Validating Predictive Sequence Analysis in Polyketide Stereochemical Determination Though the Synthesis of Stambomycin D

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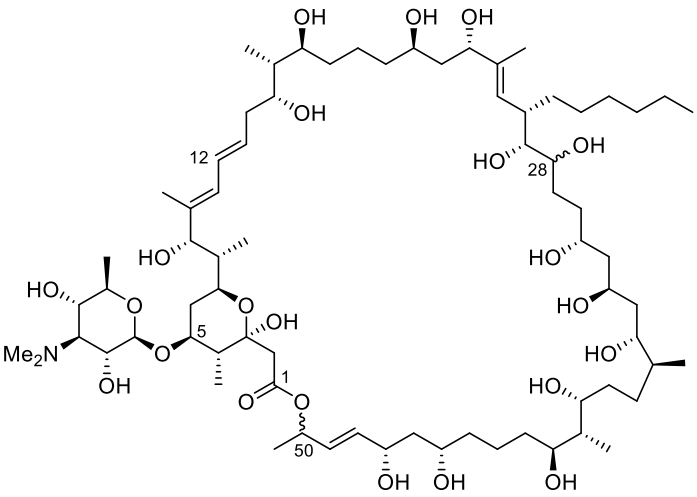

stambomycin D

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In recent years, predictive gene sequence analysis of biosynthetic enzymes has emerged as a powerful tool for the stereochemical determination of natural products. The stambomycins, a family of 51-membered bioactive macrolides isolated from *Streptomyces ambofaciens*, are examples of this, having their stereochemistry predicted entirely through gene sequence analysis of the polyketide synthase, apart from two stereocentres (C28 and C50) which were installed through cytochrome P450-catalysed oxidations. This thesis investigates the synthesis of stambomycin D, a member of the family, to validate the genomics-based stereochemical assignment of the natural product. Through the synthesis of various intermediate and model fragments of the macrolide, the synthetic route to the target natural product was established and conditions for a global deprotection were developed. Moreover, a comparative analysis of the NMR data of two of those fragments (C1–C27 and C13–C48) with that of stambomycin D provided preliminary proof of the accuracy of the genomics-based stereochemical assignment of the natural product and revealed the identity of the unassigned C28 stereocentre. This culminated in the completion of the full-length acyclic C1–C51 fragment, setting the stage for completion of the target natural product.

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Abbreviations

ACP	acyl carrier protein
ADP	adenosine diphosphate
AMP	adenosine monophosphate
app	apparent
aq.	aqueous
AT	acyltransferase
ATP	adenosine triphosphate
BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
calcd	calculated
CBS	Corey-Bakshi-Shibata
CD	circular dichroism
CoA	coenzyme A
COSY	correlation spectroscopy
CCRC	crotonyl-CoA reductase/carboxylase
CSA	camphorsulfonic acid
DBU	1,8-diazabicylco[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DH	dehydratase
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ECD	electronic circular dichroism
ER	enoylreductase
ESI	electrospray ionisation
ee	enantiomeric excess
eq.	equivalents
Hex	hexyl
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
KHMDS	potassium bis(trimethylsilyl)amide
KR	ketoreductase
KS	ketosynthase
LC-MS	liquid chromatography-mass spectrometry
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
m.p.	melting point
MS	molecular sieves

MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
n	*normal*
NADPH	nicotinamide adenine dinucleotide phosphate
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PG	protecting group
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PMBTCA	*para*-methoxybenzyl trichloroacetimidate
PMP	*para*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
RCSA	residual chemical shift anisotropy
RDC	residual dipolar coupling
R_f	retention factor
rsm	recovered starting material
rt	room temperature
t	*tertiary*
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TCBC	2,4,6-trichlorobenzoyl chloride
TE	thioesterase
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
VCD	vibrational circular dichroism
YCC	acyl-CoA carboxylase

Contents

1. Introduction

Stereochemical determination is one of the most important and possibly also one of the most challenging aspects of natural product discovery. In recent years, genome mining through sequence analysis has emerged as a powerful tool for both natural product discovery as well as structural and stereochemical determination. This was exemplified through the stambomycins, a family of 51-membered macrolides whose discovery and, more notably, stereochemical prediction were achieved using a genomics-guided approach. This remarkable achievement motivated us to synthesize stambomycin D, a member of the family, with the aim of validating this promising new approach to stereochemical determination. In this introductory chapter, the concept of genome mining will be discussed, with a focus on the genomics-based approach to structural and stereochemical determination. Other methods of stereochemical determination will then be highlighted, following which, the stambomycins will be detailed, including our group's previous synthetic efforts towards stambomycin D, the molecule of interest.

1.1. Genome mining

1.1.1. Overview

Historically, natural products have been discovered through a "grind and find" approach, whereby crude extracts are screened and metabolites are isolated based on bioactivity or some other chemical or spectroscopic properties. However, in the last two decades, the emergence of genome mining has revolutionised this, not only unlocking a wealth of possibilities for new discoveries, but also enabling the understanding of biosynthetic pathways, bioengineering of products, and structural and stereochemical elucidation. In essence, genome mining is the process of obtaining isolated natural products through genomics analysis. This encompasses identifying and analysing biosynthetic gene clusters, predicting biosynthetic pathways, manipulating gene expression, and isolating and identifying metabolites.[1] While the traditional approach to natural product discovery is tedious and often results in rediscoveries of known compounds, genome mining is targeted, efficient, and cheap, especially with the increasing availability of various

technologies which facilitate the process. Unsurprisingly, it has become important for drug discovery as many new bioactive compounds are being discovered through this method.[2,3]

The genome mining era was ushered in by several key milestones. In 2002, Hopwood *et al.* reported the complete genome sequence of *Streptomyces coelicolor*,[4] a model species studied for over fifty years to understand the biosynthetic pathways of bioactive metabolites.[5] In 2003, Ikeda *et al.* did likewise for *Streptomyces avermitilis*, another well-studied bacterial strain.[6] These first two complete genome sequences revealed the unexpected biosynthetic potential of these microorganisms. Whereas only three biosynthetic gene clusters of *Streptomyces coelicolor* were known previously, its complete genome sequence showed that it had twenty-nine.[1] With this realisation that microorganisms contain an untapped wealth of secondary metabolites came the idea of mining their genomes to obtain those products.[7] This was first accomplished by Challis *et al.* in the isolation of coelichelin in 2005,[8] five years after he and Ravel predicted its structure from sequence analysis of a nonribosomal peptide synthase which they identified from the partial genome sequence of *Streptomyces coelicolor*.[9] Remarkably, not only was their predicted structure largely accurate, but it also guided their selection of culture conditions and detection method.[10] This showcased the power of genome mining.

Since then, this emerging field has been growing rapidly. Whole-genome sequencing is now common, accompanied by a steady increase in the number of natural products discovered as a result.[2] With the large amounts of genomic data now available, many of the reported biosynthetic gene clusters remain unlinked to metabolites.[7] It is thus expected that many more novel compounds will be discovered, with new developments emerging in this field.

1.1.2. Process, methods, applications

The genome mining process typically begins with screening a microorganism's genome to identify a biosynthetic gene cluster, which includes all genes involved in a metabolite's biosynthesis (e.g., primary, tailoring, and regulatory genes).[11] Comparative analysis against other known clusters is then carried out to determine if the cluster is unique, or if homologous clusters are present in other organisms.[7] Sequence analysis of the biosynthetic genes is then performed to predict the metabolite's structure and biosynthetic pathway. Often, neighbouring genes are also analysed for insight into the compound's

role, which can aid in structural prediction (e.g., resistance genes often neighbour antibiotic compounds).[7,12] Next, gene expression is manipulated to access the metabolite; this can be homologous (within the producing organism) or heterologous (using a host organism).[1] Finally, the metabolite is isolated and its structure elucidated, allowing confirmation or refinement of the predicted structure and biosynthetic pathway.

Various methods have been used to identify a microorganism's metabolite from its gene cluster. One of these is the physico-chemical guided isolation approach.[13] In many cases, metabolites, such as polyketides and peptides, are biosynthesized in an assembly-line manner from known building blocks, which can be predicted through gene sequence analysis.[12] The manner in which they are selected, assembled, and modified can moreover be predicted, allowing the structure, and hence, physical and chemical properties of the metabolite, to be deduced. This, in turn, enables selective detection and isolation based on those properties.[13,14] Examples where this method was used include antifungal compound ECO-02301,[15] aspoquinolones A–D,[16] and the thailandamides.[17,18]

Another genome mining method is the *in vitro* reconstitution method. In this method, a biosynthetic enzyme's substrates (building blocks of the metabolite) are predicted and incubated with the enzyme, and the resulting products are determined. This can be useful for identifying the products of gene clusters without any known metabolites.[14] In a related approach, the genomisotopic method, stable isotope-labelled versions of the predicted substrates are administered to the microorganism, leading to their incorporation into the product, which can then be identified by NMR.[13,14] While valuable, as demonstrated in the discovery of the orfamides,[19] this approach is limited primarily to metabolites with unique precursors and is thus less useful for polyketides.[13]

In some cases, structural prediction is not straightforward, particularly for enzymes with unusual features. For these, the gene knockout/comparative metabolic profiling method is often used. In this method, genes deemed essential for metabolite production are inactivated, and the metabolic profile of the mutant strain is compared to that of the wild strain, usually via HPLC-MS. The products can then be identified, since the mutant strain would lack metabolite peaks.[13,14] This was used in the discovery of the toblerols,[20] emericellamides,[21] and myxochromides S.[22] Besides facilitating compound discovery, this approach can also be used to correlate metabolites with their gene clusters, as in the case of meijiemycin,[23] for example.

Heterologous expression is yet another method, advantageous where the original producing organism is difficult to culture or modify genetically, or is unable to produce sufficient amounts of the compound for analysis.[24] For this, gene fragments or clusters are transferred into a host organism for gene expression and metabolite production. This is then followed by comparative metabolic profiling of the host with and without the cloned genes, to identify the relevant metabolites.[13,25] Typically, host species are chosen based on similarity to the original producing organism and are often modified to reduce their native metabolite producing capacity.[24,26] While various novel compounds have been discovered through this method,[27–29] it is inapplicable for large gene clusters due to size constraints.[13]

Finally, an important genome mining method is the activation of silent gene clusters. As many gene clusters in microorganisms are silent (not expressed under standard lab conditions), this method is key to accessing their metabolites.[30] These secondary metabolites, named as such because they are non-essential for microorganisms' normal growth and function,[31] are often produced in response to environmental triggers (e.g., as a defense mechanism).[32] Thus, modifying culture conditions to simulate these triggers can activate these gene clusters. This includes modifying pH, light, or temperature, adding chemical elicitors, or co-cultivation with other microorganisms to mimic the competitive environment found in nature. Moreover, as production of these metabolites is regulated on various levels, controlling the relevant global or pathway-specific gene regulators can also be effective, for instance, by overexpressing positive gene regulators or deactivating negative gene regulators.[25,30–32] A noteworthy example where this method led to the discovery of novel compounds is the stambomycins, the first from actinomycetes discovered through this approach.[33]

Various technologies have been leveraged to facilitate the different genome mining methods. These include computer programs with capabilities ranging from genomic data screening to structural prediction,[34–37] mass spectrometry-based technologies,[38–40] as well as differential analysis of 2D NMR spectra.[41–44]

There are several applications of genome mining, the most obvious being natural product discovery. While initial efforts were focused on *Streptomyces* due to their predictable gene cluster organisation and prolific production of bioactive compounds, this has been expanded to various other microorganisms.[7,30,31] Accordingly, a range of polyketides,

peptides, terpenes, and alkaloids have been discovered, many exhibiting important bioactivity.[3,45,46] Besides natural product discovery, genome mining can also be used to link known compounds with their biosynthetic gene clusters; this allows insight into the biosynthetic pathways, as in the case of the brasilinolides.[47] Furthermore, it enables the bioengineering of natural products, providing better access to known compounds or potential analogues. This can be done through combinatorial biosynthesis, where biosynthetic pathways are reconstructed through gene manipulation (e.g., adding, deleting, swapping genes, etc.)[24,25] or by otherwise manipulating a producing species to engineer a more productive strain.[48] Finally, genome mining has important applications for structural and stereochemical determination, as detailed in the following section.

1.1.3. Genomics-based approach to structural and stereochemical determination

Undoubtedly, one of the most notable contributions of genome mining lies in the realm of structural and stereochemical determination. The genomics-based approach relies on sequence analysis to predict structures and their stereochemistry, which is often then confirmed by other techniques such as NMR. This predictive approach is enabled by an understanding of the architecture and biosynthetic logic of the enzymes responsible for metabolite production.

Many biosynthetic enzymes are composed of functional units known as modules, which further consist of domains, each of which has a specific function.[13] Metabolites are often biosynthesized in an assembly-line manner according to the “colinearity rule,” where the number and order of modules correspond to that of the building blocks in the final product.[14,45] This is true for many polyketide synthases (PKSs) and nonribosomal peptide synthases (NRPSs). Generally, each module of the assembly line has a domain which selects, activates, and attaches the substrate (building block) onto an adjacent carrier domain, which then transports it to other domains. The building block may be modified if tailoring domains are present in the module. It is then pieced together with the next building block in the adjacent module and, as such, grows as it moves along the assembly line until it is finally released from the enzyme.[49] Knowing which substrates are selected and how they are modified thus enables the structure of the final product to be predicted.

PKSs biosynthesize polyketides through repeated decarboxylative Claisen-like condensations of acyl-coenzyme A (CoA) building blocks, often starting with a starter unit such as acetyl-CoA and extending with extender units such as malonyl-CoA or methylmalonyl-CoA, akin to fatty acid biosynthesis (Figure 1).[50] They have three core domains which are responsible for chain elongation: the acyltransferase (AT) domain, which selects the substrate, the acyl carrier protein (ACP) domain, which transports it, and the ketosynthase (KS) domain, which condenses the building blocks. A thioesterase (TE) domain at the end of the assembly line releases the polyketide product from the enzyme either by hydrolysis or cyclisation. Tailoring domains include ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) domains.[45,49]

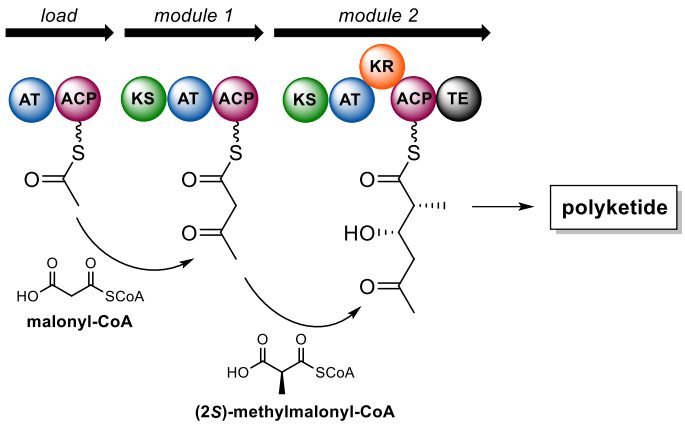


Figure 1: *Simplistic representation of polyketide biosynthesis*

PKS domains have a significant influence on the stereochemical outcome of the product. Much of this has been understood by visualisation of the active sites for the different transformations from crystal structures of the domains.[51] The substrate specificity of AT domains can be deduced from certain conserved motifs in their gene sequence, enabling each building block selected to be predicted.[10] Moreover, it has been shown that when AT domains select α-substituted extender units, only those with *S* stereochemistry are used, (2*S*)-methylmalonyl-CoA being the most common. Interestingly, when KS domains condense these units with the polyketide chain, an "inversion of configuration" occurs, and the substituent's stereochemistry in the product becomes opposite what it was in the extender unit. Although this phenomenon has been rationalised through various studies, the exact mechanism is not entirely clear.[51–53]

Most of the polyketide's stereocentres are set by KR domains, which reduce the β-carbonyl group of a β-ketothioester intermediate to a hydroxy group. They are classified into two broad types based on their stereoselectivity: A-type KRs generate an (*S)*-hydroxy group while B-type KRs give an (*R*)-hydroxy group. Additionally, KRs can also epimerise the α-substituent of an α-substituted-β-ketothioester intermediate and are thus further differentiated: A1- and B1-type KRs only catalyse carbonyl reduction, with no epimerisation of the α-substituent, whereas A2- and B2-type KRs catalyse both carbonyl reduction and epimerisation of the α-substituent. C1- and C2-type KRs also exist, C1 KRs being nonfunctional (and rare) and C2 KRs catalysing only epimerisation of the α-substituent. Each of these KR types differ in specific regions of their amino acid sequences and can be distinguished from certain conserved amino acid residues, which serve as "fingerprints."[51–53] This was first established through studies by McDaniel *et al.*[54] and Caffrey,[55] which were later expanded by Keatinge-Clay *et al.*[53,56]

PKSs also contain DH domains, which install alkenes by eliminating the β-hydroxy group and the α-proton. As elimination is carried out in a *syn*-coplanar manner, an (*R*)-β-hydroxy group results in a *trans*-alkene, while an (*S*)-β-hydroxy group gives rise to a *cis*-alkene.[51] Besides DH domains, ER domains also exist, which reduce alkenes and, as such, generate a stereocentre when an α-substituent is present. Whether an (*S*)- or (*R*)-α-substituent is generated can be deduced from the presence or absence, respectively, of a key tyrosine residue in the active site of the ER. Although other residues are also involved, ERs are still not well-studied and the mechanism of stereocontrol remains unclear.[52,57]

Overall, these predictive rules enable good structural and stereochemical prediction of polyketides, although accurate prediction may be difficult in certain cases (e.g., when initial products undergo further modifications by tailoring enzymes). Generally, these rules hold well for modular non-iterative type I PKSs, particularly *cis*-AT PKSs, which follow the colinearity rule. For other type I PKSs, such as *trans*-AT PKSs, or iterative types II and III PKSs, which do not follow the colinearity rule, structural prediction is often facilitated by other means, such as phylogenic analysis or homology-based approaches.[26,46,50] In the case of other compound classes, such as nonribosomal peptides, structural and stereochemical prediction is similarly achieved by applying the relevant predictive rules based on the substrate specificity of the domains and biosynthetic logic of the enzymes.[7,58–62]

As a predictive method, the genomics-based approach to structural determination is powerful, enabling foreknowledge of a compound's structure even without a compound in hand. Further enabling the determination of absolute stereochemistry, which remains a challenge in natural product discovery, it offers great promise indeed.

1.2. Other methods of stereochemical determination

Besides the recently emerging genomics-based approach, there are various other methods for the stereochemical determination of natural products. While some enable absolute stereochemistry to be determined, others establish only the relative stereochemistry. Often, methods are used in combination with each other for confirmation of configurational assignment. The key methods are highlighted in this section.

1.2.1. X-ray crystallography

X-ray crystallography is arguably the most powerful stereochemical determination method.[63] The x-ray diffraction pattern of a crystal allows the molecule's electron density distribution to be determined, from which the position and types of atoms, bond lengths, and bond angles can all be deduced.[64,65] By providing a three-dimensional picture of the molecule, it gives unambiguous proof of its structure and relative stereochemistry. Absolute stereochemistry can be determined from resonant scattering effects, a physical phenomenon arising from the absorption of X-ray photons by atoms' excited core electrons. More distinguishable for heavy atoms, this results in small differences in the intensities of inherently inversion-symmetrical X-ray diffractions from opposite sides of a given crystal plane. Accurate measurement of these intensity differences allows the differentiation of enantiomers, enabling the determination of absolute configuration.[63,66,67] Alternatively, this can be deduced indirectly through the incorporation of a chiral reference, for example, by derivatisation with a chiral auxiliary, formation of a diastereomeric salt, or co-crystallization with a chiral internal reference.[63,65] Despite its value, X-ray crystallography is inaccessible for many natural products due to its requirement for crystallinity; consequently, other methods are often required.[68]

1.2.2. NMR-based methods

NMR spectroscopy is an indispensable tool in the stereochemical determination of natural products.[69] There are several NMR-based approaches, the most fundamental being nOe (nuclear Overhauser effect) experiments, which correlate spatially related protons. With the ability to distinguish proximal protons yet correlate even distant protons in a molecule, nOes provide valuable spatial understanding, even for a complex molecule, allowing relative stereochemistry to be predicted/established.[70] In the case of cyclic or rigid compounds with well-defined conformational behaviours, nOes and $^{3}J_{H,H}$ coupling constants together enable reliable stereochemical determination.[68]

For acyclic compounds, however, nOes and $^{3}J_{H,H}$ values are usually insufficient for stereochemical assignment.[71] In such cases, Murata's *J*-based configurational method[72] is commonly employed. Based on a detailed conformational analysis, this method enables the relative stereochemistry of adjacent stereocentres in an acyclic system to be determined from their $^{3}J_{H,H}$ and $^{2/3}J_{C,H}$ values.[70] This is possible because vicinal H–H coupling constants ($^{3}J_{H,H}$) are directly related to dihedral angles, according to the Karplus equation.[73,74] Generalisation of the original equation, taking into account other parameters, moreover allows accurate prediction of dihedral angles from $^{3}J_{H,H}$ values, and vice versa.[75] Similarly, vicinal C–H coupling constants ($^{3}J_{C,H}$) also follow a Karplus-type equation, and geminal C–H coupling constants ($^{2}J_{C,H}$) are likewise informative when an electronegative atom is attached to the α-carbon (Figure 2).[70,76] As such, by analysing the pattern of H–H and C–H coupling constants, the relative configuration of two adjacent stereocentres can be determined through correlation to one of six possible lowest energy rotamers, each of which has a unique coupling constant pattern; this can then be further supported (often not with complete certainty) by nOe experiments.[68,71]

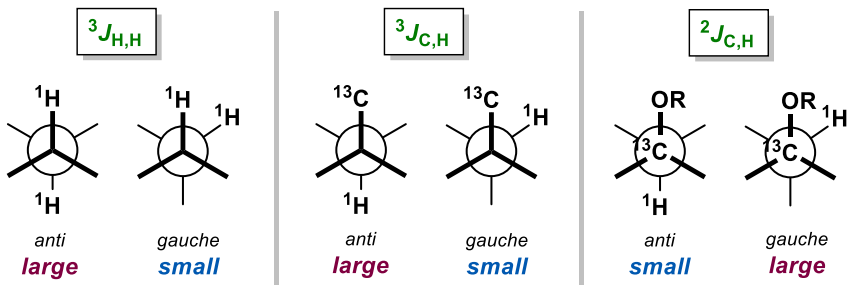


Figure 2: *General relationship between dihedral angles and J values*[72]

The *J*-based method is applicable to stereogenic carbons bearing a variety of substituents (methyl, hydroxy, alkoxy, etc.) and has proven reliable in the configurational assignment of various polysubstituted acyclic compounds and macrolides. However, limitations exist for highly flexible compounds; because coupling constants are weighted averages from that of the relevant conformers, this method is generally only applicable if the molecule exists in two major conformers.[70,76]

While the *J*-based approach allows the determination of proximal stereocentres, remote stereocentres can be assigned using anisotropic NMR parameters, such as residual dipolar coupling and residual chemical shift anisotropy.[68] Dipolar couplings, which result from dipole-dipole interactions between pairs of proximal magnetic nuclei in a magnetic field, generally average to zero in an isotropic solution. However, when the molecules in solution are partially aligned, they average to a non-zero value, known as residual dipolar coupling (RDC). Since the magnitude of the coupling is dependent on internuclear distance and the orientation of the internuclear vector relative to the external magnetic field, RDCs provide three-dimensional structural information from which relative stereochemistry can be obtained.[77] Similarly, chemical shifts have an anisotropic component which averages to a non-zero value under partial alignment conditions, giving rise to residual chemical shift anisotropy (RCSA). Typically measured from ^{13}C chemical shifts, RCSAs also provide angular information, being dependent on the direction of the chemical shielding tensor. Both RDCs and RCSAs are analysed using an alignment tensor, a global reference for the molecule, and thus allow determination of relative stereochemistry independent of the distance between stereocentres.[68] Generally, measurement of RDCs and RCSAs require introduction of the analyte into an alignment medium, which spontaneously aligns in the presence of an external magnetic field or allows tuneable, mechanical alignment.[77] Determination of relative stereochemistry from RDCs or RCSAs is then facilitated by computational approaches.[78–81]

Although used in the stereochemical elucidation of natural products,[77] RDCs and RCSAs are not routinely employed due to the specialised materials and extensive data analysis required.[68] RCSAs can moreover be difficult to extract from NMR spectra, although recent developments have improved this.[82–87] It is thus foreseeable that with further developments, the use of anisotropic parameters for stereochemical determination will become more widely used.

Kishi's universal database method[88] is another NMR-based approach. In this empirical method, the ^{1}H and ^{13}C chemical shifts of neighbouring stereocentres are compared against that of libraries of model compounds with known configuration, and the relative stereochemistry is accordingly assigned. A fundamental assumption in this approach is that specific stereochemical arrangements in a molecule are independent from the rest of the molecule and have innate NMR spectroscopic properties. Thus, a complex molecule can be viewed as individual subunits joined together, each of which can be assigned separately by comparison with a constitutionally equivalent model diastereomer.[68,70] This method, originally developed from the Kishi group's work on numerous complex polyketides, was later extended to allow the determination of both relative and absolute stereochemistry.[89–91] Notably, this method only requires standard NMR experiments and is not limited by conformational flexibility—in fact, the fragment analysed should be conformationally unconstrained. It has been successfully employed in the stereochemical assignment of various polyketides[70,76] and was moreover validated through the total synthesis of oasomycin A,[92] a 42-membered macrolide whose stereochemistry was previously assigned through Kishi's NMR database method.[93,94]

Finally, computational approaches using NMR parameters are also becoming increasingly important. Quantum mechanical calculations of chemical shifts and coupling constants have aided in the stereochemical assignment of many natural products, often through comparison of the predicted and experimental data.[68,76] Various computational methods have been developed for this (e.g., CP3, DP4, etc.),[95–99] with automation and machine learning being recently incorporated to improve their capabilities.[100,101] Calculations of homo- and heteronuclear coupling constants have moreover extended the *J*-based approach to flexible systems with multiple conformers in equilibria.[71] Additionally, molecular modelling based on nOe enhancements has also been used for the determination of relative stereochemistry.[102,103]

1.2.3. Chiroptical techniques

Chiroptical methods allow the determination of absolute stereochemistry and are based on a chiral molecule's differential interaction with left and right circularly polarised light. Optical rotation, the earliest chiroptical technique used to differentiate enantiomers, is based on the difference in refractive indices of a chiral medium for left and right circularly polarised light. It is measured by the angle of rotation of a plane of polarised light while

passing through a non-racemic solution of chiral compound. Although typically used to characterise a compound's optical property, it can also be a means of stereochemical determination, if the absolute configuration of the compound was previously established.[104] Moreover, it can be combined with computational approaches for the configurational assignment of natural products.[105]

Circular dichroism (CD) is based on a chiral compound's differential absorption of left and right circularly polarised light. Absorptions in the UV-vis region during electronic excitation give rise to electronic circular dichroism (ECD), while absorptions in the IR region during vibrational transitions lead to vibrational circular dichroism (VCD).[104] In both methods, enantiomers produce mirror-image spectra.[106] ECD is the most common chiroptical method for stereochemical determination, being highly sensitive; however, it requires that the molecule contain a chromophore, as it is reliant on UV-vis absorptions.[104] For stereochemical assignment, ECD can be used empirically, through the comparison of data with that of a closely related molecule, or semi-empirically, through use of theoretical models which correlate characteristic ECD transitions of a chromophore with absolute stereochemistry. Limitations exist with these approaches, however, resulting in non-empirical methods being the most reliable. Of these, the exciton chirality method, which relies on interactions between chromophores in a molecule, and quantum mechanical calculations are most commonly used.[107–111]

VCD typically relies on computational approaches for stereochemical determination. Unlike ECD, it does not require that a molecule be UV active. Moreover, VCD spectra are more easily modelled computationally and have more detailed bands from which configurational and conformational information can be extracted. However, due to its low sensitivity and the lack of a straightforward data interpretation method, it is not commonly used. [68] Nonetheless, it has facilitated the stereochemical determination of several natural products and may well become more widely used in the future.[112–114]

1.2.4. Synthetic approaches

Synthetic approaches are an important means of stereochemical determination. Among these are derivatisation methods, which mostly rely on NMR. Typically, a substrate is derivatised with both enantiomers of a chiral auxiliary; the differences between the ^{1}H NMR chemical shifts of the two resulting diastereomers are then used to determine

absolute stereochemistry, based on an established model.[68] Mosher ester analysis for secondary alcohols[115,116] is one such widely used method, which can also be applied to 1,3-diols.[117] Additionally, chiral silylation reagents are useful alternatives for labile alcohols incompatible with the ester-based methodology.[118] Various other derivatising agents can also be used for different functional groups,[119–121] with methods based on the NMR of different nuclei (e.g., ^{13}C, ^{19}F, ^{31}P) also being possible.[122] Other related NMR-based methods for specific moieties include Rychnovsky's acetonide method for 1,3-diols,[123] Hoffmann's method for β-alkoxy alcohols,[124] and Roush's method for β-hydroxy ketones.[125] Besides derivatisation, chemical degradation is another synthetic approach. This involves breaking down the original molecule into smaller fragments which are better suited for spectroscopic analysis, synthetic verification, or X-ray analysis.[68] Notably, derivatisation and degradation can sometimes give crystalline products from originally non-crystalline ones.[70] An example of a degradation method is the selective cleavage of a molecule's least hindered alkene under mild cross-metathesis conditions, as employed by Höfle *et al.* in their stereochemical determination of several natural products.[126,127]

Finally, chemical synthesis is an effective means of stereochemical determination. This includes both fragment and total synthesis. Although often challenging, especially for total synthesis, it enables definitive determination of a molecule's relative and absolute stereochemistry, typically through comparison of the NMR data and other relevant physical or spectroscopic properties of the synthesized and natural products. Sometimes, this involves synthesis of all possible diastereomers of a fragment or compound for unambiguous assignment.[128–132] In many cases, total synthesis has led to the revision of a natural product's originally proposed structure or stereochemistry[133–137] and thus remains a powerful approach to stereochemical determination, providing all stereochemistry is carefully assigned en route.

1.3. Stambomycins A–D

The stambomycins are a family of 51-membered glycosylated macrolides which exhibit promising antitumor and antibacterial activity, whose members (A–D) differ only at the C26 side chain (Figure 3). These polyketides were identified as secondary metabolites of *Streptomyces ambofaciens* by Challis and Aigle *et al.* through genome mining, which also enabled their production and isolation. Notably, their structure and stereochemistry (except at C28 and C50) were predicted entirely through gene sequence analysis. The isolation of the stambomycins established a general strategy for obtaining the metabolites of silent gene clusters, paving the way for future discoveries; moreover, their biosynthetic analysis provided important insight into the origins of their unusual features.[138,139]

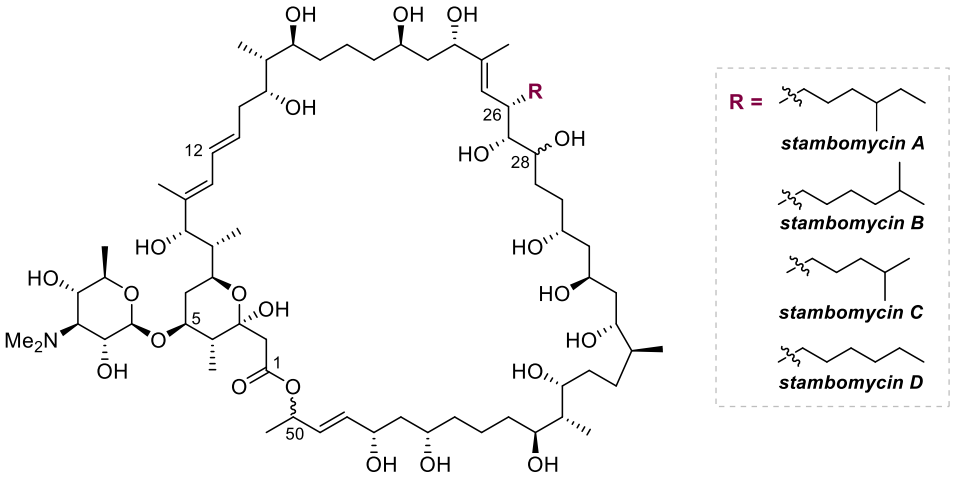


Figure 3: *The stambomycins*

1.3.1. Discovery and isolation

Prior to its genome sequencing, *Streptomyces ambofaciens* ATCC 23877 was known to produce only two natural products, the antibiotics spiramycin and congocidine. However, its genome sequence not only enabled the gene clusters of these two well-known compounds to be characterised, but it also revealed the presence of more than twenty other silent gene clusters, some of whose metabolites were later identified. Among them was found the stambomycin gene cluster, a type I PKS gene cluster spanning around 150 kB, one of the largest ever characterised, located in the right arm of the chromosome. This cluster contained twenty-five genes, nine of which were biosynthetic PKS genes, and the other sixteen consisting of regulatory, resistance, and post-PKS modification genes

(Figure 4). From sequence analysis, the polyketide product was predicted to be a high molecular weight glycosylated lactone, and database searches indicated that it was novel.[33]

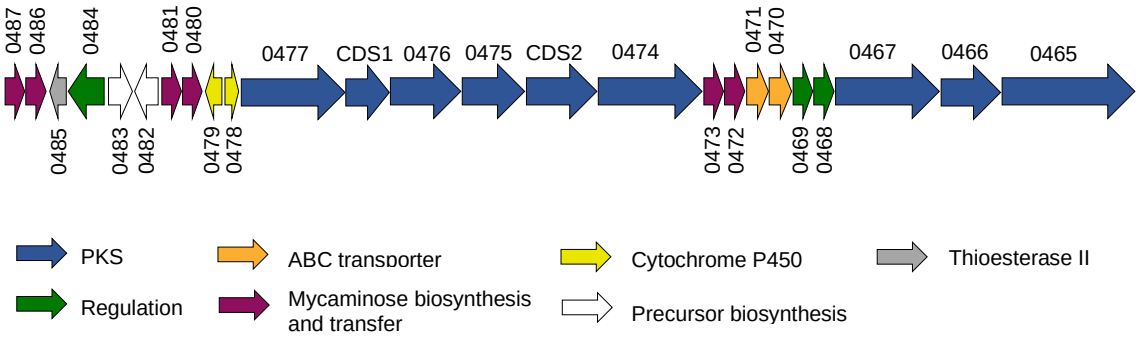


Figure 4: *Genetic organisation of the stambomycin gene cluster*[138]

Transcriptional analysis confirmed that the gene cluster was silent under standard laboratory conditions. As heterologous expression was not feasible for such a large cluster, activation of the cluster was instead attempted through manipulation of the regulatory genes. Three potential pathway-specific regulatory genes were identified.[138,139] Two of them, *samR0468* and *samR0469*, together encoded a two-component system which could regulate gene clusters either positively or negatively. The third, *samR0484*, encoded a LAL (large ATP-binding regulator of the LuxR family) regulator, a positive regulator in *Streptomyces* known to activate the biosynthesis of several macrolides. It was thus selected for manipulation.[140]

Overexpression of *samR0484* triggered the expression of the silent genes, leading to the production of the stambomycins, which were identified through comparative metabolic profiling of the strains with and without the overexpressed gene. Two high molecular weight peaks were identified from LC-MS, corresponding to compounds with molecular formulas of $C_{73}H_{133}NO_{22}$ and $C_{72}H_{131}NO_{22}$. To confirm that these were indeed products of the PKS gene cluster, the gene encoding the first PKS in the assembly line was deleted, in which case, the compounds were not observed. Furthermore, inactivation of the gene predicted to install the sugar moiety onto the polyketide (*samR0481*) resulted in the production of the corresponding compounds lacking the predicted sugar moiety.[138,139] Interestingly, overexpression or deletion of *samR0468* and *samR0469* failed to activate the gene cluster.[140] It was found, however, that culturing the bacteria using specific culture

conditions promoted expression of *samR0484* to a level sufficient for activation of the silent genes, providing an alternate means of cluster activation. Curiously, those conditions were non-typical for macrolide production but were successful for stambomycin production.[139]

The stambomycins were purified by semipreparative HPLC and characterised by NMR, which revealed stambomycins A–D. The higher molecular weight peak ($C_{73}H_{133}NO_{22}$) was found to contain stambomycins A and B (~5:1 ratio), while the lower molecular weight peak ($C_{72}H_{131}NO_{22}$) was found to contain stambomycins C and D (~3:1 ratio).[138] The isolation of the stambomycins was significant in several aspects. Not only were they the first natural products from actinomycetes obtained through gene cluster activation,[33] but they were also one of the largest macrolides ever isolated. Additionally, the method used to obtain them (via overexpression of a LAL regulator) provided a general strategy for obtaining the products of silent gene clusters, paving the way for future discoveries.[138,140]

1.3.2. Structural elucidation through gene sequence analysis

The structures of the stambomycins were predicted based on gene sequence analysis of the polyketide synthase. Analysis of the stambomycin gene cluster showed that the 9 PKSs it encoded together contained 25 modules consisting of 112 enzymatic domains (Figure 5). As the PKS genes were interspersed with the other genes in the cluster, their order in the polyketide assembly line was deduced by identifying the loading and termination modules, the first and last PKSs in the assembly line, respectively. The order of the seven remaining PKSs was then assumed to follow that of their respective genes in the cluster, as is typical of type I PKSs.[33] The loading module was identified from the presence of a ketosynthase^{Q} (KS^{Q}) domain, a unique KS domain with a glutamine residue in its active site instead of the usual cysteine (the glutamine facilitates decarboxylation of the acyl-CoA starter unit in the initiation step).[141] The termination module was identified based on the presence of the thioesterase (TE) domain, which releases the polyketide from the enzyme.[142] Of the 112 domains, all were predicted to be functional except for the KR domain in the last module.[138]

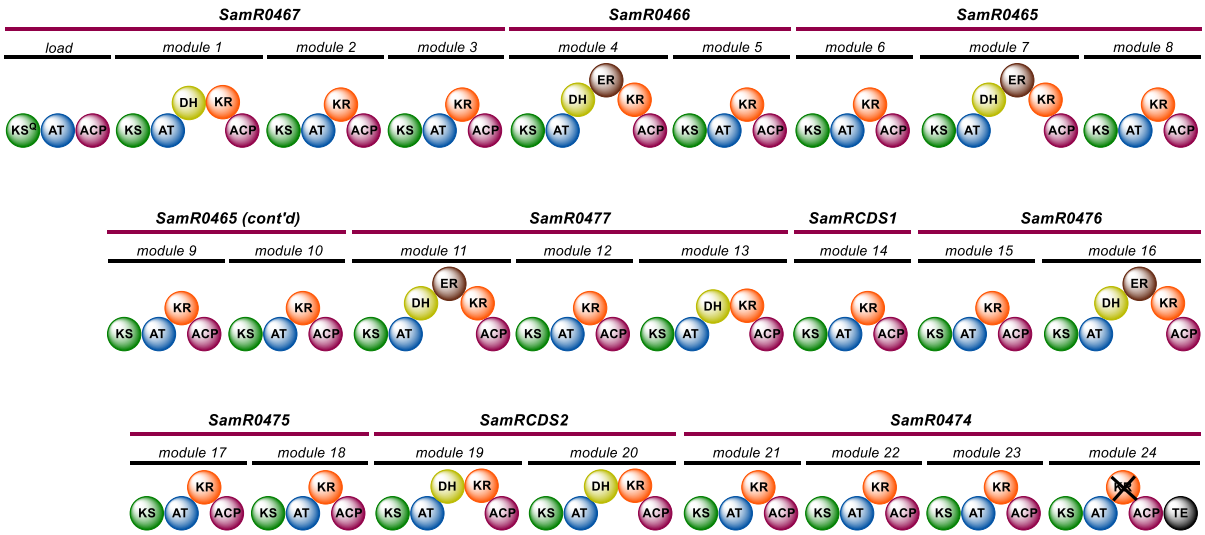


***Figure 5**: Module and domain organisation of the stambomcyin PKSs (the KR domain in the last module was predicted to be nonfunctional and is hence crossed out)[138]*

Based on the substrate specificity of the acyl transferase (AT) domains in each module (deducible from their gene sequences[52]), the polyketide was predicted to be assembled from sixteen malonyl-CoA units (by modules 1–4, 6, 8–11, 14–16, 18, 19, 22 and 24), eight methylmalonyl-CoA units (by the loading module and modules 5, 7, 13, 17, 20, 21 and 23), and one unknown extender unit (by module 12). Analysis of the dehydratase (DH) and enoylreductase (ER) domains moreover enabled the positions of the resulting alkenes and saturated moieties to be determined.[138]

Sequence analysis of the ketoreductase (KR) domains allowed the configuration of the various stereocentres (α-substituents and β-hydroxyl groups of each intermediate) to be predicted.[53] The KRs in modules 5, 6, 8, 10, 12, 14, 15, 17 and 23 were determined to be A1-type KRs (generating 2*R*, 3*S*-acyl thioester intermediates), while those in modules 1–4, 7, 9, 11, 13, 16, 19, 20 and 22 were found to be B1-type KRs (generating 2*R*, 3*R*-acyl thioester intermediates). One A2-type KR was present (in module 18, giving a 2*S*, 3*S*-acyl thioester intermediate), as well as one B2-type KR (in module 21, giving a 2*S*, 3*R*-acyl thioester intermediate).[138,139] The KR in module 24 was predicted to be nonfunctional (C1-type KR[53]) based on the lack of a key tyrosine residue.[54,139] Together, these analyses enabled the structure and stereochemistry of the full PKS-bound linear intermediate to be predicted (Figure 6), the nature of the C26 side chain (from the unknown extender unit loaded by module 12) being the only uncertainty.[138]

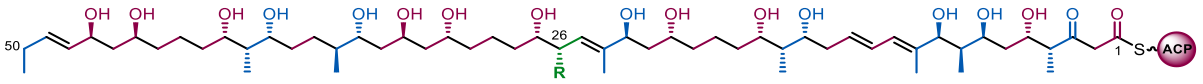


Figure 6: *Predicted structure of the fully assembled PKS-bound stambomycin intermediate (purple-coloured atoms are derived from malonyl-CoA units; blue-coloured atoms, from methylmalonyl-CoA units; and green-coloured atoms, from the unknown extender unit)*[138]

From sequence comparisons, the TE domain was determined to release the product via cyclisation to give a lactone, although the site of lactonisation could not be predicted. Among the post-PKS modification genes identified in the cluster, five genes (*samR0472*, *samR0473*, *samR0480*, *samR0486* and *samR0487*) were found to be homologous to those in the spiramycin gene cluster responsible for the biosynthesis of mycaminose, an amino sugar and one of spiramycin's three deoxysugars. They were thus predicted to convert α-D-glucose-1-phosphate into nucleotide diphosphate (NDP)-D-mycaminose (specifically, thymidine diphosphate (TDP)-D-mycaminose, based on its known biosynthetic pathway;[143] Figure 7). Moreover, another gene (*samR0481*) was found to encode a glycosyl transferase, capable of transferring a mycaminosyl residue from NDP to a hydroxy group in the PKS product. Thus, the final polyketide product was deduced to be a glycosylated macrolide (with mycaminose as the sugar moiety), approximated to have a molecular formula of $C_{69}H_{127}NO_{22}$ and a mass of 1322 Da. Other post-PKS modification genes in the cluster included two genes (*samR0478* and *samR0479*) which encoded for cytochromes P450, enzymes typically involved in post-PKS hydroxylation reactions, as well as two genes (*samR0482* and *samR0483*) deduced to be involved in precursor biosynthesis.[138,139]

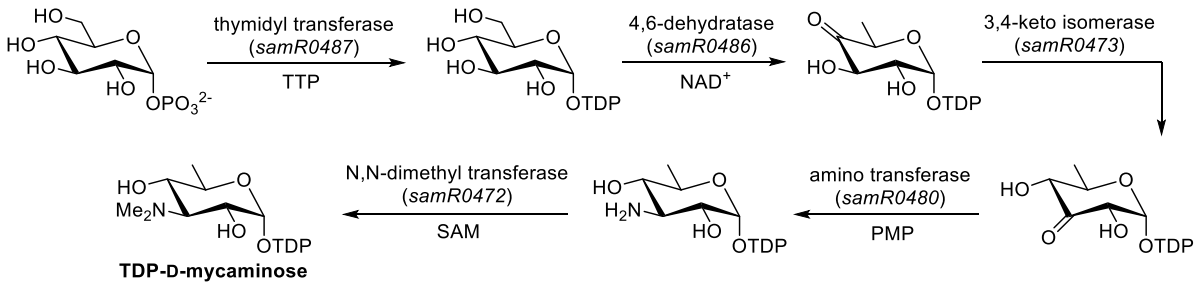


Figure 7: *Biosynthetic pathway of TDP-D-mycaminose from α-D-glucose-1-phosphate (genes in the stambomycin gene cluster proposed to encode the various enzymes are stated in parentheses; TTP: thymidine triphosphate; TDP: thymidine diphosphate; NAD+: nicotinamide adenine dinucleotide; PMP: pyridoxamine 5'-phosphate; SAM: S-adenosyl-L-methionine)*[139]

The stambomycins were found to have molecular formulas and masses which matched well with the predicted. NMR analysis of the isolated compounds showed good agreement between the planar structures of the 51-membered macrolides and the predicted PKS-bound product. From NOESY correlations and $^{3}J_{H,H}$ coupling constants, the alkenes at C10–C13, C24–C25, and C48–C49 were confirmed to be of *E* configuration. The sugar moiety in the macrolide was also confirmed to be mycaminose, both through 2D NMR experiments and comparison of NMR data with literature reported data. Furthermore, the unknown side chain at C26 was identified to be heptyl groups in stambomycins A and B and hexyl groups in stambomycins C and D (Figure 3), the side chain being the only difference among the four compounds.[138]

NMR analysis also revealed certain features of the stambomycins which were not predicted through sequence analysis. The mycaminose moiety was found to be attached to the C5 hydroxy group, from HMBC and NOESY experiments. This was further confirmed by NMR analysis of the stambomycin aglycons (products of the mutant bacterial strain with the inactivated *samR0481* gene), which showed they lacked the sugar at C5. Additionally, the stambomycins were found to contain a tetrahydropyran, arising from addition of the C7 hydroxy group to the ketone at C3. COSY and HMBC analysis also revealed hydroxy groups at C28 and C50, which were not from ketoreduction, as well as an ester bond between the C1 carbonyl and C50 hydroxy groups, revealing the site of macrolactonisation. Overall, however, the stambomycins' experimentally determined structures reflected the accuracy of the genomics-based prediction.[138]

The stambomycins' absolute stereochemistry was assigned based on the predictions made for the PKS-bound product (Figure 6). However, as the C28 and C50 hydroxy groups did not result from carbonyl reduction by ketoreductases, their stereochemistry could not be predicted. The C3 hydroxy group was assigned using a thermodynamic rationale: it would be positioned axial on the six-membered tetrahydropyran ring due to the thermodynamic driving force of the anomeric effect, as well as the bulky C2 side chain being in an equatorial position. Finally, the stereochemistry of the mycaminose moiety was predicted based on the known biosynthetic pathway of TDP-D-mycaminose[143] from D-glucose-1-phosphate (Figure 7).[138,139]

1.3.3. Biosynthetic basis of their unusual features and overall biosynthetic pathway

Two structural features of the stambomycins suggested unusual biosynthetic chemistry, one of which was the ester linkage between the C1 carbonyl and C50 hydroxy groups. This indicated a novel type of polyketide macrolactonisation, since the C50 hydroxy group did not arise from ketoreduction of a β-ketothioester intermediate,[138] which is typical of type I PKS macrolactonisation.[144] Instead, the C50 and C28 hydroxy groups were deduced to result from hydroxylation reactions catalysed by the two cytochrome P450 enzymes encoded by *samR0478* and *samR0479* in the gene cluster.[145]

To verify this, the bacteria was incubated under an $^{18}O_2$ atmosphere. Because cytochrome P450s utilise molecular oxygen for hydroxylation, they would be expected to incorporate the isotope-labelled oxygen atoms into the products. Indeed, a mixture (~3:1) of doubly and singly ^{18}O-labelled stambomycins A/B was observed from LC-MS, and similarly for stambomycins C/D; notably, unlabelled versions of the stambomycins were not observed. Furthermore, *samR0478* and *samR0479* were independently deleted. When *samR0478* was deleted, the bacteria failed to produce stambomycins A–D but instead produced 28-deoxystambomycins A–D, stambomycin derivatives lacking the C28 hydroxy group (Figure 8a), as determined by NMR analysis of the isolated compounds. On the other hand, when *samR0479* was deleted, the bacteria produced acyclic stambomycin derivatives lacking not only the C50 hydroxy group, but also the mycaminose moiety (Figure 8b). This suggests that in the absence of the C50 hydroxy group, the TE domain is unable to release the polyketide via macrolactonisation and can only do so via hydrolysis, despite many other hydroxy groups being present in the molecule. Moreover, it is significant that the acyclic stambomycin derivatives remained unglycosylated, indicating that unlike the 28-deoxystambomycin aglycons, they are not substrates of the mycaminosyl transferase encoded by *samR0481*.[145]

Together, these experiments confirmed that the hydroxy groups at C28 and C50 were installed by cytochrome P450s encoded by *samR0478* and *samR0479*, respectively. It was speculated that these hydroxylation reactions occurred on the fully assembled polyketide chain attached to the ACP domain in the last PKS module.[145] However, in recent studies where the stambomycin PKS was engineered to produce 37-membered mini stambomycin metabolites, it was shown that the *samR0479*-mediated hydroxylation

occurs at some point prior to chain extension by PKS module 14. While in the mini stambomycins, the *samR0478*-mediated hydroxylation appears to occur only after macrocyclisation,[146] the presence of the C28 hydroxy group in the acyclic stambomycin derivatives suggests that hydroxylation occurs during chain assembly, although this remains unclear.[145]

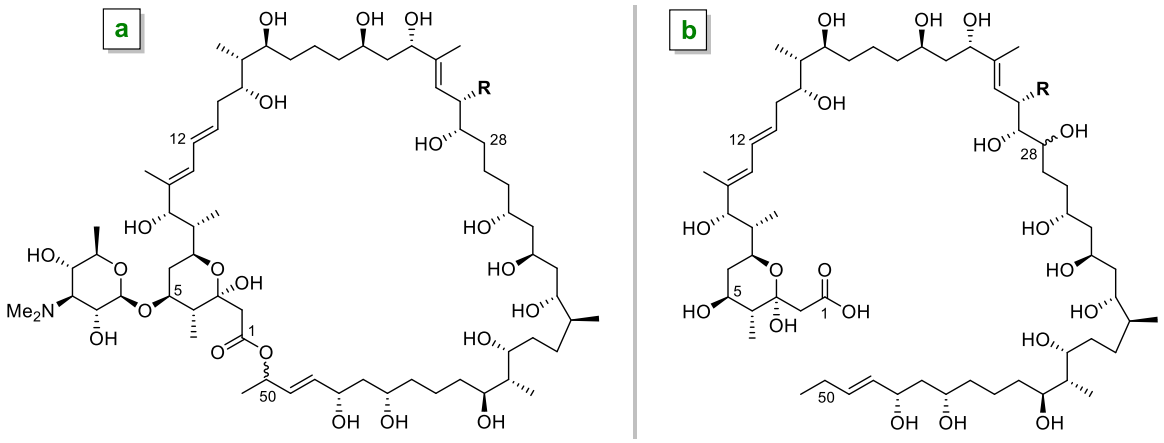


Figure 8: *(a) 28-Deoxystambomycins and (b) acyclic stambomycin derivatives, metabolites of Streptomyces ambofaciens mutant strains with deleted samR0478 and samR0479 genes, respectively; R = heptyl/hexyl groups, as in stambomycins A–D (Figure 3)*[145]

Another unusual feature of the stambomycins was the C26 side chain, which indicated that the AT domain in PKS module 12 was selective for heptyl/hexylmalonyl-CoA units. These unusual extender units were previously unknown.[138] In the biosynthesis of other unusual alkylmalonyl-CoA extender units, a crotonyl-CoA reductase/carboxylase (CCRC) is typically involved. However, no gene encoding a CCRC was detected in the stambomycin gene cluster. Instead, one of the genes (*samR0483*) was found to encode a protein similar to acyl-CoA carboxylases (YCCs), enzymes responsible for the biosynthesis of malonyl- and methylmalonyl-CoA extender units (through carboxylation of acetyl- and propionyl-CoA, respectively). It was thus speculated that the heptyl/hexylmalonyl-CoA units were biosynthesized by a YCC and were derived from fatty acids. The latter was confirmed by isotope-labelling experiments. Additionally, when heptanoic acid was fed to the bacterial strain, a novel stambomycin analogue with a *n*-pentyl side chain at C26 was produced, further supporting the fatty acid origin of the extender units. Sequence analysis also showed that the *samR0482* gene in the cluster was responsible for converting the fatty acids into their respective CoA thioesters.[147]

The formation of the novel stambomycin analogue indicated that the AT domain in PKS module 12 could accommodate unnatural substrates. [3-$^2H_2$]Heptanoic acid was thus used as a probe to determine if the biosynthesis of the extender units involved a YCC or a CRCC. In a YCC-dependent pathway, the resulting *n*-pentylmalonyl-CoA would remain doubly deuterated, whereas in a CCRC-dependent pathway, it would become singly deuterated due to an intermediate dehydrogenation step (Figure 9). Administration of [3-$^2H_2$]heptanoic acid to the bacterial strain and LC-MS analysis of the resulting stambomycin analogue showed that both deuterium atoms were retained, confirming the YCC-dependent pathway. Further experiments moreover validated the use of [3-$^2H_2$]heptanoic acid as a mechanistic probe for accurate differentiation between the two pathways. Finally, it was shown that *samR0483* indeed encoded a unique YCC responsible for the production of the heptyl/hexylmalonyl-CoA extender units.[147]

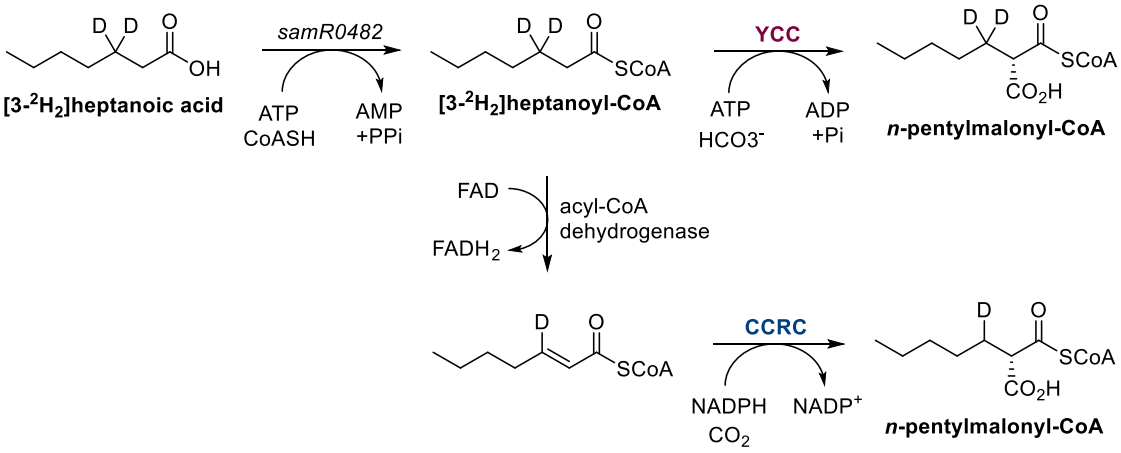
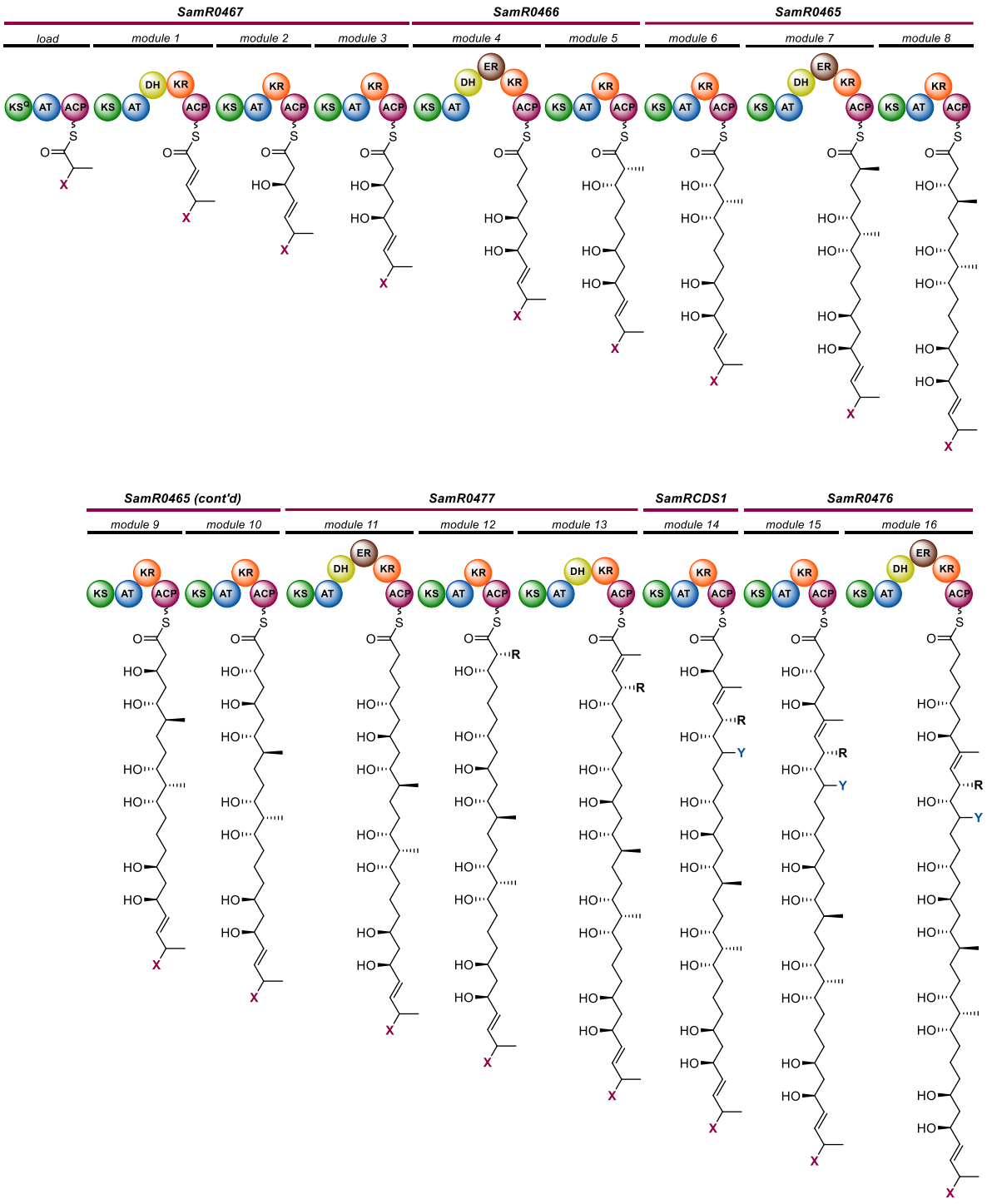


Figure 9: *YCC- versus CRCC-dependent biosynthetic pathways of n-pentylmalonyl-CoA from [3-$^2H_2$]heptanoic acid*[147]

Overall, the unusual features of the stambomycins inspired analysis into their origins, which revealed unique biosynthetic chemistry and expanded the scope of known mechanisms in polyketide biosynthesis. This moreover provided a better understanding of their biosynthetic pathway (Figure 10).



(**Figure 10**, continued on the next page)

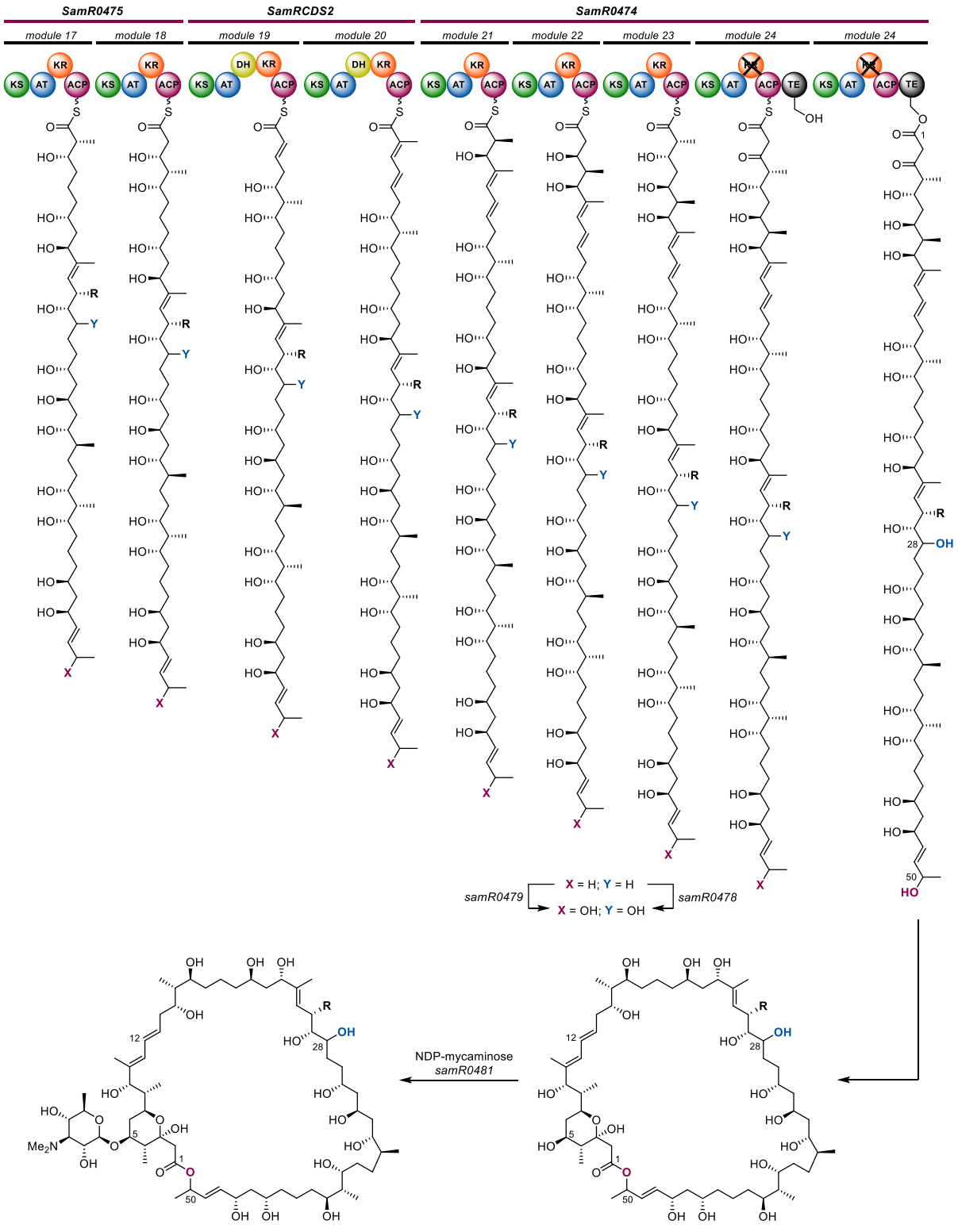


Figure 10: *Biosynthetic pathway of the stambomycins (Note: the timing of hydroxylation is unclear, although hydroxylation at C50 appears to occur before chain extension in PKS module 14, and hydroxylation at C28 is thought to occur after, possibly on the polyketide chain in the last PKS module; tetrahydropyran formation may occur during or after polyketide chain assembly; R = heptyl/hexyl groups, as in Figure 3)*[138,145,146]

1.4. Previous work towards the synthesis of stambomycin D

The stambomycins showcased the potential of gene sequence analysis for stereochemical determination, having their structure and stereochemistry predicted entirely through this approach, which is remarkable given their size and number of stereocentres. To date, they remain one of the most structurally complex polyketides for which the genomics-guided approach has been employed for total stereochemical elucidation. Other comparable examples include the niphimycins,[148] neaumycin B,[149] caniferolides A–D,[150] meijiemycin,[23] and gargantulides B and C,[151] polyketides which were only recently discovered. While the stambomycins' experimentally determined structures highlighted the reliability of the predictions made through sequence analysis, their stereochemistry remains to be unequivocally confirmed. This motivated our group to synthesize stambomycin D, with the aim of validating this promising approach to natural product stereochemical determination. This would be particularly valuable for polyketides, whose inherent flexibility often renders definitive stereochemical assignment challenging by other traditional approaches. In this section, an overview of the group's previous synthetic efforts towards the molecule is presented, highlighting the retrosynthetic strategy, as well as previous key achievements and problems encountered, which serve as the basis for the work subsequently described in this thesis.

1.4.1. Retrosynthetic strategy

Considering the stambomycin D aglycon (an equally valuable target as the glycosylated parent compound since both were isolated), the retrosynthesis began with a disconnection of the C1 ester linkage to reveal acyclic C1–C51 compound **1** (Figure 11). A disconnection of the C48/C49 alkene would enable late-stage incorporation of the allylic alcohol via a Horner-Wadsworth-Emmons olefination[152] and asymmetric reduction sequence, giving easy access to both possible configurations of the C50 hydroxy group. A disconnection across C11/C12 would allow the diene to be constructed by Suzuki[153] (or similar) cross coupling. Finally, it was envisioned that the two 1,3-*anti* diol motifs at C21–C23 and C31–C33 could both be constructed in a similar manner, via an alkyne addition across C22/C23 and C32/C33, respectively, followed by a hydroboration-oxidation and reduction sequence. Overall, this gave four building blocks to the molecule: C1–C11 fragment **2**, C13–C22 fragment **3**, C23–C31 fragment **4**, and C33–C48 fragment **5**. It was further

recognised that in fragment **4**, both the *syn* and *anti* C27/C28 diol could be installed via an asymmetric dihydroxylation or epoxidation approach, respectively, allowing both possible configurations of the C28 hydroxy group to be obtained.

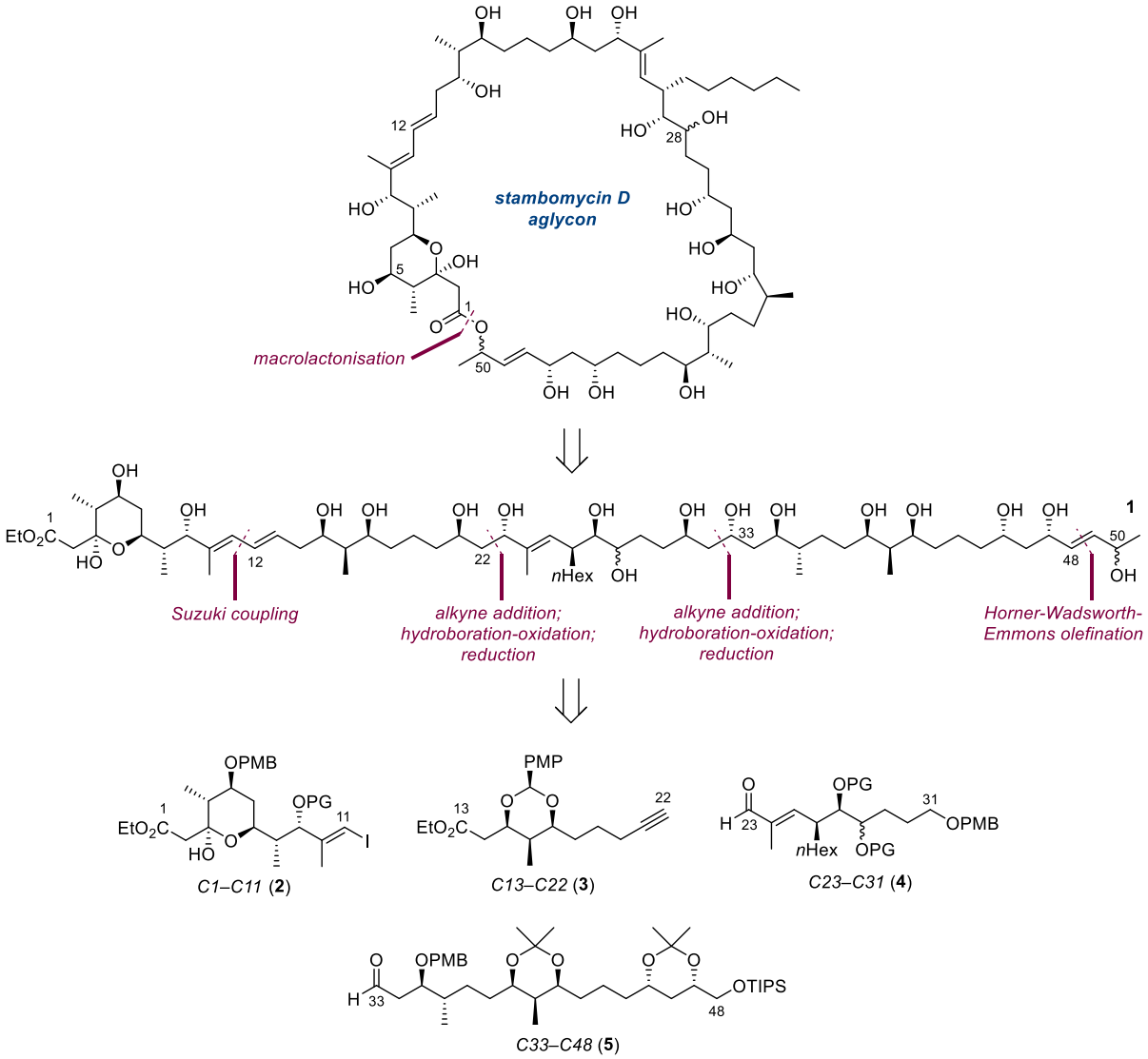


Figure 11: *Key disconnections to the stambomycin D aglycon*

1.4.2. Key fragments synthesized and problems encountered

In previous work in the group,[i] the four building blocks **2**–**5** were prepared, including both diastereomers of fragment **4**, having an *R* (**4a**) or *S* (**4a'**) hydroxy group at C28, with the C27/C28 diol protected as an acetonide (Figure 12). Two model fragments, **M1** and **M2**,

[i]Work done primarily by Dr. Venkaiah Chintalapudi and Dr. Haraldur G. Gudmundsson, former postdocs in the Anderson group

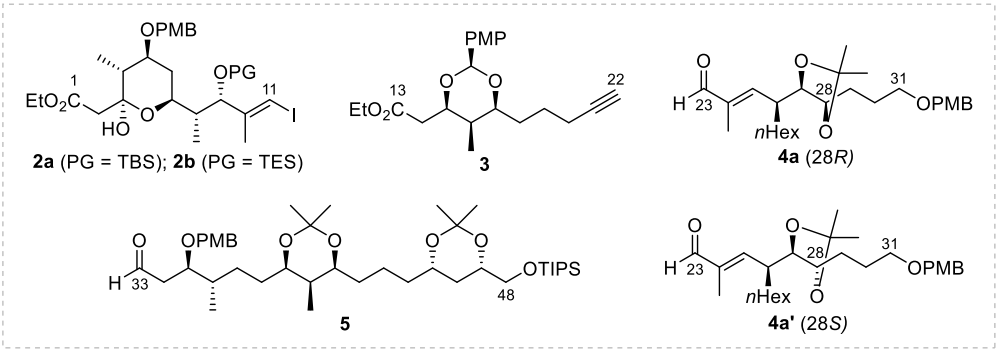


Figure 12: *Building blocks previously synthesized*

were synthesized (Figure 13). Model **M1**, derived from fragment **5** (due to availability of the compound at that time), allowed conditions for the key Suzuki coupling with fragment **2** to be established; both the TBS and TES protecting groups in **2a** and **2b**, respectively, were found to be compatible with the reaction conditions. Those conditions were then employed in the synthesis of model **M2** (C1–C31 fragment), which served to establish key steps in the overall synthetic strategy to the macrolide. Intermediate **I** (C13–C31 fragment), through which **M2** was obtained, was then carried through the entire synthetic

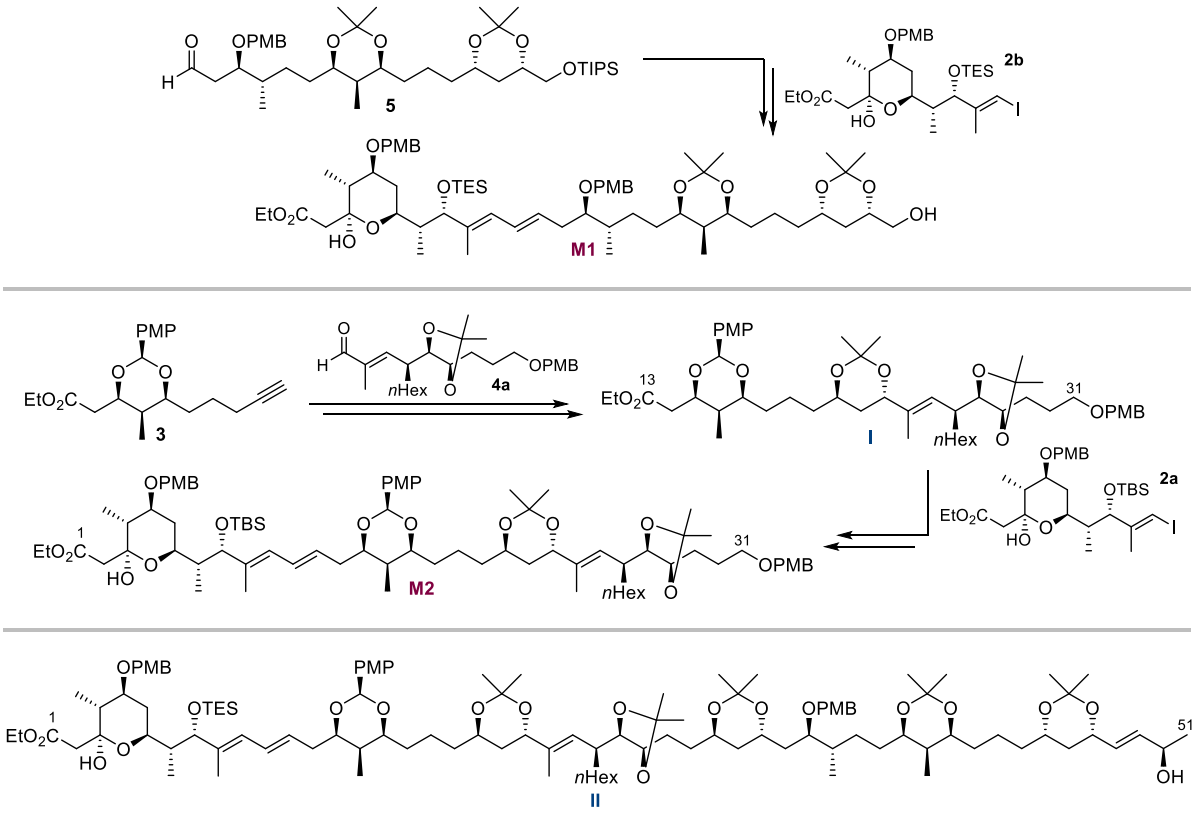


Figure 13: *Key fragments previously synthesized*

route to obtain the full-length C1–C51 fragment **II**. The limited amount of material in hand at that time, however, precluded optimisation of reaction conditions and full characterisation of several compounds in that route.

Given the scarce amount of fragment **II** obtained, models **M1** and **M2** were used to test conditions for a global deprotection of the stambomycin chain. Deprotection of **M1** proceeded smoothly; however, deprotection of **M2** revealed major issues (Figure 14). The 1,2-acetonide at C27/C28 proved unexpectedly difficult to remove, requiring rather harsh conditions. Unfortunately, those conditions then led to the isomerisation or degradation of the acid-sensitive diene at C10–C13. Despite several attempts, conditions enabling the successful cleavage of the 1,2-acetonide at C27/C28 while preserving the acid-sensitive diene at C10–C13 could not be identified, resulting in a roadblock in the project.

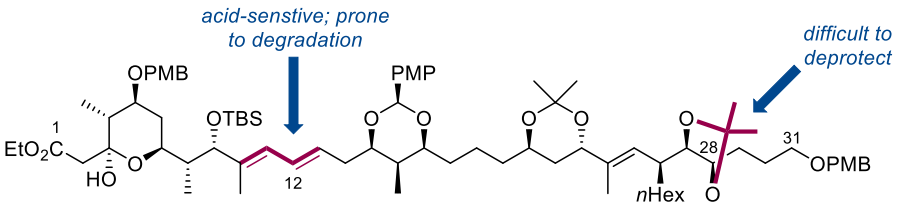


Figure 14: *Problems with deprotection of the C1–C31 fragment* ***M2***

1.5. Thesis summary

In this work, we sought to overcome the problems with deprotection of the stambomycin chain by first addressing the problematic 1,2-acetonide at C27/C28. This was replaced with a more labile protecting group in the C23–C31 fragment **4**, upon which deprotection studies were carried out to identify mild conditions under which it could be removed. Those conditions were then tested in the larger C13–C31 fragment, where other protecting groups were present. These studies are described in Chapter 2.

The stability of the acid-sensitive C10–C13 diene under the deprotection conditions was next examined in the C1–C27 fragment. This not only allowed refinement of the deprotection conditions, but it also provided an opportunity for preliminary validation of the genomics-based predictions for stambomycin D, by comparison of the NMR data of the fragment with that of the natural product. This work has since been published[154] and is detailed in Chapter 3.

To further establish the suitability of the deprotection conditions for the larger molecule, they were applied to the C13–C48 fragment, a late-stage intermediate en route to the target macrolide. This provided further validation of the genomics-based predictions for stambomycin D and moreover enabled identification of the unknown C28 stereocentre, allowing subsequent synthetic efforts to be streamlined. Details of these studies are described in Chapter 4.

Finally, in a culmination of the deprotection studies conducted on the various fragments, global deprotection of the full-length C1–C51 fragment was achieved, demonstrating the effectiveness of the conditions developed. This is described in Chapter 5 and sets the stage for completion of the target macrocycle.

2. The C13–C31 fragment

To overcome the challenges with deprotection of the stambomycin chain, it seemed logical to first address the undesirably robust 1,2-acetonide at C27/C28, one of the two main "problem spots" in the molecule. It was decided that this group should be replaced with a more labile protecting group in the C23–C31 fragment, where its deprotection could be studied in isolation, before assessing the deprotection in the larger C13–C31 fragment (Figure 15). In this chapter, the syntheses of these fragments and the associated deprotection studies are described.

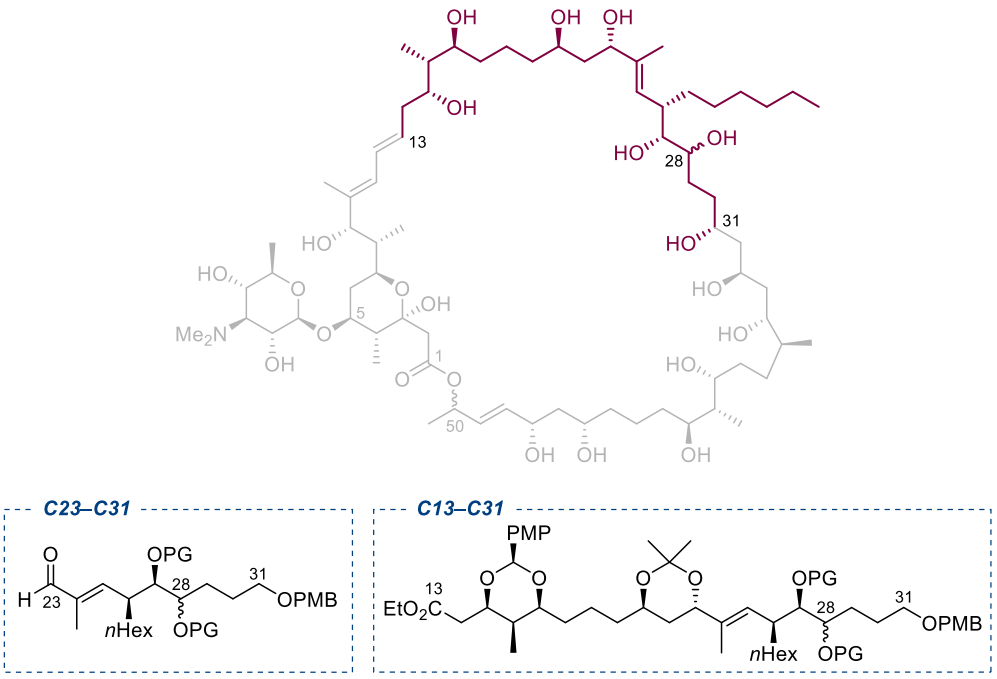


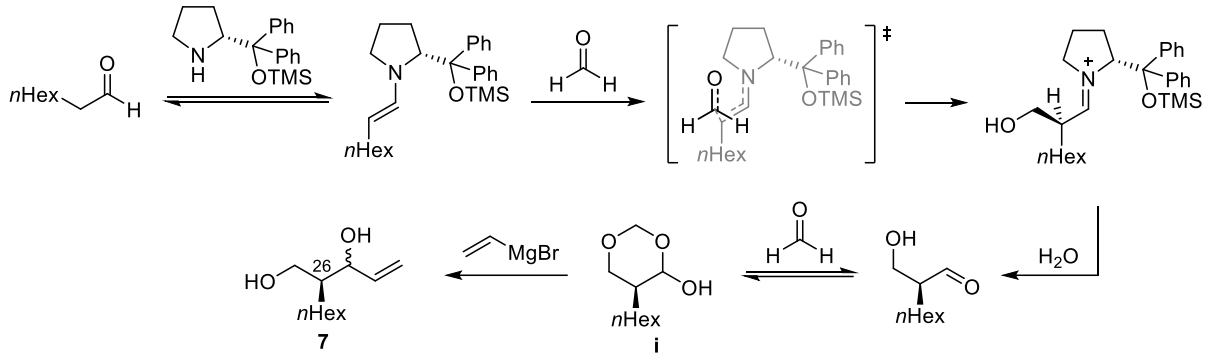
Figure 15: *Stambomycin D and intermediate C23–C31 and C13–C31 fragments*

2.1. The C23–C31 fragment

2.1.1. Synthesis

Synthesis of the C23–C31 fragment began with an enantioselective organocatalytic aldol reaction[155] of octanal and formaldehyde to install the C26 hexyl-bearing stereocentre at

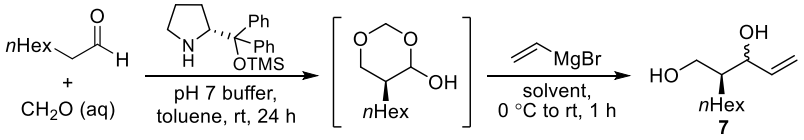
the outset. In this reaction, a β-hydroxy aldehyde is formed, whose enantioselectivity is determined by the steric bulk of the substituent on the prolinol catalyst according to the indicated transition state (Scheme 1). Under the reaction conditions, the β-hydroxy aldehyde reacts with a second molecule of formaldehyde to form an intermediate lactol, which can be further derivatised to a more stable compound. In our case, the lactol **i** was treated with vinylmagnesium bromide to obtain diol **7**.



Scheme 1: *Formation of diol **7** via an enantioselective organocatalytic aldol reaction*

Initially, three equivalents of the Grignard reagent were used. This was to ensure one equivalent was available for addition to the requisite open-form aldehyde, since two equivalents were expected to be consumed through deprotonation of the hydroxy group and addition to the formaldehyde by-product. Because the Grignard reagent was obtained as a solution in THF, THF was employed as the reaction solvent for consistency. Under these conditions, diol **7** was obtained in 30% yield, with significant amounts of side products observed (Table 1, entry 1). When the amount of the Grignard reagent was increased to four equivalents, it resulted in only a slight increase in yield (38%; entry 2).

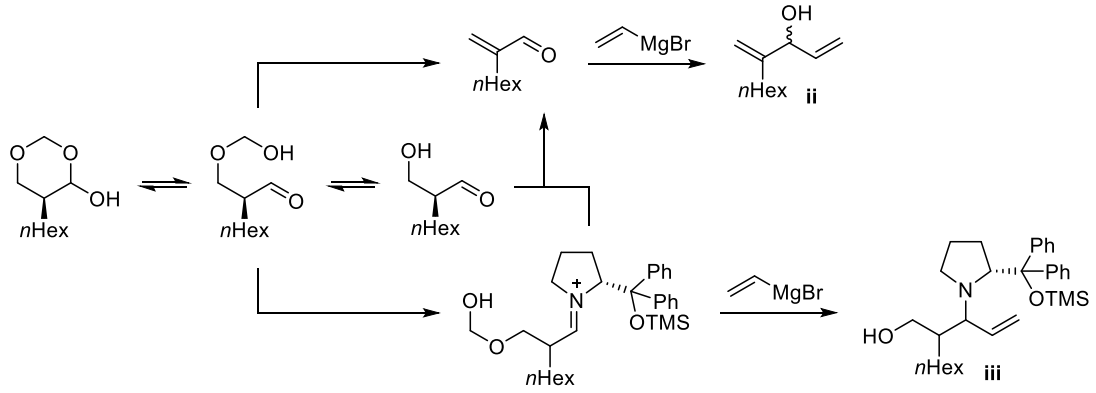
Table 1: *Optimisation of conditions for Grignard addition to lactol*[ii]



Entry	Grignard (eq.)	Solvent	Yield
1	3.0	THF	30%
2	4.0	THF	38%
3	3.0	toluene/THF (1.3:1)	51%
4	3.0	toluene/THF (2:1)	49%

[ii]Reactions were performed on a 1.5 mmol scale using 20 mol% of the catalyst.

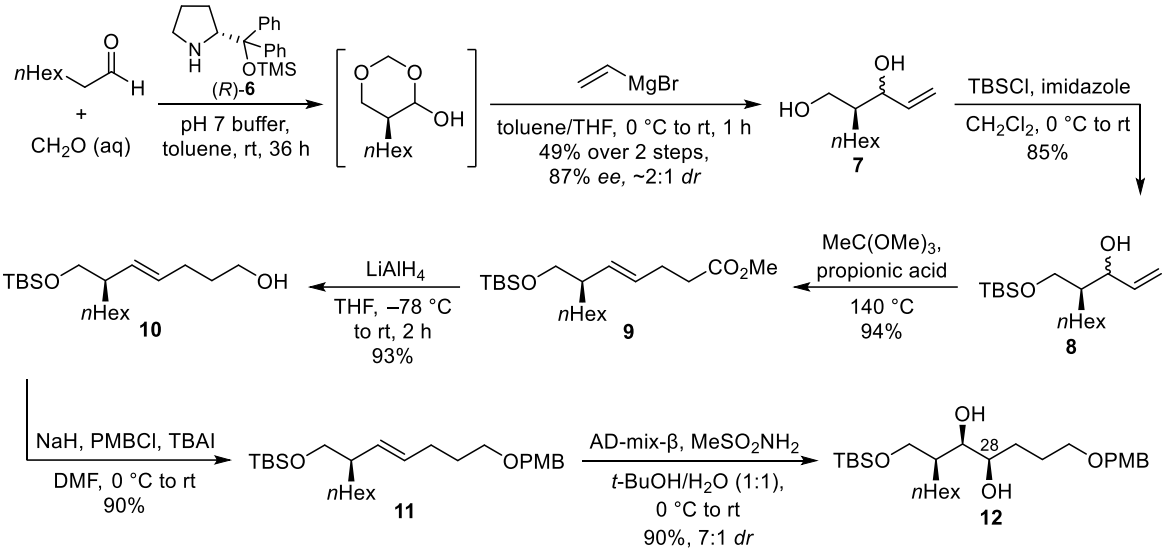
The solvent was next considered, taking into account the observations of Boeckman *et al.*,[155] who observed that nonpolar solvents and neutral pH conditions favour the formation of the lactol, which is in equilibrium with the open-chain aldehyde (~3:1 ratio in toluene). These conditions are also conducive for conversion of the lactol into stable compounds, in reactions that selectively transform the aldehyde in situ. Under conditions which shift the equilibrium to the open-form aldehyde, however, elimination and/or racemisation reactions can occur, for instance, under acidic or basic conditions or through condensation of the catalyst with the aldehyde. Indeed, compounds **ii** and **iii** were observed as major side products in our reaction (Scheme 2). As such, the reaction solvent was changed to toluene, although use of THF was unavoidable due to its presence in the Grignard reagent solution. Pleasingly, a marked increase in yield was observed (51%; entry 3), along with a reduction in the amounts of side products formed. This yield remained consistent even when the amount of toluene was increased (entry 4). Thus, the conditions giving a 51% yield were employed for scale-up.



Scheme 2: *Potential pathways to side products **ii** and **iii** (promoted by the prolinol catalyst or under basic conditions)*

On a multi-gram scale, diol **7** was obtained in 49% yield (87% *ee,* ~2:1 *dr*; Scheme 3). Protection of the primary alcohol as the TBS ether afforded allylic alcohol **8** (85%), which was subjected to a Johnson-Claisen rearrangement[156] to obtain ester **9** (94%). Reduction of ester **9** to alcohol **10** (93%) and subsequent protection as the PMB ether afforded alkene **11** (90%). This was primed for a Sharpless asymmetric dihydroxylation[157] to install the *syn* diol, through which one of the two possible configurations of the unassigned C28 hydroxy group could be obtained. Using AD-mix-β (based on the established mnemonic; Figure 16), diol **12** (90%) was obtained, bearing the (*R)*-configured C28 hydroxy group. The diastereoselectivity was observed to be only moderate (5:1 *dr*), potentially due to

steric interference from the adjacent hexyl group, but this was found to improve (7:1 *dr*) upon performing the reaction on a larger scale and using freshly prepared AD-mix-β.



Scheme 3: *Synthesis of diol* ***12***

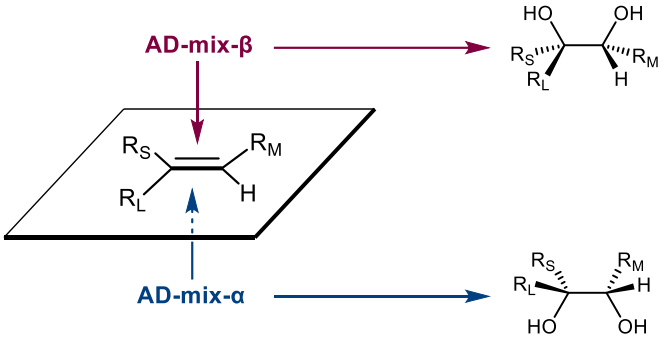


Figure 16: *Mnemonic for Sharpless asymmetric dihydroxylation*[157]

To confirm that the desired configuration of the *syn* diol had indeed been obtained, the relative stereochemistry with respect to the hexyl group was examined. It was envisioned that conversion of diol **12** to a 1,3-diol acetal would lock the protons at C26 and C27 in a six-membered ring, thus allowing their relative stereochemistry (and hence, that of the hexyl group and *syn* diol) to be determined, based on NMR coupling constants and nOe enhancements (Figure 17). Formation of the 1,3-acetal from diol **12** was expected to be unfavourable, however, as the bulky hexyl or C27 side chain would be positioned axial in the resulting chair conformation. On the other hand, for the diastereomer **12'**, those groups would be in more favourable equatorial positions.

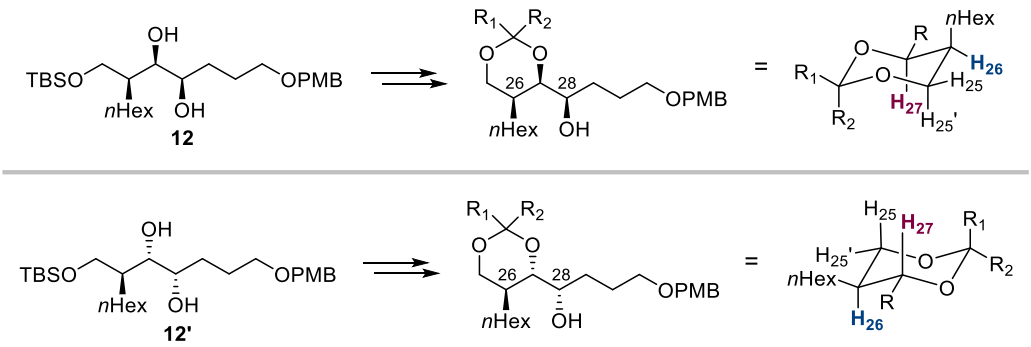
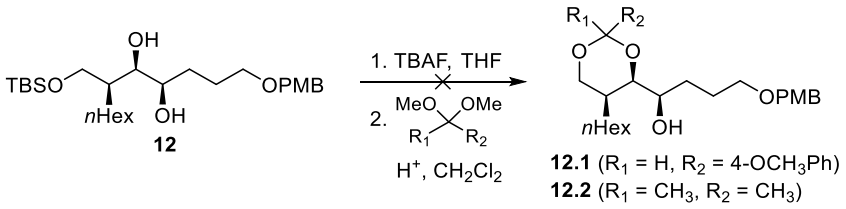


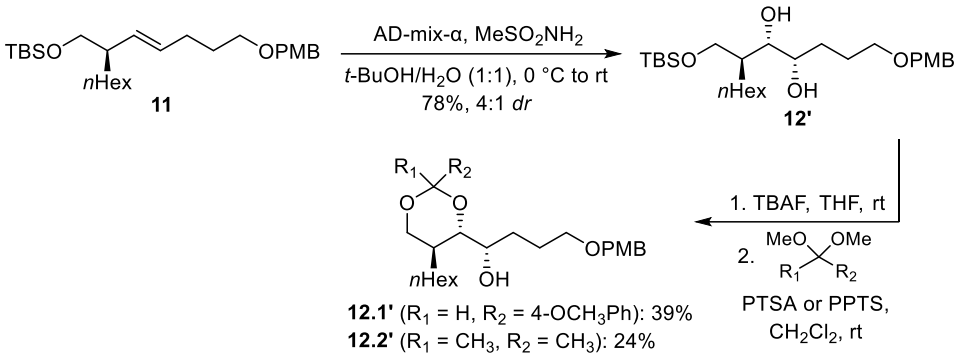
Figure 17: *Proposed 1,3-acetals from diols* ***12*** *and* ***12'***

Nonetheless, conversion of diol **12** to the 1,3-acetal was attempted. Upon cleavage of the TBS ether with TBAF, the resulting triol was treated with anisaldehyde dimethyl acetal or 2,2-dimethoxypropane under acidic conditions to form 1,3-PMP acetal **12.1** or 1,3-acetonide **12.2**, respectively (Scheme 4). Unfortunately, in both cases, a mixture of products was observed, which contained the seven-membered 1,4-acetal but not the desired 1,3-acetal.



Scheme 4: *Attempted synthesis of 1,3-acetals from diol* ***12***

Attention then turned to obtaining the 1,3-acetal from diol **12'** instead. Dihydroxylation of alkene **11** using AD-mix-α furnished diol **12'** (78%, 4:1 *dr*; Scheme 5). Pure diol **12'**, which was partially separable from the mixture of diastereomers obtained, was treated with TBAF, following which, the resulting triol was treated with anisaldehyde dimethyl acetal or 2,2-dimethoxypropane under acidic conditions. PMP acetal **12.1'** was obtained in 39% yield over two steps. NMR coupling constants of the various protons in the six-membered ring indicated that it was in a chair conformation with the side chains in equatorial positions; this was further confirmed by NOESY correlations of H25' and H27 with the acetal proton (Figure 18). More importantly, the coupling constant between H26 and H27 (10.1 Hz), as well as the lack of nOe enhancement between them, established their *anti* relationship.



Scheme 5: *Synthesis of 1,3-acetals **12.1'** and **12.2'***

Acetonide **12.2'** was obtained in 24% yield over two steps as a ~1:1 mixture with the 1,4-acetonide (49% total yield) and was only partially separable from it. ^{1}H NMR coupling constants indicated that the six-membered ring was in a chair conformation, with the ^{13}C NMR chemical shifts of the acetonide methyl groups (19.7 and 29.4 ppm) also being diagnostic of this.[123] Similar to **12.1'**, the coupling constant between H26 and H27 (10.3 Hz) was indicative of their *anti* relationship, as was the absence of nOe between them. Together, NMR analysis of both PMP acetal **12.1'** and acetonide **12.2'** established that the *syn* diol of **12'** is *anti* with respect to the hexyl group; thus, by inference, the diol of **12** is *syn* with respect to the hexyl group.

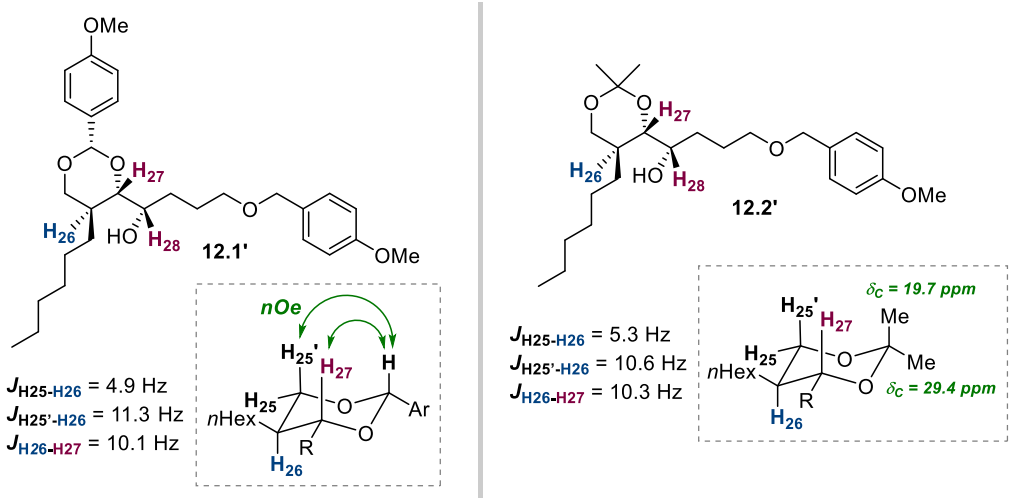
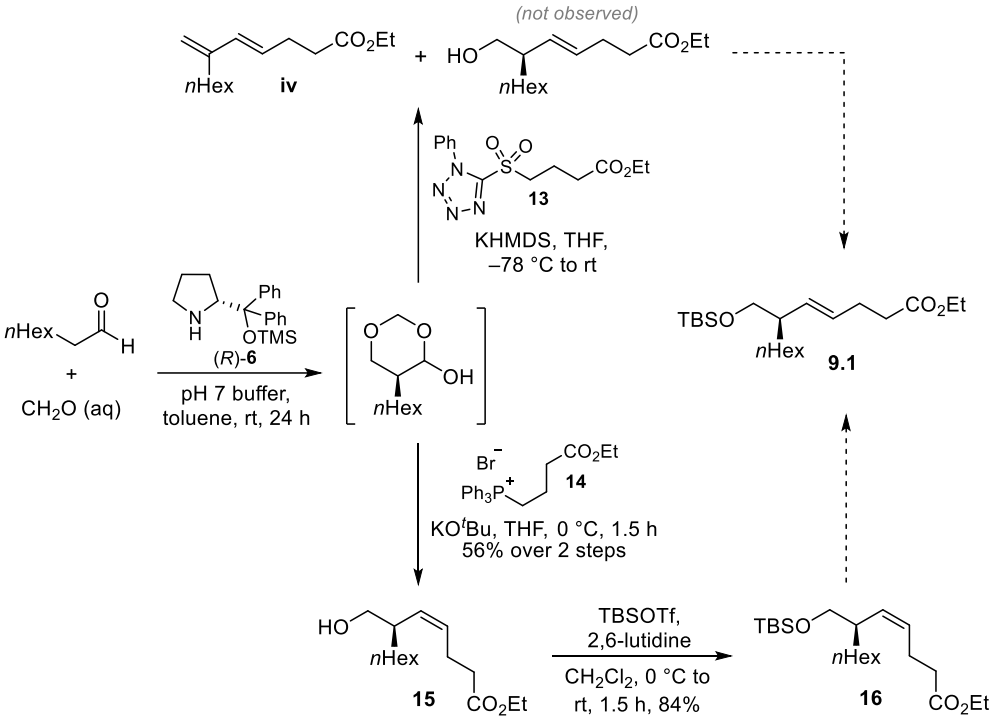


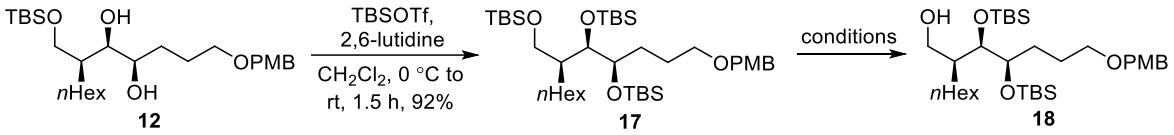
Figure 18: *Key NMR coupling constants and NOESY correlations of acetals **12.1'** and **12.2'***

Having established the route to diol **12**, other potentially more efficient or economical routes were considered. A Julia-Kocienski olefination[158] of the lactol was explored, by which ester **9.1**, the ethyl ester equivalent of **9**, could potentially be obtained (Scheme 6). This was performed using known phenyl-tetrazolyl sulfone **13**, prepared in two steps from commercially available ethyl 4-bromobutyrate. Unfortunately, the desired product was not observed, and only elimination product **iv** was obtained. As an alternative, a Wittig olefination[159] using triphenylphosphonium bromide **14** was also carried out. This furnished alcohol **15** (56%) but required five equivalents of the Wittig reagent for a decent yield, due to the competing formation of the elimination product. Interestingly, when toluene was used as a co-solvent, it failed to improve the yield. Following this, alcohol **15** was protected as the TBS ether **16** (84%). Preliminary attempts to isomerise **16** to the *E*-isomer proved unsuccessful; consequently, this route was not pursued.



Scheme 6: *Alternate routes attempted*

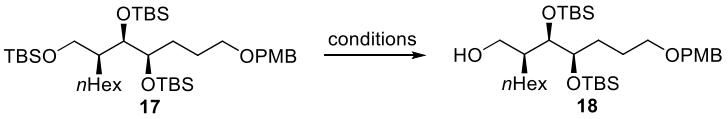
With **12** in hand, an appropriate protecting group more labile than the acetonide was next considered for the 1,2-diol. The TBS group was initially deemed suitable, being expected to be easily removed under acidic conditions or with a fluoride source. Diol **12** was thus converted to tris-TBS ether **17** (92%; Scheme 7). Selective deprotection of the primary TBS ether was then carried out for further manipulation of the primary alcohol. This proved



Scheme 7: *Protection of the 1,2-diol and selective deprotection of the primary TBS ether*

unexpectedly challenging, despite similar deprotections on closely related molecules being well-precedented in the literature. Many conditions were tested, using a range of different acids, solvents, and temperature (Table 2). In all cases, formation of the desired alcohol **18** was accompanied by over-deprotection to the diol and/or triol, which occurred before consumption of **17**. In most cases, the over-deprotected products were moreover the predominant products. Despite multiple attempts, reaction conditions enabling alcohol **18** to be obtained in good yield were elusive. At best, it was obtained in around 30% yield, with **17** recovered in low to moderate yields.

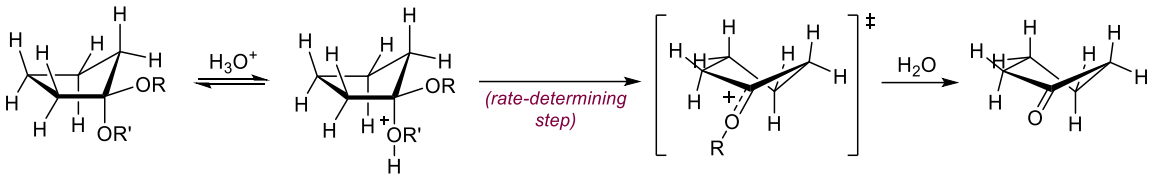
Table 2: *Conditions tested for selective deprotection of the primary TBS ether*[iii]



Entry	Reagent	Solvent	Temperature	Time	Observations / Results
1	TBAF (1.0 eq.)	THF	0 °C	1 h	**18** not observed; **17** > over-deprotected product
2	10% TBAF in AcOH	THF	rt	18 h	**17** > over-deprotected product > **18**
3	AcOH	THF/H_2O (1:1)	0 °C to rt	20 h	**17** largely unreacted
4	5% aq. TFA	THF	–15 °C to rt	>40 h	**17** mostly unreacted; **18** and over-deprotected product observed
5	10% aq. TFA	THF	0°C to rt	18 h	**18**: 31%; rec **17**: 35%
6	PPTS (0.2 eq.)	CH_2Cl_2/ MeOH (3:2)	rt	18 h	over-deprotected products > **18**; **17** unconsumed
7	PTSA (0.5 eq.)	MeOH	0 °C	1.5 h	over-deprotected products > **18**; **17** unconsumed
8	PTSA (0.2 eq.)	CH_2Cl_2/ MeOH (1:1)	–15 °C	1 h	over-deprotected products > **18** > **17**
9	PTSA (0.1 eq.)	CH_2Cl_2/ MeOH (4:1)	rt	3 h	**17** consumed; over-deprotected product >> **18**
10	PTSA (0.1 eq.)	CH_2Cl_2/ MeOH (4:1)	–15 °C	1.5 h	**18**: 22%; rec **17**: 54%
11	PTSA (0.1 eq.)	CH_2Cl_2/ MeOH (5:1)	–15 °C	1.5 h	**18**: 18%; rec **17**: 15%
12	CSA (0.2 eq.)	CH_2Cl_2/ MeOH (1:1)	–15 °C	1 h	**18**: 27%; rec **17**: 39%
13	CSA (0.1 eq.)	CH_2Cl_2/ MeOH (1:1)	0 °C	1.5 h	**18**: 34%; rec **17**: 26%

[iii]Reactions were performed on a 0.03 mmol scale; yields refer to isolated yields; rec = recovered.

As such, it was decided that TBS ethers were ill-suited replacements for the acetonide, and that a cyclic acetal would likely be a better alternative. The cyclopentylidene acetal was thus chosen, being known to be more labile than the acetonide.[160] This is due to the release of torsional strain as the acetal sp^3 centre is converted to an sp^2 centre during the acid-catalysed hydrolysis (Scheme 8),[161] which moreover lowers the barrier for the rate-determining step and thus provides a stronger driving force for the hydrolysis as compared to that of the acetonide. Although bond angle strain increases with the hydrolysis of the cyclopentylidene acetal, slightly offsetting the effects of torsional strain release,[161] its hydrolysis is still significantly faster than that of the acetonide, especially when the acetal is cyclic. This was demonstrated through the half-lives of various uridine 2',3'-acetals under acidic hydrolysis (Table 3).[160]



Scheme 8: *Acidic hydrolysis of the cyclopentylidene acetal*[161]

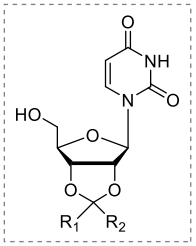
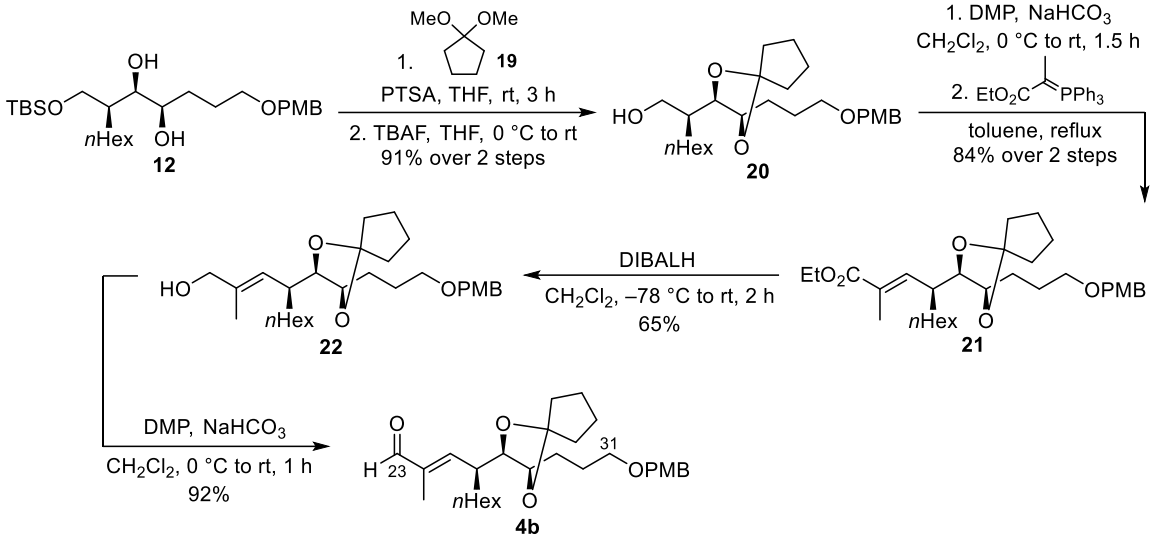


Table 3: *Rates of hydrolysis of uridine 2',3'-acetals at pH 2, 26 °C*[160]

2',3'-Substituent	Half-life (h)
Isopropylidene	20
Cyclopentylidene	4
Cycloheptylidene	3
Cyclooctylidene	2.5

Thus, diol **12** was converted to the cyclopentylidene acetal using 1,1-dimethoxycyclopentane **19**, following which, the primary TBS ether was cleaved with TBAF to reveal alcohol **20** (91% over two steps; Scheme 9). Upon oxidation of the alcohol, the resulting aldehyde was subjected to a Wittig reaction, which furnished enoate **21** (84% over two steps). Enoate **21** was reduced to the alcohol, enabling separation of the diastereomers introduced during the dihydroxylation of alkene **11** (Scheme 3). Finally, the pure alcohol **22** (65%) was oxidised to the aldehyde **4b** (92%), completing the synthesis of the C23–C31 fragment (13% over 13 steps).



Scheme 9: *Synthesis of the C23–C31 fragment* ***4b***

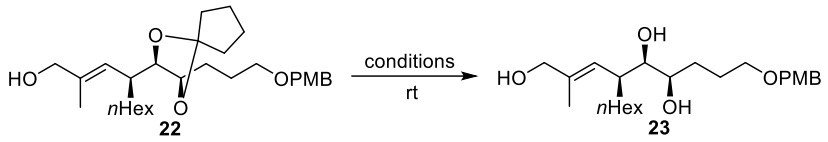
2.1.2. Deprotection studies on the 1,2-acetal

With the C23–C31 fragment in hand, deprotection of the 1,2-cyclopentylidene acetal was carried out to identify mild conditions under which it could be removed, considering the acid-sensitive C10–C13 diene in the larger molecule. To avoid potential side reactions, the more stable alcohol **22** was used instead of the aldehyde **4b**, and all reactions were conducted at room temperature.

To begin with, deprotection was tested using Amberlyst® 15, an acidic ion exchange resin, in MeOH/water (10:1). Under these conditions, the reaction was found to be very sluggish, giving the desired triol in 49% yield after seven days, with some starting material still remaining (Table 4, entry 1). Next, three equivalents of PTSA in THF/water (3:2) was used. This gave a similarly slow reaction, with triol **23** obtained in 26% yield after four days and a significant amount of alcohol **22** still unconsumed (entry 2). Increasing the amount of PTSA to ten equivalents enabled a better conversion of **22**, affording triol **23** in 69% yield after four days (entry 3). Interestingly, when the solvent was changed to methanol, a significant decrease in yield was observed (40%; entry 4), along with the formation of a side product. Following this, deprotection was tested using 1.0 M aqueous HCl in methanol (1:2). Pleasingly, alcohol **22** was consumed after just 24 hours, in stark contrast to the other conditions employed, affording **23** in 78% yield (entry 5). When the

solvent was changed to THF, it resulted in a slower reaction, giving triol **23** in 57% yield after five days (entry 6).

Table 4: *Deprotection of the 1,2-cyclopentylidene acetal*[iv]



Entry	Acid	Solvent	Reaction time	Yield
1	Amberlyst® 15	MeOH/H_2O (10:1)	7 d	49%[v]
2	PTSA (3 eq.)	THF/H_2O (3:2)	4 d	26%
3	PTSA (10 eq.)	THF/H_2O (3:2)	4 d	69%
4	PTSA (10 eq.)	MeOH	4 d	40%[vi]
5	1.0 M aq. HCl	MeOH	24 h	78%
6	1.0 M aq. HCl	THF	5 d	57%

[iv]Reactions were performed on a 0.03–0.05 mmol scale; yields refer to isolated yields. [v]The PMB-deprotected starting material was used. [vi]The product was obtained with an inseparable impurity/side-product.

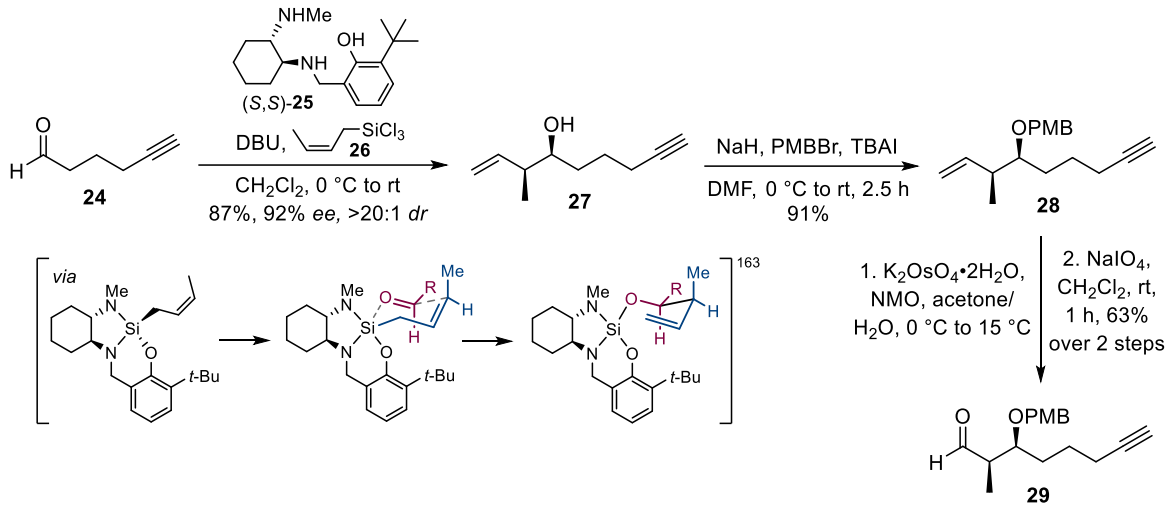
Among these conditions tested, 1.0 M aqueous HCl in methanol (1:2) proved to be the most effective, giving the desired product in the highest yield and in the shortest amount of time. However, a good yield was also obtained when ten equivalents of PTSA in THF/water (3:2) was used. Despite the significantly longer reaction time required, it was deemed to be a potentially milder condition. Thus, these two reaction conditions were selected for further testing on the larger C13–C31 fragment (see below).

2.2. The C13–C31 fragment

2.2.1. Synthesis of the C13–C22 fragment

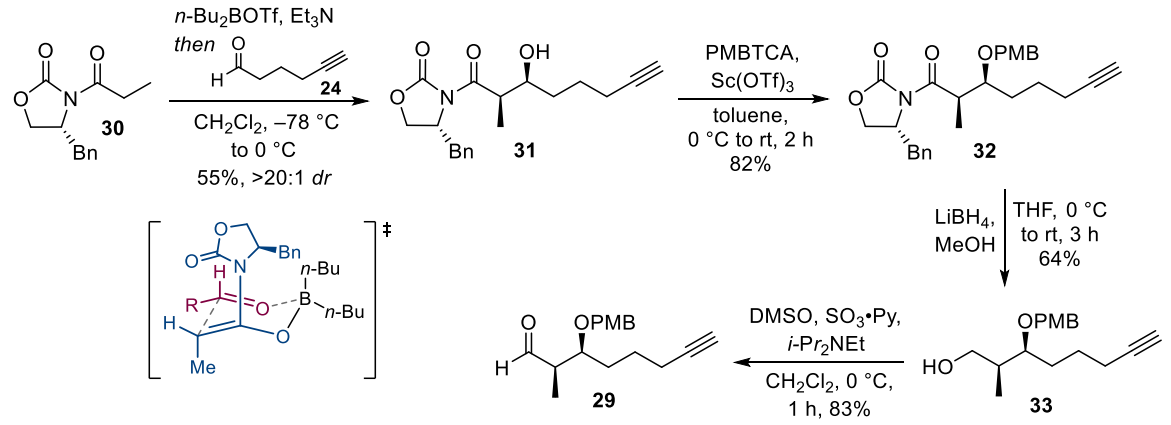
Having completed the synthesis of the C23–C31 fragment and preliminary deprotection studies, attention turned to the synthesis of the C13–C22 fragment for construction of the C13–C31 fragment. It was envisaged that two of its adjacent stereocentres could be installed in a single step through a Leighton crotylation reaction[162] of 5-hexynal **24** (Scheme 10). Employing diaminophenol ligand (*S*,*S*)-**25** and *cis*-crotyltrichlorosilane **26**, the resulting crotylsilane reagent formed in situ was reacted with 5-hexynal **24**, affording homoallylic alcohol **27** (87%, 92% *ee*, >20:1 *dr*). Following protection of the alcohol as

the PMB ether **28** (91%), oxidative cleavage of the terminal alkene gave aldehyde **29** (63% over two steps).



Scheme 10: *Synthesis of aldehyde **29** via a Leighton crotylation reaction*

It was recognised that aldehyde **29** could also be synthesized through an alternate route, employing an Evans aldol reaction[164] to install the two adjacent stereocentres. This route was thus explored (Scheme 11). Imide **30**, upon formation of its boron enolate, was reacted with 5-hexynal **24** to give aldol adduct **31** (55%, >20:1 *dr*), the *syn* adduct being formed due to the formation of the *Z*-enolate.[165] Despite several attempts, the yield was only moderate at best, which could be due to the alkynyl aldehyde employed, since a high yield (93%) was obtained when an alkyl aldehyde (octanal) was used.

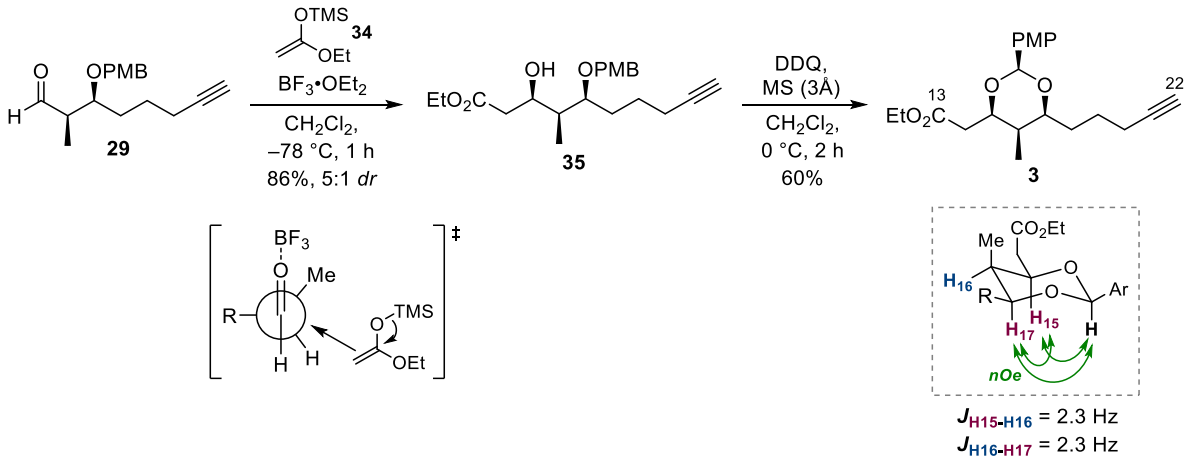


Scheme 11: *Synthesis of aldehyde **29** via an Evans aldol reaction*

Upon protection of the alcohol as the PMB ether **32** (82%), reductive cleavage of the chiral auxiliary afforded alcohol **33** (64%), which was then oxidised to aldehyde **29**. Notably, when the oxidation was carried out using Dess-Martin periodinane or under Swern[166] conditions, the aldehyde suffered low yields and/or considerable epimerisation. However, under the Parikh-Doering oxidation[167] conditions, aldehyde **29** was obtained in good yield (83%), with a relatively insignificant amount of epimerisation observed (>16:1 *dr*).

Comparing these two routes, the Leighton crotylation approach was deemed to be more scalable, giving a significantly better overall yield (50% versus 24% over four steps) and products that were generally easier to purify, although careful handling of homoallylic alcohol **27** was required due to its volatility. This route was thus selected for scale-up of the fragment.

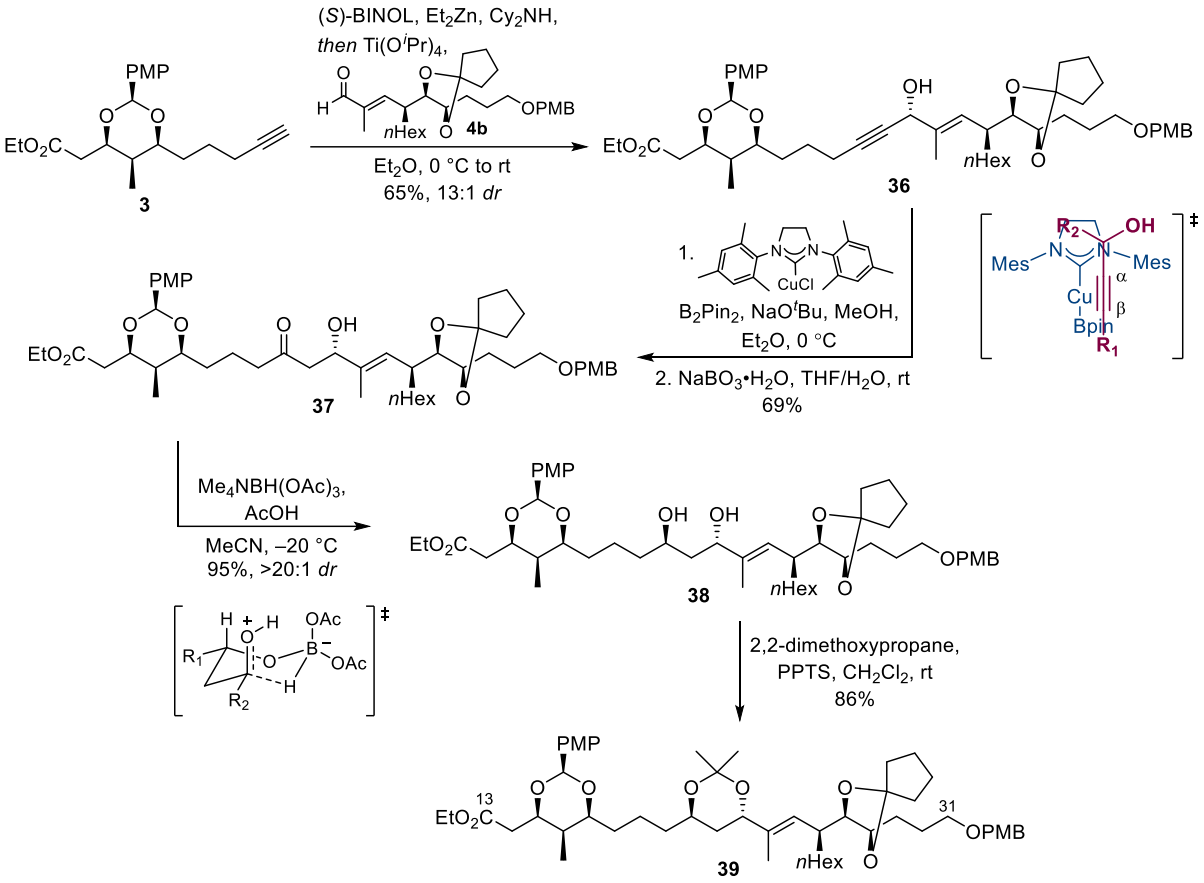
To complete the synthesis of the C13–C22 fragment, aldehyde **29** was subjected to a Mukaiyama aldol reaction[168] with silyl ketene acetal **34**, prepared from ethyl acetate; this furnished β-hydroxy ester **35** (86%, 5:1 *dr*; Scheme 12). The stereochemistry of the alcohol, which was proposed based on the Felkin-Ahn model transition state,[169] was confirmed by Mosher ester analysis.[115] Finally, upon treatment of **35** with DDQ under anhydrous conditions, the PMP acetal **3** (60%) was formed, which also enabled removal of the minor diastereomer. NMR coupling constants and NOESY correlations of the various protons in the six-membered ring confirmed the relative stereochemistry of its substituents. With this, the synthesis of the C13–C22 fragment was completed (26% over six steps).



Scheme 12: *Completion of the C13–C22 fragment* ***3***

2.2.2. Combination of fragments to the C13–C31 fragment

The C13–C22 alkyne **3** and C23–C31 aldehyde **4b** were next combined towards the C13–C31 fragment through a diastereoselective alkynylzinc addition reaction[170] (Scheme 13). In this reaction, the alkyne reacts with diethylzinc to form a nucleophilic alkynylzinc reagent—presumably the mixed ethylalkynylzinc species[171]—which then adds to the aldehyde, catalysed by titanium isopropoxide and (*S*)-BINOL, which forms a chiral Lewis acid complex.[170] This afforded propargylic alcohol **36** (65%, 13:1 *dr*), whose stereochemistry was confirmed by Mosher ester analysis.[115]



Scheme 13: *Synthesis of the C13–C31 fragment* ***39***

Alcohol **36** was then subjected to a regioselective NHC-copper catalysed hydroboration-oxidation reaction,[172] employing a modification of Hoveyda's conditions,[173] to obtain β-hydroxy ketone **37** (69%). The regioselectivity of the reaction arises from the electronic and steric properties of the alkyne substrate and NHC-copper complex. In this case, borylation at the β-position is favoured due to the electron-donating effects of the hydroxy

group; selectivity for the α-position can be achieved when electron-withdrawing or bulky groups are present on the alkyne and/or NHC catalyst.[172,173] Following this, β-hydroxy ketone **37** was reduced via an Evans-Saksena reduction,[174] which afforded 1,3-*anti* diol **38** (95%, >20:1 *dr*), the *anti* diol being formed due to the chair-like transition state through which the reaction occurs. Diol **38** was then protected as the acetonide **39** (86%). This moreover served to confirm the relative stereochemistry of the diol, through the Rychnovsky method,[123] where the ^{13}C NMR chemical shifts of the acetonide methyl groups are indicative of the *syn* or *anti* relationship of the diol, due to the conformation adopted by the six-membered ring (Figure 19). The ^{13}C NMR chemical shift of the acetonide carbon can likewise be informative, based on Evans' extension of the method,[175] although this may not always be accurate.[176] Having obtained **39**, the synthesis of the C13–C31 fragment was completed.

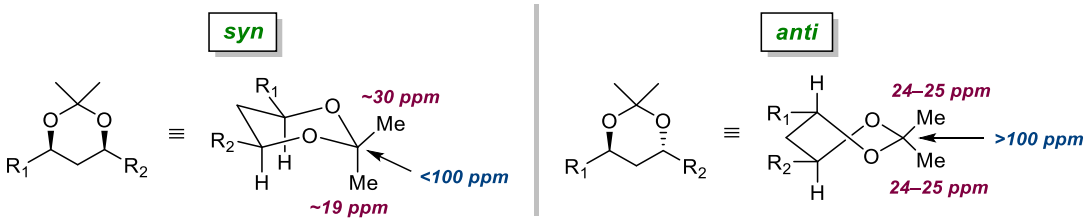
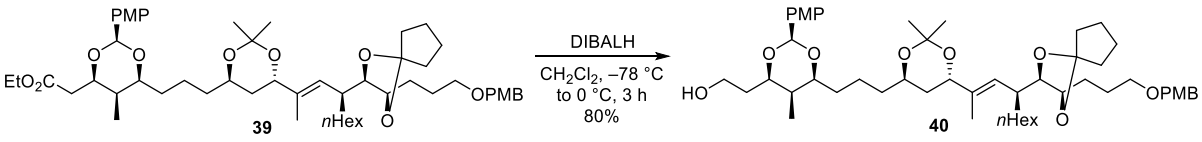


Figure 19: *^{13}C NMR chemical shifts of acetonide methyl groups and quaternary carbons of 1,3-syn and 1,3-anti acetonides, according to Rychnovsky[123] and Evans[175]*

2.2.3. Further deprotection studies on the 1,2-acetal

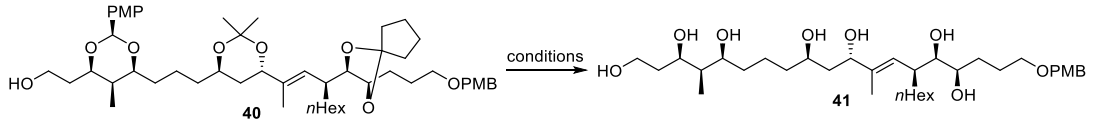
Deprotection of the C13–C31 fragment **39** was next examined using the conditions identified earlier for the C23–C31 fragment **22**, to evaluate their efficacy in deprotecting the 1,2-cyclopentylidene acetal in the presence of other protecting groups. For this, ester **39** was reduced to alcohol **40** (80%) to prevent potential lactonisation reactions during deprotection (Scheme 14).

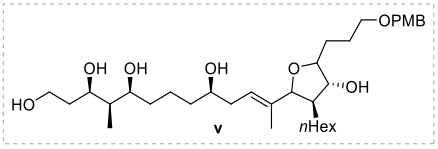


Scheme 14: *Reduction of ester to alcohol*

Alcohol **40** was first treated with ten equivalents of PTSA in THF/water (Table 5, entry 1), one of the two successful conditions for the C23–C31 fragment **22**. After four days, multiple products were observed, including a compound with a partially cleaved cyclopentylidene acetal. Unfortunately, the desired heptaol **41** was not observed. Next, deprotection was performed using 1.0 M aqueous HCl in methanol (entry 2), the other successful deprotection condition. After 24 hours, the desired heptaol **41** was obtained in 19% yield, along with a closely related side product in 45% yield, which was deduced to be allylic rearrangement product **v**. Notably, when heptaol **41** was resubjected to the reaction conditions, conversion to this undesired side product was observed after just two hours, with approximately 50% and 100% conversion observed after one and two days, respectively. On the other hand, when the side product was resubmitted to the reaction conditions, conversion back to heptaol **41** did not occur; instead, degradation was observed after a day. These results suggested that while ten equivalents of PTSA in THF/water was too weak to effect full deprotection of the cyclopentylidene acetal in **40**, 1.0 M aqueous HCl in methanol was too harsh, promoting formation of the side product.

Table 5: *Deprotection of the C13–C31 compound* ***40***[vii]



Entry	Acid, Solvent	Observations / Results
1	10 eq. PTSA, THF/H_2O (3:2)	Multiple products formed; **41** not observed
2	1.0 M aq. HCl, MeOH (1:2)	**41**: 19%; side product: 45% 
3	1.0 M aq. HCl, THF (1:2)	PMP acetal and acetonide deprotected but not cyclopentylidene acetal
4	0.5 M aq. HCl, THF/ethylene glycol (2:1:1)	**41** observed but other products also formed
5	50% aq. TFA, THF (1:1)	PMP acetal and acetonide deprotected but not cyclopentylidene acetal
6	0.2 M aq. HCl, MeOH (1:1)	**41** observed as the major product
7	0.1 M aq. HCl, MeOH (1:1)	**41** observed as the major product (longer reaction time required)
8	0.2 M aq. HCl, MeOH (1:1)	**41**: 44%

[vii]For entries 1, 2 and 8, reactions were performed on a ~10 mg scale; for entries 3–7, reactions were performed on a ~1 mg scale.

As such, various other deprotection conditions were tested. These were conducted as TLC experiments on ~1 mg of **40**, with the reaction progress monitored by TLC every few hours and then over a few days, depending on the reaction outcome. Because 1.0 M aqueous HCl in methanol gave the desired product, albeit in low yield, these conditions were taken as a starting point for further modification. First, the solvent was changed to THF (entry 3), since this had resulted in a slower reaction for the C23–C31 fragment **22**. In this case, it proved too weak, deprotecting only the PMP acetal and acetonide. Prolonging the reaction time to a few days and heating the reaction mixture to 35 °C failed to deprotect the cyclopentylidene acetal, resulting only in degradation. Next, deprotection was tested using 0.5 M aqueous HCl in THF/ethylene glycol (entry 4). Ethylene glycol was used since it has been shown to promote deprotection of the acetonide through diol exchange, enabling it to proceed at a significantly faster rate and under milder conditions.[160] With this, the desired product was observed, but along with other products. Subsequently, 50% aqueous TFA in THF was also tested (entry 5). This enabled deprotection of the PMP acetal and acetonide but not the cyclopentylidene acetal. Prolonging the reaction time to a few days and heating the reaction mixture gave some of the desired product, but not to an appreciable extent; moreover, considerable degradation was observed.

Since 1.0 M aqueous HCl in methanol remained the most promising among the conditions tested, it was postulated that reducing the acid concentration or reaction time could potentially prevent the formation of the undesired product and improve the yield of **41**. Thus, deprotection was tested using 0.2 M aqueous HCl in methanol (entry 6). Pleasingly, the desired heptaol **41** was observed as the major product after a day, with relatively insignificant amounts of the partially deprotected and undesired side products observed. Remarkably, it remained the major product even after two days, although the amount of the side product also increased. When the concentration of HCl was further reduced to 0.1 M, similar results were obtained but with roughly double the reaction time; heptaol **41** remained the major product even after four days (entry 7). With these results, deprotection of **40** was carried out using 0.2 M aqueous HCl in methanol for 24 hours (entry 8). This afforded heptaol **41** in 44% yield, confirming the results of the TLC experiment. With these improved deprotection conditions in hand, they were primed for further testing on the acid-sensitive C10–C13 diene.

3. The C1–C27 fragment

Having identified mild conditions to deprotect the 1,2-cyclopentylidene acetal in the C13–C31 fragment, the acid-sensitive C10–C13 diene was next considered. Its stability under the deprotection conditions was examined in the context of the C1–C27 fragment (Figure 20). This also provided an opportunity for preliminary validation of the genomics-based stereochemical assignment of stambomycin D, as it constitutes the "northern hemisphere" of the natural product while avoiding the uncertainty at the C28 position. In this chapter, the synthesis of this fragment, its deprotection, and a comparative analysis of the NMR data are described.

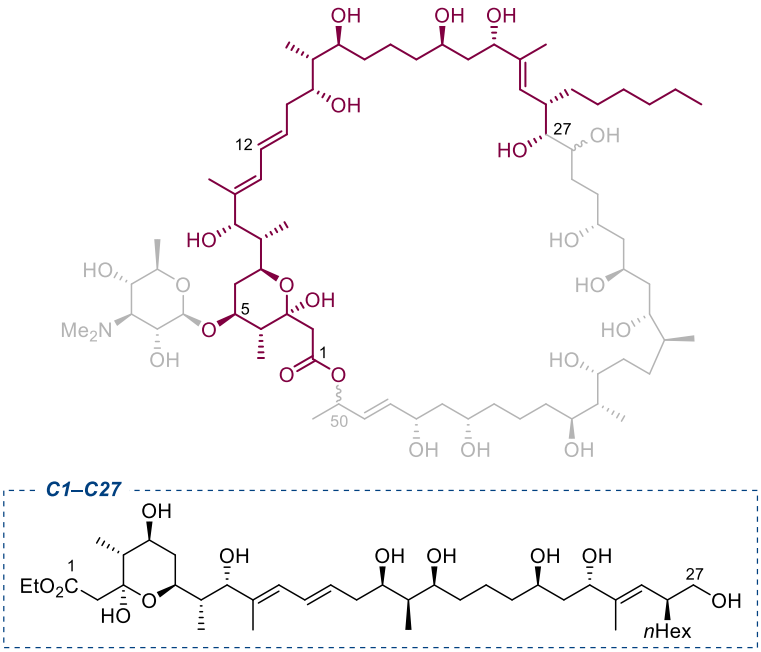
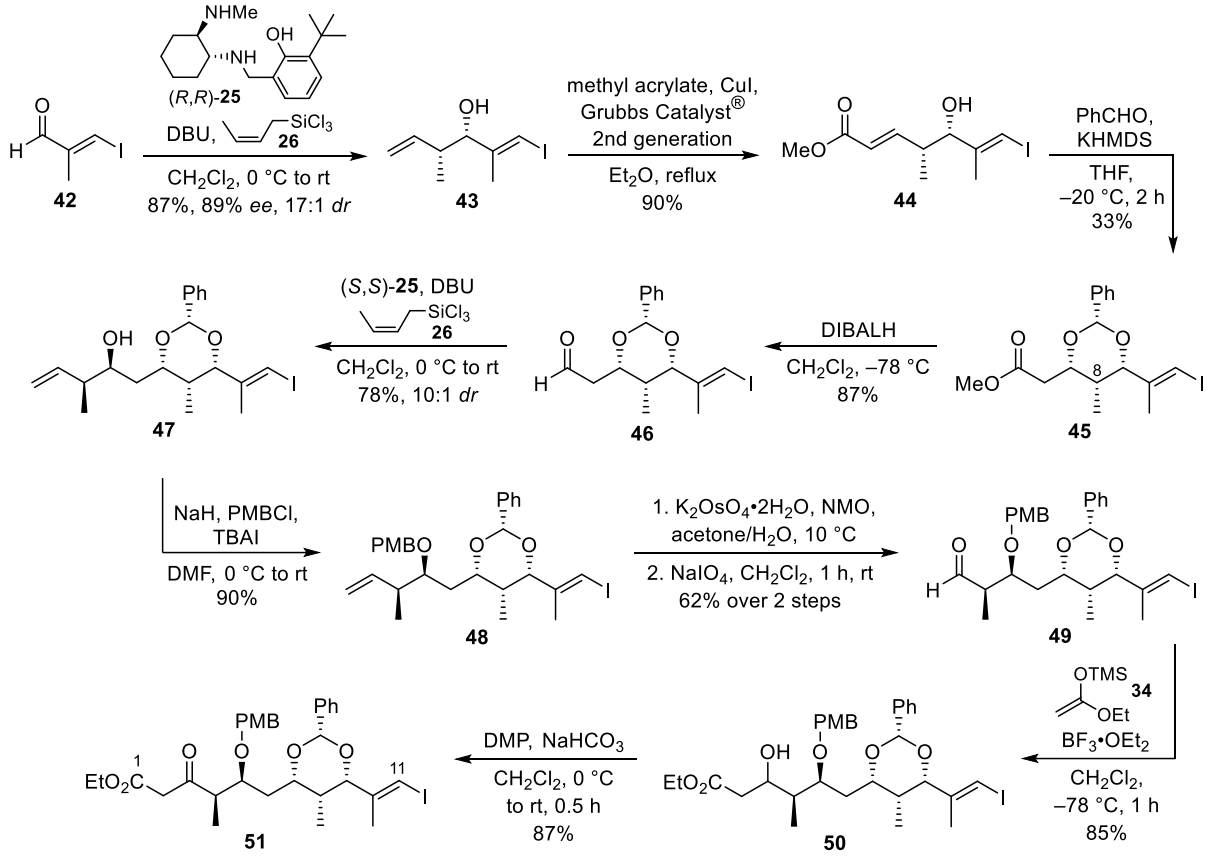


Figure 20: *Stambomycin D and the C1–C27 fragment*

3.1. Synthesis of the C1–C11 and C23–C27 fragments

The synthesis of the C1–C27 fragment began with the synthesis of the C1–C11 fragment. This commenced with a Leighton crotylation[162] of aldehyde **42**, employing diaminophenol ligand (*R*,*R*)-**25** and *cis*-crotyltrichlorosilane **26**, to obtain homoallylic alcohol **43** (87%,

89% *ee*, 17:1 *dr*; Scheme 15), whose stereochemistry was confirmed by Mosher ester analysis.[115] Cross metathesis of **43** with methyl acrylate afforded δ-hydroxy enoate **44** (90%). It was found that the Grubbs catalyst loading could be reduced from 1 mol%, which was initially used, to 0.5 mol% without a reduction in yield.



Scheme 15: *Synthesis of the C1–C11 β-keto ester* ***51***

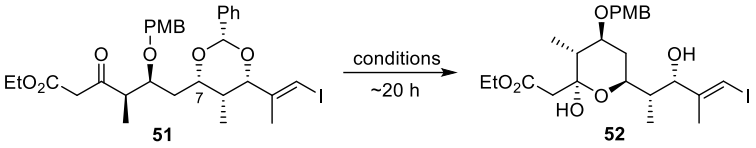
Enoate **44** was then subjected to an Evans-Prunet acetalization[177] to form the *syn*-1,3-benzylidene acetal **45** (33%), the stereochemistry of the acetal being thermodynamically controlled. In this case, formation of the acetal appeared to be unfavourable, as reflected in the low yield; the reaction moreover failed to go to completion even with prolonged reaction times. This is presumably due to the presence of the C8 (*R)*-methyl group, which must adopt an axial position in the six-membered ring. Initially, the reaction was performed using four additions of 1.1 eq. benzaldehyde and 0.15 eq. KHMDS. This gave **45** in low yield (33%), with recovered starting material that had mostly converted to the *Z*-alkene, likely occurring during the retro-Michael reaction which is in equilibrium with the cyclisation reaction. It was observed, however, that using three additions of 1.1 eq.

benzaldehyde and 0.1 eq. KHMDS allowed a better recovery of the original starting material, although the yield was similar. Under these conditions but with extended reaction times (6 and 15 hours), the yield was likewise similar; however, it was found that with a longer reaction time, more of the recovered starting material was converted to the *Z*-alkene. As such, a 2–3 hour reaction time was found to be optimal, allowing a decent amount of starting material to be recovered, which could then be resubmitted to the reaction conditions for a better overall yield.

With **45** in hand, the ester was reduced to aldehyde **46** (87%). Another Leighton crotylation reaction was carried out to afford homoallylic alcohol **47** (78%, 10:1 *dr*), which was protected as the PMB ether **48** (90%). Oxidative cleavage of the terminal alkene furnished aldehyde **49** (62% over two steps); it was found necessary to conduct the oxidation reaction at a low temperature to minimise undesired oxidation of **48** at the tri-substituted iodoalkene. Following this, a Mukaiyama aldol reaction[168] of aldehyde **49** with silyl ketene acetal **34** was performed, giving β-hydroxy ester **50** (85%) as a single diastereomer. The stereochemistry of the alcohol was not confirmed, however, as it was then oxidised to the β-keto ester **51** (87%).

It was anticipated that deprotection of the benzylidene acetal of **51** under acidic conditions would be followed by cyclisation of the resulting C7 hydroxy group onto the ketone to form the desired tetrahydropyran. Deprotection of **51** was thus carried out using 1.0 M aqueous HCl in methanol at room temperature (Table 6, entry 1), since these conditions were found to be effective in earlier deprotection studies. No reaction occurred, however, this later being attributed to the insolubility of the starting material in the reaction medium. Use of THF as a co-solvent resolved this issue; however, the acetal was found to be surprisingly robust and difficult to deprotect. With heating at 30 °C, some product was observed, but the conversion was poor and degradation products were also observed (entry 2). Increasing the acid concentration to 2.0 M did not improve the conversion at room temperature (entry 3). With heating at 30 °C, the starting material was consumed but considerable degradation also ensued, along with the formation of a side product which was difficult to separate from the desired product (entry 4). Notably, more degradation was observed when the reaction was performed in the absence of methanol than in its presence (entry 5).

Table 6: *Deprotection of the benzylidene acetal of* ***51***[viii]



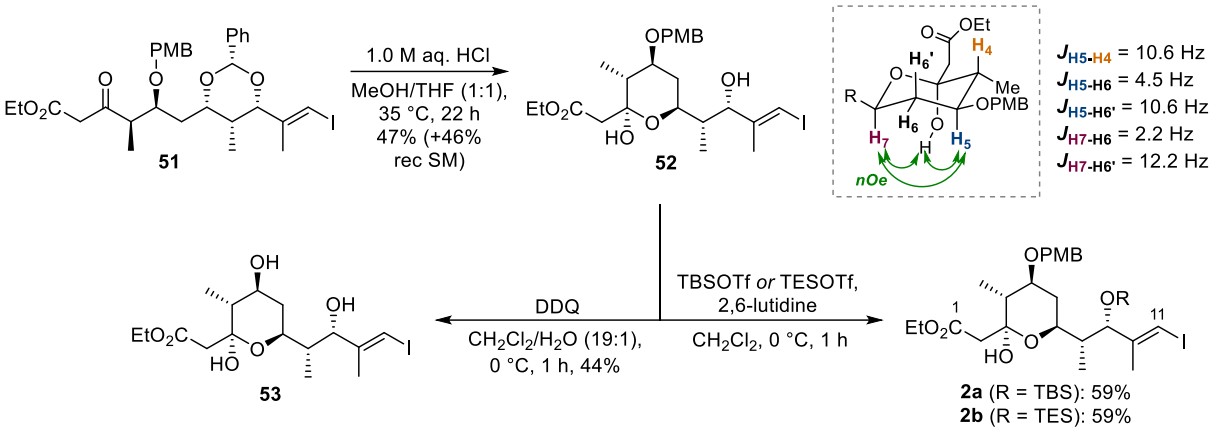
Entry	Acid, Solvent	Temperature	Observations
1	1.0 M aq. HCl, MeOH (1:1)	rt	no reaction (solubility issues)
2	1.0 M aq. HCl, MeOH/THF (1:1:1)	30 °C	**51** > **52** > degradation products
3	2.0 M aq. HCl, MeOH/THF (1:1:1)	rt	**51** > **52**
4	2.0 M aq. HCl, MeOH/THF (1:1:1)	30 °C	**51** consumed; degradation products > **52** (24%)
5	2.0 M aq. HCl, THF (1:1.5)	rt	**51** > degradation products > **52**
6	0.5 M aq. HCl, MeOH/THF (1:1:1)	35 °C	**51** ≥ **52** > degradation products
7	1.0 M aq. HCl, MeOH/THF (1:1:1)	35 °C	**52** > **51** > degradation products
8	1.0 M aq. HCl, MeOH/THF (1:1:0.5)	35 °C	**52** > degradation products > **51**
9	80% aq. AcOH	60 °C	degradation products > **52** > **51**

[viii]Reactions were performed as TLC experiments on a ~2 mg scale, except for entries 1 and 4, where they were performed on a 30 mg scale.

Given the challenge in deprotecting the acetal without causing degradation, an optimal balance between conversion of the starting material and product formation was sought. Lowering the acid concentration to 0.5 M and heating the reaction at 35 °C gave similar amounts of the starting material and product, along with some degradation products (entry 6). Use of 1.0 M HCl under these conditions improved the ratio between the product and starting material (entry 7). Decreasing the amount of THF resulted in increased degradation (entry 8). Finally, for comparison, the reaction was also conducted in 80% aqueous acetic acid at 60 °C, the conditions previously employed in the group by Dr. Chintalapudi. This produced a significant amount of degradation, with comparatively little desired product (entry 9). As such, 1.0 M HCl in methanol/THF (1:1) at 35 °C was identified to be the optimal set of conditions.

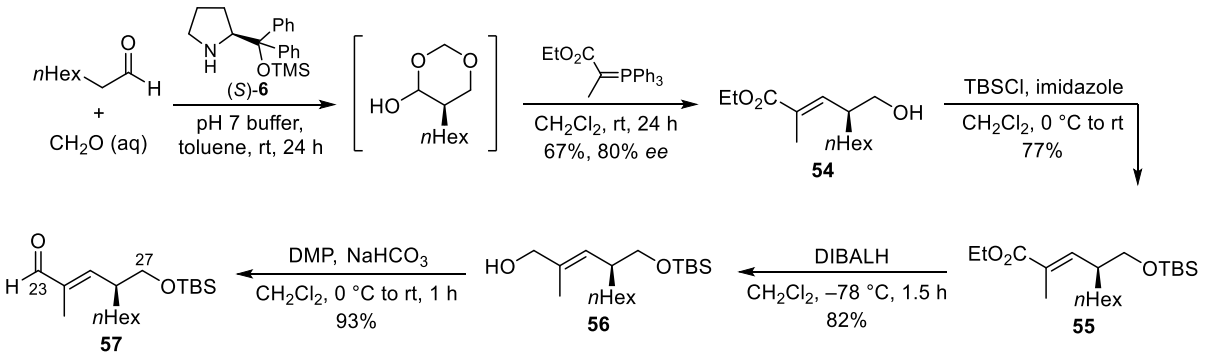
Deprotection of **51** was thus carried out using these conditions (Scheme 16). This afforded **52** in 47% yield, with a good recovery of the starting material (46%). While it was difficult to obtain **52** cleanly due to the presence of a side product, this could be removed in the subsequent step. NMR coupling constants and NOESY correlations of the various protons in the six-membered ring confirmed the relative stereochemistry of its substituents. Following this, the secondary alcohol of **52** was protected, both as the TBS

(**2a**) and TES (**2b**) ethers (59%). Deprotection of the PMB ether of **52** was also carried out, giving alcohol **53** (44%). With this, the synthesis of the C1–C11 fragment was complete, with three variants of the fragment in hand.



Scheme 16: *Completion of the C1–C11 fragment*

Attention then turned to the synthesis of the C23–C27 fragment (Scheme 17). Being a truncated form of the C23–C31 fragment **4b**, it was constructed in a similar manner to **4b**, beginning with an enantioselective organocatalytic aldol reaction[155] of octanal and formaldehyde to install the hexyl-bearing stereocentre. The resulting lactol was subjected to a Wittig olefination to furnish enoate **54** (67%, 80% *ee*[ix]). Protection of the alcohol as the TBS ether **55** (77%) and subsequent reduction of the ester afforded alcohol **56** (82%). Alcohol **56** was finally oxidised to the aldehyde **57** (93%), completing the synthesis of the C23–C27 fragment.

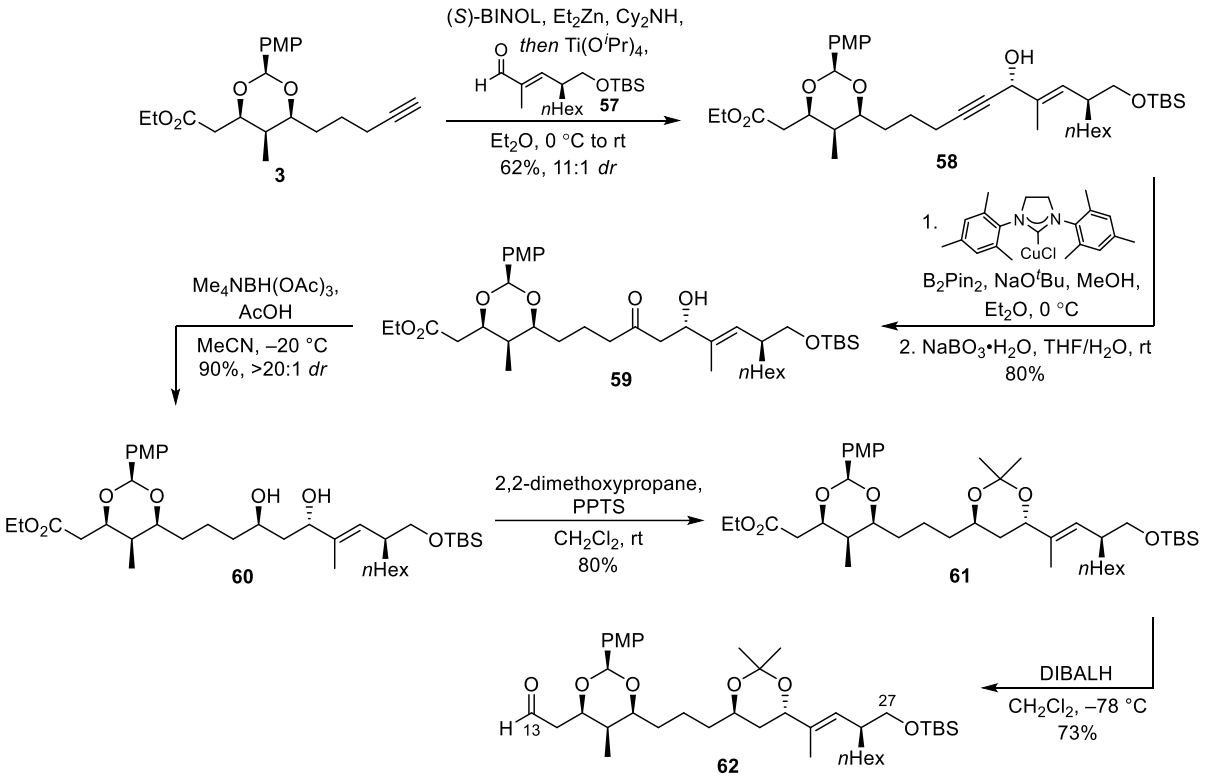


Scheme 17: *Synthesis of the C23–C27 fragment* ***57***

[ix]An 88% *ee* was obtained when former postdoc Dr. Venkaiah Chintalapudi carried out the reaction; this difference could be due to various factors, such as the quality of the catalyst.

3.2. Combination of fragments to the C1–C27 fragment

With the C1–C11 and C23–C27 fragments in hand, they were combined with the C13–C22 fragment towards the C1–C27 fragment. Following a similar route as the C13–C31 fragment **39** (Chapter 2), this commenced with a diastereoselective alkynylzinc addition[170] of the C13–C22 alkyne **3** to the C23–C27 aldehyde **57**, which afforded propargylic alcohol **58** (62%, 11:1 *dr*; Scheme 18). Alcohol **58** was subjected to a regioselective hydroboration-oxidation reaction[172] to obtain β-hydroxy ketone **59** (80%). An Evans-Saksena reduction[174] of ketone **59** furnished the 1,3-*anti* diol **60** (90%, >20:1 *dr*), which was protected as the acetonide **61** (80%), this once again serving as a means of confirming the relative stereochemistry of the diol.[123,175] Following this, the ester of **61** was reduced to the aldehyde **62** (73%).

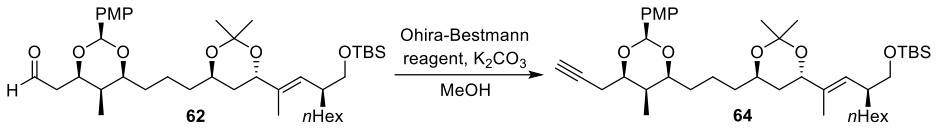


Scheme 18: *Synthesis of C13–C27 aldehyde* ***62***

Alkynylation of aldehyde **62** using the Ohira-Bestmann reagent[178] was next carried out. Initially, two equivalents of the reagent were used (Table 7, entry 1). However, the yield was low (40%), owing to the formation of a side product from ring-opening of the PMP acetal, presumably through enolisation of the adjacent ester under the mildly basic

conditions and E1cB elimination. This moreover produced another impurity which was difficult to separate from the desired product. Lowering the temperature to 0 °C did not suppress this side reaction; in fact, it appeared to proceed at a similar rate, if not faster than the desired reaction. Hence, the reaction mixture was eventually warmed to room temperature to promote full conversion of the starting material (entry 2).

Table 7: *Alkynylation of aldehyde* ***62***



Entry	Ohira-Bestmann reagent (eq.)	Temperature	Yield[x]
1	2.0	rt	40%
2	2.0	0 °C to rt	41%
3	4.0	rt	53%
4	7.0	rt	85%
5	8.0	rt	82%

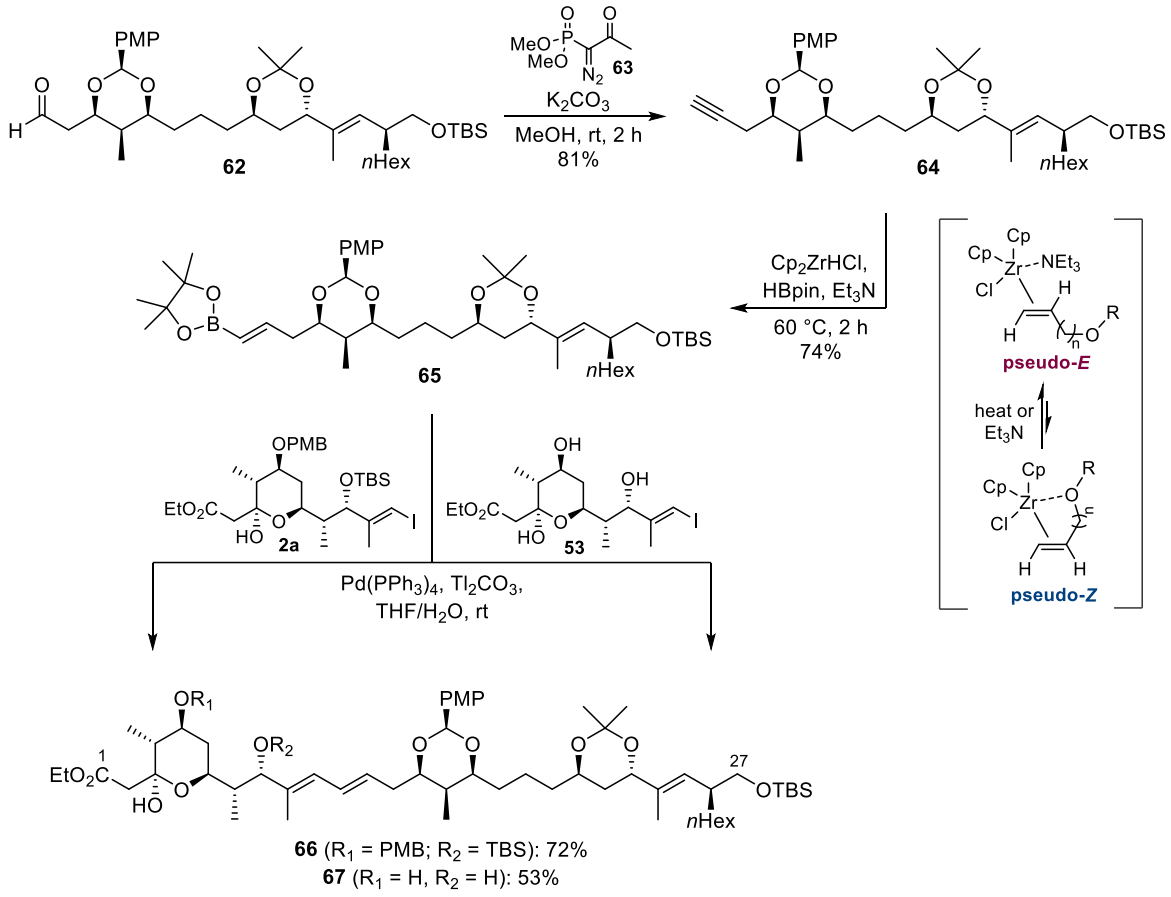
[x]For entries 1–4, the product was obtained with an inseparable impurity.

It was postulated that using an excess of the Ohira-Bestmann reagent could potentially drive the reaction in favour of the desired product over the side product. Indeed, when four equivalents of the reagent were used, a modest increase in yield was observed (53%; entry 3). Increasing this further to seven equivalents afforded the product in a pleasing 85% yield, although a small amount of the side product was still observed (entry 4). This yield remained consistent with eight equivalents of the reagent, but less of the undesired product was formed (entry 5). As such, this condition was selected for scale-up. Despite the undesirable stoichiometry of the reaction, it was felt that the benefit and cost of the substrate outweighed that of the alkynylation reagent.

Upon scale-up, alkyne **64** was obtained in 81% yield (Scheme 19). It was then subjected to a stereoselective zirconium-mediated hydroboration reaction,[179] where use of a catalytic amount of triethylamine and heating at 60 °C promotes the formation of a pseudo-(*E)* intermediate by disrupting intramolecular Zr-O interactions which favour the formation of a pseudo-(*Z)* intermediate. This leads to the formation of the (*E)*-vinylboronic ester. The obtained vinylboronic ester **65** (74%) was then coupled to the C1–C11 fragment via a Suzuki coupling.[153] In previous model studies,[xi] the Suzuki coupling was tested using

[xi]Performed by Dr. Venkaiah Chintalapudi

various bases and palladium catalysts, such as $Pd(PPh_3)_2Cl_2$, $Pd(dppf)Cl_2$ and $Pd(PPh_3)_4$; however, use of Tl_2CO_3[180] with $Pd(PPh_3)_4$ was found to be essential for a successful reaction. Employing these conditions, vinylboronic ester **65** was coupled with both C1–C11 fragments **2a** and **53**, affording C1–C27 compounds **66** (72%) and **67** (53%), respectively. Although **67** was obtained in a considerably lower yield than **66**, it was expected to be easier to deprotect. With these two full-length C1–C27 compounds in hand, deprotection studies was next carried out to examine the stability of the C10–C13 diene.

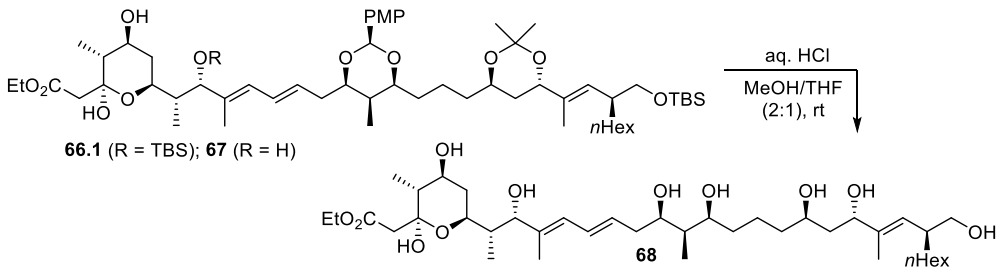


Scheme 19: *Synthesis of C1–C27 compounds* ***66*** *and* ***67***

3.3. Deprotection studies and completion of the C1–C27 fragment

Deprotection of the C1–C27 compound **66** began with cleavage of the PMB ether using DDQ. The resulting alcohol **66.1** was found to be relatively unstable and prone to degradation; nonetheless, its global deprotection was tested (Table 8). Given the acid-sensitivity of the C10–C13 diene, deprotection was first tested using 0.1 M aqueous HCl in methanol, the milder of the two conditions found to be successful with the C13–C31 fragment **40**. As **66.1** was insoluble in methanol, THF was added as a co-solvent. Under these conditions, a small amount of the desired product was observed after five hours, along with many other side products; unfortunately, over time, degradation became predominant (entry 1). Using a lower acid concentration of 0.05 M gave similar results, with some desired product observed after a day, as well as many other side products, which were predominant (entry 2). Further lowering the acid concentration to 0.02 M gave a slightly more promising result; the desired product was formed after three days, and in a similar amount as the degradation products (entry 3).

Table 8: *Deprotection of C1–C27 compounds* ***66.1*** *and* ***67***[xii]



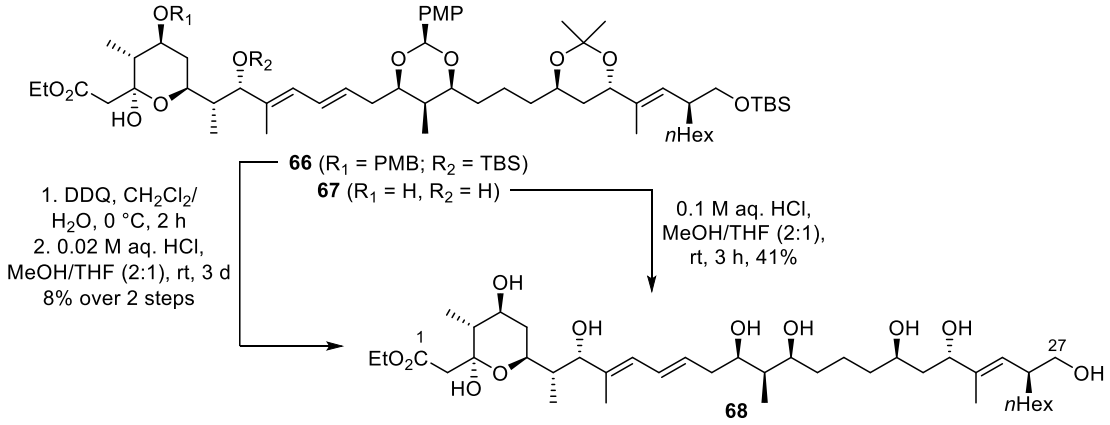
Entry	Compound	HCl concentration	Observations
1		0.1 M	degradation products > **68**
2	**66.1**	0.05 M	degradation products > **68**
3		0.02 M	**68** ≈ degradation products
4		0.1 M	**68** formed as major product after 3 hours
5	**67**	0.05 M	**68** formed as major product after 6 hours
6		0.02 M	**68** formed as major product after 1 day

[xii]Reactions were performed as TLC experiments on a ~0.5 mg scale.

Deprotection of compound **67** was next investigated using the conditions tested on **66.1**. With 0.1 M HCl, the desired product was observed to be the major product after three hours, with some partially deprotected products also observed (Table 8, entry 4). While prolonging the reaction time enabled consumption of the partially deprotected products, it also gave rise to degradation products, which became predominant after a day. Using

0.05 M HCl, the desired product was formed as the major product after six hours; pleasingly, it remained the major product even after a day, although degradation products were also observed (entry 5). Finally, with 0.02 M HCl, the desired product was observed to be the major product after a day, remaining as such up to three days, with some degradation products forming over time (entry 6). In all cases, the deprotection reaction of **67** was observed to be cleaner than that of **66.1**, with fewer side products produced.

With these results, deprotection of both C1–C27 compounds **66** and **67** was carried out (Scheme 20). Upon cleavage of the PMB ether of **66** with DDQ under hydrolytic conditions, treatment of the resulting alcohol with 0.02 M aqueous HCl in methanol/THF (2:1) for three days afforded the fully deprotected C1–C27 fragment **68** in 8% yield over two steps. For **67**, deprotection was performed using 0.1 M aqueous HCl in methanol/THF (2:1), the conditions requiring the shortest amount of time; this afforded **68** in 41% yield after three hours.



Scheme 20: *Deprotection of C1–C27 compounds **66** and **67***

Pleasingly, the ^{1}H NMR spectrum of **68** showed that the C10–C13 diene remained fully intact (Figure 21), highlighting the effectiveness of the deprotection conditions in tolerating this vulnerable motif. Notably, the latter set of conditions also subsequently enabled deprotection of the C33–C51 "southern" fragment of stambomycin D,[181] a work carried out during the course of this work and completed after its publication.[154] Whereas the many other deprotection conditions initially tested on that fragment were problematic and failed to give the fully deprotected product, these conditions proved successful, reinforcing their effectiveness.

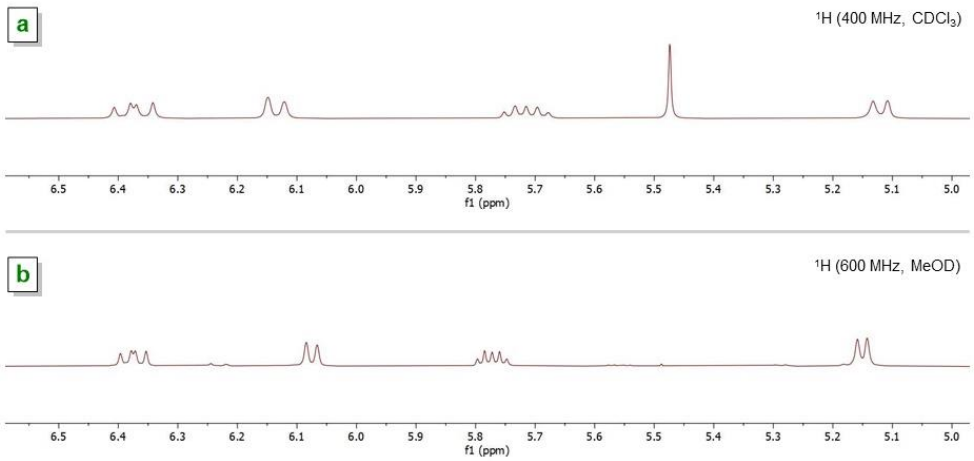
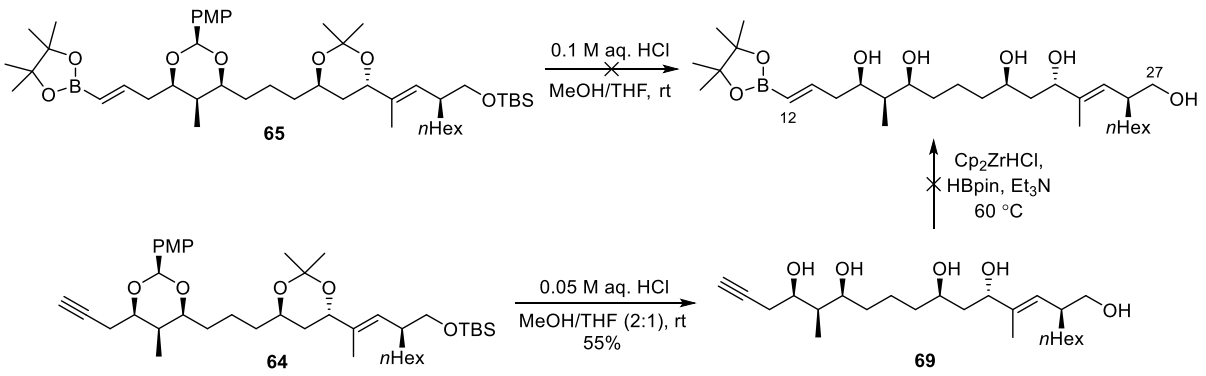


Figure 21: *Alkene region of the ^{1}H NMR spectra of (a)* ***67*** *and (b)* ***68***

Since deprotection of compound **67**, bearing the deprotected C1–C11 fragment, was found to be significantly easier and higher yielding than **66**, it was envisioned that deprotection of vinylboronic ester **65** prior to coupling with the C1–C11 fragment **53** could potentially enable a higher yielding route to the C1–C27 fragment **68**. If successful, this strategy could moreover be applied to the synthesis of the larger stambomycin chain. Deprotection of vinylboronic ester **65** was thus attempted but resulted in degradation (Scheme 21). As an alternative, deprotection of alkyne **64**, a potential precursor to the desired vinylboronic ester, was also performed. Treatment of **64** with 0.05 M aqueous HCl in methanol/THF (2:1) afforded pentaol **69** in 55% yield (0.1 M aqueous HCl was also found to be successful). However, hydroboration of **69** failed to give the desired boronic ester. As such, this route to the C1–C27 fragment **68** was not pursued.



Scheme 21: *Attempted synthesis of the deprotected C12–C27 vinylboronic ester*

With the fully deprotected C1–C27 fragment **68** in hand, a comparison of the NMR data with that of stambomycin D[138] was carried out. This showed a remarkably good agreement for both the ^{1}H and ^{13}C NMR data (Figure 22 and Table 9). Although slight discrepancies were observed, this was expected due to the structural and potential conformational differences between the acyclic fragment and the cyclic natural product. In particular, there were observable differences in the ^{13}C NMR data for C27, the point of truncation for the acyclic fragment, and for C5, where the acyclic fragment bore a free hydroxy group instead of a mycaminose moiety present in the natural product. Compared to the stambomycin D aglycon,[138] however, this difference at C5 was trivial (δ_C of aglycon: 70.1 ppm; δ_C of C1–C27 fragment: 70.4 ppm). Additionally, a discrepancy at the C19 protons was observed, which, upon re-examination of the spectroscopic data of the natural product, confirmed that those signals should be reassigned.[154] Overall, the ^{1}H and ^{13}C NMR data of the C1–C27 fragment matched closely with the reported data for stambomycin D, supporting the genomics-based stereochemical assignments of this region of the natural product.

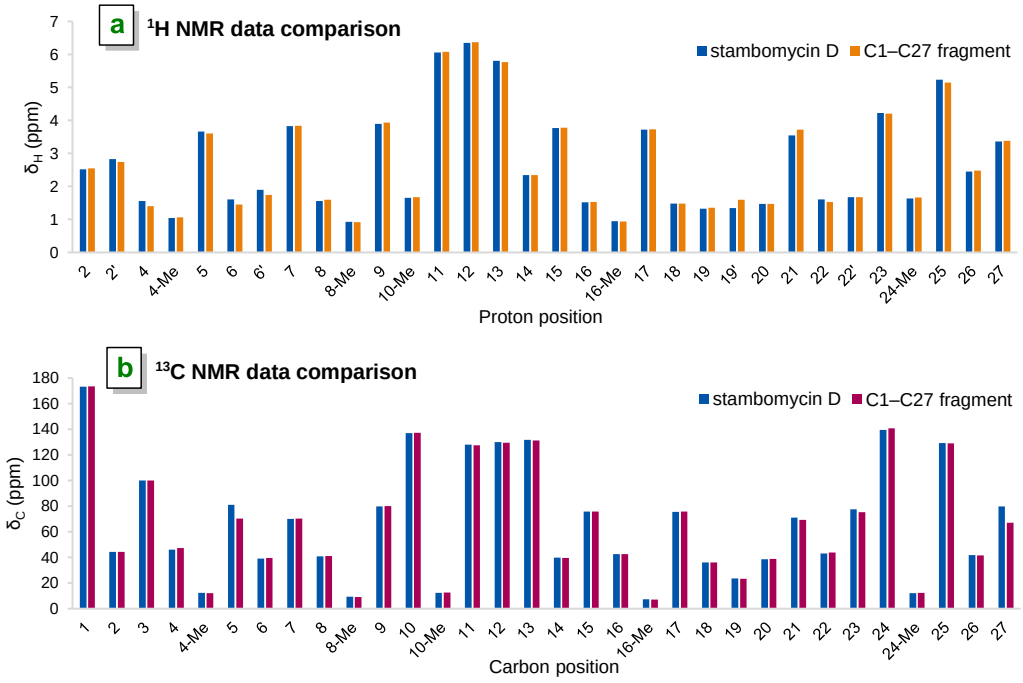
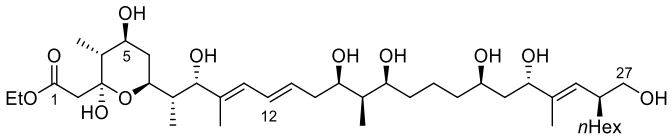


Figure 22: *Graphical comparison of the (a) ^{1}H and (b) ^{13}C NMR data of stambomycin D and the C1–C27 fragment*

Table 9: *NMR data comparison of stambomycin D and the C1–C27 fragment*



	stambomycin D[138] (MeOD, 700 MHz)		C1–C27 fragment (MeOD, 600 MHz)	
Position	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)
1	173.3		173.6	
2	44.3	2.52, 2.83	44.4	2.55, 2.74
3	100.0		100.0	
4	46.2	1.56	47.3	1.40
4-Me	12.4	1.04	12.2	1.06
5	81.0	3.66	70.4	3.60
6	39.1	1.61, 1.90	39.5	1.45, 1.74
7	70.0	3.83	70.4	3.84
8	40.8	1.56	41.2	1.60
8-Me	9.3	0.93	9.2	0.92
9	79.9	3.90	80.1	3.93
10	137.1		137.3	
10-Me	12.4	1.65	12.5	1.67
11	128.0	6.06	127.6	6.08
12	129.9	6.35	129.6	6.37
13	131.7	5.81	131.3	5.77
14	39.8	2.34	39.7	2.34
15	75.8	3.77	75.9	3.78
16	42.6	1.52	42.5	1.53
16-Me	7.4	0.95	7.0	0.94
17	75.5	3.72	75.7	3.73
18	36.1	1.48	36.1	1.48
19	23.5	1.32, 1.34	23.3	1.35, 1.60
20	38.5	1.47	38.8	1.47
21	71.1	3.55	69.2	3.72
22	43.1	1.61, 1.67	43.8	1.53, 1.67
23	77.5	4.23	75.4	4.21
24	139.4		140.8	
24-Me	12.2	1.64	12.4	1.66
25	129.3	5.23	129.1	5.15
26	41.9	2.45	41.7	2.48
27	79.7	3.36	67.0	3.38, 3.43

4. The C13–C48 fragment

Having refined the deprotection conditions for the acid-sensitive C10–C13 diene in the C1–C27 fragment, the suitability of these conditions for the larger molecule was examined. This was achieved through the C13–C48 fragment (Figure 23), a late-stage intermediate en route to the target macrolide, which allowed further validation of the genomics-based stereochemical assignment of stambomycin D. More significantly, as it contained the unassigned C28 stereocentre, this provided an important opportunity for its identification, through the synthesis of both possible diastereomers of the fragment and a comparison of their NMR data with that of the natural product. In this chapter, the synthesis of these fragments, their deprotection, and an analysis of their NMR data are described.

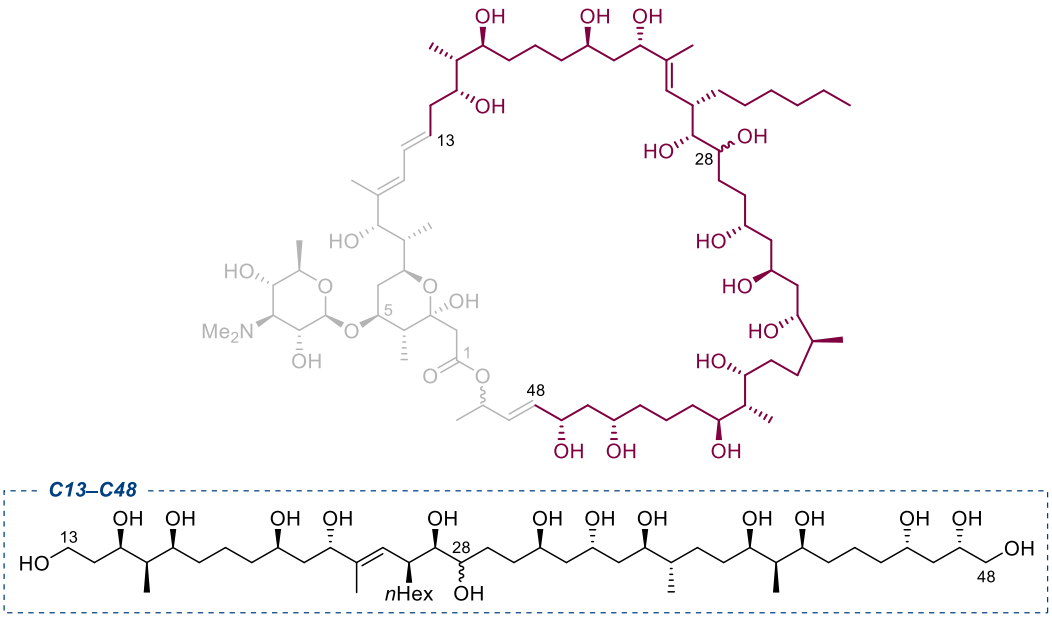
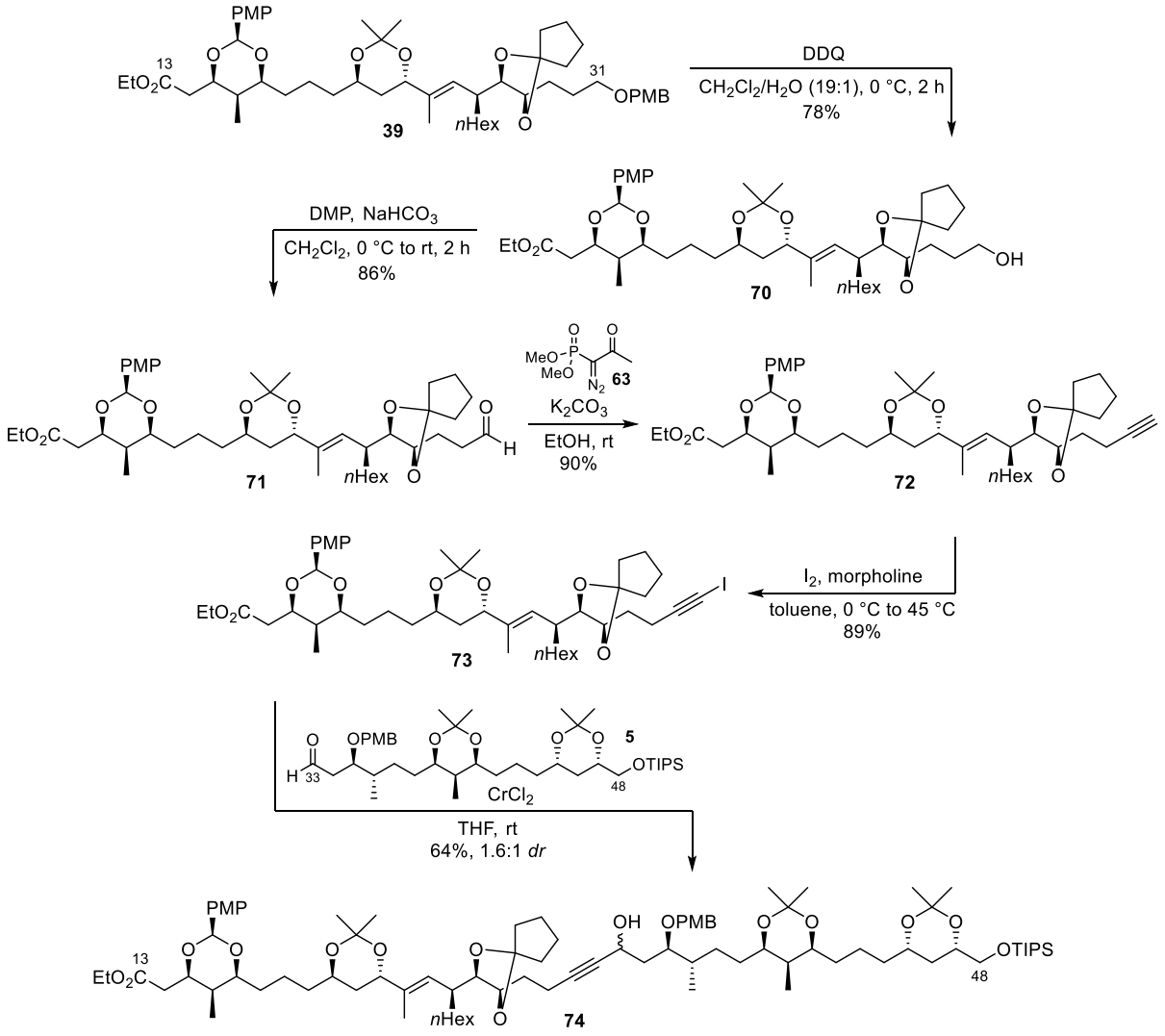


Figure 23: *Stambomycin D and the C13–C48 fragment*

4.1. Synthesis of the C13–C32 fragment and initial coupling with the C33–C48 fragment

The synthesis of the C13–C48 fragment commenced by converting the C13–C31 compound **39** to the corresponding alkyne, setting the stage for coupling with the C33–

C48 aldehyde **5**[xiii] (Scheme 22). As such, the PMB ether of **39** was cleaved with DDQ under hydrolytic conditions to reveal alcohol **70** (78%), which was subsequently oxidised to give aldehyde **71** (86%). Next, homologation of aldehyde **71** to the corresponding alkyne was carried out using the Ohira-Bestmann reagent **63**.[178] When the reaction was performed in methanol, the solvent typically used in this reaction, transesterification to the methyl ester was observed; hence, ethanol was used instead, affording alkyne **72** (90%).



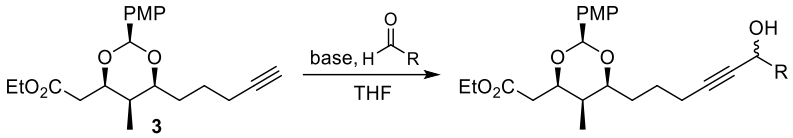
Scheme 22: *Synthesis of C13–C48 propargylic alcohol **74***

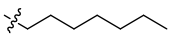
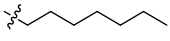
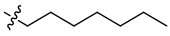
[xiii]Synthesized by Dr. Venkaiah Chintalapudi and DPhil student Yongchen Wang

A Nozaki-Hiyama-Kishi (NHK) reaction[182] was selected as the method of choice for coupling alkyne **72** with the C33–C48 aldehyde **5**, being widely employed in natural product synthesis for its mild conditions and wide functional group tolerance.[183] The chromium-mediated NHK reaction requires an alkynyl iodide; thus alkyne **72** was iodinated to give alkynyl iodide **73** (89%), which was then coupled with the C33–C48 aldehyde **5**, affording propargylic alcohol **74** (64%, 1.6:1 *dr*). Although a moderately good yield was obtained, this result was found to be irreproducible, with the reaction often giving yields of 30–40% in the hands of the author. Despite exercising stringent care with the reaction setup, employing various sources of $CrCl_2$, and adding $NiCl_2$ as a co-catalyst, a good yield could not be reliably obtained, even after multiple attempts. Thus, alternate means of coupling the alkyne with the aldehyde were explored.

For this, the C13–C22 alkyne **3** was employed as a model alkyne for coupling with commercially available tiglic aldehyde or octanal. Their direct coupling was tested using various bases deemed capable of deprotonating the alkyne without causing ring-opening of the PMP acetal. When ethylmagnesium chloride was used, it resulted in addition of the Grignard reagent to the ester, giving the tertiary alcohol instead of the desired coupling product (Table 10, entry 1). With LHMDS, some of the desired product was observed; however, a side product arising from ring-opening of the PMP acetal was formed as the major product. This was the case irrespective of the aldehyde used (entries 2 and 3).

Table 10: *Coupling of alkyne with aldehyde (model studies)*[xiv]

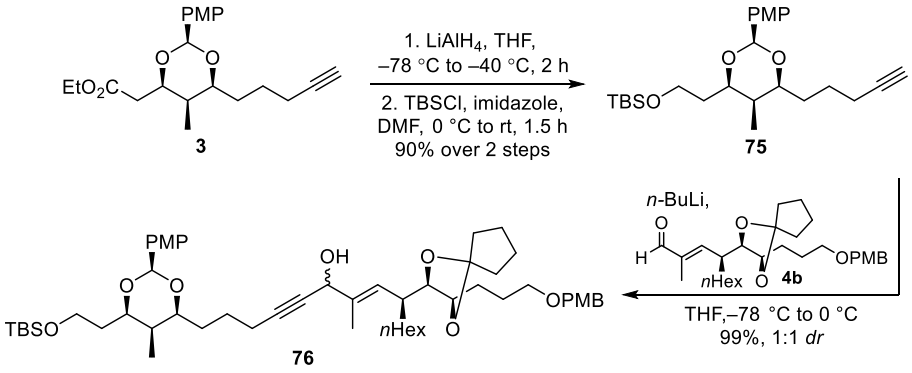


Entry	R	Base	Temperature	Observations / Results
1		EtMgCl	–78 °C to 0 °C	Grignard addition product obtained
2		LHMDS	–78 °C	Ring-opening of PMP acetal observed
3		LHMDS	–78 °C	Ring-opening of PMP acetal observed
4		TMPMgCl•LiCl	–78 °C to 0 °C	Desired product obtained (48%)
5		*t*-BuLi	–78 °C	Ring-opening of PMP acetal observed

[xiv]Reactions were performed on a 20 mg scale; for entry 5, the alkynyl iodide was used instead of the terminal alkyne.

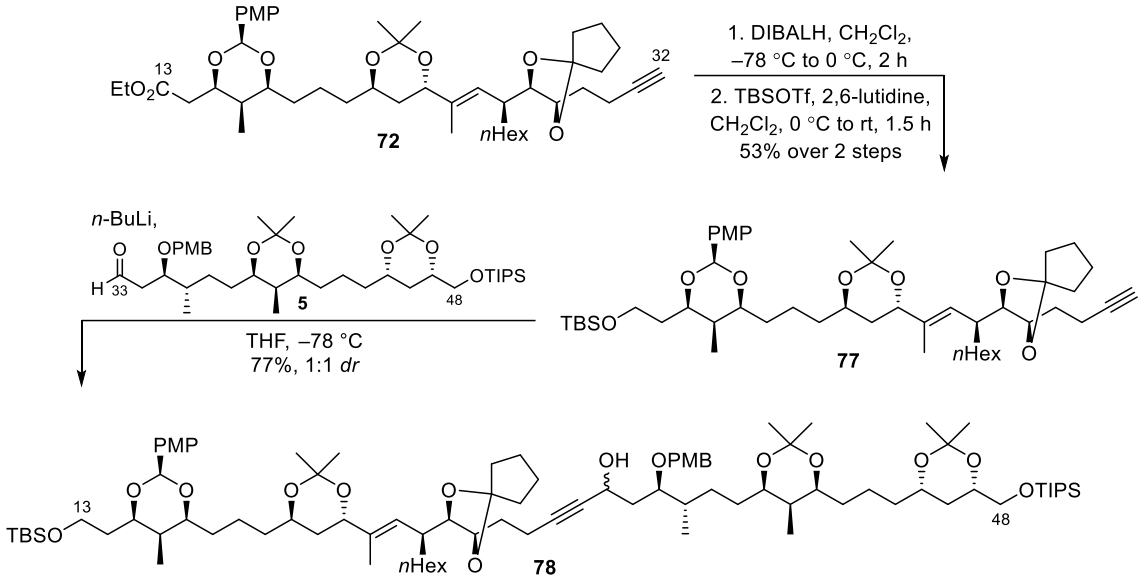
Using TMPMgCl•LiCl, the desired product was obtained in 48% yield, but a substantial amount of the side product from ring-opening of the PMP acetal was also observed (entry 4). Finally, the coupling was attempted via a lithium-halogen exchange using *t*-BuLi and the alkynyl iodide of **3**. Unfortunately, this also gave the PMP acetal ring-opened side product as the major product, along with some of the desired product (entry 5).

Since these attempts at coupling the alkyne with the aldehyde were unsuccessful or low yielding primarily due to ring-opening of the PMP acetal, presumably due to enolisation of the adjacent ester under the basic conditions, it was thought that this problem could be avoided by converting the ester to a silyl ether. The ester of **3** was thus reduced to the alcohol, which was then protected as the TBS ether **75** (90% over two steps; Scheme 23). To test the coupling, *n*-BuLi was employed as the base, and the C23–C31 aldehyde **4b** served as the aldehyde, being more representative of the complexity of the fragment than octanal. Pleasingly, the desired propargylic alcohol **76** was obtained in near quantitative yield (99%).



Scheme 23: *Synthesis of propargylic alcohol* ***76***

With this promising result, the C13–C32 alkyne **72** was similarly converted to the TBS ether **77** (53% over two steps; Scheme 24). Initially, attempts at coupling **77** with aldehyde **5** gave low yields due to the formation of a side product, which formed through elimination of the PMB ether of **5**. It was eventually found that this side reaction could be prevented by maintaining the reaction temperature at –78 °C. This afforded propargylic alcohol **78** in good yield (77%) and proved to be a reliable means of coupling the C13–C32 and C33–C48 fragments.

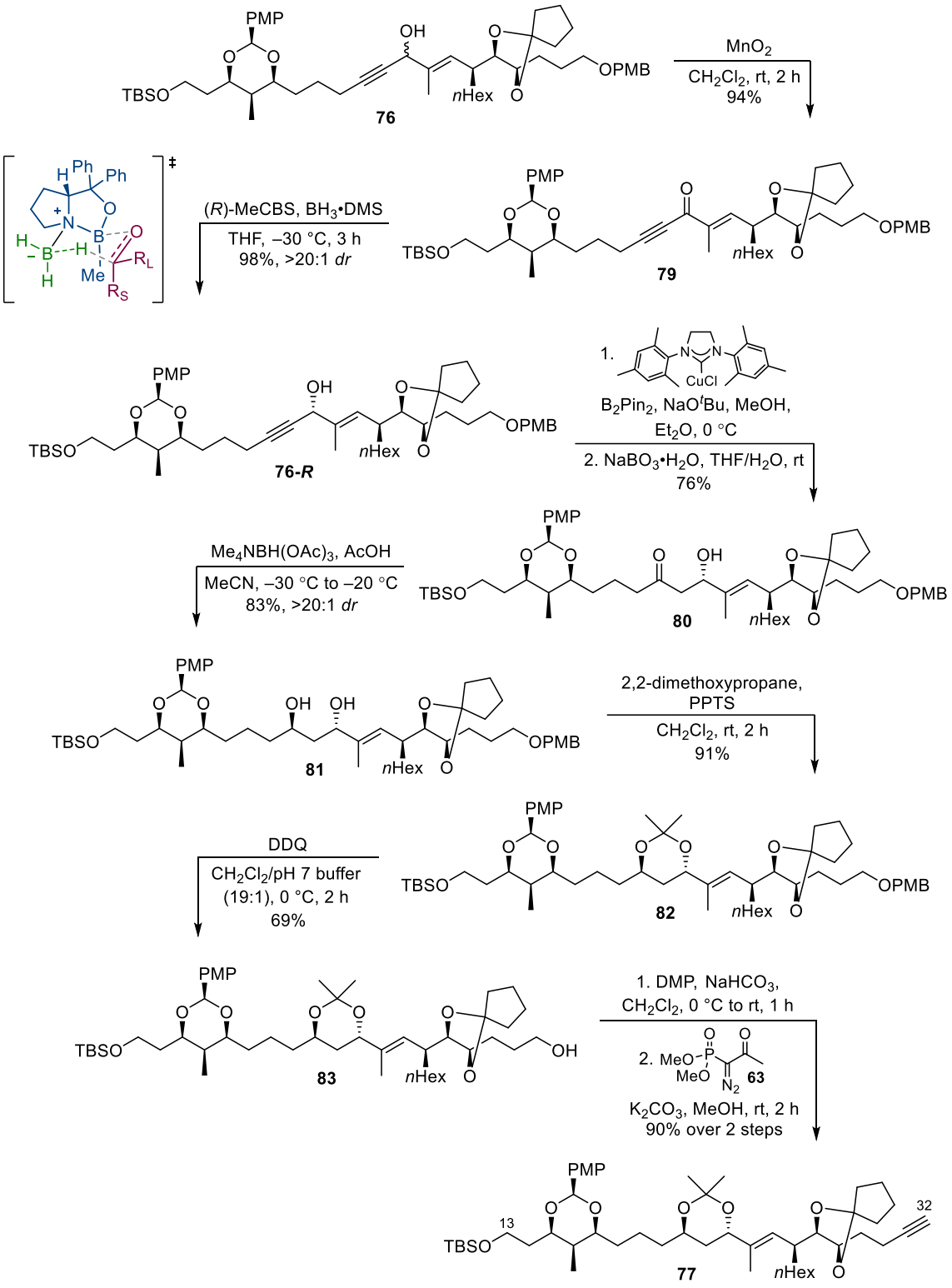


Scheme 24: *Synthesis of C13–C48 propargylic alcohol* ***78***

4.2. Scalable approach to the C13–C32 fragment

With this reliable method of obtaining the C13–C48 framework in hand, it was recognised that this also presented an alternative approach to the C13–C32 alkyne **77**, via propargylic alcohol **76**, which served as a model for the coupling. This slightly modified route was thus explored (Scheme 25), being potentially more scalable than the alternative alkynylzinc route, which employs three equivalents of alkyne—albeit unreacted alkyne is typically recovered. Upon oxidation of alcohol **76**, the resulting ynone **79** (94%) was subjected to a Corey-Bakshi-Shibata (CBS) reduction.[184] In this reaction, the oxazaborolidine catalyst, upon complexation with borane, coordinates to the ketone in a manner which minimises steric interactions between them; hydride transfer from the borane then occurs face-selectively via a six-membered chair transition state in which the "large" group of the ketone is positioned pseudo-equatorial.[185] This afforded propargylic alcohol **76-*R*** (98%, >20:1 *dr*), which matched the diastereomer (**36**) obtained through the alkynylzinc addition reaction (Chapter 2, Scheme 13).

Alcohol **76-*R*** was then carried through the same sequence used to transform alcohol **36** to alkyne **72**. Upon hydroboration-oxidation of **76-*R***, the resulting β-hydroxy ketone **80** (76%) was reduced via an Evans-Saksena reduction[174] to obtain 1,3-*anti* diol **81** (83%, >20:1 *dr*). Diol **81** was protected as the acetonide **82** (91%) and treated with DDQ, which



Scheme 25: *Synthesis of the C13–C32 alkyne* ***77*** *via propargylic alcohol* ***76***

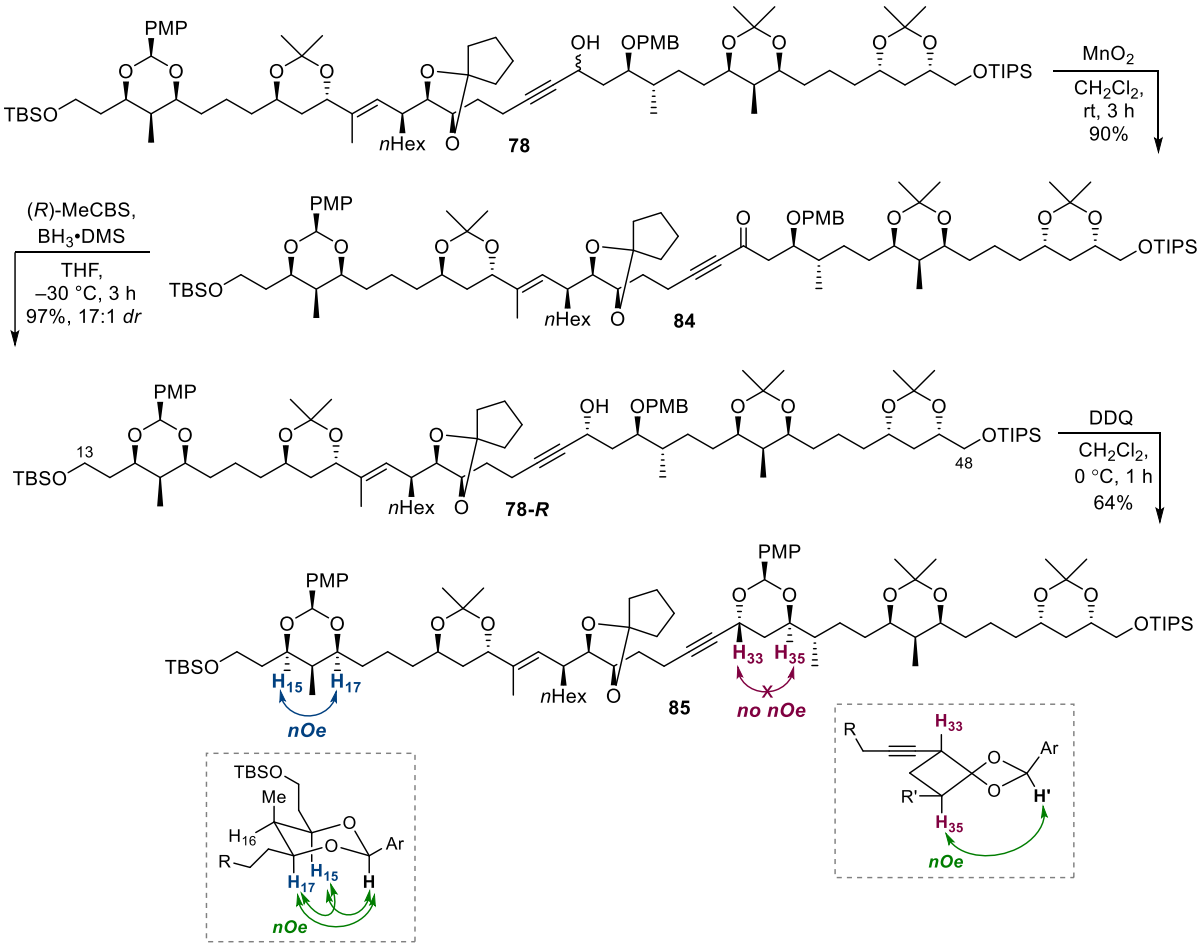
afforded alcohol **83** (69%). Finally, oxidation of the alcohol and alkynylation of the resulting aldehyde with diazophosphonate **63** gave alkyne **77** (90% over two steps).

Overall, this route to alkyne **77** proved to be more scalable than the original approach. Although the non-diastereoselective route to propargylic alcohol **76-*R*** appeared less elegant than the corresponding diastereoselective alkynylzinc addition reaction, the overall yield from the respective C13–C22 alkyne was substantially higher (91% versus 65%). Additionally, it gave alcohol **76-*R*** as a single diastereomer, as compared to the diastereomeric mixture (13:1 *dr*) previously obtained. More importantly, as noted above, while the alkynylzinc addition reaction required three equivalents of the alkyne with respect to the aldehyde, the coupling using *n*-BuLi could be performed with just a slight excess of it. This thus facilitates easier scale-up of the fragment, particularly on a multi-gram scale.

4.3. Completion of the C13–C48 fragments, deprotection, and identification of the C28 stereocentre

With the C13–C48 propargylic alcohol **78** in hand, the diastereomeric mixture was oxidised to the ynone **84** (90%; Scheme 26), following which, an asymmetric reduction was carried out employing the (*R*)-MeCBS catalyst; this afforded propargylic alcohol **78-*R*** (97%, 17:1 *dr*). To establish the stereochemistry of the newly installed C33 hydroxy group, alcohol **78-*R*** was converted to PMP acetal **85** (64%). By placing the C33 and C35 stereocentres in a six-membered ring, their relative stereochemistry could be determined based on NOESY correlations, or the lack thereof, between the protons at those positions. Indeed, the NOESY spectrum of **85** showed an absence of nOe between the protons at C33 and C35 (Figure 24), confirming their *anti* relationship. In contrast, NOESY correlations were observed between the protons at C15 and C17, which were previously also observed in the C13–C22 fragment **3** (Chapter 2). As the C35 stereocentre had been previously determined through Mosher ester analysis,[115] this then established that the C33 hydroxy group was of the desired *R* configuration.

Following this, propargylic alcohol **78-*R*** was converted to the 1,3-*anti* diol using the same strategy employed for the C13–C32 fragment. Firstly, a regioselective hydroboration-oxidation reaction[172] of propargylic alcohol **78-*R*** gave the corresponding β-hydroxy ketone



Scheme 26: *Synthesis of C13–C48 propargylic alcohol* ***78-R*** *and its conversion to PMP acetal* ***85***

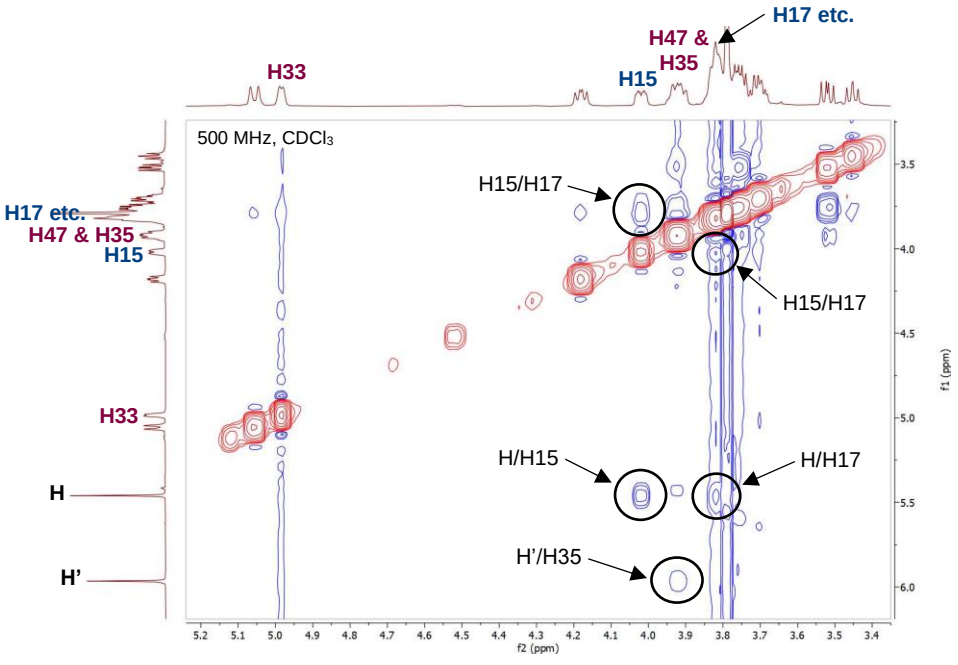
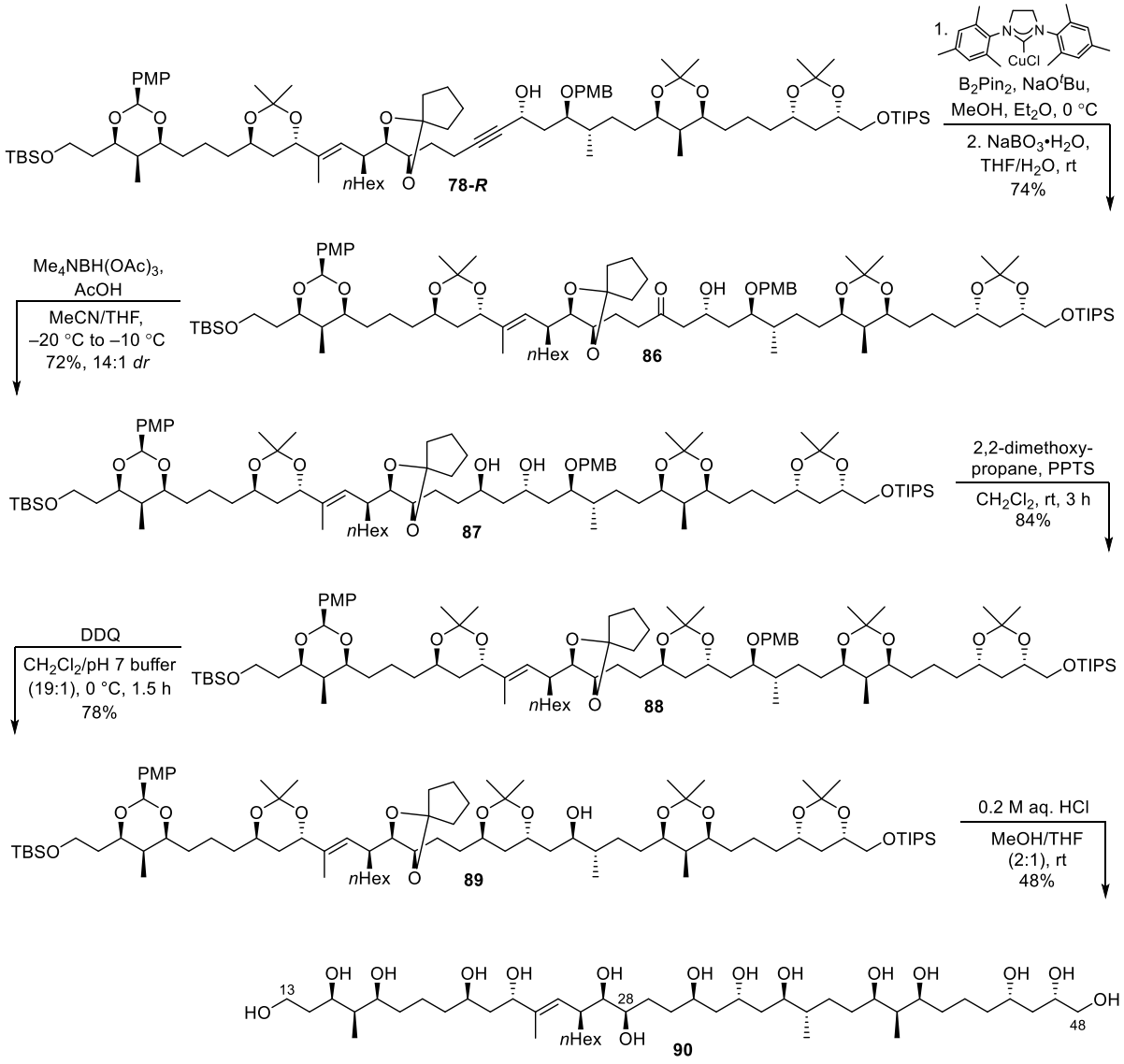


Figure 24: *NOESY spectrum of* ***85***

86 (74%; Scheme 27), which was then reduced via an Evans-Saksena reduction[174] to obtain the 1,3-*anti* diol **87** (72%, 14:1 *dr*). Diol **87** was protected as the acetonide **88** (84%), which also served to confirm the relative stereochemistry of the diol, based on the ^{13}C NMR chemical shifts of the acetonide methyl groups and quaternary acetonide carbon.[123,175] Subsequently, cleavage of the PMB ether of **88** was carried out using DDQ, which afforded alcohol **89** (78%).



Scheme 27: *Synthesis of the C13–C48 (28R) fragment* ***90***

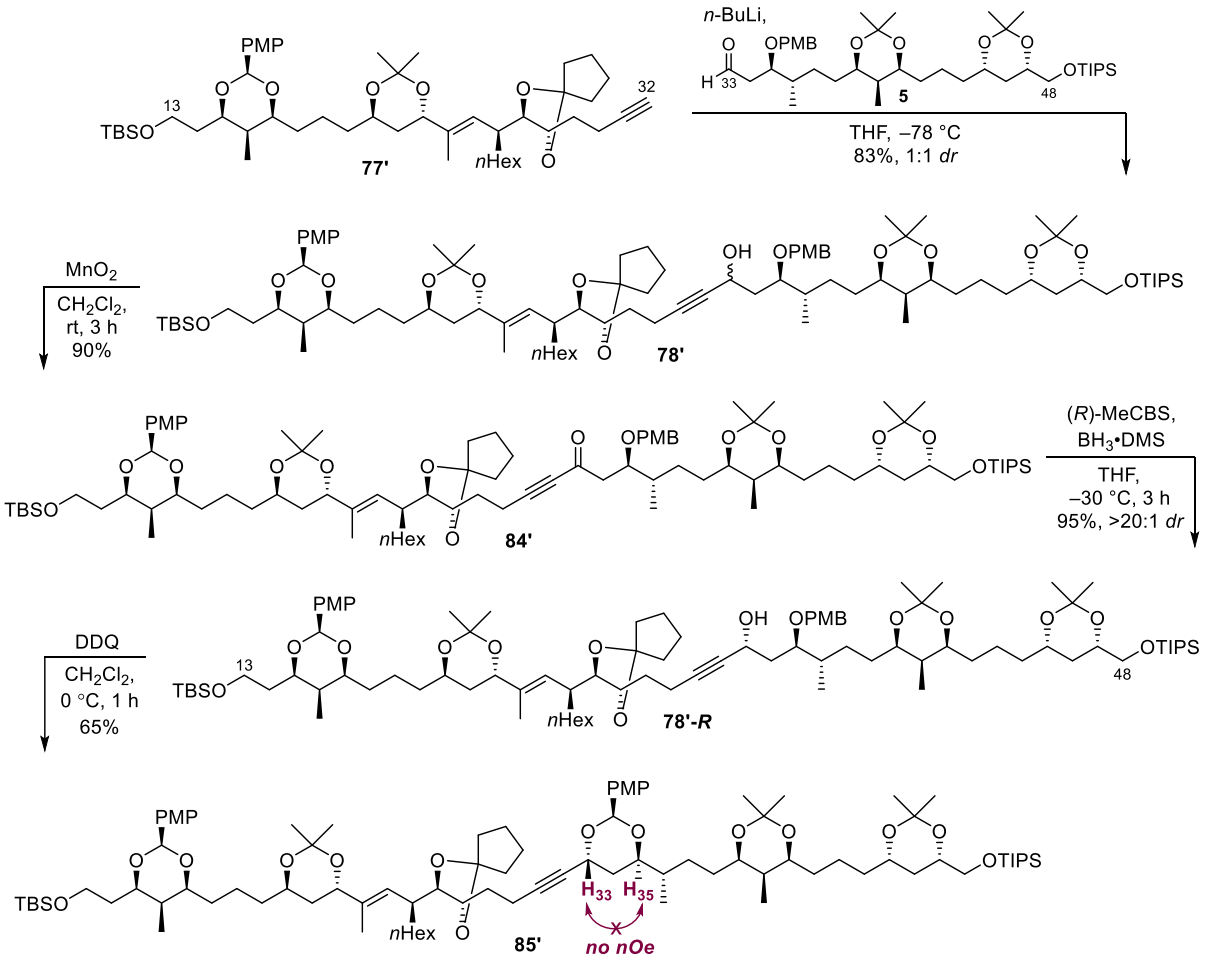
To achieve a global deprotection of **89**, the deprotection conditions optimised for the C1–C27 fragment **67** (Chapter 3) were tested. Using these conditions (0.1 M aqueous HCl in methanol/THF (2:1)), two products were observed after two days, both of which were

formed in similar amounts. These were deduced to be the fully deprotected product and the partially deprotected product (with all protecting groups deprotected, except the 1,2-cyclopentylidene acetal), based on TLC and MS analysis. After four days, the fully deprotected product became the predominant product, with relatively insignificant amounts of the partially deprotected product observed, along with trace amounts of an elimination product, potentially at the C23 allylic alcohol.

Given the long reaction time, deprotection of **89** was also tested using 0.2 M aqueous HCl in methanol/THF (2:1). These slightly harsher conditions were expected to achieve deprotection more efficiently, as with the C13–C31 fragment **40** (Chapter 2), since the fragment did not contain the acid-sensitive C10–C13 diene. Indeed, the reaction time was reduced by half, and the fully deprotected product was formed as the major product after two days. Employing these conditions on a larger (more isolable) scale, it was observed that **89** was not fully soluble in the reaction medium; this resulted in incomplete conversion of the starting material, which was only evident upon workup of the reaction mixture. While increasing the amount of solvent (and acid) improved this minimally, prolonging the reaction time merely resulted in increased formation of the elimination product. It was eventually found that performing the workup and resubmitting the crude product to the reaction conditions overcame this problem, enabling full conversion of the starting material. This afforded the fully deprotected C13–C48 (28*R*) fragment **90** in 48% yield, completing the synthesis of one of the C28 diastereomers of the fragment.

With **90** in hand, synthesis of the other diastereomer, bearing an (*S)*-hydroxy group at C28, was next carried out. Following the same route used to obtain **90**, the C13–C32 alkyne **77'**,[xv] containing an *anti* diol at C27/C28, was coupled with aldehyde **5** to obtain propargylic alcohol **78'** (83%, 1:1 *dr*; Scheme 28). Oxidation of **78'** afforded ynone **84'** (90%), which was reduced using the (*R*)-MeCBS catalyst. The resulting propargylic alcohol **78'-*R*** (95%, >20:1 *dr*) was then treated with DDQ under anhydrous conditions to form PMP acetal **85'** (65%), which served to confirm the stereochemistry of the C33 hydroxy group. Similar to PMP acetal **85**, the NOESY spectrum of **85'** showed a lack of nOe between the protons at C33 and C35, confirming their *anti* relationship.

[xv]Synthesized in a similar manner as alkyne **77** (by Yongchen Wang)



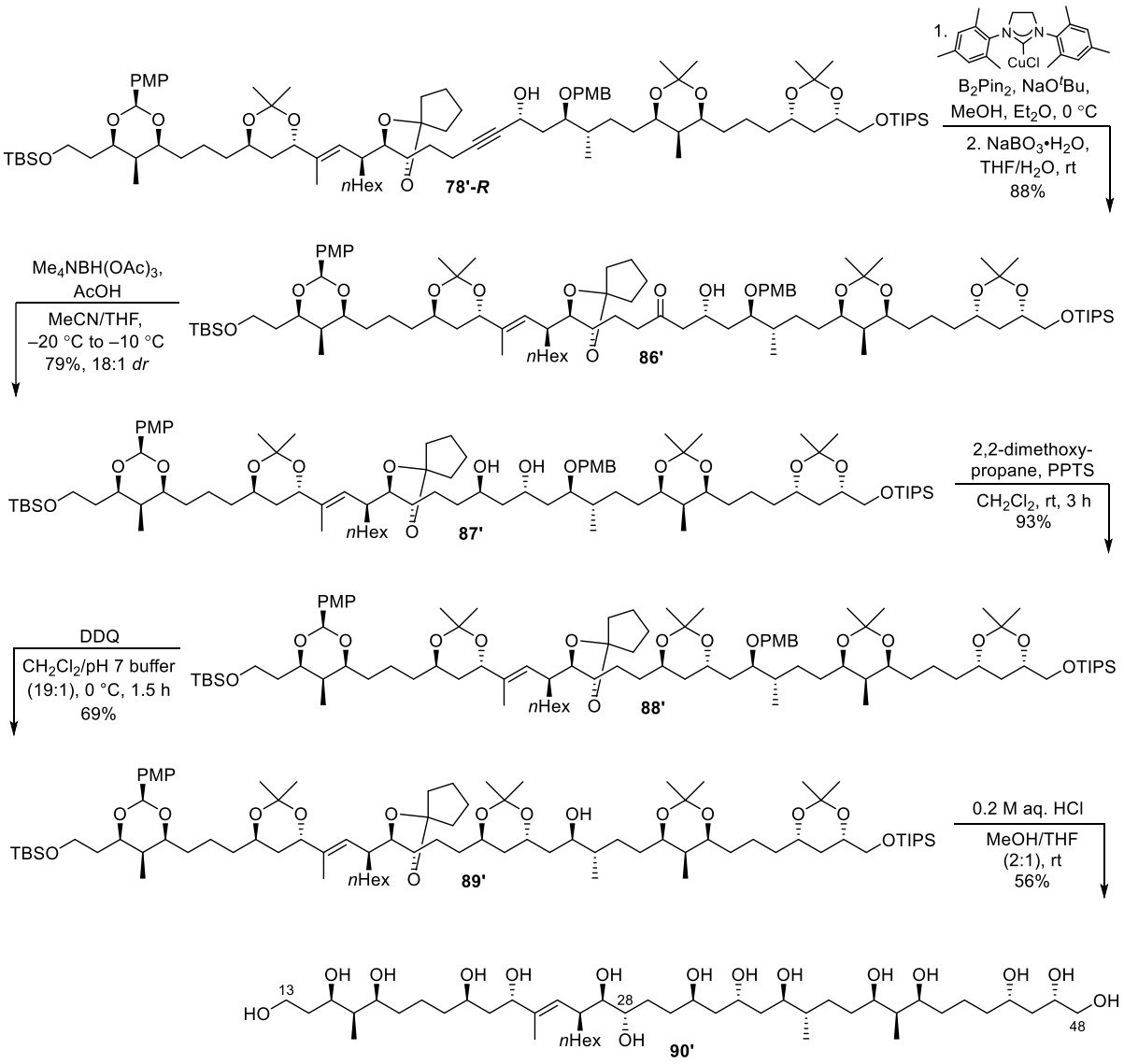
Scheme 28: *Synthesis of C13–C48 propargylic alcohol **78'-R** and its conversion to PMP acetal **85'***

In accordance with the aforementioned synthetic strategy, propargylic alcohol **78'-*R*** was first subjected to a regioselective hydroboration-oxidation reaction,[172] which afforded β-hydroxy ketone **86'** (88%; Scheme 29). This was followed by an Evans-Saksena reduction[174] of **86'** to obtain 1,3-*anti* diol **87'** (79%, 18:1 *dr*), which was protected as the acetonide **88'** (93%). With **88'** in hand, deprotection was carried out, beginning with cleavage of the PMB ether using DDQ. The resulting alcohol **89'** (69%) was then treated with 0.2 M aqueous HCl in methanol/THF (2:1) for a global deprotection.

Notably, deprotection of **89'** was found to proceed significantly faster than that of **89**, with the reaction giving the fully deprotected product cleanly after just 15 hours. This greater lability of the 1,2-*anti* cyclopentylidene acetal in **89'** as compared to the 1,2-*syn* cyclopentylidene acetal in **89** is attributed to the greater torsional strain of the former. This is due to its two bulky substituents being positioned *"syn"* in the five-membered ring, resulting in increased steric interactions, as one of them would need to occupy a pseudo-

axial position. On the other hand, in the 1,2-*syn* acetal, those two substituents are placed *"**anti**"* in the five-membered ring and are both able to occupy pseudo-equatorial positions, which results in a more stable acetal (Figure 25).

As with **89**, when deprotection of **89'** was carried out on a larger scale, two cycles of the reaction were required for full consumption of the starting material, due to solubility issues. This eventually gave the fully deprotected C13–C48 fragment **90'** (56%), completing the synthesis of both C28 diastereomers of the fragment (Figure 26).



Scheme 29: *Synthesis of the C13–C48 (28S) fragment* ***90'***

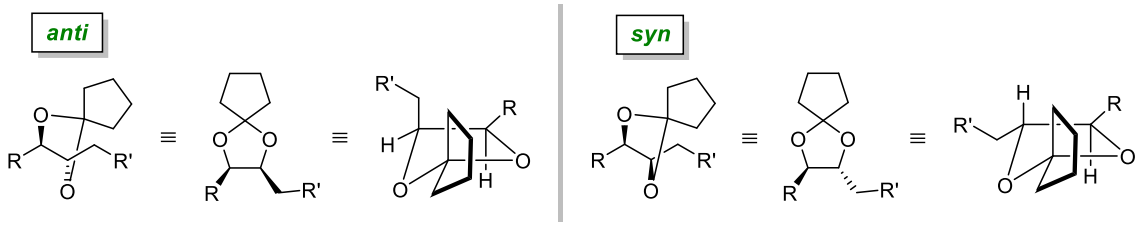


Figure 25: *1,2-anti and 1,2-syn cyclopentylidene acetals*

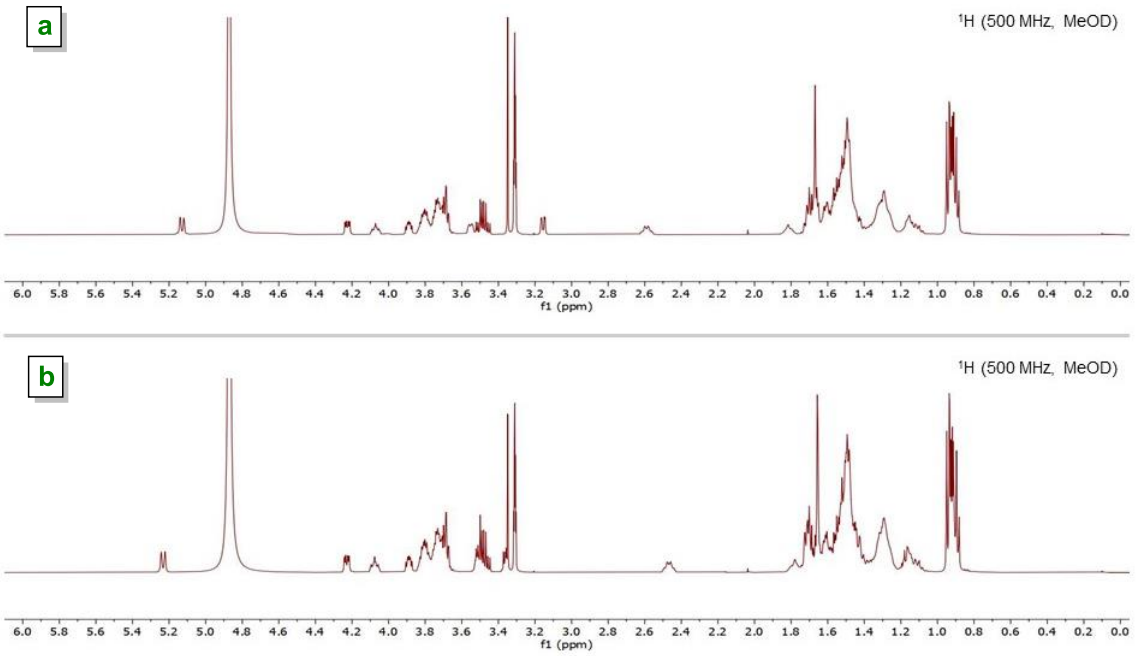


Figure 26: *^{1}H NMR spectra of (a)* ***90*** *and (b)* ***90'***

With both C28 diastereomers of the C13–C48 fragment in hand, their NMR data was compared with the reported data of stambomycin D[138] (Figure 27 and Tables 11–12). Overall, the ^{1}H and ^{13}C NMR data of both diastereomers showed good agreement with that of the natural product. Although significant discrepancies were observed at the regions of truncation, particularly at C13 and C48, this was expected, given the significantly different chemical environments of those carbons in the fragment as compared to the natural product (alkyl versus alkenyl). Additionally, discrepancies were observed at the C19 and C37 protons, as was previously noted in the C1–C27[154] and C33–C51[181] fragments, which revealed that reassignment of those signals in the natural product was needed.

Importantly, examination of the data of the C28 region showed distinct differences between the diastereomers of the C13–C48 fragment. In the case of the 28*R* diastereomer, there was a considerable discrepancy between the ^{13}C NMR data for C28 (72.7 ppm) and that of stambomycin D (74.2 ppm). This discrepancy was even more pronounced for the adjacent C27 and C29 carbons (2.1 and 3.9 ppm difference, respectively; Table 12). On the other hand, for the 28*S* diastereomer, the ^{13}C NMR data for C28 (73.9 ppm) matched closely with that of stambomycin D (74.2 ppm), as well as the aglycon (73.7 ppm). This promising agreement in NMR data was also exhibited by the neighbouring carbons and protons. Given this close alignment in the NMR data of the 28*S* diastereomer and stambomycin D, both in the C28 region and overall, this indicates that the unassigned C28 stereocentre in the natural product is most likely of *S* configuration. Moreover, this remarkable agreement in the NMR data of the fragment and stambomycin D provides further validation of the genomics-based stereochemical assignment of the natural product.

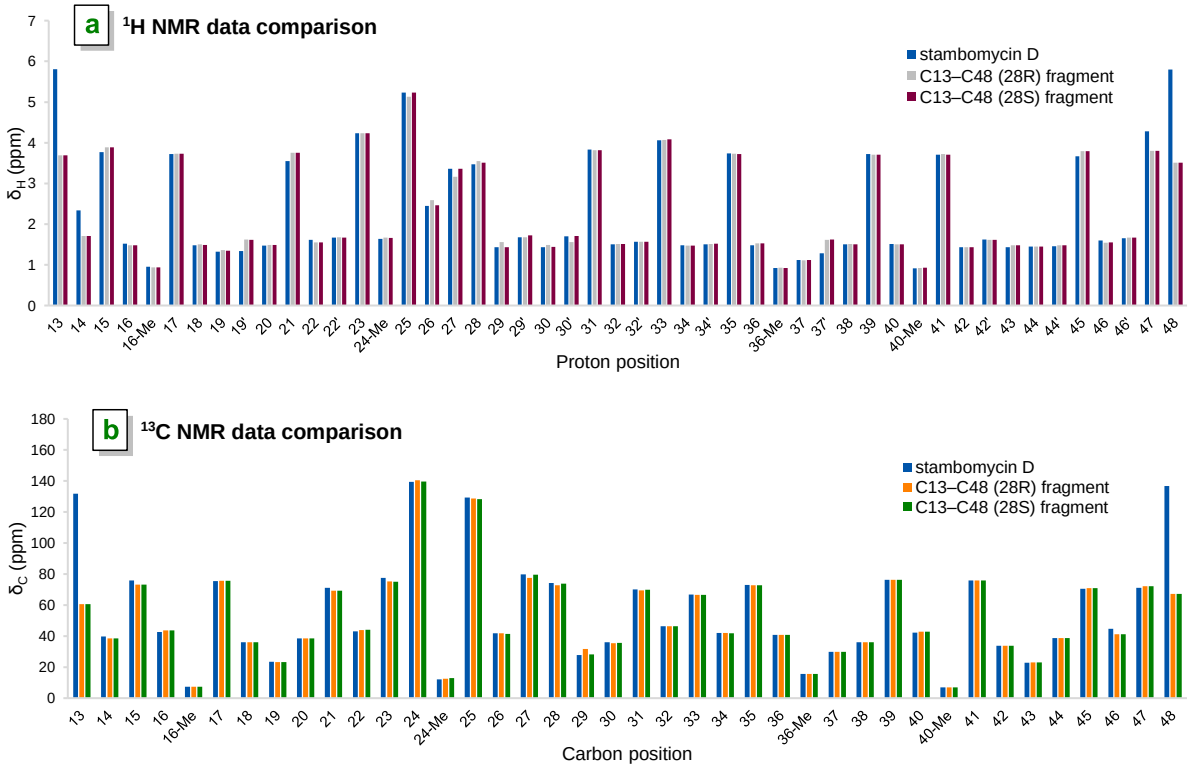
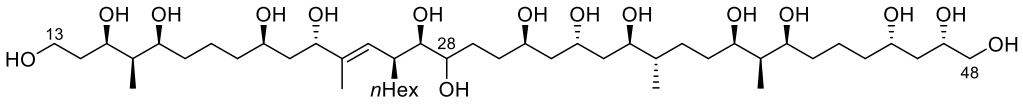


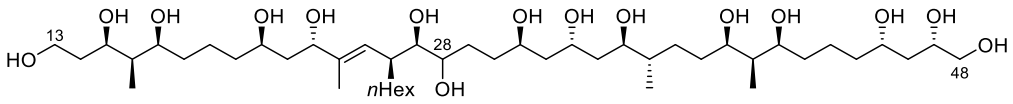
Figure 27: *Graphical comparison of the (a) ^{1}H and (b) ^{13}C NMR data of stambomycin D and the C13–C48 fragments*

Table 11: *NMR data comparison of stambomycin D, the stambomycin D algycon, and the C13–C48 fragments*



	stambomycin D[138] (MeOD, 700 MHz)		stambomycin D aglycon[138] (MeOD, 700 MHz)		C13–C48 (28*R*) fragment (MeOD, 500 MHz)		C13–C48 (28*S*) fragment (MeOD, 500 MHz)	
Position	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)
13	131.7	5.81	131.2	5.79	60.5	3.69	60.5	3.69
14	39.8	2.34	39.6	2.34	38.5	1.71	38.6	1.71
15	75.8	3.77	75.4	3.78	73.2	3.89	73.2	3.89
16	42.6	1.52	42.7	1.53	43.7	1.48	43.7	1.48
16-Me	7.4	0.95	7.3	0.95	7.4	0.94	7.4	0.94
17	75.5	3.72	75.3	3.72	75.6	3.73	75.6	3.73
18	36.1	1.48	36.0	1.48	36.1	1.50	36.1	1.49
19	23.5	1.32, 1.34	23.1	1.32	23.3	1.36, 1.62	23.2	1.35, 1.61
20	38.5	1.47	38.4	1.45	38.6	1.49	38.5	1.49
21	71.1	3.55	70.6	3.54	69.3	3.75	69.3	3.75
22	43.1	1.61, 1.67	42.8	1.61, 1.67	43.9	1.55, 1.68	44.0	1.55, 1.67
23	77.5	4.23	77.1	4.23	75.3	4.23	75.1	4.23
24	139.4		138.6		140.5		139.7	
24-Me	12.2	1.64	12.1	1.66	12.6	1.67	12.9	1.66
25	129.3	5.23	129.4	5.22	128.7	5.13	128.2	5.23
26	41.9	2.45	41.6	2.44	41.9	2.59	41.5	2.46
27	79.7	3.36	79.4	3.36	77.6	3.16	79.6	3.36
28	74.2	3.47	73.7	3.47	72.7	3.55	73.9	3.51
29	27.8	1.43, 1.68	27.6	1.44, 1.67	31.7	1.56, 1.68	28.3	1.43, 1.72
30	36.1	1.43, 1.70	35.7	1.43, 1.71	35.4	1.49, 1.56	35.7	1.44, 1.71
31	70.1	3.83	69.5	3.83	69.4	3.82	69.8	3.82
32	46.4	1.50, 1.57	46.0	1.51, 1.57	46.4	1.51, 1.57	46.3	1.51, 1.57
33	66.8	4.06	66.4	4.07	66.6	4.07	66.6	4.08
34	42.0	1.48, 1.50	41.6	1.47, 1.51	42.0	1.47, 1.51	41.9	1.47, 1.52
35	72.9	3.74	72.6	3.75	72.8	3.73	72.8	3.72
36	40.8	1.48	41.6	1.49	40.7	1.53	40.7	1.53
36-Me	15.6	0.92	15.6	0.93	15.7	0.93	15.7	0.92
37	29.8	1.12, 1.28	30.5	1.13, 1.29	29.8	1.11, 1.61	29.8	1.12, 1.62
38	36.0	1.50	35.9	1.50	36.0	1.51	36.0	1.50
39	76.3	3.72	76.0	3.71	76.3	3.71	76.3	3.71
40	42.3	1.51	42.1	1.51	42.8	1.50	42.8	1.50
40-Me	7.0	0.91	6.8	0.91	7.0	0.92	7.0	0.93
41	75.9	3.71	75.5	3.71	75.9	3.72	75.9	3.71
42	33.8	1.43, 1.62	33.4	1.44, 1.62	33.7	1.43, 1.61	33.8	1.43, 1.61
43	22.9	1.43	22.7	1.45	23.0	1.48	23.0	1.48
44	38.8	1.45, 1.46	39.1	1.47, 1.51	38.8	1.45,1.48	38.8	1.45, 1.48
45	70.6	3.67	70.4	3.68	71.0	3.79	71.0	3.79
46	44.8	1.60, 1.65	44.7	1.60, 1.63	41.3	1.54, 1.67	41.2	1.55, 1.67
47	71.1	4.28	70.7	4.28	72.1	3.80	72.1	3.80
48	136.7	5.80	136.5	5.78	67.2	3.46, 3.51	67.2	3.46, 3.51

Table 12: *^{13}C NMR shift differences between stambomycin D and the C13–C48 fragments*



	stambomycin D[138] (MeOD, 700 MHz)	**C13–C48 (28*R*) fragment (MeOD, 500 MHz)**		**C13–C48 (28*S*) fragment (MeOD, 500 MHz)**	
Position	δ_C (ppm)	δ_C (ppm)	$\lvert\Delta\delta_C\rvert$ (ppm)	δ_C (ppm)	$\lvert\Delta\delta_C\rvert$ (ppm)
13	131.7	60.5	*71.2*	60.5	*71.2*
14	39.8	38.5	*1.3*	38.6	*1.2*
15	75.8	73.2	*2.6*	73.2	*2.6*
16	42.6	43.7	*1.1*	43.7	*1.1*
16-Me	7.4	7.4	*0.0*	7.4	*0.0*
17	75.5	75.6	*0.1*	75.6	*0.1*
18	36.1	36.1	*0.0*	36.1	*0.0*
19	23.5	23.3	*0.2*	23.2	*0.3*
20	38.5	38.6	*0.1*	38.5	*0.0*
21	71.1	69.3	*1.8*	69.3	*1.8*
22	43.1	43.9	*0.8*	44.0	*0.9*
23	77.5	75.3	*2.2*	75.1	*2.4*
24	139.4	140.5	*1.1*	139.7	*0.3*
24-Me	12.2	12.6	*0.4*	12.9	*0.7*
25	129.3	128.7	*0.6*	128.2	*1.1*
26	41.9	41.9	*0.0*	41.5	*0.4*
27	79.7	77.6	*2.1*	79.6	*0.1*
28	74.2	72.7	*1.5*	73.9	*0.3*
29	27.8	31.7	*3.9*	28.3	*0.5*
30	36.1	35.4	*0.7*	35.7	*0.4*
31	70.1	69.4	*0.7*	69.8	*0.3*
32	46.4	46.4	*0.0*	46.3	*0.1*
33	66.8	66.6	*0.2*	66.6	*0.2*
34	42.0	42.0	*0.0*	41.9	*0.1*
35	72.9	72.8	*0.1*	72.8	*0.1*
36	40.8	40.7	*0.1*	40.7	*0.1*
36-Me	15.6	15.7	*0.1*	15.7	*0.1*
37	29.8	29.8	*0.0*	29.8	*0.0*
38	36.0	36.0	*0.0*	36.0	*0.0*
39	76.3	76.3	*0.0*	76.3	*0.0*
40	42.3	42.8	*0.5*	42.8	*0.5*
40-Me	7.0	7.0	*0.0*	7.0	*0.0*
41	75.9	75.9	*0.0*	75.9	*0.0*
42	33.8	33.7	*0.1*	33.8	*0.0*
43	22.9	23.0	*0.1*	23.0	*0.1*
44	38.8	38.8	*0.0*	38.8	*0.0*
45	70.6	71.0	*0.4*	71.0	*0.4*
46	44.8	41.3	*3.5*	41.2	*3.6*
47	71.1	72.1	*1.0*	72.1	*1.0*
48	136.7	67.2	*69.5*	67.2	*69.5*

5. The C1–C51 fragment

Having established the effectiveness of the deprotection conditions for the C13–C48 fragment, they were finally examined in the context of the full-length C1–C51 fragment (Figure 28), in a culmination of the deprotection studies carried out on the various fragments. This was achieved using the 28*S* diastereomer of the fragment, since the C28 stereocentre was identified to most likely be of *S* configuration. In this chapter, the synthesis and deprotection of this fragment are described, concluding with a summary of the work achieved in this thesis, as well as future directions for the project.

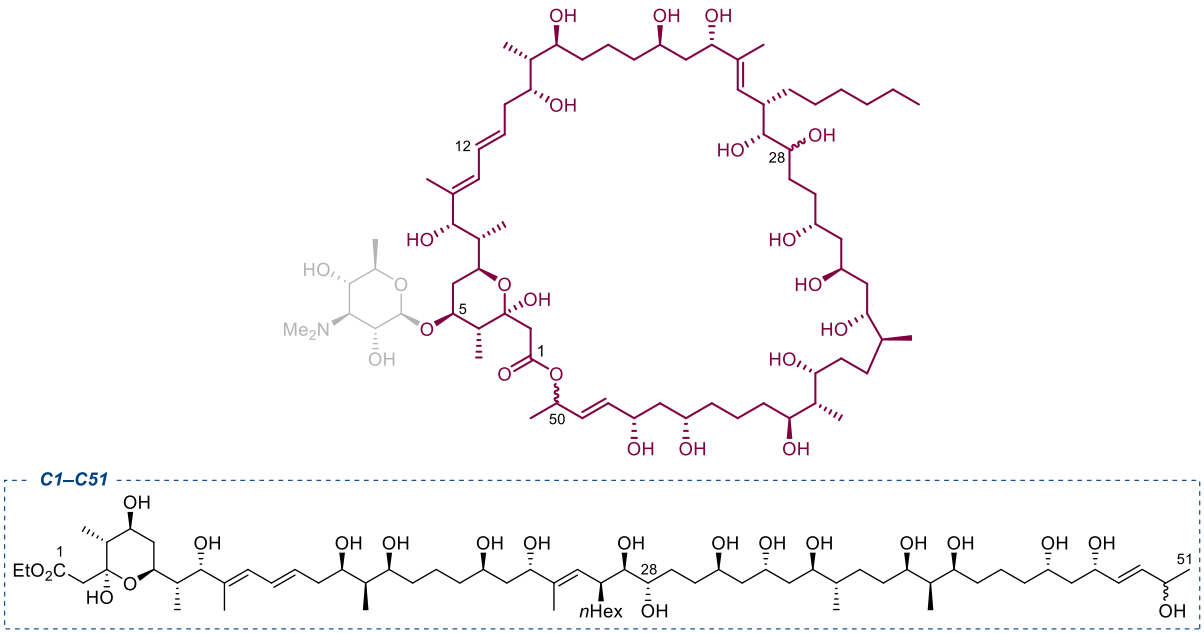


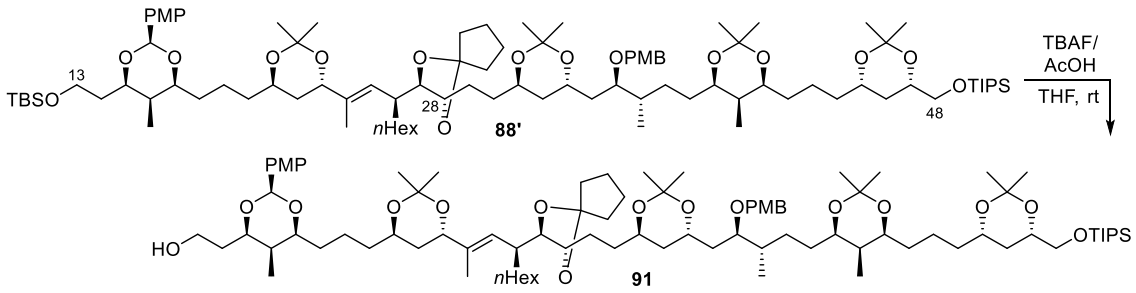
Figure 28: *Stambomycin D and the C1–C51 fragment*

5.1. Synthesis and deprotection of the C1–C51 fragment

To achieve the C1–C51 fragment, the C13–C48 compound **88'** was subjected to a chemoselective deprotection of the TBS ether for further manipulation of the primary alcohol. This was initially attempted using TBAF buffered with acetic acid in a 1:1 ratio (1.0 equivalent each with respect to **88'**; Table 13, entry 1). Under these conditions, the reaction was observed to be rather sluggish; after 16 hours, some product was observed,

but there was still a significant amount of starting material remaining. Upon isolation, the product was obtained in 29% yield, with **88'** recovered in 62% yield. Pleasingly, the product proved to be the desired TBS-deprotected alcohol **91**, although it was in a 9:1 mixture with the TIPS-deprotected alcohol, which evidently had the same R_f as **91**. Since the conversion of **88'** was poor, the reaction time was prolonged to 36 hours (entry 2). Unfortunately, this improved the yield only marginally (38%), owing to the formation of the over-deprotected product (not isolated); the starting material moreover remained unconsumed (33%). Curiously, the product was obtained as a 1.4:1 mixture of the TBS- and TIPS-deprotected alcohols, suggesting that selectivity for the TBS ether decreased over time, or that deprotection of the TBS-deprotected alcohol to the diol occurred more rapidly than deprotection of **88'** or the TIPS-deprotected alcohol.

Table 13: *Screening of conditions for chemoselective deprotection of the TBS ether*[xvi]



Entry	TBAF/ AcOH (eq.)	Reaction time	Recovered 88'	Yield	Ratio of TBS-:TIPS-deprotected alcohols
1	1:1	16 h	62%	29%	9:1
2	1:1	36 h	33%	38%	1.4:1
3	1:0.3	3 h	25%	51%	1:17
4	1:1.5	36 h	10%	44%	18:1
5	1:2	24 h	13%	57%	27:1
6	1:2	17 h	24%	72%	29:1
7	1:3	18 h	19%	46%	24:1

[xvi]Reactions were mostly performed on a 10–15 mg scale. In all cases, the over-deprotected product was observed (in varying amounts) but was not isolated.

Following this, the amount of acetic acid was reduced to 0.3 equivalents (entry 3). This significantly improved the conversion of **88'**, giving the product in 51% yield after just three hours, with a small amount of the over-deprotected product also formed, and **88'** recovered in 25% yield. However, the product was obtained as a 1:17 mixture of the TBS- and TIPS-deprotected alcohols. This suggested that, strangely, the chemoselectivity of the reaction is reversed when the amount of acetic acid is less than that of TBAF. As such, the amount of acetic acid was increased to 1.5 equivalents (entry 4). After 17 hours,

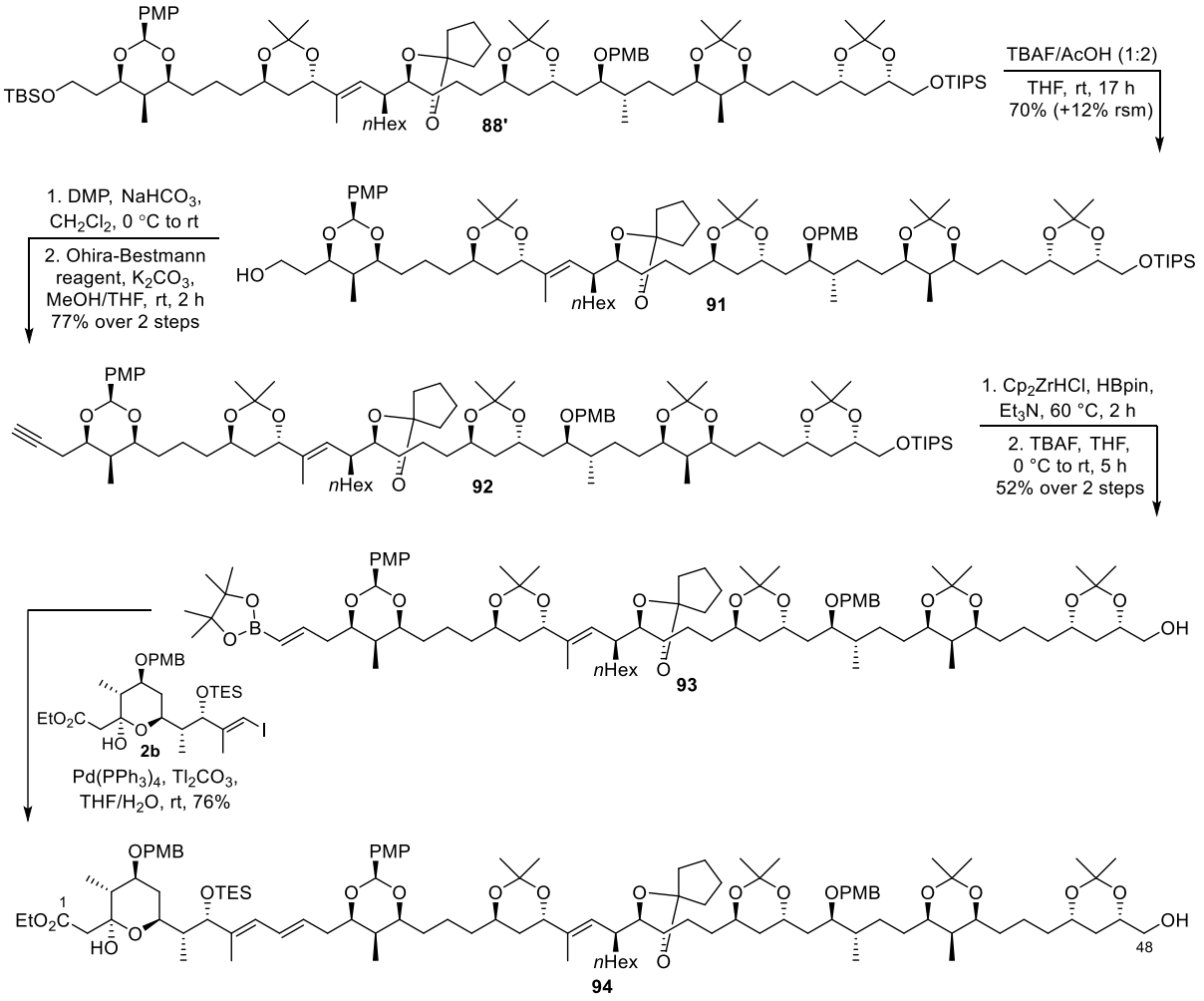
some product was formed, but as the conversion of **88'** appeared to be less than 50%, the reaction time was extended to 36 hours. This gave alcohol **91** in 44% yield, with **88'** recovered in 10% yield. Remarkably, there was a significant improvement in the ratio of the TBS- and TIPS-deprotected alcohols (18:1), despite the prolonged reaction time.

Thus, the amount of acetic acid was further increased to 2.0 equivalents (entry 5). This further improved the selectivity for the TBS ether. After 24 hours, alcohol **91** was obtained in 57% yield, in a 27:1 ratio with the TIPS-deprotected alcohol, and **88'** was recovered in 13% yield. To minimise the formation of the over-deprotected product, the reaction time was reduced to 17 hours (entry 6). Pleasingly, this improved the yield of **91** to 72%, as well the ratio with respect to the TIPS-deprotected alcohol (29:1); it also enabled a better recovery of **88'** (24%). Finally, the amount of acetic acid was increased to 3.0 equivalents (entry 7). Interestingly, this resulted in a decrease in both the yield and the ratio of the TBS- to TIPS-deprotected alcohols. After 18 hours, alcohol **91** was obtained in 46% yield, in a 24:1 ratio with the TIPS-deprotected alcohol; and **88'** was recovered in 19% yield.

With these results, the selective deprotection of the TBS ether of **88'** was carried out using TBAF buffered with acetic acid in 1:2 equivalents for 17 hours. This afforded alcohol **91** in 70% yield, with **88'** recovered in 12% yield (Scheme 30). Upon oxidation of alcohol **91**, the resulting aldehyde was alkynylated using the Ohira-Bestmann reagent.[178] Similar to the C1–C27 aldehyde **62** (Chapter 3), the PMP acetal adjacent to the aldehyde was prone to ring-opening under the mildly basic reaction conditions; thus, an excess of the reagent was required to minimise this side reaction. This gave alkyne **92** in 77% yield over two steps. To avoid this need for an excess amount of the reagent, alkynylation of the aldehyde was also attempted using the Colvin rearrangement ($TMSCHN_2$, *n*-BuLi).[186] However, this gave alkyne **92** in a significantly lower yield (32% over two steps), with several side products moreover observed.

With alkyne **92** in hand, it was subjected to a stereoselective zirconium-mediated hydroboration reaction,[179] which furnished the (*E*)-vinylboronic ester. This was then treated with TBAF buffered with acetic acid, in 1:0.3 equivalents, to cleave the TIPS ether, since these conditions proved effective in deprotecting the TIPS ether in **88'**. Curiously, no reaction was observed, even after three hours. Hence, TBAF was directly used, which afforded vinylboronic ester **93** (52% over two steps); this was primed for coupling with the C1–C11 fragment. Given the issues with deprotection of the C1–C27 compound **66**

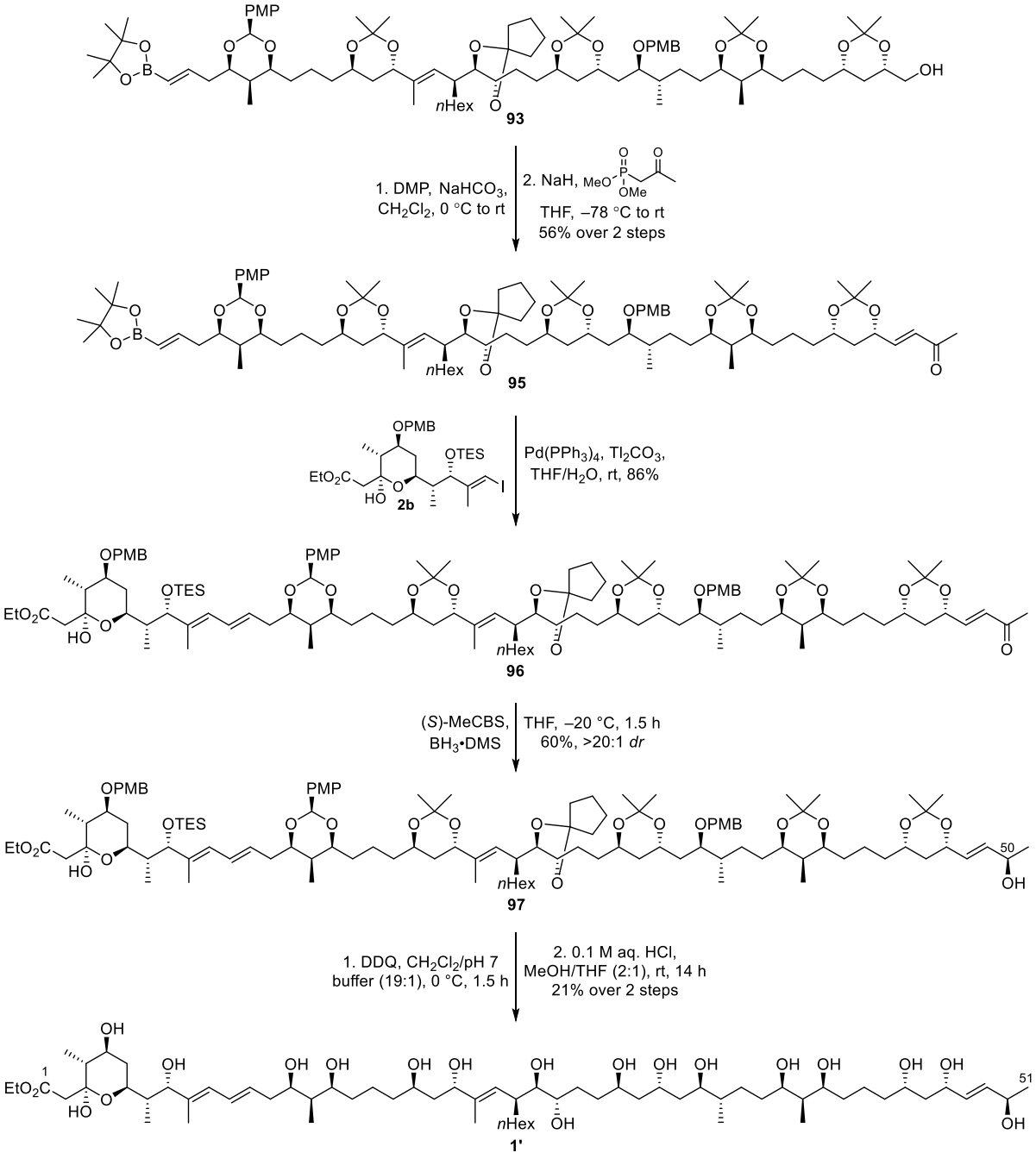
(Chapter 3), which contained the TBS-protected C1–C11 fragment **2a**, it was anticipated that using the TES-protected fragment **2b** instead would facilitate easier deprotection of the target C1–C51 fragment. A Suzuki coupling of vinylboronic ester **93** with the C1–C11 fragment **2b** was thus carried out using the reaction conditions established for the C1–C27 fragment; this afforded the C1–C48 alcohol **94** (76%).



Scheme 30: *Synthesis of C1–C48 compound* ***94***

To complete the C1–C51 framework, alcohol **94** was oxidised to the aldehyde for a subsequent olefination to the enone. However, oxidation of **94** appeared sluggish and difficult to monitor by TLC; moreover, the aldehyde seemed prone to degradation, presumably due to the acid-sensitive diene. Thus, the enone was installed on **93** instead, prior to coupling with the C1–C11 fragment, as it was envisioned that this would potentially enable a more robust route to the C1–C51 fragment (Scheme 31). Upon oxidation of **93**, the resulting aldehyde was subjected to a Horner-Wadsworth-Emmons olefination[152] to

obtain enone **95** (56% over two steps). A Suzuki coupling of **95** with the C1–C11 fragment **2b** was then carried out, affording the C1–C51 compound **96** (86%). With **96** in hand, it presented the opportunity for both C50 diastereomers to be obtained, via asymmetric reduction of the enone. Employing the (*S*)-MeCBS catalyst, the enone was reduced to the enol **97** (60%, >20:1 *dr*), giving one of the two possible C50 diastereomers. The stereochemistry of the alcohol was assigned based on the CBS mnemonic.[184,185]



Scheme 31: *Completion of the C1–C51 fragment* ***1'***

Having obtained **97**, its deprotection was carried out, beginning with cleavage of the PMB ethers using DDQ. This proceeded smoothly, albeit also achieving partial deprotection of the TES ether, giving the desired product as a ~7:1 mixture with the TES-deprotected product. This was then subjected to a global deprotection, employing the deprotection conditions optimised for the acid-sensitive C10–C13 diene. Upon treatment of the mixture of products with these conditions (0.1 M aqueous HCl in methanol/THF (2:1)), a single major product was observed after 14 hours. This was deduced to be the desired fully-deprotected product, based on TLC and MS analysis. Notably, it was observed that upon workup of the reaction, the crude product gradually converted to another product over time; this became the predominant product after a day (in the freezer), with a few minor side products also observed. Based on the polarity of the new product, it was presumed that hydrolysis of the ester to the acid had occurred, potentially under the mildly basic workup condition ($NaHCO_3$). Thus, it appeared crucial to purify the product immediately after the reaction workup in order to retain the ethyl ester.

With these observations, deprotection was carried out using the little amount of the PMB-deprotected **97** left in hand (2.9 mg). Upon subjecting this to 0.1 M aqueous HCl in methanol/THF (2:1) for 14 hours, it was purified immediately upon workup, giving the fully-deprotected C1–C51 fragment **1'** (21% over two steps). Gratifyingly, not only did HRMS confirm that the 1,2-cyclopentylidene acetal was successfully cleaved (along with the other acetals), but the ^{1}H NMR spectrum also showed that the acid-sensitive C10–C13 diene, as well as the C24/C25 and C48/C49 alkenes, remained fully intact (Figure 29). This highlighted the effectiveness of the deprotection conditions. Although the scarce amount of **1'** in hand precluded full characterisation and assignment of the ^{1}H and ^{13}C NMR signals, the ^{1}H NMR spectrum nonetheless showed a pleasing resemblance to that of the stambomycin D aglycon[138] (Figure 30). This promising result thus sets the stage for completion of the target macrocycle.

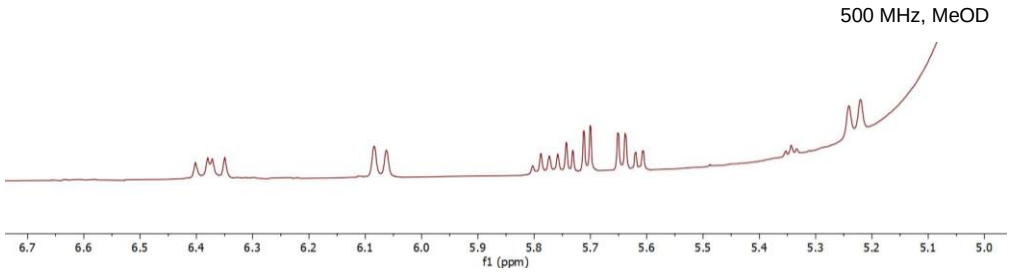


Figure 29: *Alkene region of the ^{1}H NMR spectra of **1'***

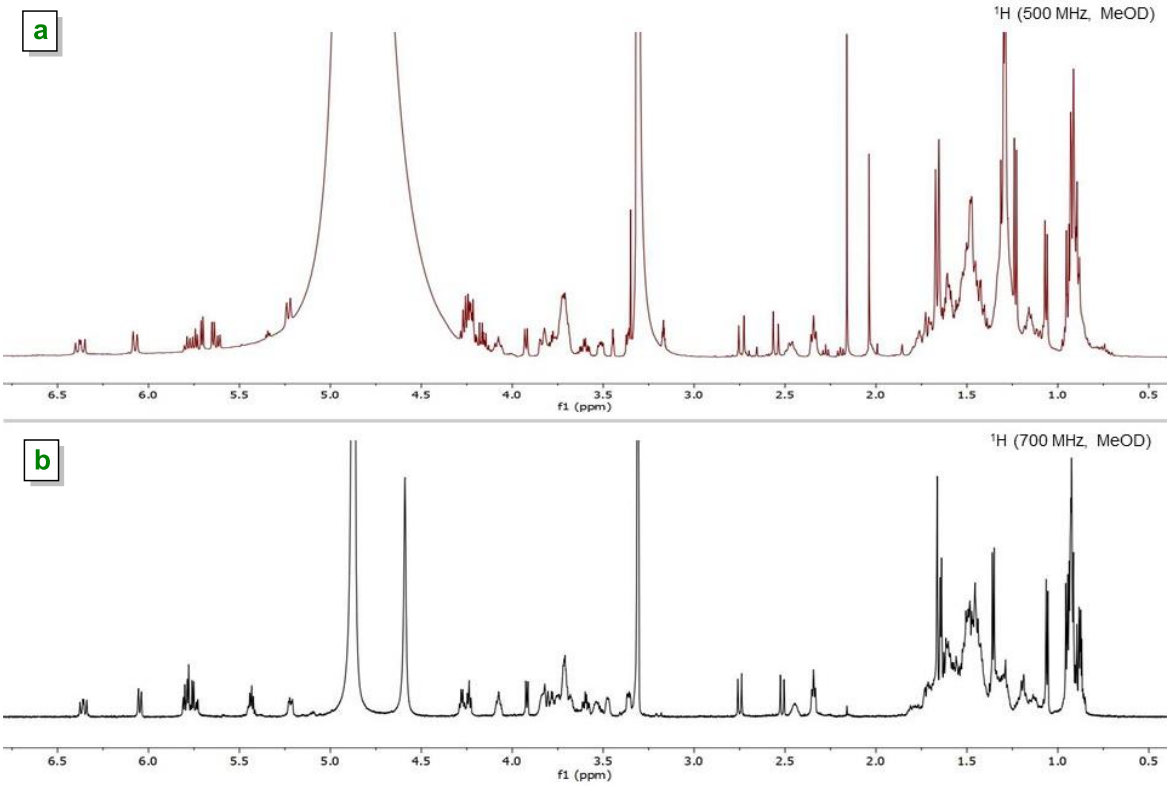


Figure 30: *^{1}H NMR spectra of the (a) C1–C51 fragment **1'** and (b) stambomycin C/D aglycons (spectrum provided by Prof. Gregory Challis and Dr. Lijiang Song)*

5.2. Conclusions and future work

In summary, the synthesis of the stambomycin D aglycon was undertaken to validate the genomics-based stereochemical assignment of the natural product. This was carried out through the assembly of four key building blocks: the C1–C11, C13–C22, C23–C31, and C33–C48 fragments.

Synthesis of the C23–C31 fragment **4b** (Figure 31), bearing a *syn* diol at C27/C28, was achieved in 13 steps from octanal (13% overall yield), employing an enantioselective organocatalytic aldol reaction[155] and a Sharpless asymmetric dihydroxylation reaction[157] to install the hexyl-bearing stereocentre and *syn* diol, respectively. Deprotection studies on the fragment enabled the identification of mild conditions to cleave the 1,2-acetal, one of the two "problem spots" which had hindered deprotection of the stambomycin chain, in previous work in the group. The C13–C22 fragment **3** was next prepared in 6 steps from 5-hexynal (26% overall yield), utilising a Leighton crotylation reaction[162] and a Mukaiyama aldol reaction[168] to install the methyl- and hydroxy-bearing stereocentres. An alternate route to the fragment via an Evans aldol reaction[164] was also explored but proved to be lower yielding. Fragments **3** and **4b** were then combined to construct the C13–C31 fragment **39** (Figure 32), which facilitated further deprotection studies on the 1,2-acetal and enabled refinement of the deprotection conditions.

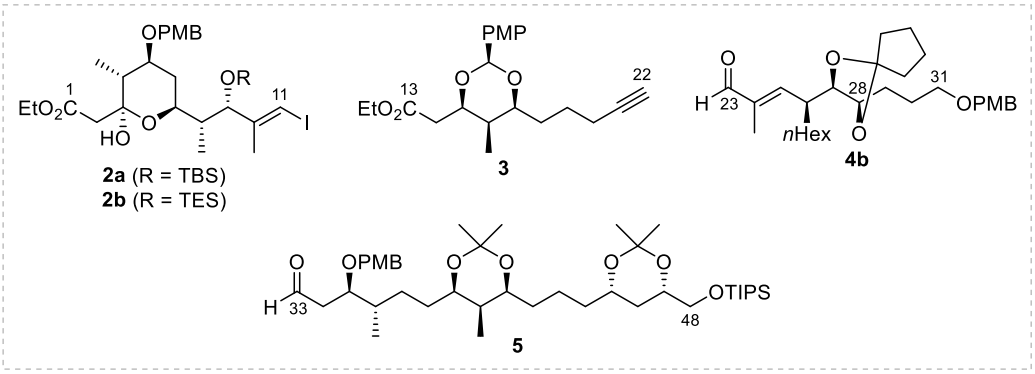


Figure 31: *Building blocks to stambomycin D*

Synthesis of the C1–C11 fragment **2a**/**b** was achieved in 12 steps from *(E)*-3-iodo-2-methylacrylaldehyde (2% overall yield). An Evans-Prunet acetalization[177] and two Leighton crotylation reactions[162] were employed for installation of its stereocentres. Assembly of **2a**, **3**, and a truncated analogue of **4b** afforded the C1–C27 fragment **68**,

which served as a model to test the stability of the acid-sensitive C10–C13 diene under the deprotection conditions, allowing further refinement of those conditions. Through a comparative analysis of the NMR data with that of stambomycin D, this fragment moreover provided preliminary proof of the accuracy of the genomics-based stereochemical assignment of the natural product.

The C13–C48 fragment **90**, a late-stage intermediate en route to the target macrolide, was next constructed from the C13–C31 fragment **39** and the C33–C48 fragment **5**. The suitability of the deprotection conditions for the larger molecule was examined through the deprotection of this fragment. Additionally, the synthesis of both C28 diastereomers of the fragment (**90** and **90'**) enabled the identity of the unassigned C28 stereocentre to be determined: it was deduced to be of *S* configuration. This allowed subsequent synthetic efforts towards the natural product to be streamlined. Moreover, a comparison of the NMR data of the fragment with that of stambomycin D further supported its genomics-based stereochemical assignment.

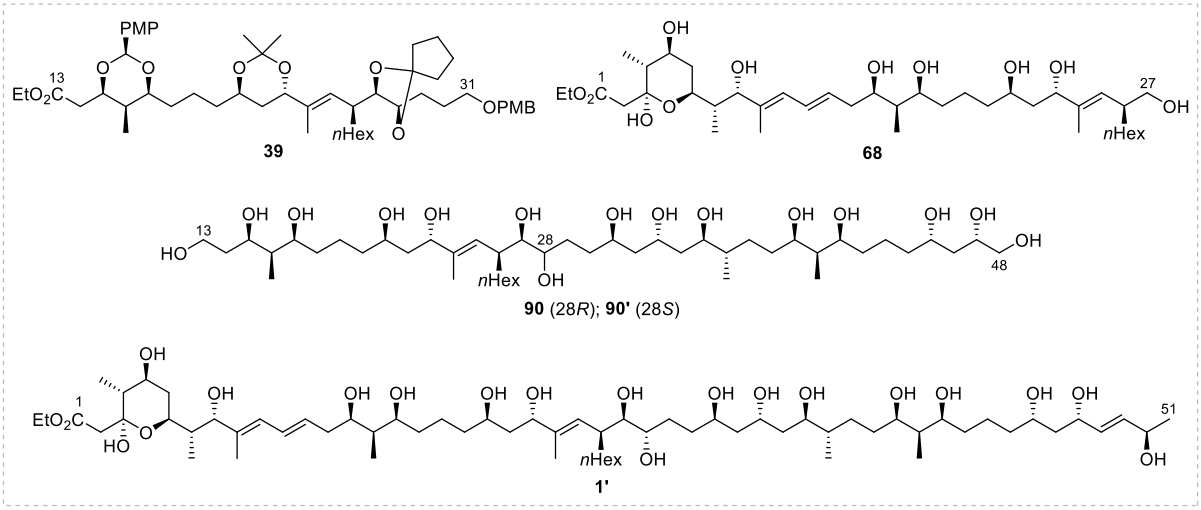


Figure 32: *Key fragments synthesized*

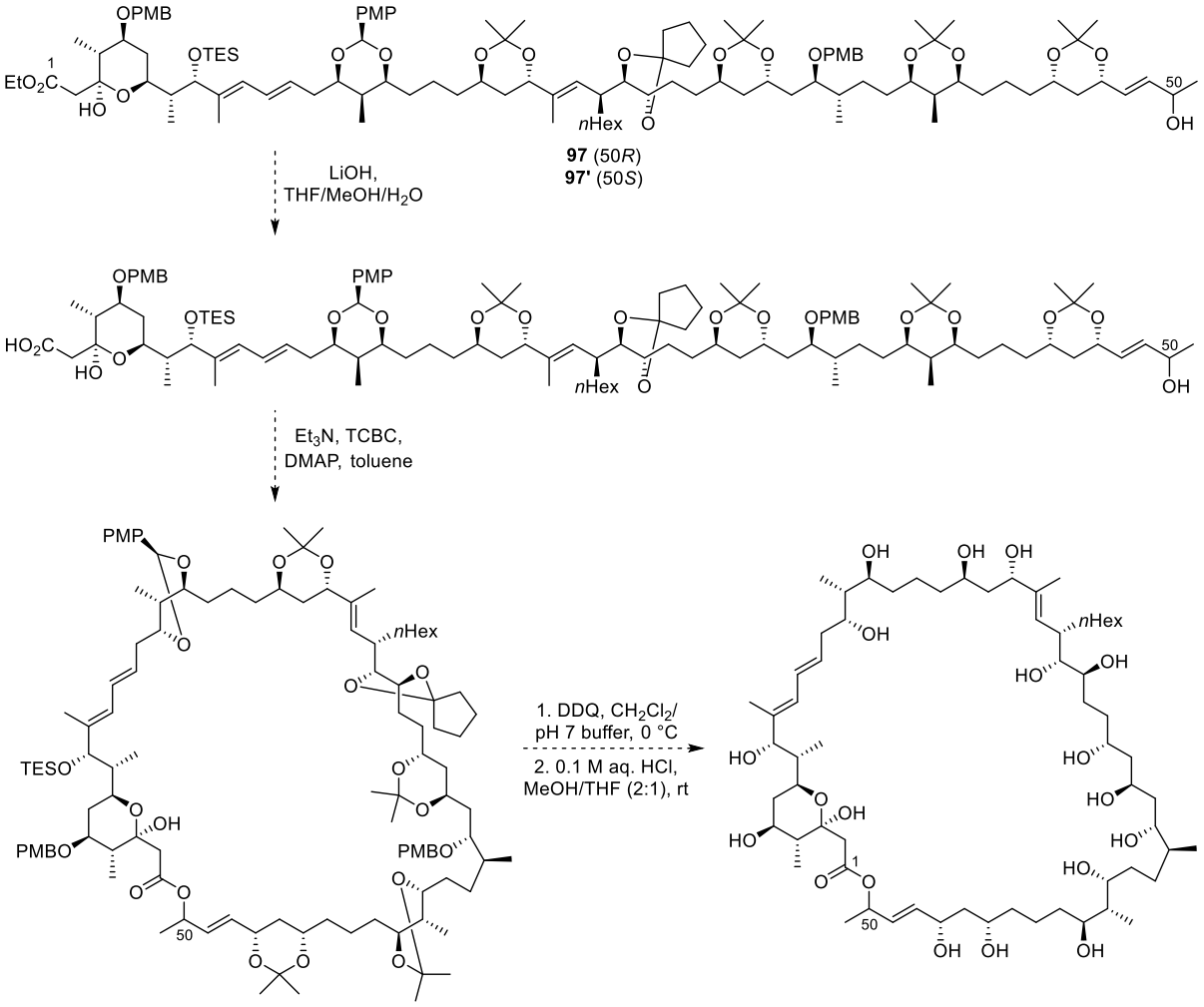
Finally, the full-length C1–C51 fragment **1'** was synthesized from the C1–C11 fragment **2b** and the C13–C48 fragment **90'**. A global deprotection of the fragment was successfully demonstrated, proving the effectiveness of the deprotection conditions developed through the various deprotection studies. With the capability to deprotect the entire C1–C51 framework, this paves the way for completion of the target natural product.

Looking forward, the next step in the project involves the macrocyclisation of the C1–C51 framework and the identification of the C50 stereocentre. While the identity of the C28 stereocentre was determined through the C13–C48 fragment, it is expected that the configuration of the C50 centre would not be deducible through a comparison of the NMR data of the acyclic C1–C51 fragment with that of stambomycin D. This is due to the considerable difference in chemical environment of the C50 centre in the acyclic fragment as compared to the macrocycle allylic ester. However, if an authentic sample of the natural product were available, it could be hydrolysed to the acyclic natural product, which would then allow a direct comparison of the NMR data of the synthetic C1–C51 fragment with that of the natural product. Although the C50 diastereomers of the C33–C51 fragment[181] exhibited nearly identical NMR data for their C50 carbon, there was a slight difference nonetheless ($\Delta\delta_C$: <0.1 ppm), which was more pronounced for the neighbouring carbons. Therefore, the configuration of the C50 centre should be deducible from the C50 diastereomers of the C1–C51 fragment, if compared to the acyclic natural product.

In any case, it would be ideal to obtain the target macrocycle; this should enable definitive identification of the unassigned C50 stereocentre. To achieve this, a Yamaguchi macrolactonisation[187] strategy is envisaged, being commonly employed in natural product synthesis.[188] This would first involve a base-mediated hydrolysis of **97** and its C50 diastereomer (obtainable by reduction of enone **96** with the (*R*)-MeCBS catalyst; Scheme 31) to convert the ester to the acid (Scheme 32). The obtained hydroxy acid would then be subjected to the Yamaguchi macrolactonisation conditions to form the macrolactone. As the classical Yamaguchi conditions traditionally require the use of high temperatures, which could lead to alkene isomerisation, a modification of the original procedure would likely be more appropriate. Yonemitsu's modifications,[189,190] for example, allow efficient macrolactonisation under room temperature and are typically used for large macrocycles.[188] Alternatively, Evans' modification, which overcame problems with Yamaguchi's and Yonemitsu's conditions in the synthesis of oasomycin A,[92c] could also be employed.

Upon obtaining the desired macrocycle, deprotection would then be carried out, beginning with cleavage of the PMB ethers using DDQ, followed by a global deprotection using 0.1 M aqueous HCl in methanol/THF (2:1). As these conditions were found successful for the acyclic C1–C51 fragment, it is anticipated that they would prove similarly effective for the macrocycle. Having achieved this, the NMR data of the two synthetic C50 diastereomers

of the stambomycin D aglycon would then be compared with that of the natural product and its aglycon. This would hopefully reveal not only the identity of the unassigned C50 stereocentre, but also comprehensively validate the accuracy of the genomics-based stereochemical assignment of the natural product. If this indeed proves to be accurate, it would in turn demonstrate the value and accuracy of genomics-based methods for polyketide stereochemical determination, thus achieving the ultimate goal of the project.



Scheme 32: *Proposed route to the C50 diastereomers of the stambomycin D aglycon*

6. Experimental

6.1. General experimental considerations

Reagents, Solvents and Reactions

Commercial reagents and solvents were used without further purification, unless specified. Anhydrous solvents were obtained either commercially or from an MBRAUN SPS-800 solvent purification system, having been passed through an activated alumina column under nitrogen. Reactions in anhydrous solvents were performed in glassware dried by a heat gun. Reactions conducted below room temperature were cooled using an ice/water bath (for 0 °C), a dry ice/acetone bath (for temperatures below 0 °C), or an immersion cooler. Heated reactions were heated using an oil bath.

Chromatography

Analytical thin layer chromatography (TLC) was performed using Merck TLC Silica gel 60 F_{254} plates; reversed phase TLC was performed using Merck TLC Silica gel 60 RP-18 F_{254}s plates. TLC plates were visualised under a UV lamp (254 nm) or with vanillin or phosphomolybdic acid (PMA) stain. Flash column chromatography was carried out using Merck silica gel (technical grade, pore size 60 Å, 230–400 mesh particle size) under positive pressure. Reversed phase column chromatography was carried out using silica from a Biotage® Sfär C18 Duo 100 Å 30 µm column.

Physical and Spectroscopic Data

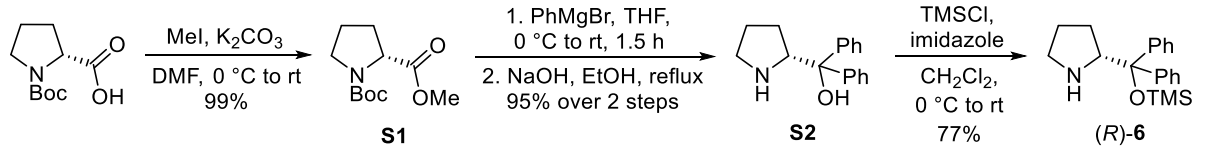
Optical rotations were measured at 589 nm (Na-D line) on a PerkinElmer 341 polarimeter with a 1 dm pathlength cell using solutions of chloroform or methanol. Specific rotations ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$) are given in deg dm^2g^{-1} and concentration (c) is reported in g/100 mL. Melting points were obtained using a Griffin melting point apparatus. Infrared (IR) spectra were measured on a Bruker Tensor 27 Fourier FT-IR spectrometer using material applied as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). Proton (^1H), carbon (^{13}C), and fluorine (^{19}F) NMR spectra were measured on a Bruker AVIII HD 400, AVIII HD 500, or AVIII HD 600 nuclear magnetic resonance spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to the residual solvent peak ($CDCl_3$: δ 7.26/77.16; MeOD: δ 3.31/49.00).

^{19}F NMR spectra were not externally referenced. Multiplicities are reported as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, and combinations thereof, and m = multiplet. Coupling constants are reported in hertz (Hz). Proton and carbon assignments were made with the aid of COSY, HSQC, and HMBC spectra; numbering is based on the stambomcyin D numbering system. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics microTOF spectrometer (resolution = 5000 FWHM) by the University of Oxford departmental mass spectrometry service.

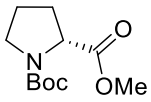
6.2. The C13–C31 fragment

6.2.1. The C23–C31 fragment

*Synthesis of catalyst (R)-**6**[155]*



1-(*tert*-Butyl) 2-methyl (*R*)-pyrrolidine-1,2-dicarboxylate (S1)

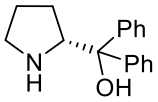


To a solution of *N*-Boc-D-proline (10.76 g, 50.0 mmol, 1.0 eq.) in DMF (100 mL) at 0 °C was added K_2CO_3 (8.29 g, 60.0 mmol, 1.2 eq.). The mixture was stirred for 10 minutes, after which iodomethane (3.7 mL, 60.0 mmol, 1.2 eq.) was added. The reaction mixture was stirred at room temperature overnight. It was quenched with water (100 mL), diluted with diethyl ether (100 mL), and extracted with diethyl ether (2 × 100 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound (11.30 g, 49.3 mmol, 99%) as a colourless oil. It was taken to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 – 4.19 (m, 1H), 3.72 – 3.71 (m, 3H), 3.58 – 3.36 (m, 2H), 2.27 – 1.82 (m, 4H), 1.45 – 1.41 (m, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.9/173.7, 154.5/153.9, 80.0/79.9, 59.2/58.8, 52.3/52.1, 46.7/46.4, 31.0/30.1, 28.6/28.4, 24.5/23.8. Rotameric mixture.

The physical and spectroscopic data were consistent with literature reported data.[191]

(*R*)-Diphenyl(pyrrolidin-2-yl)methanol (S2)

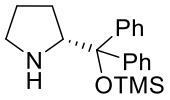


(1) PhMgBr addition to ester: To a solution of ester **S1** (11.30 g, 49.3 mmol, 1.0 eq.) in anhydrous THF (99 mL) under argon at 0 °C was added phenylmagnesium bromide solution (3.0 M in diethyl ether, 41.1 mL, 123.3 mmol, 2.5 eq.) dropwise via dropping funnel. The reaction mixture was stirred at room temperature for 1.5 hours. It was cooled to 0 °C, quenched with saturated aqueous NH_4Cl (60 mL), and extracted with diethyl ether (3 × 60 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford colourless crystals. *(2) Boc deprotection:* The crystals were dissolved in EtOH (200 mL), and NaOH (19.7 g, 493.0 mmol, 10.0 eq.) was added. The reaction mixture was stirred at reflux overnight. It was concentrated under reduced pressure; the residue was dissolved in diethyl ether (100 mL) and water (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% MeOH/CH_2Cl_2 + 1% Et_3N) to afford the title compound (12.0 g, 47.4 mmol, 95%) as an orange oil, which crystallized upon standing.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.46 (m, 4H), 7.34 – 7.23 (m, 4H), 7.21 – 7.13 (m, 2H), 4.26 (t, *J* = 7.6 Hz, 1H), 3.09 – 2.86 (m, 2H), 1.81 – 1.51 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.2, 145.5, 128.4, 128.1, 126.6, 126.5, 126.0, 125.6, 77.2, 64.6, 46.9, 26.4, 25.6.

The physical and spectroscopic data were consistent with literature reported data.[192]

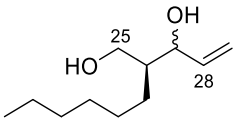
(*R*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine ((*R*)-6)



To a solution of imidazole (9.69 g, 142.3 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (90 mL) at 0 °C under argon was added chlorotrimethylsilane (15.0 mL, 118.5 mmol, 2.5 eq.) dropwise. The solution was stirred for 10 minutes, after which a solution of alcohol **S2** (12.0 g, 47.4 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Water (100 mL) was added and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% diethyl ether/pentane → 100% diethyl ether) to afford the title compound (11.95 g, 36.7 mmol, 77%) as a yellow oil.

$[\alpha]_D^{25}$ +53.8 (*c* = 1.0, $CHCl_3$), (lit.[193] $[\alpha]_D^{33}$ –52.4 (*c* = 1.0, $CHCl_3$) for (*S*)-isomer); **R_f** 0.26 (pentane/ether = 1/4); **IR** (thin film): ν_{max}/cm^{-1} 2957, 1249, 1072, 838, 701; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.35 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.31 – 7.16 (m, 6H), 4.03 (t, *J* = 7.4 Hz, 1H), 2.90 – 2.75 (m, 2H), 1.69 (brs, 1H), 1.63 – 1.34 (m, 4H), –0.09 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.9, 145.9, 128.6, 127.7, 127.7, 127.7, 127.0, 126.9, 83.3, 65.6, 47.3, 27.7, 25.2, 2.3; **HRMS** (ESI) m/z calcd for $C_{20}H_{27}NOSi$ $[M+H]^+$: 326.1935, found 326.1935.

(2*S*)-2-Hexylpent-4-ene-1,3-diol (7)

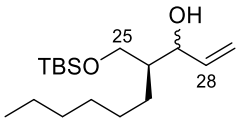


Synthesized according to a modified literature procedure.[155] To a solution of catalyst (*R*)-**6** (1.46 g, 4.50 mmol, 0.1 eq.) in toluene (90 mL) was added solid pH 7 potassium phosphate buffer[xvii] (15.7 g) and formaldehyde[xviii] (37% in water, 10.1 mL, 135.0 mmol, 3.0 eq.). The mixture was stirred vigorously for 15 minutes, after which freshly distilled octanal (7.0 mL, 45.0 mmol, 1.0 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 36 hours. It was diluted with water (30 mL), the organic layer was separated, and the aqueous layer was extracted with toluene (30 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure (keeping the water bath at room temperature). The residue was dissolved in anhydrous toluene (180 mL) under argon and the solution was cooled to 0 °C. Vinylmagnesium bromide (1.0 M in THF, 135 mL, 135.0 mmol, 3.0 eq.) was added dropwise via dropping funnel, and the reaction mixture was stirred at room temperature for 1 hour. It was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1 → 3/2) to afford the title compound (4.13 g, 22.17 mmol, 49%, 87% *ee*,[xix] ~2:1 *dr*) as a light yellow oil.

R_f 0.26 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3361, 2956, 2928, 2858, 1466, 1027, 992, 922; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.98 – 5.87 (m, 1H, *H28*), 5.34 – 5.18 (m, 2H, *H29*), 4.39 – 4.36 (m, 0.3H, $H27_{minor}$), 4.16 (tt, *J* = 6.3, 1.3 Hz, 0.7H, $H27_{major}$), 3.88 (dd, *J* = 11.0, 2.9 Hz, 0.7H, $H25_{major}$), 3.74 – 3.63 (m, 1.3H, $H25'_{major}$, $H25_{minor}$ and $H25'_{minor}$), 2.76 (brs, 2H, O*H* × 2), 1.89 – 1.82 (m, 0.3H, $H26_{minor}$), 1.59 – 1.52 (m, 0.7H, $H26_{major}$), 1.42 – 1.18 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.2/138.1, 116.1/116.0, 77.6/76.2, 64.6/64.5, 44.8/44.7, 31.9/31.9, 29.7/29.6, 28.2/27.7, 27.3/26.2, 22.8, 14.2; **HRMS** (ESI) m/z calcd for $C_{11}H_{22}O_2$ $[M+Na]^+$: 209.1512, found 209.1514.

[xvii]Prepared according to the procedure in reference 155. [xviii]For an optimal yield, a fresh bottle of formaldehyde should be used. [xix]Determined by ^{19}F NMR analysis of **11.2** (Mosher ester derivative of **11**).

(4*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)dec-1-en-3-ol (8)

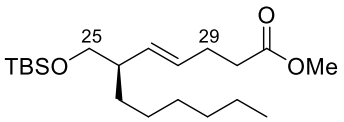


To a solution of diol **7** (1.98 g, 10.63 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (17.5 mL) under argon was added imidazole (1.45 g, 21.26 mmol, 2.0 eq.). The solution was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (1.60 g, 10.63 mmol, 1.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. It was quenched with water (17.5 mL), the organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 17.5 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 97/3) to afford the title compound (2.70 g, 8.98 mmol, 85%, ~2:1 *dr*[xx]) as a colourless oil.

R_f 0.53 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3448, 2928, 2857, 1470, 1255, 1090, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.93 – 5.84 (m, 1H, *H28*), 5.31 (dt, *J* = 17.1, 1.7 Hz, 1H, *H29*), 5.21 – 5.15 (m, 1H, *H29'*), 4.33 – 4.29 (m, 0.3H, $H27_{minor}$), 4.17 – 4.13 (m, 0.7H, $H27_{major}$), 3.92 (dd, *J* = 10.0, 2.9 Hz, 0.7H, $H25_{major}$), 3.73 – 3.69 (m, 1.6H, O*H* and $H25_{minor}$), 3.61 (dd, *J* = 10.0, 4.7 Hz, 0.7H, $H25'_{major}$), 1.84 – 1.78 (m, 0.3H, $H26_{minor}$), 1.53 – 1.47 (m, 0.7H, $H26_{major}$), 1.45 – 1.18 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.90 – 0.86 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.08 – 0.07 (m, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.6/138.4, 115.3/115.0, 76.5/75.9, 65.6/65.0, 44.6/44.3, 31.9/31.9, 29.7/29.6, 28.3/27.7, 27.4, 26.0/25.9, 22.8, 18.2, 14.2, –5.5/–5.5, –5.5/–5.6; **HRMS** (ESI) m/z calcd for $C_{17}H_{36}O_2Si$ $[M+Na]^+$: 323.2377, found 323.2378.

[xx]Mixture of diastereomers carried over from the starting material

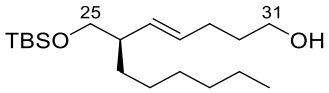
Methyl (*R*,*E*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)dodec-4-enoate (9)



Allylic alcohol **8** (3.89 g, 12.94 mmol, 1.0 eq.), trimethyl orthoacetate (8.2 mL, 64.70 mmol, 5.0 eq.) and propionic acid (97 µL, 1.29 mmol, 0.1 eq.) were heated in a sealed tube at 140 °C overnight. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (25 mL), and washed with saturated aqueous $NaHCO_3$ (25 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 97/3) to afford the title compound (4.35 g, 12.20 mmol, 94%) as a colourless oil.

$[\alpha]_D^{25}$ –13.8 (c = 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.51 (pentane/diethyl ether = 19/1); **IR** (thin film): ν_{max}/ cm^{-1} 2928, 2856, 1744, 1253, 1096, 836, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.42 (dt, *J* = 15.3, 6.1 Hz, 1H, *H28*), 5.24 (ddt, *J* = 15.3, 8.6, 1.2 Hz, 1H, *H27*), 3.66 (s, 3H, OCH_3), 3.44 (dd, *J* = 6.4, 1.5 Hz, 2H, *H25*), 2.41 – 2.28 (m, 4H, *H29* and *H30*), 2.12 – 2.03 (m, 1H, *H26*), 1.48 – 1.10 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.89 – 0.87 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.02 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.8, 133.5, 129.2, 67.1, 51.6, 45.5, 34.4, 32.0, 31.2, 29.6, 28.2, 27.1, 26.1, 22.8, 18.5, 14.3, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{20}H_{40}O_3Si$ $[M+H]^+$: 357.2820, found 357.2821.

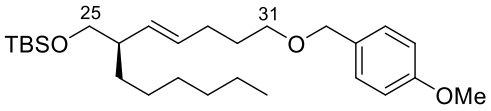
(*R*,*E*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)dodec-4-en-1-ol (10)



To a stirred suspension of $LiAlH_4$ (509 mg, 13.42 mmol, 1.1 eq.) in anhydrous THF (35 mL) under argon at –78 °C was added dropwise a solution of ester **9** (4.35 g, 12.20 mmol, 1.0 eq.) in anhydrous THF (5 mL). The reaction mixture was stirred at –78 °C for 1 hour and at room temperature for 1 hour. It was cooled to 0 °C and quenched with successive dropwise addition of water (520 µL), 15% aqueous NaOH (520 µL), and water (1.6 mL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 4/1) to afford the title compound (3.73 g, 11.35 mmol, 93%) as a colourless oil.

$[\alpha]_D^{25}$ –11.8 (c = 1.0, $CHCl_3$); **R_f** 0.46 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3349, 2928, 2856, 1471, 1254, 1097, 836, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.44 (dt, *J* = 15.3, 6.7 Hz, 1H, *H28*), 5.22 (ddt, *J* = 15.3, 8.6, 1.4 Hz, 1H, *H27*), 3.68 – 3.63 (m, 2H, *H31*), 3.45 (d, *J* = 6.4 Hz, 2H, *H25*), 2.12 – 2.05 (m, 3H, *H26* and *H29*), 1.68 – 1.61 (m, 2H, *H30*), 1.48 – 1.10 (m, 11H, O*H* and *n*-Hex-(CH_2)$_5$), 0.89 – 0.86 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.03 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 132.9, 130.8, 67.2, 62.7, 45.6, 32.6, 32.0, 31.2, 29.6, 29.3, 27.2, 26.1, 22.8, 18.5, 14.3, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{19}H_{40}O_2Si$ $[M+Na]^+$: 351.2690, found 351.2690.

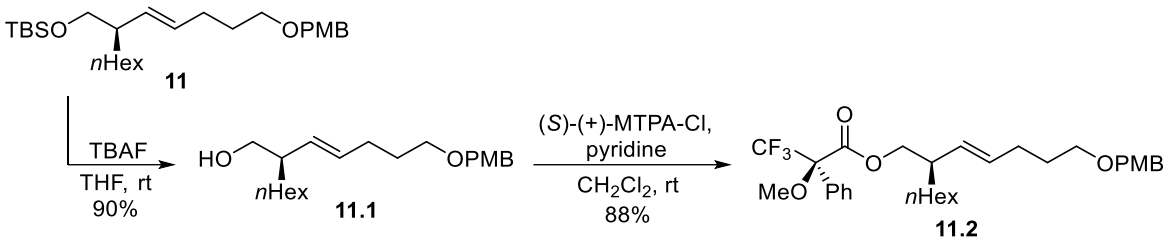
(*R*,*E*)-*tert*-Butyl((2-(5-((4-methoxybenzyl)oxy)pent-1-en-1-yl)octyl)oxy)dimethyl silane (11)



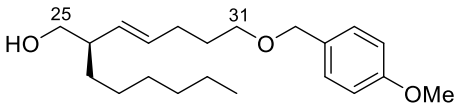
To a solution of alcohol **10** (3.42 g, 10.41 mmol, 1.0 eq.) in anhydrous DMF (9.5 mL) under argon at 0 °C was added NaH (60% in mineral oil, 256 mg, 6.39 mmol, 1.5 eq.). The mixture was stirred for 30 minutes, after which PMBCl (2.1 mL, 15.62 mmol, 1.5 eq.) was added, followed by TBAI (192.1 mg, 0.52 mmol, 5 mol%). The reaction mixture was stirred at room temperature overnight. It was quenched slowly with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (4.19 g, 9.34 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25}$ –11.0 (c = 1.0, $CHCl_3$); **R**$_f$ 0.55 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2928, 2855, 1513, 1464, 1248, 1099, 1040, 836, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.41 (dt, *J* = 15.3, 6.8 Hz, 1H, *H28*), 5.18 (ddt, *J* = 15.3, 8.6, 1.4 Hz, 1H, *H27*), 4.42 (s, 2H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.48 – 3.41 (m, 4H, *H25* and *H31*), 2.13 – 2.02 (m, 3H, *H26* and *H29*), 1.72 – 1.61 (m, 2H, *H30*), 1.49 – 1.10 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.89 – 0.86 (m, 12H, *n*-Hex-C*H*$_3$ and SiC(C*H*$_3$)$_3$), 0.03 (s, 3H, SiC*H*$_3$), 0.02 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 132.6, 130.9, 130.8, 129.4, 113.9, 72.7, 69.7, 67.3, 55.4, 45.6, 32.0, 31.3, 29.8, 29.6, 29.4, 27.2, 26.1, 22.8, 18.5, 14.3, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{27}H_{48}O_3Si$ $[M+H]^+$: 471.3265, found 471.3254.

*Synthesis of **11.2** for ee determination*



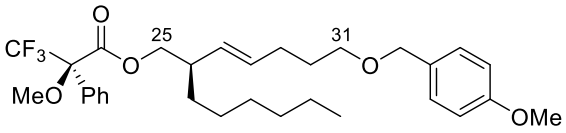
(*R*,*E*)-2-(5-((4-Methoxybenzyl)oxy)pent-1-en-1-yl)octan-1-ol (11.1)



To a solution of TBS ether **11** (26.4 mg, 0.059 mmol, 1.0 eq.) in anhydrous THF (150 µL) was added TBAF (1.0 M in THF, 71 µL, 0.071 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (17.7 mg, 0.053 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25}$ –1.7 (c = 1.8, $CHCl_3$); **R_f** 0.17 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3400, 2925, 1513, 1464, 1247, 1099, 1037, 821; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.53 (dt, *J* = 15.3, 6.8 Hz, 1H, *H28*), 5.15 (ddt, *J* = 15.3, 8.9, 1.4 Hz, 1H, *H27*), 4.42 (s, 2H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.55 – 3.48 (m, 1H, *H25*), 3.44 (t, *J* = 6.4 Hz, 2H, *H31*), 3.31 (dd, *J* = 10.5, 8.5 Hz, 1H, *H25'*), 2.15 – 2.10 (m, 3H, *H26* and *H29*), 1.72 – 1.65 (m, 2H, *H30*), 1.49 (brs, 1H, O*H*), 1.36 – 1.15 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.88 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ133.2, 132.1, 130.8, 129.4, 113.9, 72.7, 69.5, 66.1, 55.4, 46.1, 31.9, 31.2, 29.7, 29.5, 29.5, 27.2, 22.8, 14.2; **HRMS** (ESI) m/z calcd for $C_{21}H_{34}O_3$ $[M+Na]^+$: 357.2400, found 357.2400.

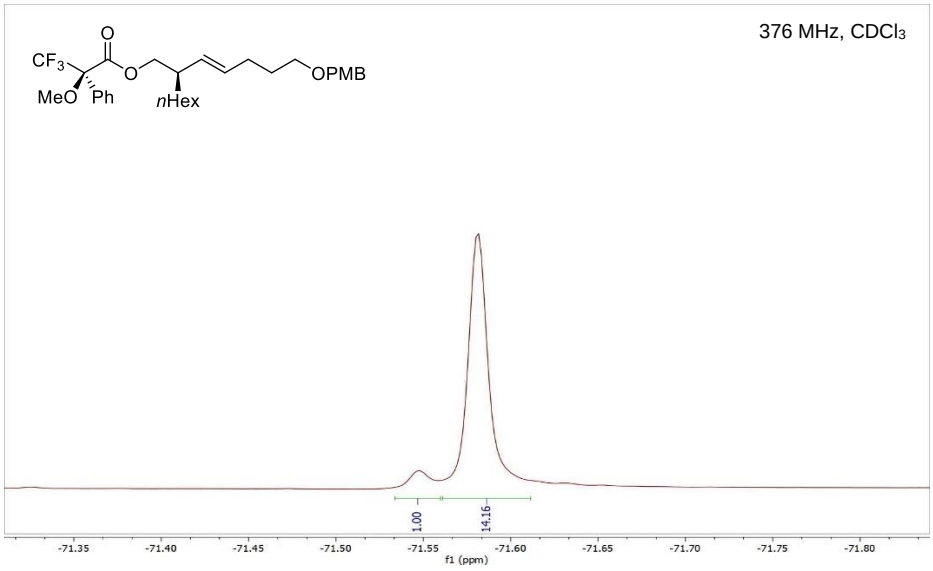
(*R*)-2-((*E*)-5-((4-Methoxybenzyl)oxy)pent-1-en-1-yl)octyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (11.2)



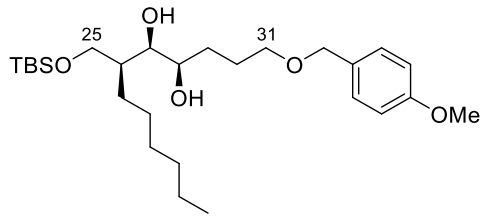
Synthesized according to a modified literature procedure.[194] To a solution of alcohol **11.1** (14.5 mg, 0.043 mmol, 1.0 eq.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (20.7 mg, 0.082 mmol, 1.9 eq.) in anhydrous CH_2Cl_2 (540 µL) was added pyridine (11 µL, 0.133 mmol, 3.1 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1) to afford the title compound (20.8 mg, 0.038 mmol, 88%) as a colourless oil.

$[\alpha]_D^{25}$ +21.9 (c = 2.1, $CHCl_3$); **R_f** 0.35 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 2929, 2855, 1749, 1513, 1465, 1248, 1170, 1121, 1103, 1023; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 – 7.51 (m, 2H, Ar*H*), 7.41 – 7.38 (m, 3H, Ar*H*), 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.45 (dt, *J* = 15.3, 6.7 Hz, 1H, *H28*), 5.17 (ddt, *J* = 15.3, 8.4, 1.4 Hz, 1H, *H27*), 4.41 (s, 2H, OCH_2Ar), 4.23 (dd, *J* = 10.6, 6.8 Hz, 1H, *H25*), 4.14 (dd, *J* = 10.6, 6.0 Hz, 1H, *H25'*), 3.80 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.42 (t, *J* = 6.5 Hz, 2H, *H31*), 2.38 – 2.33 (m, 1H, *H26*), 2.08 – 2.03 (m, 2H, *H29*), 1.66 – 1.59 (m, 2H, *H30*), 1.39 – 1.16 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.87 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.7, 159.3, 132.5, 132.5, 130.9, 130.4, 129.7, 129.4, 128.5, 127.5, 123.5 (q, *J* = 290 Hz), 113.9, 84.8 (q, *J* = 28 Hz), 72.7, 69.9, 69.5, 55.6, 55.4, 41.9, 31.9, 31.3, 29.5, 29.3, 29.3, 26.8, 22.7, 14.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –71.6; **HRMS** (ESI) m/z calcd for $C_{31}H_{41}F_3O_5$ $[M+Na]^+$: 573.2798, found 573.2795.

*Determination of ee by ^{19}F NMR analysis of **11.2**: 87% ee*



(4*R*,5*R*,6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy) dodecane-4,5-diol (12)

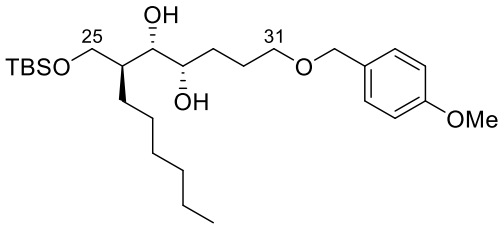


To a solution of AD-mix-β[xxi] (9.98 g) in water (35.7 mL) and *t*-BuOH (25.7 mL) was added methanesulfonamide (1.36 g, 14.26 mmol, 2.0 eq.). The solution was cooled to 0 °C and a solution of alkene **11** (3.20 g, 7.13 mmol, 1.0 eq.) in *t*-BuOH (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 36 hours. It was diluted with ethyl acetate, quenched with saturated aqueous $Na_2S_2O_3$/solid $Na_2S_2O_3$, and stirred for 15–20 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (3.10 g, 6.42 mmol, 90%, 7:1 *dr*) as a colourless oil.

R_f 0.22 (pentane/ethyl acetate = 5/1); **IR** (thin film): ν_{max}/cm^{-1} 3414, 2928, 2856, 1513, 1464, 1248, 1091, 1037, 835, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.43 (s, 2H, OC*H*$_2$Ar), 3.81 – 3.78 (m, 1H, *H25*), 3.80 (s, 3H, OC*H*$_3$), 3.68 – 3.64 (m, 2H, *H25'* and *H27*), 3.57 (d, *J* = 3.5 Hz, 1H, O*H*), 3.51 – 3.45 (m, 3H, *H28* and *H31*), 3.05 (d, *J* = 6.2 Hz, 1H, O*H*), 1.83 – 1.66 (m, 2H, *H29*), 1.64 – 1.55 (m, 3H, *H26* and *H30*), 1.36 – 1.24 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.89 – 0.86 (m, 12H, Si(C*H*$_3$)$_3$ and *n*-Hex-C*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 130.7, 129.4, 113.9, 76.2, 72.7, 70.2, 70.1, 63.1, 55.4, 43.7, 31.9, 30.6, 29.7, 27.7, 26.3, 26.2, 25.9, 22.8, 18.3, 14.2, –5.5; **HRMS** (ESI) m/z calcd for $C_{27}H_{50}O_5Si$ $[M+Na]^+$: 505.3320, found 505.3316.

[xxi]Prepared according to the procedure in reference 157

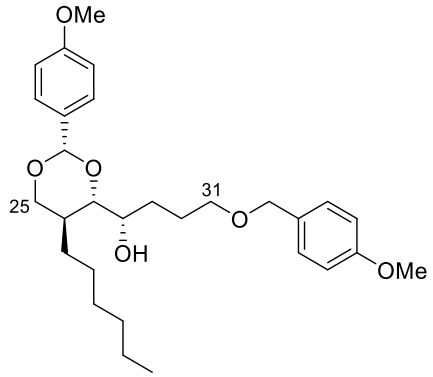
(4*S*,5*S*,6*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy) dodecane-4,5-diol (12')



To a solution of AD-mix-α (616 mg) in water (2.2 mL) and *t*-BuOH (1.2 mL) was added methanesulfonamide (41.9 mg, 0.44 mmol, 1.0 eq.). The solution was cooled to 0 °C and a solution of alkene **11** (200 mg, 0.44 mmol, 1.0 eq.) in *t*-BuOH (1 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. It was diluted with ethyl acetate, quenched with saturated aqueous $Na_2S_2O_3$/solid $Na_2S_2O_3$, and stirred for 15–20 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (165.9 mg, 0.34 mmol, 78%, 4:1 *dr*) as a colourless oil.

R_f 0.22 (pentane/ethyl acetate = 5/1); **IR** (thin film): ν_{max}/cm^{-1} 3414, 2928, 1513, 1464, 1248, 1091, 1037, 835, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.44 (s, 2H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.78 – 3.76 (m, 1H, *H25*), 3.69 (d, *J* = 6.9 Hz, 1H, *OH*), 3.68 – 3.59 (m, 2H, *H25'* and *H27*), 3.52 – 3.41 (m, 3H, *H28* and *H31*), 3.37 (d, *J* = 4.7 Hz, 1H, *OH*), 1.86 – 1.66 (m, 2H, *H29*), 1.62 – 1.53 (m, 3H, *H26* and *H30*), 1.44 – 1.25 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.92 – 0.87 (m, 12H, Si(C*H*$_3$)$_3$ and *n*-Hex-C*H*$_3$), 0.08 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 130.7, 129.4, 113.9, 77.1, 72.7, 72.3, 70.2, 64.5, 55.4, 42.5, 31.9, 30.9, 29.7, 29.4, 27.4, 26.3, 25.9, 22.8, 18.2, 14.2, –5.4, –5.5; **HRMS** (ESI) m/z calcd for $C_{27}H_{50}O_5Si$ $[M+H]^+$: 483.3500, found 483.3499.

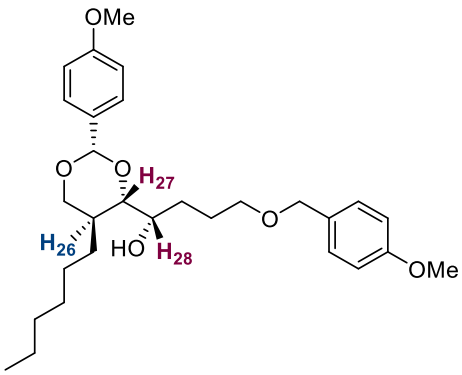
(*S*)-1-((2*S*,4*S*,5*S*)-5-Hexyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-4-((4-methoxybenzyl)oxy)butan-1-ol (12.1')

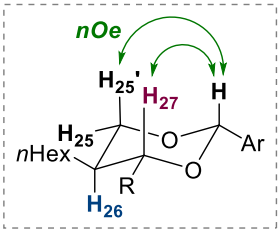


To a solution of diol **12'**[xxii] (84.0 mg, 0.17 mmol, 1.0 eq.) in anhydrous THF (560 µL) under argon was added TBAF (1.0 M in THF, 200 µL, 0.20 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (850 µL) under argon and the solution was cooled to 0 °C. Anisaldehyde dimethyl acetal (35 µL, 0.20 mmol, 1.2 eq.) and *p*-toluenesulfonic acid monohydrate (3.2 mg, 0.017 mmol, 0.1 eq.) were added. The reaction mixture was stirred at 0 °C for 2 hours. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (32.3 mg, 0.07 mmol, 39% over two steps) as a colourless oil.

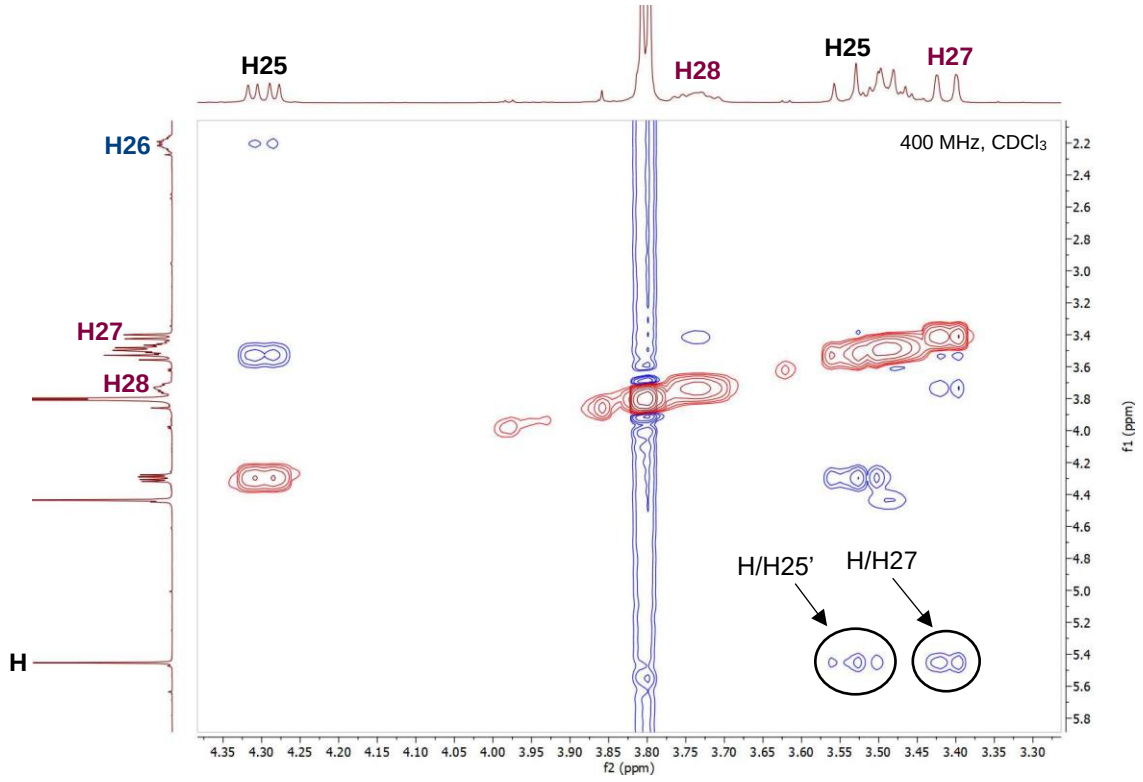
$[\alpha]_D^{25}$ –3.9 (c = 0.6, $CHCl_3$); **R_f** 0.35 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3465, 2929, 2855, 1514, 1463, 1248, 1092, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.90 – 6.85 (m, 4H, Ar*H*), 5.45 (s, 1H, C*H*PMP), 4.44 (s, 2H, OC*H*$_2$Ar), 4.30 (dd, *J* = 11.2, 4.9 Hz, 1H, *H25*), 3.81 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.77 – 3.71 (m, 1H, *H28*), 3.53 (dd, *J* = 11.2, 11.3 Hz, 1H, *H25'*), 3.52 – 3.46 (m, 2H, *H31*), 3.41 (dd, *J* = 10.1, 1.3 Hz, 1H, *H27*), 2.25 – 2.15 (m, 1H, *H26*), 1.97 (d, *J* = 10.4 Hz, 1H, O*H*), 1.84 – 1.60 (m, 4H, *H29* and *H30*), 1.41 – 0.95 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.89 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 159.3, 131.2, 130.7, 129.4, 127.4, 113.9, 113.7, 100.8, 83.4, 72.7, 71.7, 70.2, 69.8, 55.4, 55.4, 34.2, 31.8, 31.5, 29.8, 27.7, 26.6, 26.5, 22.8, 14.2; **HRMS** (ESI) m/z calcd for $C_{29}H_{42}O_6$ $[M+H]^+$: 487.3054, found 487.3056.

*NOESY spectrum of **12.1'***

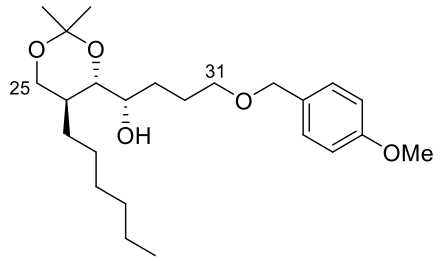




$J_{H25\text{-}H26}$ = 4.9 Hz
$J_{H25'\text{-}H26}$ = 11.3 Hz
$J_{H26\text{-}H27}$ = 10.1 Hz



(*S*)-1-((4*S*,5*S*)-5-Hexyl-2,2-dimethyl-1,3-dioxan-4-yl)-4-((4-methoxybenzyl)oxy) butan-1-ol (12.2')

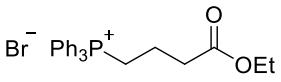


To a solution of diol **12'**[xxii] (90.0 mg, 0.19 mmol, 1.0 eq.) in anhydrous THF (480 µL) was added TBAF (1.0 M in THF, 230 µL, 0.23 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in 2,2-dimethoxypropane/CH_2Cl_2 (1.5 mL, 1:1) and pyridinium *p*-toluenesulfonate (3.8 mg, 0.015 mmol, 8 mol%) was added. The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound[xxiii] (18.6 mg, 0.05 mmol, 24% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ +20.6 (c = 0.8, $CHCl_3$); **R_f** 0.17 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3445, 2929, 2856, 1513, 1463, 1378, 1247, 1200, 1171, 1099, 1074, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.44 (s, 2H, OC*H*$_2$Ar), 3.85 (dd, *J* = 11.6, 5.3 Hz, 1H, *H25*), 3.80 (s, 3H, OC*H*$_3$), 3.62 (dddd, *J* = 10.1, 8.2, 4.8, 1.3 Hz, 1H, *H28*), 3.54 (dd, *J* = 11.6, 10.6 Hz, 1H, *H25'*), 3.51 – 3.45 (m, 2H, *H31*), 3.39 (dd, *J* = 10.3, 1.3 Hz, 1H, *H27*), 2.04 (d, *J* = 10.1 Hz, 1H, O*H*), 2.01 – 1.93 (m, 1H, *H26*), 1.81 – 1.62 (m, 3H, *H29* and *H30*), 1.55 – 1.46 (m, 1H, *H29'*), 1.40 (m, 3H, acetonide-C*H*$_3$), 1.37 (s, 3H, acetonide-C*H*$_3$), 1.30 – 0.96 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.87 (t, *J* = 7.0 Hz, 1H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 130.8, 129.4, 113.9, 98.2, 75.6, 72.7, 70.2, 69.9, 64.2, 55.4, 34.4, 31.9, 31.3, 29.7, 29.4, 28.3, 26.5, 26.5, 22.7, 19.7, 14.2; **HRMS** (ESI) m/z calcd for $C_{24}H_{40}O_5$[M+Na]$^+$: 431.2768, found 431.2759.

[xxii]Pure diol **12'**, partially separable from the diastereomeric mixture obtained in the previous step, was used. [xxiii]Obtained as a ~1:1 mixture with the 1,4-acetonide (total yield: 49%) and only partially separable from it (the pure compound was used for characterisation).

(4-Ethoxy-4-oxobutyl)triphenylphosphonium bromide (14)

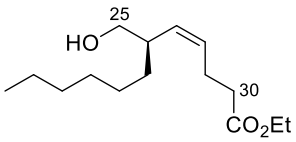


Synthesized according to a literature procedure.[195] To a solution of ethyl 4-bromobutyrate (4.3 mL, 30.0 mmol, 1.0 eq.) in anhydrous toluene (30 mL) was added triphenylphosphine (7.87 g, 30.0 mmol, 1.0 eq.). The reaction mixture was heated at reflux under argon overnight, upon which a white insoluble solid formed. The mixture was cooled to room temperature; and the solid was collected via filtration, washed with diethyl ether, and dried under vacuum to afford the title compound (9.60 g, 21.0 mmol, 70%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.81 (m, 6H), 7.78 – 7.73 (m, 3H), 7.69 – 7.63 (m, 6H), 4.05 (q, *J* = 7.2 Hz, 2H), 4.00 – 3.93 (m, 2H), 2.83 (td, *J* = 6.6, 1.4 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.2, 135.1 (d, *J* = 3.2 Hz), 133.8 (d, *J* = 10.0 Hz), 130.5 (d, *J* = 12.6 Hz), 118.2 (d, *J* = 86.4 Hz), 60.7, 33.3 (d, *J* = 18.3 Hz), 21.8 (d, *J* = 51.7 Hz), 18.1 (d, *J* = 3.0 Hz), 14.2.

The physical and spectroscopic data were consistent with literature reported data.[196]

Ethyl (*R*,*Z*)-6-(hydroxymethyl)dodec-4-enoate (15)

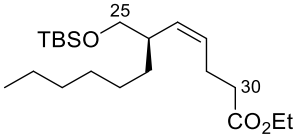


Synthesized according to modified literature procedures.[155,196] *(1) Formation of lactol:* To a solution of catalyst (*R*)-**6** (65.1 mg, 0.20 mmol, 0.2 eq.) in toluene (2 mL) was added solid pH 7 potassium phosphate buffer[xvii] (500 mg) and formaldehyde[xviii] (37% in water, 223 µL, 3.00 mmol, 3.0 eq.). The mixture was stirred vigorously for 15 minutes, after which freshly distilled octanal (156 µL, 1.00 mmol, 1.0 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 24 hours. It was diluted with water (1 mL), the organic layer was separated, and the aqueous layer was extracted with toluene (1 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure (keeping the water bath at room temperature) to afford the lactol. *(2) Wittig*

olefination: To a suspension of (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide **14** (2.29 g, 5.00 mmol, 5.0 eq.)[xxiv] in anhydrous THF (8 mL) under argon at 0 °C was added potassium *tert*-butoxide (561.0 mg, 5.00 mmol, 5.0 eq.) slowly. The resulting dark orange mixture was stirred at 0 °C for 45 minutes, after which a solution of the lactol in anhydrous THF (2 mL) was added dropwise. The light yellow mixture was stirred at 0 °C for 45 minutes. It was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (143.6 mg, 0.56 mmol, 56% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ +15.9 (c = 1.5, $CHCl_3$); **R_f** 0.24 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3428, 2956, 2926, 2857, 1736, 1458, 1373, 1251, 1161, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.54 (ddd, *J* = 10.8, 8.1, 6.1 Hz, 1H, *H28*), 5.15 (tt, *J* = 10.8, 1.5 Hz, 1H, *H27*), 4.13 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.57 (ddd, *J* = 10.5, 8.0, 5.1 Hz, 1H, *H25*), 3.33 (ddd, *J* = 10.5, 8.7, 4.2 Hz, 1H, *H25'*), 2.67 – 2.58 (m, 1H, *H26*), 2.52 – 2.29 (m, 4H, *H29* and *H30*), 1.77 (dd, *J* = 8.0, 4.2 Hz, 1H, O*H*), 1.40 – 1.12 (m, 13H, *n*-Hex-$(CH_2)_5$ and $CO_2CH_2CH_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.5, 133.2, 131.0, 66.7, 60.6, 40.8, 34.3, 31.9, 31.6, 29.6, 27.2, 23.3, 22.8, 14.4, 14.2; **HRMS** (ESI) m/z calcd for $C_{15}H_{28}O_3$ [M+Na] : 279.1931, found 279.1930.

Ethyl (*R*,*Z*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)dodec-4-enoate (16)



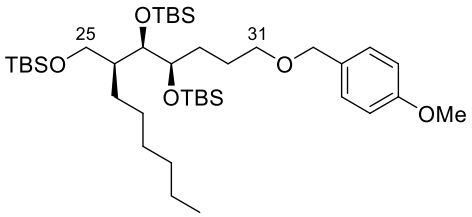
To a solution alcohol **15** (70 mg, 0.27 mmol, 1.0 eq.) and 2,6-lutidine (94 µL, 0.81 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (1.4 mL) at 0 °C under argon was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (93 µL, 0.41 mmol, 1.5 eq.). The reaction mixture was stirred at 0 °C for 1.5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

[xxiv] When three equivalents of **14** were used, a 33% yield was obtained.

(pentane/diethyl ether = 49/1) to afford the title compound (84.3 mg, 0.23 mmol, 84%) as a colourless oil.

$[\alpha]_D^{25}$ –8.2 (c = 1.2, $CHCl_3$); **R_f** 0.47 (pentane/diethyl ether = 19/1); **IR** (thin film): ν_{max}/cm^{-1} 2956, 2929, 2857, 1739, 1470, 1255, 1161, 1097, 837, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.43 (dt, *J* = 11.0, 6.7 Hz, 1H, *H28*), 5.15 (dd, *J* = 11.0, 9.9 Hz, 1H, *H27*), 4.13 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.43 (d, *J* = 6.3 Hz, 2H, *H25*), 2.54 – 2.45 (m, 1H, *H26*), 2.39 – 2.31 (m, 4H, *H29* and *H30*), 1.55 – 1.10 (m, 13H, *n*-Hex-$(CH_2)_5$ and $CO_2CH_2CH_3$), 0.88 – 0.86 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), –0.03 (s, 6H, $SiCH_3 \times 2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.4, 133.5, 128.8, 67.0, 60.4, 40.5, 34.8, 32.0, 31.7, 29.7, 27.2, 26.1, 23.5, 22.8, 18.5, 14.4, 14.2, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{21}H_{42}O_3Si$ $[M+Na]^+$: 393.2795, found 393.2797.

(5*R*,6*R*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-hexyl-5-(3-((4-methoxybenzyl)oxy) propyl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (17)

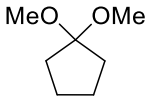


To a solution of diol **12** (100 mg, 0.21 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under argon was added 2,6-lutidine (164 µL, 1.41 mmol, 6.7 eq.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (145 µL, 0.63 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 1.5 hours. It was cooled to 0 °C, quenched with MeOH (0.5 mL), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 49/1) to afford the title compound[xxv] (137.4 mg, 0.19 mmol, 92%) as a colourless oil.

R_f 0.75 (pentane/diethyl ether = 19/1); **IR** (thin film): ν_{max}/cm^{-1} 2954, 2928, 2856, 1249, 1514, 1471, 1249, 1090, 834, 774; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.43 (d, *J* = 2.0 Hz, 2H, OCH_2Ar), 3.80 (s, 3H, OCH_3), 3.71 (dd, *J* = 4.5, 4.5 Hz, 1H, *H25*), 3.65 – 3.56 (m, 2H, *H25'* and *H28*), 3.45 – 3.41 (m, 3H, *H27* and *H31*), 1.82 – 1.75 (m, 2H, *H29*), 1.51 – 1.42 (m, 2H, *H30*), 1.41 – 1.08 (m,

11H, *H26* and *n*-Hex-(C*H*$_2$)$_5$), 0.88 – 0.86 (m, 30H, *n*-Hex-C*H*$_3$ and SiC(C*H*$_3$)$_3$ × 3), 0.05 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.03 (s, 3H, SiC*H*$_3$), 0.02 (s, 6H, SiC*H*$_3$ × 2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 131.0, 129.3, 113.8, 76.1, 73.3, 72.5, 70.6, 64.3, 55.4, 41.7, 32.1, 30.1, 28.2, 27.8, 27.6, 27.2, 26.2, 26.2, 26.1, 22.9, 18.6, 18.3, 18.2, 14.3, –3.5, –3.8, –4.5, –4.5, –5.1, –5.1; **HRMS** (ESI) m/z calcd for $C_{39}H_{78}O_5Si_3$ $[M+H]^+$: 711.5230, found 711.5228.

1,1-Dimethoxycyclopentane (19)



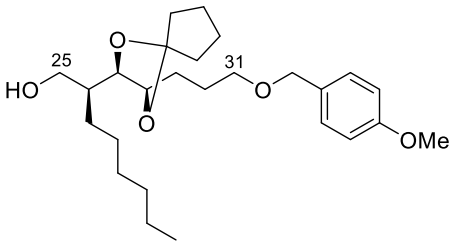
Synthesized according to a literature procedure.[197] To a solution of cyclopentanone (24.8 mL, 280.0 mmol, 1.0 eq.) and trimethyl orthoformate (36.8 mL, 336.0 mmol, 1.2 eq.) in MeOH (147.4 mL) was added *p*-toluenesulfonic acid monohydrate (266.3 mg, 1.4 mmol, 0.5 mol%). The reaction mixture was stirred at room temperature for 1 hour. It was quenched with sodium methoxide (25 wt% in MeOH, 1.3 mL, 5.6 mmol, 2 mol%), and pentane (150 mL) and water (150 mL) were added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound (32.0 g, 246.0 mmol, 88%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 6H), 1.78 – 1.74 (m, 4H), 1.67 – 1.63 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 112.4, 49.4, 34.3, 23.3.

The physical and spectroscopic data were consistent with literature reported data.[198]

[xxv]Obtained as a mixture of diastereomers (carried over from the starting material)

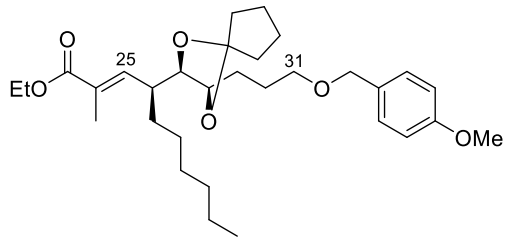
(*S*)-2-((2*R*,3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)octan-1-ol (20)



To a solution of diol **12** (2.11 g, 4.37 mmol, 1.0 eq.) and 1,1-dimethoxycyclopentane **19** (6.0 mL, 43.70 mmol, 10.0 eq.) in THF (7.3 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (41.6 mg, 0.22 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 3 hours. It was diluted with diethyl ether, quenched with saturated aqueous $NaHCO_3$, and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (10.9 mL) and TBAF (1.0 M in THF, 5.2 mL, 5.24 mmol, 1.2 eq.) was added. The reaction mixture was stirred at room temperature under argon overnight. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound[xxv] (1.72 g, 3.96 mmol, 91% over two steps) as a colourless oil.

R_f 0.24 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3467, 2928, 2857, 1513, 1465, 1333, 1247, 1099, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.43 (s, 2H, OCH_2Ar), 3.85 (td, *J* = 7.9, 3.6 Hz, 1H, *H28*), 3.80 (s, 3H, OCH_3), 3.79 – 3.77 (m, 1H, *H27*), 3.75 – 3.60 (m, 2H, *H25*), 3.53 – 3.43 (m, 2H, *H31*), 2.27 (dd, *J* = 6.3, 4.9 Hz, 1H, O*H*), 1.84 – 1.56 (m, 13H, *H26*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.41 – 1.23 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.88 (t, *J* = 6.8 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 130.7, 129.4, 118.2, 113.9, 83.5, 77.6, 72.7, 69.8, 64.0, 55.4, 41.5, 37.7, 37.4, 31.9, 30.6, 29.7, 27.8, 26.5, 25.7, 23.8, 23.4, 22.8, 14.3; **HRMS** (ESI) m/z calcd for $C_{26}H_{42}O_5$ $[M+Na]^+$: 457.2925, found 457.2925.

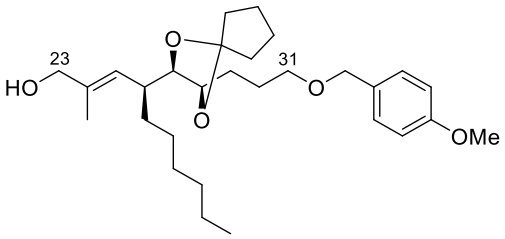
Ethyl (*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4] nonan-2-yl)-2-methyldec-2-enoate (21)



To a solution of alcohol **20** (2.95 g, 6.79 mmol, 1.0 eq.) in CH_2Cl_2 (68 mL) was added $NaHCO_3$ (1.71 g, 20.37 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (4.32 g, 10.19 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1.5 hours. It was diluted with diethyl ether (90 mL), quenched with saturated aqueous $Na_2S_2O_3$, and stirred until the mixture became a clear solution. The layers were separated, and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (24.3 mL) and (carbethoxyethylidene)triphenylphosphorane (7.38 g, 20.37 mmol, 3.0 eq.) was added. The mixture was stirred at reflux for 6 hours. It was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in a pentane/diethyl ether (4:1) solution, filtered through celite, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound[xxv] (2.94 g, 5.69 mmol, 84% over two steps) as a colourless oil.

R_f 0.37 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2929, 2856, 1711, 1513, 1465, 1247, 1099, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.24 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.45 (dq, *J* = 11.0, 1.5 Hz, 1H, *H25*), 4.40 (s, 2H, OCH_2Ar), 4.23 – 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.80 (s, 3H, OCH_3), 3.65 – 3.60 (m, 1H, *H28*), 3.52 (dd, *J* = 7.9, 6.3 Hz, 1H, *H27*), 3.42 (td, *J* = 6.5, 1.6 Hz, 2H, *H31*), 2.60 – 2.52 (m, 1H, *H26*), 1.86 (d, *J* = 1.5 Hz, 3H, CCH_3), 1.79 – 1.51 (m, 12H, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.31 – 1.10 (m, 13H, *n*-Hex-(CH_2)$_5$ and $CO_2CH_2CH_3$), 0.86 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.9, 159.3, 141.8, 130.8, 129.7, 129.3, 118.4, 113.9, 83.4, 79.6, 72.6, 69.9, 60.7, 55.4, 43.4, 37.8, 37.7, 31.9, 31.7, 30.8, 29.5, 27.2, 26.4, 23.7, 23.6, 22.8, 14.4, 14.2, 13.4; **HRMS** (ESI) m/z calcd for $C_{31}H_{48}O_6$ $[M+Na]^+$: 539.3343, found 539.3342.

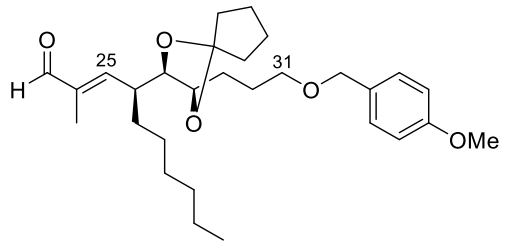
(*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methyldec-2-en-1-ol (22)



To a solution of ester **21** (2.0 g, 3.87 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (39 mL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 9.7 mL, 9.68 mmol, 2.5 eq.) dropwise. The reaction mixture was stirred at –78 °C for 1 hour and at room temperature for 1 hour. It was cooled to 0 °C and quenched slowly with water (540 µL), 15% aqueous NaOH (540 µL), then water (1.1 mL). It was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound as a colourless oil (pure major diastereomer: 1.19 g, 2.51 mmol, 65%; mixture of major and minor diastereomers: 410.2 mg, 0.86 mmol, 22%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +15.1 (c = 1.1, $CHCl_3$); **R_f** 0.32 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3435, 2927, 2856, 1514, 1455, 1362, 1248, 1099, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.06 (dq, *J* = 10.6, 1.4 Hz, 1H, *H25*), 4.42 (s, 2H, OCH_2Ar), 3.92 (d, *J* = 6.7 Hz, 2H, *H23*), 3.80 (s, 3H, OCH_3), 3.57 (dt, *J* = 2.4, 7.7 Hz, 1H, *H28*), 3.49 – 3.33 (m, 3H, *H27* and *H31*), 2.47 – 2.35 (m, 1H, *H26*), 2.29 (t, *J* = 6.7 Hz, 1H, O*H*), 1.82 – 1.57 (m, 15H, *H29, H30* and cyclopent-(CH_2)$_4$), 1.69 (d, *J* = 1.4 Hz, 3H, CCH_3), 1.51 – 1.10 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.87 (t, *J* = 6.8 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 137.5, 130.3, 129.6, 126.2, 118.1, 113.9, 83.8, 80.3, 72.5, 69.2, 68.9, 55.4, 42.7, 37.6, 37.6, 32.5, 32.0, 30.8, 29.6, 27.1, 26.6, 23.7, 23.6, 22.8, 14.8, 14.3; **HRMS** (ESI) m/z calcd for $C_{29}H_{46}O_5$ $[M+Na]^+$: 497.3238, found 497.3237.

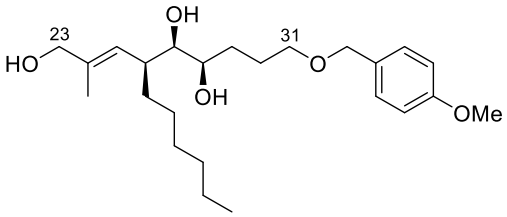
(*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methyldec-2-enal (4b)



To a solution of alcohol **22** (1.25 g, 2.63 mmol, 1.0 eq.) in CH_2Cl_2 (33 mL) was added $NaHCO_3$ (662.8 mg, 7.89 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (1.67 g, 3.95 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was diluted with diethyl ether (50 mL), quenched with saturated aqueous $Na_2S_2O_3$ (30 mL), and stirred until the mixture became a clear solution. The layers were separated, and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (1.14 g, 2.41 mmol, 92%) as a colourless oil.

$[\alpha]_D^{25}$ +28.0 (c = 1.4, $CHCl_3$); **R_f** 0.56 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 2928, 2856, 1689, 1513, 1465, 1247, 1099, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.42 (s, 1H, C*H*O), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.22 (dq, *J* = 10.7, 1.4 Hz, 1H, *H25*), 4.40 (s, 2H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.68 (td, *J* = 6.7, 4.3 Hz, 1H, *H28*), 3.59 (t, *J* = 6.7 Hz, 1H, *H27*), 3.43 (td, *J* = 6.2, 1.4 Hz, 2H, *H31*), 2.81 – 2.74 (m, 1H, *H26*), 1.81 – 1.51 (m, 12H, *H29*, *H30* and cyclopent-(C*H*$_2$)$_4$), 1.78 (d, *J* = 1.4 Hz, 3H, CC*H*$_3$), 1.42 – 1.13 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.1, 159.3, 154.2, 140.9, 130.7, 129.3, 118.6, 113.9, 83.1, 79.2, 72.6, 69.7, 55.4, 43.2, 37.8, 37.7, 31.8, 31.2, 31.0, 29.5, 27.3, 26.3, 23.7, 23.6, 22.7, 14.2, 10.2; **HRMS** (ESI) m/z calcd for $C_{29}H_{44}O_5$ $[M+Na]^+$: 495.3081, found 495.3080.

(4*S*,5*R*,6*R*,*E*)-4-Hexyl-9-((4-methoxybenzyl)oxy)-2-methylnon-2-ene-1,5,6-triol (23)

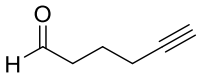


To a solution of acetal **22** (23.7 mg, 0.050 mmol, 1.0 eq.) in MeOH (1.1 mL) was added 1.0 M aqueous HCl (0.5 mL). The reaction mixture was stirred at room temperature for 24 hours. It was diluted with CH_2Cl_2, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 49/1) to afford the title compound (16.0 mg, 0.039 mmol, 78%) as a colourless oil.

$[\alpha]_D^{25}$ +6.2 (c = 1.6, $CHCl_3$); **R_f** 0.32 (CH_2Cl_2/MeOH = 19/1); **IR** (thin film): ν_{max}/cm^{-1} 3380, 2925, 2856, 1613, 1513, 1457, 1248, 1094, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.15 (dq, *J* = 10.2, 1.4 Hz, 1H, *H25*), 4.44 (s, 2H, OC*H*$_2$Ar), 3.98 (s, 2H, *H23*), 3.80 (s, 3H, OC*H*$_3$), 3.56 – 3.53 (m, 1H, *H28*), 3.47 (td, *J* = 5.9, 2.4 Hz, 2H, *H31*), 3.19 – 3.15 (m, 1H, *H27*), 3.02 (brs, 1H, O*H*), 2.50 (tdd, *J* = 10.4, 7.7, 3.1 Hz, 1H, *H26*), 2.38 (d, *J* = 7.3 Hz, 1H, O*H*), 1.91 (brs, 1H, O*H*), 1.74 – 1.58 (m, 4H, *H29* and *H30*), 1.67 (d, *J* = 1.4 Hz, 3H, CC*H*$_3$), 1.34 – 1.06 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.86 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.4, 136.8, 130.2, 129.5, 127.3, 114.0, 77.1, 72.9, 71.4, 70.3, 68.8, 55.4, 41.5, 32.3, 32.0, 31.2, 29.7, 27.3, 26.4, 22.8, 14.5, 14.2; **HRMS** (ESI) m/z calcd for $C_{24}H_{40}O_5$ $[M+Na]^+$: 431.2768, found 431.2764.

6.2.2. The C13–C22 fragment

5-Hexynal (24)



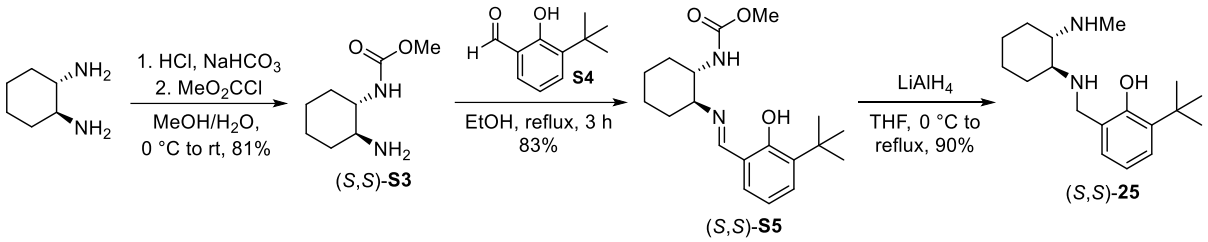
Synthesized according to a modified literature procedure.[199] To a solution of TEMPO (593.8 mg, 3.80 mmol, 0.1 eq.) and (diacetoxyiodo)benzene (14.7 g, 45.60 mmol, 1.2 eq.) in anhydrous CH_2Cl_2 (25.3 mL) under argon was slowly added 5-hexyn-1-ol (4.2 mL, 38.00 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 3 hours. It was quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and carefully concentrated under reduced pressure (*note: the product is volatile and the water bath should be kept at room temperature*). The residue was purified by flash chromatography on silica gel (pentane/dichloromethane = 4/1 → 1/4) to afford the title compound[xxvi] (2.73 g, 28.40 mmol, 75%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, *J* = 1.3 Hz, 1H), 2.61 (td, *J* = 7.2, 1.3 Hz, 2H), 2.27 (td, *J* = 6.9, 2.7 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.85 (quint, *J* = 7.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 201.8, 83.3, 69.5, 42.7, 21.0, 17.9.

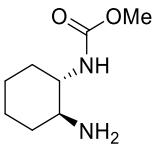
The physical and spectroscopic data were consistent with literature reported data.[200]

[xxvi] The aldehyde can be used as a solution in CH_2Cl_2 after most of the solvent is removed.

*Synthesis of diaminophenol ligand (S,S)-**25***[163]



Methyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate ((*S*,*S*)-S3)

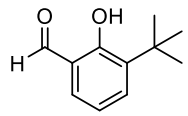


Synthesized according to a literature procedure.[163] To a solution of concentrated HCl (6.2 mL, 75.9 mmol, 1.0 eq.) in MeOH (33 mL) at 0 °C was added (*S*,*S*)-(+)-1,2-diaminocyclohexane (8.67 g, 75.9 mmol, 1.0 eq.). The mixture was stirred at room temperature for 15 minutes, after which water (10 mL) and $NaHCO_3$ (7.65 g, 91.1 mmol, 1.2 eq.) were added. After stirring for an additional 30 minutes, the resulting thick mixture was cooled to 0 °C. A solution of methyl chloroformate (5.9 mL, 75.9 mmol, 1.0 eq.) in MeOH (7.8 mL) was added dropwise and the reaction mixture was stirred at 0 °C overnight, allowing the ice bath to warm to room temperature. The mixture was diluted with water (40 mL) and extracted with diethyl ether (3 × 40 mL). The organic layers were discarded, and the aqueous layer was treated with 15% aqueous NaOH until the pH was >10. It was extracted with CH_2Cl_2 (5 × 40 mL), and the organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound (10.57 g, 61.4 mmol, 81%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 (brs, 1H), 3.67 (s, 3H), 3.21 – 3.13 (m, 1H), 2.37 – 2.31 (m, 1H), 2.03 – 1.92 (m, 2H), 1.73 – 1.68 (m, 2H), 1.31 – 1.09 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.4, 58.3, 55.7, 52.2, 35.5, 33.0, 25.3, 25.2.

The physical and spectroscopic data were consistent with literature reported data.[201]

3-(*tert*-Butyl)-2-hydroxybenzaldehyde (S4)

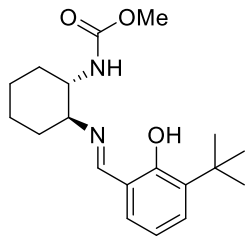


Synthesized according to a literature procedure.[162] To a solution of 2-*tert*-butylphenol (30.7 mL, 0.20 mol, 1.0 eq.) in anhydrous acetonitrile (400 mL) was added paraformaldehyde (40.5 g, 1.35 mol, 6.75 eq.), $MgCl_2$ (28.6 g, 0.30 mol, 1.5 eq.), and anhydrous Et_3N (104.3 mL, 0.75 mol, 3.74 eq.). The reaction mixture was stirred at reflux for 5 hours. Upon cooling to room temperature, 5% aqueous HCl (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 125 mL). The organic layers were concentrated under reduced pressure and the residue was partitioned between diethyl ether (250 mL) and water (250 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by vacuum distillation (b.p. 94 °C @ ~2 mbar) to afford the title compound (21.0 g, 0.12 mol, 59%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.79 (s, 1H), 9.88 (s, 1H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.40 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 197.3, 161.4, 138.4, 134.2, 132.1, 120.8, 119.3, 35.0, 29.3.

The physical and spectroscopic data were consistent with literature reported data.[162]

Methyl ((1*S*,2*S*)-2-(((*E*)-3-(*tert*-butyl)-2-hydroxybenzylidene)amino)cyclohexyl) carbamate ((*S*,*S*)-**S5)**



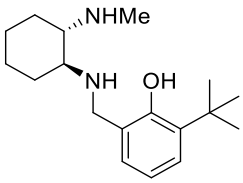
Synthesized according to a literature procedure.[163] To a solution of amine (*S,S*)-**S3** (10.57 g, 61.4 mmol, 1.0 eq.) in EtOH (153 mL) was added aldehyde **S4** (12.03 g, 67.5 mmol, 1.1 eq.). The reaction mixture was stirred at reflux for 3 hours. It was cooled to

room temperature and concentrated under reduced pressure. The solid was recrystallized from minimal boiling hexanes to afford the title compound (16.96 g, 51.0 mmol, 83%) as light yellow crystals.

m.p. 123–125 °C; $[\alpha]_D^{25}$ +95.2 (c = 1.2, $CHCl_3$); **IR** (thin film): ν_{max}/cm^{-1} 3312, 2939, 2859, 1697, 1630, 1539, 1436, 1263, 751; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.7 (s, 1H), 8.32 (s, 1H), 7.31 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 4.53 (brs, 1H), 3.69 – 3.61 (m, 1H), 3.56 (s, 3H), 3.10 (brs, 1H), 2.12 (d, *J* = 10.4 Hz, 1H), 1.90 – 1.75 (m, 3H), 1.74 – 1.64 (m, 1H), 1.43 (s, 9H), 1.43 – 1.29 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.1, 160.5, 137.5, 129.9, 129.5, 118.7, 117.9, 55.1, 34.9, 33.6, 31.8, 29.5, 24.8, 24.2; **HRMS** (ESI) m/z calcd for $C_{19}H_{28}N_2O_3$ $[M+H]^+$: 333.2173, found 333.2171.

The physical and spectroscopic data were consistent with literature reported data.[163]

2-(*tert*-Butyl)-6-((((1*S*,2*S*)-2-(methylamino)cyclohexyl)amino)methyl)phenol ((*S*,*S*)-**25)**

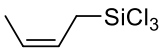


Synthesized according to a literature procedure.[163] To a suspension of $LiAlH_4$ (3.15 g, 83.1 mmol, 3.0 eq.) in anhydrous THF (200 mL) at 0 °C under argon was added a solution of imine (*S*,*S*)-**S5** (9.21 g, 27.7 mmol, 1.0 eq.) in anhydrous THF (77 mL) dropwise via addition funnel. The reaction mixture was stirred at room temperature for 1 hour and at reflux overnight. It was cooled to 0 °C and carefully quenched with successive dropwise addition of water (3.2 mL), 15% aqueous NaOH (3.2 mL), and water (9.6 mL). The mixture was stirred at room temperature for 10 minutes, $MgSO_4$ was added, and it was stirred for another 20 minutes. It was filtered and concentrated under reduced pressure. The resulting solid was recrystallized from minimal boiling hexanes to afford the title compound (7.26 g, 25.0 mmol, 90%) as white crystals.

m.p. 116–118 °C; $[\alpha]_D^{25}$ +112.4 (c = 0.8, $CHCl_3$); **IR** (thin film): ν_{max}/cm^{-1} 3223, 2930, 2856, 1434, 1242, 1087, 749; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.88 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 2.39 (s, 3H), 2.24 – 2.09 (m, 4H), 1.78 – 1.70 (m, 2H), 1.42 (s, 9H), 1.29 – 1.17 (m, 3H), 1.02 – 0.91 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.5, 136.9, 126.2, 125.7, 124.4, 118.1, 62.4, 62.2, 51.0, 34.8, 33.6, 31.2, 31.1, 29.7, 25.3, 24.8; **HRMS** (ESI) m/z calcd for $C_{18}H_{30}N_2O$ $[M+H]^+$: 291.2431, found 291.2430.

The physical and spectroscopic data were consistent with literature reported data.[163]

cis-Crotyltrichlorosilane (26)

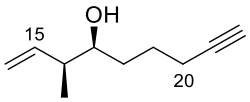


Synthesized according to a modified literature procedure.[162] To a solution of $Pd(PPh_3)_4$ (289 mg, 0.25 mmol, 0.25 mol%) in anhydrous THF (25 mL) at –78 °C under argon was added 1,3-butadiene (2.0 M in THF, 50.0 mL, 100.0 mmol, 1.0 eq.) and trichlorosilane (12.1 mL, 120.0 mmol, 1.2 eq.). The reaction mixture was stirred at –78 °C for 15 minutes and at room temperature for 24 hours. The solvent was removed by distillation and the residue was purified by vacuum distillation (b.p. 54 °C @ ~40 mbar) to afford the title compound (15.5 g, 81.7 mmol, 82%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 – 5.68 (m, 1H), 5.46 – 5.38 (m, 1H), 2.36 (ddq, *J* = 8.2, 1.3, 0.8 Hz, 2H), 1.66 (ddt, *J* = 6.8, 1.7, 0.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 128.5, 118.7, 24.9, 13.2.

The physical and spectroscopic data were consistent with literature reported data.[162]

(3*S*,4*S*)-3-Methylnon-1-en-8-yn-4-ol (27)



Synthesized according to a modified literature procedure.[162] To a solution of (*S*,*S*)-**25** (5.65 g, 19.45 mmol, 1.1 eq.) in anhydrous CH_2Cl_2 (55 mL) at 0 °C under argon was added DBU (8.7 mL, 58.34 mmol, 3.3 eq.), followed by slow addition of *cis*-crotyltrichlorosilane **26** (4.02 g, 21.22 mmol, 1.2 eq.). The solution was stirred at room temperature for 1 hour, after which it was recooled to 0 °C. A solution of 5-hexynal **24** (1.70 g, 17.68 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 1 hour. The mixture was treated with TBAF (1.0 M in THF, 23.0 mL, 23.0 mmol, 1.3 eq.) at 0 °C, stirred at room temperature for 1 hour, and carefully concentrated under reduced pressure (*note: the product is volatile*). The residue was suspended in diethyl ether (90 mL) and the mixture was stirred vigorously for 20 minutes. The resulting precipitated DBU•HCl salts were removed by filtration and the filtrate was treated with 1 M aqueous HCl (97.2 mL, 97.2 mmol, 5.5 eq.). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (2 × 90 mL). The organic layers were washed with water (2 × 90 mL) and saturated aqueous $NaHCO_3$ (90 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 9/1 → 4/1) to afford the title compound (2.33 g, 15.30 mmol, 87%, 92% *ee*,[xxvii] >20:1 *dr*) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –37.9 (c = 1.0, $CHCl_3$); **R_f** 0.23 (pentane/diethyl ether = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3384, 3306, 2934, 2870, 1639, 1456, 1105, 1072, 997, 954, 915; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.5, 9.9, 7.4 Hz, 1H, *H15*), 5.11 – 5.06 (m, 2H, *H14*), 3.51 (ddd, *J* = 9.2, 5.0, 3.1 Hz, 1H, *H17*), 2.32 – 2.25 (m, 1H, *H16*), 2.23 (td, *J* = 6.6, 2.6 Hz, 2H, *H20*), 1.95 (t, *J* = 2.6 Hz, 1H, *H22*), 1.79 – 1.41 (m, 4H, *H18* and *H19*), 1.03 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.9, 115.6, 84.5, 74.4, 68.6, 43.8, 33.1, 25.2, 18.5, 14.3; **HRMS** not found.

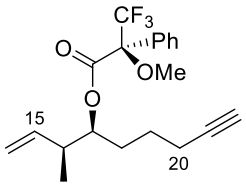
[xxvii] Determined by ^{1}H NMR analysis of the Mosher esters of **27** (^{19}F NMR peaks were overlapping)

*Recovery of (S,S)-**25** ligand*

The combined aqueous acid and water layers were treated with 1 M aqueous NaOH (194.5 mL, 194.5 mmol, 10 eq. with respect to the ligand) and extracted with CH_2Cl_2 (4 × 90 mL). The organic layers were washed with water (2 × 90 mL) and brine (90 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was recrystallized from minimal boiling hexanes to afford the recovered (*S*,*S*)-**25** ligand (4.50 g, 15.49 mmol, 80%) as white crystals.

*Mosher ester analysis of **27***

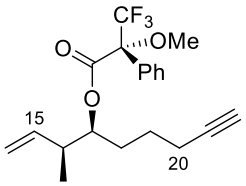
(*S*)-MTPA ester of 27



Synthesized according to a modified literature procedure.[194] To a solution of alcohol **27** (10.0 mg, 0.066 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (63.3 mg, 0.251 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (660 µL) was added pyridine (33 µL, 0.409 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 49/1) to afford the title compound (22.9 mg, 0.062 mmol, 94%) as a colourless oil.

$[\alpha]_D^{25}$ –51.3 (c = 2.3, $CHCl_3$); R_f 0.49 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3307, 2953, 1743, 1259, 1169, 1123, 1018, 994; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 6.9, 2.8 Hz, 2H, Ar*H*), 7.41 – 7.38 (m, 3H, Ar*H*), 5.76 (ddd, *J* = 16.9, 10.8, 7.1 Hz, 1H, *H15*), 5.09 – 5.05 (m, 3H, *H14* and *H17*), 3.54 (s, 3H, OCH_3), 2.57 – 2.50 (m, 1H, *H16*), 2.12 (td, *J* = 6.8, 2.7 Hz, 2H, *H20*), 1.93 (t, *J* = 2.7 Hz, 1H, *H22*), 1.77 – 1.63 (m, 2H, *H18*), 1.49 – 1.33 (m, 2H, *H19*), 1.04 (d, *J* = 6.9 Hz, 3H, CHCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.5, 139.1, 132.3, 129.7, 128.5, 127.6, 123.5 (q, *J* = 289 Hz), 116.1, 84.8 (q, *J* = 28 Hz), 83.7, 79.7, 68.9, 55.6, 40.8, 30.0, 24.0, 18.2, 15.0; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.1; **HRMS** (ESI) m/z calcd for $C_{20}H_{23}F_3O_3$ $[M+Na]^+$: 391.1492, found 391.1493.

(*R*)-MTPA ester of 27



Synthesized in the same manner as the (*S*)-MTPA ester of **27** using 0.066 mmol of alcohol **27** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound (24.0 mg, 0.065 mmol, 99%) was obtained as a colourless oil.

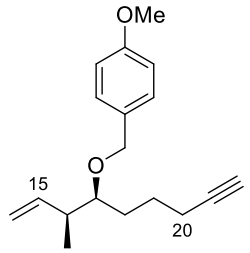
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +7.3 (c = 2.4, $CHCl_3$); **R_f** 0.49 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3307, 2952, 1744, 1259, 1169, 1123, 1018, 994; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 7.0, 3.0 Hz, 2H, Ar*H*), 7.41 – 7.39 (m, 3H, Ar*H*), 5.65 (ddd, *J* = 17.4, 10.5, 7.4 Hz, 1H, *H15*), 5.07 (ddd, *J* = 8.0, 5.7, 4.0 Hz, 1H, *H17*), 5.02 – 4.96 (m, 2H, *H14*), 3.55 (s, 3H, OCH_3), 2.51 – 2.44 (m, 1H, *H16*), 2.19 (td, *J* = 6.8, 2.7 Hz, 2H, *H20*), 1.95 (t, *J* = 2.7 Hz, 1H, *H22*), 1.82 – 1.69 (m, 2H, *H18*), 1.60 – 1.47 (m, 2H, *H19*), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.5, 139.0, 132.4, 129.7, 128.5, 127.6, 123.5 (q, *J* = 289 Hz), 116.0, 84.6 (q, *J* = 28 Hz), 83.7, 79.7, 69.0, 55.6, 40.9, 30.3, 24.3, 18.3, 14.9; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.1; **HRMS** (ESI) m/z calcd for $C_{20}H_{23}F_3O_3$ $[M+Na]^+$: 391.1492, found 391.1496.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
H14	5.07	4.99	+0.08
H15	5.76	5.65	+0.11
H16	2.54	2.48	+0.06
CH_3	1.04	0.96	+0.08
H18	1.70	1.75	–0.05
H19	1.41	1.53	–0.12
H20	2.12	2.19	–0.07
H22	1.93	1.95	–0.02

Analysis indicates that the C17 centre is of *S* configuration.

1-Methoxy-4-((((3*S*,4*S*)-3-methylnon-1-en-8-yn-4-yl)oxy)methyl)benzene (28)

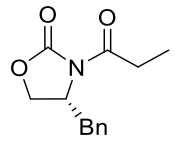


To a solution of alcohol **27** (2.33 g, 15.30 mmol, 1.0 eq.) in anhydrous DMF (30.6 mL) at 0 °C under argon was added NaH (60% in mineral oil, 1.22 g, 30.60 mmol, 2.0 eq.). The mixture was stirred at 0 °C for 30 minutes, after which PMBBr[xxviii] (4.4 mL, 30.60 mmol, 2.0 eq.) and TBAI (1.13 g, 3.06 mmol, 0.2 eq.) were added. The reaction mixture was stirred at room temperature for 2.5 hours. It was quenched slowly with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 49/1) to afford the title compound (3.78 g, 13.88 mmol, 91%) as a colourless oil.

$[\alpha]_D^{25}$ –38.9 (c = 1.1, $CHCl_3$); **R_f** 0.43 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3300, 2954, 2936, 2867, 1612, 1513, 1247, 1173, 1078, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.84 (ddd, *J* = 17.2, 10.4, 7.4 Hz, 1H, *H15*), 5.08 – 5.01 (m, 2H, *H14*), 4.50 (d, *J* = 11.0 Hz, 1H, OCH_2Ar), 4.44 (d, *J* = 11.0 Hz, 1H, OCH'_2Ar), 3.80 (s, 3H, OCH_3), 3.26 (ddd, *J* = 7.4, 5.7, 3.5 Hz, 1H, *H17*), 2.54 – 2.45 (m, 1H, *H16*), 2.19 – 2.14 (m, 2H, *H20*), 1.94 (t, *J* = 2.7 Hz, 1H, *H22*), 1.73 – 1.50 (m, 4H, *H18* and *H19*), 1.05 (d, *J* = 6.9 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 140.9, 131.1, 129.5, 114.6, 113.9, 84.7, 82.2, 71.5, 68.5, 55.4, 40.8, 30.2, 24.6, 18.6, 15.9; **HRMS** (ESI) m/z calcd for $C_{18}H_{24}O_2$ $[M+Na]^+$: 295.1669, found 295.1670.

[xxviii] Prepared according to the procedure in reference 202

(*R*)-4-Benzyl-3-propionyloxazolidin-2-one (30)

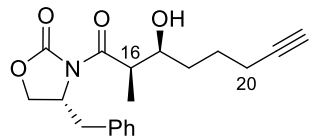


Synthesized according to a literature procedure.[203] To a solution of (*R*)-4-benzyl-2-oxazolidinone (10.0 g, 56.4 mmol, 1.0 eq.) in anhydrous THF (94 mL) at –78 °C under argon was added *n*-BuLi (1.6 M in hexanes, 38.8 mL, 62.0 mmol, 1.1 eq.) over 15 minutes. The resulting orange solution was stirred at –78 °C for 10 minutes, after which propionyl chloride (6.4 mL, 73.3 mmol, 1.3 eq.) was added. The colourless solution was stirred at –78 °C for 30 minutes, allowed to warm to room temperature, and stirred for an additional 30 minutes. The mixture was quenched with saturated aqueous NH_4Cl (30 mL). THF was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (12.59 g, 54.0 mmol, 92%) as white needle-like crystals.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ –60.1 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.17 (m, 5H), 4.67 (ddt, *J* = 9.6, 7.3, 3.3 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.31 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.08 – 2.85 (m, 2H), 2.77 (dd, *J* = 13.3, 9.6 Hz, 1H), 1.21 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.2, 153.7, 135.5, 129.6, 129.1, 127.5, 66.4, 55.3, 38.1, 29.4, 8.4.

The physical and spectroscopic data were consistent with literature reported data.[203]

(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyloct-7-ynoyl)oxazolidin-2-one (31)

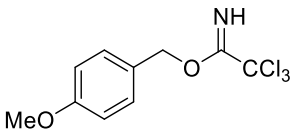


Synthesized according to a modified literature procedure.[204] To a solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone **30** (8.67 g, 37.2 mmol, 1.05 eq.) in anhydrous CH_2Cl_2 (60.8 mL) under argon at 0 °C was added dibutylboron triflate (1.0 M in CH_2Cl_2, 49.6 mL, 49.6 mmol, 1.4 eq.) dropwise, followed by anhydrous triethylamine (7.9 mL, 56.6 mmol, 1.6

eq.). The solution was stirred for 45 minutes, after which it was cooled to –78 °C. A solution of 5-hexynal **24** (3.40 g, 35.4 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 30 minutes and at 0 °C overnight (allowing the ice bath to melt). It was quenched with 1 M pH 7 phosphate buffer (46 mL) and MeOH (36 mL) at 0 °C. A mixture of MeOH/30% aqueous H_2O_2 (1:1, 120 mL) was added and the mixture was stirred at room temperature for 1 hour. It was extracted with CH_2Cl_2, and the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1 → 7/3) to afford the title compound (6.46 g, 19.6 mmol, 55%, >20:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ –54.1 (c = 1.0, $CHCl_3$); **R_f** 0.19 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3524, 3290, 1776, 1693, 1386, 1210, 1109; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.26 (m, 3H, Ar*H*), 7.23 – 7.18 (m, 2H, Ar*H*), 4.71 (ddt, *J* = 9.3, 7.4, 3.2 Hz, 1H, C*H*Bn), 4.29 – 4.16 (m, 2H, oxazolidinone-C*H*$_2$), 4.02 – 3.93 (m, 1H, *H17*), 3.75 (qd, *J* = 7.1, 2.6 Hz, 1H, *H16*), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H, C*H*$_2$Ph), 2.94 (d, *J* = 2.3 Hz, 1H, O*H*), 2.79 (dd, *J* = 13.4, 9.4 Hz, 1H, C*H'*$_2$Ph), 2.27 – 2.22 (m, 2H, *H20*), 1.95 (t, *J* = 2.6 Hz, 1H, *H22*), 1.79 – 1.52 (m, 4H, *H18* and *H19*), 1.27 (d, *J* = 7.1 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.7, 153.1, 135.1, 129.6, 129.1, 127.6, 84.3, 71.1, 68.8, 66.3, 55.2, 42.4, 37.9, 32.8, 25.1, 18.4, 10.6; **HRMS** (ESI) m/z calcd for $C_{19}H_{23}NO_4$ $[M+H]^+$: 330.1700, found 330.1697.

4-Methoxybenzyl 2,2,2-trichloroacetimidate



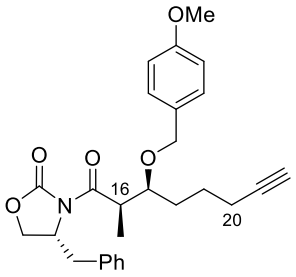
Synthesized according to a modified literature procedure.[205] To a solution of *p*-methoxybenzyl alcohol (5.0 mL, 40.00 mmol, 1.0 eq.) in anhydrous diethyl ether (14.8 mL) under argon was added NaH (60% in mineral oil, 400 mg, 10.00 mmol, 0.25 eq.). The mixture was stirred at room temperature for 30 minutes, after which it was cooled to 0 °C. Trichloroacetonitrile (4.0 mL, 40.00 mmol, 1.0 eq.) was added, and the reaction mixture was stirred at room temperature for 3 hours. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a pad of

aluminium oxide, washing with pentane/diethyl ether (9:1), to afford the title compound (10.40 g, 36.81 mmol, 92%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (brs, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.27 (s, 2H), 3.82 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.8, 159.9, 129.9, 127.7, 114.1, 77.4, 70.9, 55.4.

The physical and spectroscopic data were consistent with literature reported data.[205]

(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-((4-methoxybenzyl)oxy)-2-methyloct-7-ynoyl)oxazolidin-2-one (32)

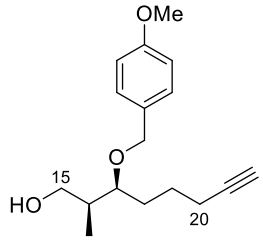


Synthesized according to a modified literature procedure.[206] To a solution of alcohol **31** (4.19 g, 12.72 mmol, 1.0 eq.) and $Sc(OTf)_3$ (187.0 mg, 0.38 mmol, 3 mol%) in anhydrous toluene (88 mL) at 0 °C under argon was added 4-methoxybenzyl 2,2,2-trichloroacetimidate (5.3 mL, 25.44 mmol, 2.0 eq.) dropwise. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 1 hour. It was concentrated under reduced pressure, and the residue was taken up in a pentane/CH_2Cl_2 (5:1) solution. The mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (4.67 g, 10.39 mmol, 82%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –58.8 (c = 1.0, $CHCl_3$); **R_f** 0.46 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3290, 2952, 1777, 1697, 1513, 1383, 1246, 1211, 1108, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.17 (m, 7H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.53 – 4.47 (m, 1H, C*H*Bn), 4.46 (s, 2H, OCH_2Ar), 4.14 – 4.05 (m, 2H, oxazolidinone-CH_2 and *H16*), 4.04 – 3.97 (m, 1H, oxazolidinone-C*H'*$_2$), 3.77 (s, 3H, OCH_3), 3.65 (dt, *J* = 5.7, 5.7 Hz, 1H, *H17*), 3.27 (dd, *J* = 13.3, 3.2 Hz, 1H, CH_2Ph), 2.74 (dd, *J* = 13.3, 9.7 Hz, 1H, C*H'*$_2$Ph), 2.19 (td,

J = 6.6, 2.6 Hz, 2H, *H20*), 1.95 (t, *J* = 2.6 Hz, 1H, *H22*), 1.74 – 1.50 (m, 4H, *H18* and *H19*), 1.27 (d, *J* = 6.9 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.2, 159.3, 153.3, 135.5, 130.5, 129.9, 129.6, 129.1, 127.5, 113.8, 84.4, 79.0, 71.7, 68.7, 66.1, 55.9, 55.4, 41.1, 37.8, 30.9, 24.7, 18.5, 12.4; **HRMS** (ESI) m/z calcd for $C_{27}H_{31}NO_5$ $[M+Na]^+$: 472.2094, found 472.2094.

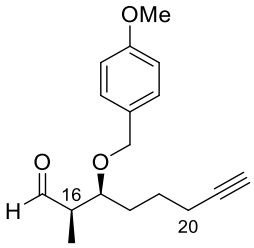
(2*S*,3*S*)-3-((4-Methoxybenzyl)oxy)-2-methyloct-7-yn-1-ol (33)



To a solution of imide **32** (4.67 g, 10.39 mmol, 1.0 eq.) in anhydrous THF (69.3 mL) under argon at 0 °C was added anhydrous MeOH (1.3 mL, 31.17 mmol, 3.0 eq.) dropwise, followed by $LiBH_4$ (2.0 M in THF, 15.6 mL, 31.17 mmol, 3.0 eq.). The reaction mixture was stirred at 0 °C for 45 minutes and at room temperature for 1 hour. It was cooled to 0 °C, carefully quenched with 1 M NaOH (45 mL) and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (1.83 g, 6.62 mmol, 64%) as a colourless oil.

$[\alpha]_D^{25}$ –1.0 (c = 1.0, $CHCl_3$); **R$_f$** 0.20 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3420, 3293, 2937, 1612, 1514, 1248, 1035, 821; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.50 (dd, *J* = 26.7, 11.1 Hz, 2H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.69 (dd, *J* = 10.8, 8.1 Hz, 1H, C*H*$_2$OH), 3.58 – 3.47 (m, 2H, C*H'*$_2$OH and *H17*), 2.52 (brs, 1H, O*H*), 2.22 – 2.17 (m, 2H, *H20*), 2.14 – 2.08 (m, 1H, *H16*), 1.96 (t, *J* = 2.6 Hz, 1H, *H22*), 1.74 – 1.48 (m, 4H, *H18* and *H19*), 0.88 (d, *J* = 7.1 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.4, 130.5, 129.7, 114.0, 84.3, 81.5, 71.5, 68.8, 66.1, 55.4, 36.8, 28.9, 25.2, 18.6, 12.2; **HRMS** (ESI) m/z calcd for $C_{17}H_{24}O_3$ $[M+Na]^+$: 299.1618, found 299.1617.

(2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)-2-methyloct-7-ynal (29)



*From alkene **28**:* To a solution of alkene **28** (1.49 g, 5.47 mmol, 1.0 eq.) in acetone (54.7 mL) and water (18.2 mL) at 0 °C was added 4-methylmorpholine *N*-oxide (NMO) monohydrate (1.48 g, 10.94 mmol, 2.0 eq.), followed by potassium osmate dihydrate (60.4 mg, 0.164 mmol, 3 mol%). The reaction mixture was stirred at 0 °C overnight, allowing the cooling bath (acetone/dry ice) to warm to ~15 °C. Saturated aqueous $Na_2S_2O_3$ (45 mL) was added, and the mixture was stirred vigorously for 2 hours. It was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a 3:1 diastereomeric mixture of diols (1.46 g, 4.77 mmol). The diol mixture was dissolved in CH_2Cl_2 (47.7 mL), and $NaIO_4$ (14 wt% on silica,[207] 18.2 g, 11.93 mmol, 2.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (940 mg, 3.43 mmol, 63% over two steps) as a colourless oil.

*From alcohol **33**:* To a solution of alcohol **33** (1.83 g, 6.62 mmol, 1.0 eq.) in anhydrous DMSO (11.0 mL) and anhydrous CH_2Cl_2 (22.1 mL) at 0 °C under argon was added anhydrous *i*-Pr_2NEt (4.6 mL, 26.48 mmol, 4.0 eq.) and sulfur trioxide pyridine complex (4.21 g, 26.48 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 1 hour. It was quenched with water and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound[xxix] (1.51 g, 5.50 mmol, 83%) as a colourless oil.

[xxix]Some epimerisation of the product was observed (>16:1 *dr*).

$[\alpha]_D^{25}$ –36.8 (c = 0.6, $CHCl_3$); **R_f** 0.42 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3291, 2939, 1720, 1613, 1514, 1249, 1174, 1065, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.76 (d, *J* = 1.1 Hz, 1H, C*H*O), 7.23 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.45 (s, 2H, OCH_2Ar), 3.84 – 3.81 (m, 1H, *H17*), 3.80 (s, 3H, OCH_3), 2.58 (qdd, *J* = 7.1, 3.9, 1.0 Hz, 1H, *H16*), 2.23 – 2.18 (m, 2H, *H20*), 1.96 (t, *J* = 2.6 Hz, 1H, *H22*), 1.75 – 1.51 (m, 4H, *H18* and *H19*), 1.13 (d, *J* = 7.0 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.7, 159.4, 130.3, 129.5, 114.0, 84.1, 77.8, 71.6, 68.9, 55.4, 49.8, 31.0, 24.9, 18.5, 8.5; **HRMS** (ESI) m/z calcd for $C_{17}H_{22}O_3$ $[M+Na]^+$: 297.1461, found 297.1463.

((1-Ethoxyvinyl)oxy)trimethylsilane (34)

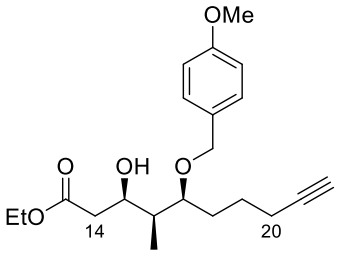
Synthesized according to a modified literature procedure.[208] To a solution of anhydrous diisopropylamine (20.2 mL, 144.0 mmol, 1.2 eq.) in anhydrous THF (70 mL) at 0 °C under argon was added *n*-BuLi (2.5 M in hexanes, 57.6 mL, 144.0 mmol, 1.2 eq.) dropwise. The light yellow solution was stirred for 15 minutes, cooled to –78 °C, and ethyl acetate (11.7 mL, 120.0 mmol, 1.0 eq.) was added. The solution was stirred for 1 hour, after which freshly distilled chlorotrimethylsilane (19.8 mL, 156.0 mmol, 1.3 eq.) was added dropwise over 10 minutes. The white reaction mixture was stirred at –78 °C for 30 minutes and at room temperature for 1.5 hours. It was filtered through celite and concentrated under reduced pressure. The residue was diluted with pentane (200 mL), filtered through celite, and concentrated under reduced pressure. The residue was purified by vacuum distillation (b.p. 52 °C @ ~35 mbar) to afford the title compound[xxx] (6.49 g, 40.5 mmol, 34%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (q, *J* = 7.0 Hz, 2H), 3.20 (d, *J* = 2.6 Hz, 1H), 3.06 (d, *J* = 2.6 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.23 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.2, 63.6, 60.3, 14.5, 0.2.

The physical and spectroscopic data were consistent with literature reported data.[208]

[xxx]Obtained as a ~10:1 mixture with the *C*-silylation product

Ethyl (3*R*,4*S*,5*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-4-methyldec-9-ynoate (35)

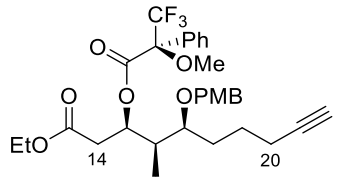


To a solution of aldehyde **29** (1.51 g, 5.50 mmol, 1.0 eq.) and ((1-ethoxyvinyl)oxy)trimethylsilane **34** (2.64 g, 16.50 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (110 mL) at –78 °C under argon was added boron trifluoride diethyl etherate (679 µL, 5.50 mmol, 1.0 eq.) dropwise over 5 minutes. The reaction mixture was stirred at –78 °C for 1 hour, after which it was quenched with pH 7 phosphate buffer and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (1.71 g, 4.72 mmol, 86%, 5:1 *dr*) as a colourless oil.

R_f 0.32 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3498, 3293, 2938, 1730, 1612, 1514, 1248, 1176, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.7, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.55 (d, *J* = 11.0 Hz, 1H, OC*H*$_2$Ar), 4.39 (d, *J* = 11.0 Hz, 1H, OC*H'*$_2$Ar), 4.22 – 4.15 (m, 1H, *H15*), 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.79 (s, 3H, OC*H*$_3$), 3.57 (ddd, *J* = 7.3, 5.7, 3.6 Hz, 1H, *H17*), 3.34 (d, *J* = 2.3 Hz, 1H, O*H*), 2.52 (dd, *J* = 15.9, 8.6 Hz, 1H, *H14*), 2.40 (dd, *J* = 15.9, 4.5 Hz, 1H, *H14'*), 2.21 (tdd, *J* = 6.9, 2.6, 1.1 Hz, 2H, *H20*), 1.97 (t, *J* = 2.6 Hz, 1H, *H22*), 1.87 – 1.60 (m, 4H, *H16* and *H18*), 1.57 – 1.50 (m, 2H, *H19*), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.97 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.8, 159.4, 130.4, 129.5, 114.0, 84.2, 82.1, 71.0, 71.0, 68.9, 60.7, 55.4, 40.0, 39.5, 29.6, 24.8, 18.7, 14.3, 7.6; **HRMS** (ESI) m/z calcd for $C_{21}H_{30}O_5$ $[M+Na]^+$: 385.1986, found 385.1988.

*Mosher ester analysis of **35***

(*S*)-MTPA ester of 35

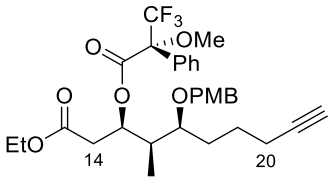


Synthesized according to a modified literature procedure.[194] To a solution of alcohol **35** (10.0 mg, 0.028 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (26.8 mg, 0.106 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (400 µL) was added pyridine (14 µL, 0.174 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound[xxxi] (14.2 mg, 0.025 mmol, 89%) as a colourless oil.

R_f 0.34 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3288, 2952, 1746, 1514, 1250, 1172, 1022; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.57 – 7.54 (m, 2H, Ar*H*), 7.40 – 7.39 (m, 3H, Ar*H*), 7.21 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.52 (dt, *J* = 7.7, 4.9 Hz, 1H, *H15*), 4.38 (d, *J* = 11.1 Hz, 1H, OC*H*$_2$Ar), 4.29 (d, *J* = 11.1 Hz, 1H, OC*H'*$_2$Ar), 4.09 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.80 (s, 3H, OC*H*$_3$), 3.55 (s, 3H, OC*H*$_3$), 3.22 – 3.18 (m, 1H, *H17*), 2.75 – 2.63 (m, 2H, *H14*), 2.14 (tdd, *J* = 6.8, 2.7, 1.0 Hz, 2H, *H20*), 2.07 – 2.02 (m, 1H, *H16*), 1.96 (t, *J* = 2.6 Hz, 1H, *H22*), 1.61 – 1.57 (m, 2H, *H18*), 1.50 – 1.41 (m, 2H, *H19*), 1.22 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.91 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.5, 165.9, 159.3, 132.4, 130.6, 129.7, 129.5, 128.5, 127.5, 123.5 (q, *J* = 289 Hz), 113.9, 84.5 (q, *J* = 28 Hz), 84.2, 78.3, 74.9, 71.1, 68.8, 61.0, 55.6, 55.4, 38.8, 36.9, 29.8, 24.4, 18.6, 14.2, 10.4; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.1; **HRMS** (ESI) m/z calcd for $C_{31}H_{37}F_3O_7$ $[M+Na]^+$: 601.2384, found 601.2377.

[xxxi] Obtained as a mixture of diastereomers (carried over from the starting material)

(*R*)-MTPA ester of 35



Synthesized in the same manner as the (*S*)-MTPA ester of **35** using 0.028 mmol of alcohol **35** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound[xxxi] (13.6 mg, 0.024 mmol, 85%) was obtained as a colourless oil.

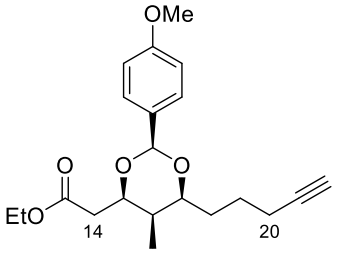
R_f 0.34 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3302, 2950, 1745, 1514, 1250, 1173, 1030; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 – 7.51 (m, 2H, Ar*H*), 7.43 – 7.37 (m, 3H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.53 (dt, *J* = 7.4, 5.1 Hz, 1H, *H15*), 4.43 (d, *J* = 11.0 Hz, 1H, OCH_2Ar), 4.35 (d, *J* = 11.0 Hz, 1H, OC*H'*$_2$Ar), 4.05 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.80 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.35 – 3.30 (m, 1H, *H17*), 2.73 – 2.57 (m, 2H, *H14*), 2.18 (tdd, *J* = 6.8, 2.7, 1.4 Hz, 2H, *H20*), 2.13 – 2.07 (m, 1H, *H16*), 1.97 (t, *J* = 2.7 Hz, 1H, *H22*), 1.71 – 1.65 (m, 2H, *H18*), 1.61 – 1.47 (m, 2H, *H19*), 1.21 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.98 (d, *J* = 7.1 Hz, 3H, CHCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.3, 165.9, 159.3, 132.0, 130.6, 129.7, 129.5, 128.6, 127.8, 123.5 (q, *J* = 289 Hz), 113.9, 84.8 (q, *J* = 28 Hz), 84.2, 78.6, 75.1, 71.1, 68.9, 60.9, 55.4, 55.4, 38.7, 36.9, 29.7, 24.5, 18.6, 14.2, 10.5; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.2; **HRMS** (ESI) m/z calcd for $C_{31}H_{37}F_3O_7$ $[M+Na]^+$: 601.2384, found 601.2380.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
ester CH_3	1.22	1.21	+0.01
ester CH_2	4.09	4.05	+0.04
H14	2.69	2.66	+0.03
H16	2.04	2.09	–0.05
CH_3	0.91	0.98	–0.07
H17	3.20	3.33	–0.13
H18	1.59	1.68	–0.09
H19	1.46	1.52	–0.06
H20	2.14	2.18	–0.04
H22	1.96	1.97	–0.01

Analysis indicates that the C15 centre is of *R* configuration.

Ethyl 2-((4*R*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-(pent-4-yn-1-yl)-1,3-dioxan-4-yl) acetate (3)

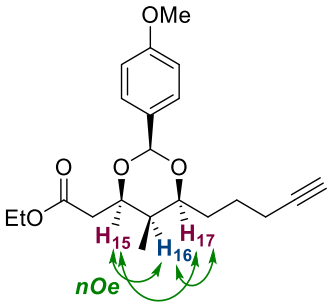


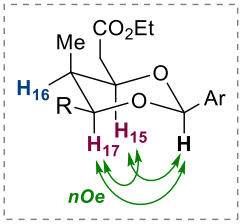
To a solution of alcohol **35** (3.11 g, 8.58 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (170 mL) under argon was added molecular sieves (3Å, 9.0 g). The mixture was cooled to 0 °C and DDQ (3.90 g, 17.16 mmol, 2.0 eq.) was added slowly in three portions. The reaction mixture was stirred at 0 °C for 2 hours.[xxxii] It was filtered through celite, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound[xxxiii] (1.86 g, 5.16 mmol, 60%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –5.8 (c = 1.0, $CHCl_3$); **R_f** 0.42 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3290, 2941, 1734, 1518, 1249, 1182, 1063, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 4.38 (ddd, *J* = 7.9, 5.9, 2.3 Hz, 1H, *H15*), 4.15 (qd, *J* = 7.1, 0.9 Hz, 2H, $CO_2CH_2CH_3$), 3.89 (ddd, *J* = 8.4, 4.6, 2.3 Hz, 1H, *H17*), 3.79 (s, 3H, OCH_3), 2.69 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.47 (dd, *J* = 15.7, 5.9 Hz, 1H, *H14'*), 2.29 – 2.18 (m, 2H, *H20*), 1.96 (t, *J* = 2.6 Hz, 1H, *H22*), 1.84 – 1.66 (m, 2H, *H18* and *H19*), 1.65 – 1.51 (m, 3H, *H16*, *H18'* and *H19'*), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.99 (d, *J* = 6.9 Hz, 3H, $CHCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 160.0, 131.4, 127.5, 113.7, 101.6, 84.4, 80.5, 77.3, 68.7, 60.7, 55.4, 38.2, 34.6, 31.9, 24.8, 18.5, 14.4, 6.1; **HRMS** (ESI) m/z calcd for $C_{21}H_{28}O_5$ $[M+Na]^+$: 383.1829, found 383.1826.

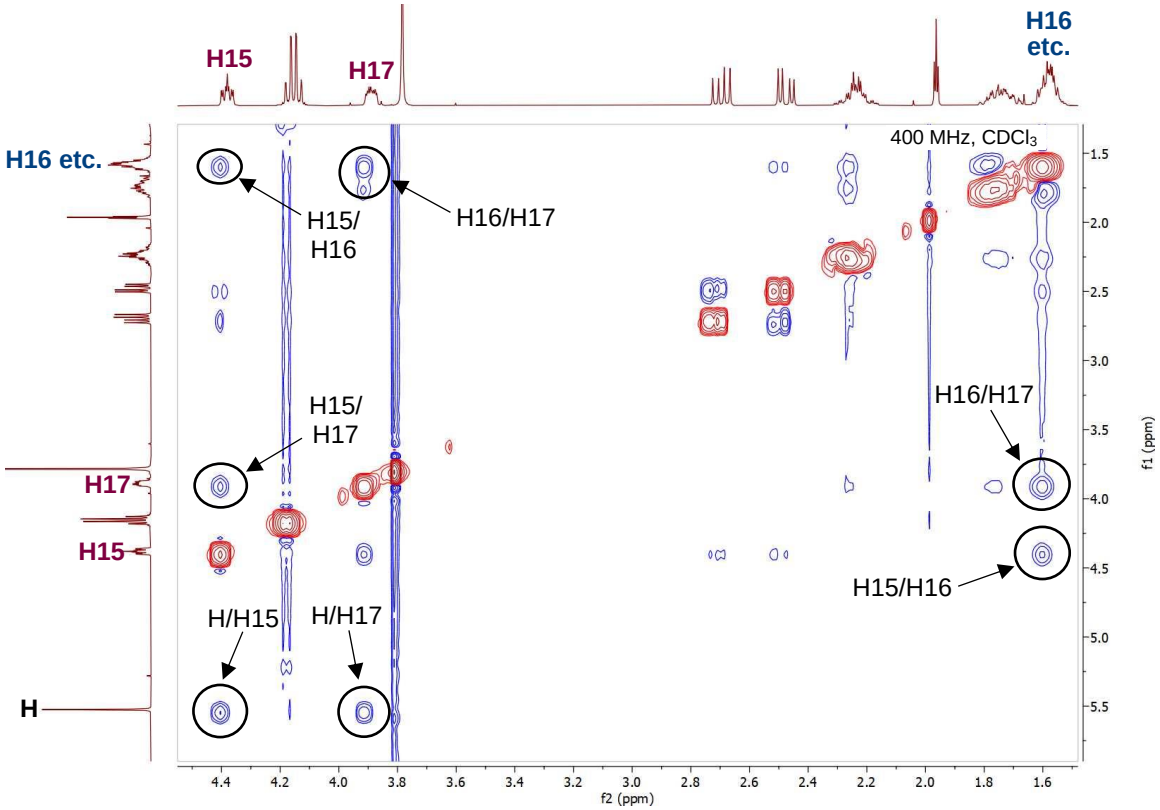
[xxxii]Note: it is important to maintain the temperature at 0 C. [xxxiii]The mixture of diastereomers from the starting material is separable at this point; only the pure major diastereomer was collected.

*NOESY spectrum of **3***



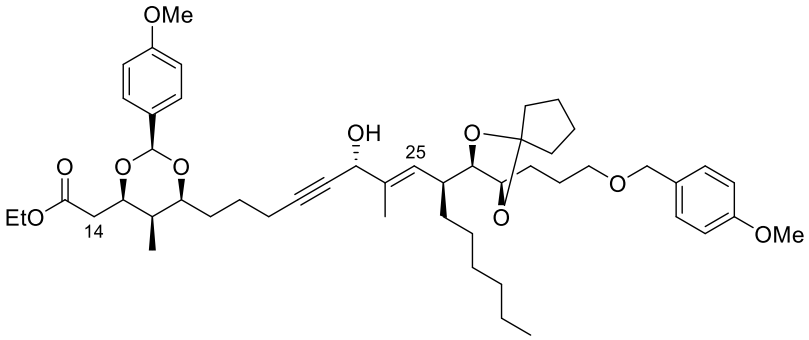


$J_{H15\text{-}H16}$ = 2.3 Hz
$J_{H16\text{-}H17}$ = 2.3 Hz



6.2.3. The C13–C31 fragment

Ethyl 2-((4*R*,5*R*,6*S*)-6-((6*R*,9*S*,*E*)-6-hydroxy-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy) propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-4-yn-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (36)



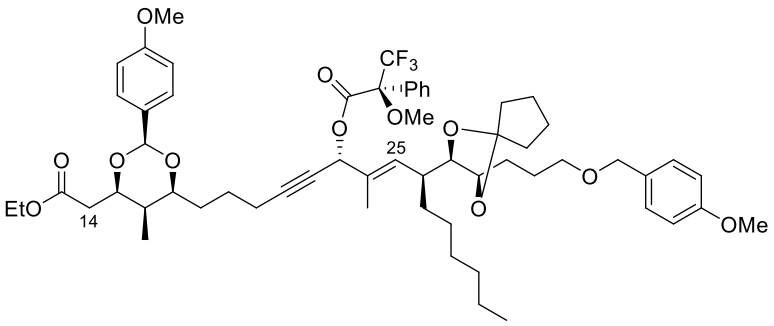
Synthesized according to a modified literature procedure.[170] To a solution of alkyne **3** (1.15 g, 3.18 mmol, 3.0 eq.) and (*S*)-BINOL (121.4 mg, 0.42 mmol, 0.4 eq.) in anhydrous diethyl ether (10.3 mL) under argon was added dicyclohexylamine (42 µL, 0.21 mmol, 0.2 eq.), followed by dropwise addition of diethyl zinc (1.0 M in hexanes, 3.2 mL, 3.18 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 2–3 days (*Note: argon flow was removed from the flask and the septum was parafilmed to prevent the evaporation of solvent; after 2–3 days, the mixture should become cloudy with precipitate*). Distilled titanium(IV) isopropoxide (314 µL, 1.06 mmol, 1.0 eq.) was added dropwise and the resulting yellow-orange mixture was stirred at room temperature for 2 hours. It was cooled to 0 °C, and a solution of aldehyde **4b** (501.0 mg, 1.06 mmol, 1.0 eq.) in anhydrous diethyl ether (3 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 2 hours. It was cooled to 0 °C, quenched slowly with saturated aqueous NH_4Cl, filtered through celite, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 7/3) to afford the title compound (573.4 mg, 0.69 mmol, 65%, 13:1 *dr*) as a colourless oil; alkyne **3** (845.9 mg, 2.35 mmol) was also recovered.

Pure **36**: $[\alpha]_D^{25}$ –12.4 (c = 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.11 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3445, 2929, 2856, 1736, 1614, 1515, 1463, 1248, 1181, 1099, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 4H, Ar*H*), 5.51 (s, 1H, *CH*PMP), 5.15 (d, *J* = 10.9 Hz, 1H, *H25*), 4.69 – 4.68

(m, 1H, *H23*), 4.41 (s, 2H, OCH_2Ar), 4.37 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H, *H15*), 4.15 (qd, *J* = 7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.88 – 3.84 (m, 1H, *H17*), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.60 – 3.55 (m, 1H, *H28*), 3.48 – 3.31 (m, 3H, *H27* and *H31*), 2.92 (d, *J* = 4.7 Hz, 1H, O*H*), 2.68 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.46 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.42 – 2.36 (m, 1H, *H26*), 2.31 – 2.20 (m, 2H, *H20*), 1.78 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.77 – 1.43 (m, 17H, *H16*, *H18*, *H19*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.30 – 1.12 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.97 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.86 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 159.9, 159.3, 137.7, 131.3, 130.2, 129.5, 127.5, 127.3, 118.1, 113.8, 113.6, 101.5, 85.7, 83.6, 80.4, 80.2, 79.9, 77.2, 72.3, 69.0, 68.4, 60.6, 55.3, 55.3, 42.7, 38.1, 37.5, 37.5, 34.5, 32.4, 31.9, 31.9, 30.6, 29.4, 26.9, 26.5, 24.9, 23.6, 23.5, 22.7, 18.9, 14.3, 14.2, 13.0, 6.0; **HRMS** (ESI) m/z calcd for $C_{50}H_{72}O_{10}$ $[M+Na]^+$: 855.5018, found 855.5019.

*Mosher ester analysis of **36***

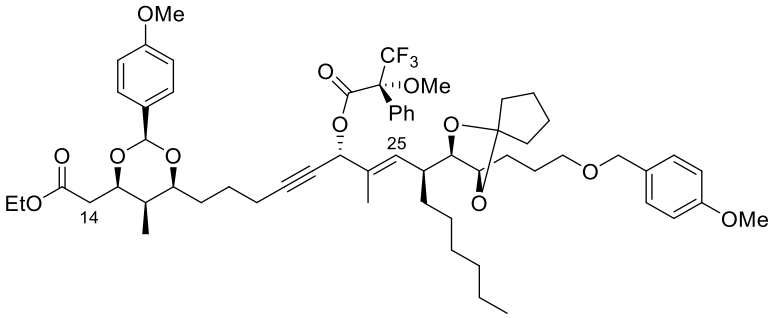
(*S*)-MTPA ester of 36



Synthesized according to a modified literature procedure.[194] To a solution of alcohol **36** (10.0 mg, 0.012 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11.6 mg, 0.046 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (500 µL) was added pyridine (6 µL, 0.074 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature for 24 hours. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/1) to afford the title compound (11.8 mg, 0.011 mmol, 94%) as a colourless oil.

$[\alpha]_D^{25}$ –10.2 (c = 1.2, $CHCl_3$); **R_f** 0.51 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 2933, 2856, 1745, 1516, 1454, 1248, 1172, 1101, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 – 7.50 (m, 2H, Ar*H*), 7.39 – 7.36 (m, 5H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 4H, Ar*H*), 5.91 (t, *J* = 2.0 Hz, 1H, *H23*), 5.50 (s, 1H, C*H*PMP), 5.42 (d, *J* = 10.7 Hz, 1H, *H25*), 4.38 (s, 2H, OCH_2Ar), 4.36 (ddd, *J* = 8.0, 5.7, 2.2 Hz, 1H, *H15*), 4.15 (qd, *J* = 7.1, 1.1 Hz, 2H, $CO_2CH_2CH_3$), 3.86 – 3.81 (m, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.62 (ddd, *J* = 8.0, 5.9, 3.8 Hz, 1H, *H28*), 3.50 (s, 3H, OCH_3), 3.46 (dd, *J* = 8.0, 6.3 Hz, 1H, *H27*), 3.39 (t, *J* = 6.5 Hz, 2H, *H31*), 2.68 (dd, *J* = 15.7, 8.0 Hz, 1H, *H14*), 2.45 (dd, *J* = 15.7, 5.7 Hz, 1H, *H14'*), 2.45 – 2.39 (m, 1H, *H26*), 2.31 – 2.16 (m, 2H, *H20*), 1.78 – 1.47 (m, 17H, *H16*, *H18*, *H19*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.73 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.29 – 1.08 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.86 (d, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 165.5, 160.0, 159.2, 132.5, 132.1, 131.7, 131.3, 131.0, 129.7, 129.3, 128.5, 127.7, 127.6, 123.4 (q, *J* = 289 Hz), 118.3, 113.9, 113.7, 101.6, 88.4, 84.9 (q, *J* = 28 Hz), 83.5, 80.5, 79.6, 77.3, 75.4, 72.6, 71.8, 70.0, 60.7, 55.5, 55.4, 55.4, 42.3, 38.2, 37.8, 37.8, 34.6, 32.0, 32.0, 31.9, 30.8, 29.5, 26.9, 26.3, 24.8, 23.7, 23.6, 22.7, 18.8, 14.3, 14.2, 13.9, 6.1; **HRMS** (ESI) m/z calcd for $C_{60}H_{79}F_3O_{12}$ $[M+Na]^+$: 1071.5416, found 1071.5408.

(*R*)-MTPA ester of 36



Synthesized in the same manner as the (S)-MTPA ester of **36** using 0.012 mmol of alcohol **36** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound (11.7 mg, 0.011 mmol, 93%) was obtained as a colourless oil.

$[\alpha]_D^{25}$ +10.2 (c = 1.2, $CHCl_3$); **R_f** 0.51 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 2933, 2856, 1746, 1515, 1454, 1248, 1171, 1100, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$):

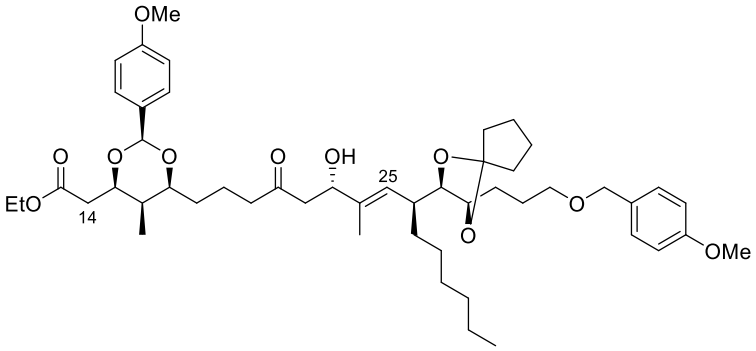
δ 7.55 – 7.53 (m, 2H, Ar*H*), 7.39 – 7.35 (m, 5H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 4H, Ar*H*), 5.94 (t, *J* = 2.2 Hz, 1H, *H23*), 5.50 (s, 1H, C*H*PMP), 5.36 (d, *J* = 10.6 Hz, 1H, *H25*), 4.40 (s, 2H, OCH_2Ar), 4.36 (ddd, *J* = 8.0, 5.7, 2.2 Hz, 1H, *H15*), 4.15 (qd, *J* = 7.2, 0.9 Hz, 2H, $CO_2CH_2CH_3$), 3.86 – 3.82 (m, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.63 – 3.58 (m, 1H, *H28*), 3.55 (s, 3H, OCH_3), 3.45 – 3.40 (m, 3H, *H27* and *H31*), 2.68 (dd, *J* = 15.7, 8.0 Hz, 1H, *H14*), 2.45 (dd, *J* = 15.7, 5.7 Hz, 1H, *H14'*), 2.42 – 2.36 (m, 1H, *H26*), 2.35 – 2.20 (m, 2H, *H20*), 1.76 – 1.45 (m, 17H, *H16*, *H18*, *H19*, *H29*, *H30* and cyclopent-$(CH_2)_4$), 1.64 (d, *J* = 1.1 Hz, 3H, CCH_3), 1.28 – 1.05 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.95 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.86 (t, *J* = 7.1 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 165.6, 160.0, 159.2, 132.5, 132.4, 131.3, 131.3, 129.8, 129.3, 128.5, 127.5, 127.5, 123.4 (q, *J* = 290 Hz), 118.3, 113.9, 113.7, 101.6, 88.6, 84.6 (q, *J* = 28 Hz), 83.6, 80.5, 79.7, 77.3, 75.6, 72.6, 71.4, 70.1, 60.7, 55.5, 55.4, 55.4, 42.4, 38.2, 37.8, 37.8, 34.6, 32.0, 31.9, 30.8, 30.5, 29.4, 26.9, 26.3, 24.8, 23.7, 23.6, 22.7, 18.9, 14.3, 14.2, 13.7, 6.1; **HRMS** (ESI) m/z calcd for $C_{60}H_{79}F_3O_{12}$ $[M+Na]^+$: 1071.5416, found 1071.5408.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
H17	3.83	3.84	–0.01
H20	2.23	2.27	–0.04
CCH_3	1.73	1.64	+0.09
H25	5.41	5.36	+0.05
H26	2.43	2.40	+0.03
H27	3.46	3.43	+0.03

Analysis indicates that the C23 centre is of *R* configuration.

Ethyl 2-((4*R*,5*R*,6*S*)-6-((6*S*,9*S*,*E*)-6-hydroxy-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy) propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methyl-4-oxopentadec-7-en-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (37)

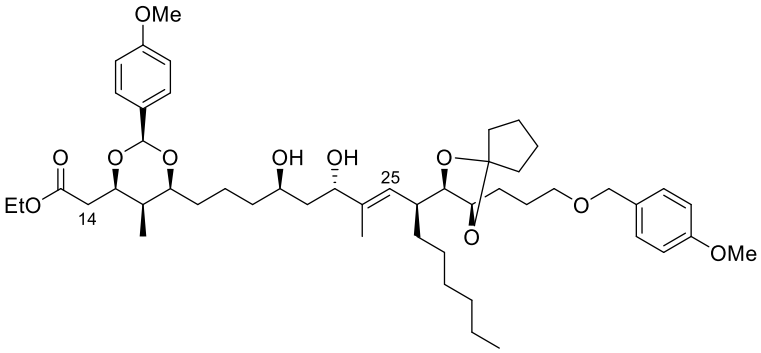


Synthesized according to a modified literature procedure.[172] To a solution of alcohol **36** (554.0 mg, 0.66 mmol, 1.0 eq.) in anhydrous diethyl ether (3.3 mL) under argon was added bis(pinacolato)diboron (401.2 mg, 1.58 mmol, 2.4 eq.), followed by sodium *tert*-butoxide (38.4 mg, 0.40 mmol, 0.6 eq.) in one portion. The mixture was cooled to 0 °C and [(IMes)CuCl][209] (13.3 mg, 0.033 mmol, 5 mol%) was added, followed by anhydrous methanol (107 µL, 2.64 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 45 minutes. The dark-coloured mixture was quenched with 2–3 drops of triethanolamine and stirred at 0 °C for 10 minutes and at room temperature for 10 minutes. It was filtered through celite and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in THF (8.2 mL) and water (8.2 mL), and sodium perborate monohydrate (329.4 mg, 3.30 mmol, 5.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3 → 7/3) to afford the title compound (385.5 mg, 0.45 mmol, 69%) as a colourless oil.

$[\alpha]_D^{25}$ +1.4 (c = 1.0, $CHCl_3$); **R_f** 0.21 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3480, 2927, 2857, 1735, 1716, 1517, 1458, 1249, 1182, 1100, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.22 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 4H, Ar*H*), 5.49 (s, 1H, C*H*PMP), 5.08 (d, *J* = 10.2 Hz, 1H, *H25*), 4.44 – 4.42 (m, 1H, *H23*), 4.40 (s, 2H, OCH_2Ar), 4.36 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H, *H15*), 4.14 (qd, *J* = 7.2, 1.1 Hz, 2H, $CO_2CH_2CH_3$), 3.86 – 3.83 (m, 1H, *H17*), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.59 – 3.54 (m, 1H, *H28*), 3.47 (dt, *J* = 10.4, 5.3 Hz, 1H, *H31*), 3.39 – 3.33 (m, 2H, *H27* and

H31'), 3.24 (d, *J* = 2.9 Hz, 1H, O*H*), 2.70 – 2.62 (m, 2H, *H14* and *H22*), 2.48 – 2.34 (m, 5H, *H14*', *H20*, *H22'* and *H26*), 1.80 – 1.40 (m, 17H, *H16*, *H18*, *H19*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.1 Hz, 3H, CCH_3), 1.30 – 1.07 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.86 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 210.2, 171.1, 156.0, 159.3, 138.4, 131.3, 130.3, 129.5, 127.5, 127.1, 118.1, 113.9, 113.7, 101.6, 83.8, 80.8, 80.2, 77.3, 73.8, 72.4, 69.2, 60.6, 55.4, 55.3, 48.0, 43.6, 42.5, 38.1, 37.6, 37.5, 34.4, 32.4, 32.1, 31.9, 30.9, 29.5, 27.0, 26.6, 23.7, 23.6, 22.8, 19.6, 14.3, 14.2, 12.4, 6.0; **HRMS** (ESI) m/z calcd for $C_{50}H_{74}O_{11}$ [M+Na]$^+$: 873.5123, found 873.5128.

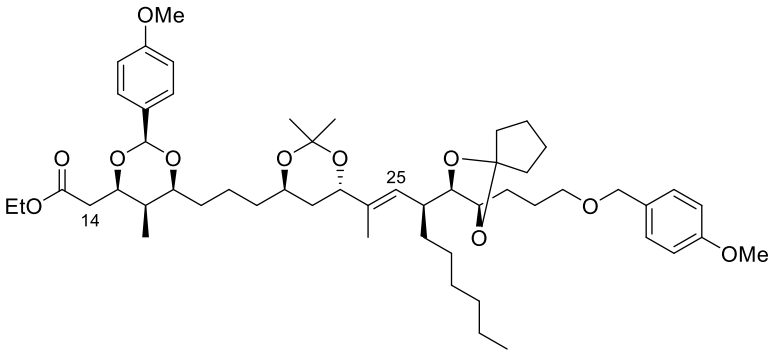
Ethyl 2-((4*R*,5*R*,6*S*)-6-((4*R*,6*S*,9*S*,*E*)-4,6-dihydroxy-9-((2*R*,3*R*)-3-(3-((4-methoxy benzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (38)



Synthesized according to a modified literature procedure.[210] To a stirred suspension of tetramethylammonium triacetoxyborohydride (642.0 mg, 2.44 mmol, 5.8 eq.) in anhydrous acetonitrile (11 mL) under argon was added glacial acetic acid (2.4 mL). The solution was cooled to –20 °C and a solution of β-hydroxy ketone **37** (358.5 mg, 0.42 mmol, 1.0 eq.) in anhydrous acetonitrile (3 mL) was added dropwise. The reaction mixture was stirred at –20 °C overnight. It was quenched with saturated aqueous potassium sodium tartrate (10 mL), warmed to room temperature, and stirred for 30 minutes, upon which a white precipitate formed. The mixture was poured over ice, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 7/3) to afford the title compound (342.1 mg, 0.40 mmol, 95%, >20:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ +3.5 (c = 1.0, $CHCl_3$); **R_f** 0.16 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3435, 2931, 2857, 1736, 1515, 1461, 1248, 1180, 1100, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.39 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.8, 4H, Ar*H*), 5.50 (s, 1H, C*H*PMP), 5.16 (d, *J* = 10.7 Hz, 1H, *H25*), 4.40 – 4.33 (m, 3H, *H15* and OCH_2Ar), 4.18 – 4.11 (m, 3H, $CO_2CH_2CH_3$ and *H23*), 3.84 – 3.79 (m, 1H, *H17*), 3.77 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.70 – 3.64 (m, 1H, *H21*), 3.53 – 3.47 (m, 2H, *H28* and *H31*), 3.38 (dd, *J* = 9.2, 7.0 Hz, 1H, *H27*), 3.31 (td, *J* = 9.2, 2.9 Hz, 1H, *H31'*), 3.27 (brs, 1H, O*H*), 2.68 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.45 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.42 – 2.36 (m, 1H, *H26*), 1.84 – 1.32 (m, 21H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30* and cyclopent-$(CH_2)_4$), 1.59 (d, *J* = 1.1 Hz, 3H, CCH_3), 1.29 – 1.08 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.97 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.86 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 160.0, 159.4, 139.2, 131.4, 129.9, 129.7, 127.5, 125.0, 118.1, 113.9, 113.6, 101.6, 84.2, 80.8, 80.6, 77.3, 74.7, 72.6, 69.4, 69.1, 60.6, 55.3, 55.3, 43.1, 39.2, 38.1, 37.8, 37.4, 37.4, 34.4, 33.0, 32.8, 31.9, 31.7, 29.5, 27.0, 26.9, 23.6, 23.5, 22.7, 21.6, 14.3, 14.2, 13.4, 6.0; **HRMS** (ESI) m/z calcd for $C_{50}H_{76}O_{11}$ $[M+Na]^+$: 875.5280, found 875.5283.

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy) propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (39)

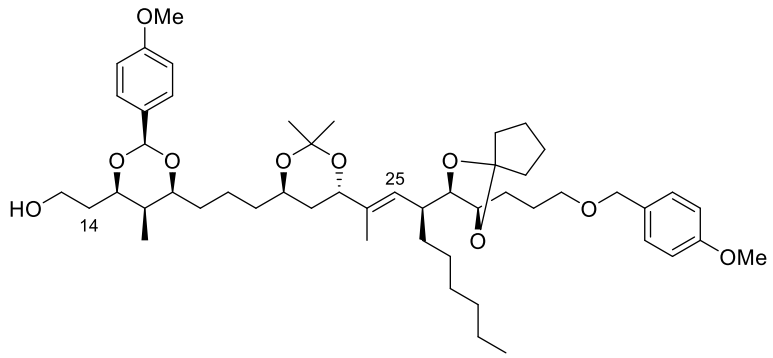


To a solution of diol **38** (342.1 mg, 0.40 mmol, 1.0 eq.) in 2,2-dimethoxypropane/CH_2Cl_2 (3 mL, 1:1) was added pyridinium *p*-toluenesulfonate (8.0 mg, 0.032 mmol, 8 mol%). The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (306.8 mg, 0.34 mmol, 86%) as a colourless oil.

$[\alpha]_D^{25}$ –7.8 (c = 1.0, $CHCl_3$); **R_f** 0.39 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 2930, 2856, 1737, 1515, 1463, 1248, 1172, 1101, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.8, 4H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.6 Hz, 1H, *H25*), 4.41 (s, 2H, OCH_2Ar), 4.37 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H, *H15*), 4.20 – 4.13 (m, 3H, $CO_2CH_2CH_3$ and *H23*), 3.86 (ddd, *J* = 7.6, 5.2, 2.1 Hz, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.76 – 3.73 (m, 1H, *H21*), 3.65 (ddd, *J* = 8.0, 6.5, 3.4 Hz, 1H, *H28*), 3.45 – 3.41 (m, 3H, *H27* and *H31*), 2.69 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.47 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.43 – 2.38 (m, 1H, *H26*), 1.84 – 1.45 (m, 21H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.33 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.10 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.98 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.87 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 160.0, 159.2, 137.1, 131.4, 130.8, 129.2, 127.5, 125.8, 118.0, 113.8, 113.6, 101.6, 100.3, 83.9, 80.8, 79.8, 77.3, 72.5, 71.5, 71.0, 66.6, 60.6, 55.4, 55.3, 41.9, 38.2, 37.7, 37.7, 37.1, 35.9, 34.2, 32.5, 32.1, 31.9, 31.0, 29.5, 27.0, 26.5, 25.0, 24.9, 23.7, 23.6, 22.7, 21.3, 14.3, 14.2, 13.2, 6.0; **HRMS** (ESI) m/z calcd for $C_{53}H_{80}H_{11}$ $[M+Na]^+$: 915.5593, found 915.5592.

2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethan-1-ol (40)

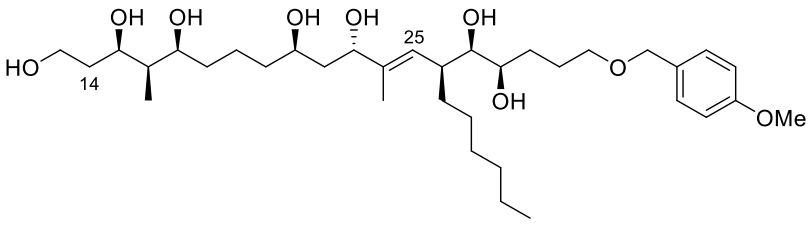


To a solution of ester **39** (50 mg, 0.056 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (560 µL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 140 µL, 0.140 mmol, 2.5 eq.)

dropwise. The mixture was stirred at –78 °C for 2 hours and at 0 °C for 1 hour. The mixture was quenched with successive dropwise addition of water (8 µL), 15% aqueous NaOH (8 µL), and water (16 µL). It was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 3/1) to afford the title compound (38.3 mg, 0.045 mmol, 80%) as a colourless oil.

$[\alpha]_D^{25}$ –5.3 (c = 2.0, $CHCl_3$); **R_f** 0.19 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3454, 2933, 2856, 2342, 1615, 1515, 1461, 1248, 1171, 1101, 1010; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.23 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.51 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.41 (s, 2H, OCH_2Ar), 4.17 (dd, *J* = 9.5, 6.1 Hz, 1H, *H23*), 4.07 (dt, *J* = 9.9, 2.9 Hz, 1H, *H15*), 3.85 – 3.74 (m, 10H, *H13*, *H17*, *H21*, OCH_3 × 2), 3.65 (ddd, *J* = 8.0, 6.5, 3.5 Hz, 1H, *H28*), 3.45 – 3.40 (m, 3H, *H27* and *H31*), 2.45 – 2.37 (m, 1H, *H26*), 2.08 – 1.96 (m, 2H, *H14*), 1.81 – 1.45 (m, 21H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.33 (s, 6H, acetonide-CH_3 × 2), 1.28 – 1.14 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.99 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0, 159.2, 137.2, 131.5, 130.9, 129.3, 127.6, 125.9, 118.1, 113.9, 113.8, 101.7, 100.4, 84.0, 81.2, 80.4, 79.9, 72.6, 71.6, 70.2, 66.7, 61.2, 55.4, 55.4, 42.0, 37.7, 37.7, 37.2, 36.0, 35.5, 35.1, 32.5, 32.1, 32.0, 31.0, 29.5, 27.0, 26.5, 25.1, 24.9, 23.7, 23.6, 22.8, 21.3, 14.2, 13.3, 6.2; **HRMS** (ESI) m/z calcd for $C_{51}H_{78}O_{10}$ [M+Na]$^+$: 873.5487, found 873.5482.

(3*R*,4*R*,5*S*,9*R*,11*S*,14*S*,15*R*,16*R*,*E*)-14-hexyl-19-((4-methoxybenzyl)oxy)-4,12-dimethyl-nonadec-12-ene-1,3,5,9,11,15,16-heptaol (41)



To a solution of acetal **40** (10.5 mg, 0.012 mmol) in MeOH (700 µL) was added 0.2 M aqueous HCl (700 µL). The reaction mixture was stirred at room temperature for 24 hours. It was diluted with chloroform, quenched with saturated aqueous $NaHCO_3$, and extracted with chloroform. The organic layers were washed with saturated aqueous $NaHCO_3$ and

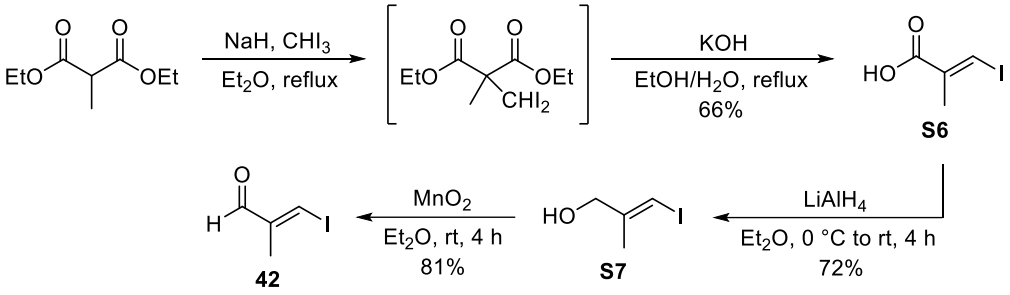
brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 24/1 → 23/2) to afford the title compound (3.3 mg, 0.005 mmol, 44%) as a colourless oil.

$[\alpha]_D^{25}$ +4.8 (c = 0.3, $CHCl_3$); **R_f** 0.12 (CH_2Cl_2/MeOH = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3393, 2928, 2857, 1612, 1513, 1248, 1099, 1038; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.28 (d, *J* = 10.1 Hz, 1H, *H25*), 4.44 (s, 2H, OCH_2Ar), 4.30 (dd, *J* = 7.0, 2.6 Hz, 1H, *H23*), 4.10 (dt, *J* = 9.9, 2.4 Hz, 1H, *H15*), 3.95 (s, 1H, O*H*), 3.87 – 3.75 (m, 4H, *H13*, *H17* and *H21*), 3.80 (s, 3H, OCH_3), 3.60 – 3.58 (m, 1H, *H28*), 3.54 (s, 1H, O*H*), 3.50 – 3.47 (m, 2H, *H31*), 3.40 (s, 1H, O*H*), 3.34 (s, 1H, O*H*), 3.27 (s, 1H, O*H*), 3.23 (s, 1H, *H27*), 2.91 (s, 1H, O*H*), 2.60 (s, 1H, O*H*), 2.53 – 2.48 (m, 1H, *H26*), 1.86 – 1.80 (m, 1H, *H16*), 1.78 – 1.34 (m, 17H, *H14*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30* and CCH_3), 1.27 – 1.08 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.92 (d, *J* = 7.1 Hz, 3H, CHCH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 159.4, 138.8, 130.1, 129.6, 126.7, 114.0, 76.5, 74.7, 72.9, 71.3, 70.2, 69.2, 66.0, 61.7, 55.4, 41.6, 41.5, 40.6, 37.3, 36.8, 35.1, 32.1, 32.0, 31.2, 29.7, 27.4, 26.3, 22.8, 22.3, 15.4, 14.3, 13.4, 5.2; **HRMS** (ESI) m/z calcd for $C_{35}H_{62}O_9$ $[M+Na]^+$: 649.4286, found 649.4283.

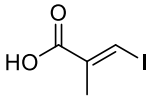
6.3. The C1–C27 fragment

6.3.1. The C1–C11 fragment

*Synthesis of aldehyde **42***



***(E)*-3-Iodo-2-methylacrylic acid (S6)**



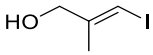
Synthesized according to a modified literature procedure.[211] To a suspension of NaH (60% in mineral oil, 8.64 g, 216.0 mmol, 1.2 eq.) in anhydrous diethyl ether (112.5 mL) under argon was added diethyl methylmalonate (30.7 mL, 180.0 mmol, 1.0 eq.) dropwise over 30 minutes. The resulting thick white suspension was stirred at reflux for 4 hours. Upon cooling to room temperature, iodoform (70.87 g, 180.0 mmol, 1.0 eq.) was added and the mixture was stirred at reflux for 36 hours. It was cooled to 0 °C and 1 M aqueous HCl (120 mL) was added. The resulting dark reddish-brown solution was stirred at 0 °C for 20 minutes. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOH/H_2O (3:1, 546 mL), and KOH (27.27 g, 486.0 mmol) was added. The reaction mixture was stirred at reflux for 24 hours. It was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 10% aqueous K_2CO_3 (300 mL), and the resulting precipitated iodoform was removed by filtration, washing with 10% aqueous K_2CO_3. The filtrate was washed with CH_2Cl_2 (2 × 100 mL) and the organic layers were discarded. The aqueous layer was acidified with concentrated HCl (140 mL) and extracted with CH_2Cl_2 (7 × 40 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced

pressure to afford the crude product (25.18 g, 118.8 mmol, 66%) as an orange-brown oil, which solidified over time. The crude product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.77 (brs, 1H), 8.03 (q, *J* = 1.3 Hz, 1H), 2.06 (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.1, 139.1, 102.0, 19.9.

The physical and spectroscopic data were consistent with literature reported data.[212]

(E)-3-Iodo-2-methylprop-2-en-1-ol (S7)

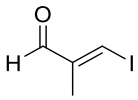


Synthesized according to a modified literature procedure.[212] To a solution of acid **S6** (10.27 g, 48.5 mmol, 1.0 eq.) in anhydrous diethyl ether (32 mL) at 0 °C under argon was added $LiAlH_4$ (4.0 M in diethyl ether, 12.6 mL, 50.4 mmol, 1.04 eq.) dropwise. The reaction mixture was stirred at room temperature for 4 hours. It was cooled to 0 °C and quenched with successive dropwise addition of water (2.1 mL), 15% aqueous NaOH (2.1 mL), and water (6.4 mL). The mixture was stirred at room temperature for 30 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 4/1) to afford the title compound (6.93 g, 35.0 mmol, 72%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (q, *J* = 1.2 Hz, 1H), 4.14 (dq, *J* = 6.2, 0.5 Hz, 2H), 1.85 (dt, *J* = 1.2, 0.5 Hz, 3H), 1.54 (t, *J* = 6.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.4, 77.4, 67.4, 21.5.

The physical and spectroscopic data were consistent with literature reported data.[212]

(E)-3-Iodo-2-methylacrylaldehyde (42)

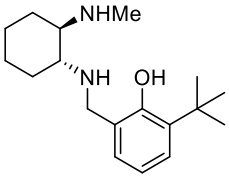


Synthesized according to a modified literature procedure.[213] To a solution of alcohol **S7** (5.0 g, 25.3 mmol, 1 eq.) in anhydrous diethyl ether (100 mL) under argon was added MnO_2 (33.0 g, 379.5 mmol, 15.0 eq.). The reaction mixture was stirred at room temperature for 4 hours. Celite (~16 g) was added and the mixture was stirred for 20 minutes. It was filtered through celite and concentrated under reduced pressure (*note: the product is volatile*). The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 9/1) to afford the title compound (4.0 g, 20.4 mmol, 81%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.81 (q, *J* = 1.2 Hz, 1H), 1.92 (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 189.5, 151.0, 109.5, 16.6.

The physical and spectroscopic data were consistent with literature reported data.[213]

2-(*tert*-Butyl)-6-((((1*R*,2*R*)-2-(methylamino)cyclohexyl)amino)methyl)phenol ((*R*,*R*)-**25)**



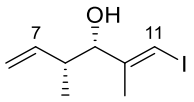
Synthesized from (*R*,*R*)-(–)-1,2-diaminocyclohexane in the same manner as (*S*,*S*)-**25.**

White crystals; **m.p.** 116–118 °C; $[\alpha]_D^{25}$ –112.5 (c = 1.1, $CHCl_3$); **IR** (thin film): ν_{max}/cm^{-1} 3223, 2930, 2856, 1434, 1242, 1087, 749; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.88 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 4.03 (d, *J* = 13.5 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 2.41 (s, 3H), 2.21 – 2.14 (m, 4H), 1.79 – 1.71 (m, 2H), 1.45 (s, 9H), 1.29 – 1.18 (m, 3H), 1.02 – 0.92 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.4,

136.8, 126.2, 125.7, 124.4, 118.1, 62.4, 62.2, 51.0, 34.8, 33.5, 31.2, 31.1, 29.7, 25.3, 24.8; **HRMS** (ESI) m/z calcd for $C_{18}H_{30}N_2O$ $[M+H]^+$: 291.2431, found 291.2429.

The physical and spectroscopic data were consistent with literature reported data.[163]

(3*S*,4*R*,*E*)-1-Iodo-2,4-dimethylhexa-1,5-dien-3-ol (43)



Synthesized according to a modified literature procedure.[162] To a solution of (*R*,*R*)-**25** (8.36 g, 28.79 mmol, 1.1 eq.) in anhydrous CH_2Cl_2 (80 mL) at 0 °C under argon was added DBU (12.9 mL, 86.36 mmol, 3.3 eq.), followed by slow addition of *cis*-crotyltrichlorosilane **26** (5.95 g, 31.40 mmol, 1.2 eq.). The solution was stirred at room temperature for 1 hour, after which it was recooled to 0 °C. A solution of aldehyde **42** (5.13 g, 26.17 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (7 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 hour. The mixture was treated with TBAF (1.0 M in THF, 34.0 mL, 34.0 mmol, 1.3 eq.) at 0 °C, stirred at room temperature for 1 hour, and concentrated under reduced pressure. The residue was suspended in diethyl ether (130 mL) and the mixture was stirred vigorously for 20 minutes. The resulting precipitated DBU•HCl salts were removed by filtration and the filtrate was treated with 1 M aqueous HCl (143.9 mL, 143.9 mmol, 5.5 eq.). The organic layer was separated, and the aqueous layer was further extracted with diethyl ether (2 × 130 mL). The organic layers were washed with water (2 × 130 mL) and saturated aqueous $NaHCO_3$ (130 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 9/1) to afford the title compound (5.77 g, 22.89 mmol, 87%, 89% *ee*, 17:1 *dr*) as a colourless oil.

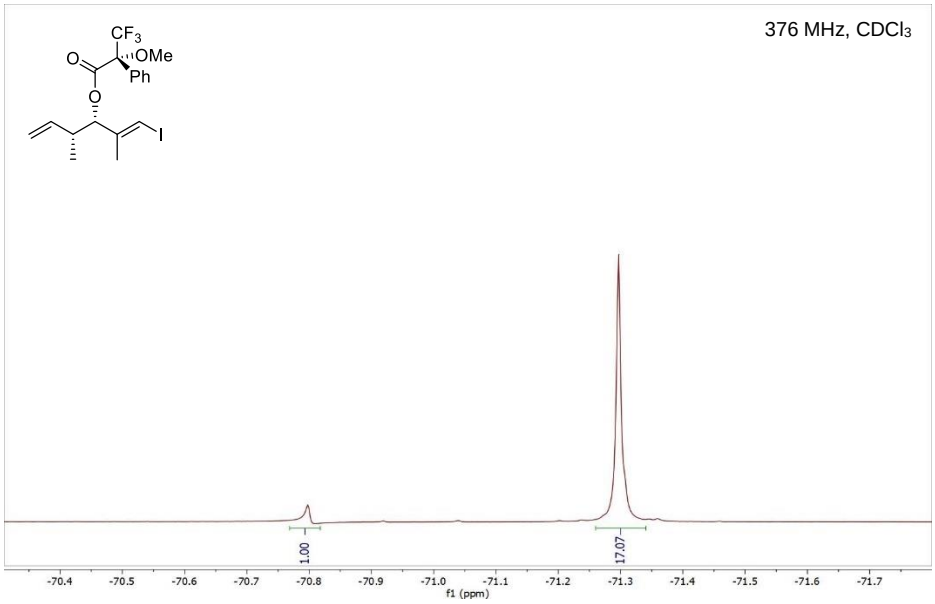
$[\alpha]_D^{25}$ –8.2 (c = 1.0, $CHCl_3$); **R_f** 0.30 (pentane/diethyl ether = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3380, 3079, 2975, 2928, 1640, 1615, 1455, 1377, 1266, 1011, 917, 783, 665; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.26 (app t, *J* = 1.0 Hz, 1H, *H11*), 5.72 (ddd, *J* = 17.1, 10.5, 7.1 Hz, 1H, *H7*), 5.10 (app dt, *J* = 8.1, 1.2 Hz, 1H, *H6*), 5.06 (app d, *J* = 1.2 Hz, 1H, *H6'*), 4.04 (dd, *J* = 5.9, 3.5 Hz, 1H, H9), 2.49 – 2.40 (m, 1H, *H8*), 1.80 (d, *J* = 1.0 Hz, 3H, CC*H*$_3$), 1.71 (d,

J = 3.5 Hz, 1H, O*H*), 1.01 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.4, 140.1, 115.6, 79.8, 79.1, 41.1, 20.7, 14.1; **HRMS** not found.

*Recovery of (R,R)-**25** ligand*

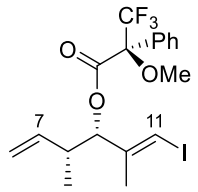
The combined aqueous acid and water layers were treated with 1 M aqueous NaOH (287.9 mL, 287.9 mmol, 10 eq. with respect to the ligand) and extracted with CH_2Cl_2 (4 × 130 mL). The organic layers were washed with water (2 × 130 mL) and brine (130 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was recrystallized from minimal boiling hexanes to afford the recovered (*R*,*R*)-**25** ligand (6.96 g, 24.0 mmol, 83%) as white crystals.

*Determination of ee by ^{19}F NMR analysis of the Mosher ester of **43**: 89% ee*



*Mosher ester analysis of **43***

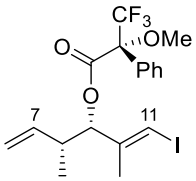
(*S*)-MTPA ester of 43



Synthesized according to a modified literature procedure.[194] To a solution of alcohol **43** (10.0 mg, 0.040 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (38.4 mg, 0.152 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (800 µL) was added pyridine (20 µL, 0.248 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 49/1) to afford the title compound (18.3 mg, 0.039 mmol, 98%) as a colourless oil.

$[\alpha]_D^{25}$ –35.1 (c = 1.8, $CHCl_3$); **R_f** 0.74 (pentane/diethyl ether = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 2980, 1749, 1271, 1242, 1170, 1121, 1016, 994; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.40 (m, 5H, Ar*H*), 6.39 – 6.38 (m, 1H, *H11*), 5.55 (ddd, *J* = 17.0, 10.5, 7.7 Hz, 1H, *H7*), 5.34 (d, *J* = 8.4 Hz, 1H, *H9*), 5.05 (app dt, *J* = 7.4, 1.1 Hz, 1H, *H6*), 5.02 (app d, *J* = 1.1 Hz, 1H, *H6'*), 3.49 (s, 3H, OCH_3), 2.60 – 2.50 (m, 1H, *H8*), 1.78 (d, *J* = 1.1 Hz, 3H, CCH_3), 0.93 (d, *J* = 6.7 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.0, 143.9, 137.8, 132.3, 129.8, 128.6, 127.5, 123.5 (q, *J* = 290 Hz), 116.4, 84.7 (q, *J* = 28 Hz), 83.5, 83.1, 55.5, 40.0, 20.6, 15.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –70.8; **HRMS** (ESI) m/z calcd for $C_{18}H_{20}F_3IO_3$ $[M+Na]^+$: 491.0301, found 491.0300.

(*R*)-MTPA ester of 43



Synthesized in the same manner as the (*S*)-MTPA ester of **43** using 0.042 mmol of alcohol **43** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound (19.5 mg, 0.042 mmol, 99%) was obtained as a colourless oil.

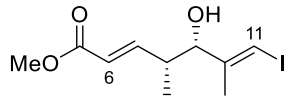
$[\alpha]_D^{25}$ +23.9 (c = 1.9, $CHCl_3$); **R_f** 0.74 (pentane/diethyl ether = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 2980, 1748, 1272, 1247, 1169, 1123, 1016, 994; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.40 (m, 5H, Ar*H*), 6.27 – 6.21 (m, 1H, *H11*), 5.59 (ddd, *J* = 17.2, 10.4, 7.5 Hz, 1H, *H7*), 5.27 (d, *J* = 8.0 Hz, 1H, *H9*), 5.08 (app dt, *J* = 7.9, 1.1 Hz, 1H, *H6*), 5.04 (app d, *J* = 1.1 Hz, 1H, *H6'*), 3.57 (s, 3H, OC*H*$_3$), 2.62 – 2.52 (m, 1H, *H8*), 1.62 (d, *J* = 1.1 Hz, 3H, CC*H*$_3$), 1.05 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.9, 143.7, 138.1, 132.2, 129.8, 128.6, 127.3, 123.4 (q, *J* = 290 Hz), 116.4, 84.8 (q, *J* = 28 Hz), 83.2, 83.0, 56.0, 39.7, 20.6, 15.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –71.3; **HRMS** (ESI) m/z calcd for $C_{18}H_{20}F_3IO_3$ $[M+Na]^+$: 491.0301, found 491.0299.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
H6	5.05	5.08	–0.03
H6'	5.02	5.04	–0.02
H7	5.55	5.59	–0.04
H8	2.55	2.57	–0.02
CHC*H*$_3$	0.93	1.05	–0.12
CC*H*$_3$	1.78	1.62	+0.16
H11	6.38	6.24	+0.14

Analysis indicates that the C9 centre is of *S* configuration.

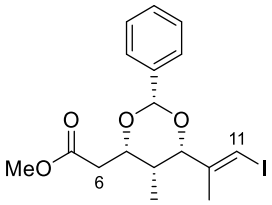
Methyl (2*E*,4*R*,5*S*,6*E*)-5-hydroxy-7-iodo-4,6-dimethylhepta-2,6-dienoate (44)



To an oven dried flask under argon was added alcohol **43** (5.77 g, 22.89 mmol, 1.0 eq.), methyl acrylate (6.2 mL, 68.67 mmol, 3.0 eq.), copper(I) iodide (65.3 mg, 0.343 mmol, 1.5 mol%), and Grubbs Catalyst® 2nd generation (96.8 mg, 0.114 mmol, 0.5 mol%). Anhydrous degassed diethyl ether (65 mL) was added, and the reaction mixture was stirred at reflux overnight. It was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (6.37 g, 20.54 mmol, 90%) as an orange oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –2.4 (c = 1.1, $CHCl_3$); **R_f** 0.26 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3460, 2950, 1704, 1654, 1436, 1284, 1179, 1009; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 15.8, 7.6 Hz, 1H, *H7*), 6.29 (app t, *J* = 1.0 Hz, 1H, *H11*), 5.83 (dd, *J* = 15.8, 1.3 Hz, 1H, *H6*), 4.10 (dd, *J* = 5.6, 3.9 Hz, 1H, *H9*), 3.71 (s, 3H, OCH_3), 2.61 – 2.52 (m, 1H, *H8*), 2.22 (d, *J* = 3.9 Hz, 1H, O*H*), 1.77 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.05 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.0, 150.4, 148.0, 121.2, 80.0, 79.1, 51.7, 40.1, 20.7, 13.9; **HRMS** not found.

Methyl 2-((4*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-2-phenyl-1,3-dioxan-4-yl)acetate (45)

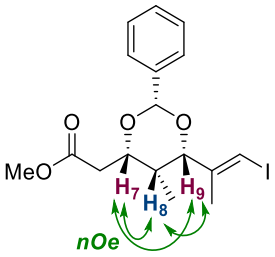


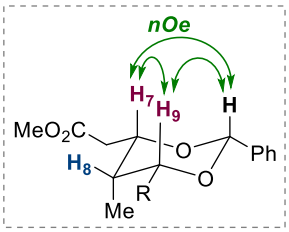
Synthesized according to a modified literature procedure.[177] To a solution of ester **44** (5.80 g, 18.70 mmol, 1.0 eq.) in anhydrous THF (93.5 mL) at –20 °C under argon was added dropwise freshly distilled benzaldehyde (2.1 mL, 20.57 mmol, 1.1 eq.), followed by KHMDS (1.0 M in THF, 1.9 mL, 1.87 mmol, 0.1 eq.); and the resulting yellow solution was stirred for 15 minutes. This addition/stirring sequence was repeated twice, after which the reaction mixture was stirred at –20 °C for 2 hours. It was quenched with pH 7 phosphate buffer and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (2.58 g, 6.20 mmol, 33%) as a pale yellow oil, which solidified over time; ester **44** (1.81 g, 5.84 mmol, 31%) was also recovered.[xxxiv]

m.p. 92–94 °C; $[\alpha]_D^{25}$ –25.7 (c = 2.0, $CHCl_3$); $\mathbf{R_f}$ 0.38 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/cm^{-1} 2950, 1739, 1437, 1349, 1176, 1132, 1031, 699; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.5, 2.0 Hz, 2H, Ar*H*), 7.38 – 7.35 (m, 3H, Ar*H*), 6.35 – 6.34 (m, 1H, *H11*), 5.63 (s, 1H, C*H*Ph), 4.47 (ddd, *J* = 7.8, 5.9, 2.3 Hz, 1H, *H7*), 4.42 (brs, 1H, *H9*), 3.71 (s, 3H, OCH_3), 2.73 (dd, *J* = 16.0, 7.8 Hz, 1H, *H6*), 2.52 (dd, *J* = 16.0, 5.9 Hz, 1H, *H6'*), 1.89 (qdd, *J* = 7.0, 2.3, 2.3 Hz, 1H, *H8*), 1.80 (s, 3H, CCH_3), 0.87 (d, *J* = 7.0 Hz, 3H, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.4, 143.9, 138.2, 129.1, 128.4, 126.4, 101.5, 83.6, 78.4, 76.8, 52.0, 37.9, 33.2, 21.5, 6.3; **HRMS** (ESI) m/z calcd for $C_{17}H_{21}IO_4$ $[M+Na]^+$: 439.0377, found 439.0374.

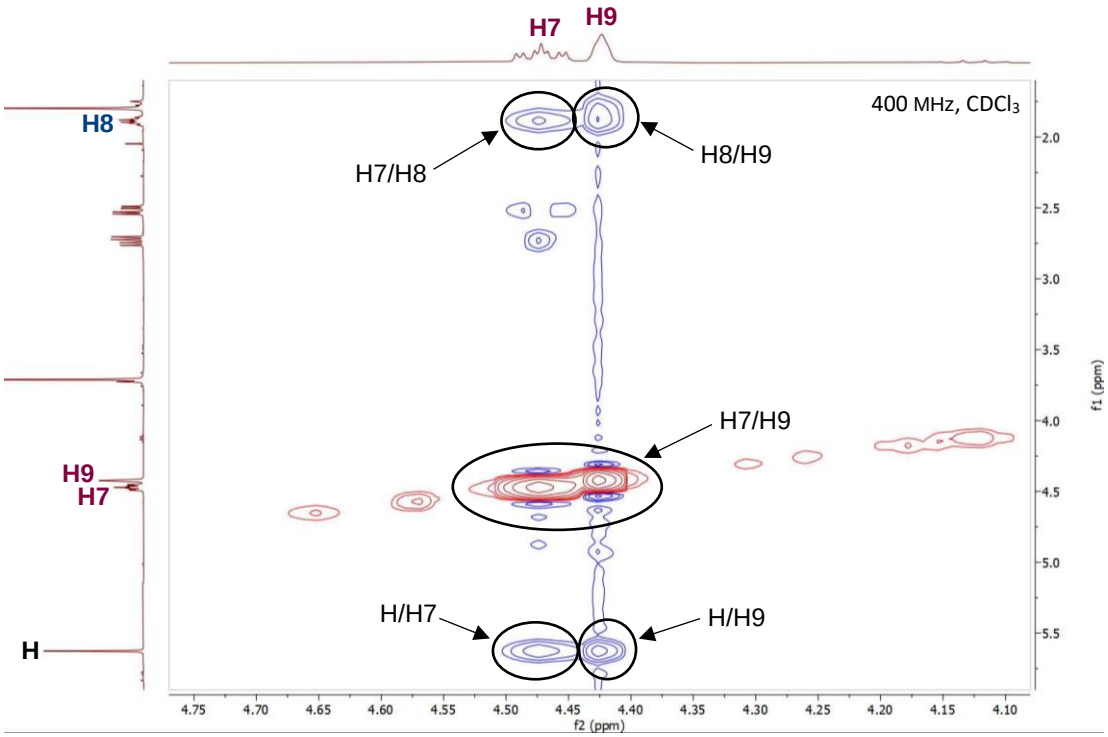
[xxxiv]Note: the reaction does not go to completion even with extended reaction times, likely due to a retro Michael reaction of the product (which causes some of the starting material to become converted to the *Z*-alkene); recovered **44** was slightly impure.

*NOESY spectrum of **45***

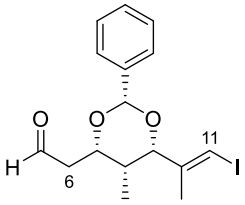




$J_{H7\text{-}H8}$ = 2.3 Hz
$J_{H8\text{-}H9}$ = 2.3 Hz



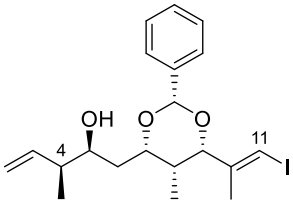
2-((4*S*,5*R*,6*S*)-6-((*E*)-1-Iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl) acetaldehyde (46)



To a solution of ester **45** (1.77 g, 4.25 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (42.5 mL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 4.5 mL, 4.5 mmol, 1.07 eq.) dropwise. The reaction mixture was stirred at –78 °C for 15 minutes. It was quenched with ethyl acetate at –78 °C, followed by water (560 µL), 15% aqueous NaOH (560 µL), and water (1.2 mL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered through celite, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (1.42 g, 3.68 mmol, 87%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ –43.4 (c = 1.0, $CHCl_3$); **R_f** 0.31 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 2975, 2729, 1726, 1385, 1347, 1133, 1107, 1028, 1008, 762, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.83 (t, *J* = 1.6 Hz, 1H, C*H*O), 7.49 (dd, *J* = 7.6, 2.1 Hz, 2H, Ar*H*), 7.40 – 7.36 (m, 3H, Ar*H*), 6.37 – 6.36 (m, 1H, *H11*), 5.65 (s, 1H, C*H*Ph), 4.56 (ddd, *J* = 8.4, 4.7, 2.3 Hz, 1H, *H7*), 4.44 (brs, 1H, *H9*), 2.87 (ddd, *J* = 17.2, 8.4, 1.6 Hz, 1H, *H6*), 2.54 (ddd, *J* = 17.2, 4.7, 1.6 Hz, 1H, *H6'*), 1.87 (qdd, *J* = 6.9, 2.3, 2.3 Hz, 1H, *H8*), 1.81 (s, 3H, CC*H*$_3$), 0.88 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 200.1, 143.7, 138.1, 129.2, 128.4, 126.3, 101.6, 83.6, 78.5, 75.4, 46.9, 33.5, 21.5, 6.5; **HRMS** (ESI) m/z calcd for $C_{16}H_{19}IO_3$ $[M+Na]^+$: 409.0271, found 409.0272.

(2*S*,3*S*)-1-((4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol (47)



Synthesized according to a modified literature procedure.[162] To a solution of (*S*,*S*)-**25** (4.37 g, 15.04 mmol, 1.1 eq.) in anhydrous CH_2Cl_2 (39 mL) at 0 °C under argon was added DBU (6.7 mL, 45.11 mmol, 3.3 eq.), followed by slow addition of *cis*-crotyltrichlorosilane **26** (3.11 g, 16.40 mmol, 1.2 eq.). The mixture was stirred at room temperature for 1 hour, after which it was recooled to 0 °C. A solution of aldehyde **46** (5.28 g, 13.67 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (6 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 1 hour. The mixture was treated with TBAF (1.0 M in THF, 17.8 mL, 17.8 mmol, 1.3 eq.) at 0 °C, stirred at room temperature for 1 hour, and concentrated under reduced pressure. The residue was suspended in diethyl ether (70 mL) and the mixture was stirred vigorously for 20 minutes. The resulting precipitated DBU•HCl salts were removed by filtration and the filtrate was treated with 1 M aqueous HCl (75.2 mL, 75.2 mmol, 5.5 eq.). The organic layer was separated, and the aqueous layer was further extracted with diethyl ether (2 × 70 mL). The organic layers were washed with water (2 × 70 mL) and saturated aqueous $NaHCO_3$ (70 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 4/1) to afford the title compound (4.69 g, 10.60 mmol, 78%, 10:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ –60.0 (c = 0.6, $CHCl_3$); **R_f** 0.39 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3415, 2971, 1408, 1384, 1347, 1107, 1029, 915, 756, 699; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.8, 1.9 Hz, 2H, Ar*H*), 7.41 – 7.35 (m, 3H, Ar*H*), 6.33 – 6.32 (m, 1H, *H11*), 5.80 (ddd, *J* = 17.5, 10.0, 7.3 Hz, 1H, *H3*), 5.61 (s, 1H, C*H*Ph), 5.14 – 5.08 (m, 2H, *H2* and *H2'*), 4.40 (brs, 1H, *H9*), 4.26 (td, *J* = 10.1, 2.3 Hz, 1H, *H7*), 3.82 (ddd, *J* = 10.0, 5.1, 2.2 Hz, 1H, *H5*), 2.35 – 2.27 (m, 1H, *H4*), 1.85 (ddd, *J* = 14.4, 10.1, 2.2 Hz, 1H, *H6*), 1.78 (s, 3H, CC*H*$_3$), 1.77 – 1.72 (m, 1H, *H8*), 1.62 (brs, 1H, O*H*), 1.42 (ddd, *J* = 14.4, 10.0, 2.3 Hz, 1H, *H6'*), 1.05 (d, *J* = 6.9 Hz, 3H, H4C*H*$_3$), 0.85 (d, *J* = 6.9 Hz, 3H, H8C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 144.1, 140.8, 138.6, 128.9, 128.3, 126.3, 115.8, 101.4,

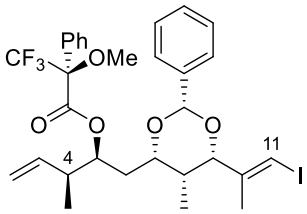
83.9, 78.1, 77.3, 70.9, 43.8, 37.5, 34.6, 21.5, 14.2, 6.5; **HRMS** (ESI) m/z calcd for $C_{20}H_{27}IO_3$ $[M+Na]^+$: 465.0897, found 465.0895.

*Recovery of (S,S)-**25** ligand*

The combined aqueous acid and water layers were treated with 1 M aqueous NaOH (150.4 mL, 150.4 mmol, 10 eq. with respect to the ligand) and extracted with CH_2Cl_2 (4 × 70 mL). The organic layers were washed with water (2 × 70 mL) and brine (70 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was recrystallized from minimal boiling hexanes to afford the recovered (*S,S*)-**25** ligand (4.0 g, 13.77 mmol, 92%) as white crystals.

*Mosher ester analysis of **47***

(*S*)-MTPA ester of 47

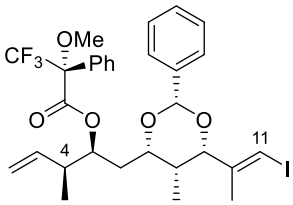


Synthesized according to a modified literature procedure.[194] To a solution of alcohol **47** (15.0 mg, 0.034 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (32.6 mg, 0.129 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (680 µL) was added pyridine (17 µL, 0.211 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1) to afford the title compound (21.6 mg, 0.033 mmol, 96%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –82.1 (c = 2.2, $CHCl_3$); $\mathbf{R_f}$ 0.55 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 2976, 1745, 1259, 1169, 1028, 996, 698; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 – 7.61 (m, 2H, Ar*H*), 7.51 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*), 7.42 – 7.36 (m, 6H, Ar*H*), 6.33 (s, 1H, *H11*), 5.81 (ddd, *J* = 17.1, 10.5, 6.6 Hz, 1H, *H3*), 5.40 (ddd, *J* = 10.5, 4.3, 2.3 Hz, 1H, *H5*), 5.34 (s, 1H, C*H*Ph), 5.11 – 5.04 (m, 2H, *H2* and *H2'*), 4.08 (s, 1H, *H9*), 3.60 – 3.56 (m,

1H, *H7*), 3.59 (s, 3H, OCH_3), 2.64 – 2.59 (m, 1H, *H4*), 1.87 (ddd, *J* = 14.8, 10.6, 2.3 Hz, 1H, *H6*), 1.73 (s, 3H, CCH_3), 1.57 (ddd, *J* = 14.8, 10.5, 2.0 Hz, 1H, *H6'*), 1.51 (qdd, *J* = 6.9, 2.3, 2.3 Hz, 1H, *H8*), 1.06 (d, *J* = 6.9 Hz, 3H, H4CH_3), 0.76 (d, *J* = 6.8 Hz, 3H, H8CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.4, 143.9, 138.9, 138.3, 132.5, 129.8, 128.9, 128.6, 128.4, 127.5, 126.1, 123.6 (q, *J* = 290 Hz), 116.2, 100.9, 84.5 (q, *J* = 27 Hz), 83.7, 78.1, 76.8, 76.1, 55.8, 41.1, 34.5, 34.2, 21.5, 14.6, 6.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –70.6; **HRMS** (ESI) m/z calcd for $C_{30}H_{34}F_3IO_5$ $[M+Na]^+$: 681.1295, found 681.1291.

(*R*)-MTPA ester of 47



Synthesized in the same manner as the (*S*)-MTPA ester of **47** using 0.034 mmol of alcohol **47** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound (19.4 mg, 0.029 mmol, 87%) was obtained as a colourless oil.

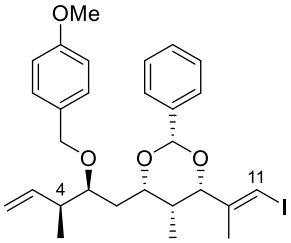
$[\alpha]_D^{25}$ –38.6 (c = 1.9, $CHCl_3$); **R_f** 0.55 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 2975, 1746, 1255, 1168, 1027, 997, 698; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 – 7.60 (m, 2H, Ar*H*), 7.50 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*), 7.42 – 7.36 (m, 6H, Ar*H*), 6.35 (s, 1H, *H11*), 5.73 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H, *H3*), 5.40 (ddd, *J* = 10.3, 4.7, 2.6 Hz, 1H, *H5*), 5.37 (s, 1H, C*H*Ph), 5.06 – 5.00 (m, 2H, *H2* and *H2'*), 4.15 (s, 1H, *H9*), 3.71 (td, *J* = 10.5, 2.2 Hz, 1H, *H7*), 3.53 (s, 3H, OCH_3), 2.61 – 2.53 (m, 1H, *H4*), 1.93 (ddd, *J* = 14.8, 10.5, 2.7 Hz, 1H, *H6*), 1.77 (s, 3H, CCH_3), 1.66 – 1.61 (m, 1H, *H6'*), 1.61 – 1.57 (m, 1H, *H8*), 1.04 (d, *J* = 6.9 Hz, 3H, H4CH_3), 0.80 (d, *J* = 6.9 Hz, 3H, H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.2, 143.9, 138.9, 138.3, 132.3, 129.8, 128.9, 128.6, 128.3, 127.8, 126.2, 123.6 (q, *J* = 290 Hz), 116.1, 101.1, 84.6 (q, *J* = 28 Hz), 83.7, 78.2, 76.8, 76.4, 55.5, 41.2, 34.9, 34.3, 21.5, 14.5, 6.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –70.5; **HRMS** (ESI) m/z calcd for $C_{30}H_{34}F_3IO_5$ $[M+Na]^+$: 681.1295, found 681.1289.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
H2/H2'	5.08	5.03	+0.05
H3	5.81	5.73	+0.08
H4	2.62	2.57	+0.05
H6	1.87	1.93	–0.06
H6'	1.57	1.63	–0.06
H7	3.58	3.71	–0.13
H8	1.51	1.59	–0.08
H9	4.08	4.15	–0.07
H11	6.33	6.35	–0.02

Analysis indicates that the C5 centre is of *S* configuration.

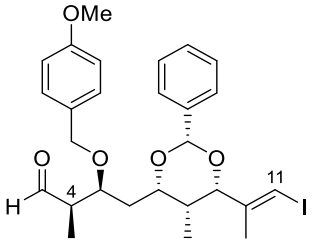
(4*S*,5*R*,6*S*)-4-((*E*)-1-Iodoprop-1-en-2-yl)-6-((2*S*,3*S*)-2-((4-methoxybenzyl)oxy)-3-methylpent-4-en-1-yl)-5-methyl-2-phenyl-1,3-dioxane (48)



To a solution of alcohol **47** (940 mg, 2.13 mmol, 1.0 eq.) in anhydrous DMF (4.3 mL) under argon at 0 °C was added NaH (60% in mineral oil, 170.4 mg, 4.26 mmol, 2.0 eq.). The mixture was stirred for 30 minutes, after which PMBCl (578 µL, 4.26 mmol, 2.0 eq.) and TBAI (158.8 mg, 0.43 mmol, 0.2 eq.) were added. The reaction mixture was stirred at room temperature for 24 hours. It was quenched slowly with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (1.08 g, 1.92 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25}$ –83.1 (c = 1.1, $CHCl_3$); **R_f** 0.32 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2930, 2885, 1612, 1513, 1457, 1348, 1248, 1059, 1035, 699; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.7, 2.0 Hz, 2H, Ar*H*), 7.40 – 7.35 (m, 3H, Ar*H*), 7.28 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.30 – 6.29 (m, 1H, *H11*), 5.92 (ddd, *J* = 17.7, 10.0, 6.9 Hz, 1H, *H3*), 5.36 (s, 1H, C*H*Ph), 5.10 – 5.05 (m, 2H, *H2* and *H2'*), 4.64 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.40 (d, *J* = 11.2 Hz, 1H, OC*H'*$_2$Ar), 4.29 (brs, 1H, *H9*), 4.06 (td, *J* = 10.3, 2.2 Hz, 1H, *H7*), 3.73 (s, 3H, OCH_3), 3.63 (ddd, *J* = 10.7, 4.7, 2.2 Hz, 1H, *H5*), 2.60 – 2.55 (m, 1H, *H4*), 1.77 – 1.71 (m, 1H, *H6*), 1.74 (s, 3H, CCH_3), 1.67 (qdd, *J* = 6.9, 2.3, 2.3 Hz, 1H, *H8*), 1.39 (ddd, *J* = 14.5, 10.7, 2.1 Hz, 1H, *H6'*), 1.05 (d, *J* = 6.9 Hz, 3H, H4CH_3), 0.79 (d, *J* = 7.0 Hz, 3H, H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.4, 144.2, 140.4, 138.8, 131.0, 129.8, 128.8, 128.2, 126.2, 114.9, 114.0, 101.1, 84.0, 78.3, 77.9, 76.9, 72.1, 55.3, 40.5, 35.2, 34.4, 21.5, 15.2, 6.5; **HRMS** (ESI) m/z calcd for $C_{28}H_{35}IO_4$ $[M+Na]^+$: 585.1496, found 585.1469.

(2*R*,3*S*)-4-((4*S*,5*R*,6*S*)-6-((*E*)-1-Iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-((4-methoxybenzyl)oxy)-2-methylbutanal (49)

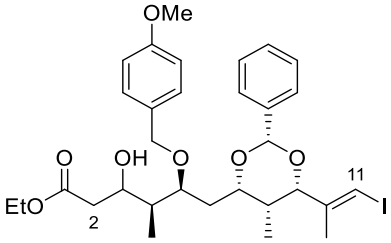


To a solution of alkene **48** (900 mg, 1.60 mmol, 1.0 eq.) in acetone (16.0 mL) and water (5.3 mL) at 10 °C was added 4-methylmorpholine *N*-oxide (NMO) monohydrate (432.5 mg, 3.20 mmol, 2.0 eq.) and potassium osmate dihydrate (14.7 mg, 0.040 mmol, 2.5 mol%). The reaction mixture was stirred at 10 °C overnight. Saturated aqueous $Na_2S_2O_3$ (18 mL) was added and the mixture was stirred vigorously for 2 hours. It was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, and the aqueous layer was further extracted with ethyl acetate. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 7/3 → 3/2) to afford a 3:1 diastereomeric mixture of diols (620.0 mg, 1.10 mmol). The mixture of diols was dissolved in CH_2Cl_2 (11 mL), and $NaIO_4$ (14 wt% on silica,[207] 5.04 g, 3.30 mmol, 3.0 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (595.6 mg, 1.06 mmol, 62% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ –94.4 (c = 0.5, $CHCl_3$); **R_f** 0.31 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 2939, 2914, 2881, 1721, 1612, 1513, 1454, 1347, 1249, 1056, 1033, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.84 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.45 (dd, *J* = 7.8, 2.0 Hz, 2H, Ar*H*), 7.41 – 7.35 (m, 3H, Ar*H*), 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.32 – 6.31 (m, 1H, *H11*), 5.39 (s, 1H, C*H*Ph), 4.57 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.39 (d, *J* = 11.2 Hz, 1H, OC*H'*$_2$Ar), 4.31 (brs, 1H, *H9*), 4.16 – 4.12 (m, 1H, *H5*), 4.07 (td, *J* = 10.3, 2.2 Hz, 1H, *H7*), 3.74 (s, 3H, OCH_3), 2.65 (qdd, *J* = 7.0, 3.4, 1.0 Hz, 1H, *H4*), 1.83 – 1.76 (m, 1H, *H6*), 1.76 (s, 3H, CCH_3), 1.72 – 1.67 (m, 1H, *H8*), 1.58 (ddd, *J* = 14.3, 10.3, 2.1 Hz, 1H, *H6'*), 1.13 (d, *J* = 7.1 Hz, 3H, H4CH_3), 0.81 (d, *J* = 6.8 Hz, 3H, H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 204.6, 159.6, 144.0, 138.5, 130.2, 129.9, 129.0, 128.3, 126.2, 114.1,

101.2, 83.9, 78.1, 76.7, 74.6, 72.3, 55.4, 50.4, 36.6, 34.3, 21.5, 8.6, 6.5; **HRMS** (ESI) m/z calcd for $C_{27}H_{33}IO_5$ $[M+Na]^+$: 587.1265, found 587.1264.

Ethyl (4*S*,5*S*)-3-hydroxy-6-((2*S*,4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-5-((4-methoxybenzyl)oxy)-4-methylhexanoate (50)



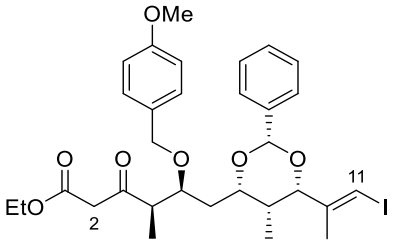
To a solution of aldehyde **49** (416.5 mg, 0.74 mmol, 1.0 eq.) and ((1-ethoxyvinyl)oxy)trimethylsilane **34** (354.9 mg, 2.21 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (14.8 mL) at –78 °C under argon was added boron trifluoride diethyl etherate (91 µL, 0.74 mmol, 1.0 eq.) dropwise over 5 minutes. The reaction mixture was stirred at –78 °C for 1 hour, after which it was quenched with pH 7 phosphate buffer and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound[xxxv] (409.4 mg, 0.63 mmol, 85%) as a colourless oil.

$[\alpha]_D^{25}$ –49.1 (c = 1.1, $CHCl_3$); **R_f** 0.34 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3498, 2976, 2936, 2908, 1612, 1728, 1513, 1456, 1348, 1249, 1176, 1033, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.7, 2.0 Hz, 2H, Ar*H*), 7.40 – 7.35 (m, 3H, Ar*H*), 7.27 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.33 – 6.32 (m, 1H, *H11*), 5.42 (s, 1H, C*H*Ph), 4.55 (d, *J* = 11.2 Hz, 1H, OC*H*$_2$Ar), 4.46 (d, *J* = 11.2 Hz, 1H, OC*H'*$_2$Ar), 4.32 (brs, 1H, *H9*), 4.26 – 4.21 (m, 1H, *H3*), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.02 (td, *J* = 9.7, 2.5 Hz, 1H, *H7*), 3.80 – 3.76 (m, 1H, *H5*), 3.75 (s, 3H, OC*H*$_3$), 3.11 (d, *J* = 3.2 Hz, 1H, O*H*), 2.56 (dd, *J* = 16.2, 8.7 Hz, 1H, *H2*), 2.49 (dd, *J* = 16.2, 4.2 Hz, 1H, *H2'*), 1.92 – 1.82 (m, 2H, *H4* and *H6*), 1.78 (s, 3H, CC*H*$_3$), 1.74 – 1.62 (m, 2H, *H6'* and *H8*), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.00 (d, *J* = 7.1 Hz, 3H, H4C*H*$_3$), 0.84 (d, *J* = 7.0 Hz, 3H,

[xxxv] Obtained as a single diastereomer

H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 159.4, 144.1, 138.5, 130.4, 129.7, 128.9, 128.3, 126.2, 114.0, 101.1, 83.9, 78.7, 78.1, 77.3, 71.9, 69.4, 60.7, 55.3, 40.3, 40.2, 35.2, 34.3, 21.5, 14.3, 9.2, 6.5; **HRMS** (ESI) m/z calcd for $C_{31}H_{41}IO_7$ $[M+Na]^+$: 675.1789, found 675.1779.

Ethyl (4*R*,5*S*)-6-((4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-5-((4-methoxybenzyl)oxy)-4-methyl-3-oxohexanoate (51)

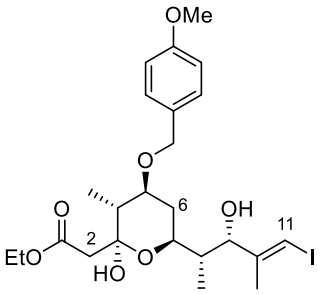


To a solution of β-hydroxy ester **50** (521.8 mg, 0.80 mmol, 1.0 eq.) in CH_2Cl_2 (16 mL) was added $NaHCO_3$ (336.0 mg, 4.00 mmol, 5.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (509.0 mg, 1.20 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 30 minutes. It was diluted with diethyl ether, quenched with saturated aqueous $Na_2S_2O_3$, and stirred until the mixture became a clear solution. The layers were separated, and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (452.1 mg, 0.69 mmol, 87%) as a colourless oil.

$[\alpha]_D^{25}$ –113.8 (c = 0.6, $CHCl_3$); **R_f** 0.46 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/ cm^{-1} 2980, 2936, 2909, 1743, 1710, 1513, 1457, 1304, 1249, 1057, 1030, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 – 7.40 (m, 2H, Ar*H*), 7.39 – 7.35 (m, 3H, Ar*H*), 7.28 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.30 – 6.29 (m, 1H, *H11*), 5.31 (s, 1H, C*H*Ph), 4.66 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 4.42 (d, *J* = 11.3 Hz, 1H, OC*H'*$_2$Ar), 4.28 (brs, 1H, *H9*), 4.18 (qd, *J* = 7.2, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.99 (dt, *J* = 10.5, 2.0 Hz, 1H, *H7*), 3.89 (ddd, *J* = 10.5, 3.8, 2.5 Hz, 1H, *H5*), 3.73 (s, 3H, OCH_3), 3.60 (d, *J* = 1.2 Hz, 2H, *H2*), 3.14 (qd, *J* = 7.1, 3.8 Hz, 1H, *H4*), 1.81 – 1.74 (m, 1H, *H6*), 1.76 (s, 3H, CCH_3), 1.70 –1.64 (m, 1H, *H8*), 1.37 (ddd, *J* = 14.3, 10.5, 2.0 Hz, 1H, *H6'*), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.10 (d, *J* = 7.0 Hz, 3H, H4CH_3), 0.79 (d, *J* = 6.9 Hz, 3H, H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$):

δ 205.4, 167.6, 159.6, 144.1, 138.6, 130.1, 130.0, 128.9, 128.3, 126.2, 126.2, 114.1, 101.1, 83.9, 78.1, 76.5, 72.2, 61.4, 55.3, 50.2, 48.7, 35.3, 34.3, 21.5, 14.3, 12.0, 6.4; **HRMS** (ESI) m/z calcd for $C_{31}H_{39}IO_7$ $[M+Na]^+$: 673.1635, found 673.1630.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2-hydroxy-6-((2*S*,3*S*,*E*)-3-hydroxy-5-iodo-4-methylpent-4-en-2-yl)-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (52)



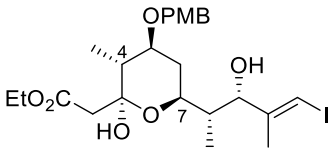
To a solution of β-keto ester **51** (106.8 mg, 0.164 mmol, 1.0 eq.) in THF (4.1 mL) and MeOH (4.1 mL) was added 1.0 M aqueous HCl (4.1 mL). The reaction mixture was stirred at 35 °C for 22 hours. It was diluted with CH_2Cl_2, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 9/1 → 4/1) to afford the title compound[xxxvi] (43.4 mg, 0.077 mmol, 47%) as a colourless oil; β-keto ester **51** (49.0 mg, 0.075 mmol, 46%) was also recovered.

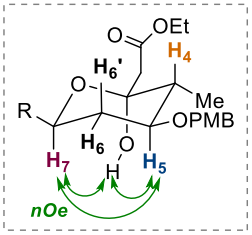
$[\alpha]_D^{25}$ +29.2 (c = 0.4, $CHCl_3$); $\mathbf{R_f}$ 0.39 (pentane/diethyl ether = 1/1); **IR** (thin film): ν_{max}/cm^{-1} 3477, 2979, 2949, 2920, 2358, 1710, 1514, 1459, 1337, 1248, 1186, 1082, 1034, 821; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.32 – 6.31 (m, 1H, *H11*), 4.82 (d, *J* = 1.9 Hz, 1H, O*H*), 4.57 (d, *J* = 11.0 Hz, 1H, OC*H*$_2$Ar), 4.39 (d, *J* = 11.0 Hz, 1H, OC*H'*$_2$Ar), 4.26 (d, *J* = 2.3 Hz, 1H, *H9*), 4.20 (qd, *J* = 7.1, 3.4 Hz, 2H, $CO_2CH_2CH_3$), 4.11 (dt, *J* = 12.2, 2.2 Hz, 1H, *H7*), 3.80 (s, 3H, OC*H*$_3$), 3.56 (td, *J* = 10.6, 4.5 Hz, 1H, *H5*), 2.87 (brs, 1H, O*H*), 2.81 (d, *J* = 15.5 Hz, 1H, *H2*), 2.52 (d, *J* = 15.5 Hz, 1H, *H2'*), 1.96 (ddd, *J* = 12.2, 4.5, 2.2 Hz, 1H, *H6*), 1.75 (d, *J* = 0.7 Hz, 3H, CC*H*$_3$), 1.73 – 1.70 (m, 1H, *H8*), 1.54 – 1.44 (m, 2H, *H4* and *H6'*), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.09 (d, *J* = 6.6 Hz, 3H, H4C*H*$_3$), 0.84 (d, *J* = 7.0 Hz, 3H, H8C*H*$_3$); **^{13}C NMR**

[xxxvi] Obtained with an inseparable impurity

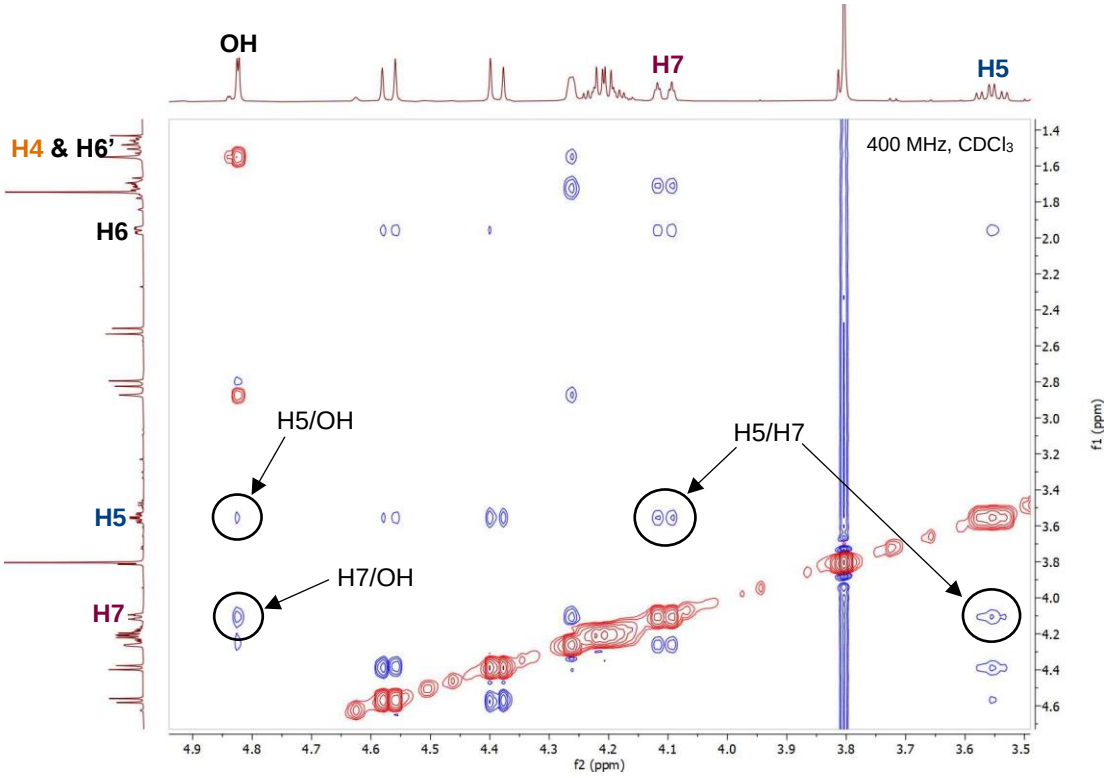
(101 MHz, $CDCl_3$): δ 173.1, 159.4, 147.0, 130.8, 129.5, 114.0, 99.3, 80.0, 78.7, 76.3, 71.9, 71.0, 61.6, 55.4, 45.2, 42.6, 39.3, 35.1, 21.7, 14.2, 12.4, 6.2; **HRMS** (ESI) m/z calcd for $C_{24}H_{35}IO_7$ $[M+Na]^+$: 585.1320, found 585.2321.

*NOESY spectrum of **52***

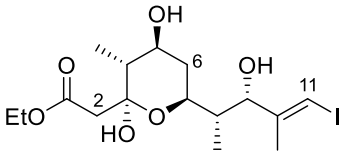




$J_{H5\text{-}H4}$ = 10.6 Hz
$J_{H5\text{-}H6}$ = 4.5 Hz
$J_{H5\text{-}H6'}$ = 10.6 Hz
$J_{H7\text{-}H6}$ = 2.2 Hz
$J_{H7\text{-}H6'}$ = 12.2 Hz



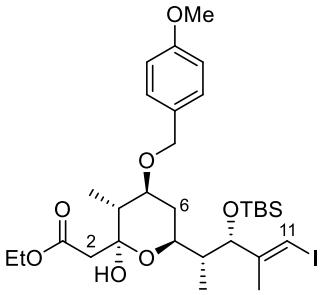
Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2,4-dihydroxy-6-((2*S*,3*S*,*E*)-3-hydroxy-5-iodo-4-methylpent-4-en-2-yl)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (53)



To a solution of PMB ether **52** (36.3 mg, 0.065 mmol, 1.0 eq.) in CH_2Cl_2 (2.2 mL) and water (116 µL) at 0 °C was added DDQ (26.6 mg, 0.117 mmol, 1.8 eq.). The reaction mixture was stirred at 0 °C under argon for 1 hour. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the title compound (12.5 mg, 0.028 mmol, 44%) as a colourless oil.

$[\alpha]_D^{25}$ +14.7 (c = 1.2, $CHCl_3$); **R_f** 0.28 (pentane/ethyl acetate = 1/1); **IR** (thin film): ν_{max}/ cm^{-1} 3443, 2978, 2919, 2851, 1711, 1375, 1262, 1194, 1018, 987; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.32 – 6.31 (m, 1H, *H11*), 4.81 (brs, 1H, O*H*), 4.26 (d, *J* = 2.8 Hz, 1H, *H9*), 4.21 (qd, *J* = 7.2, 3.1 Hz, 2H, $CO_2CH_2CH_3$), 4.15 (dt, *J* = 12.1, 2.2 Hz, 1H, *H7*), 3.81 (td, *J* = 10.8, 4.7 Hz, 1H, *H5*), 2.81 (d, *J* = 15.5 Hz, 1H, *H2*), 2.53 (d, *J* = 15.5 Hz, 1H, *H2'*), 1.81 (ddd, *J* = 12.1, 4.7, 2.2 Hz, 1H, *H6*), 1.74 (d, *J* = 0.6 Hz, 3H, CCH_3), 1.72 – 1.69 (m, 1H, *H8*), 1.53 (td, *J* = 12.1, 10.8 Hz, 2H, *H6'*), 1.36 – 1.33 (m, 1H, *H4*), 1.29 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.11 (d, *J* = 6.7 Hz, 3H, H4CH_3), 0.84 (d, *J* = 7.0 Hz, 3H, H8CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.0, 147.0, 99.2, 79.9, 78.7, 71.9, 69.5, 61.6, 46.8, 42.5, 39.1, 38.5, 21.7, 14.2, 12.1, 6.2; **HRMS** (ESI) m/z calcd for $C_{16}H_{27}IO_6$ $[M+Na]^+$: 465.0749, found 465.0745.

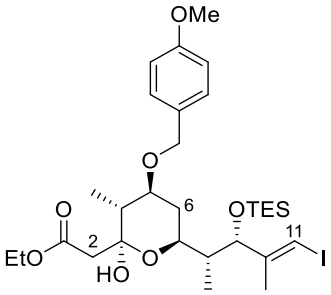
Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-6-((2*R*,3*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-5-iodo-4-methylpent-4-en-2-yl)-2-hydroxy-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (2a)



To a solution of alcohol **52** (43.4 mg, 0.077 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C under argon was added 2,6-lutidine (27 µL, 0.231 mmol, 3.0 eq.), followed by dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (32 µL, 0.139 mmol, 1.8 eq.). The reaction mixture was stirred at 0 °C for 1 hour. It was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic layers were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 49/1) to afford the title compound (30.6 mg, 0.045 mmol, 59%) as a colourless oil.

$[\alpha]_D^{25}$ +24.9 (c = 1.2, $CHCl_3$); **R_f** 0.43 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 3478, 2952, 2929, 2856, 1712, 1514, 1463, 1333, 1249, 1187, 1078, 1064, 1036, 864, 837, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.24 – 6.23 (m, 1H, *H11*), 4.59 (d, *J* = 1.9 Hz, 1H, O*H*), 4.56 (d, *J* = 10.9 Hz, 1H, OC*H*$_2$Ar), 4.37 (d, *J* = 10.9 Hz, 1H, OC*H'*$_2$Ar), 4.19 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.98 (d, *J* = 8.8 Hz, 1H, *H9*), 3.80 (s, 3H, OC*H*$_3$), 3.67 (dt, *J* = 12.2, 2.2 Hz, 1H, *H7*), 3.53 (td, *J* = 10.6, 4.5 Hz, 1H, *H5*), 2.74 (d, *J* = 14.9 Hz, 1H, *H2*), 2.46 (d, *J* = 14.9 Hz, 1H, *H2'*), 1.86 (ddd, *J* = 12.2, 4.5, 2.2 Hz, 1H, *H6*), 1.72 (d, *J* = 1.0 Hz, 3H, CC*H*$_3$), 1.60 – 1.53 (m, 1H, *H8*), 1.47 – 1.37 (m, 2H, *H4* and *H6'*), 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.07 (d, *J* = 6.6 Hz, 3H, H4C*H*$_3$), 0.93 (d, *J* = 6.8 Hz, 3H, H8C*H*$_3$), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 0.00 (s, 3H, SiC*H*$_3$), –0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.3, 159.3, 148.7, 131.0, 129.4, 113.9, 98.8, 80.2, 79.7, 76.9, 71.0, 67.1, 61.0, 55.4, 45.5, 42.8, 41.2, 35.0, 25.9, 19.1, 18.4, 14.4, 12.4, 10.1, –4.7, –5.1; **HRMS** (ESI) m/z calcd for $C_{30}H_{49}IO_7Si$ $[M+Na]^+$: 699.2184, found 699.2180.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2-hydroxy-6-((2*R*,3*S*,*E*)-5-iodo-4-methyl-3-((triethylsilyl) oxy)pent-4-en-2-yl)-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (2b)

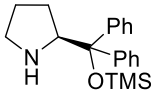


To a solution of alcohol **52** (38.4 mg, 0.068 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.4 mL) at 0 °C under argon was added 2,6-lutidine (24 µL, 0.204 mmol, 3.0 eq.), followed by dropwise addition of triethylsilyl trifluoromethanesulfonate (28 µL, 0.122 mmol, 1.8 eq.). The reaction mixture was stirred at 0 °C for 1 hour. It was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic layers were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 49/1) to afford the title compound (27.2 mg, 0.040 mmol, 59%) as a white solid.

m.p. 48–50 °C; $[\alpha]_D^{25}$ +25.1 (c = 2.7, $CHCl_3$); $\mathbf{R_f}$ 0.48 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3476, 2957, 2879, 1716, 1516, 1458, 1336, 1249, 1192, 1080, 1064, 1038, 844, 745; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.27 (s, 1H, *H11*), 4.61 (d, *J* = 1.9 Hz, 1H, O*H*), 4.56 (d, *J* = 10.9 Hz, 1H, OC*H*$_2$Ar), 4.37 (d, *J* = 10.9 Hz, 1H, OC*H'*$_2$Ar), 4.19 (app quint, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.00 (d, *J* = 8.9 Hz, 1H, *H9*), 3.80 (s, 3H, OC*H*$_3$), 3.66 (dt, *J* = 12.2, 2.4 Hz, 1H, *H7*), 3.53 (td, *J* = 10.6, 4.5 Hz, 1H, *H5*), 2.74 (d, *J* = 15.0 Hz, 1H, *H2*), 2.46 (d, *J* = 15.0 Hz, 1H, *H2'*), 1.86 (ddd, *J* = 12.2, 4.6, 2.2 Hz, 1H, *H6*), 1.73 (d, *J* = 1.0 Hz, 3H, CC*H*$_3$), 1.59 – 1.53 (m, 1H, *H8*), 1.46 – 1.38 (m, 2H, *H4* and *H6'*), 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.08 (d, *J* = 6.7 Hz, 3H, H4C*H*$_3$), 0.95 (d, *J* = 6.8 Hz, 3H, H8C*H*$_3$), 0.92 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.54 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.3, 159.3, 148.8, 131.0, 129.4, 113.9, 98.8, 80.3, 79.5, 76.9, 71.0, 67.1, 61.0, 55.4, 45.5, 42.7, 41.2, 35.0, 19.0, 14.3, 12.4, 9.9, 7.0, 4.9; **HRMS** (ESI) m/z calcd for $C_{30}H_{49}IO_7Si$ $[M+Na]^+$: 699.2185, found 699.2169.

6.3.2. The C23–C27 fragment

(*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine ((*S*)-**6)**

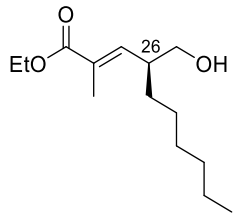


To a solution of imidazole (1.6 g, 23.7 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (21.6 mL) at 0 °C under argon was added chlorotrimethylsilane (2.5 mL, 19.73 mmol, 2.5 eq.) dropwise. The solution was stirred for 10 minutes, after which a solution of (*S*)-(–)-diphenylprolinol (2.0 g, 7.9 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol = 49/1) to afford the title compound (2.2 g, 6.8 mmol, 86%) as a light yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –49.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.35 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.30 – 7.21 (m, 6H), 4.04 (t, *J* = 7.4 Hz, 1H), 2.89 – 2.75 (m, 2H), 1.78 (brs, 1H), 1.63 – 1.53 (m, 3H), 1.42 – 1.33 (m, 1H), –0.10 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.9, 145.9, 128.6, 127.8, 127.7, 127.7, 127.1, 126.9, 83.3, 65.6, 47.3, 27.6, 25.2, 2.3.

The physical and spectroscopic data were consistent with literature reported data.[193]

Ethyl (*S*,*E*)-4-(hydroxymethyl)-2-methyldec-2-enoate (54)

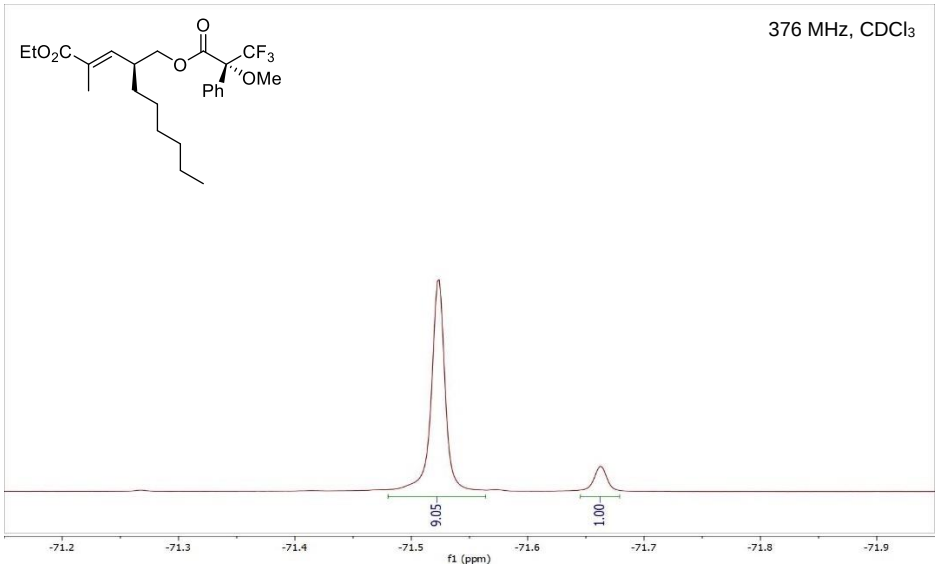


Synthesized according to a modified literature procedure.[155] To a solution of catalyst (*S*)-**6** (488.3 mg, 1.50 mmol, 0.3 eq.) in toluene (10 mL) was added solid pH 7 potassium phosphate buffer[xxxvii] (2.5 g) and formaldehyde[xxxviii] (37% in water, 1.1 mL, 15.00 mmol, 3.0 eq.). The mixture was stirred vigorously for 15 minutes, after which freshly distilled octanal (782 µL, 5.00 mmol, 1.0 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 24 hours. It was diluted with water (2.5 mL), the organic layer was separated, and the aqueous layer was further extracted with toluene (2.5 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure (keeping the water bath at room temperature). The residue was dissolved in CH_2Cl_2 (5 mL) and added dropwise via glass pipet to a solution of ethyl 2-(triphenylphosphoranylidene) propionate (5.44 g, 15.00 mmol, 3.0 eq.) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 24 hours. It was concentrated under reduced pressure and the residue was taken up in a pentane/diethyl ether (4:1) solution. The mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (814.5 mg, 3.36 mmol, 67%, 80% *ee*) as a colourless oil.

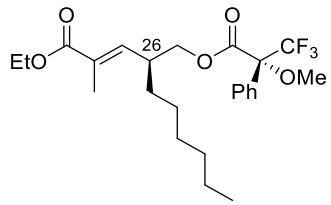
$[\alpha]_D^{25}$ +4.0 (c = 1.0, $CHCl_3$); **R_f** 0.27 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3426, 2956, 2928, 2857, 1710, 1650, 1465, 1368, 1273, 1100, 1035, 751; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.53 (dq, *J* = 10.4, 1.5 Hz, 1H, *H25*), 4.20 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.63 (ddd, *J* = 10.6, 7.3, 5.4 Hz, 1H, *H27*), 3.51 (ddd, *J* = 10.6, 7.6, 4.7 Hz, 1H, *H27'*), 2.70 – 2.61 (m, 1H, *H26*), 1.89 (d, *J* = 1.5 Hz, 3H, CCH_3), 1.53 – 1.21 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.2, 143.4, 130.3, 66.2, 60.8, 42.1, 31.9, 31.2, 29.6, 27.3, 22.8, 14.4, 14.2, 13.2; **HRMS** (ESI) m/z calcd for $C_{14}H_{26}O_3$ $[M+Na]^+$: 265.1774, found 265.1774.

[xxxvii]Prepared according to the procedure in reference 155. [xxxviii]For an optimal yield, a fresh bottle of formaldehyde should be used.

*Determination of ee by ^{19}F NMR analysis of the Mosher ester of **54**: 80% ee*



(*R*)-MTPA ester of 54

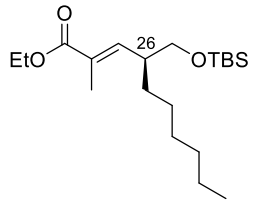


To a solution of alcohol **54** (12.0 mg, 0.050 mmol, 1.0 eq.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (24.0 mg, 0.095 mmol, 1.9 eq.) in anhydrous CH_2Cl_2 (630 µL) was added pyridine (13 µL, 0.155 mmol, 3.1 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 49/1) to afford the title compound (14.8 mg, 0.032 mmol, 65%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ +37.1 (c = 1.3, $CHCl_3$); **R_f** 0.51 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 2956, 2930, 2857, 1751, 1712, 1452, 1269, 1241, 1184, 1170, 1124, 1105, 1023, 720; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 – 7.48 (m, 2H, Ar*H*), 7.41 – 7.35 (m, 3H, Ar*H*), 6.47 (dq, *J* = 10.3, 1.4 Hz, 1H, *H25*), 4.29 – 4.15 (m, 4H, $CO_2CH_2CH_3$ and *H27*), 3.50 (s, 3H, OCH_3), 2.88 – 2.79 (m, 1H, *H26*), 1.79 (d, *J* = 1.4 Hz, 3H, CCH_3), 1.50 – 1.19 (m, 13H,

$CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.9, 166.7, 141.4, 132.2, 130.5, 129.7, 128.5, 127.4 123.4 (q, *J* = 289 Hz), 84.7 (q, *J* = 28 Hz), 68.9, 60.8, 55.5, 38.2, 31.8, 31.2, 29.4,27.0, 22.7, 14.4, 14.2, 12.9; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –71.5; **HRMS** (ESI) m/z calcd for $C_{24}H_{33}F_3O_5$ $[M+Na]^+$: 481.2172, found 481.2168.

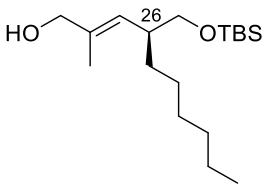
Ethyl (*S*,*E*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyldec-2-enoate (55)



To a solution of alcohol **54** (1.57 g, 6.48 mmol, 1.0 eq.) and imidazole (882.3 mg, 12.96 mmol, 2.0 eq.) in anhydrous CH_2Cl_2 (21.6 mL) at 0 °C under argon was added *tert*-butyldimethylsilyl chloride (1.95 g, 12.96 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature overnight. It was quenched with water and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (1.79 g, 5.02 mmol, 77%) as a colourless oil.

$[\alpha]_D^{25}$ +11.3 (c = 1.0, $CHCl_3$); **R_f** 0.54 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2956, 2929, 2857, 1713, 1470, 1253, 1233, 1100, 837, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.53 (dq, *J* = 10.3, 1.4 Hz, 1H, *H25*), 4.19 (qd, *J* = 7.1, 6.2 Hz, 2H, $CO_2CH_2CH_3$), 3.52 (qd, *J* = 9.8, 6.2 Hz, 2H, *H27*), 2.62 – 2.53 (m, 1H, *H26*), 1.85 (d, *J* = 1.4 Hz, 3H, CCH_3), 1.55 – 1.21 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.89 – 0.85 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4, 144.4, 128.8, 66.1, 60.5, 42.0, 31.9, 31.3, 29.6, 27.3, 26.0, 22.8, 18.4, 14.4, 14.2, 13.1, –5.2, –5.3; **HRMS** (ESI) m/z calcd for $C_{20}H_{40}O_3Si$ $[M+Na]^+$: 379.2639, found 379.2639.

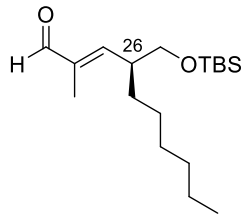
(*S*,*E*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyldec-2-en-1-ol (56)



To a solution of ester **55** (773.3 mg, 2.17 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (2.7 mL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 5.4 mL, 5.43 mmol, 2.5 eq.) dropwise. The reaction mixture was stirred at –78 °C for 1.5 hours. It was quenched with dropwise addition of water (290 µL), 15% aqueous NaOH (290 µL), then water (580 µL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (558.5 mg, 1.78 mmol, 82%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +14.2 (c = 1.0, $CHCl_3$); **R_f** 0.32 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3319, 2955, 2928, 2856, 1470, 1254, 1096, 836, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.14 (dq, *J* = 9.8, 1.4 Hz, 1H, *H25*), 4.01 (s, 2H, *H23*), 3.44 (d, *J* = 6.8 Hz, 2H, *H27*), 2.49 – 2.40 (m, 1H, *H26*), 1.68 (d, *J* = 1.4 Hz, 3H, CC*H*$_3$), 1.57 – 1.10 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.89 – 0.86 (m, 12H, *n*-Hex-C*H*$_3$ and SiC(C*H*$_3$)$_3$), 0.03 (s, 3H, SiC*H*$_3$), 0.02 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.1, 128.4, 69.2, 66.8, 40.8, 32.0, 31.8, 29.7, 27.3, 26.1, 22.8, 18.5, 14.4, 14.3, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{18}H_{38}O_2Si$ $[M+Na]^+$: 337.2533, found 337.2534.

(*S*,*E*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyldec-2-enal (57)

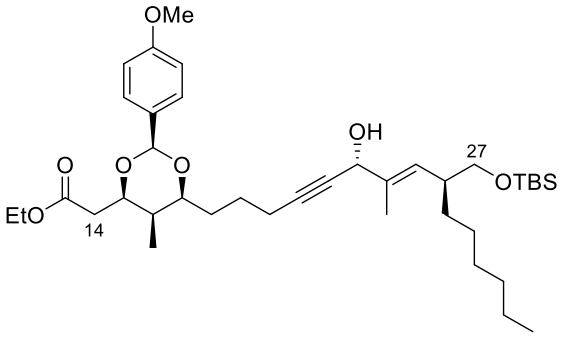


To a solution of alcohol **56** (1.18 g, 3.75 mmol, 1.0 eq.) in CH_2Cl_2 (40 mL) was added $NaHCO_3$ (945.1 mg, 11.25 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (2.39 g, 5.63 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was diluted with diethyl ether (60 mL), quenched with saturated aqueous $Na_2S_2O_3$ (40 mL), and stirred until the mixture became a clear solution. The layers were separated, and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (1.09 g, 3.49 mmol, 93%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +17.0 (c = 1.2, $CHCl_3$); **R_f** 0.69 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2955, 2928, 2856, 1691, 1470, 1253, 1104, 836, 775; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.42 (s, 1H, C*H*O), 6.30 (dq, *J* = 10.2, 1.4 Hz, 1H, *H25*), 3.63 (dd, *J* = 9.8, 5.4 Hz, 1H, *H27*), 3.56 (dd, *J* = 9.8, 6.5 Hz, 1H, *H27'*), 2.78 (dddt, *J* = 10.2, 6.5, 5.4, 8.7 Hz, 1H, *H26*), 1.77 (d, *J* = 1.4 Hz, 3H, CC*H*$_3$), 1.58 – 1.20 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.87 – 0.85 (m, 12H, *n*-Hex-C*H*$_3$ and SiC(C*H*$_3$)$_3$), 0.02 (s, 3H, SiC*H*$_3$), 0.02 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 195.6, 157.2, 140.3, 65.8, 42.3, 31.9, 31.1, 29.5, 27.3, 26.0, 22.7, 18.4, 14.2, 9.9, –5.3, –5.3; **HRMS** (ESI) m/z calcd for $C_{18}H_{36}O_2Si$ $[M+H]^+$: 313.2557, found 313.2558.

6.3.3. The C1–C27 fragment

Ethyl 2-((4*R*,5*R*,6*S*)-6-((6*R*,9*S*,*E*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-7-methylpentadec-7-en-4-yn-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (58)



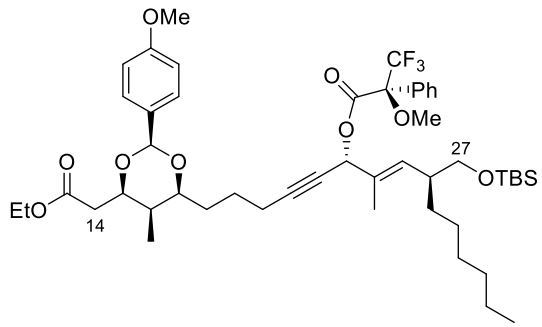
Synthesized according to a modified literature procedure.[170] To a solution of alkyne **3** (865.1 mg, 2.40 mmol, 3.0 eq.) and (*S*)-BINOL (91.6 mg, 0.32 mmol, 0.4 eq.) in anhydrous diethyl ether (8 mL) under argon was added dicyclohexylamine (31.8 µL, 0.16 mmol, 0.2 eq.), followed by dropwise addition of diethyl zinc (1.0 M in hexanes, 2.4 mL, 2.40 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 2–3 days (*Note: argon flow was removed from the flask and the septum was parafilmed to prevent the evaporation of solvent; after 2–3 days, the mixture should become cloudy with precipitate*). Distilled titanium(IV) isopropoxide (237 µL, 0.80 mmol, 1.0 eq.) was added dropwise and the resulting yellow-orange mixture was stirred at room temperature for 2 hours. It was cooled to 0 °C, and a solution of aldehyde **57** (250.0 mg, 0.80 mmol, 1.0 eq.) in anhydrous diethyl ether (2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour and at room temperature for 2 hours. It was cooled to 0 °C, quenched slowly with saturated aqueous NH_4Cl, filtered through celite, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (331.7 mg, 0.49 mmol, 62%, 11:1 *dr*) as a colourless oil; alkyne **3** (525.0 mg, 1.46 mmol) was also recovered.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –11.7 (c = 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.28 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3439, 2953, 2928, 2856, 1735, 1518, 1248, 1182, 1097, 1033, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.51 (s, 1H, C*H*PMP), 5.32 (d, *J* = 9.9 Hz, 1H, *H25*), 4.75 – 4.68 (m, 1H, *H23*), 4.37 (ddd, *J* = 7.9, 5.8,

2.2 Hz, 1H, *H15*), 4.14 (qd, *J* = 7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.88 (ddd, *J* = 8.4, 4.5, 2.1 Hz, 1H, *H17*), 3.77 (s, 3H, OCH_3), 3.46 (dd, *J* = 6.3, 1.8 Hz, 2H, *H27*), 2.68 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.46 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.45 – 2.38 (m, 1H, *H26*), 2.31 – 2.23 (m, 2H, *H20*), 2.09 (d, *J* = 5.1 Hz, 1H, O*H*), 1.75 (d, *J* = 1.4 Hz, 3H, CCH_3), 1.74 – 1.50 (m, 5H, *H16*, *H18* and *H19*), 1.34 – 1.08 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.98 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 0.89 – 0.85 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.03 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 159.9, 136.0, 131.3, 129.5, 127.4, 113.6, 101.5, 85.9, 80.4, 77.2, 68.2, 66.5, 60.6, 55.3, 40.7, 38.1, 34.4, 31.9, 31.9, 31.6, 29.5, 27.0, 26.0, 24.8, 22.7, 18.8, 18.4, 14.2, 14.2, 12.9, 6.0, –5.3, –5.3; **HRMS** (ESI) m/z calcd for $C_{39}H_{64}O_7Si$ $[M+Na]^+$: 695.4314, found 695.4307.

*Mosher ester analysis of **58***

(*S*)-MTPA ester of 58

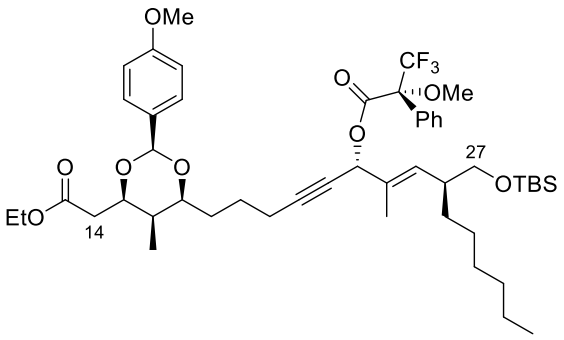


Synthesized according to a modified literature procedure.[194] To a solution of alcohol **58** (23.0 mg, 0.034 mmol, 1.0 eq.) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (32.6 mg, 0.129 mmol, 3.8 eq.) in anhydrous CH_2Cl_2 (680 µL) was added pyridine (17 µL, 0.211 mmol, 6.2 eq.). The reaction mixture was stirred at room temperature for 24 hours. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (24.3 mg, 0.027 mmol, 80%) as a colourless oil.

$[\alpha]_D^{25}$ –20.9 (c = 2.4, $CHCl_3$); **R_f** 0.38 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2953, 2929, 2856, 1745, 1518, 1249, 1183, 1171, 1102, 1034, 1014, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 6.7, 3.0 Hz, 2H, Ar*H*), 7.39 (d, *J* = 8.8 Hz, 2H, Ar*H*),

7.38 – 7.36 (m, 3H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.95 (s, 1H, *H23*), 5.51 (s, 1H, C*H*PMP), 5.50 (d, *J* = 10.0 Hz, 1H, *H25*), 4.37 (ddd, *J* = 8.0, 5.7, 2.3 Hz, 1H, *H15*), 4.16 (qd, *J* = 7.2, 1.8 Hz, 2H, $CO_2CH_2CH_3$), 3.85 (ddd, *J* = 8.6, 4.3, 2.2 Hz, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.45 (d, *J* = 6.2 Hz, 2H, *H27*), 2.69 (dd, *J* = 15.7, 8.0 Hz, 1H, *H14*), 2.46 (dd, *J* = 15.7, 5.7 Hz, 1H, *H14'*), 2.46 – 2.40 (m, 1H, *H26*), 2.31 – 2.21 (m, 2H, *H20*), 1.76 – 1.66 (m, 2H, *H18* and *H19*), 1.73 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.56 – 1.50 (m, 3H, *H16*, *H18'* and *H19'*), 1.31 – 1.10 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.96 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 0.88 – 0.85 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.2, 165.6, 160.0, 134.1, 132.3, 131.4, 131.4, 129.7, 128.4, 127.7, 127.6, 123.4 (q, *J* = 289 Hz), 113.7, 101.6, 88.1, 84.8 (q, *J* = 28 Hz), 80.5, 77.3, 75.7, 72.2, 66.3, 60.7, 55.5, 55.4, 41.1, 38.2, 34.6, 32.0, 31.9, 31.5, 29.6, 27.1, 26.0, 24.8, 22.7, 18.9, 18.4, 14.3, 14.2, 13.4, 6.1, –5.2, –5.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.8; **HRMS** (ESI) m/z calcd for $C_{49}H_{71}F_3O_9Si$ $[M+Na]^+$: 911.4712, found 911.4712.

(*R*)-MTPA ester of 58



Synthesized in the same manner as the (*S*)-MTPA ester of **58** using 0.034 mmol of alcohol **58** and substituting (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The title compound (23.1 mg, 0.026 mmol, 76%) was obtained as a colourless oil.

$[\alpha]_D^{25}$ +9.7 (c = 2.3, $CHCl_3$); **R_f** 0.38 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2952, 2929, 2856, 1745, 1518, 1249, 1183, 1171, 1106, 1034, 1014, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 6.7, 2.9 Hz, 2H, Ar*H*), 7.39 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.37 – 7.35 (m, 3H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.97 (s, 1H, *H23*), 5.51 (s, 1H, C*H*PMP), 5.45 (d, *J* = 10.0 Hz, 1H, *H25*), 4.37 (ddd, *J* = 8.0, 5.7, 2.3 Hz, 1H, *H15*), 4.15

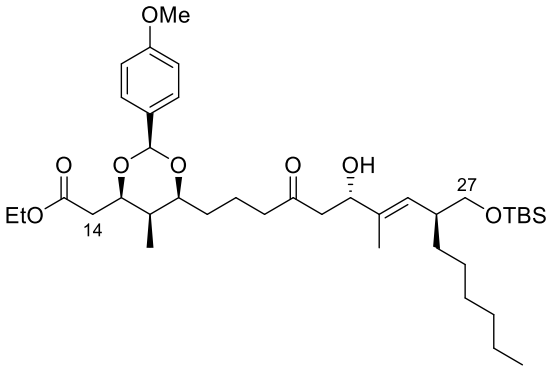
(qd, *J* = 7.1, 1.6 Hz, 2H, $CO_2CH_2CH_3$), 3.86 (ddd, *J* = 8.3, 4.6, 2.1 Hz, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.43 (dd, *J* = 6.2, 2.0 Hz, 2H, *H27*), 2.69 (dd, *J* = 15.7, 8.0 Hz, 1H, *H14*), 2.46 (dd, *J* = 15.7, 5.7 Hz, 1H, *H14'*), 2.44 – 2.38 (m, 1H, *H26*), 2.34 – 2.25 (m, 2H, *H20*), 1.77 – 1.68 (m, 2H, *H18* and *H19*), 1.64 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.58 – 1.51 (m, 3H, *H16*, *H18'* and *H19'*), 1.31 – 1.10 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.96 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.88 – 0.85 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.00 (s, 3H, $SiCH_3$), –0.01 (s, 3H, $SiCH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.2, 165.6, 160.0, 133.7, 132.6, 131.3, 131.2, 129.7, 128.4, 127.5, 127.5, 123.4 (q, *J* = 289 Hz), 113.7, 101.6, 88.3, 84.5 (q, *J* = 28 Hz), 80.5, 77.3, 75.8, 71.8, 66.3, 60.7, 55.6, 55.4, 41.0, 38.2, 34.6, 32.0, 31.9, 31.5, 29.5, 27.1, 26.0, 24.8, 22.7, 18.9, 18.4, 14.3, 14.2, 13.2, 6.1, –5.2, –5.3; **^{19}F NMR** (470 MHz, $CDCl_3$): δ –71.7; **HRMS** (ESI) m/z calcd for $C_{49}H_{71}F_3O_9Si$ $[M+Na]^+$: 911.4712, found 911.4713.

Comparison of the ^{1}H NMR data of the two Mosher ester derivatives is shown below.

Assignment	δ, (*S*)-ester (ppm)	δ, (*R*)-ester (ppm)	$\Delta\delta^{SR}$
H17	3.85	3.86	–0.01
H20	2.26	2.29	–0.03
CCH_3	1.73	1.64	+0.09
H25	5.50	5.45	+0.05
H26	2.43	2.41	+0.02
H27	3.45	3.43	+0.02

Analysis indicates that the C23 centre is of *R* configuration.

Ethyl 2-((4*R*,5*R*,6*S*)-6-((6*S*,9*S*,*E*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-7-methyl-4-oxopentadec-7-en-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (59)

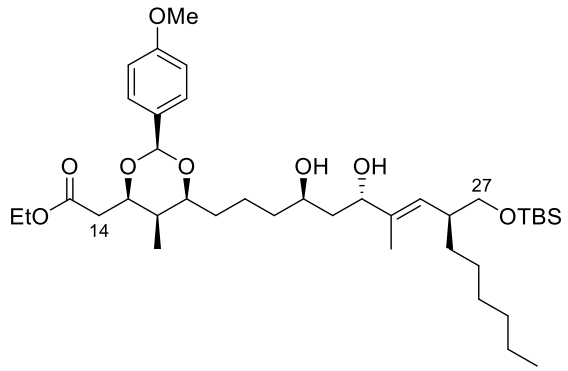


Synthesized according to a modified literature procedure.[172] To a solution of alcohol **58** (580.7 mg, 0.86 mmol, 1.0 eq.) in anhydrous diethyl ether (4.3 mL) under argon was added bis(pinacolato)diboron (523.1 mg, 2.06 mmol, 2.4 eq.), followed by sodium *tert*-butoxide (50.0 mg, 0.52 mmol, 0.6 eq.) in one portion. The mixture was cooled to 0 °C and [(IMes)CuCl][209] (17.3 mg, 0.043 mmol, 5 mol%) was added, followed by anhydrous methanol (139 µL, 3.44 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 30 minutes. The dark-coloured mixture was quenched with 2–3 drops of triethanolamine and stirred at 0 °C for 10 minutes and at room temperature for 10 minutes. It was filtered through celite and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in THF (10.7 mL) and water (10.7 mL), and sodium perborate monohydrate (429.2 mg, 4.30 mmol, 5.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (476.4 mg, 0.69 mmol, 80%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ +0.8 (c = 1.2, $CHCl_3$); $\mathbf{R_f}$ 0.41 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3497, 2954, 2928, 2855, 1736, 1714, 1518, 1248, 1181, 1097, 1032, 833; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.48 (s, 1H, C*H*PMP), 5.15 (d, *J* = 9.9 Hz, 1H, *H25*), 4.42 (dd, *J* = 9.6, 3.5 Hz, 1H, *H23*), 4.34 (ddd, *J* = 8.0, 5.8, 2.2 Hz, 1H, *H15*), 4.12 (qd, *J* = 7.1, 1.3 Hz, 2H, $CO_2CH_2CH_3$), 3.83 (ddd, *J* = 7.8 , 5.0, 2.0 Hz, 1H, *H17*), 3.74 (s, 3H, OCH_3), 3.45 – 3.37 (m, 2H, *H27*), 2.87 (s, 1H,

O*H*), 2.68 – 2.59 (m, 2H, *H14* and *H22*), 2.51 – 2.35 (m, 5H, *H14'*, *H20*, *H22'* and *H26*), 1.72 – 1.38 (m, 5H, *H16*, *H18* and *H19*), 1.61 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.53 – 1.06 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.95 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.87 – 0.83 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.01 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 210.9, 170.9, 159.9, 137.0, 131.2, 128.4, 127.4, 113.5, 101.5, 80.6, 77.2, 73.2, 66.5, 60.5, 55.2, 48.1, 43.4, 40.5, 38.0, 34.3, 32.0, 31.8, 31.6, 29.5, 27.1, 25.9, 22.6, 19.6, 18.3, 14.2, 14.1, 12.4, 5.9, –5.3, –5.3; **HRMS** (ESI) m/z calcd for $C_{39}H_{66}O_8Si$ $[M+Na]^+$: 713.4430, found 713.4412.

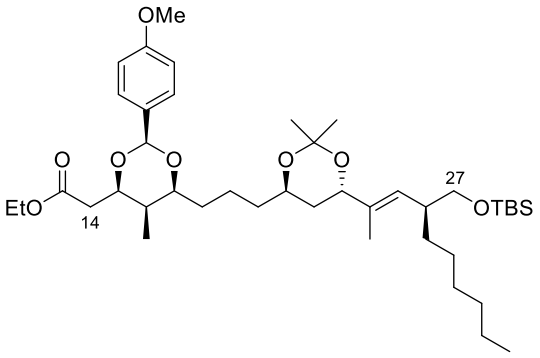
Ethyl 2-((4*R*,5*R*,6*S*)-6-((4*R*,6*S*,9*S*,*E*)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,6-dihydroxy-7-methylpentadec-7-en-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (60)



Synthesized according to a modified literature procedure.[210] To a stirred suspension of tetramethylammonium triacetoxyborohydride (1.05 g, 4.00 mmol, 5.8 eq.) in anhydrous acetonitrile (18 mL) under argon was added glacial acetic acid (3.8 mL). The solution was cooled to –20 °C and a solution of β-hydroxy ketone **59** (476.4 mg, 0.69 mmol, 1.0 eq.) in anhydrous acetonitrile (5 mL) was added dropwise. The reaction mixture was stirred at –20 °C overnight. It was quenched with saturated aqueous potassium sodium tartrate (16 mL), warmed to room temperature, and stirred for 30 minutes, upon which a white precipitate formed. The mixture was poured over ice, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 7/3) to afford the title compound (432.1 mg, 0.62 mmol, 90%, >20:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ +2.6 (c = 1.1, $CHCl_3$); **R_f** 0.27 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3413, 2952, 2928, 2856, 1736, 1518, 1248, 1181, 1098, 1060, 1032, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.49 (s, 1H, C*H*PMP), 5.17 (d, *J* = 9.9 Hz, 1H, *H25*), 4.34 (ddd, *J* = 8.0, 5.7, 2.2 Hz, 1H, *H15*), 4.26 (dd, *J* = 8.3, 3.5 Hz, 1H, *H23*), 4.12 (qd, *J* = 7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.86 – 3.78 (m, 2H, *H17* and *H21*), 3.74 (s, 3H, OCH_3), 3.43 (d, *J* = 6.5 Hz, 2H, *H27*), 2.80 (s, 1H, O*H*), 2.66 (dd, *J* = 15.7, 8.0 Hz, 1H, *H14*), 2.44 (dd, *J* = 15.7, 5.7 Hz, 1H, *H14'*), 2.44 – 2.37 (m, 1H, *H26*), 1.75 – 1.32 (m, 9H, *H16*, *H18*, *H19*, *H20* and *H22*), 1.60 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.54 – 1.06 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.95 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.88 – 0.84 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.02 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 159.8, 138.4, 131.3, 127.4, 113.5, 101.5, 80.8, 77.2, 74.4, 68.9, 66.8, 60.5, 55.2, 41.0, 40.5, 38.1, 37.2, 34.3, 32.6, 31.8, 31.7, 29.5, 27.1, 26.0, 22.7, 21.7, 18.3, 14.2, 14.1, 12.9, 6.0, –5.3, –5.3; **HRMS** (ESI) m/z calcd for $C_{39}H_{68}O_8Si$ $[M+Na]^+$: 715.4587, found 715.4569.

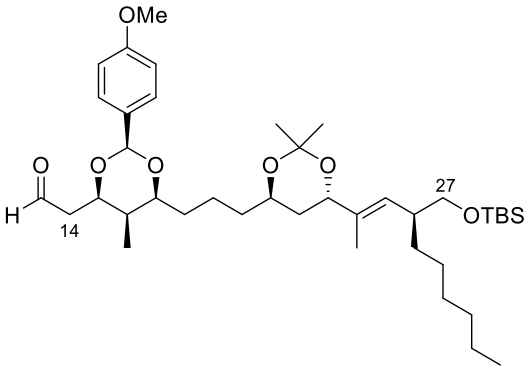
Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl) dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (61)



To a solution of diol **60** (365.3 mg, 0.53 mmol, 1.0 eq.) in 2,2-dimethoxypropane/CH_2Cl_2 (3.8 mL, 1:1) was added pyridinium *p*-toluenesulfonate (10.6 mg, 0.042 mmol, 8 mol%). The reaction mixture was stirred at room temperature overnight. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 17/3) to afford the title compound (311.7 mg, 0.43 mmol, 80%) as a colourless oil.

$[\alpha]_D^{25}$ –10.0 (c = 1.1, $CHCl_3$); **R_f** 0.39 (pentane/diethyl ether = 3/1); **IR** (thin film): ν_{max}/cm^{-1} 2951, 2928, 2856, 1738, 1518, 1377, 1249, 1171, 1101, 1034, 835; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 5.14 (d, *J* = 9.7 Hz, 1H, *H25*), 4.37 (ddd, *J* = 7.8, 5.8, 2.2 Hz, 1H, *H15*), 4.21 – 4.12 (m, 3H, *H23* and $CO_2CH_2CH_3$), 3.87 (ddd, *J* = 7.6, 5.4, 2.1 Hz, 1H, *H17*), 3.83 – 3.78 (m, 1H, *H21*), 3.77 (s, 3H, OCH_3), 3.49 (dd, *J* = 9.8, 5.7 Hz, 1H, *H27*), 3.43 (dd, *J* = 9.8, 6.9 Hz, 1H, *H27'*), 2.69 (dd, *J* = 15.7, 7.8 Hz, 1H, *H14*), 2.47 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.39 – 2.46 (m, 1H, *H26*), 1.86 – 1.40 (m, 9H, *H16*, *H18*, *H19*, *H20* and *H22*), 1.65 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.36 (s, 3H, acetonide-CH_3), 1.36 (s, 3H, acetonide-CH_3), 1.56 – 1.09 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.98 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 0.89 – 0.86 (m, 12H, *n*-Hex-CH_3 and $SiC(CH_3)_3$), 0.03 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.1, 159.9, 136.0, 131.4, 127.9, 127.5, 113.6, 101.6, 100.3, 80.8, 77.3, 71.7, 66.6, 66.6, 60.6, 55.3, 40.4, 38.2, 37.0, 35.9, 34.2, 32.4, 31.9, 31.7, 29.6, 27.1, 26.0, 25.1, 24.9, 22.7, 21.2, 18.4, 14.3, 14.2, 12.7, 6.0, –5.2, –5.3; **HRMS** (ESI) m/z calcd for $C_{42}H_{72}O_8Si$ $[M+Na]^+$: 755.4889, found 755.4886.

2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetaldehyde (62)

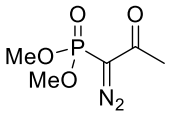


To a solution of ester **61** (327.3 mg, 0.45 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (4.5 mL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 540 µL, 0.54 mmol, 1.2 eq.) dropwise. The reaction mixture was stirred at –78 °C for 15 minutes. It was quenched with ethyl acetate, followed by slow addition of water (65 µL), 15% aqueous NaOH (65 µL), and water (130 µL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (227.4 mg, 0.33 mmol, 73%) as a colourless oil.

$[\alpha]_D^{25}$ –3.7 (c = 1.1, $CHCl_3$); **R_f** 0.41 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 2950, 2928, 2856, 1729, 1518, 1378, 1249, 1224, 1170, 1111, 1063, 1036, 835; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.83 (t, *J* = 1.8 Hz, 1H, C*H*O), 7.40 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.54 (s, 1H, C*H*PMP), 5.13 (d, *J* = 9.7 Hz, 1H, *H25*), 4.46 (ddd, *J* = 8.7, 4.5, 2.2 Hz, 1H, *H15*), 4.19 (dd, *J* = 9.3, 6.1 Hz, 1H, *H23*), 3.90 (ddd, *J* = 7.5, 5.3, 2.2 Hz, 1H, *H17*), 3.82 – 3.76 (m, 1H, *H21*), 3.79 (s, 3H, OCH_3), 3.48 (dd, *J* = 9.8, 5.7 Hz, 1H, *H27*), 3.42 (dd, *J* = 9.8, 6.9 Hz, 1H, *H27'*), 2.84 (ddd, *J* = 17.0, 8.7, 1.8 Hz, 1H, *H14*), 2.48 (ddd, *J* = 16.9, 4.5, 1.8 Hz, 1H, *H14'*), 2.45 – 2.38 (m, 1H, *H26*), 1.82 (ddd, *J* = 12.8, 9.3, 5.8 Hz, 1H, *H22*), 1.73 – 1.67 (m, 1H, *H18*), 1.65 (d, *J* = 1.3 Hz, 3H, CCH_3), 1.60 – 1.35 (m, 7H, *H16*, *H18'*, *H19*, *H20* and *H22'*), 1.36 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.56 – 1.09 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.99 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.89 – 0.86 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.02 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 200.8, 160.1, 136.0, 131.2, 128.0, 127.6, 113.8, 101.7, 100.4, 80.9, 75.9, 71.8, 66.7, 66.6, 55.4, 46.9, 40.5, 37.0, 36.0, 34.5, 32.5, 32.0, 31.8, 29.6, 27.2, 26.1, 25.1, 24.9, 22.8, 21.2, 18.5, 14.2, 12.8, 6.2, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{40}H_{68}O_7Si$ $[M+Na]^+$: 711.4627, found 711.4623.

Dimethyl (1-diazo-2-oxopropyl)phosphonate (63)



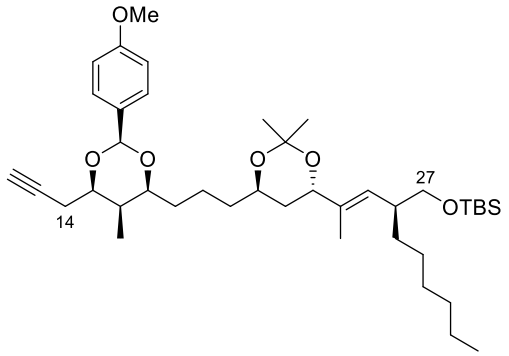
Synthesized according to a modified literature producedure.[214] To a suspension of NaH (60% in mineral oil, 475.2 mg, 11.88 mmol, 1.1 eq.) in anhydrous THF (34 mL) at 0 °C under argon was added a solution of dimethyl 2-oxopropylphosphonate (1.5 mL, 10.80 mmol, 1.0 eq.) in anhydrous THF (20 mL) dropwise, upon which a white solid formed. The mixture was stirred at 0 °C for 1 hour, after which *p*-toluenesulfonyl azide solution (30% in toluene, 8.8 mL, 11.56 mmol, 1.07 eq.) was added. The resulting yellow reaction mixture was stirred at 0 °C for 3 hours. It was filtered through celite, washing with ethyl acetate, and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (pentane/ethyl acetate = 3/2 → 1/4) to afford the title compound (1.82 g, 9.47 mmol, 88%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.81 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 190.0, 189.9, 53.7, 53.7, 27.3.

The physical and spectroscopic data were consistent with literature reported data.[214]

tert-Butyl(((2*S*)-2-((*E*)-2-((4*S*,6*R*)-6-(3-((4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-(prop-2-yn-1-yl)-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)octyl)oxy)dimethylsilane (64)

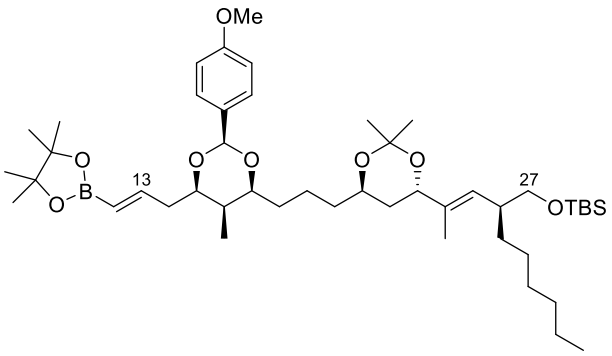


To a solution of dimethyl (1-diazo-2-oxopropyl) phosphonate **63** (441.1 mg, 2.30 mmol, 8.0 eq.) in anhydrous MeOH (4.2 mL) under argon was added K_2CO_3 (325.2 mg, 2.35 mmol, 8.2 eq.), followed by a solution of aldehyde **62** (197.9 mg, 0.29 mmol, 1.0 eq.) in anhydrous MeOH (3 mL). The reaction mixture was stirred at room temperature for 2 hours. It was quenched with saturated aqueous NH_4Cl, diluted with water, and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1) to afford the title compound (158.6 mg, 0.23 mmol, 81%) as a colourless oil.

$[\alpha]_D^{25}$ –16.3 (c = 1.0, $CHCl_3$); **R_f** 0.47 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 3313, 2951, 2928, 2856, 1517, 1378, 1249, 1171, 1105, 1062, 1037, 832; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.49 (s, 1H, C*H*PMP), 5.14 (d, *J* = 9.7 Hz, 1H, *H25*), 4.20 (dd, *J* = 9.2, 6.2 Hz, 1H, *H23*), 4.04 (ddd, *J* = 9.3, 6.0, 2.3 Hz, 1H, *H15*), 3.86 – 3.77 (m, 2H, *H17* and *H21*), 3.79 (s, 3H, OCH_3),

3.49 (dd, *J* = 9.8, 5.7 Hz, 1H, *H27*), 3.43 (dd, *J* = 9.8, 6.9 Hz, 1H, *H27'*), 2.59 (ddd, *J* = 16.7, 6.0, 2.7 Hz, 1H, *H14*), 2.44 (ddd, *J* = 16.7, 9.3, 2.7 Hz, 1H, *H14'*), 2.46 – 2.40 (m, 1H, *H26*), 2.00 (t, *J* = 2.7 Hz, 1H, *H12*), 1.87 – 1.75 (m, 2H, *H16* and *H22*), 1.72 – 1.36 (m, 7H, *H18*, *H19*, *H20* and *H22'*), 1.66 (d, *J* = 1.3 Hz, 3H, CCH_3), 1.37 (s, 3H, acetonide-CH_3), 1.36 (s, 3H, acetonide-CH_3), 1.59 – 1.09 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.99 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.90 – 0.86 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.03 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 136.1, 131.4, 127.9, 127.6, 113.8, 101.7, 100.3, 81.0, 80.1, 79.0, 71.8, 70.2, 66.7, 66.6, 55.4, 40.5, 37.0, 36.0, 33.2, 32.6, 32.0, 31.8, 29.6, 27.2, 26.1, 25.2, 25.0, 22.8, 22.5, 21.3, 18.5, 14.2, 12.8, 5.4, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{41}H_{68}O_6Si$ $[M+Na]^+$: 707.4688, found 707.4672.

tert-Butyl(((2*S*)-2-((*E*)-2-((4*S*,6*R*)-6-(3-((4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)octyl)oxy)dimethylsilane (65)

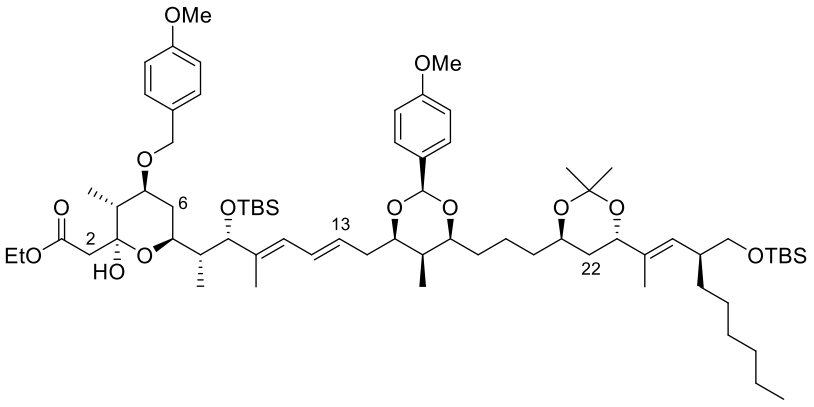


Synthesized according to a modified literature procedure.[179] To a mixture of alkyne **64** (71.3 mg, 0.104 mmol, 1.0 eq.) and pinacolborane (189 µL, 1.300 mmol, 12.5 eq.) under argon was added bis(cyclopentadienyl)zirconium chloride hydride (2.7 mg, 0.0104 mmol, 0.1 eq.) and anhydrous triethylamine (14.5 µL, 0.104 mmol, 1.0 eq.). The reaction mixture was stirred at 60 °C for 2 hours. Upon cooling to room temperature, the mixture was diluted with diethyl ether, quenched with brine, and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1) to afford the title compound (62.7 mg, 0.077 mmol, 74%) as a colourless oil.

$[\alpha]_D^{25}$ +4.0 (c = 1.2, $CHCl_3$); **R_f** 0.43 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 2951, 2928, 2855, 1640, 1518, 1358, 1248, 1144, 1100, 1063, 1003, 834; **^{1}H NMR** (400

MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.59 (ddd, *J* = 18.0, 7.6, 5.8 Hz, 1H, *H13*), 5.56 (d, *J* = 18.0 Hz, 1H, *H12*), 5.47 (s, 1H, C*H*PMP), 5.12 (d, *J* = 9.8 Hz, 1H, *H25*), 4.18 (dd, *J* = 9.4, 6.1 Hz, 1H, *H23*), 3.93 (td, *J* = 7.0, 2.0 Hz, 1H, *H15*), 3.81 – 3.76 (m, 2H, *H17* and *H21*), 3.79 (s, 3H, OCH_3), 3.48 (dd, *J* = 9.9, 5.7 Hz, 1H, *H27*), 3.42 (dd, *J* = 9.8, 7.0 Hz, 1H, *H27'*), 2.59 – 2.52 (m, 1H, *H14*), 2.46 – 2.32 (m, 2H, H14' and *H26*), 1.82 (ddd, *J* = 12.8, 9.4, 5.9 Hz, 1H, *H22*), 1.69 – 1.34 (m, 8H, *H16*, *H18*, *H19*, *H20* and *H22'*), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.36 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.58 – 1.09 (m, 22H, Bpin-CH_3 × 4 and *n*-Hex-(CH_2)$_5$), 0.97 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.89 – 0.85 (m, 12H, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.02 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0, 149.4, 136.1, 131.7, 127.9, 127.6, 113.7, 101.7, 100.4, 83.3, 81.1, 80.1, 71.8, 66.7, 66.7, 55.4, 40.5, 39.4, 37.1, 36.1, 34.1, 32.6, 32.0, 31.8, 29.7, 27.2, 26.1, 25.2, 24.9, 24.9, 22.8, 21.3, 18.5, 14.3, 12.8, 5.8, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{47}H_{81}BO_8Si$ [M+Na]$^+$: 834.5722, found 834.5717.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-6-((2*R*,3*S*,4*E*,6*E*)-3-((*tert*-butyldimethylsilyl)oxy)-8-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylocta-4,6-dien-2-yl)-2-hydroxy-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (66)



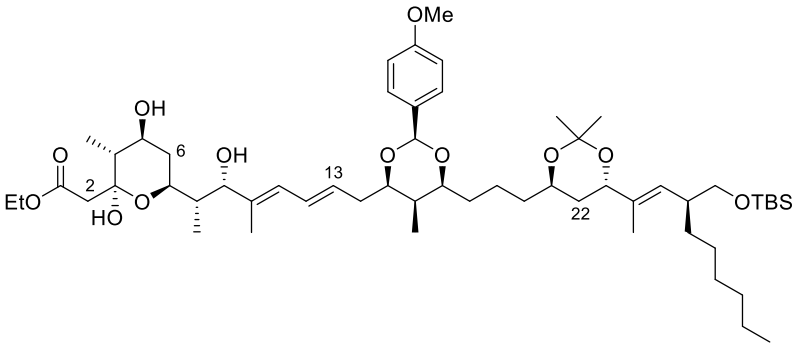
To a solution of iodide **2a** (14.9 mg, 0.022 mmol, 1.1 eq.), boronic ester **65** (16.3 mg, 0.020 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol, 0.3 eq.) in degassed anhydrous[xxxix,xl] THF (2.5 mL) under argon was added dropwise a solution of Tl_2CO_3 (16.9 mg, 0.036 mmol, 1.8 eq.) in degassed[xxxix] water (0.8 mL) over 5 minutes. (Note: Tl_2CO_3 was dissolved in degassed water under argon and stirred for 30 minutes prior to addition to the reaction

mixture.) The reaction mixture was stirred at room temperature overnight. It was diluted with diethyl ether, water was added, and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (17.9 mg, 0.014 mmol, 72%) as a colourless oil.

$[\alpha]_D^{25}$ +21.8 (c = 0.4, $CHCl_3$); **R_f** 0.31 (pentane/ethyl acetate = 9/1); **IR** (thin film): ν_{max}/ cm^{-1} 3483, 2927, 2855, 1716, 1516, 1459, 1248, 1183, 1081, 1060, 1038, 836, 775; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.35 (dd, *J* = 15.1, 11.0 Hz, 1H, *H12*), 5.97 (d, *J* = 11.0 Hz, 1H, *H11*), 5.77 (dt, *J* = 15.1, 7.2 Hz, 1H, *H13*), 5.49 (s, 1H, C*H*PMP), 5.12 (d, *J* = 9.7 Hz, 1H, *H25*), 4.54 (d, *J* = 10.9 Hz, 1H, OC*H*$_2$Ar), 4.42 (d, *J* = 1.9 Hz, 1H, O*H*), 4.33 (d, *J* = 10.9 Hz, 1H, OC*H'*$_2$Ar), 4.22 – 4.15 (m, 3H, $CO_2CH_2CH_3$ and *H23*), 3.89 (td, *J* = 7.2, 2.1 Hz, 1H, *H15*), 3.82 – 3.77 (m, 3H, *H9*, *H17* and *H21*), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.70 (dt, *J* = 12.2, 2.2 Hz, 1H, *H7*), 3.50 – 3.45 (m, 2H, *H5* and *H27*), 3.41 (dd, *J* = 9.7, 6.9 Hz, 1H, *H27'*), 2.70 (d, *J* = 14.5 Hz, 1H, *H2*), 2.52 (dt, *J* = 14.2, 7.2 Hz, 1H, *H14*), 2.46 (d, *J* = 14.5 Hz, 1H, *H2'*), 2.45 – 2.38 (m, 1H, *H26*), 2.30 (dt, *J* = 14.2, 7.2 Hz, 1H, *H14'*), 1.87 (ddd, *J* = 12.2, 4.5, 2.2 Hz, 1H, *H6*), 1.82 (td, *J* = 7.1, 3.6 Hz, 1H, *H22*), 1.71 – 1.34 (m, 11H, *H4*, *H6'*, *H8*, *H16*, *H18*, *H19*, *H20* and *H22'*), 1.64 (d, *J* = 1.1 Hz, 3H, CC*H*$_3$), 1.64 (s, 3H, CC*H*$_3$), 1.35 (s, 3H, acetonide-C*H*$_3$), 1.35 (s, 3H, acetonide-C*H*$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.56 – 1.09 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 1.06 (d, *J* = 6.7 Hz, 3H, H4C*H*$_3$), 0.98 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.93 (d, *J* = 6.7 Hz, 3H, H8C*H*$_3$), 0.89 – 0.86 (m, 21H, *n*-Hex-C*H*$_3$ and SiC(C*H*$_3$)$_3$ × 2), 0.02 (s, 3H, SiC*H*$_3$), 0.02 (s, 3H, SiC*H*$_3$), 0.00 (s, 3H, SiC*H*$_3$), –0.06 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.9, 159.9, 159.3, 136.6, 136.1, 131.9, 131.1, 129.4, 129.1, 128.8, 128.0, 127.6, 127.4, 113.9, 113.7, 101.5, 100.3, 98.8, 81.2, 81.0, 80.7, 77.2, 71.9, 70.9, 67.5, 66.7, 66.7, 60.9, 55.4, 55.4, 45.4, 43.1, 41.4, 40.5, 37.1, 36.4, 36.1, 35.2, 34.2, 32.6, 32.0, 31.8, 29.7, 27.2, 26.1, 26.0, 25.2, 25.0, 22.8, 21.3, 18.5, 18.4, 14.4, 14.3, 12.8, 12.4, 11.7, 10.1, 5.8, –4.4, –5.0, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{71}H_{118}O_{13}Si_2$ $[M+Na]^+$: 1257.8003, found 1257.8010.

[xxxix] Degassed for at least 1 hour before use. [xl] Freshly taken from the solvent purification system

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-6-((2*S*,3*S*,4*E*,6*E*)-8-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-(((*tert*-butyl-dimethylsilyl)oxy)methyl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-hydroxy-4-methylocta-4,6-dien-2-yl)-2,4-dihydroxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (67)

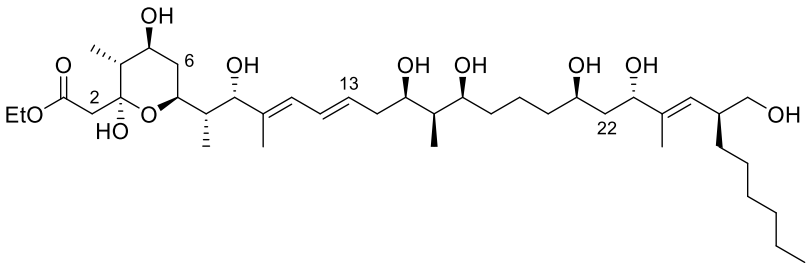


To a solution of iodide **53** (8.4 mg, 0.019 mmol, 1.1 eq.), boronic ester **65** (14.0 mg, 0.017 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (5.9 mg, 0.0051 mmol, 0.3 eq.) in degassed anhydrous [xxxix,xl] THF (2.1 mL) under argon was added dropwise a solution of Tl_2CO_3 (14.5 mg, 0.031 mmol, 1.8 eq.) in degassed[xxxix] water (680 µL) over 5 minutes. (Note: Tl_2CO_3 was dissolved in degassed water under argon and stirred for 30 minutes prior to addition to the reaction mixture.) The reaction mixture was stirred at room temperature overnight. It was diluted with ethyl acetate, water was added, and the mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 3/1) to afford the title compound (9.1 mg, 0.009 mmol, 53%) as a colourless oil.

$[\alpha]_D^{25}$ +18.8 (c = 0.8, $CHCl_3$); **R_f** 0.35 (pentane/ethyl acetate = 1/1); **IR** (thin film): ν_{max}/ cm^{-1} 3459, 2928, 2855, 1713, 1518, 1462, 1376, 1249, 1193, 1172, 1099, 1033, 986, 835, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.37 (dd, *J* = 15.0, 11.0 Hz, 1H, *H12*), 6.14 (d, *J* = 11.0 Hz, 1H, *H11*), 5.72 (dt, *J* = 15.0, 7.2 Hz, 1H, *H13*), 5.47 (s, 1H, C*H*PMP), 5.12 (d, *J* = 9.7 Hz, 1H, *H25*), 4.74 (d, *J* = 1.9 Hz, 1H, O*H*), 4.25 – 4.17 (m, 3H, $CO_2CH_2CH_3$ and *H23*), 4.16 – 4.07 (m, 2H, *H7* and *H9*), 3.86 (td, *J* = 7.2, 2.1 Hz, 1H, *H15*), 3.82 – 3.74 (m, 3H, *H5*, *H17*, *H21*), 3.79 (s, 3H, OCH_3), 3.48 (dd, *J* = 9.8, 5.7 Hz, 1H, *H27*), 3.42 (dd, *J* = 9.8, 7.0 Hz, 1H, *H27'*), 2.79 (d, *J* = 15.3 Hz, 1H, *H2*), 2.54 – 2.46 (m, 2H, *H2'* and *H14*), 2.45 – 2.38 (m, 1H, *H26*), 2.31 (dt, *J* = 14.4, 7.2 Hz, 1H, *H14'*), 1.87 – 1.78 (m, 2H, *H6* and *H22*), 1.70 – 1.35 (m, 10H, *H6'*, *H8*, *H16*, *H18*, *H19*, *H20, H22'*), 1.67 (s, 3H, CCH_3), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.36 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.34 – 1.31 (m, 1H, *H4*), 1.30 (t, *J* =

7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.58 – 1.09 (m, 10H, *n*-Hex-$(CH_2)_5$), 1.10 (d, *J* = 6.6 Hz, 3H, H4CH_3), 0.97 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.89 – 0.85 (m, 15H, H8CH_3, *n*-Hex-CH_3 and SiC(CH_3)$_3$), 0.02 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.8, 160.0, 136.1, 136.0, 131.8, 129.2, 128.7, 128.0, 127.6, 125.0, 113.7, 101.6, 100.4, 99.0, 81.2, 81.1, 79.5, 71.9, 71.7, 69.7, 66.7, 66.7, 61.4, 55.5, 46.8, 42.6, 40.5, 39.5, 38.7, 37.1, 36.4, 36.1, 34.1, 32.6, 32.0, 31.8, 29.7, 27.2, 26.1, 25.2, 25.0, 22.8, 21.3, 18.5, 14.3, 14.3, 13.8, 12.8, 12.1, 6.8, 5.8, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{57}H_{96}O_{12}Si$ $[M+Na]^+$: 1023.6587, found 1023.6552.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2,4-dihydroxy-3-methyl-6-((2*S*,3*S*,4*E*,6*E*,9*R*,10*R*,11*S*, 15*R*,17*S*,18*E*, 20*S*)-3,9,11,15,17-pentahydroxy-20-(hydroxymethyl)-4,10,18-trimethylhexacosa-4,6,18-trien-2-yl)tetrahydro-2*H*-pyran-2-yl)acetate (68)

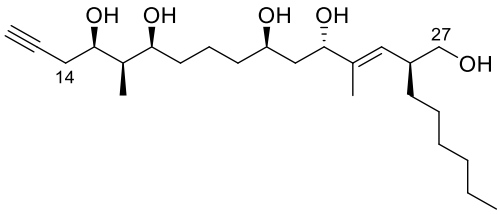


*From **66*:** To a solution of PMB ether **66** (12.4 mg, 0.010 mmol, 1.0 eq.) in CH_2Cl_2 (330 µL) and water (17 µL) at 0 °C was added DDQ (2.8 mg, 0.013 mmol, 1.25 eq.). The reaction mixture was stirred at 0 °C under argon for 2 hours. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the PMB-deprotected compound. It was dissolved in THF (300 µL) and MeOH (600 µL), and 0.02 M aqueous HCl (600 µL) was added. The reaction mixture was stirred at room temperature for 3 days. It was diluted with chloroform, quenched with saturated aqueous $NaHCO_3$, and extracted with chloroform. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 24/1 → 47/3) to afford the title compound (0.6 mg, 0.82 µmol, 8% over two steps) as a colourless oil.

*From **67***: To a solution of **67** (18.0 mg, 0.018 mmol, 1.0 eq.) in THF (1 mL) and MeOH (2 mL) was added 0.1 M aqueous HCl (2 mL). The reaction mixture was stirred at room temperature for 3 hours. It was diluted with chloroform, quenched with saturated aqueous $NaHCO_3$, and extracted with chloroform. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 24/1 → 47/3) to afford the title compound (5.4 mg, 0.007 mmol, 41%) as a colourless oil.

$[\alpha]_D^{25}$ +7.4 (c = 0.4, $CHCl_3$); **R_f** 0.14 (CH_2Cl_2/MeOH = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3352, 2924, 2855, 1713, 1459, 1375, 1331, 1193, 1019, 986, 756; **^{1}H NMR** (600 MHz, MeOD): δ 6.37 (dd, *J* = 15.0, 10.9 Hz, 1H, *H12*), 6.08 (d, *J* = 10.9 Hz, 1H, *H11*), 5.77 (dt, *J* = 15.0, 7.3 Hz, 1H, *H13*), 5.15 (d, *J* = 9.8 Hz, 1H, *H25*), 4.24 – 4.15 (m, 3H, *H23* and $CO_2CH_2CH_3$), 3.93 (d, *J* = 7.0 Hz, 1H, *H9*), 3.84 (dt, *J* = 12.2, 2.7 Hz, 1H, *H7*), 3.78 (td, *J* = 6.5, 3.7 Hz, 1H, *H15*), 3.75 – 3.71 (m, 2H, *H17* and *H21*), 3.60 (td, *J* = 10.7, 4.6 Hz, 1H, *H5*), 3.43 (dd, *J* = 10.7, 6.3 Hz, 1H, *H27*), 3.38 (dd, *J* = 10.7, 6.8 Hz, 1H, *H27'*), 2.74 (d, *J* = 14.3 Hz, 1H, *H2*), 2.55 (d, *J* = 14.3 Hz, 1H, *H2'*), 2.51 – 2.44 (m, 1H, *H26*), 2.34 (app t, *J* = 6.9 Hz, 2H, *H14*), 1.76 – 1.73 (m, 1H, *H6*), 1.71 – 1.66 (m, 1H, *H22*), 1.67 (s, 3H, CCH_3), 1.66 (s, 3H, CCH_3), 1.63 – 1.33 (m, 11H, *H4*, *H6'*, *H8*, *H16*, *H18*, *H19*, *H20* and *H22'*), 1.53 – 1.09 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 1.06 (d, *J* = 6.5 Hz, 3H, H4CH_3), 0.94 (d, *J* = 7.0 Hz, 3H, H16CH_3), 0.92 (d, *J* = 6.8 Hz, 3H, H8CH_3), 0.90 (t, *J* = 7.1 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (151 MHz, MeOD): δ 173.6, 140.8, 137.3, 131.3, 129.6, 129.1, 127.6, 100.0, 80.1, 75.9, 75.7, 75.4, 70.4, 70.4, 69.2, 67.0, 61.9, 47.3, 44.4, 43.8, 42.5, 41.7, 41.2, 39.7, 39.5, 38.8, 36.1, 33.1, 32.9, 30.6, 28.3, 23.7, 23.3, 14.6, 14.5, 12.5, 12.4, 12.2, 9.2, 7.0; **HRMS** (ESI) m/z calcd for $C_{40}H_{72}O_{11}$ $[M+Na]^+$: 751.4991, found 751.4967.

(2*S*,5*S*,7*R*,11*S*,12*R*,13*R*,*E*)-2-Hexyl-4,12-dimethylhexadec-3-en-15-yne-1,5,7,11,13-pentaol (69)



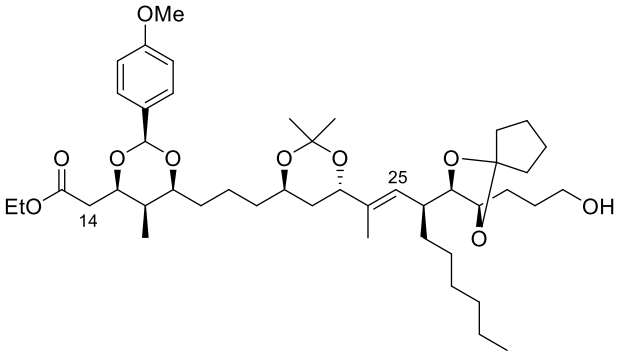
To a solution of alkyne **64** (25.0 mg, 0.036 mmol, 1.0 eq.) in THF (1.5 mL) and methanol (3 mL) was added 0.05 M aqueous HCl (3 mL). The reaction mixture was stirred at room temperature overnight. It was diluted with chloroform, quenched with saturated aqueous $NaHCO_3$, and extracted with chloroform. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 49/1 → 47/3) to afford the title compound (8.2 mg, 0.020 mmol, 55%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +1.3 (c = 0.8, $CHCl_3$); **R_f** 0.24 (CH_2Cl_2/MeOH = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3341, 3312, 2925, 2856, 1458, 1099, 1061, 1041; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.22 (d, *J* = 9.8 Hz, 1H, *H25*), 4.32 (dd, *J* = 8.1, 3.2 Hz, 1H, *H23*), 4.03 (td, *J* = 7.0, 2.2 Hz, 1H, *H15*), 3.87 – 3.81 (m, 2H, *H17* and *H21*), 3.60 (dd, *J* = 10.6, 4.6 Hz, 1H, *H27*), 3.35 (dd, *J* = 10.6, 8.7 Hz, 1H, *H27'*), 3.25 (brs, 5H, O*H* × 5), 2.55 – 2.49 (m, 1H, *H26*), 2.46 (ddd, *J* = 16.7, 7.0, 2.7 Hz, 1H, *H14*), 2.33 (ddd, *J* = 16.7, 7.0, 2.7 Hz, 1H, *H14'*), 2.02 (t, *J* = 2.7 Hz, 1H, *H12*), 1.78 (ddd, *J* = 14.5, 8.1, 2.7 Hz, 1H, *H22*), 1.72 (qt, *J* = 7.1, 2.2 Hz, 1H, *H16*), 1.64 (d, *J* = 0.7 Hz, 3H, CC*H*$_3$), 1.61 – 1.54 (m, 3H, *H18*, *H19* and *H22'*), 1.52 – 1.47 (m, 2H, *H20*), 1.45 – 1.38 (m, 1H, *H18'*), 1.37 – 1.33 (m, 1H, *H19'*), 1.38 – 1.12 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.92 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.87 (t, *J* = 6.9 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 139.8, 128.1, 81.3, 76.6, 75.1, 74.8, 70.5, 69.2, 66.8, 40.8, 40.7, 39.9, 37.3, 35.3, 32.0, 31.7, 29.6, 27.3, 24.9, 22.8, 22.5, 14.2, 13.0, 4.6; **HRMS** (ESI) m/z calcd for $C_{24}H_{44}O_5$ $[M+Na]^+$: 435.3081, found 435.3081.

6.4. The C13–C48 fragment

6.4.1. The C13–C32 fragment (both approaches) and initial combination towards the C13–C48 fragment

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(3-hydroxypropyl)-1,4-dioxaspiro[4.4] nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (70)

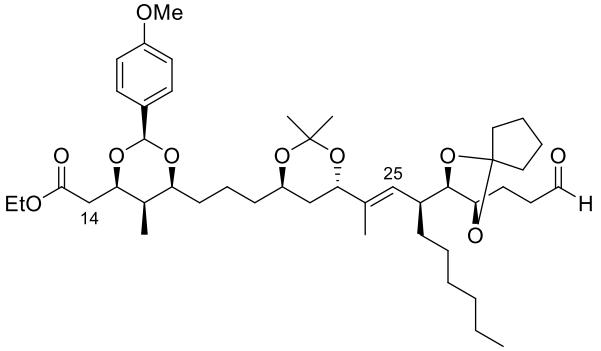


To a solution of PMB ether **39** (346.4 mg, 0.39 mmol, 1.0 eq.) in CH_2Cl_2 (13 ml) and water (680 µL) at 0 °C was added DDQ (158.9 mg, 0.70 mmol, 1.8 eq.). The reaction mixture was stirred at 0 °C under argon for 2 hours. It was filtered through celite, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3 → 4/1) to afford the title compound (234.0 mg, 0.30 mmol, 78%) as a colourless oil.

$[\alpha]_D^{25}$ –13.7 (c = 1.0, $CHCl_3$); **R_f** 0.20 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3508, 2933, 2858, 1737, 1518, 1459, 1249, 1171, 1103, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.51 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.6 Hz, 1H, *H25*), 4.36 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H, *H15*), 4.20 (dd, *J* = 9.4, 6.3 Hz, 1H, *H23*), 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.86 (ddd, *J* = 7.6, 5.2, 1.9 Hz, 1H, *H17*), 3.80 – 3.75 (m, 1H, *H21*), 3.78 (s, 3H, OCH_3), 3.64 (ddd, *J* = 9.4, 7.0, 2.4 Hz, 1H, *H28*), 3.58 (t, *J* = 5.7 Hz, 2H, *H31*), 3.38 (dd, *J* = 8.7, 7.0 Hz, 1H, *H27*), 2.68 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.47 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.43 – 2.37 (m, 1H, *H26*), 1.83 – 1.45 (m, 21H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30* and cyclopent-$(CH_2)_4$), 1.65 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.34 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.09 (m, 13H, $CO_2CH_2CH_3$

and *n*-Hex-(C*H*$_2$)$_5$), 0.98 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 160.0, 137.0, 131.4, 127.6, 126.6, 118.1, 113.7, 101.6, 100.5, 83.9, 80.8, 80.0, 77.4, 72.1, 66.7, 62.2, 60.7, 55.4, 42.5, 38.2, 37.5, 37.5, 36.8, 35.9, 34.3, 32.5, 32.4, 31.9, 30.8, 29.6, 29.5, 26.9, 25.1, 24.9, 23.7, 23.5, 22.8, 21.3, 14.3, 14.2, 13.0, 6.0; **HRMS** (ESI) m/z calcd for $C_{45}H_{72}O_{10}$ $[M+Na]^+$: 795.5018, found 795.5010.

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-2,2-dimethyl-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(3-oxopropyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (71)

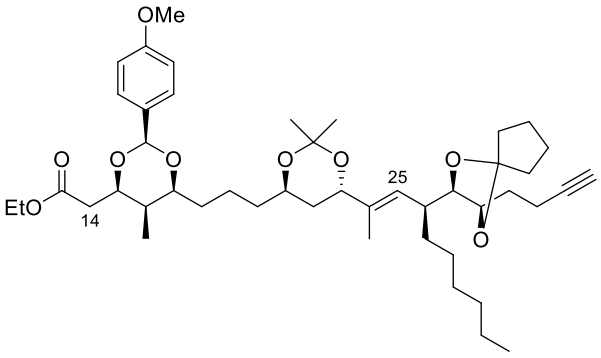


To a solution of alcohol **70** (234.0 mg, 0.30 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) was added $NaHCO_3$ (75.6 mg, 0.90 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (190.9 mg, 0.45 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 2 hours. It was diluted with diethyl ether (10 mL), quenched with saturated aqueous $Na_2S_2O_3$ (6 mL), and stirred until the mixture became a clear solution. The layers were separated, and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (200.0 mg, 0.26 mmol, 86%) as a colourless oil.

$[\alpha]_D^{25}$ –12.7 (c = 0.6, $CHCl_3$); **R$_f$** 0.61 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 2930, 2856, 1733, 1518, 1460, 1248, 1171, 1101, 1031; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.5 Hz, 1H, C*H*O), 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.37 (ddd, *J* = 8.0, 5.8, 2.2 Hz, 1H, *H15*), 4.21 – 4.12 (m, 3H, *H23* and $CO_2CH_2CH_3$), 3.86 (ddd, *J* = 7.6, 5.2, 2.1 Hz,

1H, *H17*), 3.80 – 3.75 (m, 1H, *H21*), 3.79 (s, 3H, OCH_3), 3.62 (ddd, *J* = 8.6, 6.8, 3.3 Hz, 1H, *H28*), 3.42 (dd, *J* = 8.6, 6.8 Hz, 1H, *H27*), 2.69 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.62 – 2.38 (m, 4H, *H14'*, *H26* and *H30*), 1.95 – 1.43 (m, 19H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.33 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.11 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(CH_2)$_5$), 0.98 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 202.0, 171.2, 160.0, 137.6, 131.5, 127.6, 125.5, 118.3, 113.7, 101.6, 100.4, 83.9, 80.8, 79.2, 77.4, 71.6, 66.6, 60.7, 55.4, 42.2, 40.7, 38.2, 37.6, 37.5, 37.1, 36.0, 34.3, 32.5, 32.4, 31.9, 29.5, 26.9, 26.8, 25.0, 24.9, 23.7, 23.5, 22.8, 21.3, 14.3, 14.2, 13.3, 6.0; **HRMS** (ESI) m/z calcd for $C_{45}H_{70}O_{10}$ [M+Na]$^+$: 793.4861, found 793.4863.

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(but-3-yn-1-yl)-1,4-dioxaspiro[4.4] nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (72)

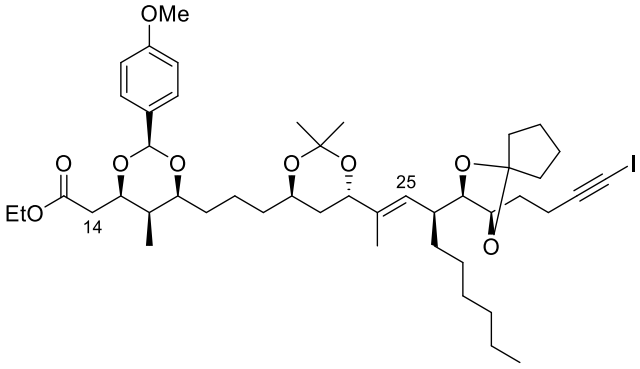


To a solution of dimethyl (1-diazo-2-oxopropyl) phosphonate **63** (69.2 mg, 0.36 mmol, 3.0 eq.) in anhydrous EtOH[xli] (3 mL) under argon was added K_2CO_3 (58.0 mg, 0.42 mmol, 3.5 eq.), followed by a solution of aldehyde **71** (90.4 mg, 0.12 mmol, 1.0 eq.) in anhydrous EtOH (1.8 mL). The reaction mixture was stirred at room temperature for 24 hours. It was quenched with saturated aqueous NH_4Cl, diluted with water, and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (82.6 mg, 0.11 mmol, 90%) as a colourless oil.

[xli]When MeOH was used, transesterification to the methyl ester was observed.

$[\alpha]_D^{25}$ –8.4 (c =0.6, $CHCl_3$); **R_f** 0.51 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3303, 2928, 2856, 1737, 1518, 1458, 1249, 1171, 1103, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.37 (ddd, *J* = 7.9, 5.8, 2.3 Hz, 1H, *H15*), 4.20 – 4.12 (m, 3H, *H23* and $CO_2CH_2CH_3$), 3.87 (ddd, *J* = 7.0, 5.3, 1.9 Hz, 1H, *H17*), 3.81 – 3.76 (m, 1H, *H21*), 3.79 (s, 3H, OCH_3), 3.70 (ddd, *J* = 8.8, 6.7, 3.2 Hz, 1H, *H28*), 3.43 (dd, *J* = 8.5, 6.7 Hz, 1H, *H27*), 2.69 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.47 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.44 – 2.39 (m, 1H, *H26*), 2.36 – 2.18 (m, 2H, *H30*), 1.90 (t, *J* = 2.6 Hz, 1H, *H32*), 1.81 – 1.48 (m, 19H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29* and cyclopent-$(CH_2)_4$), 1.65 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.36 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.28 – 1.14 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.98 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 160.0, 137.4, 131.4, 127.5, 125.2, 118.2, 113.7, 101.6, 100.4, 84.1, 83.7, 80.8, 78.8, 77.3, 71.2, 68.5, 66.6, 60.6, 55.4, 42.2, 38.2, 37.6, 37.5, 37.1, 35.9, 34.2, 33.5, 32.4, 32.3, 31.9, 29.5, 26.9, 25.0, 24.9, 23.7, 23.6, 22.7, 21.2, 15.5, 14.3, 14.2, 13.4, 6.0; **HRMS** (ESI) m/z calcd for $C_{46}H_{70}O_9$ $[M+Na]^+$: 789.4912, found 789.4907.

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(4-iodobut-3-yn-1-yl)-1,4-dioxaspiro-[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (73)



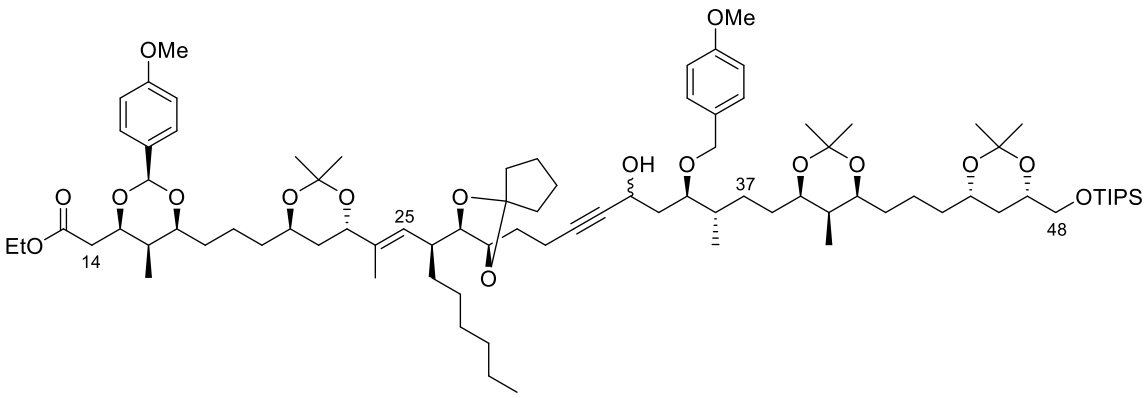
Synthesized according to a modified literature procedure.[215] To a solution of iodine (205.6 mg, 0.810 mmol, 15.0 eq.) in anhydrous toluene (225 µL, 3.6 M) at 0 °C under argon was added a solution of morpholine (142 µL, 1.620 mmol, 30.0 eq.) in anhydrous toluene (186 µL, 8.7 M). The mixture was warmed to 45 °C and stirred for 1 hour, after which a solution of alkyne **72** (41.3 mg, 0.054 mmol, 1.0 eq.) in anhydrous toluene (270 µL, 0.2 M) was

added. The reaction mixture was stirred at 45 °C overnight. It was filtered through celite, washing with toluene. Saturated aqueous $Na_2S_2O_3$ (6 mL) was added and the solution was stirred for 30 minutes. It was extracted with diethyl ether, and the organic layers were washed with brine and dried over Na_2SO_4. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 4/1) to afford the title compound[xlii] (43.0 mg, 0.048 mmol, 89%) as a pale yellow oil.

$[\alpha]_D^{25}$ –5.6 (c = 2.7, $CHCl_3$); **R_f** 0.47 (pentane/diethyl ether = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 2931, 2856, 1736, 1518, 1456, 1248, 1171, 1103, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.52 (s, 1H, C*H*PMP), 5.05 (d, *J* = 10.5 Hz, 1H, *H25*), 4.37 (ddd, *J* = 7.8, 5.9, 2.2 Hz, 1H, *H15*), 4.20 – 4.12 (m, 3H, *H23* and $CO_2CH_2CH_3$), 3.90 – 3.86 (m, 1H, *H17*), 3.81 – 3.77 (m, 1H, *H21*), 3.79 (s, 3H, OCH_3), 3.71 – 3.64 (m, 1H, *H28*), 3.41 (dd, *J* = 8.8, 6.7 Hz, 1H, *H27*), 2.69 (dd, *J* = 15.7, 7.8 Hz, 1H, *H14*), 2.52 – 2.37 (m, 4H, *H14'*, *H26*, *H30*), 1.81 – 1.48 (m, 19H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29* and cyclopent-$(CH_2)_4$), 1.65 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.37 (s, 3H, acetonide-CH_3), 1.36 (s, 3H, acetonide-CH_3), 1.29 – 1.14 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-$(CH_2)_5$), 0.98 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 0.87 (t, *J* = 6.8 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 160.0, 137.5, 131.4, 127.6, 124.9, 118.2, 113.7, 101.6, 100.4, 94.1, 83.7, 80.8, 78.8, 77.4, 71.0, 66.7, 60.7, 55.4, 42.3, 38.2, 37.6, 37.5, 37.1, 36.0, 34.2, 33.4, 32.5, 32.4, 31.9, 29.5, 26.9, 25.0, 24.9, 23.7, 23.6, 22.8, 21.3, 17.9, 14.3, 14.2, 13.7, 6.0, –6.6; **HRMS** (ESI) m/z calcd for $C_{46}H_{69}IO_9$ $[M+Na]^+$: 915.3879, found 915.3872.

[xlii] Obtained along with a small amount of morpholine/morpholine by-product

Ethyl 2-((4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((4*S*,*E*)-4-((2*R*,3*R*)-3-((7*R*,8*S*)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (74)

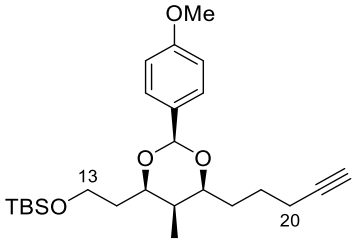


Synthesized according to a modified literature procedure.[216] A Schlenk tube containing $CrCl_2$ (59.0 mg, 0.480 mmol, 10.0 eq.) was heated under vacuum until $CrCl_2$ became a free-flowing powder. Upon cooling, it was filled with argon. Anhydrous THF (1 mL) was added, and the suspension was stirred for 20–30 minutes, upon which it became a light mint green colour. A solution of iodide **73** (43.0 mg, 0.048 mmol, 1.0 eq.) and aldehyde **5** (38.2 mg, 0.053 mmol, 1.1 eq.) in anhydrous THF (1.4 mL) was added. The reaction mixture was stirred at room temperature in the dark (covered with aluminium foil) for 24 hours. It was quenched with water and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 4/1 → 7/3) to afford the title compound (45.5 mg, 0.031 mmol, 64%, 1.6:1 *dr*) as a colourless oil.

R_f 0.22 and 0.11 (pentane/diethyl ether = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3472, 2940, 2866, 1737, 1516, 1460, 1378, 1249, 1172, 1112, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.27 – 7.22 (m, 2H, Ar*H*), 6.87 – 6.85 (m, 4H, Ar*H*), 5.51 (s, 1H, C*H*PMP), 5.04 (d, *J* = 10.6 Hz, 1H, *H25*), 4.52 – 4.49 (m, 2H, *H33* and OCH_2Ar), 4.40 – 4.34 (m, 2H, *H15* and OC*H'*$_2$Ar), 4.21 (dd, *J* = 9.6, 6.1 Hz, 1H, *H23*), 4.15 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.93 (dddd, *J* = 11.5, 6.7, 5.2, 2.2 Hz, 1H, *H47*), 3.89 – 3.68 (m, 14H, *H17*, *H21*, *H28*, *H35*, *H39*, *H41*, *H45*, *H48* and OCH_3 × 2), 3.52 (dd, *J* = 9.8, 6.7 Hz, 1H, *H48'*), 3.42 (dd, *J* = 8.4, 6.6 Hz, 1H, *H27*), 3.24 (d, *J* = 3.0 Hz, 0.27H, OH_{minor}), 3.10 (d, *J*

= 6.0 Hz, 0.43H, O*H*$_{major}$), 2.68 (dd, *J* = 15.7, 7.9 Hz, 1H, *H14*), 2.46 (dd, *J* = 15.7, 5.8 Hz, 1H, *H14'*), 2.43 – 2.38 (m, 1H, *H26*), 2.33 – 2.28 (m, 2H, *H30*), 1.93 – 1.86 (m, 1H, *H36*), 1.84 – 1.30 (m, 37H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46*, CC*H*$_3$ and cyclopent-(C*H*$_2$)$_4$), 1.44 (s, 3H, acetonide-C*H*$_3$), 1.41 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.37 (s, 3H, acetonide-C*H*$_3$), 1.36 – 1.35 (m, 6H, acetonide-C*H*$_3$ × 2), 1.27 – 1.17 (m, 13H, $CO_2CH_2CH_3$ and *n*-Hex-(C*H*$_2$)$_5$), 1.08 – 1.03 (m, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.97 (d, *J* = 6.9 Hz, 3H, H16C*H*$_3$), 0.92 – 0.89 (m, 3H, H36C*H*$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.82 (d, *J* = 6.8 Hz, 3H, H40C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 160.0, 159.3/159.3, 137.3, 131.4, 130.8/130.5, 129.5/129.5, 127.6, 126.1/125.6, 118.4/118.3, 114.0/113.9, 113.7, 101.6, 100.5, 98.8, 98.5, 84.6/84.3, 83.9/83.7, 81.9/81.8, 80.8, 79.9, 78.8/78.8, 77.3, 73.9, 73.4, 72.2/72.1, 71.3/71.0, 70.2, 69.0, 67.4, 66.7, 60.7, 61.9/60.0, 55.4, 55.4, 42.2, 38.2, 37.7/37.7, 37.6/37.6, 37.2, 37.1, 36.7, 36.0, 34.9/34.9, 34.7/34.6, 34.4, 34.3, 33.9/33.7, 32.9, 32.5, 32.3/32.2, 31.9, 31.3/31.2, 30.4, 30.2, 29.8, 29.5, 29.0/28.9, 26.9, 25.1, 24.8/24.8, 23.7, 23.6, 22.8, 21.3, 21.1, 20.0, 19.8, 18.1, 15.8/15.8, 14.3, 14.2, 14.0/13.8, 13.0/13.0, 12.1, 6.0, 4.8/4.8; **HRMS** (ESI) m/z calcd for $C_{87}H_{142}O_{17}Si$ $[M+Na]^+$: 1509.9909, found 1509.9915.

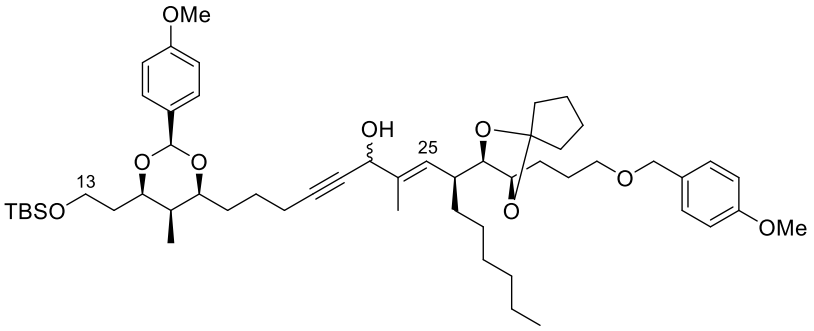
tert-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-(pent-4-yn-1-yl)-1,3-dioxan-4-yl)ethoxy)dimethylsilane (75)



To a solution of ester **3** (1.28 g, 3.55 mmol, 1.0 eq.) in anhydrous THF (35.5 mL) at –78 °C under argon was added $LiAlH_4$ (2.4 M in THF, 1.8 mL, 4.26 mmol, 1.2 eq.) dropwise. The reaction mixture was stirred at –78 °C for 1 hour and at –40 °C for 1 hour. It was quenched with successive dropwise addition of water (155 µL), 15% aqueous NaOH (155 µL), and water (465 µL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous DMF (7.1 mL) under argon and the solution was cooled to 0 °C. Imidazole (725.1 mg, 10.65 mmol, 3.0 eq.) and *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol, 2.0 eq.) were added. The reaction mixture was stirred at room temperature for 1.5 hours. It was quenched with water and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (1.39 g, 3.21 mmol, 90% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ +14.7 (c = 1.2, $CHCl_3$); **R_f** 0.37 (pentane/diethyl ether = 9/1); **IR** (thin film): ν_{max}/cm^{-1} 3310, 2953, 2857, 1518, 1249, 1098, 1068, 1036, 1010, 833; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.47 (s, 1H, C*H*PMP), 4.04 (ddd, *J* = 9.0, 4.0, 2.2 Hz, 1H, *H15*), 3.85 (ddd, *J* = 8.3, 4.7, 2.2 Hz, 1H, *H17*), 3.80 (s, 3H, OCH_3), 3.79 – 3.69 (m, 2H, *H13*), 2.32 – 2.17 (m, 2H, *H20*), 1.96 (t, *J* = 2.6 Hz, 1H, *H22*), 1.87 (ddt, *J* = 13.9, 9.0, 4.8 Hz, 1H, *H14*), 1.80 – 1.54 (m, 5H, *H14'*, *H18* and *H19*), 1.46 (qdd, *J* = 6.9, 2.2, 2.2 Hz, 1H, *H16*), 0.98 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9, 131.8, 127.5, 113.7, 101.6, 84.5, 80.8, 77.4, 68.6, 59.5, 55.4, 36.1, 35.3, 31.9, 26.1, 24.8, 18.6, 18.5, 6.2, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{25}H_{40}O_4Si$ $[M+Na]^+$: 455.2588, found 455.2591.

(9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxy phenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4] nonan-2-yl)-7-methylpentadec-7-en-4-yn-6-ol (76)

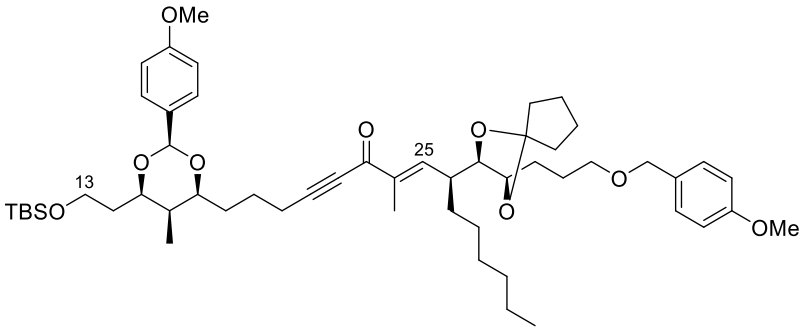


To a solution of alkyne **75** (1.35 g, 3.13 mmol, 1.3 eq.) in anhydrous THF (18 mL) under argon at –78 °C was added *n*-BuLi (2.5 M in hexanes, 1.2 mL, 2.89 mmol, 1.2 eq.) dropwise. The solution was stirred at –78 °C for 1.5 hours, after which a solution of aldehyde **4b** (1.14 g, 2.41 mmol, 1.0 eq.) in anhydrous THF (6.1 mL) was added dropwise. The mixture was stirred at –78 °C for 1 hour, at –40 °C for 1 hour, and at 0 °C for 1 hour. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 4/1) to afford the title compound (2.16 g, 2.39 mmol, 99%, 1:1 *dr*) as a colourless oil; alkyne **75** (289 mg, 0.67 mmol) was also recovered.

R_f 0.47 and 0.42 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/cm^{-1} 3445, 2954, 2857, 1516, 1464, 1249, 1099, 1069, 1037, 1009, 833; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7, 2H, Ar*H*), 7.23 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 0.5H, C*H*PMP), 5.45 (s, 0.5H, C*H*PMP), 5.37 (d, *J* = 10.7 Hz, 0.5H, *H25*), 5.14 (d, *J* = 10.6 Hz, 0.5H, *H25*), 4.70 – 4.69 (m, 0.5H, *H23*), 4.67 (d, *J* = 7.1 Hz, 0.5H, *H23*), 4.42 (s, 2H, OCH_2Ar), 4.04 – 4.00 (m, 1H, *H15*), 3.84 – 3.81 (m, 1H, *H17*), 3.79 (s, 6H, OCH_3 × 2), 3.78 – 3.68 (m, 2H, *H13*), 3.59 – 3.59 (m, 1H, *H28*), 3.47 – 3.41 (m, 1H, *H31*), 3.40 – 3.37 (m, 1H, *H27*), 3.36 – 3.32 (m, 1H, *H31'*), 2.83 (d, *J* = 4.6 Hz, 0.5H, O*H*), 2.68 (d, *J* = 7.1 Hz, 0.5H, O*H*), 2.45 – 2.37 (m, 1H, *H26*), 2.32 – 2.20 (m, 2H, *H20*), 1.89 – 1.82 (m, 1H, *H14*), 1.80 – 1.51 (m, 16H, *H14'*, *H18*, *H19*, *H29, H30* and cyclopent-(CH_2)$_4$), 1.78 (d, *J* = 0.9 Hz, 1.5H, CCH_3), 1.76 (d, *J* = 0.9 Hz, 1.5H, CCH_3), 1.47 – 1.39 (m, 2H, *H16* and *H29'*), 1.33 – 1.10 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3);

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.9, 159.4/159.3, 137.9/137.2, 131.8/131.8, 130.4/130.3, 129.7/129.5, 127.5, 127.5/127.2, 118.2, 113.9/113.9, 113.7, 101.6, 86.7/85.9, 83.7/83.6, 80.9, 80.3/80.2, 79.9/79.8, 77.4, 72.4/72.3, 69.20/69.0, 68.6/67.9, 59.5, 55.4, 55.4, 42.8/42.7, 37.6, 37.6/37.5, 36.1, 35.3/35.3, 32.5/32.5, 32.1/32.1, 32.0, 30.8/30.7, 29.5/29.5, 27.1/26.9, 26.6/26.6, 26.1, 25.1/25.0, 23.7, 23.6, 22.8/22.8, 19.0, 18.5, 14.3/14.2, 13.0, 6.3/6.2, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{54}H_{84}O_9Si$ $[M+Na]^+$: 927.5777, found 927.5760.

(*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxy phenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4] nonan-2-yl)-7-methylpentadec-7-en-4-yn-6-one (79)

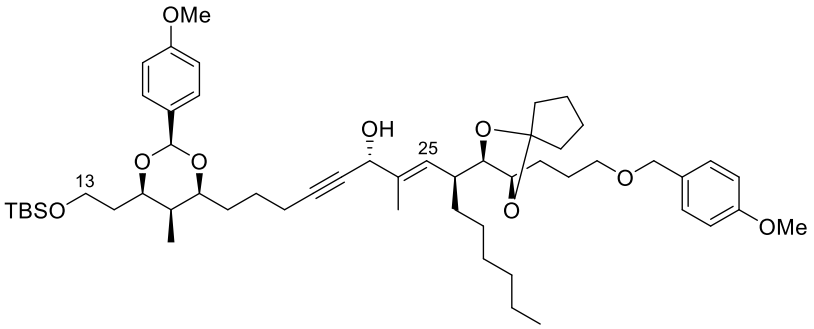


To a solution of alcohol **76** (2.16 g, 2.39 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (48 mL) was added MnO_2 (6.23 g, 71.70 mmol, 30.0 eq.). The reaction mixture was stirred at room temperature under argon for 2 hours. It was filtered through silica and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1) to afford the title compound (2.04 g, 2.26 mmol, 94%) as a colourless oil.

$[\alpha]_D^{25}$ +4.0 (c = 1.1, $CHCl_3$); **R_f** 0.36 (pentane/ethyl acetate = 17/1); **IR** (thin film): ν_{max}/ cm^{-1} 2931, 2857, 2214, 1635, 1517, 1249, 1100, 1037, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.22 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 6.79 (d, *J* = 10.8 Hz, 1H, *H25*), 5.45 (s, 1H, C*H*PMP), 4.38 (s, 2H, OCH_2Ar), 4.03 (ddd, *J* = 9.3, 3.9, 2.2 Hz, 1H, *H15*), 3.84 – 3.80 (m, 1H, *H17*), 3.79 (s, 6H, OCH_3 × 2), 3.78 – 3.69 (m, 2H, *H13*), 3.63 (ddd, *J* = 8.0, 6.4, 3.6 Hz, 1H, *H28*), 3.56 (dd, *J* = 7.8, 6.4 Hz, 1H, *H27*), 3.40 (t, *J* = 6.4 Hz, 2H, *H31*), 2.67 (ddt, *J* = 10.8, 7.8, 3.4 Hz, 1H, *H26*), 2.48 – 2.35 (m, 2H, *H20*), 1.89 – 1.48 (m, 18H, *H14*, *H18*, *H19*, *H29, H30* and cyclopent-(CH_2)$_4$), 1.83 (d,

J = 1.0 Hz, 3H, CC*H*$_3$), 1.43 (qdd, *J* = 6.9, 2.2, 2.1 Hz, 1H, *H16*), 1.38 – 1.12 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.97 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 180.4, 159.9, 159.2, 149.0, 140.0, 131.7, 130.7, 129.3, 127.5, 118.6, 113.9, 113.7, 101.6, 94.7, 83.2, 80.7, 79.5, 79.1, 77.4, 72.6, 69.8, 59.5, 55.4, 55.4, 44.0, 37.8, 37.7, 36.1, 35.4, 32.2, 31.9, 31.8, 30.8, 29.5, 27.3, 26.4, 26.1, 24.4, 23.7, 23.6, 22.7, 19.2, 18.5, 14.2, 11.7, 6.3, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{54}H_{82}O_9Si$ [M+Na]$^+$: 925.5620, found 925.5592.

(6*R*,9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxy phenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4] nonan-2-yl)-7-methylpentadec-7-en-4-yn-6-ol (76-*R*)

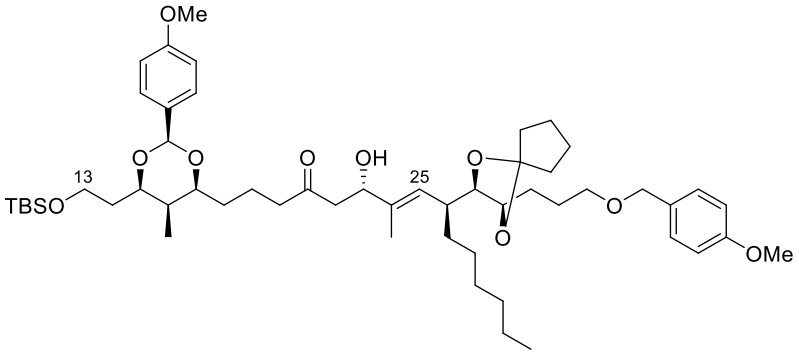


To a solution of ynone **79** (1.54 g, 1.70 mmol, 1.0 eq.) in anhydrous THF (34 mL) at –30 °C under argon was added (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 2.6 mL, 2.55 mmol, 1.5 eq.) dropwise, followed by dropwise addition of borane dimethyl sulfide complex (2.0 M in THF, 3.4 mL, 6.80 mmol, 4.0 eq.). The reaction mixture was stirred at –30 °C for 3 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (1.50 g, 1.66 mmol, 97%, >20:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ –2.5 (c = 1.2, $CHCl_3$); **R$_f$** 0.42 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/cm^{-1} 3445, 2955, 2858, 1517, 1464, 1250, 1100, 1070, 1038, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.14 (d, *J* = 10.5 Hz, 1H, *H25*), 4.70 – 4.69 (m, 1H, *H23*), 4.42 (s, 2H, OC*H*$_2$Ar), 4.03 (ddd, *J* = 9.2, 3.9, 2.2 Hz, 1H, *H15*), 3.85 – 3.81 (m, 1H, *H17*), 3.79 (s,

3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.78 – 3.69 (m, 2H, *H13*), 3.57 (td, *J* = 7.7, 2.3 Hz, 1H, *H28*), 3.46 – 3.42 (m, 1H, *H31*), 3.38 (dd, *J* = 8.8, 7.1 Hz, 1H, *H27*), 3.36 – 3.32 (m, 1H, *H31'*), 2.83 (d, *J* = 4.6 Hz, 1H, O*H*), 2.43 – 2.37 (m, 1H, *H26*), 2.32 – 2.20 (m, 2H, *H20*), 1.89 – 1.82 (m, 1H, *H14*), 1.81 – 1.52 (m, 16H, *H14'*, *H18*, *H19*, *H29, H30* and cyclopent-(CH_2)$_4$), 1.78 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.47 – 1.41 (m, 2H, *H16* and *H29'*), 1.30 – 1.12 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.4, 137.9, 131.8, 130.3, 129.7, 127.5, 127.5, 118.2, 113.9, 113.7, 101.6, 85.9, 83.6, 80.9, 80.3, 79.9, 77.4, 72.4, 69.0, 68.6, 59.5, 55.4, 55.4, 42.8, 37.6, 37.5, 36.1, 35.3, 32.5, 32.1, 32.0, 30.7, 29.5, 26.9, 26.6, 26.1, 25.0, 23.7, 23.6, 22.8, 19.0, 18.5, 14.3, 13.0, 6.2, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{54}H_{84}O_9Si$ $[M+Na]^+$: 927.5777, found 927.5753.

(6*S*,9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6-hydroxy-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-4-one (80)

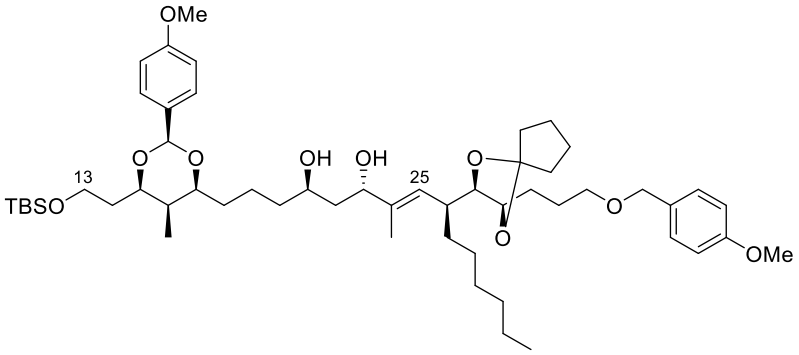


Synthesized according to a modified literature procedure.[172] To a solution of alcohol **76-*R*** (1.50 g, 1.66 mmol, 1.0 eq.) in anhydrous diethyl ether (8.3 mL) under argon was added bis(pinacolato)diboron (1.01 g, 3.98 mmol, 2.4 eq.), followed by sodium *tert*-butoxide (96.1 mg, 1.00 mmol, 0.6 eq.) in one portion. The mixture was cooled to 0 °C and [(IMes)CuCl][209] (33.5 mg, 0.083 mmol, 5 mol%) was added, followed by anhydrous methanol (269 µL, 6.64 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 45 minutes. The dark-coloured mixture was quenched with 2–3 drops of triethanolamine and stirred at 0 °C for 10 minutes and at room temperature for 10 minutes. It was filtered through celite and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in THF (20.8 mL) and

water (20.8 mL), and sodium perborate monohydrate (828.5 mg, 8.30 mmol, 5.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3 → 3/1) to afford the title compound (1.17 g, 1.27 mmol, 76%) as a colourless oil.

$[\alpha]_D^{25}$ +10.4 (c = 1.3, $CHCl_3$); **R_f** 0.26 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/ cm^{-1} 3462, 2931, 2857, 1715, 1616, 1517, 1464, 1250, 1100, 1069, 1037, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.22 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.45 (s, 1H, C*H*PMP), 5.08 (d, *J* = 10.5 Hz, 1H, *H25*), 4.44 – 4.40 (m, 1H, *H23*), 4.40 (s, 2H, OC*H*$_2$Ar), 4.02 (ddd, *J* = 9.1, 3.8, 2.1 Hz, 1H, *H15*), 3.83 – 3.79 (m, 1H, *H17*), 3.79 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.78 – 3.68 (m, 2H, *H13*), 3.56 (ddd, *J* = 8.6, 7.0, 2.3 Hz, 1H, *H28*), 3.48 (dt, *J* = 9.6, 5.3 Hz, 1H, *H31*), 3.38 – 3.33 (m, 2H, *H27* and *H31'*), 3.24 (d, *J* = 2.9 Hz, 1H, O*H*), 2.66 (dd, *J* = 15.9, 9.3 Hz, 1H, *H22*), 2.47 – 2.35 (m, 4H, *H20*, *H22'* and *H26*), 1.88 – 1.81 (m, 1H, *H14*), 1.80 – 1.54 (m, 15H, *H14'*, *H18*, *H19*, *H29, H30* and cyclopent-(C*H*$_2$)$_4$), 1.47 – 1.39 (m, 3H, *H16*, *H18'* and *H29'*), 1.64 (d, *J* = 1.0 Hz, 3H, CC*H*$_3$), 1.30 – 1.07 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.95 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 210.4, 159.9, 159.4, 138.5, 131.8, 130.3, 129.6, 127.5, 127.1, 118.2, 113.9, 113.7, 101.6, 83.8, 81.2, 80.3, 77.4, 73.8, 72.5, 69.2, 59.5, 55.4, 55.4, 48.0, 43.8, 42.5, 37.6, 37.6, 36.1, 35.1, 32.4, 32.2, 32.0, 30.9, 29.5, 27.1, 26.7, 26.1, 23.7, 23.6, 22.8, 19.7, 18.5, 14.3, 12.4, 6.1, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{54}H_{86}O_{10}Si$ $[M+Na]^+$: 945.5883, found 945.5850.

(4*R*,6*S*,9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-ene-4,6-diol (81)

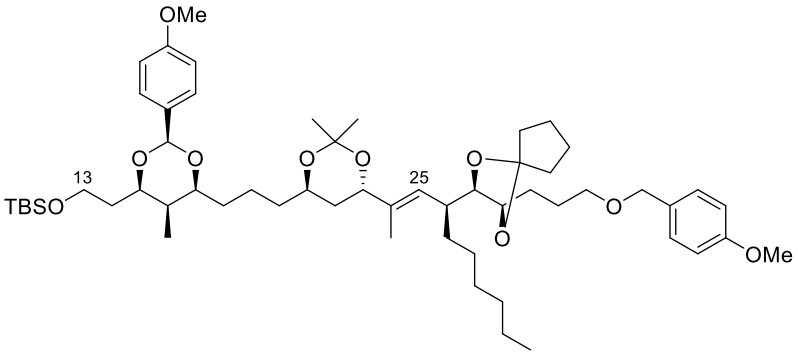


To a stirred suspension of $Me_4NBH(OAc)_3$ (1.16 g, 4.41 mmol, 5.8 eq.) in anhydrous acetonitrile (18.3 mL) under argon was added glacial acetic acid (5.3 mL). The solution was stirred for 20 minutes at room temperature, after which it was cooled to –30 °C. A solution of β-hydroxy ketone **80** (705 mg, 0.76 mmol, 1.0 eq.) in anhydrous acetonitrile (7 mL) was added dropwise. The reaction mixture was stirred at –30 °C for 1 hour and at –20 °C overnight. It was quenched with saturated aqueous potassium sodium tartrate (17 mL), warmed to room temperature, and stirred for 30 minutes, upon which a white precipitate formed. The mixture was poured over ice, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the title compound (580.4 mg, 0.63 mmol, 83%, >20:1 *dr*) as a light yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +13.3 (c = 1.5, $CHCl_3$); **R_f** 0.24 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/ cm^{-1} 3434, 2931, 2858, 1517, 1464, 1250, 1100, 1038, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.20 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.45 (s, 1H, C*H*PMP), 5.17 (d, *J* = 10.7 Hz, 1H, *H25*), 4.37 (d, *J* = 3.3 Hz, 2H, OCH_2Ar), 4.17 (dd, *J* = 6.9, 3.4 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.2, 3.9, 2.2 Hz, 1H, *H15*), 3.85 (brs, 1H, O*H*), 3.80 – 3.77 (m, 1H, *H17*), 3.79 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.76 – 3.64 (m, 3H, *H13* and *H21*), 3.53 – 3.46 (m, 2H, *H28* and *H31*), 3.38 (dd, *J* = 9.3, 7.0 Hz, 1H, *H27*), 3.31 (td, *J* = 9.3, 2.9 Hz, 1H, *H31'*), 3.28 (brs, 1H, O*H*), 2.45 – 2.38 (m, 1H, *H26*), 1.89 – 1.57 (m, 15H, *H14*, *H18*, *H22*, *H29, H30* and cyclopent-(CH_2)$_4$), 1.59 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.54 – 1.48 (m, 2H, *H19* and *H30'*), 1.46 – 1.29 (m, 6H, *H16*, *H18'*, *H19'*, *H20* and *H29'*), 1.29 – 1.10 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.90 (s,

9H, SiC(C*H*$_3$)$_3$), 0.86 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.5, 139.2, 131.9, 130.0, 129.6, 127.6, 125.0, 118.1, 113.9, 113.7, 101.7, 84.3, 81.3, 80.7, 77.4, 74.8, 72.7, 69.4, 69.3, 59.5, 55.4, 55.4, 43.3, 39.0, 38.0, 37.4, 37.4, 36.1, 35.2, 33.1, 32.9, 32.0, 31.9, 29.6, 27.1, 26.9, 26.1, 23.7, 23.6, 22.8, 21.7, 18.5, 14.3, 13.5, 6.2, –5.1, –5.2; **HRMS** (ESI) m/z calcd for $C_{54}H_{88}O_{10}Si$ [M+Na]$^+$: 947.6039, found 947.6008.

tert-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (82)

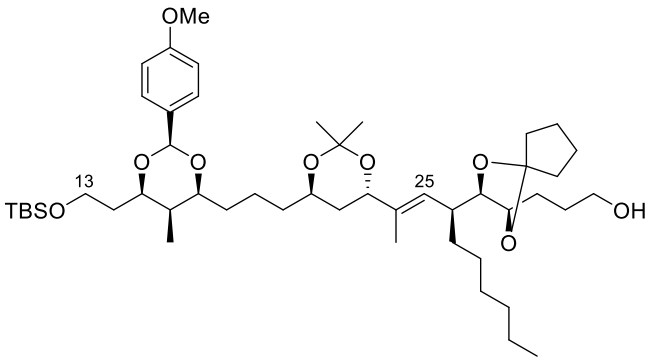


To a solution of diol **81** (580 mg, 0.63 mmol, 1.0 eq.) in 2,2-dimethoxypropane/CH_2Cl_2 (4.5 mL, 1:1) was added pyridinium *p*-toluenesulfonate (12.6 mg, 0.05 mmol, 8 mol%). The reaction mixture was stirred at room temperature for 2 hours. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (550.0 mg, 0.57 mmol, 91%) as a colourless oil.

$[\alpha]_D^{25}$ +2.4 (c = 1.1, $CHCl_3$); **R$_f$** 0.42 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2934, 2858, 1516, 1464, 1249, 1101, 1038, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.41 (s, 2H, OC*H*$_2$Ar), 4.18 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.0, 4.2, 2.2 Hz, 1H, *H15*), 3.82 (ddd, *J* = 7.8, 5.6, 2.1 Hz, 1H, *H17*), 3.79 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.79 – 3.69 (m, 3H, *H13* and *H21*), 3.65 (ddd, *J* = 8.3, 6.6, 3.5 Hz, 1H, *H28*), 3.45 – 3.41 (m, 3H, *H27* and *H31*), 2.44 – 2.38 (m,

1H, *H26*), 1.89 – 1.82 (m, 1H, *H14*), 1.81 – 1.42 (m, 21H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22, H29*, *H30* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.37 – 1.31 (m, 1H, *H19'*), 1.33 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.09 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.2, 137.2, 131.9, 130.8, 129.3, 127.6, 125.9, 118.1, 113.9, 113.7, 101.6, 100.4, 84.0, 81.2, 79.9, 77.5, 72.6, 71.6, 70.2, 66.7, 59.5, 55.4, 55.4, 42.0, 37.7, 37.7, 37.1, 36.1, 36.0, 34.9, 32.5, 32.1, 32.0, 31.0, 29.5, 27.0, 26.5, 26.1, 25.1, 24.9, 23.7, 23.6, 22.8, 21.3, 18.5, 14.2, 13.2, 6.1, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{57}H_{92}O_{10}Si$ $[M+Na]^+$: 987.6352, found 987.6338.

3-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl) oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)propan-1-ol (83)

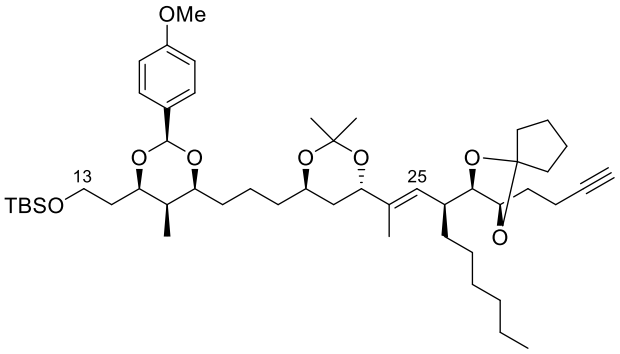


To a solution of PMB ether **82** (550 mg, 0.57 mmol, 1.0 eq.) in CH_2Cl_2 (19 mL) and pH 7 buffer (1 M potassium phosphate buffer, 1 mL) at 0 °C was added DDQ (324.6 mg, 1.43 mmol, 2.5 eq.). The reaction mixture was stirred at 0 °C under argon for 2 hours. It was filtered through celite, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 4/1) to afford the title compound (334.6 mg, 0.40 mmol, 69%) as a colourless oil.

$[\alpha]_D^{25}$ –4.2 (c = 1.4, $CHCl_3$); **R$_f$** 0.34 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/cm^{-1} 3494, 2930, 2858, 1518, 1463, 1250, 1170, 1103, 1067, 1037, 1010, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.46 (s, 1H,

C*H*PMP), 5.07 (d, *J* = 10.5 Hz, 1H, *H25*), 4.21 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.03 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.83 (ddd, *J* = 7.8, 5.5, 2.2 Hz, 1H, *H17*), 3.82 – 3.68 (m, 3H, *H13* and *H21*), 3.79 (s, 3H, OCH_3), 3.64 (ddd, *J* = 9.3, 7.0, 2.5 Hz, 1H, *H28*), 3.60 – 3.56 (m, 2H, *H31*), 3.39 (dd, *J* = 8.8, 7.0 Hz, 1H, *H27*), 2.46 – 2.38 (m, 2H, *H26* and O*H*), 1.89 – 1.81 (m, 1H, *H14*), 1.80 – 1.45 (m, 21H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22, H29*, *H30* and cyclopent-(CH_2)$_4$), 1.66 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.38 – 1.33 (m, 1H, *H19'*), 1.35 (s, 6H, acetonide-CH_3 × 2), 1.30 – 1.09 (m, 10H, *n*-Hex-(CH_2)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 137.0, 131.8, 127.6, 126.6, 118.1, 113.7, 101.6, 100.5, 83.9, 81.2, 80.0, 77.5, 72.2, 66.7, 62.1, 59.5, 55.4, 42.5, 37.5, 37.5, 36.8, 36.0, 36.0, 34.9, 32.5, 32.4, 31.94, 30.8, 29.6, 29.5, 26.9, 26.1, 25.1, 24.9, 23.7, 23.5, 22.8, 21.3, 18.5, 14.2, 13.0, 6.1, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{49}H_{84}O_9Si$ $[M+Na]^+$: 867.5777, found 867.5757.

(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(But-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)(*tert*-butyl)dimethylsilane (77)



*From ester **72**:* To a solution of ester **72** (40.7 mg, 0.053 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (530 µL) at –78 °C under argon was added DIBALH (1.0 M in hexanes, 133 µL, 0.133 mmol, 2.5 eq.) dropwise. The reaction mixture was stirred at –78 °C for 1 hour and at 0 °C for 1 hour. It was quenched slowly with water (10 µL), 15% aqueous NaOH (10 µL), then water (20 µL). The mixture was stirred at room temperature for 15 minutes, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (530 µL) under argon and the solution was cooled to 0 °C. 2,6-Lutidine (19 µL, 0.159 mmol, 3.0 eq.) was added, followed by dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (18 µL, 0.080 mmol, 1.5 eq.). The

reaction mixture was stirred at room temperature for 1.5 hours. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 19/1) to afford the title compound (23.4 mg, 0.028 mmol, 53% over two steps) as a colourless oil.

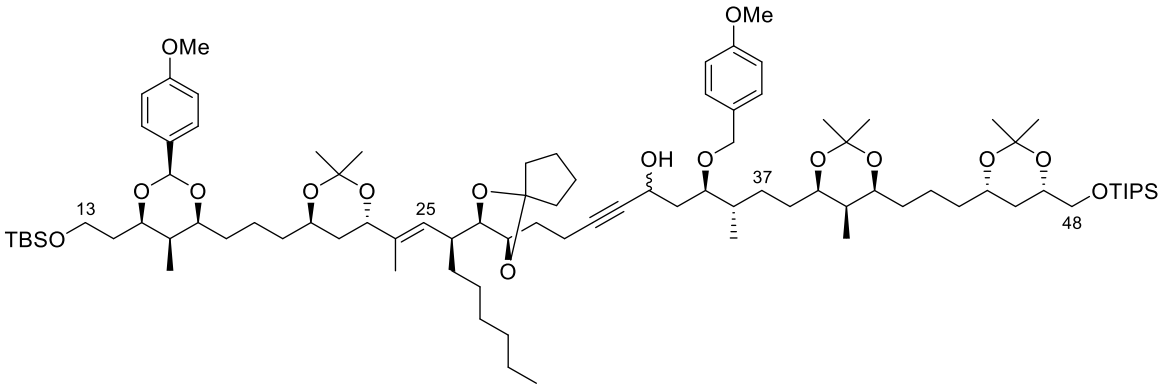
*From alcohol **83**: (1)* To a solution of alcohol **83** (334 mg, 0.40 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) was added $NaHCO_3$ (100.8 mg, 1.20 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (254.5 mg, 0.60 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was diluted with diethyl ether, quenched with saturated aqueous $Na_2S_2O_3$, and stirred until the mixture became a clear solution. The layers were separated and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a short silica plug, washing with pentane/ethyl acetate (9:1), and concentrated under reduced pressure to afford the aldehyde. *(2)* To a solution of dimethyl (1-diazo-2-oxopropyl) phosphonate **63** (307.4 mg, 1.60 mmol, 4.0 eq.) in anhydrous MeOH (7 mL) under argon was added K_2CO_3 (248.8 mg, 1.80 mmol, 4.5 eq.), followed by a solution of the aldehyde in anhydrous MeOH (3 mL). The reaction mixture was stirred at room temperature for 2 hours. It was quenched with saturated aqueous NH_4Cl, diluted with water, and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/diethyl ether = 9/1) to afford the title compound (301.1 mg, 0.36 mmol, 90% over two steps) as a colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +0.6 (c = 1.2, $CHCl_3$); **R_f** 0.38 (pentane/diethyl ether = 17/3); **IR** (thin film): ν_{max}/cm^{-1} 3313, 2935, 2858, 1519, 1464, 1250, 1225, 1106, 1067, 1038, 1011, 836; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.47 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.19 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.03 (ddd, *J* = 9.0, 4.0, 2.1 Hz, 1H, *H15*), 3.83 (ddd, *J* = 7.6, 5.5, 2.0 Hz, 1H, *H17*), 3.81 – 3.68 (m, 4H, *H13*, *H21* and *H28*), 3.79 (s, 3H, OCH_3), 3.43 (dd, *J* = 8.6, 6.6 Hz, 1H, *H27*), 2.46 – 2.39 (m, 1H, *H26*), 2.32 (dddd, *J* = 16.7, 8.2, 5.2, 2.7 Hz, 1H, *H30*), 2.23 (dtd, *J* = 16.7, 8.0, 2.7 Hz, 1H, *H30'*), 1.90 (t, *J* = 2.7 Hz, 1H, *H32*), 1.88 – 1.83 (m, 1H, *H14*), 1.81 – 1.43 (m, 19H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22, H29* and cyclopent-(CH_2)$_4$), 1.65 (d, *J* = 1.0 Hz, 3H,

CC*H*$_3$), 1.38 – 1.33 (m, 1H, *H19'*), 1.36 (s, 3H, acetonide-C*H*$_3$), 1.35 (s, 3H, acetonide-C*H*$_3$), 1.30 – 1.10 (m, 10H, *n*-Hex-(C*H*$_2$)$_5$), 0.96 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 137.5, 131.9, 127.6, 125.2, 118.3, 113.7, 101.6, 100.4, 84.1, 83.8, 81.1, 78.9, 77.4, 71.3, 68.5, 66.7, 59.5, 55.4, 42.2, 37.6, 37.6, 37.2, 36.0, 36.0, 34.9, 33.5, 32.5, 32.3, 32.0, 29.5, 27.0, 26.1, 25.0, 24.9, 23.7, 23.6, 22.8, 21.2, 18.5, 15.5, 14.2, 13.5, 6.1, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{50}H_{82}O_8Si$ $[M+Na]^+$: 861.5671, found 861.5659.

6.4.2. The C13–C48 (28*R*) fragment

(7*R*,8*S*)-1-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-ol (78)

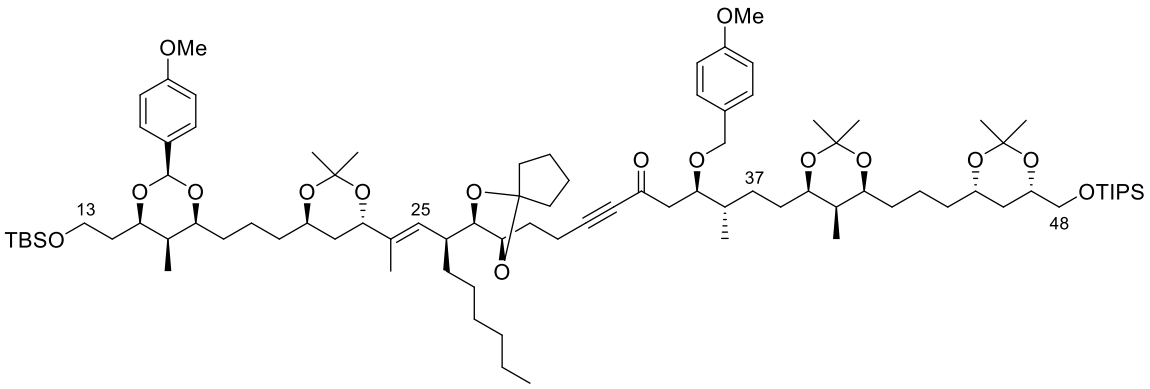


To a solution of alkyne **77** (75 mg, 0.089 mmol, 1.2 eq.) in anhydrous THF (430 µL) at –78 °C under argon was added *n*-BuLi (0.5 M in hexanes, 178 µL, mmol, 1.2 eq.) dropwise. The solution was stirred at –78 °C for 1.5 hours, after which a solution of aldehyde **5** (52.8 mg, 0.073 mmol, 1.0 eq.) in anhydrous THF (300 µL) was added dropwise. The reaction mixture was stirred at –78 °C for 5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 17/3) to afford the title compound (87.7 mg, 0.056 mmol, 77%, ~1:1 *dr*) as a colourless oil; alkyne **77** (28 mg, 0.033 mmol) was also recovered.

R_f 0.41 and 0.29 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3463, 2941, 2866, 1516, 1463, 1379, 1249, 1172, 1111, 1037, 1010, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.27 – 7.23 (m, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.03 (d, *J* = 10.4 Hz, 1H, *H25*), 4.53 – 4.49 (m, 2H, *H33* and OCH_2Ar), 4.39 (d, *J* = 10.9 Hz, 0.5H, OC*H'*$_2$Ar), 4.33 (d, *J* = 10.9 Hz, 0.5H, OC*H'*$_2$Ar), 4.22 (dd, *J* = 9.7, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.85 – 3.80 (m, 3H, *H17*, *H41* and *H45*), 3.81 – 3.68 (m, 6.5H, *H13*, *H21*, *H28*, *H35*, *H39* and

H48), 3.60 – 3.56 (m, 0.5H, *H35*), 3.79 (s, 6H, OCH_3 × 2), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.42 (dd, *J* = 8.5, 6.5 Hz, 1H, *H27*), 3.26 (d, *J* = 2.9 Hz, 0.5H, O*H*), 3.11 (d, *J* = 5.9 Hz, 0.5H, O*H*), 2.45 – 2.39 (m, 1H, *H26*), 2.36 – 2.23 (m, 2H, *H30*), 1.92 – 1.87 (m, 1H, *H36*), 1.86 – 1.35 (m, 36H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46,* CCH_3 and cyclopent-(CH_2)$_4$), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.36 (s, 3H, acetonide-CH_3), 1.36 (s, 1.5H, acetonide-CH_3), 1.35 (s, 1.5H, acetonide-CH_3), 1.33 – 1.29 (m, 1H, *H40*), 1.30 – 1.10 (m, 11H, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.03 – 0.98 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.92 – 0.89 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.4/159.3, 137.3/137.3, 131.9, 130.8/130.5, 129.6/129.5, 127.6, 128.8/126.2, 118.4/118.3, 114.0/113.9, 113.7, 101.6, 100.6/100.5, 98.8, 98.5, 84.6/84.3, 83.9/83.8, 81.9/81.8, 81.2, 81.5/79.9, 78.8/78.8, 77.5, 73.9, 73.4, 72.3/72.2, 71.3/71.0, 70.2, 69.0, 67.4, 66.8, 61.9/60.0, 59.5, 55.4, 55.4, 42.2, 37.7/37.7, 37.6/37.6, 37.2, 37.1/37.1, 36.7, 36.0, 36.0, 34.9, 34.9/34.9, 34.7/34.6, 34.4, 33.9/33.7, 32.9, 32.5, 32.3/32.2, 31.9, 31.3/31.2, 30.2, 30.2, 29.5, 29.0/28.9, 26.9, 26.1, 25.1, 24.8/24.8, 23.7, 23.7, 22.8, 21.3, 21.2, 20.0, 19.8, 18.5, 18.1, 15.8/15.8, 14.2, 14.0/13.8, 13.0/13.0, 12.1, 6.1, 4.8/4.8, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1582.0668, found 1582.0629.

(7*R*,8*S*)-1-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-one (84)

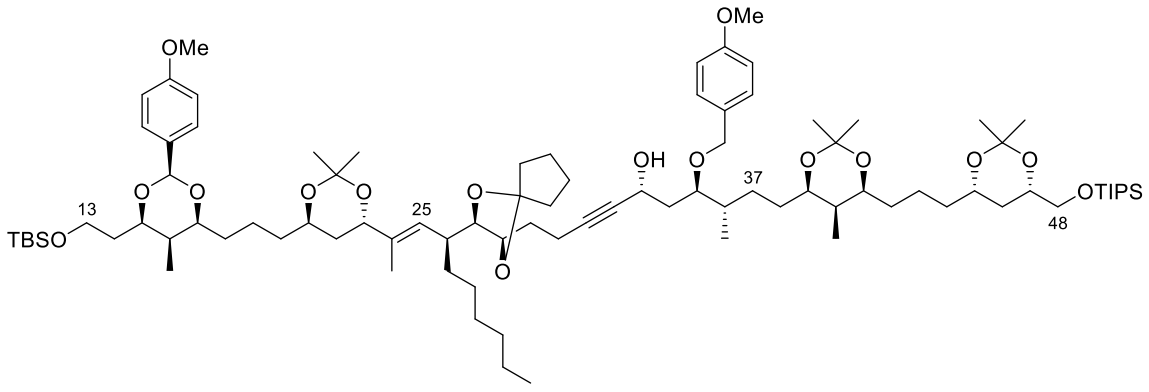


To a solution of alcohol **78** (125.7 mg, 0.081 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.6 mL) was added MnO_2 (352.1 mg, 4.050 mmol, 50.0 eq.). The reaction mixture was stirred at room temperature under argon for 3 hours. It was filtered through silica and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (113.5 mg, 0.073 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25}$ +1.5 (c = 1.1, $CHCl_3$); **R_f** 0.46 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2942, 2867, 1677, 1515, 1463, 1379, 1249, 1217, 1173, 1114, 1039, 1011, 832; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.23 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.04 (d, *J* = 10.5 Hz, 1H, *H25*), 4.43 (app d, *J* = 2.9 Hz, 2H, OCH_2Ar), 4.18 (dd, *J* = 9.5, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 2H, *H35* and *H47*), 3.86 – 3.80 (m, 3H, *H17*, *H41* and *H45*), 3.80 – 3.74 (m, 4H, *H13*, *H21*, *H39* and *H48*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 – 3.68 (m, 1H, *H13'*), 3.65 (ddd, *J* = 9.5, 6.7, 3.2 Hz, 1H, *H28*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.41 (dd, *J* = 8.4, 6.7 Hz, 1H, *H27*), 2.78 (dd, *J* = 16.2, 8.7 Hz, 1H, *H34*), 2.55 (dd, *J* = 16.2, 3.4 Hz, 1H, *H34'*), 2.52 – 2.46 (m, 1H, *H30*), 2.45 – 2.36 (m, 2H, *H26* and *H30'*), 1.89 – 1.83 (m, 1H, *H14*), 1.83 – 1.59 (m, 17H, *H14'*, *H18*, *H22*, *H29*, *H36*, *H46* and cyclopent-(CH_2)$_4$), 1.65 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.58 – 1.31 (m, 14H, *H16*, *H19*, *H20*, *H37, H38, H42, H43* and *H44*), 1.44 (s, 3H,

acetonide-CH_3), 1.40 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.30 – 1.10 (m, 12H, *H40*, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 – 0.98 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.91 – 0.89 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.81 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.5, 159.9, 159.2, 137.8, 131.9, 130.8, 129.5, 127.6, 125.6, 118.4, 113.8, 113.7, 101.6, 100.4, 98.9, 98.5, 94.0, 83.8, 81.5, 81.2, 78.8, 78.8, 77.5, 73.8, 73.4, 71.8, 71.7, 70.2, 69.0, 67.4, 66.7, 59.5, 55.4, 55.4, 47.2, 42.1, 37.6, 37.6, 37.0, 36.7, 36.2, 36.0, 36.0, 34.9, 34.6, 34.4, 32.9, 32.7, 32.5, 32.2, 31.9, 30.9, 30.3, 30.2, 29.5, 28.6, 27.0, 26.1, 25.1, 24.9, 23.7, 23.6, 22.8, 21.3, 21.2, 20.0, 19.8, 18.5, 18.1, 16.1, 14.7, 14.2, 13.2, 12.1, 6.1, 4.8, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{152}O_{16}Si_2$ $[M+Na]^+$: 1580.0511, found 1580.0475.

(5*R*,7*R*,8*S*)-1-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-ol (78-*R*)

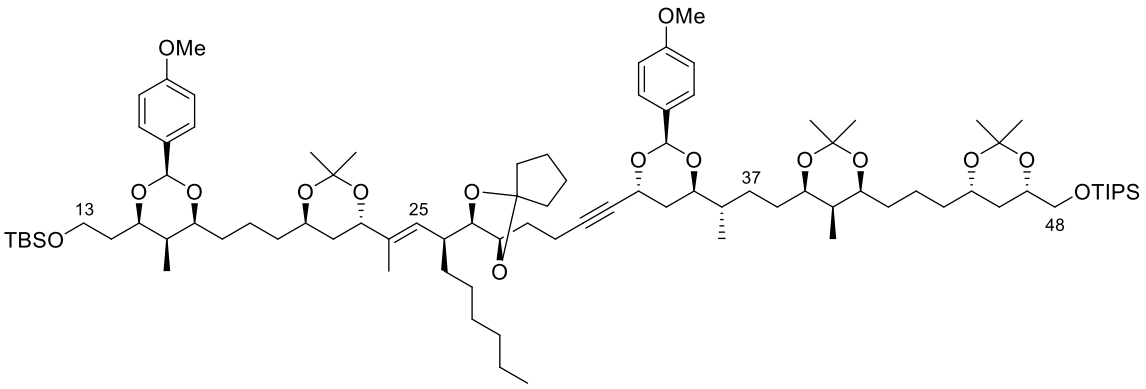


To a solution of ynone **84** (113.5 mg, 0.073 mmol, 1.0 eq.) in anhydrous THF (1.5 mL) at –30 °C under argon was added (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 146 µL, 0.146 mmol, 2.0 eq.) dropwise, followed by dropwise addition of borane dimethyl sulfide complex (2.0 M in THF, 183 µL, 0.365 mmol, 5.0 eq.). The reaction mixture was stirred at –30 °C for 3 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated

under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the title compound (110.0 mg, 0.070 mmol, 97%, 17:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ +10.2 (c = 0.5, $CHCl_3$); **R_f** 0.41 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3481, 2942, 2866, 1517, 1463, 1380, 1250, 1172, 1114, 1039, 1011, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.03 (d, *J* = 10.4 Hz, 1H, *H25*), 4.53 – 4.49 (m, 1H, *H33*), 4.51 (d, *J* = 10.8 Hz, 2H, OCH_2Ar), 4.39 (d, *J* = 10.8 Hz, 1H, OC*H'*$_2$Ar), 4.21 (dd, *J* = 9.6, 6.2 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.0, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.85 – 3.80 (m, 3H, *H17*, *H41* and *H45*), 3.81 – 3.68 (m, 7H, *H13*, *H21*, *H28*, *H35*, *H39* and *H48*), 3.79 (s, 6H, OCH_3 × 2), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.42 (dd, *J* = 8.5, 6.4 Hz, 1H, *H27*), 3.10 (d, *J* = 5.9 Hz, 1H, O*H*), 2.45 – 2.39 (m, 1H, *H26*), 2.36 – 2.24 (m, 2H, *H30*), 1.91 – 1.83 (m, 2H, *H14* and *H36*), 1.83 – 1.34 (m, 32H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.67 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.36 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.32 – 1.29 (m, 1H, *H40*), 1.29 – 1.10 (m, 11H, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.09 – 1.05 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.03 – 0.97 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.91 – 0.90 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.3, 137.3, 131.9, 130.8, 129.6, 127.6, 126.2, 118.4, 113.9, 113.7, 101.6, 100.6, 98.9, 98.5, 84.3, 83.9, 81.9, 81.2, 79.9, 78.8, 77.5, 73.9, 73.4, 72.3, 71.3, 70.2, 69.0, 67.4, 66.8, 60.0, 59.5, 55.4, 55.4, 42.2, 37.7, 37.6, 37.1, 37.1, 36.7, 36.1, 36.0, 35.0, 34.9, 34.7, 34.4, 33.9, 33.0, 32.5, 32.3, 32.0, 31.2, 30.3, 30.3, 29.5, 28.9, 27.0, 26.1, 25.1, 24.8, 23.7, 23.7, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 15.8, 14.2, 14.0, 13.0, 12.1, 6.1, 4.8, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1582.0668, found 1582.0627.

***tert*-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(4-((2*S*,4*R*,6*R*)-6-((*S*)-4-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-yl)-2-(4-methoxy phenyl)-1,3-dioxan-4-yl)but-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (85)**

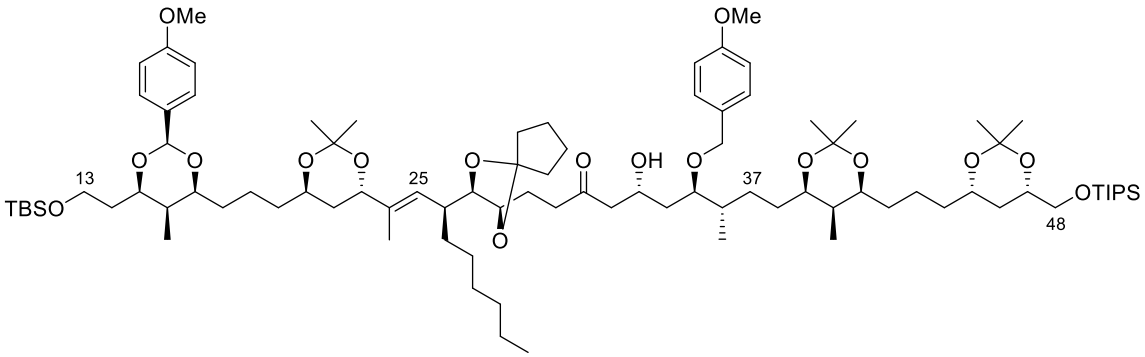


To a solution of alcohol **78-*R*** (13.9 mg, 0.009 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (300 µL) at 0 °C under argon was added DDQ (4.1 mg, 0.018 mmol, 2.0 eq.). The reaction mixture was stirred at 0 °C for 1 hour. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (8.9 mg, 0.006 mmol, 64%) as a colourless oil.

$[\alpha]_D^{25}$ –3.2 (c = 0.3, $CHCl_3$); **R_f** 0.50 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2941, 2865, 1519, 1464, 1379, 1250, 1201, 1172, 1112, 1037, 1011, 833; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 – 7.39 (m, 4H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.97 (s, 1H, C*H*PMP), 5.46 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.5 Hz, 1H, *H25*), 4.99 – 4.98 (m, 1H, *H33*), 4.18 (dd, *J* = 9.4, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.1, 2.2 Hz, 1H, *H15*), 3.95 – 3.90 (m, 2H, *H35* and *H47*), 3.84 – 3.80 (m, 4H, *H17*, *H39*, *H41* and *H45*), 3.79 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.79 – 3.74 (m, 3H, *H13*, *H21* and *H48*), 3.73 – 3.68 (m, 2H, *H13'* and *H28*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.45 (dd, *J* = 8.3, 6.8 Hz, 1H, *H27*), 2.44 – 2.30 (m, 3H, *H26* and *H30*), 1.96 (td, *J* = 12.4, 5.6 Hz, 1H, *H34*), 1.89 – 1.84 (m, 1H, *H14*), 1.82 – 1.32 (m, 34H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34'*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.63 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.37 (s, 3H,

acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.29 – 1.10 (m, 12H, *n*-Hex-(CH_2)$_5$, *H37'* and *H46'*), 1.11 – 1.05 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.93 (d, *J* = 6.8 Hz, 3H, H36CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.86 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.80 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.9, 137.5, 131.9, 131.6, 127.6, 127.6, 125.9, 118.3, 113.7, 113.6, 101.6, 100.4, 98.8, 98.5, 95.5, 88.1, 83.7, 81.2, 79.0, 77.9, 77.5, 76.8, 73.8, 73.4, 71.8, 70.2, 69.0, 67.4, 66.7, 64.8, 59.5, 55.4, 55.4, 42.1, 37.8, 37.6, 37.6, 37.0, 36.7, 36.0, 36.0, 34.9, 34.4, 34.2, 33.5, 33.3, 33.0, 32.5, 32.2, 32.0, 30.3, 30.3, 29.9, 29.5, 27.4, 27.0, 26.1, 25.0, 24.9, 23.7, 23.6, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 15.9, 15.1, 14.3, 13.2, 12.1, 6.1, 4.6, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{152}O_{16}Si_2$ $[M+Na]^+$: 1580.0511, found 1580.0505.

(5*R*,7*R*,8*S*)-1-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-8-methyldecan-3-one (86)

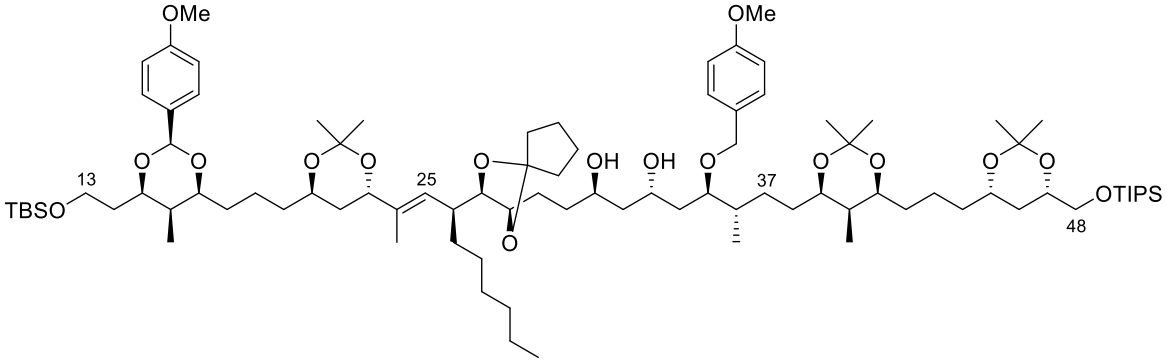


Synthesized according to a modified literature procedure.[172] To a solution of alcohol **78-*R*** (96 mg, 0.062 mmol, 1.0 eq.) in anhydrous diethyl ether (310 µL) under argon was added bis(pinacolato)diboron (37.8 mg, 0.149 mmol, 2.4 eq.), followed by sodium *tert*-butoxide (3.6 mg, 0.037 mmol, 0.6 eq.) in one portion. The mixture was cooled to 0 °C and [(IMes)CuCl][209] (2.5 mg, 0.006 mmol, 0.1 eq.) was added, followed by anhydrous methanol (10 µL, 0.248 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 1 hour. The dark-coloured mixture was quenched with 2–3 drops of triethanolamine and stirred at 0 °C for 10 minutes and at room temperature for 10 minutes. It was filtered

through celite and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in THF (780 µL) and water (780 µL), and sodium perborate monohydrate (30.9 mg, 0.310 mmol, 5.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (71.7 mg, 0.045 mmol, 74%) as a colourless oil.

$[\alpha]_D^{25}$ +0.4 (c = 2.5, $CHCl_3$); **R_f** 0.34 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/cm^{-1} 3497, 2943, 2866, 1707, 1517, 1463, 1379, 1249, 1172, 1112, 1038, 1010, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.05 (d, *J* = 10.4 Hz, 1H, *H25*), 4.51 (d, *J* = 10.8 Hz, 1H, OC*H*$_2$Ar), 4.40 (d, *J* = 10.8 Hz, 1H, OC*H'*$_2$Ar), 4.28 – 4.23 (m, 1H, *H33*), 4.20 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.86 – 3.80 (m, 3H, *H17*, *H41* and *H45*), 3.80 – 3.68 (m, 5H, *H13*, *H21*, *H39* and *H48*), 3.79 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.61 – 3.57 (m, 2H, *H28* and *H35*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.41 (dd, *J* = 8.2, 6.7 Hz, 1H, *H27*), 3.30 (d, *J* = 3.3 Hz, 1H, O*H*), 2.60 – 2.48 (m, 3H, *H30* and *H32*), 2.48 – 2.38 (m, 2H, *H26* and *H30'*), 1.88 – 1.82 (m, 3H, *H14*, *H29* and *H36*), 1.81 – 1.59 (m, 15H, *H18*, *H20*, *H22*, *H29'*, *H46* and cyclopent-(C*H*$_2$)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CC*H*$_3$), 1.58 – 1.34 (m, 16H, *H14'*, *H16*, *H19*, *H20'*, *H34, H37, H38, H42, H43* and *H44*), 1.44 (s, 3H, acetonide-C*H*$_3$), 1.41 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.38 (s, 3H, acetonide-C*H*$_3$), 1.33 (s, 6H, acetonide-C*H*$_3$ × 2), 1.32 – 1.29 (m, 1H, *H40*), 1.28 – 1.11 (m, 11H, *n*-Hex-(C*H*$_2$)$_5$ and *H46'*), 1.09 – 1.04 (m, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.02 – 0.99 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.90 – 0.85 (m, 6H, H36C*H*$_3$ and *n*-Hex-C*H*$_3$), 0.82 (d, *J* = 6.9 Hz, 3H, H40C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 211.3, 159.9, 159.3, 137.6, 131.9, 130.9, 129.6, 127.6, 125.7, 118.3, 114.0, 113.7, 101.6, 100.4, 98.9, 98.5, 84.0, 81.2, 79.6, 79.1, 77.5, 73.8, 73.4, 71.8, 71.6, 70.2, 69.0, 67.4, 66.7, 65.1, 59.5, 55.4, 55.4, 50.0, 41.9, 40.1, 37.6, 37.5, 37.1, 36.7, 36.5, 36.0, 36.0, 35.3, 34.9, 34.6, 34.4, 33.0, 32.5, 32.2, 32.0, 31.1, 30.3, 30.2, 29.5, 28.9, 28.0, 27.0, 26.1, 25.1, 24.9, 23.7, 23.6, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.2, 14.2, 13.1, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{156}O_{17}Si_2$ $[M+Na]^+$: 1600.0773, found 1600.0712.

(3*R*,5*S*,7*R*,8*S*)-1-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethyl-silyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldecane-3,5-diol (87)



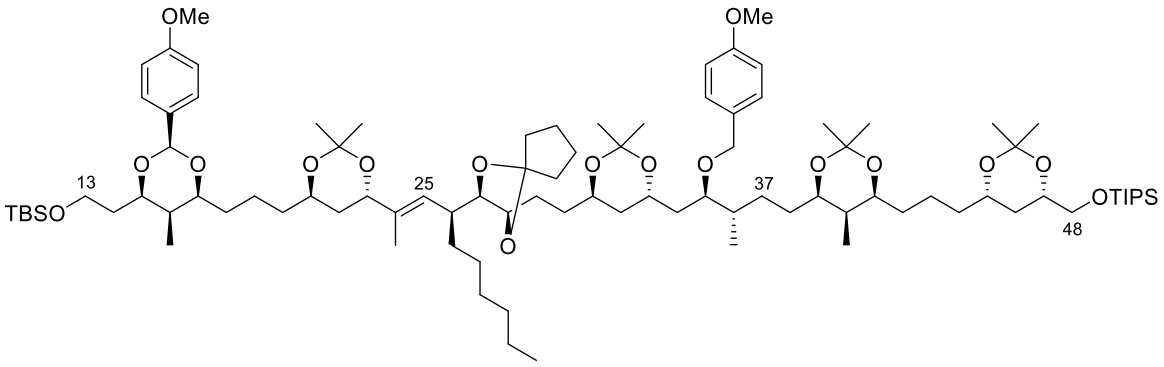
To a stirred suspension of $Me_4NBH(OAc)_3$ (54.7 mg, 0.208 mmol, 8.0 eq.) in anhydrous acetonitrile (570 µL) under argon was added glacial acetic acid (520 µL). The solution was stirred for 30 minutes at room temperature, after which it was cooled to –20 °C. A solution of β-hydroxy ketone **86** (40.7 mg, 0.026 mmol, 1.0 eq.) in anhydrous acetonitrile (300 µL) and anhydrous THF (80 µL, to aid solubility) was added dropwise. The reaction mixture was stirred at –20 °C for 3 hours and at –10 °C for 36 hours. (*Note: a larger stir bar should be used as the reaction tends to form a sticky residue*). It was quenched with saturated aqueous potassium sodium tartrate (600 µL), warmed to room temperature, and stirred for 30 minutes, upon which a white precipitate formed. The mixture was poured over ice, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the title compound (29.2 mg, 0.018 mmol, 72%, 14:1 *dr*[xliii]) as a colourless oil.

$[\alpha]_D^{25}$ –0.4 (c = 2.9, $CHCl_3$); **R_f** 0.31 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3491, 2938, 2865, 1516, 1463, 1379, 1250, 1172, 1110, 1037, 1011, 834, 763; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.5 Hz, 1H, *H25*), 4.49 (d, *J* = 11.0 Hz, 1H, OC*H*$_2$Ar), 4.43 (d, *J* = 11.0 Hz, 1H, OC*H'*$_2$Ar), 4.22 (dd, *J* = 9.4, 6.2 Hz, 1H, *H23*),

4.19 – 4.13 (m, 1H, *H33*), 4.02 (ddd, *J* = 9.0, 4.0, 2.1 Hz, 1H, *H15*), 3.96 – 3.90 (m, 1H, *H47*), 3.90 – 3.68 (m, 9H, *H13*, *H17*, *H21*, *H31*, *H39*, *H41*, *H45* and *H48*), 3.79 (s, 6H, OC$H_3 \times 2$), 3.66 – 3.61 (m, 1H, *H28*), 3.60 – 3.49 (m, 3H, O*H*, *H35* and *H48'*), 3.39 (dd, *J* = 8.6, 7.0 Hz, 1H, *H27*), 3.30 (d, *J* = 3.6 Hz, 1H, O*H*), 2.45 – 2.37 (m, 1H, *H26*), 1.89 – 1.85 (m, 1H, *H36*), 1.84 – 1.32 (m, 37H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.66 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.34 (s, 6H, acetonide-C$H_3 \times 2$), 1.32 – 1.11 (m, 12H, *H40*, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 – 0.99 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.90 – 0.85 (m, 6H, H36CH_3 and *n*-Hex-CH_3), 0.81 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9, 159.3, 137.0, 131.9, 130.9, 129.6, 127.6, 127.0, 118.2, 113.9, 113.7, 101.6, 100.6, 98.8, 98.5, 83.8, 81.2, 80.3, 80.0, 77.5, 73.9, 73.5, 72.5, 71.4, 70.2, 69.0, 68.4, 67.4, 66.8, 66.4, 59.5, 55.4, 55.4, 43.7, 42.5, 37.5, 37.5, 36.7, 36.7, 36.6, 36.0, 36.0, 35.3, 34.9, 34.6, 34.4, 34.4, 33.0, 32.5, 32.3, 31.9, 31.0, 30.8, 30.3, 30.2, 29.5, 28.9, 26.9, 26.1, 25.1, 24.9, 23.7, 23.6, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.5, 14.2, 12.8, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{158}O_{17}Si_2$ $[M+Na]^+$: 1602.0930, found 1602.0881.

[xliii] Estimated from alcohol **89**

***tert*-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*R*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)dimethyl-silane (88)**

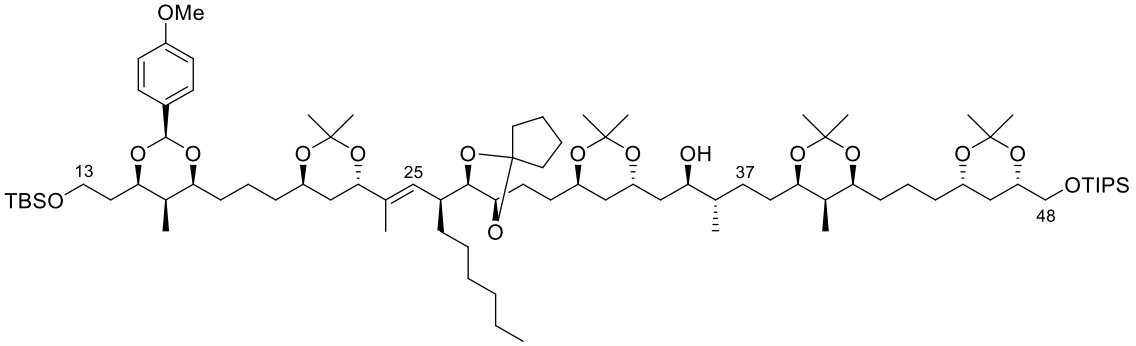


To a solution of diol **87** (37.7 mg, 0.024 mmol, 1.0 eq.) in 2,2-dimethoxypropane/CH_2Cl_2 (240 µL, 1:1) was added pyridinium *p*-toluenesulfonate (0.5 mg, 0.002 mmol, 8 mol%). The reaction mixture was stirred at room temperature for 3 hours. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (32.7 mg, 0.020 mmol, 84%) as a colourless oil.

$[\alpha]_D^{25}$ +1.3 (c = 0.7, $CHCl_3$); **R_f** 0.41 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2940, 2866, 1516, 1462, 1379, 1249, 1224, 1172, 1110, 1038, 1011, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.4 Hz, 1H, *H25*), 4.49 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.33 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.18 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.04 – 4.01 (m, 2H, *H15* and *H33*), 3.96 – 3.90 (m, 1H, *H47*), 3.86 – 3.80 (m, 3H, *H17*, *H41* and *H45*), 3.80 – 3.69 (m, 6H, *H13*, *H21*, *H31*, *H39* and *H48*), 3.79 (s, 6H, OCH_3 × 2), 3.69 – 3.64 (m, 1H, *H28*), 3.54 – 3.51 (m, 2H, *H35* and *H48'*), 3.45 (dd, *J* = 7.9, 6.4 Hz, 1H, *H27*), 2.44 – 2.38 (m, 1H, *H26*), 1.89 – 1.82 (m, 2H, *H14* and *H36*), 1.81 – 1.32 (m, 37H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.45 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-

C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.31 (s, 3H, acetonide-C*H*$_3$), 1.30 (s, 3H, acetonide-C*H*$_3$), 1.28 – 1.10 (m, 11H, *n*-Hex-(C*H*$_2$)$_5$ and *H46'*), 1.11 – 1.04 (m, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.04 – 1.01 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.90 – 0.89 (m, 12H, SiC(C*H*$_3$)$_3$ and H36C*H*$_3$), 0.86 (d, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.82 (d, *J* = 6.9 Hz, 3H, H40C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.2, 137.3, 131.9, 131.3, 129.4, 127.6, 126.1, 118.1, 113.9, 113.7, 101.6, 100.3, 100.3, 98.8, 98.5, 83.9, 81.2, 79.4, 79.1, 77.5, 73.9, 73.5, 71.8, 71.5, 70.2, 69.0, 67.4, 66.7, 66.6, 63.6, 59.5, 55.4, 55.4, 41.8, 39.2, 37.8, 37.7, 37.2, 36.8, 36.7, 36.1, 36.0, 35.3, 34.9, 34.5, 34.4, 33.0, 32.5, 32.2, 32.0, 32.0, 31.3, 30.3, 30.3, 29.9, 29.5, 28.7, 27.0, 26.1, 25.2, 25.2, 25.1, 24.9, 23.8, 23.6, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.2, 14.1, 13.1, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{94}H_{162}O_{17}Si_2$ $[M+Na]^+$: 1642.1243, found 1642.1183.

(2*R*,3*S*)-1-((4*R*,6*R*)-6-(2-((2*R*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-methylpentan-2-ol (89)

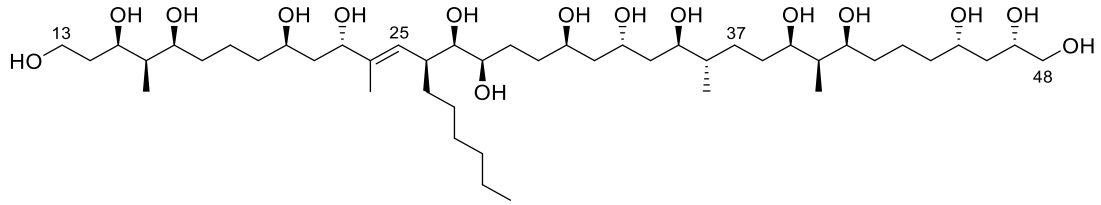


To a solution of PMB ether **88** (32.7 mg, 0.020 mmol, 1.0 eq.) in CH_2Cl_2 (670 µL) and pH 7 buffer (1 M potassium phosphate buffer, 35 µL) at 0 °C was added DDQ (11.4 mg, 0.050 mmol, 2.5 eq.). The reaction mixture was stirred at 0 °C under argon for 1.5 hours. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (23.5 mg, 0.016 mmol, 78%) as a colourless oil.

$[\alpha]_D^{25}$ –5.8 (c = 0.4, $CHCl_3$); **R_f** 0.29 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3425, 2942, 2866, 1519, 1463, 1380, 1251, 1201, 1172, 1113, 1070, 1011, 836; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.05 (d, *J* = 10.5 Hz, 1H, *H25*), 4.18 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.16 – 4.11 (m, 1H, *H33*), 4.02 (ddd, *J* = 9.0, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.85 – 3.80 (m, 4H, *H17*, *H39*, *H41* and *H45*), 3.80 – 3.74 (m, 4H, *H13*, *H21*, *H31* and *H48*), 3.79 (s, 3H, OCH_3), 3.73 – 3.69 (m, 1H, *H13'*), 3.68 – 3.61 (m, 2H, *H28* and *H35*), 3.52 (dd, *J* = 9.8, 6.7 Hz, 1H, *H48'*), 3.45 (dd, *J* = 8.0, 6.5 Hz, 1H, *H27*), 2.69 (d, *J* = 4.3 Hz, 1H, O*H*), 2.44 – 2.38 (m, 1H, *H26*), 1.89 – 1.82 (m, 1H, *H14*), 1.81 – 1.32 (m, 38H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-

CH_3), 1.34 (s, 6H, acetonide-CH_3 × 2), 1.33 (s, 3H, acetonide-CH_3), 1.31 (s, 3H, acetonide-CH_3), 1.28 – 1.09 (m, 11H, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.11 – 1.01 (m, 22H, Si(C*H*(CH_3)$_2$)$_3$ and *H37'*), 0.96 (d, *J* = 6.9 Hz, 3H, H16CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.89 – 0.85 (m, 6H, H36CH_3 and *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 137.3, 131.9, 127.6, 126.0, 118.1, 113.7, 101.6, 100.5, 100.3, 98.8, 98.5, 83.8, 81.1, 79.5, 77.5, 73.9, 73.4, 72.7, 71.7, 70.2, 69.0, 67.4, 66.7, 66.7, 64.8, 59.5, 55.4, 41.9, 39.0, 38.3, 37.9, 37.7, 37.7, 37.2, 36.7, 36.1, 36.0, 34.9, 34.4, 34.2, 32.9, 32.5, 32.2, 32.1, 32.0, 30.5, 30.3, 30.2, 29.8, 29.5, 27.6, 27.0, 26.1, 25.2, 25.1, 24.9, 24.9, 23.8, 23.6, 22.8, 21.3, 21.1, 20.0, 19.8, 18.5, 18.1, 15.7, 14.2, 13.1, 12.1, 6.1, 4.6, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{86}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1522.0668, found 1522.0629.

(2*S*,4*S*,8*S*,9*R*,10*R*,13*S*,14*R*,16*S*,18*R*,21*R*,22*R*,23*S*,26*S*,28*R*,32*S*,33*R*,34*R*,*E*)-23-Hexyl-9,13,25,33-tetramethylhexatriacont-24-ene-1,2,4,8,10,14,16,18,21,22,26,28, 32,34,36-pentadecaol (90)



To a solution of acetal **89** (15 mg, 0.010 mmol, 1.0 eq.) in MeOH (6 mL) and THF (3 mL) was added 0.2 M aqueous HCl (6 mL). The reaction mixture was stirred at room temperature for 2 days. It was quenched with saturated aqueous $NaHCO_3$ (1.5 mL) and concentrated using a stream of nitrogen. The residue was taken up in MeOH and the solids were removed by filtration (through a cotton plug and syringe filter). Upon concentration, the residue was resubmitted to the reaction conditions,[xliv] stirred at room temperature for 2 days, and quenched and worked up as before. The residue was purified by reversed phase C18 column chromatography (water/acetonitrile = 19/1 → 4/1) to afford the title compound (4.2 mg, 0.005 mmol, 48%) as a colourless oil, which solidified upon standing.

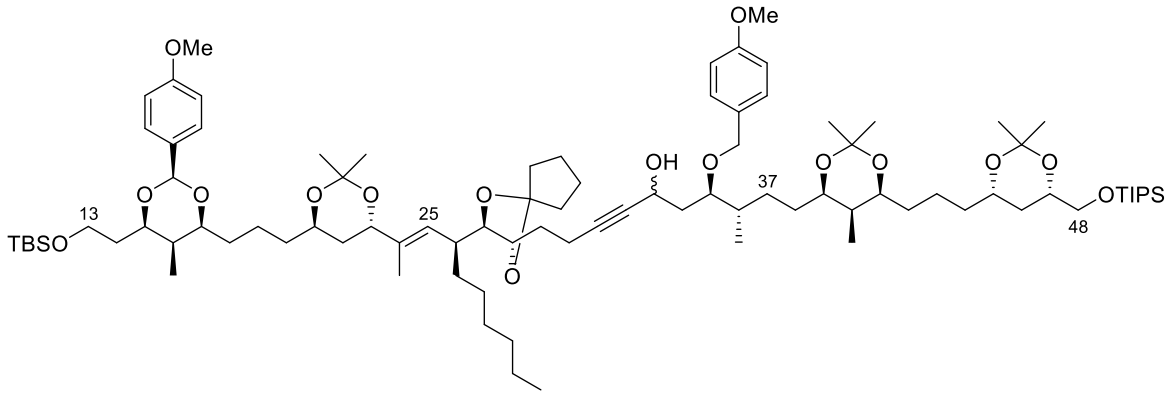
$[\alpha]_D^{25}$ +2.9 (c = 0.7, MeOH); **R_f** 0.23 (ethyl acetate/methanol = 7/3) *or* 0.32 (water/acetonitrile = 7/3, reversed phase C18 TLC); **IR** (thin film): ν_{max}/cm^{-1} 3348, 2932,

2858, 1670, 1458, 1329, 1097, 1048; **^{1}H NMR** (500 MHz, MeOD): δ 5.13 (d, *J* = 10.2 Hz, 1H, *H25*), 4.23 (dd, *J* = 9.0, 3.9 Hz, 1H, *H23*), 4.07 (tt, *J* = 9.3, 3.1 Hz, 1H, *H33*), 3.89 (ddd, *J* = 7.6, 5.3, 3.7 Hz, 1H, *H15*), 3.84 – 3.77 (m, 3H, *H31, H45* and *H47*), 3.77 – 3.66 (m, 7H, *H13*, *H17*, *H21*, *H35*, *H39* and *H41*), 3.55 (ddd, *J* = 8.5, 4.3, 2.1 Hz, 1H, *H28*), 3.51 (dd, *J* = 11.2, 4.6 Hz, 2H, *H48*), 3.46 (dd, *J* = 11.2, 5.9 Hz, 2H, *H48'*), 3.16 (dd, *J* = 8.8, 2.1 Hz, 1H, *H27*), 2.62 – 2.56 (m, 1H, *H26*), 1.85 – 1.78 (m, 1H, *n*-Hex-CH_2 × 1H), 1.73 – 1.65 (m, 5H, *H14*, *H22*, *H29* and *H46*), 1.67 (d, *J* = 1.0 Hz, CCH_3), 1.63 – 1.59 (m, 3H, *H19*, *H37* and *H42*), 1.59 – 1.40 (m, 23H, *H16*, *H18*, *H20*, *H22'*, *H29'*, *H30*, *H32*, *H34*, *H36*, *H38*, *H40*, *H42'*, *H43*, *H44* and *H46'*), 1.39 – 1.13 (m, 10H, *H19'* and *n*-Hex-CH_2 × 9H), 1.14 – 1.07 (m, 1H, *H37'*), 0.94 (d, *J* = 7.0 Hz, 3H, H16CH_3), 0.93 (d, *J* = 6.9 Hz, 3H, H36CH_3), 0.92 (d, *J* = 6.9 Hz, 3H, H40CH_3), 0.90 (d, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (126 MHz, MeOD): δ 140.5, 128.7, 77.6, 76.3, 75.9, 75.6, 75.3, 73.2, 72.8, 72.7, 72.1, 71.0, 69.4, 69.3, 67.2, 66.6, 60.5, 46.4, 43.9, 43.7, 42.8, 42.0, 41.9, 41.3, 40.7, 38.8, 38.6, 38.5, 36.1, 36.0, 35.4, 33.7, 33.2, 32.7, 31.7, 30.8, 29.8, 28.3, 23.8, 23.3, 23.0, 15.7, 14.5, 12.6, 7.4, 7.0; **HRMS** (ESI) m/z calcd for $C_{46}H_{92}O_{15}$ $[M+Na]^+$: 907.6329, found 907.6313.

[xliv] Due to solubility issues, resubmission of the crude product to the reaction conditions is necessary for full conversion of the starting material.

6.4.3. The C13–C48 (28*S*) fragment

(7*R*,8*S*)-1-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-ol (78')

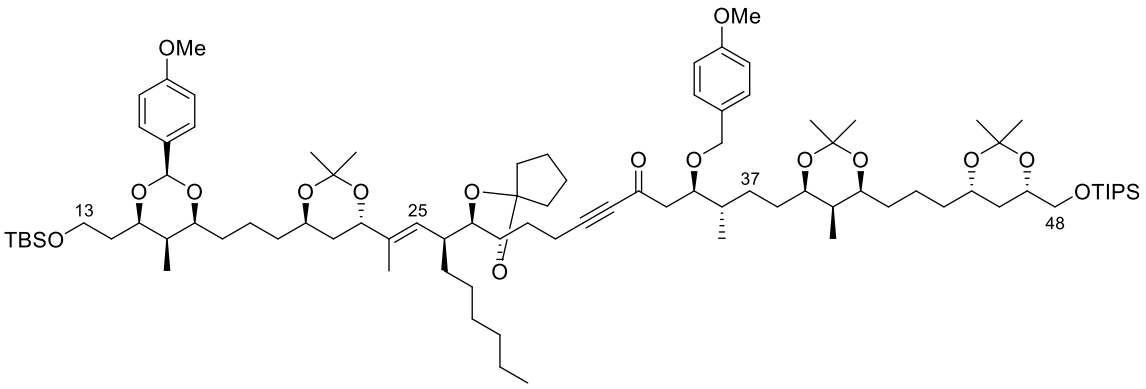


To a solution of alkyne **77'** (806 mg, 0.96 mmol, 1.3 eq.) in anhydrous THF (4 mL) at –78 °C under argon was added *n*-BuLi (2.5 M in hexanes, 380 µL, 0.96 mmol, 1.3 eq.) dropwise. The solution was stirred at –78 °C for 1.5 hours, after which a solution of aldehyde **5** (537 mg, 0.74 mmol, 1.0 eq.) in anhydrous THF (3.4 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 17/3) to afford the title compound (950.5 mg, 0.61 mmol, 83%, ~1:1 *dr*) as a colourless oil; alkyne **77'** (268 mg, 0.32 mmol) was also recovered.

R_f 0.39 and 0.27 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3465, 2942, 2866, 1516, 1464, 1379, 1250, 1172, 1110, 1038, 1010, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.27 – 7.22 (m, 2H, Ar*H*), 6.88 – 6.84 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.1 Hz, 1H, *H25*), 4.54 – 4.49 (m, 2H, *H33* and OCH_2Ar), 4.39 (d, *J* = 10.9 Hz, 0.5H, OC*H'*$_2$Ar), 4.31 (d, *J* = 10.9 Hz, 0.5H, OC*H'*$_2$Ar), 4.16 (dd, *J* = 9.5, 6.2 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 2H, *H28* and *H47*), 3.86 – 3.73 (m, 8.5H, *H13*, *H17*, *H21*, *H27*, *H35*, *H39*, *H41*, *H45* and *H48*), 3.78 (s, 6H,

OCH_3 × 2), 3.73 – 3.68 (m, 1H, *H13'*), 3.61 – 3.57 (m, 0.5H, *H35*), 3.52 (dd, *J* = 9.8, 6.7 Hz, 1H, *H48'*), 3.17 (d, *J* = 2.9 Hz, 0.5H, O*H*), 3.07 (d, *J* = 7.0 Hz, 0.5H, O*H*), 2.44 – 2.35 (m, 2H, *H26* and *H30*), 2.26 – 2.18 (m, 1H, *H30'*), 1.92 – 1.32 (m, 34H, *H14*, *H16*, *H18, H19*, *H20*, *H22*, *H29*, *H34*, *H36*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.63 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.32 – 1.10 (m, 12H, *H40*, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.11 – 1.05 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.03 – 0.98 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.92 – 0.90 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.4/159.3, 137.0, 131.9, 130.6/130.3, 129.6/129.5, 127.5, 124.7/124.7, 117.5/117.5, 114.0/113.9, 113.7, 101.6, 100.4, 98.8/98.8, 98.4, 84.9, 81.6, 81.3/81.3, 81.1, 82.1/80.3, 77.4, 76.5/76.4, 73.8, 73.4, 71.2, 71.2/70.9, 70.1, 68.9, 67.4, 66.6, 62.2/60.5, 59.5, 55.4, 55.3, 38.0/37.9, 37.7/37.6, 37.5/37.5, 37.4/37.3, 36.7, 36.6, 36.0, 36.0, 34.9, 34.8/34.7, 34.7/34.6, 34.3, 33.0/33.0, 32.9, 32.5, 31.9, 31.3/31.2, 30.2, 30.2, 29.7, 29.0, 28.9/28.9, 26.4, 26.1, 25.1, 24.9/24.9, 23.8, 23.5, 22.7, 21.3, 21.1, 19.9, 19.8, 18.5, 18.0, 15.6, 14.2, 13.9/13.7, 13.6/13.6, 12.0, 6.0, 4.7/4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1582.0668, found 1582.0636.

(7*R*,8*S*)-1-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-one (84')

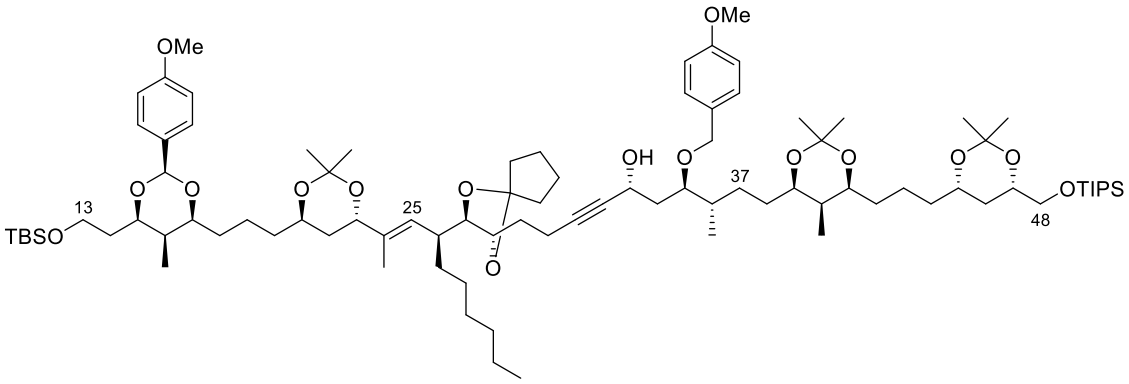


To a solution of alcohol **78'** (950 mg, 0.61 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (12.2 mL) was added MnO_2 (2.65 g, 30.50 mmol, 50.0 eq.). The reaction mixture was stirred at room temperature under argon for 3 hours. It was filtered through silica and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (851.0 mg, 0.55 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25}$ –16.2 (c = 1.3, $CHCl_3$); **R_f** 0.42 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2941, 2866, 1676, 1517, 1464, 1379, 1250, 1200, 1172, 1111, 1039, 1011, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.1 Hz, 1H, *H25*), 4.44 (s, 2H, OCH_2Ar), 4.15 (dd, *J* = 9.4, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.0, 4.0, 2.1 Hz, 1H, *H15*), 3.96 – 3.89 (m, 3H, *H28*, *H35* and *H47*), 3.86 – 3.73 (m, 8H, *H13*, *H17*, *H21*, *H27*, *H39*, *H41*, *H45* and *H48*), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.73 – 3.68 (m, 1H, *H13'*), 3.52 (dd, *J* = 9.8, 6.6 Hz, 1H, *H48'*), 2.78 (dd, *J* = 16.1, 8.7 Hz, 1H, *H34*), 2.56 (dd, *J* = 16.1, 3.5 Hz, 1H, *H34'*), 2.56 – 2.49 (m, 1H, *H30*), 2.43 – 2.33 (m, 2H, *H26* and *H30'*), 1.88 – 1.33 (m, 32H, *H14*, *H16*, *H18, H19*, *H20*, *H22*, *H29*, *H36*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.62 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.40 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.34 (s, 6H, acetonide-CH_3 × 2), 1.31 – 1.11 (m, 12H, *H40*, *n*-Hex-

(CH_2)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 – 0.98 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.91 – 0.90 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3), 0.81 (d, *J* = 6.7 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.5, 159.9, 159.2, 137.3, 131.9, 130.7, 129.4, 127.5, 124.3, 117.7, 113.8, 113.6, 101.6, 100.4, 98.8, 98.4, 94.4, 81.4, 81.2, 81.1, 78.9, 77.4, 76.1, 73.8, 73.4, 71.7, 71.1, 70.1, 68.9, 67.3, 66.6, 59.5, 55.3, 55.3, 47.2, 37.9, 37.6, 37.4, 37.4, 36.7, 36.1, 36.0, 36.0, 34.9, 34.6, 34.3, 33.1, 32.9, 32.5, 31.9, 30.9, 30.2, 30.2, 29.6, 28.5, 28.1, 26.3, 26.1, 25.1, 24.8, 23.8, 23.4, 22.7, 21.3, 21.1, 19.9, 19.8, 18.4, 18.0, 15.8, 14.7, 14.2, 13.6, 12.0, 6.0, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{152}O_{16}Si_2$ $[M+Na]^+$: 1580.0511, found 1580.0468.

(5*R*,7*R*,8*S*)-1-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethyl-silyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldec-3-yn-5-ol (78'-*R*)

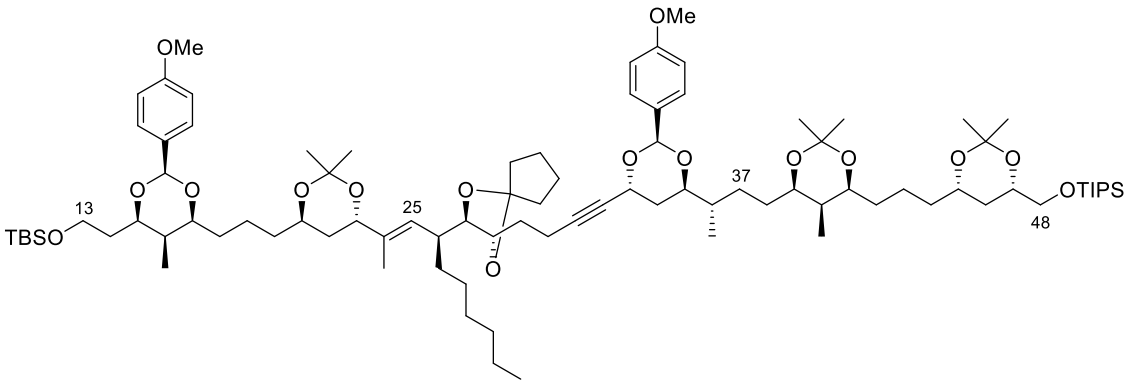


To a solution of ynone **84'** (851.0 mg, 0.55 mmol, 1.0 eq.) in anhydrous THF (11 mL) at –30 °C under argon was added (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 1.1 mL, 1.10 mmol, 2.0 eq.) dropwise, followed by dropwise addition of borane dimethyl sulfide complex (2.0 M in THF, 1.4 mL, 2.75 mmol, 5.0 eq.). The reaction mixture was stirred at –30 °C for 3 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

(pentane/ethyl acetate = 17/3) to afford the title compound (814.7 mg, 0.52 mmol, 95%, >20:1 *dr*) as a colourless oil.

$[\alpha]_D^{25}$ –3.5 (c = 0.8, $CHCl_3$); **R_f** 0.39 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 3478, 2940, 2865, 1516, 1464, 1379, 1250, 1172, 1111, 1039, 1011, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.1 Hz, 1H, *H25*), 4.54 – 4.51 (m, 1H, *H33*), 4.51 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.39 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.16 (dd, *J* = 9.5, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 2H, *H28* and *H47*), 3.86 – 3.74 (m, 9H, *H13*, *H17*, *H21*, *H27*, *H35*, *H39*, *H41*, *H45* and *H48*), 3.78 (s, 6H, OCH_3 × 2), 3.73 – 3.68 (m, 1H, *H13'*), 3.52 (dd, *J* = 9.7, 6.6 Hz, 1H, *H48'*), 3.07 (d, *J* = 7.0 Hz, 1H, O*H*), 2.44 – 2.37 (m, 2H, *H26* and *H30*), 2.26 – 2.19 (m, 1H, *H30'*), 1.93 – 1.88 (m, 1H, *H36*), 1.87 – 1.34 (m, 33H, *H14*, *H16*, *H18, H19*, *H20*, *H22*, *H29*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.63 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.34 (s, 6H, acetonide-CH_3 × 2), 1.32 – 1.11 (m, 12H, *H40*, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 – 0.98 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.92 – 0.90 (m, 12H, H36CH_3 and SiC(CH_3)$_3$), 0.87 (t, *J* = 6.9 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.7 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.3, 137.0, 131.9, 130.6, 129.7, 127.5, 124.8, 117.5, 114.0, 113.7, 101.6, 100.4, 98.8, 98.5, 84.9, 81.6, 81.3, 81.1, 80.3, 77.4, 76.4, 73.8, 73.4, 71.2, 71.2, 70.1, 69.0, 67.4, 66.6, 60.5, 59.5, 55.4, 55.3, 38.0, 37.6, 37.5, 37.4, 36.7, 36.6, 36.0, 36.0, 34.9, 34.7, 34.6, 34.4, 33.0, 32.9, 32.5, 32.0, 31.2, 30.2, 30.2, 29.7, 29.0, 28.9, 26.4, 26.1, 25.1, 24.9, 23.8, 23.5, 22.7, 21.3, 21.1, 20.0, 19.8, 18.5, 18.1, 15.6, 14.2, 13.9, 13.6, 12.0, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1582.0668, found 1582.0599.

***tert*-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(4-((2*S*,4*R*,6*R*)-6-((*S*)-4-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-yl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)but-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (85')**

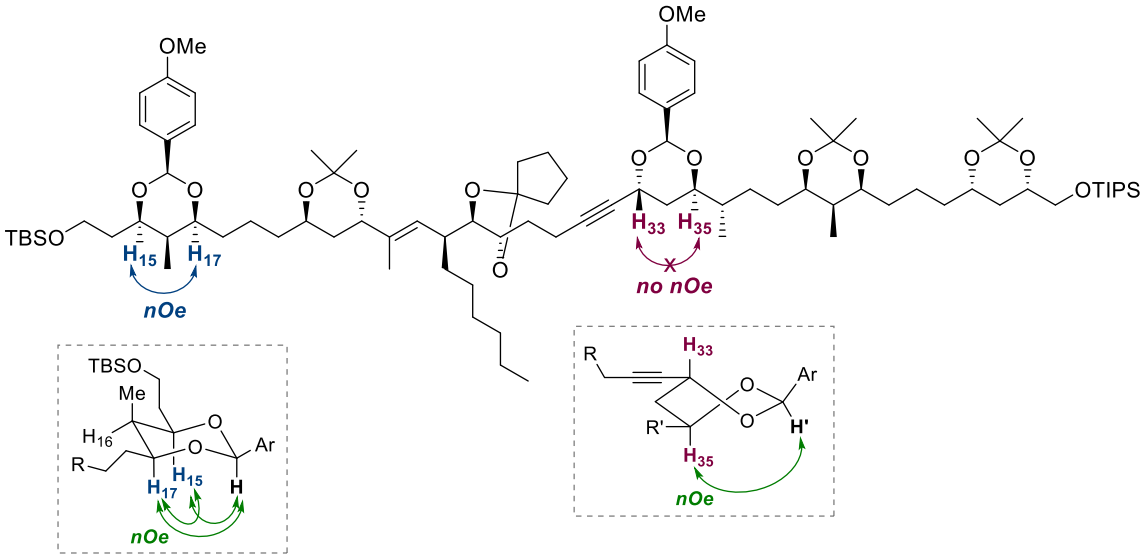


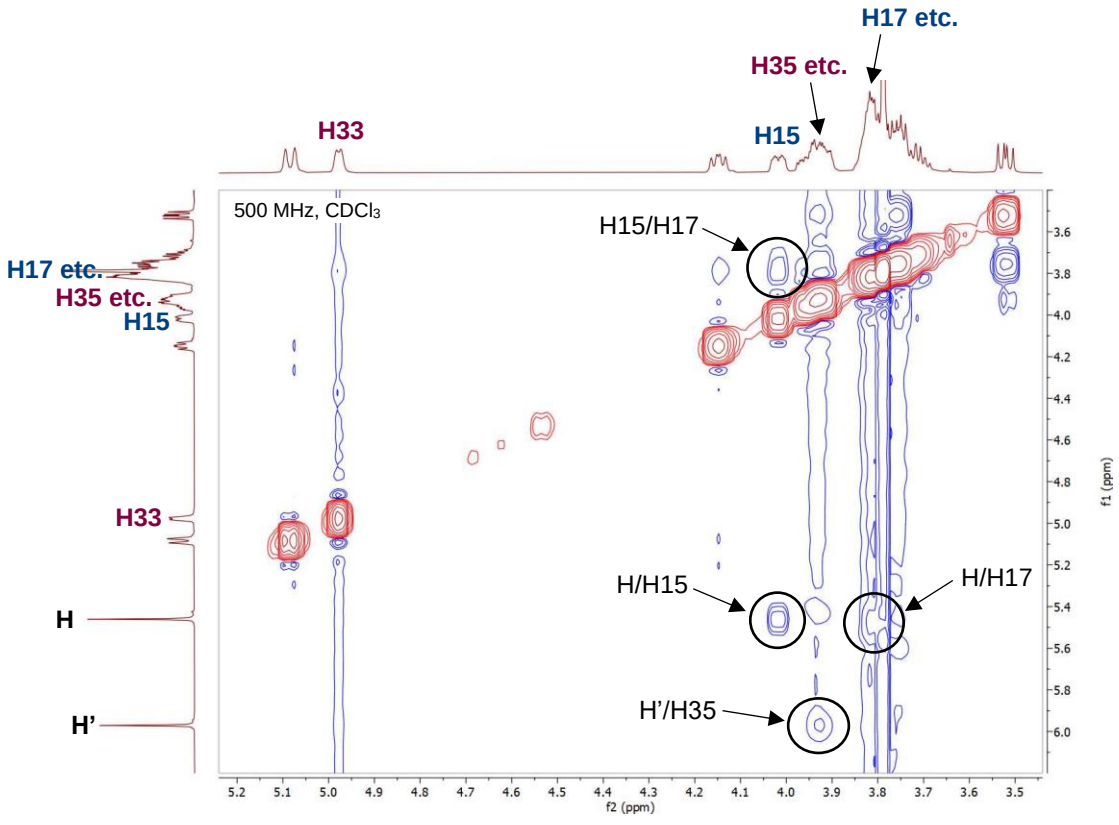
To a solution of alcohol **78'-*R*** (18 mg, 0.012 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (400 µL) at 0 °C under argon was added DDQ (5.4 mg, 0.024 mmol, 2.0 eq.). The reaction mixture was stirred at 0 °C for 1 hour. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 19/1 → 9/1) to afford the title compound (12.2 mg, 0.008 mmol, 65%) as a colourless oil.

$[\alpha]_D^{25}$ –13.4 (c = 1.2, $CHCl_3$); **R_f** 0.53 (pentane/ethyl acetate = 17/3); **IR** (thin film): ν_{max}/ cm^{-1} 2941, 2865, 1519, 1464, 1379, 1251, 1201, 1172, 1112, 1038, 1012, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 – 7.39 (m, 4H, Ar*H*), 6.88 – 6.86 (m, 4H, Ar*H*), 5.97 (s, 1H, C*H*PMP), 5.46 (s, 1H, C*H*PMP), 5.08 (d, *J* = 10.7 Hz, 1H, *H25*), 4.99 – 4.97 (m, 1H, *H33*), 4.15 (dd, *J* = 9.6, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.98 – 3.90 (m, 3H, *H28*, *H35* and *H47*), 3.85 – 3.78 (m, 5H, *H17*, *H27*, *H39*, *H41* and *H45*), 3.79 (s, 6H, OCH_3 × 2), 3.78 – 3.69 (m, 4H, *H13*, *H21* and *H48*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 2.48 – 2.40 (m, 2H, *H26* and *H30*), 2.30 (dtd, *J* = 16.7, 8.1, 2.0 Hz, 1H, *H30'*), 1.96 (td, *J* = 12.4, 5.6 Hz, 1H, *H34*), 1.89 – 1.31 (m, 34H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34'*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.63 (d, *J* = 0.9 Hz, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.33 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.10

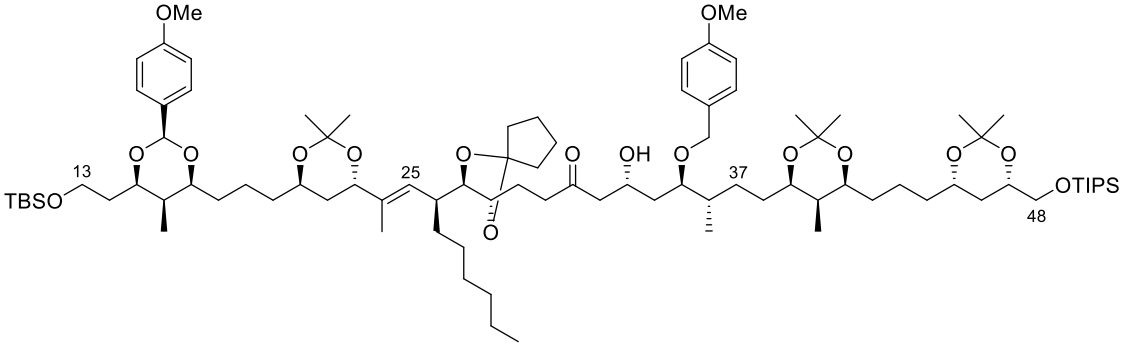
(m, 12H, *n*-Hex-(C*H*$_2$)$_5$, *H37'* and *H46'*), 1.10 – 1.03 (m, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.96 (d, *J* = 6.9 Hz, 3H, H16C*H*$_3$), 0.93 (d, *J* = 6.8 Hz, 3H, H36C*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.80 (d, *J* = 6.8 Hz, 3H, H40C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.9, 137.1, 131.9, 131.6, 127.6, 127.6, 124.6, 117.6, 113.7, 113.6, 101.6, 100.4, 98.8, 98.5, 95.5, 88.4, 81.3, 81.2, 77.9, 77.5, 76.9, 76.5, 73.8, 73.4, 71.1, 70.2, 69.0, 67.4, 66.7, 64.8, 59.5, 55.4, 55.4, 38.0, 37.8, 37.7, 37.5, 37.4, 36.7, 36.1, 36.1, 34.9, 34.4, 34.2, 33.3, 33.1, 33.0, 32.5, 32.0, 30.3, 30.3, 29.9, 29.7, 29.0, 27.5, 26.4, 26.1, 25.1, 24.9, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 15.8, 15.1, 14.3, 13.7, 12.1, 6.1, 4.6, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{152}O_{16}Si_2$ $[M+Na]^+$: 1580.0511, found 1580.0464.

*NOESY spectrum of **85'***





(5*R*,7*R*,8*S*)-1-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethyl-silyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-8-methyldecan-3-one (86')

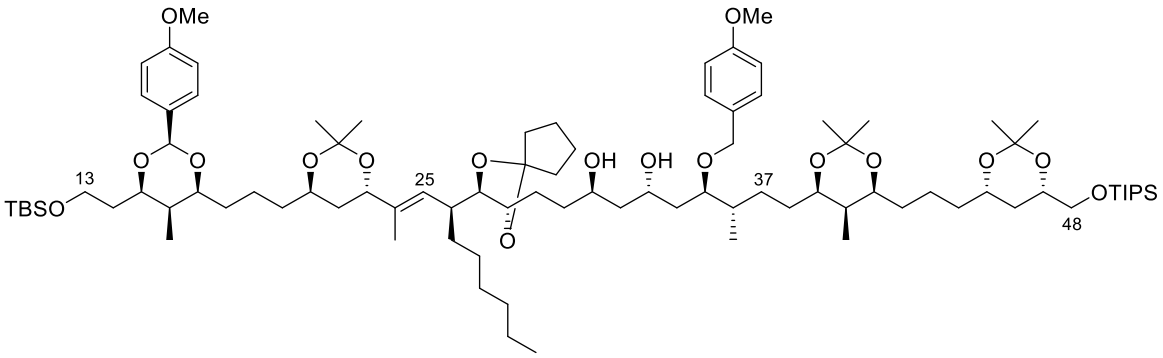


Synthesized according to a modified literature procedure.[172] To a solution of alcohol **78'-*R*** (800 mg, 0.51 mmol, 1.0 eq.) in anhydrous diethyl ether (2.6 mL) under argon was added bis(pinacolato)diboron (309.8 mg, 1.22 mmol, 2.4 eq.), followed by sodium *tert*-butoxide (29.8 mg, 0.31 mmol, 0.6 eq.) in one portion. The mixture was cooled to 0 °C and [(IMes)CuCl][209] (20.6 mg, 0.051 mmol, 0.1 eq.) was added, followed by anhydrous methanol (83 µL, 2.04 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 1 hour. The dark-coloured mixture was quenched with 2–3 drops of triethanolamine and stirred at 0 °C for 10 minutes and at room temperature for 10 minutes. It was filtered through celite and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in THF (6.4 mL) and water (6.4 mL), and sodium perborate monohydrate (254.5 mg, 2.55 mmol, 5.0 eq.) was added. The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (704.7 mg, 0.45 mmol, 88%) as a colourless oil.

$[\alpha]_D^{25}$ –13.9 (c = 1.2, $CHCl_3$); **R_f** 0.28 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/ cm^{-1} 3500, 2940, 2865, 1716, 1516, 1464, 1379, 1249, 1172, 1111, 1038, 1010, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.1 Hz, 1H, *H25*), 4.51 (d, *J*

= 10.8 Hz, 1H, OC*H*$_2$Ar), 4.40 (d, *J* = 10.8 Hz, 1H, OC*H'*$_2$Ar), 4.29 – 4.23 (m, 1H, *H33*), 4.16 (dd, *J* = 9.5, 6.1 Hz, 1H, *H23*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.86 – 3.73 (m, 9H, *H13*, *H17*, *H21*, *H27*, *H28*, *H39*, *H41*, *H45* and *H48*), 3.78 (s, 3H, OC*H*$_3$ × 2), 3.72 – 3.68 (m, 1H, *H13'*), 3.59 (dt, *J* = 8.3, 4.3 Hz, 1H, *H35*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 3.33 (d, *J* = 3.5 Hz, 1H, O*H*), 2.60 – 2.49 (m, 3H, *H30* and *H32*), 2.48 – 2.38 (m, 2H, *H26* and *H30'*), 1.88 – 1.83 (m, 2H, *H14* and H*36*), 1.82 – 1.34 (m, 32H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(C*H*$_2$)$_4$), 1.64 (s, 3H, CC*H*$_3$), 1.44 (s, 3H, acetonide-C*H*$_3$), 1.40 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.37 (s, 3H, acetonide-C*H*$_3$), 1.35 (s, 3H, acetonide-C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.32 – 1.10 (m, 12H, *H40*, *n*-Hex-(C*H*$_2$)$_5$ and *H46'*), 1.10 – 1.04 (m, 21H, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.02 – 0.99 (m, 1H, *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.90 – 0.85 (m, 6H, H36C*H*$_3$ and *n*-Hex-C*H*$_3$), 0.81 (d, *J* = 6.8 Hz, 3H, H40C*H*$_3$), 0.06 (s, 3H, SiC*H*$_3$), 0.05 (s, 3H, SiC*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 211.7, 159.8, 159.3, 137.3, 131.9, 130.9, 129.6, 127.5, 124.5, 117.5, 113.9, 113.7, 101.6, 100.4, 98.8, 98.5, 81.4, 81.1, 79.6, 77.5, 76.7, 73.8, 73.4, 71.6, 71.1, 70.1, 69.0, 67.4, 66.6, 65.1, 59.5, 55.4, 55.4, 50.0, 40.1, 37.8, 37.6, 37.4, 37.3, 36.7, 36.5, 36.0, 36.0, 35.3, 34.9, 34.5, 34.4, 33.1, 32.9, 32.5, 32.0, 31.1, 30.2, 30.2, 29.7, 28.8, 26.4, 26.1, 25.1, 24.9, 23.8, 23.5, 23.4, 22.7, 21.3, 21.1, 20.0, 19.8, 18.5, 18.1, 14.2, 14.1, 13.7, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{156}O_{17}Si_2$ $[M+Na]^+$: 1600.0773, found 1600.0707.

(3*R*,5*S*,7*R*,8*S*)-1-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethyl-silyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-10-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-7-((4-methoxybenzyl)oxy)-8-methyldecane-3,5-diol (87')



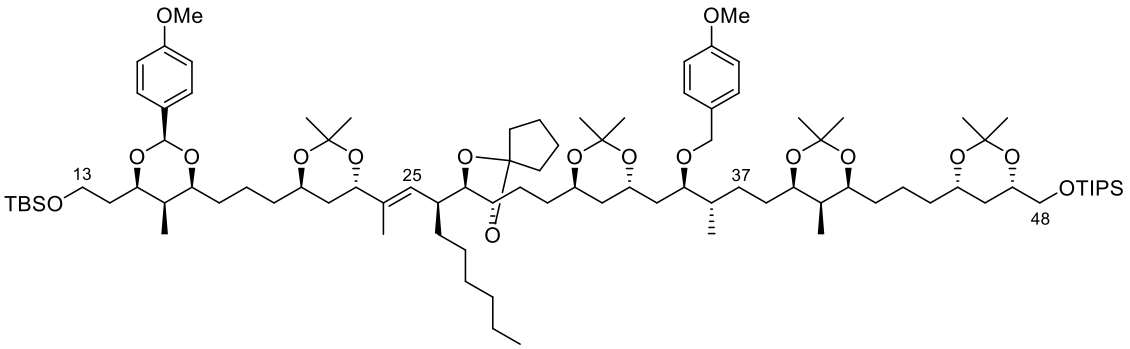
To a stirred suspension of $Me_4NBH(OAc)_3$ (947.2 mg, 3.60 mmol, 8.0 eq.) in anhydrous acetonitrile (11 mL) under argon was added glacial acetic acid (9 mL). The solution was stirred for 30 minutes at room temperature, after which it was cooled to –20 °C. A solution of β-hydroxy ketone **86'** (704.7 mg, 0.45 mmol, 1.0 eq.) in anhydrous acetonitrile (4 mL) and anhydrous THF (1.5 mL, to aid solubility) was added dropwise. The reaction mixture was stirred at –20 °C for 3 hours and at –10 °C for 36 hours. (*Note: a larger stir bar should be used as the reaction tends to form a sticky residue*). It was quenched with saturated aqueous potassium sodium tartrate (11 mL), warmed to room temperature, and stirred for 30 minutes, upon which a white precipitate formed. The mixture was poured over ice, neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the title compound (558.8 mg, 0.35 mmol, 79%, 18:1 *dr*[xlv]) as a colourless oil.

$[\alpha]_D^{25}$ –7.0 (c = 0.6, $CHCl_3$); **R_f** 0.26 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3480, 2941, 2865, 1517, 1471, 1379, 1249, 1172, 1111, 1039, 1011, 835, 764; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.09 (d, *J* = 10.2 Hz, 1H, *H25*), 4.49 (d, *J* = 11.0 Hz, 1H, OC*H*$_2$Ar), 4.42 (d, *J* = 11.0 Hz, 1H, OC*H'*$_2$Ar), 4.20 – 4.15 (m, 2H, *H23* and *H33*), 4.02 (ddd, *J* = 9.1, 4.1, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.89 – 3.73 (m, 10H,

H13, *H17*, *H21*, *H27*, *H28*, *H31*, *H39*, *H41*, *H45* and *H48*), 3.79 (s, 6H, OC$H_3 \times 2$), 3.73 – 3.68 (m, 1H, *H13'*), 3.56 – 3.51 (m, 1H, *H35*), 3.52 (dd, *J* = 9.7, 6.8 Hz, 1H, *H48'*), 3.19 (d, *J* = 4.3 Hz, 1H, O*H*), 2.81 (d, *J* = 5.2 Hz, 1H, O*H*), 2.47 – 2.40 (m, 1H, *H26*), 1.91 – 1.87 (m, 1H, *H36*), 1.86 – 1.32 (m, 37H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H37*, *H38*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.64 (d, *J* = 1.0 Hz, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.32 – 1.09 (m, 12H, *H40*, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.09 – 1.04 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 – 0.99 (m, 1H, *H37'*), 0.96 (d, *J* = 6.9 Hz, 3H, H16CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.89 – 0.85 (m, 6H, H36CH_3 and *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.4, 136.6, 131.9, 130.7, 129.7, 127.6, 126.4, 117.4, 114.0, 113.7, 101.6, 100.5, 98.9, 98.5, 81.3, 81.1, 80.3, 78.4, 77.5, 73.9, 73.4, 72.0, 71.3, 70.2, 69.6, 69.0, 67.4, 66.7, 66.5, 59.5, 55.4, 55.4, 43.3, 38.1, 37.8, 37.3, 37.0, 36.7, 36.2, 36.0, 36.0, 35.1, 34.9, 34.6, 34.5, 34.4, 32.9, 32.8, 32.5, 32.0, 30.9, 30.3, 30.2, 29.7, 29.0, 26.5, 26.1, 25.9, 25.2, 24.9, 23.8, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.5, 14.2, 13.3, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{91}H_{158}O_{17}Si_2$ $[M+Na]^+$: 1602.0930, found 1602.0884.

[xlv] Estimated from alcohol **89'**

tert-Butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (88')

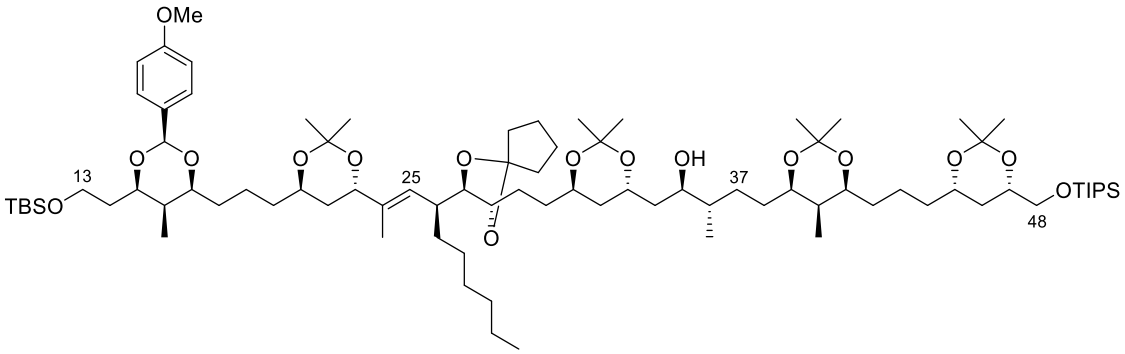


To a solution of diol **87'** (558.8 mg, 0.35 mmol, 1.0 eq.) in 2,2-dimethoxypropane/CH_2Cl_2 (3.6 mL, 1:1) was added pyridinium *p*-toluenesulfonate (7.0 mg, 0.028 mmol, 8 mol%). The reaction mixture was stirred at room temperature for 3 hours. It was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (525.5 mg, 0.32 mmol, 93%) as a colourless oil.

$[\alpha]_D^{25}$ –9.4 (c = 0.5, $CHCl_3$); **R_f** 0.48 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/cm^{-1} 2948, 2867, 1517, 1463, 1379, 1250, 1224, 1173, 1112, 1039, 1012, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 – 6.85 (m, 4H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.2 Hz, 1H, *H25*), 4.48 (d, *J* = 10.7 Hz, 1H, OC*H*$_2$Ar), 4.33 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.15 (dd, *J* = 9.3, 6.1 Hz, 1H, *H23*), 4.06 – 4.00 (m, 2H, *H15* and *H33*), 3.96 – 3.91 (m, 1H, *H47*), 3.86 – 3.74 (m, 9H, *H13*, *H17*, *H21*, *H27*, *H28*, *H39*, *H41*, *H45* and *H48*), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.73 – 3.68 (m, 2H, *H13'* and *H31*), 3.54 – 3.51 (m, 2H, *H35* and *H48'*), 2.46 – 2.40 (m, 1H, *H26*), 1.89 – 1.30 (m, 39H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(C*H*$_2$)$_4$), 1.62 (s, 3H, CC*H*$_3$), 1.45 (s, 3H, acetonide-C*H*$_3$), 1.41 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.38 (s, 3H, acetonide-C*H*$_3$), 1.35 (s, 3H, acetonide-C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.31 (s, 3H, acetonide-C*H*$_3$), 1.30 (s, 3H, acetonide-C*H*$_3$), 1.28 – 1.10 (m, 11H, *n*-Hex-(C*H*$_2$)$_5$ and

H46'), 1.10 – 0.99 (m, 22H, Si(C*H*(CH_3)$_2$)$_3$ and *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.90 – 0.88 (m, 12H, SiC(CH_3)$_3$ and H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.9 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 159.2, 136.9, 131.9, 131.2, 129.4, 127.6, 124.8, 117.3, 113.9, 113.7, 101.6, 100.3, 100.3, 98.8, 98.5, 81.4, 81.2, 79.1, 78.1, 77.5, 73.9, 73.4, 71.5, 71.1, 70.2, 69.0, 67.4, 67.2, 66.6, 63.6, 59.5, 55.4, 55.4, 39.4, 38.0, 37.8, 37.5, 37.3, 36.7, 36.7, 36.1, 36.0, 35.3, 34.9, 34.5, 34.4, 33.0, 33.0, 33.0, 32.5, 32.0, 31.3, 30.3, 30.2, 29.7, 28.7, 26.4, 26.1, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 22.8, 21.3, 21.1, 20.0, 19.9, 18.5, 18.1, 14.2, 14.1, 13.6, 12.1, 6.1, 4.7, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{94}H_{162}O_{17}Si_2$ $[M+Na]^+$: 1642.1243, found 1642.1172.

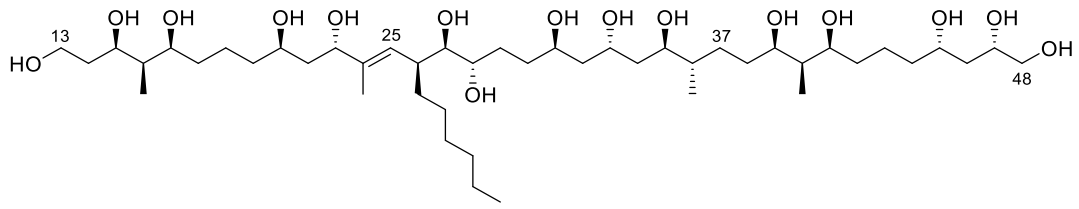
(2*R*,3*S*)-1-((4*R*,6*R*)-6-(2-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-methylpentan-2-ol (89')



To a solution of PMB ether **88'** (48.1 mg, 0.030 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) and pH 7 buffer (1 M potassium phosphate buffer, 53 µL) at 0 °C was added DDQ (17.0 mg, 0.075 mmol, 2.5 eq.). The reaction mixture was stirred at 0 °C under argon for 1.5 hours. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1 → 17/3) to afford the title compound (30.9 mg, 0.021 mmol, 69%) as a colourless oil.

$[\alpha]_D^{25}$ –21.3 (c = 0.5, $CHCl_3$); **R_f** 0.37 (pentane/ethyl acetate = 3/1); **IR** (thin film): ν_{max}/ cm^{-1} 3526, 2941, 2866, 1519, 1463, 1380, 1250, 1224, 1171, 1112, 1070, 1011, 835; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 5.46 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.2 Hz, 1H, *H25*), 4.17 – 4.11 (m, 2H, *H23* and *H33*), 4.02 (ddd, *J* = 9.1, 4.0, 2.1 Hz, 1H, *H15*), 3.95 – 3.90 (m, 1H, *H47*), 3.85 – 3.80 (m, 5H, *H17*, *H28*, *H39*, *H41* and *H45*), 3.79 (s, 3H, OCH_3), 3.79 – 3.74 (m, 4H, *H13*, *H21*, *H27* and *H48*), 3.73 – 3.68 (m, 2H, *H13'* and *H31*), 3.67 – 3.62 (m, 1H, *H35*), 3.52 (dd, *J* = 9.7, 6.7 Hz, 1H, *H48'*), 2.70 (d, *J* = 4.4 Hz, 1H, O*H*), 2.46 – 2.39 (m, 1H, *H26*), 1.89 – 1.32 (m, 39H, *H14*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.62 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.37 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.32 (s, 3H, acetonide-CH_3), 1.31 (s, 3H, acetonide-CH_3), 1.29 – 1.10 (m, 11H, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.10 – 1.01 (m, 22H, Si(C*H*(CH_3)$_2$)$_3$ and *H37'*), 0.96 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.90 – 0.85 (m, 15H, SiC(CH_3)$_3$, H36CH_3 and *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.9, 136.9, 131.9, 127.6, 124.7, 117.4, 113.7, 101.6, 100.5, 100.3, 98.8, 98.5, 81.4, 81.2, 78.1, 77.5, 74.0, 73.4, 72.7, 71.0, 70.2, 69.0, 67.4, 67.4, 66.6, 64.8, 59.5, 55.4, 39.0, 38.3, 38.1, 38.0, 37.8, 37.5, 37.4, 36.7, 36.1, 36.0, 34.9, 34.4, 34.2, 33.1, 33.0, 32.9, 32.5, 32.0, 30.5, 30.3, 30.2, 29.7, 27.6, 26.4, 26.1, 26.0, 25.2, 25.0, 25.0, 24.9, 23.9, 23.5, 22.8, 21.3, 21.1, 20.0, 19.8, 18.5, 18.1, 15.7, 14.2, 13.7, 12.1, 6.1, 4.6, –5.2, –5.2; **HRMS** (ESI) m/z calcd for $C_{86}H_{154}O_{16}Si_2$ $[M+Na]^+$: 1522.0668, found 1522.0615.

(2*S*,4*S*,8*S*,9*R*,10*R*,13*S*,14*R*,16*S*,18*R*,21*S*,22*R*,23*S*,26*S*,28*R*,32*S*,33*R*,34*R*,*E*)-23-Hexyl-9,13,25,33-tetramethylhexatriacont-24-ene-1,2,4,8,10,14,16,18,21,22,26,28, 32,34,36-pentadecaol (90')



To a solution of acetal **89'** (30 mg,[xlvi] 0.020 mmol, 1.0 eq.) in MeOH (12 mL) and THF (6 mL) was added 0.2 M aqueous HCl (12 mL). The reaction mixture was stirred at room

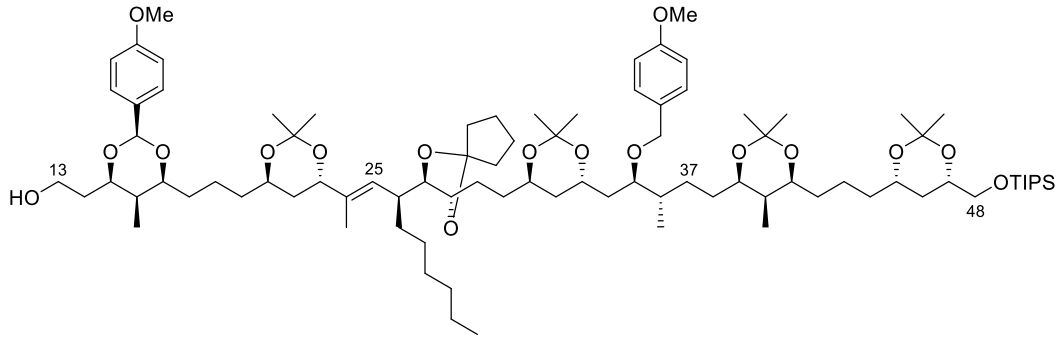
temperature overnight (15 hours).[xlvii] It was quenched with saturated aqueous $NaHCO_3$ (3 mL) and concentrated using a stream of nitrogen. The residue was taken up in MeOH and the solids were removed by filtration (through a cotton plug and syringe filter). Upon concentration, the residue was resubmitted to the reaction conditions,[xlviii] stirred at room temperature overnight (15 hours), and quenched and worked up as before. The residue was purified by reversed phase C18 column chromatography (water/acetonitrile = 19/1 → 4/1) to afford the title compound (9.9 mg, 0.011 mmol, 56%) as a colourless oil, which solidified over time.

$[\alpha]_D^{25}$ –8.1 (c = 1.0, MeOH); $\mathbf{R_f}$ 0.21 (ethyl acetate/methanol = 7/3) *or* 0.36 (water/acetonitrile = 7/3, reversed phase C18 TLC); **IR** (thin film): ν_{max}/cm^{-1} 3346, 2934, 2857, 1670, 1458, 1321, 1098, 1047; **^{1}H NMR** (500 MHz, MeOD): δ 5.23 (d, *J* = 11.3 Hz, 1H, *H25*), 4.23 (dd, *J* = 9.1, 3.7 Hz, 1H, *H23*), 4.08 (tt, *J* = 9.2, 3.1 Hz, 1H, *H33*), 3.89 (ddd, *J* = 7.5, 5.3, 3.7 Hz, 1H, *H15*), 3.84 – 3.77 (m, 3H, *H31*, *H45* and *H47*), 3.77 – 3.67 (m, 7H, *H13*, *H17*, *H21*, *H35*, *H39* and *H41*), 3.54 – 3.49 (m, 1H, *H28*), 3.51 (dd, *J* = 11.2, 4.6 Hz, 1H, *H48*), 3.46 (dd, *J* = 11.2, 5.9 Hz, 1H, *H48'*), 3.36 (dd, *J* = 7.3, 4.6 Hz, 1H, *H27*), 2.50 – 2.44 (m, 1H, *H26*), 1.83 – 1.76 (m, 1H, *n*-Hex-CH_2 × 1H), 1.74 – 1.64 (m, 6H, *H14*, *H22*, *H29*, *H30* and *H46*), 1.66 (d, *J* = 1.0 Hz, CCH_3), 1.63 – 1.59 (m, 3H, *H19*, *H37* and *H42*), 1.59 – 1.40 (m, 22H, *H16*, *H18*, *H20*, *H22'*, *H29'*, *H30'*, *H32*, *H34*, *H36*, *H38*, *H40*, *H42'*, *H43*, *H44* and *H46'*), 1.39 – 1.13 (m, 10H, *H19'* and *n*-Hex-CH_2 × 9H), 1.14 – 1.06 (m, 1H, *H37'*), 0.94 (d, *J* = 7.0 Hz, 3H, H16CH_3), 0.93 (d, *J* = 7.0 Hz, 3H, H40CH_3), 0.92 (d, *J* = 6.8 Hz, 3H, H36CH_3), 0.90 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3); **^{13}C NMR** (126 MHz, MeOD): δ 139.7, 128.2, 79.6, 76.3, 75.9, 75.6, 75.1, 73.9, 73.2, 72.8, 72.1, 71.0, 69.8, 69.3, 67.2, 66.6, 60.5, 46.3, 44.0, 43.7, 42.8, 41.9, 41.5, 41.2, 40.7, 38.8, 38.6, 38.5, 36.1, 36.0, 35.7, 33.8, 33.1, 32.1, 30.8, 29.8, 28.3, 28.3, 23.8, 23.2, 23.0, 15.7, 14.5, 12.9, 7.4, 7.0; **HRMS** (ESI) m/z calcd for $C_{46}H_{92}O_{15}$ $[M+Na]^+$: 907.6329, found 907.6298.

[xlvi] The experiment was performed in two batches of 15 mg each and the products were combined for purification.
[xlvii] Prolonging the reaction time results in increased formation of a side product. [xlviii] Due to solubility issues, resubmission of the crude product to the reaction conditions is necessary for full conversion of the starting material.

6.5. The C1–C51 fragment

2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethan-1-ol (91)



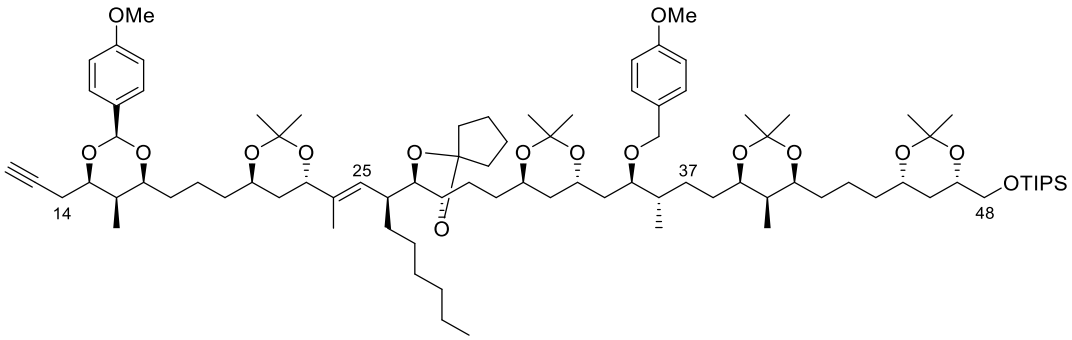
To a solution of TBS ether **88'** (400 mg, 0.247 mmol, 1.0 eq.) in anhydrous THF (4.9 mL) was added a solution of TBAF (1.0 M in THF, 250 µL, 1.0 eq.) and AcOH (1.0 M in THF,[xlix] 494 µL, 2.0 eq.). The reaction mixture was stirred at room temperature for 17 hours.[l] It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/1 → 7/3) to afford the title compound (259.4 mg, 0.172 mmol, 70%) as a colourless oil; TBS ether **88'** (48 mg, 0.030 mmol, 12%) was also recovered.

$[\alpha]_D^{25}$ –15.1 (c = 0.5, $CHCl_3$); **R_f** 0.42 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/ cm^{-1} 3485, 2941, 2867, 1516, 1463, 1379, 1249, 1224, 1172, 1111, 1070, 1038, 1010, 736; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.88 – 6.84 (m, 4H, Ar*H*), 5.51 (s, 1H, C*H*PMP), 5.07 (d, *J* = 10.1 Hz, 1H, *H25*), 4.48 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.32 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.15 (dd, *J* = 9.3, 6.1 Hz, 1H, *H23*), 4.07 (dt, *J* = 10.2, 3.0 Hz, 1H, *H15*), 4.05 – 4.00 (m, 1H, *H33*), 3.96 – 3.90 (m, 1H, *H47*), 3.86 – 3.74 (m, 10H, H13, *H17*, *H21*, *H27*, *H28*, *H39*, *H41*, *H45* and *H48*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.72 – 3.68 (m, 1H, *H31*), 3.54 – 3.51 (m, 2H, *H35* and *H48'*), 2.45 – 2.39 (m, 1H, *H26*), 2.10 (brs, 1H, O*H*), 2.03 – 1.96 (m, 1H, *H14*),

1.87 – 1.31 (m, 38H, *H14'*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(C*H*$_2$)$_4$), 1.61 (s, 3H, CC*H*$_3$), 1.44 (s, 3H, acetonide-C*H*$_3$), 1.41 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.38 (s, 3H, acetonide-C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.33 (s, 3H, acetonide-C*H*$_3$), 1.30 (s, 6H, acetonide-C*H*$_3$ × 2), 1.29 – 1.10 (m, 11H, *n*-Hex-(C*H*$_2$)$_5$ and *H46'*), 1.10 – 1.00 (m, 22H, Si(C*H*(C*H*$_3$)$_2$)$_3$ and *H37'*), 0.98 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H36C*H*$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.82 (d, *J* = 6.8 Hz, 3H, H40C*H*$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.0, 159.2, 136.9, 131.5, 131.2, 129.5, 127.6, 124.6, 117.4, 113.9, 113.8, 101.7, 100.3, 100.3, 98.8, 98.5, 81.4, 81.1, 80.3, 79.1, 78.1, 73.9, 73.4, 71.5, 70.9, 70.2, 69.0, 67.4, 67.2, 66.6, 63.6, 61.1, 55.4, 55.4, 39.4, 38.0, 37.8, 37.5, 37.4, 36.7, 36.7, 36.0, 35.4, 35.3, 35.1, 34.5, 34.4, 33.0, 33.0, 32.9, 32.4, 32.0, 31.3, 30.3, 30.2, 29.7, 28.7, 26.4, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 22.7, 21.3, 21.1, 20.0, 19.9, 18.1, 14.2, 14.1, 13.7, 12.1, 6.1, 4.7; **HRMS** (ESI) m/z calcd for $C_{88}H_{148}O_{17}Si$ $[M+Na]^+$: 1528.0378, found 1528.0322.

[xlix] Prepared from glacial acetic acid and anhydrous THF. [l] Prolonging the reaction time results in increased formation of the over-deprotected product.

Triisopropyl(((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*,4*R*)-4-((4-methoxybenzyl)oxy)-5-((4*S*,6*R*)-6-(2-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-(prop-2-yn-1-yl)-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpentyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)silane (92)

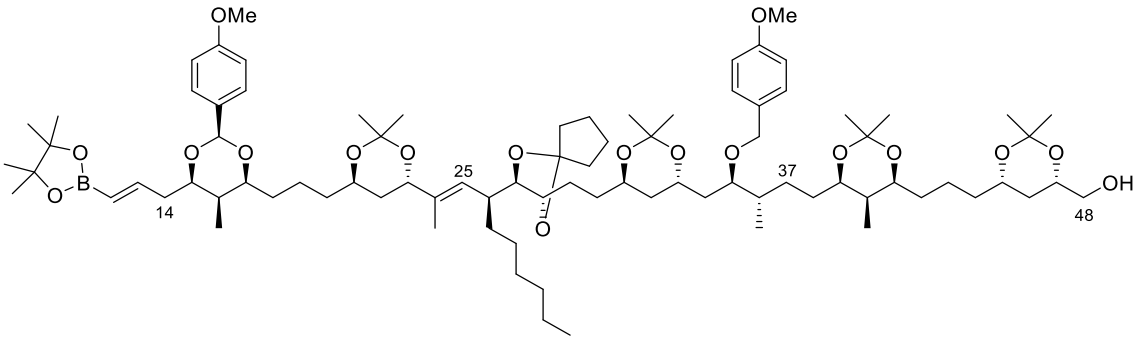


(1) To a solution of alcohol **91** (259 mg, 0.17 mmol, 1.0 eq.) in CH_2Cl_2 (3.4 mL) was added $NaHCO_3$ (42.8 mg, 0.51 mmol, 3.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (110.3 mg, 0.26 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was diluted with diethyl ether, quenched with saturated aqueous $Na_2S_2O_3$, and stirred until the mixture became a clear solution. The layers were separated and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a short silica plug, washing with pentane/ethyl acetate (4:1), and concentrated under reduced pressure to afford the aldehyde. *(2)* To a solution of dimethyl (1-diazo-2-oxopropyl) phosphonate **63** (489.9 mg, 2.55 mmol, 15.0 eq.) in anhydrous MeOH (4 mL) under argon was added K_2CO_3 (356.6 mg, 2.58 mmol, 15.2 eq.), followed by a solution of the aldehyde in anhydrous MeOH (1.7 mL)/THF (600 µL). The reaction mixture was stirred at room temperature for 2 hours. It was quenched with saturated aqueous NH_4Cl, diluted with water, and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 9/1) to afford the title compound (195.2 mg, 0.13 mmol, 77% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ –18.1 (c = 3.0, $CHCl_3$); **R_f** 0.44 (pentane/ethyl acetate = 4/1); **IR** (thin film): ν_{max}/ cm^{-1} 3310, 2941, 2866, 1516, 1463, 1379, 1249, 1224, 1200, 1172, 1111, 1066, 1039,

1011; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.48 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.2 Hz, 1H, *H25*), 4.48 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.32 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.15 (dd, *J* = 9.3, 6.2 Hz, 1H, *H23*), 4.06 – 4.00 (m, 2H, *H15* and *H33*), 3.96 – 3.91 (m, 1H, *H47*), 3.86 – 3.74 (m, 9H, *H17*, *H21*, *H27*, *H28*, *H39*, *H41*, *H45* and *H48*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 – 3.68 (m, 1H, *H31*), 3.54 – 3.51 (m, 2H, *H35* and *H48'*), 2.57 (ddd, *J* = 16.7, 6.0, 2.7 Hz, 1H, *H14*), 2.46 – 2.39 (m, 2H, *H14'* and *H26*), 1.99 (t, *J* = 2.7 Hz, 1H, *H12*), 1.90 – 1.32 (m, 37H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.62 (s, 3H, CCH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.38 (s, 3H, acetonide-CH_3), 1.35 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.30 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.10 (m, 11H, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.11 – 1.00 (m, 22H, Si(C*H*(CH_3)$_2$)$_3$ and *H37'*), 0.97 (d, *J* = 6.9 Hz, 3H, H16CH_3), 0.90 (d, *J* = 6.9 Hz, 3H, H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.1, 159.2, 136.9, 131.3, 131.2, 129.4, 127.6, 124.8, 117.3, 113.9, 113.8, 101.7, 100.3, 100.3, 98.8, 98.5, 81.4, 81.0, 80.1, 79.1, 79.0, 78.1, 73.9, 73.4, 71.5, 71.0, 70.2, 70.2, 69.0, 67.4, 67.2, 66.6, 63.6, 55.4, 55.4, 39.4, 38.0, 37.8, 37.5, 37.3, 36.7, 36.7, 36.0, 35.3, 34.5, 34.4, 33.2, 33.0, 33.0, 32.6, 32.0, 31.3, 30.3, 30.2, 29.8, 29.7, 28.7, 26.4, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 22.8, 22.5, 21.3, 21.1, 20.0, 19.9, 18.1, 14.3, 14.1, 13.7, 12.1, 5.4, 4.7; **HRMS** (ESI) m/z calcd for $C_{89}H_{146}O_{16}Si$ $[M+Na]^+$: 1522.0272, found 1522.0198.

((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*,4*R*)-4-((4-Methoxybenzyl)oxy)-5-((4*S*,6*R*)-6-(2-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpentyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methanol (93)

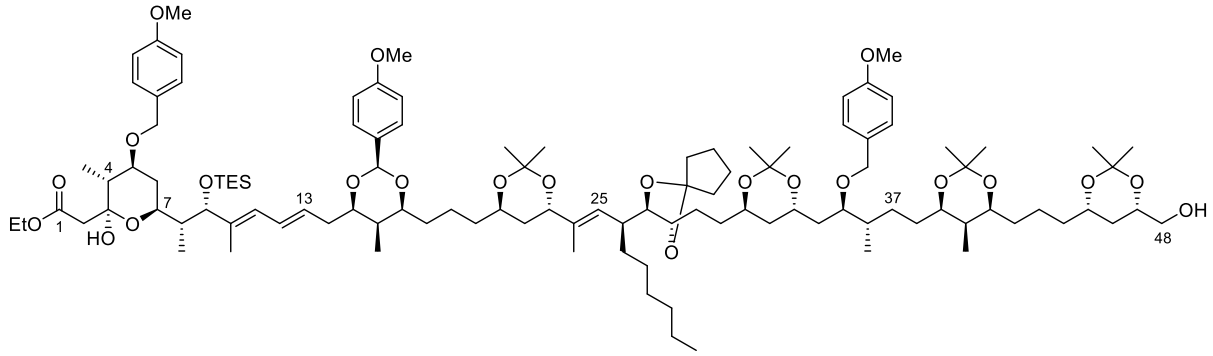


(1) Synthesized according to a modified literature procedure.[179] To a mixture of alkyne **92** (60 mg, 0.040 mmol, 1.0 eq.) and pinacolborane (87 µL, 0.600 mmol, 15.0 eq.) under argon was added bis(cyclopentadienyl)zirconium chloride hydride (3.1 mg, 0.012 mmol, 0.3 eq.) and anhydrous triethylamine (7 µL, 0.048 mmol, 1.2 eq.). The reaction mixture was stirred at 60 °C for 2 hours. Upon cooling to room temperature, it was diluted with diethyl ether, quenched with brine, and extracted with diethyl ether. The organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3) to afford the vinylboronic ester (slightly impure with HBpin residues). *(2)* The vinylboronic ester was dissolved in anhydrous THF (800 µL) under argon, cooled to 0 °C, and TBAF (1.0 M in THF, 100 µL, 2.5 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 15 minutes and at room temperature for 5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1 → 7/3) to afford the title compound (30.8 mg, 0.021 mmol, 52% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ –7.4 (c = 0.7, $CHCl_3$); **R_f** 0.26 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3489, 2985, 2938, 2872, 1518, 1458, 1379, 1354, 1250, 1224, 1171, 1144, 1111, 1065, 1038, 1009; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.6

Hz, 2H, Ar*H*), 6.88 – 6.84 (m, 4H, Ar*H*), 6.59 (ddd, *J* = 17.9, 7.5, 5.8 Hz, 1H, *H13*), 5.56 (d, *J* = 17.9 Hz, 1H, *H12*), 5.46 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.0 Hz, 1H, *H25*), 4.48 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.32 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.15 (dd, *J* = 9.3, 6.2 Hz, 1H, *H23*), 4.05 – 3.99 (m, 1H, *H33*), 4.00–3.96 (m, 1H, *H47*), 3.92 (td, *J* = 7.0, 2.1 Hz, 1H, *H15*), 3.88 – 3.73 (m, 7H, *H17*, *H21*, *H27*, *H28*, *H39*, *H41*, *H45*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 – 3.68 (m, 1H, *H31*), 3.60 (ddd, *J* = 10.8, 7.3, 3.2 Hz, 1H, *H48*), 3.54 – 3.46 (m, 2H, *H35* and *H48'*), 2.55 (dt, *J* = 14.8, 6.4 Hz, 1H, *H14*), 2.45 – 2.39 (m, 1H, *H26*), 2.35 (dt, *J* = 14.8, 7.5 Hz, 1H, *H14'*), 1.98 (dd, *J* = 7.3, 5.4 Hz, 1H, O*H*), 1.88 – 1.29 (m, 38H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.62 (s, 3H, CCH_3), 1.46 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.40 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.30 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.10 (m, 22H, Bpin-CH_3 × 4 and *n*-Hex-(CH_2)$_5$), 1.05 – 0.99 (m, 1H, *H37'*), 0.96 (d, *J* = 6.9 Hz, 3H, H16CH_3), 0.90 (d, *J* = 6.8 Hz, 3H, H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.0, 159.2, 149.5, 136.9, 131.7, 131.2, 129.5, 127.7, 124.8, 117.4, 113.9, 113.7, 101.6, 100.3, 100.3, 98.9, 98.8, 83.3, 81.4, 81.1, 80.1, 79.2, 78.1, 73.8, 73.4, 71.6, 71.1, 69.8, 68.6, 67.3, 66.6, 66.3, 63.6, 55.4, 55.4, 39.4, 39.4, 38.0, 37.8, 37.5, 37.3, 36.8, 36.6, 36.6, 36.1, 35.3, 34.4, 34.1, 33.0, 33.0, 33.0, 32.6, 32.5, 32.0, 31.2, 30.3, 30.3, 29.7, 28.6, 26.4, 26.0, 25.2, 25.1, 25.0, 25.0, 24.9, 24.9, 23.9, 23.5, 22.8, 21.4, 21.1, 20.1, 19.9, 14.3, 14.1, 13.7, 5.8, 4.7; **HRMS** (ESI) m/z calcd for $C_{86}H_{139}BO_{18}$ $[M+Na]^+$: 1493.9947, found 1493.9916.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2-hydroxy-6-((2*R*,3*S*,4*E*,6*E*)-8-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl) oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyl-3-((triethylsilyl)oxy)octa-4,6-dien-2-yl)-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (94)



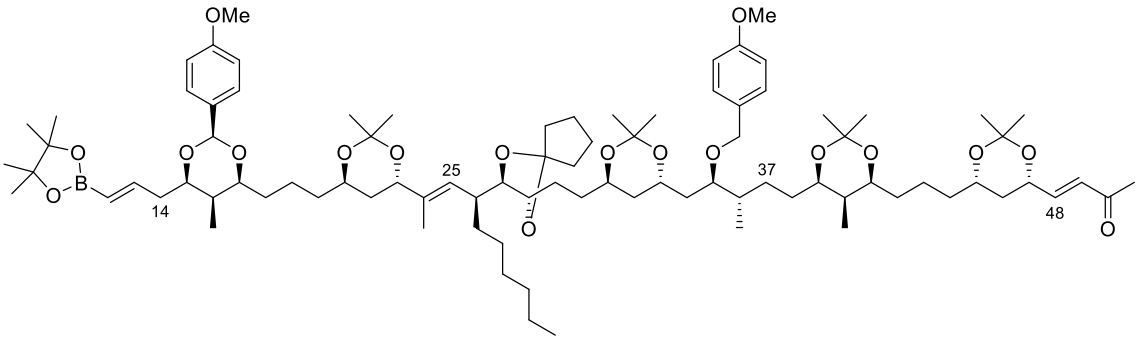
To a solution of iodide **2b** (6.7 mg, 0.0099 mmol, 1.1 eq.), boronic ester **93** (13.2 mg, 0.0090 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (4.2 mg, 0.0036 mmol, 0.4 eq.) in degassed anhydrous[li,lii] THF (1.1 mL) under argon was added dropwise a solution of Tl_2CO_3 (7.6 mg, 0.0162 mmol, 1.8 eq.) in degassed[li] water (360 µL) over 5 minutes. (Note: Tl_2CO_3 was dissolved in degassed water under argon and stirred for 30 minutes prior to addition to the reaction mixture.) The reaction mixture was stirred at room temperature overnight. It was diluted with diethyl ether, water was added, and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3 → 7/3) to afford the title compound (13.0 mg, 0.0069 mmol, 76%) as a yellow oil.

$[\alpha]_D^{25}$ +5.9 (c = 0.7, $CHCl_3$); **R_f** 0.37 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 3496, 2944, 2872, 1714, 1614, 1516, 1462, 1379, 1249, 1224, 1198, 1173, 1108, 1064, 1039, 827, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.25 – 7.23 (m, 4H, Ar*H*), 6.88 – 6.85 (m, 6H, Ar*H*), 6.35 (dd, *J* = 15.0, 10.9 Hz, 1H, *H12*), 5.99 (d, *J* = 10.9 Hz, 1H, *H11*), 5.78 (dt, *J* = 15.0, 7.3 Hz, 1H, *H13*), 5.49 (s, 1H, C*H*PMP), 5.05 (d, *J* = 10.1 Hz, 1H, *H25*), 4.54 (d, *J* = 10.9 Hz, 1H, OC*H*$_2$Ar), 4.48 (d, *J* = 10.7 Hz, 1H, OC*H*$_2$Ar), 4.45 (d, *J* = 1.9 Hz, 1H, O*H*), 4.33 (d, *J* = 10.9 Hz, 2H, OC*H'*$_2$Ar), 4.32 (d, *J* =

10.7 Hz, 2H, OC*H'*$_2$Ar), 4.20 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.15 (dd, *J* = 9.3, 6.2 Hz, 1H, *H23*), 4.05 – 4.00 (m, 1H, *H33*), 3.98 (ddt, *J* = 12.0, 6.0, 3.2 Hz, 1H, *H47*), 3.89 (td, *J* = 7.3, 2.2 Hz, 1H, *H15*), 3.87 – 3.73 (m, 8H, *H9*, *H17*, *H21*, *H27*, *H28*, *H39*, *H41* and *H45*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.72 – 3.67 (m, 2H, *H7* and *H31*), 3.60 (ddd, *J* = 10.8, 7.3, 3.2 Hz, 1H, *H48*), 3.54 – 3.44 (m, 3H, *H5*, *H35* and *H48'*), 2.71 (d, *J* = 14.7 Hz, 1H, *H2*), 2.52 (dt, *J* = 14.3, 7.3 Hz, 1H, *H14*), 2.46 (d, *J* = 14.7 Hz, 1H, *H2'*), 2.45 – 2.39 (m, 1H, *H26*), 2.29 (dt, *J* = 14.3, 7.3 Hz, 1H, *H14'*), 1.98 (dd, *J* = 7.3, 5.4 Hz, 1H, O*H*), 1.88 – 1.30 (m, 41H, *H4*, *H6*, *H8*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.65 (s, 3H, CCH_3), 1.62 (s, 3H, CCH_3), 1.46 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.31 (s, 3H, acetonide-CH_3), 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.29 – 1.11 (m, 14H, acetonide-CH_3, *H46'* and *n*-Hex-(CH_2)$_5$), 1.05 (d, *J* = 6.6 Hz, 3H, H4CH_3), 1.03 – 0.99 (m, 1H, *H37'*), 0.97 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.94 (d, *J* = 7.0 Hz, 3H, H8CH_3), 0.91 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.54 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.9, 159.9, 159.3, 159.2, 136.9, 136.7, 131.9, 131.2, 131.0, 129.4, 129.4, 129.2, 128.7, 127.6, 127.3, 124.9, 117.4, 113.9, 113.9, 113.7, 101.5, 100.3, 100.3, 98.9, 98.8, 81.4, 81.2, 80.9, 80.6, 79.2, 78.1, 77.2, 73.9, 73.4, 71.6, 71.1, 70.9, 69.8, 68.7, 67.5, 67.3, 66.6, 66.3, 63.6, 60.9, 55.4, 55.4, 55.4, 45.4, 42.9, 41.3, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.6, 36.5, 36.1, 35.3, 35.2, 34.4, 34.1, 33.0, 33.0, 33.0, 32.6, 32.5, 32.0, 31.3, 30.3, 30.3, 29.7, 28.6, 26.4, 26.0, 25.2, 25.1, 25.0, 25.0, 25.0, 23.9, 23.5, 22.8, 21.4, 21.1, 20.1, 19.9, 14.4, 14.3, 14.1, 13.6, 12.5, 11.6, 9.9, 7.0, 5.7, 5.0, 4.7; **HRMS** (ESI) m/z calcd for $C_{110}H_{176}O_{23}Si$ $[M+Na]^+$: 1916.2264, found 1916.2253.

[li]Degassed for at least 1 hour before use. [lii]Freshly taken from the solvent purification system

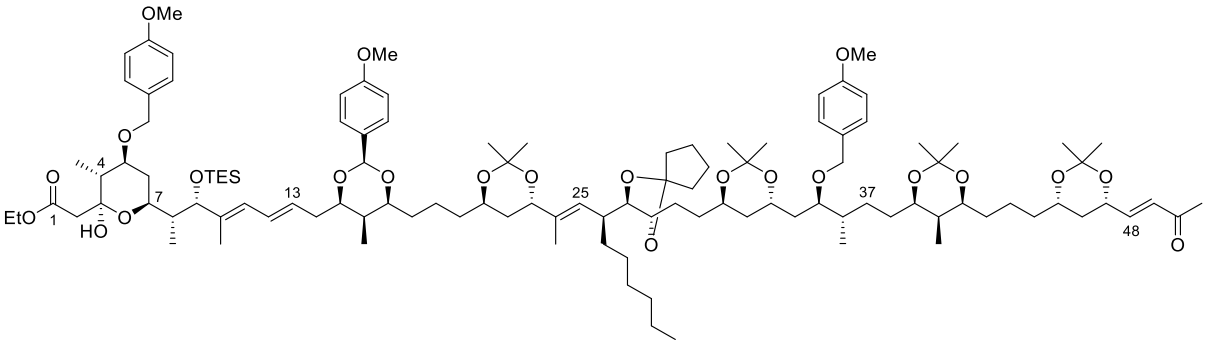
(*E*)-4-((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*,4*R*)-4-((4-Methoxybenzyl)oxy)-5-((4*S*,6*R*)-6-(2-((2*S*,3*R*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpentyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-3-en-2-one (95)



(1) To a solution of alcohol **93** (4.9 mg, 0.0033 mmol, 1.0 eq.) in CH_2Cl_2 (160 µL) was added $NaHCO_3$ (2.2 mg, 0.0264 mmol, 8.0 eq.). The mixture was cooled to 0 °C and Dess-Martin periodinane (4.2 mg, 0.0099 mmol, 3.0 eq.) was added. The reaction mixture was stirred at room temperature for 1 hour. It was diluted with diethyl ether, quenched with saturated aqueous $Na_2S_2O_3$, and stirred until the mixture became a clear solution. The layers were separated and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude aldehyde, which was used directly in the next step. *(2)* To a suspension of NaH (60% in mineral oil, 4.0 mg, 0.0924 mmol, 28.0 eq.) in anhydrous THF (800 µL) at 0 °C under argon was added dimethyl 2-oxopropylphosphonate (14 µL, 0.0990 mmol, 30.0 eq.) dropwise. The mixture was stirred at room temperature for 1.5 hours. The resulting thick white mixture was cooled to –78 °C, and a solution of the aldehyde in anhydrous THF (300 µL) was added dropwise. The mixture was gradually warmed to room temperature over 30 minutes and stirred at room temperature for 2.5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 4/1) to afford the title compound (2.8 mg, 0.0019 mmol, 56% over two steps) as a colourless oil.

$[\alpha]_D^{25}$ –6.7 (c = 0.3, $CHCl_3$); **R_f** 0.58 (pentane/ethyl acetate = 3/2); **IR** (thin film): ν_{max}/cm^{-1} 2950, 2927, 2855, 1681, 1645, 1517, 1465, 1357, 1261, 1252, 1224, 1171, 1145, 1103, 1037, 824, 762; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.85 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.69 (dd, *J* = 16.1, 4.6 Hz, 1H, *H48*), 6.59 (ddd, *J* = 18.0, 7.6, 5.9 Hz, 1H, *H13*), 6.27 (dd, *J* = 16.1, 1.6 Hz, 1H, *H49*), 5.56 (d, *J* = 18.0 Hz, 1H, *H12*), 5.47 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.1 Hz, 1H, *H25*), 4.54 (ddt, *J* = 11.9, 4.6, 2.1 Hz, 1H, *H47*), 4.48 (d, *J* = 10.7 Hz, 1H, OCH_2Ar), 4.32 (d, *J* = 10.7 Hz, 1H, OC*H'*$_2$Ar), 4.15 (dd, *J* = 9.3, 6.1 Hz, 1H, *H23*), 4.05 – 4.00 (m, 1H, *H33*), 3.94 – 3.86 (m, 2H, *H15* and *H45*), 3.85 – 3.74 (m, 6H, *H17*, *H21*, *H27*, *H28*, *H39* and *H41*), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 – 3.68 (m, 1H, *H31*), 3.52 (dt, *J* = 10.1, 2.8 Hz, 1H, *H35*), 2.55 (dt, *J* = 14.6, 6.5 Hz, 1H, *H14*), 2.45 – 2.40 (m, 1H, *H26*), 2.36 (dt, *J* = 14.6, 7.6 Hz, 1H, *H14'*), 2.27 (s, 3H, COCH_3), 1.87 – 1.30 (m, 37H, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.62 (s, 3H, CCH_3), 1.48 (s, 3H, acetonide-CH_3), 1.44 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.31 (s, 6H, acetonide-CH_3 × 2), 1.29 – 1.10 (m, 23H, Bpin-CH_3 × 4, *n*-Hex-(CH_2)$_5$ and *H46'*), 1.05 – 1.00 (m, 1H, *H37'*), 0.96 (d, *J* = 6.9 Hz, 3H, H16CH_3), 0.90 (d, *J* = 6.7 Hz, 3H, H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.7, 160.0, 159.3, 149.5, 146.1, 136.9, 131.7, 131.2, 129.5, 129.4, 127.7, 124.8, 117.4, 114.0, 113.7, 101.7, 100.4, 100.3, 99.0, 98.9, 83.3, 81.4, 81.1, 80.1, 79.2, 78.1, 73.9, 73.4, 71.6, 71.1, 68.9, 68.5, 67.3, 66.6, 63.6, 55.5, 55.4, 39.4, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.5, 36.3, 36.1, 35.3, 34.5, 34.1, 33.0, 33.0, 33.0, 32.6, 32.0, 31.3, 30.3, 30.2, 29.9, 29.8, 28.6, 27.5, 26.5, 26.0, 25.2, 25.1, 25.0, 25.0, 24.9, 24.9, 23.9, 23.5, 22.8, 21.4, 21.2, 19.9, 19.9, 14.3, 14.1, 13.7, 5.8, 4.7; **HRMS** (ESI) m/z calcd for $C_{89}H_{141}BO_{18}$ $[M+Na]^+$: 1532.0103, found 1532.0114.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-6-((2*R*,3*S*,4*E*,6*E*)-8-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-2,2-dimethyl-6-((*E*)-3-oxobut-1-en-1-yl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyl-3-((triethylsilyl)oxy)octa-4,6-dien-2-yl)-2-hydroxy-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (96)

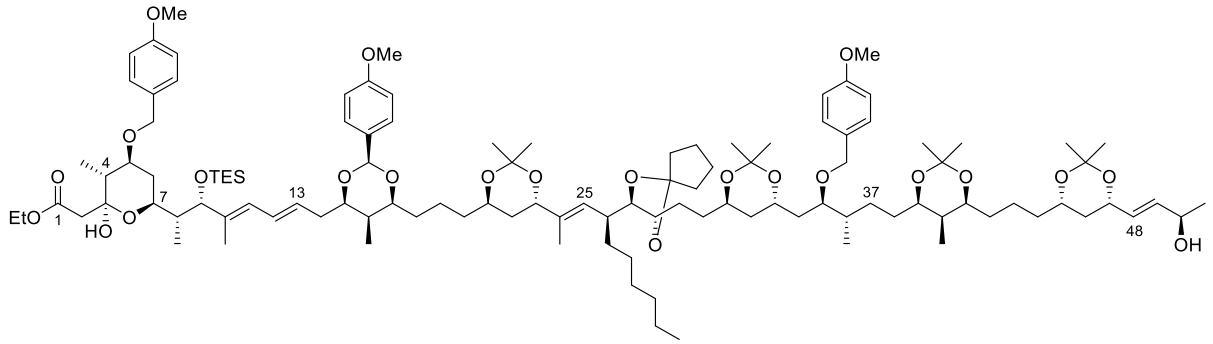


To a solution of iodide **2b** (5.1 mg, 0.0075 mmol, 1.1 eq.), boronic ester **95** (10.3 mg, 0.0068 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (3.1 mg, 0.0027 mmol, 0.4 eq.) in degassed anhydrous[li,liii] THF (850 µL) under argon was added dropwise a solution of Tl_2CO_3 (5.7 mg, 0.0122 mmol, 1.8 eq.) in degassed[li] water (270 µL) over 5 minutes. (Note: Tl_2CO_3 was dissolved in degassed water under argon and stirred for 30 minutes prior to addition to the reaction mixture.) The reaction mixture was stirred at room temperature overnight. It was diluted with diethyl ether, water was added, and the mixture was extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/ethyl acetate = 17/3 → 4/1) to afford the title compound (11.3 mg, 0.0058 mmol, 86%) as a yellow oil.

$[\alpha]_D^{25}$ +3.2 (c = 0.5, $CHCl_3$); **R_f** 0.26 (pentane/ethyl acetate = 7/3); **IR** (thin film): ν_{max}/cm^{-1} 3587, 2942, 2855, 1717, 1683, 1616, 1517, 1465, 1379, 1334, 1303, 1249, 1222, 1199, 1064, 1038, 825, 761; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.25 – 7.23 (m, 4H, Ar*H*), 6.88 – 6.85 (m, 6H, Ar*H*), 6.69 (dd, *J* = 16.0, 4.5 Hz, 1H, *H48*), 6.35 (dd, *J* = 15.0, 10.9 Hz, 1H, *H12*), 6.27 (dd, *J* = 16.0, 1.6 Hz, 1H, *H49*), 5.99 (d, *J* = 10.9 Hz, 1H, *H11*), 5.78 (dt, *J* = 15.0, 7.3 Hz, 1H, *H13*), 5.49 (s, 1H, C*H*PMP), 5.06 (d, *J* = 10.1 Hz, 1H, *H25*), 4.56 – 4.52 (m, 1H, *H47*), 4.54 (d, *J* = 10.9 Hz, 1H, OCH_2Ar), 4.48 (d, *J* =

10.7 Hz, 1H, OC*H*$_2$Ar), 4.45 (d, *J* = 1.8 Hz, 1H, O*H*), 4.33 (d, *J* = 10.9 Hz, 2H, OC*H'*$_2$Ar), 4.33 (d, *J* = 10.7 Hz, 2H, OC*H'*$_2$Ar), 4.20 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.15 (dd, *J* = 9.3, 6.2 Hz, 1H, *H23*), 4.06 – 4.00 (m, 1H, *H33*), 3.92 – 3.87 (m, 2H, *H15* and *H45*), 3.84 – 3.75 (m, 7H, *H9*, *H17*, *H21*, *H27*, *H28*, *H39* and *H41*), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.73 – 3.68 (m, 2H, *H7* and *H31*), 3.52 (dt, *J* = 9.9, 3.0 Hz, 1H, *H35*), 3.48 (td, *J* = 10.5, 4.3 Hz, 1H, *H5*), 2.71 (d, *J* = 14.7 Hz, 1H, *H2*), 2.52 (dt, *J* = 14.3, 7.3 Hz, 1H, *H14*), 2.46 (d, *J* = 14.7 Hz, 1H, *H2'*), 2.45 – 2.39 (m, 1H, *H26*), 2.29 (dt, *J* = 14.3, 7.3 Hz, 1H, *H14'*), 2.27 (s, 3H, COC*H*$_3$), 1.88 – 1.31 (m, 41H, *H4*, *H6*, *H8*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(C*H*$_2$)$_4$), 1.65 (s, 3H, CC*H*$_3$), 1.62 (s, 3H, CC*H*$_3$), 1.48 (s, 3H, acetonide-C*H*$_3$), 1.44 (s, 3H, acetonide-C*H*$_3$), 1.41 (s, 3H, acetonide-C*H*$_3$), 1.39 (s, 3H, acetonide-C*H*$_3$), 1.34 (s, 3H, acetonide-C*H*$_3$), 1.33 (s, 3H, acetonide-C*H*$_3$), 1.31 (s, 6H, acetonide-C*H*$_3$ × 2), 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.29 – 1.12 (m, 11H, *H46'* and *n*-Hex-(C*H*$_2$)$_5$), 1.05 (d, *J* = 6.6 Hz, 3H, H4C*H*$_3$), 1.04 – 1.00 (m, 1H, *H37'*), 0.97 (d, *J* = 6.8 Hz, 3H, H16C*H*$_3$), 0.94 (d, *J* = 6.9 Hz, 3H, H8C*H*$_3$), 0.92 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H36C*H*$_3$), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-C*H*$_3$), 0.82 (d, *J* = 6.8 Hz, 3H, H40C*H*$_3$), 0.55 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 198.6, 172.9, 159.9, 159.3, 159.3, 146.1, 136.9, 136.7, 131.9, 131.2, 131.1, 129.4, 129.4, 129.4, 129.2, 128.7, 127.6, 127.3, 124.9, 117.4, 113.9, 113.9, 113.7, 101.5, 100.3, 100.3, 99.0, 98.9, 98.8, 81.4, 81.2, 80.9, 80.6, 79.2, 78.1, 77.2, 73.9, 73.4, 71.6, 71.1, 70.9, 68.9, 68.5, 67.5, 67.3, 66.6, 63.6, 60.9, 55.4, 55.4, 55.4, 45.4, 42.9, 41.3, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.5, 36.5, 36.3, 36.1, 35.4, 35.2, 34.5, 34.2, 33.0, 33.0, 32.6, 32.0, 31.3, 30.3, 30.2, 29.8, 29.7, 28.6, 27.5, 26.5, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 22.8, 21.4, 21.2, 19.9, 19.9, 14.4, 14.3, 14.1, 13.6, 12.5, 11.6, 9.9, 7.0, 5.8, 5.0, 4.7; **HRMS** (ESI) m/z calcd for $C_{113}H_{178}O_{23}Si$ $[M+Na]^+$: 1954.2420, found 1954.2419.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2-hydroxy-6-((2*R*,3*S*,4*E*,6*E*)-8-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*R*,3*S*)-3-(2-((4*R*,6*S*)-6-((2*R*,3*S*)-5-((4*R*,5*R*,6*S*)-6-(3-((4*S*,6*S*)-6-((*R*,*E*)-3-hydroxybut-1-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)-3-methylpentyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methyl-3-((triethylsilyl)oxy)octa-4,6-dien-2-yl)-4-((4-methoxybenzyl)oxy)-3-methyltetrahydro-2H-pyran-2-yl)acetate (97)

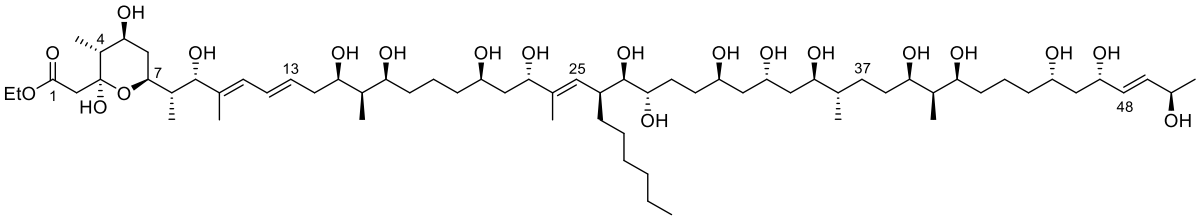


To a solution of enone **96** (11.3 mg, 0.0058 mmol, 1.0 eq.) in anhydrous THF (290 µL) at –20 °C under argon was added (*S*)-(–)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 17 µL, 0.0174 mmol, 3.0 eq.) dropwise, followed by dropwise addition of borane dimethyl sulfide complex (0.5 M in THF, 87 µL, 0.0435 mmol, 7.5 eq.). The reaction mixture was stirred at –20 °C for 1.5 hours. It was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 99/1) to afford the title compound (6.7 mg, 0.0035 mmol, 60%, >20:1 *dr*) as a colourless oil.

R_f 0.41 (CH_2Cl_2/MeOH = 19/1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.24 (d, *J* = 8.6 Hz, 4H, Ar*H*), 6.88 – 6.85 (m, 6H, Ar*H*), 6.35 (dd, *J* = 15.1, 10.9 Hz, 1H, *H12*), 5.99 (d, *J* = 10.9 Hz, 1H, *H11*), 5.81 – 5.75 (m, 2H, *H13* and *H48*), 5.66 (ddd, *J* = 15.6, 6.0, 1.2 Hz, 1H, *H49*), 5.49 (s, 1H, C*H*PMP), 5.05 (d, *J* = 10.1 Hz, 1H, *H25*), 4.54 (d, *J* = 10.9 Hz, 1H, OC*H*$_2$Ar), 4.48 (d, *J* = 10.8 Hz, 1H, OC*H*$_2$Ar), 4.45 (d, *J* = 1.8 Hz, 1H, O*H*), 4.37 – 4.30 (m, 4H, *H47*, *H50* and OC*H'*$_2$Ar × 2), 4.20 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.15 (dd, *J* = 9.4, 6.2 Hz, 1H, *H23*), 4.05 – 4.00 (m, 1H, *H33*), 3.91 – 3.75 (m, 9H, *H9*, *H15*, *H17*, *H21*, *H27*, *H28*, *H39*, *H41* and *H45*), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.72 – 3.67 (m, 2H, *H7* and *H31*), 3.54 – 3.51 (m, 1H,

H35), 3.48 (td, *J* = 10.5, 4.4 Hz, 1H, *H5*), 2.71 (d, *J* = 14.7 Hz, 1H, *H2*), 2.52 (dt, *J* = 14.4, 7.3 Hz, 1H, *H14*), 2.46 (d, *J* = 14.7 Hz, 1H, *H2'*), 2.45 – 2.39 (m, 1H, *H26*), 2.29 (dt, *J* = 14.4, 7.3 Hz, 1H, *H14'*), 1.88 – 1.31 (m, 41H, *H4*, *H6*, *H8*, *H16*, *H18*, *H19*, *H20*, *H22*, *H29*, *H30*, *H32*, *H34*, *H36*, *H37*, *H38*, *H40*, *H42*, *H43*, *H44*, *H46* and cyclopent-(CH_2)$_4$), 1.65 (s, 3H, CCH_3), 1.62 (s, 3H, CCH_3), 1.47 (s, 3H, acetonide-CH_3), 1.42 (s, 3H, acetonide-CH_3), 1.41 (s, 3H, acetonide-CH_3), 1.39 (s, 3H, acetonide-CH_3), 1.34 (s, 3H, acetonide-CH_3), 1.33 (s, 3H, acetonide-CH_3), 1.30 (s, 6H, acetonide-CH_3 × 2), 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.28 (d, *J* = 6.5 Hz, 3H, H50CH_3), 1.27 – 1.11 (m, 11H, *H46'* and *n*-Hex-(CH_2)$_5$), 1.05 (d, *J* = 6.6 Hz, 3H, H4CH_3), 1.04 – 1.00 (m, 1H, *H37'*), 0.97 (d, *J* = 6.8 Hz, 3H, H16CH_3), 0.94 (d, *J* = 6.9 Hz, 3H, H8CH_3), 0.92 (t, *J* = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H36CH_3), 0.87 (t, *J* = 7.0 Hz, 3H, *n*-Hex-CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, H40CH_3), 0.54 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.9, 159.9, 159.3, 159.3, 136.9, 136.7, 135.4, 131.9, 131.3, 131.1, 130.6, 129.4, 129.4, 129.2, 128.7, 127.6, 127.3, 124.9, 117.4, 114.0, 113.9, 113.7, 101.5, 100.3, 100.3, 98.9, 98.8, 98.8, 81.4, 81.2, 81.0, 80.6, 79.2, 78.1, 77.3, 73.9, 73.5, 71.6, 71.1, 70.9, 69.6, 68.9, 68.4, 67.5, 67.3, 66.6, 63.6, 60.9, 55.4, 55.4, 55.4, 45.4, 43.0, 41.3, 39.4, 38.0, 37.8, 37.5, 37.4, 37.1, 36.8, 36.6, 36.5, 36.1, 35.3, 35.2, 34.5, 34.2, 33.0, 33.0, 32.6, 32.0, 31.3, 30.4, 30.3, 29.8, 29.7, 29.5, 28.6, 26.5, 26.0, 25.2, 25.1, 25.1, 25.0, 23.9, 23.5, 22.8, 21.4, 21.2, 20.0, 19.9, 14.4, 14.3, 14.1, 13.6, 12.5, 11.6, 9.9, 7.0, 5.8, 5.0, 4.7; **HRMS** (ESI) m/z calcd for $C_{113}H_{180}O_{23}Si$ $[M+Na]^+$: 1956.2577, found 1956.2571.

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-6-((2*S*,3*S*,4*E*,6*E*,9*R*,10*R*,11*S*,15*R*,17*S*,18*E*,20*S*,21*R*,22*S*,25*R*,27*S*,29*R*,30*S*,33*R*,34*R*,35*S*,39*S*,41*S*,42*E*,44*R*)-20-hexyl-3,9,11,15,17,21,22,25,27,29,33,35,39,41,44-pentadecahydroxy-4,10,18,30,34-pentamethylpentatetraconta-4,6,18,42-tetraen-2-yl)-2,4-dihydroxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (1')



(1) To a solution of PMB ether **97** (6.7 mg, 0.0035 mmol, 1.0 eq.) in CH_2Cl_2 (230 µL) and pH 7 buffer (1 M potassium phosphate buffer, 12 µL) at 0 °C was added DDQ (4.0 mg, 0.0175 mmol, 5.0 eq.). The reaction mixture was stirred at 0 °C under argon for 1.5 hours. It was quenched with saturated aqueous $NaHCO_3$, stirred until it became a clear solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 99/1 → 98/2) to afford the PMB-deprotected compound (2.9 mg; ~7:1 mixture with the TES-deprotected product). *(2)* The PMB-deprotected compound (2.9 mg, 0.017 mmol, 1.0 eq.) was dissolved in MeOH (600 µL) and THF (300 µL), and 0.1 M aqueous HCl (600 µL) was added. The reaction mixture was stirred at room temperature for 14 hours. It was quenched with saturated aqueous $NaHCO_3$ (100 µL) and concentrated using a stream of nitrogen. The residue was purified by reversed phase C18 column chromatography (water/acetonitrile = 19/1 → 13/7) to afford the title compound (0.9 mg, 0.00073 mmol, 21% over two steps) as a white solid.

R_f 0.42 (ethyl acetate/MeOH = 7/3); **^{1}H NMR** (500 MHz, MeOD): δ 6.38 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.07 (d, *J* = 10.9 Hz, 1H), 5.77 (dt, *J* = 15.0, 7.4 Hz, 1H), 5.72 (dd, *J* = 15.4, 5.8 Hz, 1H), 5.63 (ddd, *J* = 15.4, 6.6, 1.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 4.28 – 4.13 (m, 6H), 4.01 – 4.05 (m, 1H), 3.92 (d, *J* = 7.0 Hz, 1H), 3.85 – 3.68 (m, 7H), 3.60 (td, *J* = 10.8, 4.7 Hz, 1H), 3.51 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.36 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.33 – 3.32 (m, 1H), 2.74 (d, *J* = 14.3 Hz, 1H), 2.55 (d, *J* = 14.3 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.34 (t, *J* = 7.0 Hz, 1H), 1.79 – 1.08 (m, 49H), 1.67 (s, 3H), 1.65 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.98 – 0.85 (m, 15H); **HRMS** (ESI) m/z calcd for $C_{66}H_{122}O_{20}$ $[M+Na]^+$: 1257.8422, found 1257.8416.

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