Total Synthesis and Structural Assignment of Curvicollide C and Derivatives of Fusaequisin A

Dissertation

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By

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from Göttingen

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The present thesis was carried out under the guidance and supervision of Prof. Dr. Martin Hiersemann from October 2012 to August 2017 at the department of Organic Chemistry of the Technische Universität Dortmund.

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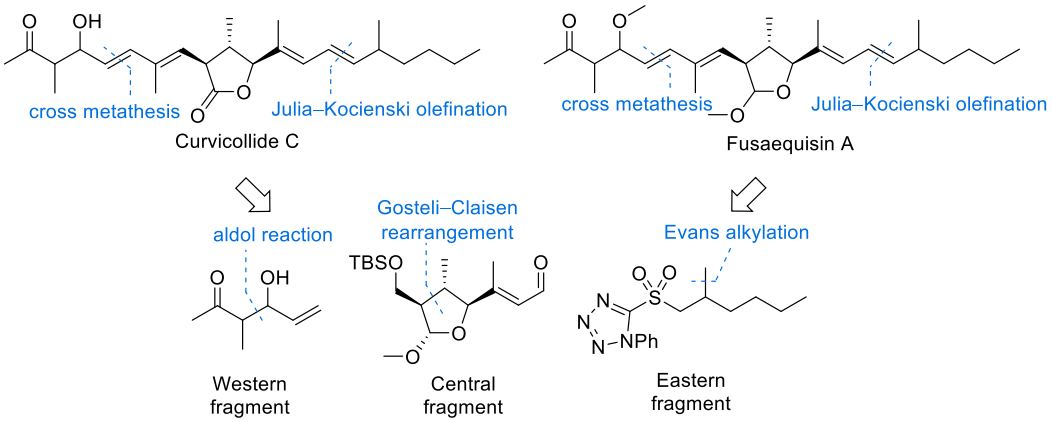
Abstract

von Kiedrowski, Valeska – Total Synthesis and Structural Assignment of Curvicollide C and Derivatives of Fusaequsin A

key words: natural product synthesis, total synthesis, structural elucidation, polyketides, Curvicollide, Fusaequisin

(–)-Curvicollide C, a polyketide metabolite isolated from the mycoparasitic fungus *Podospora curvicolla* (left, Illinois 2004), shows striking structural similarity to (–)-Fusaequisin A, isolated from the endophytic fungus *Fusarium equiseti* (right, Cameroon 2013). As these fungi originate from different habitats and remote geographic locations, and, as they also differ in their morphological characteristics and phylogenetic classification the question arises why these fungi produce secondary metabolites of close structural relationship.

In both cases the relative configuration was only partially elucidated while the absolute configuration remained unknown. The central heterocycles were determined to exhibit an all-*trans* configuration. This inspired us to initiate a research project aiming towards the total synthesis of both natural products, also because the unique combination of structural characteristics, imposed a synthetic challenge.



Herein we report the first total synthesis of (+)-Curvicollide C and of a non-natural diastereomer of Fusaequisin A. Cross-metathesis and Julia–Kocienski olefination were chosen as the key coupling steps resulting in three retrosynthetic fragments, namely the Western, the Central, and the Eastern fragment. The synthesis was desined to rely on late-stage coupling of the configurationally and constitutionally customizable Western and Eastern fragements with the Central fragment of defined absolute configuration. The resulting highly modular synthesis provided access to a collection of five individually synthesized diastereomers of Curvicollide C, which enabled the full structural assignment of Curvicollide C by comparative NMR spectroscopic analysis.

Figure left: http://www.nocrotec.com/Schwammer/2015-10-31/mush-10124.jpg; figure right: http://fungi.myspecies.info/sites/fungi.myspecies.info/files/DSC_0059.jpg (28.08.2017)

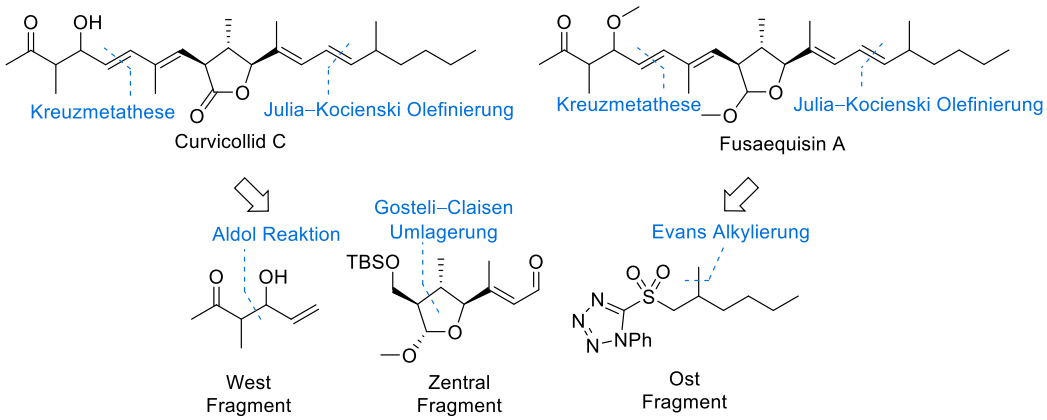
Zusammenfassung

von Kiedrowski, Valeska – Totalsynthese und Struturaufklärung von Curvicollid C und Derivaten von Fusaequisin A

Schlagwörter: Naturstoffsynthese, Totalsynthese, Strukturaufklärung, Polyketide, Curvicollid, Fusaequisin

Der polyketide Metabolit (–)-Curvicollid C, welcher aus dem mycoparasitären Pilz Podospora curvicolla (links, Illinois 2004) isoliert wurde, zeigt eine auffällige strukturelle Ähnlichkeit zu (–)-Fusaequisin A. Dieser Metabolit wurde aus dem endophytischem Pilz Fusarium equiseti (rechts, Cameroon 2013) gewonnen. Da die beiden genannten Pilze aus unterschiedlichen biologischen Habitaten und geographischen Lagen stammen und sich zudem in ihren morphologischen Charakteristka und ihrer phylogenetischen Klassifikation unterscheiden stellt sich die Frage warum diese Pilze Sekundärmetabolite mit einem derart hohen strukturellen Verwandschaftsgrad bilden.

Für beide Naturstoffe wurde die relative Konfiguration nur teilweise aufgeklärt und die absolute Konfiguration verblieb unbekannt. Den zentralen Heterozyklen wurde eine all-*trans* Konfiguration zugeordnet. Die unvollständige Strukturaufklärung forderte uns heraus ein Forschungsprojekt mit dem Ziel der Totalsynthese beider Naturstoffe anzugehen. Zudem sahen wir eine synthetische Herausforderung in der einzigartigen Kombination von strukturellen Charakterisika der beiden Naturstoffe.



Im Folgenden berichten wir über die Totalsynthese von (+)-Curvicollid C sowie eines nicht natürlichen Diastereomers von Fusaequisin A. Als zentrale Verknüpfungsschritte wurden eine Kreuzmetathese und eine Olefinierung gewählt, wobei drei retrosynthetische Fragmente resultierten, welche im Folgenden als West-, Zentral- und Ost-Fragment bezeichnet werden. Die Synthese wurde aufbauend auf der Idee geplant, die Verknüpfungen der Fragmente auf einer möglichst späten Stufe durchzuführen, wobei das West- und Ost-Fragment in ihrer Konfiguration und Konstitution flexibel anpassbar sein sollten und das Zentral-Fragment in einer festgelegten absoluten Konfiguration vorliegt. Die resultierende modulare Synthese ermöglichte den Zugang zu einer Kollektion von fünf einzeln synthetisierten Diastereomeren von Curvicollid C. Durch vergleichende NMR Analyse dieser Diastereomere konnte schließlich eine zuverlässige Strukturaufklärung von Curvicollid C erzielt werden.

Bild links: http://www.nocrotec.com/Schwammer/2015-10-31/mush-10124.jpg; Bild rechts: http://fungi.myspecies.info/sites/fungi.myspecies.info/files/DSC_0059.jpg (28.08.2017)

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Publications

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Catalytic Asymmetric Claisen Rearrangement of Gosteli-Type Allyl Vinyl Ethers: Total Synthesis of (−)-9,10-Dihydroecklonialactone B
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Org. Lett. **2013**, *15*, 5982–5985

Oral Presentations

February 24, 2017
10. Tag der Chemie, TU Dortmund, Dortmund, Germany

Poster

September 5 – 7, 2016
ORCHEM 2016, 20. Lecture Conference, Weimar, Germany

February 13, 2015
8. Tag der Chemie, TU Dortmund, Dortmund, Germany

February 1, 2013
6. Tag der Chemie, TU Dortmund, Dortmund, Germany

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List of Abbreviations, Acronyms and Symbols

%	procent
1D	one-dimensional
2D	two-dimensional
$[a]_D^T$	specific rotation at temperature T at the sodium D line
A	Ampere
Å	Ångstrom
Ac	Acetyl
ACP	acyl carrier protein
app	apparent
aq.	Aqueous
atm	Atmosphere
AT	acyl transferase
AVE	allyl vinyl ether
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
2,2'-bpy	2,2′-bipyridine
Bu	butyl
Bz	benzoyl
°C	degree centigrade
CAGC	catalytic asymmetric Gosteli–Claisen
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
cm^{-1}	reciprocal centimeters
c-hex	cyclohexyl
CM	cross-metathesis
COSY	Correletion Spectroscopy
Cp	cyclopentadienyl
δ	NMR chemical shift in ppm downfield from a standard
d	day, doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DEPT	Distortionless enhancement by polarisation transfer
DFG	Deutsche Forschungsgemeinschaft
DH	dehydratase
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPA	
DMAP	4-dimethylaminopyridine
3,4-DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethyl formamide
3,4-DMP	3,4-dimethoxyphenyl
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
EtOAc	ethyl acetate
ER	enoyl reductase
et al.	and others
FAB	fast atom bombardement
FT	Fourier transformation
g	gram
h	hour
HDAC	histone deacetylase
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HR	high resolution
HSQC	heteronuclear single quantum coherence
HWE	Horner–Wadsworth–Emmons (olefination)
Hz	Hertz
i	iso
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
kcal	kilocalorie
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
KR	ketoacylreductase
KS	ketoacylsynthase
K-selectride	potassium tri-sec-butylborohydride
L	ligand
LA	Lewis acid
LDA	lithium diisopropyl amide
m	meter, milli, multiplet
m	meta
M	molar
MALDI	matrix-assisted laser desorption ionization
mbar	millibar
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
mg	milligram
MHz	megahertz
min	minute
ml	milliliter
mp	melting point
µl	microliter
mmol	millimole
µm	micromole
Ms	methylsulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide

NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
o	ortho
p	para
PDA	potato dextrose agar
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
PhSH	thiopenol
PIDA	diacetoxy iodo benzene
PIFA	bis(trifluoroacetoxy) iodo benzene
PKS	polyketide synthetase
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
proton sponge	1,8-bis(dimethylamino)naphthalene
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
py	pyridine
q	quartet
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
RMS	root mean square
RP	reversed phase
R_t	retention time
rt	room temperature
s	singlet
SEM	trimethylsilylethoxymethyl
SET	single electron transfer
ST	sulfotransferase
t	triplet
t	tert
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TE	thioesterase
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TPS	*tert*-butyldiphenylsilyl
Ts	4-methylphenylsulfonyl
UV	ultraviolet
ν	vibration frequency in cm^{-1}
X-ray	Röntgen radiation

Chapter 1 - Introduction

1.1 Why Total Synthesis today?

In a well-recognized review article[1] for Angewandte Chemie, S.A. Snyder and K.C. Nicolaou summarized in the abstract:

"Over the course of the past half century, the structural elucidation of unknown natural products has undergone a tremendous revolution. Before World War II, a chemist would have relied almost exclusively on the art of chemical synthesis, primarily in the form of degradation and derivatization reactions, to develop and test structural hypotheses in a process that often took years to complete when grams of material were available. Today, a battery of advanced spectroscopic methods, such as multidimensional NMR spectroscopy and high-resolution mass spectrometry, not to mention X-ray crystallography, exist for the expeditious assignment of structures to highly complex molecules isolated from nature in milligram or sub-milligram quantities. In fact, it could be argued that the characterization of natural products has become a routine task, one which no longer even requires a reaction flask! This Review makes the case that imaginative detective work and chemical synthesis still have important roles to play in the process of solving nature's most intriguing molecular puzzles."

Nicolaou's conjecture on the role of total synthesis is still valid a decade later. It becomes particularly relevant in cases where the natural product contains stereocenters at remote positions which do not show a spectroscopically measurable "communication". In a recent example of a divergent total synthesis, the group of Fürstner encountered such a situation and concluded[2]:

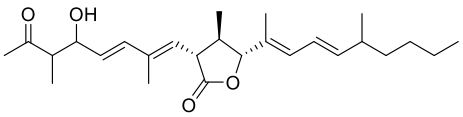
"At the same time this investigation shows that total synthesis remains an indispensable tool for structure elucidation, even in the age of spectroscopy, when dealing with compounds that contain spatially segregated stereoclusters."

Spatially segregated stereocenters prevented also the full structural elucidation of the natural products Curvicollide C and Fusaequisin A targeted in the present thesis (Scheme 1). In both cases the discoverers of the natural products could not assign the structure at the level of its relative and absolute configuration. This is why we expressed our motivation for doing total synthesis in the letter which accompanied the manuscript of our publication as follows:

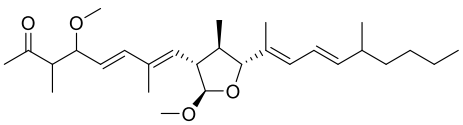
"Dear editor,

please find attached to this letter a manuscript entitled „Total Synthesis and Structural Assignment of Curvicollide C" [**1**] *which we submit for publication as a letter. The manuscript describes the first total synthesis of this fungal natural product which was originally reported in 2004 without full characterization of its stereochemical structure.[3] Thus we were enforced to develop a synthetic methodology allowing us to synthesize a complete set of diastereomers for the sake of structural elucidation. As a result our manuscript not only reports on the first total synthesis of Curvicollide C but also completes its structural elucidation. This aspect of our work is particularly relevant in the field of polyketide research, as in 2013 Fusaequisin A* [**2**],[4] *another closely related fungal metabolite was reported, again not fully characterized with respect to questions of relative and absolute configuration.*

We are aware that our case is not a rare one and calls for a new perspective of total synthesis, namely to facilitate structural analysis of natural products by means of modern synthetic methodology. While in principle it is possibly to apply degradation studies to split the natural product into smaller fragments, the amount of material researcher typically isolate from natural sources today very often do not allow such studies. Furthermore, degradation may be hampered by undesired and unforeseen side reactions and in any case do not leave the natural product intact. On the other hand, the determination of the relative and absolute configuration is particularly difficult for flexible molecules, especially in those where the asymmetric units are rather distant from each other. Here a total synthesis of all necessary diastereomers and their comparative NMR analysis can be even the only methodology to allow structural elucidation…"



(–)-Curvicollide C (**1**)



(–)-Fusaequisin A (**2**)

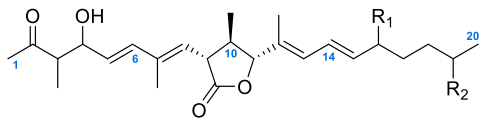
Scheme 1

[1] Nicolaou, K. C.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.
[2] Willwacher, J.; Kausch-Busies, N.; Fürstner, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 12041-12046.
[3] Che, Y.; Gloer, J. B.; Wicklow, D. T. *Org. Lett.* **2004**, *6*, 1249–1252.
[4] Shiono, Y.; Shibuya, F.; Murayama, T.; Koseki, T.; Poumale, H. M. P.; Ngadjui, B. T. *Z. Naturforsch.* **2013**, *68*, 289–292.

1.2 Curvicollides A-C and Fusaequisin A

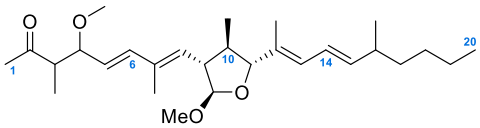
In 2004, Gloer et al. reported on the isolation, constitutional and partly configurational assignment of Curvicollides A-C as part of a study aiming to find novel anti-*Aspergillus* fungicides.[3]

In general, *Aspergillus flavus* is one of the major producers of aflatoxin[5] and causes diseases on many important agricultural crops.[6] In this context, the sclerotia[7] of *Aspergillus* species were buried in a corn field for an extended period of time with the aim of growing mycoparasitic fungi, which cause a reduced viability of *Aspergillus* species (and thereby serve as potential sources of anti-*Aspergillus* agents). Indeed, several mycoparasitic species could be found, which colonized the sclerotia of *Aspergillus flavus*. One of them could be identified as *Podospora curvicolla*. Screening of several extracts of the fermentation broth of *P. curvicolla* for antifungal activity led to the isolation of three new secondary metabolites, which were named as Curvicollide A (**3**) (6.5 mg), Curvicollide B (**4**) (2.1 mg) and Curvicollide C (3.0 mg) (**1**).



Curvicollides A-C (**3**,**4**,**1**)

curvicollide	R^1	R^2
(–)-A (**3**)	CH_2OH	H
(–)-B (**4**)	CH_3	OH
(–)-C (**1**)	CH_3	H



(–)-Fusaequisin A (**2**)

Scheme 2

In 2013, Shiono et al. reported on the isolation, constitutional and partly configurational assignment of Fusaequisin A in a different biological context.[4] The motivation behind this study was the screening of medicinal plants used as folk medicine in Cameroon for new natural products. In the course of the study an endophytic fungus, *Fusarium equiseti*, was discovered whose crude culture extract exhibited good antifungal activity against *Aspergillus clavatus* and antibacterial activity against *Pseudomonas aeruginosa*. These findings prompted further investigation of the chemical constituents of the extract leading to the discovery of a new secondary metabolite, named Fusaequisin A (**2**) (10 mg).

In the following, a brief overview on fungi as the producers of the targeted natural products will be presented.

1.3 The basics of fungi

Fungi (singular fungus) are a group of eukarotic organisms which constitute a separate kingdom, distinct from animalia and plants. From a fundamental biological perspective, fungi are heterotrophic organisms (from the greek heteros = different, trophe = nourishing) which differ from so called autotrophic organisms in their inability to feed their metabolism on primitive sources of carbon (CO_2) and energy (such as of photochemical of lithochemical origin).[8] Thus heterotrophs depend on the existence of autotrophic organisms. Fungi as sessile heterotrophs obtain their nutrition by secreting digestive enzymes and absorbing the thereby dissolved energy-rich organic molecules.[9] While in contrast to plants, a photosynthetic apparatus is missing, fungi differ from animalia in the existence of cell wall and vacuoles. Their morphological structures are often attributed to their fruiting bodies, but this association is incomplete or even incorrect as the fundamental structure is the mycelium, which is organized as a branched network of hyphae (Figure 1).

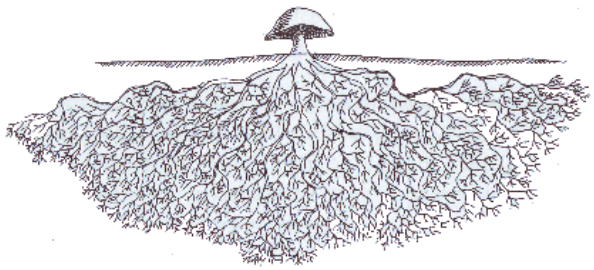


Figure 1 Sketch of a fungus.[10] The recognizable part of the fungus is represented by the fruiting body above-ground. The fundamental structure is the often invisible mycelium growing in the underground soil.

[5] Klich, M. A. *Mol. Plant Pathol.* **2007**, *8*, 713–722.
[6] Amaike, S.; Keller, N. *Annu. Rev. Phytopathol.* **2011**, *49*, 107–133.
[7] Sclerotia are resistant bodies of fungi, usually consisting of densely packed hardened mycelium containing food reserves. As dormant, reproductive structures they germinate on the return of favorable conditions.

[8] Lwoff, A.; van Niel, C.B.; Ryan, P.J.; Tatum, E.L. *Nomenclature of nutritional types of microorganisms*, Cold Spring Harbor Symp. Quantit. Biol.: NY, **1946**, *11*, pp. 302–303.
[9] Sinsabaugh, R. L. *Biol Fertil Soils* **1994**, *17*, 69–74.
[10] https://philosophenstuebchen.files.wordpress.com/2013/01/myzel.gif?w=510 (27.06.2017)

1.3.1 *Podospora curvicolla*[11]

The coprophilous[12] („dung loving“) fungus *Podospora curviolla* is a fast growing sapotroph belonging to the family of *Lasiosphaeriaceae*[13] (Table 1). Typical for a coprophilous fungus is a fruiting body, the so called *Perithecium*[14], which appears as a bulbous flask-shaped structure, opening via a pore through which sexual spores escape (Figure 2). Characteristic for *Podospora curvicolla* is a rather wide spore ejection of nearly half a meter[15]. It should be mentioned that in the case of Gloer et al. a specimen of *P. curvicolla* was discovered which colonized the sclerotium of *Aspergillus flavus*.[3] The latter had been buried in a corn field in Illinois in order to stimulate the growth of mycoparasitic fungi. Whether the Curvicollides isolated from this specimen are the result of this special adaptation, or whether they can be found in other sources remains an open question.

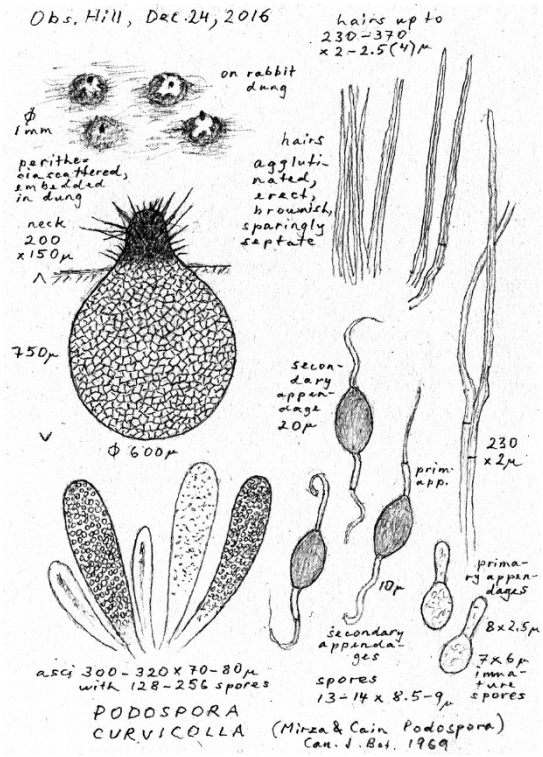


Figure 2 *Podospora curvicolla* depicted by Oluna & Adolf Ceska.[16]

1.3.2 How does mycoparasitism work?

Mycoparasitic fungi parasitize other fungi and can generally be divided into two groups: the necrotrophic and the biotrophic mycoparasites.[17] Necrotrophic mycoparasites are destructive parasites in the sense that they invade and kill their hosts. This happens through damaging the cell walls of host cells and consequently feeding on the cell contents. In contrary, biotrophic mycoparasites establish a specialized feeding relationship, usually by producing haustoria (suction apparatus) to penetrate and absorb nutrients from living fungal hyphae.[18]

In any case the crucial question is: How can a mycoparasitic fungus attack its host without attacking itself, considering that its cell wall is not different from the one of its host? Generally, fungi secrete hydrolytic enzymes[9] such as chitinases to exploit their substrates, and in the same manner pathogenic fungi penetrate their host. While the above question has not been answered yet, Gruber and Seidl-Seiboth conjectured that the difference between self and non-self is not based on chitinases or other hydrolytic enzymes, as these enzymes are also involved in the recycling and remodeling of the fungus' own cell wall.[19] It is more likely that the difference is based on the vitality of fungal hyphae which is influenced by secondary metabolites[20] and expressed by the level of protection of the cell wall (Figure 3).

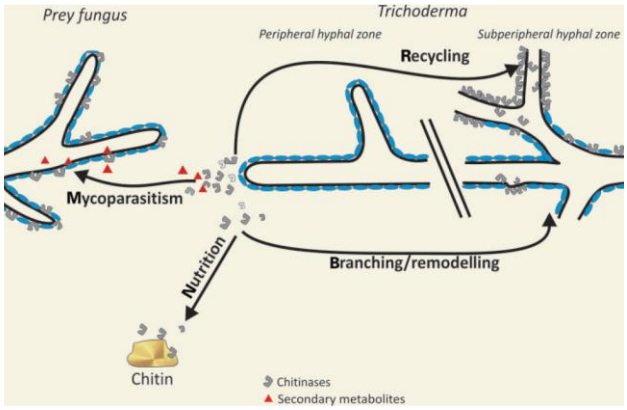


Figure 3 Double role of chitinases involved in the lysis of the own less viable parts of the cell wall and the cell wall of the prey fungus.[19]

[11] Podospora curvicolla (G. Winter): Niessl, G. *Hedwigia* **1883**, *22*, 153–156.
[12] Wicklow, D. T.;Yokum, D. H. *Trans. Brit. Mycol. Soc.* **1981**, *76*, 29–32.
[13] Huhndorf, S. M.; Miller, A. N.; Fernández, F. A. *Mycologia* **2004**, *96*, 368–387.
[14] Bell, A. An Illustrated Guide to Coprophilous Fungi in New Zealand., in *Dung Fungi*; Victoria University Press: Wellington, **1983**, pp 39–40
[15] Weimer, J. L. *Amer. Jour. Bot.* **1920,** *7*, 75–77.
[16] http://mushroomobserver.org/image/show_image/709842?q=71Oc (20.06.17)
[17] Jeffries, P. *Can. J. Bot.* **1995**, *73*, 1284–1290.
[18] Mendgen, K.; Hahn, M. *Trends Plant Sci.* **2002**, *7*, 352–356.
[19] Gruber, S.; Seidl-Seiboth, V. *Microbiology* **2012**, *158*, 26–34.
[20] Chamoun, R.; Aliferis, K.A.; Jabaji, S. *Front. Microbiol.* **2015**, *6*, 353.

1.3.3 *Fusarium equiseti*[21]

The fungus *Fusarium equiseti* is widely found in soil, often in association with plants where it acts as an endophyte. Its distribution is cosmopolitan[22], commonly in warm temperate and subtropical areas.[23] Joffe and Palti perceived *F. equiseti* to be pathogenic to cucurbits and avocado, and stated that its pathogenicity had been underestimated.[24] Concerning its morphological appearance, colonies of *Fusarium equiseti* on potato dextrose agar (PDA) develop a dense to floccose white mycelium (Figure 4) usually with at least a central mass one orange sporondochia[25] (compact structures of hyphae on which the asexual spores are formed).[26]

Figure 4 *Fusarium equiseti*, colony on potato sucrose agar.[27]

In the case of Shiono's discovery, the specimen SF-3-17 was isolated as an endophyte from the herbaceous plant[4] *Ageratum conyzoides* L. which is traditionally used as a folk medicine in Cameroon and the Congo, for the treatment of fever, rheumatism, headache, and colic.[28]

1.3.4 What makes up an endophyte?

Endophytic fungi[29] colonize living plants, expressing a relationship that lays between the extreme poles of symbiosis and parasitism. There is a fluent passage between these extremes which often reflects the vital state of the plant as the host organism. While in a healthy plant the relationship starts as symbiotic, it often switches into a parasitic one, once the plant loses its vitality. Symbiosis is based on a mutual life support where the plant supports the fungus by providing water, nutrients, and a protected habitat while the fungus protects the plant from an infection by other microorganisms as well as from herbivores[30] by means of secondary metabolites acting as chemical repellants. In addition, the plant benefits from the presence of the fungus with respect to an increased resistance against drought[31] and low temperatures[32].

1.3.5 Structural similarity in spite of biological diversity: On the relationship between *Podospora Curvicolla* and *Fusarium equiseti*

As the above fungi originate from remote geographic locations and biological habitats and as they also differ in their morphological characteristics and phylogenetic classification (Table 1), the question remains why these fungi produce such closely related and structurally similar secondary metabolites. As their biosynthesis is based on a machinery of enzymes known as polyketide synthetases (PKS), the latter question breaks down to the question of a similarity encoded in the respective PKS genes.

Table 1 Scientific classification of *F. equiseti* and *P. Curvicolla*, which differ in the subclass concerning their taxonomic rank.

Kingdom:	Fungi		
Subkingdom:	*Dikarya*		
Division:	*Ascomycota*		
Class:	*Sordariomycetes*		
Subclass:	Hypocreomycetidae	**Subclass:**	Sordariomycetidae
Order:	Hypocreales	**Order:**	Sordariales
Family:	Nectriaceae	**Family:**	Lasiosphaeriaceae
Genus:	*Fusarium*	**Genus:**	*Podospora*
Species:	*Fusarium equiseti*	**Species:**	*Podospora curvicolla*

[21] Fusarium equiseti (Corda) Sacc.: Syll. Fung. **1886**, *4*, 707.; Matsushima, T. **1975**. Icones Microfungorum a Matsushima lectorum, p. 72.
[22] Nelson, P.E.; Toussoun, T.A.; Marasas, W.F.O. *Fusarium* species. *A manual for identification*. Ed. The Pennsylvania State University Press: USA, 1983.
[23] Messiaen, C.M.; Casini, R. *Ann. Epiphyte* 1968, 19,387–454.
[24] Joffe, A. Z.; Palti, J. *Isr J Bot Basic Appl Plant Sci*. **1967**, *16*, 1–18.
[25] Pitt, J.I; Hocking, A.D. *Fungi and Food Spoilage*; Springer Science & Business Media, New York, **2012**, pp. 119–120
[26] Mehrotra, R.S.; Aneja, K. R. *An Introduction to Mycology*; New Age International, **1990** p 563.
[27] http://fungi.myspecies.info/sites/fungi.myspecies.info/files/DSC_0059.jpg (20.06.2017)
[28] Sofowora, A. *Medicinal Planls and Traditional Medicine in Africa*; Wiley: Chichester, **1984**, p. 67.
[29] Proksch, P.; Kjer, J.; Aly, A. H.; Debbab, A. Pharmazeutische Wissenschaft **2010,** 8–12.
[30] Herbivores are animals which are adapted to feed on plant material.
[31] Naveed, M.; Mitter, B.; Reichenauer, T. G.; Wieczorek, K.; Sessitsch, A. *Environ Exp Bot* **2014**, *97*, 30–39.
[32] Redman, R. S.; Kim, Y. O.; Woodward, C. J.; Greer, C.; Espino, L.; Doty, S. L.; Rodriguez, R.J. *PLoS One*. **2011**, *6*, e14823.

Is there a common ancestor which provided both lineages leading to the above fungi with the same set of PKS genes? Or did horizontal gene transfer lead to an exchange of the respective genes? As a last option, is the structural similarity of the secondary metabolites the result of a completely independent evolution of PKS genes meaning that there is no close link between these organisms at all?

While a definite answer to the above questions is currently not possible, the hypothesis of a common ancestor may be seen supported when considering the option of sleeping genes for the evolution of the PKS apparatus.

1.3.6 Curvicollides as silent secondary metabolites sleeping in other fungi?

Although each fungal strain contains genes that encode the enzymes to synthesize a plethora of potential secondary metabolites, only a fraction is expressed. Activation of these cryptic pathways is the subject of current research.[33] In 2016, Genilloud et al. studied the effects of epigenetic small-molecule modifiers of DNA methyltransferase (DNMT) and histone deacetylase (HDAC) activities in order to perturb the fungal secondary biosynthetic mechanisms.[34] In genereal, a HDAC inhibitor suppresses the activity of HDAC, leading to an increase in histone acetylation which in turn causes a more loosely packaged DNA and thus induces an enhancement of the expression of specific genes. An inhibitor of DNMT causes the suppression of DNA methylation which again enables the expression of the respective genes.[35]

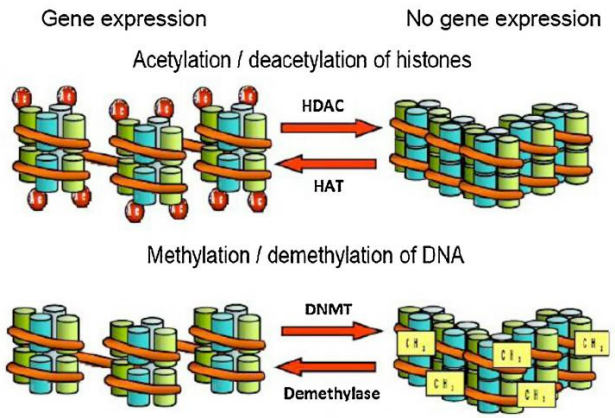
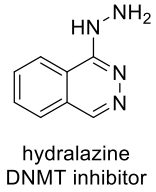


Figure 5 Chromatin compaction and gene expression are modulated by DNMT and HDAC activity.[36]

Upon treatment of the fungal strain *Dothiora* sp. with hydralazine (Figure 6) as the epigenetic modifier, the presence of Curvicollide A or B (*m/z* 432; $C_{26}H_{40}O_5$) could be identified among the metabolites exhibiting increased production. It should be mentioned that *Dothiora* sp. belongs to the class of the *Dothideomycetes* while both *P. curvicolla* and *F. equiseti* are members of the class of *Sordariomycetes* which means that their common ancestor is expected to reside in an even higher taxonomic rank.



hydralazine
DNMT inhibitor

Dothiora sp.

Figure 6 Structure of hydralazine and cultures of the endophytic fungi *Dothiora sp*.[37]

Again, while the latter finding could mean that the natural products targeted in this thesis might exist in a much broader variety of fungi and may be found after suitable stimulation, the current evidence is too limited to allow more profound conclusions. Further evidence for a common ancestor could arise from the assignment of the missing relative and absolute configuration of Curvicollides and Fusaequisin. If both classes of natural products also share the same relative and absolute configuration this could hint at a strong sequence homology of their respective PKS genes.

1.4 Structural assignment of Curvicollides and Fusaequisin A

So far, both natural products were characterized by a common set of spectroscopic and spectrometric methods including IR, one and two dimensional NMR spectroscopy as well as HRMS-spectrometry.[3,4] While evidence for the existence of characteristic functional groups such as carbon-carbon double bonds, carbonyl and hydroxyl groups as well as a lactone (Curvicollides) came from IR-studies, the composition (molecular formula) was derived from HRMS-spectrometry. The constitution was derived from selected NMR-methods including simple 1D-spectra (^{1}H and ^{13}C NMR) as well as 2D-spectra based on ^{1}H^{1}H

[33] Cichewicz, R.H. Nat. Prod. Rep. 2010, 27, 11–22.
[34] González-Menéndez, V.; Pérez-Bonilla, M.; Pérez-Victoria, I.; Martín, J.; Muñoz, F.; Reyes, F.; Tormo, J.R.; Genilloud, O. *Molecules* **2016**, *21*, 234.
[35] Cichewicz, R.H. *Nat. Prod. Rep.* **2010**, *27*, 11–22.
[36] Vandermeers, F.; Sriramareddy, S. N.; Costa, C.; Hubaux, R.; Cosse, J.-P.; Willems, L. *Lung Cancer* **2013,** *81*, 311– 318 (picture 08.06.17)
[37] Pérez-Bonilla, M.; González-Menéndez, V.; Pérez-Victoria, I.; de Pedro, N.; Martín, J.; Molero-Mesa, J.; Casares-Porcel, M.; González-Tejero, M. R.; Vicente, F.; Genilloud, O.; Tormo, J.; Reyes, F. *J. Nat. Prod.*, **2017**, *80*, 845–853. (picture 08.06.17)

COSY, $^{1}H^{13}C$ HSQC, $^{1}H^{13}C$ HMBC experiments. The relative configuration, which could only be established for the central heterocycle as all-*trans*, was derived from $^{1}H^{1}H$ NOESY spectra in conjunction with coupling constants taken from ^{1}H NMR spectra (Figure 7).

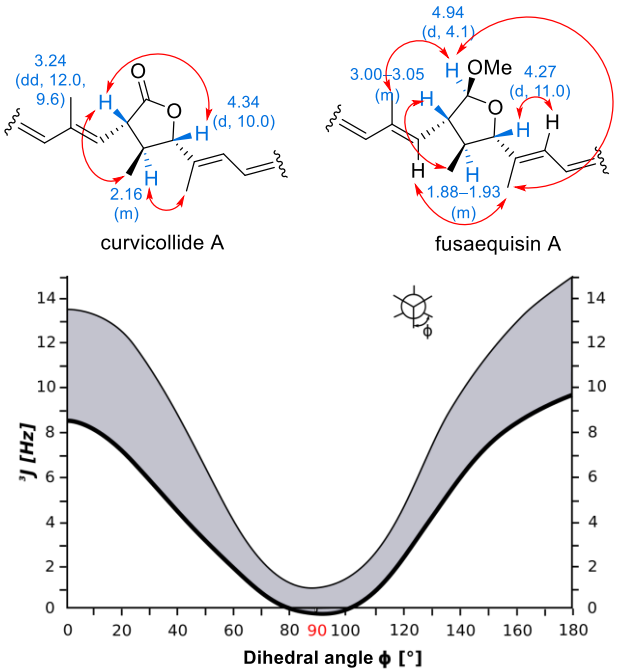


Figure 7 Assignment of the relative configuration in the central cyclic part of Curvicollide C (left) and Fusaequisin A (right) by NOESY experiments (red arrows) and analysis of the chemical shifts and coupling constants (blue). The curve shown represents the Karplus equation for the dependence of the vicinal coupling constant on the dihedral angle.[38] The range of expectation is marked by grey color.

For the case of the Curvicollides, the latter methods for the determination of the connectivity and the relative configuration of the central γ-lactone were applied to Curvicollide A exclusively. It was assumed that Curvicollides B and C do not differ from Curvicollide A with respect to the relative configuration of the γ-lactone. While the absolute configuration could not be determined at all, the relative configuration of chiral centers in the side chains also remained unassigned for both classes of natural products.

1.5 Biological activity of Curvicollide A and Fusaequisin A

Curvicollide A revealed antifungal activity in disk assays[39] against *Aspergillus flavus* (NRRL 6541) and *Fusarium verticillioides* (NRRL 25457) at 200 µg/disk, producing a 24 mm inhibitory zone in each case. As a reference nystatin (Figure 8), a potent antifungal medication,[40] shows comparable inhibitory zones in an eight times lower dosage (25 µg/disk). Limited availability of Curvicollide B and C prevented testing of their respective antifungal activities.

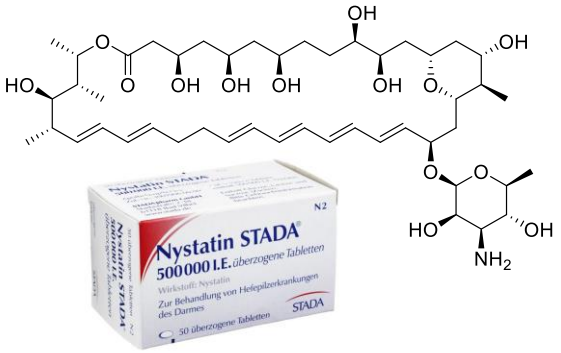


Figure 8 Molecular structure of the antifungal drug Nystatin®[41]

Fusaequisin A was found to exhibit moderate antibacterial activity against both, Gram-positive *Staphylococcus aureus* NBRC 13276 and Gram-negative *Pseudomonas aeruginosa* ATCC 15442, leading to zones of inhibition with diameters of 13 mm and 12 mm, respectively, at a concentration of 200 µg per disk. The activity against both, Gram-positive and Gram-negative bacteria is in so far remarkable as these differ in their cell architecture, which greatly affects the permeability and efflux of compounds.[42]

Surprisingly, and in sharp contrast to Curvicollide A, no antifungal activity against *Aspergillus clavatus* F 318a or *Candida albicans* ATCC 2019 (> 200 µg per disk) could be observed. Shiono et al. conjectured „*that the γ-lactone moiety may be a requisite for, or the compound's polarity may determine, the antifungal activity of Curvicollide A.*" The difference in polarity between Curvicollide A and Fusaequisine A is determined by an aldol moiety versus an *O*-methylated aldol, a lactone versus methyl lactol ether, and a C-16 hydroxymethyl versus a C-16 methyl group.

[38] a) Karplus, M. *J. Chem. Phys*.**1959**, *30*, 11–15. b) Karplus, M. *J. Am. Chem. Soc*. **1963**, *85*, 2870–2871.
[39] Wicklow, D.T.; Joshi, B. K.; Gamble, W. R.; Gloer, J. B.; Dowd, P. F. *Appl. Environ. Microbiol*. **1988**, *64*, 4482−4484.
[40] Sweetman SC, ed. Martindale: The Complete Drug Reference. 36th ed. London, England: Pharmaceutical Press, **2009**, 543-544.
[41] https://images.medpex.de/medias/33516/12T1ERVqMhV27DeVn-FIVka-30.jpg (20.06.2017)
[42] O'Shea, R.; Moser, H. E. *J. Med. Chem.*, **2008**, *51*, 2871–2878.

Thus, there are three individual components which make Curvicollide A more polar than Fusaequisin A. With respect to Shiono's considerations on polarity, the antifungal activity of Curvicollide C might be interesting as its polarity is expected to fall somewhere between Curvicollide A and Fusaequisin A.

With respect to Shiono's conjecture concerning a potential biological involvement of the lactone moiety, lactones are widely distributed structural motifs in biologically active molecules, indeed. They either directly interact with their target site as in Camptothecin[43] (Figure 9) or indirectly modulate the biological activity by affecting the structural rigidity of the molecule as in Discodermolide (Figure 9).[44]

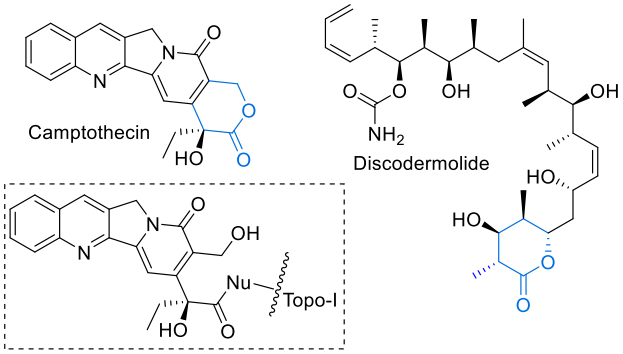


Figure 9 Molecular structures of Camptothecin and Discodermolide as well as the binding mode of Camptothecin to topoisomerase I.

From a recent conference abstract[45] it follows that Curvicollides A-C were identified to exhibit trypanocidal activity. *Trypanosomes* are parasites which cause infections known as sleeping sickness (African trypanosomiasis)[46] in both humans and livestock.

1.6 Conjecture on the biosynthesis of Curvicollide C

Curvicollides A-C as well as Fusaequisin A are polyketides. Polyketides constitute one of the major classes of natural products with over 7000 known compounds[47] exhibiting immense structural complexity and diversity.[48] As a common denominator they all share the same kind of biosynthesis, carried out by multifunctional enzyme complexes called polyketide synthases (PKS) and fall back on the same building units, namely an acyl thioester and an activated malonate derivative. These are always linked via decarboxylative Claisen condensations[49] catalyzed by ketoacylsynthases (KS) (Figure 10). Further steps are optional and can be partly or fully omitted before the next round of elongation. These may typically include a reduction of a β-keto thioester to a β-hydroxy thioester catalyzed by ketoacylreductases (KR), a dehydration of a β-hydroxy thioester to an α,β-unsaturated thioester catalyzed by dehydratases (DH), and a reduction of a α,β-unsaturated to a saturated thioester catalyzed by enoylreductases (ER). This process is repeated until a β-keto acyl polymer of predefined length is produced.[50]

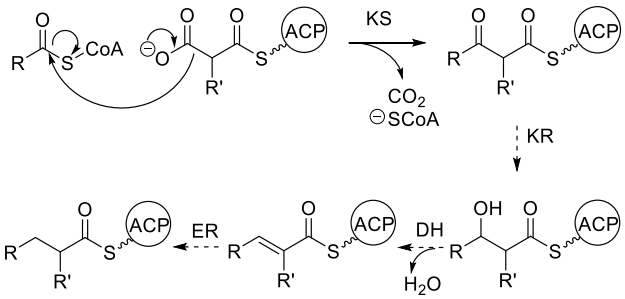


Figure 10 Decarboxylative Claisen condensation and further optional steps. KS = ketoacylsynthase, KR = ketoacylreductase, DH = dehydratase, ER = enoylreductase.

A fundamental insight into the biosynthesis of Curvicollides was reported by Gloer et al.: "*Moreover, on the basis of the patterns of oxidation and methylation, curvicollides A-C appear to be derived from condensation of two polyketide units rather than from a single polyketide precursor. The occurrence of dimeric, pseudodimeric, or heterodimeric polyketide fungal metabolites is not unusual, although most such fusions involve two aromatic subunits or, in some instances, an ester linkage. In the case of the curvicollides, two connections between the putative polyketide chains would be required, one of which is a carbon-carbon bond.*" Following this insight, one may consider two possible ways to construct the central γ-lactone ring among which one (pathway A, Figure 11) seems to be more naturally embedded into the modularity of biosynthetic routes employing polyketide synthetases.

[43] a) Hertzberg, R. P.; Caranfa, M. J.; Hecht, S. M. *Biochemistry* **1989**, *28*, 4629–4638. b) Jaxel, C.; Kohn, K. W.; Wani, M. C.; Wall, M. E.; Pommier, Y. *Cancer Res*. **1989**, *49*, 1465–1469.
[44] Shaw, S.J.; Sundermann, K.F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B. J. Am. Chem. Soc. 2005, 127, 6532–6533
[45] http://www.simposiosaludtropical.com/wp-content/uploads/2017/05/IV-Symposium-of-Tropical-Health-COST-Book-of-Abstracts-and-Program-v3.2.2.pdf (p. 64, 04.07.2017)
[46] Kennedy, P.G. *Lancet neurology*. **2013**, *12*, 186–194.
[47] Weissman, K. J.; Leadlay, P. F. *Nat. Rev. Microbiol.* **2005**, *3*, 925–936.
[48] Hertweck, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688–4716.
[49] a) Rawlings, B. J. *Nat. Prod. Rep.* **1998**, *15*, 275–308. b) Smith, S. N.; Tsai, S. C. *Nat. Prod. Rep.* **2007**, *24*, 1041–1072.
[50] Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380–416.

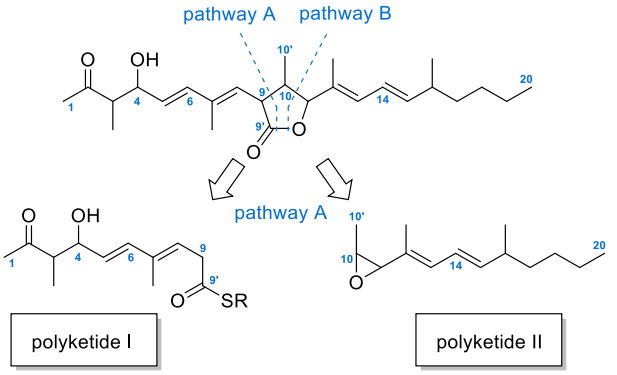


Figure 11 Proposal of a possible biosynthesis following Gloer's conjectures.

Note that the following proposal for a possible biosynthesis of Curvicollide C is speculative and aims to emphasize deviations from a standard and well-known mode of operation for fungal PKS.[51] Based on chemical conjectures it is proposed that the γ-lactone results from an α-acidic thioester of polyketide I reacting with an epoxide moiety of polyketide II. In the first step, the thioester enolate is supposed to attack the epoxide under carbon-carbon-bond formation. The alcohol(ate) oxygen released, then undergoes nucleophilic attack resulting in the γ-lactone (Figure 11). Figure 12 summarizes how the two polyketide precursors may be assembled in a modular fashion on a fungal PKS. The biosynthesis of polyketide I appears to be straightforward and embeds the usual steps based on repetitive decarboxylative Claisen condensations followed by optional processing employing KR, DH, ER. Less usual processing is supposed for module 4 which bears a non-classical dehydratase with a functionality known as a "shift domain".[52] The latter is needed to convert the usual pattern of conjugated double-bonds into a deconjugated form resulting in α-CH-acidity. While most steps for the biosynthesis of polyketide II again appear straightforward, product release is supposed to utilize a procedure known as decarboxylative chain termination.[53] The procedure involves enzymatic *O*-sulfonation, subsequent thioester hydrolysis, and fragmentation via decarboxylative elimination to generate the olefine moiety as a precursor for the epoxide, which may be formed by a post PKS step.

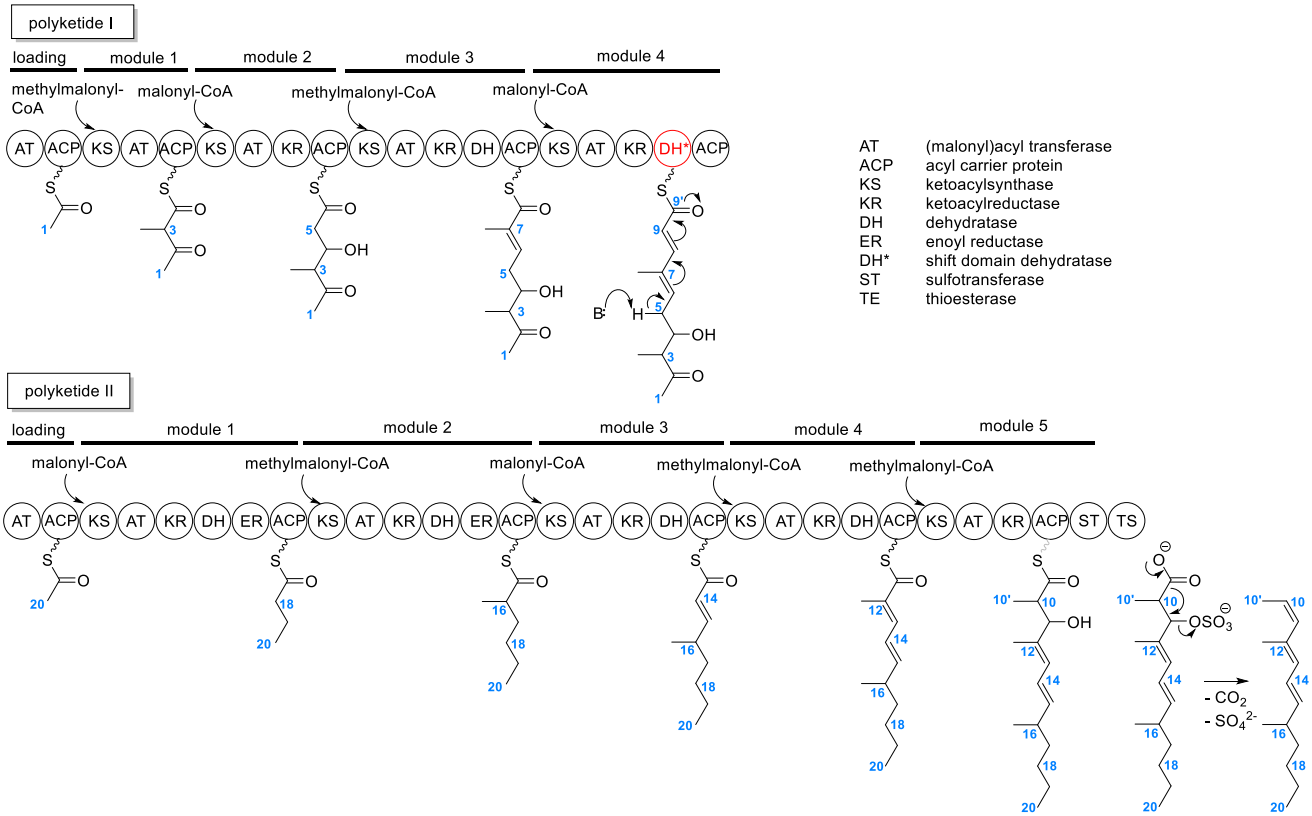


Figure 12 Proposal for a possible PKS-catalyzed biosynthesis of polyketides I and II.

[51] Keller, N.P.; Turner, G.; Bennett, J.W. *Nat. Rev. Microbiol.* **2005**, *3*, 937–947.

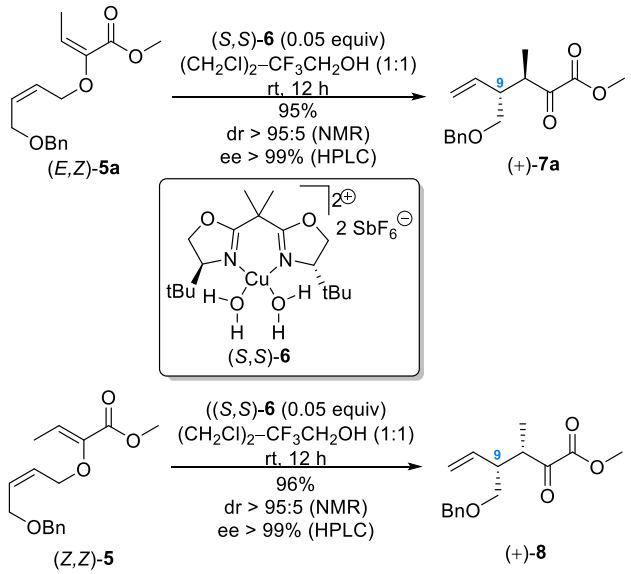
[52] a) Kusebauch, B., Busch, B., Scherlach, K., Roth, M., Hertweck, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 1460–1464. b) Lohr, F. thesis **2014**, Rheinischen Friedrich-Wilhelms-Universität Bonn

[53] a) Chang, Z., Sitachitta, N., Rossi, J. V., Roberts, M. A., Flatt, P. M., Jia, J., Sherman, D. H., Gerwick, W. H. *J. Nat. Prod.* **2004**, *67*, 1356–1367. b) Gu, L.; Wang, B.; Kulkarni, A.; Gehret, J. J.; Lloyd, K. R.; Gerwick, L.; Gerwick, W. H.; Wipf, P.; Håkansson, K.; Smith, J. L.; Sherman, D. H. *J. Am. Chem. Soc.* **2009**, *131*, 16033–16035.

1.7 Current state of research

1.7.1 Results from the thesis of Marleen Körner[54,55,56]

Shortly after the discovery of the Curvicollides A-C in 2004, our group initiated a research project aiming at the total synthesis of these natural products. For the synthesis of the central, all-*trans* configured γ-lactone, a suitable building block was required enabling a reliable entry to the desired configuration in both enantiomeric forms. As our group had previously elaborated the catalytic asymmetric Gosteli–Claisen (CACG) rearrangement[57] in a number of synthetic applications with good success,[58] it was decided to start from products of this reaction ((+)-**7a** and (+)-**8**) also here. The synthesis of the allyl vinyl ether (AVE) (*E*,*Z*)-**5a** and (*Z*,*Z*)-**5** has been already published[54,59] and will be described in Chapter 3.1.

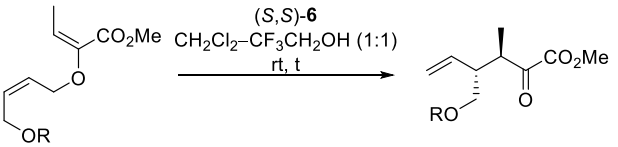


Scheme 3

α-Keto esters (+)-**7a** and (+)-**8** are epimers which can be understood as quasi-enantiomers from a functional perspective. This is because the substituents at C9 (namely the vinyl and benzyloxymethyl group) can be considered as pseudo-diastereotopic groups which may lead to enantiomeric products when applying the synthetic transformations in different sequences. Consequently, product (+)-**7** and (+)-**8** resemble *both enantiomeric* building blocks for the central γ-lactone.

Allyl vinyl ethers bearing a *tert*-butyldimethylsilyl (TBS) or *tert*-butyldiphenylsilyl (TPS) protecting group instead of the benzyl group in **5** were also synthesized, but provided unsatisfactory diastereoselectivities in CAGC rearrangements (Table 2) and were consequently excluded from further studies.

Table **2**: Enantio- and diastereoselectivities of differently protected products of the CAGC rearrangement.



(*E*,*Z*)-**5a**: R = Bn
(*E*,*Z*)-**5b**: R = TBS
(*E*,*Z*)-**5c**: R = TPS

7a: R = Bn
7b: R = TBS
7c: R = TPS

entry	compound	(S,S)-**6** equiv	t [h]	dr	ee
1	**7a**	0.05	12	95:5	99%
2	**7b**	0.25	12	80:20	n. d.
3	**7c**	0.08	24	83:17	90%

As depicted in Scheme 4, reduction of the α-keto ester (+)-**8** employing K[(*s*-Bu)$_3$BH][60] provided the respective α-hydroxy ester in excellent diastereoselectivities. After protection of the hydroxyl group as a TBS ether,[61] the ester (–)-**9** was converted into the aldehyde (+)-**10** by a redox sequence consisting of diisobutylaluminiumhydride (DIBAL-H) reduction and Dess–Martin periodinane (DMP) oxidation.[62] Chain elongation towards the Eastern part was achieved by a Wittig-type chloromethylenation[63] followed by a subsequent Fritsch–Buttenberg–Wiechell[64] rearrangement to afford the alkyne (+)-**11**. Chemoselective ozonolysis of the vinyl group under reductive workup conditions and in situ reduction[65] of the transient aldehyde provided a primary alcohol, which was then protected as TBS-ether (–)-**12**.[61] The construction of the (*E*)-configured, trisubstituted C12-C13 double bond in product **13** was accomplished next. For this purpose, the terminal alkyne (–)-**12** was treated with LDA and isopropyl chloroformate resulting in the respective isopropyl alkynoate. The latter was exposed to methylmagnesium bromide in the presence of suprastoichiometric amounts of copper bromide dimethyl sulfide complex to react in a 1,4-selective methylcupration.[66] The corresponding α,β-unsaturated

[54] Körner, M. Dissertation 2009, TU Dortmund.
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[58] a) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705–5708. B) Wang, Q.; Millet, A.; Hiersemann, M. *Synlett* **2007**, 1683−1686.
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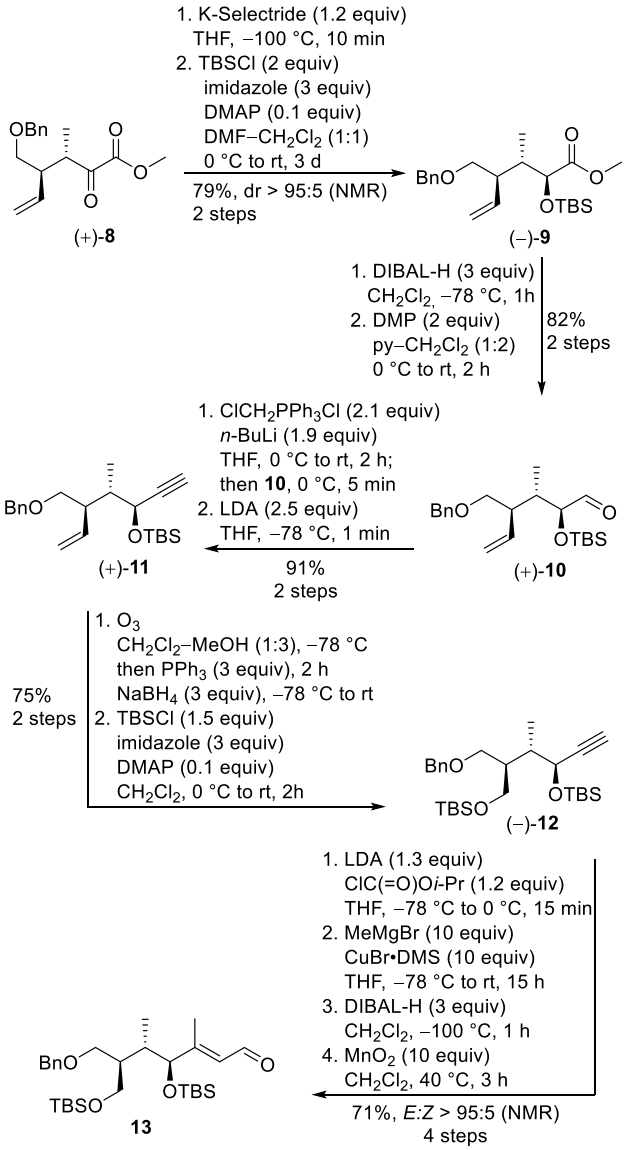
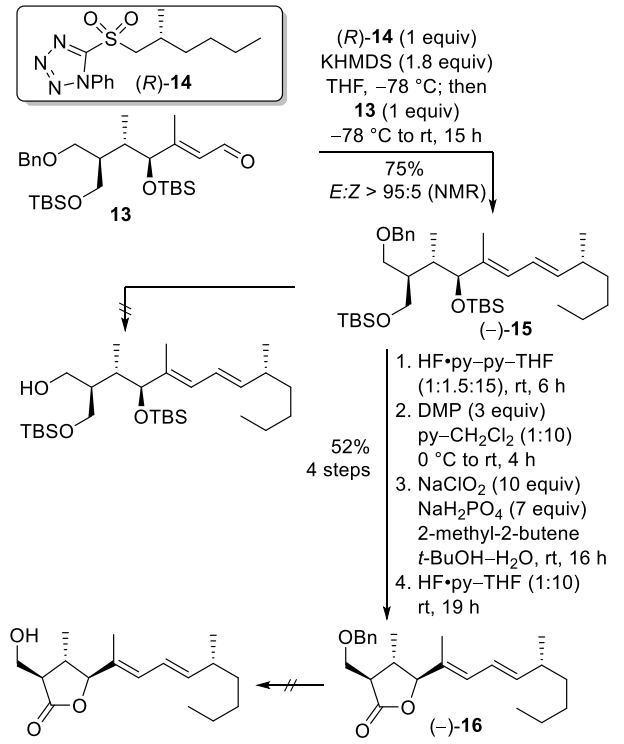
[61] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.
[62] a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287
[63] Seyferth, D.; Grim, S. O.; Read, T. O. *J. Am. Chem. Soc.* **1961**, *83*, 1617−1620.
[64] Knorr, R. *Chem. Rev.* **2004**, *104*, 3795−3850.
[65] Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 3855−3860
[66] Williams, D.R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721–2724

ester was delivered in excellent (*E*)-selectivities. Subsequent redox transformation afforded the dienal **13**, ready for coupling with the Eastern fragment (*R*)-**14**, whose synthesis has been already published[55] and will be described in Chapter 3.3.



Scheme 4

The construction of the C14-C15 double bond was accomplished using a Julia–Kocienski olefination as a well-established, robust and reliable method for the synthesis of (*E*)-configured double bonds (Scheme 5).[67] After the successful synthesis of the Central-Eastern fragment, the next challenge was posed by the elongation towards the Western part. For this purpose, the benzyl protecting group had to be removed. Unfortunately, no conditions could be found to achieve this apparently simple deprotection (Lewis acid catalyzed as well as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) promoted reactions were tested). However, conversion of (–)-**15** into the corresponding γ-lactone (–)-**16** was realized by a sequence consisting of selective deprotection of the primary TBS ether, successive two-stage oxidation[68] delivering the corresponding carboxylic acid, and deprotection of the secondary TBS ether[69] followed by intramolecular lactonization. Attempts to cleave the benzyl ether at the stage of (–)-**16** were fruitless as in the case of (–)-**15**. As mentioned earlier, a replacement of the benzyl group by silyl groups led to poor diastereoselectivities in the previously applied CAGC rearrangement (Table 2).



Scheme 5

Further studies were carried out employing the undesired configuration in the Central part of the targeted molecule (Scheme 6). The rationale for this undertake was to establish the synthetic methodology for the elongation towards the Western end. The undesired configuration resulted from the non-cleavability of the benzyl-group in (–)-**15** while its primary silyl group could be removed without difficulties. It should be highlighted, that the results from these studies are particularly relevant for this thesis, as they establish the principal feasibility of the planned synthetic route.

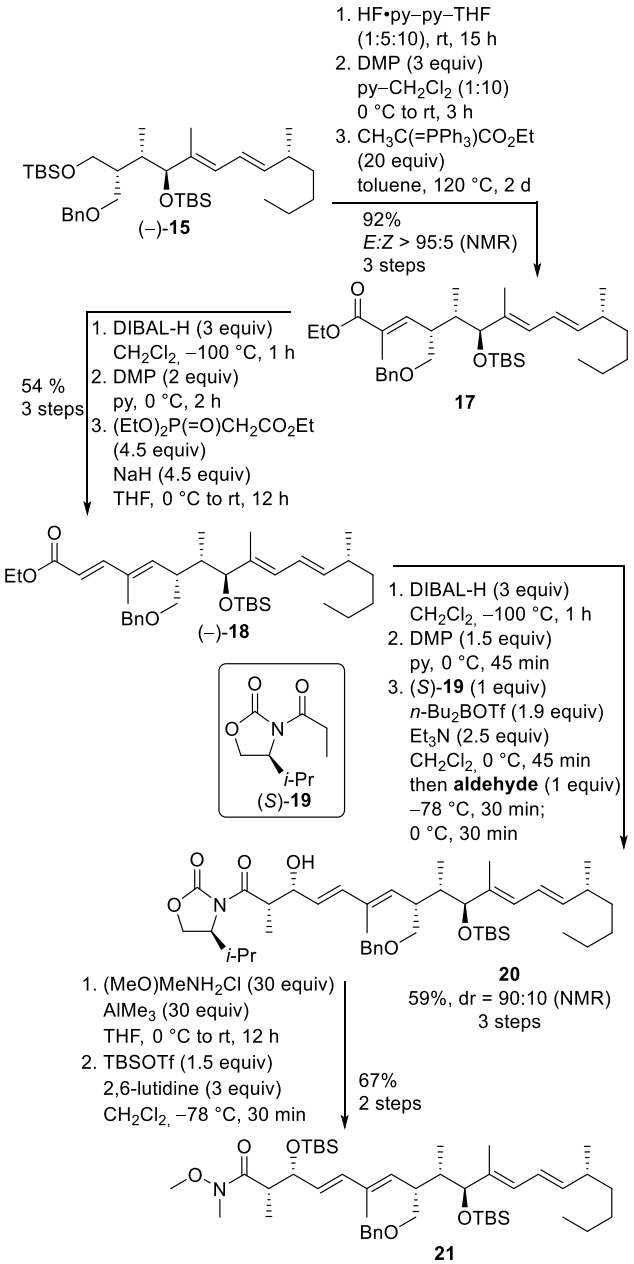
The construction of the trisubstituted, (*E*)-configured double bond in **17** was achieved by a three step sequence consisting of the selective removal of the primary TBS ether

[67] 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.

[68] Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

[69] Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011−4013.

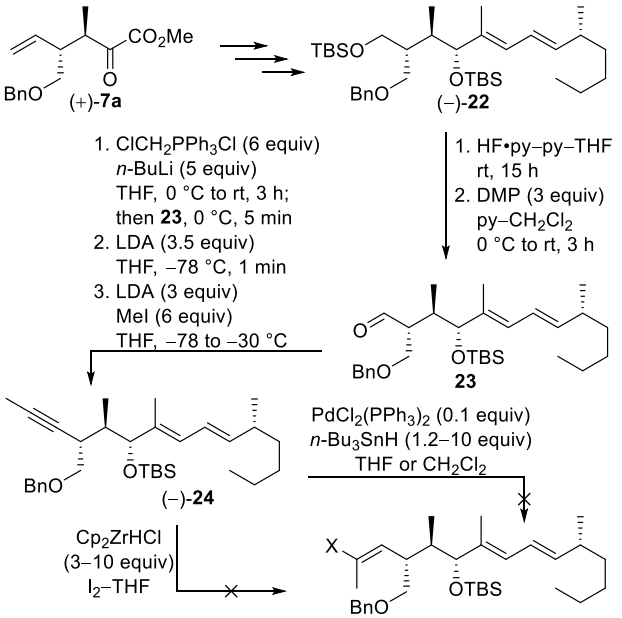
in (–)-**15**, DMP-oxidation of the resulting hydroxyl group and a Wittig olefination[70] to yield the α,β-unsaturated ester **17**. Further elongation required a redox transformation of the ester into the corresponding aldehyde followed by a Horner−Wadsworth−Emmons (HWE) olefination[71] to afford the α,β-γ,δ-unsaturated ester (–)-**18**.



Scheme 6

Another redox transformation yielded its respective aldehyde which underwent an Evans aldol reaction[72] to result in the *syn*-configured *N*-acyloxazolidinone **20**. The latter was converted into the corresponding Weinreb amide,[73] whose aldol hydroxyl group was protected as the TBS-ether **21**. An attempt to convert the Weinreb amide **21** into the corresponding methyl ketone provided preliminary evidence that this transformation is feasible albeit a side reaction was detected which was interpreted as an epimerization.

In analogy to the previously described route (Scheme 4), the α-keto ester **7a**, resulting from the AVE (*E*,*Z*)-**5a**, was converted into the bissilylether (–)-**22** (Scheme 7). Selective removal of the primary TBS ether and subsequent DMP oxidation yielded the aldehyde **23**. The further plan intended to construct the C6-C7 bond through a cross-coupling or a Heck reaction[74]. Therefore, an aldehyde-to-alkyne homologation was implemented and the 7'-CH_3 group was introduced to result in the dienyne (–)-**24**. Attempts to convert the dienyne into the corresponding vinyl iodide employing a hydrozirconation-iodination reaction with Schwartz's reagent[75] failed or delivered an inseparable product mixture. As an alternative, a palladium-catalyzed hydrostannation[76] was addressed but led to no conversion either.



Scheme 7

[70] Wittig, G.; Geissler, G. *Liebigs Ann.* **1953**, *580*, 44−57.
[71] a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. b) Horner, L.; Hoffman, H. G. *Chem. Ber*. **1958**, *91*, 61−63.
[72] Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.
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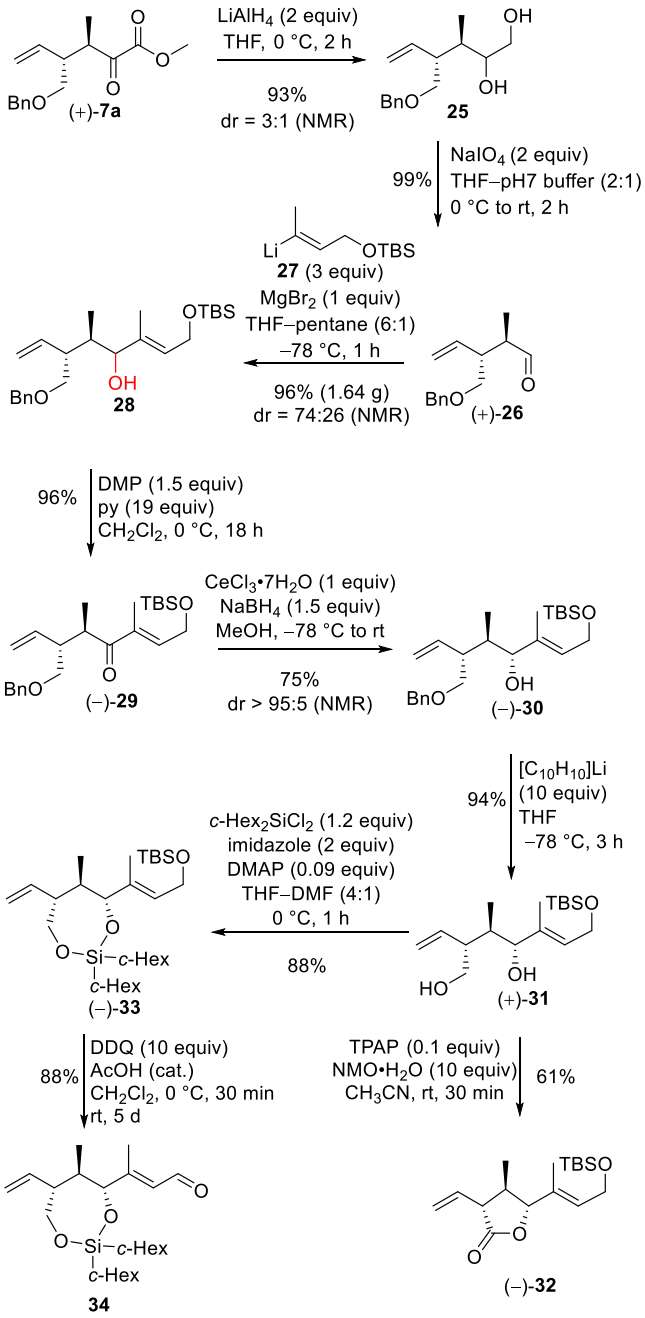
1.7.2 Results from the thesis of Florian Quentin[77]

From the above results, it was concluded that the deprotection of the benzyl group has to be performed at a suitable early stage of the synthesis. Further rethinking led to the consideration that the general synthetic strategy might benefit from a higher degree of convergence. Thus, the strategy was redesigned to reduce the number of elongation steps (Scheme.8). Paradoxically this meant that the α-ketoester (+)-**7a** from the Gosteli–Claisen-rearrangement[57] should undergo truncation before elongation. Truncation was implemented by reduction of α-keto ester (+)-**7a** to the corresponding diol **25** which then was cleaved by periodate oxidation. The resulting aldehyde (+)-**26** was elongated by the addition of the in situ generated vinyllithium species **27.** The synthesis of this four carbon atoms bearing building block has been already published.[78] In principle, the latter elongation could have been performed with a vinyllithium species carrying the whole Eastern side chain. While the synthesis of such a species proved to be feasible, its addition to aldehyde **26** did not. A general problem of vinyllithium addition reactions (in our hands) is their low or even undesired diastereoselectivity. This is why a workaround had to be found which is able to convert the low or even improper diastereoselectivity into a high and proper diastereoselectivity. Utilization of a DMP oxidation of **28** followed by a diastereoselective Luché-reduction[79] of the resulting ketone (–)-**29** fulfilled this requirement.

At the stage of secondary alcohol (–)-**30** the removal of the benzyl group was achieved by treatment with lithium naphtalenide.[80] The resulting diol (+)-**31** was protected as a cyclic 1,3-dioxasilepane (–)-**33** utilizing the silylation reagent dicyclohexyldichlorosilane (*c*-Hex_2SiCl_2).[81] Conditions were found allowing to cleave the terminal TBS ether in (–)-**33** without affecting the integrity of the 1,3-dioxasilepane ring. These conditions utilize acetic acid in the presence of DDQ as an oxidant and led to the α,β-unsaturated aldehyde **34**.[82] It was furthermore demonstrated that the diol (+)-**31** can be transformed into γ-lactone (–)-**32** by selective oxidation of the primary alcohol using modified conditions[83] for the Ley–Griffith oxidation[84].



Scheme 8

A major focus in the synthetic route towards Curvicollide C was based on the idea to employ cross-metathesis reactions for the construction of the trisubstituted double bond in the Western side chain. The common denominator of the targeted reactions is the existence of a vinyl group in the respective Central fragment (+)-**31** or (–)-**33**, while the

[77] Quentin, F. Dissertation **2015**, TU Dortmund.
[78] Seebach, D.; Maestro, M. A.; Sefkow, M.; Adam, G.; Hintermann, S.; Neidlein, A. *Liebigs Ann. Chem*. **1994**, 701−717.
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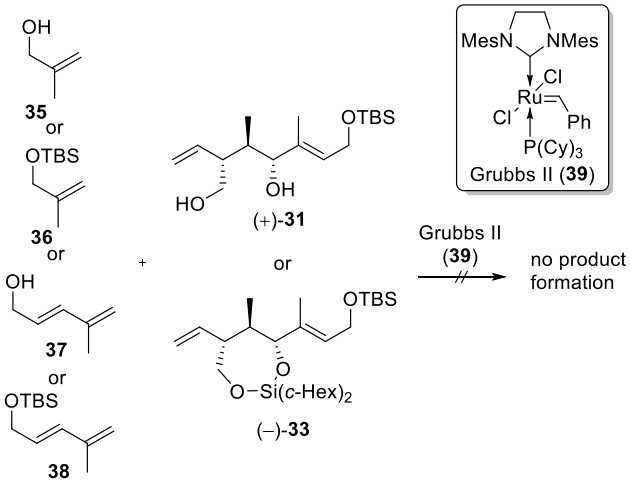
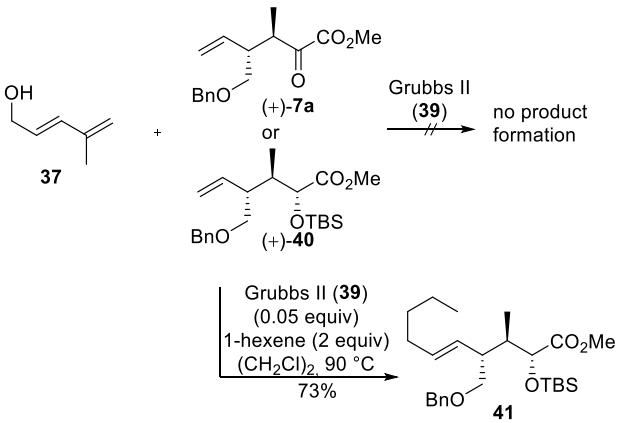
[84] Griffith, W. P.; Ley, S. V.; Whitcomb, G. P.; White, A. D. J. *Chem. Commun.* **1987**, 1625−1627.

building blocks for the elongation towards the Western end (**35**, **36**, **37**, **38**) all contain the isobutene skeleton as a substructure (Scheme 9). In none of the studied combinations, product formation was detectable using Grubbs II[85] (**39**) as the catalyst.



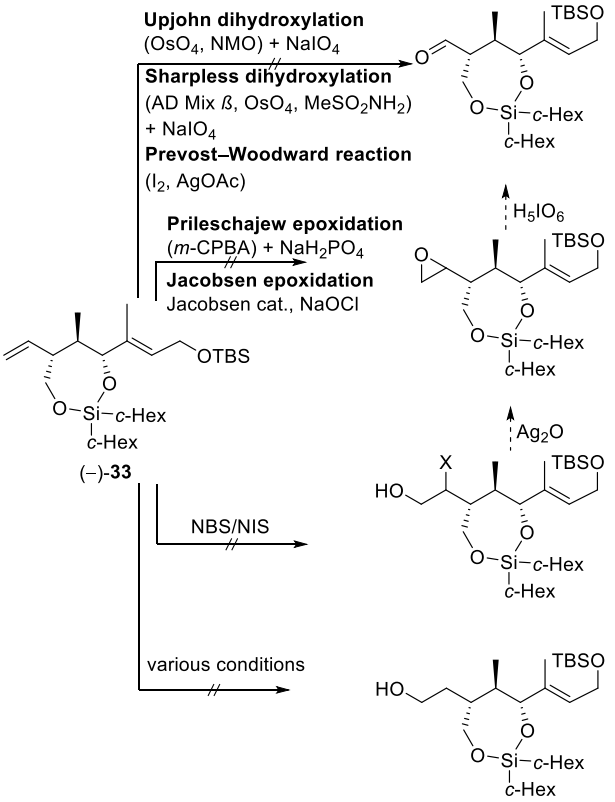
Scheme 9

Further cross-metathesis reactions were tested using vinyl -containing products ((+)-**7a** and (+)-**40)** from earlier synthetic stages (Scheme 10). Again, metathesis failed when employing conjugated diene **37** as the reaction partner. Nevertheless, a successful cross-metathesis could be achieved using 1-hexene as a simple monosubstituted model substrate. These results are insofar relevant for potential strategies towards Curvicollide C via cross-metathesis as they exclude a retrosynthetic scission for each trisubstituted double bond.



Scheme 10

Toward this end and intending to circumvent cross-metathesis, the next idea was to convert the terminal double bond into an aldehyde in order to further elongate by olefination chemistry (Scheme 11). Attempts included various oxidative double bond cleavages consisting of dihydroxylation and diol cleavage, epoxidation[86,87] (followed by treatment with periodic acid), as well as conversion into the corresponding halohydrine. Unfortunately, all attempts failed. Even regioselective hydroboration[88] including bulky hydroboranes[89] did not result in a successful transformation, as either no reaction or decomposition was observed.



Scheme 11

Further synthetic studies were based on diastereomer (+)-**8** (Scheme 12) resulting from the CACG[57] rearrangement of the AVE (*Z*,*Z*)-**5a** (Scheme 3). In analogy to the previously described route (Scheme 8), the α-keto ester (+)-**8** was reduced to the diol **42** which was then cleaved to give the aldehyde (+)-**43**. Two differently protected vinyllithium reagents (**27** or **44**) were utilized in nuceophilic additions. The insufficient diasteroselectivities could be corrected by a redox sequence consisting of DMP oxidation and diastereoselective Red-Al[90] reduction. For the TBS ether (+)-**47b** a selective oxidative conversion of the vinyl group into the corresponding aldehyde (which is expected

[85] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
[86] Prileschajew, N. *Chem. Ber.* **1909**, *42*, 4811−4815.
[87] a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801−2803. b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron: Asymmetry* **1991**, *2*, 481−494.
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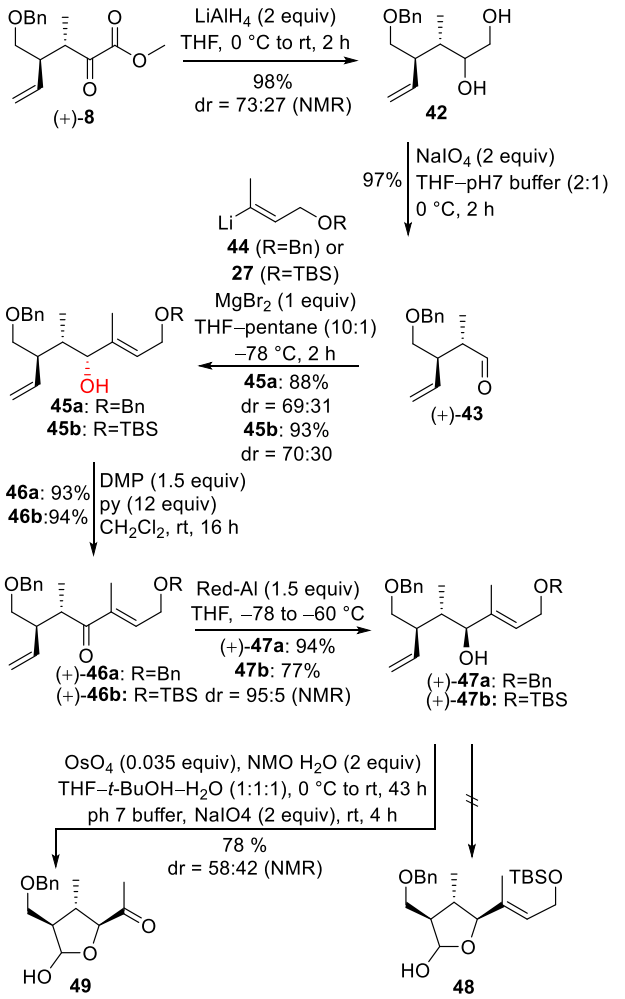
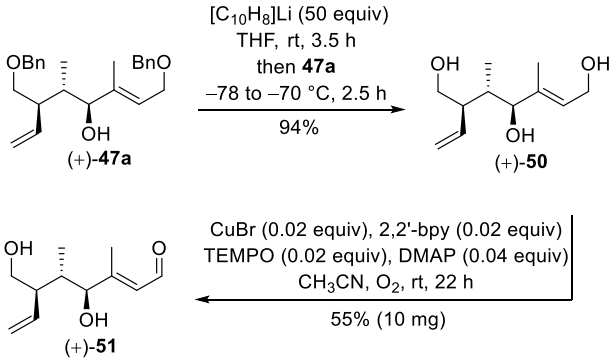
[89] Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5281−5283.
[90] a) Vit, J.; Casensky, B.; Machacek, J. Fr. Patent 1, 615, 582, **1967**; b) Čapka, M.; Chvalovský, V.; Kochloefl, K.; Kraus, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 118–124; c) Bajwa, N.; Jennings, M. P. *J. Org. Chem.*, **2008**, *73*, 3638–3641.

to yield lactol **48** by cyclization) could not be achieved even after testing a broad variety of conditions. Upjohn conditions[91] led to the cleavage of both double bonds resulting in product **49**. This result meant that a selective oxidation of a vinyl group in the presence of an electron-rich trisubstituted double bond is an intrinsic problem of the synthetic strategy employed. Successful oxidation is always expected to result in an undesired exhaustive cleavage. Thus, in order to allow a selective oxidative cleavage of the vinyl group, the trisubstituted double bond must exist in an electron-deficient variant such as the α,β-unsaturated aldehyde (+)-**51** which was recognized as a new key intermediate in the present thesis.



Scheme 12

For the purpose of its synthesis, benzyl cleavage in (+)-**47a** was achieved by treatment with lithium naphtalenide[80] (Scheme 13). First attempts to oxidize triol (+)-**50** selectively, using the conditions of Stahl et al.,[92] showed promising results indeed but required further optimization.



Scheme 13

[91] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976.

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Chapter 2 - Task of this thesis

The task of this thesis was the enantioselective total synthesis of Curvicollide C (**1**) as proposed by M. Hiersemann within a DFG project. The proposal was filed under the following description:

"Project Description The elucidation of the configuration of natural products and the supply of derivatives for biological studies is of premiere importance. In this regard, the aim of the present project is to establish an enantioselective total synthesis of curvicollide C, a polyketide isolated from the mycoparasitic fungi Podospora curvicolla. Our extensive exploratory efforts have culminated into the credible research proposal at hand which defines important and interesting scientific questions. The isolation and structural elucidation of the C26-curvicollides A-C was first reported by Gloer et al. in 2004. The relative configuration of the polyketide was only partially elucidated and the absolute configuration remains unknown. Our project is aimed at the elucidation of the absolute configuration of curvicollide C by total synthesis of diastereomers of the natural product and their characterization by chiroptical methods. Furthermore, since it has been reported that curvicollide A shows promising antifungal activities but curvicollide C could not be tested due to lack of material, providing access to the natural product and derivatives thereof would enable a comprehensive biological study. The unique constitution of the curvicollides implicates a rather unusual biosynthetic pathway in which the carbon backbone of the curvicollides is assembled by the condensation of a hexa- and a pentaketide to establish the characteristic central lactone moiety. The projected synthesis of the lactone with the two attached 1,3-diene segments defines one of the central scientific challenges which we hope to resolve relying on a highly modular synthetic strategy. Because the curvicollides A-C are only distinguished by the substituent pattern in the eastern part of the molecule, a successful modular synthesis of curvicollide C should enable the synthesis of the other members of this family of polykketides."

From the dissertation theses of M. Körner and F. Quentin, outlined in Chapter 1.7, the following insights could be gained:

- α-Keto ester (+)-**7a** or (+)-**8** are suitable starting substrates for the synthesis of the central γ-lactone of Curvicollide C as they already contain 2 chiral centers of the central stereotriade. The new plan considered to keep this chemistry explored by M. Körner as its fundament.

- F. Quentin had shown that the addition of a vinyllithium species for the introduction of the trisubstituted double bond in the C12-C14 fragment facilitated a reduction of steps in comparison to M. Körner's procedure which comprised the synthesis of an alkynoate and a 1,4-selective methylcupration. Quentin's procedure was also embarked as a well-elaborated synthetic module for this thesis.

- While the benzyl-protected allyl vinyl ethers gave excellent diastereoselectivities in the CAGC rearrangements, it was found by M. Körner that the removal of the benzyl group was not successful at a late stage of synthesis when the diene side chains are present. Benzyl deprotection thus required its implementation at an early stage of synthesis which was realized by F. Quentin through treatment with lithium naphtalenide.

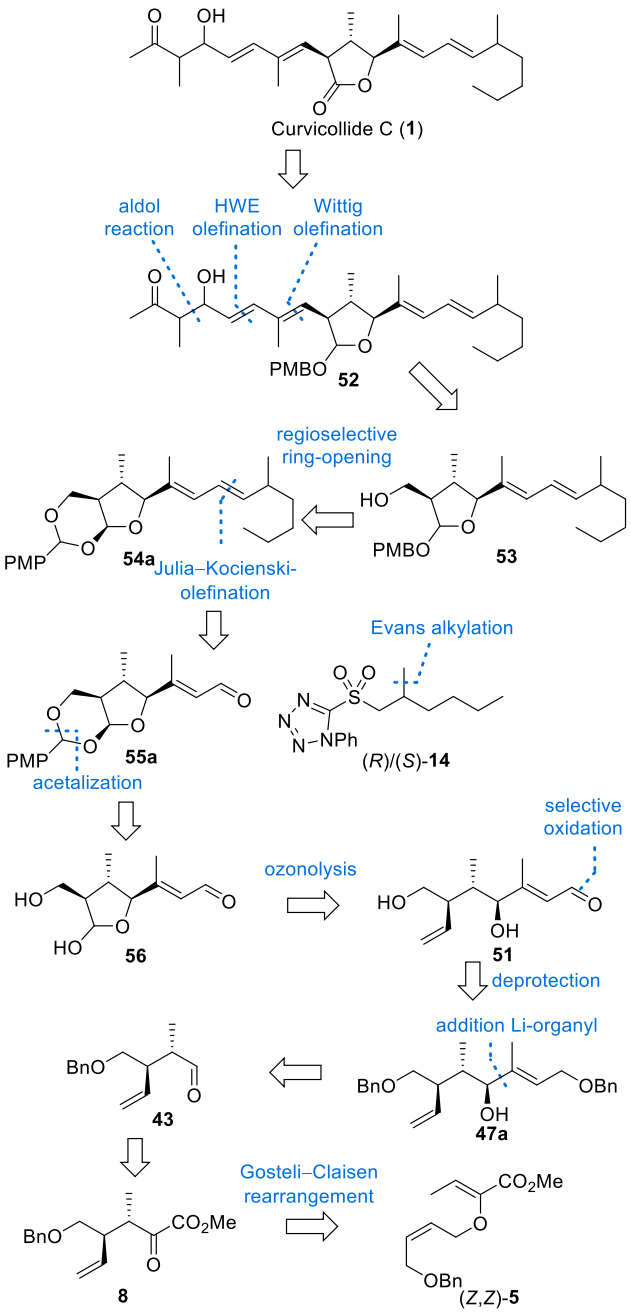
- As a further component of the plan, it was decided to follow M. Körner's work on the Julia–Kocienski olefination as a modular and convergent way to introduce the Eastern fragment in a single coupling step.

- It was found by F. Quentin that the formation of the trisubstituted double bond at C7/C8 via cross-metathesis is not feasible at all. Furthermore, M. Körner's attempts to utilize Heck-reactions as an alternative failed due to the synthetic inaccessibility of the trisubstituted vinyl iodide required as the substrate.

- Instead, as shown by M. Körner, a stepwise procedure employing a Wittig olefination, a HWE olefination and an aldol reaction as carbon-carbon bond forming steps was successfully elaborated for the Western fragment, albeit with the improper stereochemistry.

The above findings and insights were incorporated as a frame for the plan whose retrosynthetic analysis is depicted in Scheme 14.

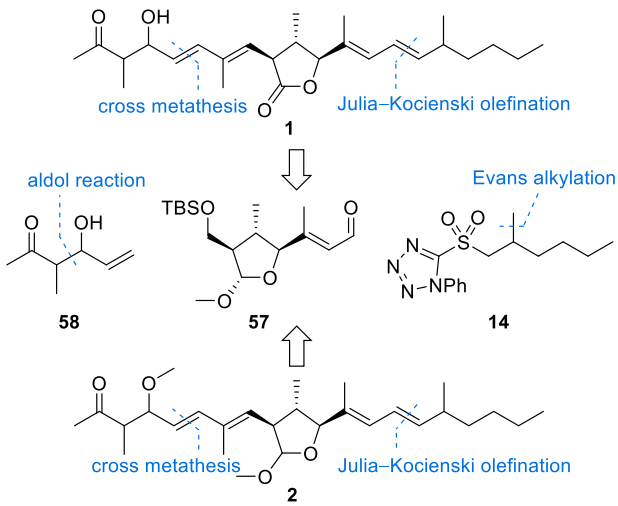
Curvicollide C (**1**) was planned to be synthesized from the lactol ether **52** bearing the *p*-methoxybenzyl (PMB) group. The synthesis of the Western side chain was conceived to rely on successive olefination and aldol formation steps starting from **53** as the synthetic precursor. As the stereochemistry in the aldol part was unknown, care had to be taken that all possible diastereomers could be made accessible. This requirement was seen fulfilled in the application of *syn*- and *anti*-aldol chemistry utilizing enantiomerically pure auxiliaries.



Scheme 14

The PMB group in **53** was selected as its generation was planned to be based on a regioselective ring opening by reductive cleavage of the *p*-methoxyphenyl (PMP) precursor acetal **54a**. The Eastern side chain was supposed to be generated using a Julia–Kocienski olefination employing the individual enantiomers of sulfone **14**, essentially following the synthetic methodology previously applied by M. Körner. The PMP acetal in **55** was considered to be obtained from the corresponding α-hydroxymethyl lactol **56**. Thus the selection of a PMP acetal was based on the consideration that it allows the simultaneous protection of two hydroxyl groups and, in addition, may be transformed into a monoprotective group, when needed. The α-hydroxymethyl lactol **56** was conceived to be the result of a selective ozonolysis when starting from diol (+)-**51** containing the aldehyde in the latent form of a vinyl group. The synthesis of the latter molecule was already explored by F. Quentin, who showed in first test reactions that the α,β-unsaturated aldehyde in (+)-**51** is accessible by selective oxidation of the respective triol resulting from benzyl deprotection of (+)-**47a**. The latter can be obtained via addition of a vinyllithium species to the aldehyde (+)-**43**, which derives from the α-keto ester (+)-**8**. As already published, α-keto ester (+)-**8** results from a highly enantio- and diastereoselective CAGC rearrangement of the allyl vinyl ether (*Z*,*Z*)-**5**.

It should be emphasized that in the course of the experimental realization of the above proposal, the discovery of Fusaequisin A (**2**) was reported. This is why the DFG proposal did not address a synthetic route which could lead to both natural products. However, the discovery deeply affected our work and finally ended in a rethinking of several critical steps. The replanning caused by Fusaequisin A (**2**) is depicted in Scheme 15 to give a first impression of modular redesign but will be introduced later (Chapter 3.13).

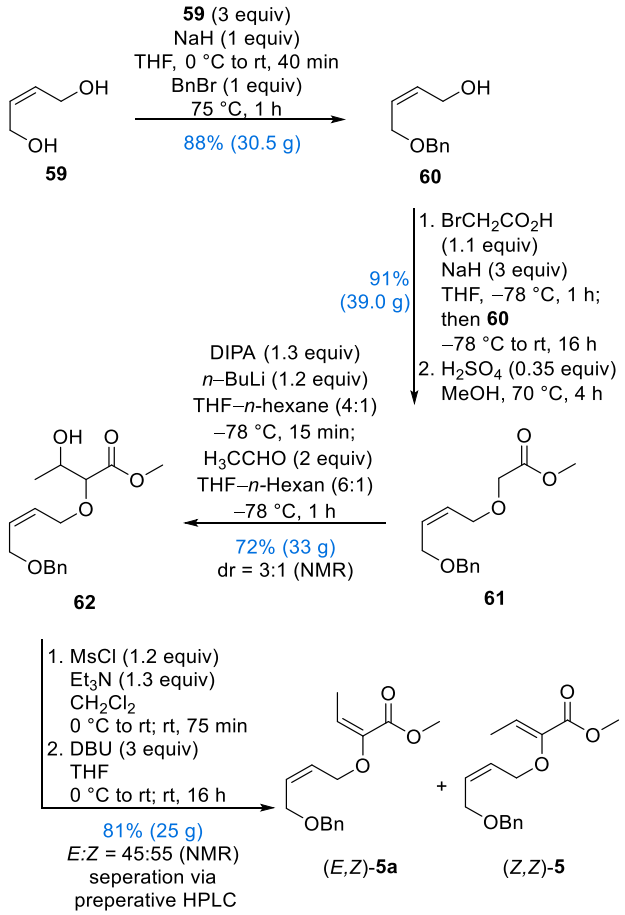


Scheme 15

Chapter 3 - Results and Discussion

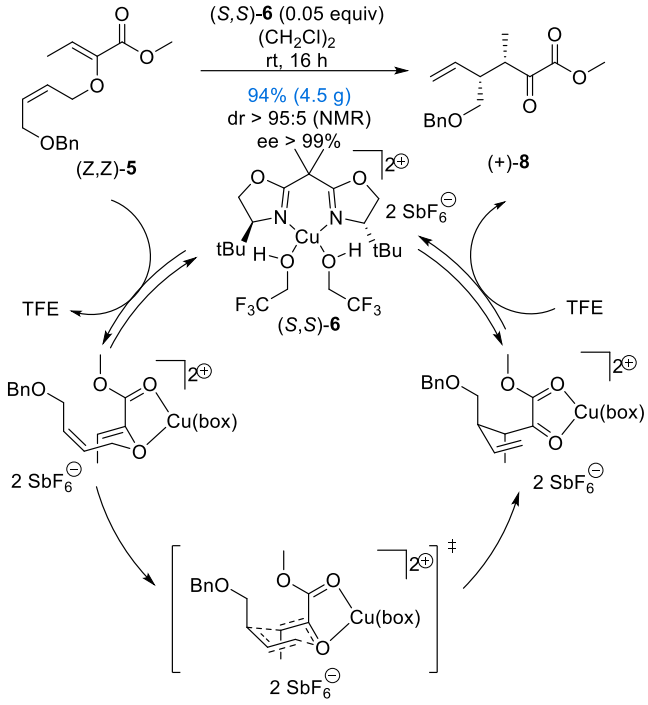
3.1 Synthesis of the α-keto ester (+)-8[54]

Beginning with the commercially available (*Z*)-2-butene-1,4-diol (**59**) two consecutive Williamson etherifications[93] and a Fischer esterification[94] were performed to deliver the methyl ester **61** (Scheme 16). Aldol addition of the enolate of allyloxy-substituted acetic acid ester **61** with acetaldehyde at −78 °C afforded the β-hydroxy ester **62** as a mixture of diastereomers (dr = 3:1) in satisfactory yields. Attempts to assign the relative configuration were omitted as found to be unnecessary for further transformations. Mesylation of **62** followed by elimination, mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), provided the desired allyl vinyl ether **5** as a mixture of double bond isomers in the ratio of *E*/*Z* = 45:55 (in accordance to the expected higher thermodynamic stability of the (*Z*)-isomer).[95] Subsequent separation by preparative HPLC yielded the allyl vinyl ethers (*E*,*Z*)-**5a** and (*Z*,*Z*)-**5** as pure vinyl ether double bond isomers.



Scheme 16

Catalytic asymmetric Gosteli–Claisen (CAGC) rearrangement[57] of the allyl vinyl ether (*Z*,*Z*)-**5** in the presence of 5 mol% of [Cu{(S,S)-*tert*-Bu-box}](tfe)$_2$(SbF$_6$)$_2$[96] [(S,S)-**6**] provided the α-keto ester (+)-**8**, essentially as an enantio- and diastereomerically pure compound (Scheme 17). The relative and absolute configuration was assigned based on the well-established stereochemical course of the CAGC rearrangement.



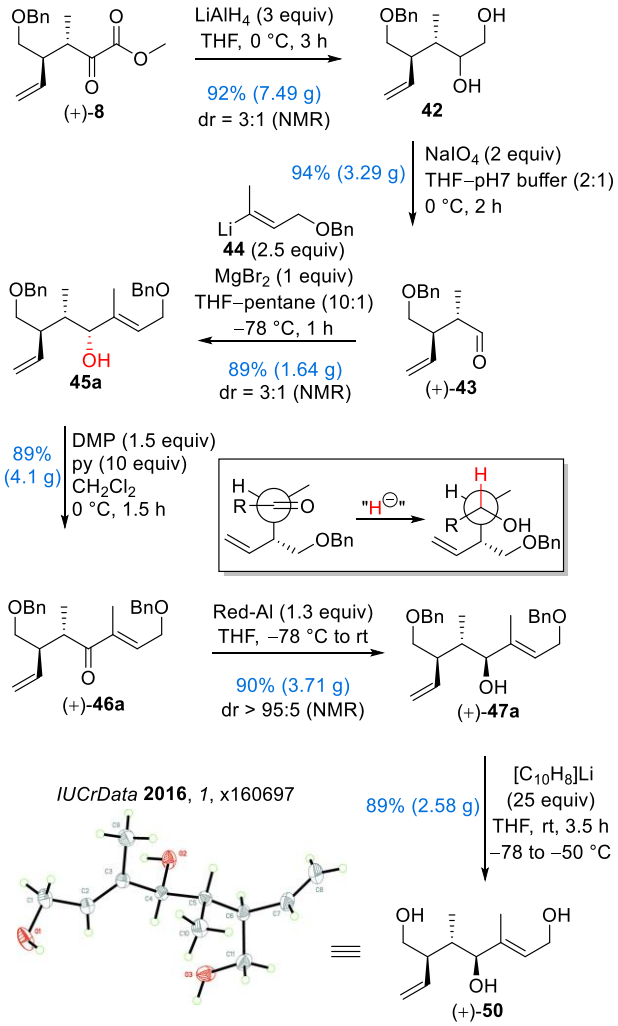
Scheme 17

The mechanism of the CAGC rearrangement is depicted in Scheme 17. In the first step, the copper ion of catalyst (*S*,*S*)-**6** coordinates the allylic ether and the ester carbonyl oxygen atom of (*Z*,*Z*)-**5** in a bidentate fashion. In this step, the high enantioselectivity of the rearrangement is caused by the enantioface-differentiating capability of the catalyst, as the latter coordinates only to one of the two enantiotopic electron pairs of the allylic ether oxygen. Thus, the allylic ether segment favorably approaches the vinyl ether segment from the face opposite to the bulky *tert*-butyl substituent on the box ligand. The allylic oxygen becomes polarized by the inductive effect of the copper ion which facilitates the formation of a polarized cyclic chair-like transition state of a concerted [3,3]-sigmatropic rearrangement. The resulting α-keto ester **8**, still complexed to the catalyst, can be replaced by a new molecule of the allyl vinyl ether (*Z*,*Z*)-**5** or by two molecules of trifluoroethanol.

[93] a) Williamson, W. *Liebigs Ann. Chem.* **1851**, *79*, 37−49. b) Williamson, W. *J. Chem. Soc.* **1852**, *106*, 229−239
[94] Fischer, E.; Speier, A. *Chem. Ber.* **1895**, *28*, 3252−3528.
[95] Hiersemann, M. *Synthesis* **2000**, 1279−1290.
[96] Jaschinski, T.; Hiersemann, M. *Org. Lett.* **2012**, *14*, 4114−4117.

3.2 Synthesis of the Central fragment

With the α-keto ester (+)-**8** as the precursor of the Central building block in hand, the synthesis commenced with an exhaustive $LiAlH_4$ reduction of the α-keto ester (+)-**8** to deliver a mixture of diastereomers (dr = 3:1) of the vicinal diol **42 (**Scheme 18). The assignment of the diastereomers of the diol **42** was neglected, as a subsequent diol cleavage led to the α-chiral aldehyde (+)-**43**. The diol cleavage was performed with sodium periodate employing phosphate buffer[97] (pH 7) to avoid a possible epimerization of the α-chiral aldehyde (+)-**43**. As the next step, a sidechain elongation by stereoselective construction of the C12-C13 double bond was addressed.



Scheme 18

The required chemistry is based on the addition of a vinyllithium species **44** and had been established in a previous thesis as described earlier (Chapter 1.7.2). The vinyllithium species **44** was obtained by lithium halogen exchange from the corresponding vinyl bromide **66** whose synthesis is the subject of the next paragraph. Elaborate studies revealed that the nucleophilic addition of vinyl reagent **44** works best in the presence of an excess of the vinyl bromide, magnesium bromide as the Lewis acid[98] for the activation of the aldehyde (+)-**43**, and addition of the vinyllithium species at −78 °C. Furthermore, it should be emphasized that both is important (a) to purify the vinyl bromide **66** just before its utilization and (b) to check the quality of the applied *t*-BuLi solution in a preceding test reaction. While the nucleophilic addition ensures the construction of the correctly (*E*)-configured trisubstituted double bond indeed, the alcohol **45a** was obtained in the undesired (11*R*) configuration with poor diastereoselectivity (dr = 3:1). The latter problem was however solved by Dess–Martin oxidation yielding the enone (+)-**46a** which could be reduced in a diastereoselective fashion with Red-Al[90], affording the secondary allylic alcohol (+)-**47a** in the proper (11*S*) configuration. The diastereoselectivity of the reduction can be explained using the Cram–Felkin–Anh model (Box in Scheme 18).[99] Benzyl ether cleavage with excess amounts of lithium naphtalenide[80] (25 equiv) led to triol (+)-**50**. A proof of the desired relative configuration of the stereotriade was provided by an X-ray crystal-structure analysis of the triol (+)-**50**.[100] Note that the relative configuration of triol (+)-**50** reflects the stereostructural features of the central cyclic part of both natural products targeted in this thesis.

The synthesis of the required vinyl bromide **66** (Scheme 19) was accomplished by applying the published procedure of D. Seebach et al.[78] Bromination of the commercially available (*E*)-but-2-en-1-ol (**63**) afforded the dibromide **64** in excellent yield.[101] Diastereoselective elimination with double amounts of the strong base LDA and hexamethylphosphoramide (HMPA) as an additive – generating more "naked" anions by chelation[102] - delivered the vinyl bromide **65** in moderate yield but excellent diastereoselectivity.[103] The assignment of the (*E*)-configured double bond is corroborated by X-ray crystallography of compound (+)-**50** previously described. The selection of a benzyl ether as protecting group was based on the consideration to be able to remove both benzyl groups in (+)-**47a** in a single step. Benzylation was achieved by employing

[97] According to conditions of Sørensen: Stoll, V. S.; Blanchard, J. S. *Methods Enzymol*. **2009**, *463*, 43−56.
[98] Seebach, D.; Neumann, H. *Chem. Ber*., **1978** *111*, 2785−2812.
[99] a) Cram, D. J.; Elhafez, F. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828−5835. b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *9*, 2199−2204. c) Anh, N. T.; Eisenstein, O.; Lefour, J. M.; Dau, M. E. *J. Am. Chem. Soc*. **1973**, *95*, 6146−6147.
[100] von Kiedrowski, V.; Quentin, F.; Golz, C.; Strohmann, C.; Preut, H.; Hiersemann, M. *IUCrData* **2016**, *1*, x160697.
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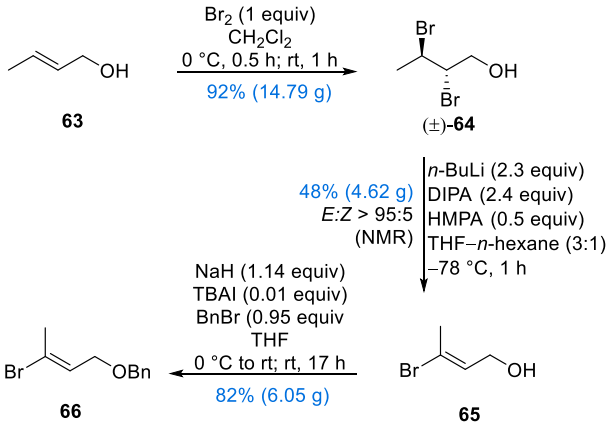
[103] Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc*. **1993**, *115*, 2268−2278.

NaH for deprotonation of **65** and benzyl bromide in combination with catalytic amounts of tetrabutylammonium iodide (TBAI) for Finkelstein exchange[104] to deliver the benzyl ether **66.**

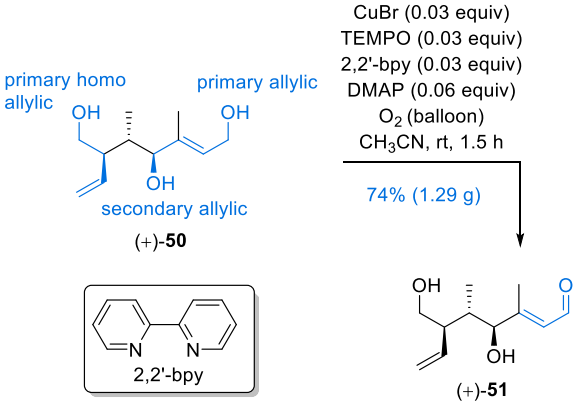


Scheme 19

For the construction of the central heterocycle, the functionalization of the terminal double bond was addressed. Previous studies revealed that the selective functionalization of the terminal double bond is not possible in the presence of the internal trisubstituted double bond. Therefore, the idea came up to convert the internal double bond into an electron deficient one. As a consequence, the relative reactivity of the terminal double bond towards electrophiles is expected to increase. Realization seemed to be possible by the selective oxidation of the primary allylic alcohol in (+)-**50** which generates an electron deficient enone.

3.2.1 Selective oxidation of the primary allylic alcohol

Triol (+)-**50** bears a primary allylic, a secondary allylic and a primary homo allylic alcohol, thus, a highly selective oxidation is required to differentiate between the three hydroxyl groups. In 2011, Stahl reported a catalyst system that enables a selective aerobic oxidation of a broad range of primary alcohols. Indeed, the catalyst system consisting of CuBr, 2,2'-bipyridine, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 4-(dimethylamino)pyridine (DMAP) under an oxygen atmosphere allowed to convert triol (+)-**50** into the α,β-unsaturated aldehyde (+)-**51** in satisfactory yields (Scheme 20).



Scheme 20

The reaction has to be carefully monitored by TLC, however, as otherwise an irregular fast formation of undesired side products is observed. The structural assignment of the unpolar side products could not be achieved because chromatographical separation was not possible. In case of extensive build-up of the undesired side products, the reaction was immediately quenched. This modus operandi served to avoid the formation of byproducts and enable recovery of starting material.

The next step aimed to functionalize the terminal double bond selectively. Ozonolysis[105] as a well-established method was tested first. For this purpose a solution of diol (+)-**51** in CH_2Cl_2–MeOH (3:1) was treated with an ozone gas stream passed into the solvent mixture at –78 °C in the presence of the indicator dye Sudan red B[106]. As soon as the slight pink color of Sudan red B disappeared, the injection of ozone was stopped and a reductive workup employing PPh_3 (3 equiv) was applied. However, ozonolysis resulted in a non-selective cleavage of both double bonds and could not be steered towards selectivity.

As an alternative, a Lemieux–Johnson oxidation[107], viz. dihydroxylation using OsO_4 followed by diol cleavage employing $NaIO_4$ was performed (Scheme 21). The reaction was carried out in the presence of methane sulfonamide known to accelerate dihydroxylation.[108] In our hands, the catalyst slightly improved the overall yield. We found that the yields were generally unsteady over the batches which caused a later study to derive insights into the reaction. Nevertheless, the main products are the anomers of the lactol **56** (dr = 1:1.6) derived from the intermediate **67** by spontaneous intramolecular lactolization.

[104] Finkelstein, H. *Ber. Dtsch. Chem. Ges*. **1910**, *43*, 1528–1532.
[105] a) Harries, C. *Liebigs Ann. Chem.* **1905**, *343*, 311−344. b) Harries, C. *Liebigs Ann. Chem.* **1910**, *374*, 288−368. c) Harries, C. *Liebigs Ann. Chem.* **1912**, *390*, 235−268. d) Harries, C. *Liebigs Ann. Chem.* **1915**, *410*, 1−21.
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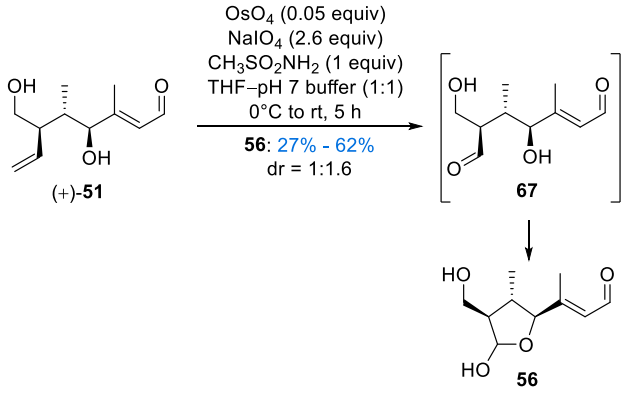
[107] Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478−479;
Example of a chemoselective Lemieux–Johnson oxidation: White, D.; Kuntiyong, P.; Lee, T. H. *Organic Letters* **2006**, *26*, 6039−6042
[108] a) Sharpless, K. B.; Amberg, W.; Youssef, L. B.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. b) Junttila, M. H.; Hormi, O. O. E. *J. Org. Chem.* **2009**, *74*, 3038−3047



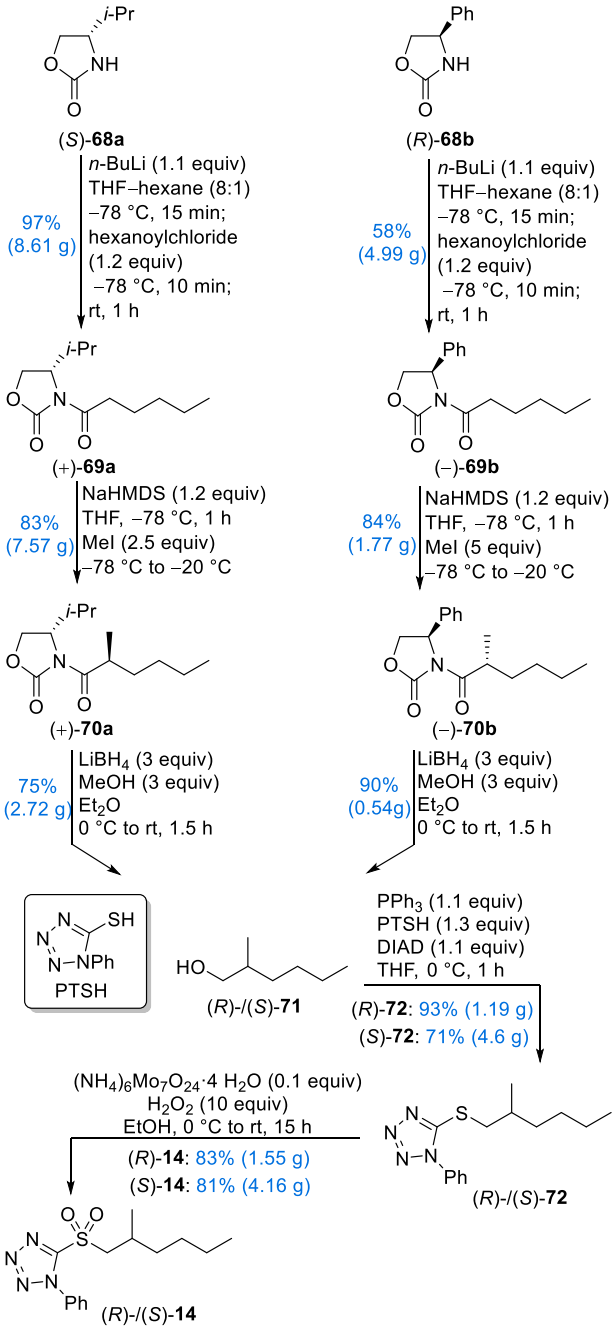
Scheme 21

As a reminder, further development of the synthesis was planned to be based on the simultaneous protection of the two hydroxyl groups in **56** enabling an unimpeded Julia–Kocienski olefination between the aldehyde **55** and the sulfone **14** representing the Eastern part of Curvicollide C. The synthesis of the latter building block is described below.

3.3 Synthesis of the Eastern fragment[55,56]

For the synthesis of both enantiomeric sulfones (*R*)-**14** and (*S*)-**14** a procedure was employed, which enables an enantioselective and reliable pathway to enantiomerically pure precursors. As explored by M. Körner, Evans alkylation fulfilled this requirement.

Starting from either valinol derived auxiliary (*S*)-**68a** or phenylglycine derived auxiliary (*R*)-**68b,** the synthesis commenced with acylation employing *n*-BuLi as the base and hexanoyl chloride as the electrophile (Scheme 22). Evans asymmetric alkylation[109] of (+)-**69a** and (–)-**69b** under the conventional conditions using sodium bis(trimethylsilyl)amide (NaHMDS) and methyl iodide delivered the alkylated products (+)-**70a** and (–)-**70b** in good yields and excellent diastereoselectivities.[110] Reductive removal of the chiral auxiliaries was achieved by using $LiBH_4$ as a mild reducing agent[111] delivering either the (*R*)-or (*S*)-configured alcohol **71**[112] in good yields. Assignment of the absolute configuration of the alcohols relies on the expected stereochemical model controlled by Evans-auxiliaries. Conversion of (*R*)-**71** and (*S*)-**71** into their corresponding sulfones (*R*)-**14** and (*S*)-**14** was realized employing a Mitsonobu reaction[113] with phenyltetrazole-5-thiol (PTSH) to afford the sulfides (*R*)-**72** and (*S*)-**72** in the first step. Secondly, oxidation of the latters with hydrogen peroxide in the presence of catalytic amounts of ammonium heptamolybdate[114] delivered the Eastern Fragment **14** in both enantiomeric forms.



Scheme 22

[109] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.
[110] Ager, D.J.; Babler, S.;Froen, D. E.; Laneman, S. A.; Pantaleone, D. P.: Prakash, I.; Zhi, B. Org. Process Res. Dev. 2003, 7, 369−378.
[111] Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.*, **1949**, *71*, 3245–3246.
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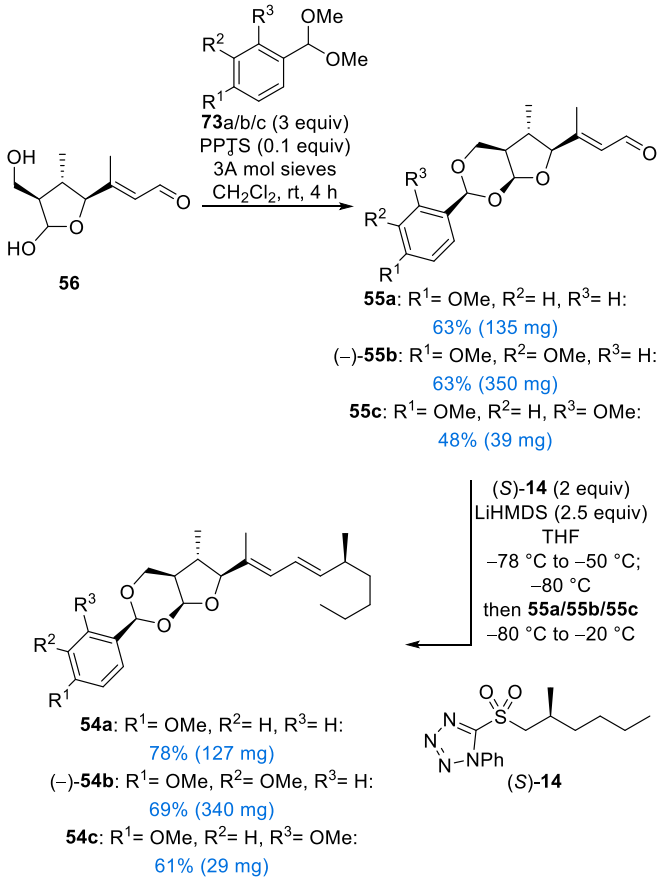
[114] Schultz, H.S.; Freyermuth, H.B.; Buc, S.R. *J. Org. Chem.* **1963**; *28*, 1140−1142

3.4 Exploration of benzylidene acetal protection for the Julia–Kocienski olefination

Aldehyde **56** bears an α-hydroxymethyl lactol whose hydroxyl groups need protection in order to facilitate Julia–Kocienski olefination. Protection is especially required for the hydroxyl group of the lactol as the latter is in equilibrium with a free aldehyde, which could also react in the Julia–Kocienski olefination. We saw advantages to protect both hydroxyl groups as a cyclic acetal derived from suitable benzaldehyde derivatives.

Generally, benzylidene acetals are either obtained from diols and corresponding benzaldehydes by dehydration,[115] or by transacetalization[116] starting from dimethyl acetals of the respective benzaldehydes. We decided to explore the latter chemistry for the test set consisting of *p*-methoxybenzylidene acetal[117] **55a**, 3,4-dimethoxybenzylidene acetal[118] (–)-**55b** and 2,4-dimethoxybenzylidene acetal[119] **55c**. Introduction of the benzylidene acetals was realized via transacetalization using the respective dimethyl acetals **73a-c**, catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) as a mild acid,[120] and molecular sieves for the removal of water from whatever source. The yields in Scheme **23** obviously reflect the stabilities of the corresponding acetals which are expected to increase in the order **55c** < (–)-**55b** < **55a** when considering the electron donating effect of the arrangement of methoxy groups.[121]

Interestingly, the above stability effects on the yields are also observed for the products of the Julia–Kocienski olefination **54c**, (–)-**54b**, and **54a**, respectively, which can only be explained by partial hydrolysis during workup and/or chromatography. The insufficient stability of product **54c** caused its exclusion in the subsequent study of reductive ring openings.



Scheme 23

The assignment of the relative configuration rests on the interpretation of a NOE experiment of diene **54a** (Figure 13) and is supposed to be applicable to diene (–)-**54b** and **54c** in analogy. NOE correlations were observed between benzylidene-CH and 8-CH and 9'-CH as well as between 9'-CH and 9-CH and 8-CH.

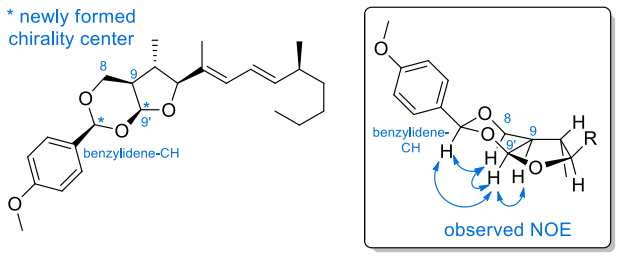


Figure 13 NOE effects as observed in the $^{1}H^{1}H$ NOESY spectrum of **54a** (see spectral part) which allowed to determine the relative configuration depicted.

[115] Hall, D. M. *Carbohydr. Res.* **1980**, *86*, 158–160.
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[120] a) Isobe, M.; Takahashi, H.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 717−718. b) Ohnishi, Y.; Ando, H.; Kawai, T.; Nakahara, Y.; Ito, Y. *Carbohydr. Res.* **2000**, *328*, 263−276. c) Nakamura, S.; Inagaki, J.; Sugimoto, T.; Kudo, M.; Nakajima, M.; Hashimoto, S. *Org. Lett.* **2001**, *3*, 4075−4078.
[121] Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430−440.

3.5 Regioselective reductive acetal opening

Once again, the benzylidene protecting group was favoured over suitable alternatives, because it allows the simultaneous blocking of both hydroxyl groups during Julia–Kocienski olefination while providing the option to deprotect one of the two hydroxyl groups by reductive cleavage which transforms the other into a benzyl protected form.
Generally, lactol **56** (Scheme 23) exhibits a certain structural similarity to carbohydrates for which most applications of benzyliden acetal chemistry were reported.[122] Figure 14 summarizes the basic pathways leading to the acetal opening by hydride transfer in the presence of a Lewis acid. The main advantage of benzylidene acetals is their potential for regioselective openings. As shown in Figure 14, the acetal can be opened selectively to yield either a free secondary (4-OH) or a free primary (6-OH) hydroxy group.

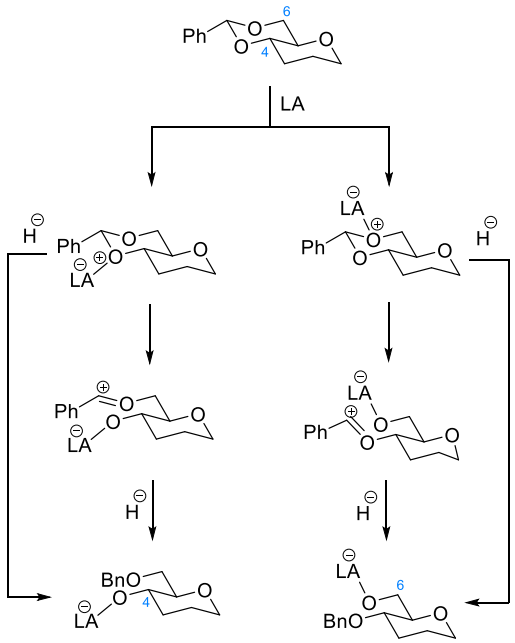

Figure 14 Regioselective opening of benzylidene acetals using hydride transfer in the presence of a Lewis acid (LA).

The selectivity is determined by the coordination preference of the Lewis acid as well as the source of hydride[123,124] and the nature of the solvent.[125] In any case the coordination of the Lewis acid determines the oxygen atom which will end as a free hydroxyl group (after removal of the Lewis acid).

Following Garegg's interpretation, for each mode of benzylidene opening there are two mechanistic possibilities.[126] The benzyl ether is either formed by hydride attack to an oxocarbenium ion intermediate, or by direct nucleophilic substitution of the coordination complex (Figure 14).

After having achieved the coupling of the Central and the Eastern part in accordance to our original planning, we were not aware that the regioselective opening of the acetal moiety would pose a larger challenge. In our expectations, the opening of the acetal moiety would lead to a primary alcohol and a PMB protected lactol which should allow us to directly elongate towards the Western part in the course of the synthesis. However, one should consider that unlike in classical examples of regioselective acetal openings (Figure 14), in our case we are dealing with a delicate oxygen-linked diacetal expected to exhibit three "active" coordination sites for the Lewis acid. To our best knowledge, structures of this kind so far have not undergone studies on their reductive opening. The extended spectrum of reaction pathways makes this acetal opening challenge much more complicated than expected, especially when considering the possibility for a second hydride transfer (Figure 15).

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[125] a) Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. J. *Carbohydr. Chem.* **1983**, *2*, 305–311. b) Fugedi, P.; Garegg, P. J.; Kvarnström, I.; Svansson, L. *J. Carbohydr. Chem.* **1988**, *7*, 389–397. c) Fügedi, P.; Birberg, W.; Garegg, P. J.; Pilotti, A. *Carbohydr. Res.* **1987**, *164*, 297–312.
[126] Garegg, P. J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, **1996**; pp 53–67.

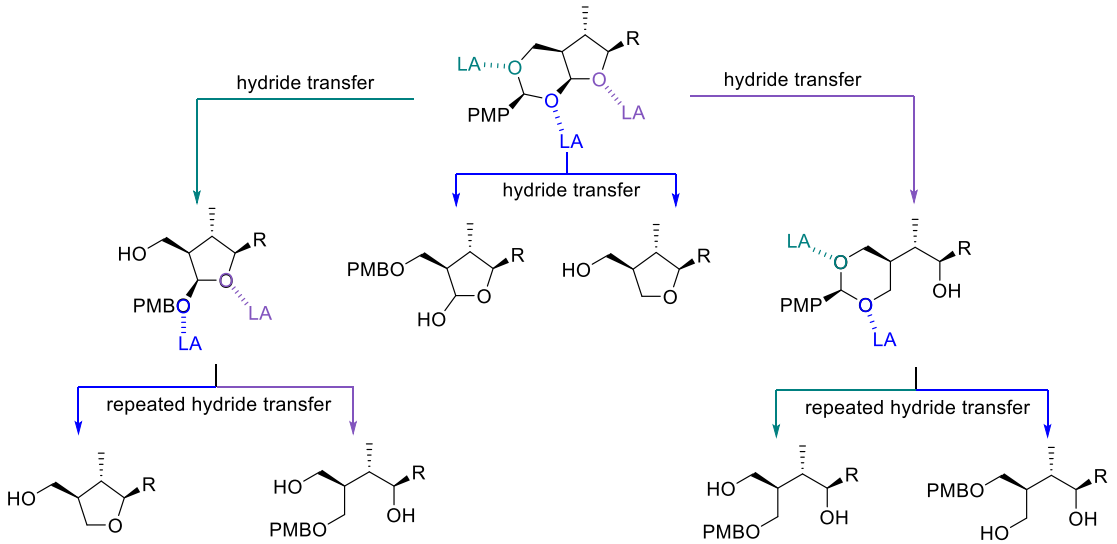

Figure 15 Conceivable pathways for the reductive opening of bicyclic oxygen-linked diacetals yielding four primary reduction products. Two of the latter may further undergo hydride uptake.

Table 3 compiles the results of our study. In all listed entries, a reagent combination consisting of a Lewis acid and a reducing agent was employed: DIBAL-H,[127] $AlCl_3$–$LiAlH_4$,[128] $AlCl_3$–Et_3SiH,[129] TMSCl–$NaCNBH_3$,[130] TBSOTf–BH_3•SMe_2,[131] $Cu(OTf)_2$–Et_3SiH,[132] TFA–$NaCNBH_3$[130]. Entries include reagent combinations which were reported to deliver free primary alcohols (shaded in grey) as well as reagent combinations accounted to obtain secondary alcohols (no shading). It should be emphasized, however, that the outcome of such reductive openings highly depends on the structure of the substrate. As such, the shading just indicates what was reported in previous studies and thus should be understood as orientation course.

Entries 1-8 relate to the utilization of acetal **54a** bearing a *p*-methoxyphenyl (PMP) group. Here, no conditions could be found for the desired transformation. PMP acetal **54a** was initially subjected to DIBAL-H[127] which serves simultaneously as a Lewis acid and a reducing agent. Regardless of the choice of the solvent (CH_2Cl_2 and/or toluene) we only noticed the unselective formation of inseparable isomers (entry: 1 and 3) as well as no conversion (entry 2). Using either TBSOTf–BH_3•SMe_2[131] (entry 4) or $Cu(OTf)_2$–Et_3SiH[132] (entry 5) as reagent combinations led to an even less selective conversion in which the number of products remained unclear. A further well-established reagent combination is $AlCl_3$–$LiAlH_4$[129] (entry 6) which resulted in an overreduction leading to diol **73a**. As depicted in Figure 15, product **73a** was already suggested to result from a repeated hydride transfer. Employment of TMSCl as the Lewis acid and $NaCNBH_3$ as the reducing agent[130] at 0 °C delivered an unexpected product (entry 7). Analysis of its NMR spectroscopic data (Figure 16) revealed that the structure is most likely consistent with the tetrahydrofuran **73b.** The formation of tetrahydrofuran **73b** is insofar remarkable as it cannot be explained by the pathways listed in Figure 15. Instead, a possible explanation assumes that the silyl lactol ether formed after reductive acetal opening undergoes additional coordination at its silyl ether oxygen. This coordination transforms the silyl ether as a poor leaving group into a reactive disilyloxonium ion which then splits off the disilyl ether generating an oxocarbenium ion ready for hydride uptake (Figure 17). Considering that this product could be a result of two consecutive Lewis-acid mediated hydride transfer steps, the reaction was repeated at lower temperatures and by decreasing the equivalents of both reagents (entry 8). However, in this case again, the undesired tetrahydrofuran **73b** together with starting material **54a** were isolated indicating that the reaction cannot be halted after the first reduction step.

[127] a) Tanaka, N.; Ogawa, I.; Yoshigase, S.; Nakami, *Carbohydr. Res.* **2008**, *343*, 2675–2679; b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593–1596; c) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033–2036.
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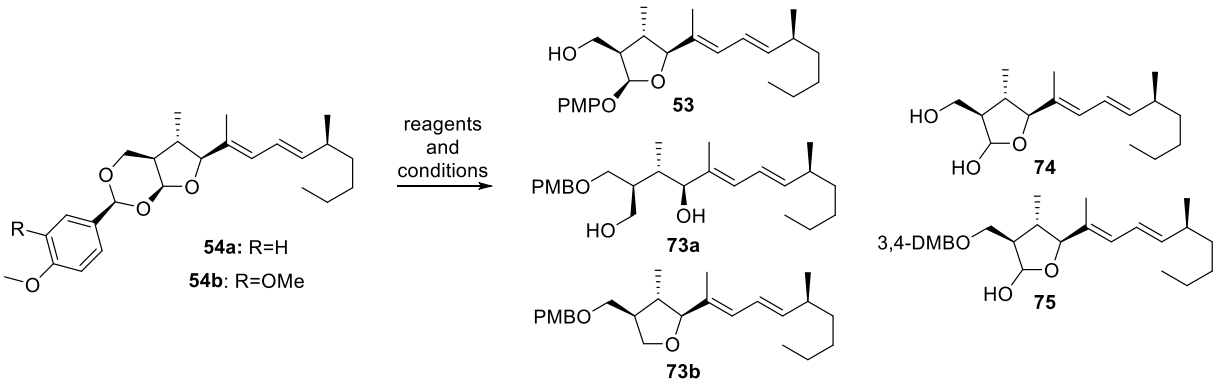
[129] Sakagami, M.; Hamana, H. *Tetrahedron Lett.* **2000**, *41*, 5547–5551
[130] Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans.* **1984**, 2371–2374.
[131] Daragics, K.; Fügedi, P. *Tetrahedron Lett.* **2009**, *50*, 2914–2916. (Employment of TMSOTf instead of TBSOTf)
[132] a) Shie, C.R.; Tzeng, Z.H.; Wang, C.C.; Hung, S.C. *J. Chin. Chem. Soc.*, **2009**, *56*, 510–523 b) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665–1668. ($Cu(OTf)_2$- Me_2EtSiH)

Table 3 Study of regioselective reductive acetal openings. Conditions reported to yield a primary hydroxy group are shaded in grey whereas those reported to lead to a secondary hydroxy group are listed without shading.



entry	R	Lewis acid (equiv)	hydride (equiv)	conditions	result
1	H	DIBAl-H (3)	DIBAl-H	CH_2Cl_2, –78 °C to 0 °C, 6 h	4 unseparable isomers
2	H	DIBAl-H (3)	DIBAl-H	toluene, –78 °C to rt, 7 h	no conversion
3	H	DIBAl-H (3)	DIBAl-H	toluene–CH_2Cl_2, 0 °C, 1 h	4 unseparable isomers
4	H	TBSOTf (3)	BH_3•SMe_2 (1.1)	THF, –78 °C to –30 °C, 3 h	unseparable mixture
5	H	$CuOTf_2$ (0.1)	Et_3SiH (2)	CH_3CN, 0 °C to rt, 2 h	unseparable mixture
6	H	$AlCl_3$ (3)	$LiAlH_4$ (3)	CH_2Cl_2–Et_2O, –50 °C to 0 °C, 4h	**73a**: 36% (4.4 mg)
7	H	TMSCl (10)	$NaCNBH_3$ (10)	CH_3CN, 0 °C to rt, 0.5 h	**73b**: 77% (8.8 mg)
8	H	TMSCl (1.5) [a]	$NaCNBH_3$ (1.5)	CH_3CN, –40 °C to –16 °C, 3.5 h	**54a** 53% (8 mg)+ **73b**: 21% (3 mg)
9	OMe	$CuOTf_2$ (0.1)	Et_3SiH (1.5)	CH_3CN, –30 °C to –20 °C, 1 h	no conversion
10	OMe	$CuOTf_2$ (0.1)	Et_3SiH (1.5)	CH_3CN, –30 °C to 0 °C, 3 h	**74**: 68% (4.5 mg)
11	OMe	TFA (4)	$NaCNBH_3$ (1.5)	CH_3CN, –40 °C to rt, 18 h	no conversion
12	OMe	$AlCl_3$ (1.75)	Et_3SiH (1.5)	CH_3CN, –40 °C to rt, 5 h	decomposition
13	OMe	DIBAl-H (2.5)	DIBAl-H	toluene, –78 °C to rt, 7 h	no conversion
14	OMe	TMSCl (1.2+1)[a]	$NaCNBH_3$ (2+1.2)	CH_3CN, –40 °C to –30 °C	**75**: 70% (60 mg)
15	OMe	HCl in Et_2O [a, b]	$NaCNBH_3$ (6)	THF, –40 °C to rt	decomposition
16	OMe	TBSOTf (4) [a]	$NaCNBH_3$ (3)	CH_3CN, –40 °C to –30 °C, 1.5h	**75**: 64% (18 mg)
17	OMe	TBSCl (2) [a]	$NaCNBH_3$ (1.2)	CH_3CN, –40 °C to –30 °C, 1.5h	unseparable mixture
18	OMe	TPSCl (2) [a]	$NaCNBH_3$ (1.2)	CH_3CN, –40 °C to –30 °C, 1.5h	**75**: 86% (130 mg)

[a] Employment of molecular sieves 4A

[b] HCl in Et_2O was prepared by bubbling HCl (in situ generated from NaCl and dropwise addition of H_2SO_4) through Et_2O. Wetted pH indicator paper turned red.

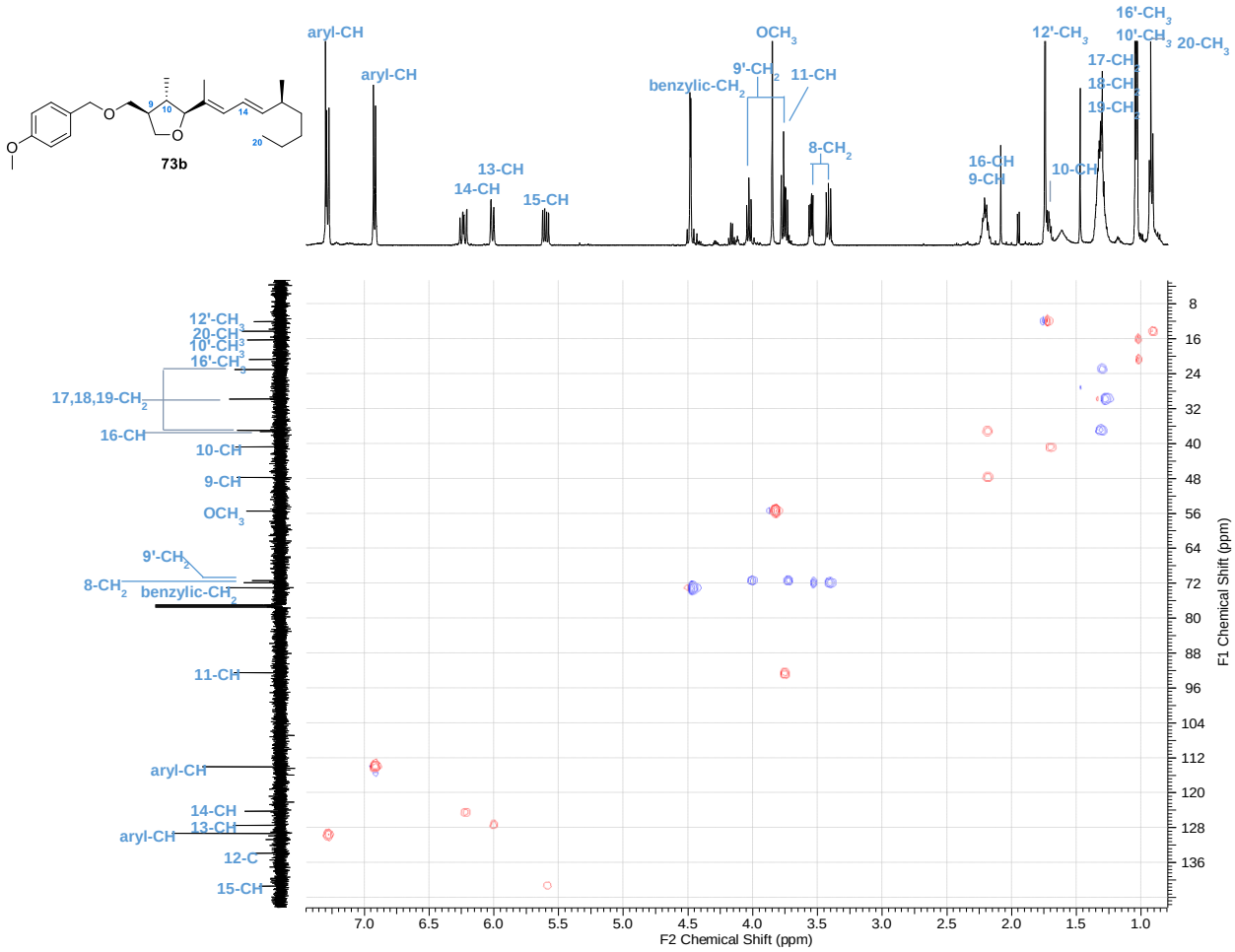


Figure 16 $^{1}H^{13}C$ HSQC spectrum of the tetrahydrofuran **73b** observed as an undesired and unexpected product during regioselective reductive acetal opening. The absence of the anomeric OH group as well as the presence of the two protons of 9'-CH_2 (showing a cross peak to one and the same CH_2-carbon (blue)) indicate the proposed structure of **73b**. (Solvent impurity: EtOAc)

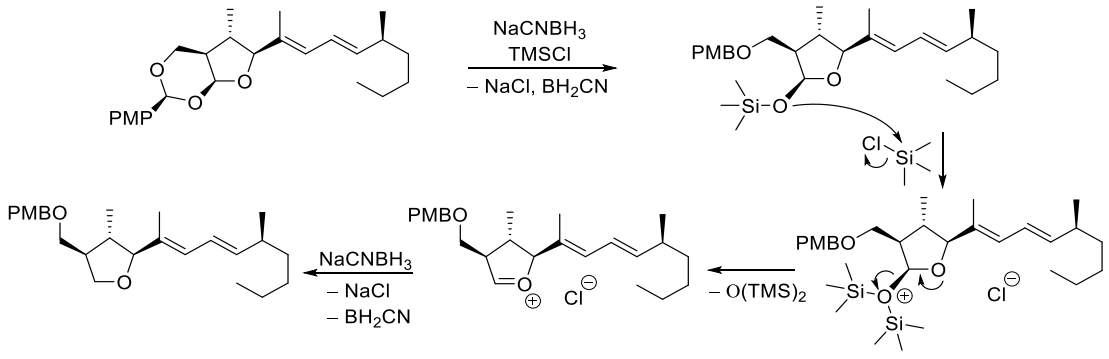


Figure 17 Proposed mechanism for the two consecutive Lewis-acid mediated hydride transfer steps.

In entries 9-18 the PMP-group of entries 1-8 is replaced by the more electron donating 3,4-dimethoxyphenyl (3,4-DMP) group. While most conditions and reagents tested did not lead to results enabling further exploration (entries 9-13), the combination of $NaCNBH_3$ with TMSCl (entry 14) did. It enabled a regioselective pathway leading to product **75** which bears a protected primary alcohol and a free lactol moiety, as a mixture of anomers (dr = 1:1.2). Note that this reagent combination had resulted in the formation of tetrahydrofuran **73b** (entry 7) in the case of PMP acetal **54a**. Obviously, the additional methoxy group in **54b** suffices to facilitate halting the reaction after the first reduction step. Whether this is due to a slight increase of electron density in the phenyl ring, or to an additional mode of Lewis acid coordination remains an open question. Nevertheless, the result was viewed as encouraging enough to explore further variations (entries 15-18). The original conditions (entry 14) consisted of $NaCNBH_3$ as the reducing agent, trimethylsilyl chloride (TMSCl) as the Lewis acid and molecular sieves for the removal of water in acetonitrile as the solvent. Special care was taken to keep the temperature in the range of –40 °C to –30 °C.[133] The utilization of TFA[130] or HCl[134] instead of TMSCl was reported to yield the reversed regioselectivity in carbohydrate based examples, but in our case led to no conversion (entry 11) or to decomposition (entry 15). Interestingly and unexpectedly, the employment of bulky TPSCl (entry 18) instead of TMSCl as the electrophile even increased the yield of reductive opening whereas the utilization of TBSCl yielded an unselective, inseparable mixture of products (entry 17). This result is insofar surprising as we expected that the reaction mechanism would proceed through a TMS protected lactol (due to coordination), which hydrolyses during workup. In the case of TPSCl the formation and later the hydrolysis of the TPSCl protected lactol is questionable however. Thus, a different mechanism may be involved here (entry 18).

A similar irregular picture was observed in the study of Kihlberg et al. in 2004.[135] The employment of TBSCl and $NaCNBH_3$ in acetonitrile delivered the protected TBS ether. But when either smaller silyl chlorides (triethylsilyl chloride (TESCl) or TMSCl) or larger silyl chlorides (TPSCl or triisopropylsilyl chloride (TIPSCl) were used instead of TBSCl, the free secondary alcohol was obtained as the major product (Figure 18).

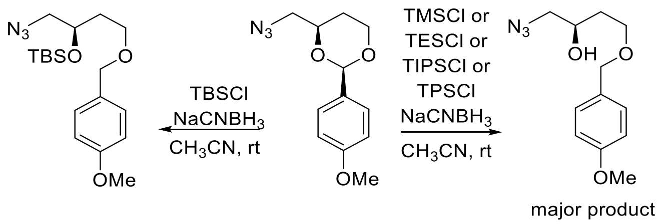


Figure 18 Reductive regioselective acetal openings depend on the nature of silylating agents as reported by Kihlberg et al.

In summary, a reductive ring opening of benzyliden acetal **54b** leading to a benzyl protected lactol as needed according to the proposed plan could not be achieved. Instead, all successful attempts yielded product **75** with a protected primary hydroxyl group in combination with a free lactol moiety.

The reason for the undesired regioselectivity may be guessed by taking into account possible no bond resonance structures for the different pathways (Figure 19): The number of no bond resonance structures, in which the 3,4-DMB group is located at the primary oxygen exceeds the ones for the attachment of 3,4-DMB at the secondary oxygen.

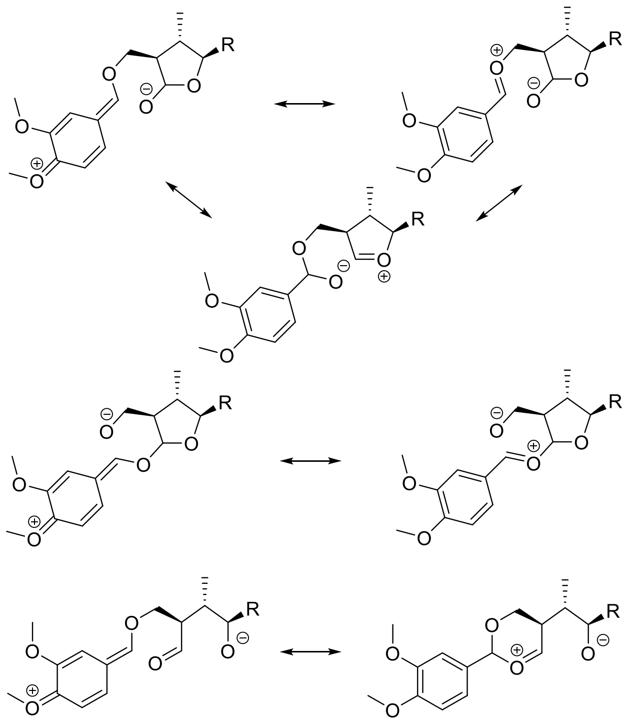


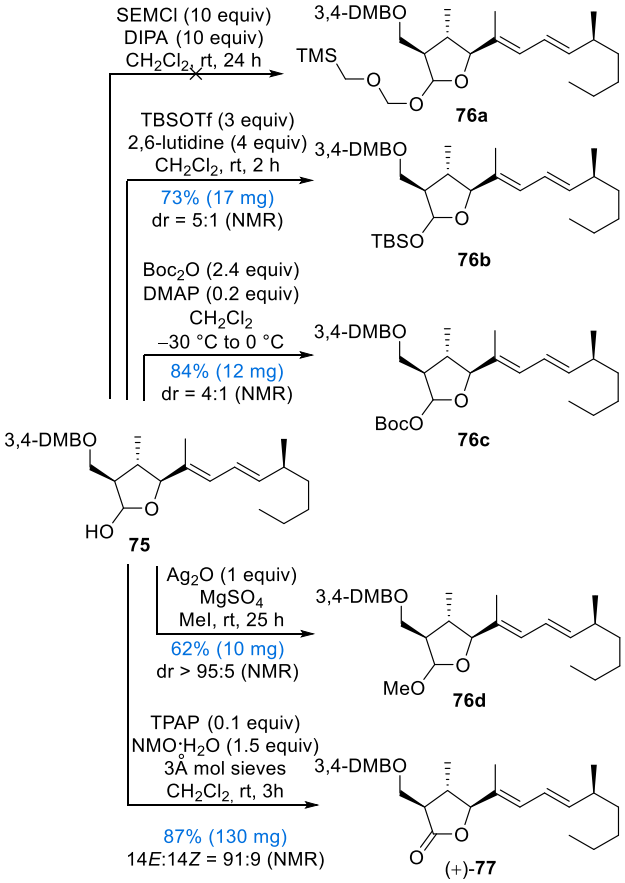
Figure 19 No bond resonance structures as an explanation for the observed regioselectivity in reductive acetal opening.

[133] The temperature range of –40 °C to –30 °C was chosen, because temperatures below –40 °C caused freezing of the solvent and temperatures above –30 °C the formation of the undesired tetrahydrofuran (Tab. Product D).

[134] Garegg, P.J.; Hultberg, H. *Carbohydr. Res*. **1981**, *93*, C10-C11
[135] Gustafsson, T.; Schou, M.; Almqvist, F.; Kihlberg J. *J. Org. Chem.*, **2004**, *69*, 8694–8701

3.6 Chemoselective deprotection of the 3,4-DMB ether

With lactol **75** in hand, a proper protecting group for the anomeric hydroxy group had to be found enabling the selective deprotection of the 3,4-dimethoxybenzyl group. Therefore, a set of four protecting groups was chosen (Scheme 24) which were considered to give some degree of stability during test reactions aiming to remove the 3,4-DMB group selectively: a trimethylsilylethoxymethyl-ether[136] (SEM), a TBS-ether[137], a *tert*-butyl carbonate[138] (Boc), and a methyl ether. Employing SEMCl in the presence of DIPA led to no conversion of **75** to the desired SEM-lactol **76a**.



Scheme 24

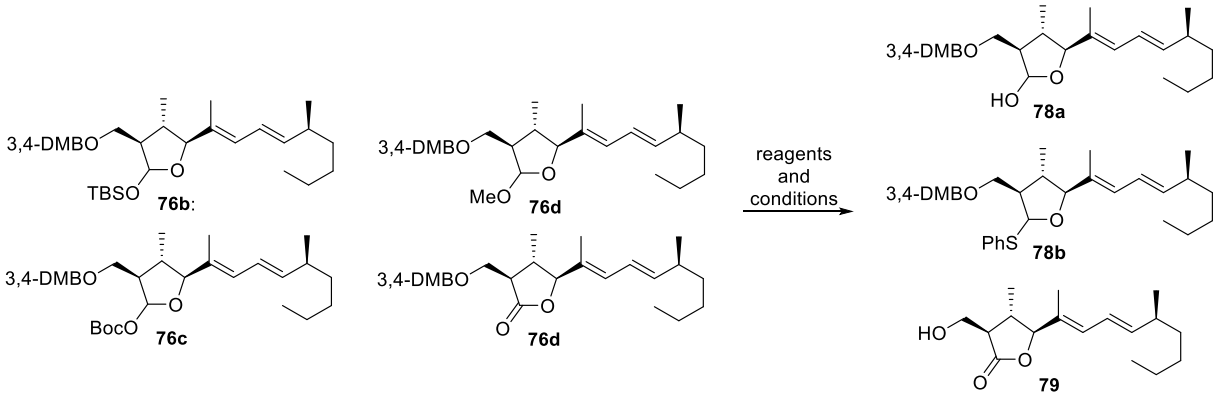
As an established reagent combination, TBS triflate in the presence of 2,6-lutidine[139] was applied to synthesize the TBS lactol ether **76b** in good diastereoselectivities (dr = 9:1). Treatment of the lactol **75** with Boc_2O and DMAP as a nucleophilic catalyst delivered the Boc protected lactol **76c** as a mixture of diastereomers (dr = 4:1). Methyl lactol ether **76d** was obtained from a treatment of **75** with Ag_2O and MeI. In addition, Ley–Griffith oxidation[84] of the lactol **75** using tetra-*n*-propylammonium perruthenate (TPAP) in catalytic amounts and *N*-methylmorpholine *N*-oxide (NMO) as a stoichiometric co-oxidant was performed to yield the lactone (+)-**77** which can be considered as a latent functionality for a lactol moiety.

The chemoselective cleavage of the 3,4-DMB group posed a further major obstacle (Table 4). Reductive conditions were avoided due to the presence of the diene moiety. The reagents tested fall into 4 groups: (i) single electron transfer (SET) oxidants[140], (ii) hypervalent iodine (III) reagents[141], (iii) Lewis acids combined with nucleophiles[142,143] and (iv) Brønsted acids.[144] Oxidants like DDQ led to a destructed diene moiety (entry 1), whereas ceric ammonium nitrate (CAN) resulted in the deprotection of the lactol (entry 2) or decomposition (entry 13). In a recent study, it was found that 3,4-DMB-ethers can also be selectively cleaved by hypervalent iodine(III) reagents which are supposed to form charge transfer complexes with the 3,4-DMB-ethers facilitating single electron transfer reactions. Among the hypervalent iodine(III) reagents, diacetoxy iodo benzene (PIDA) led to decomposition (entry 6, 15) while bis(trifluoroacetoxy) iodo benzene (PIFA) either did not react at all (entry 9) or caused the removal of the wrong protecting group (entry 7, product **78a**). Application of Lewis acid-catalyzed cleavage with $BF_3{\bullet}OEt_2$ in the presence of PhSH triggered decomposition (entry 3, 4) or the formation of a cyclic *S*,*O*-acetal (entry 8, product **78b**).[145] Using $MgBr_2{\bullet}OEt_2$ in the presence of Me_2S resulted in the deprotection of the lactol (entry 5, product **78a**) or decomposition (entry 14). Only trifluoroacetic acid (TFA) as a strong Brønsted acid in anisole[146] afforded the cleavage of the 3,4-DMB ether at the stage of the lactone (entry 16, product (–)-**79**).

[136] a) Lipshutz, B.H.; Pegram , J.J. *Tetrahedron Lett.* **1980**, *21*, 3343–3346. b) Nakata, M.; Ishiyama, T.; Akamatsu, S.; Hirose, Y.; Maruoka, H.; Suzuki, R.; Tatsuta, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 967–989.
[137] Nagorny, P.; Fasching, B.; Li, X.; Chen, G.; Aussedat, B.; Danishefsky, S. J. *J Am Chem Soc*. **2009**, *131*, 5792–5799.
[138] Guo, H.; O'Doherty, G. A. *Org. Lett.*, **2006**, *8*, 1609–1612.
[139] Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett*. **1981**, *22*, 3455−3458
[140] Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 3253−3256
[141] Watanabe, K.; Katoh, T. *Tetrahedron Lett.* **2011**, *52*, 5395−5397
[142] Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc*. **1986**,108, 5221−5229
[143] Onoda, T.; Shirai, R.; Iwasaki, S.*Tetrahedron Lett.* **1997**, *38*, 1443−1446
[144] Weygand, F.; Hunger, K. *Chem Ber*. **1962**, *95*, 1−16
[145] Evidence for the proposed structure of **78b** is based on ^{1}H NMR data indicating a missing lactolic methyl group and additional aromatic signals instead.
[146] a) De Medeiros, E. F.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2725–2730. b) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*,1777−1778, Chen, M.; Roush, W.R. *Org. Lett.* **2012**, *14*, 426−428

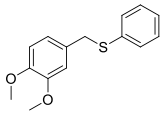
During protolytic cleavage of the ether bond in (+)-**77** a resonance stabilized 3,4-dimethoxybenzyl cation is generated. The role of anisole is to trap the 3,4-dimethoxybenzyl cation by electrophilic aromatic substitution. Unlike for the case of the lactone, it is due to the acid-sensitive nature of lactol derivatives **76b**-**76d** that reagents which exhibited acidity in a latent or direct form, always resulted in the undesired lactol ether cleavage.

Table 4 Study of chemoselective removal of the 3,4-DMB-ether.



entry	R	reagent (equiv)	conditions	result
1	OTBS	DDQ (2)	CH_2Cl_2–pH7-buffer, –15 to 0 °C, 2 h	diene not intact
2	OTBS	CAN (1.3)	CH_3CN–H_2O (9:1), –8 to 8 °C, 4 h	**78a**: 54% (3 mg)
3	OTBS	PhSH (10), BF_3•OEt_2 (4)	CH_2Cl_2, –30 °C, 0.5 h	decomposition [a]
4	OTBS	PhSH (10), BF_3•OEt_2 (2)	CH_2Cl_2, –50 °C, 10 min	decomposition [a]
5	OTBS	Me_2S (10), $MgBr_2$•OEt_2 (3)	CH_2Cl_2, –20 °C to rt, 4 h	**78a**: 42% (4 mg)
6	OTBS	PIDA (2), K_2CO_3 (10)	CH_2Cl_2, rt, 20 h; 45 °C, 4h	decomposition
7	OTBS	PIFA (2), K_2CO_3 (10)	CH_2Cl_2, rt, 6 h	**78a**: 46% (2.2 mg)
8	OMe	PhSH (10), BF_3•OEt_2 (2)	CH_2Cl_2, –50 °C, 10 min	**78b**: 55% (4 mg)
9	OMe	PIFA (2), K_2CO_3 (10)	CH_2Cl_2, rt, 30 h	no conversion
10	OMe	TFA–anisole (1:3.5)	0 °C, 0.5 h	decomposition
11	OBoc	PIFA (2), K_2CO_3 (10)	CH_2Cl_2, rt, 6 h	decomposition
12	OBoc	TFA–anisole (1:100)	0°C, 0.5 h	**78a**: 44% (1 mg)
13	=O	CAN (2)	CH_3CN–H_2O (10:1), 0°C to rt, 0.5 h	decomposition
14	=O	Me_2S (10), $MgBr_2$•OEt_2 (3) [b]	CH_2Cl_2, –20°C to rt, 4 h	decomposition
15	=O	PIDA (2), K_2CO_3 (10)	CH_2Cl_2, 45°C, 4 h	decomposition
16	=O	TFA–anisole (1:3)	rt, 1 h	(–)-**79**: 90% (11 mg)

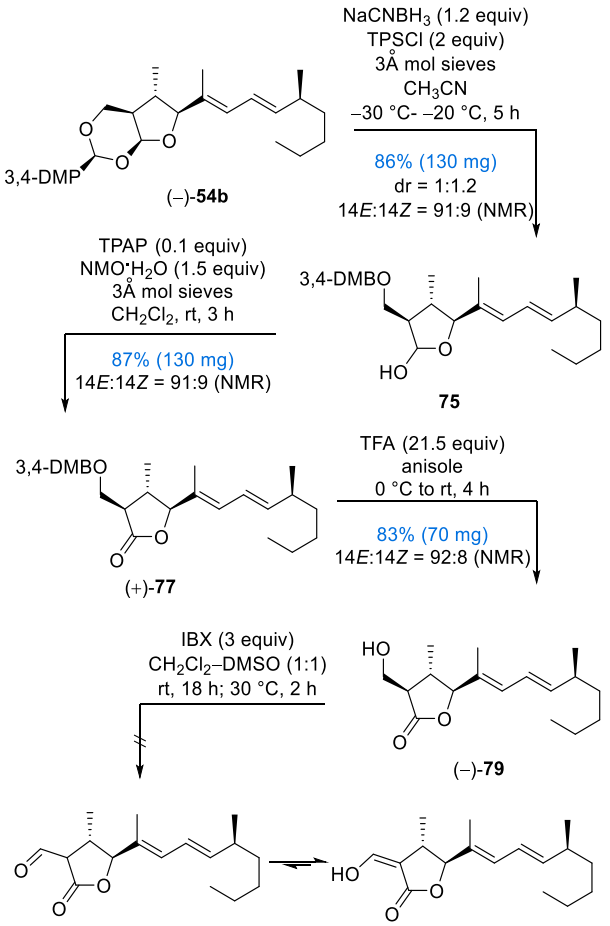
[a] Formation of (3,4-dimethoxybenzyl)phenylsulfide was observed, indicating a cleavage of the 3,4-DMB group.



[b] Employment of 1,3 dimethoxybenzene (3 equiv) as a scavenger.[147]

[147] Jung, M. E.; Koch, P. *Tetrahedron Lett.* **2011**, *52*, 6051–6054.

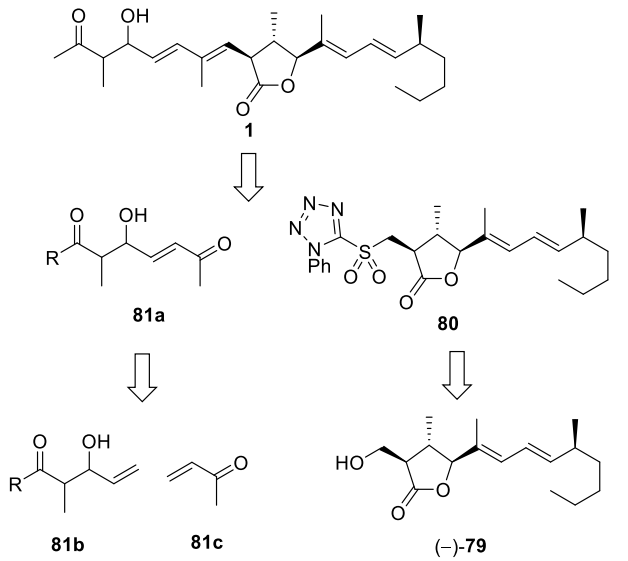
As a result of the above study, the original synthetic strategy had to be changed. A test reaction aiming to oxidize the α-hydroxy methyl lactone (–)-**79** (Scheme 25) by employing iodoxy benzoic acid (IBX)[148] in CH_2Cl_2–DMSO (1:1) at a temperature of 30 °C failed (conversion could be observed but no product could be isolated) and thus destroyed the plan to continue synthesis employing Wittig reactions. In retrospect even if the oxidation had been successful, the reaction product most likely had suffered rapid epimerization, as α-formyl lactones coexist in the tautomeric form of α-hydroxymethylen lactones (Scheme 25, bottom).[149]



Scheme 25

3.7 A new strategy for the attachment of the Western part

In principle, a carbon-carbon double bond is formed from an electrophilic and a nucleophilic compound. So far, the Central-Eastern part had been designed to react as an electrophile as the aldehyde in any type of olefination fulfils this role. Consequently, the new strategy (Scheme 26) is based on the utilization of the Central-Eastern part as a nucleophile needing an Umpolung of reactivity when starting from (–)-**79** as a precursor molecule. We considered a Julia–Kocienski olefination which required to convert the alcohol (–)-**79** into a suitable sulfone **80**. This might enable to introduce the complete Western fragment **81a** of the molecule in a single step. A cross-metathesis reaction between the aldol **81b** and methyl vinyl ketone **81c** might provide access to the Western fragment **81a**.



Scheme 26

So far, access to trisubstituted olefins through Julia–Kocienski olefination is quite limited.[150] In a recent promising example of Sasaki and co-workers, a methyl ketone is utilized in a $CeCl_3$-promoted Julia–Kocienski olefination providing the desired trisubstituted (*E*)-alkene in 58% yield, along with the corresponding (*Z*)-isomer in 18% yield (Figure 20).[151]

[148] a) Caraway, W. T.; Hellerman, L. *J. Am. Chem. Soc*. **1953**, *75*, 5334–5340.
b) Frigerio, M.; Sanagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

[149] Korte, F.; Büchel, K.-H.; Scharf, D.; Zschocke, A. *Chem. Ber*. **1959**, *92*, 884–894.

[150] Aïssa, C. *Eur. J. Org. Chem*. **2009**, 1831–1844

[151] Ishigai, K.; Fuwa, H.; Hashizume, K.; Fukazawa, R.; Cho, Y.; Yotsu-Yamashita, M.; Sasaki, M. *Chem. Eur. J*. **2013**, *19*, 5276–5288.

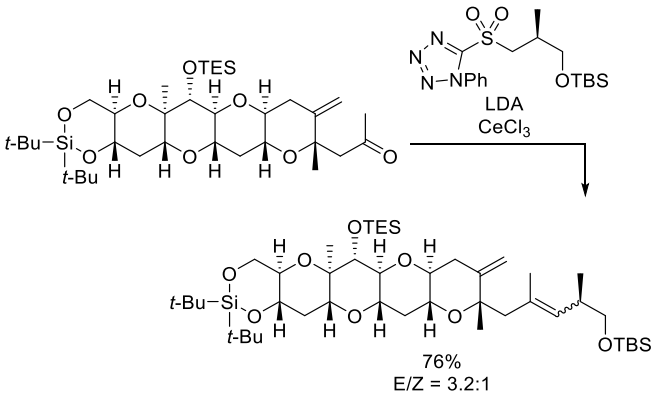
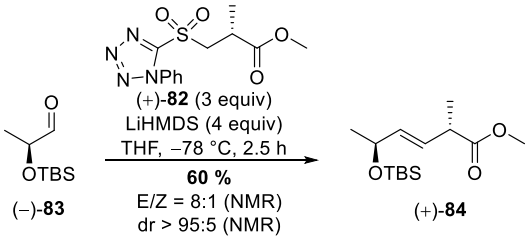


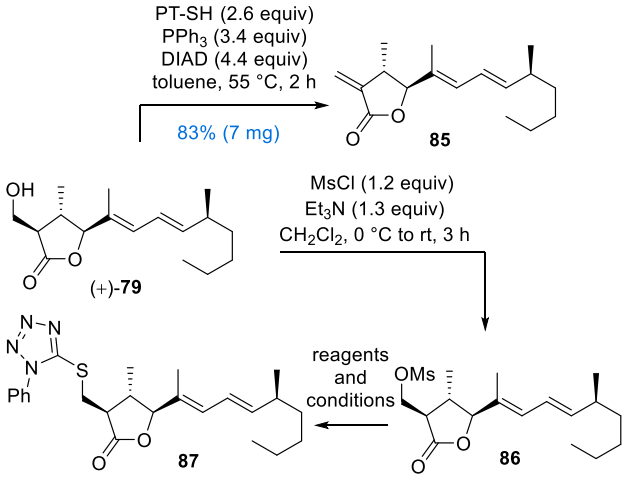
Figure 20 Employment of a Julia–Kocienski olefination for the formation of a trisubstituted double bond in the Total Synthesis of (+)-Gambieric Acid A.

For a successful Julia–Kocienski olefination, sulfone **80** needs to be deprotonated in α-position to the sulfone moiety. However, sulfone **80** exhibits also an α-acidic lactone which may compete for the consumption of the base. In a previous Bachelor thesis[152] dealing with a similar situation, the α-acidic ester (+)-**82** equipped with a β-sulfone was deprotonated and then allowed to react with aldehyde (–)-**83** (Scheme 27).[153] The reaction yielded the desired product (+)-**84** without notable epimerization at the α-acidic ester moiety. This example can be viewed as a model reaction for the targeted Julia–Kocienski olefination.



Scheme 27

For the synthesis of the sulfone **80** via a suitable sulfide, attempts to directly convert the alcohol via Mitsonobu reaction[113] failed (Scheme 28, top). Instead, the formation of product **85** was observed resulting from the β-elimination of the oxyphosphonium ion as a reaction intermediate.[154] As a workaround, alcohol (–)-**79** was initially converted to the corresponding mesylate **86**. Subsequent nucleophilic substitution employing the thiolate from PTSH delivered the sulfide **87** in poor yields (Table in Scheme 28).



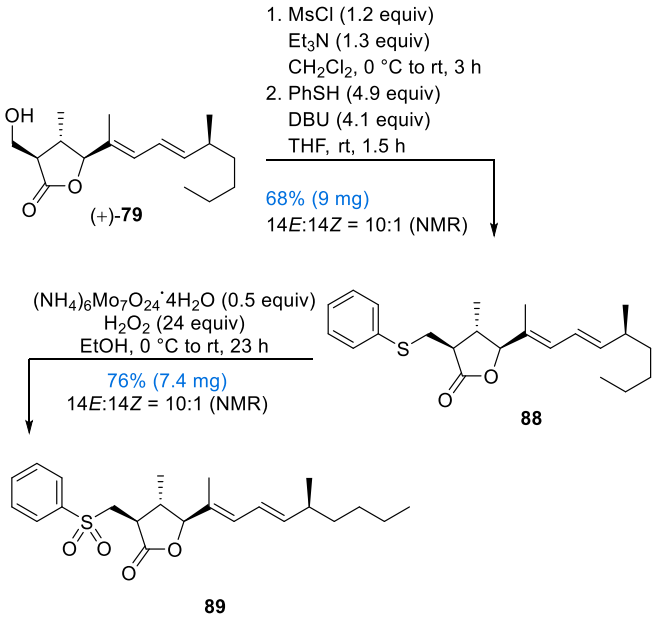
entry	base	conditions	yield
1	NaH (2.8 equiv)	PTSH (3 equiv), THF, rt to 40 °C, 18 h	24%
2	NaH (4.5 equiv)	TBAI (1 equiv), PTSH (5 equiv) THF, 50 °C, 18 h	35%
3	*n*-BuLi (3.3 equiv)	PTSH (3.5 equiv), THF, 30 °C, 18 h	38%
4	KHMDS (8.4 equiv)	PTSH (9 equiv) THF, 30 °C, 18 h	36%

Scheme 28

In all of the tabulated reactions, PTSH was converted into its anion by the action of a suitable base before the mesylate **86** was added. In no case, the reaction condition allowed an excess of base and thus elimination to give **85** was not expected to occur and could indeed not be observed. In all cases the yields were moderate (Table in Scheme 28) exhibiting no big influence of the nature of the counterion.[155] In addition, DBU (2.4 equiv) using either THF or CH_3CN as solvents at room temperature was explored but no conversion was achieved in both cases.[156] As the yields of the conversion to **87** were considered as unsatisfactory, the selection of a more nucleophilic thiol was taken into account. As a matter of fact, the employment of

[152] Schmidt, A.-C. *bachelor thesis* **2015**, Technische Universität Dortmund.
[153] Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.*, **1980**, *45*, 3846–3856.
[154] Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.
[155] Jones, P.; Harrison, P.; Wynne-Jones, L. *J. Chem. Soc. Perkin Trans.* **1979**, *2*, 1679–1685.
[156] Wu, J.-Z.; Wang, Z.; Qiao, C. *Tetrahedron Lett.* **2012**, *53*, 1153–1155

thiophenol in the presence of DBU resulted in an improvement of yields of the nucleophilic substitution (Scheme 29). Oxidation of the resulting sulfide **88** in the presence of catalytic amounts of ammonium heptamolybdate[114] finally afforded the Central-Eastern part **89** bearing the desired functionality.



Scheme 29

Consequently, this exchange of PTSH with PhSH in the latter reaction meant for the key coupling step to switch from a Julia–Kocienski[67]- to a Julia–Lythgoe[157] olefination. In analogy to the Julia–Kocienski olefination, the sulfone is firstly deprotonated by a suitable base and subsequently the aldehyde or ketone is added. While in the case of the Julia–Kocienski olefination[67], the elimination occurs spontaneously due to the presence of the phenyl tetrazol moiety, in the case of the Julia–Lythgoe olefination[157] (Figure 21) it does not. Instead, the alcohol moiety of the addition product has to be converted into a good leaving group by means of treatment with acetyl- or benzoyl anhydride or the corresponding acyl halogenides. In the next step, a reductive elimination takes place using sodium amalgam or samarium iodide[158].

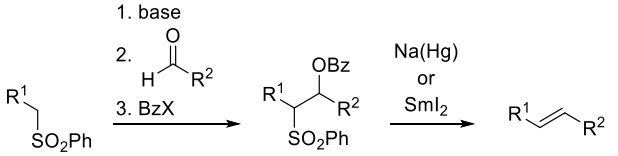
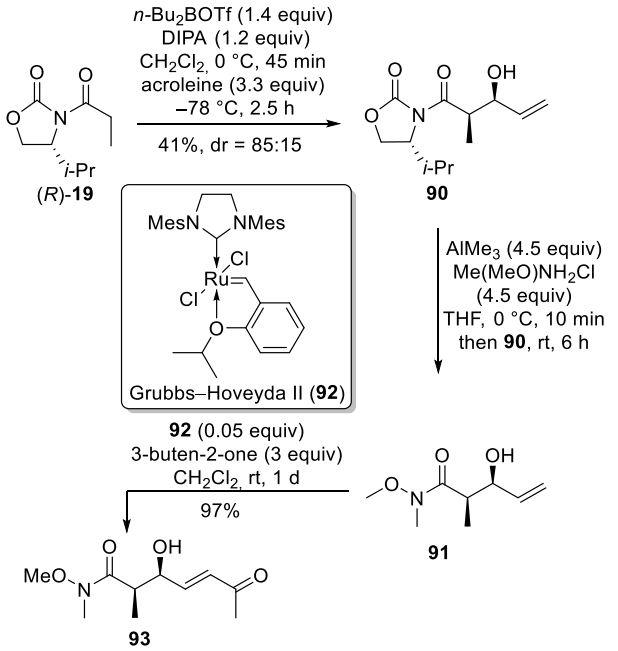


Figure 21 General reaction scheme for a Julia–Lythgoe olefination. (X = halogenide)

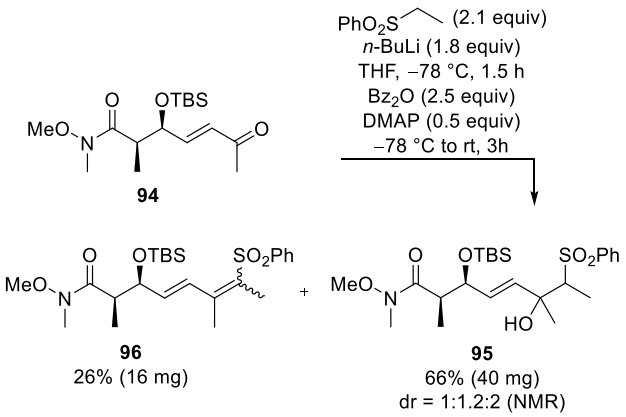
The synthesis of a suitable Western fragment (Scheme 30) was achieved by Philipp Baumann during his advanced practical course in our research group. The aim was to find a synthetic access to compound **93** utilizing a cross-metathesis reaction without setting a focus on the optimization of the individual steps. Acylated oxazolidinone (*R*)-**19** was converted into the corresponding vinylated *syn*-aldol **90** employing the conditions of an already published Evans-aldol reaction.[159] Treatment of **90** with the in situ generated aluminium amide reagent[73] derived from trimethylaluminium and *N*-methoxymethylamine hydrochloride delivered the Weinreb amide **91**. After some experimental trials, conditions were found which afforded the cross-metathesis product **93** in excellent yields. Freshly distilled methyl vinyl ketone was employed as the cross-metathesis partner in the presence of Grubbs–Hoveyda II[160] (**92**) as the catalyst.



Scheme 30

[157] a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836. b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. c) Kelly, S. E. *Comp. Org. Syn.* **1991**, *1*, 792–806.
[158] Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194–3204.
[159] Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **2002**, *55*, 173−181.
[160] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179; b) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

Driven by curiosity, the methyl ketone **93** serving as a potential Western fragment was examined in a test reaction (Scheme 31) aiming to get first insights into the planned Julia–Lythgoe olefination[157]. For this purpose, ethyl phenyl sulfone was deprotonated and then allowed to react with the methyl ketone **94** at –78 °C. The mixture was finally treated with benzoic anhydride in the presence of DMAP which is expected to yield the benzoylated addition product. Surprizingly however, a benzoylated product was not observed. Instead, addition product **95** was isolated as the main product while the diene **96** was obtained as the side product. The latter is expected to result from the benzoylated (but not observable) precursor via β-elimination, as the benzoate is known to serve as a good leaving group.



Scheme 31

It was originally intended to use the benzoate of **95** as a model compound to test suitable conditions for the planned reductive elimination. We therefore aimed to synthesize the benzoate in a separate reaction starting from the isolated alcohol **95**. Preliminary attempts to introduce the benzoyl group, however, did not show any conversion. While the acylation of a tertiary alcohol such as **95** is generally known as a difficult reaction,[161] it remains an open question why a β-elimination product indicating the temporal existence of the desired benzoate was found in the Julia–Lythgoe reaction.

In summary, a suitable Western fragment was shown to react in the addition step with a simple test substrate, but a careful screening of conditions would be necessary to enable benzoylation. Furthermore, the elimination under reductive conditions is expected to exhibit an additional challenge. Finally, it should be emphasized again that the ethyl phenyl sulfone employed above is just a model of the "real" sulfone **89** which is expected to exhibit even more unpredictable behaviour due to its more complex structure bearing a β-sulfonyl lactone moiety. In any case, for an intensive study of the intended Julia–Lythgoe olefination[157], the lack of material at the level of the sulfone **89** turned out to be an ever-growing logistic problem. Therefore, we decided to break the bottleneck induced by the unreliable Johnson–Lemieux reaction (Chapter 3.2.1, Scheme 21, yields between 27% and 62%) either by obtaining a better insight into the causes of yield variations or by finding an alternative.

3.8 Identifying the need for protection

Anticipating the results of the studies which follow, the alternative was identified in the necessity to restrict the reaction freedom causing undesired side reactions at the stage of vinyl group oxidations. It became clear to us – also when considering the selectivity of the subsequent transformations – that both, the primary and the secondary hydroxyl group of (+)-**51** had to be protected in an orthogonal manner. Unfortunately, this insight meant to restart the synthesis from a much earlier stage, where individual protecting groups had to be introduced in a selective fashion.

Table 5 and the reaction scheme included summarize the steps leading to the above conclusions. Note that the introduction of the silyl groups employed will be presented in the following chapter.

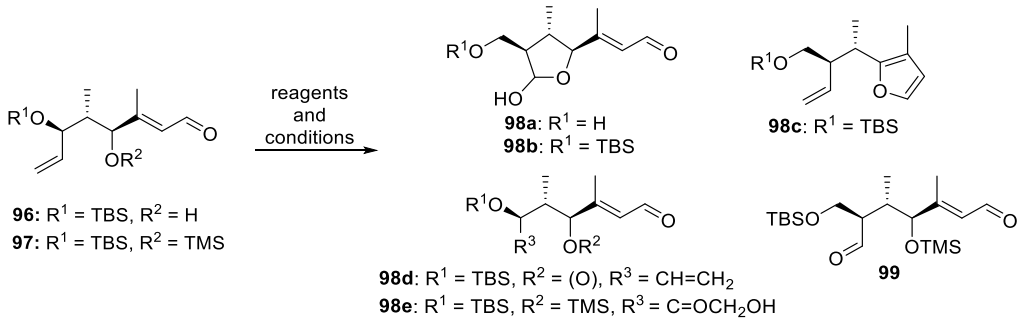
The original transformation of the vinyl group in (+)-**51** was based on its oxidative cleavage employing Lemieux conditions. As an alternative, a Lemieux-von Rudloff oxidation[162] was tested first, utilizing ruthenium tetroxide for dihydroxylation which is in situ formed from ruthenium trichloride and $NaIO_4$.[163] This oxidation usually results in the formation of the respective carboxylic acids. Under the given conditions[164] (entry 1), however, the corresponding aldehyde was expected but no conversion was observed. To gain more insight, the idea was to separate the oxidative cleavage of the vinyl group into its individual steps. When using Sharpless dihydroxylation conditions,[165] viz. OsO_4

[161] Spivey, A. C.; Maddaford, A.; Redgrave, A. *J. Org. Prep. Proced. Int.* **2000**, *32*, 331−365.
[162] Lemieux, R. U.; von Rudloff, E. *Can. J. Chem*. **1955**, *33*, 1701−1709.
[163] Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, B. *J. Org. Chem.* **1981**, *46*, 3936−3938
[164] Yang, D.; Zhang, C. *J. Org. Chem.*, **2001**, *66*, 4814–4818
[165] a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968−1970. b) Kolb, H. C.; VanNieuwenhze, S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483−2547.

and AD-mix-β[166] in the presence of methanesulfonamide, neither a product nor the starting material could be isolated (entry 2). Presumably, the resulting tetraol stays in the aqueous phase during work up.

To prevent this outcome the primary hydroxy group was protected as the TBS ether (+)-**96** causing a significant decrease of polarity/water-solubility.

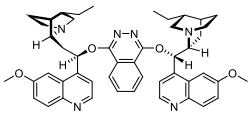
Table 5: Study of oxidative double bond cleavage



entry	R^1	R^2	reagents	conditions	result
1	H	H	$RuCl_3$ (0.035 equiv), $NaIO_4$ (2 equiv)	CH_3CN-H_2O (6:1), rt, 7 h	no conversion
2	H	H	OsO_4 (0.02 equiv) AD-mix-ß (1.4g/mmol) $CH_3SO_2NH_2$ (2 equiv)	*t*-BuOH−H_2O (1:1), rt, 16 h	decomposition
3	H	H	OsO_4 (0.02 equiv) 2,6-lutidine (2 equiv) NMO•H_2O (2.8 equiv) $PhI(OAc)_2$ (2.8 equiv)	aceton−pH7 buffer (10:1), rt, 5 h	**98a**: 42%
4	TBS	H	OsO_4 (0.02 equiv) AD-mix-ß (1.4g/mmol) $CH_3SO_2NH_2$ (2 equiv)	*t*-BuOH−H_2O (1:1), rt, 21 h	**98c**: 64% (12 mg) + **98d**: 15% (3 mg)
5	TBS	H	OsO_4 (0.03 equiv) $NaIO_4$ (3 equiv)	THF−pH7 buffer (5:1), −7 °C – 0 °C, 8h	**98b**: 23% (7 mg), unidentified side products
6	TBS	TMS	OsO_4 (0.02 equiv) AD-mix-ß (1.4g/mmol) $CH_3SO_2NH_2$ (2 equiv)	*t*-BuOH−H_2O (1:1), rt, 21 h	no conversion
7	TBS	TMS	$RuCl_3$ (0.15 equiv), $NaIO_4$ (6 equiv)	$(CH_2Cl)_2$−pH8 buffer (1:1), rt, 5 d	no conversion
8	TBS	TMS	OsO_4 (0.025 equiv) $NaIO_4$ (3 equiv) $CH_3SO_2NH_2$ (1.2 equiv)	THF−pH8 buffer (1.5:1), 0 °C to rt, 19 h	(+)-**99**: 49% (39 mg) + **98e**: 17% (15 mg)
9	TBS	TMS	OsO_4 (0.069 equiv) $NaIO_4$ (3.3 equiv) $CH_3SO_2NH_2$ (1.2 equiv)	pH7 buffer (1:1), 0 °C to rt, 4 h	(+)-**99**, 75% (91 mg)
10	TBS	TMS	OsO_4 (0.069 equiv) $NaIO_4$ (3.3 equiv) $CH_3SO_2NH_2$ (1.2 equiv)	THF−pH7 buffer (1:1), 0 °C to rt, 4 h	(+)-**99**, 53% (155 mg) larger batch in contrast to entry 9
11	TBS	TMS	OsO_4 (0.035 equiv) 2,6-lutidine (4 equiv) NMO•H_2O (3 equiv) $PhI(OAc)_2$ (1.2 equiv)	THF−H_2O (10:1), rt, 66 h	(+)-**99**: 75% (225 mg) + (+)-**97** 10% (31 mg)

[166] AD-mix-β is a commercially available mixture of reagents consisting of: $K_2OsO_2(OH)_4$ as a source of osmium tetroxide, $K_3Fe(CN)_6$ as an re-oxidant during the catalytic cycle, K_2CO_3 and as the chriral ligand

$(DHQD)_2PHAL$:



The exposure of (+)-**96** to Sharpless dihydroxylation conditions yielded two unexpected products, the furan **98c** as well as the enone **98d** which gave insight into undesired parallel pathways (entry 4 in Table 5). Figure 22 depicts the first pathway which is induced by a double bond isomerization, subsequent intramolecular lactolization and final dehydration to yield the thermodynamically stable furan **98c**. The product was detected by the resonances of the furan ring in the raw $^{1}H^{1}H$ COSY spectrum (Figure 23).

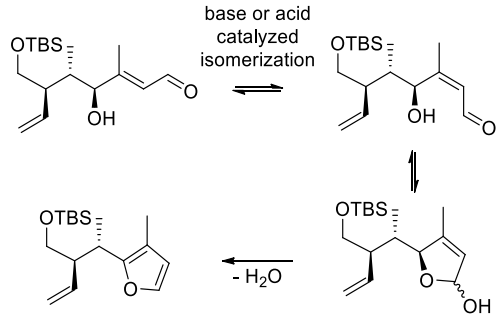


Figure 22 Proposal for the formation of an undesired furan during the attempted Sharpless dihydroxylation

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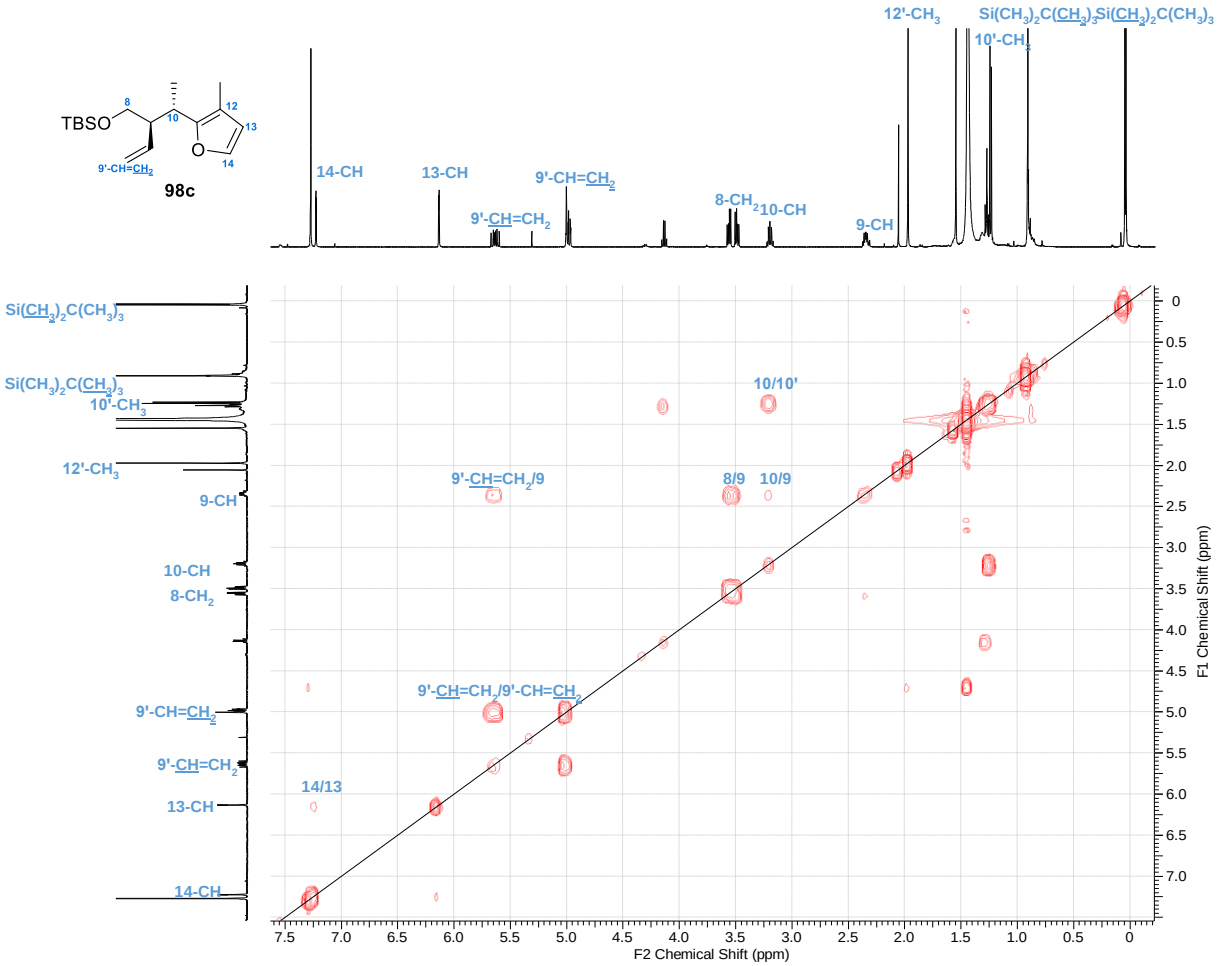


Figure 23 $^{1}H^{1}H$ COSY spectrum of the furan **98c** observed during intended dihydroxylation of the terminal double bond. The absence of the proton for 11-CH as well as the presence of the two olefinic protons 13-CH and 14-CH indicate the proposed structure of **98c.**

The second pathway involves the oxidation of the allylic hydroxyl group to yield the enone **98d** (entry 4 in Table 5). In order to suppress these pathways, the secondary allylic alcohol in (+)-**96** was protected as its TMS ether (+)-**97** expected to be less stable than the TBS ether in the same molecule. Suprisingly, when exposing the bis-silyl ether (+)-**97** to the conditions of the originally attempted Lemieux reaction, a third undesired product was observed, namely the α-hydroxy ketone **98e** shown in Table 5 (entry 8). As Figure 24 explains, α-hydroxy ketones[167] presumably resulting from an α-deprotonation have been frequently observed during OsO_4-mediated dihydroxylations:

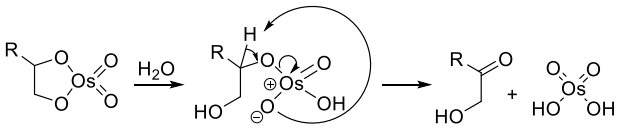


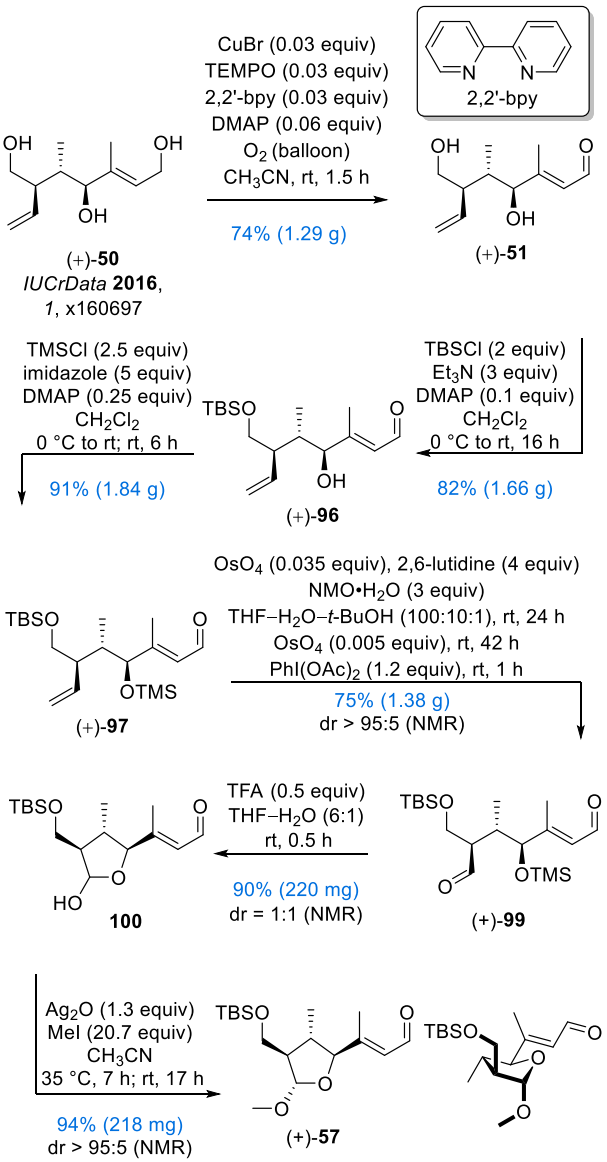
Figure 24 Formation of an α-hydroxyketone during osmate ester hydrolysis.

While searching for conditions to avoid this undesired side product we came across the ones explored by Nicolaou[168] (entry 10 in Table 5). These conditions employ the utilization of 2,6-lutidine as a ligand and are known to diminish the formation of α-hydroxyketones such as **98e**. In addition, the conditions of Nicolaou offer another advantage: While the dihydroxylation is a time intensive transformation,[169] the diol cleavage proceeds rather rapidly and delivers the α-epimerizable aldehyde (+)-**99**. The conditions developed by Nicolaou enable a temporal separation of the dihydroxylation and the diol cleavage. As the latter transformation is initiated by the addition of PIDA, the time for undesired side reactions such as the epimerization of aldehydes formed by the diol cleavage can be shortened to effectively suppress such side reactions. The optimal time for the addition of PIDA depends on the degree of conversion during dihydroxylation which can be monitored by TLC.

As a result of the above insight, namely the need for protection of both hydroxy groups in (+)-**51**, the synthesis of **1** via benzylidene acetal **54b** was recognized to be inappropriate as a practical route to deliver the Central-Eastern fragment. Therefore, we abandoned it in favor of another synthetic plan.

3.9 Synthesis of the Central fragment involving silyl and methyl protection

The new plan (Scheme 32) was based on the introduction of two quasi orthogonal silyl groups. Hence, the primary hydroxyl group of diol (+)-**51** was selectively protected as TBS ether to yield (+)-**96** and the remaining secondary hydroxyl group was temporarily masked as TMS ether to afford bis-silyl ether (+)-**97**. The oxidative cleavage of the terminal double bond applying Nicolaou's conditions afforded the dialdehyde (+)-**99** in fair yields along with recovered starting material (+)-**97**.

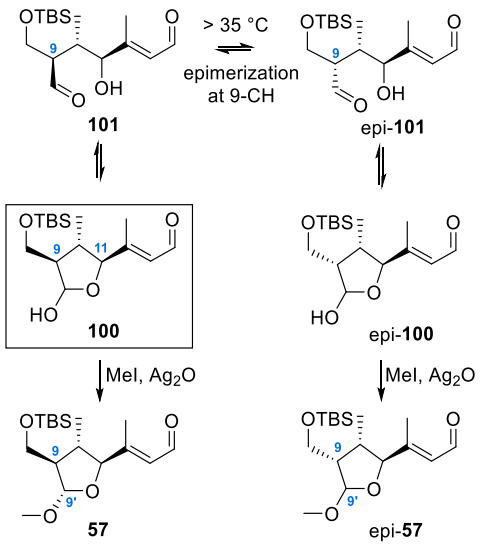


Scheme 32

[167] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
[168] Nicolaou, K.C., Adsool, V.A., Hale, C.R.H. *Org. Lett.*, **2010**, *12*, 1552−1555.
[169] Donohoe, T. J.; Harris, R. M.; Butterworth, S.; Burrows, J. N.; Cowley, A.; Parker, J. S. *J. Org. Chem.* **2006**, *71*, 4481-4489.

Treatment of the dialdehyde (+)-**99** with substoichiometric amounts of the Brønsted acid TFA in a solvent mixture of THF and water resulted in the selective hydrolysis of the TMS ether, delivering the lactol **100** as a mixture of anomers (dr = 1.1:1). Naturally, for the course of future transformations the lactol hydroxyl group of **100** also needed a suitable protecting group. Among the set of protectiving groups which are considerable here, the methyl group as the smallest one has found wide usage in carbohydrate chemistry where methyl glycosides belong to the standard derivatives.[170] It was expected that the stability of a methyl lactol ether is sufficient for the upcoming set of transformations involving bases, nucleophilic reagents and redox chemistry. The question came up, however, whether or not the hydrolysis of such acetals is possible without affecting the other sensitive moieties of the target natural product. It was during this time on the fence of decision which lactol protection to be chosen, that the coincident finding of Fusaequsin A proved to be a real serendipity. With the insight that Curvicollide C has a twin-like sister, named Fusaequisin A, based on a methyl lactol ether as an integral element of its structure, the decision for methyl lactol ether protection became easy. It meant that even if the hydrolysis of such a methyl lactol ether would prove difficult or even unsuccessful, total synthesis could still end in a natural product. Indeed, the choice of the methyl protecting group in (+)-**57** was rewarded by an unexpected high degree of diastereoselectivity (dr > 95:5) in the desired *all-trans* configuration as observed in the natural product Fusaequisine A.

The introduction of the methyl group was achieved by utilization of silver oxide and an excess of methyl iodine.[171] Care had to be taken that the temperature did not exceed 35 °C to prevent an epimerization presumably at 9-CH, which was observed at higher temperatures resulting in a diastereomeric ratio of 3:1 (Scheme 33). In principle, the decreased diastereoselectivity may be due to an epimerization at either 9-CH or 11-CH, or by a less selective methylation at the anomeric center leading to the methyl ether (+)-**57** in a mixture of anomers. A possibly decreased diastereoselectivity at the anomeric center (9‘-CH) of (+)-**57** could be excluded, because further conversion to lacton **120** resulted in no change of the diastereoselectvity. When comparing epimerization at 9-CH versus 11-CH it seems more favourable to invoke the α-acidity at 9-CH instead of the γ-acidity at 11-CH.[172] In any case, the lactol **100** is supposed to be in an equilibrium with its open form, viz. the corresponding hydroxyaldehyde **101**. As the methylation of **100** is a rather slow reaction, the lactol **100** initially stays in its equilibrium with **101**. It was found that when exceeding the temperature above 35 °C, an epimerization of the α-acidic aldehyde presumably at 9’-CH of **101** delivered epi-**101**. It was not determined whether this epimerization is caused by either the slightly acidic nature[173] of methyl iodide or the basic character[174] of silver oxide. However, epi-**101**, passing through its equilibrium to *epi*-**100,** can also be methylated. No effort was undertaken to determine the configuration at the anomeric 9’-CH of *epi*-**57**. In any case it should be emphasized that conditions were found allowing to convert a 1:1 mixture of lactols **100** into a highly enriched 95:5 mixture of methyl lactol ethers in the desired all-*trans* configuration.



Scheme 33

The assignment of the relative configuration relies on the interpretation of a NOE experiment detecting spatial proximity between 11-CH and the methyl group as depicted in Figure 25.

[170] Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. *Glycoscience: Chemistry and Chemical Biology I–III*; Springer, Berlin, **2012,** p. 1515.
[171] a) Purdie, T.; Irvine, J.C. *J. Chem. Soc., Trans*., **1903**, 83, 1021−1037. b) Kuhn, R.; Trischmann H.; Low, I. *Angew. Chem*.**1955**, *67*, 32

[172] Furthermore, the coupling constants for 11-CH in **57** (J = 9.1 Hz) and epi-**57** (J =9.3 Hz) are almost identical, which also does not indicate an epimerization at 11-CH.
[173] Partial hydrolysis of methyl iodine leads to the strong acid hydrogen iodide and methanol.
[174] Ren, B.; Wang, M.; Liu, J.; Ge, J.; Dong, H. *ChemCatChem* **2015**, *7*, 761–765.

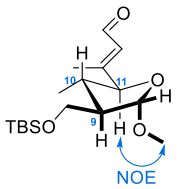


Figure 25 Assignment of the relative configuration of the anomeric methoxy group is based on the decipted NOE.

One may wonder how the above lactol methylation can result in a diastereoselectivity of 95:5 when starting from a lactol existing as an anomeric mixture in a diastereoselectivity of 1:1. In general, the potential outcome of a reaction is usually influenced by two factors:
1) The relative stability of the products (thermodynamic control).
2) The rate of product formation (kinetic control).

Assuming the reaction was steered by kinetic control, the methylation of the α-anomeric lactol has to proceed faster than in the case of the β-anomeric lactol. Both lactol forms are assumed to exist in a rapid equilibrium by mutarotation,[175] viz. spontaneous ring opening and ring closure reactions via γ-hydroxyaldehydes (Figure 26). This equilibrium ensures that the preferred consumption of the α-anomeric lactol by methylation is continuously replenished from the β-lactol.[176]

Thermodynamic control is only possible when the formation of products proceeds reversibly.[177] In carbohydrate chemistry, it is conjectured that anomerization of the structurally related methyl furanosides is most likely based on the Brønsted acid catalyzed heterolysis of the glycosidic bond, involving cyclic oxocarbenium ions as intermediates[178] (Figure 26). It is not clear whether silver ions as a soft Lewis acid can replace the role of Brønsted acids here. However, the higher thermodynamic stability of the α-anomeric lactol methyl ether can be understood by the anomeric effect[179] in any case. The anomerization of methyl lactol ethers via oxocarbenium ions should be understood as a formal possibility to account for and not as the most likely reaction model to explain the diastereoselectivity found.

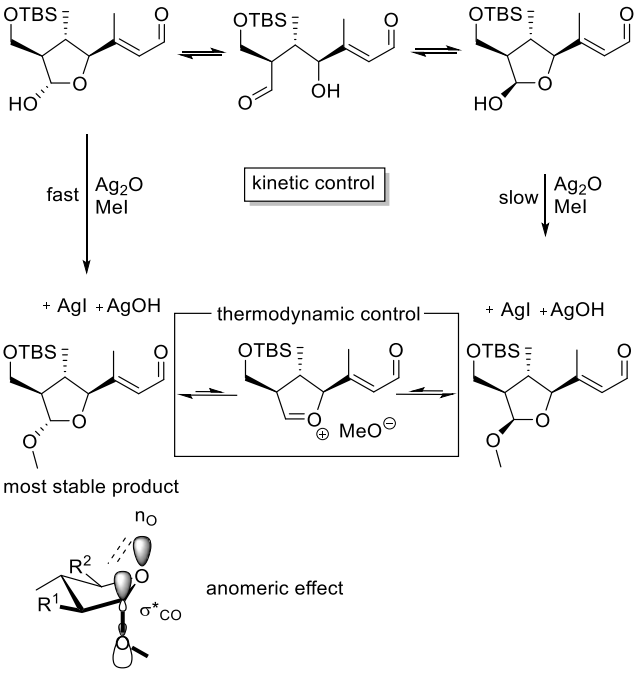


Figure 26. Thermodynamic vs kinetic control during the methyl lactol ether formation.

Initially, it was not expected that methylation of **100** would proceed so smoothly in the presence of silver oxide, as it is well known that aldehydes are oxidized to carbocylic acids while Ag_2O is reduced to elementary Ag(0) (silver mirror).[180,181] However, this procedure has proved to work best. An attempted test reaction to convert dialdehyde (+)-**99** into the methyl lactol ether (+)-**57** in a single step by using PPTS (0.4 equiv) as a mild acid in methanol at room temperature led to decomposition. Methylation with Me_3OBF_4 (7.5 equiv) and proton sponge[182] (6.5 equiv) in CH_2Cl_2 at room temperature yielded the methyl lactol ether (+)-**57** in moderate yields (58%, 22 mg) and slightly deteriorated diastereoselectivities (dr = 93:7). Methylation with MeOTf (4 equiv) and 2,6-di-*tert*-butylmethylpyridine[183] (4 equiv) in CH_2Cl_2 at 0 °C delivered a non methyl-bearing product distinguishable from the starting lactol by both NMR and TLC (probably the triflate of the lactol).

[175] Mutarotation occurs rapidly in the presence of MeI (a) and Ag_2O (b): (a) Ferguson, A.C.; Haines, A.H. *J. Chem. Soc*. (C), **1969**, 1372–1375. (b) Haines, A. R. *Tetrahedron Lett*. **1969**, 1201–1202
[176] Reisolation of the unconverted educt **100** revealed that the ratio of the anomers (dr = 1:1) was identical to the inital situation confirming an equilibrium.
[177] McMurry, J. E. *Organic Chemistry*, 8 ed.; Brooks Cole: Belmont, **2011**, p. 509.
[178] a) Capon, B.; Thacker, D. *J. Chem. Soc. B. Phys. Org.* **1967**, 185–189. b) Lonnberg, H.; Kankaanperä, A.; Haapakka, K *Carbohydr. Res.* **1977**, *56*, 277–287. c) Lonnberg, H.; Kulonpaa, A. *Acta. Chem. Scand.* **1977**, *A31*, 306–312
[179] Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.
[180] Wagner, R. B.; Zook, H. D., *Synthetic Organic Chemistry*; John Wiley & Sons, Inc., New York, **1953**, p. 419
[181] Walker, H.G.; Gee, M.; McCready, R.M. *J. Org. Chem*., **1962**, 27, 2100–2102.
[182] 1,8-Bis(*N*,*N*-dimethylamino)naphthalene
[183] Arnarp, J.; Kenne, L.; Lindberg, B.; Lönngren, J. *Carbohydr. Res.* **1975**, *44*, C5–C7

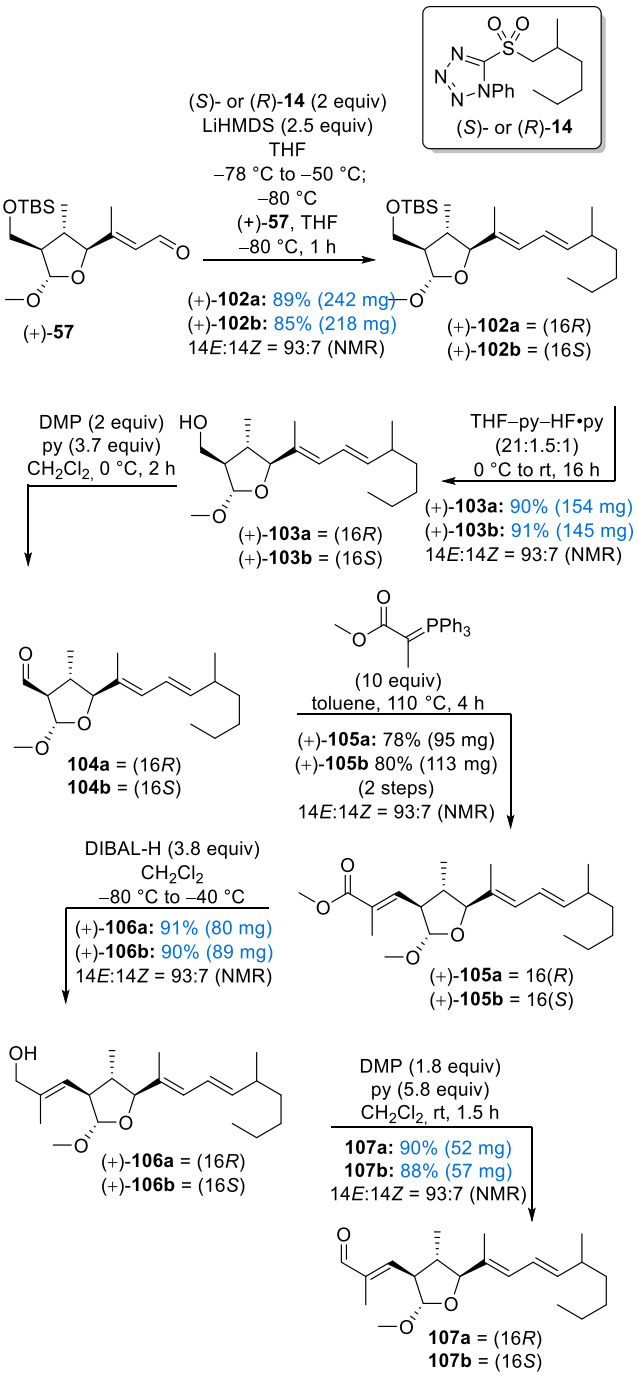
3.10 Eastern and Western elongation of the Central fragment (+)-57

The basic synthetic transformations for the attempted elongation of the Central fragment were previously established by M. Körner et al. for structurally related compounds (cf. Chapter 1.7.1). The general synthetic strategy envisioned the usage of a Julia–Kocienski olefination for the Eastern part and a more elaborate step-by-step sequence for the Western part. This sequence consisted of deprotection, elongation and modification steps creating a rather laborious mode of construction. Its advantage, however, is based on the already existing "knowledge of synthesis" and the robustness of the chosen synthetic transformations.

We first turned to the coupling of (+)-**57** with both enantiomers of the Eastern fragment (*S*)/(*R*)-**14 (**Scheme 34), as the natural product may have either configuration at C-16. Depending on the applied (*S*)- or (*R*)-configured sulfones, Julia–Kocienski olefination[67] delivered the dienes (+)-**102a** and (+)-**102b** in good yields and proper configuration of the double bonds (*E*/*Z* = 93:7 for both cases). The assignment of the C14-C15 double bond configuration rests on the evaluation of the NMR coupling constants of 15-CH: J = 10.3 Hz for (*Z*)-**102** and J = 15.0 Hz for (*E*)-**102**. Chromatographic separation of the double bond isomers was impossible at this stage and unfortunately also during the following steps of the synthesis.

Unlike as in many reported cases of the Julia–Kocienski olefination, LiHMDS was employed instead of KHMDS[184,185] or NaHMDS[185,186] as the base. It is well known that the cation has an important influence on the diastereoselectivity.[187] Problems with the unsteady quality of commercially purchased NaHMDS and KHMDS led to the utilization of LiHMDS, which was generated in situ from *n*-BuLi and HMDS. Furthermore, a test reaction employing NaHMDS did not deliver an increased diastereoselectivity compared to LiHMDS.

Cleavage of the TBS-ether in the presence of the lactol methyl ether moiety of dienes (+)-**102a** and (+)-**102b** proceeded without any side reactions when employing a mixture of HF-pyridine and "extra" pyridine in CH_2Cl_2. Both alcohols (+)-**103a** and (+)-**103b** were obtained in excellent yields. Dess–Martin oxidation delivered the aldehydes (+)-**104a** and (+)-**104b** in good yields without notable epimerization at 9-CH within one day. It was nevertheless taken into account that the aldehydes (+)-**104a** and (+)-**104b** may not be the most stable compounds for long-time storage. Thus, subsequent olefination reactions usually followed immediately after chromatographic purification.



Scheme 34

For the construction of the trisubstituted double bond, a reliable method which ensures a high degree of (*E*)-selectivity had to be chosen. This called for a Wittig reaction with

[184] a) Pospisil, J.; Marko, I. E. *Org. Lett.*, **2006**, *8*, 5983−5986. b) Billard, F.; Robiette, R.; Pospisil, J. *J. Org. Chem.*, **2012**, *77*, 6358−6364. c) Chin, Y.J.; Wang, S.Y.; Loh, T.P. *Org. Lett.* **2009**, *11*, 3674-3676.

[185] Aïssa, C. *Eur. J. Org. Chem*. **2009**, 1831–1844

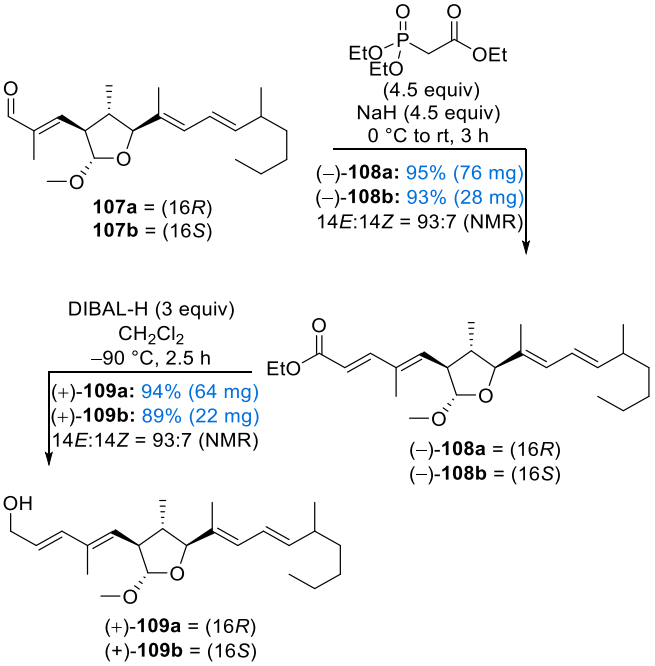
[186] Smith, III A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685–1688.

[187] Blakemore, P. R.; Cole, W. J.; Kocienski, J. P.; Morley, A. *Synlett* **1998**, 26−28.

stabilized ylides. Indeed, Wittig olefinations[70] employing an excess of known methyl (triphenylphosphoranylidene) acetate[188] in toluene at 110 °C under neutral conditions afforded (+)-**105a** and (+)-**105b** in excellent yields. Besides the C14-C15 double bond isomer introduced in the previous Julia–Kocienski olefination, no further C7-C8 double bond isomer could be detected by means of ^{1}H NMR spectroscopy. Redox transformation consisting of exhaustive DIBAL-H reduction and DMP oxidation afforded the α,β-unsaturated aldehydes **107a** and **107b** in good yields. As in the case of (+)-**104a** and (+)-**104b** long-time-storage was avoided.

Attempts to selectively reduce the enoates (+)-**105a** and (+)-**105b** directly into the corresponding aldehydes **107a** and **107b** proved to be difficult since TLC showed the simultaneous formation of both alcohol and aldehyde even if only one drop of DIBAL-H was added at –90°C. Based on this finding, conditions were provided to allow exhaustive reduction.

A Horner–Wadsworth–Emmons (HWE) olefination[71] using commercially available ethyl 2-diethoxyphosphorylacetate and NaH as the base were employed to build the (*E*)-configured C5-C6 double bond delivering the dienoates (–)-**108a** and (–)-**108b** in excellent yields (Scheme 35). Again, no evidence for an additional isomer was detected by ^{1}H NMR. The assignment of the C5-C6 double bond configuration rests on the evaluation of the NMR coupling constants of 6-CH: J = 15.8 Hz as expected for an (*E*)-configured double bond. DIBAL-H reduction led to the α,β-γ,δ-unsaturated alcohols (+)-**109a** and (+)-**109b** which were used as storage compounds as well as a logistic pool for the upcoming transformations targeting *syn*- and *anti*-configured aldols as characteristic structural elements of both natural products.



Scheme 35

The synthesis of aldols obviously relies on one or the other stereoselective aldol chemistry. The selection of a suitable method should both take into account a high *syn*/*anti* diastereoselectivity, as well as a high diastereofacial selectivity induced by auxiliaries.

[188] Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1242−1249

3.11 A *syn*-configured isomer of Fusaequisin A via Evans' asymmetric aldol chemistry

It should be mentioned again that no structural assignments concerning the absolute configuration and the relative configuration in the non-cyclic parts of both title natural products were undertaken so far. While Gloer, in the absence of clear evidence, introduced some conjectures favoring *anti*- over *syn*-aldols for the case of Curvicollides, no such reflections were assumed by Shiono for the case of Fusaequisin A. We decided to investigate the *syn*-case at first, as only the result of the synthesis may enable its later exclusion. Furthermore, the synthesis of *syn*-aldols is more frequently described in the literature.[189]

Evans' asymmetric chemistry is based on the utilization of oxazolidinones as chiral auxiliaries. The corresponding imides formed by acylation of oxazolidinones are converted selectively into either (*Z*)-lithium or (*Z*)-boron enolates. For the latter conversion, imide (*R*)-**19** based on the (*R*)-valin derived oxazolidinone was treated with dibutylboron triflate[190] in the presence of trimethylamine as base (Scheme 36). Evans' asymmetric aldol reaction[72] delivered the *syn*-configured aldol **111** in moderate yield but high diastereoselectivity (dr = 95:5). The unsatisfactory yield was due to an incomplete conversion into aldol **111** but did not cause a logistic problem, as reisolation of the starting material was possible. It was important to add molecular sieves as no conversion was observed in its absence. Thus, water from whatever source could be a reason, responsible for the incomplete conversion.

The next transformation was based on the need to convert the aldol **111** bearing an *N*-acyloxazolidinone moiety into a methyl ketone moiety which is present in the natural product **2**. For this purpose, a well-established procedure was employed which first converts acylated oxazolidinones into their corresponding Weinreb amides. The latter can be transformed into ketones or aldehydes in a single step by treatment with a suitable nucleophile. Over-addition of the nucleophile to result in an alcohol is prevented by stabilisation of the respective tetrahedral intermediate through chelation (Figure 27).

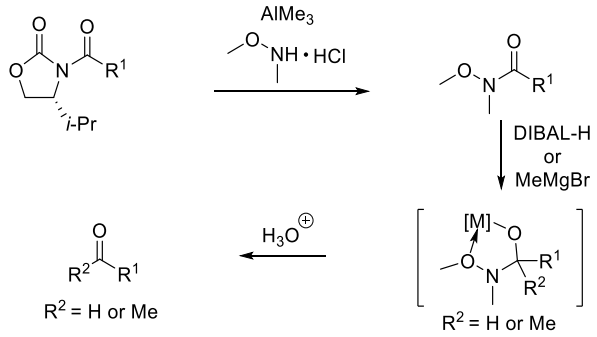
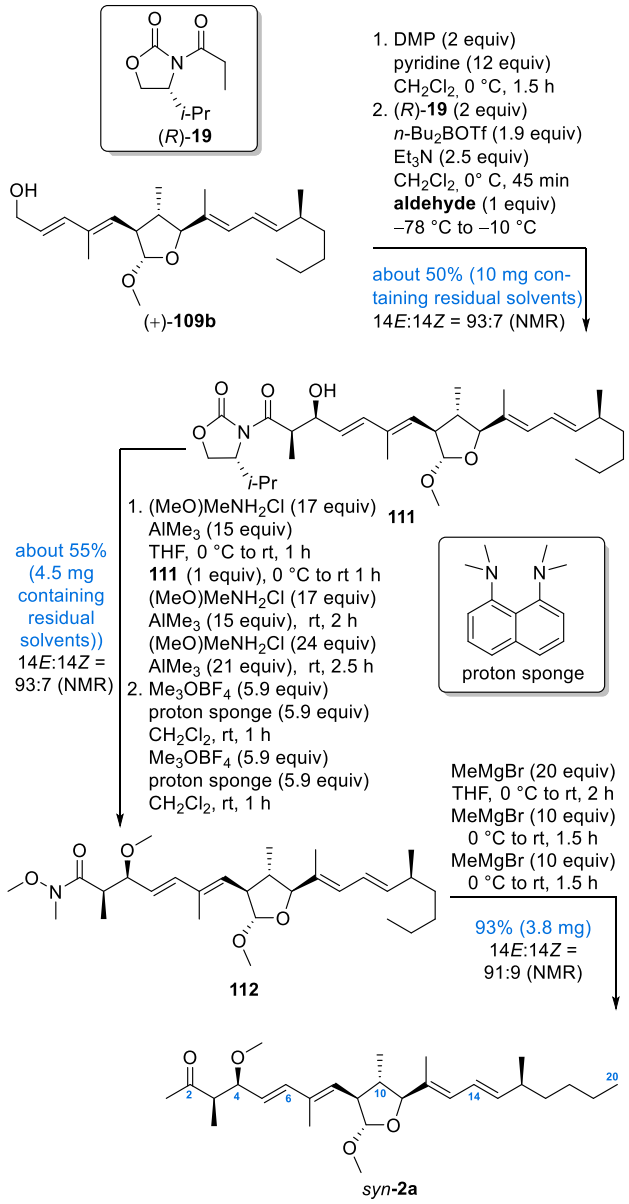


Figure 27 General reaction scheme for a Weinreb–Nahm ketone synthesis.

Unlike in Curvicollide C, the aldol of Fusaequisin A exists in its *O*-methylated form. While *O*-methylation of the hydroxyl group in **110** using hard conditions (Me_3OBF_4 (5 equiv), proton sponge (5 equiv) in CH_2Cl_2 at room temperature, 88% (9 mg))[191] was successful, a subsequent conversion of the methyl ether to the corresponding Weinreb amide ($AlMe_3$ (14 equiv), $(MeO)MeNH_2Cl$ (14 equiv) in THF at room temperature) was not. It was found that a free hydroxyl group is required for transamination.[192] Consequently, a methylation at the stage of the corresponding Weinreb amide was taken into account. The conversion of imide **110** into its respective Weinreb amide was facilitated by the aluminium amide reagent[73] derived from trimethylaluminium and *N*-methoxymethylamine hydrochloride. The progress of the reaction was monitored by TLC. A complete conversion of **111** required to replenish the freshly prepared aluminium amide reagent in several additions. Methylation using Meerwein's reagent and proton sponge delivered the methyl ether **112** in good yield. Finally, treatment of methylated Weinreb amide **112** with excessive MeMgBr[193] resulted in the first synthetic isomer *syn*-**2a** having the proper constitution of Fusaequisin A. Comparison of spectroscopic data revealed that synthetic product *syn*-**2a** is not identical with Fusaequisin A (**2**) which is most likely *anti*-configured in the *O*-methylated aldol part. This comparison is outlined extensively in Chapter 4.2.

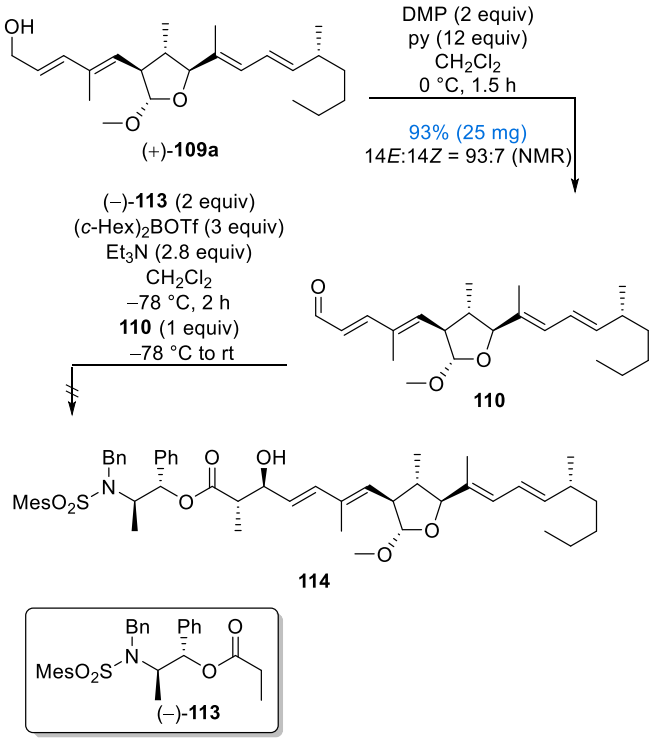
[189] Crimmins, M.T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.
[190] Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
[191] Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.
[192] Evans, D. A.; Gage, J. R.; Leighton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453
[193] Nahm, S.; Weinreb, S.,M. *Tetrahedron Lett.* **1981**, 22, 3815−3818.



Scheme 36

3.12 An *anti*-configured isomer of Desmethylfusaequisin A via Paterson asymmetric aldol chemistry

For the diastereoselective construction of an *anti*-configured aldol moiety, the well-established Abiko–Masamune asymmetric aldol reaction was tested at first (Scheme 37).[194] This chemistry employs ephedrine or norephedrine derived propionate esters as chiral reagents, which are converted into the corresponding (*E*)-boron enolates on treatment with the bulky dicyclohexyl boron triflate in the presence of triethylamine as base. The propionate ester **113** derived from norephidrine as chriral auxiliary was synthesized and kindly provided by André Klüppel. To our dismay, no conversion to **114** was observed while the aldehyde **110** was reisolated in a partly epimerized form (dr = 6:1) as observed by the appearance of a second doublet for the aldehyde proton in the ^{1}H NMR spectrum. No effort was taken to determine the nature of epimerization which may be due to either a double bond isomerization or an epimerization at 9-CH.



Scheme 37

[194] a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc*. **1997**, *119*, 2586−2587. b) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387−395.

In order to ensure that the reaction did not fail due to the sensible nature of dicyclohexylboron triflate,[195] the latter reagent was tested by André Klüppel in an independent aldol reaction where it behaved as expected.

After to the failure of the Abiko–Masamune *anti*-aldol reaction, we turned our attention to the Paterson *anti*-aldol method,[196] which is based on the utilization of the lactate-derived ketone (+)-**124**[197] as chiral reagent (Scheme 38). Here, the formation of the (*E*)-configured boron enolate is facilitated by the application of commercially available dicyclohexyl boron chloride[198] in the presence of triethylamine as a base. The Paterson method led to the *anti*-aldol (+)-**115** in good yield and excellent diastereoselectivity. The facial selectivity which controls the absolute configuration of the aldol moiety was rationalized by Paterson et al. as an attractive interaction (a weak hydrogen bond) between the formyl hydrogen and the carbonyl oxygen of the benzoate (Figure 28).[199]

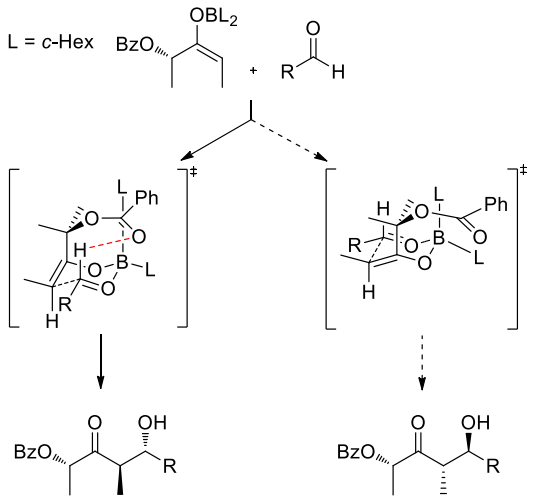
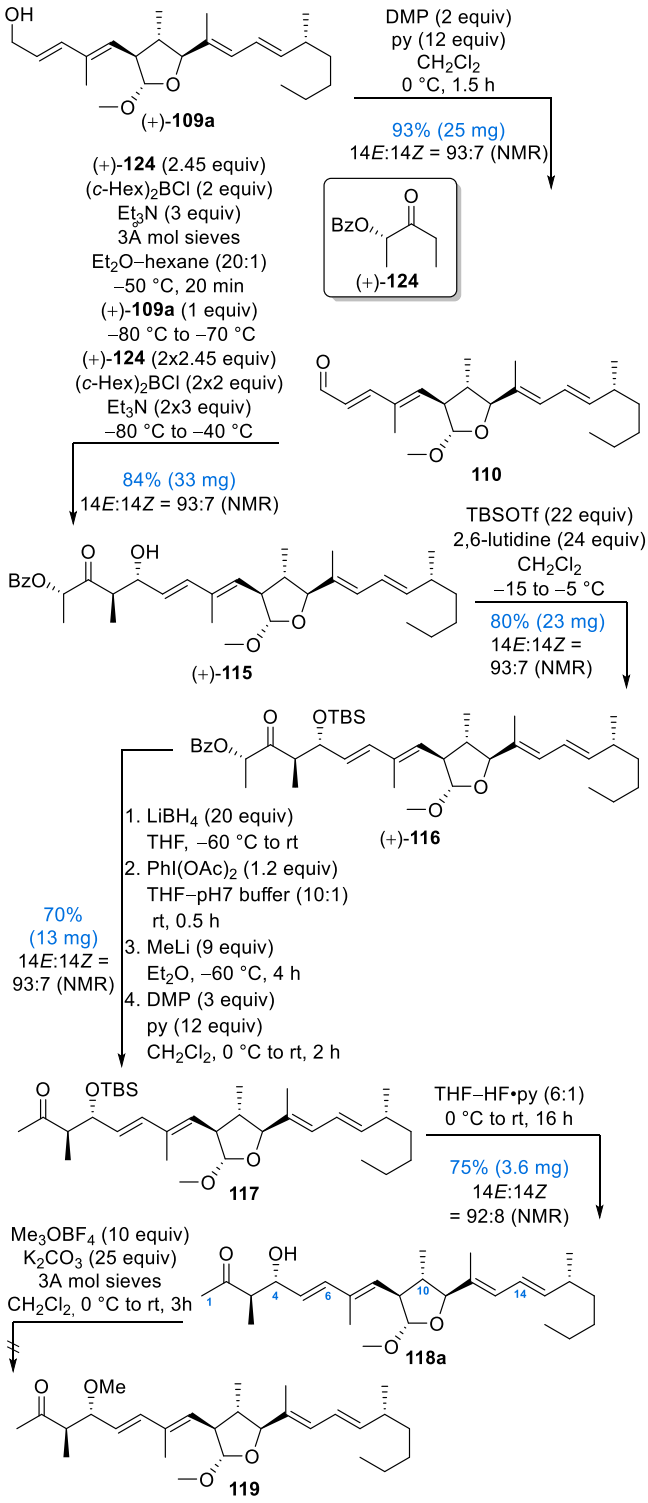


Figure 28 Model for enantio- and diastereoselectivity in the Paterson aldol reaction. Attractive interaction between the formyl hydrogen and the carbonyl oxygen of the benzoate is marked in red.

While an attempted *O*-methylation of the resulting aldol (+)-**115** using hard conditions (Me_3OBF_4 (5 equiv), proton sponge (5 equiv) in CH_2Cl_2, 1 h) at room temperature resulted in a decomposition, methylation using soft conditions (Ag_2O (1.8 equiv) in MeI)[200] at room temperature led to a retro-aldol reaction yielding dienal **110** which was also observed when using hard conditions (MeOTf (7 equiv), 2,6-di-*tert*-butyl-methylpyridine (9 equiv) in CH_2Cl_2)[201] at 0 °C. These findings called for a change in the synthetic plan which incorporates the methylation at a late stage of the synthesis. The new plan conceived the introduction of a suitable protecting group preventing a retro-aldol reaction or an elimination yielding a trienone moiety in the course of the reaction. Due to the structural constraints in (+)-**115** we decided for a silyl group and selected TBS triflate in the presence of 2,6 lutidine as a suitable reagent combination. At low temperatures and when using an excess of both reagents, the TBS ether (+)-**116** was obtained in good yield. Stepwise chain degradation[202] consisting of exhaustive reduction (causing hydride transfer to both keton and ester moiety), diol cleavage, nucleophilic addition and oxidation all proceeded uneventfully to yield the TBS protected ketone **117**. Noteworthy in the transformation of **116** to **117** is the utilization of diacetoxy iodobenzene for the cleavage of the diol.[203] In our hands, this reagent proved to work faster and more efficiently as compared to sodium periodate. Exposure of **117** to TBAF[204] resulted in a retro-aldol reaction delivering the dienal **110** in a "jump to start" fashion. Successful deprotection of TBS was achieved using HF•pyridine yielding product **118a** which has the proper constitution of Desmethylfusaequisin A. Attempts to convert **118a** into the targeted natural product by employing hard conditions (Me_3OBF_4 (10 equiv), K_2CO_3 (25 equiv), 3Å molecular sieves in CH_2Cl_2, 0 °C to room temperature 3 h) failed, as a retro-aldol reaction leading to "jump back" dienal **110** could not be avoided. However, no final conclusion on the feasibility of methylation should be derived here, as limited synthetic material of **118a** caused a shortage of test reactions.

[195] Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem*. **1993**, *58*, 147−153.
[196] Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083−9086.
[197] Trost, B. M.; Urabe. H. L. *Org. Chem* **1990**, *55*, 3982−3983.
[198] Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499–504.
[199] Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652.
[200] Greene, A. E.; Drian, C. L.; Crabbe. P. *J. Am. Chem. Soc.*, **1980**, *102*, 7583–7584.
[201] Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046−1056.
[202] Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429–2444.
[203] a) Banks, D. F. *Chem. Rev*., **1966**, *66*, 243–266.; b) Criegee R. in *Oxidation in Organic Chemistry*, Academic Press, New York, **1965**, pp 277–365.
[204] Undesired side reactions evoked by TBAF are often found in literature and can be explained by it's relative high basicity. Buffering the reaction with acetic acid is one option to solve this problem. Examples in which also a retroaldol reaction was observed are: a) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 16403–16416. b) Gong, J., *Total Synthesis of (±)-Maoecrystal V*. Springer Berlin Heidelberg: 2014.



Scheme 38

3.13 Final strategy for the synthesis of Curvicollide C and Fusaequisin A employing cross-metathesis reactions

Synthesis of natural products is usually based on the knowledge of the target structure. While there are cases where the absolute configuration is not known, the constitution and the relative configuration of the target structure typically is. It became more and more obvious that the previously elaborated synthetic plans for Curvicollide C und Fusaequisin A do not match the level of ignorance on the stereochemical structure of these targets. First of all, the syntheses elaborated are far too long with respect to the number of steps that follow after having fixed the configuration of the aldol moiety in the Western part. Secondly, the transformation of a methyl lactol ether into the corresponding lactone imposes constraints which are most likely not innocent with respect to epimerizations, double bond isomerizations, eliminations and retro-aldol reactions. As some of these side reactions were observed in the synthetic pathways elaborated so far, one has to expect their occurance if the synthetic plan is not fundamentally changed with respect to the chemistries explored. Thirdly, a step by step construction of the Western part in which the delicate aldol moiety is introduced at a rather late stage contradicts the idea that a complex natural product should be synthesized from fragments of similar complexity. The first issue calls for a synthetic strategy which outperforms the previous plans with respect to modularity and logistics. The second issue restricts the set of potential new strategies to one which starts from a common precursor for both targets, thus embedding a higher degree of diversity. The third issue calls for a less linear but more convergent synthesis, perhaps embedding the aldol moiety of the Western part in a suitable fragment.

While any fundamental change of a synthetic strategy is difficult in a kind of “end game” situation, especially if only one step is missing to complete the synthesis, we became inspired by an idea which we could not resist to elaborate. The idea was to construct the target molecules by cross-metathesis reactions. Indeed, even after the Nobel prize in chemistry had been given for the development of metathesis chemistry,[205] the field is still in its growing stage[206] and also has stimulated research in our group.[207]

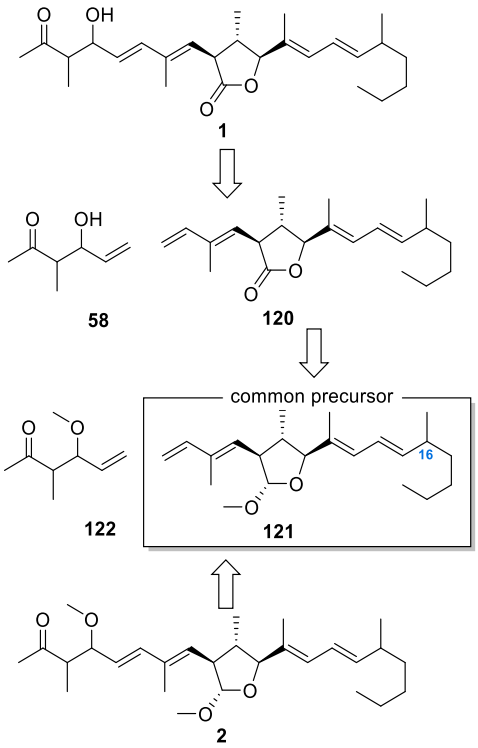
Scheme 39 depicts the essentials of the final strategy for the total synthesis of our target molecules based on cross-

[205] The Royal Swedish Academy of Sciences T*he Nobel Prize in Chemistry 2005*

[206] a) Grubbs, R.H. *Angew. Chem*. **2006**, *118*, 3845–3850. b) Connon, S. J.; Blechert, S. *Angew. Chem*. **2003**, *115*, 1944−1968. c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900−1923

[207] a) Schäfer, A.; Hiersemann, M. *Org. Lett.*, **2017**, *19*, 814–817. b) Becker, J.; Butt, L.; von Kiedrowski, V.; Mischler, E.; Quentin, F.; Hiersemann, M. *Org. Lett.*, **2013**, *15*, 5982–5985. c) Gille, A.; Hiersemann, M. *Org. Lett.*, **2010**, *12*, 5258–5261. d) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, 11, 2555–2558

metathesis reactions. Note that the common precursors are the 16-CH epimers of a tetraene **121**, which can be derived from aldehydes **107a** and **107b** which were previously described in this thesis (Scheme 34 of Chapter 3.10). The new chemistry to be developed concerned both enantiomeric forms of the *anti*-configured vinyl-containing aldols **58** as cross-metathesis partners. A diastereo- and enantioselective synthesis of the enantiomers of **58** seemed rather straightforward when applying the asymmetric aldol reactions described in the previous chapter. Also, the conversion of the lactol methyl ether in the common precursors **121** into the corresponding lactones **120** were thought to be less complicated at the stage of tetraenes compared to more functionalized molecules containing the aldol part (e.g. **118a**).



Scheme 39

We felt furthermore encouraged to follow this plan because allylic alcohols were reported to react smoothly in metathesis reactions.[208] This includes the example of Crimmins[209] et al. which exhibits a high similarity to our attempted cross-metathesis when considering the functionality in the vicinity of the reaction site (Figure 29).

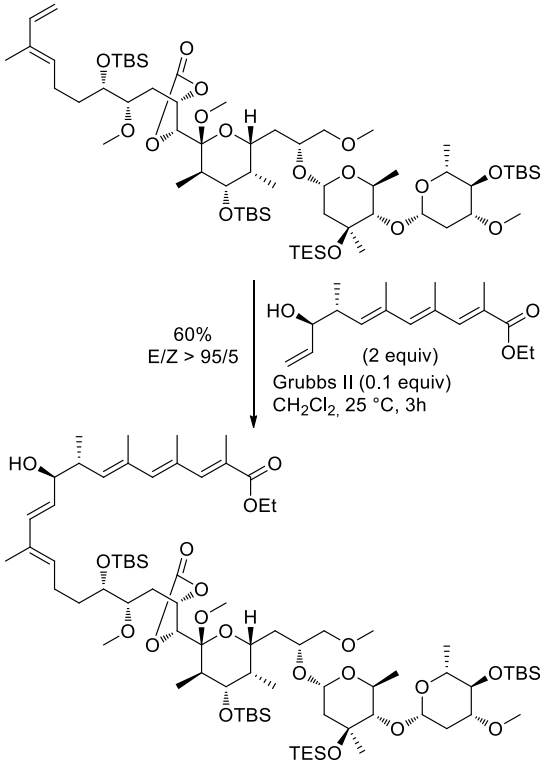


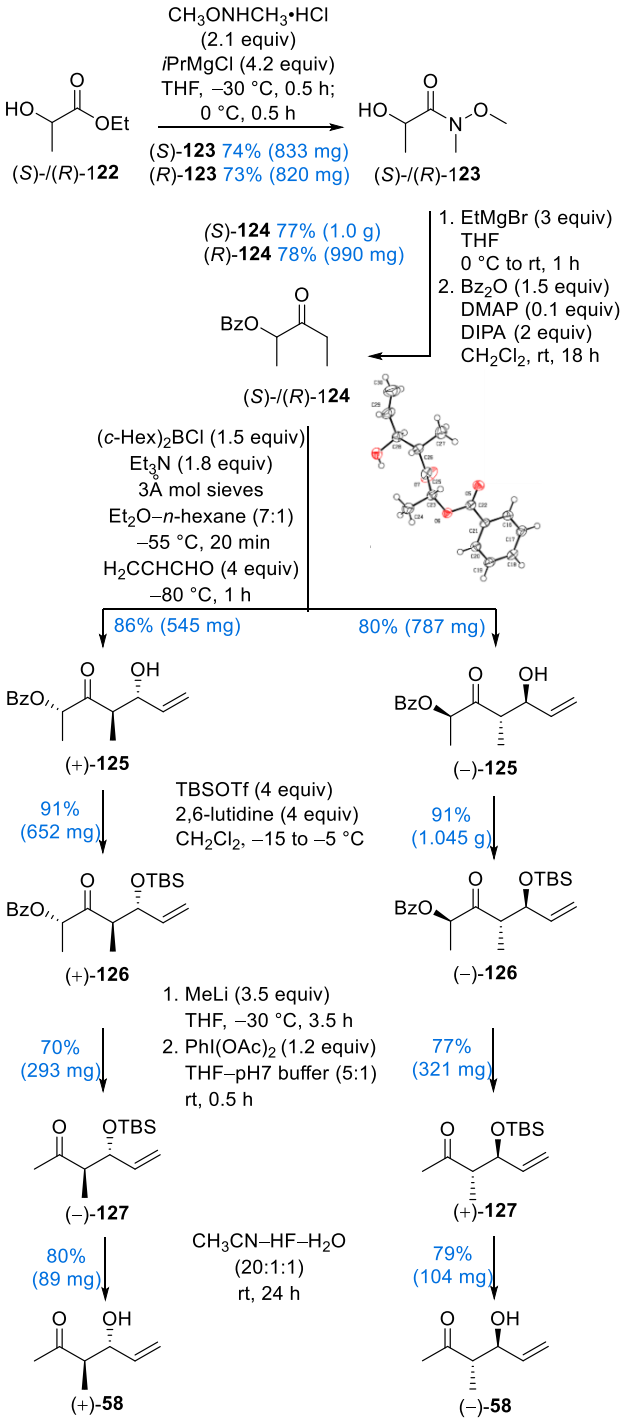
Figure 29 Cross-metathesis employing an allylic alcohol in the total synthesis of Apoptolidin A.

3.14 Synthesis of vinyl-containing aldols as Western fragments

To our astonishment, the structurally simple enantiomeric vinyl aldols **58** are not known in the literature so far. Their synthesis was planned to take advantage from synthetic methodology which had been previously employed with good success (Scheme 38, Chapter 3.12). Thus, the asymmetric synthesis of both enantiomers was based on Paterson's aldol chemistry utilizing both enantiomerically pure ethyl ketones **124** and acroleine (Scheme 40). Enantiopure ethyl ketones **124** were synthesized in accordance to published procedures starting from either (*R*)-or (*S*)-ethyl lactate (**122**). Treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride delivered the corresponding Weinreb amides (*R*)-or (*S*)-**123**, respectively. After Grignard reaction with ethyl magnesium bromide the corresponding α-hydroxy ethyl ketones were immediately converted into the corresponding benzoates (*R*)- or (*S*)-**124** using benzoic anhydride, DMAP as nucleophilic catalyst and DIPA as the base.

[208] Lin, Y.A.; Davis, B.G. *Beilstein J.Org. Chem.* **2010**, *6*, 1219−1228

[209] Crimmins, M. T.; Christie, H. S.; Long, A.; Chaudhary, K. *Org. Lett.* **2009**, *11*, 831−834.

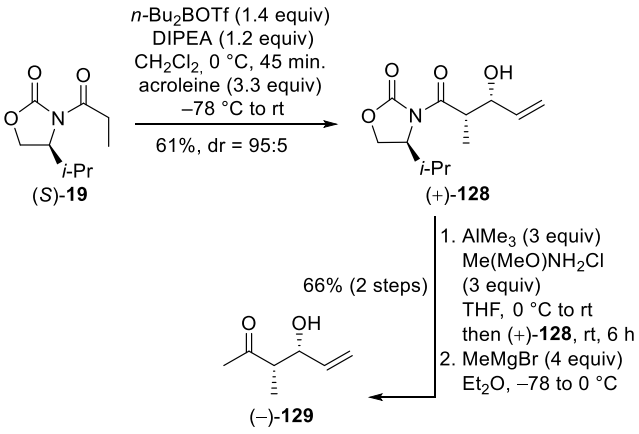


Scheme 40

In the following hitherto unpublished examples of Paterson aldol reactions, dicyclohexyl boron chloride in the presence of trimethylamine were employed to generate (*E*)-configured boron enolates of (*R*)-and (*S*)-**124** which were treated with an excess of acroleine as the electrophile.

The aldols (+)-**125** and (–)-**125** were obtained in good yields and excellent diastereoselectivities. To our advantage, the products crystallized as thin needles, which enabled us to determine the relative configuration of (–)-**125** by X-ray crystallography.[210] The relative configuration was in accordance with the accepted stereochemical model. With the knowledge that in comparable structures, retro-aldol reactions had played a role as "trouble makers", the β-hydroxyl group in (+)- and (–)-**125** was protected as its silyl ether to prevent this undesired side reaction. Silylation was achieved by the utilization of TBSOTf and 2,6-lutidine delivering the silyl ethers (+)- and (–)-**126** in good yields. Stepwise chain degradation consisting of a nucleophilic attack of MeLi to both ketone and benzoate moieties afforded the respective diols which were directly treated with diacetoxy iodo benzene resulting in the methyl ketones (+)- and (–)-**127**. Cleavage of the TBS ethers in (+)- and (–)-**127** using HF in a solvent mixture of H_2O and acetonitrile finally afforded the required vinyl-containing aldols (+)- and (–)-**58.**

In order to test a cross-metathesis reaction also for the case of a vinylated *syn*-aldol, compound (–)-**129** was available as legacy from previous work and could be used without purification after confirming its identity by ^{1}H NMR. *Syn*-aldol (–)-**129** had been previously synthesized by Marleen Körner (Scheme 41) to test palladium catalyzed cross-coupling reactions.[54] Synthesis was based on an Evans aldol[72] reaction employing acroleine as the aldehyde to obtain the aldol (+)-**128**.[54]

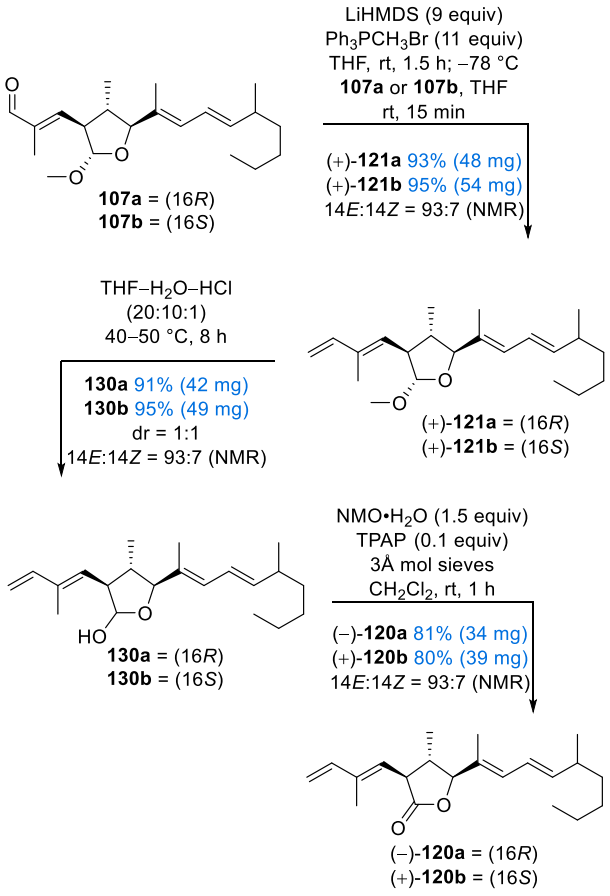


Scheme 41

[210] von Kiedrowski, V.; God, C.; Knauer, L.; Strohmann, C.; Preut, H.; Hiersemann, M. *IUCrData* **2017** (submitted)

3.15 Synthesis of tetraenes as cross-metathesis substrates

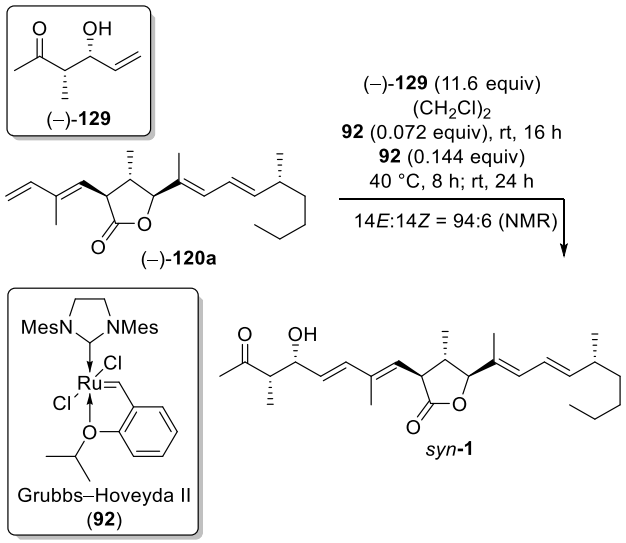
The starting material for the synthesis of tetraenes (–)-**120a** and (+)-**120b** are the aldehydes **107a** and **107b** which stem from the synthetic pathway as described in Scheme 34 of Chapter 3.10. Wittig methylenation of the latter furnished the tetraenes (+)-**121a** and (+)-**121b** in excellent yields (Scheme 42). Note that the lactol ethers (+)-**121a** and (+)-**121b** are the last common precursors for both natural products as these represent the branching points for any further synthetic extension. Targeting Curvicollide C, the latter were hydrolyzed using HCl in a solvent mixture of THF and H_2O to yield the lactols **130a** and **130b** as a mixture of anomers (1:1). Ley-Griffith oxidation[84] of the lactols with TPAP and NMO delivered the lactones (–)-**120a** and (+)-**120b** in good yields. No double bond isomerization leading to conjugated lactones was observed in contrast to similar vinylated lactones which underwent isomerization after exposure to the reaction conditions for longer times (Tab. 3.5, S. 45 in ref. 77).



Scheme 42

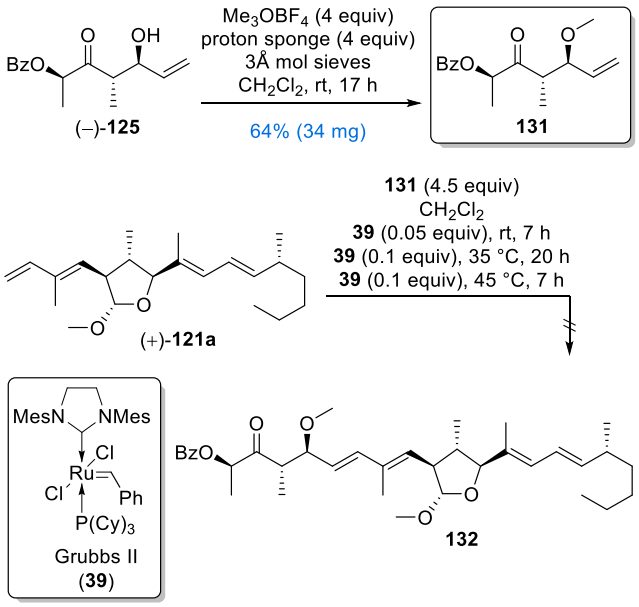
3.16 Cross-metathesis: First insights and conclusions from test reactions

With the various Western fragments and tetraenes now in hand, we began the task of joining them together via construction of the C5-C6 double bond. Our first approach was to test the cross-metathesis using the allylic *cis*-aldol (–)-**129** and tetraene (–)-**120a** employing the Grubbs–Hoveyda II catalyst[160] (**92**) (Scheme 43). This test reaction was meant to be able to exclude allylic *syn*-aldols in the upcoming systematic metathesis studies, as Gloer et al. had already mentioned that the natural Curvicollides most likely bear an *anti*-aldol moiety in the Western side chain. Indeed, as it will be discussed in Chapter 4.1, a comparison of the ^{1}H NMR spectra of the natural product **1** and the crude synthetic product *syn*-**1** revealed that Gloer was right in his assumption. Consequently, no further effort was undertaken to elaborate the chemistry of products in the *syn*-aldol series.



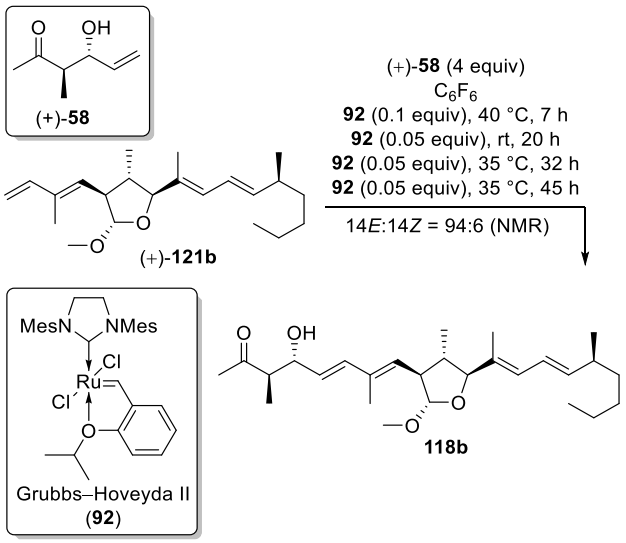
Scheme 43

It is well known that allylic alcohols react rapidly in cross-metathesis reactions while substrates bearing no free hydroxyl groups in the allylic position generally react much slower. Indeed, a test reaction employing methyl ether **131** (derived from aldol (–)-**125**) and the tetraene (+)-**121a**-as the precursor of Fusaequisin A showed no conversion when applying the Grubbs II catalyst[85] (**39**) (Scheme 44). While for the case of a simple test reaction, the absence of evidence does not mean evidence for the absence of feasibility, this result calls for more elaborate studies we were not able to carry out.



Scheme 44

We nevertheless succeeded in demonstrating that the tetraenes **121** bearing a methyl lactol moiety are suitable substrates for cross-metathesis reactions and exhibit no disadvantages when compared with the corresponding lactones (–)-**120a** and (+)-**120b**. Tetraene (+)-**121b** was converted into Desmethylfusaequisin **118b** upon treatment with allylic *anti*-aldol (+)-**58** in the presence of the Grubbs-Hoveyda II catalyst[160] (**92**) (Scheme 45). No effort was undertaken to develop this chemistry beyond the level of a simple test reaction.



Scheme 45

As a result of the above test reactions, we decided to focus on systematic studies and the structural elucidation of Curvicollide C.

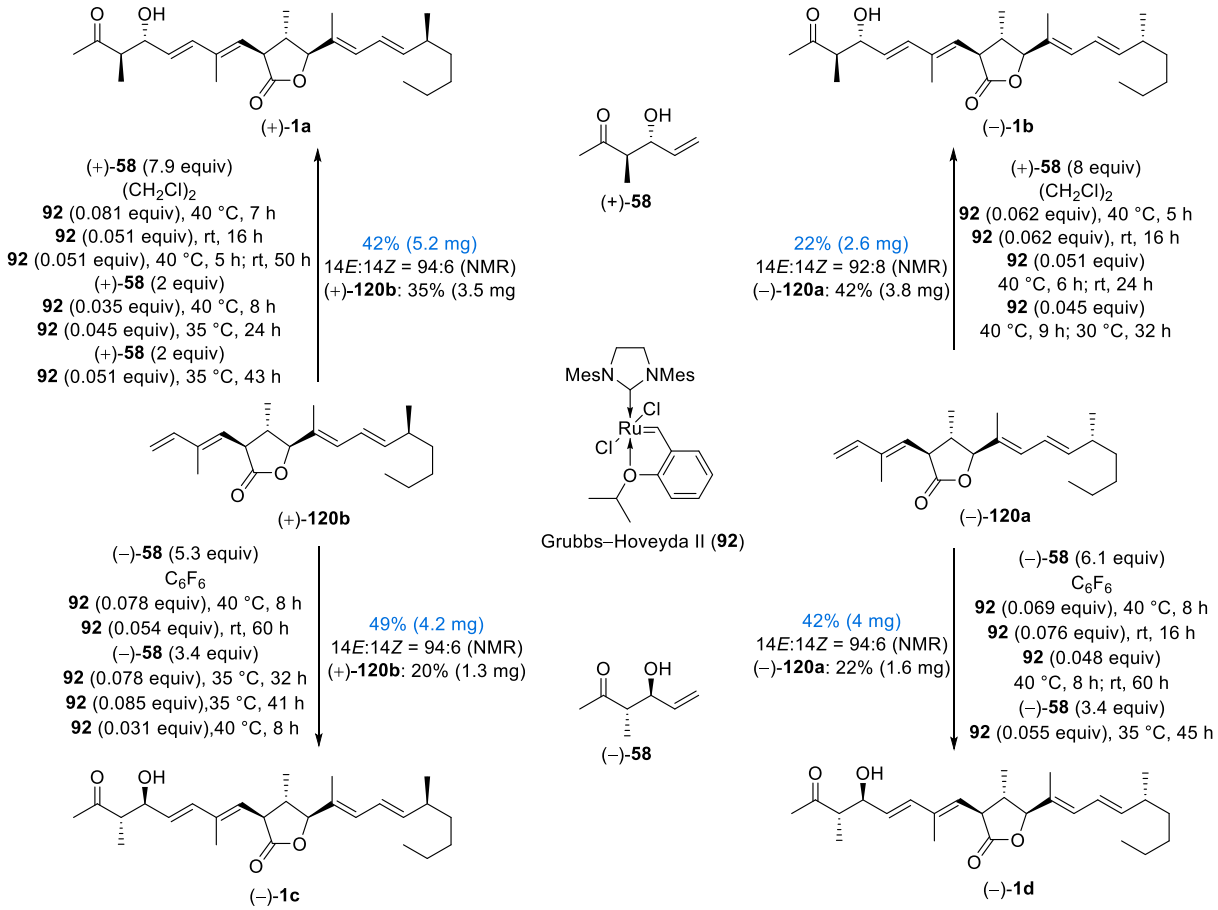
3.17 Cross-metathesis: Generating a small library of Curvicollide C isomers

From the two enantiomeric allylic *anti*-aldols (+)-**58** and (–)-**58** and the two diastereomeric lactone tetraenes (–)-**120a** and (+)-**120b**, the four diastereomers **1a** – **1d** were synthesized applying the Grubbs–Hoveyda II catalyst[160] (Scheme 46). In order to avoid a homodimerisation of the logistically demanding tetraenes, the allylic *anti*-aldols were always introduced in high excess. From a technical perspective, the reactions were carried out in a closed tube which did not allow the removal of ethylene in a continuous fashion.[211] The reason for this unusual mode of operation is caused by the volatility of the Western fragments (+)-**58** and (–)-**58** at the reaction temperature. While the yields of the reactions were not yet at a satisfactory level, all reactions proceeded smoothly and enabled the recovery of non-converted tetraenes (–)-**120a** and (+)-**120b**. It was observed by TLC that the homodimer of the respective allylic *anti*-aldol is rapidly formed prior to any cross-metathesis product. It is even conceivable that the latter is formed *from* this homodimer in a consecutive fashion. If this is indeed the predominant pathway, one may succeed to optimize the reaction by starting from the homodimer instead of the aldols **58** – also when taking into account the volatility of the homodimer versus its precursor. Needless to say that inspite of its synthetic versatility any cross-metathesis reaction suffers from its reversibility in the sense that also non-desired combinations of fragments are possible. Given the fact that the starting tetraenes offer not only one mode of a metallacyclobutane[212] formation, the results and yields achieved so far may be even viewed as better than expected.

At this point it should be emphasized that the goal of this thesis is not to synthesize a given natural product with maximal yield and highest degree of strategic elegance, but to contribute to the structural elucidation of a natural product by means of synthesis. This perspective naturally calls for a synthetic methodology which ranks modular constructability higher than yields.

[211] Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869–1874.

[212] Chauvin, Y.; Hérisson, J. L. *Makromol. Chem.*, **1971**, *141*, 161–176.


(+)-1a
(+)-58 (7.9 equiv)
(CH2Cl)2
92 (0.081 equiv), 40 °C, 7 h
92 (0.051 equiv), rt, 16 h
92 (0.051 equiv), 40 °C, 5 h; rt, 50 h
(+)-58 (2 equiv)
92 (0.035 equiv), 40 °C, 8 h
92 (0.045 equiv), 35 °C, 24 h
(+)-58 (2 equiv)
92 (0.051 equiv), 35 °C, 43 h
42% (5.2 mg)
14E:14Z = 94:6 (NMR)
(+)-120b: 35% (3.5 mg
(+)-120b
(–)-58 (5.3 equiv)
C6F6
92 (0.078 equiv), 40 °C, 8 h
92 (0.054 equiv), rt, 60 h
(–)-58 (3.4 equiv)
92 (0.078 equiv), 35 °C, 32 h
92 (0.085 equiv),35 °C, 41 h
92 (0.031 equiv),40 °C, 8 h
49% (4.2 mg)
14E:14Z = 94:6 (NMR)
(+)-120b: 20% (1.3 mg)
(–)-1c
(+)-58
Grubbs–Hoveyda II (92)
(–)-58
(–)-1b
(+)-58 (8 equiv)
(CH2Cl)2
92 (0.062 equiv), 40 °C, 5 h
92 (0.062 equiv), rt, 16 h
92 (0.051 equiv)
40 °C, 6 h; rt, 24 h
92 (0.045 equiv)
40 °C, 9 h; 30 °C, 32 h
22% (2.6 mg)
14E:14Z = 92:8 (NMR)
(–)-120a: 42% (3.8 mg)
(–)-120a
(–)-58 (6.1 equiv)
C6F6
92 (0.069 equiv), 40 °C, 8 h
92 (0.076 equiv), rt, 16 h
92 (0.048 equiv)
40 °C, 8 h; rt, 60 h
(–)-58 (3.4 equiv)
92 (0.055 equiv), 35 °C, 45 h
42% (4 mg)
14E:14Z = 94:6 (NMR)
(–)-120a: 22% (1.6 mg)
(–)-1d

Scheme 46

Chapter 4 - Structural assignments

4.1 Structural elucidation of (−)-Curvicollide C via comparison with synthetic diastereomers

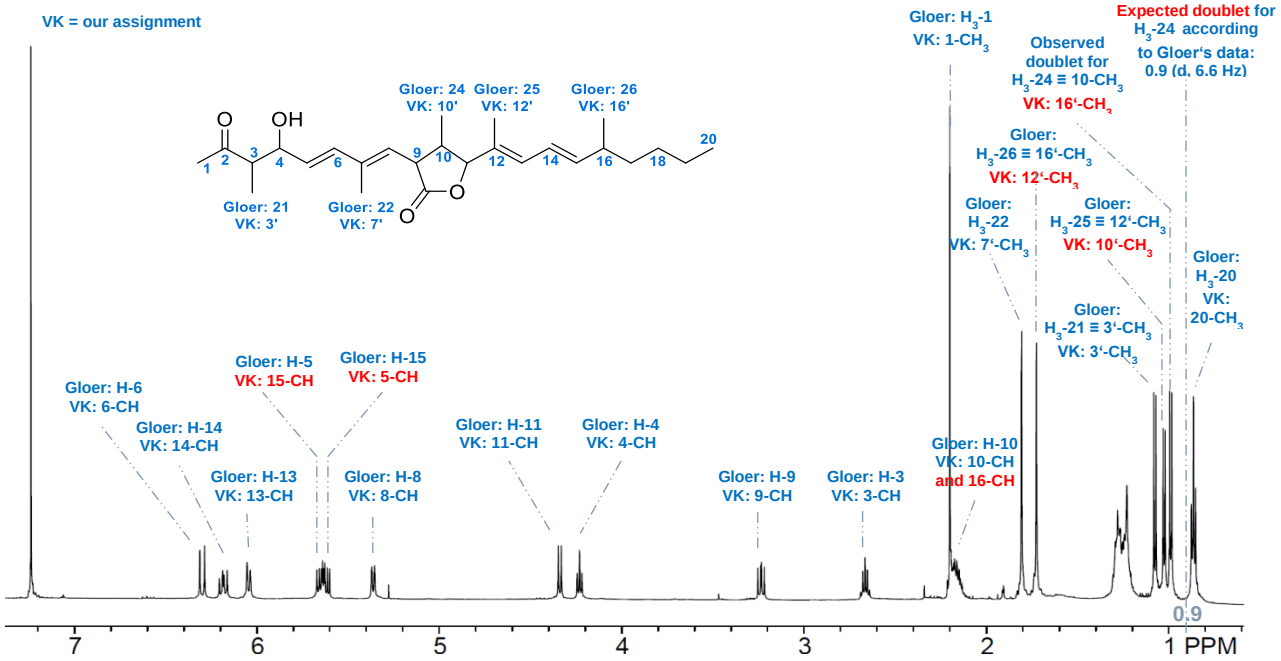
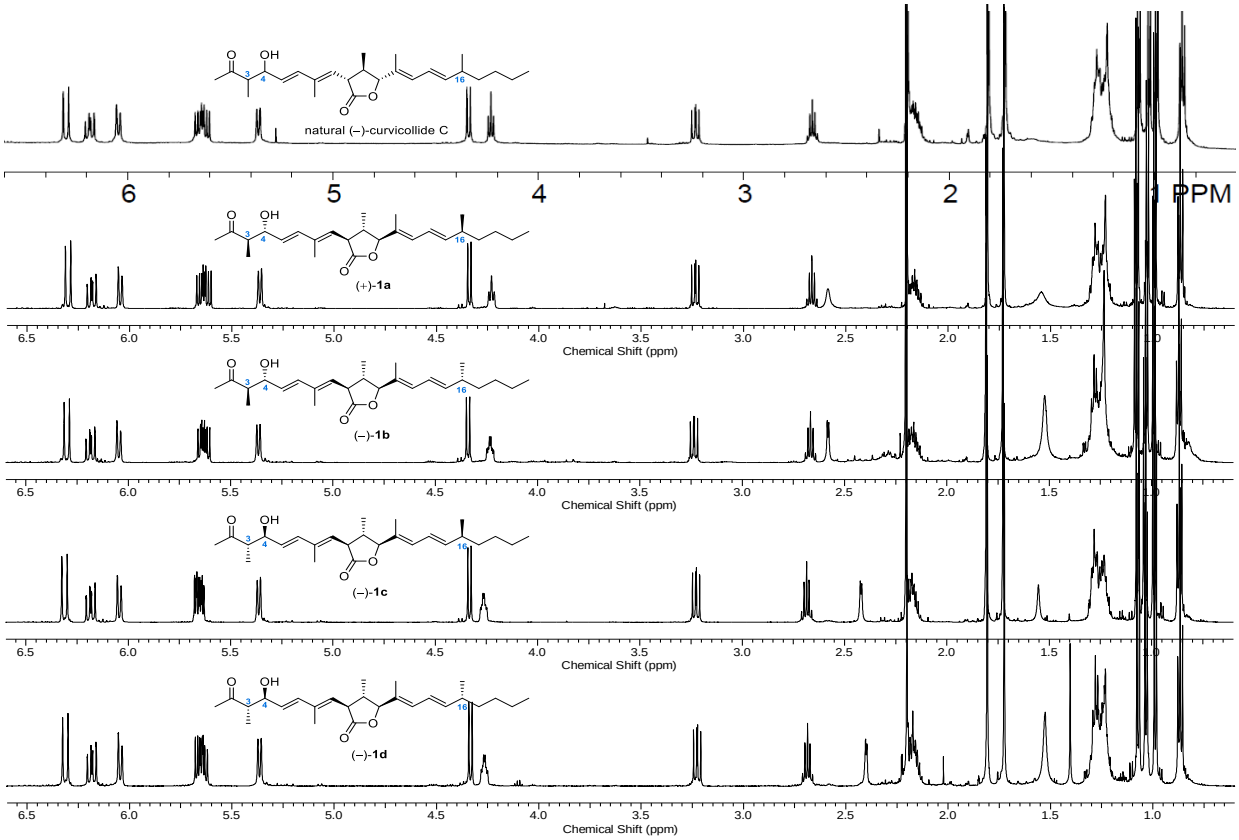
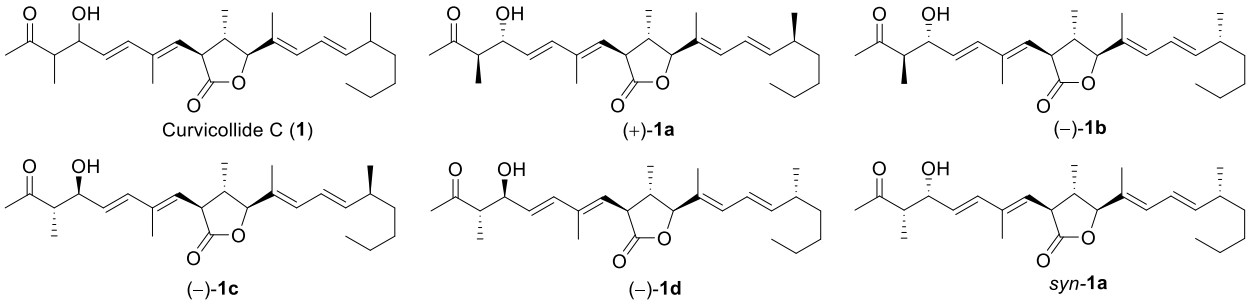


Figure 30 ^{1}H NMR spectrum of natural Curvicollide C (**1**) in $CDCl_3$ at 600 MHz reproduced from the Supporting Information of Gloer et al. with added peak assignments. Carbon atom numbering system and peak assignment according to Gloer et al. as well as von Kiedrowski et al. (VK). Differences in peak assignment are highlighted in red.



Firgure 31 Comparison of ^{1}H NMR spectra of natural Curvicollide C (reproduced from Supporting Information of ref. 3) and synthetic *anti*-isomers **1a-1d**, all recorded at 600 MHz in $CDCl_3$ and referenced to to $CHCl_3$ at 7.239 ppm.

Table 6. Comparison of selected ^{1}H NMR data. Chemical Shifts (δ) reported in ppm relative to $CHCl_3$ at 7.239 ppm.



Entry		curvicollide C[a]	(3*R*,4*R*,16*S*)-**1**[b]	(3*R*,4*R*,16*R*)-**1**[b]	(3*S*,4*S*,16*S*)-**1**[b]	(3*S*,4*S*,16*R*)-**1**[b]	(3*S*,4*R*,16*R*)-**1**[b]
1	1-CH_3	2.20	2.20	2.20	2.20	2.20	2.19
2	3-CH	2.67	2.67	2.67	2.69	2.69	2.68
3	3'-CH_3	1.08	1.08	1.08	1.07	1.07	1.15
4	4-CH	4.23	4.23	4.23	4.26	4.27	4.51
5	5-CH[c]	5.63	5.62	5.62	5.66	5.66	5.66
6	6-CH	6.30	6.30	6.30	6.31	6.31	6.30
7	7'-CH_3	1.81	1.81	1.81	1.81	1.81	1.80
8	8-CH	5.36	5.36	5.36	5.36	5.36	5.34
9	9-CH	3.24	3.24	3.24	3.23	3.23	3.23
10	10-CH	2.16	2.11−2.23	2.11−2.22	2.12−2.24	2.12−2.22	2.10−2.23
11	10'-CH_3[c]	1.03	1.03	1.02	1.03	1.03	1.02
12	11-CH	4.34	4.34	4.34	4.33	4.33	4.34
13	12'-CH_3[c]	1.73	1.73	1.73	1.73	1.73	1.72
14	13-CH	6.04	6.05	6.05	6.04	6.05	6.04
15	14-CH	6.18	6.18	6.18	6.18	6.18	6.18
16	15-CH[c]	5.65	5.65	5.64	5.65	5.64	5.64
17	16-CH	[e]	2.11−2.23	2.11−2.22	2.12−2.24	2.12−2.22	2.10−2.23
18	16'-CH_3[c]	[d]	0.99	0.99	0.99	0.99	0.99
19	20-CH_3	0.87	0.87	0.87	0.86	0.87	0.86
20	RMS[f]	0.0000	0.0035	0.0050	0.0120	0.0130	0.0727

[a] NMR spectrum recorded at 600 MHz in $CDCl_3$; chemical shifts taken from Gloer et al. Electronic data are not available (personal communication J. B. Gloer by E-mail, 24.10.2016).
[b] NMR spectra recorded at 600 MHz in $CDCl_3$; compound accessed by total synthesis as a 14E/14Z = 94:6 mixture of isomers.
[c] Table presents assignments corrected in accordance to Figure 30. Based on extensive $^{1}H^{1}H$ COSY and $^{1}H^{13}C$ HSQC studies of the synthetic natural product as well as synthetic intermediates downstream to (+)-curvicollide, we propose a mistakenly switched assignment of 5-CH and 15-CH as well as a misassignment of 16'-CH_3, 10'-CH_3, and 12'-CH_3 by Gloer et al.
[d] Excluded because of ambiguities in the original data set: There is no signal at 0.90 ppm in the original spectrum of (–)-curvicollide (see Figure SI-1) [e] Missing data. No chemical shift is reported for 16-CH in original data. [f] root mean square.

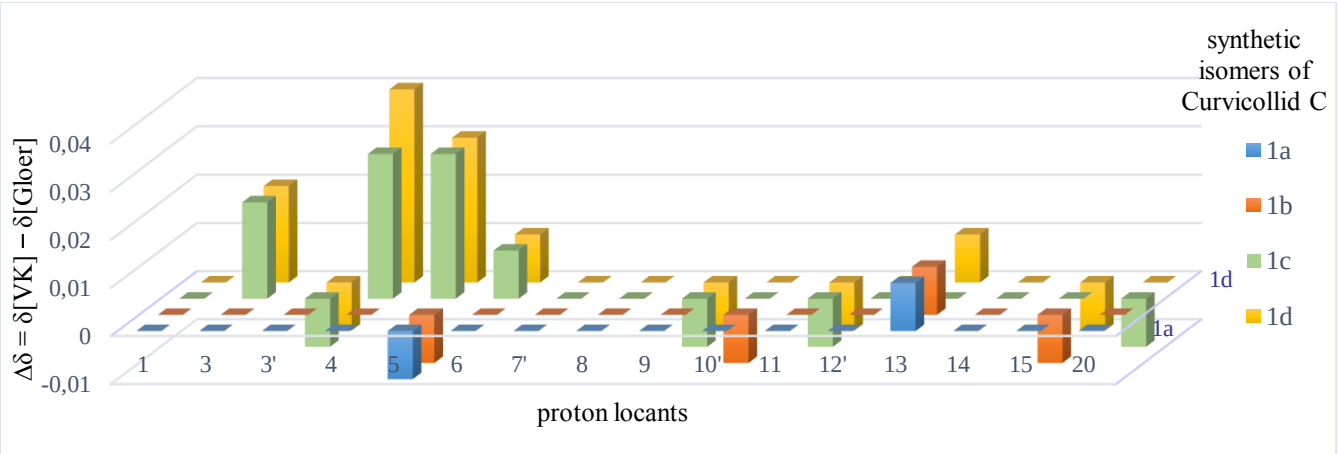
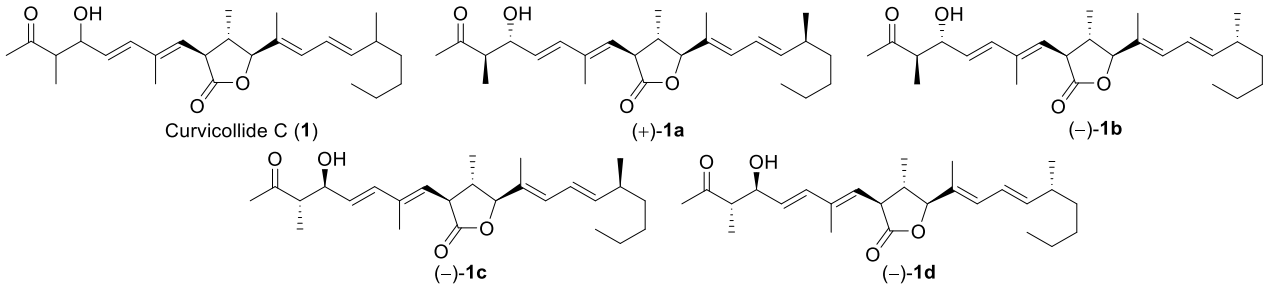


Figure 32 Graphical representation of ^{1}H NMR shift differences for the synthetic isomers with respect to natural Curvicollide C

Table 7 Comparison of ^{13}C NMR data. Chemical shifts (δ) reported in ppm relative to $CDCl_3$ at 76.99 ppm.



Entry		curvicollide C[a]	(3*R*,4*R*,16*S*)-**1c**[b]	(3*R*,4*R*,16*R*)-**1c**[b]	(3*S*,4*S*,16*S*)-**1c**[b]	(3*S*,4*S*,16*R*)-**1c**[b]
1	1-CH_3	29.8 or 29.81	29.8	29.8	30.0	30.0
2	2-C	213.2	213.2	213.3	212.9	212.8
3	3-CH	52.3	52.3	52.3	52.2	52.2
4	3'-CH_3	13.9	14.0	14.0	13.8	13.8
5	4-CH	75.1	75.1	75.2	74.7	74.7
6	5-CH	128.9	128.9	128.9	129.0	129.0
7	6-CH	136.4	136.5	136.5	135.9	135.9
8	7-C	128.8	128.8	128.8	128.8	128.8
9	7'-CH_3	13.2	13.2	13.2	13.3	13.3
10	8-CH	126.1	126.2	126.2	126.0	126.0
11	9-CH	48.5	48.5	48.4	48.4	48.4
12	9'-C	176.3	176.3	176.3	176.2	176.1
13	10-CH	42.6	42.6	42.5	42.5	42.5
14	10'-CH_3	14.8	14.8	14.7	14.8	14.8
15	11-CH	90.7	90.7	90.7	90.6	90.6
16	12-C	138.4	138.4	138.4	138.4	138.4
17	12'-CH_3	11.4	11.5	11.4	11.5	11.4
18	13-CH	130.4	130.4	130.5	130.4	130.5
19	14-CH	123.3	123.3	123.3	123.3	123.3
20	15-CH	143.7	143.7	143.7	143.7	143.6
21	16-CH	37.1	37.1	37.1	37.1	37.1
22	16'-CH_3	20.4	20.4	20.4	20.4	20.4
23	17/18/19-CH_2	22.8	22.8	22.8	22.8	22.8
24	17/18/19-CH_2	29.8 or 29.81	29.5	29.5	29.5	29.5
25	17/18/19-CH_2	36.6	36.6	36.6	36.6	36.6
26	20-CH_3	14.1	14.1	14.2	14.1	14.0
27	RMS[c]	0.0000	0.0707	0.0855	0.1676	0.1808
28	RMS-corrected[d]	0.0000	0.0400	0.0632	0.1600	0.1744

[a] (75 MHz, $CDCl_3$), chemical shifts taken from Gloer et al. [b] (151 MHz, $CDCl_3$), compound accessed by total synthesis as a 14E/14Z = 94:6 mixture of isomers [c] root mean square [d] RMS-corrected was calculated omitting the signal at 29.8 ppm for 17/18/19-CH_2

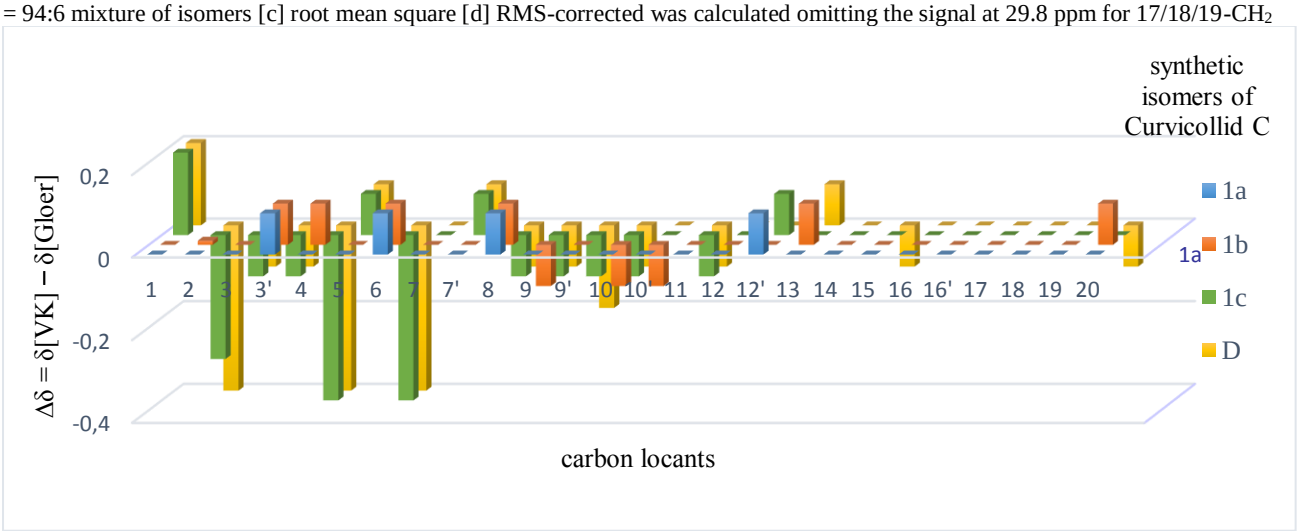


Figure 33 Graphical representation of ^{13}C NMR shift differences for the synthetic isomers with respect to natural Curvicollide C

The relative configuration of (−)-Curvicollide C was determined by comparison of ^{1}H NMR and ^{13}C NMR data with those measured for diastereomers (+)-**1a**, (–)-**1b**, (–)-**1c**, (–)-**1d**. Figure 30 outlines the different conclusions regarding the ^{1}H NMR peak assignment by Gloer et al. and those proposed by us. It should be mentioned that the assignment of ^{1}H and ^{13}C NMR data are based on 2D NMR experiments ($^{1}H^{1}H$ COSY and $^{1}H^{13}C$ HSQC) which were routinely applied in our case. This allowed us to correct Gloers assignment as shown in Figure 30. Therefore, the following discussion rests on our numbering system and our NMR peak assignment (VK). Figure 31 depicts the complete ^{1}H NMR spectra of Curvicollide C (**1**) in comparison to the four synthetic *anti*-aldol diastereomers prepared **1a**-**1d** in this thesis. Table 6 compiles chemical shifts for the protons of natural Curvicollide C and the synthetic diastereomers including also the *syn*-configured example *syn*-**1a**. Figure 32 depicts the chemical shift differences of all analyzable protons of the four *anti*-configured diastereomers with respect to natural Curvicollide C. Table 7 compiles the chemical shifts of ^{13}C NMR signals for natural Curvicollide C (**1**) and the four synthetic *anti*-configured diastereomers **1a**-**1d**, while Figure 33 again depicts the chemical shift differences for the the respective ^{13}C NMR signals. Summarized, these data form the basis of our structural assignment with respect to the relative configuration of Curvicollide C.

In the following, the rational for our assignment is outlined in detail. Gloer had already conjectured that the Curvicollides A−C most likely bear an *anti*-configuration in the aldol-part.[3] The evidence was however estimated as subcritical to claim this configuration as proven. A systematic study of NMR data of *syn*- and *anti*-aldols later revealed that the chemical shifts for the carbinol proton of anti-aldols is always observed upfield compared to the *syn*-diastereomers.[213] The difference between chemical shifts of the carbinol protons in such pairs ranges between $\Delta\delta^{syn\ anti}$= 0.049−0.236 ppm. The authors propose the presence of a half chair conformation in aldol moieties due to an intramolecular hydrogen bond between the β-hydroxy and the carbonyl group.[214] The shielding effects have been interpreted to result from this conformational fixation.

While the set of compounds in this study did not include stuctures bearing carbon-carbon double bonds in the allylic position, the enantiomeric anti aldols (+)-**58** and (–)-**58**, as well as *syn*-aldol (–)-**129,** which we synthesized for the cross-metathesis, do. We thus consider our Western fragments as NMR models of the closest structural relationship with respect to the Curvicollides. Again, the carbinol protons (4-CH) of *anti*-aldol **58** is found with a difference of $\Delta\delta^{syn\ anti}$= 0.28 ppm upfield from the *syn*-counterpart (–)-**129**, while all other signals exhibit smaller differences. Based on this finding, it became clear to us that for the purpose of structural elucidation of Curvicollides, only the *anti*-aldols qualify as synthetic entries. Nevertheless, we also performed the cross-metathesis with *syn*-aldol (–)-**129**, just to confirm that the general trend is not broken at the level of diastereomers of the natural product.

Table 6 (comparison of ^{1}H data) compiles the chemical shifts for Curvicollide C and the synthetic diastereomers. All data were referenced to δ = 7.2328 ppm of the chloroform signal. We included only those signals which allowed a clearcut determination of shifts due to sufficient signal separation (no overlap). We thus omitted protons 10-CH, 16-CH, 17-CH_2, 18-CH_2, 19-CH_2 in the comparison. Table 6 confirms that the natural product contains an *anti*-aldol moiety, as the above findings are also evident when comparing the natural product with a *syn*-configurated diastereomer. As it becomes obvious from Figure 31, the differences between the four possible anti-diastereomers and the natural product are much less pronounced. We nevertheless were able to assign the relative configuration of the natural product based on three criteria: (1) minimal difference of ^{1}H-NMR shifts (Table 6) (2) minimal difference of ^{13}C-NMR shifts (Table 7) (3) maximal similarity of the signal appearance for 5-CH and 15-CH, which combine to form a very characteristic pattern, which can be taken as a visual fingerprint (Figure 34). As a metric for the average shift difference we also computed the root mean square (RMS) according to the equation:

$$RMS = \sqrt{\frac{\sum_{i=1}^{n}\left(\delta_{i,isolated} - \delta_{i,synthetic}\right)^{2}}{n}}$$

The RMS differences between the *anti*-isomers **1a**-**1d** are almost marginal when compared to RMS of the representant *syn*-**1a** for the *syn*-isomers in the ^{1}H NMR data. The RMS results clearly indicate that the influences on the chemical shifts are more pronounced for the correct versus incorrect *anti*-configuration in the Western part, than for the correct (16*R*) versus incorrect (16*S*) configuration in the Eastern part.

[213] Kalaitzakis, D.; Smonou, I. *J. Org. Chem.* **2008**, *73*, 3919–3921.

[214] Interestingly the crystal structure of anti aldol (–)-**125** does not show such an intramolecular hydrogen bond between the β-hydroxy and the carbonyl group. Instead, a conformation is adopted in which the CH bond of the carbinol proton lays in the plane of the double bond.

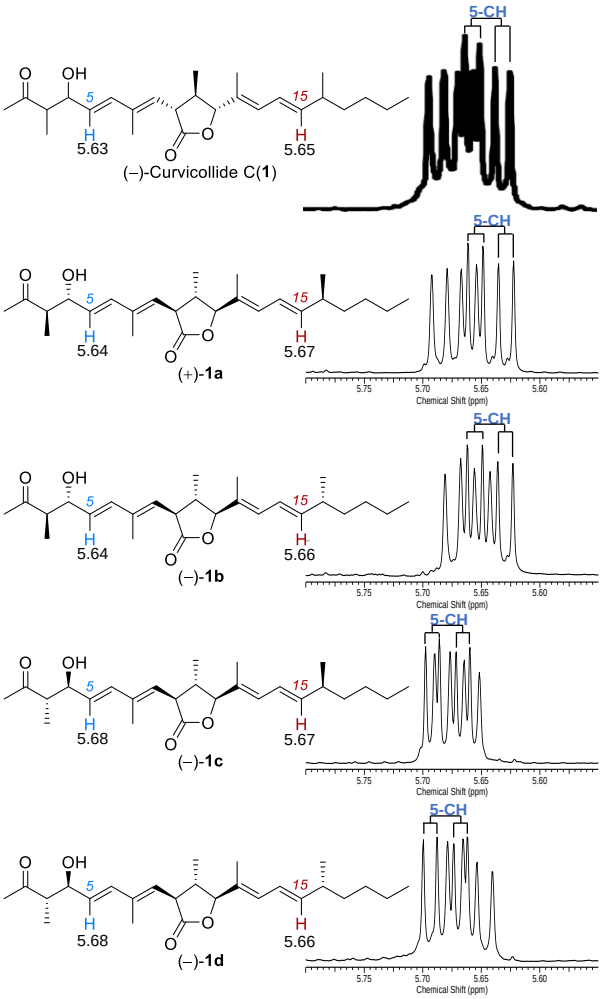
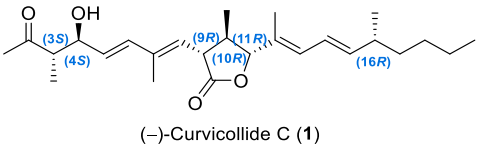


Figure 34 Comparison of characteristic patterns of the overlapping ^{1}H NMR signals of the vinylic protons 5-CH (dd) and 15-CH (dd) of natural Curvicollide C and the synthetic diastereomers at 600 MHz in $CDCl_3$. ^{1}H NMR spectrum of **1** was reproduced from the Supporting Infortmation of ref. 3. δ in ppm referenced to $CHCl_3$ at 7.239 ppm.

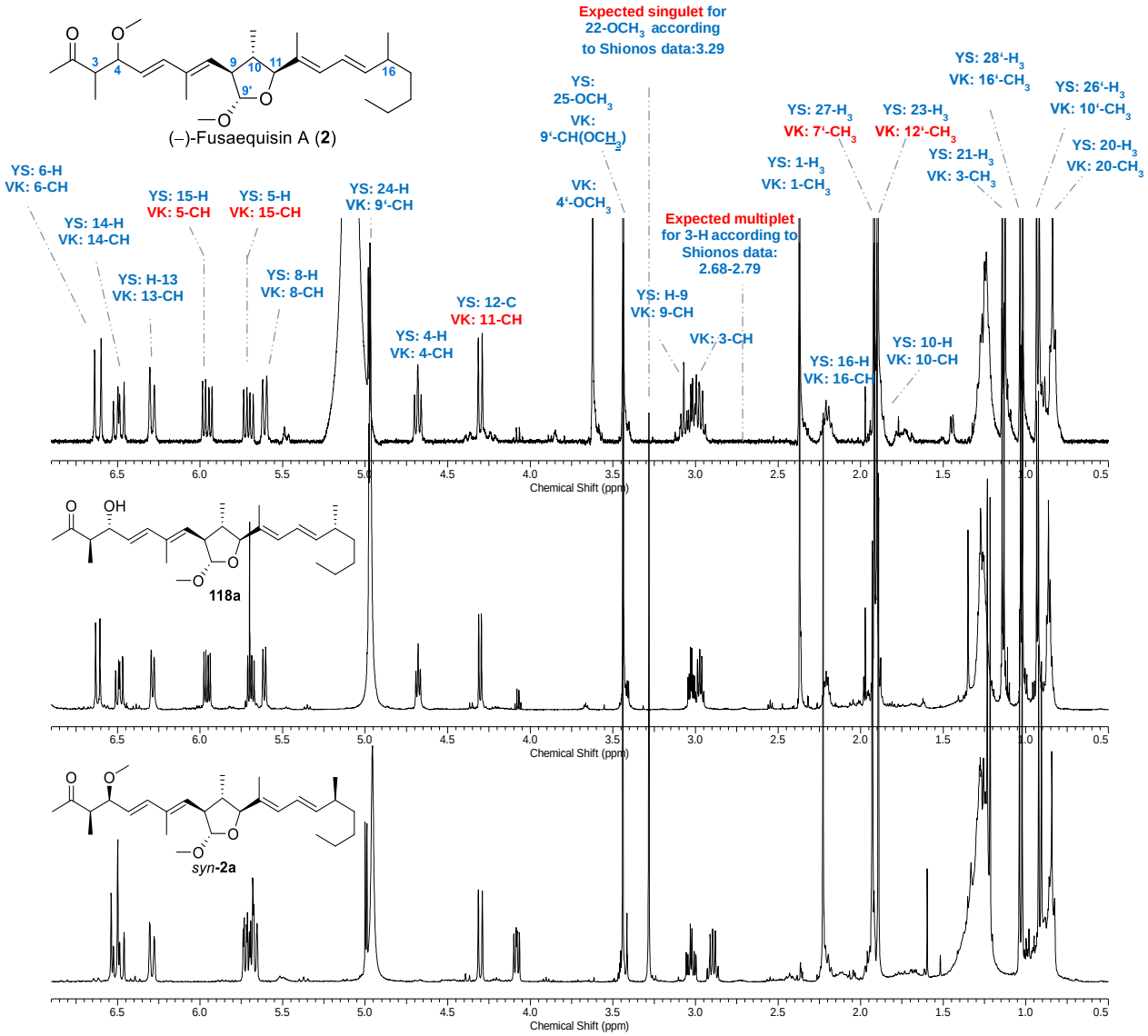
For the case of ^{13}C NMR data (Table **7**) the RMS values contain a significant "offset" caused by the influence of the signal at δ = 29.8 ppm for 17/18/19-CH_2 of the natural product, which compares to δ = 29.5 ppm in *all* synthetic diastereomers. If one omits this contribution, the resulting corrected RMS values indicate the preference for the (3*R*,4*R*,16*S*) diastereomer even more clearly (Table **7**). Finally, the absolute configuration of natural (–)-Curvicollide C (**1**), $[\alpha]_D$ –13 (c 0.11, CH_2Cl_2) was assigned by comparing the sign of the optical rotation with the synthetic (+)-**1a**, $[\alpha]_D^{20}$ +6.1 (c 0.37, CH_2Cl_2). At this point, we relate the difference in the reported $[\alpha]_D$ value for natural (–)-**1** and synthetic (+)-**1a** to the contamination by about 5% of the 14(*Z*)-configured double bond isomer of synthetic (+)-**1a**. In summary, a confident assignment of natural (–)-Curvicollide C became possible due to the successful synthesis of a complete set of four anti-diastereomers in spite of their minute spectroscopic differences. Natural (–)-Curvicollide C as the enantiomer of the synthetic product (+)-**1a** bears the following configuration: (3*S*,4*S*,9*R*,10*R*,11*R*,16*R*) (Figure 35).



(–)-Curvicollide C (**1**)

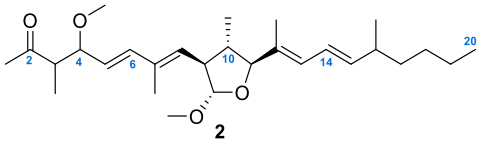
Figure 35 Proposed relative and absolute configuration of (–)-Fusaequisin A based on the conjectures derived from NMR spectroscopic data.

4.2 Towards structural elucidation of Fusaequisin A: First insights via comparison with synthetic products.



Firgure 36 Comparison of ^{1}H NMR spectra of natural Fusaequisin A (electronic version provided by Shiono, 400 MHz) and synthetic isomers *syn*-**2a** (400 MHz) and **118a** (600 MHz) in pyridine-d_5 (referenced to most downfield shifted signal of pyridine at δ = 8.74 ppm).

Table 8 Comparison of selected ^{1}H NMR data. Chemical Shifts (δ) reported in ppm relative to pyridine-d_5 at 8.740 ppm (for the most downfield shifted reference signal).



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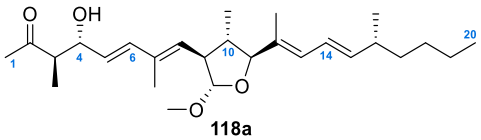
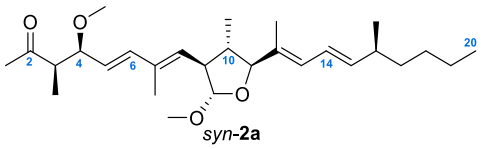


118a



syn-**2a**

Entry		Fusaequisin A (**2**)[a]	Fusaequisin A(**2**)[b]	**118a**[c]	*syn*-**2a**[d]
1	1-CH_3	2.33 (s)	2.37 (s)	2.37 (s)	2.23 (s)
2	2-C				
3	3-CH	2.68-2.79	2.98 (dq, 7.7, 7.0)	2.97 (dq, 8.2, 7.0)	2.90 (qd, 7.0, 5.4)
4	3'-CH_3	1.09 (d, 7.1)	1.13 (d, 7.0)	1.14 (d, 7.3)	1.22 (d, 7.0)
5	4-CH	4.67 (t, 8.1)	4.68 (t, 7.7)	4.68 (dd, *J* = 8.2, 7.3)	4.08 (dd, 7.8, 5.4)
6	4'-OCH_3	3.29 (s)	3.62 (s)		3.28 (s)
7	5-CH	5.67 (dd, 15.0, 8.1)	5.96 (dd, 15.7, 7.7)	5.96 (dd, 15.8, 7.3)	5.70 (dd, 15.8, 7.8)
8	6-CH	6.58 (d, 15.0)	6.62 (15.7)	6.62 (d, 15.8)	6.52 (d, 15.8)
9	7-C				
10	7'-CH_3	1.88 (d, 1.2)	1.90 (s)	1.90 (s)	1.89 (s)
11	8-CH	5.57 (d, 9.7)	5.61 (d, 9.8)	5.61 (d, 9.9)	5.67 (d, 10.1)
12	9-CH	3.00-3.05	3.02 (ddd, 9.8, 9.5, 4.1)	3.03 (ddd, 9.9, 9.7, 4.0)	3.03 (ddd, 10.1, 9.5, 4.2)
13	9'-CH	4.94 (d, 4.1)	4.98 (d, 4.1)	4.97 (d, 4.2)	4.99 (d, 4.2)
14	9'-CH($O\underline{CH_3}$)	3.40 (s)	3.44 (s)	3.44 (s)	3.44 (s)
15	10-CH	1.88-1.93	1.84-1.95	1.88–1.93 (m)	1.87-1.99
16	10'-CH_3	0.89 (d, 6.6)	0.93 (d, 6.6)	0.93 (d, 6.6)	0.91 (d, 6.8)
17	11-CH		4.30 (d, 9.8)	4.30 (d, 9.9)	4.30 (d, 9.3)
18	12-C	4.27 (d, 11.0)			
19	12'-CH_3	1.85 (s)	1.92 (s)	1.92 (s)	1.93 (s)
20	13-CH	6.25 (d, 11.0)	6.29 (d, 10.8)	6.29 (d, 10.6)	6.29 (d, 10.8)
21	14-CH	6.46 (dd, 15.0, 11.0)	6.49 (dd, 15.1, 10.8)	6.49 (dd, 15.0, 10.6)	6.49 (dd, 15.2, 10.8)
22	15-CH	5.92 (dd, 15.0, 8.0)	5.71, (dd, 15.1, 7.8)	5.69 (dd, 15.0, 8.1)	5.71 (dd, 15.2, 8.1)
23	16-CH	2.17-2.23	2.15-2.26	2.17–2.25 (m)	2.16-2.26
24	16'-CH_3	0.99 (d, 6.6)	1.03 (d, 6.6)	1.02 (d, 7.0)	1.03 (d, 6.4)
25	17/18/19-CH_2	1.21-1.26	1.16-1.35	1.21–1.32 (m	1.19-1.39
26	17/18/19-CH_2	1.21-1.26	1.16-1.35	1.21–1.32 (m	1.19-1.39
27	17/18/19-CH_2	1.21-1.26	1.16-1.35	1.21–1.32 (m	1.19-1.39
28	20-CH_3	0.81 (t, 7.1)	0.84 (dd, 6.7)	0.86 (dd, 7.0)	0.84 (dd, 6.8)

[a] NMR spectrum recorded at 400 MHz in pyridine-d_5; chemical shifts taken from Shiono et al. [b] NMR spectrum recorded at 400 MHz in pyridine-d_5, our own reevaluation based on (FID) file from Shiono; assignments corrected in accordance to Figure 36 [c] NMR spectrum recorded at 600 MHz in pyridine-d_5; compound accessed by synthesis as a 14E/14Z = 92:8 mixture of double bond isomers. [d] NMR spectrum recorded at 400 MHz in pyridine-d_5; compound accessed by total synthesis as a 14E/14Z = 91:9 mixture isomers.

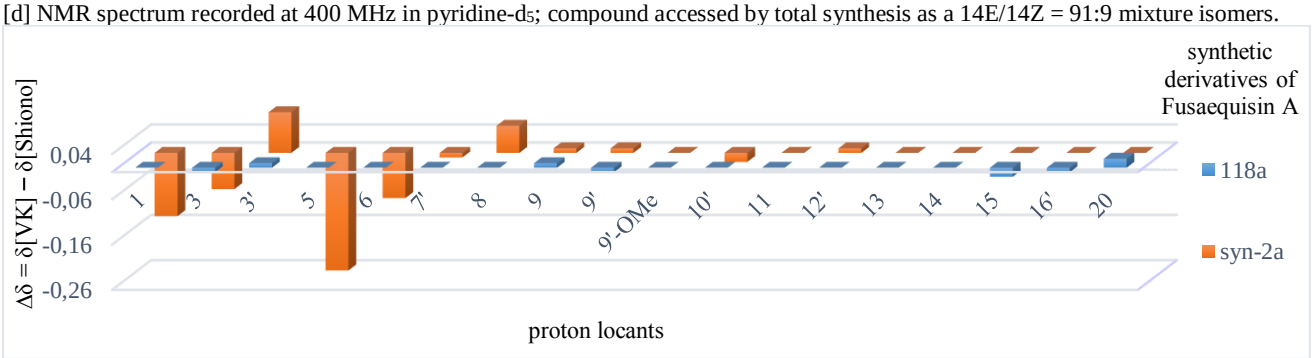
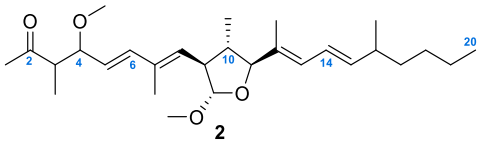
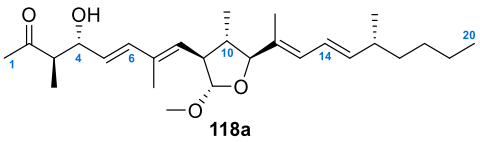


Figure 37 Graphical representation of selected ^{1}H NMR shift differences for the synthetic derivatives with respect to revised data of Fusaequisin A. Proton 4-CH was excluded due to the high value of Δδ = 0.6 for *syn*-**2a.**

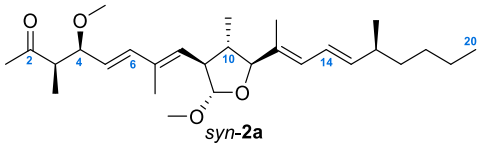
Table 9 Comparison of ^{13}C NMR data. Chemical shifts (δ) reported in ppm relative to pyridine-d_5 at 150.350 ppm (for the most down-field shifted reference signal)..



2



118a



syn-**2a**

Entry		Fusaequisin A (**2**)[a]	Fusaequisin A (**2**)[b]	**118a**	*syn*-**2a**[b]
1	1-CH_3	30.0	30.4	30.5	30.4
2	2-C	211.6	212.1	212.0	210.0
3	3-CH	53.7	54.1	54.2	52.5
4	3'-CH_3	14.2	14.5	14.1	12.4
5	4-CH	75.4	75.8	75.9	84.1
6	4'-OCH_3	49.6	50.0		56.9
7	5-CH	128.8	129.2	131.0	126.6
8	6-CH	136.1	136.6	136.6	138.9
9	7-C	136.0	136.5	133.8/136.5	136.3
10	7'-CH_3	13.2	13.5	13.7	13.6
11	8-CH	133.0	133.8	132.6	133.3
12	9-CH	54.2	54.6	54.7	54.7
13	9'-CH	110.1	110.5	110.6	110.5
14	9'-CH($O\underline{CH_3}$)	55.6	56.0	56.1	56.1
15	10-CH	45.3	45.6	45.7	45.6
16	10'-CH_3	13.6	14.0	14.7/14.8	14.8
17	11-CH	90.5	90.9	91.0	91.0
18	12-C	132.0	132.5	133.8/136.5	133.7
19	12'-CH_3	11.9	12.2	12.3	12.3
20	13-CH	130.5	131.0	129.3	129.3
21	14-CH	124.7	125.1	125.2	125.1
22	15-CH	141.9	142.4	142.4	142.4
23	16-CH	37.4	37.7	37.9	37.9
24	16'-CH_3	20.8	21.2	21.3	21.3
25	17/18/19-CH_2	22.8	23.4	23.5	23.5
26	17/18/19-CH_2	29.6	30.2	30.3	30.3
27	17/18/19-CH_2	36.7	37.3	37.4	37.4
28	20-CH_3	14.3	14.7	14.7/14.8	14.7

[a] NMR spectrum recorded at 100 MHz in pyridine-d_5, chemical shifts taken from. Gloer et al. [b] NMR spectrum recorded at 100 MHz in pyridine-d_5, our own reevaluation based on raw Free Induction Decay (FID) data from Shiono. [c] NMR spectrum recorded at 126 MHz in pyridine-d_5; compound accessed by synthesis as a 14E/14Z = 92:8 mixture of double bond isomers. [d] NMR spectrum recorded at 151 MHz in pyridine-d_5; compound accessed by total synthesis as a 14E/14Z = 91:9 mixture of double bond isomers.

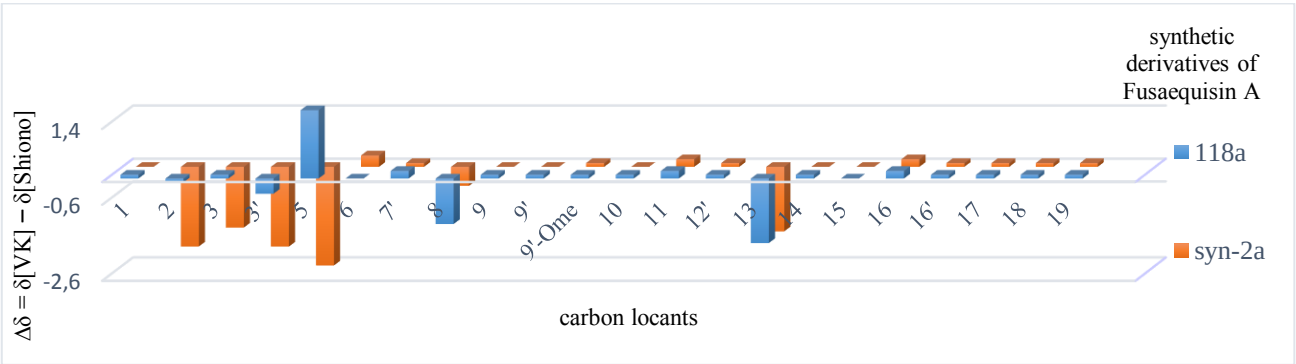


Figure 33 Graphical representation of selected ^{13}C NMR shift differences for the synthetic derivatives with respect to revised data of Fusaequisin A. Carbon 4-CH was excluded due to the high value of Δδ = 8.3 for *syn*-**2a.**

In contrast to the case of Curvicollide C, where at least an educated guess was given for the relative configuration of the aldol part, Fusaequisin A was reported without any conjectures concerning its stereochemistry. There are two further reasons why the structural elucidation of Fusaequisin A is expected to be even more demanding than in the case of Curvicollide. First of all, to the best of our knowledge and in contrast to Curvicollide C, there is no systematic study on the dependence of NMR signals from the configuration in the aldol part, which is *O*-methylated here. Secondly, the NMR characterization of Fusaequisin A was undertaken using pyridine-d_5 as a rather uncommon NMR solvent. These considerations taken together call for the need to include at least one *syn*-configured diastereomer in the *O*-methylated aldol part.

Table 8 compiles the ^{1}H NMR data of Fusaequisin A (**2**) as reported by Shiono et al. in comparison to our own reevaluation based on raw Free Induction Decay (FID) data from Shiono,[215] our synthetic *anti*-configured diastereomer of *O*-4-Desmethylfusaequisin A (**118a**), as well as our synthetic *syn*-diastereomer of Fusaequisin A (*syn*-**2a**), all measured in pyridine-d_5. As in the case of Curvicollide C, we dare to reassign the NMR data with respect to the signals of 5-CH versus 15-CH, 7'-CH_3 versus 12'-CH_3, and furthermore 11-CH versus 12-C. The 4'-OCH_3 signal was reported at δ = 3.29 ppm, but is at δ = 3.62 ppm according to our interpretation based on Shiono's fid. All further comparisons thus relate to the reassigned NMR data of natural Fusaequisin A. Small differences in the chemical shifts between the reported and the reevaluated spectrum are attributed to a difference in referencing with respect to pyridine-d_5. In the reevaluated case, reference was always given to the most downfield shifted signal of pyridine at δ = 8.74 ppm. Small differences in the coupling constants are most likely due to software/user issues. Nevertheless, the FID processing of Fusaequisin A was performed equally to that of the synthetic products, allowing for a quantitative comparison here.

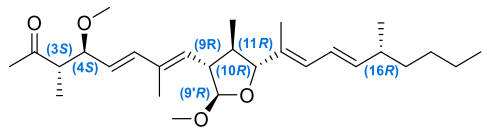
It becomes obvious from Table 8, as well as from the ^{1}H NMR spectra depicted in Figure 35, that a *syn*-configuration in the methylated aldol part causes a strong deviation of spectral data. Indeed, the deviation is so pronounced that *syn*-isomers can be excluded for the further stereochemical assignment of the natural product. One particularly important difference between the aldol part of Curvicollide C and its *O*-methylated sibling in Fusequisin A is revealed when comparing the chemical shifts of 4-CH in *syn*- and *anti*-products: The proton for the natural *anti*-aldol methyl ether is observed downfield compared to the synthetic *syn*-isomer, just the opposite to our results for non-methylated aldols. This shift reversal may be due to the fact that an *O*-methylated aldol does not necessarily adopt the conformation which was assumed for the free aldol-part. Only the free aldol can be rigidized by an intramolecular hydrogen bond between the hydroxyl-hydrogen and the keto carbonyl group. As proposed in the study by Smonou et al. it is however completely unexpected that the spectral differences between natural Fusaequisin A (**2**) and the synthetic *anti*-diastereomer of Desmethylfusaequisin A **118a** are almost negligible:[216] The shift differences never exceed δ = 0.02 ppm, and are even below this value for most signals.

Taking a look at the signal with the largest shift difference, we find this signal originates from proton 15-CH in the Eastern side chain which is not expected to sense the presence or absence of a methyl group at the aldol periphery of the Western side. We thus propose that the deviation at 15-CH (0.02 ppm) results from an inverse configuration at 16-CH as this has been observed as a general trend also in the Curvicollide series. This assumption is further supported by comparing ^{1}H NMR data of (16*R*)-**118a** and the additional synthetic isomer (16*S*)-**118b** (from cross-metathesis), both measured in $CDCl_3$. Indeed the (16*S*)-isomer is observed exactly 0.02 ppm downfield to the (16*R*)-isomer in this solvent. Under the assumption that solvent effects on the ordering of chemical shifts are negligible here, we dare to propose that the relative configuration of natural Fusaequisine A is identical to Curvicollide C, both, in the Eastern and the Western part. We also assume that the PKS-based biosynthesis of both natural products is closely related to each other.

Consequently, the absolute configuration of Fusaequisin A is expected to be analoguous to Curvicollide C. A tentative

[215] An electronic version of the untransformed ^{1}H and ^{13}C spectrum of natural Fusaequisin A was kindly provided by Shiono (22.02.2016).
[216] This unexpected finding may be due to a non hydrogen bonded conformation for the anti aldol, in contrast to Smonou's interpretation. Evidence for the absence of a hydrogen bond in the aldol moiety was found indeed in the crystal structure of (–)-**125** which may serve as a model compound here. This finding however does not exclude the existence of hydrogen bonds in *syn*-aldols.

assignment of Fusaequisin A is thus based on the following configuration: (3*S*,4*S*,9*R*,9'*R*,10*R*,11*R*,16*R*) (Figure 37).



(–)-Fusaequisin A (**2**)

Figure 37 Proposed relative and absolute configuration of (–)-Fusaequisin A based on the conjectures derived from NMR spectroscopic data and biosynthetic considerations.

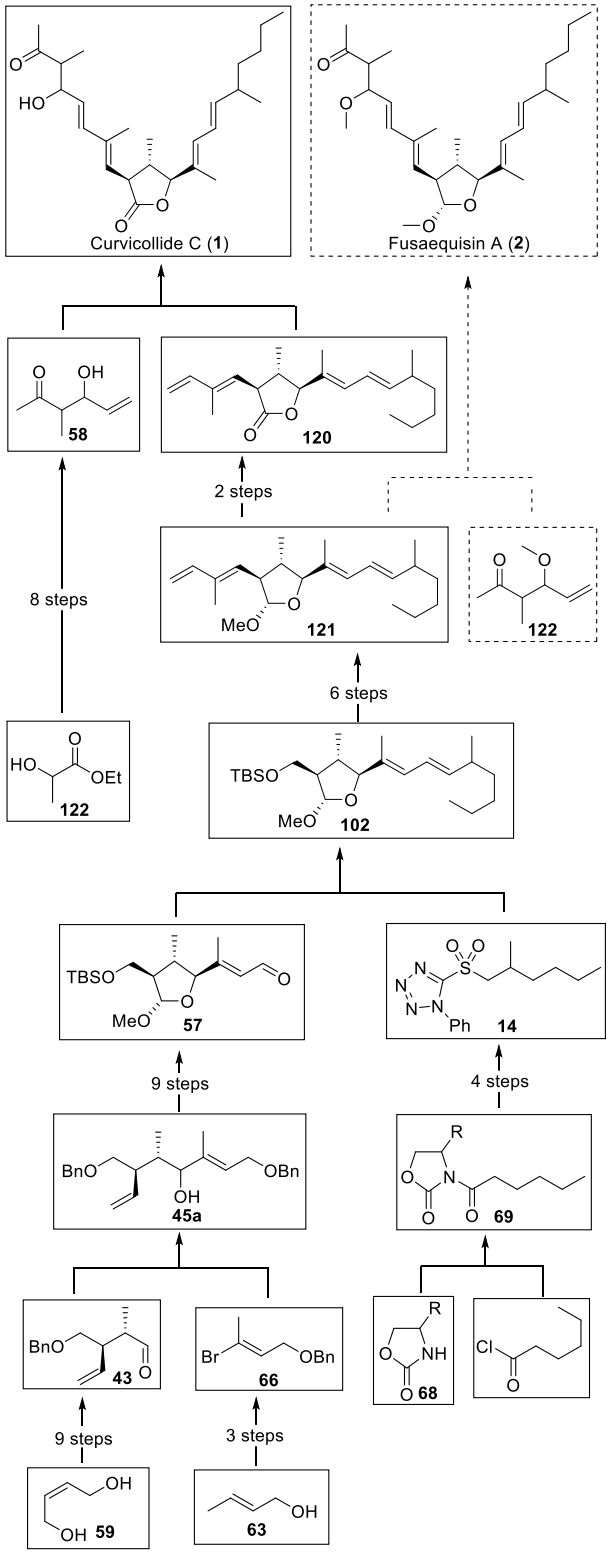
However, this prediction is to be understood as an educated guess only. "The truth lies in the flask" however. We are keen to learn it in future research.

Chapter 5 - Summary

Curvicollide C (**1**) and Fusaequisin A (**2**) are structurally related secondary metabolites of polyketide origin, isolated by Gloer et al. (2004) and Shiono et al. (2013) from fungi differing in their geographic locations, biological habitats, morphological characteristics and phylogenetic classification. The structure of both natural products could only be resolved with respect to the constitution and the relative configuration of the respective central heterocycle.

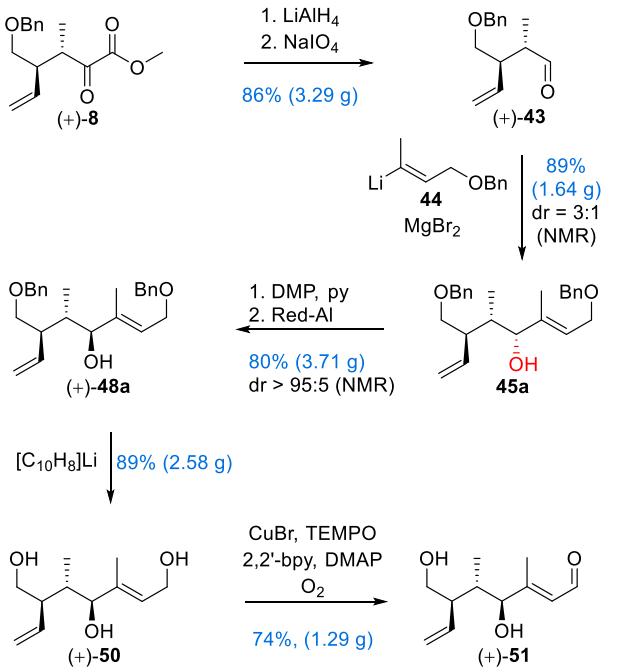
The present thesis describes the first total synthesis of both, (+)-Curvicollide C and a non-natural diastereomer of Fusaequisin A. In this Chapter, the synthetic pathways elaborated are presented in the order of their significance. The finally established synthetic route enabled the full structural assignment of Curvicollide C by means of its NMR spectroscopic comparison with a collection of four individually synthesized diastereomers, differing in the anti-aldol moiety in the Western side chain, as well as the isolated center of chirality in the Eastern side chain. A quantitative comparison of spectroscopic data, including ^{1}H and ^{13}C-NMR as well as a highly characteristic visually distinguishable pattern of signals for olefinic protons 5-CH/15-CH, enabled to determine the relative stereochemistry for all chirality centers involved. Together with optical rotation data it followed that the synthesis had led to the enantiomer of natural Curvicollide C, whose absolute configuration could be determined as (3*S*,4*S*,9*R*,10*R*,11*R*,16*R*). In the case of Fusaequisin A, first insights into the structural assignment were accomplished providing evidence for an *anti*-configuration in the Western part.

For the sake of structural elucidation, the synthetic design called for a high degree of modularity, whereas the targeting of both natural products required a convergent synthesis which is identical for both products up to a branching point at a rather late stage. This topology, based on initial convcergene and final branching, is shown Scheme 47, which depicts an overview of the synthetic plan. The concise route towards (+)-Curvicollide C (longest linear sequence of 22 steps from α-keto ester (+)-**8** with an overall yield of 2.7%) relies on an enantioselective central-to-lateral synthetic strategy employing a cross-metathesis and a Julia–Kocienski olefination as the key coupling steps.



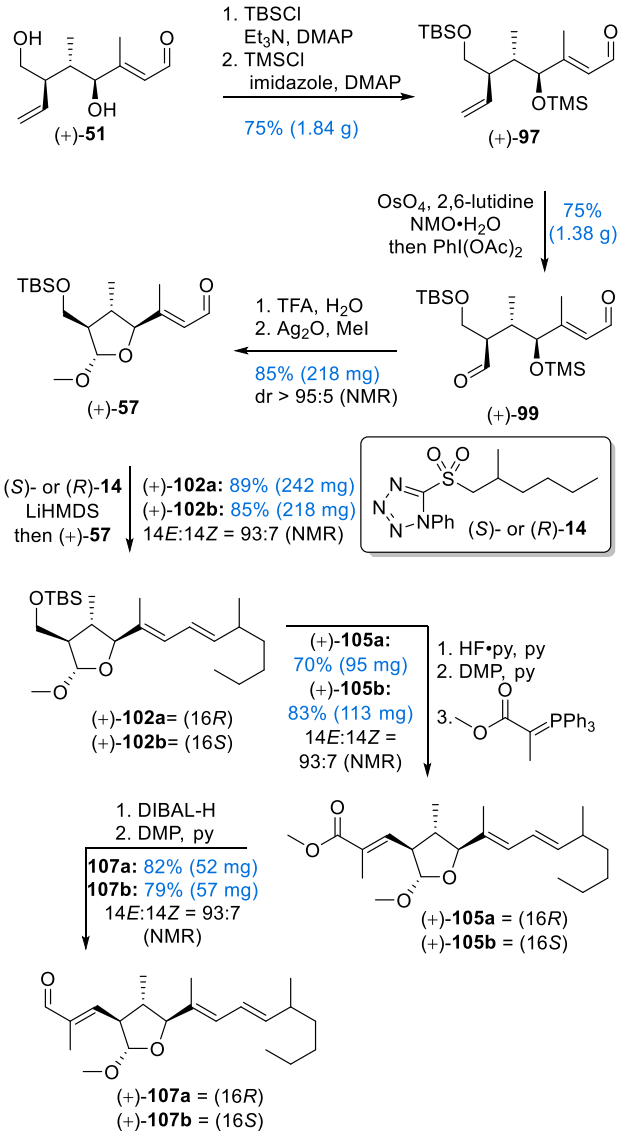
Scheme 47

The synthesis of the Central building block (+)-**57** (Scheme 48) commenced with $LiAlH_4$ reduction of the known α-keto ester (+)-**8** and subsequent oxidative cleavage to deliver the aldehyde (+)-**43**. Nucleophilic addition of the in situ generated vinyllithium species **44** afforded the alcohol **45a** mainly in the undesired (11*R*)-configuration**.** The proper (11*S*)-configuration was obtained after a corrective two step redox process yielding alcohol (+)-**48a**. Exhaustive benzyl deprotection of (+)-**48a** applying a large excess of lithium naphthalenide afforded the triol (+)-**50.**



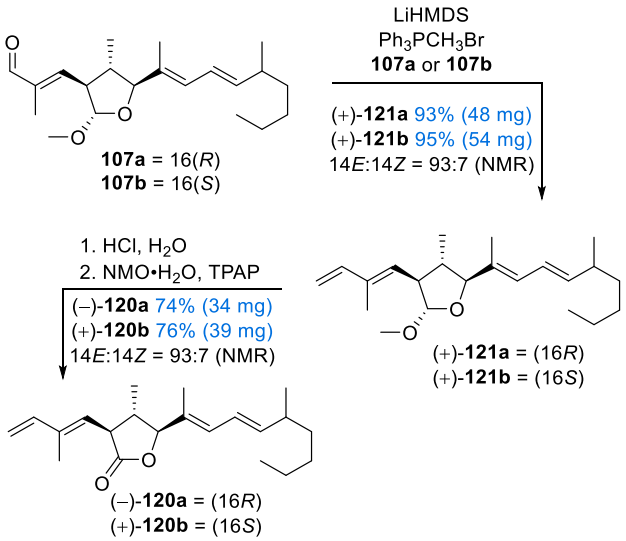
Scheme 48

Site-selective oxidization of the primary allylic alcohol resulted in the α,β-enal (+)-**51** which - due to its electron deficiency - enabled the selective oxidative cleavage of the terminal double bond. Further studies revealed the necessity to protect both hydroxyl groups for an unimpeded selective double bond cleavage (Scheme 49). Following protection of both hydroxyl groups, the dialdehyde (+)-**99** could be obtained by employing conditions developed by Nicolaou and co-workers. Selective removal of the TMS group of (+)-**99** and methylation of the resulting lactol delivered the methyl lactol ether (+)-**57**. Julia–Kocienski olefinations with either the (*R*)- or the (*S*)- configured sulfones **14** delivered dienes (+)-**102a** and (+)-**102b**, respectively. Based on the above dienes, two separate but parallel synthetic pathways were started to deliver two diastereomeric rows of products. This is also the reason why in the following all yields are listed twice. For each diastereomeric diene (+)-**102a** and (+)-**102b**, a five step transformation was carried out consisting of a desilylation step, oxidation to the corresponding aldehyde, Wittig-olefination using an ester-stabilized ylide, reduction of the ester to the corresponding alcohol and reoxidation to yield the α,β-unsaturated aldehyde **107a** and **107b**, respectively.



Scheme 49

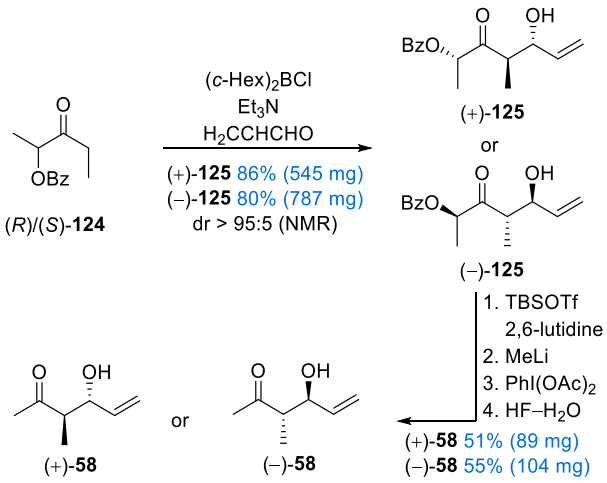
The above unsaturated aldehydes were converted via Wittig-methenylation into the corresponding tetraenes (+)-**121a** and (+)-**121b**, which served as the last common precursors for both, the Curvicollide and the Fusaequisine branch (Scheme 50). On the way to the Curvicollides the methyl lactol ethers (+)-**121a** and (+)-**121b** were converted into the corresponding lactones (–)-**120a** and (+)-**120b** by acetal hydrolysis and subsequent oxidation.



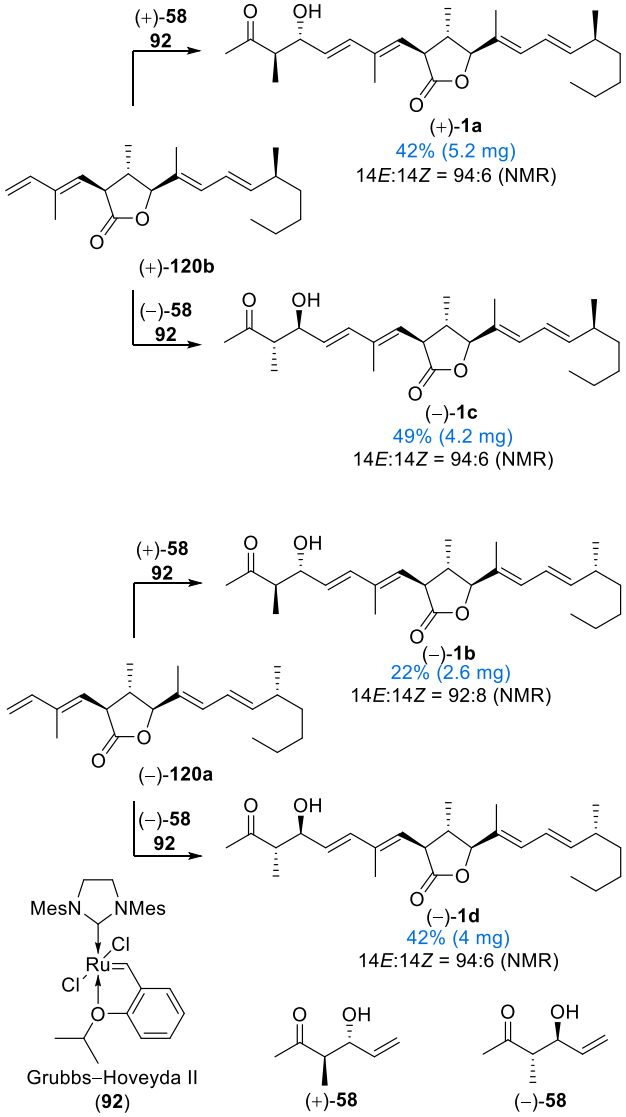
Scheme 50

The resulting lactones (–)-**120a** and (+)-**120b** served as further branching points to deliver the target set of four diastereomers of Curvicollide C via cross-metathesis reactions (Scheme 52).

Vinyl-containing aldols (+)-**58** and (–)-**58** as cross-metathesis partners were synthesized via Paterson's *anti*-aldol methodology employing acroleine in combination with the known ketones **124** and **124** (Scheme 51). The resulting *anti*-aldols (+)-**125** and (–)-**125** were subjected to a procedure consisting of TBS protection, exhaustive nucleophilic methylation, diol cleavage and TBS deprotection yielding (+)-**58** and (–)-**58** as required for cross-metathesis.

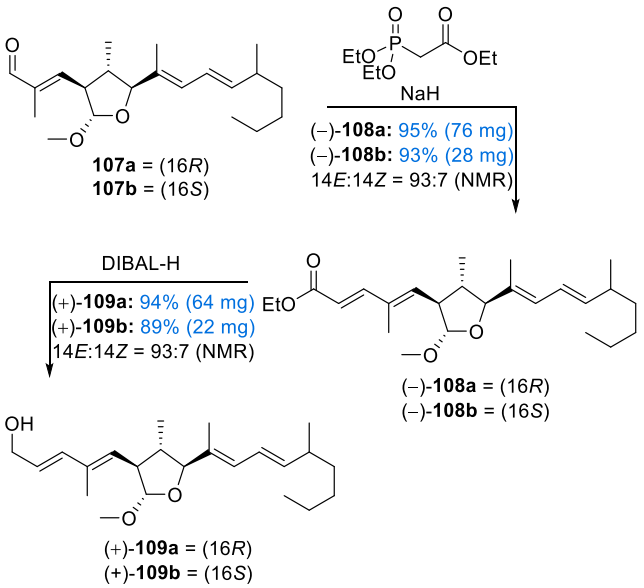


Scheme 51



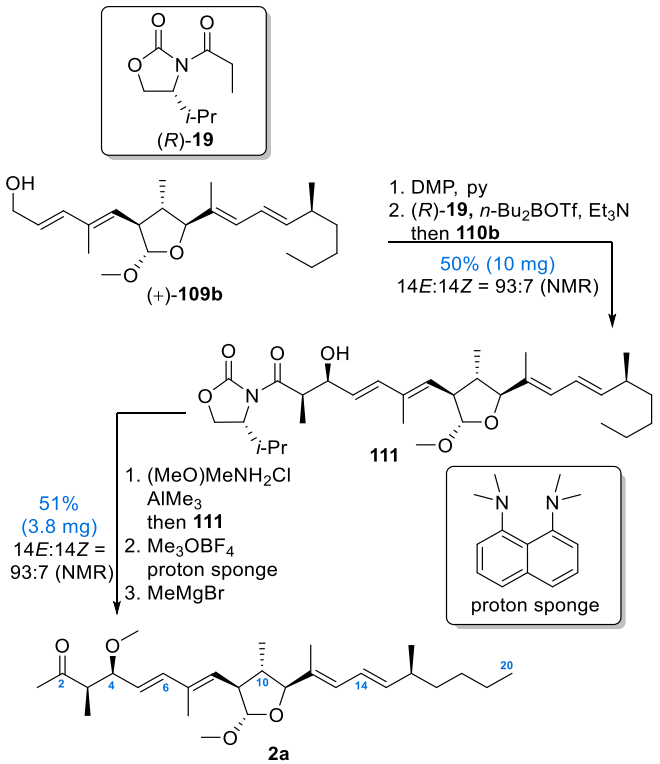
Scheme 52

In previously elaborated parallel pathways of this thesis, the above aldehydes **107a** and **107b** also served as starting materials for the stepwise construction of the respective Western side chain (Scheme 53). This methodology was based on HWE-olefination and reduction of the resulting α,β-γ,δ-unsaturated esters (–)-**108a** and (–)-**108b** to the corresponding alcohols (+)-**109a** and (+)-**109b**. The latter served as the starting points and storage materials for the synthesis and spectroscopic evaluation of *syn*- versus *anti*-aldol derivatives of Fusaequisin A.



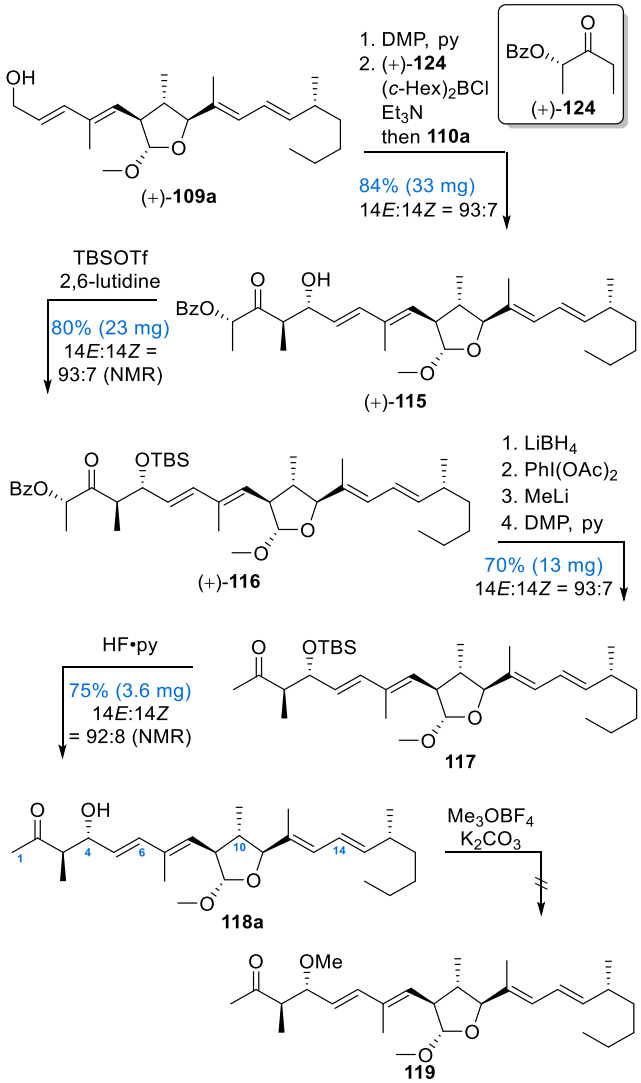
Scheme 53

In the *syn*-aldol series, Evans aldol chemistry was employed following the oxidation of alcohol (+)-**109b** to the respective aldehyde (Scheme 54). The *syn*-aldol **111** was then transformed into the diastereomer *syn*-**2a** of Fusaequisin A (**2**) via Weinreb amidation, *O*-methylation with Meerwein salt in the presence of proton sponge, and final nucleophilic methylation employing MeMgBr as a Grignard reagent.



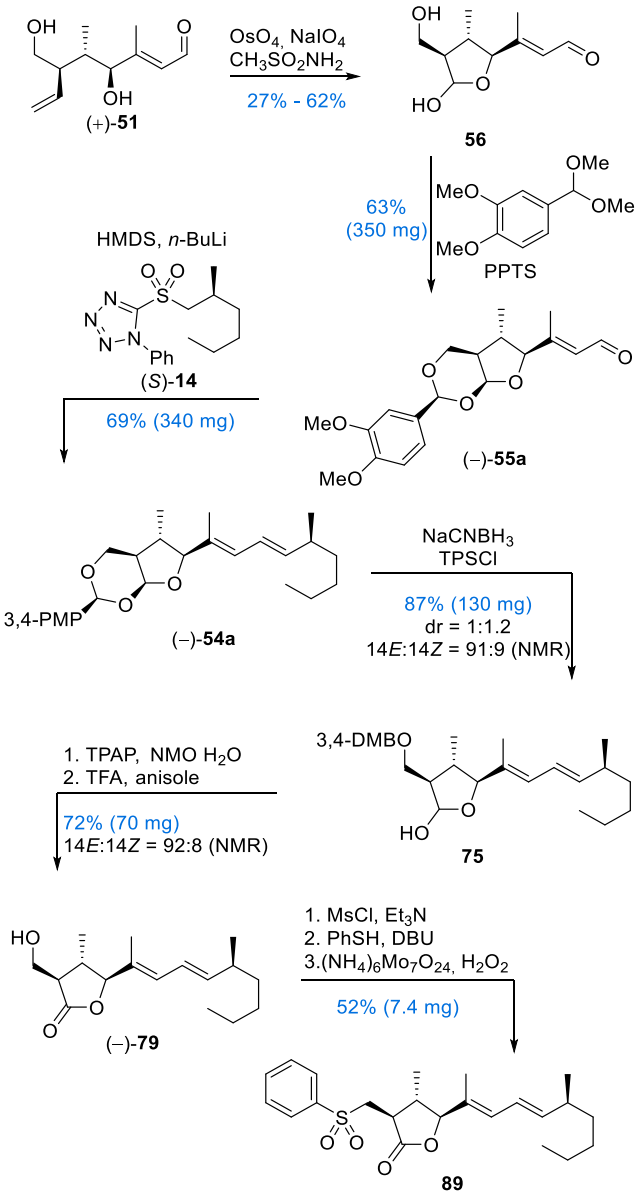
Scheme 54

In the *anti*-aldol series, the alcohol (+)-**109a** was again oxidized to the respective aldehyde which was then converted into aldol (+)-**115** employing Paterson *anti*-aldol methodology (Scheme 55). After TBS-protection, the silyl ether (+)-**116** was transformed into the methylketone **117** utilizing a procedure consisting of exhaustive reduction, diol cleavage, nucleophilic methylation and oxidation. The resulting silyl ether was deprotected to yield an *anti*-configured diastereomer of *O*-Desmethylfusaequisin A **118a**, which exhibited a high degree of NMR-spectroscopic similarity when compared to the data of the natural product. Preliminary attempts to introduce the methyl ether did not succeed due to a retro-aldol reaction occurring under the reaction conditions.



Scheme 55

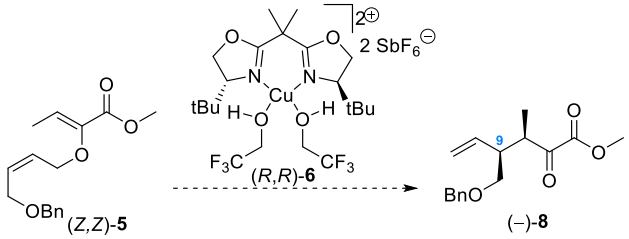
The thesis furthermore describes synthetic approaches aiming to explore the reductive ring opening of electron rich benzyliden acetals in the presence of Lewis acids for the purpose of selective transformations of central fragments (Scheme 56). Here, the vinyl group of open-chain diol (+)-**51** was oxidatively cleaved to result in an intermediate γ-hydroxyaldehyde, which spontaneously cyclized to yield an α-hydroxymethyl lactol **56** as a 1:1-mixture of anomers. The yields were however found to vary substantially. Transacetalization with the dimethylacetal of 3,4-dimethoxybenzaldehyde allowed to convert this mixture into the 3,4-DMP-acetal (–)-**55b,** highly enriched in diastereoselectivity, whose Julia–Kocienski olefination proceeded easily. Among numerous attempts to achieve a selective transformation of (–)-**54b**, its reductive acetal opening using $NaCNBH_3$ in the presence of TPSCl proved useful, as it resulted in lactol **75** selectively. The latter had to be protected in order to allow the construction of the Western side chain after removal of the 3,4-DMB ether. While this protection could be performed successfully using a number of reagents, only the lactone (+)-**77** as a latent form of protection proved to be compatible with the conditions required for 3,4-DMB removal. The resulting α-hydroxymethyl lactone (–)-**79** was converted into sulfone **89** via a three-step sequence including mesylation, thioether formation and oxidation to the sulfone. Attempts to utilize the sulfone as a nucleophilic fragment in Julia–Lythgoe olefinations were not elaborated due to better alternatives previously described.



Scheme 56

Chapter 6 - Outlook

Based on the results of the structural assignment of Curvicollide C, it is obvious that future work should address the synthesis of the natural enantiomer. As the absolute configuration of the central building block is derived from the two chiral centers generated during CAGC rearrangement, one may restart the whole synthesis using the enantiomeric catalyst (*R*,*R*)-**6** (Scheme 57).



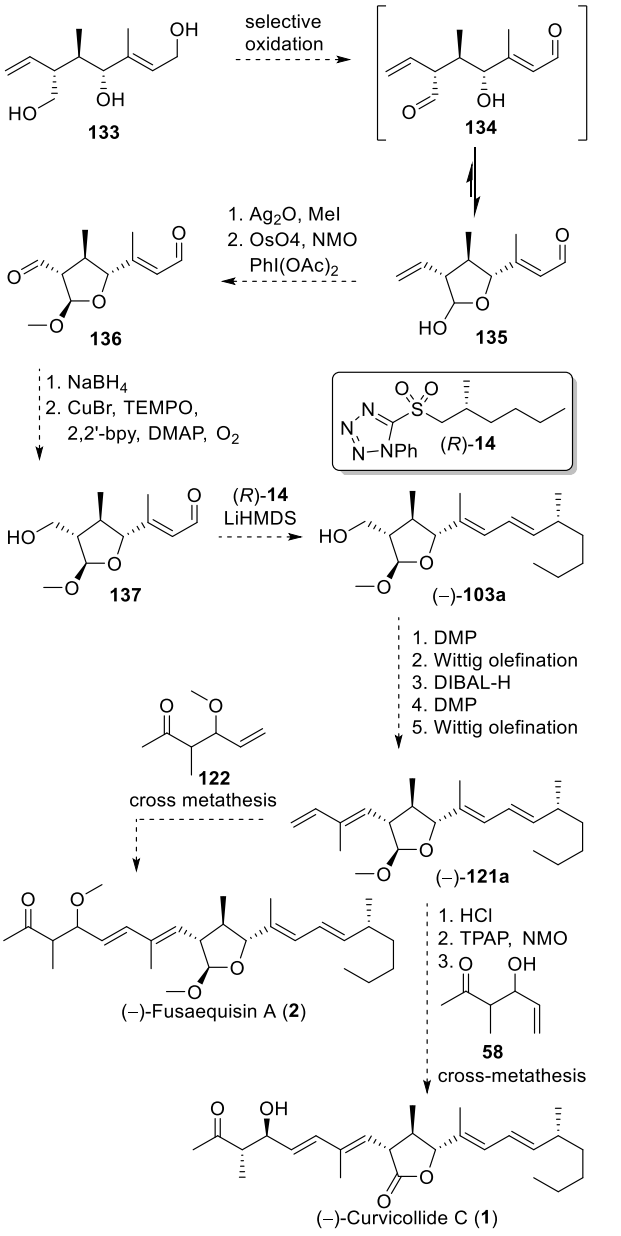
Scheme 57

As an alternative, one may consider to start from the diasteromeric α-keto ester **7a** obtained by application of the original catalyst. From the synthetic perspective, this α-keto ester resembles the required configuration for the central γ-lactone when considering its pseudo diastereotopic groups at C9. A slight variation of the central fragment's synthesis is expected to result in the proper relative and absolute configuration as needed for the natural products.

The synthetic plan commences with the triol **133** for which F. Quentin already explored a synthetic entry (Scheme 58). The next step will already decide whether the proposed route is feasible or not. A selective oxidation has to be found in which both, the oxidation of the primary allylic and homoallylic alcohol is kinetically favored over the oxidation of the secondary allylic alcohol. In this case, the secondary allylic alcohol in **133** is supposed to become trapped as the lactol **135**, thus diminishing its concentration via equilibrium. As a result, the selective oxidation is expected to run smoothly in the desired direction.

Product **135** contains an electron-rich as well as an electron-deficient double bond, of which the former is expected to be selectively cleavable after having protected the lactol as its methyl ether. Both transformations are expected to be performable in good yields as they have been established in this thesis with structurally similar substrates. Any further extension of product **136** needs to distinguish between the two aldehyde groups, which is most likely to be accomplished by a sequence of exhaustive reduction followed by a selective oxidation of the allylic alcohol. The resulting α,β-unsaturated aldehyde is supposed to react in a Julia–Kocienski olefination when applying at least two equivalents of the base. If for any reason the yields are unsatisfactory, there is still the option to protect the hydroxyl group in **137** before olefination and deprotection afterwards. All further steps towards Curvicollide C are identical to the ones elaborated in this thesis.

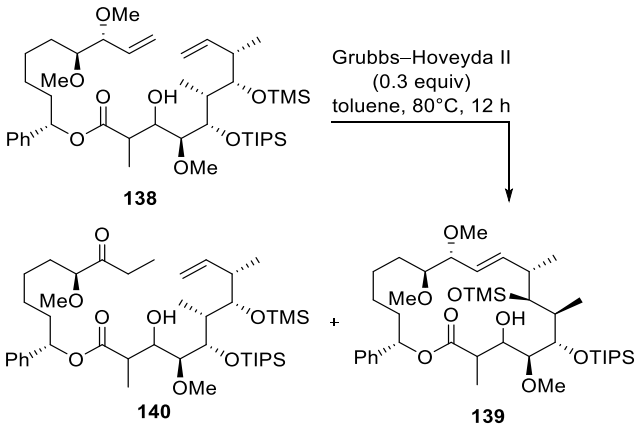
For the finalization of the total synthesis of the properly configured Fusaequisin A, three strategies may be taken into consideration. The first is based on a cross-metathesis employing the allylic methyl ether **122**. While an attempt in this thesis based on the employment of Grubbs II as catalyst did not result in the desired reaction, Grubbs–Hoveyda II could not be further explored due to limitations in time and materials.



Scheme 58

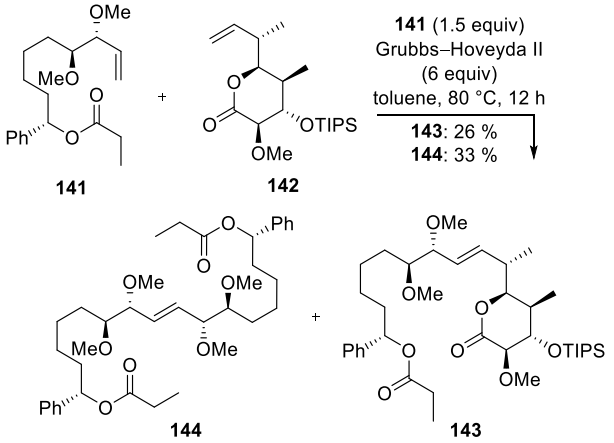
So far, the number of examples of cross-metathesis reactions employing an *O*-methylated allylic alcohol is limited.

One of these examples was published by Ciufolini et al. as part of a study toward the synthesis of Soraphen A.[217] A ring closing metathesis (RCM) of **138** was attempted which delivered the desired product **139** in moderate yields (30%) together with ketone **140** (43%) (Scheme 59). The origin of ketone **140** was considered to result from the isomerization of the *O*-methylated allylic alcohol into the corresponding methyl enol ether. Due to its intrinsic lability, the latter is cleaved to give an ethyl ketone during aqueous workup.



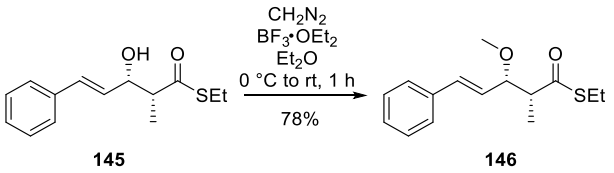
Scheme 59

Furthermore, a cross-metathesis reaction of **141** and **142** was investigated (Scheme 60). The desired product **143** was formed in moderate yields together with the homodimer of **144** indicating the general reactivity of *O*-methylated allylic alcohols in cross-metathesis. As progress in the field of metathesis reactions is fast, one may expect further improvements from the development of new catalysts and methodologies.



Scheme 60

The second strategy explores allylic alcohols instead of allyl methyl ethers in the cross-metathesis and subsequent introduction of the *O*-methyl group. While the cross-metathesis has been already demonstrated in this thesis to work with suitable substrates for the total synthesis of Fusaequisin A, methylation was found to be difficult. Future work thus may address the task of avoiding a retro-aldol reaction during *O*-methylation as well as β-elimination leading to a conjugated triene. Examples of successful *O*-methylations dealing with a similar situation, in which the substrates seem to be also prone to retro-aldol reactions or β-eliminations, were reported. Kobayashi and co-workers utilized diazomethane in the presence of the Lewis acid BF_3•OEt_2 allowing to avoid basic conditions (Scheme 61).[218] Further examples employing typical conditions for *O*-methylations were also elaborated (Scheme 62).[219,220]With respect to the biosynthesis of Fusaequisin A, it might also be interesting to search for *O*-methyl transferases which succeed in the desired transformation.



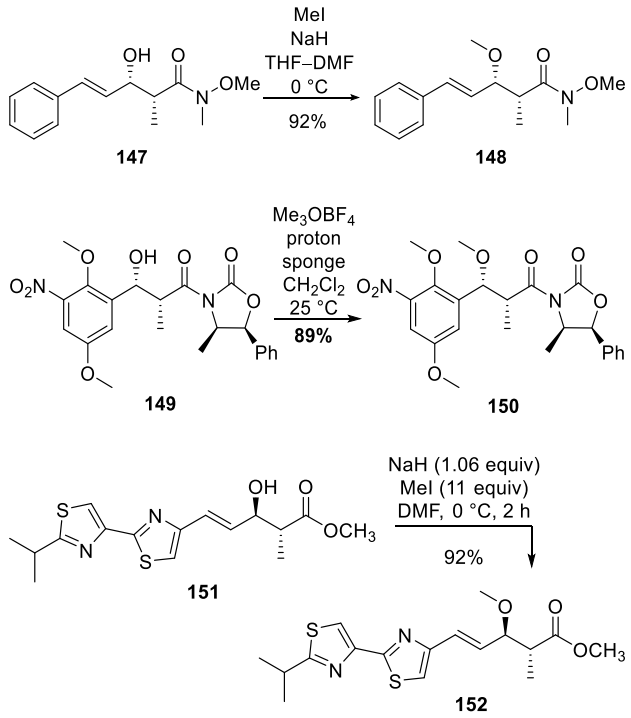
Scheme 61

[217] Vincent, G.; Mansfield, D.J.; Vors, J.P.; Ciufolin, M.A. *Org. Lett.*, **2006**, *8*, 2791–2794

[218] Uchiro, H.; Nagasawa, K.; Kotake, T.; Hasegawa, D.; Tomita, A.; Kobayashi, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2821–2824.

[219]Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067–1069.

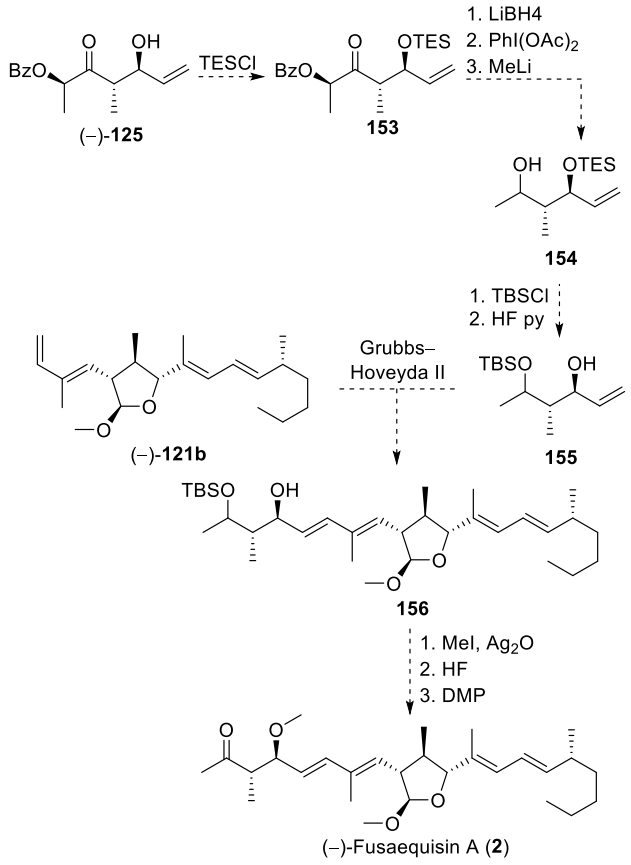
[220] Ojika, M.; Watanabe, T.; Qi, J.; Tanino, T.;Sakagami, Y. *Tetrahedron* **2004**, *60*, 187–194.



Scheme 62

.

The third strategy does not sparkle in elegance but is expected to have a rather high probability of success. Here, the synthesis of the Western fragment is slightly modified, incorporating a cross-metathesis with a free allylic alcohol and a later methylation of a masked aldol moiety (Scheme 63). The synthesis of the required Western fragment commences with the aldol (–)-**125**. Unlike the previously described route for the Western fragment, the alcohol is protected as the TES ether **153**. The following chain degradation as previously explored on the way to Desmethylfusaequisin (Chapter 3.12; Scheme 38) includes the reduction with $LiBH_4$, diol cleavage with $PhI(OAc)_2$ and nucleophilic addition of MeLi to deliver the secondary alcohol **154**. Silylation of **154** with TBSCl should result in the corresponding bissilylether, which should enable selective cleavage of the less stable TES ether also because of its allylic environment. The resulting allylic alcohol **155** should act as an appropriate partner in the cross-metathesis with the tetraenes (–)-**121a** or (–)-**121b**. The following methylation should proceed without difficulties as there is neither a possibility for a retroaldol reaction nor a good opportunity for β-elimination due to lack of an α-acidic proton in **156**. Finally, deprotection of the TBS ether and subsequent oxidation of the secondary alcohol should deliver the natural product without foreseeable difficulties.



Scheme 63

Chapter 7 - Experimental Section

This PhD. thesis contains an appendix printed as a seperate volume (Total Synthesis and Structural Assignment of Curvicollide C and Derivatives of Fusaequisin A; Appendix; PhD. Dissertation Valeska von Kiedrowski; 364 pages). Note that the ordering of information in the appendix reflects the ordering of compounds in the the experimental part.

7.1 Materials and Methods

General methods

All moisture-sensitive reactions were performed in flame-dried (630 °C) septum-sealed glassware under an atmosphere of argon. Reagents were transferred by means of syringe. Solids were introduced under a counter-flow of argon. Reactions were magnetically stirred if not indicated otherwise and monitored by thin layer chromatography using precoated Merck silica gel foils type 60 F_{254} (4 cm). Visualization was achieved using 254 nm ultraviolet irradiation followed by staining with the Kägi−Miescher reagent (*p*-anisaldehyde 2.53% v/v, acetic acid 0.96% v/v, ethanol 93.06% v/v, concd H_2SO_4 3.45% v/v) or the $KMnO_4$ reagent: $KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (0.25 g in 5 mL H_2O), H_2O (300 mL). Chromatographic purification was performed according to Still, Kahn and Mitra[221] on silica gel (particle size 0.040−0.063 mm). Mixtures of cyclohexane and ethyl acetate or n-pentane and diethyl ether were used as eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure (Büchi rotavapor R-200 rotary evaporator). Kugelrohr distillation was performed under high vacuum (Pfeiffer Duo 5M vacuum pump, Pfeiffer RVC 300 control unit as well as Büchi GKR-51 glass tube oven). Collection of the distillate was assured by cooling the receiving bulb with dry ice. Non volatile compounds were dried under high vacuum ($5 \cdot 10^{-2}$ mbar) in a temperature range of 25 to 60 °C. Preperative HPLC was performed on a Knauer HPLC consisting of a pump K-1800, an UV detector 2600 (254 nm) and the peak recognition software ChromGate® Software V3.1.6. As the stationary phase the colum Nucleosil 50-5 (32x237 mm ID) was employed.

Analytic methods

^{1}H NMR spectra were recorded at 300, 400, 500, 600 or 700 MHz. Chemical shifts (δ) are reported in ppm relative to chloroform (7.26 ppm), unless stated otherwise.[222] Signal splitting patterns are labeled by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet or overlap of nonequivalent resonances, app = apparent (used if long range couplings are involved which are not resolvable). Coupling constants (Hz) are given as reported by the NMR processing and analysis software. ^{13}C NMR spectra were recorded at 75, 101, 126, 151, 176 MHz. All ^{13}C NMR spectra were obtained with broadband proton decoupling. Chemical shifts are reported in ppm relative to $CDCl_3$ (77.16 ppm) unless stated otherwise; the total number of reported ^{13}C atom signals may fall short of the expected number because of coincidental chemical shifts, even for constitutopic or diastereotopic carbon atoms. The NMR peak assignment as well as the assignment of the relative configuration rests on the interpretation of ^{1}H^{1}H COSY, ^{1}H^{13}C HSQC and ^{1}H^{1}H NOESY experiments.

FT-IR spectra were recorded as a thin film on an FT-IR Tensor 27 spectrometer (Bruker) using ATR. Infrared absorptions are reported in reciprocal wavelength ν (cm^{-1}) and are adjusted down- or upward to 0 or 5 cm^{-1}. Relative intensities are indicated as they appear using the following abbreviations: s = strong, m = middle, w = weak.

Molecular formula assignment was confirmed by combustion elemental analysis using the elemental analyzers Leco CHNS-932 or Elementar Vario Micro Cube.

High resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer using electrospray ionization (ESI).

Optical rotations were measured with an A. Krüss Optronic polarimeter operating on the sodium D-line (589 nm) using a 2 mL cuvette and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

Melting points (m.p.) are uncorrected and were recorded on a Büchi B-540 or Krüss Optronic KSP1N melting point apparatus.

Analytical HPLC was conducted on a Knauer HPLC (Smartline series) with UV detector 2600 (254 nm) using Chiralpak IA (0.46 cm × 25 cm).

Reagents and solvents

Unless otherwise stated, commercially available reagents, catalysts and solvents were used as purchased. Toluene, tetrahydrofuran, diethyl ether, dichloromethane, 1,2-dichloroethane and acetonitrile were dried deploying a commercially available solvent purification system (Braun MB SPS 500). Methanol was distilled from magnesium and stored over

[221] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[222] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.

activated 4 Å molecular sieves Triethylamine, diisopropylamine and pyridine were distilled from CaH_2 and stored under an atmosphere of argon over activated 4 Å molecular sieves. 2,2,2- trifluorethanol and $CDCl_3$ were stored over activated 3 Å molecular sieves. Pyridine-d5, for NMR, was stored in packaged 1.00 mL ampoules.
Reagents were purchased from the following supplier:
ABCR: diisopropyl azodicarboxylate (94%), diisopropylamine (99%), methanesulfonamide (98%), mol sieves (3 Å), silver(I) oxide (99%)
Acros: anisole (99%), 2,2′-bipyridine (>99%), *n*-butyl lithium (2.5 M in hexane), *t*-butyl lithium (1.9 M in pentane), bromine (>99%) chlorodicyclohexylborane (1 M in hexane), copper(I)bromide (99%), ethyl 2-diethoxyphosphorylacetate (98%), 4-dimethylaminopyridine (99%), dibutylboron triflate (1M in CH_2Cl_2), ethyl magnesium bromide (2 M in THF), hydrofluoric acid (48−51% w/w HF in H_2O), hydrogen fluoride•pyridine (65−70% w/w HF in pyridine), hexamethylphosphoramide (99%), hexanoyl chloride (97%), isopropylmagnesium chloride (2.5 M in THF), lithium (99%), lithium aluminium hydride (95%), lithium borohydride (95%), 2,6-lutidine (99%), mesyl chloride (99.5%), *p*-methoxybenzaldehyde dimethylacetal (98%), 4-methylmorpholine *N*-oxide monohydrate (97%), methyl lithium (1.6 M in Et_2O), methyltriphenylphosphonium bromide (98%), osmium tetroxide (2.5% w/w OsO_4 in *t*-BuOH), 1-phenyl-1*H*-tetrazole-5-thiol (99%), pyridine (99%), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 3.5 M in toluene), sodium borohydride (98%), bis(trimethylsilyl)amine (98%), tetra-*n*-butylammonium fluoride (1M in THF), tetrabutylammonium iodide (98%), 2,2,6,6-tetramethylpiperidine 1-oxyl (98%), tetra-*n*-propylammonium perruthenate, thiophenol (>99%), trifluoroacetic acid (99%), 2,2,2-trifluoroethanol (99.8%), trimethylaluminum ($AlMe_3$, 1 M in heptane), trimethylsilyl chloride (98%).
Alfa: 3,4-dimethoxybenzaldehyde (99%), sodium cyanoborohydride (95%)
Carbolution: imidazole (95%), *tert*-butyldimethylsilyl chloride (99%), *tert*-butyldiphenysilyl chloride (98%)
Fisher Scientific: L-valine
Fluka: acetaldehyde (99.5%), ammonium heptamolybdate tetrahydrate (>99%), benzyl bromide (>98%), naphthalene (>98%), *p*-toluenesulfonic acid monohydrate
Grüssing: ammonium chloride (99%), iodine (99.5%), potassium sodium tartrate tetrahydrate (99%), potassium carbonate (99.5%), magnesium sulfate (99%), sodium chloride (99.5%), sodium bicarbonate (99%), sodium thiosulfate pentahydrate (99%), Seesand (0.3 mm), triethylamine (99%), hydrogen peroxide (30%)
Janssen Chimica: benzoic anhydride (98%)
Merck: bromoacetic acid (>98%), (*Z*)-2-butene-1,4-diol (95%), disodium phosphate (>99%), 2-iodobenzoic acid (>99%)
Sigma Aldrich: acrolein (95%), Celite®, diisobutylaluminum hydride (1M in CH_2Cl_2), Grubbs™ 2. generation, Hoveyda-Grubbs™ 2. generation (97%), iodobenzene diacetate (98%), magnesium bromide (98%), sodium bis(trimethylsilyl)amide (2 M in THF), sodium hydride (60% w/w in mineral oil), sodium periodate (>99.8%)
TCI Europe: 1,8-diazabicyclo[5.4.0]undec-7-ene (>98%), *N*-methylhydroxylamine hydrochloride (98%), methylmagnesium bromide (1 M in THF), silver hexafluoroantimonate (>98%), trimethyloxonium tetrafluoroborate (>95%), triphenylphosphine (>95%),
VWR Chemicals: hydrochloric acid (35%), sulfuric acid (95%)

Buffer and prepared reagents

Aqueous phosphate buffer (pH 7) was prepared by the addition of aqueous sodium dihydrogen phosphate (0.1 M NaH_2PO_4, 430 mL) to aqueous sodium hydrogen phosphate (0.1 M Na_2HPO_4, 1000 mL).
[Cu{(S,S)-*tert*-Bu-box}Cl_2](CH_2Cl)$_2$ was prepared according to the literature and stored at room temperature.[223]
DMP was prepared according to the literature and stored in the refrigerator.[224]
TBSOTf was prepared according to the literature and stored in the freezer.[225]
Methyl 2-(triphenylphosphoranylidene)propanoate was prepared according to the literature and stored at room temperature.[187]
Pyridinium *p*-toluenesulfonate was prepared according to the literature and stored at room temperature.[226]
3,4-Dimethoxybenzaldehyde was prepared according to the following procedure: To 3,4-dimethoxybenzaldehyde ($C_9H_{10}O_3$, 166.18 g/mol, 701 mg, 4.22 mmol, 1 equiv) was added Amberlyst 15 (80 mg) and trimethyl orthoformate ($C_4H_{10}O_3$, 106.12 g/mol, 0.968 g/mL, 3 mL, 3.1 g, 29.21 mmol, 6.92 equiv) at room temperature. The reaction mixture was stirred at room temperature for 4.5 h. The resin was then filtered off and thoroughly washed with CH_2Cl_2 (20 mL). The reaction mixture was concentrated under reduced pressure and the oily coloress residue was used without purification in the following transacetalization step.

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[224] (a) D. B. Dess, J. C. Martin, *J. Org. Chem*. **1983**, *48*, 4155; (b) R. E. Ireland, L. Liu, *J. Org. Chem*. **1993**, *58*, 2899.
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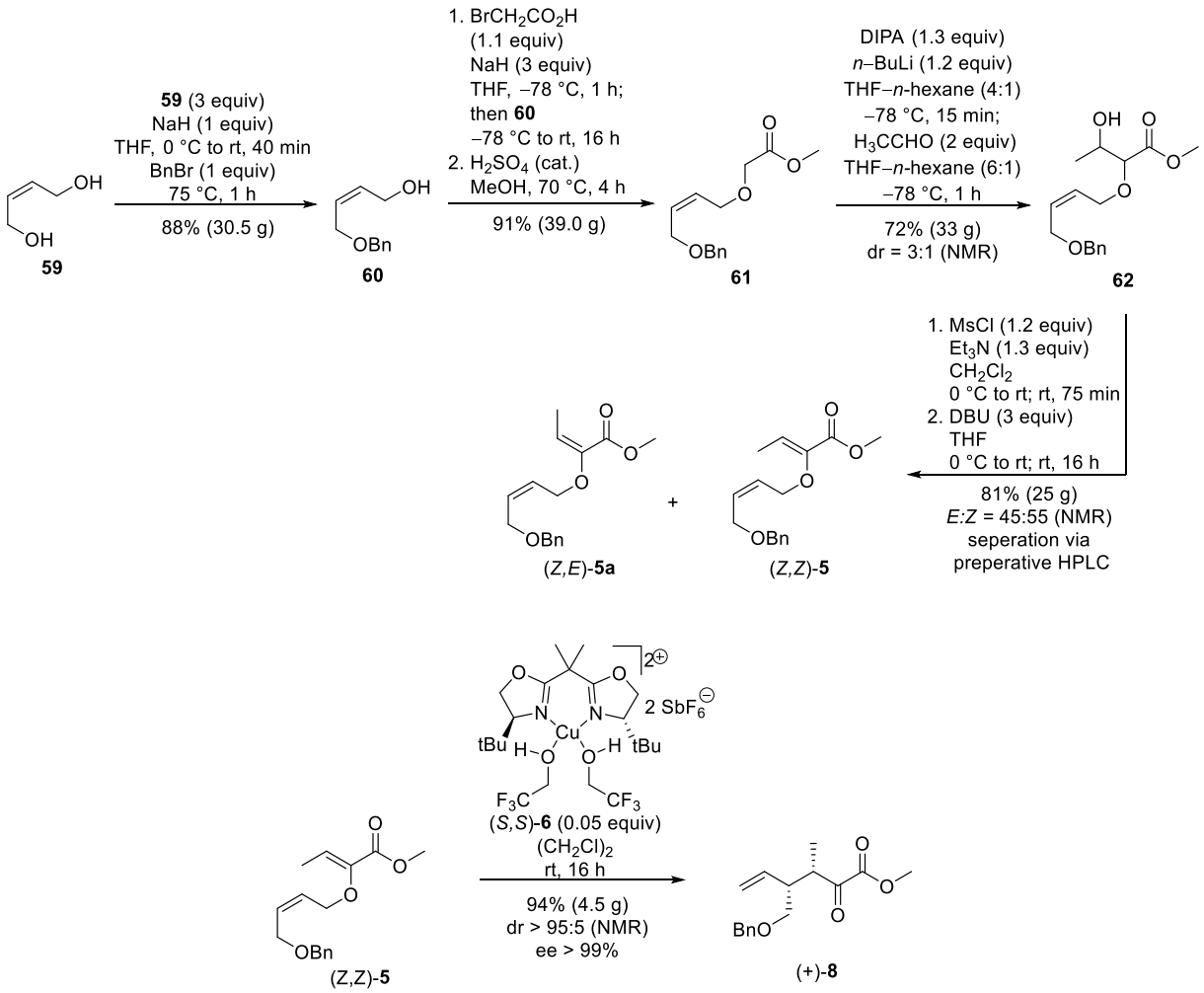
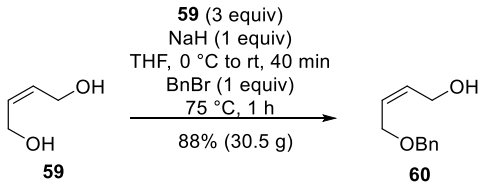
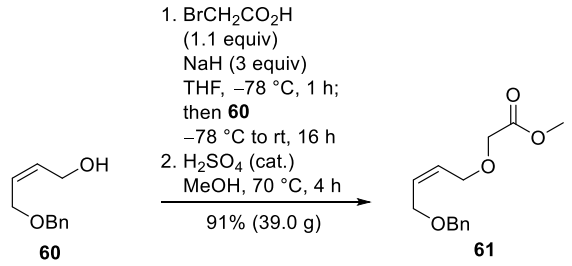
7.2 Synthesis of the α-keto ester (+)-8

Synopsis



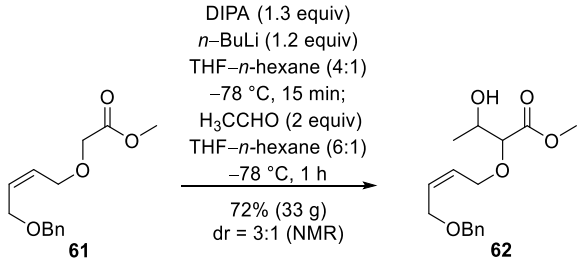


Benzyl Ether 60 by Monoprotection.To an ice-cooled solution of (*Z*)-2-butene-1,4-diol (**59**) ($C_4H_8O_2$, 88.11 g/mol, 1.07 g/ml, 46.6 ml, 50 g, 567.5 mmol, 2.93 equiv) in THF (230 mL) was carefully added natrium hydride (NaH, 60% w/w in mineral oil, 23.99 g/mol, 7.8 g, 195.1 mmol, 1.01 equiv) in three portions in intervals of five minutes. The resulting grey suspension was allowed to warm to room temperature and was stirred for 40 minutes at room temperature. To the grey suspension benzyl bromide (BnBr, C_7H_7Br, 171.03 g/mol, 1.44 g/mL, 23.0 mL 33.12 g, 193.7 mmol, 1 equiv) was added at room temperature and the orange brown reaction mixture was stirred for 1 h at 75 °C. The reaction mixture was cooled to room temperature and was diluted by the addition of saturated aqueous NH_4Cl solution (200 mL), H_2O (50 mL) and CH_2Cl_2 (100 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1) to deliver the benzyl ether **60** ($C_{11}H_{14}O_2$, 178.23 g/mol, 30.5 g, 171.1 mmol, 88%) as a colorless oil. R_f 0.28 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.87–1.96 (br s, 1H), 4.11 (d, J = 6.2 Hz, 2H), 4.18 (t, J = 5.5 Hz, 2H), 4.53 (s, 2H), 5.72–5.78 (m, 1H), 5.79–5.87 (m, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 58.84, 65.74, 72.57, 127.88, 127.93, 128.39, 128.55, 132.42, 137.93; IR ν 3750 (m), 3025 (m), 2860 (m), 1735 (w), 1495 (m), 1455 (w), 1385 (w), 1330 (w), 1240 (m), 1205 (m), 1070 (s), 1025 (s), 940 (m), 735 (s), 695 (s), 605 (m) cm^{-1}

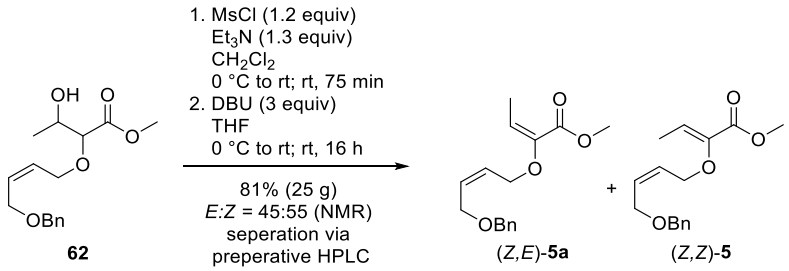


Methyl ester 61 by Etherification and Esterification. To a solution of bromoacetic acid ($BrCH_2CO_2H$, 138.95 g/mol, 26.2 g, 188.56 mmol, 1.1 equiv) in THF (300 mL) was portionwise added natrium hydride (NaH, 60% w/w in mineral oil, 23.99 g/mol, 22.6 g, 565.23 mmol, 3.3 equiv) at −78 °C. The grey suspension was stirred at −78 °C for 1 h and a solution of the benzyl ether **60** ($C_{11}H_{14}O_2$, 178.23 g/mol, 30.5 g, 171.13 mmol, 1 equiv) in THF (80 mL) was added. The reaction mixture was allowed to warm to room temperature overnight. The orange brown suspension was carefully diluted with a solution of potassium hydroxide (KOH, 1 M, 150 mL) at 0 °C and the phases were separated. While the organic phase was discarded the aqueous phase was carefully acidified with concentrated sulfuric acid (98% v/v) (pH<4) and slightly yellow color of the solution disappeared. organic phase. The acidic aqueous layer was extracted with CH_2Cl_2 (3x150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The orange oily residue was used without purification in the following step. To a solution of the crude residue in methanol (170 mL) was added concentrated sulfuric acid (H_2SO_4, 98.08 g/mol, 1.84 g/mL, 2.73 mL, 5.02 g, 51.18 mmol, 0.3 equiv–based on initial amount of **60**) at 0 °C. The yellow solution was stirred at 70 °C for 4 h. The reaction mixture was cooled to room temperature and was diluted by the addition of H_2O (100 mL). The phases were separated and the organic phase was washed with saturated aqueous NaCl solution (80 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3x150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1) to deliver the methyl ester **61** ($C_{14}H_{18}O_4$, 250.29 g/mol, 39.0 g, 155.82 mmol, 91% from **60**) as a yellowish oil. R_f 0.60 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.07 (s, 2H), 4.09 (d, J = 5.9 Hz, 2H), 4.15 (d, J = 6.4 Hz, 2H), 4.51 (s, 2H), 5.71–5.79 (m, 1H), 5.80–5.88 (m, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.94, 65.74, 67.03, 67.32, 72.45, 127.79, 127.87, 128.49, 128.51, 130.56, 138.13, 170.79; IR ν 3030 (w), 2855 (m), 1755 (s), 1495 (m),

1455 (m), 1435 (w), 1365 (w), 1330 (m), 1275 (s), 1205 (s), 1110 (s), 1070 (s), 1025 (m), 1000 (m), 945 (m), 845 (w), 735 (s), 700 (s), 605 (m), 460 (w) cm^{-1}.



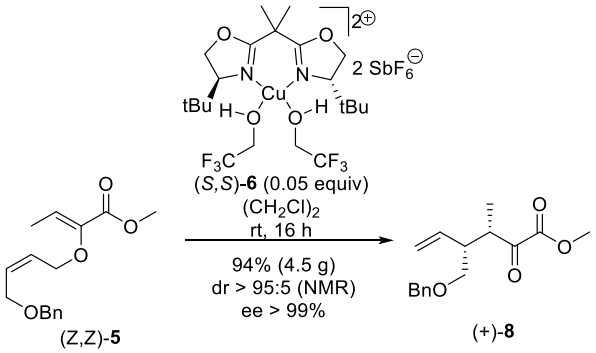
β-Hydroxy Ester 62 by Aldol Addition. The reaction was carried out in four parallel batches To each solution of LDA prepared from diisopropylamine ($C_6H_{15}N$, 101.19 g/mol, 0.72 g/mL, 28.8 mL, [4×7.2 mL], 20.74 g, 204.96 mmol, 1.32 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 76 mL overall [4×19 mL], 190.0 mmol, 1.22 equiv) in THF (320 mL [4×80 mL]) at –78 °C for 10 min, was added a precooled –78 °C solution of the methyl ester **61** ($C_{14}H_{18}O_4$, 250.29 g/mol, 39 g overall [4×9.75 g], 155.82 mmol, 1 equiv) in THF (160 mL [4×40 mL]). The reaction mixtures were stirred at –78 °C for 15 min and to each solution freshly distilled acetaldehyde (C_2H_4O, 44.05 g/mol, 0.78 g/mL, 18 mL overall [4×4.5 mL], 14.04 g, 318.73 mmol, 2.05 equiv) was added at –78 °C. The reaction mixtures were stirred at –78 °C for 1 h and diluted by the addition of saturated aqueous NH_4Cl solution (160 mL [4×40 mL]) and CH_2Cl_2 (120 mL [4×30 mL]). The mixtures were then warmed to room temperature and transferred into a single separatory funnel using CH_2Cl_2 for rinsing. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 10:1 to 5:1 to 3:1) to deliver an inseparable mixture of diastereomers of the β-hydroxy ester **62** ($C_{16}H_{22}O_5$, 294.34 g/mol, 33 g, 112.16 mmol, 72%, dr = 3:1) as a colorless oil. R_f 0.30 (cyclohexane–ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J = 6.4 Hz, 3H^{major}), 1.21 (d, J = 6.5 Hz, 3H^{minor}), 2.31 (d, J = 6.9 Hz, 1H^{major}), 2.42 (d, J = 5.9 Hz, 1H^{minor}), 3.72 (d, J = 4.9 Hz, 1H^{minor}), 3.75 (s, 3H), 3.90 (d, J = 4.4 Hz, 1H^{major}), 4.00 (m, 1H^{minor}), 4.05 (d, J = 7.3 Hz, 1H), 4.07 (dd, J = 6.1, 3.2 Hz, 3H), 4.27 (m, 1H^{major}), 4.51 (s, 2H), 5.72–5.79 (m, 1H), 5.79–5.86 (m, 1H), 7.27–7.38 (m, 4H); IR ν 3470 (br m), 3030 (w), 2860 (m), 1740 (s), 1495 (w), 1455 (m), 1435 (m), 1430 (m), 1375 (w), 1330 (w), 1365 (m), 1205 (m), 1180 (m), 1145 (s), 1090 (s), 1070 (s), 1005 (m), 740 (s), 700 (s), 605 (m), 460 (m) cm^{-1}



Allyl vinyl ethers (*E*,*Z*)-5a and (*Z*,*Z*)-5 by Mesylation and Elemination. To an ice-cooled solution of the β-hydroxy ester **62** ($C_{16}H_{22}O_5$, 294.34 g/mol, 33 g, 112.16 mmol, 1 equiv) in CH_2Cl_2 (330 mL) were succesivly added triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 20.2 mL, 14.67 g, 144.97 mmol, 1.29 equiv) and mesyl chloride (CH_3ClO_2S, 114.55 g/mol, 1.45 g/mL, 10.6 mL, 15.37 g, 134.18 mmol, 1.2 equiv). The orange suspension was stirred at room temperature for 1 h and was then diluted by the addition of saturated aqueous $NaHCO_3$ solution (150 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The brown oily residue was used without purification in the following step. To a solution of the crude residue in THF (330 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, $C_9H_{16}N_2$, 152.24 g/mol, 1.02 g/mL, 50.2 mL, 51.20 g, 336.31 mmol, 3 equiv-based on initial amount of **62**) at 0 °C. The reaction mixture was stirred at room temperature for 17 h and was

then diluted by the addition of H_2O (150 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 20:1) to deliver a mixture of double bond isomers of **5** ($C_{16}H_{20}O_4$, 276.33 g/mol, 25 g, 90.47 mmol, 81% from **62**, *E:Z* = 45:55) as a slightly yellowish oil. The double bond isomers were separated by preparative HPLC: 32×250 mm, Nucleosil 50-5, heptane/ethyl acetate 8/1, 25 mL/min, R_t (*Z*,*Z*)-**5** = 23.0 min, R_t (*E*,*Z*)-**5a** = 27.0 min. (*E*,*Z*)-**5a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (d, J = 7.5 Hz, 3H), 3.78 (s, 3H), 4.10 (d, J = 4.3 Hz, 2H), 4.32 (d, J = 4.3 Hz, 2H), 4.51 (s, 2H), 5.37 (q, J = 7.50 Hz, 1 H), 5.76–5.87 (m, 2H), 7.22–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.58, 51.73, 64.91, 65.78, 112.73, 127.67, 127.74, 127.93. 128.39, 129.72, 138.00, 144.77, 164.02; (*Z*,*Z*)-**5** ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR 1.79 (d, *J* = 7.0 Hz, 3H), 3.75 (s, 3H), 4.12 (d, *J* = 5.0 Hz, 2H), 4.45 (d, *J* = 5.3 Hz, 2H), 4.53 (s, 2H), 5.75–5.92 (m, 2H), 6.39 (q, *J* = 7.0 Hz, 1H), 7.21–7.42 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.48, 51.84, 65.66, 67.50, 72.32, 124.94, 127.69, 127.77, 128.36, 128.42, 130.27, 138.09, 145.26, 164.22. Retentionszeiten

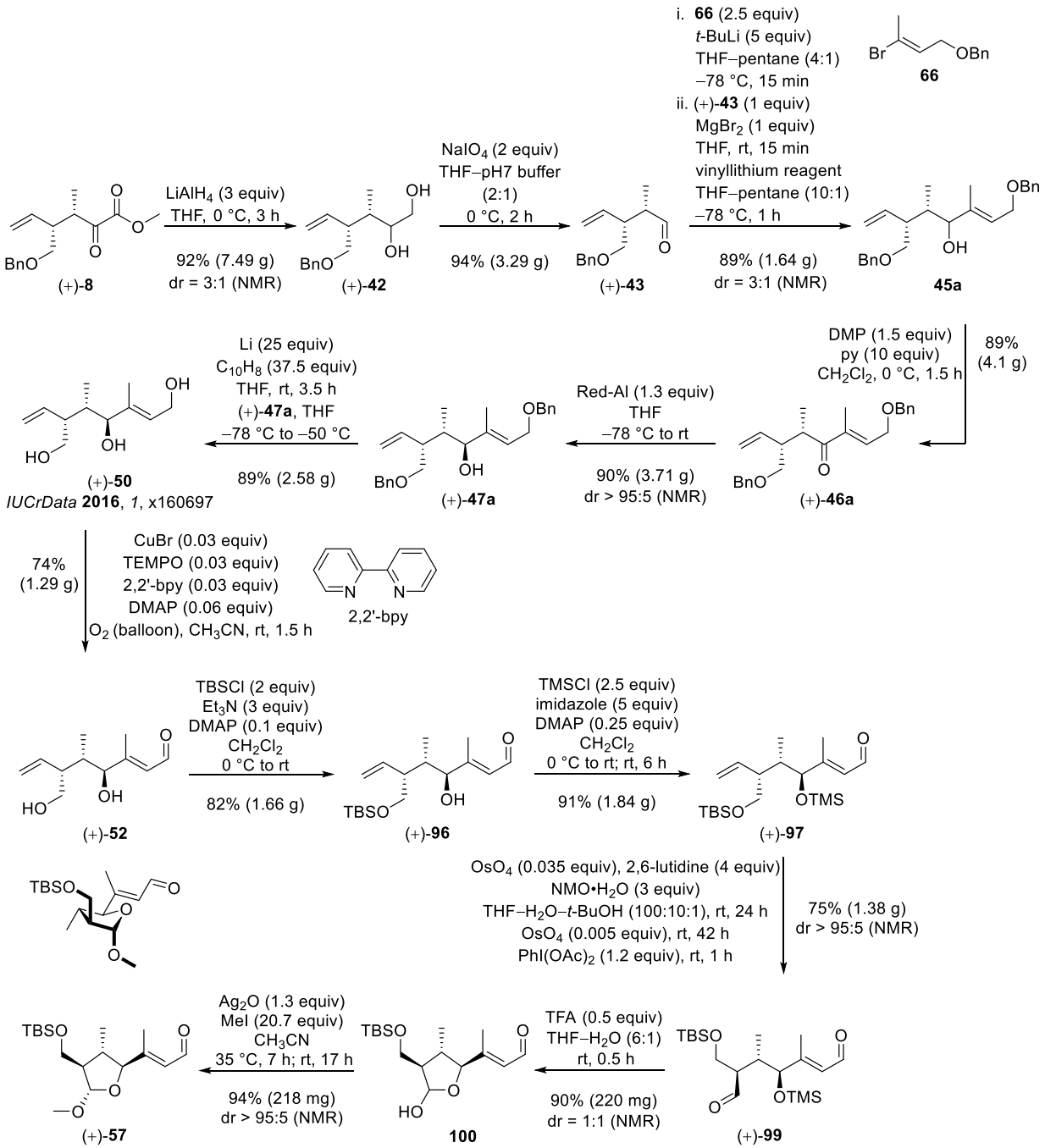
Catalyst (*S*,*S*)-6 by Anion Metathesis. To an ice-cooled solution of the copper(II)chloride complex ($C_{17}H_{30}Cl_2CuN_2O_2$•$(CH_2Cl)_2$, 527.84 g/mol, 550 mg, 1.042 mmol, 1 equiv) in $(CH_2Cl)_2$ (40 mL) was added silver hexafluoroantimonate ($AgSbF_6$, 343.62 g/mol, 715 mg, 2.081 g/mol, 2 equiv). The resulting green suspension was stirred for 3 h at room temperature in the absence of light. Subsequently the magnetic mixer was removed and the green suspension was allowed to stand for 30 min in order to enable sedimentation. The green suspension was poured through a styrene filter (PTFE, 0.45 µm pore size) into a freshly dried Schlenk tube and 2,2,2-trifluoroethanol ($C_2H_3F_3O$, 100.04 g/mol, 1.38 g/mL, 0.31 mL, 224.6 mg, 2.245 mmol, 2.15 equiv) was added and stirred for 3 minutes to give the catalyst solution which was directly used after preparation.

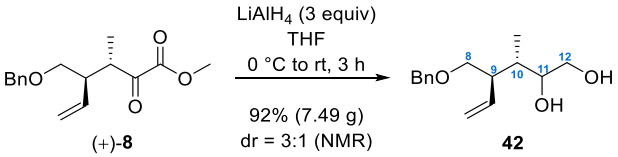


α-Ketoester (+)-8 by Catalytic Asymmetric Gosteli–Claisen rearrangement. To a solution of the allyl vinyl ether (*Z*,*Z*)-**5** ($C_{16}H_{20}O_4$, 276.33 g/mol, 4.8 g, 17.371 mmol, 1 equiv) in $(CH_2Cl)_2$ (40 mL) was added a solution of (*S*,*S*)-**6** ([Cu{(*S*,*S*)-*t*-Bu-box}(tfe)$_2$]$(SbF_6)_2$, 0.026 M in $(CH_2Cl)_2$, 34 mL, 0.884 mmol, 0.051 equiv) at room temperature. The dark green solution was stirred for 16 h at room temperature. The solvent was removed under reduced pressure and the green viscous residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 20:1) to deliver the α-ketoester (+)-**8** ($C_{16}H_{20}O_4$, 276.33 g/mol, 4.5 g, 16.285 mmol, 94%, %, dr > 95:5, ee > 99%) as a colorless oil. The enantiomeric excess was determined by analytical HPLC: Chiralpak IA, 4.6×250 mm, heptane/ethyl acetate 99:1, 1 ml/min, R_t (+)-8 = 11.5 min. R_f 0.45 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +45.1 (c = 1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, ^{3}J = 7.1 Hz, 3H, 10'-CH_3), 2.96 (dddd, ^{3}J = 8.4, 7.3, 5.8, 4.6 Hz, 1H, 9-CH), 3.40 (dd, ^{2}J = 9.2 Hz, ^{3}J = 7.3 Hz, 1H, 8-CH), 3.48 (qd, ^{3}J = 7.1, 5.8 Hz, 1H, 10-CH), 3.52 (dd, ^{2}J = 9.2 Hz, ^{3}J = 4.6 Hz, 1H, 8-CH), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 4.35−4.44 (m, 2H, benzylic-CH_2), 5.08 (d, ^{3}J = 17.2 Hz, 1H, 9'-CH=C$\underline{H}^E$), 5.12 (d, ^{3}J = 10.3 Hz, 1H, 9'-CH=C$\underline{H}^Z$), 5.82 (ddd, ^{3}J=17.2, 10.3, 8.4 Hz, 1H, 9'-C$\underline{H}$=CH_2), 7.23−7.30 (m, 3H, aryl-CH), 7.30−7.36 (m, 2H, aryl-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ^{13}C NMR 11.86 (10'-CH_3), 43.22 (10-CH), 46.47 (9-CH), 52.67 ($CO_2\underline{CH}_3$), 70.25 (8-CH_2), 73.22 (benzylic-CH_2), 117.47 (9'-CH=$\underline{CH}_2$) 127.73 (aryl-CH), 127.81 (aryl-CH), 128.42 (aryl-CH), 136.40 (9'-$\underline{C}$H=CH_2), 137.94 (aryl-C), 162.04 ($\underline{C}O_2CH_3$), 195.75 (11-C).

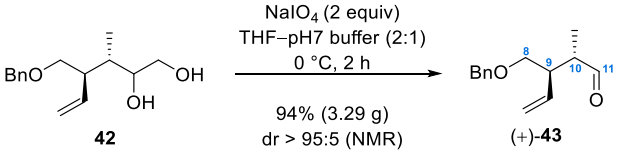
7.3 Synthesis of the Central fragment

Synopsis

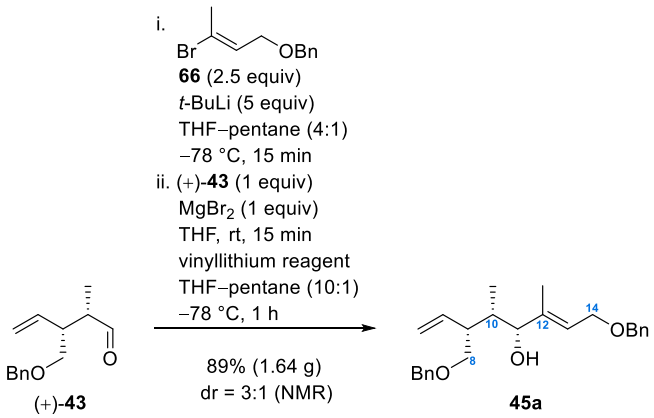




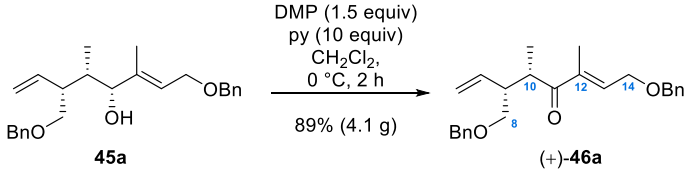
Diol 42 by $LiAlH_4$ Reduction. To an ice-cooled solution of the known α-ketoester (+)-**8**[55] ($C_{16}H_{20}O_4$, 276.33 g/mol, 9.00 g, 32.57 mmol, 1 equiv, dr > 95:5, 99% ee) in THF (200 mL) was carefully added lithium aluminium hydride ($LiAlH_4$, 37.95 g/mol, 3.7 g, 97.50 mmol, 2.99 equiv). The resulting grey suspension was allowed to warm to room temperature and was stirred for 3 h at room temperature. The reaction mixture was diluted by the dropwise addition of saturated aqueous NH_4Cl solution (50 mL), saturated aqueous potassium sodium tartrate solution (100 mL) and CH_2Cl_2 (50 mL) at 0 °C. The biphasic mixture was stirred for 1 h at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1) to deliver a mixture of diastereomers of the diol **42** ($C_{15}H_{22}O_3$, 250.33 g/mol, 7.49 g, 29.92 mmol, dr = 3:1, 92%) as a colorless oil. The ratio of diastereomers was determined by integration of the ^{1}H NMR signals of 9-CH at 2.45−2.53 ppm (minor) and 2.65−2.77 ppm (major). A diastereomerically enriched sample (dr = 8:1) of the major diastereomer was obtained by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1). Characterization data are reported for the major diastereomer. R_f 0.30 (cyclohexane−ethyl acetate, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, ^3J = 7.3 Hz, 3H, 10'-CH_3), 1.75−1.87 (m, 1H, 10-CH), 2.29 (br. s., 1H, OH), 2.65−2.77 (m, 1H, 9-CH), 3.44−3.83 (m, 6H, OH, 8-CH_2, 11-CH, 12-CH_2), 4.48−4.57 (m, 2H, benzylic-CH_2), 5.00−5.13 (m, 2H, 9'-CH=C$\underline{H}_2$), 5.77 (ddd, ^3J = 17.5, 10.2, 7.9 Hz, 1H, 9'-C$\underline{H}$=CH_2) 7.27−7.39 (5H, aryl-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 12.76 (10'-CH_3), 38.85 (10-CH), 44.43 (9-CH), 65.45; 70.70 (8-CH_2, 12-CH_2), 73.78 (benzylic-CH_2), 74.38 (11-CH), 116.36 (9'-CH=$\underline{C}H_2$), 127.97; 128.12; 128.70 (aryl-CH), 137.50 (aryl-C), 137.99 (9'-$\underline{C}$H=CH_2); IR ν 3385 (m), 3065 (w), 3030 (w), 2875 (m), 1640 (w), 1495 (w), 1455 (m), 1420 (m), 1360 (m), 1205 (w), 1070 (s), 1030 (s), 1000 (s), 915 (s), 735 (s), 695 (s), 610 (m) cm^{-1}; Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; Found: C, 71.9; H, 8.9.



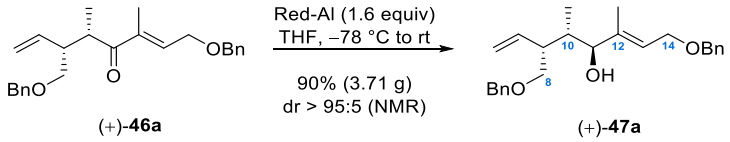
Aldehyde (+)-43 by Periodate Cleavage. To an ice-cooled solution of the diol **42** ($C_{15}H_{22}O_3$, 250.33 g/mol, 4.00 g, 15.98 mmol, 1 equiv) in THF (140 mL) and aqueous phosphate pH 7 buffer (70 mL) was added sodium periodate ($NaIO_4$, 213.89 g/mol, 6.85 g, 32.03 mmol, 2 equiv). The white flaky suspension was stirred at 0 °C for 2 h and was then diluted by the successive addition of H_2O (50 mL) and CH_2Cl_2 (100 mL) at 0 °C. The biphasic mixture was stirred for 10 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver the aldehyde (+)-**43** ($C_{14}H_{18}O_2$, 218.29 g/mol, 3.29 g, 15.07 mmol, dr > 95:5, 94%) as a colorless oil. R_f 0.67 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{25}$ = +84.0 (c = 1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, ^3J = 6.9 Hz, 3H, 10'-CH_3), 2.51−2.58 (m, 1H, 10-CH), 2.85−2.93 (m, 1H, 9-CH), 3.49 (dd, ^2J = 9.4 Hz, ^3J = 8.0 Hz, 1H, 8-CH), 3.54 (dd, ^2J = 9.4 Hz, ^3J = 5.5 Hz, 1H, 8-CH), 4.48 (s, 2H, benzylic-CH_2), 5.13 (d, ^3J = 17.2 Hz, 1H, 9'-CH=C$\underline{H}^E$), 5.16 (d, ^3J = 10.3 Hz, 1H, 9'-CH=C$\underline{H}^Z$), 5.79 (ddd, ^3J = 17.2, 10.7, 8.0 Hz, 1H, 9'-C$\underline{H}$=CH_2), 7.26−7.40 (m, 5H, aryl-CH), 9.70 (d, ^3J = 1.1 Hz, 1H, 11-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.85 (10'-CH_3), 45.07 (9-CH), 47.70 (10-CH), 70.23 (8-CH_2), 73.42 (benzylic-CH_2), 117.46 (9'-CH=$\underline{C}H_2$), 127.76; 128.51 (aryl-CH), 136.55 (9'-$\underline{C}$H=CH_2), 138.13 (aryl-C), 204.39 (11-CH); IR ν 2975 (w), 2860 (w), 2715 (w), 1720 (s), 1640 (w), 1495 (w), 1455 (m), 1420 (w), 1365 (m), 1205 (w), 1095 (s), 1030 (m), 995 (m), 920 (m), 880 (m), 735 (s), 695 (s), 605 (w), 460 (w) cm^{-1}; Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; Found: C, 77.0; H, 8.3.



Allylic Alcohol 45a by Nucleophilic Addition. The reaction was carried out in two parallel batches. To each of the two solutions of the aldehyde (+)-**43** ($C_{14}H_{18}O_2$, 218.29 g/mol, 1.06 g overall, [2×530 mg], 4.856 mmol, 1 equiv) in THF (62 mL [2×31 mL]) was added dried (0.1 mbar, 100 °C, 1 h) magnesium bromide ($MgBr_2$, 184.11 g/mol, 894 mg [2×447 mg], 4.856 mmol, 1 equiv) at room temperature. The white suspensions were stirred for 15 min at room temperature. The resulting clear and colorless solutions were then cooled to –78 °C. Meanwhile, to each of the two solutions of the vinyl bromide **66**[78] ($C_{11}H_{13}BrO$, 241.12 g/mol, 2.92 g [2×1.46 g], 12.11 mmol, 2.49 equiv) in THF (52 mL [2×26 mL]) at –78 °C was dropwise added *t*-BuLi (1.9 M in *n*-pentane, 12.8 mL [2×6.4 mL], 24.32 mmol, 5.01 equiv). The resulting bright yellow solutions were stirred for 15 min at –78 °C and were then added dropwise to the mixture of the aldehyde **43** and $MgBr_2$ in THF at –78 °C. The two light yellow reaction mixtures were stirred at –78 °C for 1 h and were then diluted by the addition of saturated aqueous NH_4Cl solution (60 mL [2×30 mL]) and CH_2Cl_2 (60 mL [2×30 mL]). The decolorized mixtures were then warmed to room temperature and transferred into a single separatory funnel using CH_2Cl_2 (30 mL) for rinsing. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 50:1 to 20:1 to 10:1) to deliver an inseparable mixture of diastereomers of the alcohol **45a** ($C_{25}H_{32}O_3$, 380.52 g/mol, 1.64 g, 4.310 mmol, dr = 3:1, 89%) as a colorless oil. The ratio of diastereomers was determined by integration of the ^{1}H NMR signals of 13-CH at 5.62 ppm (minor) and 5.73 ppm (major) Analytical data are reported for the mixture of diastereomers. R_f 0.32 (cyclohexane–ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82 (d, ^3J = 7.0 Hz, 6H, 2×10'-CH_3), 1.59 (s, 3H, 12'-CH_3^{major}), 1.61 (s, 3H, 12'-CH_3^{minor}), 1.82–1.90 (m, 1H, 10-CH^{major}), 1.90–1.98 (m, 1H, 10-CH^{minor}), 2.44–2.52 (m, 2H, OH^{major}, 9-CH^{major}), 2.68–2.75 (m, 1H, 9-CH^{minor}), 3.39 (br. s., 1H, OH^{minor}), 3.50 (dd, ^2J = 9.5 Hz, ^3J = 5.9 Hz, 2H, 2×8-CH), 3.52–3.59 (m, 2H, 2×8-CH), 3.88 (dd, ^3J = 8.1, 5.1 Hz, 1H, 11-CH^{minor}), 4.08–4.15 (m, 5H, 11-CH^{major}, 14-CH_2^{minor}, 14-CH_2^{major}), 4.50–4.58 (m, 8H, 4×benzylic-CH_2), 5.02–5.14 (m, 4H, 2×9'-CH=C$\underline{H}_2$), 5.62 (t, ^3J = 6.6 Hz, 1H, 13-CH^{minor}), 5.73 (t, ^3J = 6.6 Hz, 1H, 13-CH^{major}), 5.77–5.88 (m, 2H, 2×9'-C$\underline{H}$=CH_2), 7.26–7.39 (m, 20H, aryl-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 8.82 (10'-CH_3^{major}), 12.13 (12'-CH_3^{minor}), 13.37 (10'-CH_3^{minor}), 14.22 (12'-CH_3^{major}), 37.49 (10-CH^{major}), 39.02 (10-CH^{minor}), 43.80 (9-CH^{minor}), 47.34 (9-CH^{major}), 66.47; 66.53 (2×14-CH_2), 70.64; 70.97 (2×8-CH_2), 72.14; 72.18; 73.41; 73.54 (4×benzylic-CH_2), 77.00 (11-CH^{major}), 79.70 (11-CH^{minor}), 116.05; 116.10 (2×9'-CH=C$\underline{H}_2$), 121.43 (13-CH^{major}), 123.94 (13-CH^{minor}), 126.48; 127.67; 127.69; 127.83; 127.84; 127.89; 127.92; 127.96; 128.48; 128.5; 128.54; 128.62 (aryl-CH), 137.68; 138.06; 138.57;138.60; 138.64; 139.62; 140.53; 140.65 (2×9'-C$\underline{H}$=CH_2, 2×12-C, 4×aryl-C); IR ν 3425 (w), 3030 (w), 2860 (m), 1640 (w), 1495 (w), 1455 (m), 1365 (m), 1255 (w), 1205 (w), 1090 (s), 1070 (s), 1025 (s), 915 (m), 820 (w), 735 (s), 695 (s), 605 (m), 460 (w) cm^{-1}; Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48; Found: C, 78.5; H, 8.4.

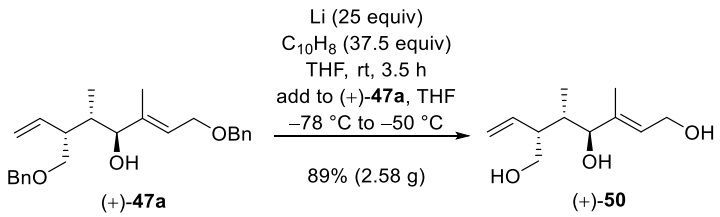


α,β-Enone (+)-46a by Dess−Martin Oxidation. To an ice-cooled solution of the alcohol **45a** ($C_{25}H_{32}O_3$, 380.52 g/mol, 4.65 g, 12.22 mmol, 1 equiv) in CH_2Cl_2 (250 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 9.8 mL, 9.604 g, 121.42 mmol, 9.94 equiv) was added the Dess−Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 7.77 g, 18.32 mmol, 1.5 equiv). The white suspension was stirred at 0 °C for 2 h. The resulting yellowish suspension was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (100 mL) and CH_2Cl_2 (50 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The orange viscous residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver the ketone (+)-**46a** ($C_{25}H_{30}O_3$, 378.50 g/mol, 4.10 g, 10.83 mmol, 89%) as a colorless oil. R_f 0.52 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +42.7 (c = 1 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.04 (d, ^3J = 7.1 Hz, 3H, 10'-CH_3), 1.70 (d, ^4J = 1.1 Hz, 3H, 12'-CH_3), 2.61 (dddd, ^3J = 8.3, 7.6, 5.6, 5.1 Hz, 1H, 9-CH), 3.45 (dd, ^2J = 9.4 Hz, ^3J = 5.1 Hz, 1H, 8-CH), 3.52 (dd, ^2J = 9.4 Hz, ^3J = 5.5 Hz, 1H, 8-CH) overlapped by 3.52−3.57 (m, 1H, 10-CH), 4.26 (app d, ^3J = 5.5 Hz, 2H, 14-CH_2), 4.44 (d, ^2J = 12.0 Hz, 1H, benzylic-CH), 4.50 (d, ^2J = 12.0 Hz, 1H, benzylic-CH), 4.53−4.58 (m, 2H, benzylic-CH_2), 4.99−5.04 (m, 2H, 9'-CH=C$\underline{H}_2$), 5.77−5.84 (m, 1H, 9'-C$\underline{H}$=CH_2), 6.70 (app t, ^3J = 5.5 Hz, 1H, 13-CH), 7.23−7.39 (m, 10H, aryl-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 12.15 (12'-CH_3), 15.52 (10'-CH_3), 39.87 (10-CH), 47.25 (9-CH), 67.65 (14-CH_2), 71.04 (8-CH_2), 73.21; 73.33 (2×benzylic-CH_2), 116.65 (9'-CH=$\underline{C}H_2$), 127.69; 127.80; 128.04; 128.07; 128.47; 128.68 (aryl-CH), 137.82 (13-CH) 138.02; 138.48 (12-C, 2×aryl-C) 138.19 (9'-$\underline{C}$H=CH_2), 205.00 (11-C); IR ν 3030 (w), 2855 (w), 1665 (s), 1495 (w), 1495 (w), 1455 (m), 1360 (m), 1205 (w), 1095 (s), 1025 (m), 915 (m), 820 (w), 735 (s), 695 (s), 605 (w), 465 (w) cm^{-1}; Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99; Found: C, 79.1; H, 8.0.

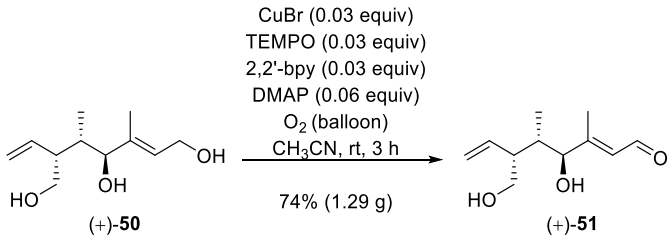


(+)-**46a** (+)-**47a**

Allylic Alcohol (+)-**47a by Diastereoselective Red-Al Reduction.** To a solution of the enone (+)-**46a** ($C_{25}H_{30}O_3$, 378.50 g/mol, 4.10 g, 10.83 mmol, 1 equiv) in THF (150 mL) was dropwise added sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 3.5 M in toluene, 5 mL, 17.5 mmol, 1.62 equiv) over a period of time of 15 min at −78 °C. The resulting yellow solution was allowed to warm to room temperature overnight and the color of the reaction mixture faded. The colorless solution was diluted by the addition of saturated aqueous potassium sodium tartrate solution (100 mL) and CH_2Cl_2 (100 mL) at 0 °C. The biphasic mixture was vigorously stirred for 1 h at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to deliver the allylic alcohol (+)-**47a** ($C_{25}H_{32}O_3$, 380.52 g/mol, 3.71 g, 9.75 mmol, dr > 95:5, 90%) as a colorless oil. R_f 0.29 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +23.8 (c = 1 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.81 (d, ^3J = 7.0 Hz, 3H, 10'-CH_3), 1.61 (s, 3H, 12'-CH_3), 1.94 (dqd, ^3J = 7.7, 7.0, 2.2 Hz, 1H, 10-CH), 2.67−2.74 (m, 1H, 9-CH), 3.34 (d, ^3J = 5.1 Hz, 1H, OH), 3.49 (dd, ^2J = 9.2 Hz, ^3J = 4.8 Hz, 1H, 8-CH), 3.57 (dd, ^2J = 9.2 Hz, ^3J = 8.6 Hz, 1H, 8-CH), 3.88 (dd, ^3J = 7.7, 5.1 Hz, 1H, 11-CH), 4.10 (app d, ^3J = 6.4 Hz, 2H, 14-CH_2), 4.48−4.58 (m, 4H, 2×benzylic-CH_2), 5.02−5.10 (m, 2H, 9'-CH=C$\underline{H}_2$), 5.62 (t, ^3J = 6.4 Hz, 1H, 13-CH), 5.80 (ddd, ^3J = 17.5, 10.0, 8.1 Hz, 1H, 9'-C$\underline{H}$=CH_2), 7.26−7.39 (m, 10H, aryl-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 12.14 (12'-CH_3), 13.39 (10'-CH_3), 39.05 (10-CH), 43.85 (9-CH), 66.51 (14-CH_2), 70.69 (8-CH_2), 72.17; 73.57 (2×benzylic-CH_2), 79.75 (11-CH), 116.06 (9'-CH=$\underline{C}H_2$), 123.99 (13-CH), 127.69; 127.90; 127.96; 127.98; 128.50; 128.63 (aryl-CH), 137.72; 138.61; 138.64; 140.54 (9'-$\underline{C}$H=CH_2, 12-C, 2×aryl-C); IR ν 3410 (w), 3030 (w), 2860 (m), 1640 (w), 1495 (w), 1455 (s), 1365 (m), 1310, 1205 (w), 1070 (s), 1025 (s), 910 (s), 820 (w), 735 (s), 695 (s), 605 (m) cm^{-1}; Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48; Found: C, 78.7; H, 8.4.

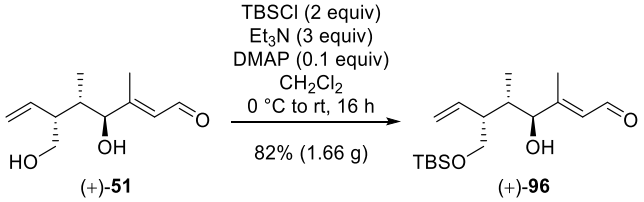


Triol (+)-50 by Benzyl Ether Cleavage. To a solution of naphthalene ($C_{10}H_8$, 128.17 g/mol, 69.5 g, 542.25 mmol, 37.4 equiv) in THF (300 mL) at room temperature were added small pieces of freshly cut lithium metal (Li, 6.94 g/mol, 2.51 g, 361.67 mmol, 25 equiv). Within 30 minutes, the color of the heterogenous reaction mixture turned to dark green. In order to complete the dissolving of the metal, the reaction mixture was stirred for 3 h at room temperature. The resulting homogenous dark green mixture was transferred to a solution of the benzylether (+)-**47a** ($C_{25}H_{32}O_3$, 380.52 g/mol, 5.51 g, 14.48 mmol, 1 equiv) in THF (65 mL) at –78 °C via cannula and over a period of time of 45 min. The reaction mixture was allowed to warm to –50 °C over a period of time of 2 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (100 mL) at –50 °C. The decolorized mixture was then was warmed to room temperature. The phases were separated and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. The light yellow solid residue was purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 2:1 to 0:100) to deliver the triol (+)-**50** ($C_{11}H_{20}O_3$, 200.27 g/mol, 2.58 g, 12.88 mmol, 89%) as a pale yellow solid. Crystallization of (+)-**50** from diethyl ether (0.4 mL) and *n*-pentane (6 mL) by slow evaporation under air provided colorless needles.[100] R_f 0.28 (ethyl acetate); m.p. 62.5–64.5 °C; $[\alpha]_D^{20}$ = +46 (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, ^3J = 7.3 Hz, 3H, 10'-CH_3), 1.59 (s, 3H, 12'-CH_3), 1.96 (qdd, ^3J = 7.3, 6.6, 1.9 Hz, 1H, 10-CH), 2.42 (dddd, ^3J = 8.3, 8.1, 4.9, 1.9 Hz, 1H, 9-CH), 3.54 (dd, ^2J = 11.0 Hz, ^3J = 4.9 Hz, 1H, 8-CH), 3.61 (dd, ^2J = 11.0 Hz, ^3J = 8.1 Hz, 1H, 8-CH), 3.84 (d, ^3J = 6.6 Hz, 1H, 11-CH), 3.95 (br s, 1H, OH), 4.11 (dd, ^2J = 12.8 Hz, ^3J = 5.9 Hz, 1H, 14-CH), 4.22 (dd, ^2J = 12.8 Hz, ^3J = 7.0 Hz, 1H, 14-CH), 4.94–5.15 (m, 3H, 9'-CH=C$\underline{H}_2$, OH), 5.18 (br s, 1H, OH), 5.58 (dd, ^3J = 7.0, 5.9 Hz, 1H, 13-CH), 5.77 (ddd, ^3J = 17.0, 10.4, 8.3 Hz, 1H, 9'-C$\underline{H}$=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.38 (12'-CH_3), 13.91 (10'-CH_3), 38.65 (10-CH), 46.54 (9-CH), 58.86 (14-CH_2), 62.73 (8-CH_2), 78.59 (11-CH), 116.48 (9'-CH=$\underline{C}H_2$), 125.75 (13-CH), 137.99 (9'-$\underline{C}$H=CH_2), 139.12 (12-C); IR ν 3335 (br s), 2965 (s), 2880 (s), 1665 (w), 1635 (w), 1455 (m), 1385 (m) 1005 (s) 920 (w), 755 (s), 665 (w) cm^{-1}; HRMS (ESI): m/z $[M + Na]^+$ Calcd. for $C_{11}H_{20}O_3Na$: 223.13047; Found 223.12963; Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; Found: C, 65.7; H, 9.9.

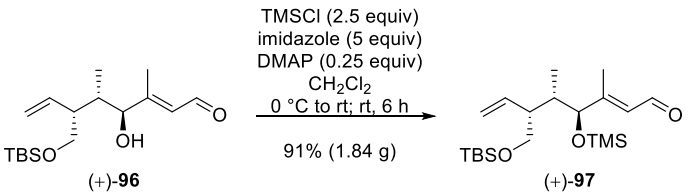


α,β-Unsaturated Aldehyde (+)-51 by Triol Oxidation. To a solution of the triol (+)-**50** ($C_{11}H_{20}O_3$, 200.27 g/mol, 1.75 g, 8.738 mmol, 1 equiv) in CH_3CN (22 mL) was added half of the volume (25 mL) of a brown stock solution [prepared from copper bromide (CuBr, 143.45 g/mol, 38 mg, 0.2649 mmol, 0.03 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl, (TEMPO, $C_9H_{18}NO$, 156.25 g/mol, 41 mg, 0.2624 mmol, 0.03 equiv), 2,2′-bipyridine (2,2'-bpy, $C_{10}H_8N_2$, 156.19 g/mol, 41 mg, 0.2625 mmol, 0.03 equiv) and 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 64 mg, 0.5239 mmol, 0.06 equiv) in CH_3CN (50 mL), subsequently stirred for 10 min at room temperature]. Subsequently, gaseous oxygen from a balloon was vigorously bubbled via cannula through the stirred reaction mixture for about 30 minutes at room temperature (one balloon filling). A further volume (12.5 mL) of the stock solution of the oxidant was added to the reaction mixture at room temperature and gaseous oxygen from a balloon was vigorously bubbled via cannula through the stirred reaction mixture for about 30 minutes. The final volume (12.5 mL) of the stock solution was then added and oxygen was bubbled through the reaction mixture as describe above. During the procedure, the color of the reaction

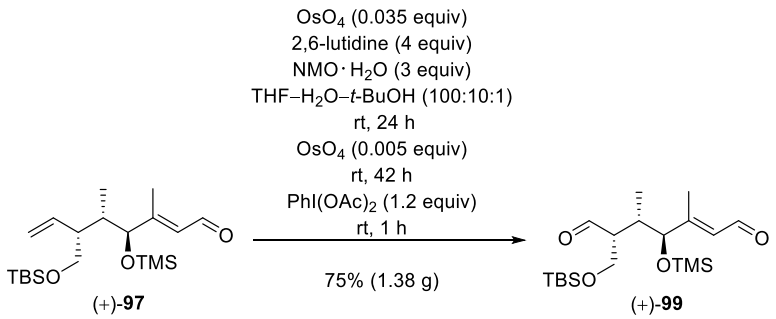
mixture turned from brown to green. The clear green reaction mixture was diluted by the successive addition of H_2O (50 mL) and ethyl acetate (70 mL) at room temperature. The biphasic mixture was vigorously stirred for 20 min at room temperature. The phases were separated and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the yellowish oily residue by flash chromatography (cyclohexane–ethyl acetate, 10:1 to 5:1 to 2:1 to 0:100) delivered the α,β-unsaturated aldehyde (+)-**51** ($C_{11}H_{18}O_3$, 198.26 g/mol, 1.29 g, 6.507 mmol, 74%) as a colorless oil. Note: The progress of the consumption of the starting material was carefully monitored by TLC. In the case of the extensive build-up of an undesired TLC spot at R_f 0.83 (ethyl acetate), the reaction mixture was immediately quenched. This modus operandi served to avoid the formation of undesired products and to enable the recovery starting material. R_f 0.65 (ethyl acetate); $[\alpha]_D^{20}$ = 78.4 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, ^3J = 7.0 Hz, 3H, 10'-CH_3), 2.14 (d, ^4J = 1.3 Hz, 3H, 12'-CH_3) overlapped by 2.09−2.18 (m, 1H, 10-CH), 2.38−2.46 (m, 1H, 9-CH), 2.99 (br.s, 1H, OH), 3.59−3.70 (m, 2H, 8-CH_2), 4.05 (d, ^3J = 6.0 Hz, 1H, 11-CH), 4.35 (br. s, 1H, OH), 5.07 (app d, ^3J = 17.3 Hz, 1H, 9'-CH=C$\underline{H}^E$), 5.12 (app d, ^3J = 10.5 Hz, 1H, 9'-CH=C$\underline{H}^Z$), 5.73 (ddd, ^3J = 17.3, 10.5, 8.2 Hz, 1H, 9'-C$\underline{H}$=CH_2), 6.13 (app d, ^3J = 8.0 Hz, 1H, 13-CH), 10.07 (d, ^3J = 8.0 Hz, 1H, 14-CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.37 (10'-CH_3), 13.96 (12'-CH_3), 38.92 (10-CH), 45.84 (9-CH), 62.31 (8-CH_2), 78.97 (11-CH), 117.00 (9'-CH=$\underline{C}H_2$), 127.28 (13-CH), 137.56 (9'-$\underline{C}$H=CH_2), 164.01 (12-C), 191.80 (14-CH); IR ν 3425 (s), 2975 (s), 2930 (s), 2875 (s), 1715 (m), 1455 (m), 1380 (m), 1100 (s), 1070 (s), 1050 (s), 1000 (s), 920 (m) cm^{-1}; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{18}O_3Na$: 221.11482, Found 221.11426; $[(M – H_2O)+H]^+$ calcd for $C_{11}H_{17}O_2$: 181.12231, Found 181.12146.



Silyl Ether (+)-96 by Silylation. To an ice-cooled solution of the diol (+)-**51** ($C_{11}H_{18}O_3$, 198.26 g/mol, 1.29 g, 6.507 mmol, 1 equiv) in CH_2Cl_2 (250 mL) were successively added triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 2.7 mL, 1.96 g, 19.37 mmol, 2.98 equiv), *tert*-butyldimethylsilyl chloride (TBSCl, $C_6H_{15}ClSi$, 150.72 g/mol, 1.96 g, 13.004 mmol, 2 equiv) and 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 79 mg, 0.6466 mmol, 0.1 equiv). The clear, colorless solution was allowed to warm to room temperature overnight and was then diluted by the addition of aqueous phosphate pH 7 buffer (70 mL). After being stirred for 15 min at room temperature, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver the silyl ether (+)-**96** ($C_{17}H_{32}O_3Si$, 312.52 g/mol, 1.665 g, 5.328 mmol, 82%) as a colorless oil. R_f 0.55 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +64.9 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3H, Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), 0.13 (s, 3H, Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), 0.93 (s, 9H, Si(CH_3)$_2$C(C$\underline{H}_3$)$_3$), 1.00 (d, ^3J = 7.0 Hz, 3H, 10'-CH_3), 2.13 (d, ^4J = 1.4 Hz, 3H, 12'-CH_3) overlapped by 2.07–2.16 (m, 1H, 10-CH), 2.42 (ddd, ^3J = 9.1, 8.3, 3.9 Hz, 1H, 9-CH), 3.58 (dd, ^2J = 10.3 Hz, ^3J = 3.9 Hz, 1H, 8-CH), 3.63 (dd, ^2J = 10.3 Hz, ^3J = 9.1 Hz, 1H, 8-CH), 3.98 (dd, ^3J = 6.4 Hz, 1H, 11-CH), 4.78 (d, ^3J = 6.4 Hz, 1H, OH), 5.04 (app d, ^3J = 17.1 Hz, 1H, 9'-CH=C$\underline{H}^E$), 5.09 (app d, ^3J = 10.3 Hz, 1H, 9'-CH=C$\underline{H}^Z$), 5.73 (ddd, ^3J = 17.1, 10.3, 8.3 Hz, 1H, 9'-C$\underline{H}$=CH_2), 6.14 (app d, ^3J = 7.8 Hz, 1H, 13-CH), 10.08 (d, ^3J = 7.8 Hz, 1H, 14-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.62 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), −5.41 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 13.58 (10'-CH_3), 13.89 (12'-CH_3), 18.45 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 25.98 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 39.41 (10-CH), 45.54 (9-CH), 63.70 (8-CH_2), 78.96 (11-CH), 116.61 (9'-CH=$\underline{C}H_2$), 127.43 (13-CH), 137.44 (9'-$\underline{C}$H=CH_2), 164.20 (12-C), 191.70 (14-CH); IR ν 3370 (w), 2930 (m), 2855 (m), 1675 (s), 1460 (w), 1380 (w), 1255 (m), 1200 (w), 1095 (s), 1005 (m), 915 (w), 835 (s), 775 (s), 665 (w) cm^{-1}; Anal. Calcd. for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32; Found: C, 65.2; H, 10.2.

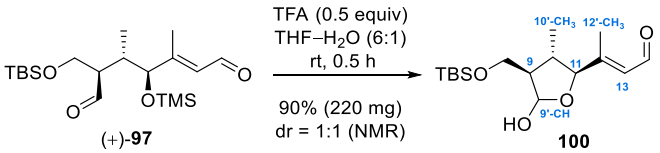


Bis-Silyl Ether (+)-97 by Silylation. To an ice-cooled solution of the alcohol (+)-**96** ($C_{17}H_{32}O_3Si$, 312.52 g/mol, 1.64 g, 5.248 mmol, 1 equiv) in CH_2Cl_2 (150 mL) were successively added imidazole ($C_3H_4N_2$, 68.08 g/mol, 1.79 g, 26.293 mmol, 5.01 equiv), trimethylsilyl chloride (TMSCl, C_3H_9ClSi, 108.64 g/mol, 0.854 g/mL, 1.68 mL, 1.43 g, 13.163 mmol, 2.51 equiv, used as purchased) and 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 160 mg, 1.310 mmol, 0.25 equiv). The resulting white suspension was stirred at room temperature for 6 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (70 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford the bis-silyl ether (+)-**97** ($C_{20}H_{40}O_3Si_2$, 384.70 g/mol, 1.84 g, 4.783 mmol, 91%) as a colorless oil. R_f 0.65 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +38.9 (c = 1.0 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.04 (s, 3H, Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), 0.04 (s, 3H, Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), 0.09 (s, 9H, Si(CH_3)$_3$), 0.75 (d, ^{3}J = 7.3 Hz, 3H, 10'-CH_3), 0.89 (s, 9H, Si(CH_3)$_2$C(C$\underline{H}_3$)$_3$), 1.90 (dqd, ^{3}J = 8.1, 7.3, 3.3 Hz, 1H, 10-CH), 2.11 (d, ^{4}J = 1.3 Hz, 3H, 12'-CH_3), 2.42–2.49 (m, 1H, 9-CH), 3.63 (dd, ^{2}J = 9.9 Hz, ^{3}J = 7.0 Hz, 1H, 8-CH), 3.71 (dd, ^{2}J = 9.9 Hz, ^{3}J = 5.9 Hz, 1H, 8-CH), 4.08 (d, ^{3}J = 8.1 Hz, 1H, 11-CH), 5.03–5.11 (m, 2H, 9'-CH=C$\underline{H}_2$), 5.78 (ddd, ^{3}J = 17.2, 10.6, 8.1 Hz, 1H, 9'-C$\underline{H}$=CH_2), 5.93 (app d, ^{3}J = 8.1 Hz, 1H, 13-CH), 10.05 (d, ^{3}J = 8.1 Hz, 1H, 14-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.17 (Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), −5.16 (Si(C$\underline{H}_3$)$_2$C(CH_3)$_3$), 0.31 (Si(CH_3)$_3$), 12.69 (12'-CH_3), 13.31 (10'-CH_3), 18.48 (Si(CH_3)$_2$C$\underline{C}$(CH_3)$_3$), 26.11 (Si(CH_3)$_2$C(C$\underline{H}_3$)$_3$), 39.13 (10-CH), 46.72 (9-CH), 64.25 (8-CH_2), 80.47 (11-CH), 116.29 (9'-CH=C$\underline{H}_2$), 127.99 (13-CH), 139.26 (9'-C$\underline{H}$=CH_2), 163.74 (12-C), 191.60 (14-CH); IR ν 2955 (m), 2930 (m), 2855 (m), 1680 (s), 1460 (w), 1385 (w), 1250 (s), 1070 (s), 1005 (m), 880 (s), 835 (s), 775 (s), 750 (m), 665 (w) cm^{-1}; Anal. Calcd. for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48; Found: C, 62.2; H, 10.5.

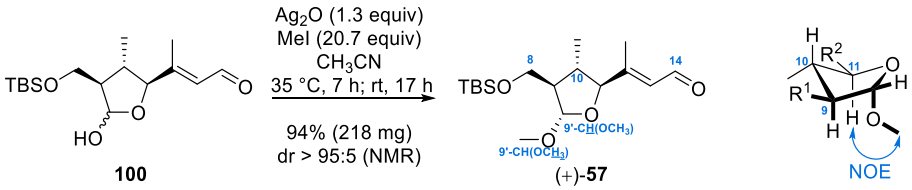


Aldehyde (+)-99 by Oxidative Cleavage. To a solution of (+)-**97** ($C_{20}H_{40}O_3Si_2$, 384.70 g/mol, 1.84 g, 4.783 mmol, 1 equiv) in THF (200 mL) and H_2O (20 mL) were successively added 2,6-lutidine (C_7H_9N, 107.15 g/mol, 0.923 g/mL, 2.2 mL, 2.031 g, 18.955 mmol, 3.96 equiv), 4-methylmorpholine *N*-oxide monohydrate (NMO•H_2O, $C_5H_{11}NO_2$•H_2O, 135.16 g/mol, 1.95 g, 14.427 mmol, 3.02 equiv) and osmium tetroxide (2.5% w/w OsO_4 in *t*-BuOH, 42.5 mg OsO_4, 254.23 g/mol, 1.7 g, 0.1672 mmol, 0.035 equiv) at room temperature. The opalescent, colorless solution was stirred at room temperature for 24 h. Additional osmium tetroxide (2.5% w/w OsO_4 in *t*-BuOH, 6.08 mg OsO_4, 254.23 g/mol, 243 mg, 0.0239 mmol, 0.005 equiv) was added and the reaction mixture was stirred for 42 h at room temperature. To the resulting opalescent, slightly brownish solution was added solid iodobenzene diacetate ($PhI(OAc)_2$, $C_{10}H_{11}IO_4$, 322.10 g/mol, 1.85 g, 5.744 mmol, 1.2 equiv) at room temperature. After the solid had been dissolved, the opalescent, slightly brownish mixture was stirred at room temperature for 1 h. The opalescent, slightly brownish solution was diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution (50 mL) and CH_2Cl_2 (50 mL) and the biphasic mixture was vigorously stirred at room temperature for 15 min. The phases were separated and the dark brown aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily

brownish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to deliver the dialdehyde (+)-**99** ($C_{19}H_{38}O_4Si_2$, 386.67 g/mol, 1.387 g, 3.587 mmol, 75%) as a colorless oil along with recovered starting material (+)-**97** ($C_{20}H_{40}O_3Si_2$, 384.70 g/mol, 0.183 g, 0.476 mmol, 10%). R_f 0.69 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +3.9 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.04 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.07 (s, 9H, Si(CH$_3$)$_3$), 0.82 (d, ^{3}J = 7.0 Hz, 3H, 10'-CH$_3$), 0.87 (s, 9H, Si(CH$_3$)$_2$C(C$\underline{H_3}$)$_3$), 2.13 (d, ^{4}J = 1.2 Hz, 3H, 12'-CH$_3$), 2.38–2.48 (m, 2H, 10-CH, 9-CH), 3.88–3.96 (m, 3H, 8-CH$_2$, 11-CH), 5.96 (app d, ^{3}J = 7.9 Hz, 1H, 13-CH), 9.73 (d, ^{3}J = 2.1 Hz, 1H, 9'-CH), 10.05 (d, ^{3}J = 7.9 Hz, 1H, 14-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.48 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), −5.44 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), 0.05 (Si(CH$_3$)$_3$), 12.70 (12'-CH$_3$), 13.83 (10'-CH$_3$), 18.31 (Si(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_3$), 25.92 (Si(CH$_3$)$_2$C($\underline{C}H_3$)$_3$), 34.64 (10-CH), 54.81 (9-CH), 60.91 (8-CH$_2$), 81.46 (11-CH), 128.30 (13-CH), 162.54 (12-C), 191.37 (14-CH), 204.93 (9'-CH); IR ν 2955 (w), 2930 (w), 2855 (w), 1720 (m), 1675 (s), 1460 (w), 1385 (w), 1250 (s), 1070 (s), 1005 (w), 875 (s), 835 (s), 775 (s), 670 (w) cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ Calcd. for $C_{19}H_{39}O_4Si_2$: 387.23814; Found: 387.23815.



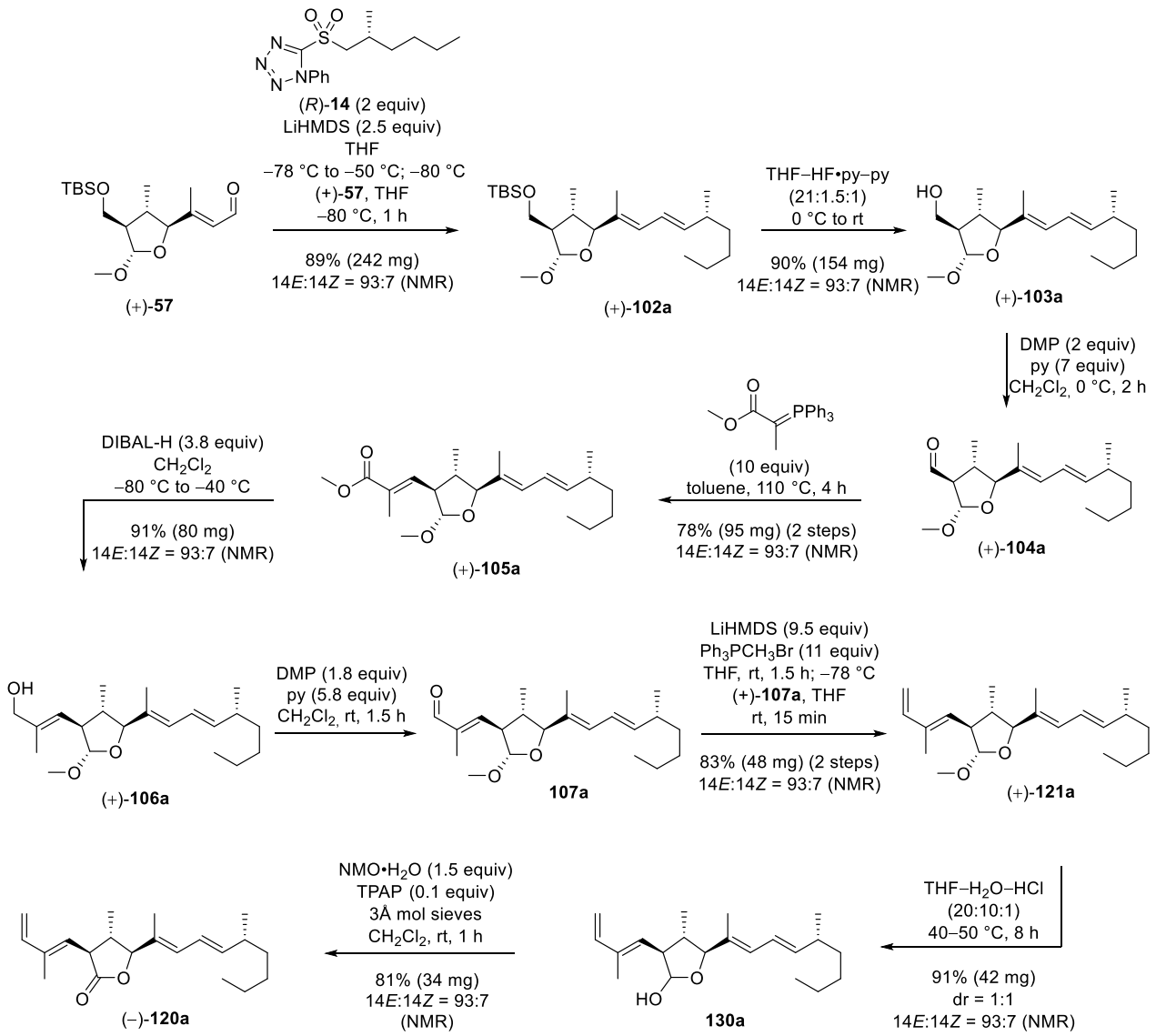
Lactol 100 by TMS Ether Cleavage. To a solution of the dialdehyde (+)-**97** ($C_{19}H_{38}O_4Si_2$, 386.67 g/mol, 300 mg, 0.7759 mmol, 1 equiv) in THF (15 mL) and H_2O (2.5 mL) was added trifluoroacetic acid (TFA, C_2F_3O, 114.02 g/mol, 1.48 g/mL, 30 µL, 44.4 mg, 0.3894 mmol, 0.502 equiv) at room temperature. The clear, colorless solution was stirred at room temperature for 0.5 h and was then diluted by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (10 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily colorless residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford the lactol **100** ($C_{16}H_{30}O_4Si$, 314.49 g/mol, 220 mg, 0.6995 mmol, dr = 1:1, 90%) as a colorless viscous oil that solidified upon storage in the freezer. The ratio of anomers was determined by integration of the ^{1}H NMR signals for the anomeric protons at 5.43 and 5.49 ppm. The relative configuration was not assigned. Analytical data are reported for the mixture of diastereomers. R_f 0.34 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{25}$ = –3.4 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.08 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.09 (s, 3H, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), 0.88 (s, 9H, Si(CH$_3$)$_2$C(C$\underline{H_3}$)$_3$), 0.89 (s, 9H, Si(CH$_3$)$_2$C(C$\underline{H_3}$)$_3$), 1.04 (d, ^{3}J = 6.4 Hz, 3H, 10'-CH$_3$), 1.09 (d, ^{3}J = 6.4 Hz, 3H, 10'-CH$_3$), 1.87−2.00 (m, 3H, 9-CH, 9-CH, 10-CH), 2.14 (d, ^{4}J = 1.1 Hz, 3H, 12'-CH$_3$) overlapped by 2.12–2.20 (m, 1H, 10-CH), 2.22 (d, ^{4}J = 1.1 Hz, 3H, 12'-CH$_3$), 3.62 (dd, ^{2}J = 10.4 Hz, ^{3}J = 4.9 Hz, 1H, 8-CH), 3.69 (dd, ^{2}J = 10.4 Hz, ^{3}J = 4.3 Hz, 1H, 8-CH), 3.82 (dd, ^{2}J = 10.5 Hz, ^{3}J = 5.2 Hz, 1H, 8-CH), 3.91 (dd, ^{2}J = 10.5 Hz, ^{3}J = 3.4 Hz, 1H, 8-CH), 4.03 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 4.28 (d, ^{3}J = 8.9 Hz, 1H, 11-CH), 5.43 (d, ^{3}J = 3.1 Hz, 1H, 9'-CH), 5.49 (d, ^{3}J = 4.9 Hz, 1H, 9'-CH), 6.02 (app d, ^{3}J = 7.9 Hz, 2H, 13-H, 13-CH), 10.05 (d, ^{3}J = 7.9 Hz, 2H, 14-CH, 14-CH); no OH signals detected by NMR. ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.53 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), −5.43 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), −5.38 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), 12.72 (12'-CH$_3$), 12.88 (12'-CH$_3$), 15.13 (10'-CH$_3$), 16.21 (10'-CH$_3$), 18.23 (Si(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_3$), 25.89 (Si(CH$_3$)$_2$C($\underline{C}H_3$)$_3$), 25.94 (Si(CH$_3$)$_2$C($\underline{C}H_3$)$_3$), 36.95 (10-CH), 40.41 (10-CH), 52.58 (9-CH), 57.27 (9-CH), 59.92 (8-CH$_2$), 61.39 (8-CH$_2$), 88.44 (11-CH), 90.42 (11-CH), 99.90 (9'-CH), 101.02 (9'-CH), 126.78 (13-CH), 127.20 (13-CH), 160.44 (12-C), 161.58 (12-C), 191.39 (14-CH), 191.57 (14-CH); IR ν 2955 (m), 2930 (m), 2860 (m), 1720 (w), 1620 (w), 1460 (w), 1380 (w), 1250 (m), 1100 (m), 1055 (m), 1005 (w), 965 (m), 875 (m), 835 (s), 775 (m), 750 (w), 670 (w) cm^{-1}; HRMS (ESI): m/z [M + H]$^+$ Calcd. for $C_{16}H_{31}O_4Si$: 315.19861; Found: 315.19834.

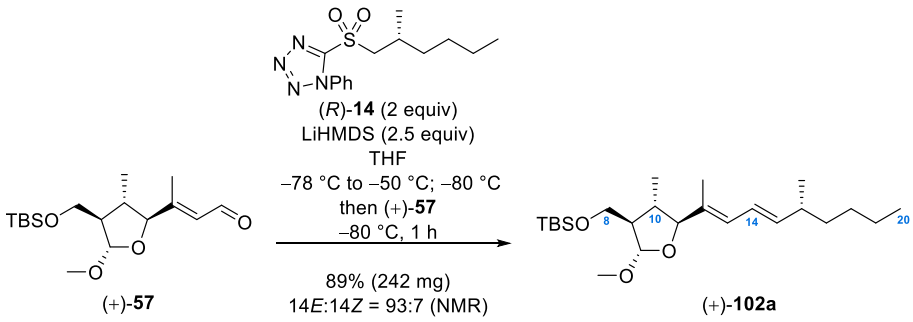


Lactol Methyl Ether (+)-57 by *O*-Methylation. A sealable glass pressure tube was charged with a solution of the lactol **100** ($C_{16}H_{30}O_4Si$, 314.49 g/mol, 220 mg, 0.6995 mmol, 1 equiv) in acetonitrile (15 mL). Methyl iodide (MeI, CH_3I, 141.94 g/mol, 2.28 g/mL, 0.9 mL, 2.052 g, 14.457 mmol, 20.7 equiv) and dried (0.1 mbar, 90 °C, 1 h) silver oxide (Ag_2O, 231.74 g/mol, 210 mg, 0.9062 mmol, 1.3 equiv) were added at room temperature to give a dark colored suspension with a clear liquid phase. The tube was sealed with a Teflon screw cap and placed in an oil bath which was slowly heated to 35 °C (should not exceed 40 °C) for 7 h. The reaction mixture was allowed to cool to room temperature overnight. The resulting dark colored suspension with a turbid, milky yellow liquid phase was then filtered through a plug of Celite®. The filter cake was thoroughly washed with ethyl acetate and the combined filtrates were concentrated under reduced pressure. The oily yellow residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford (+)-**57** ($C_{17}H_{32}O_4Si$, 328.52 g/mol, 218 mg, 0.6636 mmol, dr > 95:5, 94%) as a colorless oil. The assignment of the relative configuration rests on the interpretation of a NOE experiment: NOE correlation observed between 9-CH(OC<u>H</u>$_3$) and 11-H; R_f 0.69 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +46.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.05 (s, 3H, Si(C<u>H</u>$_3$)$_2$C(CH_3)$_3$), 0.06 (s, 3H, Si(C<u>H</u>$_3$)$_2$C(CH_3)$_3$), 0.90 (s, 9H, Si(CH_3)$_2$C(C<u>H</u>$_3$)$_3$), 1.08 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 1.84 (ddq, ^{3}J = 9.0, 8.2, 6.7 Hz, 1H, 10-CH), 1.94 (dddd, ^{3}J = 8.2, 6.0, 5.3, 2.8 Hz, 1H, 9-CH), 2.16 (s, 3H, 12'-CH_3), 3.38 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 3.60 (dd, ^{2}J = 10.2 Hz, ^{3}J = 6.0 Hz, 1H, 8-CH), 3.65 (dd, ^{2}J = 10.2 Hz, ^{3}J = 5.3 Hz, 1H, 8-CH), 4.13 (d, ^{3}J = 9.0 Hz, 1H, 11-CH), 4.91 (d, ^{3}J = 2.8 Hz, 1H, 9'-C<u>H</u>(OCH$_3$)), 6.03 (d, ^{3}J = 7.9 Hz, 1H, 13-CH), 10.07 (d, ^{3}J = 7.9 Hz, 1H, 14-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.33 (Si(<u>C</u>H$_3$)$_2$C(CH_3)$_3$), −5.33 (Si(<u>C</u>H$_3$)$_2$C(CH_3)$_3$), 12.98 (12'-CH_3), 16.50 (10'-CH_3), 18.36 (Si(CH_3)$_2$<u>C</u>(CH_3)$_3$), 25.97 (Si(CH_3)$_2$C(<u>C</u>H$_3$)$_3$), 40.45 (10-CH), 55.70 (9'-CH(O<u>C</u>H$_3$)), 56.57 (9-CH), 62.07 (8-CH_2), 88.22 (11-CH), 107.84 (9'-<u>C</u>H(OCH$_3$)), 126.85 (13-CH), 160.35 (12-C), 191.33 (14-CH); IR ν 2955 (m), 2930 (m), 2855 (m), 1735 (w), 1680 (s), 1465 (w), 1385 (w), 1255 (m), 1195 (w), 1100 (s), 995 (m), 835 (s), 775 (m), 670 (w) cm^{-1}; Anal. Calcd. for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82; Found: C, 61.9; H, 9.8.

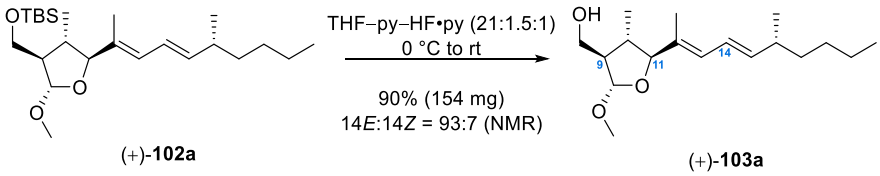
7.4 Synthesis of the cross-metathesis precursor (–)-120a

Synopsis



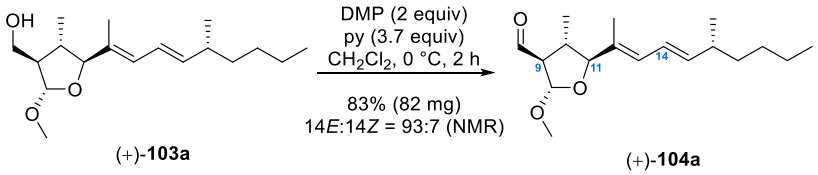


(12*E*,14*E*,16*R*)-Diene (+)-102a by Julia–Kocienski Olefination. To a solution of the known sulfone (*R*)-**14**[56] ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 401 mg, 1.300 mmol, 1.96 equiv) in THF (14 mL) at –78 °C was added a clear, colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 336 µL, 262.1 mg, 1.624 mmol, 2.45 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 650 µL, 1.625 mmol, 2.45 equiv) in THF (10 mL) at 0 °C for 30 min. The resulting bright yellow solution was warmed to –50 °C over a period of time of 0.5 h and was then cooled to –80 °C. A precooled –80 °C solution of the enal (+)-**57** ($C_{17}H_{32}O_4Si$, 328.52 g/mol, 218 mg, 0.6636 mmol, 1 equiv) in THF (10 mL) was added dropwise down along the walls of the flask causing a color change to light yellow. The resulting light yellow solution was stirred at –80 °C for 1 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (15 mL) and CH_2Cl_2 (15 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver (+)-**102a** as a mixture of 14-C/15-C double bond isomers ($C_{24}H_{46}O_3Si$, 410.71 g/mol, 242 mg, 0.5892 mmol, 89%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.24 ppm [(*Z*)-**102a**] and 5.56 ppm [(*E*)-**102a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**102a** and J = 15.0 Hz for (*E*)-**102a**. $[\alpha]_D^{25}$ = +33.6 (c = 0.81 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**102a**: R_f 0.80 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.06 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.90 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$) overlapped by 0.85−0.91 (m, 3H, 20-CH_3), 0.98 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.6 Hz, 3H, 16'-CH_3), 1.19−1.32 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.73 (s, 3H, 12'-CH_3), 1.77−1.84 (m, 1H, 10-CH), 1.88 (dddd, ^{3}J = 8.4, 6.2, 5.1, 2.9 Hz, 1H, 9-CH), 2.12−2.20 (m, 1H, 16-CH), 3.37 (s, 3H, 9'-CH(OC$\underline{H}_3$)), 3.62 (dd, ^{2}J = 10.3 Hz, ^{3}J = 6.2 Hz, 1H, 8-CH), 3.67 (dd, ^{2}J = 10.3 Hz, ^{3}J = 5.1 Hz, 1H, 8-CH), 4.00 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 4.83 (d, ^{3}J = 2.9 Hz, 1H, 9'-C$\underline{H}$(OCH_3)), 5.56 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 6.02 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.0, 10.8 Hz, 1H, 14-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.31 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), −5.29 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 11.76 (12'-CH_3), 14.25 (20-CH_3), 15.86 (10'-CH_3), 18.38 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 20.84 (16'-CH_3), 22.97; 29.75; 36.96 (17,18,19-CH_2), 26.00 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 37.33 (16-CH), 38.90 (10-CH), 55.54 (9'-CH(O$\underline{C}H_3$)), 56.62 (9-CH), 62.51 (8-CH_2), 90.43 (11-CH), 107.41 (9'-$\underline{C}$H(OCH_3)), 124.25 (14-CH), 128.53 (13-CH), 132.70 (12-C), 141.71 (15-CH); IR ν 2955 (m), 2925 (m), 2855 (m), 1460 (w), 1375 (w), 1255 (m), 1190 (w), 1095 (s), 1025 (m), 995 (s), 965 (s), 910 (w), 885 (w), 835 (s), 775 (s), 735 (m), 670 (w) cm^{-1}; Anal. Calcd. for $C_{24}H_{46}O_3Si$: C, 70.19; H, 11.29; Found: C, 70.5; H, 11.3.



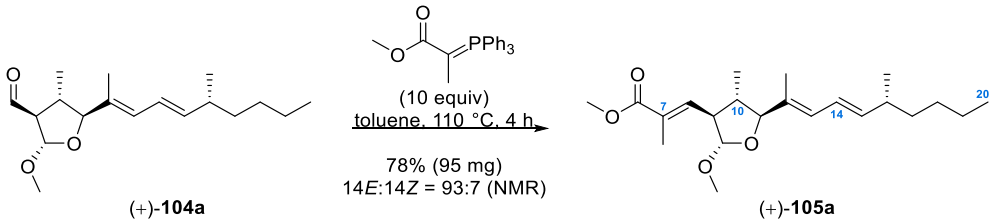
Alcohol (+)-103a by TBS Ether Cleavage. A polypropylene reaction vessel was charged with a solution of hydrogen fluoride•pyridine (HF•pyridine, C_5H_6FN, 65−70% w/w HF in pyridine (py), 1.1 mL) in THF (6 mL). To the clear, slightly brownish solution was dropwise added pyridine (py, C_5H_5N, 1.6 mL) at room temperature and the mixture was stirred for 15 min at room temperature. The clear, slightly brownish solution was dropwise transferred to a solution of (+)-**102a** ($C_{24}H_{46}O_3Si$, 410.71 g/mol, 237 mg, 0.5771 mmol, 1 equiv) in THF (17 mL) at 0 °C in a separate sealable polypropylene

reaction vessel. The reaction vessel was sealed with a polypropylene screw cap and the reaction mixture was allowed to warm to room temperature overnight. The clear, slightly brownish solution was diluted by the successive addition of saturated aqueous $NaHCO_3$ solution (30 mL), H_2O (10 mL) and CH_2Cl_2 (30 mL) at 0 °C. The biphasic mixture was vigorously stirred for 20 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver (+)-**103a** as a mixture of 14-C/15-C double bond isomers ($C_{18}H_{32}O_3$, 296.44 g/mol, 154 mg, 0.5195 mmol, 90%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**103a**] and 5.57 ppm [(*E*)-**103a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.8 Hz for (*Z*)-**103a** and J = 15.1 Hz for (*E*)-**103a**. A diastereomerically enriched sample (dr = 96:4) of the major diastereomer was obtained by flash chromatography (cyclohexane−ethyl acetate, 20:1). Analytical data are reported for (12*E*,14*E*)-**103a**: $[\alpha]_D^{20}$ = +59.9 (c = 0.7 in $CHCl_3$); R_f 0.31 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.99 (d, ^{3}J = 7.0 Hz, 3H, 16'-CH_3), 1.01 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.17−1.34 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.57 (br. s, 1H, OH), 1.73 (s, 3H, 12'-CH_3) overlapped by 1.68−1.76 (m, 1H, 10-CH), 1.95 (dddd, ^{3}J = 8.4, 7.7, 5.1, 2.9 Hz, 1H, 9-CH), 2.11−2.21 (m, 1H, 16-CH), 3.39 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 3.65 (dd, ^{2}J = 10.6 Hz, ^{3}J = 7.7 Hz, 1H, 8-CH), 3.75 (dd, ^{2}J = 10.6 Hz, ^{3}J = 5.1 Hz, 1H, 8-CH), 4.02 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 4.89 (d, ^{3}J = 2.9 Hz, 1H, 9'-C<u>H</u>(OCH$_3$)), 5.57 (dd, ^{3}J = 15.1, 8.1 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.1, 10.7 Hz, 1H, 14-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 11.84 (12'-CH_3), 14.24 (20-CH_3), 15.94 (10'-CH_3), 20.81 (16'-CH_3), 22.95; 29.75; 36.93 (17,18,19-CH_2), 37.32 (16-CH), 39.24 (10-CH), 55.49 (9'-CH(O<u>C</u>H$_3$)), 56.59 (9-CH), 63.25 (8-CH_2), 90.20 (11-CH), 107.63 (9'-<u>C</u>H(OCH$_3$)), 124.14 (14-CH), 128.74 (13-CH), 132.18 (12-C), 141.98 (15-CH); IR ν 3420 (w), 2955 (m), 2925 (m), 2870 (m), 1455 (w), 1380 (w), 1215 (w), 1090 (s), 995 (s), 965 (s), 885 (w), 755 (s), 665 (w), 510 (w) cm^{-1}; Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88; Found: C, 72.8; H, 10.9.

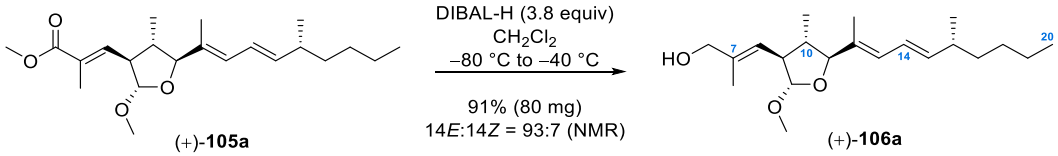


(+)-**103a** (+)-**104a**

Aldehyde (+)-104a by Dess−Martin Oxidation. To an ice-cooled solution of the alcohol (+)-**103a** ($C_{18}H_{32}O_3$, 296.44 g/mol, 99 mg, 0.3340 mmol, 1 equiv) in CH_2Cl_2 (12 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 0.1 mL, 98 mg, 1.239 mmol, 3.71 equiv) was added the Dess−Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 283 mg, 0.6672 mmol, 2 equiv). The white suspension was stirred at 0 °C for 2 h and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver the aldehyde as a mixture of 14-C/15-C double bond isomers (+)-**104a** ($C_{18}H_{30}O_3$, 294.43 g/mol, 82 mg, 0.2785 mmol, 83%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.28 ppm [(*Z*)-**104a**] and 5.59 ppm [(*E*)-**104a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.5 Hz for (*Z*)-**104a** and J = 15.1 Hz for (*E*)-**104a**. $[\alpha]_D^{20}$ = +45.9 (c = 1 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**104a**: R_f 0.63 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H), 1.00 (d, ^{3}J = 6.7 Hz, 3H), 1.09 (d, ^{3}J = 6.7 Hz, 3H), 1.18−1.36 (m, 6H), 1.72 (d, ^{4}J = 0.9 Hz, 3H), 2.13−2.21 (m, 1H), 2.26 (ddq, ^{3}J = 9.2, 8.5, 6.7 Hz, 1H), 2.72 (ddd, ^{3}J = 8.5, 2.7, 1.8 Hz, 1H), 3.40 (s, 3H), 4.07 (d, ^{3}J = 9.2 Hz, 1H), 5.21 (d, ^{3}J = 2.7 Hz, 1H), 5.59 (dd, ^{3}J = 15.1, 8.1 Hz, 1H), 6.04 (d, ^{3}J = 10.8 Hz, 1H), 6.21 (ddd, ^{3}J = 15.1, 10.8 Hz, ^{4}J = 0.9 Hz, 1H), 9.76 (d, ^{3}J = 1.8 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.66, 14.25, 15.99, 20.78, 22.95, 29.75, 36.89, 37.34, 38.13, 55.61, 66.75, 90.30, 103.83, 123.97, 129.5, 131.09, 142.56, 199.30; IR ν 2960 (s), 2925 (s), 2875 (m), 1730 (s), 1460 (m), 1375 (m), 1100 (s), 1030 (s), 995 (s), 965 (s), 885 (w) cm^{-1}. No further analytical data were obtained.

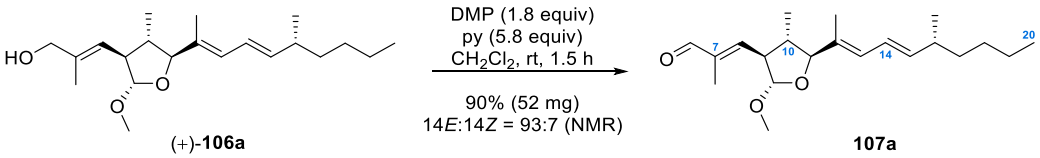


α,β-Unsaturated Ester (+)-105a by Wittig Reaction. A sealable glass pressure tube was charged with a solution of the aldehyde (+)-**104a** ($C_{18}H_{30}O_3$, 294.43 g/mol, 82 mg, 0.2785 mmol, 1 equiv) in toluene (15 mL). Methyl 2-(triphenylphosphoranylidene)propanoate ($CH_3C(=PPh_3)CO_2CH_3$, $C_{22}H_{21}O_2P$, 348.37 g/mol, 970 mg, 2.784 mmol, 10 equiv) was added at room temperature to deliver a light yellow suspension. The tube was sealed with a Teflon screw cap, placed in a pre-heated oil bath (110 °C) and the light yellow suspension was stirred for 4 h at 110 °C. The resulting intensive yellow suspension was cooled to room temperature and was then transferred into a round-bottom flask using ethyl acetate for rinsing. The combined organic phases were concentrated under reduced pressure. The viscous yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to afford the enoate as a mixture of 14-C/15-C double bond isomers (+)-**105a** ($C_{22}H_{36}O_4$, 364.52 g/mol, 95 mg, 0.2606 mmol, 94%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.26 ppm [(*Z*)-**105a**] and 5.58 ppm [(*E*)-**105a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.5 Hz for (*Z*)-**105a** and J = 15.2 Hz for (*E*)-**105a**. $[\alpha]_D^{20}$ = +13.4 (c = 0.5 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**105a**: R_f 0.43 (cyclohexane−ethyl acetate, 10:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.93 (d, ^{3}J = 6.5 Hz, 3H, 10'-CH_3), 1.00 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.19−1.34 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.74 (d, ^{4}J = 1.1 Hz, 3H, 12'-CH_3), 1.88 (ddq, ^{3}J = 9.7, 9.5, 6.6 Hz, 1H, 10-CH), 1.91 (d, ^{4}J = 1.3 Hz, 3H, 7'-CH_3), 2.13−2.21 (m, 1H, 16-CH), 2.78 (ddd, ^{3}J = 10.3, 9.5, 3.9 Hz, 1H, 9-CH), 3.37 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 3.76 (s, 3H, CO_2C<u>H</u>$_3$), 4.07 (d, ^{3}J = 9.7 Hz, 1H, 11-CH), 4.81 (d, ^{3}J = 3.9 Hz, 1H, 9'-C<u>H</u>(OCH$_3$)), 5.58 (dd, ^{3}J = 15.2, 8.1 Hz, 1H, 15-CH), 6.03 (dd, ^{3}J = 10.8 Hz, ^{4}J = 1.1 Hz, 1H, 13-CH), 6.21 (ddd, ^{3}J = 15.2, 10.8, 1Hz, 1H, 14-CH), 6.68 (dq, ^{3}J = 10.3 Hz, ^{4}J = 1.3 Hz, 1H, 8-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.70 (12'-CH_3), 13.06 (7'-CH_3), 14.24 (20-CH_3), 14.55 (10'-CH_3), 20.80 (16'-CH_3), 22.95; 29.75; 36.93 (17,18,19-CH_2), 37.33 (16-CH), 44.52 (10-CH), 52.03 (CO_2<u>C</u>H$_3$), 54.37 (9-CH), 56.04 (9'-CH(O<u>C</u>H$_3$)), 90.43 (11-CH), 109.12 (9'-<u>C</u>H(OCH$_3$)), 124.12 (14-CH), 129.36 (13-CH), 130.11 (7-C), 131.63 (12-C), 140.60 (8-CH) 142.21 (15-CH) 168.53 (<u>C</u>O$_2$CH$_3$); IR ν 2955 (m), 2925 (m), 2870 (w), 1715 (s), 1625 (m), 1455 (m), 1365 (m), 1305 (m), 1265 (m), 1165 (s), 1120 (m), 1095 (s), 1025 (m), 995 (s), 960 (s), 885 (w), 845 (m), 725 (w) cm^{-1}Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95; Found: C, 72.3; H, 9.9.

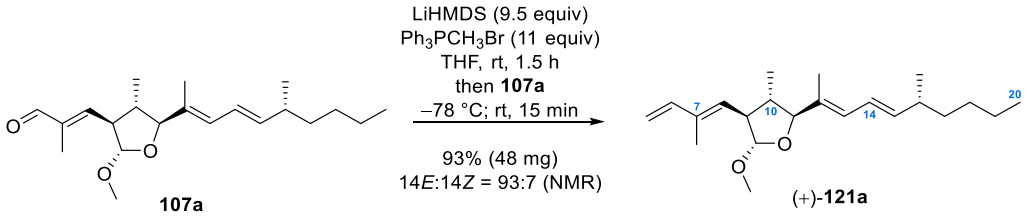


Allylic Alcohol (+)-106a by DIBAL-H Reduction. To a solution of the enoate (+)-**105a** ($C_{22}H_{36}O_4$, 364.52 g/mol, 95 mg, 0.2606 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was dropwise added DIBAL-H (1 M in CH_2Cl_2, 1 mL, 1 mmol, 3.84 equiv) over a period of time of 10 min at −80 °C. The resulting light yellow solution was warmed to –40 °C over a period of time of 1.5 h and the color of the reaction mixture faded. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (10 mL), CH_2Cl_2 (10 mL) and saturated aqueous potassium sodium tartrate solution (10 mL) at –40 °C. The cloudy biphasic mixture was warmed to room temperature and stirring was continued for 30 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver the allylic alcohol (+)-**106a** as a mixture of 14-C/15-C double bond isomers ($C_{21}H_{36}O_3$, 336.51 g/mol, 80 mg, 0.2377 mmol, 91%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**106a**] and 5.57 ppm [(*E*)-**106a**]. The assignment of the 14-C/15-C double bond configuration

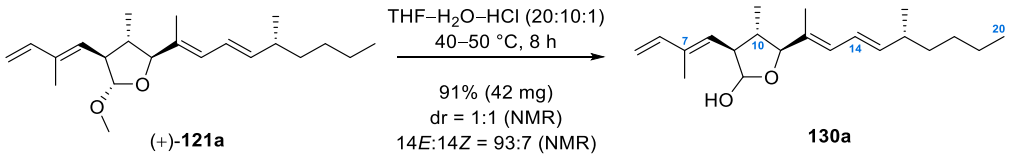
rests on the evaluation of the NMR coupling constants of 15-H: J = 10.4 Hz for (*Z*)-**106a** and J = 15.1 Hz for (*E*)-**106a**. $[\alpha]_D^{20}$ = +70.1 (c 0.2 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**106a**: R_f 0.34 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.90 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.18−1.33 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.37 (br. s., 1H, OH), 1.72 (d, ^{4}J = 1.3 Hz, 3H, 7'-CH_3), 1.74 (d, ^{4}J = 1.0 Hz, 3H, 12'-CH_3), 1.74−1.81 (m, 1H, 10-CH), 2.11−2.22 (m, 1H, 16-CH), 2.67 (ddd, ^{3}J = 9.8, 9.5, 4.2 Hz, 1H, 9-CH), 3.38 (s, 3H, 9'-CH(OC$\underline{H}_3$)), 4.02−4.08 (m, 3H, 6-CH_2, 11-CH), 4.73 (d, ^{3}J = 4.2 Hz, 1H, 9'-C$\underline{H}$(OCH$_3$)), 5.38 (dd, ^{3}J = 9.8 Hz, ^{4}J = 1.3 Hz, 1H, 8-CH), 5.57 (dd, ^{3}J = 15.1, 8.1 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (ddd, ^{3}J = 15.1, 10.8 Hz, ^{4}J = 1.0 Hz, 1H, 14-CH); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.75 (12'-CH_3), 14.25 (20-CH_3), 14.32 (7'-CH_3), 14.44 (10'-CH_3), 20.83 (16'-CH_3), 22.95; 29.76; 36.94 (17,18,19-CH_2), 37.34 (16-CH), 44.61 (10-CH), 53.29 (9-CH), 56.02 (9'-CH(O$\underline{C}$H$_3$)), 68.51 (6-CH_2), 90.40 (11-CH), 110.02 (9'-$\underline{C}$H(OCH$_3$)), 124.20 (14-CH), 124.49 (8-CH), 129.05 (13-CH), 132.10 (12-C), 138.01 (7-C), 141.95 (15-CH); IR ν 3405 (w), 2955 (s), 2925 (s), 2870 (m), 1455 (w), 1375 (w), 1190 (w), 1095 (m), 1005 (s), 965 (s), 885 (w) cm^{-1}; Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; Found: C, 74.3; H, 10.8; HRMS (ESI): m/z $[(M - CH_3O)]^+$ calcd for $C_{20}H_{33}O_2$: 305.24751; Found: 305.24752.



α,β-Unsaturated Aldehyde 107a by Dess−Martin Oxidation. To a solution of the alcohol (+)-**106a** ($C_{21}H_{36}O_3$, 336.51 g/mol, 58 mg, 0.1724 mmol, 1 equiv) in CH_2Cl_2 (6 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 80 µL, 78.4 mg, 0.9912 mmol, 5.75 equiv) was added the Dess−Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 134 mg, 0.3159 mmol, 1.83 equiv) at room temperature. The white suspension was stirred for 1.5 h at room temperature and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver the aldehyde as a mixture of 14-C/15-C double bond isomers **107a** ($C_{21}H_{34}O_3$, 334.49 g/mol, 52 mg, 0.1555 mmol, 90%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.28 ppm [(*Z*)-(16*R*)-**23**] and 5.60 ppm [(*E*)-**107a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**107a** and J = 15.1 Hz for (*E*)-**107a**. Analytical data are reported for (12*E*,14*E*)-**107a**: R_f 0.72 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.88 (dd, ^3J = 7.1 Hz, 3H), 0.97 (d, ^3J = 6.7 Hz, 3H), 1.00 (d, ^3J = 6.7 Hz, 3H), 1.18−1.35 (m, 6H), 1.76 (d, ^4J = 1.1 Hz, 3H), 1.82 (d, ^4J = 1.3 Hz, 3H), 1.93 (ddq, ^3J = 9.5, 9.1, 6.7 Hz, 1H), 2.14−2.21 (m, 1H), 2.97 (ddd, ^3J = 10.1, 9.1, 3.7 Hz, 1H), 3.38 (s, 3H), 4.12 (d, ^3J = 9.5 Hz, 1H), 4.86 (d, ^3J = 3.7 Hz, 1H), 5.60 (dd, ^3J = 15.1, 8.1 Hz, 1H), 6.06 (d, ^3J = 10.9 Hz, 1H), 6.22 (ddd, ^3J = 15.1, 10.9 Hz, ^4J = 1.0 Hz, 1H), 6.40 (dd, ^3J = 10.1 Hz, ^4J = 1.3 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 9.87, 11.76, 14.24, 14.83, 20.78, 22.95, 29.75, 36.91, 37.34, 44.82, 54.65, 55.98, 90.42, 108.77, 124.02, 129.46, 131.28, 141.21, 142.47, 152.14, 194.98. No further analytical data were obtained.

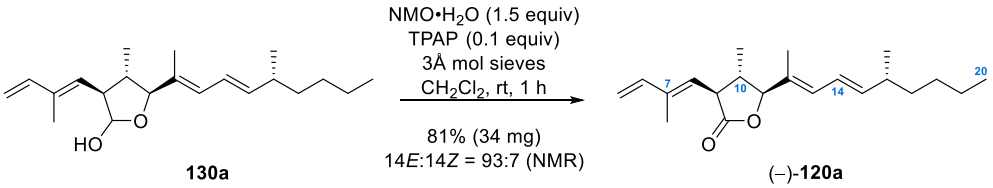


Tetraene (+)-121a by Wittig Reaction. To a suspension of methyltriphenylphosphonium bromide (Ph_3PCH_3Br, $C_{19}H_{18}BrP$, 357.22 g/mol, 611 mg, 1.71 mmol, 11 equiv) in THF (10 mL) at room temperature was added a clear, colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 305 µL, 238 mg, 1.475 mmol, 9.49 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 590 µL, 1.475 mmol, 9.49 equiv) in THF (8 mL) at 0 °C for 30 min. The resulting bright yellow suspension was stirred for 1.5 h at room temperature and was then cooled to –78 °C. A precooled (–78 °C) solution of the enal **107a** ($C_{21}H_{34}O_3$, 334.49 g/mol, 52 mg, 0.1555 mmol, 1 equiv) in THF (5 mL) was added dropwise down along the walls of the flask at –78 °C. The cooling bath was removed and stirring was continued at room temperature for 15 min. The yellow suspension was diluted by successive addition of saturated aqueous NH_4Cl solution (15 ml), H_2O (10 mL) and CH_2Cl_2 (20 mL) at 0 °C. The biphasic decolorized mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1) to afford a mixture of 14-C/15-C double bond isomers of tetraene (+)-**121a** as a colorless oil ($C_{22}H_{36}O_2$, 332.52 g/mol, 48 mg, 0.1444 mmol, 93%, 14*E*:14*Z* = 93:7). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 11-H at 4.05 ppm [(*E*)-**121a**] and 4.09 ppm [(*Z*)-**121a**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. $[\alpha]_D^{20}$ = +36.4 (c = 0.7 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**121a**: R_f 0.72 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H, 20-CH_3), 0.91 (d, ^{3}J = 6.4 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.16−1.36 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.74 (s, 3H, 12'-CH_3), 1.81 (s, 3H, 7'-CH_3) overlapped by 1.75−1.83 (m, 1H, 10-CH), 2.10−2.22 (m, 1H, 16-CH), 2.77 (ddd, ^{3}J = 9.8, 4.0 Hz, 1H, 9-CH), 3.38 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 4.05 (d, ^{3}J = 9.8 Hz, 1H, 11-CH), 4.75 (d, ^{3}J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH_3)), 5.01 (d, ^{3}J = 10.7 Hz, 1H, 5-CH^Z), 5.15 (d, ^{3}J = 17.4 Hz, 1H, 5-CH^E), 5.42 (d, ^{3}J = 9.8 Hz, 1H, 8-CH), 5.57 (dd, ^{3}J = 15.1, 8.1 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.1, 10.8 Hz, 1H, 14-CH), 6.40 (dd, ^{3}J = 17.4, 10.7 Hz, 1H, 6-CH); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.76 (12'-CH_3) 12.40 (7'-CH_3), 14.25 (20-CH_3), 14.51 (10'-CH_3), 20.83 (16'-CH_3), 22.95; 29.76; 36.93 (17,18,19-CH_2), 37.34 (16-CH), 44.87 (10-CH), 53.98 (9-CH), 56.02 (9'-CH(O<u>C</u>H_3)), 90.39 (11-CH), 109.95 (9'-<u>C</u>H(OCH_3)), 112.13 (5-CH_2), 124.19 (14-CH), 129.06 (13-CH), 131.77 (8-CH), 132.03 (12-C), 136.58 (7-C), 141.25 (6-CH), 141.96 (15-CH); IR ν 2955 (m), 2925 (m), 2870 (w), 1455 (w), 1375 (w), 1260 (w), 1185 (w), 1095 (m), 1005 (s), 965 (s), 895 (m), 755 (m) cm^{-1}, Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91; Found: C, 79.2; H, 10.9.



Lactol 130a by Lactol Ether Hydrolysis. A sealable glass pressure tube was charged with a solution of the tetraene (+)-**121a** ($C_{22}H_{36}O_2$, 332.52 g/mol, 48 mg, 0.14435 mmol, 1 equiv) in THF (6 mL) and H_2O (3 mL). Hydrochloric acid (HCl, 37% w/w HCl in H_2O, 0.3 mL) was added dropwise at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear, colorless solution was stirred for 8 h at 40−50 °C. The clear, light yellow solution was cooled to 0 °C and was then diluted by the addition of CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ solution (around 10 mL) until no further evolution of gas was observed. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford a mixture of anomers and 14-C/15-C double bond isomers of lactol **130a** as a colorless viscous oil ($C_{21}H_{34}O_2$, 318.49 g/mol, 42 mg, 0.13187 mmol, 91 %, dr = 1:1, 14*E*:14*Z* = 93:7). The ratio of anomers was determined by integration of the ^{1}H NMR signals of 11-CH at 3.97 ppm and 4.19 ppm and the ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 11-CH at 4.19 ppm [(*E*)-**130a**] and 4.23 ppm [(*Z*)-**130a**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. Analytical data are reported for (12*E*,14*E*)-**130a** as the mixture of anomers: R_f 0.43 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.85−0.91 (m, 9H, 10'-CH_3, 2×20-CH_3), 0.93 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 0.96−1.02 (m, 6H, 2×16'-CH_3), 1.24−1.31 (m, 12H, 2×(17-CH_2, 18-CH_2, 19-CH_2)), 1.58 (br. s., 1H, OH), 1.73 (s, 3H, 12'-CH_3), 1.78−1.85 (m, 10H, 12'-CH_3, 2×7'-CH_3, 10-H), 2.10−2.14 (m, 1H, 10-CH), 2.15−2.19 (m, 2H, 2×16-CH), 2.53−2.59 (m, 1H, OH), 2.72−2.79 (m, 2H, 2×9-CH), 3.97 (d, ^{3}J = 9.9 Hz, 1H, 11-CH), 4.19 (d, ^{3}J = 9.7 Hz, 1H, 11-CH), 4.98−5.04 (m, 2H, 2×5-CH^Z), 5.12−5.19 (m, 2H, 2×5-CH^E), 5.23 (d, ^{3}J = 4.7 Hz, 1H, 9'-CH), 5.31

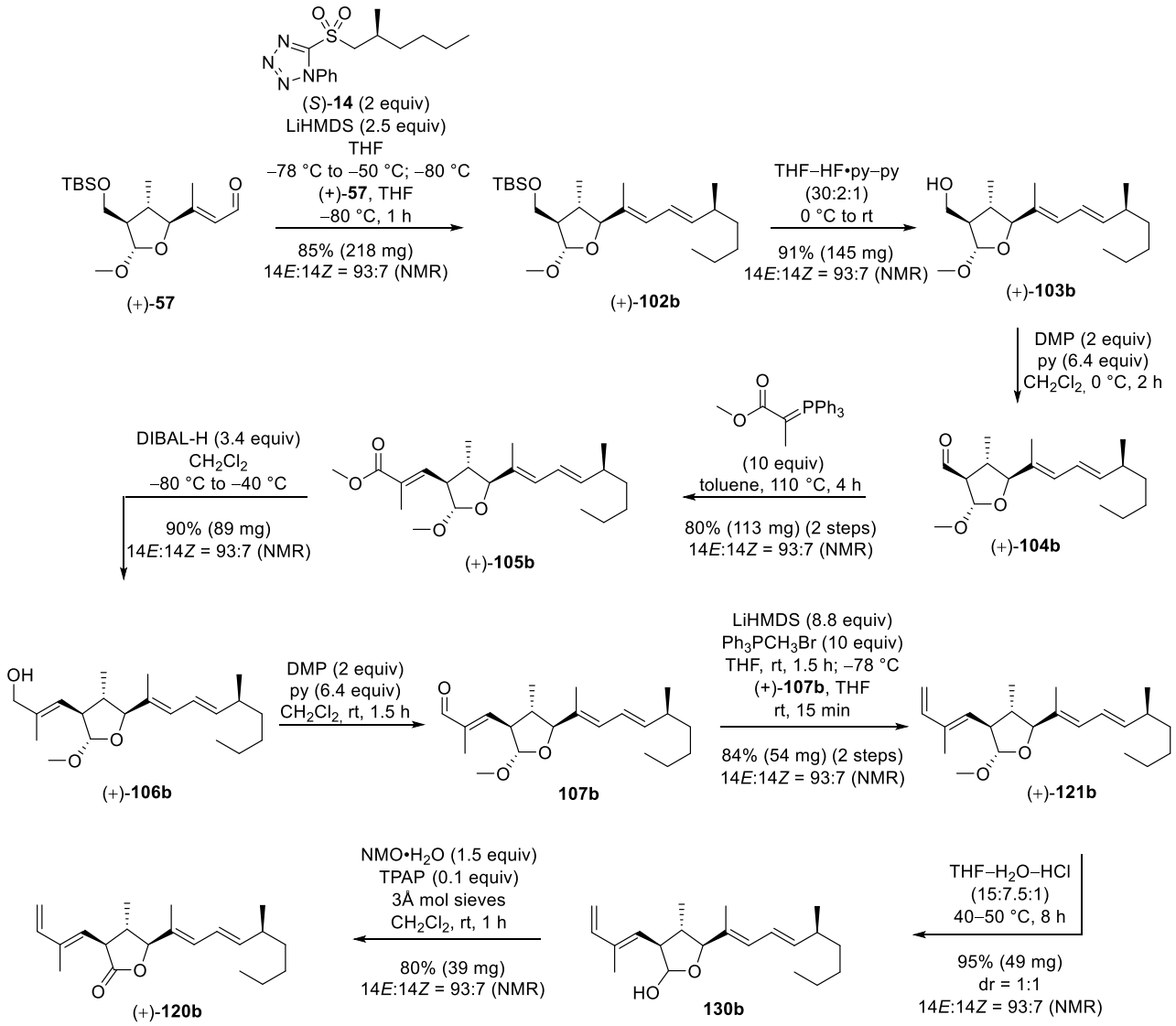
(d, ^3J = 4.7 Hz, 1H, 9'-CH), 5.40 (d, ^3J = 9.9 Hz, 1H, 8-CH), 5.53 (d, ^3J = 9.9 Hz, 1H, 8-CH), 5.55−5.62 (m, 2H, 2×15-CH), 5.98−6.05 (m, 2H, 2×13-CH), 6.18−6.24 (m, 2H, 2×14-CH), 6.42−6.47 (m, 2H, 2×6-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.74 (12'-CH_3), 11.76 (12'-CH_3), 12.50 (7'-CH_3), 12.64 (7'-CH_3), 14.24; 14.35; 14.44 (2×20-CH_3, 2×10'-CH_3), 20.74 (16'-CH_3), 20.76 (16'-CH_3), 22.96; 22.96; 29.74; 29.74; 36.93; 36.94 (2×17,18,19-CH_2), 37.28 (16-CH), 37.28 (16-CH), 40.43 (10-CH), 45.11 (10-CH), 51.52 (9-CH), 55.06 (9-CH), 90.69 (11-CH), 93.41 (11-CH), 98.31 (9'-CH), 103.15 (9'-CH), 111.92 (5-CH_2), 112.23 (5-CH_2), 124.10 (14-CH), 124.34 (14-CH), 128.69; 128.76; 128.82 (2×13-CH, 8-CH), 131.10 (8-CH), 132.11; 133.19; 136.98; 137.14 (2×7-C, 2×12-C), 141.21 (6-CH), 141.48 (6-CH), 141.80 (15-CH), 142.00 (15-CH); IR ν 3395 (w), 2955 (s), 2925 (s), 2855 (m), 1610 (w), 1455 (m), 1375 (w), 1260 (w), 1080 (m), 990 (s), 960 (s), 890 (m), 805 (w) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{35}O_2$: 319.26316; Found: 319.26318; m/z $[(M - H_2O)+H]^+$ calcd for $C_{21}H_{33}O$: 301.25259; Found: 301.25272.

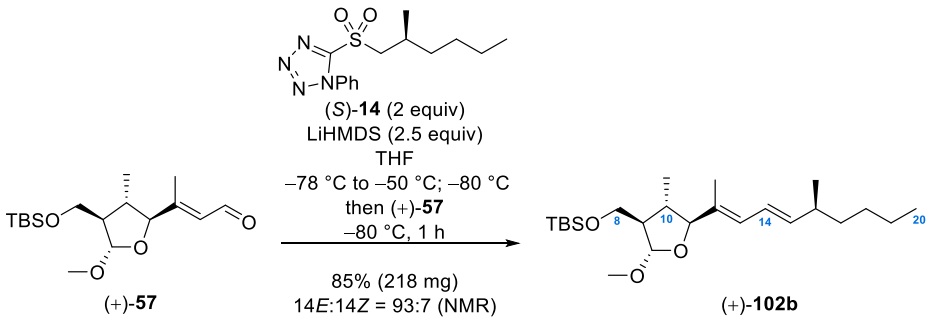


Lactone (–)-120a by Oxidation. To a solution of **130a** ($C_{21}H_{34}O_2$, 318.49 g/mol, 42 mg, 0.13187 mmol, 1 equiv) in CH_2Cl_2 (7 mL) were added molecular sieves (80 mg, 3Å, powdered and dried: 0.1 mbar, 200 °C, 1 h) and 4-methylmorpholine *N*-oxide monohydrate (NMO•H_2O, $C_5H_{11}NO_2$•H_2O, 135.16 g/mol, 27 mg, 0.19976 mmol, 1.51 equiv) at room temperature. The colorless suspension was stirred for 30 minutes at room temperature. Tetra-*n*-propylammonium perruthenate (TPAP, $C_{12}H_{28}NRuO_4$, 351.43 g/mol, 5 mg, 0.01423 mmol, 0.108 equiv) was subsequently added at room temperature. The resulting black suspension was stirred at room temperature for 1 h and was then filtered through a plug of Celite®. The filter cake was thoroughly washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The oily dark residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (–)-**120a** as a colorless oil ($C_{21}H_{32}O_2$, 316.48 g/mol, 34 mg, 0.10743 mmol, 14*E*:14*Z* = 93:7, 81%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.36 ppm [(*E*)-**120a**] and 4.40 ppm [(*Z*)-**120a**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. $[\alpha]_D^{20}$ = –21.2 (c = 0.3 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**120a**: R_f 0.58 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, ^3J = 6.7 Hz, 3H, 20-CH_3), 1.01 (d, ^3J = 6.7 Hz, 3H, 16'-CH_3), 1.05 (d, ^3J = 6.4 Hz, 3H, 10'-CH_3), 1.19−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (s, 3H, 12'-CH_3), 1.83 (d, ^4J = 0.9 Hz, 3H, 7'-CH_3), 2.12−2.25 (m, 2H, 10-CH, 16-CH), 3.26 (dd, ^3J = 11.7, 9.3 Hz, 1H, 9-CH), 4.36 (d, ^3J = 9.8 Hz, 1H, 11-CH), 5.08 (d, ^3J = 10.7 Hz, 1H, 5-CH^Z), 5.23 (d, ^3J = 17.4 Hz, 1H, 5-CH^E), 5.37 (d, ^3J = 9.3 Hz, 1H, 8-CH), 5.66 (dd, ^3J = 15.0, 7.9 Hz, 1H, 15-CH), 6.07 (d, ^3J = 10.9 Hz, 1H, 13-CH), 6.21 (dd, ^3J = 15.0, 10.9 Hz, 1H, 14-CH), 6.42 (dd, ^3J = 17.4, 10.7 Hz, 1H, 6-CH); ^{13}C NMR (126 MHz $CDCl_3$): δ 11.54 (12'-CH_3), 12.67 (7'-CH_3), 14.24 (20-CH_3), 14.93 (10'-CH_3), 20.62 (16'-CH_3), 22.94; 29.72; 36.79 (17,18,19-CH_2), 37.32 (16-CH), 42.68 (10-CH), 48.53 (9-CH), 90.81 (11-CH), 113.55 (5-CH_2), 123.50 (14-CH), 125.49 (8-CH), 129.04 (12-C) 130.58 (13-CH), 139.78 (7-C) 140.52 (6-CH), 143.77 (15-CH) 176.56 (9'-C); IR ν 2960 (m), 2925 (m), 2870 (w), 1770 (s), 1610 (w), 1455 (m), 1380 (w), 1300 (m), 1225 (m), 1195 (w), 1155 (s), 1060 (w), 965 (s), 895 (m), 845 (w), 755 (m), 730 (w), 665 (w), 560 (w), 510 (w), 435 (w) cm^{-1}; Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; Found: C, 79.3; H, 10.2.

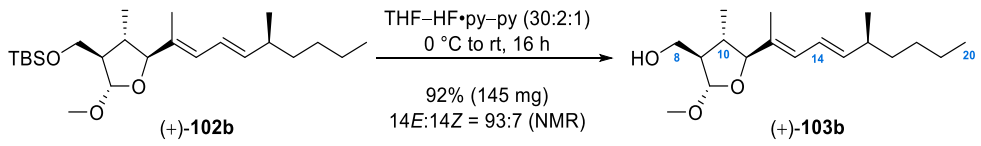
7.5 Synthesis of the cross -metathesis precursor (+)-120b

Synopsis



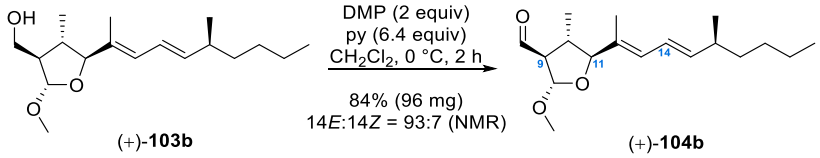


(12*E*,14*E*)-Diene (+)-102b by Julia–Kocienski Olefination. To a solution of the known sulfone (*S*)-**14**[9] ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 390 mg, 1.265 mmol, 2.03 equiv) in THF (14 mL) at –78 °C was added a clear, colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 320 µL, 249.6 mg, 1.547 mmol, 2.48 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 620 µL, 1.550 mmol, 2.48 equiv) in THF (10 mL) at 0 °C for 30 min. The resulting bright yellow solution was warmed to –50 °C over a period of time of 0.5 h and was then cooled to –80 °C. A precooled –80 °C solution of the enal (+)-**57** ($C_{17}H_{32}O_4Si$, 328.52 g/mol, 205 mg, 0.6240 mmol, 1 equiv) in THF (10 mL) was added dropwise down along the walls of the flask causing a color change to light yellow. The resulting light yellow solution was stirred at –80 °C for 1 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (15 mL) and CH_2Cl_2 (15 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver (+)-**102b** as a mixture of 14-C/15-C double bond isomers ($C_{24}H_{46}O_3Si$, 410.71 g/mol, 218 mg, 0.5308 mmol, 85%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**102b**] and 5.58 ppm [(*E*)-**102b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**102b** and J = 15.0 Hz for (*E*)-**102b**. $[\alpha]_D^{25}$ = +55.4 (c = 1 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**102b**: R_f 0.80 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 3H, Si(CH_3)$_2$C(CH_3)$_3$), 0.06 (s, 3H, Si(CH_3)$_2$C(CH_3)$_3$), 0.90 (s, 9H, Si(CH_3)$_2$C(CH_3)$_3$) overlapped by 0.86−0.91 (m, 3H, 20-CH_3), 0.98 (d, ^{3}J = 6.1 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.6 Hz, 3H, 16'-CH_3), 1.19−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.73 (s, 3H, 12'-CH_3), 1.76−1.84 (m, 1H, 10-CH), 1.88 (dddd, ^{3}J = 8.4, 6.2, 5.4, 2.9 Hz, 1H, 9-CH), 2.13−2.22 (m, 1H, 16-CH), 3.37 (s, 3H, 9'-CH(OCH_3)), 3.62 (dd, ^{2}J = 10.1 Hz, ^{3}J = 6.2 Hz, 1H, 8-CH), 3.66 (dd, ^{2}J = 10.1 Hz, ^{3}J = 5.4 Hz, 1H, 8-CH), 4.00 (d, ^{3}J = 9.2 Hz, 1H, 11-CH), 4.83 (d, ^{3}J = 2.9 Hz, 1H, 9'-CH(OCH$_3$)), 5.58 (dd, ^{3}J = 15.0, 7.7 Hz, 1H, 15-CH), 6.02 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.0, 10.8 Hz, 1H, 14-CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ −5.31 (Si(CH_3)$_2$C(CH_3)$_3$), −5.29 (Si(CH_3)$_2$C(CH_3)$_3$), 11.89 (12'-CH_3), 14.24 (20-CH_3), 15.92 (10'-CH_3), 18.38 (Si(CH_3)$_2$C(CH_3)$_3$), 20.72 (16'-CH_3), 22.99; 29.72; 36.91 (17,18,19-CH_2), 26.00 (Si(CH_3)$_2$C(CH_3)$_3$), 37.19 (16-CH), 38.99 (10-CH), 55.50 (9'-CH(OCH_3)), 56.63 (9-CH), 62.55 (8-CH_2), 90.34 (11-CH), 107.39 (9'-CH(OCH$_3$)), 124.12 (14-CH), 128.36 (13-CH), 132.76 (12-C), 141.70 (15-CH); IR ν 2955 (m), 2930 (m), 2855 (m), 1460 (w), 1375 (w), 1255 (m), 1215 (w), 1190 (w), 1095 (s), 995 (m), 965 (m), 885 (w), 835 (s), 775 (m), 755 (s), 670 (w), 630 (w) cm^{-1}; Anal. Calcd. for $C_{24}H_{46}O_3Si$: C, 70.19; H, 11.29; Found: C, 70.2; H, 11.3.



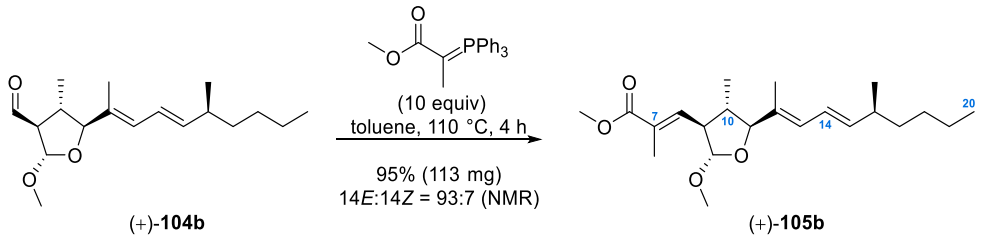
Alcohol (+)-103b by TBS Ether Cleavage. A polypropylene reaction vessel was charged with a solution of hydrogen fluoride•pyridine (HF•pyridine, C_5H_6FN, 65−70% w/w HF in pyridine (py), 1 mL) in THF (3 mL). To the clear, slightly brownish solution was dropwise added pyridine (py, C_5H_5N, 0.5 mL) at room temperature and the mixture was stirred for 15 min at room temperature. The clear, slightly brownish solution was dropwise transferred to a solution of (+)-**102b** ($C_{24}H_{46}O_3Si$, 410.71 g/mol, 218 mg, 0.5308 mmol, 1 equiv) in THF (12 mL) at 0 °C in a separate sealable polypropylene reaction vessel. The reaction vessel was sealed with a polypropylene screw cap and the reaction mixture was allowed to

warm to room temperature overnight. The clear, slightly brownish solution was diluted by the successive addition of saturated aqueous $NaHCO_3$ solution (30 mL), H_2O (10 mL) and CH_2Cl_2 (30 mL) at 0 °C. The biphasic mixture was vigorously stirred for 20 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate: 20:1 to 10:1 to 5:1) to deliver (+)-**103b** as a mixture of 14-C/15-C double bond isomers ($C_{18}H_{32}O_3$, 296.44 g/mol, 145 mg, 0.4891 mmol, 92%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.26 ppm [(*Z*)-**103b**] and 5.59 ppm [(*E*)-**103b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.5 Hz for (*Z*)-**103b** and J = 15.2 Hz for (*E*)-**103b**. Analytical data are reported for (12*E*,14*E*)-**103b**: R_f 0.31 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +81.8 (c = 1 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.1 Hz, 3H, 20-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.02 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 1.18−1.34 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.43 (dd, 1H, ^{3}J = 4.9 Hz, OH), 1.73 (s, 3H, 12'-CH_3) overlapped by 1.68−1.77 (m, 1H, 10-CH), 1.95 (dddd, ^{3}J = 8.4, 7.9, 5.1, 2.9 Hz, 1H, 9-CH), 2.14−2.21 (m, 1H, 16-CH), 3.39 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 3.65 (ddd, ^{2}J = 10.3 Hz, ^{3}J = 7.9, 4.9 Hz, 1H, 8-CH), 3.75 (ddd, ^{2}J = 10.3 Hz, ^{3}J = 5.1, 4,9 Hz, 1H, 8-CH), 4.02 (d, ^{3}J = 9.2 Hz, 1H, 11-CH), 4.89 (d, ^{3}J = 2.9 Hz, 1H, 9'-C<u>H</u>(OCH$_3$)), 5.59 (dd, ^{3}J = 15.2, 7.9 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.9 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.2, 10.9 Hz, 1H, 14-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 11.99 (12'-CH_3), 14.24 (20-CH_3), 16.03 (10'-CH_3), 20.70 (16'-CH_3), 22.98; 29.71; 36.89 (17,18,19-CH_2), 37.19 (16-CH), 39.34 (10-CH), 55.47 (9'-CH(O<u>C</u>H$_3$)), 56.62 (9-CH), 63.30 (8-CH_2), 90.09 (11-CH), 107.59 (9'-<u>C</u>H(OCH$_3$)), 124.03 (14-CH), 128.54 (13-CH), 132.28 (12-C), 141.98 (15-CH); IR ν 3425 (w), 2955 (m), 2925 (m), 2870 (w), 1455 (w), 1375 (w), 1090 (s), 995 (s), 965 (s), 885 (w), 755 (s), 665 (w), 510 (w) cm^{-1}; Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88; Found: C, 72.7; H, 10.9.

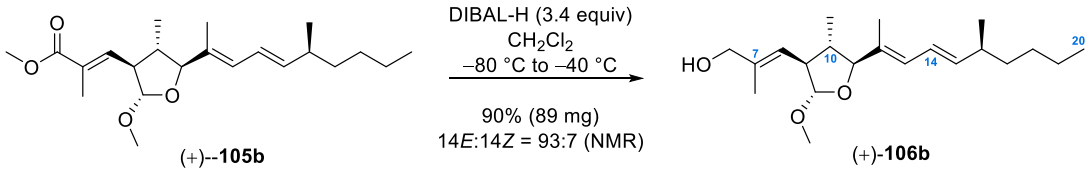


(+)-**103b** (+)-**104b**

Aldehyde (+)-104b by Dess−Martin Oxidation. To an ice-cooled solution of the alcohol (+)-**103b** ($C_{18}H_{32}O_3$, 296.44 g/mol, 115 mg, 0.3879 mmol, 1 equiv) in CH_2Cl_2 (16 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 0.2 mL, 196 mg, 2.478 mmol, 6.39 equiv) was added the Dess−Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 329 mg, 0.7757 mmol, 2 equiv). The white suspension was stirred at 0 °C for 2 h and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to deliver the aldehyde as a mixture of 14-C/15-C double bond isomers (+)-**104b** ($C_{18}H_{30}O_3$, 294.43 g/mol, 96 mg, 0.3261 mmol, 84%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.29 ppm [(*Z*)-**104b**] and 5.61 ppm [(*E*)-**104b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.5 Hz for (*Z*)-**104b** and J = 15.2 Hz for (*E*)-**104b**. $[\alpha]_D^{20}$ = +84.9 (c = 1 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**104b**: R_f 0.85 (cyclohexane−ethyl acetate, 1:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.9 Hz, 3H), 1.00 (d, ^{3}J = 6.7 Hz, 3H), 1.10 (d, ^{3}J = 6.7 Hz, 3H), 1.17−1.36 (m, 6H), 1.72 (s, 3H), 2.13−2.21 (m, 1H), 2.26 (ddq, ^{3}J = 9.3, 8.6, 6.7 Hz, 1H), 2.72 (ddd, ^{3}J = 8.6, 2.6, 1.9 Hz, 1H), 3.39 (s, 3H), 4.07 (d, ^{3}J = 9.3 Hz, 1H), 5.21 (d, ^{3}J = 2.6 Hz, 1H), 5.61 (dd, ^{3}J = 15.2, 7.9 Hz, 1H), 6.04 (d, ^{3}J = 10.8 Hz, 1H), 6.21 (ddd, ^{3}J = 15.2, 10.8 Hz, 1H), 9.76 (d, ^{3}J = 1.9 Hz, 1H); ^{13}C NMR (176 MHz $CDCl_3$) δ 11.79, 14.23, 16.06, 20.66, 22.97, 29.70, 36.85, 37.20, 38.23, 55.57, 66.79, 90.22, 103.84, 123.86, 129.32, 131.21, 142.54, 199.26; IR ν 2960 (s), 2925 (s), 2875 (m), 1730 (s), 1460 (m), 1375 (m), 1100 (s), 1030 (s), 995 (s), 965 (s), 885 (w) cm^{-1}; Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; Found: C, 73.0; H, 10.2.

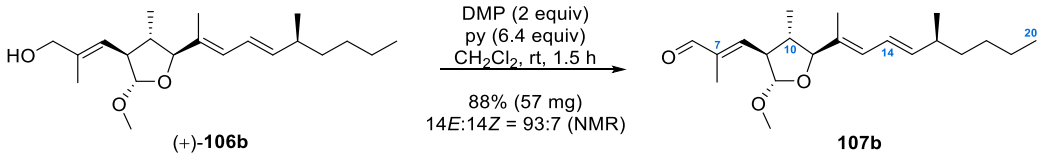


α,β-Unsaturated Ester (+)-105b by Wittig Reaction. A sealable glass pressure tube was charged with a solution of the aldehyde (+)-**104b** ($C_{18}H_{30}O_3$, 294.43 g/mol, 96 mg, 0.3261 mmol, 1 equiv) in toluene (17 mL). Methyl 2-(triphenylphosphoranylidene)propanoate ($CH_3C(=PPh_3)CO_2CH_3$, $C_{22}H_{21}O_2P$, 348.37 g/mol, 1.136 g, 3.261 mmol, 10 equiv) was added at room temperature to deliver a light yellow suspension. The tube was sealed with a Teflon screw cap, placed in a pre-heated oil bath (110 °C) and the light yellow suspension was stirred for 4 h at 110 °C. The resulting intensive yellow suspension was cooled to room temperature and was then transferred into a round-bottom flask using ethyl acetate for rinsing. The combined organic phases were concentrated under reduced pressure. The viscous yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to afford the enoate as a mixture of 14-C/15-C double bond isomers (+)-**105b** ($C_{22}H_{36}O_4$, 364.52 g/mol, 113 mg, 0.3100 mmol, 95%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.27 ppm [(*Z*)- **105b**] and 5.60 ppm [(*E*)-**105b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**105b** and J = 15.2 Hz for (*E*)-**105b**. $[\alpha]_D^{20}$ = +42.5 (c = 1 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**105b**: R_f 0.81 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H, 20-CH_3), 0.93 (d, ^{3}J = 6.8 Hz, 3H, 10'-CH_3), 1.00 (d, ^{3}J = 6.8 Hz, 3H, 16'-CH_3), 1.19−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.74 (d, ^{4}J = 1.0 Hz, 3H, 12'-CH_3), 1.91 (d, ^{4}J = 1.5 Hz, 3H, 7'-CH_3) overlapped by 1.82−1.93 (m, 1H, 10-CH), 2.12−2.23 (m, 1H, 16-CH), 2.78 (ddd, ^{3}J = 10.3, 9.5, 3.9 Hz, 1H, 9-CH), 3.37 (s, 3H, 9'-CH(OC$\underline{H}_3$)), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 4.07 (d, ^{3}J = 9.8 Hz, 1H, 11-CH), 4.80 (d, ^{3}J = 3.9 Hz, 1H, 9'-C$\underline{H}$(OCH$_3$)), 5.60 (dd, ^{3}J = 15.2, 7.8 Hz, 1H, 15-CH), 6.03 (dd, ^{3}J = 10.8 Hz, ^{4}J = 1.0 Hz, 1H, 13-CH), 6.21 (app dd, ^{3}J = 15.2, 10.8, Hz, 1H, 14-CH), 6.68 (dq, ^{3}J = 10.3 Hz, ^{4}J = 1.5 Hz, 1H, 8-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.70 (12'-CH_3), 13.06 (7'-CH_3), 14.24 (20-CH_3), 14.55 (10'-CH_3), 20.80 (16'-CH_3), 22.95; 29.75; 36.93 (17,18,19-CH_2), 37.33 (16-CH), 44.52 (10-CH), 52.03 ($CO_2C\underline{H}_3$), 54.37 (9-CH), 56.04 (9'-CH(O$\underline{C}$H$_3$)), 90.43 (11-CH), 109.12 (9'-$\underline{C}$H(OCH$_3$)), 124.12 (14-CH), 129.36 (13-CH), 130.11 (7-C), 131.63 (12-C), 140.60 (8-CH) 142.21 (15-CH) 168.53 ($\underline{C}O_2CH_3$); IR ν 2955 (m), 2925 (m), 2870 (w), 1715 (s), 1650 (w), 1435 (m), 1375 (w), 1290 (m), 1245 (m), 1215 (w), 1190 (w), 1140 (m), 1095 (s), 1015 (s), 965 (s), 825 (w), 750 (s), 665 (w), 515 (w) cm^{-1}Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95; Found: C, 72.5; H, 10.0.

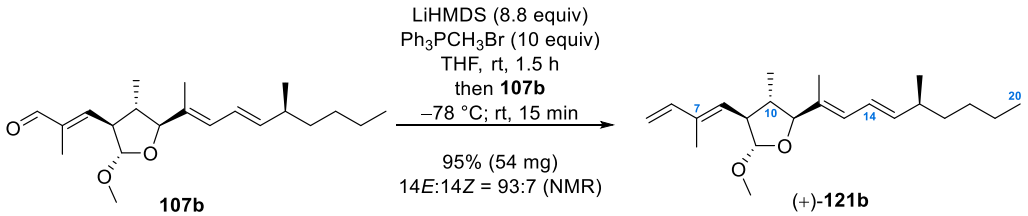


Allylic Alcohol (+)-106b by DIBAL-H Reduction. To a solution of the enoate (+)-**105b** ($C_{22}H_{36}O_4$, 364.52 g/mol, 107 mg, 0.2935 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was dropwise added DIBAL-H (1 M in CH_2Cl_2, 1 mL, 1 mmol, 3.41 equiv) over a period of time of 10 min at −80 °C. The resulting light yellow solution was warmed to –40 °C over a period of time of 1.5 h and the color of the reaction mixture faded. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (10 mL), CH_2Cl_2 (10 mL) and saturated aqueous potassium sodium tartrate solution (10 mL) at –40 °C. The cloudy biphasic mixture was warmed to room temperature and stirring was continued for 30 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver a mixture of 14-C/15-C double bond isomers of the allylic alcohol (+)-**106b** ($C_{21}H_{36}O_3$, 336.51 g/mol, 89 mg, 0.2645 mmol, 90%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR

signal of 15-H at 5.26 ppm [(*Z*)-**106b**] and 5.59 ppm [(*E*)-**106b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.6 Hz for (*Z*)-**106b** and J = 15.1 Hz for (*E*)-**106b**. A diastereomerically enriched sample (dr = 94:6) of the major diastereomer was obtained by flash chromatography (cyclohexane–ethyl acetate, 20:1). $[\alpha]_D^{20}$ = +129.1 (c 0.85 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*,16*S*)-**22**: R_f 0.34 (cyclohexane–ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.91 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.8 Hz, 3H, 16'-CH_3), 1.20–1.33 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.34–1.40 (m, 1H, OH), 1.72 (s, 3H, 7'-CH_3), 1.74 (s, 3H, 12'-CH_3), 1.73–1.80 (m, 1H, 10-CH), 2.12–2.22 (m, 1H, 16-CH), 2.67 (ddd, ^{3}J = 9.7, 9.5, 4.0 Hz, 1H, 9-CH), 3.38 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 4.01–4.08 (m, 3H, 6-CH_2, 11-CH), 4.73 (d, ^{3}J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH_3)), 5.38 (d, ^{3}J = 9.5 Hz, 1H, 8-CH), 5.59 (dd, ^{3}J = 15.1, 7.7 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (ddd, ^{3}J = 15.1, 10.8 Hz, 1H, 14-CH); ^{13}C NMR (176 MHz $CDCl_3$) δ 11.90 (12'-CH_3), 14.24 (20-CH_3), 14.31 (7'-CH_3), 14.52 (10'-CH_3), 20.69 (16'-CH_3), 22.98; 29.70; 36.89 (17,18,19-CH_2), 37.18 (16-CH), 44.73 (10-CH), 53.32 (9-CH), 55.96 (9'-CH(O<u>C</u>H_3)), 68.53 (6-CH_2), 90.30 (11-CH), 110.00 (9'-<u>C</u>H(OCH_3)), 124.07 (14-CH), 124.58 (8-CH), 128.85 (13-CH), 132.22; 137.99 (7-C, 12-C), 141.93 (15-CH); IR ν 3395 (w), 2955 (m), 2925 (m), 2860 (m), 1455 (m), 1375 (m), 1260 (w),1185 (w), 1095 (m), 1000 (s), 960 (s), 885 (m) cm^{-1}; Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; Found: C, 74.9; H, 10.9.

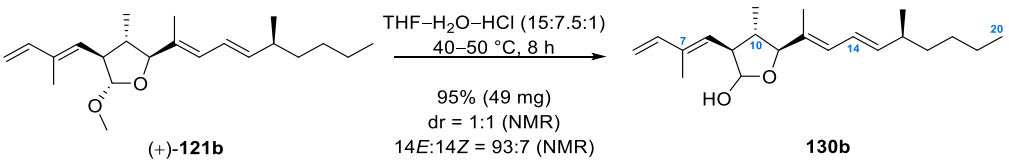


α,β-Unsaturated Aldehyde 107b by Dess–Martin Oxidation. To a solution of the alcohol (+)-**106b** ($C_{21}H_{36}O_3$, 336.51 g/mol, 65 mg, 0.1932 mmol, 1 equiv) in CH_2Cl_2 (10 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 100 µL, 98 mg, 1.2389 mmol, 6.41 equiv) was added the Dess–Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 164 mg, 0.3867 mmol, 2 equiv) at room temperature. The white suspension was stirred for 1.5 h at room temperature and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane–ethyl acetate, 100:1 to 50:1) to deliver a mixture of 14-C/15-C double bond isomers of the aldehyde **107b** ($C_{21}H_{34}O_3$, 334.49 g/mol, 57 mg, 0.1704 mmol, 88%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.29 ppm [(*Z*)-**107b**] and 5.62 ppm [(*E*)-**107b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.4 Hz for (*Z*)-**107b** and J = 15.1 Hz for (*E*)-**107b**. Analytical data are reported for (12*E*,14*E*)-**107b**: R_f 0.48 (cyclohexane–ethyl acetate,5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.9 Hz, 3H), 0.97 (d, ^{3}J = 6.7 Hz, 3H), 1.00 (d, ^{3}J = 6.7 Hz, 3H), 1.19–1.34 (m, 6H), 1.76 (s, 3H), 1.81 (s, 3H), 1.92 (ddq, ^{3}J = 9.6, 9.5, 6.7 Hz, 1H), 2.13–2.23 (m, 1H), 2.97 (ddd, ^{3}J = 10.1, 9.6, 3.7 Hz, 1H), 3.38 (s, 3H), 4.12 (d, ^{3}J = 9.5 Hz, 1H), 4.86 (d, ^{3}J = 3.7 Hz, 1H), 5.62 (dd, ^{3}J = 15.1, 7.9 Hz, 1H), 6.06 (d, ^{3}J = 10.9 Hz, 1H), 6.22 (ddd, ^{3}J = 15.1, 10.9 Hz, 1H), 6.40 (dd, ^{3}J = 10.1 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 9.88, 11.87, 14.25, 14.86, 20.68, 22.99, 29.71, 36.85, 37.22, 44.86, 54.64, 55.98, 90.33, 108.71, 123.89, 129.35, 131.30, 141.16, 142.49, 152.20, 195.05; no further analytical data were obtained.



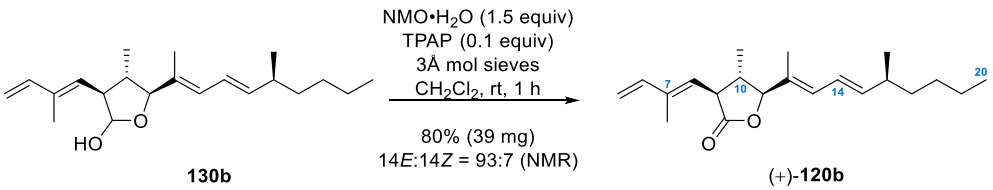
Tetraene (+)-121b by Wittig Reaction. To a suspension of methyltriphenylphosphonium bromide (Ph_3PCH_3Br, $C_{19}H_{18}BrP$, 357.22 g/mol, 610 mg, 1.7076 mmol, 10.02 equiv) in THF (10 mL) at room temperature was added a clear,

colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 310 µL, 241.8 mg, 1.498 mmol, 8.79 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 600 µL, 1.500 mmol, 8.80 equiv) in THF (8 mL) at 0 °C for 30 min. The resulting bright yellow suspension was stirred for 1.5 h at room temperature and was then cooled to –78 °C. A precooled (–78 °C) solution of the enal **107b** ($C_{21}H_{34}O_3$, 334.49 g/mol, 57 mg, 0.1704 mmol, 1 equiv) in THF (5 mL) was added dropwise down along the walls of the flask at –78 °C. The cooling bath was removed and stirring was continued at room temperature for 15 min. The yellow suspension was diluted by successive addition of saturated aqueous NH_4Cl solution (15 ml), H_2O (10 mL) and CH_2Cl_2 (20 mL) at 0 °C. The biphasic decolorized mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1) to afford a mixture of 14-C/15-C double bond isomers of tetraene (+)-**121b** as a colorless oil ($C_{22}H_{36}O_2$, 332.52 g/mol, 54 mg, 0.1624 mmol, 95%, 14*E*:14*Z* = 93:7). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 11-H at 4.05 ppm [(*E*)-**121b**] and 4.09 ppm [(*Z*)-**121b**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. $[\alpha]_D^{20}$ = +64.3 (c = 0.82 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**121b**: R_f 0.72 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.92 (d, ^{3}J = 6.5 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.19−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (d, ^{4}J = 1.2 Hz, 3H, 12'-CH_3), 1.81 (d, ^{4}J = 1.2 Hz, 3H, 7'-CH_3) overlapped by 1.75−1.82 (m, 1H, 10-CH), 2.12−2.22 (m, 1H, 16-CH), 2.77 (ddd, ^{3}J = 9.8, 9.5, 4.0 Hz, 1H, 9-CH), 3.37 (s, 3H, 9'-CH(OC$\underline{H}_3$)), 4.05 (d, ^{3}J = 9.8 Hz, 1H, 11-CH), 4.75 (d, ^{3}J = 4.0 Hz, 1H, 9'-C$\underline{H}$(OCH_3)), 5.01 (d, ^{3}J = 10.7 Hz, 1H, 5-CH^Z), 5.15 (d, ^{3}J = 17.4 Hz, 1H, 5-CH^E), 5.42 (d, ^{3}J = 9.8 Hz, 1H, 8-CH), 5.60 (dd, ^{3}J = 15.1, 7.9 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.7 Hz, ^{4}J = 1.2 Hz, 1H, 13-CH), 6.21 (app dd, ^{3}J = 15.1, 10.8 Hz, 1H, 14-CH), 6.40 (dd, ^{3}J = 17.4, 10.7 Hz, 1H, 6-CH); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.90 (12'-CH_3) 12.41 (7'-CH_3), 14.26 (20-CH_3), 14.57 (10'-CH_3), 20.71 (16'-CH_3), 22.99; 29.71; 36.88 (17,18,19-CH_2), 37.20 (16-CH), 44.95 (10-CH), 54.00 (9-CH), 56.00 (9'-CH(O$\underline{C}H_3$)), 90.30 (11-CH), 109.92 (9'-$\underline{C}$H(OCH_3)), 112.13 (5-CH_2), 124.06 (14-CH), 128.90 (13-CH), 131.81 (8-CH), 132.11; 136.56 (7-C, 12-C), 141.26 (6-CH), 141.97 (15-CH); IR ν 2955 (m), 2925 (m), 2870 (w), 1610 (w),1455 (w), 1375 (w), 1305 (w), 1260 (w), 1185 (w), 1095 (m), 1000 (s), 960 (s), 895 (m), 800 (w), 730 (w), 525 (w), 435 (w) cm^{-1}, Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91; Found: C, 79.3; H, 11.0.



Lactol 130b by Lactol Ether Hydrolysis. A sealable glass pressure tube was charged with a solution of the tetraene (+)-**121b** ($C_{22}H_{36}O_2$, 332.52 g/mol, 54 mg, 0.1624 mmol, 1 equiv) in THF (6 mL) and H_2O (3 mL). Hydrochloric acid (HCl, 37% w/w HCl in H_2O, 0.4 mL) was added dropwise at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear, colorless solution was stirred for 8 h at 40−50 °C. The clear, light yellow solution was cooled to 0 °C and was then diluted by the addition of CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ solution (around 10 mL) until no further evolution of gas was observed. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford a mixture of anomers and 14-C/15-C double bond isomers of lactol **130b** as a colorless viscous oil ($C_{21}H_{34}O_2$, 318.49 g/mol, 49 mg, 0.1539 mmol, 95 %, dr = 1:1, 14*E*:14*Z* = 93:7). The ratio of anomers was determined by integration of the ^{1}H NMR signals of 11-CH at 3.98 ppm and 4.19 ppm and the ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 11-CH at 4.19 ppm [(*E*)-**130b**] and 4.24 ppm [(*Z*)-**130b**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. Analytical data are reported for (12*E*,14*E*)-**130b** as the mixture of anomers: R_f 0.43 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.86−0.92 (m, 9H), 0.94 (d, ^{3}J = 6.5 Hz, 3H), 1.00 (d, ^{3}J = 6.7 Hz, 6H), 1.21−1.34 (m, 12H), 1.73 (s, 3H), 1.79 (s, 3H), 1.81 (s, 3H), 1.83 (s, 3H) overlapped by 1.81−1.87 (m, 1H), 2.08−2.15 (m, 1H), 2.15−2.21 (m, 2H), 2.43 (d, ^{3}J = 2.9 Hz, 1H), 2.62 (d, ^{3}J = 3.9 Hz, 1H), 2.71−2.79 (m, 2H), 3.98 (d, ^{3}J = 9.7 Hz, 1H), 4.19 (d, ^{3}J = 9.7 Hz, 1H), 4.99−5.04 (m, 2H), 5.13−5.19 (m, 2H), 5.23 (dd, ^{3}J = 4.5, 3.9 Hz, 1H), 5.31 (dd, ^{3}J = 4.5, 2.9 Hz, 1H), 5.40 (d, ^{3}J = 9.9 Hz, 1H), 5.52 (d, ^{3}J = 9.7 Hz, 1H), 5.59 (dd, ^{3}J = 15.2, 7.9 Hz, 2H), 5.98−6.05 (m, 2H), 6.18−6.24 (m, 2H), 6.37−6.48 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.83 (CH_3), 11.89 (CH_3),

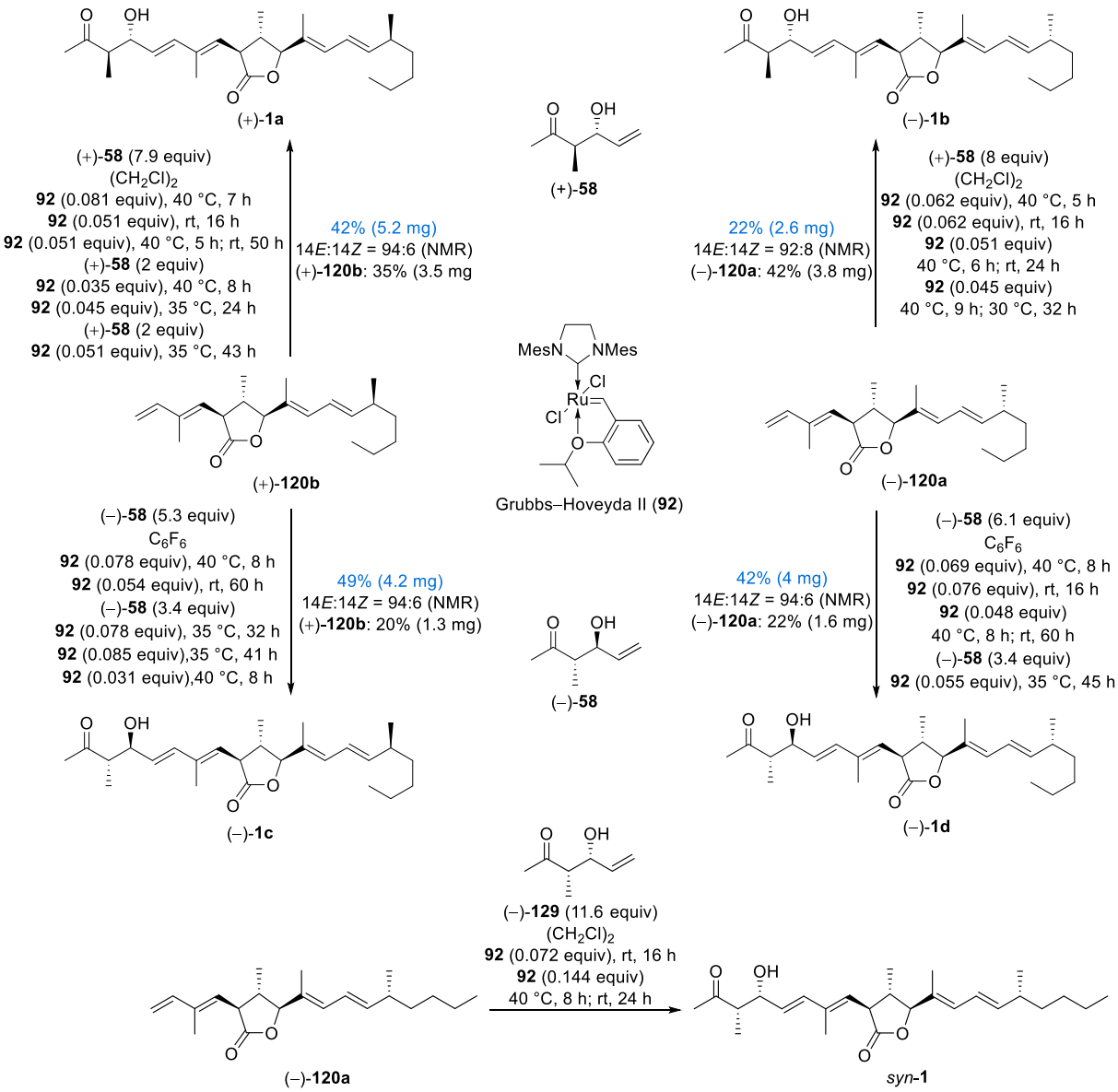
12.51 (CH_3), 12.65 (CH_3), 14.24 (CH_3), 14.40 (CH_3), 14.51 (CH_3), 20.66 (CH_3), 20.67 (CH_3), 22.99 (CH_2), 29.71 (CH_2), 36.89 (CH_2), 36.90 (CH_2), 37.17 (CH), 37.19 (CH), 40.49 (CH), 45.22 (CH), 51.56 (CH), 55.12 (CH), 90.61 (CH), 93.35 (CH), 98.33 (CH), 103.15 (CH), 111.94 (CH_2), 112.23 (CH_2), 124.01 (CH), 124.24 (CH), 128.54 (CH), 128.64 (CH), 128.76 (CH), 131.12 (CH), 132.20 (C), 133.27 (C), 137.00 (C), 137.14 (C), 141.22 (CH), 141.48 (CH), 141.81 (CH), 142.00 (CH); IR ν 3390 (w), 2955 (m), 2925 (m), 2855 (w), 1610 (w), 1455 (m), 1375 (w), 1080 (m), 990 (s), 960 (s), 890 (s), 620 (w) cm^{-1}; no further analytical data were obtained.

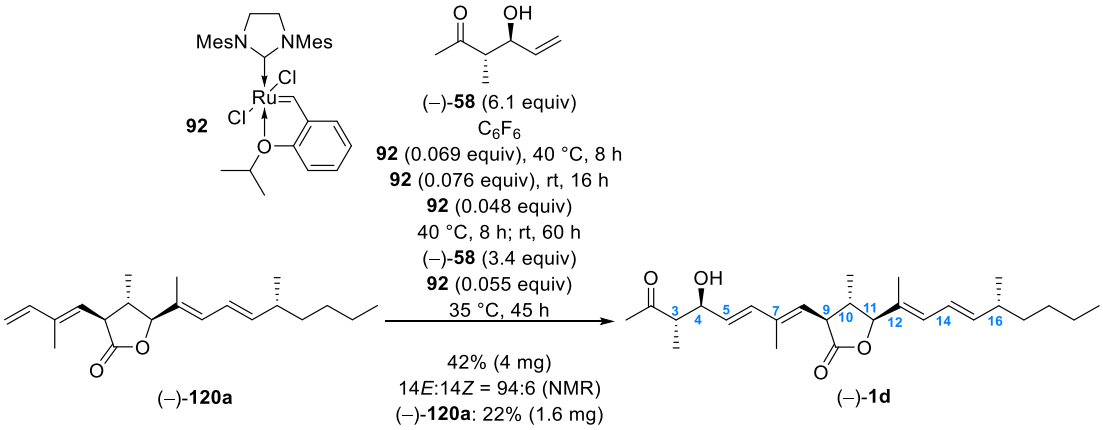


Lactone (+)-120b by Oxidation. To a solution of **130b** ($C_{21}H_{34}O_2$, 318.49 g/mol, 49 mg, 0.15385 mmol, 1 equiv) in CH_2Cl_2 (10 mL) were added molecular sieves (100 mg, 3Å, powdered and dried: 0.1 mbar, 200 °C, 1 h) and 4-methylmorpholine *N*-oxide monohydrate (NMO•H_2O, $C_5H_{11}NO_2$•H_2O, 135.16 g/mol, 32 mg, 0.23676 mmol, 1.54 equiv) at room temperature. The colorless suspension was stirred for 30 minutes at room temperature. Tetra-*n*-propylammonium perruthenate (TPAP, $C_{12}H_{28}NRuO_4$, 351.43 g/mol, 6 mg, 0.01707 mmol, 0.11 equiv) was subsequently added at room temperature. The resulting black suspension was stirred at room temperature for 1 h and was then filtered through a plug of Celite®. The filter cake was thoroughly washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The oily dark residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (+)-**120b** as a colorless oil ($C_{21}H_{32}O_2$, 316.48 g/mol, 39 mg, 0.12323 mmol, 14*E*:14*Z* = 93:7, 80%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.36 ppm [(*E*)-**120b**] and 4.40 ppm [(*Z*)-**120b**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. $[\alpha]_D^{20}$ = +4.6 (c = 0.52 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**120b**: R_f 0.58 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, ^{3}J = 7.0 Hz, 3H), 1.01 (d, ^{3}J = 6.6 Hz, 3H), 1.06 (d, ^{3}J = 6.2 Hz, 3H), 1.21−1.34 (m, 6H), 1.75 (s, 3H), 1.83 (s, 3H), 2.14−2.23 (m, 2H), 3.26 (dd, ^{3}J = 11.7, 9.2 Hz, 1H), 4.36 (d, ^{3}J = 9.9 Hz, 1H), 5.08 (d, ^{3}J = 11.0 Hz, 1H), 5.23 (d, ^{3}J = 17.6 Hz, 1H), 5.37 (d, ^{3}J = 9.2 Hz, 1H), 5.67 (dd, ^{3}J = 15.0, 7.7 Hz, 1H), 6.07 (d, ^{3}J = 10.8 Hz, 1H), 6.21 (dd, ^{3}J = 15.0, 10.8 Hz, 1H), 6.42 (dd, ^{3}J = 17.6, 11.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.63 (CH_3), 12.68 (CH_3), 14.23 (CH_3), 14.99 (CH_3), 20.54 (CH_3), 22.97 (CH_2), 29.70 (CH_2), 36.78 (CH_2), 37.25 (CH), 42.73 (CH), 48.57 (CH), 90.76 (CH), 113.53 (CH_2), 123.46 (CH), 125.52 (CH), 129.11 (C), 130.50 (CH), 139.80 (C), 140.55 (CH), 143.78 (CH), 176.51 (C); IR ν 2960 (m), 2925 (m), 2875 (m), 1770 (s), 1455 (m), 1375 (m), 1300 (m), 1230 (m), 1195 (w), 1155 (s), 1135 (m), 1060 (w), 985 (s), 965 (s), 935 (m), 895 (s), 845 (w), 730 (w), 660 (w), 560 (w), 435 (w) cm^{-1}; Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; Found: C, 76.9; H, 9.9; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{21}H_{33}O_2$: 317.24751; Found: 317.24762.

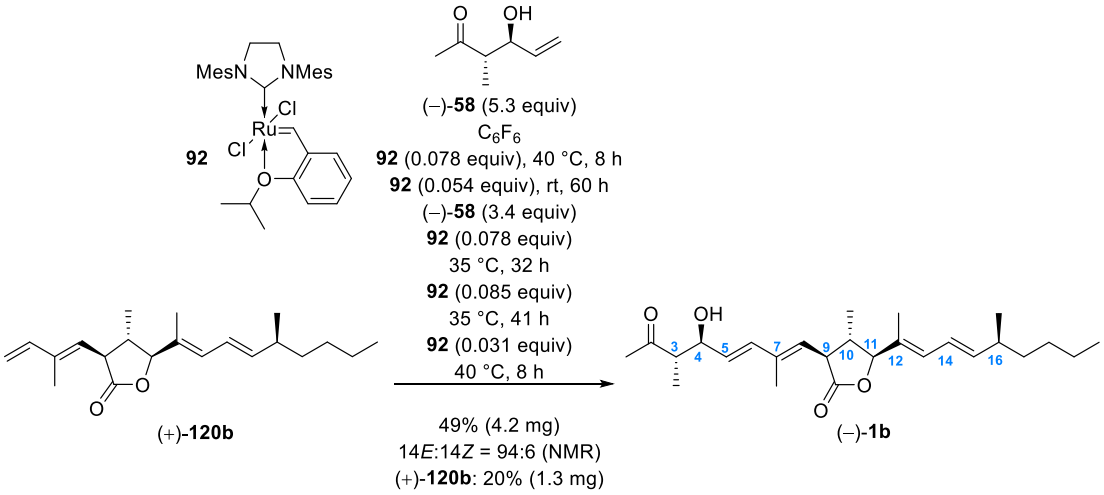
7.6 Synthesis of one *syn*- and four *anti*-configured isomers of Curvicollid C

Synopsis

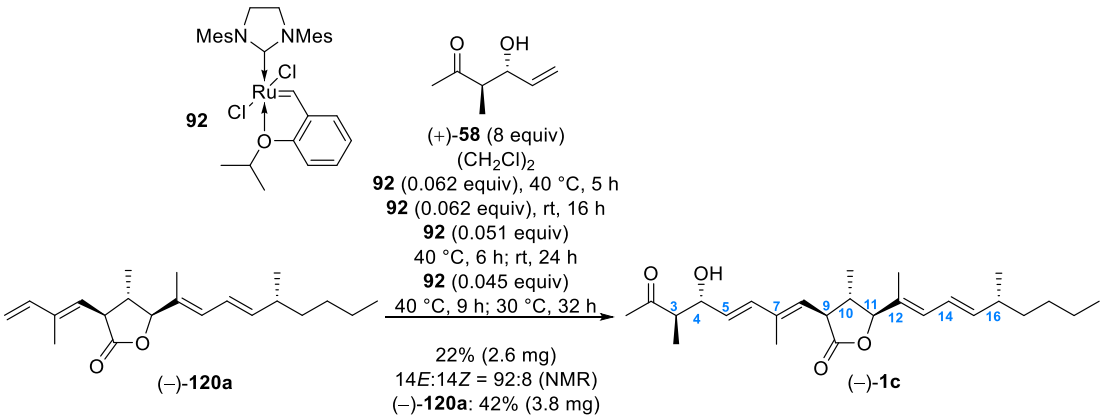




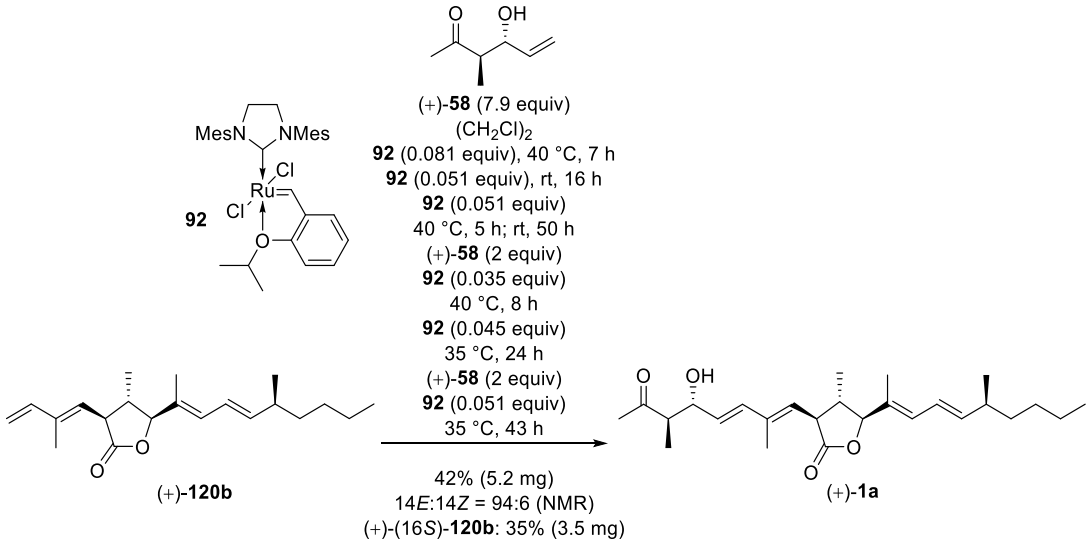
(−)-(3*S*,4*S*,5*E*,7*E*,9*S*,10*S*,11*S*,12*E*,14*E*,16*R*)-Curvicollide C (−)-1d by Cross Metathesis. *The following procedure was performed once and is unoptimized.* A sealable glass pressure tube was charged with a solution of the lactone (−)-**120a** ($C_{21}H_{32}O_2$, 316.48 g/mol, 7.3 mg, 23.066 µmol, 1 equiv) in hexafluorobenzene (1.3 mL, used as purchased). The allylic alcohol (−)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 18 mg, 140.438 µmol, 6.09 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.069 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear green solution was stirred at 40 °C for 8 h. The reaction mixture was cooled to room temperature and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.1 mg, 1.7554 µmol, 0.076 equiv) was added; the reaction mixture was stirred for 16 h at room temperature. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.1171 µmol, 0.048 equiv) was added at room temperature; the reaction mixture was stirred at 40 °C for 8 h. The brown reaction mixture was allowed to cool to room temperature and was stirred for 60 h at room temperature. Allylic alcohol (−)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 10 mg, 78.021 µmol, 3.38 equiv) and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.8 mg, 1.2767 µmol, 0.055 equiv) were subsequently added at room temperature. The dark brown reaction mixture was stirred at 35 °C for 45 h. The turbid dark brown solution was directly purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (−)-**1d** as a light brownish oil ($C_{26}H_{40}O_4$, 416.59 g/mol, 4 mg, 9.602 µmol, 14*E*:14*Z* = 94:6, 42%) along with recovered starting material (−)-**120a** ($C_{21}H_{32}O_2$, 316.48 g/mol, 1.6 mg, 5.056 µmol, 22%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.35 ppm [(*E*)-**1d**] and 4.40 ppm [(*Z*)-**1d**]. The assignment of the 5-C/6-C double bond configuration rests on on the evaluation of the NMR coupling constant of 5-CH: J = 15.8 Hz. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constant of 15-CH: J = 15.0 Hz. $[\alpha]_D^{20}$ = –32.6 (c = 0.2 in CH_2Cl_2) analytical data are reported for (12*E*,14*E*)-**1d**: R_f 0.44 (cyclohexane−ethyl acetate, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 1.01 (d, ^{3}J = 7.0 Hz, 3H, 16'-CH_3), 1.05 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.09 (d, ^{3}J = 7.3 Hz, 3H, 3'-CH_3), 1.21−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (d, ^{4}J = 0.7 Hz, 3H, 12'-CH_3), 1.83 (d, ^{4}J = 1.1 Hz, 3H, 7'-CH_3), 2.22 (s, 3H, 1-CH_3) overlapped by 2.14−2.24 (m, 2H, 10-CH, 16-CH), 2.42 (d, ^{3}J = 4.1 Hz, 1H, OH), 2.71 (dq, ^{3}J = 7.3 Hz, 1H, 3-CH), 3.25 (dd, ^{3}J = 11.7, 9.2 Hz, 1H, 9-CH), 4.29 (ddd, ^{3}J = 7.3, 7.0, 4.1 Hz, 1H, 4-CH), 4.35 (d, ^{3}J = 9.9 Hz, 1H, 11-CH), 5.39 (d, ^{3}J = 9.2 Hz, 1H, 8-CH), 5.66 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 5.68 (dd, ^{3}J = 15.8, 7.0 Hz, 1H, 5-CH), 6.07 (app d, ^{3}J = 10.6 Hz, 1H, 13-CH), 6.20 (dd, ^{3}J = 15.0, 10.6 Hz, 1H, 14-CH), 6.33 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.56 (12'-CH_3), 13.46 (7'-CH_3), 13.93 (3'-CH_3), 14.22 (20-CH_3), 14.98 (10'-CH_3), 20.60 (16'-CH_3), 22.94; 29.71; 36.79 (17,18,19-CH_2), 30.15 (1-CH_3), 37.31 (16-CH), 42.66 (10-CH), 48.61 (9-CH), 52.41 (3-CH), 74.83 (4-CH), 90.81 (11-CH), 123.50 (14-CH), 126.18 (8-CH), 128.99 (12-C), 129.20 (5-CH), 130.63 (13-CH), 136.04 (6-CH), 138.60 (7-C), 143.83 (15-CH), 176.31 (9'-C) 213.03 (2-C); IR ν 3360 (w), 3350 (w), 2960 (m), 2925 (m), 2870 (w), 2855 (m), 1770 (s), 1710 (m), 1665 (s), 1625 (w), 1455 (m), 1421 (w), 1375 (m), 1355 (m), 1300 (w), 1230 (w), 1195 (w), 1160 (s), 1105 (w), 1080 (w), 1020 (w), 965 (s), 940 (w), 890 (w) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{26}H_{41}O_4$: 417.29994; Found: 417.29947; m/z $[M + Na]^+$ Calcd. for $C_{26}H_{40}O_4Na$: 439.28188; Found: 439.28115.



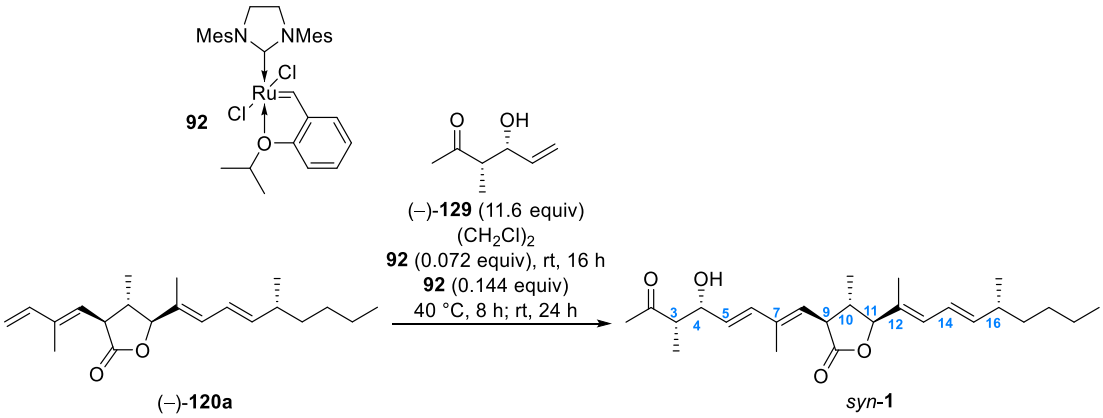
(−)-(3*S*,4*S*,5*E*,7*E*,9*S*,10*S*,11*S*,12*E*,14*E*,16*S*)-Curvicollide C (−)-1b by Cross Metathesis. *The following procedure was performed once and is unoptimized*. A sealable glass pressure tube was charged with a solution of the lactone (+)-**120b** ($C_{21}H_{32}O_2$, 316.48 g/mol, 6.5 mg, 20.538 µmol, 1 equiv) in hexafluorobenzene (1 mL, used as purchased). The allylic alcohol (−)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 14 mg, 109.23 µmol, 5.32 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.078 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear green solution was stirred at 40 °C for 8 h. The brown reaction mixture was cooled to room temperature and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.1171 µmol, 0.054 equiv) was added; the reaction mixture was stirred for 60 h at room temperature. Allylic alcohol (−)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 9 mg, 70.219 µmol, 3.42 equiv) and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.078 equiv) were subsequently added at room temperature. The dark brown reaction mixture was stirred at 35 °C for 32 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.1 mg, 1.7554 µmol, 0.085 equiv) was added at room temperature; the reaction mixture was stirred at 35 °C for 41 h. Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.4 mg, 0.6383 µmol, 0.031 equiv) was added at room temperature; the reaction mixture was stirred at 40 °C for 8 h. The turbid dark brown solution was directly purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (−)-**1b** as a light brownish oil ($C_{26}H_{40}O_4$, 416.59 g/mol, 4.2 mg, 10.082 µmol, 14*E*:14*Z* = 94:6, 49%) along with recovered starting material (+)-**120b** ($C_{21}H_{32}O_2$, 316.48 g/mol, 1.3 mg, 4.108 µmol, 20%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.35 ppm [(*E*)-**1b**] and 4.40 ppm [(*Z*)-**1b**]. The assignment of the 5-C/6-C double bond configuration rests on the evaluation of the NMR coupling constant of 5-CH: J = 15.8 Hz. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constant of 15-CH: J = 15.0 Hz. $[\alpha]_D^{20}$ = –22.5 (c = 0.25 in CH_2Cl_2); analytical data are reported for (12*E*,14*E*)-**1b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 1.01 (d, ^{3}J = 7.0 Hz, 3H, 16'-CH_3), 1.05 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.09 (d, ^{3}J = 7.3 Hz, 3H, 3'-CH_3), 1.21−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (d, ^{4}J = 1.1 Hz, 3H, 12'-CH_3), 1.83 (d, ^{4}J = 0.9 Hz, 3H, 7'-CH_3), 2.22 (s, 3H, 1-CH_3) overlapped by 2.14−2.26 (m, 2H, 10-CH, 16-CH), 2.44 (d, ^{3}J = 4.1 Hz, 1H, OH), 2.71 (dq, ^{3}J = 7.3 Hz, 1H, 3-CH), 3.25 (dd, ^{3}J = 11.7, 9.2 Hz, 1H, 9-CH), 4.28 (ddd, ^{3}J = 7.3, 7.0, 4.1 Hz, 1H, 4-CH), 4.35 (d, ^{3}J = 9.9 Hz, 1H, 11-CH), 5.38 (d, ^{3}J = 9.2 Hz, 1H, 8-CH), 5.67 (dd, ^{3}J = 15.0, 7.9 Hz, 1H, 15-CH), 5.68 (dd, ^{3}J = 15.8, 7.0 Hz, 1H, 5-CH), 6.06 (app d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.20 (app dd, ^{3}J = 15.0, 10.8 Hz, 1H, 14-CH), 6.33 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.62 (12'-CH_3), 13.46 (7'-CH_3), 13.93 (3'-CH_3), 14.22 (20-CH_3), 15.00 (10'-CH_3), 20.52 (16'-CH_3), 22.96; 29.69; 36.77 (17,18,19-CH_2), 30.15 (1-CH_3), 37.24; 42.67 (10,16-CH), 48.62 (9-CH), 52.42 (3-CH), 74.83 (4-CH), 90.78 (11-CH), 123.43 (14-CH), 126.17 (8-CH), 129.01 (12-C), 129.20 (5-CH), 130.55 (13-CH), 136.04 (6-CH), 138.60 (7-C), 143.83 (15-CH), 176.33 (9'-C) 213.03 (2-C); IR ν 3465 (w), 2960 (m), 2925 (m), 2870 (w), 1775 (s), 1710 (m), 1455 (w), 1355 (w), 1300 (w), 1230 (w), 1165 (m), 965 (s) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{26}H_{41}O_4$: 417.29994; Found: 417.29974.



(−)-(3*R*,4*R*,5*E*,7*E*,9*S*,10*S*,11*S*,12*E*,14*E*,16*R*)-Curvicollide C (−)-1c by Cross Metathesis. *The following procedure was performed once and is unoptimized.* A sealable glass pressure tube was charged with a solution of the lactone (−)-**120a** ($C_{21}H_{32}O_2$, 316.48 g/mol, 9 mg, 28.438 µmol, 1 equiv) in ($CH_2Cl)_2$ (2 mL). The allylic alcohol (+)-**2** ($C_7H_{12}O_2$, 128.17 g/mol, 29 mg, 226.262 µmol, 7.96 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.1 mg, 1.7554 µmol, 0.062 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear green solution was stirred at 40 °C for 5 h. The resulting brown reaction mixture was cooled to room temperature and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.1 mg, 1.7554 µmol, 0.062 equiv) was added; the reaction mixture was stirred for 16 h at room temperature. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.9 mg, 1.4363 µmol, 0.051 equiv) was added at room temperature; the reaction mixture was stirred at 40 °C for 6 h and at room temperature for 24 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.8 mg, 1.2767 µmol, 0.045 equiv) was added at room temperature and the dark brown reaction mixture was stirred at 40 °C for 9 h and at 30 °C for 32 h. The turbid dark brown solution was directly purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (−)-**1c** as a light brownish oil ($C_{26}H_{40}O_4$, 416.59 g/mol, 2.6 mg, 6.241 µmol, 14*E*:14*Z* = 92:8, 22%) along with recovered starting material (−)-**120a** ($C_{21}H_{32}O_2$, 316.48 g/mol, 3.8 mg, 12.007 µmol, 42%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.36 ppm [(*E*)-**1c**] and 4.40 ppm [(*Z*)-**1c**]. The assignment of the 5-C/6-C double bond configuration rests on the evaluation of the NMR coupling constant of 5-CH: J = 15.7 Hz. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constant of 15-CH: J = 15.2 Hz. $[\alpha]_D^{20}$ = –12.2 (c = 0.17 in CH_2Cl_2);. Analytical data are reported for (12*E*,14*E*)-**1c**, showing impurities of silicon grease and cyclohexane: R_f 0.44 (cyclohexane−ethyl acetate, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (dd, J = 7.0 Hz, 3H), 1.01 (d, ^{3}J = 7 Hz, 3H), 1.05 (d, ^{3}J = 6.6 Hz, 3H), 1.10 (d, ^{3}J = 7.3 Hz, 3H), 1.19−1.37 (m, 6H), 1.75 (d, ^{4}J = 0.7 Hz, 3H), 1.83 (d, ^{4}J=1.1 Hz, 3H), 2.22 (s, 3H) overlapped by 2.13−2.24 (m, 2H), 2.59 (d, ^{3}J = 4.3 Hz, 1H), 2.69 (dq, ^{3}J = 7.8, 7.3 Hz, 1H), 3.26 (dd, ^{3}J = 11.7, 9.2 Hz, 1H), 4.25 (ddd, ^{3}J = 7.8, 7.7, 4.3 Hz, 1H), 4.36 (d, ^{3}J = 9.9 Hz, 1H), 5.38 (d, ^{3}J = 9.2 Hz, 1H), 5.64 (dd, ^{3}J = 15.7, 7.8 Hz, 1H), 5.66 (dd, ^{3}J = 15.0, 8.1 Hz, 1H), 6.07 (app d, ^{3}J = 10.8 Hz, 1H), 6.21 (app dd, ^{3}J = 15, 10.8 Hz, 1H), 6.32 (d, ^{3}J = 15.8 Hz, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.56, 13.37, 14.16, 14.24, 14.90, 20.61, 22.95, 29.72, 30.01, 36.79, 37.32, 42.70, 48.62, 52.44, 75.33, 90.89, 123.47, 126.32, 128.93, 129.08, 130.66, 136.65, 138.61, 143.86, 176.50, 213.46; HRMS (ESI): m/z $[M + Na]^+$ Calcd. for $C_{26}H_{40}O_4Na$: 439.28188; Found: 439.28133.



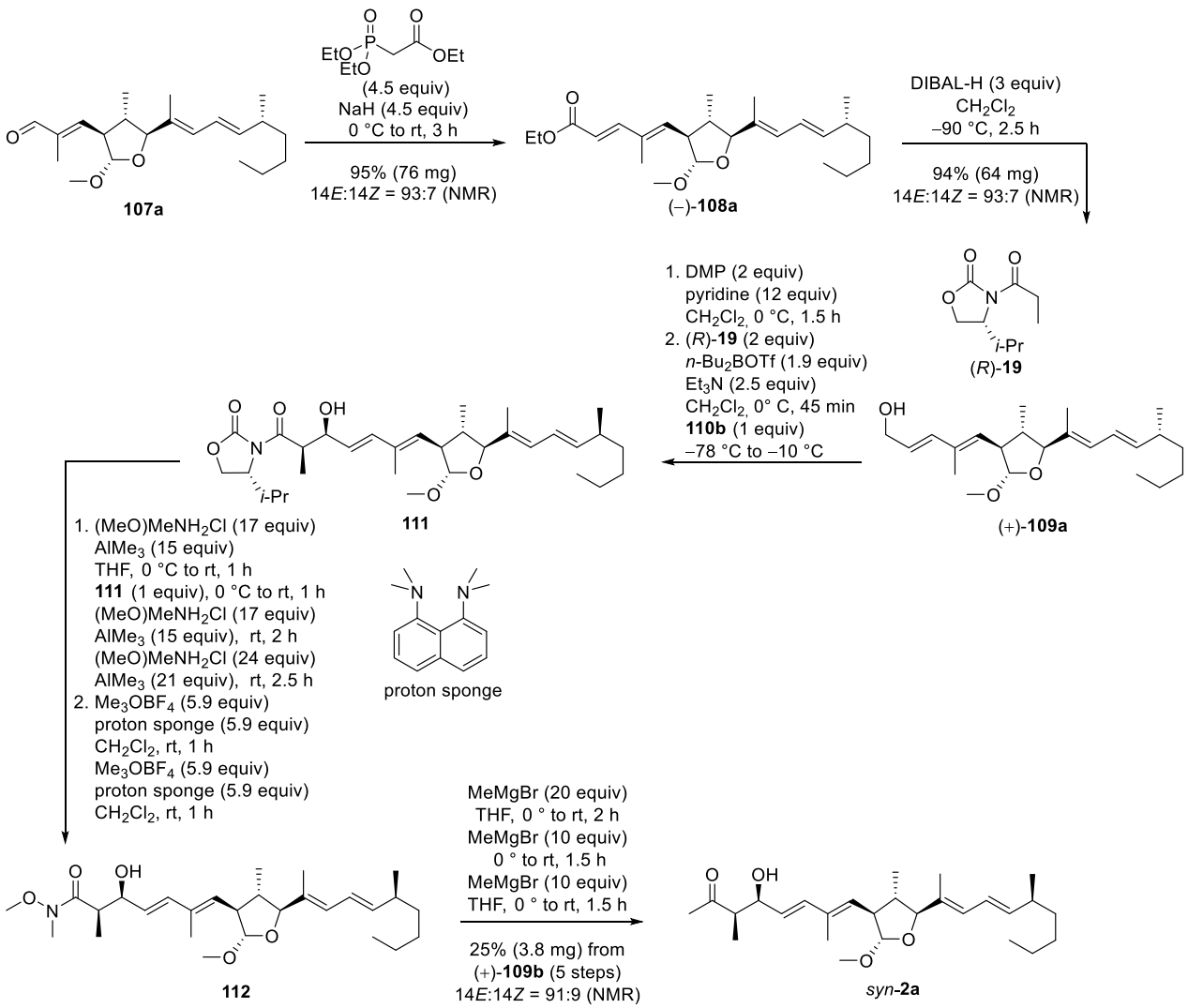
(+)-(3*R*,4*R*,5*E*,7*E*,9*S*,10*S*,11*S*,12*E*,14*E*,16*S*)-Curvicollide C (+)-1a by Cross Metathesis. *The following procedure was performed twice and is still unoptimized*. A sealable glass pressure tube was charged with a solution of the lactone (+)-**120b** ($C_{21}H_{32}O_2$, 316.48 g/mol, 10 mg, 31.598 µmol, 1 equiv) in $(CH_2Cl)_2$ (2 mL). The allylic alcohol (+)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 32 mg, 249.668 µmol, 7.9 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.6 mg, 2.5534 µmol, 0.081 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and placed in a pre-heated oil bath (40 °C). The clear green solution was stirred at 40 °C for 7 h. The brown reaction mixture was cooled to room temperature and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.051 equiv) was added; the reaction mixture was stirred for 16 h at room temperature. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.051 equiv) was added at room temperature; the reaction mixture was stirred at 40 °C for 5 h and at room temperature for 50 h. Allylic alcohol (+)-**2** ($C_7H_{12}O_2$, 128.17 g/mol, 8 mg, 62.417 µmol, 1.98 equiv) and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.1171 µmol, 0.035 equiv) were subsequently added at room temperature. The dark brown reaction mixture was stirred at 40 °C for 8 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.9 mg, 1.4363 µmol, 0.045 equiv) was added at room temperature; the reaction mixture was stirred at 35 °C for 24 h. Allylic alcohol (+)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 8 mg, 62.417 µmol, 1.98 equiv) and **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.051 equiv) were subsequently added at room temperature. The dark brown reaction mixture was stirred at 35 °C for 43 h. The turbid dark brown solution was directly purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (+)-**1a** as a light brownish oil ($C_{26}H_{40}O_4$, 416.59 g/mol, 5.2 mg, 12.482 µmol, 14*E*:14*Z* = 94:6, 40%) along with recovered starting material (+)-**120b** ($C_{21}H_{32}O_2$, 316.48 g/mol, 3.5 mg, 11.059 µmol, 35%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 11-CH at 4.36 ppm [(*E*)-**1a**] and 4.41 ppm [(*Z*)-**1a**]. The assignment of the 5-C/6-C double bond configuration rests on the evaluation of the NMR coupling constant of 5-CH: J = 15.8 Hz. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constant of 15-CH: J = 15.0 Hz. $[\alpha]_D^{20}$ =+6.1 (c = 0.37 in CH_2Cl_2); analytical data are reported for (12*E*,14*E*)-**1a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 1.01 (d, ^{3}J = 6.8 Hz, 3H, 16'-CH_3), 1.05 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.10 (d, ^{3}J = 7.3 Hz, 3H, 3'-CH_3), 1.21−1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (d, ^{4}J = 1.1 Hz, 3H, 12'-CH_3), 1.83 (d, ^{4}J = 1.1 Hz, 3H, 7'-CH_3), 2.22 (s, 3H, 1-CH_3) overlapped by 2.13−2.25 (m, 2H, 10-CH, 16-CH), 2.61 (br s, 1H, OH), 2.69 (dq, ^{3}J = 7.8, 7.3 Hz, 1H, 3-CH), 3.26 (dd, ^{3}J = 11.7, 9.2 Hz, 1H, 9-CH), 4.25 (dd, ^{3}J = 7.8, 7.7 Hz, 1H, 4-CH), 4.36 (d, ^{3}J = 9.9 Hz, 1H, 11-CH), 5.38 (d, ^{3}J = 9.2 Hz, 1H, 8-CH), 5.64 (dd, ^{3}J = 15.8, 7.7 Hz, 1H, 5-CH), 5.67 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 6.07 (app d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (app dd, J = 15.0, 10.8 Hz, 1H, 14-CH) 6.32 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.63 (12'-CH_3), 13.37 (7'-CH_3), 14.14 (3'-CH_3), 14.22 (20-CH_3), 14.94 (10'-CH_3), 20.53 (16'-CH_3), 22.96; 29.69; 36.77 (17,18,19-CH_2), 30.00 (1-CH_3), 37.25 (16-CH), 42.74 (10-CH), 48.64 (9-CH), 52.46 (3-CH), 75.32 (4-CH), 90.84 (11-CH), 123.43 (14-CH), 126.33 (8-CH) 128.97 (12-C) 129.10 (5-CH), 130.57 (13-CH), 136.64 (6-CH) 138.61 (7-C) 143.86 (15-CH), 176.46 (9'-C) 213.40 (2-C); IR ν 3355 (w), 3210 (w), 2955 (m), 2925 (m), 2870 (w), 1670 (s), 1620 (w), 1455 (w), 1380 (w), 1090 (s), 1040 (w), 995 (s), 965 (s), 570 (w) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{26}H_{41}O_4$: 417.29994; Found: 417.29971.

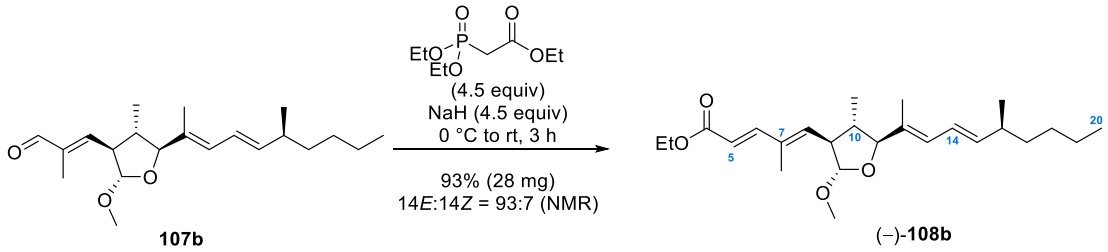


(3*S*,4*R*,5*E*,7*E*,9*S*,10*S*,11*S*,12*E*,14*E*,16*R*)-Curvicollide C (3*S*,4*R*,16*R*)-*syn*-1a by Cross Metathesis. *The following procedure was performed once and is still unoptimized*. A sealable glass pressure tube was charged with a solution of the lactone (−)-**120a** ($C_{21}H_{32}O_2$, 316.48 g/mol, 7 mg, 22.118 µmol, 1 equiv) in $(CH_2Cl)_2$ (1.5 mL). The allylic alcohol (−)-**129** ($C_7H_{12}O_2$, 128.17 g/mol, 33 mg, 257.47 µmol, 11.64 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1 mg, 1.5959 µmol, 0.072 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and stirred at room temperature for 16 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 2 mg, 3.1917 µmol, 0.144 equiv) was added at room temperature; the reaction mixture was stirred at 40 °C for 8 h and at room temperature for 24 h. The turbid dark brown solution was directly purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1 to 2:1 to 1:1) to afford lactone (3*S*,4*R*,16*R*)-*syn*-**1** as a light brownish oil contaminated with residual solvents (diethyl ether, ethyl acetate, cyclohexane) and unidentified impurities. The sample was sufficiently pure to obtain a ^{1}H NMR spectrum to support structural assignment of the natural product. R_f 0.42 (hexane−ethyl acetate, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^3J = 7.0 Hz, 3H), 1.01 (d, ^3J = 6.6 Hz, 3H), 1.04 (d, ^3J = 6.6 Hz, 3H), 1.17 (^{3}d, J = 7.3 Hz, 3H), 1.74 (s, 3H), 1.82 (d, ^4J = 1.1 Hz, 3H), 2.22 (s, 3H) overlapped by 2.12−2.25 (m, 2H), 2.70 (qd, ^3J = 7.3, 3.3 Hz, 1H), 2.76 (d, ^3J = 3.5 Hz, 1H), 3.25 (dd, ^3J = 11.7, 9.3 Hz, 1H), 4.36 (d, ^3J = 9.9 Hz, 1H), 4.53 (ddd, ^3J = 6.6, 3.5, 3.3 Hz., 1 H), 5.37 (d, ^3J = 9.3 Hz, 1H), 5.66 (dd, ^3J = 15.0, 8.1 Hz, 1H), 5.68 (dd, ^3J = 15.8, 6.6 Hz, 1H), 6.06 (d, ^3J = 10.6 Hz, 1H), 6.20 (dd, ^3J = 15.0, 10.6 Hz, 1H), 6.33 (d, ^3J = 15.8 Hz, 1H).

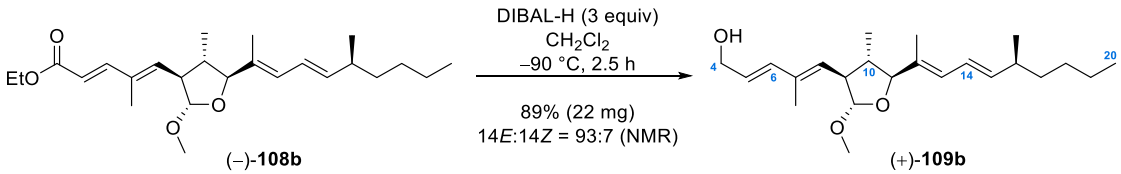
7.7 Synthesis of a *syn*-configured diastereomer of Fusaequisin A

Synopsis



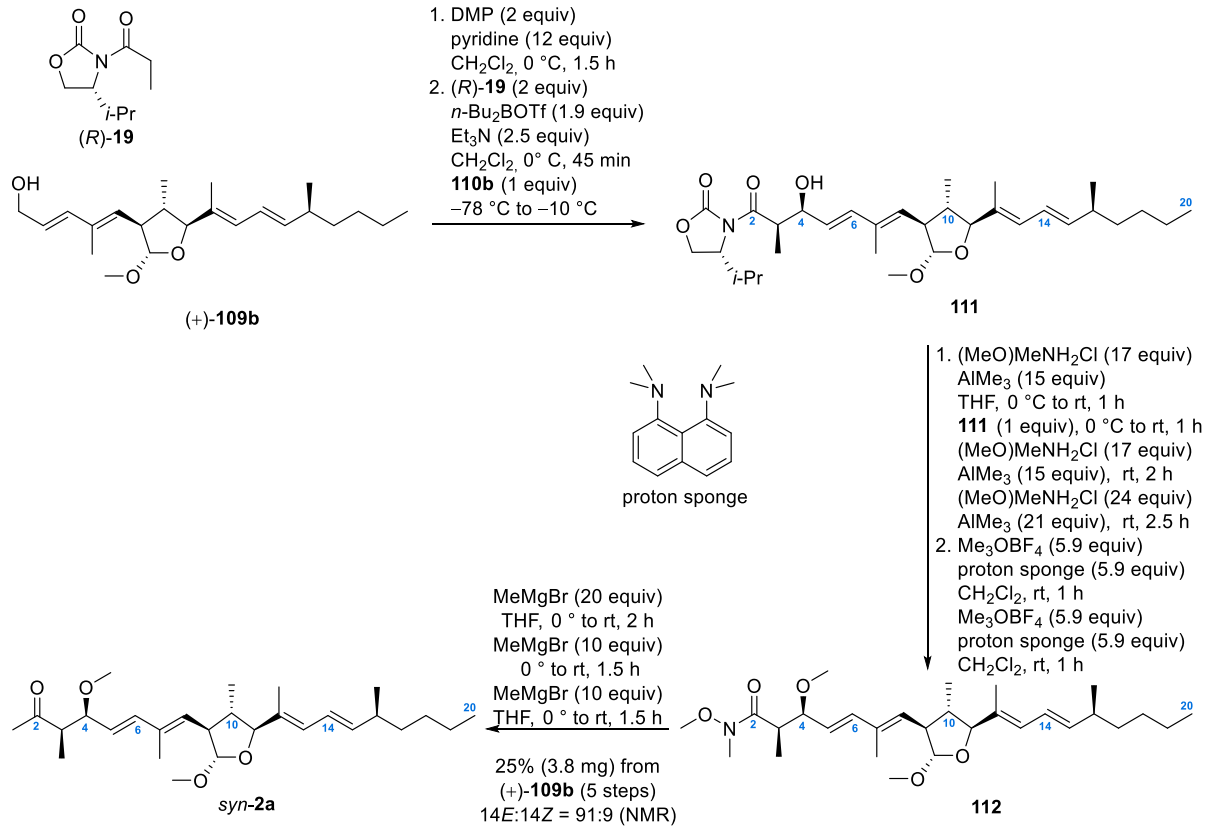


Dienoate (−)-108b by HWE Olefination. To an ice-cooled solution of ethyl 2-diethoxyphosphorylacetate ($(EtO)_2P(O)CH_2CO_2Et$, $C_8H_{17}O_5P$, 224.19 g/mol, 1.13 g/mL, 67 µL, 75.7 mg, 0.3377 mmol, 4.52 equiv) in THF (4 mL) was added natrium hydride (NaH, 60% w/w in mineral oil, 24.00 g/mol, 13.5 mg, 0.3375 mmol, 4.51 equiv). The clear, colorless solution was stirred at room temperature for 30 min and was then cooled to 0 °C. A precooled 0 °C solution of **107b** ($C_{21}H_{34}O_3$, 334.49 g/mol, 25 mg, 0.0747 mmol, 1 equiv) in THF (2 mL) was dropwise added. The clear, colorless solution was stirred at room temperature for 2 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (5 mL) and CH_2Cl_2 (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1) to deliver (−)-**108b** as a mixture of 14-C/15-C double bond isomers ($C_{25}H_{40}O_4$, 404.58 g/mol, 28 mg, 0.0692 mmol, 93%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.27 ppm [(*Z*)-**108b**] and 5.61 ppm [(*E*)-**108b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**108b** and J = 15.2 Hz for (*E*)-**108b**. The assignment of the 5-C/6-C double bond configuration rests on the evaluation of the NMR coupling constant of 5-CH: J = 15.8 Hz.; $[\alpha]_D^{20}$ = −19.7 (c = 0.5 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**108b**: R_f 0.56 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H), 0.93 (d, ^{3}J = 6.6 Hz, 3H), 1.00 (d, ^{3}J = 6.6 Hz, 3H), 1.19−1.35 (m, 9H), 1.75 (s, 3H), 1.84 (s, 3H) overlapped by 1.78−1.87 (m, 1H), 2.13−2.22 (m, 1H), 2.81 (ddd, ^{3}J = 9.9, 9.6, 3.8 Hz, 1H), 3.37 (s, 3H), 4.07 (d, ^{3}J = 9.5 Hz, 1H), 4.22 (q, ^{3}J = 7.3 Hz, 2H), 4.77 (d, ^{3}J = 3.8 Hz, 1H), 5.60 (dd, ^{3}J = 15.2, 7.9 Hz, 1H), 5.81 (d, ^{3}J = 9.9 Hz, 1H), 5.85 (d, ^{3}J = 15.8 Hz, 1H), 6.04 (d, ^{3}J = 10.8 Hz, 1H), 6.21 (dd, ^{3}J = 15.2, 10.8 Hz, 1H), 7.34 (d, ^{3}J = 15.8 Hz, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.89 (CH_3), 12.85 (CH_3), 14.25 (CH_3), 14.48 (CH_3), 14.70 (CH_3), 20.69 (CH_3), 22.99 (CH_2), 29.71 (CH_2), 36.87 (CH_2), 37.20 (CH), 44.97 (CH), 54.52 (CH), 55.99 (CH_3), 60.43 (CH_2), 90.33 (CH), 109.41 (CH), 117.10 (CH), 124.01 (CH), 129.05 (CH), 131.82 (C), 135.12 (C), 140.02 (CH), 142.18 (CH), 148.98 (CH), 167.49 (C); IR ν 2960 (w), 2930 (w), 2875 (w), 1710 (m), 1625 (m), 1460 (w), 1380 (w), 1305 (m), 1270 (w), 1175 (m), 1095 (m), 1025 (m), 1000 (m), 980 (m), 845 (w), 750 (s), 665 (w) cm^{-1}.



Allylic Alcohol (+)-109b by DIBAL-H Reduction. To a solution of the enoate (−)-**108b** ($C_{25}H_{40}O_4$, 404.58 g/mol, 28 mg, 0.0692 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was dropwise added DIBAL-H (1 M in CH_2Cl_2, 0.23 mL, 0.23 mmol, 3.32 equiv) over a period of time of 10 min at −90 °C. The resulting colorless solution was stirred at −90 °C for 2.5 h. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (5 mL), CH_2Cl_2 (10 mL) and saturated aqueous potassium sodium tartrate solution (10 mL) at –90 °C. The cloudy biphasic mixture was warmed to room temperature and stirring was continued for 30 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver a mixture of 14-C/15-C double bond isomers of the allylic alcohol (+)-**109b** ($C_{23}H_{38}O_3$, 362.55 g/mol, 22.4 mg, 0.0618 mmol, 89%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.26 ppm [(*Z*)-**109b**] and 5.59 ppm [(*E*)-**109b**]. The

assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.4 Hz for (*Z*)-**109b** and J = 15.1 Hz for (*E*)-**109b**. $[\alpha]_D^{20}$ = +32.8 (c 0.4 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**109b**: R_f 0.46 (cyclohexane–ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.9 Hz, 3H), 0.91 (d, ^{3}J = 6.4 Hz, 3H), 0.99 (d, ^{3}J = 7.0 Hz, 3H), 1.17–1.34 (m, 6 H), 1.38 (br. s, 1H), 1.74 (s, 3H) overlapped by 1.68–1.79 (m, 1H), 1.82 (s, 3), 2.12–2.22 (m, 1H), 2.76 (ddd, ^{3}J = 10.0, 9.4, 4.0 Hz, 1H), 3.37 (s, 3H), 4.05 (d, ^{3}J = 9.5 Hz, 1H), 4.22 (d, ^{3}J = 5.8 Hz, 2H), 4.73 (d, ^{3}J = 4.0 Hz, 1H), 5.42 (d, ^{3}J = 10.0 Hz, 1H), 5.59 (dd, ^{3}J = 15.1, 7.8 Hz, 1H), 5.80 (dt, ^{3}J = 15.7, 5.8 Hz, 1H), 6.03 (d, ^{3}J = 10.7 Hz, 1H), 6.21 (dd, ^{3}J = 15.1, 10.7 Hz, 1H), 6.29 (d, ^{3}J = 15.7 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.89 (CH_3), 13.14 (CH_3), 14.25 (CH_3), 14.55 (CH_3), 20.70 (CH_3), 22.98 (CH_2) 29.70 (CH_2), 36.86 (CH_2), 37.19 (CH), 44.96 (CH), 54.00 (CH), 56.00 (CH_3), 63.97 (CH_2), 90.30 (CH), 109.88 (CH), 124.03 (CH), 126.75 (CH), 128.91 (CH), 131.97 (CH), 132.06 (C), 135.57 (C), 136.20 (CH), 142.01 (CH).



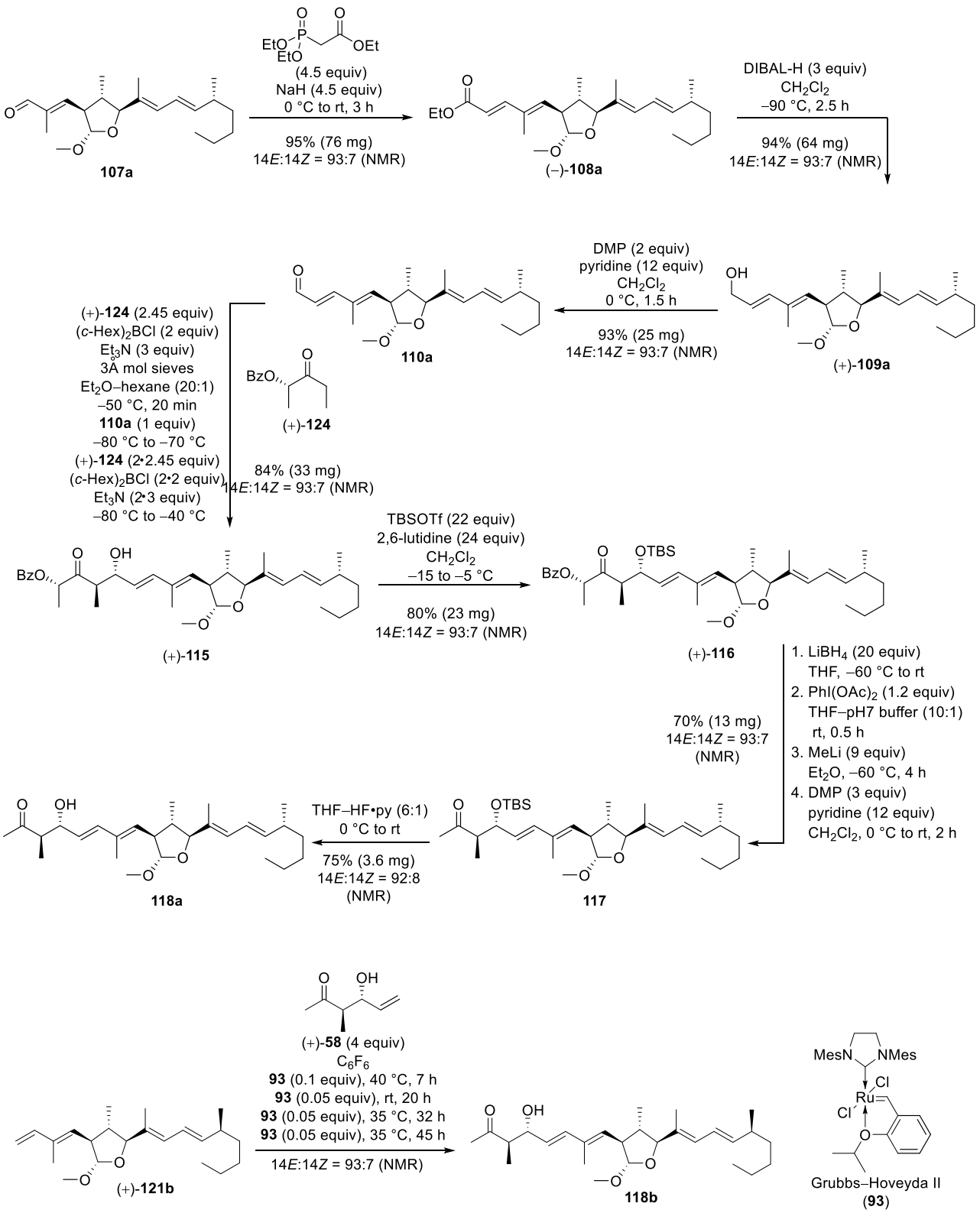
(3*R*,4*S*,5*E*,7*E*,9*S*,9'*S*,10*S*,11*S*,12*E*,14*E*,16*S*)-Fusaequisin A (3*R*,4*S*,16*S*)-*syn*-2a. To an ice-cooled solution of the alcohol (+)-**109b** ($C_{23}H_{38}O_3$, 362.55 g/mol, 12.4 mg, 0.0342 mmol, 1 equiv) in CH_2Cl_2 (5 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 30 µL, 29.4 mg, 0.3717 mmol, 10.87 equiv) was added the Dess–Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 26 mg, 0.0613 mmol, 1.79 equiv). The white suspension was stirred at 0 °C for 1.5 h and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane–ethyl acetate, 50:1 to 20:1 to 10:1) to deliver the aldehyde **110b** ($C_{23}H_{36}O_3$, 360.53 g/mol, 12 mg) that was used in the following Evans-Aldol without proof of structure or of purity. To an ice cooled solution of the ketone (*R*)-**19** ($C_9H_{15}NO_3$, 185.22 g/mol, 13 mg, 70.19 µmol, 2.11 equiv) in CH_2Cl_2 (3 mL) were successively added dried 3 Å molecular sieves (50 mg, 0.1 mbar, 200 °C, 1 h), dibutylboron triflate (*n*-Bu_2BOTf, 1 M in CH_2Cl_2, 65 µL, 65.00 µmol, 1.95 equiv) and triethylamin ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 10 µL, 7.26 mg, 71.75 µmol, 2.16 equiv). The light yellowish solution was stirred at 0 °C for 45 min. To the reaction mixture a solution of the aldehyde **110b** ($C_{23}H_{36}O_3$, 360.53 g/mol, 12 mg, 33.28 µmol, 1 equiv) in CH_2Cl_2 (2 mL) was dropwise added at –78 °C. The reaction mixture was allowed to warm to –20 °C over a period of time of 4 h and was then diluted by the addition of aqueous phosphate pH 7 buffer

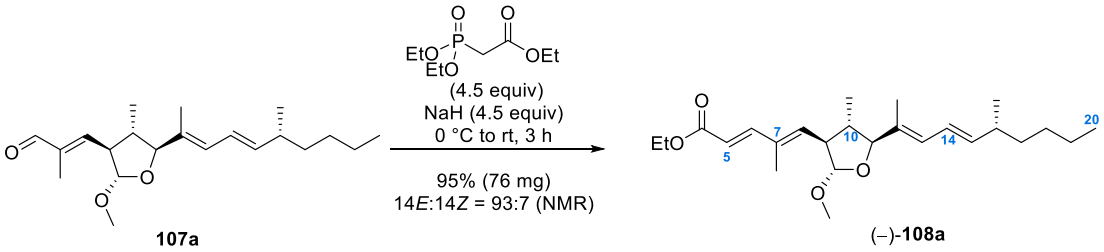
(5 mL), MeOH (5 mL) and a solution of H_2O_2 (30% w/w in H_2O, 3 mL). The biphasic mixture was stirred for 20 min at 0 °C. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light yellow residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1) to afford the aldol **111** ($C_{32}H_{51}NO_6$, 545.75 g/mol, 10 mg, 14*E*:14*Z* > 90:10) as a viscous oil contaminated with residual solvents (ethyl acetate, cyclohexane. The ratio of the 14-C/15-C double bond isomers can not be reliable assigned due to signal overlap. R_f 0.44 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.94 (m, 12H, 10'-CH_3, 20-CH_3, *i*-Pr-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.18–1.34 (m, 9H, 17-CH_2, 18-CH_2, 19-CH_2, 3'-CH_3), 1.74 (s, 3H, 12'-CH_3), 1.80 (s, 3H, 7'-CH_3) overlapped by 1.71–1.83 (m, 1H, 10-CH), 2.12–2.22 (m, 1H, 16-CH), 2.35 (sptd, ^{3}J = 7.0, 3.8 Hz, 1H, *i*-Pr-CH), 2.75 (ddd, ^{3}J = 9.9, 9.6, 4.0 Hz, 1H, 9-CH), 3.04 (d, ^{3}J = 1.5 Hz, 1H, OH), 3.37 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 3.89 (qd, ^{3}J = 7.0, 3.4 Hz, 1H, 3-CH), 4.04 (d, ^{3}J = 9.8 Hz, 1H, 11-CH), 4.22 (dd, ^{2}J = 9.2 Hz, ^{3}J = 3.2 Hz, 1H, O-C<u>H</u>$_2$-CH), 4.28 (dd, ^{2}J = 9.2 Hz, ^{3}J = 8.5 Hz, 1H, O-C<u>H</u>$_2$-CH), 4.48 (ddd, ^{3}J = 8.5, 3.8, 3.2 Hz, 1H, O-CH_2-C<u>H</u>), 4.57 (ddd, ^{3}J = 5.8, 3.4, 1.5 Hz, 1H, 4-CH), 4.73 (d, ^{3}J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH_3)), 5.43 (d, ^{3}J = 9.9 Hz, 1H, 8-CH), 5.59 (dd, ^{3}J = 15.0, 8.0 Hz, 1H, 15-CH), 5.60 (dd, ^{3}J = 15.8, 5.8 Hz, 1H, 5-CH), 6.02 (d, ^{3}J = 10.9 Hz, 1H, 13-CH), 6.21 (ddd, ^{3}J = 15.0, 10.9 Hz, 1H, 14-CH), 6.34 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); No further analytical data were obtained. To an ice-cooled suspension of *N*-methylhydroxylamine hydrochloride ((MeO)$MeNH_2Cl$, CH_5NO•HCl, 83.52 g/mol, 24 mg, 0.2874 mmol, 17.42 equiv) in THF (3 mL) was added trimethylaluminum ($AlMe_3$, C_3H_9Al, 1 M in *n*-heptane, 0.25 mL, 0.25 mmol, 15.15 equiv). The suspension was stirred at 0 °C for 10 min and then at room temperature for 1 h. To the clear, colorless solution was dropwise added a solution of the aldol **111** ($C_{32}H_{51}NO_6$, 545.75 g/mol, 9 mg, 0.0165 mmol, 1 equiv) in THF (2 mL) at 0 °C. The clear, colorless solution was stirred at room temperature for 1 h. In a separate reaction vessel an additional solution of the (N-methyl-*N*-methoxyamino)dimethylaluminium chloride was prepared from *N*-methylhydroxylamine hydrochloride ((MeO)$MeNH_2Cl$, CH_5NO•HCl, 83.52 g/mol, 24 mg, 0.2874 mmol, 17.42 equiv) and trimethylaluminum ($AlMe_3$, C_3H_9Al, 1 M in *n*-heptane, 0.25 mL, 0.25 mmol, 15.15 equiv) in THF (2 mL) at room temperature for 30 min and added to the original reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 2 h. In a separate reaction vessel a an another additional solution of the (*N*-methyl-*N*-methoxyamino)dimethylaluminium chloride was prepared from *N*-methylhydroxylamine hydrochloride ((MeO)$MeNH_2Cl$, CH_5NO•HCl, 83.52 g/mol, 33 mg, 0.3951 mmol, 23.95 equiv) and trimethylaluminum ($AlMe_3$, C_3H_9Al, 1 M in *n*-heptane, 0.25 mL, 0.35 mL, 0.35 mmol, 21.21 equiv) in THF (2 mL) at room temperature for 30 min and added to the original reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted by the dropwise addition of aqueous phosphate pH 7 buffer (7 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford the amide ($C_{28}H_{47}NO_5$, 477.68 g/mol, 6 mg) as a colorless oil that was used in the following methylation without proof of structure or of purity. To a solution of trimethyloxonium tetrafluoroborate (Me_3OBF_4, $C_3H_9BF_4O$, 147.91 g/mol, 11 mg, 0.0744 mmol, 5.90 equiv) in CH_2Cl_2 (3 mL) 1,8-bis(dimethylamino)naphthalene (proton sponge®, $C_{14}H_{18}N_2$, 214,31 g/mol, 16 mg, 0.0747 mmol, 5.93 equiv) was added at room temperature. To the clear, colorless solution was added a solution of the amide ($C_{28}H_{47}NO_5$, 477.68 g/mol, 6 mg, 0.0126 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 1 h. In a separate reaction vessel an additional solution of trimethyloxonium tetrafluoroborate (Me_3OBF_4, $C_3H_9BF_4O$, 147.91 g/mol, 11 mg, 0.0744 mmol, 5.90 equiv) and 1,8-bis(dimethylamino)naphthalene (proton sponge®, $C_{14}H_{18}N_2$, 214,31 g/mol, 16 mg, 0.0747 mmol, 5.93 equiv) in CH_2Cl_2 (1 mL) at room temperature was prepared and added to the original reaction mixture. The reaction mixture was stirred at room temperature for 1 h. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver a mixture of 14-C/15-C double bond isomers of the amide **112** ($C_{29}H_{49}NO_5$, 491.70 g/mol, 4.5 mg, 14*E*:14*Z* = 93:7) as a colorless oil contaminated with residual solvents (ethyl acetate) and silicon grease. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.26 ppm [(*Z*)-**112**] and 5.60 ppm [(*E*)-**112**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**112** and J = 15.0 Hz for (*E*)-**112**; analytical data are reported for (12*E*,14*E*)-**112**: R_f 0.71 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.92 (m, 6H), 1.00 (d, ^{3}J = 6.4 Hz, 3H), 1.16–1.36 (m, 9H), 1.74 (s, 3H), 1.79 (s, 3H) overlapped by 1.69–1.84 (m, 1H), 2.11–2.24 (m, 1H), 2.74 (ddd, ^{3}J = 10.1, 9.3, 3.9 Hz, 1H), 3.11 (s, 3H) overlapped by 3.09–3.19 (m, 1H), 3.29 (s, 3H), 3.37 (s, 3H), 3.66 (s, 3H) overlapped by 3.63–3.71 (m, 1H), 4.04 (d, ^{3}J = 9.8 Hz, 1H), 4.73 (d, ^{3}J = 3.9 Hz, 1H), 5.40 (d, ^{3}J = 10.1 Hz, 1H), 5.52 (dd, ^{3}J = 15.7, 8.3 Hz, 1H), 5.60 (dd, ^{3}J = 15.0, 8.1 Hz, 1H), 6.03 (d, ^{3}J = 10.8 Hz, 1H), 6.22 (d, ^{3}J = 15.7 Hz, 1H), 6.22 (dd, ^{3}J = 15.0, 10.8 Hz, 1H); No further analytical data were obtained.To an ice-cooled solution of the amide **112** ($C_{29}H_{49}NO_5$, 491.70 g/mol, 4.5 mg, 0.00915 mmol, 1 equiv) in THF (2 mL) was

added methylmagnesium bromide (MeMgBr, 1 M in THF, 0.18 mL, 0.18 mmol, 19.67 equiv). The light brownish solution was allowed to warm to room temperature and was stirred at room temperature for 2 h. To the light brownish solution was added in two portions in an interval of 0.5 h methylmagnesium bromide (MeMgBr, 1 M in THF, 2×90 µL, 2×90 µmol, 2×9.84 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (5 mL) and CH_2Cl_2 (5 mL) The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford the ketone *syn*-**2a** ($C_{28}H_{46}O_4$, 446.66 g/mol, 3.8 mg, 0.00851 mmol, 25% from (+)-**109b** (5 steps), 14*E*:14*Z* = 91:9) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.27 ppm [(*Z*)-*syn*-**2a**] and 5.60 ppm [(*E*)-*syn*-**2a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-*syn*-**2a** and J = 15.2 Hz for (*E*)-*syn*-**2a**; analytical data are reported for (12*E*,14*E*)-*syn*-**2a**: R_f 0.50 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H), 0.91 (d, ^{3}J = 6.6 Hz, 3H), 1.00 (d, ^{3}J = 6.6 Hz, 3H), 1.13 (d, ^{3}J = 7.0 Hz, 3H), 1.20–1.34 (m, 6H), 1.75 (s, 3H), 1.80 (s, 3H) overlapped by 1.73–1.82 (m, 1H), 2.17 (s, 3H), 2.70–2.79 (m, 2H), 3.25 (s, 3H), 3.37 (s, 3H), 3.81 (dd, ^{3}J = 7.7, 5.9 Hz, 1H), 4.05 (d, ^{3}J = 9.5 Hz, 1H), 4.75 (d, ^{3}J = 3.7 Hz, 1H), 5.39–5.45 (m, 2H), 5.60 (dd, ^{3}J = 15.2, 7.7 Hz, 1H), 6.03 (d, ^{3}J = 11.0 Hz, 1H), 6.22 (dd, ^{3}J = 15.2, 10.6 Hz, 1H), 6.23 (d, ^{3}J = 15.6 Hz, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.90, 12.26, 13.20, 14.25, 14.59, 20.70, 22.99, 29.71, 30.45, 36.87, 37.20, 44.93, 52.26, 54.04, 55.95, 56.73, 83.57, 90.31, 109.84, 124.04, 125.32, 128.95, 132.03, 132.40, 135.34, 138.46, 142.03, 210.90; ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.84 (dd, ^{3}J = 6.8 Hz, 3H, 20-CH_3), 0.91 (d, ^{3}J = 6.8 Hz, 3H, 10'-CH_3), 1.03 (d, ^{3}J = 6.4 Hz, 3H, 16'-CH_3), 1.22 (d, ^{3}J = 7.0 Hz, 3H, 3'-CH_3) overlapped by 1.19–1.39 (m, 6H), 1.89 (s, 3H, 7'-CH_3), 1.93 (s, 3H, 12'-CH_3) overlapped by 1.87–1.99 (m, 1H, 10-CH), 2.23 (s, 3H, 1-CH_3) overlapped by 2.16–2.26 (m, 1H, 16-CH), 2.90 (qd, ^{3}J = 7.0, 5.4 Hz, 1H, 3-CH), 3.03 (ddd, ^{3}J = 10.1, 9.5, 4.2 Hz, 1H, 9-CH), 3.28 (s, 3H, , 4'-OCH_3), 3.44 (s, 3H, 9'-CH(O$\underline{CH_3}$)), 4.08 (dd, ^{3}J = 7.8, 5.4 Hz, 1H, 4-CH), 4.30 (d, ^{3}J = 9.3 Hz, 1H, 11-CH), 4.99 (d, ^{3}J = 4.2 Hz, 1H, 9'-C$\underline{H}$(OCH_3) overlapped by H_2O), 5.67 (d, ^{3}J = 10.1 Hz, 1H, 8-CH), 5.70 (dd, ^{3}J = 15.8, 7.8 Hz, 1H, 5-CH), 5.71 (dd, ^{3}J = 15.2, 8.1 Hz, 1H, 15-CH), 6.29 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.49 (dd, ^{3}J = 15.2, 10.8 Hz, 1H, 14-CH), 6.52 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); ^{13}C NMR (126 MHz, pyridine-d_5) δ 12.33 (12'-CH_3), 12.38 (3'-CH_3), 13.59 (7'-CH_3), 14.69 (20-CH_3), 14.80 (10'-CH_3), 21.30 (16'-CH_3), 23.54; 30.32; 37.41 (17,18,19-CH_2), 30.38 (1-CH_3), 37.87 (16-CH), 45.61 (10-CH), 52.53 (3-CH), 54.67 (9-CH), 56.13 (9'-CH(O$\underline{CH_3}$), 56.85 (4'-OCH_3), 84.07 (4-CH), 91.01 (11-CH), 110.53 (9'-$\underline{CH}$(OCH_3), 125.13 (14-CH), 126.57 (5-CH), 129.32 (13-CH), 133.30 (8-CH), 133.66; 136.28 (7-C, 12-C), 138.87 (6-CH), 142.41 (15-CH), 210.02 (2-C); HRMS (ESI): m/z $[M + Na]^+$ Calcd. for $C_{28}H_{46}O_4Na$: 469.32883; Found: 469.32838.

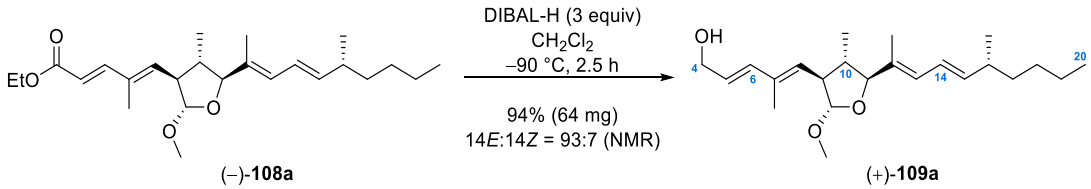
7.8 Synthesis of two diastereomers of Desmethylfusaequisin A

Synopsis



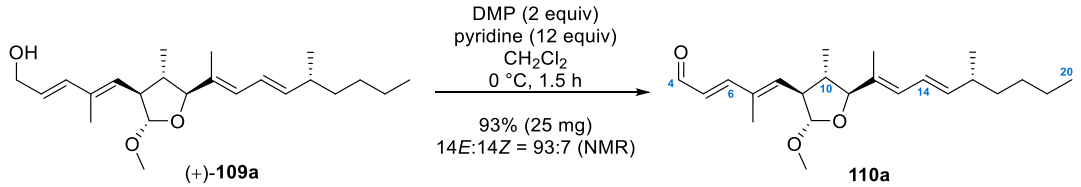


Dienoate (−)-108a by HWE Olefination. To an ice-cooled solution of ethyl 2-diethoxyphosphorylacetate ($(EtO)_2P(O)CH_2CO_2Et$, $C_8H_{17}O_5P$, 224.19 g/mol, 1.13 g/mL, 180 µL, 203.4 mg, 0.9073 mmol, 4.56 equiv) in THF (7 mL) was added natrium hydride (NaH, 60% w/w in mineral oil, 24.00 g/mol, 36 mg, 0.9000 mmol, 4.56 equiv). The clear, colorless solution was stirred at room temperature for 30 min and was then cooled to 0 °C. A precooled 0 °C solution of **107a** ($C_{21}H_{34}O_3$, 334.49 g/mol, 66 mg, 0.1973 mmol, 1 equiv) in THF (3 mL) was dropwise added. The clear, colorless solution was stirred at room temperature for 3 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1) to deliver (−)-**108a** as a mixture of 14-C/15-C double bond isomers ($C_{25}H_{40}O_4$, 404.58 g/mol, 76 mg, 0.1878 mmol, 95%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.27 ppm [(*Z*)-**108a**] and 5.61 ppm [(*E*)-**108a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**108a** and J = 15.2 Hz for (*E*)-**108a**. The assignment of the 5-C/6-C double bond configuration rests on the evaluation of the NMR coupling constant of 5-CH: J = 15.7 Hz.; $[\alpha]_D^{20} = -40.2$ (c = 0.5 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**108a**: R_f 0.56 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H, 20-CH_3), 0.93 (d, ^{3}J = 6.8 Hz, 3H, 10'-CH_3), 1.00 (d, ^{3}J = 6.4 Hz, 3H, 16'-CH_3), 1.19−1.35 (m, 9H, $CO_2CH_2C\underline{H_3}$, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (d, ^{4}J = 1 Hz, 3H, 12'-CH_3), 1.85 (s, 3H, 7'-CH_3) overlapped by 1.78−1.87 (m, 1H, 10-CH), 2.12−2.23 (m, 1H, 16-CH), 2.81 (ddd, ^{3}J = 9.9, 9.6, 3.9 Hz, 1H, 9-CH), 3.37 (s, 3H, 9'-CH(OC$\underline{H_3}$)), 4.06 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 4.22 (q, ^{3}J = 7.3 Hz, 2H, $CO_2C\underline{H_2}CH_3$), 4.77 (d, ^{3}J = 3.9 Hz, 1H, 9'-C$\underline{H}$(OCH$_3$)), 5.61 (dd, ^{3}J = 15.2, 7.8 Hz, 1H, 15-CH), 5.81 (d, ^{3}J = 9.9 Hz, 1H, 8-CH), 5.85 (d, ^{3}J = 15.7 Hz, 1H, 5-CH), 6.04 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.2, 10.8 Hz, 1H, 14-CH), 7.34 (d, ^{3}J = 15.7 Hz, 1H, 6-CH); ^{13}C NMR (176 MHz $CDCl_3$) δ 11.76 (12'-CH_3), 12.84 (7'-CH_3), 14.24 (20-CH_3CH_3), 14.47 ($CO_2CH_2\underline{CH_3}$), 14.64 (10'-CH_3), 20.81 (16'-CH_3), 22.95; 29.75; 36.93 (17,18,19-CH_2), 37.33 (16-CH), 44.90 (10-CH), 54.51 (9-CH), 56.01 (9'-CH(O$\underline{CH_3}$)), 60.42 ($CO_2\underline{CH_2}CH_3$), 90.42 (11-CH), 109.45 (9'-$\underline{CH}$(OCH$_3$)), 117.10 (5-CH), 124.13 (14-CH), 129.21 (13-CH), 131.76; 135.14 (7-C, 12-C), 139.98 (8-CH), 142.17 (15-CH), 148.97 (6-CH), 167.48 ($\underline{C}O_2CH_2CH_3$); IR ν 2955 (w), 2925 (w), 2870 (w), 1715 (s), 1625 (m), 1455 (w), 1365 (w), 1305 (m), 1265 (m), 1165 (s), 1120 (m), 1095 (s), 1025 (m), 995 (s), 960 (s), 885 (w), 845 (w), 725 (w) cm^{-1}; Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97; Found: C, 74.0; H, 10.0.

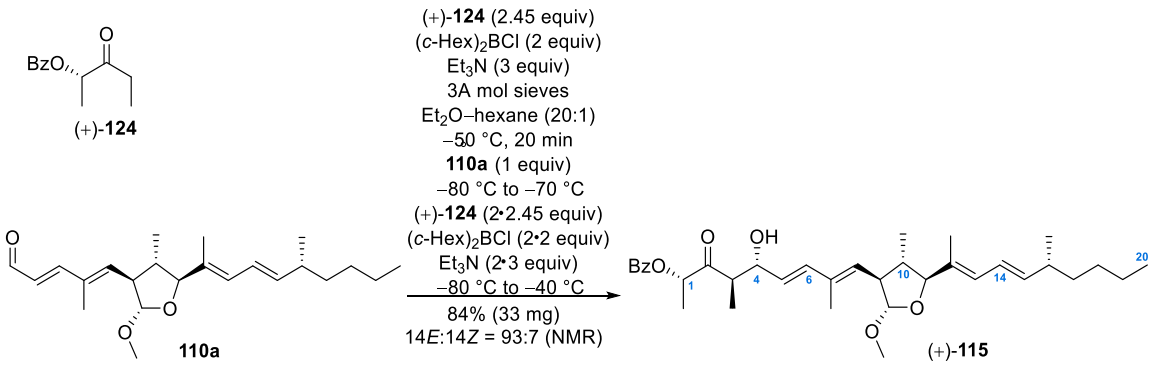


Allylic Alcohol (+)-109a by DIBAL-H Reduction. To a solution of the enoate (−)-**108a** ($C_{25}H_{40}O_4$, 404.58 g/mol, 76 mg, 0.1878 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was dropwise added DIBAL-H (1 M in CH_2Cl_2, 0.57 mL, 0.57 mmol, 3.04 equiv) over a period of time of 10 min at −90 °C. The resulting colorless solution was stirred at −90 °C for 2.5 h. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (10 mL), CH_2Cl_2 (10 mL) and saturated aqueous potassium sodium tartrate solution (10 mL) at –90 °C. The cloudy biphasic mixture was warmed to room temperature and stirring was continued for 30 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concen-

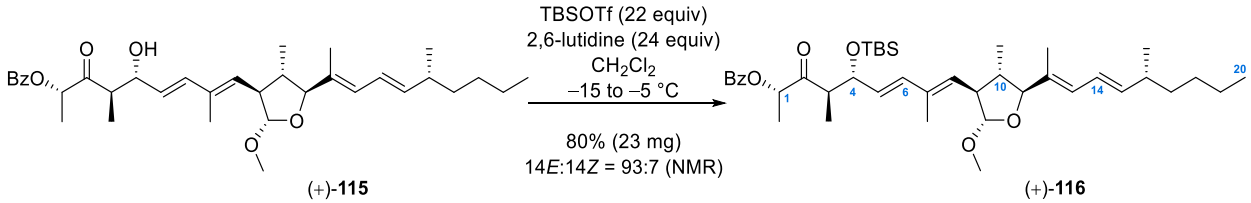
trated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver a mixture of 14-C/15-C double bond isomers of the allylic alcohol (+)-**109a** ($C_{23}H_{38}O_3$, 362.55 g/mol, 64 mg, 0.1765 mmol, 94%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**109a**] and 5.57 ppm [(*E*)-**109a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.4 Hz for (*Z*)-**109a** and J = 15.0 Hz for (*E*)-**109a**. $[\alpha]_D^{20}$ = +10.0 (c 0.5 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**109a**: R_f 0.46 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.90 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.17−1.34 (m, 6 H, 17-CH_2, 18-CH_2, 19-CH_2), 1.38 (br. s, 1H, OH), 1.74 (s, 3H, 12'-CH_3) overlapped by 1.68−1.79 (m, 1H, 10-CH), 1.82 (s, 3H, 7'-CH_3), 2.10−2.22 (m, 1H, 16-CH), 2.76 (ddd, ^{3}J = 10.1, 9.4, 4.0 Hz, 1H, 9-CH), 3.37 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 4.05 (d, ^{3}J = 9.8 Hz, 1H, 11-CH), 4.22 (d, ^{3}J = 6.1 Hz, 2H, 4-CH_2), 4.73 (d, ^{3}J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH_3)), 5.42 (d, ^{3}J = 10.1 Hz, 1H, 8-CH), 5.57 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 5.79 (dt, ^{3}J = 15.6, 6.1 Hz, 1H, 5-CH), 6.03 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.0, 10.7 Hz, 1H, 14-CH), 6.29 (d, ^{3}J = 15.6 Hz, 1H, 6-CH); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.76 (12'-CH_3), 13.14 (7'-CH_3), 14.25 (20-CH_3), 14.49 (10'-CH_3), 20.83 (16'-CH_3), 22.94; 29.75; 36.93 (17,18,19-CH_2), 37.34 (16-CH), 44.88 (10-CH), 53.99 (9-CH), 56.03 (9'-CH(OC<u>H</u>$_3$)), 63.96 (4-CH_2), 90.40 (11-CH), 109.92 (9'-<u>CH</u>(OCH_3)), 124.17 (14-CH), 126.76 (5-CH), 129.08 (13-CH), 131.95; 131.98; 135.59 (8-CH, 7-C, 12-C), 136.19 (6-CH), 142.00 (15-CH); IR ν 3400 (w), 2955 (m), 2925 (m), 2870 (m), 1675 (w), 1455 (m), 1375 (m), 1305 (w), 1260 (w), 1185 (w), 1095 (s), 1025 (m), 995 (s), 960 (s), 885 (w), 800 (w), 755 (w), 510 (w) cm^{-1}; Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.57; Found: C, 76.1; H, 10.6.



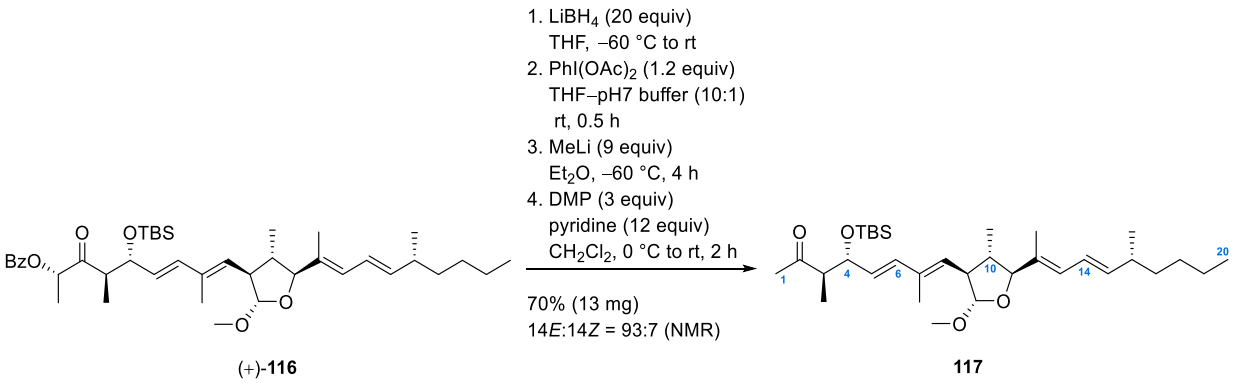
Aldehyde 110a by Dess−Martin Oxidation. To an ice-cooled solution of the alcohol (+)-**109a** ($C_{23}H_{38}O_3$, 362.55 g/mol, 27 mg, 0.0745 mmol, 1 equiv) in CH_2Cl_2 (13 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 70 µL, 68.6 mg, 0.8673 mmol, 11.64 equiv) was added the Dess−Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 63 mg, 0.1485 mmol, 1.99 equiv). The white suspension was stirred at 0 °C for 1.5 h and was then diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to deliver the aldehyde as a mixture of 14-C/15-C double bond isomers **110a** ($C_{23}H_{36}O_3$, 360.53 g/mol, 25 mg, 0.0693 mmol, 93%, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.27 ppm [(*Z*)-**110a**] and 5.59 ppm [(*E*)-**110a**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**110a** and J = 15.0 Hz for (*E*)-**110a**. Analytical data are reported for (12*E*,14*E*)-**110a**: R_f 0.79 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H), 0.95 (d, ^{3}J = 6.6 Hz, 3H), 1.00 (d, ^{3}J = 6.6 Hz, 3H), 1.18−1.34 (m, 6H), 1.75 (s, 3H) overlapped by 1.73−1.78 (m, 1H), 1.89 (s, 3H), 2.13−2.22 (m, 1H), 2.85 (ddd, ^{3}J = 10.0, 9.4, 3.8 Hz, 1 H), 3.38 (s, 3H), 4.09 (d, ^{3}J = 9.5 Hz, 1H), 4.80 (d, ^{3}J = 3.8 Hz, 1H), 5.59 (dd, ^{3}J = 15.0, 8.1 Hz, 1H), 5.94 (d, ^{3}J = 10.0 Hz, 1H), 6.05 (d, ^{3}J = 10.6 Hz, 1H), 6.16 (dd, ^{3}J = 15.4, 7.7 Hz, 1H), 6.21 (dd, ^{3}J = 15.0, 10.6 Hz, 1H), 7.14 (d, ^{3}J = 15.4 Hz, 1H), 9.59 (d, ^{3}J = 7.7 Hz, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.76, 13.01, 14.25, 14.69, 20.81, 22.95, 29.75, 36.92, 37.35, 44.92, 54.72, 56.03, 90.41, 109.20, 124.06, 127.96, 129.36, 131.48, 135.63, 142.27, 142.34, 157.05, 194.20.



Aldol (+)-115 by Asymmetric Paterson Aldol Reaction. To a solution of the ketone (+)-**124** ($C_{12}H_{14}O_3$, 206.24 g/mol, 35 mg, 0.1697 mmol, 2.45 equiv) in Et_2O (5 mL) were successively added dried 3 Å molecular sieves (50 mg, 0.1 mbar, 200 °C, 1 h), chlorodicyclohexylborane ((*c*-Hex)$_2$BCl, 1 M in hexane, 0.21 mL, 0.21 mmol, 3.03 equiv) and triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 30 µL, 21.8 mg, 0.2154 mmol, 3.11 equiv) at −50 °C. The clear, colorless suspension was stirred for 20 min at −50 °C and the color of the suspension turned to white. The white, turbid suspension was cooled to −80 °C and dienal **110a** $C_{23}H_{36}O_3$, 360.53 g/mol, 25 mg, 0.0693 mmol, 1 equiv) was dropwise added over a period of time of 10 min at −80 °C. The white suspension was strirred at −70 °C for1 h. Because TLC indicated incomplete conversion, in parallel two additional batches of the boron enolate were prepared: To the solutions of the ketone (+)-**124** ($C_{12}H_{14}O_3$, 206.24 g/mol, 2×35 mg, 2×0.1697 mmol, 2×2.45 equiv) in Et_2O (2×5 mL) were successively added dried 3 Å molecular sieves (2×50 mg, 0.1 mbar, 200 °C, 1 h), chlorodicyclohexylborane ((*c*-Hex)$_2$BCl, 1 M in hexane, 2×0.21 mL, 2×0.21 mmol, 2×3.03 equiv) and triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 2×30 µL, 2×21.8 mg, 2×0.2154 mmol, 2×3.11 equiv) at −50 °C. The clear, colorless suspensions were stirred for 20 min at −50 °C and the color of the suspensions turned to white. All flasks were cooled to −80 °C and the two batches of the boron enolate were added to the original solution (already containing the dienal **110a**) at −80 °C in intervals of 0.5 h. The reagent mixture was allowed to warm to –40 °C for 3 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (10 mL) and CH_2Cl_2 (10 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×0 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1 to 5:1) to deliver the aldol as a mixture of 14-C/15-C double bond isomers (+)-**115** ($C_{35}H_{50}O_6$, 566.77 g/mol, 33 mg, 0.0582 mmol, 84 %, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 11-CH at 4.05 ppm [(*E*)-**115**] and 4.09 ppm [(*Z*)-**115**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. $[\alpha]_D^{20}$ = +20.0 (c 1.0 in $CHCl_3$); Analytical data are reported for (12*E*,14*E*)-**115**: R_f 0.41 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.90 (d, ^{3}J = 6.7 Hz, 3H, 10'-CH_3), 0.99 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.20 (d, ^{3}J = 6.9 Hz, 3H, 3'-CH_3) overlapped by 1.17−1.32 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.57 (d, ^{3}J = 7.0 Hz, 3H, 1'-CH_3), 1.74 (s, 3H, 12'-CH_3) overlapped by 1.70−1.82 (m, 1H, 10-CH), 1.79 (s, 3H, 7'-CH_3), 2.10−2.21 (m, 1H, 16-CH), 2.75 (ddd, ^{3}J = 10.1, 9.5, 4.0 Hz, 1H, 9-CH), 2.95 (dq, J = 7.9, 7.0 Hz, 1H, 3-CH), 3.37 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 4.05 (d, J = 9.8 Hz, 1H, 11-CH), 4.33 (dd, ^{3}J = 7.9, 7.5 Hz, 1H, 4-CH), 4.74 (d, ^{3}J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH$_3$)), 5.40−5.48 (m, 2H, 1-CH, 8-CH), 5.53−5.61 (m, 2H, 5-CH, 15-CH), 6.03 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.21 (dd, ^{3}J = 15.0, 10.7 Hz, 1H, 14-CH), 6.30 (d, ^{3}J = 15.6 Hz, 1H, 6-CH), 7.43−7.52 (m, 2H, aryl-CH), 7.55−7.63 (m, 1H, aryl-CH), 8.07−8.11 (m, 2H, aryl-CH); ^{13}C NMR (126 MHz $CDCl_3$) δ 11.73 (12'-CH_3), 13.13 (7'-CH_3), 14.25 (20-CH_3), 14.44 (10'-CH_3), 14.77 (3'-CH_3), 15.78 (1'-CH_3), 20.82 (16'-CH_3), 22.94; 29.74; 36.92 (17,18,19-CH_2), 37.33 (16-CH), 44.86 (10-CH), 48.46 (3-CH), 54.02 (9-CH), 56.02 (9'-CH(O<u>C</u>H$_3$)), 74.99 (1-CH), 75.33 (4-CH), 90.40 (11-CH), 109.81 (9'-<u>C</u>H(OCH$_3$)), 124.16 (14-CH), 127.63 (5-CH), 128.60 (aryl-CH), 129.12 (13-CH), 129.57 (aryl-C), 129.95 (aryl-CH), 131.93; 135.28 (C-7, C-12,) 132.68 (8-CH), 133.50 (aryl-CH), 137.44 (6-CH), 142.02 (15-CH), 165.99 (<u>C</u>O$_2$Ph) 211.39 (C-2); IR ν 3470 (w), 2930 (w), 1715 (m), 1450 (m), 1375 (w), 1265 (m), 1215 (s), 1095 (m), 1000 (m), 965(m), 750 (s), 710 (s), 665 (s) cm^{-1}; HRMS (ESI): m/z [M + Na]$^+$ Calcd. for $C_{35}H_{50}O_6Na$: 589.34996; Found: 589.34954.

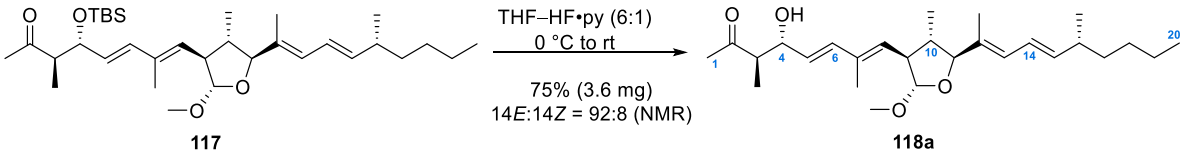


Silyl Ether (+)-116 by Silylation. To a solution of the aldol (+)-**115** ($C_{35}H_{50}O_6$, 566.77 g/mol, 24 mg, 0.0423 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) and 2,6-lutidine (C_7H_9N, 107.16 g/mol, 0.923 g/mL, 0.12 mL, 110.8 mg, 1.0340 mmol, 24.44 equiv) was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, $C_7H_{15}F_3O_3SSi$, 264.34 g/mol, 1.15 g/mL, 0.21 mL, 241.5 mg, 0.9136 mmol, 21.60 equiv) at –15 °C. The clear colorless solution was allowed to warm to –5 °C over a period of time of 1 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (5 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane–ethyl acetate, 100:1 to 50:1 to 20:1 to 10:1) to afford the silyl ether as a mixture of 14-C/15-C double bond isomers (+)-**116** ($C_{41}H_{64}O_6Si$, 681.03 g/mol, 23 mg, 0.0338 mmol, 80%, 14*E*:14*Z* = 91:9) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**116**] and 5.57 ppm [(*E*)-**116**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**116** and J = 15.0 Hz for (*E*)-**116**. Analytical data are reported for (12*E*,14*E*)-**116**: R_f 0.72 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +5.7 (c = 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.03 (s, 3H), −0.02 (s, 3H), 0.82 (s, 9H), 0.86–0.92 (m, 6H), 0.99 (d, ^{3}J = 6.7 Hz, 3H), 1.04 (d, ^{3}J = 7.0 Hz, 3H), 1.19–1.33 (m, 6H), 1.54 (d, ^{3}J = 7.0 Hz, 3H), 1.75 (s, 3H), 1.78 (s, 3H) overlapped by 1.76–1.82 (m, 1H), 2.13–2.22 (m, 1H), 2.75 (ddd, ^{3}J = 10.0, 9.5, 4.0 Hz, 1H), 2.93 (dq, ^{3}J = 8.9, 7.0 Hz, 1H), 3.38 (s, 3H), 4.05 (d, ^{3}J = 9.8 Hz, 1H), 4.34 (dd, ^{3}J = 8.9 Hz, 1H), 4.75 (d, ^{3}J = 4.0 Hz, 1H), 5.37–5.48 (m, 3H), 5.57 (dd, ^{3}J = 15.0, 8.2 Hz, 1H), 6.03 (d, ^{3}J = 11.0 Hz, 1H) 6.16 (d, ^{3}J = 15.9 Hz, 1H), 6.21 (dd, ^{3}J = 15.0, 11.0 Hz, 1H), 7.41–7.49 (m, 3H), 7.54–7.62 (m, 1H), 8.06–8.11 (m, 2H); ^{13}C NMR (126 MHz $CDCl_3$) δ −4.66, −4.02, 11.76, 13.19, 14.25, 14.45, 14.54, 15.30, 18.17, 20.83, 22.95, 25.78, 25.99, 29.76, 36.9, 37.34, 44.89, 49.35, 54.01, 56.01, 75.43, 76.67, 90.39, 109.86, 124.18, 128.55, 128.89, 129.12, 129.81, 129.96, 131.82, 132.00, 133.37, 135.46, 136.78, 141.99, 165.89, 209.44; IR ν 2955 (m), 2930 (m), 2855 (w), 1720 (s), 1450 (m), 1375 (w), 1315 (w), 1260 (m), 1175 (w), 1095 (m), 1070 (m), 1000 (s), 965 (m), 835 (m), 780 (m), 755 (s), 710 (s), 665 (w) cm^{-1}; HRMS (ESI): m/z [M + Na]$^+$ Calcd. for $C_{41}H_{64}O_6NaSi$: 703.43644; Found: 703.43658.



Methyl Ketone 117 by Chain Degradation. To a solution of silyl ether (+)-**116** ($C_{41}H_{64}O_6Si$, 681.03 g/mol, 23 mg, 0.0338 mmol, 1 equiv) in THF (4 mL) was added lithium borohydride ($LiBH_4$, 21.78 g/mol, 15 mg, 0.6887 mmol, 20.36 equiv) at –60 °C. The colorless suspension was allowed to warm to room temperature over night and was carefully diluted by the addition of aqueous phosphate pH 7 buffer (2 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light yellow residue was used without isolation, purification or characterization of the putative diastereomeric diols. TLC of the solution showed a spot at R_f

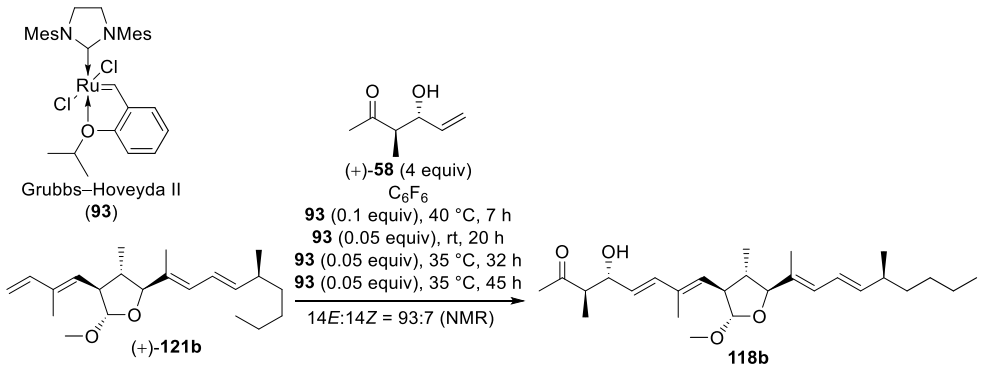
0.18 (cyclohexane–ethyl acetate, 5:1). The light yellow residue was then transferred into a round-bottom flask using THF (5 mL) for rinsing. aqueous phosphate pH 7 buffer (1 mL) and iodobenzene diacetate ($PhI(OAc)_2$, $C_{10}H_{11}IO_4$, 322.10 g/mol, 13 mg, 0.0404 mmol, 1.2 equiv, – based on initial amount of (+)-**116**) were subsequently added at room temperature. The clear colorless reaction mixture was stirred for 0.5 h at room temperature and was then diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution (10 mL) and CH_2Cl_2 (20 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane–ethyl acetate, 50:1 to 20:1) to deliver a colorless viscous oil (16 mg, assumed to be the aldehyde A, $C_{32}H_{56}O_4Si$, 578.94 g/mol) that was used in the following nucleophilic addition without proof of structure or of purity. R_f 0.79 (cyclohexane–ethyl acetate, 2:1). To a solution of the product from above (16 mg) in Et_2O (5 mL) was added in three portions in intervals of 10 min methyl lithium (CH_3Li, 1.6 M in Et_2O, 3×60 µL, 3×0.096 mmol = 0.288 mmol, 3×2.84 equiv = 8.52 equiv, – based on initial amount of (+)-**116**)) at –30 °C. The clear colorless solution was stirred at –30 °C for 4h and was then carefully diluted by the addition of aqueous phosphate pH 7 buffer (2 mL) and CH_2Cl_2 (5 mL) at –30 °C. The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light yellow residue was used without isolation, purification or characterization of the putative diastereomeric alcohols. TLC of the solution showed two spots at R_f 0.42 and R_f 0.35 (cyclohexane–ethyl acetate, 5:1). To an ice-cooled solution of the residue from above in CH_2Cl_2 (6 mL) and pyridine (py, C_5H_5N, 79.10 g/mol, 0.98 g/mL, 30 µL, 29.4 mg, 0.3717 mmol, 11.00 equiv – based on initial amount of (+)-**116**)) was added the Dess–Martin periodinane ($C_{13}H_{13}IO_8$, 424.14 g/mol, 43 mg, 0.1014 mmol, 3.0 equiv – based on initial amount of (+)-**116**)). The white suspension was allowed to warm to room temperature and was stirred at room temperature for 2 h. The white suspension was diluted by the successive addition of saturated aqueous $Na_2S_2O_3$ solution (5 mL), H_2O (5 mL) and CH_2Cl_2 (5 mL) at 0 °C. The biphasic mixture was stirred at room temperature until a clear organic layer appeared (about 20 min). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane–ethyl acetate, 50:1 to 20:1) to deliver the ketone as a mixture of 14-C/15-C double bond isomers **117** ($C_{33}H_{58}O_4Si$, 546.90 g/mol, 13 mg, 0.0238 mmol, 70% from (+)-**116**, 14*E*:14*Z* = 93:7) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^1H NMR signal of 11-CH at 4.05 ppm [(*E*)-**117**] and 4.09 ppm [(*Z*)-**117**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. Analytical data are reported for (12*E*,14*E*)-**117**: R_f 0.59 (cyclohexane–ethyl acetate, 5:1); ^1H NMR (600 MHz, $CDCl_3$) δ –0.02 (s, 3H, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.01 (s, 3H, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.84 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.88 (dd, ^3J = 6.8 Hz, 3H, 20-CH_3), 0.91 (d, ^3J = 6.6 Hz, 3H, 10'-CH_3), 0.93 (d, ^3J = 7.3 Hz, 3H, 3'-CH_3), 0.99 (d, ^3J = 6.6 Hz, 3H, 16'-CH_3), 1.19–1.34 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (s, 3H, 12'-CH_3), 1.78 (s, 3H, 7'-CH_3) overlapped by 1.72–1.82 (m, 1H, 10-CH), 2.20 (s, 3H, 1-CH_3) overlapped by 2.12–2.21 (m, 1H, 16-CH), 2.70 (dq, ^3J = 8.4, 7.0 Hz, 1H, 3-CH), 2.75 (ddd, ^3J = 9.9, 9.5, 4.0 Hz, 1H, 9-CH), 3.38 (s, 3H, 9'-CH($OC\underline{H}_3$)), 4.05 (d, ^3J = 9.5 Hz, 1H, 11-CH), 4.23 (dd, ^3J = 8.4, 7.7 Hz, 1H, 4-CH), 4.75 (d, ^3J = 4.0 Hz, 1H, 9'-C<u>H</u>(OCH_3)), 5.38 (d, ^3J = 9.9 Hz, 1H, 8-CH), 5.44 (dd, ^3J = 15.8, 7.7 Hz, 1H, 5-CH), 5.57 (dd, ^3J = 15.0, 8.1 Hz, 1H. 15-CH), 6.03 (d, ^3J = 10.6 Hz, 1H, 13-CH), 6.15 (d, ^3J = 15.8 Hz, 1H, 6-CH), 6.20 (d, ^3J = 15.0, 10.6 Hz, 1H, 14-CH); ^{13}C NMR (151 MHz $CDCl_3$) δ −4.93 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −3.80 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 11.77 (12'-$CH_3$), 13.21 (7'-$CH_3$), 13.42 (3'-$CH_3$), 14.25 (20-$CH_3$), 14.48 (10'-$CH_3$), 18.18 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 20.84 (16'-$CH_3$), 22.95; 29.76; 36.94 (17,18,19-CH_2), 25.94 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 31.28 (1-$CH_3$), 37.34 (16-CH), 44.90 (10-CH), 53.37 (3-CH), 54.02 (9-CH), 56.00 (9'-CH($O\underline{C}H_3$)), 77.25 (4-CH), 90.38 (11-CH), 109.88 (9'-<u>C</u>H(OCH_3)), 124.19 (14-CH), 128.87 (5-CH), 129.12 (13-CH), 131.76 (8-CH), 132.01; 135.49 (7-C, 12-C), 136.42 (6-CH), 142.01 (15-CH), 212.39 (2-C). No further analytical data were obtained.



117 **118a**

Allylic Alcohol 118a by TBS Ether Cleavage. A polypropylene reaction vessel was charged with a solution of ketone **117** ($C_{33}H_{58}O_4Si$, 546.90 g/mol, 6 mg, 0.011 mmol, 1 equiv) in THF (3 mL). To the ice-cooled solution was dropwise

added hydrogen fluoride•pyridine (HF•pyridine, C_5H_6FN, 65−70% w/w HF in pyridine (py), 0,5 mL). The clear, slightly brownish solution was allowed to warm to room temperature over night and was diluted by the addition of saturated aqueous $NaHCO_3$ solution (around 10 mL) and CH_2Cl_2 (10 mL). The biphasic mixture was stirred at room temperature for 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver the allylic alcohol as a mixture of 14-C/15-C double bond isomers **118a** ($C_{27}H_{44}O_4$, 432.64 g/mol, 3.6 mg, 0.0083 mmol, 75% , 14*E*:14*Z* = 92:8) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 8-CH at 5.44 ppm [(*E*)-**118a**] and 5.47 ppm [(*Z*)-**118a**]. The assignment of the 14-C/15-C double bond configuration by coupling constant comparison was complicated by signal overlap. Analytical data are reported for (12*E*,14*E*)-**118a**: R_f 0.38 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.90 (d, ^{3}J = 6.6 Hz, 3H), 1.00 (d, ^{3}J = 6.8 Hz, 3H), 1.09 (d, ^{3}J = 7.0 Hz, 3H), 1.21–1.35 (m, 6H), 1.74 (s, 3H), 1.78 (s, 3H) overlapped by 1.72–1.83 (m, 1H), 2.13–2.20 (m, 1H), 2.21 (s, 3H), 2.48 (d, ^{3}J = 3.2 Hz, 1H), 2.70 (dq, ^{3}J = 7.7, 7.3 Hz, 1H) 2.76 (ddd, ^{3}J = 9.9, 9.6, 4.0 Hz, 1H) 3.37 (s, 3H), 4.05 (d, ^{3}J = 9.9 Hz, 1H), 4.26 (ddd, ^{3}J = 7.7, 3.2 Hz, 1H), 4.74 (d, ^{3}J = 4.0 Hz, 1H), 5.44 (d, ^{3}J = 9.9 Hz, 1H), 5.57 (dd, ^{3}J = 15.8, 7.7 Hz, 1H), 5.57 (dd, ^{3}J = 15.0, 8.1 Hz, 1H), 6.03 (d, ^{3}J = 10.8 Hz, 1H), 6.21 (dd, ^{3}J = 15.0, 10.8 Hz, 1H), 6.29 (d, ^{3}J = 15.8 Hz, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ 11.78, 13.15, 14.07 , 14.25, 14.49, 20.82, 22.96, 29.75, 30.09, 36.95, 37.33, 44.92, 52.53, 54.05, 56.00, 75.37, 90.42, 109.85, 124.18, 127.67, 129.09, 132.00, 132.61, 135.36, 137.38, 142.02, 213.32; ^{1}H NMR (600 MHz, pyridine-d_5) δ 0.86 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 0.93 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.02 (d, ^{3}J = 7.0 Hz, 3H, 16'-CH_3), 1.14 (d, ^{3}J = 7.3 Hz, 3H, 3'-CH_3), 1.21–1.32 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.90 (s, 3H, 7'-CH_3), 1.92 (s, 3H, 12'-CH_3) overlapped by 1.88–1.93 (m, 1H, 10-CH), 2.17–2.25 (m, 1H, 16-CH), 2.37 (s, 3H, 1-CH_3), 2.97 (dq, ^{3}J = 8.2, 7.0 Hz, 1H, 3-CH), 3.03 (ddd, ^{3}J = 9.9, 9.7, 4.0 Hz, 1H, 9-CH), 3.44 (s, 3H, 9'-CH(OC<u>H</u>$_3$)), 4.30 (d, ^{3}J = 9.9 Hz, 1H, 11-CH), 4.68 (dd, ^{3}J = 8.2, 7.3 Hz, 1H, 4-CH), 4.97 (d, ^{3}J = 4.2 Hz, 1H, C<u>H</u>(OCH_3) overlapped by H_2O), 5.61 (d, ^{3}J = 9.9 Hz, 1H, 8-CH), 5.69 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 5.96 (dd, ^{3}J = 15.8, 7.3 Hz, 1H, 5-CH), 6.29 (d, ^{3}J = 10.6 Hz, 1H, 13-CH), 6.49 (dd, ^{3}J = 15.0, 10.6 Hz, 1H, 14-H), 6.62 (d, ^{3}J = 15.8 Hz, 1H, 6-CH); ^{13}C NMR (151 MHz, pyridine-d_5) δ 12.30 (12'-CH_3), 13.67 (7'-CH_3), 14.13 (3'-CH_3), 14.70; 14.77 (10'-CH_3, 20-CH_3) 21.34 (16'-CH_3), 23.52; 30.33; 37.48 (17,18,19-CH_2), 30.52 (1-CH_3), 37.93 (16-CH), 45.73 (10-CH), 54.21 (3-CH) 54.67 (9-CH), 56.12 (9'-CH(O<u>C</u>H_3)), 75.89 (4-CH), 90.99 (11-CH), 110.57 (9'-<u>C</u>H(OCH_3)), 125.22 (14-CH), 129.26 (13-CH) 131.02 (5-CH) 132.49 (8-CH) 133.76; 136.46 (C-7; C-12), 136.58 (6-CH), 142.36 (15-CH), 212.00 (2-C); HRMS (ESI): m/z [M + Na]$^+$ Calcd. for $C_{27}H_{44}O_4Na$: 455.31318; Found: 455.31318.

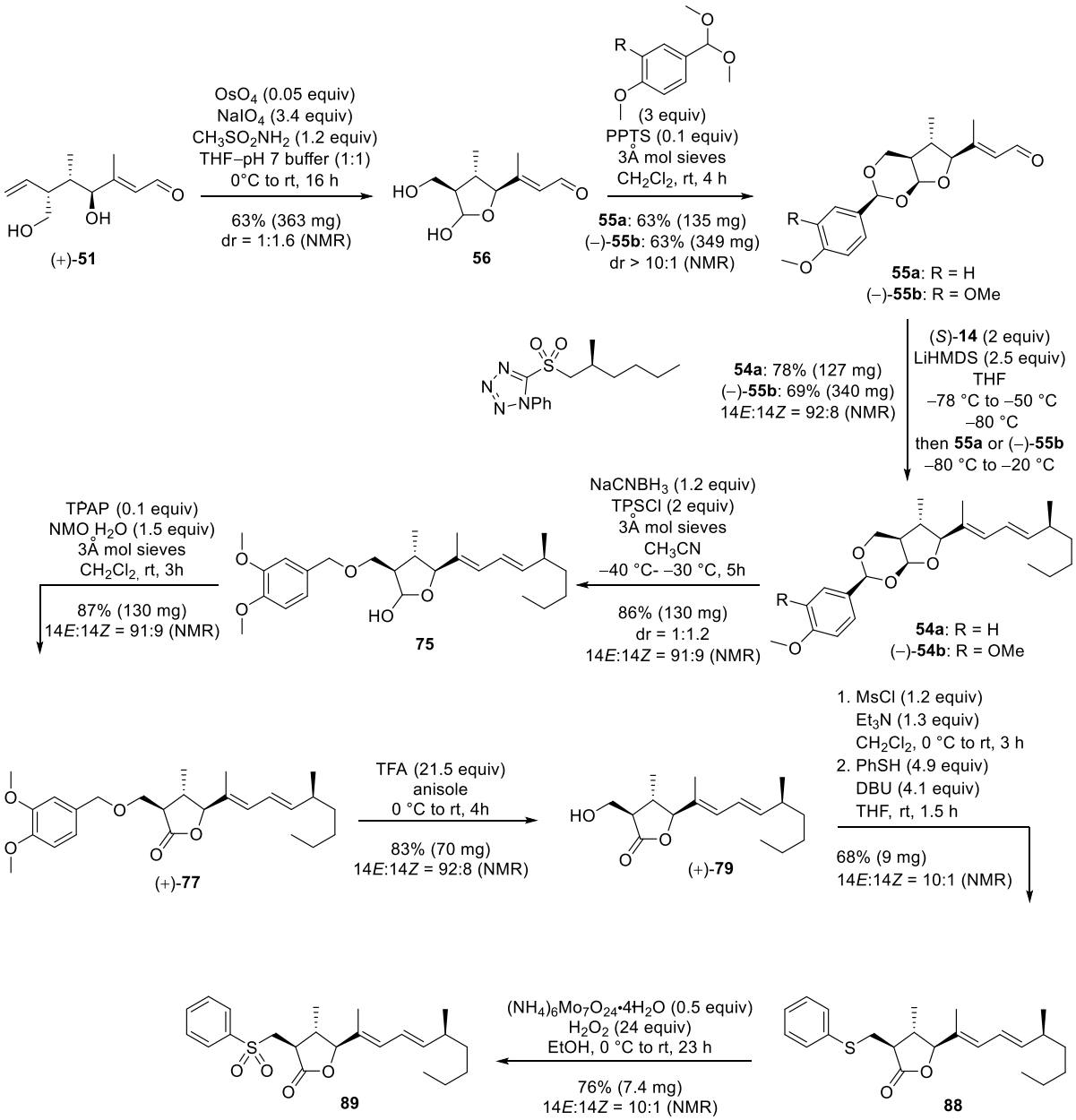


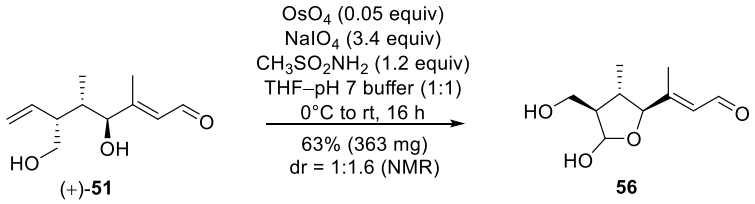
Desmethylfusaequisin 118b by Cross Metathesis. A sealable glass pressure tube was charged with a solution of the lactol methyl ether (+)-**121b** ($C_{22}H_{36}O_2$, 332.53 g/mol, 7.5 mg, 22.55 µmol, 1 equiv) in hexafluorobenzol (1.5 mL). The allylic alcohol (+)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 12 mg, 93.63 µmol, 4.15 equiv) and the Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 1.5 mg, 2.394 µmol, 0.106 equiv) were subsequently added at room temperature. The tube was sealed with a Teflon screw cap and stirred at 40 °C for 7 h. Hoveyda−Grubbs catalyst II (**92**) ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.117 µmol, 0.049 equiv) was added at room temperature; the reaction mixture was stirred at room temperature for 20 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.117 µmol, 0.049 equiv) was added at room temperature; the reaction mixture was stirred at 35 °C for 32 h. Additional **92** ($C_{31}H_{38}Cl_2N_2ORu$, 626.62 g/mol, 0.7 mg, 1.117 µmol, 0.049 equiv) was added at room temperature; the reaction mixture was stirred at 35 °C for 45 h The turbid dark brown solution was only rawly purified by flash chromatography (cyclohexane−ethyl acetate, 2:1 to 1:1) to

afford lactol methyl ether **118b** ($C_{27}H_{44}O_4$, 432.65 g/molas a light brownish oil with solvent impurities of diethyl ether, ethyl acetate, cyclohexane and non identified impurities. No further effort was undertaken to purify the product. Thus, the reaction yield was not specified. A ^{1}H NMR spectrum was recorded exclusively for confirming the general accessibility of **118b** via cross-metathesis. R_f 0.40 (hexane−ethyl acetate, 2:1) ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^3J = 7.2 Hz, 3H), 0.91 (d, ^3J = 7.0 Hz, 3H), 1.00 (d, ^3J = 6.6 Hz, 3H), 1.09 (d, ^3J = 7.3 Hz, 3H), 1.21–1.33 (m, 6H), 1.74 (d, ^4J = 1.1 Hz, 3H), 1.80 (d, ^4J = 1.1 Hz, 3H) overlapped by 1.72–1.83 (m, 1H), 2.13–2.20 (m, 1H), 2.22 (s, 3H), 2.48 (d, ^3J = 3.5 Hz, 1H), 2.70 (dq, ^3J = 7.7, 7.3 Hz, 1H), 2.73–2.79 (m, 1H), 3.37 (s, 3H), 4.05 (d, ^3J = 9.5 Hz, 1H), 4.25 (ddd, ^3J = 7.7, 3.5 Hz, 1H), 4.74 (d, ^3J = 4.0 Hz, 1H), 5.44 (d, ^3J = 9.9 Hz, 1H), 5.57 (dd, ^3J = 15.8, 7.3 Hz, 1H), 5.60 (dd, ^3J = 15.0, 8.1 Hz, 1H), 6.03 (d, ^3J = 11.0, 1.1 Hz, 1H), 6.21 (dd, ^3J = 15.0, 11.0, 1.1 Hz, 1H), 6.29 (d, ^3J = 15.8 Hz, 1H).

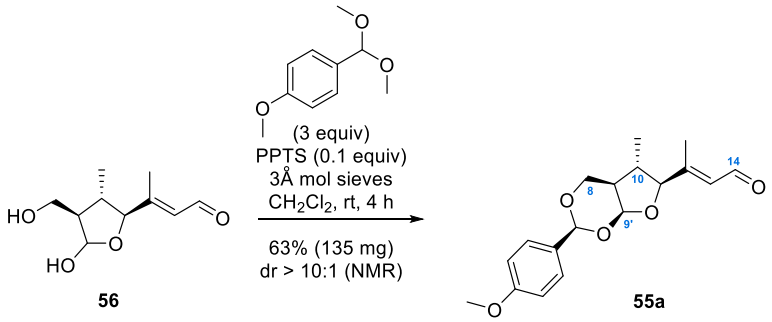
7.9 Synthesis of Sulfone 89 via reductive opening of benzylidene acetal.

Synopsis



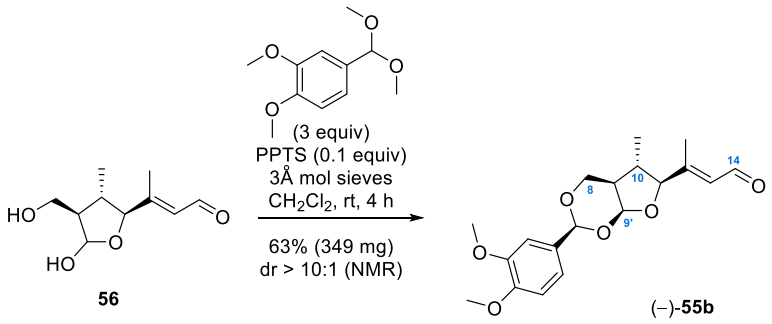


Lactol 56 by Oxidative Cleavage. To an ice cooled solution of the diol (+)-**51** ($C_{11}H_{18}O_3$, 198.26 g/mol, 570 mg, 2.875 mmol, 1 equiv) in THF (40 mL) and aqueous phosphate pH 7 buffer (40 mL) were subsequently added osmium tetroxide (2.5% w/w OsO_4 in *t*-BuOH, 37.5 mg OsO_4, 254.23 g/mol, 1.5 g, 0.1475 mmol, 0.051 equiv), methanesulfonamide (CH_5NO_2S, 95.13 g/mol, 334 mg, 3.511 mmol, 1.22 equiv) and sodium periodate ($NaIO_4$, 213.89 g/mol, 2.06 g, 9.631 mmol, 3.35 equiv). The colorless solution was allowed to warm to room temperature and was strirred at room temperature for 16 h. The slightly yellowish solution was diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution (25 mL) and CH_2Cl_2 (25 mL) and the biphasic mixture was vigorously stirred at room temperature for 15 min. The phases were separated and the dark brown aqueous layer was extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily brownish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 10:1 to 5:1 to 2:1 to 1:1 to 1:2) to deliver a mixture of anomers of the lactol **56** ($C_{10}H_{16}O_4$, 200.23 g/mol, 363 mg, 1.813 mmol, 63%, dr = 1:1.5) as a colorless viscous oil. The ratio of anomers was determined by integration of the ^{1}H NMR signals for the 13-CH protons at 6.02 and 6.06 ppm. The relative configuration was not assigned. Analytical data are reported for the mixture of diastereomers. R_f 0.41 (ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, ^3J = 6.9 Hz, 3H, 10'-CH_3^{major}), 1.14 (d, ^3J = 6.5 Hz, 3H, 10'-CH_3^{minor}), 1.76–1.87 (m, 1H, 10-CH^{minor}), 1.91–2.03 (m, 2H, 9-$CH^{major+minor}$), 2.16 (s, 3H, 16'-CH_3^{minor}), 2.22 (s, 3H, 16'-CH_3^{major}), 2.25–2.35 (m, 1H, 10-CH^{major}), 3.62 (dd, ^2J = 11.1 Hz, ^3J = 7.6 Hz, 1H, 8-CH_2^{minor}), 3.71–3.81 (m, 1H, 8-$CH_2^{major+minor}$), 3.92 (dd, ^2J = 11.5 Hz, ^3J = 2.7 Hz, 1H, 8-CH_2^{major}), 4.09 (d, ^3J = 9.6 Hz, 1H, 11-CH^{major}), 4.29 (d, ^3J = 8.8 Hz, 1H, 11-CH^{minor}), 5.48 (d, ^3J = 3.4 Hz, 1H, 9'-CH^{minor}), 5.57 (d, ^3J = 4.6 Hz, 1H, 9'-CH^{major}), 6.06 (d, ^3J = 8.0 Hz, 1H, 13-CH^{minor}), 6.10 (app d, ^3J = 8.0 Hz, 1H, 13-CH^{major}), 10.04 (d, ^3J = 8.0 Hz, 1H, 14-$CH^{major+minor}$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.23 (12'-$CH_3^{major+minor}$), 15.42 (10'-CH_3^{major}), 16.58 (10'-CH_3^{minor}), 36.72 (10-CH^{major}), 40.90 10-CH^{minor}), 52.84 (9-CH^{major}), 57.07 (9-CH^{minor}), 58.98 (8-CH_2^{major}), 62.03 (8-CH_2^{minor}), 88.00 (11-CH^{minor}), 90.59 (11-CH^{major}), 99.74 (9'-CH^{major}), 101.33 (9'-CH^{minor}), 126.52 (13-CH^{minor}), 126.69 (13-CH^{major}), 160.59 (12-C^{minor}), 162.21 (12-C^{major}), 191.63 (14-CH^{minor}), 191.90 (14-CH^{major}); IR ν 3390, 2959, 2931, 2876, 1668, 1384, 1126, 1089, 1008 cm^{-1} **;** No further analytical data were obtained

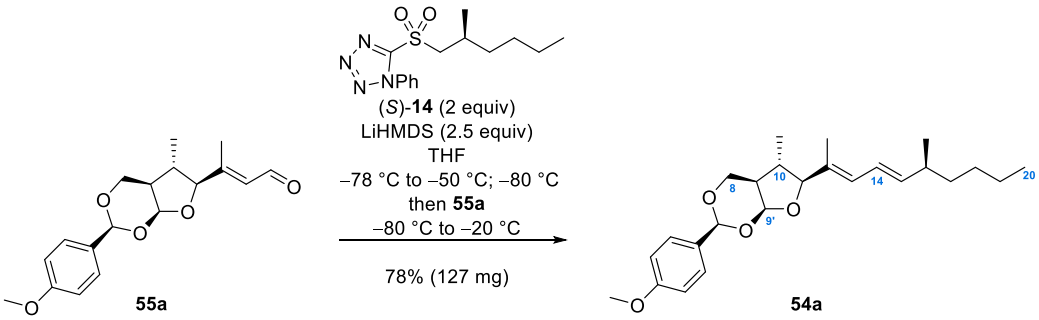


PMP-Acetal 55a by Transacetalization. To a solution of the lactol **56** ($C_{10}H_{16}O_4$, 200.23 g/mol, 135 mg, 0.674 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were subsequently added molecular sieves (100 mg, 3Å, dried: 0.1 mbar, 200 °C, 1 h), *p*-methoxybenzaldehyde dimethylacetal ($C_{10}H_{14}O_3$, 182.22 g/mol, 0.367 g, 2.014 mmol, 2.99 equiv) and pyridinium *p*-toluenesulfonate ($C_{12}H_{13}NO_3S$, 251.30 g/mol, 17 mg, 0.068 mmol, 0.1 equiv) at room temperature. The light yellowish solution was stirred at room temperature for 4 h and was then was diluted by the addition of aqueous phosphate pH 7 buffer (30 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and ethyl acetate (1×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish oily residue was purified by flash chromatography (cyclohexane–ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1) to deliver the acetal **55a** ($C_{18}H_{22}O_5$, 318.37 g/mol, 135 mg, 0.424 mmol, 63%, dr = 93:7) as a colorless oil. R_f 0.64 (cyclohexane–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ

1.11 (d, ^3J = 6.5 Hz, 3H, 10'-CH_3), 1.82 (ddd, ^3J = 11.4, 3.1 Hz, 1H, 9-CH), 2.29 (s, 3H, 12'-CH_3), 2.54-2.65 (m, 1H, 10-CH), 3.81 (s, 3H, OCH_3), 4.17 (d, ^2J = 12.4 Hz, 1H, 8-CH_2), 4.21–4.26 (m, 2H, 8-CH_2, 11-CH), 5.46–5.55 (m, 2H, 9'-CH, 4(OMe)PhC<u>H</u>), 6.05 (d, ^3J = 7.9 Hz, 1H, 13-CH), 6.86–6.95 (m, 2H, aryl-CH), 7.34–7.45 (m, 2H, aryl-CH), 10.07 (d, J = 7.9 Hz, 1H, 14-CH); ^{13}C NMR ($CDCl_3$, 126 MHz, δ) 12.76, 14.58, 36.48, 46.92, 55.45, 60.51, 64.55, 92.39, 98.27, 101.23, 113.88, 127.33, 127.45, 130.38, 160.26, 160.97, 191.37. No further analytical data were obtained.

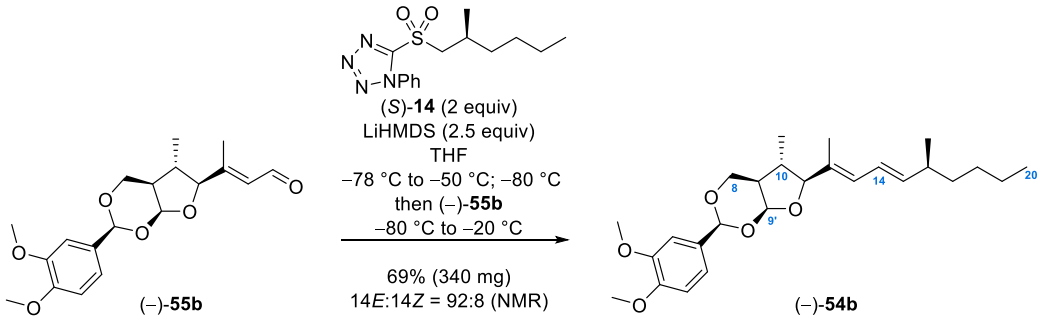


3,4-DMP-Acetal (−)-55b by Transacetalization. To a solution of the lactol **56** ($C_{10}H_{16}O_4$, 200.23 g/mol, 320mg, 1.598 mmol, 1 equiv) in CH_2Cl_2 (64 mL) were subsequently added molecular sieves (400 mg, 3Å, dried: 0.1 mbar, 200 °C, 1 h), 3,4-dimethoxybenzaldehyde dimethylacetal ($C_{11}H_{16}O_4$, 212.24 g/mol, 1.02 g, 4.806 mmol, 3.01 equiv) and pyridinium *p*-toluenesulfonate ($C_{12}H_{13}NO_3S$, 251.30 g/mol, 40 mg, 0.159 mmol, 0.1 equiv) at room temperature. The light yellowish solution was stirred at room temperature for 4 h and was then was diluted by the addition of aqueous phosphate pH 7 buffer (30 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and ethyl acetate (1×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light pink oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1) to deliver the acetal (−)-**55b** ($C_{19}H_{24}O_6$, 348.39 g/mol, 349 mg, 1.002 mmol, 63%, dr > 10:1) as a colorless oil. R_f 0.64 (cyclohexane−ethyl acetate, 1:1); $[\alpha]_D^{20}$ = −34.1 (c = 0.55 in $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (d, ^3J = 6.5 Hz, 3H, 10'-CH_3), 1.85 (ddd, ^3J = 11.4, 3.1 Hz, 1H, 9-CH), 2.31 (d, ^4J = 1.0 Hz, 3H, 12'-CH_3), 2.62 (ddq, ^3J = 11.4, 9.7, 6.5 Hz, 1H, 10-CH), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.19 (d, ^2J = 12.3 Hz, 1H, 8-CH_2), 4.23–4.28 (m, 2H, 8-CH_2, 11-CH), 5.38–5.58 (m, 2H, 9'-CH, 3,4(OMe)$_2$PhC<u>H</u>), 6.11 (dd, ^3J = 7.9 Hz, ^4J = 1.0 Hz, 1H, 13-CH), 6.87 (d, ^3J = 8.2 Hz, 1H, aryl-CH), 6.97–7.08 (m, 2H, aryl-CH), 10.08 (d, ^3J = 7.9 Hz, 1H, 14-CH); ^{13}C NMR ($CDCl_3$, 126 MHz, δ) 12.79 (12'-CH_3), 14.68 (10'-CH_3), 36.56 (10-CH), 46.92 (9-CH), 55.95 (OCH_3), 64.53 (8-CH_2), 92.27 (11-CH), 98.15; 101.17 (9'-CH, 3,4(OMe)$_2$Ph<u>CH</u>), 109.14 (Ar), 110.98 (Ar), 118.74 (Ar), 127.24 (13-CH), 130.62 (Ar), 149.06 (Ar), 149.66 (Ar), 160.85 (12-C), 191.30 (14-CH); IR ν 2960 (m), 2935 (m), 2360 (m), 1715 (m), 1670 (s), 1520 (s), 1465 (m), 1405 (m), 1265 (s), 1235 (s), 1160 (s), 1135 (s), 1100 (s), 1025 (s), 970 (m), 855 (m) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{19}H_{25}O_6$: 349.16456; Found: 349.16490; m/z $[M + Na]^+$ Calcd. for $C_{19}H_{24}O_6Na$: 371.14651; Found: 372.14666.



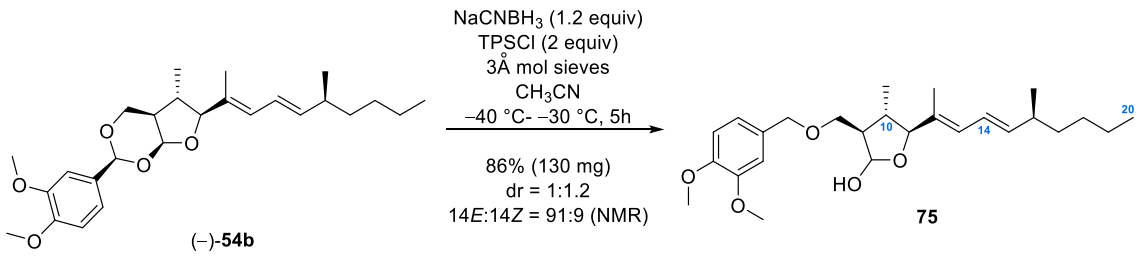
(12*E*,14*E*)-Diene 54a by Julia–Kocienski Olefination. To a solution of the known sulfone (*S*)-**14**[9] ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 250 mg, 0.811 mmol, 1.99 equiv) in THF (10 mL) at –78 °C was added a clear, colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 210 µL, 163.8 mg,

1.015 mmol, 2.49 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 0.4 mL, 1.0 mmol, 2.45 equiv) in THF (10 mL) at 0 °C for 30 min. The resulting bright yellow solution was warmed to –50 °C over a period of time of 0.5 h and was then cooled to –80 °C. A precooled –80 °C solution of the enal **55a** ($C_{18}H_{22}O_5$, 318.37 g/mol, 130 mg, 0.408 mmol, 1 equiv) in THF (10 mL) was added dropwise down along the walls of the flask causing a color change to light yellow. The resulting light yellow solution was allowed to warm to –20 °C over a period of time of 4 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (20 mL) and CH_2Cl_2 (20 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 100:1 to 50:1) to deliver **54a** as a mixture of 14-C/15-C double bond isomers ($C_{25}H_{36}O_4$, 400.56 g/mol, 127 mg, 0.317 mmol, 78%, *E/Z* selectivity was not determined) as a colorless oil. R_f 0.85 (cyclohexane–ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (dd, ^3J = 6.8 Hz, 3H, 20-CH_3), 1.02 (d, ^3J = 7.0 Hz, 3H, 16'-CH_3), 1.03 (d, ^3J = 6.0 Hz, 3H, 10'-CH_3), 1.20–1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.74 (ddd, ^3J = 11.5, 3.9, 2.9 Hz, 1H, 9-CH), 1.88 (s, 3H, 12'-CH_3), 2.12–2.25 (m, 1H, 16-CH), 2.52–2.66 (m, 1H, 10-CH), 3.80 (s, 3H, OCH_3), 4.10 (d, ^3J = 9.8 Hz, 1H, 11-CH), 4.16 (d, ^2J = 12.2 Hz, 1H, 8-CH_2), 4.23 (dd, ^2J = 12.2 Hz, ^3J = 3.3 Hz, 1H, 8-CH_2), 5.43 (d, ^3J = 3.8 Hz, 1H, 9'-CH), 5.50 (s, 1H, 4(OCH_3)$_2$PhC<u>H</u>), 5.59 (dd, ^3J = 15.3, 7.8 Hz, 1H, 15-CH), 6.03 (d, ^3J = 10.8 Hz, 1H, 13-CH), 6.23 (dd, ^3J = 15.3, 10.8 Hz, 1H, 14-CH), 6.86–6.92 (m, 2H, aryl-CH), 7.39–7.44 (m, 2H, aryl-CH);.

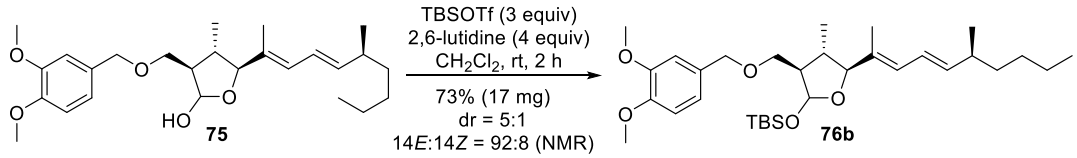


(12*E*,14*E*)-Diene (−)-54b by Julia–Kocienski Olefination. To a solution of the known sulfone (*S*)-**14**[9] ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 717 mg, 2.325 mmol, 2.03 equiv) in THF (20 mL) at –78 °C was added a clear, colorless solution of LiHMDS, prepared from bis(trimethylsilyl)amine (HMDS, $C_6H_{19}NSi_2$, 161.39 g/mol, 0.78 g/mL, 600 µL, 468 mg, 2.900 mmol,2.53 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 1.15 mL, 2.875 mmol, 2.49 equiv) in THF (20 mL) at 0 °C for 30 min. The resulting bright yellow solution was warmed to –50 °C over a period of time of 0.5 h and was then cooled to –80 °C. A precooled –80 °C solution of the enal (−)-**55b** ($C_{19}H_{24}O_6$, 348.39 g/mol, 400 mg, 1.148 mmol, 1 equiv) in THF (20 mL) was added dropwise down along the walls of the flask causing a color change to light yellow. The resulting light yellow solution was allowed to warm to –20 °C over a period of time of 4 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (20 mL) and CH_2Cl_2 (20 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 100:1 to 50:1) to deliver (−)-**54b** as a mixture of 14-C/15-C double bond isomers ($C_{26}H_{38}O_5$, 430.58 g/mol, 340 mg, 0.790 mmol, 69%, 14*E*:14*Z* = 92:8) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-CH at 5.27 ppm [(*Z*)-**54b**] and 5.60 ppm [(*E*)-**54b**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-CH: J = 10.3 Hz for (*Z*)-**54b** and J = 15.2 Hz for (*E*)-**54b**. A diastereomerically enriched sample (14*E*:14*Z* = 96:4) of the major diastereomer was obtained by flash chromatography (cyclohexane–ethyl acetate, 100:1 to 50:1 to 20:1).Analytical data are reported for (12*E*,14*E*)-**54b**: R_f 0.80 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = −19.5 (c = 1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^3J = 6.8 Hz, 3H, 20-CH_3), 1.00 (d, ^3J = 6.8 Hz, 3H, 16'-CH_3), 1.03 (d, ^3J = 6.4 Hz, 3H, 10'-CH_3), 1.18–1.37 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.75 (ddd, ^3J = 11.5, 3.9, 2.9 Hz, 1H, 9-CH), 1.91 (d, ^4J = 1.0 Hz, 3H, 12'-CH_3), 2.18 (ddq, ^3J = 6.8 Hz, 1H, 16-CH), 2.60 (ddq, ^3J = 11.5, 9.8, 6.4 Hz, 1H, 10-CH), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.11 (d, ^3J = 9.8 Hz, 1H, 11-CH), 4.16 (d, ^2J = 12.2 Hz, 1H, 8-CH_2), 4.22 (dd, ^2J = 12.2 Hz, ^3J = 2.9 Hz, 1H, 8-CH_2), 5.43 (d, ^3J = 3.9 Hz, 1H, 9'-CH), 5.50 (s, 1H, 3,4(OCH_3)$_2$PhC<u>H</u>), 5.60 (dd, ^3J = 15.2, 7.8 Hz, 1H, 15-CH), 6.03 (d, ^3J = 10.8 Hz, 1H, 13-CH), 6.22 (app dd, ^3J = 15.2, 10.8 Hz, 1H, 14-CH), 6.84 (d, ^3J = 8.3 Hz, 1H, aryl-CH), 7.02 (app d, ^3J = 8.3 Hz, 1H, aryl-CH), 7.08 (app s, 1H, aryl-CH); ^{13}C NMR (126 MHz, $CDCl_3$)

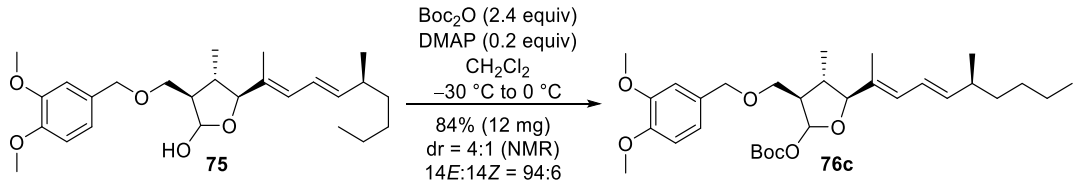
δ 11.63 (12'-CH_3), 14.20 (20-CH_3, 10'-CH_3), 20.61 (16'-CH_3), 22.95; 29.67; 36.86 (17/18/19-CH_2) 34.59 (10-CH), 37.12 (16-CH), 46.83 (9-CH), 55.85 (2xOCH_3), 64.87 (8-CH_2), 71.61 94.94 (11-CH), 98.09 (3,4$(OMe)_2$PhC<u>H</u>), 100.69 (9'-CH), 109.17 (aryl-CH), 110.81 (aryl-CH,) 118.87 (aryl-CH), 124.22 (14-CH), 128.79 (13-CH), 132.25; 133.34 (12-C, aryl-C), 141.85 (15-CH), 149.01 (aryl-C), 149.52 (aryl-C) (unidentified peak at 71.61); IR ν 2955 (s), 2865 (m), 1600 (w), 1515 (m), 1460 (m), 1395 (m), 1325 (m), 1265 (s), 1155 (s), 1105 (s), 1030 (s), 965 (s), 860 (m), 810 (w), 760 (m) cm^{-1}; Anal. Calcd. for $C_{26}H_{38}O_5$: C,72.53; H, 8.9; Found: C, 72.5; H, 8.8.



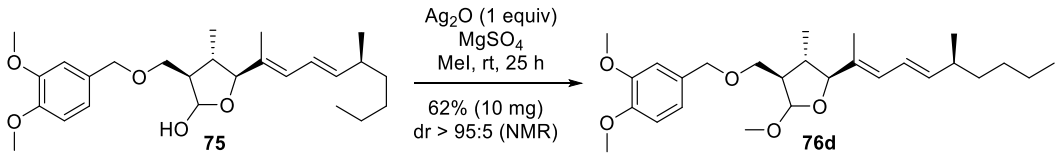
Lactol 75 by Reductive Acetal Opening. To a solution of the diene (−)-**54b** ($C_{26}H_{38}O_5$, 430.58 g/mol, 150 mg, 348.4 µmol, 1 equiv) in CH_3CN (15 mL) were successively added dried 3 Å molecular sieves (200 mg, 0.1 mbar, 200 °C, 1 h) and sodium cyanoborohydride ($NaCNBH_3$, 62.84 g/mol, 26 mg, 413.7 µmol, 1.19 equiv) at –30 °C. *Tert*-butyldiphenysilyl chloride (TPSCl, $C_{16}H_{19}ClSi$, 274.86 g/mol, 1.06 g/mL, 180 µL, 190.8 mg, 694.2 µmol, 1.99 equiv) was added in several portions over a period of time of 1 h. The suspension was kept between –30 °C and –20 °C over a period of time of 5 h. The clear, colorless suspension was diluted by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (10 mL) at –20 °C. The biphasic mixture was warmed to room temperature and stirring was continued for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1 to 2:1) to afford a mixture of anomers and 14-C/15-C double bond isomers of lactol **75** as a colorless viscous oil ($C_{26}H_{40}O_5$, 432.59 g/mol, 130 mg, 300.5 µmol, 86%, dr = 1:1.2, 14*E*:14*Z* = 91:9). The ratio of anomers was determined by integration of the ^{1}H NMR signals for the anomeric protons at 5.36 and 5.44 ppm and the ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.25 ppm [(*Z*)-**75**] and 5.58 ppm [(*E*)-**75**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**75** and J = 15.0 Hz for (*E*)-**75**. The relative configuration was not assigned. Analytical data are reported for (12*E*,14*E*)-**75** as the mixture of anomers: R_f 0.76 (cyclohexane−ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (dd, ^{3}J = 6.8 Hz 6H, 2×20-CH_3), 0.94–1.04 (m, 12H, 2×(10'-CH_3, 16'-CH_3)), 1.18–1.35 (m, 12H, 2×(17-CH_2, 18-CH_2, 19-CH_2)), 1.70 (s, 3H, 12'-CH_3^{major}), 1.77 (s, 3H, 12'-CH_3^{minor}) overlapped by 1.73−1.83 (m, 2H, 2×10-CH), 1.97–2.10 (m, 2H, 2×9-CH), 2.12–2.21 (m, 2H, 2×16-CH), 2.77 (br. s., 1H, OH^{major}) 3.30 (d, ^{3}J = 4.4 Hz 1H, OH^{minor}), 3.43–3.55 (m, 2H, 8-CH_2^{major}), 3.61 (dd, ^{2}J = 9.8 Hz, ^{3}J = 3.9 Hz, 1 H, 8-CH_2^{minor}), 3.68 (dd, ^{2}J = 9.8 Hz, ^{3}J = 6.4 Hz, 1 H, 8-CH_2^{minor}), 3.83–3.94 (m, 12H, 4xOCH_3), 4.16 (d, ^{3}J = 9.3 Hz, 2H, 2×11-CH), 4.43−4.53 (4H, 2×benzylic-CH_2), 5.36 (d, ^{3}J = 2.9 Hz, 1H, 9'-CH^{major}), 5.44 (dd, ^{3}J = 4.4 Hz, 1H, 9'-CH^{minor}), 5.54−5.62 (m, 2H, 2×15-CH), 5.93−6.05 (2H, 2×13-CH), 6.14−6.24 (m, 2H, 2×14-CH), 6.80−6.93 (m, 6H, aryl-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 11.76; 11.89 (2×12'-CH_3) 14.22 (2×20-CH_3) 14.89; 15.74 (2×10'-CH_3), 20.64; 20.72 (2×16'-CH_3), 22.93; 22.96; 29.68; 29.71; 36.86; 36.89 (2×17,18,19-CH_2), 37.16, 37.25 (2×16-CH), 40.01; 40.09 (2×10-CH), 51.56; 55.22 (2×9-CH), 55.93, 56.03 (4×OCH_3), 67.57; 69.73 (2×8-CH_2), 73.03; 73.41 (2×benzylic-CH_2), 90.28; 90.37 (2×11-CH), 98.30; 100.98 (2×9'-CH), 110.93; 110.98 (2×aryl-CH), 120.17 (2×aryl-CH), 124.05; 124.28 (2×14-CH), 128.40; 128.60 (2×13-CH), 130.65; 130.92; 132.25; 133.19 (2×12-C; 2×aryl-C) 141.68; 141.90 (2×15-CH), 148.64; 149.11 (2×aryl-C); Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; Found: C, 72.1; H, 9.3; $[\alpha]_D^{20} = -6.0$ (c, 1, $CHCl_3$)



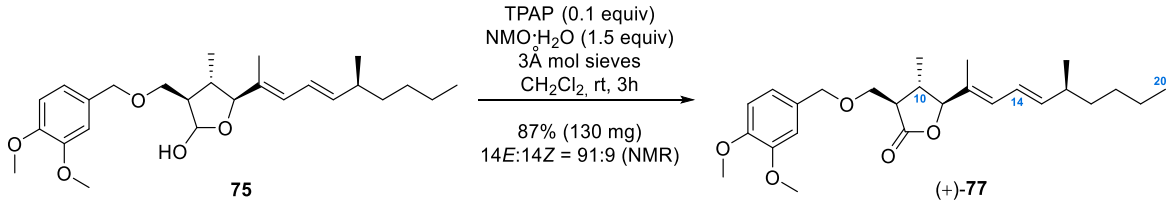
Silyl ether 76b by Silylation. To a solution of **75** ($C_{26}H_{40}O_5$, 432.59 g/mol, 18.5 mg, 42.77 µmol, 1 equiv) in CH_2Cl_2 and 2,6-lutidine (C_7H_9N, 107.16 g/mol, 0.923 g/mL, 20 µL, 18.5 mg, 0.1726 mmol, 4.03 equiv) was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, $C_7H_{15}F_3O_3SSi$, 264.34 g/mol, 1.15 g/mL, 30 µL, 34.5 mg, 0.1305 mmol, 3.05 equiv) at 0 °C. The colorless reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 2 h. The reaction mixture was diluted by the addition of aqueous phosphate pH 7 buffer (5 mL) and the biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford a seperable mixture of anomers of the silyl ether. The major anomer was delivered as a mixture of 14-C/15-C double bond isomers **76b** ($C_{32}H_{54}O_5Si$, 546.86 g/mol, 14 mg, 25.60 µmol, 60%, 14*E*:14*Z* = 92:8) as a colorless oil; the minor anomer of **76b** ($C_{32}H_{54}O_5Si$, 546.86 g/mol, 3 mg, 5.49 µmol, 13%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 4.12 ppm [(*Z*)-**76b**] and 4.09 ppm [(*E*)-**76b**]. Analytical data are reported for the major anomer of (12*E*,14*E*)-**76b**: R_f 0.82 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H) overlapped by 0.86–0.91 (m, 3H) 1.00 (d, ^{3}J = 6.7 Hz, 3H), 1.05 (d, ^{3}J = 6.7 Hz, 3H), 1.20–1.35 (m, 6H), 1.69 (s, 3H) overlapped by 1.65–1.71 (m, 1H), 2.00–2.07 (m, 1H), 2.11–2.22 (m, 1H), 3.37–3.48 (m, 2H), 3.88 (s, 6H), 4.09 (d, ^{3}J = 8.7 Hz, 1H), 4.41–4.51 (m, 2H), 5.31 (d, ^{3}J = 2.4 Hz, 1H), 5.57 (dd, ^{3}J = 15.1, 7.6 Hz, 1H), 5.99 (d, ^{3}J = 10.9 Hz, 1H), 6.20 (dd, ^{3}J = 15.1, 10.9 Hz, 1H), 6.79–6.99 (m, 3H); No further analytical data were obtained.



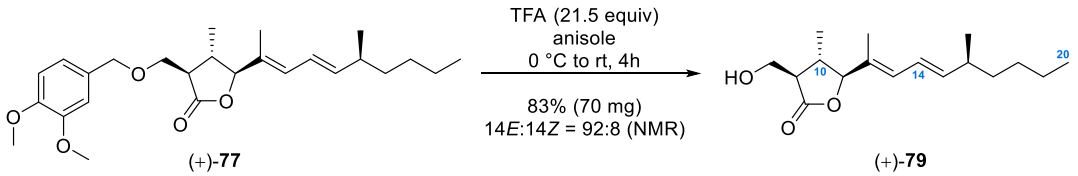
Boc carbonate 76c by Treatment with Boc_2O. To a solution of **75** ($C_{26}H_{40}O_5$, 432.59 g/mol, 12 mg, 27.74 µmol, 1 equiv) in CH_2Cl_2 (5 mL) were subsequently added di-*tert*-butyl dicarbonate (Boc_2O, $C_{10}H_{18}O_5$, 218.25 g/mol, 7 mg, 32.07 µmol, 1.16 equiv) and 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 0.5 mg, 4.09 µmol, 0.15 equiv) at –30 °C. The reaction mixture was allowed to warm to 0 °C and was then diluted by the addition of saturated aqueous $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (5 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford the carbonate **76c** as a seperable mixture of anomers. The major anomer was delivered as a mixture of 14-C/15-C double bond isomers **76c** ($C_{31}H_{48}O_7$, 532.72 g/mol, 10 mg, 18.77 µmol, 68%, 14*E*:14*Z* = 94:6) as a colorless oil; the minor anomer of **76c** ($C_{31}H_{48}O_7$, 532.72 g/mol, 2.3 mg, 4.32 µmol, 16%). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 4.19 ppm [(*Z*)-**76c**] and 4.14 ppm [(*E*)-**76c**]. Analytical data are reported for the major anomer of (12*E*,14*E*)-**76c**: R_f 0.72 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, ^{3}J = 6.7 Hz, 3H), 0.99 (d, ^{3}J = 6.7 Hz, 3H), 1.02 (d, ^{3}J = 6.6 Hz, 3H), 1.20–1.34 (m, 6H), 1.48 (s, 9H), 1.70 (s, 3H), 1.81–1.90 (m, 1H), 2.12–2.20 (m, 1H), 2.22–2.29 (m, 1H), 3.46–3.57 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 4.14 (d, ^{3}J = 9.6 Hz, 1H), 4.44–4.52 (m, 2H), 5.58 (dd, ^{3}J = 15.0, 7.8 Hz, 1H), 6.01 (d, ^{3}J = 10.7 Hz, 1H), 6.05 (d, ^{3}J = 3.0 Hz, 1H), 6.18 (dd, ^{3}J = 15.0, 10.7 Hz, 1H), 6.78–6.95 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.78, 14.23, 15.59, 20.67, 22.99, 28.00, 29.71, 36.88, 37.18, 39.78, 53.50, 56.00, 56.09, 69.38, 73.11, 82.44, 91.80, 103.03, 110.91, 111.06, 120.10, 123.96, 129.00, 130.96, 131.59, 142.15, 148.73, 149.27, 152.83. No further analytical data were obtained.



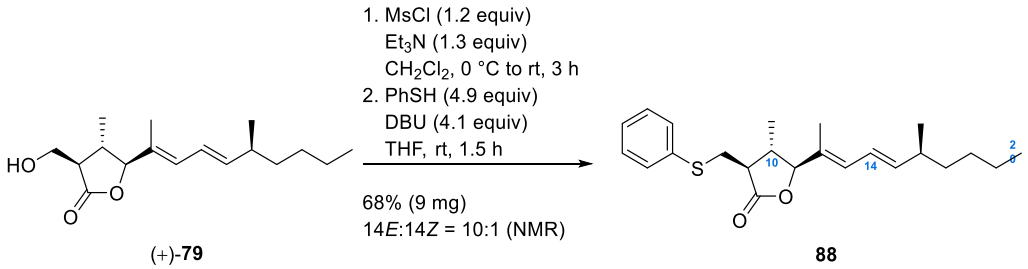
Methyl lactol ether 76d by Methylation. To a solution of **75** ($C_{26}H_{40}O_5$, 432.59 g/mol, 10 mg, 23.12 µmol, 1 equiv) in methyl iodide (1 mL) were subsequently added $MgSO_4$ (about 20 mg) and silver oxide (Ag_2O, 231.75 g/mol, 11 mg, 47.46 µmol, 2.05 equiv) at room temperature. The suspension was stirred at room temperature for 25 h was then filtered through a plug of Celite®. The filter cake was thoroughly washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The oily brownish residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 10:1 to 5:1) to afford the lactol methyl ether **76d** ($C_{27}H_{42}O_5$, 446.63 g/mol, 6.4 mg, 14.33 mmol, 62%, dr>95:5) as a colorless oil. R_f 0.68 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, ^3J = 7.1 Hz, 3H), 0.99 (d, ^3J = 6.5 Hz, 3H) 1.00 (d, ^3J = 6.5 Hz, 3H), 1.16–1.33 (m, 6H), 1.72 (s, 3H) overlapped by 1.64–1.78 (m, 1H), 2.00–2.10 (m, 1H), 2.12–2.23 (m, 1H), 3.36 (s, 3H), 3.42–3.51 (m, 2H), 3.88 (s, 3H), 3.88 (s, 3H), 4.00 (d, ^3J = 9.6 Hz, 1H), 4.41–4.53 (m, 2H), 4.84 (d, ^3J = 2.7 Hz, 1H), 5.58 (dd, ^3J = 15.1, 7.8 Hz, 1H), 6.02 (d, ^3J = 10.3 Hz, 1H), 6.20 (dd, ^3J = 15.1, 10.4 Hz, 1H), 6.80–6.93 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.01, 14.22, 16.15, 20.70, 22.98, 29.71, 36.91, 37.18, 39.97, 54.45, 55.37, 55.99, 56.11, 70.24, 73.01, 89.99, 107.65, 111.07, 111.12, 120.21, 124.08, 128.42, 131.12, 132.45, 141.85, 148.75, 149.24. No further analytical data were obtained



Lactone (+)-77 by Oxidation. To a solution of **75** ($C_{26}H_{40}O_5$, 432.59 g/mol, 150 mg, 346.7 µmol, 1 equiv) in CH_2Cl_2 (10 mL) were added molecular sieves (200 mg, 3Å, powdered and dried: 0.1 mbar, 200 °C, 1 h) and 4-methylmorpholine *N*-oxide monohydrate (NMO•H_2O, $C_5H_{11}NO_2$•H_2O, 135.16 g/mol, 70 mg, 517.9 µmol, 1.49 equiv) at room temperature. The colorless suspension was stirred for 30 minutes at room temperature. Tetra-*n*-propylammonium perruthenate (TPAP, $C_{12}H_{28}NRuO_4$, 351.43 g/mol, 12 mg, 34.15 µmol, 0.1 equiv) was subsequently added at room temperature. The resulting black suspension was stirred at room temperature for 3 h and was then filtered through a plug of Celite®. The filter cake was thoroughly washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The oily dark residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford a mixture of 14-C/15-C double bond isomers of lactone (+)-77 as a colorless oil ($C_{26}H_{38}O_5$, 430.58 g/mol, 130 mg, 301.9 µmol, 14*E*:14*Z* = 91:9, 87%). Analytical data are reported for (12*E*,14*E*)-**77**: R_f 0.55 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +10.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (dd, ^3J = 6.9 Hz, 3H, 20-CH_3), 1.01 (d, ^3J = 6.5 Hz, 3H, 16'-CH_3), 1.11 (d, ^3J = 6.1 Hz, 3H, 10'-CH_3), 1.19–1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.73 (s, 3H, 12'-CH_3), 2.14–2.24 (m, 1H, 16-CH), 2.38–2.53 (m, 2H, 9-CH, 10-CH), 3.72 (dd, ^2J = 9.8 Hz, ^3J = 3.3 Hz, 1H, 8-CH_2), 3.80 (dd, ^2J = 9.8 Hz, ^3J = 4.6 Hz, 1H, 8-CH_2), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.28 (d, ^3J = 9.2 Hz, 1H, 11-CH), 4.44–4.56 (m, 2H, benzylic-CH_2), 5.65 (dd, ^3J = 15.1, 7.8 Hz, 1H, 15-CH), 6.04 (d, J = 10.6 Hz, 1H, 13-CH), 6.19 (dd, J = 15.1, 10.6 Hz, 1H, 14-CH), 6.78–6.92 (m, 3H, aryl-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.58 (12'-CH_3), 14.22 (20-CH_3), 15.73 (10'-CH_3), 20.54 (16'-CH_3), 22.96; 29.70; 36.79 (17,18,19-CH_2), 37.22; 37.23 (10-CH, 16-CH), 49.16 (9-CH), 55.99 (OCH_3), 56.08 (OCH_3), 66.77 (8-CH_2), 73.41 (benzylic-CH_2), 90.65 (11-CH), 110.95; 111.03; 120.06 (aryl-CH), 123.51 (14-CH), 129.76; 130.78 (12-C; aryl-C), 130.13 (13-CH), 143.51 (15-CH), 148.73; 149.20 (aryl-C), 176.47 (9'-C); IR ν 2955 (m), 2930 (m), 2860 (w), 1775 (s), 1715 (m), 1590 (w), 1515 (s),1460 (m), 1420 (m), 1360 (w), 1310 (m), 1265 (s), 1235 (s), 1170 (s), 1155 (s), 1140 (s), 1100 (s), 1030 (s), 1010 (s), 965 (s), 855 (w), 810 (w), 760 (m), 735 (m), 705 (m), 505 (m) cm^{-1}; Anal. Calcd. for $C_{26}H_{38}O_5$: C,72.53; H, 8.90; Found: C, 72.3; H, 8.9.



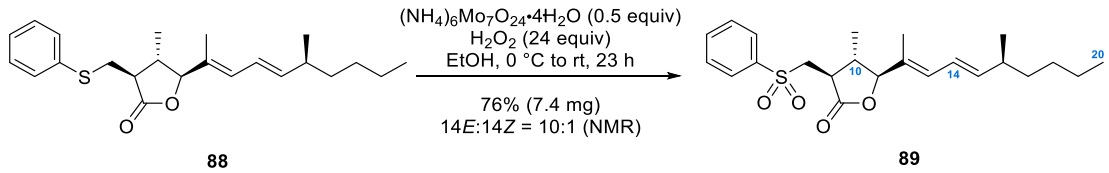
Alcohol (+)-79 by Benzyl Ether Cleavage. To an ice-cooled solution of lactone (+)-77 ($C_{26}H_{38}O_5$, 430.58 g/mol, 130 mg, 301.9 µmol, 1 equiv) in anisole (5 mL, used as purchased) was dropwise added trifluoroacetic acid (TFA, C_2F_3O, 114.02 g/mol, 1.48 g/mL, 500 µL, 740 mg, 6.49 mmol, 21.5 equiv. The clear, colorless solution was allowed to warm to room temperature and was strirred at room temperature for 4 h. The resulting clear, light pink solution was transferred into a round-bottom flask using CH_2Cl_2 (30 mL) for rinsing. The combined organic phases were concentrated under reduced pressure. The light pink residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1 to 2:1 to 1:1) to afford the alcohol as a mixture of 14-C/15-C double bond isomers (+)-**79** ($C_{17}H_{28}O_3$, 280.40 g/mol, 70 mg, 249.6 µmol, 83%, 14*E*:14*Z* = 92:8) as a colorless oil. The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signal of 15-H at 5.35 ppm [(*Z*)-**79**] and 5.68 ppm [(*E*)-**79**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.4 Hz for (*Z*)-**79** and J = 15.1 Hz for (*E*)-**79**. A diastereomerically enriched sample (14*E*:14*Z* = 96:4) of the major diastereomer was obtained by flash chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1 to 2:1).Analytical data are reported for (12*E*,14*E*)-**79**: R_f 0.55 (cyclohexane−ethyl acetate, 1:1); $[\alpha]_D^{20}$ = +20.7 (c = 0.72 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 7.1 Hz, 3H, 20-CH_3), 1.01 (d, ^{3}J = 7.1 Hz, 3H, 16'-CH_3), 1.12 (d, ^{3}J = 6.5 Hz, 3H, 10'-CH_3), 1.18–1.37 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.74 (app s, 3H, 12'-CH_3), 2.13–2.24 (m, 1H, 16-CH), 2.30–2.39 (m, 1H, 10-CH), 2.40–2.48 (m, 1H, 9-CH), 3.79 (dd, ^{2}J = 11.5 Hz, ^{3}J = 5.4 Hz, 1H, 8-CH_2), 4.02 (dd, ^{2}J = 11.5 Hz, ^{3}J = 3.4 Hz, 1H, 8-CH_2), 4.34 (d, ^{3}J = 9.6 Hz, 1H, 11-CH), 5.68 (dd, ^{3}J = 15.1, 7.9 Hz, 1H, 15-CH), 6.07 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.20 (app dd, ^{3}J = 15.1, 10.7 Hz, 1H, 14-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.59 (12'-CH_3), 14.21 (20-CH_3), 15.20 (10'-CH_3), 20.51 (16'-CH_3), 22.96; 29.69, 36.77 (17,18,19-CH_2), 36.34 (10-CH), 37.23 (16-CH), 50.57 (9-CH), 59.92 (8-CH_2), 91.14 (11-CH), 123.43 (14-CH), 129.19 (12-C), 130.59 (13-CH), 143.84 (15-CH), 177.90 (9'-C); IR ν 3450 (m), 2960 (s), 2925 (s), 2865 (m), 1765 (s), 1460 (m), 1320 (m), 1170 (s), 975 (s) cm^{-1}; Anal. Calcd. for $C_{17}H_{28}O_3$: C,72.82; H, 10.6; Found: C, 70.6; H, 9.6; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{17}H_{29}O_3$: 281.21112, Found: 281.21098.



Sulfide 88 by Mesylation and Nucleopulic Substitution. To an ice-cooled solution of the alcohol (+)-**79** ($C_{17}H_{28}O_3$, 280.40 g/mol, 30 mg, 107.0 µmol, 1 equiv) in CH_2Cl_2 (3mL) were subsequently added triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 20 µL, 14.5 mg, 143.3 µmol, 1.34 equiv) and methanesulfonyl chloride (MsCl, CH_3ClO_2S, 114.55 g/mol, 1.48 g/mL, 10 µL, 14.8 mg, 129.2 µmol, 1.21 equiv). The clear, colorless solution was allowed to warm to room temperature and was stirred at room temperature for 3 h. The clear, colorless solution was diluted by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (10 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$). Removal of the solvents under reduced pressure delivered the crude mesylate **86** ($C_{18}H_{30}O_5S$, 358.49 g/mol, 30 mg) [contaminated with CH_2Cl_2]) as a light yellowish oil: R_f 0.49 (cyclohexane−ethyl acetate, 1:1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H), 1.01 (d, ^{3}J = 6.8 Hz, 3H), 1.16 (d, ^{3}J = 6.5 Hz, 3H), 1.21–1.34 (m, 6H), 1.74 (s, 3H), 2.13–2.25 (m, 1H), 2.45 (ddq, ^{3}J = 11.6, 9.8, 6.5 Hz, 1H), 2.58 (ddd, ^{3}J = 11.6, 3.9, 3.4 Hz, 1H), 3.06 (s, 3H), 4.34 (d, ^{3}J = 9.8 Hz, 1H), 4.46 (dd, ^{2}J = 10.8 Hz, ^{3}J = 3.4 Hz, 1H), 4.55 (dd, ^{2}J = 10.8 Hz, ^{3}J =

3.9 Hz, 1H), 5.67 (dd, ^{3}J = 15.0, 7.8 Hz, 1H), 6.07 (d, ^{3}J = 10.8 Hz, 1H), 6.20 (dd, ^{3}J = 15.0, 10.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.46, 14.20, 15.12, 20.57, 22.93, 29.69, 36.40, 36.76, 37.30, 37.36, 48.27, 66.01, 90.91, 123.37, 128.50, 131.14, 144.22, 174.51. No further analytical data were obtained.

To a solution of the crude mesylate **86** ($C_{18}H_{30}O_5S$, 358.49 g/mol, 10 mg, 27.89 µmol, 1 equiv) in THF (2 mL) were added subsequently thiophenol (C_6H_6S, 110.18 g/mol, 1.08 g/mL,14 µL, 15.1 mg, 137 µmol, 4.91 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, $C_9H_{16}N_2$, 152.24 g/mol, 1.02 g/mL, 17 µL, 17.3 mg, 113.6 µmol, 4.07 equiv). The clear, colorless solution was stirred at room temperature for 1.5 h and was then diluted by the addition of saturated aqueous NH_4Cl solution (5 mL) and CH_2Cl_2 (5 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford a mixture of 14-C/15-C double bond isomers of sulfide **88** ($C_{23}H_{32}O_2S$, 372.56 g/mol, 9 mg, 24.16 µmol, 87%, 14*E*:14*Z* = 90:10). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 15-CH at 5.34 ppm [(*Z*)-**88**] and 5.64 ppm [(*E*)-**88**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.3 Hz for (*Z*)-**88** and J = 15.0 Hz for (*E*)-**88**; analytical data are reported for (12*E*,14*E*)-**88**: R_f 0.65 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 1.00 (d, ^{3}J = 6.6 Hz, 3H, 16'-CH_3), 1.12 (d, ^{3}J = 6.6 Hz, 3H, 10'-CH_3), 1.20–1.35 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.73 (s, 3H, 12'-CH_3), 2.15–2.22 (m, 1H, 16-CH), 2.33 (ddq, ^{3}J = 11.1, 9.5, 6.6 Hz, 1H, 10-CH), 2.54 (ddd, ^{3}J = 11.1, 7.2, 4.0 Hz, 1H, 9-CH), 3.14 (dd, ^{2}J = 13.6 Hz, ^{3}J = 7.2 Hz, 1H, 8-CH_2), 3.52 (dd, ^{2}J = 13.6, ^{3}J = 4.0 Hz, 1H, 8-CH_2), 4.24 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 5.64 (dd, ^{3}J = 15.0, 8.1 Hz, 1H, 15-CH), 6.03 (d, ^{3}J = 10.6 Hz, 1H, 13-CH), 6.19 (dd, ^{3}J = 15.0, 10.6 Hz, 1H, 14-CH), 7.19–7.24 (m, 1H, aryl-CH), 7.28–7.33 (m, 2H, aryl-CH), 7.37–7.42 (m, 2H, aryl-CH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 11.48 (12'-CH_3), 14.23 (20-CH_3), 16.05 (10'-CH_3), 20.60 (16'-CH_3), 22.94; 29.71; 36.78 (17,18,19-CH_2), 33.67 (8-CH_2), 37.30 (16-CH), 39.83 (10-CH) 47.84, (9-CH), 90.49 (11-CH), 123.46 (14-CH), 126.74 (aryl-CH), 129.16; 135.71 (12-C, aryl-C), 129.27 (aryl-CH), 129.78 (aryl-CH), 130.58 (13-CH), 143.80 (15-CH), 176.71 (9'-C); HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{23}H_{33}O_2S$: 373.21958, Found: 373.21967; No further analytical data were obtained



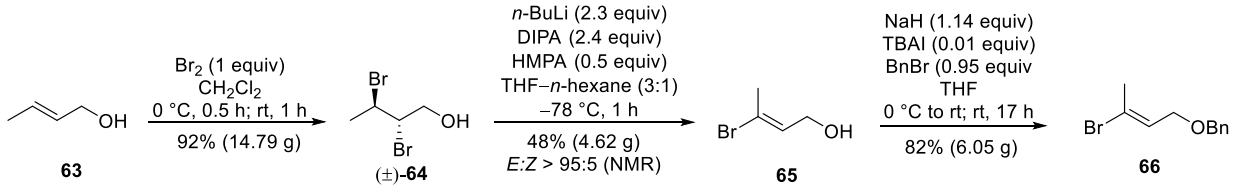
Sulfone 89 by Oxidation. To an ice-cooled solution of the sulfide **88** ($C_{23}H_{32}O_2S$, 372.56 g/mol, 9 mg, 24.16 µmol, 1 equiv) in EtOH (2 mL) was added a yellow solution of ammonium heptamolybdate tetrahydrate ($(NH_4)_6Mo_7O_{24}$•$4H_2O$, 1235.99 g/mol, 15 mg, 12.14 µmol, 0.5 equiv) in hydrogen peroxide (H_2O_2, 30% w/w H_2O_2 in H_2O, 34.02 g/mol, 1.11 g/mL, 60 µL, 20 mg, 0.588 mmol, 24.34 equiv). The cooling bath was removed and the mixture was stirred at room temperature for 23 h. The yellow solution was diluted by the addition of saturated aqueous NaCl solution (1 mL) and CH_2Cl_2 (2 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 0:1 to 0:1 to :1) to afford a mixture of 14-C/15-C double bond isomers of sulfone **89** as a colorless oil ($C_{23}H_{32}O_4S$, 404.56 g/mol, 7.4 mg, 18.29 µmol, 76%, 14*E*:14*Z* = 90:10). The ratio of the 14-C/15-C double bond isomers was determined by integration of the ^{1}H NMR signals of 15-CH at 5.37 ppm [(*Z*)-**89**] and 5.68 ppm [(*E*)-**89**]. The assignment of the 14-C/15-C double bond configuration rests on the evaluation of the NMR coupling constants of 15-H: J = 10.6 Hz for (*Z*)-**89** and J = 15.1 Hz for (*E*)-**89**; analytical data are reported for (12*E*,14*E*)-**89**: R_f 0.46 (cyclohexane−ethyl acetate, 2:1);

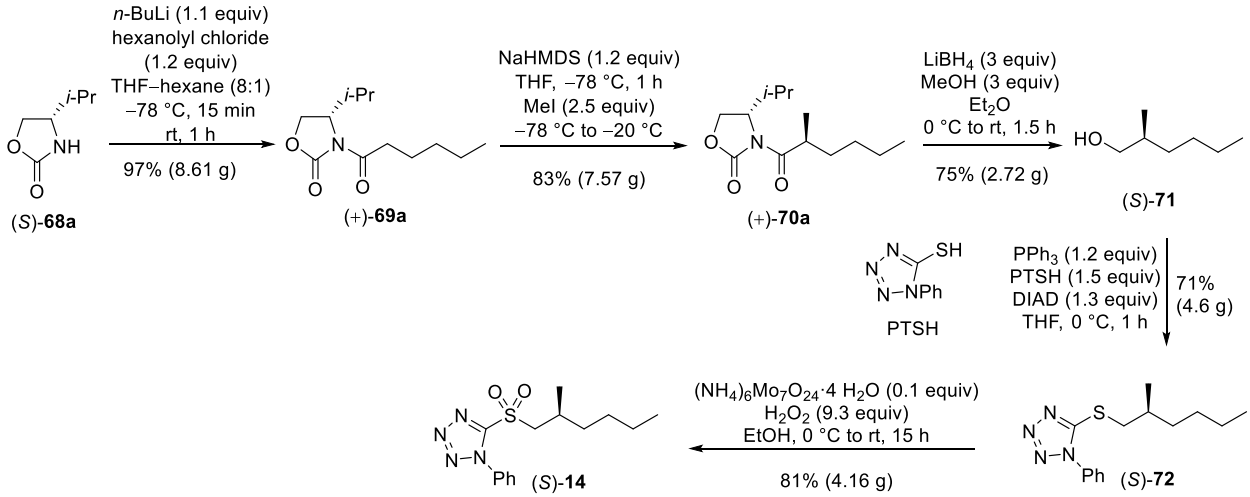
^{1}H NMR (700 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 7.0 Hz, 3H, 20-CH_3), 1.01 (d, ^{3}J = 6.7 Hz, 3H, 16'-CH_3), 1.19–1.36 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2) overlapped by 1.32 (d, ^{3}J = 6.4 Hz, 3H, 10'-CH_3), 1.73 (s, 3H, 12'-CH_3), 2.16–2.23 (m, 1H, 16-CH), 2.41 (ddq, ^{3}J = 11.1, 9.5, 6.4 Hz, 1H, 10-CH), 2.88 (ddd, ^{3}J = 11.1, 8.2, 3.0 Hz, 1H, 9-CH), 3.24 (dd, ^{2}J = 14.4 Hz, ^{3}J = 8.2 Hz, 1H, 8-CH_2), 3.76 (dd, ^{2}J = 14.4 Hz, ^{3}J = 3.0 Hz, 1H, 8-CH_2), 4.36 (d, ^{3}J = 9.5 Hz, 1H, 11-CH), 5.68 (dd, ^{3}J = 15.1, 8.0 Hz, 1H, 15-CH), 6.08 (d, ^{3}J = 10.8 Hz, 1H, 13-CH), 6.20 (dd, ^{3}J = 15.1, 10.8 Hz, 1H, 14-CH), 7.56–7.62 (m, 2H, aryl-CH), 7.66–7.72 (m, 1H, aryl-CH), 7.92–7.99 (m, 2H, aryl-CH); ^{13}C NMR (176 MHz, $CDCl_3$) δ 11.50 (12'-CH_3),14.22 (20-CH_3), 15.70 (10'-CH_3), 20.57 (16'-CH_3), 22.94; 29.71; 36.76 (17,18,19-CH_2), 37.32 (16-CH), 40.66 (10-

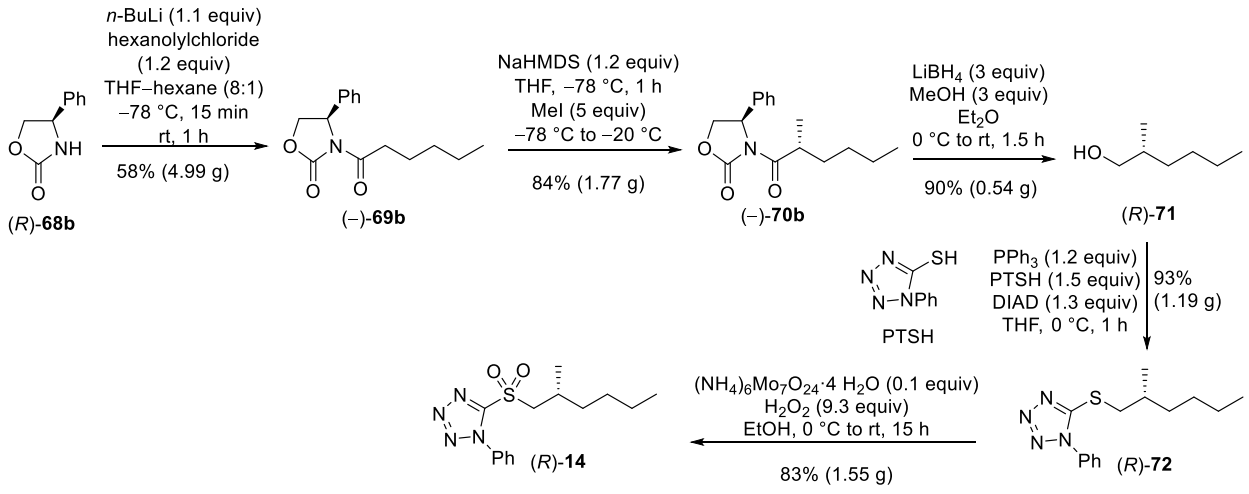
CH), 43.24 (9-CH), 56.61 (8-CH_2), 91.15 (11-CH), 123.37 (14-CH), 128.09 (aryl-CH), 128.41 (12-C), 129.63 (aryl-CH), 131.14 (13-CH), 134.27 (aryl-CH), 139.57 (aryl-C), 144.24 (15-CH), 175.64 (9'-C). HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{23}H_{32}O_4NaS$: 427.19135, Found: 427.19121. No further analytical data were obtained.

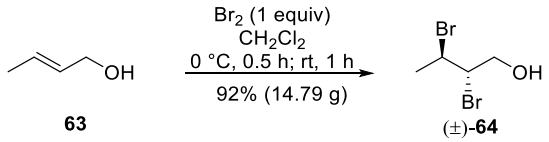
7.10 Synthesis of the Vinyl Bromide 66 and the Eastern fragments (*S*)-14 and (*R*)-14

Synopsis

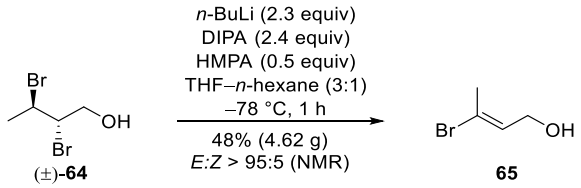




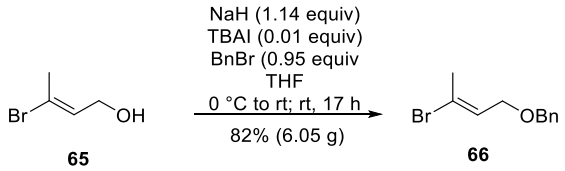




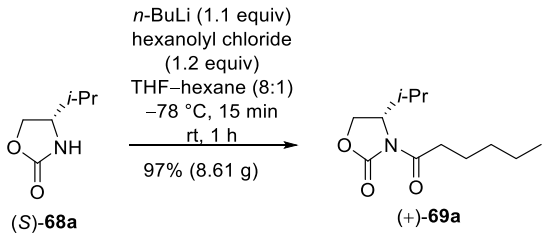
Dibromide (±)-64 by Bromination. To an ice-cooled solution of (*E*)-but-2-en-1-ol (**63**) (C_4H_8O, 72.11 g/mol, 0.85 g/mL, 5.88 mL, 5.0 g, 69.33 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was dropwise added a solution of bromine (Br_2, 159.81 g/mol, 3.12 g/mL,11.11 g, 3.56 mL, 69.52 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) over a period a time of 0.5 h. The clear, orange solution was stirred at room temperature for 1 h then diluted by the addition of saturated aqueous $Na_2S_3O_3$ solution (15 mL). The biphasic mixture was stirred for 15 min at room temperature until the orange color disappeared. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1) to deliver *anti*-2,3- dibromobutan-1-ol (**64**) ($C_4H_8Br_2O$, 231.91 g/mol, 14.79 g, 63.77 mmol,92%) as a colorless oil. R_f 0.28 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.90 (d, ^3J = 6.6 Hz, 3H), 2.06−2.20 (m, 1H), 4.00−4.12 (m, 2H), 4.22−4.26 (m, 1H), 4.37 (dq, ^3J = 9.5, 6.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.68, 47.76, 62.46, 66.23; IR ν 3370 (m), 2930 (m), 1710 (m), 1450 (s), 1380 (s), 1245 (s), 1200 (s), 1155 (m), 1100 (s), 1065 (s), 1010 (s), 935 (m), 840 (m), 670 (m), 545 (ss), 480 (s) cm^{-1}.



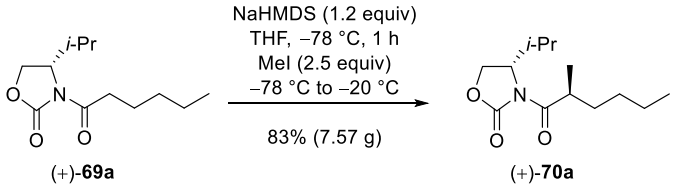
Vinylbromide 65 by Elemination. To a solution of LDA prepared from diisopropylamine ($C_6H_{15}N$, 101.19 g/mol, 0.72 g/mL, 21.52 mL, 15.49 g, 153.08 mmol, 2.4 equiv) and *n*-BuLi (2.5 M in *n*-hexane, 58.7 mL, 146.75 mmol, 2.3 equiv) in THF (128 mL) at –78 °C for 20 min, were added hexamethylphosphoramide (HMPA, $C_6H_{18}N_3OP$, 179.20 g/mol, 1.03 g/mL, 5.55 mL, 5.72 g, 31.92 mmol, 0.5 equiv, used as purchased) at –78 °C. To the resulting yellow solution was dropwise added a solution of *anti*-2,3- dibromobutan-1-ol (**64**) ($C_4H_8Br_2O$, 231.91 g/mol, 14.79 g, 63.77 mmol, 1 equiv) in THF (16 mL) at –78 °C. The orange solution was stirred at –78 °C for 1 h and was then diluted by the addition of H_2O (40 mL) and CH_2Cl_2 (40 mL). The mixture was warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×70 mL). The combined organic phases were washed with a saturated aqueous NaCl solution (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The oily brownish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to deliver (*E*)-3-bromobut-2-en-1-ol (**65**) (C_4H_7BrO, 151.00 g/mol, 4.619 g, 30.59 mmol, 48 %, E/Z >95/5 (NMR)) as a light yellow oil. The configuration of the double bond was later corroborated by X-ray crystallography of compound **50**. R_f 0.38 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (br. s., 1H), 2.30 (d, ^4J = 0.8 Hz, 3H), 4.11 (dd, ^3J = 7.3 Hz, ^4J = 0.8 Hz, 2H), 6.10 (app t, J = 7.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.77, 59.75, 124.39, 130.95; IR ν 3305 (m), 2875 (w), 1740 (w), 1650 (s), 1555 (w), 1430 (m), 1380 (m), 1225 (m), 1165 (m), 1105 (s), 1065 (s), 1000 (s), 925 (w), 835 (w), 635 (m), 500 (m), 410 (m) cm^{-1}.



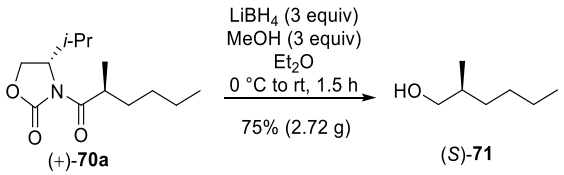
Benzyl Ether 66 by Benzylation. To an ice-cooled solution of (*E*)-3-bromobut-2-en-1-ol (**65**) (C_4H_7BrO, 151.00 g/mol, 4.619 g, 30.59 mmol, 1 equiv) in THF (61 mL) was carefully added natrium hydride (NaH, 60% w/w in mineral oil, 24.00 g/mol, 1.4 g, 35 mmol, 1.14 equiv). To the orange suspension were subsequently added benzyl bromide (C_7H_7Br, 171.04 g/mol, 1.45 g/mL, 3.45 mL, 5.0 g, 29.25 mmol, 0.96 equiv) and tetrabutylammonium iodide (TBAI, $C_{16}H_{36}IN$, 369.37 g/mol, 113 mg, 0.306 mmol, 0.01 equiv) at 0 °C. The orange suspension was stirred at room temperature for 16 h and was then diluted by the addition of H_2O (20 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 50mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 1:0 to 50:1) to deliver the benzyl ether **66** ($C_{11}H_{13}BrO$, 241.13 g/mol, 6.05 g, 25.09 mmol, 82%) as a light yellowish oil. R_f 0.65 (cyclohexane−ethyl acetate, 5:1); ^{1}H NMR (700 MHz, $CDCl_3$) δ 2.26 (d, ^4J = 0.7 Hz, 3H) 3.98 (dd, ^3J = 7.1 Hz, ^4J = 0.7 Hz, 2H), 4.51 (s, 2H), 6.09 (app t, ^3J = 7.1 Hz, 1H) 7.28−7.42 (m, 5H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 23.97, 66.46, 72.28, 124.75, 127.95, 127.97, 128.61, 128.62, 128.82, 138.01; IR ν 3030 (w), 2855 (w), 1650 (m), 1495 (w), 1455 (m), 1430 (m), 1380 (m), 1360 (m), 1240 (w), 1205 (w), 1115 (s), 1090 (s), 1050 (s), 1030 (s), 945 (m), 830 (m), 735 (s), 695 (s), 645 (m), 605 (m), 525 (w), 465 (w), 420 (w) cm^{-1}.



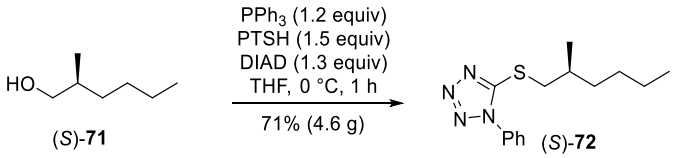
Acylated Oxazolidinone (+)-69a by Acylation.To a solution of (*S*)-**68a** ($C_6H_{11}NO_2$, 129.16 g/mol, 5.02 g, 38.87 mmol, 1 equiv) in THF (116 mL) was dropwise added *n*-BuLi (2.5 M in *n*-hexane, 17.1 mL, 42.75 mmol, 1.1 equiv) at −78 °C. The light yellowish solution was stirred at −78 °C for 15 min. Hexanoyl chloride ($C_6H_{11}ClO$, 134.6 g/mol, 0.963 g/mL, 6.6 mL, 6.356 g, 47.22 mmol, 1.21 equiv, used as purchased) was added at −78 °C and the reaction mixture was stirred −78 °C for further 15 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (50 mL) at 0 °C. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to afford (+)-**69a** ($C_{12}H_{21}NO_3$, 227.3 g/mol, 8.61 g, 37.88 mmol, 97%) as a colorless oil. R_f 0.43 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +70.9 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, ^3J = 7.0 Hz, 3H) overlapped by 0.90 (dd, ^3J = 7.0 Hz, 3H), 0.91 (d, ^3J = 7.0 Hz, 3H), 1.29−1.38 (m, 4H), 1.60−1.71 (m, 2H), 2.37 (sptd, ^3J = 7.0, 3.8 Hz, 1H), 2.85 (ddd, ^2J = 16.5 Hz, ^3J = 8.2, 6.7 Hz, 1H), 2.98 (ddd, ^2J = 16.5 Hz, ^3J = 8.5, 6.4 Hz, 1H), 4.20 (dd, ^2J = 9.2 Hz, ^3J = 3.3 Hz, 1H), 4.26 (dd, ^2J = 9.2 Hz, ^3J = 8.5 Hz, 1H), 4.43 (ddd, ^3J = 8.3, 3.8, 3.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.08, 14.77, 18.13, 22.56, 24.27, 28.49, 31.41, 35.63, 58.50, 63.43, 154.22,173.60; IR ν 2960 (m), 2875 (m), 1780 (s), 1700 (s), 1485 (w), 1465 (w), 1385 (s), 1300 (m), 1250 (m), 1205 (s), 1120 (w), 1090 (m), 1060 (m), 1020 (m), 970 (w), 775 (w) cm^{-1}



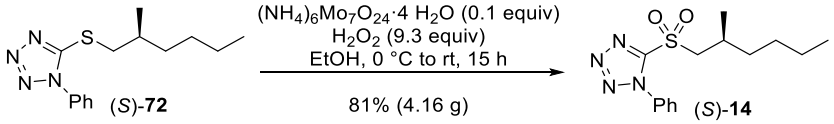
Oxazolidinone (+)-70a by Asymmetric Alkylation. To a solution of (+)-**69a** ($C_{12}H_{21}NO_3$, 227.3 g/mol, 8.61 g, 37.88 mmol, 1 equiv) in THF (76 mL) was dropwise added sodium bis(trimethylsilyl)amide (NaHMDS, $C_6H_{18}NNaSi_2$, 2 M in THF, 22.72 mL, 45.44 mmol, 1.2 equiv) at −78 °C. The clear, colorless solution was stirred at −78 °C for 1 h. Methyl iodide (MeI, CH_3I, 141.94 g/mol, 2.28 g/mL, 5.94 mL, 13.54 g, 95.39 mmol, 2.52 equiv) was slowly added at −78 °C and the reaction mixture was allowed to warm to −20 °C over a period of time of 3 h. The reaction mixture was diluted by the addition of saturated aqueous NH_4Cl solution (30 mL) and CH_2Cl_2 (30 mL) at −20 °C. The biphasic mixture was stirred at room temperature for 15 min; the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 20:1) to afford (+)-**70a** ($C_{13}H_{23}NO_3$, 241.17 g/mol, 7.57 g, 31.39 mmol, 83%) as a coloress oil. R_f 0.40 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +60.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, ^{3}J = 6.8 Hz, 3H), overlapped by 0.88 (dd, ^{3}J = 6.8 Hz, 3H), 0.91 (d, ^{3}J = 6.8 Hz, 3H), 1.20 (d, ^{3}J = 6.9 Hz, 3H), 1.17−1.44 (m, 5H), 1.66−1.79 (m, 1H), 2.35 (sptd, ^{3}J = 7.1, 3.9 Hz, 1H), 3.68−3.78 (m, 1H), 4.19 (dd, ^{2}J = 9.2 Hz, ^{3}J = 3.0 Hz, 1H), 4.26 (dd, ^{2}J = 9.2Hz, ^{3}J = 8.3 Hz, 1H), 4.45 (ddd, ^{3}J = 8.3, 3.9, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.12, 14.83, 18.01, 18.10, 22.88, 28.58, 29.62, 32.97, 37.83, 58.58, 63.33, 153.83, 177.49; IR ν 2960 (m), 2875 (m), 1780 (s), 1700 (s), 1485 (w), 1465 (m), 1385 (s), 1300 (m), 1250 (m), 1205 (s), 1120 (w), 1090 (m), 1060 (m), 1020 (m), 920 (w), 775 (w) cm^{-1}.



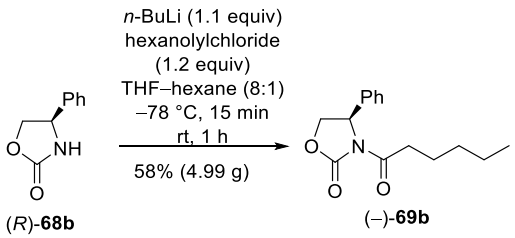
Alcohol (*S*)-71 by Reductive Cleavage. To an ice-cooled solution of (+)-**70a** ($C_{13}H_{23}NO_3$, 241.17 g/mol, 7.57 g, 31.39 mmol, 1 equiv) and methanol (CH_3OH, 32.04 g/mol, 0.792 g/mL, 3.81 mL, 3.02 g, 94.26 mmol, 3 equiv) in Et_2O (313 mL) was added lithium borohydride ($LiBH_4$, 21.78 g/mol, 2.05 g, 94.12 mmol, 3 equiv) in several portions. The cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. The slightly white turbid solution was carefully diluted by the addition of saturated aqueous potassium sodium tartrate solution (160 mL) at 0 °C and subsequently stirred at room temperature for 30 min. The phases were separated and the aqueous layer was extracted with Et_2O (4×100 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 700 mbar, 40 °C). The yellowish residue was purified by Kugelrohr distillation (20 mbar, 100 °C) affording the distillate (–)-(S)-**71** ($C_7H_{16}O$, 116.2 g/mol, 2.72 g, 23.41 mmol, 75%) as a colorless liquid. R_f 0.20 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = –9.1 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 7.0 Hz, 3H) overlapped by 0.91 (d, ^{3}J = 6.7 Hz, 3H), 1.06−1.14 (m, 1H), 1.18−1.44 (m, 6H), 1.56−1.66 (m, 1H), 3.37−3.45 (m, 1H), 3.47−3.55 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.25, 16.72, 23.13, 29.34, 32.97, 35.89, 68.59; IR ν 3335 (m), 2955 (m), 2925 (s), 2875 (m), 2860 (m), 1465 (m), 1380 (w), 1260 (w), 1040 (s), 980 (w), 800 (m) cm^{-1}.



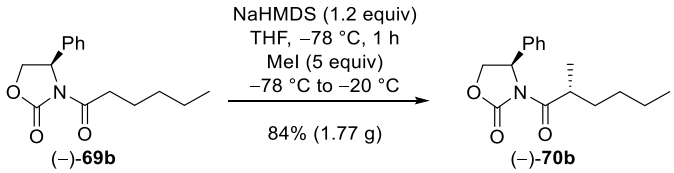
Sulfide (*S*)-72 by Mitsonobu Reaction. To an ice-cooled solution of (*S*)-**71** ($C_7H_{16}O$, 116.2 g/mol, 2.72 g, 23.41 mmol, 1 equiv) in THF (24 mL) were successively added triphenylphosphine (PPh_3, $C_{18}H_{15}P$, 262.28 g/mol, 7.36 g, 28.06 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, $C_7H_6N_4S$, 178.21 g/mol, 6.26 g, 35.13 mmol, 1.5 equiv) and diisopropyl azodicarboxylate (DIAD, $C_8H_{14}N_2O_4$, 202.21 g/mol, 1.027 g/mL, 5.97 mL, 6.13 g, 30.32 mmol, 1.3 equiv). The yellow solution was stirred at room temperature for 1 h and was then diluted by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1) to afford the sulfide (+)-(*S*)-**72** ($C_{14}H_{20}N_4S$, 276.4 g/mol, 4.602 g, 16.65 mmol, 71%) as a colorless viscous oil. R_f 0.75 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +2.6 (c = 1.0 in $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (dd, ^3J = 6.8 Hz, 3H), 1.04 (d, ^3J = 6.8 Hz, 3H), 1.20−1.39 (m, 5H), 1.43−1.53 (m, 1H), 1.87−2.00 (m, 1H), 3.26 (dd, ^2J = 12.7 Hz, ^3J = 7.3 Hz, 1H), 3.47 (dd, ^2J = 12.7 Hz, ^3J = 5.9 Hz, 1H), 7.46−7.75 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.17, 19.27, 22.93, 29.14, 33.08, 35.77, 40.71, 124.05, 129.91, 130.20, 133.95, 154.93; IR ν 2955 (m), 2930 (m), 2860 (m), 1595 (m), 1500 (s), 1460 (m), 1410 (m), 1385 (m), 1280 (w), 1240 (m), 1090 (m), 1075 (m), 1055 (w), 1015 (m), 980 (w), 915 (w), 760 (s), 695 (m), 555 (w) cm^{-1}.



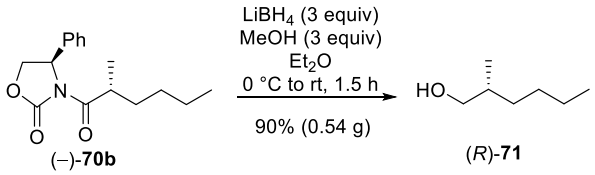
Sulfone (*S*)-14 by Oxidation. To an ice-cooled solution of the sulfide (*S*)-**72** ($C_{14}H_{20}N_4S$, 276.4 g/mol, 4.602 g, 16.65 mmol, 1 equiv) in EtOH (166 mL) was added a yellow solution of ammonium heptamolybdate tetrahydrate ($(NH_4)_6Mo_7O_{24}$•$4H_2O$, 1235.99 g/mol, 209 mg, 0.169 mmol, 0.01 equiv) in hydrogen peroxide (H_2O_2, 30% w/w H_2O_2 in H_2O, 34.02 g/mol, 1.11 g/mL, 15.89 mL, 5.29 g, 155.5 mmol, 9.34 equiv). The cooling bath was removed and the mixture was stirred at room temperature for 18 h. The yellow solution was diluted by the addition of saturated aqueous NaCl solution (80 mL) and CH_2Cl_2 (50 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to afford the sulfone (−)-(*S*)-**14** ($C_{14}H_{20}N_4O_2S$, 308.4 g/mol, 4.16 g, 13.49 mmol, 81%). R_f 0.65 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = –2.2 (C = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (dd, ^3J = 7.1 Hz, 3H), 1.16 (d, ^3J = 6.8 Hz, 3H), 1.23−1.43 (m, 5H), 1.47−1.60 (m, 1H), 2.26−2.44 (m, 1H), 3.59 (dd, ^2J = 14.6 Hz, ^3J = 8.1 Hz, 1H), 3.81 (dd, ^2J = 14.6 Hz, ^3J = 4.9 Hz, 1H), 7.53−7.75 (m, 5H); IR ν 2960 (m), 2930 (m), 2860 (m), 1595 (m), 1500 (m), 1460 (w), 1335 (s), 1265 (w), 1150 (s), 1100 (w), 1075 (m), 1045 (m), 1015 (m), 920 (w), 825 (m), 760 (s), 690 (s), 630 (s), 575 (m), 520 (s) cm^{-1}.



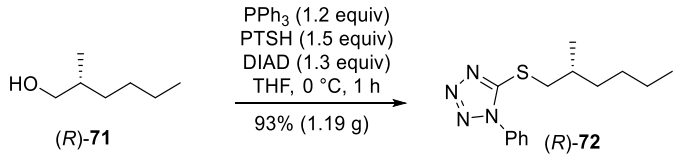
Acylated Oxazolidinone (−)-69b by Acylation To a solution of (*R*)-**68b** ($C_9H_9NO_2$, 163.2 g/mol, 5.37 g, 32.90 mmol, 1 equiv) in THF (100 mL) was dropwise added *n*-BuLi (2.5 M in *n*-hexane, 14.5 mL, 36.25 mmol, 1.1 equiv) at −78 °C. The light yellowish solution was stirred at −78 °C for 15 min. Hexanoyl chloride ($C_6H_{11}ClO$, 134.6 g/mol, 0.963 g/mL, 5.6 mL, 5.393 g, 40.07 mmol, 1.22 equiv, used as purchased) was added at −78 °C and the reaction mixture was stirred −78 °C for further 15 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The clear, colorless solution was diluted by the addition of saturated aqueous NH_4Cl solution (50 mL) at 0 °C. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1 to 5:1) to afford (−)-**69b** ($C_{12}H_{21}NO_3$, 261.3 g/mol, 4.99 g, 19.1 mmol, 58%) as a colorless oil which solified upon storage. R_f 0.65 (cyclohexane–ethyl acetate, 2:1); $[\alpha]_D^{20} = -55.9$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, ^3J = 7.0 Hz, 3H), 1.21−1.35 (m, 4H), 1.63−1.67 (m, 2H), 2.83−3.00 (m, 2H), 4.25 (dd, ^3J = 8.8 Hz, ^2J = 3.5 Hz, 1H), 4.67 (dd, ^3J = 8.8 Hz, 1H), 5.41 (dd, ^3J = 8.8 Hz, ^2J = 3.5 Hz, 1H), 7.21−7.43 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.97, 22.45, 23.89, 31.22, 35.58, 57.62, 70.02, 125.97, 128.73, 129.22, 139.30, 153.82, 172.93.



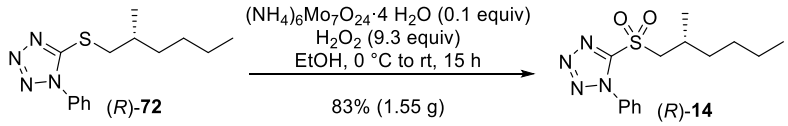
Oxazolidinone (−)-70b by Asymmetric Alkylation. To a solution of (−)-**69b** ($C_{12}H_{21}NO_3$, 261.3 g/mol, 2.00 g, 7.654 mmol, 1 equiv) in THF (16 mL) was dropwise added sodium bis(trimethylsilyl)amide (NaHMDS, $C_6H_{18}NNaSi_2$, 2 M in THF, 4.66 mL, 9.32 mmol, 1.22 equiv) at −78 °C. The clear, colorless solution was stirred at −78 °C for 1 h. Methyl iodide (MeI, CH_3I, 141.94 g/mol, 2.28 g/mL, 2.4 mL, 5.47 g, 38.54 mmol, 5.04 equiv) was slowly added at −78 °C and the reaction mixture was allowed to warm to −20 °C over a period of time of 3 h. The reaction mixture was diluted by the addition of saturated aqueous NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL) at −20 °C. The biphasic mixture was stirred at room temperature for 15 min; the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1) to afford (−)-**70b** ($C_{16}H_{21}NO_3$, 275.3 g/mol, 1.77 g, 6.43 mmol, 84%) as a coloress oil. R_f 0.70 (cyclohexane–ethyl acetate, 2:1); $[\alpha]_D^{20} = -98.5$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, ^3J = 7.0 Hz, 3H), 1.10 (d, ^3J = 6.5 Hz, 3H), 1.21−1.41 (m, 5H), 1.63−1.78 (m, 1H), 3.66−3.80 (m, 1H), 4.25 (dd, ^3J = 8.8 Hz, ^2J = 3.8 Hz, 1H), 4.68 (t, ^3J = 8.3 Hz, 1H), 5.43 (dd, ^3J = 8.8 Hz, ^2J = 3.8 Hz, 1H), 7.23−7.43 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.13, 17.48, 22.88, 29.59, 32.89, 37.90, 57.86, 69.88, 125.83, 128.77, 129.32, 139.44, 153.51, 176.81.



Alcohol (*R*)-71 by Reductive Cleavage. To an ice-cooled solution of (−)-**70b** ($C_{16}H_{21}NO_3$, 275.3 g/mol, 1.43 g, 5.194 mmol, 1 equiv) and methanol (CH_3OH, 32.04 g/mol, 0.792 g/mL, 0.63 mL, 499 mg, 15.57 mmol, 3 equiv) in Et_2O (53 mL) was added lithium borohydride ($LiBH_4$, 21.78 g/mol, 338 mg, 15.52 mmol, 2.99 equiv) in several portions. The cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. The slightly white turbid solution was carefully diluted by the addition of saturated aqueous potassium sodium tartrate solution (30 mL) at 0 °C and subsequently stirred at room temperature for 30 min. The phases were separated and the aqueous layer was extracted with Et_2O (4×50 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 700 mbar, 40 °C). The yellowish residue was purified by Kugelrohr distillation (20 mbar, 100 °C) affording the distillate (+)-(*R*)-**71** ($C_7H_{16}O$, 116.2 g/mol, 0.540 g, 4.647 mmol, 89%) as a colorless liquid. R_f 0.20 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ =+7.9 (c = 1.0 in $CHCl_3$); Further analytical data are identical to (*S*)-**71.**



Sulfide (*R*)-72 by Mitsonobu Reaction. To an ice-cooled solution of (*R*)-**71** ($C_7H_{16}O$, 116.2 g/mol, 0.54 g, 4.647 mmol, 1 equiv) in THF (4 mL) were successively added triphenylphosphine (PPh_3, $C_{18}H_{15}P$, 262.28 g/mol, 1.3 g, 4.957 mmol, 1.06 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, $C_7H_6N_4S$, 178.21 g/mol, 1.1 g, 6.172 mmol, 1.33 equiv) and diisopropyl azodicarboxylate (DIAD, $C_8H_{14}N_2O_4$, 202.21 g/mol, 1.027 g/mL, 1.05 mL, 1.08 g, 5.34 mmol, 1.15 equiv). The yellow solution was stirred at room temperature for 1 h and was then diluted by the addition of saturated aqueous $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1) to afford the sulfide (−)-(*R*)-**72** ($C_{14}H_{20}N_4S$, 276.4 g/mol, 1.192 g, 4.313 mmol, 71%) as a colorless viscous oil. R_f 0.75 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = −3.5 (c = 1.0 in $CHCl_3$); Further analytical data are identical to (*S*)-**72.**

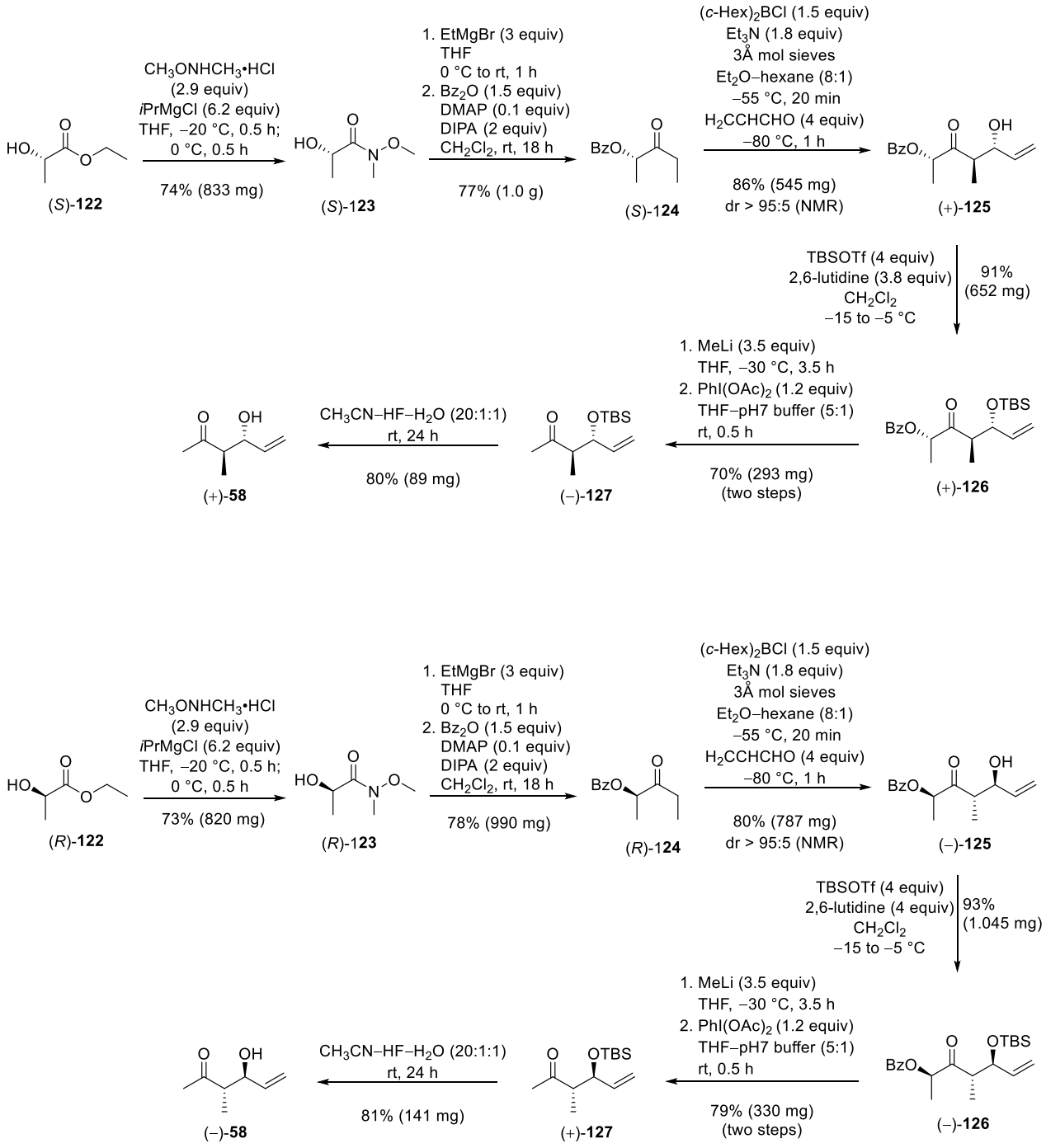


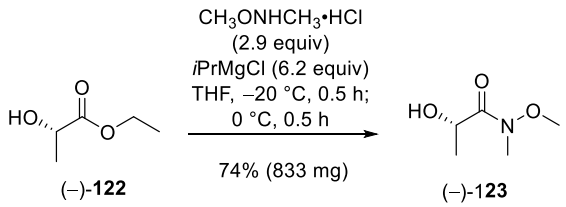
Sulfone (*R*)-14 by Oxidation. To an ice-cooled solution of the sulfide (*R*)-**72** ($C_{14}H_{20}N_4S$, 276.4 g/mol, 1.67 g, 6.042 mmol, 1 equiv) in EtOH (60 mL) was added a yellow solution of ammonium heptamolybdate tetrahydrate ($(NH_4)_6Mo_7O_{24}$•$4H_2O$, 1235.99 g/mol, 740 mg, 0.599 mmol, 0.01 equiv) in hydrogen peroxide (H_2O_2, 30% w/w H_2O_2 in H_2O, 34.02 g/mol, 1.11 g/mL, 6.23 mL, 2.075 g, 60.99 mmol, 10.1 equiv). The cooling bath was removed and the mixture was stirred at room temperature for 18 h. The yellow solution was diluted by the addition of saturated aqueous NaCl solution (20 mL) and CH_2Cl_2 (20 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1) to afford the sulfone (+)-(*R*)-**14** ($C_{14}H_{20}N_4O_2S$, 308.4 g/mol, 1.55 g, 5.026 mmol,

83%). R_f 0.65 (cyclohexane–ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +3.0 (C = 1.0 in $CHCl_3$); Further analytical data are identical to (*S*)-**14.**

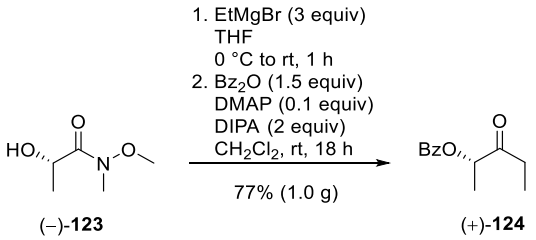
7.11 Snythesis of the Western Fragments (+)-58 and (−)-58

Synopsis

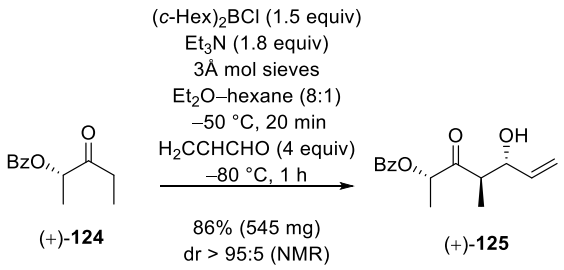




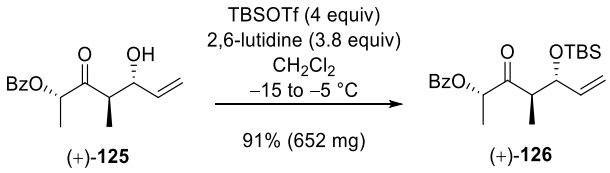
Weinreb amide (−)-**123 by Amidation.** To a solution of (*S*)-ethyl lactate ((−)-**122**) ($C_5H_{10}O_3$, 118.13 g/mol, 1 g, 8.47 mmol, 1 equiv) in THF (25 mL) were subsequently added *N*-methylhydroxylamine hydrochloride ((MeO)MeNH$_2$Cl, CH_5NO•HCl, 83.52 g/mol, 2.05 g, 24.55 mmol, 2.9 equiv) in one portion and isopropylmagnesium chloride (*i*PrMgCl, C_3H_7MgCl, 2.5 M in THF, 21 mL, 52.5 mmol, 6.2 equiv) dropwise over a period of time of 0.5h at –20 °C. The brownish grey suspension was stirred at –20 °C for 30 min and at 0 °C for further 30 min. The brownish grey suspension was carefully diluted by the addition of saturated aqueous NH_4Cl solution (20 mL) and H_2O (10 mL) at 0 °C. The phases were separated and the aqueous layer was extracted with Et_2O (4×40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1 to 2:1) to afford (−)-**123** ($C_5H_{11}NO_3$, 133.14 g/mol, 833 mg, 6.26 mmol, 74%) as a colorless oil. R_f 0.26 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = –47.3 (c = 1.0 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.36 (d, ^3J = 6.8 Hz, 3H), 3.24 (s, 3H), 3.33 (d, ^3J = 7.5 Hz, 1H), 3.72 (s, 3H), 4.48 (dq, ^3J = 7.5, 6.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.19, 32.60, 61.48, 65.15, 175.93.



Ketone (+)-**124 by Nucleophilic Addition and Benzoylation.**To an ice cooled solution of the amide (−)-**123** ($C_5H_{11}NO_3$, 133.14 g/mol, 833 mg, 6.257 mmol, 1 equiv) in THF (25 mL) was dropwise added ethyl magnesium chloride (EtMgBr, C_2H_5MgBr, 3 M in THF, 6.3 mL, 18.9 mmol, 3.02 equiv).The reaction mixture was stirred at room temperature for 1 h and was carefully diluted by the addition of saturated aqueous NH_4Cl solution (mL) and Et_2O (mL). The phases were separated and the aqueous layer was extracted with Et_2O (1×40 mL) and CH_2Cl_2 (2×40 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 300 mbar, 40 °C) to a total volume of about 30 mL. The colorless solution was used without isolation, purification or characterization of the putative ketone. The colorless solution was then transferred into a round-bottom flask using CH_2Cl_2 (10 mL) for rinsing. To the solution were subsequently added benzoic anhydride (Bz_2O, $C_{14}H_{10}O_3$, 226.23 g/mol, 2.12 g, 9.37 mmol, 1.5 equiv), 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 76 mg, 0.622 mmol, 0.1 equiv) and diisopropylamine ($C_6H_{15}N$, 101.19 g/mol, 0.72 g/mL, 2 mL, 1.44 g, 14.231 mmol, 2.27 equiv). The reaction mixture was stirred at room temperature for 16 h and was diluted by the addition of H_2O (10 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford (+)-**124** ($C_{12}H_{14}O_3$, 206.24 g/mol, 1.0 g, 4.849 mmol, 77%) as a colorless oil. R_f 0.70 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +24.9 (c = 1.1 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12 (t, ^3J = 7.2 Hz, 3H), 1.56 (d, ^3J = 7.0 Hz, 3H), 2.56 (dq, ^2J = 18.2 Hz, ^3J = 7.2 Hz, 1H), 2.68 (dq, ^2J = 18.2 Hz, ^3J = 7.2 Hz, 1H), 5.39 (q, ^3J = 7.0 Hz, 1H), 7.47−7.52 (m, 2H), 7.60−7.64 (m, 1H), 8.07−8.14 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 7.38, 16.67, 31.63, 75.29, 128.63, 129.64, 129.95, 133.52, 166.08, 208.70; IR ν 2985 (m), 2940 (m), 1715 (s), 1600 (w), 1450 (m), 1315 (m), 1265 (s), 1175 (m), 1095 (s), 1070 (s), 1025 (m), 975 (m), 800 (w), 710 (s), 690 (m) cm^{-1}

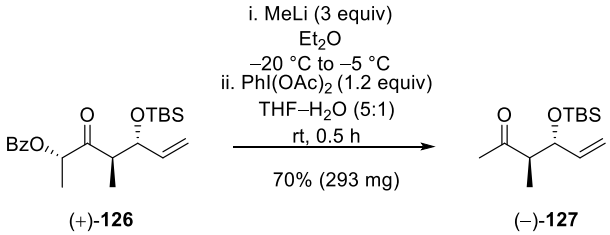


Aldol (+)-125 by Asymmetric Paterson Aldol Reaction. To a solution of the ketone (+)-**124**[196] ($C_{12}H_{14}O_3$, 206.24 g/mol, 500 mg, 2.424 mmol, 1 equiv) in Et_2O (30 mL) were successively added dried 3 Å molecular sieves (200 mg, 0.1 mbar, 200 °C, 1 h), chlorodicyclohexylborane ((*c*-Hex)$_2$BCl, 1 M in hexane, 3.75 mL, 3.75 mmol, 1.55 equiv) and triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 0.63 mL, 457.4 mg, 4.52 mmol, 1.86 equiv) at −50 °C. The clear, colorless suspension was stirred for 20 min at −50 °C and the color of the suspension turned to white. The white, turbid suspension was cooled to −80 °C and freshly distilled acrolein (C_3H_4O, 56.06 g/mol, 0.839 g/mL, 0.670 mL, 562.1 mg, 10.027 mmol, 4.14 equiv) was dropwise added over a period of time of 10 min at −80 °C. The white suspension was stirred at –80 °C for 1 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (10 mL) and CH_2Cl_2 (10 mL). The decolorized mixture was then warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1 to 5:1) to deliver the aldol (+)-**125** ($C_{15}H_{18}O_4$, 262.30 g/mol, 545 mg, 2.078 mmol, 86%) as a white solid. R_f 0.45 (cyclohexane−ethyl acetate, 2:1); m.p. 92–96 °C; $[\alpha]_D^{20}$ = +43.4 (c = 0.75 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, ^3J = 7.3 Hz, 3H), 1.57 (d, ^3J = 7.0 Hz, 3H), 2.37 (d, ^3J = 4.9 Hz, 1H), 2.93 (quin, ^3J = 7.3 Hz, 1H), 4.24−4.30 (m, 1H), 5.21 (app d, ^3J = 10.5 Hz, 1H), 5.31 (app d, ^3J = 17.4 Hz, 1H), 5.44 (q, ^3J = 7.0 Hz, 1H), 5.84 (ddd, ^3J = 17.4, 10.5, 6.6 Hz, 1H), 7.43−7.49 (m, 2H), 7.56−7.62 (m, 1H), 8.06−8.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.55 (CH_3), 15.84 (CH_3), 47.93 (CH), 74.91 (CH), 75.29 (CH), 117.32 (CH_2), 128.61 (CH), 129.61 (C), 129.96 (CH), 133.51 (CH), 138.40 (CH), 165.99 (C), 211.25 (C); IR ν 3325 (w), 2975 (w), 2935 (w), 1720 (s), 1600 (w), 1585 (w), 1450 (m), 1420 (w), 1375 (w), 1350 (w), 1315 (m), 1300 (m), 1265 (s), 1175 (w), 1115 (s), 1065 (m), 1000 (s), 945 (m), 920 (m), 855 (w), 805 (w) 745 (w), 705 (s), 685 (m), 615 (w), 555 (w), 440 (w) cm^{-1}; Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; Found: C, 68.7; H, 7.0.



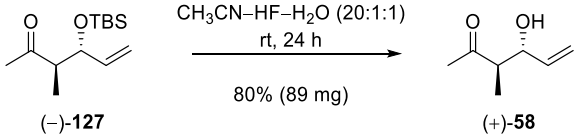
Silyl Ether (+)-126 by Silylation. To a solution of the aldol (+)-**125** ($C_{15}H_{18}O_4$, 262.30 g/mol, 500 mg, 1.906 mmol, 1 equiv) in CH_2Cl_2 (20 mL) and 2,6-lutidine (C_7H_9N, 107.16 g/mol, 0.923 g/mL, 0.84 mL, 775.3 mg, 7.235 mmol, 3.8 equiv) was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, $C_7H_{15}F_3O_3SSi$, 264.34 g/mol, 1.15 g/mL, 1.75 mL, 2.013 g, 7.615 mmol, 4 equiv) at –15 °C. The clear colorless solution was allowed to warm to –5 °C over a period of time of 1 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (10 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light pink biphasic residue was purified by flash chromatography (cyclohexane−ethyl acetate, 100:1 to 50:1 to 20:1 to 10:1) to afford the silyl ether (+)-**126** ($C_{21}H_{32}O_4Si$, 376.56 g/mol, 652 mg, 1.731 mmol, 91%) as a colorless oil. R_f 0.79 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +4.1 (c = 1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 1.05 (d, ^3J = 7.0 Hz, 3H), 1.53 (d, ^3J = 7.0 Hz, 3H), 2.89 (dq, ^3J = 8.5, 7.0 Hz, 1H), 4.29 (t, ^3J = 8.5 Hz, 1H), 5.16 (d, ^3J = 10.1 Hz, 1H), 5.18 (d, ^3J = 17.4 Hz, 1H), 5.42 (q, ^3J = 7.0 Hz, 1H), 5.69 (ddd, ^3J = 17.4, 10.1, 8.5 Hz, 1H), 7.43−7.48 (m, 2H), 7.55−7.61 (m, 1H), 8.05−8.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.73 (CH_3), −4.16 (CH_3), 14.28 (CH_3), 15.35 (CH_3), 18.16 (C), 25.97 (CH_3), 48.80 (CH), 75.35 (CH), 76.75 (CH), 117.21

(CH_2), 128.54 (CH), 129.80 (C), 129.95 (CH), 133.37 (CH), 139.34 (CH), 165.89 (C), 209.27 (C); IR ν 2955 (m), 2930 (m), 2855 (m), 1720 (s), 1605 (w), 1460 (m), 1360 (w), 1315 (w), 1300 (w), 1250 (s), 1175 (w), 1115 (m), 1070 (s), 1005 (s), 925 (w), 835 (s), 775 (s), 710 (s), 675 (m), 575 (w) cm^{-1}; Anal. Calcd. for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57; Found: C, 67.1; H, 8.6.



(+)-**126** (–)-**127**

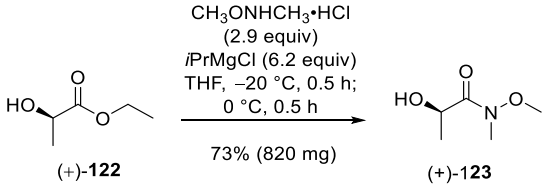
Methyl Ketone (–)-127 by Chain Degradation. To a solution of the silyl ether (+)-**126** ($C_{21}H_{32}O_4Si$, 376.56 g/mol, 650 mg, 1.726 mmol, 1 equiv) in Et_2O (35 mL) was dropwise added methyl lithium (CH_3Li, 1.6 M in Et_2O, 3.2 mL, 5.12 mmol, 2.97 equiv) at –20 °C. The clear colorless solution was allowed to warm to –5 °C over a period of time of 1.5 h and was then carefully diluted by the addition of aqueous phosphate pH 7 buffer (10 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with Et_2O (3×30 mL) and CH_2Cl_2 (1×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to a total volume of about 20 mL. The solution was used without isolation, purification or characterization of the putative diastereomeric diols. TLC of the solution showed two spots at R_f 0.26 and 0.36 (cyclohexane−ethyl acetate, 5:1). The clear and colorless solution was then transferred into a round-bottom flask using THF (20 mL) for rinsing. H_2O (4 mL) and iodobenzene diacetate ($PhI(OAc)_2$, $C_{10}H_{11}IO_4$, 322.10 g/mol, 667 mg, 2.071 mmol, 1.2 equiv) were subsequently added at room temperature. The clear colorless reaction mixture was stirred for 0.5 h at room temperature and was then diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution (10 mL) and CH_2Cl_2 (20 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (*n*-pentane−Et_2O, 50:1 to 20:1) to deliver the ketone (–)-**127** ($C_{13}H_{26}O_2Si$, 242.43 g/mol, 293 mg, 1.209 mmol, 70%) a colorless oil. R_f 0.67 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = –14.3 (c = 0.78 in $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 0.94 (d, J = 7.1 Hz, 3H), 2.18 (s, 3H), 2.65 (dq, ^3J = 8.0, 7.1 Hz, 1H), 4.18 (dd, ^3J = 8.0, 7.7 Hz, 1H), 5.13 (app d, ^3J = 10.3 Hz, 1H), 5.16 (app d, ^3J = 17.2 Hz, 1H), 5.68 (ddd, ^3J = 17.2, 10.3, 7.7 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −4.99 (CH_3), −3.98 (CH_3), 13.15 (CH_3), 18.19 (C), 25.92 (CH_3), 31.16 (CH_3), 52.91 (CH), 77.20 (CH), 116.69 (CH_2), 139.29 (CH), 212.09 (C); IR ν 2955 (w), 2930 (w), 2860 (w), 1720 (m), 1460 (w), 1420 (w), 1360 (w), 1255 (m), 1175 (w), 1070 (m), 1005 (w), 995 (w), 925 (w), 885 (w), 835 (s), 775 (s), 675 (w), 600 (w) cm^{-1}; Anal. Calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81; Found: C, 64.4; H, 10.6.



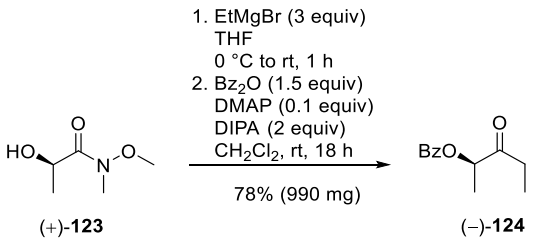
(–)-**127** (+)-**58**

Allylic Alcohol (+)-58 by TBS Ether Cleavage. A sealable polypropylene reaction vessel was charged with a solution of (−)-**127** ($C_{13}H_{26}O_2Si$, 242.43 g/mol, 210 mg, 0.8662 mmol, 1 equiv) in CH_3CN (10 mL). Hydrofluoric acid (48−51% w/w HF in H_2O, 1 mL) was added at room temperature and the reaction vessel was sealed with a polypropylene screw cap. The clear, colorless solution was stirred at room temperature overnight and was then cooled to 0 °C. The reaction mixture was diluted by the addition of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ solution (around 10 mL) until no further evolution of gas was observed. The phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 150 mbar, 40 °C). The oily yellowish residue was purified by flash chromatography (*n*-pentane−Et_2O, 10:1 to

5:1 to 2:1) to deliver the allylic alcohol (+)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 89 mg, 0.6944 mmol, 80%) as a colorless oil. R_f 0.28 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +31.3 (c = 0.26 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (d, ^3J = 7.2 Hz, 3H), 2.21 (s, 3H), 2.50−2.54 (m, 1H), 2.67 (dq, ^3J = 7.6, 7.2 Hz, 1H), 4.17−4.22 (m, 1H), 5.20 (app d, ^3J = 10.4 Hz, 1H), 5.29 (app d, ^3J = 17.1 Hz, 1H), 5.83 (ddd, ^3J = 17.1, 10.4, 7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 13.86 (CH_3), 30.10 (CH_3), 51.93 (CH), 75.29 (CH), 117.10 (CH_2), 138.43 (CH) 213.22 (C); IR 3430 (m), 2980 (w), 2935 (w), 1705 (s), 1460 (w), 1425 (m),1360 (m), 1240 (w), 1175 (w), 1090 (w), 1045 (m), 995 (m), 930 (m) cm^{-1}; Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44; Found: C, 64.6; H, 10.5; no further analytical data were obtained.

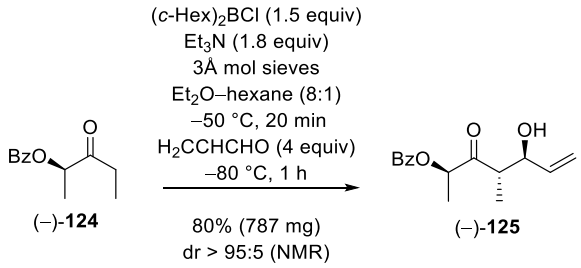


Weinreb amide (+)-**123 by Amidation.** To a solution of (*R*)-ethyl lactate ((+)-**122**) ($C_5H_{10}O_3$, 118.13 g/mol, 1 g, 8.47 mmol, 1 equiv) in THF (25 mL) were subsequently added *N*-methylhydroxylamine hydrochloride ((MeO)MeNH$_2$Cl, CH_5NO•HCl, 83.52 g/mol, 2.05 g, 24.55 mmol, 2.9 equiv) in one portion and isopropylmagnesium chloride (*i*PrMgCl, C_3H_7MgCl, 2.5 M in THF, 21 mL, 52.5 mmol, 6.2 equiv) dropwise over a period of time of 0.5h at –20 °C. The brownish grey suspension was stirred at –20 °C for 30 min and at 0 °C for further 30 min. The brownish grey suspension was carefully diluted by the addition of saturated aqueous NH_4Cl solution (20 mL) and H_2O (10 mL) at 0 °C. The phases were separated and the aqueous layer was extracted with Et_2O (4×40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellowish residue was purified by chromatography (cyclohexane−ethyl acetate, 10:1 to 5:1 to 2:1) to afford (+)-**123** ($C_5H_{11}NO_3$, 133.14 g/mol, 820 mg, 6.16 mmol, 73%) as a colorless oil. R_f 0.26 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = +45.7 (c = 1.0 in $CHCl_3$); Further analytical data are identical to (−)-**123.**

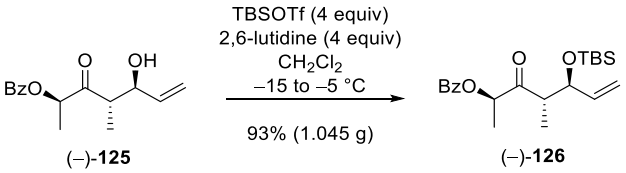


Ketone (−)-**124 by Nucleophilic Addition and Benzoylation.**To an ice cooled solution of the amide (+)-**123** ($C_5H_{11}NO_3$, 133.14 g/mol, 820 mg, 6.16 mmol, 1 equiv) in THF (25 mL) was dropwise added ethyl magnesium chloride (EtMgBr, C_2H_5MgBr, 3 M in THF, 6.3 mL, 18.9 mmol, 3.07 equiv).The reaction mixture was stirred at room temperature for 1 h and was carefully diluted by the addition of saturated aqueous NH_4Cl solution (mL) and Et_2O (mL). The phases were separated and the aqueous layer was extracted with Et_2O (1×40 mL) and CH_2Cl_2 (2×40 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 300 mbar, 40 °C) to a total volume of about 30 mL. The colorless solution was used without isolation, purification or characterization of the putative ketone. The colorless solution was then transferred into a round-bottom flask using CH_2Cl_2 (10 mL) for rinsing. To the solution were subsequently added benzoic anhydride (Bz_2O, $C_{14}H_{10}O_3$, 226.23 g/mol, 2.12 g, 9.37 mmol, 1.52 equiv), 4-dimethylaminopyridine (DMAP, $C_7H_{10}N_2$, 122.17 g/mol, 76 mg, 0.622 mmol, 0.1 equiv) and diisopropylamine ($C_6H_{15}N$, 101.19 g/mol, 0.72 g/mL, 2 mL, 1.44 g, 14.231 mmol, 2.31 equiv). The reaction mixture was stirred at room temperature for 16 h and was diluted by the addition of H_2O (10 mL) and CH_2Cl_2 (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless residue was purified by chromatography (cyclohexane−ethyl acetate, 50:1 to 20:1 to 10:1) to afford (−)-**124** ($C_{12}H_{14}O_3$, 206.24 g/mol, 990 mg, 4.80 mmol, 78%) as a

colorless oil. R_f 0.70 (cyclohexane–ethyl acetate, 2:1); $[\alpha]_D^{20}$ = −22.3 (c = 1.1 in $CHCl_3$); Further analytical data are identical to (+)-**124.**

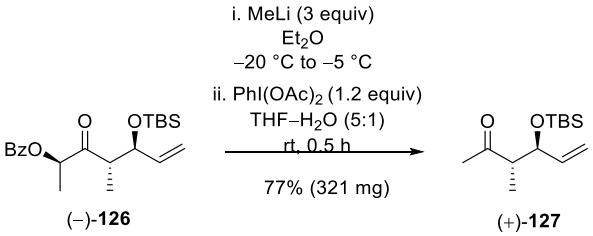


Aldol (−)-125 by Asymmetric Paterson Aldol Reaction. The reaction was carried out in two parallel batches. To each of the two solutions of the ketone (−)-**124** ($C_{12}H_{14}O_3$, 206.24 g/mol, 778 mg overall [393 mg and 385 mg], 3.772 mmol, 1 equiv) in Et_2O (32 mL [2×16 mL]) were successively added dried 3 Å molecular sieves (200 mg [2×100 mg], 0.1 mbar, 200 °C, 1 h), chlorodicyclohexylborane ((*c*-Hex)$_2$BCl, 1 M in hexane, 5.79 mL [2.94 mL and 2.85 mL], 5.79 mmol, 1.53 equiv) and triethylamine ($C_6H_{15}N$, 101.19 g/mol, 0.726 g/mL, 0.97 mL [0.49 mL and 0.48 mL], 704.2 mg, 6.959 mmol, 1.84 equiv) at −50 °C. The clear, colorless suspensions were stirred for 20 min at −50 °C and the color of the suspensions turned to white. The white, turbid suspensions were cooled to −80 °C and to each of the two solutions freshly distilled acrolein (C_3H_4O, 56.06 g/mol, 0.839 g/mL, 1.05 mL [0.53 mL and 0.52 mL], 881 mg, 15.715 mmol, 4.17 equiv) was dropwise added over a period of time of 10 min at −80 °C. The white suspensions were stirred at –80 °C for 1 h and were then diluted by the addition of aqueous phosphate pH 7 buffer (20 mL [2×10 mL]) and CH_2Cl_2 (20 mL [2×10 mL]). The decolorized mixture was then warmed to room temperature and transferred into a single separatory funnel using CH_2Cl_2 (10 mL) for rinsing. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily yellowish residue was purified by flash chromatography (cyclohexane–ethyl acetate, 50:1 to 20:1 to 10:1 to 5:1) to deliver the aldol (−)-**125** ($C_{15}H_{18}O_4$, 262.30 g/mol, 787 mg, 3.000 mmol, 80%) as a white solid. Spectroscopic and analytical data of (−)-**125** were found to be identical to those reported for the enantiomer (+)-**125** within the limits of precision. Crystallization of (−)-**125** was accomplished in hot cyclohexane (50 mL, 60 °C) by slow cooling to room temperature under air to provide colorless needles. R_f 0.45 (cyclohexane–ethyl acetate, 2:1); m.p. 92–96 °C; $[\alpha]_D^{20}$ = −39.7 (c = 0.6 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, ^3J = 7.3 Hz, 3H), 1.57 (d, ^3J = 7.0 Hz, 3H), 2.36 (d, ^3J = 5.4 Hz, 1H), 2.93 (quin, ^3J = 7.3 Hz, 1H), 4.24–4.30 (m, 1H), 5.21 (app d, ^3J = 10.3 Hz, 1H), 5.31 (app d, ^3J = 17.1 Hz, 1H), 5.44 (q, ^3J = 7.0 Hz, 1H), 5.84 (ddd, ^3J = 17.1, 10.3, 6.8 Hz, 1H), 7.43–7.49 (m, 2H), 7.56–7.62 (m, 1H), 8.06–8.11 (m, 2H); ^{13}C NMR (151 MHz $CDCl_3$) δ 14.55 (CH_3), 15.84 (CH_3), 47.93 (CH), 74.91 (CH), 75.29 (CH), 117.32 (CH_2), 128.61 (CH), 129.61 (C), 129.96 (CH), 133.51 (CH), 138.40 (CH), 165.99 (C), 211.25 (C); IR ν 3330 (w), 2980 (w), 2935 (w), 1720 (s), 1605 (w), 1450 (m), 1380 (m), 1350 (m), 1315 (m), 1300 (m), 1265 (s), 1175 (w), 1115 (s), 1065 (m), 1015 (m), 1000 (s), 950 (m), 920 (m), 745 (w), 710 (s), 685 (w) cm^{-1}; Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; Found: C, 68.7; H, 7.0.

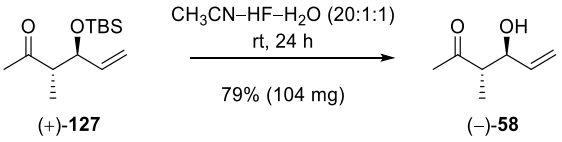


Silyl Ether (−)-126 by Silylation. To a solution of the aldol (−)-**125** ($C_{15}H_{18}O_4$, 262.30 g/mol, 787 mg, 3.000 mmol, 1 equiv) in CH_2Cl_2 (55 mL) and 2,6-lutidine (C_7H_9N, 107.16 g/mol, 0.923 g/mL, 1.39 mL, 1.283 g, 11.973 mmol, 3.99 equiv) was dropwise added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, $C_7H_{15}F_3O_3SSi$, 264.34 g/mol, 1.15 g/mL, 2.75 mL, 3.163 g, 11.966 mmol, 3.99 equiv) at –15 °C. The clear colorless solution was allowed to warm to –5 °C over a period of time of 1 h and was then diluted by the addition of aqueous phosphate pH 7 buffer (15 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The light pink biphasic residue was purified by flash chromatography (cyclohexane–ethyl acetate, 100:1 to

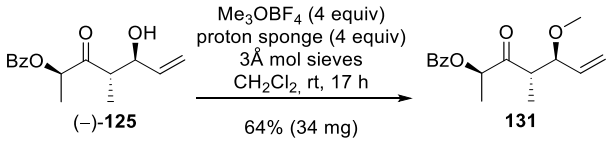
50:1 to 20:1 to 10:1) to afford the silyl ether (−)-**126** ($C_{21}H_{32}O_4Si$, 376.56 g/mol, 1.045 g, 2.775 mmol, 93%) as a colorless oil. Spectroscopic and analytical data of (−)-**126** were found to be identical to those reported for the enantiomer (+)-**126** within the limits of precision. R_f 0.79 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20}$ = −4.1 (c = 1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 1.05 (d, ^3J = 7.0 Hz, 3H), 1.53 (d, ^3J = 7.1 Hz, 3H), 2.89 (dq, ^3J = 8.5, 7.1 Hz, 1H), 4.29 (dd, ^3J = 8.5, 7.9 Hz, 1H), 5.16 (d, ^3J = 10.1 Hz, 1H), 5.18 (d, ^3J = 17.7 Hz, 1H), 5.42 (q, ^3J = 7.0 Hz, 1H), 5.69 (ddd, ^3J = 17.7, 10.1, 7.9 Hz, 1H), 7.43−7.48 (m, 2H), 7.55−7.61 (m, 1H), 8.05−8.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.73 (CH_3), −4.16 (CH_3), 14.28 (CH_3), 15.34 (CH_3), 18.16 (C), 25.97 (CH_3), 48.80 (CH), 75.35 (CH), 76.75 (CH), 117.20 (CH_2), 128.54 (CH), 129.80 (C), 129.95 (CH), 133.37 (CH), 139.34 (CH), 165.89 (C), 209.26 (C); IR ν 2930 (m), 2855 (m), 1720 (s), 1605 (w), 1450 (m), 1360 (w), 1315 (w), 1300 (w), 1265 (s), 1175 (w), 1115 (m), 1030 (m), 1005 (s), 950 (w), 925 (w), 880 (w), 835 (s), 775 (s), 710 (s), 685 (m) cm^{-1}; Anal. Calcd. for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57; Found: C, 66.8; H, 8.8.



Methyl Ketone (+)- by Chain Degradation. To a solution of the silyl ether (+)-**126** ($C_{21}H_{32}O_4Si$, 376.56 g/mol, 650 mg, 1.726 mmol, 1 equiv) in Et_2O (35 mL) was dropwise added methyl lithium (CH_3Li, 1.6 M in Et_2O, 3.24 mL, 5.184 mmol, 3 equiv) at –20 °C. The clear colorless solution was allowed to warm to –5 °C over a period of time of 1.5 h and was then carefully diluted by the addition of aqueous phosphate pH 7 buffer (10 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with Et_2O (3×30 mL) and CH_2Cl_2 (1×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to a total volume of about 20 mL. The solution was used without isolation, purification or characterization of the putative diastereomeric diols. TLC of the solution showed two spots at R_f 0.26 and 0.36 (cyclohexane−ethyl acetate, 5:1). The clear and colorless solution was then transferred into a round-bottom flask using THF (20 mL) for rinsing. H_2O (4 mL) and iodobenzene diacetate ($PhI(OAc)_2$, $C_{10}H_{11}IO_4$, 322.10 g/mol, 670 mg, 2.080 mmol, 1.21 equiv) were subsequently added at room temperature. The clear colorless reaction mixture was stirred for 0.5 h at room temperature and was then diluted by the addition of saturated aqueous $Na_2S_2O_3$ solution (10 mL) and CH_2Cl_2 (20 mL). The biphasic mixture was stirred for 15 min at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The yellow oily residue was purified by flash chromatography (*n*-pentane−Et_2O, 50:1 to 20:1) to deliver the ketone (+)-**127** ($C_{13}H_{26}O_2Si$, 242.43 g/mol, 320 mg, 1.32 mmol, 76%) a colorless oil. Spectroscopic and analytical data of (+)-**127** were found to be identical to those reported for the enantiomer (−)-**127** within the limits of precision. R_f 0.67 (cyclohexane−ethyl acetate, 5:1); $[\alpha]_D^{20}$ = +17.6 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 0.94 (d, J = 7.0 Hz, 3H), 2.19 (s, 3H), 2.66 (dq, ^3J = 8.1, 7.0 Hz, 1H), 4.18 (dd, ^3J = 8.1, 7.3 Hz, 1H), 5.14 (app d, ^3J = 10.3 Hz, 1H), 5.17 (app d, ^3J = 17.3 Hz, 1H), 5.69 (ddd, ^3J = 17.3, 10.3, 7.3 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.01, −3.98, 13.18, 18.19, 25.91, 31.23, 52.87, 77.23, 116.73, 139.27, 212.23; IR ν 2955 (w), 2930 (w), 2860 (w), 1720 (m), 1460 (w), 1420 (w), 1355 (w), 1250 (m), 1175 (w), 1065 (m), 1005 (w), 995 (w), 925 (w), 885 (w), 835 (s), 775 (s), 675 (w), 655 (w), 600 (w), 440 (w) cm^{-1}; HRMS (ESI): m/z $[M + H]^+$ Calcd. for $C_{13}H_{27}O_2Si$: 243.17748; Found: 243.17761.

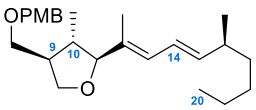
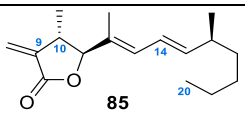
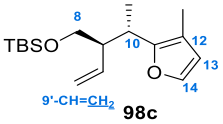
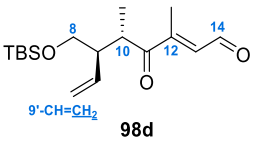
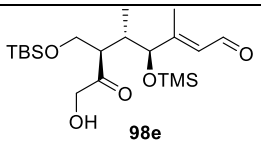


Allylic Alcohol (−)-58 by TBS Ether Cleavage. A sealable polypropylene reaction vessel was charged with a solution of (+)-**127** ($C_{13}H_{26}O_2Si$, 242.43 g/mol, 250 mg, 1.0312 mmol, 1 equiv) in CH_3CN (12 mL). Hydrofluoric acid (48−51% w/w HF in H_2O, 1.2 mL) was added at room temperature and the reaction vessel was sealed with a polypropylene screw cap. The clear, colorless solution was stirred at room temperature overnight and was then cooled to 0 °C. The reaction mixture was diluted by the addition of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ solution (around 10 mL) until no further evolution of gas was observed. The phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated under reduced pressure (should not fall below 150 mbar, 40 °C). The oily yellowish residue was purified by flash chromatography (*n*-pentane−Et_2O, 10:1 to 5:1 to 2:1) to deliver the allylic alcohol (−)-**58** ($C_7H_{12}O_2$, 128.17 g/mol, 104 mg, 0.8114 mmol, 79%) as a colorless oil. Spectroscopic and analytical data of (−)-**58** were found to be identical to those reported for the enantiomer (+)-**58** within the limits of precision. R_f 0.28 (cyclohexane−ethyl acetate, 2:1); $[\alpha]_D^{20} = -20.9$ (c = 0.54 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, ^3J = 7.3 Hz, 3H), 2.21 (s, 3H), 2.56 (d, ^3J = 5.2 Hz, 1H), 2.67 (dq, ^3J = 7.6, 7.3 Hz, 1H), 4.15−4.25 (m, 1H), 5.20 (app d, ^3J = 10.4 Hz, 1H), 5.29 (app d, ^3J = 17.1 Hz, 1H), 5.83 (ddd, ^3J = 17.1, 10.4, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.87 (CH_3), 30.12 (CH_3), 51.89 (CH), 75.28 (CH), 117.13 (CH_2), 138.39 (CH) 213.31 (C).



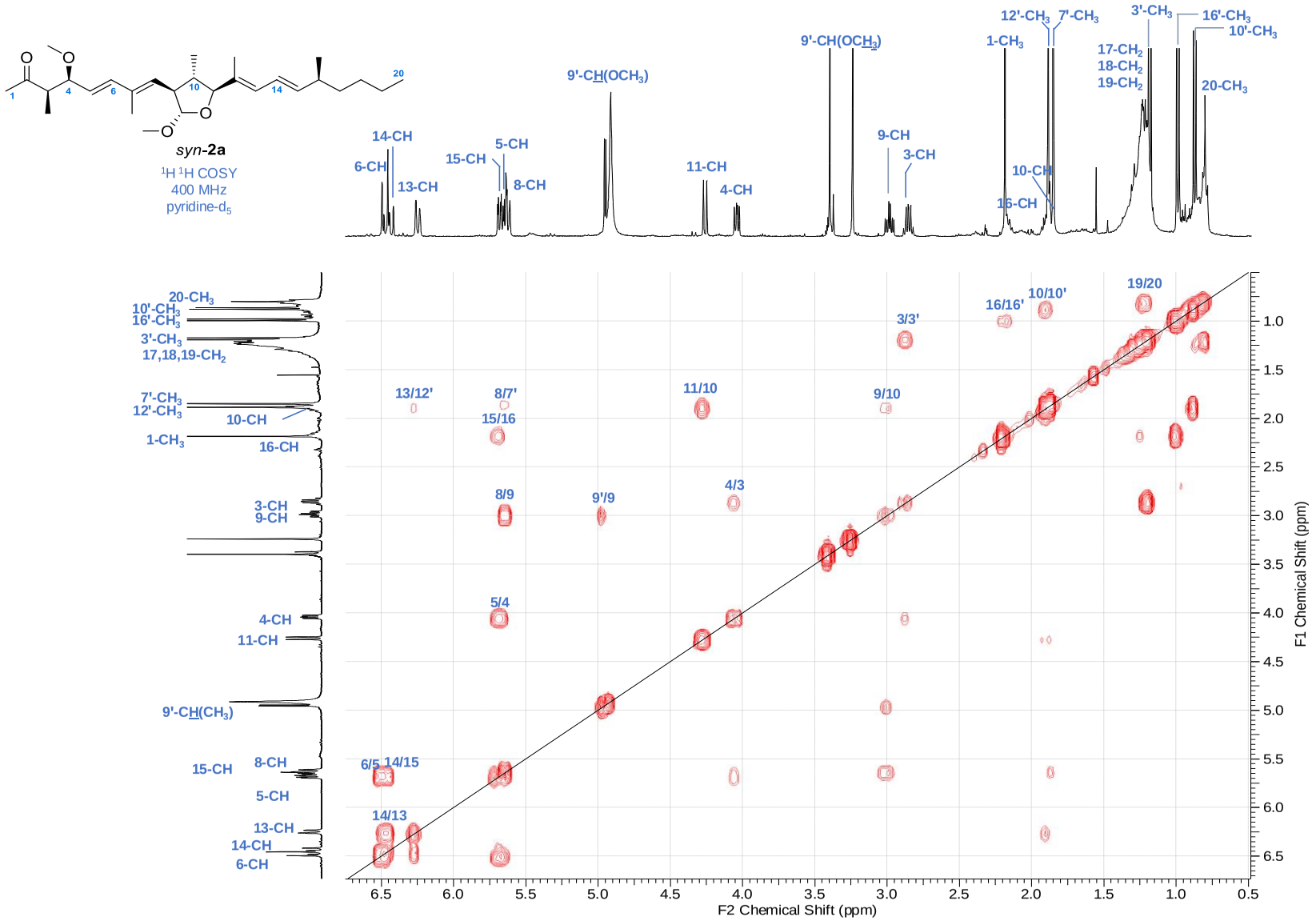
Methyl ether 131 by Methylation. To a solution of trimethyloxonium tetrafluoroborate (Me_3OBF_4, $C_3H_9BF_4O$, 147.91 g/mol, 85 mg, 0.575 mmol, 3.01 equiv) in CH_2Cl_2 (3 mL) was added molecular sieves (50 mg, 3Å, dried: 0.1 mbar, 200 °C, 1 h) and 1,8-bis(dimethylamino)naphthalene (proton sponge®, $C_{14}H_{18}N_2$, 214,31 g/mol, 123 mg, 0.574 mmol, 3 equiv) at room temperature. To the clear, colorless solution was added a solution of the aldol (−)-**125** ($C_{15}H_{18}O_4$, 262.30 g/mol, 50 mg, 0.191 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 1 h. The reaction mixture was stirred at room temperature for 1 h. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The colorless oily residue was purified by flash chromatography (cyclohexane−ethyl acetate, 20:1 to 10:1 to 5:1) to deliver the methyl ether **131** ($C_{16}H_{20}O_4$, 276.33 g/mol, 34 mg, 0.123 mmol, 64%) as a white solid. R_f 0.68 (cyclohexane−ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, ^3J = 7.0 Hz, 3H), 1.55 (d, ^3J = 7.0 Hz, 3H), 2.93 (dq, ^3J = 9.8, 7.0 Hz, 1H), 3.15 (s, 3H), 3.70 (dd, ^3J = 9.8, 8.2 Hz, 1H), 5.27 (appd, ^3J = 17.1 Hz, 1H), 5.33 (appd, ^3J = 10.4 Hz, 1H), 5.41 (q, ^3J = 7.0 Hz, 1H), 5.56 (ddd, ^3J = 17.1, 10.4, 8.2 Hz, 1H), 7.42−7.48 (m, 2H), 7.54−7.61 (m, 1H), 8.03−8.13 (m, 2H). No further analytical data were obtained.

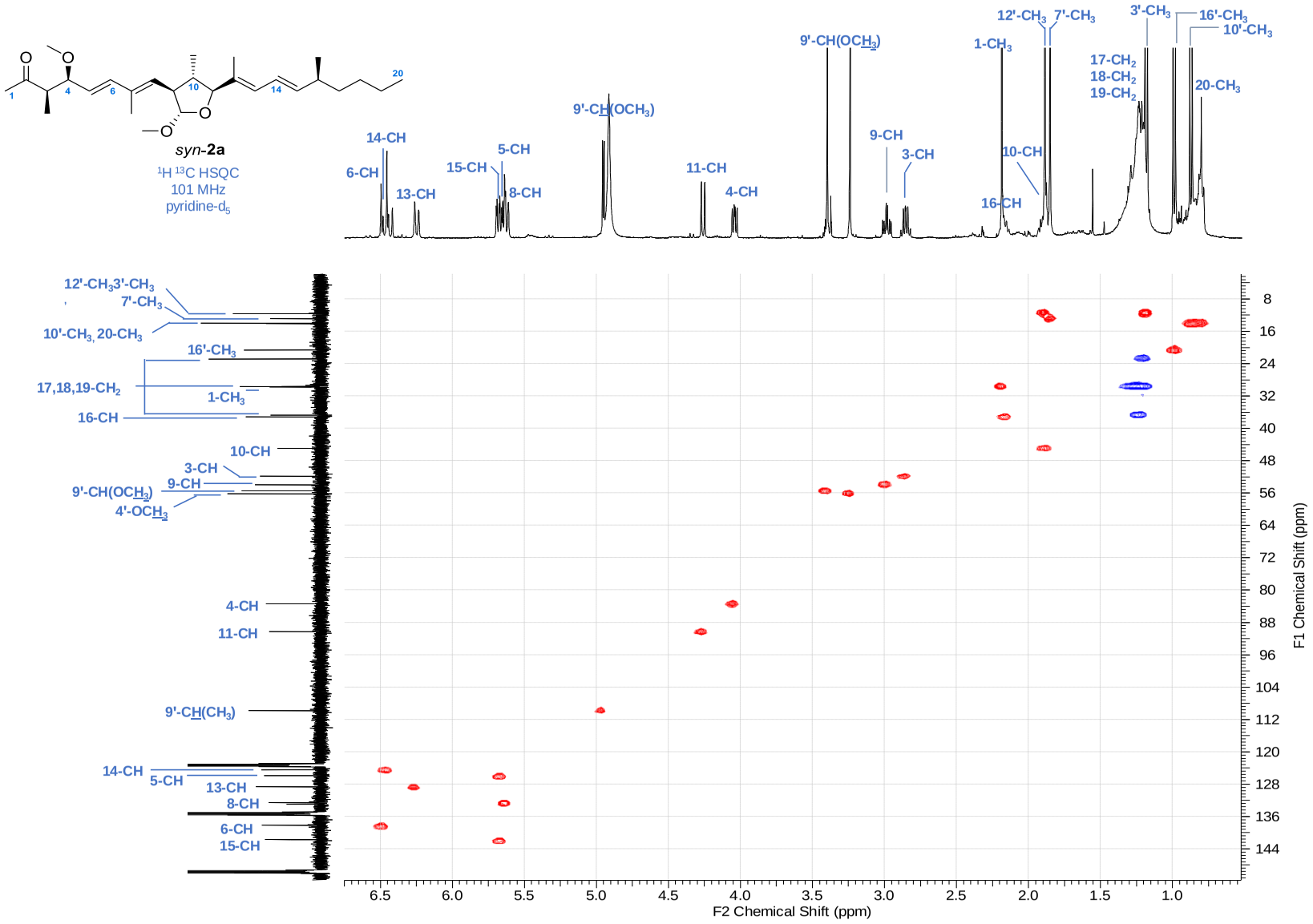
7.12 Spectroscopic data of side products.

 **73b**	^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (dd, ^{3}J = 6.8 Hz, 3H, 20-CH_3), 1.00 (d, ^{3}J = 6.9 Hz, 3H, 16'-CH_3), 1.00 (d, ^{3}J = 6.5 Hz, 3H, 10'-CH_3), 1.20−1.33 (m, 6H, 17-CH_2, 18-CH_2, 19-CH_2), 1.70 (s, 3H, 12'-CH_3) overlapped by 1.63−1.72 (m, 1H, 10-CH), 2.11−2.21 (m, 2H, 16-CH, 9-CH), 3.37 (dd, ^{2}J = 9.2 Hz, ^{3}J = 8.6 Hz, 1H, 8-CH), 3.51 (dd, ^{2}J = 9.2 Hz, ^{3}J = 5.4 Hz, 1H, 8-CH), 3.71 (dd, ^{2}J = 8.8 Hz, ^{3}J = 7.3 Hz, 1H, 9'-CH), 3.73 (d, ^{3}J = 8.8 Hz, 1H, 11-CH), 3.81 (s, 3H, OCH_3), 3.99 (dd, ^{2}J = 8.8 Hz, ^{3}J = 8.0 Hz, 1H, 9'-CH), 4.43 (d, ^{2}J = 11.5 Hz, 1H, benzylic-CH_2), 4.45 (d, ^{2}J = 11.5 Hz, 1H, benzylic-CH_2), 5.56 (dd, ^{3}J = 15.1, 7.8 Hz, 1H, 15-CH), 5.97 (d, ^{3}J = 10.7 Hz, 1H, 13-CH), 6.19 (dd, ^{3}J = 15.1, 10.7 Hz, 1H, 14-CH), 6.88 (d, ^{3}J = 8.8 Hz, 2H, aryl-CH), 7.24 (d, ^{3}J = 8.8 Hz, 2H, aryl-CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.98 (12'-CH_3), 14.22 (20-CH_3), 16.18 (10'-CH_3), 20.68 (16'-CH_3), 22.99; 29.71; 36.93 (17/18/19-CH_2), 37.15 (16-CH), 40.69 (10-CH), 47.72 (9-CH), 55.44 (OCH_3), 71.35 (9'-CH_2), 71.84 (8-CH_2), 73.01 (benzylic-CH_2), 92.43 (11-CH), 113.98 (aryl-CH), 124.15 (14-CH), 127.40 (13-CH), 129.27 (aryl-CH, aryl-C) 133.79 (12-C), 141.33 (15-CH), 159.35 (aryl-C).
 **85**	^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (dd, ^{3}J = 6.4 Hz, 3H), 1.01 (d, ^{3}J = 7.0 Hz, 3H), 1.24 (d, ^{3}J = 6.6 Hz, 3H) overlapped by 1.16−1.34 (m, 6H), 1.73 (s, 3H), 2.10−2.26 (m, 1H), 2.85 (qd, J = 7.0, 3.7 Hz, 1 H), 4.34 (d, ^{3}J = 7.3 Hz, 1H), 5.55 (d, ^{2}J = 3.3 Hz, 1H), 5.67 (dd, ^{3}J = 15.0, 7.7 Hz, 1H), 6.06 (d, ^{3}J = 10.8 Hz, 1H), 6.20 (dd, ^{3}J = 15.0, 10.8 Hz, 1H), 6.26 (d, ^{2}J = 3.3 Hz, 1H).
 **98c**	^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.04 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.91 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 1.24 (d, ^{3}J = 7.0 Hz, 3H, 10'-CH_3), 1.97 (s, 3H, 12'-CH_3), 2.35 (dddd, ^{3}J = 9.3, 6.4, 6.4, 5.4 Hz, 1H, 9-CH), 3.20 (qd, ^{3}J = 7.0, 6.3 Hz, 1H, 10-CH), 3.49 (dd, ^{2}J = 9.8 Hz, ^{3}J = 6.4 Hz, 1H, 8-CH), 3.56 (dd, ^{2}J = 9.8 Hz, ^{3}J = 5.4 Hz, 1H, 8-CH), 4.99 (d, ^{3}J = 17.1 Hz, 1H, 9'-CH=C$\underline{H}^{E}$) overlapped by 4.99 (d, ^{3}J = 10.8 Hz, 1H, 9'-CH=C$\underline{H}^{Z}$), 5.64 (ddd, ^{3}J = 17.1, 10.8, 9.3 Hz, 1H, 9'-C$\underline{H}$=CH_2), 6.13 (d, ^{3}J = 1.5 Hz, 1H, 13-CH), 7.22 (d, J = 1.5 Hz, 1H, 14-CH).
 **98d**	^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.04 (s, 3H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.89 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 1.13 (d, ^{3}J = 7.0 Hz, 3H, 10'-CH_3), 2.24 (d, ^{4}J = 1.5 Hz, 3H, 12'-CH_3), 2.44 (dddd, ^{3}J = 9.0, 7.8, 5.4, 4.9 Hz, 1H, 9-CH), 3.50 (dq, ^{3}J = 7.8, 7.0 Hz, 1H, 10-CH), 3.58 (dd, ^{2}J = 10.3 Hz, ^{3}J = 5.4 Hz, 1H, 8-CH), 3.71 (dd, ^{2}J = 10.3 Hz, ^{3}J = 4.9 Hz, 1H, 8-CH), 5.00 (d, ^{3}J = 17.1 Hz, 1H, 9'-CH=C$\underline{H}^{E}$) overlapped by 5.03 (dd, ^{3}J = 10.3 Hz, 1H, 9'-CH=C$\underline{H}^{Z}$), 5.79 (ddd, ^{3}J=17.1, 10.3, 9.0 Hz, 1H, 9'-C$\underline{H}$=CH_2), 6.53 (dd, ^{3}J = 7.3 Hz, ^{4}J = 1.5 Hz, 1H, 13-CH), 10.26 (d, ^{3}J = 7.3 Hz, 1H, 14-CH).
 **98e**	^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.09 (s, 9H), 0.83−0.86 (m, 12H), 2.07 (d, ^{4}J = 1.2 Hz, 3H), 2.27 (dqd, ^{3}J=7.3, 7.0, 6.8 Hz, 1H), 2.78 (ddd, ^{3}J = 8.2, 6.8, 5.5 Hz, 1H), 3.10 (t, ^{3}J = 4.3 Hz, 1H), 3.76 (d, ^{3}J = 8.2 Hz, 1H) overlapped by 3.76 (d, ^{3}J = 5.5 Hz, 1H), 3.85 (d, J = 7.3 Hz, 1H), 4.28 (d, ^{3}J = 4.3 Hz, 2H), 5.95 (appd, ^{3}J = 7.9 Hz, 1H), 10.01 (d, ^{3}J = 7.9 Hz, 1H).

Note:

Two dimensional NMR spectra ($^{1}H^{1}H$ COSY and $^{1}H^{13}C$ HSQC) of the *syn*-configured diastereomer of Fusaequisin A (*syn*-**2a**) were not included in the appendix and are therefore presented hereafter.


syn-2a
^{1}H ^{1}H COSY
400 MHz
pyridine-d$_5$
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)


syn-2a
^{1}H ^{13}C HSQC
101 MHz
pyridine-d_5
14-CH
6-CH
13-CH
15-CH
5-CH
8-CH
9'-CH(OCH3)
11-CH
4-CH
9-CH
3-CH
9'-CH(OCH3)
12'-CH3
7'-CH3
1-CH3
10-CH
16-CH
3'-CH3
16'-CH3
10'-CH3
17-CH2
18-CH2
19-CH2
20-CH3
12'-CH3 3'-CH3
7'-CH3
10'-CH3, 20-CH3
16'-CH3
17,18,19-CH2
1-CH3
16-CH
10-CH
3-CH
9-CH
9'-CH(OCH3)
4'-OCH3
4-CH
11-CH
9'-CH(CH3)
14-CH
5-CH
13-CH
8-CH
6-CH
15-CH
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)