Total Synthesis of the Proposed Structure of the Macrolide Queenslandon
and Towards the Total Synthesis of Natural Products Leiodermatolide and (–)-Englerin A

DISSERTATION

der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard-Karls-Universität Tübingen
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)

vorgelegt von

Vaidotas Navickas

aus Alytus, Litauen

Tübingen

2011

Tag der mündlichen Prüfung:	03.03.2011
Dekan:	Prof. Dr. W. Rosenstiel
1. Berichterstatter:	Prof. Dr. M. E. Maier
2. Berichterstatter:	Prof. Dr. Th. Ziegler

This doctoral thesis was carried out from November 2007 to October 2010 at the Institut für Organische Chemie, der Mathematisch-Naturwissenschaftlichen Fakultät, Eberhard-Karls-Universität Tübingen, Germany, under the guidance of Professor Dr. Martin E. Maier.

I am indebted to say a few words about my supervisor Prof. Dr. Martin E. Maier. During my stay in Tübingen, I felt enormous freedom in setting my own ideas in the research where those were accompanied by kind support, numerous advices and excellent guidance. I thank him also for being a great inspirator as he always tried to present and share new ideas and literature examples with the group members.

I personally thank Mr. Graeme Nicholson and Dr. Dorothee Wistuba for their skilful technical assistance in numerous HRMS measurements, Mrs. Maria Munari for well-organized supply of chemicals and her great help in the laboratory.

I thank my working group members Anton S. Khartulyari, Viktor Vintonyak, Alexander Zhdanko and Christian Rink for valuable discussions and their friendly nature.

Especially I would like to thank Dmitry Ushakov for being a great team mate. His valuable discussions on our research work and his help in solving many synthetic puzzles were irreplaceable.

For many X-ray crystallography experiments I thank Markus Ströbele and Prof. Dr. Jürgen H. Meyer

I thank Prof. Dr. Sigitas Tumkevicius, Prof. Dr. Eugenijus Butkus and Dr. Mindaugas Dailide for teaching me chemistry and laboratory skills during my studies in Lithuania.

Finally, I am thankful to the love and support that my parents and family gave to me.

my Family

***Publications**:*

Navickas, V.; Rink, Ch.; Maier, M. E. Synthetic Studies towards Leiodermatolide: Rapid Stereoselective Syntheses of Key Fragments. *Synlett* **2010**, e-First, doi: 10.1055/s-0030-1259286.

Navickas, V.; Ushakov, B. U.; Maier, M. E.; Ströbele, M.; Meyer, H. J. Synthesis of the Guaianolide Ring System via Cycloaddition of a Bicyclic Carbonyl Ylide with Allyl Propiolate. *Org. Lett.* **2010**, *12*, 3418–3421.

Navickas, V.; Maier, M. E. Synthesis of the Proposed Structure of Queenslandon. *Tetrahedron* **2010**, *66*, 94–101.

Tumkevicius, S.; Navickas, V.; Dailide, M. Oxidation of Benzylic Alcohols with I_2/K_2CO_3/*tert*-butanol: Formation of Aldehydes or Dimeric Esters. *Pol. J. Chem.* **2006**, *80*, 1377–1383.

Tumkevicius, S.; Navickas, V.; Dailide, M. First Example of Synthesis of Thieno-[2,3-*d*]pyrimidine-6-carbaldehydes by Oxidation of Thieno[2,3-*d*]pyrimidin-6-yl Methanols With Molecular Iodine. *Chem. Het. Comp.* **2005**, *41*, 800–801.

Navickas, V.; Tamosiunas, P. L.; Butkus, E. *Chemijos olimpiadu uzduotys*/*Problems and Solutions in Chemistry Olympiads*, Vilnius, Lithuania, **2006**, ISBN 9955-9894-2-4. (*Book*).

Poster presentations:

Navickas, V.; Ushakov, B. U.; Maier, M. E. Towards the Synthesis of (–)-Englerin A, Balticum, Organicum, Syntheticum (BOS 2010), Riga, Latvia 2010.

Navickas, V.; Maier, M. E. Study on The Synthesis of The Macrolide Queenslandon, Balticum, Organicum, Syntheticum (BOS 2008), Vilnius, Lithuania 2008.

Tumkevicius, S.; Navickas, V.; Dailide, M. Synthesis and DHFR Inhibitory Activity of 6-Substituted 2-Amino-4-oxo- And 2,4-diaminothieno[2,3-d]pyrimidines, Balticum, Organicum, Syntheticum (BOS-2006), Tallinn, Estonia 2006.

Table of Contents

Abbreviations

abs.	absolute
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	aqueous
ar. (arom.)	aromatic
Bn	Benzyl
br	broad (NMR)
b.p.	Boiling point
Bu	Butyl
Bz	Benzoyl
c	Concentration
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
CSA	Camphor sulfonic acid
Cy	cyclohexyl
δ	Chemical shift in ppm (NMR)
d	Doublet (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	trans
ee	Enantiomeric excess
EI	Electron impact
Eq.	equation
ESI	Electronspray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

g	gram(s)
h	hour(s)
HMBC	Heteronuclear Multiple Bond Correlation (NMR)
HMPA	Hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
*i*Pr	isopropyl
J	coupling constant
L	liter(s)
LDA	Lithium diisopropylamide
m	Multiplet (NMR)
M	mol/L
*m*CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
mg	milligram
µg	microgram
MOM	Methoxymethyl
Ms	Methanesulfonyl
NBS	N-bromosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PCC	Pyridinium chlorochromate
Piv	Pivaloyl
ppm	parts per million
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *para*-toluene sulfonate
*p*TSA	*para*-Toluene sulfonic acid
Py	Pyridine
q	Quartet (NMR)
RALs	Resorcylic acid lactones
RCM	Ring-closing metathesis
R_f	Retention factor (TLC)
rt	Room temperature (ca. 23 °C)

s	Singlet (NMR)
sec	secondary
t	Triplet (NMR)
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxid
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TfO	Trifluoromethanesulfonate
TMS	Trimethylsilyl
Triflate	Trifluoromethane sulfonate
Z	cis

Introduction and the Goal of Research

Natural product synthesis serves as an inspiration for invention in organic chemistry for many years. Selection of a specific molecule for the synthesis is dependant on many issues: impressive biological activity, mode of action, structural assignment, an idea to test scope and limitation of newly developed methods and etc. Historically, students and individuals entering in this field are prone to concentrate on the synthetic approaches that share two main features: the so-called stop-and-go approach,[1] and the implementation of orthogonal protecting-group strategies.[2,3] However, recent decades clearly set guidelines for organic synthesis indicating, for example, an urgent need for new chemoselective methods and more efficient catalyst that would allow scalable and more efficient processes in industrial area. To support this, in 2007 R. H. Grubbs (2005 Nobel laureate in chemistry) stated, that *"the major challenges are the construction of the molecules without using protecting group chemistry and the ability to put molecules together in fast and efficient ways"*.[4] In recent years several new (or reintroduced) concepts for improving the synthesis towards natural and non-natural molecules have been brought forward. Terms like atom,[5] step,[6] redox[7] economies and protecting group-free (PGF) synthesis[8] could be found titled in many research publications indicating the impact of those on a current art and state of natural products synthesis. One should say those concepts became a "fashion line", as several outstanding syntheses were realized with those guidelines setting very high standards in organic synthesis.[9]

References mentioned above and willingness to follow those concepts of synthesis economies were part of an inspiration for preparing this thesis, where the purpose was to address synthetic challenges posed by three natural products. The chapter associated with the synthesis of the molecule queenslandon has a historical background. The study toward the synthesis was a long marathon where several graduate students and a postdoc tried to tackle the molecule unsuccessfully. Thus, an individual intention finally to complete the synthesis and to be the first one was a driving force. As it turned out, the synthesis presented for queenslandon revealed that the originally published structure requires revision. The work on leiodermatolide presented in the second part will be important for the determination of the stereochemistry of the macrolide, as the absolute and relative stereochemistry is not known for sure. In addition to that, a wish to develop a new strategy for the construction of the stereotetrad in this molecule and to test scope and limitations of several know methods were the purpose to choose the project. Terms of synthetic economies were the inspiration for the last part of the thesis. To exclude the extensive protecting group usage and to follow the redox economy concept were major reasons to select terpene englerin A as a study object.

Chapter I

Total Synthesis of the Proposed Structure of the Macrolide Queenslandon

Introduction

Natural polyketides cover an enormous structural space, even though simple building blocks like acetate and propionate are being used. Among the polyketides resorcylic acid lactones (RALs) represent a unique family of privileged structures.[10] These 14-membered lactones are mycotoxins and are produced by fungal strains. The modes of action of RALs are also impressive and diverse. These were nicely described and summarized in many publications and theses inclusive our group.[11] Furthermore, the discovery, that radicicol (**10**) is a potent and selective Hsp90 inhibitor renewed the interest in the RALs (**Figure 1**). Several RALs, which are characterized by a *cis*-enone in the macrocyclic ring, like LL-Z1640-2[12] (**5**) or radicicol A[13] (**4**) are potent kinase inhibitors.[14]

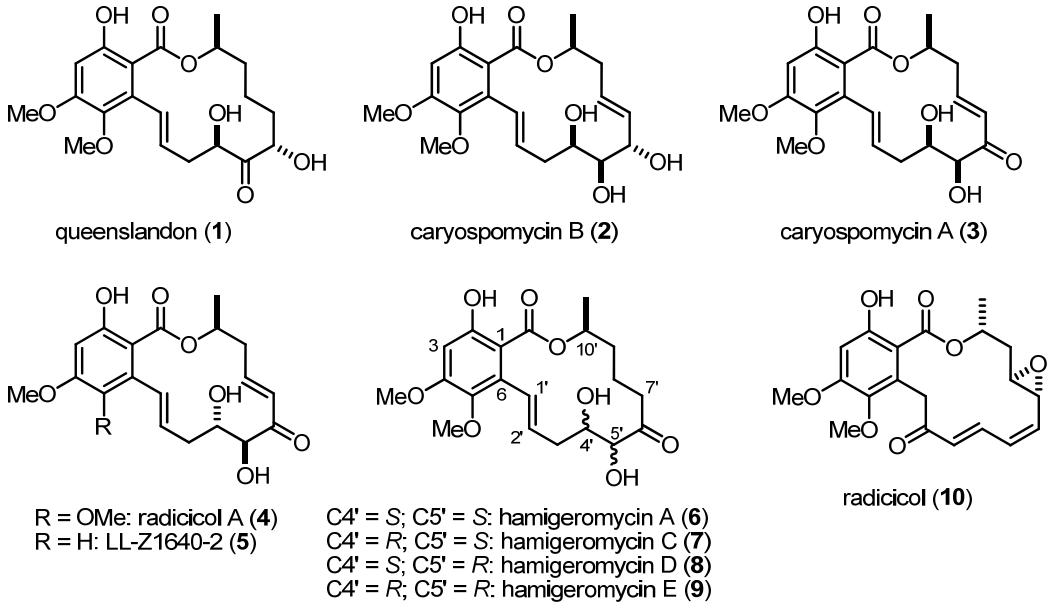
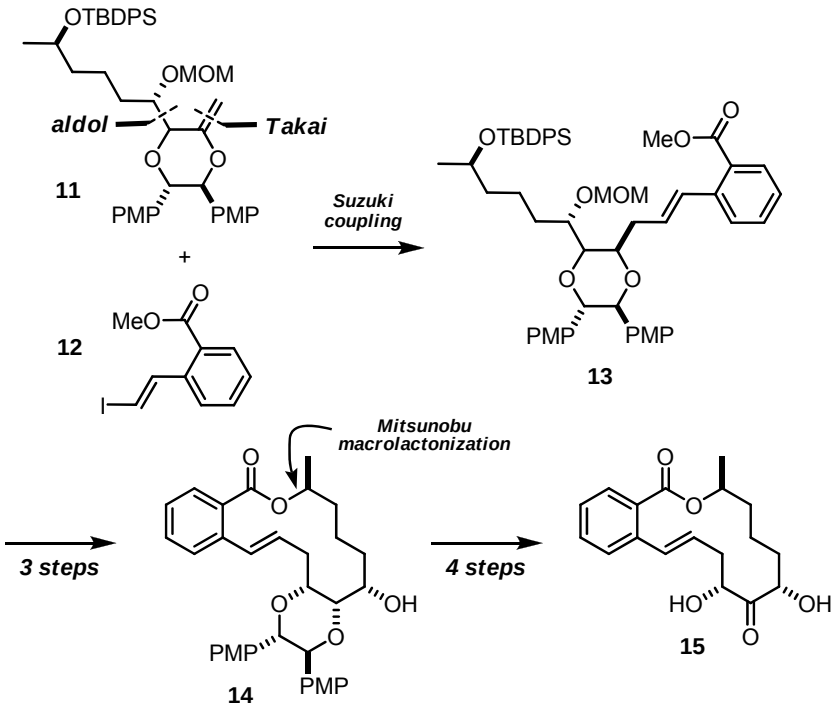


Figure 1. Structures of resorcylic acid lactones (RALs) bearing highly oxidized benzoic acid motif.

Among the RALs, macrolides like **6-9** are unique since they feature a highly oxidized benzoic acid motif. Furthermore, they are closely related to radicicol A (**4**) in structure. For example, hamigeromycin A[15] (**6**) possesses completely the same structure like radicicol A, except for the lack of an enone double bond. According to recent work of Altmann et al., these structural similarities imply that the compound could be selective for kinases as well.[16]

Among the mentioned RALs, queenslandon[17] (**1**) is unique since it features a dihydroxyacetone subunit. It was isolated from the strain *Chrysosporium queenslandadicum* IFM51121. According to the original report queenslandon showed activity against several fungal strains but no bacteria. In order to further delineate its biological properties a synthetic route to queenslandon seemed highly desirable.

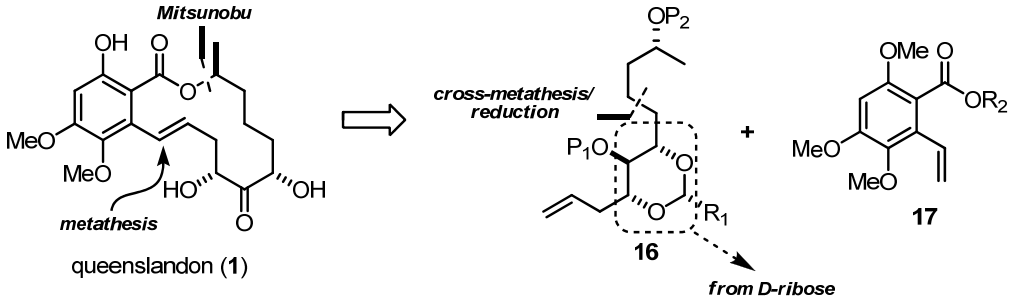
A strategy towards the core structure **15** of macrolide queenslandon was already described (**Scheme 1**).[18] However, the approach turned out to be not flexible enough and failed to deliver the proposed structure of queenslandon itself.[11c] Thus, the aim of the synthesis is not even to design an efficient synthesis that would deliver the natural product, but also to confirm the relative stereochemistry of the molecule.



Scheme 1. Key reaction in the synthesis towards the core structure **15** of queenslandon.

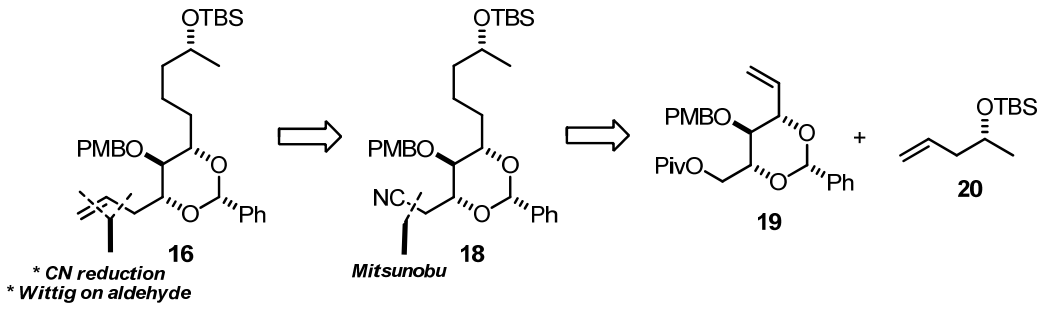
Retrosynthetic Consideration

The major retrosynthetic cuts for the proposed structure of queenslandon (**1**) are metathesis (ring-closing[19] or cross metathesis[20]) and Mitsunobu reaction[21] (**Scheme 2**), these are the most obvious and widely used transformations in the synthesis of resorcylic acid lactones. Because of steric hindrance around the carboxylic function in hydroxy acids of RAL's classical macrolactonization strategies frequently fail to give high yield of the macrolactone. Thus, advanced building block **16**, carrying all the stereochemical information of **1**, could come from *D*-ribose, which is relatively cheap and commercially available. The synthesis of styrene **17** could be easily achieved from the corresponding, literature known hydroxyphthalide (see results and discussion).



Scheme 2. Retrosynthetic analysis of queenslandon (**1**).

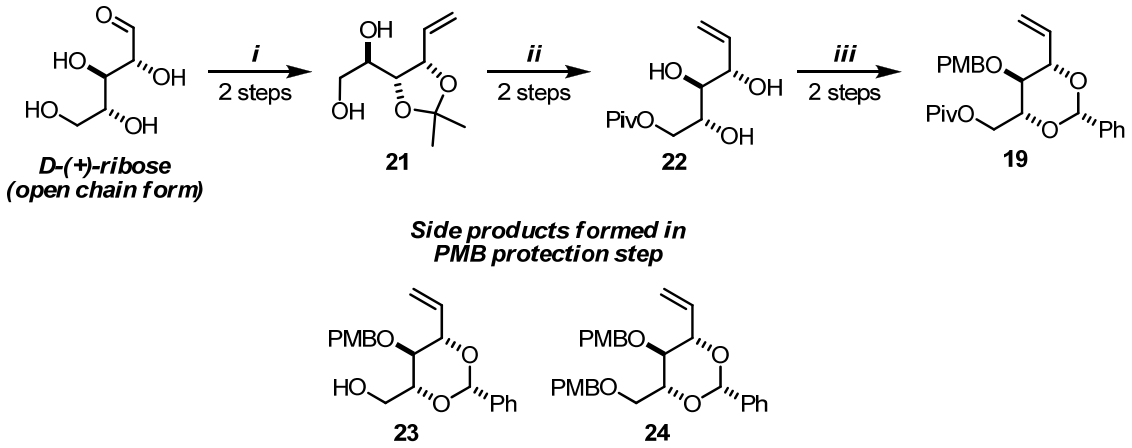
A more detailed disconnection of **16** is shown in **Scheme 3**. Here the allyl group in the aliphatic part could be formed from a pivaloyl protected alcohol function. Thus, the chain could be elongated via Mitsunobu reaction to give nitrile **18**. This would be reduced to an aldehyde followed by Wittig olefination. A cross-metathesis between *D*-ribose derivative **19** and silyl protected 1-pentenol **20** would be perfect and allow for fast access to building block **16**.



Scheme 3. Retrosynthetic analysis of queenslandon's aliphatic part **16**.

Results and Discussion

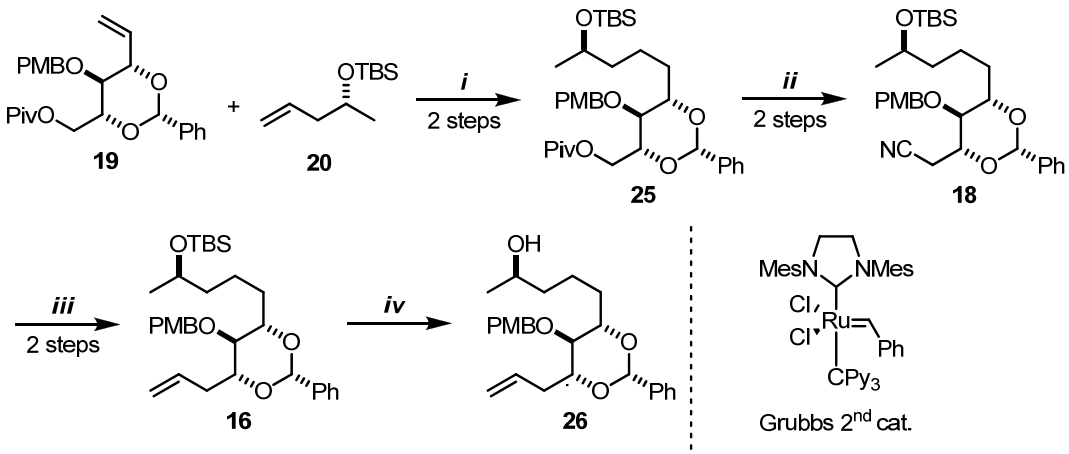
We started the synthesis by converting *D*-(+)-ribose into diol **21** via acetonide formation and Wittig olefination (**Scheme 4**).[22] A subsequent pivaolylation followed by hydrolysis of the acetal, mediated by $CuCl_2 \cdot 2H_2O$[23] led to triol **22** in 63% yield over two steps. A transacetalization on benzaldehyde dimethylacetal produced functionalized 1,3-dioxane thereby exposing the central hydroxyl function. This was then protected as PMB ether to give differentely protected **19**. Yield in this step was 57% due to side products which are alcohol **23** and bis-PMB ether **24**. Other methods to improve the yield, like PMB imidate, cat. TfOH, Et_2O, gave exclusively triol **22**.



Conditions: i. a) acetone, H^+; b) $MePPh_3Br$, KO*t*Bu, THF (65% over 2 steps). ***ii.*** a) PivCl, Py, CH_2Cl_2 (95%); b) $CuCl_2 \cdot 2H_2O$, CH_3CN (73%). ***iii.*** a) $PhCH(OMe)_2$, CSA, CH_2Cl_2 (67%); b) PMBBr, NaH, DMF (57%).

Scheme 4. Synthesis of cross-metathesis precursor **19**.

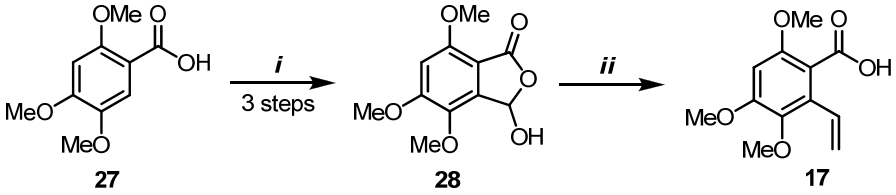
As next, a cross-metathesis reaction between alkene **19** and pent-4-en-2-ol derivative[24] **20** (1 equiv.) using Grubbs 2nd generation catalyst (5 mol%) at 80 °C in toluene provided the corresponding alkene in an excellent yield (**Scheme 5**). A subsequent catalytic hydrogenation of the double bond furnished the differently protected dioxane **25**. The next steps were calling for deprotection of the pivalic ester, chain extension via Mitsunobu reaction to a nitrile followed by reduction to an aldehyde and olefination. Thus, 6.0 equiv. of DIBAL-H easily reduced ester **25** at −80 °C delivering an alcohol which was then subjected to a Mitsunobu reaction with acetone cyanohydrine[25] to produce nitrile **18** in 72% yield over two steps. Subsequent DIBAL-H reduction gave the corresponding aldehyde which successfully underwent Wittig olefination with PPh_3MeBr resulting in alkene **16**. This two steps protocol was achieved in 96% and 75% yields respectively. Deprotection of the TBS group proceeded cleanly (quantitative yield) by treatment of silyl ether **16** with a 33% solution of HF·pyridine complex in THF at −15 °C.



Conditions: i. a) Grubbs 2nd, $PhCH_3$, 80 °C (74%); b) H_2, Pd/C, EtOAc (98%). ***ii.*** a) DIBAL-H, $PhCH_3$, –80 °C (81%); b) $Me_2C(OH)CN$, PPh_3, DEAD (89%). ***iii.*** a) DIBAL-H, $PhCH_3$, –80 °C (96%); b) $MePPh_3Br$, KO*t*Bu, THF, 0 °C (75%). ***iv.*** HF·Py, THF, –15 °C (quant.)

Scheme 5. Synthesis of alcohol **26** featuring cross-metathesis reaction.

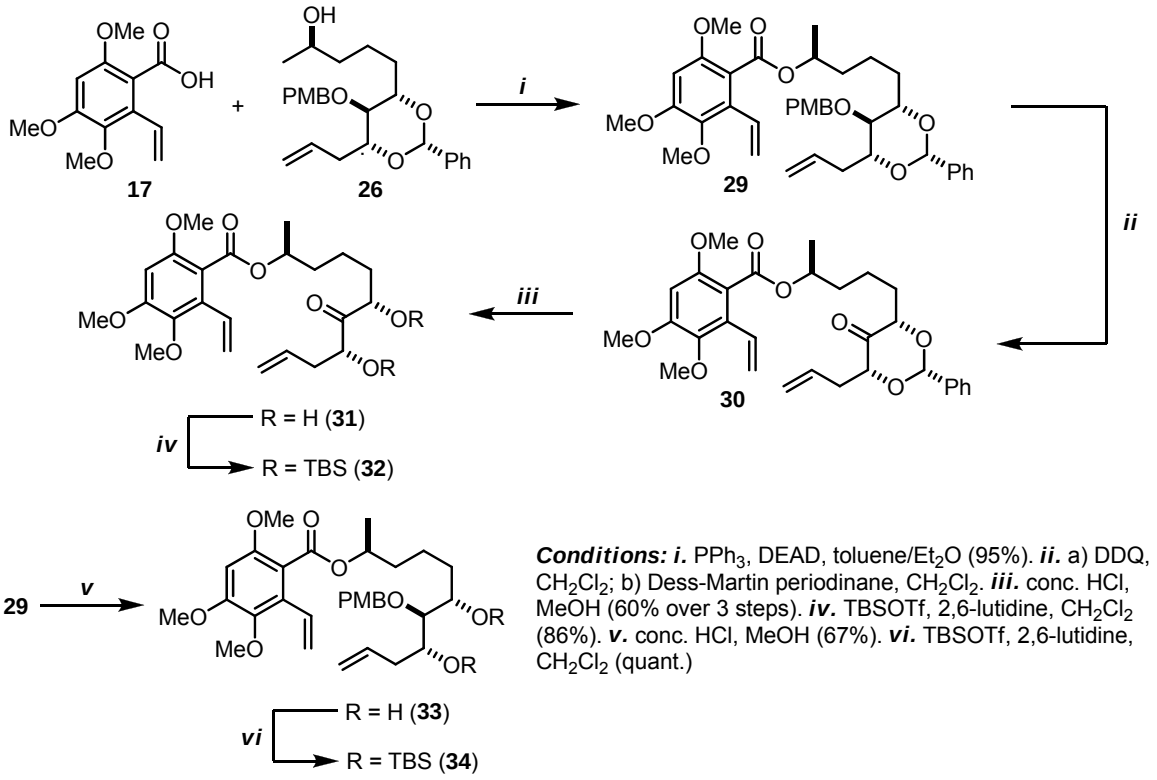
As it was mentioned before, the aromatic part was prepared via Wittig olefination on literature known hydroxyphthalide **28** (**Scheme 6**). The starting material for olefination was synthesized from commercially available 2,4,5-trimethoxybenzoic acid (**27**) utilizing literature procedures.[26] Thus, amide formation was followed by directed metalation, formylation and hydrolysis phtalide **28**.



Conditions: i. a) $SOCl_2$, $HNEt_2$, PhH; b) *sec*-BuLi, DMF, THF, –80 °C; c) 10% HCl, AcOH, reflux (44% over 3 steps). ***ii.*** $MePPh_3Br$, KO*t*Bu, THF, 0 °C (76%).

Scheme 6. Synthesis of 3,4,6-trimethoxy-2-vinylbenzoic acid (**17**).

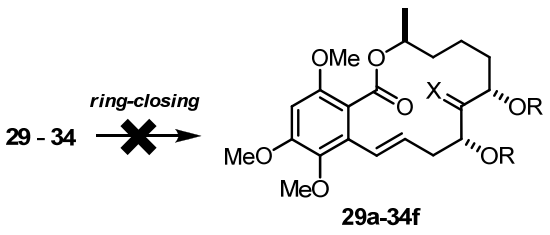
The aromatic acid **17** and alcohol **26** were combined via Mitsunobu esterification[27] to provide benzoic ester **29** in excellent yield (**Scheme 7**). The ester **29** served as a precursor for various substrates **30**-**34** that were intended for RCM. The preparation of RCM precursors is summarized in **Scheme 7**. Thus, DDQ mediated deprotection of the PMB group, followed by Dess-Martin periodinane oxidation delivered ketone **30**. This was then further modified via deprotection of the benzylidene acetal and protection of the two hydroxyl functions as TBS ether. We were also able to prepare metathesis precursors bearing a PMB group in the central position of the triol part (compounds **33**-**34**).



Scheme 7. Preparation of different RCM precursors.

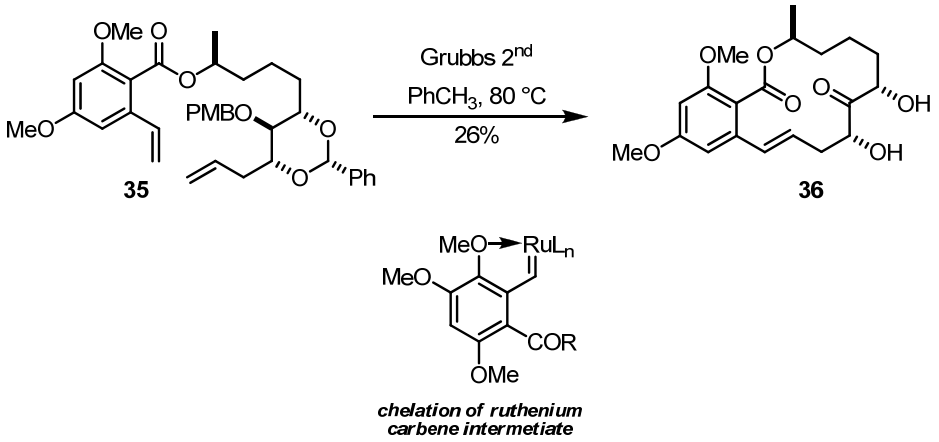
Unfortunately, none of the substrates **29**-**34** could be cyclized with the Grubbs 2nd generation catalyst (5 mol%, $PhCH_3$, 80 °C, 0.002-0.004M). In case of Grubbs 1st generation carbene no desired product could be obtained as well (**Scheme 8**).

	X	R
29, 29a	H, OPMB	CHPh
30, 30b	O	CHPh
31, 31c	O	H
32, 32d	O	TBS
33, 33e	H, OPMB	H
34, 34f	H, OPMB	TBS



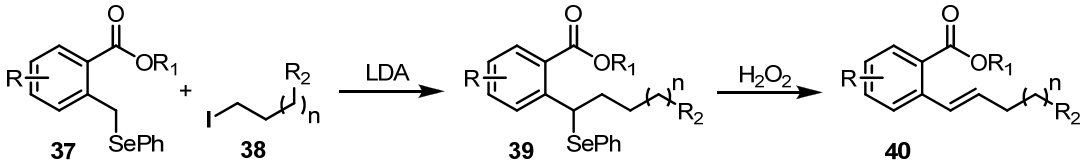
Scheme 8. Metathesis study on various substrates (**29**-**34**).

The fact that the nor-methoxy substrate **35** gave macrolactone **36** (26%) in the presence of Grubbs 2nd catalyst (5 mol%, $PhCH_3$, 80 °C, 0.002-0.004M) points presumably to formation of a chelate of ruthenium carbene intermediate with the Lewis basic 4-methoxy ether unit (**Scheme 9**).[28,29]



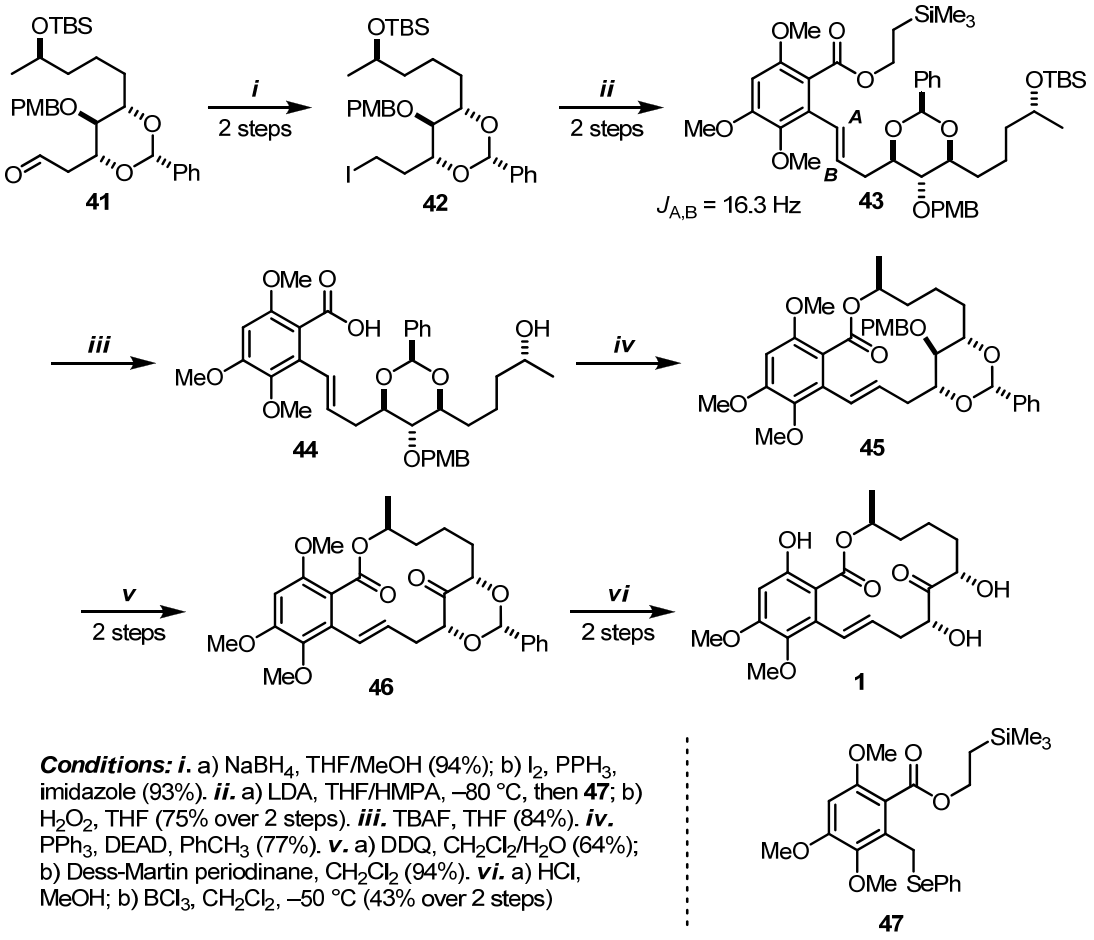
Scheme 9. Cyclization of alkene **35** and proposed chelation of ruthenium carbine that inhibits the cyclization.

With these results, we turned to a strategy pioneered by Winssinger et al. for the synthesis of other resorcylic acid lactones.[14,30] This is characterized by alkylation of a 2-(phenylselanylmethyl)benzoate **37** with an alkyl iodide **38** followed by elimination of the derived phenylselenoxide (**Scheme 10**).



Scheme 10. Establishing *E*-double bond geometry via selenium chemistry.

Accordingly, aldehyde **41** was reduced with $NaBH_4$ to give the corresponding alcohol, which was converted to alkyl iodide **42** by treating it with iodine and PPh_3 in dichloromethane (**Scheme 11**). Then alkyl iodide **42** was combined with seleno ether[31] **47**. Thus, selenide **47** was treated with LDA at −80 °C in THF/HMPA (10:1) and the resulting lithium anion was quenched with iodide **42**. After work up crude selenoether was oxidized leading after elimination to *E*-alkene **43** in 75% yield. The coupling constant between the double bond protons is 16.3 Hz that clearly indicates *E* configuration. Simultaneous cleavage of the trimethylsilylethanyl (TMSE) ester and the TBS ether furnished hydroxyl acid **44**. A smooth cyclization of acid **44** took place under Mitsunobu conditions delivering macrocycle **45** in 77% yield.

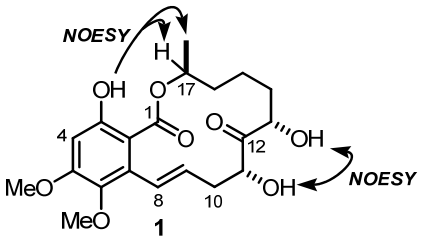


Scheme 11. Synthesis of the proposed structure of macrolide queendlandon (**1**) via Mitsunobu macrolactonization.

Selective removal of the PMB protecting group was followed by oxidation to give ketone **46**. Finally, the benzylideneacetal was cleaved by acid-catalyzed transacetalization. Treatment of the crude dihydroxy ketone with BCl_3 (4.0 equiv) at −50 °C, gave rise to the proposed structure of queenslandon (**1**). The chemoselective ether cleavage next to a carboxylic group is well known.[32] However, this is also evident from the NOESY spectrum (see experimental section, p. 115) where the phenolic OH (3-OH) showed correlelations to 17-H and 17-CH_3. In addition, the HMBC spectrum (see experimental section, p. 116) displays the expected correlations (5-OCH_3/C-5 and 6-OCH_3/C-6).

The ^{1}H-NMR signatures of **1** matched nicely the ones published for the simple model compound **15**. In particular, a NOESY cross peak between 11-H (4.60−4.67) and 13-H (4.36−4.41) suggests the *cis*-orientation at these methine carbons. However, with regard to the published data for queenslandon some distinct discrepancies were observed (**Figure 2**). For example, there are big differences (δ ppm>3) for C12, C9, and C11 (δ ppm = 6.4). Thus, one might conclude that something is wrong with

C11 since both C9 and C12 are in vicinity to C11. Further support for this hypothesis comes from a comparison of the queenslandon structure **1** with the related compounds **5** and **8**. The measured optical rotations for **1** are $[\alpha]^{20}_{D}$ = −41.0 (*c* 0.5, CH_2Cl_2), $[\alpha]^{20}_{D}$ = −51.0 (*c* 0.1, CH_3OH) and they differ from those reported in original paper. The literature value for the isolated queenslandon amounts to $[\alpha]^{20}_{D}$ = +24.4 (*c* 0.028, CH_3OH).[17] Macrolactone **1** showed moderate cytostatic activity with an IC_{50} of 33 µg mL^{-1} (84 µM) against the mouse fibroblast cell line L929.

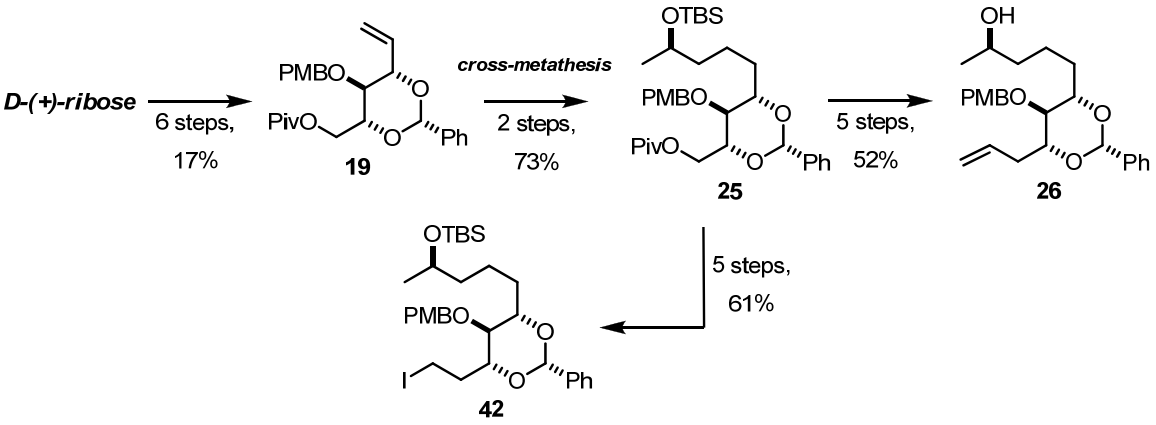


position	shift Mikami	shift comp. 1	shift difference
12	***209,7***	***213,0***	***3,3***
1	171,1	170,7	0,4
3	161,4	160,9	0,5
5	158,9	158,7	0,2
6	140,1	140,3	0,2
7	***132,2***	***133,5***	***1,3***
9	130,4	127,3	3,1
8	126,9	126,6	0,3
2	103,6	103,7	0,1
4	99,4	99,7	0,3
11	***79,8***	***73,4***	***6,4***
17	74,3	73,2	1,0
13	***73,0***	***75,0***	***2,0***
20	60,2	60,5	0,3
19	55,9	55,9	0,0
16	***39,5***	***37,0***	***2,5***
10	***37,9***	***35,6***	***2,3***
15	34,9	32,5	2,4
14	20,9	20,7	0,2
18	20,0	20,5	0,5

Figure 2. Listing of ^{13}C shifts of natural queenslandon and macrolactone 1.

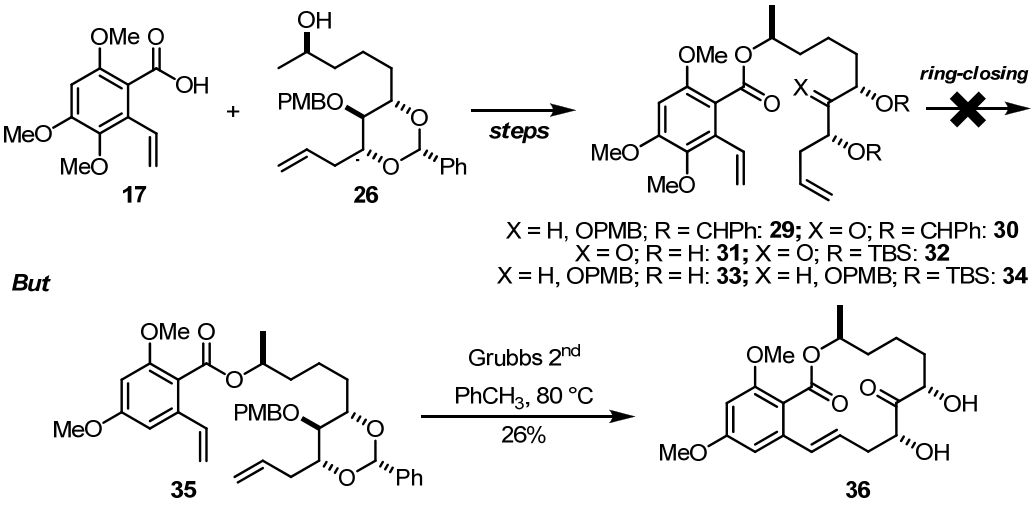
Conclusion

In summary, the synthesis of the proposed structure of the macrolide queenslandon (**1**) was accomplished. The structural challenges of this molecule were a highly substituted electron-rich benzoic acid part and an aliphatic region featuring a dihydroxy ketone subunit. The aliphatic part was synthesized from *D*-(+)-ribose featuring hydroxyl function differentiation in triol **22** via benzylidene acetal formation and cross metathesis to extend the chain (**Scheme 12**).



Scheme 12. Synthesis of the aliphatic part for RCM (alkene **26**) and alkylation (alkyliodide **42**).

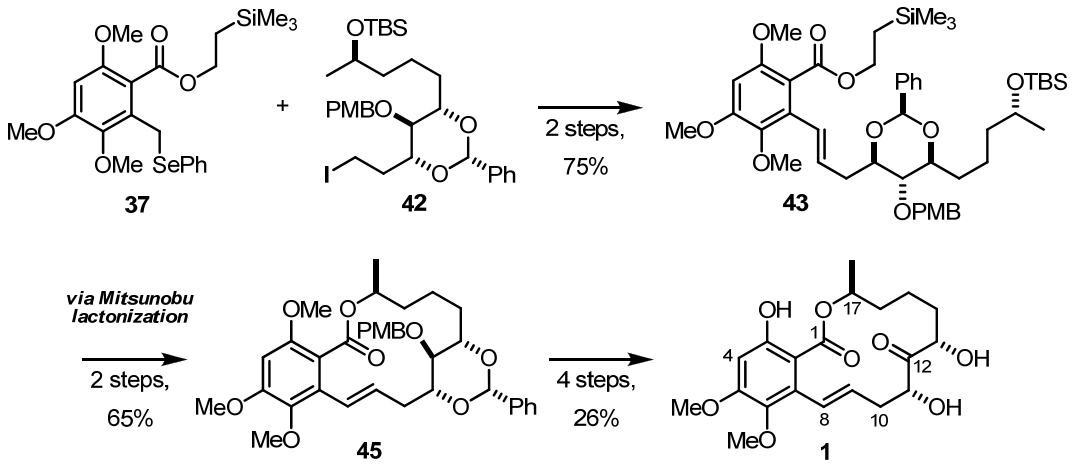
A ring-closing metathesis was studied on various substrates synthesized from alkene **26** and styrene **17** (**Scheme 13**).



Scheme 13. A ring-closing metathesis study on various substrates.

It turned out that none of the RCM precursors underwent ring closure. On the other hand, 6-nor-methoxy macrolactone **36** was obtained in a moderate yield, indicating the influence of the 6-OMe group into a chelate with the ruthenium complex.

Finally, an iodide **42** was used to alkylate the trimethylsilylethyl 2-methyl-benzoate derivative **37**. This led after elimination of phenylselanol to seco acid **43**. The next six steps provided macrolactone **1**, which spectral data did not correspond to queenslandon (**Scheme 14**). Since the biggest differences are observed for the chemical shifts around C11 it is likely that the configuration of C11 should be inverted. Thus, it is clear that the structure requires revision.[33]



Scheme 14. An alkylation protocol leading to the proposed structure of macrolide queenslandon (**1**).

Chapter II

Approach Towards the Total Synthesis of the Macrolide Leiodermatolide

Introduction

Leiodermatolide (**48**) is a potent antimitotic agent, recently isolated by the group of Amy Wright from the sponge *Leiodermatium*, which belongs to the order Lithistida (**Figure 3**).[34] It exhibits a nanomolar level cytotoxicity against a variety of human tumor cell lines (see **Figure 3**) while showing reduced toxicity to normal cell lines. Furthermore, it does not directly bind to tubulin. Leiodermatolide does not show much similarity to other cytotoxic polyketides, however it shares the carbamate function with palmerolide[35] (**49**) and discodermolide[36] (**50**). This novel polyketide features a 16-membered macrolide, with a 6-membered lactone ring on the side chain and has nine stereocenters together with a *Z*,*Z* and an *E*,*E* - diene system. Although, a report of Wright et. al. was based just on a flat structure of this macrolide, more recently additional data with stereochemical information appeared on the web.[37]

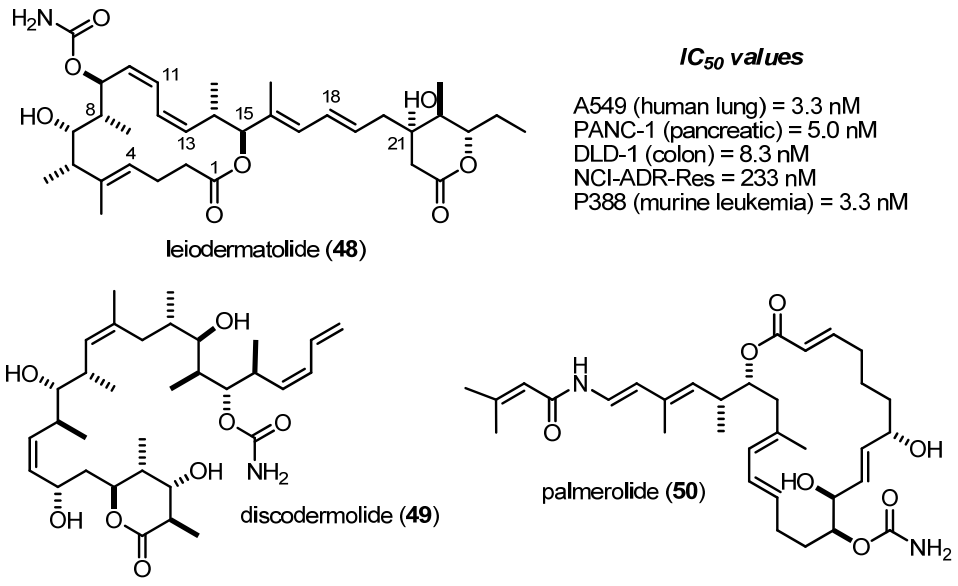
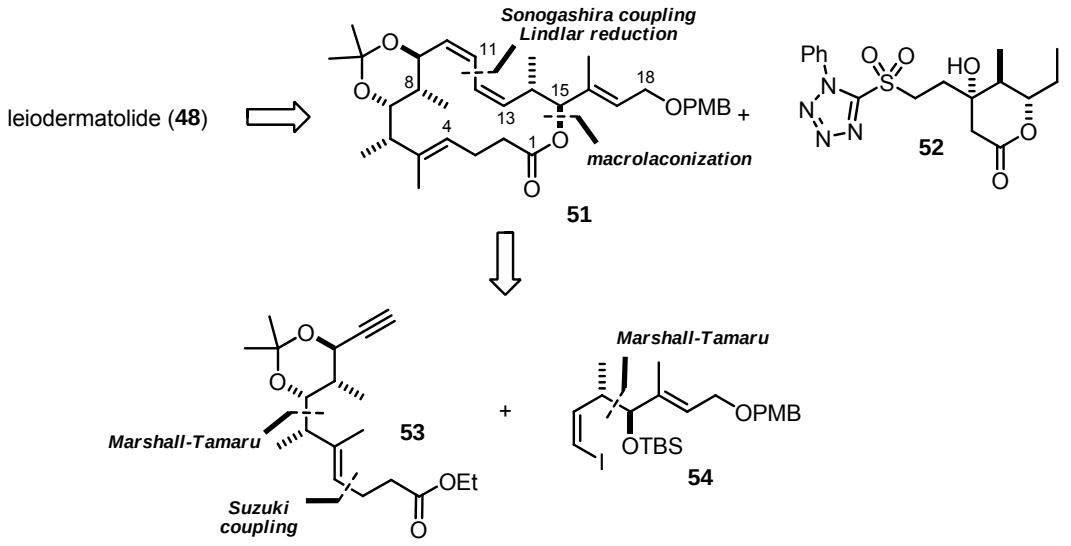


Figure 3. Proposed structure of leiodermatolide (**48**) and structures of related compounds.

Taking into account the remarkably potent antiproliferative activity and structural features which are calling for proof, leiodermatolide (**48**) deserves an attention for total synthesis.

Retrosynthetic Consideration

As outlined in the retrosynthetic plan in **Scheme 15**, we decided to remove part of the side chain by cutting the C18-C19 *trans* double bond (Julia-Kocienski olefination).[38] For macrolactone formation lactonization reactions (Yamaguchi/Mitsunobu) were considered. Alternatively, other C-C bond forming reactions like ring-closing metathesis[19,39] might be options. The internal *Z,Z*-diene would come from an enyne precursor. This way, a Sonogashira cross-coupling followed by *Z* selective reduction is obvious. This leads to two building blocks **53** and **54**, both having roughly equal size.

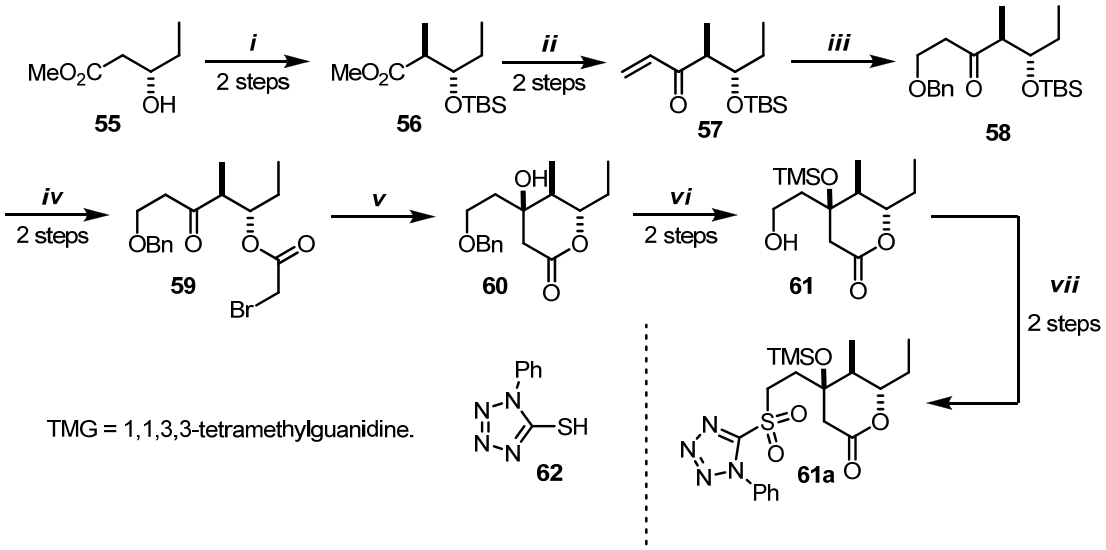


Scheme 15. Retrosynthetic analysis of leiodermatolide (**48**).

For the alkyne **53** we were optimistic about a Marshall-Tamaru reaction[40,41] on a chiral aldehyde, where the *E*-double bond geometry would come from a carbometalation/Suzuki coupling sequence. The *anti*-stereochemistry at C14/C15 in **54** could be secured by applying the same Marshall-Tamaru reaction as well.

Results and Discussion

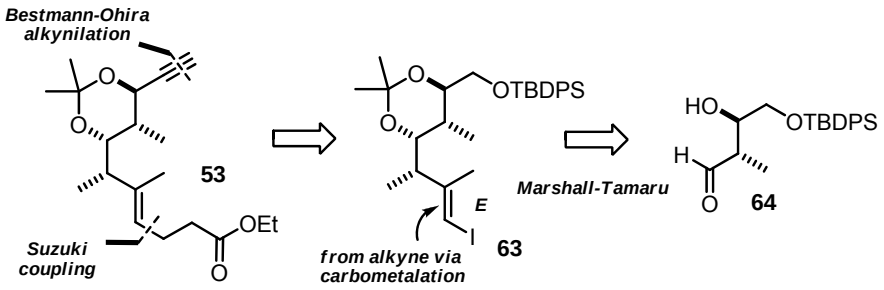
A side chain (sulfone **52**) was synthesized by a graduate student Christian Rink (**Scheme 16**). Here he started the synthesis from known methyl (3*S*)-3-hydroxypentanonate[42] (**55**), which was alkylated with MeI (Fráter-Seebach protocol[43]) and the free hydroxyl function protected as TBS ether to provide silyl ether **56**. This was then converted to Weinreib amide followed by Grignard reaction to give enone **57**. Subsequent Michael addition of benzyl alcohol induced by 1,1,3,3-tetramethylguanidine[44] resulted in ketone **58** in 76% yield. In the next two steps, which were TBS deprotection and esterification, a Reformatsky precursor **59** was obtained. A smooth intramolecular Reformatsky reaction[45,46] took place when ester **59** was introduced to a SmI_2 solution at –78 °C giving alcohol **60** as a single isomer. However, the isomer formed in this step was wrong in regard to the proposed stereochemistry. The synthesis was continued towards the sulfone **52**. Thus, protection of the tertiary hydroxyl function as TMS ether and debenzylation with H_2/Pd delivered alcohol **61** in 77% yield over two steps. Triazole **62** moiety was installed via Mitsunobu reaction and the sulphur atom was oxidized with H_2O_2 to deliver sulfone **61a** in 97% yield.



Conditions: i. a) LDA, MeI, HMPA, THF, –78 °C, (70%, *dr* = 85:15); b) TBSCl, DMAP, imid., DMF (93%). ***ii.*** a) MeONHMe·HCl, *i*PrMgCl, THF (88%); b) vinylMgCl, THF, –10 °C to 0 °C (90%). ***iii.*** BnOH, TMG (76%). ***iv.*** a) HCl, MeOH (89%); b) $BrCH_2COCl$, Py, DMAP, CH_2Cl_2 (100%). ***v.*** Sm, CH_2I_2, THF, –78 °C (88%); ***vi.*** a) TMSCl, imid., CH_2Cl_2 (96%); b) H_2, Pd/C, THF (80%). ***vii.*** a) **62**, PPh_3, DEAD, THF (92%); b) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH (97%).

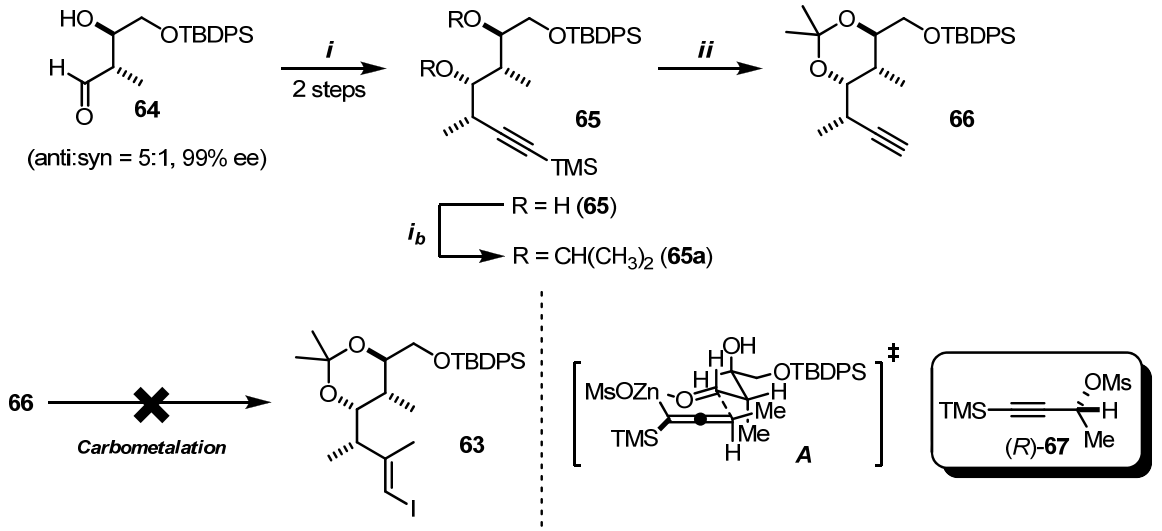
Scheme 16. Synthesis of leiodermatolide's side chain via Reformatsky reaction.

For the synthesis of alkyne **53** we thought about Suzuki coupling[47] on *E*-iodoalkene **63** and Bestmann-Ohira alkynylation[48] (**Scheme 17**). For the synthesis of *E*-vinyliodide **63** a zirconium mediated selective carboalumination/halogenation[49] seemed to be obvious and a Marshall-Tamaru reaction on chiral aldehyde **64** should secure an *anti*-Me/OH relationship.



Scheme 17. Retrosynthetic scheme for ester **53**.

As a starting material we selected aldehyde **64**, which was obtained via *L*-Proline catalyzed cross-aldol reaction of α-silyloxyacetaldehyde using a known literature procedure (**Scheme 18**).[50]



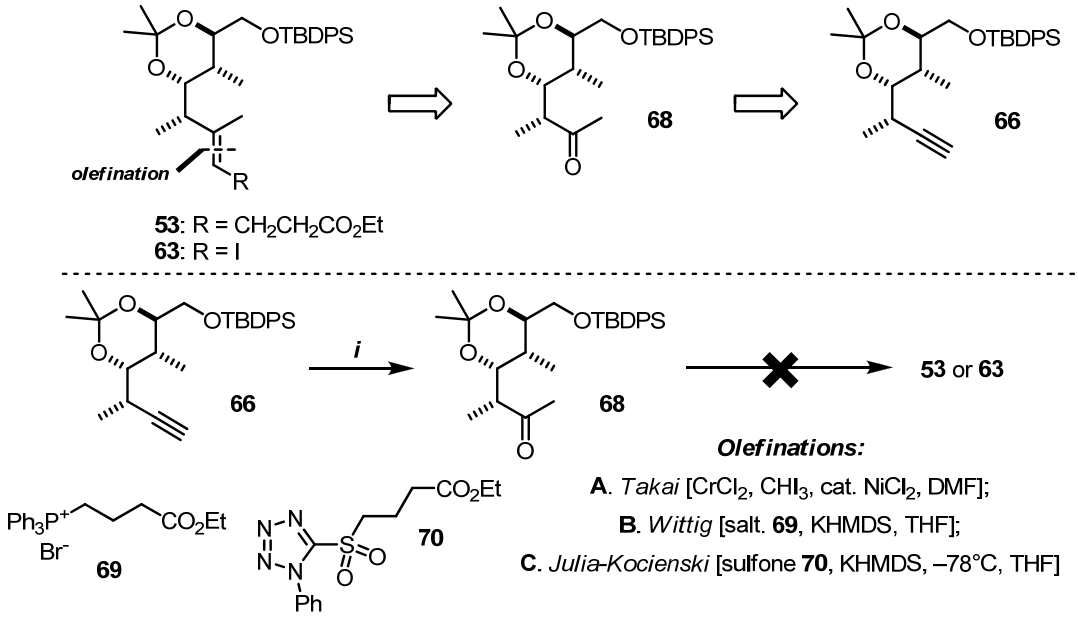
Conditions: i. a) PPh_3 (5 mol%), $Pd(OAc)_2$ (5 mol %), (*R*)-**67**, Et_2Zn, THF, –78°C to –10°C (61%); b) Dimethoxypropane, CSA (10 mol%), CH_2Cl_2, r.t. (82%). ***ii.*** K_2CO_3, MeOH, r.t. (97%).

Scheme 18. Synthesis of carbometalation precursor **66** and attempts to secure *E*-vinyliodide **63**.

With this aldehyde in hand we tested the Marshall-Tamaru conditions hoping for separable diastereomeric diols. To our surprise, when (*R*)-mesylate **67**[51] (2.0 equiv.) was subjected into the reaction mixture containing $Pd(OAc)_2$ (0.05 equiv.), PPh_3 (0.05 equiv.) and aldehyde **64** followed by slow addition of diethyl zinc (3.0 equiv.) and stirring for 48 hours, diol **65** was isolated as a single isomer in 61% yield after chromatographic purification (**Scheme 18**). This reaction outcome can be understood based on Felkin-Anh-like transition state ***A*** which is akin to attack of an *E*-enolate to an α-substituted aldehyde (**Scheme 18**). Due to an angle of 120 ° between the C=O- and the OH-dipole this transition state also minimizes dipole interactions.[52] We also assume that the major *anti* diastereomer **64** reacts faster than the corresponding *syn* isomer.[53] Subsequent diol protection as acetal **65a**

additionally proved the 1,3-*anti* relationship. In particular, the two methyl groups of the acetal appear at similar chemical shifts in the ^{13}C NMR spectrum (23.7 and 24.9 ppm, respectively).[54]

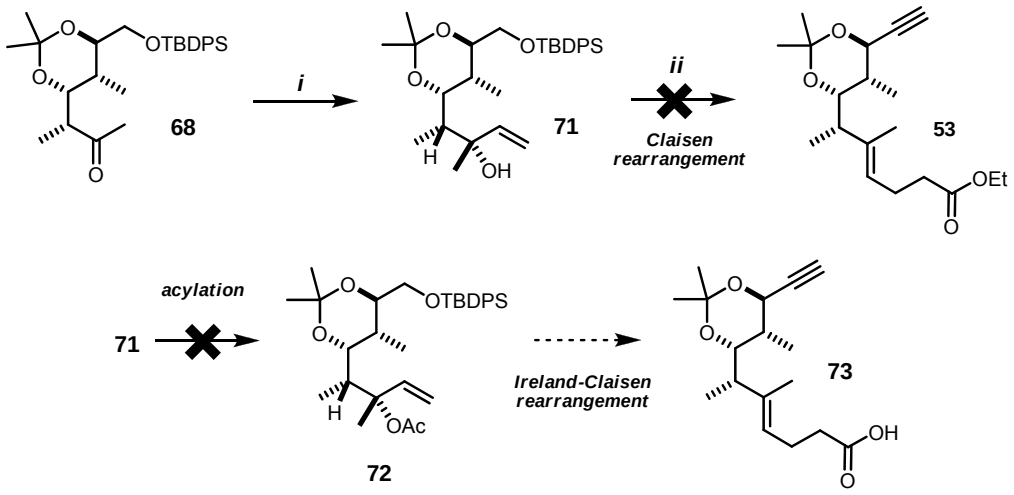
After the TMS group was removed with K_2CO_3 in MeOH, a carboalumination procedure was evaluated. However, no desired product could be obtained employing known procedures ($AlMe_3$, $[Cp_2ZrCl_2]$, I_2, solvent). In the case of water-accelerated carboalumination[55], just acetal deprotection could be observed. Thus, other strategies like olefination to prepare *E*-vinyliodide **63** were considered (Scheme 19). Thus, an olefination precursor **68** was prepared form alkyne **66** via Kutscheroff hydration[56] in 76% yield. Then, Takai olefination[57] conditions were tested to prepare **63**. However no reaction was observed. An olefination with ethyl ester **69** was also taken into account. Again, reaction with Wittig salt **69** failed to provide the desired product. The same observation was made in the case of Julia-Kocienski olefination.[38a]



Scheme 19. Attempts to prepare **53** or **63** via olefination.

With disappointing results mentioned above, we came to the idea to establish the *E*-double bond via Claisen[58] or Ireland-Claisen[59] rearrangements. Thus, vinyl magnesium bromide addition to ketone **68** at −78 °C led to a smooth formation of a single isomer and in 65% yield (**Scheme 20**). This is propably isomer **71**, who's formation could be probably explained by chelation control (six-membered chelate complex). In addition, literature examples also support this outcome.[60,61] This was then heated with 1,1,1-trimethoxyethane in the presence of catalytic amounts of propionic acid. However, even at a temperature of 110 °C the desired rearrangement did not take place. Temperature increase led to

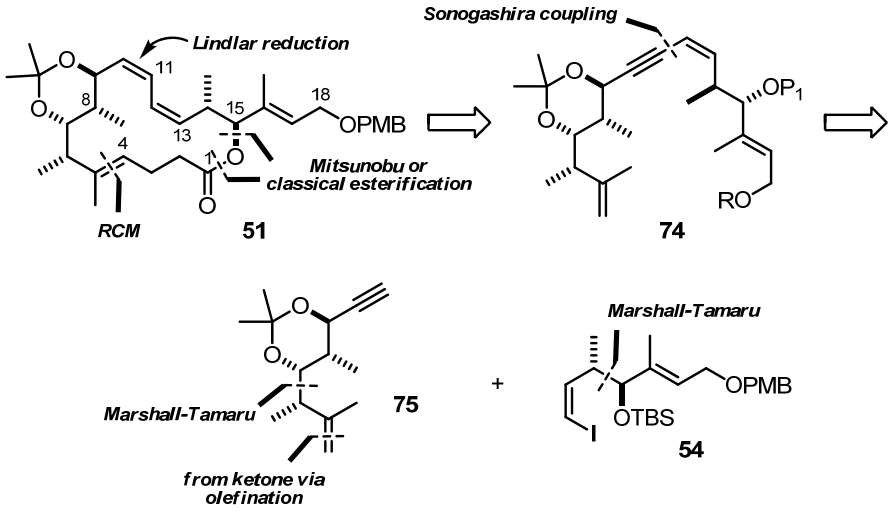
decomposition of starting material. In the case of the Ireland-Claisen rearrangement we faced the problem at the acylation step, as all attempts to acylate the OH function failed.



Conditions: i. vinyMgBr, THF, –78 °C (65%); ***ii.*** 1,1,1-trimethoxyethane, cat. 1-propionic acid, xylene, heat.

Scheme 20. An attempt to secure the *E*-double bond via Claisen or Ireland-Claisen rearrangement.

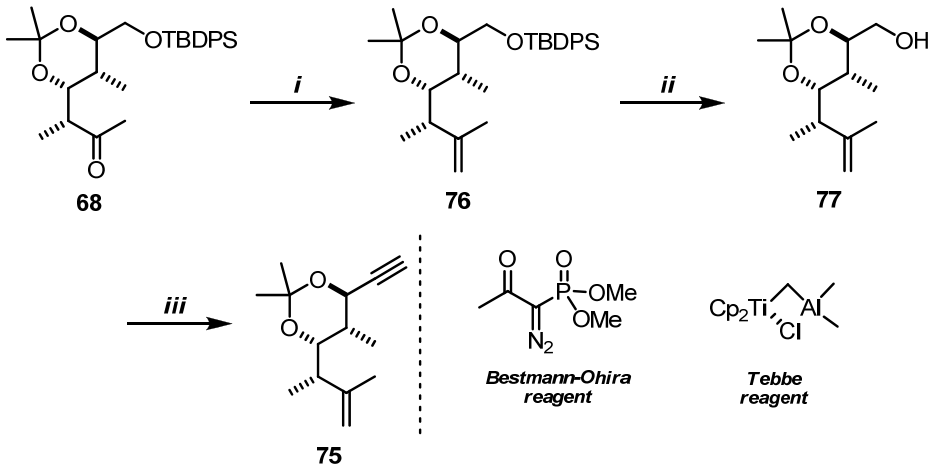
After unsuccessful efforts to establish the *E*-substituted double bond in vinyl iodide **63** or ester **53** we decided to modify the retrosynthetic scheme namely to concentrate on ring-closing metathesis that would possibly create the desired double bond configuration at a later stage (**Scheme 21**).



Scheme 21. A modified retrosynthetic scheme for leiodermatolide core **51**.

Thus, Sonogashira coupling partner alkyne **75** would come from a ketone via olefination and the carboxyl function on 15-OH would be installed via esterification with 1-pentenoic acid.

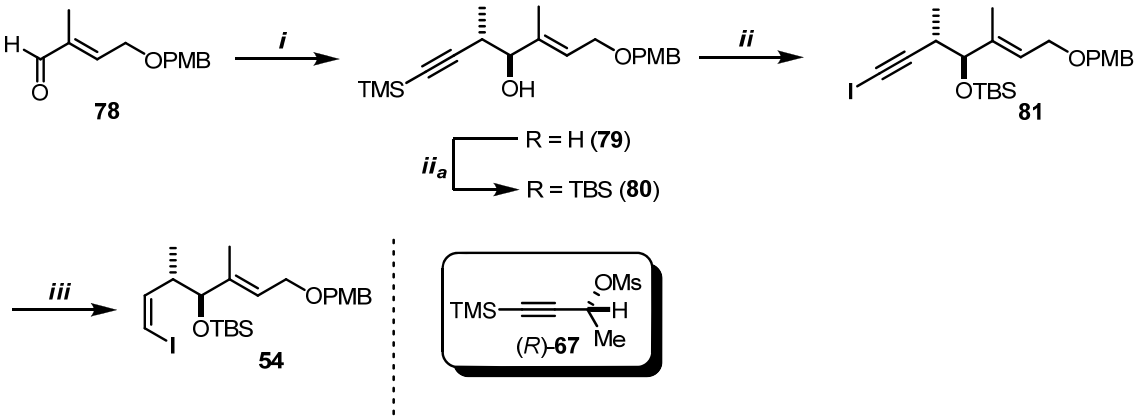
The synthesis of alkyne **75** we started with Tebbe olefination[62] on ketone **68**, followed by silyl deprotecting with TBAF. The resulting alcohol **77** was then treated with Dess-Martin periodinane followed by reaction with Bestman's reagent to give corresponding alkyne **75** in 40% yield over two steps (**Scheme 22**).



Conditions: i. Tebbe reagent, THF, –40 °C (92%). ***ii.*** TBAF, THF, 0 °C (85%). ***iii.*** a) Dess-Martin periodinane, DCM, 0 °C; b) Bestmann's reagent, MeOH (40% over 2 steps).

Scheme 22. Transforming ketone **68** into Sonogashira coupling precursor **75**.

With alkyne **75** in hand, we now concentrated on the construction of *Z*-vinyl iodide **54** (**Scheme 23**).



Conditions: i. PPh_3 (5 mol%), $Pd(OAc)_2$ (5 mol %), (*R*)-**67**, Et_2Zn, THF, –78°C to –5°C (58%); ***ii***. a) TBSOTf, CH_2Cl_2, 2,6-lutidine, –50°C to 0°C (78%); b) $AgNO_3$, NIS, DMF, r.t. ***iii.*** $KO_2CN{=}NCO_2K$, MeOH, py, r.t. (77%, 2 steps)

Scheme 23. Synthesis of *Z*-vinyl iodide **54**.

As it was mentioned before vinyl iodide **54** could be accessed via Marshall-Tamaru reaction on an appropriate aldehyde. Thus, as a starting aldehyde we chose aldehyde[63] **78**, which easily underwent allelnyl zincate addition to give alcohol **79** as a single isomer. The enantiomeric ratio of this was determined by Mosher analysis to be 97:3 (**Figure 4**). Subsequent alcohol protection with TBSOTf in presence of 2,6-lutidine furnished the corresponding silyl ether **80** in 70% yield.

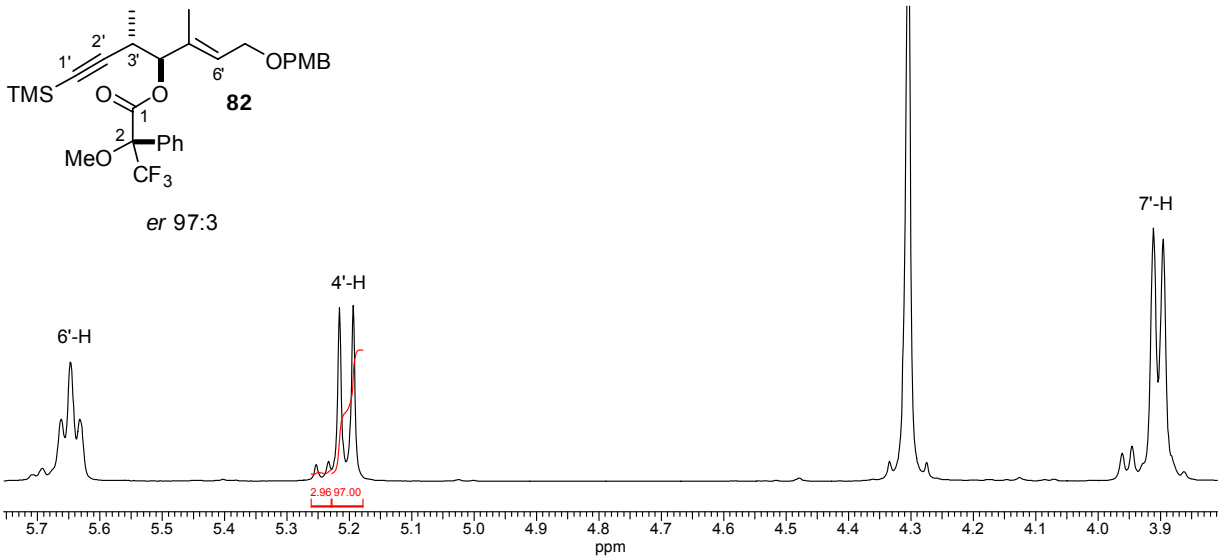
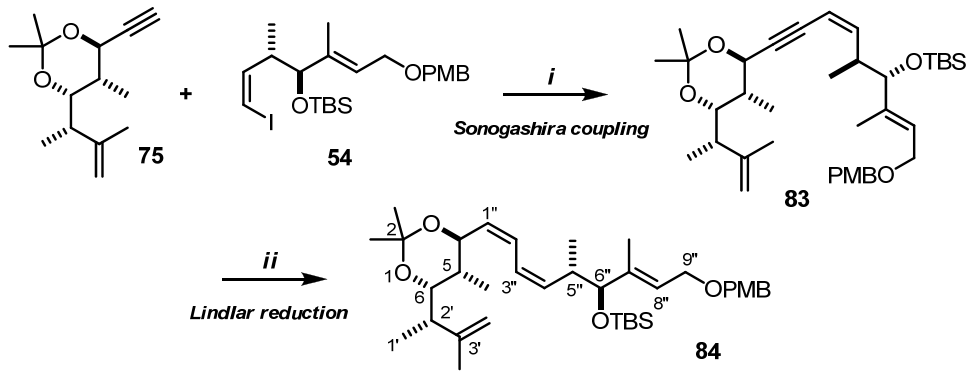


Figure 4. Fragment of ^{1}H NMR spectrum of Mosher ester **82**.

Further functionalization of the triple bond called for terminal iodination and *Z*-selective reduction. Thus, treatment of trimethylsilyl alkyne **80** with *N*-iodosuccinimide in the presence of silver nitrate[64] resulted in almost quantitative converson to iodoalkyne **81**, which was directly subjected to *Z*-specific diimide reduction.[65] Thus, slow addition (6 h) of acetic acid to a solution of the iodoalkyne, potassium azodicarboxylate and pyridine gave *Z*-iodoalkene **54** in 77% yield over two steps.

Both building blocks **54** and **75** were then combined in a Sonogashira coupling reaction. Here, optimal conditions found to be $Pd(PPh_3)_4$ (5 mol%), CuI (50 mol%) and diethylamine as a solvent and base. These conditions led to complete conversion to enyne **83** in 68% yield (Scheme 24). The *Z*-selective reduction of the triple bond turned out to be challenging, as many of known literature methods (P2-Ni reduction;[66] $NbCl_5$, Zn, HMPA, THF;[67] Rieke Zn, THF, MeOH, H_2O[68]) failed to provide desired diene **84**, resulting mainly in a complex mixture of overreduction products (detected by HPLC). However, carefully optimized Lindlar reduction[69] conditions allowed us to isolate diene **84** in 59% yield after chromatographic purification (**Scheme 24**).



Conditions: i. Pd(PPh$_3$)$_4$ (5 mol%), CuI (50 mol%), Et$_2$NH, r.t. ***ii*** Lindlar cat., quinoline, EtOAc:1-hexene (1:1) (40% over 2 steps).

Scheme 24. Sonogashira coupling and Lindlar reduction leading to *Z*,*Z*-diene system.

The ^{1}H NMR data nicely indicate a *cis*-relationship of the 11-H and 12-H protons, where coupling constant is 11.4 Hz (**Figure 5**).

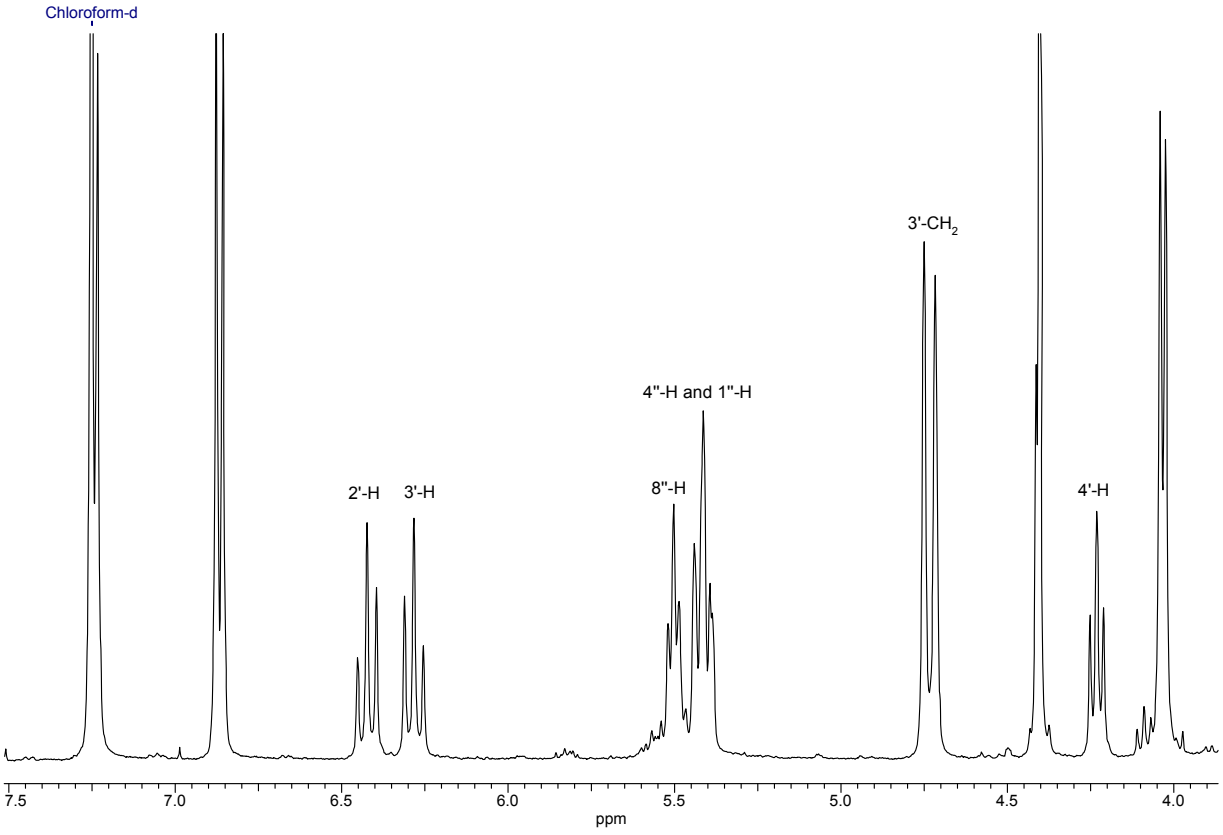
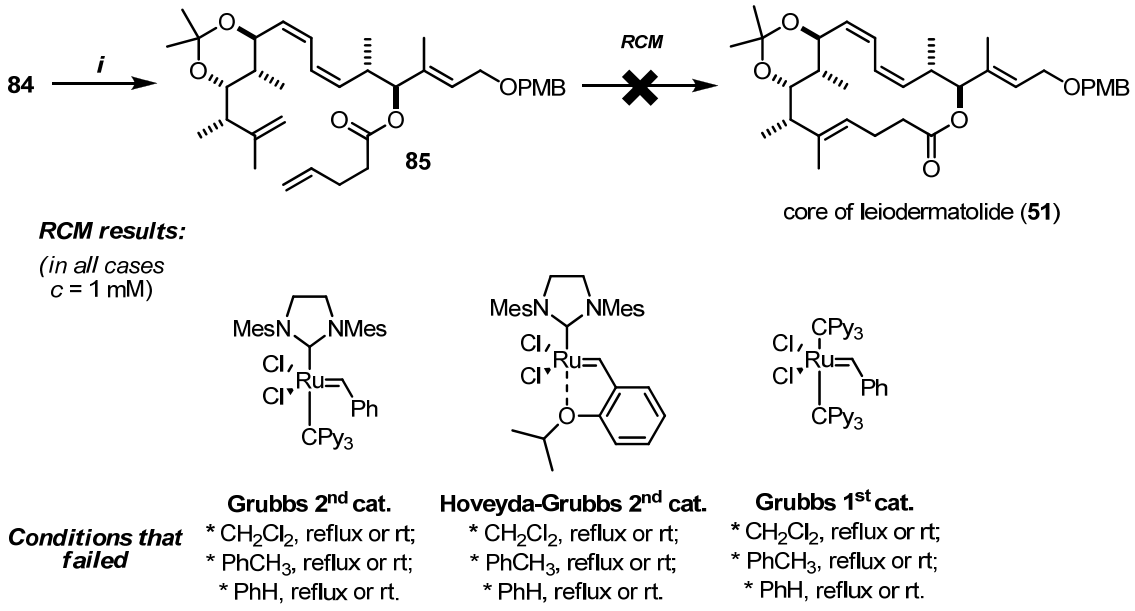


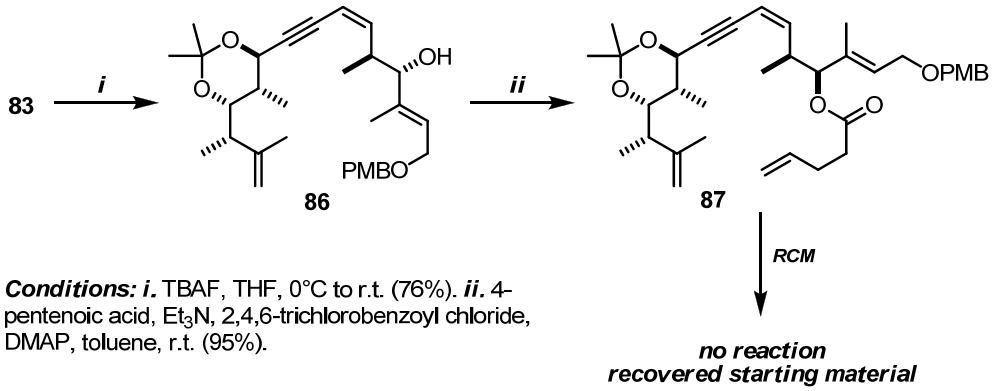
Figure 5. Fragment of the ^{1}H NMR spectrum of *Z*,*Z*-diene **84**.

The TBS protecting group in **84** was removed with TBAF and simple Yamaguchi esterification with 1-pentenoic acid secured RCM precursor **85** in 63% yield over two steps (**Scheme 25**). A ring-closing metathesis on substrate **85** represents a big challenge as it contains five double bond where each those could participate in the metathesis reaction. For the RCM study we chose three readily available ruthenium catalysts – Grubbs 2nd,[70] Hoveyda-Grubbs 2nd,[71] and Grubbs 1st [72] (**Scheme 25**). All of these catalysts were tested in CH_2Cl_2, $PhCH_3$ and PhH solvents at a substrate concentration of 1 mM. Stirring the RCM precursor **85** at room temperature in toluene or benzene gave no cyclized lactone. Just starting material was recovered in all cases. However, when the RCM reaction on ester **85** was tried in CH_2Cl_2 containing Grubbs 2nd generation catalyst a complex mixture of products formed. According to HPLC data, no molecular peak of the desired product could be detected. The increase in temperature (starting from 80 °C) resulted in decomposition of starting material with all three catalysts.



Scheme 25. Preparation of RCM precursor **85** and attempts to prepare macrocycle **51**.

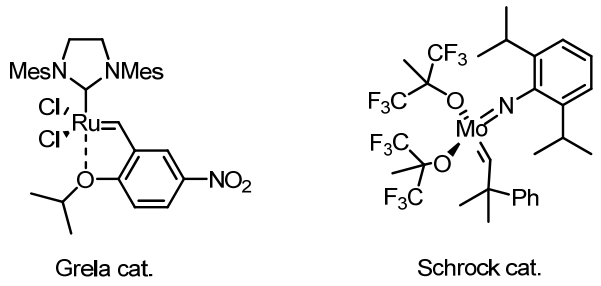
Next RCM precursor **87** with a triple bond was prepared following essentially the same procedures as for **85** (**Scheme 26**).



Scheme 26. Synthesis of RCM precursor-enyne **87**.

Again, running experiments with RCM catalyst mentioned in **Scheme 25** no desired product was obtained, but in all cases starting material was isolated. Probably, due to the linear triple bond the molecule it self can not undergo ring-closing for steric reasons.

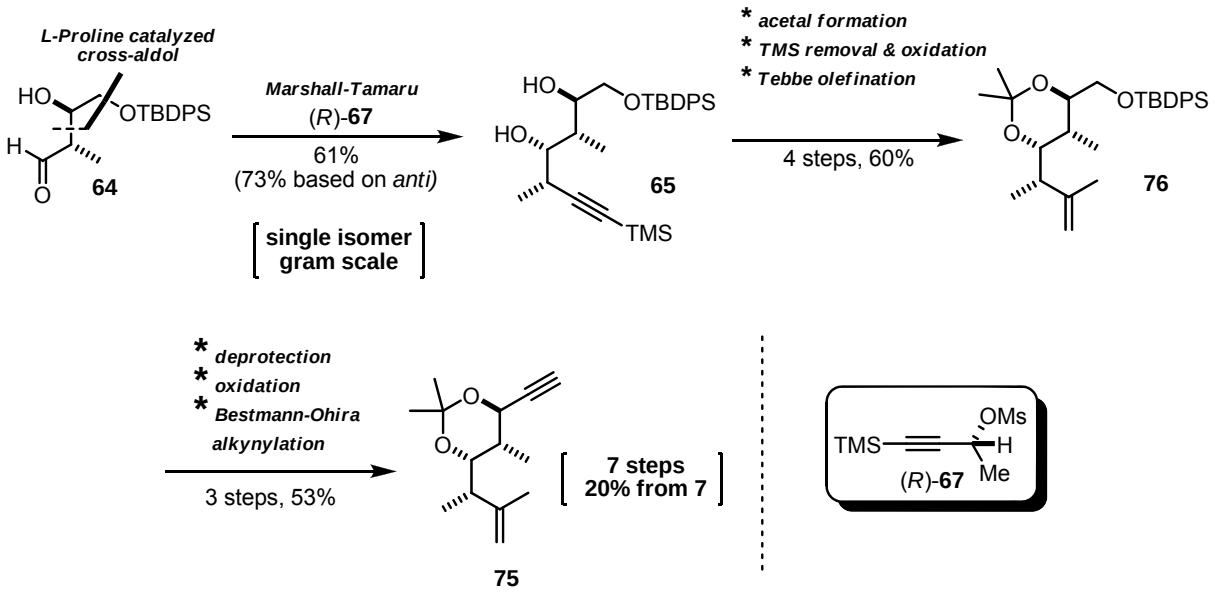
With these unsuccessful results toward the preparation of leiodermatolide core **51**, we decided to cancel the study of this route. On the other hand, there is still a play ground to continue the study on ring-closing metathesis while screening other catalysts like Schrock's molybdenum based catalyst[73] or Grela's ruthenium catalyst[74] which are known to be one of most active metathesis carbenes[75] in the literature (**Scheme 27**).



Scheme 27. Highly active ruthenium and molybdenum RCM catalysts.

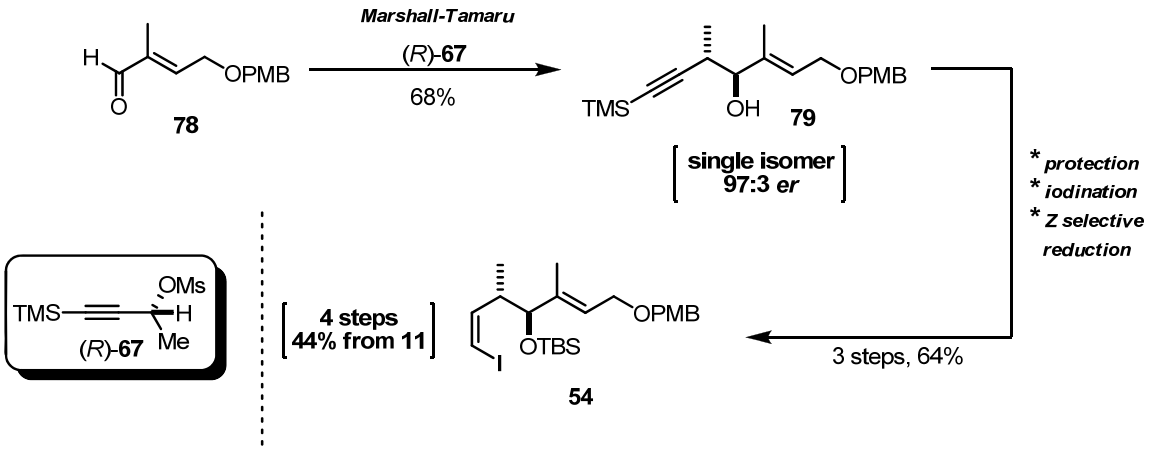
Conclusion

In summary, a ring-closing metathesis approach towards the macrolactone of leiodermatolide (**51**) was studied. The key fragments – alkyne **75** and *Z*-iodoalkene **54** were prepared featuring a Marshall-Tamaru reaction (**Scheme 28**). An efficient protocol for preparation of the stereotetrad was developed starting from aldehyde **64**, which was obtained via organocatalysis. This was then converted to diol **65** setting four stereocenters selectively and representing one of the shortest procedures to set this type of stereochemistry.[76] Further four steps converted the triple bond into a propenyl moiety in 60% overall yield. Redox operations and Bestmann-Ohira alkynylation starting from silyl ethers **76** secured us to prepare alkyne **75** in overall 20% yield over 7 steps.



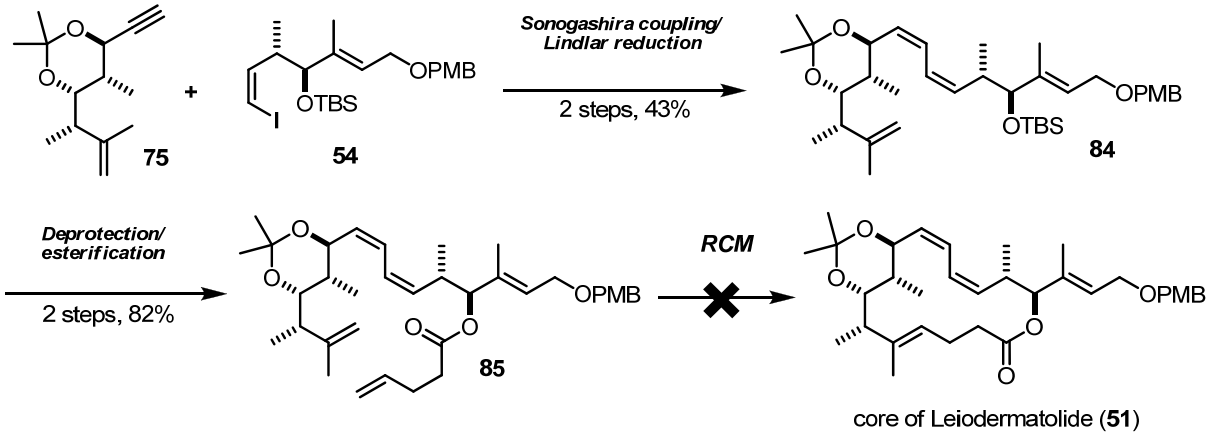
Scheme 28. Synthesis of Sonogashira precursor **75** featuring a Marshall-Tamaru reaction.

The same Marshall-Tamaru reaction served as a perfect synthetic tool for the synthesis of *Z*-iodoalkene **54**. A rapid construction of two sterocenters followed by protection, terminal iodination and *Z*-selective reduction delivered PMB ether **54** in 44% yield over four steps starting from literature known aldehyde **78** (**Scheme 29**).



Scheme 29. Summary of the synthesis of *Z*-iodoalkene **54**.

The Sonogashira coupling of the fragment mentioned above led to an enyne, which was then selectively hydrogenated under Lindlar conditions to give the conjungated Z,Z-double system in compound **84** (**Scheme 30**).



Scheme 30. Synthesis of RCM precursor **85**.

The following two steps delivered ester **85**, which unfortunately has failed to participate in a ring-closing metathesis reaction to secure leidermatolide core **51**.

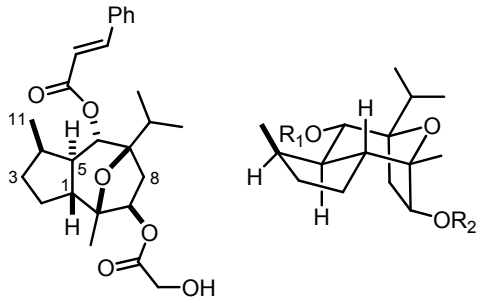
Chapter III

Approach Towards the Total Synthesis of Terpene (–)-Englerin A*

* This work was done together with graduate student Dmitry B. Ushakov.

Introduction

The guaiane (–)-englerin A (**88**) is a sesquiterpene recently isolated from the plant *Phyllanthus engleri* by the group of Beutler et al.[77] Englerin A (**88**) is an attractive synthetic target not only for his molecular architecture but also for its high selectivity and potency against various cell lines typical for renal cancer (**Figure 6**).



(–)-englerin A (**88**)

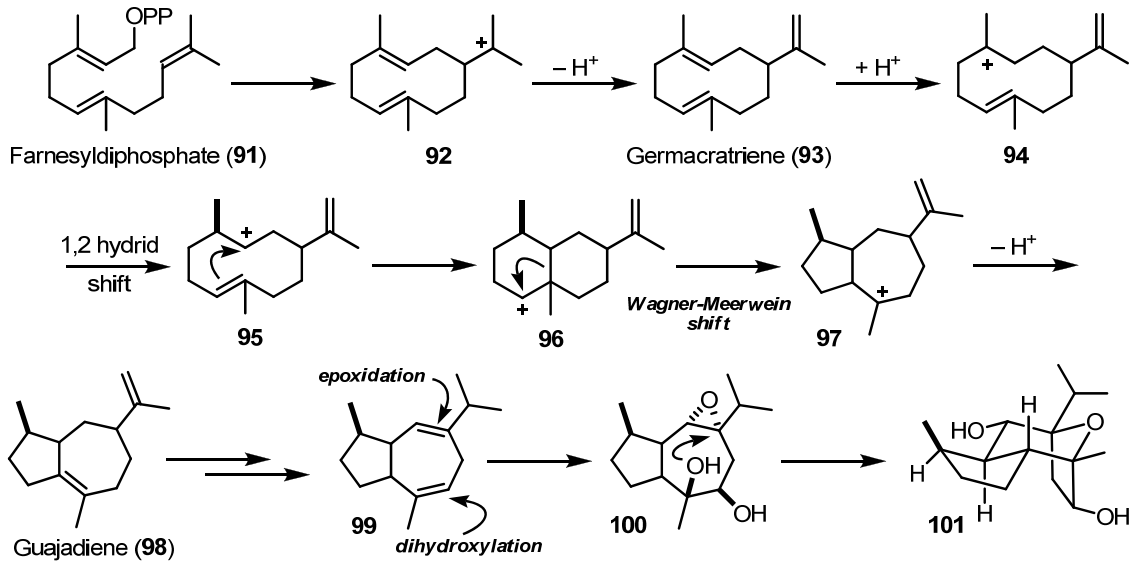
(–)-englerin A (**88**): R_1 = COCH=CHPh; R_2 = $COCH_2OH$
(–)-englerin B (**89**): R_1 = COCH=CHPh; R_2 = H
(–)-englerin B acetate (**90**): R_1 = COCH=CHPh; R_2 = Ac

Renal Cancer Cell Growth Inhibition Data (Mean GI_{50} in μM) for (–)-englerin A (88), Compared to Average Values for Taxol

renal cell line	(–)-englerin A (**88**)	Taxol
786-0	<0.01	0.034
A498	<0.01	0.10
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

Figure 6. Structure of (–)-englerins A-B (**88-90**) and inhibition data of (–)-englerin A (**88**) on various renal cell lines.

The compound features an oxygen bridge in the seven-membered ring and seven contiguous stereocenters, including two quarternary centers. Most likely, this motif originates from a more common bicyclic sesquiterpene core. For this and for an option to find a more simple and readily available natural building block for a possible semisynthetic approach, one should take a glance on the likely biosynthetic pathway of (–)-englerin A (**88**) (**Scheme 31**).[78] As it can be seen, a decalin structure, namely germacratriene (**93**) in nature is arising from farnesyl pyrophosphate (**91**) via a cationic cyclization. Macrocycle **93** is protonated and a subsequent 1,2-hydride shift delivers carbocation **95**, which then through Wagner-Meerwein shift is converted to guaiene (**98**) which undergoes double bond migration processes to give **99**. Further steps to englerin A core involve oxidation processes. In addition, this is a typical feature in terpene biosynthesis. First, the carbocyclic core is constructed followed by redox reactions to set the oxygen functionalities.

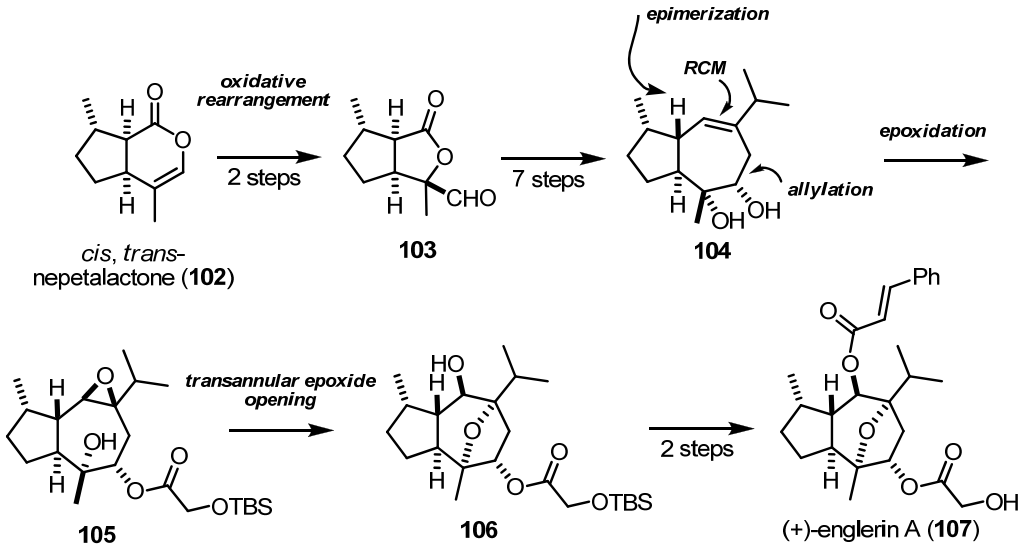


Scheme 31. Possible key intermediates in the biosynthesis of (–)-enlgerin A.

Taking into advance promising anticancer activity and its scarcity from natural sources, englerin A deserves attention as a synthetic target. Furthermore, the structure serves as an inspiration to invent new approaches and strategies towards bridged guainolides also.[79]

Overview of Previous Syntheses

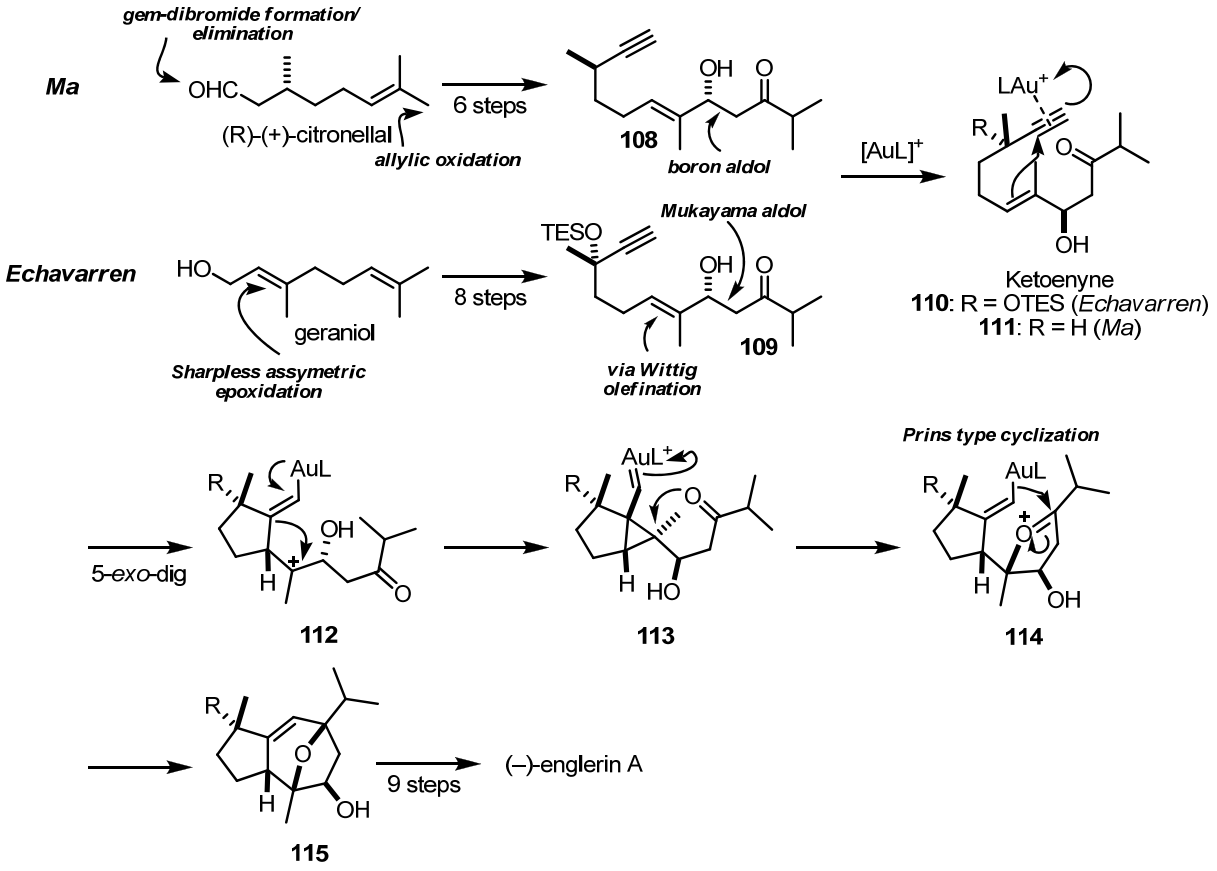
Less than one year after Beutler and co-workers reported the isolation of (–)-englerin (**88**), Christmann and co-workers completed the total synthesis of the (+)-enantiomer (**107**),[80] thereby establishing the previously unknown absolute configuration of the natural product. The key features of this synthesis can be seen in **Scheme 32**. Here *cis*, *trans*-nepetalactone (**102**) served as a starting material, which could be easily obtained by distillation of commercially available catnip oil.[81] Nepetalactone **102** was converted to aldehyde **103** in two steps which involved epoxidation and oxidative rearrangement. Diol **104** was synthesized in seven steps utilizing a diastereoselective Barbier reaction,[82] epimerization and ring-closing metathesis as a key reactions. Then, selective protection of the secondary alcohol function as glycolate ester, epoxidation and transannular epoxide opening[83] secured the core structure of (+)-englerin A and two further steps provided (+) enantiomer **107** itself.



Scheme 32. Retrosynthetic analysis of (+)-englerin A (**88**) according to Christmann et al.

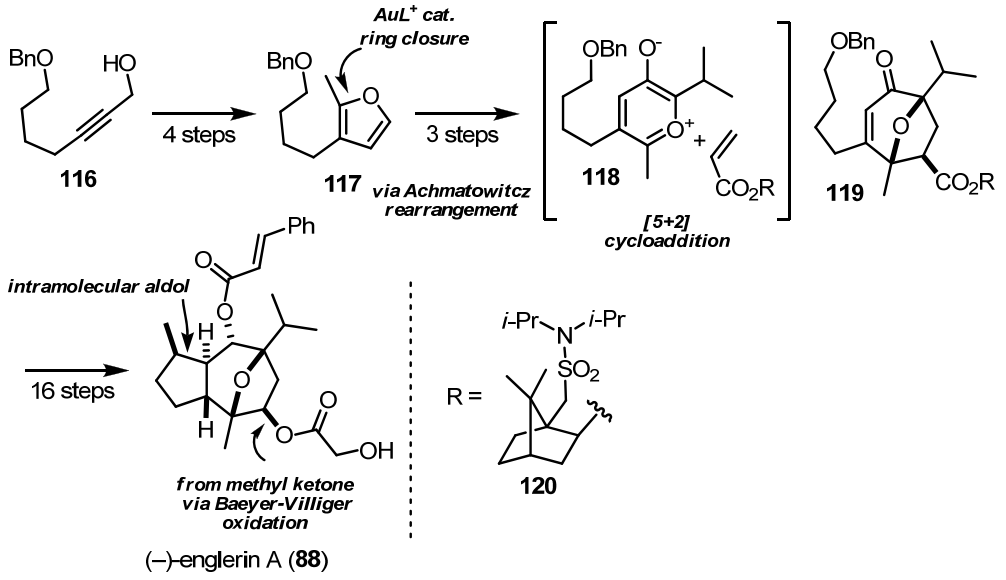
Soon therafter, two conceptually similar syntheses of (–)-englerin A (**88**) appeared from research groups of Ma and Echavarren.[84,85] Here both strategies rely on a gold(I)-catalysed formal domino reaction on a linear ketoenyne precursor for the generation of englerin's tricyclic core (**Scheme 31**). The two syntheses differ in their choice of the cyclization precursor and the gold(I) catalyst. The group of Echevarren chose geraniol as a starting material and in eight steps converted this to ketoenyne precursor (R = OTES) using Sharpless asymmetric epoxidation and a Mukayama aldol[86] to generate two stereocenters. Ma's cyclization precursor (R = H) was obtained in five steps from (*R*)-(+)-citronellal featuring a boron-aldol reaction. Both groups then utilized an intramolecular [2+2+2] ketoenyne cycloaddition.[87] Here in the first step, a 5-*exo*-dig cyclization takes place leading to cyclopropyl gold carbene **113** which reacts with carbonyl oxygen releasing the strain on the cyclopropane ring and

producing oxonium ion **114**. Then, a Prins-cyclization takes place followed by proto-demetalation to give englerin's A tricyclic skeleton. Both syntheses relied on functionalization of **115** featuring allylic oxidation and selective reduction of the double bond to establish a *trans*-fused ring orientation. While the core system **115** could be reached very fast, the subsequent functional group manipulations required a number of steps.



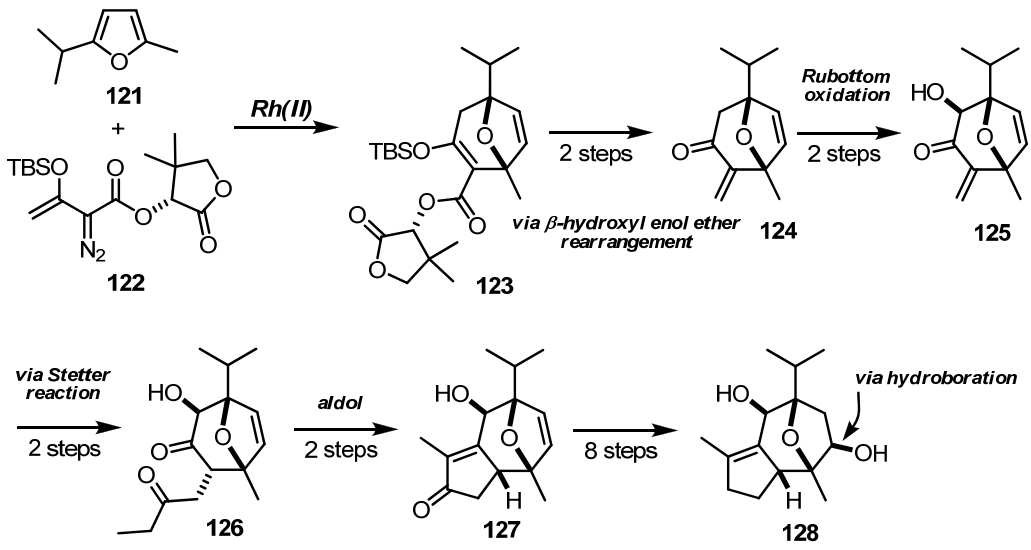
Scheme 33. A Comparative scheme for the synthesis of (–)-englerin A by Ma and Echavarren.

A [5+2] cycloaddition tactic was used in the total synthesis of (–)-englerin A by the Nicolaou/Chen group (**Scheme 34**).[88] The synthesis they started from propargylic alcohol **116** which was converted to furan **117** featuring a gold(I)-catalyzed ring closure.[89] An oxidopyrilium species **118**, obtained in four steps via Achmatowitcz rearrangement,[90] in the presence of chiral Oppolzer's sulfonamide acrylate derivative **120** participated in a [5+2] cycloaddition reaction delivering oxabicyclic enone **119**. As next, the group took a part in a rather long (16 steps) functionalization marathon featuring an intramolecular aldol reaction to form the cyclopentane ring and a Baeyer-Villiger oxidation[91] to convert the methyl ketone moiety to an alcohol function. One should mention that together with the total synthesis first steps towards structure-activity relationship (SAR) of (–)-englerin A were made indicating the importance of the glycolic acid moiety.



Scheme 34. Retrosynthetic disconnection of (–)-englerin A (**88**) by the Nicolaou/Chen group.

The group of Theodorakis achieved an enantioselective formal synthesis of (–)-englerin A (**88**) via a Rh-catalyzed [4+3] cycloaddition reaction.[92] The key oxa-tricyclic compound **123** was obtained via the Davies Rh-catalyzed ring formation,[93] from readily available staring materials, namely substituted furan **121** and chiral diazo ester **122** (**Scheme 35**).

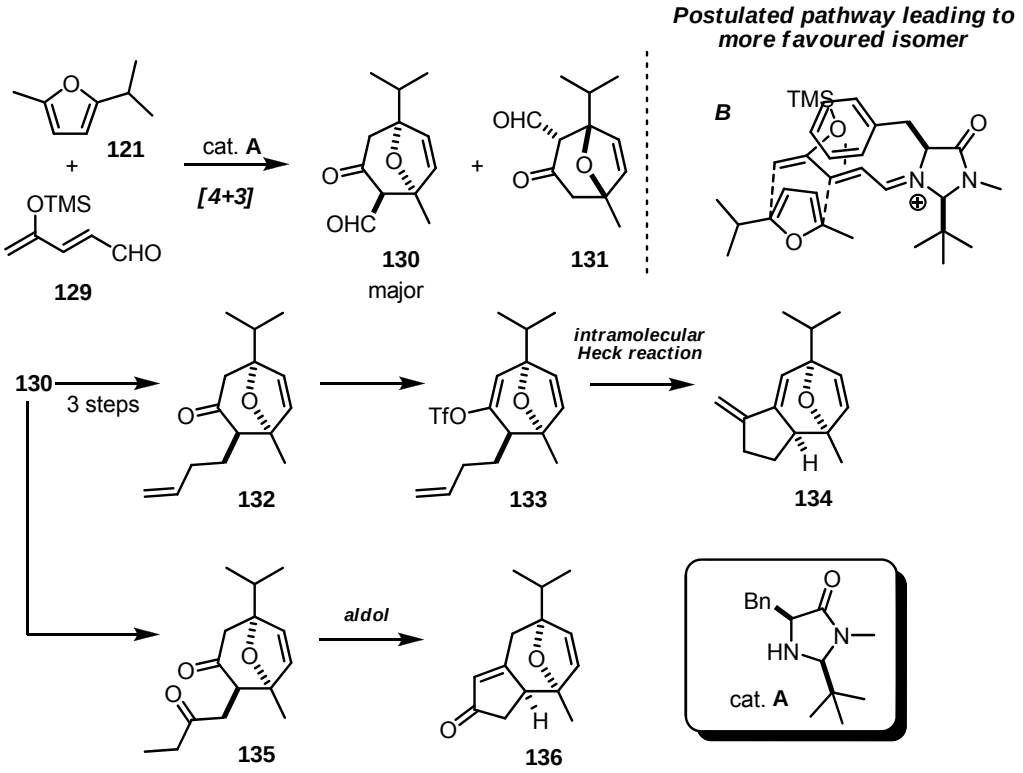


Scheme 35. A formal total synthesis of (–)-englerin A (**88**) by Theodorakis et al.

In the next step a Lewis acid incuced rearrangement of a β-hydroxyl enol ether[94] took place securing ketone **124**. Subsequent Rubottom oxidation[95] and Stetter reaction[96] delivered diketone **125**. The next

steps involved elaboration of the enone system to the five-membered ring. Thus, an intramolecular aldol condensation and $NaBH_4$ reduction furnished the tricyclic englerin A skeleton. A selective hydroboration delivered the hydroxyl function at C9, while the Burgess protocol removed hydroxyl from the cyclopentene ring. Then reduction of the less substituted double bond and silyl deprotection gave rise to diol **128**, which was described by Ma.

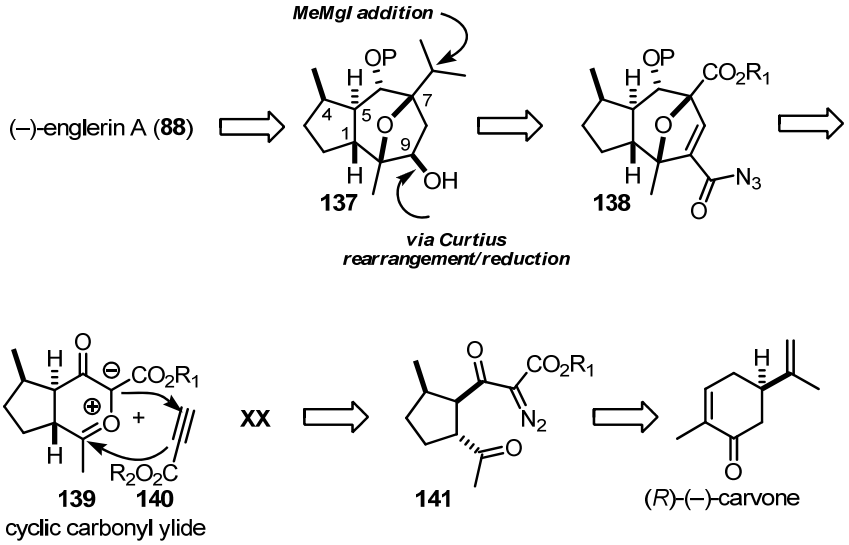
A conceptually very similar work recently appeared in Tetrahedron Letters from the group of Sun and Lin, where they utilized a cation-triggered asymmetric organocatalytic [4+3] cycloaddition reaction (**Scheme 36**).[97] According to work reported from Harmata et al. a [4+3] cycloaddition could be catalyzed by MacMillan's catalyst (cat. **A**) giving a functionalized 8-oxa-bicyclo[3.2.1]octane structure.[98] Thus, starting from readily available starting materials – disubstituted furan **121** and dienal **129**, a mixture of regioisomers **130** and **131** could be obtained (63%, 2.4:1, **130**:**131**). In this case, the major isomer turned out to be the non-required one. Further steps they performed on a mixture of those. These included Grignard addition, acylation and catalytic deoxygenation. The five membered ring was constructed via intramolecular Heck reaction on triflate **133**. In the second approach the group prepared the higher functionalized (+)-englerin's A core structure **136** via Grignard addition on aldehyde **130** followed by intramolecular aldol condensation.



Scheme 36. Asymmetric organocatalytic [4+3] cycloaddition approach to the (–)-englerin A core.

1st Generation Retrosynthetic Consideration

Our retrosynthetic analysis of (–)-englerin A was based on a bimolecular carbonyl ylide-alkyne cycloaddition reaction (**Scheme 37**).[99,100]

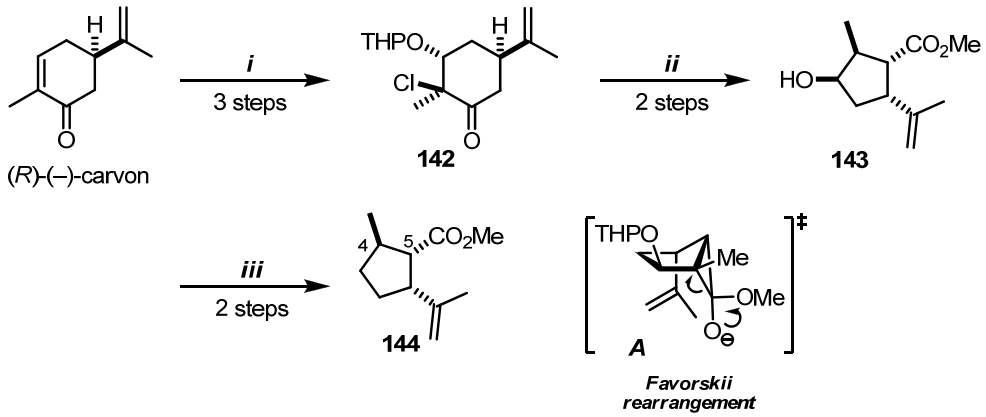


Scheme 37. Retrosynthetic analysis for englerin A (**88**).

The advantage of this strategy is the simultaneous formation of the oxygen bridge in the course of the cycloaddition. Thus, carbonyl ylide **139** would react with propiolate **140** giving a bicyclic addition product (dipolarophile should approach the carbonyl ylide **139** opposite to the C4 methyl group). The intermediate carbonyl ylide should be available by rhodium(II)-catalyzed decomposition of diazoketoester **141**. The latter can be traced back to (*R*)-(–)-carvone. Further functional group manipulation towards **88** would involve Curtius rearrangement of acrylazide **138**, hydrolysis of the resulting vinyl isocyanate to give a ketone, which then would be reduced. The isopropyl group in **137** would come from an ester function, via a MeMgI addition/deoxygenation pathway.

Results and Discussion

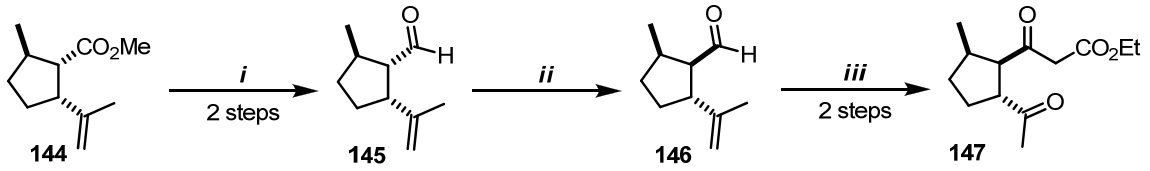
We started the synthesis from commercially available and cheap (*R*)-(–)-carvone. Following known procedures, this terpene was easily transformed into alcohol **143** featuring enone epoxidation, regioselective epoxide opening and Favorskii rearrangement (**Scheme 38**).[101,102] This five step synthetic protocol allowed us to prepare multigram quantities of alcohol **143**. The hydroxyl group was then removed utilizing the Barton−McCombie[103] protocol on the corresponding xanthogenate giving ester **144** in 67% yield over two steps (**Scheme 38**).



Conditions: ***i***. a) H_2O_2, MeOH, NaOH; b) TFA, LiCl, THF; c) PPTS, DHP, CH_2Cl_2 (82%, 3 steps). ***ii***. a) NaOMe, MeOH, Et_2O; b) PPTS, MeOH, 50 °C (94%, 2 steps). ***iii***. a) NaH, CS_2, MeI, THF; b) Bu_3SnH, AIBN, PhMe, reflux (67%, 2 steps).

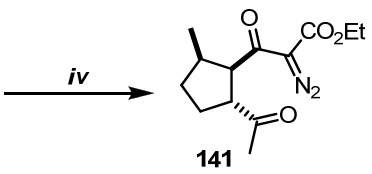
Scheme 38. Transforming (*R*)-(–)-carvone into ester **144**.

As next, epimerization at C-5 was considered. However, all attempts to invert the configuration on ester **144**, under basic conditions, gave inferior results. Thus, the ester function was successfully transformed into a corresponding aldehyde utilizing a two step protocol, namely $LiAlH_4$ reduction and Parikh−Doering oxidation.[104] We found that this two step procedure was more reliable to perform on a large scale (25 g, 87%), as DIBAL-H reduction gave just the corresponding alcohol which was then oxidized with Dess-Martin periodinane[105] (5.0 g, 49% over two steps). Base-induced epimerization of aldehyde **145** was achieved with DBU in refluxing toluene (see **Scheme 39**) leading to *trans* orientation of the aldehyde group with respect to the larger isopropenyl group (*trans*/*cis* = 2:1). Subsequent ozonolysis of aldehyde **146** and reaction with ethyl diazoacetate, catalyzed by tin (II) chloride,[106] provided β-ketoester **147** as a single isomer in 66% yield over two steps. One should mention that the other diasteroemer was not detected.



Screening for optimal epimerization conditions (step ii)

entry	*base*	*solvent*	*conditions*	*c*, [M]	*time*, [h]	*ratio*, **146**:**145**
1	DIPEA	CH_2Cl_2	reflux	0.2	30	1:1
2	DBU	CH_2Cl_2	reflux	0.07	48	1.3:1
3	DBU	$PhCH_3$	reflux	0.03	48	1.7:1
4	DBU	CH_2Cl_2	r.t.	0.005	30	1:4
5	LDA	THF	r.t.	0.03	20	1:1
6	LDA	THF	reflux	0.03	20	decomp.
7	***DBU***	***$PhCH_3$***	***reflux***	***0.58***	***30***	***2:1***

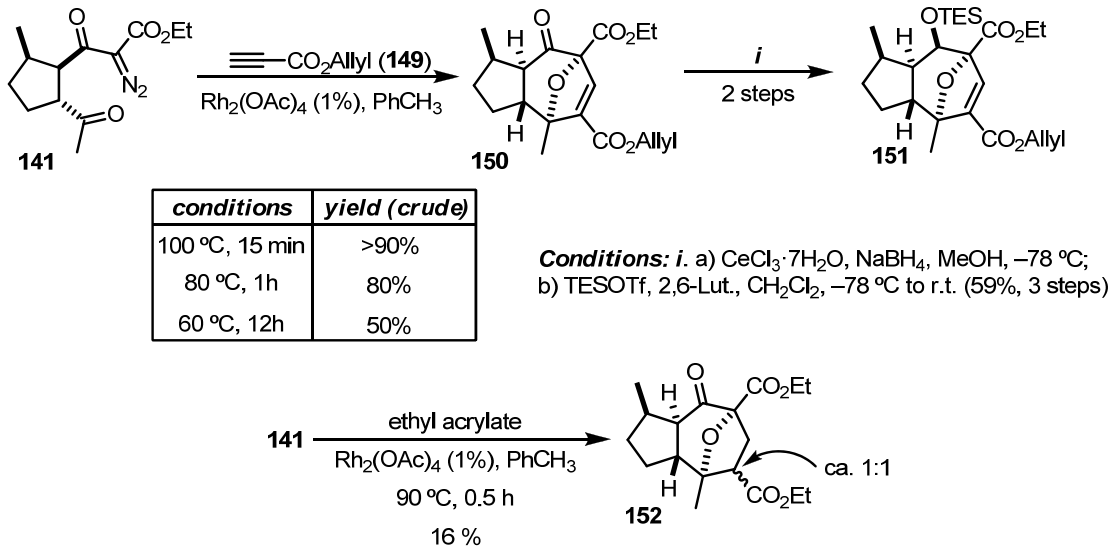


Conditions: i. a) $LiAlH_4$, Et_2O; b) $SO_3{\cdot}Py$, DMSO, CH_2Cl_2 (87%, 2 steps). ***ii***. DBU cat., PhMe, reflux, (90%, 2:1 *dr*). ***iii***. a) O_3, CH_2Cl_2, PPh_3, –78 ºC; b) $SnCl_2$, N_2CHCO_2Et (66%, 2 steps). ***iv***. *p*MeCONHPhSO$_2$N$_3$ (**148**), Et_3N, MeCN, 0 ºC to r.t. (71%).

Scheme 39. Synthesis of diazoketone **141**.

Finally, a diazotransfer reaction with sulfonyl azide[107] **148** furnished diazoketone **141** in 71% yield. This thirteen step sequence allowed us to prepare gram quantities of β-ketoester **141** starting from (*R*)-(–)-carvone.

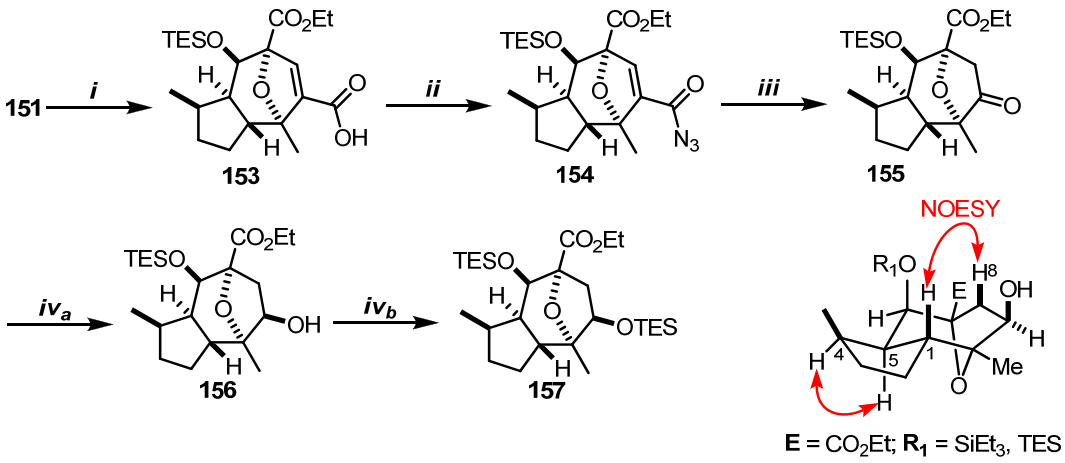
Bearing in hand diazoketone **141**, we now were ready to test the proposed (see retrosynthesis) intramolecular carbonyl ylide formation promoted by Rh(II) and its subsequent cycloadition. Here we decided to use allylpropiolate (**149**) as a dipolarophile due to ease of further functionalization (**Scheme 40**). After careful experimentation, we found that heating of a mixture containing allylester **149**, 1 mol % of $Rh_2(OAc)_2$, and diazo comnpound **141** in toluene (100 °C) for 15 min led to the formation of cycloaddition product **150** as a single isomer. Lower temperatures and longer times gave inferior results (see **Scheme 40**).



Scheme 40. $Rh_2(OAc)_4$-catalyzed carbonyl ylide formation and subsequent 1,3-dipolar cycloaddition with allyl propiolate (**149**).

When ethyl acrylate was used as a dipolarophile a mixture of diastereomers **152** was isolated in 16% yield. In the case of methyl vinyl ketone no desired product was detected. The cycloadduct **150** turned out to be sensitive to epimerization, for example, upon silica gel chromatography, leading exclusively to the corresponding *cis*-isomer. Therefore, crude ketodiester **150** was selectively reduced with $NaBH_4$ and the resulting alcohol converted to TES-ether **151** in 59% over three steps (starting from **141**). At this stage we were not able to unambiguously determine the stereochemistry of the newly formed centers (orientation of oxygen bridge). This was clarified at a later stage (vide infra).

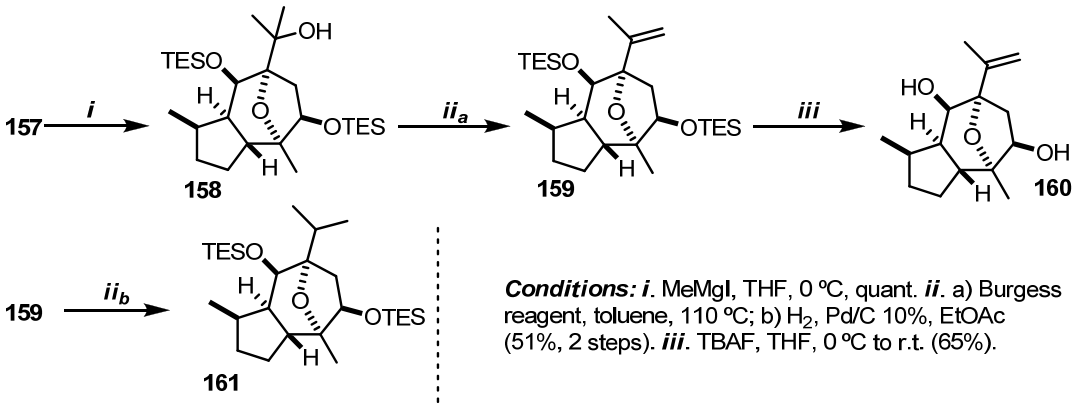
Further functionalization of the seven-membered ring called for degradation of the acrylate to a keto function. This was achieved via a classical Curtius rearrangement/hydrolysis sequence (**Scheme 41**).[108] It was found that the allyl ester could be easily cleaved using 10 mol% of Wilkinson's catalyst in an ethanol/water mixture (10:1) at 100 °C in 84% yield.[109] In contrast, palladium-based methods failed to provide carboxylic acid **153**. Now, acid **153** was converted to azide **154** in the presence of trichloroacetonitrile and PPh_3.[110] Upon heating, azide **154** rearranged to the vinyl isocyanate which under acidic conditions was selectively hydrolyzed to ketone **155**. It should be noted that under these conditions (HCl (5%), THF, rt) no deprotection of the TES group was observed. Subsequent reduction with $NaBH_4$ provided alcohol **156** as a single isomer. At this stage, key NOESY cross peaks between 1-H/8-H, 4-H/5-H, and 5-H/6-H (guanolide numbering) suggested a structure of **156** where the oxygen bridge is on the opposite site with respect to the C4 methyl group (**Scheme 41**).



Conditions: i. $RhCl(PPh_3)_3$ (10 mol%), $EtOH/H_2O$ (10:1), 100 ºC (84%). ***ii***. NaN_3, PPh_3, Cl_3CCN, r.t. (90%). ***iii***. $PhCH_3$, 100 ºC then 5% HCl, THF, r.t. (83%). ***iv***. a) $NaBH_4$, MeOH/THF (1:10), –10 ºC to r.t.; b) TESOTf, 2,6-Lut., CH_2Cl_2, –78 ºC to r.t. (85%, 2 steps).

Scheme 41. Transformation of cycloadduct **151** into TES-ether **157**.

Nevertheless, we continued with further functional group manipulation that would allow for either a chemical correlation with a known compound or an X-ray structure. Thus, alcohol **156** was converted into bis silyl-ether **157** which called for ester conversion of the ester function to isopropyl group (**Scheme 42**). Accordingly, addition of freshly prepared MeMgI (6.0 equiv) to ester **157** at 0 °C gave tertiary alcohol **158** in quantitative yield. As next, we thought to apply the same radical deoxygenation conditions applied earlier. However, neither xanthogenate nor trifluoro acetate, did undergo deoxygenation. On the other hand, Burgess reagent[111] ($MeO_2CN^-SO_2N^+Et_3$) did the job providing alkene **159** which led to silyl ether **161** via catalytic hydrogenation (51% over 2 steps). TES deprotection on alkene **159** was achieved with TBAF to give alkenediol **160** in 65% yield.



Conditions: i. MeMgI, THF, 0 ºC, quant. ***ii***. a) Burgess reagent, toluene, 110 ºC; b) H_2, Pd/C 10%, EtOAc (51%, 2 steps). ***iii***. TBAF, THF, 0 ºC to r.t. (65%).

Scheme 42. Synthesis of diol **160**.

Crystallization of **160** from a hexane/diethyl ether mixture provided crystals suitable for X-ray analysis (**Figure 7**) indicating the configuration of the stereocenters and conformation of the structure. The X-ray structure structure additionally proved the facial selectivity in the cycloaddition step which corroborated the NOESY data of ester **156**.

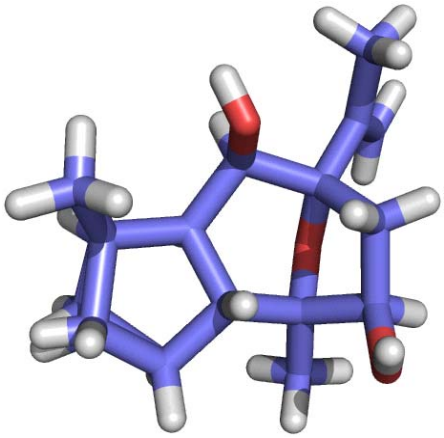
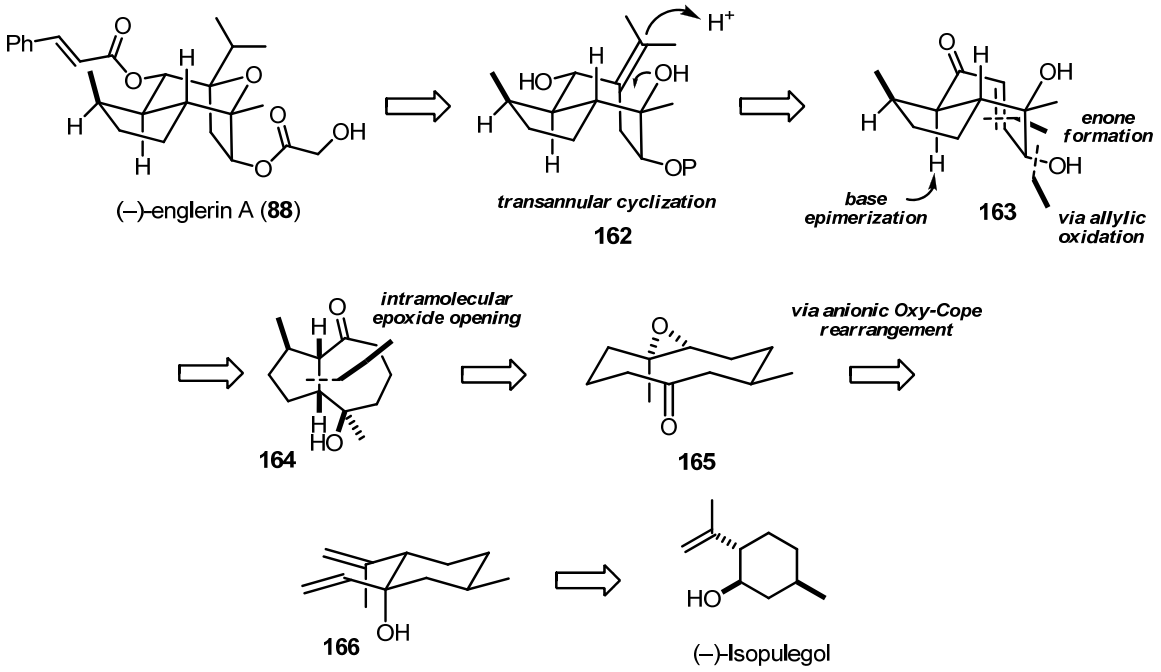


Figure 7. X-ray structure of diol **160**.

With these results in hand we took an effort to design a second generation approach for (–)-englerin A.

2nd Generation Retrosynthetic Consideration

The 2nd generation retrosynthetic analysis was based on a transannular cyclization of guaianolide **162**, which could be induced by acid or by activating the double via a bromonium or mercurinium ion (**Scheme 43**).

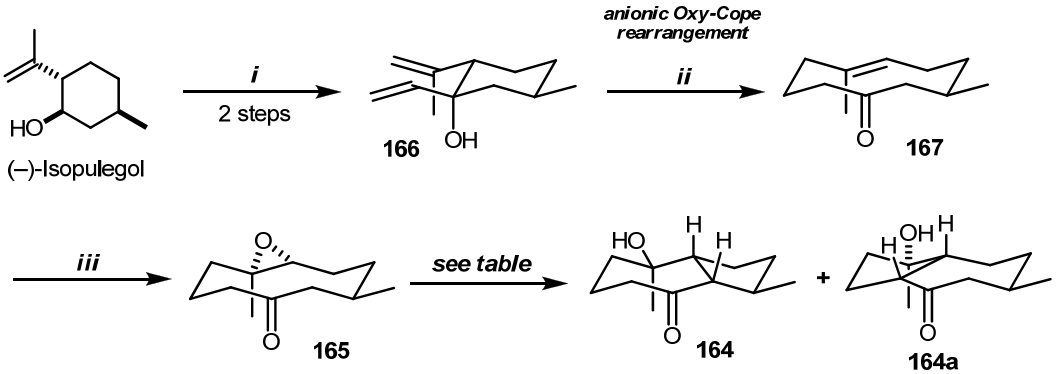


Scheme 43. 2nd generation retrosynthetic analysis of (–)-englerin A (**88**).

Thus, alkene **162** could be generated from enone **163** via reduction of the double bond and isopropenyl installation via aldol condensation with acetone. For diol **163** we considered allylic oxidation of the corresponding enone, which may a rise from keto epoxide **165** by intramoleculer epoxide opening.[112] Thus, an Oxy-Cope rearrangement[113] would be possible for the synthesis of the decalin carbon framework. As it can be seen in **Scheme 43**, (–)-isopulegol was found to be a perfect precursor for **88** as it is a readily available starting material providing stereochemical information for C4 in (–)-englerin A.

Results and Discussion

The synthesis started with known literature procedures to prepare (–)-isopulegone.[114] Thus, smooth PCC oxidation of (–)-isopulegol, followed by vinyl magnesium bromide addition gave multigram quantities of vinyl alcohol **166** in 92% yield (**Scheme 44**).



Conditions: i. a) PCC, CH_2Cl_2; b) vinylMgBr, THF, –50°C (92%, 2 steps). ***ii***. KH, THF, reflux, 12 h (71%). ***iii***. *m*CPBA, CH_2Cl_2 (90%).

Scheme 44. Synthesis of hydroxy ketone **164** via anionic Oxy-Cope rearrangement and transannular epoxide opening.

Here is worth to mention that in the case of freshly, self made vinyl magnesium bromide the reaction proceeds very clean and the desired product could be distilled at low pressure. However, when commercially available vinyl magnesium bromide was used many side products were observed. Next, an anionic Oxy-Cope rearrangement was studied. Following classical conditions[115] (KH, 18-crown-6 ether, THF) ketone **167** could be isolated in 71% yield. Although, this procedure allows for a rapid formation of the ten-membered ring, a crown ether issue should be considered as for 1 g of starting material we needed 3.3 g (3.0 equiv.) of 18-crown-6 ether! After careful experimentation we found that running the reaction without the crown ether mentioned above, just extension of reaction time (2 h *vs*. 12 h) led to the desirred product as well. No loss in the yield could be detected. Simple *m*CPBA mediated epoxidation secured epoxide **165**, who's structure was confirmed by X-ray analysis (**Figure 8**).

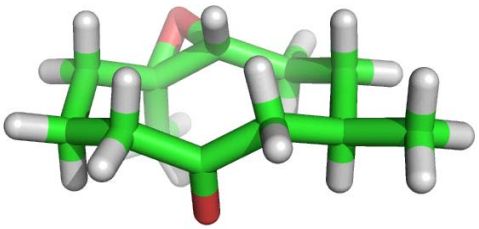
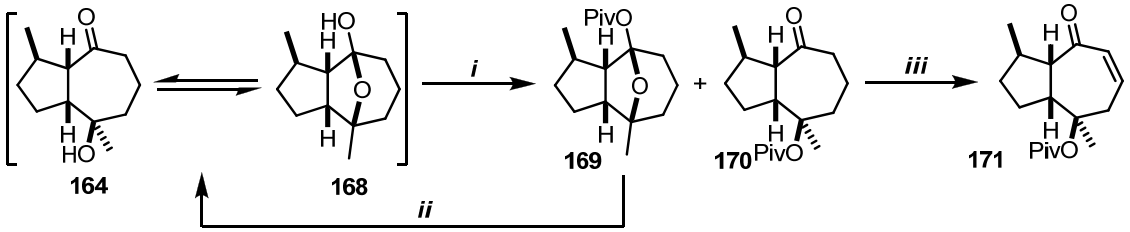


Figure 8. X-ray structure of epoxide **165**.

A regioselective enolate formation on ketoepoxide **165** in order to prepare the 5,7-fused ring system was found to be quite challenging. First attempts to override this problem gave interesting results. When freshly prepared LDA solution was added dropwise to a solution of ketone **165** at −78 °C a mixture of regioisomers **164** and **164a** was obtained. Temperature change allowed us to increase the amount of the desired isomer. Furthermore, when NaH was added to a solution of **165** and the resulting suspension was immersed to a preheated (60 °C) oil bath for 5 min just the desired isomer **164** was formed in 90% yield. It can be assumed that the small hydride selectively deprotonates 5-H which is perfectly orthogonal to the keto group.



Conditions*: *i. $Sc(OTf)_3$ (1 mol%), Piv_2O, CH_3CN, 0°C (60%); ***ii.*** K_2CO_3, MeOH, reflux (95%). ***iii.*** a) LDA, TBSCl, HMPA, –78°C; b) $Pd(OAc)_2$ (15 mol%), DMSO, 80 °C (80%, over 2 steps).

Scheme 45. Traping ketone **164** as a pivalic ester **170**.

As can be seen in **Scheme 45**, the hydroxyl ketone **164** exists in equilibrium with cyclic hemiacetal **168**. We found that for further functionalization of the seven-membered ring it was necessary to trap the compound as a ketone. We assumed that protection of hydroxy function by deprotonating the OH function with base would shift the equilibrium towards acetal **168**. Thus, esterification in the presence of catalytic amount of acid (or Lewis acid) would be optimal. A selective C4-OH protection as a pivalic ester[116] allowed us to separate ketone **170** in 60% yield from oxygen bridged pivalic ester **169**. Furthermore, acetal **169** could be easily recycled via K_2CO_3 deprotection in methanol. An interesting result was

obtained, when ketone **170** was treated with phenyltrimethylammonium tribromide ($C_6H_5N^+(CH_3)_3Br_3^-$)[117] in THF. As an X-ray structure shows (**Figure 9**) a bromide atom was introduced at the more substituted position of the keto function. This has additionally proven formation of the 5,7-fused ring system in the transannular epoxide opening.

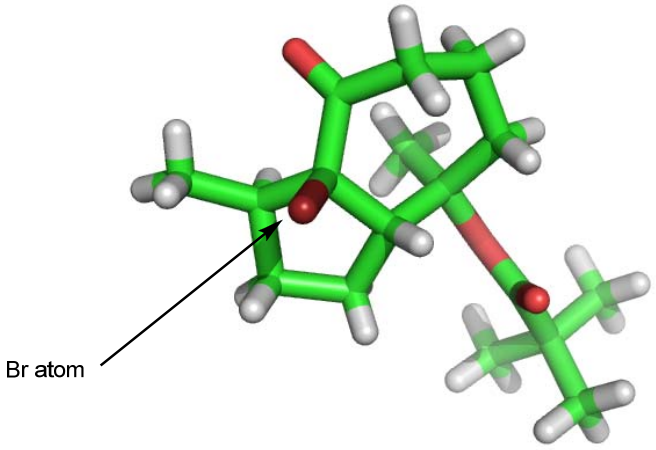
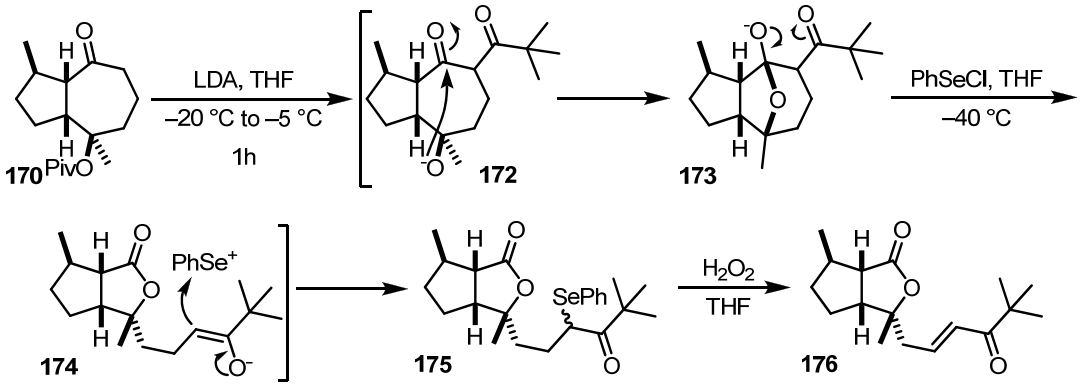


Figure 9. X-ray structure of bromo-**170**.

With ketone **170** in hand, we tested various conditions in order to prepare enone **171**. After careful experimentation we found that the kinetic enolate of **170** could be easily trapped as silyl ether at −40 °C and in subsequent $Pd(OAc)_2$ mediated Saegusa-Ito oxidation converted to enone **171**. Other methods, like phenylselenyl ether formation and subsequent elimination via selenoxide gave an unexpected product, enone **176** (**Scheme 46**).



Scheme 46. Mechanistic rationale for the formation of lactone **176**.

It was observed that upon treating ketone **170** with LDA in absolute THF at −20 °C and then warming the reaction mixture to −5 °C in an ice/salt bath, a pivaloyl migration (Claisen condensation) occurred, followed by *retro*-Claisen condensation. The enolate **174** was quenched with PhSeCl to give selenide **175**, which after oxidation with hydrogen peroxide resulted in enone **176**. The structure of this was proven by X-ray crystallography (**Figure 10**).

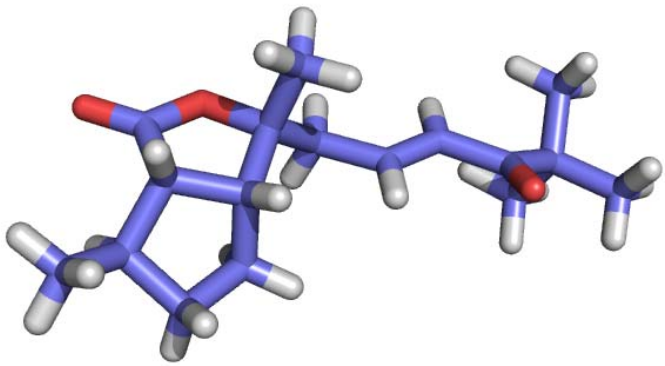
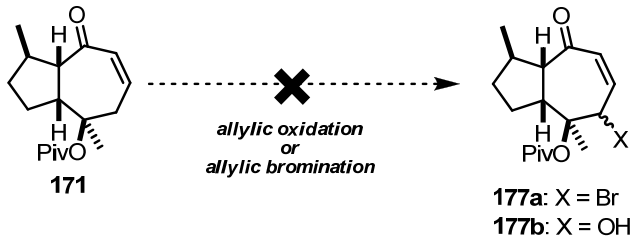


Figure 10. X-ray structure of rearrangement product **176**.

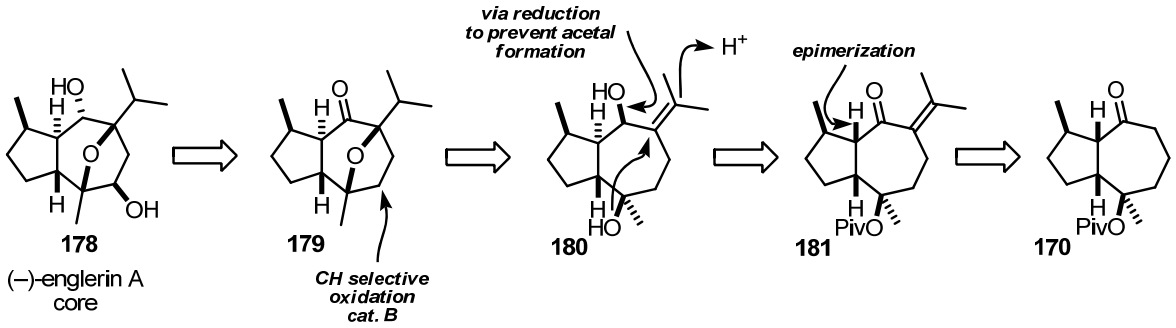
Further functionalization of the seven-membered ring was calling for allylic oxidation or allylic halogenation and subsequent S_N2 reaction with acetate (**Scheme 47**).



Scheme 47. Attempts on allylic substitution.

However, allylic oxidation (methods like SeO_2; SeO_2, TBHP; SeO_2, AcOH (glac.)) on enone **171** has failed to work. Neither of the applied methods gave desired diol **177b** and just starting material could be recovered. In the case of allylic bromination (NBS, AIBN, CCl_4) no desired allyl bromide could be isolated as well. Thus, concidering these results, a new functionalization strategy which was based on oxygen

bridge formation in the first steps and then OH function installation via CH selective oxidation was started (**Scheme 48**)*.



Scheme 48. Modified strategy for functionalization of the seven-membered ring.

According to the proposed functionalization strategy, disubstituted alkene **181** could arise from pivalic ester **170**. Further modification would involve deprotection of the pivalic ester and reductionof a ketone function to prevent acetal formation. Then, by activating the double bond a transannular cyclization should take place. For the hydroxyl installation we were optimistic about Ch. White catalyst (**Figure 11**), which is known to oxidize the 4th CH bond from a keto or ester function.[118,119]

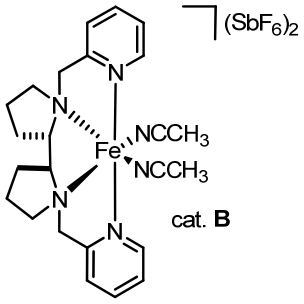
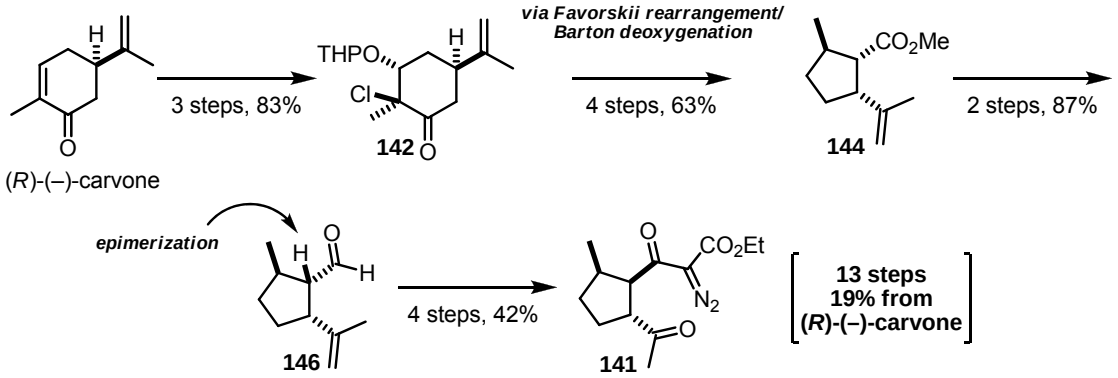


Figure 11. Structure of White catalyst **B**.

* Independent work of graduate student Dmitry B. Ushakov.

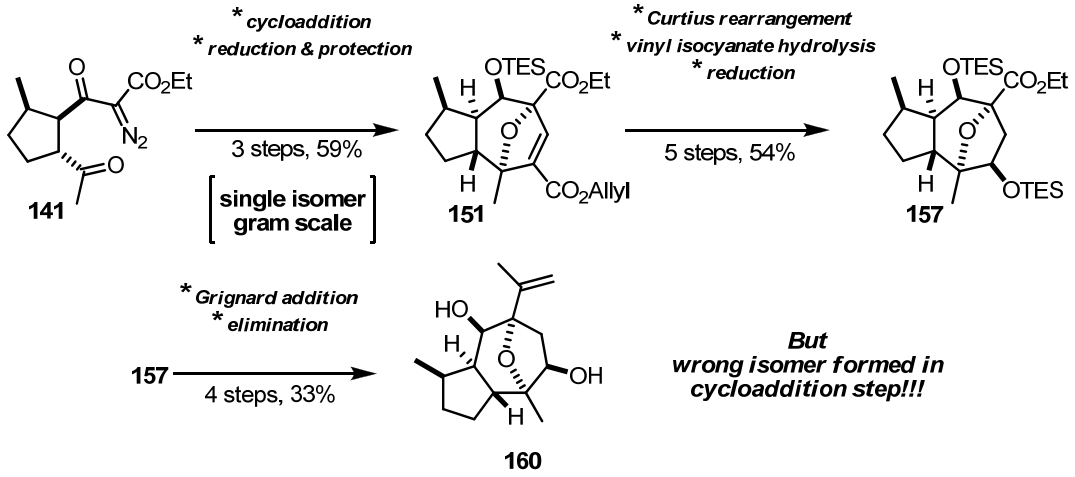
Conclusion

In summary, two different approaches towards the natural product (–)-englerin A have been studied. The first of them, was based on a 1,3-dipolar cycloaddition of a chiral carbonyl ylide (**Scheme 49**). Here (*R*)-(–)-carvone served as a perfect starting material delivering the stereochemical information at C4. Thus, in thirteen steps and 19% overall yield diazoketo ester **141** was obtained.



Scheme 49. Transforming (*R*)-(–)-carvone into diazoketo ester **141**.

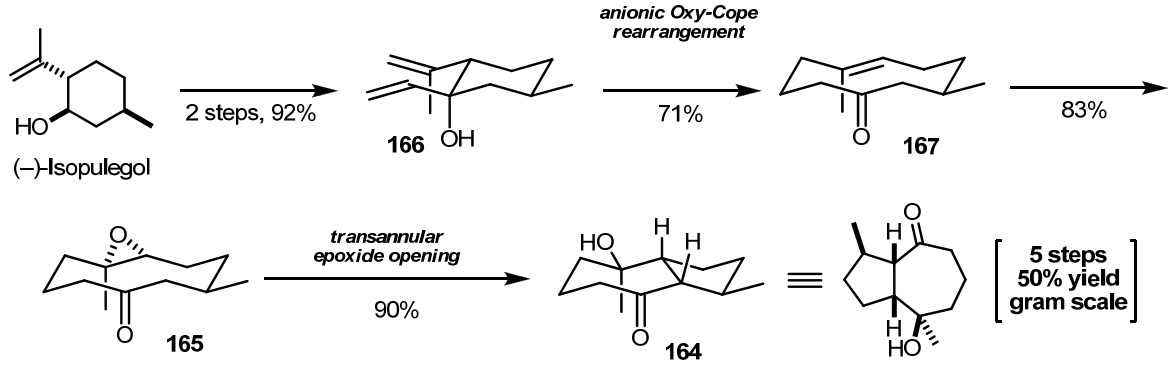
Further studies on the cycloaddition startegy revealed that the wrong isomer was formed in cycloaddition step. However, the studies on the functionalization of the seven membered ring was explored (**Scheme 50**).



Scheme 50. Rhodium (II) catalyzed 1,3-dipolar cycloaddition strategy to form an oxygen bridge in guaianolides.

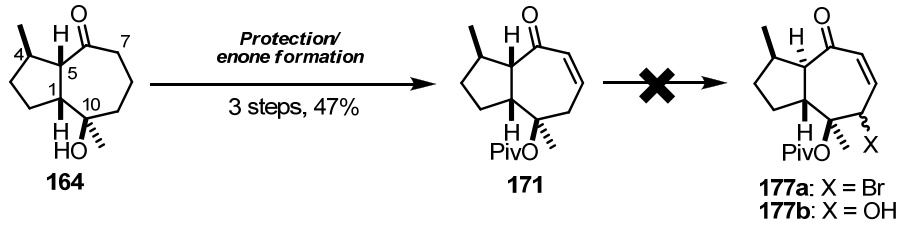
Starting from di-ester **151**, the TES ether **157** was synthesized in five steps featuring Curtius rearrangement, vinyl isocyanate hydrolysis and reduction of the keto function.

A second generation approach to (–)-englerin A was based on transannular epoxide opening in decalin structure **165** to form the 5,7-fused ring system. Thus, readily available (–)-isopulegol was transformed to **167** via anionic oxy-Cope rearrangement. Further two steps, which involved selective epoxidation and transannular epoxide opening, resulted in hydroxyketone **164** in 75% yield over two steps (**Scheme 51**).



Scheme 51. Synthesis of hydroxyketone **164**.

Next, functionalization of the seven membered ring was studied (**Scheme 52**). Firstly, the free hydroxyl function was protected as pivalic ester and the Saegusa-Ito oxidation protocol delivered enone **171**. Hovewer, further attempts to substitute the allylic position failed.



Scheme 52. Synthesis of the deoxy-(–)-englerin A core and attempts on its allylic substitution.

Experimental Section

General Remarks

Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine, pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

NMR-spectroscopy

All the spectra were measured on a Bruker Advance 400 spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$ or [D_6]DMSO; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH = 7.25 ppm, δC = 77.0 ppm), [D_6]DMSO (δH = 2.49 ppm, δC = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, app. d = looks like doublet, *J* = coupling constant (Hz), integration, peak assignment.

Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray

ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: $[\alpha]^{temperature}_{D}$ (concentration, solvent). The unit of c is g/100 mL. Anhydrous CH_2Cl_2 or MeOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

Chromatographic Methods

Flash column chromatography was performed using flash silica gel (40-63 µm, 230-400 mesh ASTM) from Macherey-Nagel.

Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H_2. Chiral gas chromatographic analyses were carried out on a 13.5 m × 0.25 mm column filled with deactivated fused silica with 30% 6-TBDMS-2,3-diacetyl-β-cyclodextrin in PS 086 (df = 0.13 µm) and carrier gas H_2 at 50 kPa and 30 °C.

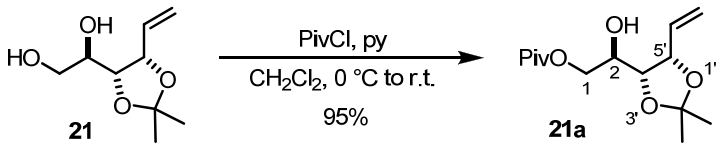
For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.

Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates (Merck) or Polygram Sil G/UV_{254} (Macherey Nagel). The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}•4H_2O$] and 0.4 g $Ce(SO_4)_2•4H_2O$ were dissolved in 400 mL of 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

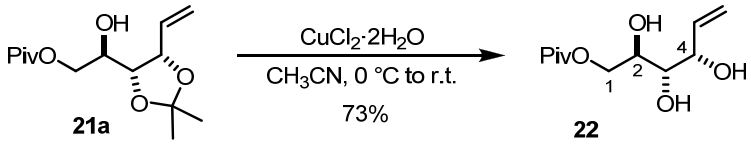
Experimental procedures

All the experimental procedures are arranged in the ascending order as they appeared on the synthetic schemes.

I. Total Synthesis of the Proposed Structure of the Macrolide Queenslandon



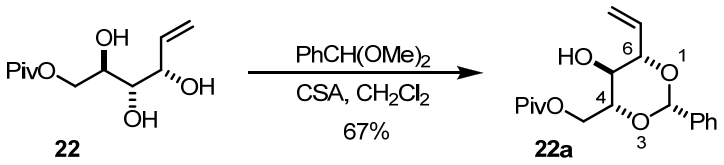
(*R*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-hydroxyethyl pivalate (21a). To an ice-cooled solution of diol[1] **21** (16.65 g, 88.6 mmol) and DMAP (1.07 g, 8.8 mmol) in a CH_2Cl_2/pyridine mixture (120 mL, 5:1) was added PivCl (11.0 mL, 106.3 mmol) in a dropwise fashion. After the addition, the reaction mixture was allowed to warm to room temperature. Stirring was continued for 2 h before the reaction mixture was washed with 1N HCl (5 × 100 mL) and saturated NaCl (100 mL) solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude pivaloate **21a** (22.8 g, 95%) was pure enough to be introduced to the next step without additional purification. R_f = 0.25 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +9.7 (*c* 2.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.21 (s, 9H, $C(CH_3)_3$), 1.34 (s, 3H, 2'-CH_3), 1.46 (s, 3H, 2'-CH_3), 3.84 (ddd, *J* = 8.8, 6.4, 2.4 Hz, 1H, 2-H), 4.06 (dd, *J* = 8.9, 6.4 Hz, 1H, 1-H), 4.15 (dd, *J* = 11.7, 6.4 Hz, 1H, 1-H), 4.36 (dd, *J* = 11.7, 2.3 Hz, 1H, 4'-H), 4.69 (app t, *J* = 6.6, 6.6 Hz, 1H, 5'-H), 5.30 (app d, *J* = 10.4 Hz, 1H, CH_2 vinyl), 5.44 (app d, *J* = 10.4 Hz, 1H, CH_2 vinyl), 5.98 (ddd, *J* = 17.1, 10.4, 6.9 Hz, 1H, CH vinyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 25.3 ($C(CH_3)_3$), 27.2 (2'-CH_3), 27.7 (2'-CH_3), 38.9 ($C(CH_3)_3$), 66.6 (C-1), 68.8 (C-4'), 77.5 (C-2), 78.5 (C-5'), 109.0 (C-2'), 118.3 (CH_2 vinyl), 133.7 (CH vinyl), 179.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{24}O_5Na$ 295.15159, found 295.15162.



(2*R*,3*S*,4*S*)-2,3,4-Trihydroxyhex-5-enyl pivalate (22). To an ice-cooled solution of acetonide **21a** (10.56 g, 38.8 mmol) in acetonitrile (100 mL) was added $CuCl_2 \cdot 2H_2O$ (46.0 g, 271.6 mmol) portionwise within 1 h and then the reaction mixture was allowed to warm to room temperature. After being stirred for 12 h at room temperature, inorganic solids were filtered off, and the filter cake washed with acetonitrile (100 mL). The combined filtrates were washed with saturated NH_4Cl (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give triol **22** (6.59 g, 73%) as a white amorphous solid. R_f = 0.26 (petroleum ether/ EtOAc, 1:1); $[\alpha]^{20}_D$ = −6.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$):

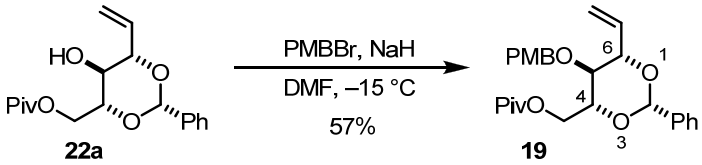
[1] Moon, H. R.; Choi,W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189–1193.

δ[ppm] = 1.22 (s, 9H, C(CH_3)$_3$), 2.54 (br s, 3H, 3 × OH), 3.55 (dd, *J* = 7.9, 5.3 Hz, 1H, 3-H), 3.84 (ddd, *J* = 7.6, 4.3, 4.0 Hz, 1H, 2-H), 4.32–4.35 (m, 3H, 1-H, and 4-H), 5.32 (app d, *J* = 10.6 Hz, 1H, 6-H), 5.41 (app d, *J* = 17.2 Hz, 1H, 6-H), 5.99 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H, 5-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 27.2 (C(CH_3)$_3$), 39.0 (*C*(CH_3)$_3$), 66.3 (C-1), 72.4 (C-2), 72.8 (C-3), 74.7 (C-4), 118.3 (C-6), 136.3 (C-5), 179.8 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for $C_{11}H_{20}O_5Na$ 255.12029, found 255.12023.



22 **22a**

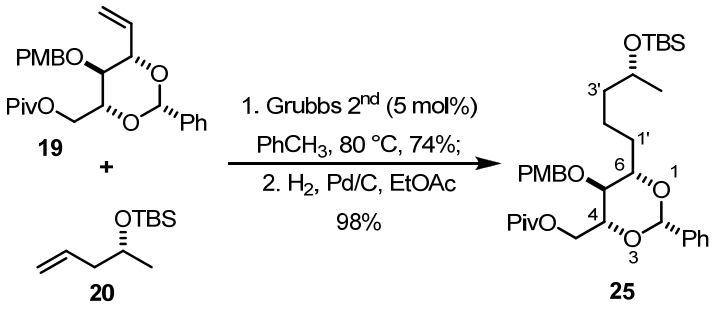
((4*R*,5*S*,6*S*)-5-Hydroxy-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (22a). To a solution of triol **22** (6.59 g, 28.0 mmol) in abs. CH_2Cl_2 (80 mL) was added CSA (1.29 g, 5.6 mmol) followed by the dropwise addition of benzaldehydedimethylacetal (5.1 mL, 33.6 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was washed with saturated $NaHCO_3$ (100 mL) and NaCl (100 mL) solutions, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give hydroxydioxane **22a** (8.3 g, 91%) as a colorless oil. R_f = 0.17 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −31.3 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.23 (s, 9H, C(CH_3)$_3$), 3.30 (app t, *J* = 9.2, 9.2 Hz, 1H, 5-H), 3.84 (ddd, *J* = 9.3, 4.1, 2.8 Hz, 1H, 4-H), 4.07–4.11 (m, 1H, 6-H), 4.35 (dd, *J* = 12.1, 2.5 Hz, 1H, CH_2), 4.56 (dd, *J* = 12.3, 4.6 Hz, 1H, CH_2), 5.32 (app d, *J* = 10.6, 1H, CH_2 vinyl), 5.48 (app d, *J* = 17.2 Hz, 1H, CH_2 vinyl), 5.63 (s, 1H, CHPh), 6.00 (ddd, *J* = 17.3, 10.4, 6.4, 1H, CH vinyl), 7.34–7.37 (m, 3H, *m*CH, *p*CH ar Ph), 7.48–7.50 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 27.2 (C(CH_3)$_3$), 39.0 (*C*(CH_3)$_3$), 63.5 (PivOCH_2), 66.2 (C-5), 79.4 (C-4), 81.8 (C-6), 100.6 (C-2), 118.9 (CH vinyl), 126.2 (*p*CH ar Ph), 128.2 (*o*CH ar Ph), 129.0 (*m*CH ar Ph), 134.5 (2-CPh), 137.4 (CH_2 vinyl), 179.5 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for $C_{18}H_{24}O_5Na$ 343.15159, found 343.15164.



22a **19**

((2*S*,4*R*,5*S*,6*S*)-5-(4-Methoxybenzyloxy)-2-phenyl-6-vinyl-1,3-dioxan-4-yl)methyl pivalate (19). To a cooled (−5 °C) suspension of NaH (0.54 g, 13.4 mmol, 60% in mineral oil) in anhydrous DMF (40 mL) was added dropwise a solution of alcohol **22a** (1.23 g, 3.8 mmol) in DMF (5 mL) at the same temperature. After complete addition, the reaction mixture was stirred for 1 h at −5 °C before a solution

of freshly prepared PMBBr[2] (1.28 g, 6.4 mmol) in DMF (5 mL) was added. After being stirred for additional 2 h at −5 °C, the reaction was quenched with saturated NH_4Cl (10 mL) and the product was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give PMB ether **19** (0.97 g, 57%) as a colorless oil. R_f = 0.26 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +5.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.26 (s, 9H, $C(CH_3)_3$), 3.40 (app t, *J* = 9.4, 9.4 Hz, 1H, 5-H), 3.83 (s, 3H, OCH_3), 3.92 (ddd, *J* = 9.4, 4.6, 2.2 Hz, 1H, 4-H), 4.21 (dd, *J* = 9.1, 6.6 Hz, 1H, 6-H), 4.34 (dd, *J* = 12.0, 4.7 Hz, 1H, CH_2PMP), 4.41–4.49 (m, 2H, CH_2PMP, PivOCH_2), 4.63 (app d, *J* = 10.1 Hz, 1H, PivOCH_2), 5.39 (app d, *J* = 10.4 Hz, 1H, CH_2 vinyl), 5.58 (d, *J* = 10.4 Hz, 1H, CH_2 vinyl), 5.63 (s, 1H, 2-H), 6.09 (ddd, *J* = 17.3, 10.7, 6.6, 1H, CH vinyl), 6.90–6.92 (m, 2H, *m*CH ar PMB), 7.25–7.29 (m, 2H, *o*CH ar PMB), 7.35–7.39 (m, 3H, *m*CH, *p*CH ar Ph), 7.50–7.52 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 27.2 ($C(CH_3)_3$), 38.9 ($C(CH_3)_3$), 55.3 (OCH_3), 62.9 (CH_2PMP), 73.8 (C-5), 74.4 (PivOCH_2), 78.4 (C-4), 81.6 (C-6), 100.3 (C-2), 114.0 (*o*CH ar PMB), 118.8 (CH_2 vinyl), 126.2 (*o*CH ar Ph), 128.2 (*m*CH ar PH), 128.9 (*p*CH ar Ph), 129.4 ($CHCH_2$ ar PMB), 129.8 (*m*CH ar PMB), 135.1 (CH vinyl), 137.5 (*C*CH ar Ph), 159.6 ($COCH_3$ ar PMB), 178.2 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{32}O_6Na$ 463.20911, found 463.20878.

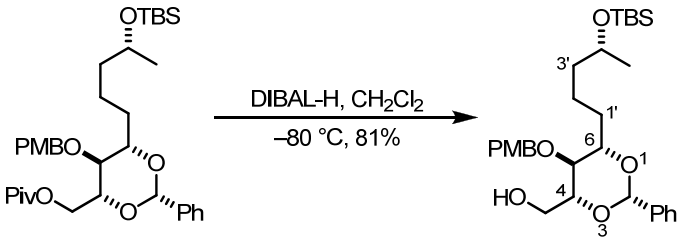


((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl pivalate (25). *Cross-metathesis*: Alkene **19** (1.76 g, 4.0 mmol) was dissolved in degassed toluene (17.6 mL) and then alkene[3] **20** (0.8 g, 4.0 mmol) was added. The reaction mixture was slightly warmed (to around 40–50 °C) and then Grubbs second generation catalyst (170 mg, 5 mol %) was added. The temperature was brought to 80 °C and maintained for 2 h. After that, air was bubbled through the reaction (for approx. 5 min) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give metathesis product (1.80 g, 74%) as a colorless oil. R_f = 0.34 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −9.8 (*c* 0.4,

[2] Khartulyari, A. S.; Kapur, M.; Maier, M. *Org. Lett.* **2006**, *8*, 5833.

[3] (a) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990; (b) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. A Eur. J.* **2006**, *12*, 1397.

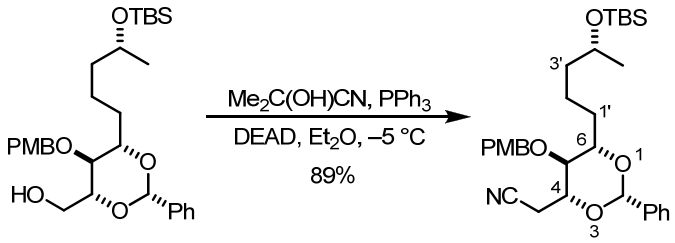
CH_2Cl_2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{35}H_{52}O_7SiNa$ 635.35310, found 635.34213. *Hydrogenation*: Metathesis product, obtained above (1.64 g, 2.67 mmol) was dissolved in abs. EtOAc (5 mL), Pd/C (10% wt) was added and a balloon, filled with hydrogen, was attached through a rubber septum. The reaction mixture was stirred for 5 h at room temperature and then the palladium catalyst was filtered off through a pad of Celite®, which was washed with EtOAc (2 × 10 mL). The filtrate was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/ EtOAc, 10:1) to give protected polyol **25** (1.60 g, 98%) as colorless oil. R_f = 0.34 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −0.1 (*c* 4.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.13 (d, *J* = 6.1 Hz, 3H, 4'-CH_3), 1.25 (s, 9H, $C(CH_3)_3$), 1.39–1.62 (m, 4H, 2 × CH_2), 1.85–1.90 (m, 2H, CH_2), 3.32 (app t, *J* = 9.1, 9.1 Hz, 1H, 5-H), 3.66 (app td, *J* = 8.7, 8.7, 2.4 Hz, 1H, 6-H), 3.77–3.80 (m, 4H, OCH_3, 4'-H), 3.86 (ddd, *J* = 9.4, 4.6, 2.0 Hz, 1H, 4-H), 4.30 (dd, *J* = 12.1, 4.7 Hz, 1H, $PivOCH_2$), 4.50–4.57 (m, 3H, $PivOCH_2$, CH_2PMP), 5.54 (s, 1H, 2-H), 6.88–6.91 (m, 2H, *m*CH ar PMB), 7.25–7.27 (m, 2H, *o*CH ar PMB), 7.33–7.36 (m, 3H, *m*CH, *p*CH ar Ph), 7.46–7.48 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.4 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 21.3 (CH_2), 23.8 (C-5'), 25.9 ($SiC(CH_3)_3$), 27.2 ($C(CH_3)_3$), 32.1 (CH_2), 38.9 ($C(CH_3)_3$), 39.6 (CH_2), 55.3 (OCH_3), 63.0 (CH_2PMP), 68.5 (C-4'), 74.1 (C-5), 74.7 ($PivOCH_2$), 78.5 (C-4), 80.4 (C-6), 100.2 (C-2), 114.0 (*o*CH ar PMB), 126.0 (*o*CH ar Ph), 128.1 (*m*CH ar Ph), 128.6 (*p*CH ar Ph), 129.5 ($CHCH_2$ ar PMB), 129.7 (*m*CH ar PMB), 137.8 (*C*CH ar Ph), 159.6 ($COCH_3$), 178.2 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{35}H_{54}O_7SiNa$ 637.35310, found 637.35287.



25 **25a**

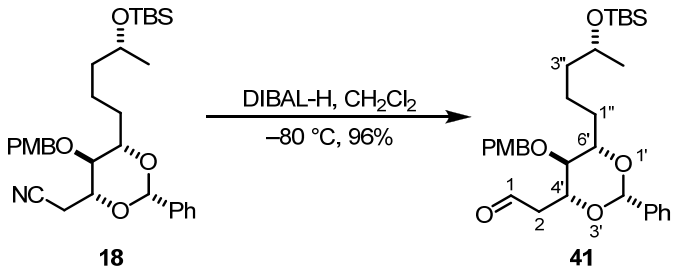
((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)methanol (25a). A solution of pivaloate **25** (1.18 g, 1.92 mmol) in abs. CH_2Cl_2 (15 mL) was cooled to −80 °C and then DIBAL-H (11.52 mL,11.5 mmol, 1M in hexane) was added over 1 h at the same temperature. The reaction mixture was stirred for an additional 1 h before saturated NH_4Cl (5 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **25a** (0.82 g, 81%) as a colorless oil. R_f = 0.17 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −22.4 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H,

$Si(CH_3)_3$), 1.12 (d, *J* = 6.1 Hz, 3H, 4'-CH_3), 1.36–1.60 (m, 4H, 2 × CH_2), 1.82–1.88 (m, 2H, CH_2), 1.95 (br s, 1H, OH), 3.38 (app t, *J* = 9.2 Hz, 1H, 5-H), 3.62–3.66 (m, 1H, 6-H), 3.70–3.73 (ddd, *J* = 9.2, 4.1, 2.5 Hz, 1H, 4-H), 3.77–3.80 (m, 4H, OCH_3, $HOCH_2$), 3.93–3.96 (m, 1H, $HOCH_2$), 4.58 (s, CH_2PMP), 5.56 (s, 1H, 2-H), 6.88–6.90 (m, 2H, *m*CH ar PMB), 7.25–7.28 (m, 2H, *o*CH ar PMB), 7.34–7.38 (m, 3H, *m*CH, *p*CH ar Ph), 7.47–7.49 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.4 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 21.3 (CH_2), 23.8 (C-5'), 25.9 ($SiC(CH_3)_3$), 32.0, 39.7 (CH_2), 55.3 (OCH_3), 62.2 (CH_2PMP), 68.5 (C-4'), 73.3 (C-5), 74.7 ($PivOCH_2$), 80.4 (C-4), 80.7 (C-6), 100.3 (C-2), 114.0 (*o*CH ar PMB), 126.1 (*o*CH ar Ph), 128.2 (*m*CH ar Ph), 128.8 (*p*CH ar Ph), 129.8 (*m*CH ar PMB), 137.8 (*C*CH ar Ph), 159.5 ($COCH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{46}O_6SiNa$ 553.29559, found 553.29557.



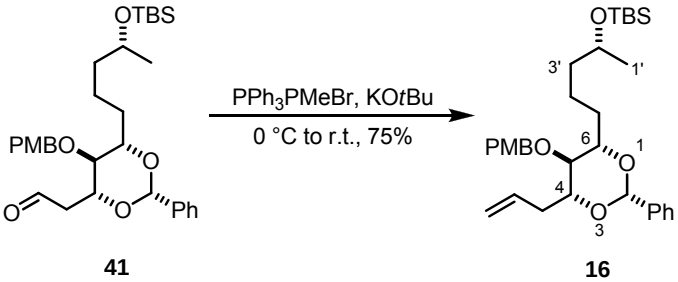
25a **18**

2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetonitrile (18). To a stirred solution of alcohol **25a** (0.54 g, 1.0 mmol) in abs. diethyl ether (3.4 mL) was added PPh_3 (0.59 g, 2.2 mmol) at −5 °C. The mixture was stirred at the same temperature for 15 min before DEAD (0.98 mL, 2.2 mmol) was added dropwise. The reaction mixture became like a white paste. After 20 min acetone cyanohydrine (0.21 mL, 2.2 mmol) was added dropwise and the solids dissolved. The mixture was stirred at −5 °C for 6 h and for additional 12 h at room temperature. After that, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give nitrile **18** (0.487 g, 89%) as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −1.0 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (app d, *J* = 6.1 Hz, 3H, 4'-CH_3), 1.37–1.65 (m, 4H, 2 × CH_2), 1.86–1.88 (m, 2H, CH_2), 2.58 (dd, *J* = 17.0, 6.4, 1H, $NCCH_2$), 2.72 (dd, *J* = 17.1, 6.4 Hz, 1H, $NCCH_2$) 3.23 (app t, *J* = 9.2 Hz, 5-H), 3.63–3.68 (m, 1H, 6-H), 3.76–3.85 (m, 5H, OCH_3, 4-H, 4'-H), 4.52 (d, *J* = 10.9 Hz, 1H, CH_2PMP), 4.68 (d, *J* = 10.9 Hz, 1H, CH_2PMP), 5.54 (s, 1H, 2-H), 6.89–6.92 (m, 2H, *m*CH ar PMB), 7.25–7.27 (m, 2H, *o*CH ar PMB), 7.34–7.35 (m, 3H, *m*CH, *p*CH ar Ph), 7.47–7.49 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.4 ($Si(CH_3)_2$),18.1 ($SiC(CH_3)_3$), 21.3 ($NCCH_2$), 21.4 (CH_2), 23.8 (C-5'), 25.9 ($SiC(CH_3)_3$), 32.1, 39.6 (CH_2), 55.3 (OCH_3), 68.4 (C-4'), 75.0 (CH_2PMP), 75.6 (C-6), 76.8 (C-4), 80.6 (C-5), 100.4 (C-2), 114.0 (*o*CH ar PMB), 116.9 (NC), 126.1 (*o*CH ar Ph), 128.2 (*m*CH ar Ph), 128.9 (*p*CH ar Ph), 129.2 (*m*CH ar PMB), 129.9 (*m*CH ar PMB), 137.1 (*C*CH ar Ph), 159.8 ($COCH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{45}NO_5SiNa$ 562.29592, found 562.29624.



18 **41**

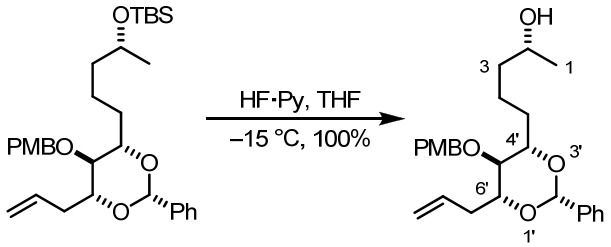
2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (41). A solution of nitrile **18** (0.49 g, 0.90 mmol) in abs. CH_2Cl_2 (10 mL) was cooled to −80 °C followed by slow addition of DIBAL-H (5.4 mL, 1M in hexane, 5.4 mmol). After being stirred for 1 h at −80 °C, saturated NH_4Cl solution was added and the mixture allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give aldehyde **41** (469 mg, 96%) as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = −7.8 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.06 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.16 (d, *J* = 6.1 Hz, 3H, 4''-CH_3), 1.41–1.65 (m, 4H, 2 × CH_2), 1.87– 1.91 (m, 2H, CH_2), 2.69 (ddd, *J* = 16.0, 7.6, 2.5 Hz, 1H, 2-H), 2.80 (ddd, *J* = 16.0, 4.5, 2.2 Hz, 1H, 2-H), 3.14 (app t, *J* = 9.2, 9.2 Hz, 1H, 5'-H), 3.61 (m, 1H, 6'-H), 3.80–3.84 (m, 4H, OCH_3, 4''-H), 4.20 (m, 1H, 4'-H), 4.50 (d, *J* = 10.7 Hz, 1H, CH_2PMP), 4.61 (d, *J* = 10.7 Hz, 1H, CH_2PMP), 5.59 (s,1H, 2'-H), 6.90–6.92 (m, 2H, *m*CH ar PMB), 7.25–7.27 (m, 2H, *o*CH ar PMB), 7.34–7.36 (m, 3H, *m*CH, *p*CH ar Ph), 7.46–7.48 (m, 2H, *o*CH ar Ph), 9.82 (app t, *J* = 2.3 Hz, 2.3 Hz, 1H, 1-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.4 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 21.3 (CH_2), 23.8 (4''-CH_3), 25.9 ($SiC(CH_3)_3$), 32.1 (CH_2), 39.6 (CH_2), 46.3 (C-2), 55.3 (OCH_3), 68.5 (C-4''), 74.7 (CH_2PMP), 75.9 (C-6'), 77.4 (C-5'), 80.8 (C-4'), 100.3 (C-2'), 114.0 (*o*CH ar PMB), 126.0 (*o*CH ar Ph), 128.1 (*p*CH ar Ph), 128.8 (*m*CH ar Ph), 129.3 (*m*CH ar PMB), 129.8 (*m*CH ar PMB), 137.5 (2'-CPh), 159.7 ($COCH_3$), 200.2 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{32}H_{50}O_7SiNa$ 597.32180, found 597.32221.



41 **16**

(2*S*,4*R*,5*S*,6*S*)-4-Allyl-6-((*R*)-2-*tert*-butyldimethylsilyloxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxane (16). To an ice-cooled suspension of PPh_3MeBr (0.36 g, 1.00 mmol) in THF (3

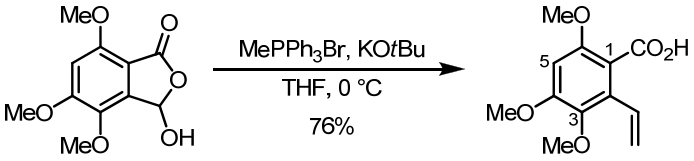
mL) was added KO*t*Bu (0.11 g, 1.00 mmol) in two portions. The resulting yellow mixture was stirred for 15 min at the same temperature and then 0.5 h at room temperature. Then the suspension was recooled (ice/salt bath) before a solution of aldehyde **41** (0.18 g, 0.30 mmol) in THF (1 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature (ca. 2 h). After that, water (2 mL) was added, the organic layer was separated and the aqueous phase extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give alkene **16** (135 mg, 75%) as a colorless oil. R_f = 0.65 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = –14.3 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.13 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 1.35–1.41 (m, 1H, CH_2), 1.49–1.59 (m, 4H, CH_2), 1.83–1.86 (m, 1H, CH_2), 2.39–2.49 (m, 1H, CH_2), 2.65–2.69 (m, 1H, CH_2), 3.10 (m, 1H, 5-H), 3.55–3.81 (m, 6H, OCH_3, 4-H, 6-H, 2'-H), 4.58 (dd, *J* = 15.8, 10.7 Hz, 2H, CH_2PMP), 5.11–5.19 (m, 2H, C*H*$_2$=CH), 5.51 (s, 1H, 2-H), 5.96–6.06 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H, CH_2=C*H*), 6.89–6.91 (m, 2H, *m*CH ar PMB), 7.25–7.28 (m, 2H, *o*CH ar PMB), 7.31–7.36 (m, 3H, *m*CH, *p*CH ar Ph), 7.48–7.49 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = –4.7, –4.4 ($Si(CH_3)_2$), 18.1 (Si*C*$(CH_3)_3$), 21.4 (CH_2), 23.8 (2'-CH_3), 25.9 ($SiC(CH_3)_3$), 32.2 (CH_2), 36.4 (CH_2 allyl), 39.7 (CH_2), 55.3 (OCH_3), 68.6 (C-2'), 74.9 (CH_2PMP), 77.8 (C-4), 80.0 (C-6), 80.4 (C-5), 100.0 (C-2), 113.9 (*o*CH ar PMB), 117.1 (*C*H_2=CH), 126.0 (*o*CH ar Ph), 128.0 (*p*CH ar Ph), 128.5 (*m*CH ar Ph), 129.6 (*m*CH ar PMB), 129.9 (CH_2*C*H ar PMB), 134.6 (CH_2=*C*H), 138.2 (2-CPh), 159.5 (*C*OCH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{32}H_{48}O_5SiNa$ 563.31632, found 563.33628.



16 **26**

(*R*)-5-((2*S*,4*S*,5*S*,6*R*)-6-Allyl-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)pentan-2-ol (26). A plastic test tube was charged with silyl ether **16** (0.11 g, 0.20 mmol) and abs. THF (15 mL). The solution was cooled to –30 °C and then HF·pyridine complex (1.8 mL, 70% HF) was added dropwise. The reaction mixture was allowed to warm to –15 °C and stirred overnight at this temperature. Then the mixture was partioned between an ice-cooled mixture of EtOAc (10 mL) and saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give alcohol **26** (87 mg, quant.) as a colorless oil. R_f = 0.43 (petroleum ether/EtOAc, 1:5); $[\alpha]^{20}_D$ = –22.1 (*c* 4.0, CH_2Cl_2); ^{1}H

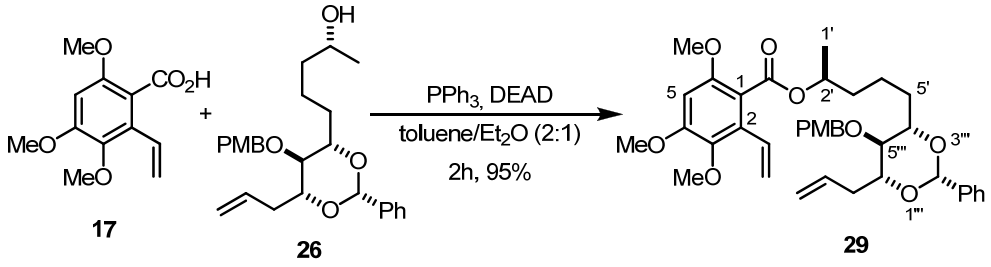
NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.18 (d, *J* = 6.1 Hz, 3H, 2-CH_3), 1.40–1.63 (m, 6H, 3 × CH_2), 1.85–1.89 (m, 1H, CH_2), 2.40–2.47 (m, 1H, CH_2), 2.65–2.69 (m, 1H, OH), 3.11 (app t, *J* = 9.2, 9.2 Hz, 1H, 5'-H), 3.61–3.81 (m, 6H, OCH_3, 6'-H, 2-H, 4'-H), 4.58 (dd, *J* = 20.8, 10.4 Hz, 2H, CH_2PMP), 5.11–5.19 (m, 2H, C*H*$_2$=CH), 5.51 (s, 1H, 2'-H), 5.96–6.06 (dddd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H, CH_2=C*H*), 6.89–6.91 (m, 2H, *m*CH ar Ph), 7.25–7.28 (m, 2H, *o*CH ar Ph), 7.33–7.36 (m, 3H, *m*CH, *p*CH ar Ph), 7.48–7.49 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 21.4 (CH_2), 23.5 (C-1), 31.9 (CH_2), 36.3 (CH_2), 39.2 (CH_2), 55.3 (OCH_3), 67.9 (C-2), 74.6 (CH_2PMP), 77.4 (C-6'), 80.0 (C-4'), 80.4 (C-5'), 100.1 (C-2'), 113.9 (*o*CH ar PMB), 117.2 (*C*H_2=CH), 126.0 (*o*CH ar Ph), 128.1 (*p*CH ar Ph), 128.6 (*m*CH ar Ph), 129.6 (*m*CH ar PMB), 129.9 (CH_2*C*H ar PMB), 134.4 (CH_2=*C*H), 138.1 (2'-CPh), 159.5 (*C*OCH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{34}O_5Na$ 449.22985, found 449.22978.



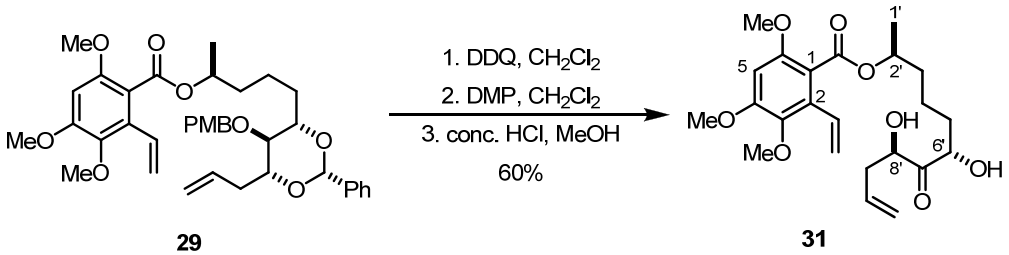
26 **17**

3,4,6-Trimethoxy-2-vinylbenzoic acid (17). KO*t*Bu (0.41 g, 3.34 mmol) was added in one portion to a stirred suspension of PPh_3MeBr (1.22 g, 3.34 mmol) in abs. THF (12 mL) at 0 °C. After 0.5 h hydroxyphthalide[4] **26** (0.10 g, 0.42 mmol) was added in one portion and the mixture was allowed to warm to room temperature. After 2 h, water (2 mL) was added followed by addition of 1N HCl until the pH of the reaction mixture was approx. 2. The organic layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:4) to give styrene **17** (76 mg, 76%) as a white crystalline solid. R_f = 0.56 (petroleum ether/EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.49 (dd, *J* = 11.7, 1.3 Hz, 1H, CH_2 vinyl), 7.75 (dd, *J* =17.8, 1.3 Hz, 1H, CH_2 vinyl), 6.46 (s, 1H, 5-H), 6.84 (dd, *J* = 17.8, 11.5 Hz, 1H, CH vinyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 56.0, 56.7, 60.4 (OCH_3), 96.3 (C-5), 113.7 (CH_2 vinyl), 120.4, 130.4 (C aryl), 132.0 (CH vinyl), 141.0, 153.6, 154.8 (C aryl), 171.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{14}O_5Na$ 261.07390, found 261.07378.

[4] (a) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183; (b) Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519; (c) Watanabe, M.; Ijichi, S.; Furukawa, S. *Synthesis* **1993**, 94.

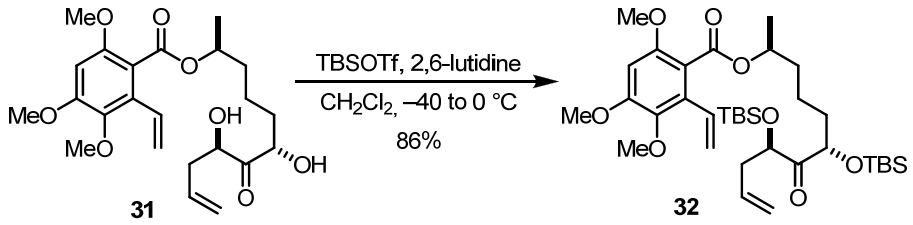


(*S*)-5-((2*S*,4*S*,5*S*,6*R*)-6-Allyl-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)pentan-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (29). DEAD (0.064 mL, 0.14 mmol) was added to a solution of styrene **17** (33.6 mg, 0.14 mmol) and alcohol **26** (40.0 mg, 0.09 mmol) in a toluene/Et_2O mixture (1.5 mL, 2:1) at 0 °C. Then the reaction was allowed to warm to room temperature and stirred for 2 h. Thereafter, the solvents were evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give benzoic ester **29** (57.7 mg, 95%) as a white amorphous solid. R_f = 0.61 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = –6.0 (*c* 2.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 1.44–1.80 (m, 4H, 2 × CH_2), 1.87–1.90 (m, 2H, CH_2), 2.38–2.45 (m, 1H, CH_2), 2.63–2.67 (m, 1H, CH_2), 3.08 (app t, *J* = 9.2, 9.2 Hz, 1H, 5'''-H), 3.59–3.71 (m, 8H, 2 × OCH_3, 6'''-H, 4'''-H), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.55 (dd, *J* = 18.3, 10.7 Hz, CH_2PMP), 5.09–5.17 (m, 3H, C*H*$_2$=CH allyl, 2'-H), 5.39 (m, 1H, C*H*$_2$=CH vinyl), 5.48 (s, 1H, CHPh), 5.70 (d, *J* = 17.8 Hz, 1H, C*H*$_2$=CH vinyl), 5.94–6.04 (m, 1H, H_2C=C*H* allyl), 6.37 (s, 1H, 5-H), 6.72 (dd, *J* = 17.8, 11.4 Hz, 1H, C*H*=CH_2 vinyl), 6.85–6.87 (m, 2H, *m*CH ar PMP), 7.23–7.25 (m, 2H, *o*CH ar PMB), 7.30–7.32 (m, 3H, *m*CH, *p*CH ar Ph), 7.45–7.46 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 19.9 (CH_2), 21.2 (C-1'), 31.9 (CH_2), 35.9 (CH_2), 36.3 (CH_2), 55.2 (CH_3 of PMB), 56.0 (OCH_3), 56.3 (OCH_3), 60.4 (OCH_3), 71.9 (C-2'), 74.6 (CH_2PMP), 77.4 (C-6'''), 80.0 (C-4'''), 80.5 (C-5'''), 96.6 (C-5), 100.1 (C-2'''), 113.9 (*o*CH ar PMB), 116.1 (C aryl), 117.2 (*C*H_2=CH vinyl), 120.4 (C aryl), 126.1 (*o*CH ar Ph), 128.0 (*m*CH ar Ph), 128.5 (*p*CH ar Ph), 129.6 (*m*CH ar PMB), 129.8 (CH_2*C*H ar PMB), 130.2 (*C*H_2=CH allyl), 130.4 (CH_2=*C*H allyl), 134.5 (CH_2=*C*H vinyl), 138.1 (2'''-CPh), 140.7 (C aryl), 153.0 (C aryl), 153.8 (C aryl), 159.5 (*C*OCH_3 ar PMB), 167.4 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{38}H_{46}O_9Na$ 669.30340, found 669.30375.



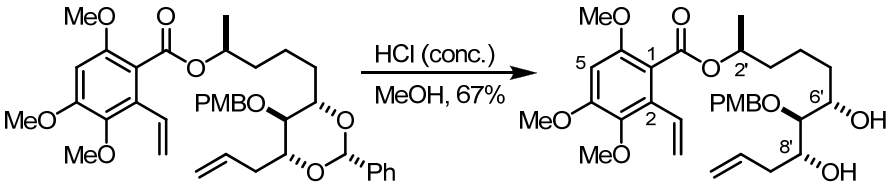
(2*S*,6*S*,8*R*)-6,8-Dihydroxy-7-oxoundec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (31). a) *PMB deprotection:* To a cooled (0 °C) solution of benzoic ester **29** (57.0 mg, 0.09 mmol) in a mixture of

CH_2Cl_2/pH 7 phosphate buffer (2.4 mL, 5:1) was added DDQ (123 mg, 0.54 mmol) in one portion. After being stirred for 3 h at room temperature, the reaction mixture was recooled to 0 °C and saturated $NaHCO_3$ solution (2 mL) was added dropwise. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL) and NaCl (20 mL) solutions, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude deprotection product (49.5 mg) which was directly introduced to the oxidation step. R_f = 0.55 (petroleum ether/EtOAc, 1:1). *Oxidation*: A stirred solution of the deprotection product obtained above (49.5 mg, 0.09 mmol) in abs. CH_2Cl_2 (1 mL) was cooled in an ice/salt bath and then a solution of Dess−Martin periodinane (0.40 mL, 0.19 mmol, 15% wt in CH_2Cl_2) was added. The cooling bath was removed and after being stirred for 2 h at room temperature the reaction mixture was concentrated and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ketone **30** (47.9 mg, 97%) as a colorless oil wich was directly introduced to the next step (acetal cleavage). R_f = 0.58 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +4.1 (*c* 1.2, CH_2Cl_2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{36}O_8Na$ 547.23024, found 547.23021. *Acetal cleavage*: To a solution of ketone **30** obtained above (47.9 mg, 0.09 mmol) in MeOH (1 mL) was added a mixture of conc. HCl/MeOH (1.05 mL, 20:1) dropwise. After 1.5 h dry K_2CO_3 was added until pH = 7 was reached. Then the solids were filtered off, washed with MeOH (5 mL) and the filtrate was then concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give dihydroxy ketone **31** (38.4 mg, 60% over 3 steps) as a colorless oil. R_f = 0.24 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +26.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 1.50–1.70 (m, 4H, 2 × CH_2), 1.78–1.84 (m, 1H, CH_2), 1.96–1.98 (m, 1H, CH_2), 2.32 (ddd, *J* = 14.5, 7.6, 7.4 Hz, 1H, 9'-H), 2.63–2.69 (m, 1H, 9'-H), 3.68 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 4.44 (dd, *J* = 7.5, 4.2 Hz, 1H, 6'-H), 4.49 (dd, *J* = 7.0, 4.3 Hz, 1H, 8'-H), 5.11–5.20 (m, 3H, 11'-H, 2'-H), 5.43 (dd, *J* = 11.7, 1.5 Hz, 1H, CH_2 vinyl), 5.70 (dd, *J* = 17.8, 1.5 Hz, 1H, CH_2 vinyl), 5.72–5.76 (m, 1H, 10'-H), 6.44 (s, 1H, 5-H), 6.70–6.77 (m, 1H, CH vinyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 19.9 (C-1'), 20.9, 33.3, 35.5 (CH_2), 38.1 (C-5'), 56.1, 56.5, 60.5 (OCH_3), 71.5 (C-2'), 73.8 (C-8'), 74.7 (C-6'), 96.7 (C-5), 115.9 (CH_2 vinyl), 119.5 (C-11'), 120.5 (C aryl), 130.3 (C-10'), 130.5 (C aryl), 132.7 (CH vinyl), 140.8, 153.0, 154.0 (C aryl), 167.6 (C=O), 213.5 (C-9'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{32}O_8Na$ 459.19894, found 459.19900.



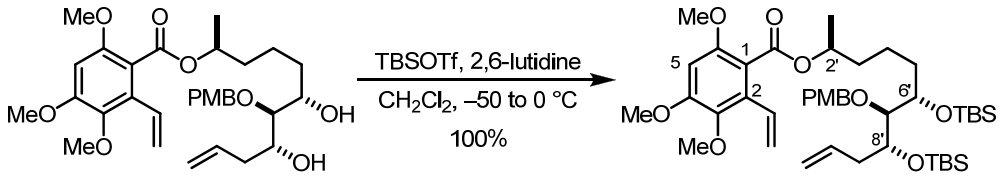
(2*S*,6*S*,8*R*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-7-oxoundec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (32). A solution of dihydroxy ketone **31** (3.0 mg, 0.007 mmol) in CH_2Cl_2 (0.5 mL) was cooled to –40 °C. Then 2,6-lutidine (0.004 mL, 0.035 mmol) was added followed by addition of TBSOTf

(0.0064 mL, 0.028 mmol). The temperature was raised to 0 °C and the mixture stirred overnight at 0 °C. After that, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with 1N HCl (10 mL), saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude ketone **32** (3.9 mg, 86%) was directly introduced into the subsequent RCM reaction. R_f = 0.69 (petroleum ether/EtOAc, 1:1).



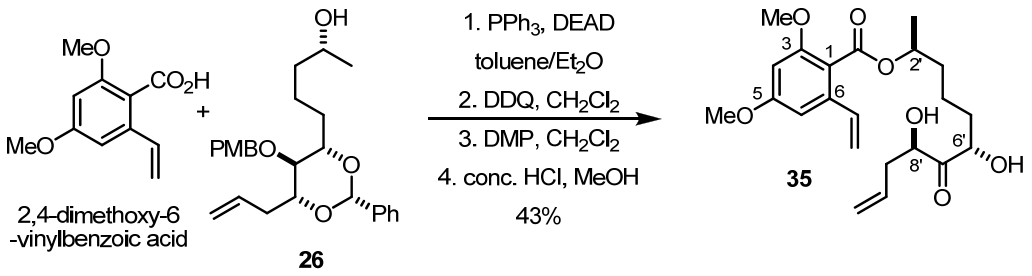
29 **33**

(2*S*,6*S*,7*S*,8*R*)-6,8-Dihydroxy-7-(4-methoxybenzyloxy)undec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (33). To a solution of benzoic ester **29** (57.7 mg, 0.09 mmol) in MeOH (2 mL) was added a mixture of conc. HCl/MeOH (1.05 mL, 20:1) dropwise. After being stirred overnight, dry K_2CO_3 was added until pH = 7 was reached. Then the solids were filtered off, washed with MeOH (10 mL), and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give diol **33** (33.4 mg, 67%) as a colorless oil. R_f = 0.21 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = –8.3 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 1.40–1.70 (m, 6H, 3 × CH_2), 1.98 (br.s, 2H, OH), 2.21–2.29 (m, 1H, 9'-H), 2.55–2.58 (m, 1H, 9'-H), 3.28 (app t, *J* = 5.8, 5.8 Hz, 1H, 7'-H), 3.69 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × OCH_3), 3.81–3.85 (m, 2H, 6'-H, 8'-H), 3.87 (s, 3H, OCH_3), 4.56 (s, 2H, CH_2PMP), 5.14–5.18 (m, 3H, CH_2 11'-H, 2'-H), 5.42 (app d, *J* = 17.8 Hz, 1H, CH_2 vinyl), 5.71 (app d, *J* = 17.8 Hz, 1H, CH_2 vinyl), 5.79–5.91 (m, 1H, 10'-H), 6.43 (s, 1H, 5-H), 6.74 (dd, *J* = 17.8, 11.7 Hz, CH vinyl), 6.86–6.88 (m, 2H, *m*CH ar PMP), 7.23–7.25 (m, 2H, *o*CH ar PMP); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 19.8 (C-1'), 21.6, 32.6, 35.8 (CH_2), 38.3 (C-5'), 55.3, 56.1, 56.5, 60.4 (OCH_3), 71.7 (C-2'), 71.9 (C-7'), 72.9 (C-6'), 73.7 (C-8'), 83.8 (CH_2PMP), 96.7 (C-5), 113.9 (*o*CH ar PMB), 116.2 (C aryl), 118.5 (CH_2 vinyl), 120.5 (C aryl), 129.5 (*m*CH ar PMB), 130.2 (CH_2*C*H ar PMB), 130.3 (C-11'), 130.5 (C-10'), 134.8 (CH vinyl), 140.8, 153.0, 153.9 (C aryl), 159.4 (*C*OCH_3 ar PMB), 167.5 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{42}O_9Na$ 581.27265, found 581.27260.



33 **34**

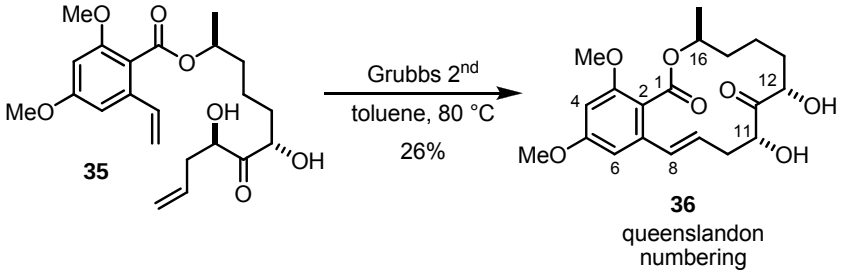
(2*S*,6*S*,7*S*,8*R*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)undec-10-en-2-yl 3,4,6-trimethoxy-2-vinylbenzoate (34). To a stirred and cooled (–50 °C) solution of diol **33** (9.6 mg, 0.017 mmol) in CH_2Cl_2 (2 mL), 2,6-lutidine (0.01 mL, 0.086 mmol) was added followed by addition of TBSOTf (0.016 mL, 0.071 mmol). After complete addition, the temperature was raised to 0 °C (approx. within 1 h) and the mixture was stirred overnight. Then water (1 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed with 1N HCl (10 mL), saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give protected diol **34** (13.5 mg, quant.) as a colorless oil. R_f = 0.75 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = –5.0 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.01, 0.04, 0.05, 0.06 (4 s, 3H each, $Si(CH_3)_2$), 0.85–0.89 (m, 18H, 2 × $SiC(CH_3)_3$), 1.05–1.70 (m, 8H, 3 × CH_2, 2'-CH_3), 2.26–2.29 (m, 1H, 9'-H), 2.42–2.47 (m, 1H, 9'-H), 3.47–3.48 (m, 1H, 7'-H), 3.68 (s, 3H, OCH_3), 3.78 (s, 6H, 2 × OCH_3), 3.83–3.86 (m, 5H, 6'-H, 8'H, OCH_3), 4.58–4.70 (dd, *J* = 17.8, 10.7 Hz, 2H, CH_2PMP), 5.04–5.07 (m, 3H, 12'-H, 2'-H), 5.42 (app d, *J* = 11.7 Hz, 1H, CH_2 vinyl), 5.71 (app d, *J* = 17.8 Hz, 1H, CH_2 vinyl), 5.86–5.92 (m, 1H, 10'-H), 6.42 (s, 1H, 5-H), 6.74 (m, 1H, CH vinyl), 6.82–6.84 (m, 2H, *m*CH ar PMB), 7.23–7.25 (m, 2H, *o*CH ar PMB); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = –4.5, –4.2, –4.3, –3.0 ($Si(CH_3)_2$), 18.0, 19.5 (C-1'), 21.0 (CH_2), 25.7, 25.9, 26.0, 27.0, 27.2, 29.7 ($SiC(CH_3)_3$), 32.0, 36.4 (CH_2), 37.1 (C-9'), 55.3, 56.1, 56.5, 60.4 (OCH_3), 72.1 (C-7'), 72.4 (C-2'), 72.6 (C-8'), 74.0 (C-6'), 84.5 (CH_2PMP), 96.7 (C-5), 113.7 (*o*CH ar PMB), 116.2 (C aryl), 117.0 (C-11'), 119.1 (CH_2 vinyl), 120.4 (C aryl), 129.4 (*m*CH ar PMB), 130.3 (CH_2*C*H ar PMB), 130.5 (C-11'), 131.3 (C-10'), 135.3 (CH vinyl), 140.8, 153.1, 153.9 (C aryl), 159.0 (*C*OCH_3 ar PMB), 167.4 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{43}H_{70}O_9Si_2Na$ 810.44561, found 810.44582.



26 **35**

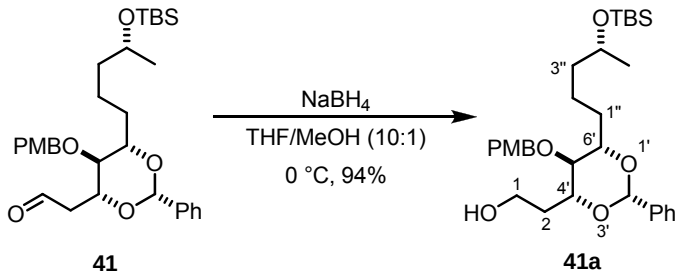
(2*S*,6*S*,8*R*)-6,8-Dihydroxy-7-oxoundec-10-en-2-yl-2,4-dimethoxy-6-vinylbenzoate (35). Nor-methoxy substrate (2,4-dimethoxy-6-vinylbenzoic acid) was prepared in four steps (43% overall yield)

from 2,4-dimethoxy-6-vinylbenzoic acid[5] following essentially the same procedures as for dihydroxy ketone **35**. R_f = 0.44 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +35.4 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.33 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 1.56–1.59 (m, 4H, 2 × CH_2), 1.68–1.74 (m, 1H, CH_2), 1.97–1.99 (m, 1H, CH_2), 2.37–2.45 (m, 1H, 9'-H), 2.64–2.67 (m, 1H, 9'-H), 2.83 (br, 2H, OH), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.41–4.44 (m, 1H, 6'-H), 4.49–4.50 (m, 1H, 8'-H), 5.16–5.19 (m, 3H, 11'-H, 2'-H), 5.32 (m, 1H, CH_2 vinyl), 5.70 (m, 1H, CH_2 vinyl), 5.75–5.80 (m, 1H, 10'-H), 6.39 (s, 1H, H aryl), 6.63 (m, 1H, H aryl), 6.72 (m, 1H, CH vinyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 20.1 (C-1'), 21.0, 33.3, 35.5 (CH_2), 38.1 (C-9'), 55.4, 55.9 (OCH_3), 71.5 (C-2'), 73.8 (C-8'), 74.7 (C-6'), 98.3 (C aryl), 101.5 (C aryl), 116.5 (C-11''), 117.1 (C aryl), 119.5 (CH vinyl), 132.7 (C-10'), 133.7 (C aryl), 137.4 (CH_2 vinyl), 157.9, 161.4 (C aryl), 167.7 (C=O), 213.5 (C-7'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{30}O_7Na$ 429.18893, found 429.18887.



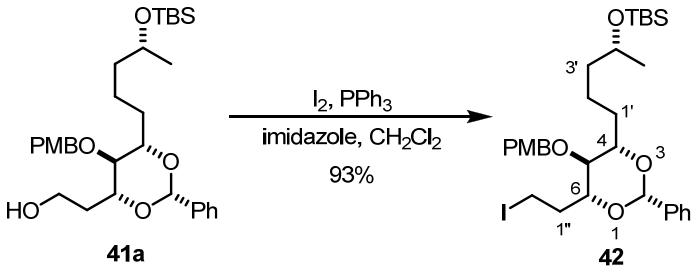
Macrolactone (36). Dihydroxy ketone **35** was dissolved in degassed toluene (4.4 mL, 0.004 M) and then Grubbs 2nd catalyst (1.49 mg, 10 mol %) was added. The resulting mixture was heated for 1 h at 80 °C. After this time, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give macrolactone **36** (1.7 mg, 26%) as a white amorphous paste. R_f = 0.46 (petroleum ether/EtOAc, 1:2); $[\alpha]^{20}_D$ = –8.4 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.32 (d, *J* = 5.9 Hz, 3H, 17-CH_3), 1.47–1.83 (m, 4H, 2 × CH_2), 2.02–2.16 (m, 2H, CH_2), 2.58–2.65 (m, 1H, 11-H), 3.09–3.12 (m, 2H, 11-OH, 13-OH), 3.79–3.84 (m, 4H, 11-OH, OCH_3), 3.92 (s, 3H, OCH_3), 4.13–4.17 (m, 1H, 13-H), 4.58–4.60 (m, 1H, 11-H), 5.31–5.38 (m, 1H, 17-H), 5.84 (m, 1H, 9-H), 6.43–6.47 (m, 2H, 4-H, 6-H), 6.65 (m, 1H, 8-H); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{26}O_7Na$ 401.15762, found 401.15752.

[5] Ugele, M.; Sasse, F.; Knapp, S.; Fedorov, O.; Zubriene, A.; Matulis, D.; Maier, M. E. *ChemBioChem* **2009**, *10*, 2203.



41 **41a**

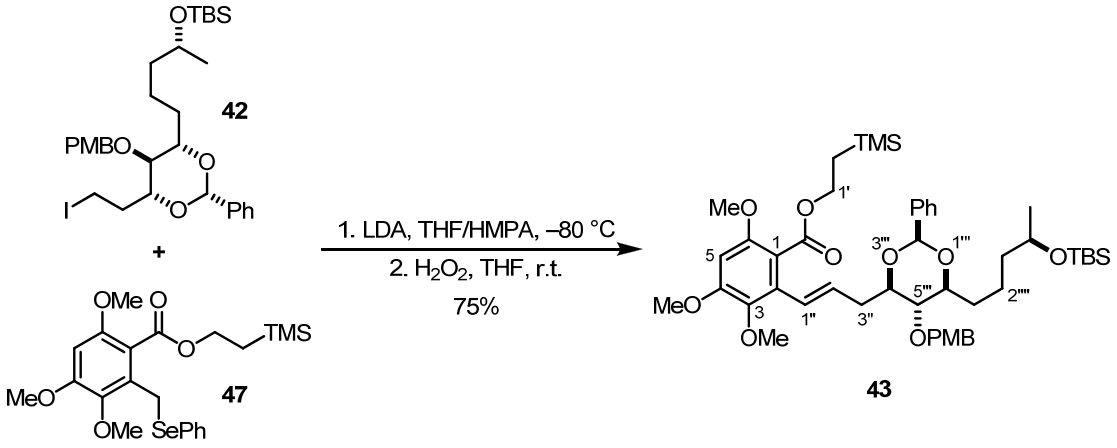
2-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)ethanol (41a). A solution of aldehyde **41** (107 mg, 0.20 mmol) in a THF/MeOH mixture (3.3 mL, 10:1) was cooled in an ice/salt bath and $NaBH_4$ (17.1 mg, 0.24 mmol) was added in one portion. The reaction mixture was stirred in an ice bath for 1 h followed by the addition of saturated NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **41a** (102 mg, 94%) as a colorless oil. R_f = 0.77 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = −2.3 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 6H, $SiC(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, *J* = 6.1 Hz, 3H, 4''-CH_3), 1.37–1.47 (m, 2H, CH_2), 1.58–1.73 (m, 2H, CH_2), 1.83–1.91 (m, 2H, CH_2), 2.13–2.18 (dddd, *J* = 14.4, 5.7, 5.7, 2.9 Hz, 2H, 2-H), 3.12 (app t, *J* = 9.0, 9.0 Hz, 1H, 5'-H), 3.64 (app td, *J* = 9.1, 9.1, 2.4 Hz, 1H, 6'-H), 3.77–3.88 (m, 7H, OCH_3, 4''-H, 1-H, 4'-H), 4.53–4.56 (m, 2H, CH_2PMP), 5.53 (s, 1H, 2'-H), 6.88–6.90 (m, 2H, *m*CH ar PMB), 7.24–7.26 (m, 2H, *o*CH ar PMB), 7.33–7.36 (m, 3H, *m*CH, *p*CH ar Ph), 7.44–7.46 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.3 ($Si(CH_3)_2$),18.1 ($SiC(CH_3)_3$), 21.5 (CH_2), 23.8 (4''-CH_3), 25.9 ($SiC(CH_3)_3$), 32.2 (CH_2), 34.3 (C-2) 39.7 (CH_2), 55.3 (OCH_3), 60.7 (C-1), 68.5 (C-4''), 74.9 (CH_2PMP), 77.8 (C-6'), 80.2 (C-5'), 80.7 (C-4'), 100.2 (C-2'), 114.0 (*o*CH ar PMB), 125.9 (*o*CH ar Ph), 128.2 (*p*CH ar Ph), 128.7 (*m*CH ar Ph), 129.7 (*m*CH ar PMB), 137.8 (2'-CPh), 159.6 ($COCH_3$); HRMS (ESI): HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{48}O_6SiNa$ 567.31124, found 567.31077.



41a **42**

(2*S*,4*S*,5*S*,6*R*)-4-((*R*)-4-(*tert*-Butylsilyloxy)pentyl)-6-(2-iodoethyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxane (42). Iodine (407 mg, 1.60 mmol) was added to a cooled solution (ice bath) of PPh_3 (392 mg, 1.49 mmol) and imidazole (131 mg, 1.91 mmol) in abs. CH_2Cl_2 (3 mL). The resulting yellow suspension was stirred for 20 min at the same temperature before a solution of alcohol **41a** (584

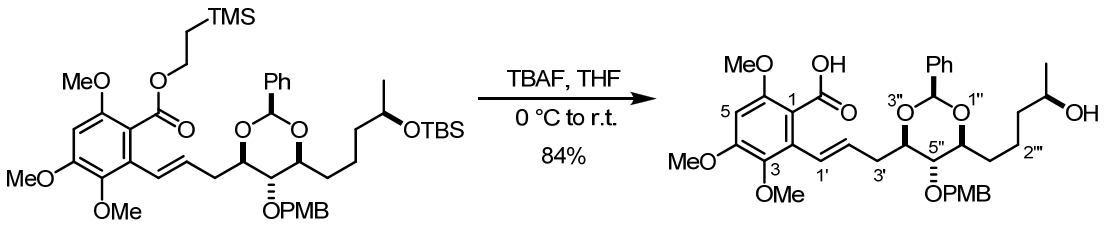
mg, 1.07 mmol) in abs. CH_2Cl_2 (1 mL) was added. The cooling bath was removed and the resulting yellowish suspension was stirred for additional 12 h at ambient temperature. After that, the CH_2Cl_2 was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give primary iodide **42** (655 mg, 93%) as a slightly yellow oil. R_f = 0.59 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +19.2 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.13 (d, *J* = 6.1 Hz, 3H, 4'-CH_3), 1.37–1.47 (m, 4H, 2 × CH_2), 1.48–1.62 (m, 2H, CH_2), 1.67–1.76 (m, 1H, 1''-H), 1.86–1.93 (m, 1H, 1''-H), 2.02 (dddd, *J* = 14.2, 9.4, 7.6, 4.5 Hz, 1H, 2''-H), 2.37 (dddd, *J* = 14.3, 8.6, 8.6, 2.4 Hz, 1H, 2''-H), 3.07 (app t, *J* = 9.2 Hz, 1H, 5-H), 3.25–3.36 (m, 2H, 6-H, 4-H), 3.77–3.81 (m, 4H, OCH_3, 4'-H), 4.50–4.60 (m, 2H, CH_2PMP), 5.52 (s, 1H, 2-H), 6.89–6.91 (m, 2H, *m*CH ar PMB), 7.25–7.27 (m, 2H, *o*CH ar PMB), 7.25–7.27 (m, 3H, *m*CH, *p*CH ar Ph), 7.46–7.48 8 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.3 ($Si(CH_3)_2$), 1.6 (C-2''), 18.1 ($SiC(CH_3)_3$), 21.5 (CH_2), 23.8 (C-1'), 25.9 ($SiC(CH_3)_3$), 32.2 (CH_2), 36.3 (C-1'') 39.7 (CH_2), 55.3 (OCH_3), 68.5 (C-4'), 74.8 (CH_2PMP), 77.6 (C-4), 80.0 (C-5), 80.6 (C-6), 100.0 (C-2), 114.0 (*o*CH ar PMB), 126.0 (*o*CH ar Ph), 128.1 (*p*CH ar Ph), 128.7 (*m*CH ar Ph), 129.6 (*m*CH ar PMB), 129.7 (CH_2CH ar PMB), 137.9 (2-CPh), 159.6 ($COCH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{47}IO_5SiNa$ 677.21297, found 677.21222.



2-(Trimethylsilyl)ethyl-2-((*E*)-3-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-(*tert*-butyldimethylsilyloxy)pentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoate (43).
Alkylation: To a solution of phenylbenzyl selenoether[6] **47** (65.4 mg, 0.14 mmol) in a THF/HMPA mixture (3.3 mL, 10:1) was added dropwise a preformed solution of LDA (0.22 mmol) in THF (0.54 mL)

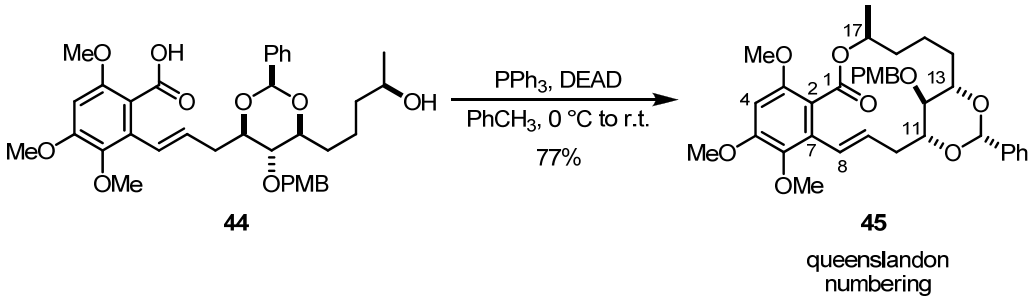
[6] Seleno ether **47** was prepared in eight steps from 5-bromovanillin: (a) Sánchez, I. H.; Larraza, M. I.; Basurto, F.; Yafnez, R.; Avila, S.; Tovar, R.; Joseph-Nathan, P. *Tetrahedron* **1985**, *41*, 2355; (b) Evans, G. E.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 755; (c) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem. A Eur. J.* **2002**, *8*, 1856; d) Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951.

at −80 °C whereby the reaction mixture turned red. After 20 min, a precooled (−40 °C) solution of alkyl iodide **42** (89.2 mg, 0.1 mmol) in abs. THF (0.5 mL) was added slowly and the resulting reaction mixture was stirred for 2 h at −80 °C before saturated NH_4Cl solution (5 mL) was added. The reaction mixture was allowed to warm to room temperature, then the layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of around 2 mL. This solution was filtered through a short pad of Celite® and the Celite® washed with EtOAc (2 × 10 mL). The combined organic washings were evaporated to give crude alkylation product (118.9 mg), which was directly introduced to the next step. R_f = 0.43 (petroleum ether/EtOAc, 3:1). *Elimination*: The crude alkylation product obtained above (119 mg, 0.1 mmol) was dissolved in abs. THF (2 mL) and H_2O_2 (0.026 mL, 0.25 mmol, 30%) was added at r.t. After being stirred for 2 h, the reaction was quenched with saturated $Na_2S_2O_8$ solution (2 mL), and the mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 8:1) to give styrene **43** (85.5 mg, 75% over 2 steps) as a colorless oil. R_f = 0.41 (petroleum ether/EtOAc, 3:1); $[\alpha]^{20}_D$ = +10.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = −0.04 (s, 9H, $Si(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.12 (d, *J* = 6.1 Hz, 3H, 4''''-CH_3), 1.40–1.88 (m, 8H, 3 × CH_2, 2'-H), 2.53–2.63 (m, 1H, 3''-H), 2.78 (dd, *J* = 14.8, 7.6 Hz, 1H, 3''-H), 3.14 (app t, *J* = 9.2 Hz, 1H, 5'''-H), 3.58–3.62 (m, 4H, OCH_3, 4''''-H), 3.71–3.80 (m, 8H, 2 × OCH_3, 4'''-H, 6'''-H), 3.87 (s, 3H, OCH_3), 4.20–4.35 (m, 2H, 1'-H), 4.56–4.65 (m, 2H, CH_2PMP), 5.49 (s, 1H, 2'''-H), 6.34–6.41 (m, 2H, 2'-H, 5-H), 6.55 (d, *J* = 16.3 Hz, 1H, 1'-H), 6.87–6.89 (m, 2H, *m*CH ar PMB), 7.25–7.32 (m, 5H, *o*CH ar PMB, *m*CH, *p*CH ar Ph), 7.47–7.49 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = −4.7, −4.4 ($Si(CH_3)_2$), −1.6 (TMS), 17.3 ($SiC(CH_3)_3$), 18.1 (C-2'), 21.6 (CH_2), 23.8 (4''''-CH_3), 25.9 ($SiC(CH_3)_3$), 32.8 (CH_2), 36.2 (C-3''), 39.7 (CH_2), 55.3, 56.1, 56.5, 60.4 (OCH_3), 63.5 (C-1'), 68.6 (C-4''''), 74.8 (CH_2PMP), 77.5 (C-6'''), 80.0 (C-5'''), 80.7 (C-4'''), 96.1 (C-5), 100.0 (C-2'''), 113.9 (*o*CH ar PMB), 116.1 (C aryl), 125.6 (*o*CH ar Ph), 126.1 (C-2''), 128.0 (*p*CH ar Ph), 128.4 (*m*CH ar Ph), 129.5 (*m*CH ar PMB), 130.0 (CH_2*C*H ar PMB), 130.5 (C aryl), 132.5 (C-1''), 138.3 (2-CPh), 140.7, 153.1, 153.8 (C aryl), 159.4 (*C*OCH_3 ar PMB), 168.1 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{47}H_{70}O_{10}Si_2Na$ 873.43997, found 873.43955.



43 **44**

2-((*E*)-3-((2*S*,4*R*,5*S*,6*S*)-6-((*R*)-4-hydroxypentyl)-5-(4-methoxybenzyloxy)-2-phenyl-1,3-dioxan-4-yl)prop-1-enyl)-3,4,6-trimethoxybenzoic acid (44). To a cooled (ice bath) solution of ester **43** (85.5 mg, 0.1 mmol) in abs. THF (1.5 mL) was added TBAF (0.6 mL, 0.8 mmol, 1M in THF) and the mixture was allowed to warm to room temperature. After being stirred overnight, saturated NH_4Cl solution (3 mL) was added to the mixture. The layers were separated and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/ EtOAc, 1:2) to give hydroxy acid **44** (53.5 mg, 84%) as a white amorphous solid. R_f = 0.68 (petroleum ether/EtOAc, 1:5); $[\alpha]^{20}_D$ = +8.0 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.13 (d, *J* = 6.1 Hz, 3H, 4'''-CH_3), 1.50–1.82 (m, 6H, 3 × CH_2), 2.63–2.64 (m, 1H, 3'-H), 2.78– 2.82 (m, 1H, 3'-H), 3.23–3.27 (app t, *J* = 9.2, 9.2 Hz, 1H, 5''-H), 3.62–3.65 (m, 4H, OCH_3, 4'''-H), 3.75–3.81 (m, 8H, 2 × OCH_3, 4''-H, 6''-H), 3.86 (s, 3H, OCH_3), 4.55–4.66 (m, 2H, CH_2PMP), 5.48 (s, 1H, 2''-H), 6.37–6.42 (m, 2H, 5-H, 2'-H), 6.61–6.65 (app d, *J* = 16.3 Hz, 1'-H), 6.85–6.87 (m, 2H, *m*CH ar PMB), 7.25–7.33 (m, 5H, *m*CH, *p*CH ar Ph, *o*CH ar PMB), 7.46–7.48 (m, 2H, *o*CH ar Ph), 8.58 (br s, 1H, CO_2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 20.8 (CH_2), 23.2 (C-5'''), 31.5 (CH_2), 35.8 (C-3'), 38.8 (CH_2), 55.2, 56.0, 56.5, 60.4 (OCH_3), 68.1 (C-4'''), 74.6 (CH_2PMP), 75.7 (C-6''), 79.8 (C-4''), 80.6 (C-5''), 96.0 (C-5), 100.5 (C-2''), 113.9 (*o*CH ar PMB), 126.2 (C-2'), 128.1 (*p*CH ar Ph), 128.6 (*m*CH ar Ph), 129.5 (*m*CH ar PMB), 130.1 (CH_2*C*H ar PMB), 131.1 (C aryl), 132.4 (C-1'), 138.0 (2''-CPh), 140.6, 153.2, 154.2 (C aryl), 159.3 (*C*OCH_3 ar PMB), 176.8 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{44}O_{10}Na$ 659.28267, found 659.28274.

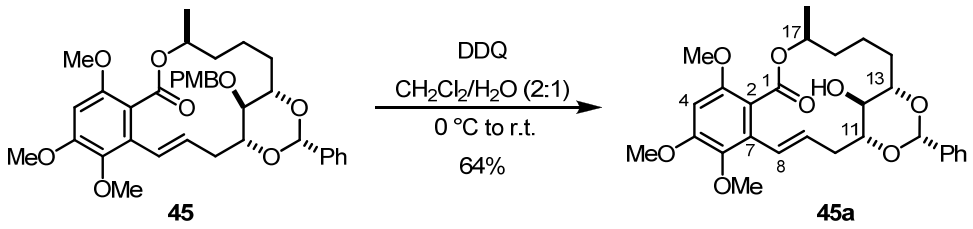


44 **45**

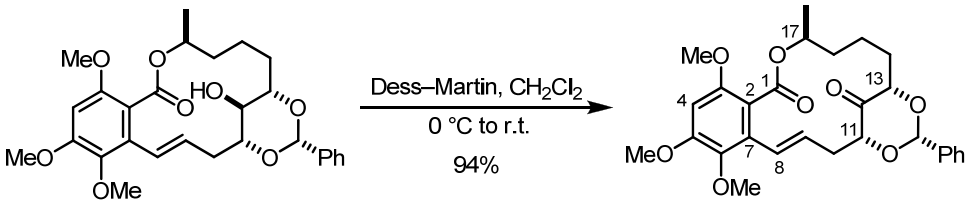
queenslandon numbering

Macrolactone 45. To a solution of acid **44** (60.2 mg, 0.095 mmol) in abs. toluene (9.5 mL) was added PPh_3 (55.6 mg, 0.19 mmol) at 0 °C. After being stirred for 15 min at 0 °C, DEAD (0.097 mL, 0.19 mmol)

was added dropwise and the resulting mixture was allowed to warm to room temperature. After 12 h the toluene was evaporated and the crude material purified by flash chromatography (petroleum ether/ EtOAc, 3:1) to give macrolactone **45** (45.3 mg, 77%) as a colorless oil. R_f = 0.41 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +52.4 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.31 (d, *J* = 6.3 Hz, 3H, 17-CH_3), 1.54–1.81 (m, 2H, CH_2), 1.98–2.00 (m, 2H, CH_2), 2.24–2.30 (m, 2H, CH_2), 2.67–2.74 (m, 1H, 10-H), 2.80–2.84 (m, 1H, 10-H), 3.69 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.80–3.85 (m, 4H, OCH_3, 12-H), 3.88–3.91 (m, 4H, OCH_3, 13-H), 4.54–4.64 (m, 2H, CH_2PMP), 5.35–5.39 (m, 1H, 17-H), 5.50 (s, 1H, CHPh), 6.46 (s, 1H, 4-H), 6.53–6.60 (m, 1H, 9-H), 6.66–6.70 (app d, *J* = 16.7 Hz, 1H, 8-H), 6.82–6.84 (m, 2H, *m*CH ar PMB), 7.21–7.41 (m, 5H, *m*CH, *p*CH ar Ph, *o*CH ar PMB), 7.64–7.66 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 17.9 (C-18),18.9, 30.0, 34.1 (CH_2), 36.4 (C-10), 55.2, 56.1, 56.5, 60.5 (OCH_3), 70.1 (CH_2PMP), 73.0 (C-17), 73.2 (C-13), 77.8 (C-11), 78.9 (C-12), 96.3 (C-4), 101.3 (CHPh), 113.9 (*o*CH ar PMB), 116.8 (C aryl), 126.8 (C-9), 127.0 (*p*CH ar Ph), 128.4 (*m*CH ar Ph), 129.1, 129.2 (*m*CH ar PMB), 130.3 (CH_2*C*H ar PMB), 132.4 (C-8), 138.5 (CH*C*Ph), 140.6, 153.0, 153.5 (C aryl), 159.3 (*C*OCH_3 ar PMB), 167.9 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{42}O_9Na$ 657.24604, found 657.24650.

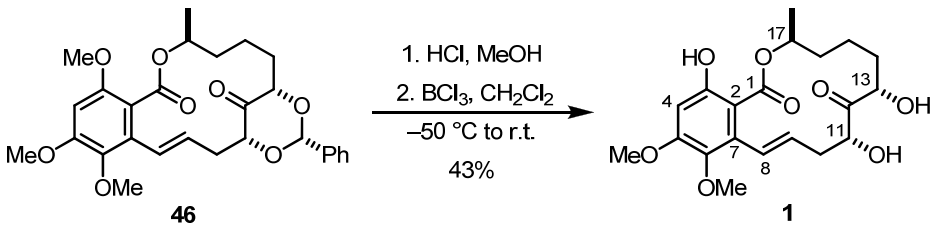


Alcohol 45a. Macrolactone **45** (12.7 mg, 0.021 mmol) was dissolved in abs. CH_2Cl_2 (0.5 mL), then water was added (0.25 mL) followed by DDQ (5.7 mg, 0.025 mmol). The resulting mixture was stirred for 1 h at room temperature and then saturated $NaHCO_3$ solution was added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and NaCl solutions (5 mL each), dried over $MgSO_4$, and filtered. The solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give alcohol **45a** (6.6 mg, 64%) as a white amorphous solid. R_f = 0.28 (petroleum ether/ EtOAc, 1:1); $[\alpha]^{20}_D$ = +55.7 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.30 (d, *J* = 6.4 Hz, 3H, 17-CH_3), 1.50–1.75 (m, 4H, 2 × CH_2), 2.08–2.22 (m, 2H, CH_2), 2.64–2.77 (m, 2H, 10-H), 3.71 (s, 3H, OCH_3), 3.74–3.72 (m, 5H, OCH_3, 12-H, 13-H), 3.86–3.91 (m, 4H, OCH_3, 11-H), 5.34–5.38 (m, 1H, 17-H), 5.46 (s, 1H, CHPh), 6.38–6.45 (m, 2H, 4-H, 9-H), 6.69 (d, *J* = 16.5 Hz, 1H, 8-H), 7.32–7.41 (m, 3H, *m*CH, *p*CH ar Ph), 7.65–7.67 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 17.2 (C-18), 19.0, 29.4, 34.5 (CH_2), 35.1 (C-10), 56.1, 56.5, 60.7 (OCH_3), 62.9 (C-17), 73.6 (C-13), 78.8 (C-11), 79.1 (C-12), 96.4 (C-4), 102.1 (CHPh), 116.8 (C aryl), 126.6 (C-9), 127.0 (*o*CH ar Ph), 129.1 (*m*CH ar Ph), 129.7 (*p*CH ar PMB), 132.0 (C-8), 138.2 (CH*C*Ph), 140.4, 153.1, 153.3 (C aryl), 167.8 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{34}O_8Na$ 521.21459, found 521.21456.



45a **46**

Ketone 46. Dess–Martin periodinane (0.063 mL, 0.03 mmol, 15wt % in CH_2Cl_2) was added dropwise to a cooled (ice bath) solution of alcohol **45a** (9.8 mg, 0.02 mmol) in abs. CH_2Cl_2 (1 mL). Then the reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. After that, the resulting suspension was loaded directly on a flash column. Elution (petroleum ether/EtOAc, 1:1) gave ketone **46** (9.2 mg, 94%) as a white amorphous solid. R_f = 0.34 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +25.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.28 (d, *J* = 6.4 Hz, 3H, 17-CH_3), 1.41–1.64 (m, 4H, 2 × CH_2), 1.88–1.93 (m, 1H, CH_2), 2.10–2.14 (m, 1H, CH_2), 2.72–2.80 (m, 1H, 10-H), 3.09–3.15 (m, 1H, 10-H), 3.68 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.50–4.55 (m, 2H, 11-H, 13-H), 5.13–5.17 (m, 1H, 17-H), 5.94 (s, 1H, CHPh), 6.30 (app dt, *J* = 16.1, 7.0, 7.0 Hz, 1H, 9-H), 6.41 (s, 1H, 4-H), 6.47 (d, *J* = 16.3 Hz, 1H, 8-H), 7.35–7.44 (m, 3H, *m*CH, *p*CH ar Ph), 7.62–7.64 (m, 2H, *o*CH ar Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 19.9 (C-18), 20.4, 30.1, 36.4 (CH_2), 36.6 (C-10), 56.1, 56.5, 60.3 (OCH_3), 72.0 (C-17), 81.7 (C-13), 82.8 (C-11), 96.5 (C-4), 99.9 (CHPh), 116.2 (C aryl), 126.5 (C-9), 126.8 (*o*CH ar Ph), 128.5 (C aryl), 129.1 (*m*CH ar Ph), 129.3(*p*CH ar Ph), 129.5 (C-8), 138.0 (CH*C*Ph), 140.8, 152.7, 153.8 (C aryl), 167.4 (C=O ester), 207.5 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{32}O_8Na$ 519.19894, found 519.19936.

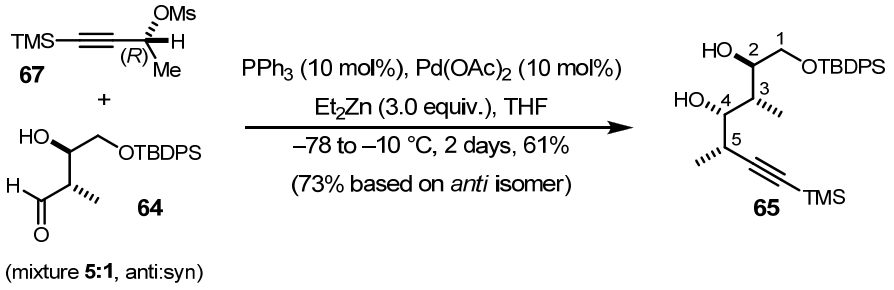


46 **1**

Dihydroxy ketone 1. *Acetal cleavage*: Ketone **46** (15.5 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and then a solution of MeOH/HCl conc. (1.05 mL, 20:1) was added dropwise at room temperature. After being stirred for 0.5 h, the solution was neutralized with saturated $NaHCO_3$ and the mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide the dihydroxy ketone (8.0 mg) as a yellow oil. The compound was directly introduced to the next step. *OMe cleavage:* To a solution of crude dihydroxy ketone obtained above (8.0 mg, 0.02 mmol) in abs. CH_2Cl_2 (1 mL) was added BCl_3 (0.08 mL, 0.08 mmol, 1M sol in CH_2Cl_2) dropwise at −50 °C. After 20 min the reaction was quenched with saturated NaOAc (3 mL). The layers were separated and aqueous phase extracted with

CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with saturated NaCl solution, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified via flash chromatography (CH_2Cl_2/MeOH, 40:1) to give corresponding dihydroxy acetone **1** (5.2 mg, 43% over 2 steps) as a colorless crystalline solid. R_f = 0.47 (petroleum ether/EtOAc, 1:5); $[\alpha]^{20}_D$ = −41.0 (*c* 0.5, CH_2Cl_2), $[\alpha]^{20}_D$ = −51.0 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.18–1.33 (m, 2H, CH_2), 1.37 (d, *J* = 6.1 Hz, 3H, 17-CH_3), 1.45–1.75 (m, 3H, CH_2), 2.12–2.20 (m, 1H, CH_2), 2.70–2.76 (m, 1H, 9-H), 3.03–3.09 (m, 2H, 9-H, 13-OH), 3.44–3.49 (m, 1H, 11-OH), 3.58 (s, 3H, OCH_3), 3.86 (s, 3H. OCH_3), 4.36–4.41 (m, 1H, 13-H), 4.60–4.67 (m, 1H, 11-H), 5.00–5.06 (m, 1H, 17-H), 5.84 (ddd, *J* = 15.3, 8.9, 3.3 Hz, 1H, 9-H), 6.40 (s, 1H, 4-H), 6.65 (app d, *J* = 15.3 Hz, 1H, 8-H), 11.56 (br s, 1H, OH aromatic); ^{13}C NMR (150 MHz, $CDCl_3$): δ[ppm] = 20.5 (CH_2), 20.7 (17-CH_3), 32.5, 35.6 (CH_2), 37.0 (C-10), 55.9, 60.6 (OCH_3), 73.2 (C-17), 73.4 (C-11), 75.0 (C-13), 99.7 (C-4), 103.7 (C aryl), 126.6 (C-9), 127.3 (C-8), 133.5, 140.3, 158.7, 160.9 (C aryl), 170.7 (C=O ester), 213.0 (C=O ketone); HRMS (ESI): HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{26}O_8Na$ 417.15199, found 417.15197.

II. Approach Towards the Total Synthesis of the Macrolide Leiodermatolide

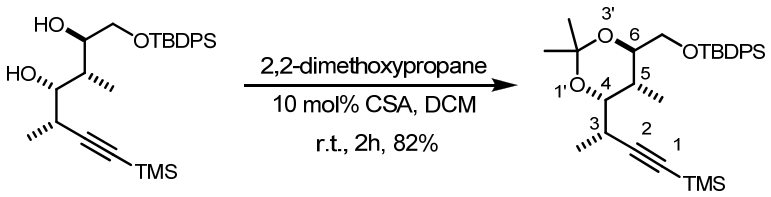


(2*R*,3*R*,4*S*,5*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethyl-7-(trimethylsilyl)hept-6-yne-2,4-diol (65). A suspension of $Pd(OAc)_2$ (0.181 g, 0.810 mmol, 10 mol%) in abs. THF (50 mL) was cooled to –78 °C. Then finely powdered PPh_3 (0.212 g, 0.810 mmol, 10 mol%) was added under a slight flow of nitrogen. The resulting yellow solution was stirred for ca. 5 min. In separate flasks solutions of (*R*)-mesylate[7] **67** (3.58 g, 1.62 mmol) and aldehyde[8] **64** (2.90 g, 8.10 mmol) were prepared (both containing 2.0 mL of abs. THF). Then both were added dropwise to a solution of prepared catalyst at the same time. The resulting yellow solution was stirred for 20 min at –78 °C and then Et_2Zn (24.4 mL, 2.43 mmol, 1.0M in hexane) was introduced over 30 min. (syringe pump used). After complete addition, the reaction was allowed to warm to –10 °C (the cooling machine was switched off: in ca. 50 min reaction reached –10 °C) and stirred for ca. 2 d (TLC and HPLC monitoring). During this time the color changed to dark brown. Work up was done by dropwise addition of saturated NH_4Cl solution (ca. 200 mL) directly to the reaction mixture. Then the mixture was warmed to room temperature, the layers were separated, and the aqueous phase extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried over Na_2SO_4 containing norite decolorizing charcoal. After filtration and evaporation of solvents the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give diol **65** (2.38 g, 61%, 73% based on *anti* isomer) as a colorless oil. R_f = 0.50 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = –1.4 (*c* 6.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.17 (s, 9H, TMS), 0.85 (d, *J* = 7.1 Hz, 3H, 3-CH_3), 1.08 (s, 9H, $C(CH_3)_3$), 1.14 (d, *J* = 6.9 Hz, 3H, 5-CH_3), 1.88–1.91 (m, 1H, 3-H), 2.61–2.66 (m, 2H, 2 × OH), 3.05–3.07 (m, 1H, 5-H), 3.65–3.70 (m, 1H, 6-H), 3.76–3.81 (m, 3H, 2-H, CH_2), 7.38–7.46 (m, 6H, *m*CH, *p*CH ar Ph), 7.67–7.69 m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 0.1 (TMS), 9.2 (3-CH_3), 17.2 (5-CH_3), 19.2 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 32.0 (C-5), 35.8 (C-3), 65.9 (CH_2), 73.9 (C-4), 74.4 (C-2), 87.2

[7] For preparation, see: Marshall, J. A.; Yanik, M. M., Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005**, *81*, 157. The ee value of (*R*)-mesylate **67** was determined to be >99%.

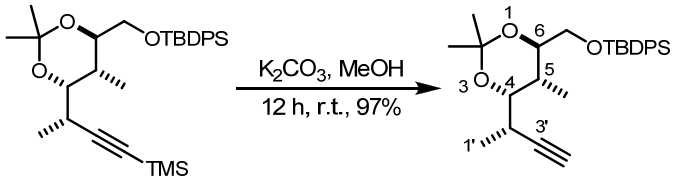
[8] Smith, A. B.; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359. The aldehyde **64** was additionally purified by passing it through a short column of silica (petroleum ether/EtOAc, 9:1).

(C≡*C*TMS), 108.5 (*C*≡CTMS), 127.7, 129.8, 133.1, 135.5 (C of $SiPh_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{42}O_3Si_2Na$ 505.25647, found 505.25627.



65 **65a**

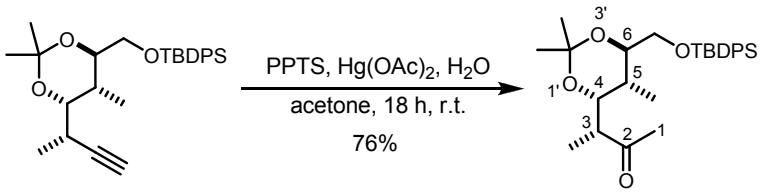
((*S*)-3-((4*S*,5*R*,6*R*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)but-1-ynyl)trimethylsilane (65a). To a solution of diol **65** (2.88 g, 5.97 mmol) in a mixture of abs. CH_2Cl_2 (8.0 mL) and 2,2-dimethoxypropane (3.0 mL) was added CSA (0.139 g, 0.60 mmol, 10 mol%) and the resulting solution stirred for 24 h at ambient temperature. After this time, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and shaken with saturated $NaHCO_3$ solution (10 mL). The layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give acetonide **65a** (2.32 g, 82%) as a colorless oil. R_f = 0.43 (petroleum ether/EtOAc, 20:1); $[\alpha]^{20}_D$ = +25.8 (*c* 8.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.13 (s, 9H, TMS), 0.74 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 1.05–1.06 (m, 12H, C(CH_3)$_3$, 3-CH_3), 1.37 (s, 6H, 2 × 2'-CH_3), 1.70 (app. ddq, *J* = 13.6, 11.2, 6.7 Hz, 1H, 5-H), 2.48 (app dq, *J* = 10.7, 6.7 Hz, 1H, 3-H), 3.37 (dd, *J* = 6.7, 3.9 Hz, 1H, 4-H), 3.58–3.66 (m, 2H, CH_2, 6-H), 3.71–3.76 (m, 1H, CH_2), 3.35–3.47 (m, 6H, *m*CH, *p*CH ar Ph), 7.68–7.70 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 0.2 (TMS), 11.4 (5-CH_3), 16.5 (3-CH_3), 19.3 (*C*(CH_3)$_3$), 23.7 (2'-CH_3), 24.9 (2'-CH_3), 26.8 (C(*C*H_3)$_3$), 28.1 (C-3), 34.1 (C-5), 65.9 (CH_2), 72.5 (C-6), 75.9 (C-4), 84.4 (C≡*C*TMS), 101.1 (C-2'), 109.5 (*C*≡CTMS), 127.6, 129.6 × 2, 133.6, 133.8, 135.7 (C of $SiPh_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{46}O_3Si_2Na$ 545.28777, found 545.288039.



65a **66**

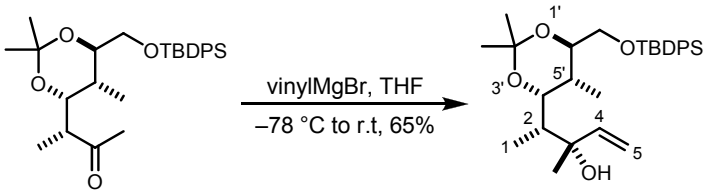
(4*S*,5*R*,6*R*)-4-((*S*)-But-3-yn-2-yl)-6-((*tert*-butyldiphenylsilyloxy)-2,2,5-trimethyl-1,3-dioxane (66). A solution of acetonide **65a** (0.082 g, 0.16 mmol) in dry MeOH (2.0 mL) and K_2CO_3 (0.044 g, 0.32 mmol) was stirred for 12 h at room temperature. Thereafter, the reaction mixture was poured into a separatory funnel containing saturated NH_4Cl (5 mL) solution and Et_2O (10 mL). The water layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent

was evaporated to give alkyne **66** (0.069 g, 97%) as a colorless oil. The resulting compound was pure enough to be introduced to the next step. R_f = 0.40 (petroleum ether/EtOAc, 20:1); $[\alpha]^{20}_D$ = +19.8 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.76 (d, *J* = 6.8 Hz, 3H, 5-CH_3), 1.06 (s, 9H, C(CH_3)$_3$, 1.09 (d, *J* = 6.8 Hz, 3H, 2'-CH_3), 1.38 (s, 6H, 2 × 2-CH_3), 1.73 (m, 1H, 5-H), 2.03 (d, *J* = 2.0 Hz, 1H, 4'-H), 2.50 (m, 1H, 2'-H), 3.38 (dd, *J* = 6.7, 4.0 Hz, 1H, 4-H), 3.60–3.67 (m, 2H, 6-H, CH_2), 3.72–3.76 (m, 1H, CH_2), 7.35–7.44 (m, 6H, *m*CH, *p*CH ar Ph), 7.69–7.70 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.5 (5-CH_3), 16.7 (2'-CH_3), 19.3 (*C*(CH_3)$_3$), 23.7 (2-CH_3), 24.9 (2-CH_3), 26.8 (C(*C*H_3)$_3$), 27.1 (C-5), 34.1 (C-2'), 65.9 (CH_2), 68.6 (C-3'), 72.3 (C-6), 75.8 (C-4), 86.8 (C-4'), 101.1 (C-2), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of $SiPh_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{38}O_3SiNa$ 473.24824, found 473.24794.



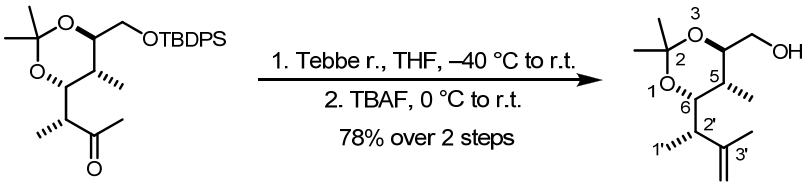
66 **68**

(*R*)-3-((4*R*,5*R*,6*R*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-one (68). To a solution of alkyne **66** (2.06 g, 4.60 mmol) in acetone (49 mL), PPTS (1.68 g, 6.90 mmol), $Hg(OAc)_2$ (0.427 g, 1.38 mmol) and water (0.158 mL, 9.2 mmol) were added. The resulting clear solution was stirred for 18 h at ambient temperature. After this time the mixture was diluted with Et_2O (ca. 20 mL). White precipitates were removed by filtration through a short pad of silica gel and washed with Et_2O (2 × 20 mL). The filtrate was concentrated in vacuo, and residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give methyl ketone **68** (1.62 g, 76%) as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +2.6 (*c* 2.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.77 (d, *J* = 6.9 Hz, 3H, 3-CH_3), 0.89 (d, *J* = 6.9 Hz, 3H, 5-CH_3), 1.05 (s, 9H, C(CH_3)$_3$), 1.24 (s, 3H, 2'-CH_3), 1.28 (s, 3H, 2'-CH_3), 1.72 (app. td, *J* = 6.9, 6.9, 4.5 Hz, 1H, 5-H), 2.14 (s, 3H. 2-CH_3), 2.67 (app. dq, *J* = 10.9, 6.9, 6.9, 6.9 Hz, 1H, 3-H), 3.37 (app. td *J* = 6.7, 6.7, 4.1 Hz, 1H, 6-H), 3.70 (m, 2H, CH_2OTBDPS), 3.83 (dd, *J* = 10.7, 4.3 Hz, 1H, 4-H), 7.35–7.43 (m, 6H, *m*CH, *p*CH ar Ph), 7.68–7.69 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.8 (5-CH_3), 12.3 (3-CH_3), 19.3 (*C*(CH_3)$_3$), 23.6 (2'-CH_3), 24.9 (2'-CH_3), 26.8 (C(*C*H_3)$_3$), 30.2 (2-CH_3), 33.4 (C-5), 46.6 (C-3), 65.9 (CH_2), 71.2 (C-6), 75.8 (C-4), 100.7 (C-2'), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of $SiPh_2$), 211.8 (C-2). HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{40}O_4SiNa$ 491.25881, found 491.258623.



68 **71**

(*R*)-4-((4*R*,5*R*,6*R*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-methylpent-1-en-3-ol (71). Ketone **68** (27.3 mg, 0.058 mmol) was dissolved in abs. THF (1.0 mL), cooled to –78 °C and then vinyl magnesium bromide (0.47 mL, 0.47 mmol, 1.0M in THF) was added dropwise. The cooling bath was removed and the reaction mixture in ca. 30 min. reached room temperature. Saturated NH_4Cl solution (0.5 mL) was introduced followed by dilution with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 5 mL). After drying and evaporating the solvent, the residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give alcohol **71** (18.9 mg, 65%). R_f = 0.29 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +42.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.75 (d, *J* = 6.9 Hz, 3H, 1-H), 0.80 (d, *J* = 6.9 Hz, 3H, 5'-CH_3), 1.04 (s, 9H, C(CH_3)$_3$), 1.19 (s, 3H, 3-CH_3), 1.33 (s, 6H, 2 ×2'-CH_3), 1.71 (app. tq, *J* = 6.9, 3.4, 3.4, 3.4, 3.4 Hz, 1H, 5'-H), 1.83 (app. dq, *J* = 10.8, 7.0, 7.0, 7.0 Hz, 1H, 2-H), 3.40 (app. td, *J* = 6.6, 6.6, 3.8 Hz, 1H, 6'-H), 3.61–3.72 (m, 3H, CH_2OTBDPS, 4'-H), 4.94 (s, 1H, OH), 5.13 (dd, *J* = 10.7, 1.8 Hz, 1H, 5-H), 5.36 (dd, *J* = 10.7, 1.8 Hz, 1H, 5-H), 5.97 (dd, *J* = 17.0, 10.7 Hz, 1H, 4-H), 7.34–7.43 (m, 6H, *m*CH, *p*CH ar Ph), 7.66–7.69 (m, 4H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 12.0 (2-CH_3, 5'-CH_3), 19.2 (*C*(CH_3)$_3$), 23.9 (2'-CH_3), 26.4 (2'-CH_3), 26.8 (C(*C*H_3)$_3$), 28.0 (3-CH_3), 34.0 (C-5'), 42.2 (C-2), 65.9 (CH_2OTBDPS), 73.2 (C-4'), 76.0 (C-6'), 76.2 (C-3), 101.1 (C-2'), 113.9 (C-5), 127.6, 127.7, 129.6, 129.7, 133.6, 133.7, 135.6, 135.7 (C of $SiPh_2$), 140.7 (C-4). $[M+Na]^+$ calcd for $C_{30}H_{44}O_4SiNa$ 519.29011, found 519.290362.

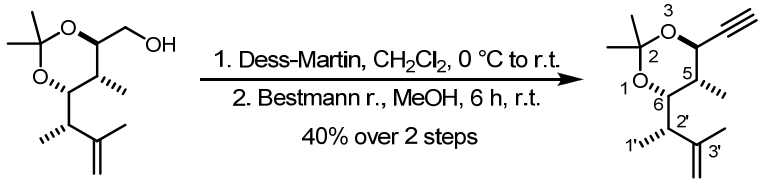


68 **77**

((4*R*,5*R*,6*S*)-2,2,5-Trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)methanol (77). *Tebbe olefination:* A solution of ketone **68** (0.577 g, 1.2 mmol) in abs. THF (4.0 mL) was cooled to –40 °C. Then a solution of Tebbe reagent[9] (6.70 mL, 4.8 mmol, 1.0M in $PhCH_3$) was added dropwise. After complete addition (ca. 20 min), the cooling bath was removed and stirring continued for additional 1 h. The reaction mixture was diluted with Et_2O (10 mL), and then 1N NaOH (ca. 2 mL) was added very

[9] For preparation, see: Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1993**, *8*, 512.

slowly, followed by anhydrous Na_2SO_4 (for drying). The resulting suspension was transferred on a wet silica column (ca. 10 cm long) and eluted with a petroleum ether/EtOAc mixture (40:1) to give Tebbe olefination product (0.527 g, 92%, R_f = 0.28, petroleum ether/EtOAc, 40:1), which was pure enough to be introduced to the next step. *Deprotection:* To cooled solution (ice/salt bath) of foregoing silyl ether in abs. THF (5 mL) was added TBAF·$3H_2O$ was added in one portion followed by stirring for 12 h. Saturated NH_4Cl solution was added, layers were separated, and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organics layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and the filtrate concentrated in vacuo. The residue was purified via flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **77** (0.30 g, 85%, 78% over 2 steps). R_f = 0.24 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +16.3 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.89 (d, *J* = 2.3 Hz, 3H, 2'-CH_3), 0.91 (d, *J* = 2.3 Hz, 3H, 5-CH_3), 1.28 (s, 3H, 2-CH_3), 1.32 (s, 3H, 2-CH_3), 1.68 (s, 3H, 3'-CH_3), 1.76 (m, 1H, 2'-H), 2.17 (br. s, 1H, OH), 2.29 (m, 1H, 5-H), 3.38 (ddd, *J* = 7.3, 7.3, 2.9 Hz, 1H, 4-H), 3.53–3.66 (m, 3H, CH_2, 6-H), 4.72 (d, *J* = 9.1 Hz, 2H, 3'=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.8 (5-CH_3), 16.0 (C-1'), 19.3 (3'-CH_3), 23.9 (2-CH_3), 25.1 (2-CH_3), 33.5 (C-2'), 41.0 (C-5), 64.4 (CH_2), 71.3 (C-4), 75.8 (C-6), 100.9 (C-2), 110.6 (3'=CH_2), 148.1 (C-3'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.32822, found 251.32856.

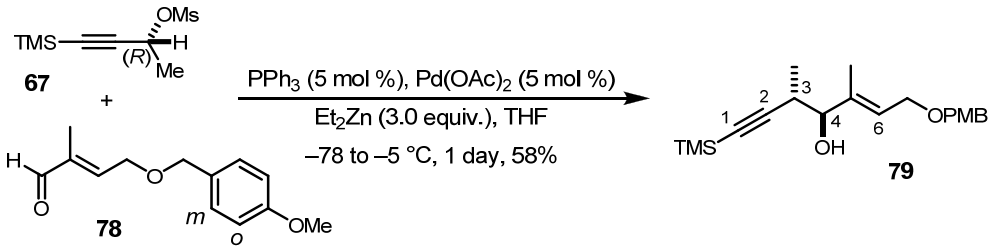


77 **75**

(4*R*,5*R*,6*S*)-4-Ethynyl-2,2,5-trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxane (75). *Oxidation*: To a cooled solution (ice/salt bath) of alcohol **77** (0.290 g, 1.27 mmol) in abs. CH_2Cl_2 (2.0 mL) were added solid $NaHCO_3$ (0.640 g, 7.62 mmol) and Dess-Martin periodinane (0.638 g, 1.52 mmol) were added. After being stirred for 20 min, the cooling bath was removed and the mixture stirred for additional 2 h. After this time, resulting suspension was transferred to a baker, which already contained mixture of saturated solutions of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 5 mL). The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated to give corresponding aldehyde and white solids, which were removed by filtration through a cotton plug and washing with Et_2O (ca. 3 mL). R_f = 0.57 (petroleum ether/EtOAc, 5:1). *Alkynylation*: To a solution of foregoing aldehyde in MeOH (5 mL) obtained above, was added diethyl-1-diazo-2-oxopropylphosphonate[10] (0.620 g, 2.54 mmol) and K_2CO_3 (0.701 g, 5.01 mmol). The resulting yellow solution was stirred for 6 h at room temperature. The

[10] For preparation, see: Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. Synth. Commun. **1987**, *17*, 1709.

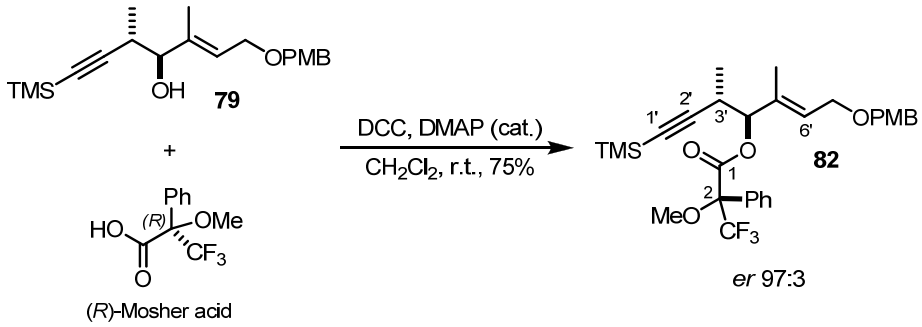
reaction mixture was diluted with Et_2O (20 mL) and washed with an aqueous 5% $NaHCO_3$ solution. The layers were separated and the organic layer was washed with saturated NaCl solution and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified via flash chromatography (petroleum ether/EtOAc, 80:1) to give alkyne **75** (0.113 g, 40% over 2 steps) as a colorless oil. R_f = 0.52 (petroleum ether/EtOAc, 40:1); $[\alpha]^{20}_D$ = +6.4 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.93 (d, *J* = 7.1 Hz, 3H, 2'-CH_3), 1.07 (d, *J* = 7.1 Hz, 3H, 5-CH_3), 1.33 (s, 3H, 2-CH_3), 1.53 (s, 3H, 2-CH_3), 1.70 (s, 3H, 3'-CH_3), 1.92 (app. qt, *J* = 6.9, 6.9, 6.9, 3.7, 3.5 Hz, 1H, 5-H), 2.29 (app. dq, *J* = 10.3, 7.0, 7.0, 7.0 Hz, 1H, 2'-H), 2.50 (d, *J* = 2.5 Hz, 1H, C≡CH), 4.01 (dd, *J* = 10.4, 3.0 Hz, 1H, 6-H), 4.33 (dd, *J* = 3.9, 2.4 Hz, 1H, 4-H), 4.74 (d, *J* = 6.3 Hz, 2H, 3'-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.3 (5-CH_3), 15.6 (C-1'), 19.2 (C-4'), 23.2 (2-CH_3), 28.2 (2-CH_3), 36.5 (C-6), 41.8 (C-2'), 66.9 (C-4), 70.1 (C-5), 73.8 (C≡*C*H), 84.4 (*C*≡CH), 100.8 (C-2), 110.8 (3'=CH_2), 147.9 (C-3'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{22}O_2Na$ 245.31308, found 245.31315.



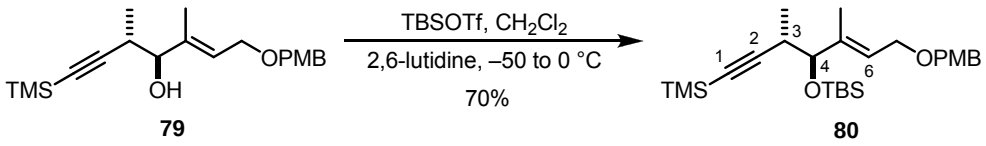
(3*S*,4*S*,*E*)-7-(4-Methoxybenzyloxy)-3,5-dimethyl-1-(trimethylsilyl)hept-5-en-1-yn-4-ol (79). A suspension of $Pd(OAc)_2$ (0.072 g, 0.32 mmol, 5 mol%) in abs. THF (40 mL) was cooled to –78 °C. Then finely powdered PPh_3 (0.085 g, 0.32 mmol, 5 mol%) was added under a slight flow of nitrogen. The resulting yellow solution was stirred for ca. 5 min. In separate flasks solutions of (*R*)-mesylate **67** (2.13 g, 9.67 mmol) and aldehyde[11] **78** (1.42 g, 6.45 mmol) were prepared (both containing 1.5 mL of abs. THF). Then both were added dropwise to a solution of prepared catalyst at the same time. The yellow solution was stirred for 20 min at –78 °C before Et_2Zn (19.4 mL, 19.3 mmol, 1.0M in hexane) was introduced over 30 min using syringe pump. After complete addition, the reaction was allowed to warm to –5 °C (the cooling machine was switched off: within ca. 50 min reaction mixture reached –5 °C) and stirred for ca. 1 d (TLC and HPLC monitoring). During this time color changed to dark brown. For work-up saturated NH_4Cl solution (ca. 100 mL) was added dropwise directly to the reaction mixture. After the mixture was warmed to room temperature, the layers were separated and the aqueous phase extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution and dried over Na_2SO_4 containing norite decolorizing charcoal. After filtration and evaporation of solvents, the residue was purified by flash chromatography (petroleum ether/EtOAc,

[11] For preparation, see: Kanada, R.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350.

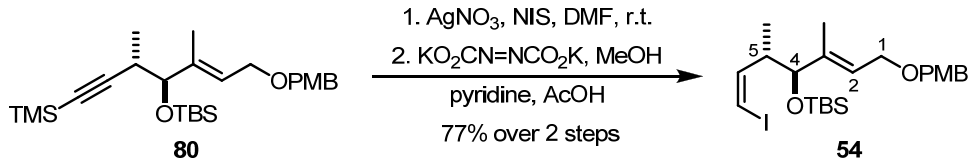
5:1) to give alcohol **79** (1.30 g, 58%) as a colorless oil. R_f = 0.36 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +10.6 (*c* 3.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.15 (s, 9H, TMS), 1.10 (d, *J* = 7.1 Hz, 3H, 3-CH_3), 1.61 (s, 3H, 5-CH_3), 2.67 (dq, J = 7.2, 7.0 Hz, 1H, 3-H), 3.79–3.80 (m, 4H, 4-H, OCH_3), 4.05 (d, *J* = 6.4 Hz, 2H, CH_2OPMB), 4.43 (s, 2H, CH_2PMP), 5.64 (dd, *J* = 6.2. 6.2 Hz, 1H, 6-H), 6.86 (d, *J* = 8.7 Hz, 2H, *m*CH ar Ph), 7.23 (d, *J* = 8.7 Hz, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 0.1 (TMS), 11.7 (5-CH_3), 17.5 (3-CH_3), 32.5 (C-3), 55.2 (OCH_3), 65.9 (C-7), 71.8 (CH_2PMP), 80.0 (C-4), 87.7 (C-1), 107.6 (C-2), 113.7 (*o*CH ar PMB), 125.6 (C-6), 129.3 (*m*CH ar PMB), 130.3 (*C*CH_2 ar PMB), 137.8 (C-5), 159.2 (*C*OCH_3); HRMS (ESI): $[M+K]^+$ calcd for $C_{20}H_{30}O_3SiK$ 385.15958, found 385.18061.



(*R*)-((3*S*,4*S*,*E*)-7-(4-Methoxybenzyloxy)-3,5-dimethyl-1-(trimethylsilyl)hept-5-en-1-yn-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (82). To a solution of alcohol **79** (50.0 mg, 0.14 mmol) in abs. CH_2Cl_2 (1 mL) were added (*R*)-Mosher acid (43.6 mg, 0.21 mmol), DCC (55.0 mg, 0.24 mmol) and DMAP (few crystals). After 1 h, the reaction mixture was concentrated and the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to yield Mosher ester **82** (61 mg, 70%) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +57.1 (*c* 5.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.05 (s, 9H, TMS), 1.06 (d, *J* = 7.1 Hz, 3H, 3'-CH_3), 1.31 (s, 3H, 5'-CH_3), 2.73–2.82 (m, 1H, 3'-H), 3.62 (s, 3H, 2-OCH_3), 3.75 (s, 3H, OCH_3 ar PMB), 3.96 (d, *J* = 6.4 Hz, 2H, 7'-H), 4.35 (s, 2H, CH_2PMP), 5.26 (d, *J* = 8.7 Hz, 1H, 4'-H), 5.70 (t, *J* = 6.0 Hz, 1H, 6'-H), 6.82–6.84 (m, 2H, ar-H), 7.19–7.21 (m, 2H, ar-H), 7.25–7.32 (m, 5H, ar-H), 7.47–7.49 (m, 2H, ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –0.1 (TMS), 11.8 (5'-CH_3), 17.5 (3'-CH_3), 29.6 (C-3'), 55.2 (OCH_3), 56.0 (OCH_3), 65.4 (C-7'), 71.7 (CH_2PMP), 83.1 (C-2), 83.7 (C-1'), 84.4, 84.6 (C-2), 86.5 (C-4'), 107.4 (C-2'), 113.8 (C aryl), 127.2 (C-6'), 128.2 (C aryl), 128.3 (CF_3) 129.2, 129.4, 129.4 (C=O aryl), 130.1 (CF_3), 132.4, 133.4, 159.2 (C=O aryl), 165.4 (C=O ester).

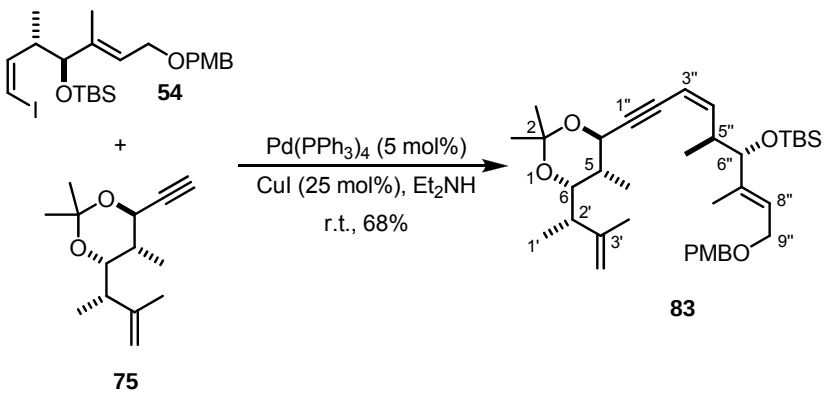


((3*S*,4*S*,*E*)-4-*tert*-Butyldimethylsilyloxy-7-(4-methoxybenzyloxy)-3,5-dimethylhept-5-en-1-ynyl)trimethylsilane (80). Alcohol **79** (1.12 g, 3.23 mmol) was dissolved in abs. CH_2Cl_2 (15 mL) and cooled to –50 °C. 2,6-Lutidine (1.12 mL, 9.7 mmol) was added followed by TBSOTf (0.97 mL, 4.2 mmol). The cooling bath was removed and the mixture was allowed to stir overnight. Then it was diluted with water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 1N HCl solution, saturated solutions of $NaHCO_3$ (20 mL) and NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Flash chromatography (petroleum ether/EtOAc, 20:1) of the residue gave silyl ether **80** (1.04 g, 70%) as a colorless oil. R_f = 0.51 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +9.9 (*c* 9.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.01 (s, 3H, Si(C*H*$_3$)$_2$*t*Bu), 0.09 (s, 3H, Si(C*H*$_3$)$_2$*t*Bu), 0.12 (s, 9H, TMS), 0.89 (s, 9H, *t*Bu), 1.00 (d, *J* = 7.1 Hz, 3H, 3-CH_3), 1.56 (s, 3H, 5-CH_3), 2.57 (m, 1H, 3-H), 3.80 (s, 3H, OCH_3), 3.88 (d, *J* = 8.1 Hz, 1H, 4-H), 4.03 (d, *J* = 4.0 Hz, 2H, CH_2OPMB), 4.41 (s, 2H, CH_2PMP), 5.52 (dd, *J* = 6.1, 6.1 Hz, 1H, 6-H), 6.87 (d, *J* = 8.7 Hz, 2H, *m*CH ar Ph), 7.24 (d, *J* = 8.7 Hz, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 (Si(CH_3)$_2$*t*Bu), –4.7 (Si(CH_3)$_2$*t*Bu), 0.2 (TMS), 11.4 (5-CH_3), 17.7 (3-CH_3), 18.3 (*C*(CH_3)$_3$), 25.9 (C(*C*H_3)$_3$), 32.8 (C-3), 55.3 (OCH_3), 65.9 (C-7), 71.5 (CH_2OPMP), 81.6 (C-4), 84.8 (C-1), 110.4 (C-2), 113.8 (*o*CH ar PMB), 125.0 (C-6), 129.3 (*m*CH ar PMB), 130.5 (*C*CH_2 ar PMB), 139.2 (C-5), 159.1 (*C*OCH_3); HRMS (ESI): $[M+H]^+$ calcd for $C_{26}H_{45}O_3Si_2$ 461.29017, found 461.19662.



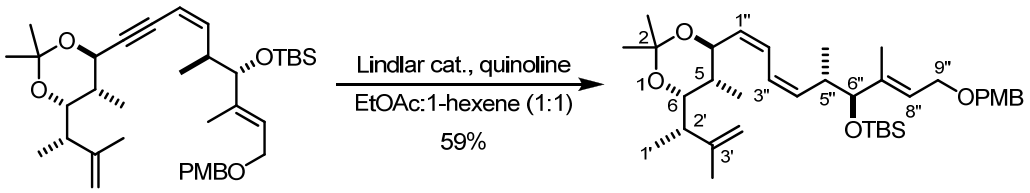
1-(((2*E*,4*S*,5*S*,6*Z*)-4-*tert*-Butyldimethylsilyloxy-7-iodo-3,5-dimethylhepta-2,6-dienyloxy)methyl)-4-methoxybenzene (54). To a solution of silyl acetylene **80** (0.627 g, 1.36 mmol) in dry DMF (2 mL) were added NIS (0.470 g, 1.92 mmol) and $AgNO_3$ (0.054 g, 0.32 mmol). The resulting solution was protected from light and stirred for 5 h at ambient temperature. Then the reaction mixture was diluted with EtOAc (20 mL), washed with water (2 × 10 mL), dried over $NaSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give corresponding iodoalkyne (0.767 g, 94%) as slightly yellow oil. It was introduced directly to the next step. *Z-selective reduction*: To a solution of foregoing iodoalkyne (0.767 g, 1.49 mmol) in abs. MeOH (6.0 mL) were added pyridine (0.725 mL, 8.95 mmol) and $KO_2CN=NCO_2K$ (1.49 g, 7.45 mmol) followed by the slow addition of acetic acid (0.5 mL, 8.95 mmol) over 6 h (syringe pump used). After this time,

the mixture was diluted with EtOAc (20 mL), washed with water (2 × 20 mL), saturated $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give *Z*-iodoalkene **54** (0.629 g, 82%, 77% over 2 steps) as a slightly yellow oil. R_f = 0.45 (petroleum ether/EtOAc, 20:1); $[\alpha]^{20}_D$ = –15.6 (*c* 2.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = –0.01 (s, 3H, Si(C*H*$_3$)$_2$*t*Bu), 0.04 (s, 3H, Si(C*H*$_3$)$_2$*t*Bu), 0.90 (s, 9H, *t*Bu), 0.94 (d, *J* = 6.9 Hz, 3H, 5-CH_3), 1.61 (s, 3H, 3-CH_3), 2.67-2.76 (m, 1H, 5-H), 3.80 (s, 3H, OCH_3), 3.91 (d, *J* = 5.1 Hz, 1H, 4-H), 4.06 (d, *J* = 6.4 Hz, 2H, CH_2OPMB), 4.42 (s, 2H, CH_2OPMP), 5.54 (dd, *J* = 6.4, 6.4 Hz, 1H, 2-H), 6.07 (dd, *J* = 8.9, 7.4 Hz, 1H, 6-H), 6.15 (d, *J* = 7.4 Hz, 1H, 7-H), 6.88 (d, *J* = 8.7, 2H, *m*CH ar Ph), 7.26 (d, *J* = 8.7, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.1 (Si(CH_3)$_2$*t*Bu), –4.5 (Si(CH_3)$_2$*t*Bu), 12.6 (5-CH_3), 16.6 (3-CH_3), 18.1 (*C*(CH_3)$_3$), 25.8 (C(*C*H$_3$)$_3$), 44.1 (C-5), 55.2 (OCH_3), 65.9 (C-1), 71.3 (CH_2PMP), 80.6 (C-7), 81.7 (C-4), 113.7 (*o*CH ar PMB), 123.5 (C-2), 129.2 (*m*CH ar PMB), 130.6 (*C*CH_2 ar PMB), 139.8 (CH_2OPMP), 143.7 (C-6), 159.1 (*C*OCH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{37}IO_3SiNa$ 539.14489, found 539.145186.



(4*R*,5*R*,6*S*)-4-((3*Z*,5*S*,6*S*,7*E*)-6-*tert*-Butyldimethylsilyloxy-9-(4-methoxybenzyloxy)-5,7-dimethylnona-3,7-dien-1-ynyl)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxane (83). To a Schlenk tube were added *Z*-iodoalkene **54** (16.3 mg, 0.032 mmol) and alkyne **75** (7.0 mg, 0.032 mol). Then freshly distilled Et_2NH (1 mL) was added followed by CuI (1.5 mg, 0.008 mmol, 25 mol%) and $Pd(PPh_3)_4$ (1.9 mg, 0.0016 mmol, 5 mol%). The resulting solution was allowed to stir for 2 h at r.t. After this time, the solvent was evaporated under nitrogen flow and Et_2O (3 mL) and sat. NH_4Cl (1 mL) were introduced. The layers were separated and the organic layer washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 30:1) to give enyne **83** (13.5 mg, 68%) as a slightly yellow oil. R_f = 0.59 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = +61.0 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = –0.03 (Si(C*H*$_3$)$_2$*t*Bu), 0.01 (Si(C*H*$_3$)$_2$*t*Bu), 0.87 (s, 9H, *t*Bu), 0.91 (d, *J* = 3.0 Hz, 3H, 2'-CH_3), 0.93 (d, *J* = 3.0 Hz, 3H, 5''-CH_3), 1.07 (d, *J* = 7.0 Hz, 3H, 5-CH_3), 1.33 (s, 3H, 2-CH_3), 1.55 (s, 3H, 2-CH_3), 1.57 (s, 3H, 7''-CH_3), 1.69 (s, 3H, 3'-CH_3), 1.85–1.88 (m, 1H, 5-H), 2.25–2.33 (m, 1H, 2'-H), 2.87–2.95 (m, 1H,

5''-H), 3.80 (s, 3H, OCH_3), 3.81–3.82 (m, 1H, 6''-H), 4.01–4.04 (m, 3H, 6-H, CH_2OPMB), 4.40 (s, 2H, CH_2PMP), 4.47–4.54 (m, 1H, 4-H), 4.74 (d, *J* = 5.6 Hz, 2H, 3'-CH_2), 5.47–5.43 (m, 2H, 3''-H, 8''-H), 5.83 (dd, *J* = 10.2 Hz, 1H, 4''-H), 6.87 (d, *J* = 8.7 Hz, 2H, *m*CH ar Ph), 7.24 (d, *J* = 8.7 Hz, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.0 ($Si(CH_3)_2tBu$), –4.5 ($Si(CH_3)_2tBu$), 11.3 (5-CH_3), 12.3 (C-4'), 15.6 (2'-CH_3), 17.6 (5''-CH_3), 18.2 ($C(CH_3)_3$), 19.2 (7''-CH_3), 23.4 (2-CH_3), 25.8 ($C(CH_3)_3$), 28.7 (2-CH_3), 36.4 (C-5), 39.8 (C-5''), 41.9 (C-2'), 55.3 (OCH_3), 65.9 (C-1), 67.9 (C-4), 70.2 (C-6), 71.3 (CH_2PMP), 81.4 (C-1''), 82.9 (C-6''), 93.0 (C-2''), 100.4 (C-2), 108.5 (C-3''), 110.5 (3'-CH_2), 113.8 (*o*CH ar PMB), 123.6 (C-8''), 129.3 (*m*CH ar PMB), 130.6 (CCH_2 ar PMB), 140.0 (C-7''), 147.0 (C-4''), 148.0 (C-3'), 159.1 ($COCH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{37}H_{58}O_5SiNa$ 633.92865, found 633.92893.

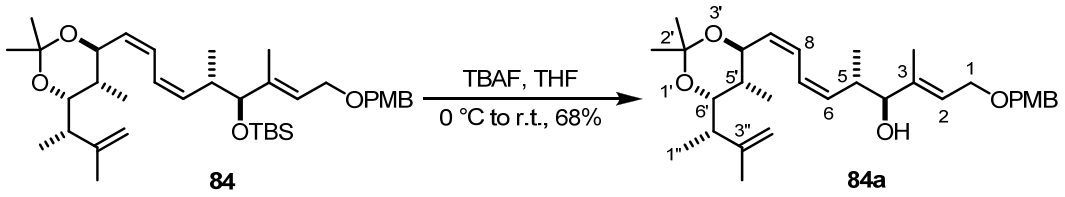


83 **84**

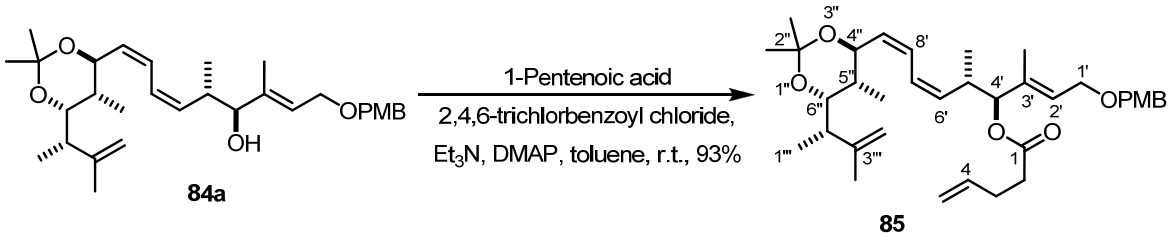
(4*S*,5*S*,6*S*)-4-((1*Z*,3*Z*,5*S*,6*S*,7*E*)-6-*tert*-Butyldimethylsilyloxy-9-(4-methoxybenzyloxy)-5,7-dimethylnona-1,3,7-trienyl)-2,2,5-trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxane (84). Enyne **83** (51.5 mg, 0.08 mmol) was dissolved in a mixture of abs. EtOAc and 1-hexene (1:1, 10 mL) and Lindlar cat.[12] (5 wt% Pd on $CaCO_3$, poisoned with lead, 25.8 mg, 50 wt%) and quinoline (25.8 mg, 0.20 mmol) were added. The flask was closed with a rubber septum and a balloon with hydrogen was attached. The system was filled with hydrogen and stirred for 36 h (HPLC monitoring). Then the solvents were evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 30:1) to give *Z*,*Z*-diene **84** (30.6 mg, 59%) as a colorless oil. R_f = 0.59 (petroleum ether/EtOAc, 10:1); $[\alpha]^{20}_D$ = –12.6 (*c* 0.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = –0.04 ($Si(CH_3)_2tBu$), 0.01 ($Si(CH_3)_2tBu$), 0.84 (m, 12H, *t*Bu, 5''-CH_3), 0.85 (d, *J* = 2.3 Hz, 5-CH_3), 0.87 (d, *J* = 6.8 Hz, 3H, 2'-CH_3), 1.31 (s, 3H, 2-CH_3), 1.37 (s, 3H, 2-CH_3), 1.58 (s, 3H, 7''-CH_3), 1.70 (s, 3H, 3'-CH_3), 1.77 (app. ddq, *J* = 13.9, 11.6, 6.8 Hz, 1H, 5-H), 2.32 (app. dq, *J* = 10.7, 6.9 Hz, 1H, 2'-H), 2.79 (app. ddq, *J* = 16.8, 14.0, 7.3 Hz, 1H, 5''-H), 3.69–3.75 (m, 2H, 6-H, 6''-H), 3.80 (s, 3H, OCH_3), 4.03 (d, *J* = 6.3 Hz, 2H, 9''-H), 4.23 (dd, *J* = 8.2, 8.2 Hz, 1H, 4'-H), 4.40 (s, 2H, CH_2PMP), 4.73 (d, *J* = 12.9 Hz, 2H, 3'-CH_2), 5.39–5.44 (m, 2H, 4''-H, 1''-H), 5.47–5.53 (m, 1H, 8''-H), 6.28 (dd, *J* = 11.4, 11.4 Hz, 1H, 3''-H), 6.43 (dd, *J* = 11.4, 11.4 Hz, 1H, 2''-H), 6.86 (d, *J* = 8.7 Hz, 2H, *m*CH ar Ph), 7.24 (d, *J* = 8.7 Hz, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.0 ($Si(CH_3)_2tBu$), –4.5 ($Si(CH_3)_2tBu$), 10.9 (5-CH_3), 11.9 (7''-CH_3), 16.1 (C-2'), 17.9 (5''-CH_3), 18.2 ($C(CH_3)_3$), 19.2 (C-4'), 24.3 (2-CH_3), 25.8 (2-CH_3), 25.9 ($C(CH_3)_3$), 36.7 (C-5''), 39.0 (C-5), 41.3 (C-2'), 55.3 (OCH_3), 65.9 (C-9''), 70.7 (C-4'), 71.0 (C-6), 71.4 (CH_2PMP), 82.2 (C-

[12] Catalyst was ordered from Merck Schuchardt OHG company. Product number in catalog: 8.10489.0005

6''), 100.8 (C-2), 110.6 (3'-CH_2), 113.8 (*o*CH ar PMB), 123.1(C-3''), 124.0 (C-8''), 126.9 (C-2''), 129.3 (*m*CH ar PMB), 129.8 (C-4''), 130.6 (*C*CH_2 ar PMB), 138.0 (C-1'), 140.2 (C-7''), 148.3 (C-3'), 159.1 (*C*OCH_3); HRMS (ESI): [M+Na] calcd for $C_{37}H_{60}O_5SiNa$ 635.41022, found 635.41073.

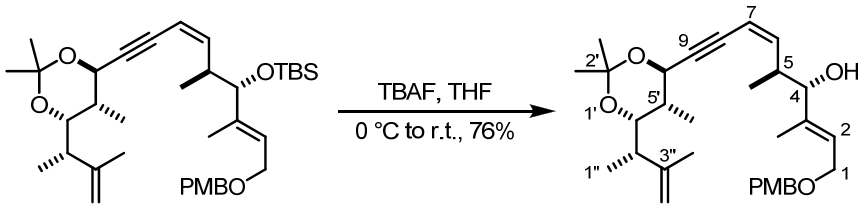


(2E,4S,5S,6Z,8Z)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4S,5S,6S)-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6,8-trien-4-ol (84a). Silyl ether **84** (30.6 mg, 0.048 mmol) was dissolved in abs. THF (1 mL) and cooled in an ice/salt bath. Then TBAF·$3H_2O$ was added in one portion and the resulting solution was allowed to stir for 12 h. The reaction mixture was diluted with EtOAc (10 mL) and saturated NH_4Cl solution (3 mL). The layers were separated and aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was then purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **84a** (16.9 mg, 68%) as a colorless oil, which was directly introduced to the next step. R_f = 0.72 (petroleum ether/EtOAc, 1:1).



(2*E*,4*S*,5*S*,6*Z*,8*Z*)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4*S*,5*S*,6*S*)-2,2,5-trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6,8-trien-4-yl pent-4-enoate (85). A round bottom flask was charged with alcohol **84a** (6.0 mg, 0.012 mmol), abs. toluene (0.4 mL) and 4-pentenoic acid (1.5 µL, 0.015 mmol) followed by abs. Et_3N (5.1 µL, 0.036 mmol). Then 2,4,6-trichlorbenzoyl chloride (2.3 µL, 0.015 mmol) was added and the resulting solution stirred for 40 min. After this time, solution of DMAP (1.5 mg, 0.012 mmol) in abs. toluene (0.2 mL) was added and the resulting solution stirred for 30 min. White solids formed. Toluene was evaporated under a flow of nitrogen and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ester **85** (6.5 mg, 93%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +8.5 (*c* 1.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.86 (d, *J* = 6.8 Hz, 3H, 5''-CH_3), 0.91 (d, *J* = 1.8, 3H, 2'''-CH_3), 0.92 (d, *J* = 1.6 Hz, 3H, 7'-CH_3), 1.31 (s, 3H, 2''-CH_3), 1.36 (s, 3H, 2''-CH_3), 1.63 (s, 3H, 3'-CH_3), 1.70 (s, 3H, 3'''-CH_3), 1.76 (m, 1H, 5''-H), 2.27–2.40 (m, 5H, 2'''-H, 2-H, 3-H), 2.95–3.04 (m, 1H, 5'-H), 3.71 (dd, *J* = 10.9, 4.6 Hz, 1H,

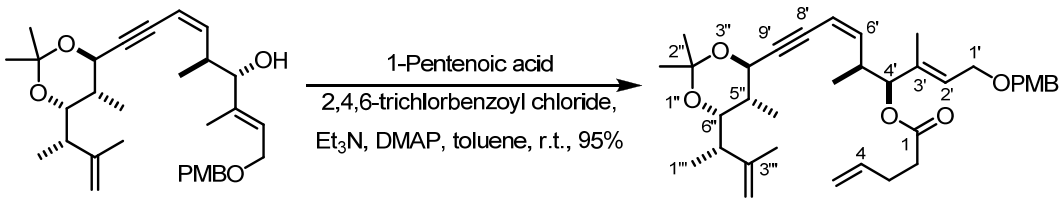
6''-H), 3.79 (s, 3H, OCH_3), 4.02 (d, *J* = 6.3 Hz, 2H, 1'-H), 4.22 (m, 1H, 4''-H), 4.40 (s, 2H, CH_2PMP), 4.73 (d, *J* = 11.6 Hz, 2H, 3'''-CH_2), 4.91–5.06 (m, 3H, 5-H, 4'-H), 5.35 (dd, *J* = 10.4, 10.4 Hz, 1H, 6'-H), 5.49 (dd, *J* = 10.4, 10.4 Hz, 1H, 9'-H), 5.65 (dd, *J* = 6.2, 6.2 Hz, 1H, 2'-H), 5.72–5.83 (m, 1H, 4-H), 6.31 (dd, *J* = 11.4, 11.4 Hz, 1H, 7'-H), 6.42 (dd, *J* = 11.4, 11.4 Hz, 1H, 8'-H), 6.86 (d, *J* = 8.6 Hz, 2H, *m*CH ar Ph), 7.24 (d, *J* = 8.6 Hz, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.0 (5''-CH_3), 12.7 (3'-CH_3), 16.1 (C-1'''), 17.3 (7'-CH_3), 19.2 (3'''-CH_3), 24.2 (2''-CH_3), 24.9 (2''-CH_3), 28.8 (C-3), 33.7 (C-2), 34.3 (C-5'), 39.0 (C-5), 41.3 (C-2'''), 55.3 (OCH_3), 65.7 (C-1'), 70.6 (C-4''), 71.0 (C-6''), 71.7 (CH_2PMP), 81.6 (C-4'), 100.9 (C-2''), 110.6 (3'''-CH_2), 113.8 (*o*CH ar PMB), 115.3 (C-5), 124.0 (C-7'), 126.1 (C-8'), 126.6 (C-2'), 129.4 (*m*CH ar PMB), 130.3 (C-9'), 130.9 (*C*CH_2 ar PMB), 135.3 (C-6'), 135.8 (C-4), 136.7 (C-3'), 148.1 (C-3'''), 159.2 (*C*OCH_3), 171.9 (C-1). HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{52}O_6Na$ 603.36561, found 603.36559.



83 **86**

(2*E*,4*S*,5*S*,6*Z*)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4*R*,5*R*,6*S*)-2,2,5-trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6-dien-8-yn-4-ol (86). To a cooled (ice/salt bath) solution of TBS ether **83** (10.0 mg, 0.016 mmol) in abs. THF (1.0 mL) was added solid TBAF·$3H_2O$ in one portion. Then the flask was removed from the cooling bath and allowed to stir overnight at room temperature. The reaction was diluted with Et_2O (10 mL) and washed with saturated NH_4Cl solution. The aqueous phase was additionally extracted with Et_2O (3 × 5 mL) and the combined organic layers dried over Na_2SO_4. After filtration the solvent was evaporated, and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol **86** (6.0 mg, 76%). R_f = 0.72 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = +71.0 (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.92 (d, *J* = 6.8 Hz, 3H, 2''-CH_3), 0.95 (d, *J* = 7.0 Hz, 3H, 5-CH_3), 1.08 (d, *J* = 7.0 Hz, 3H, 5'-CH_3), 1.33 (s, 3H, 2'-CH_3), 1.54 (s, 3H, 2'-CH_3), 1.63 (s, 3H, 3-CH_3), 1.69 (s, 3H, 3''-CH_3), 1.90 (app. ddq, *J* = 10.2, 6.8, 3.4 Hz, 1H, 5'-H), 2.29 (app. ddq, *J* = 13.9, 10.5, 7.0 Hz, 1H, 2''-H), 2.96 (app. ddq, *J* = 9.5, 7.2, 7.2 Hz, 1H, 5-H), 3.79–3.82 (m, 4H, OCH_3, 4-H), 3.97–4.06 (m, 3H, CH_2OPMB, 6'-H), 4.43 (m, 2H, CH_2PMP), 4.50 (dd, *J* = 3.5, 2.0 Hz, 1H, 4'-H), 4.73–4.75 (m, 2H, 3''-CH_2), 5.60–5.64 (m, 2H, 7-H, 2-H), 5.79–5.88 (m, 1H, 6-H), 6.85–6.89 (m, 2H, *m*CH ar Ph), 7.24–7.26 (m, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.3 (5'-CH_3), 11.8 (3-CH_3), 15.6 (2''CH_3), 17.2 (5-CH_3), 19.3 (3''-CH_3), 23.4 (2'-CH_3), 28.5 (2'-CH_3), 36.5 (C-5'), 38.8 (C-5), 41.9 (C-2''), 55.3 (OCH_3), 65.9 (CH_2OPMB), 67.8 (C-4'), 70.3 (C-6'), 71.9 (CH_2PMP), 81.1 (C-4), 82.2 (C-8), 94.1 (C-9), 100.5 (C-2'), 110.2 (C-2), 110.8 (3''-CH_2), 113.8 (*o*CH ar PMB), 124.9 (C-7), 129.4 (*m*CH ar PMB), 130.4 (*C*CH_2 ar PMB), 139.0 (C-3), 145.8 (C-6),

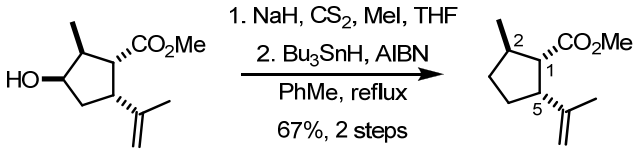
147.9 (C-3''), 159.2 (*C*OCH$_3$); HRMS (ESI): [M+Na]$^+$ calcd for $C_{31}H_{44}O_5SiNa$ 519.30810, found 519.30844.



86 **87**

(2*E*,4*S*,5*S*,6*Z*)-1-(4-Methoxybenzyloxy)-3,5-dimethyl-9-((4*R*,5*R*,6*S*)-2,2,5-trimethyl-6-((*S*)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)nona-2,6-dien-8-yn-4-yl pent-4-enoate (87). A round bottom flask was charged with alcohol **86** (9.0 mg, 0.018 mmol), abs. toluene (0.6 mL) and 4-pentenoic acid (2.3 µL, 0.023 mmol) followed by abs. Et_3N (7.7 µL, 0.054 mmol). Then 2,4,6-trichlorbenzoyl chloride (3.5 µL, 0.029 mmol) was added and the resulting solution stirred for 40 min. After this time, solution of DMAP (2.3 mg, 0.018 mmol) in abs. toluene (0.4 mL) was added and the resulting solution stirred for 30 min. White solids formed. Toluene was evaporated under a flow of nitrogen and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ester **87** (10.0 mg, 95%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc, 5:1); $[\alpha]^{20}_D$ = +75.0 (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.92 (d, *J* = 7.1 Hz, 3H, 2'''-CH_3), 0.96 (d, *J* = 6.8 Hz, 3H, 5'-CH_3), 1.07 (d, *J* = 6.8 Hz, 3H, 5''-CH_3), 1.34 (s, 3H, 2''-CH_3), 1.54 (s, 3H, 2''-CH_3), 1.63 (s, 3H, 3'-CH_3), 1.69 (s, 3H, 3'''-CH_3), 1.90 (app. qt, *J* = 6.7, 6.7, 6.7, 3.4, 3.4 Hz, 1H, 5''-H), 2.26–2.42 (m, 5H, 3-H, 2-H, 2'''-H), 3.08–3.17 (m, 1H, 5'-H), 3.79 (s, 3H, OCH_3), 3.97–4.05 (m, 3H, CH_2OPMB, 6''-H), 4.40 (s, 2H, CH_2PMP), 4.50 (dd, *J* = 3.4, 1.9 Hz, 1H, 4''-H), 4.73–4.77 (m, 2H, 3'''-CH_2), 4.96–5.09 (m, 3H, 4'-H, 5-H), 5.49–5.54 (m, 1H, 7'-H), 5.60 (app. t, *J* = 6.3, 6.3 Hz, 1H, 2'-H), 5.71–5.84 (m, 2H, 6'-H, 4-H), 5.85–5.87 (m, 2H, *m*CH ar Ph), 7.23–7.25 (m, 2H, *o*CH ar Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.3 (5''-CH_3), 12.8 (2'-CH_3), 15.6 (2'''-CH_3), 17.0 (5'-CH_3), 19.3 (3'''-CH_3), 23.4 (2''-CH_3), 28.5 (2''-CH_3), 28.8 (C-3), 33.7 (C-2'''), 36.6 (C-5'), 37.3 (C-5''), 41.9 (C-2), 55.3 (OCH_3), 65.7 (CH_2OPMB), 67.8 (C-4''), 70.3 (C-6''), 71.6 (CH_2PMP), 81.0 (C-4'), 82.2 (C-8'), 93.9 (C-9'), 100.4 (C-2''), 109.7 (C-2'), 110.8 (3'''-CH_2), 113.8 (*o*CH ar PMB), 115.4 (C-5), 125.9 (C-7'), 129.4 (*m*CH ar PMB), 130.3 (*C*CH_2 ar PMB), 135.2 (C-3'), 136.7 (C-6'), 145.0 (C-4), 147.8 (C-3'''), 159.2 (*C*OCH_3), 172.0 (C=O). HRMS (ESI): [M+Na]$^+$ calcd for $C_{36}H_{50}O_6Na$ 601.34996, found 601.349374.

III. Approach Towards the Total Synthesis of Terpene (–)-Englerin A

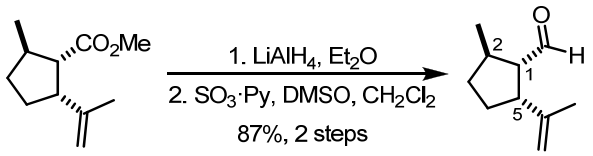


143 **144**

(1*S*,2*R*,5*R*)-Methyl 2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate (144). *Xanthate formation*: NaH (60% dispersion in oil, 22.0 g, 550 mmol) was added to a stirred solution of alcohol[13] **143** (11.2 g, 57.0 mmol) and imidazole (ca. 300 mg) in THF (200 mL) at 0 °C. The cooling bath was removed. After 15 min the reaction was recooled to 0 °C and CS_2 (38 mL, 612 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature and after 1 h recooled to 0 °C before MeI (40 mL, 600 mmol) was added dropwise. After 3 h the reaction was quenched by careful addition of water (200 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in petroleum ether) to give the titled xanthate (16.2 g, 98%) as a yellow oil which was directly introduced to the next step. R_f = 0.43 (petroleum ether/EtOAc, 9:1). *Reduction*: Tributylstannane (20.0 mL, 77.0 mmol) was added to a stirred solution of xanthate (16.2 g, 56.0 mmol) in dry toluene (200 mL) under N_2. The mixture was stirred for 5 min, and then AIBN (ca. 100 mg) was added. The resulting mixture was heated under reflux for 1 h and then the reaction was allowed to cool to ambient temperature, washed with water (3 × 100 mL) and saturated NaCl solution (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting colorless oil was distilled under reduced pressure (b.p. 90–95 °C, 25 mbar) to afford the title compound **144** (6.9 g, 67%, over 2 steps). R_f = 0.60 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +19.8 (*c* 1.00, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.02 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.16 (dddd, *J* = 12.5, 10.5, 8.7, 7.8 Hz, 1H, 3-H), 1.71 (s, 3H, CH_2=CC*H*$_3$), 1.71–1.77 (m, 1H, 4-H), 1.83 (dddd, *J* = 12.6, 10.2, 10.2, 7.6 Hz, 1H, 4-H), 2.02 (dddd, *J* = 12.5, 7.7, 7.7, 2.4 Hz, 1H, 3-H), 2.41 (dddq, *J* = 14.2, 14.2, 6.6, 6.6 Hz, 1H, 2-H), 2.56 (dd, *J* = 8.9, 6.1 Hz, 1H, 1-H), 2.76 (ddd, *J* = 9.4, 9.4, 6.7 Hz, 1H, 5-H), 3.55 (s, 3H, OCH_3), 4.67 (br s, 1H, C*H*$_2$=CCH_3), 4.72 (br s, 1H, C*H*$_2$=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.2 (CH*C*H$_3$), 22.6 (CH_2=C*C*H$_3$), 29.7 (C-4), 33.7 (C-3), 36.9 (C-2), 49.7 (C-5), 51.0 (OCH_3), 55.6 (C-1), 110.7 (*C*H$_2$=CCH_3), 145.5 (CH_2=*C*CH_3), 175.1 (*C*O$_2$$CH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{18}O_2Na$ 205.11990, found 205.11972; The spectral data are identical to those previously reported.[14]

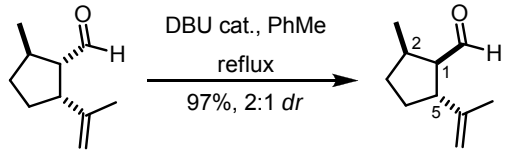
[13] Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Högenauer, K.; Simic, O.; Antonello, A.; Hünger, U.; Smith, M. D.; Ley, S. V. *Chem. Eur. J.* **2007**, *13*, 5688.

[14] Dawson, G. W.; Pickett, J. A.; Smiley, D. W. M. *Bioorg. Med. Chem.* **1996**, *4*, 351.



144 **145**

(1*S*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehyde (145). *Reduction*: a solution of ester **144** (25.1 g, 0.14 mol) in diethyl ether (200 mL) was added dropwise to a suspension of lithium aluminium hydride (6.3 g, 0.17 mol) in diethyl ether (300 mL) at 0 °C. The mixture was stirred at room temperature for 2 d and then was quenched by careful addition of 15% NaOH (70 mL) and water (200 mL). Stirring was continued for 15 min, before $MgSO_4$ was added, the mixture stirred for additional 15 min, and filtered to remove salts. Evaporation of the solvent yielded crude alcohol (21.0 g), which was introduced to the next reaction without further purification. R_f = 0.25 (petroleum ether/EtOAc, 9:1). To a stirred solution of the foregoing alcohol (21.0 g, 0.14 mol) in CH_2Cl_2 (700 mL) were added at room temperature Et_3N (230 mL, 1.66 mol) and a solution of SO_3×Py (125 g, 0.78 mol) in DMSO (400 mL). The reaction mixture was stirred for 1 h before it was quenched with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water (200 mL), 1 N HCl (2 × 200 mL), water (2 × 200 mL), saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 100–105 °C, 25 mbar) to give aldehyde **145** as a colorless oil (18.0 g, 87%, over 2 steps). R_f = 0.65 (petroleum ether/EtOAc, 9:1); The spectral data are identical to those previously reported.[15]

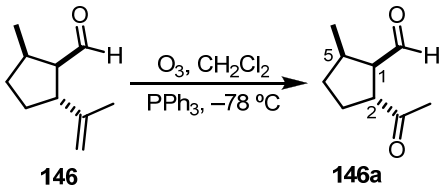


145 **146**

(1*R*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehyde (146). DBU (0.2 mL) was added to a stirred solution of aldehyde **145** (17.0 g, 0.11 mol) in toluene (150 mL). The resulting mixture was stirred under reflux for 2 d. Then the solvent was carefully evaporated to afford a mixture of two stereoisomers **146/145** in a ratio of 2:1 (16.5 g, 97%) [as determined by ^{1}H NMR spectroscopy via integration of the aldehyde signals (**145**: 9.48 ppm, **146**: 9.72 ppm). ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.98 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.13–1.34 (m, 2H), 1.43–1.54 (m, 1H), 1.84–2.02 (m, 1H), 1.63 (s, 3H, C*H*$_3$C=CH$_2$), 2.41–2.49 (m, 1H, 2-H), 2.62 (ddd, *J* = 8.7, 8.7, 3.4 Hz, 1H, 1-H), 2.98 (ddd, *J* = 8.5,

[15] Sakai, T.; Morita, K.; Matsumura, C.; Sudo, A.; Tsuboi, S.; Takeda, A. *J. Org. Chem.* **1981**, *46*, 4774.

8.5, 8.5 Hz, 1H, 5-H), 4.64 (br s, 1H, $CH_3C=CH_2$), 4.65 (br s, 1H, $CH_3C=CH_2$), 9.72 (d, *J* = 3.8 Hz, 1H, CH=O).



146 **146a**

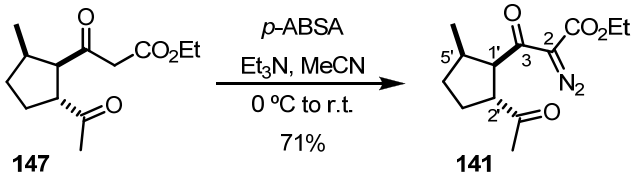
(1*R*,2*R*,5*R*)-2-Acetyl-5-methylcyclopentanecarbaldehyde (146a). Nitrogen was bubbled through the solution of aldehyde **146** (4.0 g, 27 mmol) in CH_2Cl_2 (40 ml) at –78 °C before ozone was bubbled until a deep blue color was observed. Nitrogen was again applied until no blue color remained. After the addition of PPh_3 (10.5 g, 40 mmol) the reaction mixture was stirred overnight at room temperature. R_f (ketoaldehyde **146a**) = 0.43 (petroleum ether/EtOAc, 4:1). This solution was used as such for the subsequent keto ester formation. An analytical sample was prepared after evaporation of the solvent followed by flash chromatography (petroleum ether/Et_2O, 9:1). $[\alpha]^{20}_D$ = +25.5 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.32 (ddd, *J* = 15.4, 12.5, 7.6 Hz, 1H, 4-H), 1.65 (ddd, *J* = 16.1, 12.8, 8.0 Hz, 1H, 3-H), 1.88 (dddd, *J* = 12.6, 7.8, 6.4, 5.0 Hz, 1H, 4-H), 2.10 (dddd, *J* = 9.9, 7.5, 5.0, 2.5 Hz, 1H, 3-H), 2.17 (s, 3H, $CH_3C=O$), 2.56 (app dddq, *J* = 14.5, 14.5, 7.4, 7.1 Hz, 1H, 5-H), 3.25 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H, 1-H), 3.48 (ddd, *J* = 9.5, 7.6, 7.5 Hz, 1H, 2-H), 9.81 (d, *J* = 0.8 Hz, 1H, CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.4 (CH*C*H$_3$), 27.7 (C-3), 29.1 (*C*H$_3$C=O), 34.2 (C-4), 36.6 (C-5), 49.5 (C-2), 56.4 (C-1), 203.1 (CH=O), 209.0 (CH$_3$*C*=O); HRMS (ESI): $[M+Na+MeOH]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.11429, found 209.11450.

146a **147**

Ethyl 3-((1'*R*,2'*R*,5'*R*)-2'-acetyl-5'-methylcyclopentyl)-3-oxopropanoate (147). Anhydrous tin (II) chloride[16] (9.0 g, 47 mmol) was added, followed by dropwise addition of ethyl diazoacetate (8 mL, 73 mmol) to the foregoing solution of crude ketoaldehyde **146a** in CH_2Cl_2 (the quenched ozonolysis solution). Stirring was continued for 2 h, and then the mixture was transferred to a separatory funnel,

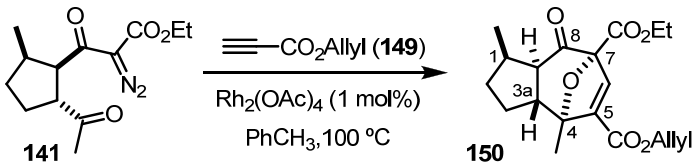
[16] $SnCl_2 \times H_2O$ was dehydrated by slow addition to a vigorously stirred solution of acetic anhydride (120 g salt per 100 g anhydride). After 1 h, the anhydrous $SnCl_2$ was filtered, washed with anhydrous Et_2O to remove acetic acid and anhydride, and dried under vacuum. Armarego, W.L.F., Chai, C.L.L., Purification of laboratory chemicals, **2003**, 5th edition, p 478.

containing saturated NaCl (100 mL) and diethyl ether (200 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/Et_2O, 4:1) to give β-keto ester **147** (2.5 g, 66%, over 2 steps) as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = –11.7 (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.83 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$), 1.24 (dd, *J* = 7.3, 7.3 Hz, 3H, $OCH_2C\mathit{H}_3$), 1.42–1.50 (m, 1H, 4'-H), 1.58–1.67 (m, 1H, 3'-H), 1.82–1.92 (m, 1H, 4'-H), 2.07–2.20 (m, 1H, 3'-H), 2.13 (s, 3H, CH_3C=O), 2.54 (app dddq, *J* = 13.7, 11.3, 7.0, 7.0 Hz, 1H, 5'-H), 3.40–3.48 (m, 2H, 1'-H, 2'-H), 3.47 (s, 2H, 2-H), 4.11–4.30 (m, 2H, $OC\mathit{H}_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.0 ($OCH_2\mathit{C}H_3$), 16.4 (CH*C*H$_3$), 27.0 (C-3'), 29.3 ($\mathit{C}H_3C$=O), 33.8 (C-4'), 37.0 (C-5'), 49.8 (C-3), 51.2 (C-1'), 57.0 (C-2'), 61.3 (OCH_2CH_3), 166.8 (C-1), 203.3 (C-3), 209.2 ($CH_3\mathit{C}$=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{20}O_4Na$ 263.12538, found 263.12538.

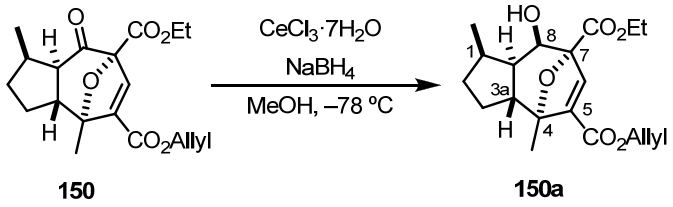


Ethyl 3-((1'*R*,2'*R*,5'*R*)-2'-acetyl-5'-methylcyclopentyl)-2-diazo-3-oxopropanoate (147). Triethylamine (3.9 mL, 28.0 mmol) was added dropwise at 0 °C to a solution of β-keto ester **147** (3.4 g, 14 mmol) and *p*-acetamidobenzenesulfonyl azide[17] (*p*-ABSA) (4.3 g, 18 mmol) in acetonitrile (60 mL). The mixture was stirred for 2 h and quenched with saturated NH_4Cl solution (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give diazo compound **141** (2.7 g, 71%) as a yellow oil. R_f = 0.70 (petroleum ether/EtOAc, 2:1); $[\alpha]^{20}_D$ = –39.2 (*c* 1.76, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.80 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.30 (dd, *J* = 7.2, 7.2 Hz, 3H, $OCH_2C\mathit{H}_3$), 1.39 (dddd, *J* = 12.8, 7.6, 7.4, 5.8 Hz, 1H, 4'-H), 1.63 (dddd, *J* = 12.5, 8.9, 8.8, 8.2 Hz, 1H, 3'-H), 1.94 (dddd, *J* = 12.4, 8.6, 6.8, 5.0 Hz, 1H, 4'-H), 2.07–2.13 (m,1H, 3'-H), 2.12 (s, 3H, CH_3C=O), 2.61 (app dddq, *J* = 14.2, 14.2, 6.9, 6.8 Hz, 1H, 5'-H), 3.56 (ddd, *J* = 18.7, 9.4, 9.4 Hz, 1H, 2'-H), 4.07 (dd, *J* = 8.6 Hz, 1H, 1'-H), 4.23–4.31 (m, 2H, $OC\mathit{H}_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.2 ($OCH_2\mathit{C}H_3$), 16.8 (CH*C*H$_3$), 27.4 (C-3'), 29.1 ($\mathit{C}H_3C$=O), 34.0 (C-4'), 36.2 (C-5'), 52.6 (C-2'), 53.1 (C-1'), 61.4 (OCH_2CH_3), 160.9 (C-1), 192.9 (C-3), 209.2 ($CH_3\mathit{C}$=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{18}O_4N_2Na$ 289.11588, found 289.11592.

[17] Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.



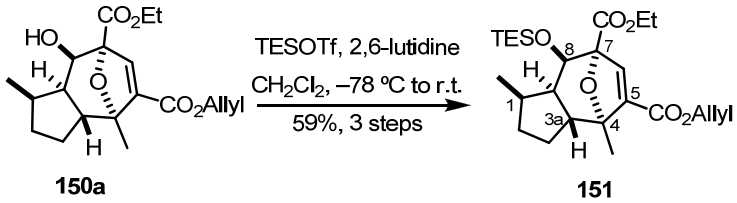
(1*R*,3a*R*,4*R*,7*R*,8a*R*)-5-Allyl 7-ethyl 1,4-dimethyl-8-oxo-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (150). $Rh_2(OAc)_4$ (30 mg, 1 mol%) was added to a mixture of diazo compound **141** (1.0 g, 3.8 mmol) and allyl propiolate[18] **149** (2 mL) in toluene (50 mL) at room temperature. Then the closed Schlenck tube was transferred to a preheated oil bath (100 ºC) and kept with stirring at this temperature for 15 min. The mixture was allowed to cool to room temperature and filtered through a pad of Celite, using diethyl ether as a rinse. The filtrate was concentrated in vacuo to afford crude cycloadduct **150** (1.32 g) as a yellowish oil, which was used in the next step without further purification (epimerization at C-8a was detected while purifying by silica flash chromatography). R_f = 0.50 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +74.4 (*c* 1.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] : 0.95 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.31 (dd, *J* = 7.1, 7.1Hz, 3H, OCH$_2$C*H*$_3$), 1.69 (s, 3H, OCCH$_3$), 3.28 (dd, *J* = 11.7, 6.4 Hz, 8a-H), 1.27–1.42 (m, 2H, OC*H*$_2$CH$_3$), 4.67 (dd, *J* = 5.8, 5.8 Hz, 2H, OC*H*$_2$CH=CH$_2$), 5.26 (dd, *J* = 10.4, 1.0 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.0, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.92 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 6.93 (s, 1H, 6-H); further protons could not be assigned. ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.1 (OCH$_2$*C*H$_3$), 17.7 (OC*C*H$_3$), 18.8 (CH*C*H$_3$), 27.0 (C-3), 29.0 (C-2), 29.8 (C-1), 47.1 (C-3a), 57.0 (C-8a), 62.5 (O*C*H$_2$CH$_3$), 65.6 (O*C*H$_2$CH=CH$_2$), 87.2 (C-4), 93.2 (C-7), 118.9 (OCH$_2$CH=*C*H$_2$), 131.4 (OCH$_2$*C*H=CH$_2$), 137.2 (C-6), 146.0 (C-5), 162.0 (CO_2Allyl), 164.3 (CO_2Et), 201.4 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{19}H_{24}O_6Na$ 371.14651, found 371.14627.



(1*R*,3a*R*,4*R*,7*R*,8*S*,8a*R*)-5-Allyl 7-ethyl 8-hydroxy-1,4-dimethyl-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (150a). Cerium (III) chloride heptahydrate (3.5 g, 9.5 mmol) was added to the solution of crude ketone **150** (1.1 g, 3.2 mmol) in methanol (20 mL) and the mixture stirred for 30 min at room temperature, before it was cooled to –78 °C and sodium borohydride (240 mg, 6.4 mmol) was added in portions. Stirring was continued for 2 h at the same temperature. The reaction was quenched by slow addition of water, and most of methanol was removed in vacuo. Diethyl ether (100

[18] For the preparation of allyl propiolate **149** see: Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164.

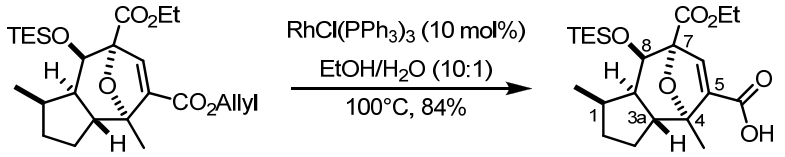
mL) and water (100 mL) were added, the layers separated, and the aqueous layer was extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude alcohol **150a** (1.1 g) as a yellowish oil, which was used in the next step without further purification. R_f = 0.20 (petroleum ether/EtOAc, 4:1); An analytical sample was obtained by flash chromatography (petroleum ether/EtOAc, 9:1). $[\alpha]^{20}_D$ = +17.0 (*c* 2.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.98–1.03 (m, 1H, 2-H), 1.23–1.34 (m, 1H, 3-H), 1.31 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.56 (s, 1H, OCC*H*$_3$), 1.72–1.78 (m, 1H, 3-H), 1.87 (ddd, *J* = 12.1, 12.1, 6.5 Hz, 1H, 3a-H), 1.94–2.02 (m, 2H, 2-H, OH), 2.17 (ddd, *J* = 12.5, 7.4, 4.6 Hz, 1H, 8a-H), 2.25 (app dddq, *J* = 7.4, 7.4, 2.9 Hz, 1H, 1-H), 4.28 (2 app dq, *J* = 14.2, 7.1, 2H, OC*H*$_2$CH$_3$), 4.51 (dd, *J* = 4.7, 4.7 Hz, 1H, 9-H), 4.66 (dd, *J* = 13.3, 5.7 Hz, 2H, OC*H*$_2$CH=CH$_2$), 5.24 (dd, *J* = 10.4, 1.0 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.0, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.93 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 7.02 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.2 (OCH$_2$*C*H$_3$), 19.1 (OC*C*H$_3$), 20.1 (CH*C*H$_3$), 25.8 (C-3), 31.1 (C-2), 32.5 (C-1), 35.7 (C-3a), 47.8 (C-8a), 61.9 (O*C*H$_2$CH$_3$), 65.3 (O*C*H$_2$CH=CH$_2$), 73.5 (C-8), 87.2 (C-4), 88.4 (C-7), 118.5 (OCH$_2$CH=*C*H$_2$), 131.7 (OCH$_2$*C*H=CH$_2$), 141.9 (C-6), 144.6 (C-5), 162.6 (CO_2Allyl), 170.2 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{19}H_{26}O_6Na$ 373.16216, found 373.16217.



150a **151**

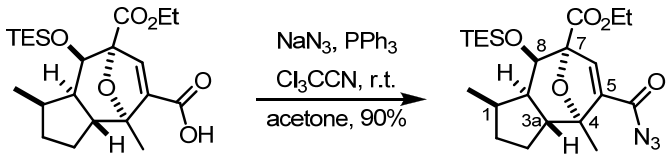
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-5-Allyl 7-ethyl 1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (151). 2,6-Lutidine (0.2 mL, 1.7 mmol) was added dropwise to a solution of alcohol **150a** (150 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) at –78 °C. Then TES-triflate (0.2 mL, 0.8 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature, filtered through a pad of silica gel, washed with 50% solution of ethyl acetate in petroleum ether, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give TES-ether **151** (118 mg, 59% over 3 steps) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +28.2 (*c* 2.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.61 (ddd, *J* = 15.8, 7.6, 7.6 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.93 (dd, *J* = 7.9, 7.9 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.97–1.05 (m, 1H, 2-H), 1.24–1.33 (m, 1H, 3-H), 1.33 (dd, *J* = 7.4, 7.4 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 (s, 3H, OCCH$_3$), 1.68–1.75 (m, 1H, 3-H), 1.87–1.96 (m, 2H, H-2, 3a-H), 2.07 (ddd, *J* = 12.5, 6.4, 4.3 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, *J* = 10.9, 7.4 Hz, 2H, OC*H*$_2$CH$_3$), 4.60–4.75 (m, 3H, 8-H, OC*H*$_2$CH=CH$_2$), 5.24 (dd, *J* = 10.4, 0.8 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.3, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.93 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 6.98 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.8

($Si(CH_2CH_3)_3$), 14.2 (OCH_2CH_3), 19.4 ($OCCH_3$), 19.6 ($CHCH_3$), 24.8 (C-3), 31.1 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 61.9 (OCH_2CH_3), 65.0 ($OCH_2CH=CH_2$), 73.3 (C-8), 86.8 (C-4), 89.2 (C-7), 118.0 ($OCH_2CH=CH_2$), 132.0 ($OCH_2CH=CH_2$), 142.8 (C-6), 143.1 (C-5), 162.8 (CO_2Allyl), 170.1 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{25}H_{40}O_6SiNa$ 487.24864, found 487.24857.



151 **153**

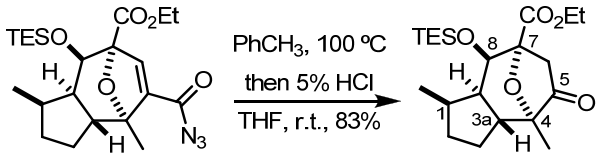
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-7-(Ethoxycarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5-carboxylic acid (153). $RhCl(PPh_3)_3$ (10 mg) was added to a solution of allyl ester **151** (42 mg, 0.09 mmol) in a mixture of water/ethanol (2 mL, 1:10). Then the closed flask was transferred to a preheated (100 °C) oil bath. The mixture was stirred for 1 h at this temperature, cooled, and then the solvents were removed in vacuo. The residue was purified by flash chromatography (petroleum ether/Et_2O/AcOH (glac.), 4:1:0.01) to give carboxylic acid **153** (32 mg, 84%) as a colorless oil. R_f = 0.2 (petroleum ether/Et_2O/AcOH (glac.), 4:1:0.01); $[\alpha]^{20}_D$ = +50.6 (*c* 3.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.62 (ddd, *J* = 15.9, 7.8, 7.8 Hz, 6H, $Si(CH_2CH_3)_3$), 0.90 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 0.94 (dd, *J* = 8.1, 8.1 Hz, 9H, $Si(CH_2CH_3)_3$), 0.99–1.07 (m, 1H, 2-H), 1.26–1.37 (m, 1H, 3-H), 1.33 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH_2CH_3), 1.55 (s, 3H, $OCCH_3$), 1.68–1.76 (m, 1H, 3-H), 1.88–1.96 (m, 2H, 3a-H, 2-H), 2.09 (ddd, *J* = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.17–2.26 (m, 1H, 1-H), 4.29 (2 app dq, *J* = 10.9, 7.4 Hz, 2H, OCH_2CH_3), 4.67 (d, *J* = 4.3 Hz, 1H, 8-H), 7.14 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 ($Si(CH_2CH_3)_3$), 6.9 ($Si(CH_2CH_3)_3$), 14.1 (OCH_2CH_3), 19.4 ($OCCH_3$), 19.6 ($CHCH_3$), 24.8 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.4 (C-8a), 61.9 (OCH_2CH_3), 73.4 (C-8), 86.7 (C-4), 89.2 (C-7), 142.8 (C-5), 145.7 (C-6), 168.2 (CO_2Et), 169.9 (CO_2H); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{36}O_6SiNa$ 447.21734, found 447.21730.



153 **154**

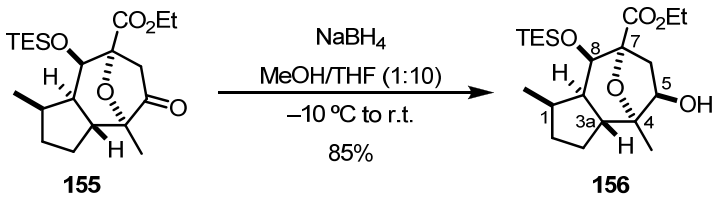
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-Ethyl 5-(azidocarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-7-carboxylate (154). Trichloroacetonitrile (0.03 mL, 0.33 mmol) was added dropwise to a stirred solution of carboxylic acid **153** (70 mg, 0.16 mmol), sodium azide (16 mg, 0.25 mmol), PPh_3 (86 mg, 0.33 mmol) in acetone (2 mL) at room temperature. After 30 min the solvent was removed by a flow of nitrogen and the residue was purified by flash

chromatography (petroleum ether/EtOAc, 25:1) to give azide **154** (66 mg, 90%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +40.1 (*c* 1.63, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.61 (ddd, *J* = 15.9, 7.8, 7.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.94 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.97–1.05 (m, 1H, 2-H), 1.25–1.37 (m, 1H, 3-H), 1.32 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 (s, 3H, OCCH$_3$), 1.68–1.76 (m, 1H, 3-H), 1.81–1.95 (m, 2H, 3a-H, 2-H), 2.06 (ddd, *J* = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, *J* = 10.9, 7.4 Hz, 2H, OC*H*$_2$CH$_3$), 4.66 (d, *J* = 4.3 Hz, 1H, 8-H), 7.06 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm]: 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 14.1 (OCH$_2$*C*H$_3$), 19.2 (OC*C*H$_3$), 19.5 (CH*C*H$_3$), 24.7 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 62.0 (O*C*H$_2$CH$_3$), 73.4 (C-8), 86.9 (C-4), 89.2 (C-7), 144.4 (C-5), 145.8 (C-6), 168.4 (CO_2Et), 169.7 (CON_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{35}N_3O_5SiNa$ 472.22382, found 472.22384.



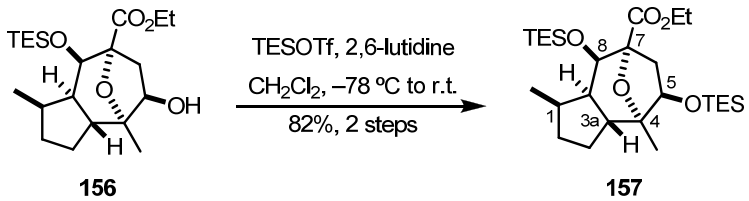
154 **155**

(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-Ethyl 1,4-dimethyl-5-oxo-8-((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (155). Azide **154** (66 mg, 0.15 mmol) was dissolved in toluene (2 mL) and stirred for 1 h at 100 °C. Then the solvent was removed in vacuo, the residue was dissolved in THF (2 mL) followed by the addition of 5% HCl (0.5 mL) and THF (0.5 mL). Stirring was continued for 15 min, then the reaction was quenched with triethylamine (0.5 mL) and the solvents were evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give ketone **155** (48 mg, 83%) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +0.5 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.60 (dddd, *J* = 16.8, 9.9, 8.4, 1.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.92 (d, *J* = 9.4 Hz, 3H, CHC*H*$_3$), 0.93 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.13–1.21 (m, 1H, 2-H), 1.26 (s, 3H, OCCH$_3$), 1.32 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.40 (ddd, *J* = 10.9, 7.2, 1.3 Hz, 1H, 3-H), 1.60–1.68 (m, 1H, 3-H), 1.85 (ddd, *J* = 13.2, 10.7, 7.4 Hz, 1H, 3a-H), 1.92–2.02 (m, 2H, 2-H, 8a-H), 2.22–2.31 (m, 1H, 1-H), 2.60 (d, *J* = 18.1 Hz, 1H, 6-H), 3.10 (d, *J* = 18.1 Hz, 1H, 6-H), 4.28 (2 app dq, *J* = 10.8, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.73 (d, *J* = 4.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 14.1 (OCH$_2$*C*H$_3$), 16.5 (OC*C*H$_3$), 19.2 (CH*C*H$_3$), 24.0 (C-3), 32.4 (C-1), 32.6 (C-2), 36.4 (C-3a), 38.8 (C-6), 45.2 (C-8a), 62.0 (O*C*H$_2$CH$_3$), 71.2 (C-8), 83.0 (C-4), 84.2 (C-7), 171.4 (CO_2Et), 214.6 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{21}H_{36}O_5SiNa$ 419.22242, found 419.22238.



155 **156**

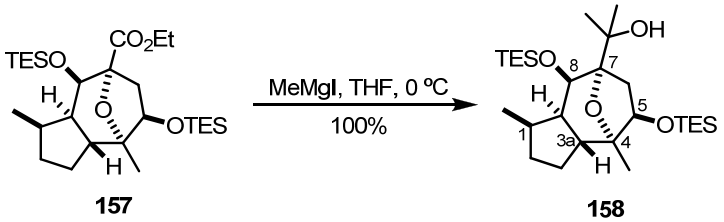
(1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-Ethyl 5-hydroxy-1,4-dimethyl-8-((triethylsilyl)oxy)deca-hydro-4,7-epoxyazulene-7-carboxylate (156). Sodium borohydride (21 mg, 0.55 mmol) was added in portions to a stirred solution of ketone **155** (150 mg, 0.38 mmol) in methanol/THF (6.6 mL, 1:10) at –10 °C. The mixture was allowed to warm to room temperature, and then quenched by careful addition of water. Most of the organic solvents were evaporated in vacuo, the residue was diluted with water (10 mL), and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give alcohol **156** (150 mg, 85%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +5.8 (*c* 2.46, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO): δ[ppm] = 0.48–0.55 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.96 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.09 (s, 3H, OCCH$_3$), 1.10–1.35 (m, 2H, 2-H, 3-H), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.47 (dddd, *J* = 12.4, 8.3, 8.3, 4.3 Hz, 1H, 3-H), 1.71 (ddd, *J* = 13.8, 6.2, 6.1, 1H, 8a-H), 1.87–1.96 (m, 1H, 2-H), 2.14 (dd, *J* = 13.3, 8.0 Hz, 1H, 6-H), 2.19–2.35 (m, 3H, 1-H, 3a-H, 6-H), 3.60 (ddd, *J* = 8.6, 8.6, 4.3 Hz, 1H, 5-H), 4.10 (2 app dq, *J* = 10.9, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.63 (d, *J* = 6.1 Hz, 1H, 8-H), 5.20 (d, *J* = 4.3 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.3 (Si*C*H$_2$CH$_3$), 6.7 (SiCH$_2$*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$), 18.8 (CH*C*H$_3$), 19.9 (OC*C*H$_3$), 23.8 (C-3), 32.0 (C-1), 32.7 (C-3a), 32.8 (C-6), 33.6 (C-2), 44.2 (C-8a), 61.0 (O*C*H$_2$CH$_3$), 70.8 (C-8), 76.8 (C-5), 82.5 (C-4), 83.3 (C-7), 171.8 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{21}H_{38}O_5SiNa$ 421.23807, found 421.23845.



156 **157**

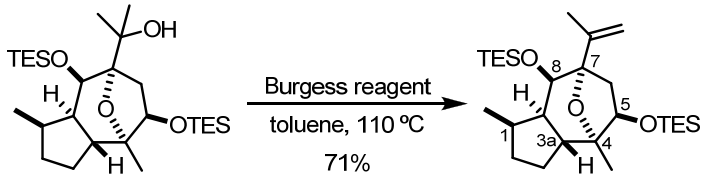
(1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-Ethyl 1,4-dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (157). 2,6-Lutidine (0.13 mL, 1.15 mmol) was added dropwise to a solution of alcohol **156** (150 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) at –78 °C. Then TES-triflate (0.13 mL, 0.58 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature (ca 3 h), filtered through a pad of silica gel, the filter cake was washed with mixture of petroleum ether/EtOAc (1:1), and the filtrates concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to afford TES-ether **157** (159 mg, 82% over 2 steps). R_f = 0.55 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +2.0 (*c* 6.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm]

= 0.51–0.61 (m, 12H, (Si(C*H*$_2$CH$_3$)$_3$)$_2$), 0.92 (dd, *J* = 7.9, 7.9 Hz, 9H, (Si(C*H*$_2$CH$_3$)$_3$), 0.95 (dd, *J* = 8.1, 8.1 Hz, 9H, (Si(CH$_2$C*H*$_3$)$_3$), 1.00 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.18–1.26 (m, 1H, 2-H), 1.20 (s, 3H, OCCH$_3$), 1.30 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.30–1.39 (m, 1H, 3-H), 1.53 (dddd, *J* = 16.9, 8.8, 8.5, 4.7 Hz, 1H, 3-H), 1.81 (ddd, *J* = 14.0, 6.1, 6.1 Hz, 1H, 8a-H), 1.87–1.96 (m, 1H, 2-H), 2.22–2.51 (m, 4H, 1-H, 3a-H, 6-H, 6-H), 3.77 (dd, *J* = 9.3, 7.5 Hz, 1H, 5-H), 4.21 (2 app dq, *J* = 10.8, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.66 (d, *J* = 5.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ[ppm] = 4.8 (Si*C*H$_2$CH$_3$), 4.9 (Si*C*H$_2$CH$_3$), 6.7 (SiCH$_2$*C*H$_3$), 6.8 (SiCH$_2$*C*H$_3$), 14.1 (OCH$_2$*C*H$_3$), 18.7 (CH*C*H$_3$), 20.2 (OC*C*H$_3$), 24.2 (C-3), 32.7 (C-1), 33.2 (C-3a), 34.1 (C-6), 44.6 (C-2), 61.5 (O*C*H$_2$CH$_3$), 71.6 (C-8), 78.1 (C-5), 83.2 (C-4), 84.4 (C-7), 172.7 (CO$_2$Et); HRMS (ESI): [M+Na]$^+$ calcd for $C_{27}H_{52}O_5Si_2Na$ 535.32455, found 535.325022.



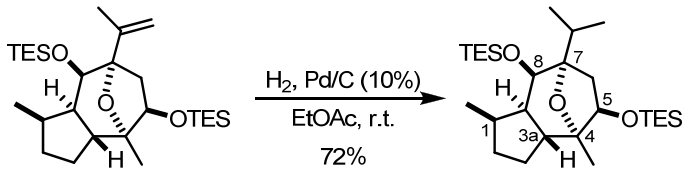
157 **158**

2-((1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-1,4-Dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulen-7-yl)propan-2-ol (158). Freshly prepared methylmagnesium iodide (0.12 mL, 1M solution in Et$_2$O, 0.12 mmol) was added dropwise to a stirred solution of ester **157** (10 mg, 0.019 mmol) in THF (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and quenched with saturated NH$_4$Cl (0.5 mL), diluted with water (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (2 × 10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give tertiary alcohol **158** (9.7 mg, 100%) as a colorless oil. R$_f$ = 0.48 (petroleum ether/EtOAc, 9:1); [α]$^{20}_D$ = +3.4 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ[ppm] = 0.57 (ddd, *J* = 16.7, 8.6, 1.3 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.65 (ddd, *J* = 15.9, 7.9, 2.3 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.94 (dd, *J* = 7.8, 7.8 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.96 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.00 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.14 (s, 3H, OCCH$_3$), 1.16 (s, 3H, C(CH$_3$)$_2$), 1.18 (s, 3H, C(CH$_3$)$_2$), 1.22–1.28 (m, 1H, 2-H), 1.35 (dddd, *J* = 12.2, 10.3, 10.3, 6.2 Hz, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.69 (ddd, *J* = 13.6, 6.4, 4.7 Hz, 1H, 8a-H), 1.88 (dddd, *J* = 12.1, 10.5, 7.1, 4.9 Hz, 1H, 2-H), 1.98 (dd, *J* = 13.0, 9.7 Hz, 1H, 6-H), 2.15–2.24 (m, 2H, 1-H, 6-H), 2.55 (ddd, *J* = 13.6, 10.0, 9.0 Hz, 1H, 3a-H), 3.66 (dd, *J* = 9.6, 6.6 Hz, 1H, 5-H), 4.45 (d, *J* = 4.6 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ[ppm] = 4.9 (Si*C*H$_2$CH$_3$), 5.9 (Si*C*H$_2$CH$_3$), 6.8 (SiCH$_2$*C*H$_3$), 7.2 (SiCH$_2$*C*H$_3$), 18.6 (CH*C*H$_3$), 21.2 (OC*C*H$_3$), 24.0 (C-3), 24.8 (C(*C*H$_3$)$_2$), 24.8 (C(*C*H$_3$)$_2$), 32.6 (C-1), 32.7 (C-6), 33.1 (C-3a), 34.9 (C-2), 45.9 (C-8a), 71.0 (C-8), 73.3 (*C*(CH$_3$)$_2$), 79.6 (C-5), 81.4 (C-4), 89.1 (C-7); HRMS (ESI): [M+Na]$^+$ calcd for $C_{27}H_{54}O_4Si_2Na$ 521.34528, found 521.345436.



158 **159**

(((1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) (159). Burgess reagent[19] (10 mg, 0.040 mmol) was added to a stirred solution of alcohol **158** (5 mg, 0.010 mmol) in abs. toluene (1 mL) and the mixture was stirred at 110 °C for 5 min. Then the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 30:1) providing alkene **159** (3.4 mg, 71%) as a colorless oil. R_f = 0.31 (petroleum ether/EtOAc, 33:1); $[\alpha]^{20}_D$ = +4.8 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.50–0.60 (m, 12H, $(Si(CH_2CH_3)_3)_2$), 0.92 (dd, *J* = 7.8, 7.8 Hz, 9H, $Si(CH_2CH_3)_3$), 0.95 (dd, *J* = 8.1, 8.1 Hz, 9H, $Si(CH_2CH_3)_3$), 1.00 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.16 (s, 3H, $OCCH_3$), 1.21–1.27 (m, 1H, 2-H), 1.30–1.39 (m, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.73 (ddd, *J* = 14.0, 5.9, 5.8 Hz, 1H, 8a-H), 1.77 (s, 3H, $CH_2=CCH_3$), 1.84–1.93 (m, 1H, 2-H), 2.04 (dd, *J* = 13.0, 9.2 Hz, 1H, 6-H), 2.19–2.24 (m, 1H, 1-H), 2.29 (dd, *J* = 13.1, 7.3 Hz, 1H, 6-H), 2.49 (ddd, *J* = 14.0, 10.1, 8.7 Hz, 1H, 3a-H), 3.68 (dd, *J* = 9.3, 7.3 Hz, 1H, 5-H), 4.25 (d, *J* = 6.1 Hz, 1H, 8-H), 4.88 (dd, *J* = 1.4, 1.4 Hz, 1H, $C=CH_2$), 4.91 (br.s, 1H, $C=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 5.0 ($SiCH_2CH_3$), 5.4 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 18.4 ($CH_3C=CH_2$), 18.6 ($CHCH_3$), 20.7 ($OCCH_3$), 23.9 (C-3), 32.8 (C-3a), 32.9 (C-1), 34.0 (C-2), 35.0 (C-6), 45.7 (C-8a), 72.4 (C-8), 78.7 (C-5), 80.9 (C-4), 85.9 (C-7), 112.1 ($CH_3C=CH_2$), 147.0 ($CH_3C=CH_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{52}O_3Si_2Na$ 503.33472, found 503.33510.

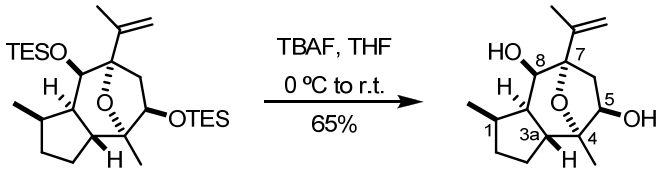


159 **161**

(((1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) (161). A 5 mL round-bottom flask was charged with alkene **159** (3.40 mg, 0.007 mmol) and a stirring bar. Absolute ethyl acetate (1 mL) and Pd/C 10% (4.00 mg) were added with stirring. The reaction was placed under H_2 atmosphere and stirred for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 100:1) to afford the title

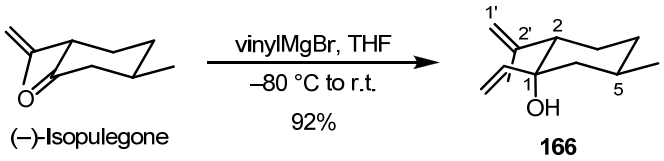
[19] For the preparation of Burgess reagent see: Burgess, E.M., Penton, H.R., Taylor, E.A. *J. Org. Chem.* **1973**, *38*, 26.

compound **161** (2.5 mg, 72%) as a colorless oil. R_f = 0.60 (petroleum ether/ EtOAc, 60:1); $[\alpha]^{20}_D$ = +2.7 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.52–0.64 (m, 12H, ($Si(CH_2CH_3)_3)_2$), 0.92–1.01 (m, 27H, ($Si(CH_2CH_3)_3)_2$, ($CHCH_3)_3$, 1.12 (s, 3H, $OCCH_3$), 1.17–1.35 (m, 2H, 2-H, 3-H), 1.47–1.52 (m, 1H, 3-H), 1.60–1.74 (m, 3H, 8a-H, 6-H $CH(CH_3)_2$), 1.85–1.94 (m, 1H, 2-H), 2.17–2.24 (m, 2H, 6-H, 1-H), 2.40 (ddd, *J* = 13.8, 10.4, 8.6 Hz, 1H, 3a-H), 3.52 (dd, *J* = 8.6, 8.6 Hz, 1H, 5-H), 4.36 (d, *J* = 6.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 5.0 ($SiCH_2CH_3$), 5.3 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 16.6 ($CH(CH_3)_2$), 16.8 ($CH(CH_3)_2$), 18.9 ($CHCH_3$), 20.4 ($OCCH_3$), 24.0 ($CH(CH_3)_2$), 31.6 (C-3), 32.6 (C-3a), 33.6 (C-1), 34.1 (C-2), 34.7 (C-6), 46.0 (C-8a), 71.3 (C-8), 78.9 (C-5), 80.6 (C-4), 85.4 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{54}O_3SiNa$ 505.35037, found 505.35007.

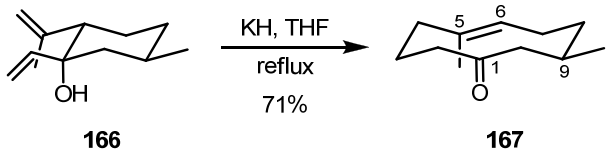


159 **160**

(1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diol (160). TBAF × $3H_2O$ (38.5 mg, 0.120 mmol) was added in one portion to a stirred solution of silyl ether **159** (6.9 mg, 0.012 mmol) in anhydrous THF (1 mL) at 0 °C. Then the cooling bath was removed and the mixture stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol **160** (2.0 mg, 6.5%) as white crystals. R_f = 0.32 (petroleum ether/EtOAc, 2:1); $[\alpha]^{20}_D$ = +2.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 1.19–1.27 (m, 1H, 2-H), 1.27 (s, 3H, $OCCH_3$), 1.36 (dddd, *J* = 11.6, 11.6, 9.2, 9.1 Hz, 1H, 3-H), 1.58–1.65 (m, 1H, 3-H), 1.75 (dd, *J* = 1.4, 0.9 Hz, 3H, $CH_3C=CH_2$), 1.86 (ddd, *J* = 13.6, 8.0, 4.2 Hz, 1H, 8a-H), 1.97 (dd, *J* = 13.4, 9.6 Hz, 1H, 6-H), 2.07–2.15 (m, 1H, 2-H), 2.24–2.37 (m, 3H, 1-H, 3a-H, 6-H), 3.91 (dd, *J* = 9.6, 4.8 Hz, 1H, 5-H), 4.17 (d, *J* = 4.3 Hz, 1H, 8-H), 4.70 (ddd, *J* = 3.2, 1.5, 1.4 Hz, 1H, $CH_3C=CH_2$), 4.93 (dd, *J* = 1.9, 0.9 Hz, 1H, $CH_3C=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.5 ($CH_3C=CH_2$), 20.4 ($CHCH_3$), 21.5 ($OCCH_3$), 26.0 (C-3), 31.4 (C-3a), 33.8 (C-1), 34.4 (C-2), 38.4 (C-6), 44.8 (C-8a), 73.8 (C-8), 78.9 (C-5), 81.7 (C-4), 86.0 (C-7), 107.9 ($CH_3C=CH_2$), 148.4 ($CH_3C=CH_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{24}O_3Na$ 275.16177, found 275.16169.



(1*R*,2*S*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (166). Freshly prepared vinylmagnesium bromide[20] (250 mL, 1.7M solution in THF, 0.42 mol) was added dropwise to a stirred solution of (–)-isopulegone (47.0 g, 0.33 mol) in THF (300 mL) at –80 °C. The reaction mixture was allowed to warm to room temperature and quenched with saturated NH_4Cl (50 mL), diluted with water (200 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 45–50 °C, 6 × 10^{-3} mbar) to give alcohol **166** as a colorless oil (55.7 g, 92%). R_f = 0.69 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +17.2 (*c* 2.49, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.86 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 0.90–1.01 (m, 1H, 4-H), 1.10 (ddd, *J* = 14.0, 12.2, 2.0 Hz, 1H, 6-H), 1.47 (ddd, *J* = 13.2, 6.4, 3.6 Hz, 1H, 3-H), 1.61 (ddd, *J* = 13.7, 3.3, 2.3 Hz, 1H, 6-H), 1.74 (s, 3H, 2'-CH_3), 1.76–1.83 (m, 3H, 3-H, 4-H, 5-H), 1.98 (dd, *J* = 13.0, 3.3 Hz, 1H, 2-H), 4.73 (s, 1H, 1'-H), 4.87 (s, 1H, 1'-H), 4.96 (dd, *J* = 10.7, 1.3 Hz, 1H, CH_2 vinyl), 5.16 (dd, *J* = 17.2, 1.1 Hz, 1H, CH_2 vinyl), 5.86 (dd, *J* = 17.0, 10.7 Hz, 1H, CH vinyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.2 (5-CH_3), 25.7 (2'-CH_3), 27.4 (C-5, C-3), 34.8 (C-4), 46.5 (C-6), 52.0 (C-2), 73.2 (C-1), 110.6 (CH_2 vinyl), 111.7 (C-1'), 146.2 (CH vinyl), 148.1 (C-2'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}ONa$ 203.14064, found 203.140504.

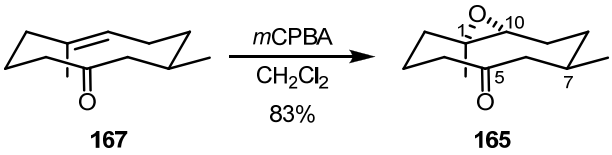


(9*R*,*E*)-5,9-Dimethylcyclodec-5-enone (167). A solution of alcohol **166** (3.0 g, 16.7 mmol) in abs. THF (20 mL) was added to a stirred suspension of KH (2.0 g, 50 mmol)[21] in THF (40 mL). The resulting mixture was stirred under reflux for 12 h. Then the reaction mixture was quenched with ethanol (10 mL) at –78 °C, diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (55−60 °C, 10^{-2} mbar) to give ketone **167** as a colorless oil (2.13 g, 71%). R_f = 0.59 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +2.9 (*c* 1.0,

[20] For preparation, see: Werner, B.; Brügger, P.; Daly, J. J.; Englert, G.; Schönholzer, H. -J. *Helv. Chim. Acta* **1985**, *68*, 1010-1024.

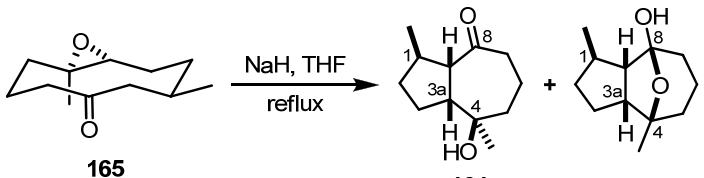
[21] KH was washed with abs. *n*-hexane (3 × 10 mL) before it was used.

MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.92 (d, *J* = 6.8 Hz, 3H, 9-CH_3), 1.17–1.23 (m, 1H), 1.43 (s, 3H, 5-CH_3), 1.60–1.68 (m, 2H), 1.80–1.85 (m, 1H), 1.95–2.15 (m, 1H, 9-H), 2.20–2.35 (m, 2H), 2.57–2.63 (m, 1H), 5.12–5.14 (m, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.9 (5-CH_3), 24.8 (9-CH_3), 25.8, 27.3 (CH_2), 28.8 (C-9), 37.3, 41.3, 43.1, 53.3 (CH_2), 126.4 (C-6), 138.0 (C-5), 208.7 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}ONa$ 203.14064, found 203.140461.



167 **165**

(1*R*,7*R*,10*R*)-1,7-Dimethyl-11-oxa-bicyclo[8.1.0]undecan-5-one (165). *m*CPBA (11.5 g, 47.0 mmol, 70–75%) was added to a stirred solution of ketone **167** (7.0 g, 39 mmol) in CH_2Cl_2 (400 mL) and stirred overnight at ambient temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (100 mL) and stirred for additional 1 hour. The organic layer was separated and washed with saturated $NaHCO_3$ solution (2 × 100 mL), water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give epoxide **165** (6.3 g, 83%) as a white crystals (m.p. 66–67.5 °C, from petroleum ether). R_f = 0.24 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –0.4 (*c* 1.29, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.84–0.92 (ddd, *J* = 13.7, 13.7, 3.3 Hz, 1H, 2-H), 0.96 (d, *J* = 7.4 Hz, 3H, 7-CH_3), 1.15 (s, 3H, 1-CH_3), 1.25–1.45 (m, 2H, 8-H, 9-H), 1.55–1.65 (m, 1H, 3-H), 1.79–1.85 (m, 2H, 8-H, 9-H), 2.10–2.20 (m, 2H, 2-H, 3-H), 2.24–2.43 (m, 4H, 4-H, 4-H, 6-H, 7-H), 2.56 (dd, *J* = 17.5, 10.3 Hz, 1H, 6-H), 2.63 (dd, *J* = 7.5, 0.9 Hz, 1H, 10-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.1 (1-CH_3), 20.2 (C-3), 23.4 (7-CH_3), 26.4 (C-9), 28.8 (C-7), 35.9 (C-8), 40.5 (C-2), 43.2 (C-4), 52.3 (C-6), 61.5 (C-1), 63.2 (C-10), 210.3 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}O_2Na$ 219.13555, found 219.135501.

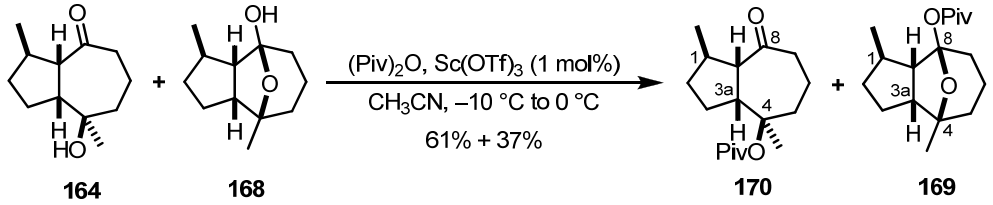


165 **164** **168**

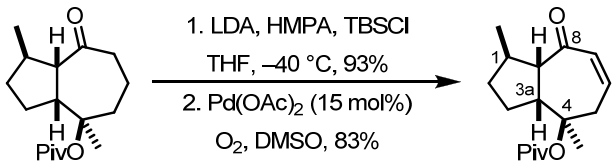
(1*R*,3a*R*,4*R*,8a*S*)-4-Hydroxy-1,4-dimethyl-octahydroazulen-4(2*H*)-one (164) and (1*R*,3a*R*,4*R*,8*S*,8a*S*)-1,4-Dimethyldecahydro-4,8-epoxyazulen-8-ol (168). A solution of epoxide **165** (7.0 g, 35.7 mmol) in THF (50 mL) was added to the suspension of NaH[22] (6.0 g, 150.0 mmol, 60% dispersed in mineral oil) in THF (200 mL) and stirred under reflux for 1 h. Then the reaction mixture was cooled to –10 °C and quenched with saturated NH_4Cl solution (50 mL), diluted with water (100

[22] NaH was washed with abs. *n*-hexane (3 × 10 mL) before it was used.

mL), and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1M HCl solution (50 mL), water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give an inseparable mixture of ketone **164** and hemiketal **168**, which were introduced in the next step without further purification (6.0 g, quant.). R_f = 0.32 (petroleum ether/EtOAc, 2:1).

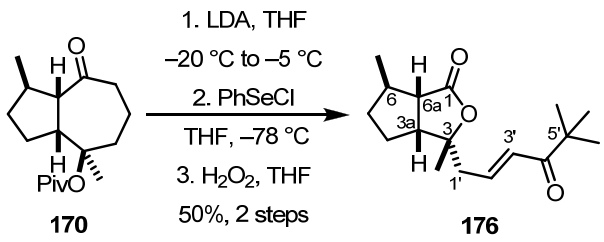


(1*R*,3a*R*,4*R*,8a*S*)-1,4-Dimethyl-8-oxo-decahydroazulen-4-yl-pivalate (170). Pivalic anhydride (16 ml, 79.1 mmol) was added dropwise to a stirred solution of a mixture of **164** and **168** (4.3 g, 21.9 mmol) in dry acetonitrile (90 mL) at –10 °C, followed by addition of $Sc(OTf)_3$ (0.1 g, 0.2 mmol) solution in acetonitrile (1 mL) at the same temperature. The resulting mixture was stirred overnight at 0 °C, quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give pivalic ketone **170** (3.7 g, 61%) and protected hemiketal **169** (2.3 g, 37%) as colorless oils. Hemiketal **169**: R_f = 0.75 (Petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +10.7 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.99 (d, *J* = 6.1 Hz, 3H, 1-CH_3), 1.15 (s, 9H, $(CH_3)_3$), 1.26 (s, 3H, 4-CH_3), 1.40–1.68 (m, 6H, 5-H, 6-H, 2-H), 1.88–1.99 (m, 2H, 7-H), 2.14–2.22 (m, 2H, 3-H), 2.31–2.35 (ddd, *J* = 11.9, 11.7, 6.2 Hz, 1H, 1-H), 2.46 (dd, *J* = 13.8, 8.2 Hz, 3a-H), 2.79 (ddd, *J* = 13.6, 8.6, 8.6 Hz, 1H, 8a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 17.9 (1-CH_3), 20.9 (CH_2), 25.0 (4-CH_3), 27.0 (CO(CH_3)$_3$), 27.9, 28.9, 31.8, 33.7, 38.5, 39.0 (CH_2), 41.1 (C-1), 54.5 (C-8a), 62.5 (C-3a), 82.1 (C-8), 110.0 (C-4), 185.0 (*C*O(CH_3)$_3$). Pivalic ketone **170**: R_f = 0.65 (Petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +22.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.05 (d, *J* = 6.4 Hz, 3H, 1-CH_3), 1.12 (s, 9H, $(CH_3)_3$), 1.20–1.25 (m, 1H, 2-H), 1.48 (s, 3H, 4-CH_3), 1.54–1.85 (m, 4H, 2 × 3-H, 5-H, 2 × 6-H), 1.96–2.12 (m, 2H, 1-H, 2-H), 2.31–2.43 (m, 3H, 5-H, 7-H, 8a-H), 2.61 (ddd, *J* = 11.7, 11.7, 3.3 Hz, 1H, 7-H), 2.95 (ddd, *J* = 11.2, 11.2, 7.1 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.9 (1-CH_3), 21.2 (CH_2), 26.2 (4-CH_3), 27.1 (CO(CH_3)$_3$), 29.4, 35,3, 35.4, 39.2 (CH_2), 39.6 (*C*O(CH_3)$_3$), 41.6 (C-1), 49.5 (C-3a), 61.4 (C-8a), 86.1 (C-4), 177.7 (C=O ester), 212.4 (C=O ketone).



170 **171**

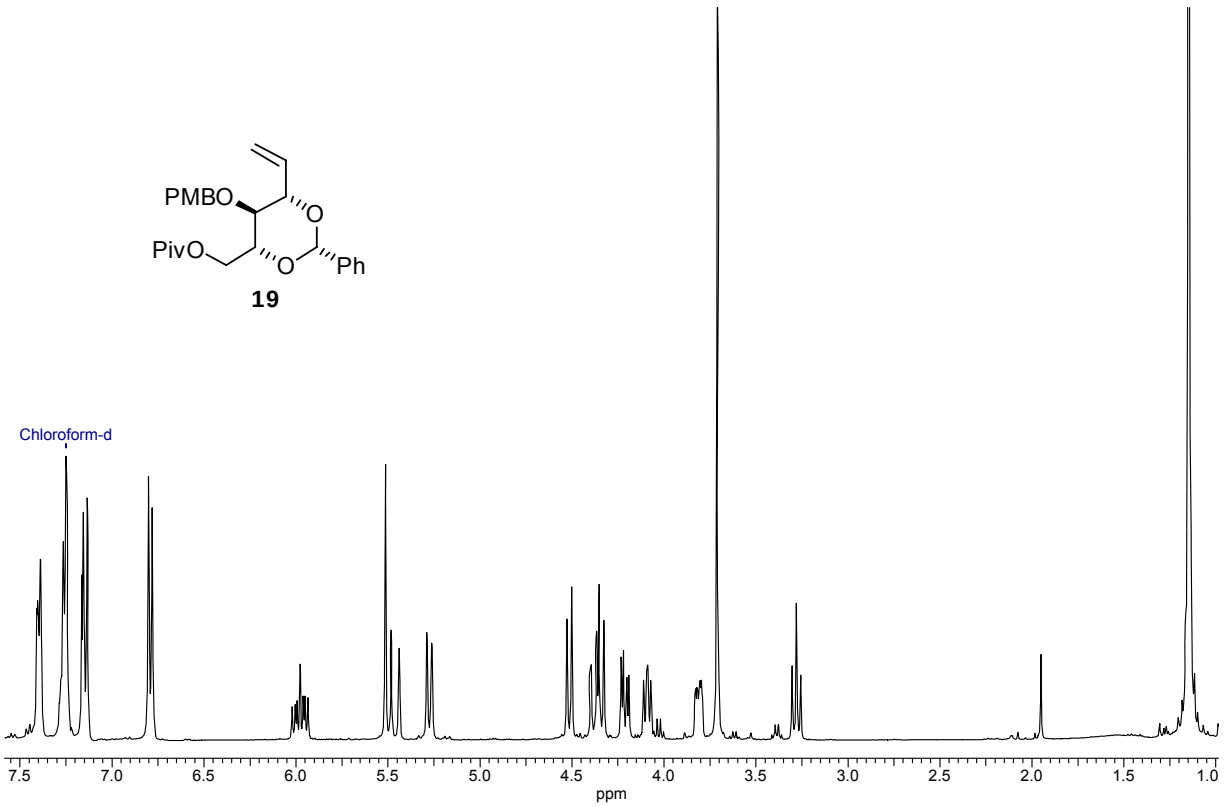
(1*R*,3a*R*,4*R*,8a*S*)-1,4-Dimethyl-8-oxo-1,2,3,3a,4,5,8,8a-octahydroazulen-4-yl pivalate (171). *TBS enol ether formation*. *n*-BuLi (0.43 mL, 2.5M in THF) was added to a flask containing abs. THF (1.5 mL). The resulting solution was cooled to –20 °C and then DIPEA (0.17 mL, 1.18 mmol) was added. The resulting LDA solution was stirred at –20 °C for 1 h and recooled to –40 °C. A solution of ketone **170** (100 mg, 0.36 mmol) in abs. THF (1.0 mL) was introduced dropwise at –40 °C. The resulting solution was stirred at the same temperature for 2 h and then a solution of TBSCl (217 mg, 1.44 mmol) in abs. THF (1.0 mL) was added followed by HMPA (0.1 mL, 0.54 mmol). The reaction mixture was allowed to warm to room temperature. After being stirred overnight, water (10 mL) was added. The organic layer was separated and the water phase extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc/Et_3N, 40:1:0.12) to give TBS enol ether (131 mg, 93%) as a colorless oil. R_f = 0.37 (Petroleum ether/EtOAc, 33:1). The compound was directly introduced to the next step. *Saegusa-Ito oxidation*. To a solution of TBS enol ether obtained above in dry DMSO (3.0 mL) was added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol). The reaction mixture was placed under oxygen and stirred at 50 °C for 24 h. After this time, the reaction mixture was diluted with Et_2O (10 mL) followed by water addition (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.The residue was purified via flash chromatography (petroleum ether/EtOAc, 9:1) to give enone **171** (76 mg, 83%) as a colorless oil. R_f = 0.42 (Petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –21.3 (*c* 0.39, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.97 (d, *J* = 5.8 Hz, 3H, 1-CH_3), 1.06 (s, 9H, *t*Bu), 1.15–1.24 (m, 2H, CH_2), 1.46 (s, 3H, 4-CH_3), 1.86–2.03 (m, 2H, 3a-H, CH_2), 2.50 (dd, *J* = 10.6, 10.6 Hz, 1H, CH_2), 2.61–2.67 (m, 1H, 5-H), 2.80–2.87 (m, 1H, 8a-H), 3.26–3.32 (m, 1H, 5-H), 5.90 (dd, *J* = 12.1, 2.9 Hz, 1H, 7-H), 6.10 (ddd, *J* = 12.1, 6.7, 2.7 Hz 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.2 (1-CH_3), 25.0 (4-CH_3), 27.0 (C(*C*H_3)$_3$), 28.5 (CH_2), 34.8 (CH_2), 36.9 (C-1), 39.4 (*C*(CH$_3$)$_3$), 40.8 (C-5), 50.6 (C-3a), 63.7 (C-8a), 85.0 (C-4), 130.9 (C-7), 137.0 (C-6), 177.9 (C=O ester), 204.2 (C=O ketone).

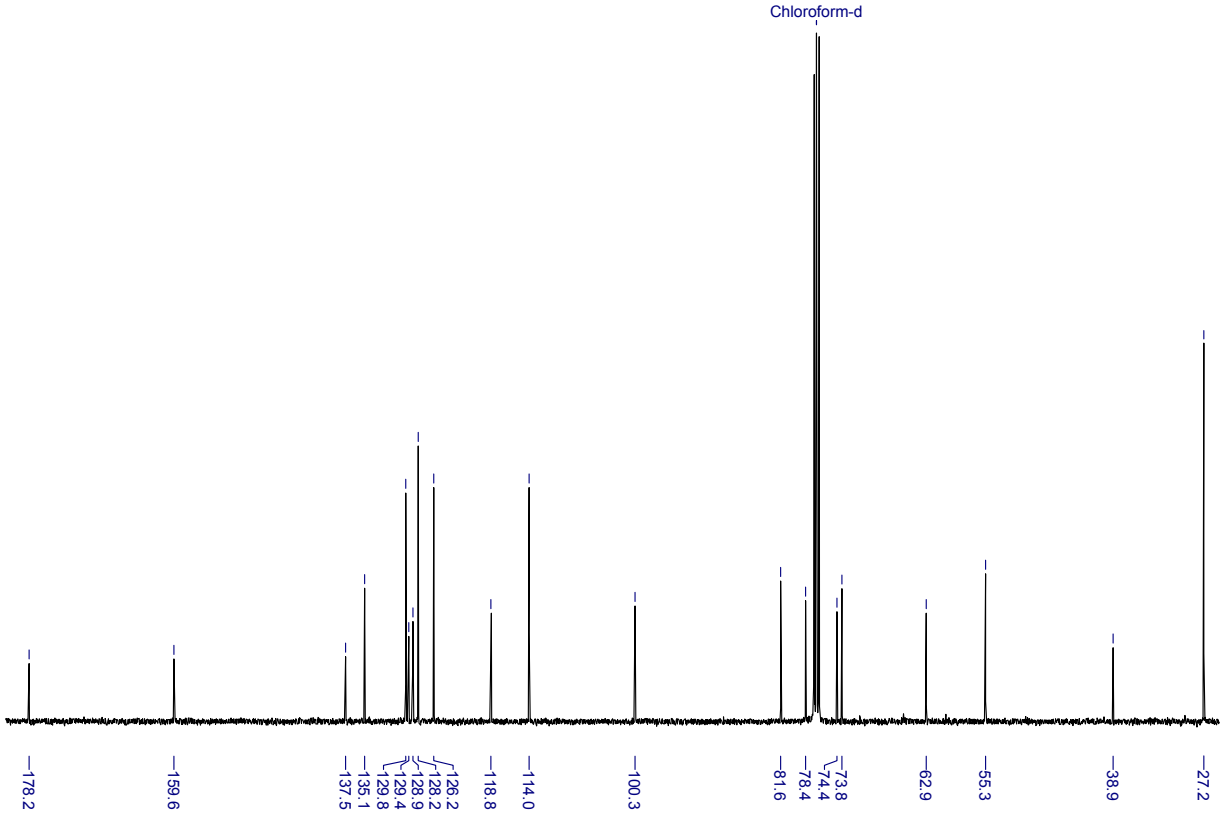


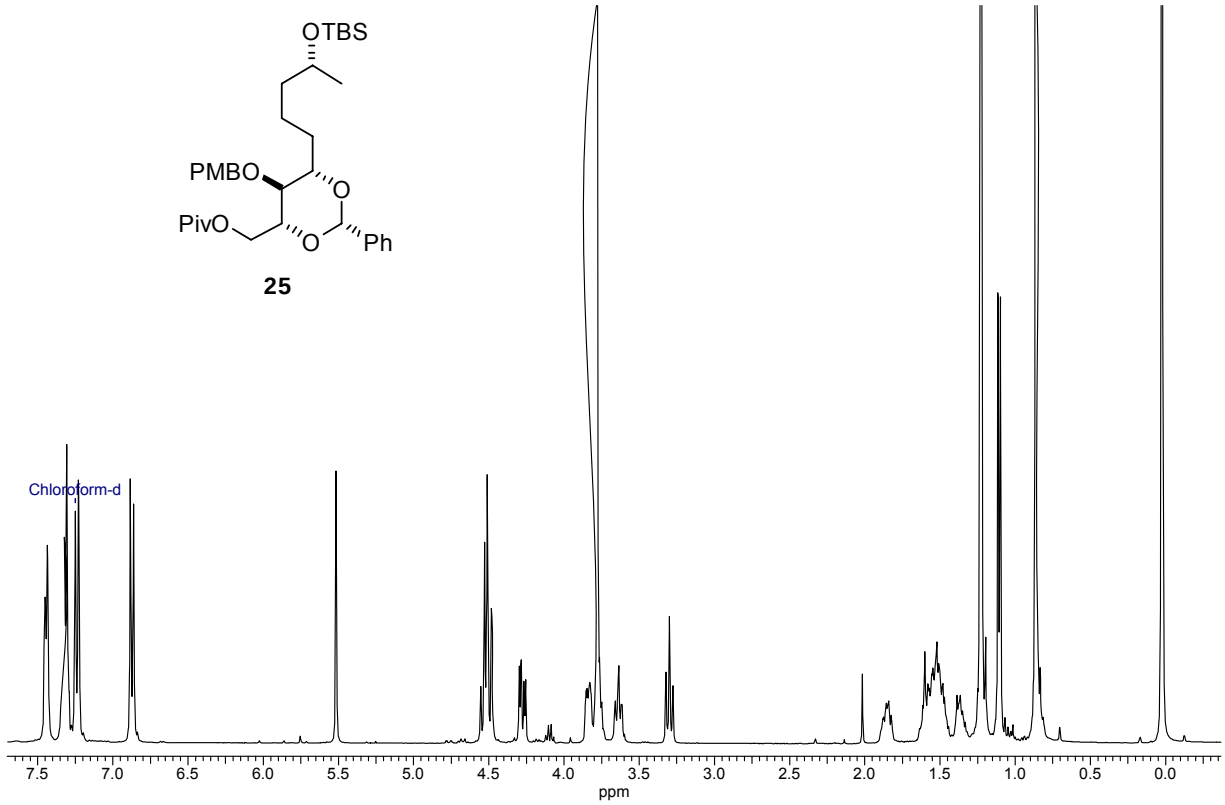
(3*R*,3a*R*,6*R*,6a*S*)-3-((*E*)-5,5-Dimethyl-4-oxohex-2-enyl)-3,6-dimethylhexahydro-1H-cyclopenta[*c*]furan-1-one (176). *n*-BuLi (0.20 mL, 2.5M in THF) was added to a flask containing abs. THF (1.0 mL). The resulting solution was cooled to –20 °C and then DIPEA (0.07 mL, 0.40 mmol) was added. The resulting LDA solution was stirred at –20 °C for 1 h. Then a solution of ketone **170** (30.0 mg, 0.11 mmol) in abs. THF (1.0 mL) was added at –20 °C. The resulting solution was warmed to –5 °C and stirred for 40 min. After this time, the reaction mixture was recooled to –78 °C and a solution of PhSeCl (57.4 mg, 0.33 mmol) in THF (0.5 mL) was added dropwise. The resulting yellow solution was allowed to stir overnight at –40 °C and then quenched with saturated NH_4Cl solution (5 mL). The layers were separated and aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in THF (1 mL) and H_2O_2 (0.1 mL, 1.1 mmol, 30% in water) was added in one portion. The resulting solution was stirred overnight and then diluted with water (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated $Na_2S_2O_8$ solution (2 × 10 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give enone **176** (15 mg, 50%) as a colorless oil. R_f = 0.42 (Petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +10.7 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.13–1.14 (m, 12H, 5'-$(CH_3)_3$, 6-CH_3), 1.17–1.25 (m, 1H, 5-H), 1.35 (s, 3H, 3-CH_3), 1.52–1.57 (m, 1H, 5-H), 1.80–1.96 (m, 2H, 4-H), 2.33–2.40 (m, 1H, 6-H), 2.53–2.69 (m, 3H, 1'-H, 3a-H), 2.76 (dd, *J* = 8.6, 4.1 Hz, 1H, 6a-H), 6.60 (app d, *J* = 15.2 Hz, 1H, 3'-H), 6.83 (ddd, J = 15.2, 7.6, 7.6, 1H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.3 (6-CH_3), 26.0 (5-$(CH_3)_3$), 27.0 (3-CH_3), 27.6 (C-4), 35.4 (C-5), 37.7 (C-6), 40.0 (C-1'), 42.9 (C-5'), 49.8 (C-3a), 53.5 (C-6a), 84.7 (C-3), 128.2 (C-3'), 140.2 (C-2'), 179.3 (C=O ester), 203.7 (C=O ketone).

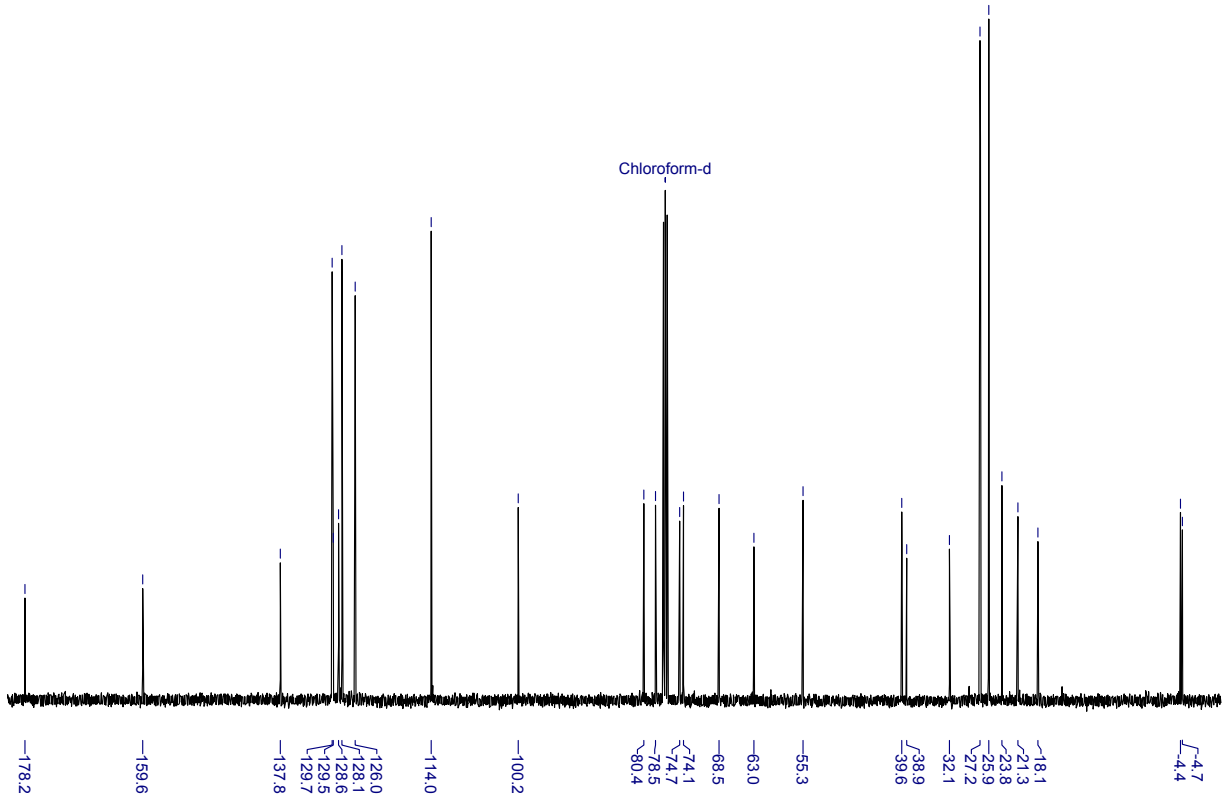
Selected NMR spectra for important compounds

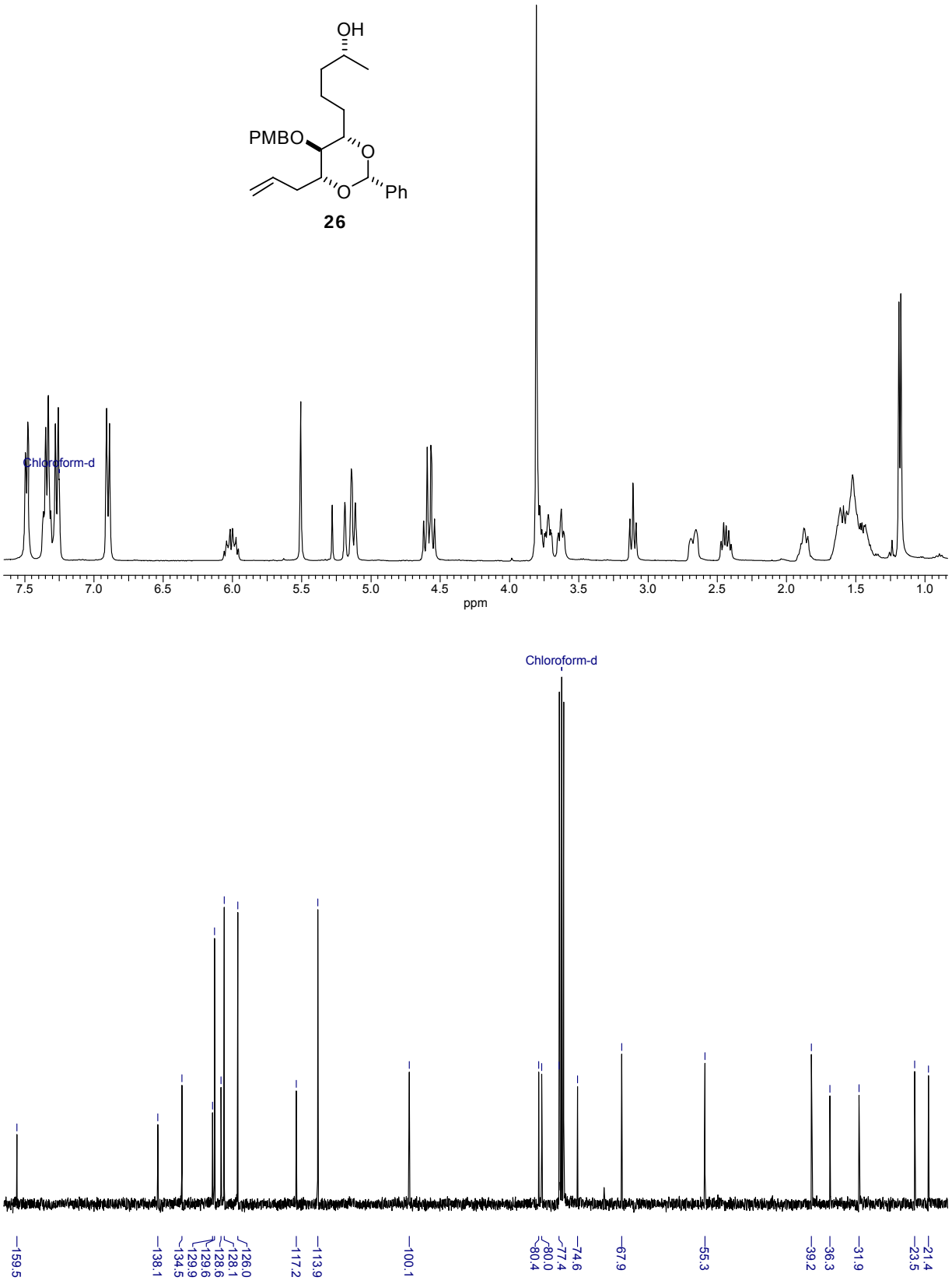
Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at http://www.sciencedirect.com/, http://pubs.acs.org and http://www.thieme-chemistry.com/products/journals/synlett.html

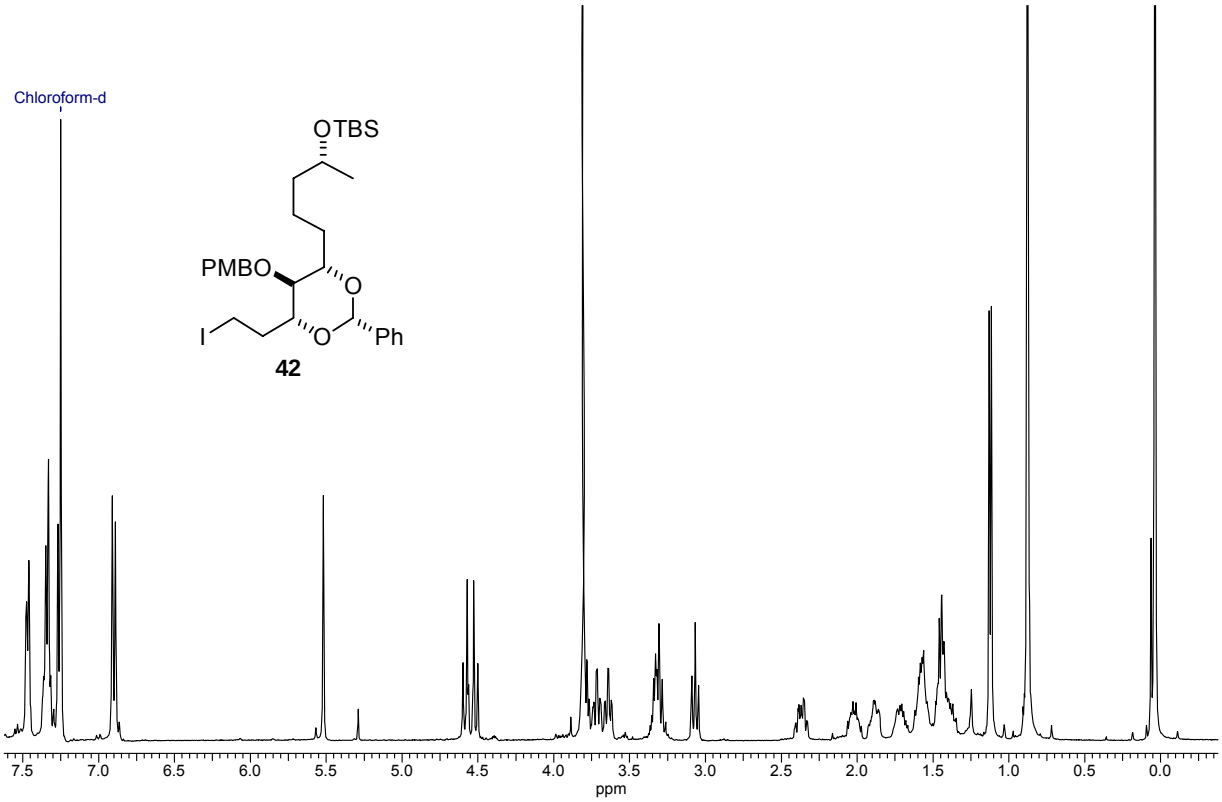

PMBO
PivO
O
O
Ph
19
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

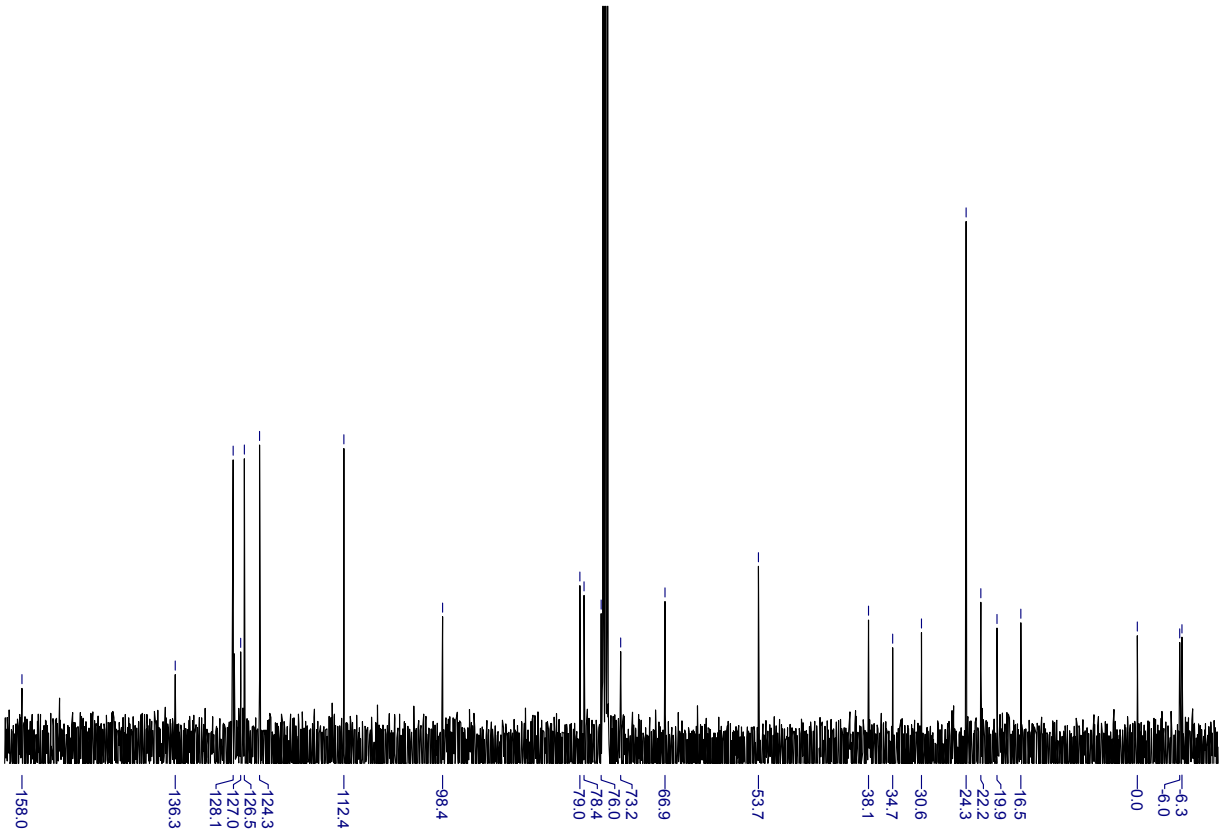

Chloroform-d
178.2
159.6
137.5
135.1
129.8
129.4
128.9
128.2
126.2
118.8
114.0
100.3
81.6
78.4
74.4
73.8
62.9
55.3
38.9
27.2

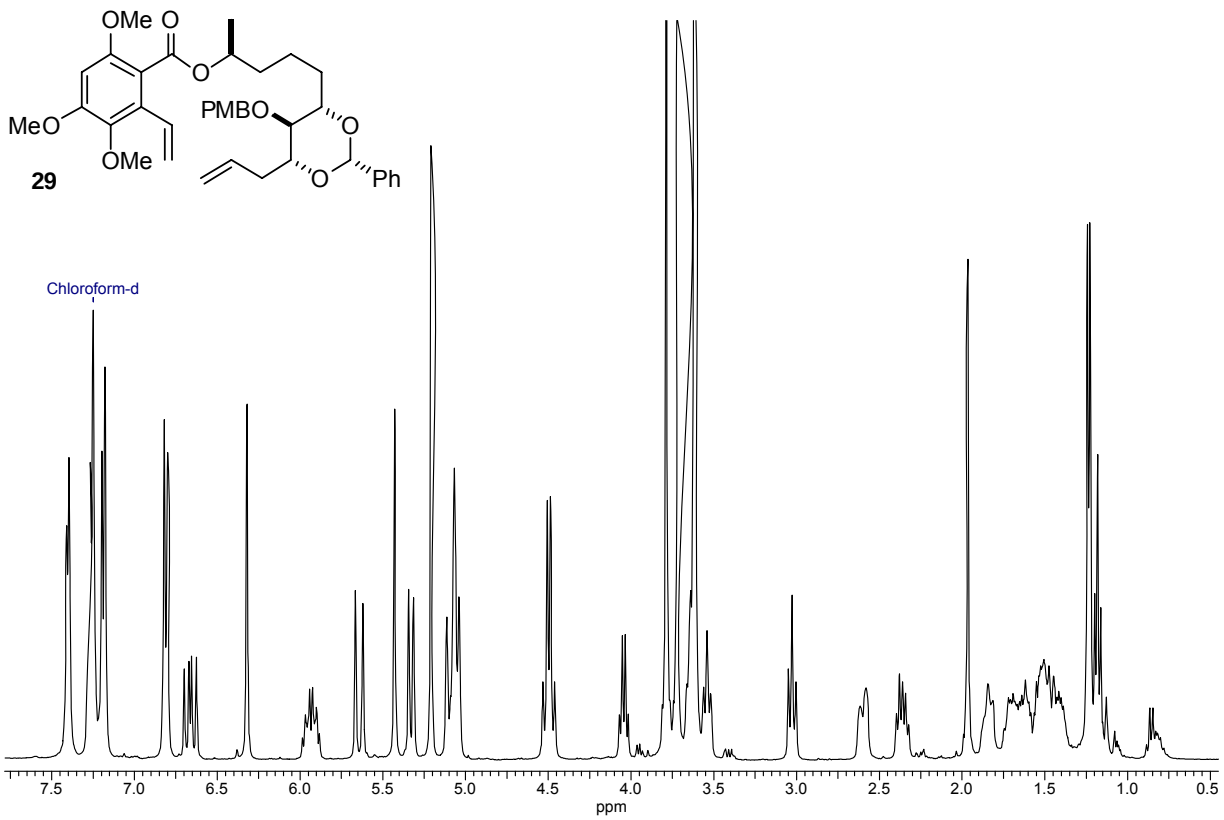

OTBS
PMBO
O
PivO
O
Ph
25
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

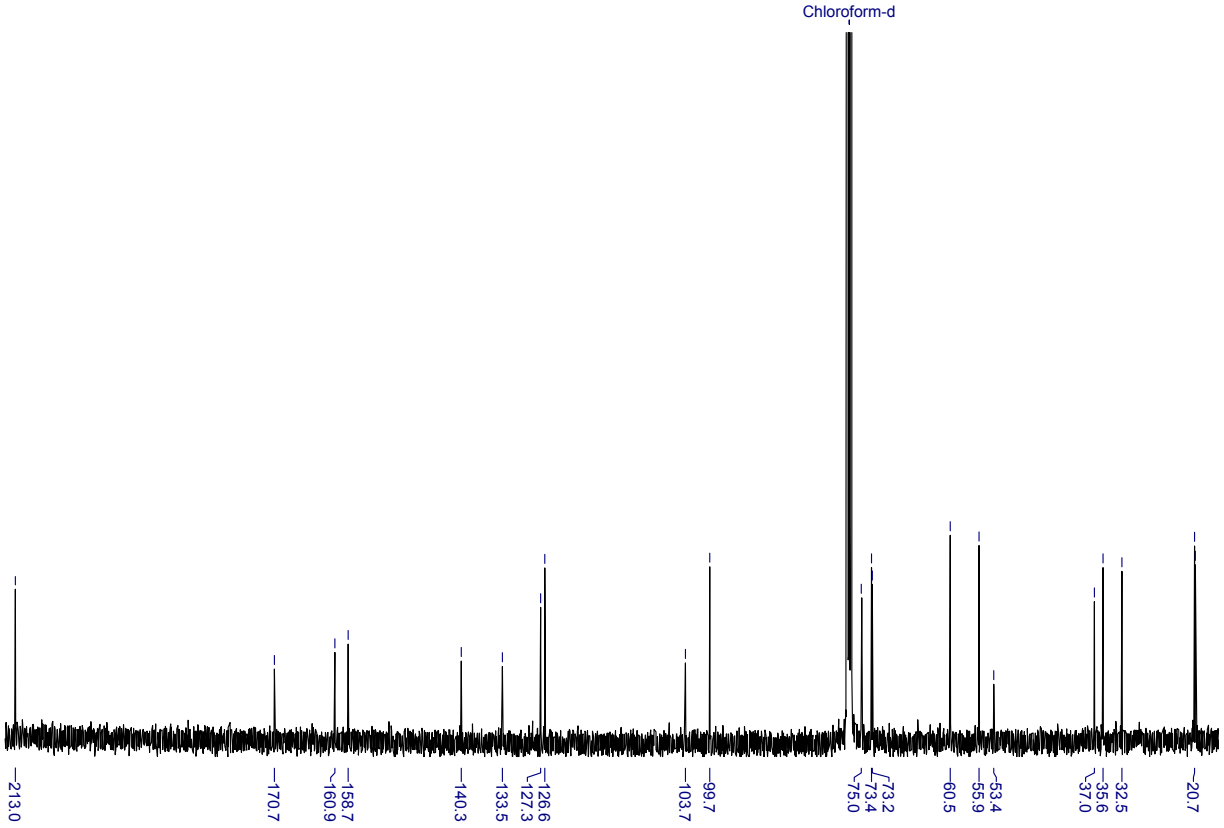

Chloroform-d
178.2
159.6
137.8
129.7
129.5
128.6
128.1
126.0
114.0
100.2
80.4
78.5
74.7
74.1
68.5
63.0
55.3
39.6
38.9
32.1
27.2
25.9
23.8
21.3
18.1
4.4
-4.7

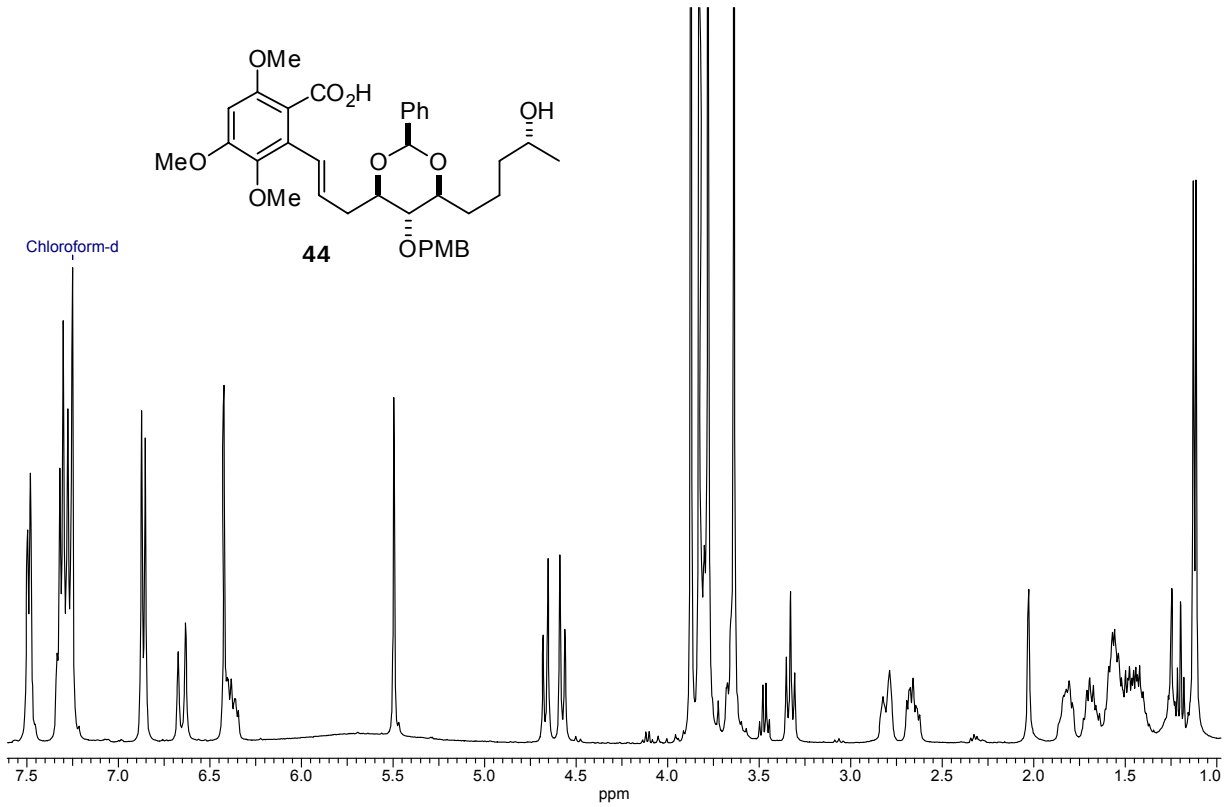

OH
PMBO
O
O
Ph
26
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
Chloroform-d
159.5
138.1
134.5
129.9
129.6
128.6
128.1
126.0
117.2
113.9
100.1
80.4
80.0
77.4
74.6
67.9
55.3
39.2
36.3
31.9
23.5
21.4


Chloroform-d
OTBS
PMBO
O
I
O
Ph
42
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

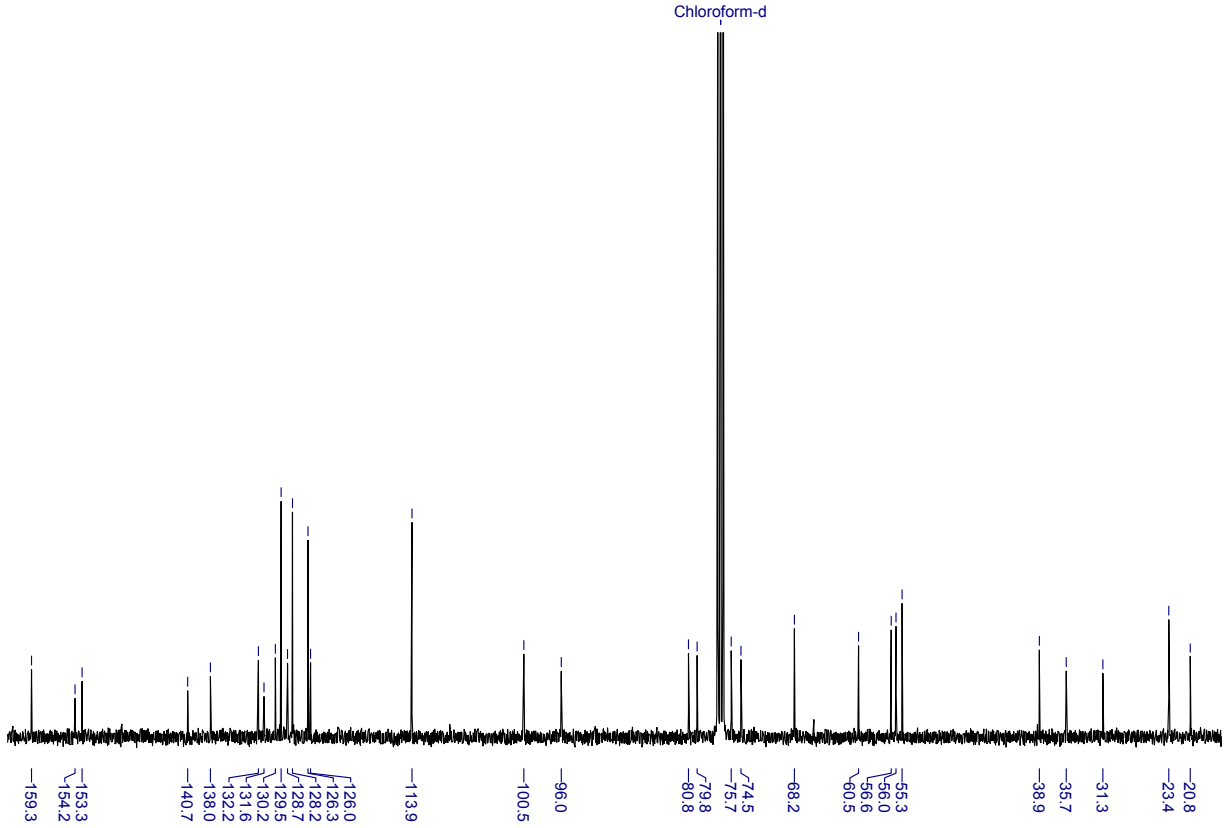

158.0
136.3
128.1
127.0
126.5
124.3
112.4
98.4
79.0
78.4
76.0
73.2
66.9
53.7
38.1
34.7
30.6
24.3
22.2
19.9
16.5
0.0
6.0
-6.3

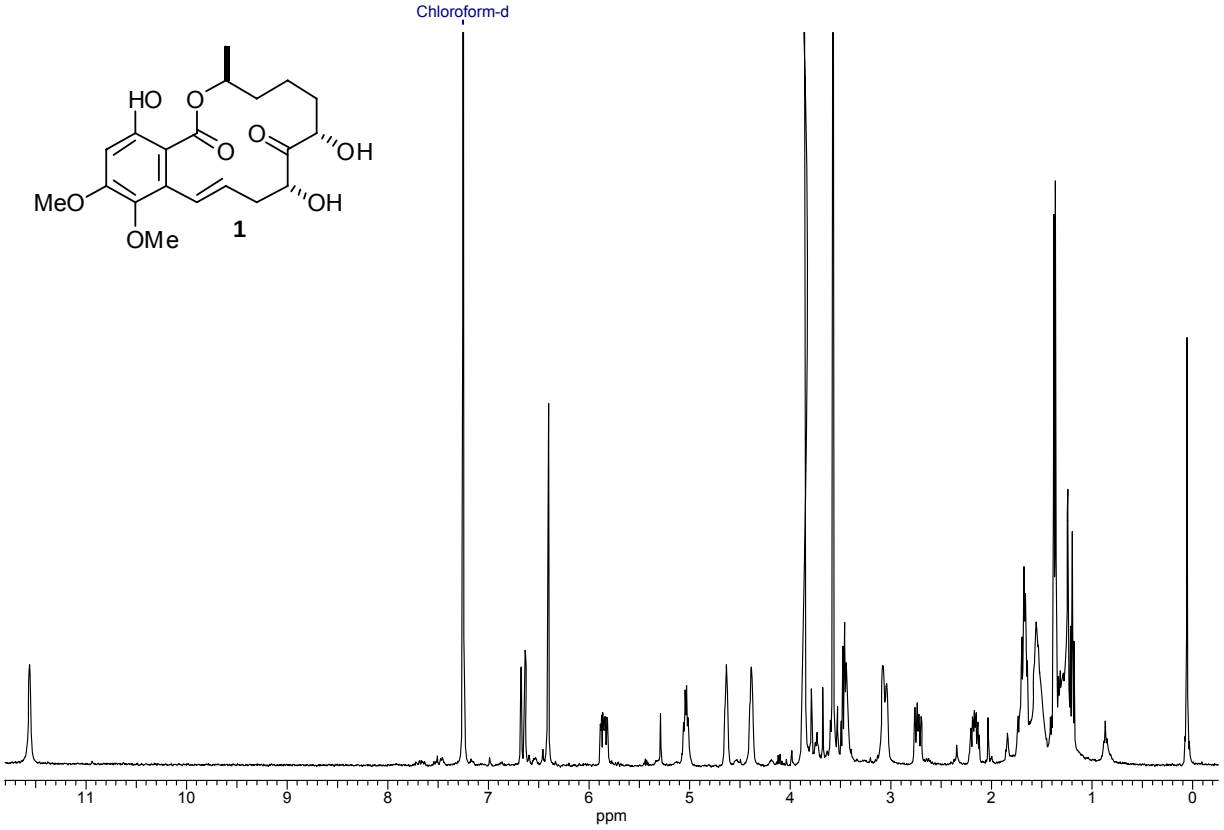

OMe O
O
MeO
PMBO
O
OMe
O
Ph
29
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

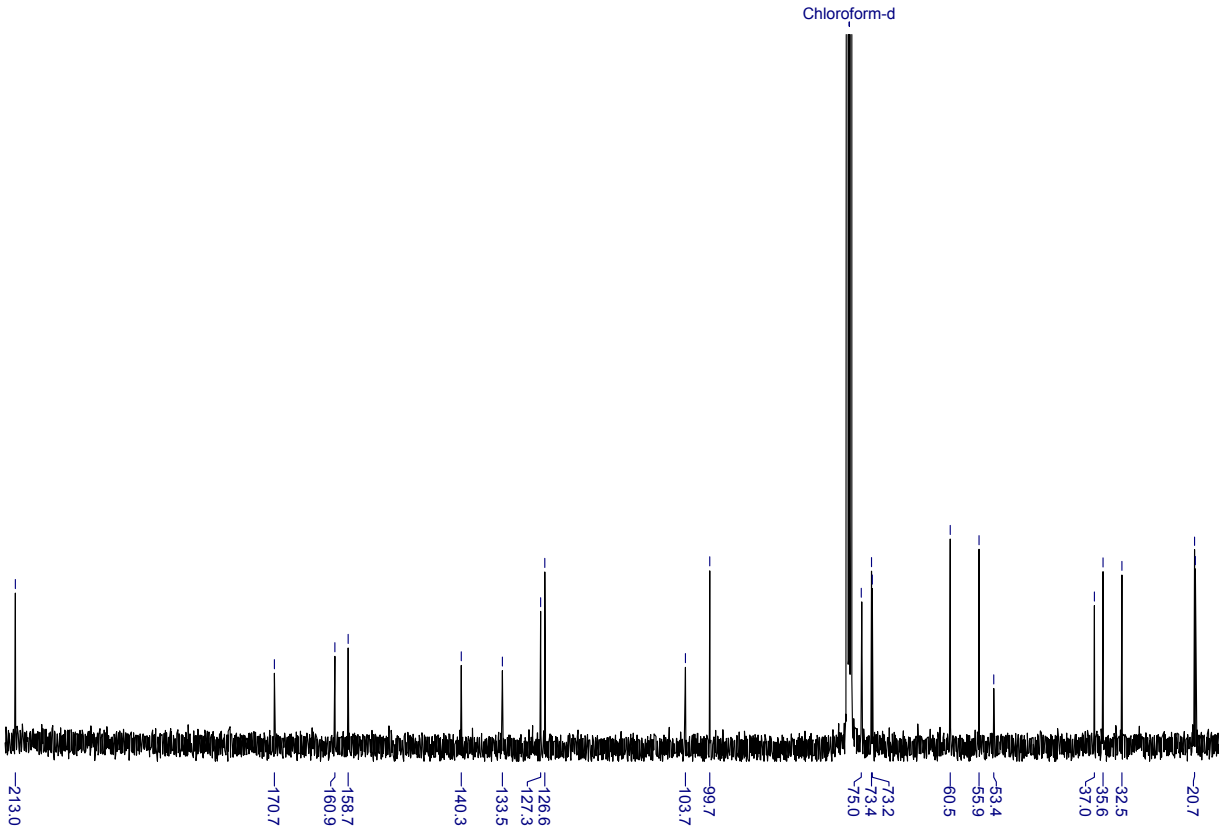

Chloroform-d
213.0
170.7
160.9
158.7
140.3
133.5
127.3
126.6
103.7
99.7
75.0
73.4
73.2
60.5
55.9
53.4
37.0
35.6
32.5
20.7


OMe
CO2H
Ph
OH
MeO
O
O
OMe
OPMB
Chloroform-d
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

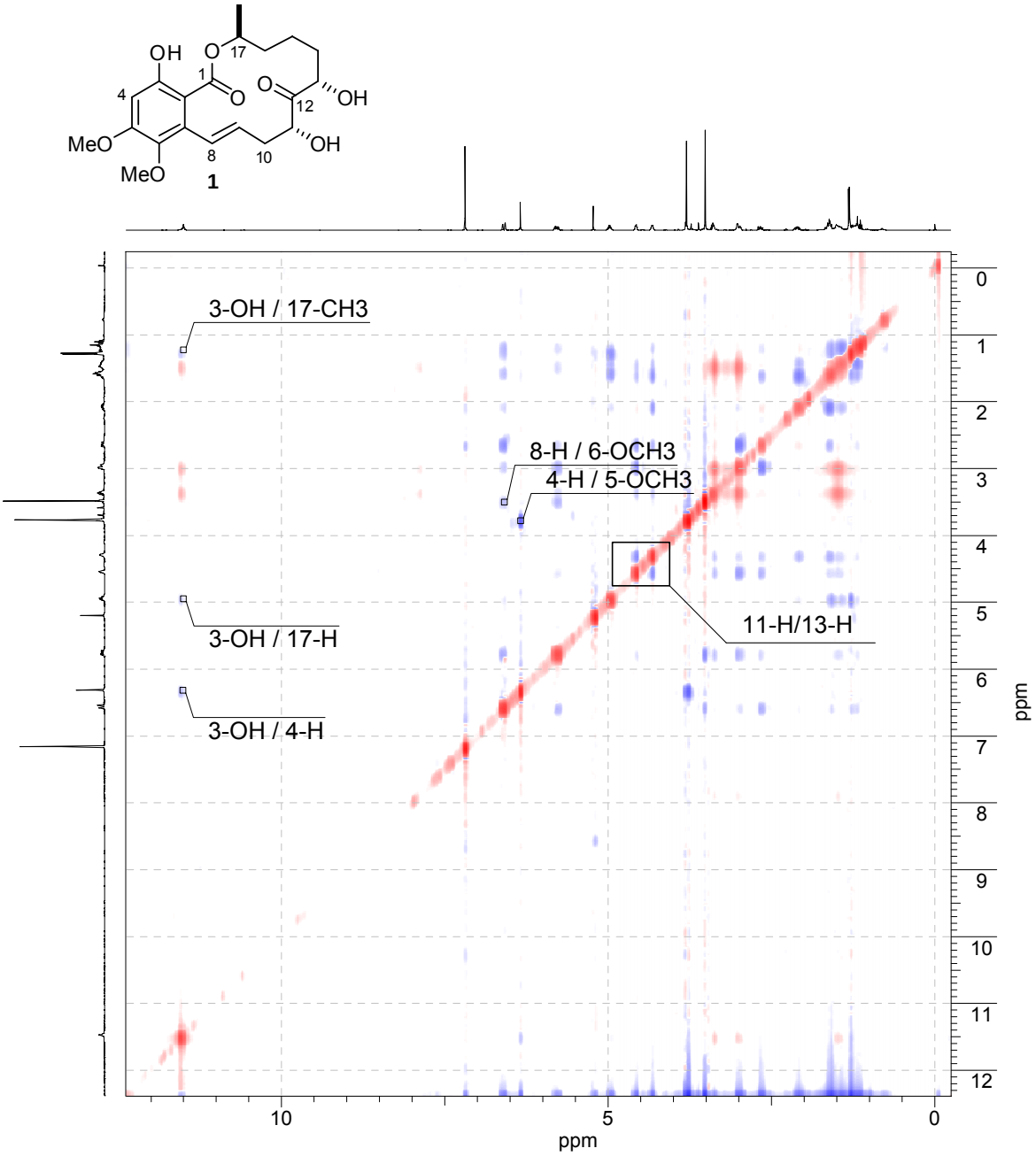
44


Chloroform-d
159.3
154.2
153.3
140.7
138.0
132.2
131.6
130.2
129.5
128.7
128.2
126.3
126.0
113.9
100.5
96.0
80.8
79.8
75.7
74.5
68.2
60.5
56.6
56.0
55.3
38.9
35.7
31.3
23.4
20.8

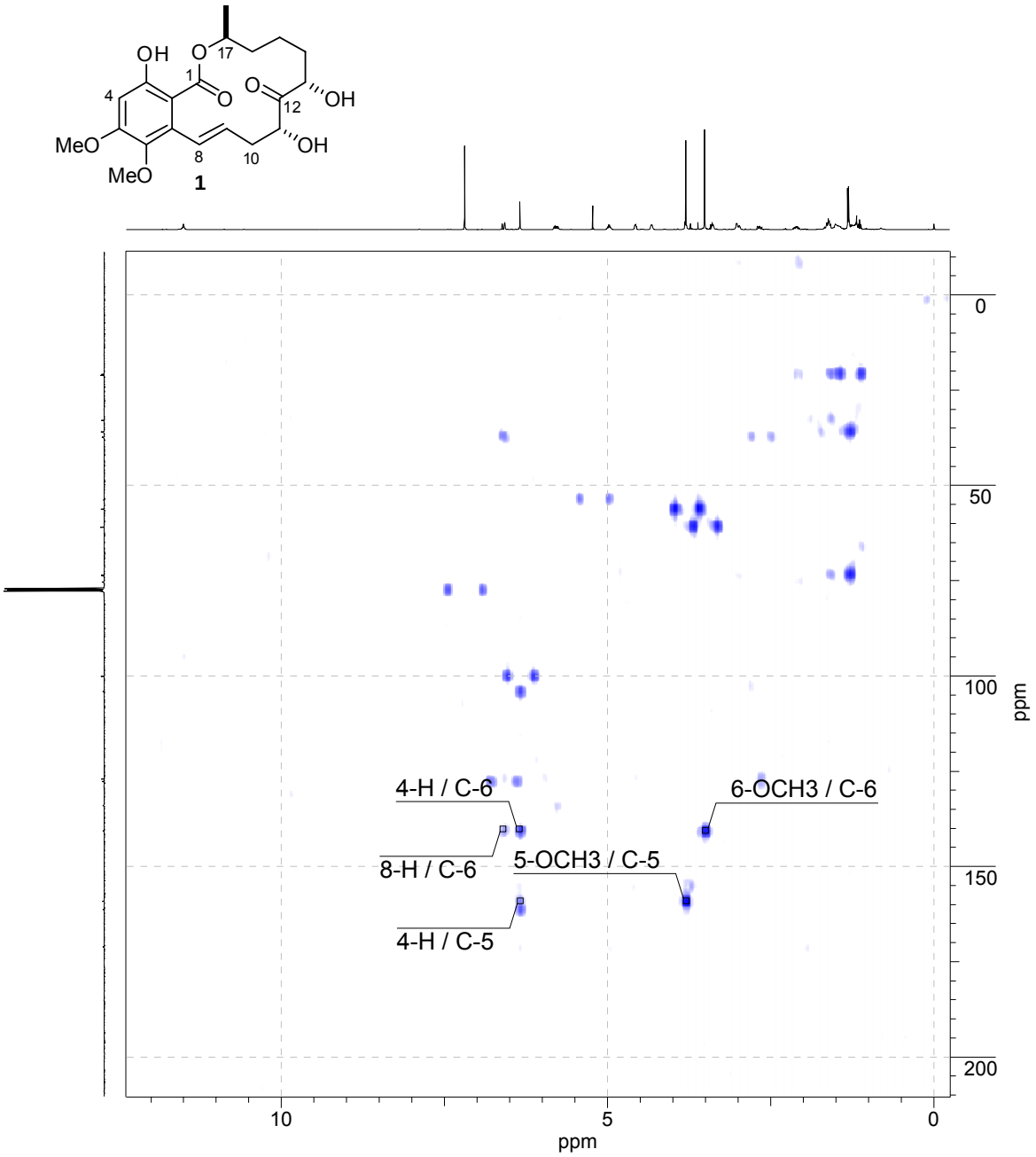

Chloroform-d
HO
O
O
O
OH
MeO
OH
OMe
1
11
10
9
8
7
6
5
4
3
2
1
0
ppm

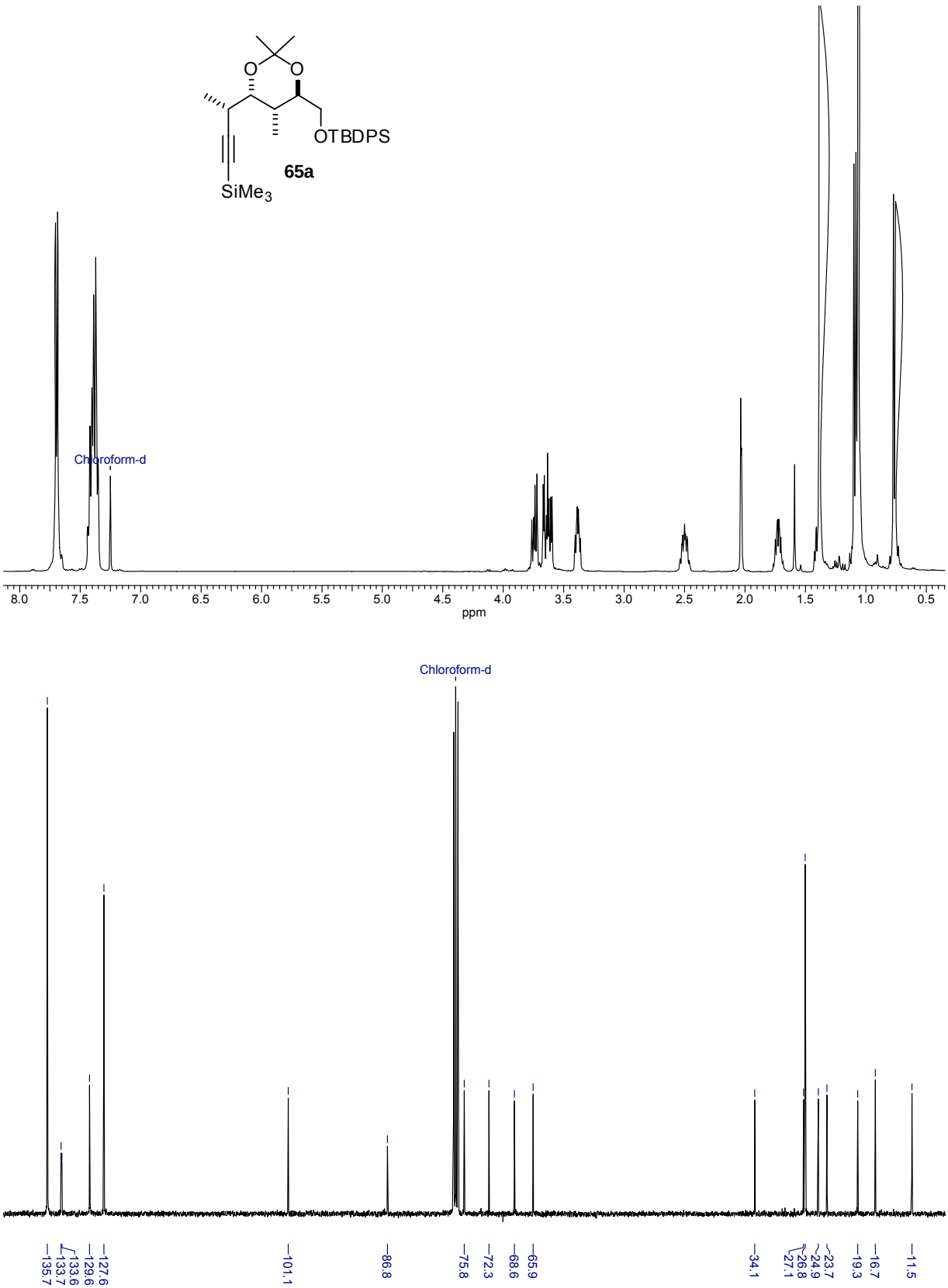

Chloroform-d
213.0
170.7
160.9
158.7
140.3
133.5
127.3
126.6
103.7
99.7
75.0
73.4
73.2
60.5
55.9
53.4
37.0
35.6
32.5
20.7

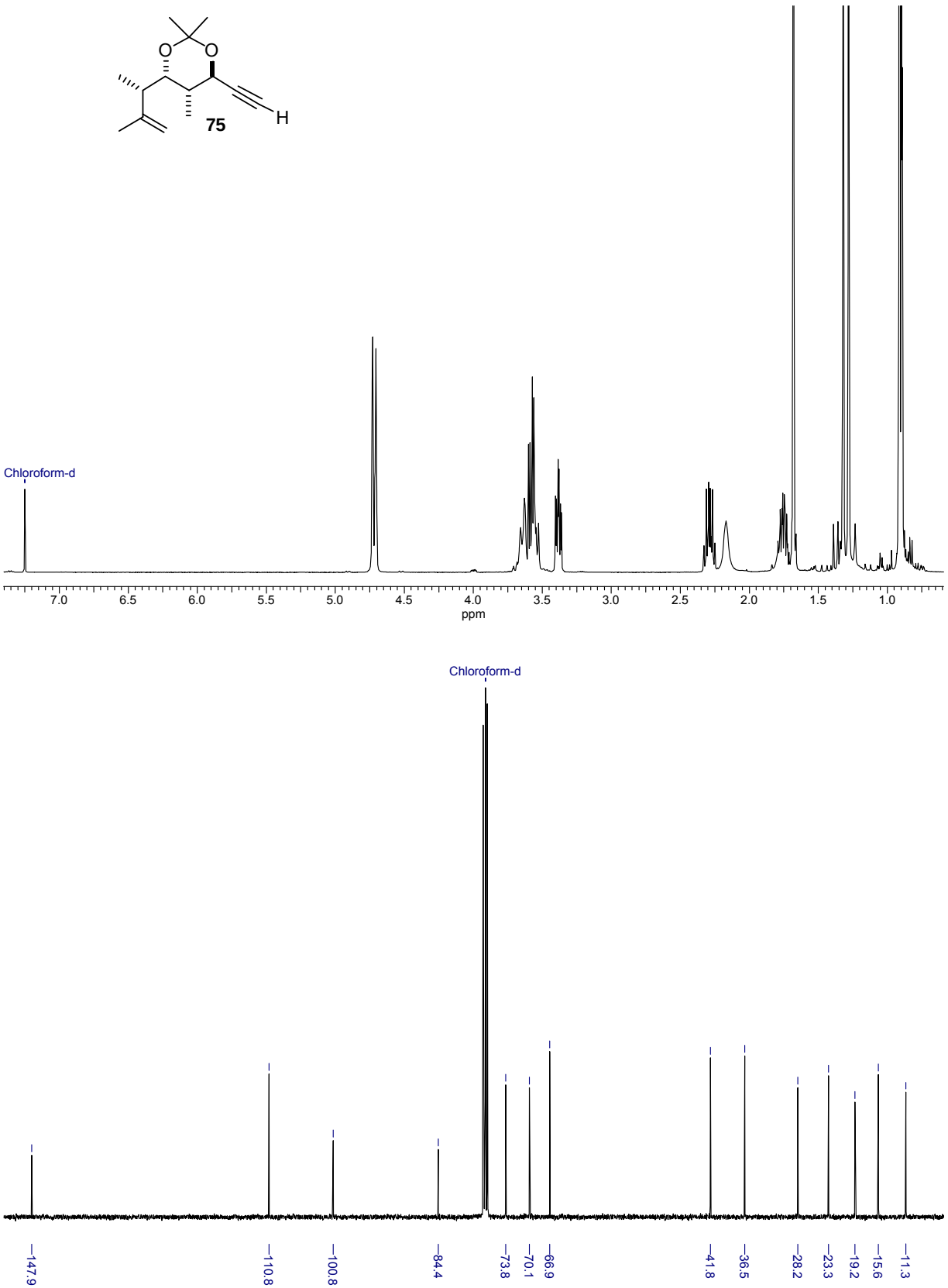
NOESY spectrum of **1**

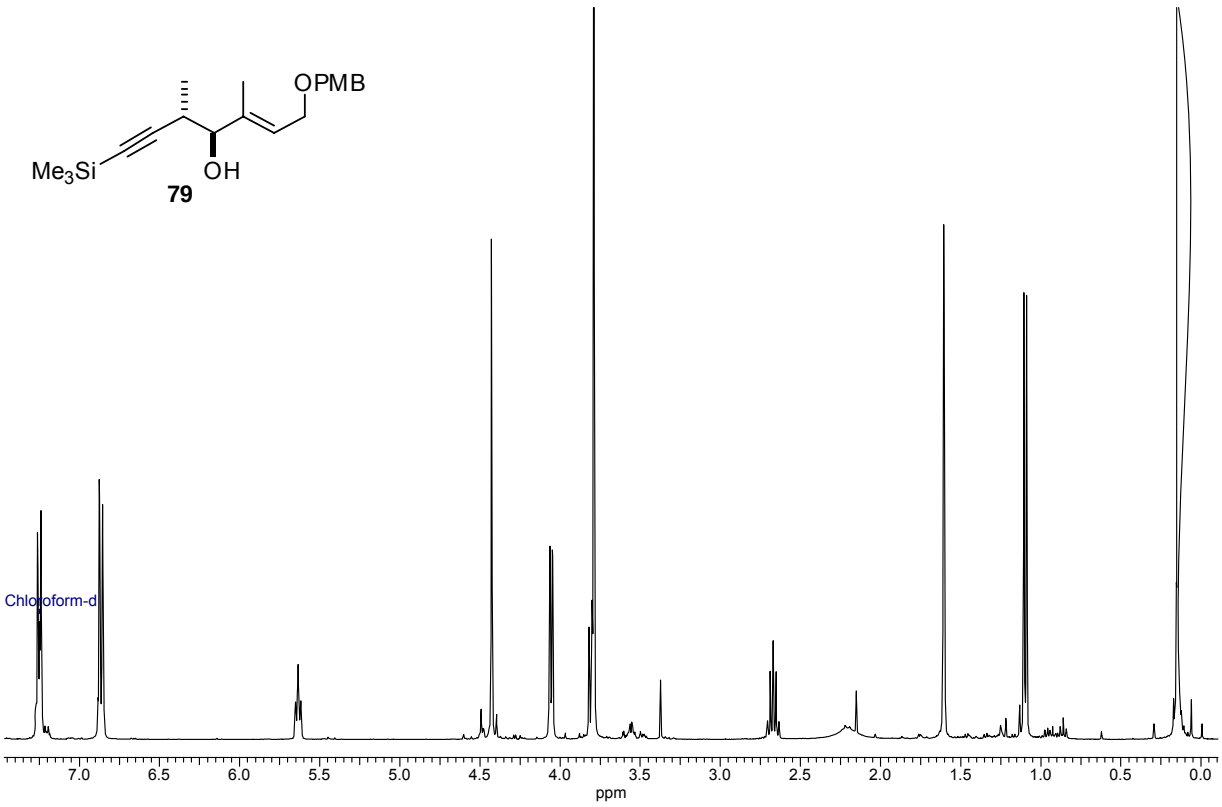


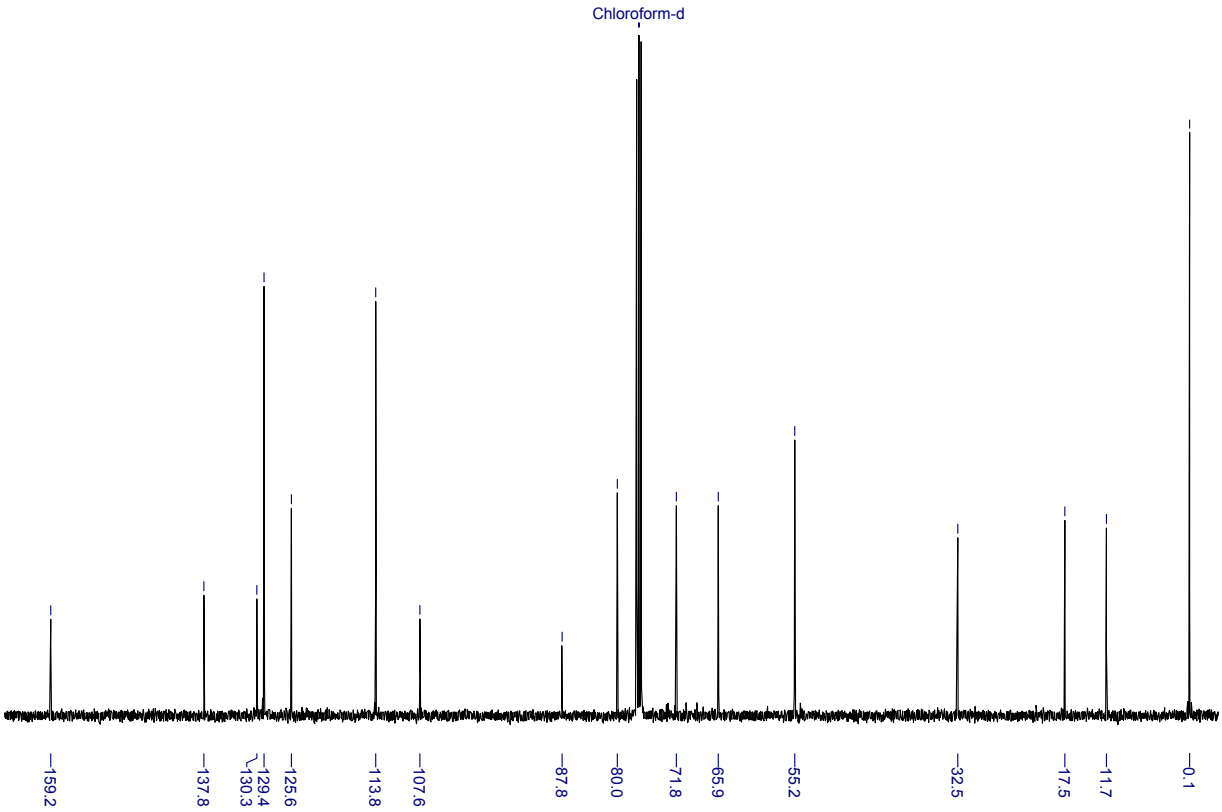
HMBC spectrum of **1**

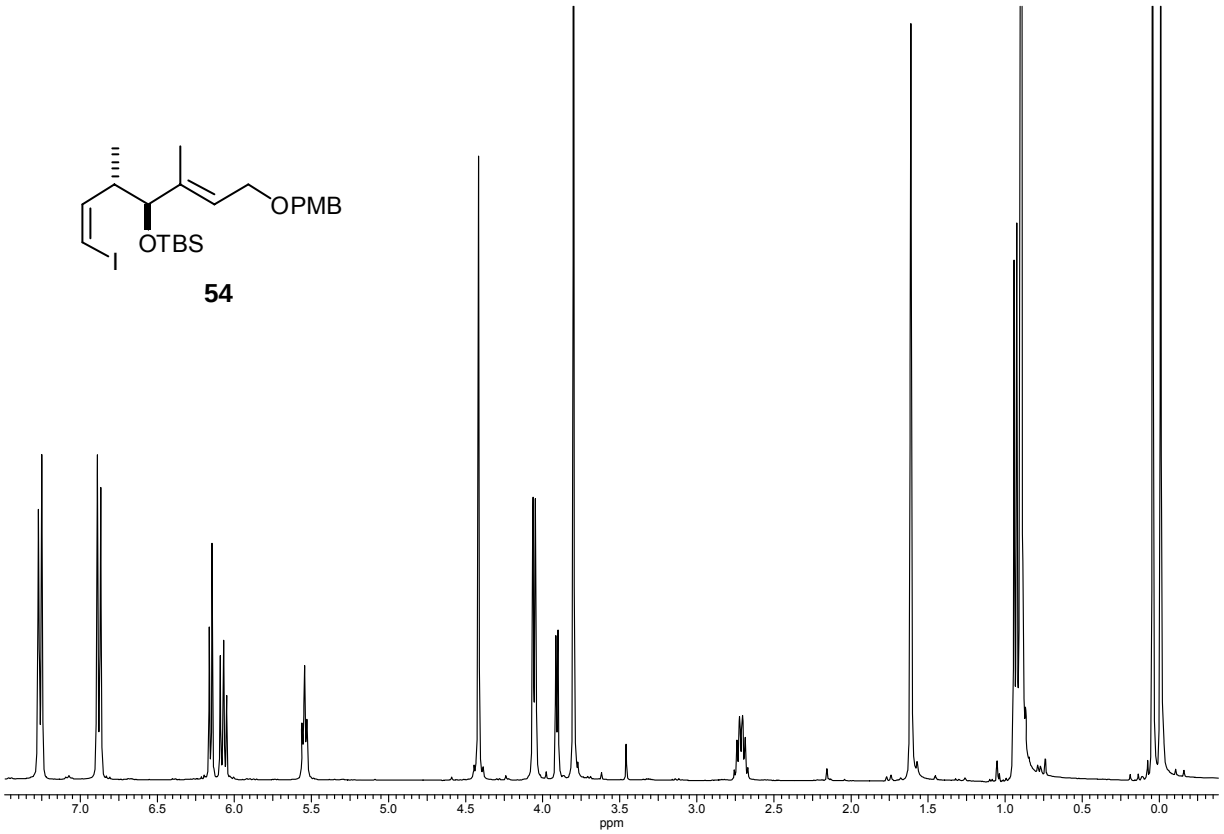


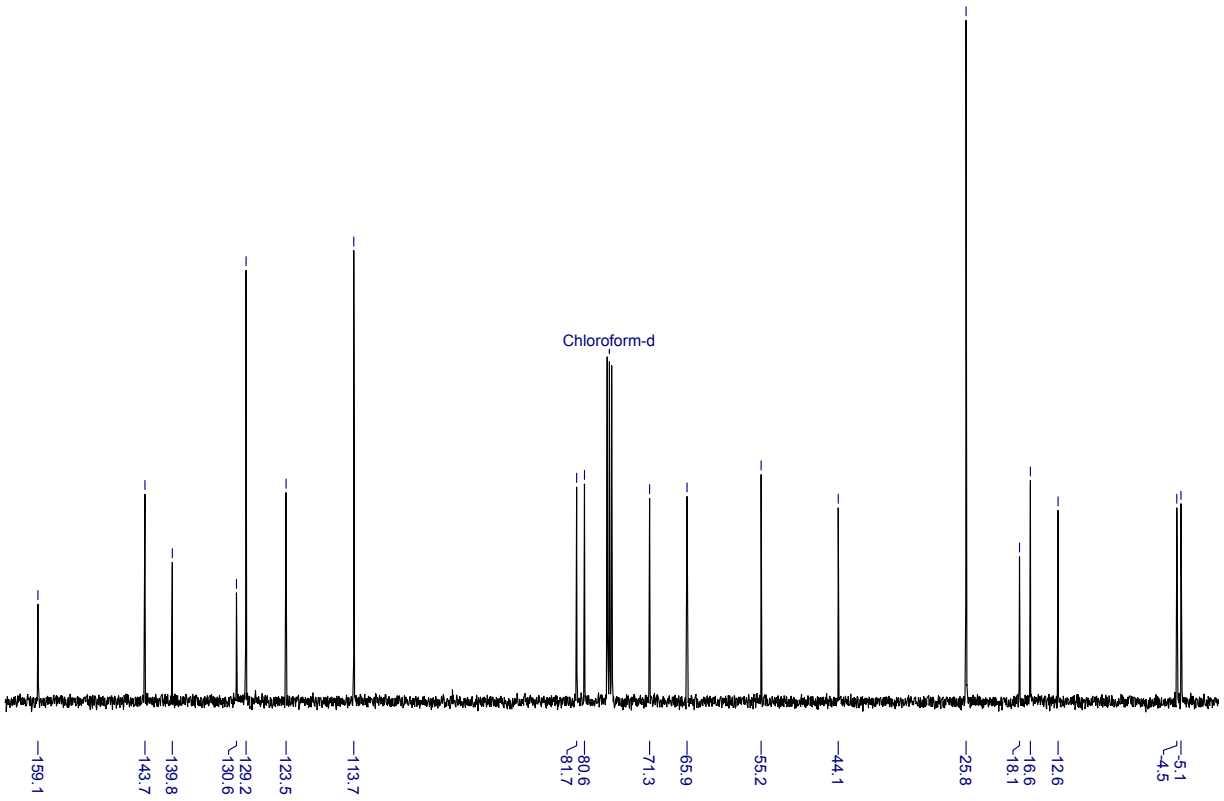

O
O
OTBDPS
SiMe3
65a
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
Chloroform-d
135.7
133.7
133.6
129.6
127.6
101.1
86.8
75.8
72.3
68.6
65.9
34.1
27.1
26.8
24.9
23.7
19.3
16.7
11.5

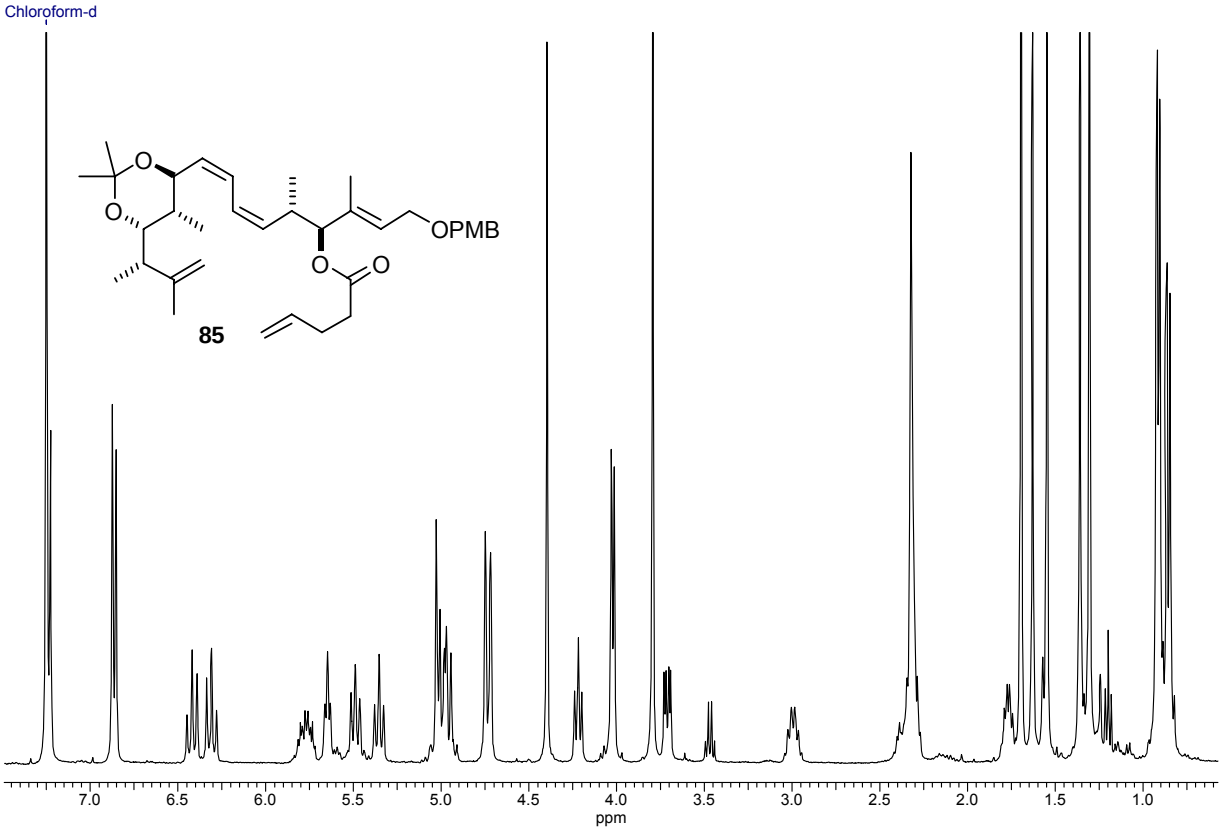

75
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
Chloroform-d
147.9
110.8
100.8
84.4
73.8
70.1
66.9
41.8
36.5
28.2
23.3
19.2
15.6
11.3


OPMB
Me3Si
OH
79
Chloroform-d
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

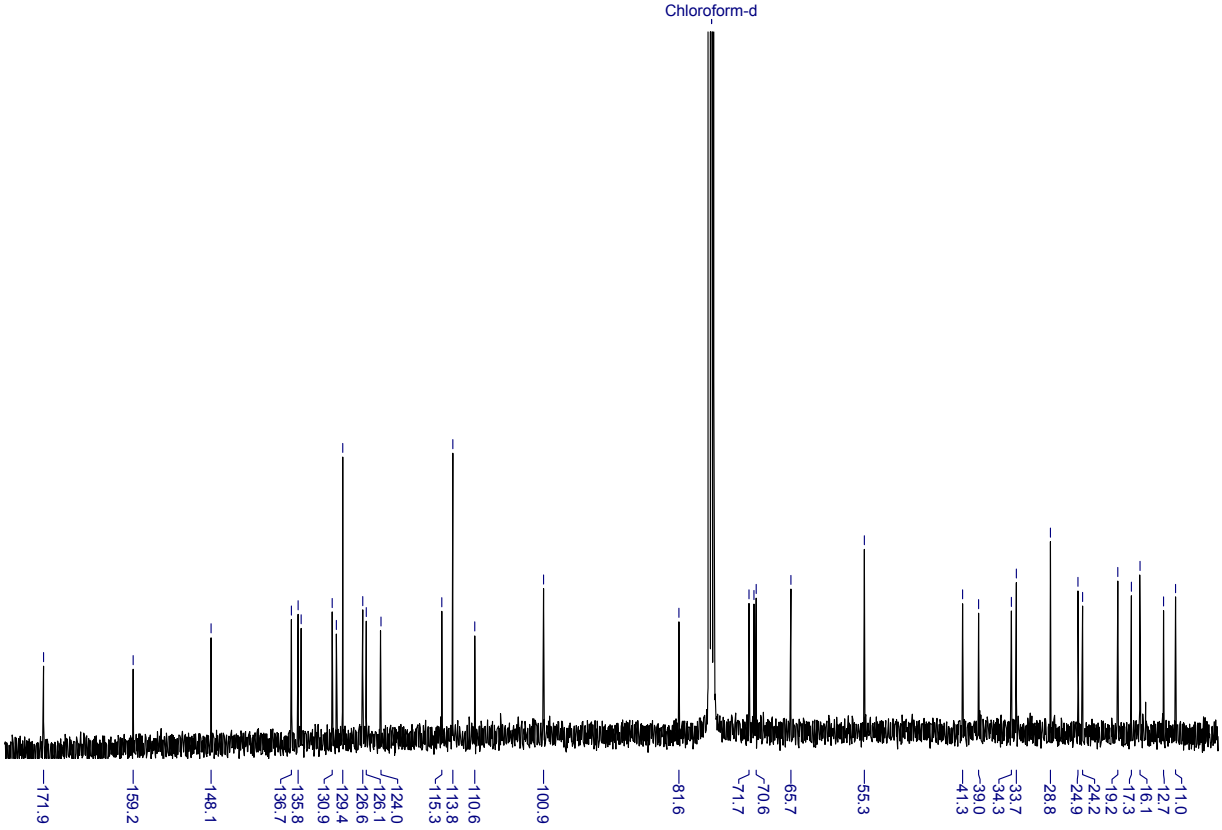

Chloroform-d
159.2
137.8
130.3
129.4
125.6
113.8
107.6
87.8
80.0
71.8
65.9
55.2
32.5
17.5
11.7
0.1

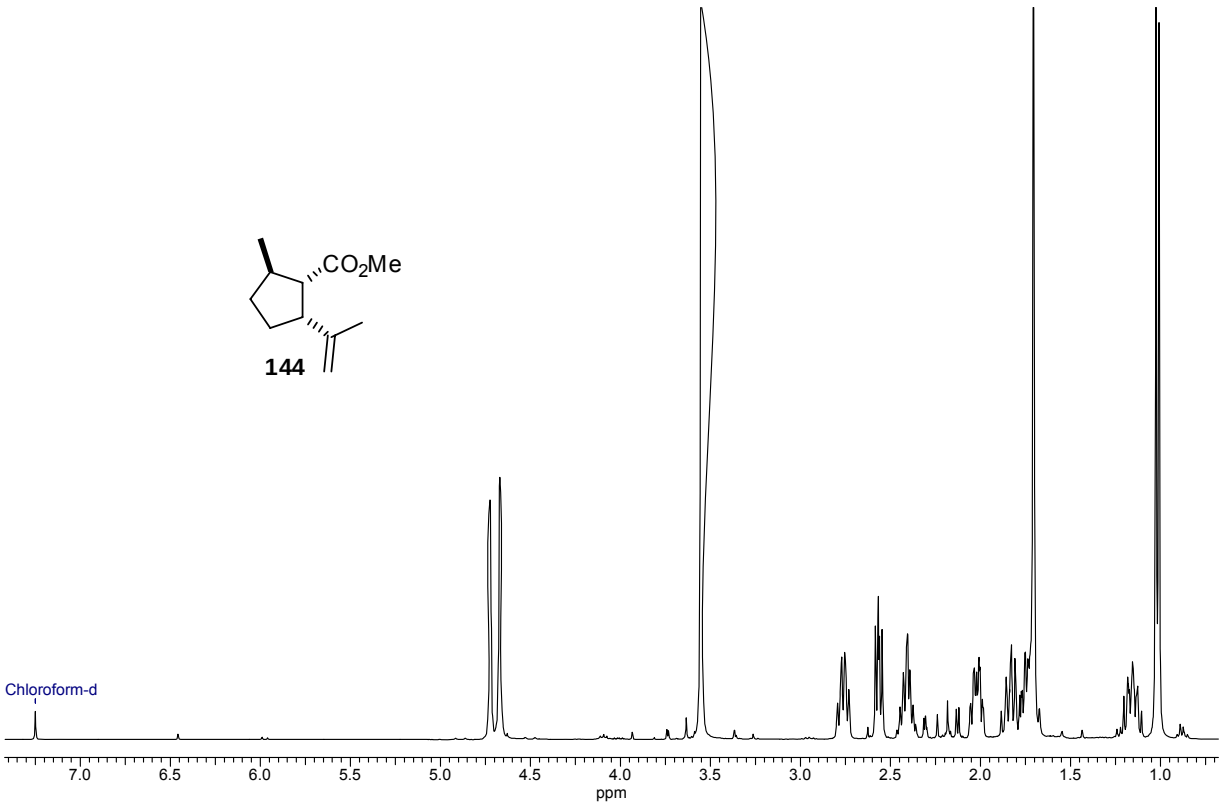

OPMB
OTBS
I
54
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

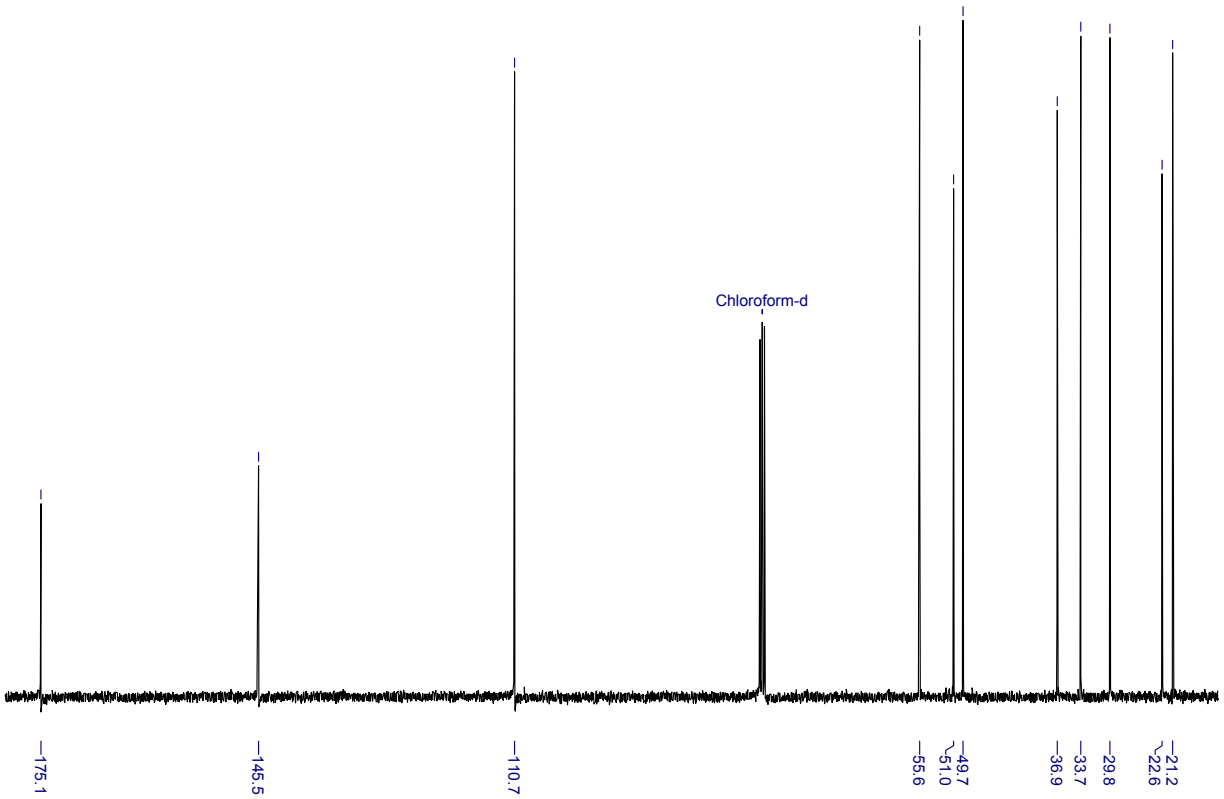

Chloroform-d
159.1
143.7
139.8
129.2
130.6
123.5
113.7
80.6
81.7
71.3
65.9
55.2
44.1
25.8
16.6
18.1
12.6
5.1
4.5

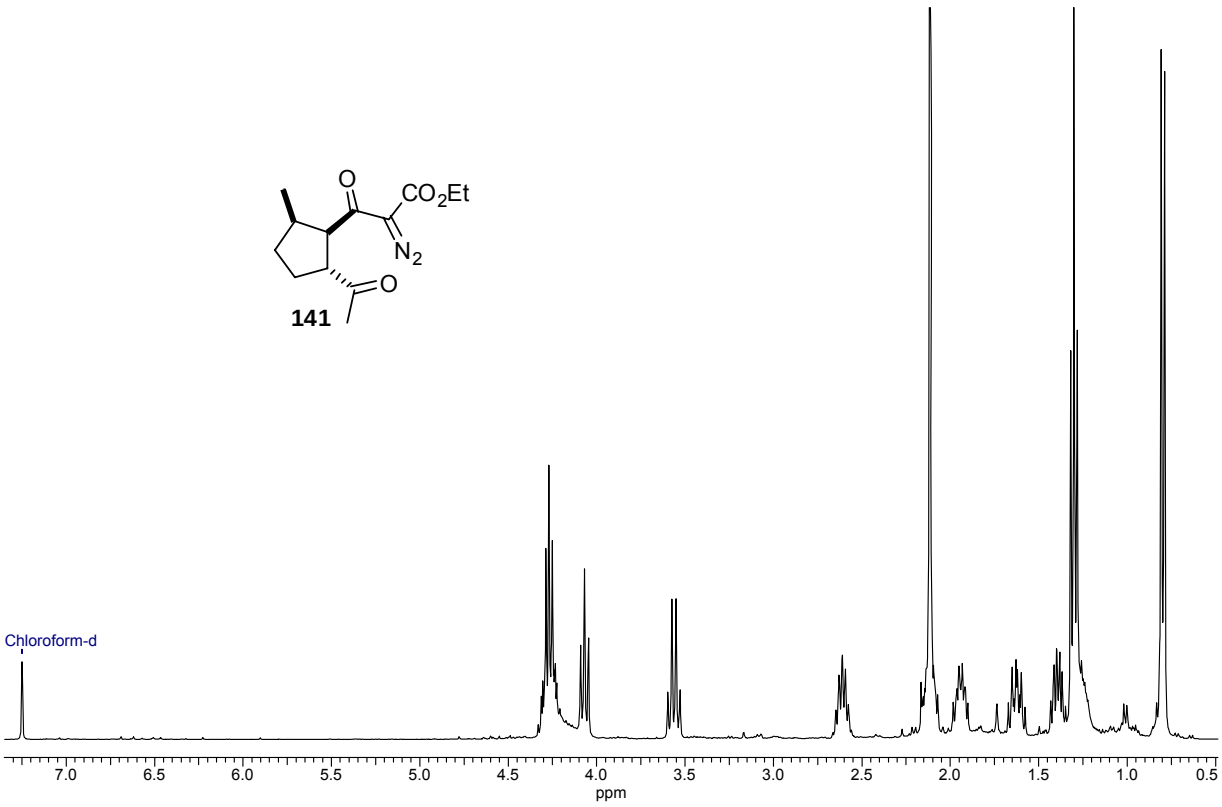

Chloroform-d
OPMB
O
O
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

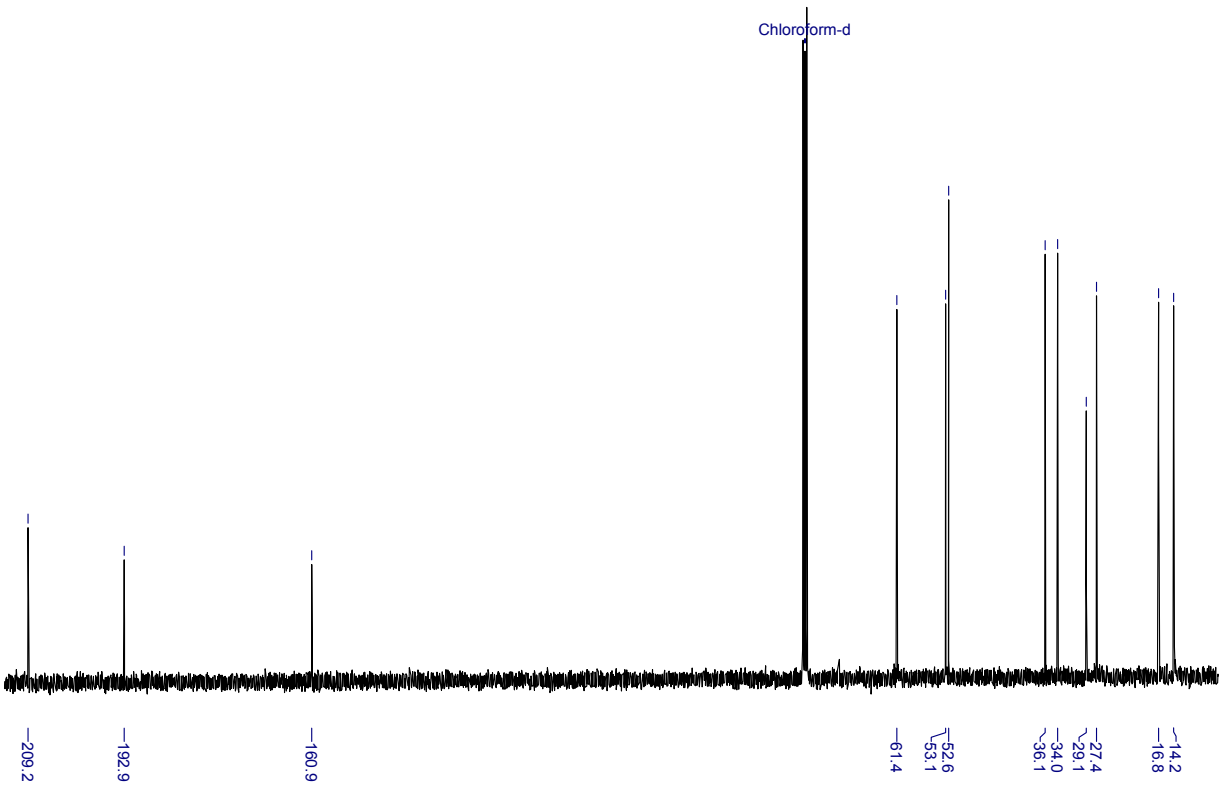
85

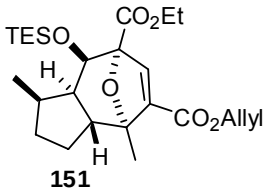

Chloroform-d
171.9
159.2
148.1
135.8
136.7
130.9
129.4
126.6
126.1
124.0
115.3
113.8
110.6
100.9
81.6
71.7
70.6
65.7
55.3
41.3
39.0
34.3
33.7
28.8
24.9
24.2
19.2
17.3
16.1
12.7
11.0


CO2Me
144
Chloroform-d
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


Chloroform-d
175.1
145.5
110.7
55.6
51.0
49.7
36.9
33.7
29.8
22.6
21.2

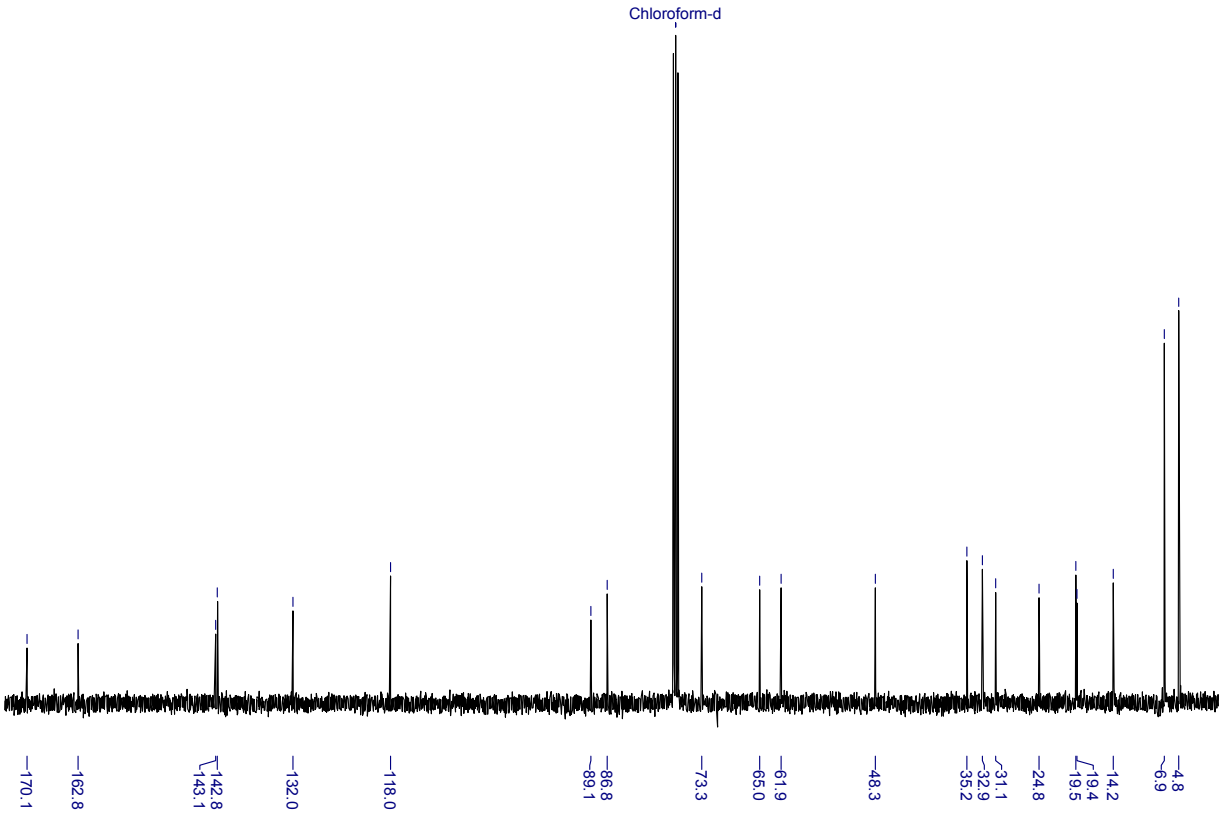

O
CO2Et
N2
O
141
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

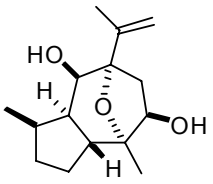

Chloroform-d
209.2
192.9
160.9
61.4
53.1
52.6
36.1
34.0
29.1
27.4
16.8
14.2


TESO
H
O
CO_2Et
CO_2Allyl
H

151

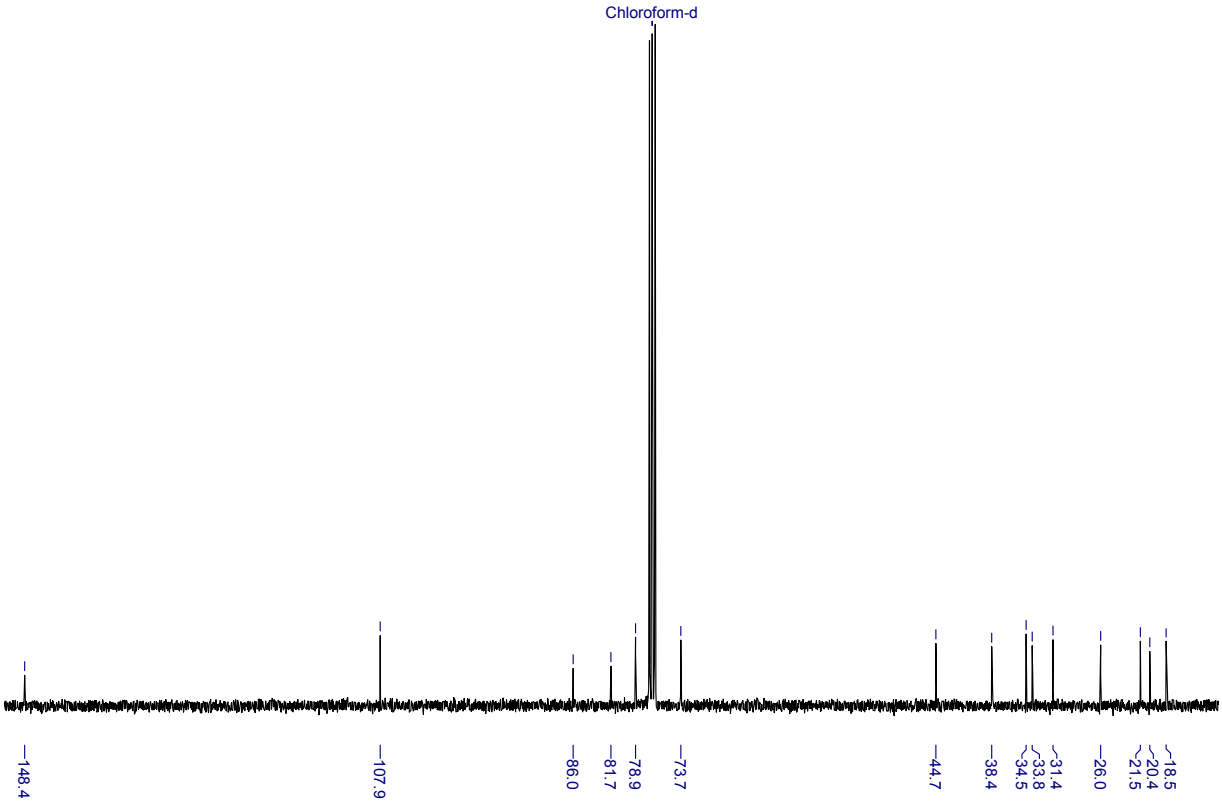
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

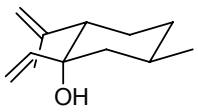

Chloroform-d
170.1
162.8
142.8
143.1
132.0
118.0
89.1
86.8
73.3
65.0
61.9
48.3
35.2
32.9
31.1
24.8
19.5
19.4
14.2
6.9
4.8


HO
H
O
OH
H

160

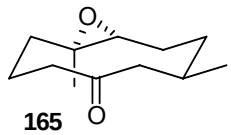
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
148.4
107.9
86.0
81.7
78.9
73.7
44.7
38.4
34.5
33.8
31.4
26.0
21.5
20.4
18.5


OH

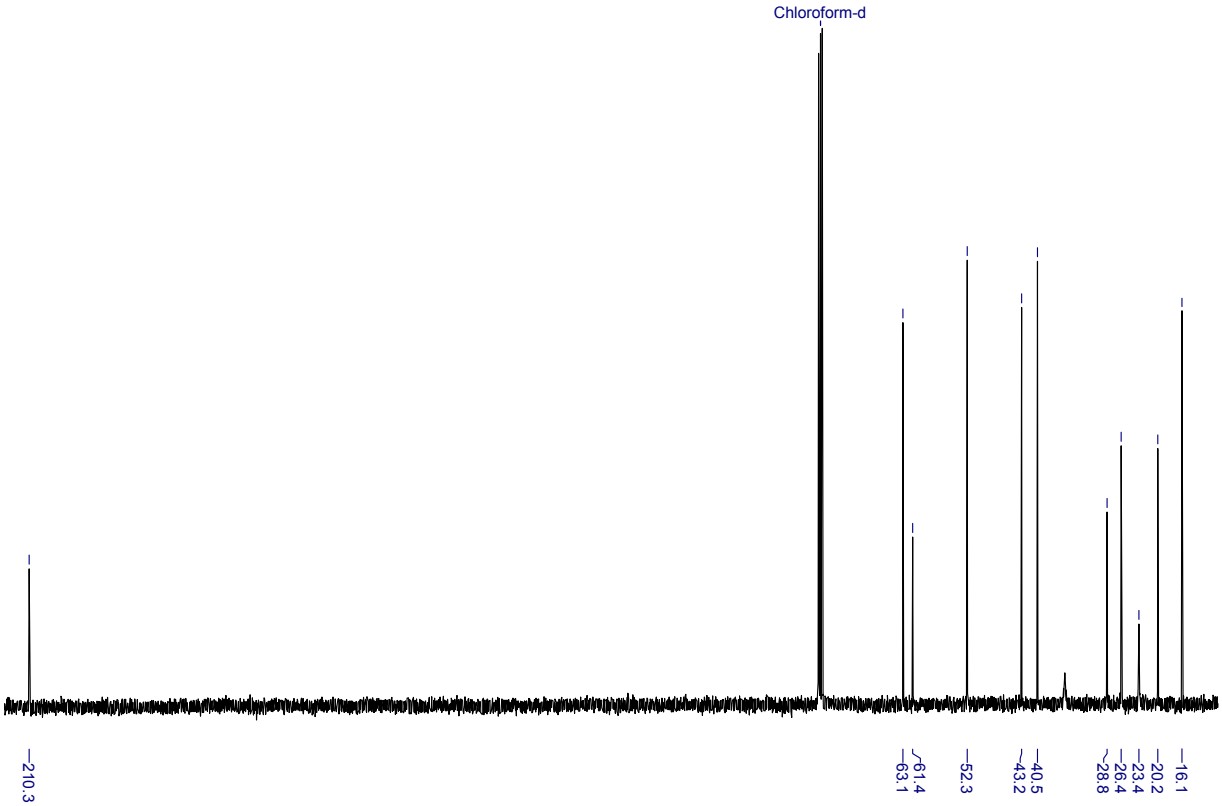
166

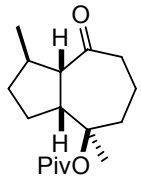
Chloroform-d
88.9
84.0
70.5
44.3
44.5
33.8
32.5
30.1
28.2
27.6
24.7
24.5
19.8
17.8
15.9
Chloroform-d
148.1
146.2
111.7
110.6
73.1
52.0
46.5
34.8
27.3
25.7
22.1



165

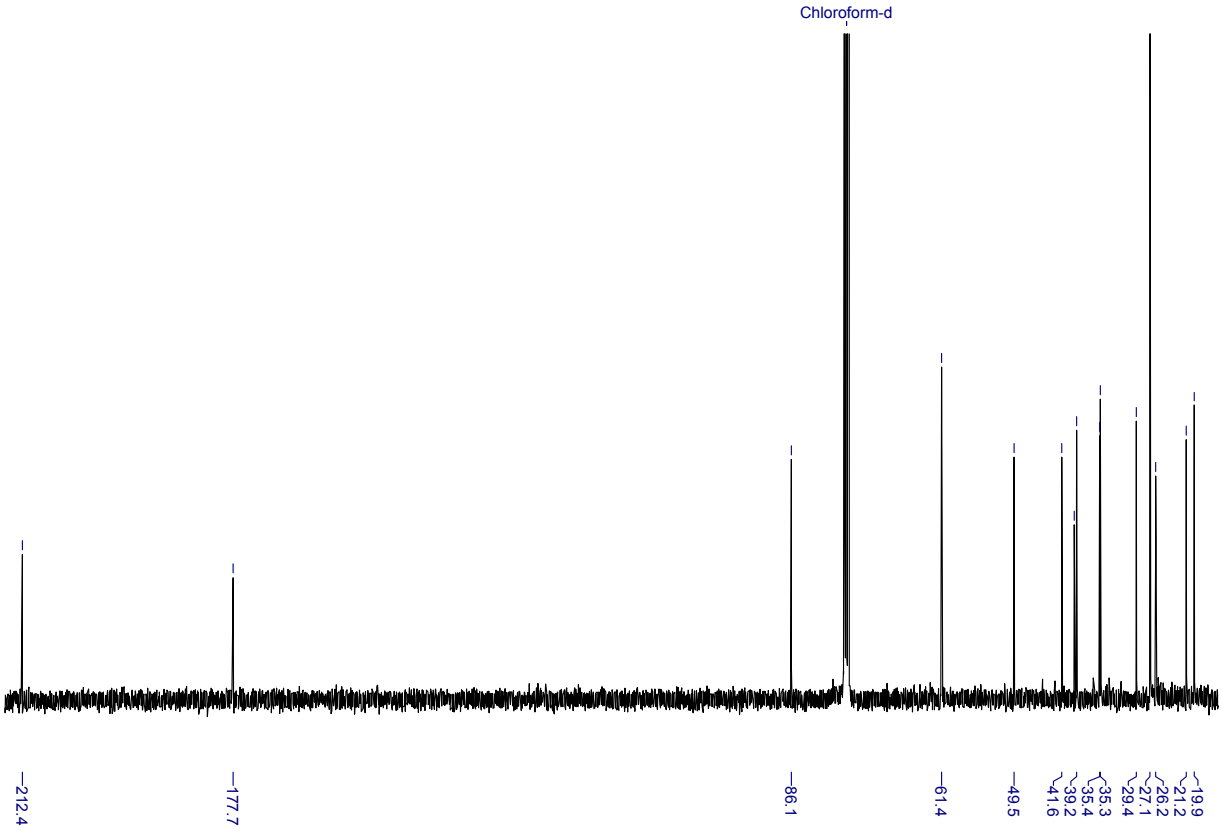
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

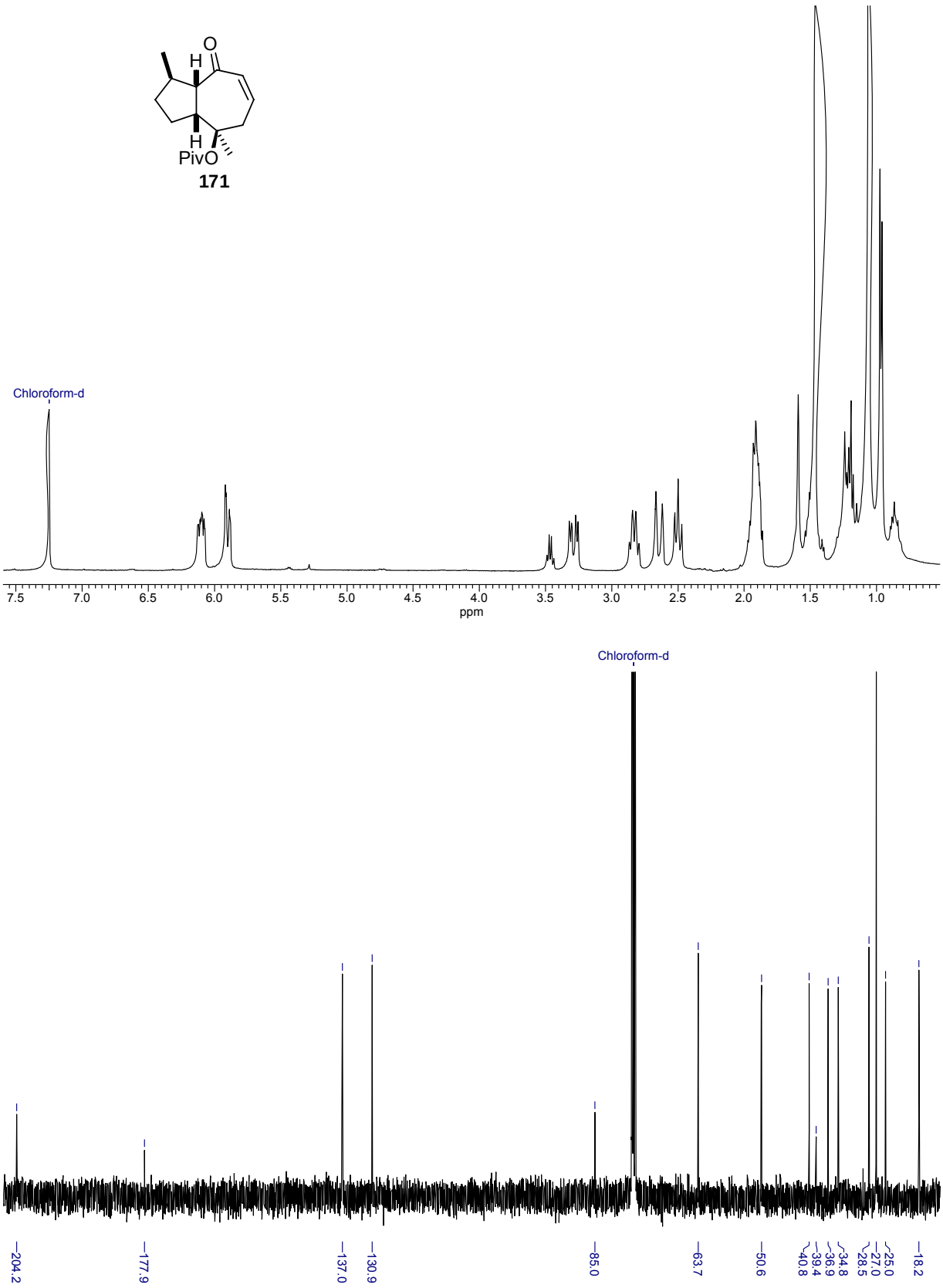

Chloroform-d
210.3
63.1
61.4
52.3
43.2
40.5
28.8
26.4
23.4
20.2
16.1

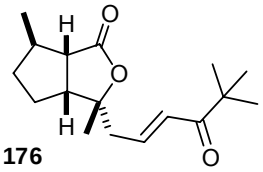

O
H
H
PivO

170

Chloroform-d
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

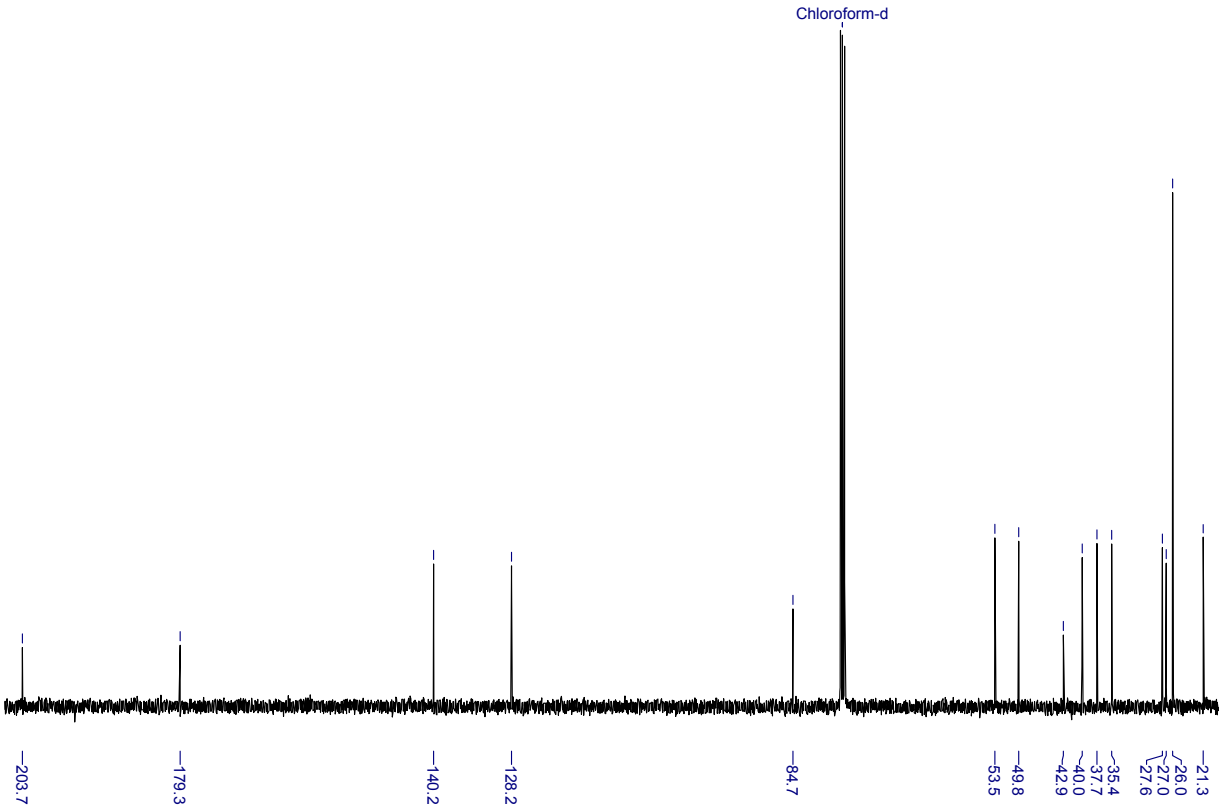

Chloroform-d
212.4
177.7
86.1
61.4
49.5
41.6
39.2
35.4
35.3
29.4
27.1
26.2
21.2
19.9


O
H
H
PivO
171
Chloroform-d
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
Chloroform-d
204.2
177.9
137.0
130.9
85.0
63.7
50.6
40.8
39.4
36.9
34.8
28.5
27.0
25.0
18.2


H
O
O
H
O

176

Chloroform-d
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


Chloroform-d
203.7
179.3
140.2
128.2
84.7
53.5
49.8
42.9
40.0
37.7
35.4
27.6
27.0
26.0
21.3

Bibliography

[1] Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477-1489.

[2] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, Wiley-VCH, Weinheim, **1995**.

[3] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**.

[4] Grubbs, R. H. *Chem. Sci.* **2007**, *4*, C69.

[5] Trost, B. M. *Science* **1991**, *254*, 1471-1477.

[6] Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40-49.

[7] Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

[8] Young, I. S.; Baran, P. S.; *Nature Chem.* **2009**, *1*, 193-205.

[9] For selected synthesis, see: a) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404-408. b) Trost, B. M.; Dong, G.; *Nature* **2008**, *456*, 485-488. c) Chen, K.; Baran, P. S.; *Nature* **2009**, *459*, 824-828. d) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *47*, 17066-17067.

[10] For review, see: Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22-36.

[11] For theses, see: a) Moulin, E. *PhD Thesis*, Louis Pasteur University, Strasbourg, **2006** and references therein. b) Khartulyari, A. S. *PhD Thesis*, University of Tuebingen, **2007** and references therein. c) Ugele, M. *PhD Thesis*, University of Tuebingen, **2009** and references therein. d) Zimmermann, T. J.; Niesen, F. H.; Pilka, E. S.; Knapp, S.; Oppermann, U.; Maier, M. E. *Bioorg. Med. Chem.* **2009**, *17*, 530-536.

[12] Ellestad, G. A.; Lovell, F. M.; Perkinson, N. A.; Hargreaves, R. T.; McGahren, W. J. *J. Org. Chem.* **1978**, *43*, 2339-2343.

[13] Zhao, A.; Lee, S. H.; Mojena, M.; Jenkins, R. G.; Patrick, D. R.; Huber, H. E.; Goetz, M. A.; Hensens, O. D.; Zink, D. L.; Vilella, D.; Dombrowski, A. W.; Lingham, R. B.; Huang, L. *J. Antibiot.* **1999**, *52*, 1086-1094.

[14] Dakas, P.-Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6899-6902 and references therein.

[15] Isaka, M.; Chinthanom, P.; Kongthong, S.; Supothina, S.; Ittiworapong, P. *Tetrahedron* **2010**, *66*, 955-961.

[16] Liniger, M.; Neuhaus, C.; Hofmann, T.; Fransioli-Ignazio, L.; Jordi, M.; Drueckes, P.; Trappe, J. r.; Fabbro, D.; Altmann, K.-H. *ACS Med. Chem. Lett.* **2010**, *ASAP*. Accessed on November 29, 2010.

[17] Hoshino, Y.; Ivanova, V. B.; Yazawa, K.; Ando, A.; Mikami, Y.; Zaki, S. M.; Karam, A.-Z. A.; Youssef, Y. A.; Gräfe, U. *J. Antibiotics* **2002**, *55*, 516-519.

[18] Khartulyari, A. S.; Kapur, M.; Maier, M. E. *Org. Lett.* **2006**, *8*, 5833-5836.

[19] For some review, see: a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199-2238. b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490-4527. c) Gradillas, A.; Castells, J.

P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101. d) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708-3742.

[20] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

[21] Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-2382. For a review, see: Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551-2651.

[22] Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189-1193.

[23] Liu, Z.-Y.; Chen, Z.-C.; Yu, C.-Z.; Wang, R.-F.; Zhang, R.-Z.; Huang, C.-S.; Yan, Z.; Cao, D.-R.; Sun, J.-B.; Li, G. *Chem.–Eur. J.* **2002**, *8*, 3747-3756.

[24] a) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. b) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem.–Eur. J.* **2006**, *12*, 1397-1402.

[25] a) Wilk, B. K. *Synth. Commun.* **1993**, *23*, 2481-2484. b) Aesa, M. C.; Baán, G.; Novák, L.; Szántay, C. *Synth. Commun.* **1995**, *25*, 1545-1550.

[26] a) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183-188. b) Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519-5527. c) Watanabe, M.; Ijichi, S.; Furukawa, S. *Synthesis* **1993**, 94-98.

[27] Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911-939.

[28] Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488-1489.

[29] Pragani, R.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4613-4616.

[30] Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 3951-3954. For a recent application of this methodology, see: a) Jogireddy, R.; Dakas, P.-Y.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.–Eur. J.* **2009**, *15*, 11498-11506. b) Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.–Eur. J.* **2009**, *15*, 11490-11497.

[31] Seleno ether **47** was prepared in eight steps from 5-bromovanillin: a) Sánchez, I. H.; Larraza, M. I.; Basurto, F.; Yafnez, R.; Avila, S.; Tovar, R.; Joseph-Nathan, P. *Tetrahedron* **1985**, *41*, 2355-2359. b) Evans, G. E.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 755-761. c) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem.–Eur. J.* **2002**, *8*, 1856-1871.

[32] a) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, *7*, 4153-4159. b) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899-902. c) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249-282.

[33] Maier, M. E.; *Nat. Prod. Rep.* **2009**, *26*, 1105-1124.

[34] Wright, A. E.; Reed, J. K.; Roberts, J.; Longley, R. E. U.S. Pat. Appl. Publ.; US, **2008** 033035; pp. 14 pp; CAN 148:230104.

[35] a) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630-5631. b) Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386-6389.

[36] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912-4915.

[37]http://www.rsmas.miami.edu/groups/ohh/courses/23nov12wrightmarinenaturalproductsdrugdiscovery.pdf

[38] a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26-28. b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563-2585.

[39] For examples of relay metathesis, see: a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211. b) Wallace, D. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912-1915. c) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4261-4263.

[40] a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812-3813. b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201-5204. c) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840-4844.

[41] see also: Jägel, J.; Maier, M. E. *Synlett* **2006**, 693-696.

[42] Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1-13.

[43] a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825-2828. b) Zünger, M.; Weller, T.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005-2009.

[44] a) Fehr, C.; Guntern, O. *Helv. Chim. Acta* **1992**, *75*, 1023-1028. b) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **2005**, *88*, 3128-3136.

[45] Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036-8045.

[46] For a review, see: Fürstner, A. *Synthesis* **1989**, 571-590.

[47] a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. For reviews, see: a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419-2440.

[48] (a) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709-1716. (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59-62.

[49] Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252-2254. For review, see: Negishi, E.-i.; Tan, Z. *Top. Organomet. Chem.* **2004**, *8*, 139-176.

[50] Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152-2154. For a large scale synthesis of **64**, see: Smith, A. B.; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359-4362.

[51] a) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369-3372. b) Marshall, J. A.; Yanik, M. M., Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005**, 81, 157-170.

[52] a) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825-7831. b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.

[53] It is assumed that the minor *syn*-isomer in organocatalytic aldol reactions has the OH inverted. The configuration of the methyl-bearing stereocenter would remain the same: (a) Bahmanyar, S.; Houk, K.

N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479. (b) Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705-7714.

[54] Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9-17.

[55] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* **1993**, *32*, 1068-1071.

[56] Kutscheroff, M. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 13-23. For a review, see: Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121-1150.

[57] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.

[58] Claisen, L.; *Ber. Dtsch. Chem. Ges.* **1912**, 45, 3157-3166. For a review, see: Martín Castro, A. M. *Chem. Rev.* **2004**, 104, 2939-3002.

[59] Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898. For reviews, see: a) Pereira, S.; Srebnik, M. *Aldrichim. Acta* **1993**, *26*, 17-29. b) Chai, Y. H.; Hong, S. P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905-2928.

[60] Rodeschini, V.; Weghe, van de P.; Tarnus, C.; Eustache, J. *Tetrahedron. Lett.* **2005**, *46*, 6691-6695.

[61] For a rewiev, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191-1223.

[62] a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613. b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386-2387. For a review, see: Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825-4864.

[63] Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350-4355.

[64] Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485-486.

[65] Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432-12440 and references therein.

[66] a) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc. Chem. Commun.* **1973**, 553-554. b) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226-2230.

[67] Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1615-1618.

[68] Chou, W. N.; Clark, D. L.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 299-302.

[69] Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446-450.

[70] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

[71] a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179. b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973-9979.

[72] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

[73] a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886. b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5424.

[74] Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038-4040.

[75] Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388.

[76] Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677-690. b) Li, J.; Menche, D. *Synthesis* **2009**, *2009*, 2293-2315.

[77] Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57-60.

[78] a) Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089-1103. b) Beale, M. H. *Nat. Prod. Rep.* **1990**, *7*, 25-39.

[79] Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396-407.

[80] Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105-9108.

[81] K. R. Chauhan, A. Zhang, US 7,375,239, **2008**.

[82] Barbier, P. *Compt. Rend.* **1899**, *128*, 110-111.

[83] Yoshikawa, M.; Fukuda, Y.; Hatekeyama, S.; Tanaka, N.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1993**, *41*, 1194-1196.

[84] Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

[85] Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

[86] Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837-8847.

[87] Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.

[88] Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 8219-8222.

[89] Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839-1845.

[90] Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165-176.

[91] Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625-3633.

[92] Xu, J.; Caro-Diaz, E. J.; Theodorakis, E. A. *Org. Lett.* **2010**, *12*, 3708-3711.

[93] Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774-10782.

[94] Poirier, J.-M.; Hennequin, L. *Tetrahedron* **1989**, *45*, 4191-4202.

[95] Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319-4322.

[96] Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639-647.

[97] Sun, B.-F.; Wang, C.-L.; Ding, R.; Xu, J.-Y.; Lin, G.-Q. *Tetrahedron Lett.*, In Press. Accessed on 7th October, 2010.

[98] Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058-2059.

[99] For reviews, see: a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223-270. b) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357-1374. c) Singh, V.; Murali Krishna, U.; Vikrant; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405-3428. d) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577-6605. e) Muthusamy, S.; Krishnamurthi, J. *Top. Heterocycl. Chem.* **2008**, *12*, 147-192.

[100] For representative bimolecular examples, see: a) Pirrung, M. C.; Lee, Y. R. *Tetrahedron Lett.* **1994**, *35*, 6231-6234. b) Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432-3443. c) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097-2098. d) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5351-5355. e) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 6532-6535. f) Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki,

S.; Shiro, M.; Hashimoto, S. *Chem.–Eur. J.* **2006**, *12*, 8898-8925. g) Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873-874. h) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4009-4011. i) Shimada, N.; Anada, M.; Nakamura, S.; Nambu, H.; Tsutsui, H.; Hashimoto, S. *Org. Lett.* **2008**, *10*, 3603-3606. j) Suga, H.; Higuchi, S.; Ohtsuka, M.; Ishimoto, D.; Arikawa, T.; Hashimoto, Y.; Misawa, S.; Tsuchida, T.; Kakehi, A.; Baba, T. *Tetrahedron* **2010**, *66*, 3070-3089.

[101] Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479-481.

[102] Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Högenauer, K.; Simic, O.; Antonello, A.; Hünger, U.; Smith, M. D.; Ley, S. V. *Chem.–Eur. J.* **2007**, *13*, 5688-5712.

[103] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-1585.

[104] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

[105] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.

[106] Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258-3260.

[107] Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709-1716.

[108] See, for example: Prusov, E.; Maier, M. E. *Tetrahedron* **2007**, *63*, 10486-10496.

[109] Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572-2582, and references cited therein.

[110] Kim, J.-G.; Jang, D. O. *Synlett* **2008**, 2072-2074.

[111] Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26-31.

[112] For non-selective intramolecular epoxide opening, see: Paquette, L. A.; Sauer, D. R.; Edmondson, S. D.; Friedrich, D. *Tetrahedron* **1994**, *50*, 4071-4086.

[113] a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441-444. For reviews, see a) Paquette, L. A. *Angew. Chem., Int. Ed.* **1990**, *29*, 609-626. b) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971-14020.

[114] Moreira, J. A.; Corrêa, A. G. *Tetrahedron: Asymm.* **2003**, *14*, 3787-3795.

[115] Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765-4766.

[116] Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560-4567.

[117] Jacques, J., Marquet, A. *Org. Synth* **1973**, *58*, 111-116.

[118] Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783-787.

[119] a) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566-571. b) Vermeulen, N. A., Chen, M. S., White, M, C. *Tetrahedron* **2009**, *65*, 3078-3084.