universität wien

DISSERTATION

Titel der Dissertation

„Terpenoids as Synthetic Targets: The Pursue for Providencin and the Total Syntheses of Penifulvins A, B and C“

Verfasserin

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Meinen Eltern Monika und Helmut

Und meinem Onkel Franz

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Ein unsichtbarer Feind ist's, den ich fürchte,
Der in der Menschen Brust mir widersteht,
Durch feige Furcht allein mir fürchterlich--
Nicht, was lebendig kraftvoll sich verkündigt,
Ist das gefährlich Furchtbare. Das ganz
Gemeine ist's, das ewig Gestrige,
Was immer war, und immer wiederkehrt
Und morgen gilt, weil's heute hat gegolten!
Denn aus Gemeinem ist der Mensch gemacht,
Und die Gewohnheit nennt er seine Amme.

(*Friedrich Schiller *Wallensteins Tod)

Publications, Oral Presentations and Poster Presentations resulting from this Thesis

Publications:

1. Gaich, T.; Arion, V.; Mulzer, J. Synthesis of the cyclobutane moiety of providencin. Heterocycles **2007**, 855-862.

2. Schweizer, Eliane; Gaich, Tanja; Brecker, Lothar; Mulzer, Johann. Synthetic studies towards the total synthesis of providencin. Synthesis, **2007**, 3807-3814.

3. Gaich, Tanja; Weinstabl, Harald; Mulzer, Johann. Synthetic efforts towards the complex diterpene Providencin. Synthesis **2009**, ASAP.

4. Gaich, Tanja; Mulzer, Johann. Total Synthesis of (-)-Penifulvin A, an Insecticide with a Dioxafenestrane Skeleton. Journal of the American Chemical Society **2009**, 452-453.

Oral and Poster Presentations:

1. Poster presentation at the Gordon Research Conference Tilton School, USA, 22-27 July
Title of Presentation: "Towards the Total Synthesis of Providencin"

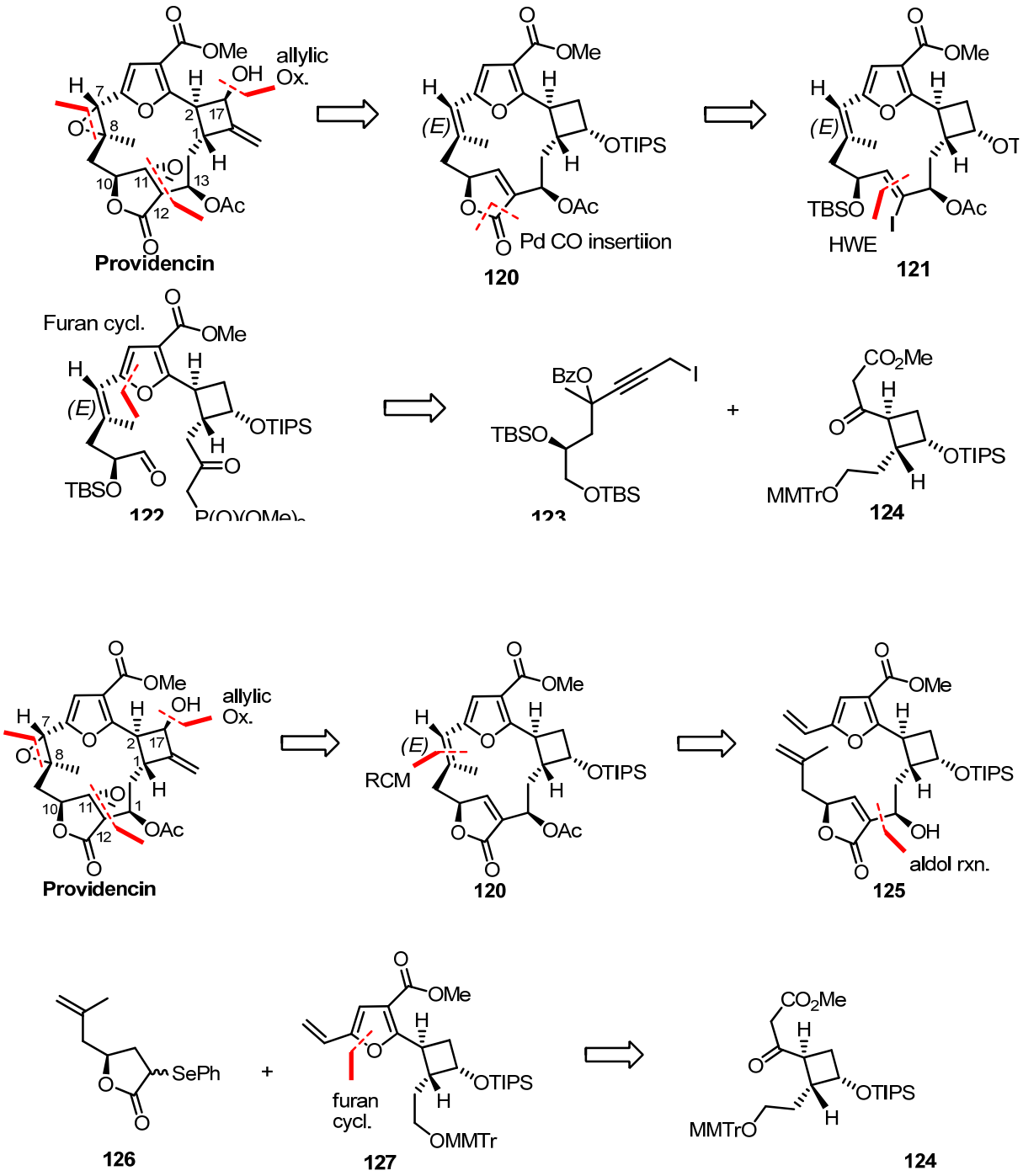
2. Oral presentation at the 3rd Doktoranden workshop Universität Freiburg, 27-29 February 2008
Title: " Towards the Total Synthesis of Providencin"

3. Short presentation in the course of the H.C. Brown lecture, Purdue University, USA, April 2006
Title of Presentation: "Towards the Total Synthesis of Providencin"

4. Poster presentation at the BOSS 11 meeting**,** Ghent, Belgium, 13-18 July 2008
Title of Presentation: "The Pursue for Providencin".

A. Graphical Abstract

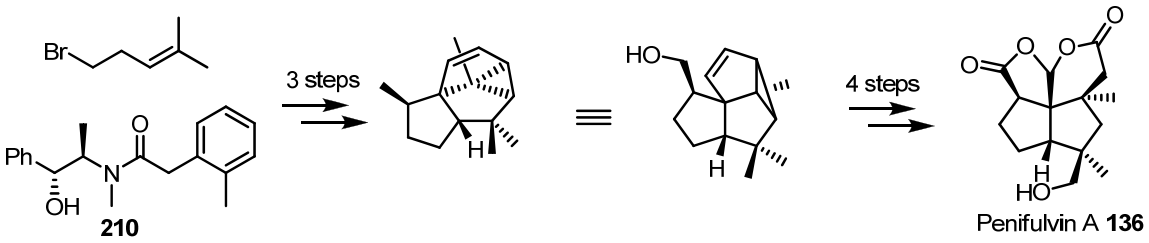
Synthetic Studies towards Providencin



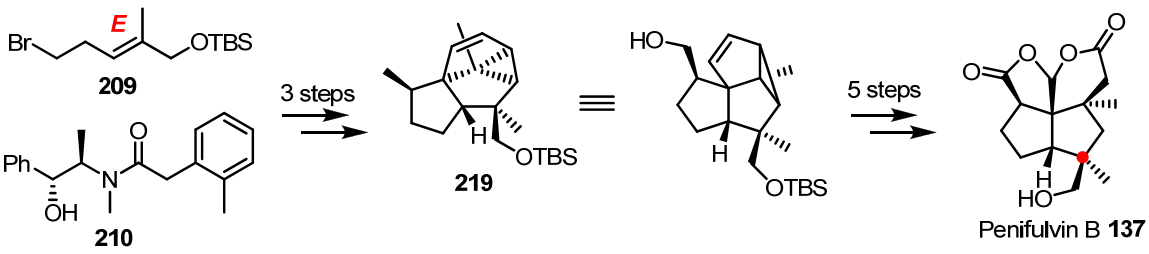
B. Graphical Abstract

Biomimetic Total Syntheses of Penifulvins A, B and C

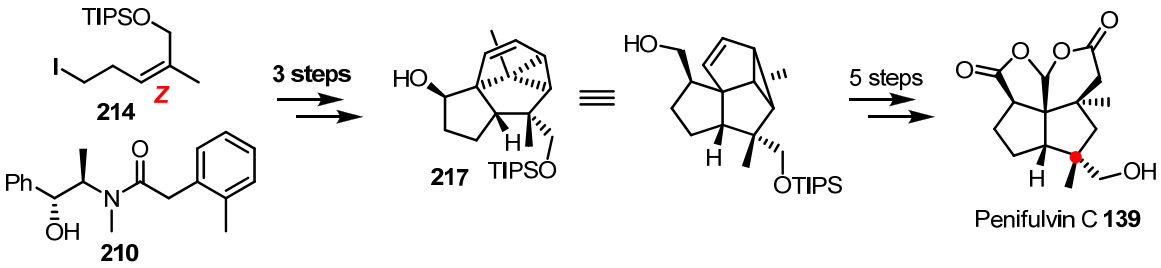
Total Synthesis of Penifulvin A



Total Synthesis of Penifulvin B



Total Synthesis of Penifulvin C



C. Summary

This Ph.D Thesis describes the first total syntheses of penifulvin A, B and C and synthetic efforts towards the total synthesis of providencin.

Penifulvins are sesquiterpenoids that represent an unprecedented dioxa[5.5.5.6]fenestrane structure type. Amongst all five members of this family, penifulvin A is biologically the most interesting one. It displays a very potent antiinsectan activity especially against the fall armyworm *Spodoptera frugiperda*, which is the mayor pest of corn on the North- and South-American continent and in China. So far no SAR data are available and a short, flexible and stereoselective synthesis of this compound is strongly required.

The syntheses are based on their biosynthetic relationship to silphinene and mimic the possible biosynthetic pathway. The key step for the formation of the carbon-skeleton is the *meta*-photocycloaddition of an alkene with a benzene ring. The application of this key step to penifulvins B and C disclosed a new scope of this reaction, which is the stereoselective introduction of a quaternary carbon atom depending on the double bond geometry.

Providencin is a highly oxygenated diterpene belonging to the huge family of furanocembranoids. It exhibits an unprecedented hexacyclic structure containing a cyclobutane ring – a structure element that is very scarce in nature. Providencin shows modest anti cancer activity and up to date no total synthesis was achieved.

The synthetic studies to providencin conducted here, describe two approaches with different macrocyclization strategies, one being a Horner-Wadsworth –Emmons reaction and the latter a ring-closing metathesis reaction. The closure of this macrocycle is the most challenging part in this synthesis as the ring is extremely strained. Both synthetic studies take advantage of Wipf's furan cyclization and start from bicyclo[3.2.0]heptenone, which is commercially available, and brings with it the cyclobutane ring. A versatile chiral resolution for this compound is presented here. Additionally model studies on the functionalization of the cyclobutane ring have been carried out.

D. Zusammenfassung

Die vorliegende Doktorarbeit beschreibt die erste Totalsynthese von Penifulvin A, B und C, und synthetische Studien zur Totalsynthese von Providencin

Penifulvine sind Sesquiterpene mit einem neuartigen Dioxa[5.5.5.6]fenestrane Strukturtyp. Unter den fünf Mitgliedern dieses Strukturtyps ist Penifulvin biologisch der interessanteste Naturstoff. Es sehr gute insektizide Eigenschaften besonders gegen *Spodoptera frugiperda.* Dabei handelt es sich um einen der Hauptschädlinge der Landwirtschaft am gesamten amerikanischen ontinent und in China. Bis jetzt sind noch keine SAR Daten von Penifulvin A verfügba. Aufgrund dieser biologischen Wirksamkeit ist besonders für Penifulvin A ein schneller, flexibler und stereoselektiver Zugang erforderlich.

Die durchgeführten Synthesen basieren auf der biogenetischen Verwandtschaft der Penifulvine zu Silphinen. Dabei wurde ein möglicher biosynthetischer Zugang nachgestellt.

Um das Kohlenstoffgerüst aufzubauen wird eine *meta*-Photocycloaddition zwischen einem Olefin und einem Benzen Ring verwendet. Die Anwendung dieser Reaktion auf Penifulvin B und C hat gezeigt, dass auch bei Verwendung einer dreifach-substituierten Doppelbindung das beim neu entstandenen quartärnaren Kohlenstoffzentrum die Konfiguration mit der Doppelbindungsgeometrie korreliert.

Providencin ist ein hochoxygeniertes Diterpen, welches der Furanocembranolid Familie angehört. Es besitzt eine komplexe hexacyklische Struktur mit einem Cyclobutan Ring – einem sehr seltenenStrukturelement bei Naturstoffen. Providencin zeigt Anticancer Eigenschaften, wenn auch mit mässiger Aktivität. Bis heute wurde noch keine Totalsynthese erfolgreich zu Ende geführt.

Die hier durchgeführten synthetischen Studien von Providencin beinhalten zwei Strategien zur Makrozyklisierung. Die erste ist die Horner-Wadsworth-Emmons reaktion und die zweite ist eine ringschliessende Metathese Reaktion. Diese Makrozyklisierung stellt die synthetische Hauptherausforderung dar, da der Ring sehr hohe Ringspannung aufweist. Beide Zugänge verwenden die Wipfsche Furansynthese, und beginnen bei dem käuflichen Bicyclo[3.2.0]heptenon. Dadurch wird der Cyclobutan Ring mitgebracht, mit dem Nachteil dass das Material optisch aktiv gemacht werden muss. Wir haben für dieses Problem eine enzymatische kinetische Racematspaltung entwickelt die schnell und in grossen Mengen optisch aktives Material (98%ee) zugänglich macht. Zusätzlich wurden noch Modellstudien zur Funktionalisierung des Cyclobutan Rings durchgeführt.

Table of Contents

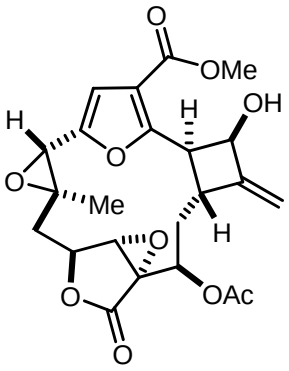
1. Providencin: Synthetic Studies on Macrocyclization Reactions

1.1 Introduction

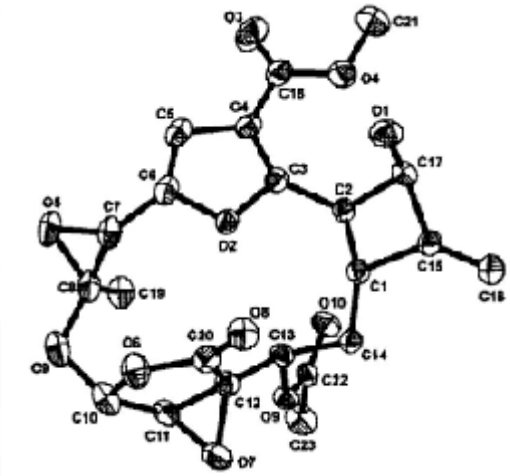
Providencin **1** (0.012% dry weight) has been isolated by Rodriguez *et al.* in 2003 from the seaplume *Pseudopterogorgia kallos* (Bielschowsky, 1918), collected in the Southwestern Carribean Sea near Providencia Island.[1] (Figure **1**)[2]

Figure 1

The highly oxygenated hexacyclic structure of **1** is based on a previously undescribed bicyclo[12.2.0]hexadecane ring system, and was established through spectroscopic analysis and X-ray crystallographic analysis. Providencin was shown to exhibit *in vitro* anticancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. So far there is no detailed biological data available and no total synthesis of this compound was achieved. Furthermore the absolute configuration of the molecule is unknown. All this together, the low abundance, the unprecedented carbon-skeleton, the high oxidation state, the complex hexacyclic structure, the lack of biological data and the unknown absolute configuration make it an utmost attractive target for total synthesis – the sheer beauty of the molecular architecture notwithstanding.

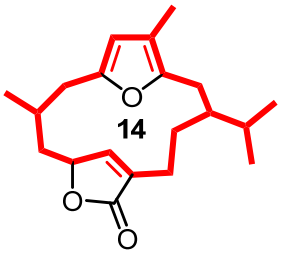


Providencin **1**

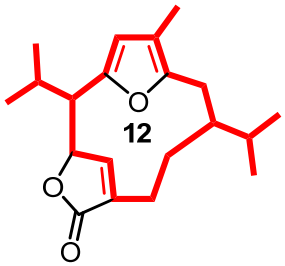


1.2 Biogenetic Origin of Providencin- the Furanocembranoid Family

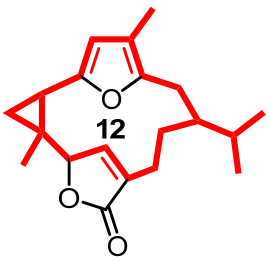
Providencin is a highly oxygenated diterpene that belongs to the family of furanocembranoides **2**[3]. Due to their rich functionalization and diverse biological activities furanocembranoides have received enormous attention over the past few years.



Furanocembranoid skeleton **2**



Pseudopterane skeleton **3**

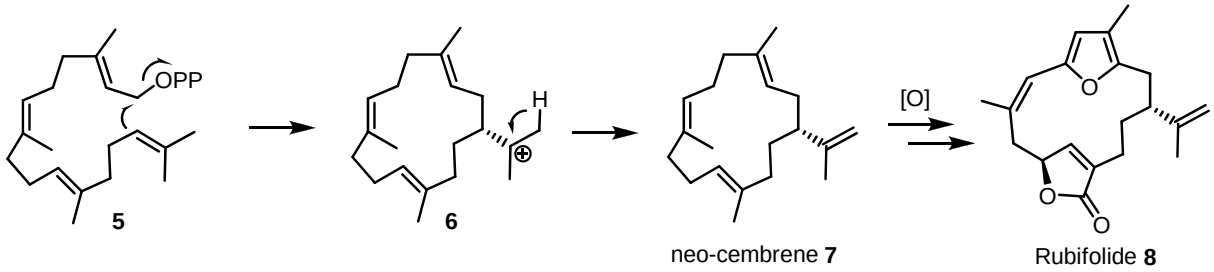


Gersolane skeleton **4**

Figure 2

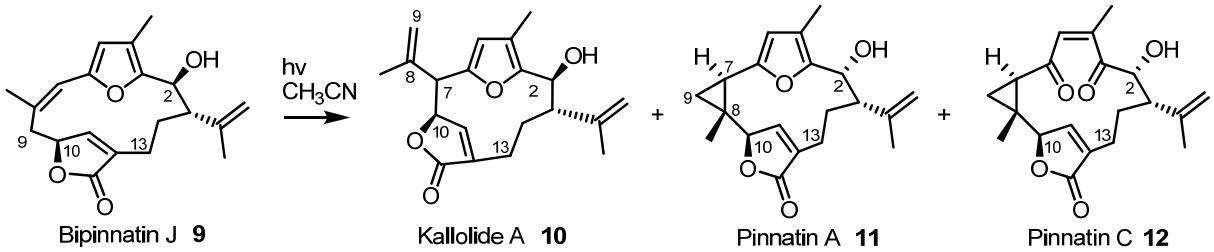
Structurally, these secondary metabolites feature a 14-membered carbocyclic framework with varying degrees of oxygenation, into which a substituted furan ring and a butenolide subunit are embedded. Two other structural families the pseudopteranes **3** and the gersolanes **4** can be biosynthetically delineated from the furanocembranoids (figure **2**). Both exhibit a 12-membered macrocycle gained by skeletal rearrangement of the furanocembranoid carbon-framework. They are therefore called "rearranged furanocembranoids". They too exhibit a furan ring and a butenolide moiety.

The biosynthesis of furanocembranoids starts with a cationic macrocyclization of geranylgeranyl-pyrophosphate **5**, leading to intermediate carbenium ion **6** which upon proton loss gives the natural product *neo*-cembrene **7**[4]. Further selective oxidations introduce the furan ring, the butenolide moiety and the specific oxidation pattern of the particular furanocembranoid congener (rubifolide **8** shown in scheme **1**).



Scheme 1

The skeletal rearrangement of furanocembranoids leading to pseudopteranes and gersolides is considered to be a photochemical reaction. This assumption is further substantiated by experiments performed by Rodriguez and co-workers[5]. Irradiation of bipinnatin J **9** in acetonitrile for one hour gave a mixture of products **10**:**11**:**12** in a 120:1:6 ratio. The major pseudopterane framework results from a suprafacial photochemically allowed 1,3-allyl-shift. Thereby C9-C10-bond is homolytically cleaved and C10 reacts with C7 and thus performs the ring contraction (scheme **2**). Concomitant rearrangement of the π-system gives Kallolide A **10**. The minor gersolide framework results from an antarafacial photochemically allowed 1,2-shift, giving rise to a bi-radical which recombines by forming the cyclopropane ring. Pinnatin C **12** is formed due to traces of singlet oxygen present during the reaction.



Scheme 2

It is noteworthy that the configuration of the benzylic alcohol is inverted during the formation of the gersolane pinnatin A **11**.

The vast number of structures belonging to these families arises from selective oxidations most likely performed by P450 cytochrome monooxygenases, albeit not much is known about these specific enzymes. Despite this large diversity almost all structures share a common oxidation pattern: a) The Methyl group on the furan ring can be oxidized up to a carboxylic acid functional group. b) C-2 is sometimes hydroxylated. c) C-13 position is very often hydroxylated and acetylated. d) The butenolide moiety is in some cases epoxidized. e) The $\Delta^{7,8}$-double bond can be oxidized, sometimes leading to consecutive transannular reactions. f) Oxidation of the furan ring occurs, and leads to a variety of structurally complex congeners. Almost all furanocembranoids, pseudopterolides and gersolides have exclusively been isolated from marine habitats, thereof mainly gorgonian octocorals. It is therefore very likely that they are biogenetically closely related, moreover that they represent different "oxidation stages" *en route*. Some prominent members are depicted in figure **3**. For instance

bipinnatin J **9** and bipinnatin E **15** were isolated from *Pseudopterogorgia bipinnata*[6]. **9** serves as a key compound for speculations about biosynthetic diversification of this family, whereas bipinnatin E **15** is considered to be the direct precursor of Providencin (see chapter **1.4**). Rubifolide **8** and pukalide **18** were isolated from the nudibranch *Tochuina tetraquetra*[7]. Coralloidolide **13** stems from *Alcyonium coralloides*[8]. Lophotoxin is a potent neurotoxic agent. It irreversibly inhibits the nicotinic acetylcholine receptor, thereby acting as a neuromuscular toxin. It was isolated from several *lophogorgia* species and extensive biological testings have been done with it[91011]. Deoxylophotoxin **17** differs from **14** only by the epoxide functionality on the butenolide and was isolated from *lophogorgia peruana*[12].

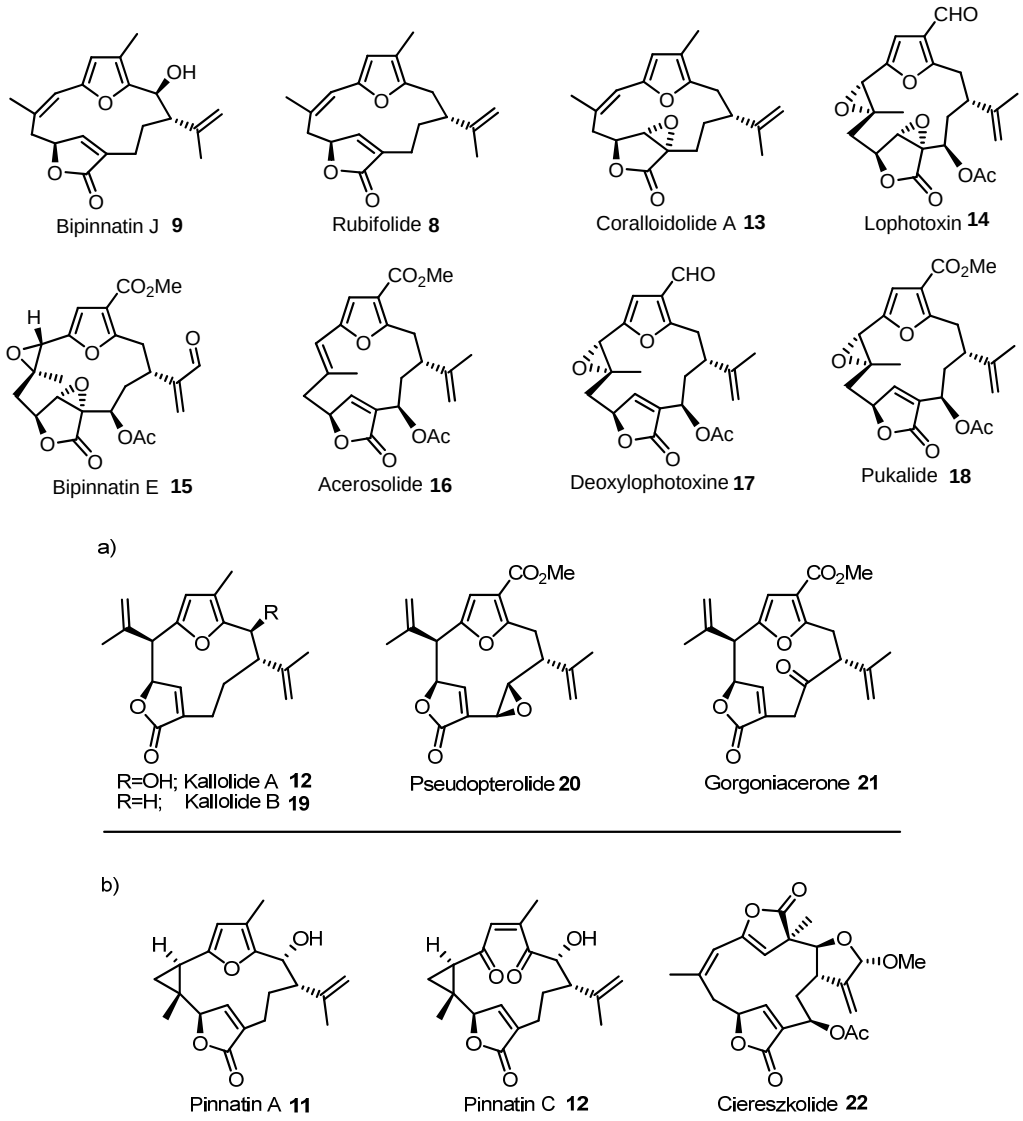


Figure 3

Higher oxidized congeners are shown in figure **4**. Very often the furan ring is oxidatively cleaved, leading to new transannular ring formations in the case of bipinnatolide E[13] **24** and corallodiolide B[14] **27**. Pinnatin C **12**, kallolide C[15] **28**, gersemolide **29**[15], rubifol[16] **24**, bipinnatolide J **25**[13] and lophodione[17] **26** exhibit a 1,4-diketone as a result of the oxidative furan cleavage.

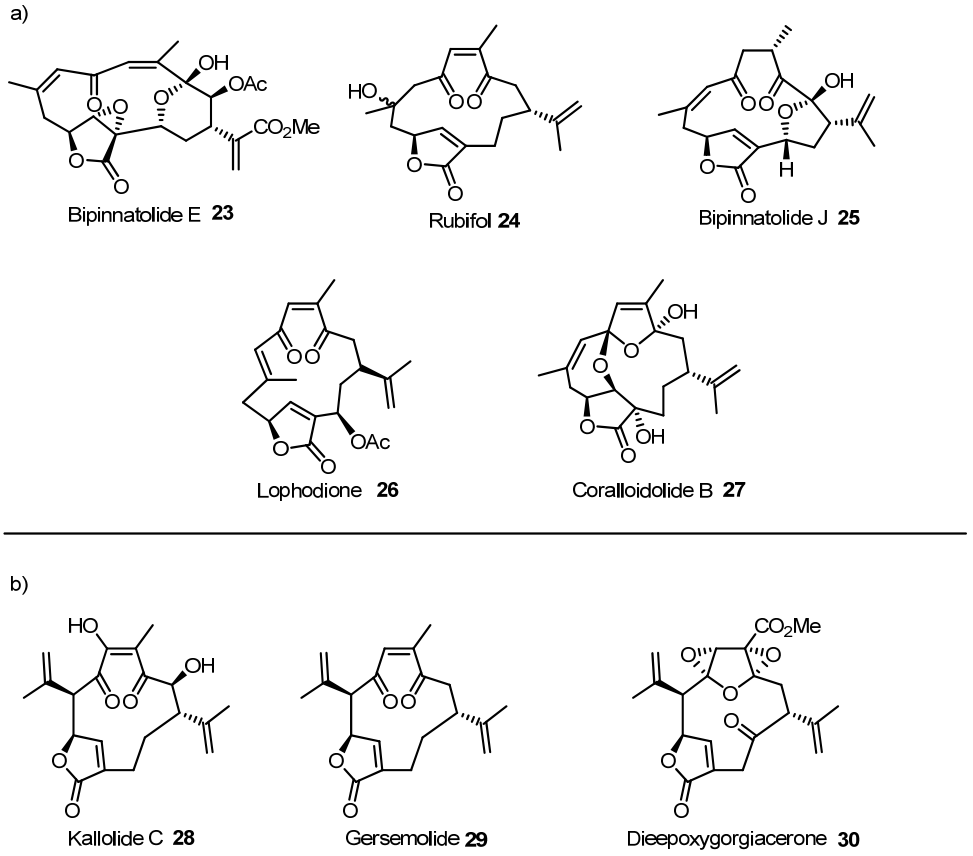


Figure 4

1.3 Proposed Biosynthetic Relations on Furanocembranoid Derivatives

Biosynthetic considerations become ever more important in total synthesis. The sheer beauty, elegance and ease with which nature puts together enormously complex structures, has inspired many chemists and the lessons acquired thereby, always lead to new insights and discoveries in organic synthesis. Albeit structurally very different from furanocembranoids in figures **3** and **4**, furanocembranoid derivatives (figure **5**) are closely related to them. Strong evidence provides the source of isolation. Just like other furanocembranoids, compounds in figure **5** have all been isolated from gorgonian octocorals.

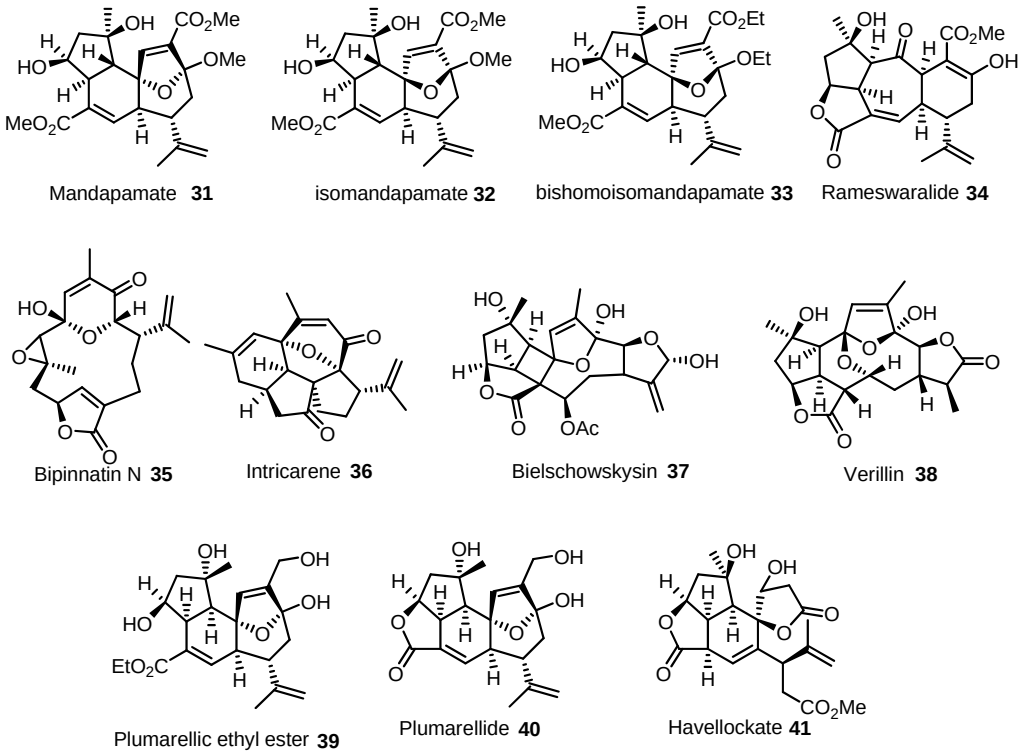
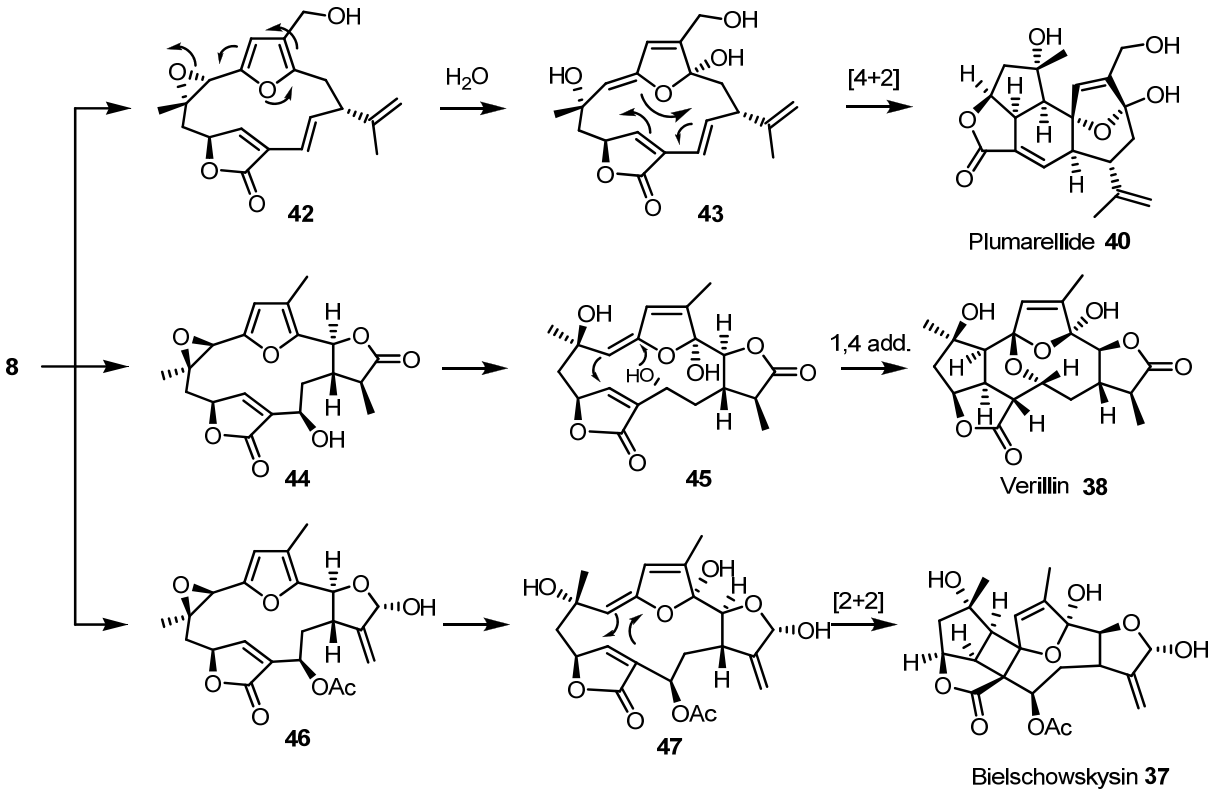


Figure 5

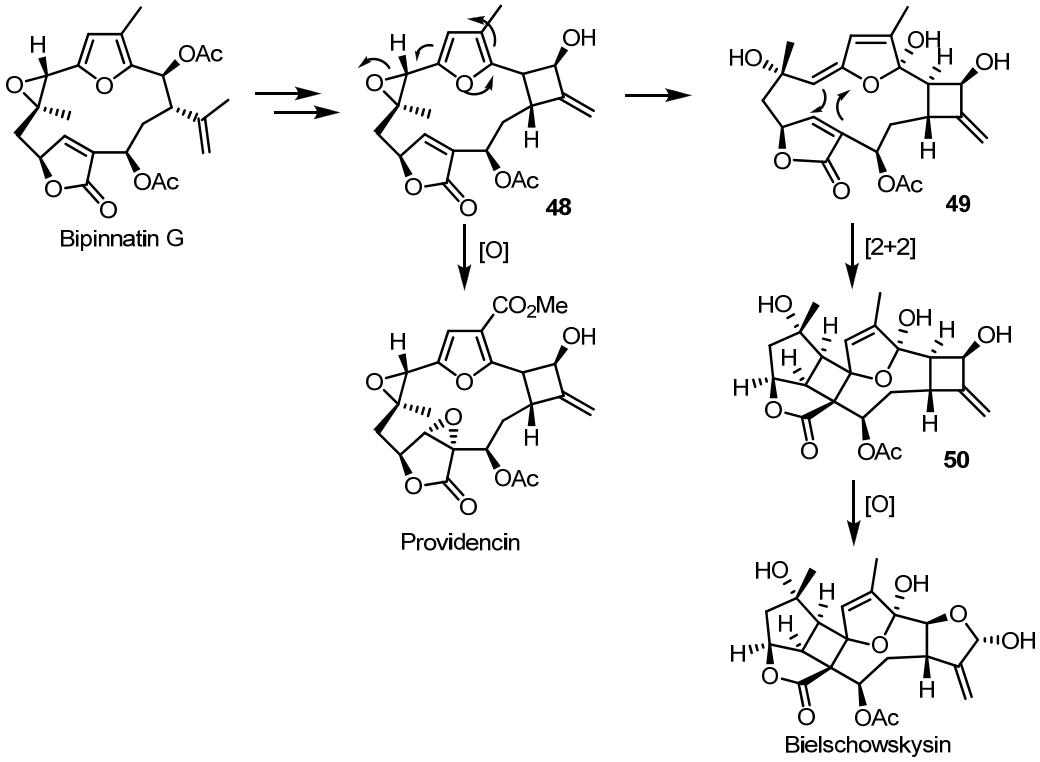
The key to the breathtaking structural variety in furanocembranoids in terms of biosynthesis is the furan ring, as it encompasses a rich spectrum of oxidation chemistry. The new functionality generated in these oxidations, discloses possibilities for C-C-bond formations *in situ*. The cascades triggered thereby lead to highly complex polycyclic structures, named furanocembranoid derivatives to which providencin **1** belongs. This characteristic nature of furanocembranoids has prompted many biosynthetic proposals and culminated in a biomimetic total synthesis of intricarene which is discussed in chapter **1.5.5**.

Trauner *et al.* have put foreward several biosynthetic hypotheses between furanocembranoids and their derivatives[18]. For example plumarellide[19] verillin[20] and bielschowskysin[21] can be obtained *via* very elegant cascades from rubifolide **8** as outlined in scheme **3**. In the case of plumarellide **40**, rubifolide **8** is oxidized at the methyl group of the furan ring to give an allylic alcohol. Additionally a conjugated double bond to the butenolide is introduced yielding compound **42**. The cascade starts with an epoxidation of the benzylic double bond. The epoxide is opened by the furan ring leading to compound **43**. The reaction sequence terminates with a transannular Diels Alder reaction giving plumarellide. The natural products mandapamate[22] **31**, isomandapamate[23] **32** and bishomoisomandapamate[23] **33** represent diastereomers of plumarellide **40** and are supposed to be obtained through the same cascade. The different relative stereochemistry arises from the epoxidation and the diastereofaciality of the Diels Alder reaction.



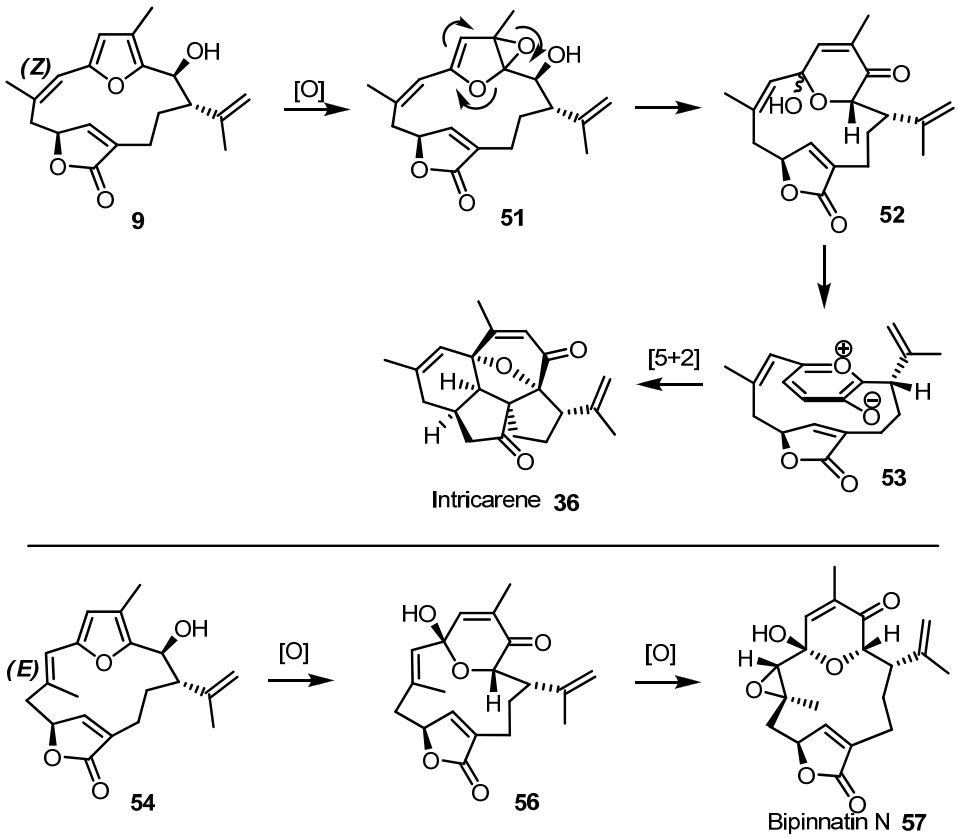
Scheme 3

The proposed route to verillin **38** involves the synthesis of the higher oxidized precursor **44**. Again epoxidation of the benzylic double bond induces the cascade, but this time a transannular 1,4-addition with acetal formation leads to verillin **38**. The carbon-skeleton of bielschowskysin **37** is thought to be obtained *via* a transannular [2+2]-cycloaddition of **47**, which again comes from the opening of the benzylic epoxide by the furan ring. This last proposal for the generation of bielschowskysin caused us some doubts, as it discounts the fact that bielschowskysin **37** and providencin **1** were both isolated from (*Pseudopterogorgia kallos*). According to literature proposals bielschowskysin is generated from rubifolide **8**, which was isolated from different organisms *Gersemia rubiformis* and from the nudibranch *Tochuina tetraquerta.* As both **37** and **1** were isolated from the same specimen, we think that a common precursor for bielschowskysin and providencin leads to both natural products as depicted in scheme **4**. Therby bipinnatin G serves as a biogenetic precursor. It is epoxidized at the benzylic double bond leading to compound **48**, which can be either transformed to providencin, or opening of the benzylic epoxide in scheme **4** facilitates the transannular [2+2]-cycloaddition cascade yielding **50**. This undergoes a Baeyer-Villiger type oxidation leading to bielschowskysin.



Scheme 4

At first glance intricarene **36** doesn't seem to have structurally anything in common with furanocembranoids. But after a detailed analysis it can elegantly be deduced from bipinnatin J **9** (scheme **5**)[24]. This domino reaction starts with an Achmatowicz type oxidation of the furan ring giving compound **52**. Dehydratisation yields oxopyrylium **53**, which undergoes a transannular [5+2]-cycloaddition with the butenolide moiety, and thus yields intricarene **36**. Just recently bipinnatin N[25] **57** a new exponent of bipinnatins has been isolated. The structure of this congener is especially interesting as it strongly supports the propsed intricarene biosynthesis. We think nature makes **57** in the same way as intricarene **36** but starting from **54** (scheme **5**). The *E*-double bond of **54** prevents a transannular [5+2]-cycloaddition reaction. Epoxidation of the trisubstituted double bond then gives **57** (scheme **5**).

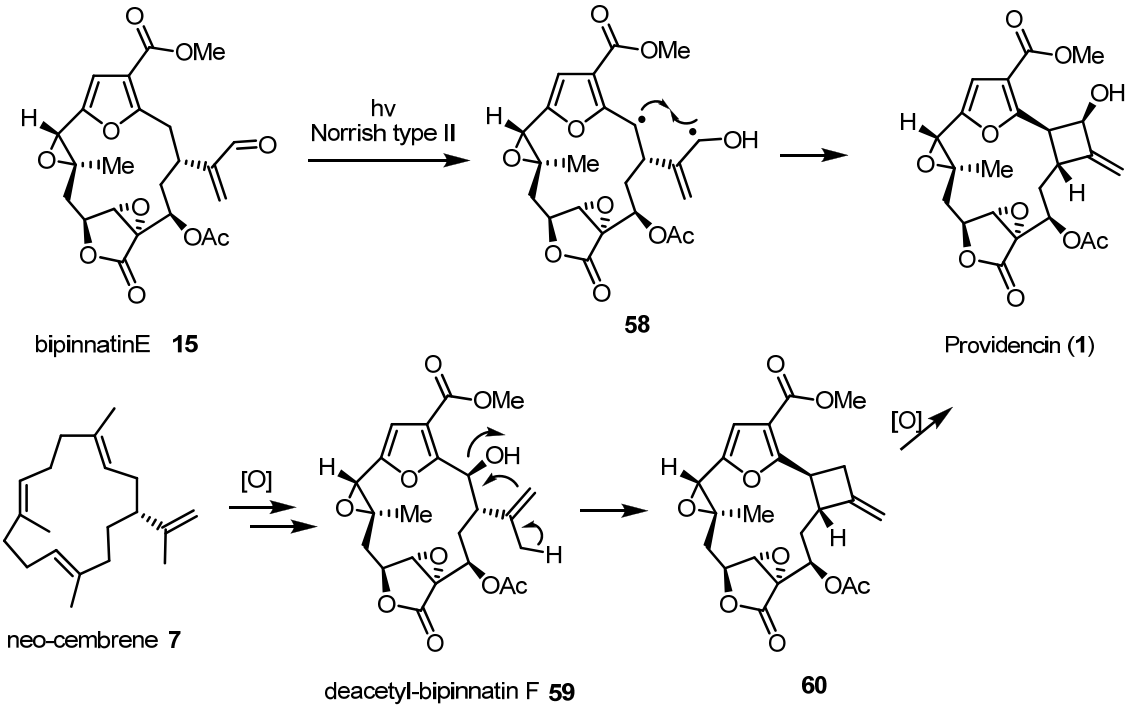


Scheme 5

Havellockate[26] **41** is obtained from a rearrangement of the isomandapamate skeleton, and rameswaralide[26] **34** stems from the mandapamate skeleton (for details see ref 18).

1.4 Biosynthetic Proposal for Providencin

The biosynthetic proposal in literature presumes bipinnatin E **15** is the direct predecessor of providencin[18] **1**. It contains a Norrish type II reaction that should form the cyclobutane ring, as shown in scheme **6**.



Scheme 6

Although there is some experimental evidence for this transformation that was done by Pattenden *et al.* on a test system,[27] (discussed in chapter **1.5.8**) there exists a second probable pathway nature can take.

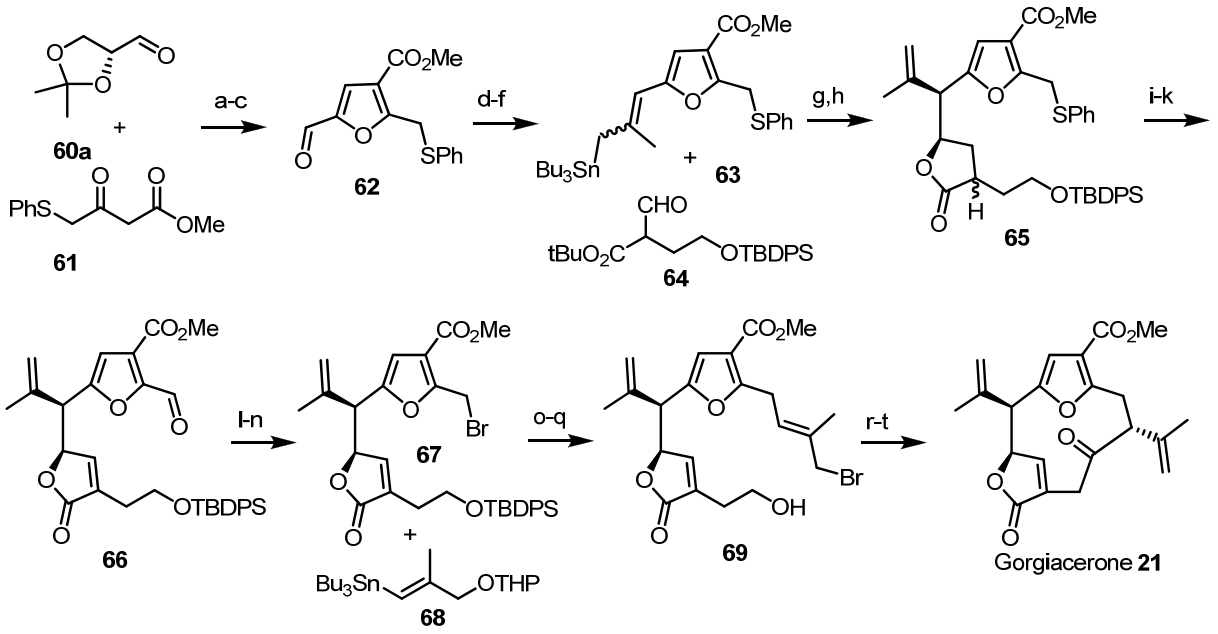
Our proposal for the biosynthesis of the cyclobutane involves a homoallyl-cation-cyclization starting from bipinnatin F. The resulting cyclobutylidene ring is hydroxylated in an allylic oxidation reaction, giving rise to providencin **1** (scheme **6**).

1.5 Previous Synthetic Works on Members of the Furanocembranolide Family.

Not surprisingly in view of the highly demanding architecture of the furanocembranoides relatively few target molecules have been synthesized so far.

*1.5.1 Paquette's Total Synthesis of Gorgiacerone[28] **21***

Gorgiacerone[29] was one of the first structures of this family to be synthesized by Paquette *et al.* in 1992. The strategic bond connections are the Lewis acid catalyzed addition of allylstannane **63** to aldehyde **64**, which brings in the carbon atoms required for the butenolide moiety. The second strategic bond connection is Nozaki Hiyama Kishi reaction used as a macrocyclization **69** → **21** (scheme **7**). Paquette and co-workers started the synthesis by condensing glyceraldehydes **60a** to thiophenyl-acetylacetonate **61** under acidic conditions. Dehydratisation gave a thio-furyl alcohol, which was oxidized in a Swern oxidation, yielding 54% of aldehyde **62**.



Scheme 7

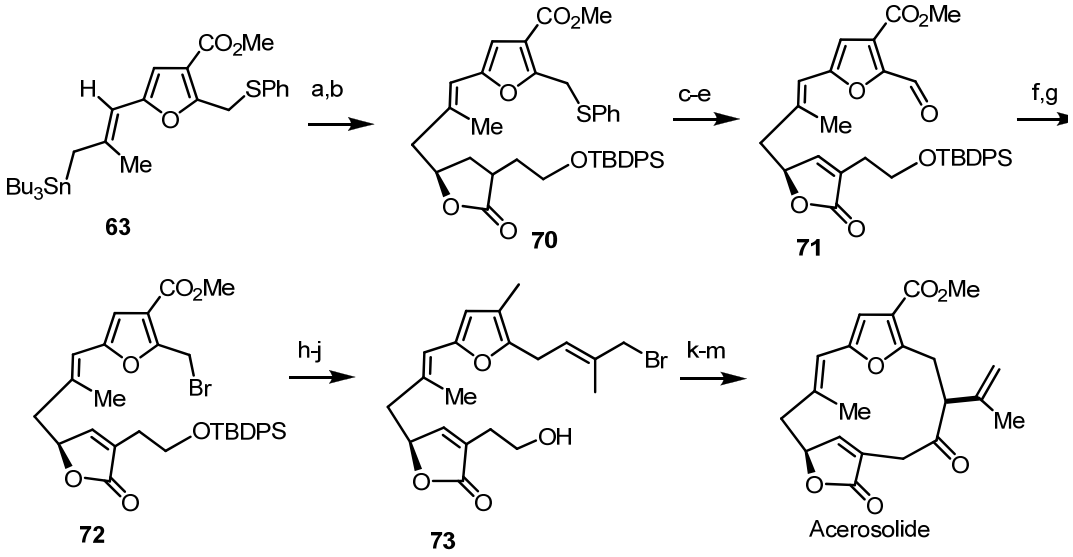
Scheme **7** Paquette's synthesis of gorgiacerone. Reagents and conditions: (a) neat; (b) HOAc, H_2O, EtOH, 80°C, 60%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, NEt_3, 90%; (d) 2-propenylmagnesium bromide, Et_2O, THF, -30°C; (e) Ac_2O, DMAP, pyridine, CH_2Cl_2; (f) $Me_2AlSnBu_3$, $Pd(PPh_3)_4$, THF, -78°C to rt, 64% over three steps; (g) BF_3 OEt_2, **64**, -78°C; (h) CSA, PhH, Δ, 67%; (i) KHMDS (2eq.), THF, -78°C, PhSeCl (2 eq.), 74%; (j) $AgClO_4$, PhH, H_2O; (k) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, THF, 90% over two steps; (l) $NaBH_4$, MeOH; (m) MsCl, NEt_3; (n) LiBr, THF, 99% over three steps; (o) $Pd(PPh_3)_4$, PhH, **68**, Δ, 75%; (p) diphenylphosphinoethane*$2Br_2$, CH_2Cl_2, 0°C o rt, 65%; (q) 40%-HF-pyridine, CH_3CN, 68%; (r) PDC, CH_2Cl_2, 0°C, 46%; (s) $CrCl_2$ (20 eq. 4Å MS THF, 20%; (t) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, NEt_3, 91%.

Addition of isopropenylmagnesium bromide and subsequent acetylation with acetic anhydride gave an allylic acetate which upon treatment with palladium tetrakistriphenylphosphine and dimethyl aluminium tributylstannane yields allyl-stannane **63** with 64% yield. This stannane was added to aldehyde **64** with borontrifluoride etherate at -78°C. Camphorsulphonic acid formed the butyrolactone (67%), which was converted to butenolide **66** *via* the introduction of a phenylselenyl group in α-position to the lactone, and a consecutive oxidative elimination reaction (66% over four steps). Compound **66** was converted to benzyl bromide **67** in a three step sequence and after sp^2-sp^3-coupling with vinyl stannane **68** the TBDPS-group was removed with 40% HF-pyridine to give **69** (33% yield). Alcohol **69** was oxidized to the corresponding aldehyde with pyridinium dichromate and submitted to a Nozaki-Hiyama-Kishi coupling, leading to the desired macrocycle in 9% yield. Oxidation of the so generated alcohol gave gorgiacerone **21**.

*1.5.2 Paquette's Total Synthesis of Acerosolide[30] **16***

Acerosolide[31] **16** was the second furanocembranoid to be completed by Paquette *et al.* one year later in 1993 (scheme **8**). The synthesis started from the same allylstannane **63** that they had used in the gorgiacerone synthesis. Stannane **63** and aldehyde **64** were treated with stannous tetrachloride in tetrahydrofuran at -78°C, establishing the benzylic trisubstituted *E*-double bond in 55% yield. The butenolide moiety and the benzylic aldehyde were introduced analogously to the gorgiacerone synthesis yielding 50% of **71**. After converting this aldehyde to bromide **72** in 95%, a sp^2-sp^3-coupling with vinyl stannane **68** led to alcohol **73** after TBDPS-deprotection (28%yield). Oxidation to the

aldehyde and Nozaki-Hiyama-Kishi macrocyclization gave the corresponding alcohol, which was oxidized to give acerosolide in 2% yield over the last three steps.

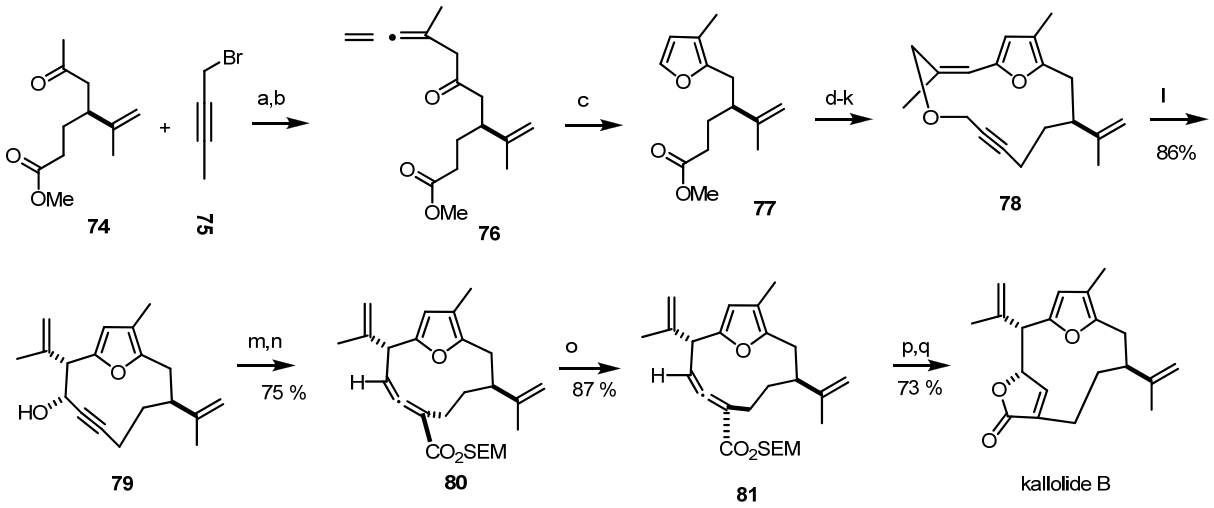


Scheme 8

Scheme **8** Paquette's synthesis of acerosolide. Reagents and conditions: (a) $SnCl_4$, THF, -78°C, **64**, 55%; (b) CSA, PhH, Δ, 90%; (c) KHMDS (2eq.), THF, -78°C, PhSeCl (2 eq.); (d) $AgClO_4$, PhH, H_2O; (e) $NaIO_4$, $NaHCO_3$; (f) $NaBH_4$, MeOH, -20°C, 50%; (g) NBS, DMS, CH_2Cl_2,95%; (h) $Pd(PPh_3)_4$, **68**, $CHCl_3$, Δ,65%; (i) diphenylphosphinoethane*$2Br_2$, CH_2Cl_2, 0°C o rt, 65%; (j) aq. HF-pyridine, CH_3CN, 68%; (k) PDC, CH_2Cl_2, 0°C, 46%; (l) $CrCl_2$ (20 eq. 4Å MS THF, 20%; (m) PDC, 4Å MS, DMF, 0°C, 25%.

*1.5.3 Marshall's Kallolide[32] B **19** Total Synthesis*

The Marshall group has succeeded in the total syntheses of rubifolide[33] **8**, deoxypukalide[34], kallolide A[35] **10** and B **19**. Marshall's group developed new furan and butenolide syntheses from allenes and silver salts, and applied the 2,3-Wittig-ring-contraction of cyclic allylic propargyl ethers to form the macrocyclic ring of furancembranoides. As an illustration the synthesis of kallolide B **19** is shown in Scheme **9**. Thus, the furan ring in intermediate **77** was generated from allenyl ketone **76** and silver nitrate. After conversion into ether **78** a [2,3]-Wittig-Still ring-contraction furnished **79**, which was converted into allene ester **80** and isomerized to **81**. Reaction with silver nitrate closed the butenolide ring to give the natural product.

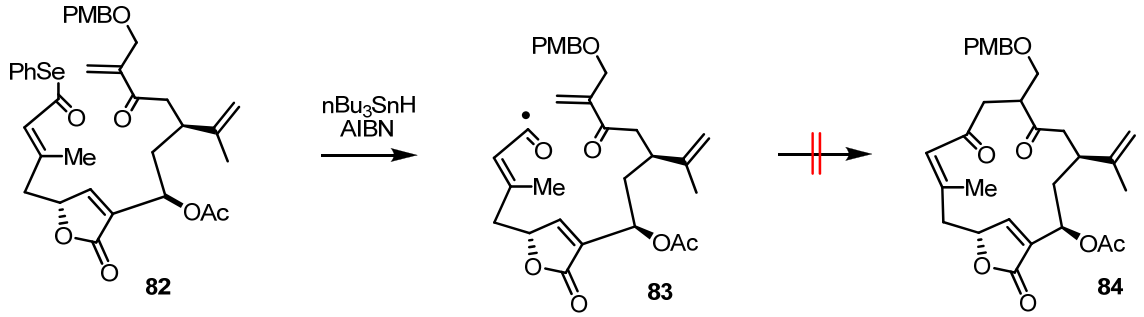


Scheme 9

Scheme **9**Marshall's synthesis of kallolide B. Reagents and conditions: (a) 1-bromo-2-butyne, $SnCl_2$, NaI, DMPU; (b) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, NEt_3; (c) $AgNO_3$, acetone; (d) DIBAL-H, $PhCH_3$, -78°C; (e) CBr_4, PPh_3, NEt_3, CH_2Cl_2; (f) *n*-BuLi, THF, -78°C, $(CHO)_n$, -78°C to rt; (g) *sec*-BuLi, DMF, -78°C; (h) $(CF_3CH_2O)_2P(O)CH(Me)CO_2Et$, KHMDS, 18-c-6, THF, -78°C; (i) MsCl, LiCl, 2,6-lutidine, DMF; (j) DIBAL-H, CH_2Cl_2, -78°C (k) NaH, 18-c-6, $PhCH_3$, Δ; (l) *n*-BuLi, THF, -78°C (m) MsCl, NEt_3, -78°C; (n) Pd_2dba_3, PPh_3, 2,6-lutidine, 2-(trimethylsilyl)ethanol, CO, THF; (o) PPh_3, CH_3CN, 55°C; (p) TBAF,DMF, THF; (q) $AgNO_3$, acetone.

1.5.4 Pattenden's Total Synthesis of Bis-deoxylophotoxin[36] ***94***

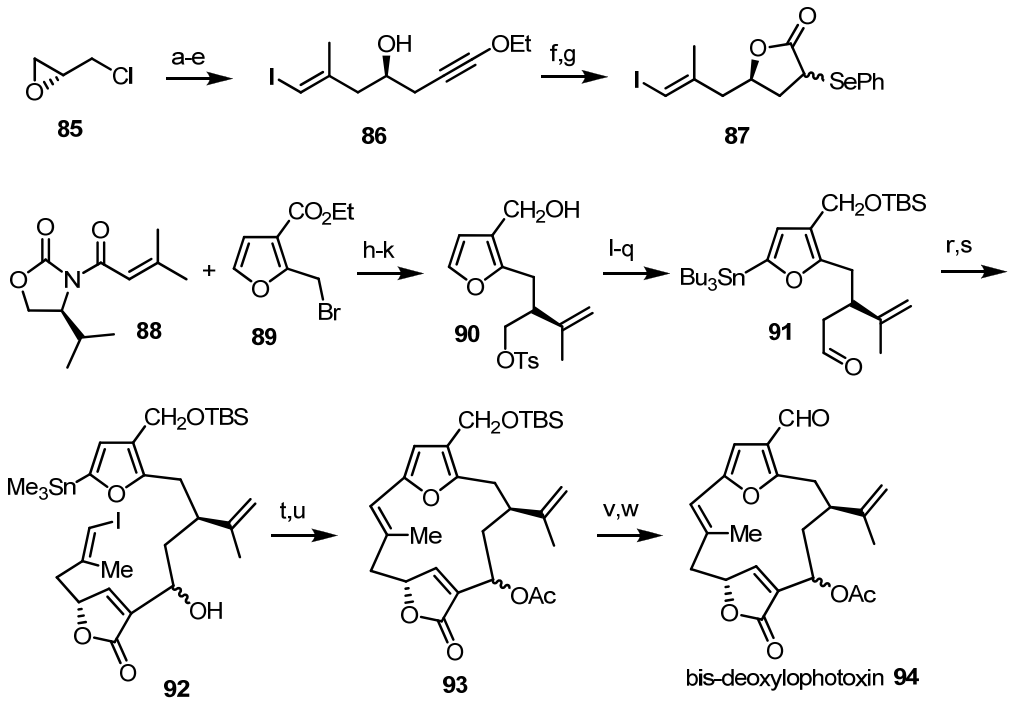
In their synthesis of *bis*-deoxy-lophotoxin **94** Pattenden *et al* first tried to prepare a 1,4-diketone *via* a free radical cyclization of phenylselenyl ester **82**. However, free radical **83** did not form **84** as desired, but underwent addition to the butenolide double bond instead (scheme **10**).



Scheme 10

The approach to *bis*-deoxylophotoxin starts with the addition of trimethylsilylacetylene to (*R*)-epichlorhydrine (scheme **11)**. Removal of the TMS-group was followed by carbometallation with iodine quench, leading to the vinyl iodide functionality. Under basic conditions the chlorhydrine was converted to the epoxide which was opened by ethoxyacetylene giving **86** in 19% yield. Ethoxyacetylene **86** was hydrolyzed under acidic conditions and converted to the γ-lactone upon heating in chloroform. Treatment of the lactone with LiHMDS and phenyl-selenyl bromide gave **87** in 59% yield. The synthesis of the furan fragment starts with a stereoselective alkylation of **88** with **89** followed by superhydride reduction to cleave off the auxiliary. The alcohol generated thereby was

tosylated and the ester at the furan was reduced to the alcohol **90** (yield 37 %). Subsequent TBS-protection, C1-chain elongation with reduction of the nitrile to the alcohol, and stannylation of the furan ring, gave after reoxidation to the aldehyde compound **91** in 29% yield. Aldolreaction of this aldehyde with **87** and oxidative elimination to the butenolide led to **92** in 74% yield. Stille coupling with compound **92** and acetylation of the alcohol gave macrocycle **93** in 11% yield. Deprotection of the TBS-group and oxidation to the aldehyde eventually yielded 47% of bis-deoxylophotoxin **94**.



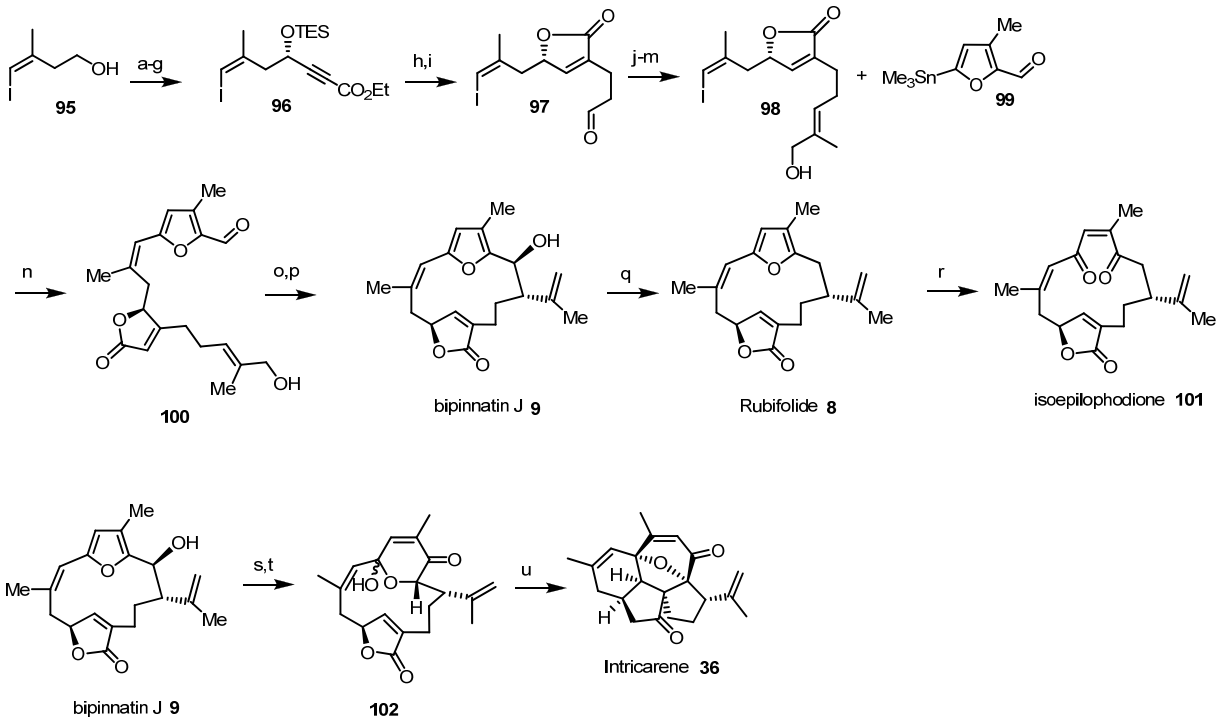
Scheme 11

Scheme **11** Pattenden's synthesis of bis-deoxylophotoxin. Reagents and conditions: (a) trimethylsilylacetylene, *n*-BuLi, BF_3, -78°C (b) TBAF, HCl, THF, 42% over two steps; (c) Me_3Al, $ZrCp_2Cl_2$, CH_2Cl_2, 3 days, I_2, THF, -30°C to rt, 60%; (d) NaOH, Et_2O, 84%; (e) 1-ethoxyacetylene, *n*-BuLi, BF_3; (f) *p*-TsOH, EtOH, 2h, then $CHCl_3$, reflux 14h, 82% over two steps; (g) LiHMDS, THF, then PhSeBr, -78°C,72%; (h) NaHMDS, THF, -78°C, then **89**, 65%; (i) Super Hydride, $PhCH_3$, -78°C, 80%; (j) TsCl, NEt_3, DMAP, 75%; (k) DIBAL-H, CH_2Cl_2, -78°C, 95%; (l) n-Bu_4CN, DMSO, 60°C, 90%; (m) TSCl, NEt_3, DMAP, 91%; (n) DIBAL-H, $PhCH_3$, -78°C to rt, 85%; (o) $NaBH_4$, MeOH, 0°C, 70%; (p), *n*-BuLi, TMEDA, *n*-BuLi then Me_3SnCl, 0°C to rt, 80%; (q) TPAP, NMO, 4Å MS, CH_2Cl_2, 75%; (r) **87**, LiHMDS, -78°C, then **91**, 93%; (s) H_2O_2, CH_2Cl_2-pyridine, 0°C; (t) $AsPh_3$, Pd_2dba_3, 40°C, 20% over two steps; (u) Ac_2O, NEt_3, DMAP, 54%; (v) CSA, MeOH-CH_2Cl_2, 0°C, 78%; (w) Dess-Martin periodinane, CH_2Cl_2, 0°C, 61%.

1.5.5 Trauner's Total Synthesis of Bipinnatin J[37] ***9***

Syntheses of bipinnatin J **9** have been reported by Trauner, Pattenden[38] and Rawal[39]. Trauner's synthesis (scheme **12**) starts from known vinyl iodide **95**. Conversion to **96** is straight forward and proceeds with 85% yield. Deprotection of the TES group and ruthenium catalyzed *retro*-ene-reaction gave butenolide **97** (52% yield). This was elaborated to allylic alcohol **98** by a reduction/oxidation sequence. Stille coupling with furylaldehyde **99** gave **100** in 92 % yield. Allylic alcohol was transformed to the corresponding bromide and then the macrocycle was closed in a Nozaki-Hiyama-Kishi allylation to give bipinnatin J **9** in 63% yield. Rubifolide **8** was then obtained from **9** by a hydrosilylation reaction (99% yield). Isoepilophodione **101** was obtained by treating **8** with *meta*-chlorobenzoic acid. Additionally Trauner *et al.* have shown that intricarene **36** can be obtained from **9**

by a transannular [5+2] cycloaddition, as it was hypothesized for its biosynthesis. For this purpose bipinnatin J was treated with *meta*-chlorobenzoic acid in an Achmatowicz type reaction to give compound **102**, which upon dehydratisation underwent transannular [5+2]-cycloaddition to give intricarene in 21% yield.

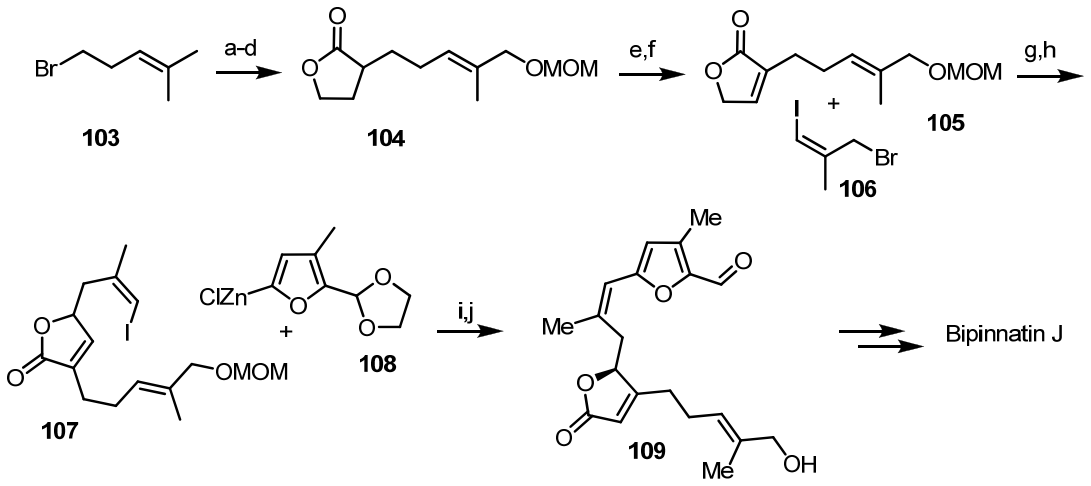


Scheme 12

Scheme **12** Trauner's synthesis of bipinnatin J. Reagents and conditions: (a) Dess-martin periodinane, CH_2Cl_2, 0°C. (b) trimethylsilylacetylene, *n*-BuLi, THF, -78°C; (c) Dess-martin periodinane, CH_2Cl_2, 0°C. (d) (S)-Alpine borane, THF, 55% over four steps; (e) K_2CO_3, MeOH; (f) TESOTf, 2,6-lutidine, THF; (g) LiHMDS, $ClCO_2Et$, THF, -78°C to -50°C; (h) aq. HF-pyridine, 85% over four steps; (i) $RuCp(MeCN)_3PF_6$, allyl alcohol, CSA, THF-acetone, 52%; (j) $Ph_3P{=}(Me)CO_2Et$, CH_2Cl_2, 84%; (k) DIBAL-H, , CH_2Cl_2, $PhCH_3$, -78°C; (l) PDC, , CH_2Cl_2, 0°C to rt (m) $NaBH_4$, MeOH, 70% over three steps; (n) $Pd(PPh_3)_4$, **99**, CuI, CsF, DMF, 92%; (o) NBS, PPh_3, , CH_2Cl_2, -5°C, 87%; (p) $CrCl_2$(10 eq.) 4Å MS, THF, 72%; (q) TFA, $HSiEt_3$, , CH_2Cl_2, 0°C, 99%; (r) *m*-CPBA, , CH_2Cl_2, 0°C, 88%; (s) *m*-CPBA, , CH_2Cl_2, 0°C; (t) Ac_2O, pyridine, DMAP, CH_2Cl_2, 81% over two steps; (u) TMP, DMSO, 140°C, 26%.

1.5.6 Rawal's Total Synthesis of Bipinnatin J[39] **9**

Rawal's synthesis of bipinnatin J **9** starts from olefin **103** (scheme **13**). Alkylation of γ-butyrolactone and allylic oxidation with selenium dioxide with subsequent MOM-protection gave **104** in 44% yield. The γ-butyrolactone moiety was transformed to butenolide **105**. This was deprotonated and alkylated with copound **106** leading to **107** in 60% yield. Negishi coupling of vinyl iodide with furan **108** and MOM-deprotection gave **109** in 81% yield. For the completion of the synthesis Rawal *et al.* performed the same endgame as Trauner' group, with a Nozaki-Hiyama-Kishi reaction for the formation of the macrocycle.

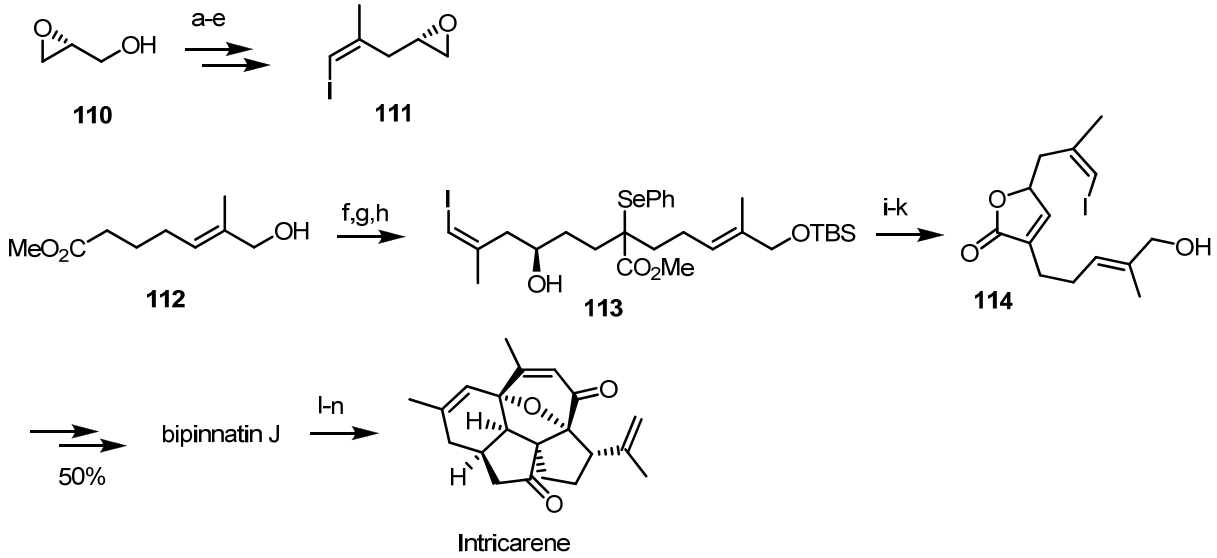


Scheme 13

Scheme **13** Rawal's synthesis of bipinnatin J. Reagents and conditions: (a) SeO_2, *t*-BuOOH, CH_2Cl_2, 67%; (b) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0°C to rt, 92%; (c) NaI, acetone, 100%; (d) LDA, γ-butyrolactone, HMPA, THF, -78°C, 72%; (e) LDA, PhSeCl, THF, HMPA, -78°C, 66%; (f) aq. H_2O_2, THF, 0°C to rt, 82%; (g) LDA, TBSCl, THF, -78°C, 100%; (h) AgO_2CCF_3, **106**, CH_2Cl_2, -40°C to rt, 60%; (i) $PdCl_2$(dppf), **108**, THF, 0°C to rt, 100%; (j) PPTS, *t*-BuOH, 90°C, 81%.

1.5.7 Pattenden's Total Synthesis of Bipinnatin J[38] **9**

Pattenden *et al.* also published a bipinnatin J and a biomimetic intricarene total synthesis (scheme **14**). Pattenden too used a Nozaki-Hiyama-Kishi allylation for macrocyclization. To build up the carbon skeleton of bipinnatin J he started from glycidol. Epoxide **111** was obtained *via* standard reactions in 31% yield. This epoxide is opened by α-seleno-ester obtained from **112** to give **113** in 60% yield. Lactonization and oxidative elimination, followed by TBS-deprotection led to butenolide **114** in 62 %yield. The completion of the synthesis was achieved *via* Trauner's endgame. Intricarene was obtained by oxidizing bipinnatin J with vanadium acetoacetate. Dehydratisation with acetic anydride and heating gave then the natural product in 3% yield over three steps.

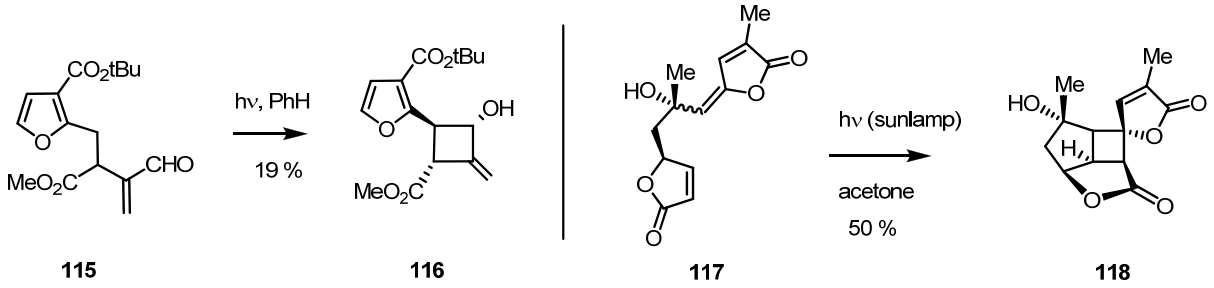


Scheme 14

Scheme **14** Pattenden's synthesis of bipinnatin J. Reagents and conditions: (a) trimethylsilylacetylene, *n*-BuLi, BF_3, -78°C to -30°C, 97%; (b) K_2CO_3, MeOH, 92%; (c) Me_3Al, $ZrCp_2Cl_2$, CH_2Cl_2, 3 days, I_2, THF, -30°C to rt; (d) TsCl, pyridine, 48% over two steps; (e) K_2CO_3, MeOH, 73%; (f) TBSCl, imidazole, DMF, 0°C,; (g) LDA, TMSCl, PhSeBr, THF, -78°C to rt; (h) NaHMDS, THF, -78°C, then **111**, BF_3 OEt_2, -78°C to rt, 60%; (i) *p*-TsOH, CH_2Cl_2; (j) H_2O_2, THF, 0°C; (k) PPTS, CH_2Cl_2, 62% over three steps; (l) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, -20°C; (m) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 30% over two steps; (n) DBU, CH_3CN, Δ, 10%.

1.5.8 Biosynthetic Studies on Bielschowskysin and Providencin

To probe the proposed biosyntheses of providencin and bielschowskysin, two model experiments for forming the cyclobutane rings for both molecules have been reported recently (scheme **15**). Pattenden published a bio-inspired photocyclization of aldehyde[27] **115** to the methylene-cyclobutanol moiety of providencin **116**, however with incorrect configuration of the secondary alcohol. Sulikowski *et al.* investigated a photo-[2+2]-cycloaddition of the bis-butenolide **117** (E/Z-mixture), which gave the highly strained bielschowskysin fragment **118** with 5:1-stereoselectivity[40].



115 **116** **117** **118**

Scheme 15

From the completed total syntheses it can be concluded that cyclizations of furancembranolide *seco*-precursors having both the furan and the butenolide rings do work under Nozaki-Hiyama-Kishi conditions. Stille cyclizations onto the furan ring are encumbered by high ring strain. Marshall avoids this strain by using a ring contraction and forming the butenolide after macrocyclic ring closure.

1.6 Retrosynthetic Analysis of Providencin based on its Structural Features.

Providencin **1** is a highly oxygenated member of the furanocembranoid family. It has an unprecedented [12.2.0] hexadecane system. It exhibits a hexacyclic structure with a furan ring, a butenolide moiety two epoxides, a cyclobutane ring and a 13-membered macrocycle. The ring strain in the macrocycle is very high making the molecule very rigid. There are two other main indications for the ring strain. Firstly the benzylic epoxide in the X-ray is orientated such, that the foregoing double bond is out of plane with the furan. In this way no conjugation can occur, and only the outer face of the double bond is accessible for epoxidation. Second, the butenolide moiety is captivated perpendicular to the furan ring thereby being conformationally locked. In this way only one face of the double bond accessible for epoxidation (figure **6**). These two points were very important for the retrosynthetic analysis. It suggests to introduce both epoxides in the last steps as the ring geometry will control the stereoselectivity of both epoxidations, and hence introduce four of the overall nine stereogenic centers of providencin in the last two steps of providencin.

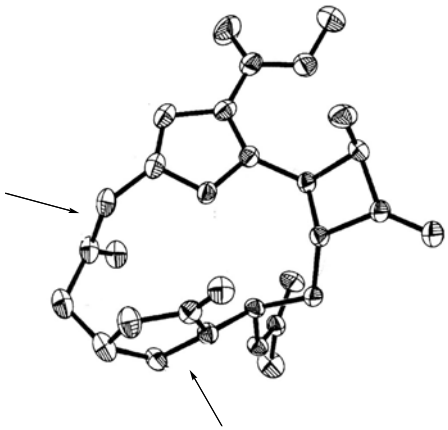
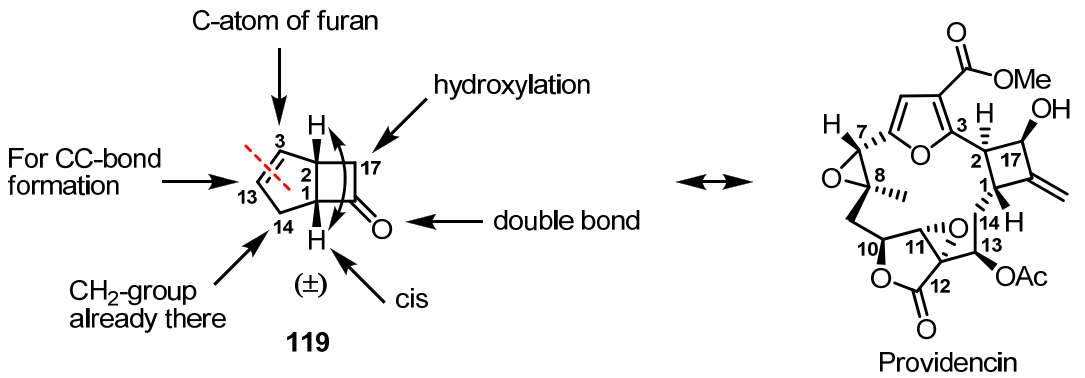


Figure 6

Another synthetically very challenging part of the molecule displays the cyclobutane ring. It is tetrasubstituted with three stereogenic centers and an exocyclic double bond. A cyclobutane ring as structure element is scarce in natural products. Examinating existing cyclobutane ring syntheses, we therefore had to realize that they were unsuitable for the application to our target molecule. Further we were aware that due to the complexity of providencin we were going to face a long and laborious synthesis, leaving us behind with the requirement of large quantities of material. Therefore we decided to start with the commercially available bicycle **119**. A short structure comparison of this bicycle with providencin makes the versatility and the synthetic problems by using it evident (figure **7**). The versatility of **119** lies in the availability of large quantities. The cyclopentene ring can be easily cleaved by ozonolysis, resulting in the formation of two adjacent substituents on the cyclobutane with different chain lengths. These two chains (at C1 and C2) have a *cis*-relationship. To get the correct *trans*-relationship, the configuration at C2 is inverted by capitalizing from the thermodynamically favored *trans*-substitution pattern at the cyclobutane ring *via* enolization. The drawback by using **119,** is the need for a hydroxylation at C17. For this purpose an allylic oxidation with selenium dioxide was envisaged.



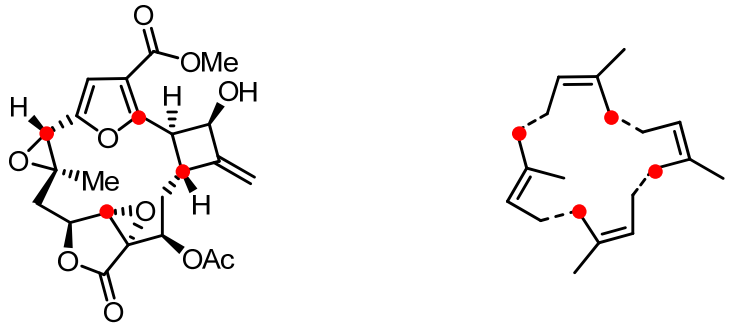
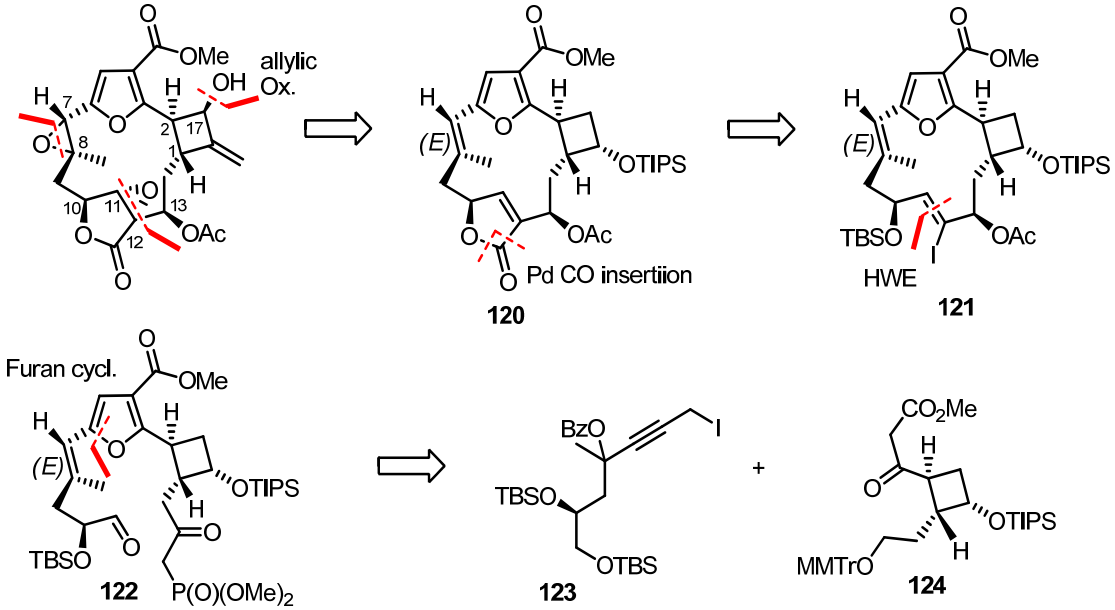


Figure 7

1.6.1 Retrosynthetic Analysis I

Our first retrosynthetic analysis used a Horner-Wadsworth-Emmons reaction as macrocyclization reaction (scheme **16**). We chose this reaction because of its huge driving force, and so hoped to overcome the ring strain thereby. In retrosynthetic view the first transformation would be the allylic oxidation followed by two epoxidations leading to **120**. The butenolide should be generated by CO-insertion into vinyl iodide **121**. The latter would be generated from the corresponding enone which would be derived in the macrocyclization giving open chain precursor **122**. For the synthesis of the furan ring we wanted to take advantage of Wipf's palladium catalyzed furan synthesis starting from propargylic β-ketoester. This would be generated by alkylation of β-ketoester **124** with iodide **123**.

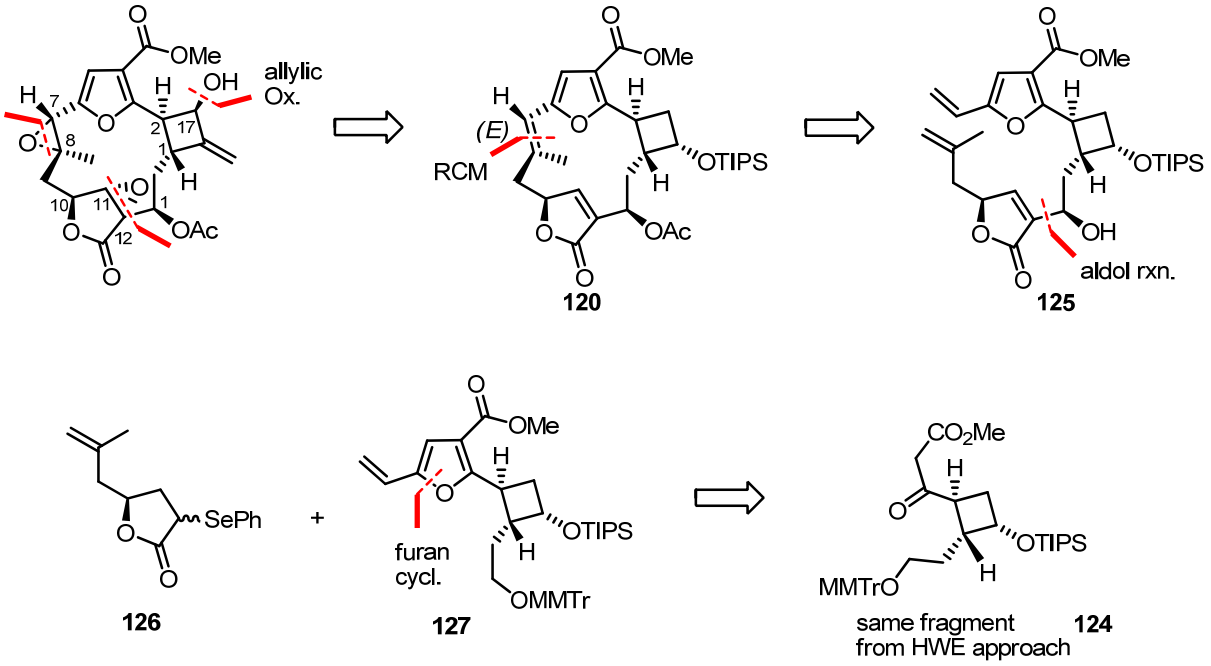


Scheme 16

1.6.2 Retrosynthetic Analysis II

The second retrosynthesis involves a ring closing metathesis reaction as macrocyclization (scheme **17**). The first retrosynthetic steps are as above an allylic oxidation and *bis*-epoxidation to give **120**. Then ring closing metathesis should lead to open chain precursor **125**. This is constructed *via* an aldol

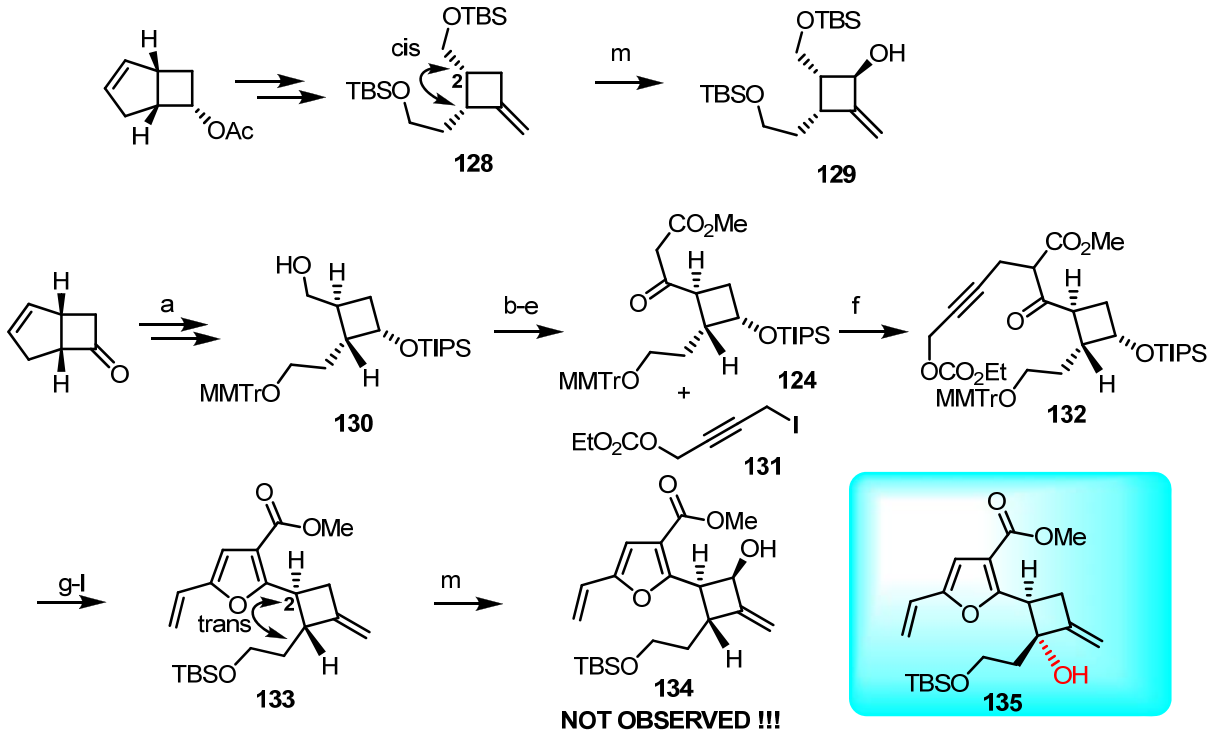
reaction to attach the butenolide, leading to fragments **123** and **124**. Again Wipf's furan synthesis would be used leading to the same β-ketoester **124** as in the former approach.



Scheme 17

1.7 Unpublished Work – A Model Study on Allylic Oxidations of Cyclobutene-ringsystems

To the best of our knowledge allylic oxidations with exocyclic cyclobutenes are completely unknown. To probe the allylic oxidation of the cyclobutene ring we did some model experiments (scheme **18**). The first model system **128** contained the exocyclic double bond and the two chains for further CC-bond formation in a *cis*-relationship. Allylic oxidation proceeded smoothly albeit with moderate 52% yield.



Scheme 18

Scheme **18** Synthesis of the modelsystem **133** for allylic oxidation: Reagents and conditions: (a) see Appendix 1; (b) EtOAc, IBX (3 eq.), Δ, 94% (c) K_2CO_3, MeOH, rt, 97%; (d) α-bromo methylacetate, Zn, THF, Δ, 95%; (e) EtOAc, IBX (3 eq.), Δ, 90%; (f) THF, NaH, **124**, then **131**, rt, 85%; (g) THF, $Pd(OAc)_2$, dppf, K_2CO_3, Δ, 72%; (h) 1,1,1,3,3,3-hefafluoroisopropanol, CH_2Cl_2, MeOH, 89%; (i) TBAF, THF, 88%; (j) TBSCl, imidazole, DMF, 76%; (k) IBX, DMSO, 92% (l) PPh_3MeBr, KO*t*Bu, 88% (m) *t*-BuOOH, SeO_2, CH_2Cl_2, 42%.

As the real system would contain the two substituents at the cyclobutane ring not in a *cis*- but a *trans*-relationship we decided to synthesize a more similar model system with the correct relative stereochemistry. For this purpose alcohol **130** was converted to furan **133** as shown in scheme **18**. When we executed the allylic oxidation on this system, to our surprise not the desired compound **134** was formed, but the tertiary alcohol **135** instead. It seems therefore that the allylic oxidation is regio-sensitive to the stereochemistry at C2. The model system has one major drawback. It lacks the macrocycle with the butenolide being perpendicular to the furan. We conclude from the X-ray structure (figure **8**) that this butenolide moiety will reverse the regiochemistry of the allylic oxidation, driving the reagent back from the tertiary position, and thus form the desired secondary alcohol.

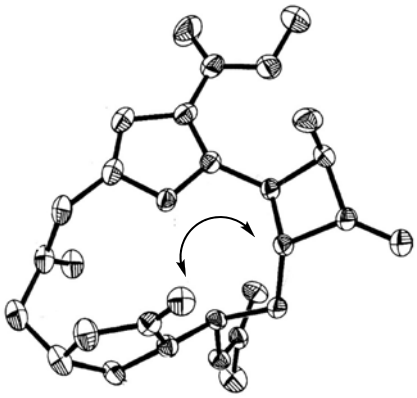


Figure 8

1.8 Experimental of the Model Study on Allylic Oxidations

See Appendix 1

1.9 Published Work – Synthetic Studies towards the Total Synthesis of Providencin

See Appendix 2

1. Gaich, Tanja; Arion, Vladimir; Mulzer, Johann. **Synthesis of the cyclobutane moiety of providencin.** Heterocycles (2007), 855-862.
2. Schweizer, Eliane; Gaich, Tanja; Brecker, Lothar; Mulzer, Johann. **Synthetic studies towards the total synthesis of providencin.** Synthesis (2007), (24), 3807-3814.
3. Gaich, Tanja; Weinstabl, Harald; Mulzer, Johann. **Synthetic efforts towards the complex diterpene Providencin.** Synthesis (2009), ASAP.

1.10 Experimental - Synthetic Studies towards the Total Synthesis of Providencin

See Appendix 3

1.11 Conclusion

In conclusion we have developed 2 synthetic routes to providencin **1**. The major synthetic challenge in the total synthesis of this natural product is the highly strained macrocycle. We were able to work out two different macrocyclizations, the first one being a Horner-Wadsworth-Emmons reaction (scheme **16**), and the second one being a metathesis reaction (scheme **17**).

Our syntheses are both centered around Wipf's palladium catalyzed method[41] for furan synthesis and the use of bicycle **119** (figure **7**).

Bicycle **119** was a crucial building block, as it is commercially available in large quantities, albeit only in racemic form. Therefore we were forced to develop a chiral resolution giving large quantities of enantiopure **119** in a short time. The macrocyclic building blocks which we elaborated further gave us very precious insights in the reactivity of such strained compounds, which are currently used in the ongoing synthetic studies and will hopefully lead to the total synthesis of providencin.

2. The Biomimetic Total Syntheses of (-)-Penifulvin A, B and C.

2.1 Introduction

The media resound with alarming reports of how the prices for corn and other field crops have increased dramatically over the past few months. In this respect pest control to avoid crop damage is of ever increasing importance. The fall armyworm (*Spodoptera frugiperda*) is native to the tropical regions of the western hemisphere from the United States to Argentina and its larvae cause enormous damage by consuming foliage of a variety of field crops, including barley, buckwheat, cotton, corn, oat, rice, sugarcane, soybean, tobacco, wheat and others[42] (figure **9**)[43]. In Florida, for example, fall armyworm is the most important pest of corn. Resistance to pesticides has been noted and is expected to become increasingly problematic from year to year. The only way out of this dilemma is the introduction of new environmentally benign pesticides.

Figure 9

In this respect we were intrigued by two recent papers of Gloer et al., which describe the isolation of novel sesquiterpenoids named penifulvin A, B, C, D, E and hydroxyl-silphinenic acid from the fungus *Penicillium griseofulvum* (syn. *P. patulum* Bain.; *P. urticae* bain.).[4445] From these metabolites penifulvin A shows significant antiinsectan activity in assays against the fall armyworm. *Penicillium griseofulvum* is distributed worldwide and has been recorded from grassland, desert soil, decaying plants, cereal grains and animal feed. Among its bioactive metabolites are, *inter alia*, roquefortine C, griseofulvin, patulin and cyclopiazonic acid.[2] Guided by preliminary antifungal and antiinsectan assays, Gloer et al obtained Penifulvins in mg quantities from an organic extract from cultures of an isolate of *Penicillium griseofulvum* Dierckx (MYC-1728= NRRL 35584). This sample was obtained from a white mycelia growth on a dead hardwood branch collected in a Hawaiian forest. The overall structures of penifulvin A, B, C, D, E and hydroxyl-silphinenic acid, including the relative stereochemistry, were secured by X-ray crystallographic analysis and revealed a highly complex

dioxa[5.5.5.6]fenestrane structure in which four rings share a central quaternary carbon atom (figure **10**).

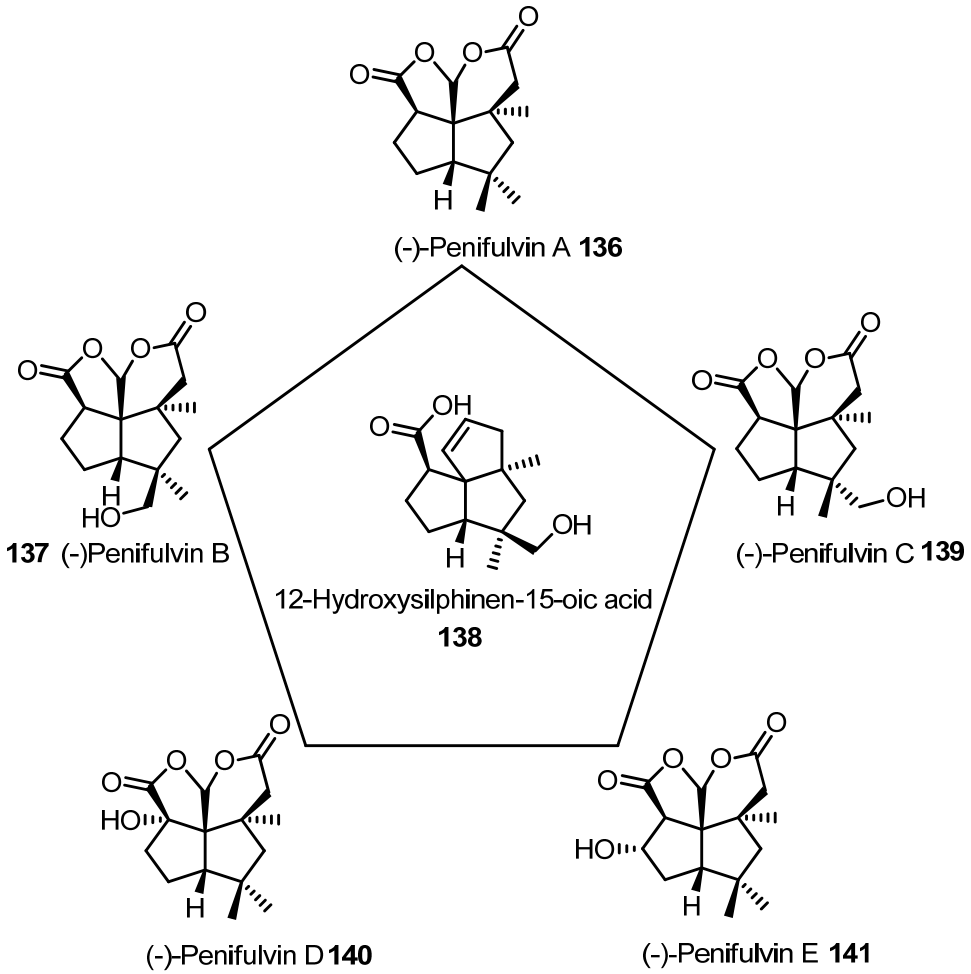


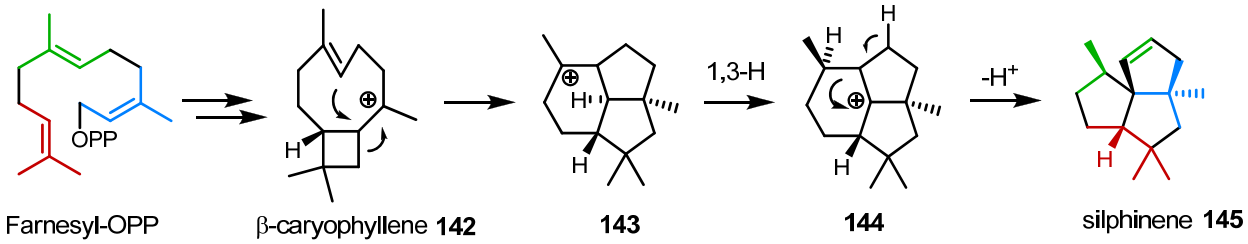
Figure 10

Additionally there are two more quaternary carbon atoms, a γ-and a δ-lactone sharing an acylal center and a total of five stereogenic centers in penifulvin A. All other penifulvins bear six stereogenic centers as they represent oxidized analogues of penifulvin A and contain an additional hydroxyl group at different positions in the carbo-skeleton. All stereogenic centers are adjacent to each other, and two quaternary carbon atoms are vicinal to each other. This dioxafenestrane ring system whose absolute configuration is unknown, previously has not been described in literature. Due to their unusual and complex molecular architecture, penifulvins represent attractive targets for total synthesis. Furthermore, for acquiring SAR data and elucidating the full bioprofile of penifulvin A, a rational access is of the essence to procure unnatural analogs.

2.2 The Penifulvin Family: Isolation and Biogenetic Origin.

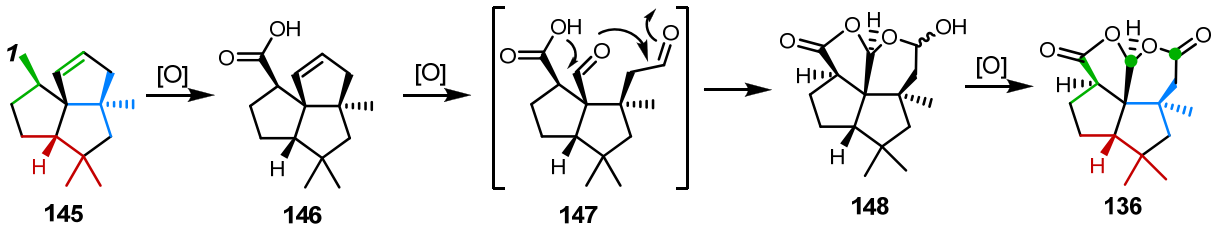
The biosynthesis of penifulvins starts, like all other sesquiterpenoid biosynthesis, from farnesyl-pyrophosphate (scheme **19**). A cationic cyclization cascade provides the the silphinene **145** carbon-skeleton. This is achieved *via* cyclization of farnesyl-pyrophosphate to the β-caryophyllene cyclobutyl

carbo-cation **142**. This rearranges with ring enlargement to a secondary carbenium ion, which is immediately trapped by the trisubstituted double bond, resulting in the formation of the second cyclopentane ring of tertiary carbenium ion **143**. A 1,3-H-shift moves the positive charge to the central atom in structure **144**. From there a Wagner-Meerwein rearrangement with ring contraction occurs, and upon deprotonation silphinene **145** is generated. For better visualization the three isoprenoid units of farnesylpyrophosphate are differently colored and it is thus easily observable how splinted the three isoprenoid starter units get incorporated into the silphinene backbone.



Scheme 19

Our proposal of the penifulvin biosynthesis implies an oxidation of methyl group ***1*** to the carboxylic acid functional group **146** (scheme **20**). In the next step the cyclopentene ring is oxidatively cleaved yielding an intermediate dialdehyde **147**, which collapses to lactol **148** exhibiting the desired dioxafenestrane ring system. A last step is an oxidation to the δ-lactone giving penifulvin A.



Scheme 20

The other members of the family are derived in analogous fashion. We propose that the additional hydroxyl-groups are incorporated at the stage of the silphinene skeleton, and thus before the oxidative cleavage of the cyclopentene ring. This hypothesis is supported by the existence of 12-hydroxysilphinene-15-oic acid, which as we think is the direct precursor of penifulvin B. Therefore we propose that the corresponding hydroxysilphinene acids for penifulvins C, D and E exist.

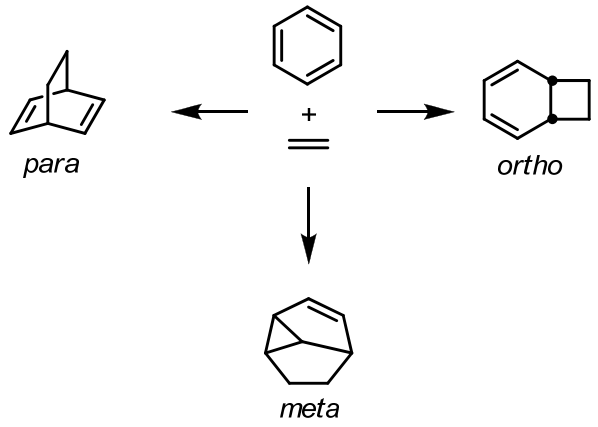
2.3 Previous Synthetic Works on Silphinene and related Terpenoids using the meta-Photo-Cycloaddition as the Key Step.

In 1981, 28 years ago, Wender *et al.* introduced the alkene-arene *meta*-photocycloaddition to the synthetic community by completing the total synthesis of α-cedrene in only four steps[46]. Since then much work was performed in this area and many applications of this most versatile reaction have

commenced in the total synthesis of complex polycyclic natural products. The *meta*-photocycloaddition was first reported simultaneously by Bryce-Smith *et al*[47]. and Wilzbach Kaplan in 1966[48]. The first intramolecular examples were published in 1969 by Morrison and Ferree[49].

2.4 Some general Aspects of the Alkene-Arene meta-Photo-Cycloaddition[50].

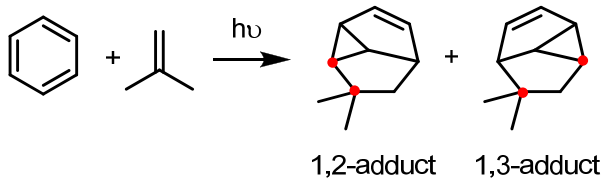
The *meta*-photocycloadditon is a photochemical reaction between an aromatic moiety and an olefin. Typically the benzene reacts from its first excited state. This requires a light source capable of emitting light with a wavelength of 253.7 nm. The mode of the reaction with the olefin can be in *ortho*-, *meta*- or *para*-fashion, and in the course of the reaction the benzene ring is doomed (scheme **21**). The *ortho*- and *meta*-adducts are more common. The focus here will lie on the *meta*-adducts (reviews dealing with other aspects see[51]).



Scheme 21

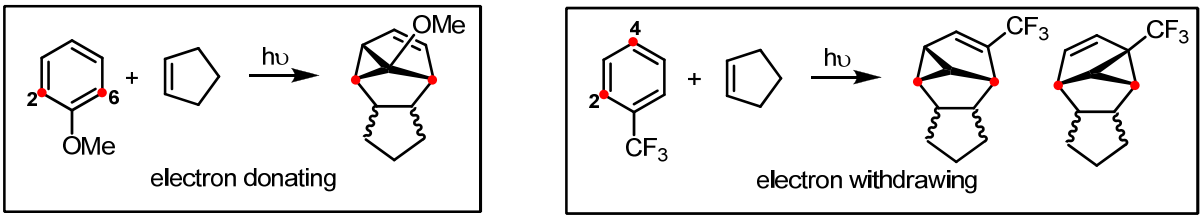
2.4.1 Intermolecular reactions

As soon as substituents are attached, either to the aromatic ring or the alkene, regioselectivity becomes an issue (for example see scheme **22**)[52]. In both products the cyclopropane ring is in allyl position to the double bond, but the distance between the olefin substituents and the cyclopropane ring is different. This is either vicinal (1,2-adduct) or in *meta*-position (1,3-adduct) (scheme **22**).



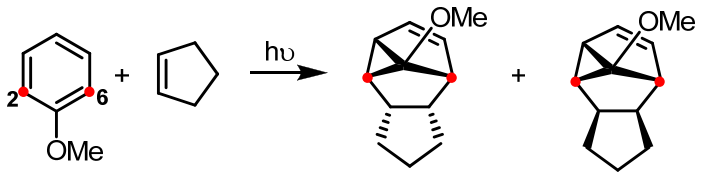
Scheme 22

The picture gets even more complicated when the benzene ring bears a substituent. It is generally observed that the alkene addition takes place preferentially 2,6-across the benzene ring if the substituent is electron donating, and preferentially 2,4 across the benzene with an electron withdrawing substituent (scheme **23**)[53].



Scheme 23

The stereoselectivity of the *meta*-photocycloaddition can be explained in the same way as in the Diels-Alder reaction *via* the *endo* rule. Secondary molecular orbital interactions as well, play an important role in this reaction. The preference in the addition of cyclopentene to anisol is depicted in scheme **24** and shows high *endo*-selectivity[54].

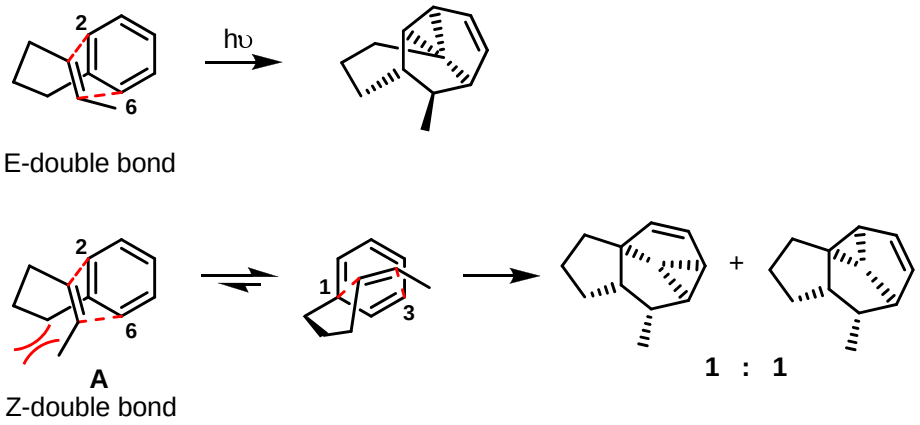


endo **87** : **13** *exo*

Scheme 24

2.4.2 Intramolecular reactions:

In intramolecular reactions regio and stereoselectivity problems do not occur independently from each other as the tether length influences the position of attack (regiochemistry), and the spatial approach of the double bond (stereochemistry). Interestingly the regiochemistry of the *meta*-photocycloaddition is also influenced by the double bond geometry. An (*E*)-double bond on a three carbon atom tether adds to the benzene ring across the 2,6- positions on the aromatic ring. Whereas a (*Z*)-double bond adds in a 1,3-fashion. Additionally the attack of the (*E*)-double bond follows the *endo*-rule but the (*Z*)-double bond attacks in an *exo*-fashion (scheme **25**)[55]. The reason for the different regio and stereochemical outcome is the ring strain, and the steric hindrance which conformation **A** exerts on the tether.



Scheme 25

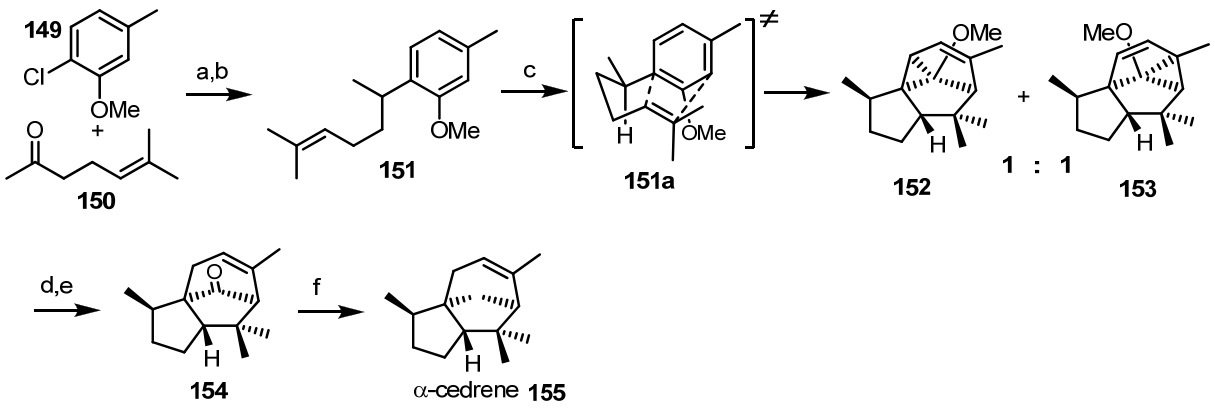
The picture changes again when an electron donating substituent *ortho* to the tether is attached to the benzene ring. The regiochemistry then changes regardless of the double bond geometry to the preferred 1,3-attack, albeit still with *endo*-selectivity for the *E*- and *exo*-selectivity for the *Z*-double bond. These *ortho*-substituted tether systems are the most reliable photocycloaddition precursors in terms of regio and stereocontrol and have been extensively used in total synthesis. The examples given below therefore contain exclusively these *ortho*-substituted precursors. Concerning the tether length the most frequently used is the three-carbon-atom tether. It forms a cyclopentane ring which is kinetically the most favourable ring size. Tether lengths of four to five carbon atoms are also known.

2.4.3 The Application of the meta-Photocycloaddition in Total Synthesis

To expediently use the *meta*-photocycloaddition in natural product synthesis, certain criteria have to be fulfilled. The photocycloaddition precursor has to be easily accessible, the cycloaddition itself should be selective or the isomers at least separable. And last but not least the conversion of the cycloaddition product to the target structure should not be cumbersome. Paul Wender's group pioneered this field but of course other groups have done significant contributions[56].

2.4.4 The Total Synthesis of α-Cedrene[46]

The first example comprises the total synthesis α-cedrene by Wender *et al.*(scheme **26**). Synthesis of cycloaddition precursor **151** was achieved by addition of an aryllithium species generated from **149** to ketone **150**. The benzylic alcohol was reduced to give **151**. The stereogenic center in **151** allows to control the stereoselectivity of the photo cycloaddition in such a way that according to the $A^{1,3}$-strain model the proton stays in-plane with the aromatic ring. The regioisomers **152/153** are converted to ketone **154** *via* a bromonium ion catalyzed fragmentation reaction of the cyclopropane ring. The allylic bromides are defunctionalized in a Barton McCombie reaction yielding only one double bond isomer **154**. This compound is further defunctionalized in a Wolff Kishner reduction giving α-cedrene **155**.

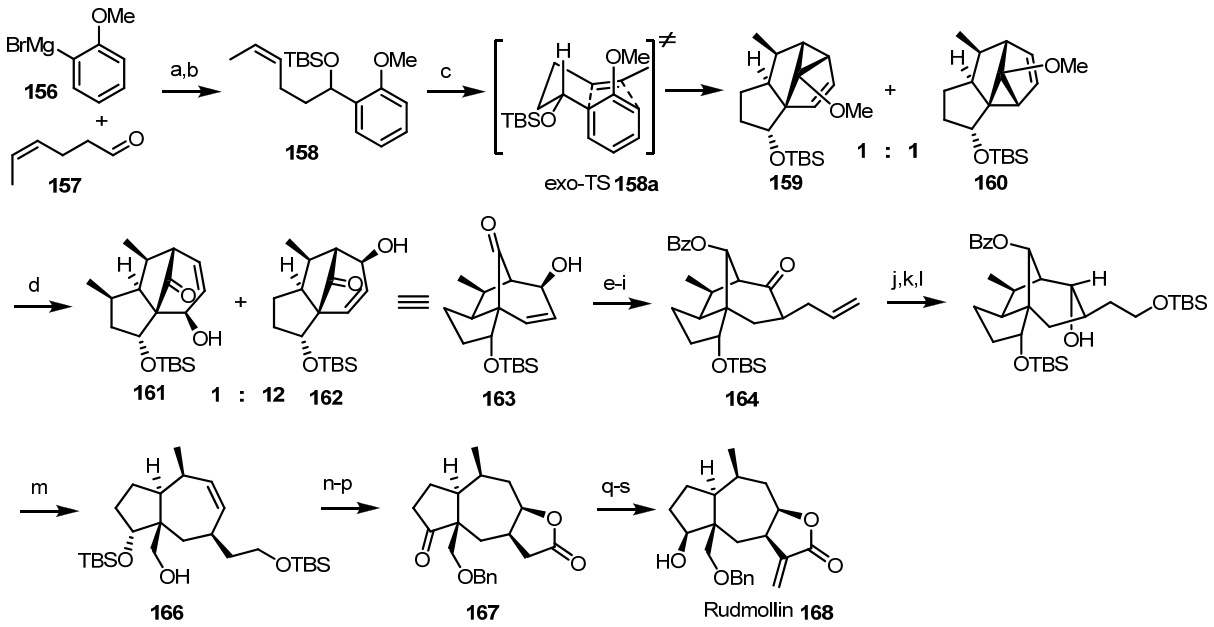


Scheme 26

Scheme **26**Wender's synthesis of α-cedrene: Reagents and conditions: (a) Li, Et_2O, then **150**; (b) Li, NH_3, then NH_4Cl, 74% over two steps; (c) hυ (vycor filter) pentane, 65%; (d) Br_2, CH_2Cl_2; (e) Bu_3SnH (neat), 59% over two steps; (f) NH_2NH_2, KOH, $(OHCH_2CH_2)O$, 200°C, 58%.

2.4.5 The Total Synthesis of Rudmollin[57]

Rudmollin was also completed by the Wender group. It is far more oxidized and the sequence is longer. Again the photo-addition precursor is rapidly accessible (**156**/**157** → **158** scheme **27**). In this synthesis the tether contains a Z-double bond, and thus the *exo*-transition state is formed. Regiomers **159** and **160** are formed in a 1:1 ratio, but are both submitted to the next step – an oxy-mercuration with concomitant fragmentation – to give a 12:1 mixture in favour of the desired regioisomer **162**. This is reduced to the diol, and treatment with manganese dioxide selectively reoxidizes the allylic alcohol, giving an enone-sytem. The double bond is hydrogenated, the remaining alcohol benzoylated and the ketone is alkylated with allyl iodide yielding **164**. Ketone **164** is reduced to give 3:1 in favour of the α- isomer. The double bond is cleaved by ozonolysis, and the resulting aldeyde is reduced and selectively protected with TBSCl at the primary position giving **165**. Mesylation of the secondary alcohol in **165** with subsequent treatment with lithium aluminum hydride resulted in fragmentation to give compound **166**. Benzylation of the primary alcohol, iodolactonization and Barton-McCombie dehalogenation introduced the γ-lactone. The *exo*-methylene-double bond was introduced by a procedure from Wassermann[58] yielding rudmollin.

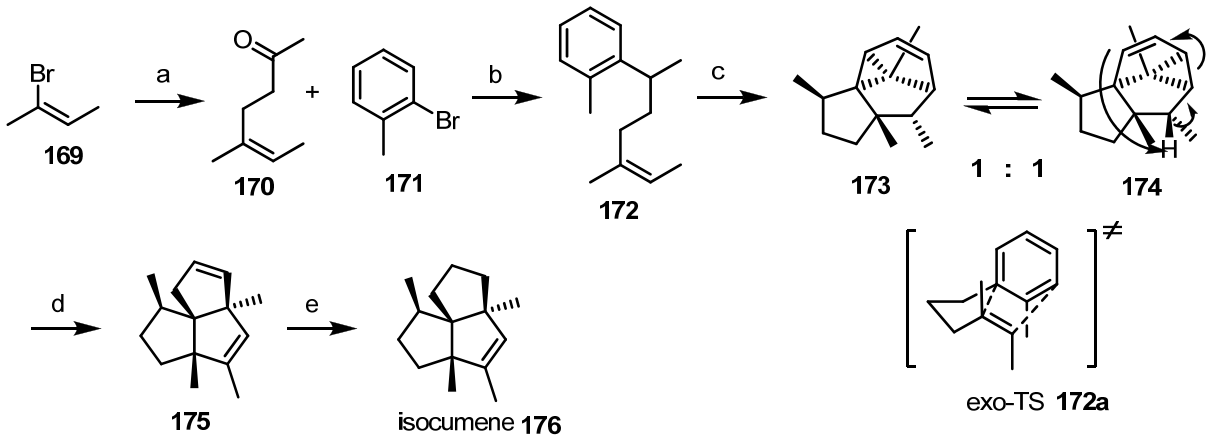


Scheme 27

Scheme **27** Wender's synthesis of rudmollin: Reagents and conditions: (a) THF, 0°C, then **156**, 98%; (b) TBSCl, DMF, NEt_3, DMAP, 97%; (c) hυ (vycor filter) pentane, 63%; (d) $Hg(OAc)_2$, THF, H_2O (71% **159** + 6% **160**); (e) $NaBH_4$, MeOH, 94%; (f) MnO_2, CH_2Cl_2, 93%; (g) H_2, 5%Pd/C, Et_2O, 99%; (h) $(PhO)_2O$, DMAP, NEt_3, DMF, 50°C, 95%; (i) KHMDS, DME, 0°C, then BEt_3, THF, allyl iodide, 50% (j) $NaBH_4$, $CeCl_3$, MeOH, 72% (α:β=3:1); (k) O_3, MeOH, CH_2Cl_2, -78°C then $NaBH_4$ 98%; (l) TBSCl, imidazole, DMF, 97%; (m) MsCl, pyridine, then $LiAlH_4$, DME, 0-25°C, 84%; (n) KH, THF, BnBr, 96%; (o) HF-H_2O, CH_3CN, THF, Jones acetone, 82%; (p) I_2, *sym*-collidine, CH_3CN, Bu_3SnH, AIBN, PhH, 80°C, 53%; (q) $NaBH_4$, MeOH, -78-25°C, 92%; (r) H_2 (40 psi), 10% Pd/C, 70% $HClO_4$ (cat.), MeOH, 82%; (s) $(Me_2N)_3CH$, 90°C, then DIBAL, THF, 0°C, 54%.

2.4.6 The Total Synthesis of Isocumene[59]

Isocumene a member of the pentalene family was synthsized by Wender *et al. via* photoaddition precursor **172** yielding isomers **173** and **174**. In this case only one isomer was of further use in the synthesis, but fortunately the undesired **173** could be equilibrated to the desired isomer **174** upon further irradiation. Dehydroisocumene was obtained *via* a 1,5-H-shift. The last step is a selective hydrogenation of the less substituted double bond yielding isocumene (scheme **28**).

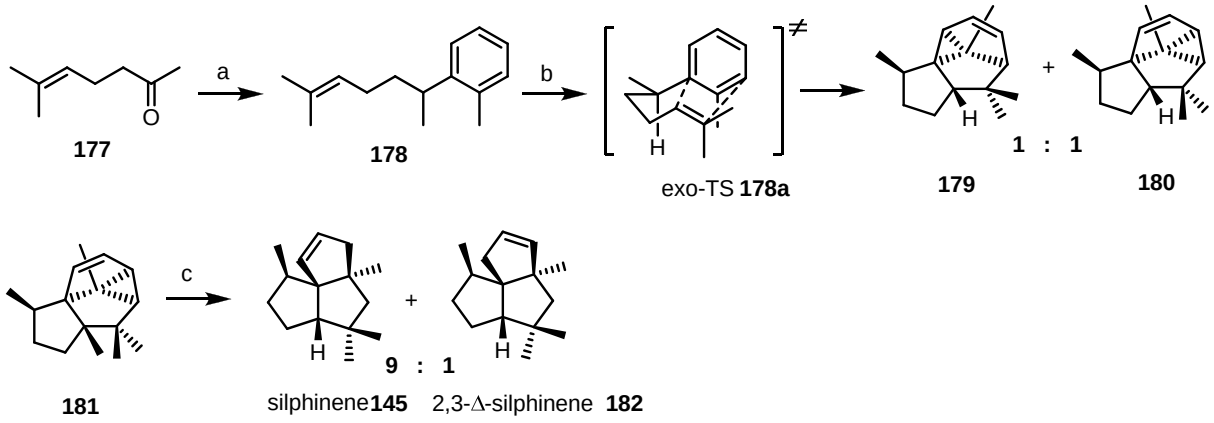


Scheme 28

Scheme **28** Wender's synthesis of isocumene: Reagents and conditions: (a) Li, Et_2O then CuI, -65°C, MVK, 56%; (b) *ortho*-bromotoluene, Li, Et_2O, rt, then **170** then NH_3, -78°C, 78%; (c) hυ (vycor filter) cyclohexane, 72%; (d) 235-240°C, 69%; (e) H_2, 5% Pd/C, hexane, 98%.

2.4.7 The Total Synthesis of Silphinene[60]

Silphinene **145** is the structure biogenetically related to penifulvins. Wender *et al.* performed a most elegant and rapid access to this structure without the introduction of any unnecessary functional group (scheme **29**). As in the foregoing syntheses the stereochemical course of the cycloaddition is governed by the $A^{1,3}$-allyl-strain model leading to regioisomers **179** and **180**. The tricyclic carbon-skeleton is set up in this way except that the cyclopropane ring needs to be cleaved. This was achieved by a Birch reduction giving silphinene and its 2,3-Δ-double bond isomer in a 9:1 ratio for the desired natural product.

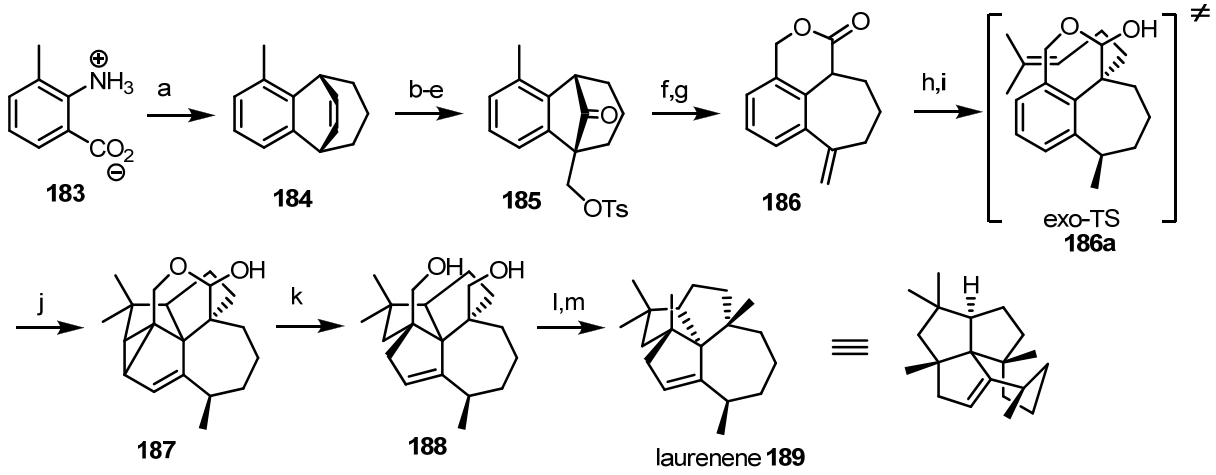


Scheme 29

Scheme **29** Wender's synthesis of silphinene: Reagents and conditions: (a) Li, Et_2O, then *ortho*-bromotoluene, then NH_4Cl, 87%; (b) hυ (vycor filter) pentane, 72%; (c) Li, $MeNH_2$, -78°C, 74%.

2.4.8 The Total Synthesis of Laurene[61]

Laurene **189** is one of the most complex natural products synthesized by using the *meta* photocycloaddition (scheme **30**). In contrast to the foregoing examples it belongs to the diterpenes and has a fenestrane-type structure. The synthesis of the photoaddition precursor is a little bit more laborious but proceeds in standard steps. Like in the silphinene synthesis, the cyclopropane ring is removed in a Birch reduction, but additional deoxygenations have to be performed to reach laurellene.

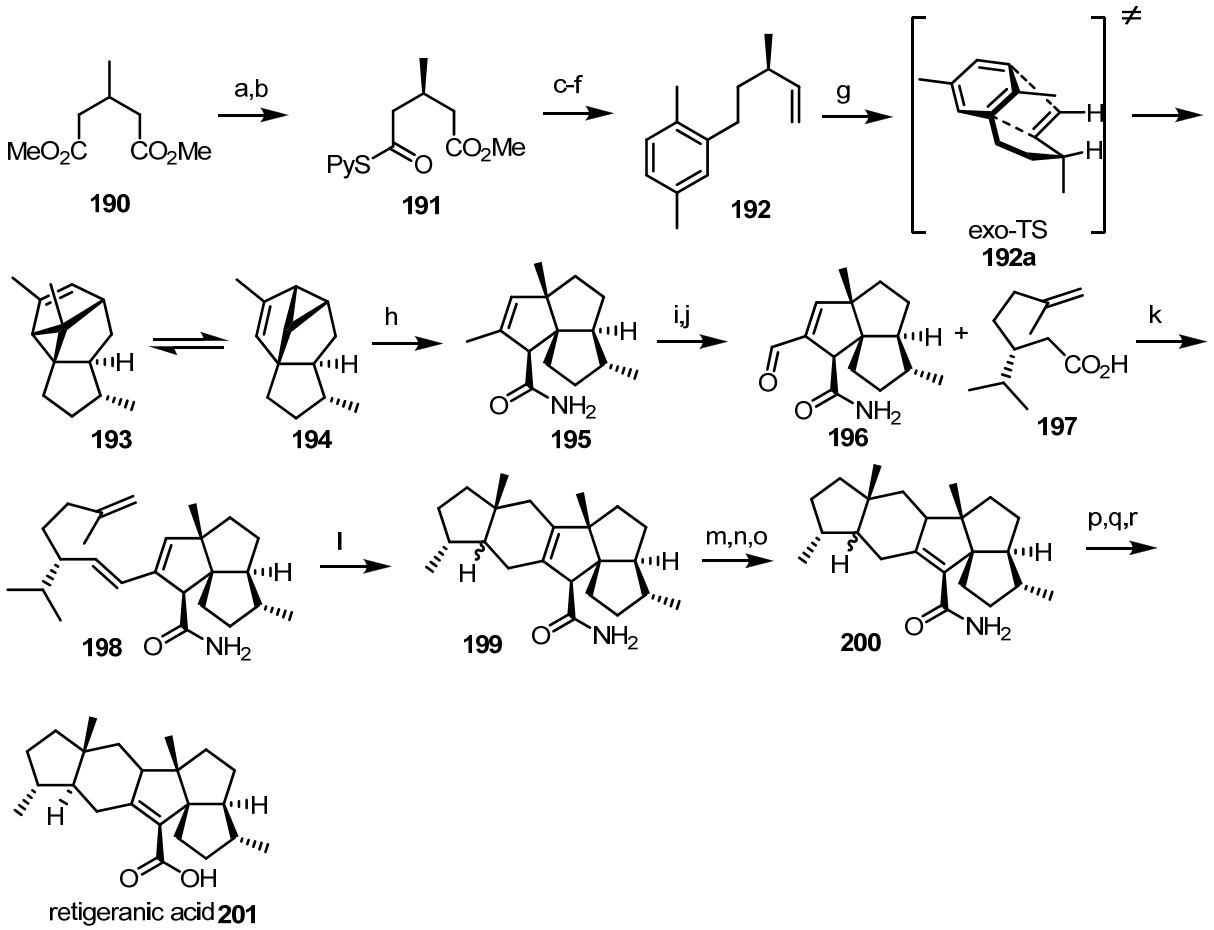


Scheme 30

Scheme **30** Wender's synthesis of laurenene: Reagents and conditions: (a) isopentyl nitrite, Cl_3CCO_2H, cycloheptadiene, $CH2Cl_2$, 84% brsm.; (b) O_3, DMS, NEt_3, 68%; (c) $Zn(BH_4)_2$, Et_2O, 98%; (d) TsCl, 72%; (e) PCC, 98%; (f) NBS, AIBN, then KOH, 72%; (g) H_2, Pt, 96%; (h) LDA, DMPU, hompoprenyl iodide, 48%; (i) $LiALH_4$, THF, 95%; (j) hυ, ($BiCl_3$-filter), 51%; (k) Li, $MeNH_2$, -60°C, 96%; (l) KHMDS, HMPA, $ClPO(NMe_2)_2$, 55%; (m) Li, $EtNH_2$, 65%.

2.4.9 The Total Synthesis of Retigeranic acid[62]

Retigeranic is a most complex pentacyclic structure which contains the pentalene core in the shape of three adjacent cyclopentane rings. The cyclohexane and the terminal cyclopentane ring are formed in an intramolecular Diels-Alder reaction (scheme **31**). Further functional group manipulations finally lead to the natural product. Remarkable in this synthesis is the possibility to interconvert the two regioisomers evolving from the photocycloaddition, and the radical ring cleavage of the cyclopropane ring which introduces the carbon atom that finally represents the carboxylic acid in the natural product.

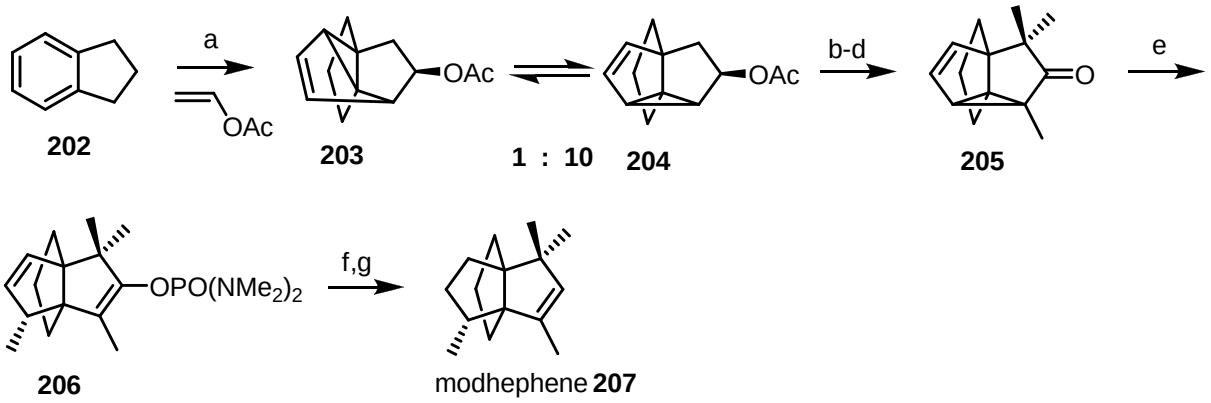


Scheme 31

Scheme **31** Wender's synthesis of retigeranic acid: Reagents and conditions: (a) PLE; (b) dipyridyl disulfide, PPh_3, CH_2Cl_2, 96%; (c) *p*-xylyl bromide, Li, Et_2O, CuI, -78°C to 0°C then **191**, -78°C, 90%; (d) $LiAlH_4$, Et_2O; (e) H_2, 10% Pd/C, EtOH-$HClO_4$ (100:1), 93% 2 steps; (f) *n*-Bu_3P, *o*-nitrophenylSeCN, H_2O_2 30%, 84%; (g) hυ (vycor filter) pentane, 72%; (h) hυ (pyrex filter) acetone, $HCONH_2$, $_t$BuOH; (i) KOH, DMSO, MeI, 80%; (j) SeO_2, t-BuOOH, $(CH_2Cl_2)_2$, Δ, 53%; (k) **197**, LDA, 50°C to 0°C then **196** (at -78°C), to 25°C, AcOH, N,N-dimethylformamide dimethyl acetal, Δ, 65%; (l) 230°C, $PhCH_3$, 65%; (m) *m*-CPBA, NaOAc, CH_2Cl_2; (n) *t*-BuOK, DMSO, 100°C; (o) 10%-Pd/C, H_2, PhH, 400psi; (p) $LiAlH_4$, THF,(q) PDC, CH_2Cl_2; (r) oxidation to acid.

2.4.10 The Total Synthesis of Modhephene[63]

Modhephene (scheme **32**) represents the intermolecular application of the *meta*-photocycloaddition in total synthesis and varies in this respect from the previous applications. Dihydroindane and vinylacetate undergo the photo-reaction to give regioisomers **203** and **204** (10:1 for the desired compound). The acetate group is cleaved under basic conditions and oxidized to the ketone. Then extensive α-methylation of the ketone followed by a homo-1,4-addition of dimethyl-cuprate introduces the missing methyl groups, and opens the cyclopropane ring. The ketone is reduced and thus modhephene obtained.



Scheme 32

Scheme **32** Wender's synthesis of modhephene: Reagents and conditions: (a) hυ (vycor filter) cyclohexane, 21%; (b) KOH, MeOH, 86%; (c) $Ba(MnO_4)_2$, 95%; (d) *t*-BuOK (15 eq), MeI, THF, 68%; (e) Me_2CuLi, THF, -78°C, $ClPO(NMe_2)_2$, then Me_2NH, 76%; (f) Li, $EtNH_2$, THF, *t*-BuOH, 0°C, 93%; (g) H_2, PtO_2, 100%.

2.5 Own Synthetic Work – The Biomimetic Total Synthesis of (-)-Penifulvin A

Appendix 4

Gaich, Tanja; Mulzer, Johann. **Total Synthesis of (-)-Penifulvin A, an Insecticide with a Dioxafenestrane Skeleton.** Journal of the American Chemical Society (2009), 131(2), 452-453.

2.6 Experimental (-)-Penifulvin A

Appendix 5

2.7 Unpublished Work – Biomimetic Total Synthesis of Penifulvin B and C)

After we had completed the total synthesis of penifulvin A we wanted to apply the *meta*-photocycloaddition to the other members of the family, to show that we were able to provide access to all penifulvins with this method.

We chose penifulvins B and C because both structures contain an additional stereogenic quaternary carbon atom (figure **11**). This additional quaternary carbon atom makes these two members the most challenging ones of this family, and can be directly formed from the olefin in the *meta*-photocycloaddition. This provides us with the opportunity to test whether this additional quaternary carbon stereogenic center is as well formed stereoselectively in the course of the reaction.

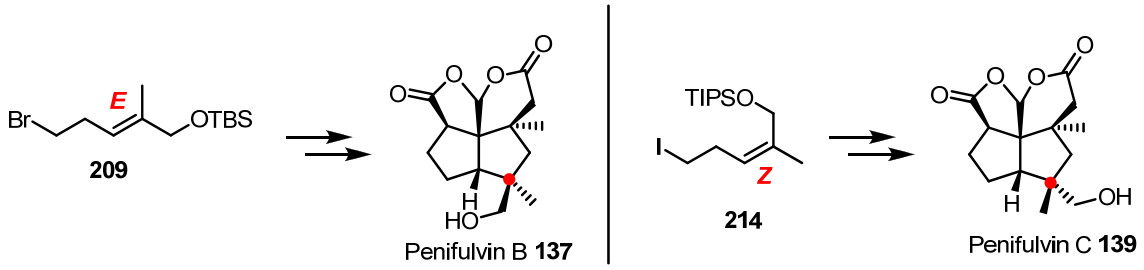
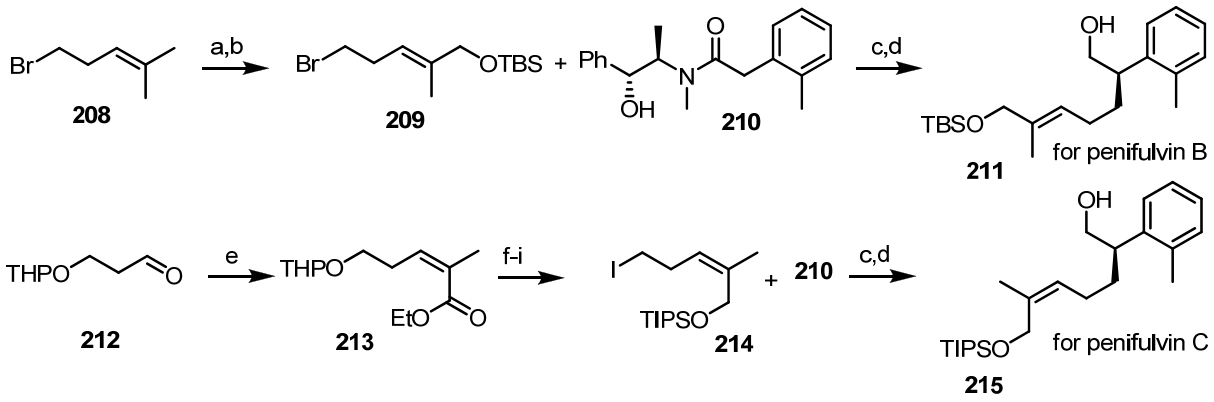


Figure 11

To the best of our knowledge no examples in total synthesis are known, where a quaternary stereogenic center in this position was generated *via* the photo-cycloaddition. If the 1,3-*exo*-addition during this reaction remains unbiased, penifulvin B **137** is exclusively formed from the *E*-double bond **209**, whereas penifulvin C **139** is generated from the corresponding *Z*-double bond **214**. In this way we could additionally contribute to the mechanistic considerations of this reaction.

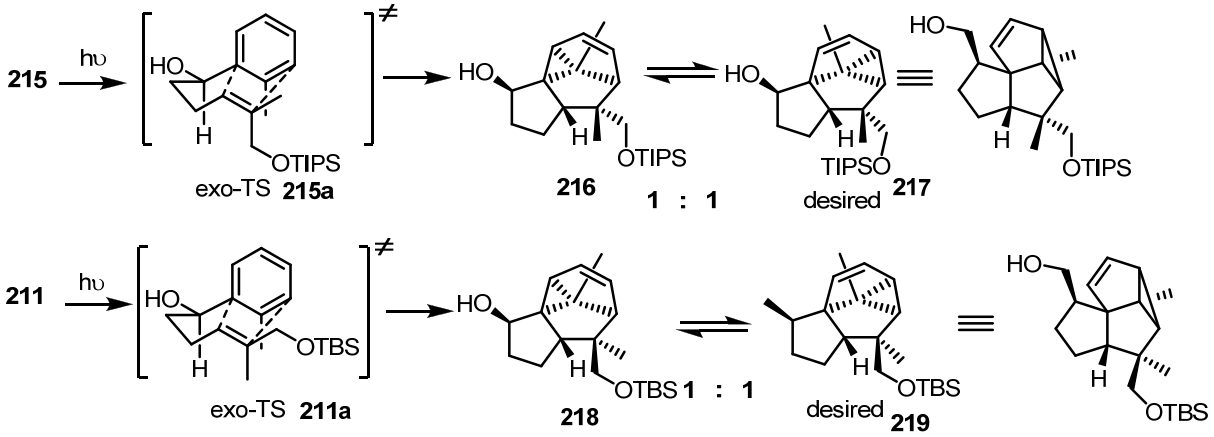
We therefore prepared both trisubstituted *E*- and *Z*-double bond precursors **209** and **214** and attached them to compound **210** *via* Myers alkylation (scheme **33**). Reductive cleavage of the auxiliary gave the corresponding alcohols **211** and **215**, which were submitted to the photocycloaddition respectively (scheme **34**).



Scheme 33

Scheme **33** Synthesis of the *meta*-photocycloaddition precursors of penifulvins B and C: Reagents and conditions: (a) SeO_2, *t*-BuOOH, CH_2Cl_2, 61%; (b) TBSCl, imidazole, DMF; (c) LiCl (6eq), LDA (2.2 eq), THF, 0°C to rt; (d) BH_3*NH_3, LDA, THF, 0°C; (e) THF, KHMDS, $(CF_3CH_2O)_2P(O)CH(Me)CO_2Et$, -78°C; (f) DIBAL, hexane, -78°C, 43% two steps; (g) TIPSCl, imidazole, DMF, 98%; (h) montmorillionite K10 MeOH, 68%; (i) MsCl, pyridine then acetone, NaI, 98%.

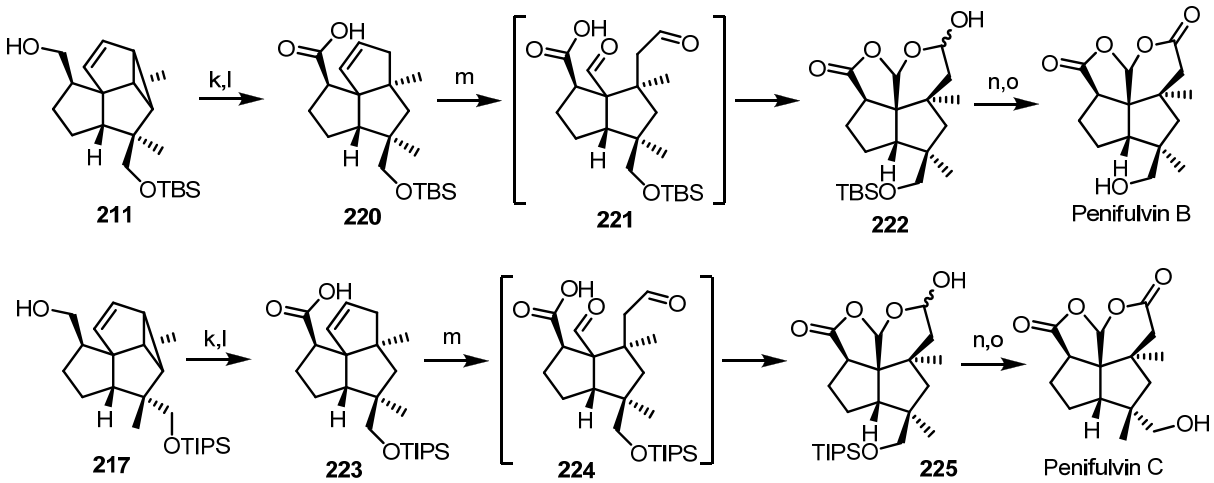
To our delight we found that the **211** (containing the *E*-double bond), indeed only gave the quaternary stereogenic center found in Penifulvin B, and **215** (containing the *Z*-double bond) exclusively gave the stereogenic center with the configuration found in penifulvin C.



Scheme 34

Scheme **34** *meta*-photocloaddition of **211** and **215**.

Completion of the syntheses was achieved in analogue fashion to the total synthesis of penifulvin A, plus an additional deprotection of the silyl-protecting group in the last step (scheme **35)**.



Scheme 35

Scheme **35** Completion of the synthesis of penifulvins B and C: Reagents and conditions: (k) Li (6 eq.), $EtNH_2$; (l) IBX, DMSO, rt then $NaClO_2$, *t*-BuOH, NaH_2PO_4;96% (m) O_3, thiourea, CH_2Cl_2, -78°C to rt, 36%; (n) AcOH cat., CH_2Cl_2, PDC, 83%; (o) 50% HF-pyridine in CH_3CN, 82%.

2.8 Summary

In conclusion we have developed the first total syntheses to Penifulvins A, B and C, which have been isolated from the fungus *Penicillium griseofulvum.*. The dioxa[5.5.5.6]fenestrane ring system of these natural products is unprecedented in nature.

The total synthesis of penifulvin A **136** is the shortest one with 5 steps from commercially available starting materials for the racemic route, and 8 steps for the enantioselective route.

The enantioselective synthesis of penifulvin B **137** takes 10 steps and requires only one protecting group. For the synthesis of penifulvin C **139** 13 steps are required, as the synthesis of the *Z*-double dond in **214** takes more steps. Like in penifulvin B **137** only one protecting group is required.

The three syntheses represent a biomimetic approach to this family, as they use the well known silphinene carbon framework to build up the final acylal structure. Silphinene **145** is considered to be biogenetically related to penifulvins. This hypothesis is substantiated by the fact that 12-hydroxysilphinen-15-oic-acid **138** was also isolated from the same natural source.

2.9 Experimental – Total Syntheses of Penifulvins B and C

Appendix 6

3.0 Appendix 1(Experimental of unpublished work of Providencin) page 43-48

4.0 Appendix 2 (Publications Providencin) page 49-76

5.0 Appendix 3 (Experimental of Providencin) page 77-135

6.0 Appendix 4 (Publication of Penifulvin A) page 136-138

7.0 Appendix 5 (Experimental of Penifulvin A) page 139-156

8.0 Appendix 6 (Experimental of Penifulvins B and C) page157-181

9.0 Literature

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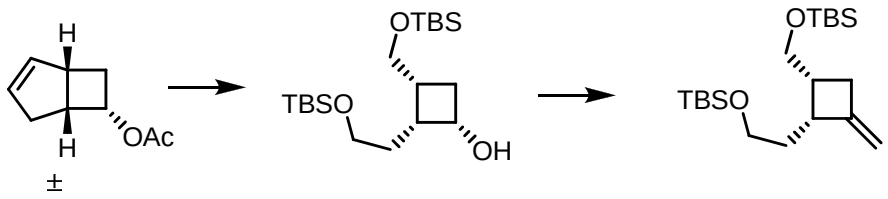
Appendix 1

tert-butyl((-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-methylenecyclobutyl)methoxy)dimethylsilane **128**



Literature known acetate (1g, 6.6 mmol, 1eq) was dissolved in 40 mL DCM/methanol 4:1 and cooled to -78°C. . Ozone was bubbled through until the solution turned dark blue. Air was then bubbled through until the color deceased again and the cooling bath was removed. 20 mL MeOH and $NaBH_4$ (19.7 mmol, 745 mg, 3eq) were added. The reaction mixture was stirred at room temperature for two hours and quenched by slow addition of water (5 mL then 50 mL 1M HCl). The phases were separated and the water phase was further extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed under reduced pressure and crude product was submitted to the next reaction without further purification.

This diol was dissolved in 7 mL DMF and imidazole (31.6 mmol, 2.2 g, 4.8 eq) and TBS-Cl (13.8 mmol, 2.1 g, 2.1eq) were added sequentially. After stirring the reaction over night at room temperature it was diluted with water. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was hydrolyzed with ethanolic KOH (30%) to give the corresponding alcohol, which was again submitted crude to the next reaction.

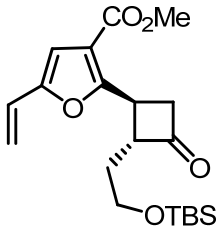
IBX (7.8 mmol, 2.2 g, 1.2 eq) was added to a solution of the crude alcohol in DMSO. The reaction was stirred for 1 hour and was diluted with water and diethyl ether. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was added to a solution of methyl triphenyl phosphonium ylid (20 mmol, 3eq, 0.5M in THF) at -78°C. After stirring the reaction mixture for 30 minutes at that temperature it was quenched with ammonium chloride. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed in vacuo and the crude product was purified by flash column chromatography (hexane:ethylacetate 40:1) to give 1.4 g 57% of olefin **128**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.00-4.98 p.p.m. (m, 1H), 4.85 (m, 1H), 3.94 (ddd, *J*=10.2, 10.2, 3.3 Hz, 1H), 3.85-3.80 (m, 1H), 3.71-3.70 (m, 2H), 2.45-2.34 (m, 2H), 2.17-2.07 (m, 1H), 1.97 (ddd, *J*=14.6, 10.2, 4.5 Hz, 1H), 1.77 (dt, *J*=14.4, 3.5 Hz, 1H), 0.86 (s, 9H), 0.84 (s, 9H), 0.05 (d, *J*=3.3 Hz, 3H), 0.00 (d, *J*=2.0 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 154.46 p.p.m., 105.91, 62.24, 61.53, 47.56, 34.32, 28.44, 26.59, 26.46, 19.36, -4.91.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{20}H_{42}O_2Si_2$ 370.2723; found, 370.2711.

Methyl-2-((1*S*,2*R*)-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-oxocyclobutyl)-5-vinylfuran-3-carboxylate **132b**



Furan **132a** (230 mg, 0.54 mmol, 1eq), was dissolved in 5mL THF and tetrabutyl ammonium fluoride (1M in THF, 1.6 mL, 1.6 mmol, 3 eq) was added at room temperature. The mixture was stirred for 4.5 hours, quenched with brine and the phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 1:1) to give the corresponding diol which was immediately used in the next step.

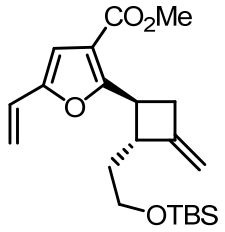
The diol was dissolved in 2mL DMF and imidazole (1.3 mmol, 90 mg, 2.4 eq), and TBS-Cl (0.54 mmol, 82 mg, 1eq) were added sequentially at room temperature. The reaction was stirred over night then it was diluted with water and diethyl ether. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was dissolved in 2mL DMSO. IBX (0.81 mmol, 228 mg, 1.5eq) was added and after stirring at ambient temperature for one hour the reaction was quenched with water, diluted with diethyl ether and extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 7:1) to give 125 mg 61% of ketone **132b**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.55 p.p.m. (s, 1H), 6.45 (dd, *J*=17.6, 11.2 Hz, 1H), 5.68 (d, *J*=17.7 Hz, 1H), 5.24 (d, *J*=11.1 Hz, 1H), 4.29 (dd, *J*=14.3, 7.2 Hz, 1H), 4.17-4.09 (m, 1H), 3.83 (s, 3H), 3.81-3.68 (m, 2H), 3.55 (ddd, *J*=17.4, 8.3, 2.8 Hz, 1H), 3.31 (ddd, *J*=17.4, 8.9, 2.1 Hz, 1H), 2.02-1.90 (m, 2H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 208.89 p.p.m., 160.34, 151.51, 128.22, 124.55, 116.21, 113.76, 108.61, 64.23, 60.80, 52.46, 49.77, 32.11, 28.44, 14.46.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{14}H_{16}O_5$ 378.1862; found, 378.1854.

Methyl-2-((1*S*,2*R*)-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-3-methylenecyclobutyl)-5-vinylfuran-3-carboxylate **133**



Ketone **132b** (125 mg, 0.33 mmol, 1eq) was added at -78°C to a 0.5M solution of methyl triphenylphosphonium ylide in THF (1 mmol, 2mL, 3eq). The reaction was stirred for one hour at that temperature before it was quenched with a saturated ammonium chloride solution. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 15:1) to give 110 mg 88% of olefin **133**

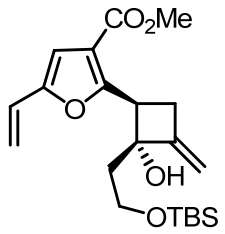
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.56 p.p.m. (s, 1H), 6.51 (dd, *J*=17.8, 11.3 Hz, 1H), 5.76 (d, 17.8 Hz, 1H), 5.28 (dd, *J*=11.2, 0.9 Hz, 1H), 4.97 (dd, *J*=5.1, 2.5 Hz, 1H), 4.94 (dd, *J*=4.1, 2.6 Hz, 1H), 4.00 (dd, *J*=17.0, 8.7 Hz, 1H), 3.90 (s, 3H), 3.73-3.68 (m, 1H), 3.67-3.62 (m, 1H), 3.59-3.54 (m, 1H), 3.14-3.08 (m, 1H), 3.03-2.98 (m, 1H), 2.09-2.03 (m, 1H), 1.84-1.78 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.61 p.p.m, 163.20, 150.35, 136.23, 124.71, 114.81, 113.57, 108.98, 104.52, 60.82, 51.83, 47.97, 37.08, 35.98, 35.24, 30.16, 26.19, -5.07.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{32}O_4Si$ 376.2069; found, 376.2057.

$[\alpha]_D$= +21 (c 0.37g/100mL, $CHCl_3$).

Methyl-2-((1*S*,2*S*)-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2-hydroxy-3-methylenecyclobutyl)-5-vinylfuran-3-carboxylate **135**



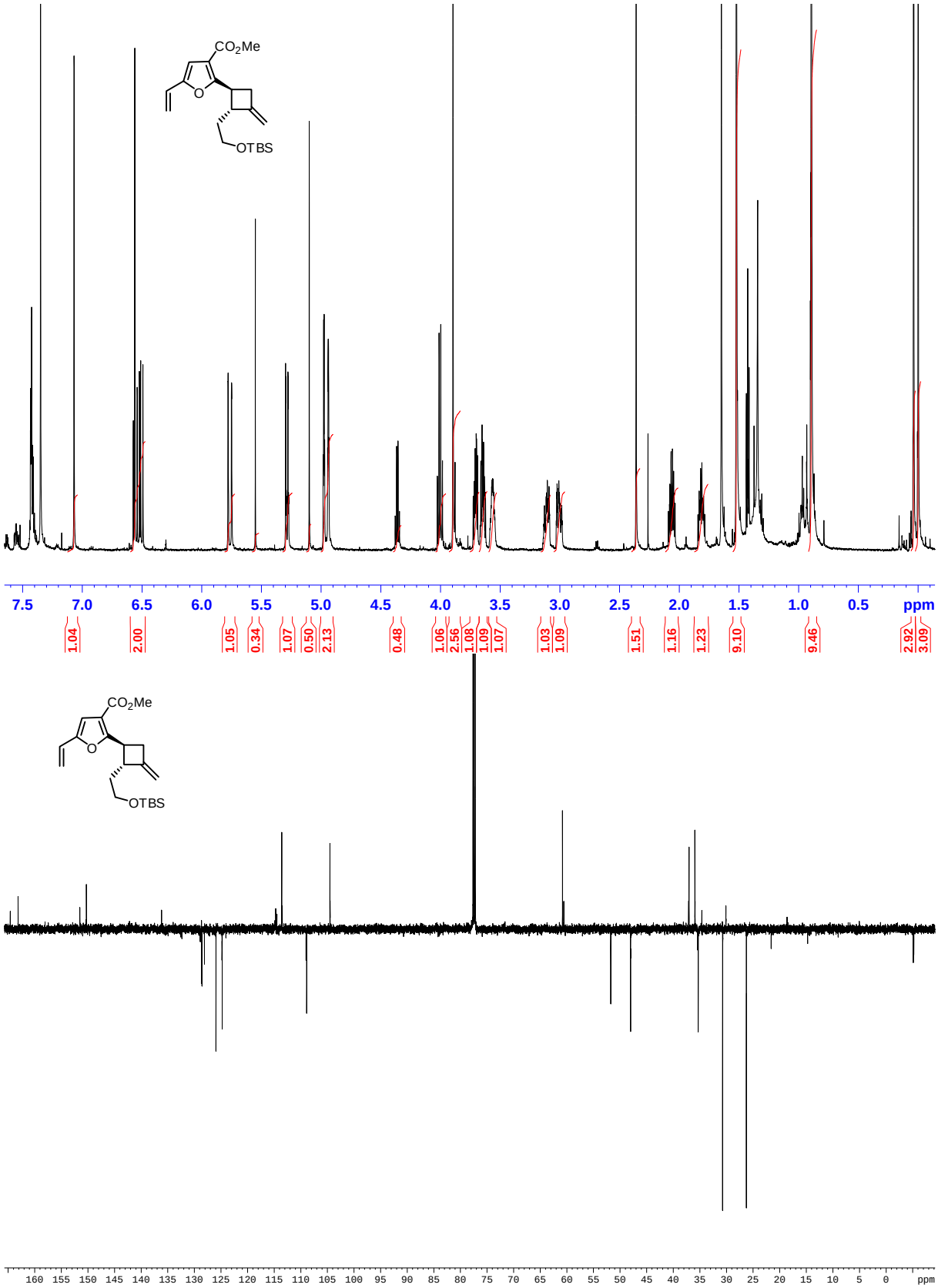
Selenium dioxide (146 µmol, 16 mg, 0.5 eq) was suspended in 500µL DCM and cooled to 0°C. tert-butyl-hydroperoxide (5.5 M in decane, 0.58mmol, 106µL, 2eq) was slowly added. After the addition was completed the ice bath was removed and the suspension was stirred at ambient temperature for 30 minutes. The reaction mixture was cooled to 0°C and the olefin **133** (110 mg, 0.29mmol, 1eq) was added in 0.5mL DCM. The ice bath was removed and the mixture was stirred for 10 hours. The reaction was quenched with 30% KOH (5mL), diluted with diethyl ether and the phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 10:1) to give 48 mg 42% of alcohol **135**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.55 p.p.m. (s, 1H), 6.44 (dd, *J*=17.4, 11.4 Hz, 1H), 5.62 (d, *J*=17.4 Hz, 1H), 5.20 (d, *J*=11.4 Hz, 1H), 5.17 (dd, *J*=2.4, 2.4 Hz, 1H), 5.02 (dd, *J*=1.9, 1.9 Hz, 1H), 4.26 (dd, *J*=9.8, 9.8 Hz, 1H), 3.87-3.80 (m, 1H), 3.82 (s, 3H), 3.57 (dt, *J*=10.6, 5.3 Hz, 1H), 2.98-2.90 (m, 1H), 2.76 (ddt, *J*=15.1, 9.5, 1.7 Hz, 1H), 1.88-1.82 (m, 1H), 1.79-1.72 (m, 1H), 0.91 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.26, p.p.m., 151.83, 127.98, 124.39, 116.21, 113.20, 108.90, 106.12, 84.49, 77.32, 77.00, 76.68, 60.28, 51.52, 43.46, 35.70, 29.69, 28.21, 25.80, -5.63.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{32}O_5Si$ 392.2019; found, 392.2009.

$[\alpha]_D$= +24 (c 0.14g/100mL, $CHCl_3$).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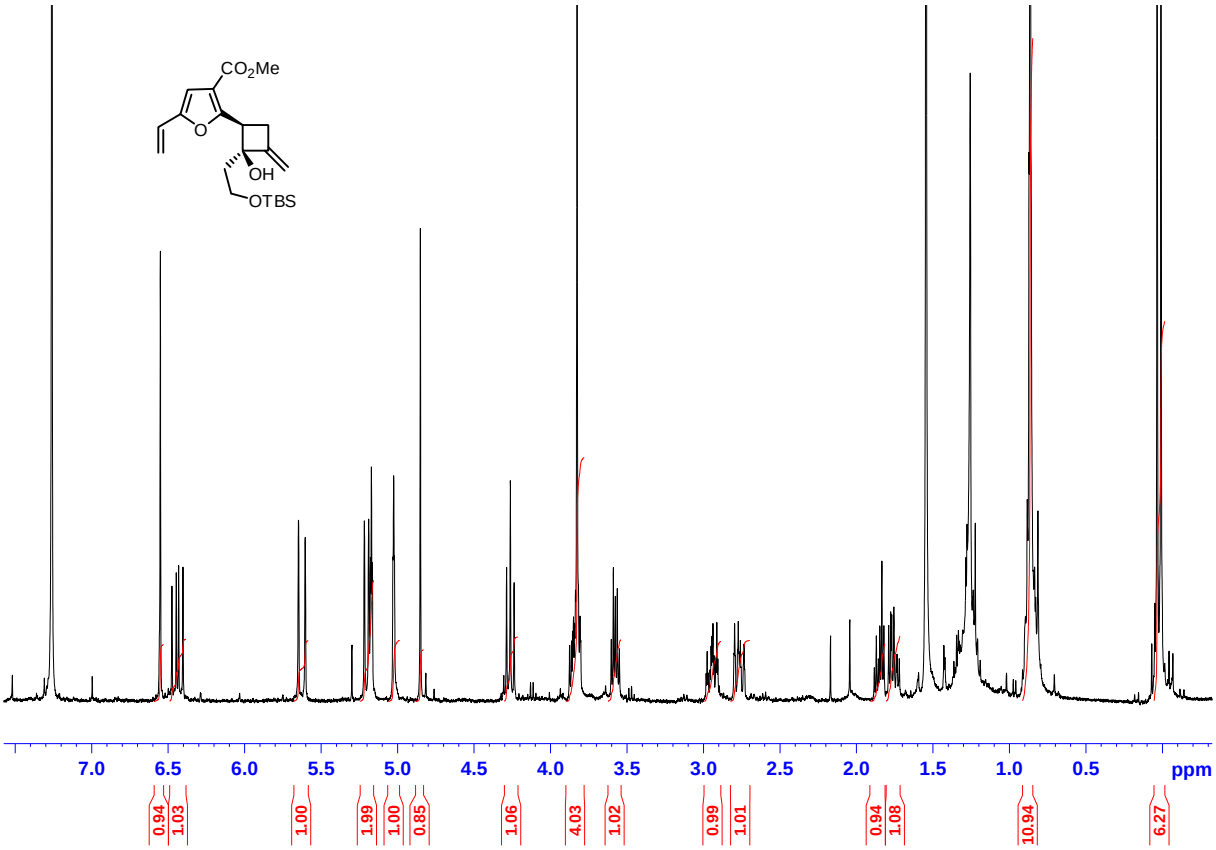
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4.03
1.02
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1.08
10.94
6.27

Synthetic efforts towards the synthesis of the complex diterpene Providencin

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In memoriam Peter Welzel.

Abstract: Providencin is a novel highly oxygenated marine furanocembranolide featuring a cyclobutane ring and a highly strained 7,8-*trans*-epoxide. Various approaches to the total synthesis of this compound are reported. The cyclobutane moiety is generated *via* [2+2]-cycloaddition and the furan ring is constructed *via* a Wipf palladium catalyzed alkynone cyclization. The macrocyclic ring was closed *via* HWE olefination and RCM. The latter reaction, however, produced the undesired 7,8-*Z*-olefin exclusively, and thus far, the conversion into the *cis*-isomer has been unsuccessful.

Key words: furanocembranolides, total synthesis, Horner-Wadsworth-Emmons-olefination, macrocyclization, ring closing metathesis

1. Introduction

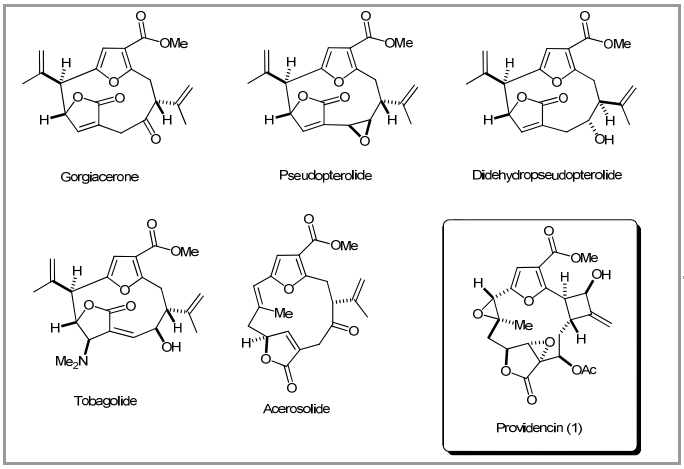


Figure 1 Some Representative Furanocembranolides

The class of the furanocembranolides offers a diverse sprectrum of structurally interesting natural compounds which are effective against various cancer types, reveal analgesic or anti-inflammatory activity, or display potent neuro- and cytotoxic properties.[1] Common structural features are the 2,5-bridged furan ring, a more or less modified butenolide moiety, and two isopropenyl side chains, placed on a macrocyclic *ansa* carbon chain for example in gorgiacerone, pseudopterolide, didehydro-pseudopterolide and tobagolide (Figure 1). From this general pattern acerosolide is different by the fact that one of the two isopropenyls is incorporated into the macrocyclic ring, where it forms an *E*-olefin.[2] A similar motif is found in providencin (**1**), however, now also the second isopropenyl moiety is modified by forming a cyclobutanol ring which is *trans* annulated to the macrocycle. Additionally two epoxides are incorporated, which makes **1** the most highly oxygenated member of the family.

Providencin was isolated by the Rodriguez group[3] from the sea plume *Pseudopterogorgia kallos* (Bielschowsky, 1918), which was collected near Providencia (Old Providence) Island located in the Southwestern Caribbean Sea. 1.07 kg dry animal specimens gave 20 mg **1** (0.012% dry weight). The relative configuration was secured *via* single-crystal X-ray analysis (Figure 2). The absolute configuration is unknown. Biologically, **1** exhibits moderate antibacterial activity.

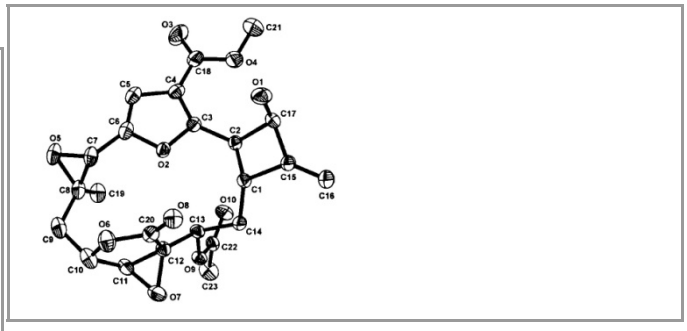


Figure 2 Crystal structure of providencin (**1**)

The crystal structure shows the perpendicular arrangement of the butenolide and the macrocyclic ring. The high ring strain became noticeable when we attempted to build a Dreiding model. This turned out impossible without breaking the bonds. Quite obviously the ring strain is mainly due to the *trans*-arrangement of the C7/C8-epoxide and the rigid 120°-angle between the C7 and C2 appendages around the furan ring.

Biogenetically **1** can be considered to be the result of a head-to-tail- oligomerization of four isoprenoid moieties (Figure 3) with subsequent ring contraction under

cyclobutane formation and finally poly-oxygenation. A more detailed biosynthesis was suggested by Pattenden,[4a] by starting from 13-acetoxy-11β,12β-epoxy-pukalide, which is also found in Nature.[4b] Oxidation to bipinnatin E should be followed by photochemical formation of a biradical which could cyclize to **1**.

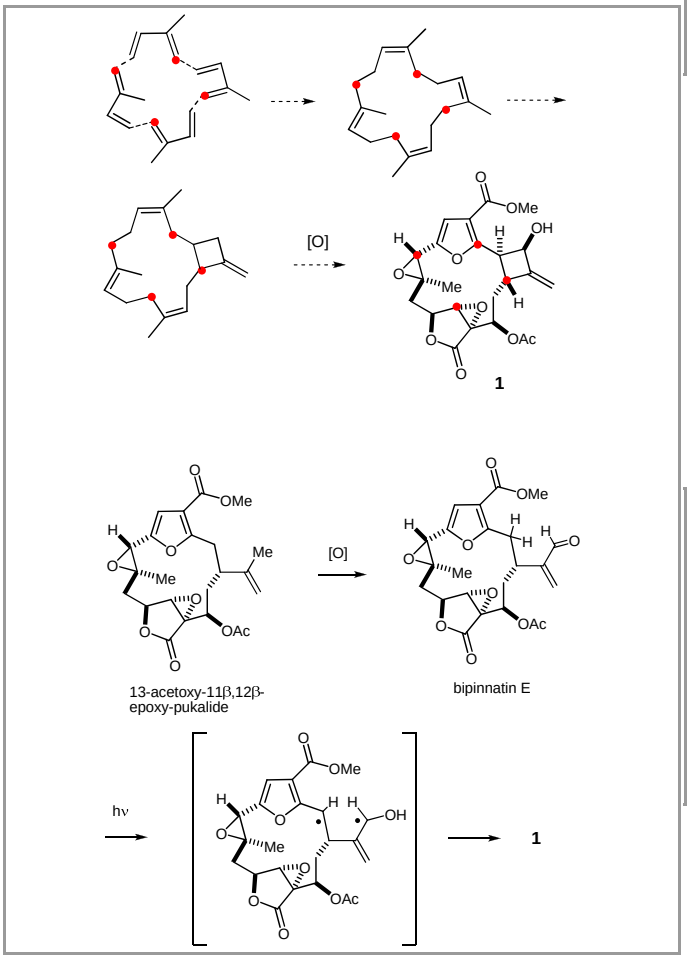
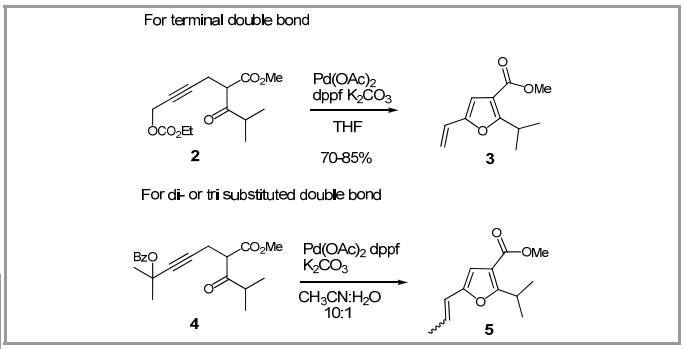


Figure 3 Postulated biosynthetic origin of providencin

In any event, the unusual molecular architecture and in particular the ring strain and the high densitiy of oxygenated stereocenters makes **1** a desirable synthetic target.

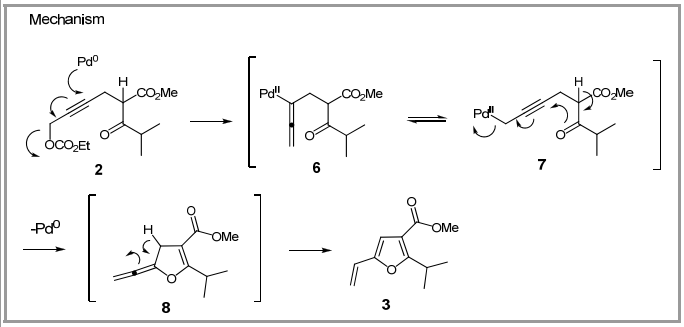
2. Retrosynthetic analysis

So far, there is only one model study towards the synthesis of providencin.[4a] From the very beginning it was clear to us that the synthesis required careful consideration how to prepare the three key fragments (furan, butenolide and cyclobutane), how to connect them, and finally how to close the highly strained macrocyclic ring.[5] We decided to center our strategy around the formation of the furan *via* a protocol by Wipf (Scheme 1),[6] which furnishes the desired vinyl furan moiety in one step.



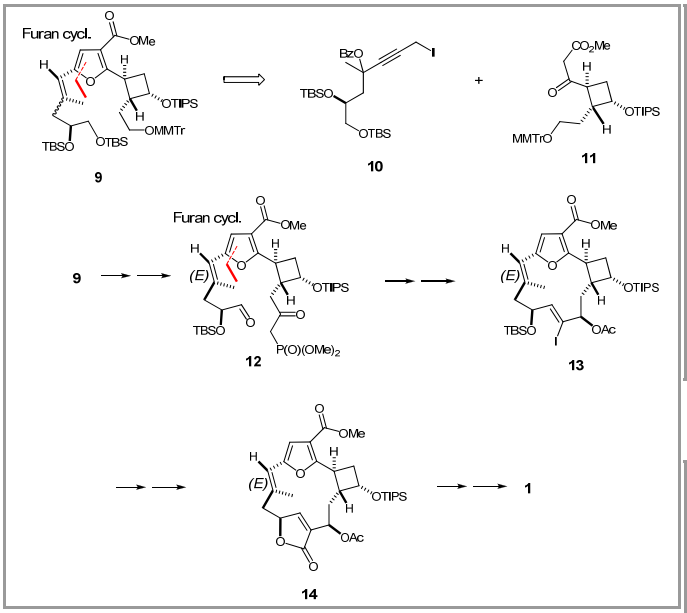
Scheme 1 The Wipf cyclization approach to furan carboxylates[6]

More specifically, compounds **2** or **4** were treated with a palladium catalyst to form furan esters **3** and **5** under elimination of carbon dioxide and ethanol. Mechanistically (Scheme 2) it may be assumed that palladium(0) attacks **2** under formation of the C-Pd-tautomers **6** and **7**. Enolate formation and cyclization leads to allene **8** which tautomerizes to **3** eventually. If the reaction is applied to the tertiary benzoate **4**, an *E*/*Z*-mixture of olefin **5** has to be expected.



Scheme 2 Suggested mechanism of the Wipf cyclization

Attempting to incorporate this methodology into our synthetic concept (Scheme 3) we came up with fragments **10** and **11**, which should be connected *via* alkylation and then converted to furan **9** *via* Wipf cyclization. *Seco*-intermediate **9**, in turn, would have to be transformed into the Horner-Wadsworth-Emmons (HWE)-precursor **12**, and after macrocyclization be converted to vinyl iodide **13**. Pd-catalyzed carbonylation would then serve to generate butenolide **14** which has finally to be elaborated into **1**.

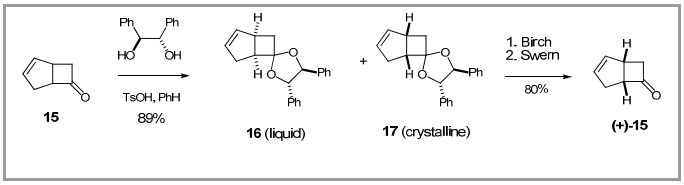


Scheme 3 Retrosynthetic analysis of **1**

3. First Generation Approach

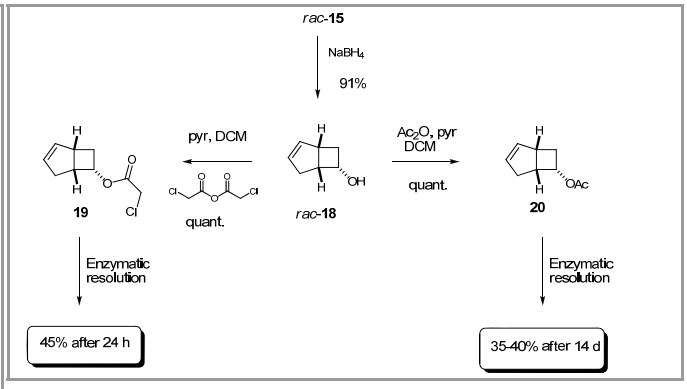
3.1 Synthesis of the Cyclobutane Moiety.

We started with the synthesis of cyclobutane fragment **11** in optically pure form.[5a] Known racemic bicyclic ketone **15** was chirally resolved *via* the diastereomeric ketals **16** and **17**. The crystalline diastereomer **17** was isolated and cleaved to give enantiomerically pure (+)-**15** (Scheme 4).

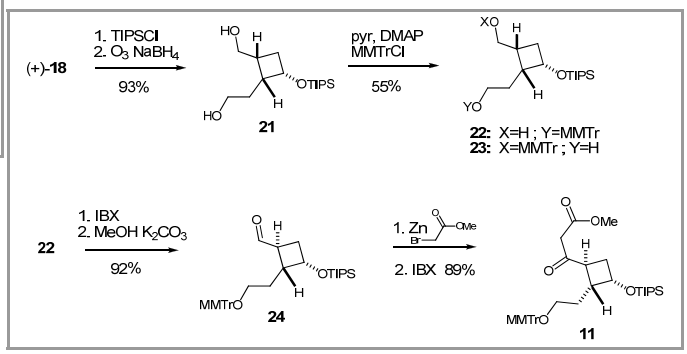


Scheme 4 Synthesis of nonracemic ketone **15**

In a second approach we used enzymatic resolution (Scheme 5). Chloroacetate **19** was hydrolyzed with lipase to give **(+)-18** in 24h with >95% ee, whereas acetate **20** required 14 days! With multigram quantities of **(+)-18** in hand we went for the preparation of fragment **11** (Scheme 6). TIPS-protection of the secondary alcohol followed by ozonolysis/reduction gave diol **21**. The differentiation of the primary OH-functions turned out to be cumbersome, until we found that treatment of diol **21** with one equivalent of MMTrCl furnished an easily separable 4:1-mixture of the mono-tritylated derivatives **22** and **23**, respectively. **22** was oxidized to the aldehyde which was *in situ* converted to the *trans*-diastereomer **24** by base catalyzed epimerization. Reformatsky reaction with bromoacatete followed by oxidation furnished ketoester **11** in excellent overall yield. Regioisomer **23** was recycled to **21** by MMTr-removal.



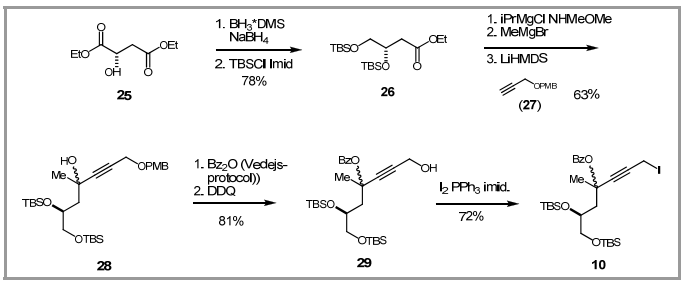
Scheme 5 Lipase catalyzed chiral resolution of alcohol **18**



Scheme 6 Synthesis of the cyclobutane fragment **11**

3.2 Western Fragment.

For the synthesis of the western fragment **10** (Scheme 7) we started from (*S*)-malic ester **25** which was transformed into the protected diol **26**. Conversion of the ester into the Weinreb amide was followed by addition of methylmagnesium bromide to furnish the methyl ketone. Addition of alkyne **27** generated the tertiary alcohol **28** as an inconsequential diastereomeric mixture. O-Benzoylation proved difficult and could only be achieved by means of Vedejs' protocol.[7] Removal of the PMB-group led to alcohol **29**, which was iodinated to **10**.

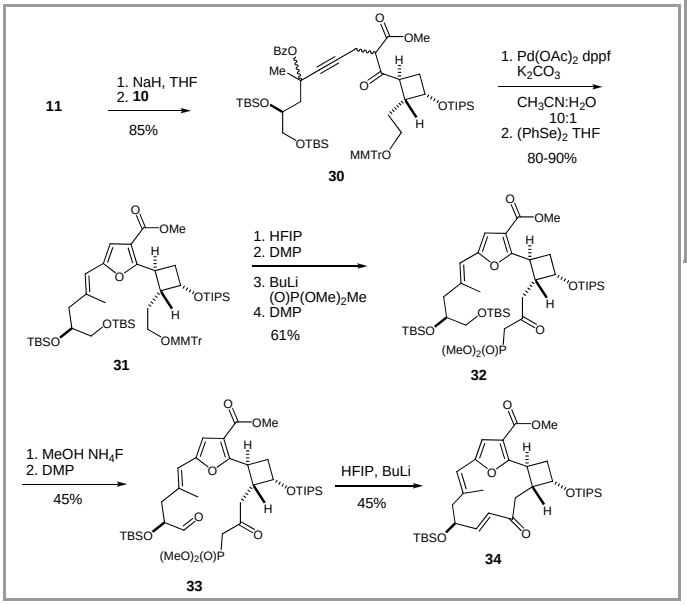


Scheme 7 Synthesis of the propargylic iodide **10**

3.3 Combination of Both Fragments and Ring Closure *via* HWE.

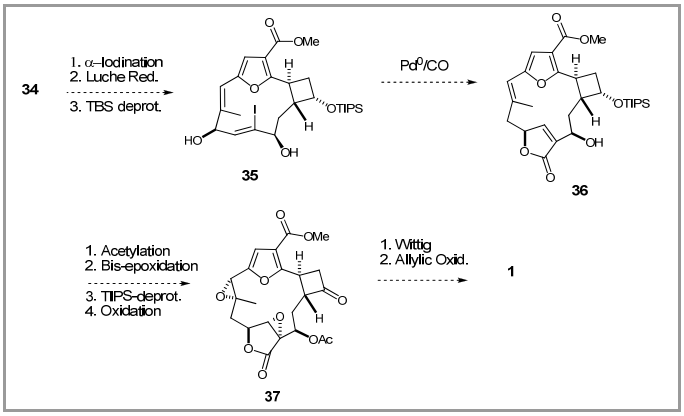
Now the stage was set for the connection of both fragments by alkylation of the keto ester **11** with propargyl iodide **10** (Scheme 8). In fact, compound **30** was obtained in 85% yield. Wipf-cyclization gave a

quantitative yield of a 1:1-mixture of *E*- and *Z*-propenyl furan which was equilibrated to the *E*-isomer **31** by reversible addition/elimination of phenylselenyl radical. Detritylation with hexafluoro-isopropanol (HFIP) and oxidation of the primary alcohol gave the aldehyde which was converted to keto-phosphonate **32** in two steps. The primary TBS-ether was desilylated selectively and the resulting alcohol was oxidized to aldehyde **33**. HWE-macrocyclization with *n*-butyllithium in HFIP under high dilution conditions proceeded in moderate yield to furnish the providencin skeleton **34**.



Scheme 8 Successful Ring closure *via* HWE cyclization of keto phosphonate **33**

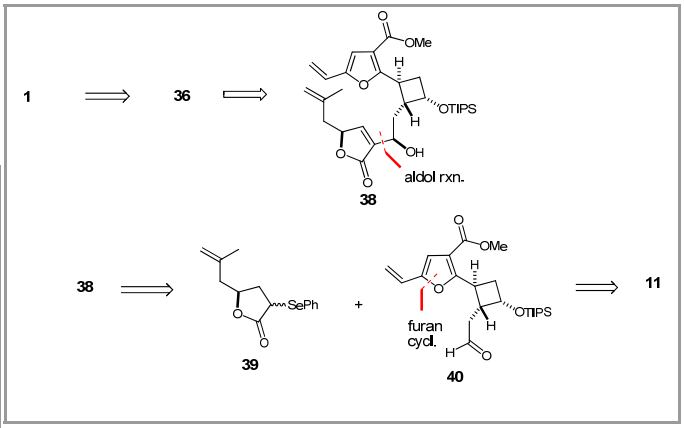
From **34**, several steps were envisaged to complete the synthesis (Scheme 9). Thus, a sequence of α-iodination, Luche reduction of the ketone and deprotection should provide **35** as a suitable substrate for palladium mediated carbonylation to give butenolide **36**. From there six more steps should lead to **1**.



Scheme 9 Planned endgame

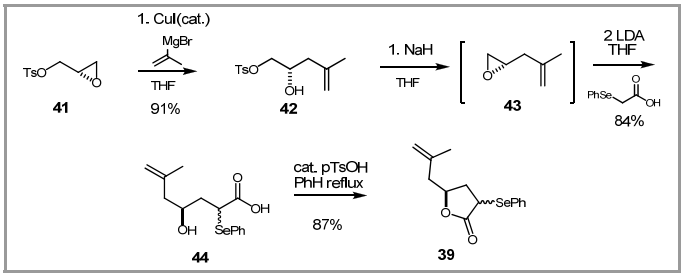
4. Second Generation Approach *via* RCM

As a backup we initiated a second approach which was centered around a RCM reaction[8] of intermediate **38** which should produce **36** directly (Scheme 10). **38** in turn should be formed *via* an aldol type addition[2d] of lactone **39** to aldehyde **40**, which was to be elaborated from intermediate **11**.



Scheme 10 Retrosynthetic analysis *via* RCM

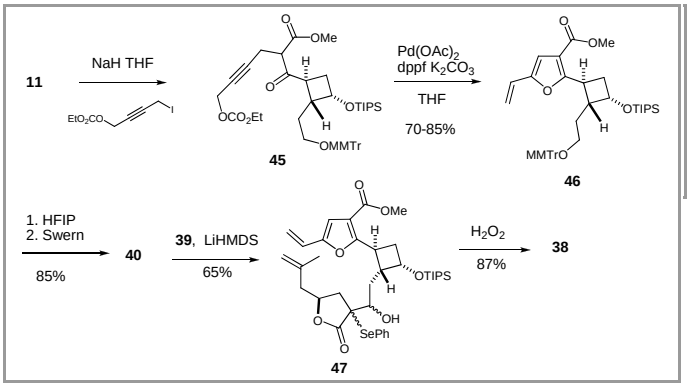
Selenolactone **39** was prepared (Scheme 11) from (*R*)-glycidyl tosylate (**41**) *via* cuprate addition to furnish alcohol **42**, which was converted into epoxide **43** under retention of configuration. *In situ* treatment with the dianion of phenylselenyl acetic acid[2d] furnished hydroxyl acid **44** which was cyclized to **39** under acidic conditions.



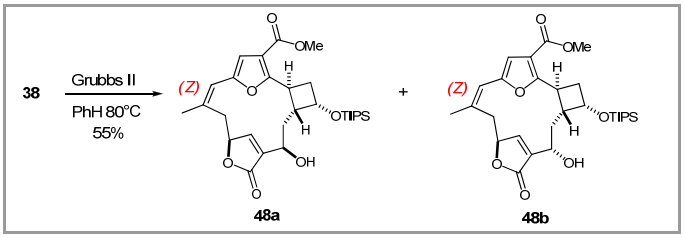
Scheme 11 Synthesis of seleno lactone **39**

The synthesis of compound **40** started with the alkylation of **11** to give **45**, which was cyclized to vinyl furan **46**. Detritylation and Swern oxidation gave aldehyde **40** which was treated with deprotonated lactone **39** to give the aldol adduct **47** as a mixture of four diastereomers. Oxidative elimination of the selenide led to *seco* intermediate **38** as a mixture of two epimers. Grubbs II catalyst mediated RCM furnished macrocycles **48a,b** as a readily separable diastereomeric 1:1-mixture. All attempts to invert *Z*-olefins **48** to the *E*-isomers failed. Therefore it was decided to proceed with the formation of the epoxides. Hence, alcohol **48a** was converted to acetate **49**, whose reaction with hydrogen peroxide under basic conditions gave a diastereomerically pure compound which we thought to be epoxy alcohol **50**. Treatment with acetic anhydride, however, failed to produce the expected acetate, and furnished ketone **51**

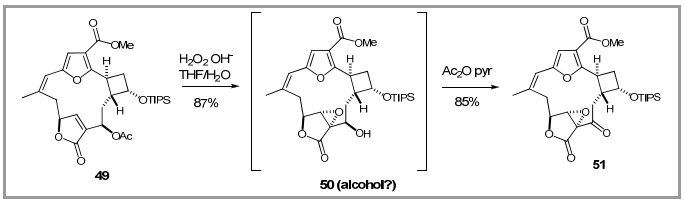
instead (Schemes 12-14), which was unambiguously characterized by its ^{1}H and ^{13}C NMR spectra.



Scheme 12 Synthesis of RCM-seco precursor **38**

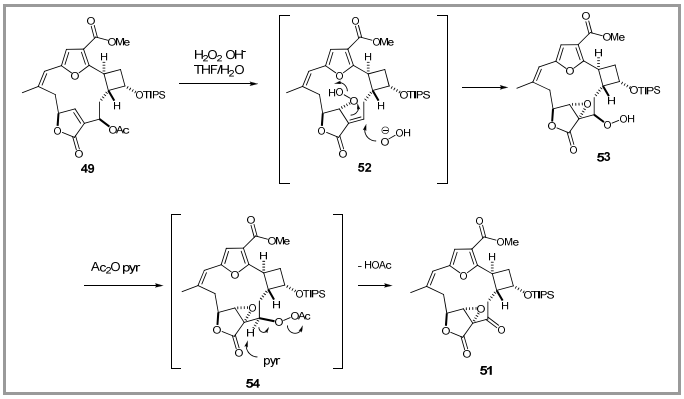


Scheme 13 Successful RCM of precursor **38**



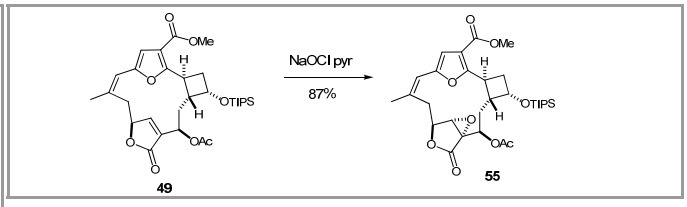
Scheme 14 Unexpected result of the Scheffer-Weitz-epoxidation of butenolide **49**

After some consideration the following mechanism was devised (Scheme 15). 1,4-Addition of hydroperoxide anion to **49** led to **52** under elimination of acetate. A second 1,4-attack of the hydroperoxide anion generated epoxy hydroperoxide **53**, which we had mistaken for alcohol **49**. Treatment with acetic anhydride led to intermediate **54** which eliminated acetic acid under the basic conditions to give ketone **51** eventually.



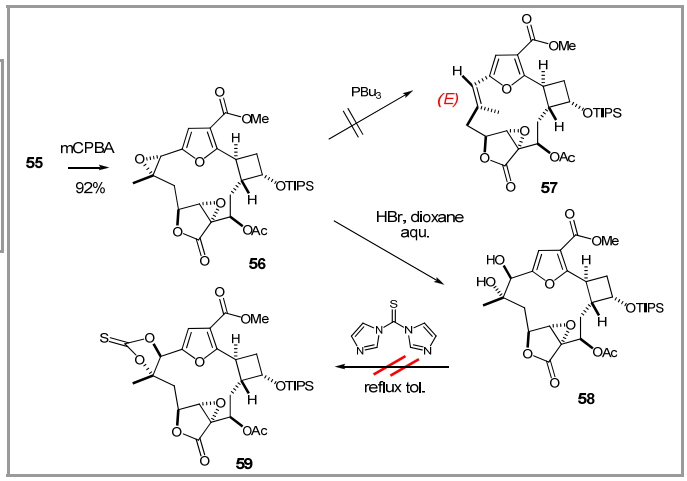
Scheme 15 Suggested mechanism of the epoxidation of **49**

In contrast, when acetate **49** was treated with NaOCl, epoxy acetate **55** was formed smoothly (Scheme 16).



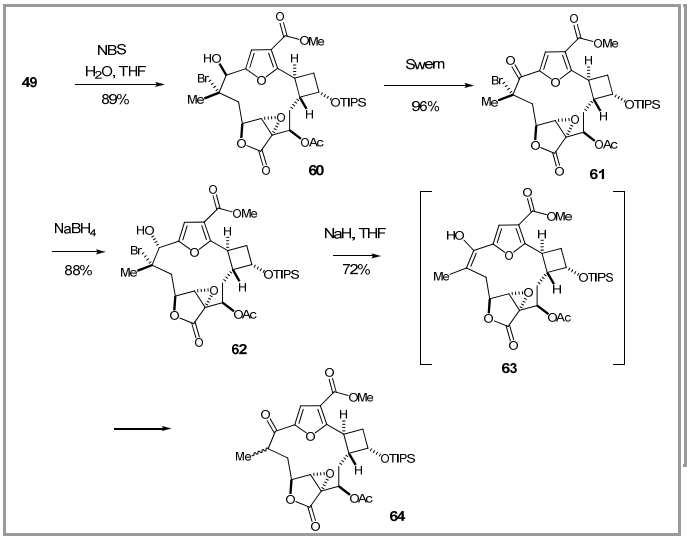
Scheme 16 Uneventful epoxidation of **49** with NaOCl

Next, the second epoxide was introduced stereoselectively with *m*CPBA to give *bis*-epoxide **56**. Various methods were tried to achieve inversion of the *trans*-epoxide to the *cis*-isomer (Scheme 17). For instance, addition of PBu_3 and subsequent Wittig elimination[9] to form **57** failed. On the other hand, acid induced conversion of **56** into diol **58** under inversion of configuration was achieved without problems, however, the Corey-Winter-deoxygenation protocol[10] to obtain the *trans*-olefin was totally unsuccessful, as not even thiocarbonate **59** could be formed.



Scheme 17 Unsuccessful attempts to invert the configuration of the 7,8-epoxide in **55**

In another attempt to switch to the *trans*-series, *Z*-olefin **49** was converted into bromohydrin **60** stereoselectively (Scheme 18). Swern-oxidation smoothly gave ketone **61**, which was reduced with sodium borohydride to form diastereomerically pure bromohydrin **62**. However, the attempt to eliminate HBr under formation of the *trans*-epoxide, failed. Instead, HBr-elimination furnished ketone **64** as an epimeric mixture, presumably *via* an E2-type mechanism generating enol **63** first.



Scheme 18 Further attempts to invert the 7,8-*cis*-configuration

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5. Cyclobutane Model studies

It was our permanent concern how to introduce the allylic OH-function onto the cyclobutane ring (Figure 4).

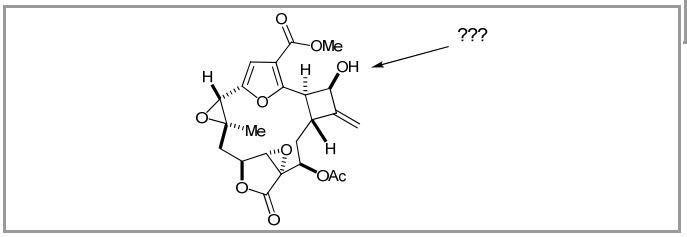
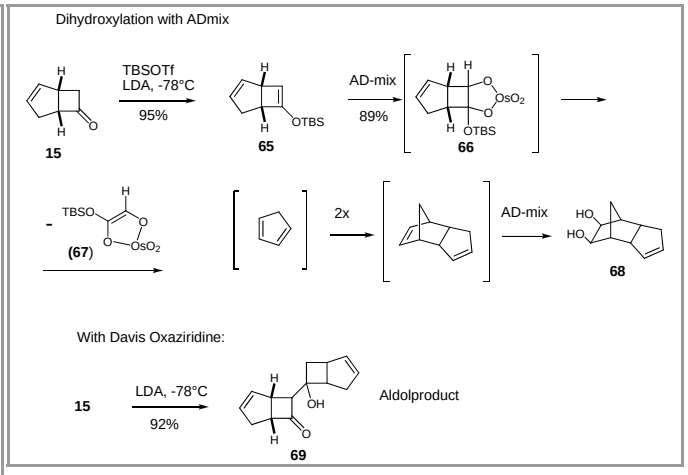
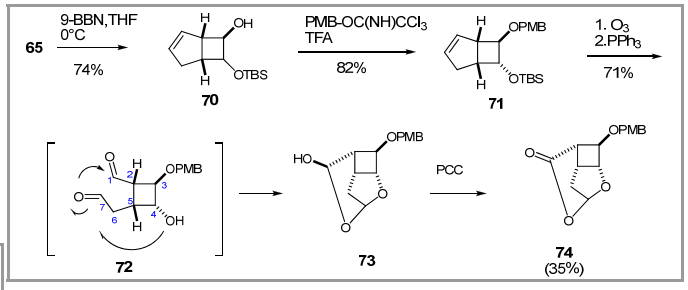


Figure 4 Problem of allylic oxidation

Therefore, model studies were undertaken from the very beginning (Scheme 19). For instance, racemic ketone **15** was converted into the TBS-enol ether **65** and then treated with AD-mix. To our surprise, diol **68** was the only product. We speculate that the primary adduct **66** undergoes a retro-[2+2] cycloaddition to form cyclopentadiene, which undergoes *in situ* dimerization. The dimer is then dihydroxylated to give **68**. Another attempt was made with Davis' oxaziridine.[11] However, on deprotonating **15** with LDA, a rapid aldol dimerization to **69** was observed.

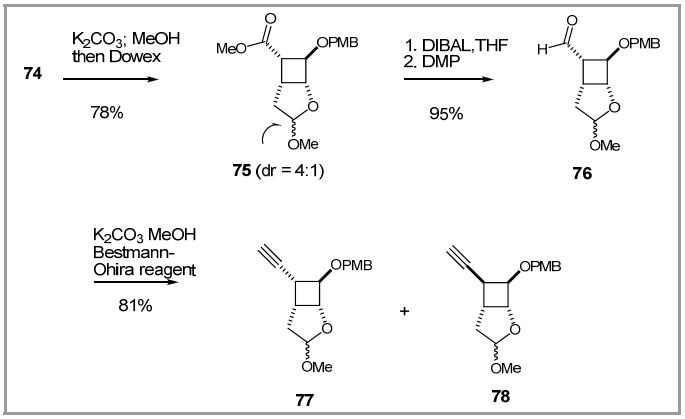


Scheme 19 Unsuccessful attempt to introduce a second oxygen onto the cyclobutane ring



Scheme 20 Unexpected formation of the caged lactone **84**

Another option for introducing the desired OH-function was hydroboration/reduction of enolsilane **65** (Scheme 20). Hence, treatment of **65** with 9-BBN furnished diol **70** which was OPMB-protected to **71** and then subjected to ozonolysis/reduction. Presumably, di-aldehyde **72** was formed first which under loss of the OTBS-group cyclized to the stable hemiacetal **73**. PCC-oxidation furnished lactone **74**.



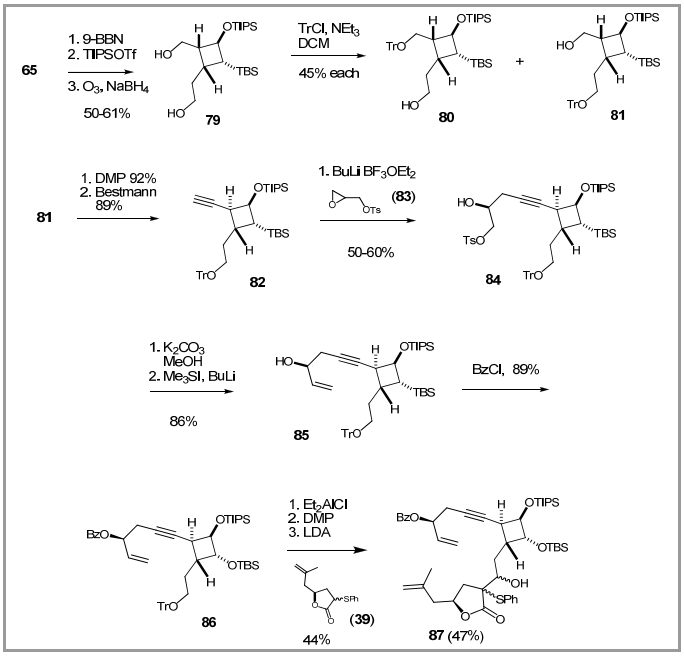
Scheme 21 Synthesis of oxygenated cyclobutane derivatives

To continue in the synthesis (Scheme 21), lactone **74** was converted into methyl acetal **75** and then reduced to the labile aldehyde **76**. On treatment with the Bestmann-Ohira reagent,[12] **76** was partially epimerized under the basic conditions and gave a mixture of alkynes **77**/**78**.

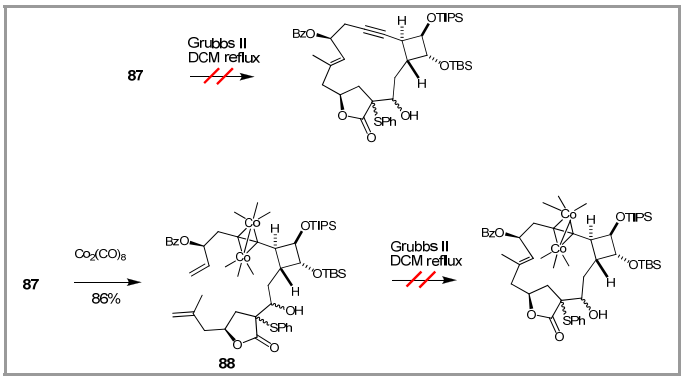
However, the bicyclic system of **77** was so stable, that all attempts to open the acetal cage resulted in destruction of the material. To avoid this problem (Scheme 22), **65** was converted into diol **79**, which was monotritylated to a separable mixture of regioisomers **80** and **81**. Compound **81** was oxidized to the aldehyde, epimerized and converted into isomerically pure alkyne **82**. Chain elongation with epoxide **83** gave diol **84**, which was transformed into allylic alcohol **85** *via* the epoxide. Benzoylation furnished **86**, which was detritylated, oxidized to the aldehyde and then subjected to an aldol addition with lactone **39** to give diene **87** in 47% overall yield. However, all attempts to use **87** in a RCM reaction failed. Even delinearizing the alkyne moiety by converting **87** into cobalt complex **88** did not help (Scheme 23).

6. **Conclusion**.

In conclusion, the characteristic fragments of providencin, namely the furan, cyclobutane and the butenolide rings, have been prepared and assembled in a linear arrangement. The ring closure has turned out to be the bottleneck of the synthesis, undoubtedly due to the ring strain exerted by the *trans*-configuration of the 7,8-olefin. The corresponding *Z*-olefin can be generated smoothly by RCM, however, inversion to the E-geometry has been unsuccessful thus far. This called for alternative strategies which are focused on the installation of an (*E*)-double bond prior to closing the macrocycle. Alternative efforts to close the macrocyclic ring by RCM have been unsuccessful and show the limitations of this method, however a macrocyclic derivative devoid of the butenolide ring has been prepared by HWE ring closure. Although the missing butenolide has yet to be annulated, we are confident to complete the synthesis along this route.



Scheme 22 Synthesis of **87** as another RCM precursor



Scheme 23 Unsuccessful RCM attempts with **87**

Acknowledgment

The authors thank Hanspeter Kählig, Lothar Brecker and Susanne Felsinger for NMR assistance and Peter Unteregger for recording the mass spectra. Financial support by the Austrian Science Fund (FWF project P 19792-N19) is gratefully acknowledged.

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TITLE : SYNTHESIS OF THE CYCLOBUTANE MOIETY OF PROVIDENCIN (MS WORD STYLE "01 HET-TITLE")

Tanja Gaich,[1] Vladimir Arion,[2] and Johann Mulzer[1]* (MS Word Style "02 Het-Author's name")

[1] Institute for Organic Chemistry, University of Vienna, Waehringerstrasse 38, A-1090 Wien, Austria, [2] Institute of Bioinorganic Chemistry,– University of Vienna, Waehringerstrasse 42, A-1090 Wien, Austria. johann.mulzer@univie.ac.at (MS Word Style "03 Het-Author's address")

Abstract –A short and stereoselective synthesis of the protected cyclobutane diol moiety of the natural compound providencin is reported. Key step is the chemo- and stereoselective hydroboration of the silyl-enol ether obtained from commercially available bicyclo[3.2.0]hept-6-en-2-one. (MS Word Style "04 Het-Abstract")

INTRODUCTION (MS Word Style "06 Het-Sub-heading")

Quite recently, the diterpene providencin ((+)-**1**)[1] was isolated from the gorgonian octocoral *Pseudopterogorgia kallos*, featuring an uncommon furyl cyclobutane ring system. The synthesis of highly functionalized cyclobutanes still represents a challenge for synthetic chemists, as substituents and functional groups attached to the cyclobutane ring are highly congested and the ring-geometry forces them into a fully eclipsed conformation[2]. The cyclobutane ring in **1** is *trans*-fused to the 13-membered macrocycle. Furthermore it exhibits an *exo*-methylene group with an allylic alcohol. In our retrosynthetic analysis we planned to introduce this allylic alcohol *via* an α-hydroxylation of commercially available non-racemic bicyclo[3.2.0]cyclo-hept-6-en-2-one (**3**) (Figure 1).

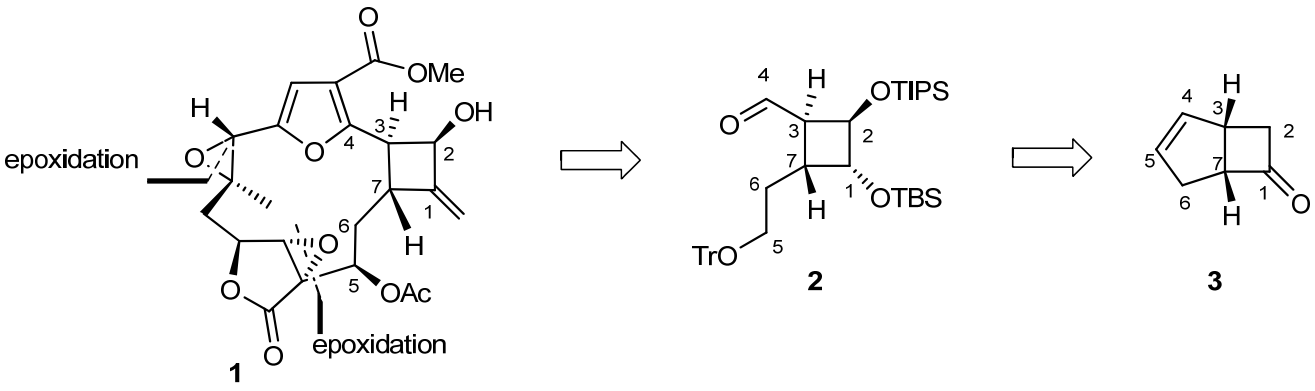
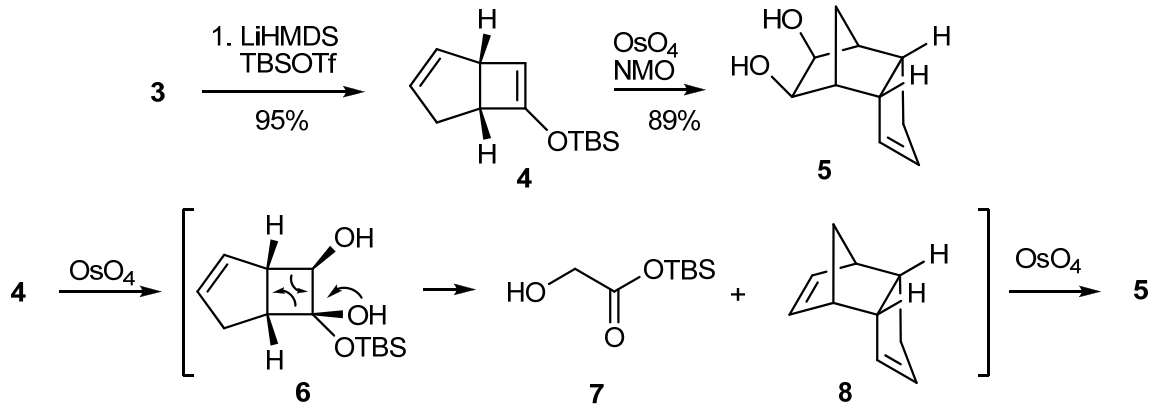


Figure 1. Retrosynthetic considerations

The use of **3** has the big advantage to provide us, not only the cyclobutanone ring, but to give after ozonolysis, two differentiable carbon appendages of suitable length for further elaboration. The *cis*-stereochemistry of the two carbon chains originates from bicycle **3** and was to be inverted to the desired *trans*-relation as shown in figure 1. In our current studies, racemic **3** was used to keep costs low.

RESULTS AND DISCUSSION

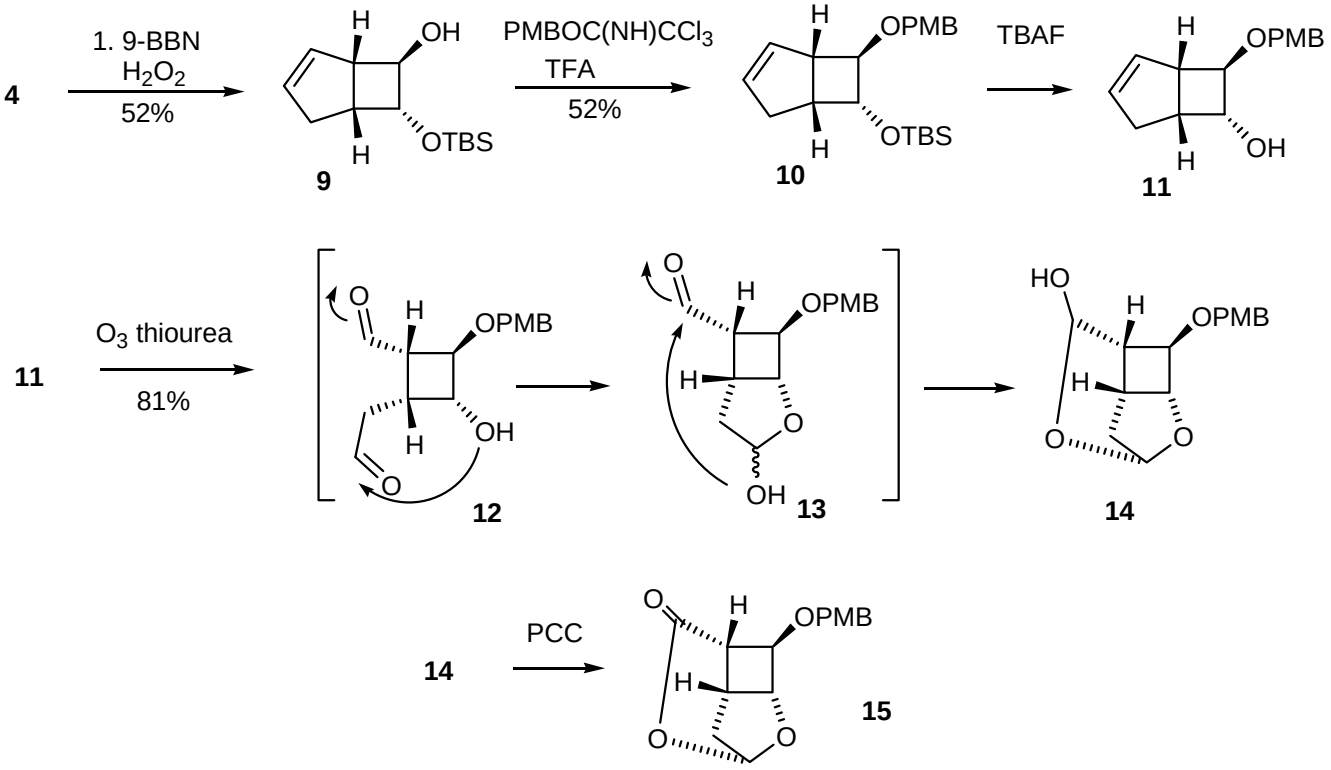
We tried various methods for the α-hydroxylation of bicyclic structure **3**.[3,4] Unfortunately we either got decomposition of starting material, or unwanted side products. For instance, after converting **3** into the silyl enol ether **4**, reaction with osmium tetroxide did not lead to α-hydroxylation. Instead compound **5** was isolated, obviously resulting from a sequential dihydroxylation retro-[2+2]–cycloaddition to give glycolic ester **7** and cyclopentadiene, which immediately undergoes Diels-Alder dimerization (**8**) /dihydroxylation to **5** (Scheme 1).



Scheme 1. Osmylation of **4** unexpectedly leads to **5**

As we could not introduce the hydroxyl group by α-hydroxylation, we tried a hydroboration of **4** with 9-BBN. To our delight, the desired diol **9** was formed in 52% yield (Scheme 2). The reaction not only established a *trans*-configuration of the diol, but also allowed complete differentiation of the two hydroxy-groups, as the former enol ether was converted to a TBS-protected alcohol and the free hydroxy group was protected as PMB ether **10**.

Next we aimed for cleaving the cyclopentene ring and inverting the configuration at C-3. To differentiate the two aldehyde functions resulting from ozonolysis we removed the TBS group to obtain **11** and hoped for an intramolecular lactol formation to give **13** from di-aldehyde **12**. However, the lactol OH function in **13** immediately added to the second aldehyde group to give **14** instead (Scheme 2).



Scheme 2. Formation of cage lactol **15**

This result is a nice illustration for the ease of transannular reactions in this bicyclic system. For further differentiation of the two acetals, we converted lactol **14** with PCC to lactone **15** in 35% yield. To corroborate the structure of **14** we performed an analogous sequence with dichloro-compound **16** (Scheme 3). In this case, lactol **17** crystallized nicely and we were able to confirm the cage structure via single crystal diffraction (Figure 2).

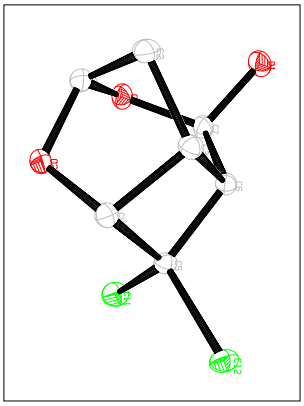
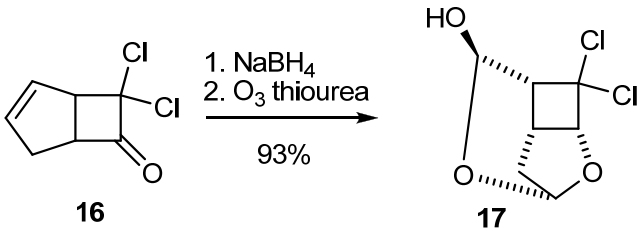
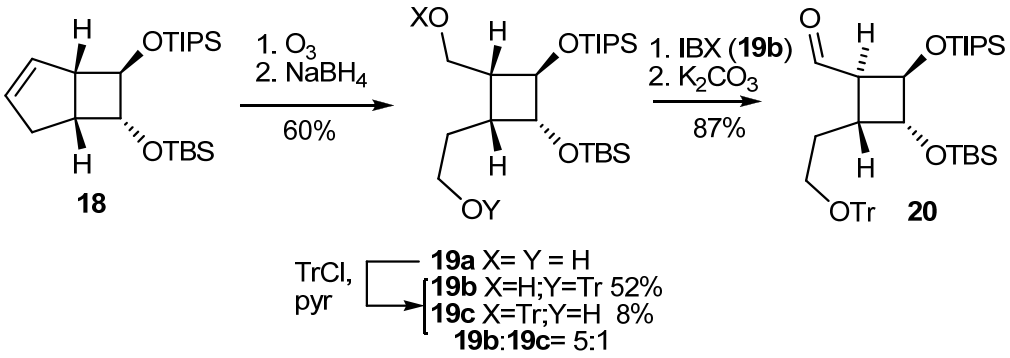


Figure 2. Crystal structure of compound **17**



Scheme 3. Synthesis of crystalline compound **17**

To avoid the low yielding oxidation of **14** we decided to prevent the double acetalization of **13** and used the doubly silylated diol **18** in the ozonolysis step.



Scheme 4. Synthesis of providencin fragment **20**

This time we used a reductive work up to get diol **19a**. To our delight we found that mono-tritylation furnished **19b** and **19c** with 5:1 regioselectivity, The regioisomers were easily separated by column chromatography. Oxidation of **19b** to the aldehyde and base catalyzed isomerization to the *trans* isomer **20** proceeded smoothly in 92% yield with 9:1 diastereomeric excess (Scheme 4). Evidence for this isomerization has been found in the ^{1}H NMR spectrum. The signal of the aldehyde-H changes its position from 9.67 to 9.74 ppm. By detritylation with formic acid, **19c** could be recycled to **19a** so that no material was lost.

In conclusion we have developed a stereoselective and short approach to the tetrasubstituted cyclobutane moiety of providencin **1**.(MS Word Style "05 Het-Text")

EXPERIMENTAL

Analytical data of key intermediates:

Compound **4** (Bicyclo[3.2.0]hepta-2,6-dien-6-yloxy) (*tert*-butyl)dimethylsilane):

To a solution of **3** (1.00 g, 9.24 mmol, 1eq.) in 40 mL dry THF at -78°C was slowly added TBSOTf (6.4 mL, 27.7 mmol, 3eq.). To this mixture at -78°C was rapidly added LiHMDS (1M in hexane, 46 mL, 46 mmol, 5eq.). The reaction mixture was stirred for one hour at -78°C, and then quenched with saturated NH_4Cl solution and extracted two times with diethylether (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was filtered over silica gel with (hexane/ethylacetate 20:1 and 5% triethylamine) and was then further purified *via* a bulb to bulb distillation to yield 95% 1.95 g of pure **4**.

^{1}H-NMR: □ 5.90-5.85 (m, 1H), 5.62-5.57 (m, 1H), 4.99 (s, 1H), 3.51-3.44 (m, 1H), 3.25-3.20 (m, 1H), 2.46-2.17 (m, 2H), 0.95 (s, 9H), 0.19 (s, 6H). ^{13}C-NMR: □ 134.97, 130.52, 111.52, 49.09, 45.52, 30.77, 26.04, -4.17, -4.33. HRMS (EI) *m/z* calcd for $C_{13}H_{22}OSi$ 222.3987, found 222.3982.

Compound **5** (4,7-Methano-1*H*-indene-5,6-diol, 3a,4,5,6,7,7a-hexahydro-, (3a□,4□,5□,6□,7□,7a□):

To a solution of **4** (743 mg, 3.3 mmol, 1eq.) in *t*BuOH:H_2O (1:1, 30 mL) at 0°C was added OsO_4 (4 mg, 0.016 mmol, 0.5mol%) and N-morpholine-N-oxid (390 mg, 3.3 mmol, 1eq.). The reaction mixture was stirred for 20 hours, quenched with an aqueous sodium thiosulfate solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure. Crude **5** was purified by chromatography (silica gel, hexane/ethyl acetate 1:1) to yield 488 mg 89% of pure **5**.

^{1}H-NMR: □ 5.45-5.37 (m, 2H), 3.61 (d, *J* = 5.38 Hz, 1H), 3.52 (d, *J* = 5.56 Hz, 1H), 2.94-2.88 (m, 1H), 2.69-2.59 (m, 2H OH broad), 2.42-2.35 (m, 1H), 2.15-2.06 (m, 3H), 1.92 (d, *J* = 4.29 Hz, 1H), 1.70-1.67 (m, 1H), 116-1.12 (m, 1H). ^{13}C-NMR: □ 131.33, 131.13, 71.81, 70.19, 51.29, 48.47, 46.87, 40.92, 35.35, 32.35. HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_2$ 166.2170, found 166.2178.

Compound **9** (7-(*tert*-butyldimethylsilyloxy)bicyclo[3.2.0]hept-3-en-6-ol):

To a solution of **4** (743 mg, 3.3 mmol, 1eq.) in dry THF (7 mL) at 0°C was added 9-BBN (0.5M in THF 6.6 mL, 1eq.). The reaction mixture was warmed to room temperature and stirred for 14 hours. The reaction was quenched with 3mL 0.5M NaOH and 1mL H_20_2 (30%), diluted with brine and extracted two times with

diethylether (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under vacuum. Crude **9** was purified by flash column chromatography (hexane/ethylacetate 3:1) to yield 412 mg 52% of pure **9**.

^{1}H-NMR: δ 5.79-5.72 (m, 2H), 4.11 (dd, *J* = 8.96, 4.92 Hz, 1H), 3.59-3.56 (m, 1H), 2.96-2.88 (m, 1H), 2.67-2.60 (m, 2H), 2.25-2.17 (m, 1H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR: δ 134.46, 131.79, 84.38, 74.59, 49.47, 37.69, 26.24, -4.47. (HRMS (EI) *m/z* calcd for $C_{13}H_{24}O_2Si$ 240.4140, found 240.4133.

Compound **10** (*tert*-butyl(-7-(4-methoxybenzyloxy)bicyclo[3.2.0]hept-2-en-6-yloxy)dimethylsilane):

To a solution of alcohol **9** (2.1 g, 8.7 mmol, 1eq.) in dry DCM (10 mL) was added a solution of Bundles reagent (5 g, 17.5 mmol, 2eq.) in hexane (30 mL) and cooled to 0°C. Then 20 mg of camphor sulfonic acid were added and the reaction mixture was stirred over night. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted two times with diethylether (100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **10** was purified by column chromatography (silicagel, hexane/ethylacetate 7:1) to yield 1.63 g 52% of pure **10**.

^{1}H-NMR: δ 7.30-7.26 (m, 2H), 6.92-6.88 (m, 2H), 5.83-5.79 (m, 1H), 5.76-5.71 (m, 1H), 4.44 (s, 2H), 3.83 (s, 3H), 3.49-3.45 (m, 1H), 3.09-2.96 (m, 1H), 2.81-2.69 (m, 2H), 2.38-2.24 (m, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR: δ 159.71, 134.31, 131.75, 129.82, 129.61, 114.27, 91.22, 74.59, 73.18, 55.86, 49.47, 37.69, 26.24, 18.43, -4.51. HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_3Si$ 360.5625, found 360.5620.

Compound **14** 2-(4-methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-8-ol:

Ozone was bubbled through a solution of **11** (219 mg, 0.89 mmol, 1eq.) in DCM/MeOH 4:1 (5 mL) at -78°C for 10 minutes. To remove unreacted ozone, air was subsequently bubbled through the reaction mixture at the same temperature for 5 minutes. Then thiourea (71 mg, 0.93 mmol, 1.05 eq.) was added and the reaction was warmed to room temperature. The solid was filtered off, the solvents were removed under reduced pressure and crude **14** was submitted to flash column chromatography (silicagel, hexane/ethyl acetate 2:1) to yield 200 mg 81% of pure **14**.

^{1}H-NMR: δ 7.30-7.21 (m, 2H), 6.90-6.82 (m, 2H), 5.67-5.54 (m, 1H), 5.17 (s, 1H), 4.63-4.35 (m, 3H), 3.78 (s, 3H), 3.51-3.22 (m, 1H), 3.06-2.91 (m, 1H), 2.75-2.69 (m, 1H), 2.64-2.55 (m, 1H), 1.55-1.45 (m, 1H). HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_5$ 278.3004, found 278.2999.

Compound **15** 2-(4-methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-3-one

Lactol **14** (200 mg, 0.72 mmol, 1eq.) was dissolved in dry DCM (12 mL) at 0°C. The PCC (170 mg, 0.8 mmol, 1.2 eq.) was added. After 30 minutes another portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was

added and a last portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was added after 2 hours. The reaction was then stirred for 24 hours, quenched with saturated $NaHCO_3$ solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **15** was purified by column chromatography (silicagel, hexane/ethyl acetate 2:1) to yield 70 mg 35% of pure **15**.

^{1}H-NMR: δ 7.32-7.26 (m, 2H), 6.94-6.89 (m, 2H), 5.99 (dd, *J* = 3.08, 1.03 Hz, 1H), 4.62-4.46 (m, 3H), 3.93 (s, 1H), 3.83 (s, 3H), 3.66-3.59 (m, 1H), 3.28-3.24 (m, 1H), 2.11-2.04 (m, 1H), 2.00-1.91 (s, 1H). HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_5$ 276.2845, found 276.2855.

Compound **17 (**5,5-Dichloro-2,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-3-ol):

See procedure for compound **14.**

^{1}H-NMR: δ 5.70 (dd, *J* = 3.48, 0.50 Hz, 1H), 5.41 (s, 1H), 4.76-4.73 (m, 1H), 3.62-3.58 (m, 1H), 3.26-3.22 (s, 1H OH, broad), 3.19 (ddd, *J* = 7.39, 4.47, 1.57 Hz, 1H), 2.78 (d, *J* = 12.28 Hz, 1H), 1.70 (ddd, *J* = 12.14, 4.16, 4.16 Hz, 1H) ^{13}C-NMR: δ 101.60, 90.31, 88.38, 82.36, 56.06, 35.22, 31.26. HRMS (EI) *m/z* calcd for $C_7H_8Cl_2O_3$ 211.0426, found 211.0420.

Compound **19a** ((3-(*tert*-butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)-cyclobutyl)methanol):

Ozone was bubbled through a solution of **18** (385 mg, 1.0 mmol, 1eq.) in DCM/MeOH 4:1 (7 mL) at -78°C for 10 minutes. To remove unreacted ozone air was bubbled through the reaction mixture at the same temperature for 5 minutes. Then $NaBH_4$ (71 mg, 2.0 mmol, 2 eq.) were added and the reaction was warmed to room temperature. The reaction was then stirred for 2 hours, quenched with saturated NH_4Cl solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **19a** (330 mg, 0.76 mmol, 1eq.) was directly used in the next step. **19a** was dissolved in dry DCM (15 mL) cooled to 0°C and pyridine (250µl, 2.28 mmol, 3eq.) were added at that temperature. To this solution was added dropwise tritylchloride in dry DCM (2 mL) and the reaction was stirred over night. The mixture was quenched with brine and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude product was purified by flash column chromatography (silicagel, hexane/ethyl acetate 7:1) to yield 267 mg 52% of **19b** and 41 mg 8% of **19c** 35% of pure **15**.

^{1}H-NMR: δ 7.54-7.25 (m, 15H), 4.00-3.62 (m, 4H), 3.37-3.14 (m, 2H), 2.34 (ddd, *J* = 16.9, 8.79, 4.23 Hz, 1H), 2.08-1.94 (m, 2H), 1.76-1.61 (m, 1H), 1.69 (s, broad 1H), 1.12 (s, 21H), 0.95 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). HRMS (EI) *m/z* calcd for $C_{41}H_{62}O_4Si_2$ 675.0996, found 675.0989.

Compound **20** (3-(*tert*-butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)-cyclobutanecarbaldehyde):

Alcohol **19b** (175 mg, 0.26 mmol, 1eq.) was dissolved in ethyl acetate (3 mL) and IBX (218 mg, 0.78 mmol, 3eq.) was added. The suspension was refluxed for 2 hours, and then cooled to room temperature and the solid was filtered off. The organic layer was concentrated, re-dissolved in MeOH (10 mL) and K_2CO_3 (361 mg, 2.6 mmol, 10eq.) was added to the solution. The reaction was stirred for 1.5 hours, diluted with diethylether, the solids filtered off, and extracted with saturated NH_4Cl solution. The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **20** was purified by flash column chromatography (silicagel, hexane/ethyl acetate 7:1) to yield 152 mg 87% of pure **20**.

^{1}H-NMR: δ 9.74 (t, *J* = 1.37 Hz, 1H), 4.13-4.05 (m, 1H), 3.77-3.71 (m, 1H), 3.53 (dd, *J* = 9.50, 4.23 Hz, 1H), 3.17-3.05 (m, 1H), 2.86 (t, *J* = 10.16 Hz, 1H), 2.46-2.18 (m, 2H), 1.02 (s, 21H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). HRMS (EI) *m/z* calcd for $C_{22}H_{45}O_3Si_2$ 413.7619, found 413.7611.

Crystal Data of Compound **17**.

Symmetry cell setting monoclinic, symmetry space group P21, a =5.9039(2), b= 10.8209(4), c= 6.4507(2), alpha =90.00, beta =90.510(2), gamma = 90.00, V = 412.09(2), Z = 2, density calc = 1.710, T = 373 K, diffrn radiation wavelength 0.71073 ,diffrn radiation type MoKα, graphite, diffrn reflns number 15712, diffrn reflns av R equivalents 0.0202, diffrn reflns av_sigmaI/netI 0.0128, diffrn reflns limit h min 8, diffrn reflns limit h max 8, diffrn reflns limit k min -15, diffrn reflns limit k max 15, diffrn reflns limit l min 9, diffrn reflns limit l max 9, diffrn reflns heta min 3.16, diffrn reflns theta max 30.02, reflns number total 2409, reflns number gt 2379, reflns threshold expression >2sigma(I), computing structure solution SHELXS-97 (Sheldrick, 1990),' computing structure refinement SHELXL-97 (Sheldrick, 1997).' Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger. Refine ls number reflns 2409, refine, ls

number parameters 111, refine ls number restraints 1, refine ls R factor all 0.0161, refine ls R factor gt 0.0158, refine ls wR factor ref 0.0427, refine ls wR _factor gt 0.0424, refine ls goodness of fit ref 1.069.
Abbreviations: TBSOf *tert*Butyldimethylsilyltriflate, LiHMDS lithium hexamethyldisilazide, DCM dichloromethane, PCC pyridinium chlorochromate, IBX *o*-iodoxy-benzoxy acid.

ACKNOWLEDGEMENTS

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Synthetic Studies towards the Total Synthesis of Providencin

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Abstract: A synthetical approach to assemble the uncommon furylcyclobutane substructure in providencin ((+)-**1**) has been developed starting from a commercially available cyclobutane precursor.

Key words: Furan - Cyclization - Natural product - Stereoselective synthesis - Total synthesis.

The abundance of variably functionalized furans in biologically active compounds has stimulated considerable synthetic interest.[1] Hence, a variety of methods have been devised to assemble furan intermediates.[2] to Furanocembranes have received particular attention (Figure 1), because they are effective against various cancer types, reveal analgesic or anti-inflammatory activity, or display potent neuro- and cytotoxic properties.[3] Most notable contributions came from the groups of Paquette, Marshall, Wipf, and Pattenden,[4] who developed "furan first"[5] or "furan last" strategies, depending on the stage at which the furan moiety was introduced into the carbon skeleton.

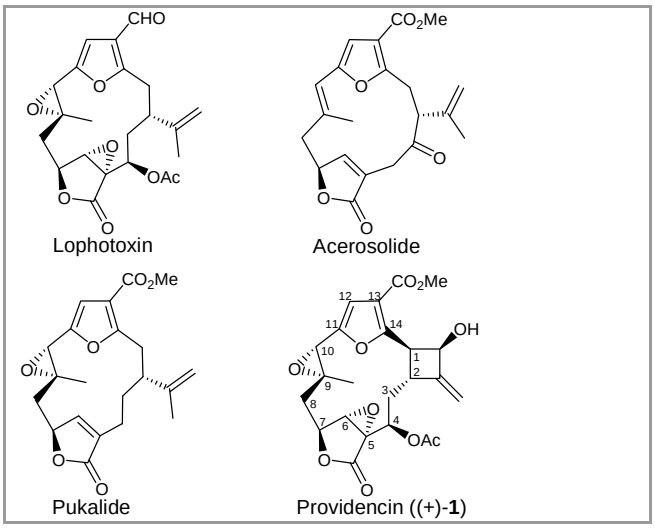
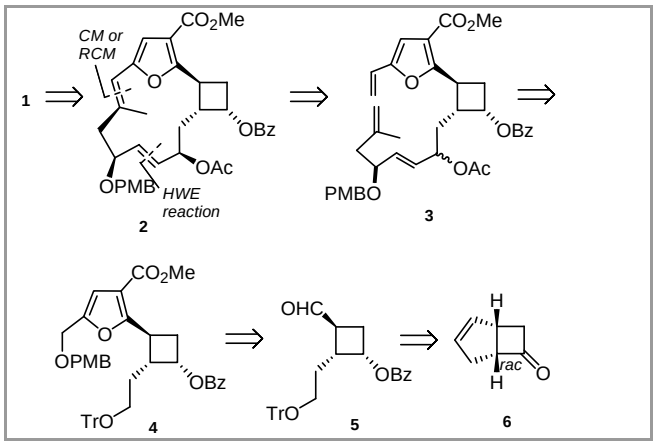


Figure 1 Examples of furanocembranolides isolated from marine invertebrates.

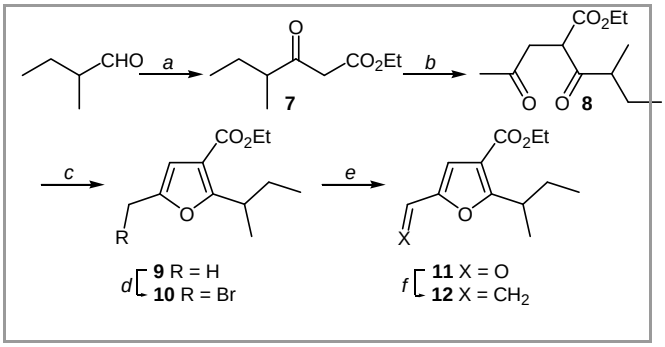
Quite recently, the diterpene providencin ((+)-**1**)[6] was isolated from the gorgonian octocoral *Pseudopterogorgia kallos*, featuring an uncommon furyl cyclobutane ring system. *Bray* and *Pattenden* lately reported a photochemical access to the furyl cyclobutane segment of **1**.[7] We also envisaged a "furan first" strategy for the synthesis of **1** starting from a readily available cyclobutane. Thus, the deoxy compound **2** would serve as a late stage key intermediate, which might be accessible *via* metathesis and *Horner-Wadsworth-Emmons* (*HWE*) olefination from the cyclobutyl furan **4** (Scheme 1).



Scheme 1 Retrosynthetic considerations for the total synthesis of providencin ((+)-**1**).

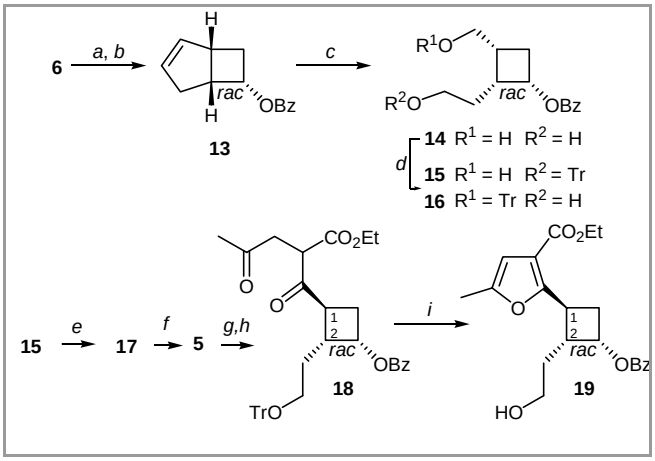
Fragment **4** can be further disconnected to aldehyde **5**, in turn obtainable from the commercially available bicycloheptenone **6**.

First we had to develop methodology for attaching a highly substituted furan ring to the cyclobutane moiety present in **5**. After extensive experimentation, a *Paal-Knorr* type reaction turned out to be the method of choice. Therefore, in a preliminary model study, ethyl ester **7**, obtained *via Roskamp* reaction[8] from 2-methylbutyraldehyde and commercially available ethyl diazoacetate, was alkylated with chloroacetone, leading to the 1,4-diketone **8**. Microwave assisted cyclization led to furan **9** in excellent yield (Scheme 2). Further functionalization by selective bromination at the less substituted α-position afforded furans **10**–**12** as versatile intermediates for a variety of potential coupling reactions.



Scheme 2 Synthesis of the furans **9**-**12**. *Reagents and conditions:* (a) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 25 °C, 4 h (97%); (b) chloroacetone, NaH (60% in mineral oil), THF, 25 °C, 36 h (63%); (c) concd HCl, EtOH, microwaves, 100 °C, 8 min (98%); (d) NBS, AIBN, CCl_4, 76 °C, 1 h (79%); (e) Me_2SO, 190 °C, 10 min (45%); (f) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C to 25 °C, 12 h (55%).

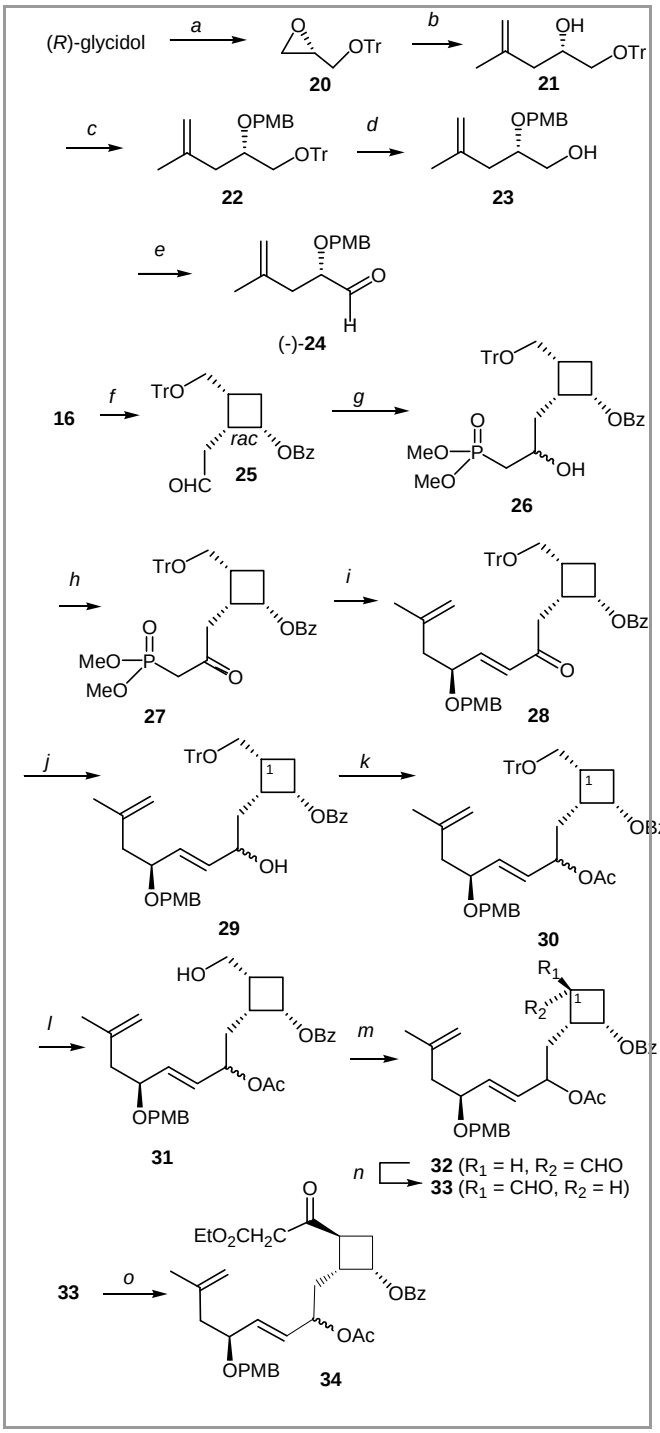
For the synthesis of furylcyclobutane **19** racemic bicycloheptenone **6** was stereoselectively reduced to the alcohol and converted to the corresponding benzoate **13**. Ozonolysis of the double bond followed by reductive workup with $NaBH_4$ afforded the diol **14** which was tritylated with TrCl to both monoprotected regioisomers **15** and **16** in a 4:1 ratio, separable by column chromatography. *Bis*-tritylated diol and unreacted starting material was recovered and recycled. Alcohol **15** was oxidized to aldehyde **17** which was isomerized at C(1) with aqueous K_2CO_3 and then converted to the 1,4-diketone **18** by using the protocol described in Scheme 3. Microwave irradiation led finally to the desired furan **19,** under cleavage of the trityl protecting group (Scheme 3).



Scheme 3 Synthesis of the C(1),C(2) *trans*-substituted furylcyclobutane **19**. *Reagents and conditions:* (a) $NaBH_4$, MeOH, –78 °C, 1 h; (b) benzoyl chloride, pyridine, 0 °C to 25 °C, 4 h (97% over two steps); (c) i) O_3, CH_2Cl_2, –78 °C, 20 min; ii) PPh_3, 25 °C, 4 h (85%); (d) TrCl, NEt_3, 4- dimethylamino-pyridine, CH_2Cl_2, 25 °C, 18 h (**15**: 35%; **16**: 9%); (e) *Dess-Martin* periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h (87%); (f) 0.1 M K_2CO_3, MeOH, CH_2Cl_2, 25 °C, 15 min (87%); (g) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 25 °C, 2 h (73%); (h) chloroacetone, NaH (60% in mineral oil), THF, 25 °C, 50 h (46%); (i) concd HCl, MeOH, CH_2Cl_2, microwaves, 100 °C, 10 min (90%).

For the synthesis of enantiomerically pure compounds bicycloheptenone **6** was reduced with $NaBH_4$ and converted to the corresponding acetate. Digestion with lipase SAM-II afforded the undesired alcohol and the desired enantiomer as unreacted acetate, which was hydrolyzed with LiOH. The alcohol thus obtained can be benzoylated and further transformed as described for the racemate **13**.

To validate our approach towards the total synthesis of the providencin ((+)-**1**) macrolide, (*R)*-glycidol was tritylated to **20**, and then treated with *i*-propenylmagnesium bromide in the presence of CuI to give alcohol **21** which was protected as the PMB ether **22**. After detritylation alcohol **23** was formed and oxidized to aldehyde **24**. In a parallel sequence, alcohol **16** was oxidized to aldehyde **25**, which was converted to β-ketophosphonate **27** and coupled with aldehyde **24** to give ketone **28**, which was reduced to alcohol **29** and acetylated. After detritylation alcohol **31** was obtained which was oxidized to aldehyde **32**. Base catalyzed epimerization delivered aldehyde **33**, which corresponds to the C14-C9-fragment of (+)-**1.** *Roskamp* reaction finally led to ketoester **34** (Scheme 4).



Scheme 4 Synthesis of the fragment **34**. *Reagents and conditions:* (a) TrCl, NEt_3, 4-dimethylamino-pyridine, CH_2Cl_2, 0 °C to 25 °C, 24 h (quant.); (b) *i*-propenylmagnesium bromide, CuI, THF, –78 °C to –40 °C, 2 h (quant.); (c) i) PMBCl, NaH (60% in mineral oil), tetrabutyl ammonium bromide, THF, 25 °C, 1 h, 60 °C, 24 h; (d) *p*-TsOH, MeOH, 25 °C, 30 min (71%); (e) $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, –78 °C, 1 h, 0 °C, 2 h (88%). (f) *Dess-Martin* periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h (95%); (g) $MeP(O)(OMe)_2$, *n*-BuLi, THF, –78 °C, 6 h (84%); (h) *Dess-Martin* periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 2 h (78%); (i) NaH (60% in mineral oil), (–)-**24**, THF, –10 °C, 10 min, 25 °C, 2 h (92%); (j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –78 °C, 3 h (78%); (k) Ac_2O, Et_3N, 4-dimethylamino-pyridine, CH_2Cl_2, 25 °C, 2 h (97%); (l) *p*-TsOH, MeOH, 25 °C, 2 h (81%); (m) *Dess-Martin* periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 2 h (85%); (n) 0.1 M K_2CO_3, MeOH, 25 °C, 15 min (66%); (n) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 25 °C, 2 h (79%).

In conclusion, we have described the synthesis of the *trans*-fused furylcyclobutane moiety **34** of providencin ((+)-**1**), starting from the commercially available cyclobutane derivative **6**. Functionalization of the substituents at both the C(1) and C(2) position of the cyclobutane ring was possible, thus corroborating our strategy. Moreover, the synthesis of highly functionalized furan derivatives provided versatile intermediates, which might be employed in a variety of coupling reactions.

All ^{1}H NMR (250 MHz or 400 MHz) and ^{13}C NMR (63 MHz or 100 MHz) spectra were recorded on Bruker Avance DPX 250 or DRX 400 spectrometers. The chemical shifts are reported in δ values (ppm) relative to the solvent peak as internal standard. IR spectra were recorded as a film on NaCl plates with a Perkin-Elmer Spectrum 1600 Series FTIR spectrometer. MS spectra were recorded on a Finnigan MAT 8230 apparatus with a resolution of 10000. Products were purified by flash column chromatography (silica gel from Merck, 40–63 μm, 240–400 mesh). THF was distilled from sodium/benzophenone.

General procedure for the microwave assisted furan cyclization

The diketone (1.75 mmol) was dissolved in MeOH or EtOH (3 mL), then concd HCl (30 μL) was added and the mixture was subjected to microwave irradiation (Biotage Initiator) for 4–15 min at 100–120° C. Saturated aq $NaHCO_3$ soln (5 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*.

2-*sec*-Butyl-5-methylfuran-3-carboxylic acid ethyl ester (9)

SnCl2 (38 mg, 0.2 mmol), ethyl diazoacetate (126 μL, 1.2 mmol) and isobutyraldehyde (107 μL, 1.0 mmol) in CH_2Cl_2 (2 mL) were stirred for 4 h. The mixture was quenched with sat. aqueous ammonium fluoride and extracted with Et_2O. the organic layer was dried over $MgSO_4$, evaporated and purified by chromatography (silicagel, hexane/AcOEt 3:1) to give ketoester **7** (171 mg, quant.). as a colorless oil.

IR: 2961, 2930, 2870, 1740, 1709, 1649, 1626, 1459, 1406, 1368, 1307, 1224, 1171, 1148, 1125, 1095, 1027 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (*t*, *J* = 7.4 Hz, 3 H, H-C(1)), 1.13 (*d*, *J* = 7.0 Hz, 3 H, H-C(4)), 1.30 (*t*, *J* = 7.2 Hz, 3 H, H-C(7)), 1.38–1.55 (*m*, 1 H, H-C(2)), 1.62–1.84 (*m*, 1 H, H-C(2)), 2.53–2.68 (*m*, 1 H, H-C(3)), 3.49 (*s*, 2 H, H-C(5)), 4.22 (*q*, *J* = 7.2 Hz, 2 H, H-C(6)).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.8, 14.5, 15.8, 26.0, 48.1, 48.4, 61.6, 167.7, 206.8.

NaH ((60% suspension in mineral oil) (650 mg, 16.3 mmol) and ketoester **7** (2.80 g, 16.3 mmol) in THF (20 mL) were stirred at 25°C for 1h. Chloroacetone (1.2 mL, 15.5 mmol) was added dropwise and the mixture was stirred at 25°C for 50h. Workup with water and ether furnished after chromatography (silicagel, hexane/EtOAc 20:1) diketone **8** (2.24 g, 63%) as a colorless oil, which was used in the next step without further purification.

Diketone 8 (400 mg, 1.75 mmol), EtOH (3 mL), and concd HCl (30 μL) were reacted according to general procedure A. The residue was purified by column chromatography on silicagel (hexane/AcOEt 20:1) to yield 9 as pale yellow oil (360 mg, 98%).

IR: 2968, 2930, 1709, 1580, 1383, 1277, 1231, 1201, 1064 cm-1.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (*t*, *J* = 7.5 Hz, 3 H), 1.23 (*d*, *J* = 6.9 Hz, 3 H), 1.33 (*t*, *J* = 6.9 Hz, 3 H), 1.49–1.79 (m, 2 H), 2.24 (*d*, *J* = 0.9 Hz, 3 H), 3.45–3.61 (m, 1 H), 4.24 (*q*, *J* = 6.9 Hz, 2 H), 6.20 (*d*, *J* = 0.9 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.3, 13.5, 14.7, 18.9, 28.9, 34.2, 60.1, 106.4, 113.7, 150.1, 164.6, 165.2.

HRMS (EI) *m/z* calcd for $C_{12}H_{18}O_3$: 210.1256, found: 210.1258.

5-Bromomethyl-2-*sec*-butylfuran-3-carboxylic acid ethyl ester (10)

Methylfuran **9** (360 mg, 1.71 mmol), *N*-bromosuccinimide (320 mg, 1.80 mmol), and azobisisobutyronitrile (32 mg, 0.19 mmol) were dissolved in CCl_4 (10 mL) and the reaction mixture was refluxed for 1 h. The succinimide was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica (hexane/AcOEt 10:1) to afford **10** as a pale yellow oil (390 mg, 79%).

IR: 2968, 2930, 1709, 1611, 1558, 1216, 1057 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (*t*, *J* = 7.4 Hz, 3 H), 1.26 (*d*, *J* = 6.9 Hz, 3 H), 1.33 (*t*, *J* = 7.1 Hz, 3 H), 1.56–1.84 (*m*, 2 H), 3.49–3.62 (m, 1 H), 4.25 (*q*, *J* = 7.1 Hz, 2 H), 4.44 (*s*, 2 H), 6.63 (*s*, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.4, 14.6, 18.8, 23.6, 28.8, 34.5, 60.5, 110.9, 114.6, 148.3, 167.1, 167.7.

HRMS (EI) *m/z* calcd for $C_{12}H_{17}O_3Br$: 288.0361, found: 288.0332.

2-*sec*-Butyl-5-formylfuran-3-carboxylic acid ethyl ester (11)

Bromide **10** (40 mg, 0.14 mmol) was dissolved in dry dimethylsulfoxide (5 mL) and the solution was heated under reflux at 190 °C for 10 min, then H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O (60 mL) and brine (60 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silicagel (hexane/AcOEt 5:1) to yield **11** as pale yellow oil (14 mg, 45%).

IR: 2968, 2930, 1721, 1688, 1586, 1535, 1459, 1216, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.6 Hz, 3 H), 1.31 (d, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.61–1.86 (m, 2 H), 3.62–3.71 (m, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 7.47 (s, 1 H), 9.57 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 14.6, 18.5, 28.7, 34.9, 60.8, 110.6, 116.2, 150.7, 163.0, 172.3, 177.6.

HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_4$: 224.1049, found: 224.1047.

2-*sec*-Butyl-5-vinylfuran-3-carboxylic acid ethyl ester (12)

Ph_3PCH_3Br (96 mg, 0.27 mmol) was dissolved under Ar in dry THF (2 mL) and the suspension was cooled to 0 °C. *n*-BuLi (2.5 M, 0.1 mL, 0.25 mmol) was added, the mixture was warmed to 25 °C, and stirred for 1 h before aldehyde **11** (50 mg, 0.22 mmol) in THF (3 mL) was added. The reaction mixture was stirred for 12 h at 25 °C, and treated with sat. aq $NaHCO_3$ soln (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silicagel (hexane/AcOEt 20:1) to give **12** as pale yellow oil (27 mg, 55%).

IR: 2961, 2930, 2877, 1717, 1588, 1535, 1451, 1375, 1209, 1057 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3 H), 1.30 (d, *J* = 7.1 Hz, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.56–1.89 (m, 2 H), 3.52–3.68 (m, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 5.19 (d, *J* = 11.3 Hz, 1 H), 5.66 (d, *J* = 17.5 Hz, 1 H), 6.45 (dd, *J* = 17.5, 11.3 Hz, 1 H), 6.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 14.7, 18.9, 29.0, 34.4, 60.4, 108.7, 113.0, 114.6, 124.9, 151.1, 164.3, 166.3.

HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256, found: 222.1245.

(1*SR*,5*RS*,6*SR*)-Bicyclo[3.2.0]hept-2-en-6-benzoate (13)

A suspension of $NaBH_4$ (870 mg, 23.0 mmol) in MeOH (75 mL) at –78 °C was treated dropwise with racemic bicycloheptenone **6** (4.9 mL, 46.0 mmol) in MeOH (25 mL). The mixture was stirred for 1 h at –78 °C, warmed to 25°C and diluted with Et_2O and 2 N

HCl. The organic layer was dried over $MgSO_4$, concentrated and diluted with CH_2Cl_2 (50 mL) and pyridine (7.5 mL, 92.0 mmol). Benzoyl chloride (7.5 mL, 64.4 mmol) was added dropwise and the mixture was stirred at 25 °C for 4 h, quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give after chromatography (silicagel, hexane/AcOEt 10:1) benzoate **13** (9.6 g, 97% over 2 steps) as a colorless oil.

IR: 3056, 2939, 2850, 1716, 1602, 1585, 1491, 1452, 1347, 1314, 1271, 1176, 1113, 1070, 1046 cm^{-1}.

^1H -NMR ($CDCl_3$, 250 MHz): δ = 1.90–2.01 (*m*, 1 H, H-C(2)), 2.50 (*dd*, *J* = 17.1 Hz, 9.8, 1 H, H-C(6)), 2.60–2.73 (*m*, 1 H, H-C(6)), 2.88 (*dt*, *J* = 8.0, 2.2 Hz, 1 H, H-C(2)), 3.10–3.23 (*m*, 1 H, H-C(3)), 3.36–3.50 (*m*, 1 H, H-C(7)), 5.41–5.52 (*m*, 1 H, H-C(1)), 5.88 (*s*, 2 H, H-C(4), H-C(5)), 7.46 (*t*, *J* = 7.6 Hz, 2 H, Ph), 7.59 (*t*, *J* = 7.6 Hz, 1 H, Ph), 8.07 (*d*, *J* = 7.6 Hz, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 33.1, 37.1, 41.3, 41.7, 69.8, 128.7, 130.0, 130.1, 132.6, 133.2, 134.6, 144.4.

EI-HR-MS: *m*/*z* calcd for 214.0994 (*M*+, $C_{14}H_{14}O_2$+, found:. 214.0991.

(1*SR*,2*RS*,3*RS*)-2-(2-Hydroxyethyl)-3-hydroxymethyl-cyclobutyl-benzoate (14)

Olefin **13** (4.60 g, 21.5 mmol) in CH_2Cl_2 (30 mL) was treated at –78 °C with ozone for 20 min, then warmed to 0°C and diluted with MeOH (30 mL). Solid $NaBH_4$ (3.25 g, 85.9 mmol) was added in small portions and the mixture was stirred for 2 h at 0° C, quenched with 2 N HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, evaporated and purified by chromatography (silicagel, AcOEt) to give **14** (4.6 g, 85% over 2 steps) as a colorless oil.

IR: 3339, 2944, 2874, 1720, 1699, 1278, 1177, 1115, 1071, 1050, 1025 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.70–2.07 (*m*, 3 H, H-C(2), H-C(6)), 2.38–2.59 (*m*, 2 H, H-C(2), H-C(3)), 2.83–2.99 (*m*, 1 H, H-C(7)), 3.52–3.67 (*m*, 2 H, H-C(4)), 3.73–4.00 (*m*, 4 H, H-C(5), OH), 5.25–5.37 (*m*, 1 H, H-C(1)), 7.38–7.48 (*m*, 2 H, Ph), 7.51–7.60 (*m*, 1 H, Ph), 7.99–8.06 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.4, 30.9, 34.4, 40.6, 62.8, 62.9, 69.4, 128.8, 129.9, 130.5, 133.5, 166.5.

ESI-MS: 273.0 *m*/*z* calcd for $C_{14}H_{18}O_4Na$+ (*M*Na^+), 273.1103, found 273.1105.

(1*SR*,2*RS*,3*RS*)-2-(2-Hydroxyethyl)-3-trityloxymethyl-cyclobutyl-benzoate (15) and (1*SR*,2*RS*,3*RS*)-3-Hydroxymethyl-2-(2-trityloxyethyl)-cyclobutyl-benzoate (16)

Tritylchloride (4.66 g, 16.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with NEt_3 (5.1 mL, 36.8 mmol) and 4-dimethylamino-pyridine (22 mg, 0.18 mmol). Diol **14** (4.60 g, 18.4 mmol.) in CH_2Cl_2 (60 mL) was added dropwise and the mixture was stirred for 18 h at 25 °C. the mixture was quenched with aqueous NH_4Cl, extracted with Et_2O the organic layer was washed with brine, dried over $MgSO_4$ concentrated and purified by chromatography (silicagel, hexane/AcOEt 5:1, then 1:1) to give **15** ((1.63 g, 35%) and **16** (600 mg, 9%) as colorless oils.

15: IR: 1716, 1490, 1449, 1314, 1275, 1176, 1112,, 1070, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (*t*, *J* = 5.1 Hz, 1 H, OH), 1.77–2.01 (*m*, 3 H, H-C(2), H-C(6)), 2.23–2.34 (*m*, 1 H, H-C(3)), 2.43–2.52 (*m*, 1 H, H-C(2)), 2.78–2.86 (*m*, 1 H, H-C(7)), 3.02 (*dd*, *J* = 15.0, 7.7 Hz, 1 H, H-C(5)), 3.13 (*dd*, *J* = 15.0, 7.7 Hz, 1 H, H-C(5)), 3.52–3.60 (*m*, 1 H, H-C(4)), 3.63–3.71 (*m*, 1 H, H-C(4)), 5.17 (*q*, *J* = 7.0 Hz, 1 H, H-C(1)), 7.07–7.19 (*m*, 9 H, $C(Ph)_3$), 7.29–7.35 (*m*, 8 H, Ph, $C(Ph)_3$), 7.47 (*t*, *J* = 8.1, 1 H, Ph), 7.85 (*d*, *J* = 8.1 Hz, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 31.5, 34.0, 39.2, 63.2, 63.7, 69.1, 87.1, 127.4, 128.1, 128.8, 129.0, 130.0, 130.6, 133.3, 144.6, 166.3.

ESI-HRMS: *m*/*z* calcd for $C_{33}H_{32}O_4Na^+$ (*M*Na^+) 515.2198 , found 515.2196.

16. IR: 3456, 3060, 2938, 1717, 1699, 1601, 1490, 1451, 1314, 1276, 1113, 1069, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (*t*, *J* = 5.7 Hz, 1 H, OH), 1.60–1.81 (*m*, 2 H, H-C(6)), 1.85–2.00 (*m*, 1 H, H-C(2)), 2.57–2.71 (*m*, 2 H, H-C(2), H-C(3)), 2.91–3.03 (*m*, 1 H, H-C(7)), 3.21 (*dd*, *J* = 9.4, 7.8 Hz, 1 H, H-C(4)), 3.32 (*dd*, *J* = 9.4, 5.3, 1 H, H-C(4)), 4.83–4.64 (*m*, 2 H, H-C(5)), 5.29–5.40 (*m*, 1 H, H-C(1)), 7.20–7.38 (*m*, 9 H, $C(Ph)_3$), 7.39–7.51 (*m*, 8 H, Ph, $C(Ph)_3$), 7.53–7.63 (*m*, 1 H, Ph), 7.90–7.96 (*m*, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 31.7, 32.3, 39.2, 62.3, 64.3, 69.8, 87.2, 127.4, 128.2, 128.8, 129.0, 129.9, 130.5, 133.4, 144.4, 166.3.

ESI-HRMS: *m*/*z* calcd for $C_{33}H_{32}O_4Na$+ 515.2198 (*M*Na^+), found 515.2189.

(1*SR*,2*RS*,3*RS*)-3-Formyl-2-(2-trityloxyethyl)-cyclobutyl-benzoate (17)

Alcohol **15** (1.63 g, 3.31 mmol.) was treated with $NaHCO_3$ (1.3 g, 14.9 mmol) and *Dess-Martin*-periodinane (2.1 g, 4.96 mmol) in CH_2Cl_2 (30 mL) for 2 h. The mixture was quenched with aqueous dithionite and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and purified by chromatography (silicagel, hexane/AcOEt 10:1) to give aldehyde **17** (1.41 g, 87%) as a colorless oil.

IR: 3060, 3032, 2937, 2870, 2723, 1716, 1601, 1490, 1449, 1386, 1314, 1274, 1224, 1177, 1153, 1115, 1070, 1026, 1002 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.86–2.08 (*m*, 2 H, H-C(6)), 2.43–2.55 (*m*, 1 H, H-C(2)), 2.65–2.78 (*m*, 1 H, H-C(2)), 3.03–3.16 (*m*, 3 H, H-C(3), H-C(5)), 3.35–3.53 (*m*, 1 H, H-C(7)), 5.29–5.43 (*m*, 1 H, H-C(1)), 7.18–7.36 (*m*, 9 H, $C(Ph)_3$), 7.38–7.47 (*m*, 8 H, Ph, $C(Ph)_3$), 7.55–7.61 (*m*, 1 H, Ph), 7.95–7.97 (*m*, 2 H, Ph), 9.71 (*d*, *J* = 1.9 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 27.9, 42.0, 43.0, 62.5, 68.3, 87.1, 127.4, 128.2, 128.8, 129.0, 130.0, 130.3, 133.5, 144.5, 166.2, 202.0.

ESI-HRMS: *m*/*z* calcd for $C_{33}H_{30}O_4Na^+$ (*M*Na^+) 513.2042, found 513.2053.

(1*SR*,2*RS*,3*SR*)-3-Formyl-2-(2-trityloxyethyl)-cyclobutyl-benzoate (5)

Aldehyde **17** (290 mg, 0.59 mmol) in CH_2Cl_2 (2 mL) was treated with a 0.1 M soln of K_2CO_3 in MeOH (10 mL) according to general procedure B. The residue was purified by column chromatography on silicagel (hexane/AcOEt 7:1) to furnish **5** as a colorless oil (252 mg, 87%).

IR: 3059, 2946, 1709, 1595, 1489, 1451, 1307, 1277, 1178, 1155, 1110, 1072, 1027 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.84–2.19 (m, 2 H), 2.24–2.37 (m, 1 H), 2.63–2.81 (m, 1 H), 2.98–3.16 (m, 3 H), 3.17–3.24 (m, 1 H), 5.27–5.39 (m, 1 H), 7.20–7.33 (m, 9 H), 7.41–7.48 (m, 8 H), 7.50–7.60 (m, 1 H), 8.01–8.09 (m, 2 H), 9.64 (d, *J* = 1.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 27.6, 29.0, 39.3, 47.2, 61.3, 69.3, 86.7, 127.0, 127.8, 128.4, 128.6, 129.6, 129.9, 133.1, 144.0, 165.8, 201.4.

HRMS (ESI): *m*/*z* calcd for $C_{33}H_{30}O_4Na^+$ (*M*Na^+): 513.2042, found: 513.2053.

(1*SR*,2*RS*,3*SR*)-3-(2-Ethoxycarbonyl-4-oxopentanoyl)-2-(2-trityloxyethyl)-cyclobutylbenzoate (18)

$SnCl_2$ (62 mg), methyl diazoacetate (206 μL, 1.96 mmol) and aldehyde **5** (800 mg, 1.64 mmol) in CH_2Cl_2 (6 mL) were converted into the β-ketoester (690 mg, 73%) as described for the preparation of **7**. The crude ester was transformed into diketone **18** as described for the preparation of **8**. Purification of the crude product by chromatography (silicagel, hexane/EtOAc 10:1, then 5:1) furnished **18** (138 mg, 46%) as a colorless oil.

IR: 3059, 2984, 2946, 2870, 1740, 1717, 1599*w*, 1489, 1448, 1398, 1364, 1311, 1269, 1228, 1178, 1155, 1114, 1068, 1023 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.18–1.33 (*m*, 3 H, CH_2CH_3), 1.84–2.10 (*m*, 1 H, H-C(6)), 2.10–2.54 (*m*, 2 H, H-C(2), H-C(6)), 2.18 (*s*, 3 H, H-C(11)), 2.66–2.80 (*m*, 1 H, H-C(2)), 2.85–3.29 (*m*, 5 H, H-C(3), H-C(5), H-C(7), H-C(9)), 3.38–3.57 (*m*, 1 H, H-C(9)), 3.88–4.03 (*m*, 1 H, H-C(8)), 4.05–4.42 (*m*, 2 H, CH_2CH_3), 5.27–5.38 (*m*, 1 H, H-C(1)), 7.14–7.32 (*m*, 9 H, $C(Ph)_3$), 7.36–7.52 (*m*, 8 H, Ph, $C(Ph)_3$), 7.56–7.66 (*m*, 1 H, Ph), 7.99–8.09 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.4, 29.8, 30.0, 31.0, 31.6, 40.8, 42.0, 47.6, 52.7, 62.1, 69.5, 87.1, 127.3, 128.1, 128.8, 129.0, 130.0, 130.6, 133.4, 144.6, 166.2, 168.9, 205.0, 205.5.

2-[(1*SR*,2*RS*,3*SR*)-3-Benzoyloxy-2-(2-hydroxyethyl)-cyclobutyl]-5-methylfuran-3-carboxylic acid ethyl ester (19)

Diketone **18** (63 mg, 0.1 mmol), MeOH (1 mL), CH_2Cl_2 (0.5 mL) and concd HCl (30 μL) were reacted according to the general procedure. The residue was purified by column chromatography on silicagel (hexane/AcOEt 3:1) to afford **19** as pale yellow oil (27 mg, 90%).

IR: 3515, 2946, 1717, 1580, 1451, 1375, 1315, 1277, 1209, 1110, 1057 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 1.83 (br s, 1 H), 1.88–2.02 (m, 2 H), 2.29 (s, 3 H), 2.51–2.62 (m, 1 H), 2.74–2.85 (m, 1 H), 3.02–3.12 (m, 1 H), 3.66 (t, *J* = 6.4 Hz, 2 H), 4.16–4.23 (m, 1 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 5.55–5.61 (m, 1 H), 6.23 (s, 1 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.58 (t, *J* = 7.7 Hz, 1 H), 8.08 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7, 14.7, 32.3, 32.6, 34.8, 43.8, 60.6, 61.1, 70.8, 106.9, 122.8, 128.8, 130.0, 130.6, 133.5, 150.9, 161.4, 164.7, 166.7.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{24}O_6$: 372.1573, found: 372.1584.

(*S*)-2-Trityloxymethyloxiran ((–)-20)[9]

TrCl (2.46 g, 8.8 mmol) in CH_2Cl_2 (8 mL) was treated under Ar at 0 °C with NEt_3 (2.2 mL, 16.0 mmol) and (*R*)-glycidol **(+)-21** (540 μL, 8.0 mmol) in CH_2Cl_2 (4 mL). 4-dimethylamino-pyridine (10 mg, 0.08 mmol) was added and the mixture was stirred for 24 h at 25 °C. The mixture was quenched with NH_4Cl and extracted with ether. The organic Phase was washed with brine, dried over $MgSO_4$ and concentrated to give white crystals which were recrystallized from MeOH. Yield 2.5 g (quant.), mp. 94–96 °C (MeOH) (ref[9]: 100 °C). $[\alpha]_D^{25}$ = –9.7 (c = 1.0, $CHCl_3$) ref[9]: $[\alpha]_D^{25}$ = –10.5 (c = 1, $CHCl_3$)).

IR: 3023, 2925, 2874, 1595, 1490, 1448, 1158, 1071, 1032, 1002 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.68 (*dd*, *J* = 4.9, 2.2 Hz, 1 H, H-C(3)), 2.82 (*dd*, *J* = 4.9, 3.9 Hz, 1 H, H-C(3)), 3.17–3.28 (*m*, 2 H, H-C(1)), 3.38–3.48 (*m*, 1 H,

H-C(2)), 7.26–7.45 (*m*, 9 H, C(Ph) $_3$), 7.51–7.62 (*m*, 6 H, $C(Ph)_3$).

(*S*)-4-Methyl-1-trityloxypent-4-en-2-ol ((–)-21)[9]

CuI (121 mg, 0.63 mmol) under Ar in THF (2 mL) was treated dropwise at –78 °C with isopropenylmagnesiumbromide (0.5 M in THF, 13.3 mL, 6.64 mmol). After 30 min **(-)-20** (1.0 g, 3.16 mmol) in THF (1 mL) was added and the mixture was stirred for 2 h at –40 °C, quenched with NH_4Cl and stirred for 30 min at 25 °C. Workup with water and ether furnished after chromatography (silicagel, hexane/AcOEt 5:1) **(-)-21** (1.14 g, quant.).as a colorless oil with $[\alpha]_D^{25}$ = –3.8 ° (c = 0.6, $CHCl_3$). Ref[9]: $[\alpha]_D^{25}$ = –3.0 (c = 1.15, $CHCl_3$)).

IR: 3058, 3020, 2926, 2875, 1595, 1489, 1449, 1220, 1103, 1071 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.74 (*s*, 3 H, H-C(5)), 2.19 (*d*, *J* = 6.7 Hz, 2 H, H-C(3)), 2.25 (*d*, *J* = 3.3 Hz, 1 H, OH), 3.11–3.24 (*m*, 2 H, H-C(1)), 3.87–4.00 (*m*, 1 H, H-C(2)), 4.75 (*s*, 1 H, H-C(6)), 4.82 (*s*, 1 H, H-C(6)), 7.23–7.38 (*m*, 9 H, C(Ph) $_3$), 7.44–7.50 (*m*, 6 H, $C(Ph)_3$).

(*S*)-2-(4-Methoxybenzyloxy)-4-methylpent-4-en-1-ol ((+)-23)

NaH, (60% suspension in mineral oil, 633 mg, 15.8 mmol) in THF (15 mL) was treated dropwise at 0 °C with **(–)-21** (3.78 g, 10.6 mmol) in THF (5 mL). The mixture was stirred at 25 °C for 1 h, then p-methoxybenzyl chloride (2.14 mL, 15.8 mmol) and tetrabutylammonium bromide (68 mg, 0.21 mmol) were added and the mixture was stirred for 24 h at 60°C. Usual workup with NH_4Cl, water and ether furnished **22** after chromatography (silicagel, hexane/AcOEt 20:1), which was detritylated in MeOH (20 mL) with $TsOH•H_2O$ (200 mg, 1.1 mmol) for 30 min at 25°C. Usual workup and chromatography (silicagel, hexane/AcOEt 5:1, then AcOEt) gave alcohol **23** (1.77 g (71%, 2 steps) as a colorless oil. $[\alpha]_D^{25}$ = +14.7 (c = 0.3, $CHCl_3$).

IR: 3401, 2929, 1738, 1713, 1613, 1514, 1455, 1301, 1249, 1173, 1103, 1035 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79 (*s*, 3 H, H-C(5)), 1.94 (*dd*, *J* = 6.9, 5.6 Hz, 1 H, OH), 2.22 (*dd*, *J* = 14.1, 7.2 Hz, 1 H, H-C(3)), 2.42 (*dd*, *J* = 14.1, 5.6, 1 H, H-C(3)), 3.47–3.59 (*m*, 1 H, H-C(2)), 3.64–3.76 (*m*, 2 H, H-C(1)), 3.84 (*s*, 3 H, OCH_3), 4.50, 4.64 (*AB*, *J* = 11.2 Hz, 2 H, $CH_2C_6H_4OCH_3$), 4.81 (*s*, 1 H, H-C(6)), 4.85 (*s*, 1 H, H-C(6)), 6.91, 7.30 (*AA'BB'*, *J* = 8.5 Hz, 4 H, $C_6H_4OCH_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.2, 39.9, 55.7, 64.7, 71.6, 78.1, 113.6, 114.3, 129.8.

EI-HRMS: *m*/*z* calcd for *M*+, $C_{14}H_{20}O_3$+, 236.1412, found 236.1417.

(*S*)-2-(4-Methoxybenzyloxy)-4-methylpent-4-enal ((–)-24)

Oxalylchloride (100 μL, 1.18 mmol) under Ar in CH_2Cl_2 (3 mL) was treated at –78 °C with dimethylsulfoxide (167 μL, 2.36 mmol) After 15 min **(+)-23** (254 mg, 1.07 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred for1 h at –78 °C. NEt_3 (748 μL, 5.37 mmol) was added and the mixture was warmed to 0 °C and stirred for 2 h. Usual workup with water and ether furnished after chromatography (silicagel, hexane/AcOEt 5:1) aldehyde **(-)-24** (220 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ = –44.9 (c = 2.0, $CHCl_3$).

IR: 3078, 2936, 2839, 1733, 1700, 1652, 1613, 1514, 1464, 1456, 1375, 1303, 1250, 1174, 1103, 1035 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.76 (*s*, 3 H, H-C(5)), 2.43 (*d*, *J* = 6.6 Hz, 2 H, H-C(3)), 3.84 (*s*, 3 H, OCH_3), 3.92 (*dt*, *J* = 6.6 Hz, 2.2, 1 H, H-C(2)), 4.55, 4.63 (*AB*, *J* = 11.3 Hz, 2 H, $CH_2C_6H_4OCH_3$), 4.83 (*s*, 1 H, H-C(6)), 4.89 (*s*, 1 H, H-C(6)), 6.91, 7.30 (*AA'BB'*, *J* = 8.5 Hz, 4 H, $C_6H_4OCH_3$), 9.65 (*d*, *J* = 2.2 Hz, 1 H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.1, 38.8, 55.6, 72.6, 82.0, 114.2, 114.3, 129.7, 129.9, 140.8, 160.0, 203.6.

EI-HRMS: *m*/*z* calcd for *M*+, $C_{14}H_{18}O_3$+ 234.1261, found 234.1261.

(1*SR*,2*RS*,3*RS*)-2-(2-Oxoethyl)-3-trityloxymethylcyclobutylbenzoate (**25**)

Alcohol **16** (600 mg, 1.22 mmol), $NaHCO_3$ (460 g, 5.48 mmol) and *Dess-Martin*-periodinane (776 mg, 1.83 mmol) in CH_2Cl_2 (10 mL) were stirred at 25°C for 2 h. Usual workup and chromatography (silicagel, hexane/AcOEt 10:1) furnished aldehyde **25** (570 mg, 95%) as a colorless oil.

IR: 3060, 2935, 1721, 1601, 1490, 1450, 1314, 1275, 1154, 1112, 1069, 1026 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.88–2.05 (*m*, 1 H, H-C(2)), 2.59 (*d*, *J* = 9.1 Hz, 2 H, H-C(6)), 2.64–2.78 (*m*, 2 H, H-C(2), H-C(3)), 3.02–3.17 (*m*, 1 H, H-C(4)), 3.22–3.33 (*m*, 1 H, H-C(4)), 3.37–3.57 (*m*, 1 H, H-C(7)), 5.33–5.46 (*m*, 1 H, H-C(1)), 7.21–7.37 (*m*, 9 H, $C(Ph)_3$), 7.40–7.49 (*m*, 8 H, Ph, $C(Ph)_3$), 7.54–7.63 (*m*, 1 H, Ph), 7.86–7.93 (*m*, 2 H, Ph), 9.69 (*t*, *J* = 1.4 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 31.6, 36.7, 39.2, 64.0, 68.6, 87.2, 127.5, 128.2, 128.8, 129.0, 129.9, 130.5, 133.5, 144.3, 166.1, 201.8.

ESI-HRMS: *m*/*z* calcd for *M*+ $C_{33}H_{30}O_4Na^+$ 513.2042, found 513.2028.

(1*SR*,2*RS*,3*RS*)-2-[3-(Dimethoxyphosphoryl)-2-hydroxypropyl]-3-trityloxymethylcyclobutylbenzoate (**26**)

Dimethylmethanephosphonate (138 µl, 1.16 mmol) in THF (7 mL) was treated dropwise at –78 °C under Ar with *n*-BuLi (2.5 M in hexane, 464 µl, 1.16 mmol). After 30 min aldehyde **(-)-24** (570 mg, 1.16 mmol) in THF (3 mL) was added and the mixture was stirred for 4 h at –78 °C. Workup with $NaHCO_3$, water and ether furnished after chromatography (silicagel, hexane/AcOEt 5:1, then AcOEt) **26** (380 mg, 84%, based on recovered starting material) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. Rf 0.21 (hexane/AcOEt 5:1).

IR: 3392, 3058, 3033, 2953, 2874, 1716, 1601, 1490, 1450, 1449, 1360, 1314, 1275, 1223, 1178, 1154, 1113*s*, 1064, 1032 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.57–1.97 (*m*, 3 H, H-C(2), H-C(6)), 2.59–2.75 (*m*, 2 H, H-C(2), H-C(3)), 3.02–3.42 (*m*, 4 H, H-C(4), H-C(5), H-C(7)), 3.57–3.85 (*m*, 8 H, H-C(8), 2 × OCH_3), 3.86–4.09 (br. *s*, 1 H, OH), 5.30–5.42 (*m*, 1 H, H-C(1)), 7.20–7.36 (*m*, 9 H, C(Ph) $_3$), 7.39–7.49 (*m*, 8 H, Ph, C(Ph) $_3$), 7.50–7.65 (*m*, 1 H, Ph), 7.86–8.06 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.8, 32.7, 34.2, 38.5, 39.0, 52.6, 52.7, 64.4, 65.5, 70.2, 87.1, 127.4, 128.2, 128.8, 129.1, 129.9, 130.6, 133.3, 144.4, 166.2.

ESI-HRMS: *m*/*z* calcd for $C_{36}H_{39}O_7PNa^+$ 637.2331, (*M*Na^+), found 637.2344.

(1*SR*,2*RS*,3*RS*)-2-[3-(Dimethoxyphosphoryl)-2-oxopropyl]-3-trityloxymethylcyclobutylbenzoate (**27**)

Alcohol **26** (472 mg, 0.77 mmol), $NaHCO_3$ (291 mg, 3.47 mmol) and *Dess-Martin*-periodinane (489 mg, 1.15 mmol) in CH_2Cl_2 (20 mL) were stirred for 2 h at 25°C. Workup as before including chromatography (silicagel, AcOEt) furnished ketophosphonate **27** (370 mg, 78%) as a colorless oil.

IR: 3058, 2953, 1716, 1600, 1490, 1449, 1399, 1314, 1274, 1179, 1112, 1028 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.83–1.96 (*m*, 1 H, H-C(2)), 2.59–2.77 (*m*, 2 H, H-C(2), H-C(3)), 2.87 (*s*, 1 H, H-C(8)), 2.96 (*s*, 1 H, H-C(8)), 3.13 (*dd*, *J* = 9.6, 8.4 Hz, 1 H, H-C(4)), 3.26 (*dd*, *J* = 9.6, 5.4 Hz, 1 H, H-C(4)), 3.34–3.46 (*m*, 1 H, H-C(7)), 5.32–5.42 (*m*, 1 H, H-C(1)), 7.21–7.37 (*m*, 9 H, $C(Ph)_3$), 7.39–7.48 (*m*, 8 H, Ph, $C(Ph)_3$), 7.53–7.62 (*m*, 1 H, Ph), 7.83–7.89 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.3, 31.9, 37.2, 39.7, 42.5, 64.3, 69.4, 88.0, 127.4, 128.2, 128.8, 129.0, 129.9, 130.5, 133.4, 144.4, 166.1, 201.9.

ESI-HRMS: *m*/*z* calcd for $C_{36}H_{37}O_7PNa^+$ (*M*Na^+) 635.2175, found 635.2182.

(1*SR*,2*RS*,3*RS*)-2-[(*E*)-(5*S*)-5-(4-Methoxybenzyloxy)-7-methyl-2-oxoocta-3,7-dienyl]-3-trityloxymethylcyclobutylbenzoate (**28**)

NaH, (60% suspension in mineral oil, 26 mg, 0.66 mmol) in THF (6 mL) was treated dropwise at -10 °C with **27** (370 mg, 0.60 mmol) in THF (2 mL). After 10 min aldehyde **25** (155 mg, 0.66 mmol) in THF (2 mL) was added and the mixture was stirred for 2 h at 25 °C. Usual workup with water and ether including chromatography (silicagel, hexane/AcOEt 5:1) furnished **28** (400 mg, 92%, colorless oil) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. R_f 0.38 (hexane/AcOEt 5:1).

IR: 2934, 1718, 1684, 1654, 1560, 1512, 1448, 1274, 1148, 1068 cm^{-1}.

Major diastereomer:

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (*s*, 3 H, H-C(13)), 1.84–1.93 (*m*, 1 H, H-C(2)), 2.05–2.13 (*m*, 1 H, H-C(11)), 2.25–2.34 (*m*, 1 H, H-C(11)), 2.60–2.76 (*m*, 3 H, H-C(2), H-C(3), H-C(6)), 2.77–2.87 (*m*, 1 H, H-C(6)), 3.09 (*t*, *J* = 8.9 Hz, 1 H, H-C(4)), 3.26 (*dd*, *J* = 9.4, 5.0 Hz, 1 H, H-C(4)), 3.42–3.52 (*m*, 1 H, H-C(7)), 3.80 (*s*, 3 H, OCH_3), 3.95–4.01 (*m*, 1 H, H-C(10)), 4.20, 4.39 (*AB*, *J* = 11.6 Hz, 2 H, CH_2 $C_6H_4OCH_3$), 4.65 (*s*, 1 H, H-C(14)), 4.75 (*s*, 1 H, H-C(14)), 5.34–5.40 (*m*, 1 H, H-C(1)), 6.13 (*ddd*, *J* = 16.0, 4.5, 1.1 Hz, 1 H, H-C(8)), 6.51 (*dt*, *J* = 16.0, 6.0, 1 H, H-C(9)), 6.81–6.86 (*m*, 2 H, $C_6H_4OCH_3$), 7.13–7.18 (*m*, 2 H, $C_6H_4OCH_3$), 7.19–7.25 (*m*, 9 H, $C(Ph)_3$), 7.33–7.39 (*m*, 2 H, Ph), 7.41–7.45 (*m*, 6 H, $C(Ph)_3$), 7.48–7.53 (*m*, 1 H, Ph), 7.78–7.83 (*m*, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 31.5, 31.6, 35.8, 37.2, 43.8, 55.7, 64.2, 69.3, 71.1, 76.9, 86.9, 113.8, 114.2, 127.4, 128.2, 128.7, 129.0, 129.7, 129.9, 130.3, 130.4, 130.6, 133.2, 141.6, 144.4, 145.8, 159.6, 166.1, 198.8.

ESI-HRMS: *m*/*z* calcd for $C_{38}H_{48}O_6Na^+$ (*M*Na^+) 743.3349, found 743.3343.

(1*SR*,2*RS*,3*RS*)-2-[(*E*)-(5*S*)-2-Hydroxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-trityloxymethylcyclobutylbenzoate (**29**)

Ketone **28** (91 mg, 0.13 mmol.) and $CeCl_3 \cdot H_2O$ (48 mg, 0.13 mmol) were stirred for 30 min in MeOH (4 mL) at –78 °C. $NaBH_4$ (6 mg, 0.14 mmol) was added and the mixture was stirred for 3 h at –78 °C. Usual workup with NH_4Cl, water and ether gave after chromatography (silicagel, hexane/AcOEt 1:1) **29** (73 mg, 78%, colorless oil) as an inseparable diastereomeric

mixture. The NMR data are provided for the major diastereomer. R_f 0.38 (hexane/AcOEt 1:1).

IR: 3468, 3061, 2934, 2862, 1717, 1612, 1514, 1490, 1450, 1368, 1314, 1276, 1249, 1174, 1111, 1069, 1033 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.58–1.76 (*m*, 2 H, H-C(6), OH), 1.70 (*s*, 3 H, H-C(13)), 1.76–1.96 (*m*, 2 H, H-C(2), H-C(6)), 2.11–2.24 (*m*, 1 H, H-C(11)), 2.29–2.45 (*m*, 1 H, H-C(11)), 2.59–2.78 (*m*, 2 H, H-C(2), H-C(3)), 2.98–3.14 (*m*, 1 H, H-C(4)), 3.17–3.30 (*m*, 1 H, H-C(4)), 3.31–3.41 (*m*, 1 H, H-C(7)), 3.82 (*s*, 3 H, OCH_3), 3.84–3.95 (*m*, 1 H, H-C(10)), 4.06–4.21 (*m*, 1 H, H-C(5)), 4.31, 4.50 (*AB*, *J* = 11.4 Hz, 2 H, C*H*$_2$ $C_6H_4OCH_3$), 4.73 (*s*, 1 H, H-C(14)), 4.78 (*s*, 1 H, H-C(14)), 5.29–5.65 (*m*, 3 H, H-C(1), H-C(8), H-C(9)), 6.83–6.93 (*m*, 2 H, $C_6H_4OCH_3$), 7.17–7.38 (*m*, 11 H, $C_6H_4OCH_3$, $C(Ph)_3$), 7.39–7.53 (*m*, 8 H, Ph, $C(Ph)_3$), 7.54–7.64 (*m*, 1 H, Ph), 7.87–7.97 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.3, 31.8, 32.0, 32.8, 38.5, 44.6, 55.7, 64.6, 70.2, 70.4, 71.3, 78.0, 87.2, 113.1, 114.1, 127.4, 128.2, 128.8, 129.0, 129.7, 129.9, 130.6, 131.2, 131.8, 133.4, 136.1, 142.5, 144.4, 159.5, 166.3.

ESI-HRMS: *m*/*z* calcd for $C_{48}H_{50}O_6Na^+$ (*M*Na^+) 745.3505, found 745.3489.

(1*SR*,2*RS*,3*RS*)-2-[(*E*)-(5*S*)-2-Acetoxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-trityloxymethylcyclobutylbenzoate (**30**)

Alcohol **29** (82 mg, 0.11 mmol.) in CH_2Cl_2 (5 mL) was treated with Ac_2O (32 µl, 0.34 mmol), NEt_3 (63 µl, 0.45 mmol) and 4-dimethylamino-pyridine (3 mg, 0.02 mmol) for 2 h at 25 °C. Usual workup and chromatography (silicagel, hexane/AcOEt 5:1) gave **30** (84 mg, 97%, colorless oil) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. R_f 0.32 (hexane/AcOEt 5:1).

IR: 3061, 2934, 1737, 1717, 1612, 1514, 1490, 1450, 1370, 1314, 1274, 1247, 1174, 1155, 1111, 1069, 1027 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.66–1.96 (*m*, 3 H, H-C(2), H-C(6)), 1.69 (*s*, 3 H, H-C(13)), 2.02 (*s*, 3 H, CH_3CO), 2.07–2.21 (*m*, 1 H, H-C(11)), 2.28–2.43 (*m*, 1 H, H-C(11)), 2.57–2.77 (*m*, 2 H, H-C(2), H-C(3)), 2.84–3.00 (*m*, 1 H, H-C(4)), 3.17–3.39 (*m*, 2 H, H-C(4), H-C(7)), 3.78–3.92 (*m*, 1 H, H-C(10)), 3.83 (*s*, 3 H, OCH_3), 4.24, 4.46 (*AB*, *J* = 11.6 Hz, 2 H, C*H*$_2$$C_6H_4OCH_3$), 4.71 (*s*, 1 H, H-C(14)), 4.77 (*s*, 1 H, H-C(14)), 5.25–5.58 (*m*, 4 H, H-C(1), H-C(5), H-C(8), H-C(9)), 6.83–6.91 (*m*, 2 H, $C_6H_4OCH_3$), 7.18–7.38 (*m*, 11 H, $C_6H_4OCH_3$, $C(Ph)_3$), 7.40–7.54 (*m*, 8 H, Ph, $C(Ph)_3$), 7.55–7.64 (*m*, 1 H, Ph), 7.90–7.99 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 29.5, 31.7, 32.9, 38.4, 44.4, 55.7, 64.5, 70.2, 70.3, 73.4, 77.7, 87.1, 113.2, 114.1, 127.4, 128.2, 128.8, 129.1, 129.7, 130.0, 130.6, 131.0, 131.5, 133.3, 134.0, 142.4, 144.5, 159.5, 166.3, 170.6.

ESI-HRMS: *m*/*z* calcd for $C_{50}H_{52}O_7Na^+$ (*M*Na^+) 787.3611, found 787.3626.

(1*SR*,2*RS*,3*RS*)-2-[(*E*)-(5*S*)-2-Acetoxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-hydroxymethylcyclobutylbenzoate (**31**)

Trityl ether **30** (72 mg, 0.094 mmol) in MeOH (2 mL) was detritylated with *p*-TsOH (4 mg, 0.019 mmol) for 2 h at 25 °C. Workup as described for **22** gave after chromatography (silicagel, hexane/AcOEt 1:2) **31** (40 mg, 81%, colorless oil) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. R_f 0.45 (hexane/AcOEt 1:2).

IR: 3467, 2935, 2870, 1718, 1612, 1513, 1452, 1371*m*, 1275, 1248, 1175, 1111, 1071, 1027 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.70 (*s*, 3 H, H-C(13)), 1.86–2.03 (*m*, 3 H, H-C(2), H-C(6)), 2.02 (*s*, 3 H, CH_3CO), 2.11–2.27 (*m*, 1 H, H-C(11)), 2.33–2.68 (*m*, 3 H, H-C(2), H-C(3), H-C(11)), 2.81–2.96 (*m*, 1 H, H-C(7)), 3.70–3.99 (*m*, 3 H, H-C(4), H-C(10)), 3.82 (*s*, 3 H, OCH_3), 4.31, 4.49 (*AB*, *J* = 11.4 Hz, 2 H, C*H*$_2$$C_6H_4OCH_3$), 4.72 (*s*, 1 H, H-C(14)), 4.78 (*s*, 1 H, H-C(14)), 5.28–5.40 (*m*, 1 H, H-C(1)), 5.41–5.53 (*m*, 1 H, H-C(5)), 5.59–5.68 (*m*, 2 H, H-C(8), H-C(9)), 6.83–6.92 (*m*, 2 H, $C_6H_4OCH_3$), 7.20–7.31 (*m*, 2 H, $C_6H_4OCH_3$), 7.42–7.52 (*m*, 2 H, Ph), 7.55–7.65 (*m*, 1 H, Ph), 8.02–8.13 (*m*, 2 H, Ph).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 29.7, 31.3, 34.3, 38.4, 44.4, 55.7, 63.5, 69.0, 70.4, 73.2, 77.7, 113.3, 114.2, 126.9, 128.8, 129.7, 130.0, 130.5, 131.2, 133.5, 134.0, 142.4, 159.5, 170.9.

ESI-HRMS: *m*/*z* calcd for $C_{31}H_{38}O_7Na^+$ (*M*Na^+) 545.2515, found 545.2498.

(1*SR*,2*RS*,3*RS*)-2-[(*E*)-(5*S*)-2-Acetoxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-formylcyclobutylbenzoate (**32**)

Alcohol **31** (14 mg, 0.027 mmol) was oxidized with $NaHCO_3$ (10 mg, 0.122 mmol) and *Dess-Martin*-periodinane (17 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) as described before to give after chromatography (silicagel, hexane/AcOEt 2:1) aldehyde **32** (12 mg, 85%) as a colorless oil.

IR: 2930, 2855, 1717, 1649, 1611, 1512, 1451, 1375, 1315, 1277, 1246, 1178, 1118, 1072, 1027 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.66 (*s*, 3 H, H-C(13)), 1.88–1.99 (*m*, 2 H, H-C(6)), 2.04 (*s*, 3 H, CH_3CO), 2.15 (*dd*, *J* = 13.9, 6.4 Hz, 1 H, H-C(11)), 2.36 (*dd*, *J* = 13.9, 7.3 Hz, 1 H, H-C(11)), 2.46–2.68 (*m*, 2 H, H-C(2)), 3.05–3.31 (*m*, 2 H, H-C(3), H-C(7)),

3.79 (*s*, 3 H, OCH_3), 3.82–3.93 (*m*, 1 H, H-C(10)), 4.27, 4.45 (*AB*, *J* = 11.5 Hz, 2 H, $CH_2C_6H_4OCH_3$), 4.69 (*s*, 1 H, H-C(14)), 4.75 (*s*, 1 H, H-C(14)), 5.21–5.32 (*m*, 1 H, H-C(1)), 5.33–5.44 (*m*, 1 H, H-C(5)), 5.53–5.59 (*m*, 2 H, H-C(8), H-C(9)), 6.84, 7.20 (*AA'BB'*, *J* = 8.5 Hz, 4 H, $C_6H_4OCH_3$), 7.40–7.50 (*m*, 2 H, Ph), 7.53–7.63 (*m*, 1 H, Ph), 8.00–8.09 (*m*, 2 H, Ph), 9.99 (*s*, 1 H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.6, 23.3, 28.1, 30.1, 41.1, 43.3, 44.4, 55.7, 68.5, 70.4, 72.6, 77.7, 113.3, 114.2, 128.9, 129.7, 130.0, 130.5, 130.9, 133.7, 134.1, 142.3, 202.1.

ESI-MS: *m*/*z* calcd for $C_{31}H_{36}O_7Na^+$ (*M*Na$^+$) 543.2359, found 543.2361.

(1*SR*,2*RS*,3*SR*)-2-[(*E*)-(5*S*)-2-Acetoxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-formylcyclobutylbenzoate (**33**)

Following general procedure B, aldehyde **32** (160 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was stirred with K_2CO_3, 0.1 M in MeOH/H_2O 10:1, 5 mL) for 15 min at 25°C. Usual workup gave after chromatography (silicagel, hexane/AcOEt 5:1) aldehyde **33** (106 mg, 66%, colorless oil) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. R_f 0.33 (hexane/AcOEt 5:1).

IR: 2995, 2976, 2938, 1769, 1757, 1720, 1612, 1513, 1452, 1375, 1247, 1112, 1057 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67 (*s*, 3 H, H-C(13)), 1.91–2.08 (*m*, 2 H, H-C(6)), 2.04 (*s*, 3 H, CH_3CO), 2.09–2.22 (*m*, 1 H, H-C(11)), 2.30–2.42 (*m*, 2 H, H-C(2), H-C(11)), 2.65–2.81 (*m*, 1 H, H-C(2)), 2.97–3.26 (*m*, 2 H, H-C(3), H-C(7)), 3.79 (*s*, 3 H, OCH_3), 3.83–3.96 (*m*, 1 H, H-C(10)), 4.28, 4.47 (*AB*, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4OCH_3$), 4.69 (*s*, 1 H, H-C(14)), 4.75 (*s*, 1 H, H-C(14)), 5.24–5.44 (*m*, 2 H, H-C(1), H-C(5)), 5.57–5.62 (*m*, 2 H, H-C(8), H-C(9)), 6.85, 7.21 (*AA'BB'*, *J* = 8.5 Hz, 4 H, $C_6H_4OCH_3$), 7.42–7.51 (*m*, 2 H, Ph), 7.54–7.64 (*m*, 1 H, Ph), 8.01–8.09 (*m*, 2 H, Ph), 9.79 (*d*, *J* = 1.7 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.3, 28.4, 33.7, 37.8, 44.4, 47.7, 55.7, 69.6, 70.5, 71.9, 77.7, 113.4, 114.1, 128.9, 129.7, 130.0, 130.5, 130.6, 130.9, 133.8, 134.1, 142.3, 159.5, 166.3, 170.5, 203.0.

ESI-MS: *m*/*z* calcd for $C_{31}H_{36}O_7Na^+$ (*M*Na$^+$) 543.2359, found 543.2358.

(1*SR*,2*RS*,3*SR*)-2-[(*E*)-(5*S*)-2-Acetoxy-5-(4-methoxybenzyloxy)-7-methylocta-3,7-dienyl]-3-(2-ethoxycarbonylacetyl)cyclobutylbenzoate (**34**)

$SnCl_2$ (8 mg, 0.04 mmol), ethyl diazoacetate (25 µl, 0.24 mmol) and aldehyde **33** (106 mg, 0.20 mmol) in CH_2Cl_2 (8 mL) were treated as described for **5** to give after chromatography (silicagel, hexane/AcOEt 2:1) **34** (96 mg, 79%, colorless oil) as an inseparable diastereomeric mixture. The NMR data are provided for the major diastereomer. R_f 0.29 (hexane/AcOEt 2:1).

IR: 2976, 2938, 2862, 2839, 1740, 1717, 1650, 1611, 1512, 1451, 1368, 1315, 1277, 1239, 1178, 1110, 1072, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (*t*, *J* = 7.2 Hz, 3 H, CH2CH3), 1.67 (*s*, 3 H, H-C(13)), 1.80–1.96 (*m*, 1 H, H-C(6)), 2.04 (*s*, 3 H, CH_3CO), 2.06–2.20 (*m*, 2 H, H-C(6), H-C(11)), 2.31–2.46 (*m*, 2 H, H-C(2), H-C(11)), 2.58–2.69 (*m*, 1 H, H-C(2)), 2.91–3.14 (*m*, 1 H, H-C(7)), 3.30–3.42 (*m*, 1 H, H-C(3)), 3.43, 3.48 (*AB*, *J* = 15.4 Hz, 2 H, H-C(15)), 3.79 (*s*, 3 H, OCH_3), 3.85–3.92 (*m*, 1 H, H-C(10)), 4.20 (*q*, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.27, 4.47 (*AB*, *J* = 11.6 Hz, 2 H, $CH_2C_6H_4OCH_3$), 4.69 (*s*, 1 H, H-C(14)), 4.75 (*s*, 1 H, H-C(14)), 5.25–5.41 (*m*, 2 H, H-C(1), H-C(5)), 5.56–5.63 (*m*, 2 H, H-C(8), H-C(9)), 6.84, 7.21 (*AA'BB'*, *J* = 8.0 Hz, 4 H, $C_6H_4OCH_3$), 7.42–7.49 (*m*, 2 H, Ph), 7.55–7.62 (*m*, 1 H, Ph), 8.01–8.10 (*m*, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.2, 31.3, 33.7, 38.8, 44.3, 47.4, 48.4, 55.7, 61.9, 69.4, 70.4, 71.9, 77.7, 113.3, 114.1, 128.9, 129.7, 130.0, 130.3, 130.6, 130.9, 133.6, 134.5, 142.3, 159.5, 166.3, 167.4, 170.5, 203.0.

ESI-HRMS: *m/z* calcd for $C_{35}H_{42}O_9Na$+ (MNa+) 629.2727, found 629.2723.

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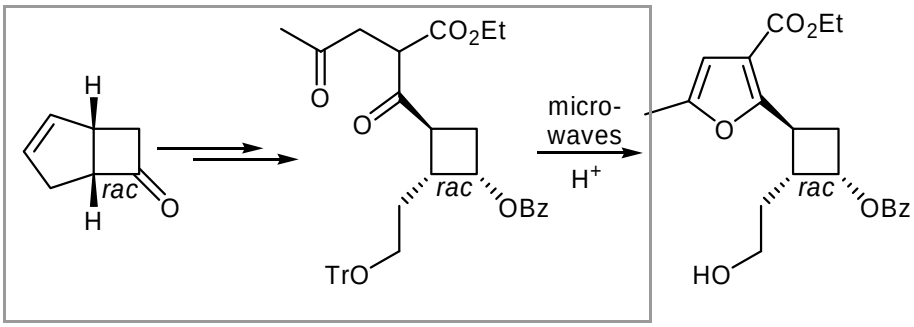


Short title: Synthesis of the furylcyclobutane moiety of providencin

Appendix 3

Synthetic efforts towards the complex Diterpene Providencin

Tanja Gaich, Harald Weinstabl and Johann Mulzer*

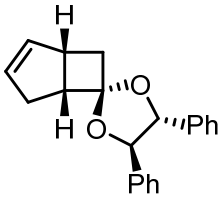
Supporting Information

1. **Procedures**

General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous CH_2Cl_2 (DCM) was distilled from CaH_2 under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofuran) was purchased (99.85%, water < 50 ppm). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel (0.04-0.063mm, 240-400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm; ^{13}C, δ =77.00 ppm). All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured at 20°C. High resolution mass spectra (HRMS) were performed with a resolution of 10000. Compound names were generated using AutoNom.

(1*S*,4'*R*,5*R*,5'*R*)-4',5'-diphenylspiro[bicyclo[3.2.0]hept[2]ene-6,2'-[1,3]dioxolane] **17**



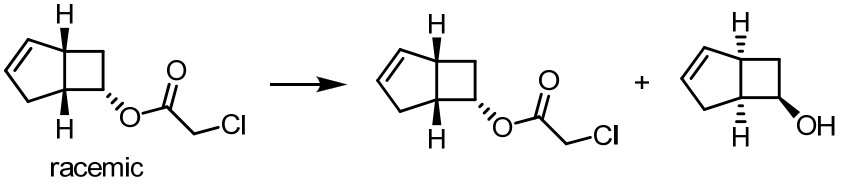
(R,R)-diphenyl ethandiol (2g, 9.3 mmol, 1eq), ketone **15** (1g, 9.3 mmol, 1eq) and p-toluolsulfonic acid (0.46 mmol, 88 mg, 5 mol%) were added to 90 mL benzene and heated at reflux with a Dean Stark trap for 50 minutes. The reaction was cooled to room temperature the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography leading to crystalline **17**.

^1H-NMR (400MHz, $CDCl_3$): δ= 7.37-7.33 p.p.m. (m, 6H), 7.28-7.24 (m, 4H), 5.88-5.82 (m, 2H), 4.73-4.70 (m, 1H), 4.71 (d, *J*=8.3 Hz, 1H), 4.63 (d, *J*=8.3 Hz, 1H), 3.57-3.52 (m, 1H), 3.23-3.16 (m, 1H), 2.92 (ddd, *J*=13.1, 8.8, 2.0 Hz, H), 2.80-2.73 (m, 1H), 2.58-2.50 (m, 1H), 2.42 (ddd, *J*=13.1, 4.0, 1.3 Hz, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 137.44 p.p.m., 137.15, 133.59, 132.27, 128.88, 128.85, 127.30, 127.07, 110.62, 86.99, 85.26, 50.58, 44.70, 37.32, 33.21.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{20}O_2$ 304.1463; found, 304.1457.

(1*S*,5*R*,6*S*)-bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate **19a**



Potassium dihydrogenphosphate buffer (50mM, 150 mL) 50 mL pentane and racemic **19** (58.4 mmol, 10.9 g 58.4 mmol) dissolved in 50 mL *tert*-butyl methyl ether were vigorously stirred at room temperature. The pH was adjusted to 7.0 and SAM II amino lipase (60 mg) was added. The resolution was stopped after 55% conversion, the phases were separated and the aqueous phase was extracted two times with diethyl ether. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (pentane:diethyl ether 5:1) to give 4.9 g of acetate **19a**, and 3.5 g of alcohol **19b**.

Acetate **19a**:

^{1}H-NMR ($CDCl_3$, 400 MHz): 1.83 (*ddt*, *J* = 13.1, 5.6, 1.2, 1 H, H-C(2)); 2.41–2.59 (*m*, 2 H, H-C(6)); 2.78 (*ddt*, *J* = 13.1, 8.0, 2.0, 1 H, H-C(2)); 3.04–3.12 (*m*, 1 H, H-C(3)); 3.28–3.38 (*m*, 1 H, H-C(7)); 4.06 (*s*, 2 H, CH_2Cl); 5.25–5.33 (*m*, 1 H, H-C(1)); 5.79–5.85 (*m*, 2 H, H-C(4), H-C(5)).

^{13}C-NMR ($CDCl_3$, 100 MHz): 32.9; 36.9; 41.0; 41.3; 41.5; 70.0; 132.7; 134.5; 167.1.

EI-HR-MS: 186.0445 (M^+, $C_9H_{11}O_2Cl^+$; Ber. 186.0448).

IR: 2940*m*; 1757*s*; 1412*w*; 1347*w*; 1312*m*; 1287*m*; 1185*m*; 1047*w*; 1001*w*.

$[\alpha]_D^{25} = -19.5$ (c = 0.65g/100mL, $CHCl_3$).

Alcohol **19b**:

^{1}H-NMR ($CDCl_3$, 400 MHz): 1.60 (*ddt*, *J* = 13.0, 4.4, 1.1, 1 H, H-C(2)); 2.34–2.46 (*m*, 1 H, H-C(6)); 2.67–2.78 (*m*, 2 H, H-C(2), H-C(6)); 2.98–3.06 (*m*, 1 H, H-C(3)); 3.12–3.20 (*m*, 1 H, H-C(7)); 3.28 (*br*, 1 H, OH); 4.43 (*ddt*, *J* = 7.8, 4.7, 1.6, 1 H, H-C(1)); 5.83–5.87 (*m*, 2 H, H-C(4), H-C(5)).

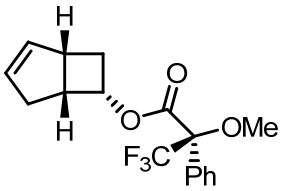
^{13}C-NMR ($CDCl_3$, 100 MHz): 31.9; 40.2; 41.1; 42.5; 67.9; 132.9; 136.0.

EI-HR-MS: 110.0735 (M^+, $C_7H_{10}O^+$; Ber. 110.0732).

IR: 3351*br*; 3049*m*; 2933*s*; 2851*m*; 1733*s*; 1607*w*; 1411*w*; 1350*m*; 1319*w*; 1210*m*; 1168*m*; 1108*s*; 1082*m*; 1048*w*; 1001*w*.

$[\alpha]_D^{25} = -57.6$ (c = 1.0, $CHCl_3$) (Lit. [21]: $[\alpha]_D^{25} = -68.0$ (c = 1.1, $CHCl_3$)).

(*R*)-((1*S*,5*R*,6*S*)-bicyclo[3.2.0]hept-2-en-6-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **A**



19a was hydrolyzed with 30 % KOH in ethanol to give optical active alcohol **18** 2.5 g in 87% yield. This alcohol (20 mg, 0.18 mmol, 1eq) was dissolved in 1 mL DCM and pyridine (50µL, 1 mmol, 5eq) was added. Then (*S)*-Mosher chloride (51µL, 0.27 mmol, 1.5eq) was added and the reaction was stirred for one hour at room temperature. The reaction was quenched with 1M HCl and diluted with diethyl ether. The phases were separated and the aqueous phase was extracted two times with diethyl ether. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexanes ethylacetate 3:1) to give 60 mg 100% of compound **A**.

The ^{19}-F-NMR revealed 98% ee.

^{1}H-NMR ($CDCl_3$, 400 MHz): 1.86 (*ddt*, *J* = 13.3, 5.2, 1.2, 1 H, H-C(2)); 2.34–2.43 (*m*, 1 H, H-C(6)); 2.45–2.53 (*m*, 1 H, H-C(6)); 2.84 (*ddt*, *J* = 13.5, 8.0, 2.4, 1 H, H-C(2)); 3.05–3.14 (*m*, 1 H, H-C(3)); 3.29–3.38 (*m*, 1 H, H-C(7)); 3.55 (*d*, *J* = 1.0, 3 H, OCH_3); 5.39 (*ddt*, *J* = 8.1, 5.4, 1.0, 1 H, H-C(1)); 5.73–5.80 (*m*, 2 H, H-C(4), H-C(5)); 7.37–7.42 (*m*, 3 H, C_6H_5); 7.53–7.57 (*m*, 2 H, C_6H_5).

^{13}C-NMR ($CDCl_3$, 100 MHz): 32.9; 37.2; 41.3; 41.5; 55.8; 71.9; 123.7 (*q*, *J* = 288.8, CF_3); 127.8; 128.7; 129.9; 132.8; 132.9; 134.0; 166.3.

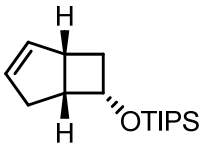
^{19}F-NMR ($CDCl_3$, 376 MHz): –71.9.

IR: 2947*w*; 1747*m*; 1451*w*; 1270*m*; 1169*m*; 1125*w*; 1017*w*.

EI-HR-MS: 326.1327 (M^+, $C_{17}H_{17}O_3F_3^+$; Ber. 326.1130).

$[\alpha]_D^{25}$=+58.4 (c = 1.0, $CHCl_3$).

((1*S*,5*R*,6*S*)-bicyclo[3.2.0]hept-2-en-6-yloxy)triisopropylsilane **18a**



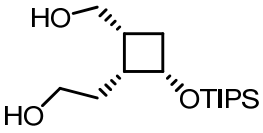
Alcohol **18** (15.2 g, 138 mmol, 1eq) was dissolved in 100 mL DMF. To this solution imidazole (331 mmol, 22.5 g, 2.4 eq) and TIPSCl (152 mmol, 29.2 g, 1.1 eq) were added. The reaction was stirred over night, quenched with water and diluted with diethyl ether. The phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 20:1) to give 36.7 g 99% of compound **18a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.83-5.81 p.p.m. (m, 1H), 5.79-5.76 (m, 1H), 4.53 (dd, *J*=14.0, 7.2 Hz, 1H), 3.16-3.08 (m, 1H), 2.99-2.92 (m, 1H), 2.61 (dddd, *J*=12.1, 8.5, 7.2, 1.9 Hz, 2.31 (dddd, *J*=17.0, 10.2, 1.8, 1.8 Hz, 1H), 1.66-1.64 (m, 1H), 1.03 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 134.49 p.p.m., 132.85, 65.46, 43.97, 40.93, 38.77, 31.27, 17.94, 17.91, 12.05.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{16}H_{30}OSi$ 266.2065; found, 266.2054.

2-((1*R*,2*R*,4*S*)-2-(hydroxymethyl)-4-(triisopropylsilyloxy)cyclobutyl)ethanol **21**



Bicycle **18a** (13.3 g, 50 mmol 1eq.) was dissolved in 300 mL DCM and 100 mL MeOH and cooled to -78°C. Ozone was bubbled through until the solution turned dark blue. Air was then bubbled through until the color deceased again and the cooling bath was removed. 200 mL MeOH were added and $NaBH_4$ (5.7g, 150 mmol, 3eq) was added. The reaction mixture was stirred at room temperature for two hours and quenched by slow addition of water (50 mL then 500 mL 1M HCl). The phases were separated and the water phase was further extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed under reduced pressure and submitted to flash column chromatography (hexane:ethylacetate 1:1) to yield 14.1 g diol **21** in 93% over two steps.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 4.33 p.p.m. (dd, *J*=14.1, 7.3 Hz, 1H), 3.79 (ddd, *J*=10.4, 5.8, 4.6 Hz, 1H), 3.70 (dd, *J*=11.0, 9.2 Hz, 1H), 3.66-3.62 (m, 1H), 3.57 (dd, *J*=11.1, 5.0 Hz, 1H), 2.70-2.58 (m, 3H), 2.32-2.24 (m, 1H), 2.23-2.14 (m, 1H), 2.02-1.94 (m, 1H) 1.81 (ddd, *J*=14.8, 7.7, 4.9 Hz, 1H), 1.68-1.61 (m, 1H), 1.05 (s, 20H).

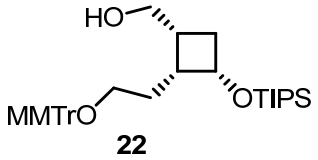
^{13}C-NMR (100MHz, $CDCl_3$): δ= 65.93 p.p.m.,63.48, 62.86, 42.91, 34.61, 32.27, 25.56, 18.12, 18.05, 12.21.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{16}H_{34}O_3Si$ 302,2277; found, 302,2270.

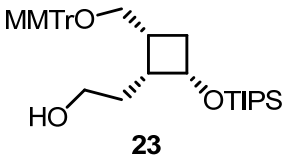
$[\alpha]_D$= +45.7 (c 0.7g/100mL, $CHCl_3$).

((1*R*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutyl)methanol **22** and

2-((1*R*,2*R*,4*S*)-2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-4-(triisopropylsilyloxy)cyclobutyl)ethanol **23**



22



23

Diol **21** (14.1 g, 46.5 mmol, 1eq) was dissolved in 500 mL pyridine and cooled to -42°C. Dimethyl aminopyridine (284 mg, 2.3 mmol, 5 mol%) was added and MMTrCl (10.8 g, 34.8 mmol, 75 mol%) dissolved in 50 mL pyridine was added dropwise. The reaction was stirred over night, and was then concentrated. The residue was re-dissolved in 200 mL DCM and extracted with 0.5M HCl. The phases were separated and the water phase was extracted two times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed under reduced pressure and the crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to yield 14.7 g of **22** 55% and 5.4 g of **23** 20% yield.

22:

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.44-7.39 p.p.m. (m, 4H), 7.32-7.16 (m, 8H), 6.85-6.81 (m, 2H), 4.33 (dd, *J*=14.6, 7.6 Hz, 1H), 3.79 (s, 3H), 3.63-3.49 (m, 2H), 3.14 (dd, *J*=9.3, 5.8 Hz, 1H), 2.98 (t, *J*=8.7 Hz, 1H), 2.70-2.62 (m, 1H), 2.59 (dd, *J*=5.8, 4.5 Hz, 1H), 2.35-2.24 (m, 2H), 1.88-1.77 (m, 1H), 1.67 (dd, *J*=17.7, 9.3 Hz, 1H), 1.48 (ddd, *J*=14.5, 9.9, 5.0 Hz, 1H), 1.03 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 158.46 p.p.m., 144.56, 135.90, 130.28, 129.20, 128.39, 127.88, 127.73, 127.18, 126.80, 113.02, 65.89, 63.82, 62.65, 55.18, 43.02, 35.43, 29.15, 26.45, 17.94, 17.85, 12.04.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{36}H_{50}O_4Si$ 574.3478; found, 574.3469.

$[\alpha]_D$= 17.3 (c 1.05g/100mL, $CHCl_3$).

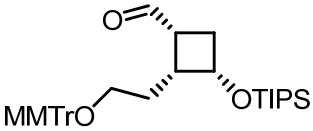
^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.45-7.41 p.p.m. (m, 4H), 7.32-7.18 (m, 8H), 6.81 (d, *J*=9.1 Hz, 2H), 4.25 (dd, *J*=13.3, 6.7 Hz, 1H), 3.79 (s, 3H), 3.67-3.61 (m, 1H), 3.59-3.53 (m, 1H), 3.21 (dt, *J*=8.8, 6.7 Hz, 1H), 3.04 (dt, *J*=8.8, 6.8 Hz, 1H), 2.63 (ddd, *J*=14.7, 10.0, 7.3 Hz, 1H), 2.34-2.27 (m, 1H), 2.20-2.11 (m, 1H), 2.07-1.98 (m, 1H), 1.85-1.74 (m, 2H), 1.68 (ddd, *J*=11.1, 8.5, 6.7 Hz, 1H), 0.96 (s, 20H.

^{13}C-NMR (100MHz, $CDCl_3$): δ= 158.39 p.p.m., 144.84, 136.13, 130.35, 128.50, 127.73, 126.70, 112.98, 66.44, 63.38, 63.05, 55.16, 40.64, 34.34, 32.98, 24.09, 17.94, 17.89, 11.95.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{36}H_{50}O_4Si$ 574.3478; found, 574.3471.

$[\alpha]_D$= +19 (c 1.4g/100mL, $CHCl_3$).

(1*R*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutanecarbaldehyde **22a**



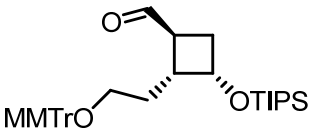
Alcohol **22** (14.7 g, 25.6 mmol, 1eq) was dissolved in ethylacetate and IBX (21.5g, 76.7 mmol, 3eq) was added. The suspension was vigorously stirred and heated at reflux for three hours. The reaction mixture was cooled to room temperature, the solids were filtered off and the solvents were removed *in vacuo*. The crude product was submitted to the next reaction without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 9.65 p.p.m. (d, *J*=2.3, 1H), 7.42-7.39 (m, 4H), 7.30-7.18 (m, 8H), 6.81 (d, *J*=8.8 Hz, 2H), 4.36 (dd, *J*=14.3, 7.2 Hz, 1H), 3.79 (s, 3H), 3.15-3.02 (m, 3H), 2.81-2.74 (m, 1H), 2.41 (ddd, *J*=11.7, 9.3, 7.9 Hz, 1H), 2.27-2.19 (m, 1), 2.10 (dt, *J*=13.9, 6.8 Hz, 1H), 1.79-1.68 (m, 1H), 0.87 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 202.94 p.p.m., 158.42, 144.83, 136.05, 130.26, 128.42, 127.77, 126.74, 112.93, 65.26, 62.66, 55.13, 43.81, 41.70, 31.36, 24.75, 17.87, 11.97.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{36}H_{48}O_4Si$ 572.3322; found, 572.3314.

(1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutanecarbaldehyde **24**



Crude aldehyde **22a** was dissolved in a minimum of DCM and then diluted with 350 mL methanol. The solution was stirred at room temperature, and potassium carbonate (17.8 g, 127.8 mmol, 5eq.) was added. The reaction mixture was stirred for 1.5 hours, diluted with water and acidified. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 10:1) to give 13.4 g, 92% of **24** over two steps.

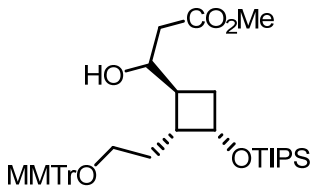
^{1}H-NMR (400MHz, $CDCl_3$): δ= 9.66 p.p.m. (d, *J*=1.5 Hz, 1H), 7.43-7.39 (m, 4H), 7.31-7.25 (m, 6H), 7.22-7.18 (m, 2H), 6.81 (d, *J*=8.8 Hz, 2H), 4.36 (dd, *J*=12.8, 6.2, Hz, 1H), 3.78 (s, 3H), 3.18-3.12 (m, 2H), 2.86-2.77 (m, 2H), 2.55-2.48 (m, 1H), 2.12-2.03 (m, 2H), 1.88-1.79 (m, 1H), 1.02 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 202.41 p.p.m., 144.93, 130.46, 128.57, 127.89, 126.92, 113.21, 66.10, 61.96, 55.35, 46.23, 41.35, 31.48, 28.71, 18.02, 12.09.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{36}H_{48}O_4Si$ 572.3322; found, 572.3313.

$[\alpha]_D$= +23.3 (c 0.57g/100mL, $CHCl_3$).

Methyl-3-hydroxy-3-((1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutyl)propanoate **24a**



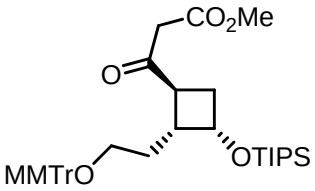
Aldehyde **24** (13.4 g, 23.4 mmol, 1eq) and bromo methyl acetate (3.8 mL ,37.4 mmol, 1.6 eq) were dissolved in 25 mL THF and dropwise added to zinc powder (2.75 g, 42 mmol, 1.8 eq) under vigorous stirring. The reaction mixture was maintained at reflux for 10 minutes and quenched with water. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 5:1) to give 14.4 g 95% of compound **24a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.45-7.41 p.p.m. (m, 4H), 7.32-7.18 (m, 10H), 6.81 (d, *J*=9.1 Hz, 2H), 4.40 (dd, *J*=13.1, 6.8 Hz, 1H), 3.93-3.84 (m, 1H), 3.78 (s, 3H), 3.72-3.70 (m, 1H), 3.67 (s, 1H), 3.66 (s, 1H), 3.15-3.01 (m, 2H), 2.75 (d, *J*=3.5 Hz, 0.7H), 2.70 (d, *J*=3.0 Hz, 0.3H), 2.39-2.20 (m, 2H), 2.15-1.66 (m, 4H), 0.99 (m, 11H), 0.98 (m, 8H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 173.49, p.p.m., 173.23, 158.38, 144.85, 136.14, 130.31, 128.39, 127.27, 126.58, 112.94, 86.43, 86.13, 70.92, 70.06, 66.15, 62.44, 61.86, 55.16, 51.68, 40.99, 40.72, 40.44, 40.18, 39.25, 33.44, 31.96, 29.14, 28.84, 17.97, 17.92, 12.02.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{39}H_{54}O_6Si$ 646.3689; found, 646.3678.

Methyl-3-((1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutyl)-3-oxopropanoate **11**



Compound **24a** (14.4 g, 22.2 mmol, 1eq), was dissolved in 70 mL ethylacetate. IBX (66.8 mmol, 18.7g, 3eq) was added and the reaction mixture was heated at reflux for five hours, cooled to room temperature and the solids were filtered off. The solution was concentrated *in vacuo* and submitted to flash column chromatography (hexane: ethylacetate= 10:1). The yield was 93% 13.3g of compound **11**.

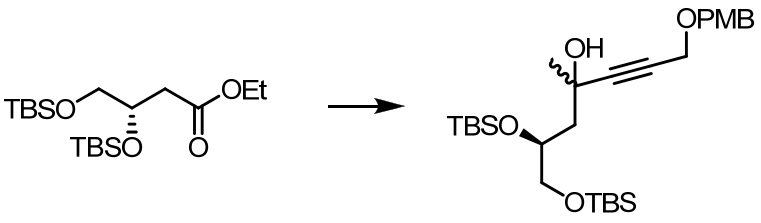
^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.40-7.42 p.p.m. (m, 4H, 7.30-7.19 (m, 10H), 6.83-6.79 (m, 2H) 4.41 (dd, *J*=13.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.31 (d, *J*=15.7 Hz, 1H), 3.24 (d, *J*=15.7 Hz, 1H), 3.21-3.11 (m, 2H), 2.95 (ddd, *J*=9.2, 4.5, 4.5 Hz, 1H), 2.82-2.74 (m, 1H), 2.51 (dddd, *J*=11.7, 4.3, 4.0, 3.3 Hz, 1H), 2.17-2.06 (m, 2H), 1.90-1.74 (m, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 203.92, 167.52, 158.50, 144.60, 135.95, 130.24, 128.36, 127.75, 126.83, 113.03, 86.30, 65.48, 61.96, 55.14, 52.19, 47.50, 45.62, 42.82, 32.99, 28.71, 17.82, 11.86. p.p.m.,

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{39}H_{52}O_6Si$ 644.3533; found, 644.3538.

$[\alpha]_D$= +26 (c 0.55g/100mL, $CHCl_3$).

(6*S*)-6,7-bis(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-4-methylhept-2-yn-4-ol **28**



Literature known ester **26** (9.1 g, 24.1 mmol, 1eq) and weinreb-amine hydrochloride (36.5 mmol, 3.53 g, 1.5 eq) were dissolved under argon in 50 mL THF at 0°C. Isopropyl magnesium chloride (2M in diethyl ether, 145 mL, 72.5 mmol, 3eq) was added slowly over 20 minutes. The reaction mixture was stirred for another 20 minutes at ambient temperature and was then carefully quenched with water. The phases were separated and the water phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were

removed *in vacuo* and the crude product was filtered over a short pad of silica gel to give 8.9 g 94% of the corresponding weinreb amide.

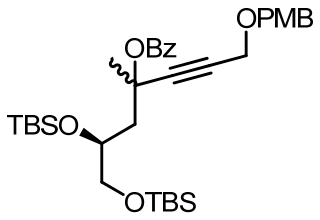
This Weinreb Amide was dissolved in 60 mL diethyl ether and was cooled to 0°C under argon. Methyllithium (3M in diethyl ether, 24.1 mmol, 8 mL, 1eq) was added dropwise to the solution. The reaction was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The phases were separated and the water phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo*. The crude ketone was added in 20 mL THF to the solution of **27** (28.9 mmol, 5.1 g, 1.2eq) deprotonated at -78°C with LHMDS (28.9 mL, 28.9 mmol, 1.2eq). After 2.5 hours the reaction was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The phases were separated and the water phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 5:1) to give 7.9 g 63% of alcohol **28**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.18-7.14 p.p.m. (m, 2H), 6.78-6.75 (m, 2H), 4.53 (s, 2H), 4.41 (s, 2H), 4.19-4.13 (m, 1H), 4.06 (s, 3H), 3.57 (dd, *J*=10.0, 5.0 Hz, 1H), 3.51 (dd, *J*=10.0, 6.7 Hz, 1H), 3.25 (s, 3H), 1.93-1.91 (m, 2H), 1.43 (s, 3H), 0.78 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.04 p.p.m., 129.67, 129.58, 113.82, 96.62, 90.46, 79.03, 71.99, 71.14, 69.99, 69.49, 57.06, 55.56, 55.29, 48.17, 31.12, 25.78, 18.00, -4.38, -4.77.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{28}H_{50}O_5Si_2$ 522.3196; found, 522.3204.

(6*S*)-6,7-bis(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-4-methylhept-2-yn-4-yl benzoate **28a**



Triethylamine (1.7 ml, 12 mmol, 3eq), benzoic-anhydride (1.8 g, 8 mmol, 2 eq) and magnesiumbromide etherate (2 g, 8 mmol, 2eq) were added to 30 mL of THF at room temperature and stirred for 15 minutes. To this suspension was added alcohol xxx (2.1 g, 4.0 mmol, 1eq) in 5 mL THF. The reaction vessel became warm and was cooled with a water bath. After 20 minutes the reaction was quenched with 5M KOH and was vigorously stirred for 30 minutes at room temperature. The phases were separated and the water phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and

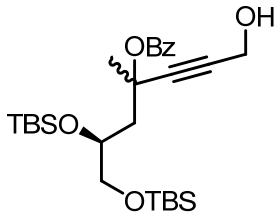
the crude product was submitted to flash column chromatography (hexane: ethylacetate 10:1) to give 2.38 g 95% of benzoate **28a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 8.06-8.02 p.p.m. (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.41 (m, 2H), 7.32-7.28 (m, 2H), 6.87-6.84 (m, 2H), 4.57 (a, 2H), 4.38-4.35 (m, 1H), 4.20 (s, 2H), 3.79 (s, 3H), 3.69-3.62 (m, 1H), 3.49-3.46 (m, 1H), 2.56-2.51 (m, 1H), 2.07-2.01 (m, 1H), 1.92 (s, 3H), 0.90-0.89 (m, 18H), 0.01 (m, 6H), -0.05 (m, 6H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.51 p.p.m., 159.61, 132.91, 132.67, 131.04, 129.89, 129.54, 128.26, 113.70, 87.16, 86.31, 82.39, 81.62, 74.85, 71.23, 70.81, 70.43, 67.65, 63.83, 56.81, 55.07, 45.55, 42.74, 33.01, 29.29, 28.04, 27.38, 25.93, 25.89, 18.34, 18.02, -4.04, -4.58, -5.29, -5.32.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{35}H_{54}O_6Si_2$ 626.3458; found, 626.3445.

(6*S*)-6,7-bis(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methylhept-2-yn-4-yl benzoate **29**



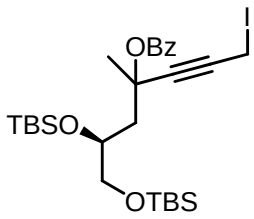
Benzoate **28a** (5.6 g, 8.9 mmol, 1eq) was dissolved in 60 mL DCM and 3 mL water were added. The solution was vigorously stirred when DDQ (3 g, 13.4 mmol, 1.5eq) were added. After stirring at room temperature for 2.5 hours the reaction was quenched with sodium thiosulfate and diluted with diethyl ether. The phases were separated and the water phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 5:1) to give 3.83 g 85% of the desired alcohol **29**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 8.01-7.99 p.p.m. (m, 2H), 7.56-7.52 (m, 1H), 7.43-7.39 (m, 2H), 4.32 (s, 2H), 4.15 (dddd, *J*=10.8, 10.8, 5.4, 5.4 Hz, 1H), 3.66-3.64 (m, 2H), 2.49 (dd, *J*=14.9, 5.8 Hz, 1H), 2.13 (s (br), 1H), 1.98 (dd, *J*=14.1, 5.6 Hz, 1H), 1.86 (s, 3H), 0.89 (s, 18H), 0.09 (s, 6H), 0.04 (s, 6H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.67 p.p.m., 132.79, 130.85, 129.58, 128.26, 85.48, 84.71, 74.93, 71.17, 67.69, 51.11, 45.53, 27.90, 25.97, 25.91, 18.41, 18.07, -3.97, -4.49, -5.21.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{27}H_{46}O_5Si_2$ 506.2883; found, 506.2879.

(6*S*)-6,7-bis(*tert*-butyldimethylsilyloxy)-1-iodo-4-methylhept-2-yn-4-yl benzoate **10**



Alcohol **29** (3.83 g, 7.55 mmol, 1eq) was dissolved in 70 mL DCM and cooled to 0°C. Then imidazole (620 mg, 9.1 mmol, 1.2eq), triphenylphosphine (2.4 g, 9.1 mmol, 1.2 eq) and iodine (2.3 g, 9.1 mmol, 1.2 eq) were added. The reaction mixture was stirred at that temperature for one hour. Then it was diluted with hexane. Triphenylphosphine oxide precipitated and was filtered off. The solution was concentrated *in vacuo* and submitted to flash column chromatography (hexane: ethylacetate= 10:1) to give 3.35 g 72% of iodide **10**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.93-7.90 p.p.m. (m, 2H), 7.46-7.42 (m, 1H), 7.34-7.30 (m, 2H), 4.09-4.03 (m, 1H), 3.65 (s, 2H), 3.56-3.54 (m, 2H), 2.41 (dd, *J*=14.3, 5.9 Hz, 1H), 1.88 (dd, *J*=14.4, 5.8 Hz, 1H), 1.75 (s, 3H), 0.81-0.79 (m, 18H), 0.04 (s, 3H), 0.03 (s, 3H), -0.04 (s, 6H).

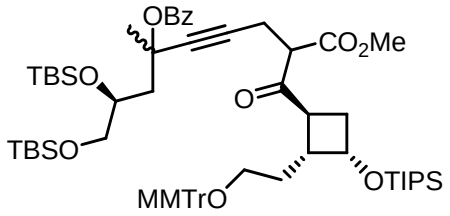
^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.51 p.p.m., 132.89, 130.98, 129.68, 128.38, 84.81, 83.24, 74.84, 71.02, 67.54, 45.68, 27.72, 26.00, 25.95, 18.43, 18.02, -3.90, -4.35, -5.22.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{27}H_{45}IO_4Si_2$ 616.1901; found, 616.1894.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.41-7.39 p.p.m.

^{13}C-NMR (100MHz, $CDCl_3$): δ= 201.78 p.p.m.,

(2*S*,4*S*)-1,2-bis(*tert*-butyldimethylsilyloxy)-9-methoxy-8-((1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutanecarbonyl)-4-methyl-9-oxonon-5-yn-4-yl benzoate **30**



A solution of β-Ketoester **11** (9.9 g, 15.35 mmol, 1eq) in 30 mL THF was added to a suspension of NaH in 50 mL THF (490 mg, 12.28 mmol, 0.8 eq) at 0°C. The reaction mixture was stirred at that temperature for 30 minutes and was then stirred at room temperature for another 30 minutes. A solution of Iodide **10** (11.51 mmol, 7.1 g, 0.75eq) in 20 mL THF was added at room temperature and the mixture was stirred for one hour. The reaction was quenched with an ammonium chloride solution and the phases were separated. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and

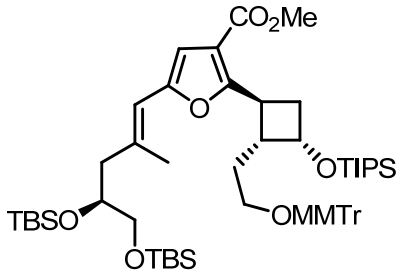
the crude product was submitted to flash column chromatography (hexane: ethylacetate 10:1) to give 11.1 g 85% of compound **30**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.98-7.95 p.p.m. (m, 2H), 7.53-7.49 (m, 1H), 7.41-7.36 (m, 6H), 7.29-7.17 (m, 10H), 6.81-6.78 (m, 2H), 4.41 (m, 1H), 4.11-4.01 (m, 1H), 3.78-3.77 (m, 3H), 3.68-3.45 (m, 6H), 3.18-3.06 (m, 2H), 2.90-2.82 (m, 1H), 2.74-2.69 (m, 0.5H), 2.64-2.58 (m, 1.4H), 2.46-2.38 (m, 2H), 2.16-1.99 (m, 3H), 1.80-1.76 (m, 4H), 0.98-0.94 (m, 20 H), 0.88-0.87 (m, 18H), 0.09-0.02 (m, 12H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 168.48 p.p.m., 158.25, 144.80, 135.84, 132.71, 130.25, 129.41, 128.39, 128.23, 127.72, 126.69, 112.92, 71.14, 67.69, 65.51, 61.57, 55.10, 52.43, 46.05, 45.42, 44.79, 42.16, 33.93, 32.98, 29.09, 28.86, 28.09, 25.92, 1836, 17.96, 11.89, -3.98, -5.29.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{66}H_{96}O_{10}Si3$ 1132.6311; found, 1132.6300.

Methyl-5-((S,E)-4,5-bis(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-2-((1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutyl)furan-3-carboxylate **31**



30 (11.2 g, 9.7 mmol, 1eq) was dissolved in 80mL 10:1 acetonitrile:water, which was degassed before. The sequentially palladium diacetate (0.5 mmol, 124 mg, 5 mol%), diphenyl-phosphino ferrocene (0.7 mmol, 380 mg, 7 mol%) and potassium carbonate (11.6 mmol, 1.61g, 1.2 eq) were added. The reaction mixture was heated at reflux for four hours, then cooled to room temperature and poured on 0.5M HCl. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 20:1) to give 8.8 g 90% of furan **31** as double bond isomers, of which an analytical sample of the *E*-isomer was separated for spectroscopic analysis.

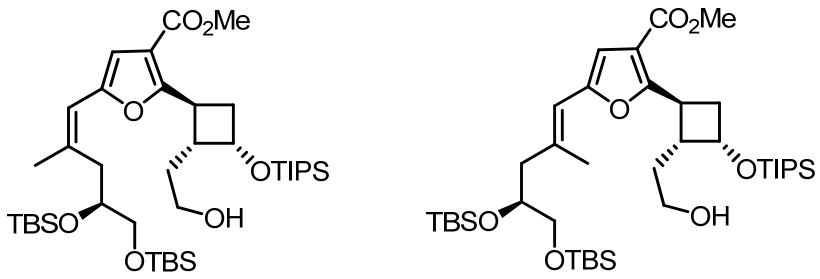
^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.37-7.33 p.p.m. (m, 4H), 7.24-7.14 (m, 9H), 6.76-6.73 (m, 2H), 6.36 (s, 1H), 6.03 (s, 1H), 4.68 (dd, *J*=12.6, 6.1 Hz, 1H), 3.86-3.78 (m, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 3.56 (dd, *J*=9.8, 5.1 Hz, 1H), 3.42 (dd, *J*=9.8, 6.8 Hz, 1H), 3.08 (dd, *J*=(13.0, 6.2 Hz, 2H), 2.96-2.88 (m, 1H), 2.48-2.41 (m, 2H), 2.36-2.29 (m, 1H), 2.17 (dd, *J*=13.1, 7.6 Hz, 1H), 2.13-2.07 (m, 1H), 1.99 (s, 3H), 1.93-1.84 (m, 1H), 1.01 (s, 20H), 0.90 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H), 0.02 (s, 3H), -0.04 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.26 p.p.m.,162.52, 158.38, 151.14, 144.88, 136.14, 130.18, 128.37, 127.62, 126.58, 116.39, 113.52, 112.84, 108.10, 72.06, 67.24, 66.48, 61.66, 55.10, 45.90, 44.85, 36.33, 32.94, 29.24, 26.00, 19.59, 18.31, 17.94, -4.52, -4.82.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{59}H_{90}O_8Si_3$ 1010.5943; found, 1010.5929.

Methyl-5-((*S*,*Z*)-4,5-bis(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-2-((1*S*,2*R*,3*S*)-2-(2-hydroxyethyl)-3-(triisopropylsilyloxy)cyclobutyl)furan-3-carboxylate **31a** and

Methyl-5-((*S*,*E*)-4,5-bis(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-2-((1*S*,2*R*,3*S*)-2-(2-hydroxyethyl)-3-(triisopropylsilyloxy)cyclobutyl)furan-3-carboxylate **31b**



Geometric isomers of furan **31** (8.8g, 8.7 mmol 1eq), were dissolved in 80 mL THF. Diphenyldiselenide (2.6 mmol,820 mg, 30 mol%) was added and the reaction mixture was refluxed for two days. The reaction was cooled to room temperature and the solvents removed *in vacuo*. The crude mixture was submitted to flash column chromatography (hexane: ethylacetate 20:1), and directly submitted to the next step.

Furan **31** (8.8 g, 8.7 mmol, 1eq) was dissolved in 25 mL DCM. To this solution 25 mL of 1,1,1,3,3,3-hexafluoro isopropanol were added dropwise. The solution turned yellow, and after stirring at room temperature for 20 minutes 3 mL methanol were added dropwise. The reaction mixture was stirred for 16 hours and was quenched with sodium hydrogen carbonate. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 5:1) to give 5.7 g 89% of alcohol **31a**. A minor geometrical *Z*-isomer **31b** could be easily separated on this step.

Z-isomer:

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.53 p.p.m. (s, 1H), 6.05 (s, 1H), 4.68 (dd, *J*=12.6, 6.3 Hz, 1H), 3.95-3.89 (m, 1H), 3.78 (s, 3H), 3.72-3.66 (m, 2H), 3.59 (dd, *J*=10.0, 5.2 Hz, 1H), 3.44 (dd, *J*=9.8, 6.6 Hz, 1H), 2.82-2.74 (m, 1H), 2.68-2.52 (m, 3H), 2.40-2.34 (m, 1H), 2.26-2.22 (m, 1H), 2.09-2.00 (m, 1H), 1.92 (s, 3H), 1.89-1.83 (m, 1H), 1.07 (s, 20H), 0.89 (s, 9H), 0.81 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), -0.03 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.73 p.p.m., 162.11, 137.63, 116.08, 113.30, 108.15, 71.78, 67.98, 66.95, 61.17, 51.18, 45.87, 38.82, 35.73, 32.88, 31.77, 25.98, 18.14, 12.28, -4.35, -4.83, -5.30.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{39}H_{74}O_7Si_3$ 738.4742; found, 738.4734.

$[\alpha]_D$= +23.5 (c 0.2g/100mL, $CHCl_3$).

E-isomer:

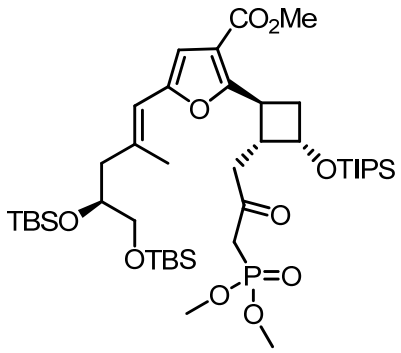
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.36 p.p.m. (s, 1H), 6.06 (s, 1H), 4.76 (dd, *J*=9.5, 4.7 Hz, 1H), 3.80 (s, 3H), 3.75-3.70 (m, 2H), 3.56 (dd, *J*=9.8, 5.0 Hz, 1H), 3.42 (dd, *J*=10.0, 6.8 Hz, 1H), 2.79-2.71 (m, 1H), 2.63-2.56 (m, 1H), 2.48-2.41 (m, 2H), 2.33-2.28 (m, 1H), 2.18 (dd, *J*=13.4, 7.3 Hz, 1H), 2.08 (dd, *J*=14.0, 7.2 Hz, 1H), 2.02 (s, 3H), 1.94-1.89 (m, 1H), 1.07 (s, 20H), 0.91 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.04 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.61 p.p.m., 162.52, 136.42, 115.92, 113.49, 108.03, 71.81, 67.09, 66.62, 61.16, 51.31, 46.32, 45.78, 35.87, 32.23, 31.82, 26.03, 19.62, 17.93, 12.20, -4.31, -4.99, -5.33.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{39}H_{74}O_7Si_3$ 738.4742; found, 738.4730.

$[\alpha]_D$= -10 (c 0.35g/100mL, $CHCl_3$).

Methyl-5-((*S*,*E*)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpent-1-enyl)-2-((1*S*,2*R*,3*S*)-2-(3-(dimethoxyphosphoryl)-2-oxopropyl)-3-(triisopropylsilyloxy)cyclobutyl)furan-3-carboxylate **32**



Oxallyl chloride (75 µL, 0.86 mmol, 2eq), was dissolved in 2 mL DCM and cooled to -78°C. Then DMSO (125 µL, 1.72 mmol, 4 eq) was added and the mixture was stirred for 15 minutes. Alcohol **31b** (318 mg, 0.43 mmol, 1eq) dissolved in 2mL DCM was added and the reaction mixture was stirred for one hour. Then triethylamine (370µL, 2.58 mmol, 6eq) was added dropwise and after stirring at -78°C for 20 minutes the reaction was warmed to 0°C and stirred for 45 minutes before it was quenched with an ammonium chloride solution. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was directly submitted to the next step.

To a solution of 2.5M n-butyllithium (345µL, 0.86 mmol, 2eq) in 2mL THF was added methyl-dimethylphosphonate (95µL, 0.86 mmol, 2 eq) at -78°C. The mixture was stirred at that temperature for one hour before the crude aldehyde in 2mL THF was added. The raction was quenched after 30 minutes with water. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was directly submitted to the next step.

Oxallyl chloride (75 µL, 0.86 mmol, 2eq), was dissolved in 2 mL DCM and cooled to -78°C. Then DMSO (125 µL, 1.72 mmol, 4 eq) was added and the mixture was stirred for 15 minutes. Phosphono-alcohol dissolved in 2mL DCM was added and the reaction mixture was stirred for one hour. Then triethylamine (370µL, 2.58 mmol, 6eq) was added dropwise and after stirring at -78°C for 20 minutes the reaction was warmed to 0°C and stirred for 45 minutes before it was quenched with an ammonium chloride solution. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 1:1) to give 255 mg 68% of the phosphonate **32**.

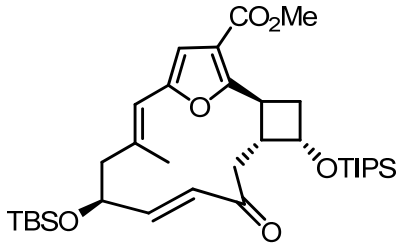
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.39 p.p.m. (s, 1H), 6.07 (s, 1H), 4.47 (dd, *J*=14.9, 7.4 Hz, 1H), 3.92-3.87 (m, 1H), 3.80 (s, 3H), 3.69 (d, *J*=5.6 Hz, 3H), 3.68 (d, *J*=6.0 Hz, 3H), 3.56 (dd, *J*=10.0, 5.2 Hz, 1H), 3.54-3.50 (m, 1H), 3.42 (dd, *J*=9.8, 6.8 Hz, 1H), 2.95-2.84 (m, 3H), 2.62-2.55 (m, 1H), 2.54-2.46 (m, 3H), 2.19 (dd, *J*=13.6, 7.5 Hz, 1H), 2.01 (s, 3H), 1.04 (s, 20H), 0.91 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 200.62 p.p.m., 164.18, 158.43, 152.08, 137.10, 116.24, 115.41, 108.21, 71.78, 67.11, 64.35, 52.73, 51.41, 45.78, 44.10, 41.70, 40.98, 39.30, 34.87, 27.08, 25.88, 19.65, 17.97, 12.10, -4.19, -4.79, -5.27.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{42}H_{79}O_{10}PSi_3$ 848.4718; found, 848.4709.

$[\alpha]_D$= -43 (c 0.5g/100mL, $CHCl_3$).

Compound **34**



Phosphonate **32** (255 mg, 0.3 mmol, 1eq) was dissolved in 1.5 mL methanol. Ammonium fluoride (15 mmol, 570 mg, 50 eq) was added and the reaction mixture was stirred for 24 hours. The mixture was

poured on a brine solution and the water phase was extracted three times with DCM, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 1:1) to give 100 mg, 45% of the primary alcohol which was directly submitted to the next reaction.

Primary alcohol was dissolved in 1 mL DCM and Dess-Martin periodinane (0.27 mmol, 114 mg, 2eq) was added. The reaction mixture was stirred at room temperature for one hour and poured on a brine solution. The water phase was extracted three times with DCM, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was filtered over a short pad of silica gel and directly submitted to the macrocyclization, as the aldehyde **33** turned out to be very instable.

10 mL 1,1,1,3,3,3-hexafluoro-isopropanol were dissolved in 50 mL THF and cooled to 0°C. n-butyllithium (2.5M, 162 µL, 3eq) was added dropwise and the reaction mixture was stirred at 0°C for 30 minutes. The crude aldehyde dissolved in 40 mL THF was then added *via* a syringe pump over 1 hour. The reaction was stirred at room temperature for another 4 hours. The reaction was the quenched with water. The aqueous phase was extracted three times with DCM, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 5:1) to give 37 mg 45% of macrocycle **34**.

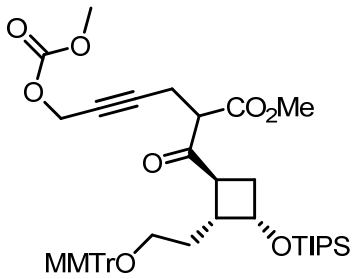
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.74 p.p.m. (dd, *J*=16.0, 4.3 Hz, 1H), 6.42 (s, 1H), 6.07 (s, 1H), 6.06 (dd, *J*=16.0, 1.3 Hz, 1H), 4.49-4.42 (m, 2H), 4.07-4.01 (m, 1H), 3.80 (s, 3H), 3.50-3.44 (m, 1H), 3.12 (dd, *J*=18.9, 10.2 Hz, 1H), 2.87 (dd, *J*=18.5, 5.3 Hz, 1H), 2.50-2.45 (m, 2H), 2.41 (dd, *J*=12.8, 7.5 Hz, 1H), 2.24 (dd, *J*=13.2, 6.4 Hz, 1H), 1.98 (s, 3H), 1.72-1.66 (m, 1H), 0.97 (s, 20H), 0.85 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 202.61 p.p.m., 164.18, 158.44, 152.11, 147.59, 128.49, 116.90, 108.49, 70.19, 64.07, 51.20, 49.82, 43.54, 36.54, 34.57, 30.40, 26.10, 25.94, 19.34, 18.30, 11.86, -5.49, -5.60.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{34}H_{56}O_6Si_2$ 616.3615; found, 616.3608.

$[\alpha]_D$= -76 (c 0.15g/100mL, $CHCl_3$).

Methyl-6-(methoxycarbonyloxy)-2-((1*S*,2*R*,3*S*)-2-(2-((4-methoxyphenyl)diphenylmethoxy)ethyl)-3-(triisopropylsilyloxy)cyclobutanecarbonyl)hex-4-ynoate **45**



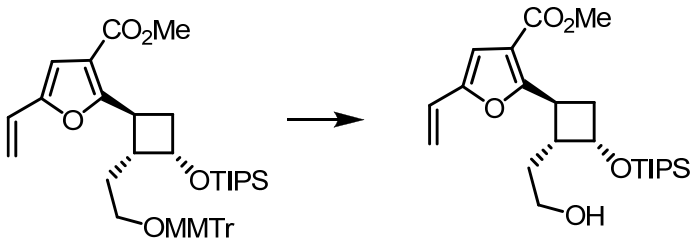
A solution of β-Ketoester **11** (9.9 g, 15.35 mmol, 1eq) in 30 mL THF was added to a suspension of NaH in 50 mL THF (490 mg, 12.28 mmol, 0.8 eq) at 0°C. The reaction mixture was stirred at that temperature for 30 minutes and was then stirred at room temperature for another 30 minutes. A solution of Iodide (10.75 mmol, 2.9 g, 0.75eq) in 20 mL THF was added at room temperature and the mixture was stirred for one hour. The reaction was quenched with an ammonium chloride solution and the phases were separated. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 10:1) to give 6.9 g 84% of compound **45**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.41-7.39 p.p.m. (m, 4H), 7.29-7.18 (m, (8H), 6.82-6.78 (m, 2H), 4.28 (dd, *J*=15.6, 7.1 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.28 (d, *J*=15.4 Hz, 1H), 3.18 (d, *J*=15.4 Hz, 1H), 3.14-2.96 (m, 4H), 2.45 (dd, *J*=19.7, 10.9 Hz, 1H), 2.18-2.07 (m, 2H), 1.63-1.55 (m, 1H), 0.98 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 201.78 p.p.m., 167.94, 158.44, 144.83, 136.10, 130.37, 128.44, 127.65, 126.68, 113.02, 64.08, 62.55, 55.29, 52.28, 48.99, 44.29, 40.09, 32.21, 24.61, 17.80, 11.85.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{45}H_{58}O_9Si$ 770.3850; found, 770.3842.

Methyl-2-((1*S*,2*R*,3*S*)-2-(2-hydroxyethyl)-3-(triisopropylsilyloxy)cyclobutyl)-5-vinylfuran-3-carboxylate **46**



45 (3 g, 3.8 mmol, 1eq) was dissolved in 130mL THF, which was degassed before. Then sequentially palladium diacetate (0.19 mmol, 49 mg, 5 mol%), diphenyl-phosphino ferrocene (0.26 mmol, 150 mg, 7 mol%) and potassium carbonate (24.6 mmol, 3.4 g, 6.5 eq) were added. The reaction mixture was heated at reflux for four hours, then cooled to room temperature and poured on 0.5M HCl. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over

magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane: ethylacetate 20:1) to give 1.2 g 75% of furan **46** which was subsequently subjected to the deprotection reaction of the MMTr-group.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.39-7.19 p.p.m. (m, 12H), 6.78 (d, *J*=8.9 Hz, 1H), 6.51-6.40 (m, 1H), 6.48 (s, 1H), 5.67 (d, *J*=17.4 Hz, 1H), 5.21 (d, *J*=11.3 Hz, 1H), 4.72-4.63 (m, 1H), 4.19 (ddd, *J*=14.3, 7.2, 7.2 Hz, 1H), 4.01-3.89 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.14-3.01 (m, 3H), 2.54-2.45 (m, 1H), 2.38-2.28 (m, 1H), 2.10 (ddd, *J*=13.4, 13.4, 6.9 Hz, 1H), 1.97-1.83 (m, 1H), 1.06 (s, 20H).

$[\alpha]_D$= +16.4 (c 0.48g/100mL, CH_2Cl_2).

MMTr-protected Furan **46** (5.3 g, 7.6 mmol, 1eq) was dissolved in 25 mL DCM. To this solution 25 mL of 1,1,1,3,3,3-hexafluoro isopropanol were added dropwise. The solution turned yellow and after stirring at room temperature for 20 minutes 3 mL methanol were added dropwise. The reaction mixture was stirred for 16 hours and was quenched with sodium hydrogen carbonate. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was filtered over a short pad silica gel to give 2.73 g, 85% of alcohol **46a**.

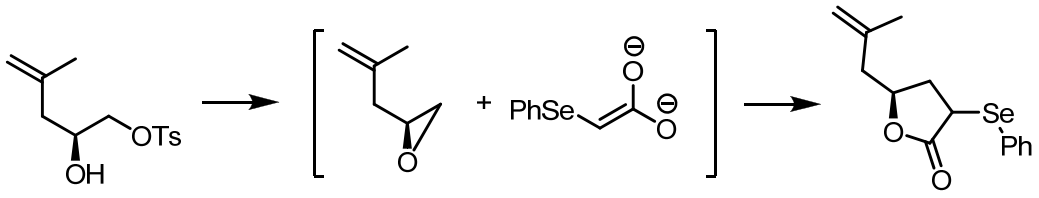
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.50-6.40 p.p.m. 6.47 (s, 1H), 5.68-5.62 (m, 1H), 5.21 (dt, *J*=11.5, 1.2 Hz, 1H), 4.77-4.69 (m, 1H), 4.15-3.95 (m, 3H), 3.81 (d, *J*=1.5 Hz, 3H), 2.86-2.75 (m, 1H), 2.61-2.53 (m, 1H), 2.41-2.31 (m, 1H), 2.18-2.09 (m, 1H), 2.06-1.97 (m, 1H), 1.07 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.18 p.p.m., 163.28, 150.78, 124.30, 112.78, 108.61, 66.64, 66.39, 51.50, 44.07, 38.27, 35.99, 33.21, 29.15, 17.99, 12.11.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{23}H_{38}O_5Si$ 422.2488; found, 422.2219.

$[\alpha]_D$= +25.4 (c 0.5g/100mL, $CHCl_3$).

(5*S*)-5-(2-methylallyl)-3-(phenylselanyl)dihydrofuran-2(3H)-one **39**



Literature known alcohol **42** (11.73 g, 43.4 mmol, 1eq) was dissolved in 40 mL THF and added to a suspension of NaH (1.82 g, 45.5 mmol, 1.05 eq) at 0°C. The epoxide formed *in situ* was then added at -78°C to a solution of dianion **B**. The dianion was prior prepared as follows: Diisopropylamine (19 mL, 134.5 mmol, 3.1eq) was added to 65 mL of THF and cooled to 0°C. Then n-butyllithium (2.5M, 53.8 mL, 134.5 mmol, 3.1 eq) was added dropwise and the reaction mixture was stirred for 20 minutes

at 0°C followed by stirring at room temperature for 30 minutes. At -20°C phenylselenyl acetic acid (14 g, 65.1 mmol, 1.5eq) in 65mL of THF is then added and the reaction mixture is stirred at that temperature for 2 hours. To this dianion is then added the epoxide **43**.

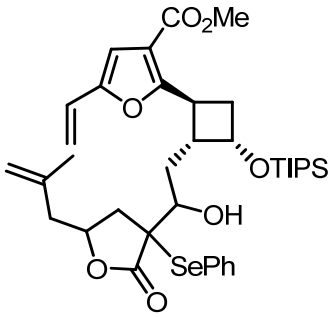
After the epoxide addition the reaction is warmed to room temperature over night. The reaction is quenched with 1M HCl and the aqueous phase is extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was dissolved in benzene and catalytic amount of *p*-toluene sulfonic acid was added. The reaction is heated at reflux with a Dean-Stark trap for one hour. Then the reaction is cooled to room temperature and the solvents are removed under reduced pressure. The crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 9.3 g 73% of lactone **39**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.69 p.p.m. (m, 2H), 7.35 (m, 1H), 7.34 (m, 2H), 4.84 (s, 1H), 4.73 (s, 1H), 4.42 (dddd, *J*=7.0, 7.0, 6.8, 6.8 Hz, 1H), 3.94 (, dd, *J*=6.5, 4.5 Hz, 1H), 2.45 (dd, *J*=14.3, 6.9 Hz, 1H), 2.35 (m, 1H), 2.23 (dd, *J*=14.3, 6.1 Hz, 1H), 1.71 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 175.58 p.p.m., 140.08, 135.89, 129.89, 129.81, 129.22, 126.70, 113.85, 77.61, 43.15, 36.91, 36.47, 22.70.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{23}H_{38}O_5Si$ 296.0315; found, 296.0301.

Methyl-2-((1*S*,2*R*,3*S*)-2-(2-hydroxy-2-(5-(2-methylallyl)-2-oxo-3-(phenylselanyl)tetrahydrofuran-3-yl)ethyl)-3-(triisopropylsilyloxy)cyclobutyl)-5-vinylfuran-3-carboxylate **47**



Oxallyl chloride (2 mL, 23.2 mmol, 2eq), was dissolved in 20 mL DCM and cooled to -78°C. Then DMSO (3.3 mL, 46.4 mmol, 4 eq) was added and the mixture was stirred for 15 minutes. Alcohol **46a** (4.9 g, 11.6 mmol, 1 eq) dissolved in 20 mL DCM was added and the reaction mixture was stirred for one hour. Then triethylamine (9.8 mL, 69.6 mmol, 6eq) was added dropwise and after stirring at -78°C for 20 minutes the reaction was warmed to 0°C and stirred for 45 minutes before it was quenched with an ammonium chloride solution. The water phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was filtered over a short pad silica gel to give the corresponding aldehyde **40** 4.9g 99% which was directly used in the next reaction.

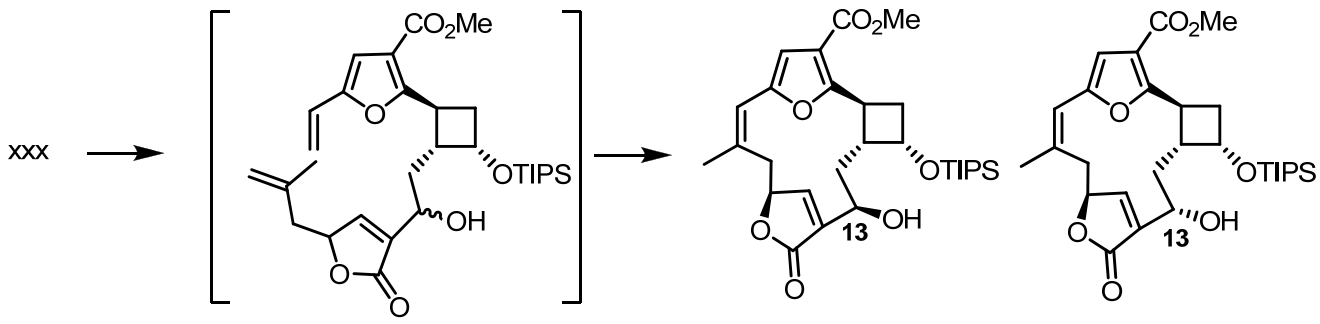
LiHMDS (1M in THF, 33.5 mL, 33.5 mmol, 3eq) was added to 40 mL of THF at -78°C. Then lactone xxx (10g, 33.5 mmol, 3eq) dissolved in 20 mL THF was added dropwise to this solution at -78°C. The reaction was stirred at that temperature for one hour. Then aldehyde **40** (4.9 g, 11.6 mmol, 1eq) was added and the reaction was left for another hour at -78°C. Then it was quenched with a saturated ammonium chloride solution. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 5.4 g 65% of seleno-lactone **47** as a mixture of diastereomers. An analytical sample of one diastereomer was separated by HPLC for spectroscopic analysis.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.70 p.p.m. (m, 2H), 7.40 (m, 1H), 7.30 (m, 2H), 6.45 (s, 1H), 6.43 (dd, *J*=17.3, 12.5 Hz, 1H), 5.65 (d, *J*=17.3 Hz, 1H), 5.20 (d, *J*=12.5 Hz, 1H), 4.81 (s, 1H), 4.58 (dddd, *J*=9.0, 6.8, 6.8, 6.8 Hz, 1H), 4.57 (m, 1H), 3.91 (ddd, *J*=9.1, 5.8, 5.9 Hz, 1H), 3.85 ((d, *J*=10.7 Hz, 1H), 3.74 (s, 3H), 3.03 (m, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 2.44 (dd, *J*=14.5, 7.0 Hz, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 2.20 (m,1 H), 2.19 (m, 1H), 2.17 (m, 1H), 1.64 (s, 3H), 1.09 (m, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 164.72 p.p.m., 163.84, 151.28, 140.47, 138.83, 130.17, 129.55, 126.11, 124.81, 114.10, 113.43, 109.02, 76.63, 72.02, 67.45, 56.69, 45.57, 43.62, 38.59, 36.05, 33.82, 32.15, 23.00, 18.44, 18.38, 12.57.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{37}H_{52}O_7SeSi$ 716.2647; found, 716.2639.

Compounds **48a** and **48b**



The diastereomeric mixture of **47** (1.55 g, 2.15 mmol, 1eq) was dissolved in 70 mL DCM and cooled to 0°C. 15 mL of a saturated ammonium chloride solution were added and the biphasic system was vigorously stirred. To this reaction mixture 75 mL of 30% hydrogen peroxide were added *via* a dropping funnel. After completion of addition the reaction mixture was stirred for another 20 minutes at room temperature before it was diluted with water and the phases were separated. The aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to filtration over a pad of silica gel to give 1.0 g 87% of metathesis precursor **38**.

The diastereomeric mixture of **38** (1 g, 1.87 mmol, 1eq) was dissolved in 1L benzene prior degassed by two pump and freeze cycles. Grubbs II catalyst (0.28 mmol, 238 mg, 15mol%) was dissolved in 5 mL benzene and added over two hours to the refluxing solution of xxx in benzene. After this time the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 310 mg 31% of compound **48a** and 238 mg 24% of compound **48b**.

13-(R)-diastereomer **48a**

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.57 p.p.m. (s, 1H), 6.45 (s, 1H), 6.12 (s, 1H), 4.92 (dd, *J*=11.2, 3.8 Hz, 1H), 4.41 (dd, 5.6, 5.6 Hz, 1H), 4.24 (m, 1H), 4.17 (ddd, *J*=9.2, 9.2, 9.2 Hz, 1H), 3.81 (s, 3H), 3.03 ((d,, *J*=12.2, 11.2 Hz, 1H), 2.75 (dd, *J*=12.2, 4.1 Hz, 1H), 2.47 (m, 1H), 2.38 (ddd, *J*=12.7, 12.7, 4.0 Hz, 1H), 2.27 (m, 1H), 2.24 (m, 1H), 2.07 (m, 1H), 2.00 (s, 3H), 1.05 (d, *J*=7.1 Hz, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 171.79 p.p.m., 163.72, 162.24, 153.55, 149.72, 131.50, 129.78, 117.10, 113.82, 111.48, 78.51, 68.34, 66.07, 51.57, 42.12, 40.28, 39.51, 37.75, 36.14, 26.37, 18.06, 18.00, 12.13.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{42}O_7Si$ 530.2699; found, 530.2687.

$[\alpha]_D$= +69.3 (c 0.42/100mL, CH_2Cl_2).

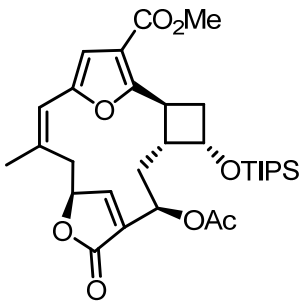
13-(S)-diastereomer **48b**

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.83 p.p.m. (s, 1H), 6.38 (s, 1H), 6.06 (s, 1H), 4.91 (dm, *J*=11.8 Hz, 1H), 4.72 (m, 1H), 4.35 (dd, *J*=15.9, 5.9 Hz, 1H), 4.23 (ddd, *J*=9.3, 9.3, 9.3 Hz, 1H), 3.73 (s, 3H), 3.05 (dd, *J*=11.7, 11.7 Hz, 1H), 2.68 (dd, *J*=11.7, 4.5 Hz, 1), 2.54 (m, 1H), 2.33 (m, 1H), 2.18 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.95 (s, 3H), 1.00 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 171.91 p.p.m., 164.41, 163.83, 152.51, 150.12, 143.43, 129.80, 117.52, 113.90, 111.79, 69.44, 67.33, 51.80, 41.32, 40.81, 38.63, 38.35, 33.28, 26.62, 18.41, 18.21, 17.49.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{42}O_7Si$ 530.2699; found, 530.2682.

Compound **49**



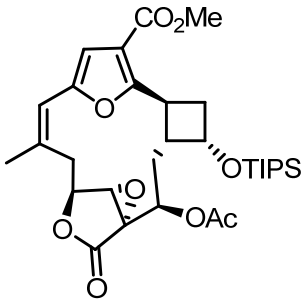
Macrocycle **48a** (310 mg, 0.58 mmol, 1eq) was dissolved in DCM and cooled to 0°C. Then sequentially pyridine (105µl, 0.93 mmol, 2 eq), dimethyl aminopyridine (3mg, 5mol%) and acetic anhydride (66µL, 0.7 mmol, 1.2 eq) were added and the reaction mixture was stirred at room temperature for three hours. The reaction was quenched with a saturated solution of ammonium chloride. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 7:1) to give 282 mg 85% of compound **49**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.94 p.p.m. (s, 1H), 6.48 (s, 1H), 6.12 (s, 1H), 5.24 (dd, *J*=12.0, 5.2 Hz, 1H), 4.97 (ddd, *J*=11.5, 4.5, 0.9 Hz, 1H), 4.46 (dd, *J*=5.9, 5.9 Hz, 1H), 4.18 (dd, *J*=18.8, 9.5 Hz, 1H), 3.83 (s, 3H), 3.02 (dd, *J*=11.8, 11.8 Hz, 1H), 2.78 (dd, *J*=11.8, 4.5 Hz, 1H), 2.59-2.48 (m, 2H), 2.32 (dd, *J*=11.6, 9.3 Hz, 1H), 2.24 (ddd, *J*=12.9, 12.9, 5.4 Hz, 1H), 2.12-2.05 (m, 1H), 2.03 (s, 3H), 2.00 (s, 3H), 1.08 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 171.62 p.p.m., 169.41, 163.53, 162.30, 158.38, 150.04, 129.69, 128.47, 116.94, 113.76, 111.55, 78.21, 68.64, 66.93, 51.48, 41.17, 40.64, 37.97, 36.52, 29.89, 26.15, 21.35, 18.14, 12.20.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{44}O_8Si$ 572.2805; found, 572.2798.

Compound **55**



Acetate **49** (282 mg, 0.48 mmol, 1eq) was dissolved in pyridine and cooled to -20°C. Sodium hypochlorite (1mL 5%chlorine) was added dropwise to this solution. After 30 minutes the reaction was quenched with 1M HCl and diluted with water. The phases were separated and the aqueous phase

was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 245 mg 87% of epoxide **55**.

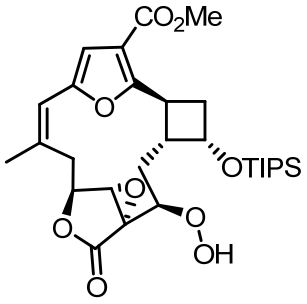
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.50 p.p.m. (s, 1H), 6.19 (s, 1H), 4.78 (dd, *J*=12.2, 4.9 Hz, 1H), 4.54 (dd, *J*=12.8, 4.2 Hz, 1H), 4.50 (dd, *J*=6.4, 6.4 Hz1H), 4.08 (dd, *J*=17.7, 8.3 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 1H), 3.50 (dd, *J*=12.6, 12.6 Hz, 1H), 2.90-2.82 (m, 1H), 2.61-2.53 (m, 2H), 2.45 (ddd, *J*=12.0, 10.0, 1.5 Hz, 1H), 2.33-2.19 (m, 2H), 2.11 (s, 3H), 2.00 (s, 3H), 1.07 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 170.01 p.p.m., 168.37, 163.45, 161.80, 149.48, 129.19, 117.61, 113.83, 111.35, 75.75, 67.90, 67.60, 65.32, 58.11, 51.60, 39.66, 38.02, 36.63, 35.99, 30.27, 25.55, 21.02, 17.99, 12.07.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{44}O_9Si$ 588.2754; found, 588.2743.

$[\alpha]_D$= +96 (c 0.9g/100mL, $CHCl_3$).

Compound **53**



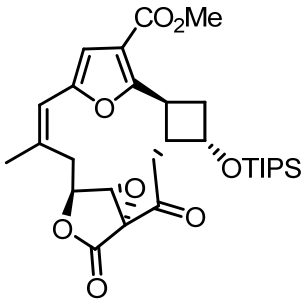
Acetate **49** (10 mg, 17.5µmol, 1eq) was dissolved in 500µL THF. Hydrogen peroxide (20µL, 0.2 mmol, 12 eq) and tetrabutyl ammonium hydroxide (1M in water, 50µL, 2eq) were added. The reaction was stirred at ambient temperature for one hour, diluted with water and diethyl ether and the phases were separated. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 3:1) to give 8 mg, 87% of peroxide **53**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 8.90 p.p.m. (s, 1H), 6.48 (s, 1H), 6.21 (s, 1H), 4.57 (dd, *J*=12.5, 4.2 Hz, 1H), 4.52-4.48 (m, 1H), 4.16-4.09 (m, 1H), 3.87 (dd, *J*=12.0, 4.4 Hz, 1H), 3.82 (s, 3H), 3.63-3.47 (m, 1H), 3.56 (s, 1H), 2.84-2.76 (m, 1H), 2.61-2.49 (m, 2H), 2.24-2.34 (m, 2H), 2.23-2.16 (m, 1H), 2.01 (s, 3H), 1.08 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 163.49 p.p.m., 161.58, 149.72, 129.64, 117.66, 113.96, 111.22, 80.22, 75.81, 67.94, 51.67, 40.35, 37.84, 36.65, 36.35, 28.78, 25.68, 18.00, 12.15.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{42}O_8Si$ 562.2598; found, 562.2587.

Compound **51**



Peroxide **53** (50 mg, 91µmol, 1eq) were dissolved in 1 mL DCM. Then sequentially pyridine (150 µl, 1.4 mmol, 15 eq), dimethyl aminopyridine (3mg, 5mol%) and acetic anhydride (20µL, 0.45 mmol, 5 eq) were added and the reaction mixture was stirred at room temperature for three hours. The reaction was quenched with a saturated solution of ammonium chloride. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 4:1) to give 42 mg 85% of ketone **51**

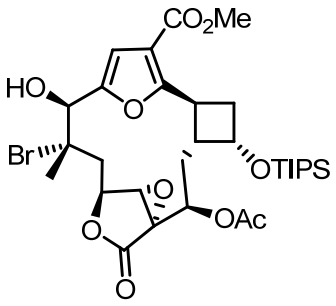
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.47 p.p.m. (s, 1H), 6.18 (d, *J*=1.3 Hz, 1H), 4.69 (dd, *J*=12.6, 4.8 Hz, 1H), 4.59 (dd, *J*=61., 6.1 Hz, 1H), 4.14 (dd, *J*=19.2, 10.0 Hz, 1H), 3.89 (s, 1H), 3.79 (s, 3H), 3.65 (dd, *J*=12.6, 4.7 Hz, 1), 3.46 (dd, *J*=12.6, 12.6 Hz, 1H), 3.19 (dddd, *J*=15.9, 6.4, 6.4, 2.9 Hz, 1H), 2.98 (dd, *J*=12.7, 12.7 Hz, 1H), 2.68 (dd, *J*=12.6, 4.8 Hz, 1H), 2.43 (dd, *J*=12.1, 9.6 Hz, 1H), 2.18-2.15 (m, 1H), 2.00 (d, *J*=0.9 Hz, 3H), 1.09-1.07 (m, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 197.07 p.p.m., 168.64, 163.73, 161.62, 150.11, 128.82, 118.44, 114.50, 112.39, 76.13, 68.78, 67.22, 52.09, 43.98, 40.15, 38.04, 37.55, 37.23, 25.61, 18.37, 12.48.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{40}O_8Si$ 544.2492; found, 544.2488.

$[\alpha]_D$= +122 (c 0.7g/100mL, $CHCl_3$).

Compound **60**



Acetate **49** (14 mg, 24 µmol, 1eq) was dissolved in 1 mL of wet THF. To this solution N-bromsuccinimide (7 mg, 39 µmol, 1.6 eq) was added. The reaction mixture was stirred for one hour and diluted with water and diethyl ether. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 4:1) to give 14 mg 89% of bromohydrine **60**.

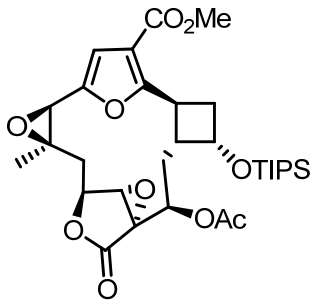
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.47 p.p.m. (s, 1H), 5.41 (d, *J*=2.5 Hz, 1H), 4.96 (dd, *J*=8.6, 2.5 Hz, 1H), 4.89 (dd, *J*=7.8, 7.8 Hz, 1H), 4.52 (dd, *J*=5.7, 5.7 Hz, 1H), 3.90 (dd, *J*=18.0, 9.6 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 1H), 3.27-3.20 (m, 1H), 2.74 (ddd, *J*=15.4, 7.7,7.7 Hz, 1H), 2.68 (d, *J*=3.3 Hz, 1H), 2.43-2.20 (m, 4H), 2.13 (s, 3H), 1.81 (s, 3H), 1.71 (dd, *J*=14.7, 3.4 Hz, 1H), 1.07 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 169.91 p.p.m., 168.11, 165.64, 163.39, 162.32, 149.78, 113.91, 110.59, 76.52, 74.21, 69.49, 68.76, 62.74, 59.15, 51.55, 42.95, 38.74, 37.72, 36.65, 29.01, 26.20, 20.91, 17.93, 12.36.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{45}O_{10}BrSi$ 684.1965; found, 684.1976.

$[\alpha]_D$= +73 (c 0.43g/100mL, $CHCl_3$).

Compound **60b**



Bromohydrine **60** (14 mg, 20µmol, 1eq) was dissolved in THF. NaH (60% mineral oil suspension, 40µmol, 2 mg, 2eq) was added at 0°C. The reaction was stirred at ambient temperature for 30 minutes before it was quenched with water. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 4:1) to give 11 mg 90% of bis-epoxide **60a**.

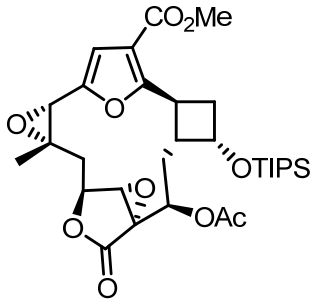
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.92 p.p.m. (s, 1H), 4.96 (dd, *J*=11.6, 4.7 Hz, 1H), 4.85 (dd, *J*=12.7, 3.8 Hz, 1H), 4.54 (s, 1H), 4.45 (dd, *J*=12.8, 6.0 Hz, 1H), 3.82 (s, 3H), 3.68-3.64 (m, 1H), 3.65 (s, 1H), 2.81-2.73 (m, 2H), 2.63-2.52 (m, 3H), 2.27 (s, 1H), 2.26 (dd, *J*=13.7, 4.5 Hz, 1H), 2.23-2.17 (m, 1H), 2.14 (s, 3H), 1.57 (s, 3H), 1.03 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 170.45 p.p.m., 168.46, 163.59, 163.14, 146.36, 116.00, 114.37, 75.95, 68.51, 66.45, 60.94, 57.31, 56.79, 51.80, 40.99, 37.79, 32.07, 30.48, 29.85, 29.67, 21.26, 18.07, 12.10.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{44}O_{10}Si$ 604.2703; found, 604.2695.

$[\alpha]_D$= +56 (c 0.47g/100mL, $CHCl_3$).

Compound **60b**



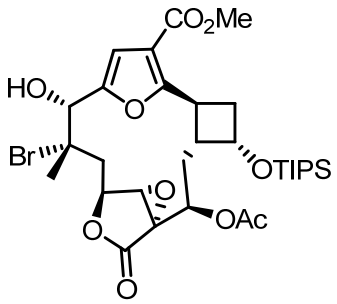
To epoxide **55** (12 mg, 20µmol, 1eq) in 500 µl DCM was added *meta*-chlorperbenzoic acid (30 µmol, 5 mg, 1.5eq). The reaction mixture was stirred for 8 hours. The reaction was quenched with a saturated sodium hydrogen carbonate solution and diluted with diethyl ether and water. The phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 4:1) to give 12 mg 92% of bis-epoxide **60b**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.84 p.p.m. (s, 1H), 4.54 (dd, *J*=11.6, 5.3 Hz, 1H), 4.46 (dd, *J*=13.0, 3.1 Hz, 1H), 4.41 (dd, *J*=5.8, 5.8 Hz, 1H), 4.31 (dd, *J*=18.0, 9.3 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 1H), 2.61-2.52 (m, 2H), 2.56 (s, 1H), 2.48-2.41 (m, 1H), 2.35-2.20 (m, 3H), 2.14 (dd, *J*=11.8, 8.8 Hz, 1H), 2.01 (s, 3H), 1.48 (s, 3H), 0.99 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 170.39 p.p.m., 168.19, 163.27, 162.79, 146.61, 124.51, 115.16, 115.02, 75.84, 68.33, 67.96, 63.64, 60.49, 58.44, 57.37, 52.31, 42.26, 37.67, 37.24, 35.86, 30.53, 30.04, 23.21, 21.37, 18.34, 12.46.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{44}O_{10}Si$ 604.2703; found, 604.2693.

Compound **62**



Oxallyl chloride (5 µL, 58 µmol mmol, 4eq), was dissolved in 0.5 mL DCM and cooled to -78°C. Then DMSO (9 µL, 116 µmol, mmol, 8 eq) was added and the mixture was stirred for 15 minutes. Alcohol **60** (10 mg, 14.6 µmol, 1 eq) dissolved in 0.5 mL DCM was added and the reaction mixture was stirred for one hour. Then triethylamine (25 µL, 175 µmol mmol, 12eq) was added dropwise and after stirring at -78°C for 20 minutes the reaction was warmed to 0°C and stirred for 45 minutes before it was quenched with an ammonium chloride solution. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was filtered over a short pad silica gel to give the corresponding ketone **61** 10 mg 99% which was directly used in the next reaction.

Bromoketone **61** (10 mg, 14.6µmol, 1eq) was dissolved in 500 µL methanol and cooled to -20°C. Then sodium borohydride (73 µmol, 3 mg, 5 eq) was added in one portion. The reaction mixture was stirred at this temperature for one hour before it was quenched with water and diluted with diethyl ether. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 4:1) to give 9 mg 88% of inverted bromohydrine **62**.

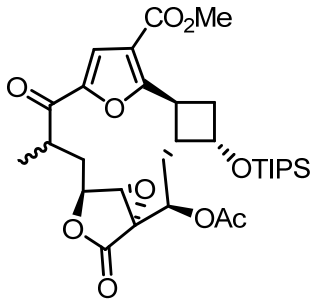
^{1}H-NMR (400MHz, $CDCl_3$): δ= 6.62 p.p.m. (s, 1H), 4.73 (dd, *J*=11.6, 4.5 Hz, 1H), 4.62 (d, *J*=4.8 Hz, 1H), 4.47 (dd, *J*=6.2, 6.2 Hz, 1H), 4.10 (dd, *J*=18.1, 9.1 Hz, 1H), 3.78 (s, 3H), 3.12-3.05 (m, 2H), 2.83-2.73 (m, 2H), 2.64 (s, 1H), 2.42-2.15 (m, 4H), 2.04 (s, 3H), 1.90 (s, 3H), 0.99 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 169.73 p.p.m., 167.02, 162.45, 147.51, 128.40, 114.12, 111.74, 76.30, 75.84, 69.03, 67.97, 67.50, 64.07, 58.58, 51.83, 40.92, 40.13, 37.35, 35.11, 29.22, 28.43, 21.02, 18.05, 12.03.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{45}O_{10}BrSi$ 684.1965; found, 684.1974.

$[\alpha]_D$= +58(c 0.5g/100mL, $CHCl_3$).

Compound **64**



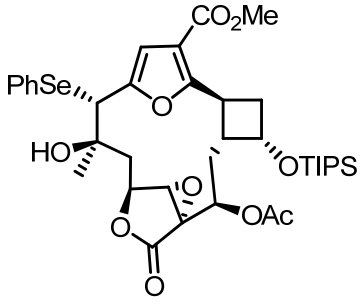
Bromohydrine **62** (8 mg, 12µmol, 1eq) was dissolved in 1 mL THF. Sodium hydride (60% mineral oil suspension, (1 mg, 26µmol, 2 eq) was added in one portion. The reaction was quenched after 25 minutes with water the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 5 mg, 72% of ketone **64** as amixture of diastereomers.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.42 p.p.m. (s, 1H), 4.61 (dd, *J*=12.0, 4.9 Hz, 1H), 4.42 (m, 1H), 3.97 (s, 1H), 3.82 (m, 1H), 3.77 (s, 3H), 3.20 (m, 1H), 2.99 (m, 1H), 2.78 (m, 1H), 2.55 (ddd, *J*=14.7, 8.3, 7.9), 2.48 (m, 1H), 2.46 (m, 1H), 2.39 (m, 1H), 2.11 (s, 3H), 1.92 (ddd, *J*=14.7, 5.7, 3.4 Hz, 1H), 1.88 (s, 1H), 1.26 (d, *J*=7.6 Hz, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 189.48 p.p.m., 170.53, 168.11, 165.82, 162.81, 150.02, 119.01, 116.66, 76.46, 70.27, 68.10, 62.13, 58.14, 52.43, 41.48, 36.54, 36.34, 35.94, 30.39, 21.29, 15.40.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{44}O_{10}Si$ 604.2703; found, 604.2712.

Compound **64a**



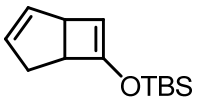
Epoxide **60a** (7 mg, 11µmol, 1eq) was dissolved in 500µL ethanol. The solution was cooled to 0°C and diphenyl diselenide (14µmol, 4 mg, 1.2 eq) was added. Then in one portion sodium borohydride (28 µmol, 1mg, 2.4 eq) was added and the reaction mixture was stirred at 0°C for 1.5 hours. The reaction was quenched with water, diluted with diethyl ether and the phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethylacetate 5:1) to give 7 mg, 84% of alcohol **64a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.52-7.49 p.p.m. (m, 2H), 7.29-7.24 (m, 3H), 6.90 (s, 1H), 4.86 (dd, *J*=12.6, 5.2 Hz, 1H), 4.74-4.70 (m, 1H), 4.72 (s, 1H), 4.50-4.46 (m, 1H), 4.07 (dd, *J*=19.2, 9.8 Hz, 1H), 3.83 (s, 3H), 3.10-3.03 (m, 1H), 2.98 (s, 1H), 2.93 (s, 1H), 2.60 (ddd, *J*=14.9, 9.1, 6.2 Hz, 1H), 2.27-2.23 (m, 2H), 2.17 (d, *J*=2.2 Hz, 2H), 2.11 (s, 3H), 1.87 (ddd, *J*=14.5, 7.6, 2.8 Hz, 1H), 1.25 (s, 3H), 1.06 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 169.97 p.p.m., 168.27, 163.60, 161.77, 152.72, 133.40, 129.70, 128.90, 128.43, 114.63, 112.21, 75.89, 73.39, 69.31, 68.63, 63.07, 59.12, 56.61, 51.77, 40.17, 39.71, 37.29, 36.35, 29.22, 21.06, 18.09, 12.44.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{37}H_{50}O_{10}SSeSi$ 762.2338; found, 762.2327.

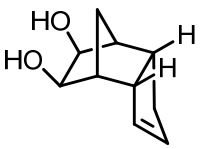
(Bicyclo[3.2.0]hepta-2,6-dien-6-yloxy) (*tert*-butyl)dimethylsilane **65**



To a solution of **15** (1.00 g, 9.24 mmol, 1eq.) in 40 mL dry THF at -78°C was slowly added TBSOTf (6.4 mL, 27.7 mmol, 3eq.). To this mixture at -78°C was rapidly added LiHMDS (1M in hexane, 46 mL, 46 mmol, 5eq.). The reaction mixture was stirred for one hour at -78°C, and then quenched with saturated NH_4Cl solution and extracted two times with diethylether (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was filtered over silica gel with (hexane/ethylacetate 20:1 and 5% triethylamine) and was then further purified via a bulb to bulb distillation to yield 95% 1.95 g of pure **65**.

^{1}H-NMR: δ 5.90-5.85 (m, 1H), 5.62-5.57 (m, 1H), 4.99 (s, 1H), 3.51-3.44 (m, 1H), 3.25-3.20 (m, 1H), 2.46-2.17 (m, 2H), 0.95 (s, 9H), 0.19 (s, 6H).
^{13}C-NMR: δ 134.97, 130.52, 111.52, 49.09, 45.52, 30.77, 26.04, -4.17, -4.33.
HRMS (EI) *m/z* calcd for $C_{13}H_{22}OSi$ 222.3987, found 222.3982.

(4,7-Methano-1*H*-indene-5,6-diol, 3a,4,5,6,7,7a-hexahydro-, (3aα,4β,5α,6α,7β,7aα) **68**



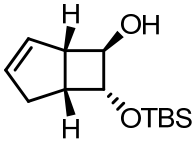
To a solution of **65** (743 mg, 3.3 mmol, 1eq.) in *t*BuOH:H_2O (1:1, 30 mL) at 0°C was added OsO_4 (4 mg, 0.016 mmol, 0.5mol%) and *N*-morpholine-*N*-oxid (390 mg, 3.3 mmol, 1eq.). The reaction mixture was stirred for 20 hours, quenched with an aqueous sodium thiosulfate solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure. Crude **68** was purified by chromatography (silica gel, hexane/ethyl acetate 1:1) to yield 488 mg 89% of pure **68**.

^{1}H-NMR: δ 5.45-5.37 (m, 2H), 3.61 (d, *J* = 5.38 Hz, 1H), 3.52 (d, *J* = 5.56 Hz, 1H), 2.94-2.88 (m, 1H), 2.69-2.59 (m, 2H OH broad), 2.42-2.35 (m, 1H), 2.15-2.06 (m, 3H), 1.92 (d, *J* = 4.29 Hz, 1H), 1.70-1.67 (m, 1H), 116-1.12 (m, 1H).

^{13}C-NMR: δ 131.33, 131.13, 71.81, 70.19, 51.29, 48.47, 46.87, 40.92, 35.35, 32.35.

HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_2$ 166.2170, found 166.2178.

(7-(*tert*-butyldimethylsilyloxy)bicyclo[3.2.0]hept-3-en-6-ol) **70**



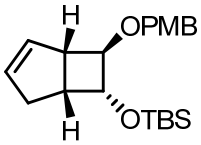
To a solution of **65** (743 mg, 3.3 mmol, 1eq.) in dry THF (7 mL) at 0°C was added 9-BBN (0.5M in THF 6.6 mL, 1eq.). The reaction mixture was warmed to room temperature and stirred for 14 hours. The reaction was quenched with 3mL 0.5M NaOH and 1mL H_20_2 (30%), diluted with brine and extracted two times with diethylether (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under vacuum. Crude **70** was purified by flash column chromatography (hexane/ethylacetate 3:1) to yield 412 mg 52% of pure **70**.

^{1}H-NMR: δ 5.79-5.72 (m, 2H), 4.11 (dd, *J* = 8.96, 4.92 Hz, 1H), 3.59-3.56 (m, 1H), 2.96-2.88 (m, 1H), 2.67-2.60 (m, 2H), 2.25-2.17 (m, 1H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR: δ 134.46, 131.79, 84.38, 74.59, 49.47, 37.69, 26.24, -4.47.

HRMS (EI) *m/z* calcd for $C_{13}H_{24}O_2Si$ 240.4140, found 240.4133.

(*tert*-butyl(-7-(4-methoxybenzyloxy)bicyclo[3.2.0]hept-2-en-6-yloxy)dimethylsilane) **71**



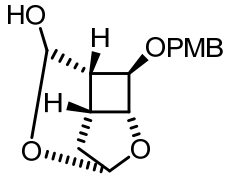
To a solution of alcohol **70** (2.1 g, 8.7 mmol, 1eq.) in dry DCM (10 mL) was added a solution of Bundles reagent (5 g, 17.5 mmol, 2eq.) in hexane (30 mL) and cooled to 0°C. Then 20 mg of camphor sulfonic acid were added and the reaction mixture was stirred over night. The reaction was quenched with saturated $NaHCO_3$ solution, and extracted two times with diethylether (100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **71** was purified by column chromatography (silicagel, hexane/ethylacetate 7:1) to yield 1.63 g 52% of pure **71**.

^{1}H-NMR: δ 7.30-7.26 (m, 2H), 6.92-6.88 (m, 2H), 5.83-5.79 (m, 1H), 5.76-5.71 (m, 1H), 4.44 (s, 2H), 3.83 (s, 3H), 3.49-3.45 (m, 1H), 3.09-2.96 (m, 1H), 2.81-2.69 (m, 2H), 2.38-2.24 (m, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C-NMR: δ 159.71, 134.31, 131.75, 129.82, 129.61, 114.27, 91.22, 74.59, 73.18, 55.86, 49.47, 37.69, 26.24, 18.43, -4.51.

HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_3Si$ 360.5625, found 360.5620.

2-(4-methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-8-ol **73**

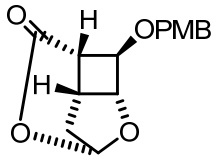


Ozone was bubbled through a solution of **71** (219 mg, 0.89 mmol, 1eq.) in DCM/MeOH 4:1 (5 mL) at -78°C for 10 minutes. To remove unreacted ozone, air was subsequently bubbled through the reaction mixture at the same temperature for 5 minutes. Then thiourea (71 mg, 0.93 mmol, 1.05 eq.) was added and the reaction was warmed to room temperature. The solid was filtered off, the solvents were removed under reduced pressure and crude **73** was submitted to flash column chromatography (silicagel, hexane/ethyl acetate 2:1) to yield 200 mg 81% of pure **73**.

^{1}H-NMR: δ 7.30-7.21 (m, 2H), 6.90-6.82 (m, 2H), 5.67-5.54 (m, 1H), 5.17 (s, 1H), 4.63-4.35 (m, 3H), 3.78 (s, 3H), 3.51-3.22 (m, 1H), 3.06-2.91 (m, 1H), 2.75-2.69 (m, 1H), 2.64-2.55 (m, 1H), 1.55-1.45 (m, 1H).

HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_5$ 278.3004, found 278.2999.

2-(4-methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-3-one **74**

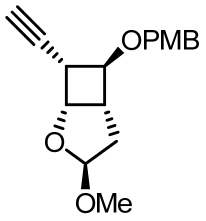


Lactol **73** (200 mg, 0.72 mmol, 1eq.) was dissolved in dry DCM (12 mL) at 0°C. The PCC (170 mg, 0.8 mmol, 1.2 eq.) was added. After 30 minutes another portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was added and a last portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was added after 2 hours. The reaction was then stirred for 24 hours, quenched with saturated $NaHCO_3$ solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **74** was purified by column chromatography (silicagel, hexane/ethyl acetate 2:1) to yield 70 mg 35% of pure **74**.

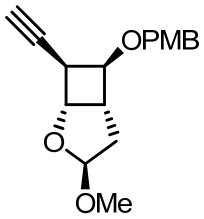
^{1}H-NMR: δ 7.32-7.26 (m, 2H), 6.94-6.89 (m, 2H), 5.99 (dd, *J*=3.08, 1.03 Hz, 1H), 4.62-4.46 (m, 3H), 3.93 (s, 1H), 3.83 (s, 3H), 3.66-3.59 (m, 1H), 3.28-3.24 (m, 1H), 2.11-2.04 (m, 1H), 2.00-1.91 (s, 1H).

HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_5$ 276.2845, found 276.2855.

(1*S*,3*S*,5*S*,6*S*,7*R*)-7-ethynyl-3-methoxy-6-(4-methoxybenzyloxy)-2-oxabicyclo[3.2.0]heptane xxx and (1*S*,3*S*,5*S*,6*S*,7*S*)-7-ethynyl-3-methoxy-6-(4-methoxybenzyloxy)-2-oxabicyclo[3.2.0]heptanes xxx



77



78

Aldehyde **76** (152 mg, 0.5 mmol, 1eq) was dissolved in 12 mL methanol and potassium carbonate (145 mg, 1.04 mmol, 2eq) was added. After stirring at room temperature for 10 minutes Ohira-Bestmann reagent (120 mg, 0.62 mmol, 1.2 eq) was added and the reaction mixture was stirred over night. The reaction was diluted with diethyl ether and quenched with brine. The phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 10:1) to give acetylene **77** and **78** 116 mg 81% combined yield.

77:

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.14 p.p.m. (d, *J*=8.3 Hz, 2H), 6.72 (d, *J*=8.3 Hz, 2H), 5.06 (dd, 5.7, 1.6 Hz, 1H), 4.36-4.30 (m, 3H), 4.04 (dd, *J*=5.9, 3.4 Hz, 1H), 3.64 (s, 3H), 3.18 (s, 3H), 2.91-2.83 (m, 1H), 2.68 (ddd, *J*=9.4, 6.6, 2.6 Hz, 1H), 2.15 (d, *J*=2.5 Hz, 1H), 2.10-2.00 (m, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.83 p.p.m., 130.10, 130.01, 114.28, 109.97, 85.31, 83.74, 72.74, 71.03, 55.75, 55.50, 36.44, 34.37, 30.19.

HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_4$ 288.1361, found 288.1354.

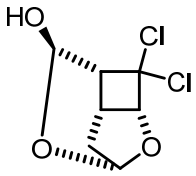
78:

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.34 p.p.m. (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 5.19 (d, *J*=4.0 Hz, 1H), 4.69 (ddd, *J*=7.8, 3.2, 1.1 Hz, 1H), 4.63 (d, *J*=11.4 Hz, 1H), 4.47 (d, *J*=11.4 Hz, 1H), 3.91 (dd, *J*=7.3, 2.5 Hz, 1H), 3.82 (s, 3H), 3.32 (s, 3H), 3.09-3.02 (m, 1H), 2.97-2.93 (m, 1H), 2.35 (d, *J*=2.5 Hz, 1H), 2.27 (dd, *J*=13.5, 9.2 Hz, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.74 p.p.m., 130.08, 129.97, 114.19, 109.25, 83.52, 78.01, 73.37, 70.91, 55.69, 55.04, 40.09, 39.44, 32.24.

HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_4$ 288.1361, found 288.1356.

(5,5-Dichloro-2,9-dioxatricyclo[3.2.2.0^{3,7}]nonan-3-ol) **73a**



See procedure for compound **73.**

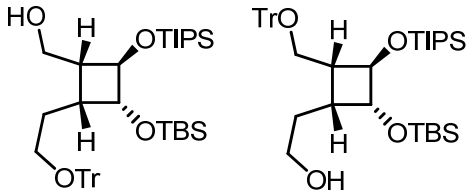
^{1}H-NMR: δ 5.70 (dd, *J* = 3.48, 0.50 Hz, 1H), 5.41 (s, 1H), 4.76-4.73 (m, 1H), 3.62-3.58 (m, 1H), 3.26-3.22 (s, 1H OH, broad), 3.19 (ddd, *J* = 7.39, 4.47, 1.57 Hz, 1H), 2.78 (d, *J* = 12.28 Hz, 1H), 1.70 (ddd, *J* = 12.14, 4.16, 4.16 Hz, 1H)

^{13}C-NMR: δ 101.60, 90.31, 88.38, 82.36, 56.06, 35.22, 31.26.

HRMS (EI) *m/z* calcd for $C_7H_8Cl_2O_3$ 211.0426, found 211.0420.

((3-(*tert*-butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)- cyclobutyl)methanol) **80**

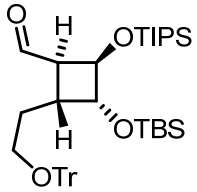
2-((1R,2R,3R,4R)-2-(tert-butyldimethylsilyloxy)-3-(triisopropylsilyloxy)-4-(trityloxymethyl)cyclobutyl)ethanol **81**



Ozone was bubbled through a solution of **65** (385 mg, 1.0 mmol, 1eq.) in DCM/MeOH 4:1 (7 mL) at -78°C for 10 minutes. To remove unreacted ozone air was bubbled through the reaction mixture at the same temperature for 5 minutes. Then $NaBH_4$ (71 mg, 2.0 mmol, 2 eq.) was added and the reaction was warmed to room temperature. The reaction was then stirred for 2 hours, quenched with saturated NH_4Cl solution, and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **79** (330 mg, 0.76 mmol, 1eq.) was directly used in the next step. **79** was dissolved in dry DCM (15 mL) cooled to 0°C and pyridine (250µl, 2.28 mmol, 3eq.) was added at that temperature. To this solution was added dropwise tritylchloride in dry DCM (2 mL) and the reaction was stirred over night. The mixture was quenched with brine and extracted two times with diethylether (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude product was purified by flash column chromatography (silicagel, hexane/ethyl acetate 7:1) to yield 267 mg 52% of **81** and 41 mg 8% of **80**.

^{1}H-NMR: δ 7.54-7.25 (m, 15H), 4.00-3.62 (m, 4H), 3.37-3.14 (m, 2H), 2.34 (ddd, *J* = 16.9, 8.79, 4.23 Hz, 1H), 2.08-1.94 (m, 2H), 1.76-1.61 (m, 1H), 1.69 (s, broad 1H), 1.12 (s, 21H), 0.95 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). HRMS (EI) *m/z* calcd for $C_{41}H_{62}O_4Si_2$ 675.0996, found 675.0989.

(3-(*tert*-butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)-cyclobutanecarbaldehyde) **81a**

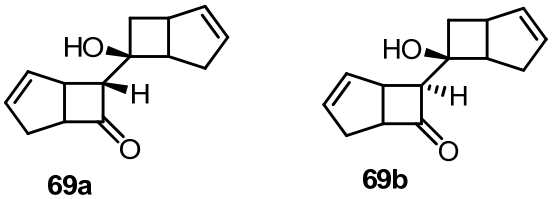


Alcohol **81** (175 mg, 0.26 mmol, 1eq.) was dissolved in ethyl acetate (3 mL) and IBX (218 mg, 0.78 mmol, 3eq.) was added. The suspension was refluxed for 2 hours, and then cooled to room temperature and the solid was filtered off. The organic layer was concentrated, re-dissolved in MeOH (10 mL) and K_2CO_3 (361 mg, 2.6 mmol, 10eq.) was added to the solution. The reaction was stirred for 1.5 hours, diluted with diethylether, the solids filtered off, and extracted with saturated NH_4Cl solution. The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **81a** was purified by flash column chromatography (silicagel, hexane/ethyl acetate 7:1) to yield 152 mg 87% of pure **81a**.

^{1}H-NMR: δ 9.74 (t, *J* = 1.37 Hz, 1H), 4.13-4.05 (m, 1H), 3.77-3.71 (m, 1H), 3.53 (dd, *J* = 9.50, 4.23 Hz, 1H), 3.17-3.05 (m, 1H), 2.86 (t, *J* = 10.16 Hz, 1H), 2.46-2.18 (m, 2H), 1.02 (s, 21H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).

HRMS (EI) *m/z* calcd for $C_{22}H_{45}O_3Si_2$ 413.7619, found 413.7611.

Aldol adduct **69**



69a (±) **69b**

Commercially available ketone **15** in 10 mL THF (250 mg, 2.3 mmol, 1eq) was added to a solution of LHMDS in 7 mL THF (1 M in THF, 3.5 mL, 3.5 mmol, 1.5 eq) at -78°C under argon. After stirring the mixture for 30 minutes at that temperature Davis-oxaziridine (1.1 g, 3.5 mmol, 1.5eq) was added in 5 mL THF. After stirring for 45 minutes the reaction was quenched with a saturated solution of ammonium sulfate and diluted with diethyl ether. The phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 3:1) to give **69a** and 69b 228 mg 92% combined yield.

Cis-isomer **69a**

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.79-5.75 p.p.m. (m, 3H), 5.70-5.68 (m, 1H), 3.70-3.64 (m, 1H), 3.32-3.27 (m, 1H), 2.98-2.91 (m, 3H), 2.63-2.51 (m, 3H), 2.46-2.35 (m, 2H), 1.83 (s, 1H), 1.66 (dd, *J* =13.4, 3.3 Hz, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 215.26 p.p.m., 135.88, 133.01, 132.83, 132.43, 77.62, 75.01, 66.25, 61.26, 45.66, 42.95, 40.63, 39.74, 35.43, 33.08.

HRMS (EI) *m/z* calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1143.

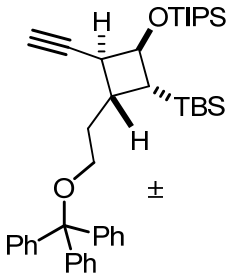
Trans-isomer **69a**

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.72-5.67 p.p.m. (m, 3H), 5.62 (m, 1H), 3.62-3.56 (m, 1H), 3.25-3.20 (m, 1H), 2.94-2.86 (m, 3H), 2.55-2.46 (m, 3H), 2.42-2.28 (m, 2H), 1.78 (d, *J* =1.0 Hz, 1H), 1.57 (dd, *J* =13.0, 2.9 Hz, 1H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 214.92 p.p.m., 136.00, 132.96, 132.93, 132.48, 75.45, 66.24, 61.34, 45.80, 42.95, 40.68, 39.89, 35.39, 32.95.

HRMS (EI) *m/z* calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1141.

tert-butyl(-3-ethynyl-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)cyclobutyl)dimethylsilane **82**



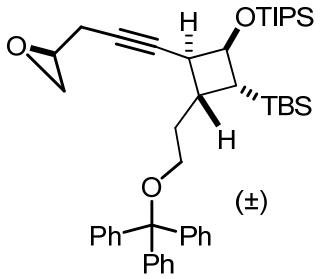
Aldehyde **81a** (1.54 g, 2.28 mmol, 1eq) was dissolved in 20 mL methanol. To this solution potassium carbonate (770 mg, 5.5 mmol, 2.4 eq) was added and stirred for 10 minutes before the Ohira-Bestmann reagent (530 mg, 2.75 mmol, 2.4eq) was added at room temperature. The reaction was stirred for 6 hours diluted with diethyl ether and quenched with a saturated ammonium chloride solution. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 20:1) to give 1.3 g 89% of acetylene **82**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.46-7.43 p.p.m., (m, 6H), 7.32-7.21 (m, 9H), 4.32 (ddd, *J*=8.5, 6.5, 1.1 Hz, 1H), 4.13 (ddd, *J*=7.8, 7.3, 0.7 Hz, 1H), 3.22-3.16 (m, 1H), 3.13-3.07 (m, 1H), 2.85-2.81 (m, 1H), 2.44-2.37 (m, 1H), 2.16 (d, *J*=2.8 Hz,1H), 1.97-1.89 (m, 1H), 1.51-1.41 (m, 1H), 1.09 (d, *J*=2.8 Hz, 20H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 144.34 p.p.m., 128.70, 127.73, 126.88, 86.63, 84.46, 75.22, 74.32, 71.32, 62.31, 39.54, 32.37, 29.20, 25.83, 17.91, 12.06, -4.81, -4.93.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{42}H_{60}O_2Si_2$ 652.4131; found, 652.4127.

tert-butyldimethyl(-3-(3-((S)-oxiran-2-yl)prop-1-ynyl)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)cyclobutyl)silane **84**



Acetylene **82** (1.1 g, 1.64 mmol, 1eq) was dissolved in 6 mL THF and cooled to -78°C. n-butyllithium (1.6M in hexane, 1.45 mL, 2.3 mmol, 1.4 eq) was added and the mixture was stirred at 0°C for 30 minutes before it was cooled again to -78°C. tosyl-glycidol **83** (600 mg, 2.63 mmol, 1.6 eq) was added in 1 mL THF followed by the dropwise addition of borontrifluor etherate (290 µL, 2.3 mmol, 1.4 eq). The reaction was stirred at -78°C for one hour before it was quenched with water. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product **84** 939 mg was directly submitted to the next reaction.

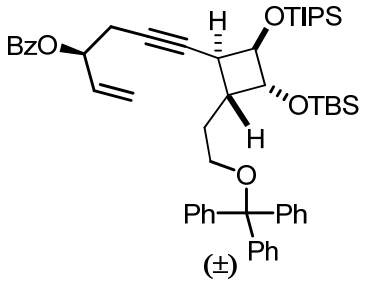
Crude product was dissolved in 15 mL methanol and cooled to 0°C. Potassium carbonate (145 mg, 1.05 mmol) was added and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with ammonium chloride diluted with diethyl ether and the phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 7:1) to give 697 mg 60% of epoxide **84a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.45-7.42 p.p.m. (m, 7H), 7.31-7.20 (m, 8H), 4.28-4.23 (m, 1H), 4.15-4.11 (m, 1H), 3.19-3.13 (m, 1H), 3.12-3.08 (m, 1H), 3.07-3.03 (m, 1H), 2.79 (d, *J*=7.6 Hz, 1H), 2.71 (t, *J*=4.4 Hz, 1H), 2.68-2.65 (m, 1H), 2.62 (ddd, *J*=15.4, 5.0, 2.5 Hz, 1H), 2.40-2.28 (m, 2H), 1.95-1.87 (m, 1H), 1.50-1.41 (m, 1H), 1.07 (s, 20H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 144.41 p.p.m., 128.71, 127.76, 126.85, 86.65, 82.48, 75.35, 74.21, 62.48, 50.33, 46.65, 39.58, 32.64, 29.22, 25.86, 23.06, 22.96, 17.91, 12.05, -4.82, -4.98.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{45}H_{64}O_3Si_2$ 708.4397; found, 708.4389.

(*S*)-6-(-3-(*tert*-butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)cyclobutyl)hex-1-en-5-yn-3-yl benzoate **86**



Trimethylsulfonium iodide (900 mg, 4.4 mmol, 4.4eq) was added to 4 mL THF under argon at -10°C. *n*-Butyllithium (1.6M in hexane, 2.75 mL, 4.4 mmol, 4.4eq) was added dropwise and the mixture was stirred at that temperature for 40 minutes. Epoxide **84a** (770 mg, 1mmol, 1eq) was added in 2 mL THF and the reaction was stirred for 45 minutes and then at room temperature for 20 minutes. The reaction was quenched with brine and diluted with diethyl ether. The phases were separated and the aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product **85** was directly submitted to the next reaction.

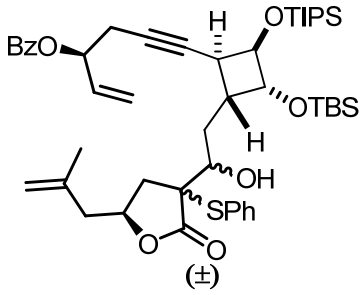
Crude **85** was dissolved in 5 mL pyridine and catalytic DMAP and benzoyl chloride (170µL, 1.5 mmol, 1.4 eq) were added. The reaction was stirred over night, quenched with 1M HCl diluted with diethyl ether and the phases were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 7:1) to give 749 mg 89% of **86**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 8.17-8.15 p.p.m. (m, 2H), 8.05-8.03 (m, 2H), 7.69-7.65 (m, 1H), 7.54-7.20 (m, 15H), 6.04 (dddd, *J*=17.2, 10.7, 6.1, 2.0 Hz, 1H), 5.58-5.53 (m, 1H), 5.40-5.34 (m, 1H), 5.21-5.18 (m, 1H), 4.26 (dd, *J*=7.7, 7.7 Hz, 1H), 4.12 (dd, *J*=7.6, 7.6 Hz1H), 3.21-3.05 (m, 2H), 2.78 (d, *J*=8.3 Hz, 1H), 2.75-2.61 (m, 2H), 2.30-2.25 (m, 1H), 1.95-1.87 (m, 1H), 1.50-1.41 (m, 1H), 1.07 (s, 20H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 166.06 p.p.m., 144.78, 135.88, 135.00, 133.40, 131.08, 130.80, 130.19, 129.30, 129.15, 128.71, 128.13, 12727, 117.59, 87.04, 83.20, 78.25, 75.68, 75.01, 73.86, 73.77, 62.89, 40.23, 33.07, 29.62, 26.27, 25.81, 18.32, 12.47, -4.40, -4.58.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{53}H_{70}O_5Si_2$ 842.4761; found, 842.4755.

(*S*)-6-(-3-(*tert*-butyldimethylsilyloxy)-2-(2-hydroxy-2-((S)-5-(2-methylallyl)-2-oxo-3-(phenylthio)tetrahydrofuran-3-yl)ethyl)-4-(triisopropylsilyloxy)cyclobutyl)hex-1-en-5-yn-3-yl benzoate **87**



Benzoate **86** (0.5g, 0.59 mmol, 1eq) was dissolved in 10 mL DCM and cooled to -78°C. To this solution was slowly added diethyl aluminum chloride (1M hexane, 1.2 mL, 1.18 mmol, 2eq). The mixture was stirred at -78°C for 50 minutes before it was quenched with a saturated solution of sodium hydrogen carbonate. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product 306 mg was dissolved in 2 mL DCM at room temperature. Dess-Martin periodinane (431 mg, 1.02 mmol, 2eq) was added together with sodium hydrogen carbonate (260 mg, 3.06 mmol, 6eq). The reaction was quenched after one hour with water and diluted with diethyl ether. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude aldehyde was filtered over a short pad of silica gel before it was directly used in the next reaction.

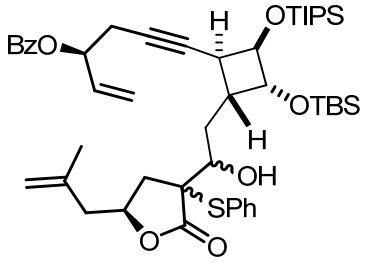
Diisopropylamine (240µL, 1.71 mmol, 3.35eq) was dissolved in 0.5 mL THF and cooled to 0°C. *n*-butyllithium (1.6M in hexane, 1 mL, 1.71 mmol, 3.35 eq) was added dropwise and the mixture was stirred at 0°C for 30 minutes. The LDA solution was then cooled to -78°C and lactone **39** (425 mg, 1.71 mmol, 3.35eq) was added in 1 mL THF. The reaction mixture was stirred at -78° for 1.25 hours before the aldehyde was added in 1 mL THF. The reaction was quenched after stirring at that temperature for 45 minutes with water and diluted diethyl ether. The aqueous phase was extracted three times with diethyl ether, the combined organic layers were washed with brine, dried over magnesium sulfate, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (hexane:ethylacetate 5:1) to give products **87a** and **87b** each as diastereomeric mixtures in 189 mg 44% yield respectively.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 808-8.05, p.p.m. (m, 2H), 7.631-7.53 (m, 3H), 7.46-7.40 (m, 3), 7.38-7.33 (m, 2H), 6.07-6.00 (m, 1H), 5.59-5.55 (m, 1H), 5.43-5.38 (m, 1H), 5.28-5.24 (m, 1H), 4.86-4.71 (m, 2H), 4.56-4.49 (m, 1H), 4.36-4.23 (m, 1H), 4.19-4.07 (m, 1H), 3.82-3.78 (m, 1H), 2.71-2.59 (m, 1H), 2.51-2.30 (m, 2H), 2.25-2.07 (m, 2H), 2.01-1.79 (m, 2H), 1.66 (s, 3H), 1.05 (s, 20H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 175.73 p.p.m., 140.53, 137.25, 133.26, 132.77, 130.44, 130.08, 129.67, 129.23, 129.11, 128.36, 117.07, 113.79, 82.11, 76.18, 75.84, 75.74, 75.02, 74.53, 74.28,

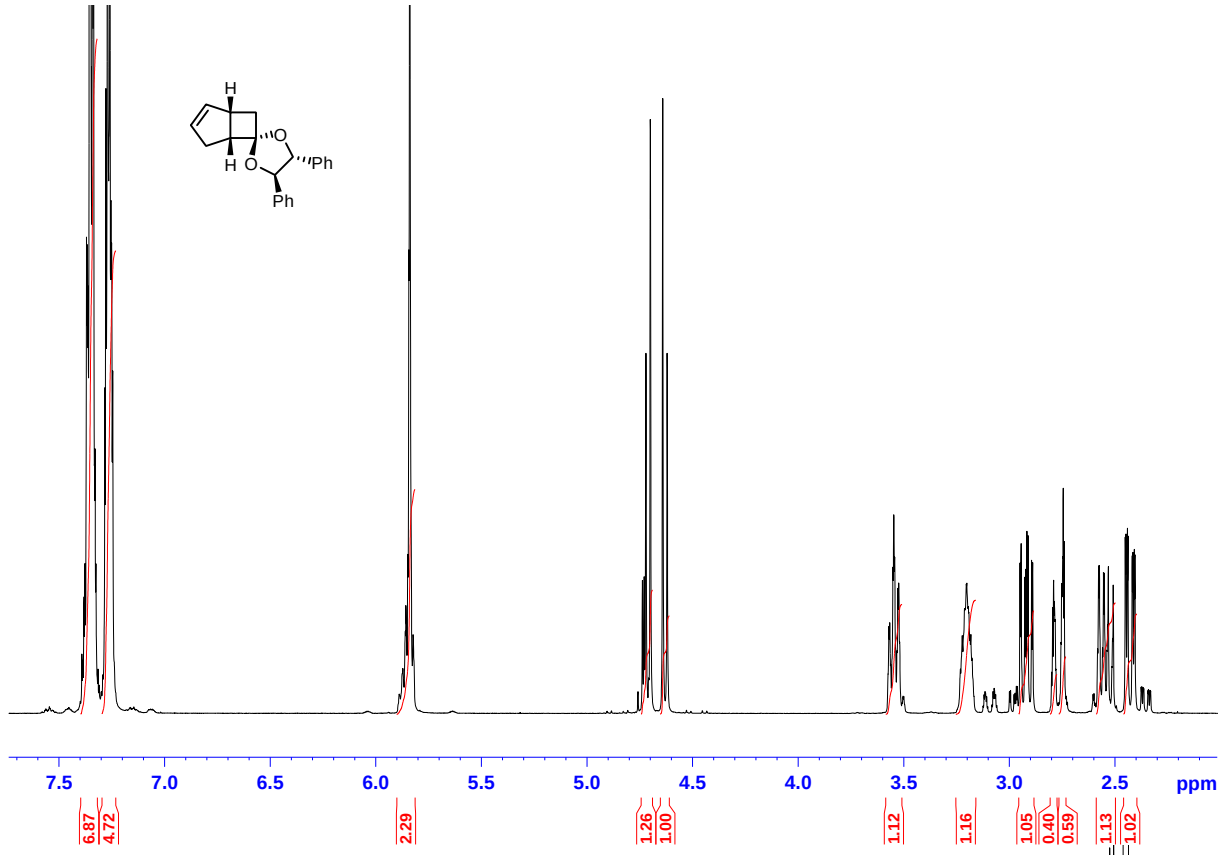
73.87, 73.36, 43.88, 40.75, 40.39, 39.44, 37.85, 37.01, 35.80, 33.19, 32.53, 30.96, 29.73, 25.94, 25.76, 25.40, 23.27, 22.71, 17.94, 11.96, -4.56, -5.02.

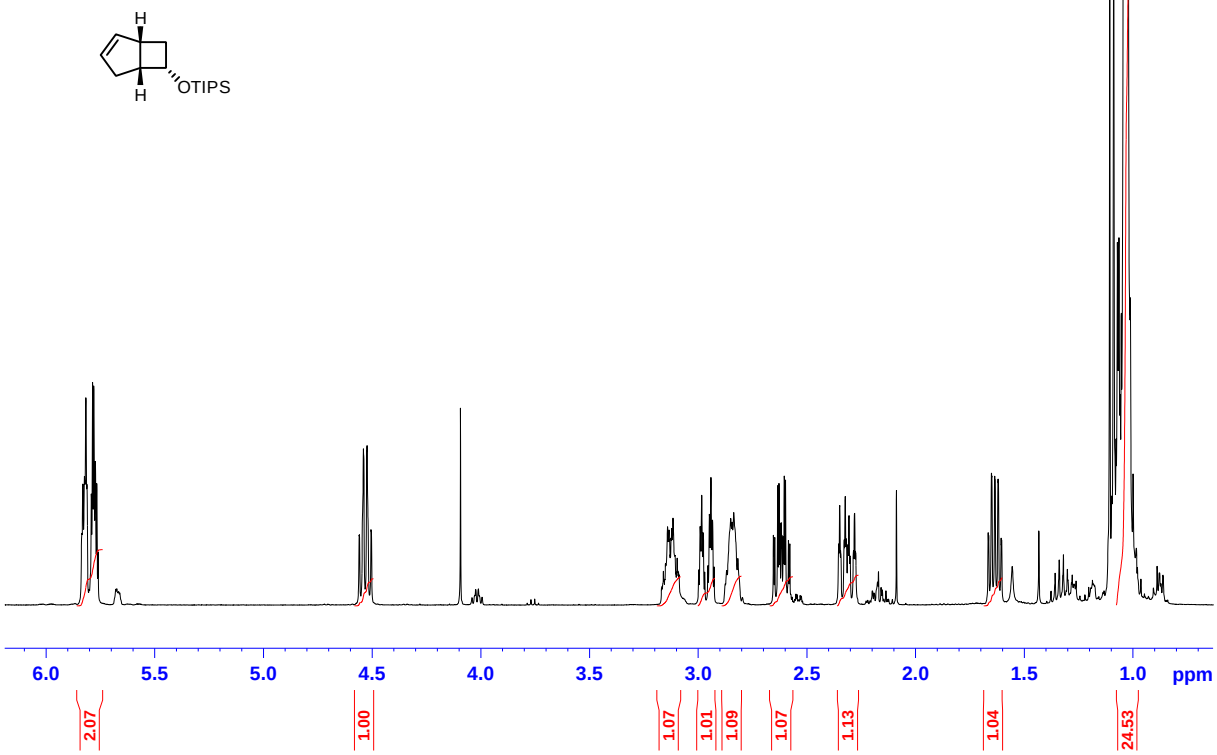
HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{48}H_{70}O_7SSi_2$ 846.4380; found, 846.4371.

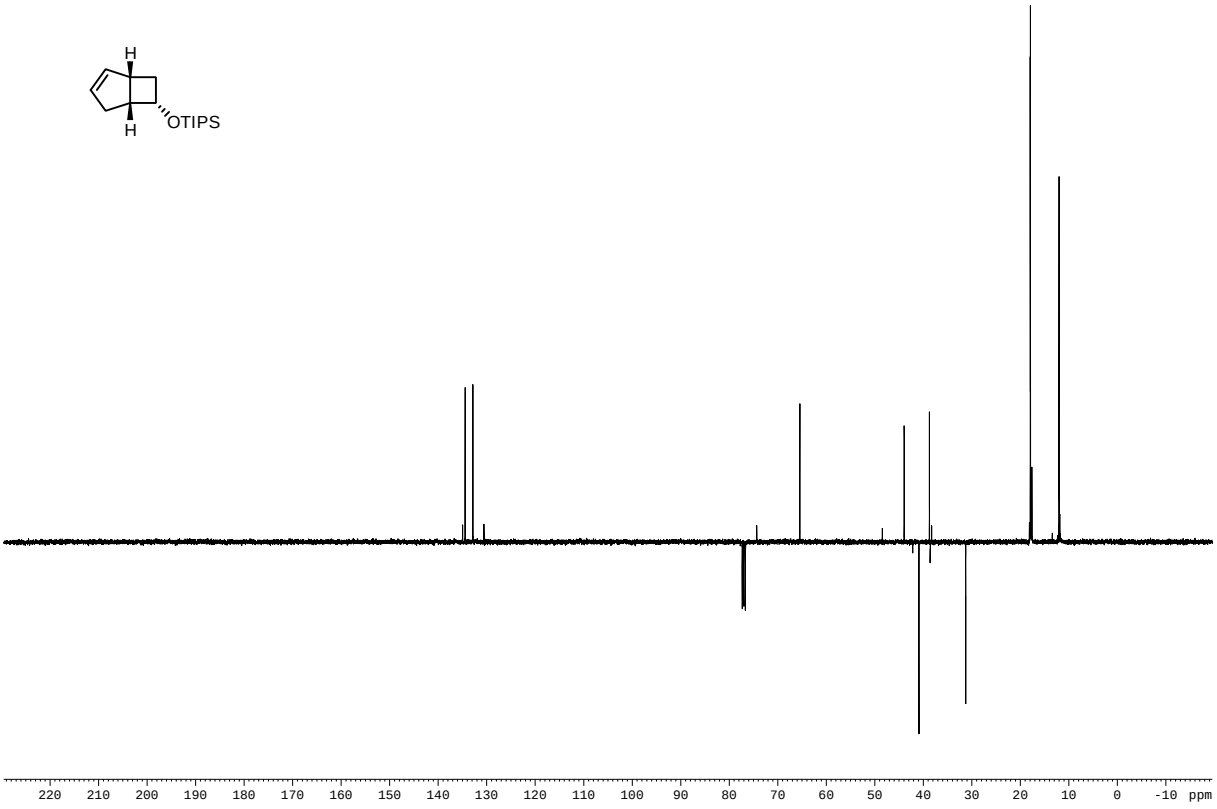


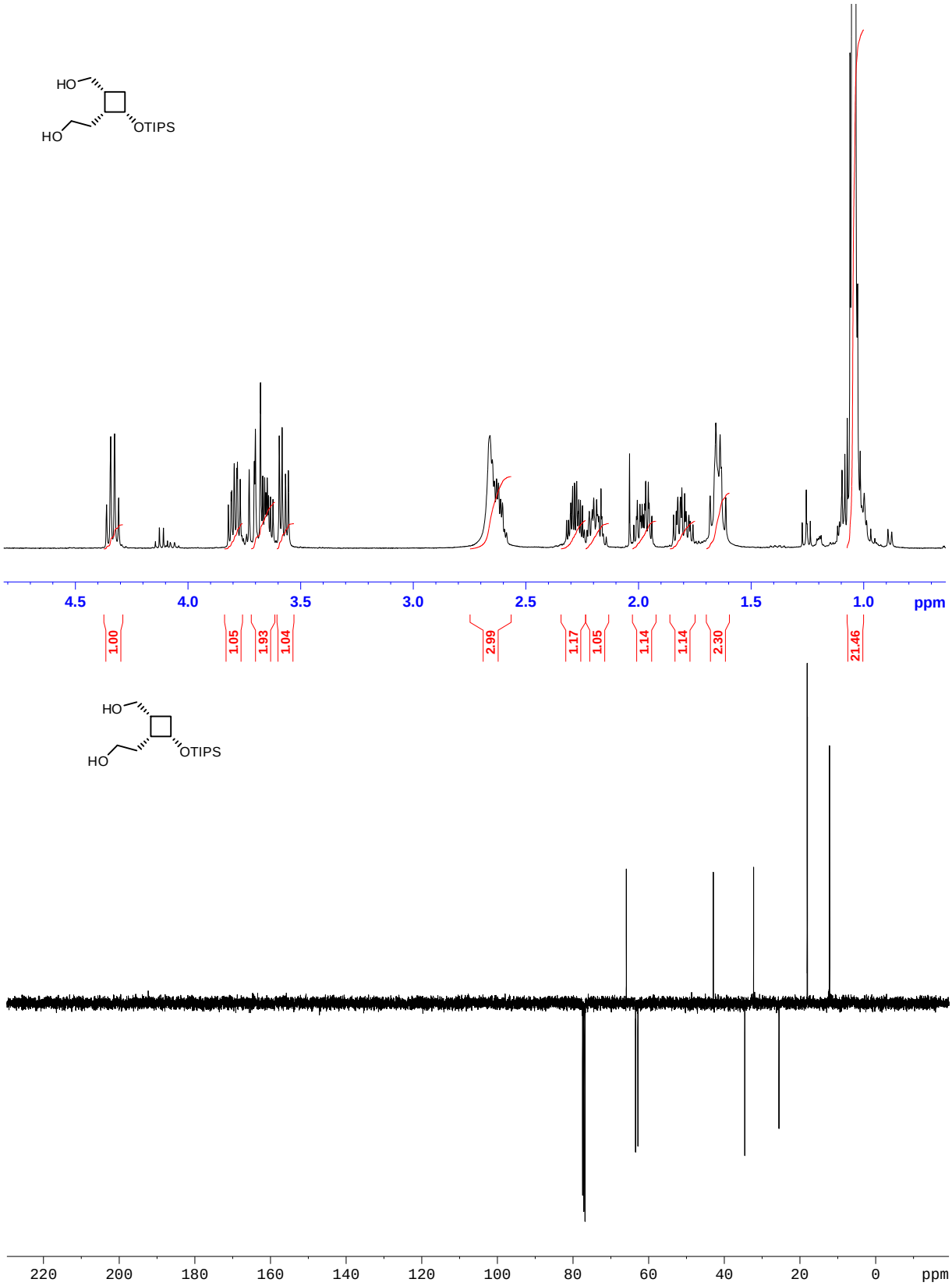
^{1}H-NMR (400MHz, $CDCl_3$): δ= 8.08-8.05 p.p.m., (m, 2H), 7.57-7.53 (m, 3H), 7.45-7.38 (m, 3H), 7.36-7.32 (m, 2H), 6.05-5.98 (m, 1H), 5.61-5.57 (m, 1H), 5.40 (dt, *J*=17.4, 1.3 Hz, 1), 5.26 (dt, *J*=10.6, 1.3 Hz, 1H), 4.81 (t, *J*=1.5 Hz, 1H), 4.65 (s, 1H), 4.58-4.52 (m, 1H), 4.29-4.26 (m, 1H), 4.17-4.12 (m, 1H), 3.92 (ddd, *J*=10.5, 4.4, 1.4 Hz, 1H), 2.81-2.76 (m, 1H), 2.70-2.59 (m, 2H), 2.38-2.34 (m, 1H), 2.33-2.28 (m, 1H), 2.17 (s, 3H), 2.03-1.96 (m, 1H), 1.86 (dd, *J*=14.3, 4.9 Hz, 1H), 1.05 (s, 20H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

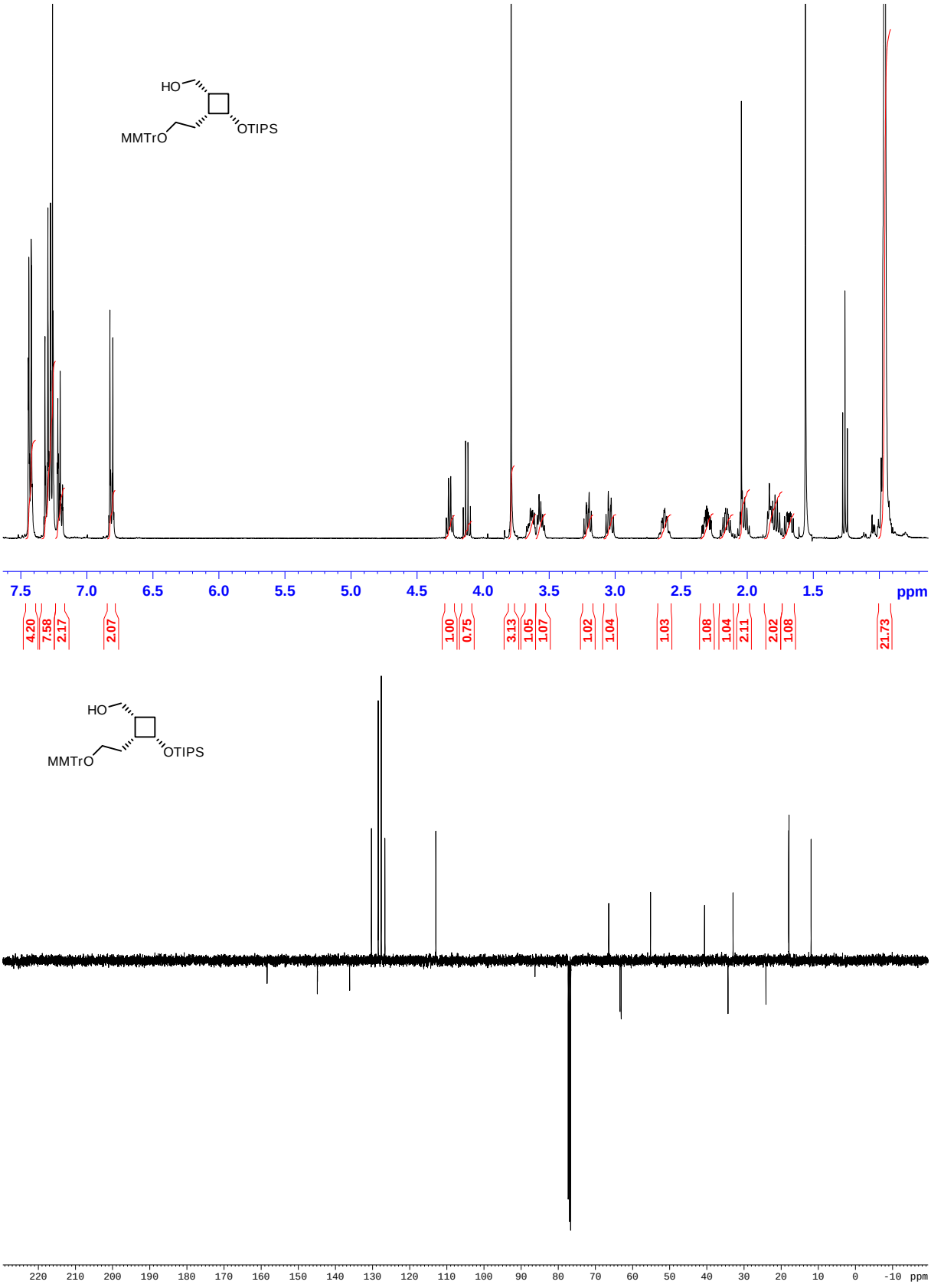
^{13}C-NMR (100MHz, $CDCl_3$): δ= 171.47 p.p.m., 140.53, 137.01, 136.80, 135.37, 133.26, 130.06, 129.67, 129.18, 128.53, 117.54, 114.02, 75.91, 75.79, 74.99, 74.75, 74.14, 73.46, 73.26, 72.95, 70.80, 43.71, 41.19, 33.17, 32.78, 29.75, 25.87, 25.43, 22.67, 17.84, 14.18, 12.17, 12,02, -4.67, -4.82.

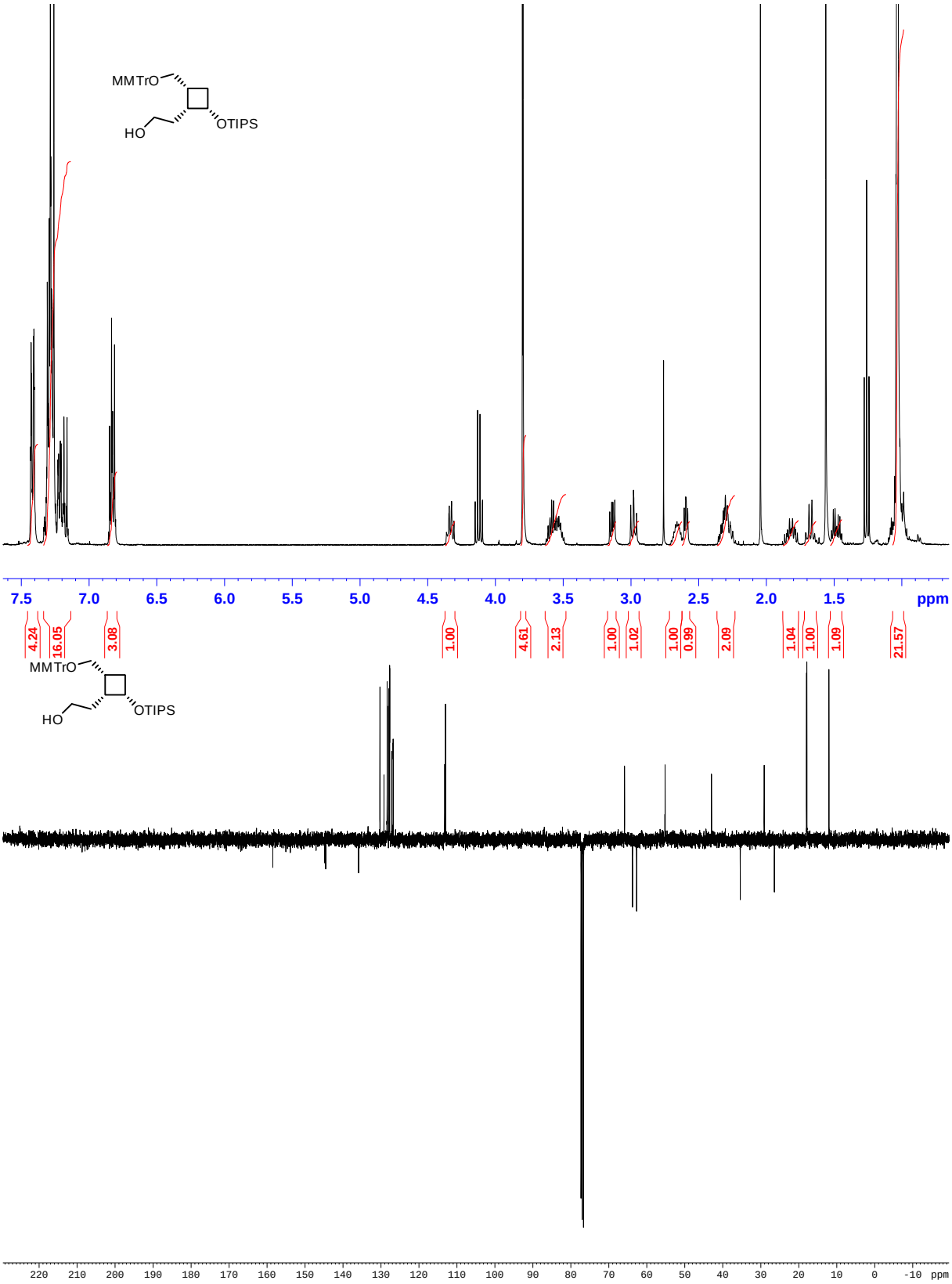

H
H
O
O
Ph
Ph
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
6.87
4.72
2.29
1.26
1.00
1.12
1.16
1.05
0.40
0.59
1.13
1.02

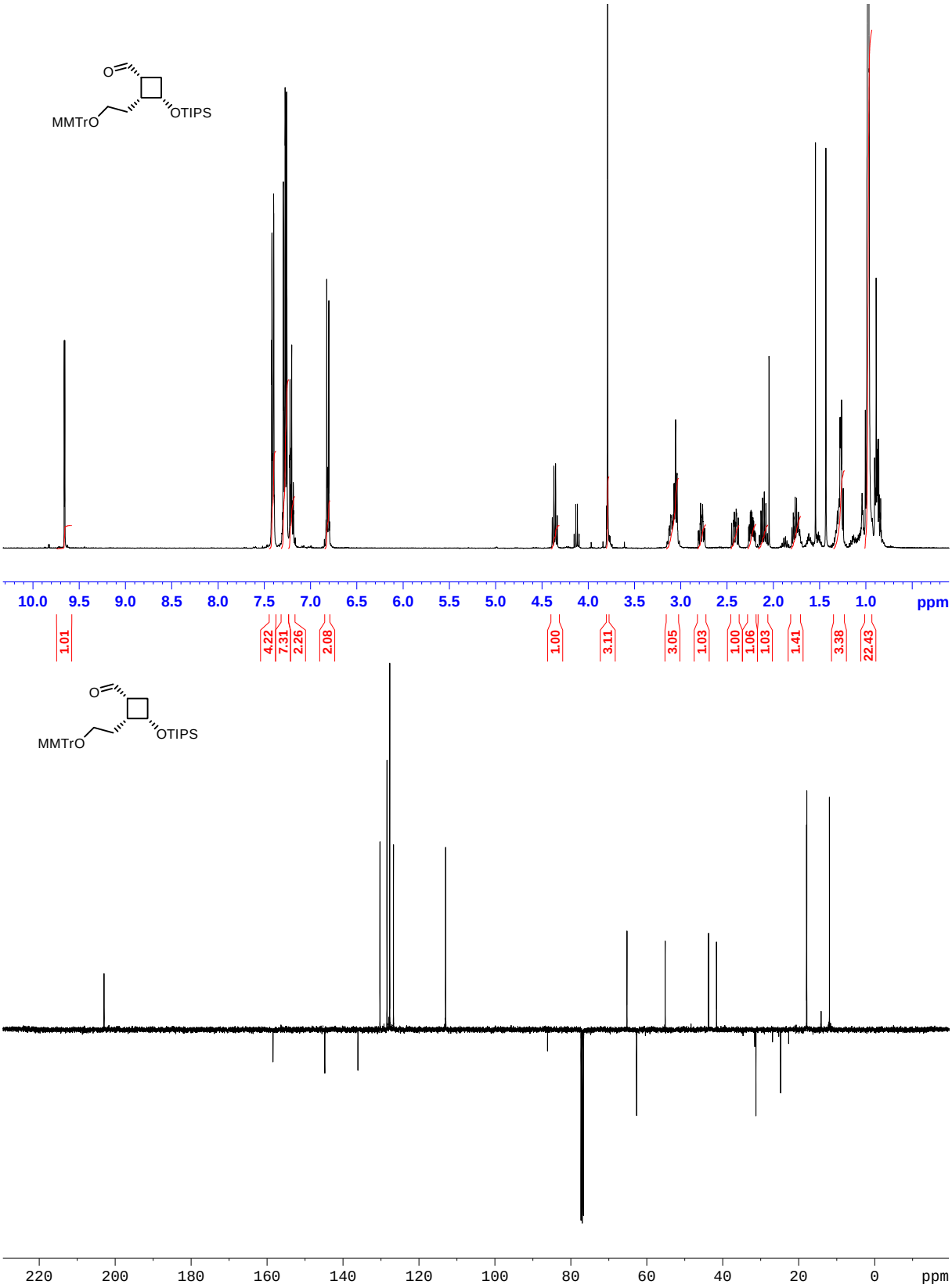

H
H
OTIPS
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.07
1.00
1.07
1.01
1.09
1.07
1.13
1.04
24.53

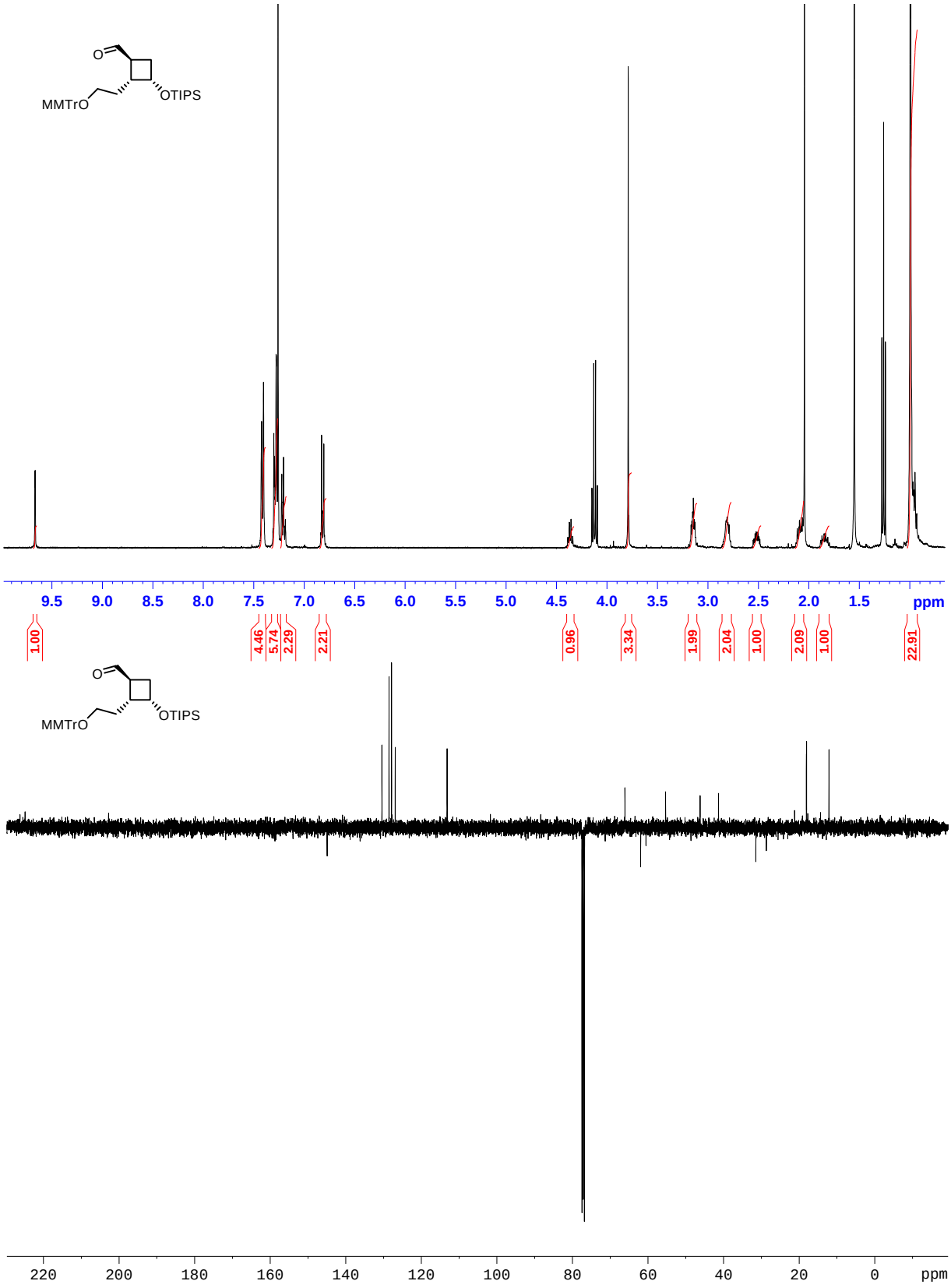

H
H
OTIPS
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

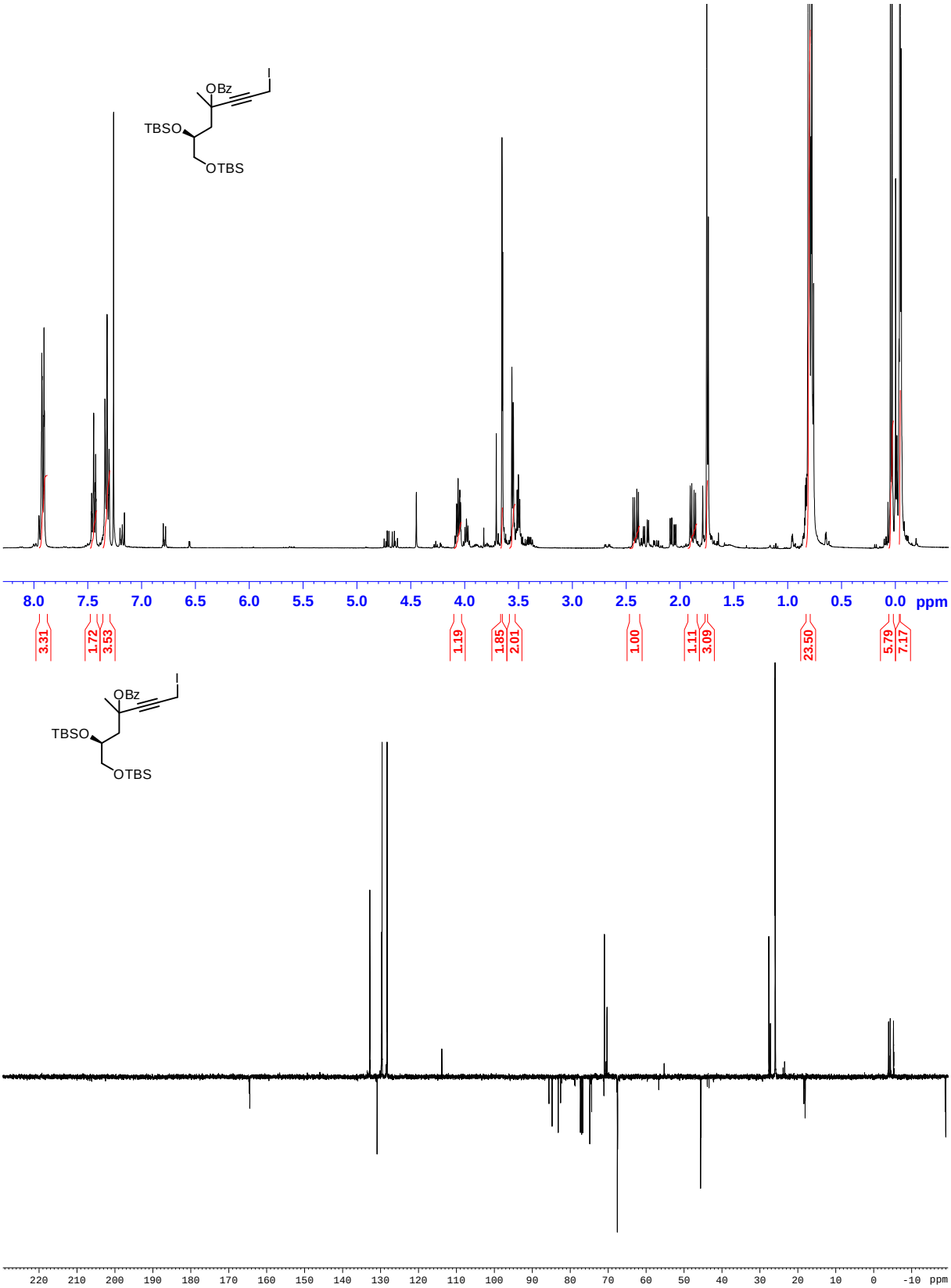

HO
HO
OTIPS
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.05
1.93
1.04
2.99
1.17
1.05
1.14
1.14
2.30
21.46
HO
HO
OTIPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

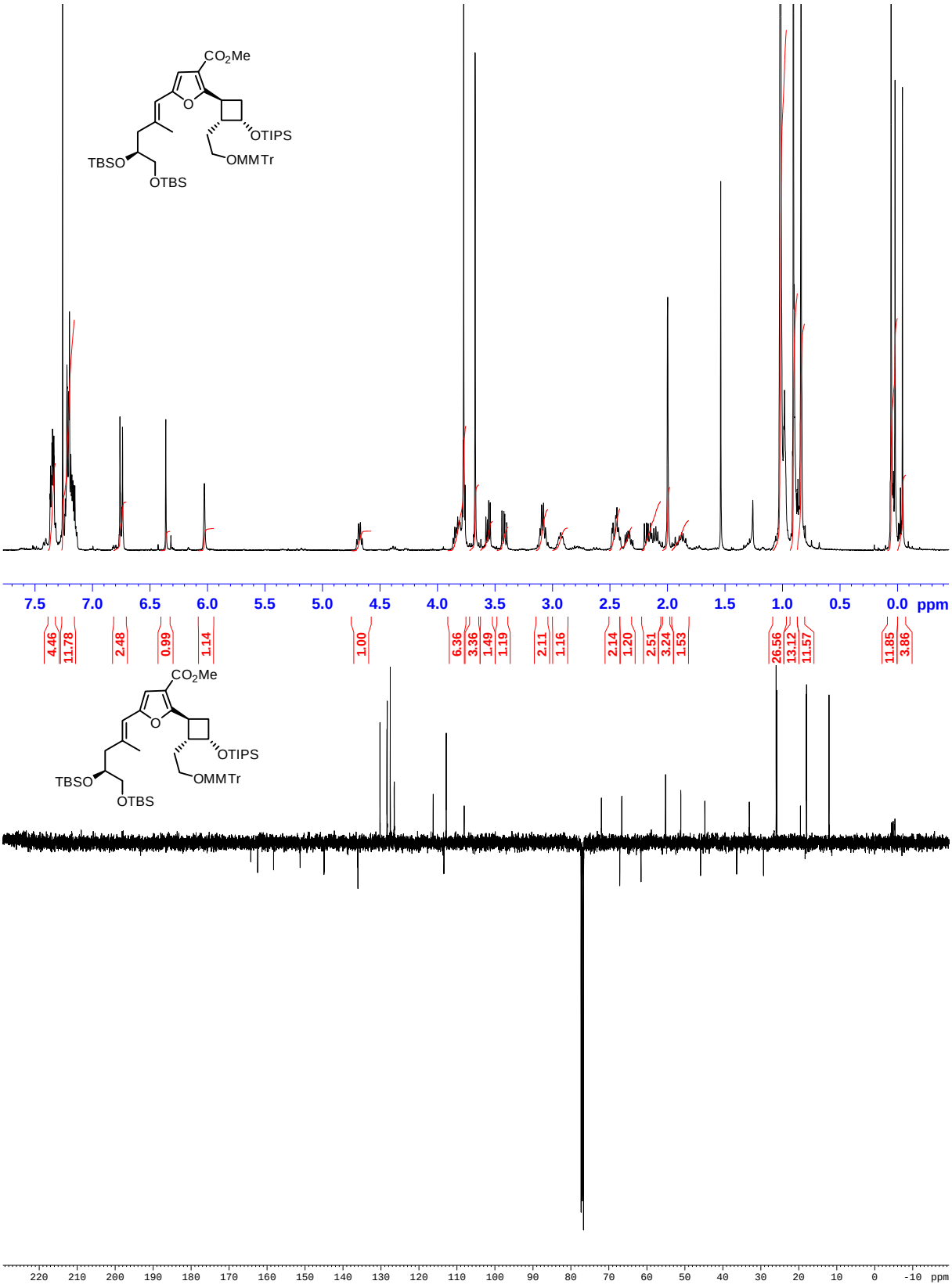

HO
MMTrO
OTIPS
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
4.20
7.58
2.17
2.07
1.00
0.75
3.13
1.05
1.07
1.02
1.04
1.03
1.08
1.04
2.11
2.02
1.08
21.73
HO
MMTrO
OTIPS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

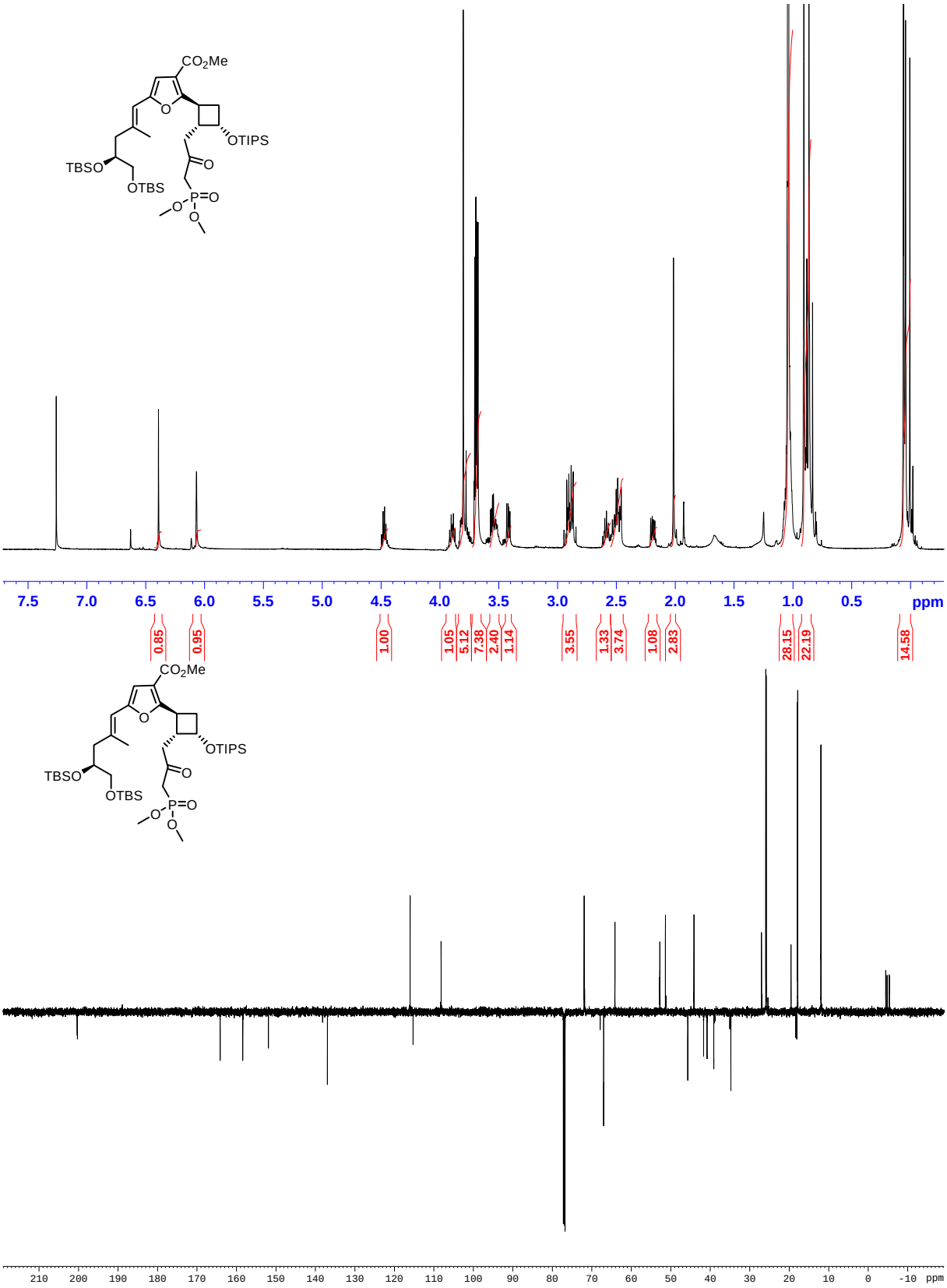

MMTrO
HO
OTIPS
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
4.24
16.05
3.08
1.00
4.61
2.13
1.00
1.02
1.00
0.99
2.09
1.04
1.00
1.09
21.57
MMTrO
HO
OTIPS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

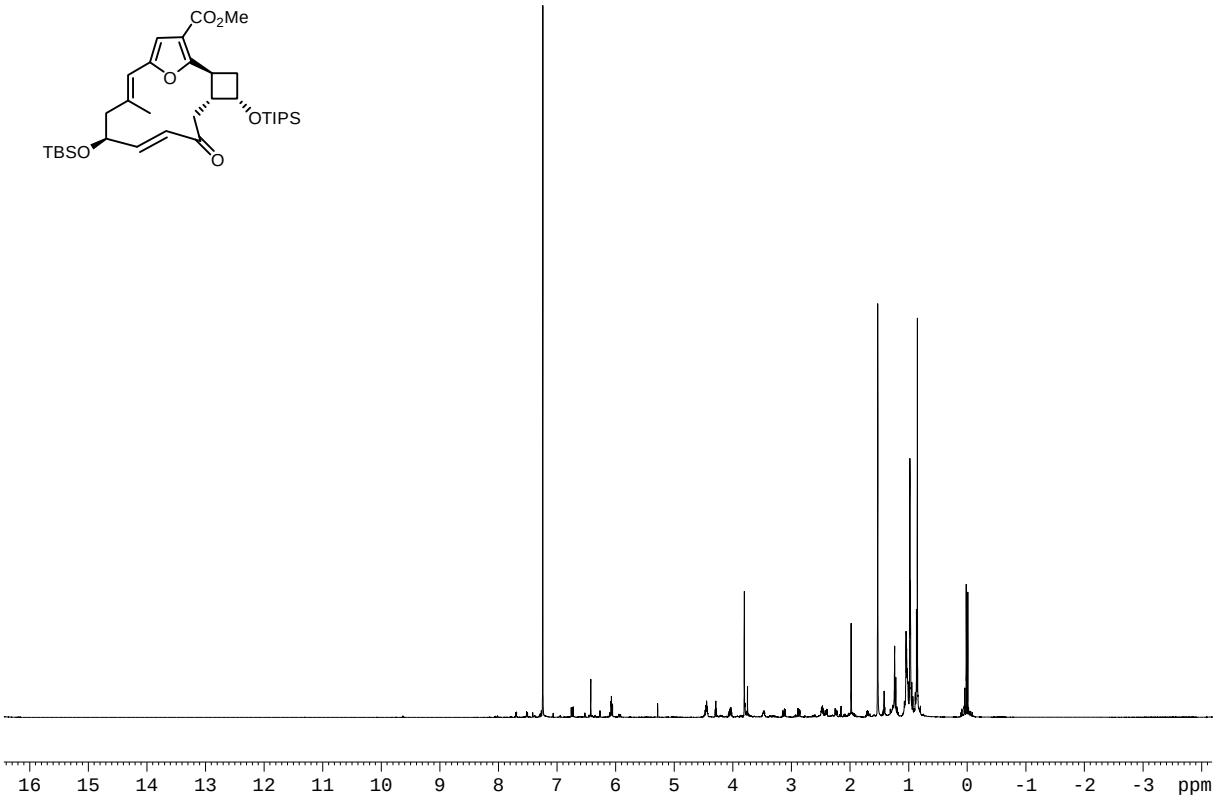

O
MMTrO
OTIPS
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.01
4.22
7.31
2.26
2.08
1.00
3.11
3.05
1.03
1.00
1.06
1.03
1.41
3.38
22.43
O
MMTrO
OTIPS
220 200 180 160 140 120 100 80 60 40 20 0 ppm

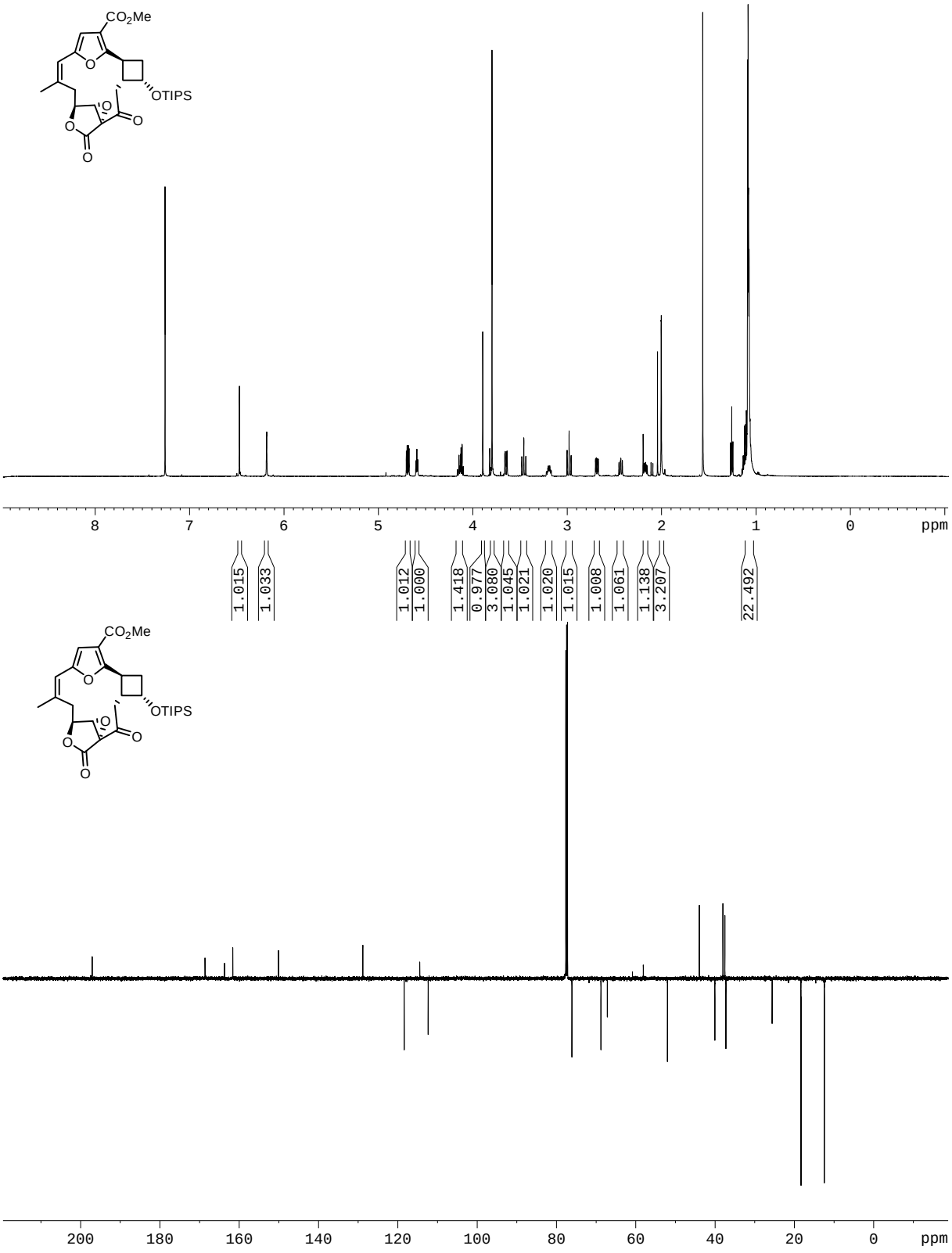

O
MMTrO
OTIPS
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
4.46
5.74
2.29
2.21
0.96
3.34
1.99
2.04
1.00
2.09
1.00
22.91
O
MMTrO
OTIPS
220
200
180
160
140
120
100
80
60
40
20
0
ppm

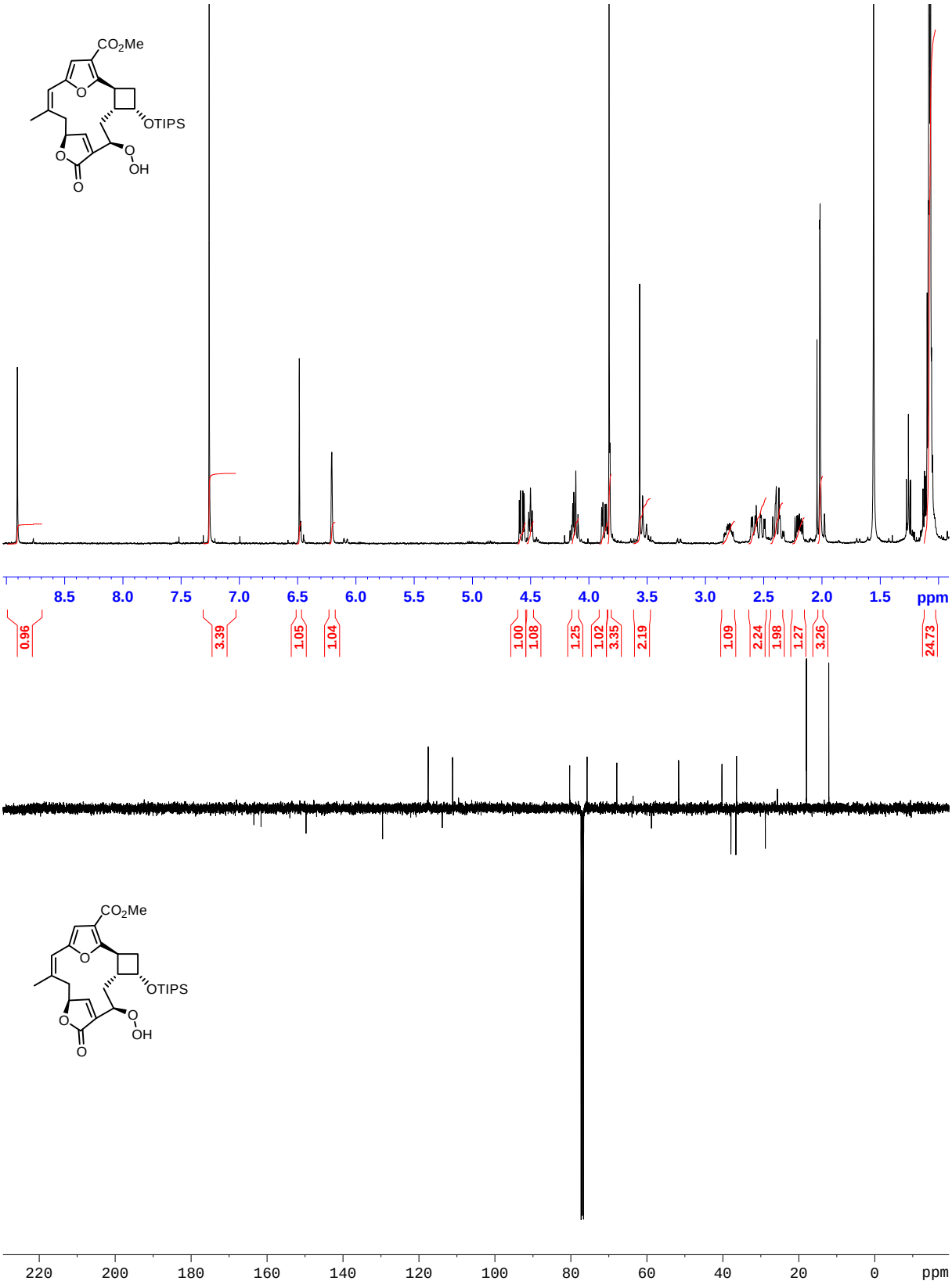

OBz
TBSO
OTBS
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.31 1.72 3.53 1.19 1.85 2.01 1.00 1.11 3.09 23.50 5.79 7.17
OBz
TBSO
OTBS
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

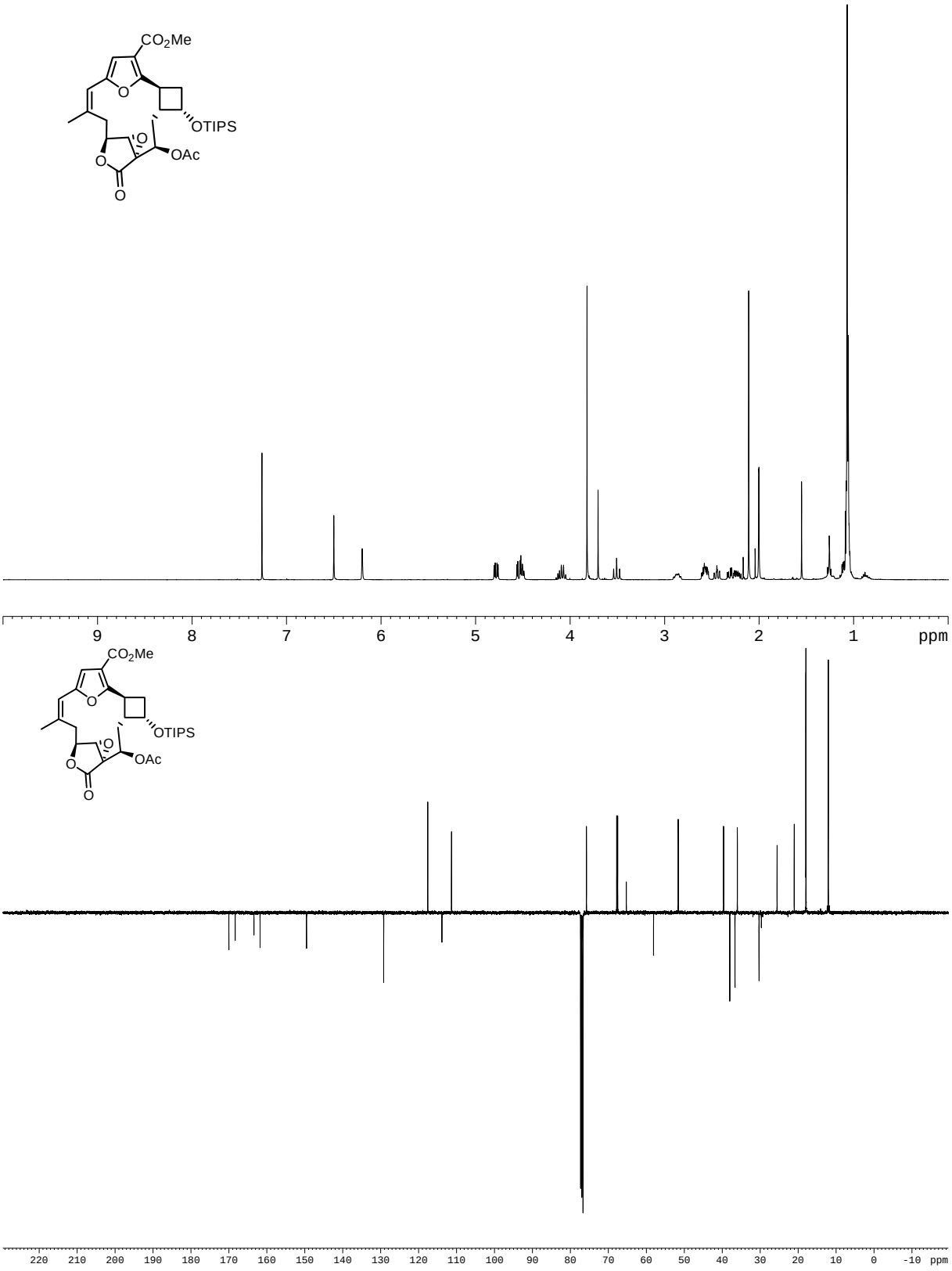

CO2Me
O
OTIPS
OMMTr
TBSO
OTBS
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
4.46 11.78 2.48 0.99 1.14 1.00 6.36 3.36 1.49 1.19 2.11 1.16 2.14 1.20 2.51 3.24 1.53 26.56 13.12 11.57 11.85 3.86
CO2Me
O
OTIPS
OMMTr
TBSO
OTBS
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

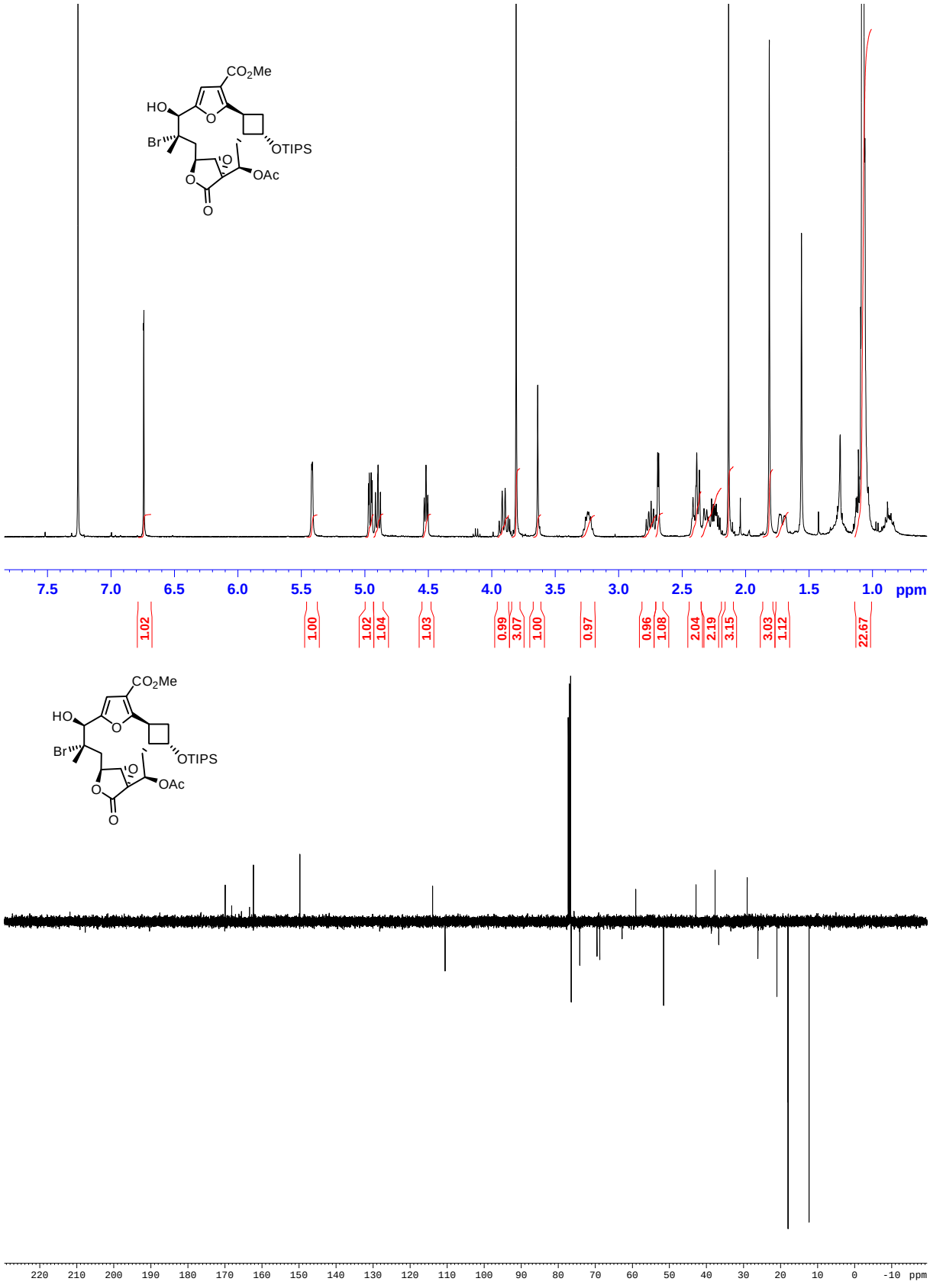

CO2Me
O
OTIPS
TBSO
OTBS
O
P=O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.85
0.95
1.00
1.05
5.12
7.38
2.40
1.14
3.55
1.33
3.74
1.08
2.83
28.15
22.19
14.58
CO2Me
O
OTIPS
TBSO
OTBS
O
P=O
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

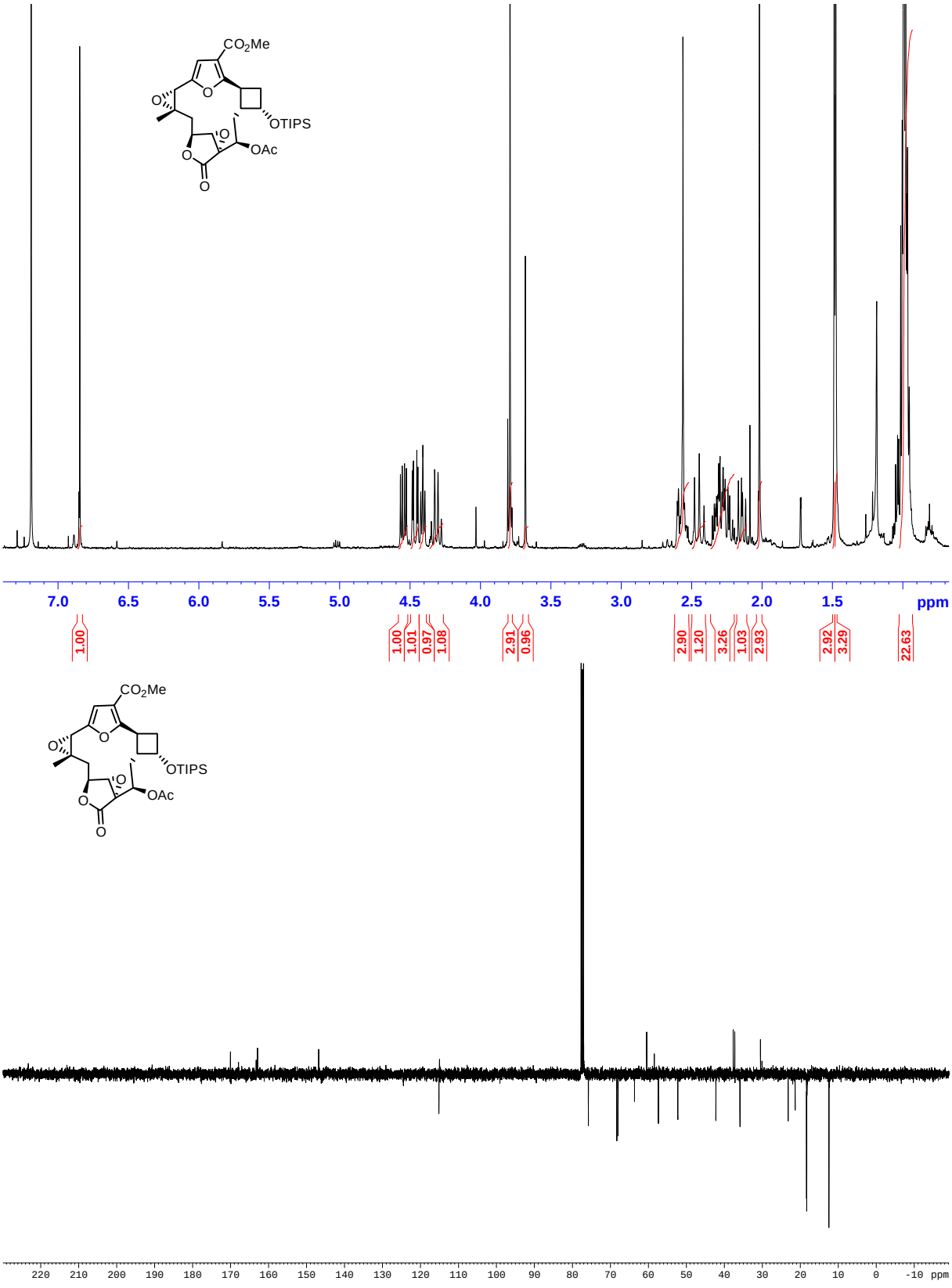

CO2Me
O
OTIPS
TBSO
O
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

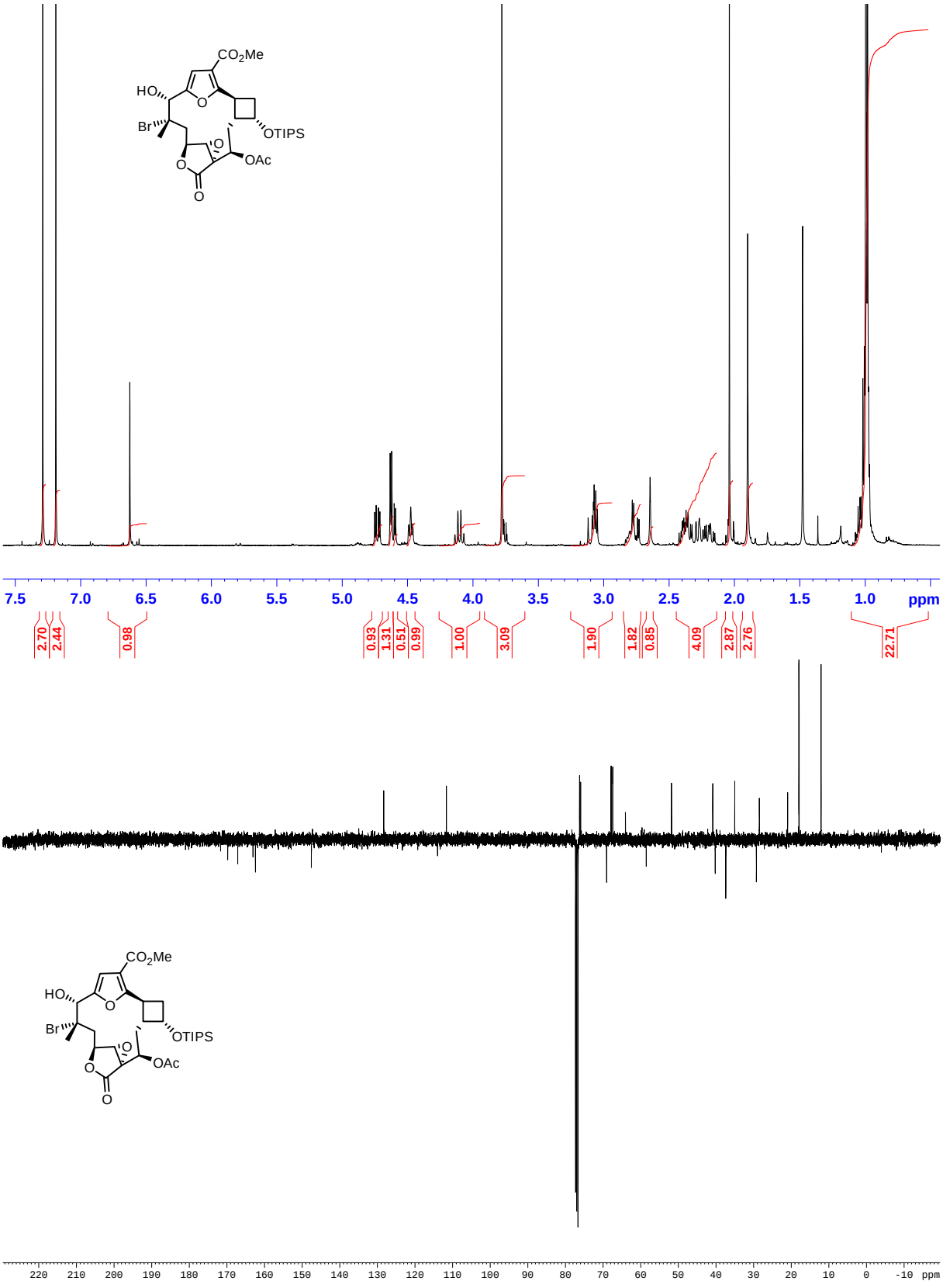

CO2Me
OTIPS
O
O
O
O
O
8
7
6
5
4
3
2
1
0
ppm
1.015
1.033
1.012
1.000
1.418
0.977
3.080
1.045
1.021
1.020
1.015
1.008
1.061
1.138
3.207
22.492
CO2Me
OTIPS
200
180
160
140
120
100
80
60
40
20
0
ppm

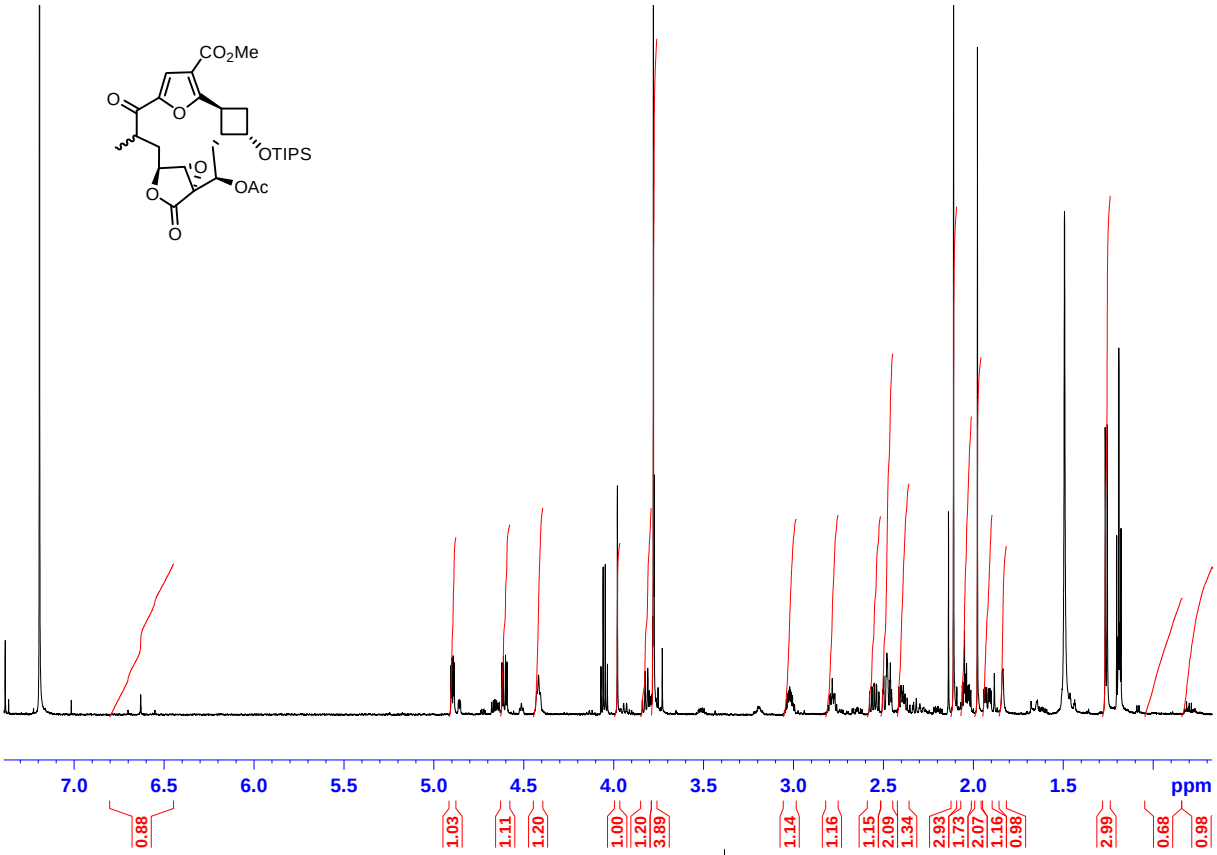

CO2Me
OTIPS
O
OH
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.96
3.39
1.05
1.04
1.00
1.08
1.25
1.02
3.35
2.19
1.09
2.24
1.98
1.27
3.26
24.73
220
200
180
160
140
120
100
80
60
40
20
0
ppm

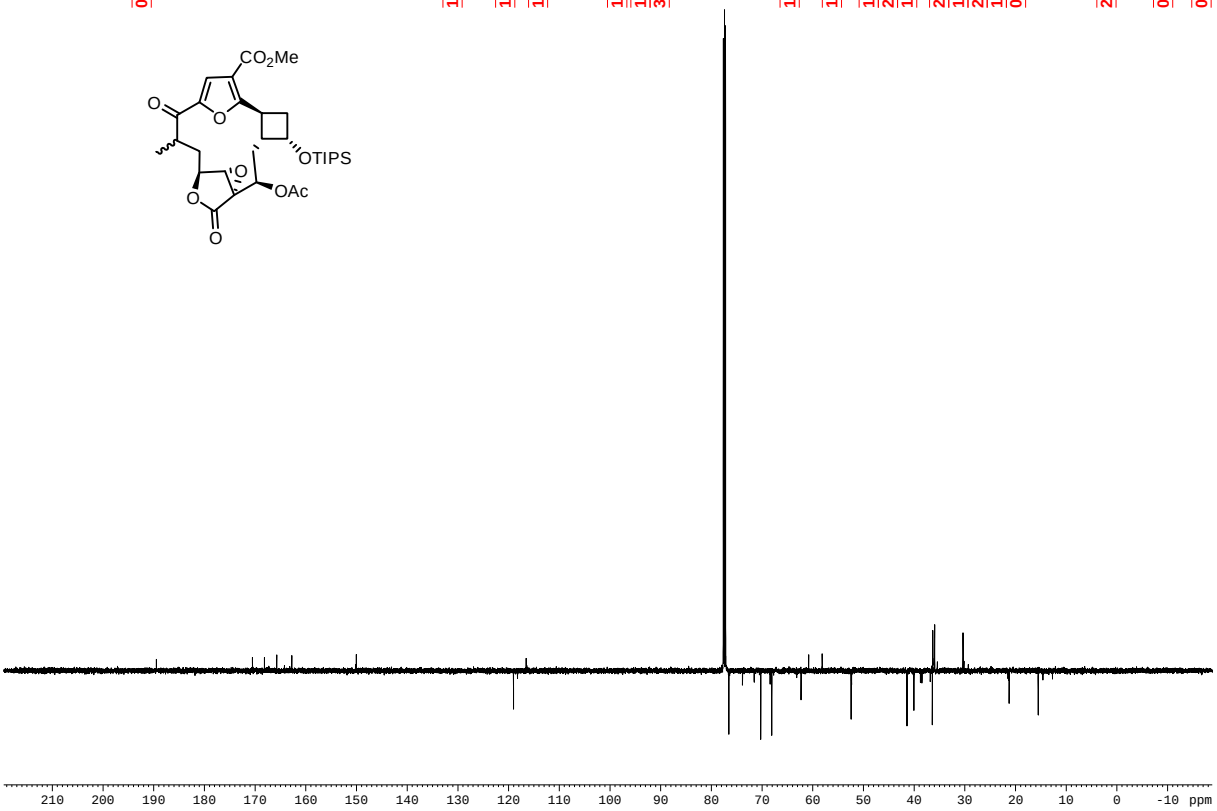

CO2Me
O
OTIPS
O
OAc
O
O
9
8
7
6
5
4
3
2
1
ppm
CO2Me
O
OTIPS
O
OAc
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

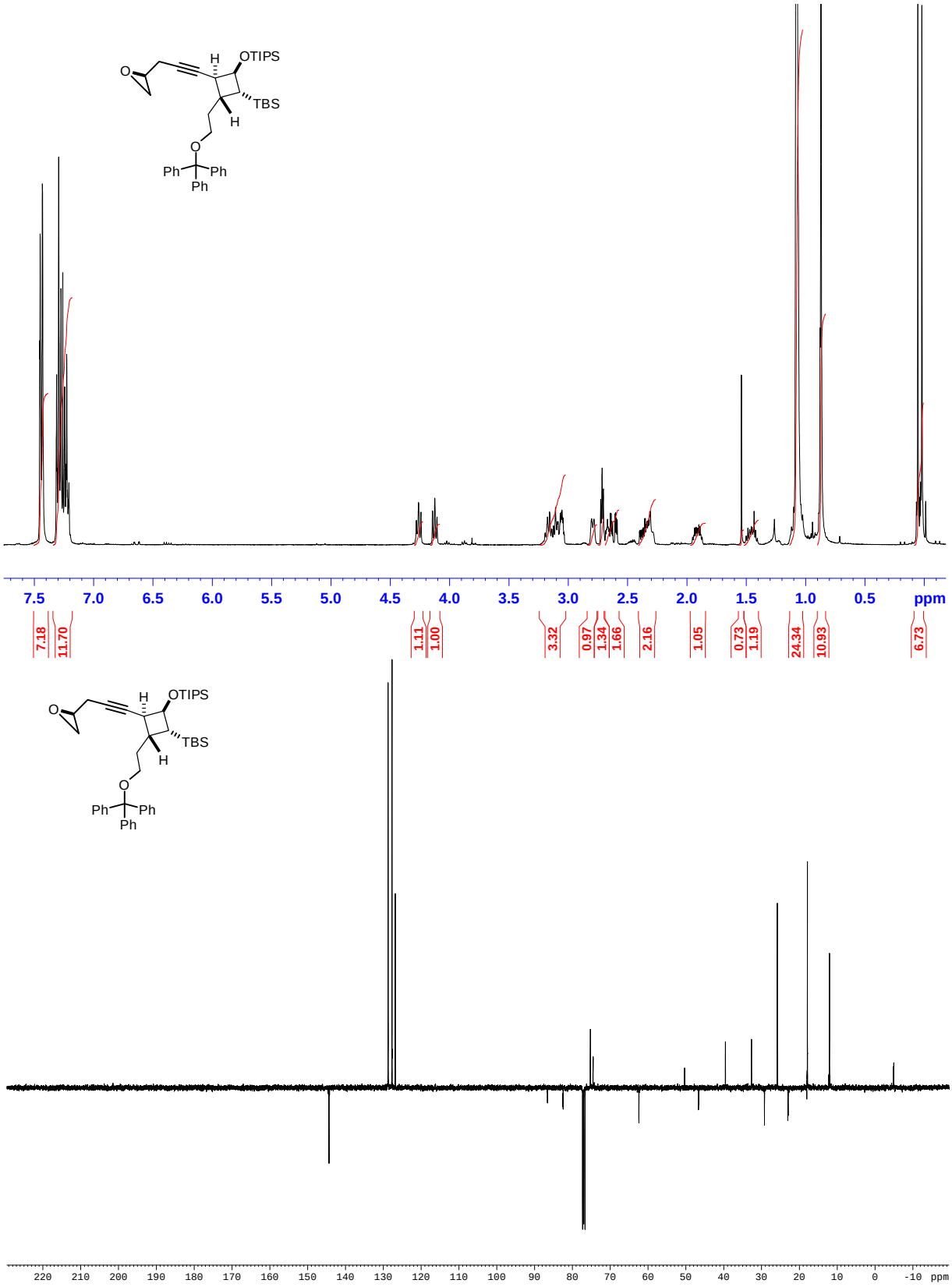

CO2Me
HO
Br
OTIPS
OAc
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.02 1.00 1.02 1.04 1.03 0.99 3.07 1.00 0.97 0.96 1.08 2.04 2.19 3.15 3.03 1.12 22.67
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

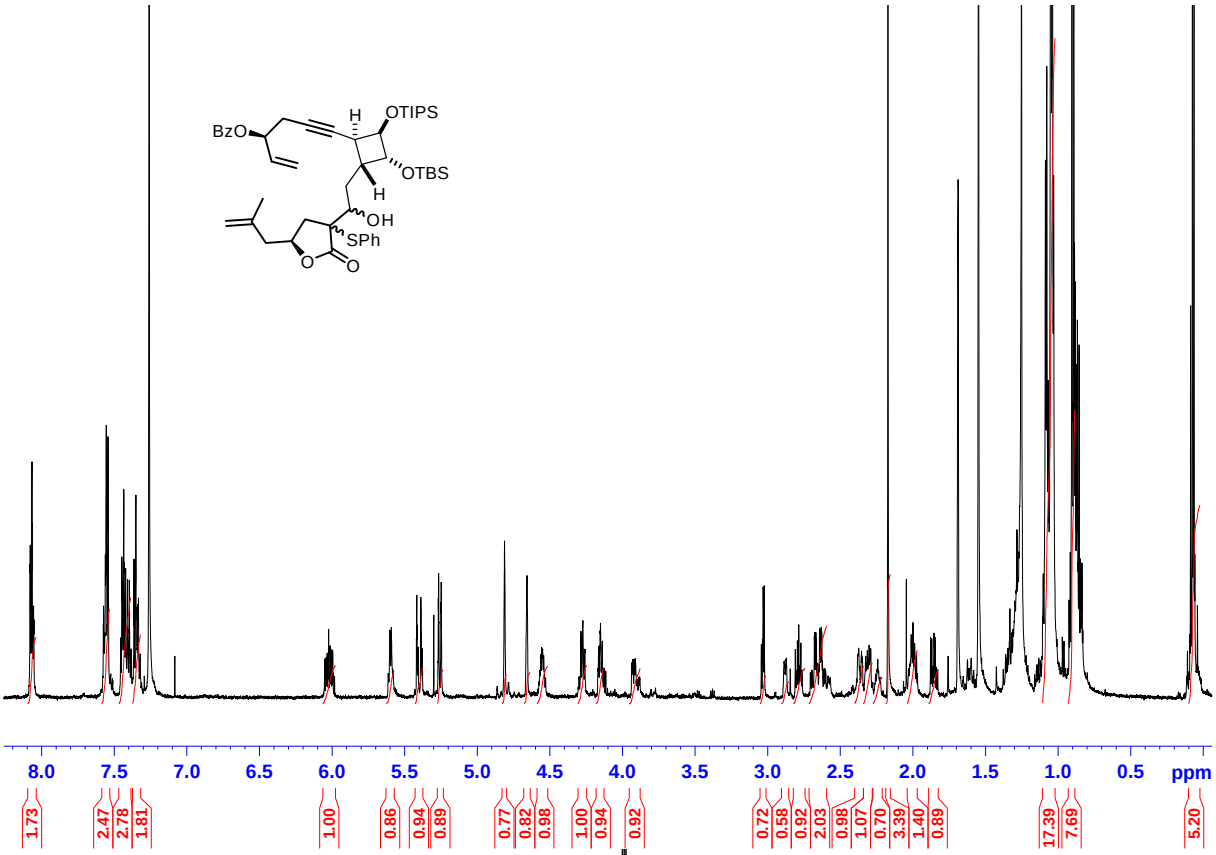

CO2Me
O
O
OTIPS
O
OAc
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.00
1.01
0.97
1.08
2.91
0.96
2.90
1.20
3.26
1.03
2.93
2.92
3.29
22.63
CO2Me
O
O
OTIPS
O
OAc
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

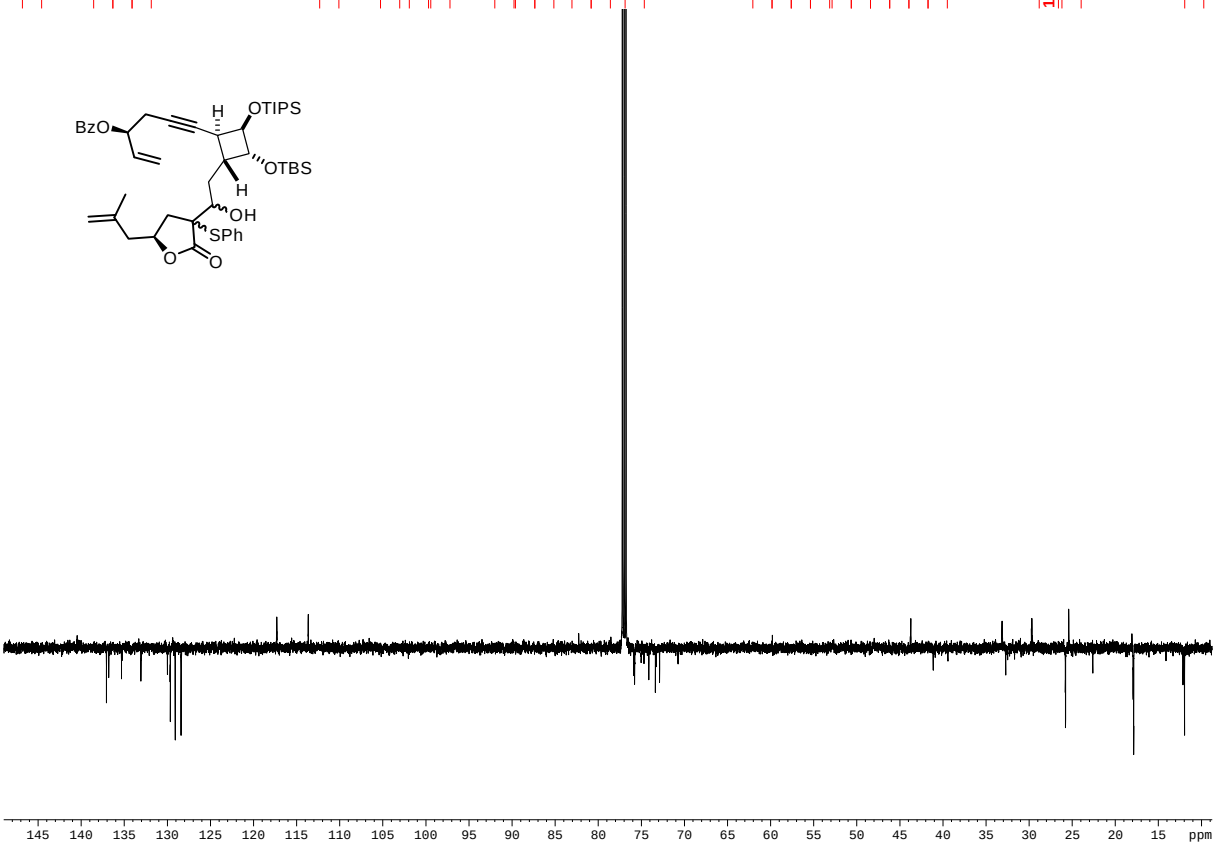

CO2Me
HO
Br
OTIPS
OAc
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.70
2.44
0.98
0.93
1.31
0.51
0.99
1.00
3.09
1.90
1.82
0.85
4.09
2.87
2.76
22.71
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm


CO2Me
O
O
OTIPS
O
OAc
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.88
1.03
1.11
1.20
1.00
1.20
3.89
1.14
1.16
1.15
2.09
1.34
2.93
1.73
2.07
1.16
0.98
2.99
0.68
0.98


CO2Me
O
O
OTIPS
O
OAc
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm


H
OTIPS
O
TBS
H
O
Ph
Ph
Ph
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
7.18
11.70
1.11
1.00
3.32
0.97
1.34
1.66
2.16
1.05
0.73
1.19
24.34
10.93
6.73
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


BzO
H
OTIPS
OTBS
H
OH
SPh
O
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.73
2.47
2.78
1.81
1.00
0.86
0.94
0.89
0.77
0.82
0.98
1.00
0.94
0.92
0.72
0.58
0.92
2.03
0.98
1.07
0.70
3.39
1.40
0.89
17.39
7.69
5.20


BzO
H
OTIPS
OTBS
H
OH
SPh
O
O
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm

Total Synthesis of (-)-Penifulvin A, an Antiinsectan with a Dioxafenestrane Skeleton.

Tanja Gaich* and Johann Mulzer*

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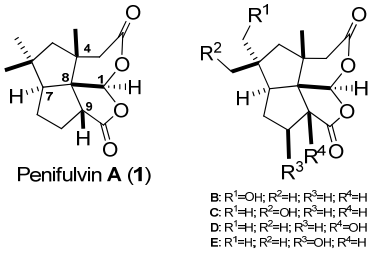
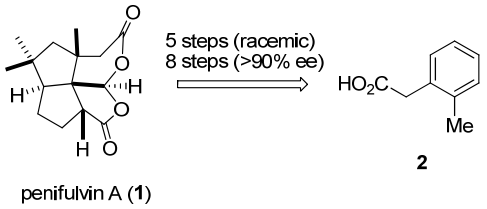
The fall armyworm (*Spodoptera frugiperda*) is native to the tropical regions of the western hemisphere from the United States to Argentina and its larvae cause enormous damage by consuming foliage of a variety of field crops, including barley, buckwheat, cotton, corn, oat, rice, sugarcane, soybean, tobacco, wheat and others.[1] In Florida, for example, fall armyworm is the most significant pest of corn. As resistance to pesticides has been noted and is expected to become increasingly problematic from year to year, a way out of this dilemma would be the introduction of new environmentally benign pesticides. In this respect we were intrigued by a recent paper[2] in which Gloer and co-workers described a novel sesquiterpenoid named penifulvin A (**1**), isolated from the fungus *Penicillium griseofulvum* (syn. *P. patulum* Bain.; *P. urticae* bain). This metabolite, which belongs to a larger family of penifulvins A - E (Figure 1),[3] not only shows significant antiinsectan activity in assays against the fall armyworm, it also appeared, due to its unusual and complex molecular architecture, an attractive target for total synthesis. Furthermore, for procuring larger quantities, acquiring SAR data and elucidating the full bioprofile of the compound, a rational non-biological access was of the essence.

Figure 1. Structures of Penifulvins A-E



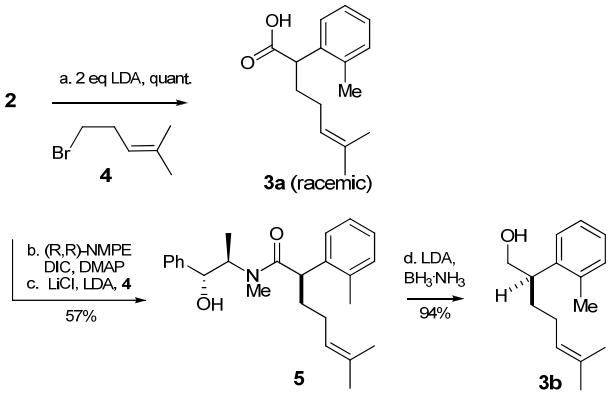
The overall structure of **1**, which has been secured by X-ray crystallographic analysis,[2] reveals a highly complex oxa-fenestrane[4] structure in which four rings share a central quaternary carbon. Additionally there are two more quaternary carbons, a γ-and a δ-lactone sharing the acylal center and a total of five stereogenic centers congested on a fifteen carbon skeleton. This ring system, whose absolute configuration is unknown, has not been described previously in literature. Herein we report the first total synthesis of racemic and optically active **1** from inexpensive o-tolylacetic acid (**2**) (Scheme 1).

Scheme 1. Retrosynthetic Overview



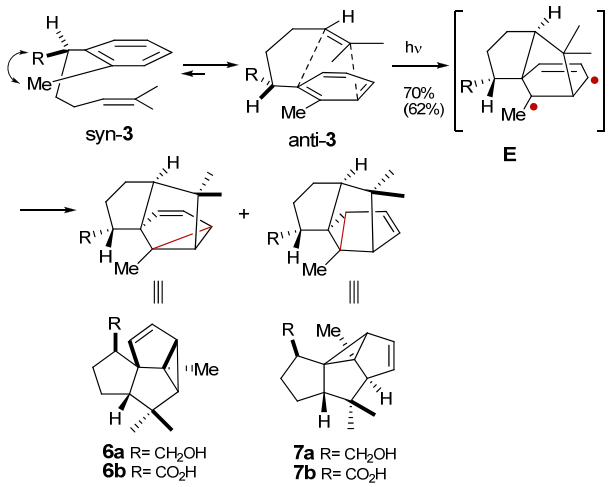
For our key transformation, we focused on Wender's marvelous photo-induced cyclization of arene olefins[5] such as **3a** (racemic) and **3b** (optically active) (Scheme 3), both readily available from **2** (Scheme 2). Racemic carboxylic acid **3a** was obtained from the alkylation of the dianion. The stereogenic center in **3b** was introduced via Myers' alkylation[6] in 95% ee leading to amide **5** in two steps. As **5** undergoes racemization on basic hydrolysis, it was reduced to the alcohol. The photo-reaction of **3a,b** (Scheme 3) starts with a formal [3+2] cycloaddition to generate exciplex **E** which undergoes 1,3-bond formation to deliver a 1:1-mixture of the allylic regioisomers **6** and **7.** The stereochemical course of the addition is controlled by the stereogenic center in compound **3**. According to the $A^{1,3}$-strain model[7] steric interactions between the aromatic methyl and the R-group are minimized. This effect strongly disfavors conformations such as **syn-3**, so that **anti-3** can be assumed to be the preferred conformation in the photocyclization.

Scheme 2. Preparation of photocyclization precursors **3a** and **3b**



Reagents and conditions: (a) 2 LDA, -78 °C, THF, **4**; (b) (*R,R*)-N-MPE, DIC, DMAP, DCM; (c) LiCl (6eq.) LDA, 5-bromo-2-methyl-2-pentene (**4**), THF, rt, 24 h; (d) LDA, BH_3NH_3, THF. (*R,R*)-N-MPE = (*R,R*)-N-methylpseudoephedrine, DIC = diisopropyl carbodiimide, DMAP = dimethyl aminopyridine, DCM = dichloromethane, LDA = lithium diisopropyl amide.

"***Scheme 3.*** Photo-cyclization of **3a,b**

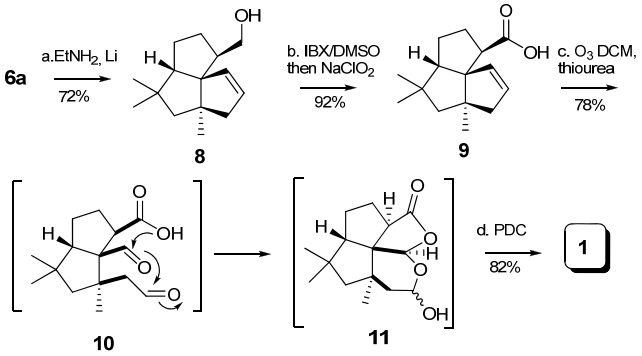


Conditions: hν, pentane, 22 °C, 2 h. (Series **a:** R = CH_2OH, optically active, 70% yield. Series **b:** R = CO_2H, racemic, 62% yield).

The synthesis was completed in parallel for both the racemic and the optically active series (Scheme 4). Thus, the regioisomers **6a** and **7a** were separated by chromatography and the cyclopropane was selectively reduced under Birch conditions to give triquinanyl alcohol **8**, which was oxidized to carboxylic acid **9**. Ozonolytic cleavage of the double bond generated the non-isolable dialdehyde **10** which immediately cyclized to lactol **11.**[8] Oxidation gave **1**, whose spectral data were in full accord with those of an authentic sample (see Supporting Information). The optical rotation of our material was $[\alpha]_D^{20}$ =-127 (c 0.35, $CHCl_3$) compared to a value of $[\alpha]_D^{20}$ =-133 (c 0.50, $CHCl_3$) of the authentic sample.[9,10,11] This result also confirms the absolute configuration (1*S*, 4*R*, 7*S*, 8*S*, 9*R*) of **1**. In the racemic series, the mixture of **6b** and **7b** was carried through the sequence without separation, and *rac*-**1** was finally obtained in pure form by column chromatography and crystallization.

In conclusion we have disclosed a concise synthesis of the antiinsectan agent penifulvin A in racemic and optically active form from o-tolylacetic acid in altogether 5 steps (14% overall yield) and 8 steps (8% overall yield), respectively. Apart from the photocyclization which leads to readily separable regioisomers, the synthesis is stereo- and regiocontrolled, does not require protecting groups or purification of intermediates and is scalable. Precursor **2** can be modified by introducing substituents onto the aromatic ring and/or the aliphatic sidechain, so that a variety of analogs, among them penifulvins B–E, should be available for performing SAR tests in the antiinsectan role.

"***Scheme 4.*** Completion of the Synthesis



Reagents and conditions: (a) $EtNH_2$, Li, THF, -78 °C 7 h; (b) IBX, DMSO, 22 °C, 20 min, then $NaClO_2$, 2-methyl-2-butene, *tert*-BuOH, NaH_2PO_4, 1 h; (c) O_3, DCM, -78 °C, 2 min, then thiourea, 22°C, 40 min; (d) PDC (4 eq.), DCM, 22 °C, 20 min, then AcOH (20 eq.), 20 min. IBX = 2-iodoxybenzoic acid, DMSO= dimethylsulfoxide, DCM = dichloromethane, PDC = pyridinium chlorochromate.

Acknowledgement We thank Hanspeter Kählig, Susanne Felsinger and Lothar Brecker for NMR analysis, Gerald Wagner for assistance, Professor J. B. Gloer, Iowa State University, for fruitful discussions and a generous sample of **1**, and the Austrian Science Fund (FWF) for financial support.

Supporting Information Available: Detailed experimental procedures and characterization of new compounds and comparison NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

REFERENCES

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(2) Shim, H. S.; Swenson, D. C.; Gloer, J. B.;.Dowd, P. F.; Wicklow, D. T. *Org. Lett*. **2006**, *8*, 1225-1228.
(3) Shim, H. S.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod*. **2006**, *69*, 1601-1605.
(4) For a review, see : Keese, R. *Chem. Rev*. **2006**, *106*, 4787-4808.
(5) Wender, P. A.; Ternansy, R. J. *Tetrahedron Lett*. **1985**, *26*, 2625-2628 (1985). For a review, see: Chappell, D.; Russell, A. T. *Org. Biomol.Chem*. **2006**, *4*, 4409-4430.
(6) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc*. **1997**, *119*, 6496-6511.
(7) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841-60.
(8) Lactol **11** was formed as a single anomer, whose relative configuration was not determined.
(9) The rotation of $[\alpha]_D^{20}$ =-3.5 (c 0.17, MeOH), reported for **1** in ref[2] is wrong. We corrected the value by measuring an authentic sample, which was kindly provided by Professor J. B. Gloer.
(10) The enantiomeric excess of our synthetic sample of **1** was determined via a chiral ^{1}H NMR shift reagent to be >90%.
(11) Rigorous purification of the intermediates proved difficult and, in the end, was unnecessary for the success of the synthesis. For derivatization alcohols **6a** and **7a** were transformed into the TBS-ethers (see Supporting Information).

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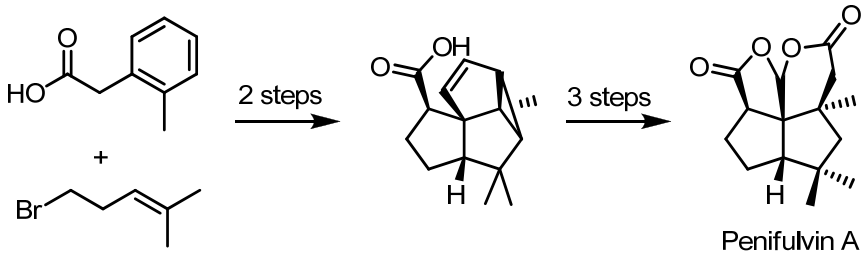


Penifulvin A

Herein we report the first total synthesis of Penifulvin A, a sesquiterpenoid with a novel dioxa-fenestrane structure. Penifulvin A is a potent antiinsectan against the fall armyworm *spodoptera frugiperda* which causes enormous damage in the US by consuming foliage of a variety of field crops. A five step racemic and an eight step enantioselective route to the natural product, and the determination of its absolute configuration are described. The key step involves a meta-photo cycloaddition, giving rapid access to the carbon skeleton of penifulvin A in a stereoselective fashion. Finally an oxidation cascade leads to the natural product The synthetic route is free from protecting groups, scalable and flexible so that a variety of analogs, among them penifulvins B–E, should be available for performing SAR tests in the antiinsectan role.

Total Synthesis of (-)-Penifulvin A, an Antiinsectan with a Dioxafenestrane Skeleton.

Tanja Gaich* and Johann Mulzer*

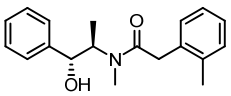
Supporting Information

1. Procedures

General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous CH_2Cl_2 (DCM) was distilled from CaH_2 under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofuran) was purchased (99.85%, water < 50 ppm). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel (0.04-0.063mm, 240-400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^{1}H, δ = 7.26 ppm; ^{13}C, δ =77.16 ppm). All ^{1}H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured at 20°C. High resolution mass spectra (HRMS) were performed with a resolution of 10000. Compound names were generated using AutoNom.

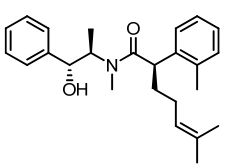
N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-*o*-tolylacetamide (A)



o-Tolylacetic acid (1.00 g, 6.7 mmol, 1 eq.), (*R,R*)-pseudoephedrine (1.20 g, 7.3 mmol, 1.1 eq.), and N,N-dimethyl-4-amino pyridine were dissolved in DCM (40 mL) at room temperature. After the starting materials had dissolved, the solution was cooled to 0°C in an ice bath and diisopropyl carbodiimide (1.1 mL, 7.3 mmol, 1.1 eq.) was added dropwise. After 20 min a precipitate was formed, and the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated on the rotatory evaporator and directly submitted to flash column chromatography (hexane:ethylacetate=3:1) yielding 1.95 g (98%) of the desired amide A.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.39-7.26 p.p.m. (m, 5H), 7.20-7.04 (m, 4H), 4.65 (t, *J*=7.3 Hz, 1H), 4.55-4.48 (m, 1H), 4.34 (s, br 1H), 3.64 (d, *J*=2.3 Hz, 2H), 2.86 (s, 3H), 2.25 (s, 3H), 1.18 (d, *J*=6.8 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 173.70 p.p.m., 142.83, 136.84, 133.81, 130.63, 129.28, 128.79, 128.04, 127.42, 126.72, 126.65, 76.88, 75.97, 59.09, 39.83, 20.02, 14.85. IR (film): 3383, 2971, 1699, 1617, 1558, 1452, 1404, 1118, 1051, 743, 702, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ c alcd for $C_{19}H_{23}NO_2$ 297.1729; found, 297.1715. $[\alpha]_D$= -96 (c 1.05g/100mL, $CHCl_3$).

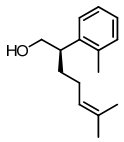
(R)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,6-dimethyl-2-*o*-tolylhept-5-enamide (5)



A solution of n-butyllithium (5.9 mL, 2.5M, 2.2 eq.) was added to a suspension of LiCl (1.65 g, 39.9 mmol, 6 eq.) and diisopropylamine (2 mL, 14.6 mmol, 2.2 eq.) in THF (7 mL) at -78°C. The resulting suspension was briefly warmed to 0°C and then cooled to -78°C. Amide **A** (1.95 g, 6.5 mmol, 1 eq.) was added to this mixture *via* cannula and stirred at that temperature for 1 h, then at 0°C for 15 min and at 23°C for 5 min. The mixture was cooled to 0°C and 5-bromo-2-methyl-2-pentene (1.44 g, 8.9 mmol) was added neat to this reaction mixture. After stirring at room temperature for 24 h the mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3x100 mL). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (hexane:ethylacetate=3:1) afforded 1.47 g (58%)of amide **5**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.38-7.04 p.p.m. (m, 9H), 5.18-5.10 (m, 1H), 4.59-4.50 (m, 1H), 4.47-4.26 (s br, 1H), 3.71-3.66 (m, 1H), 2.92 (s, 1H minor rotamer), 2.54 (s, 1H major rotamer), 2.36 (s, 1H minor rotamer), 2.30 (s, 2H major rotamer), 2.24-2.21 (m, 1H), 2.11-2.04 (m, 1H), 1.98-1.89 (m, 1H), 1.69 (s, 2H major rotamer), 1.68 (s, 1H minor rotamer), 1.59 (s, 1H minor rotamer), 1.56 (s, 2H major rotamer), 1.51-1.41 (m, 1H), 1.13 (d, *J*=4.9 Hz, 2H major rotamer), 0.39 (d, *J*=6 Hz, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 138.67p.p.m., 134.82, 132.60, 130.70, 128.78, 128.44, 127.65, 127.00, 126.90, 126.64, 126.45, 124.45, 124.08, 76.60, 75.68, 58.06, 45.28, 34.50, 34.23, 27.58, 26.74, 25.84, 19.35, 17.81, 14.19. IR (film): 3383, 2924, 1713, 1621, 1454, 1404, 1376, 1228, 1119, 1051, 895, 838, 757, 726, 702, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{25}H_{33}NO_2$ 379.2511; found, 379.2510 $[\alpha]_D$= -137° (c 0.75g/100mL, $CHCl_3$).

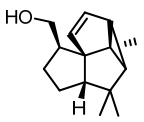
(R)-6-Methyl-2-*o*-tolylhept-5-en-1-ol (3a)



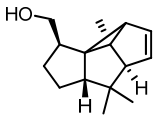
A solution of *n*-butyllithium (5.9 mL, 2.5M, 14.8 mmol, 4 eq.) in hexanes was added to a solution of diisopropylamine (2.1 mL, 14.8 mmol, 4 eq.) in THF (10 mL) at -78°C. The resulting solution was stirred at this temperature for 10 min, then warmed to 0°C and held at that temperature for 10 min. Borane-ammonia complex (456 mg, 14.8 mmol, 4 eq.) was added in one portion. The suspension was stirred at 0°C for 15 min, then at 23°C for 15 min, cooled again to 0°C and a solution of amide **5** (1.40 g, 3.7 mmol, 1 eq.) in THF (6 mL) was added *via* cannula. The reaction mixture was warmed to room temperature and stirred for 2 h before it was cooled to 0°C again and carefully quenched with 1M hydrochloric acid (40 mL). The mixture was diluted with water (100 mL) and extracted with ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **3a** (734 mg, 91%) as a yellow oil which was directly used in the next step. An analytical sample was purified by chromatography (hexane:ethyl acetate 5:1).

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.21-7.10 p.p.m. (m, 4H), 5.07 (dt, *J*=6.9,0.6 Hz, 1H), 3.76-3.69 (m, 2H), 3.19-3.15 (m, 1H), 2.33 (s, 3H), 1.89 (dd, *J*=14.9, 7.3 Hz, 2H), 1.78-1.72 (m, 1H), 1.69-1.61 (m, 1H), 1.66 (d, *J*=1.1 Hz, 3H), 1.44 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 140.73 p.p.m., 137.71, 132.32, 130.90, 126.74, 126.62, 126.27, 124.66, 67.78, 42.66, 32.55, 26.12, 25.98, 20.29, 17.97. IR (film): 3241, 2928, 2857, 1653, 1559, 1463, 1256, 1101, 836, 775, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{22}O$ 218.1671; found, 218.1665. $[\alpha]_D$= +18 (c 1.05g/100mL, $CHCl_3$).

((1aS,4R,4aR,6bS,6cS)-1,1,6c-Trimethyl-1,1a,2,3,4,6a,6b,6c-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalen-4-yl)-methanol (6a)
((2aS,3aS,6R,6bS,6cR)-3,3,6c-Trimethyl-2a,3,3a,4,5,6,6b,6c-octahydro-cyclopenta[*a*]cyclopropa[*gh*]pentalen-6-yl)-methanol (7a)



6a



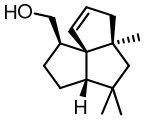
7a

Compound **3a** (1.00 g, 3.0 mmol) in pentane (100 mL) was irradiated with a Hannovia 700W medium pressure mercury lamp with a quartz filter at room temperatur for 2 h. The reaction mixture was concentrated and the crude residue was submitted to flash column chromatography (hexane) yielding **6a** and **7a** (350 mg each, total 70%) in a 1:1 ratio.

6a : ^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.76 p.p.m. (dd, *J*=5.3, 2.0 Hz, 1H), 5.44 (d, *J*=5.3 Hz, 1H), 3.68-3.61 (m, 1H), 3.58-3.48 (m, 1H), 2.47-2.38 (m, 1H), 2.01-1.85 (m, 2H), 1.84-1.74 (m, 1H), 1.67 (d *J*=1.3 Hz, 1H), 1.63-1.50 (m, 3H), 1.48-1.43 (m, 1H), 1.34 (s, 3H), 1.31 (d, *J*=7.6 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 133.61 p.p.m., 130.69, 70.95, 66.14, 64.83, 60.47, 49.77, 48.55, 42.50, 38.42, 31.09, 29.64, 29.36, 28.51, 19.15. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{22}O$ 218,1671; found, 218,1679. $[\alpha]_D$= -79 (c 1.35g/100mL, $CHCl_3$).

7a: ^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.66 p.p.m. (dd, *J*=5.6, 2.2 Hz, 1H), 5.46 (dd, *J*=5.6, 2.5 Hz, 1H), 3.44 (dd *J*=10.6, 4.3 Hz, 1H), 3.36 (dd, *J*=9.3. 4.3 Hz, 1H), 2.40, (d, *J*=2.5 Hz, 1H), 2.07 (s, br, 1H), 1.90 (dd, *J*=9.5, 3.4 Hz, 1H), 1.86-1.77 (m, 3H), 1.72-1.59 (m, 2H), 1.51 (d, *J*=2.3 Hz, 1H), 1.49-1.42 (m, 1H), 0.94, (s, 3H), 0.74 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 131.70 p.p.m., 129.84, 68.40, 64.77, 55.25, 50.85, 50.75, 46.71, 41.22, 38.16, 31.25, 23.78, 23.14, 23.03, 16.02. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{22}O$ 218,1671; found, 218,1681 $[\alpha]_D$= +58 (c 2.56g/100mL, $CHCl_3$).

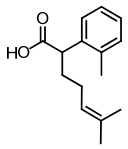
((1R,3aS,5aS,8aR)-4,4,5a-Trimethyl-1,2,3,3a,4,5,5a,6-octahydro-cyclopenta[*c*]pentalen-1-yl)-methanol (8)



A solution of **6a** (120 mg, 0.36 mmol, 1 eq.) in absolute THF (500µL) was cooled to -78°C and ethylamine (3 mL) was condensed in. Small pieces of lithium (15 mg, 2.16 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h until a deep blue color formed. The excess lithium was quenched with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **8** (118 mg, 97%) as a yellow oil which was directly subjected to the next step. A purified sample was obtained by chromatography (hexanes:ethyl acetate 10:1).

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.68 p.p.m. (dt, *J*=5.7. 2.2 Hz, 1H), 5.54 (dt, *J*=5.6. 2.4 Hz, 1H), 3.55 (dd, *J*=11.0, 7.2 Hz, 1H), 3.49-3.42 (m, 2H), 2.36 and 2.24 (AB dt, *J*=17.0 2.2 Hz, 2H), 1.95-1.87 (m, 2H), 1.69 (dd, *J*=4.8. 2.2 Hz, 3H), 1.67-1.62 (m, 3H), 1.15 (s, 3H), 0.98 (m, 3H), 0.92 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 137.51 p.p.m., 127.87, 65.31, 63.90, 58.52, 53.82, 51.12, 46.78, 42.12, 39.58, 32.20, 30.77, 28.43, 28.02, 27.57. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{24}O$ 220,1827; found, 220,1820.

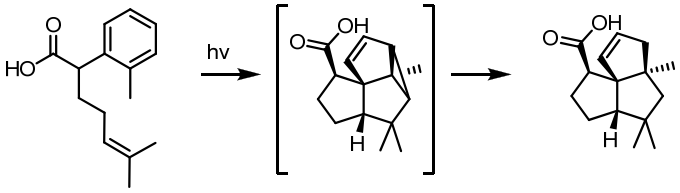
6-Methyl-2-*o*-tolyl-hept-5-enoic acid (3b)



Diisopropyl amine (1.5 mL, 10.5 mmol, 2.1 eq) was dissolved in 4 mL THF and cooled to 0°C. *n*-Butyllithium (2.5M, 4.2 mL 10.5 mmol, 2.1 eq) was added dropwise and the solution was stirred for 30 min at that temperature. The reaction mixture was cooled to -78°C and *o*-tolyl acetic acid (750 mg, 5 mmol) in THF (1 mL) was added at-78°C. The reaction was moved to a NaCl/ice bath and stirred at -20°C for 2h. After this time the reaction was cooled to -78°C and 5-bromo-2-methyl-pent-2-ene (1.21 g, 7.5 mmol) was added crude to this solution. The reaction was warmed to rt over night and quenched with aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted two times with Et_2O (50 mL). Then the aqueous phase was acidified to pH 2 and extracted four times with 100 mL of DCM. The combined DCM fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Crude **3b** was used without any further purification. Yield 1.16g (quant).

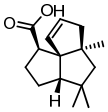
^{1}H-NMR (400MHz, $CDCl_3$): δ= 11.01 p.p.m. (s,br 1H), 7.38-7.35 (m, 1H), 7.26-7.18 (m, 3H), 5.14 (dd, *J*= 7.1Hz, 1H), 3.91 (t, *J*= 7.3Hz, 1H), 2.41 (s, 3H), 2.20 (ddd, *J*= 14.1, 7.1Hz, 1H), 2.04 (dd, *J*= 14,4, 7.1Hz, 2H), 1.90-1.81 (m, 1H), 1.73 (s, 3H), 1.55 (s, 3H).

(1aS,4R,6cS)-1,1,6c-Trimethyl-1,1a,2,3,4,6a,6b,6c-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalene-4-carboxylic acid (9)



Acid **3b** (1.14 g, 4.9 mmol) in pentane (100 mL) was irradiated with a Hanovia 700W medium pressure mercury lamp with a quartz filter at room temperatur for 1 h. The reaction mixture was concentrated and the crude mixture of **6b/7 b** was dissolved in THF (1 mL), cooled to -78°C and ethylamine (3 mL) was condensed in. Small lithium pieces (15 mg, 2.16 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h as a deep blue color formed. The excess lithium was destroyed with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **9** (along with its regioisomer, 707 mg, 62 %) as a yellow oil.

(1R,3aS,5aS,8aR)-4,4,5a-Trimethyl-1,2,3,3a,4,5,5a,6-octahydro-cyclopenta[*c*]pentalene-1-carboxylic acid (9)

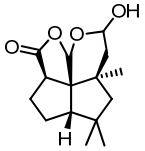


Alcohol **8** was dissolved in DMSO (1 mL) and IBX (302 mg, 1.1 mmol, 3 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 20 min until TLC control revealed full consumption of the starting material. The reaction mixture was diluted with diethyl ether (20 mL) and the solids were filtered off through a silica pad. The solvents were removed *in vacuo* and the crude aldehyde was dissolved in *tert*-butanol (5 mL) and 2-methyl-2-butene (500 µL) was added. A solution of sodium chlorite (537 mg, 5.4 mmol, 15 eq.) and sodium dihydrogenphosphate (537 mg) in water (2 mL) was added dropwise under vigorous stirring. The reaction mixture was stirred at room

temperature for 1 h and quenched with a 1M solution of potassium hydrogen sulfate in brine. The mixture was extracted with methylene chloride (3 x 50 mL), dried over magnesium sulfate and the solvents were removed *in vacuo*. Flash column chromatography (hexane:ethyl acetate=5:1) furnished 73 mg (86%) of **9** as a viscous oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.60-5.47 p.p.m. (m, 2H), 2.98 (dd, *J*=10.7, 7.0 Hz, 1H), 2.48-2.42 (m, 1H), 2.32-2.25 (m, 1H), 2.03-1.81 (m, 4H), 1.77-1.67 (m, 3H), 1.23 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 180.32 p.p.pm., 137.28, 128.60, 63.39, 58.51, 54.06, 61.32, 50.10, 45.96, 39.74, 31.29, 30.82, 28.84, 28.42, 27.95. IR (film): 3332, 3053, 2950, 1701, 1684, 1653, 1636, 1591, 1559, 1540, 1507, 1458, 1361, 1025, 957, 887, 745, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{22}O$ 218,1671; found, 218,1681. $[\alpha]_D$= -76 (c 1.05g/100mL, $CHCl_3$).

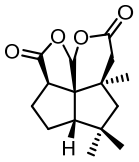
Lactol 11



Acid **9** (25 mg, 0.11mmol, 1 eq) was dissolved in dichloromethane (50 mL) in a three necked round bottom flask equipped with a gas outlet and a gas inlet-tube. The solution was cooled to -78°C and ozonized for 2 min (flow 100mL/min) until the solution was dark blue. The excess ozone was driven out with air until the solution became colorless again. Then thiourea (9 mg, 0.12 mmol, 1.1 eq.) was added in one portion and the suspension was warmed to room temperature and stirred for 40 min giving a cloudy solution. The solvent was removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethyl acetate=3:1) yielding 15 mg (56%) of lactol **11**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.69 p.p.m. (s, 1H), 5.37 (dd, *J*=8.9, 5.8 Hz, 1H), 3.24 (s, br 1H), 2.93 (d, *J*= 7.5 Hz, 1H) 2.25 (dd, *J*=9.3, 1.3 Hz, 1H) 2.16 (dd, *J*=13, 7.0 Hz, 1H), 2.01 (dd, *J*=14.2, 8.9 Hz, 1H), 1.89-1.85 (m, 2H), 1.76-1.65 (m, 1H), 1.74 (d, *J*=14 Hz, 1H), 1.54-1.47 (m, 1H), 1.47 (d, *J*=13.6 Hz, 1H), 1.22 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 179.83 p.p.pm., 101.09, 91.81, 66.90, 60.10, 58.16, 46.56, 42.39, 41.06, 40.06, 34.50, 31.21, 29.37, 28.33, 28.00. IR(film): 3449, 2958, 1792, 1559, 1457, 1132, 997, 884, 738, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{22}O_4$ 266,1518; found, 266,1509. $[\alpha]_D$= -65 (c 0.6g/100mL, $CHCl_3$)

Penifulvin A (1)



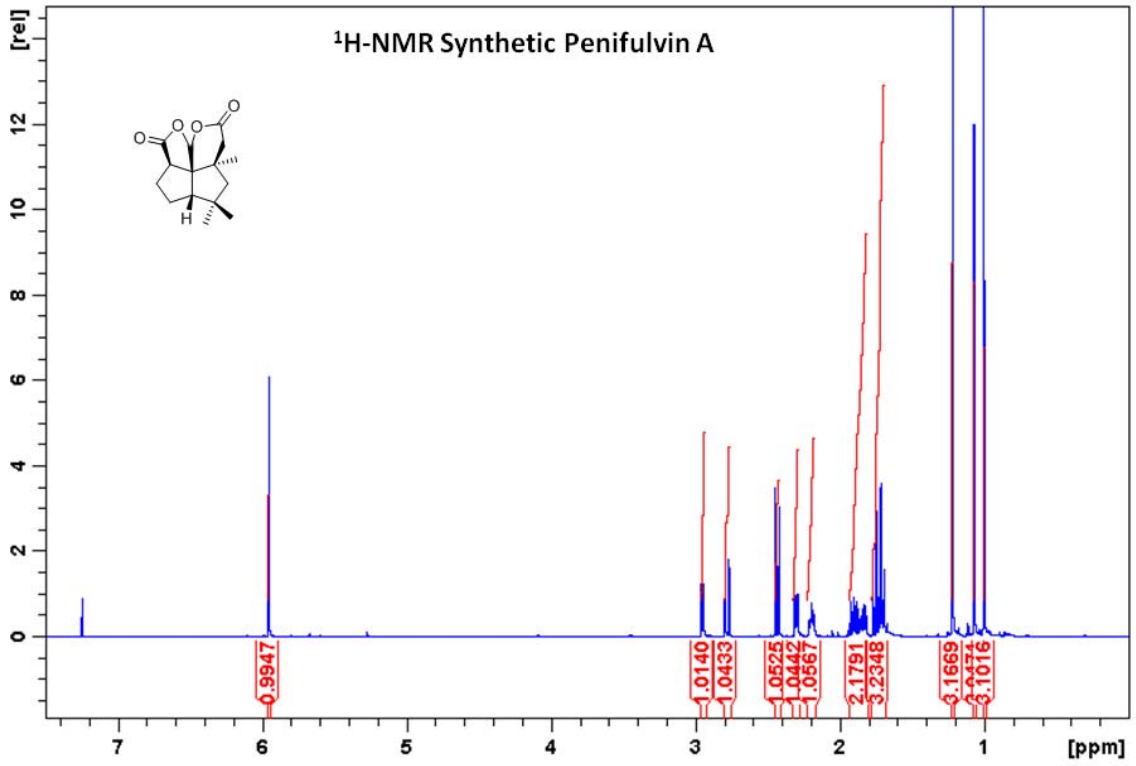
Lactol **11** (15 mg, 56 µmol, 1eq) was dissolved in dichloromethane (0.5 mL) at room temperature. PDC (84 mg, 0.22 mmol, 4 eq.) was added in one portion. After 20 min concentrated acetic acid (67 µL, 1.12 mmol, 20 eq.) was added dropwise. The reaction mixture was stirred for another hour and then diluted with diethyl ether. The suspension was filtered through a silica pad and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 12 mg (80%) of pure penifulvin A (**1**).

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.96 p.p.m. (s, 1H), 2.97 (dd, *J*=8.0, 1.0 Hz, 1H), 2.79 (d, *J*=15 Hz, 1H), 2.46 (dd, *J*=15 Hz, 1H), 2.32 (dd, *J*=9.7, 5.0 Hz, 1H), 2.23 (ddd, *J*=13.3, 8.0, 3.9, 1.8 Hz, 1H), 1.91 (ddt, *J*=14.0, 8.1, 8.2 Hz, 1H), 1.82 (m, 1H), 1.78 (d, *J*=14 Hz, 1H), 1.73 (d, *J*=14 Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 178.04 p.p.m., 168.65, 103.88, 66.73, 60.86, 55.62, 46.43, 44.10, 42.07, 40.32, 32.83, 30.11, 28.18, 27.58, 27.42. IR (film): 2960, 1799, 1771, 1653, 1559,

1507, 1458, 1367, 1115, 1043, 995, 905, 738, 610 cm^{-1}. HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{20}O_4$ 264,1362; found,, 264,1368. $[\alpha]_D$= -127 (c 0.35g/100mL, $CHCl_3$). $[\alpha]_D$= -97 (c 0.35g/100mL, MeOH).

In the racemic series, the operations from **9** to **1** were performed without isolation of the intermediates. The chromatography (hexanes:ethyl acetate 5:1) of the final mixture gave pure crystalline *rac*-**1** (23% from the **6b/7b-** mixture).

2. NMR Spectra



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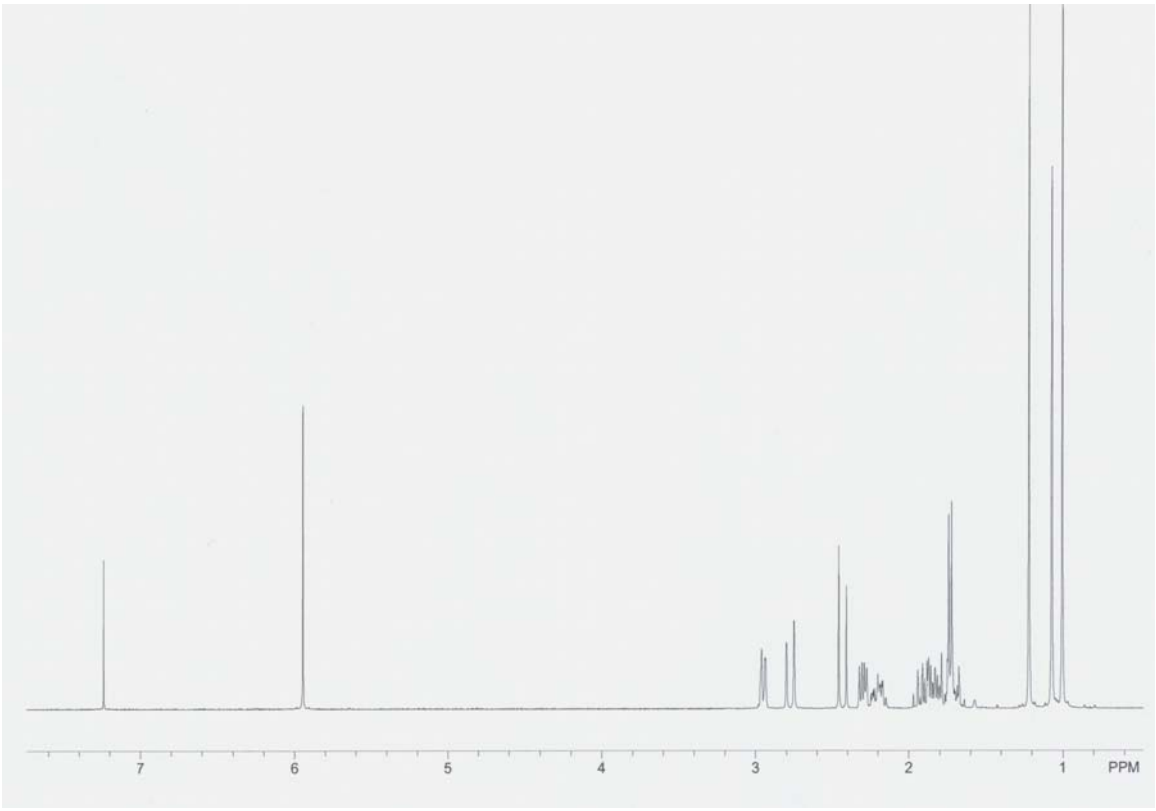

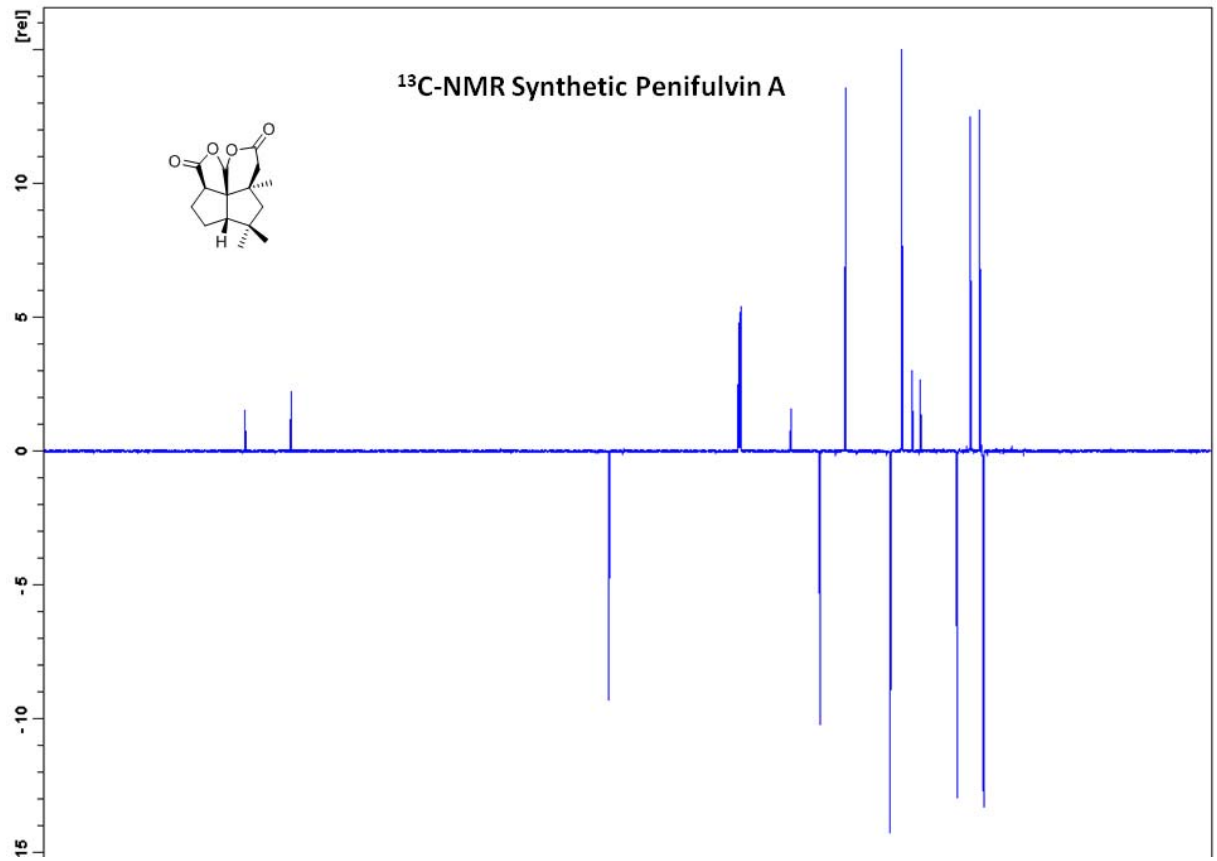

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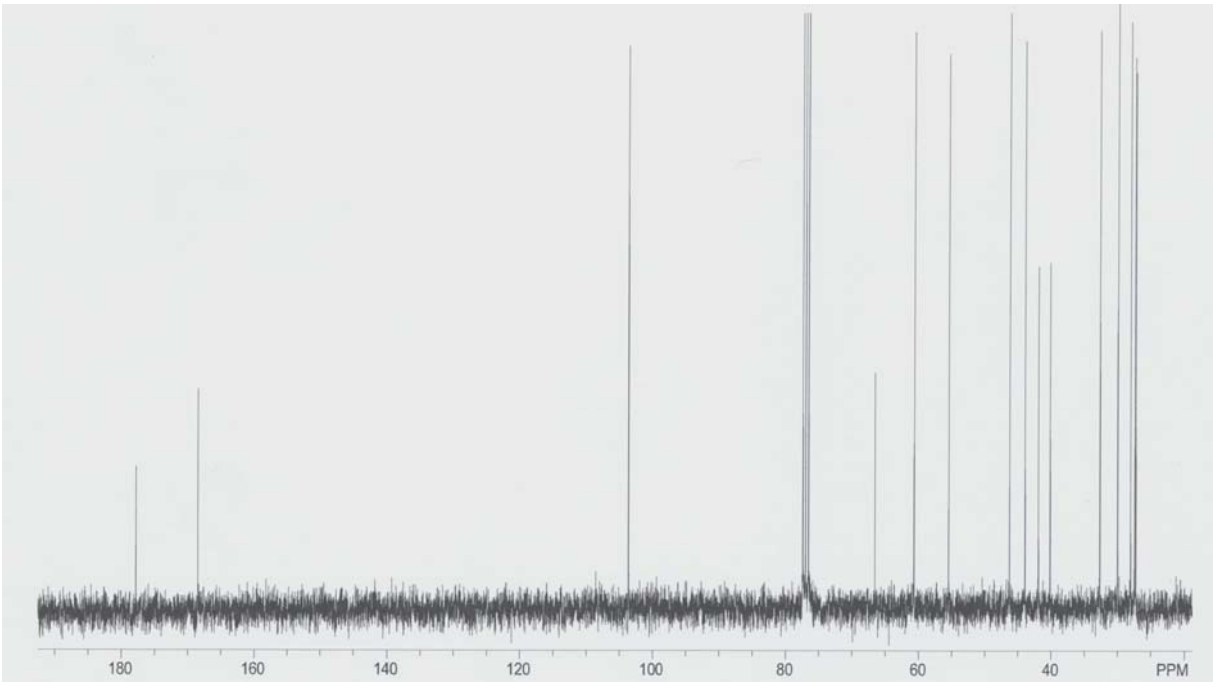
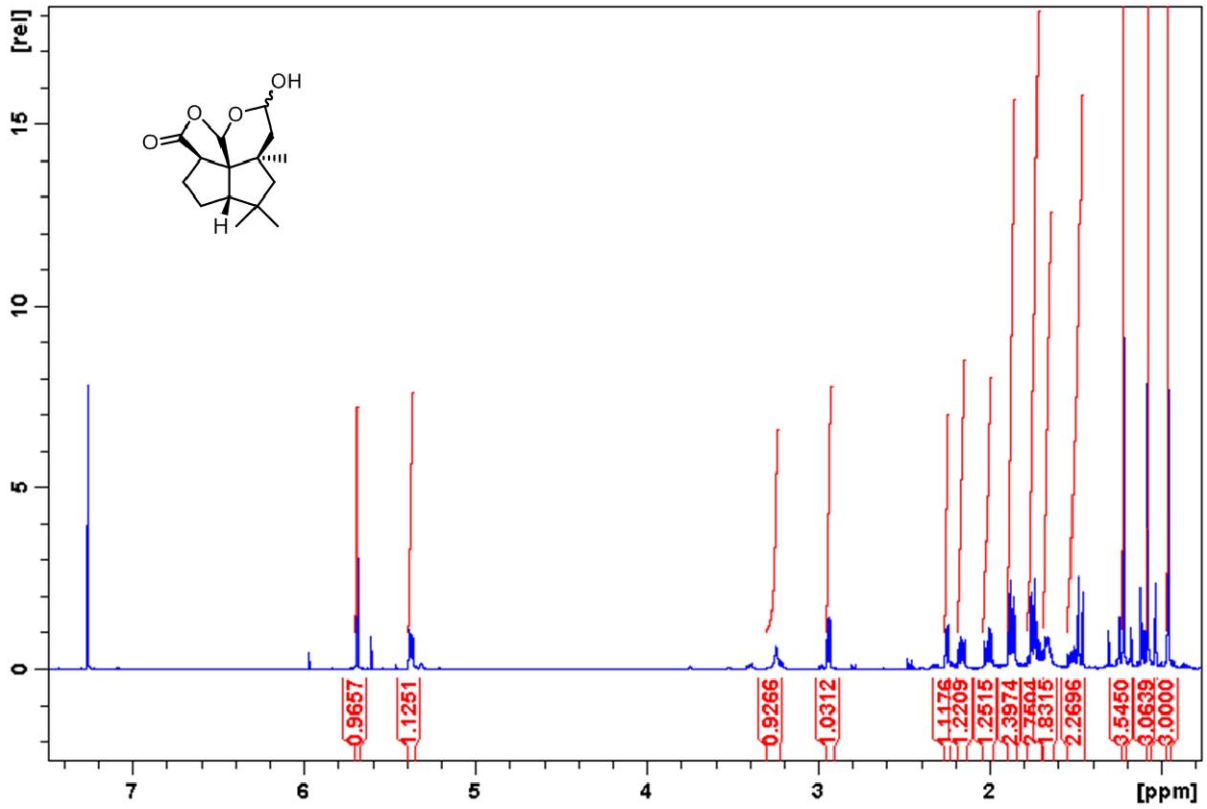


	COMPARISON of ^{1}H-NMR DATA		COMPARISON of ^{13}C-NMR DATA	
	natural	synthetic	natural	synthetic
Position	**δ_H (mult, *J* in Hz)**		**δ_C**	**δ_C**
1	5.95 (s)	5.96 (s)	103.7	103.88
2			168.3	168.65
3α	2.77 (d, 16)	2.79 (d, 15)	43.9	44.10
3β	2.43 (d, 16)	2.46 (d, 15)		
4			41.9	42.07
5α	1.76 (d, 14)	1.78 (d, 14)	55.4	55.62
5β	1.71 (d, 14)	1.73 (d, 14)		
6			40.2	40.32
7	2.30 (dd, 5.1, 9.8)	2.32 (dd, 5.0, 9.7)	60.7	60.86
8			66.7	66.73
9	2.95 (dd, 1.2, 8.0)	2.97 (dd, 1.0, 8.0)	46.2	46.43
10α	2.20 (dddd, 2.0, 3.4, 8.0, 14)	2.23 (dddd, 1.8, 3.9, 8.0, 13.6)	29.9	30.11
10β	1.90 (ddt, 8.0, 8.0, 14)	1.91 (ddt, 8.1, 8.1, 13.6)		
11α	1.71 (m)	1.74 (m)	28.0	28.18
11β	1.83 (m)	1.83 (m)		
12	1.22 (s)	1.24 (s)	32.6	32.83
13	1.00 (s)	1.03 (s)	27.4	27.58
14	1.07 (s)	1.10 (s)	27.2	27.42
15			177.8	178.04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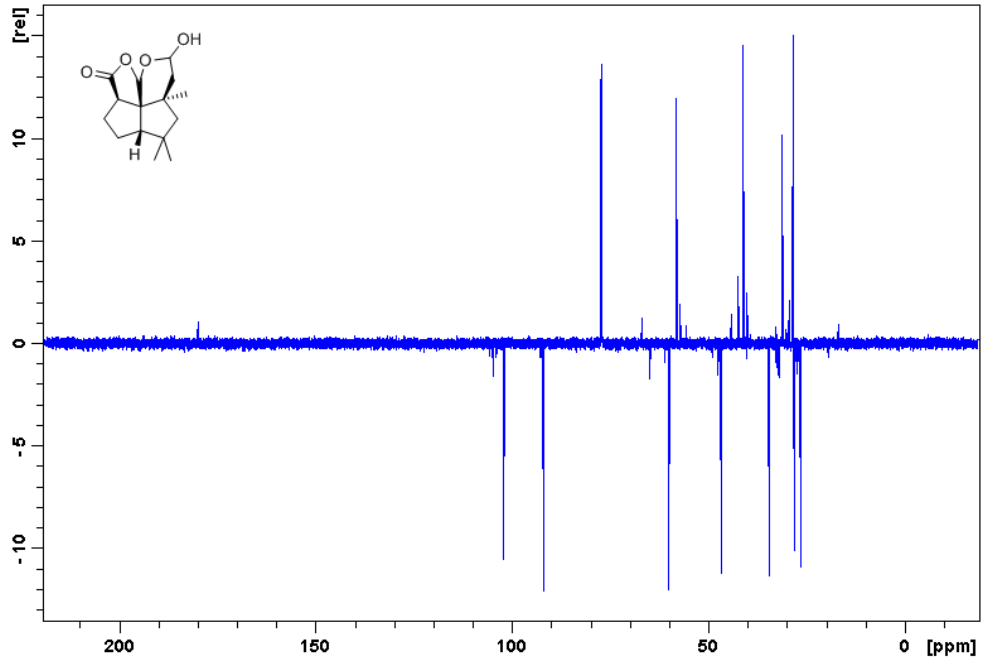
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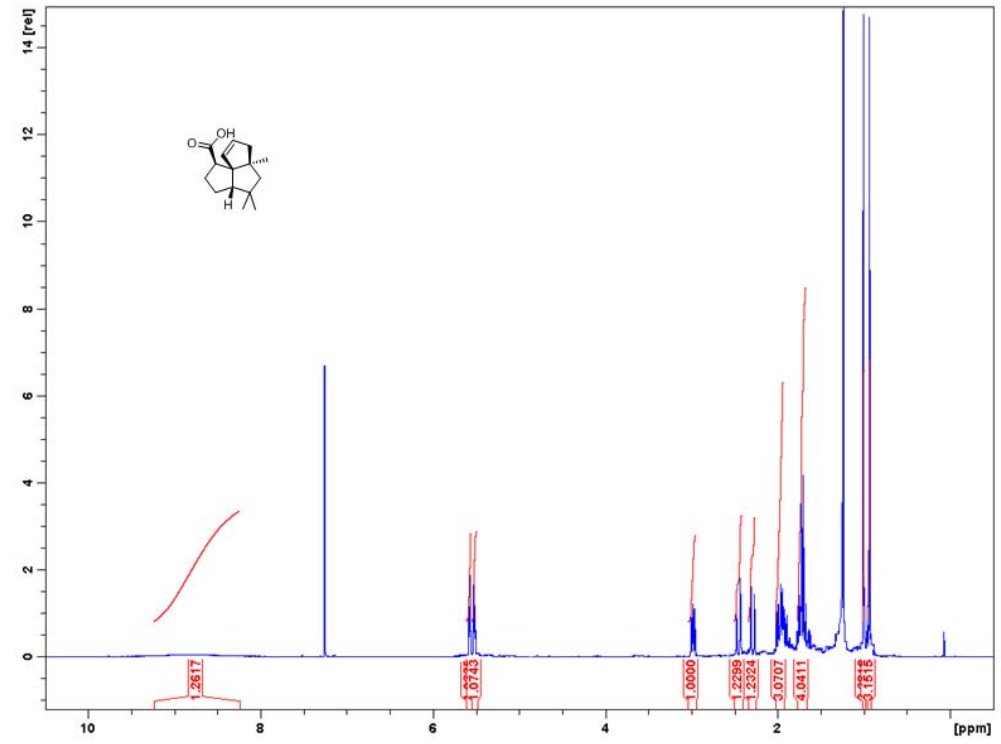
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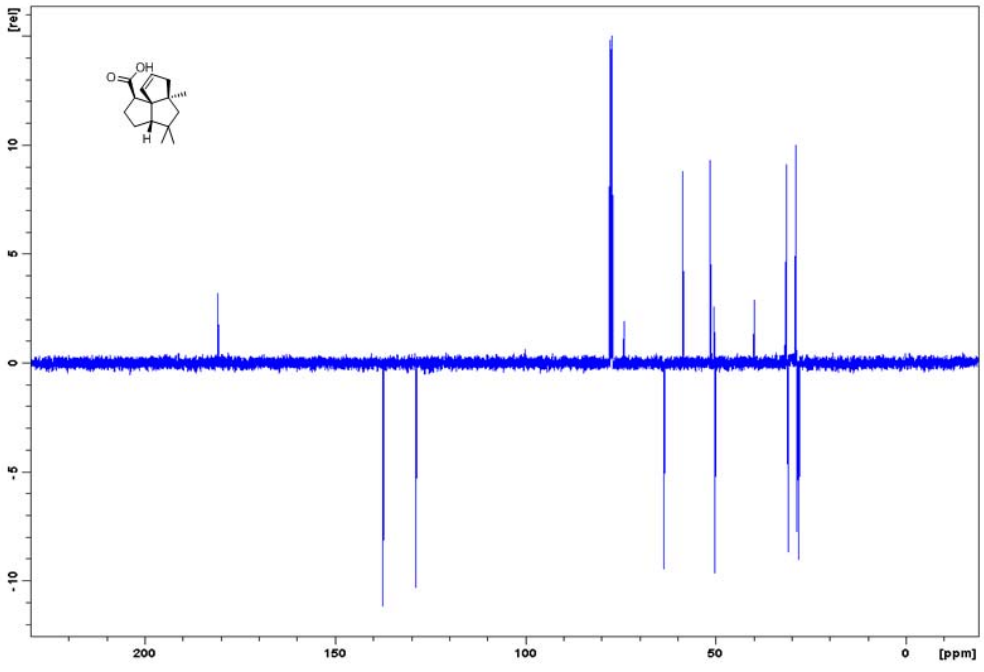
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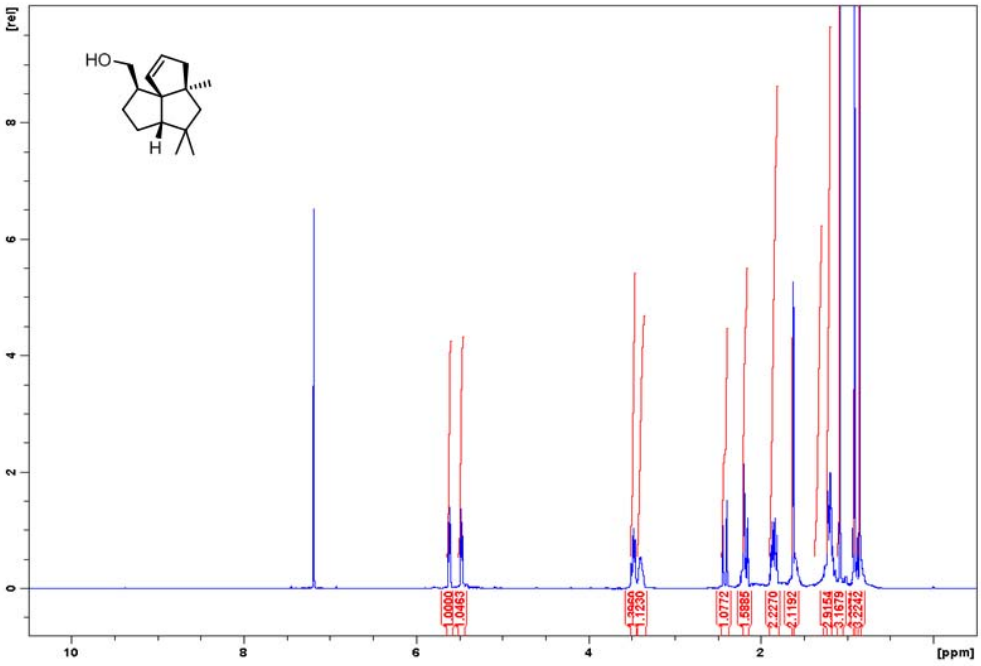
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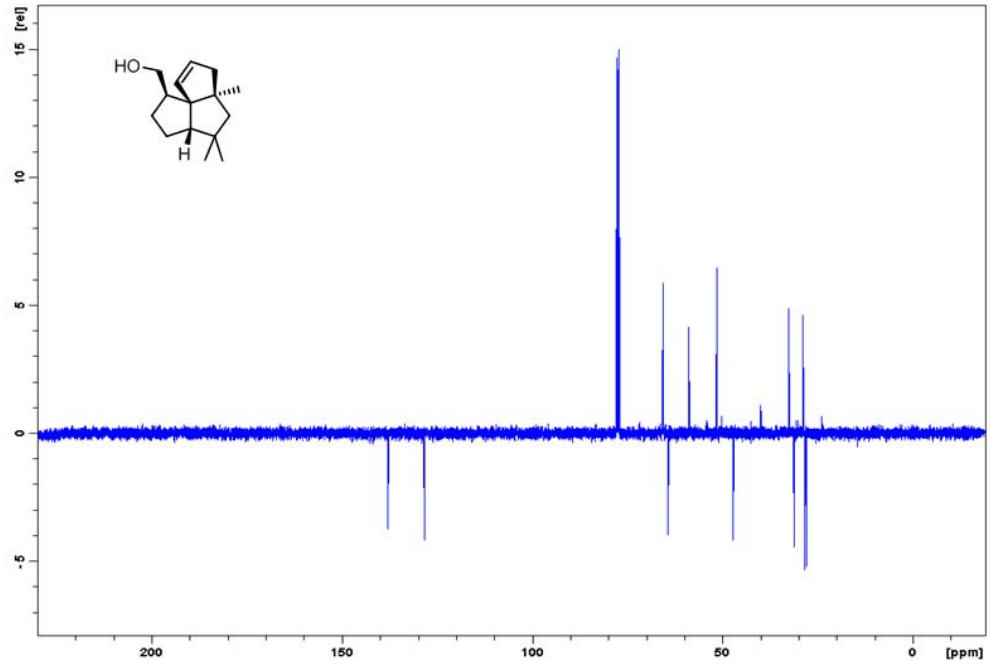
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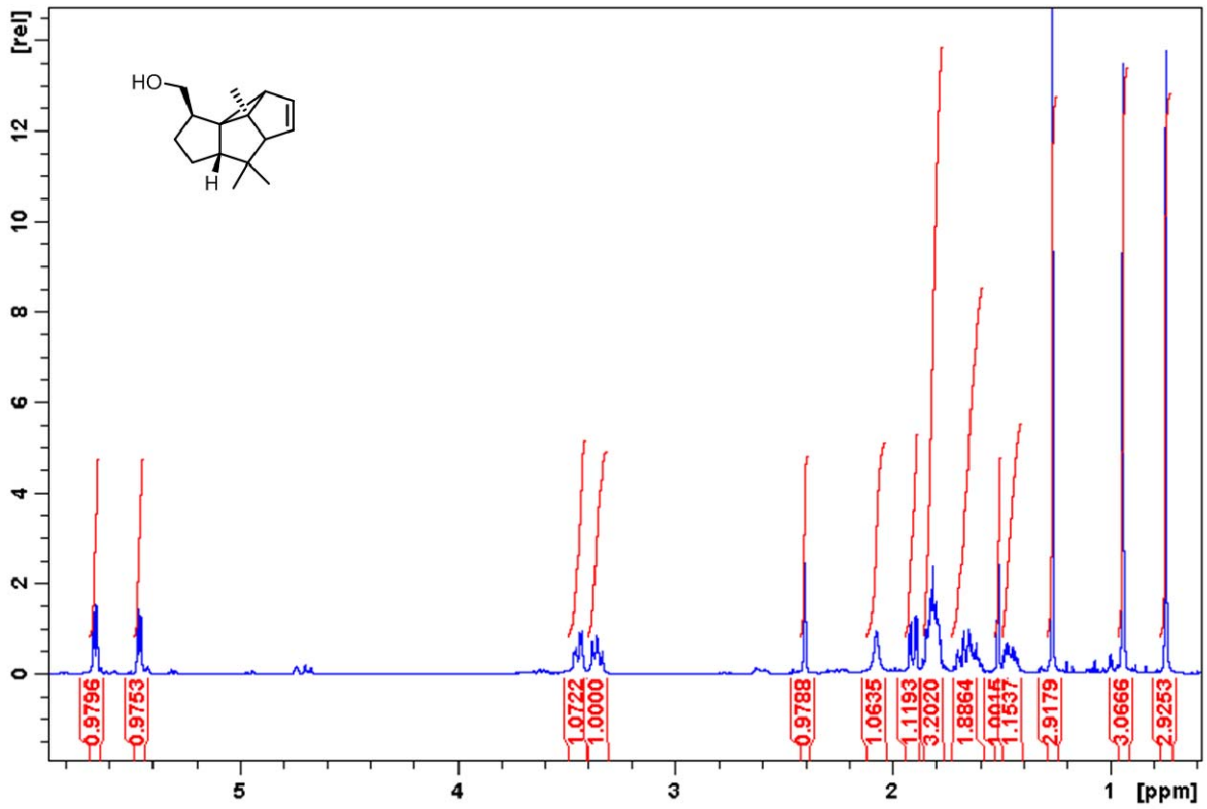
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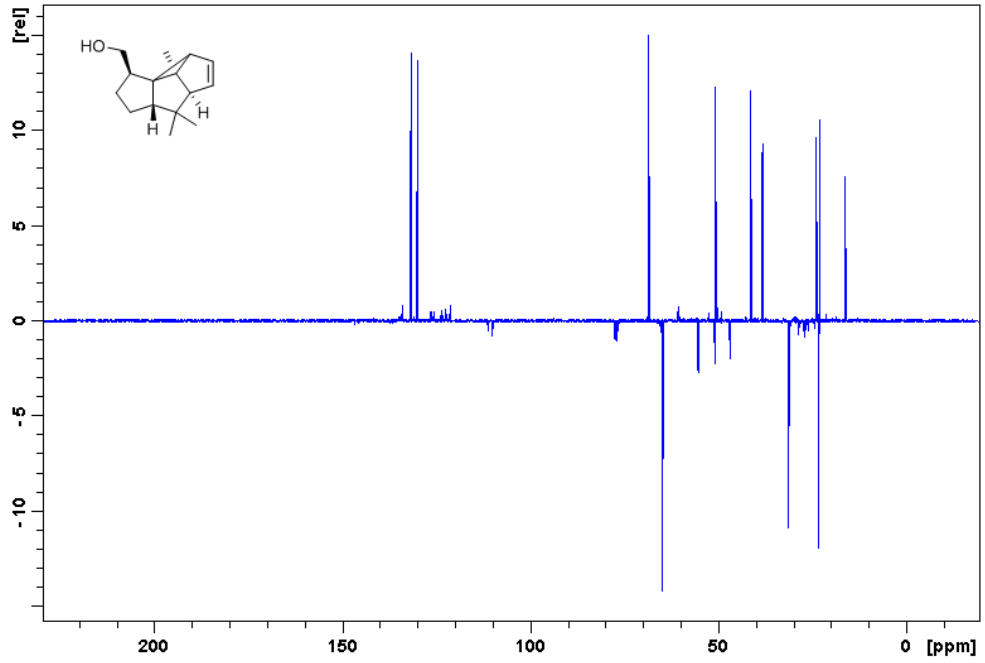
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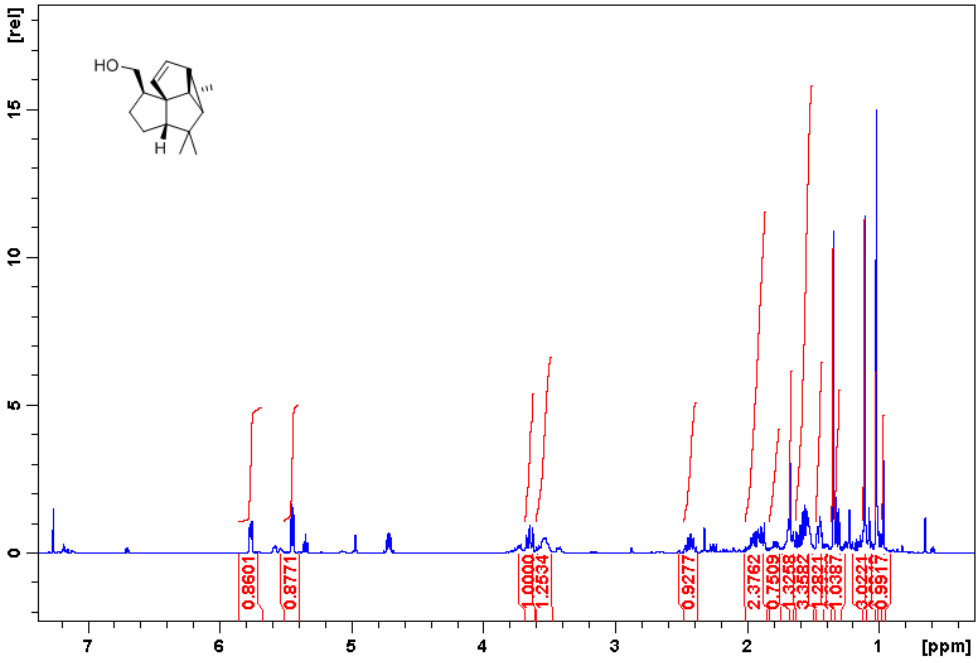
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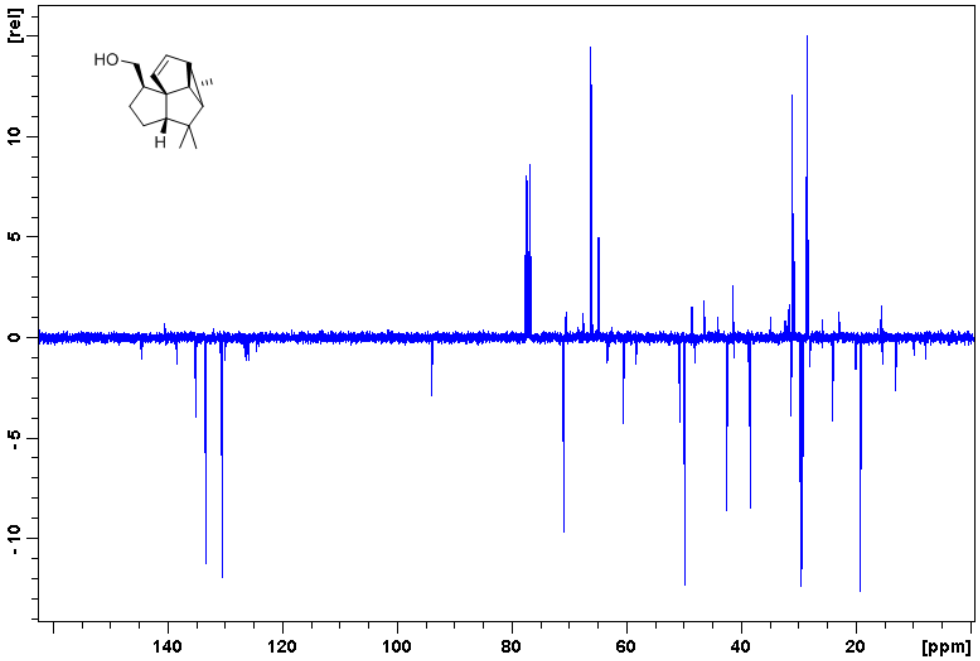
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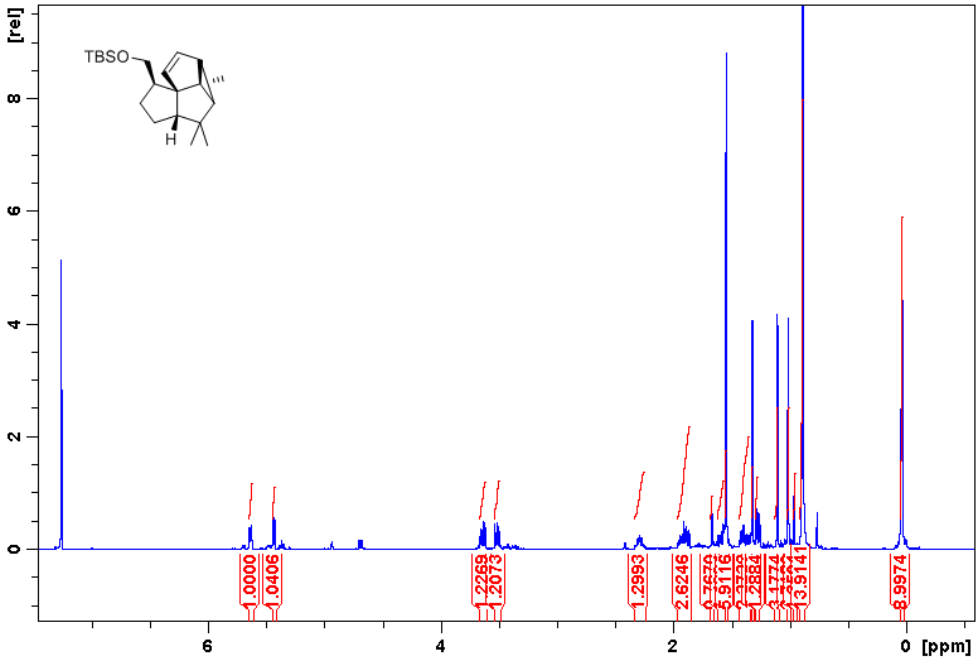
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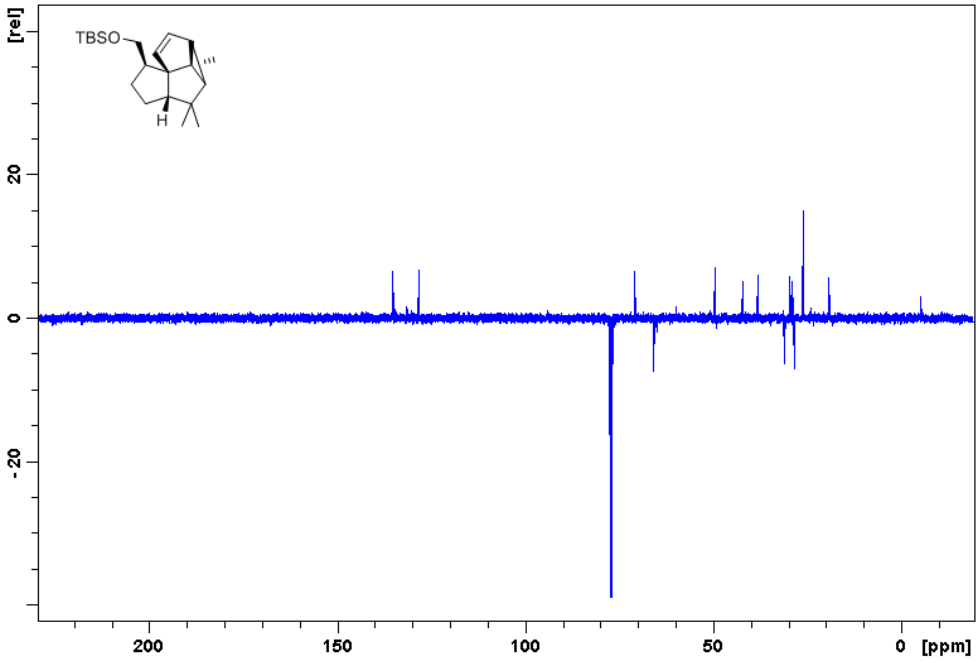
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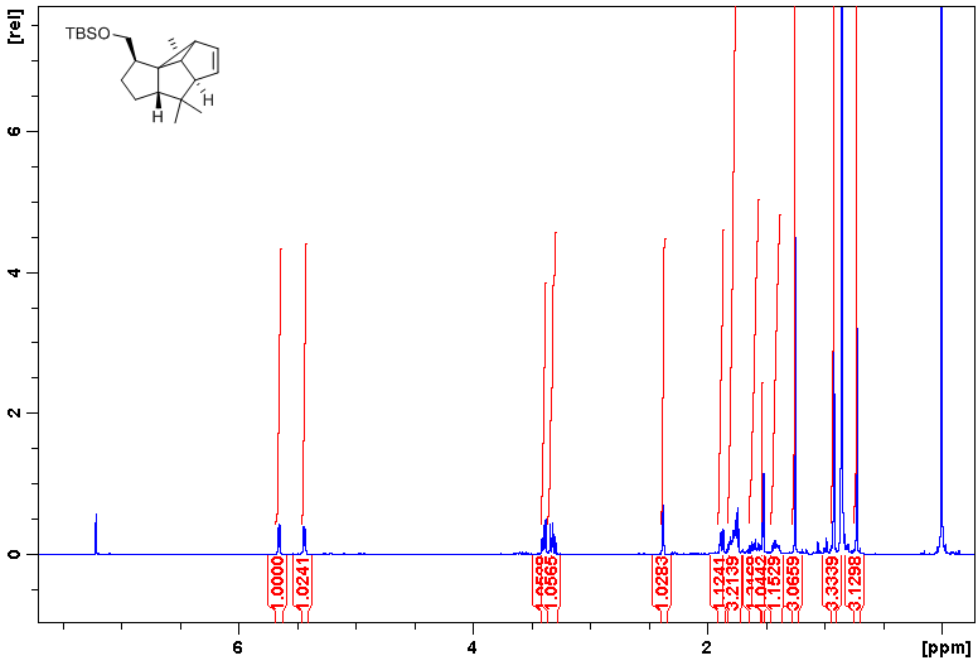
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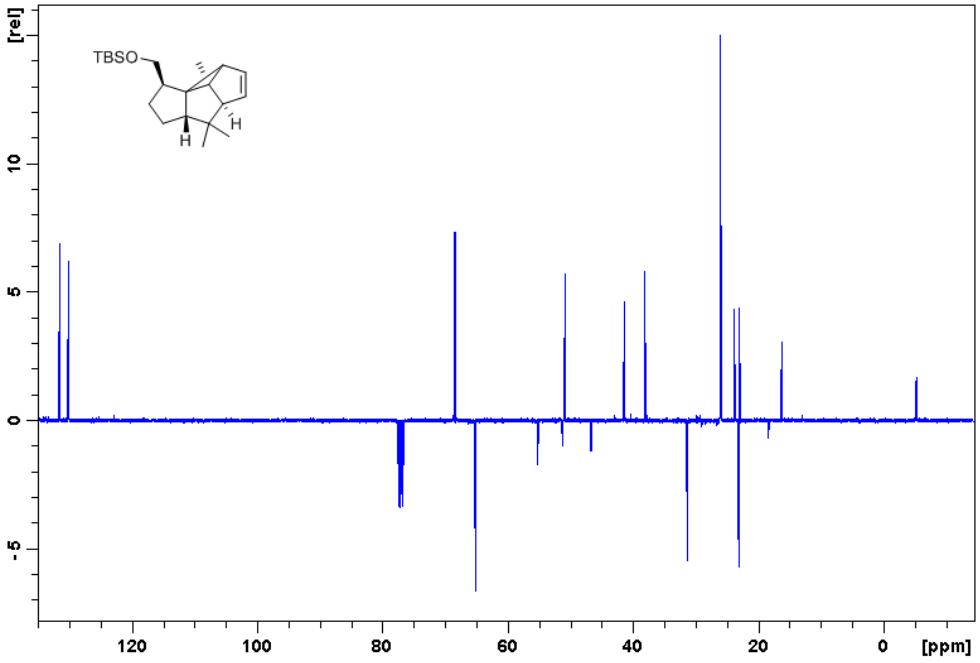
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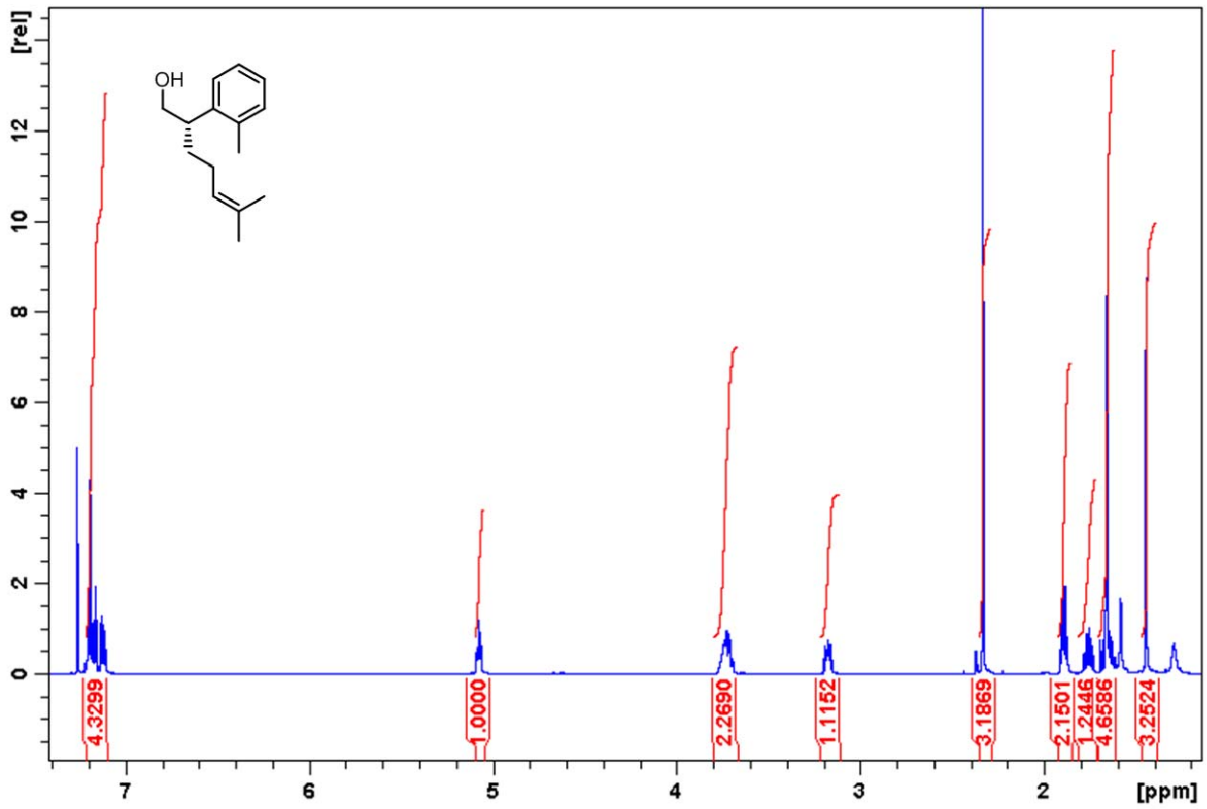
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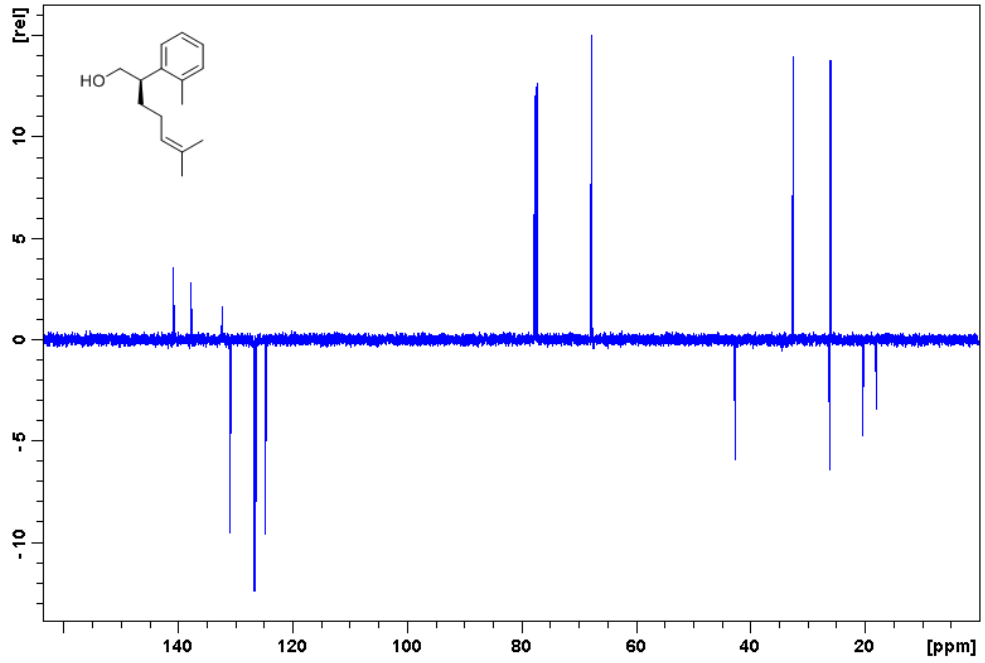
1.0000
2.2690
1.1152
3.1869
2.1501
1.2446
4.6586
3.2524
7
6
5
4
3
2
[ppm]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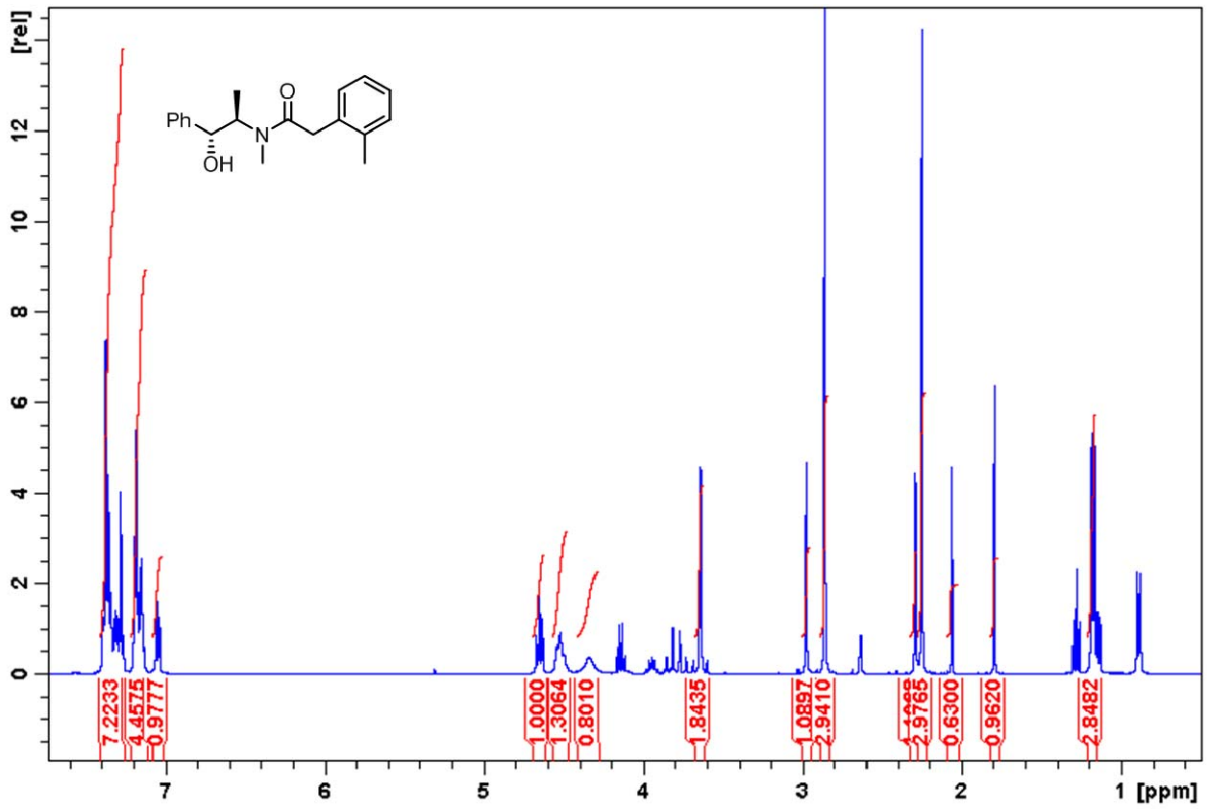
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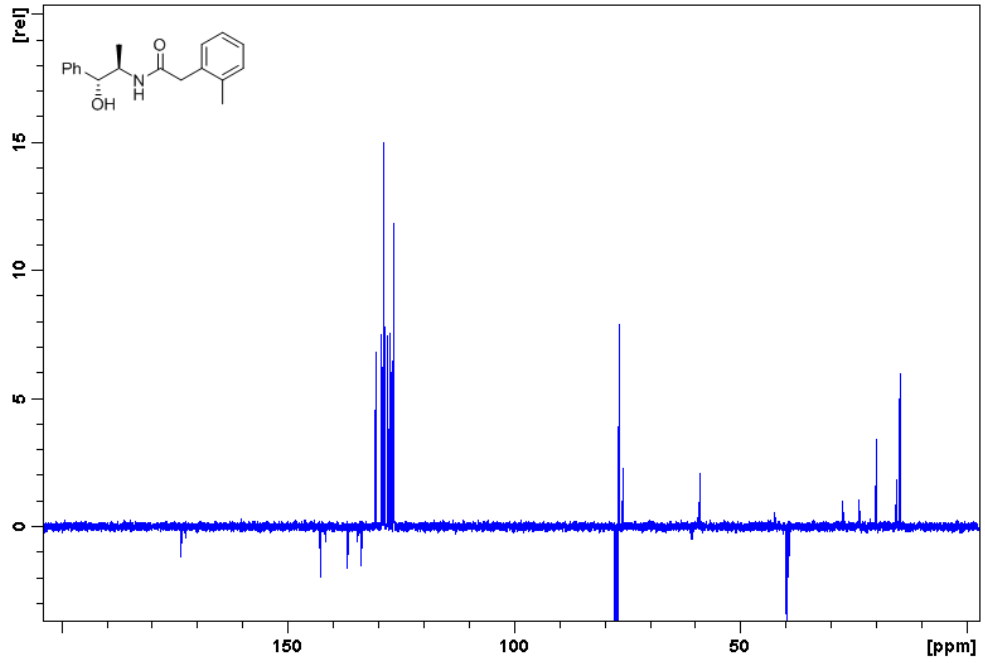
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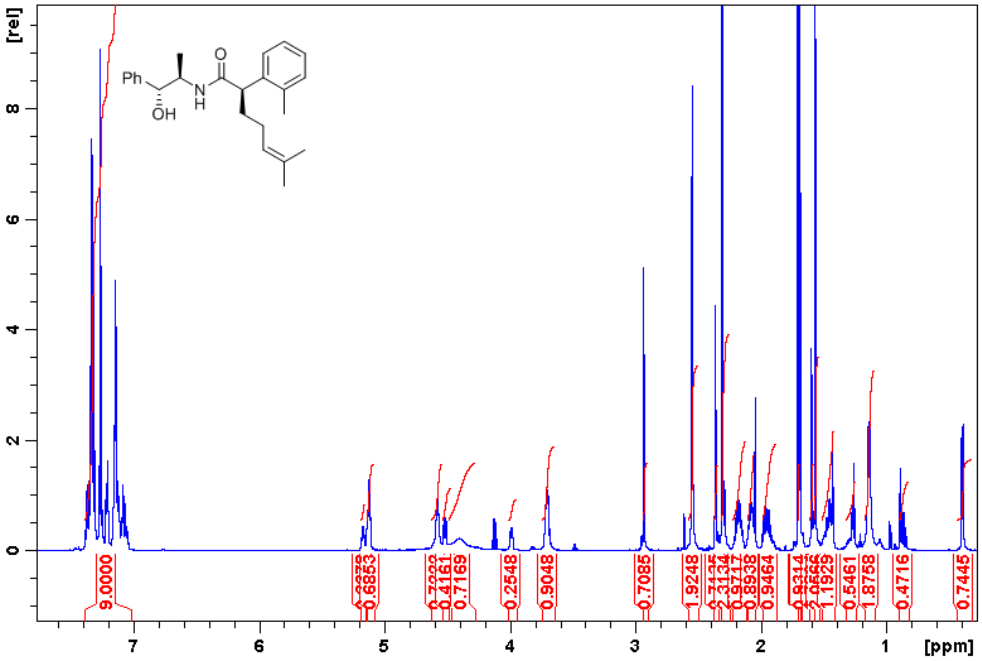
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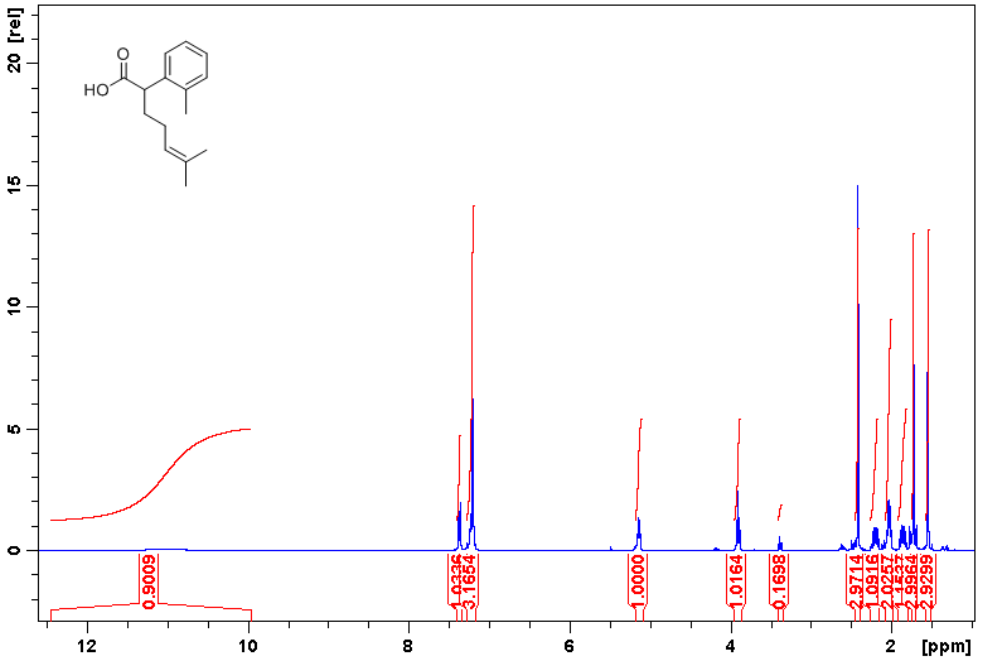
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0.1698
[ppm]

Appendix 6

Total Synthesis of (-)-Penifulvin B and C, a new Structure Type with a Dioxafenestrane Skeleton.

Tanja Gaich* and Johann Mulzer*

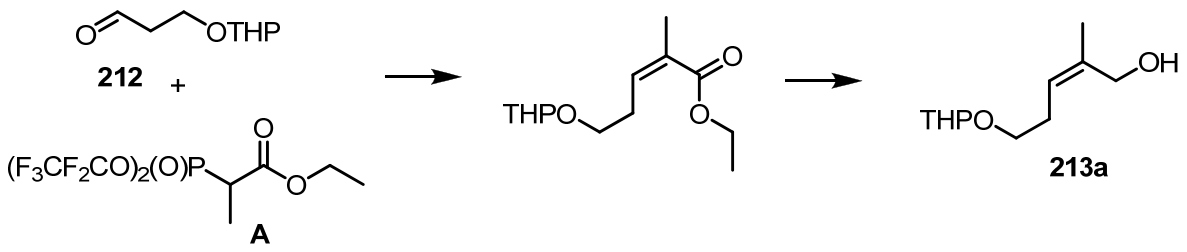
Supporting Information

1. Procedures

General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous CH_2Cl_2 (DCM) was distilled from CaH_2 under argon or reduced pressure, respectively. Anhydrous THF (tetrahydrofuran) was purchased (99.85%, water < 50 ppm). All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel (0.04-0.063mm, 240-400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm; ^{13}C, δ =77.00 ppm). All ^1H and ^{13}C shifts are given in ppm (s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy. Optical rotations were measured at 20°C. High resolution mass spectra (HRMS) were performed with a resolution of 10000. Compound names were generated using AutoNom.

(Z)-2-Methyl-5-(tetrahydro-pyran-2-yloxy)-pent-2-en-1-ol 213a



To a stirred solution of KHMDS in 30 mL THF (0.5 M in toluene, 23.6 mL, 11.8 mmol, 1.1 eq.) at -78°C phosphonate **A** (1.1 eq. 11.8 mmol, 4.1 g, in 10 mL THF)was added dropwise. After stirring at this temperature for 45 minutes, aldehyde **212** (1.0 eq, 10.7 mmol, 1.8 g) was added crude to this mixture. The reaction was quenched after stirring at -78°C for one hour with saturated NH_4Cl solution. The mixture was extracted two times with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. The crude material was submitted to the next reaction without further purification.

Compound **213**(1.6 g, 6.6 mmol, 1 eq) was dissolved in 20 mL diethylether and cooled to -78°C. diisobutylaluminum hydride (1M in hexane, 2.25eq, 14.85 mmol, 14.85mL) was added dropwise to this cooled solution and the reaction mixture was stirred for one hour at that temperature. The reaction was quenched by addition of 1mL methanol and warmed to room temperature. Then it was diluted with Na/K tartrate and stirred over night. The phases were separated and the aquaeous phase was extracted two times with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. Purification of crude **213a** by flash column chromatography (hexane: ethylacetate = 3:1) afforded 918 mg of **213a** as a 6:1 = Z:E mixture of doublebond isomers (798 mg of the Z-isomer and 120 mg of the E-isomer) in 43% over two steps.

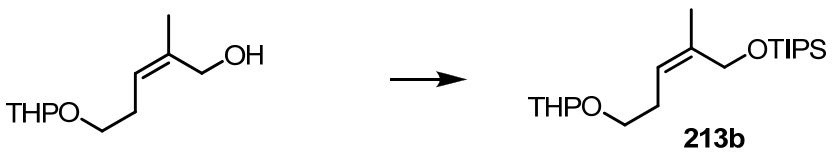
^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.34 p.p.m. (dt, *J*=8.3, 0.4 Hz, 1H), 4.60-4.58 (m, 1H), 4.09-4.00 (m, 2H), 3.87-3.73 (m, 2H), 3.52-3.34 (m, 2H), 2.39-2.33 (m, 2H), 1.82 (d, *J*= 1.26 Hz, 3H), 1.81-1.68 (m, 2H), 1.60-1.48 (m, 4H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 138.35 p.p.m., 125.05, 99.11, 67.11, 62.50, 61.84, 30.79, 28.84, 25.76, 22.83, 19.82.

IR (film): 3423, 2941, 1441, 1201, 1120, 1032, 870, 815, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{11}H_{20}O_3$ 200,1412; found, 200,1430.

Triisopropyl-[(Z)-2-methyl-5-(tetrahydro-pyran-2-yloxy)-pent-2-enyloxy]-silane 213b



213b

Alcohol **213a** (798 mg, 4 mmol, 1eq.) was dissolved in 2 mL DMF at room temperature. Imidazole (652 mg, 9.6 mmol, 2.4 eq.) was added in one portion to the stirred solution. Then

triisopropylchlorosilane (940 µl, 4.4 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred over night. The reaction was diluted with diethylether and quenched with water. The mixture was extracted twice with diethylether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. Purification of crude **213b** by flash column chromatography (hexane: ethylacetate = 10:1) afforded pure **213b**, 1.4 g in 98% yield.

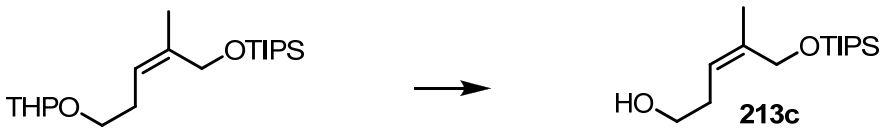
^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.23 p.p.m. (ddt, *J*=7.3, 2.4, 1.1 Hz, 1H), 4.58-4.56 (m, 1H), 4.25 (m, 2H), 3.88-3.82 (m, 1H), 3.73-3.66 (m, 1H), 3.51-3.46 (m, 1H), 3.37 (ddd, *J*= 8.5, 8.5, 7.2 Hz, 1H), 2.32 (dd, *J*= 13.7, 6.9 Hz, 2H), 1.86-1.79 (m, 1H), 1.78 (d, *J*= 1.1 Hz, 3H), 1.74-1.66 (m, 1H), 1.59-1.48 (m, 4H), 1.07 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 137.71 p.p.m., 122.03, 99.21, 67.68, 62.72, 62.47, 31.13, 28.65, 25.90, 21.37, 20.01, 18.43, 12.42.

IR (film): 2942, 1463, 1260, 1120, 1034, 986, 682, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{20}H_{30}O_3Si$ 356,2747; found, 356,2753.

(Z)-4-Methyl-5-triisopropylsilanyloxy-pent-3-en-1-ol 213c



213c

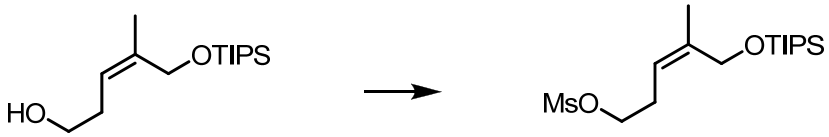
To a stirred solution of compound **213b** (2.6 g, 7.3 mmol) in 40 mL MeOH were added 500 mg Montmorillionite K10 at room temperature. The reaction mixture was stirred for 6 hours. Then it was quenched with saturated $NaHCO_3$ solution. The mixture was extracted two times with diethylether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. Purification of crude **213c** by flash column chromatography (hexane: ethylacetate = 3:1) afforded pure **213c**, 1.36g in 68% yield.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.25 p.p.m. (ddt, *J*=7.7, 2.1, 0.9 Hz, 1H), 4.23 (s, 2H), 3.61 (dd, *J*=11.6, 6.1 Hz, 2H), 2.31 (dd, *J*=12.9, 6.3 Hz, 2H), 1.82 (d, *J*=1.26 Hz, 3H), 1.77 (t, *J*=5.4 Hz, 1H), 1.08 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 138.97 p.p.m., 122.88, 62.43, 31.53, 22.08, 18.41, 6.20.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{32}O_2Si$ 272,2172; found, 272,2170.

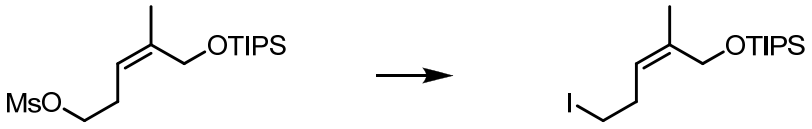
Methanesulfonic acid (Z)-4-methyl-5-triisopropylsilanyloxy-pent-3-enyl ester 213d



Alcohol **213c** (1.1 g, 4 mmol, 1eq.) was dissolved in 10 mL dichloromethane and the solution was cooled to 0°C. Pyridine (500µL, 6 mmol, 1.5eq.) and methanesulfonylchloride (345 µL, 4.4 mmol, 1.1eq.) were added sequentially and dropwise to this solution. The mixture was warmed to room temperature and stirred another two hours at this temperature. Saturated NH_4Cl solution was added and the mixture was extracted two times with diethylether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. Crude **213d** 1.4 g was directly submitted to the next reaction without further purification.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.18 p.p.m. (ddt, *J*=7.4, 2.1, 0.8 Hz, 1H), 4.23 (s, 2H), 4.18 (t, *J*=6.8 Hz, 2H), 2.99 (s, 3H), 2.50 (dd, *J*=13.8,6.8 Hz, 2H), 1.80 (d, *J*=1.2 Hz), 1.07 (s, 20 Hz).

((Z)-5-Iodo-2-methyl-pent-2-enyloxy)-triisopropyl-silane 214



Mesylate **213d** (1.4 g, 4 mmol, 1eq.) was dissolved in 8 mL acetone at room temperature. Sodium iodide (3.02 g, 20 mmol, 5eq.) was added to this mixture and stirred over night. The reaction was diluted with water and the resulting mixture was extracted two times with diethylether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo. Purification of crude **214** by flash column chromatography (hexane: ethylacetate = 20:1) afforded pure **214**, 1.5g in 98% yield.

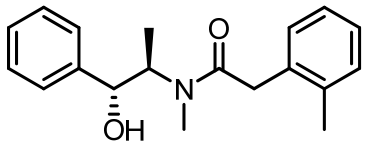
^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.16 p.p.m. (ddt, *J*=7.3, 2.4, 1.2 Hz, 1H), 4.21 (s, 2H), 3.11 (t, *J*=7.4 Hz), 2.61 (dd *J*=14.3, 7.1 Hz, 2H), 1.78 (d, *J*=1.2 Hz, 3H), 1.07 (s, 20H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 138.51 p.p.m., 124.66, 62.59, 32.33, 21.58, 18.44, 122.41, 6.20.

IR (film): 2940, 882, 739, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{32}IOSi$ 382,1189; found, 382,1178.

***N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-*o*-tolylacetamide 210**



o-Tolylacetic acid (1.00 g, 6.7 mmol, 1 eq.), (*R*,*R*)-pseudoephedrine (1.20 g, 7.3 mmol, 1.1 eq.), and *N*,*N*-dimethyl-4-amino pyridine were dissolved in DCM (40 mL) at room temperature. After the starting materials had dissolved, the solution was cooled to 0°C in an ice bath and diisopropyl carbodiimide (1.1 mL, 7.3 mmol, 1.1 eq.) was added dropwise. After 20 min a precipitate was formed, and the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated on the rotatory evaporator and directly submitted to flash column chromatography (hexane:ethylacetate=3:1) yielding 1.95 g (98%) of the desired amide **210**.

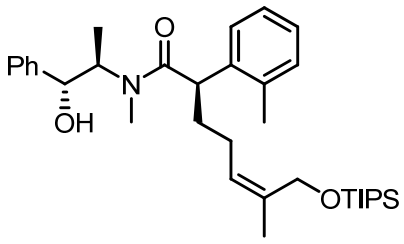
^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.39-7.26 p.p.m. (m, 5H), 7.20-7.04 (m, 4H), 4.65 (t, *J*=7.3 Hz, 1H), 4.55-4.48 (m, 1H), 4.34 (s, br 1H), 3.64 (d, *J*=2.3 Hz, 2H), 2.86 (s, 3H), 2.25 (s, 3H), 1.18 (d, *J*=6.8 Hz, 3H). ^{13}C-NMR (100MHz, $CDCl_3$): δ= 173.70 p.p.m., 142.83, 136.84, 133.81, 130.63, 129.28, 128.79, 128.04, 127.42, 126.72, 126.65, 76.88, 75.97, 59.09, 39.83, 20.02, 14.85.

IR (film): 3383, 2971, 1699, 1617, 1558, 1452, 1404, 1118, 1051, 743, 702, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ c alcd for $C_{19}H_{23}NO_2$ 297.1729; found, 297.1715.

$[\alpha]_D$= -96 (c 1.05g/100mL, $CHCl_3$).

(Z)-(R)-6-Methyl-2-*o*-tolyl-7-triisopropylsilanyloxy-hept-5-enoic acid ((1R,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide 214a



A solution of *n*-butyllithium (3.45 mL, 2.5M, 8.6 mmol, 2.2 eq.) was added to a suspension of LiCl (1.0 g, 23.5 mmol, 6 eq.) and diisopropylamine (1.2 mL, 8.6 mmol, 2.2 eq.) in THF (5 mL) at -78°C. The resulting suspension was briefly warmed to 0°C and then cooled to -78°C. Amide **210** (1.16 g, 3.9 mmol, 1 eq.) was added to this mixture *via* cannula and stirred at that temperature for 1 h, then at 0°C for 15 min and at 23°C for 5 min. The mixture was cooled to 0°C and iodide **214** (1.5 g, 3.9 mmol,

1eq.) was added neat to this reaction mixture. After stirring at room temperature for 24 h the mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3x100 mL). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (hexane:ethylacetate=3:1) afforded 1.50 g (70%)of amide **214a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.41-6.92 p.p.m. (m, 9H), 5.38 (t, *J*=7.5 Hz, 0.45H), 5.26 (t, *J*=7 Hz 0.6 Hz), 4.50-4.35 (m, 2.5H), 4.29-4.25 (m, 0.5H), 4.19-4.10 (m, 1.27H), 3.74-3.68 (m, 0.45H), 3.55-3.51 (m, 0.6H), 2.86 (s, 1H), 2.55-2.45 (m, 0.43H), 2.37 (s, 1H), 2.34-2.21 (m, 3H), 2.13-2.11 (m,6H), 1.96-1.92 (m, 3H), 1.60-1.51 (m, 1.35H), 1.32-1.24 (m, 0.8H), 1.18-1.12 (m, 20H).

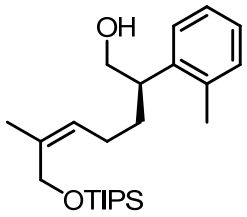
^{13}C-NMR (100MHz, $CDCl_3$): δ= 173.70 p.p.m., 137.44, 130.73, 128.33, 127.68, 126.96, 126.87, 76.41, 62.61, 35.19, 26.70, 20.85, 19.03, 18.25, 14.00, 12.68.

IR (film):3421, 2941, 1624, 1457, 1242, 882, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{34}H_{53}O_3Si$ 551,3795; found, 551,3801.

$[\alpha]_D$= -93° (c 0.55g/100mL, $CHCl_3$).

(Z)-(R)-6-Methyl-2-*o*-tolyl-7-triisopropylsilanyloxy-hept-5-en-1-ol 215



A solution of *n*-butyllithium (4.25 mL, 2.5M, 10.6 mmol, 4 eq.) in hexanes was added to a solution of diisopropylamine (1.6 mL, 11.4 mmol, 4.2 eq.) in THF (9 mL) at -78°C. The resulting solution was stirred at this temperature for 10 min, then warmed to 0°C and held at that temperature for 10 min. Borane-ammonia complex (335mg, 10.9 mmol, 4 eq.) was added in one portion. The suspension was stirred at 0°C for 15 min, then at 23°C for 15 min, cooled again to 0°C and a solution of amide **214a** (1.50 g, 2.7 mmol, 1 eq.) in THF (6 mL) was added *via* cannula. The reaction mixture was warmed to room temperature and stirred for 2 h before it was cooled to 0°C again and carefully quenched with 1M hydrochloric acid (40 mL). The mixture was diluted with water (100 mL) and extracted with ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **215** (904 mg, 91%) as a yellow oil which was directly used in the next step. An analytical sample was purified by chromatography (hexane:ethyl acetate 5:1).

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.41-6.92 p.p.m. 5.08 (ddt, *J*=7.4, 2.0, 0.9 Hz, 1H), 3.92 (dd, *J*=18.0, 11.8 Hz), 3.68-3.61 (m, 2H), 3.12-3.05 (m, 1H), 2.25 (s, 3H), 1.84 (dd, *J*=14.8, 7.3 Hz, 2H), 1.75-1.68 (m, 1H), 1.67 (d, *J*=1.25 Hz, 3H), 1.61-1.51 (m, 1H), 1.19 (t *J*=1.2 Hz, 1H), 0.94 (s, 20H).

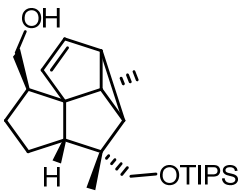
^{13}C-NMR (100MHz, $CDCl_3$): δ= 140.01 p.p.m., 137.21, 135.74, 130.59, 126.38, 125.80, 125.53, 67.33, 61.80, 42.37, 32.34, 25.16, 21.05, 19.87, 18.05, 11.99.

IR (film): 3356, 2941, 2865, 1458, 1383, 1063, 882, 610 cm^{-1}.

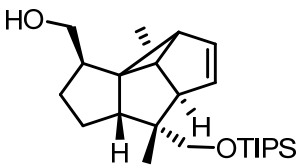
HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{24}H_{42}O_2Si$ 390,2954; found, 390,2946.

$[\alpha]_D$= -11° (c 0.55g/100mL, $CHCl_3$).

((1R,1aR,4R,4aR,6cS)-1,6c-Dimethyl-1-triisopropylsilanyloxymethyl-1,1a,2,3,4,6a,6b,6c-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalen-4-yl)-methanol 216



216



217

Compound **215** (638 mg, 1.64 mmol) in pentane (90 mL) was irradiated with a Hannovia 700W medium pressure mercury lamp with a quartz filter at room temperatur for 2 h. The reaction mixture was concentrated and the crude residue was submitted to flash column chromatography (hexane:ethylacetate = 10:1) yielding 170 mg **216** and 238 mg **217** total 64% yield) in a 1:1.4 ratio.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.78 p.p.m. (dd, *J*= 5.3, 2.7 Hz, 1H), 5.47-5.45 (m, 1H), 3.69-3.62 (m, 1H), 3.59-3.52 (m, 1H), 3.56 (d, *J*= 9.3 Hz, 1H), 3.49 (d, *J*= 9.3 Hz, 1H), 2.48-2.36 (m, 1H), 1.98-1.88 (m, 1H), 1.76-1.58 (m, 2H), 1.56 (s, 1H), 1.53-1.44 (m, 2H), 1.34 (s, 3H), 1.17 (s, 3H), 1.06 (s, 20H).

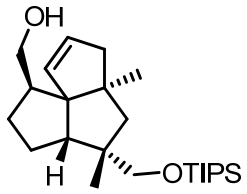
^{13}C-NMR (100MHz, $CDCl_3$): δ= 133.49 p.p.m., 130.64, 70.92, 69.17, 66.07, 48.12, 47.01, 45.50, 41.93, 37.80, 31.29, 28.51, 27.16, 24.38, 18.98, 18.18, 12.22.

IR (film): 3355, 2955, 1471, 1255, 1093, 836, 774, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{24}H_{42}O_2Si$ 390,2954, found, 390.2943.

$[\alpha]_D$= -36° (c 0.30g/100mL, $CHCl_3$).

((1R,3aR,4S,5aS,8aR)-4,5a-Dimethyl-4-triisopropylsilanyloxymethyl-1,2,3,3a,4,5,5a,6-octahydro-cyclopenta[*c*]pentalen-1-yl)-methanol 216a



A solution of **216** (170 mg, 0.43 mmol, 1 eq.) in absolute THF (200µL) was cooled to -78°C and ethylamine (5 mL) was condensed in. Small pieces of lithium (18 mg, 2.60 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h until a deep blue color formed. The excess lithium was quenched with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo*. Crude **216a** was subjected to flash column chromatography (hexanes:ethyl acetate 10:1) to give 145 mg, in 86% yield as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.70 p.p.m. (dt, *J*= 5.6, 2.2 Hz, 1H), 5.58 (dt, *J*= 5.6, 2.3 Hz, 1H), 3.59-3.54 (m, 1H), 3.52-3.45 (m, 1H), 3.50 (d, *J*= 9.1 Hz, 1H), 3.40 (d, *J*= 9.3 Hz, 1H), 2.54 (dt, *J*= 17.4, 2.3 Hz, 1H), 2.29 (dt, *J*= 17.4, 2.2 Hz, 1H), 2.28-2.11 (m, 1H), 1.80-1.75 (m, 1H), 1.70-1.50 (m, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 1.05 (s, 20H).

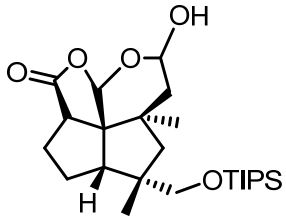
^{13}C-NMR (100MHz, $CDCl_3$): δ= 137.32 p.p.m., 128.31, 71.02, 65.22, 61.86, 53.71, 53.21, 51.35, 49.85, 46.34, 45.06, 31.75, 28.54, 27.89, 25.53, 18.10, 12.09.

IR (film): 3355, 2955, 1471, 1255, 1093, 836, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{24}H_{42}O_2Si$ 392,3111; found,392,3100.

$[\alpha]_D$= -16° (c 0.25g/100mL, $CHCl_3$).

Compound 225



Alcohol **216a** (145 mg, 0.37 mmol, 1 eq.) was dissolved in 3 mL dimethylsulfoxide. IBX (130mg, 0.46 mmol, 1.5 eq.) was added to this stirred solution at room temperature. The mixture was stirred for

one hour, diluted with diethyl ether and water and extracted two times with ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The crude aldehyde was dissolved in3 mL *tert*-butanol and 1 mL 2,3-dimthyl-2-butene was added. Sodium chlorite (370 mg, 3.7 mmol, 10 eq.) and 370 mg sodium dihydrogen phosphate were dissolved in 1.5 mL water. The solution was added dropwise to the aldehyde at room temperature, and the mixture was stirred for another 30 minutes. The reaction mixture was quenched with brine and extracted four times with dichloromethane. The combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo*.

Crude acid **223** (110 mg, 0.27 mmol, 1 eq) was dissolved in dichloromethane (6 mL) in a three necked round bottom flask equipped with a gas outlet and a gas inlet-tube. The solution was cooled to -78°C and ozonized for 2 min (flow 100mL/min) until the solution was dark blue. The excess ozone was driven out with air until the solution became colorless again. Then thiourea (25 mg, 0.33 mmol, 1.2 eq.) was added in one portion and the suspension was warmed to room temperature and stirred for 40 min giving a cloudy solution. The solvent was removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethyl acetate=5:1) yielding 62 mg 38% of lactol **225** over 3 steps.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.68 p.p.m. (s, 1H), 5.38 (ddd, *J*= 8.6, 5.8, 2.5 Hz, 1H), 3.48 (d, *J*= 9.8 Hz, 1H), 3.44 (d, *J*= 9.8 Hz, 1H), 2.93 (d, *J*= 7.6 Hz, 1H), 2.90 (d, *J*= 2.8 Hz, 1H (OH)), 2.28 (dd, *J*= 9.6, 2.0 Hz, 1H), 2.20-2.14 (m, 1H), 2.12-2.03 (m, 2H), 1.95 (dd, *J*= 14.4, 5.5 Hz, 1H), 1.83-1.73 (m, 1H), 1.57 (s, 2H), 1.27 (s, 3H), 1.09 (s, 3H), 1.06 (s, 20H).

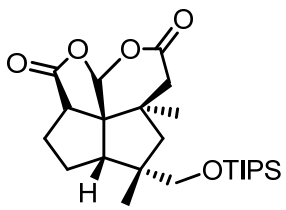
^{13}C-NMR (100MHz, $CDCl_3$): δ= 179.42 p.p.m., 101.44, 91.46, 68.94, 66.52, 58.94, 52.66, 46.75, 45.64, 42.50, 41.39, 31.22, 29.56, 27.71, 26.42, 17.92, 12.01.

IR (film): 3629, 2956, 1791, 1464, 1251, 1094, 857, 739, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{24}H_{42}O_5Si$ 438.2802, found 438.2798.

$[\alpha]_D$= -66° (c 0.85g/100mL, $CHCl_3$).

Compound 225a



Lactol **225** (31 mg, 71 µmol, 1eq) was dissolved in dichloromethane (0.5 mL) at room temperature. PDC (160 mg, 0.42 mmol, 6 eq.) was added in one portion. After 20 min acetic acid (9 µL, 28 µmol,

0.4 eq.) was added dropwise. The reaction mixture was stirred for another 24 hours and then diluted with diethyl ether. The suspension was filtered through a silica pad and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 20 mg (65% yield) of acylal **225a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.95 p.p.m., (s, 1H), 3.51 (s, 2H), 2.96 (d, *J*= 7.3 Hz, 1H), 2.83 (d, *J*= 15.1 Hz, 1H), 2.49 (d, *J*= 15.0 Hz, 1H), 2.38 (dd, *J*= 10.0, 7.3 Hz, 1H), 2.27-2.21 (m, 1H), 2.05-1.97 (m, 1H), 1.95-1.87 (m, 1H), 1.80-1.73 (m, 1H), 1.77 (d, *J*= 13.9 Hz, 1H), 1.62 (d, *J*= 13.9 Hz, 1H), 1.29 (s, 3H), 1.11 (s, 3H), 1.06 (s, 20Hz).

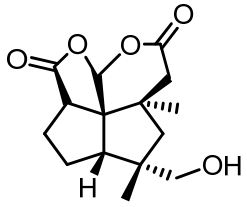
^{13}C-NMR (100MHz, $CDCl_3$): δ= 168.42 p.p.m., 167.86, 103.60, 68.89, 66.14, 59.23, 50.56, 46.35, 45.78, 44.32, 41.84, 30.04, 28.16, 27.36, 27.27, 18.02, 11.95.

IR (film): 2960, 1799, 1771, 1653, 1559, 1507, 1458, 1367, 1115, 1043, 995, 905, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{24}H_{40}O_5Si$ 436.4645, found 436. 4637.

$[\alpha]_D$= -72° (c 1.00g/100mL, $CHCl_3$).

Penifulvin C 139



Acylal **225a** (10 mg, 23 µmol, 1 eq.) was dissolved in 0.5 mL tetrahydrofuran. To this solution 200 µL 35% HF/pyridine were added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The reaction was poured on 20 mL 0.5M HCl solution and extracted four times with ethyl acetate. The combined organic layers were washed with brine dried over magnesium sulfate and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 1:2) gave 5 mg 78% yield of Penifulvin C. **139**

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.96 p.p.m., 3.49 (dd, *J*= 10.5, 4.2 Hz, 1H), 3.47 (dd, *J*= 10.5, 4.2 Hz 1H), 2.98 (d, *J*= 6.3 Hz, 1H), 2.83 (d, *J*= 14.9 Hz, 1H), 2.50 (d, *J*= 14.9 Hz, 1H), 2.41 (dd, *J*= 9.8, 4.3 Hz, 1H), 2.29-2.23 (m, 1H), 2.01-1.89 (m, 2H), 1.83-1.75 (m, 1H), 1.75 (d, *J*= 14.2 Hz, 1H), 1.68 (d, *J*= 14.2 Hz, 1H), 1.32 (s, 3H), 1.12 (s, 3H).

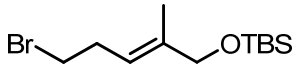
^{13}C-NMR (100MHz, $CDCl_3$): δ= 177.72 p.p.m., 168.41, 103.74, 69.38, 66.61, 59.19, 50.89, 46.31, 45.25, 44.37, 42.08, 30.31, 27.79, 27.54, 27.44.

IR (film): cm^{-1}

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1301.

$[\alpha]_D$= -72° (c 1.00g/100mL, $CHCl_3$).

((E)-5-Bromo-2-methyl-pent-2-enyloxy)-*tert*-butyl-dimethyl-silane 209



To a suspension of selenium dioxide (0.832 g, 7.5 mmol, 0.5 eq.) in dry dichloromethane (20 mL) at 0°C was added slowly anhydrous *tert*-butyl hydroperoxide (5-6 M, in decane, 5.45 mL ~30 mmol, 2.0 eq.). The mixture was stirred at 0°C for 5 minutes and then the ice bath was removed. The resulting mixture was stirred at room temperature for 30 minutes and was then cooled to 0°C again. A solution of5-Bromo-2-methyl-2-pentene (2.45 g, 15 mmol, 1eq.) in dry dichloromethane (15 mL) was added slowly. The resulting suspension was then stirred at room temperature for 12 hours. The mixture was diluted with ether (100 mL) and filtered to remove solid compounds. The filtrate was washed with 10% aq. KOH (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography (hexanes:ethyl acetate 4:1) gave 1.82g of the (*E*)-alcohol in 68% yield as a yellow oil with spectra identical to those reported in literature.

Crude alcohol (1 g, 5.6 mmol, 1 eq.) was dissolved in dimethyl formamide (6 mL). Imidazole (920 mg, 13.4 mmol, 2.4 eq.) was added and the mixture was stirred at room temperature. TBSCl (926 mg, 6.1 mmol, 1.1 eq.) was added to this mixture and stirred over night. The reaction mixture was diluted with ether and water. The water phase was extracted two times with ether. The combined organic layers were dried over magnesium sulfate, and concentrated under reduced pressure. Flash column chromatography (hexanes:ethyl acetate 20:1) gave 1.6 g, 98% of compound **209**.

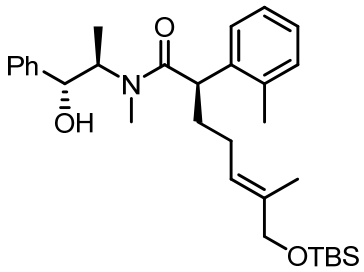
^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.35 p.p.m., (ddt, *J*= 7.2, 2.9, 1.4 Hz, 1H), 3.95 (s, 2H), 3.29 (t, *J*= 7.3 Hz, 2H), 2.55 (dd, *J*= 14.2, 7.0 Hz, 2H), 1.54 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 177.72 p.p.m., 138.01, 120.85, 68.42, 32.87, 31.63, 26.10, 18.81,14.00, -4.9.

IR (film): 2956, 1472, 1253, 1072, 837, 776, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{12}H_{25}BrOSi$ 292.0858, found 292.0864.

(E)-(R)-7-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-2-*o*-tolyl-hept-5-enoic acid ((1R,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amide 209a



A solution of *n*-butyllithium (4.50 mL, 2.5M, 11.18 mmol, 2.05 eq.) was added to a suspension of LiCl (1.42 g, 33.54 mmol, 6 eq.) and diisopropylamine (1.6 mL, 11.18 mmol, 2.05 eq.) in THF (5 mL) at -78°C. The resulting suspension was briefly warmed to 0°C and then cooled to -78°C. Amide **210** (1.78 g, 6.0 mmol, 1.1 eq.) in THF (3 mL) was added to this mixture *via* cannula and stirred at that temperature for 1 h, then at 0°C for 15 min and at 23°C for 5 min. The mixture was cooled to 0°C and bromide xxx (1.6 g, 5.5 mmol, 1eq.) was added neat to this reaction mixture. After stirring at room temperature for 24 h the mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3x100 mL). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (hexane:ethylacetate=3:1) afforded 1.90 g (68%)of amide **209a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.37-7.04 p.p.m., (m, 9H), 5.46-5.38 (m, 1H), 4.60-4.49 (m, 1H), 4.47-4.34 (m, 1H), 4.00 (s, 2H), 3.76-3.65 (m, 1H), 2.92 (s, 1H), 2.55 (s, 2H), 2.38 (s, 1H), 2.30 (s, 2H), 2.24-2.08 (m, 2H), 2.04-1.97 (m, 2H), 1.59 (s, 1H), 1.55 (s, 2H), 1.52-1.45 (m, 1H), 1.13 (s, 1H), 1.12 (s, 2H), 0.9 (s, 9H), 0.06 (s, 6H).

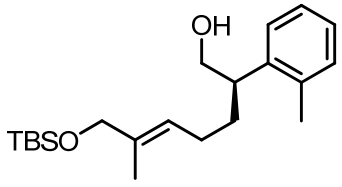
^{13}C-NMR (100MHz, $CDCl_3$): δ= 175.93 p.p.m., 142.73, 138.79, 135.90, 135.10, 131.00, 128.83, 128.03, 127.38, 126.82, 124.09, 76.91, 75.94, 68.95, 60.83, 58.26, 45.56, 34.16, 26.44, 19.69, 14.38, 13.90, -4.9.

IR (film): 2927, 1623, 1457, 1252, 1113, 837, 775, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{31}H_{47}NO_3Si$ 509.3325, found 509.3317.

$[\alpha]_D$= +103° (c 0.55g/100mL, $CHCl_3$).

(E)-(R)-7-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-2-*o*-tolyl-hept-5-en-1-ol 211



A solution of *n*-butyllithium (3.4 mL, 2.5M, 8.4 mmol, 3.9 eq.) in hexanes was added to a solution of diisopropylamine (1.27 mL, 9.06 mmol, 4.2 eq.) in THF (9 mL) at -78°C. The resulting solution was stirred at this temperature for 10 min, then warmed to 0°C and held at that temperature for 10 min. Borane-ammonia complex (266 mg, 8.6 mmol, 4 eq.) was added in one portion. The suspension was stirred at 0°C for 15 min, then at 23°C for 15 min, cooled again to 0°C and a solution of amide **209a** (1.10 g, 2.1 mmol, 1 eq.) in THF (6 mL) was added *via* cannula. The reaction mixture was warmed to room temperature and stirred for 2 h before it was cooled to 0°C again and carefully quenched with 1M hydrochloric acid (40 mL). The mixture was diluted with water (100 mL) and extracted with ether (3x 100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed *in vacuo* to give **211** (692 mg, 92%) as a yellow oil which was directly used in the next step. An analytical sample was purified by chromatography (hexane:ethyl acetate 5:1).

^{1}H-NMR (400MHz, $CDCl_3$): δ= 7.21-7.09 p.p.m., (m, 4H), 5.36 (ddt, *J*= 7.1, 2.4, 1.1 Hz, 1H), 3.97 (s, 2H), 3.77-3.68 (m, 2H), 3.18 (ddd, *J*= 13.0, 9.3, 6.0 Hz, 1H), 2.33 (s, 3H), 1.94 (dd, *J*= 14.8, 7.5 Hz, 2H), 1.83-1.75 (m, 1H), 1.72-1.63 (m, 1H), 1.44 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H).

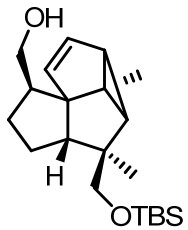
^{13}C-NMR (100MHz, $CDCl_3$): δ= 140.65 p.p.m., 137.69, 135.32, 130.91, 126.72, 126.62, 124.45, 69.01, 67.72, 42.80, 32.33, 26.45, 25.52, 20.33, 13.65, -4.90.

IR (film): 3356, 2941, 2865, 1458, 1383, 1063, 882, 610 cm^{-1}.

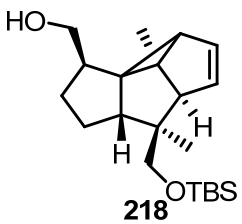
HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{36}O_2Si$ 348.2485, found 348.2492.

$[\alpha]_D$= +11° (c 0.30g/100mL, $CHCl_3$).

[(1S,1aR,4R,4aR,6cS)-1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1,6c-dimethyl-1,1a,2,3,4,6a,6b,6c-octahydro-cyclopenta[*g*]cyclopropa[*cd*]pentalen-4-yl]-methanol 218



219



218

Compound **211** (428 mg, 1.23 mmol) in pentane (90 mL) was irradiated with a Hannovia 700W medium pressure mercury lamp with a quartz filter at room temperatur for 2 h. The reaction mixture was concentrated and the crude residue was submitted to flash column chromatography (hexane:ethylacetate = 10:1) yielding 90 mg **218** and 184 mg **219** total 64% yield) in a 1:2.0 ratio.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.71 p.p.m., (dd, *J*= 5.3, 2.3 Hz, 1H), 5.46 (d, *J*= 5.1 Hz, 1H), 3.67-3.61 (m, 1H), 3.57-3.50 (m, 1H), 3.50 (d, *J*= 8.8 Hz, 1H), 3.47 (d, *J*= 9.0 Hz, 1H), 2.48-2.39 (m, 1H), 2.01-1.90 (m, 3H), 1.64-1.41 (m, 4H), 1.37 (s, 3H), 1.26 (s, 1H), 1.06 (s, 3H), 0.88 (s, 9H), -0.06 (s, 3H), -0.03 (s, 3H).

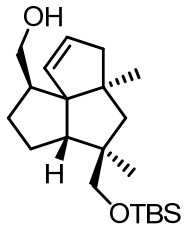
^{13}C-NMR (100MHz, $CDCl_3$): δ= 134.08 p.p.m., 129.58, 70.20, 65.74, 65.19, 47.89, 47.05, 46.72, 42.48, 37.87, 31.44, 28.42, 25.95, 24.20, 18.78, 18.24, -5.33.

IR (film): 3629, 2956, 2362, 1653, 1457, 1256, 1094, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{36}O_2Si$ 348.2485, found 348.2471.

$[\alpha]_D$= -59° (c 0.45g/100mL, $CHCl_3$).

[(1R,3aR,4R,5aS,8aR)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4,5a-dimethyl-1,2,3,3a,4,5,5a,6-octahydro-cyclopenta[*c*]pentalen-1-yl]-methanol 219a



A solution of **219** (90 mg, 0.26 mmol, 1 eq.) in absolute THF (200µL) was cooled to -78°C and ethylamine (3 mL) was condensed in. Small pieces of lithium (11 mg, 1.55 mmol, 6 eq.) were added and the reaction mixture was stirred for 7 h until a deep blue color formed. The excess lithium was quenched with saturated ammonium chloride solution and the suspension was warmed to room temperature. Diethyl ether was added and the water phase was extracted with diethyl ether (3x 100 mL). The combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo*. Crude **219a** was subjected to flash column chromatography (hexanes:ethyl acetate 10:1) to give 90 mg, in 96% yield as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.76 p.p.m., (dt, *J*= 5.4, 2.1 Hz, 1H), 5.51 (dt, *J*= 5.3, 2.1 Hz, 1H), 3.55-3.43 (m, 2H), 3.28 (d, *J*= 9.3 Hz, 1H), 3.17 (d, *J*= 9.3 Hz, 1H), 2.38 (dt, *J*= 17.2, 2.1 Hz, 1H), 2.28-2.22 (m, 1H), 2.18 (dt, *J*= 17.2, 2.1 Hz, 1H), 2.03-1.96 (m, 1H), 1.92 (d, *J*= 13.4 Hz, 1H), 1.65-1.61 (m, 1H), 1.48 (d, *J*= 13.2 Hz, 1H), 1.38-1.31 (m, 2H), 1.17 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), -0.01 (s, 6H).

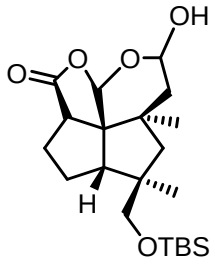
^{13}C-NMR (100MHz, $CDCl_3$): δ= 137.64 p.p.m., 127.23, 71.13, 65.09, 59.28, 53.48, 51.26, 50.32, 49.08, 46.86, 45.09, 32.51, 28.04, 27.21, 25.85, 22.40, 18.29, -5.46.

IR (film): 3629, 2956, 2362, 1653, 1457, 1256, 1094, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{38}O_2Si$ 350.2641, found 350.2634.

$[\alpha]_D$= -19° (c 0.30g/100mL, $CHCl_3$).

Compound 222



Alcohol **219a** (90 mg, 0.26 mmol, 1 eq.) was dissolved in 3 mL dimethylsulfoxide. IBX (90mg, 0.32 mmol, 1.5 eq.) was added to this stirred solution at room temperature. The mixture was stirred for one hour, diluted with diethyl ether and water and extracted two times with ether. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. The crude aldehyde was dissolved in3 mL *tert*-butanol and 1 mL 2,3-dimthyl-2-butene was added. Sodium chlorite (260 mg, 2.6 mmol, 10 eq.) and 260 mg sodium dihydrogen phosphate were dissolved in 1.5 mL water. The solution was added dropwise to the aldehyde at room temperature, and the mixture was stirred for another 30 minutes. The reaction mixture was quenched with brine and extracted four times with dichloromethane. The combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo*.

Crude acid **220** (90 mg, 0.24mmol, 1 eq) was dissolved in dichloromethane (6 mL) in a three necked round bottom flask equipped with a gas outlet and a gas inlet-tube. The solution was cooled to -78°C and ozonized for 2 min (flow 100mL/min) until the solution was dark blue. The excess ozone was driven out with air until the solution became colorless again. Then thiourea (25 mg, 0.33 mmol, 1.37 eq.) was added in one portion and the suspension was warmed to room temperature and stirred for 40 min giving a cloudy solution. The solvent was removed *in vacuo* and the crude product was submitted to flash column chromatography (hexane:ethyl acetate=5:1) yielding 37 mg 36% of lactol **222** over 3 steps.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.64 p.p.m., (s, 1H), 5.35 (ddd, *J*= 8.3, 5.5, 3.0 Hz, 1H), 3.36 (d, *J*= 1.26 Hz, 2H), 2.94 (d, *J*= 7.6 Hz, 1H), 2.84 (d, *J*= 3.3 Hz, 1H), 2.29 (d, *J*= 8.6 Hz, 1H), 2.21-2.15 (m, 1H), 2.07 (d, *J*= 14.4 Hz, 1H), 1.89-1.74 (m, 5H), 1.27 (d, *J*= 14.4 Hz, 1H), 1.10 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

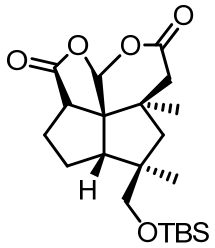
^{13}C-NMR (100MHz, $CDCl_3$): δ= 179.80 p.p.m., 101.75, 96.67, 72.22, 66.18, 55.05, 52.71, 46.47, 45.80, 41.64, 40.90, 31.51, 27.76, 26.48, 25.95, 23.00, 18.21, -5.30.

IR (film): 3629, 2956, 1791, 1464, 1251, 1094, 857, 739, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{36}O_5Si$ 396.2332, found 396.2322.

$[\alpha]_D$= -53° (c 0.90g/100mL, $CHCl_3$).

Compound 222a



Lactol **222** (24 mg, 60 µmol, 1eq) was dissolved in dichloromethane (0.5 mL) at room temperature. PDC (136 mg, 0.36 mmol, 6 eq.) was added in one portion. After 20 min acetic acid (9 µL, 28 µmol, 0.46 eq.) was added dropwise. The reaction mixture was stirred for another 24 hours and then diluted with diethyl ether. The suspension was filtered through a silica pad and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 5:1) gave 20 mg (83% yield) of acylal **222a**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.64 p.p.m., 5.88 (s, 1H), 3.37 (s, 2H), 2.99-2.95 (m, 3H), 2.49 (dd, *J*= 9.8, 2.3 Hz, 1H), 2.35 (d, *J*= 15.0 Hz, 1H), 2.30-2.25 (m, 1H), 2.09 (d, *J*= 14.4 Hz, 1H), 1.95-1.80 (m, 2H), 1.66-1.57 (m, 1H), 1.54 (d, *J*= 14.4 Hz, 1H), 1.11 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

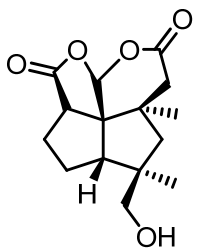
^{13}C-NMR (100MHz, $CDCl_3$): δ= 177.60 p.p.m., 168.79, 104.06, 72.39, 68.34, 56.18, 52.91, 46.36, 46.25, 43.41, 42.03, 31.37, 27.42, 27.13, 25.98, 22.75, 18.38, -5.31, -5.41.

IR (film): 2960, 1799, 1771, 1653, 1559, 1507, 1458, 1367, 1115, 1043, 995, 905, 738, 610 cm^{-1}.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{34}O_5Si$ 394.2176, found 394.2166.

$[\alpha]_D$= -75° (c 0.85g/100mL, $CHCl_3$).

Penifulvin B



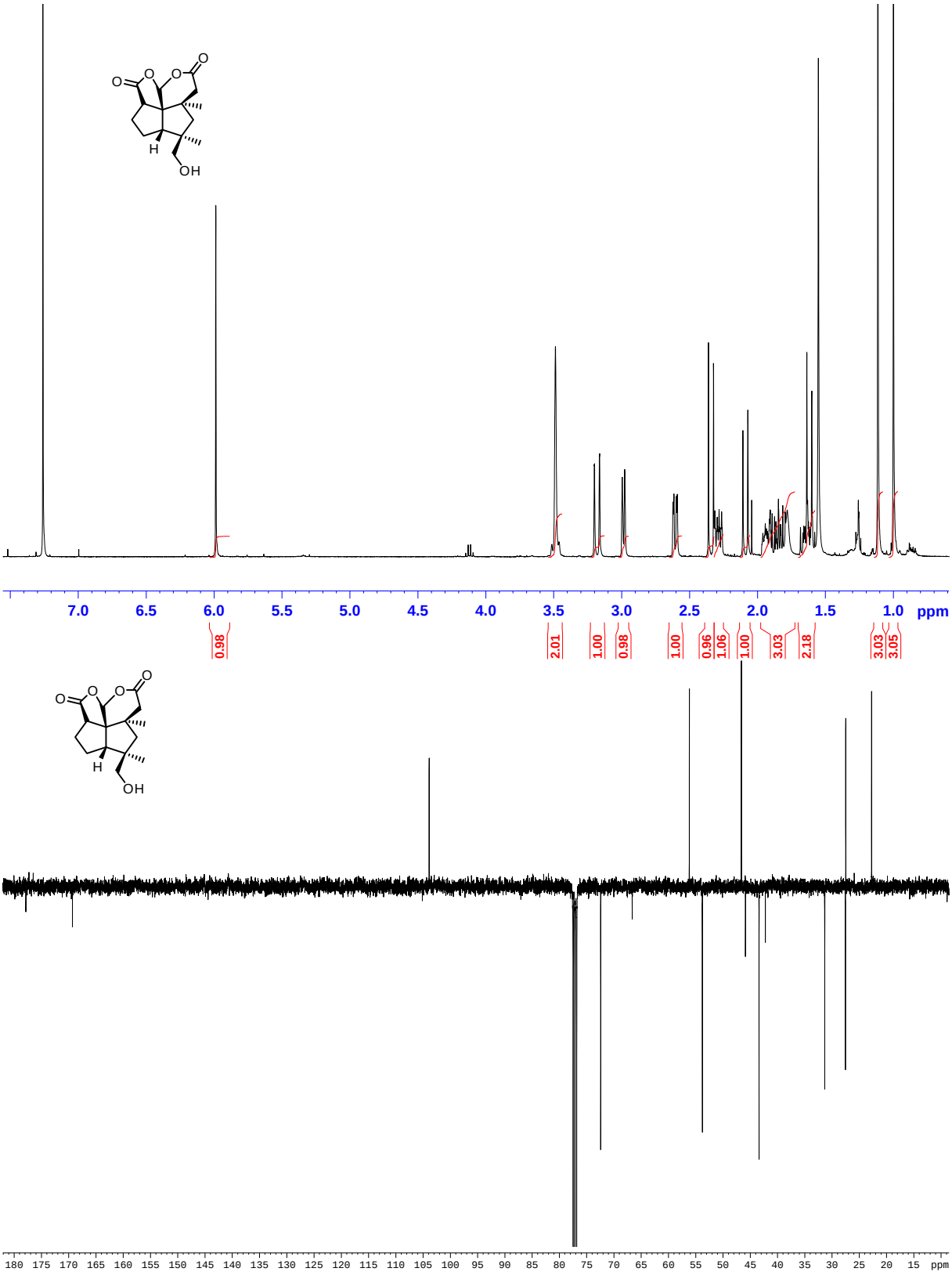
Acylal **222a** (10 mg, 25 µmol, 1 eq.) was dissolved in 0.5 mL tetrahydrofuran. To this solution 200 µL 35% HF/pyridine were added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The reaction was poured on 20 mL 0.5M HCl solution and extracted four times with ethyl acetate. The combined organic layers were washed with brine dried over magnesium sulfate and concentrated *in vacuo*. Flash column chromatography (hexanes:ethyl acetate 1:2) gave 5.8 mg 82% yield of Penifulvin B **137**.

^{1}H-NMR (400MHz, $CDCl_3$): δ= 5.98 p.p.m., (s, 1H), 3.48 (s, 2H), 3.18 (dd, *J*= 14.9, 0.8 Hz, 1H), 2.98 (d, *J*= 7.1 Hz, 1H), 2.61 (dd, *J*= 9.7, 2.7 Hz, 1H), 2.34 (d, *J*= 14.9 Hz, 1H), 2.28 (ddt, *J*= 13.1, 13.1, 2.0 Hz, 1H), 2.09 (d, *J*= 14.4 Hz, 1H), 1.97-1.79 (m, 2H), 1.78 (s, 1H(OH)), 1.68-1.58 (m, 1H), 1.62 (d, *J*= 14.6 Hz, 1H), 1.11 (s, 3H), 0.99 (s, 3H).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 177.88 p.p.m., 169.30, 103.88, 72.43, 66.65, 56.16, 53.77, 46.62, 45.87, 43.38, 42.23, 31.33, 27.54, 27.48, 22.73.

HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1304.

$[\alpha]_D$= -84° (c 1.1g/100mL, $CHCl_3$).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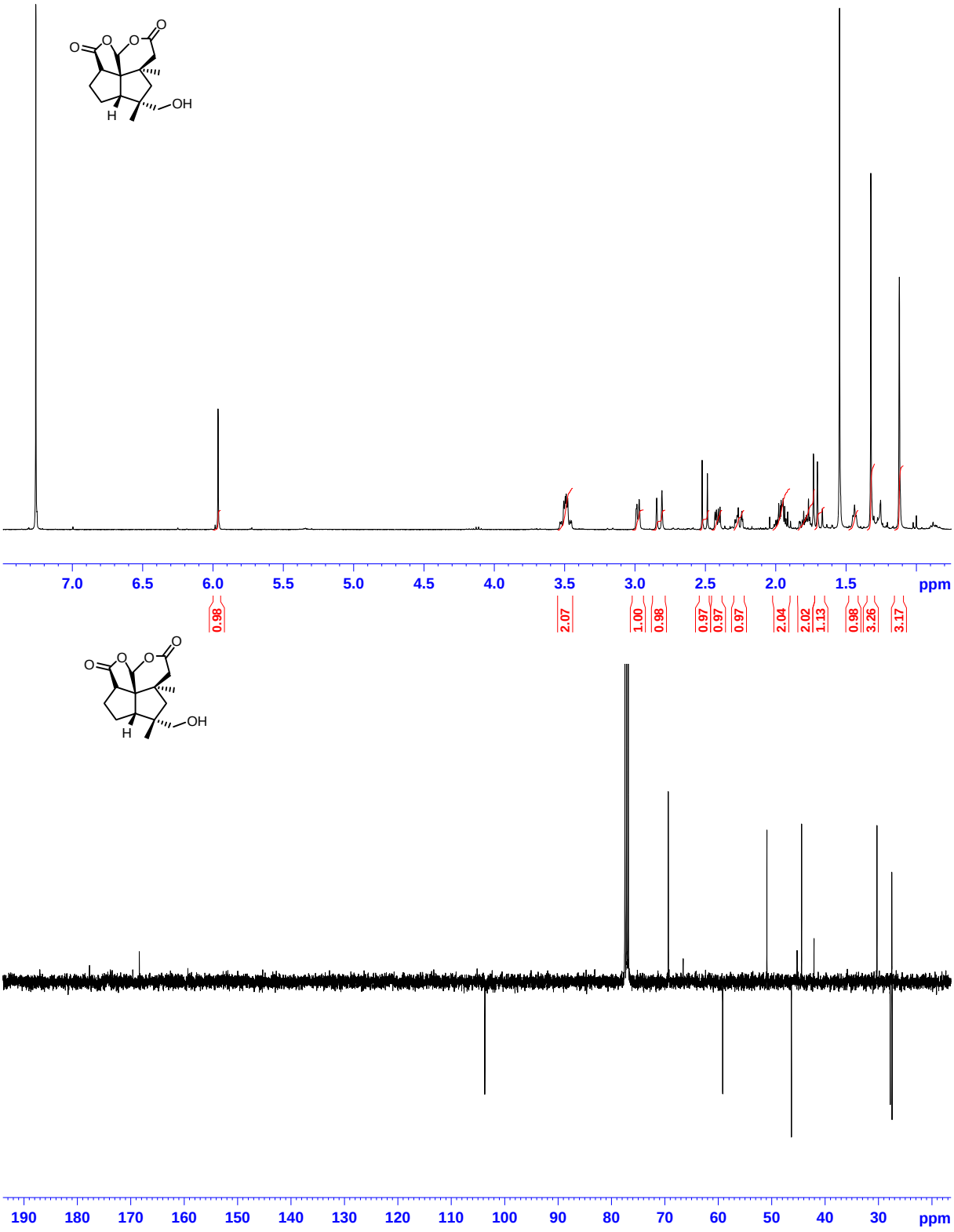
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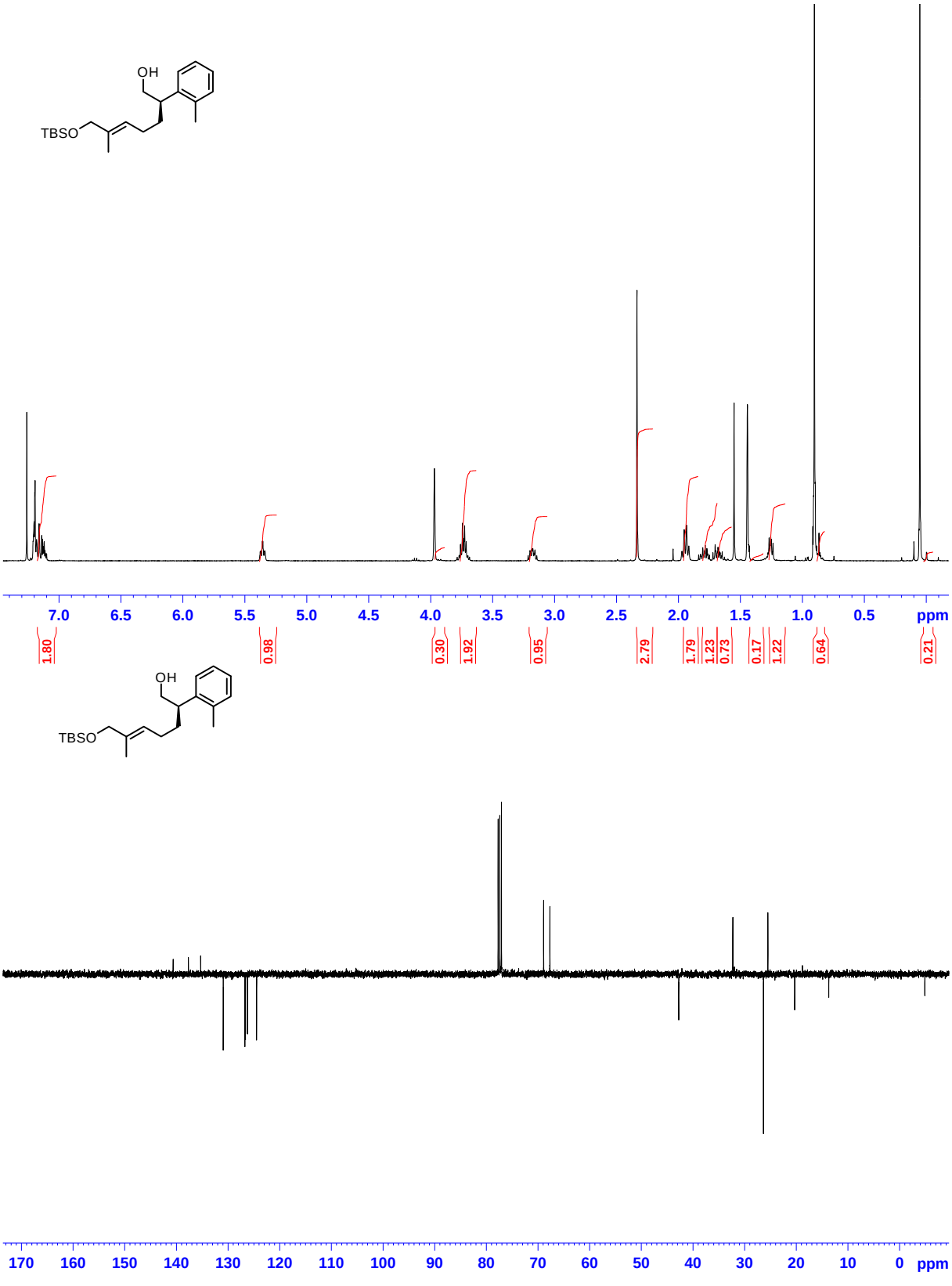
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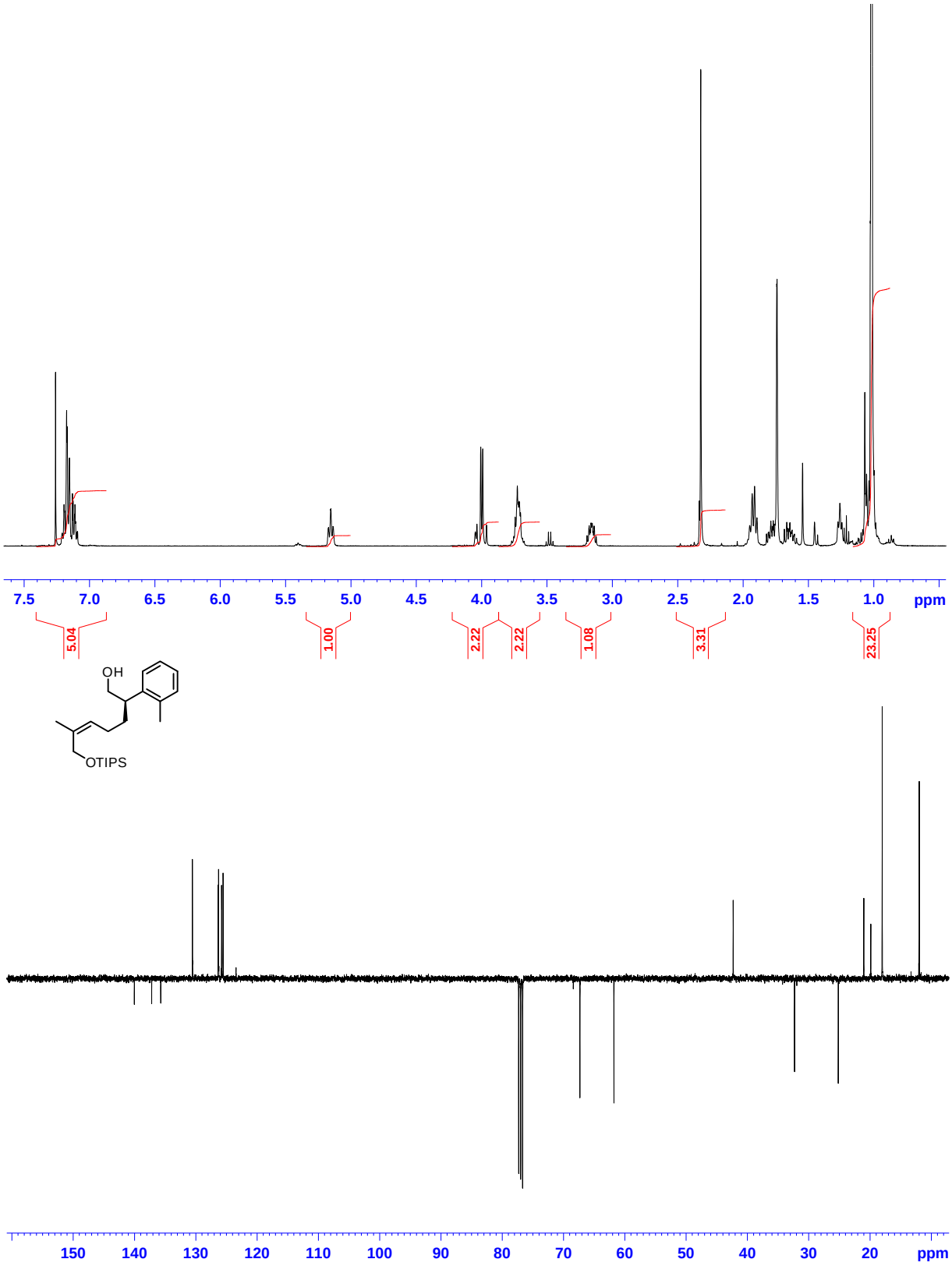
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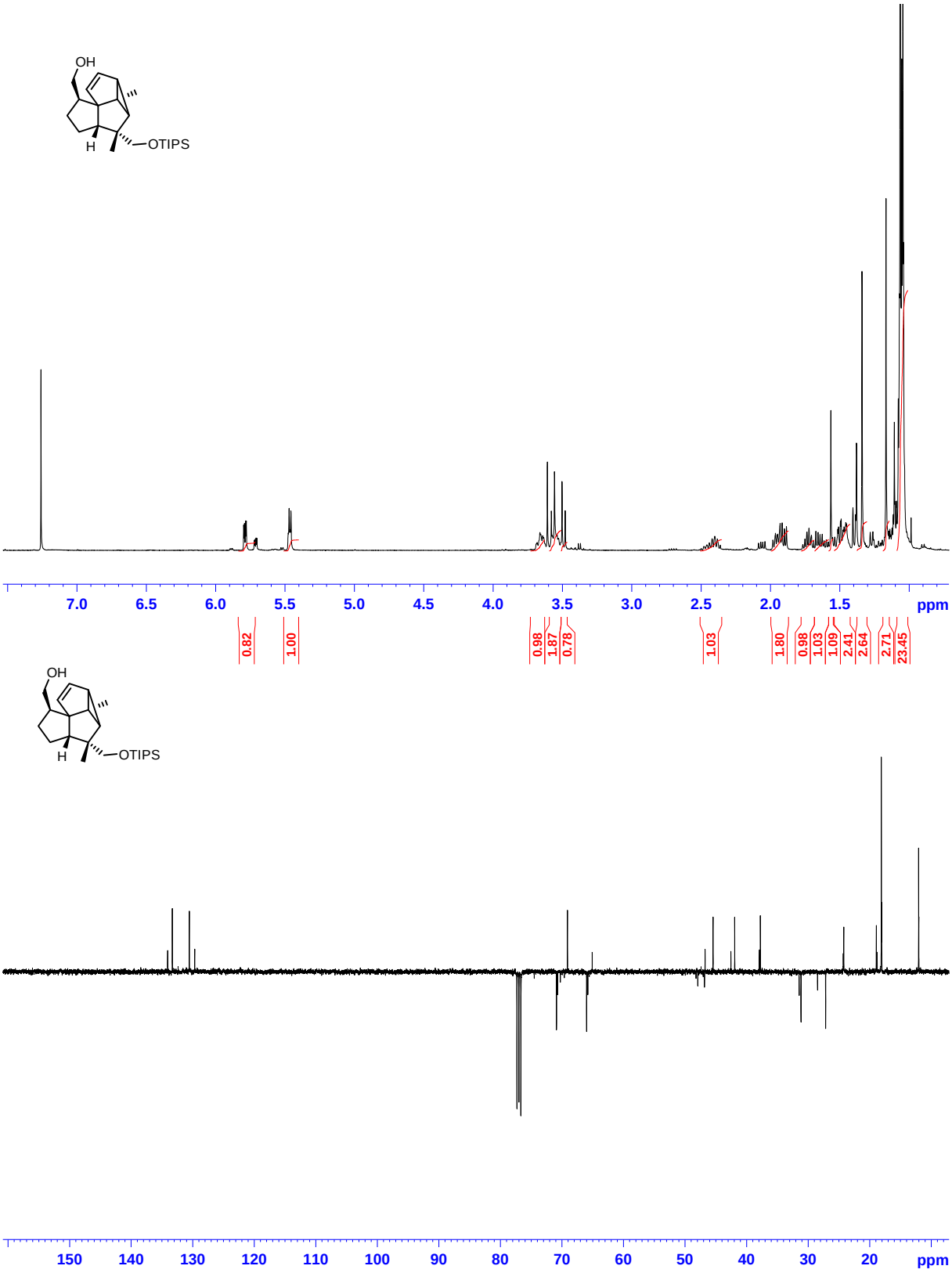
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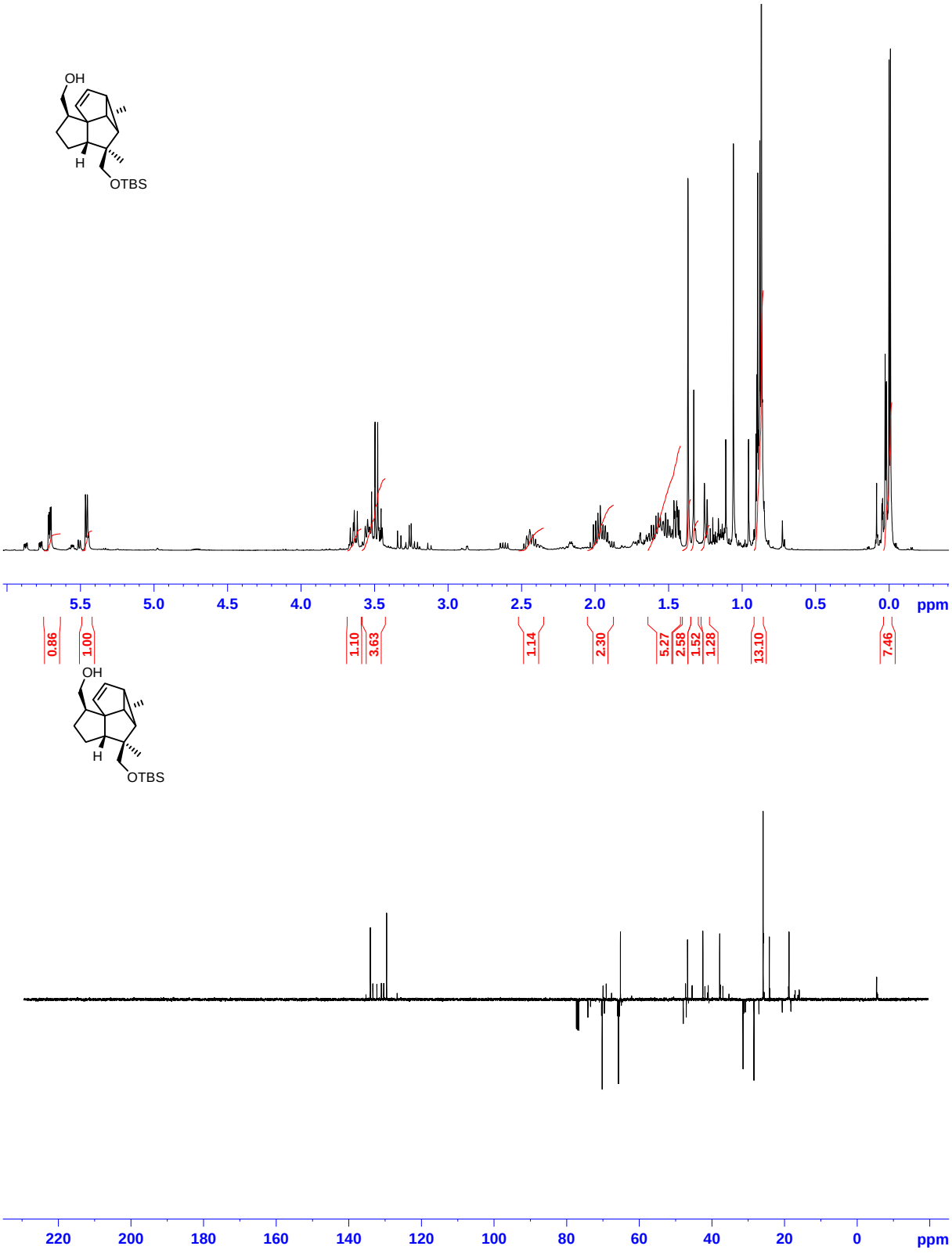
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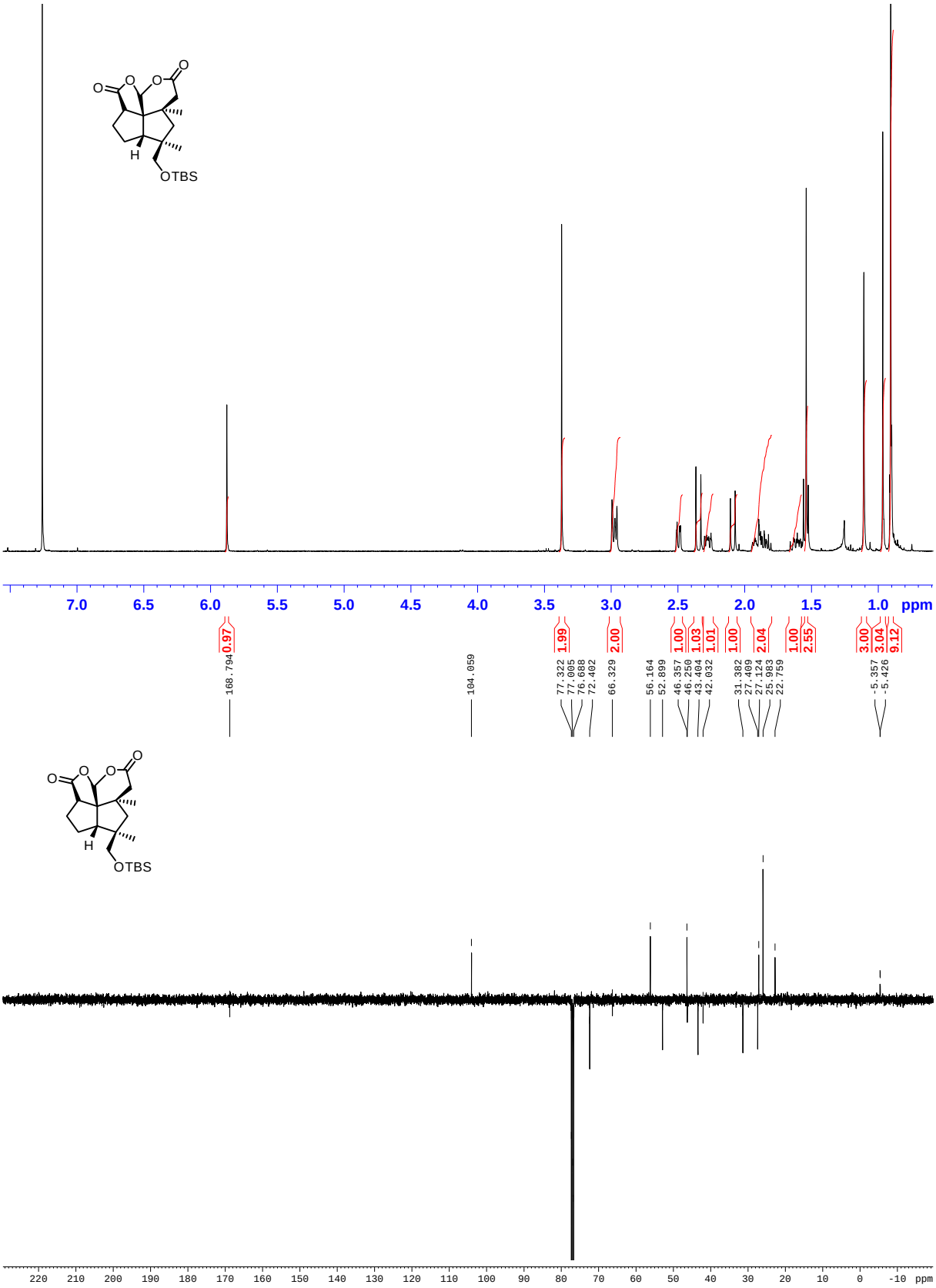
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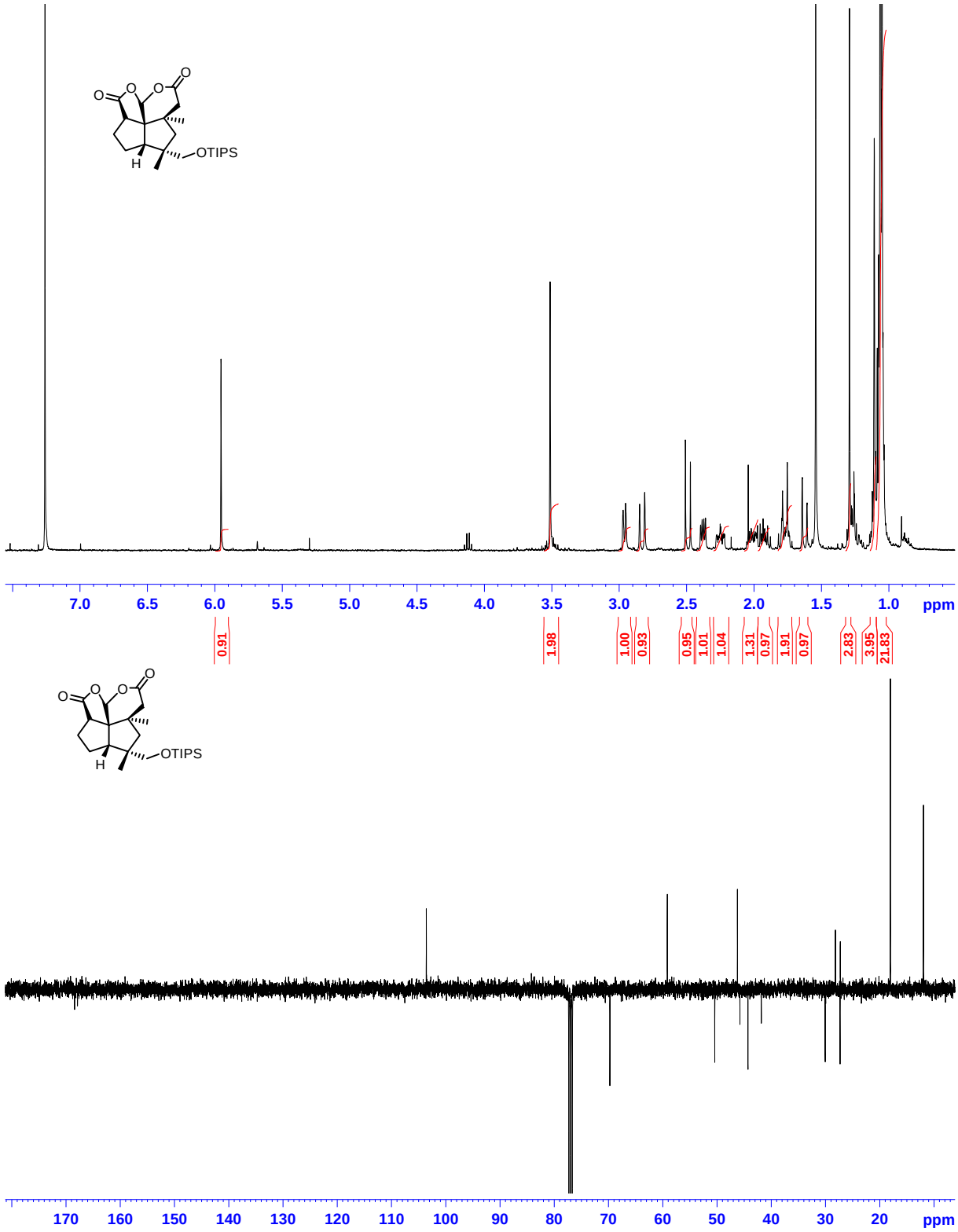
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20
ppm

TANJA GAICH

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Citizenship: Austrian
Marital Status: Single

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Währingerstrasse 38, A-1090 Vienna, Austria
tanja.gaich@univie.ac.at

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+43-669-113 74334 (mobile)
Fax: +43-1-4277 9521

EMPLOYMENT HISTORY

Since April 2005	**University of Vienna –** Teaching Assistant, Institute of Organic Chemistry, Vienna, Austria Supervision, tutoring and grading of students in the organic chemistry laboratory,
Since March 2005	**University of Vienna – Ph.D. Research:** Working towards Ph.D. degree in the field of organic chemistry under the supervision of Professor J. Mulzer. www.univie.ac.at/rg_mulzer
2002-2003	**Tutor at the University of Vienna –** Teaching undergraduate students in the Organic Chemistry laboratory.
July 2002– Oct 2002	**Vienna University of Technology –** Internship in the laboratory of Professor Dr. M. Michovilovic "Application of enantioselective Baeyer-Villiger-Oxygenase in Organic Synthesis" (whole cell systems)

EDUCATION & QUALIFICATIONS

Since Oct 2005	**University of Vienna –** Seminar on "Stereoselective Synthesis"
March 2005 - to date	**University of Vienna – Ph.D. Research:** Research topic: Total Synthesis of Providencin and Penifulvin (research group of Professor Johann Mulzer)
2.Feb 2005	**University of Vienna –** Graduation with excellence Title "Magistra rerum naturalium" (comparable to M.Sc.) (Supervisor Professor Dr. J. Mulzer)
Apr 2004 – Feb 2005	**Diploma thesis project–** "Highly efficient Formal Synthesis of Epothilone B and D with Stereoselective Construction of the 12,13-Z-Double Bond
Oct 1998 – Apr 2004	**Paris Lodron University Salzburg–** Study of Molecular Biology **University of Vienna–** Study of Chemistry with main focus on Organic Chemistry
1990 – 1998	**Grammar school (Christian Doppler Gymnasium) Salzburg**

CONFERENCES and STIPENDS

Conference-Presentations:

Jul 2008 **Poster presentation at the BOSS 11 meeting,** Ghent, Belgium

Title of Presentation: "The Pursue for Providencin"

Jul 2007 **Poster presentation at the Gordon Research Conference** Tilton School, USA

Title of Presentation: "Towards the Total Synthesis of Providencin"

Apr 2006 **Short presentation in the course of the H.C. Brown lecture,** Purdue University, USA

Title of Presentation: "Towards the Total Synthesis of Providencin"

Oct 2005 **9th International SFB Symposium : Trends and Frontiers in Organic Chemistry,** Aachen, Germany

Title of presented poster: "Formal Total Synthesis of Epothilone B and D with stereoselective construction of the 12,13-Z-Double Bond"

April 2005 **First Austrian-German-Italian Meeting of Organic Chemistry,** Vienna, Austria
Member of the local Organizing Committee

Title of presented poster: "Formal Total Synthesis of Epothilone B and D with Stereoselective Construction of the 12,13-Z-Double Bond"

June 2004 **26th Doktorandenworkshop, Presentation** Bayreuth, Germany

Title of presented talk: "Formal Total Synthesis of Epothilone B and D with Stereoselective Construction of the 12,13-Z-Double Bond"

Stipend:

Carl-Storm-Fellowship for diversity. – US-stipend for the attendance of the Gordon-Research-Conference.

LANGUAGE AND SPECIAL SKILLS

Languages	English: spoken – excellent, comprehension – excellent, written – excellent Italian: spoken – very good, comprehension – very good, written – very good
Technical	Skilled operator of HPLC systems, NMR, IR, GC and GC/MS instruments and their software (XWinNMR, WinNMR, Topspin), extensive knowledge of most common office tools and operating systems (WIN9x, Win2000, NT, XP, MSOffice), experienced with variety of chemistry software (Beilstein, CS ChemOffice, IsisBase, IsisDraw, SciFinder)
Social/ Teamwork Interests	Approved Fitness trainer (special focus badminton) by the Austrian Sports Federation Member of the Austrian Badminton Team (1996-1998) Classical music, various sports (badminton, tennis, squash, volleyball) Outdoor activities: Skiing, motorbikes.