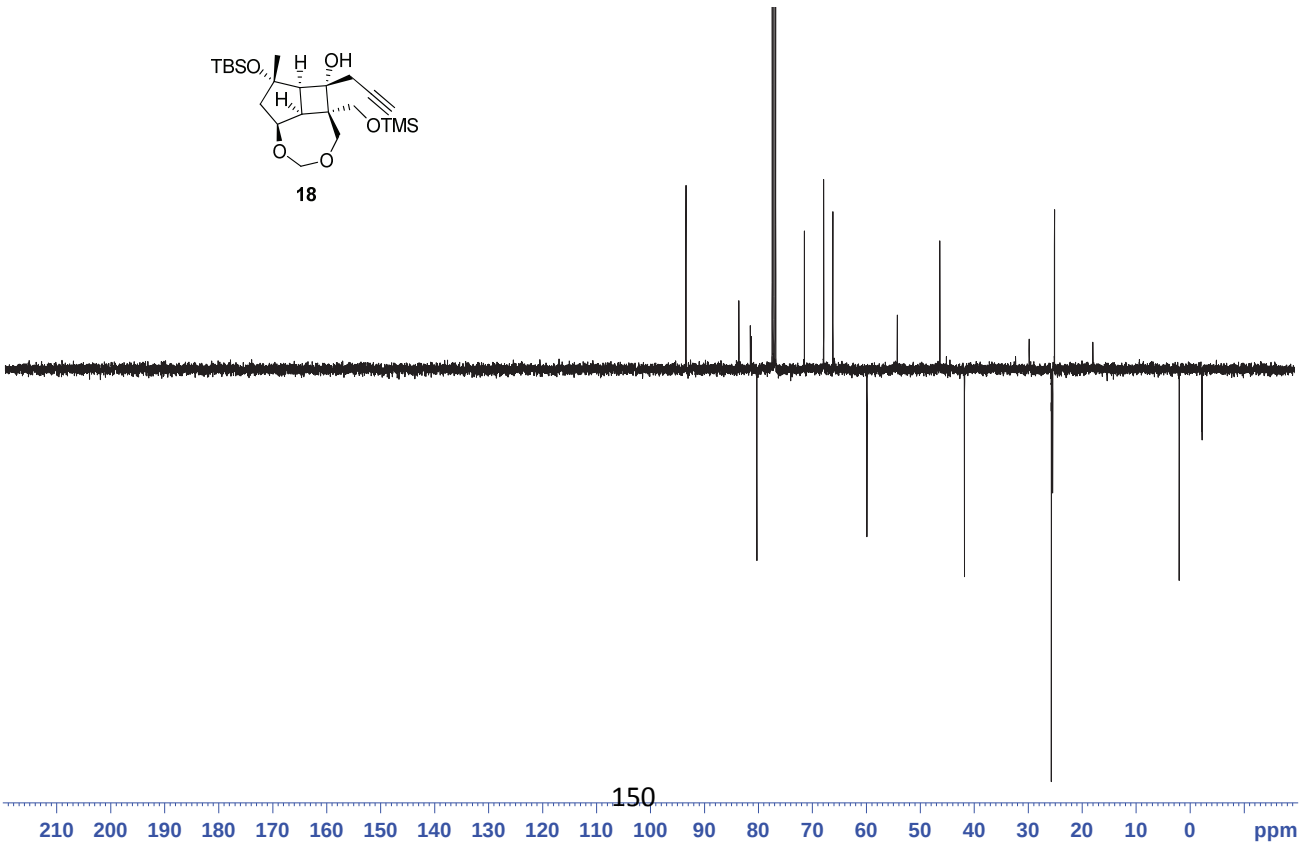
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H
OTMS
O
O
18
210
200
190
180
170
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150
140
130
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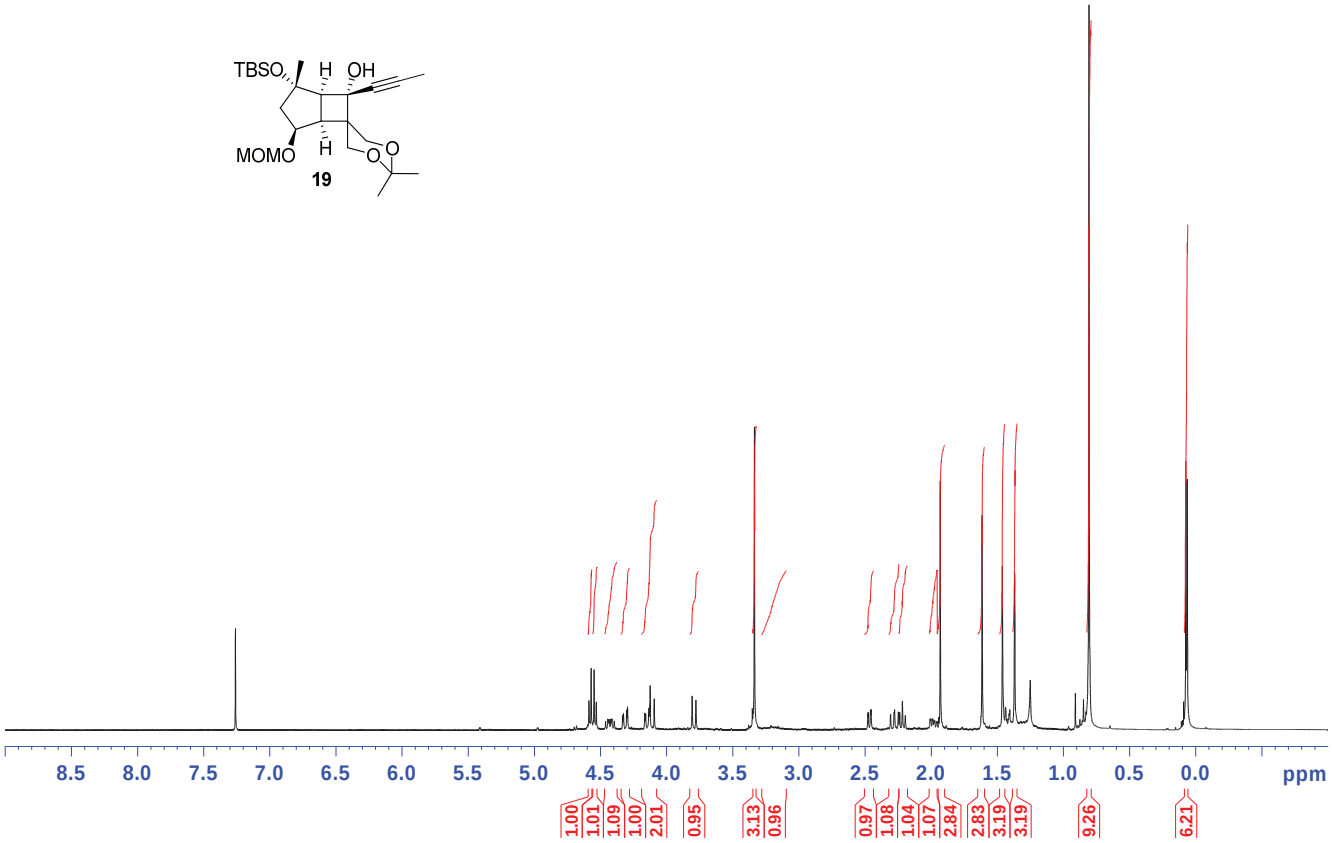
100
90
80
70
60
50
40
30
20
10
0
ppm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OH
MOMO
H
O
O
19
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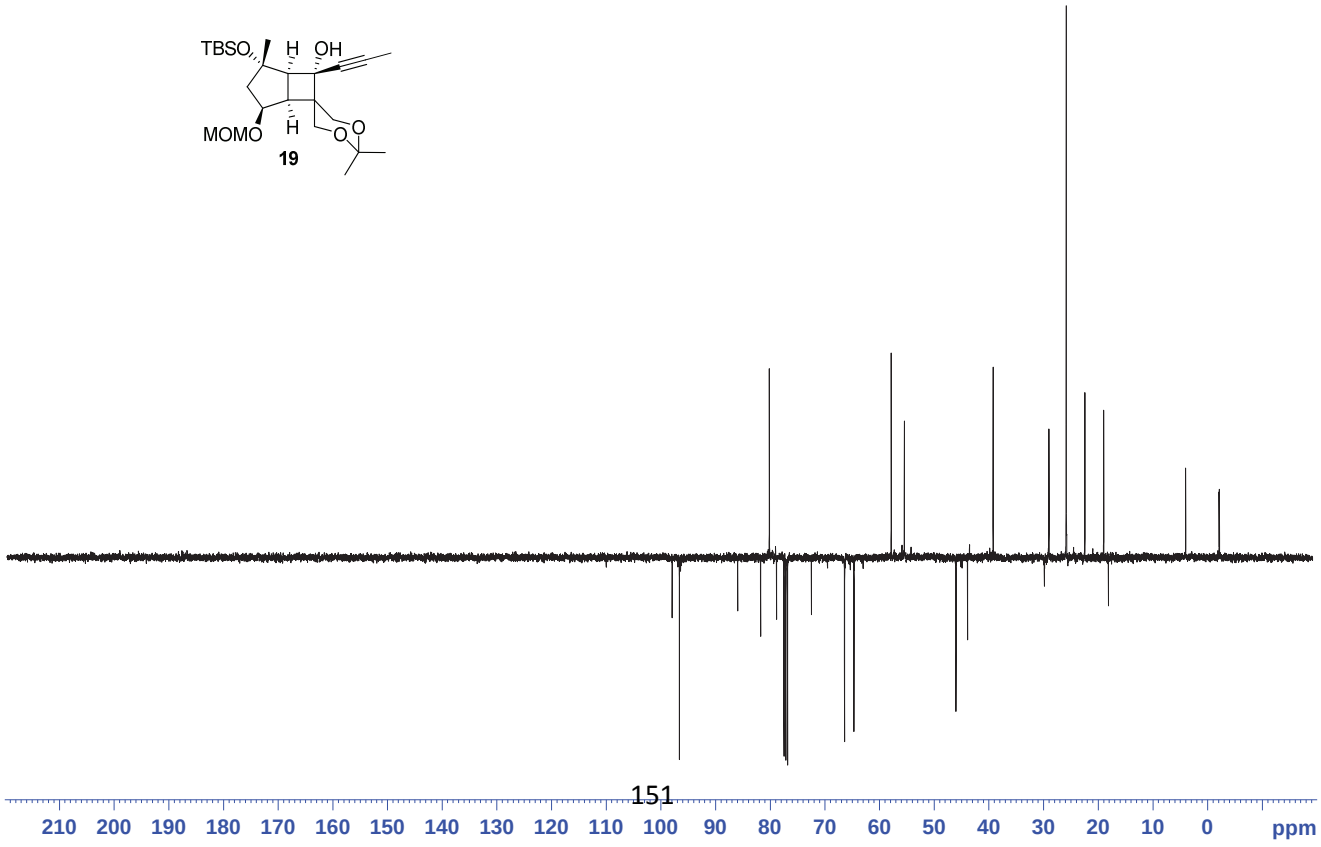
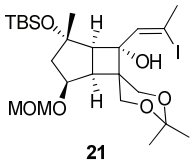

TBSO
H
OH
MOMO
H
O
O
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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OH
I
MOMO
H
O
O

21

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0.99
1.04
1.04
1.05
2.04
1.00
1.02
3.01
1.00
3.99
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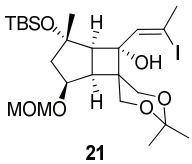
1.04
1.09
6.01
9.04
6.02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OH
I
MOMO
H
O
O

21

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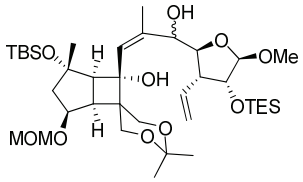
OH
TBSO
H
OMe
OH
OTES
MOMO
H
O
O

22a

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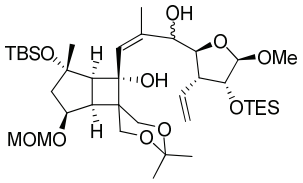
1.00 1.09 1.09 2.15 2.09 1.11 1.13 3.28 1.18 2.10 1.03 3.04 3.14 1.06 1.06 1.07 1.02 1.11 3.03 1.12 6.07 3.00 9.29 9.07 6.52 6.00


OH
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OMe
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OTES
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O

22a

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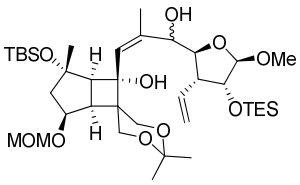
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TBSO
H
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O
OMe
OTES
MOMO
H
O
O

22b

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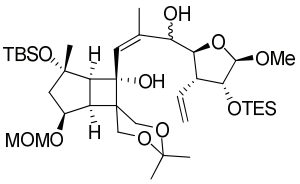
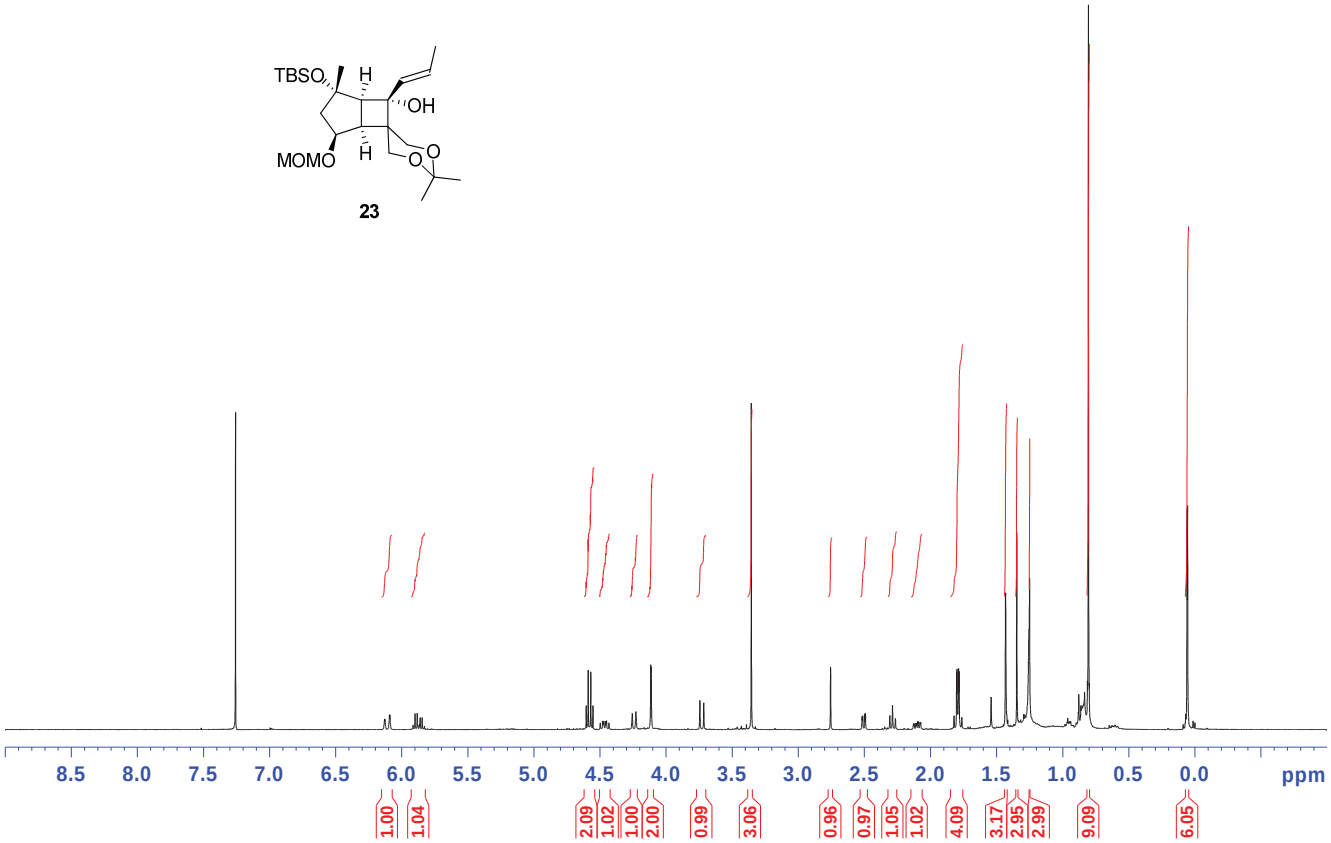
1.00 0.97 1.02 0.98 1.02 1.26 1.04 1.06 1.08 1.17 2.00 1.04 1.16 1.04 1.01 1.00 3.03 3.07 1.03 1.09 1.06 1.06 2.73 1.25 6.20 3.02 10.50 9.12 6.63 5.81


OH
TBSO
H
OH
O
OMe
OTES
MOMO
H
O
O

22b

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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OH
MOMO
H
O
O
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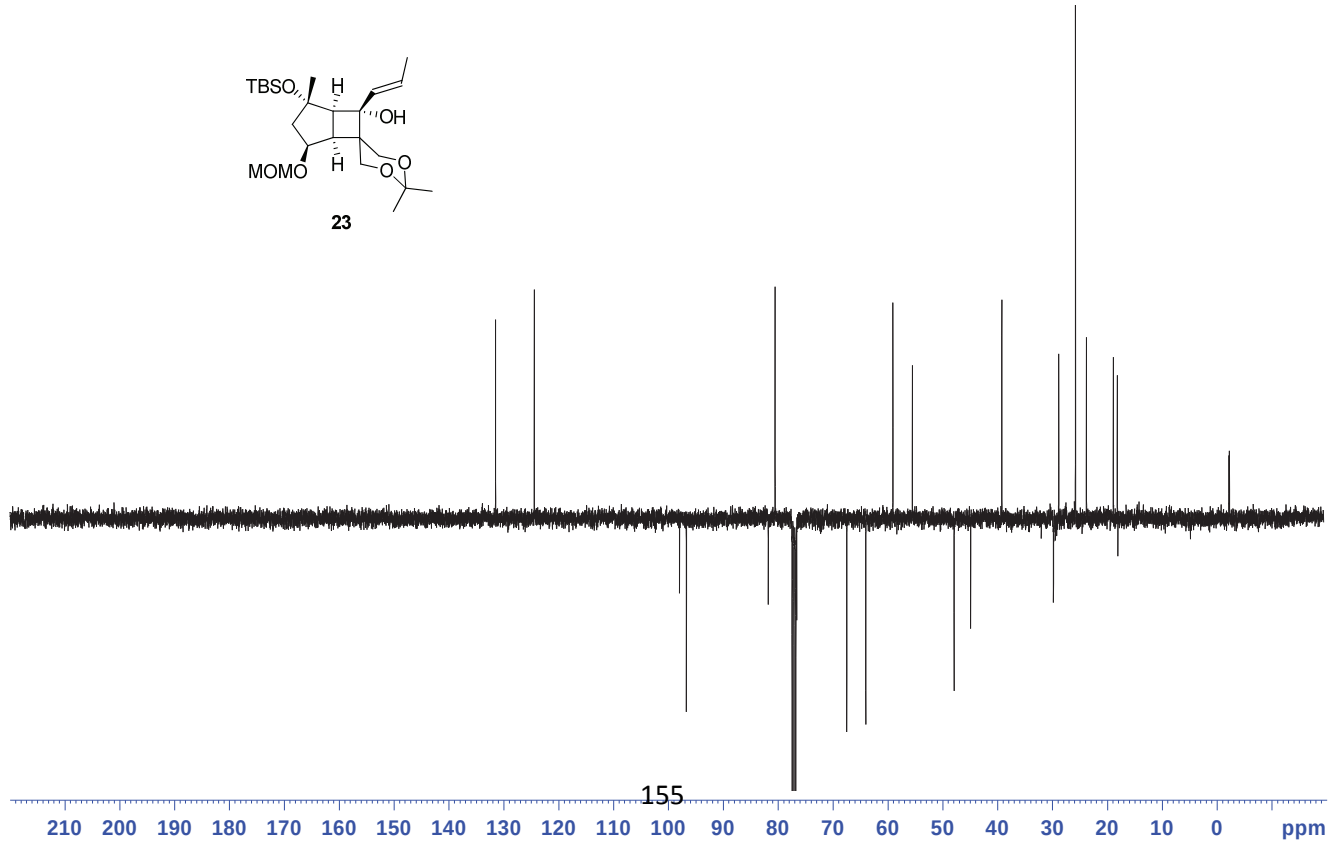
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MOMO
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23
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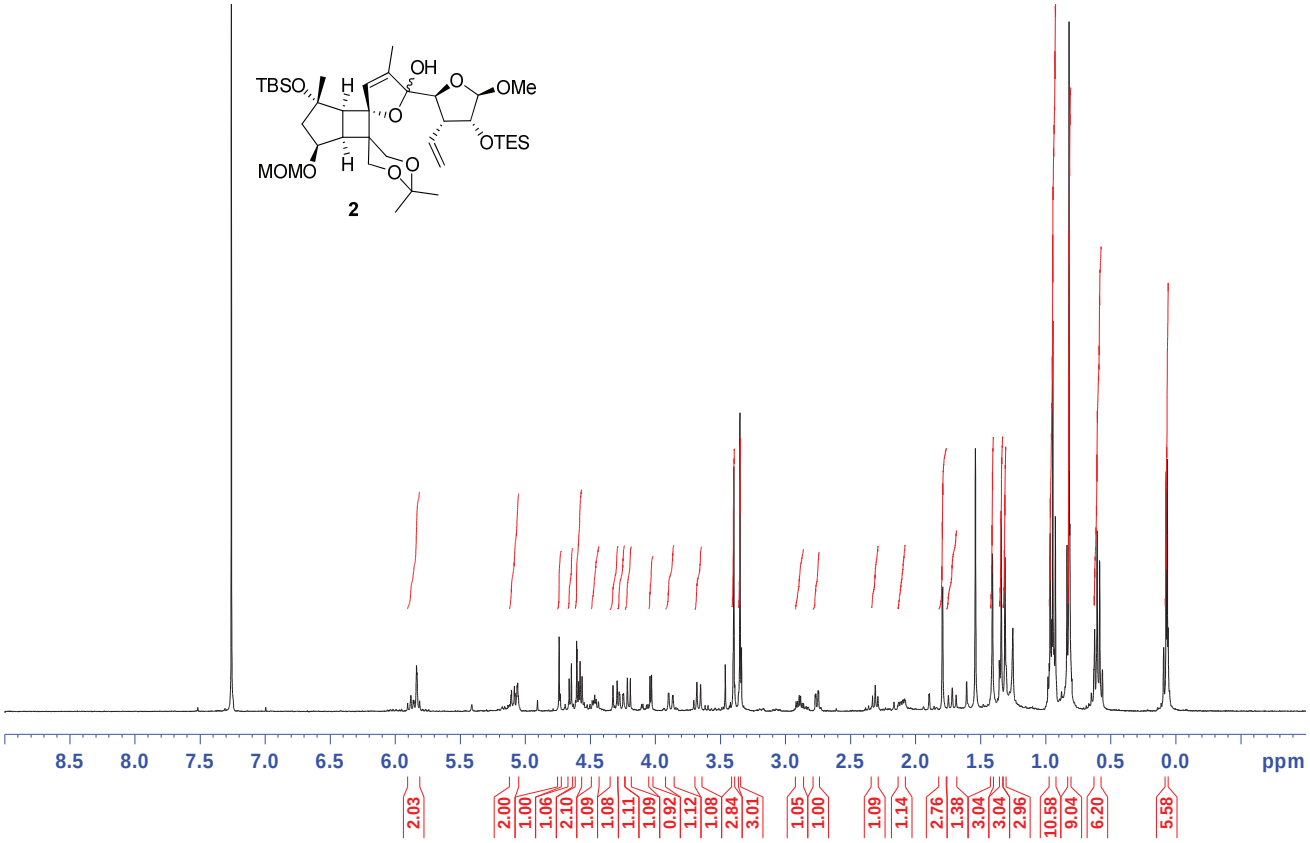
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OTES
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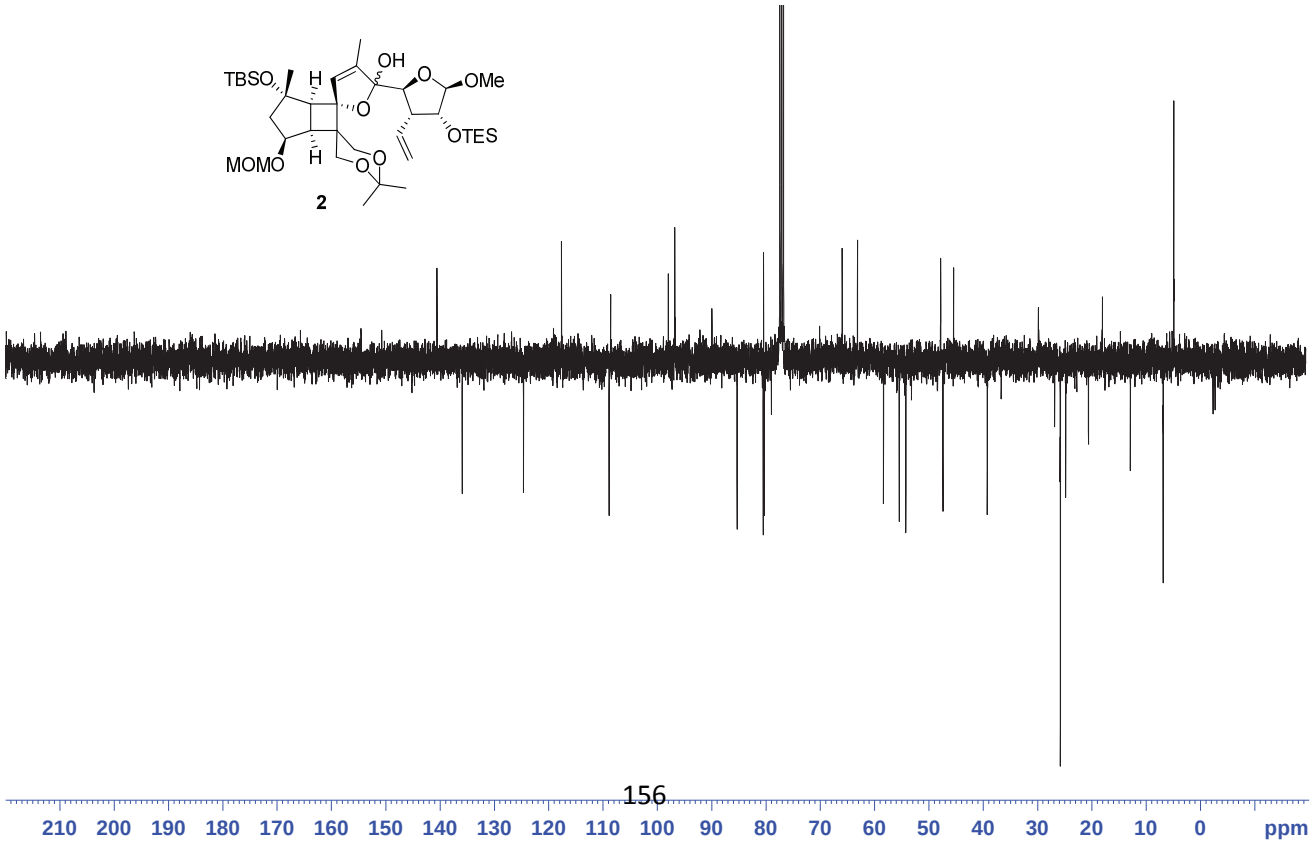
2.03 2.00 1.00 1.06 2.10 1.09 1.08 1.11 1.09 0.92 1.12 1.08 2.84 3.01 1.05 1.00 1.09 1.14 2.76 1.38 3.04 3.04 2.96 10.58 9.04 6.20 5.58


TBSO
H
OH
O
OMe
OTES
MOMO
H
O
O
2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

2D NMR Spectra for compound **22a**

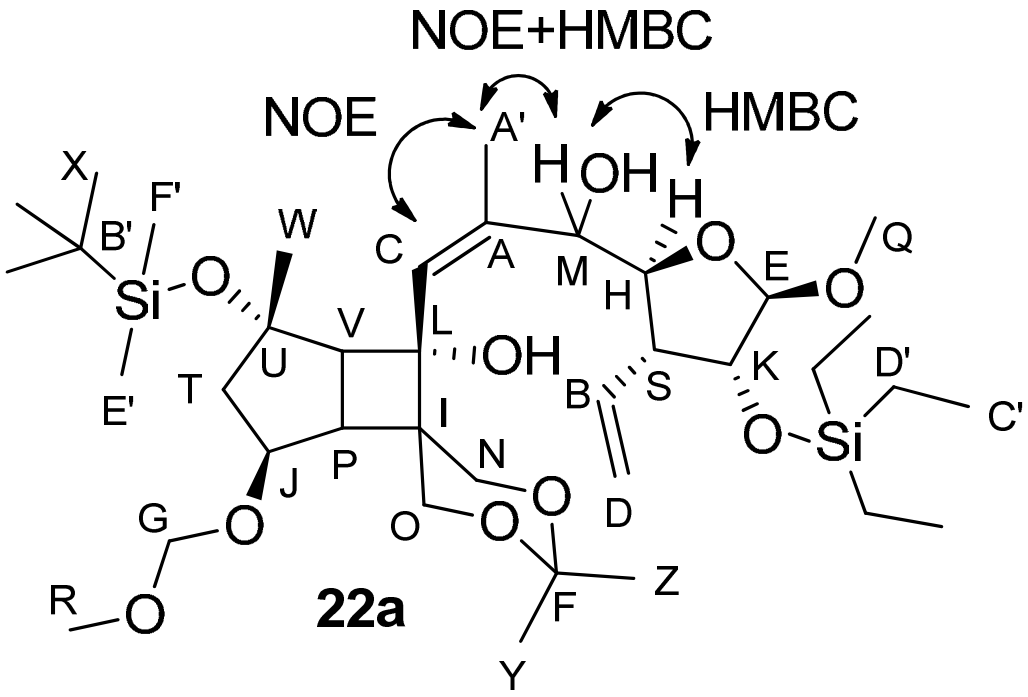
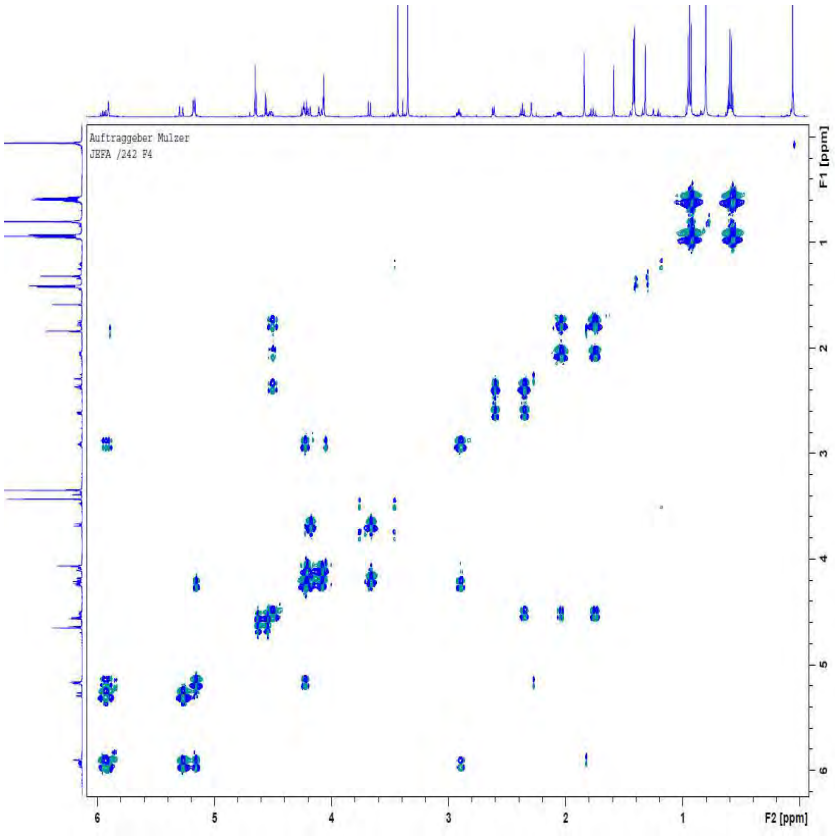


Figure 1. Carbon plotting and selected NOE/HMBC correlations

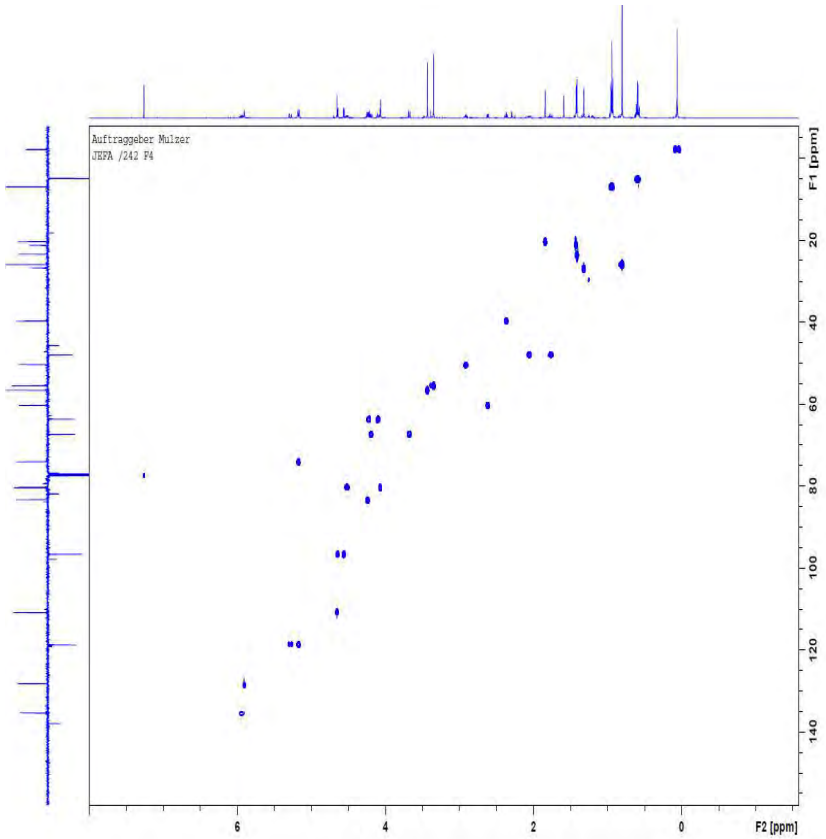
Table 1. Assignments of ^{1}H-shift and ^{13}C-shift

Atom number	^{13}C-shift (ppm)	^{1}H-shift (ppm)	Atom number	^{13}C-shift (ppm)	^{1}H-shift (ppm)
A	137.9		**Q**	56.5	3.43
B	135.3	5.94	**R**	55.5	3.35
C	128.1	5.91	**S**	50.2	2.91
D	118.6	5.28 + 5.17	**T**	48.0	2.06 + 1.77
E	110.8	4.65	**U**	45.7	
F	97.8		**V**	39.7	2.38
G	96.6	4.65 + 4.56	**W**	26.7	1.32
H	83.3		**X**	25.9 (3C)	0.81
I	81.8		**Y**	23.3	1.43
J	80.3	4.54-4.50	**Z**	21.2	1.41
K	80.2	4.06	**A'**	20.3	1.84
L	76.7		**B'**	18.1	
M	74.0	5.18	**C'**	6.9 (3C)	0.94
N	67.0	4.20 + 3.68	**D'**	4.9 (3C)	0.59
O	63.6	4.25 + 4.10	**E'**	-2.1	0.06
P	60.3	2.62	**F'**	-2.2	0.06

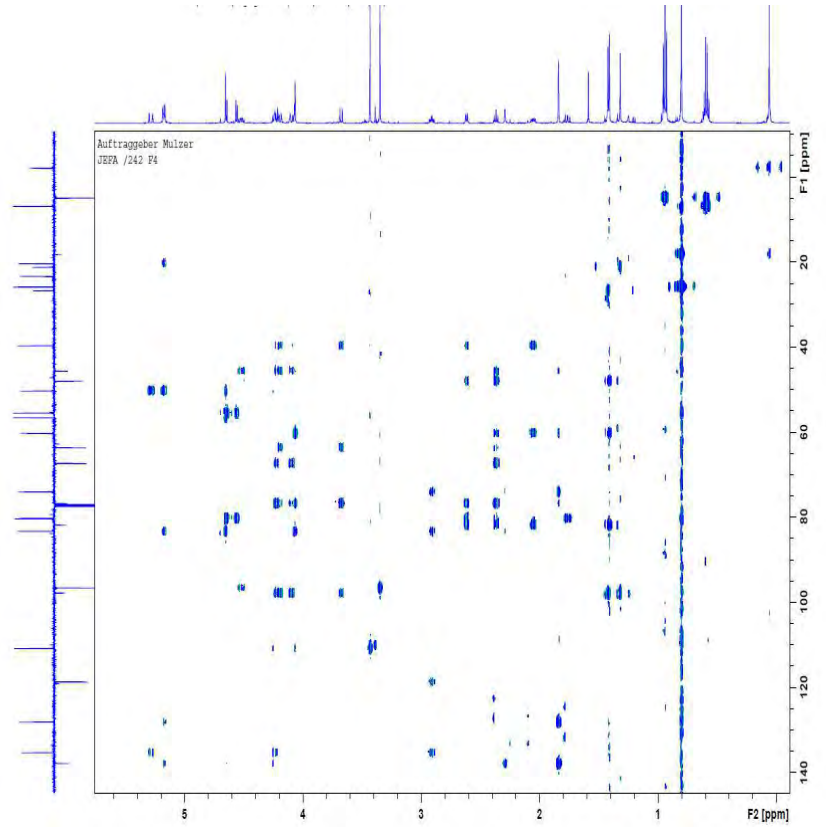
COSY spectrum:



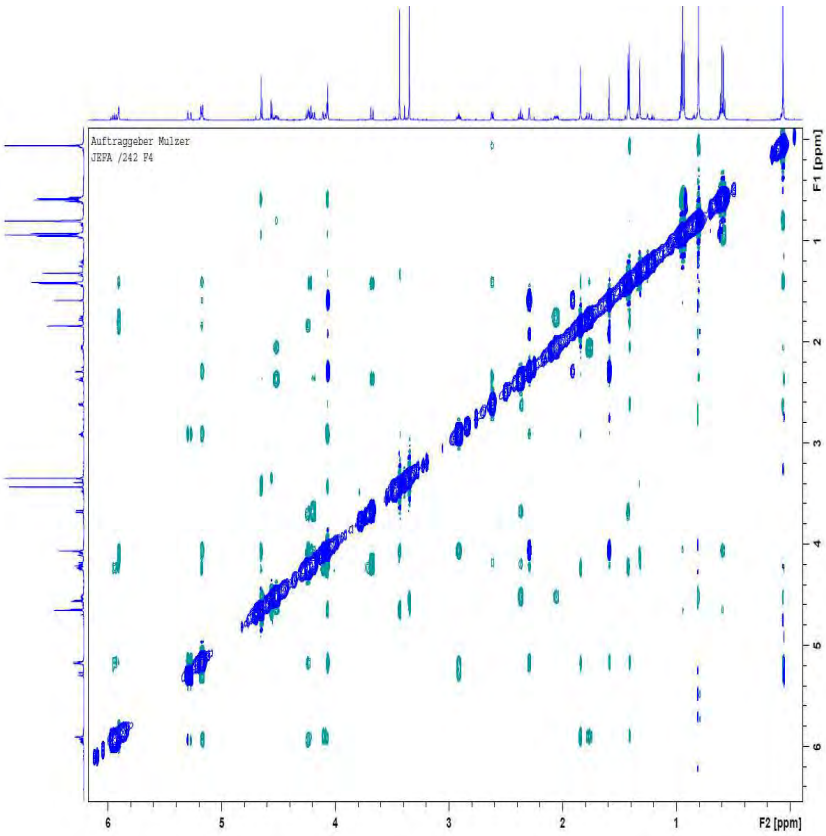
HSQC spectrum:



HMBC spectrum:

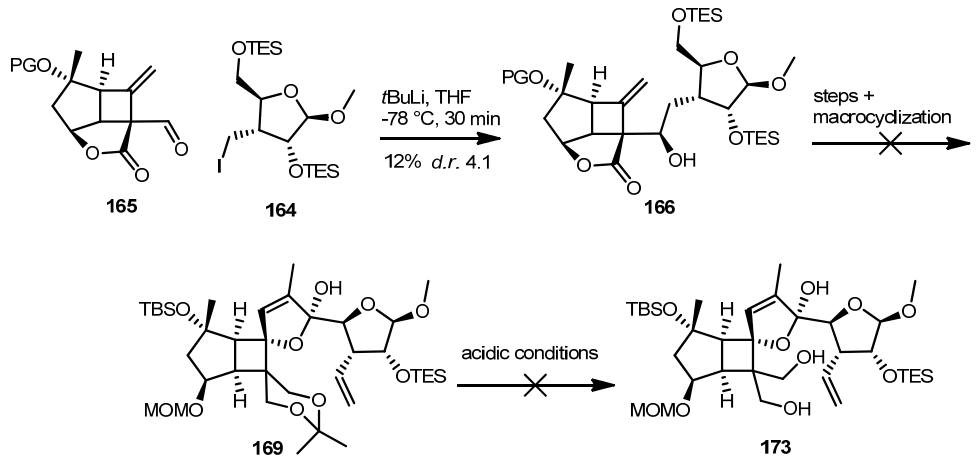


NOESY spectrum:



5 Future work

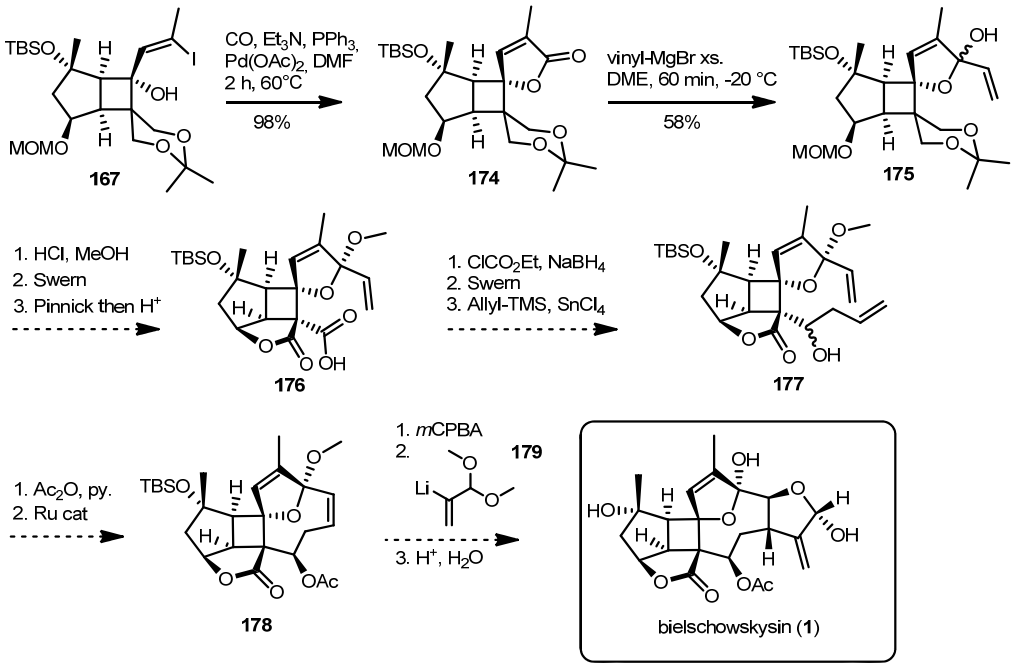
Intermediate **166** was obtained (Section 4.3)[40] using aldehyde **165** in the non-photochemical approach described in Section 4.1 and Section 4.2. In addition, our team synthesized, using a different route based on the formation of the cyclobutane ring by a photocycloaddition of an allene and a butenolide moiety, a **166** TES-analogue on large scale (Section 4.3).[38,40] However, after extensive screening of cyclization strategies, we were not able to proceed to the correct macrocyclization leading to the bielschowskysin scaffold.[38,40] In the meantime, the route leading to **169** was developed (Section 4.4). Though convergent, another 14 steps would be needed to finish the synthesis. Moreover, the presence of numerous protecting groups and diverse functionalities make **169** a very labile substrate to acidic and basic conditions. In fact, while we intended to cleave the acetonide group under various conditions, we observed formation of many side products resulting from the cleavage of the TES protecting group and possible elimination of a water molecule (Scheme 28).



Scheme 28. Difficulties encountered with building-blocks **166** and **169**.

Hence, we decided to pursue another strategy, less convergent but indeed shorter. We planned to build the furan ring using a palladium mediated reaction starting from vinyl halide **167**, which provides lactone **174** in almost quantitative yield. Next, the addition of a C2 fragment was best achieved by mixing **174** in excess of vinyl magnesium bromide in DME, which yielded **175** in satisfactory yield. Our efforts focus now on the formation of the lactone ring to give carboxylic acid **176**. Allylation of the hindered aldehyde in a neopentyl position could then be possible when done under Hosomi-Sakurai conditions to yield **177** in an unpredictable diastereoisomer outcome. Acetylation followed by RCM is

envisaged to close the 14-membered ring to give **178**. In only three steps we plan to form the last ring of the natural product. Epoxidation on the concave side of the polycyclic structure will be a challenging task. The acetate or its free alcohol might be used as an anchor to direct the formation of the oxiran (Scheme 29).



Scheme 29. Outlook of the remaining steps.

Epoxide opening from the less hindered side with vinyl lithium derivative **179** will furnish natural product bielschowskysin (**1**), after acidic global deprotection and concomitant equilibration of both hemi-acetals. This work is on-going in our laboratory and successful gram scale synthesis of **167** allows fast progress.

6 Summary

The marine diterpenoid bielschowskysin (**1**) is currently one of the most competitive synthetic targets worldwide. Many research groups are underway to reach this elusive goal, so far with limited success. In fact, the complexity of the hexacyclic structure, including eleven stereogenic centers, poses a high challenge for the synthetic chemist.

During the course of this project the asymmetric synthesis of two advanced polycyclic intermediates toward a total synthesis of the natural product bielschowskysin (**1**) was accomplished.

After screening various substrates in order to obtain bielschowskysin's bicyclo[3.2.0]heptane core via [2+2] photocycloaddition, we developed a stereoselective and optimized scalable non-photochemical route (> 30% overall yield, 16 steps) to the highly substituted and oxygenized western fragment, which for the first time, contained the all-carbon quaternary center at C-12. Even though not optimized, a coupling reaction with an eastern fragment delivered the desired product, forming the fully developed southern hemisphere of the natural product. However, this substrate was unsuitable for the completion of the synthesis.

Our flexible route allowed the development of a second approach, in which the tertiary alcohol substituted to the cyclobutane ring was obtained in a stereospecific manner. Hence, a synthesis of an advanced polycyclic precursor of bielschowskysin was developed. The main features of this route are: (1) the formation of a vinyl halide by regio- and stereoselective hydroalumination, (2) an optimized NHK coupling of two complex fragments, (3) the presence of all later-on ring carbon atoms of the target, (4) the formation of the fully substituted spirofused dihydrofuran in the northern hemisphere, (5) presence of the most demanding structural element *i.e.* the quaternary center on the cyclobutane ring, (6) a 7.4% overall yield for 21 steps.

While the presence of many protective groups demonstrates the lability of the substrate, a new approach is underway to evade those difficulties. Hence, at this stage of our research 11 steps are left to complete the synthesis of the natural product bielschowskysin.

7 Abbreviations

Ac	acetyl
Acac	acetylacetonyl
ADP	adenosinediphosphate
ATP	adenosinetriphosphate
CAN	ceric ammonium nitrate
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
CoA	coenzyme A
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DBU	1,8–diaza–bicyclo[5.4.0]–7–undecene
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine (Huenig's base)
DMF	*N,N'*–dimethylformamide
DMAAP	dimethylallyl pyrophosphate

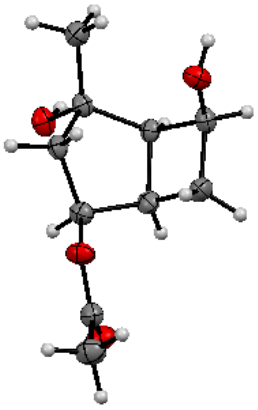
DMAP	4–dimethylaminopyridine
DME	dimethoxyethane
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact / electron ionization
EtOAc	ethylacetate
GABA	*gamma*-aminobutyric acid
GGP	geranyl–geranyl diphosphate
GI_{50}	concentration that causes 50% growth inhibition
GPP	geranyl diphosphate
HMBC	hetero nuclear multiple bond correlation
HMQC	hetero nuclear multiple quantum correlation
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IBX	2–iodoxybenzoic acid
IC_{50}	concentration that causes 50% inhibition of the desired activity
IPP	isopentenyl diphosphate
LiHMDS	lithium bis(trimethylsilyl)amide
MeOH	methanol
*m*CPBA	*meta*-chloroperoxybenzoic acid

MOM	methoxymethyl
NAD^+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide hydride
NADPH	nicotinamide adenine dinucleotide phosphate hydride
NHK	Nozaki-Hiyama-Kishi
NOESY	nuclear Overhauser enhancement spectrometry
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
PMB	*para*-methyoxybenzyl
PPOH	diphosphate
PPTS	pyridinium *para*–toluenesulfonate
RCM	ring closing metathesis
rt	room temperature
SI	supporting information
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*–butyldimethylsilyl
TEA	triethylamine
THP	tetrahydropyranyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

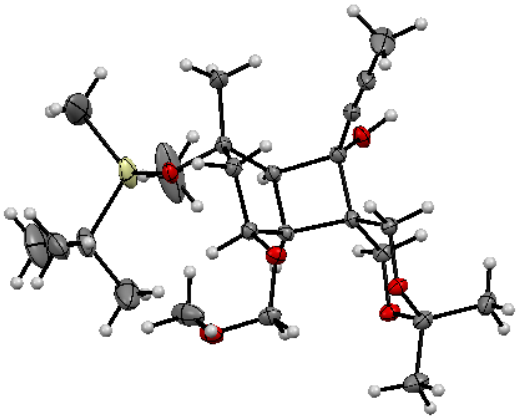
TMS	trimethylsilyl
xs.	excess

8 Annex

8.1 Single crystal diffraction of compound *rac*-16[36]/*rac*-71[37]



8.2 Single crystal diffraction of compound 19[37]



8.3 Single crystal diffraction of Bielschowskysin (1) & NMR spectra

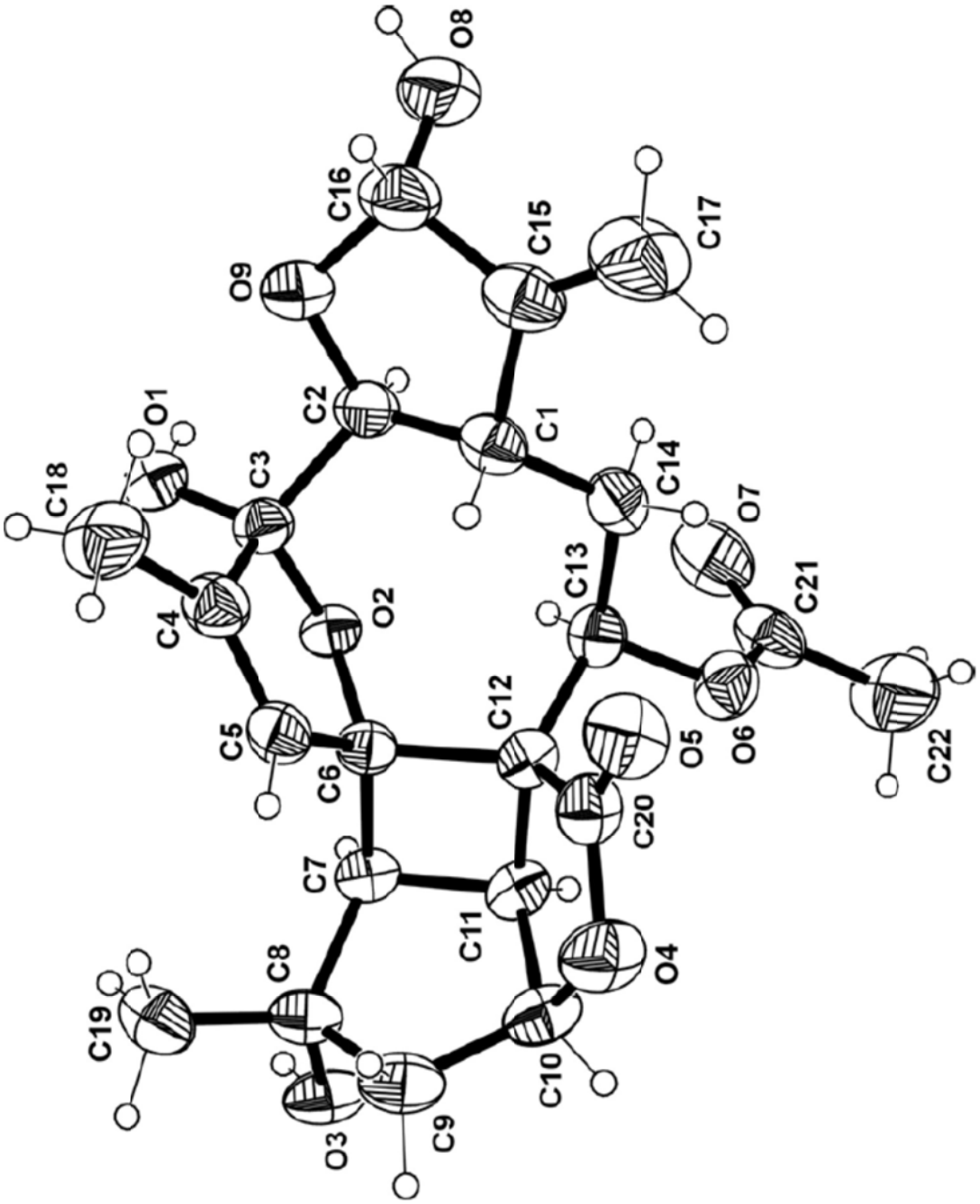
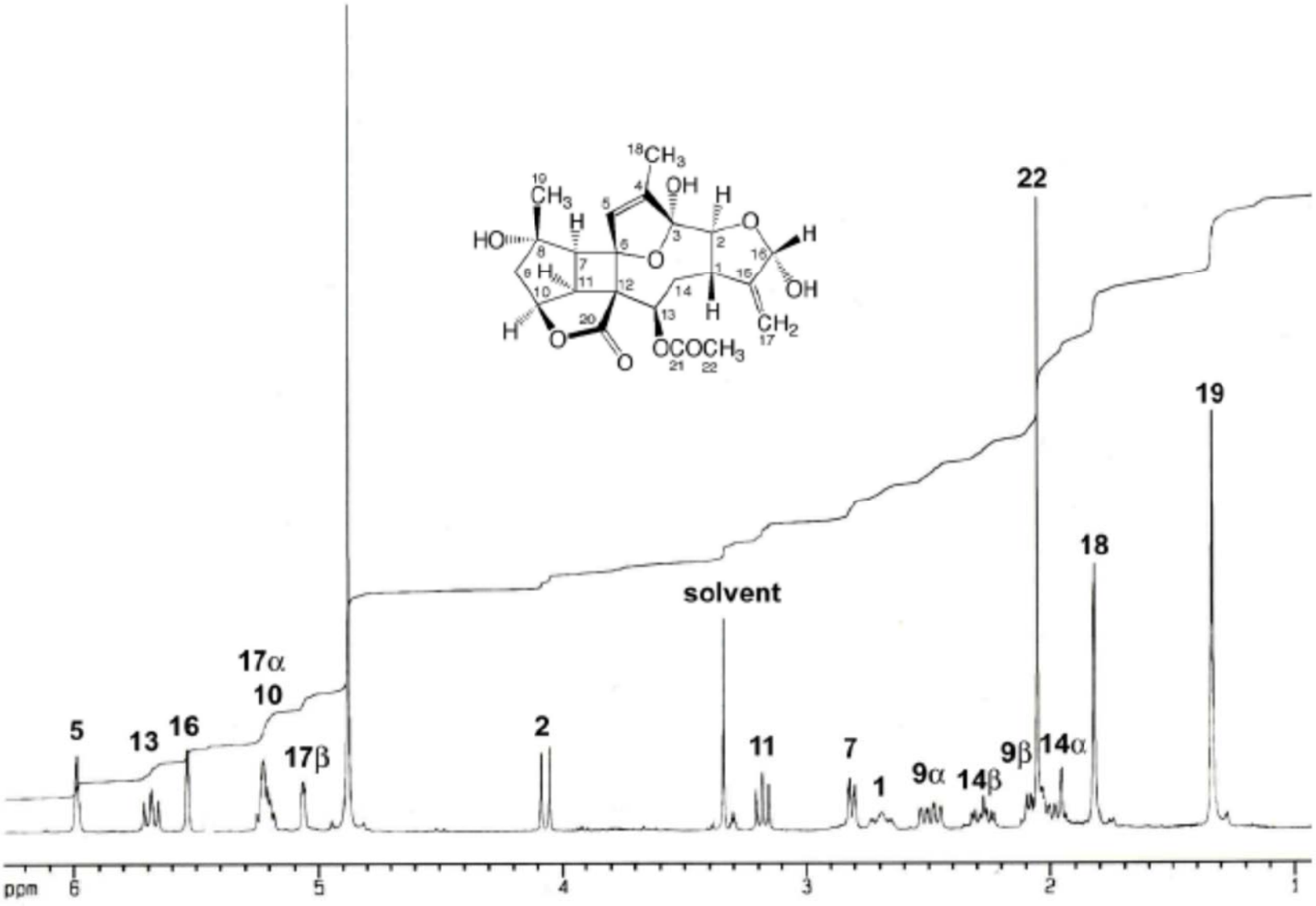


Figure 4. ORTEP diagram of bielschowskysin (C/O drawn as 50% thermal ellipsoids)


18CH3
19CH3
OH
HO
H
O
OH
CH2
OCOCH3
22
19
18
solvent
17α
10
5
13
16
17β
2
11
7
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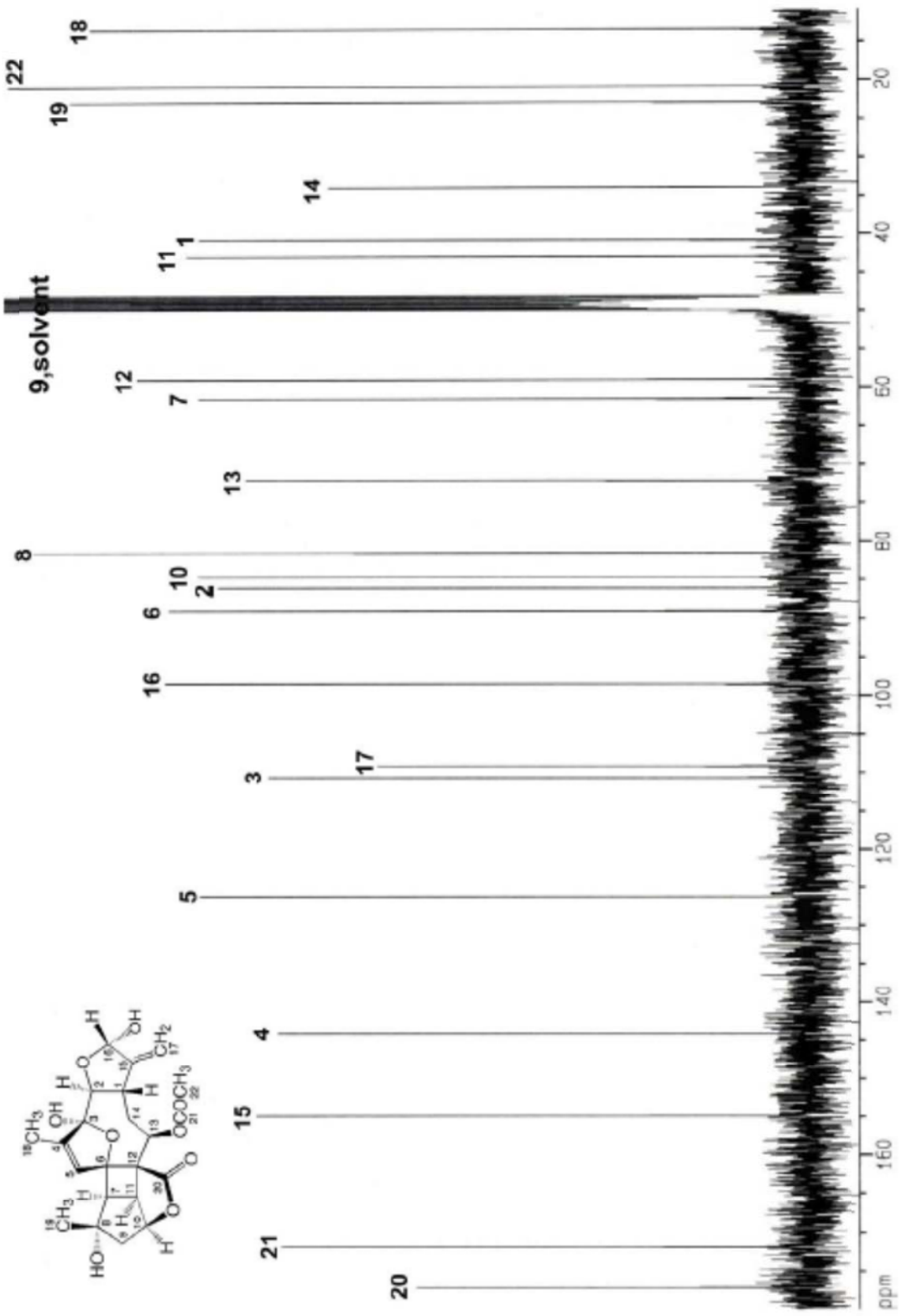
9α
14β
9β
14α
ppm
6
5
4
3
2
1


18
22
19
14
1
11
9,solvent
12
7
13
8
10
2
6
16
3
17
5
4
15
21
20
ppm
20
40
60
80
100
120
140
160

9 Curriculum Vitae

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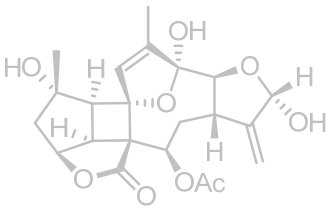
June 27th, 1983, French

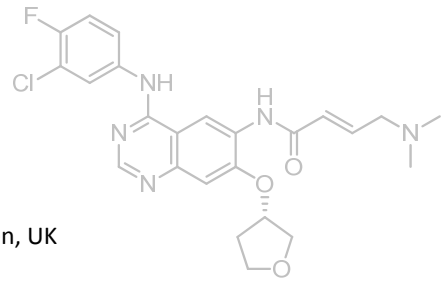
Education

Since Oct. 09	PhD **in the Mulzer group** (University of Vienna), Austria
2006 – 07	**Technical University of Vienna** (TU Wien), Austria
2005 – 06	**Sandwich Year (12-month internship)** at Boehringer-Ingelheim, Austria
2003 – 05	**Ecole Nationale Superieure de Chimie de Montpellier**, France
2001– 03	University of Orléans, **Institut Universitaire de Technologie**, France



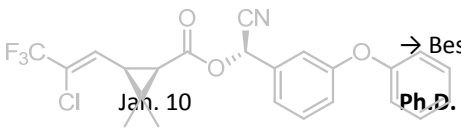
Relevant work experience

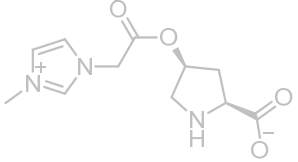
Sept. 07- Sept. 09	**Full time contract at Boehringer-Ingelheim,** Austria
	→ R&D in the Medicinal Chemistry Department
July-August 04	**Technician at Biosys**, Herts., UK
	→ Selective extraction of insecticidal pyrethrins
April – July 03	**Training placement at Rothamsted Research**, Harpenden, UK
	→ Synthesis of the sandfly *Lutzomyia longipalpis* sex pheromone



Awards

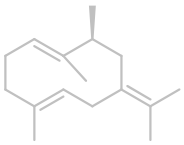
Sept. 12	**"Syngenta workshop for talented PhD chemistry students" award**, Stein, Switzerland
	→ Best contribution to all sessions (chemistry, innovative ideas, soft skills)
Jan. 10	**Ph.D. Scholarship** from the University of Vienna; Initiativkolleg "Functional Molecules"
Sept. 03	**First place award for my undergraduate studies** at the University of Orléans, France
	→ Best overall grades over 2 years out of 86 chemistry students





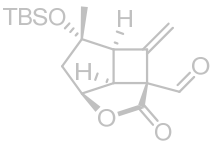
Teaching activities

Since Oct. 09	**Laboratory Assistant** at the "Organic chemistry I & II" exercises, University of Vienna
	→ Supervising undergraduate students 2 weeks/semester
Since Oct. 09	**Practical training** of Bachelor and Master students, University of Vienna
	→ Teaching laboratory practice of advanced chemical reactions 4 weeks/semester
Sept. 07- Jan. 09	Involved in the education team at Boehringer-Ingelheim in Austria
	→ Planning/organizing meetings to deepen chemistry knowledge of technical staff



Other work experience and social activities

Since 2010	Taking part in the yearly "Nikolauszug". A two day event organized by the "Arbeiter Samariter Bund", which allows disabled children to spend a week-end away during Christmas time
October 03	Work placement (drawing office) at Barry-Wehmiller Europe Ltd., St. Albans, UK
August 02	Counsellor in summer camp for children, Montalivet, France
July-August 01	Counsellor in summer camp for children, Bogève, France)

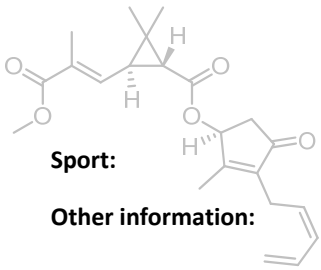


Other skills & interests

Languages: **French** Native fluency

English Fluent (with French accent)

German Fluent (with French accent)



Sport: Running, biking & climbing; Black belt in Judo, travelling to discover new dive-sites

Other information: Appointed first aider at work (renewed in 2013), full driving license

Referees

- **Prof. Johann Mulzer,** PhD advisor, University of Vienna, Austria

  johann.mulzer@univie.ac.at

- Prof. Peter Gärtner, Master thesis advisor (TU Vienna)

  peter.gaertner@tuwien.ac.at

- **Dr Tony Hooper,** advisor at Rothamsted Research, UK

  tony.hooper@bbsrc.ac.uk