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Total Syntheses of Neuroprostanes
Totalní syntézy neuroprostanů

Ph.D. Thesis

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Synthèses totales de neuroprostanes

Présentée par Tereza PAVLÍČKOVÁ

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Declaration

This work was carried out at the Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences directed by RNDr. PhDr. Zdeněk Hostomský, CSc., and at Institut des Biomolécules Max Mousseron, Faculty of Pharmacy, Université de Montpellier, directed by prof. Pascal Dumy, in the laboratory directed by Dr. Thierry Durand in 2016-2020. I declare that I have worked on the Ph.D. thesis independently with help of my Ph.D. supervisors and all used resources are properly cited.

V Praze dne

Tereza Pavlíčková

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ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
AA	arachidonic acid
Ac	acetyl
ACN	acetonitrile
AGPI	acide gras polyinsaturé
ALA	α-linolenic acid
APT	attached proton test
ATR	attenuated total reflection
BINOL	1,1'-bi-2-naphtol
n-Bu	linear butyl
br	broad
CALB	*Candida Antarctica* lipase B
cat.	catalytic amount
CI	chemical ionization
CM	cross metathesis
CNRS	Centre national de la recherche scientifique
COSY	homonuclear correlation spectroscopy
COX	cyclooxygenase
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHA	docosahexaenoic acid
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EE	1-ethoxy-ethyl
EI	electron ionization
ent	enantiomer
EOR	espèces oxygenées réactives

EPA	eicosapentaenoic acid
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EVE	ethyl vinyl ether
FGI	functional group interconversion
GC	gas chromatography
Grubbs II	2nd generation Grubbs catalyst
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HNE	4-hydroxynonenal
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
im	imidazole
IOCB	Institute of Organic Chemistry and Biochemistry
IR	infrared
IsoP	isoprostane
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropyl amide
LiHMDS	lithium bis(trimethylsilyl)amide
M	metal
m-CPBA	*m*-chloroperoxybenzoic acid
MDA	malondialdehyde
Me	methyl
MIP	1-methyl-1-methoxymethyl
mol.	molar
MS	mass spectrometry
Ms	methylsulfonyl
MTBE	methyl *tert*-butyl ether
NaHMDS	sodium bis(trimethylsilyl)amide
NCS	N-chlorosuccinimide
nd	not determined
NeuroP	neuroprostane
NMO	N-methylmorpholine N-oxide
NOESY	nuclear Overhauser effect spectroscopy
P	pentane

petroleum ether	PE
PG	prostaglandin
Pg	protecting group
PhytoP	phytoprostane
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PT	phenyltetrazoyl
PUFA	polyunsaturated fatty acid
py	pyridine
quant.	quantitative yield
rac	racemic
RCM	ring-closing metathesis
ROESY	rotating frame Overhauser effect spectroscopy
ROM	ring-opening metathesis
ROS	reactive oxygen species
rt	room temperature
satd.	saturated
SET	single-electron transfer
SFC	supercritical fluid chromatography
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEBAC	triethylbenzylammonium chloride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethyl-1-piperidinyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-tolylsulfonyl
UCT	University of Chemistry and Technology
v br	very broad

ABSTRACT

Neuroprostanes are cyclic oxygenated metabolites formed *in vivo* from docosahexaenoic acid, the main polyunsaturated fatty acid of the human brain. The non-enzymatic auto-oxidative biosynthesis provides neuroprostanes non-selectively as mixtures of regio- and diastereoisomers, making their isolation and identification difficult without primary standards. Thus, synthetic material is necessary to investigate the biological properties of individual molecules as well as the potential of neuroprostanes as biomarkers of oxidative stress in medical diagnostics. Two different synthetic approaches targeting the most abundant regioisomeric series of neuroprostanes are reported.

First, an enantioselective strategy toward an asymmetric core of cyclopentenone neuroprostanes relying on an organocatalyzed Michael addition was developed. A complementary racemic synthesis involving diastereoselective vicinal difunctionalization is also described. The assembly of the full carbon framework of the target natural product was accomplished via a double olefin metathesis and Wittig olefination.

In the second part, a unified approach to lipid metabolites bearing a 3-hydroxypentenyl side chain is reported. The key steps involved a multiple alkynylation of a central functionalized precursor, constructed by an oxidative dianion radical cyclization, and a stereoselective semihydrogenation. The strategy provides access to a wide range of neuroprostanes thanks to an orthogonal protection of the key intermediate and was applied to the total synthesis of a closely related F_{3t}-isoprostane derived from eicosapentaenoic acid.

ABSTRAKT

Neuroprostany jsou cyklické kyslíkaté metabolity kyseliny dokosahexaenové, hlavní nenasycené mastné kyseliny lidského mozku. Vznikají *in vivo* neselektivním auto-oxidativním procesem bez účasti enzymů jako směsi mnoha regioizomerů a diastereomerů, proto je obtížné je izolovat nebo identifikovat bez příslušných standardů. Synteticky připravené látky jsou nezbytné pro pochopení biologických funkcí jednotlivých neuroprostanů v organismu i pro jejich využití jakožto biomarkerů oxidačního stresu v diagnostice různých onemocnění. Tato práce se zabývá vývojem dvou nových strategií syntézy nejhojněji zastoupených regioisomerů neuroprostanů.

První přístup je založený na enantioselektivní organokatalytické Michaelově adici vedoucí k přípravě asymetrického klíčového prekurzoru pro syntézu neuroprostanů cyklopentenonového typu. Popsána je i racemická varianta syntézy zahrnující následnou dvojitou diastereoselektivní funkcionalizaci sousedních atomů uhlíku. Pro dokončení uhlíkového skeletu cílové molekuly byla použita dvojitá metateze alkenů a Wittigova olefinace.

Druhý přístup se zabývá vývojem jednotné strategie syntézy lipidových metabolitů nesoucích 3-hydroxypentenylový postranní řetězec. Klíčové kroky zahrnují násobnou alkynylaci centrálního meziproduktu, který byl připraven oxidativní radikálovou cyklizací, a stereoselektivní semihydrogenaci. Tato strategie umožňuje přístup k řadě neuroprostanů a byla aplikována na totální syntézu F_{3t}-isoprostanu, metabolitu kyseliny eikosapentaenové.

ABSTRACT

Les neuroprostanes sont des métabolites cycliques oxygénés générés *in vivo* à partir de de l'acide docosahexaénoïque, l'acide gras principal polyinsaturé le plus présent dans le cerveau humain. La biosynthèse des neuroprostanes est un processus auto-oxydant non-enzymatique, fournissant les neuroprostanes sous forme d'un mélange de régioisomères et diastéréomères. Ce fait rend l'isolation ou l'identification des neuroprostanes difficiles sans standards analytiques. Par conséquent, les composés synthétiques sont indispensables pour établir les propriétés biologiques ainsi que le potentiel de neuroprostanes en tant que biomarqueurs du stress oxydant dans le diagnostic de certaines maladies. Deux approches synthétiques différentes vers les régioisomères les plus abondants des neuroprostanes sont présentées.

La première stratégie envisage une synthèse du noyau asymétrique des neuroprostanes de type cyclopentenones par une addition de Michael énantiosélective organocatalysée. Une variante de synthèse racémique complémentaire mise en place par une double fonctionnalisation vicinale et également décrite. Le squelette de la molécule cible a été assemblé par une double métathèse d'alcènes et une oléfination de Wittig.

Dans la deuxième partie, une stratégie unifiée vers des métabolites lipidiques portant une chaine latérale de type 3-hydroxypentényl a été développée dont les étapes clés comprennent une alcynilation multiple d'un précurseur central fonctionnalisé, construit par une cyclisation radicalaire oxydante d'un dianion, et une semi-hydrogénation stéréosélective. La stratégie ouvre l'accès à une variété de neuroprostanes grâce à une protection orthogonale de l'intermédiaire clé validée par la synthèse totale de la F_{3t}-isoprostane, un métabolite de l'acide eicosapentaénoïque.

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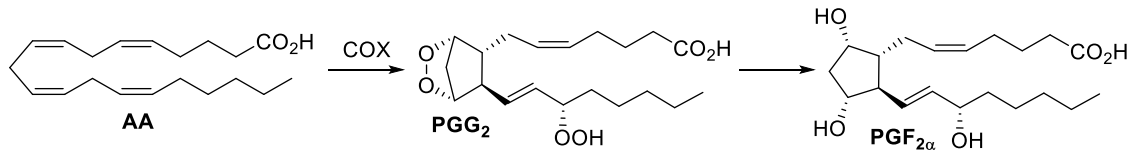
1 INTRODUCTION

1.1 Polyunsaturated fatty acids and oxidative stress

Polyunsaturated fatty acids (PUFAs) are a group of lipids essential to all living cells as constituents of the lipid cell membrane largely responsible for its fluidity.[1] Unlike saturated fatty acids, PUFAs are not inert under physiological conditions, but prone to enzymatic or non-enzymatic oxidative transformations to produce a variety of metabolites called oxylipins.[2] A well described example of oxylipins are prostaglandins (PGs), such as $PGF_{2\alpha}$, which are formed from arachidonic acid (AA, C20:4 ω–6) by a series of reactions assisted by the cyclooxygenase enzymes (COX; Scheme 1).[3]



Scheme 1. Formation of $PGF_{2\alpha}$ from AA by COX-catalyzed reactions.

Approximately 50 years after PG discovery, Morrow *et al.* found that similar metabolites were also formed without enzymatic assistance.[4] Unlike PGs, these new "non-cyclooxygenase PGs" were rather complex regio- and diastereomeric mixtures, isomers of PGs and were thus called isoprostanes (IsoPs). Based on the predicted biosynthesis and fragments observed in mass spectrometry, four IsoP classes **I**-**IV** were proposed, each comprising eight theoretical stereoisomers (Figure 1), all having relative *cis*-configuration of the two hydroxy groups at the cyclopentane ring.[5, 6]

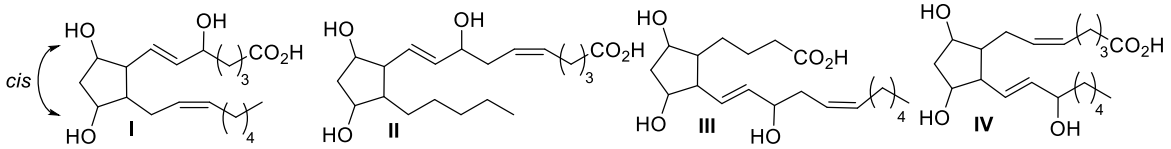


Figure 1. First four discovered IsoP classes as proposed by Morrow *et al.*

The proposed biosynthesis relied on the reaction of AA with reactive oxygen species (ROS), oxygen-based radicals produced in various biochemical pathways whose *in vivo* formation can be enhanced by various stimuli such as smoking or disease.[7] Examples include superoxide anion, hydrogen peroxide, hydroxyl radical or singlet oxygen. A healthy organism possesses numerous mechanisms against the effects of these very reactive molecules. This involves both enzymatic and non-enzymatic reactions with neutral biomolecules to produce persistent, less reactive radicals and neutral molecules that can be further metabolized or defused without causing harm to the organism. When this antioxidative defense of the organism cannot cope with ROS formation, the overall redox state shifts out of homeostasis and ROS may cause more permanent damage to tissues by reacting with important biomolecules. The resulting redox disbalance is called oxidative stress.[8]

Unlike the reaction assisted by COX, which only accepts free AA as substrate, esterified PUFAs, such as AA, α-linolenic acid (ALA, 18:3 ω–3) or docosahexaenoic acid (DHA, 22:6 ω–3), can react

with ROS inside of the phospholipid membrane (Scheme 2, part **A**, top to bottom). The first step of this reaction is abstraction of bisallylic hydrogen atoms and formation of a delocalized bisallylic PUFA radical of a general formula **V**. This radical reacts with oxygen and gives rise to an oxygen-centered conjugated peroxyl radical **VI**. At this stage, based on the oxygen level and the state of antioxidant defense of the organism, several outcomes are possible. In a well-balanced redox state (green arrow), **VI** abstracts a hydrogen atom and is reduced to a neutral product like a hydroxy PUFA. Under severe oxidative stress, the corresponding hydroperoxide of **VI** reacts further, eventually undergoing β-scission of the C-CO· bond to form small neutral, yet still highly reactive products such as 4-hydroxynonenal (HNE) or malondialdehyde (MDA, red arrow). These aldehydes can form adducts with a variety of nucleophilic functional groups of biomolecules such as thiols or amino groups and are the cause of so-called carbonyl stress.[9, 10] Amidst the two extremes, a somewhat more controlled radical cascade can produce PG-like cyclic molecules called isoprostanoids (orange arrow). Historically, three major classes of isoprostanoids are IsoPs derived from AA in animals, phytoprostanes (PhytoPs) from ALA in plants and neuroprostanes (NeuroPs) from DHA[11] in the grey matter of the nervous system.[12]

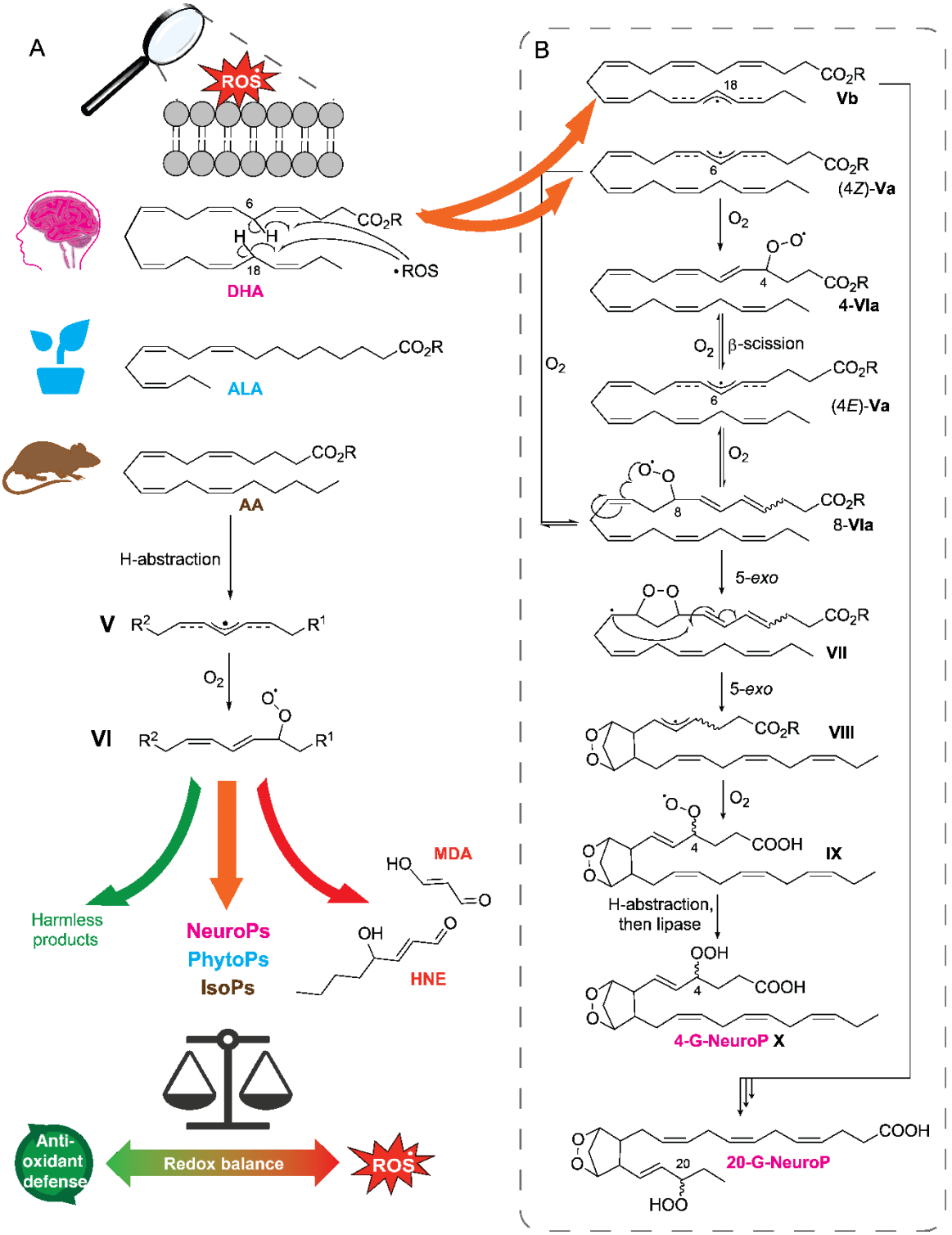
1.2 Biosynthesis of NeuroPs

Six skipped (*Z*)-double bonds make DHA the most complex natural PUFA and the most prone to peroxidation. There are five bisallylic positions in DHA and so, in theory, five possible sites for initial hydrogen atom abstraction. However, *in vivo* ROS production mostly takes place in the intracellular environment by mitochondria. Since PUFA-derived phospholipids often adapt a U-shaped conformation inside of the membrane,[13, 14] it can be hypothesized that initial hydrogen atom abstraction would likely occur at the outer positions C-6 or C-18, giving radicals **Va** and **Vb**, respectively (Scheme 2, part **B**).

Initially formed *cisoid* bisallylic radical (4*Z*)-**Va**[1] can reversibly react with oxygen either at C-4 or at C-8. Reaction at C-4 produces peroxyl radical 4-**VIa**, which does not have a productive way to react and rather undergoes β-scission to give more stable transoid radical (4*E*)-**Va**.[15, 16] Reaction of (4*Z*)- or (4*E*)-**Va** with oxygen molecule at C-8 provides peroxyl radical (*E,Z*)- or (*E*,*E*)-8-**VIa**, respectively, enabling first irreversible 5-*exo* cyclization, which gives endoperoxide radical **VII**. Second 5-*exo* cyclization furnishes radical **VIII**, which can again be *cisoid* or *transoid*. The latter reacts with a further oxygen molecule at C-4, which is followed by hydrogen atom abstraction by peroxyl radical **IX** to give an ester of 4-G-NeuroP. The latter is ultimately cleaved by phospholipase A_2 or other esterases and released from the membrane as 4-G-NeuroP **X**. The stereochemical information in **Va** is conserved throughout the pathway, resulting in **X** with different configuration at the hydroperoxy group of the side chain.[17, 18]

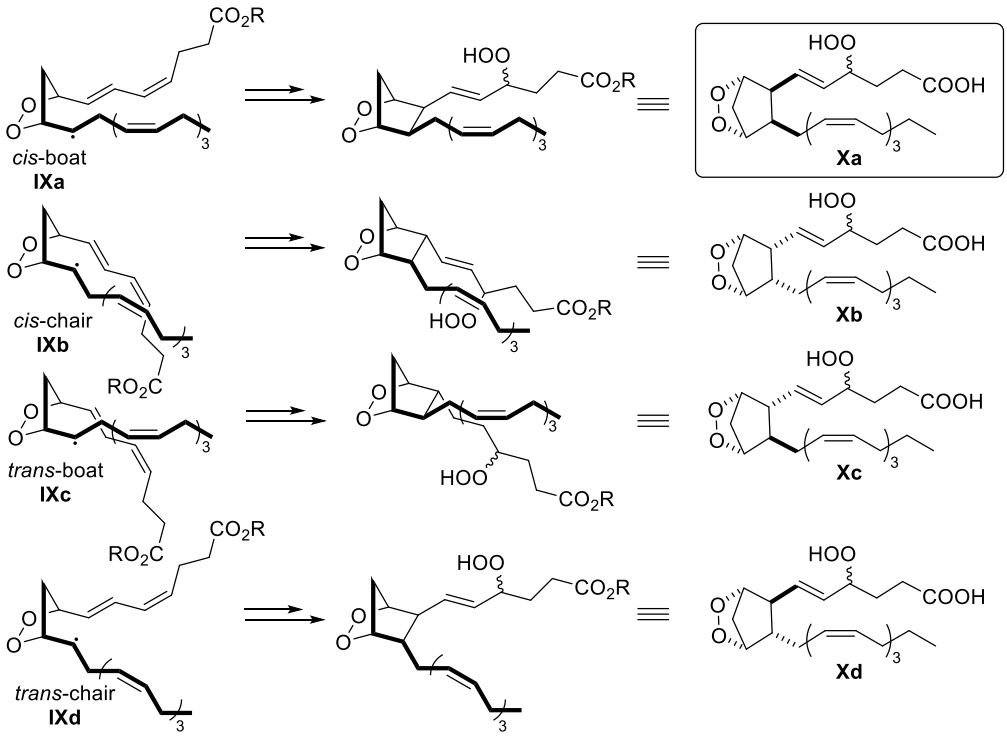
[1] Simple allylic radicals are configurationally relatively stable, with rotational barriers ranging from 10-25 kcal/mol. and rotation of conjugated pentadienyl radicals such as **Va** is even more restricted.

Analogous pathway starting from bisallylic radical **Vb** leads to 20-G-NeuroP.[19, 20] Hydrogen atom abstraction at one of the three remaining bisallylic positions results in formation of six remaining regioisomers, namely 7-, 10-, 11-, 13-, 14- and 17-NeuroP, which occur in Nature to a much lower extent.[21]



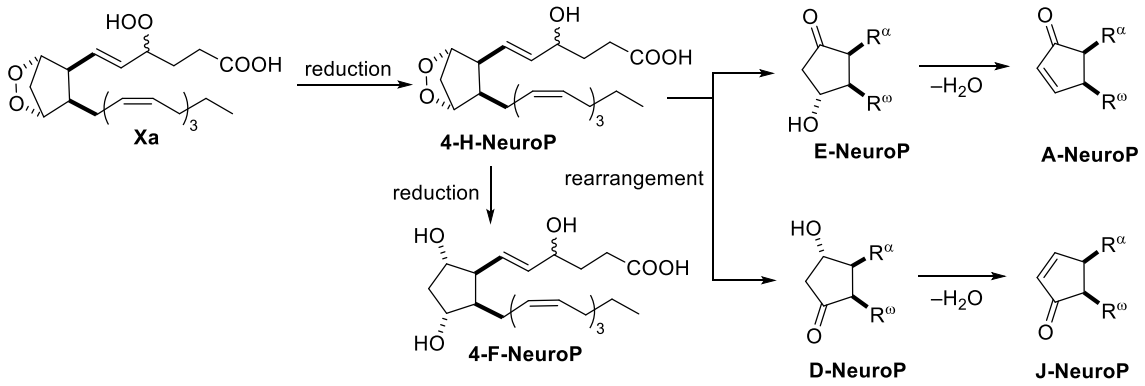
Scheme 2. PUFA peroxidation (**A**) and a closer look on NeuroP biosynthesis (**B**).

In contrast to PGs, whose absolute and relative configuration is enforced by the constraints of the COX active site,[22] the predominant relative configuration of the four centers at the cyclopentane ring in NeuroPs can be rationalized by the Beckwith-Houk transition states for the second 5-*exo* radical cyclization corresponding to main conformers of endoperoxide radical **IXa-IXd** (Scheme 3).[23, 24] The transition states for the cyclization of *cis*-conformers **IXa** and **IXb** are lower in energy than those for *trans*-conformers **IXc** and **IXd**, and consequently, the resulting *cis*-isomers **Xa** and **Xb** are dominant in Nature.[25]



Scheme 3. Main conformers of endoperoxide radical **IX** leading to different diastereomers of **X**.

The initially formed G-NeuroP **Xa** is not very stable and is rapidly transformed by facile reduction of the side chain hydroperoxide to a hydroxy group to provide H-NeuroP, which itself further reacts (Scheme 4). The endoperoxide bridge can be cleaved reductively to give F-NeuroP or by Kornblum-DeLaMare rearrangement to provide hydroxy ketone E- or D-NeuroP. These NeuroPs differ by the relative position of the two side chains, the α-chain bearing the carboxyl group (R^{α}) and the ω-chain (R^{ω}), with respect to the different oxygen functions, Subsequent conjugate elimination of water from E- or D-NeuroP gives enone A- or J-NeuroP, respectively.[12, 26]



Scheme 4. Biosynthesis of different NeuroP types from **Xa**. Only major diastereomers are shown.

1.3 Nomenclature of isoprostanoids

The structural and stereochemical diversity of isoprostanoids requires a clear system for nomenclature to address individual molecules unambiguously. Since the discovery of IsoPs in 1990,[4] two major nomenclature systems were proposed in parallel,[27, 28] however, the system of Taber *et al.* [28] was submitted to IUPAC and will thus be used throughout the manuscript, taking into account some later discussions and updates.[29-32] The nomenclature largely derives from biosynthesis and some representative examples of its application are shown in Figure 2.
To assign a name to an isoprostanoid, these rules must be followed (right to left):

- Assign the type of metabolite as PhytoP, IsoP or NeuroP based on the number of carbon atoms. Since other PUFAs such as eicosapentaenoic acid (EPA, C20:5 ω–3), docosapentaenoic acid (C22:5 ω–3) or γ-linolenic acid (C18:3 ω–6) can also produce isoprostanoids, those with 18 carbon atoms are called PhytoPs, those with 20 carbon atoms IsoPs and those with 22 carbon atoms NeuroPs, by agreement, with the exception of metabolites of adrenic acid (*vide infra*).
- Add a prefix describing the degree of oxygenation and/or unsaturation and the ring substitution pattern by a capital letter as F-, E-, D-, A-, J-, B- or L- (in blue; for all patterns see biosynthetic Scheme 4 above).
- Add a second prefix describing the side chain hydroxyl position by an arabic numeral (in red). Numbering of isoprostanoids follows the numbering of the original PUFA, assigning C-1 to the carboxyl group and continues along the chain.
- Add a subscript to the ring-substitution letter marking the total number of double bonds in the side chains of the molecule by an arabic numeral (in pink). This allows to further distinguish metabolites of different PUFAs in case of ambiguity (**XIb** from AA versus **XII** from EPA). To describe metabolites of adrenic acid (C22:4 ω–6) add a general prefix dihomo- for two additional saturated carbon atoms on carboxyl side (**XIII**).[33]
- Follow the number of double bonds with the first stereodescriptor for the relative configuration of the hydroxy group(s) with respect to the ω-chain, if applicable: t for *trans* (as in **XIa**) and c for *cis* (as in **XIb**; in green). Compounds **XIa** and **XIb** are default structures to derive the configuration of other isomers. The default relative configuration of the side chains is *cis*. The two hydroxy groups of the F-type cyclopentanediol (**XIa**) are always *cis*, inherently to the

biosynthesis, and their absolute configuration is down (α) by agreement and in analogy to PGs. Similarly, the default absolute configuration of the side chain hydroxyl is (*S*).

- Add the remaining stereodescriptors by marking every deviation from the default configuration of **XI** by prefixes. One or two such deviations (e.g. hydroxy group or α-chain) are described by a prefix *epi-* or *diepi-* preceded by the corresponding carbon atom number. If more than two stereocenters differ from the default configuration, a general prefix *ent-* for "enantiomer" should be used followed by other prefixes, if necessary. Note that the default configuration of *ent*-**XI** is the opposite to **XI** including the side chain hydroxy group, which must be (*R*). Also note that for A- and J-types, no hydroxy groups can be used to describe the relative configuration as *cis* or *trans* and these compound must always be named with regard to **XIa** (see compound **XV**).

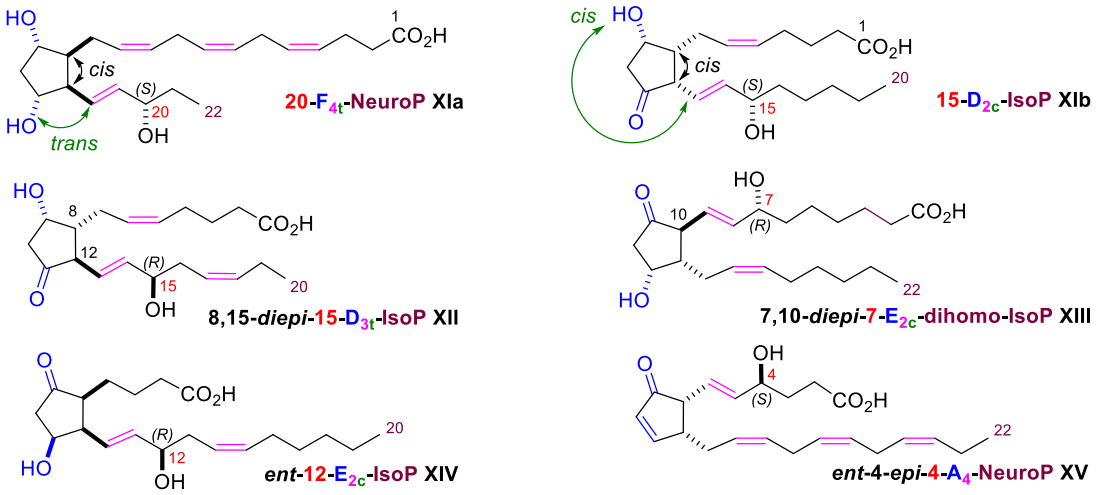


Figure 2. Stereochemical default structures **XIa** and **XIb** and some representative examples for the use of isoprostanoid nomenclature **XII**-**XV**.

2 STATE OF THE ART

2.1 Biological background

The structural similarity of isoprostanoids to PGs promises some interesting bioactivity and in fact, a number of studies on IsoPs have been carried out to date describing their indispensable role in cell signaling and other biological effects.[34]

The data on NeuroPs, which were discovered eight years later,[11] still remain scarce, mostly due to a limited number of total syntheses of these more complex metabolites, but some of the recently discovered bioactivities include anti-inflammatory activity linked particularly to enone-type A- and J-NeuroPs[35-37] or anti-arrhythmic activity of 4-F_{4t}-NeuroP.[38-41] These findings clearly imply that NeuroPs and related isoprostanoids might mediate the positive effects associated with ω–3 PUFA rich diet and food supplementation to a certain extent. This breaks the paradigm of PUFA peroxidation being an exclusively deleterious phenomenon and makes NeuroPs and oxidized PUFAs potential drug candidates.

Besides their promising bioactivities, NeuroPs are valuable biomarkers of oxidative stress. IsoPs are already widely recognized as robust and versatile markers of lipid peroxidation and oxidative stress in humans.[42] Since NeuroPs are formed *in vivo* in the neuronal membranes, they might serve as tissue-specific biomarkers and thus find application in diagnostics of some neurological diseases. Indeed, elevated levels of NeuroPs have been detected in various tissues of patients with Alzheimer's disease at different stages.[43-47] More recently, clinicians have been interested in levels of NeuroPs in Rett syndrome or Krabbe disease[48, 49] and even for monitoring the efficiency of oxygen therapy in preterm infants.[50] In these studies, a so-called targeted lipidomic approach is most often applied, requiring synthetic NeuroPs as primary standards for their detection and quantification by high-performance liquid chromatography coupled to mass spectrometry (HPLC/MS), HPLC/MS-MS or gas chromatography (GC)/MS in various biomatrices.

The interest of researchers and clinicians in NeuroPs as diagnostic tools as well as interesting bioactive compounds has been growing and more than 50 reports have been published in this topic to date. The results of these studies have been a subject to several reviews,[34, 51-55] most recently in 2020.[56]

2.2 Background in synthetic organic chemistry

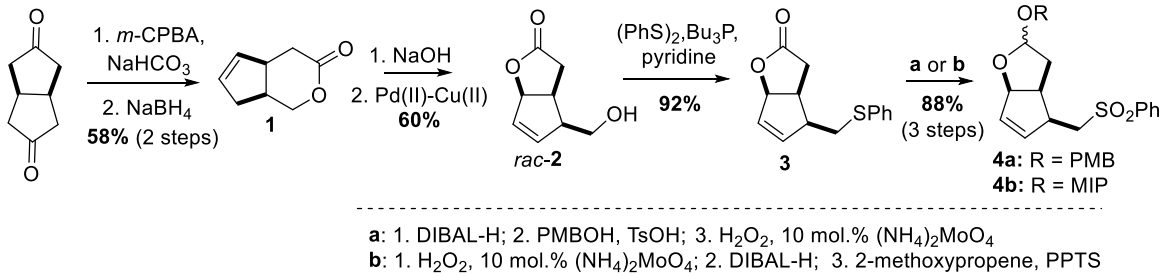
Several total syntheses of isoprostanoids have been published to date, mostly involving IsoPs but a few syntheses of PhytoPs and NeuroPs have also been accomplished. These reports have been thoroughly reviewed over the last ten years and will not be discussed in detail.[12, 52, 57-60] The following chapter covers selected topics related to the syntheses of isoprostanoids, which are relevant for this work.

2.2.1 Previous approaches to *cis*-disubstituted cyclopentenone isoprostanoids

Enone-type isoprostanoids are particularly difficult to synthesize because the C-5 position of the cyclopentenone ring is prone to epimerization to a more thermodynamically stable *trans*-configuration of the side chains. Moreover, the β,γ-unsaturation in some of these compounds can result in double bond isomerization and/or dehydration.[61] Yet, their promising biological activities make them attractive targets for total synthesis and several approaches have been reported to date. The syntheses of A- and J-type isoprostanoids and closely related *cis*-disubstituted eicosanoid preclavulone A are summarized in the following section.

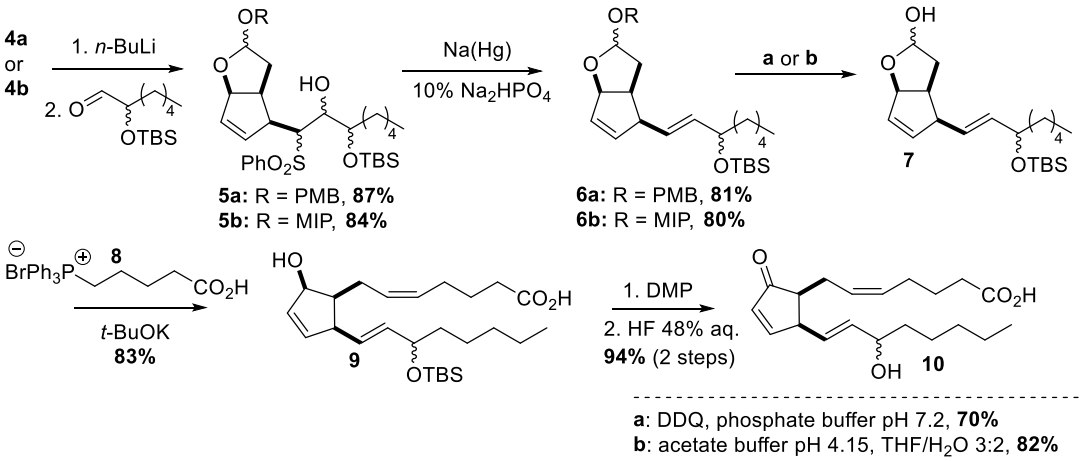
2.2.1.1 Total syntheses of J- and A-IsoPs, NeuroPs and PhytoPs

First total synthesis of these metabolite types was accomplished by Zanoni *et al.* in 2002 who synthesized mixture of four stereoiseomers 15-A_2-IsoP, 15-*epi*-15-A_2-IsoP, *ent*-15-A_2-IsoP and *ent*-15-*epi*-15-A_2-IsoP.[62] Key bicyclic lactone **1** was available on large scale in two steps from a commercially availably diketone (Scheme 5). Pd(II)-catalyzed translactonization of alkene **1** furnished Corey-like lactone *rac*-**2**, which was subsequently converted to sulfide **3**, reduced, protected as mixed acetal and oxidized to corresponding sulfone **4**.[63]



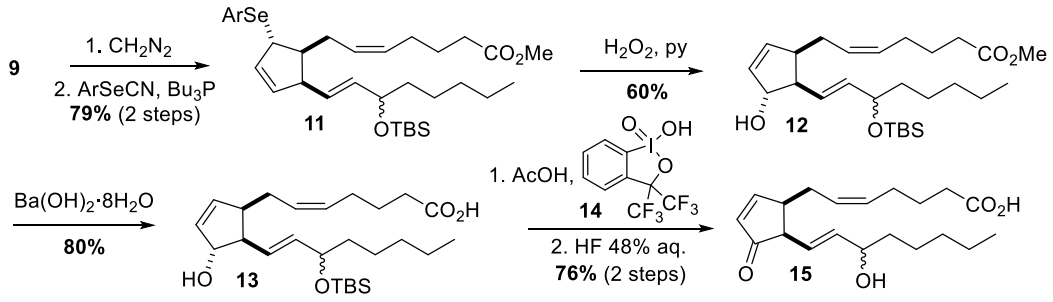
Scheme 5. Preparation of sulfones **4** by Zanoni *et al*.

Stereoselective Julia-Lythgoe olefination allowed to transform sulfoxide **4a** to alcohol **5a** and to attain the desired (*E*)-selectivity at the ω-chain in alkene **6a** after treatment with sodium amalgam (Scheme 6). Subsequent deprotection and Wittig reaction with phosphonium salt **8** to connect the α-chain proceeded with exclusive (*Z*)-selectivity. Final oxidation and deprotection furnished desired racemic 15-A_2-IsoP **10** as a 1:1 mixture of C-15 epimers in 44% overall yield over 10 steps from Corey-like lactone *rac*-**2** and in 16% yield over 14 steps from commercially available compounds.[62, 64, 65]



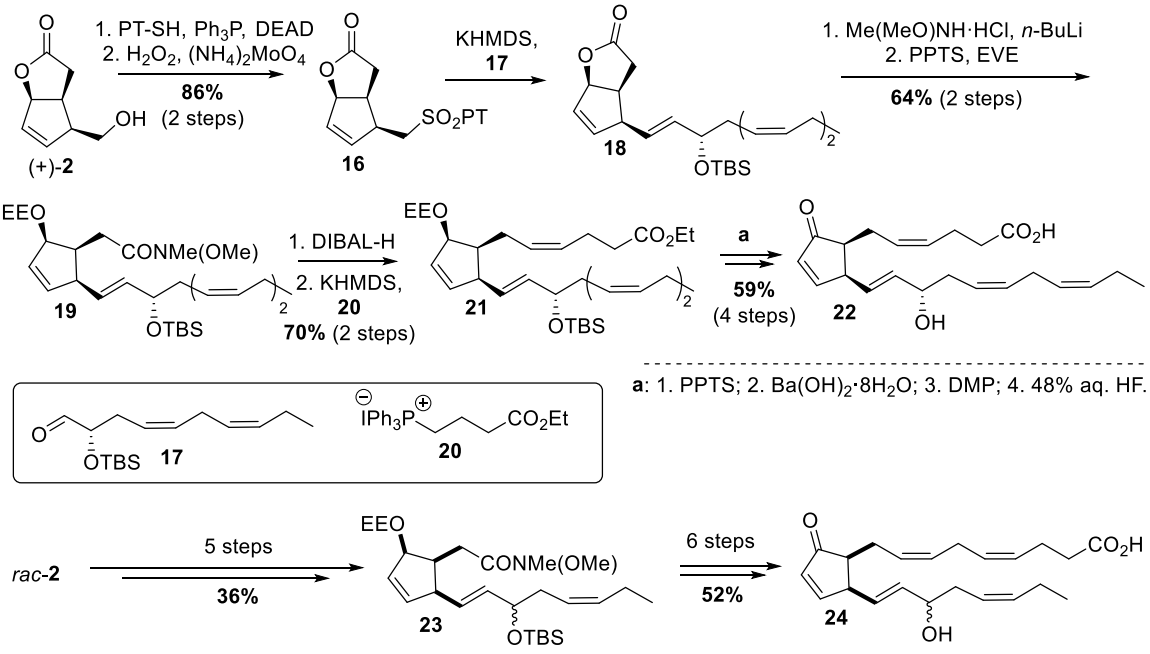
Scheme 6. Completion of the synthesis of 15-A_2-IsoP **10** by Zanoni *et al.*

A year later, the authors also reported the total synthesis of four stereoisomers of 15-J_2-IsoP using the same approach (Scheme 7). The first part of the synthesis was performed in analogy to the synthesis of 15-A_2-IsoP using compounds **4b**-**6b**. The switch of the ring substitution pattern was achieved by 1,3-allylic transposition of arylselenide **11**.[66] Final saponification, oxidation using hydroxyiodinanane oxide **14** and silyl deprotection provided racemic 15-J_2-IsoP **15** in 11% overall yield over 14 steps from *rac*-**2**. The relative trans-configuration of side chains was confirmed by NOESY experiments and based on comparision of the NMR data with the data for PGJ_2 (12-*epi*-**15**, not shown) synthesized by the same group.[67]



Scheme 7. Completion of the synthesis of 15-J_2-IsoP **15** by Zanoni *et al*.

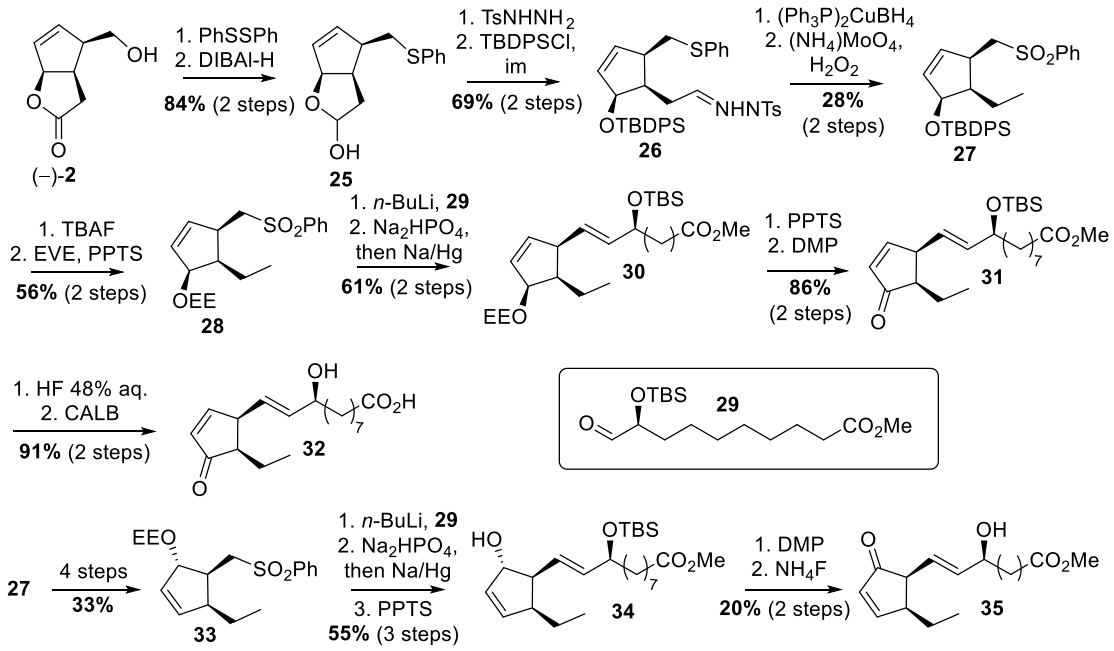
Later, the group switched to asymmetric synthesis thanks to enzymatic resolution of *rac*-**2** to (+)-**2** and (–)-**2** (not shown).[68] In the enantioselective total synthesis of 14-A_{4t}-NeuroP **22**, the initial Julia olefination was replaced by Julia-Kociensky modification using phenyltetrazoylsulfone **16** (Scheme 8).[69] For the subsequent Wittig olefination, the lactone moiety was transformed to 1-ethoxy-ethyl (EE)-protected Weinreb amide **19** as a free aldehyde precursor to prevent isomerization of the bisallylic double bonds, which occurred under the initial conditions. Final deprotections, saponification and oxidation delivered the target compound in 14% over 11 steps from enantioenriched lactone (+)-**2**. The general approach to A_4-NeuroPs was subsequently validated by applying the same strategy to the synthesis of 17-A_4-NeuroP **24**, which was completed in 18% yield over 11 steps from lactone *rac*-**2**.[70]



Scheme 8. Total synthesis of 14-A_4-NeuroP **22** and 17-A_4-NeuroP **24** by Zanoni *et al.* and Porta *et al.*

Most recently, 9-J_1-PhytoP and 9-A_1-PhytoP-OMe were synthesized using this approach starting from (–)-**2** (Scheme 9).[71] Tosylhydrazone **26** was obtained after lactol opening and used as alkane surrogate to give key ethylcyclopentane intermediate **27** after reduction and oxidation of the sulfide moiety. After protecting group exchange, Julia-Lythgoe olefination of aldehyde **29** provided ether **30**. Deprotection of EE, Dess-Martin oxidation and silyl deprotection furnished the methyl ester of 9-J_1-PhytoP, which was converted to corresponding acid **32** using mild enzymatic hydrolysis with *Candida Antarctica* lipase B (CALB).[72]

Sulfone **27** was transformed to **33** by [2,3]-sigmatropic rearrangement of the corresponding arylselenide in analogy to the synthesis of **15** (see Scheme 7). Julia olefination, deprotection, oxidation and silyl deprotection permitted access methyl ester of 9-A_1-PhytoP **35**. It should be noted that due to sensitivity of the material, the yield of the final two steps remained low despite the mild conditions applied and the attempted final enzymatic hydrolysis of the methyl ester was not successful in this case. Thus, 9-J_1-PhytoP **32** and 9-A_1-PhytoP-OMe **35** were synthesized in 4% over 10 steps and in 0.5% yield over 13 steps, respectively.

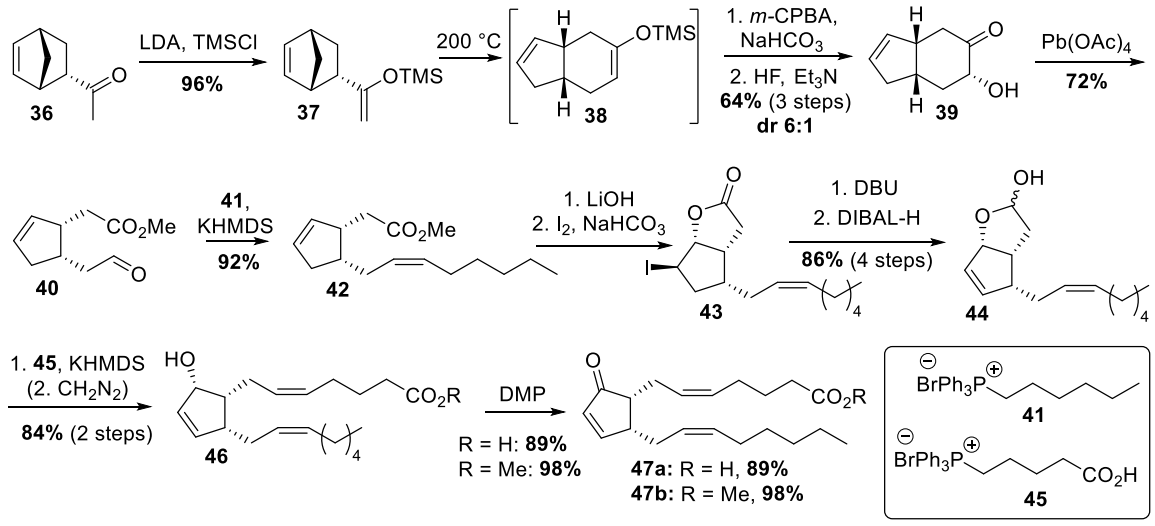


Scheme 9. Total synthesis of 9-J$_1$-PhytoP **32** and 9-A$_1$-PhytoP-OMe **35** by Porta *et al.*

2.2.1.2 Total syntheses of preclavulone A

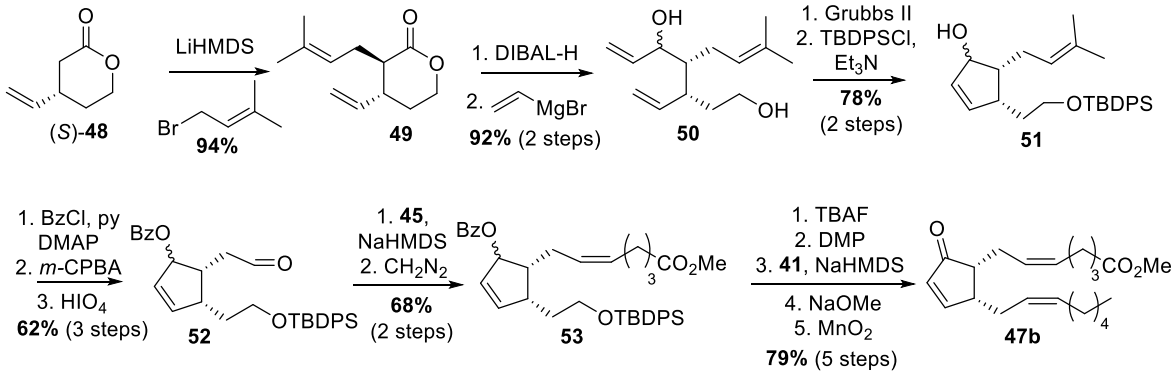
Clavulones are marine eicosanoids structurally similar to IsoPs that were isolated from the coral *Clavularia viridis*. Interestingly, natural preclavulone A occurs as a mixture of both *cis* and *trans* isomers, however, both in enantioenriched form. Their absolute configuration could not be determined due to a lack of material obtained by extraction of biological matrix.

The first total synthesis of (–)-preclavulone A and its methyl ester was accomplished by Corey and Xiang in 1988 (Scheme 10).[73] The synthesis commenced with enantiopure Diels-Alder adduct **36**. Heating its corresponding kinetic silyl enol ether **37** induced a Cope rearrangement; the resulting bicycle **38** was directly oxidized by *m*-chloroperoxybenzoic acid (*m*-CPBA) and deprotected to provide hydroxyketone **39**. Oxidative cleavage and subsequent Wittig reaction gave ester **42**, which was transformed to lactol **44** via an iodolactonization, elimination and reduction sequence. A second Wittig olefination and final oxidation provided the target compound **47a** and its methyl ester **47b** in 26% and 29% yield over 12 and 13 steps, respectively. The synthesis allowed the assignment of the natural product absolute configuration by comparison of optical rotation values.



Scheme 10. Total synthesis of (–)-preclavulone A **47a** and its methyl ester **47b** by Corey and Xiang.

Almost 20 years later, Ito *et al.* published an approach to both diastereomers of preclavulone A methyl ester based on resolution of racemic lactone **48** via the corresponding (*S*)-1-phenylethylamides and subsequent HPLC separation of diastereomers (not shown). Synthesis of the *cis* isomer departed from (*S*)-**48** (Scheme 11).[74] First, the α-chain subunit was attached by enolate alkylation and the core was subsequently formed by introduction of a second vinyl group giving triene **50**. Closure of the cyclopentane ring was achieved via ring-closing metathesis (RCM) to obtain compound **51**. Oxidative cleavage of the trisubstituted double bond provided aldehyde **52**, which allowed attachment of the α-chain by a Wittig reaction to furnish ester **53**. The ω-chain was connected by a second Wittig reaction similarly to the synthesis shown in Scheme 10. Final deprotection and mild allylic oxidation by MnO_2 furnished desired (–)-preclavulone A methyl ester **47b** in 15 steps and 22% overall yield from (*S*)-**48**.



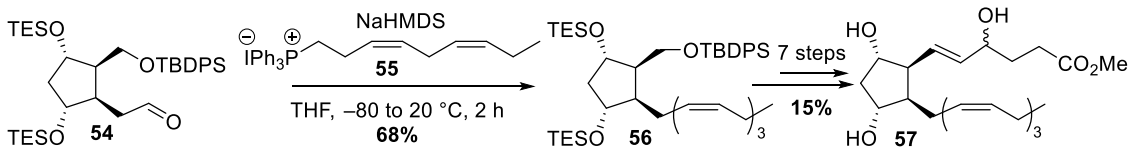
Scheme 11. Total synthesis of (–)-preclavulone A methyl ester **47b** by Ito *et al.*

2.2.2 Existing approaches to the skipped (*Z*)-polyene moiety of NeuroPs

The existing synthetic approaches to NeuroPs rely on synthesis of a properly functionalized cyclopentane core allowing subsequent attachment of one or both side chains.[12, 57, 75] Strategies applied in IsoP and PhytoP syntheses are often applicable to the synthesis of the cyclic intermediate toward NeuroPs. However, finding a proper side chain precursor as well as fitting reaction to connect it to the cyclopentane core is a crucial point in planning NeuroP synthesis. Current strategies can be divided in two major groups: Wittig homologation and other methods.

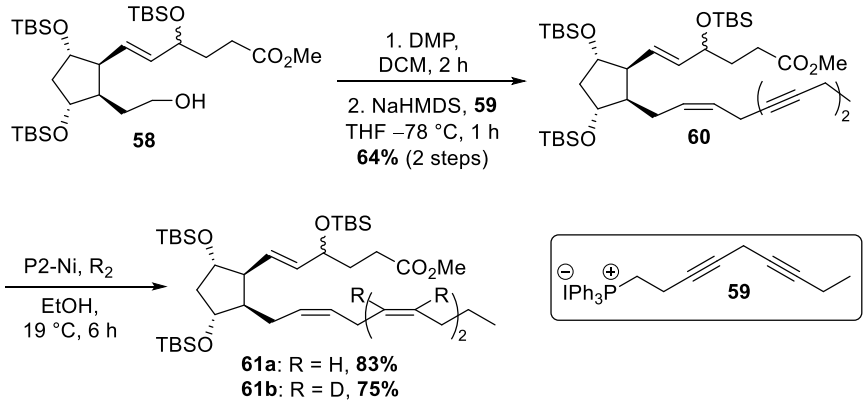
2.2.2.1 Wittig homologation

Wittig olefination using a homoallylic dienyl phosphonium salt is by far the most common strategy applied in NeuroP synthesis, widely used for both α-chain and ω-chain connection. In the first total synthesis of NeuroP reported by Durand *et al*. in 2000, phosphonium salt **55** was employed in Wittig reaction with aldehyde **54** as ω-chain precursor to furnish methyl ester of 4(*RS*)-4-F_{4t}-NeuroP **57** (Scheme 12).[76]



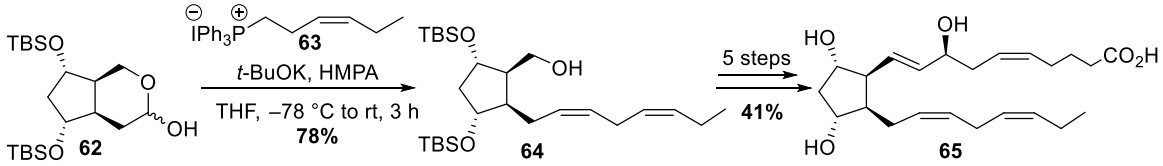
Scheme 12. Synthesis of 4(*RS*)-4-F_{4t}-NeuroP-OMe **57** by Durand et *al.*

In need of a deuterated analogue of this metabolite, Oger *et al.* made use of a skipped diyne phosphonium salt **59** in 2010 (Scheme 13).[77] This allowed subsequent introduction of deuterium or hydrogen atoms by stereoselective semideuteration/semihydrogenation of skipped ene-diyne **60**, respectively, using Brown's P2-nickel catalyst. Recently, three new metabolites, namely 18-F_{3t}-IsoP, 20-F_{4t}-NeuroP and 20-F_{3t}-NeuroP were synthesized by the group using dienyl phosphonium salts as α-chain precursors (not shown).[78]



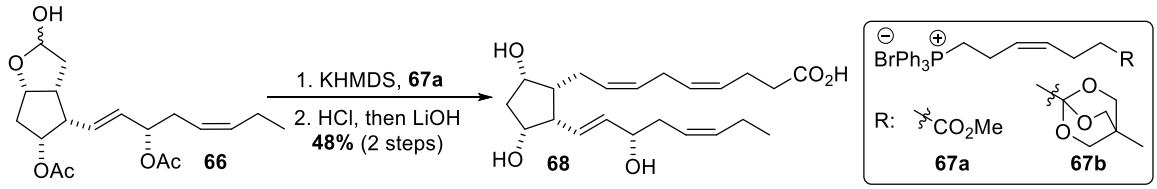
Scheme 13. Approach to 4(*RS*)-4-F_{4t}-NeuroP and its deuterated analogue by Oger *et al.*

Simpler phosphonium salt **63** was needed for reaction with lactol **62** leading to ω-chain construction in the synthesis of 7-F_{4t}-NeuroP reported by Kim *et al.* **65** (Scheme 14).[79]



Scheme 14. Total synthesis of 7-F_{4t}-NeuroP **65** by Kim *et al.*

In both reported syntheses of 17-NeuroP, similar Wittig reactions were employed for α-chain attachement but made use of different protecting groups for the carboxylic acid. Whereas Zanoni *et al.* used methyl ester salt **67a** in their approach (see Scheme 8),[70] Quan and Cha reported better results when using orthoester **67b** in the reaction with lactol **66**; subsequent hydrolysis liberated the carboxylic moiety to provide 17-F_{4c}-NeuroP **68** (Scheme 15).[59, 80]



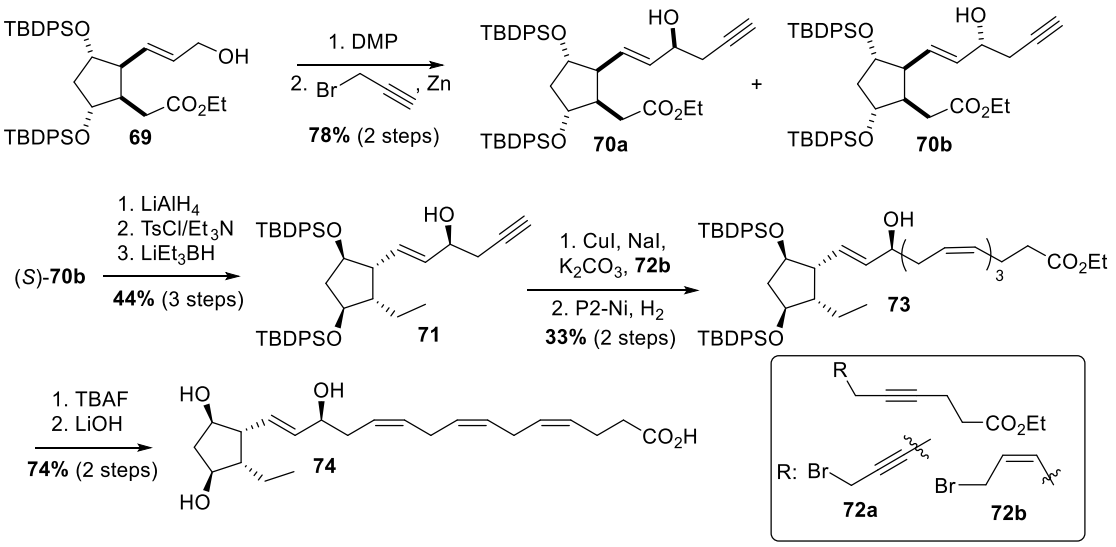
Scheme 15. Final steps of the total synthesis of 17-F_{4c}-NeuroP **68** by Quan and Cha.

It should be noted that phosphonium ylides derived from such homoallylic phosphonium salts are generally only stable at low temperatures.[59, 70, 80] The instability increases when a skipped diene or diyne moiety is already present in the phosphonium salt, such as in **55** or **59** (Scheme 12 and 13).[77, 81, 82] Wittig reactions with the corresponding ylides thus necessitate carefully controlled conditions including low reaction temperatures. This might cause reactivity problems, especially with non-reactive substrates like lactols **62** or **66** (Scheme 14 and 15), which require somewhat higher reaction temperatures up to 0 °C and such reactions are limited to simple allylic phosphonium salts.

2.2.2.2 Other methods

To the best of our knowledge, only two examples of non-Wittig strategy for synthesis of the skipped polyene chain in NeuroPs have been reported. The first one is the synthesis of 13-F_{4t}-NeuroP, which contains all four double bonds in the α-chain. This synthetic challenge was seized by Taber *et al.* who introduced the chain in three fundamental steps (Scheme 16).[83] First, a propargylic unit was connected by a nucleophilic addition of a propargyl zinc to the aldehyde derived from **69** to furnish alkyne **70** as a racemic mixture of diastereomers. The diastereomers were separated and enzymatically resolved into enantiomers using (*R*)-selective acetylation with Amano lipase AK and vinyl acetate (not shown). Secondly, after reducing the ester function, a Cu(I)-mediated coupling of allylic bromide **72b** and enantiopure alkyne (*S*)**-70b** yielded the enyne. Lastly, semihydrogenation using P2-Ni delivered desired tetraene **73**. Coupling with diyne unit **72a** was also performed but subsequent semihydrogenation of the resulting triyne only gave complex product mixtures. Target *ent*-13-*epi*-13-F_{4t}-NeuroP **74** was obtained after final deprotection and saponification. The second example is Zanoni's synthesis of 14-A_4-NeuroP (see Scheme 8) where

the skipped (*Z*)-diene was already in place in the ω-chain synthon and no new (*Z*)-double bond was formed during the key step.[69]



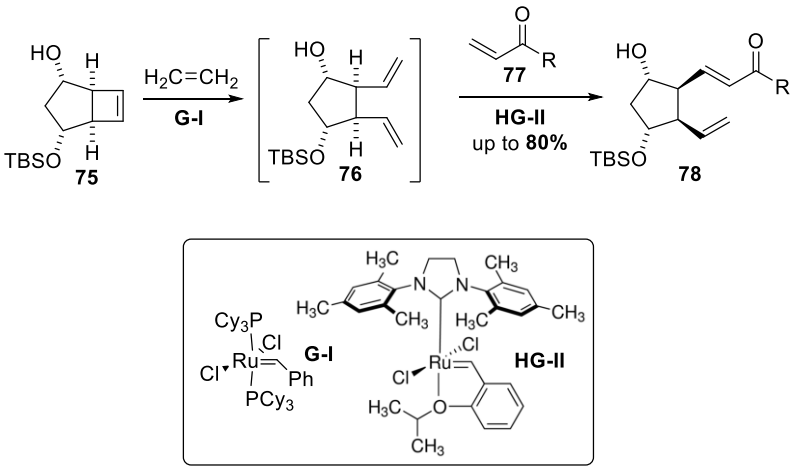
Scheme 16. Synthesis of *ent*-13-*epi*-13-F_{4t}-NeuroP **74** by Taber *et al*.

2.2.3 Cross metathesis in isoprostanoid syntheses

In contrast to the Wittig olefination often used to connect the skipped (*Z*)-polyene side chain, (*E*)-selective olefinations are often employed to construct the (*E*)-hydroxyallylic chain, such as Julia-Lythgoe and Julia-Kociensky olefinations as described in Schemes 5-9, or Horner-Wadsworth-Emmons olefinations used in the majority of other cases. However, these olefinations require basic conditions and epimerization of the α-center to the carbonyl might occur, as well as other side-reactions. Although mild protocols have been developed,[84] there is demand for neutral alternatives. In this respect, transition metal-catalyzed cross metathesis (CM) of olefins is a valuable tool.

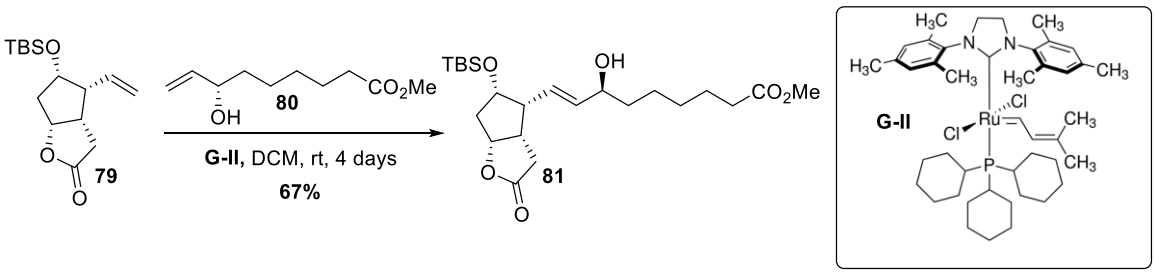
There are two notable applications of this reaction in the isoprostanoid field. The first is the ring-opening metathesis (ROM)/CM approach developed by Snapper *et al.* (Scheme 17). ROM of cyclobutene **75** catalyzed by 1st generation Grubbs catalyst **G-I** performed in an atmosphere of ethylene gas provided monoprotected diene **76**. Subsequent regioselective CM of enone **77** and diene **76** catalyzed by Hoveyda-Grubbs 2nd generation catalyst **HG-II** furnished enones **78** in good yields, leading to the synthesis of a wide range of isoprostanoid metabolites.[85-88]

The second example is the synthesis of 5-F_{3c}-IsoP by Jacobo *et al.* who used metathesis of free allylic alcohol **80** with the terminal double bond of TBS-protected Corey-like lactone **79** (Scheme 18). The reaction was promoted by Grubbs II (**G-II**) to obtain target allylic alcohol **81** in 67% yield.[89] This strategy involving CM of a homallylic silyl ether and an allylic alcohol represents a more direct approach than the one using enones **78**, which needed to be further functionalized. However, it should be noted that in case of Jacobo's IsoP synthesis, stoichiometric amounts of catalyst were required in order to achieve the stated yield.



Scheme 17. ROM/CM approach to isoprostanoids developed by Snapper *et al.*

There are a few more examples involving allylic and homoallylic alcohols or ethers in PG syntheses[90, 91] and one example in PhytoP synthesis,[92] which involved a 2,3-disubstituted cyclopentenone core and a protected allylic alcohol as side chain precursor. Recently, (*Z*)-selective CM approaches were developed and applied to the syntheses of PGs.[93-95]

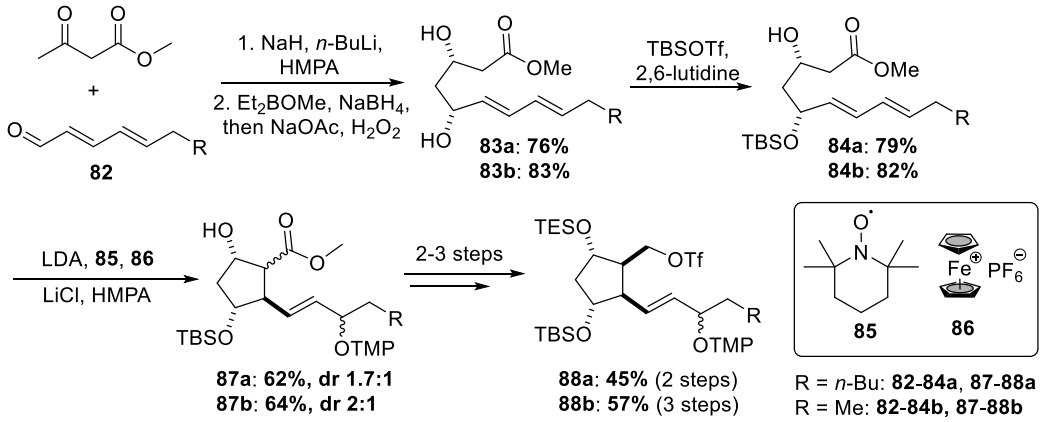


Scheme 18. Cross metathesis in the synthesis of 5-F_{3c}-IsoP by Jacobo *et al.*

2.2.4 Jahn's approach to isoprostanoid synthesis

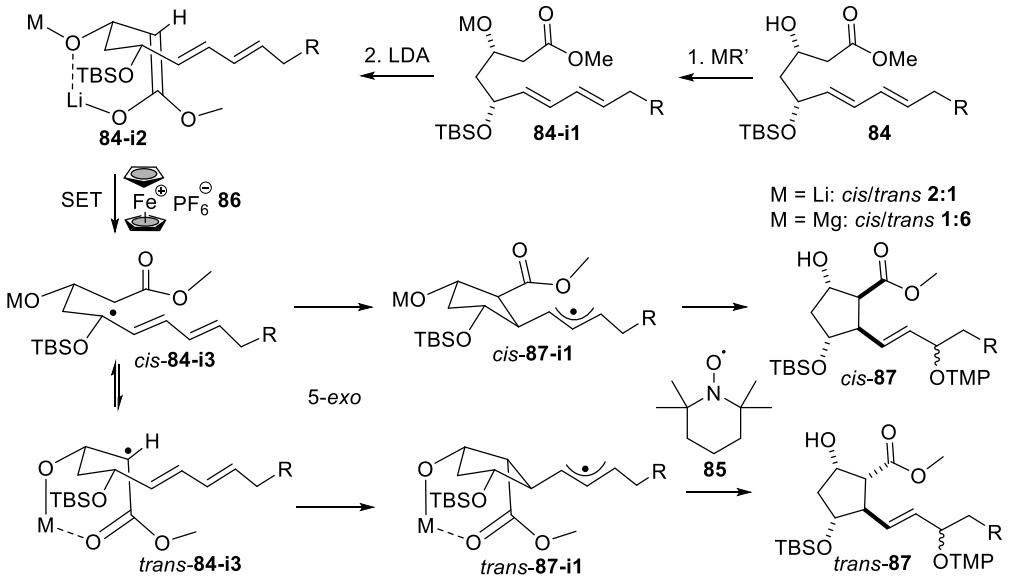
5-*exo* Radical cyclizations are a useful synthetic method to approach *cis*-disubstituted cyclopentanes. In 2002, Jahn, Hartmann *et al.* described a radical oxidative cyclization of β-hydroxyester-derived enolates using single-electron transfer oxidation/radical cyclization/TEMPO-mediated oxygenation sequence furnishing cyclopentanes fittingly functionalized for prostane synthesis.[96] This methodology was later applied to the total synthesis of 15-F_{2t}-IsoP,[97] a potential metabolite of 15-E_{2t}-IsoP[98] and, most recently, 16-PhytoPs.[99]

In both IsoP and PhytoP syntheses, central intermediates **88** were prepared first (Scheme 19). Radical cyclization precursors **84** were synthesized in three steps by an aldol addition of dianion of methyl acetoacetate to aldehydes **82**, *syn*-reduction to give diol **83** and regioselective monosilylation. Subsequent double deprotonation and SET oxidation of the enolate by ferrocenium hexafluorophosphate (**86**) followed by 5-*exo* cyclization and coupling with persistent radical TEMPO (**85**) provided esters **87** in moderate yield and diastereoselectivity. The major diastereomers of the latter were cleanly transformed to triflates **88** in two or three steps, respectively.



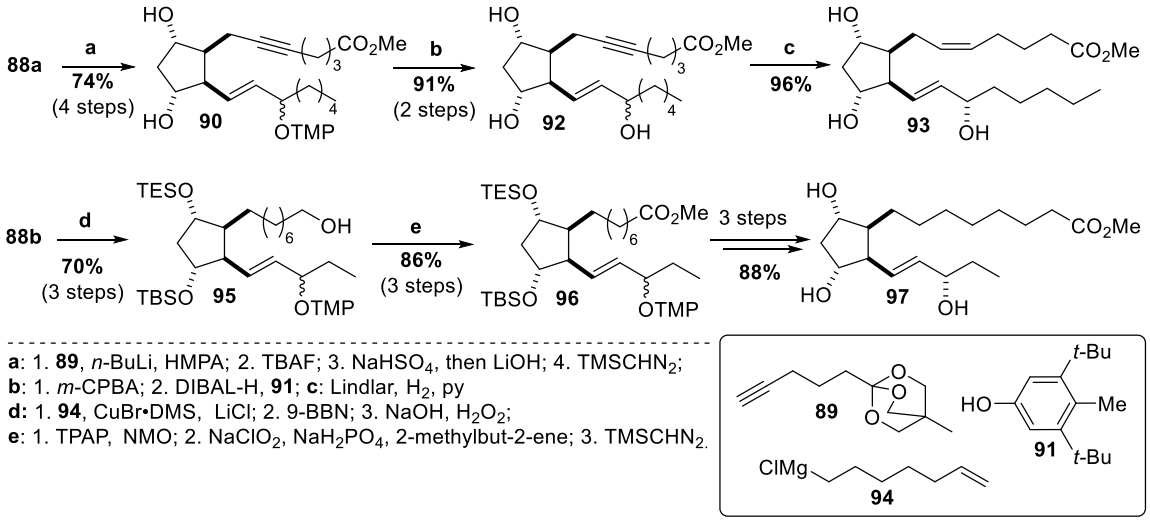
Scheme 19. Synthesis of central precursors **88** by Dinca and Smrček *et al.*

The diastereoselectivity of the key radical cyclization was rationalized as follows (Scheme 20). After SET oxidation of enolate **84-i2**, the resulting radical-anion *cis*-**84-i3** leading to allylic radical *cis*-**87-i1** via a typical Beckwith-Houk type transition state and desired diastereomer *cis*-**87** after radical coupling with **85** is in equilibrium with chelated form *trans*-**84-i3** leading to *trans*-**87**. Use of a non-nucleophilic Grignard reagent and thus a more strongly chelating metal (M = Mg^{2+}) for O-deprotonation indeed inversed the diastereoselectivity of the reaction in favor of *trans*-**87** with up to 6:1 diastereomeric ratio.



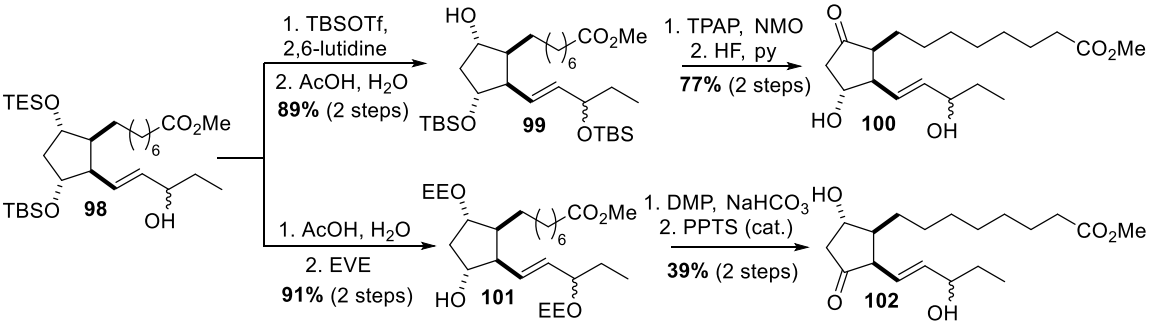
Scheme 20. Proposed rational for the diastereoselectivity of the oxidative dianion radical cyclization.

The second part of the syntheses consisted of attachment of the α-chain units. For IsoP synthesis, alkylation of the lithium acetylide of orthoester **89** by **88a** and semihydrogenation was applied (Scheme 21). In case of PhytoPs, Cu(I)-mediated C(sp3)-C(sp3) coupling of **88b** and Grignard reagent **94** was developed. Further functional group transformations to liberate the hydroxy and ester functions furnished the target compounds. Methyl esters of 15-F_{2t}-IsoP **93** and 16-F_{1t}-PhytoP **97** were hence obtained in 14% and 13% yield over 12 and 15 steps, respectively, along with their C-15 and C-16 epimers (not shown).



Scheme 21. Synthesis of methyl ester of 15-F_{2t}-IsoP **93** and 16-F_{1t}-PhytoP **97** by Dinca and Smrček *et al.*

For the synthesis of PhytoPs, a more unified approach was envisaged and three trioxygenated 16-PhytoPs were synthesized thanks to orthogonal protection (Scheme 22). Methyl ester of 16-E_{1t}-PhytoP **100** was synthesized in 9% over 18 steps as separable mixture of C-16 epimers. The synthesis of 16-D_{1t}-PhytoP-OMe **102** was accomplished for the first time, however, the compound was unstable and attempts of purification resulted in double bond isomerization into conjugation (not shown). With a proper α-chain precursor, this approach should also be suitable for the synthesis of NeuroPs.



Scheme 22. Completion of synthesis of 16-E_{1t}-PhytoP and 16-D_{1t}-PhytoP methyl esters **100** and **102** by Smrček *et al*.

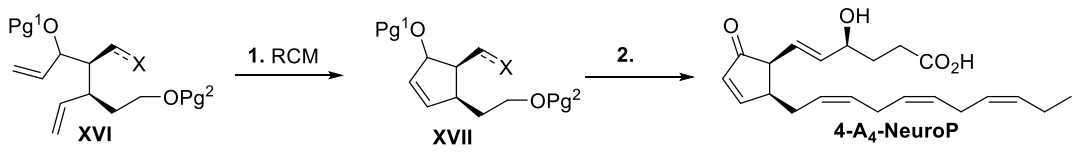
3 AIMS OF THE WORK

Access to pure synthetic material is crucial to bring more insight into the biological role of NeuroPs. To the best of our knowledge, current synthetic approaches are limited to F_4-NeuroPs[76-80, 83] and two syntheses of A-NeuroPs.[69, 70] Among the latter, only the less abundant regioisomers were synthesized to date. There is thus still need for competitive and versatile synthetic strategies to provide access to a pool of individual NeuroPs and other isoprostanoids, especially the molecules that have not yet been synthesized. Along these lines, the aims of this work were defined as follows:

A. To develop a new enantioselective strategy for the synthesis of A- and J-NeuroPs (Scheme 23).

   1. To synthesize a properly functionalized cyclopentene **XVII** based on RCM of enantioenriched precursor **XVI**.

   2. To develop an approach to introduce the side chains and to apply the strategy to the total synthesis of 4-A_4-NeuroP.



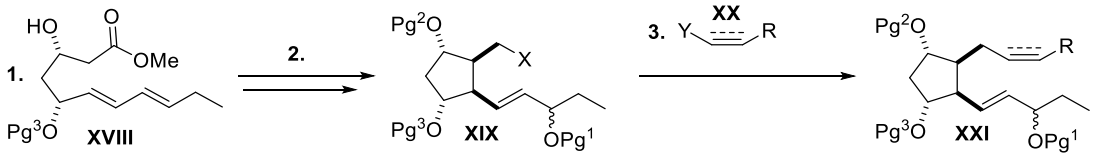
Scheme 23. Envisaged approach to A- and J-NeuroPs.

B. To develop a unified strategy of synthesis of isoprostanoids with 3-hydroxypentenyl ω-chain and a skipped polyene α-chain (Scheme 24).

   1. To provide an asymmetric approach to radical cyclization precursor **XVIII**.

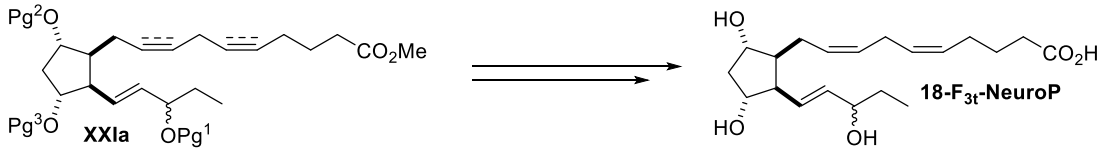
   2. To synthesize a properly functionalized 3-hydroxypentenylcyclopentane **XIX** using the previously developed oxidative dianion cyclization of **XVIII**.[96-99]

   3. To find a suitable C(sp2)-C(sp3) or C(sp)-C(sp3) coupling partner **XX** and conditions for the introduction of the α-chain.



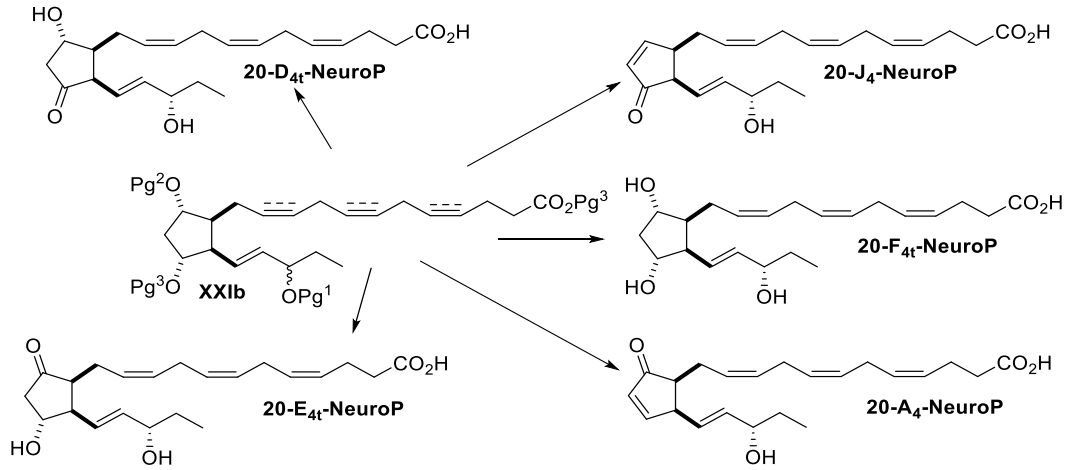
Scheme 24. Envisaged approach to isoprostanoids with 3-hydroxypentenyl ω-chain and a skipped polyene α-chain.

4. To apply the strategy to the total synthesis of 18-F_{3t}-IsoP (Scheme 25).



Scheme 25. Envisaged synthesis of 18-F_{3t}-IsoP.

5. To extend the strategy to 20-NeuroPs (Scheme 26).



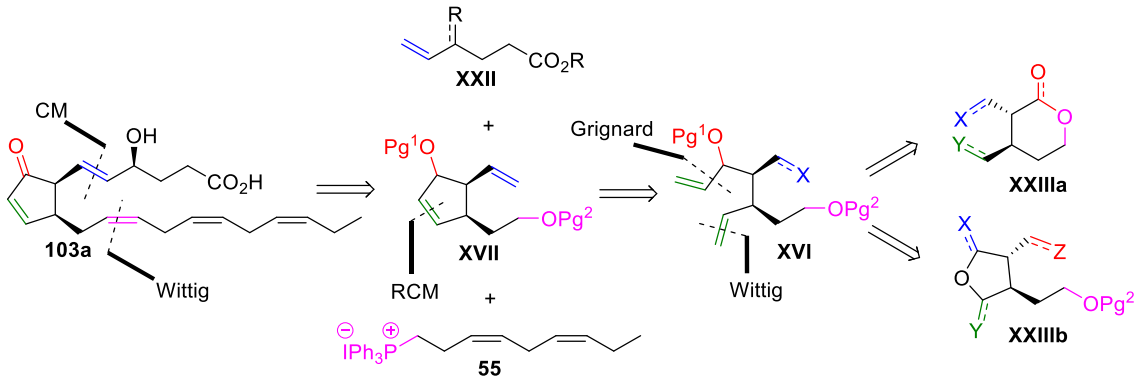
Scheme 26. Envisaged syntheses of 20-NeuroPs.

4 RESULTS AND DISCUSSION

4.1 Toward the total synthesis of cyclopentenone 4-NeuroPs

4.1.1 General retrosynthetic analysis

A general retrosynthetic analysis of target 4-A_4-NeuroP **103a** started with disconnection of the ω-chain, giving phosphonium salt **55** previously used in 4-F_{4t}-NeuroP syntheses (Scheme 27).[76] The second disconnection was envisaged at the *E*-double bond of the α-chain. Synthetically, α-chain would be linked by CM using a properly functionalized precursor **XXII**. The cyclopentene ring of **XVII** would be constructed by RCM, leading to alkene **XVI**. The terminal alkene units in **XVI** should be easily obtained by nucleophilic addition of a vinyl Grignard reagent and Wittig methylenation of **XXIIIa** or **XXIIIb**, where X, Y and Z are orthogonal aldehyde surrogates. Tethering the substituents into a *trans*-substituted six- or five-membered cycle should facilitate the access to the appropriate relative configuration at the two central asymmetric carbon atoms. Three different compounds as synthetic equivalents for synthons **XXIIIa** and **XXIIIb** were proposed and the corresponding synthetic strategies were explored.

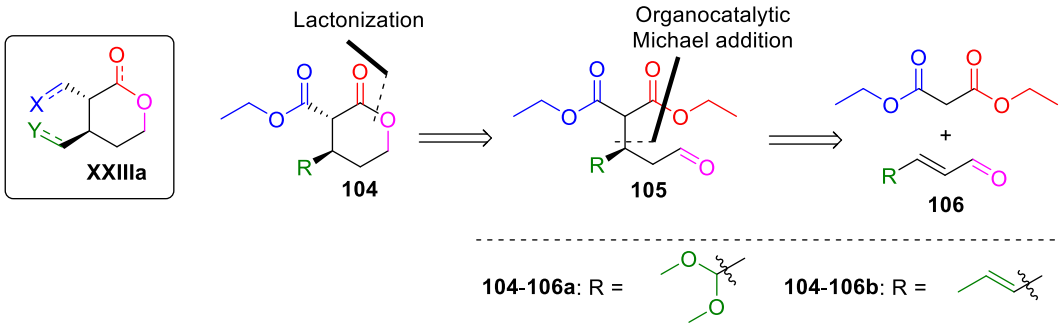


Scheme 27. General retrosynthetic analysis of 4-A_4-NeuroP **103**.

4.1.2 Synthetic strategy I

4.1.2.1 Retrosynthetic analysis

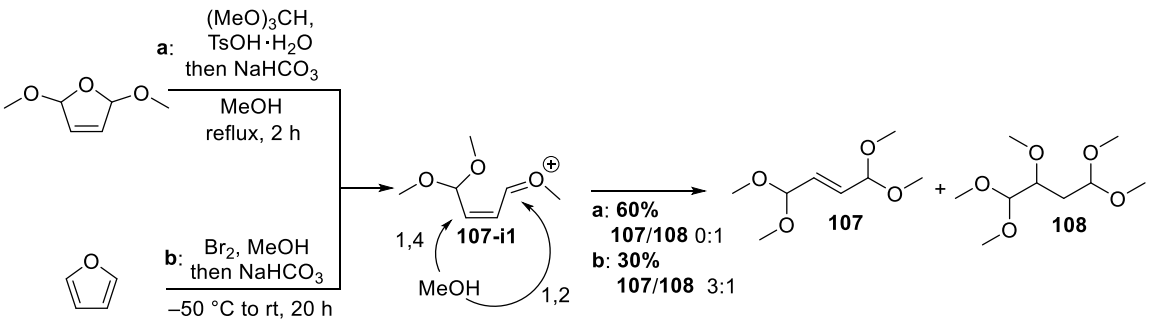
First, lactone **104** was proposed as a synthetic equivalent for synthon **XXIIIa** (Scheme 28). The compound is accessible in two steps from malonate **105**,[100] which can be obtained by Michael addition of diethyl malonate to enal **106**.[101]



Scheme 28. Retrosynthetic analysis of lactone **104**.

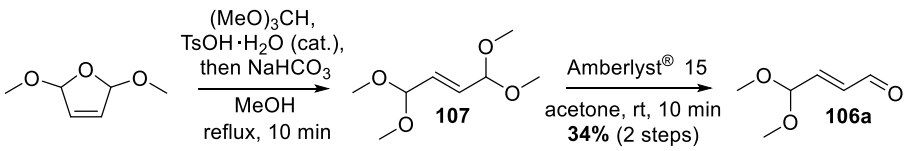
4.1.2.2 Synthesis of aldehyde **105**

Aldehyde **106a** needed for the organocatalytic reaction was synthesized in two steps by a modified published procedure.[102] As the first step, opening of 2,5-dimethoxy-2,5-dihydrofuran to obtain diprotected compound **107** was attempted. When the reaction was carried under conditions described by Weng *et al.*,[101] compound **108** resulting from competitive conjugate attack of methanol on oxonium ion **107-i1** was obtained as the only product in 60% yield (Scheme 29, conditions **a**). When conditions of one-pot furan opening according to Schöning *et al.* were used instead (conditions **b**),[102] mixture of **107** and **108** was formed in an approximately 2:1 ratio. The mixture could be further enriched in **107** after fraction distillation, but some product was lost in mixed fractions and the isolated yield was low (30%, **107**/**108** 3:1).



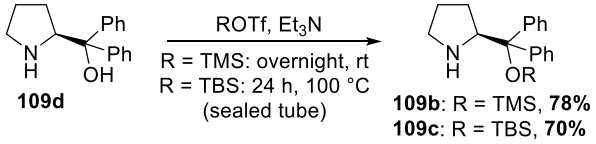
Scheme 29. Synthesis of diprotected enal **107**.

Conditions **a** were optimized by shortening the reaction time significantly and compound **107** was obtained pure enough to be used directly in the next step (Scheme 30). Monodeprotection using Amberlyst® 15 in acetone at room temperature for precisely 10 min afforded enal **106a** in 34% yield over two steps.



Scheme 30. Synthesis of enal **106a**.

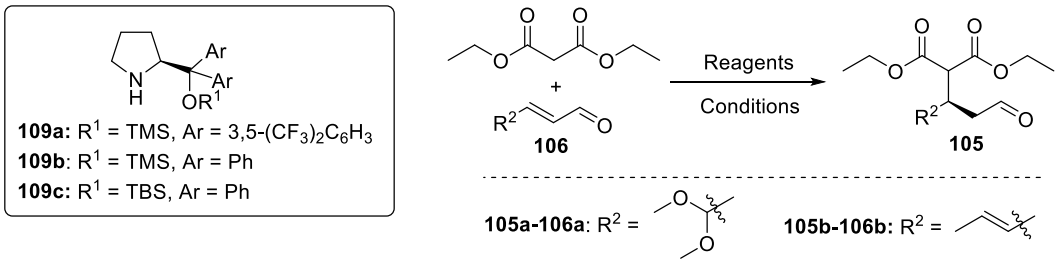
Three different pyrrolidine catalysts were selected for the organocatalytic reaction based on the existing literature and their availability.[101, 103-106] Commercially available Jørgensen catalyst **109a** was used as received whereas Hayashi TMS- and TBS-protected catalysts **109b** and **109c** were prepared from the corresponding alcohol **109d** (Scheme 31).[107]



Scheme 31. Synthesis of Hayashi pyrrolidine catalysts **109b** and **109c**.

Compound *rac*-**105a** was synthesized as racemic standard under known conditions using K_2CO_3 as base and triethylbenzylammonium chloride (TEBAC) as a phase transfer catalyst to provide the target compound in low 31% yield (Table 1, entry 1).[103] Screening of reaction conditions for the key organocatalytic reaction with diethyl malonate by means of iminium catalysis was carried out next. Jørgensen catalyst **109a** with benzoic acid as an additive was previously successful in an addition of acetoacetate in epoxy-IsoP synthesis by Weng *et al.*,[101] but these conditions did not provide the target compound (entry 2). The outcome was the same when the reaction was performed in water and AcOH was used as the acidic co-catalyst instead of benzoic acid (entry 3). Switching to non-fluorinated Hayashi pyrrolidine **109b** with LiOAc as basic additive in DCM/MeOH mixture, the reaction proceeded to full conversion, but **105a** was isolated in low 36% yield (entry 4).[104] The yield increased slightly to 39% when EtOH was applied as solvent in the absence of additive but dropped to 22% when $PhCO_2H$ was added (entries 5 and 6). With TBS-protected pyrrolidine **109c**, benzoic acid/water as additives and stirring 0 °C for 24 h,[105] **105a** was isolated in moderate 47% yield (entry 7). Under the same conditions but with warming to room temperature overnight, full conversion and good 60% isolated yield (40% on larger scale) of **105a** was reached (entry 8).
Synthesis of compound **105b** using commercially available hexadienal **106b** was attempted in analogy to the synthesis of **105a**. Organocatalytic addition of dibenzyl malonate to **106b** was previously reported by Ma *et al.* but the described conditions resulted only in very low 12% yield of **105b** (entry 9),[106] possibly due to polymerization of **106b**. The yield did not improve when TBS-protected catalyst **109c** was employed instead of **109b** (entry 10). Finally, with the previously succesful conditions for the synthesis of **105a**, aldehyde **105b** was obtained in 21% yield (entry 11).[105] Only compound **105a** was used in further development of the strategy because the yield of **105b** remained too low to access it on reasonable scale. Neither the enantiomers of both, **105a** and **105b**, nor further derivatives of **105a** (*vide infra*) were separable by chromatographic methods (GC or HPLC) using a chiral stationary phase despite large variations of separation conditions. The enantiomeric excess of the reaction was thus not determined.

Table 1. Screening of organocatalytic conditions for the synthesis of **105a** and **105b**.

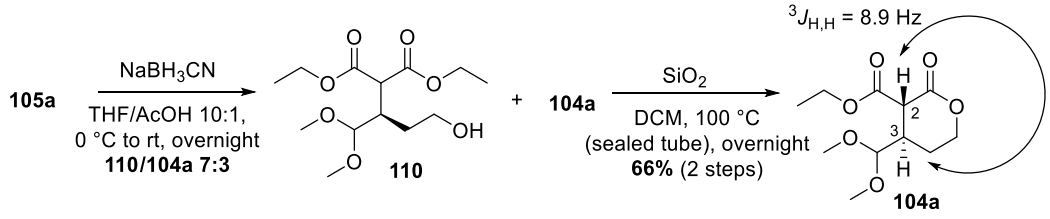


Entry	Substrate	Catalyst	Additive	Solvent	Conditions	**105** (%)[a]
1	**106a**	-	K_2CO_3, TEBAC	toluene	45 °C, 4 h	31[b]
2	**106a**	**109a**	$PhCO_2H$	toluene	rt[c]	0
3	**106a**	**109a**	AcOH	H_2O	rt[c]	0
4	**106a**	**109b**	LiOAc	DCM/MeOH 10:1	rt, 5 days	36
5	**106a**	**109b**	-	EtOH	rt, 5 days	39
6	**106a**	**109b**	$PhCO_2H$	EtOH	0 °C, 24 h	22
7	**106a**	**109c**	$PhCO_2H$, H_2O	EtOH	0 °C, 24 h	47
8	**106a**	**109c**	$PhCO_2H$, H_2O	EtOH	0 °C to rt[c]	60[d]
9	**106b**	**109b**	AcOH	H_2O	0 °C to rt[c]	12
10	**106b**	**109c**	AcOH	H_2O	0 °C to rt[c]	8
11	**106b**	**109c**	$PhCO_2H$, H_2O	EtOH	0 °C to rt[c]	21

[a] Yied of **105a** for entries 1-8, yield of **105b** for entries 9-11. [b] Yield of *rac*-**105a**. [c] Stirred overnight. [d] 40% yield at 5 mmol scale.

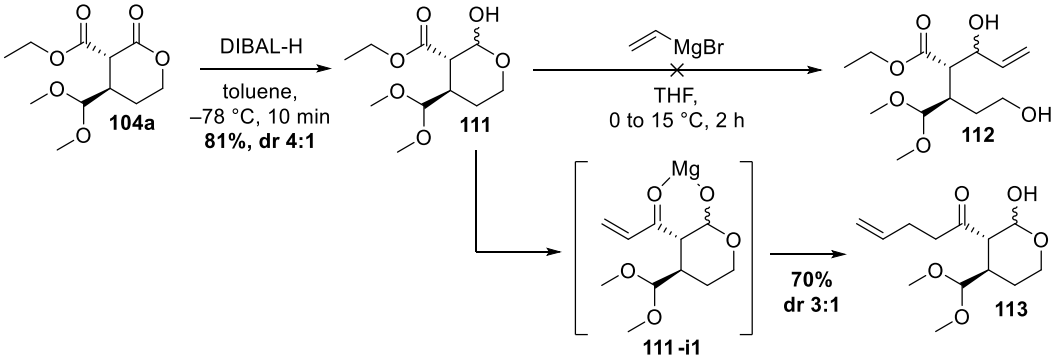
4.1.2.3 Synthesis and functionalization of lactone **104a**

To achieve desymmetrization of malonate **105a**, the aldehyde was reduced to alcohol **110** with $NaBH_3CN$ and subsequently cyclized to lactone **104a** using silica gel in DCM (Scheme 32).[100] Partial cyclization to lactone **104a** occurred under the reduction conditions. The desired product was obtained as a single diastereomer with 66% yield over two steps. The relative stereochemistry at C-2 and C-3 of the lactone ring was assigned as *trans* according to the large coupling constants of the corresponding protons in ^{1}H NMR spectroscopy ($^3J_{H,H}$ = 8.9 Hz).



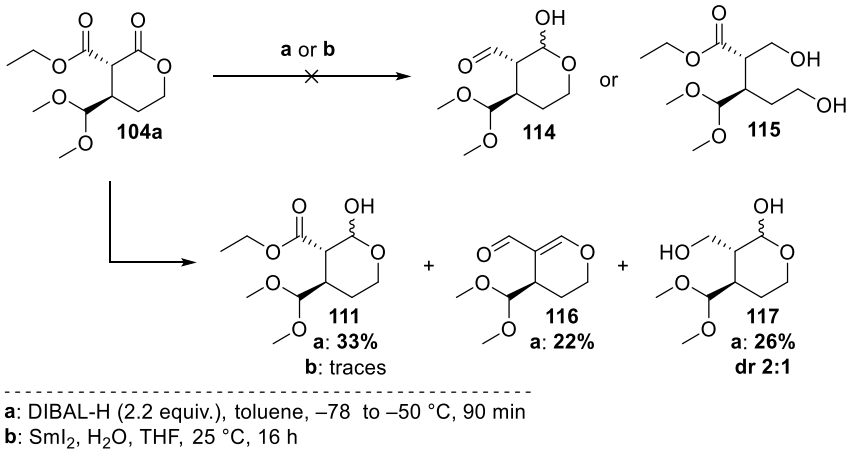
Scheme 32. Synthesis of lactone **104a**.

Subsequently, several potentially chemoselective transformations of **104a** were examined. First, the lactone was cleanly reduced with 1.2 equivalents of DIBAL-H to give lactol **111** with 81% yield (Scheme 33). The latter was subjected to reaction with excess of vinylmagnesium bromide, but lactol opening to diol **112** never occurred under the conditions. Instead, an unusual double attack at the ethyl ester function took place: 1,2-addition gave enone intermediate **111-i1** after collapse of the tetrahedral intermediate followed by 1,4-addition to furnish γ,δ-unsaturated ketone **113** with 70% crude yield after work-up. Decreasing the excess of reagent only influenced the **113/111** ratio, but other products were not isolated.



Scheme 33. Synthesis of lactol **111** and addition of vinylmagnesium bromide.

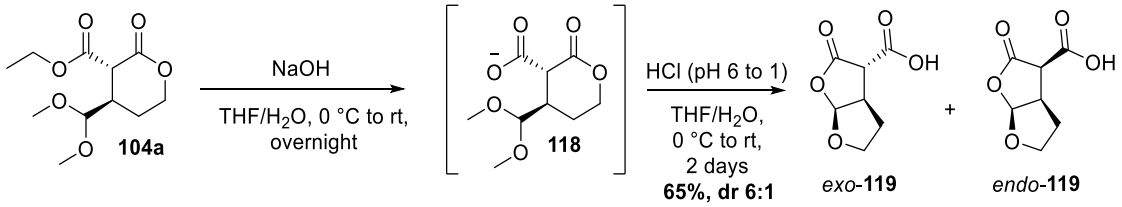
Reduction of **104a** with excess of DIBAL-H (2.2 equiv.) led to a mixture of products **111**, **116** and **117** without particular selectivity instead of desired aldehyde **114** (Scheme 34, conditions **a**). Applying SmI_2/H_2O-mediated chemoselective reduction did not afford pseudosymmetric 1,5-diol **115**.[108] Instead, lactone **104a** was reduced only partially to lactol **111** and mostly remained intact under the conditions.



Scheme 34. Further reductive tranformations of lactone **104a**.

Another option for a selective transformation of **104a** was saponification of the ethyl ester moiety in the presence of the lactone unit. Under typical saponification conditions (NaOH in THF/water), full consumption of the starting material was indicated by thin-layer chromatography suggesting formation of carboxylate salt **118** (Scheme 35) but the acidification step to isolate the corresponding

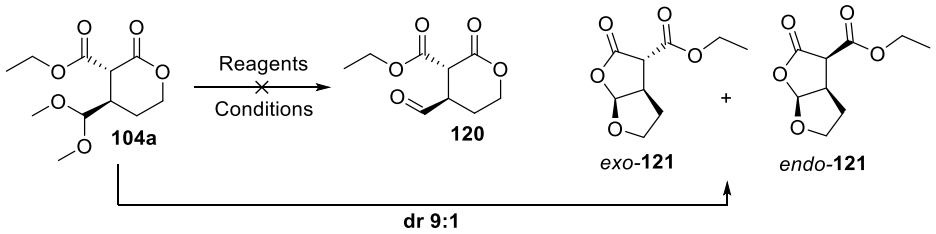
free carboxylic acid was problematic. When the reaction mixture was acidified to pH >4 or extracted immediately after acidification, no organic material was recovered after successive extractions of the reaction media with EtOAc and evaporation of the organic phase. After a night of stirring at pH 1, extractions delivered a single compound as 6:1 mixture of diastereomers, whose analytical data did not correspond to the desired product and the structure was assigned as **119**, obtained in 65% crude yield. The relative configuration of the major diastereomer was assigned as *exo* by analogy to the corresponding ethyl ester (*vide infra*). Attempts of enzymatic ester hydrolysis using CALB only recovered starting material **104a**.[72]



Scheme 35. Saponification of compound **104a**.

To explore if the transacetalization could be avoided, selective deprotection of the dimethyl acetal moiety to obtain aldehyde **120** was attempted. With $TsOH \cdot H_2O$, Amberlyst® 15 in aqueous acetone or aqueous acetic acid in water at room temperature, no reaction took place (Table 2, entries 1-3).[109, 110] When Amberlyst® 15 in refluxing acetone was used, the reaction cleanly provided compound **121** with a similar structure to **119** but with the ethyl ester intact, in 83% yield as 9:1 mixture of diastereoisomers (entry 4).[111] The proposed *exo*-configuration of the major diastereomer was confirmed by ROESY experiments (see the Experimental section). Acetal **121** was also obtained as a single product after the reaction of **104a** with 1M HCl in THF although with lower 52% yield (entry 5). Deprotection attempts in the presence of $Bi(NO_3)_3 \cdot 5H_2O$, a weak Lewis acid, also furnished compound **121** as the major product, accompanied by a small fraction of the starting material after stirring for 3.5 h (entry 6).[112] Indium(III) triflate gave a similar result albeit with only 50% conversion (entry 7).[113] No reaction took place with TESOTf in the presence of 2,6-lutidine (entry 8).[114]

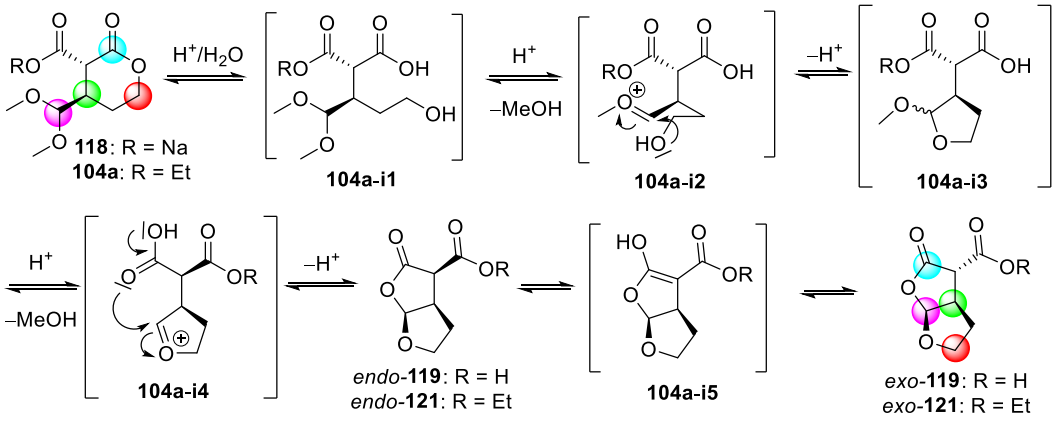
Table 2. Transacetalization of lactone **104a**.



Entry	Reagent	Solvent	Conditions	**121** (%)
1	$TsOH \cdot H_2O$	acetone/H_2O 10:1	0 °C to rt, 2 h	0
2	Amberlyst® 15	acetone/H_2O 10:1	0 °C to rt, 2 h	0
3	AcOH	AcOH/H_2O 2:1	0 °C to rt, 3 days	0
4	Amberlyst® 15	acetone/H_2O 10:1	reflux, overnight	83[a]
5	HCl 1M	THF/H_2O 1:2	0 °C to rt, 16 h	52[a]
6	$Bi(NO_3)_3 \cdot 5H_2O$	DCM	0 °C to rt, 3.5 h	86[b]
7	$In(OTf)_3$	acetone	0 °C to rt, 3.5 h	50[b]
8	TESOTf, 2,6-lutidine	DCM	0 °C to rt, 16 h	0

[a] Isolated yield. [b] Conversion of **104a** based on ^{1}H NMR analysis of the crude mixture.

A mechanism for the reaction of **118** and **104a** with acid leading to compounds **119** and **121**, respectively, via a series of equilibrium reactions was proposed (Scheme 36). First, lactone opening under protic conditions gives free alcohol **104a-i1**. Subsequent hydrolysis of the dimethyl acetal moiety leads to oxycarbenium ion **104a-i2**, which provides mixed acetal **104a-i3** by a 5-*exo* cyclization. Protonation and elimination of MeOH forms second oxycarbenium ion **104a-i4**, which is attacked by the oxygen atom of the carboxylic acid moiety in another 5-*exo* cyclization. Resulting products *endo*-**119** and *endo*-**121** can equilibrate via enol **104a-i5** under the acidic reaction conditions to furnish the major diastereomers *exo*-**119** and *exo*-**121**. It should be noted that for **118**, the malonic acid unit is symmetrical for intermediates **104a-i1-i4** (R = H) and the second 5-*exo* cyclization can lead directly to thermodynamically favored *exo*-**119**. At this point, the strategy was abandoned, as lactone **104a** was not a suitable synthetic equivalent of **XXIIIa** (see Scheme 28).

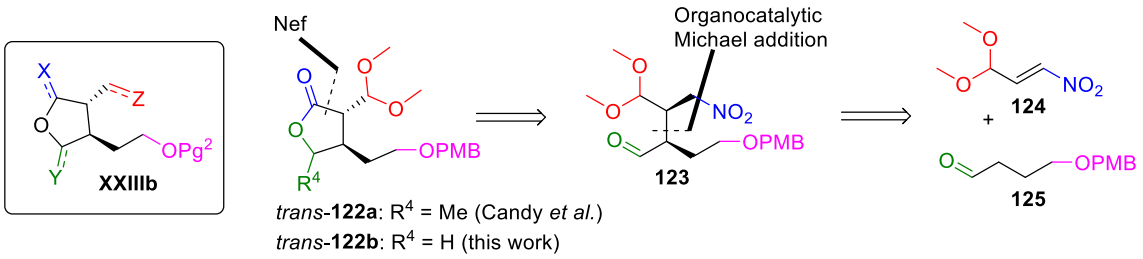


Scheme 36. Proposed mechanism of formation of bicyclic acetals **119** and **121** from **118** and **104a**, respectively.

4.1.3 Synthetic strategy II

4.1.3.1 Retrosynthetic analysis

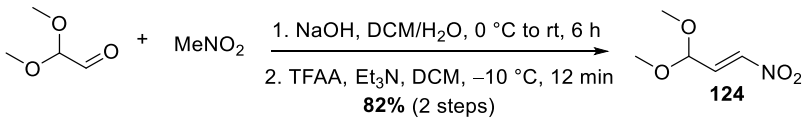
Lactone *trans*-**122b** was envisaged as a synthetic equivalent of **XXIIIb** (Scheme 37). Similar compound *trans*-**122a** was previously synthesized by Candy *et al.* and used successfully in the total synthesis of an isoketal, a different type of AA metabolite.[115] Lactone *trans*-**122b** can be easily reached from aldehyde **123** via oxidative Nef reaction. Control of the absolute stereochemistry is achieved by a disconnection of **123** leading to nitroolefin **124** and protected aldehyde **125**, which can be joined by the means of asymmetric organocatalyzed Michael addition.



Scheme 37. Retrosynthetic analysis of lactone *trans*-**122b**.

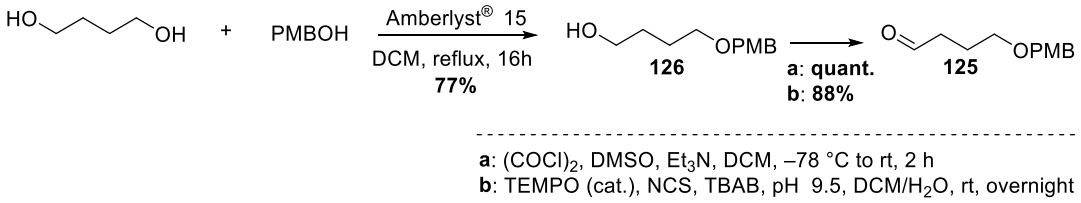
*4.1.3.2 Synthesis of lactone trans-**122b***

Synthesis of lactone *trans*-**122b** started with preparation of the starting materials **124** and **125**. Nitroolefin **124** was prepared by Henry reaction of nitromethane and glyoxal dimethyl acetal in a biphasic water/DCM solvent system followed by dehydration using trifluoroacetic acid anhydride (TFAA) in the presence of Et_3N in 82% yield over 2 steps (Scheme 38).[116]



Scheme 38. Synthesis of nitroolefin **124**.

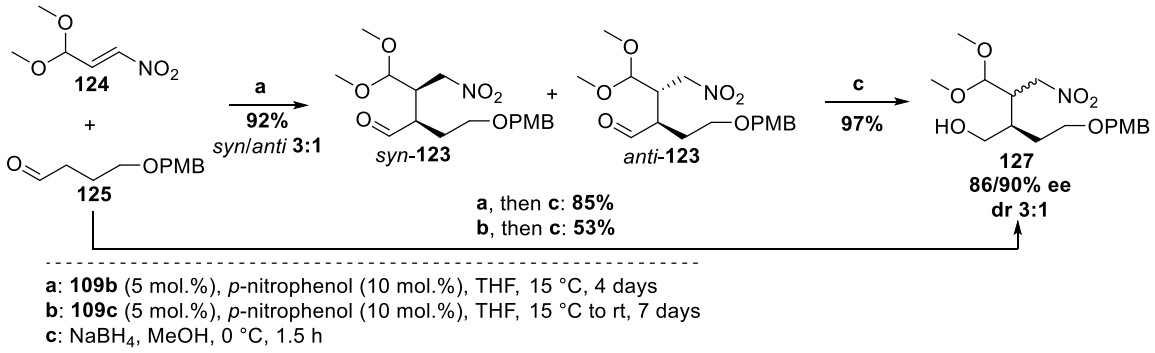
Protected aldehyde **125** was synthesized by a two-step procedure starting with monoprotection of butanediol by the PMB group in the presence of acidic ion exchange resin Amberlyst®15 (Scheme 39).[117] In contrast to the published conditions, butane-1,4-diol was used in excess instead of PMBOH. Both protocols gave the same 77% yield of monoprotected diol **126** but the chromatographic separation of excess butane-1,4-diol from **126** was easier on multigram scale. Obtained alcohol **126** was oxidized by the Swern reaction, providing the desired aldehyde **125** in quantitative yield (conditions **a**). TEMPO-catalyzed oxidation as an odourless alternative provided **125** in somewhat lower 88% yield after the chromatographic separation of the **125**/TEMPO mixture (conditions **b**). Crude aldehyde resulting from applying conditions **a** did not require further purification and was used directly in the subsequent organocatalytic reaction.



Scheme 39. Synthesis of aldehyde **125**.

In the previously reported asymmetric organocatalytic Michael addition of **125** to **124**, Hayashi pyrrolidine **109b** was successfully used as catalyst.[115] In order to miniamize the risk of TMS deprotection during storage, which would result in free alcohol **109d** acting as catalyst instead of **109b** and possibly compromising the enantioselecivity,[118] pyrrolidine **109b** was preferably freshly prepared from **109d** (see Scheme 31). For the same reason, its TBS-protected analogue **109c** offering higher stability was also tested.

The organocatalytic Michael addition was first carried out as previously reported (Scheme 40).[115] Mixing **124** and **125** with 5 mol.% of **109b**, 10 mol.% of *p*-nitrophenol and stirring in THF for four days at 15 °C furnished desired aldehyde **123** in 92% yield and 3:1 *syn*/*anti*-**123** ratio. Aldehyde **123** was subsequently reduced to alcohol **127** in almost quantitative yield. A one-pot Michael addition/reduction delivered alcohol **127** directly from **124** and **125** without isolation of **123** albeit in a slightly lower yield then the two-step protocol. When bulkier TBS-protected catalyst **109c** was used instead of **109b**, the reaction slowed down significantly, in accordance to the original report by Hayashi *et al.*,[107] and the conversion was not complete even after stirring for seven days at room temperature, decreasing the yield of **127** to 53%. Moreover, the latter was inseparable from alcohol **126** resulting from the *in situ* reduction of unreacted aldehyde **125**. The conventional Hayashi pyrrolidine **109b** thus remained the catalyst of choice.

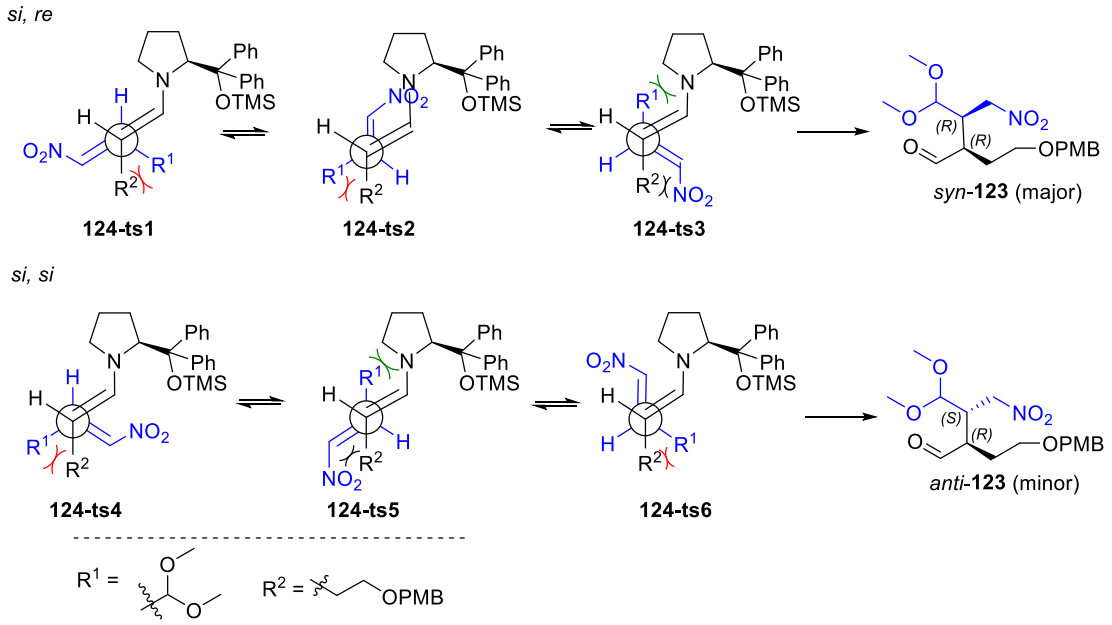


Scheme 40. Synthesis of alcohol **127**.

The enantioselectivity of the organocatalytic reaction was verified by supercritical fluid chromatography (SFC) using a chiral stationary phase after derivatization of **127** and was in good agreement with the previous report (86% ee for *syn*-**127** and 90% ee for *anti*-**127** versus 90% ee for both diastereomers[115]). This result was sufficient for the purpose of preliminary biological studies and use as analytical standard. Therefore, the reaction conditions were not further optimized.

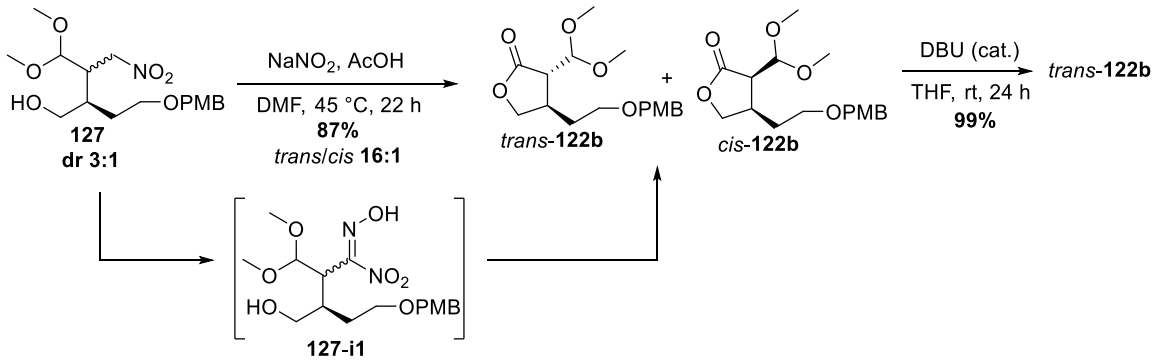
The observed diastereoselectivity can be rationalized with regard to the six depicted transition states (Scheme 41). Only *si*-face attack of the most stable s-*trans* enamine conformation to the *re*-face

(**124-ts1**-**ts3**) or *si*-face (**124-ts4**-**ts6**) of nitroolefin **124** has to be taken into account.[119] If R^1 is planar, the bulkiness of R^2 is the major factor to be considered, as only minor interactions between R^1 and R^2 are expected. The calculations for reactions of nitrostyrenes thus clearly favor transition state analogous to **124-ts2** leading to *syn*-adducts over the one corresponding to **124-ts4**, which is higher in energy and leads to the corresponding *anti*-adducts.[120] This is in agreement with the experimental observation as this well documented transformation ussually proceeds with high level of diastereoselectivity.[107] However, the diastereoselectivity drops for nitroolefins C(sp3)-hybridized at R^1, especially branched ones,[121] due the clash between R^1 and R^2 (depicted in red), which is no longer negligible. Besides, in the reaction of **124** and **125** catalyzed by **109b**, the steric and electrostatic repulsion between the electron-rich dimethyl acetal R^1 and the pyrrolidine moiety (depicted in green) should also be considered for **124-ts3** and **124-ts5**. Overall, for the reaction of **124** and **125**, the situation becomes more ambiguous as the transitions states, especially **124-ts1**, **124-ts2**, **124-ts4** and **124-ts6**, are possibly close in energy, which explains the moderate *syn*-selectivity.



Scheme 41. Transition states of the pyrrolidine-catalyzed Michael addition of **125** to **124**.

Nonetheless, the low diastereoselectivity was overcome in the following steps. The 3:1 diastereomeric mixture of alcohol **127** was subjected to an oxidative Nef reaction under Mioskowski's conditions[122] to yield lactone **122b** via nitrolic acid intermediate **127-i1** (Scheme 42). The diastereomeric ratio shifted significantly under the conditions in favor of desired isomer *trans*-**122b** furnishing partially separable 16:1 *trans*/*cis*-**122b** mixture. Moreover, subjecting the diastereomeric mixture **122b** to a catalytic amount of DBU permitted thermodynamic equilibration to further increase the *trans*/*cis*-**122b** ratio to more than 20:1, furnishing lactone *trans*-**122b** in 86% yield over two steps. The whole reaction sequence from the commercially available starting materials to *trans*-**122b** proceeded in analogy to the previous report and was routinely performed on multigram scale with well reproducible results.[115]

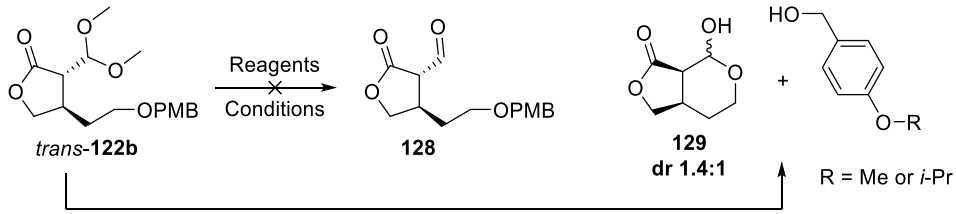


Scheme 42. Synthesis of lactone *trans*-**122b**.

4.1.3.3 Attempts of functionalization of the dimethyl acetal

Next, deprotection of the dimethyl acetal to obtain α-carbonyl lactone **128** was attempted. Applying some common conditions including AcOH/water,[110] Amberlyst® 15[111] or $TsOH \cdot H_2O$[109] in refluxing acetone recovered starting material *trans*-**122b** (Table 3, entries 1-3). Under stronger acidic conditions (10% aqueous HCl in acetone), the PMB group was partially cleaved to give an inseparable mixture of starting material *trans*-**122b**, lactol **129** and PMBOH (entry 4) with 37% conversion and 12% isolated yield of **129** as calculated from the inseparable mixture by ^{1}H NMR spectroscopy. Employing aqueous AcOH as solvent and adding a catalytic amount of HCl to the mixture, which was subsequently gradually heated to 45 °C, reaction proceeded in full conversion and **129**/PMBOH mixture was obtained with calculated 12% yield of **129** (entry 5).

Table 3. Selected attempts for dimethyl acetal deprotection of *trans*-**122b**.

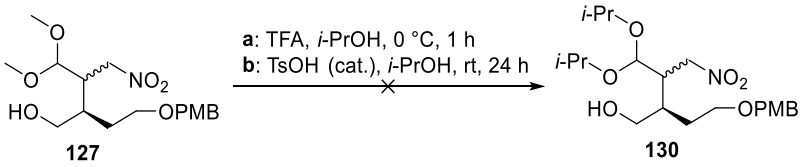


Entry	Reagent	Solvent	Temperature	Time	Conversion (%)[a]	**129** (%)[b]
1	AcOH	AcOH/H_2O 2:1	rt	16 h	0[c]	-
2	Amberlyst® 15	acetone/H_2O	reflux	2 h	0[c]	-
3	$TsOH \cdot H_2O$	acetone	reflux	1.5 h	0[c]	-
4	HCl (10%)	acetone	rt	16 h	37	12
5	HCl (cat.)	AcOH/H_2O 4:1	rt to 45 °C	8 h	100	22
6	TFA (80%)	H_2O	0 °C	1 h	0[d]	-
7	I_2 (cat.)	acetone	rt	2 h	37	15
8	$TsOH \cdot H_2O$	*i*-PrOH	rt to reflux	25 h	100	30
9	TFA	*i*-PrOH	0 °C	1 h	100[e]	0

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Yield calculated from isolated inseparable mixture of *trans*-**122b**/**129**/corresponding benzyl alcohol based on ^{1}H NMR spectroscopy. [c] Fully recovered *trans*-**122b** [d] Recovered *trans*-**122b** + degradation. [e] Degradation only.

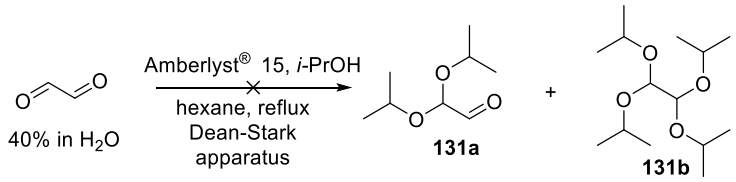
Using trifluoroacetic acid (TFA, 80%) in water recovered lactone *trans*-**122b** along with some unidentified degradation products (entry 6). Catalytic iodine in dry acetone resulted in partial dimethyl acetal deprotection along with deprotection of PMB and furnished lactol **129** with 37% conversion of *trans*-**122b** and 15% yield (entry 7).[123] A variety of other reagents including Lewis acids were also tested with similar outcomes: strong Lewis acids resulted in degradation of starting material *trans*-**122b** whereas it remained intact in the presence of weak Lewis acids (not shown).[112-114, 124]

An attempt of transacetalization of *trans*-**122b** to the corresponding diisopropyl acetal (not shown) by $TsOH \cdot H_2O$ in *i*-PrOH resulted in full conversion of *trans*-**122b** and lactol **129** was obtained in 30% yield along with *p*-isopropoxybenzylalcohol (entry 8). When TFA in i-PrOH was used, only full degradation of *trans*-**122b** was observed (entry 9). To summarize, dimethyl acetal *trans*-**122b** was particularly unreactive under most conditions for deprotection, which only occurred along with PMB hydrolysis and was driven by the subsequent cyclization. The transacetalization conditions were also applied to alcohol **127** (Scheme 43) but only corresponding lactol (conditions **a**) or cyclic acetal (conditions **b**) were obtained as main products (not shown) instead of diisopropyl acetal **130**.



Scheme 43. Attempts of transacetalization of alcohol **127**

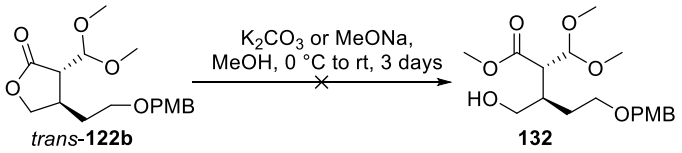
A last effort in this direction consisted of exchanging the dimethyl acetal protecting group from the very beginning of the synthesis, but different acetals of glyoxal such as **131a** are not commercially available. The isopropyl acetal **131a** has scarcely been used, but its synthesis from glyoxal is described in the literature.[125] In the attempt to reproduce the published procedure, viscous material possibly containing polymers and only trace amounts of desired product **131a** and corresponding tetraisopropyl acetal **131b** were obtained after simple evaporation of the crude mixture (Scheme 44). Neither of the products could be isolated by subsequent vacuum distillation.



Scheme 44. Attempted preparation of glyoxal diisopropyl acetal **131a**.

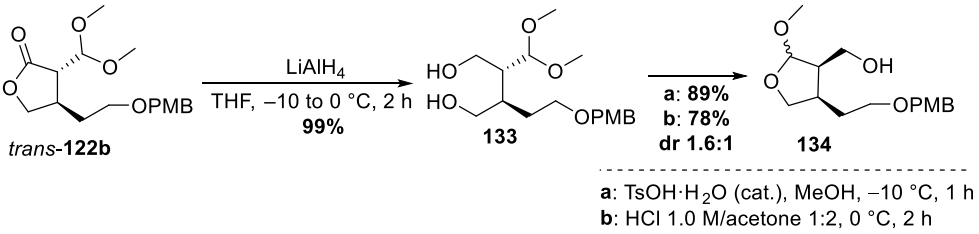
4.1.3.4 Synthesis of lactol **138**

A second approach to the functionalization of *trans*-**122b** consisted of lactone opening, hypothesizing that he dimethyl acetal deprotection might become easier on an acyclic, less conformationally restrained intermediate. First, base-catalyzed transesterification of *trans*-**122b** by MeOH to yield methyl ester **132** was attempted, but the reaction only resulted in full recovery of the starting material (Scheme 45).



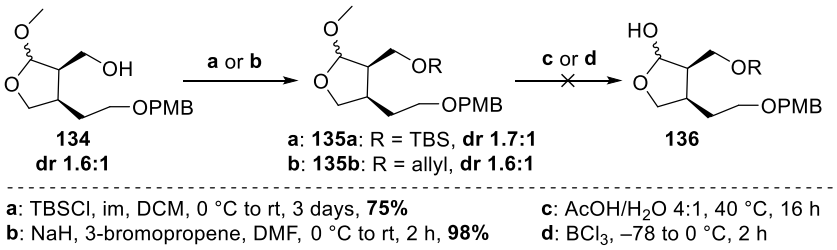
Scheme 45. Attempted transesterification of lactone *trans*-**122b**.

In contrast, reductive lactone opening using $LiAlH_4$ proceeded smoothly to afford diol **133** in quantitative yield (Scheme 46). Because of the pseudosymmetric nature of diol **133**, an intramolecular transacetalization was a suitable alternative of a protecting group as only one of the free hydroxy groups could cyclize to give the corresponding five-membered acetal, ensuring complete regioselectivity. Mixed acetal **134** was indeed obtained in very good 89% yield as 1.6:1 mixture of diastereomers after treating diol **133** with catalytic $TsOH \cdot H_2O$ in MeOH (conditions **a**). HCl (1.0 M) in acetone gave **134** with a slightly lower 78% yield (conditions **b**).



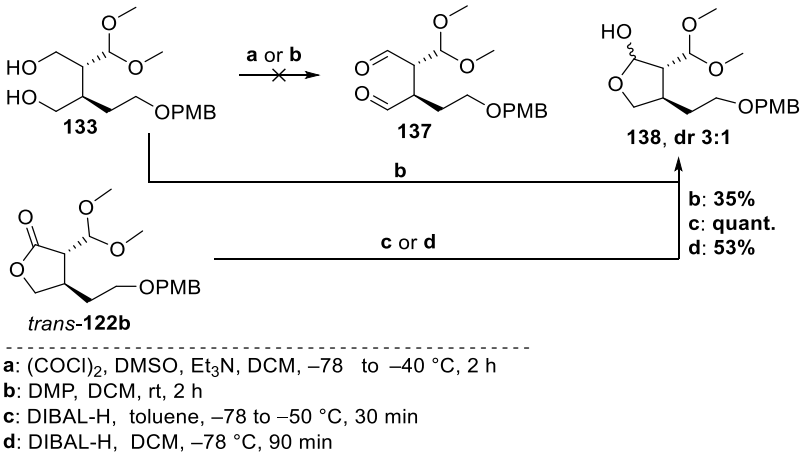
Scheme 46. Synthesis of mixed acetal **134**.

The remaining hydroxy group was subsequently protected by a TBS or allyl group with good yields of **135a** (Scheme 47, conditions **a**) or **135b** (conditions **b**), respectively. However, treating the mixed acetals with $AcOH/H_2O$ (conditions **c**) or BCl_3 (conditions **d**) did not give lactol **136**, but only PMB deprotection and degradation was observed.



Scheme 47. Synthesis of mixed acetals **135** and attempted lactol liberation.

Oxidation of diol **133** to 1,4-dialdehyde **137** was attempted next (Scheme 48). Whereas Swern oxidation gave a complex mixture of polar products, use of DMP resulted in non-selective oxidation to provide lactol **138** in 35% yield as inseparable 1:1 mixture with its corresponding regioisomer (not shown). Lactol **138** as an intermediate in lactone opening was prepared selectively by partial reduction of *trans*-**122b** using DIBAL-H in toluene at low temperature in quantitative yield. The conversion decreased when the reaction was performed in DCM, causing the yield to drop to 53%.

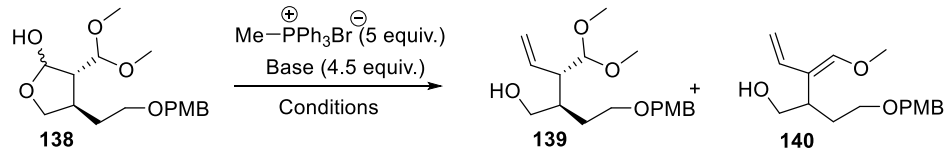


Scheme 48. Synthesis of lactol **138**.

4.1.3.5 Wittig methylenation of lactol **138**

Wittig methylenation of **138**, which would later serve to introduce the α-chain by CM, proved to be particularly challenging. First, a screening of base, solvent and temperature was performed. Both tested lithium-based reagents, *n*-BuLi and LDA, were ineffective (Table 4, entries 1 and 2) despite the bright yellow color of the reaction mixture, which persisted after addition of **138**, indicating that the corresponding phosphonium ylide formed properly. The same outcome was observed with NaHMDS as base in THF (entry 3). The reaction using potassium *tert*-butoxide in THF proceeded swiftly to full conversion, but desired alkene **139** was accompanied by racemic enol ether **140** in a roughly 1:1 molar ratio, providing the desired compound with poor 40% isolated yield (entry 4). KHMDS in THF was even less effective, resulting both in low 45% conversion and inferior **139**/**140** ratio (entry 5). In contrast, full conversion was reached when the same base was used in toluene at room temperature (entry 6), but the **139**/**140** ratio remained poor. Finally, lowering the reaction temperature to 0 °C improved the **139**/**140** and the isolated yield reached reasonable 58% (entry 7).

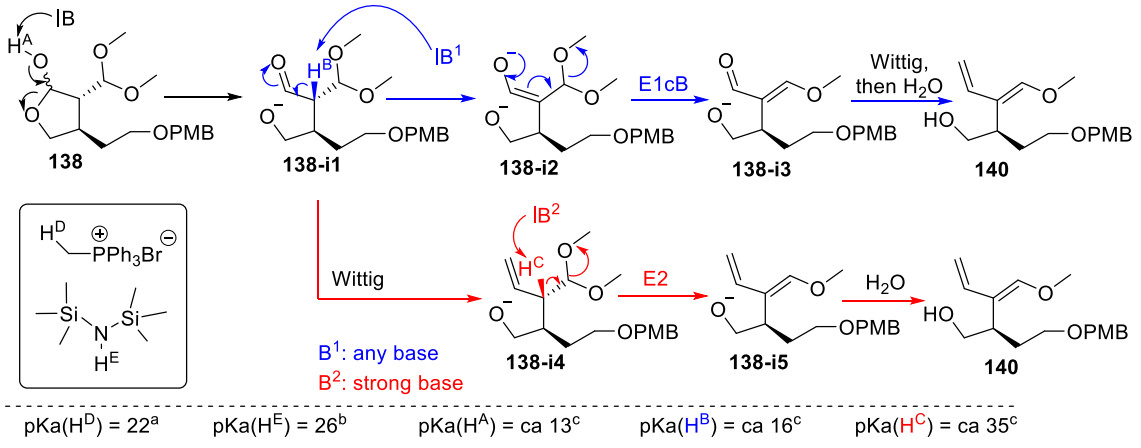
Table 4. Initial optimization of the Wittig methylenation of **138**. Study of base, solvent and temperature.



Entry	Base	Solvent	Temperature	Time	**138**/**139**/**140**[a]	**139** (%)[b]
1	*n*-BuLi	THF	0 °C to rt	16 h	1:0:0	0
2	LDA	toluene	–10 °C to rt	4 h	1:0:0	0
3	NaHMDS	THF	–50 °C to rt	2 h	1:0:0	0
4	*t*-BuOK	THF	0 °C to rt	4 h	0:45:55	40
5	KHMDS	THF	0 °C to rt	16 h	55:13:32	nd
6	KHMDS	toluene	rt	4 h	0:42:58	nd
7	KHMDS	toluene	0 °C	4 h	4:79:15	58

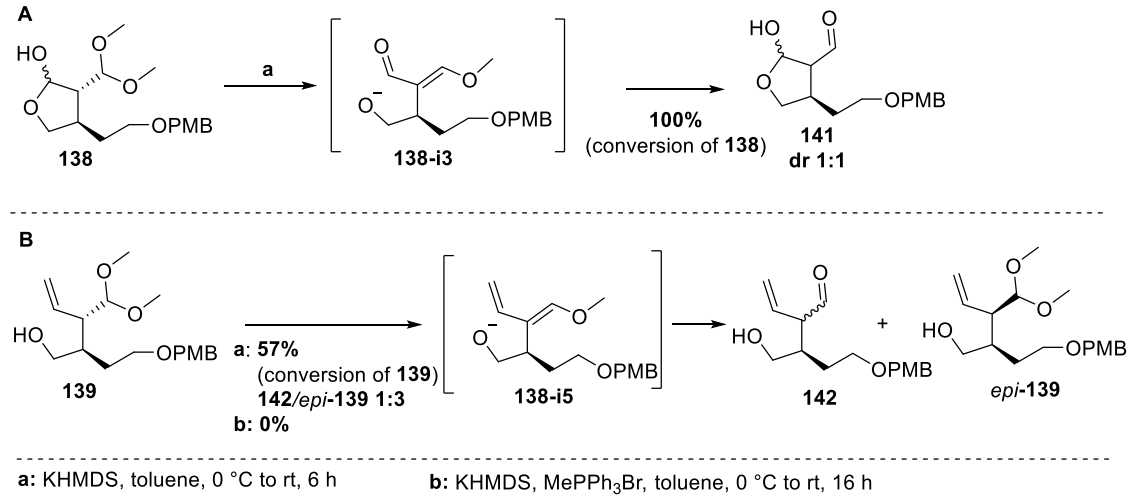
[a] Molar ratio as determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Isolated yield.

The mechanism of formation of the elimination product **140** was investigated to facilitate further optimizations and scale-up of the reaction. Two different base-promoted elimination pathways were proposed, both starting by deprotonation of the hydroxy group of lactol **138** providing aldehyde **138-i1** (Scheme 49). A second deprotonation at the α-position to the carbonyl would lead to enolate **138-i2**, triggering E1cB elimination to give **138-i3** (in blue). The Wittig reaction step would subsequently provide **140** after work-up. If the Wittig step on **138-i1** was faster, E2 elimination would be plausible for the subsequent elimination of MeOH, taking the allylic proton **138-i4** (in red). Another deprotonation of allylic hydrogen in **140** (not shown) would explain the observed racemization. By definition, E1cB elimination would be fast and facile with any base (B^1) including **138-i1** itself whereas E2 would be dependent on the strength and concentration of the base in question (B^2) as the rate determining step would include allylic deprotonation of **138-i4**. A simple comparison of the pK_a values of the corresponding protons, H^E and H^D vs. H^A gives an idea about the basicity of the reagents, but other factors need to be considered such as the counterion,[126] reaction media and possible anchimeric assistance by the substrate **138-i4**.



Scheme 49. Possible elimination mechanisms leading to enol ether **140**. [a] In DMSO.[127] [b] Median value in THF, determined by different methods.[126, 128-130] [c] Predicted values.

To investigate the feasibility of the E2 mechanism under the reaction conditions, a series of control experiments was performed. First, both lactol **138** (Scheme 50, part **A**) and Wittig product **139** (part **B**) were exposed to an excess of KHMDS (conditions **a**). Secondly, alcohol **139** was re-subjected to the conditions of the Wittig reaction (conditions **b**). The reaction with **138** proceeded to full conversion to afford a complex product mixture. Compound **141** was identified as the major product based on analysis of the ^{1}H NMR spectrum of the crude mixture, which involved distinct peaks at 9.6-9.5 ppm. Similarly, compound **142** was obtained from the reaction of **139** along with partially epimerized starting material. This suggests that elimination occurred in both cases, but was followed hydrolysis of corresponding enol ethers **138-i3** and **138-i5**, respectively. The lactol tautomer derived from **142** was not detected. Reaction of **139** with the phosphonium ylide resulted in complete recovery of the starting material.



Scheme 50. Elimination control experiments.

Formation of compounds **142** and *epi*-**139** implied that deprotonation in the allylic position of **139** and subsequent E2 can happen to a significant extent with KHMDS, but not with the less basic phosphonium ylide. While E1cB of **138-i1** is inevitable under the conditions, the E2 pathway could be avoided by proper adjustment of the reaction conditions. Along these lines, the benchmark reaction conditions from Table 4, entry 7 were studied in more detail. These studies highlighted several critical parameters:

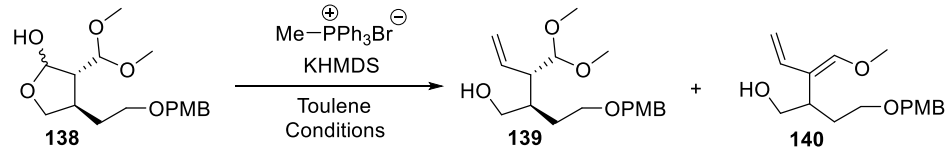
1. Time and temperature

Prolonging the reaction time to overnight stirring while maintaining the temperature at 0 °C ensured full conversion but the **139**/**140** ratio decreased (Table 5, entry 1). Reducing the starting reaction temperature to –50 °C with warming to 0 °C improved the **139**/**140** ratio and isolated yield of **139** although only 85% conversion was achieved (entry 2). Further decrease of reaction temperature to –78 °C did not further increase the yield as the conversion dropped below 80% (entry 3). In contrast, warming the reaction to room temperature overnight improved the conversion and did not negatively affect the **139**/**140** ratio (entry 4).

2. Scale and set-up method

Initially, scale-up attempts using these conditions were successful and **139** was obtained in good 64% yield in three replicates of the experiment (entry 5). Nevertheless, in another experiment using the same conditions, the yield of **139** decreased drastically to 30% and degradation was observed besides the usual side product **140** (entry 6), possibly due to slightly faster rate of cannulation of **138** into ylide (method **A**) which could mediate heat transfer. Reverse cannulation (ylide suspension into the solution of substrate, method **B**) was a proper alternative as it allowed keeping both reagents at low temperature and should maintain **138** in excess with respect to ylide. However, the reproducibility was not improved, since the ylide mixture was heterogeneous and a steady addition rate was not possible (entry 7 versus entry 8). Addition of the solution of **138** into the ylide mixture using a syringe pump was applied next, allowing a highly precise control over the addition rate (method **C**). The first experiments gave the best proportion of **139** and good 67% isolated yield (entry 9), but the reproducibility issues persisted on larger scale (entry 10).

Table 5. Further optimizations of the Wittig methylenation of **138**. Effect of scale, temperature, time and setup method.



Entry	Temperature	Time	**138** (mmol)	Method[a]	$MePPh_3Br$ /KHMDS (equiv.)		**138/139/140**[b]	**139** (%)[c]
1	0 °C	overnight	1	**A**	5	4.5	0:64:36	51
2	–50 to 0 °C	4 h	0.3	**A**	4	3.5	15:80:5	68
3	–78 to 0 °C	4 h	0.3	**A**	4	3.5	21:72:7	63
4	0 °C to rt	overnight	1	**A**	5	4.5	0:82:18	64
5[d]	0 °C to rt	overnight	3	**A**	5	4.5	0:80:20	61
6	0 °C to rt	overnight	3	**A**[e]	5	4.5	0:60:20[f]	30
7	0 to 10 °C	4 h	3	**B**	5	4.5	0:82:18	64
8	0 to 10 °C	4 h	4	**B**[g]	4	3.5	nd[f]	<10
9	0 °C to rt	overnight	1	**C**	5	4.5	0:86:14	67
10	0 °C to rt	overnight	3	**C**	5	4.5	nd[f]	0
11[d]	0 °C to rt	overnight	3	**C**	4.5	3.5	nd	76

[a] **A**: Solution of **138** added to a suspension of ylide using a cannula. **B**: Suspension of ylide added to a solution of **138** using a cannula. **C**: Solution of **138** added into the suspension of ylide using a syringe pump (5 mL/h). [b] Molar ratio as determined by ^1H NMR spectroscopy of the crude mixture. [c] Isolated yield. [d] Carried out in three replicates. [e] Fast addition rate. [f] Other byproducts present. [g] Cannula got stuck during addition.

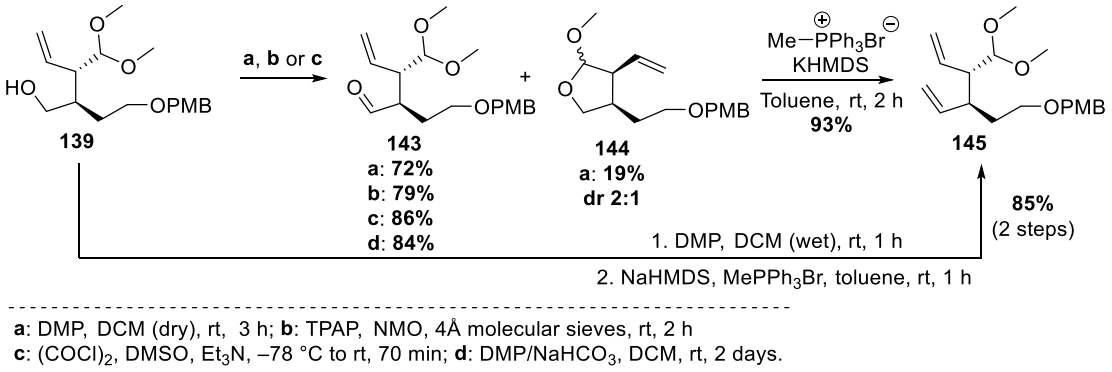
3. Excess of reagents

With persisting reproducibility issues, the concentration of KHMDS obtained from the supplier as 0.5 M solution in toluene was checked by titration to ensure that no free KHMDS remained in the reaction media to trigger E2 elimination pathways (*vide supra*).[131] The analysis revealed that the concentration varied significantly among batches and was usually around 20% higher than

indicated, implying that not all KHMDS was consumed for deprotonation in some of the experiments. Increasing the excess of phosphonium salt to 30% with respect to KHMDS, and titrating each new batch of base was prior to use ultimately resulted in a robust and reproducible isolated yield of **139** reaching 76% on gram scale (entry 11). It should be noted that all the above-mentioned parameters must be meticulously maintained.

4.1.3.6 Synthesis of metathesis substrates **148a-c**

With alcohol **139** in hands and accessible on a reasonable scale, the two remaining terminal double bonds had to be introduced. Dess-Martin oxidation of **139** furnished aldehyde **143** accompanied by 19% isolated yield of cyclic acetal **144** (Scheme 51, conditions **a**) formed in the acidic reaction media. In Ley-Grifith (conditions **b**) or Swern oxidation reactions (conditions **c**), the conversion of **139** was lower, but side product **144** did not form and applying these conditions delivered aldehyde **143** in 79% and 86% isolated yield, respectively. Similarly, buffered conditions for the Dess-Martin oxidation provided aldehyde **143** in 84% yield without formation of **144**, but the reaction did not reach full conversion (conditions **d**). It should be noted that epimerization of **143** also occurred under conditions **c** and **d** to a minor extent (<5% as determined by ^{1}H NMR spectroscopy). Subsequent Wittig reaction proceeded smoothly with 93% yield of diene **145**. An improvement was achieved when wet DCM was used for the DMP-mediated oxidation, which accelerated the reaction enough to reach full conversion in 1 h.[132] Crude aldehyde product **143** obtained by employing these conditions was engaged directly in the Wittig reaction without purification, yielding diene **145** in 85% over 2 steps.

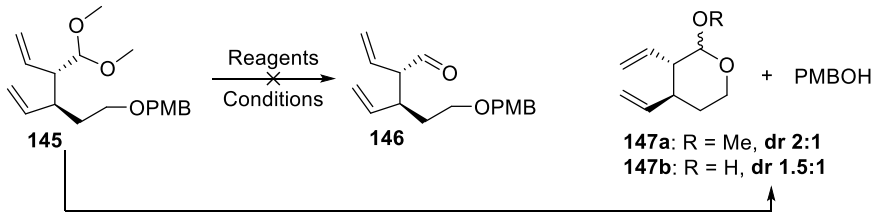


Scheme 51. Oxidation and Wittig olefination of alcohol **139**.

Subsequent deprotection of dimethyl acetal **139** proceeded analogously to the one of *trans*-**122b** (see Table 3). Protected aldehyde **146** did not form as PMB hydrolysis and cyclization occurred under the required acidic conditions to provide mixed acetal and/or hemiacetal **147a**/**147b**, respectively. Use of Amberlyst® 15 in refluxing acetone resulted in full PMB deprotection but only partial liberation of the lactol functionality, giving a mixture of **147a**/**147b** 1:2 (Table 6, entry 1).[111] TsOH in methanol only afforded mixed acetal **147a** in 75% conversion together with starting diene **145** after stirring at room temperature for three days (entry 2). $LiBF_4$ in aqueous acetonitrile gave similar results to TsOH but degradation was observed (entry 3).[133] The combination of TESOTf and 2,6-lutidine was inefficient and resulted in a full recovery of diene **145** (entry 4).[114] Finally,

dissolving **145** in a 2:1 mixture of acetic acid and water and stirring at room temperature for three days yielded hemiacetal **147b** in 74% yield as 1.5:1 mixture of diastereomers.[110]

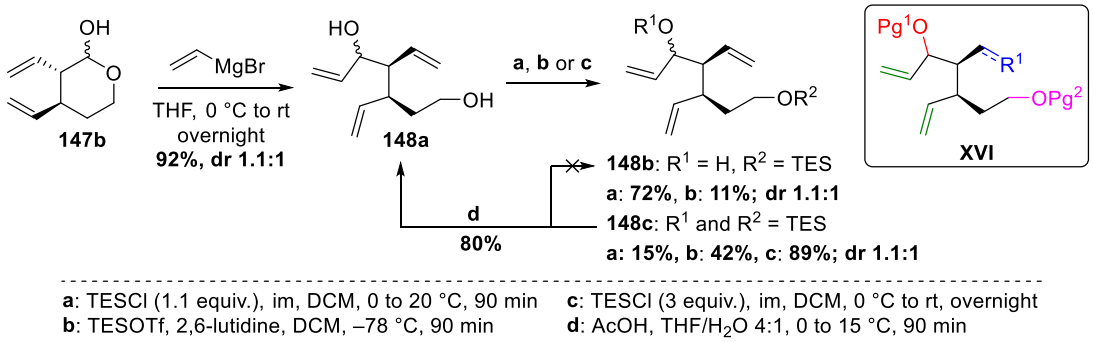
Table 6. Deprotection of dimethyl acetal and PMB group of diene **145**.



Entry	Reagent	Solvent	Temperature	Time	**145**/**147a**/**147b**[a]
1	Amberlyst® 15	acetone	reflux	3 h	0:1:2
2	TsOH	MeOH	0 °C to rt	3 days	1:3:0
3	$LiBF_4$, H_2O cat.	ACN	0 °C to rt	3 days	0:1:2[b]
4	TESOTf, 2,6-lutidine	DCM	0 °C	3 h	1:0:0
5	AcOH	AcOH/H_2O 2:1	rt	3 days	0:0:1[c]

[a] Molar ratio as determined by ^1H NMR spectroscopy of the crude mixture. [b] Degradation observed. [c] 74% isolated yield.

At this stage, addition of vinyl Grignard reagent to lactol **147b** was performed to add the last vinyl group in the desired substitution pattern in **XVI** (Scheme 63). Use of excess vinylmagnesium bromide furnished diol **148a** in 92% yield as 1.1:1 mixture of diastereomers. The diastereomers were inseparable but the new chiral center was going to be destroyed later. In order to introduce Pg^1 and Pg^2, diol **148a** was protected with a TES group, which can be cleaved relatively easily under weakly acidic conditions, including Swern oxidation, but it remains reasonably stable on silica gel to allow isolation of the protected compounds.[134] Monoprotected diol **148b** was synthesized by selective primary monosilylation using equimolar amount of TESCl in good 72% yield (conditions **a**). More reactive TESOTf with 2,6-lutidine did not provide the desired selectivity and only 11% of **148b** was isolated along with 40% **148a** and 42% of disilylated ether **148c** (conditions **b**). Fully protected diol **148c** was synthesized using an excess of TESCl with 89% yield (conditions **c**). An attempt to transform **148c** to **148b** by selective primary monodeprotection using aqueous AcOH in THF only gave diol **148a** in 80% yield (conditions **d**). Thus, the synthesis of compounds **148a**, **148b** and **148c** as suitable synthetic equivalents for **XVI** was accomplished in 43%, 31% and 34% yield over 9-10 steps, respectively, from known aldehyde **123** and with 22-30% yield over 12-13 steps from commercially available glyoxal dimethylacetal and butane-1,4-diol.

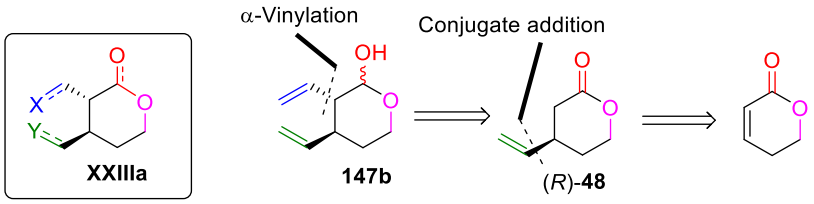


Scheme 52. Synthesis of diol **148a** and silyl ethers **148b** and **148c**.

4.1.4 Synthetic strategy III

4.1.4.1 Retrosynthetic analysis

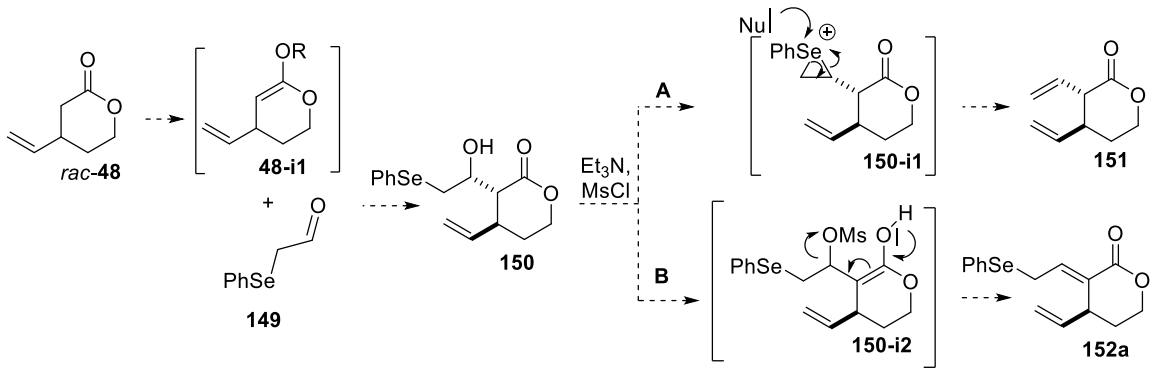
Lactol **147b**, which was obtained as a synthetic intermediate in the synthesis of **148**, is itself a suitable synthetic equivalent of **XXIIIa** and therefore, a more direct approach to this compound was envisaged (Scheme 53). First, the vinyl group α to the masked carbonyl of lactol **147b** was disconnected, suggesting an α-vinylation of lactone (*R*)-**48**. Two methods for the forward reaction developed in 1980 involve aldol addition of phenylselenyl acetaldehyde and conversion of resulting β-hydroxyselenide into olefin[135-137] and reaction of kinetic enolates with enol ether iron complexes as vinyl cation equivalents.[138] More recently, Pd(0)-catalyzed vinylations of ketone or amide enolates have emerged, allowing ligand-controlled stereoselectivity.[139, 140] In this case, regardless the method, the transformation should occur with a good substrate-controlled *trans*-diastereoselectivity to the already present vinyl group of (*R*)-**48** thanks to well-defined conformations of the six-membered ring. Lactone (*R*)-**48** is a known compound and can be obtained by 1,4-addition of a vinyl Grignard reagent to 5,6-dihydro-2*H*-pyran-2-one in the presence of copper and subsequent resolution of enantiomers (see synthesis of preclavulone A by Ito *et al.*, Scheme 11, page 24).[74] Alternatively, an enantioselective 1,4-addition using a chiral ligand on copper could be envisioned.



Scheme 53. Retrosynthetic analysis of **147b**.

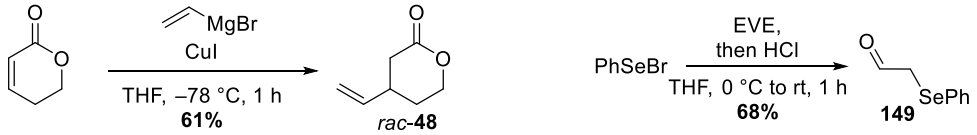
4.1.4.2 Conjugate addition/α-vinylation

Selected α-vinylation method relied on an aldol addition of cyclic enolate or silyl enol ether **48-i1** to phenylselenyl acetaldehyde **149** to form aldol adduct **150** and subsequent controlled elimination under Reich's conditions to give β,γ-unsaturated lactone **151** via phenylseleniranium intermediate **150-i1** (Scheme 54, pathway **A**).[135, 136] This method was originally reported for ketones,[137] but found application in the synthesis of tricyclic core of Phomactin A involving an α,β-disubstituted lactone as a substrate.[141] The main obstacle in the application on aldol adducts bearing α-hydrogen atoms is the competitive E1cB-like elimination providing conjugated products such as **152a** via enol **150-i2** or the corresponding enolate under basic conditions (pathway **B**). In addition, double bond migration of **151** might occur under the reaction conditions (not shown).



Scheme 54. Envisaged α-vinylation strategy using controlled elimination of phenylseleniranium salt **150-i1**.

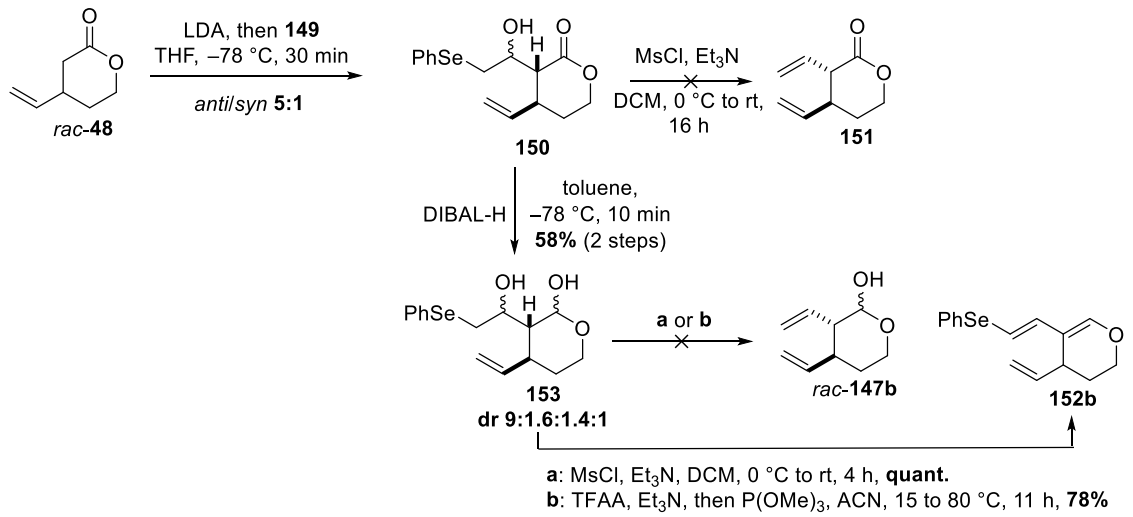
Racemic synthesis was carried out to evaluate the feasibility of the strategy. Previously described conjugate addition furnished compound *rac*-**48** in 61% yield (Scheme 55).[142] Compound **149** was prepared as reported by reaction of phenylselenyl bromide with ethyl vinyl ether followed by treatment by aqueous HCl in 68% yield.[143]



Scheme 55. Synthesis of starting materials *rac*-**48** and **149**.

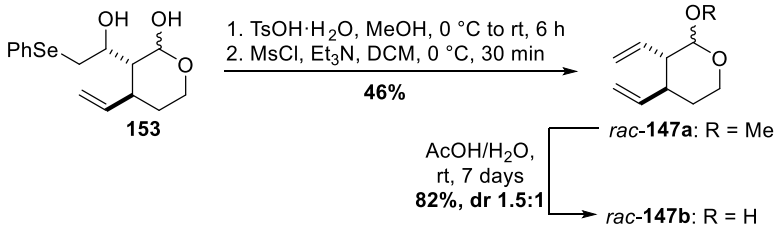
Subsequent aldol addition of lithium enolate of *rac*-**48** delivered aldol **150** with exclusive *trans*-selectivity and as 5:1 mixture of *anti* and *syn* diastereomers (Scheme 56). The latter was not isolated but directly exposed to the above described elimination conditions, however, a complex mixture of products possibly including both **152a** and the product of double bond migration was obtained instead of desired β,γ-unsaturated lactone **151**. Aldol adduct **150** was thus first reduced to corresponding lactol **153** using excess DIBAL-H with 58% yield over two steps. Yet, compound *rac*-**147b** did not form after subjecting **153** to the edescribed limination conditions (conditions **a**). and solely product of conjugate elimination without selenium loss **152b** was obtained. Alternative conditions consisting of formation of the corresponding bis-trifluoroacetate, elimination and subsequent hydrolysis of the remaining trifluoroacetyl group gave the same product with slightly

lower yield (conditions **b**).[137]



Scheme 56. Attempted α-vinylation attempts of *rac*-**48**.

In the last attempt to avoid elimination pathway **B**, lactol **153** was protected as the corresponding mixed acetal. Subsequent elimination indeed furnished *rac*-**147a** in moderate 46% yield (Scheme 57). Finally, deprotection using AcOH/H_2O delivered *rac*-**147b** in 82% yield. Thus, *rac*-**147b** was obtained in unoptimized 13% yield over five steps from commercially available 5,6-dihydro-2*H*-pyran-2-one. It should be noted that both substrates *rac*-**48** and **147b** are easily accessible on multigram scale as they are conveniently purified by distillation and only two column chromatographies were necessary throughout the synthesis, namely for compounds **153** and *rac*-**147a**. Thus, with some minor optimizations, strategy **III** represents a fast and direct approach to the synthesis of **148**, complementary to the enantioselective strategy **II**.

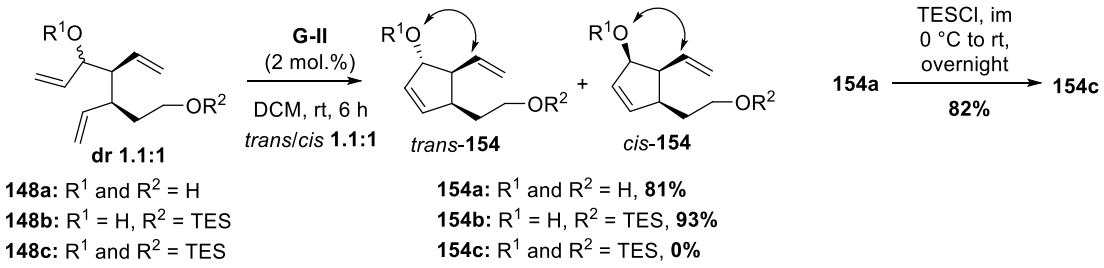


Scheme 57. Synthesis of lactol *rac*-**147b** using strategy **III**.

4.1.5 Application of strategy II to the total synthesis of 4-A4-NeuroP

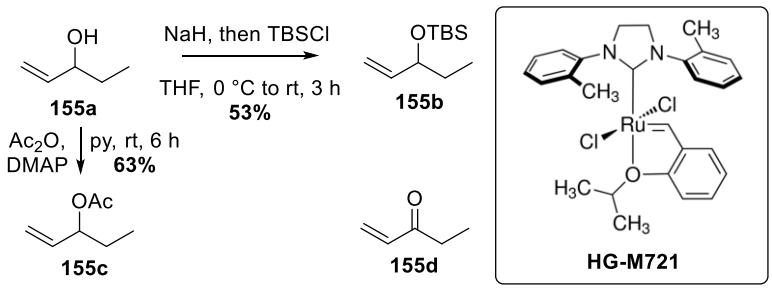
4.1.5.1 RCM and CM model studies

To form the cyclopentene ring, RCM was carried out on compounds **148a-c** using Grubbs 2nd generation catalyst **G-II**. Compounds **148a** and **148b** provided neatly cyclopentenes **154a** and **154b** with 81% and 93% isolated yield, respectively, with reasonable 2 mol.% **G-II** loading (Scheme 58). In contrast, compound **148c** remained intact under the conditions and corresponding cyclopentene **154c** was not detectable by ^{1}H NMR spectroscopy of the crude reaction mixture. For the purpose of future optimization, compound **154c** was synthesized by silylation of diol **154a** in 82% yield. The relative configuration at the allylic center of the cyclopentene ring was assigned based on ROESY experiments on compound **166b** (*vide infra*) as *trans* for the major diastereomers and *cis* for the slightly minor diastereomers of **154**.



Scheme 58. RCM of compounds **148a-c**.

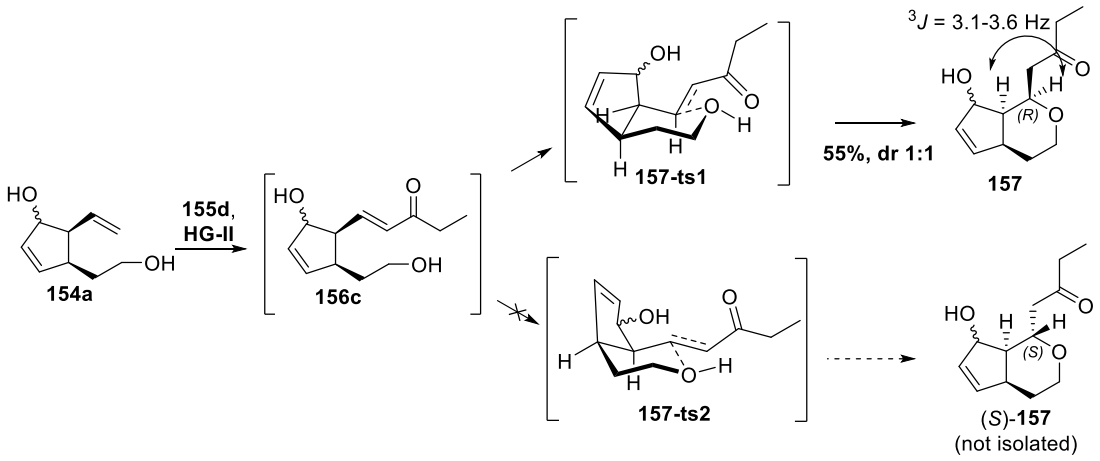
Next, a series of model CM reactions was conducted, employing compounds **155a-d** as suitable model reactants (Scheme 59). Alcohol **155a** and enone **155d** are commercially available compounds whereas **155b**[144] and **155c**[145] were prepared in a single step from **155a** in 53% and 63% yields, respectively.These compounds were allowed to react with cyclopentenes **154a-c**. In addition to previously introduced catalysts **G-II** and **HG-II**, Hoveyda-Grubbs catalyst® M721 (**HG-M721**), an analogue of **HG-II** designed for sterically demanding substrates,[146, 147] was used in these experiments.



Scheme 59. Structures and preparation of model reactants **155** and structure of catalyst **HG-M721**.

Reaction partners were selected with regard to the literature (see section 2.2.3, page 27) according to their respective polarities in order to facilitate chromatographic separation of starting materials **154** and **155**, desired products **156** and dimers **158**. The screening started with a series of experiments with free diol **154a**. Reactions with TBS-protected allylic alcohol **155b** provided

desired product **156a** in low 16% and 21% yield with **HG-II** or **G-II**, respectively (Table 7, entry 1 and 2). The outcome was similar with **155c** since corresponding acetate **156b** was isolated in 20% yield using **HG-II** (entry 3), but the yield dropped to 8% with **G-II** (entry 4). In case of pentenone **155d**, traces of enone **156c** were obtained after stirring in refluxing DCM for 4 hours (entry 5). Prolonging the reaction time to overnight stirring caused full conversion and ketone **157** was obtained as the major product as a separable 1:1 mixture of diastereomers in 55% isolated yield (entry 6). A similar cyclization has been described in the synthesis of (−)-Elegansidiol by Audran *et al.* under the conditions of Horner-Wadsworth-Emmons olefination.[148] A new chiral center was formed as a result of an intramolecular oxa-Michael cyclization of **156c**, which occurred with complete stereoselectivity. The configuration of the newly formed stereocenter was assigned based on the small coupling constant values of the neighboring protons in ^{1}H NMR spectroscopy as (*R*) for both diastereomers, suggesting the dominant role of transition state **157-ts1** over **157-ts2**, which would lead to (*S*)-**157** (Scheme 60).



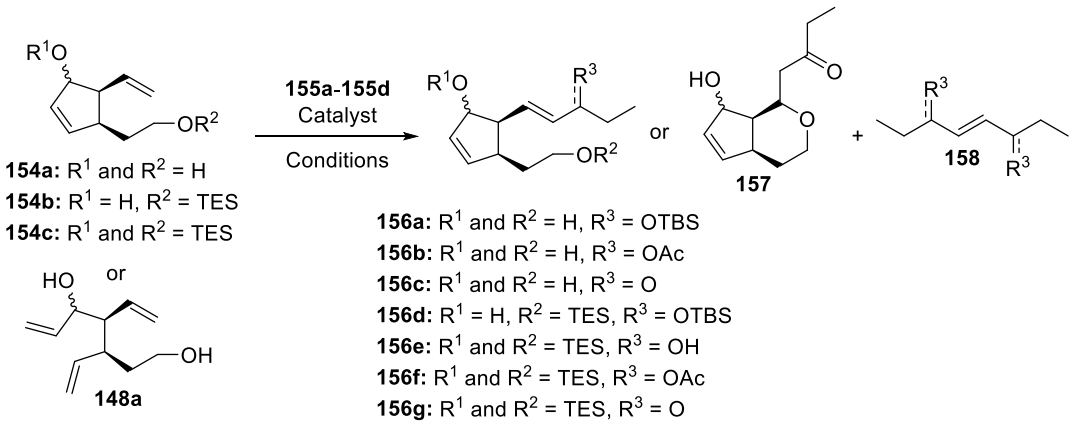
Scheme 60. Transition states for the oxa-Michael cyclization of **156c** leading to adduct **157**.

The same compound could also be obtained directly in a one-pot procedure under the same conditions from acyclic diol **148a**, albeit with lower 43% yield (entry 7). Switching to toluene as solvent decreased the yield of **157** to 20% (entry 8). Using **G-II** instead of **HG-II** as catalyst only furnished RCM product **154a** with moderate 54% yield (entry 9).

Subsequently, monoprotected compound **154b** reacted with TBS-protected allylic alcohol **155b** using **HG-M721** as catalyst but no desired product **156d** was isolated and the starting material was fully recovered (entry 10). Similarly, no reaction occurred between disilylated diol **154c** with free alcohol **155a** (entry 11). The same substrate reacted with acetate **155c** to afford protected triol **156f** in 23% yield (entry 12). Lastly, reaction of silyl ether **154c** with pentenone **155d** with proceeded to full conversion to give enone **156g** with moderate 49% yield (entry 13).

These preliminary results clearly highlighted the importance of the electronic match of the reactants since only reactions with enone **155d** provided reasonable yields. Comparing the catalyst effect in analogous reactions, **HG-II** was the catalyst of choice. The attempts to attach the chain directly as an allylic alcohol or allylic ether were unsuccessful.

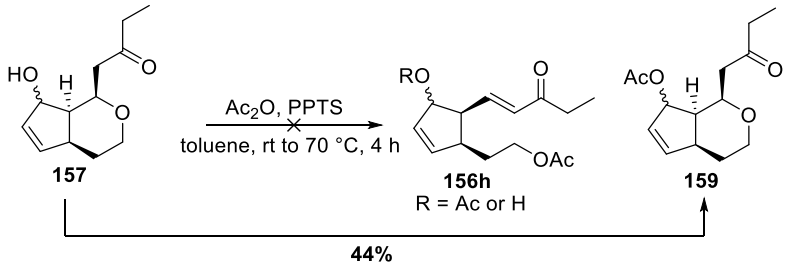
Table 7. Studies of CM of cyclopentenes **154** and oxygenated pentenes **155**.



Entry	Substrate	Reactant (3 equiv.)	Catalyst (10 mol.%)	Conditions[a]	Product	Yield (%)
1	**154a**	**155b**	**HG-II**	DCM, reflux	**156a**	16
2	**154a**	**155b**	**G-II**	DCM, reflux, 4 h	**156a**	22
3	**154a**	**155c**	**HG-II**	DCM, reflux	**156b**	20
4	**154a**	**155c**	**G-II**	DCM, reflux, 6 h	**156b**	8
5	**154a**	**155d**	**HG-II**	DCM, reflux, 4 h	**156c**	traces
6	**154a**	**155d**	**HG-II**	DCM, reflux	**157**	55
7	**148a**	**155d**	**HG-II**	DCM, reflux	**157**	43
8	**148a**	**155d**	**HG-II**	toluene, reflux	**157**	20
9	**148a**	**155d**	**G-II**	DCM, reflux	**154a**	54
10	**154b**	**155b**	**HG-M721**	DCM, reflux	**156d**	0
11	**154c**	**155a**	**HG-II**	DCM, reflux	**156e**	0
12	**154c**	**155c**	**HG-II**	DCM, reflux	**156f**	23
13	**154c**	**155d**	**HG-II**	DCM, reflux	**156g**	49

[a] Stirred overnight except for entries 2, 4 and 5.

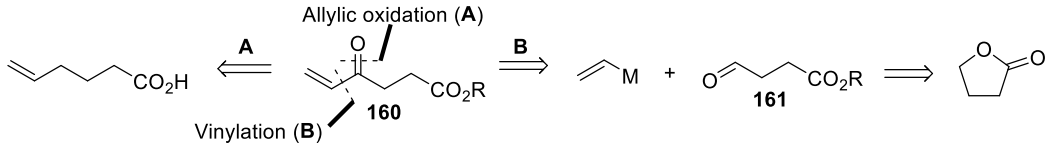
To explore possible subsequent transformation of the Michael adduct **157**, the compound was subjected to the previously reported conditions to give its open form **156h** by an elimination reaction while protecting it with an acetyl group at the same time (Scheme 61).[148] However, the conditions only furnished acetate **159** with low 44% isolated yield and prolonging the reaction time led to degradation.



Scheme 61. Attempted elimination of **157**.

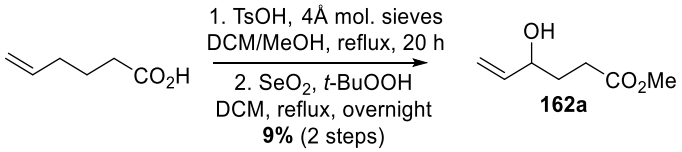
4.1.5.2 Synthesis of α-chain precursors **160**

As indicated by the model studies, the logical pair of reactants to introduce the α-chain was monoprotected diol **154b** with enone **160** as side chain precursor. Retrosynthetically, the compound was analyzed in two ways: a C-O disconnection leads to a commercially available hex-5-enoic acid (Scheme 62, disconnection **A**), from which the target compound is accessible by allylic oxygenation/oxidation. An alternative C-C disconnection (disconnection **B**) leads to 1,4-difunctional reactant **161** and a vinyl metal compound. Aldehyde **161** is accessible by γ-butyrolactone opening.



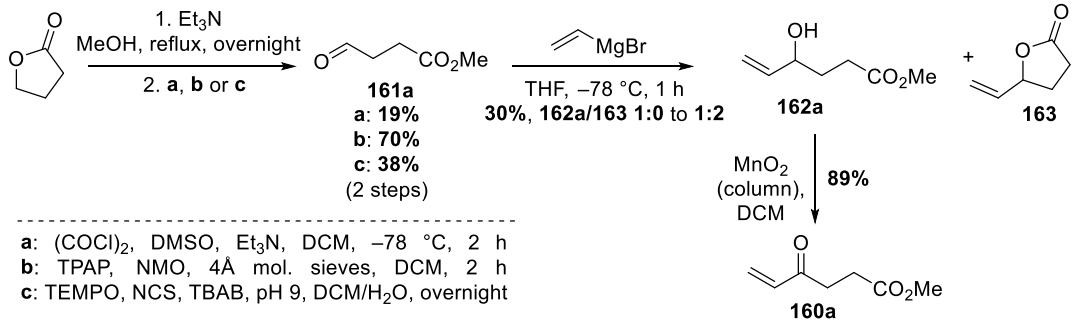
Scheme 62. Retrosynthetic analysis of enone **160**.

First, the more direct oxidative approach was investigated. The acid was converted to the corresponding methyl ester by a standard procedure and the latter was subsequently oxidized by SeO_2 using conditions reported by Guy *et al.* (Scheme 63).[92] Allylic alcohol **162a** was isolated in a very low 9% yield over two steps and the rest of the complex crude mixture consisted of unidentified degradation products. The low yield along with relatively expensive starting material limited access to a sufficient amount of material through this strategy.



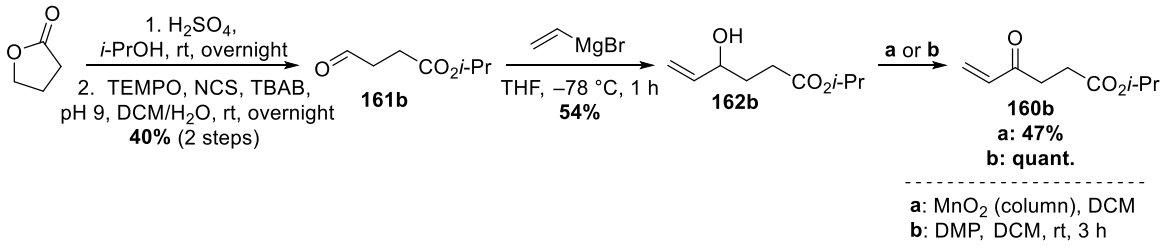
Scheme 63. Esterification and allylic oxidation of hex-5-enoic acid.

The approach involving aldehyde **161** and γ-butyrolactone as corresponding difunctional reagents was more promising as the synthesis of allylic alcohol **162a** by this approach had already been described by Sutar *et al.*[149] Along these lines, γ-butyrolactone was opened using base-catalyzed methanolysis (Scheme 64). The mixture of hydroxy ester and lactone was directly oxidized to aldehyde **161a**. Swern oxidation (conditions **a**) gave only low 19% yield of **161a**, possibly due to lactonization of the hydroxy ester, but both Ley-Griffith oxidation (conditions **b**) and the originally reported TEMPO-catalyzed oxidation (conditions **c**)[149] proceeded with 70% and 38% isolated yields of **161a** over 2 steps, respectively. Subsequent 1,2-addition of vinylmagnesium bromide at low temperature furnished desired alcohol **162a**, however, reproducibility of the reaction was low and **162a** was accompanied by up to 66 mol.% of lactone **163** and the yield of the inseparable **162a**/**163** mixture was only 30%. Besides, lactonization also occurred during storage, especially on exposure to weakly acidic conditions ($CDCl_3$ or silica gel). Nonetheless, subsequent allylic oxidation of the small pure fraction of **162a** on a MnO_2 column delivered enone **160a** with good 89% yield.[150]



Scheme 64. Synthesis of enone **160a**.

The lactonization of **162a** did not allow its synthesis in amounts necessary to perform the CM step on scale. In addition, the same type of cyclization can be expected in more advanced intermediates after introduction of the α-chain.[151] Therefore, the methyl ester moiety was replaced by an isopropyl ester in modified enone **160b**. The latter was synthesized in analogy to the synthesis of **160a** starting with opening of butyrolactone in acidic conditions followed by TEMPO-catalyzed oxidation with 40% isolated yield of **161b** over two steps (Scheme 65). The yield of the transesterification/oxidation step decreased somewhat compared to **161a** due to the equilibrium of acid-catalyzed butyrolactone opening by *i*-PrOH, which is significantly shifted to the side of the starting material.[152] On the other hand, this simple exchange of protecting group increased the yield and most notably the reproducibility of the 1,2-addition, which provided alcohol **162b** in 54% yield without any lactonization. Mild oxidation using MnO_2 (conditions **a**) only furnished enone **160b** in low 47% yield. Thanks to the increased stability of the newly installed isopropyl ester, the final oxidation step could be performed using DMP and the application of conditions **b** afforded enone **160b** in quantitative yield.



Scheme 65. Synthesis of enone **160b**.

4.1.5.3 Introduction and functionalization of the α-chain

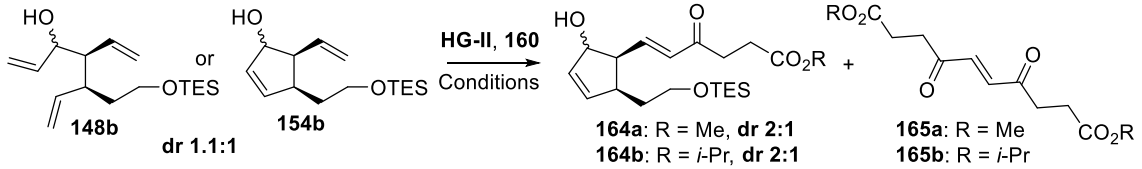
Next, the CM reaction between the newly synthesized enones **160** and monoprotected diol **154b** was carried out. Initial conditions similar to those applied in the model experiments provided desired enone **164a** in 29% yield after reaction with enone **160a** (Table 8, entry 1). The yield improved to 35% when the addition of catalyst **HG-II** was performed in small portions over the whole reaction time period (entry 2). Increasing the catalyst loading to 15 mol.% further improved the yield of **164a** to 63% (entry 3). To minimize formation of dimer **165a**, which co-eluted with the desired product during column chromatography, the excess of enone **160a** was gradually decreased

from 4 to 2 equiv. (entries 1-3), which did not negatively impact the yield, although the formation of dimer **165a** could not be avoided.

Isopropyl ester **160b** reacted similarly, although a prolonged reaction time was required to achieve full conversion, affording enone **164b** in 59% yield (entry 4). Using benzoquinone as additive to react with co-formed ruthenium hydride species did not affect the yield of **164b** (entry 5).[153] The application of **HG-M721** as catalyst provided only traces of **164b** (entry 6). Finally, a reasonable 55% yield of **164b** was achieved in a one-pot procedure starting from open monoprotected diol **148b** (entry 7). Although this result did not represent a significant improvement in terms of yield or catalyst consumption compared to the two steps performed separately, the combined reaction time shortened and a single purification by column chromatography was required. Thanks to a slight shift in polarity, dimer **165b** was easily separable from desired product **164b**.

The obtained diastereomeric product mixture was further enriched in *trans*-**164a** and *trans*-**164b**, respectively, as the ratio shifted from 1.1:1 to 2:1, suggesting that *cis*-**154b** reacts slower in the CM step and rather undergoes degradation.

Table 8. Optimizations of CM of cyclopentene **154b** and side chain precursors **160**.

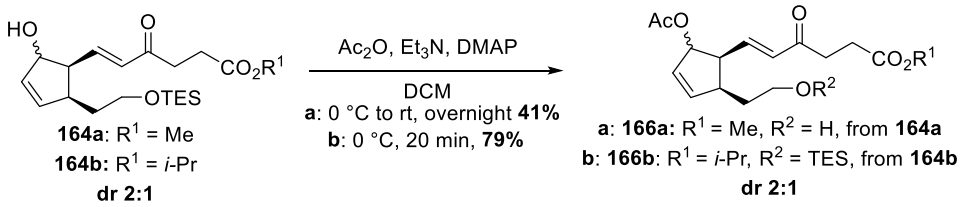


Entry	Substrate	Reactant (equiv.)	**HG-II** (mol.%)	Conditions	**164** (%)
1	**154b**	**160a** (4)	10	DCM, reflux, 16 h	29
2	**154b**	**160a** (3)	10[a]	DCM, reflux, 20 h	35
3	**154b**	**160a** (2)	15[a]	DCM, reflux, 24 h	63
4	**154b**	**160b** (2.5)	14[a]	DCM, rt to reflux, 48 h	59
5	**154b**	**160b** (2)	16[a, b]	DCM, rt to reflux, 48 h	59
6	**154b**	**160b** (2)	10[a,c]	DCM, rt to reflux, 48 h	traces
7	**148b**	**160b** (3)	15[a]	DCM, rt to reflux, 48 h	55

[a] Catalyst added in small ca 2 mol.% portions every 2 h. [b] A small portion (2 mol.%) of benzoquinone added before each addition of the catalyst. [c] **HG-M721** instead of **HG-II**.

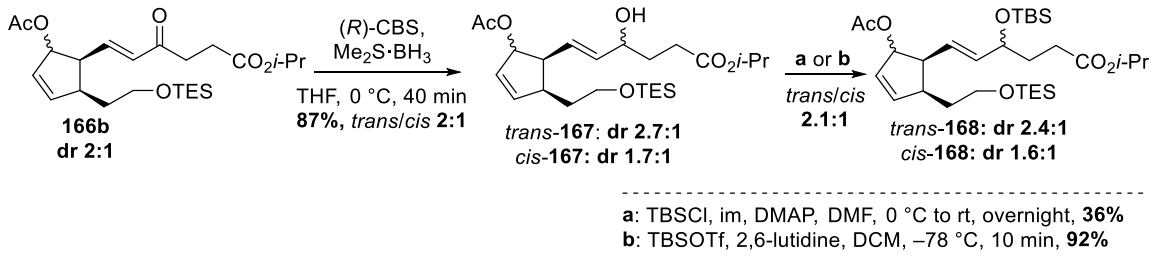
Having compound **164b** with the α-chain in place, two different protecting groups needed to be used for the two allylic positions, orthogonal to each other and each of them orthogonal to the already present TES group. Moreover, the protecting group of the side chain hydroxy group would need to be cleaved under very mild conditions in the last step of the synthesis. Taking into account some examples from the literature (see section 2.2.1.1 and synthesis of 15-D_{2t}-IsoP by Brinkmann *al.*),[154] TBS was a suitable choice for the side chain allylic hydroxy group. An acetyl was selected for the second allylic position as an acid-stable non-silylated protecting group, which could prospectively be deprotected at the same time as the isopropyl ester.

Along these lines, compounds **164a-b** were first protected as acetates (Scheme 66). When the reaction mixture with Ac_2O in the presence of Et_3N and catalytic DMAP was allowed to warm to room temperature and stirred overnight, similarly to a previous report by Candy *et al*. with a similar compound,[115] TES deprotection took place to provide **166a** in low yield along with some degradation (conditions **a**). Leaving the temperature at 0 °C and shortening the reaction time ensured good 78% yield of acetate **166b** (conditions **b**). ROESY experiments on **166b** allowed the assignement of the relative configuration at the cyclopentane ring of both diastereomers and the data could be extrapolated on all cyclic intermediates starting from **154a-c** (*vide supra*) thanks to a characteristic trend in ^{1}H NMR chemical shift of protons at C-4 and C-5 of the cyclopentene ring (see Table 15 in the Experimental section).



Scheme 66. Synthesis of silyl ethers **166**.

The stereoselective reduction was performed in Corey-Bakshi-Shibata conditions using (*R*)-2-methyl-CBS-oxazaborolidine (Scheme 67). Allylic alcohol was isolated in good 87% yield, however, the stereoselectivity of the reduction step was low for both diastereomers and the reaction the allylic alcohol as inseparable 2:1 mixture of *trans-/cis*-**167** as 2.7:1 and 1.7:1 mixture of C-4 epimers, respectively. Subsequent protection of the newly formed OH group using TBSCl/imidazole (conditions **a**) only provided protected triol **168** in low 36% yield because of low conversion. In contrast, excellent 92% yield of **168** was achieved with TBSOTf/2,6-lutidine at –78 °C within 10 min (conditions **b**). Keeping the temperature low and the reaction time short was important, otherwise degradation occurred.



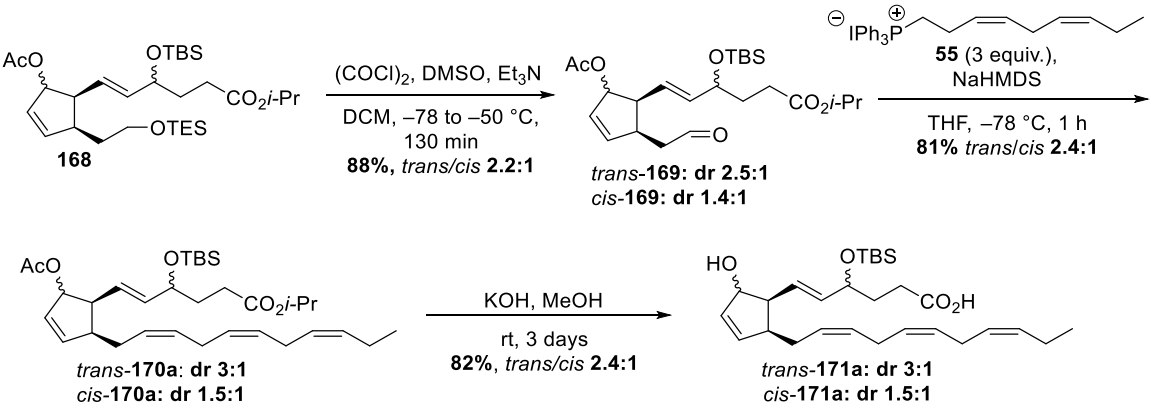
Scheme 67. Synthesis of fully protected triol **168**.

4.1.5.4 Introduction of the ω-chain

Concomitant primary TES deprotection and Swern oxidation of **168** provided aldehyde **169** in good 88% yield (Scheme 68). Next, Wittig reaction with phosphonium salt **55**[2] furnished the fully

[2] Phosphonium salt **55**[155] was prepared and kindly furnished by Dr. Valérie Bultel-Poncé, a research engineer in Thierry Durand's group.

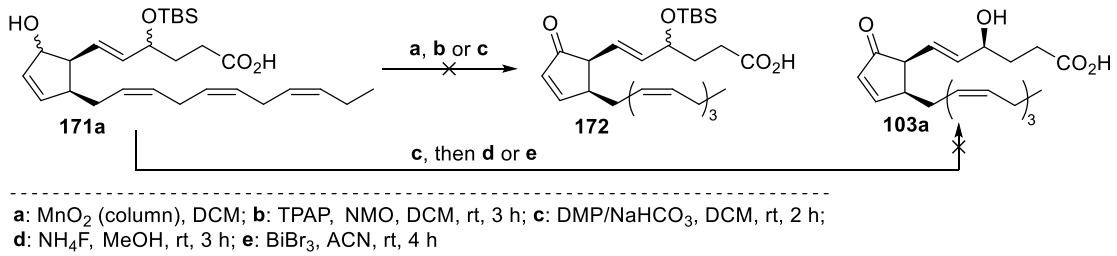
protected carbon skeleton **170a** including the skipped (*Z*)-triene in good 81% yield. Subsequent saponification permitted cleavage of both, acetyl and isopropyl ester groups at the same time. No reaction occurred with LiOH in aqueous THF, conditions commonly applied in the field for methyl ester hydrolysis (conditions **a**).[77] On the other hand, KOH in methanol provided free acid **171a** in good 82% yield.[156] No side reactions were observed under the conditions.



Scheme 68. Synthesis of acid **171a**.

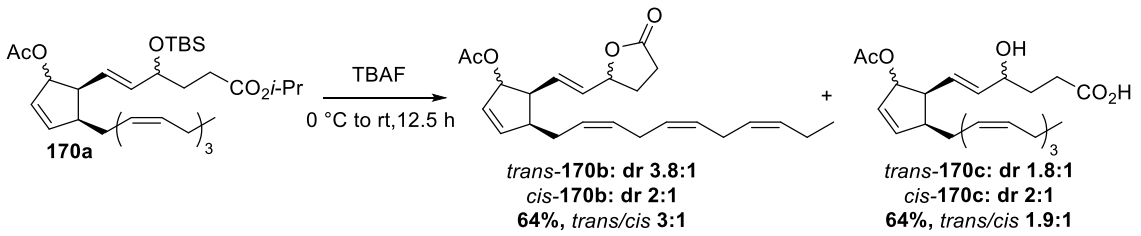
4.1.5.5 Final oxidation/deprotection attempts

With small amounts of compound **171a**, final allylic oxidation and subsequent silyl deprotection was attempted (Scheme 69). Mild oxidation on a MnO_2 column (conditions **a**) did not furnish enone **172** and the material remained on the column and could not be recovered despite repetitive extractions using various polar solvents. Ley-Griffith oxidation (conditions **b**) only resulted in recovery of **171a** along with some degradation. DMP oxidation with buffering by $NaHCO_3$ (conditions **c**) provided full conversion of **171a**, however, degradation occurred during work-up and purification, resulting in low 30% mass recovery. Moreover, the obtained product was inseparable from iodobenzoic acid resulting from reductive work-up of DMP and the analytical data did not match **172**. Performing the DMP-mediated oxidation and subjecting the crude enone to the previously reported deprotection conditions without isolation (conditions **d**[71] or **e**[154]) only gave complex product mixtures and the amount of material was too low to allow separation of the individual compounds.



Scheme 69. Attempted oxidation and deprotection of alcohol **171a**.

With the aim of using milder conditions for the final deprotection, a protecting group exchange was envisaged. Thus, Wittig product **170a** was deprotected using TBAF in order to replace the TBS group by a more easily cleavable TES group (Scheme 70). However, lactonization occurred under the conditions to provide compound **170b** in 64% yield along with 11% isolated free acid **170c**.

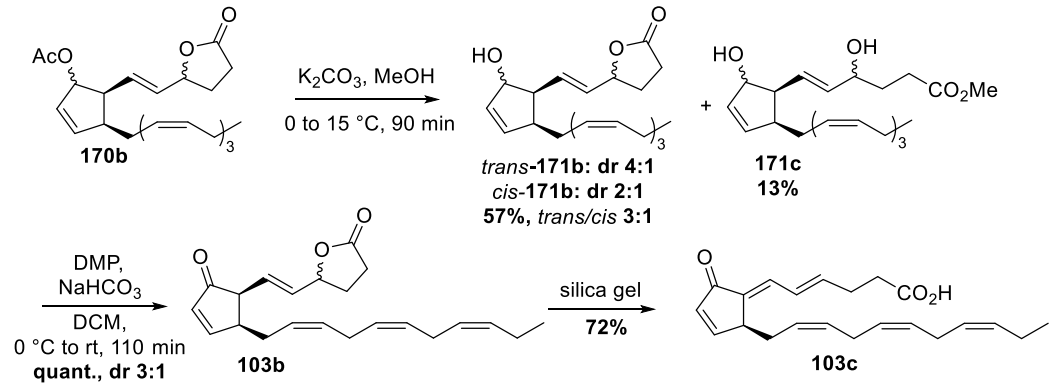


Scheme 70. Silyl deprotection of **170a**.

Subsequent transesterification of the acetyl group furnished allylic alcohol **171b** in 57% yield. Partial lactone opening also occurred to give 13% of hydroxy methyl ester **171c**, which was inseparable from the title compound. Dess-Martin oxidation of the obtained mixture afforded 4(*RS*)-4-A_4-NeuroP 1,4-lactone **103b** as a 3:1 mixture of C-4 epimers along with traces of ketones resulting from oxidation of diol **171c** (Scheme 71).

To confirm the *cis*-configuration of the side chains, ROESY experiment was conducted on **103b**. The spectra showed a very strong contact of protons at C-4 and C-5 of the cyclopentenone ring and the coupling constants between them was larger than would be expected for *trans*-substituted compound ($^3J_{H,H}$ = 8.5 Hz for major diastereomer and $^3J_{H,H}$ = 7.8 Hz for minor diastereomer). Further ROESY contacts to support the claim could not be unambiguously assigned because the resonances were overlapping. However, full epimerization of **103b** under acidic or basic conditions is highly unlikely as competitive reactions, such as vinyloguous elimination or double bond migration, should occur to a major extent, as reported several times on related molecules.[66, 71, 99, 154] Thus, it can be concluded that the *cis*-relative configuration of the side chains was preserved in **103b**.

Compound **103b** proved to be extremely unstable. In the attempt to separate the impurities from the target compound by TLC, vinyloguous elimination with butyrolactone opening occurred on silica gel to provide 4-deoxy-$\Delta^{4,6}$-A_4-NeuroP **103c** in 72% yield over two steps. Because of the instability of the system, lactone opening of **103b** by saponification was not attempted. Enzymatic hydrolysis might be considered as an alternative,[72] however, it should be noted that Porta *et al.* reported degradation of similar system even under these neutral conditions.[71] When crude lactone **103b** was stored as a neat sample at –20 °C for ten days, subsequent ^{1}H NMR and HPLC analysis revealed complete degradation. The resulting mixture was mostly insoluble in MTBE or deuterated benzene and only weak resonances corresponding to conjugated polyene system such as **103c** were detectable in the ^{1}H NMR spectra. The purity of elimination product **103c** was checked by HPLC after storage in deuterated benzene at –10 °C for 10 days and the compound did not show signs of degradation.



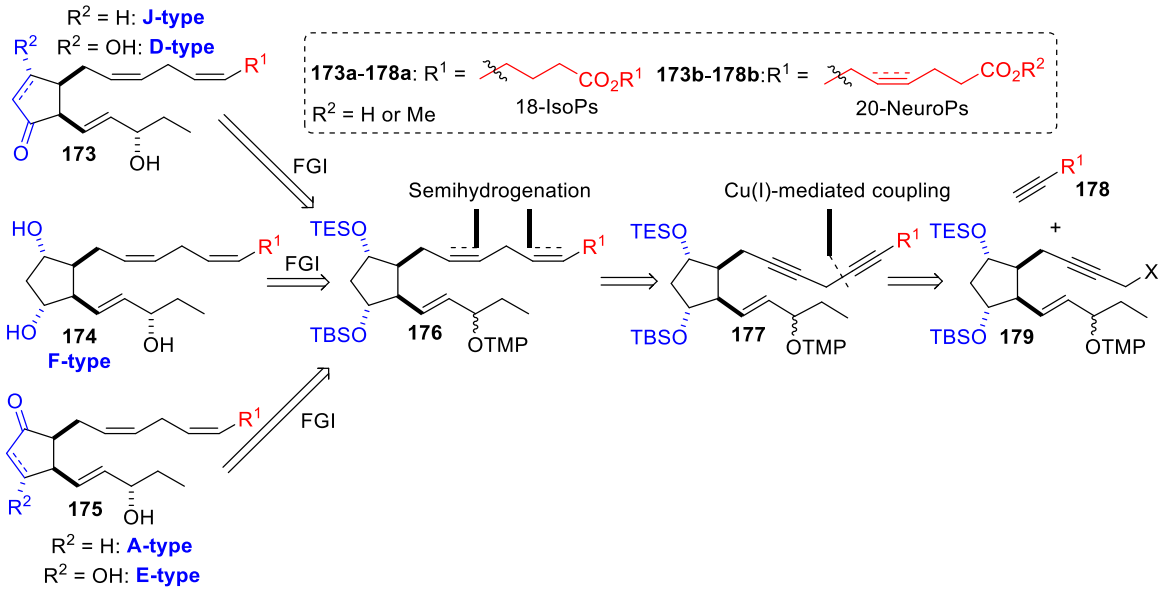
Scheme 71. Synthesis of 4-A$_4$-NeuroP 1,4-lactone **103b** and 4-deoxy-$\Delta^{4,6}$-A$_4$-NeuroP **103c**.

Although the synthesis of 4-A$_4$-NeuroP **103a** as a free acid might potentially be accomplished choosing a more appropriate protecting group pattern, these results implicate that deoxy-NeuroP **103c** is likely more stable metabolite of both lactone **103b** and **103a**. As such, its presence in biological material can be expected in comparable or higher amounts. Considering the extraction methods commonly applied in targeted lipidomics, which often include treatment of samples with formic acid or even basic hydrolysis step in order to liberate free acids from their phospholipidic form,[56, 78] it seems unlikely that **103a** or **103b** would sustain these conditions. Moreover, compounds similar to **103c** have been reported in both PhytoP and PG/IsoP series,[61] the former protecting plants from oxidative stress[157] and the latter possessing anti-inflammatory activities in human endothelial cells.[158] Thus, the total syntheses of 4(*RS*)-4-A$_4$-NeuroP 1,4-lactone **103b** and 4-deoxy-$\Delta^{4,6}$-A$_4$-NeuroP **103c** as potential metabolites of 4-A$_4$-NeuroP **103a** were accomplished in 1.7% and 1.2% isolated yield over 21 and 22 steps, respectively.

4.2 Total syntheses of isoprostanoids with 3-hydroxypentenyl ω-chain

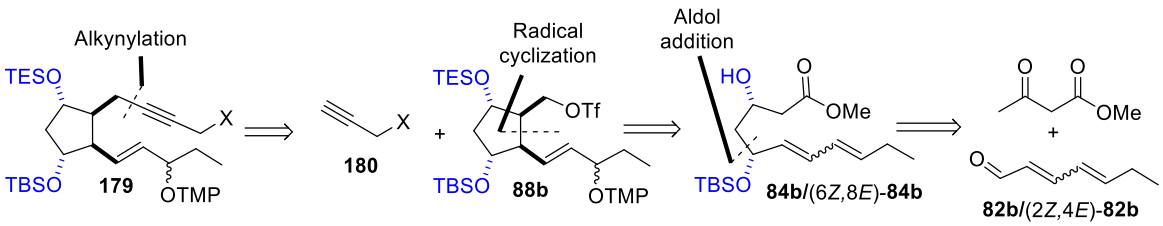
4.2.1 Retrosynthetic analysis

Retrosynthetic analysis of 18-IsoPs **173a-175a** and 20-NeuroPs **173b-174b** commenced with functional group interconversions (FGI) leading to orthogonally protected intermediate **176** (Scheme 72). Another FGI of the skipped polyene system provides polyyne **177**. Subsequent C(sp3)-C(sp) disconnection leads to central precursor **179** and alkyne **178**.



Scheme 72. Retrosynthetic analysis of 18-IsoPs and 20-NeuroPs **173**, **174** and **175**

Analysis of **179** calls for a second C(sp3)-C(sp) disconnection giving propargyl halogenide **180** and triflate **88b** (Scheme 73). The latter is a known compound and as accessible in seven steps, which involve oxidative radical cyclization of enolate and dianion aldol addition as key steps (see section 2.2.4),[96, 97] giving methyl acetoacetate and dienal **82b** as starting materials.

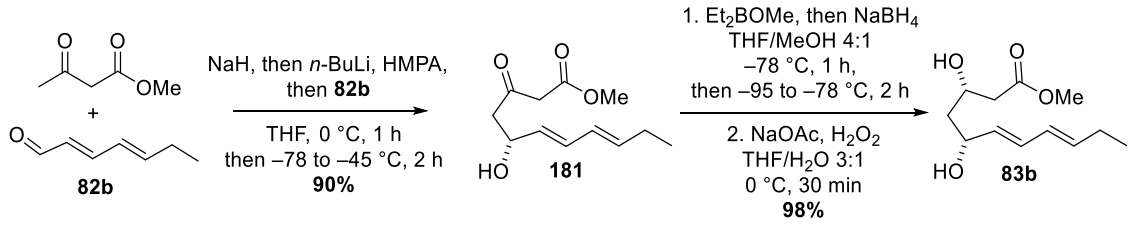


Scheme 73. Retrosynthetic analysis of central precursor **179**.

4.2.2 Synthesis of cyclization precursors 84

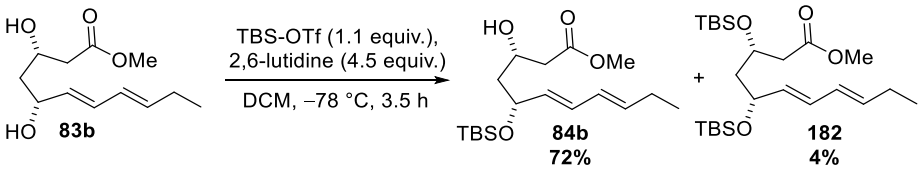
4.2.2.1 Racemic cyclization precursors **84b** *and* **84c**

The synthesis of acyclic precursor **84b** was carried out as described by Smrček *et al*.[99] The reaction sequence started with an aldol addition of methyl acetoacetate dianion to (*E*,*E*)-2,4-heptadienal **82b** in good 90% yield (Scheme 74). Subsequent *syn*-selective reduction of aldol adduct **181** using diethyl(methoxy)borane/$NaBH_4$ followed by an oxidative work-up gave desired diol **83b** in excellent yield and exclusive diastereoselectivity (dr >95:5 as determined by ^1H NMR spectroscopy).



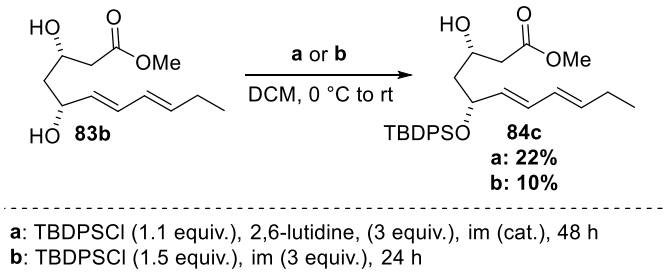
Scheme 74. Synthesis of diol **83b**.

The regioselective monosilylation of diol **83b** using TBSOTf/2,6-lutidine at low temperature to give cyclization precursor **84b** was carried out subsequently. Applying the described conditions[99] afforded desired ether **83b** only in ca 50% yield along with significant amounts of diprotected ether **182** and diol **93b**. Increasing the excess of 2,6-lutidine to 4.5 equivalents and using either freshly opened or distilled TBSOTf ensured satisfactory 72% yield of **84b** (Scheme 75). Other crucial parameters were a very slow dropwise addition of TBSOTf and proper cooling of the reaction mixture.



Scheme 75. Synthesis of silyl ether **84b**.

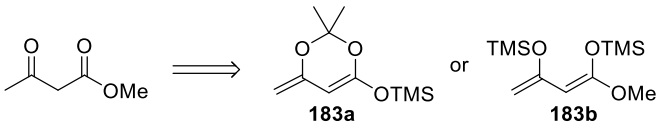
To investigate the influence of the silyl group size on yield and diastereoselectivity of the radical cyclization, bulkier TBDPS-protected cyclization precursor **84c** was prepared. Monoprotection of diol **83b** using an quimolar amount of TBDPSCl in the presence of excess 2,6-lutidine and a catalytic amount of imidazole gave ether **84c** selectively albeit in low 22% yield (Scheme 76, conditions **a**). When 2,6-lutidine was entirely replaced by imidazole and TBDPSCl used in excess, the selectivity was completely abolished and **84c** was isolated in very low 10% yield as inseparable mixture with its regioisomer and 16% of the corresponding disilylated derivative (not shown; conditions **b**). Despite the low yield, sufficient amount of material was obtained for a preliminary cyclization study and the reaction conditions were not further optimized.



Scheme 76. Synthesis of silyl ether **84c**.

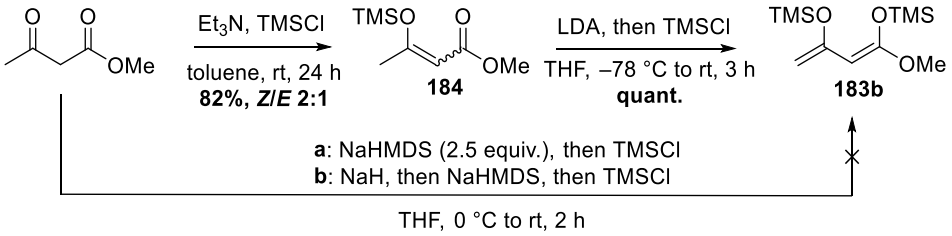
4.2.2.2 Enantiomerically enriched cyclization precursor (3*S*,5*R*)-**84b**

Although NeuroPs occur racemic in Nature, the access to enantioenriched compounds is important for in-depth biological studies. Therefore, the access to cyclization precursor (3*S*,5*R*)-**84b** via an enantioselective Mukaiyama-aldol reaction was envisaged. This reaction is well described and usually proceeds with high enantioselectivities.[159] Two silyl ketene acetals as acetoactate equivalents were envisaged (Scheme 77). Dinca and Jahn previously made use of dioxinone **183a** in the synthesis of a potential metabolite of 15-E_{2t}-IsoP.[98] In the event, the racemic version of the Mukaiyama reaction with **82a** provided the desired product in excellent yield, however, its transformation to the corresponding 3-hydroxy-5-silyloxy ester was not straightforward and added steps to the synthesis. Moreover, attempts to conduct out the reaction enantioselectively provided only low ee and yields.[160] These setbacks could hopefully be overcome by using Chan's diene **183b** instead. Recently, similar approach employing **183b** has been used in the synthesis of a novel PG-like NeuroP.[151]



Scheme 77. Dienes **183a** and **183b** as synthetic equivalents of acetoacetate.

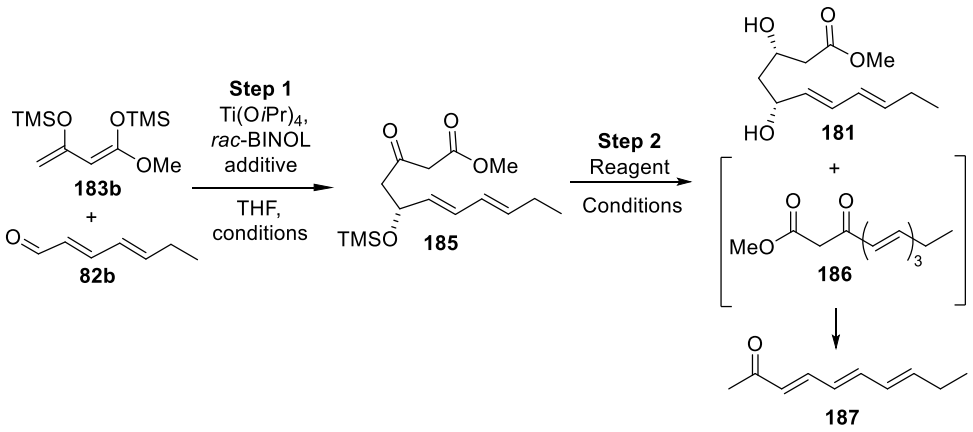
Silyl ketene acetal **183b** was synthesized by a known two-fold silyl enol ether synthesis from methyl acetoacetate.[161] The proposed one-pot synthesis using double deprotonation by NaHMDS (Scheme 78, conditions **a**) or by NaH/NaHMDS (conditions **b**)[162] gave very low conversion and **183b** decomposed in the isolation attempt.[163] Performing the two steps separately was much more efficient. First, silyl enol ether **184** was synthesized under thermodynamic conditions with good yield as 2:1 mixture of *Z* and *E* isomers. Second deprotonation by LDA and enolate trapping gave desired 1,3-bis(TMS) dienol ether **183b**, which could be used directly in the next step without purification.[161] Because of the reported low stability of diene **183b**,[163] it was prepared directly before being applied in the Mukaiyama reaction. Distilled compound **184** was sufficiently stable to be stored for months.



Scheme 78. Synthesis of Chan's diene **183b**.

Diene **183b** was tested in the Mukaiyama aldol reaction with aldehyde **82b**. To explore the general reactivity and to find suitable conditions, the reaction was first ran racemic using catalytic Ti(O*i*Pr)$_4$ and *rac*-BINOL as ligand. Soriente's original conditions with 4Å molecular sieves as additive did not provide full conversion and gave only very low yield of aldol **181** after *in situ* deprotection of the TMS groups of resulting silyl ketene acetal (not shown) and alcohol **185** by TFA (Table 9, entry 1).[164] Other authors also encountered similar reproducibility issues.[160, 165] Xu *et al*. building on Soriente's original work described that both yield and stereoselectivity of the reaction varied massively based on range of factors such as the method of molecular sieves activation.[165] The authors further explored the scope of additives and highlighting that LiCl (2 equiv. with respect to Ti(O*i*Pr)$_4$) provided the best and reproducible results. Applying the method indeed led to full conversion of the starting material with 6 mol.% catalyst loading, but the subsequent silyl deprotection by PPTS cleaved the remaining TMS groups only partially and a mixture of compounds **83b** and **154** was isolated (entry 2).[165]

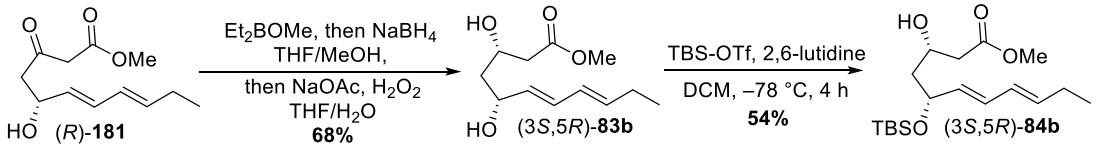
Table 9. Optimization of the Mukaiyama aldol reaction and desilylation.



Entry	**184** (equiv.)	Ti^{IV} (mol.%)[a]	**Step 1** Additive, conditions	**Step 2** Reagent, conditions	**185** (%)	**181** (%)	**187** (%)
1	2	10	4Å molecular sieves[b]	TFA, THF, –78 °C, 2 h	0	28	0
2	2.5	6	LiCl (12 mol.%)[c]	PPTS, THF/MeOH, 3 h[d]	51	40	0
3	2.1	6	LiCl (12 mol.%)[c]	KF, MeOH (wet), 20 min[d]	0	51	43
4	2.1	6[e]	LiCl (12 mol.%)[c]	KF, MeOH (dry), 1 h[d]	0	66[f]	nd

[a] With respect to **82b**. [b] Stirred at –78 °C to rt overnight. [c] Stirred at rt overnight. [d] Stirred at 0 °C. [e] With (*R*)-BINOL. [f] Yield of (*R*)-**181**, 97% ee as determined by HPLC.

The yield of the deprotection step improved with the use of potassium fluoride in MeOH at low temperature (entry 3). The conversion of the second step was complete but the yield diminished due to formation of trienone **187**, formed probably by decarboxylation of unstable elimination product **186** (not isolated). Nevertheless, this protocol was applied to the asymmetric version of the reaction using (*R*)-BINOL complex (entry 4). The reaction was performed in anhydrous MeOH and keeping the temperature strictly at 0 °C along with careful monitoring allowed to stop the reaction right at full conversion and ensured reasonable 66% yield of aldol (*R*)-**181**. The reaction proceeded with excellent 97% ee as determined by HPLC. Enantioenriched aldol product (*R*)-**181** was subsequently reduced and protected in the same way as its racemic analogue **181** to finally give enantioenriched cyclization precursor (3*S*,5*R*)-**84b** (Scheme 79).

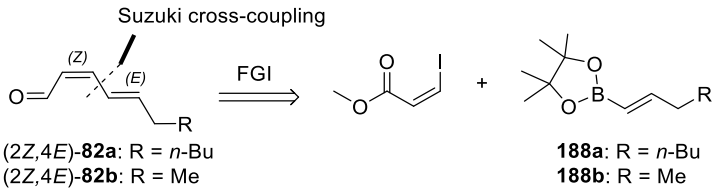


Scheme 79. Synthesis of enantioenriched monoprotected diol (3*S*,5*R*)-**84b**.

4.2.2.3 Cyclization precursor (6*Z*,8*E*)-**84a**

Second modification of the cyclization precursor involved changing the proximal double bond configuration to (*6Z,*8*E*)-**84**. The effect of the proximal and distal double bond configuration was studied before only on simpler 3-alkoxido enolates and a very small shift of diastereoselectivity in favor of the *cis*-cyclopentane was observed for (6*Z*)-substrates.[96] This influence might be amplified by using *syn*-3,5-dioxy esters as cyclization substrates with the reaction conditions already optimized for the synthesis of *cis*-configurated cyclopentanes of the ω-3 or ω-6 isoprostanoid series.[97, 99]

Compounds (*6Z,*8*E*)-**84** can be obtained from corresponding dienals (2*Z,*4*E*)-**82** in analogy to the synthesis of **84** (see Scheme 74). To ensure the correct stereochemistry of both double bonds and to minimize the risk of isomerization, a FGI to the corresponding methyl ester followed by C(sp2)-C(sp2) disconnection was envisaged (Scheme 80), leading to methyl (*Z*)-iodoacrylate and boronates **188**, suitable substrates for a Suzuki cross-coupling reaction.[166]

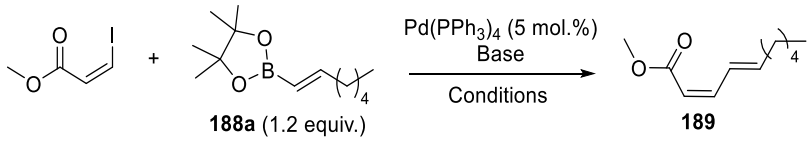


Scheme 80. Retrosynthetic analysis of (2*Z*,4*E*)-dienals (2*Z*,4*E*)-**82**.

Because of the easier accessibility of the longer-chain boronate **188a**, which was commercially available or synthesized in a single step by a known procedure,[167] the ω-6 series was selected for preliminary investigations. Palladium tetrakis(triphenylphosphine) (5 mol.%) was used as catalyst for the Suzuki reaction and the optimizations consisted of finding a proper base.[168] Initially applied

reaction protocol developed recently in Jahn's group which used MeOK as base in THF/MeOH mixture provided low 30% conversion to **189** (Table 10, entry 1).[169] When *t*-BuOK in the same solvent mixture was used instead of MeOK, no desired product was detected in the crude mixture after stirring at room temperature for 48 h (entry 2). KF in THF (entry 3)[170, 171] and K_2CO_3 in THF/water mixture gave the same result (entry 4). K_2CO_3 in dry or wet DMF provided the desired product, albeit in low 14% and 18% conversion, respectively (entries 5, 6).[172] The conversion improved notably when $K_3PO_4 \cdot H_2O$ was used, providing the desired product with 41% conversion in THF/water (entry 7) and 38% in DMF/water (entry 8), respectively.[172] CsF in THF performed similarly, leading to 43% conversion of **188a** to **189** (entry 9).[170] Ultimately applying TlOEt in THF/water mixture led to a substantial improvement with 76% conversion after stirring at room temperature for 90 min (entry 10).[173, 174] Final optimizations revealed that the excess of both boronate **188a** and TlOEt could be decreased to 1.1 equivalents and performing the reaction in THF/H_2O 3:1 mixture at room temperature for two hours resulted in full conversion of **188a** and high 87% isolated yield of (2*Z*,4*E*)-ester **189** (entry 11).

Table 10. Optimization of the Suzuki cross-coupling reaction.

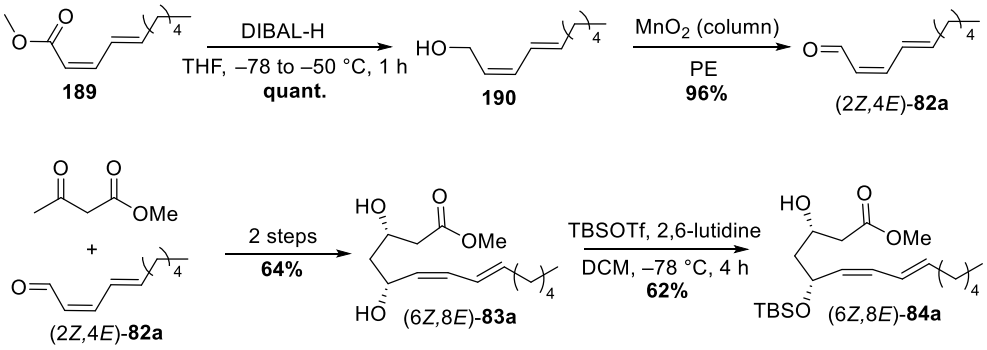


Entry	Base (equiv.)	Solvent	Conditions	**189** (%)[a]
1	MeOK (1.2)	THF/MeOH 2:1	rt to 70 °C, 48 h	30
2	*t*-BuOK (1.5)	THF/MeOH 2:1	rt, 48 h	0
3	KF (1.5)	THF	rt, 24 h	0
4	K_2CO_3 (2)	THF/H_2O 5:1	rt, 24 h	0
5	K_2CO_3 (2)	DMF	rt, 24 h	14
6	K_2CO_3 (2)	DMF/H_2O 5:1	rt, 24 h	18
7	$K_3PO_4 \cdot H_2O$ (1.5)	THF/H_2O 5:1	rt, 24 h	41
8	$K_3PO_4 \cdot H_2O$ (1.5)	DMF/H_2O 5:1	rt, 24 h	38
9	CsF (2)	THF	rt, 24 h	43
10	TlOEt (1.8)	THF/H_2O 5:1	rt, 90 min	76
11[b]	TlOEt (1.1)	THF/H_2O 5:1	rt, 2 h	87[c]

[a] Conversion determined by ^{1}H NMR analysis of the crude mixture. [b] With 1.1 equiv. of **188a**. [c] Isolated yield.

In order to preserve the (*Z*)-configuration of the proximal double bond, ester **189** was first cleanly reduced by excess of DIBAL-H at low temperature to provide corresponding allylic alcohol **190** in quantitative yield (Scheme 81). In contrast, lithium aluminum hydride was unselective and gave a complex inseparable mixture of 1,2-, 1,4- and possibly 1,6-reduction products (not shown). The allylic alcohol was filtered through a column of MnO_2 in petroleum ether solution,[150] giving aldehyde (2*Z*,4*E*)-**82a** in excellent 96% yield over two steps without formation of undesired (2*E*,4*E*)-isomer. Dienal (2*Z*,4*E*)-**82a** was subsequently used in the aldol addition and modified

cyclization substrate (6*Z*,8*E*)-**84a** was obtained in analogy to **84b** in 40% unoptimized yield over three steps.



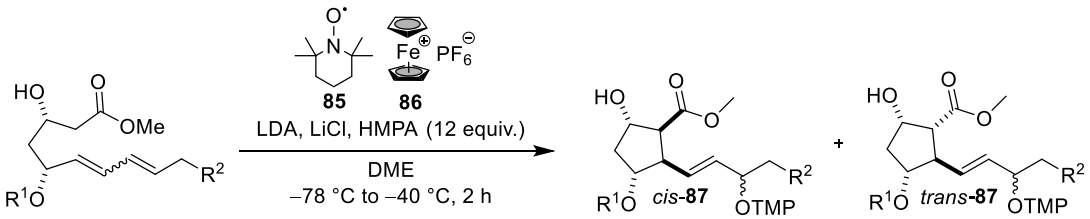
Scheme 81. Synthesis of cyclization precursor (6*Z*,8*E*)-**84a**.

4.2.3 Synthesis of central precursor 179c

4.2.3.1 Oxidative dianion cyclization

The tandem ferrocenium-mediated SET oxidation/radical cyclization/TEMPO oxygenation of β-hydroxyesters **84** was initially carried out by subjecting **84b** to the previously reported conditions (deprotonation by 2.6 equiv. of LDA in the presence of 6 equiv. of LiCl, then SET oxidation/TEMPO oxygenation in the presence of 12 equv. of HMPA) to give a mixture of products *cis*/*trans*-**87b** with somewhat lower yield and diastereoselectivity than reported (55% and *cis/trans* 1.6:1 vs 64% and *cis*/*trans* 2:1;[99] Table 11, entry 1). Changing the mode of addition of TEMPO (**85**)/ferrocenium salt (**86**) from method **A** (addition of **85** mixed with a small portion of **86** first, then more **86**) to method **B** (addition of **85**, then **86** separately) or **C** (addition of a mixture of **85** and **86** in small portions) provided comparable results and gave **87** in 2:1 diastereoselectivity and 49% and 41% yields, respectively (entries 2, 3). An improvement of the yield to 63% and dr to 2.3:1 was achieved by increasing the excess of LDA and LiCl to 3 equiv. and 8.5 equiv., respectively (entry 4). Applying the same conditions on larger scale repetitively provided **87** in slightly lower 55-60% yield while conserving the diastereoselectivity. Raising the amount of LiCl further to 10 equiv. did not significantly affect yield nor diastereoselectivity (entry 5, 59%, dr 2.5:1). In case of TBDPS-protected cyclization precursor **84c**, applying the original reaction conditions[99] while switching to THF as **84c** was insoluble in DME provided good 66% unoptimized yield and 1.5:1 diastereoselectivity of hydroxycyclopentane carboxylate **87b** (entry 6). Hydroxyester (6*Z*,8*E*)-**84a** gave comparable 1.6:1 diastereoselectivity, but only low 25% yield of product **87b** under the benchmark conditions (entry 7). Exchanging 1,2-dimethoxyethane (DME) with THF[97, 98] improved the yield to 43% but the diastereoselectivity did not increase (entry 8), suggesting negligeable influence of the double bond configuration on the cyclization transition state energies. The cyclization of (6*Z*,8*E*)-**84a** was not further studied. As silyl ether **84c** was considerably more difficult to synthesize than **84b** and both compounds behaved similarly, the synthesis was continued solely with TBS-protected hydroxycyclopentane carboxylate **87b**.

Table 11. Optimization of oxidative cyclization of the dianion of esters **84**.



R^1 = TBS, R^2 = *n*-Bu: (6*Z*,8*E*)-**84a**
R^1 = TBS, R^2 = Me: **84b**
R^1 = TBDPS, R^2 = Me: **84c**

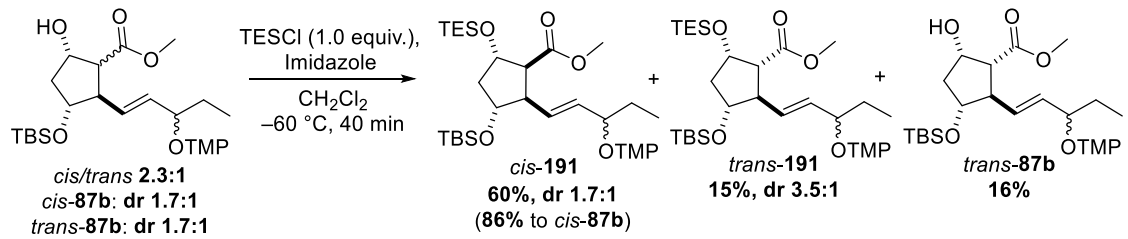
R^1 = TBS, R^2 = *n*-Bu: **87a**
R^1 = TBS, R^2 = Me: **87b**
R^1 = TBDPS, R^2 = Me: **87c**

Entry	Substrate (mmol)	Method[a]	LDA (equiv.)	LiCl (equiv.)	**87** (%)	dr (*cis*/*trans*)
1	**84b**	**A**	2.6	6	55	1.6:1
2	**84b**	**B**	2.6	6	49	2:1
3	**84b**	**C**	2.6	6	41	2:1
4	**84b**	**A**	3	8.5	63[b]	2.3:1
5	**84b**	**A**	3	10	59	2.5:1
6	**84c**	**B**[c]	2.6	6	66	1.5:1
7	(6*Z*,8*E*)-**84a**	**B**	2.6	6	23	1.6:1
8	(6*Z*,8*E*)-**84a**	**B**[c]	2.6	6	43	1.6:1

[a] **A**: **85** (1.2 Equiv.) mixed with a small portion of **86** added first, followed by **86** in small portions until the reaction mixture remained dark blue-green. **B**: **85** (1.2 equiv.) added first, followed **86** in small portions until the reaction mixture remained dark blue-green. **C**: **85** (1.2 equiv.) mixed with **86** (1.5 equiv.) added first, followed by **86** in small portions until the reaction mixture remained dark blue-green. [b] Repetitive yield on 1.5 mmol scale 55-60%. [c] In THF instead of DME.

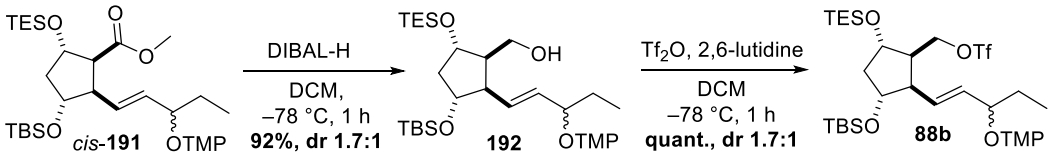
4.2.3.2 Synthesis and alkynylation of of triflate **88b**

Transformation of cyclic ester **87b** was carried out similarly to the published procedure with some minor modification.[99] First, diastereoselective silylation of sterically less hindered *cis*-**87a** was performed. Increasing the amount of TESCl compared to the reported procedure (1 equiv. with respect to **87b** vs. 1 equiv. with respect to *cis*-**87b**[99]) ensured full conversion of the diastereomer *cis*-**87b** along with partial conversion of *trans*-**87b** (Scheme 82). The diastereomerically enriched mixture of *cis*-/*trans*-**191** was still easily separable by column chromatography and the reaction conditions thus gave the desired compound *cis*-**191** in 60% yield (86% with respect to *cis*-**87b**) along with 15% of *trans*-**191** and 16% of recovered starting material *trans*-**87b**.



Scheme 82. Diastereoselective silylation of **87b**.

Disilylated ester *cis*-**191** was cleanly converted to corresponding triflate **88b** in two steps.[99] Reduction of ester by DIBAL-H provided alcohol **192**, which was transformed to **88b** using Tf_2O in the presence of 2,6-lutidine at low temperature with excellent 92% yield over two steps (Scheme 83).

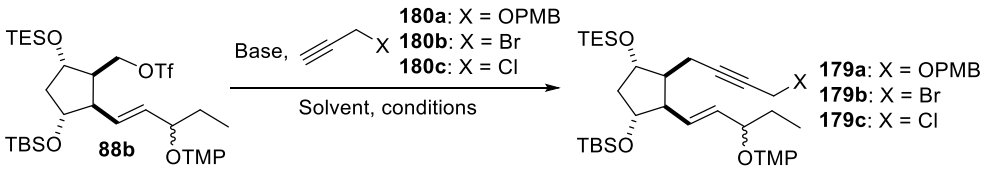


Scheme 83. Synthesis of triflate **88b**.

Triflate **88b** was a suitable substrate for alkynylation using difunctional propargylic reagents **180**. First, PMB-protected propargyl alcohol **180a**[117] was subjected to the reaction with **88b** after deprotonation by *n*-BuLi in a THF/HMPA mixture at low temperature to provide desired ether **179a** in 64% yield (Table 12, entry 1). However, attempts of subsequent deprotection of the PMB group by DDQ or cerium ammonium nitrate provided below 25% conversion of **179a** to the corresponding free alcohol, which was inseparable from *p*-methoxybenzaldehyde formed as a byproduct during the reaction (not shown). A more straightforward approach involved alkylation of anions derived from propargyl bromide **180b** and propargyl chloride **180c**. The corresponding lithium acetylides are described in the literature although their formation requires carefully controlled conditions.[175] To the best of our knowledge, they have never been used for an S_N2 reaction on carbon.

Pursuing this approach, propargyl bromide **180b** was deprotonated by LDA and reacted with **88b** but the desired (bromobutynyl)cyclopentane **179b** was not isolated and only a complex mixture of products, which further decomposed during purification, was formed in the reaction (entry 2). In contrast, deprotonation of propargyl chloride **180c** by *n*-BuLi was successful and afforded product **179c**, albeit in low 32% yield (entry 3). The yield of (chlorobutynyl)cyclopentane **179c** reached acceptable 65% when the reaction time was shortened to 2 h while warming to 0 °C instead of room temperature (entry 4). Switching back to LDA for deprotonation of **180c** and raising the temperature to –40 °C over two hours further increased the yield to 77% (entry 5). In contrast, decreasing the amount of HMPA resulted in a sharp decrease of the yield to 32% (entry 6). Final optimization revealed that performing the deprotonation at –110 °C by LDA and raising the reaction temperature to maximally –50 °C over an hour were the optimal reaction conditions, providing **179c** in 81% yield (entry 7). The use of propargyl chloride anion in alkylation reactions is a valuable synthetic tool for constructing various alkyne systems.

Table 12. Alkynylation of triflate **88b** by anions of propargylic units **180**.

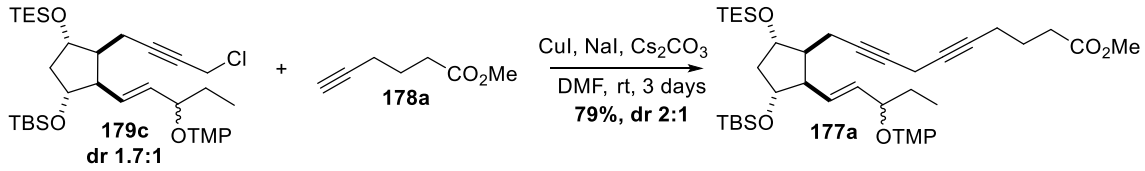


Entry	X	Base	Solvent	Conditions	**179** (%)
1	OPMB	*n*-BuLi	THF/HMPA 4:1	–78 to –10 °C, 1.5 h	64
2	Br	LDA	Et_2O/HMPA 10:1	–90 to 0 °C, 1 h	0
3	Cl	*n*-BuLi	Et_2O/HMPA 10:1	–85 °C to rt, overnight	32
4	Cl	*n*-BuLi	Et_2O/HMPA 10:1	–85 to 0 °C, 2.5 h	65
5	Cl	LDA	Et_2O/HMPA 10:1	–85 to –40 °C, 2 h	77
6	Cl	LDA	Et_2O/HMPA 20:1	–85 to –40 °C, 2 h	32
7	Cl	LDA	Et_2O/HMPA 10:1	–110 to –50 °C, 1 h	81

4.2.4 Application of the strategy to the total synthesis of 18-F_{3t}-IsoP

4.2.4.1 Synthesis and hydrogenation studies of diyne **177a**

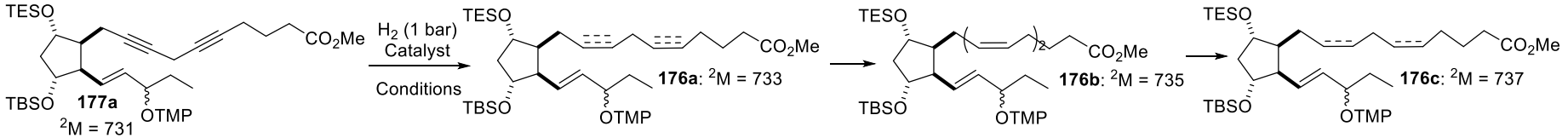
Among the isoprostanoids with 3-hydroxypentenyl omega chain and a skipped-polyene α-chain, 18-F_{3t}-IsoP was a suitable target to validate the unified strategy as its α-chain contains a single skipped diene unit. Moreover, this EPA metabolite has not yet been synthesized to date. To access the full carbon framework, (chlorobutynyl)cyclopentane **179c** was subjected to standard Cu(I)-mediated C(sp3)-C(sp) bond coupling conditions with methyl hex-5-ynoate **178a** to provide skipped diyne **177a** in good 79% yield (Scheme 84).[176] The reaction was very slow and prolonged reaction time of three days as well as three-fold excess of **178a** and the other reagents was required to reach full conversion of **179c**.



Scheme 84. Synthesis of diyne **177a**.

Next, several attempts of semihydrogenation of **177a** were conducted. Analysis of the crude mixture by MS in the positive mode of electrospray ionization (+ESI) provided quick semi-quantitative data about the relative abundance of these species. Relative peak intensities of the second most abundant isotopic mass (^{2}M) are displayed and were used for monitoring in order to minimize ambiguity, as ^{1}M of the corresponding hydrogen adducts can be confused with ^{3}M of others. If the Lindlar catalyst in cyclohexane was used, desired product **176b** was was obtained in 55% yield as calculated by ^{1}H NMR of the inseparable mixture with corresponding enyne **176a** and traces of overhydrogenated product **176c** (Table 13, entry 1).

Table 13. Semihydrogenation attempts of diyne **177a**.



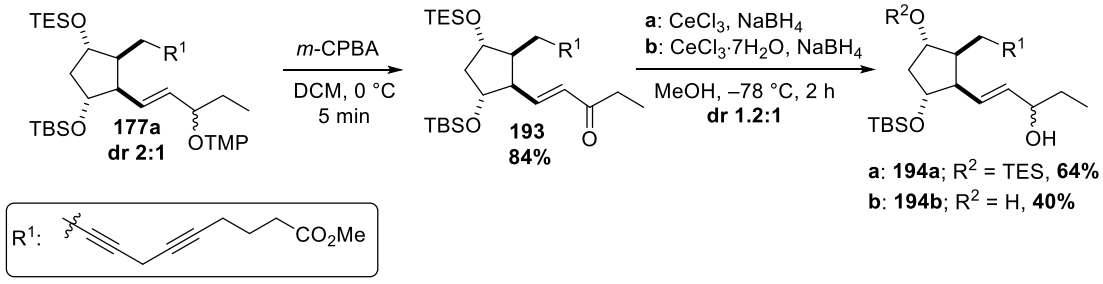
Entry	Catalyst (equiv.)	Solvent (mL/mmol)	Time (h)	MS (+ESI) m/z (%)[a]	Conversion (%)	**176b** (%)[b]	Mass balance (%)
1	Lindlar (1.3 w/w)	Cyclohexane (125)	8	738 (32) [**176c**+H]$^+$, 736 (100) [**176b**+H]$^+$, 734 (85) [**176a**+H]$^+$	100	55	82
2	Lindlar (0.5 w/w)	Cyclohexane/Py/Isoamylene (80:20:20)	16	738 (6) [**176c**+H]$^+$, 736 (42) [**176b**+H]$^+$, 734 (100) [**176a**+H]$^+$	100	25	80
3	Lindlar (0.5 w/w)	EtOAc/EtOH/Py (286:87:29)	24	732 (100) [**177a**+H]$^+$	0	0	86
4	P2-Ni[c] (4)	EtOH (400)	2	738 (17) [**176c**+H]$^+$, 736 (58) [**176b**+H]$^+$, 734 (100) [**176a**+H]$^+$ [d]	100	32	78
5	P2-Ni[c] (0.5)	EtOH (100)	60	745 (100) [**177a**+CH_2+H]$^+$	100	0	98

[a] Crude mixture analyzed after work-up. [b] Determined by ^{1}H NMR spectroscopy of the inseparable mixture of **177a** and **176a-c**. [c] Prepared by stirring $Ni(OAc)_2$ and $NaBH_4$ (2 equiv.) in EtOH in H_2 atmosphere for 15 min, then poisoning the catalyst by ethylene diamine (8 equiv.) and stirring for further 15 min under H_2 before addition of **177a**. [d] Analogous set of peaks at [**176a-c**+CH_2+H]$^+$.

Decreasing the catalyst load while adding pyridine/isoamylene for catalyst poisoning slowed down the reaction as the **176a**/**176b** ratio increased yield but did not prevent formation of **176c** and the conditions provided **176b** in 25% yield (entry 2). When the solvent was switched from cyclohexane to EtOAc/EtOH with addition of pyridine for catalyst poisoning and the dilution was increased, only starting material **177a** was recovered (entry 3).[97] Substituting the Lindlar catalyst with P2-Ni in a stochiometric amount with high dilution in EtOH provided similar results to the Lindlar catalyst-mediated reaction but the products **176a-c** were accompanied by their ethyl esters to a significant extent (entry 4). P2-Ni in a catalytic amount provided only the transesterified product of starting material **177a** (not shown, entry 5).[177] Excess $NaBH_4$/ROH was reported as a selective transesterification reagent of β-ketoesters by Padhi and Chadha[178] and transesterification as side reaction was also encountered under similar P2-Ni-catalyzed hydrogenation conditions in the synthesis of 4-F_{4t}-NeuroP performed by Oger.[81] It should be noted that the crude organic mass recovery of **176a**/**177a** from the hydrogenation experiments was around 80%, indicating low stability of the diyne, enyne and diene system under the conditions.

4.2.4.2 Completion of the total synthesis of 18-F_{3t}-IsoP

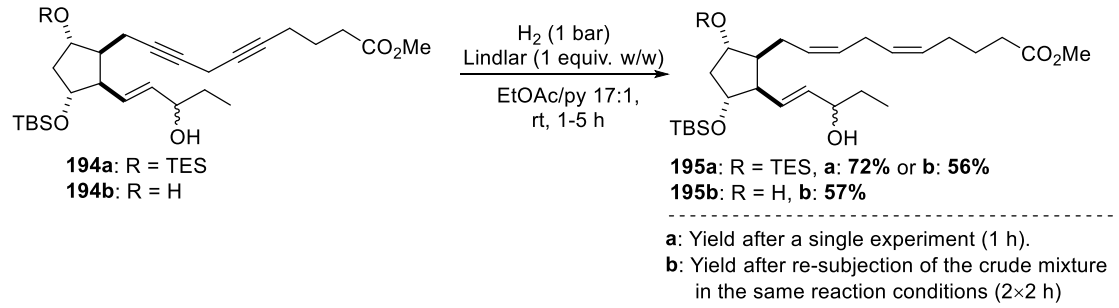
In order to achieve better selectivity in the semihydrogenation, the TMP group was deprotected under previously reported oxidative conditions using *m*-CPBA (Scheme 85).[179] Despite the sensitivity of diyne **177a**, shortening the reaction time to precisely five minutes ensured a neat reaction and enone **193** was obtained in high 84% yield. Subsequent reduction under Luche conditions provided allylic alcohol **194a** in 64% yield as 1.2:1 mixture of diastereomers (conditions **a**). The low water content in $CeCl_3$ was important: when it was used directly as its heptahydrate, TES deprotection and possibly other degradation occurred to provide diol **194b** in moderate 40% yield as a single isolated product (conditions **b**).



Scheme 85. Synthesis of allylic alcohols **194a-b**.

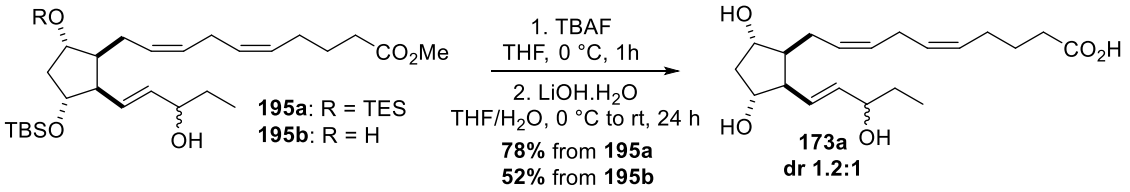
The allylic alcohols were then subjected to the hydrogenation conditions. Hydrogenation of **194a** using Lindlar catalyst (1 equiv. w/w) in EtOAc with pyridine cleanly provided desired (*Z*)-diene **195a** with 72% yield (Scheme 86, conditions **a**). Nevertheless, the outcome of the reaction varied in subsequent attempts to reproduce the initial result. Thus, if the reaction was not complete in two hours, work-up followed by re-subjecting the crude mixture to the same reaction conditions with a new batch of catalyst was necessary to prevent degradation and to ensure good selectivity. These conditions afforded desired (*Z*)-diene in lower 56% yield (conditions **b**). In the same way, applying the conditions **b** to diyne **194b** delivered (*Z*)-diene **195b** in 57% yield. Similarly to the

hydrogenation attempts of **177a**, the mass balance was low and no other product than **195** was isolated. Reproducibility issues are often described with Lindlar semihydrogenations and the reactions must be properly monitored.[180]



Scheme 86. Semihydrogenation of allylic alcohols **194**.

The remaining silyl group(s) on alcohols **195a** and **195b** were cleaved using TBAF in dry THF and subsequent saponification by $LiOH \cdot H_2O$ furnished **174a** as partially separable 1.2:1 mixture of diastereomers in 78% and 52% unoptimized yields over two steps from **195a** and **195b**, respectively (Scheme 87). The relative configuration on C-18 was assigned after comparison of ^{1}H and ^{13}C NMR data of the individual epimers 18-F_{3t}-IsoP and 18-*epi*-18-F_{3t}-IsoP. Thus, the total synthesis of 18(*RS*)-18-F_{3t}-IsoP was accomplished in 5% yield over 14 steps.[78]

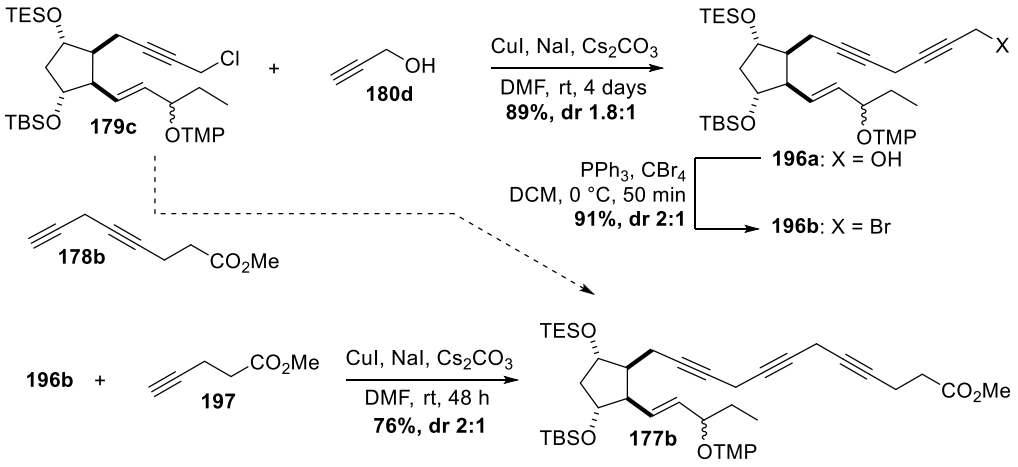


Scheme 87. Deprotection and saponification of esters **195**.

4.2.5 Application of the strategy toward the synthesis of 20-NeuroPs

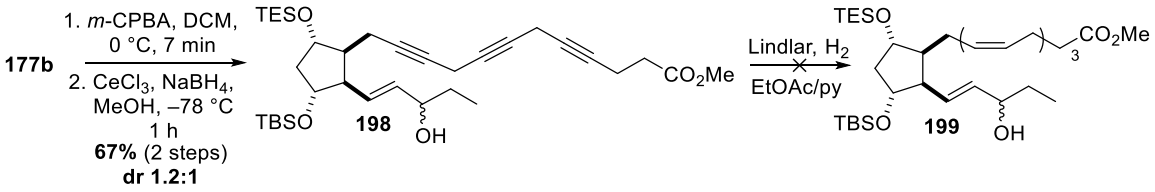
4.2.5.1 Synthesis of triyne **177b** *and initial hydrogenation attempts*

To access the full carbon framework of 20-NeuroPs from central precursor **179c**, the skipped triyne side chain was introduced in three steps. First, a second propargylic unit was installed by Cu(I)-mediated reaction of **179c** and propargyl alcohol in very good 89% yield after stirring for four days (Scheme 88). Resulting alcohol **196a** was converted to propargylic bromide **196b** using the Appel reaction in excellent yield. A second Cu(I)-mediated coupling with methyl pent-4-ynoate **197**[181] furnished triyne **177b** in 76% yield. A potentially more direct approach consisting of Cu(I)-mediated coupling reaction of **179c** with diyne **178b** was not pursued because of the long coupling times of **179c** and possible sensitivity of **178b**.



Scheme 88. Synthesis of triyne **177b**.

Triyne **177b** was subsequently converted to free alcohol **198** in analogy to **177a** in 67% unoptimized yield over two steps (Scheme 89), however, subjecting **198** to the conditions successful for hydrogenation of **194** did not provide tetraene **199**. Instead, only degradation products including corresponding conjugated species (not shown) were observed and the organic mass balance after column chromatography was below 20%.



Scheme 89. Synthesis and hydrogenation attempts of triyne **198**.

4.2.5.2 Hydrogenation studies of diynes **196a** *and* **196c**

Next, the conditions of hydrogenation of diyne **196a** were optimized through a series of small-scale (10 μmol) experiments. The reactions were monitored by TLC-MS (+ESI) and intercepted when the proportion of desired (*Z*)-diene reached a maximal value, providing a first semi-quantitative result. The inseparable product mixtures were subsequently analyzed by MS (+ESI) and ^{1}H and ^{13}C NMR spectroscopy to determine the conversion and proportion of desired triene **200b**. Isomeric species such as corresponding conjugated allenes, which are indistinguishable by MS from compounds **200a-200d**, were not detected by ^{1}H or ^{13}C NMR spectroscopy, but they might have been present in amounts below detection limit.

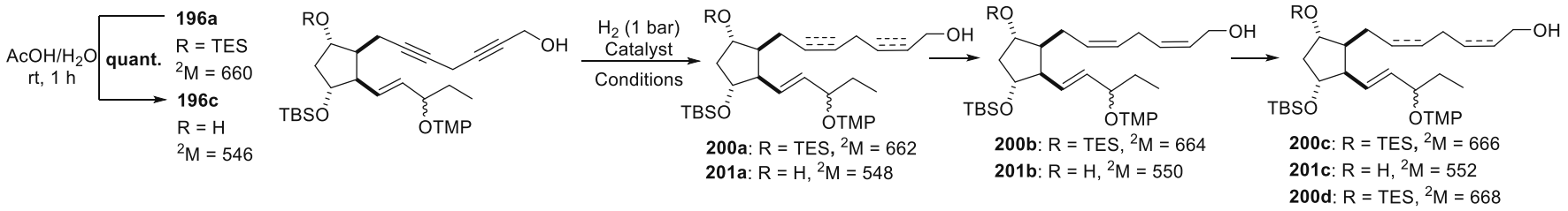
First, alcohol **196a** was hydrogenated in the presence of P2-Ni giving only small fraction of partially hydrogenated enyne **200a** along with starting material (Table 14, entry 1).[177] Applying the conditions used previously for hydrogenation of **194** (Lindlar catalyst in EtOAc/py) resulted in full conversion of **196a** but enyne **200a** was the major product with small 20% yield of desired product **200b** as calculated by ^{1}H NMR spectroscopy from the inseparable **200a**/**200b** mixture (entry 2). Increasing the reaction time to 1.5 days increased the proportion of the desired product but overhydrogenation also occurred (entry 3). Exchanging EtOAc by MeOH accelerated the reaction

significantly, but the chemoselectivity was completely abolished and only a mixture of overhydrogenated products **200c** and **200d** was obtained after stirring at room temperature for two hours (entry 4). Performing the reaction in MeOH and decreasing the reaction temperature to 0 °C did not prevent overhydrogenation, which occurred already after 1 h and alkyne **200c** was obtained as a single product (entry 5). In contrast, the reaction was complete within 45 min when carried out in a mixture of MeOH/EtOAc with pyridine at 0 °C, giving desired product **200b** in 75% calculated yield, iseparable from overhydrogenated product **200c** and enyne **200a** (entry 6).

In order to investigate the influence of free hydroxy groups on the reactivity and selectivity of the reaction, diol **196c** was synthesized by a chemoselective deprotection of the TES group. Subsequent semihydrogenation using the Lindlar catalyst in EtOAc provided desired triene **201b** quite cleanly with 79% yield as calculated by ^{1}H NMR along with some overhydrogenated product **201c** (entry 7). Conversely, the reaction in a mixture MeOH/EtOAc was slower than in case of **196a** and did not reach full conversion at 0 °C after 1 h (entry 8). When the same conditions were used at room temperature, the reaction proceeded to overhydrogenation over 3 h (entry 9). According to these results, the effect of the additional free hydroxy group on the hydrogenation was negligible. Moreover, the primary hydroxy group of diol **201b** could not be converted selectively to the corresponding bromide or tosylate required for the subsequent Cu(I)-mediated coupling reaction. Therefore, optimal conditions to pursue the synthesis relied on applying hydrogenation of **196a** under conditions of entry 6. As the first hydrogenation step was complete within minutes for both substrates **196a** and **196c** (see the Experimental section), working-up the reaction and re-subjecting the mixture of the partially hydrogenated products **200a** or **201a** to the same conditions with a new catalyst batch should be considered for future optimizations to ensure reproducible results, similarly to the hydrogenations of **194a-b** (see Scheme 86).

Thus, skipped diene **200b** as key 20-NeuroP precursor was synthesized in 14% yield over 10 steps. The remaining steps to obtain 20-F_{4t}-NeuroP involve introduction and hydrogenation of the last alkyne moiety and deprotection steps in analogy to the synthesis of 18-F_{3t}-IsoP. The experimental work to complete the total synthesis is underway but the results are beyond the timeframe of this thesis.

Table 14. Semihydrogenation of diynes **196a** and **196c**.



Entry	Substrate	Catalyst[a]	Solvent[b]	Conditions	MS (+ESI) m/z (%)[c]	Conversion (%)[d]	**201b** or **200b** (%)[d]
1	**196a**	P2-Ni	EtOH	24 h, rt	663 (30) [**200a**+H]$^+$, 661 (100) [**196a**+H]$^+$	20	0
2	**196a**	Lindlar	EtOAc/py 17:1	overnight, rt	665 (40) [**200b**+H]$^+$, 663 (100) [**200a**+H]$^+$	100	20
3	**196a**	Lindlar	EtOAc/py 17:1	1.5 days, rt	667 (30) [**200c**+H]$^+$, 665 (100) [**200b**+H]$^+$	100	50
4	**196a**	Lindlar	MeOH/py 17:1	2 h, rt	669 (10) [**200d**+H]$^+$, 667 (100) [**200c**+H]$^+$	100	0
5	**196a**	Lindlar	MeOH/py 17:1	1 h, 0 °C	667 (100) [**200c**+H]$^+$	100	0
6	**196a**	Lindlar	MeOH/EtOAc/py 12:5:1	45 min, 0 °C	667 (1) [**200c**+H]$^+$, 665 (100) [**200b**+H]$^+$, 663 (1) [**200a**+H]$^+$	100	75
7	**196c**	Lindlar	EtOAc/py 17:1	24 h, rt	553 (7) [**201c**+H]$^+$, 551 (100) [**201b**+H]$^+$	100	79
8	**196c**	Lindlar	MeOH/EtOAc/py 12:5:1	1 h, 0 °C	549 (100) [**201a**+H]$^+$, 547 (30) [**196c**+H]$^+$	62	0
9	**196c**	Lindlar	MeOH/EtOAc/py 12:5:1	3 h, rt	553 (90) [**201c**+H]$^+$, 551 (100) [**201b**+H]$^+$	100	52

[a] 40 mol.% (P2-Ni)/1 equiv. w/w (Lindlar). [b] 150 mL/mmol. [c] Crude mixture analyzed after work-up. [d] Yield of **200b** for entries 1-6, **201b** for entries 7-9, determined by ^{1}H NMR spectroscopic analysis of the inseparable mixture of **196a** or **196c** and **200a-c** or **201a-c**, respectively.

5 CONCLUSIONS AND OUTLOOK

A. Three different strategies toward the synthesis of cyclopentene core of A- and J-NeuroPs were explored. An enantioselective strategy relied on asymmetric organocatalytic Michael addition to introduce the absolute stereochemistry. The relative stereochemistry was achieved by thermodynamic equilibration; triple functionalization on carbonyl provided key orthogonally protected intermediate **148**. Besides that, a competitive, more direct albeit racemic approach to this intermediate was developed, employing diastereoselective vicinal difunctionalization of an α,β-unsaturated lactone. In order to introduce vinyl group in the α-position, phenylselenyl acetaldehyde was successfully applied as a vinyl surrogate. The second strategy is very straightforward and potentially provides fast access to racemic synthetic material. Another approach using malonate chemistry was also explored without fruitful results.

The succesful asymmetric strategy was subsequently applied on the synthesis of 4-A_4-NeuroP. Introduction of the α-chain along with the cyclopentene core was accomplished thanks to a developed double olefin metathesis reaction and a Wittig reaction was employed to connect the ω-chain. Final oxidation and deprotection steps proved to be extremely challenging due to the instability of δ-oxy β,γ-unsaturated enone framework, however, two potential metabolites of the target NeuroP, namely 4(*RS*)-4-A_4-NeuroP 1,4-lactone **103b** and 4-deoxy-$\Delta^{4,6}$-A_4-NeuroP **103c** were synthesized in 1.2 and 1.7% yield over 21 and 22 steps, respectively. The former proved to be highly unstable and decomposed during storage at low temperature within days.

B. The existing strategy of synthesis of isoprostanoids with 3-hydroxypentenyl ω-chain[99] was extended to metabolites with skipped (*Z*)-polyene α-chain. The synthesis of key central intermediate **179c** was based on previously developed oxidative radical cyclization and new acetylide alkylation of propargyl chloride **180c**. Furthermore, synthesis of enantiomerically enriched cyclization precursor via enantioselective Mukaiyama reaction was developed, providing formal access to enantiomerically enriched metabolites. Cu(I)-mediated C(sp3)-C(sp) coupling was employed for the introduction of the remaining α-chain subunits of the desired diynes and polyynes. Lindlar semihydrogenation of diynes was optimized to transform them to corresponding dienes.

The strategy was successfully applied to the total synthesis of *rac*-18(*RS*)-18-F_{3t}-IsoP, a metabolite of EPA, which was accomplished for the first time in 5% yield over 14 steps.[78] Access to 20-NeuroPs using this approach is possible from diene **200b**, which was itself synthesized in 14% yield over 10 steps. Synthesis of other types of isoprostanoids becomes feasible thanks to an orthogonal protection the central intermediates.

The question of the lipid peroxidation impact of on the human organism becomes more relevant as marine oil-based nutraceuticals containing ω-3 PUFA are on the rise. It was demonstrated recently that corresponding isoprostanoids are found in these food supplements despite the presence of antioxidants.[78] The biological activities reported to this day are significant and NeuroPs should be studied in more detail, both as potential impurities in ω-3 PUFAs and as potential drug candidates. In the field of diagnostics of neurological diseases, the search for an ideal biomarker of oxidative stress is ongoing. In this respect, the syntheses developed in this work address the need for synthetic material necessary to study the individual molecules.

However, considering the complexity of PUFAs, such as DHA, the options of auto-oxidative processes are vast and there is probably a large number of metabolites beyond NeuroPs yet to be discovered. With the recent advances in bioinformatics, expanding computational approaches to natural product discovery and molecular networks,[182] it is likely that new remarkable oxylipin molecules will be found. For this reason, total synthesis will always have its place in the field to allow single molecule-oriented studies. There is persisting need for more versatile, divergent and flexible strategies providing parallel access to various metabolites. This work is a humble contribution to the field, ultimately expanding the body of knowledge about NeuroPs and their role in human health and disease.

6 EXPERIMENTAL SECTION

6.1 General information

All reactions requiring anhydrous conditions were conducted in dry glassware (oven 120 °C or flame-dried) with magnetic stirring under an atmosphere of nitrogen unless otherwise mentioned. All anhydrous solvents and reagents were dried following standard methods under a nitrogen or argon atmosphere or used as obtained from suppliers. Reactions were monitored by TLC using plates precoated with silica gel 60 with 254 nm fluorescent indicator (Merck, Fluka or Macherey-Nagel). Reaction components were visualized by using a 254 nm UV lamp or by staining with acidic *p*-anisaldehyde or $KMnO_4$ followed by gentle heating. Column chromatography was performed using silica gel 40–63 μm 230–400 Mesh, Merck or Acros). PE (40-65°C boiling range) was used for chromatographic separations. Optical rotations of enantioenriched compounds isolated as pure diastereomers were recorded on JASCO P2000-series apparatus and the concentrations *c* for the optical rotation data are given in g/100 mL. Analytical HPLC was performed on an Agilent 1260 Infinity instrument coupled to a UV detector and light scattering detector PL-ELS 2100 (Polymer Laboratories) using Amylose SA column. SFC analyses were carried out at Laboratoire de Chimie Organique at Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris. Infrared spectra were taken on an ALPHA (Bruker) or Spectrum 1000 (Perkin-Elmer) spectrometers as neat samples using an ATR device; absorptions are given in wave numbers (cm^{-1}). EI and CI mass spectra were measured on GCT Premier orthogonal acceleration time-of-flight spectrometer (Waters). ESI/MS and HRMS spectra were measured on Q-Tof micro (resolution 100000, Waters) or Synapt G2-S mass spectrometers (Waters). Data were obtained by positive or negative ESI methods between 100 and 1500 Da by direct introduction. NMR spectra were recorded on an AV III 400 HD spectrometer (Bruker) equipped with a cryo-probe, an AV III 400 spectrometer (Bruker) equipped with an inverse broad-band probe, an AV III HD 600 spectrometer (Bruker) or at 300 MHz or 500 MHz Bruker spectrometers in $CDCl_3$ or CD_3OD. ^1H NMR chemical shifts are provided in ppm using tetramethylsilane as external standard (internal reference at $\delta = 7.26$ ppm for $CDCl_3$, $\delta = 3.31$ ppm for CD_3OD and $\delta = 7.16$ for C_6D_6) and are reported as follows: chemical shift in ppm [multiplicity, coupling constant(s) *J* in Hz, integral; attribution]. The multiplicities are defined as follow: br = broad, m = multiplet, s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet or combinations thereof. The "*Z*" lower index suffix was used for signals of (*Z*)-alkene units. ^{13}C NMR chemical shifts were referenced against the residual solvent central peak ($\delta = 77.16$ ppm for $CDCl_3$, $\delta = 49.0$ ppm for CD_3OD and $\delta = 128.06$ for C_6D_6). Connectivity was determined by ^1H-^1H COSY experiments; carbon resonances were assigned by APT, HSQC and HMBC experiments.

6.2 Known compounds prepared according to published procedures

Following compounds were prepared strictly according to published procedures or with some minor modifications (see Results and discussion).

(*E*)-4,4-Dimethoxybut-2-enal **106a** (2 steps)[101]
(*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **109b**[107]
(*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **109c**[107]
Diethyl 2-(1,1-dimethoxy-4-oxobutan-2-yl)malonate *rac*-**105a**[103]
4-((4-Methoxybenzyl)oxy)butan-1-ol **126**[117]
(2*R*)-4,4-Dimethoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-(nitromethyl)butanal **123**[115]
4-Vinyltetrahydro-2*H*-pyran-2-one *rac*-**48**[142]
2-(Phenylselanyl)acetaldehyde **149**[143]
tert-Butyldimethylsilyl pent-1-en-3-yl ether **155b**[144]
Pent-1-en-3-yl acetate **155c**[145]
Methyl 4-hydroxyhex-5-enoate **162a**[149]
Methyl (6*E*,8*E*)-5-hydroxy-3-oxoundeca-6,8-dienoate **181**[99]
Methyl (3*S**,5*R**,6*E*,8*E*)-3,5-dihydroxyundeca-6,8-dienoate **83b**[99]
Methyl (3*S**,5*R**,6*E*,8*E*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxyundeca-6,8-dienoate **84b**[99]
(*Z*)-4-Methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **183b** (2 steps)[161]
trans-1-Hepten-1-ylboronic acid pinacol ester **188a**[167]
p-Methoxybenzyl propargyl ether **180a**[117]
Methyl hex-5-ynoate **178a**[183]
Methyl pent-4-ynoate **197**[181]

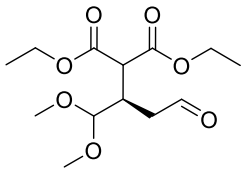
6.3 Synthesis of 4-A_4-NeuroP

6.3.1 Synthetic strategy I

6.3.1.1 Synthesis of lactone **104a**

Diethyl (*R*)-2-(1,1-dimethoxy-4-oxobutan-2-yl)malonate 105a

A solution of TBS-protected catalyst **109c**[107] (9.8 mg, 0.027 mmol) in EtOH (0.3 mL) was added to a solution of enal **106a**[57] (35 mg, 0.267 mmol), benzoic acid (3 mg, 0.027 mmol) and water (10 µL, 0.53 mmol) in EtOH (1 mL) at 0 °C. The solution turned bright yellow and was stirred at this temperature for 5 min. Diethyl malonate (61 µL, 0.40 mmol) was added dropwise and the reaction mixture was warmed to room temperature with stirring overnight. The mixture was filtered through a plug of silica gel, which was washed thoroughly with Et_2O and the filtrate was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (P/Et_2O gradient 9:1 to 7:3) to provide **105a** (46 mg, 60%) as a yellow oil. Performing the reaction with **106a** (700 mg, 5.4 mmol) scale furnished **105a** (626 mg, 40%). The enantiomeric excess was determined after reduction and cyclization to lactone **104a**.



R_f = 0.63 (P/EtOAc 2:1).

$[\alpha]_D^{20}$ = –8.0 (c = 0.52 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (dd, $^3J_{H,H}$ = 2.3, 1.2 Hz, 1H), 4.39 (d, $^3J_{H,H}$ = 5.8 Hz, 1H), 4.17 (q, $^3J_{H,H}$ = 7.1 Hz, 2H), 4.16 (q, $^3J_{H,H}$ = 7.1 Hz, 2H), 3.60 (d, $^3J_{H,H}$ = 6.0 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 3.15-2.98 (m, 1H), 2.65 (ddd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 7.2, 2.3 Hz, 1H), 2.56 (ddd, $^2J_{H,H}$ = 17.5 Hz, $^3J_{H,H}$ = 5.2, 1.2 Hz, 1H), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3H), 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7, 168.6, 168.4, 105.7, 61.7, 61.6, 55.5, 55.3, 51.5, 41.5, 36.6, 14.1 (2C).

IR (film): ν = 2983, 2938, 2836, 1724, 1448, 1370, 1252, 1175, 1154, 1129, 1093, 1064, 1028, 994, 862, 777, 715 cm^{-1}.

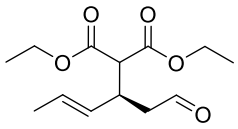
MS (+ESI) m/z (%): 313 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_{13}H_{27}O_7+Na^+$: 313.1258 $[M+Na]^+$, found: 313.1255.

The analytical data are in accordance with values of *rac*-**105a**.[103]

Diethyl (*S*,*E*)-2-(1-oxohex-4-en-3-yl)malonate 105b

Prepared in analogy to **105a** from (*E*,*E*)-hexa-2,4-dienal **106b** (45 mg, 0.468 mmol) to give **105b** (25 mg, 21%) as a yellow oil. The enantiomeric excess was not determined.



R_f = 0.38 (P/Et_2O 4:1).

$[\alpha]_D^{20}$ = –4.7 (c = 0.45 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.66 (dd, $^3J_{H,H}$ = 2.6, 1.3 Hz, 1H; C*H*=O), 5.59 (dqd, $^3J_{H,H}$ = 15.0, 6.1 Hz, $^4J_{H,H}$ = 0.6 Hz, 1H; CH=C*H*CH_3), 5.37 (ddq, $^3J_{H,H}$ = 15.1, 8.5 Hz, $^4J_{H,H}$ = 1.4, 1H; C*H*=$CHCH_3$), 4.20 (q, $^3J_{H,H}$ = 7.2 Hz, 4H; CH_2O), 3.43 (d, *J* = 8.1 Hz, 1H; C*H*C=O), 3.36-3.27 (m, 1H; C*H*CH=CH), 2.64 (ddd, $^2J_{H,H}$ = 16.3 Hz, $^3J_{H,H}$ = 4.8, 1.1 Hz, 1H; CH*H*CH=O), 2.53 (ddd, $^2J_{H,H}$ = 16.7 Hz, $^3J_{H,H}$ = 8.5, 2.5 Hz, 1H; CH*H*CH=O), 1.62 (dd, $^3J_{H,H}$ = 6.3 Hz, $^4J_{H,H}$ = 1.8 Hz, 3H; CH_3CH=CH), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 6H; C$H_3$$CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1 (*C*H=O), 168.2 (*C*O_2Et), 168.1 (*C*O_2Et), 129.3 (*C*H=CH), 129.2 (CH=*C*H), 61.7 (*C*H_2O), 61.6 (*C*H_2O), 56.1 (*C*HC=O), 46.3 (*C*H_2CH=O), 37.3 (*C*HCH=CH), 18.0 (*C*H_3CH=CH), 14.3 (*C*$H_3$$CH_2$), 14.2 (*C*$H_3$$CH_2$).

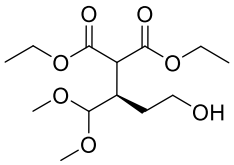
IR (film): *v* = 2981, 2937, 1726, 1447, 1369, 1301, 1245, 1174, 1155, 1096, 1030, 971, 861, 707 cm^{-1}.

MS (+ESI) m/z (%): 279 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_{13}H_{20}O_5$+Na^+: 279.1203 $[M+Na]^+$, found: 279.1201.

Diethyl (*R*)-2-(4-hydroxy-1,1-dimethoxybutan-2-yl)malonate 110

AcOH (2.4 mL) was added to a solution of **105a** (763 mg, 2.63 mmol) in dry THF (24 mL), the solution was cooled to 0 °C and $NaBH_3CN$ (248 mg, 3.94 mmol) was added in small portions. The reaction mixture was warmed to room temperature with stirring overnight. The mixture was diluted with Et_2O (ca 20 mL) and poured into satd. $NaHCO_3$ solution (50 mL). The layers were separated and the aqueous was extracted with Et_2O (3×25 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to furnish the crude product (695 mg) as a yellow oil containing 70 mol.% of alcohol **110** and 30 mol.% of lactone **104a** (*vide infra*), which was used directly in the next step without further purification.



R_f = 0.14 (P/EtOAc 7:3).

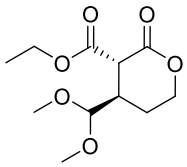
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.42 (d, $^3J_{H,H}$ = 5.7 Hz, 1H; C*H*O_2), 4.19 (q, $^3J_{H,H}$ = 7.2 Hz, 2H; CH_3CH_2O), 4.18 (q, $^3J_{H,H}$ = 7.2 Hz, 2H; CH_3CH_2O), 3.72-3.58 (m, 2H; CH_2OH), 3.61 (d,

$^{3}J_{H,H}$ = 5.8 Hz, 1H; C*H*C=O), 3.39 (s, 3H; C*H*$_3$O), 3.37 (s, 3H; C*H*$_3$O), 2.65 (s, 1H; O*H*), 2.60 (dq, $^{3}J_{H,H}$ = 7.0, 5.6 Hz, 1H; C*H*CHO$_2$), 1.84 (dtd, $^{2}J_{H,H}$ = 15.1 Hz, $^{3}J_{H,H}$ = 7.0, 5.3 Hz, 1H; CH*H*CH$_2$OH), 1.65 (ddt, $^{2}J_{H,H}$ = 14.8 Hz, $^{3}J_{H,H}$ = 6.3, 5.1 Hz, 1H; C*H*HCH$_2$OH), 1.27 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$), 1.26 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.9 (2C; *C*=O), 106.4 (*C*HO$_2$), 61.7 (CH$_2$*C*H$_2$O), 61.5 (CH$_3$*C*H$_2$O), 61.4 (*C*H$_2$OH), 55.6 (*C*H$_3$O), 55.1 (*C*H$_3$O), 52.5 (*C*HC=O), 39.1 (*C*HCH$_2$), 30.9 (*C*H$_2$CH$_2$OH), 14.2 (2C; *C*H$_3$CH$_2$).

Ethyl (3*R*,4*R*)-4-(dimethoxymethyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate 104a

The above prepared crude mixture was adsorbed on silica gel (0.8 g) and transferred into an oven-dried 50 mL round-bottom pressure flask. Dry DCM (10 mL) was added, the flask was sealed and the reaction mixture was stirred at 100°C overnight when complete conversion was indicated by TLC. The volatiles were evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography (P/EtOAc gradient 9:1 to 6:4) to furnish lactone **104a** (385 mg, 66% over two steps) as a colorless oil.



R_f = 0.50 (P/EtOAc 1:1).

$[\alpha]_D^{20}$ = +2.8 (c = 0.42 in CHCl$_3$).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.34 (ddd, $^{2}J_{H,H}$ = 11.3 Hz, $^{3}J_{H,H}$ = 7.0, 4.2 Hz, 1H; CH$_2$CH*H*O), 4.32-4.18 (m, 1H; CH$_2$C*H*HO); 4.25 (q, $^{3}J_{H,H}$ = 7.4 Hz, 2H; C*H*$_2$CH$_3$), 4.16 (d, $^{3}J_{H,H}$ = 4.9 Hz, 1H; C*H*O$_2$), 3.53 (d, $^{3}J_{H,H}$ = 8.9 Hz, 1H; C*H*C=O), 3.39 (s, 3H; C*H*$_3$O), 3.36 (s, 3H; C*H*$_3$O), 2.82 (dtd, $^{3}J_{H,H}$ = 8.9, 7.0, 4.9 Hz, 1H; C*H*CH$_2$), 1.99 (dtd, $^{2}J_{H,H}$ = 14.5 Hz, $^{3}J_{H,H}$ = 7.2, 4.2 Hz, 1H; CH*H*CH$_2$O), 1.82 (dtd, $^{2}J_{H,H}$ = 14.5 Hz, $^{3}J_{H,H}$ = 7.1, 4.2 Hz, 1H; C*H*HCH$_2$O), 1.30 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.9 (*C*=O), 168.4 (*C*O$_2$Et), 106.7 (*C*HO$_2$), 67.8 (CH$_2$*C*H$_2$O), 61.9 (CH$_3$*C*H$_2$O), 55.9 (*C*H$_3$O), 55.2 (*C*H$_3$O), 48.4 (*C*HC=O), 36.9 (*C*HCH$_2$), 23.1 (*C*H$_2$CH$_2$O), 14.2 (*C*H$_3$CH$_2$).

IR (film): *v* = 2925, 2851, 1725, 1447, 1389, 1371, 1295, 1260, 1189, 1147, 1060, 1034, 976, 844, 810, 751, 698 cm^{-1}.

MS (+ESI) m/z (%): 269 (100) [*M*+Na]$^+$.

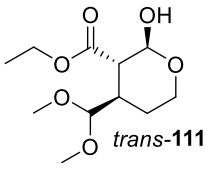
HRMS (+ESI) m/z: calcd for C$_{11}$H$_{18}$O$_6$+Na$^+$: 269.0996 [*M*+Na]$^+$, found: 269.0993.

6.3.1.2 Functionalization of lactone **104a**

Ethyl (3*S*,4*R*)-4-(dimethoxymethyl)-2-hydroxytetrahydro-2*H*-pyran-3-carboxylate 111

Lactone **104a** (27 mg, 0.110 mmol) was dissolved in dry toluene (1.2 mL), the solution was cooled to –78 °C and DIBAL-H (132 µL 1.0 M in hexanes, 0.132 mmol) was added dropwise. The reaction mixture was stirred for 10 min after which complete consumption of the starting material was indicated by TLC. The reaction was quenched by a few drops of MeOH, the cooling bath was removed and a few drops of water were added. The mixture was diluted with Et_2O to 10 mL and warmed to room temperature with vigorous stirring. Celite® and $MgSO_4$ (a tip of spatula of each) were successively added, the resulting slurry was stirred vigorously for 30 min, filtered through a pad of Celite® and sand, which was thoroughly washed with Et_2O. The filtrate was evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography (P/EtOAc gradient 4:1 to 1:1) to give lactol **111** (22 mg, 81%) as inseparable 4:1 mixture of *trans*-/*cis*-**111** as determined by ^{1}H NMR spectroscopy as a colorless oil. The compound solidified when stored at 2-8 °C

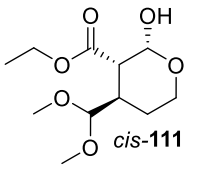
R_f = 0.25 (P/EtOAc 1:1).



trans-**111**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.72 (dd, $^3J_{H,H}$ = 7.7, 6.3 Hz, 1H; C*H*OH), 4.40 (d, $^3J_{H,H}$ = 6.5 Hz, 1H; O*H*), 4.13 (q, $^3J_{H,H}$ = 7.1 Hz, 2H; CH_2CH$_3$), 4.06 (d, $^3J_{H,H}$ = 5.3 Hz, 1H; CHO$_2$), 4.00 (dt, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 4.8 Hz, 1H; CH$_2$CH*H*O), 3.51 (ddd, $^3J_{H,H}$ = 12.2, 2.4 Hz, $^2J_{H,H}$ = 12.0 Hz, 1H; CH$_2$C*H*HO), 3.29 (s, 3H; CH_3O), 3.28 (s, 3H; CH_3O), 2.26-2.14 (m, 1H; C*H*CH$_2$), 2.20 (dd, $^3J_{H,H}$ = 11.1, 7.9 Hz, 1H; C*H*C=O), 1.61 (ddt, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 4.4, 2.2 Hz, 1H; CH*H*CH$_2$O), 1.37 (dtd, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 12.2, 4.9 Hz, 1H; C*H*HCH$_2$O), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3CH$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.9 (*C*=O), 106.7 (*C*HO$_2$), 96.8 (*C*HOH), 64.7 (CH$_2$*C*H$_2$O), 60.7 (CH$_3$*C*H$_2$O), 55.2 (*C*H$_3$O), 53.5 (*C*H$_3$O), 51.7 (*C*HC=O), 40.2 (*C*HCH$_2$), 25.1 (*C*H$_2$CH$_2$O), 14.21 (*C*H$_3$CH$_2$).



cis-**111**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.34 (dd, $^3J_{H,H}$ = 3.4, 2.9 Hz, 1H; C*H*OH), 4.14 (q, $^3J_{H,H}$ = 7.1 Hz, 2H; CH_2CH$_3$), 4.25 (d, $^3J_{H,H}$ = 4.2 Hz, 1H; CHO$_2$), 4.06-3.93 (m, 1H; CH$_2$CH*H*O), 4.05 (d, $^3J_{H,H}$ = 3.1 Hz, 1H; O*H*), 3.62 (ddd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 4.9, 2.4 Hz, 1H; CH$_2$C*H*HO), 3.34 (s, 3H; CH_3O), 3.31 (s, 3H; CH_3O), 2.65-2.46 (m, 2H; C*H*C=O, C*H*CH$_2$), 1.71-1.64 (m, 1H; CH*H*CH$_2$O), 1.54-1.42 (m, 1H; C*H*HCH$_2$O), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3CH$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 (*C*=O), 106.5 (*C*HO_2), 90.5 (*C*HOH), 60.9 (CH_2*C*H_2O), 58.7 (CH_3*C*H_2O), 55.6 (*C*H_3O), 55.3 (*C*H_3O), 47.2 (*C*HC=O), 33.9 (*C*HCH_2), 23.2 (*C*H_2CH_2O), 14.18 (*C*H_3CH_2).

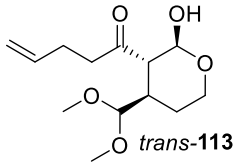
IR (film): ν = 3414, 2931, 2851, 1725, 1444, 1375, 1353, 1304, 1258, 1238, 1177, 1167, 1146, 1087, 1060, 1023, 1005, 997, 952, 899, 733, 663 cm^{-1}.

MS (+ESI) m/z (%): 271 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_{11}H_{20}O_6$+Na^+: 271.1152 $[M+Na]^+$, found: 271.1150.

1-((3*S*,4*R*)-4-(Dimethoxymethyl)-2-hydroxytetrahydro-2*H*-pyran-3-yl)pent-4-en-1-one 113

Lactol **111** (48 mg, 0.183 mmol) was dissolved in dry THF (0.7 mL) and vinylmagnesium bromide (0.68 mL, 1.0 M in THF, 0.68 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room to room temperature with stirring over 2 h. Et_2O (2 mL) was added, followed by satd. NH_4Cl solution (5 mL), the layers were separated and the aqueous was extracted with DCM (3×5 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude mixture (48 mg, 70%) did not contain starting lactol **111** and compound **113** was the dominant product as partially separable 3:1 mixture of *trans*-/*cis*-**113** along with an unidentified impurity.

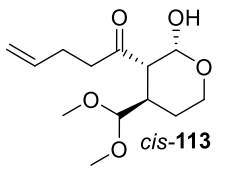


R_f = 0.49 (P/EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (ddt, $^3J_{H,H}$ = 16.8, 10.2, 6.5 Hz, 2H; C*H*=CH_2), 5.02 (dq, $^3J_{H,H}$ = 17.1 Hz, $^4J_{H,H}$ = 1.7 Hz, $^2J_{H,H}$ = 1.7 Hz 1H; CH=CH*H*), 4.93 (dq, $^3J_{H,H}$ = 10.2 Hz, $^4J_{H,H}$ = 1.4 Hz, $^2J_{H,H}$ = 1.4 Hz, 1H; CH=C*H*H), 4.60 (d, $^3J_{H,H}$ = 7.9 Hz, 1H; C*H*OH), 4.12-3.91 (m, 1H; CH_2CH*H*O), 4.03 (d, $^2J_{H,H}$ = 6.0 Hz, 1H; C*H*O_2), 3.60-3.43 (m, 1H; CH_2C*H*HO), 3.23 (s, 3H; C*H*$_3$O), 3.22 (s, 3H; C*H*$_3$O), 2.67-2.59 (m 2H; C*H*$_2$C=O), 2.47 (dd, $^3J_{H,H}$ = 11.1, 7.9 Hz, 1H; C*H*C=O), 2.43-2.17 (m, 3H; C*H*$_2$CH=CH_2, C*H*CH_2), 1.69-1.51 (m, 1H; CH*H*CH_2O), 1.46-1.30 (m, 1H; C*H*HCH_2O).

The O*H* resonance was not detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7 (*C*=O), 137.8 (*C*H=CH_2), 114.8 (CH=*C*H_2), 106.8 (*C*HO_2), 97.7 (*C*HOH), 64.7 (*C*H_2O), 55.8 (*C*HC=O), 54.3 (*C*H_3O), 53.3 (*C*H_3O), 44.9 (*C*H_2C=O), 40.1 (*C*HCH_2), 27.2 (*C*H_2CH=CH_2), 25.8 (*C*H_2CH_2O).



R_f = 0.59 (P/EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90-5.73 (m, 1H; C*H*=CH_2), 5.02 (dq, $^3J_{H,H}$ = 17.1 Hz,

$^{4}J_{H,H}$ = 1.7 Hz, $^{2}J_{H,H}$ = 1.7 Hz 1H; CH=CH*H*), 5.10-4.86 (m, 1H; CH=C*H*H), 4.73 (d, $^{3}J_{H,H}$ = 7.8 Hz, 1H; C*H*OH), 4.12-3.91 (m, 1H; CH_2CH*H*O), 4.08 (d, $^{2}J_{H,H}$ = 6.2 Hz, 1H; C*H*O_2), 3.70-3.59 (m, 1H; CH_2CH*H*O), 3.31 (s, 3H; C*H*$_3$O), 3.30 (s, 3H; C*H*$_3$O), 2.68-2.61 (m, 2H; C*H*$_2$C=O), 2.47 (dd, $^{3}J_{H,H}$ = 11.1, 7.9 Hz, 1H; C*H*C=O), 2.43-2.17 (m, 3H; C*H*$_2$CH=CH_2, C*H*CH_2), 1.69-1.51 (m, 1H; CH*H*CH_2O), 1.46-1.30 (m, 1H; C*H*HCH_2O).

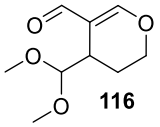
The O*H* resonance was not detected.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.7 (*C*=O), 137.2 (*C*H=CH_2), 115.3 (CH=*C*H_2), 107.0 (*C*HO_2), 96.9 (*C*HOH), 68.1 (*C*H_2O), 55.3 (*C*HC=O), 53.7 (*C*H_3O), 52.8 (*C*H_3O), 44.9 (*C*H_2C=O), 40.3 (*C*HCH_2), 25.7 (*C*H_2CH=CH_2), 25.1 (*C*H_2CH_2O).

MS (+ESI) m/z (%): 281 (100) [*M*+Na]$^+$.

4-(Dimethoxymethyl)-3,4-dihydro-2*H*-pyran-5-carbaldehyde 116 and **(3*R*,4*R*)-4-(dimethoxymethyl)-3-(hydroxymethyl)tetrahydro-2*H*-pyran-2-ol 117**

Prepared in analogy to the synthesis of **111** using lactone **104a** (42 mg, 0.171 mmol) and excess DIBAL-H (375 µL, 1.0 M in hexanes, 0.375 mmol) and warming to –50 °C over 90 min. Purification by silica gel column chromatography (P/EtOAc gradient 7:3 to 4:6) furnished racemic enal **116** (7 mg, 22%) as a yellow oil along with lactol **111** (14 mg, 33%) and alcohol **117** (9 mg, 26%) as inseparable 2:1 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy as a yellow oil.



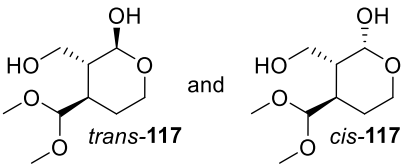
116

$[\alpha]_D^{20}$ = 0 (c = 0.24 in $CHCl_3$).

R_f = 0.30 (P/EtOAc 4:6).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (dd, $^{4}J_{H,H}$ = 2.3, 1.2 Hz, 1H; C*H*=O), 8.08-8.04 (m, 1H; C=C*H*O), 4.23 (t $^{3}J_{H,H}$ = 7.4 Hz, 2H; C*H*$_2$O), 4.20 (d, $^{3}J_{H,H}$ = 5.2 Hz, 1H; C*H*O_2), 3.38 (s, 3H; C*H*$_3$O), 3.36 (s, 3H; C*H*$_3$O), 2.50-2.38 (m, 1H; C*H*CH_2), 1.92 (dq, $^{2}J_{H,H}$ = 12.9 Hz, $^{3}J_{H,H}$ = 7.1 Hz, 1H; CH*H*CH_2O), 1.72-1.52 (m, 1H; C*H*HCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.5 (*C*=O), 161.1 (C=*C*H), 128.1 (*C*=CH), 107.3 (*C*HO_2), 62.1 (*C*H_2O), 55.7 (*C*H_3O), 54.9 (*C*H_3O), 33.9 (*C*HCH_2), 29.0 (*C*H_2CH_2).



trans-**117** *cis*-**117**

R_f = 0.20 (P/EtOAc 1:2).

trans-**117**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.24 (d, $^{3}J_{H,H}$ = 3.0 Hz, 1H; C*H*OH), 4.28 (d, $^{3}J_{H,H}$ = 4.4 Hz, 1H; C*H*O_2), 4.02 (dt, $^{2}J_{H,H}$ = 11.6 Hz, $^{3}J_{H,H}$ = 3.1 Hz, 1H; CH*H*O), 3.80 (ddd, $^{2}J_{H,H}$ = 12.2 Hz, $^{3}J_{H,H}$ = 7.9, 4.2 Hz, 1H; C*H*HOH), 3.72-3.60 (m, 1H; C*H*HOH), 3.68 (ddd,

$^{2}J_{H,H}$ = 11.4 Hz, $^{3}J_{H,H}$ = 4.7, 2.1 Hz, 1H; CH*H*O), 3.46 (s, 3H; C*H*$_3$O), 3.43 (s, 3H; C*H*$_3$O), 3.32 (br s, 1H; CHO*H*), 2.95 (dd, $^{3}J_{H,H}$ = 8.3, 5.3 Hz, 1H; CH$_2$O*H*), 2.35 (tt, $^{3}J_{H,H}$ = 11.5, 4.1 Hz, 1H; C*H*CH$_2$CH$_2$), 1.84-1.76 (m, 1H; C*H*CH$_2$OH), 1.74-1.50 (m, 2H; C*H*$_2$CH$_2$O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.6 (*C*HO$_2$), 95.2 (*C*HOH), 62.1 (*C*H$_2$O), 59.7 (*C*H$_2$OH), 56.46 (*C*H$_3$O), 55.4 (*C*H$_3$O), 42.8 (*C*HCHOH), 33.4 (*C*HCH$_2$CH$_2$), 25.8 (*C*H$_2$CH$_2$O).

cis-**117**:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.75-4.64 (m, 1H; C*H*OH), 4.30 (d, $^{3}J_{H,H}$ = 5.3 Hz, 1H; C*H*O$_2$), 4.07-3.98 (m, 1H; CH*H*O), 3.94-3.84 (m, 1H; C*H*HOH), 3.66-3.60 (m, 1H; C*H*HOH), 3.53 (dt, $^{2}J_{H,H}$ = 10.7 Hz, $^{3}J_{H,H}$ = 3.2 Hz, 1H; C*H*HO), 3.43 (s, 3H; C*H*$_3$O), 3.41 (s, 3H; C*H*$_3$O), 2.64-2.54 (m, 1H; CH$_2$O*H*), 1.94 (dq, $^{3}J_{H,H}$ = 9.9, 5.0 Hz, 1H; C*H*CH$_2$CH$_2$), 1.74-1.50 (m, 3H; C*H*$_2$CH$_2$O, C*H*CHOH).

One O*H* resonance was not detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.7 (*C*HO$_2$), 97.0 (*C*HOH), 63.7 (*C*H$_2$O), 61.3 (*C*H$_2$OH), 56.53 (*C*H$_3$O), 55.0 (*C*H$_3$O), 45.7 (*C*HCHOH), 38.3 (*C*HCH$_2$CH$_2$), 25.9 (*C*H$_2$CH$_2$O).

IR (film): ν = 3388, 2926, 2854, 1444, 1376, 1259, 1191, 1108, 1065, 993, 965, 876 cm^{-1}.

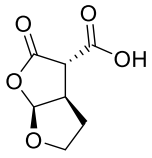
MS (+ESI) m/z (%): 229 (100) [*M*+Na]$^{+}$.

HRMS (+ESI) m/z: calcd for $C_9H_{18}O_5$+Na^{+}: 229.1046 [*M*+Na]$^{+}$, found: 229.1044.

(3a*R*,6a*S*)-2-Oxohexahydrofuro[2,3-b]furan-3-carboxylic acid 119

Lactone **104a** (125 mg, 0.51 mmol) was dissolved in THF (2 mL) and aqueous NaOH solution (1 mL, 4.0 M, 4.0 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature overnight and neutralized with HCl (1.0 M) to pH 5-6. Stirring was continued at room temperature overnight. The mixture was extracted with EtOAc (3×3 mL), the aqueous layer was acidified with aqueous HCl (1.0 M) to pH 4-5 and stirred at room temperature for 2 h. The mixture was extracted with EtOAc (3×3 mL), the aqueous phase was acidified to pH 3-4 and stirred at room temperature for 2 h. The mixture was extracted with EtOAc (3×3 mL), the aqueous phase was acidified to pH 1-2 and stirred at room temperature overnight. The mixture was extracted with EtOAc (3×3 mL), combined organic layers from the extractions at pH 3-4 and pH 1-2 were washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure to provide **119** (57 mg, 65%) as inseparable 6:1 mixture of *exo*- and *endo*-diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.13 (P/EtOAc 1:1).

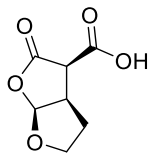


exo-**119**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60-6.27 (br s, 1H; CO$_2$*H*), 6.20 (d, $^{3}J_{H,H}$ = 5.3 Hz, 1H; C*H*O$_2$), 4.16 (td, $^{2}J_{H,H}$ = 8.6 Hz, $^{3}J_{H,H}$ = 8.7, 2.6 Hz, 1H; C*H*HO), 3.96 (td, $^{2}J_{H,H}$ = 9.3 Hz, $^{3}J_{H,H}$ = 9.3, 6.0 Hz, 1H; CH*H*O), 3.58-3.42 (m, 1H; C*H*CHO$_2$), 3.56 (d, $^{3}J_{H,H}$ = 6.2 Hz, 1H; C*H*C=O), 2.30 (dddd,

$^{2}J_{H,H}$ = 13.1 Hz, $^{3}J_{H,H}$ = 10.4, 9.1, 8.3 Hz, 1H; C*H*HCH$_2$O), 1.89 (ddt, $^{2}J_{H,H}$ = 13.1 Hz, $^{3}J_{H,H}$ = 5.7, 2.5 Hz, 1H; CH*H*CH$_2$O).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 170.6 (*C*=O), 170.3 (*C*=O), 108.6 (*C*HO$_2$), 67.9 (*C*H$_2$O), 53.5 (*C*HC=O), 43.2 (*C*HCH$_2$), 31.4 (*C*H$_2$CH$_2$).



endo-**119**

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.60-6.27 (br s, 1H; CO$_2$*H*), 6.12 (d, $^{3}J_{H,H}$ = 4.8 Hz, 1H; C*H*O$_2$), 4.21-4.06 (m, 2H; C*H*$_2$O), 3.95 (d, $^{3}J_{H,H}$ = 9.2 Hz, 1H; C*H*C=O), 3.58-3.42 (m, 1H; C*H*CHO$_2$), 2.38-2.20 (m, 1H; CH*H*CH$_2$O), 2.04-1.91 (m, 1H; CH*H*CH$_2$O).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 171.4 (*C*=O), 168.8 (*C*=O), 107.9 (*C*HO$_2$), 69.5 (*C*H$_2$O), 50.1 (*C*HC=O), 42.3 (*C*HCH$_2$), 27.2 (*C*H$_2$CH$_2$).

IR (film): *v* = 3687-2219 (v br), 3459 (br), 2958, 2925, 2855, 1774, 1730, 1455, 1359, 2298, 1260, 1171, 1119, 1092, 1022, 964, 938, 918, 852, 729, 648 cm^{-1}.

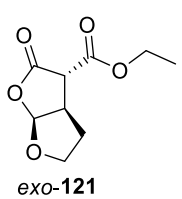
MS (–ESI) m/z (%): 171 (100) [*M*–H]$^{-}$.

HRMS (–ESI) m/z: calcd for C$_7$H$_8$O$_5$–H^{+}: 171.0299 [*M*–H]$^{-}$, found: 171.0301.

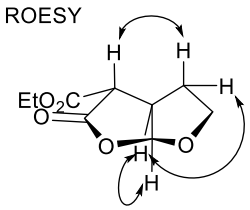
Ethyl (3a*R*,6a*S*)-2-oxohexahydrofuro[2,3-b]furan-3-carboxylate 121

Lactone **104a** (43 mg, 0.175 mmol) was dissolved in acetone (2 mL), water (0.2 mL) and Amberlyst 15® (8 mg) were added and the mixture was stirred at reflux overnight. After cooling to room temperature, MgSO$_4$ was added, the solids were filtered and washed thoroughly with Et$_2$O. The filtrate was evaporated under reduced pressure to obtain lactone **121** (29 mg, 83%) as inseparable 9:1 mixture of *exo*-/*endo*-**121** as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.48 (P/EtOAc 1:1).

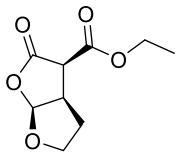


exo-**121**



^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.18 (d, $^{3}J_{H,H}$ = 5.2 Hz, 1H; C*H*O$_2$), 4.26 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2H; CH$_3$C*H*$_2$O), 4.13 (ddd, $^{2}J_{H,H}$ = 9.3 Hz, $^{3}J_{H,H}$ = 8.1, 2.8 Hz, 1H, CH$_2$CH*H*O), 3.95 (ddd, $^{3}J_{H,H}$ = 10.2, 6.2 Hz Hz, $^{2}J_{H,H}$ = 9.2 Hz, 1H; CH$_2$C*H*HO), 3.50 (d, $^{3}J_{H,H}$ = 3.6 Hz, 1H; C*H*C=O), 3.49-3.43 (m, 1H; C*H*CH$_2$), 2.41-2.19 (m, 1H; CH*H*CH$_2$O), 1.84 (ddt, $^{2}J_{H,H}$ = 13.0 Hz, $^{3}J_{H,H}$ = 6.0, 2.9 Hz, 1H; CH*H*CH$_2$O), 1.32 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.1 (*C*=O), 167.2 (*C*=O), 108.3 (*C*HO$_2$), 67.7 (CH$_2$*C*H$_2$O), 62.8 (CH$_3$*C*H$_2$O), 54.0 (*C*HC=O), 43.4 (*C*HCH$_2$), 31.3 (*C*H$_2$CH$_2$O), 14.2 (*C*H$_3$).



endo-**121**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.08 (d, $^{3}J_{H,H}$ = 5.1 Hz, 1H; C*H*O_2), 4.25 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2H; CH_3CH_2O), 4.17-4.04 (m, 2H; CH_2CH_2O), 3.54 (d, $^{3}J_{H,H}$ = 9.5 Hz 1H; C*H*C=O), 3.48-3.42 (m, 1H; C*H*CH_2), 2.34-2.22 (m, 1H; CH*H*CH_2O), 1.90-1.77 (m, 1H; CH*H*CH_2O), 1.31 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1 (*C*=O), 167.2 (*C*=O), 106.7 (*C*HO_2), 68.9 (CH_2CH_2O), 62.2 (CH_3CH_2O), 48.5 (*C*HC=O), 42.3 (*C*HCH_2), 27.2 (CH_2CH_2O), 14.2 (CH_3).

IR (film): *v* = 2924, 1780, 1728, 1455, 1370, 1358, 1238, 1262, 1163, 1117, 1090, 1032, 1011, 956, 934, 880, 856, 775, 717, 671, 647 cm^{-1}.

MS (+ESI) m/z (%): 223 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_9H_{12}O_5$+Na^+: 223.0577 $[M+Na]^+$, found: 223.0574.

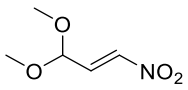
6.3.2 Synthetic strategy II and III

6.3.2.1 Synthesis of lactone trans-**122b**

(*E*)-3,3-Dimethoxy-1-nitroprop-1-ene 124[116]

Step 1: NaOH (2.4 g, 60.5 mmol) in water (35 mL) was added to a solution of 2,2-dimethoxyacetaldehyde (7.0 g, 60% w/w in water, 40.3 mmol) and nitromethane (3.2 mL, 60.5 mmol) in DCM (70 mL) at 0 °C. The biphasic mixture was warmed to room temperature with vigorous stirring over 6 h and neutralized with concentrated HCl until pH 7-8 was reached. The layers were separated and the aqueous was extracted with DCM (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure.

Step 2:[116] The crude product was dissolved in DCM (80 mL), the solution was cooled to –10 °C and TFAA (6.2 mL, 44.0 mmol) was added dropwise, followed by a dropwise addition of Et_3N (12.2 mL, 88.0 mmol) after 2 min. The solution was stirred at the same temperature for 10 min after which the reaction was finished as indicated by TLC. Satd. NH_4Cl solution (100 mL) and water (30 mL) were added, the layers were separated and the aqueous was extracted with DCM (3×70 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (P/Et_2O 4:1) to provide nitroolefin **124** (4.84 g, 82% over two steps) as a bright yellow oil.

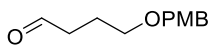


R_f = 0.56 (P/EtOAc 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (dd, $^{3}J_{H,H}$ = 13.4, $^{4}J_{H,H}$ = 1.5 Hz, 1H), 7.03 (dd, $^{3}J_{H,H}$ =13.4 Hz, 3.3 Hz, 1H), 5.12 (dd, $^{3}J_{H,H}$ = 3.3 Hz, $^{4}J_{H,H}$ = 1.5 Hz, 1H), 3.35 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 136.6, 98.1, 53.1 (2C).
The analytical data are in accordance with the published values.[116]

4-((4-Methoxybenzyl)oxy)butanal 125[184]

Swern oxidation (conditions **a**): DMSO (4.8 mL, 67.8 mmol) was added dropwise to a solution of oxalyl chloride (4.0 mL, 45.2 mmol) in dry DCM (100 mL) at –78 °C and the reaction mixture was stirred for 15 min. A solution of **126**[117] (4.8 g, 22.6 mmol) in dry DCM (30 mL) was added dropwise using a cannula. The reaction mixture became white and turbid, stirring was continued for 30 min and the reaction temperature was maintained below –60 °C. Et_3N (19 mL, 136 mmol) was added dropwise, the reaction mixture was stirred at –78 °C for 20 min and warmed to room temperature over 30 min. Water (50 mL) and satd. NH_4Cl solution (50 mL) were added, the layers were separated and the aqueous was extracted with DCM (3×200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was filtered through a pad of silica with Et_2O and the filtrate was evaporated under reduced pressure to obtain aldehyde **125** (4.7 g, quant.) as a yellow oil, which was used in the next step without further purification.
TEMPO-catalyzed oxidation (conditions **b**): Solution of $NaHCO_3$ (7.4 g, 87.4 mmol) and K_2CO_3 (2.42 g, 17.5 mmol) in water (350 mL) was added to a solution of **126**[117] (3.68 g, 17.5 mmol) in DCM (170 mL). The biphasic mixture was stirred vigorously and TBAB (0.57 g, 1.75 mmol), NCS (3.05 g, 22.8 mmol) and TEMPO (137 mg, 0.89 mmol) were successively added. The reaction mixture was stirred at room temperature overnight. The layers were separated and the aqueous was extracted with DCM (2×150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by silica gel column chromatography (gradient cyclohexane/EtOAc 93:7 to 80:20) to give aldehyde **125** (3.21 g, 88%) as a colorless oil.



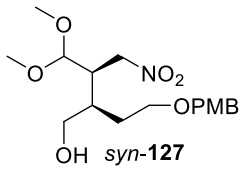
R_f = 0.43 (P/EtOAc 9:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (t, $^{3}J_{H,H}$ = 1.6 Hz, 1H), 7.29-7.18 (m, 2H), 6.91-6.84 (m, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.48 (t, $^{3}J_{H,H}$ = 6.1 Hz, 2H), 2.53 (td, $^{3}J_{H,H}$ = 7.1, 1.6 Hz, 2H), 1.93 (quint, $^{3}J_{H,H}$ = 6.6 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3, 159.4, 130.6, 129.4 (2C), 114.0 (2C), 72.8, 69.0, 55.4, 41.1, 22.8.
The analytical data are in accordance with the published values.[184]

(2*R*,3*R*)-4,4-Dimethoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-(nitromethyl)butan-1-ol *syn*-127 and **(2*R*,3*S*)-4,4-dimethoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-(nitromethyl)butan-1-ol *anti*-127**

Reduction was carried out in analogy to a previously published procedure.[115]Aldehyde **123** (5.0 g, 14 mmol) was dissolved in dry MeOH (300 mL) and $NaBH_4$ (1.1 g, 28 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at 0 °C under nitrogen for 1.5 h. Satd. NH_4Cl solution (200 mL) was added and the reaction mixture was diluted with DCM (200 mL). The layers were separated and the aqueous was extracted with EtOAc (2×200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude alcohol (4.9 g, 97%) as partially separable 3:1 mixture of *syn*/*anti*-**127** as determined by ^{1}H NMR spectroscopy as a yellow oil. The compound was used in the next step without further purification.

The enantiomeric excess was determined after derivatization by SFC using a chiral stationary phase to 86% ee for *syn*-**127** and 90% for *anti*-**127**.[115] A racemic standard for compound was prepared by Quentin Lemesre, a 1st year student at École Nationale Superieure de Chimie de Montpellier according to the previously reported procedure.[115]

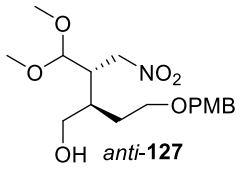
R_f = 0.23 (P/EtOAc 7:3).



syn-**127**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, $^3J_{H,H}$ = 9.7 Hz, 2H; CH_{Ar}), 6.92-6.83 (m, 2H; CH_{Ar}), 4.57 (dd, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 7.5 Hz, 1H; CHHNO$_2$), 4.48-4.38 (m, 2H; CHO$_2$, CHHNO$_2$), 4.44 (s, 2H; CH_2Ar), 3.80 (s, 3H; CH_3OAr), 3.67-3.43 (m, 4H; CH_2OH, CH_2OPMB), 3.36 (s, 3H; CH_3OCH), 3.35 (s, 3H; CH_3OCH), 2.80 (tt, $^3J_{H,H}$ = 7.5, 5.3 Hz, 1H; CHCH$_2$NO$_2$), 2.00 (dquint, $^3J_{H,H}$ = 8.7, 4.9 Hz, 1H; CHCH$_2$OH), 1.78-1.62 (m, 3H; CH_2CH$_2$O, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (C_{Ar}O), 129.9 (C_{Ar}CH$_2$), 129.6 (2C; CH$_{Ar}$), 114.0 (2C; CH$_{Ar}$), 105.3 (CHO$_2$), 74.1 (CH$_2$NO$_2$), 73.09 (CH$_2$Ar), 68.3 (CH$_2$OPMB), 63.0 (CH$_2$OH), 55.65 (CH$_3$OCH), 55.4 (CH$_3$OAr), 54.6 (CH$_3$OCH), 42.8 (CHCH$_2$NO$_2$), 37.5 (CHCH$_2$OH), 29.7 (CH$_2$CH$_2$O).



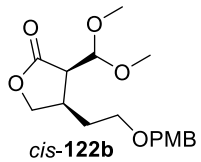
anti-**127**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, $^3J_{H,H}$ = 9.7 Hz, 2H; CH_{Ar}), 6.92-6.83 (m, 2H; CH_{Ar}), 4.58 (dd, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 6.7 Hz, 1H; CHHNO$_2$), 4.50-4.38 (m, 2H; CHO$_2$, CHHNO$_2$), 4.44 (s, 2H; CH_2Ar), 3.80 (s, 3H; CH_3OAr), 3.67-3.43 (m, 4H, CH_2OH; CH_2OPMB), 3.36 (s, 3H; CH_3OCH), 3.35 (s, 3H; CH_3OCH), 2.95-2.81 (m, 1H; CHCH$_2$NO$_2$), 1.88 (dquint, $^3J_{H,H}$ = 9.5,

4.8 Hz, 1H; C*H*CH$_2$OH), 1.83-1.62 (m, 3H, C*H$_2$*CH$_2$O; O*H*).
^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.2 (*C*$_{Ar}$O), 129.6 (*C*$_{Ar}$CH$_2$), 129.4 (2C; *C*H$_{Ar}$), 113.8 (2C; *C*H$_{Ar}$), 105.0 (*C*HO$_2$), 74.4 (*C*H$_2$NO$_2$), 72.6 (*C*H$_2$Ar), 68.3 (*C*H$_2$OPMB), 63.4 (*C*H$_2$OH), 55.73 (*C*H$_3$OCH), 55.2 (*C*H$_3$OAr), 54.6 (*C*H$_3$OCH), 42.4 (*C*HCH$_2$NO$_2$), 38.2 (*C*HCH$_2$OH), 29.3 (*C*H$_2$CH$_2$O).
IR (film): ν = 3422 (br), 2935, 1661, 1612, 1513, 1443, 1381, 1302, 1246, 1175, 1055, 819, 757, 720 cm^{-1}.
MS (–ESI) m/z (%): 356 (100) [*M*–H]$^-$.
HRMS (–ESI) m/z: calcd for C$_{17}$H$_{27}$NO$_7$–H$^+$: 356.1714 [*M*–H]$^-$, found: 356.1709.

(3*S*,4*R*)-3-(Dimethoxymethyl)-4-(2-((4-methoxybenzyl)oxy)ethyl)dihydrofuran-2(3*H*)-one *trans*-122b and **(3*R*,4*R*)-3-(dimethoxymethyl)-4-(2-((4-methoxybenzyl)oxy)ethyl)dihydrofuran-2(3*H*)-one *cis*-122b**

The Nef reaction was carried out in analogy to a previously published procedure.[115] Alcohol **127** (3.0 g, 8.4 mmol) was dissolved in dry DMF (40 mL). NaNO$_2$ (3.47 g, 50.4 mmol) was added in one portion directly followed by acetic acid (4.8 mL, 84 mmol) at room temperature. The reaction mixture was stirred at 45 °C for 22 h. After cooling to room temperature, the mixture was poured into satd. NaHCO$_3$ solution (100 mL), the layers were separated and the aqueous was extracted with EtOAc (4×150 mL). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuum. The crude product was purified by column chromatography (300 mL of silica gel, P/EtOAc gradient 9:1 to 0:1) to afford the desired lactone (2.38 g, 87%) as a yellow oil as partially separable 16:1 mixture of *trans*-**122b**/*cis*-**122b** as determined by ^{1}H NMR spectroscopy as a yellow oil.

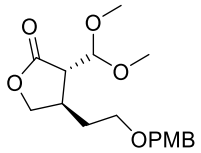


cis-**122b**

R_f = 0.38 (P/EtOAc 6:4).
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.28-7.18 (m, 2H; C*H*$_{Ar}$), 6.92-6.82 (m, 2H; C*H*$_{Ar}$), 4.60 (d, $^3J_{H,H}$ = 3.3 Hz, 1H; C*H*O$_2$), 4.41 (s, 2H; C*H$_2$*Ar), 4.28 (dd, $^2J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; CH*H*OC=O), 4.08 (t, $^2J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 8.4 Hz, 1H; C*H*HOC=O), 3.80 (s, 3H; C*H$_3$*OAr), 3.54- 3.44 (m, 2H; C*H$_2$*OPMB), 3.42 (s, 3H; C*H$_3$*OCH), 3.40 (s, 3H; C*H$_3$*OCH), 2.88-2.70 (m, 2H; C*H*C=O, C*H*CH$_2$O), 2.13-1.98 (m, 1H; CH*H*CH$_2$O), 1.86-1.69 (m, 1H; C*H*HCH$_2$O).
^{13}C NMR (75 MHz, CDCl$_3$): δ = 176.4 (*C*=O), 159.34 (*C*$_{Ar}$O), 130.3 (*C*$_{Ar}$CH$_2$), 129.45 (2C; *C*H$_{Ar}$), 113.92 (2C; *C*H$_{Ar}$), 105.49 (*C*HO$_2$), 72.85 (*C*H$_2$Ar), 72.76 (*C*H$_2$OC=O), 68.4 (C*H$_2$*OPMB), 56.5 (*C*H$_3$OCH), 56.1 (*C*H$_3$OCH), 55.42 (*C*H$_3$OAr), 46.3 (*C*HC=O), 36.5 (*C*HCH$_2$O), 27.6 (*C*H$_2$CH$_2$O).

(3*S*,4*R*)-3-(Dimethoxymethyl)-4-(2-((4-methoxybenzyl)oxy)ethyl)dihydrofuran-2(3*H*)-one *trans*-122b

The epimerization was carried out in analogy to a previously published procedure.[115] Lactone *trans*-**122b**/*cis*-**122b** (2.08 g, 6.4 mmol, dr 16:1) was dissolved in dry THF (25 mL) and DBU (176 µL, 1.28 mmol) was added. The reaction was stirred at room temperature for 24 h. Satd. NH_4Cl solution (25 mL) was added, the layers were separated and the aqueous was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain *trans*-**122b** (2.06 g, 99%) as a yellow oil. Minor diastereomer *cis*-**122b** was not detected by ^{1}H NMR spectroscopy.



R_f = 0.31 (P/EtOAc 6:4).

$[\alpha]_D^{20}$ = +25 (c = 1.0 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.18 (m, 2H; C*H*$_{Ar}$), 6.93-6.82 (m, 2H; C*H*$_{Ar}$), 4.67 (d, $^3J_{H,H}$ = 2.8 Hz, 1H; C*H*O_2), 4.43 (dd, $^2J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 8.0 Hz, 1H; CH*H*OC=O), 4.40 (s, 2H; CH_2Ar), 3.94 (dd, $^2J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; C*H*HOC=O), 3.80 (s, 3H; CH_3OAr), 3.60-3.34 (m, 2H; CH_2OPMB), 3.48 (s, 3H; CH_3OCH), 3.43 (s, 3H; CH_3OCH), 2.97-2.78 (m, 1H; C*H*CH_2O), 2.62 (dd, $^3J_{H,H}$ = 7.9, 2.8 Hz, 1H; C*H*C=O), 2.01 (dq, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 5.2 Hz, 1H; CH*H*CH_2O), 1.70 (dtd, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 8.5, 5.5 Hz, 1H; C*H*HCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4 (*C*=O), 159.30 (*C*$_{Ar}$O), 130.3 (*C*$_{Ar}$CH_2), 129.40 (2C; *C*H$_{Ar}$), 113.91 (2C; *C*H$_{Ar}$), 105.43 (*C*HO_2), 73.2 (*C*H_2OC=O), 72.92 (*C*H_2Ar), 68.3 (CH_2OPMB), 58.1 (*C*H_3OCH), 56.3 (*C*H_3OCH), 55.40 (*C*H_3OAr), 49.9 (*C*HC=O), 34.0 (*C*HCH_2O), 33.7 (*C*H_2CH_2O).

IR (film): ν = 2933, 2836, 1767, 1611, 1513, 1465, 1356, 1302, 1246, 1173, 1020, 889, 819, 755, 688 cm^{-1}.

MS (+ESI) m/z (%): 347 (100) [*M*+Na]$^+$.

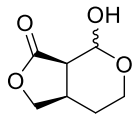
HRMS (+ESI) m/z: calcd for $C_{17}H_{24}O_6$+Na^+: 347.1465 [*M*+Na]$^+$, found: 347.1472.

6.3.2.2 Functionalization of lactone trans-**122b**

(3a*R*,7a*R*)-4-Hydroxyhexahydro-3*H*-furo[3,4-c]pyran-3-one 129

Lactone *trans*-**122b** (56 mg, 0.17 mmol) was dissolved in dry *i*-PrOH (1 mL), TsOH·H_2O (7 mg, 0.03 mmol) was added and the reaction mixture was stirred at room temperature for 24 h and at reflux for 1 h. The mixture was cooled to room temperature, a few drops of satd. $NaHCO_3$ solution followed by brine (2 mL) were added and the mixture was extracted with Et_2O (3×3 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain crude product, which did not contain *trans*-**122b** anymore. Purification by silica gel column chromatography (gradient Pe/EtOAc 1:0 to 9:1) furnished inseparable mixture of **129** (8 mg, 30%) as a 1.4:1 mixture of diastereomers and *p*-(isopropyl)benzylalcohol (6 mg, 23%) as

determined by ^{1}H NMR spectroscopy.



R_f = 0.40 (P/EtOAc 7:3).

Major diastereomer:

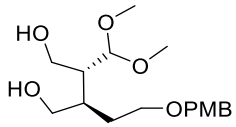
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.99 (d, $^{3}J_{H,H}$ = 2.5 Hz, 1H; C*H*O_2), 4.49-4.36 (m, 1H; CH*H*OC=O), 4.03-3.91 (m, 1H; C*H*HOC=O), 3.89-3.70 (m, 1H; CH*H*OCHOH), 3.58-3.39 (m, 1H; C*H*HOCHOH), 2.60 (br s, 1H; O*H*), 2.48 (dd, $^{3}J_{H,H}$ = 6.7, 2.6 Hz, 1H; C*H*CHOH), 2.05-1.90 (m, 1H; C*H*CH_2), 1.78-1.62 (m, 1H; CH*H*CH_2O), 1.33-1.16 (m, 1H; C*H*HCH_2O).

Minor diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.28 (br s, 1H; C*H*O_2), 4.19 (dd, $^{2}J_{H,H}$ = 9.0 Hz, $^{3}J_{H,H}$ = 4.7 Hz, 1H; CH*H*OC=O), 4.03-3.91 (m, 1H; C*H*HOC=O), 3.89-3.70 (m, 1H; CH*H*OCHOH), 3.58-3.39 (m, 1H; C*H*HOCHOH), 2.58 (br s, 1H; O*H*), 2.51-2.45 (m, 1H; C*H*CHOH), 2.05-1.90 (m, 1H; C*H*CH_2), 1.78-1.62 (m, 1H; CH*H*CH_2O), 1.33-1.16 (m, 1H; C*H*HCH_2O).

(2*R*,3*R*)-2-(Dimethoxymethyl)-3-(hydroxymethyl)-5-((4-methoxybenzyl)oxy))pentanol 133

Reduction was carried out in analogy to a previously published procedure.[115] Lactone *trans*-**122b** (303 mg, 0.934 mmol) was dissolved in dry THF (4 mL) under argon. $LiAlH_4$ (1.87 mL, 1.0 M in THF, 1.87 mmol) was added dropwise at –10 °C and the reaction mixture was warmed to 0 °C with stirring over 2 h. MeOH (1 mL) was added dropwise; after evolution of hydrogen gas ceased, the mixture was warmed to room temperature. Water (1 mL) was added dropwise, followed by Celite® (1 g) and $MgSO_4$ (1 g) and the mixture was stirred vigorously for 30 min. The slurry was filtered through a pad of Celite®, which was washed thoroughly with EtOAc. The filtrate was evaporated under reduced pressure to furnish diol **133** (304 mg, 99%), which was used in the following step without further purification.



R_f = 0.14 (P/EtOAc 6:4).

$[\alpha]_D^{20}$ = +4.3 (c = 1.05 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.19 (m, 2H; C*H*$_{Ar}$), 6.93-6.77 (m, 2H; C*H*$_{Ar}$), 4.54 (d, $^{3}J_{H,H}$ = 6.7 Hz, 1H; C*H*O_2), 4.44 (s, 2H; C*H*$_2$Ar), 3.80 (s, 3H; C*H*$_3$OAr), 3.75 (t, $^{3}J_{H,H}$ = 4.3 Hz, 2H; O_2CHCHC*H*$_2$OH), 3.63 (t, $^{3}J_{H,H}$ = 3.7 Hz, 2H; CH_2CHC*H*$_2$OH), 3.60-3.48 (m, 2H; C*H*$_2$OPMB), 3.42 (s, 3H; C*H*$_3$OCH), 3.34 (s, 3H; C*H*$_3$OCH), 2.08-1.95 (m, 2H; C*H*CH_2CH_2, O*H*), 1.94-1.77 (m, 2H; C*H*CHO_2, CH*H*CH_2O), 1.72-1.54 (m, 2H; C*H*HCH$_2$O, O*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (*C*$_{Ar}$O), 130.3 (*C*$_{Ar}$$CH_2$), 129.6 (2C; *C*H$_{Ar}$), 114.0 (2C; *C*H$_{Ar}$), 106.2 (*C*$HO_2$), 73.1 (*C*$H_2$Ar), 68.8 (*C*$H_2$OPMB), 62.2 ($CH_2$CH*C*$H_2$OH), 59.7 ($O_2$CHCH*C*$H_2$OH),

55.5 (*C*H$_3$OCH), 55.4 (*C*H$_3$OAr), 53.9 (*C*H$_3$OCH), 45.8 (*C*HCHO$_2$), 37.4 (*C*HCH$_2$CH$_2$), 30.2 (*C*H$_2$CH$_2$O).

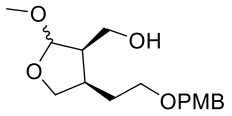
IR (film): ν = 3375 (br), 2934, 1612, 1586, 1512, 1464, 1362, 1301, 1245, 1175, 1083, 1031, 960, 818, 756, 637 cm^{-1}.

MS (+ESI) m/z (%): 351 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{17}H_{28}O_6$+Na$^+$: 351.1778 [*M*+Na]$^+$, found: 351.1775.

((3*R*,4*R*)-3-(Hydroxymethyl)-2-methoxy-4-((2-(4-methoxybenzyl)oxy)ethyl)tetrahydrofuran 134

Diol **133** (113 mg, 0.335 mmol) was dissolved in dry MeOH (2 mL) and TsOH·H$_2$O (6 mg, 34 µmol) was added at –10 °C. The reaction mixture was stirred at this temperature for 1 h after which the reaction was complete as indicated by TLC. A few drops of satd. NaHCO$_3$ solution were added, followed by Et$_2$O (10 mL) and the mixture was filtered through a pad of silica gel, which was thoroughly washed with Et$_2$O. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (5 mL of silica gel, gradient P/EtOAc 8:2 to 6:4) to furnish mixed acetal **134** (91 mg, 89%) as inseparable 1.6:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a yellow oil.



R_f = 0.54 (P/EtOAc 1:1).

Major diastereomer:

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.27-7.09 (m, 2H; C*H*$_{Ar}$), 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; C*H*$_{Ar}$), 4.86 (d, $^3J_{H,H}$ = 1.1 Hz, 1H; C*H*O$_2$), 4.42 (s, 2H; C*H*$_2$Ar), 4.06 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz, 1H; CH$_2$CHC*H*HO), 3.80 (s, 3H; C*H*$_3$OAr), 3.73 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H; CH*H*OH), 3.58 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz, 1H; CH$_2$CHC*H*HO), 3.61-3.39 (m, 3H; C*H*HOH, C*H*$_2$OPMB), 3.34 (s, 3H; C*H*$_3$OCH), 2.61 (sext, $^3J_{H,H}$ = 7.4 Hz, 1H; C*H*CH$_2$CH$_2$), 2.34-2.25 (m, 1H; C*H*CH$_2$OH), 1.83 (dq, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 7.0 Hz, 1H; C*H*HCH$_2$OPMB), 1.71-1.52 (m, 1H; CH*H*CH$_2$OPMB), 1.42 (d, $^3J_{H,H}$ = 4.0 Hz, 1H; O*H*).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.29 (*C*$_{Ar}$O), 130.2 (*C*$_{Ar}$CH$_2$), 129.38 (2C; *C*H$_{Ar}$), 113.90 (2C; *C*H$_{Ar}$), 107.9 (*C*HO$_2$), 72.9 (*C*H$_2$Ar), 72.3 (*C*H$_2$OCH), 69.5 (*C*H$_2$OPMB), 59.9 (*C*H$_2$OH), 55.33 (*C*H$_3$OAr), 54.8 (*C*H$_3$OCH), 50.1 (*C*HCHO$_2$), 36.9 (*C*HCH$_2$CH$_2$), 27.7 (*C*H$_2$CH$_2$O).

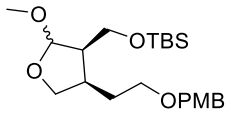
Minor diastereomer:

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.27-7.09 (m, 2H; C*H*$_{Ar}$), 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; C*H*$_{Ar}$), 5.04 (d, $^3J_{H,H}$ = 5.0 Hz, 1H; C*H*O$_2$), 4.41 (s, 2H; C*H*$_2$Ar), 3.97 (dd, $^2J_{H,H}$ = 8.3 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; CH$_2$CHC*H*HO), 3.80 (s, 3H; C*H*$_3$OAr), 3.73 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 5.8 Hz, 1H; CH*H*OH), 3.64 (dd, $^2J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 7.2 Hz, 1H; CH$_2$CHC*H*HO), 3.61-3.39 (m, 3H; C*H*HOH, C*H*$_2$OPMB), 3.38 (s, 3H; C*H*$_3$OCH), 2.61 (sext, $^3J_{H,H}$ = 7.6 Hz, 1H; C*H*CH$_2$CH$_2$), 2.44-2.36 (m, 1H; C*H*CH$_2$OH), 1.95-1.80 (m, 1H; C*H*HCH$_2$OPMB), 1.73-1.54 (m, 1H; CH*H*CH$_2$OPMB), 1.42 (d, $^3J_{H,H}$ = 4.0 Hz, 1H; O*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.26 ($C_{Ar}O$), 130.4 ($C_{Ar}CH_2$), 129.35 (2C; CH_{Ar}), 113.89 (2C; CH_{Ar}), 106.3 (CHO_2), 72.8 (CH_2Ar), 72.4 (CH_2OCH), 69.2 (CH_2OPMB), 59.2 (CH_2OH), 55.33 (CH_3OAr), 55.30 (CH_3OCH), 47.3 ($CHCHO_2$), 36.7 ($CHCH_2CH_2$), 28.9 (CH_2CH_2O).
IR (film): ν = 3438 (br), 2943, 1612, 1586, 1512, 1464, 1362, 1301, 1245, 1174, 1093, 1031, 966, 916, 818, 754, 706, 637 cm^{-1}.
MS (+ESI) m/z (%): 319 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{16}H_{24}O_5+Na^+$: 319.1516 $[M+Na]^+$, found: 319.1513.

((3*R*,4*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methoxy-4-((2-(4-methoxybenzyl)oxy) ethyl)tetrahydrofuran 135a

Mixed acetal **134** (50 mg, 0.158 mmol) was dissolved in dry DCM (1.7 mL). Imidazole (23 mg, 0.348 mmol), TBSCl (48 mg, 0.316 mmol) and DMAP (4 mg, 63 µmol) were successively added at 0 °C. The reaction mixture was stirred at room temperature overnight. The same quantities of all reagents were added at 0 °C and the reaction mixture was warmed to room temperature and stirred for 48 h. Satd. NH_4Cl solution (3 mL) was added, the layers were separated and the aqueous was extracted with DCM (3×6 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (3 mL of silica gel, gradient P/EtOAc 10:0 to 9:1) to obtain protected alcohol **135a** (49 mg, 75%) as partially separable 1.7:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.

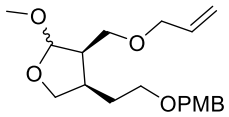


More polar major diastereomer: R_f = 0.67 (P/EtOAc 95:5).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.21 (m, 2H; CH_{Ar}), 6.91-6.80 (m, 2H; CH_{Ar}), 4.92-4.86 (m, 1H; CHO_2), 4.41 (s, 2H; CH_2Ar), 4.05 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz, 1H; $CH_2CHCHHO$), 3.80 (s, 3H; CH_3OAr), 3.67 (dd, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 5.5 Hz, 1H; CH*H*OTBS), 3.57 (t, $^3J_{H,H}$ = 8.4 Hz, $^2J_{H,H}$ = 8.5 Hz, 1H; $CH_2CHCHHO$), 3.52-3.47 (m, 1H; C*H*HOTBS), 3.50-3.36 (m, 2H; CH_2OPMB), 3.33 (s, 3H; CH_3OCH), 2.67-2.53 (m, 1H; CHCH_2CH_2), 2.30-2.16 (m, 1H; CHCH_2OTBS), 1.78 (dq, $^2J_{H,H}$ = 12.9 Hz, $^3J_{H,H}$ = 6.4 Hz, 1H; C*H*HCH_2OPMB), 1.64-1.43 (m, 1H, C*H*HCH_2OPMB), 0.88 (s, 9H; CH_3CSi), 0.03 (s, 6H; CH_3Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 ($C_{Ar}O$), 130.5 ($C_{Ar}CH_2$), 129.35 (2C; CH_{Ar}), 113.9 (2C; CH_{Ar}), 107.8 (CHO_2), 72.8 (CH_2Ar), 72.5 (CH_2OCHO), 69.5 (CH_2OPMB), 60.1 (CH_2OTBS), 55.4 (CH_3OAr), 54.9 (CH_3OCH), 50.1 ($CHCH_2OTBS$), 36.3 ($CHCH_2CH_2$), 27.9 (CH_2CH_2O), 26.0 (3C; CH_3CSi), 18.3 (CSi), –5.32 (2C; CH_3Si).
Less polar minor diastereomer: R_f = 0.82 (P/EtOAc 95:5).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, $^3J_{H,H}$ = 9.0 Hz, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 4.86 (d, $^3J_{H,H}$ = 4.3 Hz, 1H; CHO_2), 4.39 (s, 2H; CH_2Ar), 4.02-3.93 (m, 1H; $CH_2CHCHHO$), 3.80 (s, 3H; CH_3OAr), 3.78-3.71 (m, 2H; CH*H*OTBS; $CH_2CHCHHO$), 3.49-3.36 (m, 3H; C*H*HOTBS, CH_2OPMB), 3.29 (s, 3H; CH_3OCH), 2.67-2.53 (m, 1H; CHCH_2CH_2), 2.41-2.30 (m, 1H; CHCH_2OTBS), 1.78 (dq, $^2J_{H,H}$ = 13.1 Hz, $^3J_{H,H}$ = 6.6 Hz, 1H; C*H*HCH_2OPMB), 1.67-1.48 (m,

1H; CH*H*CH_2OPMB), 0.88 (s, 9H; CH_3CSi), 0.04 (s, 6H; CH_3Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_{Ar}O), 130.5 ($C_{Ar}CH_2$), 129.34 (2C; CH_{Ar}), 113.9 (2C; CH_{Ar}), 105.0 (CHO_2), 72.8 (CH_2Ar), 72.6 (CH_2OCHO), 69.4 (CH_2OPMB), 59.3 (CH_2OTBS), 55.4 (CH_3OAr), 54.8 (CH_3OCH), 49.1 (*C*HCH_2OTBS), 35.0 (*C*HCH_2CH_2), 27.2 (CH_2CH_2O), 26.0 (3C; CH_3CSi), 18.3 (*C*Si), –5.34 (2C; CH_3Si).
MS (+ESI) m/z (%): 433 (100) $[M+Na]^+$.

(3*R*,4*R*)-3-((Allyloxy)methyl)-2-methoxy-4-(2-((4-methoxybenzyl)oxy)ethyl)tetrahydrofuran 135b

Mixed acetal **134** (77 mg, 0.26 mmol) was dissolved in dry DMF (0.5 mL). NaH (21 mg, 60% in mineral oil, 0.52 mmol) was added and the suspension was cooled to 0 °C. 3-Bromopropene (22 µL, 0.26 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 2 h. A few drops of satd. NH_4Cl solution were added, followed by water (1 mL) and the mixture was extracted with EtOAc (3×2 mL). The combined organic layers were washed with water and brine dried over $MgSO_4$, filtered and evaporated under reduced pressure to furnish ether **135b** (85 mg, 98%) as inseparable 1.6:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil, which was used in the next step without further purification.
R_f = 0.87 (P/EtOAc 7:3).

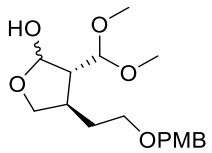


Major diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.18 (m, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 5.99-5.78 (m, 1H; C*H*=CH_2), 5.25 (dq, $^3J_{H,H}$ = 17.2 Hz, $^2J_{H,H}$ = 1.6 Hz, 1H; CH=CH*H*), 5.20-5.12 (m, 1H; CH=C*H*H), 4.91-4.89 (m, 1H; C*H*O_2), 4.41 (s, 2H; CH_2Ar), 4.05 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz, 1H; CH*H*OCHO), 4.01-3.96 (m, 2H; CH_2=CHCH_2O), 3.80 (s, 3H; CH_3OAr), 3.57 (t, $^3J_{H,H}$ = 8.7 Hz, $^2J_{H,H}$ = 8.7 Hz, 1H; C*H*HOCHO), 3.64-3.51 (m, 1H, CH*H*Oallyl), 3.53-3.37 (m, 3H; C*H*HOallyl, CH_2OPMB), 3.33 (s, 3H; CH_3OCH), 2.72-2.53 (m, 1H; C*H*CH_2Oallyl), 2.51-2.26 (m, 1H; C*H*CHO), 1.90-1.48 (m, 2H; CH_2CH_2OPMB).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_{Ar}O), 134.8 (*C*H=CH_2), 130.5 ($C_{Ar}CH_2$), 129.4 (2C; CH_{Ar}), 117.2 (CH=*C*H_2), 113.9 (2C; CH_{Ar}), 107.7 (CHO_2), 72.9 (CH_2Ar), 72.28 (2C; CH_2OCHO, CH_2=CH*C*H_2O), 69.5 (CH_2OPMB), 67.2 (CH_2Oallyl), 55.4 (CH_3OAr), 54.9 (CH_3OCH), 47.9 (*C*HCH_2Oallyl), 36.4 (*C*HCH_2CH_2), 28.0 (CH_2CH_2O).
Minor diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.18 (m, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 5.99-5.78 (m, 1H; C*H*=CH_2), 5.25 (dq, $^3J_{H,H}$ = 17.2 Hz, $^4J_{H,H}$ = 1.6 Hz, $^2J_{H,H}$ = 1.6 Hz, 1H; CH=CH*H*), 5.20-5.12 (m, 1H; CH=C*H*H), 4.89 (d, $^3J_{H,H}$ = 4.6 Hz, 1H; C*H*O_2), 4.41 (s, 2H; CH_2Ar), 4.05 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz, 1H; CH*H*OCHO), 4.01-3.96 (m, 2H; CH_2=CHCH_2O), 3.80 (s, 3H; CH_3OAr), 3.57 (t, $^3J_{H,H}$ = 8.7 Hz, $^2J_{H,H}$ = 8.7 Hz, 1H; C*H*HOCHO), 3.64-3.51 (m, 1H, CH*H*Oallyl), 3.53-3.37 (m, 3H; C*H*HOallyl, CH_2OPMB), 3.33 (s, 3H; CH_3OCH), 2.72-2.53 (m,

1H; C*H*CH_2Oallyl), 2.51-2.26 (m, 1H; C*H*CHO), 1.90-1.48 (m, 2H; C$H_2$$CH_2$OPMB).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (C_{Ar}O), 135.0 (*C*H=CH_2), 130.6 ($C_{Ar}CH_2$), 129.5 (2C; *C*H_{Ar}), 117.3 (CH=*C*H_2), 113.9 (2C; *C*H_{Ar}), 104.9 (*C*HO_2), 72.7 (*C*H_2Ar), 72.5 (*C*H_2OCHO), 72.34 (CH_2=CH*C*H_2O), 69.3 (*C*H_2OPMB), 66.3 (*C*H_2Oallyl), 55.4 (*C*H_3OAr), 54.8 (*C*H_3OCH), 46.6 (*C*HCH_2Oallyl), 35.1 (*C*HCH_2CH_2), 30.0 (*C*H_2CH_2O).
MS (+ESI) m/z (%): 359 (100) [*M*+Na]$^+$.

(3*R*,4*R*)-3-(Dimethoxymethyl)-4-(2-((4-methoxybenzyl)oxy)ethyl)tetrahydrofuran-2-ol 138

Lactone *trans*-**122b** (1.26 g, 3.88 mmol) was dissolved in dry toluene (30 mL) and DIBAL-H (5.4 mL, 1.0 M in hexanes, 5.4 mmol) was added dropwise at –78 °C. The reaction mixture was warmed to –50 °C over 30 min after which complete conversion was indicated by TLC. MeOH (1 mL) was added dropwise followed by water (1 mL), $MgSO_4$ (ca 1 g) and Celite® (ca 1 g of each). The reaction mixture was warmed to room temperature with vigorous stirring and the resulting slurry was filtered through a pad of Celite®, which was thoroughly washed with Et_2O. The filtrate was evaporated under reduced pressure to afford crude lactol **138** (1.27 g, quantitative) as inseparable 3:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil, which was used in the subsequent step without further purification.

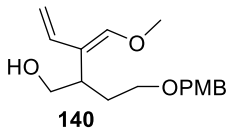


R_f = 0.28 (P/EtOAc 4:1).
Major diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, $^3J_{H,H}$ = 8.2 Hz, 2H; C*H*$_{Ar}$), 6.94-6.81 (m, 2H; C*H*$_{Ar}$), 5.42-5.36 (m, 1H; C*H*OH), 4.41 (s, 2H; CH_2Ar), 4.25 (d, $^3J_{H,H}$ = 6.9 Hz, 1H; C*H*O_2), 4.06 (dd, $^2J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 7.0 Hz, 1H; CH*H*OCHO), 3.80 (s, 3H; CH_3OAr), 3.73 (t, $^2J_{H,H}$ = 8.7 Hz, $^3J_{H,H}$ = 8.7 Hz, 1H; C*H*HOCHO), 3.52-3.39 (m, 2H; CH_2OPMB), 3.36 (s, 3H; CH_3OCH), 3.35 (s, 3H; CH_3OCH), 2.88 (br s, 1H; O*H*), 2.25-2.09 (m, 2H; C*H*CH_2O, C*H*CHO), 2.07-1.92 (m, 1H; CH*H*CH_2O), 1.80-1.65 (m, 1H; C*H*HCH_2O).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (C_{Ar}O), 130.5 ($C_{Ar}CH_2$), 129.4 (2C; *C*H_{Ar}), 113.9 (2C; *C*H_{Ar}), 105.4 (*C*HO_2), 100.4 (*C*HOH), 72.7 (*C*H_2A*r*), 72.5 (*C*H_2OCHO), 69.0 (*C*H_2OPMB), 55.52 (*C*HCHO), 55.4 (*C*H_3OAr), 54.35 (*C*H_3OCH), 53.60 (*C*H_3OCH), 38.9 (*C*HCH_2O), 33.0 (*C*H_2CH_2O).
Minor diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, $^3J_{H,H}$ = 8.2 Hz, 2H; C*H*$_{Ar}$), 6.94-6.81 (m, 2H; C*H*$_{Ar}$), 5.42-5.36 (m, 1H; C*H*OH), 4.52 (d, $^3J_{H,H}$ = 7.1 Hz, 1H; C*H*O_2), 4.42 (s, 2H; CH_2Ar), 4.28-4.19 (m, 1H; CH*H*OCHO), 3.80 (s, 3H; CH_3OAr), 3.59 (dd, $^2J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H; C*H*HOCHO), 3.52-3.39 (m, 2H; CH_2OPMB), 3.41 (s, 3H; CH_3OCH), 3.39 (s, 3H; CH_3OCH), 3.20 (br s, 1H; O*H*), 2.50-2.36 (m, 1H; C*H*CH_2O), 2.27-2-18 (m, 1H; C*H*CHO), 2.18-2-06 (m; 1H, CH*H*CH_2O), 1.51 (ddt, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 10.2, 6.4 Hz, 1H; C*H*HCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 ($C_{Ar}O$), 130.5 ($C_{Ar}CH_2$), 129.3 (2C; CH_{Ar}), 113.9 (2C; CH_{Ar}), 105.4 (CHO_2), 98.5 (*C*HOH), 73.1 (CH_2OCHO), 72.7 (CH_2Ar), 69.1 (CH_2OPMB), 55.4 (CH_3OAr), 54.63 (CH_3OCH), 53.57 (CH_3OCH), 51.9 (*C*HCHO), 36.2 ($CHCH_2O$), 33.5 (CH_2CH_2O).
IR (film): ν = 3408 (br), 2939, 2836, 1612, 1512, 1454, 1361, 1301, 1245, 1174, 1051, 926, 819, 756, 707 cm^{-1}.
MS (+ESI) m/z (%): 365 (10) [*M*+K], 349 (100) [*M*+Na]$^+$.
HRMS (+ESI) m/z: calcd for $C_{17}H_{26}O_6$+Na$^+$: 349.1622 [*M*+Na]$^+$, found: 349.1621.

(2*R*,3*S*)-3-(Dimethoxymethyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)pent-4-en-1-ol 139 and **(*Z*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethylene)pent-4-en-1-ol 140**

Method C: A two-necked oven-dried 250 mL flask was charged with methyltriphenylphosphonium bromide (4.62 g, 12.9 mmol) and filled with nitrogen by three vacuum/nitrogen cycles. Dry toluene (48 mL) was added, followed by dropwise addition of KHMDS (16.4 mL, 0.61 M in toluene, 10.1 mmol; titrated prior to use using salicylaldehyde phenylhydrazone as indicator).[131] The suspension became bright yellow. The reaction mixture was stirred for 60 min at room temperature and subsequently cooled to 0 °C. A solution of lactol **138** (0.94 g, 2.87 mmol) in dry toluene (8 mL, 1.5 mL for rinse) was added dropwise using a syringe pump and a needle (0.8 mm outer diameter; 5 mL/h). The temperature was maintained at 0 °C during the whole addition. After the addition was finished, the reaction mixture was warmed to room temperature overnight. The reaction mixture was diluted with Et_2O (20 mL), satd. NH_4Cl solution (30 mL) was added, the layers were separated and the aqueous was extracted with Et_2O (3×30 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was adsorbed on Celite®, divided in three batches and each batch was purified by flash column chromatography using the Reveleris® system (Büchi), column packed with spherical silica (25 g, 30 μM, Intershim) and cyclohexane/EtOAc gradient 9:1 to 7:3 with an isocratic window at 23% EtOAc. Purification furnished side product **140** (78 mg, 9%) and alkene **139** (0.71 g, 76%).
Note: Compound **139** should only be stored for a short period of time in the absence of acidity and used rapidly in the next step, otherwise it readily cyclizes to furnish corresponding cyclic acetal **144** (*vide infra*).



140

$[\alpha]_D^{20}$ = 0 (c = 0.68 in $CHCl_3$).
R_f = 0.43 (P/EtOAc 6:4).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.21 (m, 2H; CH_{Ar}), 6.92-6.81 (m, 2H; CH_{Ar}), 6.19 (d, $^4J_{H,H}$ = 0.8 Hz, 1H; C=C*H*OMe), 6.12 (ddd, $^3J_{H,H}$ = 17.4, 11.0 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; C*H*=CH_2), 5.11 (d, $^3J_{H,H}$ = 17.3 Hz, 1H; CH=CH*H*), 4.83 (d, $^3J_{H,H}$ = 11.3 Hz, 1H; CH=C*H*H), 4.42 (s, 2H; CH_2Ar), 3.80 (s, 3H; CH_3OAr), 3.71 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2OH), 3.63 (s, 3H; CH_3OCH), 3.53 (dt, $^2J_{H,H}$ = 9.3 Hz, $^3J_{H,H}$ = 5.6 Hz, 1H; CH*H*OPMB), 3.42 (ddd, $^2J_{H,H}$ = 9.3 Hz, $^3J_{H,H}$ = 8.0, 5.8 Hz,

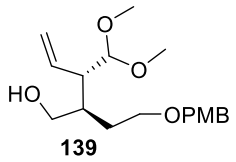
1H; C*H*HOPMB), 2.90 (quint, $^{3}J_{H,H}$ = 6.8 Hz, 1H; C*H*CH$_2$OH), 2.29 (t, $^{3}J_{H,H}$ = 6.0 Hz, 1H; O*H*), 2.04-1.80 (m, 2H; C*H*$_2$CH$_2$O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (*C*$_{Ar}$O), 150.2 (*C*HOMe), 135.6 (*C*H=CH$_2$), 130.6 (*C*$_{Ar}$CH$_2$), 129.5 (2C; *C*H$_{Ar}$), 119.1 (*C*=CHO), 113.9 (2C; *C*H$_{Ar}$), 109.3 (CH=*C*H$_2$), 72.8 (*C*H$_2$Ar), 69.1 (*C*H$_2$OPMB), 65.1 (*C*H$_2$OH), 60.4 (*C*H$_3$OCH), 55.4 (*C*H$_3$OAr), 37.2 (*C*HCH$_2$OH), 30.3 (*C*H$_2$CH$_2$O).

IR (film): *v* = 3406 (br), 2934, 2859, 1637, 1613, 1513, 1463, 1362, 1302, 1245, 1174, 1139, 1085, 1034, 822, 756 cm^{-1}.

MS (+ESI) m/z (%): 331 (65) [*M*+K]$^+$, 315 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{17}H_{24}O_4$+Na$^+$: 315.1567 [*M*+Na]$^+$, found: 315.1565.



139

R_f = 0.39 (P/EtOAc 6:4).

$[\alpha]_D^{20}$ = +6.7 (c = 0.36 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.20 (m, 2H; C*H*$_{Ar}$), 6.95-6.81 (m, 2H; C*H*$_{Ar}$), 5.75 (dt, $^{3}J_{H,H}$ = 17.1, 10.0 Hz, 1H; C*H*=CH$_2$), 5.16 (dd, $^{3}J_{H,H}$ = 10.3 Hz, $^{2}J_{H,H}$ = 2.0 Hz, 1H; C*H*=C*H*H), 5.09 (ddd, $^{3}J_{H,H}$ = 17.1 Hz, $^{2}J_{H,H}$ = 2.0 Hz, $^{4}J_{H,H}$ = 0.7 Hz, 1H; C*H*=CH*H*), 4.44 (s, 2H; C*H*$_2$Ar), 4.40 (d, $^{3}J_{H,H}$ = 6.1 Hz, 1H; C*H*O$_2$), 3.80 (s, 3H, C*H*$_3$OAr), 3.68-3.41 (m, 4H, C*H*$_2$OPMB, C*H*$_2$OH), 3.37 (s, 3H; C*H*$_3$OCH), 3.34 (s, 3H; C*H*$_3$OCH), 3.10 (t, $^{3}J_{H,H}$ = 6.2 Hz, 1H; O*H*), 2.44 (dddd, $^{3}J_{H,H}$ = 9.9, 6.1, 3.9 Hz, $^{4}J_{H,H}$ = 0.9 Hz, 1H; C*H*CH=CH$_2$), 2.02-1.94 (m, 1H; C*H*CH$_2$OH), 1.73-1.54 (m, 2H; C*H*$_2$CH$_2$O).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3 (*C*$_{Ar}$O), 134.9 (*C*H=CH$_2$), 130.1 (*C*$_{Ar}$CH$_2$), 129.6 (2C; *C*H$_{Ar}$), 118.5 (CH=*C*H$_2$), 113.9 (2C; *C*H$_{Ar}$), 105.9 (*C*HO$_2$), 72.9 (*C*H$_2$Ar), 68.7 (*C*H$_2$OPMB), 63.6 (*C*H$_2$OH), 55.4 (*C*H$_3$OAr), 54.7 (*C*H$_3$OCH), 54.2 (*C*H$_3$OCH), 50.0 (*C*HCH=CH$_2$), 39.1 (*C*HCH$_2$OH), 30.9 (*C*H$_2$CH$_2$O).

IR (film): *v* = 3441 (br), 3073, 2933, 2835, 1612, 1586, 1512, 1464, 1361, 1301, 1245, 1174, 1112, 1033, 961, 915, 819, 756, 706, 637 cm^{-1}.

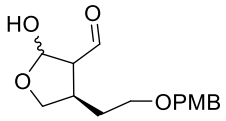
MS (+ESI) m/z (%): 363 (8) [*M*+K]$^+$, 347 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{18}H_{28}O_5$+Na$^+$: 347.1829 [*M*+Na]$^+$, found: 347.1826.

(3*S*,4*R*)-2-Hydroxy-4-(2-((4-methoxybenzyl)oxy)ethyl)tetrahydrofuran-3-carbaldehyde 141

Lactol **138** (25 mg, 77 µmol) was dissolved in dry toluene (0.4 mL) and KHMDS (306 µL, 0.5 M in toluene, 0.15 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h, diluted with Et_2O to ca 3 mL and satd. NH_4Cl solution (2 mL) was added. The layers were separated and the aqueous was extracted with Et_2O (3×3 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated to give crude product (21 mg), which did not contain **138** anymore. Aldehyde **141** was identified as the major product as 1:1 mixture of diastereomers along with an unidentified impurity based on

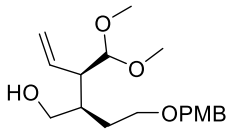
characteristic ^{1}H NMR resonances, which could not be unambiguously assigned to an individual isomer.



R_f = 0.61 (P/EtOAc 6:4).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.87 (d, $^3J_{H,H}$ = 1.6 Hz, 1H; C*H*O)/9.71 (d, $^3J_{H,H}$ = 1.6 Hz, 1H; C*H*O), 7.27-7.18 (m, 2H; CH_{Ar}), 6.88-6.81 (m, 2H; CH_{Ar}), 5.38 (dd, $^3J_{H,H}$ = 3.2, 1.8 Hz, 1H; C*H*OH)/5.32 (d, $^3J_{H,H}$ = 1.8 Hz, 1H; C*H*OH), 4.44 (s, 2H, CH_2Ar), 4.26-4.15 (m, 1H; CH*H*OCHOH)/4.11-3.99 (m, 1H; CH*H*OCHOH), 3.79 (s, 3H; CH_3)/3.77 (s, 3H; CH_3), 3.74-3.68 (m, 1H; CH*H*OCHOH), 3.49-3.41 (m, 2H; CH_2OPMB), 3.16-3.01 (m, 1H; C*H*CHOH), 2.67-2.51 (m, 1H; C*H*CH$_2$), 2.50 (d, $^3J_{H,H}$ = 1.6 Hz, 1H; O*H*)/2.48 (br s, 1H; O*H*), 1.75-1.53 (m, 2H; CH_2CH_2O).

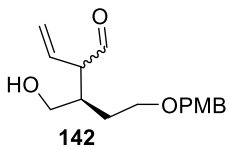
(2*R*,3*R*)-3-(Dimethoxymethyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)pent-4-en-1-ol *epi*-139 and **(3*R*)-3-(hydroxymethyl)-5-((4-methoxybenzyl)oxy)-2-vinylpentanal 142**

Obtained in analogy to aldehyde **141** from **139** (23 mg, 71 μmol) as 3:3:1 mixture of **139**, *epi*-**139** and **142** as inseparable 1:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy, along with an undentified fourth compound. Disctinct ^{1}H NMR resonances of **142** could not be unambiguously assigned to an individual isomer.



epi-**139**

Distinct ^{1}H NMR resonances:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75-5.53 (m, 1H; C*H*=CH$_2$), 5.19-4.99 (m, 2H; CH=CH_2), 4.58 (d, $^3J_{H,H}$ = 7.5 Hz, 1H; C*H*O$_2$), 3.79 (s, 3H; CH_3OAr), 3.34 (s, 3H; CH_3OCH), 3.34 (s, 3H; CH_3OCH), 2.58 (dt, $^3J_{H,H}$ = 9.9, 4.9 Hz, 1H; C*H*CH=CH$_2$), 2.07-1.93 (m, 1H; C*H*CH$_2$).



142

Distinct ^{1}H NMR resonances:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (d, $^3J_{H,H}$ = 2.1 Hz, 1H; *H*C=O)/9.55 (d, $^3J_{H,H}$ = 3.4 Hz, 1H; *H*C=O), 5.80 (td, $^3J_{H,H}$ = 18.0, 9.7 Hz, 1H; C*H*=CH$_2$), 5.25-5.10 (m, 2H; CH=CH_2), 2.95-2.86 (m, 1H; C*H*CH=CH$_2$).

6.3.2.3 Synthesis of lactol **147b** *by strategy* **II**

(2*R*,3*S*)-3-(Dimethoxymethyl)-2-(2-((4-methoxybenzyl)oxy)ethyl)pent-4-enal 143 and **(3*S*,4*R*)-2-Methoxy-4-(2-((4-methoxybenzyl)oxy)ethyl)-3-vinyltetrahydrofuran 144**

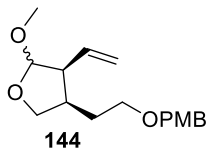
Dess-Martin oxidation (conditions **a)**: Wittig product **139** (564 mg, 1.74 mmol) was dissolved in dry DCM (17 mL) and DMP (5.42 mL, 15% in DCM, 2.61 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. $Na_2S_2O_3$/$NaHCO_3$ solution (10%, 1:1 v/v, 40 mL) was added and the biphasic mixture was stirred vigorously at room temperature for 1 h. The layers were separated and the aqueous was extracted with DCM (3×30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (gradient P/EtOAc 95:5 to 9:1) to furnish mixed acetal **144** (97 g, 19%) as inseparable 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil, followed by aldehyde **143** (405 mg, 72%) as a colorless oil.

Ley-Grifith oxidation (conditions **b**): TPAP (43 mg, 0.12 mmol) was added to a suspension of Wittig product **139** (200 mg, 0.62 mmol), NMO (144 mg, 1.23 mmol) and powdered 4Å molecular sieves (350 mg) in dry DCM (6 mL) and the reaction mixture was stirred at room temperature for 2 h. The mixture was filtered over a pad of Celite®, the filtrate was evaporated under reduced pressure and the crude was purified by silica gel column chromatography (P/EtOAc 9:1) to give aldehyde **143** (158 mg, 79%) as a colorless oil.

Swern oxidation (conditions **c**): DMSO (131 µL, 1.84 mmol) was added dropwise to a solution of oxalyl chloride (107 µL, 1.23 mmol) in dry DCM (2 mL) stirring at –78 °C and the reaction mixture was stirred at this temperature for 15 min. Solution of Wittig product **139** (199 mg, 0.61 mmol) in dry DCM (1 mL) was added using a cannula and the reaction mixture was stirred at –78 °C for 20 min. Et_3N (516 µL, 3.68 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 20 min and then warmed to room temperature over 30 min. Satd. NH_4Cl solution (2 mL) and water (2 mL) were added, the layers were separated and the aqueous was extracted with DCM (3×3 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was purified by silica gel column chromatography (P/EtOAc 9:1) to give aldehyde **143** (170 mg containing 5 mol.% of its (2*S*)-epimer, 86%) as a colorless oil.

Dess-Martin oxidation, buffered (conditions **d**): DMP (1.93 mL, 15% in DCM, 0.93 mmol) was added to a suspension of $NaHCO_3$ (78 mg, 0.93 mmol) and Wittig product **139** (200 mg, 0.62 mmol) in dry DCM (4 mL). The reaction mixture was stirred at room temperature overnight, further $NaHCO_3$ (78 mg, 0.93 mmol) and DMP (1.93 mL, 15% in DCM, 0.93 mmol) were added and the reaction mixture was stirred at room temperature for 1.5 days. The mixture was diluted with DCM to ca 10 mL, $Na_2S_2O_3$/$NaHCO_3$ solution (10%, 1:1 v/v, 10 mL) was added and the mixture was vigorously stirred at room temperature until the precipitate dissolved. The layers were separated and the aqueous was extracted with DCM (2×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was

purified by silica gel column chromatography (P/EtOAc 9:1) to give aldehyde **143** (167 mg containing 5 mol.% of its (2*S*)-epimer, 84%) as a colorless oil.



144

R_f = 0.56 (P/EtOAc 4:1).

Major diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, $^3J_{H,H}$ = 8.8 Hz, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 5.63 (ddd, $^3J_{H,H}$ = 16.8, 10.6, 9.5 Hz, 1H; C*H*=CH_2), 5.15-5.09 (m, 1H; CH=CH*H*), 5.08-5.06 (m, 1H; CH=C*H*H), 4.73-4.70 (m, 1H; C*H*O_2), 4.40 (s, 2H; CH_2Ar), 4.09 (t, $^3J_{H,H}$ = 8.2 Hz, $^2J_{H,H}$ = 8.2 Hz; 1H; CH*H*OCH), 3.79 (s, 3H; CH_3OAr), 3.58 (t, $^3J_{H,H}$ = 8.5 Hz, $^2J_{H,H}$ = 8.5 Hz, 1H; C*H*HOCH), 3.47-3.35 (m, 2H; CH_2OPMB), 3.32 (s, 3H; CH_3OCH), 2.74-2.57 (m, 2H; C*H*CH=CH_2, C*H*CH_2), 1.76-1.49 (m, 2H; CH_2CH_2O).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2 (C_{Ar}O), 134.1 (*C*H=CH_2), 130.5 ($C_{Ar}CH_2$), 129.3 (2C; *C*H_{Ar}), 117.9 (CH=*C*H_2), 113.8 (2C; *C*H_{Ar}), 109.0 (*C*HO_2), 72.7 (*C*H_2Ar), 72.1 (*C*H_2OCH), 69.0 (*C*H_2OPMB), 55.3 (*C*H_3OAr), 54.7 (*C*H_3OCH), 53.0 (*C*HCH=CH_2), 37.6 (*C*HCH_2), 28.7 (*C*H_2CH_2O).

Minor diastereomer:

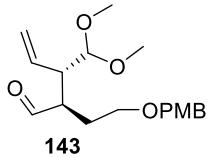
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, $^3J_{H,H}$ = 8.8 Hz, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 5.85 (dt, $^3J_{H,H}$ = 17.1, 10.1 Hz 1H; C*H*=CH_2), 5.18-5.09 (m, 2H; CH=CH_2), 4.84 (d, $^3J_{H,H}$ = 4.9 Hz, 1H; C*H*O_2), 4.40 (s, 2H; CH_2Ar), 4.01 (dd, $^2J_{H,H}$ = 8.5 Hz, $^3J_{H,H}$ = 7.6 Hz; 1H; CH*H*OCH), 3.79 (s, 3H; CH_3OAr), 3.67 (dd, $^2J_{H,H}$ = 8.5 Hz, $^3J_{H,H}$ = 6.6 Hz, 1H; C*H*HOCH), 3.48-3.33 (m, 2H; CH_2OPMB), 3.32 (s, 3H; CH_3OCH), 2.81 (td, $^3J_{H,H}$ = 9.6, 4.9 Hz, 1H; C*H*CH=CH_2), 2.48-2.31 (m, 1H; C*H*CH_2), 1.75-1.60 (m, 2H; CH_2CH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (C_{Ar}O), 133.8 (*C*H=CH_2), 130.6 ($C_{Ar}CH_2$), 129.3 (2C; *C*H_{Ar}), 118.0 (CH=*C*H_2), 113.8 (2C; *C*H_{Ar}), 106.3 (*C*HO_2), 72.6 (*C*H_2Ar), 71.9 (*C*H_2OCH), 69.0 (*C*H_2OPMB), 55.3 (*C*H_3OAr), 55.1 (*C*H_3OCH), 51.3 (*C*HCH=CH_2), 38.4 (*C*HCH_2), 30.2 (*C*H_2CH_2O).

IR (film): *v* = 2934, 1639, 1611, 1586, 1512, 1464, 1362, 1301, 1245, 1173, 1092, 1032, 957, 916, 819, 786, 756, 708, 637 cm^{-1}.

MS (+ESI) m/z (%): 315 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{17}H_{24}O_4$+Na^+: 315.1567 [*M*+Na]$^+$, found: 315.1563.



143

R_f = 0.71 (P/EtOAc 6:4).

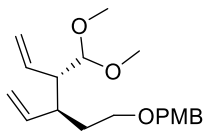
$[\alpha]_D^{20}$ = –8.9 (c = 0.54 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.64 (d, $^3J_{H,H}$ = 2.1 Hz, 1H; C*H*O), 7.27-7.18 (m, 2H; CH_{Ar}),

6.92-6.81 (m, 2H, C*H*$_{Ar}$), 5.79 (ddd, $^{3}J_{H,H}$ = 17.1, 10.4, 8.9 Hz, 1H; C*H*=CH$_2$), 5.20 (ddd, $^{3}J_{H,H}$ = 10.4 Hz, $^{2}J_{H,H}$ = 1.7, $^{4}J_{H,H}$ = 0.7 Hz, 1H; CH=CH*H*), 5.13 (ddd, $^{3}J_{H,H}$ = 17.1 Hz, $^{2}J_{H,H}$ = 1.7 Hz, $^{4}J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*H), 4.39 (s, 2H; C*H*$_2$Ar), 4.37 (d, $^{3}J_{H,H}$ = 6.4 Hz, 1H; C*H*O$_2$), 3.80 (s, 3H; C*H*$_3$OAr), 3.47 (t, $^{3}J_{H,H}$ = 6.3 Hz, 2H; C*H*$_2$OPMB), 3.35 (s, 3H; C*H*$_3$OCH), 3.33 (s, 3H; C*H*$_3$OCH), 2.80-2.64 (m, 2H; C*H*CH=O, C*H*CH=CH$_2$), 2.04 (ddt, $^{2}J_{H,H}$ = 14.6 Hz, $^{3}J_{H,H}$ = 8.7, 6.3 Hz, 1H; CH*H*CH$_2$O), 1.68 (dtd, $^{2}J_{H,H}$ = 14.3 Hz, $^{3}J_{H,H}$ = 6.2, 4.5 Hz, 1H; C*H*HCH$_2$O).
^{13}C NMR (75 MHz, CDCl$_3$): δ = 204.1 (*C*H=O), 159.3 (*C*$_{Ar}$CH$_2$), 134.1 (*C*H=CH$_2$), 130.4 (*C*$_{Ar}$O), 129.4 (2C; *C*H$_{Ar}$), 119.1 (CH=*C*H$_2$), 113.9 (2C; *C*H$_{Ar}$), 105.4 (*C*HO$_2$), 72.8 (*C*H$_2$Ar), 68.0 (*C*H$_2$OPMB), 55.4 (*C*H$_3$OAr), 55.3 (*C*H$_3$OCH), 54.0 (*C*H$_3$OCH), 49.2 (*C*HCH=CH$_2$), 48.9 (*C*HCHO), 27.2 (*C*H$_2$CH$_2$O).
IR (film): ν = 2937, 2835, 1718, 1612, 1512, 1464, 1362, 1302, 1246, 1174, 1034, 995, 968, 921, 819, 756, 709 cm^{-1}.
MS (+ESI) m/z (%): 361 (100) [*M*+K]$^+$, 345 (50) [*M*+Na]$^+$.
HRMS (+ESI) m/z: calcd for C$_{18}$H$_{26}$O$_5$+Na$^+$: 345.1672 [*M*+Na]$^+$, found: 345.1678.

1-(3*S*,4*S*)-3-Dimethoxymethyl-4-((2-(4-methoxbenzyl)oxy)ethyl)hexa-1,5-diene 145

Step 1: Performed in analogy to the synthesis of **143** from **139** (2.02 g, 6.23 mmol, combined from several Wittig reactions) in DCM (62 mL; analytical grade, not dried) with stirring at room temperature for 1 h. Crude aldehyde **143** was used in the next step withour further purification.
Step 2: An oven-dried flask was charged with methyltriphenylphosphonium bromide (5.54 g, 15.51 mmol) and filled with nitrogen through three vacuum/nitrogen cycles. Dry toluene (90 mL) was added, followed by NaHMDS (20.7 mL, 0.6 M in toluene, 12.4 mmol). The bright yellow suspension was stirred at room temperature for 50 min and crude aldehyde in dry toluene (15 mL) was added using a cannula. The reaction mixture was stirred at room temperature for 1 h after which the reaction was complete as indicated by TLC. The reaction mixture was diluted with Et$_2$O to ca 200 mL, satd. NH$_4$Cl solution (70 mL) and water (20 mL) were added, the layers were separated and the aqueous was extracted with Et$_2$O (3×100 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (120 mL of silica gel, P/Et$_2$O gradient 9:1 to 1:1) to provide diene **145** (1.68 g, 85% over two steps) as a colorless oil.



R_f = 0.56 (P/Et$_2$O 4:1).
[α]$_D^{20}$ = +15.0 (c = 1.38 in CHCl$_3$).
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.28-7.20 (m, 2H; C*H*$_{Ar}$), 6.92-6.83 (m, 2H; C*H*$_{Ar}$), 5.60 (dt, $^{3}J_{H,H}$ = 17.1, 10.1 Hz, 1H; CH$_2$=C*H*CHCHO$_2$), 5.55 (dt, $^{3}J_{H,H}$ = 14.3, 9.9 Hz, 1H; CH$_2$=C*H*CHCH$_2$), 5.16 (dd, $^{3}J_{H,H}$ = 10.3 Hz, $^{2}J_{H,H}$ = 2.0 Hz, 1H; CH*H*=CHCHCHO$_2$), 5.12-4.97 (m, 3H; C*H*$_2$=CHCHCH$_2$, C*H*H=CHCHCHO$_2$), 4.40 (d, $^{4}J_{H,H}$ = 1.9 Hz, 2H; C*H*$_2$Ar), 4.33 (d, $^{3}J_{H,H}$ = 8.3 Hz, 1H; C*H*O$_2$), 3.80 (s, 3H; C*H*$_3$OAr), 3.52-3.35 (m, 2H; C*H*$_2$OPMB), 3.32 (s, 3H; C*H*$_3$OCH), 3.26 (s,

3H; C*H*$_3$OCH), 2.53 (tdd, $^3J_{H,H}$ = 9.5, 5.5, 3.4 Hz 1H; C*H*CH$_2$), 2.39 (ddd, $^3J_{H,H}$ = 9.7, 8.4, 3.4 Hz, 1H, C*H*CHO$_2$), 1.71-1.49 (m, 2H; C*H*$_2$CH$_2$O).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.2 (*C*$_{Ar}$O), 138.5 (CH$_2$=*C*HCHCH$_2$), 134.1 (CH$_2$=*C*HCHCHO$_2$), 130.8 (*C*$_{Ar}$CH$_2$), 129.4 (2C; *C*H$_{Ar}$), 118.4 (*C*H$_2$=CHCHCHO$_2$), 117.2 (*C*H$_2$=CHCHCH$_2$), 113.8 (2C; *C*H$_{Ar}$), 104.2 (*C*HO$_2$), 72.7 (*C*H$_2$Ar), 68.1 (*C*H$_2$OPMB), 55.4 (*C*H$_3$OAr), 53.3 (*C*H$_3$OCH), 52.3 (*C*H$_3$OCH), 50.6 (*C*HCHO$_2$), 40.7 (C*H*CH$_2$), 33.0 (C*H*$_2$CH$_2$O).

IR (film): *v* = 2933, 2834, 1613, 1587, 1512, 1465, 1362, 1302, 1246, 1173, 1097, 1036, 994, 969, 914, 819, 845, 757 cm^{-1}.

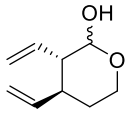
MS (+ESI) m/z (%): 343 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for C$_{19}$H$_{28}$O$_4$+Na$^+$: 343.1880 [*M*+Na]$^+$, found: 343.1885.

(3*S*,4*S*)-3,4-Divinyltetrahydro-2*H*-pyran-2-ol 147b

Diene **145** (539 mg, 1.68 mmol) was dissolved in acetic acid (10 mL), water (5 mL) was added and the mixture was stirred at room temperature until complete conversion was indicated by TLC after 3 days. The mixture was diluted with Et$_2$O (100 mL) and poured into satd. NaHCO$_3$ solution (250 mL). The mixture was extracted with Et$_2$O (5×75 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$ and carefully concentrated under reduced pressure at a bath temperature below 30 °C. The residue was purified by column chromatography (25 mL of silica gel, P/Et$_2$O 9:1) to afford lactol **147b** (192 mg, 74%) as inseparable 1.5:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil. The compound solidifies when stored at 2-8 °C.

Note: The TLC spots of the two diastereomers of **147b** are the terminal points of a broad spot, which is observed due to an equilibration on silica gel.



Major less polar diastereomer:

R_f = 0.76 (P/Et$_2$O 1:1).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.85-5.48 (m, 2H; C*H*=CH$_2$), 5.26-4.90 (m, 5H, C*H*OH, CH=C*H*$_2$), 4.05 (dt, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 3.2 Hz, 1H; CH*H*O), 3.66 (ddd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 5.0, 2.3 Hz, 1H; C*H*HO), 2.55 (tdd, $^3J_{H,H}$ = 11.5, 7.4, 4.0 Hz, 1H; C*H*CH$_2$), 2.35 (dd, $^3J_{H,H}$ = 3.4 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H; O*H*), 2.20-2.09 (m, 1H; C*H*CHOH), 1.71-1.48 (m, 2H, C*H*$_2$CH$_2$O).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.1 (CH$_2$=*C*HCHCH$_2$), 136.4 (CH$_2$=*C*HCHCH), 117.4 (*C*H$_2$=CHCHCHOH), 114.7 (*C*H$_2$=CHCHCH$_2$), 94.3 (*C*HOH), 65.3 (*C*H$_2$O), 50.7 (*C*HCHO$_2$), 37.5 (*C*HCH$_2$), 31.0 (*C*H$_2$CH$_2$O).

Minor more polar diastereomer:

R_f = 0.53 (P/Et$_2$O 1:1).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.85-5.48 (m, 2H; C*H*=CH$_2$), 5.26-4.90 (m, 4H, CH=C*H*$_2$), 4.51 (dd, $^3J_{H,H}$ = 8.1, 5.5 Hz, 1H; C*H*OH), 4.08 (dt, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 3.1 Hz, 1H; CH*H*O),

3.65-3.52 (m, 1H; C*H*HO), 2.78 (d, $^3J_{H,H}$ = 5.7 Hz, 1H; O*H*), 2.20-2.09 (m, 1H; C*H*CH_2), 1.87 (dt, $^3J_{H,H}$ = 10.9, 8.5 Hz, 1H; C*H*CHOH), 1.71-1.48 (m, 2H; CH_2CH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4 (*C*HCHCHOH), 140.3 (CH_2=*C*HCHCH_2), 118.8 (*C*H_2=CHCHCHOH), 115.0 (*C*H_2=CHCHCH_2), 98.1 (*C*HOH), 59.1 (*C*H_2O), 53.6 (*C*HCHO_2), 43.3 (*C*HCH_2), 31.1 (*C*H_2CH_2O).

IR (film): ν = 3390 (br), 3079, 2922, 2850, 1641, 1420, 1302, 1250, 1101, 1043, 989, 913, 877, 827, 733 cm^{-1}.

MS (+ESI) m/z (%): 177 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_9H_{14}O_2$+Na$^+$: 177.0886 [*M*+Na]$^+$, found: 177.0889.

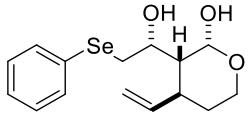
*6.3.2.4 Synthesis of lactol rac-***147b** *by strategy* **III**

(3*S,4*S**)-3-((2-Phenylselanyl-1-hydroxy)ethyl)-4-vinyltetrahydro-2*H*-pyran-2-ol 153**

Step 1: *n*-BuLi (720 µL, 1.6 M in hexanes, 1.15 mmol) was added added dropwise to a solution of *i*-Pr_2NH (170 µL, 1.20 mmol) in dry THF (3 mL) stirring at 0 °C in a flame-dried Schlenk flask. The reaction mixture was stirred at 0 °C for 15 min, cooled to –78 °C and solution of lactone *rac*-**48**[142] (132 mg, 1.05 mmol) in dry THF (1 mL) was added using a cannula. The reaction mixture was stirred at –78 °C for 1 h and aldehyde **149**[143] (199 mg, 1.00 mmol) in dry THF (1 mL) was added using a cannula. The reaction mixture was stirred at –78 °C for 30 min after which a complete conversion was indicated by TLC. The mixture was diluted with Et_2O to ca 10 mL, poured into satd. NH_4Cl solution (10 mL), diluted with water (2 mL), the layers separated and the aqueous was extracted with Et_2O (3×15 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure and dried in vacuum to give crude aldol adduct **150**, which was used in the next step without further purification.

Step 2: Crude aldol **150** was dissolved in dry toluene (10 mL) in a flame dried Schlenk flask. The solution was cooled to –78 °C and DIBAL-H (2.5 mL, 1.0 M in toluene, 2.50 mmol) was added dropwise. An evolution of hydrogen gas was observed during the addition of the first 1 mL. The reaction mixture was stirred for 10 min after which complete conversion was indicated by TLC. A few drops of MeOH were added and when evolution of hydrogen gas ceased, a few drops of water were added. The cooling bath was removed, the mixture was diluted with Et_2O to ca 30 mL, warmed to room temperature with vigorous stirring over 40 min. Celite® (2 spatulas) and $MgSO_4$ (2 spatulas) were successively added, the reaction mixture was stirred for 10 min and the resulting slurry was filtered through a pad of Celite® and sand, which was washed thoroughly with Et_2O. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography (15 mL of silica gel, PE/Et_2O 1:1) to furnish lactol **153** (191 mg, 58% over two steps) as partially separable 9:1.6:1.4:1 mixture of diastereomers as a colorless oil.

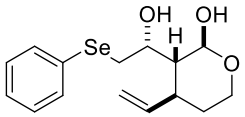
Less polar major diastereomers: R_f = 0.62 (P/EtOAc 1:1).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.44 (m, 2H; CH_{Ar}), 7.31-7.20 (m, 3H; CH_{Ar}), 5.51 (ddd, $^{3}J_{H,H}$ = 17.0 10.2, 8.6 Hz, 1H; C*H*=CH_2), 5.36 (d, $^{3}J_{H,H}$ = 3.1 Hz, 1H; C*H*O_2), 5.13 (dd, $^{3}J_{H,H}$ = 17.1 Hz, $^{2}J_{H,H}$ = 1.8 Hz, 1H; CH=CH*H*), 5.01 (dd, $^{3}J_{H,H}$ = 10.2 Hz, $^{2}J_{H,H}$ = 1.9 Hz, 1H; CH=CH*H*), 4.02 (td, $^{2}J_{H,H}$ = 11.0 Hz, $^{3}J_{H,H}$ = 11.0, 6.1 Hz, 1H; CH*H*O), 3.93-3.86 (m, 1H; C*H*OH), 3.62 (dt, $^{2}J_{H,H}$ = 11.0 Hz, $^{3}J_{H,H}$ = 2.7 Hz, 1H; C*H*HO), 3.17 (dd, $^{2}J_{H,H}$ = 12.3 Hz, $^{3}J_{H,H}$ = 8.2 Hz, 1H; CH*H*Se), 3.00 (dd, $^{2}J_{H,H}$ = 12.3 Hz, $^{3}J_{H,H}$ = 6.7 Hz, 1H; C*H*HSe), 2.80-2.70 (m, 1H; C*H*CH=CH), 1.79 (dt, $^{3}J_{H,H}$ = 11.6, 3.2 Hz, 1H; C*H*CHOH), 1.66-1.56 (m, 2H; CH_2CH_2O).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2 (*C*H=CH_2), 133.26 (2C, *C*H_{Ar}), 129.4 (*C*$_{Ar}$), 129.32 (2C, *C*H_{Ar}), 127.45 (*C*H_{Ar}), 116.5 (CH=*C*H_2), 91.9 (*C*HO_2), 69.3 (*C*HOH), 59.0 (*C*H_2O), 45.7 (*C*HCHOH), 36.0 (*C*HCH=CH_2), 33.2 (*C*H_2Se), 32.0 (*C*H_2CH_2O).

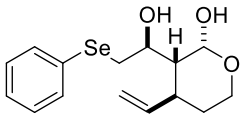


^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.44 (m, 2H; CH_{Ar}), 7.31-7.20 (m, 3H; CH_{Ar}), 5.51 (ddd, $^{3}J_{H,H}$ = 17.0 10.2, 8.6 Hz, 1H; C*H*=CH_2), 5.13 (dd, $^{3}J_{H,H}$ = 17.1 Hz, $^{2}J_{H,H}$ = 1.8 Hz, 1H; CH=CH*H*), 5.01 (dd, $^{3}J_{H,H}$ = 10.2 Hz, $^{2}J_{H,H}$ = 1.9 Hz, 1H; CH=CH*H*), 4.73 (d, $^{3}J_{H,H}$ = 9.6 Hz, 1H; C*H*O_2), 4.00-3.92 (m, 1H; CH*H*O), 3.93-3.86 (m, 1H; C*H*OH), 3.59-3.49 (dt, $^{2}J_{H,H}$ = 13.1 Hz, $^{3}J_{H,H}$ = 2.8 Hz, 1H; C*H*HO), 3.32-3.18 (m, 1H; CH*H*Se), 3.08-3.02 (m, 1H; C*H*HSe), 2.80-2.70 (m, 1H; C*H*CH=CH), 1.80-1.66 (m, 1H; C*H*CHOH), 1.72-1.62 (m, 2H; CH_2CH_2O).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6 (*C*H=CH_2), 133.31 (2C, *C*H_{Ar}), 129.4 (*C*$_{Ar}$), 129.30 (2C, *C*H_{Ar}), 127.50 (*C*H_{Ar}), 113.2 (CH=*C*H_2), 96.3 (*C*HO_2), 69.3 (*C*HOH), 65.4 (*C*H_2O), 42.4 (*C*HCHOH), 36.0 (*C*HCH=CH_2), 32.3 (*C*H_2CH_2O), 31.0 (*C*H_2Se).

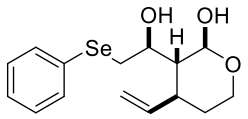
More polar minor diastereomers: R_f = 0.50 (P/Et_2O 1:1).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.44 (m, 2H; CH_{Ar}), 7.31-7.20 (m, 3H; CH_{Ar}), 5.85-5.71 (m, 1H; C*H*=CH_2), 5.32 (d, $^{3}J_{H,H}$ = 3.2 Hz, 1H; C*H*O_2), 5.07-5.03 (m, 1H; CH=CH*H*), 5.02-4.97 (m, 1H; CH=CH*H*), 4.00-3.92 (m, 1H; CH*H*O), 3.93-3.86 (m, 1H; C*H*OH), 3.59-3.49 (m, 1H; C*H*HO), 3.41-3.27 (m, 1H; CH*H*Se), 3.25-3.18 (m, 1H; C*H*HSe), 2.80-2.70 (m, 1H; C*H*CH=CH), 1.80-1.66 (m, 1H; C*H*CHOH), 1.72-1.62 (m, 2H; CH_2CH_2O).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7 (*C*H=CH_2), 133.09 (2C, *C*H_{Ar}), 129.4 (*C*$_{Ar}$), 129.23 (2C, *C*H_{Ar}), 127.3 (*C*H_{Ar}), 116.3 (CH=*C*H_2), 91.5 (*C*HO_2), 69.3 (*C*HOH), 59.5 (*C*H_2O), 50.0 (*C*HCHOH), 36.9 (*C*H_2Se), 36.0 (*C*HCH=CH_2), 31.4 (*C*H_2CH_2O).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.44 (m, 2H; CH_{Ar}), 7.31-7.20 (m, 3H; CH_{Ar}), 5.51 (ddd, $^{3}J_{H,H}$ = 17.0 10.2, 8.6 Hz, 1H; C*H*=CH_2), 5.13 (dd, $^{3}J_{H,H}$ = 17.1 Hz, $^{2}J_{H,H}$ = 1.8 Hz, 1H; CH=CH*H*), 5.01 (dd, $^{3}J_{H,H}$ = 10.2 Hz, $^{2}J_{H,H}$ = 1.9 Hz, 1H; CH=CH*H*), 4.90 (d, $^{3}J_{H,H}$ = 8.1 Hz, 1H; C*H*O_2), 4.00-3.92 (m, 1H; CH*H*O), 3.93-3.86 (m, 1H; C*H*OH), 3.54-3.46 m, 1H; C*H*HO), 3.25-3.18 (m, 1H; CH*H*Se), 3.08-3.02 (m, 1H; C*H*HSe), 2.80-2.70 (m, 1H; C*H*CH=CH), 1.80-1.66 (m, 1H; C*H*CHOH), 1.72-1.62 (m, 2H; CH_2CH_2O).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7 (*C*H=CH_2), 133.31 (2C, *C*H_{Ar}), 129.4 (*C*$_{Ar}$), 129.34 (2C, *C*H_{Ar}), 127.4 (*C*H_{Ar}), 116.3 (CH=*C*H_2), 96.1 (*C*HO_2), 69.3 (*C*HOH), 64.6 (*C*H_2O), 38.2 (*C*HCHOH), 36.0 (*C*HCH=CH_2), 33.5 (*C*H_2Se), 31.0 (CH_2CH_2O).

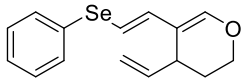
IR (film): *v* = 3332 (br), 3072, 2935, 1719, 1640, 1478, 1477, 1437, 1420, 1359, 1300, 1260, 1190, 1113, 1085, 1073, 1044, 1023, 983, 952, 918, 877, 830, 804, 736, 691, 670, 636 cm^{-1}.

MS (+ESI) m/z (%): 369 (2)/367 (9)/365 (6)/363 (2) [*M*+K]$^+$, 353 (17)/351 (100)/349 (70)/347 (31)/345 (6)[*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{15}H_{20}O_3{}^{80}Se$+Na^+: 351.0470 [*M*+Na]$^+$, found: 351.0468.

(*E*)-5-(2-(phenylselanyl)vinyl)-4-vinyl-3,4-dihydro-2*H*-pyran 152b

Et_3N (170 µL, 1.22 mmol) was added dropwise into a solution of **153** (76 mg, 0.232 mmol) in dry DCM (1.8 mL) in a flame-dried finger Schlenk flask. The solution was cooled to 0 °C and a solution of MsCl (44 µL, 0.56 mmol) in dry DCM (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 4 h. The mixture was diluted with DCM up to ca 5 mL, NaOH (0.5 M, 5 mL) was added and the biphasic mixture was stirred for 10 min. The layers were separated and the aqueous was extracted with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to furnish crude enol ether **152b** (73 mg, quant.) as a yellow oil, quickly turning brown during storage.



R_f = 0.90 (PE/Et_2O 1:1).

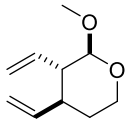
^{1}H NMR (401 MHz, $CDCl_3$): δ = 7.41-7.35 (m, 2H; CH_{Ar}), 7.30-7.14 (m, 3H; CH_{Ar}), 6.66 (s, 1H; C*H*O), 6.49 (dd, $^{3}J_{H,H}$ = 15.1 Hz, 1H; C*H*=CHSe), 6.28 (d, $^{3}J_{H,H}$ = 15.4 Hz, 1H; CH=C*H*Se), 5.85 (ddd, $^{3}J_{H,H}$ = 17.2, 10.2, 6.1 Hz, 1H; C*H*=CH_2), 5.20 (dt, $^{3}J_{H,H}$ = 10.3 Hz, $^{2}J_{H,H}$ = 1.4 Hz, $^{4}J_{H,H}$ = 1.4 Hz, 1H; CH=CH*H*), 5.11 (dt, $^{3}J_{H,H}$ = 17.2 Hz, $^{2}J_{H,H}$ = 1.6 Hz, $^{4}J_{H,H}$ = 1.6 Hz, 1H; CH=C*H*H), 4.06 (ddd, $^{4}J_{H,H}$ = 10.9 Hz, $^{3}J_{H,H}$ = 4.0, 2.9 Hz, 1H; CH*H*O), 3.96-3.86 (m, 1H; C*H*HO), 3.15 (tt, $^{3}J_{H,H}$ = 5.6 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 1H; C*H*CH_2), 2.04 (dddd, $^{2}J_{H,H}$ = 13.8 Hz, $^{3}J_{H,H}$ = 12.2, 5.9, 3.9 Hz, 1H; CH*H*CH_2O), 1.72 (dq, $^{2}J_{H,H}$ = 13.9 Hz, $^{3}J_{H,H}$ = 2.5 Hz, 1H; C*H*HCH_2O).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6 (*C*HO), 139.8 (*C*H=CH_2), 138.1 (*C*H=CHSe), 132.6 (C_{Ar}), 130.6 (2C; *C*H_{Ar}), 129.2 (2C; *C*H_{Ar}), 126.4 (*C*H_{Ar}), 117.1 (CH=*C*H_2), 114.3 (*C*=CHO), 109.6 (CH=*C*HSe), 62.5 (*C*H_2O), 33.5 (*C*HCH_2), 27.3 (*C*H_2CH_2O).

(3*S,4*S**)-2-Methoxy-3,4-divinyltetrahydro-2*H*-pyran** ***rac*-147a**

Step 1: Lactol **153** (39 mg, 0.12 mmol) was dissolved in MeOH (1.2 mL) and TsOH·H_2O (1 mg, 6 μmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 6 h after which a complete conversion was indicated by TLC. The mixture was poured into satd. $NaHCO_3$ solution (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure.

Step 2:[135] Crude acetal was dissolved in dry DCM (1.5 mL) in a flame-dried Schlenk flask. The solution was cooled to 0 °C and Et_3N (71 μL, 0.51 mmol) was added, followed by dropwise addition of of MsCl (32 μL, 0.41 mmol). The reaction mixture was stirred at 0 °C for 30 min after which a complete conversion was indicated by TLC. The mixture was diluted with DCM to ca 5 mL, aqueous NaOH (0.5 M, ca 5 mL) was added and the biphasic mixture was warmed to room temperature with vigorous stirring. The layers were separated and the aqueous was extracted with DCM (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and carefully evaporated under reduced pressure. The residue was adsorbed on silica gel and purified by column chromatography (10 mL of silica gel, gradient PE/Et_2O 100:0 to 1:1) to give *rac*-**147a** (8 mg, 46% over two steps) as a single *trans*, *trans*-diastereomer as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.62 (P/Et_2O 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (ddd, $^3J_{H,H}$ = 17.0, 10.6, 7.4 Hz, 1H; CH_2=C*H*CHCH_2), 5.56 (ddd, $^3J_{H,H}$ = 17.2, 10.5, 8.6 Hz, 1H; CH_2=C*H*CHCHO_2), 5.15 (ddd, $^3J_{H,H}$ = 10.6 Hz, $^2J_{H,H}$ = 1.8 Hz, $^4J_{H,H}$ = 0.6 Hz, 1H; CH*H*=CHCHCHO_2), 5.08 (ddd, $^3J_{H,H}$ = 17.2 Hz, $^2J_{H,H}$ = 1.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; C*H*H=CHCHCHO_2), 5.00 (ddd, $^3J_{H,H}$ = 10.4 Hz, $^2J_{H,H}$ = 1.6 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; CH*H*=CHCHCH_2), 4.98 (ddd, $^3J_{H,H}$ = 10.4 Hz, $^2J_{H,H}$ = 1.8 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H; C*H*H=CHCHCH_2), 4.10 (d, $^3J_{H,H}$ = 8.1 Hz, 1H; C*H*O_2), 4.05 (ddd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 4.6, 2.1 Hz, 1H; CH*H*O), 3.53 (td, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 2.8 Hz, 1H; C*H*HO), 3.47 (s, 3H; C*H*$_3$), 2.18-2.08 (m, 1H; C*H*CH_2), 1.95 (dt, $^3J_{H,H}$ = 10.8, 8.3 Hz, 1H; C*H*CHO_2), 1.68-1.58 (m, 1H; CH*H*CH_2O), 1.58-1.47 (m, 1H; CH*H*CH_2O).

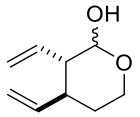
^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.6 (CH_2=*C*HCHCH_2), 136.4 (CH_2=*C*HCHCHO_2), 118.0 (*C*H_2=CHCHCHO_2), 114.8 (*C*H_2=CHCHCH_2), 105.1 (*C*HO_2), 64.8 (*C*H_2O), 56.5 (*C*H_3), 51.1 (C*H*CHO_2), 43.3 (*C*HCH_2), 31.1 (*C*H_2CH_2O).

IR (film): ν = 3070, 2957, 2926, 2852, 1641, 1579, 1477, 1465, 1438, 1383, 1366, 1256, 1212, 1193, 1141, 1084, 1022, 993, 922, 740, 691 cm^{-1}.

MS (+ESI) m/z (%): 191 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{10}H_{16}O_2+Na^+$: 191.1043 $[M+Na]^+$, found: 191.1039.

(3*S,4*S**)-3,4-Divinyltetrahydro-2*H*-pyran-2-ol *rac*-147b**

Obtained in analogy to **147b** from *rac*-**147a** (8 mg, 48 µmol) to give *rac*-**147b** (6 mg, 82%) as inseparable 1.5:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



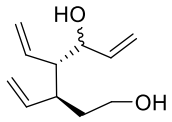
The analytical data were identical to **147b**.

6.3.3 Application of strategy II to the total synthesis of 4-A$_4$-NeuroP

6.3.3.1 Synthesis of ethers **148** *and* **154**

(3*S*,4*S*)-3,4-Divinylhept-6-ene-1,5-diol 148a

Lactol **147b** (100 mg, 0.65 mmol) was dissolved in dry THF (2 mL) under argon and vinylmagnesium bromide (2.6 mL, 1.0 M in THF, 2.6 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with Et_2O to 10 mL, water (5 mL) and satd. NH_4Cl solution (5 mL) were successively added, the layers were separated and the aqueous was extracted with Et_2O (3×10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (P/EtOAc gradient 9:1 to 7:3) to furnish diol **148a** (109 mg, 92%) as inseparable 1.1:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.25 (P/Et_2O 1:1).
Major diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04-5.43 (m, 3H; C*H*=CH_2), 5.36-4.99 (m, 6H; CH=C*H*$_2$), 4.08 (t, $^3J_{H,H}$ = 7.4 Hz, 1H; C*H*OH), 3.74-3.52 (m, 2H; C*H*$_2$OH), 2.72 (tt, $^3J_{H,H}$ = 9.6, 5.2 Hz, 1H; C*H*CH_2), 2.13 (ddd, $^3J_{H,H}$ = 9.6, 8.0, 4.0 Hz, 1H; C*H*CHOH), 1.92 (br s, 2H; O*H*), 1.71-1.46 (m, 2H; C*H*$_2$$CH_2$OH).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3 (*C*H=CH_2), 138.9 (*C*H=CH_2), 135.37 (CH_2*C*H=CH_2), 118.9 (CH=*C*H_2), 117.44 (CH=*C*H_2), 115.6 (CH=*C*H_2), 73.1 (*C*HOH), 61.0 (*C*H_2OH), 55.2 (*C*HCHOH), 40.3 (*C*HCH_2), 35.9 (*C*$H_2$$CH_2$OH).

Minor diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04-5.43 (m, 3H; C*H*=CH_2), 5.36-4.99 (m, 6H; CH=C*H*$_2$), 4.08 (dd, $^3J_{H,H}$ = 7.4 Hz, 1H; C*H*OH), 3.74-3.52 (m, 2H; C*H*$_2$OH), 2.46 (tt, $^3J_{H,H}$ = 9.4, 4.5 Hz, 1H; C*H*CH_2), 2.06 (ddd, $^3J_{H,H}$ = 9.9, 7.6, 3.7 Hz, 1H; C*H*CHOH), 1.75 (br s, 2H; O*H*), 1.71-1.46 (m, 2H; C*H*$_2$$CH_2$OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9 (*C*H=CH_2), 138.7 (*C*H=CH_2), 135.36 (CH_2*C*H=CH_2), 120.4 (CH=*C*H_2), 117.42 (CH=*C*H_2), 117.3 (CH=*C*H_2), 73.7 (*C*HOH), 60.8 (*C*H_2OH), 54.8 (*C*HCHOH), 41.2 (*C*HCH_2), 36.2 (*C*$H_2$$CH_2$OH).

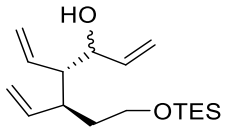
IR (film): *v* = 3324 (br), 3076, 2924, 2840, 1639, 1423, 1303, 1036, 992, 913, 767 cm^{-1}.

MS (+ESI) m/z (%): 205 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{11}H_{18}O_2$+Na^+: 205.1199 [*M*+Na]$^+$, found: 205.1198.

(4*S*,5*S*)-5-(2-((Triethylsilyl)oxy)ethyl)-4-vinylhepta-1,6-dien-3-ol 148b

Diol **148a** (183 mg, 1.00 mmol) and imidazole (171 mg, 2.51 mmol) were dissolved in dry DCM (10 mL). The solution was cooled to 0 °C and TESCl (185 µL, 1.10 mmol) was added dropwise. The reaction mixture was warmed to ca 20 °C over 90 min. Satd. NH_4Cl solution (10 mL) was added, the layers were separated and the aquoues was extracted with DCM (3×10 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient P/Et_2O 95:5 to 3:2, then 100% Et_2O) to obtain diprotected diol **148c** (61 mg, 15%, *vide infra*), **148b** (213 mg, 72%) as partially separable 1.2:1 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy as a colorless oil, and starting material **148a** (19 mg, 10%).



Major less polar diastereomer: R_f = 0.32 (P/Et_2O 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03-5.40 (m, 3H; C*H*=CH_2), 5.36-4.94 (m, 6H; CH=C*H*$_2$), 4.10 (t, $^3J_{H,H}$ = 8.0 Hz, 1H; C*H*OH), 3.68-3.42 (m, 2H; C*H*$_2$OTES), 2.45 (tt, $^3J_{H,H}$ = 9.2, 4.4 Hz, 1H; C*H*CH_2), 2.07 (ddd, $^3J_{H,H}$ = 10.1, 7.9, 4.7 Hz, 1H; C*H*CHOH), 1.74 (br s, 1H, O*H*), 1.67-1.47 (m, 2H; C*H*$_2$$CH_2$OTES), 0.94 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$), 0.57 (q, $^3J_{H,H}$ = 7.8 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5 (*C*H=CH_2), 138.7 (*C*H=CH_2), 135.5 (CH_2*C*H=CH_2), 120.3 (CH=*C*H_2), 117.2 (CH=*C*H_2), 117.1 (CH=*C*H_2), 73.8 (*C*HOH), 60.5 (*C*H_2OTES), 55.2 (*C*HCHOH), 40.8 (*C*HCH_2), 36.4 (*C*$H_2$$CH_2$OH), 6.9 (3C; *C*$H_3$), 4.5 (3C; *C*$H_2$Si).

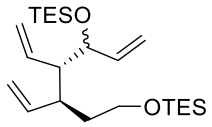
Minor more polar diastereomer: R_f = 0.20 (P/Et_2O 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03-5.40 (m, 3H; C*H*=CH_2), 5.36-4.94 (m, 6H; CH=C*H*$_2$), 4.04 (t, $^3J_{H,H}$ = 7.8 Hz, 1H; C*H*OH), 4.08-3.98 (m, 1H; C*H*OH), 3.68-3.42 (m, 2H; C*H*$_2$OTES), 2.64 (tt, $^3J_{H,H}$ = 9.5, 4.6 Hz, 1H; C*H*CH_2), 2.13 (ddd, $^3J_{H,H}$ = 10.1, 7.9, 4.7 Hz, 1H; C*H*CHOH), 1.87 (s, 1H; O*H*), 1.67-1.47 (m, 2H; C*H*$_2$$CH_2$OTES), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$), 0.58 (q, $^3J_{H,H}$ = 8.0 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8 (*C*H=CH_2), 139.0 (*C*H=CH_2), 135.7 (CH_2CHCH=CH_2), 118.7 (CH=*C*H_2), 117.0 (CH=*C*H_2), 115.4, (CH=*C*H_2), 73.2 (*C*HOH), 60.9 (*C*H_2OTES), 54.9 (*C*HCHOH), 40.2 (*C*HCH_2), 36.0 (*C*H_2CH_2OH), 6.9 (3C; *C*H_3), 4.5 (3C; *C*H_2Si).
IR (film): ν = 2959, 1568, 1437, 1405, 1361, 1319, 1251, 1189, 1150, 1122, 1067, 1034, 992, 843, 752 cm^{-1}.
MS (+ESI) m/z (%): 319 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{17}H_{32}O_2Si+Na^+$: 319.2064 $[M+Na]^+$, found: 319.2059.

(3*S*,4*S*)-3-(1-((Triethylsilyl)oxy)allyl)-4-(2-((triethylsilyl)oxy)ethyl)hexa-1,5-diene 148c

Diol **148a** (300 mg, 1.65 mmol) was dissolved in dry DCM (16 mL). The solution was cooled to 0 °C, imidazole (560 mg, 8.23 mmol) and TESCl (830 µL, 4.95 mmol) were successively added. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with DCM (20 mL), satd. NH_4Cl solution (20 mL) was added, the layers were separated and the aqueous was extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (P/Et_2O 99:1) to obtain **148c** (601 mg, 89%) as inseparable 1.1:1 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.92 (P/Et_2O 9:1).
Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04-5.29 (m, 3H; C*H*=CH_2), 5.18-4.85 (m, 6H; CH=C*H*$_2$), 4.04 (t, $^3J_{H,H}$ = 7.5 Hz, 1H; C*H*OTES), 3.71-3.39 (m, 2H; C*H*$_2$OTES), 2.36 (tt, $^3J_{H,H}$ = 9.4, 4.6 Hz, 1H; C*H*CH_2), 1.98 (ddd, $^3J_{H,H}$ = 9.9, 7.3, 4.5 Hz, 1H; C*H*CHOTES), 1.70-1.53 (m, 1H; CH*H*CH_2OTES), 1.53-1.38 (m, 1H; C*H*HCH_2OTES), 1.04-0.74 (m, 18H; C*H*$_3$), 0.67-0.39 (m, 12H; C*H*$_2$Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.7 (*C*H=CH_2), 139.4 (*C*H=CH_2), 137.0 (CH_2CHCH=CH_2), 117.7 (CH=*C*H_2), 116.3 (CH=*C*H_2), 115.7 (CH=*C*H_2), 75.4 (*C*HOTES), 60.9 (*C*H_2OTES), 55.4 (*C*HCHOTES), 40.3 (*C*HCH_2), 36.4 (*C*H_2CH_2OTES), 7.03 (3C; *C*H_3), 6.95 (3C; *C*H_3), 5.2 (3C; *C*H_2Si), 4.5 (3C; *C*H_2Si).
Minor diastereomer:
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04-5.29 (m, 3H; C*H*=CH_2), 5.18-4.85 (m, 6H; CH=C*H*$_2$), 4.04 (t, $^3J_{H,H}$ = 8.0 Hz, 1H; C*H*OTES), 3.71-3.39 (m, 2H; C*H*$_2$OTES), 2.68 (tt, $^3J_{H,H}$ = 9.2, 4.3 Hz, 1H; C*H*CH_2), 2.05 (ddd, $^3J_{H,H}$ = 10.1, 8.4, 4.0 Hz, 1H; C*H*CHOTES), 1.70-1.53 (m, 1H; CH*H*CH_2OTES), 1.53-1.38 (m, 1H; C*H*HCH_2OTES), 1.04-0.74 (m, 18H; C*H*$_3$), 0.67-0.39 (m, 12H; C*H*$_2$Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0 (*C*H=CH_2), 139.1 (*C*H=CH_2), 136.2 (CH_2CHCH=CH_2), 117.8 (CH=*C*H_2), 116.6 (CH=*C*H_2), 115.5 (CH=*C*H_2), 75.2 (*C*HOTES), 61.2 (*C*H_2OTES), 55.8

(*C*HCHOTES), 39.5 (*C*HCH$_2$), 36.3 (*C*H$_2$CH$_2$OTES), 7.1 (3C; *C*H$_3$), 6.97 (3C; *C*H$_3$), 5.5 (3C; *C*H$_2$Si), 4.5 (3C; *C*H$_2$Si).

IR (film): ν = 3077, 2954, 2912, 2877, 1640, 1462, 1459, 1238, 1082, 1004, 992, 913, 798, 723, 669 cm^{-1}.

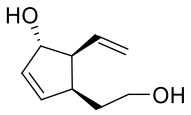
MS (+ESI) m/z (%): 433 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{23}H_{46}O_2Si+Na^+$: 433.2928 [*M*+Na]$^+$, found: 433.2923.

(4*S*,5*S*)-4-(2-Hydroxyethyl)-5-vinylcyclopent-2-en-1-ol 154a

Diol **148a** (312 mg, 1.71 mmol) was dissolved in dry DCM (6 mL) in a flame-dried two-necked flask under argon and the solution was purged with argon for 20 min. Catalyst **G-II** (26 mg, 0.034 mmol) was added and the reaction was stirred at room temperature for 6 h. A few frops of Et_3N were added, the reaction mixture was concentrated under reduced pressure, the crude residue was adsorbed on silica and purified by silica gel column chromatography (P/EtOAc gradient 6:4 to 1:1) to furnish **154a** (215 mg, 81%) as inseparable 1.1:1 mixture of *trans-/cis*-**154a** as determined by ^{1}H NMR spectroscopy as a yellow oil.

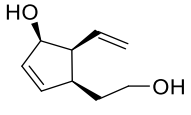
R_f = 0.15 (P/Et$_2$O 1:1).



trans-**154a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16-5.65 (m, 3H; C*H*=C*H*, C*H*=CH$_2$), 5.30-5.09 (m, 2H; CH=C*H*$_2$), 4.70-4.64 (m, 1H; C*H*OH), 3.69 (t, $^3J_{H,H}$ = 6.8 Hz, 2H; C*H*$_2$OH), 3.06-2.95 (m, 1H; C*H*CH$_2$), 2.70 (td, $^3J_{H,H}$ = 8.4, 5.3 Hz, 1H; C*H*CHOH), 1.86-1.55 (m, 2H; C*H*HCH$_2$OH, O*H*), 1.45 (br s, 1H; O*H*), 1.42 (ddt, $^2J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 9.4, 6.5 Hz, 1H; CH*H*CH$_2$OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.97 (*C*H=CHCHOH), 137.1 (*C*H=CH$_2$), 133.1 (CH=*C*HCHOH), 117.3 (CH=*C*H$_2$), 78.3 (*C*HOH), 61.8 (*C*H$_2$OH), 56.6 (*C*HCHOH), 44.3 (*C*HCH$_2$), 34.2 (*C*H$_2$CH$_2$OH).



cis-**154a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16-5.65 (m, 3H; C*H*=C*H*, C*H*=CH$_2$), 5.30-5.09 (m, 2H; CH=C*H*$_2$), 4.70-4-64 (m, 1H; C*H*OH), 3.65 (t, $^3J_{H,H}$ = 6.8 Hz, 2H; C*H*$_2$OH), 2.98-2.87 (m, 1H; C*H*CHOH), 2.85-2.74 (m, 1H; C*H*CH$_2$), 1.97 (br s, 1H; O*H*), 1.86-1.55 (m, 3H; C*H*$_2$CH$_2$OH, O*H*).

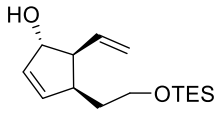
^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.00 (*C*H=CHCHOH), 135.2 (*C*H=CH$_2$), 133.2 (CH=*C*HCHOH), 119.3 (CH=*C*H$_2$), 81.4 (*C*HOH), 61.3 (*C*H$_2$OH), 51.9 (*C*HCHOH), 44.5 (*C*HCH$_2$), 34.5 (*C*H$_2$CH$_2$OH).

IR (film): ν = 3343 (br), 3074, 2929, 1639, 1421, 1351, 1184, 1116, 1043, 1002, 915, 976, 744 cm^{-1}.

MS (+ESI) m/z (%): 177 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_9H_{14}O_2+Na^+$: 177.0886 $[M+Na]^+$, found: 177.0884.

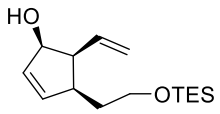
(4*S*,5*S*)-4-(2-((Triethylsilyl)oxy)ethyl)-5-vinylcyclopent-2-en-1-ol 154b

Synthesized in analogy to **154a** from monoprotected diol **148b** (182 mg, 0.61 mmol). Purification by silica gel column chromatography (P/Et_2O gradient 9:1 to 3:1) furnished **154b** (126 mg, 93%) as partially separable 1.1:1 mixture of of *trans-/cis*-**154b** as determined by ^{1}H NMR spectroscopy as a yellow oil.



trans-**154b**

R_f = 0.65 (P/Et_2O 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98 (ddd, $^3J_{H,H}$ = 5.8, 2.5 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H; C*H*=CHCHOH), 5.92-5.72 (m, 2H; CH=C*H*CHOH, C*H*=CH_2), 5.18 (ddd, $^3J_{H,H}$ = 17.1 Hz, $^2J_{H,H}$ = 2.0 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; CH=CH*H*), 5.13 (dd, $^3J_{H,H}$ = 10.1 Hz, $^2J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*H), 4.70-4.61 (m, 1H; C*H*OH), 3.61 (t, $^3J_{H,H}$ = 6.8 Hz, 2H; CH_2OTES), 3.05-2.88 (m, 1H; C*H*CH_2), 2.67 (tdd, $^3J_{H,H}$ = 8.5, 5.3 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; C*H*CHOH), 1.74 (dtd, $^2J_{H,H}$ = 12.9 Hz, $^3J_{H,H}$ = 7.1, 5.6 Hz, 1H; CH*H*CH_2OTES), 1.38 (dtd, $^2J_{H,H}$ = 13.1 Hz, $^3J_{H,H}$ = 8.2, 6.5 Hz, 1H; CH*H*CH_2OTES), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$), 0.58 (q, $^3J_{H,H}$ = 8.0 Hz, 6H; CH_2Si).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.4 (*C*H=CHCHOH), 137.2 (*C*H=CH_2), 132.7 (CH=*C*HCHOH), 117.1 (CH=*C*H_2), 81.5 (*C*HOH), 61.7 (*C*H_2OTES), 56.7 (*C*HCHOH), 44.4 (*C*HCH_2), 34.3 (*C*H_2CH$_2$OTES), 6.9 (3C; C*H*$_3$), 4.5 (3C; *C*H_2Si).



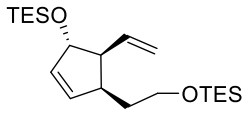
cis-**154b**

R_f = 0.55 (P/Et_2O 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96 (ddd, $^3J_{H,H}$ = 5.8, 2.2 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 5.92-5.80 (m, 2H; CH=C*H*CHOH, C*H*=CH_2), 5.27 (dd, $^3J_{H,H}$ = 10.9 Hz, $^2J_{H,H}$ = 2.1 Hz, 1H; CH=CH*H*), 5.20 (ddd, $^3J_{H,H}$ = 17.1 Hz, $^2J_{H,H}$ = 2.3 Hz, $^4J_{H,H}$ = 0.6 Hz, 1H; CH=C*H*H), 4.66 (t, $^3J_{H,H}$ = 7.2 Hz, 1H; C*H*OH), 3.65 (t, $^3J_{H,H}$ = 6.6 Hz, 2H, CH_2OTES), 2.94 (dt, $^3J_{H,H}$ = 10.1, 6.9 Hz, 1H, C*H*CHOH), 2.85-2.70 (m, 1H; C*H*CH_2), 1.82 (d, $^3J_{H,H}$ = 7.1 Hz, 1H; O*H*), 1.76-1.50 (m, 2H; CH_2CH$_2$OTES), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (*C*H=CHCHOH), 135.1 (*C*H=CH_2), 133.2 (CH=*C*HCHOH), 119.2 (CH=*C*H_2), 78.4 (*C*HOH), 61.3 (*C*H_2OTES), 52.2 (*C*HCHOH), 44.3 (*C*HCH_2), 34.8 (*C*H_2CH$_2$OH), 6.9 (3C; *C*H$_3$), 4.5 (3C; *C*H_2Si).
IR (film): ν = 3362 (br), 3073, 3954, 2937, 2911, 2876, 1458, 1415, 1387, 1238, 1093, 1004, 974, 913, 781, 742, 728, 670 cm^{-1}.

MS (+ESI) m/z (%): 291 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{15}H_{28}O_2Si+Na^+$: 291.1751 $[M+Na]^+$, found: 291.1750.
HRMS (+CI) m/z: calcd for $C_{15}H_{28}O_2Si+H^+$: 268.1937 $[M+H]^+$, found: 268.1938.

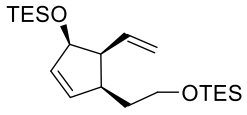
3-((Triethylsilyl)oxy)-5-(2-((triethylsilyl)oxy)ethyl)-4-vinylcyclopentene 154c

Synthesized in analogy to ether **148c** from diol **154a** (45 mg, 0.29 mmol). Purification by silica gel column chromatography (P/Et_2O 95:5) provided **154c** (92 mg, 82%) as inseparable 1.1:1 mixture of *trans-/cis*-**154c** as determined by ^1H NMR spectroscopy as a colorless oil.
R_f = 0.68 (P/Et_2O 95:5).



trans-**154c**

^1H NMR (300 MHz, $CDCl_3$): δ = 6.00-5.65 (m, 3H; C*H*=C*H*, C*H*=CH_2), 5.14 (ddd, $^3J_{H,H}$ = 11.8 Hz, $^2J_{H,H}$ = 2.2 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; CH=CH*H*), 5.11-5.07 (m, 1H; CH=C*H*H), 4.60 (ddd, $^3J_{H,H}$ = 6.3, 2.0 Hz, $^4J_{H,H}$ = 0.9 Hz; 1H, C*H*OTES), 3.60 (t, $^3J_{H,H}$ = 7.1 Hz, 2H; C*H*$_2$OTES), 2.94 (dddt, $^3J_{H,H}$ = 10.0, 8.0, 6.2 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; C*H*CH_2), 2.72-2.62 (m, 1H; C*H*CHOTES), 1.73 (dq, $^2J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 6.7 Hz, 1H; CH*H*CH_2OTES), 1.39 (dtd, $^2J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 7.0, 6.4 Hz, 1H; C*H*HCH_2OTES), 1.04-0.87 (m, 18H; C*H*$_3$), 0.66-0.44 (m, 12H; C*H*$_2$Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (*C*H=CHCHOTES), 137.7 (*C*H=CH_2), 133.0 (CH=*C*HCHOTES), 116.8 (CH=*C*H_2), 82.0 (*C*HOTES), 61.9 (*C*H_2OTES), 56.3 (*C*HCHOTES), 44.1 (*C*HCH_2), 34.3 (*C*$H_2$$CH_2$OTES), 6.93 (6C; *C*$H_3$), 5.03 (3C; *C*$H_2$Si), 4.53 (3C; *C*$H_2$Si).



cis-**154c**

^1H NMR (300 MHz, $CDCl_3$): δ = 6.00-5.65 (m, 3H; C*H*=C*H*, C*H*=CH_2), 5.08-5.04 (m, 1H; CH=CH*H*), 5.02 (ddd, $^3J_{H,H}$ = 11.8 Hz, $^2J_{H,H}$ = 2.4 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H; CH=C*H*H), 4.64 (ddd, $^3J_{H,H}$ = 6.3, 2.0 Hz, $^4J_{H,H}$ = 0.9 Hz; 1H, C*H*OTES), 3.62 (t, $^3J_{H,H}$ = 7.1 Hz, 2H; C*H*$_2$OTES), 2.79 (dt, $^3J_{H,H}$ = 10.1, 6.7 Hz, 1H; C*H*CHOTES), 2.68-2.59 (m, 1H; C*H*CH_2), 1.73 (dq, $^2J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 6.7 Hz, 1H; CH*H*CH_2OTES), 1.54 (ddt, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 8.7, 6.4 Hz, 1H; C*H*HCH_2OTES), 1.04-0.87 (m, 18H; C*H*$_3$), 0.66-0.44 (m, 12H; C*H*$_2$Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5 (*C*H=CHCHOTES), 136.9 (*C*H=CH_2), 133.3 (CH=*C*HCHOTES), 116.6 (CH=*C*H_2), 78.2 (*C*HOTES), 61.7 (*C*H_2OTES), 52.5 (*C*HCHOTES), 44.6 (*C*HCH_2), 35.3 (*C*$H_2$$CH_2$OTES), 6.95 (6C; *C*$H_3$), 4.96 (3C; *C*$H_2$Si), 4.50 (3C; *C*$H_2$Si).
IR (film): *v* = 2954, 2911, 2876, 1459, 1415, 1379, 1361, 1238, 1097, 1072, 1004, 973, 913, 880, 846, 781, 740, 727, 670 cm^{-1}.
MS (+ESI) m/z (%): 405 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{21}H_{42}O_2Si+Na^+$: 405.2615 $[M+Na]^+$, found: 405.2611.

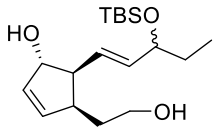
6.3.3.2 Cross-metathesis model studies

General procedure for CM model studies

Substrates **154a-c** or **148a** were dissolved in dry DCM (10 mL/mmol) in a flame-dried flask and the solution was purged with argon for 30 min. Compounds **155a-d** (3 equiv.) were added, followed by catalysts **HG-II**, **G-II** or **HG-M721** (10 mol.%; for combinations see at the individual compounds). The reaction mixtures were stirred at reflux for 4-16 h, quenched by a drop of Et_3N and concentrated under reduced pressure. The residue was adsorbed on silica and purified by silica gel column chromatography.

(4*S*,5*S*)-5-((*E*)-3-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-1-yl)-4-(2-hydroxyethyl)cyclopent-2-en-1-ol 156a

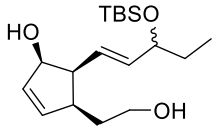
Obtained by stirring **154a** and **155b**[144] with **G-II** for 4 h in 22% yield and overnight with **HG-II** in 16% yield as inseparable 2:1 mixture of *trans*-/*cis*-**156a**, each as 1:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a yellow oil.
R_f = 0.43 (P/EtOAc 1:2).



trans-**156a**

Epimer 1:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05-5.99 (m, 1H; C*H*=CHCHOH), 5.87-5.80 (m, 1H; CH=C*H*CHOH), 5.70-5.44 (m, 2H; C*H*=C*H*CHOTBS), 4.65-4.61 (m, 1H; C*H*OH), 4.08 (q, $^3J_{H,H}$ = 5.8 Hz, 1H; C*H*OTBS), 3.77-3.60 (m, 2H; CH_2OH), 3.05-2.90 (m, 1H; C*H*CH_2CH_2), 2.74-2.65 (m, 1H; C*H*CHOH), 1.83-1.67 (m, 2H; CH*H*CH_2OH, O*H*), 1.66-1.40 (m, 4H; C*H*HCH_2OH, CH_2CH_3, O*H*), 0.95-0.81 (m, 12H; CH_3CSi, CH_3CH_2), 0.06 (s, 3H; CH_3Si), 0.05 (s, 3H; CH_3Si).
Epimer 2:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05-5.99 (m, 1H; C*H*=CHCHOH), 5.87-5.80 (m, 1H; CH=C*H*CHOH), 5.70-5.44 (m, 2H; C*H*=C*H*CHOTBS), 4.61-4.55 (m, 1H; C*H*OH), 4.03 (q, $^3J_{H,H}$ = 5.8 Hz, 1H; C*H*OTBS), 3.77-3.60 (m, 2H; CH_2OH), 3.05-2.90 (m, 1H; C*H*CH_2CH_2), 2.74-2.65 (m, 1H; C*H*CHOH), 1.83-1.67 (m, 2H; CH*H*CH_2OH, O*H*), 1.66-1.40 (m, 4H; C*H*HCH_2OH, CH_2CH_3, O*H*), 0.95-0.81 (m, 12H; CH_3CSi, CH_3CH_2), 0.05 (s, 3H; CH_3Si), 0.04 (s, 3H; CH_3Si).
^{13}C NMR resonances could not be unambiguously assigned to an individual isomer.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9/138.8 (*C*H=CHCHOH), 138.3/138.1 (*C*H=CHCHOTBS), 133.11/133.06 (CH=*C*HCHOH), 128.1/128.0 (CH=*C*HCHOTBS), 82.0/81.9 (*C*HOH), 74.7/74.5 (*C*HOTBS), 62.0/61.9 (*C*H_2OH), 55.1 (2×*C*HCHOH), 44.5/44.4 (*C*HCH_2CH_2), 34.3/34.2

(*C*$H_2$$CH_2$OH), 31.4/30.5 (*C*$H_2$$CH_3$), 26.0 (2×3C, *C*$H_3$CSi), 18.4 (2×*C*Si), 9.9/9.8 (*C*$H_3$$CH_2$), –4.54/–4.58 (2C; *C*$H_3$Si).



cis-**156a**

Epimer 1:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97-5.87 (m, 2H; C*H*=C*H*CHOH), 5.70-5.44 (m, 2H; C*H*=C*H*CHOTBS), 4.82.-4.70 (m, 1H; C*H*OH), 4.43-4.37 (m, 1H; C*H*OTBS), 3.77- 3.60 (m, 2H; C*H*$_2$OH), 3.26-3.10 (m, 1H; C*H*CHOH), 2.86-2.74 (m, 1H; C*H*CH_2CH_2), 1.83-1.67 (m, 2H; CH*H*CH_2OH, O*H*), 1.66-1.40 (m, 4H; C*H*HCH_2OH, C*H*$_2$$CH_3$, O*H*), 0.95-0.81 (m, 12H; C*H*$_3$CSi, C*H*$_3$$CH_2$), 0.07 (s, 3H; C*H*$_3$Si), 0.06 (s, 3H; C*H*$_3$Si).

Epimer 2:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05-5.99 (m, 1H; C*H*=CHCHOH), 5.87-5.80 (m, 1H; CH=C*H*CHOH), 5.70-5.44 (m, 2H; C*H*=C*H*CHOTBS), 4.71-4.65 (m, 1H; C*H*OH), 4.37-4.33 (m, 1H; C*H*OTBS), 3.77-3.60 (m, 2H; C*H*$_2$OH), 3.26-3.10 (m, 1H; C*H*CHOH), 2.86-2.74 (m, 1H; C*H*CH_2CH_2), 1.83-1.67 (m, 2H; CH*H*CH_2OH, O*H*), 1.66-1.40 (m, 4H; C*H*HCH_2OH, C*H*$_2$$CH_3$, O*H*), 0.95-0.81 (m, 12H; C*H*$_3$CSi, C*H*$_3$$CH_2$), 0.05 (s, 3H; C*H*$_3$Si), 0.04 (s, 3H; C*H*$_3$Si).

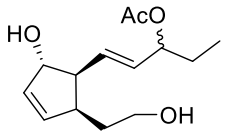
The ^{13}C NMR resonances of the two minor diastereomers were not detectable.

MS (+ESI) m/z (%): 349 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{18}H_{34}O_3Si$+Na^+: 349.2169 [*M*+Na]$^+$, found: 349.2169.

(4*S*,5*S*)-5-((*E*)-3-(Acetoxy)pent-1-en-1-yl)-4-(2-hydroxyethyl)cyclopent-2-en-1-ol 156b

Obtained by stirring **154a** and **155c**[145] with **G-II** for 6 h 8% yield and with **HG-II** overnight in 20% yield as inseparable 1.1:1 mixture of diastereomers as a colorless oil.



R_f = 0.18 (P/EtOAc 1:2).

Major epimer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (ddd, $^3J_{H,H}$ = 5.0, 2.5 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 5.85-5.78 (m, 1H; CH=C*H*CHOH), 5.74-5.61 (m, 1H; C*H*=CHCHOAc), 5.59-5.34 (m, 1H; CH=C*H*CHOAc), 5.13 (q, $^3J_{H,H}$ = 6.8 Hz, 1H; C*H*OAc), 4.60 (td, $^3J_{H,H}$ = 3.0, $^4J_{H,H}$ = 1.6 Hz, 1H; C*H*OH), 3.62 (t, $^3J_{H,H}$ = 6.9 Hz, 2H; C*H*$_2$OH), 3.03-2.90 (m, 1H; C*H*CH_2CH_2), 2.75-2.66 (m, 1H; C*H*CHOH), 2.05 (s, 3H; C*H*$_3$C=O), 1.84-1.52 (m, 6H; C*H*$_2$$CH_2$OH, C*H*$_2$$CH_3$, O*H*), 0.91 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$$CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (*C*=O), 137.9 (*C*H=CHCHOH), 132.9 (CH=*C*HCHOH), 132.6 (*C*H=CHCHOAc), 130.66 (CH=*C*HCHOAc), 81.4 (*C*HOH), 76.5 (*C*HOAc), 61.61

(*C*H_2OH), 54.7 (C*H*CHOH), 44.2 (*C*HCH$_2$CH$_2$), 34.0 (*C*H$_2$CH$_2$OH), 27.5 (*C*H$_2$CH$_3$), 21.4 (*C*H$_3$C=O), 9.6 (*C*H$_3$CH$_2$).

Minor epimer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.96 (ddd, $^3J_{H,H}$ = 5.0, 2.5 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 5.85-5.78 (m, 1H; CH=C*H*CHOH), 5.74-5.61 (m, 1H; C*H*=CHCHOAc), 5.59-5.34 (m, 1H; CH=C*H*CHOAc), 5.10 (q, $^3J_{H,H}$ = 6.8 Hz, 1H; C*H*OAc), 4.72-4.62 (m, 1H; C*H*OH), 3.60 (t, $^3J_{H,H}$ = 7.0 Hz, 2H; C*H*$_2$OH), 3.03-2.90 (m, 1H; C*H*CH$_2$CH$_2$), 2.75-2.66 (m, 1H; C*H*CHOH), 2.05 (s, 3H; C*H*$_3$C=O), 1.84-1.52 (m, 6H; C*H*$_2$CH$_2$OH, C*H*$_2$CH$_3$, O*H*), 0.90 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.9 (*C*=O), 138.4 (*C*H=CHCHOH), 132.8 (CH=*C*HCHOH), 131.9 (*C*H=CHCHOAc), 130.73 (CH=*C*HCHOAc), 81.8 (*C*HOH), 76.1 (*C*HOAc), 61.55 (*C*H$_2$OH), 54.6 (C*H*CHOH), 44.1 (*C*HCH$_2$CH$_2$), 33.8 (*C*H$_2$CH$_2$OH), 27.4 (*C*H$_2$CH$_3$), 21.4 (*C*H$_3$C=O), 9.6 (*C*H$_3$CH$_2$).

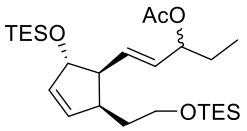
MS (+ESI) m/z (%): 277 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for C$_{14}$H$_{22}$O$_4$+Na$^+$: 277.1410 [*M*+Na]$^+$, found: 277.1406.

(*E*)-1-((1*S*,5*S*)-2-((Triethylsilyl)oxy)-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)pent-1-en-3-yl acetate 156f

Obtained by stirring of **154c** and **155c**[145] with **HG-II** overnight in 23% yield as inseparable 1.5:1 mixture of *trans*-/*cis*-**156f**, each as inseparable mixture of epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a yellow oil.

R_f = 0.50 (P/EtOAc 9:1).



trans-**156f**

Major epimer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.96 (td, $^3J_{H,H}$ = 5.8, $^4J_{H,H}$ = 2.6 Hz, 1H; C*H*=CHCHOTES), 5.90-5.81 (m, 1H; C*H*=CHCHOAc), 5.78 (dt, $^3J_{H,H}$ = 5.6, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H, CH=C*H*CHOTES), 5.52-5.40 (m, 1H; CH=C*H*CHOAc), 5.23 (dt, $^3J_{H,H}$ = 7.8, 6.3 Hz, 1H; C*H*OAc), 4.64 (dd, $^3J_{H,H}$ = 6.6, 2.4 Hz, 1H; C*H*OTES), 3.66-3.55 (m, 2H; C*H*$_2$OTES), 2.80 (dq, $^3J_{H,H}$ = 10.1, 6.8 Hz, 1H; C*H*CH$_2$CH$_2$), 2.75-2.66 (m, 1H; C*H*CHOTES), 2.06 (s, 3H; C*H*$_3$C=O), 1.81-1.58 (m, 3H; CH*H*CH$_2$OTES, C*H*$_2$CH$_3$), 1.52 (dddd, $^2J_{H,H}$ = 14.8 Hz, $^3J_{H,H}$ = 9.9, 7.1, 5.4 Hz, 1H; C*H*HCH$_2$OTES), 1.02-0.87 (m, 21H; C*H*$_3$CH$_2$), 0.65-0.53 (m, 12H; C*H*$_2$Si).

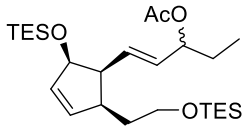
^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.5 (*C*=O), 137.60 (*C*H=CHCHOTES), 133.23 (CH=*C*HCHOTES), 132.37 (*C*H=CHCHOAc), 130.2 (CH=*C*HCHOAc), 78.2 (*C*HOTES), 76.1 (*C*HOAc), 61.59 (*C*H$_2$OTES), 51.05 (C*H*CHOTES), 44.7 (*C*HCH$_2$CH$_2$), 35.3 (*C*H$_2$CH$_2$OTES), 27.60 (*C*H$_2$CH$_3$), 21.46 (*C*H$_3$C=O), 9.72 (C*H*$_3$CH$_2$CH), 6.9 (6C; *C*H$_3$CH$_2$Si), 5.05 (3C; *C*H$_2$Si), 5.02 (3C; *C*H$_2$Si).

Minor epimer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (td, $^{3}J_{H,H}$ = 5.8 Hz, $^{4}J_{H,H}$ = 2.6 Hz, 1H; C*H*=CHCHOTES), 5.78 (dt, $^{3}J_{H,H}$ = 5.6, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H, CH=C*H*CHOTES), 5.74-5.68 (m, 1H; C*H*=CHCHOAc), 5.52-5.40 (m, 1H; CH=C*H*CHOAc), 5.20 (dt, $^{3}J_{H,H}$ = 7.8, 6.3 Hz, 1H; C*H*OAc), 4.64 (dd, $^{3}J_{H,H}$ = 5.8, 2.4 Hz, 1H; C*H*OTES), 3.66-3.55 (m, 2H; CH_2OTES), 2.80 (ddt, $^{3}J_{H,H}$ = 10.1, 6.8, 6.0 Hz, 1H; C*H*CH_2CH_2), 2.75-2.66 (m, 1H; C*H*CHOTES), 2.06 (s, 3H; CH_3C=O), 1.81-1.58 (m, 3H; CH*H*CH_2OTES, CH_2CH_3), 1.57-1.47 (m, 1H; C*H*HCH_2OTES), 1.02-0.87 (m, 21H; CH_3CH_2), 0.65-0.53 (m, 12H; CH_2Si).

Distinct ^{13}C NMR resonances:

^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.1 (*C*HOTES), 61.62 (*C*H_2OTES), 51.0 (C*H*CHOTES).



cis-**156f**

Epimer 1:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96-5.91 (m, 1H; C*H*=CHCHOTES), 5.90-5.81 (m, 1H; C*H*=CHCHOAc), 5.71-5.63 (m, 1H, CH=C*H*CHOTES), 5.52-5.40 (m, 1H; CH=C*H*CHOAc), 5.22 (dt, $^{3}J_{H,H}$ = 7.8, 6.3 Hz, 1H; C*H*OAc), 4.63-4.59 (m, 1H; C*H*OTES), 3.66-3.55 (m, 2H; CH_2OTES), 2.98 (dddd, $^{3}J_{H,H}$ = 9.9, 7.9, 5.7 Hz, $^{4}J_{H,H}$ = 2.1 Hz, 1H; C*H*CHOTES), 2.73-2.64 (m, 1H, C*H*CH_2CH_2), 2.06 (s, 3H; CH_3C=O), 1.81-1.58 (m, 3H; CH*H*CH_2OTES, CH_2CH_3), 1.57-1.47 (m, 1H; C*H*HCH_2OTES), 1.02-0.87, 1.02-0.87 (m, 21H; CH_3CH_2), 0.65-0.53 (m, 12H; CH_2Si).

Distinct ^{13}C NMR resonances:

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.2 (*C*H=CHCHOAc), 76.1 (*C*HOAc).

Epimer 2:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96-5.91 (m, 1H; C*H*=CHCHOTES), 5.74-5.68 (m, 1H; C*H*=CHCHOAc), 5.71-5.63 (m, 1H, CH=C*H*CHOTES), 5.52-5.40 (m, 1H; CH=C*H*CHOAc), 5.25-5.14 (m, 1H; C*H*OAc), 4.63-4.59 (m, 1H; C*H*OTES), 3.66-3.55 (m, 2H; CH_2OTES), 2.98 (dddt, $^{3}J_{H,H}$ = 9.9, 7.8, 5.7 Hz, $^{4}J_{H,H}$ = 2.1 Hz, 1H; C*H*CHOTES), 2.73-2.64 (m, 1H, C*H*CH_2CH_2), 2.06 (s, 3H; CH_3C=O), 1.81-1.58 (m, 3H; CH*H*CH_2OTES, CH_2CH_3), 1.57-1.47 (m, 1H; C*H*HCH_2OTES), 1.02-0.87 (m, 21H; CH_3CH_2), 0.65-0.53 (m, 12H; CH_2Si).

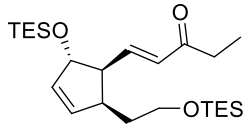
The following ^{13}C NMR resonances of the minor diastereomers could not be unambiguously assigned to an individual isomer.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (*C*=O), 137.64/137.5/137.4 (*C*H=CHCHOTES), 133.6/133.5/133.3 (CH=*C*HCHOTES), 133.18/133.0 (*C*H=CHCHOAc), 130.5/130.6/130.3 (CH=*C*HCHOAc), 82.10/82.06 (*C*HOTES), 76.0 (2C; *C*HOAc), 61.9/61.8 (*C*H_2OTES), 54.9/54.8 (C*H*CHOTES), 44.8/44.4/44.3 (*C*HCH_2CH_2), 35.5/34.6/34.3 (*C*H_2CH_2OTES), 27.86/27.70/27.66 (*C*H_2CH_3), 21.44/21.41/21.38 (*C*H_3C=O), 9.78/9.72/9.68 (*C*H_3CH_2CH), 7.01(6C)/6.99 (3C, *C*H_3CH_2Si), 5.05/5.02/4.96 (3C, *C*H_2Si).

MS (+ESI) m/z (%): 505 (100) [*M*+Na]$^+$.
HRMS (+ESI) m/z: calcd for $C_{26}H_{50}O_5Si_2$+Na^+: 505.3140 [*M*+Na]$^+$, found: 505.3133.

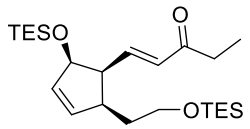
(*E*)-1-((1*S*,5*S*)-2-((Triethylsilyl)oxy)-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)pent-1-en-3-one 156g

Obtained by stirring **154c** and **155d** with **HG-II** overnight in 49% yield as inseparable 2:1 mixture of *trans-/cis*-**156g** as determined by ^{1}H NMR spectroscopy as a yellow oil.
R_f = 0.45 (P/Et_2O 9:1).



trans-**156g**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (dd, $^3J_{H,H}$ = 15.8, 10.2 Hz, 1H; C*H*=CHC=O), 6.17 (dd, $^3J_{H,H}$ = 15.8 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 5.97-5.90 (m, 1H; C*H*=CHCHOTES), 5.71 (dt, $^3J_{H,H}$ = 5.7, 1.8 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H; CH=C*H*CHOTES), 4.69-4.58 (m, 1H; C*H*OTES), 3.57 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; CH_2OTES), 3.06 (dddd, $^3J_{H,H}$ = 9.7, 7.7, 5.7, 2.1 Hz, 1H; C*H*CH_2CH_2), 2.84-2.77 (m, 1H; C*H*CHOTES), 2.55 (q, $^3J_{H,H}$ = 7.3 Hz, 2H; CH_2C=O), 1.72-1.52 (m, 1H; CH*H*CH_2OTES), 1.45-1.32 (m, 1H; C*H*HCH_2OTES), 1.09 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; CH_3CH_2), 0.97-0.76 (m, 18H; CH_3CH_2Si), 0.62-0.46 (m, 12H, CH_2Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8 (*C*=O), 145.9 (*C*H=CHC=O), 137.3 (*C*H=CHCHOTES), 133.0 (CH=*C*HCHOTES), 131.6 (CH=*C*HC=O), 81.5 (*C*HOTES), 61.6 (*C*H_2OTES), 55.1 (*C*HCHOTES), 44.7 (*C*HCH_2), 34.3 (*C*H_2CH_2O), 33.6 (*C*H_2CH_3), 8.3 (*C*H_3CH_2), 6.91 (3C; *C*H_3CH_2Si), 6.88 (3C; *C*H_3CH_2Si), 4.9 (3C; *C*H_2Si), 4.47 (3C; *C*H_2Si).



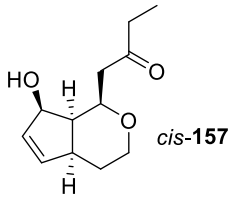
cis-**156g**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98- 6.84 (m, 1H; C*H*=CHC=O), 6.06 (d, $^3J_{H,H}$ = 16.2 Hz, 1H; CH=C*H*C=O), 5.97-5.90 (m, 1H; C*H*=CHCHOTES), 5.77 (dt, $^3J_{H,H}$ = 5.7, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOTES), 4.72 (ddd, $^3J_{H,H}$ = 6.3, 2.1 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*OTES), 3.59 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; CH_2OTES), 2.95 (dt, $^3J_{H,H}$ = 10.4, 6.8 Hz, 1H; C*H*CHOTES), 2.89-2.73 (m, 1H; C*H*CH_2CH_2), 2.58 (q, $^3J_{H,H}$ = 7.2 Hz, 2H; CH_2C=O), 1.63-1.46 (m, 1H; CH*H*CH_2OTES), 1.45-1.32 (m, 1H; C*H*HCH_2OTES), 1.08 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; CH_3CH_2), 0.97-0.76 (m, 18H; CH_3CH_2Si), 0.62-0.46 (m, 12H, CH_2Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.4 (*C*=O), 146.6 (*C*H=CHC=O), 137.0 (*C*H=CHCHOTES), 133.1 (CH=*C*HCHOTES), 132.6 (CH=*C*HC=O), 78.5 (*C*HOTES), 61.4 (*C*H_2OTES), 51.2 (*C*HCHOTES), 45.0 (*C*HCH_2), 35.3 (*C*H_2CH_2O), 32.2 (*C*H_2CH_3), 8.5 (*C*H_3CH_2), 6.93 (3C; *C*H_3CH_2Si), 6.91 (3C; *C*H_3CH_2Si), 5.0 (3C; *C*H_2Si), 4.50 (3C; *C*H_2Si).

MS (+ESI) m/z (%): 461 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{24}H_{46}O_3Si+Na^+$: 461.2878 $[M+Na]^+$, found: 461.2875.

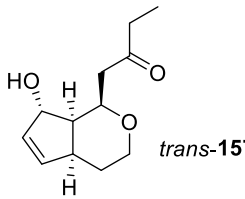
(1*R*,4aS,7aS)-1-(2-Oxobutyl)-1,3,4,4a,7,7a-hexahydrocyclopenta[c]pyran-7-ol 157

Obtained by stirring **154a** and **155d** in 54% yield with **HG-II** as partially separable 1:1 mixture of diastereomers as deteremined by ^{1}H NMR spectroscopy as a yellow oil.



cis-**157**

R_f = 0.40 (P/EtOAc 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.01 (ddd, $^3J_{H,H}$ = 5.8, 3.0, $^4J_{H,H}$ = 1.7 Hz, 1H; C*H*=CHCHOH), 5.75 (ddd, $^3J_{H,H}$ = 5.8, 1.6 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*CHOH), 4.90-4.73 (m, 1H; C*H*OH), 4.09 (td, $^3J_{H,H}$ = 6.8, 3.6 Hz, 1H; C*H*OCH$_2$), 3.87 (ddd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 4.9, 2.0 Hz, 1H; CH*H*O), 3.33 (ddd, $^3J_{H,H}$ = 12.6, 2.1 Hz, $^2J_{H,H}$ = 11.4 Hz, 1H; C*H*HO), 2.84 (d, $^3J_{H,H}$ = 6.9 Hz, 2H; C*H*$_2$C=O), 2.77-2.62 (m, 1H; C*H*CH$_2$CH$_2$), 2.50 (q, $^3J_{H,H}$ = 7.4 Hz, 2H; C*H*$_2$CH$_3$), 1.99-1.80 (m, 1H; C*H*CHOH), 1.74 (ddd, $^2J_{H,H}$ = 9.6 Hz, $^3J_{H,H}$ = 4.8, 2.1 Hz, 1H; CH*H*CH$_2$O), 1.71-1.55 (m, 2H, C*H*HCH$_2$O, O*H*), 1.04 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; C*H*$_3$).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.6 (*C*=O), 138.2 (*C*H=CHCHOH), 134.4 (CH=*C*HCHOH), 75.7 (*C*HOH), 72.8 (*C*HOCH$_2$), 66.7 (*C*H$_2$O), 50.5 (C*H*CHOH), 46.9 (CH*C*H$_2$C=O), 41.1 (*C*HCH$_2$CH$_2$), 37.0 (*C*H$_2$CH$_3$), 31.1 (*C*H$_2$CH$_2$), 7.7 (*C*H$_3$).



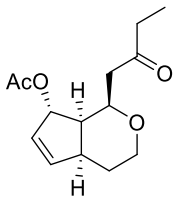
trans-**157**

R_f = 0.14 (P/EtOAc 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (dd, $^3J_{H,H}$ = 5.7, 1.7 Hz, 1H; C*H*=CHCHOH), 5.86 (dt, $^3J_{H,H}$ = 5.6, 2.2 Hz, $^4J_{H,H}$ = 2.2 Hz, 1H; CH=C*H*CHOH), 4.38-4.29 (m, 1H; C*H*OH), 3.77-3.65 (m, 1H; CH*H*O), 3.70-3.55 (m, 1H; C*H*OCH$_2$), 3.38 (ddd, $^2J_{H,H}$ = 11.2 Hz, $^3J_{H,H}$ = 9.4, 3.9 Hz, 1H; C*H*HO), 3.21-3.11 (m, 1H; C*H*CH$_2$CH$_2$), 2.73 (dd, $^2J_{H,H}$ = 15.6 Hz, $^3J_{H,H}$ = 8.9 Hz, 1H; CH*H*C=O), 2.59 (dd, $^2J_{H,H}$ = 15.6 Hz, $^3J_{H,H}$ = 3.2 Hz, 1H; C*H*HC=O), 2.49 (q, $^3J_{H,H}$ = 7.3 Hz, 2H; C*H*$_2$C=O), 2.01-1.77 (m, 1H; C*H*CHOH), 1.92-1.79 (m, 2H; CH*H*CH$_2$O, O*H*), 1.57 (dq, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 4.4 Hz, 1H; C*H*HCH$_2$O), 1.03 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; C*H*$_3$).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4 (*C*=O), 139.7 (*C*H=CHCHOH), 133.1 (CH=*C*HCHOH), 79.7 (*C*HOH), 71.9 (*C*HOCH$_2$), 63.7 (*C*H$_2$O), 50.1 (C*H*CHOH), 47.9 (CH*C*H$_2$C=O), 39.6 (*C*HCH$_2$CH$_2$), 37.2 (*C*H$_2$CH$_3$), 26.6 (*C*H$_2$CH$_2$), 7.6 (*C*H$_3$).
IR (film): *ν* = 3346 (br), 2930, 2856, 1709, 1635, 1460, 1410, 1376, 1360, 1258, 1195, 1112, 1088,

1036, 971, 835, 806, 777, 757, 694 cm^{-1}.
MS (+ESI) m/z (%): 233 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{12}H_{18}O_3+Na^+$: 233.1148 $[M+Na]^+$, found: 233.1144.

(1*R*,4a*S*,7*S*7a*R*)-7-Acetoxy-1-(2-Oxobutyl)-1,3,4,4a,7,7a-hexahydrocyclopenta[c]pyran 159

Compound *trans*-**157** (17 mg, 81 µmol) was dissolved in dry toluene (0.5 mL). $TsOH \cdot H_2O$ (8 mg, 32 µmol) and Ac_2O (31 µL, 320 µmol) were successively added at room temperature and the reaction mixture was stirred at room temperature for 4 h and at 70 °C for 1 h. The mixture was diluted with Et_2O (5 mL) and poured into satd. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (2 mL of silica gel, gradient P/EtOAc 9:1 to 4:1) to furnish acetate **159** (9 mg, 44%) as a colorless oil.

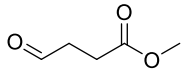


R_f = 0.60 (P/EtOAc 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.06 (dd, $^3J_{H,H}$ = 5.6, 1.8 Hz, 1H; C*H*=CHCHOAc), 5.84 (dt, $^3J_{H,H}$ = 5.6, 2.8 Hz, $^4J_{H,H}$ = 2.8 Hz, 1H; CH=C*H*CHOAc), 5.16-5.08 (m, 1H; C*H*OAc), 3.73 (dddd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 5.3, 2.8, 1.2 Hz, 1H; CH*H*O), 3.65-3.55 (m, 1H; C*H*OCH_2), 3.30 (td, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 11.6, 2.9 Hz, 1H; CH*H*O), 3.24-3.17 (m, 1H; C*H*CH_2CH_2), 2.88 (dd, $^2J_{H,H}$ = 16.4 Hz, $^3J_{H,H}$ = 2.5 Hz, 1H; CHCH*H*C=O), 2.70 (dd, $^2J_{H,H}$ = 16.4 Hz, $^3J_{H,H}$ = 9.2 Hz, 1H; CHC*H*HC=O), 2.48 (q, $^3J_{H,H}$ = 7.3 Hz, 2H; CH_2CH_3), 2.13-2.03 (m, 1H; C*H*CHOAc), 2.02 (s, 3H; CH_3C=O), 1.99-1.84 (m, 1H; CH*H*CH_2O), 1.72-1.59 (m, 1H; C*H*HCH_2O), 1.04 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; CH_2CH_3).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.0 (*C*=O), 171.3 (*C*O_2), 143.3 (*C*H=CHCHOAc), 128.9 (CH=*C*HCHOAc), 81.8 (*C*HOAc), 71.7 (*C*HO), 64.1 (*C*H_2O), 47.7 (CH*C*H_2C=O), 46.7 (*C*HCHOAc), 39.9 (*C*HCH_2CH_2), 37.2 (*C*H_2CH_3), 26.2 (*C*H_2CH_2O), 21.4 (*C*H_3C=O), 7.7 (*C*H_3CH_2).
IR (film): *v* = 2935, 2854, 1727, 1460, 1412, 1369, 1309, 1236, 1118, 1095, 1018, 996, 976, 940, 906, 875, 832, 776, 708, 605 cm^{-1}.
MS (+ESI) m/z (%): 275 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{14}H_{20}O_4+Na^+$: 275.1254 $[M+Na]^+$, found: 275.1251.

6.3.3.3 Synthesis of alpha-chain precursors **160**

Methyl 4-oxobutanoate 161a[149]

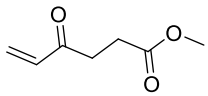
Step 1:[149] A 500 mL round-bottomed flask equipped with a condenser was charged with γ-butyrolactone (4.4 mL, 58.1 mmol). MeOH (230 mL) and Et_3N (48.5 mL, 349 mmol) were added and the reaction mixture was stirred at reflux overnight. The mixture was carefully concentrated under reduced pressure and the residual Et_3N was removed by azeotropic evaporation with P to obtain a crude mixture (6.56 g) which contained 18% butyrolactone and 82% of desired methyl 4-hydroxybutanoate.
Step 2 (conditions **b**): TPAP (600 mg, 1.71 mmol) was added to a heterogeneous mixture of crude 4-hydroxybutanoate (3.0 g, 20.3 mmol), 4Å molecular sieves (2.3 g) and NMO (4.76 g, 40.6 mmol) in dry DCM (200 mL) under nitrogen and the reaction mixture was stirred at room temperature for 2 h. The suspension was filtered through a pad of Celite®, the filtrate was concentrated under reduced pressure, the crude mixture was adsorbed on Celite® and purified by silica gel column chromatography (P/Et_2O gradient 85:15 to 75:25) to obtain **161a** (2.14 g, 70% over two steps) as a colorless oil.



R_f = 0.57 (P/Et_2O 1:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (t, $^3J_{H,H}$ = 0.7 Hz, 1H), 3.68 (s, 3H), 2.80 (dt, $^3J_{H,H}$ = 6.5, 0.7 Hz, 2H), 2.63 (t, $^3J_{H,H}$ = 6.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 172.8, 52.1, 38.7, 26.4.
The analytical data are in accordance with the published values.[149]

Methyl 4-oxohex-5-enoate 160a

Allylic alcohol **162a**[149] (56 mg, 0.39 mmol) in deuterated benzene was filtered through a column of MnO_2 (10 g) pre-washed with PE. The column was washed with PE using a gentle pressure of compressed air to ensure drop by drop elution. The filtrate was evaporated under reduced pressure to furnish enone **160a** (49 mg, 89%) as a yellow oil with a characteristic mushroom odor.

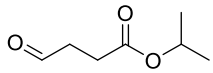


R_f = 0.77 (P/Et_2O 7:3).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dd, $^3J_{H,H}$ = 17.7, 10.4 Hz, 1H; C*H*=CH_2), 6.27 (dd, $^3J_{H,H}$ = 17.7, $^2J_{H,H}$ = 1.2 Hz, 1H; CH=C*H*H), 5.87 (dd, $^3J_{H,H}$ = 10.4 Hz, $^2J_{H,H}$ = 1.2, 1H; CH=CH*H*), 3.68 (s, 3H; CH_3), 2.93 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2C=OCH), 2.65 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2CO_2Me).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6 (*C*=O), 173.4 (*C*O_2Me), 136.3 (*C*H=CH_2), 128.7 (CH=*C*H_2), 52.0 (*C*H_3), 34.2 (*C*H_2C=OCH), 27.8 (*C*H_2CO_2Me).

IR (film): v = 2954, 1735, 1702, 1682, 1617, 1437, 1403, 1361, 1322, 1263, 1211, 1163, 1100, 1025, 986, 962, 848 cm^{-1}.
MS (+ESI) m/z (%): 165 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_7H_{10}O_3+Na^+$: 165.0522 $[M+Na]^+$, found: 165.0521.

Isopropyl 4-oxobutanoate 161b[185]

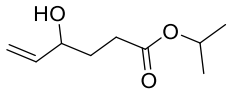
Step 1:[152] γ-Butyrolactone (13.3 mL, 122.0 mmol) was dissolved in *i*-PrOH (63.0 mL) and concentrated H_2SO_4 (100 µL, 2 mmol) was added. The solution was stirred at room temperature overnight. $CaCO_3$ (1.05 g, 10 mmol) was added and the suspension was stirred at room temperature for 3 h. The solids were filtered, washed with Et_2O and the filtrate was carefully concentrated under reduced pressure to obtain a crude mixture (11.6 g) containing 70% of isopropyl 4-hydroxybutanoate and 30% of γ-butyrolactone.
Step 2:[149] A solution of $NaHCO_3$ (9.95 g, 118 mmol) and K_2CO_3 (3.32 g, 24.0 mmol) in water (480 mL) was added to a solution of the above prepared crude mixture (5.0 g, 23.9 mmol) in DCM (240 mL). TEMPO (187 mg, 1.20 mmol), TBAB (772 mg, 2.39 mmol) and NCS (4.16 g, 31.1 mmol) were added and the reaction mixture was stirred vigorously at room temperature overnight. The layers were separated and the aqueous was extracted with DCM (2×150 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (P/Et_2O gradient 85:15 to 7:3) to obtain aldehyde **161b** (2.88 g, 40% over two steps) as a colorless oil, which was used rapidly in the next step.



R_f = 0.66 (P/Et_2O 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (t, $^3J_{H,H}$ = 0.8 Hz, 1H; *H*C=O), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 2.77 (td, $^3J_{H,H}$ = 6.5, 0.8 Hz, 2H; C*H*$_2$CH=O), 2.58 (t, $^3J_{H,H}$ = 6.6 Hz, 2H; CH_2COO*i*-Pr), 1.23 (d, $^3J_{H,H}$ = 6.3 Hz, 6H; C*H*$_3$).
The analytical data are in accordance with the published values.[185]

Isopropyl 4-hydroxyhex-5-enoate 162b

Prepared in analogy to the synthesis of **162a**[149] from **161b** (500 mg, 2.95 mmol) to yield **162b** (307 mg, 54%) as a colorless oil.

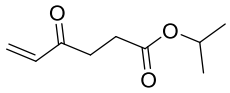


R_f = 0.63 (P/Et_2O 1:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (ddd, $^3J_{H,H}$ = 17.7, 10.4, 5.9 Hz, 1H; C*H*=CH_2), 5.24 (dt, $^3J_{H,H}$ = 17.2 Hz, $^2J_{H,H}$ = 1.5 Hz, $^4J_{H,H}$ = 1.5 Hz, 1H; CH=C*H*H), 5.12 (dt, $^3J_{H,H}$ = 10.4 Hz, $^2J_{H,H}$ = 1.4 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H; CH=CH*H*), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.24-4.08

(m, 1H; C*H*OH), 2.39 (t, *J* = 7.3 Hz, 2H; CH_2C=O), 2.05 (d, $^3J_{H,H}$ = 3.7 Hz, 1H; O*H*), 1.97-1.71 (m, 2H; CH_2CHOH), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz; 6H; CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (*C*=O), 140.6 (*C*H=CH_2), 115.2 (CH=*C*H_2), 72.4 (*C*HOH), 68.0 (*C*H$(CH_3)_2$), 31.8 (*C*H_2C=O), 30.7 (*C*H_2CH), 21.9 (2C; *C*H_3).
IR (film): *v* = 3424 (br), 2982, 2938, 1728, 1712, 1469, 1424, 1375, 1256, 1178, 1146, 1107, 1061, 992, 921, 880, 825, 674 cm^{-1}.
MS (+ESI) m/z (%): 195 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_9H_{16}O_3$+Na^+: 195.0992 $[M+Na]^+$, found: 195.0990.

Isopropyl 4-oxohex-5-enoate 160b

Allylic alcohol **162b** (710 mg, 3.92 mmol) was dissolved in dry DCM (40 mL) and DMP (1.99 g, 4.70 mmol) was added in three portions. The reaction mixture was stirred at room temperature for 3 h. $Na_2S_2O_3$/$NaHCO_3$ solution (10%, 1:1 v/v, 50 mL) was added and the biphasic mixture was stirred vigorously for 90 min. The layers were separated and the aqueous was extracted with DCM (3×40 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure to furnish crude enone **160b** (775 mg, quant.) as a yellow oil with a characteristic mushroom odor, which was used in the CM step without further purification.



R_f = 0.81 (P/Et_2O 7:3).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.38 (dd, $^3J_{H,H}$ = 17.7, 10.1 Hz, 1H; C*H*=CH_2), 6.26 (dd, $^3J_{H,H}$ = 17.7 Hz, $^2J_{H,H}$ = 1.5 Hz, 1H; CH=C*H*H), 5.87 (dd, $^3J_{H,H}$ = 10.1 Hz, $^2J_{H,H}$ = 1.5 Hz, 1H; CH=CH*H*), 4.99 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 2.91 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2C=OCH), 2.60 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2CO_2*i*-Pr), 1.22 (d, $^3J_{H,H}$ = 6.0 Hz, 6H; CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.8 (*C*=O), 172.4 (*C*O_2*i*-Pr), 136.4 (*C*H=CH_2), 128.6 (CH=*C*H_2), 68.1 (*C*H$(CH_3)_2$), 34.3 (CH_2C=OCH), 28.4 (*C*H_2CO_2*i*-Pr), 21.9 (2C; *C*H_3).
IR (film): *v* = 2982, 2937, 1728, 1704, 1684, 1617, 1469, 1403, 1375, 1263, 1212, 1167, 1146, 1107, 961, 924, 873, 826 cm^{-1}.
MS (+ESI) m/z (%): 193 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_9H_{16}O_3$+Na^+: 193.0835 $[M+Na]^+$, found: 193.0836.

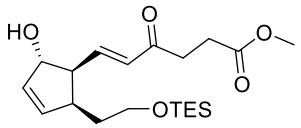
6.3.3.4 Introduction of the side chains

Methyl (*E*)-6-((1*S*,5*S*)-2-hydroxy-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)-4-oxo-hex-5-enoate 164a

A flame-dried tube equipped with a screw cap was charged with monoprotected diol **154b** (30 mg, 0.11 mmol) and filled with argon by several vacuum/argon cycles. Dry DCM (1.3 mL) was added, followed by compound **160a** (32 mg, 0.22 mmol) in dry DCM (1.3 mL). The solution was purged with argon for 30 min and ca half of the solvent was allowed to evaporate under the argon flow. The reaction was stirred at refluxing temperature and catalyst **HG-II** (7 mg, 0.01 mmol) was added

in five small portions in 90 min intervals. After the addition of the last portion, the bath temperature was decreased to 40 °C and the reaction mixture was stirred overnight. An additional portion of the catalyst (2.5 mg, 3 μmol) was added and the reaction was stirred at room temperature for 6 h. The volatiles were removed under reduced pressure and the residue was adsorbed on silica gel and purified by silica gel column chromatography (P/EtOAc gradient 85:15 to 3:1) to obtain **164a** (27 mg, 63%) as inseparable 2:1 mixture of *trans-/cis*-**164a** as determined by ^{1}H NMR spectroscopy as a yellow oil.

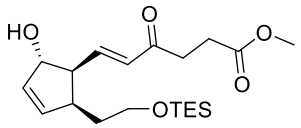
R_f = 0.50 (P/EtOAc 1:1).



trans-**164a**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (dd, $^3J_{H,H}$ = 15.8, 9.6 Hz, 1H; C*H*=CHC=O), 6.27 (dd, $^3J_{H,H}$ = 15.9, $^4J_{H,H}$ = 1.0 Hz, 1H; CH=C*H*C=O), 6.04 (ddd, $^3J_{H,H}$ = 5.8, 2.4 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 5.84 (dt, $^3J_{H,H}$ = 5.7, 1.8 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H; CH=C*H*CHOH), 4.76-4.71 (m, 1H; C*H*OH), 3.69 (s, 3H; C*H*$_3$O), 3.60 (t, $^3J_{H,H}$ = 7.0 Hz, 2H; C*H*$_2$OTES), 3.18-3.08 (m, 1H; C*H*CH$_2$), 2.91 (t, $^3J_{H,H}$ = 6.2 Hz, 2H; C*H*$_2$C=O), 2.89-2.81 (m, 1H; C*H*CHOH), 2.64 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; C*H*$_2$CO$_2$Me), 1.70 (dtd, $^2J_{H,H}$ = 13.5 Hz, $^3J_{H,H}$ = 6.7, 5.3 Hz, 1H; CH*H*CH$_2$O), 1.59 (br s, 1H; O*H*), 1.38 (ddt, $^2J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 9.9, 6.6 Hz, 1H; C*H*HCH$_2$O), 0.94 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$), 0.58 (q, $^3J_{H,H}$ = 8.1 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7 (*C*=O), 173.5 (*C*O$_2$), 145.9 (*C*H=CHC=O), 138.31 (*C*H=CHCHOH), 132.7 (CH=*C*HCHOH), 131.5 (CH=*C*HC=O), 81.1 (*C*HOH), 61.4 (*C*H$_2$OTES), 55.2 (*C*HCHOH), 51.95 (*C*H$_3$O), 44.8 (*C*HCH$_2$), 35.1 (*C*H$_2$C=O), 34.3 (*C*H$_2$CH$_2$OTES), 27.9 (*C*H$_2$CO$_2$), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si).



cis-**164a**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (dd, $^3J_{H,H}$ = 16.1, 10.2 Hz, 1H; C*H*=CHC=O), 6.24 (dd, $^3J_{H,H}$ = 16.1 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 6.06-6.03 (m, 1H; C*H*=CHCHOH), 5.95 (dt, $^3J_{H,H}$ = 5.7, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; CH=C*H*CHOH), 4.76-4.68 (m, 1H; C*H*OH), 3.68 (s, 3H; C*H*$_3$O), 3.62 (t, $^3J_{H,H}$ = 6.2 Hz, 2H; C*H*$_2$OTES), 3.08-3.00 (m, 1H; C*H*CHOH), 2.99-2.94 (m, 3H; C*H*$_2$C=O, C*H*CH$_2$), 2.69 (t, $^3J_{H,H}$ = 6.4 Hz, 2H; C*H*$_2$CO$_2$), 2.05 (d, $^3J_{H,H}$ = 8.1 Hz, 1H; O*H*), 1.70 (dtd, $^2J_{H,H}$ = 13.5 Hz, $^3J_{H,H}$ = 6.5, 5.3 Hz, 1H; CH*H*CH$_2$O), 1.38 (ddt, $^2J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 9.9, 6.1 Hz, 1H; C*H*HCH$_2$O), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$), 0.60 (q, $^3J_{H,H}$ = 7.8 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7 (*C*=O), 173.5 (*C*O$_2$), 145.7 (*C*H=CHC=O), 138.27 (*C*H=CHCHOH), 133.0 (CH=*C*HCHOH), 132.9 (CH=*C*HC=O), 78.5 (*C*HOH), 61.0 (*C*H$_2$OTES), 51.93 (*C*H$_3$O), 50.4 (*C*HCHOH), 45.4 (*C*HCH$_2$), 34.8 (*C*H$_2$C=O), 34.4 (*C*H$_2$CH$_2$OTES), 28.1 (*C*H$_2$CO$_2$), 6.9 (3C; *C*H$_3$CH$_2$), 4.4 (3C; *C*H$_2$Si).

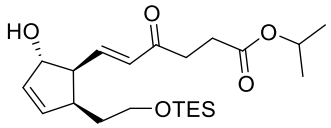
IR (film): ν = 3430 (br), 2953, 2936, 2912, 2876, 1739, 1676, 1668, 1458, 1438, 1413, 1360, 1323, 1214, 1166, 1098, 1051, 1011, 989, 781, 744 cm^{-1}.
MS (+ESI) m/z (%): 405 (100) $[M+Na]^+$, 383 (2) $[M+H]^+$, 365 (52) $[M+H-H_2O]^+$,
HRMS (+ESI) m/z: calcd for $C_{20}H_{34}O_5Si+Na^+$: 405.2068 $[M+Na]^+$, found: 405.2068; calcd for $C_{20}H_{34}O_5Si+H^+$: 383.2248 $[M+H]^+$, found: 383.2247.

Isopropyl (*E*)-6-((1*S*,5*S*)-2-hydroxy-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)-4-oxohex-5-enoate 164b

Prepared in analogy to **164a** from **154b** (125 mg, 0.47 mmol) and **160b** (198 mg, 1.16 mmol) using catalyst **HG-II** (41 mg, 0.065 mmol). Purification by column chromatography (P/Et_2O gradient 4:1 to 1:1) furnished **164b** (112 mg, 59%) and as partially separable 2:1 mixture of *trans-/cis*-**164b** as determined by ^1H NMR spectroscopy as a yellow oil.

One-pot CM/RCM procedure

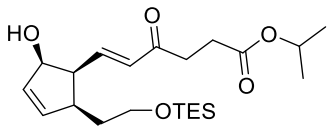
A solution of diol **154b** (177 mg, 0.60 mmol) in dry DCM (6.7 mL) was purged with argon, **HG-II** (7.5 mg, 0.012 mmol) was added and the reaction mixture was stirred at room temperature overnight when the RCM step was complete as indicated by TLC. Compound **160b** (201 mg, 1.16 mmol) was added, followed by another portion of the catalyst (7.5 mg, 0.012 mmol). The flask was equipped with a condenser and the mixture was stirred at reflux for 10 h; four additional portions of **HG-II** (each 7.5 mg, 0.012 mmol) were added every two hours. An additional portion of compound **160b** (102 mg, 0.60 mmol) was added with the last catalyst addition; the bath temperature was decreased to 35 °C and the reaction mixture was stirred overnight. The volatiles were removed under reduced pressure, the residue was adsorbed on silica and purified by silica gel column chromatography (P/Et_2O gradient 4:1 to 7:3) to furnish enone **164b** (135 mg, 55%) as partially separable 2:1 mixture of *trans-/cis*-**164b** as determined by ^1H NMR spectroscopy.



trans-**164b**

R_f = 0.14 (P/Et_2O 7:3).
^1H NMR (300 MHz, $CDCl_3$): δ = 6.85 (dd, $^3J_{H,H}$ = 15.8, 9.6 Hz, 1H; C*H*=CHC=O), 6.26 (dd, $^3J_{H,H}$ = 15.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; CH=C*H*C=O), 6.09-6.00 (m, 1H; C*H*=CHCHOH), 5.83 (dt, $^3J_{H,H}$ = 5.8, 1.8 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H; CH=C*H*CHOH), 5.00 (sept, $^3J_{H,H}$ = 5.8 Hz, 1H; C*H*$(CH_3)_2$), 4.76-4.71 (m, 1H; C*H*OH), 3.60 (t, $^3J_{H,H}$ = 6.6 Hz, 2H; C*H*$_2$OTES), 3.11 (dtdd, $^3J_{H,H}$ = 8.5, 6.3, 5.3, 2.6 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; C*H*CH_2), 2.94-2.77 (m, 3H; C*H*$_2$C=O, C*H*CHOH), 2.587 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; C*H*$_2CO_2$), 1.78-1.58 (m, 2H; CH*H*CH_2O, O*H*), 1.47-1.31 (m, 1H; C*H*HCH_2O), 1.23 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3)_2$CH), 0.936 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3CH_2$), 0.58 (q, $^3J_{H,H}$ = 7.6 Hz, 6H; C*H*$_2$Si).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9 (*C*=O), 172.5 (*C*O_2), 145.8 (*C*H=CHC=O), 138.26

(*C*H=CHCHOH), 132.7 (CH=*C*HCHOH), 131.5 (CH=*C*HC=O), 81.1 (*C*HOH), 68.1 (*C*H(CH_3)$_2$), 61.4 (*C*H_2OTES), 55.2 (*C*HCHOH), 44.8 (*C*HCH_2), 35.1 (*C*H_2C=O), 34.3 (*C*$H_2$$CH_2$OTES), 28.5 (*C*$H_2$$CO_2$), 21.9 (2C; (*C*$H_3$)$_2$CH), 6.9 (3C; *C*$H_3$$CH_2$), 4.43 (3C; *C*$H_2$Si).



cis-**164b**

R_f = 0.21 (P/Et_2O 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04 (dd, $^3J_{H,H}$ = 16.1, 10.2 Hz, 1H; C*H*=CHC=O), 6.23 (dd, $^3J_{H,H}$ = 16.1 Hz, $^4J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 6.04 (ddd, $^3J_{H,H}$ = 5.3, 2.6 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 5.94 (dt, $^3J_{H,H}$ = 5.8, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOH), 4.99 (sept, $^3J_{H,H}$ = 5.8 Hz, 1H; C*H*(CH_3)$_2$), 4.76-4.68 (m, 1H; C*H*OH), 3.71-3.59 (m, 2H; C*H*$_2$OTES), 3.08-3.00 (m, 1H; C*H*CHOH), 2.99-2.94 (m, 3H; C*H*$_2$C=O, C*H*CH_2), 2.590 (t, $^3J_{H,H}$ = 6.4 Hz, 2H; C*H*$_2$$CO_2$), 1.74-1.49 (m, 3H; C*H*$_2$$CH_2$O, O*H*), 1.23 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3$)$_2$CH), 0.942 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$$CH_2$), 0.60 (q, $^3J_{H,H}$ = 7.8 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (*C*=O), 172.6 (*C*O_2), 145.6 (*C*H=CHC=O), 138.20 (*C*H=CHCHOH), 133.1 (CH=*C*HCHOH), 133.0 (CH=*C*HC=O), 78.4 (*C*HOH), 68.1 (*C*H(CH_3)$_2$), 61.0 (*C*H_2OTES), 55.2 (*C*HCHOH)), 45.3 (*C*HCH_2), 34.8 (*C*H_2C=O), 34.4 (*C*$H_2$$CH_2$OTES), 28.6 (*C*$H_2$$CO_2$), 21.9 (2C; (*C*$H_3$)$_2$CH), 6.9 (3C; *C*$H_3$$CH_2$), 4.37 (3C; *C*$H_2$Si).

IR (film): *v* = 3442 (br), 2955, 2870, 2813, 1731, 1699, 1675, 1630, 1458, 1413, 1374, 1213, 1167, 1105, 1004, 985, 726, 672 cm^{-1}.

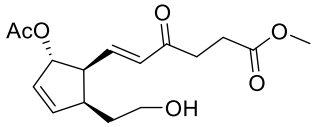
MS (+ESI) m/z (%): 393 (100) [*M*–H_2O+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{22}H_{38}O_5Si$–H_2O+H^+: 393.2461 [*M*–H_2O+H]$^+$, found: 393.2469.

Methyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-(2-hydroxyethyl)cyclopent-3-en-1-yl)-4-oxohex-5-enoate 166a

Enone **164a** (36.0 mg, 0.094 mmol) and DMAP (5.7 mg, 0.047 mmol) were dissolved in dry DCM (1 mL), the solution was cooled to 0 °C and Et_3N (20 µL, 0.144 mmol) followed by Ac_2O (13 µL, 0.138 mmol) were added. The reaction mixture was warmed to room temperature overnight. The mixture was diluted with DCM (5 mL), satd. NH_4Cl solution (5 mL) was added, the layers were separated, and the aqueous was extracted with DCM (3×5 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient P/Et_2O 3:2 to 0:1) to obtain desilylated acetate **166a** (12.0 mg, 41%) as inseparable 2:1 mixture of *trans-/cis*-**166a** as determined by ^{1}H NMR spectroscopy as a colorless oil.

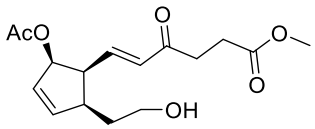
R_f = 0.15 (P/Et_2O 1:1).



trans-**166a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (dd, $^{3}J_{H,H}$ = 16.0, 9.2 Hz, 1H; C*H*=CHC=O), 6.21 (dd, $^{3}J_{H,H}$ = 15.9 Hz, $^{4}J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 6.17-6.07 (m, 1H; C*H*=CHCHOAc), 5.85 (dt, $^{3}J_{H,H}$ = 5.8, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.59 (dt, $^{3}J_{H,H}$ = 4.6, 1.5 Hz, $^{4}J_{H,H}$ = 1.5 Hz 1H; C*H*OAc), 3.68 (s, 3H; C*H*$_3$O), 3.66 (t, $^{3}J_{H,H}$ = 6.3 Hz, 2H; C*H*$_2$OH), 3.20-3.12 (m, 1H; C*H*CH_2), 3.06 (dddd, $^{3}J_{H,H}$ = 8.7, 7.6, 4.6 Hz, $^{4}J_{H,H}$ = 0.9 Hz, 1H; C*H*CHOAc), 2.94-2.85 (m, 2H; C*H*$_2$C=O), 2.64 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; C*H*$_2CO_2$), 2.04 (s, 3H; C*H*$_3$C=O), 1.67 (dq, $^{2}J_{H,H}$ = 13.3 Hz, $^{3}J_{H,H}$ = 6.6 Hz, 1H; CH*H*CH_2O), 1.66 (br s, 1H; OH), 1.63-1.52 (m, 1H; C*H*HCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9 (*C*HC=O), 173.53 (*C*O_2Me), 171.0 (CH_3*C*=O), 144.6 (*C*H=CHC=O), 140.2 (*C*H=CHCHOAc), 131.8 (CH=*C*HCHOAc), 129.2 (CH=*C*HC=O), 82.7 (*C*HOAc), 61.3 (*C*H_2OH), 52.0 (CH_3O), 51.2 (*C*HCHOAc), 44.5 (*C*HCH_2), 34.9 (CH_2C=O), 33.8 (*C*H_2CH_2OH), 27.9 (*C*H_2CO_2), 21.3 (*C*H_3C=O).



cis-**166a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83 (dd, $^{3}J_{H,H}$ = 15.8, 10.3 Hz, 1H; C*H*=CHC=O), 6.21 (dd, $^{3}J_{H,H}$ = 15.9 Hz, $^{4}J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 5.88 (dt, $^{3}J_{H,H}$ = 5.8, 2.1 Hz, $^{4}J_{H,H}$ = 2.1 Hz, 1H; C*H*=CHCHOAc), 5.88 (dt, $^{3}J_{H,H}$ = 5.8, 2.1 Hz, $^{4}J_{H,H}$ = 2.1 Hz, 1H; CH=C*H*CHOAc), 5.65-5.59 (m, 1H; C*H*OAc), 3.68 (s, 3H; C*H*$_3$O), 3.68 (t, $^{3}J_{H,H}$ = 6.2 Hz, 2H; C*H*$_2$OH), 3.28 (dt, $^{3}J_{H,H}$ = 10.5, 7.0 Hz, 1H; C*H*CHOAc), 2.99-2.90 (m, 1H; C*H*CH_2), 2.90-2.82 (m, 2H; C*H*$_2$C=O), 2.64 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; C*H*$_2CO_2$), 2.00 (s, 3H; C*H*$_3$C=O), 1.71 (dq, $^{2}J_{H,H}$ = 13.3 Hz, $^{3}J_{H,H}$ = 6.6 Hz, 1H; CH*H*CH_2O), 1.66 (br s, 1H; O*H*), 1.49 (ddt, $^{2}J_{H,H}$ = 13.7 Hz, $^{3}J_{H,H}$ = 9.1, 6.7 Hz, 1H; C*H*HCH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (CH*C*=O), 173.50 (*C*O_2Me), 170.6 (CH_3*C*=O), 143.5 (*C*H=CHC=O), 139.6 (*C*H=CHCHOAc), 132.6 (CH=*C*HCHOAc), 129.3 (CH=*C*HC=O), 80.4 (*C*HOAc), 61.2 (*C*H_2OH), 52.0 (*C*H_3O), 48.7 (*C*HCHOAc), 45.1 (*C*HCH_2), 34.9 (*C*H_2C=O), 34.7 (*C*H_2CH_2OH), 27.9 (*C*H_2CO_2), 21.2 (*C*H_3C=O).

IR (film): *v* = 3442 (br), 2955, 2870, 2813, 1731, 1698, 1612, 1586, 1512, 1464, 1362, 1301, 1245, 1174, 1093, 1032, 966, 916, 818, 754, 706, 637 cm^{-1}.

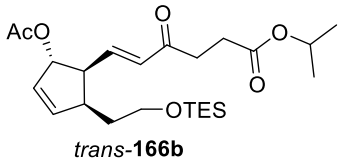
MS (+ESI) m/z (%): 333 [*M*+Na]$^{+}$.

HRMS (+ESI) m/z: calcd for $C_{16}H_{22}O_6$+Na^{+}: 333.1309, found: 333.1305.

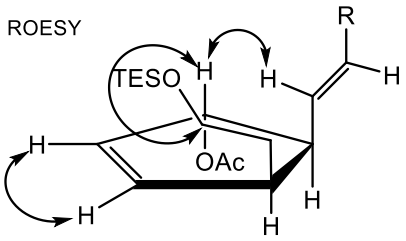
Isopropyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)-4-oxo-hex-5-enoate 166b

Enone **164b** (100 mg, 0.244 mmol) was dissolved in dry DCM (2.7 mL), the solution was cooled to 0 °C, Et_3N (102 µL, 0.731 mmol) followed by Ac_2O (34 µL, 0.357 mmol) and DMAP (15 mg, 0.12 mmol) were added. The reaction mixture was stirred at 0 °C for 20 min. The mixture was diluted with DCM (5 mL), satd. NH_4Cl solution (5 mL) was added, the layers were separated, and the aqueous was extracted with DCM (3×10 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (gradient P/Et_2O 9:1 to 3:1) to obtain acetate **166b** (87 mg, 79%) as inseparable 2:1 mixture of *trans*-/*cis*-**166b** as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.84 (P/Et_2O 7:3).

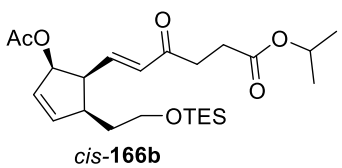


trans-**166b**

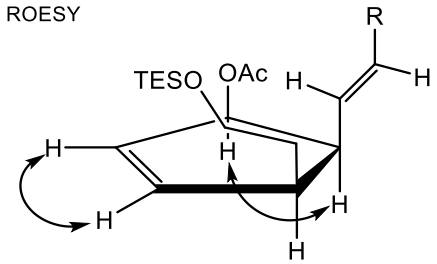


^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (dd, $^3J_{H,H}$ = 15.8, 9.5 Hz, 1H; C*H*=CHC=O), 6.32-6.09 (m, 2H; CH=C*H*C=O, C*H*=CHCHOAc), 5.82 (dt, $^3J_{H,H}$ = 5.8, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.59-5.91 (m, 1H; C*H*OAc), 4.99 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 3.60 (t, $^3J_{H,H}$ = 6.4 Hz, 2H; CH_2OTES), 3.20-3.10 (m, 1H; C*H*CH_2), 3.03 (dddd, $^3J_{H,H}$ = 9.3, 7.7, 4.6 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; C*H*CHOAc), 2.87 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH_2C=O), 2.57 (t, $^3J_{H,H}$ = 6.8 Hz, 2H; CH_2CO_2), 2.03 (s, 3H; CH_3C=O), 1.75-1.57 (m, 1H; CH*H*CH_2O), 1.48-1.30 (m, 1H; C*H*HCH_2O), 1.22 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (CH_3)$_2$CH), 0.93 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2), 0.57 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8 (*C*=O), 172.4 (*C*O_2*i*-Pr), 171.0 (CH_3*C*=O), 144.6 (*C*H=CHC=O), 140.6 (*C*H=CHCHOAc), 131.7 (CH=*C*HCHOAc), 128.9 (CH=*C*HC=O), 82.8 (*C*HOAc), 68.1 ((CH_3)$_2$*C*H), 61.3 (*C*H_2OTES), 50.9 (*C*HCHOAc), 44.6 (*C*HCH_2), 35.0 (*C*H_2C=O), 34.0 (*C*H_2CH_2OTES), 28.4 (*C*H_2CO_2), 21.9 (2C; (*C*H_3)$_2$CHO), 21.3 (*C*H_3C=O), 6.9 (3C; *C*H_3CH_2), 4.4 (3C; *C*H_2Si).



cis-**166b**



^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (dd, $^3J_{H,H}$ = 15.9, 11.0 Hz, 1H; C*H*=CHC=O), 6.20-6.09 (m, 2H; CH=C*H*C=O, C*H*=CHCHOAc), 5.85 (dt, $^3J_{H,H}$ = 6.1, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H;

CH=C*H*CHOAc), 5.59-5.51 (m, 1H; C*H*OAc), 4.99 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH_3)$_2$), 3.62 (t, $^3J_{H,H}$ = 6.4 Hz, 2H; CH_2OTES), 3.26 (dt, $^3J_{H,H}$ = 10.5, 6.8 Hz, 1H; C*H*CHOAc), 2.95-2.92 (m, 1H; C*H*CH_2), 2.86 (t, $^3J_{H,H}$ = 6.9 Hz, 2H; CH_2C=O), 2.57 (t, $^3J_{H,H}$ = 6.8 Hz, 2H; CH_2CO_2), 1.99 (s, 3H; CH_3C=O), 1.75-1.59 (m, 2H; CH_2CH_2O), 1.22 (d, $^3J_{H,H}$ = 6.2 Hz. 6H; (CH_3)$_2$CH), 0.93 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2), 0.57 (q, $^3J_{H,H}$ = 7.8 Hz, 6H; CH_2Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (*C*=O), 172.2 (*C*O_2*i*-Pr), 170.6 (CH_3*C*=O), 143.6 (*C*H=CHC=O), 139.8 (*C*H=CHCHOAc), 132.5 (CH=*C*HCHOAc), 129.0 (CH=*C*HC=O), 80.5 (*C*HOAc), 68.1 ((CH_3)$_2$*C*H), 61.1 (*C*H_2OTES), 48.9 (*C*HCHOAc), 45.0 (*C*HCH_2), 34.8 (*C*H_2C=O), 34.0 (*C*H_2CH_2OTES), 28.4 (*C*H_2CO_2), 21.9 (2C; (*C*H_3)$_2$CH), 21.1 (*C*H_3C=O), 6.9 (3C; *C*H_3CH_2), 4.4 (3C; *C*H_2Si).

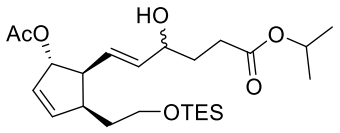
IR (film): *v* = 2955, 2877, 1732, 1701, 1678, 1633, 1458, 1414, 1373, 1235, 1166, 1106, 1014, 983, 925, 880, 727, 666, 604 cm^{-1}.

MS (+ESI) m/z (%): 475 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{24}H_{40}O_6Si$+Na$^+$: 475.2486 [*M*+Na]$^+$, found: 475.2482.

Isopropyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)-4-hydroxyhex-5-enoate 167

Dry THF (3 mL) was added to a solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine (345 µL, 1.0 M in toluene, 0.345 mmol) followed by dropwise addition of $Me_2S{\cdot}BH_3$ (144 µL, 2.0 M in THF, 0.287 mmol) at room temperature. The reaction mixture was stirred for 15 min, cooled to 0 °C and added to a solution of **166a** (104 mg, 0.230 mmol) in dry THF (3 mL) kept at 0 °C using a cannula. The reaction mixture was stirred at this temperature for 40 min when full conversion was indicated by TLC. MeOH (1 mL) was added and the mixture was warmed to room temperature with stirring over 1 h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (P/Et_2O 3:2) to obtain allylic alcohol **167** (92 mg, 87%) as partially separable 2:1 mixture of *trans*-/*cis*-**167**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.



trans-**167: dr 2.7:1**

R_f = 0.22 (P/Et_2O 1:1).

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (ddd, $^3J_{H,H}$ = 5.8, 2,3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.79 (dt, $^3J_{H,H}$ = 5.8, 1.9 Hz, $^4J_{H,H}$ = 1.9 Hz, 1H; CH=C*H*CHOAc), 5.66-5.51 (m, 2H; C*H*=C*H*CHOH), 5.48 (ddd, $^3J_{H,H}$ = 4.8, 1.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*OAc), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH_3)$_2$), 4.21-4.08 (m, 1H; C*H*OH), 3.62 (t, $^3J_{H,H}$ = 6.6 Hz, 2H; CH_2OTES), 3.01 (dddt, $^3J_{H,H}$ = 9.5, 7.5, 5.6, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; C*H*CH_2), 2.94-2.84 (m, 1H; C*H*CHOAc), 2.37 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; CH_2CO_2), 2.03 (s, 3H; CH_3C=O), 1.75-1.63 (m, 4H;

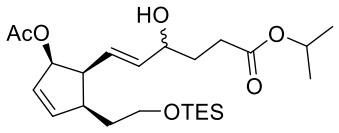
C*H*$_2$CHOH, CH*H*CH$_2$O, O*H*), 1.45-1.30 (m, 1H; C*H*HCH$_2$O), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 6H; (C*H*$_3$)$_2$CH), 1.05-0.89 (m, 9H; C*H*$_3$CH$_2$), 0.65-0.47 (m, 6H; C*H*$_2$Si).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.6 (*C*O$_2$*i*-Pr), 171.17 (CH$_3$*C*=O), 140.8 (*C*H=CHCHOAc), 135.3 (*C*H=CHCHOH), 129.33 (CH=*C*HCHOH), 128.94 (CH=*C*HCHOAc), 83.86 (*C*HOAc), 71.9 (*C*HOH), 67.92 ((CH$_3$)$_2$*C*H), 61.6 (*C*H$_2$OTES), 50.8 (*C*HCHOAc), 44.1 (*C*HCH$_2$), 34.02 (*C*H$_2$CH$_2$OTES), 32.2 (*C*H$_2$CHOH), 30.9 (*C*H$_2$C=O), 22.0 (2C; (*C*H$_3$)$_2$CHO), 21.4 (*C*H$_3$C=O), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.11 (ddd, $^3J_{H,H}$ = 4.3, 1.1 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.79 (dt, $^3J_{H,H}$ = 4.1, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; CH=C*H*CHOAc), 5.70-5.50 (m, 2H; C*H*=C*H*CHOH), 5.48 (ddd, $^3J_{H,H}$ = 4.8, 1.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*OAc), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH$_3$)$_2$), 4.36-4.27 (m, 1H; C*H*OH), 3.72-3.57 (m, 2H; C*H*$_2$OTES), 3.06-2.94 (m, 1H; C*H*CH$_2$), 2.95-2.81 (m, 1H; C*H*CHOAc), 2.37 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; C*H*$_2$CO$_2$), 2.03 (s, 3H; C*H*$_3$C=O), 1.76-1.65 (m, 3H; C*H*$_2$CHOH, O*H*), 1.63-1.49 (m, 2H; C*H*$_2$CH$_2$O), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 6H; (C*H*$_3$)$_2$CH), 1.02-0.82 (m, 9H; C*H*$_3$CH$_2$), 0.58 (q, $^3J_{H,H}$ = 7.5 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.6 (*C*O$_2$*i*-Pr), 171.18 (CH$_3$*C*=O), 140.8 (*C*H=CHCHOAc), 135.2 (*C*H=CHCHOH), 129.25 (CH=*C*HCHOH), 128.85 (CH=*C*HCHOAc), 83.90 (*C*HOAc), 71.8 (*C*HOH), 67.90 ((CH$_3$)$_2$*C*H), 61.5 (*C*H$_2$OTES), 50.9 (*C*HCHOAc), 44.1 (*C*HCH$_2$), 34.01 (*C*H$_2$CH$_2$OTES), 32.1 (*C*H$_2$CHOH), 30.8 (*C*H$_2$C=O), 21.9 (2C; (*C*H$_3$)$_2$CHO), 21.27 (*C*H$_3$C=O), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si).



***cis*-167: dr 1.7:1**

R_f = 0.12 (P/Et$_2$O 1:1).

Major C-4 *epimer:*

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.09 (ddd, $^3J_{H,H}$ = 6.0, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.83 (dt, $^3J_{H,H}$ = 6.2, 2.0 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.66-5.51 (m, 2H; C*H*=C*H*CHOH), 5.48 (ddd, $^3J_{H,H}$ = 4.8, 1.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*OAc), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH$_3$)$_2$), 4.21-4.08 (m, 1H; C*H*OH), 3.64 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; C*H*$_2$OTES), 3.15-3.06 (m, 1H; C*H*CHOAc), 2.94-2.84 (m, 1H; C*H*CH$_2$), 2.37 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; C*H*$_2$CO$_2$), 2.01 (s, 3H; C*H*$_3$C=O), 1.88-1.77 (m, 2H; C*H*$_2$CHOH), 1.77-1.63 (m, 3H; C*H*$_2$CH$_2$O, O*H*), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 6H; (C*H*$_3$)$_2$CH), 1.05-0.89 (m, 9H; C*H*$_3$CH$_2$), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; C*H*$_2$Si).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 173.5 (*C*O$_2$*i*-Pr), 171.1 (CH$_3$*C*=O), 140.4 (*C*H=CHCHOAc), 136.2 (*C*H=CHCHOH), 129.6 (CH=*C*HCHOH), 127.6 (CH=*C*HCHOAc), 80.7 (*C*HOAc), 72.1 (*C*HOH), 67.92 ((CH$_3$)$_2$*C*H), 61.4 (*C*H$_2$OTES), 48.7 (*C*HCHOAc), 44.6 (*C*HCH$_2$), 34.96 (*C*H$_2$CH$_2$OTES), 32.2 (*C*H$_2$CHOH), 30.9 (*C*H$_2$C=O), 22.0 (2C; (*C*H$_3$)$_2$CHO), 21.4 (*C*H$_3$C=O), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (ddd, $^3J_{H,H}$ = 6.0, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.86-5.80 (m, 1H; CH=C*H*CHOAc), 5.70-5.50 (m, 2H; C*H*=C*H*CHOH), 5.48 (ddd, $^3J_{H,H}$ = 4.8, 1.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*OAc), 5.00 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.21-4.08 (m, 1H; C*H*OH), 3.64 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; CH_2OTES), 3.15-3.06 (m, 1H; C*H*CHOAc), 2.94-2.84 (m, 1H; C*H*CH_2), 2.37 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; CH_2CO_2), 2.01 (s, 3H; CH_3C=O), 1.88-1.77 (m, 2H; CH_2CHOH), 1.77-1.63 (m, 3H; CH_2CH_2O, O*H*), 1.22 (d, $^3J_{H,H}$ = 6.3 Hz, 6H; $(CH_3)_2$CH), 1.05-0.89 (m, 9H; CH_3CH_2), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (CO_2*i*-Pr), 171.18 (CH_3*C*=O), 140.6 (*C*H=CHCHOAc), 136.1 (*C*H=CHCHOH), 129.5 (CH=*C*HCHOH), 127.5 (CH=*C*HCHOAc), 80.6 (*C*HOAc), 72.3 (*C*HOH), 67.90 ($(CH_3)_2$*C*H), 61.3 (*C*H_2OTES), 48.6 (*C*HCHOAc), 44.6 (*C*HCH_2), 35.04 (*C*H_2CH_2OTES), 32.1 (*C*H_2CHOH), 30.8 (*C*H_2C=O), 22.0 (2C; $(CH_3)_2$CHO), 21.31 (*C*H_3C=O), 6.9 (3C; *C*H_3CH_2), 4.5 (3C; *C*H_2Si).

IR (film): *ν* = 3450, 2928, 2856, 1732, 1464, 1373, 1239, 1176, 1108, 1103, 977, 836, 776, 745, 672 cm^{-1}.

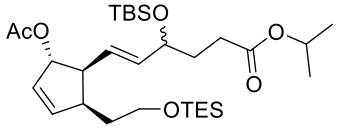
MS (+ESI) m/z (%): 477 (30) $[M+Na]^+$, 437 (100) $[M+H-H_2O]^+$.

HRMS (+ESI) m/z: calcd for $C_{24}H_{42}O_6Si-H_2O+H^+$: 437.2724 $[M+H-H_2O]^+$, found: 437.2731; calcd for $C_{24}H_{42}O_6Si+Na^+$ $[M+Na]^+$: 477.2643, found: 477.2653.

Isopropyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-(2-((triethylsilyl)oxy)ethyl)cyclopent-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)hex-5-enoate 168

A solution of alcohol **167** (92 mg, 0.203 mmol) in dry DCM (2.3 mL) was cooled to –78 °C. 2,6-Lutidine (93 µL, 0.81 mmol) was added, followed by a dropwise addition of TBSOTf (79 µL, 0.345 mmol). The reaction mixture was stirred for 10 min when complete conversion was indicated by TLC. DCM (5 mL) and satd. $NaHSO_4$ solution (5 mL) were added, the cooling bath was removed and the biphasic mixture was stirred for 15 min. Water (5 mL) and DCM (5 mL) were added, the layers were separated and the aqueous was extracted with DCM (3×10 mL). The combined organic layers were washed with satd. $NaHCO_3$ solution (20 mL) dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (P/Et_2O gradient 95:5 to 9:1) to furnish **168** (105 mg, 92%) as inseparable 2.1:1 mixture of *trans*-/*cis*-**168**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.62 (P/Et_2O 7:3).



trans-**168: dr 2.4:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (ddd, $^3J_{H,H}$ = 5.8, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H;

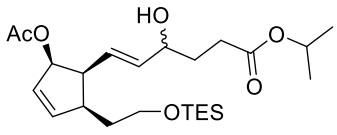
C*H*=CHCHOAc), 5.79 (dt, $^{3}J_{H,H}$ = 5.8, 1.9 Hz, $^{4}J_{H,H}$ = 1.9 Hz, 1H; CH=C*H*CHOAc), 5.66-5.48 (m, 3H; C*H*=C*H*CHOTBS, C*H*OAc), 5.00 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.22-4.08 (m, 1H; C*H*OTBS), 3.61 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; CH_2OTES), 3.04-2.96 (m, 1H; C*H*CH_2), 2.93-2.80 (m, 1H; C*H*CHOAc), 2.28 (t, $^{3}J_{H,H}$ = 7.4 Hz, 2H; CH_2CO_2), 2.02 (s, 3H; CH_3C=O), 1.83-1.69 (m, 3H; CH_2CHOTBS, CH*H*CH_2O), 1.48-1.29 (m, 1H; C*H*HCH_2O), 1.21 (d, $^{3}J_{H,H}$ = 6.3 Hz, 6H; (CH_3)$_2$CH), 0.94 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2), 0.87 (s, 9H; CH_3CSi), 0.58 (q, $^{3}J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.36 (*C*O_2*i*-Pr), 171.13 (CH_3*C*=O), 140.8 (*C*H=CHCHOAc), 135.8 (*C*H=CHCHOTBS), 129.0 (CH=*C*HCHOTBS), 128.0 (CH=*C*HCHOAc), 83.8 (*C*HOAc), 72.11 (*C*HOTBS), 67.6 ($(CH_3)_2$C*H*), 61.6 (*C*H_2OTES), 50.79 (*C*HCHOAc), 44.0 (*C*HCH_2), 34.1 (*C*H_2CH_2OTES), 33.35 (*C*H_2CHOTBS), 30.39 (*C*H_2C=O), 26.0 (3C; *C*H_3CSi), 22.0 (2C; (*C*H_3)$_2$CH), 21.4 (*C*H_3C=O), 18.27 (*C*Si), 6.9 (3C; *C*H_3CH_2), 4.5 (3C; *C*H_2Si), –4.25 (*C*H_3Si), –4.75 (*C*H_3Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.14-6.09 (m, 1H; C*H*=CHCHOAc), 5.79 (dt, $^{3}J_{H,H}$ = 5.8, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.64-5.55 (m, 1H; CH=C*H*CHOTBS), 5.46-5.40 (m, 2H; C*H*=CHCHOTBS, C*H*OAc), 4.97 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.18-4.08 (m, 1H; C*H*OTBS), 3.69-3.55 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; CH_2OTES), 3.00 (dtd, $^{3}J_{H,H}$ = 7.6, 5.5, 4.9, 2.2 Hz, 1H; C*H*CH_2), 2.93-2.80 (m, 1H; C*H*CHOAc), 2.29 (t, $^{3}J_{H,H}$ = 7.4 Hz, 2H; CH_2CO_2), 2.02 (s, 3H; CH_3C=O), 1.81-1.70 (m, 3H; CH_2CHOTBS, CH*H*CH_2O), 1.48-1.29 (m, 1H; C*H*HCH_2O), 1.21 (d, $^{3}J_{H,H}$ = 6.3 Hz, 6H; (CH_3)$_2$CH), 0.94 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2), 0.86 (s, 9H; CH_3CSi), 0.57 (q, $^{3}J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.40 (*C*O_2*i*-Pr), 171.15 (CH_3*C*=O), 140.3 (*C*H=CHCHOAc), 136.2 (*C*H=CHCHOTBS), 129.13 (CH=*C*HCHOTBS), 128.3 (CH=*C*HCHOAc), 83.9 (*C*HOAc), 72.06 (*C*HOTBS), 67.6 ($(CH_3)_2$C*H*), 61.5 (*C*H_2OTES), 50.83 (*C*HCHOAc), 44.2 (*C*HCH_2), 34.2 (*C*H_2CH_2OTES), 33.42 (*C*H_2CHOTBS), 30.25 (*C*H_2C=O), 26.0 (3C; *C*H_3CSi), 22.0 (2C; (*C*H_3)$_2$CH), 21.4 (*C*H_3C=O), 18.28 (*C*Si), 6.9 (3C; *C*H_3CH_2), 4.5 (3C; *C*H_2Si), –4.28 (*C*H_3Si), –4.75 (*C*H_3Si).



***cis*-168: dr 1.6:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.11-6.05 (m, 1H; C*H*=CHCHOAc), 5.85 (dt, $^{3}J_{H,H}$ = 5.8, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.64-5.48 (m, 2H; C*H*=C*H*CHOTBS), 5.47-5.44 (m, 1H; C*H*OAc), 4.97 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.21-4.12 (m, 1H; C*H*OTBS), 3.66-3.58 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; CH_2OTES), 3.11-3.03 (m, 1H; C*H*CHOAc), 2.83-2.69 (m, 1H; C*H*CH_2), 2.30 (t, $^{3}J_{H,H}$ = 7.4 Hz, 2H; CH_2CO_2), 2.00 (s, 3H; CH_3C=O), 1.77-1.63 (m, 3H; CH_2CHOTBS, CH*H*CH_2O), 1.54-1.38 (m, 1H; C*H*HCH_2O), 1.21 (d, $^{3}J_{H,H}$ = 6.3 Hz, 6H; (CH_3)$_2$CH), 0.94 (t,

$^{3}J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$), 0.88 (s, 9H; CH_3CSi), 0.57 (q, $^{3}J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.03 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.38 (*C*O$_2$*i*-Pr), 170.71 (CH$_3$*C*=O), 140.6 (*C*H=CHCHOAc), 136.7 (*C*H=CHCHOTBS), 129.09 (CH=*C*HCHOTBS), 126.1 (*C*H=*C*HCHOAc), 80.8 (*C*HOAc), 72.4 (*C*HOTBS), 67.6 ((CH$_3$)$_2$*C*H), 61.42 (*C*H$_2$OTES), 48.9 (*C*HCHOAc), 44.6 (*C*HCH$_2$), 35.1 (*C*H$_2$CH$_2$OTES), 33.37 (*C*H$_2$CHOTBS), 30.36 (*C*H$_2$C=O), 26.0 (3C; *C*H$_3$CSi), 22.0 (2C; (*C*H$_3$)$_2$CH), 21.3 (*C*H$_3$C=O), 18.27 (*C*Si), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si), –4.15 (*C*H$_3$Si), –4.73 (*C*H$_3$Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.11-6.05 (m, 1H; C*H*=CHCHOAc), 5.85 (dt, $^{3}J_{H,H}$ = 5.8, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.64-5.55 (m, 1H; CH=C*H*CHOTBS), 5.46-5.40 (m, 2H; C*H*=CHCHOTBS, C*H*OAc), 4.97 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH$_3$)$_2$), 4.21-4.12 (m, 1H; C*H*OTBS), 3.66-3.58 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2H; CH_2OTES), 3.11-3.03 (m, 1H; C*H*CHOAc), 2.83-2.69 (m, 1H; C*H*CH$_2$), 2.30 (t, $^{3}J_{H,H}$ = 7.4 Hz, 2H; CH_2CO$_2$), 2.00 (s, 3H; CH_3C=O), 1.77-1.63 (m, 3H; CH_2CHOTBS, CH*H*CH$_2$O), 1.54-1.38 (m, 1H; C*H*HCH$_2$O), 1.21 (d, $^{3}J_{H,H}$ = 6.3 Hz, 6H; (CH_3)$_2$CH), 0.94 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$), 0.88 (s, 9H; CH_3CSi), 0.57 (q, $^{3}J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.03 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.40 (*C*O$_2$*i*-Pr), 170.66 (CH$_3$*C*=O), 140.9 (*C*H=CHCHOAc), 136.6 (*C*H=CHCHOTBS), 129.13 (CH=*C*HCHOTBS), 126.5 (*C*H=*C*HCHOAc), 80.6 (*C*HOAc), 72.4 (*C*HOTBS), 67.6 ((CH$_3$)$_2$*C*H), 61.37 (*C*H$_2$OTES), 48.4 (*C*HCHOAc), 44.8 (*C*HCH$_2$), 35.4 (*C*H$_2$CH$_2$OTES), 33.3 (*C*H$_2$CHOTBS), 30.23 (*C*H$_2$C=O), 26.0 (3C; *C*H$_3$CSi), 22.0 (2C; (*C*H$_3$)$_2$CH), 21.4 (*C*H$_3$C=O), 18.28 (*C*Si), 6.9 (3C; *C*H$_3$CH$_2$), 4.5 (3C; *C*H$_2$Si), –4.28 (*C*H$_3$Si), –4.73 (*C*H$_3$Si).

IR (film): ν = 2955, 2929, 2857, 1734, 1472, 1373, 1239, 1174, 1108, 1007, 975, 835, 776, 744, 670 cm^{-1}.

MS (+ESI) m/z (%): 591 (20) [*M*+Na]$^{+}$, 437 (60) [*M*+H–TBSOH]$^{+}$, 377 (100) [*M*+H–TBSOH–AcOH]$^{+}$.

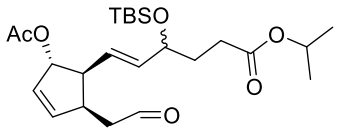
HRMS (+ESI) m/z: calcd for $C_{30}H_{56}O_6Si_2$+Na^{+}: 591.3508 [*M*+Na]$^{+}$, found: 591.3519.

Isopropyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-(2-oxoethyl)cyclopent-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)hex-5-enoate 169

DMSO (42 µL, 0.59 mmol) was added dropwise to a solution of oxalyl chloride (47 µL, 0.55 mmol) in dry DCM (0.8 mL) at –78 °C. The mixture was stirred at –78 °C for 15 min and a solution of **168** (104 mg, 0.183 mmol) in dry DCM (1 mL) was added using a cannula. The mixture was stirred for 40 min and Et$_3$N (142 µL, 1.01 mmol) was added dropwise. The reaction mixture was warmed with stirring to –50 °C over 90 min after which full conversion was indicated by TLC. Satd. NH$_4$Cl solution (2 mL) was added, the biphasic mixture was diluted with DCM to ca 4 mL and water to ca 10 mL and warmed to room temperature with stirring. The layers were separated and the aqueous was extracted with DCM (3×5 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (P/Et$_2$O gradient 9:1 to 4:1) to furnish aldehyde **169** (73 mg, 88%) as

inseparable 2.2:1 mixture of *trans*-/*cis*-**169**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.18 (P/Et_2O 7:3).



trans-**169: dr 2.5:1**

Major C-4 *epimer:*

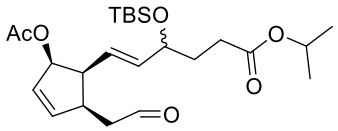
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, $^3J_{H,H}$ = 1.1 Hz, 1H; *H*C=O), 6.01 (ddd, $^3J_{H,H}$ = 5.7, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.85 (dt, $^3J_{H,H}$ = 5.8, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; CH=C*H*CHOAc), 5.62-5.40 (m, 3H; C*H*=C*H*CHOTBS, C*H*OAc), 4.98 (sept, $^3J_{H,H}$ = 6.2 Hz, 1H; C*H*$(CH_3)_2$), 4.15 (q, $^3J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 3.48-3.37 (m, 1H; C*H*CH_2), 2.98 (ddd, $^3J_{H,H}$ = 8.7, 7.6, 4.5 Hz, 1H; C*H*CHOAc), 2.60 (ddd, $^2J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 6.8, 1.0 Hz, 1H; CH*H*CH=O), 2.42-2.31 (m, 2H; CH_2CO_2), 2.38 (ddd, $^2J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 7.8, 1.0 Hz, 1H; C*H*HCH=O), 2.03 (s, 3H; CH_3C=O), 1.83-1.69 (m, 2H; CH_2CHOTBS), 1.22 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (CH_3)$_2$CH), 0.87 (s, 9H; CH_3CSi), 0.01 (s, 6H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.01 (H*C*=O), 173.26 (*C*O_2*i*-Pr), 171.0 (CH_3*C*=O), 139.4 (*C*H=CHCHOAc), 136.8 (*C*H=CHCHOTBS), 130.0 (CH=*C*HCHOAc), 126.9 (CH=*C*HCHOTBS), 83.2 (*C*HOAc), 72.7 (*C*HOTBS), 67.7 ($(CH_3)_2$*C*H), 49.8 (*C*HCHOAc), 45.0 (*C*HCH_2), 41.5 (*C*H_2CH=O), 33.25 (*C*H_2CHOTBS), 30.3 (*C*H_2C=O), 25.9 (3C; *C*H_3CSi), 22.0 (2C; (*C*H_3)$_2$CHO), 21.27 (*C*H_3C=O), 18.27 (*C*Si), –4.29 (*C*H_3Si), –4.74 (*C*H_3Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, $^3J_{H,H}$ = 1.1 Hz, 1H; *H*C=O), 6.01 (ddd, $^3J_{H,H}$ = 5.7, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.85 (dt, $^3J_{H,H}$ = 5.8, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; CH=C*H*CHOAc), 5.53-5.34 (m, 3H; C*H*=C*H*CHOTBS, C*H*OAc), 4.98 (sept, $^3J_{H,H}$ = 6.2 Hz, 1H; C*H*$(CH_3)_2$), 4.15 (q, $^3J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 3.48-3.37 (m, 1H; C*H*CH_2), 2.98 (ddd, $^3J_{H,H}$ = 8.7, 7.6, 4.5 Hz, 1H; C*H*CHOAc), 2.60 (ddd, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 6.7, 1.0 Hz, 1H; CH*H*CH=O), 2.42-2.31 (m, 2H; CH_2CO_2), 2.38 (ddd, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 8.0, 1.0 Hz, 1H; C*H*HCH=O), 2.03 (s, 3H; CH_3C=O), 1.83-1.69 (m, 2H; CH_2CHOTBS), 1.22 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (CH_3)$_2$CH), 0.89 (s, 9H; CH_3CSi), 0.02 (s, 6H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.98 (H*C*=O), 173.32 (*C*O_2*i*-Pr), 171.0 (CH_3*C*=O), 139.3 (*C*H=CHCHOAc), 137.3 (*C*H=CHCHOTBS), 130.30 (CH=*C*HCHOAc), 124.9 (CH=*C*HCHOTBS), 83.4 (*C*HOAc), 72.0 (*C*HOTBS), 67.7 ($(CH_3)_2$*C*H), 49.9 (*C*HCHOAc), 45.1 (*C*HCH_2), 41.8 (*C*H_2CH=O), 33.20 (*C*H_2CHOTBS), 30.22 (*C*H_2C=O), 25.9 (3C; *C*H_3CSi), 22.0 (2C; (*C*H_3)$_2$CHO), 21.27 (*C*H_3C=O), 18.28 (*C*Si), –4.18 (*C*H_3Si), –4.32 (*C*H_3Si).



cis-**169: dr 2.5:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.78 (t, $^{3}J_{H,H}$ = 1.3 Hz, 1H; *H*C=O), 6.09-6.04 (m, 1H; C*H*=CHCHOAc), 5.89 (dt, $^{3}J_{H,H}$ = 5.7, 2.0, Hz, $^{4}J_{H,H}$ = 2.0, Hz, 1H; CH=C*H*CHOAc), 5.53-5.42 (m, 3H; C*H*=C*H*CHOTBS, C*H*OAc), 4.98 (sept, $^{3}J_{H,H}$ = 6.2 Hz, 1H; C*H*$(CH_3)_2$), 4.15 (q, $^{3}J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 3.27-3.06 (m, 2H; C*H*CHOAc, C*H*CH_2), 2.65 (ddd, $^{2}J_{H,H}$ = 9.8 Hz, $^{3}J_{H,H}$ = 6.7, 1.0 Hz, 1H; CH*H*CH=O), 2.51-2.29 (m, 1H; C*H*HCH=O), 2.28 (t, $^{3}J_{H,H}$ = 6.7 Hz, 2H; C*H*$_2$$CO_2$), 2.01 (s, 3H; C*H*$_3$C=O), 1.83-1.69 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^{3}J_{H,H}$ = 6.2 Hz, 6H; $(CH_3)_2$CH), 0.87 (s, 9H; C*H*$_3$CSi), 0.03 (s, 3H; C*H*$_3$Si), 0.00 (s, 3H; C*H*$_3$Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.3 (H*C*=O), 173.26 (CO_2*i*-Pr), 171.5 (CH_3*C*=O), 139.2 (*C*H=CHCHOAc), 137.8 (*C*H=CHCHOTBS), 130.30 (CH=*C*HCHOAc), 127.2 (CH=*C*HCHOTBS), 80.3 (*C*HOAc), 71.6 (*C*HOTBS), 67.7 ($(CH_3)_2$*C*H), 48.0 (*C*HCHOAc), 45.0 (*C*CH_2), 42.3 (*C*H_2CH=O), 33.25 (*C*H_2CHOTBS), 30.17 (*C*H_2C=O), 25.9 (3C; *C*H_3CSi), 21.9 (2C; $(CH_3)_2$CH), 21.27 (*C*H_3C=O), 18.28 (*C*Si), –4.32 (*C*H_3Si), –4.71 (*C*H_3Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, $^{3}J_{H,H}$ = 1.1 Hz, 1H; *H*C=O), 6.01 (ddd, $^{3}J_{H,H}$ = 5.7, 2.3 Hz, $^{4}J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.85 (dt, $^{3}J_{H,H}$ = 5.8, 2.1, Hz, $^{3}J_{H,H}$ = 2.1 Hz; 1H; CH=C*H*CHOAc), 5.62-5.34 (m, 3H; C*H*=C*H*CHOTBS, C*H*OAc), 4.98 (sept, $^{3}J_{H,H}$ = 6.2 Hz, 1H; C*H*$(CH_3)_2$), 4.15 (q, $^{3}J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 3.27-3.06 (m, 2H; C*H*CHOAc, C*H*CH_2), 2.60 (ddd, $^{2}J_{H,H}$ = 9.8 Hz, $^{3}J_{H,H}$ = 6.7, 1.0 Hz, 1H; CH*H*CH=O), 2.43-2.29 (m, 1H; C*H*HCH=O), 2.31 (t, $^{3}J_{H,H}$ = 6.7 Hz, 2H; C*H*$_2$$CO_2$), 2.03 (s, 3H; C*H*$_3$C=O), 1.86-1.67 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^{3}J_{H,H}$ = 6.2 Hz, 6H; $(CH_3)_2$CH), 0.89 (s, 9H; C*H*$_3$CSi), 0.04 (s, 3H; C*H*$_3$Si), 0.02 (s, 3H; C*H*$_3$Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.3 (H*C*=O), 173.32 (CO_2*i*-Pr), 170.5 (CH_3*C*=O), 139.3 (*C*H=CHCHOAc), 137.3 (*C*H=CHCHOTBS), 130.27 (CH=*C*HCHOAc), 125.7 (CH=*C*HCHOTBS), 80.1 (*C*HOAc), 71.8 (*C*HOTBS), 67.7 ($(CH_3)_2$*C*H), 47.6 (*C*HCHOAc), 46.4 (*C*CH_2), 42.5 (*C*H_2CH=O), 33.20 (*C*H_2CHOTBS), 30.17 (*C*H_2C=O), 25.9 (3C; *C*H_3CSi), 21.9 (2C; $(CH_3)_2$CH), 21.32 (*C*H_3C=O), 18.28 (*C*Si), –4.18 (*C*H_3Si), –4.32 (*C*H_3Si).

IR (film): *v* = 2930, 2857, 1728, 1472, 1374, 1238, 1175, 1109, 1015, 979, 836, 777, 676 cm^{-1}.

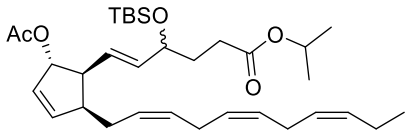
MS (+ESI) m/z (%): 475 (10) [*M*+Na]$^{+}$, 393 (20) [*M*+H–AcOH]$^{+}$, 261 (100) [*M*+H–TBSOH–AcOH]$^{+}$.

HRMS (+ESI) m/z: calcd for $C_{24}H_{40}O_6Si$+Na^{+}: 475.2486 [*M*+Na]$^{+}$, found: 475.2483.

Isopropyl (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)hex-5-enoate 170a

Phosphonium salt **55** (85 mg, 0.166 mmol; prepared by Dr. Valérie Bultel-Poncé by a modified published procedure)[155] was dissolved in dry THF (0.6 mL, degassed by three freeze/pump/thaw cycles) in a flame-dried Schlenk flask under argon. The solution was cooled to –40 °C and NaHMDS (138 µL, 1.0 M in THF, 0.138 mmol) was added dropwise. The bright orange solution was stirred for 10 min, cooled to –78 °C and a solution of aldehyde **169** (25 mg, 0.055 mmol) in dry THF (0.5 mL, degassed) stirred at –78 °C was added using a cannula. The bright orange reaction mixture was stirred for 1 h at this temperature after which a complete conversion was indicated by TLC. The mixture was diluted with PE to ca 8 mL and warmed to room temperature with vigorous stirring. The heterogeneous mixture was filtered through a pad of Celite®, which was washed thoroughly with P and P/Et_2O 4:1. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/TBME HPLC grade 9:1) to furnish pentaene **170a** (28 mg, 81%) as inseparable 2.4:1 mixture of *trans*-/*cis*-**170a**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.80 (P/Et_2O 7:3).



trans-**170a**: **dr 3:1**

Major C-4 *epimer:*

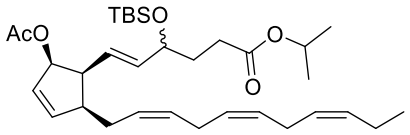
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (dt, $^3J_{H,H}$ = 5.7, 1.6 Hz, $^4J_{H,H}$ = 1.6 Hz, 1H; C*H*=CHCHOAc), 5.81 (dt, $^3J_{H,H}$ = 5.8, 1.6 Hz, $^4J_{H,H}$ = 1.6 Hz, 1H; CH=C*H*CHOAc), 5.57-5.50 (m, 2H; C*H*=C*H*CHOTBS), 5.51-5.42 (m, 7H; C*H*=C*H*z, C*H*OAc), 4.99 (sept, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH_3)$_2$), 4.16 (q, $^3J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 2.95-2.83 (m, 2H; C*H*CHOAc, C*H*CH_2), 2.84-2.69 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.36-2.25 (m, 2H; C*H*$_2CO_2$), 2.23-2.15 (m, 1H; C*H*HCH=CH_Z), 2.07 (quint, $^3J_{H,H}$ = 7.8 Hz, 2H; C*H*$_2CH_3$), 2.03 (s, 3H; C*H*$_3$C=O), 2.00-1.92 (m, 1H; CH*H*CH=CH_Z), 1.82-1.69 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3$)$_2$CH), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$), 0.88 (s, 9H; C*H*$_3$CSi), 0.04 (s, 3H, C*H*$_3$Si), 0.02 (s, 3H, C*H*$_3$Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (*C*O_2*i*-Pr), 171.2 (CH_3*C*=O), 140.2 (*C*H=CHCHOAc), 136.1 (*C*H=CHCHOTBS), 132.2 (*C*HCH_2CH_3), 129.6 (*C*H=CH_Z), 129.4 (CH=CHCHOAc), 128.8 (*C*H=CH_Z), 128.00 (3C; *C*H=*C*H_Z), 127.2 (CH=*C*HCHOTBS), 83.8 (*C*HOAc), 72.2 (*C*HOTBS), 67.6 ((CH_3)$_2$*C*H), 50.8 (*C*HCHOAc), 47.7 (*C*HCH_2), 33.4 (*C*H_2CHOTBS), 30.4 (*C*H_2C=O), 29.1 (CH*C*H_2CH=CH), 26.0 (3C; *C*H_3CSi), 25.9 (CH=CH*C*H_2CH=CH), 25.7 (CH=CH*C*H_2CH=CH), 22.0 (2C; (*C*H_3)$_2$CH), 21.4(*C*H_3C=O), 20.7 (CH_3*C*H_2), 18.3 (*C*Si), 14.5 (C*H*$_3$CH$_2$), –4.18 (*C*H_3Si), –4.3 (*C*H_3Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (dt, $^{3}J_{H,H}$ = 5.7, 1.6 Hz, $^{4}J_{H,H}$ = 1.6 Hz, 1H; C*H*=CHCHOAc), 5.81 (dt, $^{3}J_{H,H}$ = 5.8, 1.6 Hz, $^{4}J_{H,H}$ = 1.6 Hz, 1H; CH=C*H*CHOAc), 5.68-5.46 (m, 2H; C*H*=C*H*CHOTBS), 5.45-5.22 (m, 7H; C*H*=C*H*z, C*H*OAc), 4.99 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.16 (q, $^{3}J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 2.95-2.83 (m, 2H; C*H*CHOAc, C*H*CH_2), 2.84-2.69 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.37-2.24 (m, 2H; C*H*$_2CO_2$), 2.25-2.13 (m, 1H; C*H*HCH=CH_Z), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H*$_2CH_3$), 2.03 (s, 3H; C*H*$_3$C=O), 2.00-1.92 (m, 1H; CH*H*CH=CH_Z), 1.82-1.69 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^{3}J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3$)$_2$CH), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$), 0.88 (s, 9H; C*H*$_3$CSi), 0.05 (s, 3H, C*H*$_3$Si), 0.04 (s, 3H, C*H*$_3$Si).

Distinct ^{13}C NMR resonances (75 MHz, $CDCl_3$): δ = 173.4 (*C*O_2*i*-Pr), 171.2 (CH_3*C*=O), 140.1 (*C*H=CHCHOAc), 136.9 (*C*H=CHCHOTBS), 132.2 (*C*HCH_2CH_3), 127.2 (CH=*C*HCHOTBS), 83.9 (*C*HOAc), 72.4 (*C*HOTBS), 67.6 ($(CH_3)_2$*C*H), 50.8 (*C*HCHOAc), 47.9 (*C*HCH_2), 33.4 (*C*H_2CHOTBS), 30.2 (*C*H_2C=O), 29.1 (CH*C*H_2CH=CH), 26.0 (3C; *C*H_3CSi), 25.9 (CH=CH*C*H_2CH=CH), 25.7 (CH=CH*C*H_2CH=CH), 22.0 (2C; (*C*H_3)$_2$CH), 21.4 (*C*H_3C=O), 20.7 (CH_3*C*H_2), 18.3 (*C*Si), 14.5 (C*H*$_3CH_2$), –4.18 (*C*H_3Si), –4.3 (*C*H_3Si).



cis-**170a**: **dr 1.5:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.11-6.06 (m, 1H; C*H*=CHCHOAc), 5.85 (dt, $^{3}J_{H,H}$ = 5.8, 2.0 Hz, $^{4}J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*CHOAc), 5.64-5.46 (m, 2H; C*H*=C*H*CHOTBS), 5.45-5.22 (m, 7H; C*H*=C*H*z, C*H*OAc), 4.99 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*$(CH_3)_2$), 4.16 (q, $^{3}J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 3.12-3.02 (m, 1H; C*H*CHOAc), 2.84-2.69 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.73-2.61 (m, 1H; C*H*CH_2), 2.37-2.24 (m, 2H; C*H*$_2CO_2$), 2.25-2.13 (m, 1H; C*H*HCH=CH_Z), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H*$_2CH_3$), 2.03 (s, 3H; C*H*$_3$C=O), 2.00-1.92 (m, 1H; CH*H*CH=CH_Z), 1.82-1.69 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^{3}J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3$)$_2$CH), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$), 0.89 (s, 9H; C*H*$_3$CSi), 0.05 (s, 3H, C*H*$_3$Si), 0.03 (s, 3H, C*H*$_3$Si).

Distinct ^{13}C NMR resonances (75 MHz, $CDCl_3$): δ = 173.4 (*C*O_2*i*-Pr), 170.7 (CH_3*C*=O), 140.6 (*C*H=CHCHOAc), 136.5 (*C*H=CHCHOTBS), 132.2 (*C*HCH_2CH_3), 126.1 (CH=*C*HCHOTBS), 80.8 (*C*HOAc), 72.2 (*C*HOTBS), 67.6 ($(CH_3)_2$*C*H),), 48.7 (*C*HCHOAc), 48.5 (*C*HCH_2), 33.4 (*C*H_2CHOTBS), 30.3 (*C*H_2C=O), 29.1 (CH*C*H_2CH=CH), 26.0 (*C*H_3CSi), 25.9 (CH=CH*C*H_2CH=CH), 25.7 (CH=CH*C*H_2CH=CH), 22.0 (2C; (*C*H_3)$_2$CH), 21.4 (*C*H_3C=O), 20.7 (CH_3*C*H_2), 18.3 (*C*Si), 14.5 (C*H*$_3CH_2$), –4.15 (*C*H_3Si), –4.7 (*C*H_3Si).

The following ^{13}C NMR resonances (*C*H=*C*H) could not be unambiguously assigned: δ = 129.3, 129.1, 128.8 (2C), 128.7, 128.3, 128.2, 128.00 (3C), 127.96 (2C).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.12-6.07 (m, 1H; C*H*=CHCHOAc), 5.91-5.86 (m, 1H;

CH=C*H*CHOAc), 5.64-5.46 (m, 2H; C*H*=C*H*CHOTBS), 5.45-5.22 (m, 7H; C*H*=C*H*z, C*H*OAc), 4.99 (sept, $^{3}J_{H,H}$ = 6.3 Hz, 1H; C*H*(CH_3)$_2$), 4.24-4.16 (m, 1H; C*H*OTBS), 3.07-3.01 (m, 1H; C*H*CHOAc), 2.84-2.69 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.69-2.61 (m, 1H; C*H*CH_2), 2.37-2.24 (m, 2H; C*H*$_2CO_2$), 2.25-2.13 (m, 1H; C*H*HCH=CH_Z), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H*$_2CH_3$), 2.01 (s, 3H; C*H*$_3$C=O), 2.00-1.92 (m, 1H; CH*H*CH=CH_Z), 1.82-1.69 (m, 2H; C*H*$_2$CHOTBS), 1.22 (d, $^{3}J_{H,H}$ = 6.2 Hz, 6H; (C*H*$_3$)$_2$CH), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$), 0.89 (s, 9H; C*H*$_3$CSi), 0.05 (s, 3H, C*H*$_3$Si), 0.03 (s, 3H, C*H*$_3$Si).

The minor epimer was not detectable by ^{13}C NMR spectroscopy.

IR (film): ν = 3013, 2958, 2930, 2857, 1734, 1473, 1464, 1238, 1175, 1110, 976, 837, 777, 668 cm^{-1}.

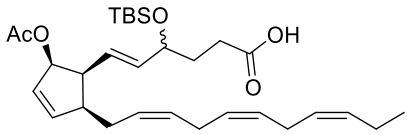
MS (+ESI) m/z (%): 581 (10) [*M*+Na]$^+$, 367 (100) [*M*+H–TBSOH–AcOH]$^+$.

HRMS (+ESI) m/z: calcd for $C_{33}H_{54}O_5Si$+Na$^+$: 581.3633 [*M*+Na]$^+$, found: 581.3627.

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-((1*S*,5*S*)-2-hydroxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)hex-5-enoic acid 171a

A solution of KOH (8 mg, 143µmol) in MeOH (200 µL) was added to ester **170a** (20 mg, 36 µmol) and the solution was stirred at room temperature for three days until both starting material **170a** and a partially deprotected compound (R_f = 0.54 in P/EtOAc 1:1 with 0.5% formic acid) were consumed as indicated by TLC. The reaction mixture was acidified with a few drops of satd. $NaHSO_4$ solution to pH 2; diluted with water to ca 2 mL and the mixture was extracted with EtOAc (HPLC grade; 3×2 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc (HPLC grade) and filtered through a small plug of silica, which was washed thoroughly with several volumes of EtOAc (HPLC grade; ca 5 mL). The filtrate was evaporated under reduced pressure to obtain acid **171a** (14 mg, 82%) as inseparable 2.4:1 mixture of *trans*-/*cis*-**171a**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.42 (P/EtOAc 1:1 with 0.5% formic acid).



trans-**171a**: **dr 3:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94 (ddd, $^{3}J_{H,H}$ = 5.8, 1.6 Hz, $^{4}J_{H,H}$ = 1.4 Hz, 1H; C*H*=CHCHOH), 5.79 (dt, $^{3}J_{H,H}$ = 5.8, 1.6 Hz, $^{4}J_{H,H}$ = 1.6 Hz, 1H; CH=C*H*CHOH), 5.74-5.49 (m, 2H; C*H*=C*H*CHOTBS), 5.50-5.23 (m, 6H; C*H*=C*H*z), 4.74-4.62 (m, 1H; C*H*OH), 4.16 (q, $^{3}J_{H,H}$ = 5.7 Hz, 1H; C*H*OTBS), 2.97-2.79 (m, 1H; C*H*CH_2), 2.84-2.69 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.64 (dt, $^{3}J_{H,H}$ = 8.3, 6.1 Hz, 1H; C*H*CHOH), 2.52-2.38 (m, 2H; C*H*$_2CO_2$), 2.27-2.15 (m, 1H; C*H*HCH=CH_Z), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H*$_2CH_3$), 1.98-1.77 (m, 3H; C*H*$_2$CHOTBS, CH*H*CH=CH_Z), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$), 0.88 (s, 9H; C*H*$_3$CSi), 0.06 (s, 3H, C*H*$_3$Si), 0.04 (s, 3H, C*H*$_3$Si).

The O*H* and COO*H* resonances were not detected.

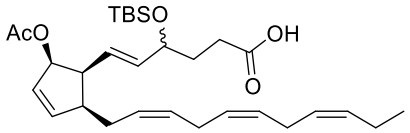
^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.38 (*C*=O), 138.0 (*C*H=CHCHOH), 135.8 (*C*H=CHCHOTBS), 132.86 (CH=*C*HCHOH), 132.17 (*C*HCH$_2$CH$_3$), 129.22 (2C; *C*H=CH$_Z$), 129.18 (CH=*C*HCHOTBS), 128.72 (*C*H=CH$_Z$), 128.1 (*C*H=CH$_Z$), 128.01 (*C*H=CH$_Z$), 81.7 (*C*HOH), 72.9 (*C*HOTBS), 55.4 (*C*HCHOH), 48.24 (*C*HCH$_2$), 32.9 (*C*H$_2$CHOTBS), 29.8 (*C*H$_2$C=O), 29.4 (CH*C*H$_2$CH=CH), 26.0 (3C; *C*H$_3$CSi), 25.83 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (CH*C*H$_2$CH$_3$), 18.3 (*C*Si), 14.4 (*C*H$_3$CH$_2$CH), –4.1 (*C*H$_3$Si), –4.7 (*C*H$_3$Si).

Minor C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.97-5.92 (m, 1H; C*H*=CHCHOH), 5.84-5.76 (m; CH=C*H*CHOH), 5.74-5.49 (m, 2H; C*H*=C*H*CHOTBS), 5.50-5.23 (m, 6H; C*H*=C*H*z), 4.74-4.62 (m, 1H; C*H*OH), 4.28 (q, $^{3}J_{H,H}$ = 6.0 Hz, 1H; C*H*OTBS), 2.97-2.79 (m, 1H; C*H*CH$_2$), 2.84-2.69 (m, 4H; CH=CHC*H$_2$*CH=CH), 2.73-2.59 (dt, $^{3}J_{H,H}$ = 8.3, 6.1 Hz, 1H; C*H*CHOH), 2.52-2.38 (m, 2H; C*H$_2$*CO$_2$), 2.27-2.15 (m, 1H; C*H*HCH=CH$_Z$), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H$_2$*CH$_3$), 1.98-1.77 (m, 3H; C*H$_2$*CHOTBS, CH*H*CH=CH$_Z$), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H$_3$*CH$_2$), 0.88 (s, 9H; C*H$_3$*CSi), 0.06 (s, 3H, C*H$_3$*Si), 0.04 (s, 3H, C*H$_3$*Si).

The O*H* and COO*H* resonances were not detected.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.44 (*C*=O), 138.1 (*C*H=CHCHOH), 135.4 (*C*H=CHCHOTBS), 132.8 (CH=*C*HCHOH), 132.17 (*C*HCH$_2$CH$_3$), 129.24 (2C; *C*H=CH$_Z$), 128.75 (*C*H=CH$_Z$), 127.97 (2C; *C*H=CH$_Z$), 127.4 (CH=*C*HCHOTBS), 81.8 (*C*HOH), 71.6 (*C*HOTBS), 55.3 (*C*HCHOH), 48.34 (*C*HCH$_2$), 33.0 (*C*H$_2$CHOTBS), 30.0 (*C*H$_2$C=O), 29.6 (CH*C*H$_2$CH=CH), 26.0 (3C; *C*H$_3$CSi), 25.83 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (CH*C*H$_2$CH$_3$), 18.3 (*C*Si), 14.4 (*C*H$_3$CH$_2$CH), –4.3 (*C*H$_3$Si), –4.8 (*C*H$_3$Si).



cis-**171a**: **dr 1.5:1**

Major C-4 *epimer:*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.99 (dt, $^{3}J_{H,H}$ = 5.3, 2.5 Hz, $^{4}J_{H,H}$ = 2.5 Hz, 1H; C*H*=CHCHOH), 5.88 (ddd, $^{3}J_{H,H}$ = 5.6, 2.0 Hz, $^{4}J_{H,H}$ = 1.8 Hz, 1H; CH=C*H*CHOH), 5.74-5.49 (m, 2H; C*H*=C*H*CHOTBS), 5.50-5.23 (m, 6H; C*H*=C*H*z), 4.70-4.58 (m, 1H; C*H*OH), 4.25-4.11 (m, 1H; C*H*OTBS), 2.97-2.82 (m, 1H; C*H*CHOH), 2.84-2.69 (m, 4H; CH=CHC*H$_2$*CH=CH), 2.71-2.58 (m, 1H; *C*HCH$_2$), 2.52-2.38 (m, 2H; C*H$_2$*CO$_2$), 2.18-2.02 (m, 2H; C*H$_2$*CH=CH$_Z$), 2.07 (quint, $^{3}J_{H,H}$ = 7.8 Hz, 2H; C*H$_2$*CH$_3$), 1.98-1.77 (m, 2H; C*H$_2$*CHOTBS), 0.97 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; C*H$_3$*CH$_2$), 0.88 (s, 9H; C*H$_3$*CSi), 0.06 (s, 3H, C*H$_3$*Si), 0.05 (s, 3H, C*H$_3$*Si).

The O*H* and COO*H* resonances were not detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.59 (*C*=O), 138.65 (*C*H=CHCHOH), 137.2 (*C*H=CHCHOTBS), 132.8 (CH=*C*HCHOH), 132.19 (*C*HCH$_2$CH$_3$), 129.14 (*C*H=CH$_Z$), 128.68 (2C; *C*H=CH$_Z$), 128.2 (2C; *C*H=CH$_Z$), 127.15 (CH=*C*HCHOTBS), 78.5 (*C*HOH), 72.7 (*C*HOTBS), 50.4 (*C*HCHOH), 48.19 (*C*HCH$_2$), 32.4 (*C*H$_2$CHOTBS), 30.3 (*C*H$_2$C=O), 29.8 (CH*C*H$_2$CH=CH),

26.0 (3C; *C*H_3CSi), 25.9 (CH=CH*C*H_2CH=CH), 25.81 (CH=CH*C*H_2CH=CH), 20.7 (CH*C*H_2CH$_3$), 18.3 (*C*Si), 14.4 (*C*H_3CH$_2$CH), –4.3 (*C*H_3Si), –4.7 (*C*H_3Si).

Minor C-4 *epimer*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.04-5.94 (m, 1H; C*H*=CHCHOH), 5.93-5.83 (m, 1H; CH=C*H*CHOH), 5.74-5.49 (m, 2H; C*H*=C*H*CHOTBS), 5.50-5.23 (m, 6H; C*H*=C*H*z), 4.70-4.58 (m, 1H; C*H*OH), 4.32-4.23 (m, 1H; C*H*OTBS), 2.97-2.82 (m, 1H; C*H*CHOH), 2.84-2.69 (m, 4H; CH=CHC*H$_2$*CH=CH), 2.71-2.58 (m, 1H; *C*HCH$_2$), 2.52-2.38 (m, 2H; C*H$_2$*CO$_2$), 2.18-2.02 (m, 2H; C*H$_2$*CH=CH$_Z$), 2.07 (quint, $^3J_{H,H}$ = 7.8 Hz, 2H; C*H$_2$*CH$_3$), 1.98-1.77 (m, 2H; C*H$_2$*CHOTBS), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H$_3$*CH$_2$), 0.88 (s, 9H; C*H$_3$*CSi), 0.06 (s, 3H, C*H$_3$*Si), 0.05 (s, 3H, C*H$_3$*Si).

The O*H* and COO*H* resonances were not detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.61 (*C*=O), 138.59 (*C*H=CHCHOH), 137.0 (*C*H=CHCHOTBS), 132.92 (CH=*C*HCHOH), 132.19 (*C*HCH$_2$CH$_3$), 129.31 (*C*H=CH$_Z$), 129.22 (*C*H=CH$_Z$), 128.65 (2C; *C*H=CH$_Z$), 128.3 (*C*H=CH$_Z$), 127.18 (CH=*C*HCHOTBS), 78.4 (*C*HOH), 72.1 (*C*HOTBS), 50.3 (*C*HCHOH), 48.30 (*C*HCH$_2$), 32.8 (*C*H$_2$CHOTBS), 30.4 (*C*H$_2$C=O), 30.0 (CH*C*H$_2$CH=CH), 26.0 (3C; *C*H$_3$CSi), 25.9 (CH=CH*C*H$_2$CH=CH), 25.81 (CH=CH*C*H$_2$CH=CH), 20.7 (CH*C*H$_2$CH$_3$), 18.3 (*C*Si), 14.4 (*C*H$_3$CH$_2$CH), –4.3 (*C*H$_3$Si), –4.8 (*C*H$_3$Si).

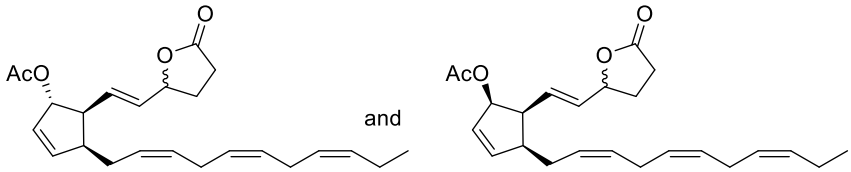
IR (film): *v* = 3700-2400 (v br), 3373 (br), 3012, 2957, 2927, 2856, 1709, 1463, 1361, 1253, 1083, 978, 938, 836, 776, 742 cm^{-1}.

MS (–ESI) m/z (%): 473 (100) [*M*–H]$^-$.

HRMS (–ESI) m/z: calcd for $C_{28}H_{46}O_4Si$–H$^+$: 473.3093 [*M*–H]$^-$, found: 473.3103.

5-((*E*)-2-((1*S*,5*S*)-2-Acetoxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)vinyl)dihydrofuran-2(3*H*)-one 170b and (*E*)-6-((1*S*,5*S*)-2-acetoxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)-4-hydroxyhex-5-enoic acid 170c

Silyl ether **170a** (25 mg, 45 μmol) was dissolved in dry THF (0.5 mL) and TBAF (67 μL, 1.0 M in THF, 67 μmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 4 h. More TBAF (22 μL, 1.0 M in THF, 22 μmol) was added at 0 °C and the reaction mixture was warmed to room temperature and stirred for 8 h. The mixture was diluted with TBME to ca 8 mL, satd. NH_4Cl solution (8 mL) was added and the biphasic mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous was extracted with TBME (3×8 mL) and EtOAc (2×8 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/MTBE HPLC grade, gradient 7:3 to 1:1) to furnish lactone **170b** (11 mg, 64%) as inseparable 3:1 mixture of *trans*-/*cis*-**170b**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil, along with free acid **170c** (2 mg, 11%) as inseparable 1.9:1 mixture of *trans*-/*cis*-**170c**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil, which quickly lactonized back to **170b**.



trans-**170b**: **dr 3.8:1** *cis*-**170b**: **dr 2:1**

R_f = 0.20 (P/Et_2O 1:1).

trans-**170b**, *major* C-4 *epimer:*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.03 (ddd, $^3J_{H,H}$ = 5.8, 2.2 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H; C*H*=CHCHOAc), 5.86-5.74 (m, 2H; CH=C*H*CHOAc, C*H*=CHCHCH_2CH_2), 5.63 (dd, $^3J_{H,H}$ = 15.1, 7.3 Hz, 1H; CH=C*H*CHCH_2CH_2), 5.60-5.54 (m, 1H; C*H*OAc), 5.46-5.26 (m, 6H; C*H*=CH_Z), 4.92 (dtd, $^3J_{H,H}$ = 7.8, 6.8 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*CH_2CH_2), 3.02-2.93 (m, 1H; C*H*CH_2CH=CH), 2.98-2.89 (m, 1H; C*H*CHOAc), 2.83-2.73 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.57-2.50 (m, 2H; C*H*$_2$C=O), 2.44-2.35 (m, 1H; CH*H*CH_2C=O), 2.16-2.09 (m, 3H; CHCH*H*CH=CH, CH_3C*H*$_2$), 2.08-1.93 (m, 2H; C*H*HCH_2C=O, CHC*H*HCH=CH), 2.04 (s, 3H; C*H*$_3$C=O), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.99 (CH_2*C*=O), 171.11 (CH_3*C*=O), 140.3 (*C*H=CHCHOAc), 132.6 (*C*H=CHCHCH_2CH_2), 132.2 (CH=C*H*CH_2CH_3), 130.36 (CH=*C*HCHCH_2CH_2), 129.6 (CH=*C*H$_Z$), 129.2 (CH=*C*HCHOAc), 128.82 (CH=*C*H$_Z$), 127.80 (CH=*C*H$_Z$), 127.6 (CH=*C*H$_Z$), 127.11 (CH=*C*H$_Z$), 83.50 (*C*HOAc), 80.7 (*C*HCH_2CH_2), 50.6 (*C*HCHOAc), 47.80 (*C*H$_2$CH=CH), 28.90 (CH*C*H$_2$CH=CH), 28.79 (*C*H$_2CH_2$C=O), 28.72 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 21.4 (*C*H$_3$C=O), 20.7 (*C*H$_2CH_3$), 14.4 (CH_2*C*H$_3$).

trans-**170b**, *minor* C-4 *epimer:*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.04-6.01 (m, 1H; C*H*=CHCHOAc), 5.86-5.74 (m, 2H; CH=C*H*CHOAc, C*H*=CHCHCH_2CH_2), 5.65 (dd, $^3J_{H,H}$ = 15.1, 7.3 Hz, 1H; CH=C*H*CHCH_2CH_2), 5.60-5.54 (m, 1H; C*H*OAc), 5.46-5.26 (m, 6H; C*H*=CH_Z), 4.92 (dtd, $^3J_{H,H}$ = 7.8, 6.8 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*CH_2CH_2), 3.02-2.93 (m, 1H; C*H*CH_2CH=CH), 2.98-2.89 (m, 1H; C*H*CHOAc), 2.83-2.73 (m, 4H; CH=CHC*H*$_2$CH=CH), 2.57-2.50 (m, 2H; C*H*$_2$C=O), 2.44-2.35 (m, 1H; CH*H*CH_2C=O), 2.16-2.09 (m, 3H; CHCH*H*CH=CH, CH_3C*H*$_2$), 2.08-1.93 (m, 2H; C*H*HCH_2C=O, CHC*H*HCH=CH), 2.01 (s, 3H; C*H*$_3$C=O), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.98 (CH_2*C*=O), 171.11 (CH_3*C*=O), 140.6 (*C*H=CHCHOAc), 132.2 (CH=C*H*CH_2CH_3), 131.8 (*C*H=CHCHCH_2CH_2), 130.37 (CH=*C*HCHCH_2CH_2), 129.5 (CH=*C*H$_Z$), 129.3 (CH=*C*HCHOAc), 128.84 (CH=*C*H$_Z$), 127.77 (CH=*C*H$_Z$), 127.7 (CH=*C*H$_Z$), 127.13 (CH=*C*H$_Z$), 83.45 (*C*HOAc), 80.6 (*C*HCH_2CH_2), 50.5 (*C*HCHOAc), 47.84 (*C*H$_2$CH=CH), 28.97 (CH*C*H$_2$CH=CH), 28.81 (*C*H$_2CH_2$C=O), 28.70 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 21.4 (*C*H$_3$C=O), 20.7 (*C*H$_2CH_3$), 14.4 (CH_2*C*H$_3$).

cis-**170b**, *major* C-4 *epimer:*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (ddd, $^3J_{H,H}$ = 5.7, 2.3 Hz, $^4J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOAc), 5.86-5.74 (m, 2H; CH=C*H*CHOAc, C*H*=CHCHCH_2CH_2), 5.63 (dd, $^3J_{H,H}$ = 15.4,

6.9 Hz, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.60-5.54 (m, 1H; C*H*OAc), 5.46-5.26 (m, 6H; C*H*=C*H*$_Z$), 4.96-4.89 (m, 1H; C*H*CH$_2$CH$_2$), 3.16 (dt, $^3J_{H,H}$ = 10.2, 6.7 Hz, 1H; C*H*CHOAc), 2.83-2.67 (m, 5H; CH=CHC*H*$_2$CH=CH, C*H*CH$_2$CH=CH), 2.57-2.51 (m, 2H; C*H*$_2$C=O), 2.42-2.31 (m, 1H; CH*H*CH$_2$C=O), 2.21-2.10 (m, 3H; CHCH*H*CH=CH, CH$_3$C*H*$_2$), 2.08-1.93 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 2.04 (s, 3H; C*H*$_3$C=O), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 176.99 (CH$_2$*C*=O), 171.11 (CH$_3$*C*=O), 140.1 (*C*H=CHCHOAc), 132.3 (CH=C*H*CH$_2$CH$_3$), 131.2 (*C*H=CHCHCH$_2$CH$_2$), 130.6 (CH=*C*HCHCH$_2$CH$_2$), 129.4 (CH=*C*H$_Z$), 128.9 (CH=*C*HCHOAc), 128.7 (CH=*C*H$_Z$), 127.92 (CH=*C*H$_Z$), 127.90 (CH=*C*H$_Z$), 127.06 (CH=*C*H$_Z$), 80.54 (*C*HCH$_2$CH$_2$), 80.3 (*C*HOAc), 48.36 (*C*HCHOAc), 48.32 (*C*HCH$_2$CH=CH), 29.84 (CH*C*H$_2$CH=CH), 28.87 (*C*H$_2$CH$_2$C=O), 28.6 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 21.24 (*C*H$_3$C=O), 20.7 (*C*H$_2$CH$_3$), 14.4 (CH$_2$*C*H$_3$).

cis-**170b**, *minor* C-4 *epimer:*

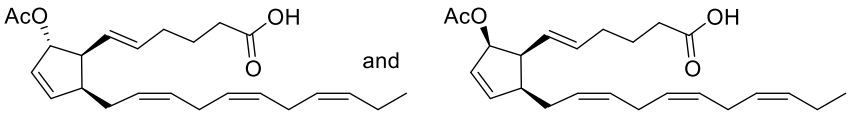
^{1}H NMR (400 MHz, CDCl$_3$) δ = 6.08-6.05 (m, 1H; C*H*=CHCHOAc), 5.86-5.74 (m, 2H; CH=C*H*CHOAc, C*H*=CHCHCH$_2$CH$_2$), 5.63 (dd, $^3J_{H,H}$ = 15.2, 6.9 Hz, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.60-5.54 (m, 1H; C*H*OAc), 5.46-5.26 (m, 6H; C*H*=C*H*$_Z$), 4.96-4.89 (m, 1H; C*H*CH$_2$CH$_2$), 3.17 (dt, $^3J_{H,H}$ = 10.1, 6.7 Hz, 1H; C*H*CHOAc), 2.83-2.67 (m, 5H; CH=CHC*H*$_2$CH=CH, C*H*CH$_2$CH=CH), 2.57-2.50 (m, 2H; C*H*$_2$C=O), 2.42-2.31 (m, 1H; CH*H*CH$_2$C=O), 2.21-2.10 (m, 3H; CHCH*H*CH=CH, CH$_3$C*H*$_2$), 2.08-1.93 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 2.02 (s, 3H; C*H*$_3$C=O), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 176.98 (CH$_2$*C*=O), 171.07 (CH$_3$*C*=O), 140.2 (*C*H=CHCHOAc), 132.3 (CH=C*H*CH$_2$CH$_3$), 131.1 (*C*H=CHCHCH$_2$CH$_2$), 130.3 (CH=*C*HCHCH$_2$CH$_2$), 129.5 (CH=*C*H$_Z$), 129.1 (CH=*C*HCHOAc), 128.84 (CH=*C*H$_Z$), 127.89 (CH=*C*H$_Z$), 127.77 (CH=*C*H$_Z$), 127.07 (CH=*C*H$_Z$), 80.46 (*C*HCH$_2$CH$_2$), 80.2 (*C*HOAc), 48.40 (*C*HCHOAc), 48.29 (*C*HCH$_2$CH=CH), 29.82 (CH*C*H$_2$CH=CH), 28.81 (*C*H$_2$CH$_2$C=O), 28.4 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 21.19 (*C*H$_3$C=O), 20.7 (*C*H$_2$CH$_3$), 14.4 (CH$_2$*C*H$_3$).

IR (film): *v* = 3010, 2963, 2932, 1776, 1733, 1541, 1507, 1457, 1422, 1372, 1327, 1239, 1176, 1119, 1013, 975, 914, 725, 606 cm^{-1}.

MS (+ESI) m/z (%): 407 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for C$_{24}$H$_{32}$O$_4$+Na$^+$: 407.2193 [*M*+Na]$^+$, found: 407.2195.



trans-**170c**: **dr 1.8:1** *cis*-**170c**: **dr 2:1**

R_f = 0.12 (P/Et$_2$O 1:1).

trans-**170c**, *major* C-4 *epimer:*

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.04 (ddd, $^3J_{H,H}$ = 5.8, 2.2 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H; C*H*=CHCHOAc), 5.79 (dt, $^3J_{H,H}$ = 5.7, 1.8 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H; CH=C*H*CHOAc), 5.68 (dd, $^3J_{H,H}$ = 15.5, 8.3 Hz, 1H; CH=C*H*CHOH), 5.63-5.55 (m, 2H; C*H*=CHCHOH, C*H*OAc), 5.46-5.25

(m, 6H; C*H*=C*H*$_Z$), 4.18 (dt, $^3J_{H,H}$ = 8.2, 6.5 Hz, 1H; C*H*OH), 2.97-2.85 (m, 2H; C*H*CHOAc, C*H*CH_2CH=CH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.46 (t, $^3J_{H,H}$ = 7.3 Hz, 2H; C*H*$_2$C=O), 2.20-2.13 (m, 1H; CHCH*H*CH=CH), 2.12-1.99 (m, 2H; C*H*$_2$$CH_3$), 2.06-1.97 (m, 1H; CHC*H*HCH=CH), 2.05 (s, 3H; C*H*$_3$C=O), 1.87 (dt, $^3J_{H,H}$ = 6.9, 7.2 Hz, 2H; C*H*$_2$$CH_2$C=O), 1.62 (br s, 1H; O*H*), 0.98 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$$CH_2$).
The COO*H* resonance was not detected.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (*C*OOH), 171.5 (CH_3*C*=O; HMBC determination), 140.6 (*C*H=CHCHOAc), 135.3 (*C*H=CHCHOH), 132.3 (CH_3CH_2*C*H=CH), 129.41 (CH=*C*HCHOH), 129.37 (CH=*C*H$_Z$), 129.2 (CH=*C*H$_Z$), 128.80 (CH=*C*HCHOAc), 128.01 (CH=*C*H$_Z$), 127.9 (CH=*C*H$_Z$), 127.1 (CH=*C*H$_Z$), 83.9 (*C*HOAc), 72.3 (*C*HOH), 50.8 (*C*HCHOAc), 47.8 (*C*HCH_2CH=CH), 32.0 (*C*H_2CH_2C=O), 30.6 (*C*H_2C=O), 28.9 (CH*C*H_2CH=CH), 25.9 (CH=CH*C*H_2CH=CH), 25.7 (CH=CH*C*H_2CH=CH), 21.5 (*C*H_2CH_3), 20.4 (*C*H_3C=O), 14.4 (CH_2*C*H_3).
trans-**170c**, *minor* C-4 *epimer:*
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06-6.00 (m, 1H; C*H*=CHCHOAc), 5.87-5.81 (m; CH=C*H*CHOAc), 5.75-5.53 (m, 3H; C*H*=C*H*CHOH, C*H*OAc), 5.46-5.25 (m, 6H; C*H*=C*H*$_Z$), 4.24-4.17 (m, 1H; C*H*OH), 2.97-2.85 (m, 2H; C*H*CHOAc, C*H*CH_2CH=CH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.49 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H*$_2$C=O), 2.20-2.13 (m, 1H; CHCH*H*CH=CH), 2.12-1.99 (m, 2H; C*H*$_2$$CH_3$), 2.06-1.97 (m, 1H; CHC*H*HCH=CH), 2.04 (s, 3H; C*H*$_3$C=O), 1.87 (dt, $^3J_{H,H}$ = 6.9, 7.3 Hz, 2H; C*H*$_2$$CH_2$C=O), 1.62 (br s, 1H; O*H*), 0.98 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$$CH_2$).
The COO*H* resonance was not detected.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (*C*OOH), 171.5 (CH_3*C*=O; HMBC determination), 140.5 (*C*H=CHCHOAc), 135.2 (*C*H=CHCHOH), 132.2 (CH_3CH_2*C*H=CH), 129.41 (CH=*C*HCHOH), 129.3 (CH=*C*H$_Z$), 129.1 (CH=*C*H$_Z$), 128.79 (CH=*C*HCHOAc), 127.98 (CH=*C*H$_Z$), 127.9 (CH=*C*H$_Z$), 127.1 (CH=*C*H$_Z$), 84.0 (*C*HOAc), 71.9 (*C*HOH), 50.8 (*C*HCHOAc), 47.9 (*C*HCH_2CH=CH), 31.8 (*C*H_2CH_2C=O), 30.5 (*C*H_2C=O), 29.0 (CH*C*H_2CH=CH), 25.9 (CH=CH*C*H_2CH=CH), 25.7 (CH=CH*C*H_2CH=CH), 21.5 (*C*H_2CH_3), 20.4 (*C*H_3C=O), 14.4 (CH_2*C*H_3).
cis-**170c**, *major* C-4 *epimer:*
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (dd, $^3J_{H,H}$ = 5.5, 2.2 Hz, 1H; C*H*=CHCHOAc), 5.86-5.82 (m; CH=C*H*CHOAc), 5.75-5.53 (m, 3H; C*H*=C*H*CHOH, C*H*OAc), 5.46-5.25 (m, 6H; C*H*=C*H*$_Z$), 4.22-4.14 (m, 1H; C*H*OH), 3.15-3.04 (m, 1H; C*H*CHOAc), 2.83-2.63 (m, 5H; CH=CHC*H*$_2$CH=CH, C*H*CH_2CH=CH), 2.47 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H*$_2$C=O), 2.20-2.13 (m, 1H; CHCH*H*CH=CH), 2.12-1.99 (m, 2H; C*H*$_2$$CH_3$), 2.06-1.97 (m, 1H; CHC*H*HCH=CH), 2.04 (s, 3H; C*H*$_3$C=O), 1.92-1.82 (dt, $^3J_{H,H}$ = 6.9, 7.3 Hz, 2H; C*H*$_2$$CH_2$C=O), 1.62 (br s, 1H; O*H*), 0.98 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$$CH_2$).
The COO*H* resonance was not detected.
cis-**170c**, *minor* C-4 *epimer:*
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (dd, $^3J_{H,H}$ = 5.5, 2.2 Hz, 1H; C*H*=CHCHOAc), 5.86-5.82 (m; CH=C*H*CHOAc), 5.75-5.53 (m, 3H; C*H*=C*H*CHOH, C*H*OAc), 5.46-5.25 (m, 6H; C*H*=C*H*$_Z$),

4.26-4.17 (m, 1H; C*H*OH), 3.15-3.04 (m, 1H; C*H*CHOAc), 2.83-2.63 (m, 5H; CH=CHC*H*$_2$CH=CH, C*H*CH$_2$CH=CH), 2.47 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H*$_2$C=O), 2.20-2.13 (m, 1H; CHCH*H*CH=CH), 2.12-1.99 (m, 2H; C*H*$_2$CH$_3$), 2.06-1.97 (m, 1H; CHC*H*HCH=CH), 2.04 (s, 3H; C*H*$_3$C=O), 1.92-1.82 (dt, $^3J_{H,H}$ = 6.9, 7.3 Hz, 2H; C*H*$_2$CH$_2$C=O), 1.62 (br s, 1H; O*H*) 0.98 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$CH$_2$).

The COO*H* resonance was not detected.

The two minor diastereomers were not detected by ^{13}C NMR spectroscopy.

MS (+ESI) m/z (%): 425 (43) [*M*+Na]$^+$, 407 (100) [*M*–H$_2$O+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{24}H_{34}O_5$+Na$^+$: 425.2299 [*M*+Na]$^+$, found: 425.2295.

MS (–ESI) m/z (%): 401 (100) [*M*–H]$^-$.

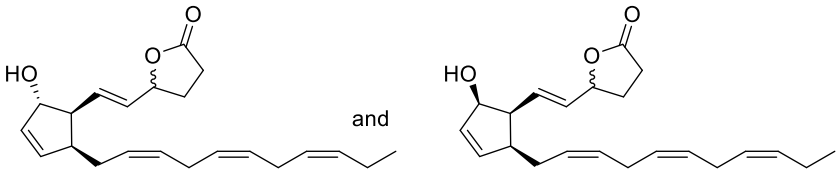
HRMS (–ESI) m/z: calcd for $C_{24}H_{34}O_5$–H$^+$: 401.2334 [*M*–H]$^-$, found: 401.2330.

5-((*E*)-2-((1*S*,5*S*)-2-Hydroxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)vinyl)dihydrofuran-2(3*H*)-one 171b and methyl (*E*)-4-hydroxy-6-((1*S*,5*S*)-2-hydroxy-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)hex-5-enoate 171c

Acetate **170b** (11 mg, 29 µmol) was dissolved in dry MeOH (0.6 mL), the mixture was cooled to 0 °C and flame-dried K_2CO_3 (20 mg, 0.15 mmol) was added. The mixture was warmed to 15 °C over 90 min when full conversion was indicated by TLC. The mixture was diluted with TBME (HPLC grade) to ca 5 mL and filtered through a small pad of silica gel, which was washed thoroughly TBME. The filtrate was evaporated and the crude product was purified by silica gel column chromatography (hexane/TBME HPLC grade, gradient 7:3 to 0:1) to furnish lactone **171b** (7 mg, 80 mol.% as determined by ^{1}H NMR spectroscopy, 57%) as inseparable 3:1 mixture of *trans*-/*cis*-**171b**, each as inseparable mixture of C-4 epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil, inseparable from corresponding hydroxy methyl ester **171c** (7 mg, 20 mol.% as determined by ^{1}H NMR spectroscopy, 13%).

R_f = 0.42 (Et$_2$O).

MS (+ESI) m/z (%): 397 (60) [*M*(**171c**)+Na]$^+$, 365 (100) [*M*(**171b**)+Na]$^+$.



trans-**171b**: **dr 4:1** *cis*-**171b**: **dr 2:1**

trans-**171b**, *major* C-4 *epimer:*

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.936 (ddd, $^3J_{H,H}$ = 6.0, 3.5 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H; C*H*=CHCHOH), 5.92-5.83 (m, 1H; C*H*=CHCHCH$_2$CH$_2$), 5.82 (dt, $^3J_{H,H}$ = 5.7, 1.9 Hz, $^4J_{H,H}$ = 1.9 Hz; 1H; CH=C*H*CHOH), 5.74-5.69 (m, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.48-5.24 (m, 6H; C*H*=C*H*$_Z$), 4.98-4.90 (m, 1H; C*H*OC=O), 4.67 (dq, $^3J_{H,H}$ = 4.9, 1.7 Hz, $^3J_{H,H}$ = 1.7 Hz, 1H; C*H*OH), 3.01-2.86 (m, 1H; C*H*CH$_2$CH=CH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.73-2.62 (m, 1H; C*H*CHOH), 2.59-2.51 (m, 2H;

C*H*$_2$C=O), 2.49-2.36 (m, 1H; CH*H*CH$_2$C=O), 2.24-2.11 (m, 1H; CHCH*H*CH=CH), 2.07 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH$_3$C*H*$_2$), 2.02-1.82 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 1.62 (br s, 1H; O*H*), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 177.0 (*C*=O), 138.1 (*C*H=CHCHOH), 133.5 (CH=*C*HCHOH), 133.05 (*C*H=CHCHCH$_2$CH$_2$), 132.20 (CH=C*H*CH$_2$CH$_3$), 130.3 (CH=*C*H$_Z$), 129.4 (CH=*C*HCHCH$_2$CH$_2$), 128.8 (CH=*C*H$_Z$), 128.3 (CH=*C*H$_Z$), 127.89 (CH=*C*H$_Z$), 127.14 (CH=*C*H$_Z$), 81.7 (*C*HOH), 80.7 (*C*HCH$_2$CH$_2$), 55.0 (*C*HCHOH), 48.15 (*C*HCH$_2$CH=CH), 29.05 (CH*C*H$_2$CH=CH), 28.99 (*C*H$_2$CH$_2$C=O), 28.7 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$).

trans-**171b**, *minor* C-4 *epimer:*

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.940 (ddd, $^3J_{H,H}$ = 6.0, 3.5 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H; C*H*=CHCHOH), 5.92-5.83 (m, 1H; C*H*=CHCHCH$_2$CH$_2$), 5.83 (dt, $^3J_{H,H}$ = 5.7, 1.9 Hz, $^4J_{H,H}$ = 1.9 Hz; 1H; CH=C*H*CHOH), 5.74-5.69 (m, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.48-5.24 (m, 6H; C*H*=C*H*$_Z$), 4.98-4.90 (m, 1H; C*H*OC=O), 4.72-4.68 (m, 1H; C*H*OH), 2.95-2.85 (m, 1H; C*H*CH$_2$CH=CH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.73-2.62 (m, 1H; C*H*CHOH), 2.59-2.51 (m, 2H; C*H*$_2$C=O), 2.49-2.36 (m, 1H; CH*H*CH$_2$C=O), 2.24-2.11 (m, 1H; CHCH*H*CH=CH), 2.07 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH$_3$C*H*$_2$), 2.02-1.82 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 1.62 (br s, 1H; O*H*), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 177.0 (*C*=O), 137.9 (*C*H=CHCHOH), 133.3 (CH=*C*HCHOH), 133.09 (*C*H=CHCHCH$_2$CH$_2$), 132.23 (CH=C*H*CH$_2$CH$_3$), 130.1 (CH=*C*H$_Z$), 129.3 (CH=*C*HCHCH$_2$CH$_2$), 128.7 (CH=*C*H$_Z$), 128.2 (CH=*C*H$_Z$), 127.87 (CH=*C*H$_Z$), 127.14 (CH=*C*H$_Z$), 81.5 (*C*HOH), 80.6 (*C*HCH$_2$CH$_2$), 54.9 (*C*HCHOH), 48.09 (*C*HCH$_2$CH=CH), 29.05 (CH*C*H$_2$CH=CH), 28.99 (*C*H$_2$CH$_2$C=O), 28.7 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$).

cis-**171b**, *major* C-4 *epimer:*

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.05-5.97 (m, 1H; C*H*=CHCHOH), 5.92-5.83 (m, 1H; C*H*=CHCHCH$_2$CH$_2$), 5.84-5.80 (m, 1H; CH=C*H*CHOH), 5.74-5.69 (m, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.48-5.24 (m, 6H; C*H*=C*H*$_Z$), 5.01-4.91 (m, 1H; C*H*OC=O), 4.61 (dq, $^3J_{H,H}$ = 6.5, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; C*H*OH), 2.97-2.92 (m, 1H; C*H*CHOH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.77-2.72 (m, 1H; C*H*CH$_2$CH=CH), 2.59-2.51 (m, 2H; C*H*$_2$C=O), 2.49-2.36 (m, 1H; CH*H*CH$_2$C=O), 2.24-2.11 (m, 1H; CHCH*H*CH=CH), 2.07 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH$_3$C*H*$_2$), 2.02-1.82 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 1.62 (br s, 1H; O*H*), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 177.0 (*C*=O), 139.1 (*C*H=CHCHOH), 135.0 (CH=*C*HCHOH), 133.2 (*C*H=CHCHCH$_2$CH$_2$), 132.1 (CH=C*H*CH$_2$CH$_3$), 130.47 (CH=*C*H$_Z$), 129.7 (CH=*C*HCHCH$_2$CH$_2$), 129.1 (CH=*C*H$_Z$), 128.4 (CH=*C*H$_Z$), 127.95 (CH=*C*H$_Z$), 127.14 (CH=*C*H$_Z$), 81.0 (*C*HCH$_2$CH$_2$), 78.2 (*C*HOH), 55.2 (*C*HCHOH), 48.4 (*C*HCH$_2$CH=CH), 29.2 (CH*C*H$_2$CH=CH), 28.87 (*C*H$_2$CH$_2$C=O), 28.7 (*C*H$_2$C=O), 25.9 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$).

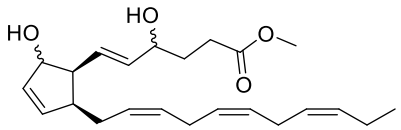
cis-**171b**, *minor* C-4 *epimer:*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98-5.95 (m, 1H; C*H*=CHCHOH), 5.92-5.83 (m, 1H; C*H*=CHCHCH$_2$CH$_2$), 5.84-5.80 (m, 1H; CH=C*H*CHOH), 5.77-5.73 (m, 1H; CH=C*H*CHCH$_2$CH$_2$), 5.48-5.24 (m, 6H; C*H*=C*H$_Z$*), 5.01-4.91 (m, 1H; C*H*OC=O), 4.61 (dq, $^3J_{H,H}$ = 6.5, 2.1 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H; C*H*OH), 2.97-2.92 (m, 1H; C*H*CHOH), 2.79 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H$_2$*CH=CH), 2.77 (t, $^3J_{H,H}$ = 6.7 Hz, 2H; CH=CHC*H$_2$*CH=CH), 2.77-2.72 (m, 1H; C*H*CH$_2$CH=CH), 2.59-2.51 (m, 2H; C*H$_2$*C=O), 2.49-2.36 (m, 1H; CH*H*CH$_2$C=O), 2.24-2.11 (m, 1H; CHCH*H*CH=CH), 2.07 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH$_3$C*H$_2$*), 2.02-1.82 (m, 2H; C*H*HCH$_2$C=O, CHC*H*HCH=CH), 1.62 (br s, 1H; O*H*), 0.97 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H$_3$*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0 (*C*=O), 139.1 (*C*H=CHCHOH), 135.1 (CH=*C*HCHOH), 133.2 (*C*H=CHCHCH$_2$CH$_2$), 132.1 (CH=C*H*CH$_2$CH$_3$), 130.52 (CH=*C*H$_Z$), 129.3 (CH=*C*HCHCH$_2$CH$_2$), 128.9 (CH=*C*H$_Z$), 128.4 (CH=*C*H$_Z$), 127.99 (CH=*C*H$_Z$), 127.10 (CH=*C*H$_Z$), 81.0 (*C*HCH$_2$CH$_2$), 78.5 (*C*HOH), 55.3 (*C*HCHOH), 48.22 (*C*HCH$_2$CH=CH), 29.13 (CH*C*H$_2$CH=CH), 28.93 (*C*H$_2$CH$_2$C=O), 28.7 (*C*H$_2$C=O), 26.0 (CH=CH*C*H$_2$CH=CH), 25.7 (CH=CH*C*H$_2$CH=CH), 20.7 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$).

IR (film): *v* = 3407 (br), 3054, 3010, 2962, 2931, 2875, 1772, 1670, 1456, 1436, 1395, 1328, 1262, 1217, 1177, 1115, 1049, 1008, 975, 916, 800, 770, 707 cm^{-1}.

HRMS (+ESI) m/z: calcd for $C_{22}H_{30}O_3$+Na$^+$: 365.2087 [*M*+Na]$^+$, found: 365.2085.



171c

Distinct NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (q, $^3J_{H,H}$ = 6.2, 1H; CH=CHC*H*OH), 3.68 (s, 3H; C*H$_3$*O).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.1 (CH=CH*C*HOH), 51.9 (*C*HCHOH), 49.8 (*C*HCH$_2$CH=CH), 32.1 (*C*H$_2$CH$_2$C=O), 30.1 (*C*H$_2$C=O).

The remaining NMR resonances were overlapping with **171b**.

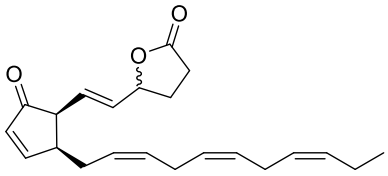
HRMS (+ESI) m/z: calcd for $C_{23}H_{34}O_4$+Na$^+$: 397.2349 [*M*+Na]$^+$, found: 397.2348.

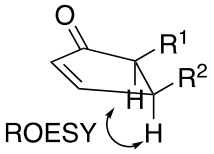
5-((*E*)-2-((1*S*,5*S*)-2-Oxo-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-yl)vinyl)dihydrofuran-2(3*H*)-one; 4(*RS*)-4-A$_4$-NeuroP 1,4-lactone 103b

Lactone **171b** (7 mg, 80 mol.%, 16 μmol) was dissolved in DCM (0.32 mL, HPLC grade), the solution was cooled to 0 °C and $NaHCO_3$ (2.7 mg, 33 μmol) was added with stirring, followed by DMP (14 mg, 33 μmol). The mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. More DMP (6 mg, 14 μmol) was added at 0 °C, the mixture was immediately warmed to room temperature and stirred for 20 min after which the reaction was complete as indicated by TLC. The mixture was diluted with DCM (HPLC grade) to ca 2 mL, $Na_2S_2O_3$ solution (2 mL, 10%) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the aqueous was extracted with DCM (3×2 mL, HPLC grade). The combined organic layers were washed with $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure using a cold water

bath (<15°C) to give crude 4(*RS*)-4-A$_4$-NeuroP 1,4-lactone **103b** (6 mg, quant.) as 3:1 mixture of C-4 epimers as determined by ^{1}H NMR spectroscopy as a colorless oil, along with traces of ketones resulting from oxidation of **171c**.

Note: Storing the compound as neat sample at –20 °C for 10 days resulted in complete degradation as determined by NMR spectroscopy and HPLC analysis (reverse phase, UV and MS detection).





R_f = 0.50 (Et_2O).

Major C-4 *epimer:*

^{1}H NMR (600 MHz, C_6D_6): δ = 6.99 (dd, $^3J_{H,H}$ = 5.8, 2.7 Hz, 1H; C*H*=CHC=O), 5.93 (dd, $^3J_{H,H}$ = 5.8 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; CH=C*H*C=O), 5.51-5.32 (m, 7H; C*H*=C*H*), 5.19-5.10 (m, 1H; CHCH$_2$C*H*=CH), 4.24 (td, $^3J_{H,H}$ = 7.4, 6.1 Hz, 1H; C*H*CH$_2$CH$_2$), 2.88-2.77 (m, 2H; CH=CHC*H*$_2$CH=CH), 2.76-2.65 (m, 2H; CH=CHC*H*$_2$CH=CH), 2.729 (dd, $^3J_{H,H}$ = 8.2, 6.7 Hz, 1H; C*H*C=O), 2.50 (dtdd, $^3J_{H,H}$ = 8.5, 6.8, 2.8 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; C*H*CH$_2$CH=CH), 2.07-1.96 (m, 3H; C*H*$_2$CH$_3$, CHCH*H*CH=CH), 1.90 (ddd, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 9.2, 4.9 Hz, 1H; CH*H*C=O), 1.86-1.79 (m, 1H; CHC*H*HCH=CH), 1.740 (dt, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 9.2 Hz, 1H; C*H*HC=O), 1.48-1.37 (m, 1H; C*H*HCH$_2$C=O), 1.27-1.17 (m, 1H, CH*H*CH$_2$C=O), 0.929 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, C_6D_6): δ = 206.3 (CH=CH*C*=O), 175.6 (O*C*=O), 165.6 (*C*H=CHC=O), 134.1 (*C*H=CHCHOC=O), 132.8 (CH=*C*HC=O), 132.4 (CH$_3$CH$_2$*C*H=CH), 130.44 (CH=*C*H$_Z$), 129.2 (CH=*C*H$_Z$), 128.4 (CH=*C*H$_Z$), 128.0 (CH=*C*HCHOC=O), 127.7 (CH=*C*H$_Z$), 126.9 (CH=*C*H$_Z$), 79.7 (*C*HO), 52.2 (*C*HC=O), 45.3 (*C*HCH$_2$CH=CH), 29.1 (CH*C*H$_2$CH=CH), 28.5 (*C*H$_2$CH$_2$C=O), 28.2 (*C*H$_2$C=O), 26.14 (CH=CH*C*H$_2$CH=CH), 25.98 (CH=CH*C*H$_2$CH=CH), 21.0 (*C*H$_2$CH$_3$), 14.5 (*C*H$_3$).

Minor C-4 *epimer:*

^{1}H NMR (600 MHz, C_6D_6): δ = 6.97 (dd, $^3J_{H,H}$ = 5.8, 2.7 Hz, 1H; C*H*=CHC=O), 5.94 (dd, $^3J_{H,H}$ = 5.6 Hz, $^4J_{H,H}$ = 1.9 Hz, 1H; CH=C*H*C=O), 5.51-5.32 (m, 7H; C*H*=C*H*), 5.19-5.10 (m, 1H; CHCH$_2$C*H*=CH), 4.31-4.26 (m, 1H; C*H*CH$_2$CH$_2$), 2.88-2.77 (m, 2H; CH=CHC*H*$_2$CH=CH), 2.76-2.65 (m, 2H; CH=CHC*H*$_2$CH=CH), 2.734 (dd, $^3J_{H,H}$ = 7.7, 6.6 Hz, 1H; C*H*C=O), 2.46 (dtdd, $^3J_{H,H}$ = 7.8, 5.7, 3.1 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; C*H*CH$_2$CH=CH), 2.09-1.94 (m, 3H; C*H*$_2$CH$_3$, CHCH*H*CH=CH), 1.95 (ddd, $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 9.0, 5.4 Hz, 1H; CH*H*C=O), 1.86-1.81 (m, 1H; CHC*H*HCH=CH), 1.742 (dt, 1H; $^2J_{H,H}$ = 17.4 Hz, $^3J_{H,H}$ = 9.1 Hz, 1H; C*H*HC=O), 1.49-1.35 (m, 1H; C*H*HCH$_2$C=O), 1.28-1.15 (m, 1H, CH*H*CH$_2$C=O), 0.927 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, C_6D_6): δ = 206.3 (CH=CH*C*=O), 175.6 (O*C*=O), 165.4 (*C*H=CHC=O), 133.7 (*C*H=CHCHOC=O), 132.9 (CH=*C*HC=O), 132.4 (CH$_3$CH$_2$*C*H=CH), 130.37 (CH=*C*H$_Z$), 129.2 (CH=*C*H$_Z$), 128.4 (CH=*C*H$_Z$), 127.3 (CH=*C*HCHOC=O), 127.0 (CH=*C*H$_Z$), 126.4 (CH=*C*H$_Z$), 78.7 (*C*HO), 51.9 (*C*HC=O), 45.2 (*C*HCH$_2$CH=CH), 29.2 (CH*C*H$_2$CH=CH), 28.4 (*C*H$_2$CH$_2$C=O), 27.9

(*C*H$_2$C=O), 26.12 (CH=CH*C*H$_2$CH=CH), 26.01 (CH=CH*C*H$_2$CH=CH), 21.0 (*C*H$_2$CH$_3$), 14.5 (*C*H$_3$).

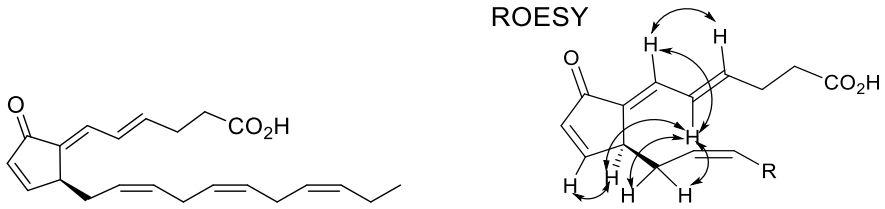
MS (+ESI) m/z (%): 395 (33), 379 (18) [*M*+K]$^+$, 363 (100) [*M*+Na]$^+$, 341 (7) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{22}H_{28}O_3$+Na$^+$: 363.1931 [*M*+Na]$^+$, found: 363.1931; calcd for $C_{22}H_{28}O_3$+H$^+$: 341.2111 [*M*+H]$^+$, found: 341.2108.

(4*E*,6*E*)-6-((*S*)-2-oxo-5-((2*Z*,5*Z*,8*Z*)-undeca-2,5,8-trien-1-yl)cyclopent-3-en-1-ylidene)hex-4-enoic acid; 4-deoxy-A$_4$-NeuroP 103c

Crude lactone **103b** (2.6 mg, 8 µmol) in TBME (0.75 mL) was deposited on a silica gel TLC plate. The sample band was narrowed by multiple short elution using Et$_2$O and the TLC was eluted using 60% Et$_2$O in PE in a preparative TLC chamber. The silica gel at the main product band (UV 254 nm visualization) was scraped off, suspended in EtOAc (10 mL, HPLC grade), sonicated and filtered over Celite®. The filtrate was evaporated to furnish 4-deoxy-Δ^{4,6}-A$_4$-NeuroP (1.5 mg, 72%) as a colorless oil.

Note: After storing the compound in deuterated benzene at –20 °C for ten days, no signs of degradation were indicated by HPLC analysis (reverse phase, UV and MS detection).



R_f = 0.72 (PE/Et$_2$O 4:6).

^{1}H NMR (500 MHz, C$_6$D$_6$): δ = 7.14 (d, $^3J_{H,H}$ = 12.0 Hz, 1H; *C*H=CC=O), 6.88 (dd, $^3J_{H,H}$ = 6.0, 2.5 Hz 1H; C*H*=CHC=O), 6.23 (dd, $^3J_{H,H}$ = 6.0 Hz, $^4J_{H,H}$ = 1.9 Hz, 1H; CH=C*H*C=O), 6.17 (ddt, $^3J_{H,H}$ = 14.9, 11.7 Hz, $^4J_{H,H}$ = 1.5 Hz, 1H; C*H*=CHCH$_2$CH$_2$), 5.63 (dt, $^3J_{H,H}$ = 15.3, 6.9 Hz, 1H; CH=C*H*CH$_2$CH$_2$), 5.50-5.28 (m, 5H; C*H*=C*H*$_Z$), 5.18 (ddt, $^3J_{H,H}$ = 10.2, 6.6 Hz, $^4J_{H,H}$ = 1.6 Hz, 1H; CHCH$_2$C*H*=CH), 3.13 (dddd, $^3J_{H,H}$ = 8.6, 4.2, 2.2 Hz, $^4J_{H,H}$ = 2.0 Hz, 1H; C*H*CH$_2$), 2.79 (t, $^3J_{H,H}$ = 6.9 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.69 (t, $^3J_{H,H}$ = 7.3 Hz, 2H; CH=CHC*H*$_2$CH=CH), 2.42-2.26 (m, 1H; CHCH*H*CH=CH), 2.20-2.08 (m, 3H; C*H*$_2$CH$_2$C=O, CHC*H*HCH=CH), 2.08-1.95 (m, 4H; C*H*$_2$C=O, C*H*$_2$CH$_3$), 0.92 (t, *J* = 7.5 Hz, 3H; C*H*$_3$).

^{13}C NMR (125 MHz, C$_6$D$_6$): δ = 195.9 (CH=CH*C*=O), 175.9 (*C*OOH; HMBC determination), 159.7 (*C*H=CHC=O), 142.5 (CH=*C*HCH$_2$CH$_2$), 136.6 (CH=*C*C=O), 135.6 (CH=*C*HC=O), 132.3 (*C*H=CH$_Z$), 130.8 (*C*H=CH$_Z$), 130.6 (*C*H=CC=O), 129.1 (*C*H=CH$_Z$), 128.3 (*C*H=CH$_Z$), 127.3 (*C*H=CH$_Z$), 127.0 (*C*H=CHCH$_2$CH$_2$), 125.7 (CHCH$_2$*C*H=CH), 43.4 (*C*HCH$_2$), 32.6 (*C*H$_2$C=O), 31.1 (CH*C*H$_2$CH=CH), 28.4 (*C*H$_2$CH$_2$C=O), 26.01 (CH=CH*C*H$_2$CH=CH), 25.96 (CH=CH*C*H$_2$CH=CH), 21.0 (*C*H$_2$CH$_3$), 14.5 (*C*H$_3$).

IR (film): *v* = 3741-2380 (v br), 3010, 2961, 2931, 2874, 1731, 1697, 1631, 1579, 1437, 1394, 1204, 1172, 1018, 979, 839, 811, 764, 732, 624, 611 cm^{-1}.

MS (–ESI) m/z (%): 339 (76) [*M*–H]$^-$, 295 (100) [*M*–H–CO$_2$]$^-$.

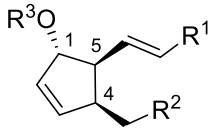
MS (+ESI) m/z (%): 409 (24), 363 (100) [*M*+Na]$^+$.

HRMS (–ESI) m/z: calcd for $C_{22}H_{28}O_3$–H^+: 339.1966, found: 339.1961.
HRMS (+ESI) m/z: calcd for $C_{22}H_{28}O_3$+Na^+: 363.1931 [*M*+Na]$^+$, found: 363.1928.

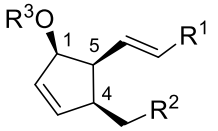
Assignment of the relative configuration at the cyclopentene ring

The relative configuration of major and minor diastereomers of the oxygenated cyclopentenes was assigned based on a ROESY experiment on compound **166b** (*vide supra*). The data can be extrapolated to all other intermediates thanks to the characteristic chemical shifts of protons at C-4 and C-5 of the cyclopentene ring (Table 15). Briefly, the chemical shift of H-4 was always more downfield than H-5 for the major *trans*-diastereomers, whereas in the minor *cis*-diastereomers, the trend was opposite. The chemical shift of H-1 was usually slightly more downfield for the major *trans*-diastereomers compared to minor *cis*-diastereomers, but this trend was less general and varied with substitution patterns (especially R^3).

Table 15. Characteristic ^{1}H NMR resonances of oxygenated cyclopentenes.



trans-**x**



cis-**x**

	δ (ppm)			δ (ppm)		
Compound **x**	H-1	H-4	H-5	H-1	H-4	H-5
154a	4.70-4.64	3.06-2.95	2.70	4.70-4-64	2.85-2.74	2.98-2.87
154b	4.70-4.61	3.05-2.88	2.67	4.66	2.85-2.70	2.94
154c	4.60	2.94	2.72-2.62	4.64	2.68-2.59	2.79
156a	4.65-4.55	3.05-2.90	2.74-2.65	4.85-4.65	2.86-2.74	3.26-3.10
156b	4.72-4.62	3.03-2.90	2.75-2.66	-	-	-
156f	4.64	2.80	2.75-2.66	4.63-4.59	2.73-2.64	2.98
156g	4.69-4.58	3.06	2.84-2.77	4.72	2.89-2.73	2.95
157	4.38-4.29	3.21-3.11	-	4.90-4.73	2.77-2.62	-
164a	4.76-4.71	3.18-3.08	2.89-2.81	4.76-4.68	2.99-2.94	3.08-3.00
164b	4.76-4.71	3.11	2.94-2.77	4.76-4.68	2.99-2.94	3.08-3.00
166a	5.59	3.20-3.12	3.06	5.65-5.59	2.99-2.90	3.28
166b	5.59-5.51	3.20-3.10	3.03	5.59-5.51	2.95-2.92	3.26
167	5.48	3.01	2.94-2.84	5.48	2.94-2.84	3.15-3.06
168	5.66-5.48	3.04-2.96	2.93-2.80	5.47-5.44	2.93-2.69	3.11-3.03
169	5.62-5.40	3.48-3.37	2.98	5.53-5.42	3.27-3.06	3.27-3.06
170a	5.51-5.42	2.95-2.83	2.95-2.83	5.45-5.22	2.73-2.61	3.12-3.02
171a	4.74-4.62	2.97-2.79	2.64	4.70-4.58	2.71-2.58	2.97-2.82
170b	5.60-5.54	3.02-2.93	2.98-2.89	5.60-5.54	2.83-2.67	3.16
170c	5.63-5.55	2.97-2.85	2.97-2.85	5.75-5.53	2.73-2.67	3.15-3.04
171b	4.67	3.01-2.86	2.73-2.62	4.61	2.77-2.72	2.97-2.92

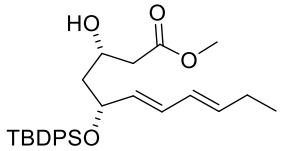
6.4 Total syntheses of isoprostanoids with 3-hydroxypentenyl ω-chain

6.4.1 Synthesis of cyclization precursors 84

6.4.1.1 3-Hydroxy-5-silyloxyesters **84c** *and* (3*S*,5*R*)-**84b**

Methyl (3*S,5*R**,6*E*,8*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxyundeca-6,8-dienoate 84c**

Diol **83b**[99] (100 mg, 0.44 mmol) was dissolved in dry DCM (4 mL), imidazole (one crystal) and 2,6-lutidine (153 µL, 1.31 mmol) were added. The solution was cooled to 0 °C and TBDPSCl (125 µL, 0.48 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 48 h. Satd. $KHSO_4$ solution (6 mL) was added, the mixture was diluted with Et_2O (6 mL), the layers were separated and the aqueous was extracted with Et_2O (3×6 mL). The combined organic layers were washed with satd. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient PE/EtOAc 95:5 to 8:2, then Et_2O) to give silyl ether **84c** (44 mg, 22%) as a very viscous colorless oil along with unreacted starting diol **83b** (54 mg, 54%).



R_f = 0.44 (PE/EtOAc 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.60 (m, 4H; CH_{Ar}), 7.48-7.31 (m, 6H; CH_{Ar}), 5.81 (ddt, $^3J_{H,H}$ = 14.6, 10.3 Hz, $^4J_{H,H}$ = 1.5 Hz, 1H; C*H*=CHCH$_2$), 5.73 (dd, $^3J_{H,H}$ = 15.2, 10.3 Hz, 1H; C*H*=CHCHO), 5.52 (dt, $^3J_{H,H}$ = 14.3, 6.6 Hz, 1H; CH=C*H*CH$_2$), 5.43 (dd, $^3J_{H,H}$ = 14.7, 7.9 Hz, 1H; CH=C*H*CHO), 4.46-4.38 (m, 1H; C*H*OTBDPS), 4.17-4.08 (m, 1H; C*H*OH), 3.67 (s, 3H; CH_3O), 3.05 (d, $^3J_{H,H}$ = 3.6 Hz, 1H; O*H*), 2.39 (d, $^3J_{H,H}$ = 6.6 Hz, 2H; CH_2C=O), 2.10-1.96 (m, 2H; CH_2CH$_3$), 1.82 (ddd, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 9.1, 6.2 Hz, 1H; CH*H*CHOTBDPS), 1.61-1.52 (m, 1H; C*H*HCHOTBDPS), 1.06 (s, 9H; CH_3CSi), 0.97 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; CH_3CH$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9 (*C*=O), 137.0 (*C*H=CHCH$_2$), 136.1 (2C; *C*H$_{Ar}$), 136.0 (2C; *C*H$_{Ar}$), 134.1 (2C; *C*$_{Ar}$), 132.3 (CH=*C*HCHO), 131.7 (*C*H=CHCHO), 129.8 (*C*H$_{Ar}$), 129.6 (*C*H$_{Ar}$), 128.4 (CH=*C*HCH$_2$), 127.7 (2C; *C*H$_{Ar}$), 127.5 (2C; *C*H$_{Ar}$), 73.2 (*C*HOTBDPS), 66.0 (*C*HOH), 51.8 (*C*H$_3$O), 44.5 (*C*H$_2$CHOTBDPS), 41.6 (*C*H$_2$C=O), 27.2 (3C; *C*H$_3$CSi), 25.7 (CH=CH*C*H$_2$), 19.4 (*C*Si), 13.5 (*C*H$_3$CH$_2$).

IR (film): *ν* = 3481 (br), 3071, 2958, 2931, 2857, 1737, 1472, 1462, 1428, 1362, 1256, 1197, 1168, 1106, 1076, 990, 822, 740, 702 cm^{-1}.

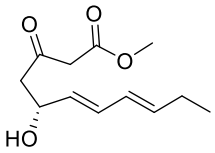
MS (+ESI) m/z (%): 489 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{28}H_{38}O_4Si$+Na$^+$: 489.2432 [*M*+Na]$^+$, found: 489.2428.

Methyl (*R*,6*E*,8*E*)-5-hydroxy-3-oxoundeca-6,8-dienoate (*R*)-181

Step 1:[165] Ti(O*i*-Pr)$_4$ (18 µL, 60 µmol) was added dropwise to a solution of (*R*)-BINOL (17 mg, 60 µmol) in dry THF (1.4 mL). The resulting bright red solution was stirred at room temperature for 30 min and subsequently added to a suspension of flame-dried LiCl (5 mg, 120 µmol) and (*E*,*E*)-hepta-2,4-dienal **82a** (110 mg, 1.00 mmol) in dry THF (1.6 mL) using a cannula. The mixture was stirred for 20 min and crude diene **183b**[161] (651 mg, 2.5 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was stirred overnight. The volatiles were removed under reduced pressure.

Step 2: The crude product was dissolved in dry MeOH, the solution was cooled to 0 °C and KF (174 mg, 3.00 mmol) was added. The reaction mixture was stirred for 1 h and filtered through a pad of silica gel, which was washed thoroughly with EtOAc. The filtrate was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (PE/EtOAc gradient 9:1 to 4:1, then Et_2O) to give aldol *(R)*-**181** (150 mg, 66%, 97% ee as determined by chiral HPLC) as a yellow oil.



R_f = 0.47 (PE/EtOAc 1:1).

$[\alpha]_D^{20}$ = +13.4 (c = 0.34 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (ddd, $^3J_{H,H}$ = 15.4, 10.4 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H), 6.00 (dddt, $^3J_{H,H}$ = 15.3, 10.4 Hz, $^4J_{H,H}$ = 2.1, 1.0 Hz, 1H), 5.76 (dt, $^3J_{H,H}$ = 15.1, 6.5 Hz, 1H), 5.56 (ddt, $^3J_{H,H}$ = 15.3, 6.4 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H), 4.63 (q, $^3J_{H,H}$ = 6.3 Hz, 1H), 3.74 (s, 3H), 3.50 (s, 2H), 2.86-2.71 (m, 2H), 2.60 (br s, 1H), 2.16-2.02 (m, 2H), 1.00 (t, $^3J_{H,H}$ = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 167.4, 138.0, 131.6, 130.8, 128.3, 68.4, 52.6, 49.9, 49.8, 25.8, 13.5.

MS (+ESI) m/z (%): 249 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_{12}H_{18}O_4+Na^+$: 249.1097 $[M+Na]^+$, found: 249.1098.

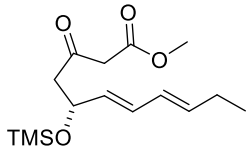
The analytical data are in accordance with the published values.[99]

Methyl (6*E*,8*E*)-3-oxo-5-((trimethylsilyl)oxy)undeca-6,8-dienoate 185

Step 1:[165] Performed in analogy to the synthesis of (*R*)-**181** from (*E*,*E*)-hepta-2,4-dienal **82a** (110 mg, 1.00 mmol), but using *rac*-BINOL. The second step was carried out *in situ*.

Step 2:[165] The reaction mixture was cooled to 0 °C and PPTS (50 mg, 0.20 mmol) in dry MeOH (2 mL) was added. The mixture was stirred at this temperature for 3 h and quenched by addition of satd. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel

column chromatography (PE/EtOAc gradient 9:1 to 6:4) to furnish silyl ether **185** (152 mg, 51%) as a yellow oil along with aldol **181** (91 mg, 40%).



R_f = 0.82 (PE/Et_2O 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23-6.08 (m, 1H; C*H*=CHCHOTMS), 6.02-5.91 (m, 1H; C*H*=CHCH$_2$), 5.72 (dt, $^3J_{H,H}$ = 15.1, 6.5 Hz, 1H; CH=C*H*CH$_2$), 5.50 (ddt, $^3J_{H,H}$ = 15.1, 6.6 Hz, $^4J_{H,H}$ = 0.6 Hz, 1H; CH=C*H*CHOTMS), 4.65-4.55 (m, 1H; C*H*OTMS), 3.74 (s, 3H; C*H*$_3$O), 3.48 (s, 2H; O=CC*H*$_2$C=O), 2.78 (dd, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,H}$ = 8.2 Hz, 1H; CH*H*CHOTMS), 2.56 (dd, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,H}$ = 4.5 Hz, 1H; C*H*HCHOTMS), 2.14-2.05 (m, 2H; C*H*$_2$CH$_3$), 0.99 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$), 0.08 (s, 9H; C*H*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4 (*C*=O), 167.6 (*C*O$_2$), 137.4 (CH=*C*HCH$_2$), 132.2 (CH=*C*HCHOTMS), 130.8 (*C*H=CHCHOTMS), 128.3 (*C*H=CHCH$_2$), 70.1 (*C*HOTMS), 52.4 (*C*H$_3$O), 51.2 (O=C*C*H$_2$C=O), 50.7 (*C*H$_2$CHOTMS), 25.8 (*C*H$_2$CH$_3$), 13.5 (CH$_2$*C*H$_3$), 0.3 (3C; *C*H$_3$Si).

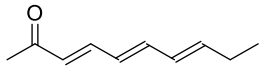
IR (film): ν = 2959, 1748, 1718, 1685, 1437, 1405, 1361, 1319, 1251, 1189, 1150, 1122, 1067, 1034, 992, 843, 752 cm^{-1}.

MS (+ESI) m/z (%): 321 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for $C_{15}H_{26}O_4Si$+Na$^+$: 321.1493 [*M*+Na]$^+$, found: 321.1488.

(3*E*,5*E*,7*E*)-Deca-3,5,7-trien-2-one 187

Obtained by an analogous procedure to the synthesis of (*R*)-**181** from (*E*,*E*)-hepta-2,4-dienal **82b** (440 mg, 4.00 mmol) using *rac*-BINOL and wet MeOH. After isolation of aldol product **181** (410 mg, 51%), the silica gel column was washed with MeOH to give major side product **187** (256 mg, 43%) as a yellow oil which instantly turned brown and viscous after re-evaporation.



R_f = 0.74 (PE/Et_2O 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, $^3J_{H,H}$ = 15.6, 11.1 Hz, 1H; C*H*=CHC=O), 6.58 (dd, $^3J_{H,H}$ = 14.9, 10.6, Hz 1H; C*H*=CHCH=CHC=O), 6.27-6.19 (m, 1H; CH=C*H*CH=CHC=O), 6.19-6.14 (m, 1H; CH$_2$CH=C*H*), 6.11 (d, $^3J_{H,H}$ = 15.4 Hz, 1H; CH=C*H*C=O), 6.06-5.94 (m, 1H; CH$_2$C*H*=CH), 2.26 (s, 3H; C*H*$_3$C=O), 2.22-2.13 (m, 2H; C*H*$_2$CH$_3$), 1.03 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH$_2$C*H*$_3$).

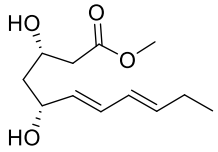
^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7 (*C*=O), 144.0 (*C*H=CHC=O), 142.6 (CH$_2$*C*H=CH), 142.3 (*C*H=CHCH=CHC=O), 129.5 (CH=*C*HC=O), 129.1 (CH$_2$CH=*C*H), 128.3 (CH=*C*HCH=CHC=O), 27.4 (*C*H$_3$C=O), 26.2 (*C*H$_2$CH$_3$), 13.2 (CH$_2$*C*H$_3$).

MS (+ESI) m/z (%): 323 (48) [2*M*+Na]$^+$, 173 (100) [*M*+Na]$^+$, 151 (8) [*M*+H]$^+$.

MS (+EI) m/z (%): 150 (100) $[M]^+$, 135 (44) $[M–CH_3]^+$, 121 (22) $[M–C_2H_5]^+$, 107 (22) $[M–H_3CC=O]^+$.
HRMS (+ESI) m/z: calcd for $C_{10}H_{14}O+Na^+$: 173.0937 $[M+Na]^+$, found: 173.0937; calcd for $C_{10}H_{14}O+H^+$: 151.1117 $[M+H]^+$, found: 151.1119.
HRMS (+EI) m/z: calcd for $C_{10}H_{14}O^+$: 150.1045 $[M]^+$, found: 150.1042.

Methyl (3*S*,5*R*,6*E*,8*E*)-3,5-dihydroxyundeca-6,8-dienoate (3*S*,5*R*)-83b

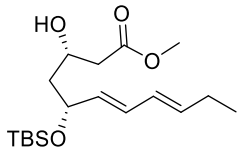
Prepared in analogy to **83b**[99] from (*R*)-**181** (100 mg, 0.44 mmol) yielding (3*S*,5*R*)-**83b** 69 mg (68%) as a colorless oil.



R_f = 0.33 (PE/EtOAc 1:1).
$[\alpha]_D^{20}$ = +8.3 (c = 0.22 in $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34-6.15 (m, 1H), 6.08-5.94 (m, 1H), 5.75 (dt, $^3J_{H,H}$ = 15.2, 6.5 Hz, 1H), 5.56 (ddt, $^3J_{H,H}$ = 15.3, 6.7 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H), 4.49-4.37 (m, 1H), 4.25-4.12 (m, 1H), 3.74-3.65 (m, 1H), 3.70 (s, 3H), 3.00 (br s, 1H), 2.54-2.42 (m, 2H), 2.16-1.99 (m, 2H), 1.72 (ddd, $^2J_{H,H}$ = 14.3 Hz, $^3J_{H,H}$ = 9.8, 9.1 Hz, 1H), 1.62 (ddd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 3.7, 2.9 Hz, 1H), 1.00 (t, $^3J_{H,H}$ = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 137.5, 132.6, 131.1, 128.5, 72.7, 68.4, 52.0, 42.8, 41.6, 25.8, 13.6.
MS (+ESI) m/z (%): 251 (100) $[M+Na]^+$.
HRMS (+ESI) m/z: calcd for $C_{12}H_{20}O_4+Na^+$: 251.1254 $[M+Na]^+$, found: 251.1254.
The analytical data are in accordance with the published values.[99]

Methyl (3*S*,5*R*,6*E*,8*E*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxyundeca-6,8-dienoate (3*S*,5*R*)-84b

Prepared in analogy to the synthesis of **84b**[99] from diol (3*S*,5*R*)-**83b** (69 mg, 0.30 mmol) yielding (3*S*,5*R*)-**84b** (56 mg, 54%) as a colorless oil.



R_f = 0.42 (PE/EtOAc 5:1).
$[\alpha]_D^{20}$ = +14.2 (c = 0.33 in $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (dd, $^3J_{H,H}$ = 14.8, 10.3 Hz, 1H), 5.98 (ddt, $^3J_{H,H}$ = 14.8, 10.4 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H), 5.72 (dt, $^3J_{H,H}$ = 14.9, 6.6 Hz, 1H), 5.49 (dd, $^3J_{H,H}$ = 15.1, 7.4 Hz, 1H), 4.40 (td, $^3J_{H,H}$ = 7.9, 5.4 Hz, 1H), 4.18 (tddd, $^3J_{H,H}$ = 9.8, 7.2, 5.2, 2.7 Hz, 1H), 3.69 (s, 3H), 3.56 (d,

$^{3}J_{H,H}$ = 2.3 Hz, 1H), 2.51 (dd, $^{2}J_{H,H}$ = 15.8 Hz, $^{3}J_{H,H}$ = 7.5 Hz, 1H), 2.45 (dd, $^{2}J_{H,H}$ = 15.8 Hz, $^{3}J_{H,H}$ = 5.2 Hz, 1H), 2.10 (dq, $^{3}J_{H,H}$ = 7.5, 6.1 Hz, 2H), 1.76 (ddd, $^{2}J_{H,H}$ = 14.1 Hz, $^{3}J_{H,H}$ = 9.4, 7.8 Hz, 1H), 1.61 (ddd, $^{2}J_{H,H}$ = 14.1 Hz, $^{3}J_{H,H}$ = 5.2, 3.0 Hz, 1H), 1.01 (t, $^{3}J_{H,H}$ = 7.5, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 137.3, 133.2, 131.0, 128.4, 73.6, 67.1, 51.8, 44.4, 41.8, 26.0 (3C), 25.8, 18.2, 13.5, –3.7, –4.6.

The analytical data are in accordance with the published values.[99]

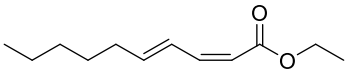
MS (+ESI) m/z (%): 365 (100) $[M+Na]^+$.

HRMS (+ESI) m/z: calcd for $C_{18}H_{34}O_4Si+Na^+$: 365.2119 $[M+Na]^+$, found: 365.2119.

6.4.1.2 (Z,E)-configurated cyclization precursor (6*Z*,8*E*)-**84a**

Ethyl (2*Z*,4*E*)-deca-2,4-dienoate 189

Methyl (*Z*)-iodoacrylate (1.0 g, 4.42 mmol) and *trans*-1-hepten-1-ylboronic acid pinacol ester **188a**[167] (1.09 g, 4.87 mmol) were dissolved in THF (15 mL) and water (5 mL). The solution was degassed by four freeze-pump-thaw cycles and $Pd(PPh_3)_4$ (256 mg, 0.22 mmol) was added. The mixture was stirred until the solids fully dissolved and TlOEt (345 µL, 4.87 mmol) was added dropwise. A yellow precipitate was formed immediately and the resulting suspension was stirred at room temperature for 2 h. Et_2O (30 mL) and satd. $KHSO_4$ solution (20 mL) were added, the biphasic mixture was stirred for 10 min and filtered through a plug of Celite®. The layers were separated and the aqueous was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (100 mL of silica, PE/MTBE gradient 1:0 to 200:1) to obtain ester **189** (759 mg, 87%) as a colorless oil.



R_f = 0.40 (PE/Et_2O 98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (ddq, $^{3}J_{H,H}$ = 15.3, 11.3 Hz, $^{4}J_{H,H}$ = 1.4 Hz, 1H; C*H*=CHCH$_2$), 6.54 (td, $^{3}J_{H,H}$ = 11.3 Hz, $^{4}J_{H,H}$ = 0.8 Hz, 1H; C*H*=CHC=O), 6.06 (dt, $^{3}J_{H,H}$ = 15.2, 7.0 Hz, 1H; CH=C*H*CH$_2$), 5.55 (dt, $^{3}J_{H,H}$ = 11.3 Hz, $^{4}J_{H,H}$ = 0.8 Hz, 1H; CH=C*H*C=O), 4.18 (q, $^{3}J_{H,H}$ = 7.1 Hz, 2H; C*H*$_2$O), 2.31-2.06 (m, 2H, CH=CHC*H*$_2$), 1.48-1.38 (m, 2H; CH=CHCH$_2$C*H*$_2$), 1.35-1.22 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 1.29 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$O), 0.88 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3H; C*H*$_3$CH$_2$CH$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (*C*=O), 145.9 (CH=*C*HCH$_2$), 145.5 (*C*H=CHC=O), 127.0 (*C*H=CHCH$_2$), 115.6 (CH=*C*HC=O), 60.0 (*C*H$_2$O), 33.1 (CH=CH*C*H$_2$), 31.6 (*C*H$_2$CH$_2$CH$_3$), 28.6 (*C*H$_2$CH$_2$CH=CH), 22.6 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$CH$_2$O), 14.1 (*C*H$_3$CH$_2$CH$_2$).

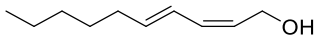
IR (film): *v* = 2957, 2928, 2858, 1713, 1637, 1601, 1464, 1421, 1388, 1275, 1166, 1139, 1096, 1031, 1000, 962, 859, 826, 728 cm^{-1}.

MS (+EI) m/z (%): 196 (46) $[M]^+$, 125 (100) $[M–C_5H_{11}]^+$, 97 (42) $[M–CH=CHCO_2Et]^+$.

HRMS (+EI) m/z: calcd for $C_{12}H_{20}O_2^+$: 196.1463 $[M]^+$, found: 196.1461.

(2*Z*,4*E*)-Deca-2,4-dien-1-ol 190

Ester **189** (127 mg, 0.65 mmol) was dissolved in dry THF (6.5 mL) and DIBAL-H (1.54 mL, 1.0 M in DCM, 1.54 mmol) was added dropwise at –78 °C. The reaction mixture was warmed to –50 °C over 1 h. MeOH (0.25 mL) and water (0.25 mL) were added dropwise. The cooling bath was removed, Et_2O (10 mL), a tip of spatula of Celite® and $MgSO_4$ were successively added and the suspension was vigorously stirred at room temperature for 40 min. The resulting slurry was filtered through a pad of Celite® and sand, which was thoroughly washed with Et_2O. The filtrate was concentrated under reduced pressure to furnish allylic alcohol **190** (100 mg, quant.) as a colorless oil, which was used in the next step without further purification.



R_f = 0.14 (PE/Et_2O 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (ddq, $^3J_{H,H}$ = 15.1, 11.1 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H; C*H*=CHCH$_2$CH$_2$), 6.07 (t, $^3J_{H,H}$ =11.3 Hz, 1H; C*H*=CHCH$_2$OH), 5.76 (dt, $^3J_{H,H}$ = 14.5, 7.0 Hz, 1H; CH=C*H*CH$_2$CH$_2$), 5.49 (dt, $^3J_{H,H}$ = 10.9, 7.0 Hz, 1H; CH=C*H*CH$_2$OH), 4.49-4.06 (m, 2H; C*H*$_2$OH), 2.10 (qd, $^3J_{H,H}$ = 7.2 Hz, $^4J_{H,H}$ = 1.4 Hz, 2H; C*H*$_2$CH=CH), 1.46-1.20 (m, 7H, C*H*$_2$, O*H*), 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3H; C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8 (CH=*C*HCH$_2$CH$_2$), 131.4 (*C*H=CHCH$_2$OH), 127.2 (CH=*C*HCH$_2$OH), 124.9 (*C*H=CHCH$_2$CH$_2$), 59.0 (*C*H$_2$OH), 33.0 (*C*H$_2$CH=CH), 31.6 (*C*H$_2$CH$_2$CH=CH), 29.0 (*C*H$_2$CH$_2$CH$_3$), 22.7 (*C*H$_2$CH$_3$), 14.2 (*C*H$_3$).

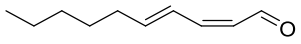
IR (film): *v* = 3314 (br), 3028, 2956, 2924, 2872, 2855, 1653, 1459, 1378, 1343, 1304, 1211, 1087, 1024, 956, 952, 849, 822, 726, 625 cm^{-1}.

MS (+EI) m/z (%): 154 (100) [*M*]$^+$, 136 (65) [*M*–H$_2$O]$^+$, 83 (79) [*M*–C$_5$H$_{11}$]$^+$.

HRMS (+EI) m/z: calcd for $C_{10}H_{18}O^+$: 154.1358 [*M*]$^+$, found: 154.1365.

(2*Z*,4*E*)-Deca-2,4-dienal (2*Z*,4*E*)-82a

Allylic alcohol **190** (100 mg, 0.65 mmol) was dissolved in PE and filtered through a column of MnO_2 (20 g, 230 mmol). The column was washed with four volumes of PE and the filtrate was evaporated under reduced pressure to obtain aldehyde (2*Z,*4*E*)-**82a** (95 mg, 96%) as a yellow oil.



R_f = 0.40 (PE/EtOAc 9:1).

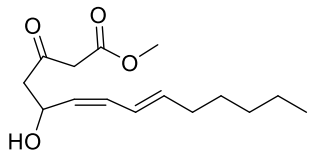
^{1}H NMR (400 MHz, C_6D_6): δ = 9.98 (d, $^3J_{H,H}$ = 7.5 Hz, 1H; C*H*O), 6.70 (ddq, $^3J_{H,H}$ = 14.7, 11.9, $^4J_{H,H}$ = 1.4 Hz, 1H; C*H*=CHCH$_2$), 6.31 (t, $^3J_{H,H}$ = 11.4 Hz, 1H; C*H*=CHCHO), 5.64 (dd, $^3J_{H,H}$ = 11.0, 7.4 Hz, 1H; CH=C*H*CHO), 5.58 (dt, $^3J_{H,H}$ = 14.6, 7.3 Hz, 1H; CH=C*H*CH$_2$), 1.81 (qd, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 1.5 Hz; 2H, C*H*$_2$CH=CH), 1.24-0.99 (m, 6H, C*H*$_2$), 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, C_6D_6): δ = 189.2 (*C*=O), 146.5 (*C*H=CHCHO), 146.0 (CH=*C*HCH$_2$), 126.2 (CH=*C*HCHO), 124.9 (*C*H=CHCH$_2$), 33.1 (*C*H$_2$CH=CH), 31.7 (*C*H$_2$CH$_2$CH=CH), 28.6 (*C*H$_2$CH$_2$CH$_3$), 22.8 (*C*H$_2$CH$_3$), 14.2 (*C*H$_3$).

IR (film): ν = 2957, 2927, 2857, 1669, 1636, 1514, 1466, 1377, 1228, 1155, 1114, 1011, 952, 830, 764 cm^{-1}.
MS (+EI) m/z (%): 152 (48) [M]$^+$, 81 (100) [M–C_5H_{11}]$^+$.
HRMS (+EI) m/z: calcd for $C_{10}H_{16}O^+$: 152.1201 [M]$^+$, found: 152.1204.

Methyl (6*Z*,8*E*)-5-hydroxy-3-oxotetradeca-6,8-dienoate (6*Z*,8*E*)-83a-i1

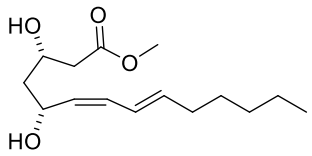
Prepared in analogy to **181**[99] from (2*Z*,4*E*)-deca-2,4-dienal (79 mg, 0.52 mmol) yielding (6*Z*,8*E*)-**83a-i1** (91 mg, 65%) as a colorless oil.



R_f = 0.17 (PE/EtOAc 4:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (ddq, $^3J_{H,H}$ = 15.2, 11.1 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H; C*H*=CHCH$_2$), 6.02 (tt, $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 0.9 Hz, 1H; C*H*=CHCHOH), 5.76 (dt, $^3J_{H,H}$ = 15.0, 7.1 Hz, 1H; CH=C*H*CH$_2$), 5.33-5.24 (m, 1H; CH=C*H*CHOH), 5.11-5.01 (m, 1H; C*H*OH), 3.75 (s, 3H; C*H*$_3$O), 3.51 (s, 2H; C*H*$_2$CO$_2$), 2.82 (dd, $^2J_{H,H}$ = 17.3 Hz, $^3J_{H,H}$ = 8.6 Hz, 1H; CH*H*CHOH), 2.72 (dd, $^2J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 3.4 Hz, 1H; C*H*HCHOH), 2.57 (d, $^3J_{H,H}$ = 3.4 Hz, 1H; O*H*), 2.10 (qd, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 1.4 Hz, 2H; C*H*$_2$CH=CH), 1.48-1.34 (m, 2H; C*H*$_2$CH$_2$CH=CH), 1.34-1.22 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3H; CH$_2$C*H*$_3$).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9 (*C*=O), 167.4 (*C*O$_2$), 138.6 (CH=*C*HCH$_2$), 131.1 (*C*H=CHCHOH), 128.5 (CH=*C*HCHOH), 124.8 (*C*H=CHCH$_2$), 64.4 (*C*HOH), 52.6 (*C*H$_3$O), 49.9 (*C*H$_2$CO$_2$), 49.8 (*C*H$_2$CHOH), 33.0 (*C*H$_2$CH=CH), 31.6 (*C*H$_2$CH$_2$CH=CH), 29.0 (*C*H$_2$CH$_2$CH$_3$), 22.7 (*C*H$_2$CH$_3$), 14.2 (CH$_2$*C*H$_3$).
IR (film): ν = 3486 (br), 3021, 2994, 2927, 2872, 1745, 1715, 1655, 1437, 1403, 1378, 1322, 1268, 1231, 1151, 1110, 1074, 1036, 1014, 990, 948, 597 cm^{-1}.
MS (+CI) m/z (%): 153 (100) [M–CH$_2$COCH$_2$CO$_2$Me]$^+$, 135 (72) [M–CH$_2$COCH$_2$CO$_2$Me–H$_2$O]$^+$.
MS (+ESI) m/z (%): 291 (100) [M+Na]$^+$.
HRMS (+ESI) m/z: calcd for $C_{15}H_{24}O_4$+Na$^+$: 291.1567 [M+Na]$^+$, found: 291.1567.

Methyl (3*S,5*R**,6*Z*,8*E*)-3,5-dihydroxytetradeca-6,8-dienoate (6*Z*,8*E*)-83a**

Prepared in analogy to **83b**[99] from aldol (6*Z*,8*E*)-**83a-i1** (91 mg, 0.34 mmol) yielding (6*Z*,8*E*)-**83a** (91 mg, 99%) as a colorless oil.



R_f = 0.19 (PE/EtOAc 1:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (ddq, $^3J_{H,H}$ = 15.0, 11.1 Hz, $^4J_{H,H}$ = 1.3 Hz, 1H; C*H*=CHCH$_2$),

6.01 (tt, $^3J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 1.0 Hz, 1H; C*H*=CHCHOH), 5.75 (dt, $^3J_{H,H}$ = 15.0, 7.1 Hz, 1H; CH=C*H*CH$_2$), 5.28 (dd, $^3J_{H,H}$ = 10.9, 8.7 Hz, 1H; CH=C*H*CHOH), 4.88 (tdd, $^3J_{H,H}$ = 8.9, 3.7 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; CH=CHC*H*OH), 4.29 (dtd, $^3J_{H,H}$ = 10.3, 7.6, 3.0 Hz, 1H; C*H*OH), 3.71 (s, 3H; C*H*$_3$O), 3.65 (br s, 1H; O*H*), 2.77 (s, 1H; O*H*), 2.57-2.43 (m, 2H; C*H*$_2$C=O), 2.10 (qd, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 1.5 Hz, 2H; C*H*$_2$CH=CH), 1.78 (ddd, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 10.2, 9.1 Hz, 1H; CH*H*CHOH), 1.58 (ddd, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 3.9, 2.7 Hz, 1H; C*H*HCHOH), 1.39 (quint, $^3J_{H,H}$ = 7.3 Hz, 2H; C*H*$_2$CH$_2$CH=CH), 1.36-1.20 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3H; CH$_2$C*H*$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.9 (*C*=O), 137.9 (CH=*C*HCH$_2$), 130.5 (*C*H=CHCHOH), 130.3 (CH=*C*HCHOH), 124.9 (*C*H=CHCH$_2$), 68.2 (*C*HOH), 68.0 (CH=CH*C*HOH), 51.8 (*C*H$_3$O), 42.7 (OH*C*H$_2$CHOH), 41.5 (*C*H$_2$C=O), 32.8 (*C*H$_2$CH=CH), 31.4 (*C*H$_2$CH$_2$CH$_3$), 28.9 (*C*H$_2$CH$_2$CH=CH), 22.5 (*C*H$_2$CH$_3$), 14.0 (CH$_2$*C*H$_3$).

IR (film): *v* = 3474 (br), 3021, 2956, 2927, 2871, 2858, 1764, 1437, 1396, 1379, 1327, 1296, 1267, 1165, 1084, 987, 949, 851, 751, 645, 621, 606 cm^{-1}.

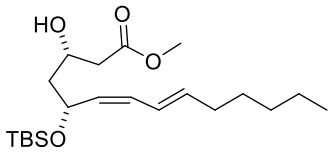
MS (+CI) m/z (%): 235 (100) [*M*–2H$_2$O+H]$^+$.

MS (+ESI) m/z (%): 563 (16) [2*M*+Na]$^+$, 293 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for C$_{15}$H$_{26}$O$_4$+Na$^+$: 293.1723 [*M*+Na]$^+$, found: 293.1724.

Methyl (3*S,5*R**,6*Z*,8*E*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxytetradeca-6,8-dienoate (6*Z*,8*E*)-84a**

Prepared in analogy to the synthesis of **84b**[99] from diol (6*Z*,8*E*)-**83a** (27 mg, 0.10 mmol) to give (6*Z*,8*E*)-**84a** (24 mg, 62%) as a colorless oil.



R_f = 0.52 (PE/EtOAc 4:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.24 (ddd, $^3J_{H,H}$ = 14.9, 11.2 Hz, $^4J_{H,H}$ = 1.5 Hz, 1H; C*H*=CHCH$_2$), 5.92 (t, $^3J_{H,H}$ = 11.1 Hz, 1H; C*H*=CHCHOTBS), 5.72 (dt, $^3J_{H,H}$ = 14.5, 7.2 Hz, 1H; CH=C*H*CH$_2$), 5.20 (dd, $^3J_{H,H}$ = 11.0, 8.9 Hz, 1H; CH=C*H*CHOTBS), 4.85 (td, $^3J_{H,H}$ = 8.6, 5.1 Hz, 1H; C*H*OTBS), 4.27-4.11 (m, 1H; C*H*OH), 3.69 (s, 3H; C*H*$_3$O), 3.63 (d, $^3J_{H,H}$ = 2.2 Hz, 1H; O*H*), 2.51 (dd, $^2J_{H,H}$ = 15.8 Hz, $^3J_{H,H}$ = 7.7 Hz, 1H; CH*H*C=O), 2.44 (dd, $^2J_{H,H}$ = 15.8 Hz, $^3J_{H,H}$ = 4.9 Hz, 1H; C*H*HC=O), 2.10 (qd, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.1 Hz, 2H; C*H*$_2$CH=CH), 1.76 (dt, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 9.0 Hz, 1H; CH*H*CHOH), 1.56 (ddd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 5.2, 2.7 Hz, 1H; C*H*HCHOH), 1.39 (quint, $^3J_{H,H}$ = 7.3 Hz, 2H; C*H*$_2$CH$_2$CH=CH), 1.35-1.21 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, $^3J_{H,H}$ = 6.8 Hz, 3H; CH$_2$C*H*$_3$), 0.87 (s, 9H; C*H*$_3$CSi), 0.08 (s, 3H; C*H*$_3$Si), 0.04 (s, 3H; C*H*$_3$Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.7 (*C*=O), 137.6 (CH=*C*HCH$_2$), 131.4 (CH=*C*HCHOTBS), 129.0 (*C*H=CHCHOTBS), 125.0 (*C*H=CHCH$_2$), 69.2 (*C*HOTBS), 67.3 (*C*HOH), 51.8 (*C*H$_3$O), 44.1 (*C*H$_2$CHOTBS), 41.9 (*C*H$_2$C=O), 32.9 (*C*H$_2$CH=CH), 31.5 (*C*H$_2$CH$_2$CH$_3$), 29.0 (*C*H$_2$CH$_2$CH=CH), 26.0 (3C, *C*H$_3$CSi), 22.6 (*C*H$_2$CH$_3$), 18.1 (*C*Si), 14.2 (CH$_2$*C*H$_3$), –3.7 (*C*H$_3$Si), –4.7 (*C*H$_3$Si).

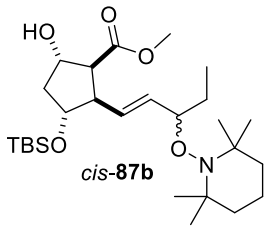
IR (film): v = 3494 (br), 2955, 2927, 2855, 1968, 1739, 1463, 1438, 1362 1255, 1199, 1167, 1073, 1006, 987, 950, 913, 874, 812, 778, 743, 629 cm^{-1}.
MS (+CI) m/z (%): 385 (27) $[M+H]^+$, 367 (43) $[M+H-H_2O]^+$, 253 (100) $[M+H-TBSO]^+$, 235 (48) $[M+H-TBSO-H_2O]^+$, 117 (46) $[CH_2CH(OH)CH_2CO_2Me]^+$, 103 (36) $[CH(OH)CH_2CO_2Me]^+$, 71 (38) $[C_5H_{11}]^+$.
HRMS (+CI) m/z: calcd for $C_{21}H_{41}O_4Si+H^+$: 385.2774 $[M+H]^+$, found: 385.2776.

6.4.2 Synthesis of common precursor 179c

6.4.2.1 Oxidative dianion cyclization of precursors **84b**, **84c** *and (6Z,8E)*-**84a**

Methyl (1*S,2*R**3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)cyclopentane-1-carboxylate *cis*-87b** and **methyl (1*R**,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)cyclopentane-1-carboxylate *trans*-87b**

Representative procedure (method **A**): Anhydrous LiCl (158 mg, 2.72 mmol) was flame-dried in a Schlenk flask at ca 580 °C under reduced pressure. After cooling to room temperature, the flask was filled with dry nitrogen by three vacuum/nitrogen cycles. Dry DME (7 mL) was added, the suspension was cooled to –78 °C (EtOH/dry ice bath) and dry *i*-Pr_2NH (245 µL, 1.75 mmol) was added, followed by dropwise addition of *n*-BuLi (1.04 mL, 1.47 M in hexanes, 1.53 mmol). The reaction mixture was stirred at this temperature for 80 min. Methyl ester **84b** (150 mg, 0.44 mmol) in dry DME (1 mL) was added by cannula and the flask was rinsed with dry DME (2×0.5 mL). The reaction mixture was quickly warmed to –50 °C and further to –35 °C over 75 min. The mixture was cooled to –78 °C, dry HMPA (914 µL, 5.25 mmol) was added and the previously turbid yellow solution became clear and bright orange. TEMPO (82 mg, 0.53 mmol) mixed with a small portion of ferrocenium hexafluorophosphate (29 mg, 0.09 mmol) was added, followed by small portions of more ferrocenium hexafluorophosphate (218 mg, 0.66 mmol) against a flow of nitrogen with vigorous stirring until a dark blue-green color of the reaction mixture persisted for more than 5 min. The reaction mixture was warmed with stirring to –55 °C over 40 min, quenched by a few drops of water, which induced a color change to maroon, diluted with Et_2O (ca 30 mL) and warmed to room temperature. The mixture was filtered through a pad of silica gel, which was thoroughly washed with Et_2O (ca 100 mL). The filtrate was directly adsorbed on silica gel and purified after evaporation of the solvent by column chromatography (50 mL silica gel, PE/EtOAc gradient 50:1 to 5:1) providing *cis*-**87b** and *trans*-**87b** (137 mg, 63%) as inseparable 2.3:1 diastereomeric mixture, each as a 1.7:1 mixture of C*H*(OTMP) epimers as determined by ^1H NMR spectroscopy, from which minor diastereomer *trans*-**87b** elutes first, as a yellow oil.
Note: The procedure on 1.5 mmol scale provided *cis*-**87b** and *trans*-**87b** with repetitive 55-60% yield and 2.3:1 diastereoselectivity.
R_f = 0.22 (PE/EtOAc 9:1).



cis-**87b**

Major diastereomer:

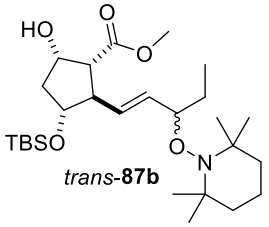
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (dd, $^{3}J_{H,H}$ = 15.4, 7.9 Hz, 1H), 5.18 (dd, $^{3}J_{H,H}$ = 15.5, 9.1 Hz, 1H), 4.56-4.50 (m, 1H), 4.10-4.05 (m, 1H), 3.92-3.87 (m, 1H), 3.67 (s, 3H), 3.27-3.22 (m, 1H), 3.07-2.99 (m, 1H), 2.53 (d, $^{3}J_{H,H}$ = 7.8 Hz, 1H), 2.39-2.34 (m, 1H), 1.78-1.69 (m, 2H), 1.47-1.41 (m, 7H), 1.16-1.00 (m, 12H), 0.88 (s, 9H), 0.80 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 135.8, 128.0, 85.7, 78.8, 74.34, 60.3, 60.0, 56.3, 53.8, 51.8, 42.6, 40.35 (2C), 35.6, 34.0, 27.3, 25.90 (3C), 20.5, 20.4, 18.1, 17.40, 9.9, –4.60, –4.75.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (dd, $^{3}J_{H,H}$ = 15.4, 7.9 Hz, 1H), 5.08 (dd, $^{3}J_{H,H}$ = 15.3, 9.9 Hz, 1H), 4.62-4.55 (m, 1H), 4.16-4.11 (m, 1H), 3.91-3.86 (m, 1H), 3.62 (s, 3H), 3.28-3.22 (m, 1H), 3.07-3.00 (m, 1H), 2.57 (d, $^{3}J_{H,H}$ = 8.3 Hz, 1H), 2.39-2.34 (m, 1H), 1.78-1.69 (m, 2H), 1.47-1.41 (m, 7H), 1.13-1.00 (m, 12H), 0.886 (s, 9H), 0.78 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.062 (s, 3H), 0.058 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 136.6, 127.8, 86.0, 78.6, 74.28, 60.3, 60.0, 56.8, 54.6, 51.6, 42.5, 40.37 (2C), 35.5, 34.0, 27.6, 25.87 (3C), 20.5, 20.4, 18.1, 17.40, 9.8, –4.65, –4.78.



trans-**87b**

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (dd, $^{3}J_{H,H}$ = 15.8, 8.5 Hz, 1H), 5.31 (dd, $^{3}J_{H,H}$ = 15.5, 8.3 Hz, 1H), 4.49-4.42 (m, 1H), 4.10-4.05 (m, 1H), 3.94 (td, $^{3}J_{H,H}$ = 8.2, 4.5 Hz, 1H), 3.72 (s, 3H), 3.32 (d, $^{3}J_{H,H}$ = 9.7 Hz, 1H), 3.26 (dt, $^{3}J_{H,H}$ = 8.0, 4.7 Hz, 1H), 2.72 (dd, $^{3}J_{H,H}$ = 8.2, 5.3 Hz, 1H), 1.99-1.90 (m, 2H), 1.78-1.70 (m, 1H), 1.52-1.36 (m, 7H), 1.13 (br s, 3H), 1.09 (br s, 3H), 1.05 (br s, 6H), 0.888 (s, 9H), 0.82 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.073 (s, 3H), 0.065 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 134.0, 131.5, 86.3, 79.7, 75.4, 60.3, 60.0, 56.7, 52.1, 51.92, 43.2, 40.33 (2C), 35.5, 34.2, 27.5, 25.92 (3C), 20.5, 20.4, 18.0, 17.39, 10.0, –4.60, –4.80.

Minor diastereomer:

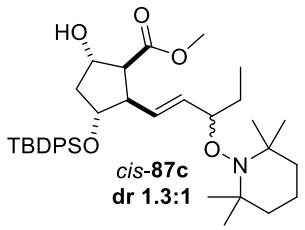
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (dd, $^{3}J_{H,H}$ = 15.2, 8.3 Hz, 1H), 5.33 (dd, $^{3}J_{H,H}$ = 15.8, 8.4 Hz, 1H), 4.49-4.42 (m, 1H), 4.16-4.10 (m, 1H), 3.92 (td, $^{3}J_{H,H}$ = 8.4, 4.2 Hz, 1H), 3.72 (s, 3H), 3.39 (d, $^{3}J_{H,H}$ = 9.8 Hz, 1H), 3.26 (dt, $^{3}J_{H,H}$ = 8.0, 4.7 Hz, 1H), 2.68 (dd, $^{3}J_{H,H}$ = 8.1, 5.2 Hz, 1H), 1.98-1.90 (m, 2H), 1.75-1.65 (m, 1H), 1.51-1.37 (m, 7H), 1.13 (br s, 3H), 1.11 (s, 3H), 1.03 (s, 6H), 0.886 (s, 9H), 0.78 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 133.6, 131.3, 86.2, 79.4, 75.2, 60.3, 60.0, 56.7, 52.1, 51.88,

43.1, 40.30 (2C), 35.5, 34.2, 27.4, 25.94 (3C), 20.5, 20.4, 18.0, 17.38, 10.0, –4.5, –4.80.
MS (+ESI) m/z (%): 498 (100) $[M+H]^+$.
HRMS (+ESI) m/z: calcd for $C_{27}H_{51}NO_5Si+H^+$: 498.3609 $[M+H]^+$, found: 498.3608.
The analytical data are in accordance with the published values.[99]

Methyl (1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldiphenylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)cyclopentane-1-carboxylate *cis*-87c** and **methyl (1*R**,2*R**,3*R**,5*S**)-3-((*tert*-butyldiphenylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)cyclopentane-1-carboxylate *trans*-87c**

Method B: Anhydrous LiCl (24 mg, 0.57 mmol) was flame-dried in a Schlenk flask at ca 580 °C under reduced pressure. After cooling to room temperature, the flask was filled with dry nitrogen by three vacuum/nitrogen cycles. Dry THF (1 mL) was added, the solution was cooled to –78 °C and dry *i*-Pr_2NH (36 µL, 0.25 mmol) was added, followed by dropwise addition of *n*-BuLi (153 µL, 1.6 M in hexanes, 0.24 mmol). The reaction mixture was stirred at this temperature for 50 min. Methyl ester **84c** (44 mg, 94 µmol) in dry THF (1 mL) was added by cannula. The reaction mixture was warmed with stirring to –40 °C over 40 min before and cooled to –78 °C. Dry HMPA (197 µL, 1.13 mmol) was added and the previously yellow solution turned bright red. TEMPO (18 mg, 113 µmol) was added in one portion, followed by small portions of ferrocenium hexafluorophosphate until a deep green color persisted (53 mg, 0.16 mmol). The reaction mixture was warmed with stirring to –35 °C over 2 h, quenched by a few drops of water, diluted with Et_2O (5 mL) and warmed to room temperature. The heterogeneous mixture was filtered through a pad of silica gel, which was washed thoroughly with Et_2O (ca 15 mL). The filtrate was directly adsorbed on silica gel and purified after evaporation of the solvent by column chromatography (20 mL of silica gel, PE/EtOAc gradient 80:1 to 2:1) providing hydroxycyclopentanecarboxylate **87c** (39 mg, 66%) as inseparable 1.5:1 *cis*-/*trans*-**87c** mixture, each as a mixture of C*H*(OTMP) epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a yellow oil.
R_f = 0.32 (PE/EtOAc 5:1).



Major diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.61 (m, 4H; CH_{Ar}), 7.48-7.34 (m, 6H; CH_{Ar}), 5.05-4.93 (m, 1H; CH=C*H*CHOTMP), 4.99-4.90 (m, 1H; C*H*=CHCHOTMP), 4.66-4.53 (m, 1H; C*H*OH), 4.05 (dt, $^3J_{H,H}$ = 4.6, 1.9 Hz, 1H; C*H*OTBDPS), 3.77-3.45 (m, 1H; C*H*OTMP), 3.66 (s, 3H, CH_3O), 3.44-3.37 (m, 1H; C*H*C=O), 3.00 (td, $^3J_{H,H}$ = 8.1, 2.2 Hz, 1H; C*H*CHOTBDPS), 2.56 (d, $^3J_{H,H}$ = 7.5 Hz, 1H; O*H*), 2.27-2.21 (m, 1H; CH*H*CHOH), 1.78-1.70 (m, 1H; C*H*HCHOH), 1.68-1.54 (m, 1H; CH*H*CHOTMP), 1.59-1.46 (m, 1H; CH*H*CH_2CN), 1.44-1.30 (m, 5H; CH_2CN, C*H*HCHOTMP),

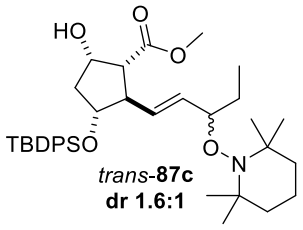
1.29-1.20 (m, 1H; CH*H*CH_2CN), 1.12-1.00 (m, 21H; C*H*$_3$CN, C*H*$_3$CSi), 0.69 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$$CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (*C*=O), 136.13 (CH=*C*HCHOTMP), 135.94 (4C; *C*H_{Ar}), 133.64 (2C; *C*$_{Ar}$Si), 129.96 (2C; *C*H_{Ar}), 127.86 (4C; *C*H_{Ar}), 127.4 (*C*H=CHCHOTMP), 85.8 (*C*HOTMP), 80.0 (*C*HOTBDPS), 74.2 (*C*HOH), 60.3 (*C*N), 58.9 (*C*N), 56.00 (*C*HC=O), 53.7 (*C*HCHOTBDPS), 52.0 (*C*H_3O), 42.1 (*C*H_2CHOH), 40.34 (2C; *C*H_2CN), 35.3 (*C*H_3CN), 34.0 (*C*H_3CN), 27.3 (*C*H_2CH_3), 27.14 (3C; *C*H_3CSi), 20.5 (*C*H_3CN), 20.4 (*C*H_3CN), 19.24 (*C*Si), 17.41 (*C*H_2CH_2CN), 9.9 (*C*H_3CH_2).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.61 (m, 4H; C*H*$_{Ar}$), 7.48-7.34 (m, 6H; C*H*$_{Ar}$), 5.24-5.19 (m, 1H; CH=C*H*CHOTMP), 4.99-4.90 (m, 1H; C*H*=CHCHOTMP), 4.66-4.53 (m, 1H; C*H*OH), 4.11-4.08 (m, 1H; C*H*OTBDPS), 3.77-3.45 (m, 1H; C*H*OTMP), 3.63 (s, 3H, C*H*$_3$O), 3.37-3.28 (m, 1H; C*H*C=O), 3.12-3.02 (m, 1H; C*H*CHOTBDPS), 2.43 (d, $^3J_{H,H}$ = 8.0 Hz, 1H; O*H*), 1.96-1.89 (m, 1H; CH*H*CHOH), 1.78-1.70 (m, 1H; C*H*HCHOH), 1.68-1.54 (m, 1H; CH*H*CHOTMP), 1.59-1.46 (m, 1H; CH*H*CH_2CN), 1.44-1.30 (m, 4H; C*H*$_2$CN), 1.29-1.20 (m, 2H; C*H*HCHOTMP, C*H*HCH_2CN), 1.12-1.00 (m, 21H; C*H*$_3$CN, C*H*$_3$CSi), 0.61 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$$CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (*C*=O), 136.4 (CH=*C*HCHOTMP), 135.88 (4C; *C*H_{Ar}), 133.58 (2C; *C*$_{Ar}$Si), 130.03 (2C; *C*H_{Ar}), 127.89 (4C; *C*H_{Ar}), 127.1 (*C*H=CHCHOTMP), 86.2 (*C*HOTMP), 80.9 (*C*HOTBDPS), 73.8 (*C*HOH), 60.3 (*C*N), 58.9 (*C*N), 56.6 (*C*HC=O), 54.0 (*C*HCHOTBDPS), 51.9 (*C*H_3O), 42.8 (*C*H_2CHOH), 40.30 (2C; *C*H_2CN), 35.3 (*C*H_3CN), 34.0 (*C*H_3CN), 27.19 (*C*H_2CH_3), 27.16 (3C; *C*H_3CSi), 20.5 (*C*H_3CN), 20.4 (*C*H_3CN), 19.17 (*C*Si), 17.35 (*C*H_2CH_2CN), 9.7 (*C*H_3CH_2).



trans-**87c**
dr 1.6:1

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.61 (m, 4H; C*H*$_{Ar}$), 7.48-7.34 (m, 6H; C*H*$_{Ar}$), 5.24-5.12 (m, 1H; CH=C*H*CHOTMP), 5.08-4.99 (m, 1H; C*H*=CHCHOTMP), 4.47-4.40 (m, 1H; C*H*OH), 4.18-4.14 (m, 1H; C*H*OTBDPS), 3.77-3.45 (m, 1H; C*H*OTMP), 3.75 (s, 3H; C*H*$_3$O), 3.44-3.37 (m, 1H; C*H*CHOTBDPS), 2.72 (dd, $^3J_{H,H}$ = 7.2, 5.2 Hz, 1H; C*H*C=O), 2.20-2.15 (m, 1H; CH*H*CHOH), 1.95-1.94 (br s, 1H; O*H*), 1.80-1.71 (m, 1H; C*H*HCHOH), 1.68-1.54 (m, 1H; CH*H*CHOTMP), 1.59-1.46 (m, 1H; CH*H*CH_2CN), 1.41-1.30 (m, 5H; CH*H*CHOTMP, C*H*$_2$CN), 1.29-1.20 (m, 1H; CH*H*CH_2CN), 1.12-1.00 (m, 21H; C*H*$_3$CN, C*H*$_3$CSi), 0.70 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$$CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (*C*=O), 136.2 (CH=*C*HCHOTMP), 135.90 (4C; *C*H_{Ar}), 133.7 (2C; *C*$_{Ar}$Si), 131.3 (*C*H=CHCHOTMP), 129.9 (2C; *C*H_{Ar}), 127.89 (4C; *C*H_{Ar}), 86.1 (*C*HOTMP), 79.0 (*C*HOTBDPS), 75.5 (*C*HOH) 60.3 (*C*N), 58.9 (*C*N), 56.4 (*C*HC=O), 52.07 (*C*H_3O), 51.7 (*C*HCHOTBDPS), 42.2 (*C*H_2CHOH), 40.34 (2C; *C*H_2CN), 35.3 (*C*H_3CN), 34.0

(*C*H$_3$CN), 27.4 (*C*H$_2$CH$_3$), 27.07 (3C; *C*H$_3$CSi), 20.5 (*C*H$_3$CN), 20.4 (*C*H$_3$CN), 19.11 (*C*Si), 17.39 (*C*H$_2$CH$_2$CN), 10.04 (*C*H$_3$CH$_2$).

Minor diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.74-7.61 (m, 4H; C*H*$_{Ar}$), 7.48-7.34 (m, 6H; C*H*$_{Ar}$), 5.27-5.18 (m, 1H; CH=C*H*CHOTMP), 5.18-5.13 (m, 1H; C*H*=CHCHOTMP), 4.41-4.35 (m, 1H; C*H*OH), 4.16-4.11 (m, 1H; C*H*OTBDPS), 3.86-3.78 (m, 1H; C*H*OTMP), 3.74 (s, 3H; C*H*$_3$O), 3.44-3.37 (m, 1H; C*H*CHOTBDPS), 2.69 (dd, $^3J_{H,H}$ = 8.7, 5.7 Hz, 1H; C*H*C=O), 1.96-1.89 (m, 2H; CH*H*CHOH, O*H*), 1.78-1.70 (m, 1H; C*H*HCHOH), 1.68-1.54 (m, 1H; CH*H*CHOTMP), 1.59-1.46 (m, 1H; CH*H*CH$_2$CN), 1.41-1.30 (m, 4H; C*H*$_2$CN), 1.29-1.20 (m, 2H; CH*H*CH$_2$CN, CH*H*CHOTMP), 1.12-1.00 (m, 21H; C*H*$_3$CN, C*H*$_3$CSi), 0.61 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.6 (*C*=O), 136.09 (CH=*C*HCHOTMP), 136.0 (4C; *C*H$_{Ar}$), 133.5 (2C; *C*$_{Ar}$Si), 131.0 (*C*H=CHCHOTMP), 130.1 (2C; *C*H$_{Ar}$), 127.92 (4C; *C*H$_{Ar}$), 86.0 (*C*HOTMP), 80.1 (*C*HOTBDPS), 75.0 (*C*HOH), 60.3 (*C*N), 58.9 (*C*N), 55.97 (*C*HC=O), 52.06 (*C*H$_3$O), 51.4 (*C*HCHOTBDPS), 42.9 (*C*H$_2$CHOH), 40.30 (2C; *C*H$_2$CN), 35.3 (*C*H$_3$CN), 34.0 (*C*H$_3$CN), 27.4 (*C*H$_2$CH$_3$), 27.10 (3C; *C*H$_3$CSi), 20.5 (*C*H$_3$CN), 20.4 (*C*H$_3$CN), 19.14 (*C*Si), 17.43 (*C*H$_2$CH$_2$CN), 9.98 (*C*H$_3$CH$_2$).

IR (film): *v* = 3443 (br), 3072, 2930, 2857, 1735, 1589, 1463, 1428, 1374, 1360, 1258, 1242, 1207, 1171, 1131, 1110, 1083, 999, 971, 917, 854, 822, 740, 702, 612 cm^{-1}.

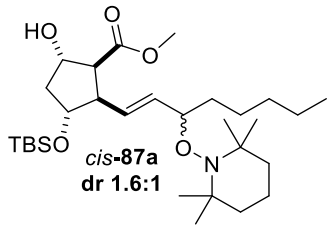
MS (+ESI) m/z (%): 1265 (10) [2*M*+Na]$^+$, 644 (15) [*M*+Na]$^+$, 622 (100) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for C$_{37}$H$_{55}$NO$_5$Si+H$^+$: 622.3922 [*M*+H]$^+$, found: 622.3917.

Methyl (1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)oct-1-en-1-yl)cyclopentane-1-carboxylate *cis*-87a** and **methyl (1*R**,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)oct-1-en-1-yl)cyclopentane-1-carboxylate *trans*-87a**

Prepared in analogy to **87c** starting from ester (6*Z*,8*E*)-**84a** (24 mg, 62 μmol) yielding **87a** (15 mg, 43%) as inseparable 1.6:1 mixture of *cis*-/*trans*-**87a**, each as a mixture of C*H*(OTMP) epimers (*vide infra*) as determined by ^{1}H NMR spectroscopy as a colorless oil.

R_f = 0.30 (PE/EtOAc 5:1).



Major diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.48 (dd, $^3J_{H,H}$ = 15.4, 7.9 Hz, 1H), 5.06 (dd, $^3J_{H,H}$ = 15.5, 9.8 Hz, 1H), 4.53 (dt, $^3J_{H,H}$ = 7.7, 4.2 Hz, 1H), 4.11-4.04 (m, 1H), 4.00-3.88 (m, 1H), 3.68 (s, 3H), 3.29-3.19 (m, 1H), 3.07-2.99 (m, 1H), 2.52 (d, $^3J_{H,H}$ = 8.0 Hz, 1H), 2.34 (dt, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H), 1.78-1.59 (m, 2H), 1.47-1.41 (m, 7H), 1.27-1.16 (m, 6H), 1.16-1.00 (m, 12H),

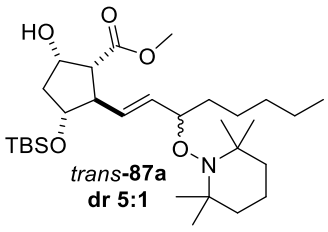
0.89 (s, 9H), 0.80 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.064 (s, 3H), 0.059 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 137.1, 127.67, 84.92, 78.69, 74.40, 59.3, 59.2, 56.8, 54.6, 51.6, 42.6, 40.4 (2C), 35.7, 35.2, 34.9, 32.3, 26.00 (3C), 25.1, 22.8, 20.6, 20.4, 18.1, 17.4, 14.2, –4.71, –4.75.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (dd, $^{3}J_{H,H}$ = 15.4, 7.9 Hz, 1H), 5.16 (dd, $^{3}J_{H,H}$ = 15.5, 9.1 Hz, 1H), 4.62-4.56 (m, 1H), 4.16-4.12 (m, 1H), 3.98-3.88 (m, 1H), 3.62 (s, 3H), 3.23 (dd, $^{3}J_{H,H}$ = 9.1, 4.5 Hz, 1H), 3.07-2.99 (m, 1H), 2.56 (d, $^{3}J_{H,H}$ = 8.0 Hz, 1H), 2.38-2.29 (m, 1H), 1.78-1.59 (m, 2H), 1.47-1.41 (m, 7H), 1.27-1.16 (m, 6H), 1.16-1.00 (m, 12H), 0.87 (s, 9H), 0.80 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.073 (s, 3H), 0.068 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 136.3, 127.9, 84.6, 78.8, 74.3, 59.3, 59.2, 56.3, 53.8, 51.8, 42.7, 40.4 (2C), 34.6, 34.3 (2C), 32.2, 25.97 (3C), 25.3, 22.9, 20.6, 20.4, 18.1, 17.5, 14.2, –4.6, –4.71.



trans-**87a**
dr 5:1

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (dd, $^{3}J_{H,H}$ = 15.7, 8.5 Hz, 1H), 5.28 (dd, $^{3}J_{H,H}$ = 15.5, 8.4 Hz, 1H), 4.50-4.44 (m, 1H), 4.08-4.05 (m, 1H), 4.00-3.92 (m, 1H), 3.72 (s, 3H), 3.33 (d, $^{3}J_{H,H}$ = 10.0 Hz, 1H), 3.26-3.21 (m, 1H), 2.72 (dd, $^{3}J_{H,H}$ = 8.2, 5.3 Hz, 1H), 1.95-1.90 (m, 1H), 1.78-1.59 (m, 2H), 1.47-1.41 (m, 7H), 1.27-1.16 (m, 6H), 1.16-1.00 (m, 12H), 0.89 (s, 9H), 0.80 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.09 (s, 3H), 0.082 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 134.5, 131.4, 85.1, 79.7, 75.4, 59.3, 59.2, 56.8, 52.1, 51.9, 43.2, 40.3 (2C), 35.4, 34.6, 34.2, 34.0, 25.9 (3C), 25.2, 22.7, 20.7, 20.5, 18.0, 17.4, 14.0, –4.6, –4.77.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (dd, $^{3}J_{H,H}$ = 15.9, 7.9 Hz, 1H), 5.32 (dd, $^{3}J_{H,H}$ = 16.3, 8.1 Hz, 1H), 4.48-4.41 (m, 1H), 4.11-4.07 (m, 1H), 4.03-3.95 (m, 1H), 3.68 (s, 3H), 3.39 (d, $^{3}J_{H,H}$ = 9.8 Hz 1H), 3.29-3.24 (m, 1H), 2.68 (dd, $^{3}J_{H,H}$ = 8.2, 5.3 Hz, 1H), 1.98-1.93 (m, 1H), 1.78-1.59 (m, 2H), 1.47-1.41 (m, 7H), 1.27-1.16 (m, 6H), 1.16-1.00 (m, 12H), 0.87 (s, 9H), 0.80 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.09 (s, 3H), 0.085 (s, 3H).

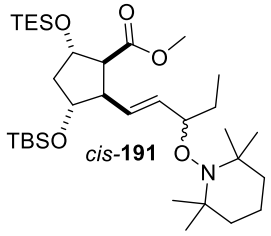
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 133.8, 130.9, 84.8, 79.1, 75.0, 59.3, 59.2, 56.5, 51.7, 51.6, 42.9, 40.0 (2C), 35.2, 34.3, 33.9, 31.7, 25.7 (3C), 25.0, 22.5, 20.3, 20.1, 17.8, 17.2, 13.9, –5.1, –5.3.

The analytical data are in accordance with the published values.[97]

6.4.2.2 Functionalization of cyclopentanecarboxylate **87b**

Methyl (1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentane-1-carboxylate *cis*-191 and Methyl (1*R**,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentane-1-carboxylate *trans*-191**

A flame dried Schlenk flask was charged with imidazole (320 mg, 4.70 mmol) and filled with nitrogen by three vacuum/nitrogen cycles. A mixture of *cis*-**87b** and *trans*-**87b** (1.17 g, 2.35 mmol, dr 2.3:1; combined from several cyclization experiments) in dry CH_2Cl_2 (30 mL) was added by cannula and the reaction mixture was cooled to –60 °C. TESCl (385 µL, 2.35 mmol) was dropwise added and the reaction mixture was stirred at this temperature for 40 min. Satd. aqueous NH_4Cl solution (20 mL) and water (10 mL) were subsequently added. After warming to room temperature, the layers were separated and the aqueous was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (100 mL silica gel, PE/Et_2O gradient 99:1 to 4:1) furnishing *cis*-**191** (858 mg, 1.39 mmol, 60%; 86% based on *cis*-**87b**) as inseparable 1.7:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil. Additionally, silylated product *trans*-**191** (221 mg, 0.36 mmol, 15%) as a mixture of diastereomers and starting *trans*-**87b** (190 mg, 16%) were isolated.



cis-**191**

R_f = 0.85 (PE/EtOAc 9:1).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52-5.44 (m, 1H), 5.22 (dd, $^3J_{H,H}$ = 15.7, 9.3 Hz, 1H), 4.45 (dt, $^3J_{H,H}$ = 7.3, 6.2 Hz, 1H), 4.01 (dt, $^3J_{H,H}$ = 6.5, 6.4 Hz, 1H), 3.98-3.90 (m, 1H), 3.66 (s, 3H), 3.05 (dd, $^3J_{H,H}$ = 9.2, 5.5 Hz, 1H), 2.93-2.82 (m, 1H), 2.44-2.31 (m, 1H), 1.78-1.66 (m, 2H), 1.65-1.56 (m, 1H), 1.50-1.34 (m, 5H), 1.34-1.24 (m, 1H), 1.12 (br s, 3H), 1.08 (br s, 3H), 1.06 (br s, 3H), 1.05 (br s, 3H), 0.93 (t, $^3J_{H,H}$ = 7.9 Hz, 9H), 0.86 (s, 9H), 0.83 (t, $^3J_{H,H}$ = 7.5 Hz, 3H), 0.56 (q, $^3J_{H,H}$ = 7.7 Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 135.9, 128.8, 85.7, 76.2, 72.76, 60.1, 59.3, 56.1, 53.1, 51.6, 44.5, 40.4 (2C), 35.1, 34.3, 27.5, 25.96 (3C), 20.6, 20.4, 18.1, 17.5, 10.0, 6.8 (3C), 4.78 (3C), –4.40, –4.54.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52-5.44 (m, 1H), 5.18 (dd, $^3J_{H,H}$ = 15.4, 8.8 Hz, 1H), 4.52 (dt, $^3J_{H,H}$ = 7.9, 6.0 Hz, 1H), 4.06 (dt, $^3J_{H,H}$ = 5.3, 5.2 Hz, 1H), 3.98-3.90 (m, 1H), 3.61 (s, 3H), 3.12 (dd,

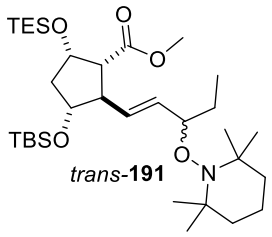
$^{3}J_{H,H}$ = 8.7, 6.2 Hz, 1H), 2.93-2.82 (m, 1H), 2.44-2.31 (m, 1H), 1.78-1.66 (m, 2H), 1.65-1.56 (m, 1H), 1.50-1.34 (m, 5H), 1.34-1.24 (m, 1H), 1.12 (br s, 3H), 1.08 (br s, 3H), 1.06 (br s, 3H), 1.05 (br s, 3H), 0.93 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H), 0.88 (s, 9H), 0.79 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.56 (q, $^{3}J_{H,H}$ = 7.7 Hz, 6H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 136.1, 128.5, 85.9, 76.5, 72.79, 60.1, 59.3, 56.5, 53.8, 51.5, 44.3, 40.5 (2C), 35.3, 34.2, 27.4, 26.02 (3C), 20.6, 20.4, 18.2, 17.5, 9.9, 6.8 (3C), 4.80 (3C), –4.39, –4.51.

MS (+ESI) m/z (%): 612 (100) $[M+H]^+$, 378 (2) $[M+Na–TEMPO]^+$.

HRMS (+ESI) m/z: calcd for $C_{33}H_{65}NO_5Si_2+H^+$: 612.4474 $[M+H]^+$, found: 612.4471.

The analytical data are in accordance with the published values.[99]



trans-**191**

R_f = 0.73 (PE/EtOAc 9:1).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (dd, $^{3}J_{H,H}$ = 15.7, 7.9 Hz, 1H), 5.37 (dd, $^{3}J_{H,H}$ = 15.5, 6.7 Hz, 1H), 4.41-4.34 (m, 1H), 3.95 (dt, $^{3}J_{H,H}$ = 7.9, 4.6 Hz, 1H), 3.75 (dt, $^{3}J_{H,H}$ = 8.7, 7.6 Hz, 1H), 3.640 (s, 3H), 3.12 (ddd, $^{3}J_{H,H}$ = 11.5, 8.6, 6.7 Hz, 1H), 2.67 (dd, $^{3}J_{H,H}$ = 11.4, 7.1 Hz, 1H), 2.28 (ddd, $^{2}J_{H,H}$ = 13.5 Hz, $^{3}J_{H,H}$ = 7.6, 6.3 Hz, 1H), 1.82-1.63 (m, 2H), 1.56-1.46 (m, 1H), 1.46-1.43 (m, 4H), 1.35-1.19 (m, 2H), 1.14 (br s, 3H), 1.09 (br s, 3H), 1.03 (br s, 3H), 1.00 (br s, 3H), 0.93 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H), 0.87 (s, 9H), 0.83 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.55 (q, $^{3}J_{H,H}$ = 8.2 Hz, 6H), 0.02 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 134.0, 131.5, 86.4, 76.1, 70.99, 60.1, 59.1, 54.0, 51.3, 50.5, 45.0, 40.34 (2C), 35.5, 34.1, 27.6, 25.88 (3C), 20.5, 20.3, 18.05, 17.41, 9.9, 6.8 (3C), 4.8 (3C), –4.3, –4.6.

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53-5.40 (m, 2H), 4.42-4.33 (m, 1H), 4.01-3.92 (m, 1H), 3.84-3.75 (m, 1H), 3.636 (s, 3H), 3.19-3.10 (m, 1H), 2.62 (dd, $^{3}J_{H,H}$ = 11.7, 6.8 Hz, 1H), 2.34-2.27 (m, 1H), 1.82-1.63 (m, 2H), 1.56-1.46 (m, 2H), 1.46-1.43 (m, 4H), 1.35-1.19 (m, 1H), 1.14 (br s, 3H), 1.09 (br s, 3H), 1.03 (br s, 3H), 1.00 (br s, 3H), 0.93 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H), 0.88 (s, 9H), 0.83 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H), 0.55 (q, $^{3}J_{H,H}$ = 8.2 Hz, 6H), 0.045 (s, 3H), 0.039 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 133.5, 131.1, 86.2, 76.3, 70.95, 60.1, 59.1, 54.2, 51.4, 50.0, 45.1, 40.30 (2C), 35.5, 34.1, 27.3, 25.94 (3C), 20.5, 20.3, 18.10, 17.44, 10.0, 6.8 (3C), 4.8 (3C), –4.4, –4.5.

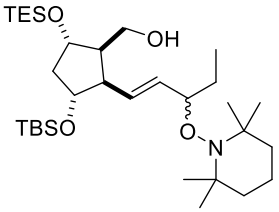
MS (+ESI) m/z (%): 612 (100) $[M+H]^+$.

HRMS (+ESI) m/z: calcd for $C_{33}H_{65}NO_5Si_2+H^+$: 612.4474 $[M+H]^+$, found: 612.4471.

The analytical data are in accordance with the published values.[99]

((1*R,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)methanol 192**

A flame-dried Schlenk flask was charged with ester *cis*-**191** (342 mg, 0.56 mmol), dry CH_2Cl_2 (5.6 mL) was added and the solution was cooled to –78 °C. DIBAL-H (1.4 mL, 1.0 M in toluene, 1.40 mmol) was added dropwise and the reaction mixture was stirred for 1 h when it was complete as indicated by TLC. After quenching with a few drops of MeOH and ceasing of hydrogen gas evolution, the reaction mixture was diluted with Et_2O (ca 30 mL), a few drops of water, Celite® (two spatulas) and $MgSO_4$ (two spatulas) were added and the mixture was warmed to room temperature with vigorous stirring over ca 20 min. The slurry was filtered through a plug of Celite® and sand, which was washed thoroughly with Et_2O. The filtrate was evaporated under reduced pressure and purified by column chromatography (20 mL silica gel, PE/Et_2O gradient 40:1 to 20:1 with 0.5 vol.% of Et_3N) affording alcohol **192** (300 mg, 92%) as inseparable 1.7:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.39 (PE/EtOAc 95:5).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61-5.37 (m, 2H), 4.17-3.98 (m, 1H), 3.89 (td, $^3J_{H,H}$ = 8.4, 6.8 Hz, 1H), 3.80 (ddd, $^3J_{H,H}$ = 7.5, 6.2, 5.0 Hz, 1H), 3.68 (d, $^3J_{H,H}$ = 5.8 Hz, 2H), 3.00 (t, $^3J_{H,H}$ = 7.0 Hz, 1H; O*H*), 2.67 (dt, $^3J_{H,H}$ = 10.1, 5.4 Hz, 1H), 2.45-2.18 (m, 2H), 1.78-1.23 (m, 9H), 1.16 (br s, 3H), 1.14 (br s, 3H), 1.07 (br s, 3H), 1.06 (br s, 3H), 0.95 (t, $^3J_{H,H}$ = 8.0 Hz, 9H), 0.91 (t, $^3J_{H,H}$ = 7.5 Hz, 3H), 0.87 (s, 9H), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H), 0.00 (s, 3H), –0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 133.6, 85.5, 76.0, 72.6, 62.0, 61.0, 59.6, 52.3, 52.0, 44.6, 39.8, 39.3, 34.3 (2C), 27.7, 25.96 (3C), 20.8, 20.73, 18.2, 17.42, 10.23, 7.0 (3C), 5.03 (3C), –4.5 (2C).

Minor diastereomer:

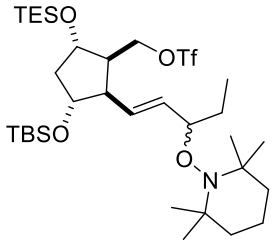
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61-5.37 (m, 2H), 4.17-3.98 (m, 3H), 3.71-3.65 (m, 1H), 3.59 (ddd, $^3J_{H,H}$ = 11.6, 7.5, 5.7 Hz, 1H), 2.80-2.71 (m, 1H), 2.57 (t, $^3J_{H,H}$ = 7.0 Hz, 1H; O*H*), 2.45-2.18 (m, 2H), 1.78-1.23 (m, 9H), 1.16 (br s, 3H), 1.12 (br s, 3H), 1.09 (br s, 3H), 1.07 (br s, 3H), 0.95 (t, $^3J_{H,H}$ = 7.5 Hz, 9H), 0.91 (t, $^3J_{H,H}$ = 7.5 Hz, 3H), 0.85 (s, 9H), 0.58 (q, $^3J_{H,H}$ = 7.9 Hz, 6H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.4, 131.2, 86.2, 74.3, 73.8, 63.0, 61.0, 59.6, 51.8, 50.7, 44.8, 40.5, 40.0, 34.4 (2C), 27.7, 25.98 (3C), 20.69, 20.66, 18.1, 17.45, 10.22, 6.9 (3C), 5.00 (3C), –4.1 (2C).

MS (+ESI) m/z (%): 584 (100) $[M+H]^+$.
HRMS (+ESI) m/z: calcd for $C_{32}H_{65}NO_4Si_2+H^+$: 584.4525 $[M+H]^+$, found: 584.4522.
The analytical data are in accordance with the published values.[99]

((1*R,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)methyl trifluoromethanesulfonate 88b**

An oven-dried round-bottomed 25 mL flask equipped with a stirring bar was charged with alcohol **192** (300 mg, 0.51 mmol) and flushed with nitrogen for 30 min. Dry CH_2Cl_2 (10 mL) was added and the reaction mixture was cooled to –78 °C. 2,6-Lutidine (89 µL, 0.77 mmol) was added, followed by dropwise addition of triflic anhydride (565 µL, 1.0 M solution in CH_2Cl_2, 0.57 mmol). The reaction mixture was stirred at the same temperature for 1 h when complete as indicated by TLC. The mixture was poured into cold PE (25 mL), filtered through a pad of Celite®, which was washed with PE, and evaporated under reduced pressure to give triflate **88b** (365 mg, quant.) as inseparable 1.7:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil, which was used without further purification.
R_f = 0.74 (PE/EtOAc 95:5).

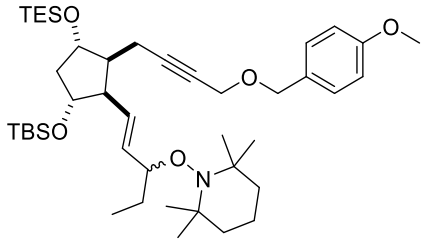


Major diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (ddd, $^3J_{H,H}$ = 15.4, 8.4 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H), 5.19 (dd, $^3J_{H,H}$ = 15.6, 9.6 Hz, 1H), 4.61 (d, $^3J_{H,H}$ = 6.3 Hz, 2H), 4.07-3.87 (m, 3H), 2.84-2.72 (m, 1H), 2.59 (dq, $^3J_{H,H}$ = 8.2, 6.4 Hz, 1H), 2.40 (ddd, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 7.9, 6.4 Hz, 1H), 1.79-1.68 (m, 1H), 1.67-1.59 (m, 1H), 1.57-1.35 (m, 6H), 1.34-1.21 (m, 1H), 1.14 (br s, 3H), 1.11 (br s, 3H), 1.06 (br s, 6H), 0.96 (t, $^3J_{H,H}$ = 8.0 Hz, 9H), 0.87 (s, 9H), 0.852 (t, $^3J_{H,H}$ = 7.4 Hz, 3H), 0.58 (q, $^3J_{H,H}$ = 7.7 Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 127.8, 118.8 (q, $^1J_{C,F}$ = 320 Hz), 85.8, 77.3, 75.82, 72.5, 60.3, 59.2, 51.7, 49.6, 44.5, 40.4 (2C), 35.0, 34.3, 27.4, 25.9 (3C), 20.5 (2C), 18.13, 17.4, 10.0, 6.8 (3C), 4.9 (3C), –4.52, –4.6.
Minor diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.56 (ddd, $^3J_{H,H}$ = 15.4, 8.4 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H), 5.12 (ddd, $^3J_{H,H}$ = 15.4, 9.6 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H), 4.58-4.44 (m, 2H), 4.07-3.87 (m, 3H), 2.84-2.72 (m, 1H), 2.68 (qd, $^3J_{H,H}$ = 7.9, 5.4 Hz, 1H), 2.44 (ddd, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 7.9, 6.4 Hz, 1H), 1.79-1.68 (m, 1H), 1.67-1.59 (m, 1H), 1.57-1.35 (m, 6H), 1.34-1.21 (m, 1H), 1.14 (br s, 3H), 1.11 (br s, 3H), 1.06 (br s, 6H), 0.95 (t, $^3J_{H,H}$ = 8.0 Hz, 9H), 0.88 (s, 9H), 0.854 (t, $^3J_{H,H}$ = 7.4 Hz, 3H), 0.59 (q, $^3J_{H,H}$ = 7.7 Hz, 6H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 126.9, 118.8 (q, $^1J_{C,F}$ = 320 Hz), 86.0, 77.2, 75.75, 72.2, 60.3, 59.2, 52.1, 49.5, 44.4, 40.4 (2C), 35.4, 34.2, 27.5, 26.0 (3C), 20.5 (2C), 18.14, 17.4, 9.9, 6.8 (3C), 4.9 (3C), –4.48, –4.52.
The analytical data are in accordance with the published values.[99]

(4-((1*R,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl))but-2-yn-1-yl *p*-methoxybenzyl ether 179a**

A flame-dried Schlenk flask was charged with *p*-methoxybenzyl propargyl ether **180a**[117] (17 µL, 94 µmol) under nitrogen. Dry THF (1.5 mL) and dry HMPA (0.4 mL) were added and the solution was cooled to –78 °C. *n*-BuLi (63 µL, 1.6 M in hexanes, 0.10 mmol) was added dropwise and the reaction mixture was stirred to –40 °C over 20 min. The mixture was cooled to –78 °C and triflate **88b** (45 mg, 63 µmol) in dry THF (0.4 mL) was added dropwise by cannula and the flask was rinsed with dry THF (0.1 mL); the solution turned dark orange. The reaction mixture was warmed to –10 °C with stirring over 90 min. Et_2O (2.5 mL) and water (5 mL) were added, the layers were separated and the aqueous was extracted with Et_2O (3×3 mL). The combined organic layers were washed with water (3 mL) and brine (3 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (5 mL of silica, PE/Et_2O gradient 20:1 to 10:1), the collected fraction (40 mg containing some **180a**) was dried at 60 °C under reduced pressure (1 mbar) for 2 h giving **179a** (30 mg, 64%) as inseparable 3.5:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.74 (PE/EtOAc 95:5).
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; CH_{Ar}), 6.87 (d, $^3J_{H,H}$ = 8.7 Hz, 2H; CH_{Ar}), 5.47 (dd, $^3J_{H,H}$ = 14.2, 8.3 Hz, 1H; CH=C*H*CHOTMP), 5.36 (dd, $^3J_{H,H}$ = 15.5, 8.8 Hz, 1H; C*H*=CHCHOTMP), 4.52 (s, 2H; ArCH_2O), 4.16-4.10 (m, 2H; CH_2OPMB), 4.08-3.93 (m, 3H; C*H*OTMP, C*H*OTBS, C*H*OTES), 3.81 (s, 3H; CH_3O), 2.82-2.71 (m, 1H; C*H*CHOTBS), 2.38 (dt, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 7.2 Hz, 1H; CH*H*CHOTBS), 2.47-2.22 (m, 3H; C*H*CHOTES, CH_2CHCHOTES), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.64-1.35 (m, 7H; C*H*HCHOTBS, C*H*HCHOTMP, CH_2CN, CH*H*CH_2CN), 1.36-1.22 (m, 1H; C*H*HCH_2CN), 1.15 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.05 (br s, 3H; CH_3CN), 0.952 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C$H_3$$CH_2$Si), 0.92-0.81 (m, 3H; C$H_3$$CH_2$CH), 0.86 (s, 9H; C$H_3$CSi), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.01 (s, 3H; CH_3Si), 0.00 (s, 3H; CH_3Si).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (*C*$_{Ar}$OMe), 135.4 (CH=*C*HCHOTMP), 130.3 (*C*H=CHCHOTMP), 129.9 (*C*$_{Ar}$$CH_2$), 129.8 (2C; *C*H$_{Ar}$), 113.9 (2C; *C*H$_{Ar}$), 86.6 (C≡*C*$CH_2$O), 86.2

(*C*HOTMP), 76.7 (*C*≡CCH$_2$O), 75.7 (*C*HOTES), 75.1 (*C*HOTBS), 70.91 (*C*H$_2$Ar), 60.2 (*C*N), 59.3 (*C*N), 57.5 (C≡C*C*H$_2$O), 55.5 (*C*H$_3$O), 52.9 (*C*HCHOTBS), 49.3 (*C*HCHOTES), 44.8 (*C*H$_2$CHOTBS), 40.4 (2C; *C*H$_2$CN), 35.0 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 27.6 (C*H$_2$*CHOTMP), 26.1 (3C; *C*H$_3$CSi), 20.6 (2C; *C*H$_3$CN), 18.5 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.5 (*C*H$_2$CH$_2$CN), 10.1 (*C*H$_3$CH$_2$CH), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.5 (2C; *C*H$_3$Si).

Minor diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28 (d, $^3J_{H,H}$ = 8.6 Hz, 2H; C*H*$_{Ar}$), 6.87 (d, $^3J_{H,H}$ = 8.7 Hz, 2H; C*H*$_{Ar}$), 5.51 (dd, $^3J_{H,H}$ = 14.9, 8.5 Hz, 1H; CH=C*H*CHOTMP), 5.24 (dd, $^3J_{H,H}$ = 15.4, 9.2 Hz, 1H; C*H*=CHCHOTMP), 4.53 (s, 2H; ArC*H$_2$*O), 4.16-4.10 (m, 2H; C*H$_2$*OPMB), 4.09-3.93 (m, 2H; C*H*OTMP, C*H*OTBS), 3.88 (dt, $^3J_{H,H}$ = 7.0, 6.9 Hz, 1H; C*H*OTES), 3.81 (s, 3H; C*H$_3$*O), 2.82-2.71 (m, 1H; C*H*CHOTBS), 2.42 (dt, $^2J_{H,H}$ = 15.5 Hz, $^3J_{H,H}$ = 7.6 Hz, 1H; CH*H*CHOTBS), 2.47-2.22 (m, 2H; C*H*CHOTES, CH*H*CHCHOTES), 2.20-2.08 (m, 1H; C*H*HCHCHOTES), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.64-1.35 (m, 7H; C*H*HCHOTBS, C*H*HCHOTMP, C*H$_2$*CN, CH*H*CH$_2$CN), 1.36-1.22 (m, 1H; C*H*HCH$_2$CN), 1.15 (br s, 3H; C*H$_3$*CN), 1.10 (br s, 6H; C*H$_3$*CN), 1.05 (br s, 3H; C*H$_3$*CN), 0.950 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H$_3$*CH$_2$Si), 0.92-0.81 (m, 3H; C*H$_3$*CH$_2$CH), 0.87 (s, 9H; C*H$_3$*CSi), 0.59 (q, $^3J_{H,H}$ = 8.0 Hz, 6H; C*H$_2$*Si), 0.03 (s, 3H; C*H$_3$*Si), 0.01 (s, 3H; C*H$_3$*Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.4 (*C*$_{Ar}$OMe), 135.7 (CH=*C*HCHOTMP), 129.9 (*C*$_{Ar}$CH$_2$), 129.8 (2C; *C*H$_{Ar}$), 128.9 (*C*H=CHCHOTMP), 113.9 (2C; *C*H$_{Ar}$), 86.5 (*C*HOTMP), 86.3 (C≡*C*CH$_2$O), 76.4 (*C*≡CCH$_2$O), 75.53 (*C*HOTES), 75.45 (*C*HOTBS), 70.87 (*C*H$_2$Ar), 60.2 (*C*N), 59.3 (*C*N), 57.4 (C≡C*C*H$_2$O), 55.5 (*C*H$_3$O), 52.4 (*C*HCHOTBS), 49.2 (*C*HCHOTES), 44.8 (*C*H$_2$CHOTBS), 40.5 (2C; *C*H$_2$CN), 35.4 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 27.6 (*C*H$_2$CHOTMP), 26.0 (3C; *C*H$_3$CSi), 20.6 (2C; *C*H$_3$CN), 18.6 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.5 (*C*H$_2$CH$_2$CN), 10.0 (*C*H$_3$CH$_2$CH), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.5 (2C; *C*H$_3$Si).

IR (film): ν = 2953, 2930, 2876, 2856, 1613, 1587, 1513, 1462, 1375, 1359, 1301, 1248, 1209, 1172, 1131, 1071, 1041, 1005, 972, 886, 834, 775, 744, 727, 671 cm^{-1}.

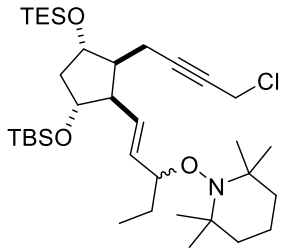
MS (+ESI) m/z (%) 765 (4) [*M*+Na]$^+$, 743 (100) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for C$_{43}$H$_{75}$NO$_5$Si$_2$+H$^+$: 742.5257 [*M*+H]$^+$, found: 742.5255.

4-((1*R,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)but-2-yn-1-yl chloride 179c**

A flame dried Schlenk flask was flushed with argon and dry *i*-Pr$_2$NH (94 µL, 0.67 mmol) and dry Et$_2$O (3 mL) were added. The solution was cooled to 0 °C, *n*-BuLi (386 µL, 1.6 M in hexanes, 0.62 mmol) was dropwise added and the reaction mixture was stirred at 0 °C for 30 min. After cooling to –100 °C (PE/liquid nitrogen bath), propargyl chloride **180c** (43 µL, 0.591 mmol) was dropwise added and the reaction mixture was stirred at the same temperature for 15 min. After cooling to –110 °C, crude triflate **88b** (365 mg, 0.51 mmol) in dry Et$_2$O (1.5 mL+ 0.2 mL rinse) was added dropwise via cannula followed by fast addition of dry HMPA (0.5 mL). The reaction mixture, which turned deep violet, was warmed with stirring to –50 °C over 1 h and poured into wet PE (50 mL). After reaching room temperature, satd. aqueous NH$_4$Cl solution (20 mL) was

added to the biphasic mixture. The layers were separated and the organic was washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (20 mL of silica, PE/MTBE) gradient 200:1 to 50:1) giving **179c** (265 mg, 81%) as inseparable 1.7:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.74 (PE/EtOAc 95:5).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (dd, $^3J_{H,H}$ = 14.5, 8.3 Hz, 1H; CH=C*H*CHOTMP), 5.32 (dd, $^3J_{H,H}$ = 15.4, 9.1 Hz, 1H; C*H*=CHCHOTMP), 4.13 (t, $^5J_{H,H}$ = 2.1 Hz, 2H; CH_2Cl), 4.00-3.91 (m, 3H; C*H*OTMP, C*H*OTBS, C*H*OTES), 2.79-2.67 (m, 1H; C*H*CHOTBS), 2.47-2.22 (m, 4H; C*H*CHOTES, CH_2CHCHOTES, CH*H*CHOTBS), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.64-1.35 (m, 7H; C*H*HCHOTBS, C*H*HCHOTMP, CH_2CN, CH*H*CH_2CN), 1.36-1.22 (m, 1H; C*H*HCH_2CN), 1.15 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.06 (br s, 3H; CH_3CN), 0.955 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C$H_3$$CH_2$Si), 0.92-0.81 (m, 3H; C$H_3$$CH_2$CH), 0.86 (s, 9H; C$H_3$CSi), 0.59 (q, $^3J_{H,H}$ = 8.0 Hz, 6H; CH_2Si), 0.02 (s, 3H; CH_3Si), 0.01 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5 (CH=*C*HCHOTMP), 130.2 (*C*H=CHCHOTMP), 87.4 (C≡*C*CH_2Cl), 86.2 (*C*HOTMP), 75.8 (*C*HOTES), 75.7 (*C*≡CCH_2Cl), 75.0 (*C*HOTBS), 60.2 (*C*N), 59.3 (*C*N), 52.5 (*C*HCHOTBS), 49.0 (*C*HCHOTES), 44.72 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.0 (*C*H_3CN), 34.3 (*C*H_3CN), 31.44 (*C*H_2Cl), 27.60 (C*H*$_2$CHOTMP), 26.00 (3C; *C*H_3CSi), 20.5 (2C; *C*H_3CN), 18.6 (*C*H_2CHCHOTES), 18.2 (*C*Si), 17.50 (*C*$H_2$$CH_2$CN), 10.1 (*C*$H_3$$CH_2$CH), 7.0 (3C; *C*$H_3$$CH_2$Si), 5.0 (3C; *C*$H_2$Si), –4.43 (*C*$H_3$Si), –4.46 (*C*$H_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (dd, $^3J_{H,H}$ = 15.5, 8.4 Hz, 1H; CH=C*H*CHOTMP), 5.21 (dd, $^3J_{H,H}$ = 15.4, 9.1 Hz, 1H; C*H*=CHCHOTMP), 4.12 (t, $^5J_{H,H}$ = 2.1 Hz, 2H; CH_2Cl), 4.00-3.91 (m, 2H; C*H*OTMP, C*H*OTBS), 3.87 (dt, $^3J_{H,H}$ = 6.9, 7.2 Hz, 1H; C*H*OTES), 2.79-2.67 (m, 1H; C*H*CHOTBS), 2.47-2.22 (m, 3H; C*H*CHOTES, CH*H*CHCHOTES, CH*H*CHOTBS), 2.14 (ddt, $^3J_{H,H}$ = 10.0, 7.6 Hz, $^5J_{H,H}$ = 2.3 Hz, 1H; C*H*HCHCHOTES), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.64-1.35 (m, 7H; C*H*HCHOTBS, C*H*HCHOTMP, CH_2CN, CH*H*CH_2CN), 1.36-1.22 (m, 1H; C*H*HCH_2CN), 1.15 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.06 (br s, 3H; CH_3CN), 0.949 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C$H_3$$CH_2$Si), 0.92-0.81 (m, 3H; C$H_3$$CH_2$CH), 0.88 (s, 9H; C$H_3$CSi), 0.58 (q, $^3J_{H,H}$ = 8.0 Hz, 6H; CH_2Si), 0.042 (s, 3H; CH_3Si), 0.039 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9 (CH=*C*HCHOTMP), 128.7 (*C*H=CHCHOTMP), 87.1 (C≡*C*CH_2Cl), 86.4 (*C*HOTMP), 75.7 (*C*≡CCH_2Cl), 75.5 (*C*HOTES), 75.4 (*C*HOTBS), 60.2 (*C*N), 59.3 (*C*N), 53.0 (*C*HCHOTBS), 48.9 (*C*HCHOTES), 44.74 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN),

35.4 (*C*H$_3$CN), 34.2 (*C*H$_3$CN), 31.42 (*C*H$_2$Cl), 27.63 (*C*H$_2$CHOTMP), 26.05 (3C; *C*H$_3$CSi), 20.5 (2C; *C*H$_3$*C*N), 18.7 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.48 (*C*H$_2$CH$_2$CN), 10.0 (*C*H$_3$CH$_2$CH), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.37 (2C; *C*H$_3$Si).

IR (film): ν = 2955, 2931, 2877, 2858, 1463, 1413, 1375, 1360, 1258, 1209, 1183, 1131, 1073, 1006, 973, 886, 836, 776, 745, 728, 697, 672, 647 cm^{-1}.

MS (+ESI) m/z (%): 642/640 (35/100) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{34}H_{67}{}^{35}ClNO_3Si_2$+H$^+$: 640.4343 [*M*(^{35}Cl)+H]$^+$, found: 640.4341.

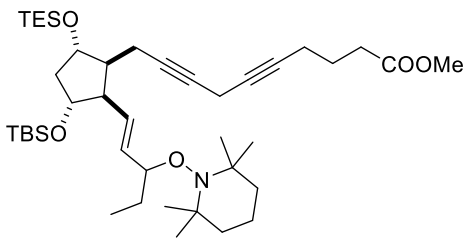
6.4.3 Total synthesis of 18-F$_{3t}$-IsoP

6.4.3.1 Assembly of the diyne scaffold

Methyl 10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)deca-5,8-diynoate 177a**

A flame-dried screw-cap tube was charged with CuI (98 mg, 0.51 mmol), NaI (77 mg, 0.51 mmol) and Cs_2CO_3 (168 mg, 0.51 mmol), sealed with a rubber septum and filled with dry argon by three vacuum/Ar cycles. A solution of propargyl chloride **179c** (110 mg, 0.17 mmol) in dry DMF (0.85 mL) and methyl hex-5-ynoate **178a** (68 μL, 0.51 mmol) were subsequently added, the septum was replaced by a screw-cap and the bright yellow suspension was stirred at room temperature for three days. The mixture was diluted with Et_2O (5 mL), quenched with satd. NH_4Cl solution (5 mL) and the biphasic mixture was vigorously stirred for 10 min. The layers were separated and the aqueous was extracted with Et_2O (3×6.5 mL). The combined organic layers were washed with satd. Na_2SO_3 solution (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (15 mL of silica gel, PE/MTBE gradient 200:1 to 25:1) providing diyne **177a** (99 mg, 79%) as inseparable 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a pale yellow oil.

Note: The product turns orange during re-evaporation and storage signaling formation of conjugated species, therefore it should be stored only under inert atmosphere at low temperature for short periods.



R_f = 0.46 (PE/EtOAc 95:5).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (dd, $^3J_{H,H}$ = 15.8, 8.0 Hz, 1H; CH=C*H*CHOTMP), 5.37 (dd, $^3J_{H,H}$ = 15.5, 8.8 Hz, 1H; C*H*=CHCHOTMP), 4.04-3.94 (m, 3H; C*H*OTES, C*H*OTBS, C*H*OTMP), 3.67 (s, 3H; C*H*$_3$O), 3.10 (quint, $^5J_{H,H}$ = 2.3 Hz, 2H;

C≡CC*H*$_2$C≡C), 2.78-2.69 (m, 1H; C*H*CHOTBS), 2.47-2.32 (m, 1H; CH*H*CHCHOTES), 2.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H*$_2$C=O), 2.38 (dt, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTBS), 2.30-2.14 (m, 2H; C*H*HCHCHOTES, C*H*CHOTES), 2.22 (tt, $^3J_{H,H}$ = 7.4 Hz, $^5J_{H,H}$ = 2.2 Hz, 2H; CH$_2$C*H*$_2$C≡C), 1.81 (quint, $^3J_{H,H}$ = 7.2 Hz, 2H; C*H*$_2$CH$_2$C=O), 1.712 (dquint, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 7.2 Hz, 1H; CH*H*CHOTMP), 1.63-1.51 (m, 1H; C*H*HCH$_2$CN), 1.57 (dt, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H; C*H*HCHOTBS), 1.52-1.35 (m, 5H; C*H*$_2$CN, C*H*HCHOTMP), 1.35-1.25 (m, 1H; CH*H*CH$_2$CN), 1.15 (br s, 3H; C*H*$_3$CN), 1.10 (br s, 6H; C*H*$_3$CN), 1.06 (br s, 3H; C*H*$_3$CN), 0.950 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.86 (s, 9H; C*H*$_3$CSi), 0.85 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$CH), 0.58 (q, $^3J_{H,H}$ = 7.7 Hz, 6H; C*H*$_2$Si), 0.012 (s, 3H; C*H*$_3$Si), 0.006 (s, 3H; C*H*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (*C*=O), 135.2 (CH=*C*HCHOTMP), 130.4 *C*H=CHCHOTMP), 86.3 (*C*HOTMP), 80.0 (CHCH$_2$*C*≡C), 79.08 (CH$_2$CH$_2$*C*≡C), 75.8 (*C*HOTES), 75.01 (CHCH$_2$C≡*C*), 75.00 (*C*HOTBS), 74.7 (CH$_2$CH$_2$C≡*C*), 60.1 (*C*N), 59.3 (*C*N), 52.4 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 49.4 (*C*HCHOTES), 44.76 (*C*H$_2$CHOTBS), 40.4 (2C; *C*H$_2$CN), 35.0 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 33.0 (*C*H$_2$C=O), 27.62 (*C*H$_2$CHOTMP), 26.02 (3C; *C*H$_3$CSi), 24.1 (*C*H$_2$CH$_2$C=O), 20.5 (2C; *C*H$_3$CN), 18.42 (*C*H$_2$CHCHOTES), 18.37 (CH$_2$*C*H$_2$C≡C), 18.2 (*C*Si), 17.49 (*C*H$_2$CH$_2$CN), 10.1 (*C*H$_3$CH$_2$CH), 9.93 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.41 (*C*H$_3$Si), –4.46 (*C*H$_3$Si).

Minor C18 epimer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (dd, $^3J_{H,H}$ = 15.3, 8.1 Hz, 1H; CH=C*H*CHOTMP), 5.22 (dd, $^3J_{H,H}$ = 15.4, 9.2 Hz, 1H; C*H*=CHCHOTMP), 4.04-3.94 (m, 2H; C*H*OTBS, C*H*OTMP), 3.88 (dt, $^3J_{H,H}$ = 7.6, 6.3 Hz, 1H; C*H*OTES), 3.67 (s, 3H; C*H*$_3$O), 3.10 (quint, $^5J_{H,H}$ = 2.3 Hz, 2H; C≡CC*H*$_2$C≡C), 2.78-2.69 (m, 1H; C*H*CHOTBS), 2.47-2.32 (m, 1H; CH*H*CHCHOTES), 2.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H*$_2$C=O), 2.38 (dt, $^2J_{H,H}$ = 14.0 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTBS), 2.30-2.14 (m, 1H; C*H*CHOTES), 2.22 (tt, $^3J_{H,H}$ = 7.4 Hz, $^5J_{H,H}$ = 2.2 Hz, 2H; CH$_2$C*H*$_2$C≡C), 2.06 (ddt, $^2J_{H,H}$ = 16.5 Hz, $^3J_{H,H}$ = 8.7 Hz, $^5J_{H,H}$ = 2.4 Hz, 1H; C*H*HCHCHOTES), 1.81 (quint, $^3J_{H,H}$ = 7.2 Hz, 2H; C*H*$_2$CH$_2$C=O), 1.706 (dquint, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.2 Hz, 1H; CH*H*CHOTMP), 1.63-1.51 (m, 1H; C*H*HCH$_2$CN), 1.56 (dt, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H; C*H*HCHOTBS), 1.52-1.35 (m, 5H; C*H*$_2$CN, C*H*HCHOTMP), 1.35-1.25 (m, 1H; CH*H*CH$_2$CN), 1.15 (br s, 3H; C*H*$_3$CN), 1.10 (br s, 6H; C*H*$_3$CN), 1.06 (br s, 3H; C*H*$_3$CN), 0.945 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.87 (s, 9H; C*H*$_3$CSi), 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; C*H*$_3$CH$_2$CH), 0.57 (q, $^3J_{H,H}$ = 7.7 Hz, 6H; C*H*$_2$Si), 0.04 (s, 3H; C*H*$_3$Si), 0.03 (s, 3H; C*H*$_3$Si).

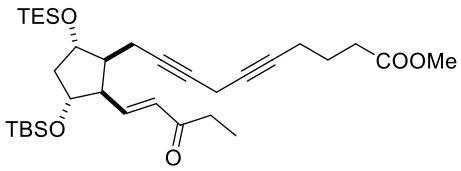
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (*C*=O), 135.6 (CH=*C*HCHOTMP), 129.0 *C*H=CHCHOTMP), 86.5 (*C*HOTMP), 79.7 (CHCH$_2$*C*≡C), 79.06 (CH$_2$CH$_2$*C*≡C), 75.6 (*C*HOTES), 75.4 (*C*HOTBS), 75.01 (CHCH$_2$C≡*C*), 74.7 (CH$_2$CH$_2$C≡*C*), 60.2 (*C*N), 59.2 (*C*N), 52.8 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 49.3 (*C*HCHOTES), 44.79 (*C*H$_2$CHOTBS), 40.4 (2C; *C*H$_2$CN), 35.4 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 33.0 (*C*H$_2$C=O), 27.64 (*C*H$_2$CHOTMP), 26.07 (3C; *C*H$_3$CSi), 24.1 (*C*H$_2$CH$_2$C=O), 20.5 (2C; *C*H$_3$CN), 18.57 (*C*H$_2$CHCHOTES), 18.37 (CH$_2$*C*H$_2$C≡C), 18.2 (*C*Si), 17.51 (*C*H$_2$CH$_2$CN), 10.0 (*C*H$_3$CH$_2$CH), 9.88 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.36 (*C*H$_3$Si), –4.44 (*C*H$_3$Si).

IR (film): *v* = 2953, 2929, 2876, 2857, 1742, 1462, 1436, 1416, 1374, 1360, 1313, 1249, 1209, 1162, 1131, 1099, 1070, 1005, 972, 886, 835, 775, 744, 727, 670 cm^{-1}.

MS (+ESI) m/z (%): 769 (5) $[M+K]^+$, 753 (45) $[M+Na]^+$, 731 (100) $[M+H]^+$.
HRMS (+ESI) m/z: calcd for $C_{42}H_{75}NO_5Si_2+H^+$: 730.5257 $[M+H]^+$, found: 730.5250.

Methyl 10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-oxopent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)deca-5,8-diynoate 193**

Protected triol **177a** (37 mg, 51 µmol) was dissolved in dry CH_2Cl_2 (3 mL), the solution was cooled to 0 °C and *m*CPBA (16 mg, 70% w/w, 66 µmol) was added. The reaction mixture was stirred at 0 °C for precisely 5 min, quenched with satd. aqueous Na_2SO_3 solution (5 mL) and diluted with water (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (5×5 mL). The combined organic layers were washed twice with satd. $NaHCO_3$ solution and water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (4 mL silica gel, hexane/HPLC-grade EtOAc gradient 20:1 with 0.5 vol.% of Et_3N) affording enone **193** (25 mg, 84%) as a yellow oil.

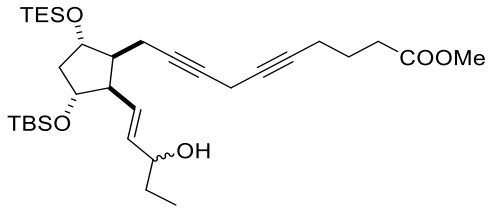


R_f = 0.21 (PE/Et_2O 95:5).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, $^3J_{H,H}$ = 15.7, 9.7 Hz, 1H; C*H*=CHC=O), 6.18 (dd, $^3J_{H,H}$ = 15.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1H; CH=C*H*C=O), 4.07-3.99 (m, 2H; C*H*OTES, C*H*OTBS), 3.67 (s, 3H; C*H*$_3$O), 3.10 (quint, $^5J_{H,H}$ = 2.3 Hz, 2H; C≡CC*H*$_2$C≡C), 2.88 (td, $^3J_{H,H}$ = 8.6, 6.3 Hz, 1H; C*H*CHOTBS), 2.57 (qd, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 0.7 Hz, 2H; CH$_3$C*H*$_2$C=O), 2.42 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; CH$_2$C*H*$_2$C=O), 2.45-2.34 (m, 1H; CH*H*CHOTES), 2.30 (quint, $^3J_{H,H}$ = 6.5 Hz, 1H; C*H*CHOTES), 2.23 (tt, $^3J_{H,H}$ = 7.0 Hz, $^5J_{H,H}$ = 2.4 Hz, 2H; CH$_2$C*H*$_2$C≡C), 2.14 (dt, $^3J_{H,H}$ = 7.0 Hz, $^5J_{H,H}$ = 2.4 Hz, 2H; C*H*$_2$CHCHOTES), 1.81 (quint, $^3J_{H,H}$ = 7.1 Hz, 2H; C*H*$_2$CH$_2$C=O), 1.68-1.57 (m, 1H; C*H*HCHOTES), 1.11 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; C*H*$_3$CH$_2$C=O), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.85 (s, 9H; C*H*$_3$CSi), 0.59 (q, $^3J_{H,H}$ = 8.2 Hz, 6H; C*H*$_2$Si), 0.01 (s, 3H; C*H*$_3$Si), –0.01 (s, 3H; C*H*$_3$Si).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8 (CH=CH*C*=O), 173.8 (CH$_3$O*C*=O), 145.0 (*C*H=CHC=O), 131.9 (CH=*C*HC=O), 79.3 (CH$_2$CH$_2$*C*≡C), 79.0 (CHCH$_2$*C*≡C), 76.0 (CH$_2$CH$_2$C≡*C*), 75.3 (CHCH$_2$C≡*C*), 75.1 (*C*HOTES), 74.7 (*C*HOTBS), 52.8 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 49.7 (*C*HCHOTES), 44.7 (*C*H$_2$CHOTBS), 33.8 (CH$_3$*C*H$_2$C=O), 33.1 (CH$_2$*C*H$_2$C=O), 25.9 (3C; *C*H$_3$CSi), 24.1 (*C*H$_2$CH$_2$C=O), 18.6 (CH*C*H$_2$C≡C), 18.4 (CH$_2$*C*H$_2$C≡C), 18.2 (*C*Si), 9.9 (C≡C*C*H$_2$C≡C), 8.3 (*C*H$_3$CH$_2$C=O), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.4 (*C*H$_3$Si), –4.5 (*C*H$_3$Si).
IR (film): ν = 2953, 2932, 2877, 2865, 1739, 1699, 1676, 1628, 1460, 1435, 1415, 1376, 1314, 1250, 1212, 1161, 1100, 1067, 1006, 835, 776, 744, 728, 698, 672 cm^{-1}.
MS (+ESI) m/z (%): 627 (6) $[M+K]^+$, 611 (100) $[M+Na]^+$, 589 (1) $[M+H]^+$.
HRMS (+ESI) m/z: calcd for $C_{33}H_{56}O_5Si_2+H^+$: 589.3739 $[M+H]^+$, found: 589.3734; calcd for $C_{33}H_{56}O_5Si_2+Na^+$: 611.3559 $[M+Na]^+$, found: 611.3553.

Methyl 10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-hydroxypent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)deca-5,8-diynoate 194a**

A solution of enone **193** (28 mg, 48 μmol) in dry MeOH (1.5 mL) was added to a flame-dried Schlenk flask under a nitrogen atmosphere. Anhydrous $CeCl_3$ (18 mg, 71 μmol) was added and the resulting slightly turbid solution was cooled to –78 °C. $NaBH_4$ (2.7 mg, 71 μmol) was added in three small portions and the reaction mixture was stirred at this temperature for 2 h. After quenching by a few drops of acetone, phosphate buffer (1.5 mL) was added, the mixture was warmed to room temperature with vigorous stirring and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (3 mL of silica gel, PE/EtOAc gradient 19:1 to 10:1 with 0.5 vol.% of Et_3N) giving **194a** (18 mg, 64%) as inseparable 1.2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.

Note: A low water content of $CeCl_3$ and performing the reaction at low temperature must be ensured, otherwise TES deprotection (*vide infra*) and other degradation occurs under the conditions.



R_f = 0.60 (PE/EtOAc 4:1).

Major C18 epimer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (dd, $^3J_{H,H}$ = 15.3, 6.4 Hz, 1H; CH=C*H*CHOH), 5.54-5.45 (m, 1H; C*H*=CHCHOH), 4.01 (dt, $^3J_{H,H}$ = 5.9, 5.4 Hz, 1H; C*H*OH), 3.98-3.90 (m, 2H; C*H*OTBS, C*H*OTES), 3.67 (s, 3H; CH_3O), 3.12-3.07 (m, 2H; C≡CCH_2C≡C), 2.76-2.68 (m, 1H; C*H*CHOTBS), 2.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; CH_2C=O), 2.35 (dt, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTES), 2.26-2.19 (m, 3H; C*H*CHOTES, CH$_2$CH_2C≡C), 2.14 (dt, $^3J_{H,H}$ = 6.3 Hz, $^3J_{H,H}$ = 2.3 Hz, 2H; CH_2CHCHOTES), 1.81 (quint, $^3J_{H,H}$ = 7.2 Hz, 2H; CH_2CH$_2$C=O), 1.64-1.47 (m, 4H; C*H*HCHOTES, CH_2CHOH; O*H*), 0.95 (t, $^3J_{H,H}$ = 8.0 Hz, 9H; CH_3CH$_2$Si), 0.93 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH_3CH$_2$CH), 0.86 (s, 9H; CH_3CSi), 0.58 (q, $^3J_{H,H}$ = 8.1 Hz, 6H; CH_2Si), 0.02 (s, 6H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (*C*=O), 135.7 (CH=*C*HCHOH), 129.5 (*C*H=CHCHOH), 79.6 (CHCH$_2$*C*≡C), 79.2 (CH$_2$CH$_2$*C*≡C), 75.7 (*C*HOTES), 75.5 (CH$_2$CH$_2$C≡*C*), 75.2 (CHCH$_2$C≡*C*), 74.9 (*C*HOTBS), 74.4 (*C*HOH), 52.6 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 49.16 (*C*HCHOTES), 44.6 (*C*H$_2$CHOTBS), 33.0 (*C*H$_2$C=O), 30.3 (CHOH*C*H$_2$), 25.99 (3C; *C*H$_3$CSi), 24.07 (*C*H$_2$CH$_2$C=O), 18.5 (CH*C*H$_2$C≡C), 18.3 (CH$_2$*C*H$_2$C≡C), 18.20 (*C*Si), 9.92 (*C*H$_3$CH$_2$CHO), 9.87 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.36 (*C*H$_3$Si), –4.37 (*C*H$_3$Si).

Minor C18 epimer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57 (dd, $^3J_{H,H}$ = 15.2, 6.0 Hz, 1H; CH=C*H*CHOH), 5.54-5.45 (m, 1H; C*H*=CHCHOH), 4.01 (dt, $^3J_{H,H}$ = 5.9, 5.4 Hz, 1H; C*H*OH), 3.98-3.90 (m, 2H; C*H*OTBS, C*H*OTES), 3.67 (s, 3H; CH_3O), 3.12-3.07 (m, 2H; C≡CCH_2C≡C), 2.76-2.68 (m, 1H; C*H*CHOTBS), 2.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; CH_2C=O), 2.35 (dt, $^2J_{H,H}$ = 13.9 Hz,

$^{3}J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTES), 2.26-2.19 (m, 3H; C*H*CHOTES, $CH_2CH_2C{\equiv}C$), 2.11 (dt, $^{3}J_{H,H}$ = 6.3 Hz, $^{5}J_{H,H}$ = 2.4 Hz, 2H; CH_2CHCHOTES), 1.81 (quint, $^{3}J_{H,H}$ = 7.2 Hz, 2H; CH_2CH$_2$C=O), 1.64-1.47 (m, 4H; C*H*HCHOTES, CH_2CHOH; O*H*), 0.95 (t, $^{3}J_{H,H}$ = 8.0 Hz, 9H; CH_3CH$_2$Si), 0.92 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3H; CH_3CH$_2$CH), 0.86 (s, 9H; CH_3CSi), 0.58 (q, $^{3}J_{H,H}$ = 8.1 Hz, 6H; CH_2Si), 0.01 (s, 3H; CH_3Si), 0.00 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8 (*C*=O), 135.8 (CH=*C*HCHOH), 129.9 (*C*H=CHCHOH), 79.8 ($CHCH_2C{\equiv}C$), 79.3 ($CH_2CH_2C{\equiv}C$), 75.7 (*C*HOTES), 75.5 ($CH_2CH_2C{\equiv}C$), 75.3 ($CHCH_2C{\equiv}C$), 74.8 (*C*HOTBS), 74.5 (*C*HOH), 52.5 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 49.20 (*C*HCHOTES), 44.6 (*C*H$_2$CHOTBS), 33.0 (*C*H$_2$C=O), 30.2 (CHOH*C*H$_2$), 25.98 (3C; *C*H$_3$CSi), 24.05 (*C*H$_2$CH$_2$C=O), 18.4 (CH*C*H$_2$C≡C), 18.3 (CH$_2$*C*H$_2$C≡C), 18.20 (*C*Si), 9.92 (*C*H$_3$CH$_2$CHO), 9.87 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.40 (*C*H$_3$Si), –4.44 (*C*H$_3$Si).

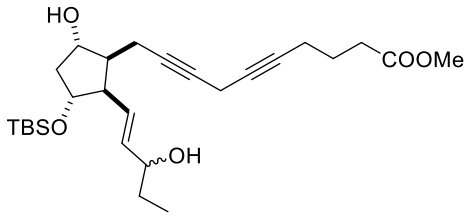
IR (film): *v* = 3466 (br), 2954, 2928, 2876, 2856, 1740, 1461, 1435, 1415, 1377, 1314, 1250, 1162, 1098, 1066, 1005, 972, 885, 834, 775, 743, 728, 698, 671 cm^{-1}.

MS (+ESI) m/z (%): 629 (5) [*M*+K]$^{+}$, 613 (100) [*M*+Na]$^{+}$.

HRMS (+ESI) m/z: calcd for $C_{33}H_{58}O_5Si_2$+Na^{+}: 613.3715 [*M*+Na]$^{+}$, found: 613.3706.

Methyl 10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-((*E*)-3-hydroxypent-1-en-1-yl)cyclopentyl)deca-5,8-diynoate 194b**

Obbtained in analogy to **194a** from enone **193** (25 mg, 43 μmol) using $CeCl_3{\cdot}7H_2O$ to yield **194b** (8 mg, 40%) as inseparable 1.2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.12 (PE/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (ddd, $^{3}J_{H,H}$ = 15.3, 6.6 Hz, $^{4}J_{H,H}$ = 0.7 Hz, 1H; CH=C*H*CHOH), 5.40 (ddd, $^{3}J_{H,H}$ = 15.3, 9.8 Hz, $^{4}J_{H,H}$ = 1.3 Hz, 1H; C*H*=CHCHOH), 4.11-3.94 (m, 3H; C*H*O), 3.68 (s, 3H; CH_3O), 3.09 (tt, $^{5}J_{H,H}$ = 2.8, 1.4 Hz, 2H; C≡CCH_2C≡C), 2.75 (td, $^{3}J_{H,H}$ = 9.4, 3.5 Hz, 1H; C*H*CHOTBS), 2.43 (t, *J* = 7.5 Hz, 2H; CH_2C=O), 2.39-2.30 (m, 1H; C*H*CHOH), 2.35 (dt, $^{2}J_{H,H}$ = 13.4 Hz, $^{3}J_{H,H}$ = 7.4 Hz, 1H; CH*H*CHOTBS), 2.26-2.20 (m, 1H; C*H*HCHCHOH), 2.23 (tt, $^{3}J_{H,H}$ = 6.9 Hz, $^{5}J_{H,H}$ = 2.4 Hz, 2H; $CH_2CH_2C{\equiv}C$), 2.16-2.08 (m, 1H; CH*H*CHCHOH), 1.81 (quint, $^{3}J_{H,H}$ = 7.1 Hz, 2H; CH_2CH$_2$C=O), 1.68 (dt, $^{2}J_{H,H}$ = 13.7 Hz, $^{3}J_{H,H}$ = 4.4 Hz, 1H; C*H*HCHOTBS), 1.63-1.46 (m, 4H; CH$_3$CH_2, O*H*), 0.91 (t, $^{3}J_{H,H}$ = 7.4 Hz, 3H; CH_3CH$_2$), 0.88 (s, 9H; CH_3CSi), 0.05 (s, 6H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (*C*=O; HMBC determination), 136.2 (CH=*C*HCHOH), 128.9 (*C*H=CHCHOH), 79.5 ($CHCH_2C{\equiv}C$), 79.1 ($CH_2CH_2C{\equiv}C$), 77.2 ($CHCH_2CHOH$), 76.8 (*C*HOTBS), 75.9 ($CH_2CH_2C{\equiv}C$), 75.4 ($CHCH_2C{\equiv}C$), 74.4 (CH=CH*C*HOH), 54.3 (*C*HCHOTBS),

51.8 (*C*H$_3$O), 49.4 (*C*HCHOH), 43.1 (*C*H$_2$CHOTBS), 33.0 (*C*H$_2$C=O), 30.33 (*C*H$_2$CH$_3$), 26.0 (3C; *C*H$_3$CSi), 24.0 (*C*H$_2$CH$_2$C=O), 19.4 (CH*C*H$_2$C≡C), 18.3 (CH$_2$*C*H$_2$C≡C), 18.2 (*C*Si; HMBC determination), 9.9 (*C*H$_3$CH$_2$), 9.8 (C≡C*C*H$_2$C≡C), –4.53 (*C*H$_3$Si), –4.56 (*C*H$_3$Si).

Minor C18 epimer:

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.56 (dd, $^3J_{H,H}$ = 15.5, 6.7 Hz, 1H; CH=C*H*CHOH), 5.37 (ddd, $^3J_{H,H}$ = 15.2, 9.8 Hz, $^4J_{H,H}$ = 1.2 Hz, 1H; C*H*=CHCHOH), 4.11-3.94 (m, 3H; C*H*O), 3.68 (s, 3H; C*H$_3$*O), 3.09 (tt, $^5J_{H,H}$ = 2.8, 1.4 Hz, 2H; C≡CC*H$_2$*C≡C), 2.75 (td, $^3J_{H,H}$ = 9.5, 3.5 Hz, 1H; C*H*CHOTBS), 2.43 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H$_2$*C=O), 2.39-2.30 (m, 1H; C*H*CHOH), 2.33 (dt, $^2J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; CH*H*CHOTBS), 2.26-2.20 (m, 1H; C*H*HCHCHOH), 2.23 (tt, $^3J_{H,H}$ = 6.9 Hz, $^5J_{H,H}$ = 2.4 Hz, 2H; CH$_2$C*H$_2$*C≡C), 2.14-2.06 (m, 1H; CH*H*CHCHOH), 1.81 (quint, $^3J_{H,H}$ = 7.2 Hz, 2H; C*H$_2$*CH$_2$C=O), 1.68 (dt, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 4.4 Hz, 1H; C*H*HCHOTBS), 1.63-1.46 (m, 4H; CH$_3$C*H$_2$*, O*H*), 0.91 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H$_3$*CH$_2$), 0.87 (s, 9H; C*H$_3$*CSi), 0.039 (s, 3H; C*H$_3$*Si), 0.036 (s, 3H; C*H$_3$*Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 173.7 (*C*=O; HMBC determination), 136.1 (CH=*C*HCHOH), 129.0 (*C*H=CHCHOH), 79.5 (CHCH$_2$*C*≡C), 79.1 (CH$_2$CH$_2$*C*≡C), 77.2 (CHCH$_2$*C*HOH), 76.8 (*C*HOTBS), 75.9 (CH$_2$CH$_2$C≡*C*), 75.4 (CHCH$_2$C≡*C*), 74.1 (CH=CH*C*HOH), 54.1 (*C*HCHOTBS), 51.8 (*C*H$_3$O), 49.4 (*C*HCHOH), 43.1 (*C*H$_2$CHOTBS), 33.0 (*C*H$_2$C=O), 30.28 (*C*H$_2$CH$_3$), 26.0 (3C; *C*H$_3$CSi), 24.0 (*C*H$_2$CH$_2$C=O), 19.3 (CH*C*H$_2$C≡C), 18.3 (CH$_2$*C*H$_2$C≡C), 18.2 (*C*Si; HMBC determination), 9.9 (*C*H$_3$CH$_2$), 9.8 (C≡C*C*H$_2$C≡C), –4.91 (*C*H$_3$Si), –4.94 (*C*H$_3$Si).

IR (film): ν = 3400 (br), 2954, 2929, 2856, 1737, 1461, 1436, 1361, 1314, 1251, 1160, 1096, 1056, 1005, 972, 836, 776 cm^{-1}.

MS (+ESI) m/z (%): 499 (100) [*M*+Na]$^+$.

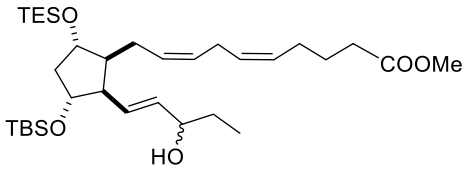
HRMS (+ESI) m/z: calcd for C$_{27}$H$_{44}$O$_5$Si+Na$^+$: 499.2850 [*M*+Na]$^+$, found: 499.2841.

6.4.3.2 Hydrogenation and deprotection

Methyl (5*Z*,8*Z*)-10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-hydroxypent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)deca-5,8-dienoate 195a**

Setup*:* Hydrogenation experiments were carried out in a stainless steel autoclave equipped with a teflon insert. The hydrogen atmosphere was generated by at least three purging cycles (20 bar/1 bar H$_2$). This cycle was repeated every time the system was opened to air. Lindlar catalyst (~5% Pd on CaCO$_3$ poisoned with lead, Fluka, lot no.: 1308420) was used for the hydrogenation experiments. Pyridine was distilled over CaH$_2$ and stored over NaOH; HPLC-grade EtOAc and hexane (Acros or MERCK) were used without further purification. The reactions were monitored by TLC (open to air); if the conversion was not complete after two one-hour cycles, the reaction was stopped, the crude mixture was passed through a short column of silica gel (eluted with hexane/EtOAc 95:5) and evaporated under reduced pressure before being re-subjected to the same hydrogenation conditions.

Representative procedure (conditions **a**): A 10 mL round-bottomed flask equipped with a stirring bar was charged with Lindlar catalyst (5.0 mg, 1.0 equiv. w/w), EtOAc (1.6 mL) and pyridine (150 μL) under air. The flask was placed in the autoclave teflon insert, the system was sealed and purged with hydrogen gas by three 20 bar/1 bar cycles with vigorous stirring and the mixture was stirred at atmospheric hydrogen gas pressure for 45 min. The reactor was shortly opened to air and a solution of diyne **194a** (5.0 mg, 8.5 μmol) in EtOAc (1.0 mL) was added by syringe. The suspension was again purged with hydrogen gas as described above and stirred at atmospheric hydrogen gas pressure for 1 h when the conversion was complete as indicated by TLC. The solution was filtered through a plug of Celite® and sand and evaporated under reduced pressure. The crude product was purified by column chromatography (1 mL silica gel, hexane/EtOAc gradient 100:1 to 20:1 with 0.5 vol.% of Et_3N) providing **195a** (3.6 mg, 72%) as inseparable 1.2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a yellow oil.



R_f = 0.38 (PE/EtOAc 4:1).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.534 (dd, $^3J_{H,H}$ = 15.3, 5.9 Hz, 1H; CH=C*H*CHOH), 5.45 (dd, $^3J_{H,H}$ = 15.4, 8.9 Hz, 1H; C*H*=CHCHOH), 5.44-5.27 (m, 4H; C*H*=CH_Z), 4.04-3.96 (m, 1H; C*H*OH), 3.97-3.86 (m, 1H; C*H*OTBS), 3.81 (q, $^3J_{H,H}$ = 6.1 Hz, 1H; C*H*OTES), 3.67 (s, 3H; CH_3O), 2.73 (t, $^3J_{H,H}$ = 6.3 Hz, 2H; CH=CHCH_2CH=CH), 2.66 (ddd, $^3J_{H,H}$ = 8.8, 5.4, 5.1 Hz, 1H; C*H*CHOTBS), 2.39-2.27 (m, 1H; CH*H*CHOTES), 2.32 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; CH_2C=O), 2.16-2.04 (m, 4H; C*H*CHOTES, CH$_2$CH_2CH=CH, C*H*HCHCHOTES), 2.03-1.89 (m, 1H; CH*H*CHCHOTES), 1.70 (quint, $^3J_{H,H}$ = 7.4 Hz, 2H; CH_2CH$_2$C=O), 1.61-1.46 (m, 4H; C*H*HCHOTES, CH_2CHOH, O*H*), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$Si), 0.91 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; CH_3CH$_2$CH), 0.87 (s, 9H; CH_3CSi), 0.57 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.02 (s, 6H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3 (*C*=O), 135.2 (CH=*C*HCHOH), 130.2 (*C*H=CHCHOH), 129.2 (*C*H=CH$_Z$), 129.02 (*C*H=CH$_Z$), 128.9 (*C*H=CH$_Z$), 128.4 (=*C*HCH$_2$CHCHOTES), 76.17 (*C*HOTBS), 75.75 (*C*HOTES), 74.5 (*C*HOH), 52.54 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 50.21 (*C*HCHOTES), 44.55 (*C*H$_2$CHOTBS), 33.5 (*C*H$_2$C=O), 30.4 (CHOH*C*H$_2$), 26.7 (*C*H$_2$CHCHOTES), 26.5 (*C*H$_2$CH$_2$CH$_2$C=O), 25.99 (3C; *C*H$_3$CSi), 25.94 (CH=CH*C*H$_2$CH=CH), 24.91 (*C*H$_2$CH$_2$C=O), 18.2 (*C*Si), 9.9 (*C*H$_3$CH$_2$CHO), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.38 (2C; *C*H$_3$Si).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.526 (dd, $^3J_{H,H}$ = 15.3, 5.9 Hz, 1H; CH=C*H*CHOH), 5.45 (dd, $^3J_{H,H}$ = 15.4, 8.9 Hz, 1H; C*H*=CHCHOH), 5.44-5.27 (m, 4H; C*H*=CH_Z), 4.04-3.96 (m, 1H; C*H*OH), 3.97-3.86 (m, 1H; C*H*OTBS), 3.81 (q, $^3J_{H,H}$ = 6.1 Hz, 1H; C*H*OTES), 3.67 (s, 3H; CH_3O), 2.74 (t, $^3J_{H,H}$ = 6.3 Hz, 2H; CH=CHCH_2CH=CH), 2.66 (ddd, $^3J_{H,H}$ = 8.8, 5.4, 5.1 Hz, 1H; C*H*CHOTBS), 2.39-2.27 (m, 1H; CH*H*CHOTES), 2.32 (t, $^3J_{H,H}$ = 7.5 Hz, 2H; CH_2C=O), 2.16-2.04 (m, 4H; C*H*CHOTES, CH$_2$CH_2CH=CH, C*H*HCHCHOTES), 2.03-1.89 (m,

1H; CH*H*CHCHOTES), 1.70 (quint, $^3J_{H,H}$ = 7.4 Hz, 2H; CH_2CH$_2$C=O), 1.61-1.46 (m, 4H; C*H*HCHOTES, CH_2CHOH, O*H*), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$Si), 0.91 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; CH_3CH$_2$CH), 0.86 (s, 9H; CH_3CSi), 0.57 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.012 (s, 3H; CH_3Si), 0.006 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 174.3 (*C*=O), 135.3 (CH=*C*HCHOH), 129.9 (*C*H=CHCHOH), 129.2 (*C*H=CH$_Z$), 129.08 (*C*H=CH$_Z$), 129.00 (*C*H=CH$_Z$), 128.4 (=*C*HCH$_2$CHCHOTES), 76.20 (*C*HOTBS), 75.70 (*C*HOTES), 74.3 (*C*HOH), 52.47 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 50.17 (*C*HCHOTES), 44.54 (*C*H$_2$CHOTBS), 33.6 (*C*H$_2$C=O), 30.3 (CHOH*C*H$_2$), 26.7 (*C*H$_2$CHCHOTES), 26.4 (*C*H$_2$CH$_2$CH$_2$C=O), 25.98 (3C; *C*H$_3$CSi), 25.91 (CH=CH*C*H$_2$CH=CH), 24.90 (*C*H$_2$CH$_2$C=O), 18.2 (*C*Si), 9.9 (*C*H$_3$CH$_2$CHO), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.42 (*C*H$_3$Si), –4.44 (*C*H$_3$Si).

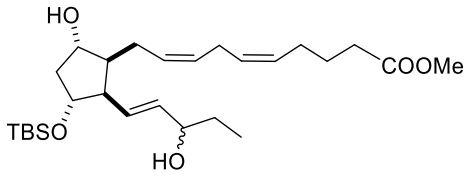
IR (film): *v* = 3506 (br), 2954, 2926, 2875, 2855, 1742, 1461, 1415, 1377, 1250, 1111, 1063, 1006, 973, 885, 836, 776, 744, 726, 672 cm^{-1}.

MS (+ESI) m/z (%): 617 (100) [*M*+Na]$^+$, 633 (1) [*M*+K]$^+$.

HRMS (+ESI) m/z: calcd for $C_{33}H_{62}O_5Si_2$+Na$^+$: 617.4028 [*M*+Na]$^+$, found: 617.4032.

Methyl (5*Z*,8*Z*)-10-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-hydroxypent-1-en-1-yl)-5-hydroxycyclopentyl)deca-5,8-dienoate 195b**

Obtained in analogy to **195a** by hydrogenation of **194b** (4.0 mg, 8.0 μmol) with stirring for 2 h, re-submitting the crude mixture to the same conditions and stirring for further 2 h (conditions **b**) to give **195b** (2.3 mg, 57%) as inseparable 1.2:1 mixture of diastereomers as a colorless oil.



R_f = 0.38 (PE/EtOAc 4:1).

Major diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.54 (dd, $^3J_{H,H}$ = 15.3, 6.4 Hz, 1H; CH=C*H*CHOH), 5.50-5.29 (m, 5H; C*H*=CHCHOH, C*H*=CH$_Z$), 4.04-3.93 (m, 2H; C*H*OH), 3.93-3.84 (m, 1H; C*H*OTBS), 3.67 (s, 3H; CH_3O), 2.82-2.69 (m, 3H; C*H*CHOTBS, CH=CHCH_2CH=CH), 2.35-2.29 (m, 1H; CH*H*CHOTBS), 2.32 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; CH_2C=O), 2.24-2.17 (m, 1H; C*H*CHOH), 2.15-1.95 (m, 2H, CH$_2$CH_2CH=CH), 1.70 (quint, $^3J_{H,H}$ = 7.5 Hz, 2H; CH_2CH$_2$C=O), 1.64-1.44 (m, 7H; C*H*HCHOTBS, CH_2CHCHOH, *C*H$_2$CH$_3$, O*H*), 0.910 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH$_2$CH_3), 0.877 (s, 9H; CH_3CSi), 0.04 (s, 6H; CH_3Si).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 174.38 (*C*=O), 135.6 (CH=*C*HCHOH), 129.40 (*C*H=CHCHOH), 129.1 (*C*H=CH$_Z$), 128.96 (2C; *C*H=CH$_Z$), 128.90 (*C*H=CH$_Z$), 78.0 (C*H*OH), 77.8 (C*H*OTBS), 74.23 (CH=CH*C*HOH), 54.3 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 50.84 (*C*HCHOH), 43.1 (*C*H$_2$CHOTBS), 33.52 (*C*H$_2$C=O), 30.4 (*C*H$_2$CH$_3$), 27.55 (*C*H$_2$CHCHOH), 26.7

(*C*H$_2$CH$_2$CH$_2$C=O), 26.0 (3C; *C*H$_3$CSi), 25.91 (CH=CH*C*H$_2$CH=CH), 24.9 (*C*H$_2$CH$_2$C=O), 18.2 (*C*Si), 9.90 (*C*H$_3$CH$_2$), –4.51 (*C*H$_3$Si), –4.55 (*C*H$_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.54 (dd, $^3J_{H,H}$ = 15.3, 6.4 Hz, 1H; CH=C*H*CHOH), 5.50-5.29 (m, 5H; C*H*=CHCHOH, C*H*=C*H$_Z$*), 4.04-3.94 (m, 2H; C*H*OH), 3.93-3.84 (m, 1H; C*H*OTBS), 3.67 (s, 3H; C*H$_3$*O), 2.81-2.69 (m, 3H; C*H*CHOTBS, CH=CHC*H$_2$*CH=CH), 2.33 (t, $^3J_{H,H}$ = 7.4 Hz, 2H; C*H$_2$*C=O), 2.33-2.25 (m, 1H; CH*H*CHOTBS), 2.25-2.17 (m, 1H; C*H*CHOH), 2.16-1.95 (m, 2H, CH$_2$C*H$_2$*CH=CH), 1.70 (quint, $^3J_{H,H}$ = 7.5 Hz, 2H; C*H$_2$*CH$_2$C=O), 1.67-1.46 (m, 7H; C*H*HCHOTBS, C*H$_2$*CHCHOH, C*H$_2$*CH$_3$, O*H*), 0.913 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH$_2$C*H$_3$*), 0.875 (s, 9H; C*H$_3$*CSi), 0.05 (s, 6H; C*H$_3$*Si).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 174.42 (*C*=O), 135.7 (CH=*C*HCHOH), 129.41 (*C*H=CHCHOH), 129.03 (*C*H=CH$_Z$), 128.96 (2C; *C*H=CH$_Z$), 128.85 (*C*H=CH$_Z$), 78.0 (C*H*OH), 77.8 (C*H*OTBS) 74.20 (CH=CH*C*HOH), 54.2 (*C*HCHOTBS), 51.7 (*C*H$_3$O), 50.79 (*C*HCHOH), 43.1 (*C*H$_2$CHOTBS), 33.49 (*C*H$_2$C=O), 30.3 (*C*H$_2$CH$_3$), 27.49 (*C*H$_2$CHCHOH), 26.7 (*C*H$_2$CH$_2$CH$_2$C=O), 26.0 (3C; *C*H$_3$CSi), 25.93 (CH=CH*C*H$_2$CH=CH), 24.8 (*C*H$_2$CH$_2$C=O), 18.2 (*C*Si), 9.87 (*C*H$_3$CH$_2$), –4.58 (*C*H$_3$Si), –4.61 (*C*H$_3$Si).

IR (film): ν = 3403 (br), 3011, 2955, 2929, 2856, 1735, 1458, 1436, 1371, 1255, 1153, 1056, 1007, 973, 837, 799, 776 cm^{-1}.

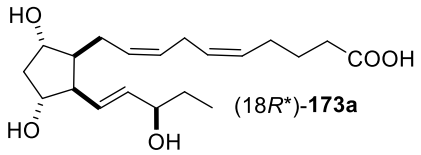
MS (+ESI) m/z (%): 503 (100) [*M*+Na]$^+$.

HRMS (+ESI) m/z: calcd for C$_{27}$H$_{48}$O$_5$Si+Na$^+$: 503.3163 [*M*+Na]$^+$, found: 503.3160.

(5*Z*,8*Z*)-10-((1*S,2*R**,3*R**,5*S**)-3,5-Dihydroxy-2-((*E*)-3-hydroxypent-1-en-1-yl)cyclopentyl)deca-5,8-dienoic acid, *rac*-(18*RS*)-18-F$_{3t}$-Isoprostane 173a**

Step 1: Disilylated ester **195a** (3.0 mg, 6.3 µmol) was dissolved in dry THF (250 µL) under a nitrogen atmosphere, the solution was cooled to 0 °C and TBAF (13 µL, 1.0 M in THF, 13 µmol) was dropwise added. The dark yellow solution was stirred at 0 °C for 1 h when the reaction was complete as indicated by TLC. The mixture was diluted with HPLC-grade EtOAc (3 mL), satd. aqueous NH$_4$Cl solution (3 mL) was added, the layers separated and the aqueous was extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and evaporated under reduced pressure.

Step 2: The crude trihydroxy ester was dissolved in THF (125 µL) and H$_2$O (250 µL) was added followed by LiOH•H$_2$O (5.2 mg, 0.12 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h when full conversion was indicated by TLC. The mixture was acidified with 1 M HCl to pH 2 and extracted with HPLC-grade EtOAc (5×2 mL). The crude product was adsorbed on silica gel and purified by column chromatography (silica gel, HPLC-grade hexane/EtOAc/MeOH gradient 10:1:0 to 0:10:1) furnishing racemic 18(*RS*)-18-F$_{3t}$-IsoP **173a** (1.7 mg, 78% over two steps) as a colorless oil and asa partially separable 1.2:1 mixture of (18*R**)/(18*S**)-**173a** as determined by ^{1}H NMR spectroscopy. The relative configuration at C-18 was assigned by comparing the ^{1}H and ^{13}C NMR spectra to those of enantiomerically enriched (18*R*)-**173a** and (18*S*)-**173a**.[78]

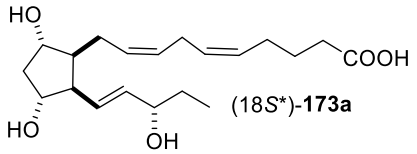


(18*R**)-**173a**

R_f = 0.20 (EtOAc).

^{1}H NMR (600 MHz, CD_3OD): δ = 5.56-5.52 (m, 2H; C*H*=C*H*CHOH), 5.45-5.29 (m, 4H; C*H*=CH_Z), 3.97 (dt, $^3J_{H,H}$ = 7.2, 5.0 Hz, 1H; OHC*H*CHCH=CH), 3.96-3.91 (m, 1H; CH=CHC*H*OH), 3.88 (dt, $^3J_{H,H}$ = 7.5, 5.4 Hz, 1H; OHC*H*CHCH$_2$), 2.83 (dt, $^2J_{H,H}$ = 15.4 Hz, $^3J_{H,H}$ = 8.1 Hz, 1H; CH=CHCH*H*CH=CH), 2.80 (dt, $^2J_{H,H}$ = 15.4 Hz, $^3J_{H,H}$ = 8.1 Hz, 1H; CH=CHC*H*HCH=CH), 2.73-2.62 (m, 1H; C*H*CH=CH), 2.487 (dt, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; OHCHCH*H*CHOH), 2.23-2.12 (m, 3H; CHCH*H*CH=CH, CH_2C=O), 2.12-2.05 (m, 3H; CH$_2$CH_2CH=CH, CHC*H*HCH=CH), 2.03 (quint, $^3J_{H,H}$ = 7.1 Hz, 1H; C*H*CH$_2$CH=CH), 1.65 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH_2CH$_2$C=O), 1.61-1.43 (m, 3H; CH_2CH$_3$, OHCHC*H*HCHOH), 0.91 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (*C*=O), 135.2 (CH=*C*HCHOH), 129.4 (*C*H=CHCHOH), 129.0 (*C*H=CH$_Z$), 128.9 (*C*H=CH$_Z$), 128.7 (*C*H=CH$_Z$), 127.54 (CHCH$_2$*C*H=CH), 76.9 (OH*C*HCHCH$_2$), 76.5 (OH*C*HCHCH=CH), 74.04 (CH=CH*C*HOH), 53.5 (*C*HCH=CH), 50.4 (*C*HCH$_2$CH=CH), 42.23 (OHCH*C*H$_2$CHOH), 32.6 (*C*H$_2$C=O), 30.16 (CH$_3$*C*H$_2$), 27.2 (CH$_2$*C*H$_2$CH=CH), 26.21 (CH*C*H$_2$CH=CH), 25.9 (CH=CH*C*H$_2$CH=CH), 24.38 (*C*H$_2$CH$_2$C=O), 9.67 (*C*H$_3$).



(18*S**)-**173a**

R_f = 0.25 (EtOAc).

^{1}H NMR (600 MHz, CD_3OD): δ = 5.52-5.49 (m, 2H; C*H*=C*H*CHOH), 5.45-5.29 (m, 4H; C*H*=CH_Z), 3.98 (dt, $^3J_{H,H}$ = 7.2, 5.0 Hz, 1H; OHC*H*CHCH), 3.96-3.91 (m, 1H; CH=CHC*H*OH), 3.88 (dt, $^3J_{H,H}$ = 7.6, 5.4 Hz, 1H; OHC*H*CHCH$_2$), 2.78 (dt, $^2J_{H,H}$ = 15.4 Hz, $^3J_{H,H}$ = 8.1 Hz, 1H; CH=CHCH*H*CH=CH), 2.76 (dt, $^2J_{H,H}$ = 15.4 Hz, $^3J_{H,H}$ = 8.1 Hz, 1H; CH=CHC*H*HCH=CH), 2.73-2.66 (m, 1H; C*H*CH=CH), 2.491 (dt, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; OHCHCH*H*CHOH), 2.23-2.12 (m, 3H; CHCH*H*CH=CH, CH_2C=O), 2.12-2.05 (m, 3H; CH$_2$CH_2CH=CH, CHC*H*HCH=CH), 2.03 (quint, $^3J_{H,H}$ = 7.2 Hz, 1H; C*H*CH$_2$CH=CH), 1.65 (quint, $^3J_{H,H}$ = 7.6 Hz, 2H; CH_2CH$_2$C=O), 1.61-1.43 (m, 3H; CH_2CH$_3$, OHCHC*H*HCHOH), 0.90 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (*C*=O), 135.2 (CH=*C*HCHOH), 129.5 (*C*H=CHCHOH), 129.1 (*C*H=CH$_Z$), 128.9 (*C*H=CH$_Z$), 128.8 (*C*H=CH$_Z$), 127.53 (CHCH$_2$*C*H=CH), 76.9 (OH*C*HCHCH$_2$), 76.5 (OHCHCHCH=CH), 74.07 (CH=CH*C*HOH), 53.9 (*C*HCH=CH), 50.4 (*C*HCH$_2$CH=CH), 42.22 (OHCH*C*H$_2$CHOH), 32.5 (*C*H$_2$C=O), 30.20 (CH$_3$*C*H$_2$), 27.1 (CH$_2$*C*H$_2$CH=CH), 26.24 (CH*C*H$_2$CH=CH), 25.9 (CH=CH*C*H$_2$CH=CH), 24.43 (*C*H$_2$CH$_2$C=O), 9.72 (*C*H$_3$).

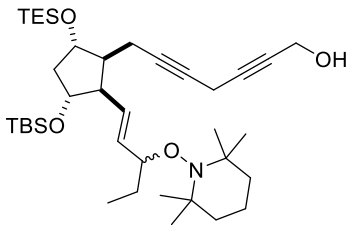
IR (film): ν = 3624-2435 (v br), 3352 (br), 3011, 2954, 2927, 2877, 1710, 1457, 1412, 1260, 1145, 1066, 1030, 1003, 970 cm^{-1}.
MS (+ESI) m/z (%): 375 (100) $[M+Na]^+$; (–ESI) m/z (%): 351 (100) $[M–H]^-$.
HRMS (–ESI) m/z: calcd for $C_{20}H_{32}O_5–H^+$: 351.2177 $[M–H]^-$, found: 351.2175; (+ESI) m/z: calcd for $C_{20}H_{32}O_5+Na^+$: 375.2142 $[M+Na]^+$, found: 375.2140.

6.4.4 Toward the synthesis of 20-NeuroPs

6.4.4.1 Assembly of the triyne scaffold

7-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)hepta-2,5-diyn-1-ol 196a**

Diyne **196a** was prepared in analogy to **177a** from propargyl choride **179c** (261 mg, 0.41 mmol) and propargyl alcohol **180d** (72 µL, 1.22 mmol). Purification by silica gel column chromatography (PE/Et_2O gradient 95:5 to 9:1) furnished propargylic alcohol **196a** (243 mg, 89%) as inseparable 1.8:1 mixture of diastereomer as determined by ^{1}H NMR spectroscopy as a yellow oil.



R_f = 0.29 (PE/Et_2O 7:3).
Major diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (dd, $^3J_{H,H}$ = 15.4, 8.0 Hz, 1H; CH=C*H*CHOTMP), 5.34 (dd, $^3J_{H,H}$ = 15.5, 8.9 Hz, 1H; C*H*=CHCHOTMP), 4.28-4.22 (m, 2H; CH_2O), 4.07-3.90 (m, 3H; C*H*O), 3.17 (quint, $^5J_{H,H}$ = 1.7 Hz, 2H; C≡CCH_2C≡C), 2.74 (td, $^3J_{H,H}$ = 9.0, 4.2 Hz, 1H; C*H*CHOTBS), 2.37 (dt, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 8.4 Hz, 1H; CH*H*CHOTBS), 2.33-2.15 (m, 3H; C*H*CHOTES, CH_2CHCHOTES), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.572 (dt, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 6.1 Hz, 1H; C*H*HCHOTBS), 1.53-1.37 (m, 6H; CH_2CN, C*H*HCHOTMP, C*H*HCH_2CN), 1.35-1.21 (m, 1H; CH*H*CH_2CN), 1.16 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.06 (br s, 3H; CH_3CN), 0.952 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2Si), 0.86 (s, 9H; CH_3CSi), 0.84 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; CH_3CH_2CH), 0.582 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.02 (s, 3H; CH_3Si), 0.01 (s, 3H; CH_3Si).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2 (CH=*C*HCHOTMP), 130.2 (*C*H=CHCHOTMP), 86.4 (*C*HOTMP), 80.93 (HOCH_2C≡*C*), 80.6 (CHCH_2*C*≡C), 78.5 (HOCH_2*C*≡C), 75.8 (*C*HOTES), 75.0 (*C*HOTBS), 74.1 (CHCH_2C≡*C*), 60.3 (*C*N), 59.4 (*C*N), 52.5 (*C*HCHOTBS), 51.4 (*C*H_2OH), 49.2 (*C*HCHOTES), 44.7 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.0 (*C*H_3CN), 34.3 (*C*H_3CN), 27.6 (*C*H_2CHOTMP), 26.0 (3C; *C*H_3CSi), 20.6 (2C; *C*H_3CN), 18.4 (*C*H_2CHCHOTES), 18.2 (*C*Si), 17.49 (*C*H_2CH_2CN), 10.08 (C≡C*C*H_2C≡C), 10.06 (*C*H_3CH_2CH), 7.0 (3C; *C*H_3CH_2Si), 5.0 (3C; *C*H_2Si), –4.41 (*C*H_3Si), –4.46 (*C*H_3Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (ddd, $^{3}J_{H,H}$ = 15.9, 8.0 Hz, $^{4}J_{H,H}$ = 1.0 Hz, 1H; CH=C*H*CHOTMP), 5.24 (dd, $^{3}J_{H,H}$ = 15.4, 9.5 Hz, 1H; C*H*=CHCHOTMP), 4.28-4.22 (m, 2H; CH_2O), 4.07-3.90 (m, 2H; C*H*OTBS, C*H*OTMP), 3.89 (td, $^{3}J_{H,H}$ = 7.5, 6.1 Hz, 1H; C*H*OTES), 3.16 (quint, $^{5}J_{H,H}$ = 1.8 Hz, 2H; C≡CCH_2C≡C), 2.72 (td, $^{3}J_{H,H}$ = 9.0, 4.2 Hz, 1H; C*H*CHOTBS), 2.40 (dt, $^{2}J_{H,H}$ = 14.2 Hz, $^{3}J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTBS), 2.35-2.19 (m, 2H; C*H*CHOTES, CH*H*CHCHOTES), 2.06 (ddt, $^{2}J_{H,H}$ = 16.5 Hz, $^{3}J_{H,H}$ = 8.9 Hz, $^{5}J_{H,H}$ = 2.4 Hz, 1H; C*H*HCHCHOTES), 1.82-1.64 (m, 1H; CH*H*CHOTMP), 1.569 (dt, $^{2}J_{H,H}$ = 13.7 Hz, $^{3}J_{H,H}$ = 6.1 Hz, 1H; C*H*HCHOTBS), 1.53-1.37 (m, 6H; CH_2CN, C*H*HCHOTMP, C*H*HCH_2CN), 1.35-1.21 (m, 1H; CH*H*CH_2CN), 1.16 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.06 (br s, 3H; CH_3CN), 0.947 (t, $^{3}J_{H,H}$ = 7.9 Hz, 9H; CH_3CH_2Si), 0.90 (t, $^{3}J_{H,H}$ = 7.4 Hz, 3H; CH_3CH_2CH), 0.87 (s, 9H; CH_3CSi), 0.575 (q, $^{3}J_{H,H}$ = 7.8 Hz, 6H; CH_2Si), 0.04 (s, 3H; CH_3Si), 0.03 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5 (CH=*C*HCHOTMP), 129.1 (*C*H=CHCHOTMP), 86.8 (*C*HOTMP), 80.87 (HOCH_2C≡*C*), 80.4 (CHCH_2*C*≡C), 78.6 (HOCH_2*C*≡C), 75.6 (*C*HOTES), 75.4 (*C*HOTBS), 73.9 (CHCH_2C≡*C*), 60.3 (*C*N), 59.4 (*C*N), 53.1 (*C*HCHOTBS), 51.3 (*C*H_2OH), 49.0 (*C*HCHOTES), 44.8 (*C*H_2CHOTBS), 40.5 (2C; *C*H_2CN), 35.4 (*C*H_3CN), 34.3 (*C*H_3CN), 27.7 (*C*H_2CHOTMP), 26.1 (3C; *C*H_3CSi), 20.6 (2C; *C*H_3CN), 18.5 (*C*H_2CHCHOTES), 18.2 (*C*Si), 17.45 (*C*H_2CH_2CN), 10.04 (C≡C*C*H_2C≡C), 10.00 (*C*H_3CH_2CH), 7.0 (3C; *C*H_3CH_2Si), 5.0 (3C; *C*H_2Si), –4.37 (*C*H_3Si), –4.45 (*C*H_3Si).

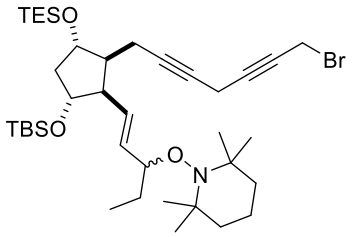
IR (film): ν = 3426 (br), 2955, 2932, 2877, 2857, 1462, 1416, 1376, 1360, 1313, 1253, 1183, 1116, 1071, 1006, 973, 886, 836, 776, 744, 727, 670 cm^{-1}.

MS (+ESI) m/z (%): 660 (100 [*M*+Na]$^{+}$.

HRMS (+ESI) m/z: calcd for $C_{38}H_{70}NO_4Si_2$+Na^{+}: 660.4838 [*M*+Na]$^{+}$, found: 660.4832.

7-((1*R,2*S**,3*S**,5*R**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)hepta-2,5--diyn-1-yl bromide 196b**

CBr_4 (20 mg, 59 µmol) and **196a** (30 mg, 45 µmol) were dissolved in dry DCM (0.45 mL) under nitrogen. The reaction mixture was cooled to 0 °C and triphenylphosphine (17 mg, 64 µmol) was added. The reaction mixture was stirred at 0 °C for 50 min when complete conversion was indicated by TLC. The mixture was warmed to room temperature and the volatiles were allowed to evaporate under a stream of nitrogen. The residue was taken up in PE and filtered through Celite®, which was washed thoroughly with PE, the filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (PE/TBME 95:5) to give bromide **196b** (30 mg, 91%) as inseparable 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.89 (PE/Et_2O 9:1).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (dd, $^3J_{H,H}$ = 15.6, 8.5 Hz, 1H; CH=C*H*CHOTMP), 5.33 (dd, $^3J_{H,H}$ = 15.4, 8.9 Hz, 1H; C*H*=CHCHOTMP), 4.09-3.93 (m, 3H; C*H*O), 3.898 (t, $^5J_{H,H}$ = 2.4 Hz, 2H; C*H*$_2$Br), 3.19 (quint, $^5J_{H,H}$ = 2.3 Hz, 2H; C≡CC*H*$_2$C≡C), 2.79-2.67 (m, 1H; C*H*CHOTBS), 2.37 (dt, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H; CH*H*CHOTBS), 2.32-2.14 (m, 3H; C*H*CHOTES, C*H*$_2$CHCHOTES), 1.81-1.64 (m, 1H; CH*H*CHOTMP), 1.63-1.54 (m, 1H; CH*H*CH$_2$CN), 1.57 (dt, $^2J_{H,H}$ = 13.8 Hz, 5.9 Hz, 1H; C*H*HCHOTBS), 1.54-1.35 (m, 5H; CH*H*CHOTMP, C*H*$_2$CN), 1.37-1.19 (m, 1H; CH*H*CH$_2$CN), 1.16 (s, 3H; C*H*$_3$CN), 1.10 (s, 6H; C*H*$_3$CN), 1.06 (s, 3H; C*H*$_3$CN), 0.954 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.87 (s, 9H; C*H*$_3$CSi), 0.85 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$CH$_2$CH), 0.59 (q, $^3J_{H,H}$ = 7.8 Hz, 6H; C*H*$_2$Si), 0.02 (s, 3H; C*H*$_3$Si), 0.01 (s, 3H; C*H*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3 (CH=*C*HCHOTMP), 130.3 (*C*H=CHCHOTMP), 86.3 (*C*HOTMP), 82.2 (*C*≡CCH$_2$Br), 80.9 (CHCH$_2$*C*≡C), 75.8 (*C*HOTES), 75.3 (C≡*C*CH$_2$Br), 75.0 (*C*HOTBS), 73.5 (CHCH$_2$C≡*C*), 60.2 (*C*N), 59.3 (*C*N), 52.5 (*C*HCHOTBS), 49.24 (*C*HCHOTES), 44.7 (*C*H$_2$CHOTBS), 40.4 (2C; *C*H$_2$CN), 35.0 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 27.6 (*C*H$_2$CHOTMP), 26.0 (3C; *C*H$_3$CSi), 20.6 (2C; *C*H$_3$CN), 18.4 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.52 (*C*H$_2$CH$_2$CN), 14.9 (*C*H$_2$Br), 10.32 (C≡C*C*H$_2$C≡C), 10.1 (*C*H$_3$CH$_2$CH), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.44 (2C; *C*H$_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (dd, $^3J_{H,H}$ = 15.8, 8.0 Hz, 1H; CH=C*H*CHOTMP), 5.21 (dd, $^3J_{H,H}$ = 15.4, 9.3 Hz, 1H; C*H*=CHCHOTMP), 4.09-3.93 (m, 2H; C*H*OTMP, C*H*OTBS), 3.904 (t, $^5J_{H,H}$ = 2.5 Hz, 2H; C*H*$_2$Br), 3.91-3.82 (m, 1H; C*H*OTES), 3.20 (quint, $^5J_{H,H}$ = 2.2 Hz, 2H; C≡CC*H*$_2$C≡C), 2.79-2.67 (m, 1H; C*H*CHOTBS), 2.40 (dt, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,H}$ = 6.8 Hz, 1H; CH*H*CHOTBS), 2.32-2.14 (m, 2H; C*H*CHOTES, CH*H*CHCHOTES), 2.06 (ddt, $^2J_{H,H}$ = 16.4 Hz, $^3J_{H,H}$ = 8.7 Hz, $^5J_{H,H}$ = 2.4 Hz, 1H; C*H*HCHCHOTES), 1.81-1.64 (m, 1H; CH*H*CHOTMP), 1.63-1.54 (m, 1H; CH*H*CH$_2$CN), 1.58 (ddd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 6.0, 5.1 Hz, 1H; C*H*HCHOTBS), 1.54-1.35 (m, 5H; CH*H*CHOTMP, C*H*$_2$CN), 1.37-1.19 (m, 1H; CH*H*CH$_2$CN), 1.16 (s, 3H; C*H*$_3$CN), 1.10 (s, 6H; C*H*$_3$CN), 1.06 (s, 3H; C*H*$_3$CN), 0.949 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.88 (s, 9H; C*H*$_3$CSi), 0.87 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3$CH$_2$CH), 0.58 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; C*H*$_2$Si), 0.043 (s, 3H; C*H*$_3$Si), 0.037 (s, 3H; C*H*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7 (CH=*C*HCHOTMP), 128.9 (*C*H=CHCHOTMP), 86.5 (*C*HOTMP), 82.2 (*C*≡CCH$_2$Br), 80.6 (CHCH$_2$*C*≡C), 75.6 (*C*HOTES), 75.4 (*C*HOTBS), 75.3 (C≡*C*CH$_2$Br), 73.3 (CHCH$_2$C≡*C*), 60.2 (*C*N), 59.3 (*C*N), 52.9 (*C*HCHOTBS), 49.15 (*C*HCHOTES), 44.8 (*C*H$_2$CHOTBS), 40.5 (2C; *C*H$_2$CN), 35.4 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 27.7

(*C*H$_2$CHOTMP), 26.1 (3C; *C*H$_3$CSi), 20.6 (2C; *C*H$_3$CN), 18.5 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.48 (*C*H$_2$CH$_2$CN), 14.9 (*C*H$_2$Br), 10.27 (C≡C*C*H$_2$C≡C), 10.0 (*C*H$_3$CH$_2$CH), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.36 (*C*H$_3$Si), –4.41 (*C*H$_3$Si).

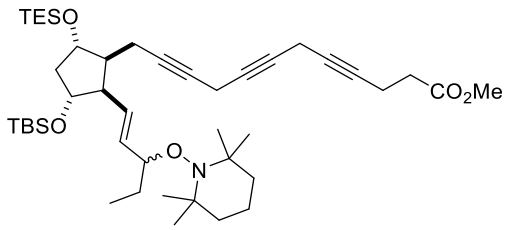
IR (film): ν = 2954, 2929, 2876, 2857, 1462, 1375, 1360, 1251, 1209, 1099, 1070, 1005, 971, 886, 834, 775, 743, 726, 670, 614 cm^{-1}.

MS (+ESI) m/z (%): 724/722 (100/97) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{38}H_{68}{}^{79}BrNO_3Si_2$+H$^+$: 722.3994 [*M*+H]$^+$, found: 722.3984.

Methyl 12-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)dodeca-4,7,10-triynoate 177b**

Prepared in analogy to **177a** from propargyl bromide **196b** (29 mg, 40 µmol) and pent-4-ynoate **197**[181] (14 mg, 120 µmol) with stirring for 48 h to give tryine **177b** (26 mg, 76%) as inseparable 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a yellow oil.



R_f = 0.17 (PE/Et$_2$O 9:1).

Major diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.46 (dd, $^3J_{H,H}$ = 15.3, 8.3 Hz, 1H; CH=C*H*CHOTMP), 5.33 (dd, $^3J_{H,H}$ = 15.5, 8.9 Hz, 1H; C*H*=CHCHOTMP), 4.03-3.93 (m, 3H; C*H*O), 3.69 (s, 3H; C*H*$_3$O), 3.110 (quint, $^5J_{H,H}$ = 2.1 Hz, 4H; C≡CC*H*$_2$C≡C), 2.79-2.68 (m, 1H; C*H*CHOTBS), 2.56-2.44 (m, 4H; C*H*$_2$C*H*$_2$C=O), 2.38 (ddd, $^2J_{H,H}$ = 13.8 Hz, $^3J_{H,H}$ = 7.3, 6.8 Hz, 1H; CH*H*CHOTBS), 2.30-2.18 (m, 3H; C*H*$_2$CHCHOTES, C*H*CHOTES), 1.78-1.64 (m, 1H; CH*H*CHOTMP), 1.64-1.50 (m, 2H; CH*H*CHOTBS, C*H*HCH$_2$CN), 1.49-1.37 (m, 5H; C*H*HCHOTMP, C*H*$_2$CN), 1.33-1.22 (m, 1H; CH*H*CH$_2$CN), 1.15 (br s, 3H; C*H*$_3$CN), 1.09 (br s, 6H; C*H*$_3$CN), 1.05 (br s, 3H; C*H*$_3$CN), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.86 (s, 9H; C*H*$_3$CSi), 0.85 (t, $^3J_{H,H}$ = 7.4 Hz, 3H; C*H*$_3$CH$_2$CH), 0.58 (q, $^3J_{H,H}$ = 8.1 Hz, 6H; C*H*$_2$Si), 0.012 (s, 3H; C*H*$_3$Si), 0.006 (s, 3H; C*H*$_3$Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.57 (*C*=O), 135.3 (CH=*C*HCHOTMP), 130.4 (*C*H=CHCHOTMP), 86.2 (*C*HOTMP), 80.3 (CHCH$_2$*C*≡C), 78.7 (CH$_2$CH$_2$*C*≡C), 75.8 (*C*HOTES), 75.09 (*C*≡C), 75.0 (*C*HOTBS), 74.9 (*C*≡C), 74.44 (*C*≡C), 74.2 (*C*≡C), 60.2 (*C*N), 59.3 (*C*N), 52.4 (*C*HCHOTBS), 51.9 (*C*H$_3$O), 49.35 (*C*HCHOTES), 44.7 (*C*H$_2$CHOTBS), 40.4 (2C; *C*H$_2$CN), 35.0 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 33.5 (*C*H$_2$C=O), 27.61 (*C*H$_2$CHOTMP), 26.01 (3C; *C*H$_3$CSi), 20.5 (2C; *C*H$_3$CN), 18.4 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.51 (*C*H$_2$CH$_2$CN), 14.8 (*C*H$_2$CH$_2$C=O), 10.1 (*C*H$_3$CH$_2$CH), 9.94 (C≡C*C*H$_2$C≡C), 9.88 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.42 (*C*H$_3$Si), –4.5 (*C*H$_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (dd, $^3J_{H,H}$ = 15.4, 8.3 Hz, 1H; CH=C*H*CHOTMP), 5.22 (dd, $^3J_{H,H}$ = 15.4, 9.2 Hz, 1H; C*H*=CHCHOTMP), 4.03-3.93 (m, 2H; C*H*OTMP, C*H*OTBS), 3.87 (dt, $^3J_{H,H}$ = 6.4, 7.1 Hz, 1H; C*H*OTES), 3.69 (s, 3H; CH_3O), 3.114 (quint, $^5J_{H,H}$ = 2.1 Hz, 4H; C≡CCH_2C≡C), 2.79-2.68 (m, 1H; C*H*CHOTBS), 2.56-2.44 (m, 4H; CH_2CH_2C=O), 2.40 (dt, $^2J_{H,H}$ = 14.8 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; CH*H*CHOTBS), 2.31-2.19 (m, 1H; C*H*CHOTES), 2.23-2.14 (m, 1H; C*H*HCHCHOTES), 2.05 (ddt, $^2J_{H,H}$ = 15.9 Hz, $^3J_{H,H}$ = 8.2 Hz, $^5J_{H,H}$ = 1.9 Hz, 1H; CH*H*CHCHOTES), 1.80-1.63 (m, 1H; CH*H*CHOTMP), 1.64-1.48 (m, 2H; CH*H*CHOTBS, C*H*HCH$_2$CN), 1.51-1.36 (m, 5H; C*H*HCHOTMP, CH_2CN), 1.35-1.20 (m, 1H; CH*H*CH$_2$CN), 1.16 (br s, 3H; CH_3CN), 1.10 (br s, 6H; CH_3CN), 1.05 (br s, 3H; CH_3CN), 0.94 (t, $^3J_{H,H}$ = 8.0 Hz, 9H; CH_3CH$_2$Si), 0.87 (s, 9H; CH_3CSi), 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3CH$_2$CH), 0.57 (q, $^3J_{H,H}$ = 8.1 Hz, 6H; CH_2Si), 0.04 (s, 3H; CH_3Si), 0.03 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.62 (*C*=O), 135.6 (CH=*C*HCHOTMP), 129.0 (*C*H=CHCHOTMP), 86.5 (*C*HOTMP), 80.0 (CHCH$_2$*C*≡C), 78.7 (CH$_2$CH$_2$*C*≡C), 75.6 (*C*HOTES), 75.4 (*C*HOTBS), 75.12 (*C*≡C), 74.9 (*C*≡C), 74.42 (*C*≡C), 74.2 (*C*≡C), 60.2 (*C*N), 59.3 (*C*N), 52.8 (*C*HCHOTBS), 51.9 (*C*H$_3$O), 49.27 (*C*HCHOTES), 44.8 (*C*H$_2$CHOTBS), 40.5 (2C; *C*H$_2$CN), 35.4 (*C*H$_3$CN), 34.3 (*C*H$_3$CN), 33.5 (*C*H$_2$C=O), 27.63 (*C*H$_2$CHOTMP), 26.06 (3C; *C*H$_3$CSi), 20.5 (2C; *C*H$_3$CN), 18.5 (*C*H$_2$CHCHOTES), 18.2 (*C*Si), 17.48 (*C*H$_2$CH$_2$CN), 14.8 (*C*H$_2$CH$_2$C=O), 10.1 (*C*H$_3$CH$_2$CH), 10.0 (C≡C*C*H$_2$C≡C), 9.85 (C≡C*C*H$_2$C≡C), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.37 (*C*H$_3$Si), –4.44 (*C*H$_3$Si).

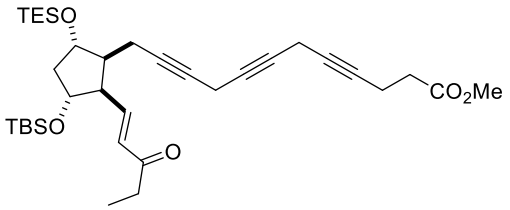
IR (film): *ν* = 2953, 2931, 2876, 2857, 1743, 1462, 1437, 1417, 1374, 1360, 1318, 1293, 1251, 1168, 1132, 1113, 1071, 1005, 972, 886, 835, 775, 744, 727, 670 cm^{-1}.

MS (+ESI) m/z (%): 754 (100) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{44}H_{75}NO_5Si_2$+H$^+$: 754.5256 [*M*+H]$^+$, found: 754.5245.

Methyl 12-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-oxopent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)dodeca-4,7,10-triynoate 198-i1**

The enone intermediate was prepared in analogy to **193** from protected triol **177b** (25 mg, 33 μmol) with stirring for 7 min to yield **198-i1** (20 mg, 98%) as a yellow oil.



R_f = 0.24 (PE/Et$_2$O 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, $^3J_{H,H}$ = 15.7, 9.7 Hz, 1H; C*H*=CHC=O), 6.18 (dd, $^3J_{H,H}$ = 15.7, $^4J_{H,H}$ = 0.9 Hz, 1H; CH=C*H*C=O), 4.07-3.95 (m, 2H; C*H*O), 3.69 (s, 3H; CH_3O), 3.15-3.07 (m, 4H; C≡CCH_2C≡C), 2.87 (td, $^3J_{H,H}$ = 9.3, 5.9 Hz, 1H; C*H*CHOTBS), 2.63-2.54 (m, 2H; CH$_3$CH_2C=O), 2.54-2.45 (m, 4H; CH_2CH_2CO$_2$Me), 2.39 (dt, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 7.1 Hz,

1H; CH*H*CHOTBS), 2.34-2.26 (m, 1H; C*H*CHOTES), 2.17-2.10 (m, 2H; CH_2CHCHOTES), 1.63 (dt, $^3J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 6.3 Hz, 1H; C*H*HCHOTBS), 1.11 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; CH_3CH$_2$C=O), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$Si), 0.85 (s, 9H; CH_3CSi), 0.59 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH$_2$Si), 0.01 (s, 3H; CH_3Si), –0.01 (s, 3H; CH_3Si).

^{13}C NMR (100 MHz, CDCl$_3$) δ = 200.8 (CH=CH*C*=O), 172.6 (CH$_3$O*C*=O), 144.9 (*C*H=CHC=O), 131.9 (CH=*C*HC=O), 79.3 (CHCH$_2$*C*≡C), 78.8 (CH$_2$CH$_2$*C*≡C), 75.4 (CHCH$_2$C≡*C*), 75.1 (*C*HOTES), 74.77 (C≡*C*), 74.76 (C≡*C*), 74.72 (*C*HOTBS), 74.69 (C≡*C*), 52.8 (*C*HCHOTBS), 51.9 (*C*H$_3$O), 49.6 (*C*HCHOTES), 44.6 (*C*H$_2$CHOTBS), 33.8 (CH$_3$*C*H$_2$C=O), 33.5 (CH$_2$*C*H$_2$C=O), 25.9 (3C; *C*H$_3$CSi), 18.6 (CH*C*H$_2$C≡C), 18.1 (*C*Si), 14.8 (*C*H$_2$CH$_2$C=O), 9.92 (C≡C*C*H$_2$C≡C), 9.86 (C≡C*C*H$_2$C≡C), 8.3 (*C*H$_3$CH$_2$C=O), 6.9 (3C; *C*H$_3$CH$_2$Si), 4.9 (3C; *C*H$_2$Si), –4.4 (*C*H$_3$Si), –4.5 (*C*H$_3$Si).

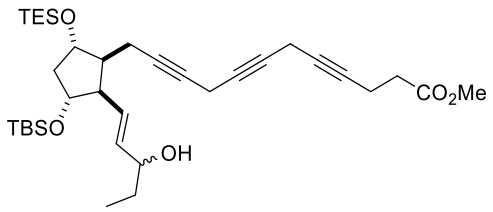
IR (film): ν = 2954, 2930, 2877, 2856, 1741, 1699, 1675, 1628, 1461, 1437, 1416, 1318, 1256, 1196, 1166, 1096, 1066, 1006, 833, 776, 743, 727, 671 cm^{-1}.

MS (+ESI) m/z (%): 635 (97) [*M*+Na]$^+$, 613 (100) [*M*+H]$^+$.

HRMS (+ESI) m/z: calcd for $C_{35}H_{56}O_5Si_2$+H$^+$: 613.3739 [*M*+H]$^+$, found: 613.3733.

Methyl 12-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-hydroxypent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)dodeca-4,7,10-triynoate 198**

Prepared in analogy to **194a** from enone **198-i1** (19 mg, 31 µmol) yielding allylic aclohol **198** (13 mg, 68%) as inseparable 1.2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a yellow oil.



R_f = 0.25 (PE/Et$_2$O 3:1).

Major diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.584 (dd, $^3J_{H,H}$ = 15.3, 6.4 Hz, 1H; CH=C*H*CHOH), 5.54-5.46 (m, 1H; C*H*=CHCHOH), 4.01 (dt, $^3J_{H,H}$ = 6.7, 5.4 Hz, 1H; C*H*OH), 3.98-3.90 (m, 2H; C*H*OTBS, C*H*OTES), 3.69 (s, 3H; CH_3O), 3.13-3.06 (m, 4H; C≡CCH_2C≡C), 2.72 (td, $^3J_{H,H}$ = 8.2, 5.3 Hz, 1H; C*H*CHOTBS), 2.57-2.43 (m, 4H; CH_2CH_2C=O), 2.35 (dt, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTBS), 2.27-2.17 (m, 1H; C*H*CHOTES), 2.14 (dt, $^3J_{H,H}$ = 8.0 Hz, $^5J_{H,H}$ = 2.3 Hz, 2H; CH_2CHCHOTES), 1.64-1.47 (m, 3H; CH*H*CHOTBS, CH_2CHOH), 1.44 (d, $^3J_{H,H}$ = 3.9 Hz, 1H; O*H*), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; CH_3CH$_2$Si), 0.92 (t, $^3J_{H,H}$ = 7.3 Hz, 3H; CH_3CH$_2$CH), 0.87 (s, 9H; CH_3CSi), 0.578 (q, $^3J_{H,H}$ = 8.1 Hz, 6H; CH_2Si), 0.02 (s, 6H; CH$_3$Si).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 172.58 (*C*=O), 135.9 (CH=*C*HCHOH), 129.5 (*C*H=CHCHOH), 79.9 (CHCH$_2$*C*≡C), 78.8 (CH$_2$CH$_2$*C*≡C), 75.7 (*C*HOTES), 75.0 (*C*≡C), 74.9 (*C*HOTBS), 74.84 (*C*≡C), 74.70 (*C*≡C), 74.6 (*C*≡C), 74.5 (*C*HOH), 52.6 (*C*HCHOTBS), 51.9 (*C*H$_3$O), 49.2

(*C*HCHOTES), 44.6 (*C*H_2CHOTES), 33.5 (*C*H_2C=O), 30.3 (*C*H_2CHOH), 25.99 (3C; *C*H_3CSi), 18.5 (CH*C*H_2C≡C), 18.21 (*C*Si), 14.8 (*C*H_2CH$_2$C=O), 9.93 (C≡C*C*H_2C≡C), 9.88 (C≡C*C*H_2C≡C), 9.86 (*C*H_3CH$_2$CHO), 7.0 (3C; *C*H_3CH$_2$Si), 5.0 (3C; *C*H_2Si), –4.40 (*C*H_3Si), –4.44 (*C*H_3Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.577 (dd, $^3J_{H,H}$ = 15.3, 6.3 Hz, 1H; CH=C*H*CHOH), 5.53-5.44 (m, 1H; C*H*=CHCHOH), 4.01 (dt, $^3J_{H,H}$ = 6.5, 5.4 Hz, 1H; C*H*OH), 3.98-3.89 (m, 2H; C*H*OTBS, C*H*OTES), 3.69 (s, 3H; C*H*$_3$O), 3.14- 3.10 (m, 4H; C≡CC*H*$_2$C≡C), 2.70 (td, $^3J_{H,H}$ = 8.2, 5.3 Hz, 1H; C*H*CHOTBS), 2.57-2.43 (m, 4H; C*H*$_2$C*H*$_2$C=O), 2.35 (dt, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 7.1 Hz, 1H; CH*H*CHOTBS), 2.27-2.17 (m, 1H; C*H*CHOTES), 2.11 (dt, $^3J_{H,H}$ = 8.0 Hz, $^5J_{H,H}$ = 2.3 Hz, 2H; C*H*$_2$CHCHOTES), 1.64-1.47 (m, 4H; CH*H*CHOTBS, C*H*$_2$CHOH, O*H*), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3$CH$_2$Si), 0.96 (t, *J* = 7.4 Hz, 3H; C*H*$_3$CH$_2$CH), 0.86 (s, 9H; C*H*$_3$CSi), 0.575 (q, *J* = 7.7 Hz, 6H; C*H*$_2$Si), 0.012 (s, 3H; CH_3Si), 0.006 (s, 3H; CH_3Si).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.55 (*C*=O), 135.8 (CH=*C*HCHOH), 129.9 (*C*H=CHCHOH), 80.0 (CHCH$_2$*C*≡C), 78.8 (CH$_2$CH$_2$*C*≡C), 75.7 (*C*HOTES), 75.0 (*C*≡C), 74.81 (*C*HOTBS), 74.78 (*C*≡C), 74.68 (*C*≡C), 74.6 (*C*≡C), 74.4 (*C*HOH), 52.5 (*C*HCHOTBS), 51.9 (*C*H$_3$O), 49.1 (*C*HCHOTES), 44.6 (*C*H$_2$CHOTES), 33.5 (*C*H$_2$C=O), 30.2 (*C*H$_2$CHOH), 25.98 (3C; *C*H$_3$CSi), 18.4 (CH*C*H$_2$C≡C), 18.20 (*C*Si), 14.8 (*C*H$_2$CH$_2$C=O), 9.93 (C≡C*C*H$_2$C≡C), 9.88 (C≡C*C*H$_2$C≡C), 9.85 (*C*H$_3$CH$_2$CHO), 7.0 (3C; *C*H$_3$CH$_2$Si), 5.0 (3C; *C*H$_2$Si), –4.36 (2C; *C*H$_3$Si).

IR (film): *v* = 3375 (br), 2955, 2931, 2877, 2857, 1742, 1669, 1541, 1459, 1437, 1416, 1367, 1317, 1251, 1171, 1098, 1070, 1006, 972, 884, 836, 796, 777, 743, 728, 700, 670 cm^{-1}.

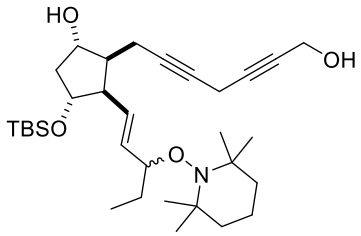
MS (+ESI) m/z (%): 637 (100) [*M*+Na]$^+$,

HRMS (+ESI) m/z: calcd for $C_{35}H_{58}O_5Si_2$+Na$^+$: 637.3715 [*M*+Na]$^+$, found: 637.3708.

6.4.4.2 Hydrogenation of diynes **196a** *and* **196c**

7-((1*S**,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-(5-hydroxycyclopentyl)hepta-2,5-diyn-1-ol 196c

Propargyl alcohol **196a** (74 mg, 0.112 mmol) was dissolved in THF (2 mL) and water (2 mL) followed by acetic acid (6 mL, 104 mmol) were added at room temperature. The reaction mixture was stirred for 1 h when complete conversion was indicated by TLC. K_2CO_3 (7.0 g, 51 mmol) was carefully added in small portions, the mixture was diluted by water to ca 10 mL, the layers were separated and the aqueous was extracted with DCM (4×10 mL). The combined organic layers were washed with water, dried over MgSO4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc gradient 9:1 to 85:15) to furnish free diol **196c** (62 mg, quant.) as inseparable 1.8:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy as a colorless oil.



R_f = 0.17 (PE/EtOAc 7:3).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (ddd, $^3J_{H,H}$ = 15.3, 8.5 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H; CH=C*H*CHOTMP), 5.18 (dd, $^3J_{H,H}$ = 15.3, 9.8 Hz, 1H; C*H*=CHCHOTMP), 4.23 (dt, $^3J_{H,H}$ = 5.9 Hz, $^5J_{H,H}$ = 2.0 Hz, 2H; CH_2OH), 4.06 (dt, $^3J_{H,H}$ = 4.7, 2.4 Hz, 1H; C*H*OH), 4.03-3.94 (m, 2H; C*H*OTMP, C*H*OTBS), 3.16 (quint, $^5J_{H,H}$ = 2.0 Hz, 2H; C≡CCH_2C≡C), 2.79-2.70 (m, 1H; C*H*CHOTBS), 2.57 (br s, 1H; O*H*), 2.48-2.38 (m, 1H; C*H*CHOH), 2.38-2.27 (m, 2H; CH*H*CHOTBS, CH*H*CHCHOH), 2.25-2.08 (m, 1H; C*H*HCHCHOH), 1.80-1.64 (m, 2H; C*H*HCHOTBS, CH*H*CHOTMP), 1.62-1.51 (m, 1H; CH*H*CH_2CN), 1.50-1.36 (m, 5H; C*H*HCHOTMP, CH_2CN), 1.35-1.22 (m, 1H; C*H*HCH_2CN), 1.14 (s, 3H; CH_3CN), 1.10 (s, 3H; CH_3CN), 1.07 (s, 3H; CH_3CN), 1.05 (s, 3H; CH_3CN), 0.87 (s, 9H; CH_3CSi), 0.83 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C$H_3$$CH_2$), 0.04 (s, 3H; C$H_3$Si), 0.03 (s, 3H; C$H_3$Si).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7 (CH=*C*HCHOTMP), 129.4 (*C*H=CHCHOTMP), 86.0 (*C*HOTMP), 80.8 (HOCH_2C≡*C*), 80.7 (CHCH_2*C*≡C), 79.19 (HOCH_2*C*≡C), 77.7 (*C*HOTBS), 77.3 (*C*HOH), 75.4 (CHCH_2C≡*C*), 60.4 (*C*N), 59.2 (*C*N), 54.6 (*C*HCHOTBS), 51.23 (*C*H_2OH), 49.3 (*C*HCHOH), 43.0 (*C*H_2CHOTBS), 40.3 (2C; *C*H_2CN), 35.6 (*C*H_3CN), 35.0 (*C*H_3CN), 27.5 (*C*H_2CHOTMP), 25.98 (3C; *C*H_3CSi), 20.6 (2C; *C*H_3CN), 19.52 (*C*H_2CHCHOH), 18.2 (*C*Si), 17.5 (*C*$H_2$$CH_2$CN), 10.14 (C≡C*C*$H_2$C≡C), 10.0 (*C*$H_3$$CH_2$), –4.61 (*C*$H_3$Si), –4.7 (*C*$H_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (ddd, $^3J_{H,H}$ = 15.2, 8.5 Hz, $^4J_{H,H}$ = 0.7 Hz, 1H; CH=C*H*CHOTMP), 5.13 (dd, $^3J_{H,H}$ = 15.3, 10.2 Hz, 1H; C*H*=CHCHOTMP), 4.24 (dt, $^3J_{H,H}$ = 6.4 Hz, $^5J_{H,H}$ = 2.0 Hz, 2H; CH_2OH), 4.16-4.07 (m, 1H; C*H*OH), 3.98-3.88 (m, 2H; C*H*OTMP, C*H*OTBS), 3.14 (quint, $^5J_{H,H}$ = 2.0 Hz, 2H; C≡CCH_2C≡C), 2.79-2.70 (m, 1H; C*H*CHOTBS), 2.54 (br s, $^3J_{H,H}$ = 6.8 Hz, 1H; O*H*), 2.50-2.36 (m, 1H; C*H*CHOH), 2.39-2.26 (m, 1H; CH*H*CHOTBS), 2.26-2.07 (m, 2H; CH_2CHCHOH), 1.82-1.63 (m, 2H; C*H*HCHOTBS, CH*H*CHOTMP), 1.62-1.51 (m, 1H; CH*H*CH_2CN), 1.52-1.36 (m, 5H; C*H*HCHOTMP, CH_2CN), 1.35-1.20 (m, 1H; C*H*HCH_2CN), 1.14 (s, 3H; CH_3CN), 1.10 (s, 3H; CH_3CN), 1.07 (s, 3H; CH_3CN), 1.05 (s, 3H; CH_3CN), 0.88 (s, 9H; CH_3CSi), 0.84 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C$H_3$$CH_2$), 0.06 (s, 6H; C$H_3$Si).

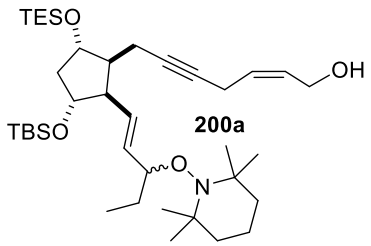
The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.3 (CH=*C*HCHOTMP), 128.6 (*C*H=CHCHOTMP), 86.7 (*C*HOTMP), 80.8 (HOCH_2C≡*C*), 80.6 (CHCH_2*C*≡C), 79.24 (HOCH_2*C*≡C), 77.6 (*C*HOTBS), 77.5 (*C*HOH), 75.1 (CHCH_2C≡*C*), 60.4 (*C*N), 59.2 (*C*N), 55.3 (*C*HCHOTBS), 51.18 (*C*H_2OH), 49.5

(*C*HCHOH), 42.9 (*C*H$_2$CHOTBS), 40.3 (2C; *C*H$_2$CN), 35.6 (*C*H$_3$CN), 35.0 (*C*H$_3$CN), 27.6 (*C*H$_2$CHOTMP), 26.01 (3C; *C*H$_3$CSi), 20.6 (2C; *C*H$_3$CN), 19.53 (*C*H$_2$CHCHOH), 18.1 (*C*Si), 17.4 (*C*H$_2$CH$_2$CN), 10.10 (C≡C*C*H$_2$C≡C), 10.08 (*C*H$_3$CH$_2$), –4.5 (*C*H$_3$Si), –4.57 (*C*H$_3$Si).
IR (film): ν = 3361 (br), 2930, 2857, 1463, 1375, 1360, 1313, 1256, 1132, 1095, 1046, 1006, 973, 877, 836, 776 cm^{-1}.
MS (+ESI) m/z (%): 546 (100) [*M*+Na]$^+$.
HRMS (+ESI) m/z: calcd for $C_{32}H_{56}NO_4Si$+Na$^+$: 546.3973 [*M*+Na]$^+$, found: 546.3970.

(*Z*)-7-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)hept-2-en-5-yn-1-ol 200a**, **(2*Z*,5*Z*)-7-((1*S**,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)hepta-2,5-dien-1-ol 200b** and **(*Z*)-7-((1*S**,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-((triethylsilyl)oxy)cyclopentyl)hept-5-en-1-ol 200c**

Dry MeOH (7 mL), EtOAc (3 mL, HPLC grade) and dry pyridine (0.6 mL) were mixed under argon and the solvent mixture was purged with argon for 1 h. In the meantime, a Schlenk flask was charged with Lindlar catalyst (5.0 mg) and filled with hydrogen gas by three vacuum/H_2 cycles. The above prepared solvent mixture (0.5 mL) was added, the mixture was purged with hydrogen for 10 min and stirred under positive pressure of hydrogen using a balloon connected to the tap of the Schlenk flask for 30 min. The suspension was cooled to 0 °C using an ice/water bath and diyne **196a** (5 mg, 8 μmol) in the same solvent mixture (0.75 mL) was added. The mixture was purged with hydrogen gas for 10 min, stirred under positive pressure of hydrogen and monitored by TLC/MS. Full conversion of the starting material was indicated after stirring for 10 min. After stirring for 45 min, partially hydrogenated enyne **200a** was almost consumed as indicated by TLC/MS and desired diene **200b** was the major product in the reaction mixture along with traces of overhydrogenated compound **200c**. The reaction mixture was purged with argon, filtered through a plug of Celite®, which was washed with EtOAc (ca 10 mL, HPLC grade). The filtrate was evaporated under reduced pressure and dried in vacuum to furnish (*Z*)-diene **200b** (4.2 mg, 91 mol.%, 75%) as a yellow oil as inseparable 1.8:1 mixture of diastereomers, inseparable from overhydrogenated compound **200c** (9 mol.%) and enyne **200a** (traces) as determined by ^{1}H NMR spectroscopy as a yellow oil.
MS (+ESI) m/z (%): 667 (1) [^{2}*M*(**200c**)+H]$^+$, 665 (100) [^{2}*M*(**200b**)+H]$^+$, 663 (1) [^{2}*M*(**200a**)+H]$^+$.

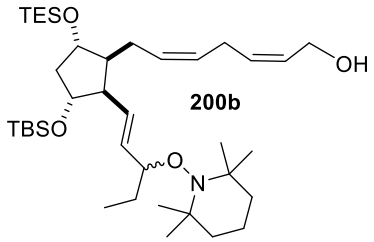


R_f = 0.25 (PE/Et_2O 3:1).

Distinct ^1H NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82-5.14 (m, 4H; C*H*=C*H*), 4.30-4.17 (m, 2H; CH_2OH), 4.06-3.91 (m, 3H; C*H*O), 2.99-2.90 (m, 2H; HC=CHCH_2C≡C).

The remaining ^{1}H NMR resonances were overlapping with **200b** and **200c**. The compound was not detectable by ^{13}C NMR spectroscopy.



R_f = 0.23 (PE/Et_2O 3:1).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73-5.54 (m, 1H; CH=C*H*CH_2OH), 5.57-5.26 (m, 3H; CH=CH_Z), 5.43 (dd, $^3J_{H,H}$ = 15.3, 8.5 Hz, 1H; CH=C*H*CHOTMP), 5.30 (dd, $^3J_{H,H}$ = 15.4, 8.8 Hz, 1H; C*H*=CHCHOTMP), 4.31-4.18 (m, 2H; CH_2OH), 4.01-3.90 (m, 2H; C*H*OTBS, C*H*OTMP), 3.81 (dt, $^3J_{H,H}$ = 7.4, 6.6 Hz, 1H; C*H*OTES), 2.94-2.83 (m, 1H; CH=CH*H*CH=CH), 2.77 (dt, $^2J_{H,H}$ = 14.9 Hz, $^3J_{H,H}$ = 7.3 Hz, 1H; CH=C*H*HCH=CH), 2.68-2.56 (m, 1H; C*H*CHOTBS), 2.36 (dt, $^2J_{H,H}$ = 14.3 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H; CH*H*CHOTBS), 2.29-2.15 (m, 1H; CH*H*CHCHOTES), 2.19-2.03 (m, 1H; C*H*CHOTES), 2.06-1.95 (m, 1H; C*H*HCHCHOTES), 1.82-1.66 (m, 1H; CH*H*CHOTMP), 1.66-1.49 (m, 3H; CH*H*CHOTBS, CH*H*CH_2CN, O*H*), 1.50-1.36 (m, 5H; C*H*HCHOTMP, CH_2CN), 1.34-1.20 (m, 1H; C*H*HCH_2CN), 1.15 (s, 3H; CH_3CN), 1.10 (s, 6H; CH_3CN), 1.06 (s, 3H; CH_3CN), 0.95 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C$H_3$$CH_2$Si), 0.86 (s, 9H; C$H_3$CSi), 0.83 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C$H_3$$CH_2$CH), 0.58 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; CH_2Si), 0.01 (s, 3H; CH_3Si), 0.00 (s, 3H; CH_3Si).

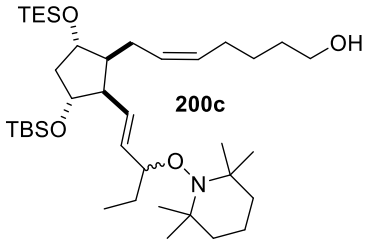
^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7 (CH=*C*HCHOTMP), 131.0 (CH=*C*HCH_2OH), 130.3 (*C*H=CHCHOTMP), 129.8 (CH=*C*H_Z), 128.7 (*C*H=CHCH_2OH), 127.66 (CH=*C*H_Z), 86.5 (*C*HOTMP), 76.2 (*C*HOTES), 76.1 (*C*HOTBS), 60.4 (*C*N), 59.0 (*C*N), 58.59 (*C*H_2OH), 52.4 (*C*HCHOTBS), 50.0 (*C*HCHOTES), 44.58 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 34.3 (*C*H_3CN), 34.2 (*C*H_3CN), 27.66 (*C*H_2CHOTMP), 26.3 (*C*H_2CHCHOTES), 26.11 (CH=CH*C*H_2CH=CH), 26.02 (3C; *C*H_3CSi), 20.5 (2C; *C*H_3CN), 18.2 (*C*Si), 17.5 (*C*$H_2$$CH_2$CN), 10.1 (*C*$H_3$$CH_2$CH), 7.0 (3C; *C*$H_3$$CH_2$Si), 5.0 (3C; *C*$H_2$Si), –4.47 (2C; *C*$H_3$Si).

Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73-5.54 (m, 1H; CH=C*H*CH_2OH), 5.57-5.28 (m, 4H; CH=C*H*CHOTMP, CH=C*H*$_Z$), 5.20 (dd, $^3J_{H,H}$ = 15.4, 9.4 Hz, 1H; C*H*=CHCHOTMP), 4.24-4.14 (m, 2H; C*H*$_2$OH), 4.04-3.94 (m, 2H; C*H*OTBS, C*H*OTMP), 3.81 (dt, $^3J_{H,H}$ = 7.5, 6.2 Hz, 1H; C*H*OTES), 2.98-2.88 (m, 1H; CH=C*H*HCH=CH), 2.78-2.69 (m, 1H; CH=CH*H*CH=CH), 2.69-2.56 (m, 1H; C*H*CHOTBS), 2.46-2.34 (m, 1H; CH*H*CHOTBS), 2.29-2.14 (m, 1H; CH*H*CHCHOTES), 2.18-2.04 (m, 1H; C*H*CHOTES), 1.94-1.81 (m, 1H; C*H*HCHCHOTES), 1.82-1.66 (m, 1H; CH*H*CHOTMP), 1.66-1.49 (m, 3H; CH*H*CHOTBS, CH*H*CH_2CN, O*H*), 1.50-1.36 (m, 5H; C*H*HCHOTMP, C*H*$_2$CN), 1.36-1.22 (m, 1H; C*H*HCH_2CN), 1.15 (s, 3H; C*H*$_3$CN), 1.10 (s, 6H; C*H*$_3$CN), 1.06 (s, 3H; C*H*$_3$CN), 0.96 (t, $^3J_{H,H}$ = 7.9 Hz, 9H; C*H*$_3CH_2Si$), 0.87 (s, 9H; C*H*$_3$CSi), 0.82 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C*H*$_3CH_2CH$), 0.58 (q, $^3J_{H,H}$ = 7.9 Hz, 6H; C*H*$_2$Si), 0.03 (s, 6H; C*H*$_3$Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0 (CH=*C*HCHOTMP), 130.9 (CH=*C*HCH_2OH), 129.42 (*C*H=CHCHOTMP), 129.40 (CH=*C*H$_Z$), 128.8 (*C*H=CHCH_2OH), 127.75 (CH=*C*H$_Z$), 86.6 (*C*HOTMP), 76.4 (*C*HOTES), 75.9 (*C*HOTBS), 60.4 (*C*N), 59.0 (*C*N), 58.61 (*C*H_2OH), 52.9 (*C*HCHOTBS), 49.9 (*C*HCHOTES), 44.55 (*C*H_2CHOTBS), 40.3 (2C; *C*H_2CN), 35.1 (*C*H_3CN), 34.2 (*C*H_3CN), 27.70 (*C*H_2CHOTMP), 26.4 (*C*H_2CHCHOTES), 26.09 (CH=CH*C*H_2CH=CH), 26.05 (3C; *C*H_3CSi), 20.5 (2C; *C*H_3CN), 18.2 (*C*Si), 17.5 (*C*H_2CH_2CN), 10.0 (*C*H_3CH_2CH), 7.0 (3C; *C*H_3CH_2Si), 5.0 (3C; *C*H_2Si), –4.49 (2C; *C*H_3Si).

HRMS (+ESI) m/z: calcd for $C_{38}H_{73}NO_4Si_2+H^+$: 664.5151 [*M*+H]$^+$, found: 664.5153.



R_f = 0.24 (PE/Et_2O 3:1).

Major diastereomer - distinct ^{1}H NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54-5.28 (m, 4H; CH=C*H*$_Z$, C*H*=C*H*CHOTMP), 4.07-3.91 (m, 2H; C*H*OTMP, C*H*OTBS), 3.87-3.74 (m, 1H; C*H*OTES), 3.69-3.58 (m, 2H; C*H*$_2$OH), 2.12-1.98 (m, 1H; CH_2CH*H*CH=CH), 2.05-1.95 (m, 1H; CH*H*CHCHOTES), 1.97-1.79 (m, 2H; CH_2C*H*HCH=CH, C*H*HCHCHOTES), 1.63-1.52 (m, 4H; C*H*$_2$C*H*$_2CH_2OH$).

The remaining ^{1}H NMR resonances were overlapping with **200a** and **200b**.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.5 (CH=*C*HCHOTMP), 130.6 (CH=C*H*), 129.95 (CH=C*H*), 129.0 (CH=C*H*), 86.52 (*C*HOTMP), 76.1 (*C*HOTES), 75.99 (*C*HOTBS), 62.97 (*C*H_2OH), 60.2 (*C*N), 59.3 (*C*N), 52.3 (*C*HCHOTBS), 50.3 (*C*HCHOTES), 44.63 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.1 (*C*H_3CN), 34.2 (*C*H_3CN), 32.5 (*C*H_2CH_2OH), 27.6 (*C*H_2CHOTMP), 27.1 (CH_2*C*H_2CH=CH), 26.3 (*C*H_2CHCHOTES), 26.0 (3C; *C*H_3CSi), 25.91 (*C*H_2CH_2CH=CH), 20.5 (2C; *C*H_3CN), 18.2 (*C*Si), 17.5 (*C*H_2CH_2CN), 10.2 (*C*H_3CH_2CH), 7.0 (3C; *C*H_3CH_2Si), 5.0 (3C; *C*H_2Si), –4.5 (2C; *C*H_3Si).

Minor diastereomer - distinct ^{1}H NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54-5.28 (m, 3H; CH=CH_Z, CH=C*H*CHOTMP), 5.21 (dd, $^3J_{H,H}$ = 15.5, 9.3 Hz, 1H; CH=C*H*CHOTMP), 4.07-3.91 (m, 2H; C*H*OTMP, C*H*OTBS), 3.87-3.74 (m, 1H; C*H*OTES), 3.69-3.58 (m, 2H; CH_2OH), 2.12-1.98 (m, 2H; CH_2CH*H*CH=CH, CH*H*CHCHOTES), 1.97-1.85 (m, 2H; CH_2C*H*HCH=CH, C*H*HCHCHOTES), 1.63-1.52 (m, 4H; CH_2C$H_2$$CH_2$OH).

The remaining ^{1}H NMR resonances were overlapping with **200a** and **200b**.

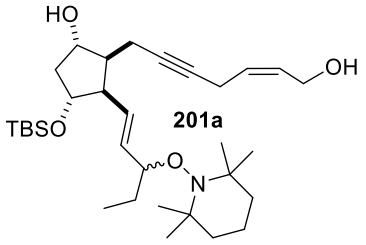
^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2 (CH=*C*HCHOTMP), 131.0 (CH=C*H*), 129.97 (CH=C*H*), 129.2 (CH=C*H*), 86.53 (*C*HOTMP), 76.2 (*C*HOTES), 75.95 (*C*HOTBS), 63.00 (*C*H_2OH), 60.2 (*C*N), 59.3 (*C*N), 52.9 (*C*HCHOTBS), 50.2 (*C*HCHOTES), 44.59 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.1 (*C*H_3CN), 34.2 (*C*H_3CN), 33.0 (*C*$H_2$$CH_2$OH), 27.7 (*C*$H_2$CHOTMP), 27.1 ($CH_2$*C*$H_2$CH=CH), 26.4 (*C*$H_2$CHCHOTES), 26.1 (3C; *C*$H_3$CSi), 25.87 (*C*$H_2$$CH_2$CH=CH), 20.5 (2C; *C*$H_3$CN), 18.2 (*C*Si), 17.5 (*C*$H_2$$CH_2$CN), 10.0 (*C*$H_3$$CH_2$CH), 7.0 (3C; *C*$H_3$$CH_2$Si), 5.0 (3C; *C*$H_2$Si), –4.4 (2C; *C*$H_3$Si).

HRMS (+ESI) m/z: calcd for $C_{38}H_{75}NO_4Si_2$+H^+: 666.5307 [*M*+H]$^+$, found: 666.5311.

(*Z*)-7-((1*S,2*R**,3*R**,5*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-hydroxy(cyclopentyl)hept-2-en-5-yn-1-ol 201a**, **(2*Z*,5*Z*)-7-((1*S**,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-hydroxy(cyclopentyl)hepta-2,5-dien-1-ol 201b** and **(*Z*)-7-((1*S**,2*R**,3*R**,5*S**)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pent-1-en-1-yl)-5-hydroxy(cyclopentyl)hept-5-en-1-ol 201c**

EtOAc (10 mL, HPLC grade) and pyridine (0.6 mL) were mixed under argon and purged with argon for 1 h. In the meantime, a Schlenk flask was charged with Lindlar catalyst (7 mg) and filled with hydrogen gas by three vacuum/H_2 cycles. The above prepared solvent mixture (0.5 mL) was added and the suspension was purged with hydrogen gas with stirring for 10 min and stirred under positive H_2 pressure using a small balloon on the Schlenk flask tap for 30 min. Diyne **196c** (7.0 mg, 13 μmol) in the same solvent mixture (1.2 mL) was added, the mixture was purged with H_2 with stirring for 10 min, and stirred under positive H_2 pressure with monitoring by TLC/MS. Full conversion of the starting material was indicated after stirring for 10 min. After 16 h of stirring, the reaction mixture was purged again with H_2 and the balloon was replaced by a new one. At 24 h of stirring, close-to full consumption of enyne **201a** was indicated. The reaction mixture was purged with argon and filtered through a plug of Celite®, which was washed with EtOAc (ca 10 mL, HPLC grade). The filtrate was evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography (hexane/EtOAc gradient 95:5 to 9:1) to furnish product **201b** (6.0 mg, 90% mol.%, 79%) as inseparable 1.5:1 mixture of diastereomers, inseparable from overhydrogenated compound **201c** (8 mol.%) and enyne **201a** (traces) as determined by ^{1}H NMR spectroscopy as a colorless oil.

MS (+ESI) m/z (%): 553 (3) [^{2}*M*(**201c**)+H]$^+$, 551 (100) [^{2}*M*(**201b**)+H]$^+$, 549 (5) [^{2}*M*(**201a**)+H]$^+$.



R_f = 0.15 (PE/EtOAc 7:3).

Major diastereomer - distinct ^{1}H NMR resonances:

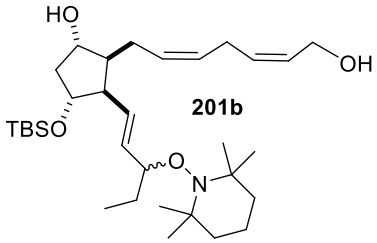
^{1}H NMR (401 MHz, $CDCl_3$): δ = 5.79-5.36 (m, 3H; CH=CH_Z, CH=C*H*CHOTMP), 5.28-5.12 (m, 1H; C*H*=CHCHOTMP), 4.29-4.20 (m, 2H; CH_2OH), 4.13-3.85 (m, 3H; C*H*OH), 2.94 (dt, $^3J_{H,H}$ = 8.8 Hz, $^5J_{H,H}$ = 2.2 Hz, 2H; HC=CHCH_2C≡C).

Minor diastereomer - distinct ^{1}H NMR resonances:

^{1}H NMR (401 MHz, $CDCl_3$): δ = 5.79-5.36 (m, 3H; CH=CH_Z, CH=C*H*CHOTMP), 5.07 (dd, 1H; $^3J_{H,H}$ = 15.2, 10.0 Hz, C*H*=CHCHOTMP), 4.29-4.20 (m, 2H; CH_2OH), 4.13-3.85 (m, 3H; C*H*OH), 2.93 (dt, $^3J_{H,H}$ = 8.8, $^5J_{H,H}$ = 2.2 Hz, 2H; HC=CHCH_2C≡C).

The compound was not detectable by ^{13}C NMR spectroscopy. The remaining ^{1}H NMR resonances were overlapping with **201b** and **201c**.

HRMS (+ESI) m/z: calcd for $C_{32}H_{57}NO_4Si+H^+$: 548.4130 [*M*+H]$^+$, found: 548.4125.



R_f = 0.15 (PE/EtOAc 7:3).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77-5.56 (m, 2H; C*H*=C*H*CH_2OH), 5.56-5.37 (m, 3H; $CHCH_2$C*H*=C*H*, CH=C*H*CHOTMP), 5.22 (dd, $^3J_{H,H}$ = 15.4, 9.7 Hz, 1H; C*H*=CHCHOTMP), 4.268 (ddd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 7.1, 5.7 Hz, 1H; CH*H*OH), 4.21-4.14 (m, 1H; C*H*HOH), 4.15-4.06 (m, 1H; C*H*OTBS), 4.10-4.04 (m, 1H; C*H*OH), 4.03-3.84 (m, 1H; C*H*OTMP), 2.93 (dt, $^2J_{H,H}$ = 16.3 Hz, $^3J_{H,H}$ = 8.2 Hz, 1H; CH=CH*H*CH=CH), 2.83-2.67 (m, 2H; CH=C*H*HCH=CH, C*H*CHOTBS), 2.30 (ddd, $^2J_{H,H}$ = 13.9 Hz, $^3J_{H,H}$ = 7.6, 5.2 Hz, 1H; CH*H*CHOTBS), 2.26-2.15 (m, 2H; C*H*CHOH, CH*H*CHCHOH), 2.14-2.05 (m, 1H; C*H*HCHCHOH), 1.78-1.68 (m, 1H; CH*H*CHOTMP), 1.68-1.58 (m, 1H; C*H*HCHOTBS), 1.59-1.49 (m, 1H; CH*H*CH_2CN), 1.50-1.35 (m, 7H; CH*H*CHOTMP, CH_2CN, O*H*), 1.34-1.23 (m, 1H; C*H*HCH_2CN), 1.14 (s, 3H; CH_3CN), 1.10 (s, 6H; CH_3CN), 1.05 (s, 3H; CH_3CN), 0.87 (s, 9H; CH_3CSi), 0.83 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C$H_3$$CH_2$), 0.04 (s, 6H; C$H_3$Si).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2 (CH=*C*HCHOTMP), 130.98 (CH=*C*HCH_2OH), 129.9 (*C*H=CHCHOTMP), 129.1 (CH=*C*H_Z), 128.5 (*C*H=CHCH_2OH), 128.1 (CH=*C*H_Z), 86.2

(*C*HOTMP), 78.3 (*C*HOTBS), 77.6 (*C*HOH), 60.2 (*C*N), 59.4 (*C*N), 58.47 (*C*H_2OH), 54.6 (*C*HCHOTBS), 50.9 (*C*HCHOH), 43.1 (*C*H_2CHOTBS), 40.38 (2C; *C*H_2CN), 35.1 (*C*H_3CN), 34.1 (*C*H_3CN), 27.59 (*C*H_2CHOTMP), 27.58 (*C*H_2CHCHOH), 26.13 (CH=CH*C*H_2CH=CH), 25.98 (3C; *C*H_3CSi), 20.6 (2C; *C*H_3CN), 18.2 (*C*Si), 17.4 (*C*$H_2$$CH_2$CN), 10.10 (*C*$H_3$$CH_2$), –4.65 (*C*$H_3$Si), –4.68 (*C*$H_3$Si).

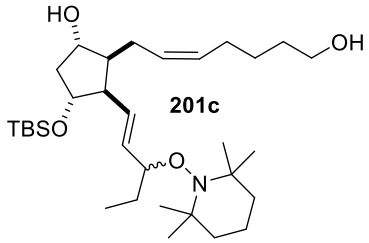
Minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74-5.58 (m, 1H; CH=C*H*CH_2OH), 5.55-5.36 (m, 4H; C*H*=CH_Z, CH=C*H*CHOTMP), 5.11 (dd, $^3J_{H,H}$ = 15.4, 10.0 Hz, 1H; C*H*=CHCHOTMP), 4.273 (ddd, $^2J_{H,H}$ = 12.7 Hz, $^3J_{H,H}$ = 7.1, 5.6 Hz, 1H; CH*H*OH), 4.24-4.15 (m, 1H; C*H*HOH), 4.15-4.06 (m, 1H; C*H*OTBS), 4.04-3.85 (m, 2H; C*H*OTMP, C*H*OH), 2.94 (dt, $^2J_{H,H}$ = 16.3 Hz, $^3J_{H,H}$ = 8.2 Hz, 1H; CH=CH*H*CH=CH), 2.83-2.69 (m, 2H; CH=C*H*HCH=CH, C*H*CHOTBS), 2.38-2.29 (m, 1H; CH*H*CHOTBS), 2.27-2.16 (m, 2H; C*H*CHOH, CH*H*CHCHOH), 2.02-1.92 (m, 1H; C*H*HCHCHOH), 1.79-1.68 (m, 1H; CH*H*CHOTMP), 1.68-1.59 (m, 1H; C*H*HCHOTBS), 1.60-1.49 (m, 1H; CH*H*CH_2CN), 1.50-1.33 (m, 7H; CH*H*CHOTMP, CH_2CN; O*H*), 1.33-1.22 (m, 1H; C*H*HCH_2CN), 1.14 (s, 3H; CH_3CN), 1.10 (s, 6H; CH_3CN), 1.05 (s, 3H; CH_3CN), 0.88 (s, 9H; CH_3CSi), 0.83 (t, $^3J_{H,H}$ = 7.5 Hz, 3H; C$H_3$$CH_2$), 0.07 (s, 3H; C$H_3$Si), 0.06 (s, 3H; C$H_3$Si).

The O*H* resonances were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (CH=*C*HCHOTMP), 130.96 (CH=*C*HCH_2OH), 130.1 (*C*H=CHCHOTMP), 129.6 (CH=*C*H_Z), 128.6 (*C*H=CHCH_2OH), 128.2 (CH=*C*H_Z), 86.6 (*C*HOTMP), 78.0 (*C*HOTBS), 77.9 (*C*HOH), 60.2 (*C*N), 59.4 (*C*N), 58.54 (*C*H_2OH), 54.9 (*C*HCHOTBS), 51.0 (*C*HCHOH), 43.1 (*C*H_2CHOTBS), 40.35 (2C; *C*H_2CN), 35.6 (*C*H_3CN), 34.1 (*C*H_3CN), 27.7 (*C*H_2CHOTMP), 27.5 (*C*H_2CHCHOH), 26.10 (CH=CH*C*H_2CH=CH), 26.02 (3C; *C*H_3CSi), 20.6 (2C; *C*H_3CN), 18.2 (*C*Si), 17.4 (*C*$H_2$$CH_2$CN), 10.07 (*C*$H_3$$CH_2$), –4.53 (*C*$H_3$Si), –4.6 (*C*$H_3$Si).

HRMS (+ESI) m/z: calcd for $C_{32}H_{59}NO_4Si+H^+$: 550.4286 [*M*+H]$^+$, found: 550.4277.



201c

R_f = 0.15 (PE/EtOAc 7:3).

Major diastereomer - distinct ^{1}H NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74-5.32 (m, 3H; C*H*=CH_Z, CH=C*H*CHOTMP), 5.23 (dd, $^3J_{H,H}$ = 15.4, 9.5 Hz, 1H; C*H*=CHCHOTMP), 4.11-3.82 (m, 3H; C*H*O), 3.64 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; CH_2OH), 2.13-2.01 (m, 2H; C*H*HCHCHOH, CH_2CH*H*CH=CH), 2.00-1.95 (m, 2H; CH_2C*H*HCH=CH, CH*H*CHCHOH), 1.48-1.40 (m, 4H; CH_2C$H_2$$CH_2$OH).

The remaining ^{1}H NMR resonances were overlapping with **201a** and **201b**.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.9 (CH=*C*HCHOTMP), 130.58 (CH=C*H*), 130.1 (CH=C*H*), 129.2 (CH=C*H*), 86.2 (*C*HOTMP), 78.2 (*C*HOH), 77.6 (*C*HOTBS), 62.8 (*C*H_2OH), 60.2 (*C*N), 59.3

(*C*N), 55.0 (*C*HCHOTBS), 51.1 (*C*HCHOH), 43.1 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.0 (*C*H_3CN), 34.1 (*C*H_3CN), 32.37 (*C*$H_2$$CH_2$OH), 27.7 ($CH_2$*C*$H_2$CH=CH), 27.5 (*C*$H_2$CHOTMP), 27.2 (*C*$H_2$CHCHOH), 25.97 (3C, *C*$H_3$CSi), 25.9 (*C*$H_2$$CH_2$CH=CH), 20.5 (2C; *C*$H_3$CN), 18.1 (*C*Si), 17.4 (*C*$H_2$$CH_2$CN), 10.05 (*C*$H_3$$CH_2$), –4.59 (*C*$H_3$Si), –4.69 (*C*$H_3$Si).

Minor diastereomer - distinct ^{1}H NMR resonances:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74-5.32 (m, 3H; CH=CH_Z, CH=C*H*CHOTMP), 5.12 (dd, $^3J_{H,H}$ = 15.3, 10.0 Hz, 1H; C*H*=CHCHOTMP), 4.11-3.82 (m, 3H; C*H*O), 3.63 (t, $^3J_{H,H}$ = 6.5 Hz, 2H; C*H*$_2$OH), 2.13-2.01 (m, 2H; C*H*HCHCHOH, CH_2CH*H*CH=CH), 2.00-1.95 (m, 2H; CH_2C*H*HCH=CH, CH*H*CHCHOH), 1.50-1.38 (m, 4H, C*H*$_2$C*H*$_2$$CH_2$OH).

The remaining ^{1}H NMR resonances were overlapping with **201a** and **201b**.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.6 (CH=*C*HCHOTMP), 130.55 (CH=C*H*), 130.0 (CH=C*H*), 129.0 (CH=C*H*), 86.6 (*C*HOTMP), 78.0 (*C*HOH), 77.9 (*C*HOTBS), 62.9 (*C*H_2OH), 60.2 (*C*N), 59.3 (*C*N), 54.5 (*C*HCHOTBS), 51.2 (*C*HCHOH), 43.0 (*C*H_2CHOTBS), 40.4 (2C; *C*H_2CN), 35.6 (*C*H_3CN), 34.3 (*C*H_3CN), 32.39 (*C*$H_2$$CH_2$OH), 27.8 ($CH_2$*C*$H_2$CH=CH), 27.6 (*C*$H_2$CHOTMP), 27.2 (*C*$H_2$CHCHOH), 25.99 (3C, *C*$H_3$CSi), 25.8 (*C*$H_2$$CH_2$CH=CH), 20.5 (2C; *C*$H_3$CN), 18.1 (*C*Si), 17.5 (*C*$H_2$$CH_2$CN), 10.10 (*C*$H_3$$CH_2$), –4.55 (*C*$H_3$Si), –4.66 (*C*$H_3$Si).

7 RÉSUMÉ

7.1 Introduction et état de l'art

7.1.1 Biosynthèse d'isoprostanoïdes

Comme les prostaglandines, les isoprostanoïdes sont des métabolites oxygénés lipidiques formés *in vivo* à partir d'acides gras polyinsaturés (AGPIs). Les principales familles comprennent les isoprostanes (IsoPs) formées à partir de l'acide arachidonique (AA, C20:6 ω–6), les phytoprostanes (PhytoPs) de l'acide α-linolénique (ALA, C18:3 ω–3) ou les neuroprostanes (NeuroPs), métabolites de l'acide docosahexaénoïque (DHA, C22:6 ω–3). Contrairement à la biosynthèse des prostaglandines, les isoprostanoïdes ne nécessitent pas d'assistance enzymatique pour être formées.[12] En revanche, les espèces oxygenées réactives (EOR) peuvent abstraire l'hydrogène de l'une des positions bisallyliques de l'APGI. Le radical stabilisé formé peut réagir par différentes voies, une d'entre elles consiste en une série de piégeage d'oxygène, de double cyclisations 5-*exo* et de réduction d'hydroperoxydes pour conduire à la formation d'isoprostanoïdes sous forme de mélange racémique de diastéréoisomères et de régioisomères.[19, 20]

Leurs caractéristiques structurelles communes sont la présence d'un noyau cyclopentanique et de deux chaînes latérales: la chaîne alpha portant le groupe carboxyle et la chaîne oméga. Ils diffèrent par le nombre de doubles liaisons dans les chaînes latérales (selon l'APGI d'origine), la position de l'hydroxyle de la chaîne latérale, le degré d'oxygénation sur le cycle, la position des deux chaînes latérales et la configuration relative. Pour cette raison, un système de nomenclature complexe a été établi.[28-32] Les cinq principaux types de NeuroPs basées sur le schéma de substitution des cycles sont de type F-, E-, D-, A- ou J- et sont formés *in vivo* à partir de type H-NeuroP instable (Schéma 1).[12]

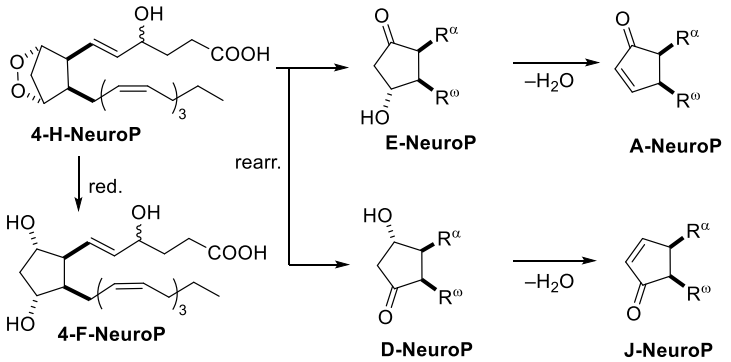


Schéma 1. Formation des cinq principaux types d'isoprostanoïdes à partir de type H-NeuroP instable.

7.1.2 Contexte biologique

Le DHA est l'APGI majoritaire du cerveu humain et du système nerveux en général, mais le DHA est également ubiquitaire dans les autres tissues humains. Il est ainsi évident que les NeuroPs se retrouvent dans les organes correspondants.[12] Le stress oxydant est un état impliquant une surproduction d'EOR dans l'organisme et est lié à diverses neuropathologies telles que la maladie

d'Alzheimer ou le syndrome de Rett. Les NeuroPs pourraient représenter un outil de diagnostic potentiellement précieux pour ces types de maladies.[43-49] En outre, certains de ces métabolites ont démontré une forte activité biologique, contribuant très probablement aux effets bénéfiques décrits dans la littérature pour les régimes alimentaires riches en APGI oméga-3. Un exemple récent est l'activité anti-arythmique exercée par 4-F_{4t}-NeuroP qui s'est avérée plus puissante que le DHA lui-même.[38-41] De plus, les activités anti-inflammatoires des isoprostanoïdes ont été découvertes pour les NeuroPs de type énone tels que la 14-A_{4t}-NeuroP.[35-37] Cependant, ces deux applications nécessitent un travail de synthèse car seuls des mélanges complexes inséparables peuvent être obtenus à partir d'huiles ou de matériel biologique. Enfin, même la détection de ces systèmes nécessite des standards analytiques.

7.1.3 Approches précédentes vers la synthèse des NeuroPs

Les approches synthétiques actuelles pour la synthèse des NeuroPs sont basées sur la synthèse d'un noyau cyclopentane fonctionnalisé, auquel une ou deux chaînes latérales sont successivement attachées. Contrairement aux IsoPs et PhytoPs, les NeuroPs portent toujours une chaîne latérale avec une unité (*Z*)-diène ou (*Z*)-polyène non-conjuguée. L'élaboration de cette chaîne latérale est une étape clé dans la planification de la synthèse et cela est réalisé dans la grande majorité des synthèses de NeuroP par oléfination de Wittig à l'aide de sels de phosphonium (bis)homoallyliques.[59, 70, 76-78, 80] Cette transformation est généralement efficace, mais la nature des substrats permettant la réaction est limité du côté de l'électrophile à cause de la faible stabilité des ylures (bis)allyliques correspondants.

À cet égard, les travaux de Taber *et al.* sont particulièrement remarquables car les auteurs ont utilisé une stratégie différente dans leur synthèse de la 13-F_{4t}-NeuroP, un métabolite très complexe.[83] Cette approche consistait en l'addition nucléophile de bromure de propargylzinc, le couplage du bromure allylique **72b** induit par du Cu(I) et la semi-hydrogénation à l'aide de P2-Ni fournissent le tétraène **73** souhaité (Schéma 2).

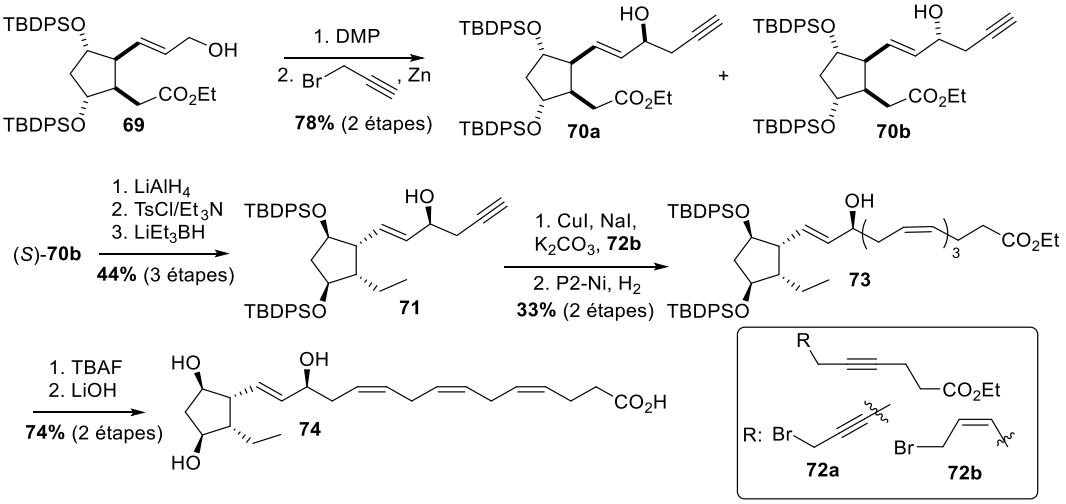


Schéma 2. L'approche de Taber *et al.* pour la 13-F_{4t}-NeuroP.

La plupart des synthèses existantes ciblent les F-NeuroPs, à l'exception des travaux de Zanoni *et al.* et Porta *et al*. qui se sont concentrés sur les isoprostanoïdes A- et J-. Les auteurs ont réalisé les synthèses totales de 14-A_4-NeuroP **22** et 17-A_4-NeuroP **24** en utilisant la lactone **2** de type Corey et les oléfinations successives de Julia-Kociensky et Wittig (Schéma 3), avec un rendement de 14% et 18% sur 11 étapes, respectivement. [69, 70]

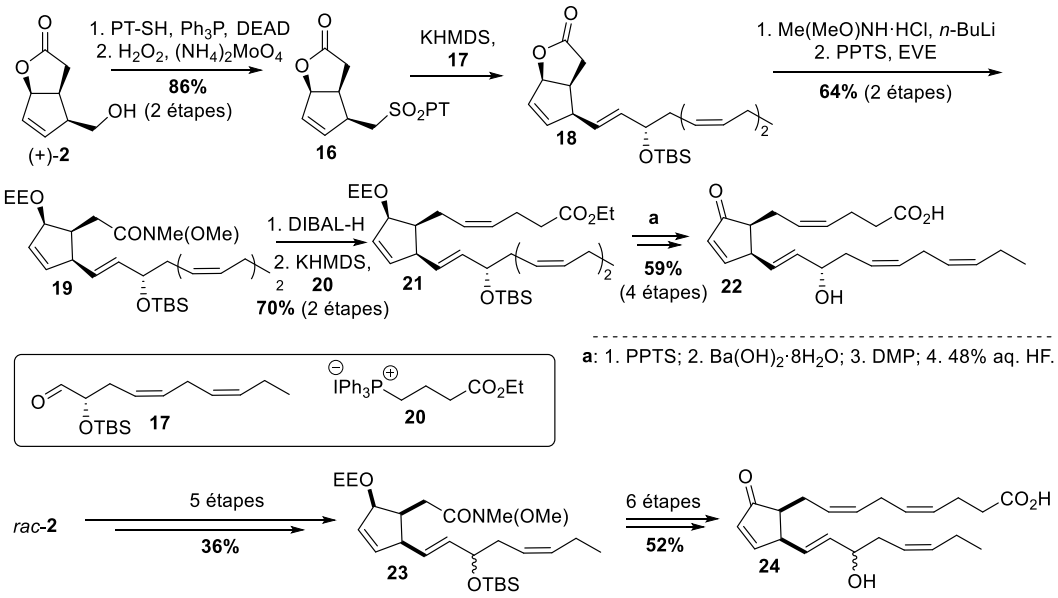


Schéma 3. L'approche de Zanoni/Porta *et al.* concernant les NeuroPs à base de cyclopenténone.

7.2 Les objectifs des travaux de thèse

A partir de cet état de l'art, les objectifs suivants ont été définis :

A. Développer une nouvelle stratégie de synthèse énantiosélective de A- et J-NeuroPs et de l'appliquer à la synthèse du 4-A_4-NeuroP.
B. Développer une stratégie unifiée de synthèse d'isoprostanoïdes avec la chaîne oméga de type 3-hydroxypentényle et la chaîne alpha du type (*Z*)-polyène. Puis, appliquer cette stratégie à la synthèse de la 18-F_{3t}-IsoP et par extension à la synthèse de 20-NeuroPs.

7.3 Résultats et discussions

7.3.1 Vers la synthèse de NeuroPs du type cyclopenténone

7.3.1.1 Analyse rétrosynthétique

L'analyse rétrospective de la cible 4-A$_4$-NeuroP **103a** commence par une déconnexion des chaînes latérales (Schéma 4). La chaîne oméga peut être connectée par oléfination de Wittig à l'aide du sel de phosphonium **55**. Pour l'introduction de la chaîne alpha une réaction de métathèse croisée entre le cyclopentène **154b** protégé orthogonalement et le précurseur **160b** a été envisagée. Le noyau cyclopenténique est ensuite déconnecté, conduisant au synthon triène **148b**. Trois stratégies différentes pour synthétiser le précurseur central **148b** ont été étudiées.

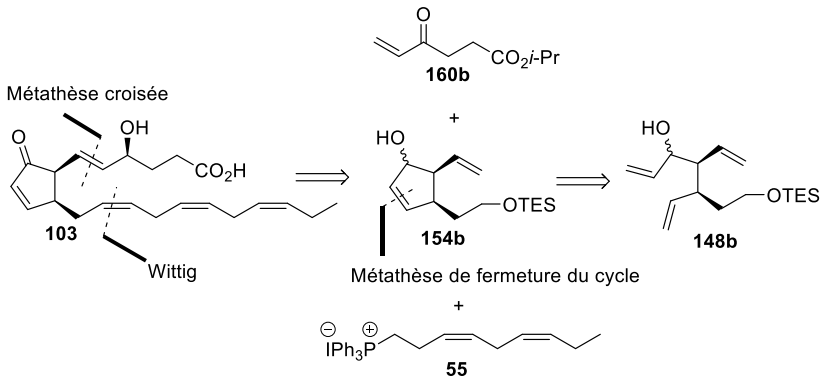


Schéma 4. Analyse de rétro-synthèse du 4-A$_4$-NeuroP **103a**.

7.3.1.2 Strategie de synthèse **I**

La première approche repose sur la synthèse et la fonctionnalisation sélective de la lactone **104a** (Schéma 5). La synthèse débute par une addition de Michael organocatalysée du malonate de diéthyle sur l'énal **160a** avec un rendement modéré de 60%. La réduction du carbonyle et la lactonisation dans des conditions thermodynamiques ont permis d'obtenir la lactone **104a** avec un rendement de 66% en deux étapes. Cette dernière a été réduite sélectivement avec du DIBAL-H pour fournir le lactol **111** correspondant, cependant, les tentatives de transformation sélective effectuées sur le lactol **111** ou sur la lactone **104a** se sont révélées infructueueses.

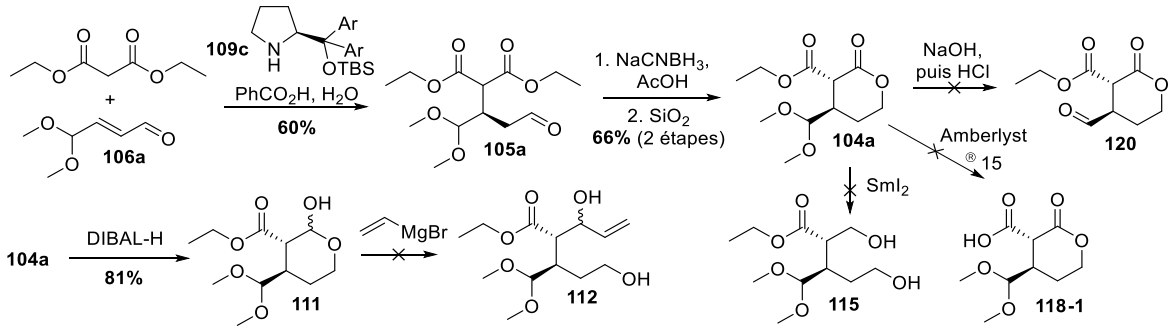


Schéma 5. Synthèse et tentative de fonctionnalisation de la lactone **104a**.

7.3.1.3 Stratégie de synthèse **II**

La deuxième stratégie consiste à synthétiser la lactone *trans*-**122b** par analogie à la synthèse décrite dans la littérature par Candy *et al.* (Schéma 6).[115] La réduction en lactol du composé *trans*-**122b** à l'aide de DIBAL-H et de la méthylation de Wittig a permis d'accéder à l'alcène **139**. La réaction de Wittig a requis un fort travail d'optimisation afin de diminuer la proportion de produit secondaire d'élimination **140**. L'oxydation à l'aide du réactif de Dess-Martin et une seconde oléfination de Wittig a permis d'obtenir le diène **145**. Lors de la déprotection du dimethylacétal, le groupement PMB a également été déprotégé pour fournir le lactol **147b** sous forme de mélange 1.5:1 de diastéréoisomères. L'ouverture de **147b** en utilisant le bromure de vinylmagnésium a fourni le diol **148a** sous forme de mélange 1.1:1 de diastéréoisomères. Enfin, la monoprotection sélective de l'alcool primaire par le TESCl a fourni le précurseur **148b** protégé de manière orthogonale.

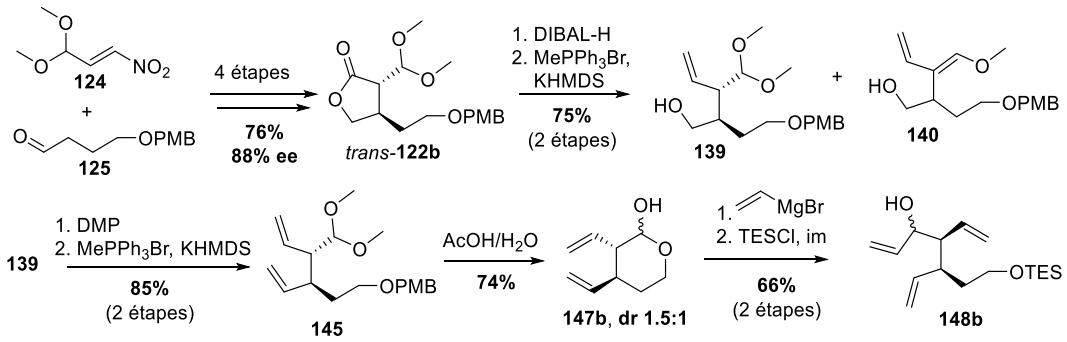


Schéma 6. Synthèse du précurseur **148b** protégé orthogonalement à partir de la lactone *trans*-**122b**.

7.3.1.4 Stratégie de synthèse **III**

La troisième stratégie envisage une approche de difonctionnalisation vicinale plus directe que la synthèse du lactol **147b**. Dans un premier temps, l'addition conjuguée du bromure de vinylmagnésium sur le pyrane en présence de CuI dans des conditions décrites a fourni la lactone *rac*-**48** (Schéma 7).[142] Ensuite, le phényl(sélényl)acétaldéhyde apparenté à un groupement vinyle a été introduit par aldolisation.[137] Après réduction de la lactone obtenue en lactol, une protection successive sous forme d'acétal mixte a été nécessaire pour éviter l'élimination conjuguée compétitive. Le groupement phénylsélényle a été éliminé en même temps que le groupement hydroxyle dans les conditions de Reich. [135] Par la suite, la déprotection de l'acétal mixte dans des conditions acidiques a permis d'obtenir le lactol *rac*-**147b**. Le rendement global non-optimisé de la synthèse est de 13% sur cinq étapes. Cette stratégie est donc complémentaire à la stratégie **II** car elle représente un accès très direct au matériel racémique.

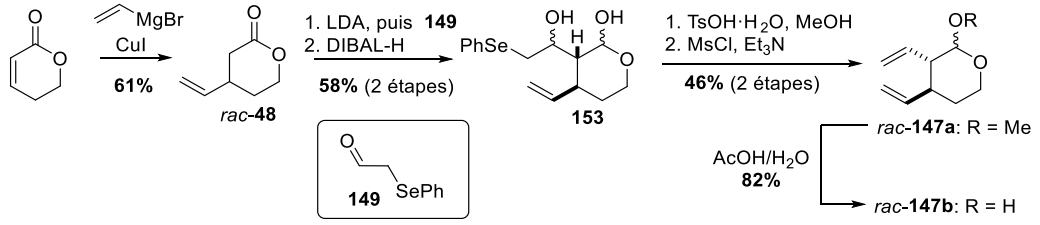


Schéma 7. Synthèse du lactol *rac*-**147b** par difonctionnalisation vicinale.

7.3.1.5 Application de la stratégie **II** *à la synthèse totale de 4-A4-NeuroP*

Pour accéder au noyau cyclopenténique, le composé **148b** est traité avec le catalyseur Grubbs de seconde génération pour fournir **154b** (Schéma 8). La métathèse croisée sur ce substrat génère l'énone **164b** avec un rendement de 59%. La réaction est menée en utilisant le catalyseur Hoveyda-Grubbs de seconde génération et un excès d'énone **160b**, préparé en quatre étapes à partir de la butyrolactone. Le composé a également pu être obtenu avec un rendement comparable de 55% par double métathèse en « one pot » à partir de **148b**. L'alcool **164b** est protégé en acétate puis réduit dans les conditions de Corey-Bakshi-Shibata avec un rendement honorable, bien que sa diastéréosélectivité soit faible. Après la protection de l'alcool allylique obtenu par TBSOTf pour fournir l'éther silylé **168**, le groupement TES est déprotégé par oxydation dans les conditions de Swern fournissant l'aldéhyde correspondant. Ce dernier est mis en jeu dans une réaction de Wittig en utilisant le sel de phosphonium **55** déprotoné par NaHMDS à basse température pour donner le (*Z*)-triène désiré. La saponification par KOH dans le MeOH a permis de déprotéger l'acétyle et l'ester isopropylique pour obtenir l'acide **171a** avec un rendement de 41% sur trois étapes.

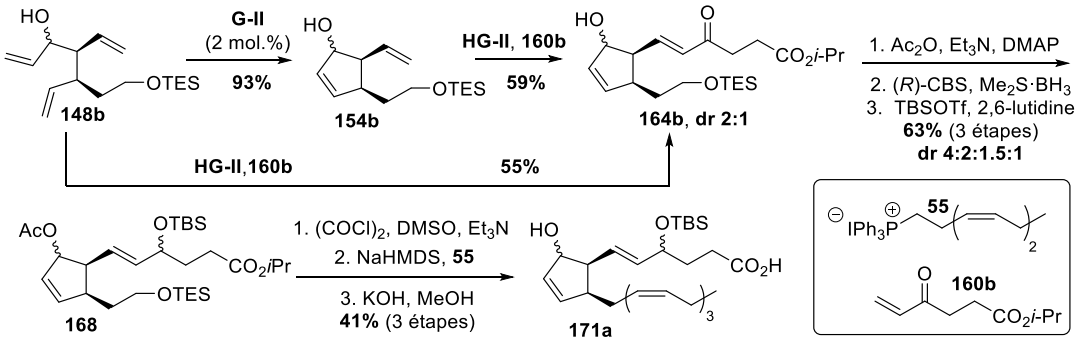


Schéma 8. Synthèse d'un intermédiaire avancé **171a**.

Les autres étapes d'oxydation et de déprotection ont été tentées, mais seuls des mélanges complexes constitués de produits d'épimérisation, d'élimination, d'isomérisation de double liaisons et d'autres dégradations ont été obtenus dans les conditions appliquées. Pendant la déprotection pour remplacer le groupement TBS par le groupment TES, une lactonisation totale a eu lieu (Schéma 9). Après la déprotection de l'acétyl pour libérer l'alcool **171b** et l'oxydation allylique, la 4-A_{4t}-NeuroP a été obtenue sous forme de sa 1,4-lactone **104b**. Néanmoins, la tentative de purification de ce composé instable sur gel de silice a résulté seulement le produit d'élimination correspondant **103c**. Ce métabolite potentiel de la 4-A_4-NeuroP a donc été synthétisé avec un randement global de 1.2% sur 22 étapes.

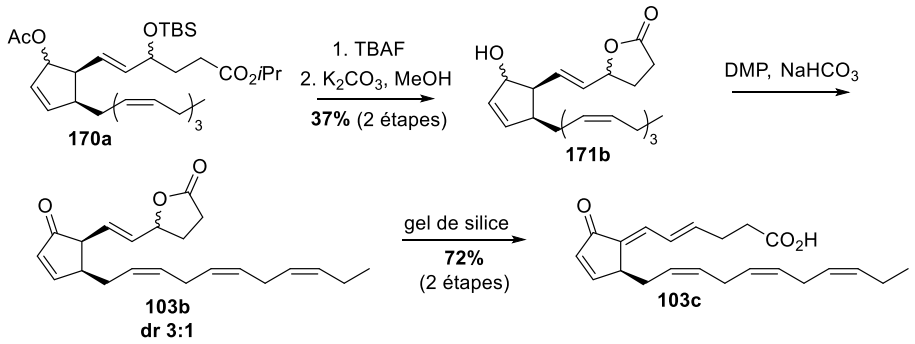


Schéma 9. Synthèse des metabolites potentiels de la 4-A_4-NeuroP **103b** et **103c**.

7.3.2 Synthèses totales d'isoprostanoïdes possédant des chaînes de type 3-hydroxypentényle

7.3.2.1 Analyse rétrosynthétique

L'analyse rétrosynthétique des 20-NeuroPs et 18-IsoPs conduit à un intermédiaire orthogonalement protégé **176** (Schéma 10). Le (*Z*)-polyène non-conjugué peut être élaboré par semi-hydrogénation du triyne correspondant, qui est ensuite déconnecté en envisageant une réaction d'alcynilation double. La première déconnexion C(sp3)-C(sp) fournit le précurseur central **179**, qui peut être synthétisé à partir de la triflate **88b** accessible en sept étapes par une procédure préalablement publiée.[99]

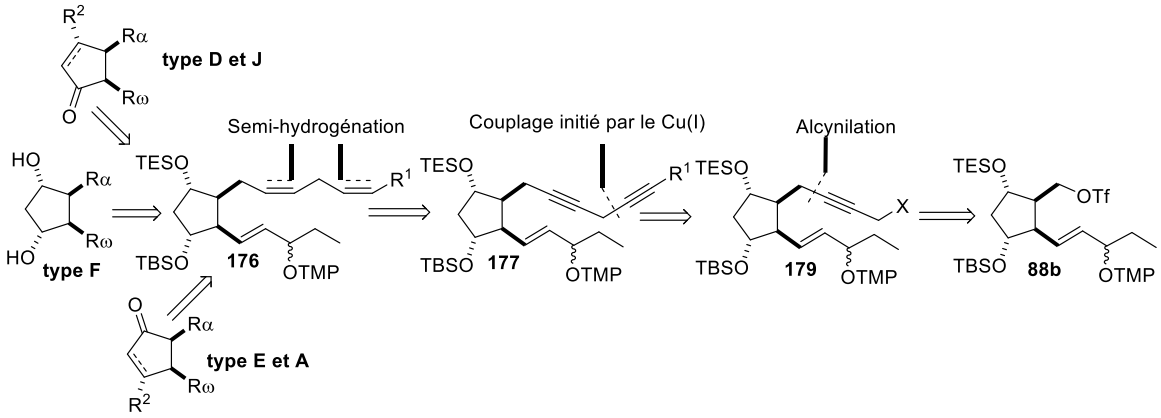


Schéma 10. Analyse rétrosynthétique des 18-IsoPs et 20-NeuroPs.

7.3.2.2 Synthèse du précurseur central **179c**

La synthèse commence par la préparation du composé **84b** selon la procédure précédemment publiée[135] et de deux nouveaux précurseurs de cyclisation (Schéma 11). Un précurseur enantiomériquement enrichi (3*S*,5*R*)-**84b** a également été synthétisé en utilisant la réaction d'aldolisation énantiosélective de Mukaiyama à partir du diene **184**. La stéréochimie des doubles liaisons dans (6*Z*,8*E*)-**84a** a été obtenue grâce à une nouvelle stratégie impliquant la réaction de couplage-croisé de Suzuki-Miyaura. Les composés **84** ont été cyclisés en utilisant l'oxydation par transfert d'un seul électron du dianion et le couplage ultérieur du radical-anion résultant avec le radical persistant TEMPO. La cyclisation du **84b** s'est déroulée avec un rendement et une diastéréosélectivité comparable aux rapports précédents.[97-99] Aucun effet sur le rendement ou la diastéréosélectivité de la cyclisation radicale n'a été observé avec les précurseurs modifiés. Le carboxylate de cyclopentane **87b** a été transformé en triflate **88b** pour obtenir le chlorure de propargyle **179c** après alkylation de l'anion de **180c** dans des conditions soigneusement contrôlées et optimisées.

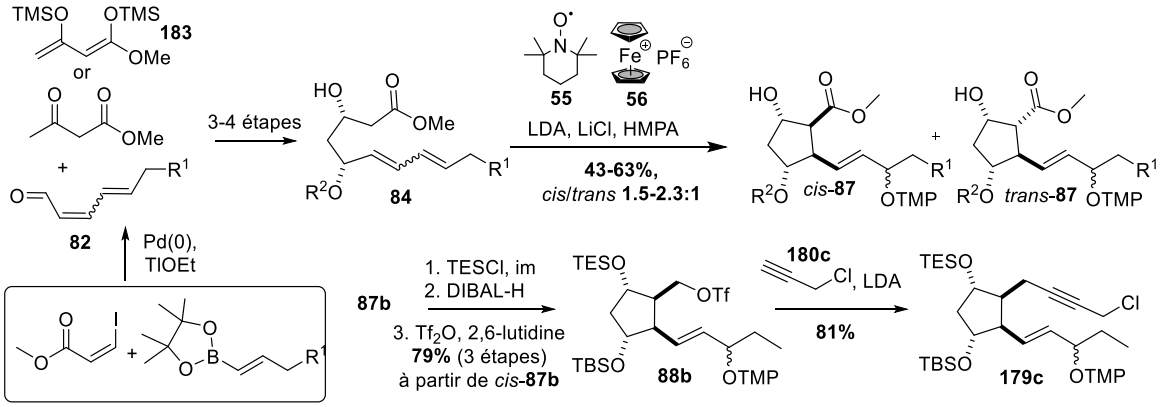


Schéma 11. Synthèse du précurseur central **179c**.

7.3.2.3 Application de la stratégie à la synthèse totale du 18-F_{3t}-IsoP **174a**

Avec le chlorure propargylique **179c**, la sous-unité restante de la chaîne alpha de la 18-F_{3t}-NeuroP a été introduite sous forme d'alcyne par couplage C(sp3)-C(sp) induite par du Cu(I) (Schéma 12). Les tentatives ultérieures de semi-hydrogénation n'ont pas réussi ; par conséquent, le groupe TMP a d'abord été déprotégé dans des conditions oxydantes et l'énone résultante a été réduite dans les conditions de Luche pour donner l'alcool allylique **194a** sous forme de mélange 1.2:1 de diastéréoisomères. L'hydrogénation utilisant le catalyseur Lindlar dans EtOAc/pyridine sous pression atmosphérique d'hydrogène a permis d'obtenir le diène non-conjugué **195a** souhaité. La déprotection du silyle et la saponification finale ont fourni la cible *rac*-18(*RS*)-18-F_{3t} IsoP **174a** en 5% de rendement sur 14 étapes.[78]

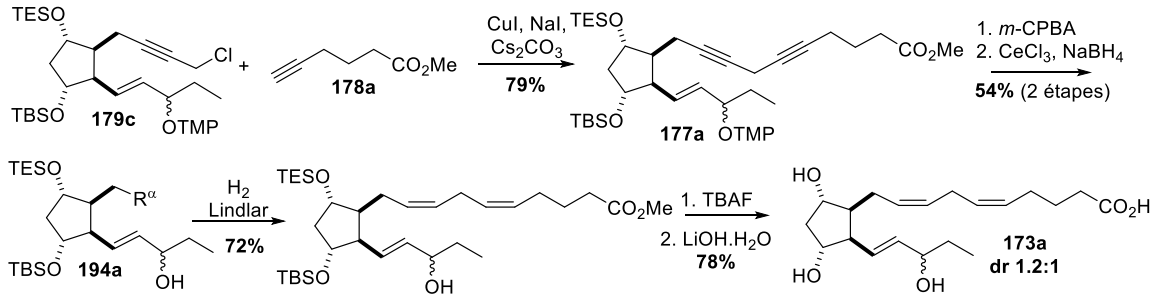


Schéma 12. Finalisation de la synthèse totale du **174a**.

7.3.2.4 Application de la stratégie vers les synthèses de 20-NeuroPs

Le squelette carboné de la 20-NeuroP a été assemblé par analogie à la synthèse de **174a** par une procédure multi-étape à partir du même précurseur central **179c**. Tout d'abord, un couplage au Cu(I) avec l'alcool propargylique a fourni le diyne correspondant, qui a été converti en bromure **196b** dans les conditions d'Appel (Schéma 13). Un second couplage au Cu(I) fournissant le triyne **177b** a été suivi d'une déprotection du groupe TMP et d'une réduction en alcool **198**. Malheureusement, les tentatives d'hydrogénation de ce composé dans les conditions précédemment décrites ont échoué, ceci probablement à cause de la grande instabilité du triyne **198** non-conjugué. Ainsi, les conditions d'hydrogénation ont été optimisées pour l'alcool propargylique **196a**, ce qui a permis de synthétiser le diène **200b** comme précurseur 20-NeuroP approprié avec une pureté acceptable et un rendement de 14% sur 10 étapes. Les efforts visant à introduire la dernière sous-unité de la chaîne alpha et à terminer la synthèse totale sont en cours de réalisation.

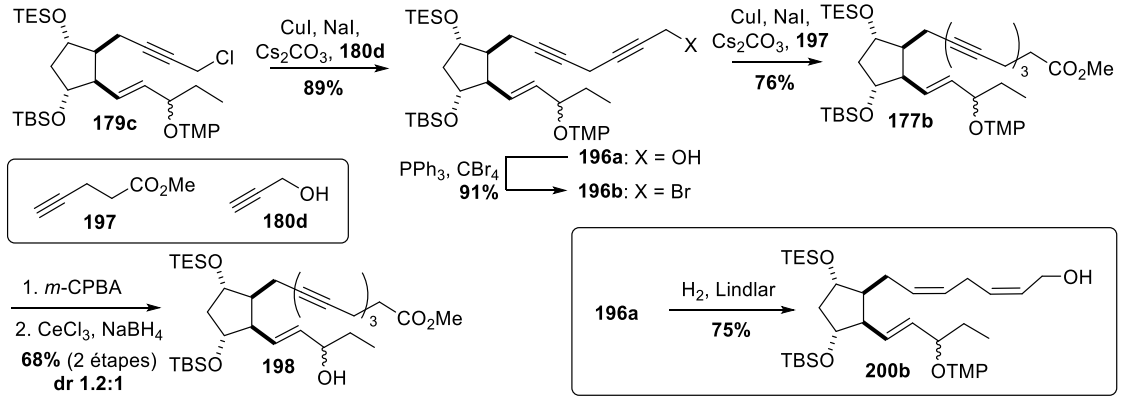


Schéma 13. Synthèse du triyne **198** et du precurseur clés **200b**.

7.3.2.5 Conclusion

En conclusion, une nouvelle stratégie énantiosélective pour la synthèse des NeuroPs de type énone a été développée. Les principales étapes ont consisté en une addition asymétrique de Michael organocatalysée et d'une réaction d'oxydation de Nef suivi d'une épimérisation, afin d'obtenir la configuration absolue et relative appropriée de la lactone *trans*-**122b**.[115] Le noyau cyclopentènique ainsi que la chaîne alpha ont été introduits par métathèse d'alcènes. La chaîne oméga a été connectée par une oléfination de Wittig et la 4(*RS*)-4-A_4-NeuroP 1,4-lactone **103b** a pu être obtenue grace à cette stratégie. Néanmoins, le composé s'est révélé instable et la purification sur le gel de silice a fourni la 4-déoxy-$\Delta^{4,6}$-A_4-NeuroP **103c**, métabolite potentiel de la 4-A_4-NeuroP, avec un randement global de 1.2% sur 22 étapes.

L'approche précédemment décrite pour les isoprostanoïdes avec la chaîne 3-hydroxypentényle oméga a été étendue aux isoprostanoïdes avec la chaîne alpha du type polyène non-conjugué. La stratégie consiste en l'alcynylation du triflate **88b** par le dianion du chlorure de propargyle comme réactif bifonctionnel. Ce dernier est un substrat approprié pour un couplage au Cu(I), ce qui a servi pour introduire le reste de la chaîne alpha. La transformation des diynes en dienes correspondants a été réalisée en utilisant la semi-hydrogénation de Lindlar. Ainsi, la première synthèse totale de *rac*-18(*RS*)-18-F_{3t} IsoP a été réalisée en 5% sur 14 étapes et le précurseur clé **200b** pour la synthèse de 20-NeuroPs a été synthétisé en 14% de rendement sur 10 étapes.

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