Towards the Total Synthesis of Stambomycin D

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Doctor of Philosophy

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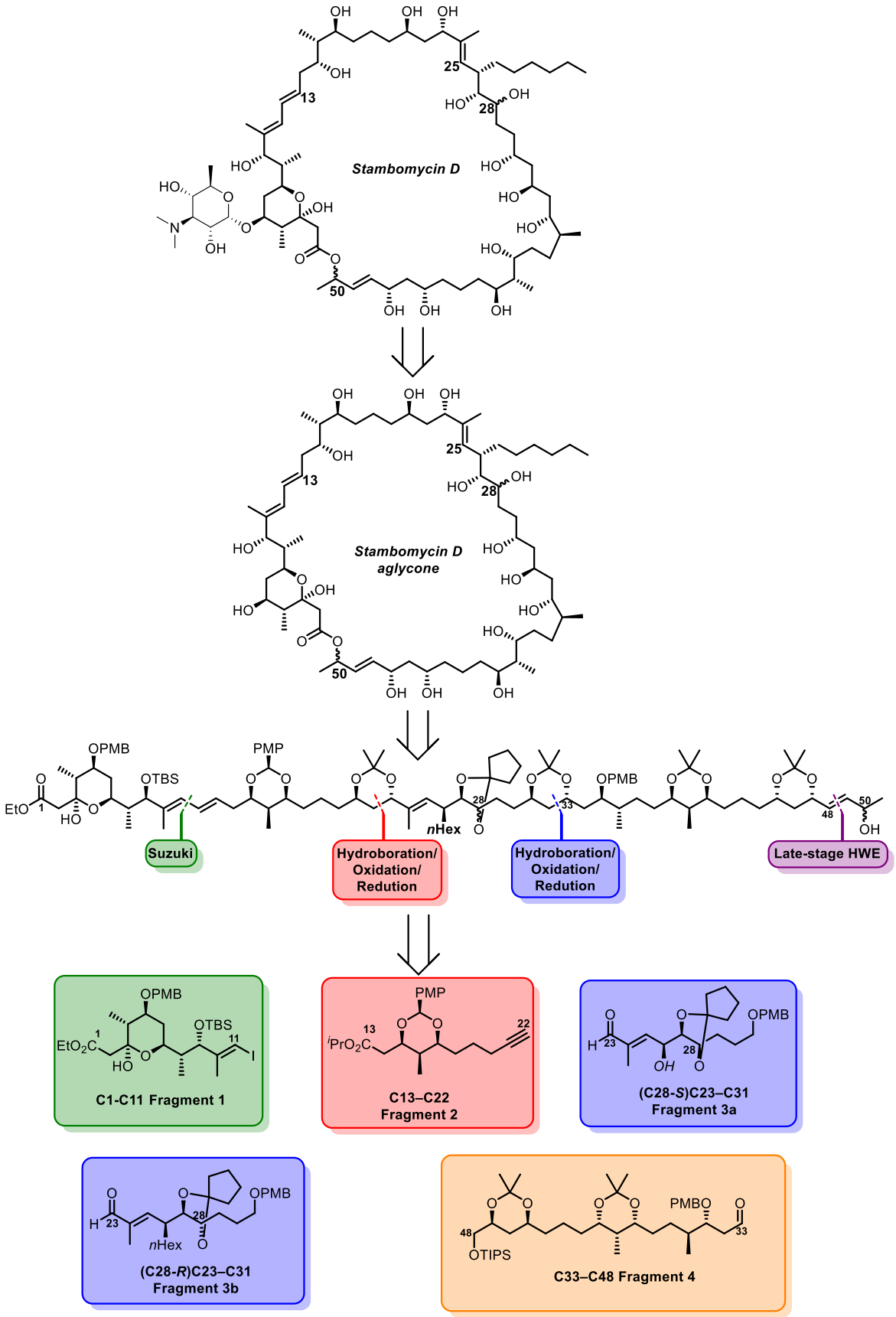
Stambomycin D, a 51-membered glycosylated macrolide, was discovered by a genome mining approach, and the predicted planar structure confirmed by NMR spectroscopic analysis. However, the sequence analysis-predicted stereocenters (except C28 and C50) remain to be validated. This thesis discusses efforts to achieve a chemical synthesis of stambomycin D to fully determine its stereochemistry, including the 'unpredictable' C28 and C50 stereocenters. To begin with, the stambomycin D aglycone was disconnected at C50 to reveal acyclic C1–C51 fragments, which could be divided into five smaller fragments (C1–C11, C13–C22, C23–C31 (1,3-*anti* or *syn* diol at C27 and C28) and C33–C48 fragments) (Scheme 1). The early chapters discuss the synthesis of these fragments as well as deprotection studies, and the later chapters focus on the union of these fragments. Regarding the order of combination, the C13–C22 fragment is coupled to the C23–C31 (1,3-*anti* diol at C27 and C28, this thesis only discusses the *anti* diol diastereomer) first to construct the C13–C31 framework. A deprotection study was successfully executed on this fragment. The subsequent union of the C13–C32 fragment and C33–C48 fragment gives the C13–C48 fragment, for which deprotection exploration was also carried out. Through these deprotection studies, we not only supported the sequence analysis-predicted assignment of most of the stereocenters of stambomycin D, but also paved the way for the deprotection of the acyclic C1–C51 fragment and ultimately synthesis of the entire macrolide.



Scheme 1. Retrosynthesis of stambomycin D.

Acknowledgements

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Finally, a big thank to my parents who fund me studying here. I am really grateful to my parents for their unlimited care, support and encouragement. Thank my parents for listening to my complaints and giving me good advice whenever I encounter difficulties. I wouldn't be here without them.

List of abbreviations

ACP	Acyl carrier protein
aq.	Aqueous
AT	Acyltransferase
BAIB	(Diacetoxyiodo)benzene
Boc	*tert*-Butoxycarbonyl
br	Broad
brsm	Based on starting material
CoA	Coenzyme A
COSY	Correlation Spectroscopy
CSA	Camphorsulfuric acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide

dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionisation
Hex	*n*-Hexane
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	Half-maximal inhibitory concentration
IR	Infrared
KR	Ketoreductase
KS	Ketosynthase
LC-MS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamine
MS	Molecular sieves
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOSEY	Nuclear Overhauser Effect Spectroscopy
pin	Pinacol

PKS	Polyketide synthase
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
Red-Al®	Sodium bis(2-methoxyethoxy)aluminum dihydride
R*f*	Retention factor
rt	Room temperature
sat.	Saturated
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TLC	Thin layer chromatography

w/v	Weight/volume

Contents

Chapter 1: Introduction

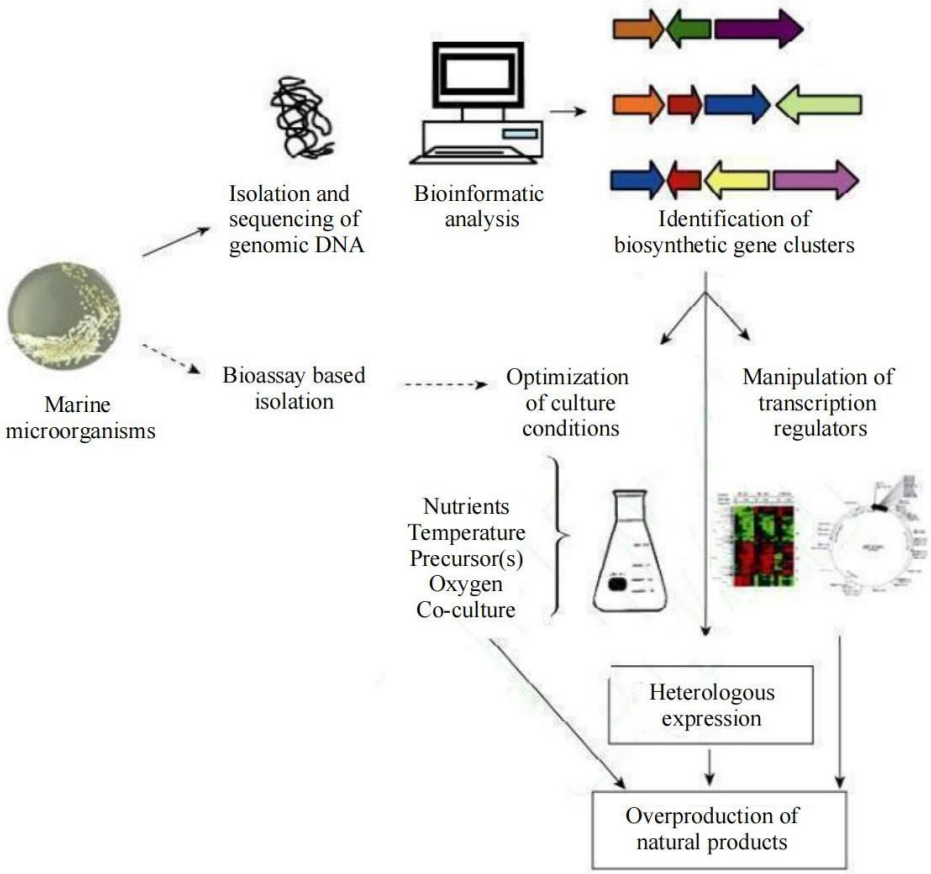
Polyketides are a large group of natural products and a class of secondary metabolites produced by eukaryotes and prokaryotes, coming from a wide variety of sources and including structures such as macrolides, tetracyclines, anthracyclines and polyethers. Polyketides are synthesized from short chain acyl units through successive Claisen-like condensations and the process is catalyzed by polyketide synthase (PKS), similar to fatty acid biosynthesis. Many polyketides are clinically important, with promising antioxidant, antitumor, antibacterial, antimicrobial, anti-inflammatory, antiparasitic and immunosuppressive properties[1,2], leading to the emergence of plenty of useful drugs such as lovastatin[3] (a blood lipid lowering drug) and erythromycin[4] (a widely used antibiotic).

In the past few decades, the discovery of polyketides has mostly adopted the conventional method of screening environmental microbial activities, involving microbial isolation and purification, massive culture, culture collection, target compound extraction, identification, development and utilization. However, the traditional discovery method has many disadvantages, for instance, compounds have a high probability of being discovered repeatedly. In addition, the broth formulation can result in low production of active secondary metabolites. Furthermore, some microorganisms grow slowly in a laboratory environment or cannot be cultivated under existing laboratory conditions. The advent of new genomic technology has greatly improved the limitations. Firstly, the bacteria that produce target active compounds can be found easily through gene-directed screening. Secondly, early identification and targeted elimination of repetitive compound-producing bacteria can be carried out, which saves time in structural analysis and the discovery of new compounds.

More importantly, the genome mining approach awakened many silent biosynthetic gene clusters which are expressed poorly, or not at all, under laboratory growth conditions, triggering the emergence of lots of structurally diverse polyketides with potent bioactivities. Stambomycins A-D[5] were discovered by such a genome-driven approach and this work will chemically synthesize stambomycin D and make comparsions on NMR data between the synthetic one and the natural one.

1.1 Genome mining approach to the discovery of natural products

Genome mining is the sequencing of the genomes encoding natural products and the use of bioinformatics to predict the natural products that may be produced. The gene cluster may then be further activated or expressed heterologously, and the target product isolated and identified. The method is efficient and is not affected by factors such as the concentration of the product in the organism and whether the target gene is expressed or not, thereby expanding the research scope of natural products. The first step of genome mining process is isolation and sequencing of the organism's genomic DNA, followed by bioinformatic analysis and structural prediction. The subsequent step is to seek for compounds produced by the organism based on the predicted structural information. If the expression of the compound is poor or the gene is not expressed at all, it is essential to activate the expression of the gene through a variety of methods such as optimization of culture conditions and overexpression of transcriptional activator genes, then find the compounds and identify the structure of the compounds (Scheme 1.1).



Scheme 1.1. The procedure of novel natural products discovery *via* genome mining.[6] (Dotted lines indicates the traditional natural product discovery procedure using activity-based screening)

Speaking of bioinformatics analysis and structure prediction, the information about type of enzyme–Catalyzed reactions, substrate specificity of the enzymes and specific functional groups, polarity, molecular weight and UV absorption of the final products of multi-enzyme–Catalyzed metabolic pathways can be inferred by comparing with the conserved sequences of known enzymes in various database. This guides the isolation and purification of natural products. purification of natural products. Gene function and compound structure prediction can be achieved by using BLAST, which is a database search program based on sequence similarity. To be specific, it's an effective tool to compare the

sequence under study with a library of DNA or protein sequences to identify the biological properties of this sequence and the possible function of the enzyme can be determined by the similarity of the amino acid sequence of the protein to other proteins of known function.

The synthesis of polyketides and non-ribosomal polypeptides were catalyzed by two classes of giant modular enzymes which are polyketide synthase (PKS) and non-ribosomal peptide synthase (NRPS) respectively. Certain rules have been found in the substrate recognition, molecular assemble and product release of these giant modular enzymes, which could be used to predict the structure of compounds. Thus, studies on these two types of compounds (polyketides and non-ribosomal polypeptides) has gained more popularity, including utilizing antiSMASH[7] and NP. Searcher[8] prediction tools. Newly developed prediction tools such as NRPSpredictor2[9] and NRPSsp[10] can be used to predict the products of non-ribosomal polypeptide gene clusters as well. The products predicted by different software may differ and the prediction of compound structure is not always correct[11] due to the limited knowledge of the specificity of enzyme function and the relationship between the spatial structure and the activity of the enzyme. Therefore, accurate gene function annotation and compound structure prediction require the development of more advanced bioinformatic analysis tools. Genome mining research has been carried out in a variety of microorganisms since the discovery of the non-ribosomal polypeptide coelichelin (Figure 1.1) by genome mining technology in 2000.[12]

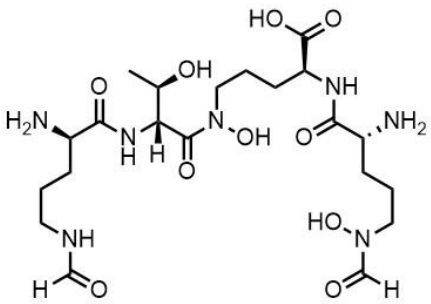


Figure 1.1. The structure of coelichelin.

Other natural products of discovered from *Streptomyces via* genome mining include holomycin, pyridomycin and chaxamycins A-D, however, there are still not many examples of genome mining of marine actinomycetes. The first marine actinomycete-derived compound is a polyene macrolactam compound salinilactam A[13] (Figure 1.2) and the gene cluster of this compound is up to 80 kb. Salinilactam A was isolated according to the unique UV absorption spectrum of polyene compounds and the discovery of the structure of the compound also facilitated the correct assemblage of the repeated sequence of PKS genes in the genome sequence.

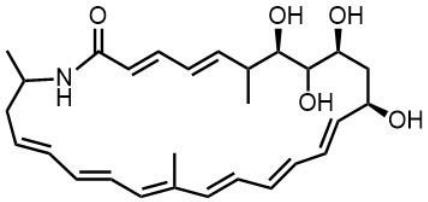


Figure 1.2. The structure of salinilactam A.

Norwegian scientists sequenced the genome of a marine strain of *Nocardia*, isolating the gene cluster of sulfur–Containing polypeptide antibiotics TP1161. Heterologous expression of this gene cluster in natural *Streptomyce*s was attempted but failed eventually.[14]

It brings difficulties to the subsequent fermentation and production of natural products since a few marine actinomycetes require special nutrient conditions such as high salinity to grow. Thus, it is of great significance to study the expression of gene clusters of marine actinomycete natural product in other hosts. It is worth pointing out that since some compounds may be sensitive to temperature, light or have low solubility and poor expression, and might also be produced at a very early stage of fermentation (such as thailandamine[15]), the prediction of their possible structures and properties through genome mining could offer good guidance for the following separation and purification and helps discover compounds which cannot be found by conventional methods.

The final product structure identification also requires the expression of the gene clusters since it is difficult for bioinformatic analysis to predict the structure of a compound with 100% accuracy. After obtaining information of possible synthetic products, if the gene or gene cluster which is interested in these products is expressed, the product can be obtained by optimizing the culture conditions or identified using genomisotope methods.[16] However, many gene clusters have low expression activity or even no expression. The expression of biosynthetic genes can be activated by optimizing the broth conditions and manipulating transcriptional regulatory genes.[11,17] In addition, heterologous expression in model strains with clear genetic background and easy genetic manipulation is also an effective and popular way to activate the expression of gene clusters in recent years.

Firstly, optimizing the culture conditions is one of the popular ways to promote the expression of gene clusters. The synthesis of some metabolites requires special nutritional conditions and the activation of these compounds needs to mimic special nutritional,

environmental and biological conditions, such as special carbon and nitrogen sources, high temperature, ultraviolet radiation, osmotic stress or co–Cultivation with other biological strains, etc. For example, the production of jadomycin B from *Streptomyce venezuelae* requires high temperature heat shock induction and the synthesis of various antibiotics such as streptomycin requires small signal molecule A-factor[18]. The growth of marine actinomycetes may require a certain salinity, higher PH, etc. For instance, some marine actinomycetes isolated from some laboratories need to grow in broths with pH up to 11.

Overexpression of some silent genes is also a commonly used approach to activate the expression of gene clusters. For example, discovery of stambomycins[5] in *Streptomyces ambofaciens* was achieved by overexpression of regulatory proteins of LuxR family. Although two–Component phylogenetic genes contained in the stambomycin biosynthetic gene clusters are also possible regulatory genes, placing these two genes under the regulation of a strong promoter and integrating them into the chromosome of the producer stain has not been found to activate the synthesis of stambomycins. It indicates that silent expression of regulatory proteins of LuxR family is critical for the regulation. A database search revealed that the LuxR family of regulatory protein genes are widely present in multiple biosynthetic gene clusters of *Streptomyces* antibiotics, suggesting that the expression of other silent genes can also be achieved in a similar manner.

Removal of transcriptional repressor proteins can also achieve the purpose of activating the expression of some compounds. For instance, *Streptomyces ambofaciens* contains the biosynthetic gene clusters of antibiotics of kinamycin family and removal of the gene encoding the transcriptional repressor protein Alpw of Tetr family could lead to the synthesis

of kinamycin antibiotics[19].

In addition to optimizing culture conditions as well as manipulating and regulating genes, heterologous expression is also an effective approach to awaken the expression of gene clusters and then obtain the product of these active natural product gene clusters. Some marine microorganisms grow slowly, or pure culture cannot be obtained under the existing technical conditions. As mentioned earlier, some strains require harsh fermentation conditions and some microbial genetic manipulation methods are imperfect or inefficient. As a consequence, the products of their biosynthetic gene clusters can be discovered through heterologous expression. For example, phenazine compounds have a number of activities including antibacterial, antitumor and anti-malaria. *Streptomyces tandae* contains biosynthetic gene clusters for phenazine compounds, whereas the formation of these phenazine compounds could not be detected in *Streptomyces tandae*. Saleh and coworkers[20] expressed the gene cluster in *Streptomyces coelicolor* M512 and successfully isolated phenazine compounds by adding a strong erythromycin resistance gene promoter ahead of the key gene.

The commonly used hosts for heterologous expression of actinomycete gene clusters are *Escherichia coli*, *Streptomyces coelicolor* and *Streptomyces albicans*[21] currently. The issue is that the same gene cluster often shows different expression levels in different hosts and the expression efficiency in different strains may vary greatly. What's more, there is no rule to follow in the selection of hosts and there is no method for directional selection of suitable hosts. In order to enhance the expression efficiency of natural product gene clusters, more heterologous expression hosts for actinomycete gene clusters should be developed and

the molecular mechanism of efficiency on different hosts expressing different antibiotics demands more exploration. Moreover, it is of importance to optimize heterologous expression hosts and heterologous expression vectors as well in terms of improving the expression efficiency of natural product gene clusters.

Apart from the genome mining technology, transcriptome mining technology gains more and more popularity. Genome mining technology analyzes all possible products of gene clusters but is not able to determine under what conditions these products can be produced. Transcriptome mining technology determines the transcription of gene clusters in certain broths and at a certain time point through the transcriptome analysis of cells in various media, proving more direct information for compounds discovery. In the study of *Sreptomyces flaveolus* DMS 9954[22], Medium V was selected for a time–Course analysis of the production of metabolites since *streptomyces flaveolus* produced the most metabolites in broths V. The mRNA samples of day 4 were reverse transcribed as the highest yields of metabolites on day 4 was observed, resulting in the formation of complementary DNA (cDNA). The cDNAs were screened by degenerate PCR and the biosynthetic genes of sanglifehrin A (Figure 1.3) were discovered.

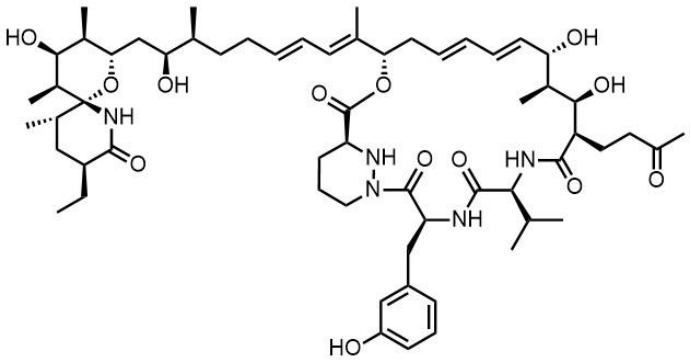


Figure 1.3. The structure of sanglifehrin A.

In addition, novel polyketide synthase and non-ribosomal peptide genes were also found. This shows that the primary advantage of transcriptome mining is that it facilitates the discovery of genes expressed under specific conditions. Secondly, the mycotrienin (MYC) antibiotics of the ansamycin family were found by removing these new genes and comparing with the wild type strain. Moreover, the biosynthetic gene cluster of mycotrienin (Figure 1.4) was further found, which reveals that the second advantage of transcriptome mining is to help discover transcriptionally active biosynthetic pathways associated with unknown natural products. Transcriptome mining combined with genome mining accelerates the correlation analysis of activation of silent gene clusters, offering a new powerful tool for the discovery of natural products.

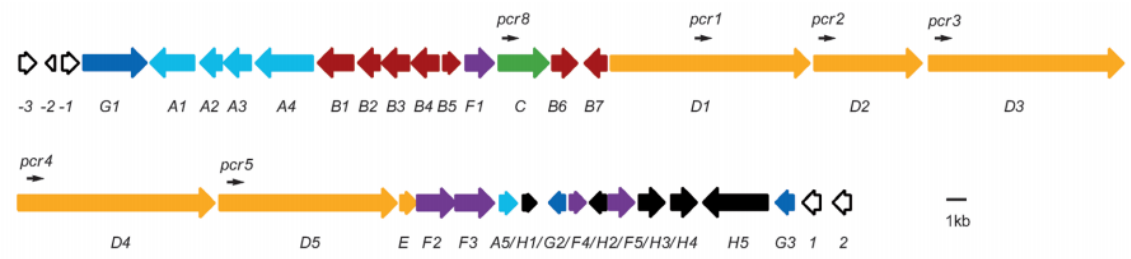


Figure 1.4. Organization of the MYC biosynthetic genes. Their deduced functions include PKS (yellow), NRPS (green), AHBA (red), CHC (light blue), regulation (dark blue), tailoring/ edition (purple), and unknown proteins (black). The cDNA-based PCR products (polyketide synthase (pks)1–5 and nonribosomal peptide synthetase (nrps)8) are shown at the corresponding positions.[21] (picture taken from reference 21)

The application of genome mining in plants is also of great significance. Plant stress resistance refers to the ability of plants to resist abiotic (drought) and biotic (pests) factors, however due to its complex genetics, improving plant stress resistance has been greatly limited. The rise of genome mining technology has played a pivotal role in the improvement

of plant stress resistance. This technology seeks to identify stress resistance genes and elucidates the regulatory role of secondary metabolites produced by stress resistance genes in the process of plant stress resistance, providing a broad prospect for crop stress resistance breeding. Devanna and coworkers[23] conducted allele mining of wild rice based on the gene *Pi*54 and found the gene *Pi*54*of*. Functional analysis shows that *Pi*54*of* has broad disease resistance property, and it could be implanted into rice *via* gene recombination technology to improve rice resistance to diseases and pests. Practice has proved that mining disease resistance genes is an important means of preventing biotic stress. Bession and coworkers[24] discovered hundreds of genes those which control lipid synthesis by mining the *Arabidopsis* genome, furnishing excellent genetic resources for improving the oil content of *Arabidopsis thaliana*.

Last but not the least, genome mining also plays a key role in the application of novel drug development. Taking advantage of genome mining to identify and develop potential new drugs refers to the analysis of genome sequences, screening and expressing target genes, followed by drug efficacy study to obtain new drug candidates, shortening the development time and reducing research expense. The Human Disease Research Center of Peking University has established a series of new technology platforms for human functional genome research based of the human functional genome. Through this platform, certain human genes have been screened and identified, uncovering the recombinant protein drugs PDCD5[25] and new anti-inflammatory peptide drugs CKLF1–C19[26]. Scherlach and coworkers[27] utilized bioinformatics software to compare gene sequence of *Aspergillus nidulans* with the known sequence that had been functionally annotated and predicted the

structure of the gene and the structure and properties of the compound it might produce through bioinformatics analysis, and finally discovered the antitumor compounds aspoquinolones A-D. With the development of genome mining technology, the research and development of novel drugs will also usher in a period of rapid development.

At present, a large number of natural products have not been discovered by humans but have the potential to be identified by biotechnology tools such as genome mining. Genome mining is able to uncover not only novel natural products and their congeners, but also their biosynthetic pathways, thereby improving the ability to discover new natural products from organisms. There are still many technical and practical problems that requires overcoming in genome mining although the potential of genome mining is huge. For example, tools for genetic manipulation and structural prediction of target compounds are scarce and the steps to separate and purify target compound from complex extracts are cumbersome. With the rapid development of natural product chemistry, molecular biology, genomics, biochemistry and high throughput genome sequencing technologies, genome mining can become more accessible, and the study of new secondary metabolites will enter an era of rapid development.

1.2 Isolation and structure elucidation of stambomycins

As members of actinomycetes, *Streptomyces ambofaciens* mainly produce two widely used antibiotics: the macrolide spiramycin and the pyrrole-amide congocidine[28]. Spiramycin has been used as an antibacterial as well as toxoplasmosis resistance agent for decades. Bioinformatics analysis of the partially sequenced chromosome of *Streptomyces*

ambofaciens disclosed the biosynthetic gene clusters of spiramycin and congocidine, revealing a great number of cryptic secondary metabolite biosynthetic gene clusters mostly located in the chromosome arms[29]. Despite some metabolic products of these gene clusters have been identified including desferrioxamines E/B, siderophores coelichelin and kanamycin angucyclinone antibiotics[30-32], most of the metabolites expressed by other cryptic biosynthetic gene clusters remain to be recognized and transcriptional analysis showed these gene clusters are not expressed under laboratory growths conditions.

Genome mining of *Streptomyces ambofaciens* by Challis and co-workers identified the macrolide antibiotics stambomycins[5] which exhibited potent antitumor activity; the gene cluster is up to 150 kb in size. The researchers achieved the activation of the gene cluster by overexpressing the LuxR family regulatory proteins, since the gene cluster was not expressed under laboratory conditions. It was also found that the structure predicted through bioinformatics analysis is incomplete. The biosynthesis of the stamobomycins possesses a new mechanism including the addition mechanism of hexyl/hepylmalonyl–CoA extension units, and the mechanism of hydroxylation of polyketide chains.

To be specific, the Challis group[5] turned their attention to a large cryptic type I modular polyketide synthase (PKS) gene cluster that is in the right arm of *Streptomyces ambofaciens* chromosome and consists of 25 genes (9 of which encode PKSs) and spans up to 150 kb. Through this genome mining approach, they discovered the 51-membered macrolide stambomycins A-D that are metabolites of the cryptic type I modular PKS gene cluster. As the gene cluster was not expressed under laboratory conditions, they achieved the expression of this biosynthetic genes of stambomycins by the constitutive expression of a regulatory

gene in the cluster, which encodes a protein similar to large ATP binding of the LuxR (LAL) family proteins. It was also found that the structure predicted through bioinformatics analysis is incomplete. The biosynthesis of the stambomycins possesses a new mechanism including the addition mechanism of hexyl/hepylmalonyl-CoA extension units, and the mechanism of hydroxylation of polyketide chains, which will be discussed further later. Besides, they emphasized genes encoding LuxR regulators within a great number of cryptic biosynthetic gene clusters in actinomycete genomes were identified by database searches and constitutive expression of such activators has become a powerful and effective way to discover more novel natural products.

Among the cryptic putative biosynthetic gene clusters, one cluster located at about 500 kb from the right end of the linear chromosome encompasses nine genes, which encoded the putative type I modular PKSs and are responsible for the biosynthesis of polyketides. The other sixteen genes, interspersed with the nine PKS genes (Figure 1.5), played different roles and show diverse functions in the biosynthesis of the stambomycins such as regulation, resistance flank, D-mycaminose biosynthesis, D-mycaminose attachment, polyketide hydroxylation, precusor biosynthesis and PKS editing.

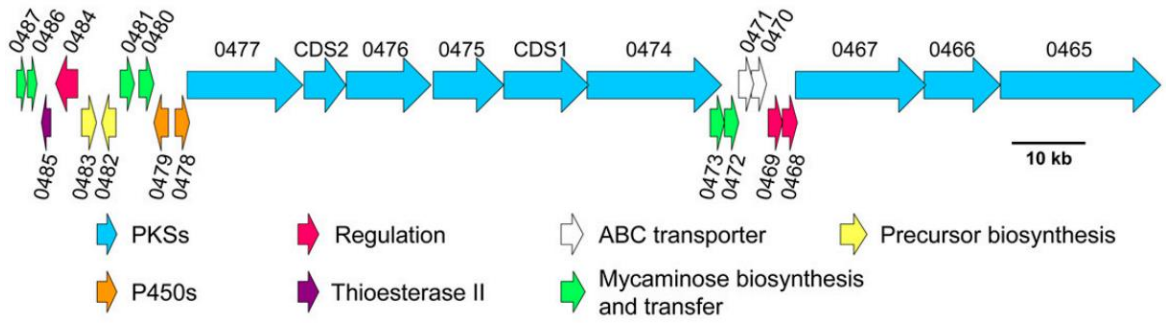


Figure 1.5. Organization of stambomycin biosynthetic gene cluster.[5] (picture taken from reference 5)

The flanking genes *samR0464* is associated with the formation of endoribonuclease and *samR0488* is assumed to encode a "cold-shock" DNA binding protein. Neither participate in the biosynthesis of stambomycins. Consequently, the starting and ending points of the biosynthetic gene cluster were considered to be *samR0465* and *samR0487* respectively based on the sequence comparisons, and the entire gene cluster contains 25 genes that span 150 kb, making it one of the largest polyketide biosynthetic gene clusters described to date. Furthermore, the PKSs contain 25 modules and 112 enzymatic domains (Figures 1.6 and 1.8), as identified through sequence analysis of the PKSs *via* SEARCHPKS program[33].

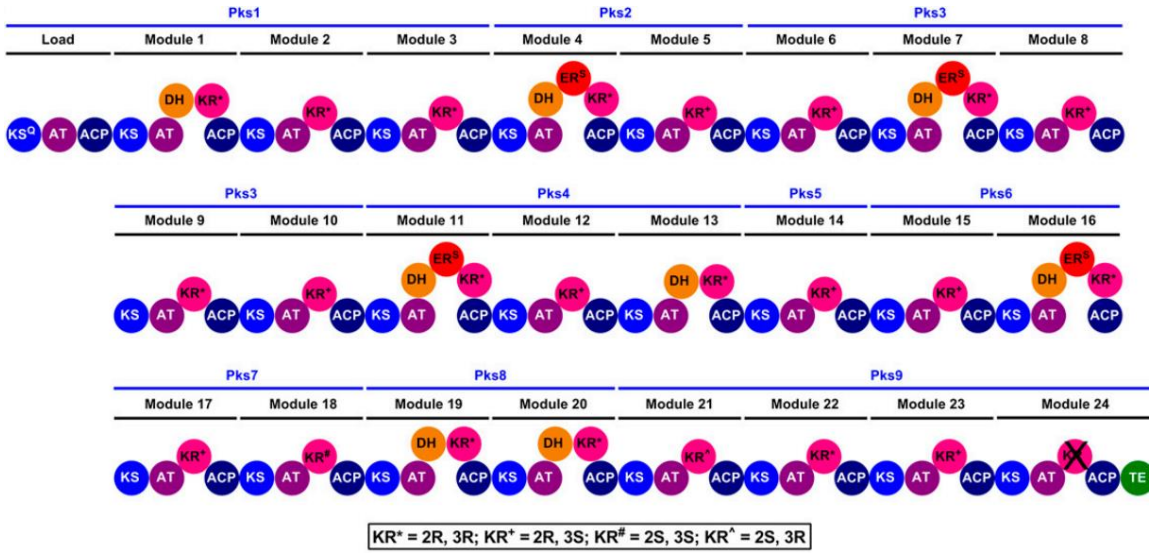


Figure 1.6. Module and domain organization of the PKS encoded by the biosynthetic gene cluster of stambomycins.[5] (picture taken from reference 5)

The meaning of each domain is as follows: ACP, acyl carrier protein; AT, acyltransferase; DH, dehydratase; KR*, ketoreductase predicted to generate a 2R, 3R-acyl thioester intermediate; KR^{+}, ketoreductase predicted to generate a 2R, 3S-acyl thioester intermediate; $KR^{\#}$, ketoreductase predicted to generate a 2S, 3S-acyl thioester intermediate;

KR^, ketoreductase predicted to generate a 2S, 3R-acyl thioester intermediate; KS, *β*-ketoacyl synthase; KS^Q, *β*-ketoacyl synthase in which the active site cysteine residue is replaced by glutamine; TE, thioesterase; ERR, enoyl reductase predicted to generate a 2R acyl thioester intermediate; ERS, enoyl reductase predicted to generate a 2S acyl thioester intermediate. The ketoreductase (KR) domain residing in the last module is non-functional as the tyrosine and asparagine residues of the catalytic triad are absent[34], whereas the rest all own their functional active sites.

Among the nine polyketide biosynthetic genes encoding putative type I modular PKSs, two genes *samR0467* and *samR0474* control the initiation and termination of polyketide chain assembly, since N terminus of *samR0467* possesses a KS^Q domain and C terminus of *samR0474* possesses a TE domain separately[35,36]. The remaining seven genes were proposed to follow the order of PKS genes in the cluster in the process of polyketide chain assembly (Figure 1.5). The product of PKSs is formed from sixteen molecules of malonyl–CoA, eight molecules of methylmalonyl–CoA and one molecule of an unknown extender unit, which is loaded by the AT13 domain[33,37] through sequence analysis of AT domain in each module. In addition, one of eight molecules of methylmalonyl–CoA is utilized as the starter unit of propionyl. The planar structure of the fully assembled polyketide chain attached to the ACP domain in the last module of the PKS was predicted by above-mentioned sequence analysis of AT domains and putative *β*–Carbon-processing domains presented in each module, but with an ambiguity at C26 substitution (Figures 1.7 and 1.8).

Figure 1.7. The predicted planar structure of the fully assembled polyketide chain.[5]

(picture taken from reference 5)

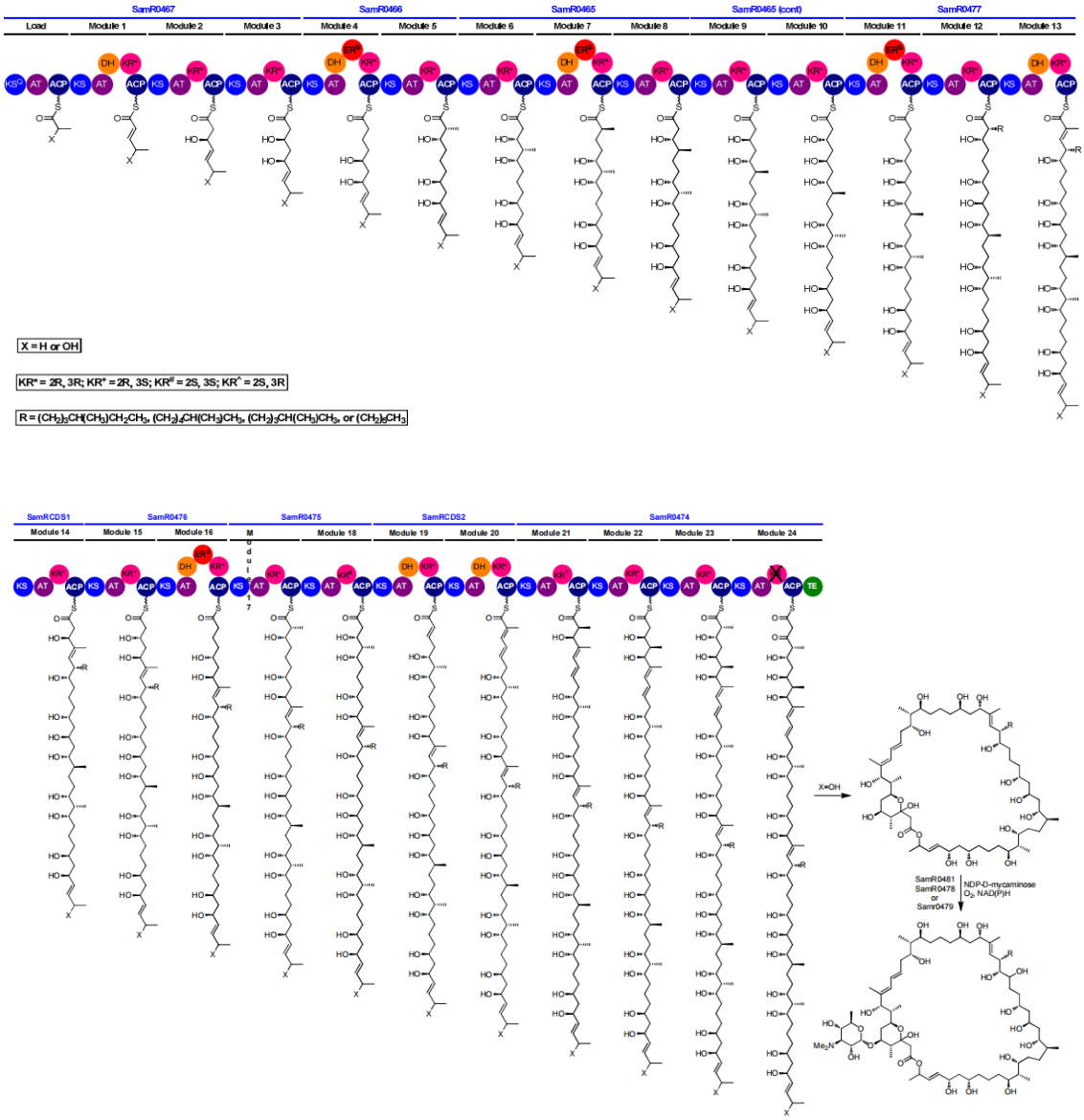


Figure 1.8 Stambomycins biosynthetic pathway.[5] (picture taken from reference 5)

The reason why the structure of the sidechain at C26 could not be predicted is that the nature of the substrate of the AT domain in module 13 could not be deduced from sequence comparisons. Atoms colored in blue and red derive from malonyl–CoA and methylmalonyl–CoA respectively. Atoms colored in purple represents unknown structure of malonyl–CoA derivative. It is worth mentioning that KR domains control the stereocenters of the α and β carbons and the ER domains can only control the α carbon stereocenters in the intermediates attached to each module of the PKS. Thereby, the stereochemistry of the intermediates was predicted by sequence analysis of KR and ER domains apart from the stereochemistry of the alcohols at C28 and C50, which were introduced after the polyketide chain assembly finished in the last module of the PKS and are of non-PKS origin.[38] The hydroxyl group attached to C28 and the oxygen atom at C50 were proposed to derive from cytochrome P450–Catalyzed hydroxylation of the polyketide chain, rather than keto reduction during polyketide chain assembly even if stambomycins PKS contains a C-terminal TE domain normally used to catalyze macrolactone formation. This is a novel mechanism for the formation of the macrolactone in polyketide biosynthesis. The cytochrome P450s are encoded by *samR0478* and *samR0479* genes and are normally used to catalyze post-PKS hydroxylation reactions.[39] Moreover, the stereochemistry of C28 and C50 stereocenters is not predictable by analysis of cytochrome P450.

Constitutive overexpression of the samR0484 gene triggers the expression of the PKS genes. To identify the metabolites of the gene cluster, liquid chromatography-electrospray ionization-time of flight-mass spectrometry (LC-ESI-TOF-MS) was used to analyze the supernatant and the mycelium extracts of the ATCC/pIB139 and ATCC/OE484 strains *via*

comparative metabolic profiling. Two major products were fund in methanolic mycelial extracts of the ATCC/OE484 strain whereas the ATCC/pIB139 strain did not contain these two products, having molecular formulas $C_{73}H_{133}NO_{22}$ (stambomycin A/B) and $C_{72}H_{131}NO_{22}$ (stambomycin C/D) separately (Figure 1.9). In order to confirm these metabolites were the products of the cryptic putative gene cluster, Challis group substituted the *samR0467* gene of ATCC/OE484 strain by a kanamycin resistance cassette, and then did not find the production of the compounds through LC-ESI-TOF-MS analysis methanolic mycelial extracts of ATCC/OE484 strain. Apart from the replacement of samR0467 gene, they also found that inactivation of the *samR0481* gene which encodes the aglycosyl transferase was not able to produce the compounds either. Instead, it produced the corresponding aglycones without the *β*-D-mycaminose branch according to the LC-ESI-TOF-MS analysis (Figure 1.10). Purification of these novel compounds from mycelial extracts of the ATCC/OE484 was carried out by semipreparative HPLC.

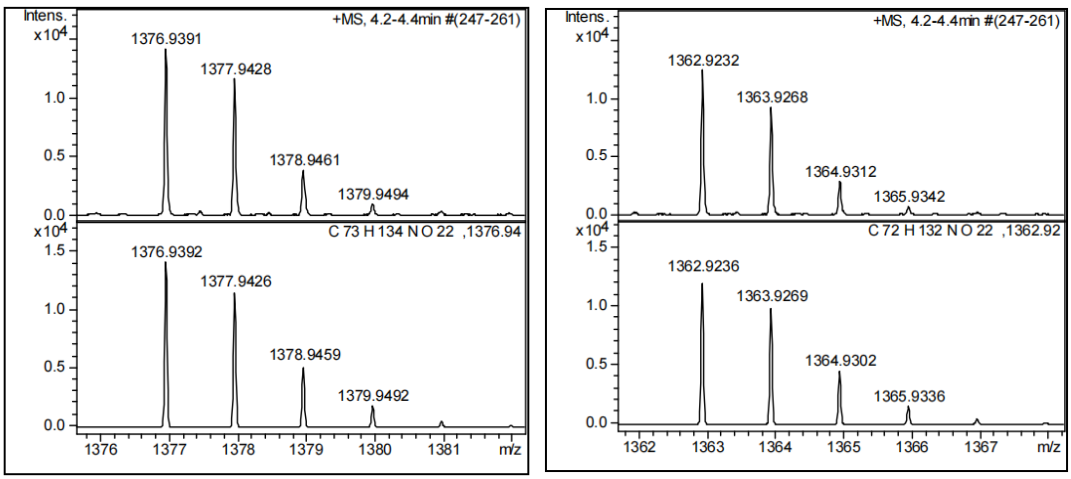


Figure 1.9. High resolution mass spectrometry analysis of stambomycin A/B (left) and stambomycin C/D (right).[5] (picture taken from reference 5)

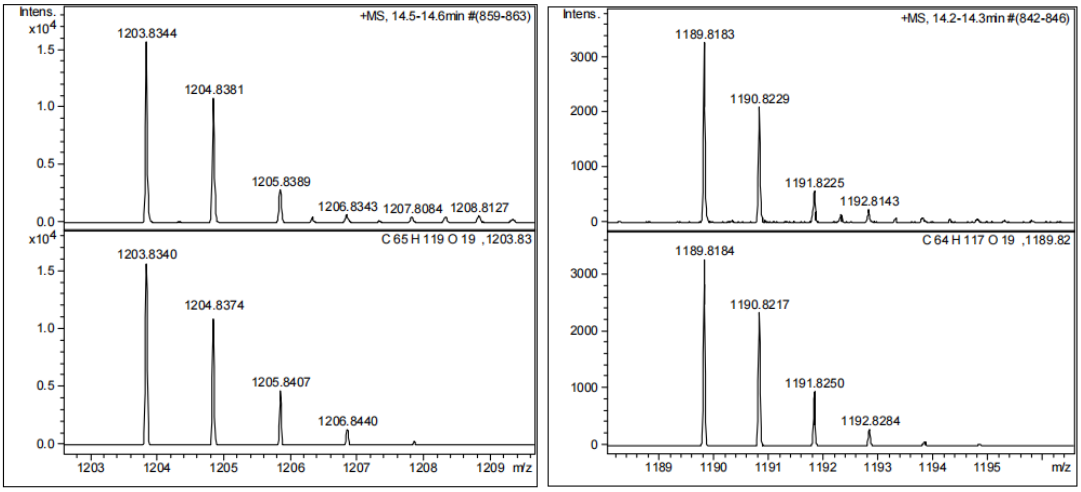


Figure 1.10. High resolution mass spectrometry analysis of stambomycin A/B aglycones (left) and stambomycin C/D aglycones (right).[5] (picture taken from reference 5)

Subsequently, ^{1}H NMR spectroscopic analysis of the higher molecular weight species revealed that they contain two similar compounds named stambomycins A and B (Figure 1.11) respectively, in a ratio of about 5:1. After further analysis of these two compounds through COSY, TOCSY, HMBC, HSQC, NOESY and PENDANT NMR experiments, stambomycins A and B were confirmed to be 51-memebered glycosylated macrolides differing at the side chain of C26 and were also confirmed to encompass a tetrahydropyran originating from the C7 hydroxyl group to the C3 keto group. Similarly, analysis of the lower molecular weight species by ^{1}H, ^{13}C, COSY, TOCSY, HMBC, HSQC, NOESY and PENDANT NMR data disclosed another two similar compounds named stambomycins C and D in a ratio of 3:1. They are different from stambomycins A and B solely in the structure of the alkyl chain attached to C26. To be specific, stambomyicn C possesses a 4-methyl-*n*-pentyl group at C26, whereas stambomycin D has an *n*-hexyl group (Figure 1.11). These NMR data also strongly validated the high accuracy of the predicted planar structure of the

final intermediate attached to the ACP domain in the last module of PKSs. The double bonds of C10/C11, C12/C13, C24/C25 and C48/C49 all show a *trans* configuration as the $^{3}J_{H\text{-}H}$ coupling constants of H12/H13 and H48/49 are 15.0 Hz and 15.2 Hz respectively, and there is correlation between C10 methyl group and H12, and between C24 methyl group and H26, based on the NOSEY spectrum (Figure 1.11). NMR spectra analysis along with literature comparisons[40,41] elucidated the attachment of *β*-mycaminose derived from glycosyltransferase encoded by *samR0481* gene to the aglycones at C5. Besides, NMR data analysis of aglycones confirmed that they lack *β*-mycaminose.

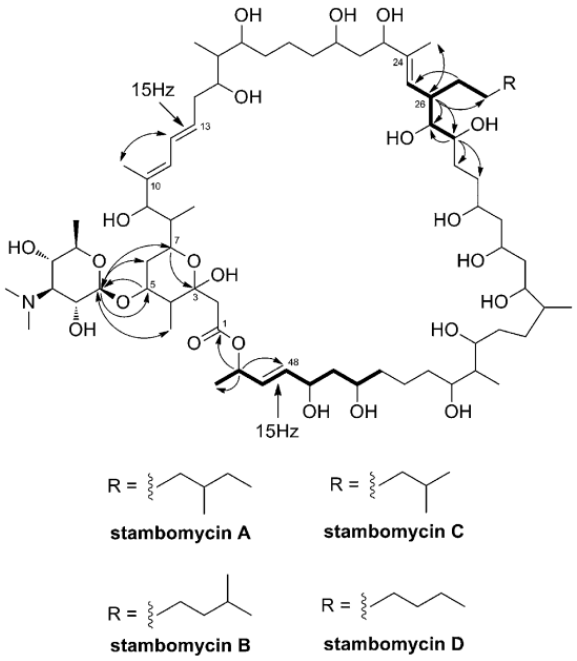


Figure 1.11. The elucidation of the structures of stambomycins A-D. Important COSY, HMBC and NOESY correlations are indicated by bold lines, single-headed arrows and double headed arrows respectively.[5] (picture taken from reference 5)

A few structural elements could not be predicted by sequence analysis of the PKSs, however these structure features were validated by NMR experiments. For instance, the side chain attached to C26 is not predictable and the glycosylation, hydroxylation and macrolactonization are of non-PKS origin. According to the COSY and HMBC correlations (Figures 1.12 and 1.13), stambomycin A was proposed to have a 4-methyl-*n*-hexyl chain at C26, while stambomycin B bears a 5-methyl-*n*-hexyl chain at C26. In addition, analysis of COSY and HMBC correlations revealed that C28 and C50 both possess hydroxyl groups and the macrolactonization occurred between C1 and C50 hydroxy group, catalyzed by cytochrome P450.

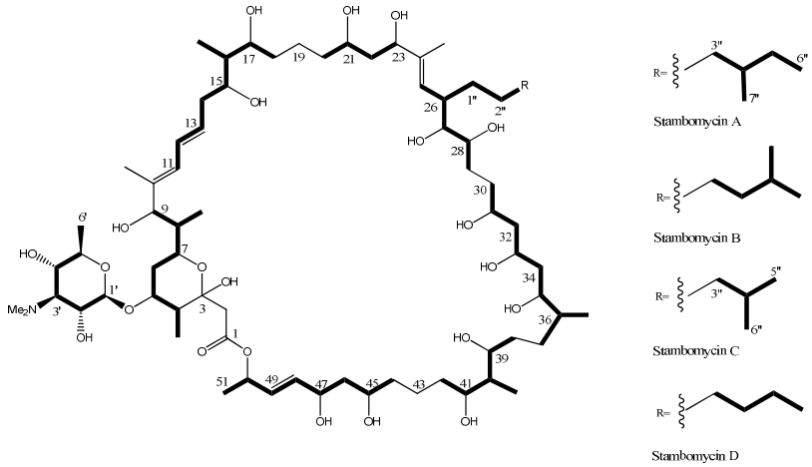


Figure 1.12. COSY NMR correlations of stambomycins A-D.[5] (picture taken from reference 5)

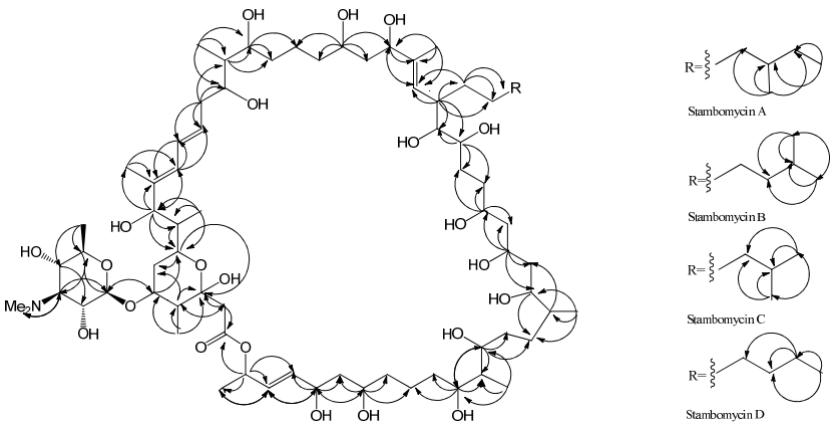


Figure 1.13. HMBC NMR correlations of stambomycins A-D.[5] (picture taken from reference 5)

1.3 Bioactivities of the stambomycins

Polyketide natural products show a variety of biological activities including antibacterial, antifungal, anti-inflammatory and antiproliferative activities[1,2]. As such, the Challis group studied the biological activities of stambomycins A-D. First of all, they observed that stambomycins displayed the moderate activity against Gram-positive bacteria, whereas they were inactive against Gram-negative bacteria.

Furthermore, stambomycins A-D inhibited the growth of *bacillus subtilis* BGSC 1A72, *enterococcus faecalis* LG40 and *staphylococcus aureus* LG21 effectively with different IC_{90} values and vancomycin was used as positive control in the antibacterial assays (Table 1.1). Although the IC_{90} values for stambomycins A and B are ambiguous, they still show promising antibacterial activity. What's more, they significantly suppressed the proliferation of human colon adenocarcinoma cell line (HT29), lung cancer cell line (H460), breast cancer line (MCF7) and prostate cancer cell line (PC3) with various IC_{50} values. (The compounds that were employed for antiproliferative activity tests are doxorubicin for HT29, mycophenolic acid and 5-fluorouracyl for H460, mitoxantrone and CD437 for MCF7 and mitoxantrone and vinorelbine for PC3.) (Table 1.1). In addition, stambomycins are much less toxic toward adult Chinese hamster ovary sane cells (CHO-K1) than doxorubicin (Table 1.1). These potent bioactivities of stambomycins could enable these compounds to be further developed as novel drugs.

Table 1.1 Bioactivities of stambomycins A-D.

Organism	Stambomycins A/B	Stambomycins C/D	vancomycin	Compounds of reference
Antibacterial activity (IC_{90}, μg/mL)				
Bacillus subtilis BGSC 1A72	ND	33.53+/-0.86	0.425+/-0.008	
Enterococcus faecalis LG40	ND	8.65+/-0.49	0.970+/-0.003	
Straphylococcus aureus LG21	ND	33.95+/-0.16	0.952+/-0.007	
Antiproliferative activity (IC_{50}, μM)				
HT29	1.77+/-0.04	1.74+/-0.04		1.32+/-0.08
H460	1.49+/-0.03	1.30+/-0.13		1.51+/-0.12; 5.21+/-0.22
MCF7	>5.34	3.51+/-0.16		3.69+/-0.11; 0.40+/-0.03
PC3	3.39+/-0.16	2.79+/-0.18		5.64+/-0.53; 15.44+/-0.77
Cytotoxicity (IC_{50}, μM)				
CHO-K1	8.47 +/- 0.67	8.46 +/- 0.52		1.99+/-0.25

1.4 Previous work in our group

Previously, our group has successfully synthesized C1-C27 fragment[42] of stambomycin D aglycon (Figure 1.14) and the spectroscopic data of the synthetic fragment shows remarkable agreement with that of the natural macrocycle, which strongly supports the sequence-based stereochemical assignment in this region and also gives us more confidence to synthesize the final natural product. In addition, our group has also successfully synthesized, in protected form, one of the four diastereomers of the 'unpredictable'

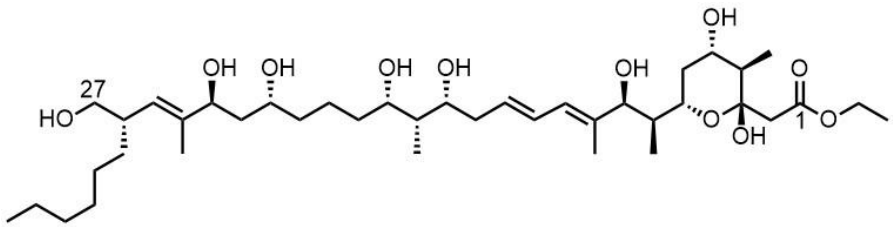


Figure 1.14. Structure of C1-C27 fragment of stambomycin D aglycon.

stereocenters at C28 and C50, the fully protected linear C1–C51 fragment (Figure 1.15) of the macrocycle. However, several deprotection attempts failed, as the acetonide protecting group at C27 and C28 requires relatively strong acid to deprotect, whereas the C10–C13 diene was found to be sensitive to strong acid. In addition, this work showed that this diene also decomposes easily if the deprotection temperature is over 40 ºC. Apart from the 1,2-acetonide at C27–C28, it appeared that all the other protecting groups can be removed smoothly without damaging the diene, although further uncertainty was observed with potential isomerization at the C24–C26 alkene. Thus, the use of other protecting groups was identified as a key aim for the eventual global deprotection, and confirmation of the total sequence-predicted stereochemical assignment of stambomycin D.

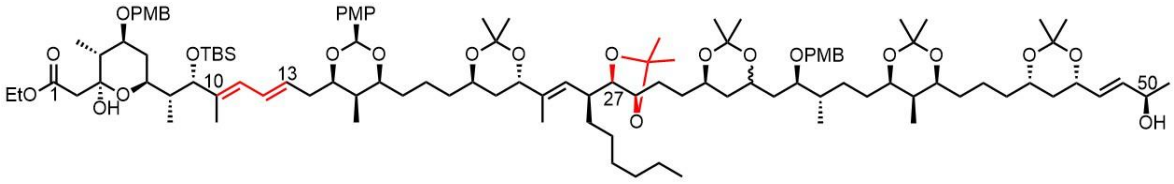


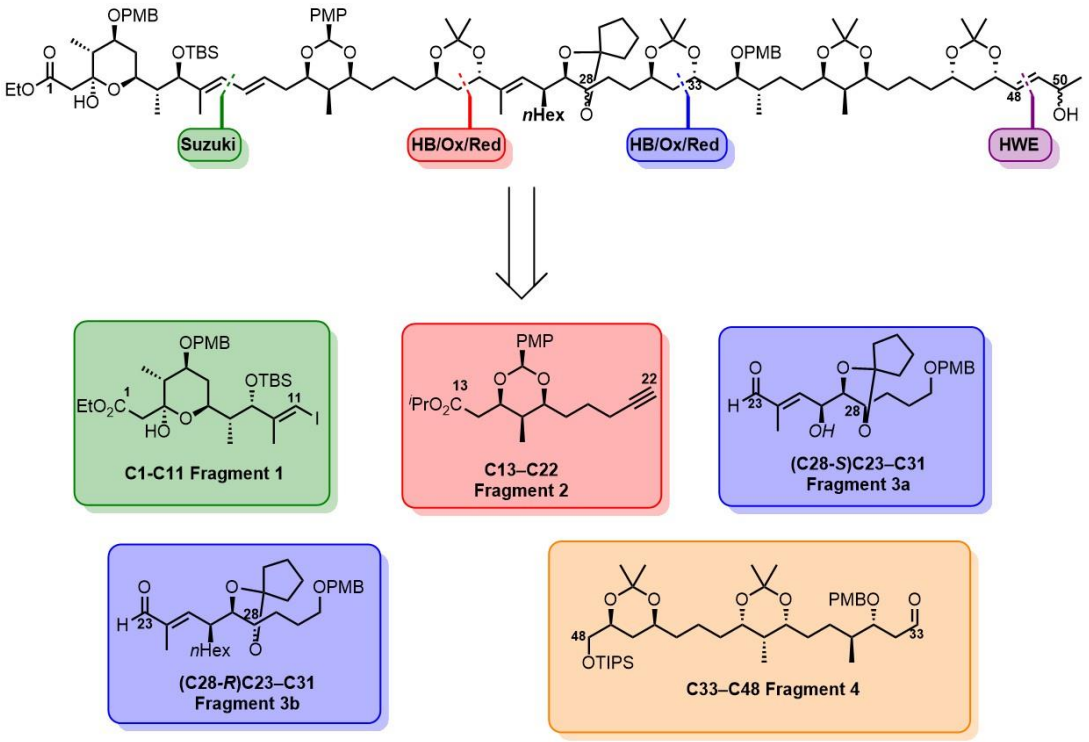
Figure 1.15. Previous synthesis of fully protected C1–C51 linear fragment of stambomycin D aglycon.

1.5 Project aims and retrosynthetic strategies

Genome mining approach allows the connectivity and stereochemistry of the carbon skeleton of stambomycins to be predicted *via* sequence analysis of the modular PKS enzymes which are responsible for the biosynthesis of stambomycins. The structural connectivity of stambomycins was then confirmed by NMR experiments, while the stereochemistry could not be completely confirmed in such manner. Although PKS-predicted polyketide stereochemical structure elucidation has been employed on some fragments of polyketides[43], it has yet to be applied to the total stereochemical elucidation of polyketides as structurally complex as stambomycins. The majority of stereocenters in stambomycins except C28 and C50 have been predicted but remain to be confirmed. Thus, our aims of this project are to chemically synthesize stambomycins and elucidate the configurations of all the stereocenters including the stereochemistry at C28 and C50, which could not be predicted by analysis of cytochrome P450. If the PKS-predicted stereochemistry of stambomycins is confirmed correctly, the predictive sequence analysis would be an effective and powerful tool for polyketide stereochemical elucidation, not least by avoiding the need for laborious NMR based studies. It will also prove that such techniques have massive potential to advance the structural assignment of complex natural products, promoting applications in drugs and agriculture.

We envisaged that synthesis of fully protected linear chain C1–C51 (Scheme 1.2) of the stambomycin D aglycon would be an ideal target for us. If this molecule could be prepared, this would also enable study of macrolactonization between the C1 ester group and C50 hydroxyl group, and potentially glycosylation. Retrosynthetically, the linear C1–

C51 fragment can be disconnected at the C11–C12 bond to reveal fragment **1**, which could be coupled with a vinyl halide at C12 by Suzuki coupling. Disconnection at C22–C23 discloses fragment **2** and fragment **3a** and **3b**, which are diastereomeric at the ambiguous stereocenter at C28. The combination of fragment **2** and fragment **3a** or **3b** could be achieved by asymmetric alkyne addition, hydroboration and Evans-Saksena reduction (see below for full discussion of this strategy). Disassembling the C32–C33 bond uncovers fragment **4**, which could be integrated into the C13–C31 fragment through a similar alkyne addition, oxidation and reduction sequence.



Scheme 1.2. Retrosynthetic routes of the linear C1–C51 fragment of stambomycin D aglycon with target fragments.

With a C1–C48 fragment in hand, a late-stage attachment of the C50 stereocenter is envisaged via Horner–Wadsworth–Emmons (HWE) olefination and Corey-Bakshi-Shibata (CBS) reduction, to complete the fully protected linear C1–C51 fragment. Notably, one

significance of the retrosynthetic route is that C50 stereocenter is installed in the final step of the synthesis of C1–C51 acyclic chain and this only leaves C28 stereocenter to be installed in the earlier step of the synthesis. That means only two diastereomers are required to be synthesized in the process of preparing acyclic C1–C51 fragment.

It is necessary to mention that we proposed to synthesize northern and southern (Figure 1.16) hemispheres[42,44] of stambomycin D aglycon first in order to attempt a preliminary comparison of NMR data between C1–C27 fragment or C33–C51 fragment and stambomycin D to support the predicted stereochemistry in these regions. Crucial to synthesizing these two fragments was identification of suitable and consistent conditions to deprotect the C1–C27 fragment and C33–C51 fragment; these conditions would lay the groundwork for the final deprotection of the full, acyclic C1–C51 fragment.

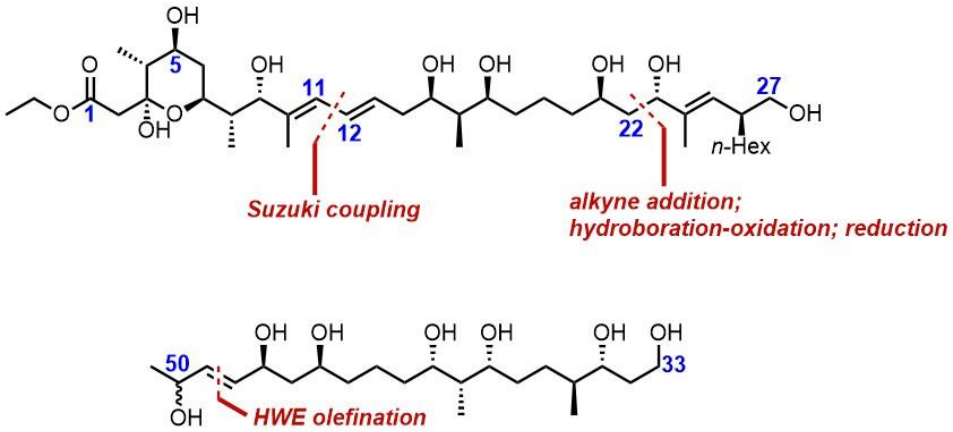
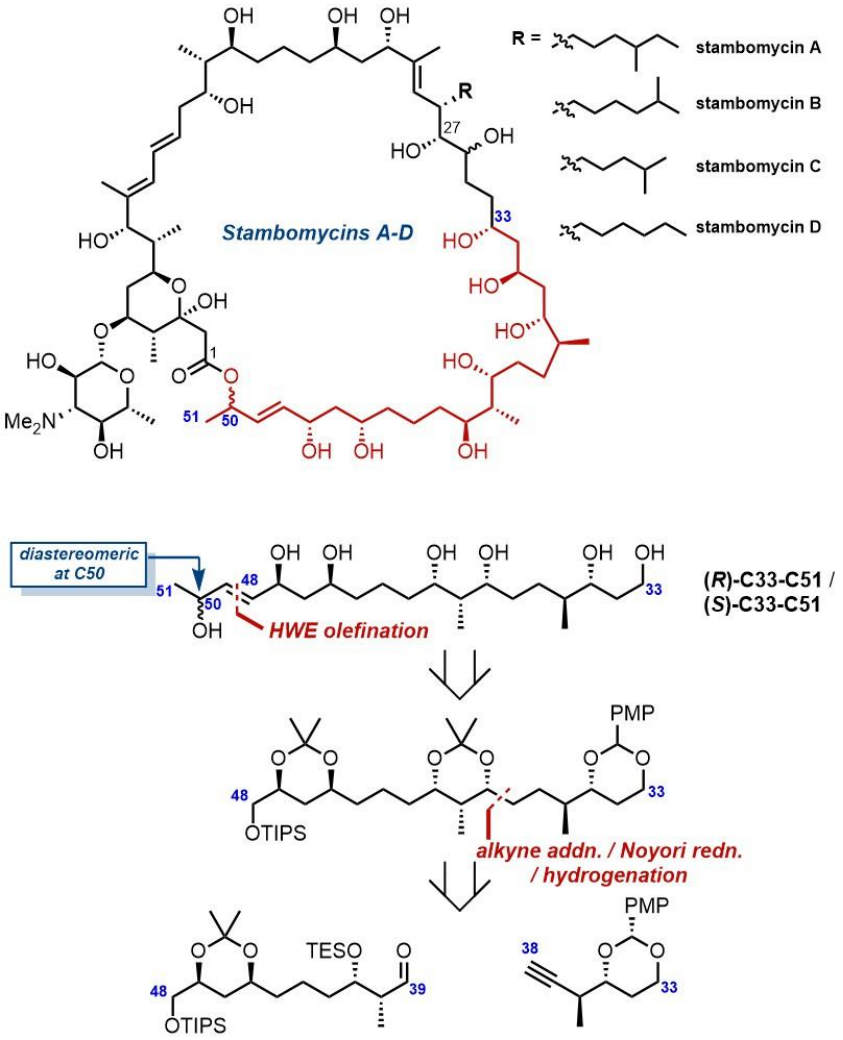


Figure 1.16. The structure of C1–C27 fragment (northern hemisphere) and C33–C51 fragment (southern hemisphere) of the stambomycin D aglycon.

Chapter 2: Synthesis of the C50 diastereomers of C33–C51 fragment

As mentioned in Chapter 1.4, the northern hemisphere of stambomycin D aglycon, C1-C27 fragment was successfully synthesized before and the spectroscopic data for this fragment shows remarkable agreement with that for the natural product, which validated the feasibility of predicted sequence analysis of PKSs for stereochemical assignment of stambomycin D. In order to further support the sequence-based stereochemistry prediction, we set about the synthesis of the two C50 diastereomers of the C33–C51 segment of stambomycin D aglycon, which is described in this chapter. This study identified mild deprotection condition for these target molecules which feature an acid sensitive C50 allylic oxygen functionality, thus providing possible conditions for the eventual deprotection of the full linear C1–C51 fragment with its own sensitive C10–C13 diene. This work also demonstrated the ability to install either stereochemistry at C50 at a late synthetic stage, thus laying the groundwork for further studies on the full-length natural product.

Retrosynthetically, the C33–C51 fragments could be disconnected at C48 to reveal the C33–C48 motif (Scheme 2.1), which could be extended to the C33–C51 fragments *via* HWE olefination and CBS reduction. Desaturation and disconnection at the C38–C39 bond reveals the C39–C48 aldehyde and C33–C38 alkyne. The union of these two fragments could be achieved by C33–C38 alkyne addition to the C39–C48 aldehyde, followed by oxidation/asymmetric reduction and hydrogenation sequence to install the *S* configuration of the C39 stereocenter and C37–C38 saturation.

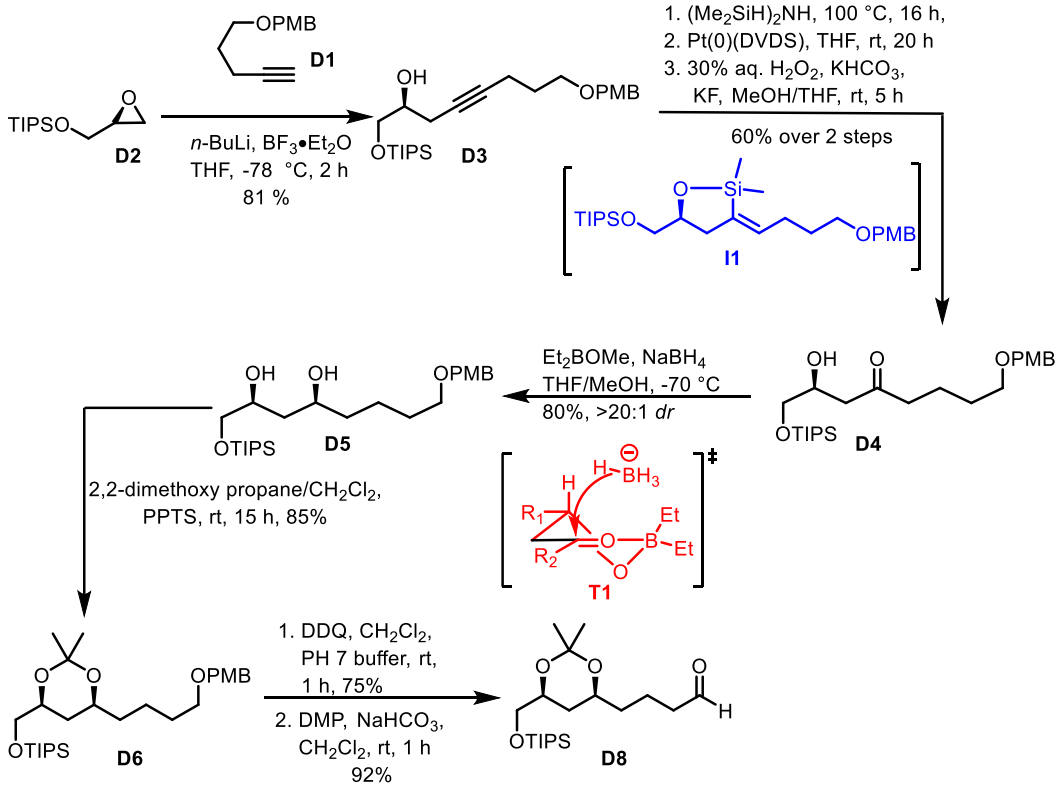


Scheme 2.1. Retrosynthetic analysis of C50 diastereomeric C33–C51 fragments.

2.1 Synthesis of the C39–C48 aldehyde

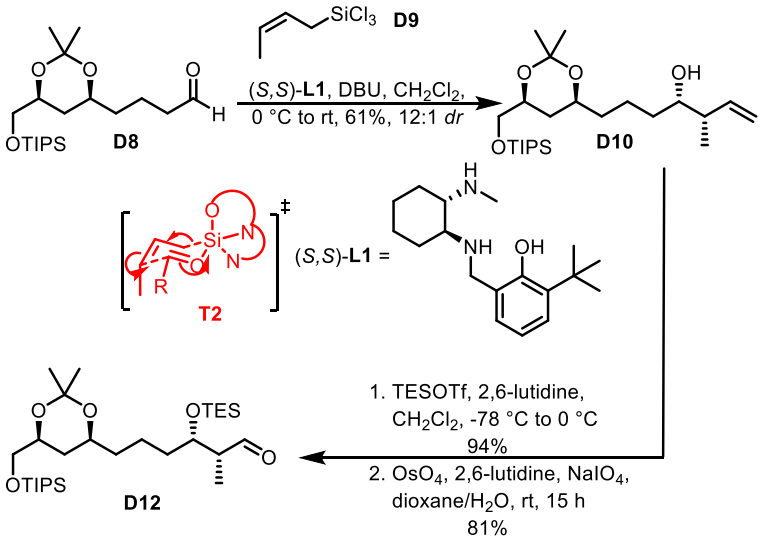
Synthesis of the C39–C48 aldehyde (Scheme 2.2) began with epoxide opening via addition of alkyne **D1** to TIPS-protected (*R*)-glycidol **D2** to afford alkynyl alcohol **D3** in 81% yield. Subsequently, intramolecular hydrosilation[45-47] of the hydrodimethylsilyl ether of homopropargylic alcohol **D3** proceeded regioselectively in a 5-*exo*-*dig* mode, catalyzed by platinum(0) 1,3-divinyl-1,1,3,3-tetramethyldisiloxane, to form the five-membered ring intermediate **I1**. This cyclic siloxane was transformed into *β*-hydroxyketone in 60% yield over two steps *via* Tamao oxidation using hydrogen peroxide and potassium fluoride. 1,3-

syn diol **D5** was then synthesized from hydroxyketone **D4** *via* Narasaka-Prasad reduction[48] with excellent diastereoselectivity and good yield (80%, >20:1 *dr*). Mechanistically, hydride delivery from sodium borohydride proceeds via an axial attack on the opposite face with respect to the existing alcohol, leading to a more stable chair-like transition state **T1**. The resulting diol **D5** was protected using catalytic *p*-TsOH and 2,2-dimethoxypropane, which furnished acetonide **D6** in 85% yield. The relative stereochemistry of the 1,3-diol of **D5** was confirmed as *syn* based on the ^{13}C NMR chemical shifts of the acetonide **D6** (ketal carbon at 98.5 ppm, methyl carbons at 30.3 and 20.0 ppm respectively) through the Rychnovsky-Evans method.[49,50] Deprotection of the PMB group in **D6** (75%), followed by Dess-Martin oxidation yielded aldehyde **D8** in excellent yield (92%), which was ready for the following transformations.



Scheme 2.2. Synthetic routes towards aldehyde **D8**.

The next step (Scheme 2.3) involved a Leighton crotylation[51] to install two adjacent stereocenters. Treatment of **D8** with crotyl trichlorosilane **D9** and chiral ligand (*S*,*S*)-**L1** gave alcohol **D10** in good diastereoselectivity and yield (61%, > 12:1 *dr*). This reaction proceeds *via* a chair-like transition state **T2** to give the desired stereocenters, where the newly-installed hydroxy-bearing stereocenter was confirmed as possessing *S* configuration through Mosher ester analysis[52,53]. Alcohol **D10** was protected as a TES ether with TES triflate and 2.6-lutidine and the following oxidative cleavage of the terminal alkene[54] produced the C39–C48 aldehyde as a coupling partner for the construction of C33–C48 skeleton.

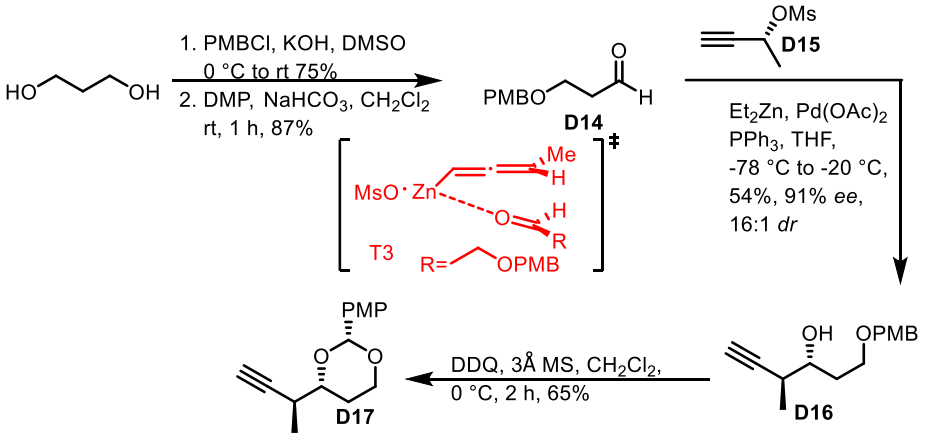


Scheme 2.3. Synthetic routes towards C39–C48 aldehyde **D12**.

2.2 Synthesis of C33–C38 alkyne

Our synthesis of the C33–C38 alkyne (Scheme 2.4) commenced with mono-PMB protection of propane-1,3-diol (75%), followed by Dess-Martin oxidation to generate aldehyde **D14** in 87% yield. An enantio- and diastereoselective allenylzinc addition[55-57] between aldehyde **D14** and propargylic mesylate **D15** gave propargylic alcohol **D16** in

moderate yield (54%) and excellent *ee* and *dr* (95% ee, 16:1 *dr*, *ee* determined by HPLC analysis, see experimental section). In the process of forming compound **D16**, first of all, zincation of propargylic mesylate **D15** was performed *via* a transient allenylpalladium species, and subsequent allenyl zinc addition to aldehyde **D14** proceeded *via* a possible cyclic transition state **T3** (less steric hindrance) to afford alcohol **D16** with the desired stereocenters. The absolute configuration of the stereocenter of the newly-introduced alcohol was confirmed as *R* by Mosher ester analysis.[52,53] Finally, alcohol **D16** was treated with DDQ at 0 ºC to furnish PMP acetal **D17** (65%),[58] an oxidation that likely proceeds *via* a single electron transfer process.

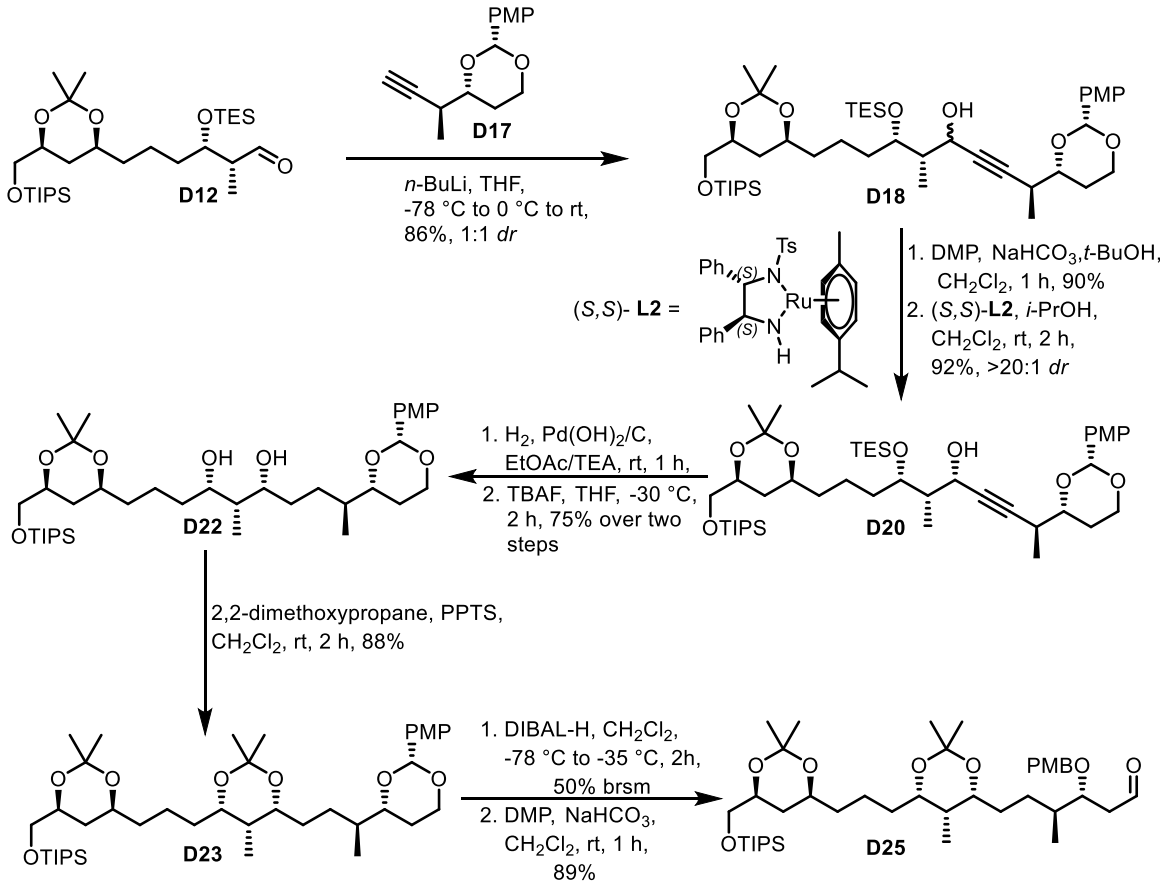


Scheme 2.4. Synthetic routes towards C33–C38 alkyne **D17**.

2.3 Union of C33–C38 alkyne and C39–C48 aldehyde

We next turned our attention to construct the C33–C48 skeleton (Scheme 2.5) with the two coupling partners in hands. The combination of these two fragments was achieved by addition of the aldehyde **D12** to alkyne **D17** using *n*-BuLi, which gave a 1:1 mixture of diastereomeric propargylic alcohols **D18** in good yield (86%). In order to build the desired

stereocenter at C39, the inseparable mixture of diastereomers was oxidized using Dess-Martin periodinane (90%), followed by Noyori asymmetric transfer hydrogenation[59] to form the required propargylic alcohol **D20** in excellent yield and diastereoselectivity (92%, >20:1 *dr*). The triple bond in **D20** was hydrogenated to smoothly afford the saturated alkyl bond in **D22**; the addition of triethylamine to the reaction mixture inhibited the potential deprotection of the TES ether and cleavage of PMP acetal. Whereafter, the crude residue resulting from hydrogenation was treated with TBAF at -30 ºC to achieve selective deprotection of the TES group in the presence of the TIPS group, and the desired diol **D22** was obtained in 75% yield over two steps.



Scheme 2.5. Synthetic routes towards C33–C48 aldehyde **D25**.

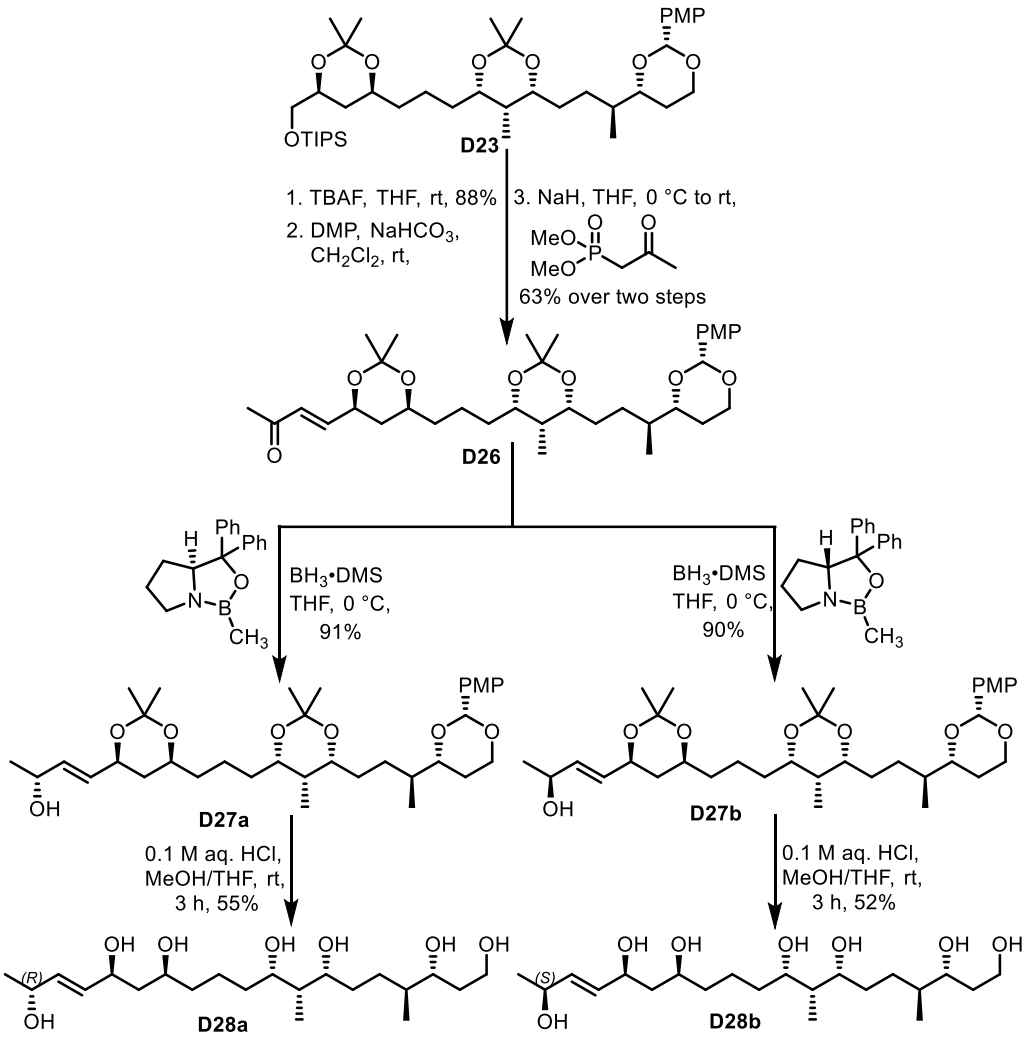
Diol **D22** was then protected as an acetonide **D23** (88%) using 2,2-dimethoxypropane. At this point, the stereocenter at C39 was confirmed as *S* configuration based on the carbon NMR chemical shift of the newly-formed acetonide in **D23** using Rychnovsky-Evans method.[49,50] Subsequent DIBAL-H induced regioselective PMP acetal cleavage (50% brsm) and Dess-Martin oxidation gave the C33–C48 aldehyde fragment (89%), which is an important coupling partner for construction of C13–C48 skeleton in Chapter 5.

2.4 Completion and deprotection study of C33–C51 (C50-*R*/*S*) fragments

With bis-acetonide **D23** in hands, preparation of fully deprotected C33–C51 fragments was also studied (Scheme 2.6). This began with deprotection of TIPS group in **D23** (88%), followed by Dess-Martin oxidation to afford the corresponding aldehyde. This aldehyde was treated with dimethyl (2-oxopropyl)phosphonate and sodium hydride to undergo HWE olefination, generating enone **D26** in 63% yield over two steps. Treatment of enone **D26** with both the (*S*)–CBS and (*R*)–CBS reagents, on account of the ambiguity at the C50 stereogenic center, gave C50-(*R*)-enol **D27a** and C50-(*S*)-enol **D27b** respectively, which are ready for the following global deprotection.

After exploring numerous deprotection conditions, eventually we found that treatment of **D27a** and **D27b** with 0.1 M aq. HCl in MeOH/THF (2:1) at ambient temperature for 3 h produced the fully deprotected C33–C51 fragments **D28a** and **D28b** in pleasing yields (55% and 52% separately). To our delight, the mild deprotection conditions that we applied to deprotect these epimeric C33–C51 fragments also enabled the deprotection of the northern hemisphere C1–C27 fragment bearing the acid sensitive C10–C13 diene with reasonable yield (The C1-C27 fragment was successfully synthesized in our previous work, which was

already mentioned in Chapter 1.), which thus lays the groundwork for the final deprotection of eventual C1–C51 fragments. Purification of polyols of **D28a** and **D28b** proved non-trivial because of their high polarity. Several attempts on normal phase chromatography could not render pure product with reasonable yield for NMR experiments.As a result, reversed phase HPLC was employed to purify **D28a** and **D28b**, and pure products were obtained with moderate yield.



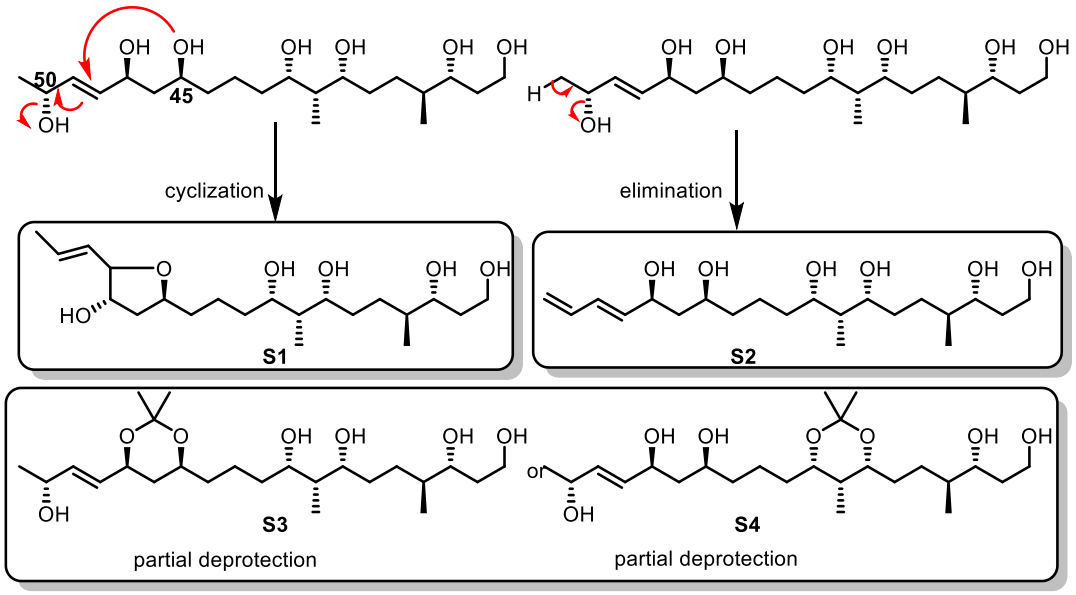
Scheme 2.6. Synthetic routes towards C50 diastereomers of C33–C51 fragment.

It is noteworthy that finding suitable conditions for deprotection of **D27a** and **D27b** was extremely challenging, as the C50 allylic alcohol proved susceptible to degradation under typical conditions utilized to deprotect 1,3-*syn*-acetonide, (e.g. 80% AcOH, TFA, PTSA and 1.0 M HCl). In order to obtain the best deprotection conditions, one epimer **D27a** was applied to various deprotection conditions and a couple of tentative side products were proposed based on the analysis of ^{1}H NMR spectroscopic data and HRMS data (Table 2.1 and Scheme 2.7). It is very likely that cyclized compound **S1** was obtained with 80% AcOH, PTSA, 1.0 M HCl and 0.5 M HCl. To explain it, the five-membered ring side product was possibly formed by the C45-hydroxyl group attacking the C48–C49 double bond. Treatment of **D27a** with 1.0 M HCl or 0.5 M HCl seemed to give small amount of elimination product **S2**. We also seemed to obtain partial deprotection products **S3**/**S4** under milder deprotection conditions (50 ºC, 80% AcOH and TFA). However, we can confirm no desired product was obtained under the above mentioned deprotection conditions. After screening a number of deprotection conditions, finally we found the desired deprotected products could be obtained with either 0.1 M HCl or 0.05 M HCl successfully. 0.1 M HCl was proved to be the most suitable deprotection condition due to less reaction time and higher yield.

Table2.1. Conditions screened for the deprotection of **D27a**.

Entry	Acid	Solvent	Temp. (ºC)	Time (h)	Yield (%)
1	AcOH (80% aq.)	H_2O	60	14	**S1** (25)
2	AcOH (80% aq.)	H_2O	50	14	**S1** (10), **S3**/**S4** (17)
3[a]	TFA	THF/H_2O	0 to rt	6	**S3**/**S4** (39)
4[a]	TFA	THF/H_2O	rt	6	**S3**/**S4** (33)
5[a]	TFA	THF/H_2O	rt	15	Degradation
6	PTSA	THF/MeOH	rt	3	**S1** (28)
7[b]	HCl (1.0 M aq.)	THF/MeOH	rt	3	**S1** (35), **S2** (5)
8[b]	HCl (0.5 M aq.)	THF/MeOH	rt	3	**S1** (35), **S2** (5)
9[b]	HCl (0.1 M aq.)	THF/MeOH	rt	3	**D28a** (37)
10[b]	HCl (0.05 M aq.)	THF/MeOH	rt	12	**D28a** (55)

[a]10 equiv. TFA was used and the ratio of THF/H_2O is 5:1. The reaction for **3a** stirred at 0 ºC for 2 h and then at rt for 4 h. [b]The ratio of THF/MeOH is 1:2.



Scheme 2.7. Possible side products observed for the deprotection of **D27a**.

With two epimeric heptaols **D28a** and **D28b** in hands, attention now turned to NMR spectroscopic data comparison between the synthesized C33–C51 fragments and stambomycin D (Figure 2.1, for further detail see experimental section). The ^{1}H and ^{13}C NMR data of the synthetic C33–C51 fragments showed a good match with that of the natural macrocycle, apart from the expected exceptions of C50 and C33–C35 at the point of truncation.

There is a free alcohol group at C50 in **D28a** and **D28b**, however C50 is incorporated into the macrolactone in stambomycin D. Another discrepancy was observed at the C37 proton assigned by HSQC data, where one of the diastereotopic protons of the synthetic fragments showed a quite different chemical shift from that of the natural material. After re-examining the original NMR data for the stambomycin D, we proposed that a minor reassignment of the ^{1}H NMR data for the natural product may be required. Moreover, the most significant NMR ^{13}C chemical shift difference between the two synthetic fragments is at C49, where the ^{13}C NMR chemical shift difference is 0.04 ppm. This suggests that with the synthetic full-length compounds and natural products in hand, there is a high likelihood to identify the C50 stereogenic center; identification of the C50 stereocenter emphasizes the sensitivity of NMR spectroscopy in the discrimination of subtle differences on stereochemistry.

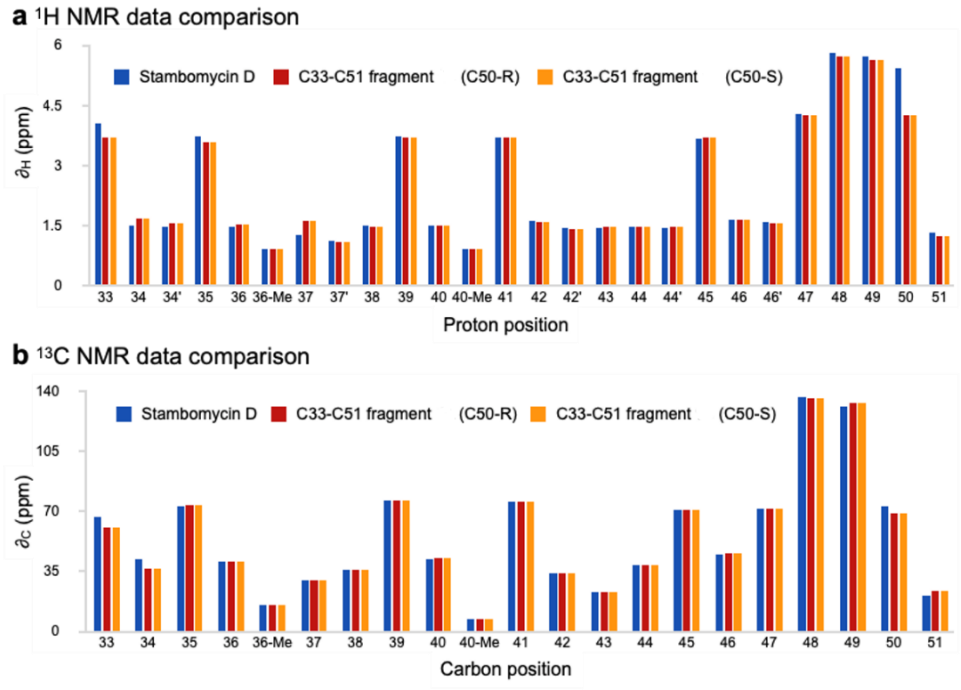


Figure 2.1. Comparison of ^{1}H NMR and ^{13}C NMR data of **D28a** and **D28b** with stambomycin D.

2.5 Summary

In conclusion, we successfully synthesized a C33–C48 fragment as a precursor for the consecutive construction of C13–C48 skeleton. Subsequently, we completed the synthesis of the southern hemisphere C33–C51 fragments; these two C50 diastereomers show remarkable agreement with natural stambomycin D, especially in the middle region (C36–C45), suggesting the predicted stereochmistry of stambomycin D in the southern hemisphere region is correct.

Perhaps more importantly, we have explored the consistent mild deprotection conditions (0.1 M HCl, MeOH/THF) for both northern (C1–C27), which was synthesized in our previous work and southern (C33–C51) hemisphere fragments and these conditions offer us hope and confidence for the deprotection of full-length compounds. This study also

proved that acetonide, PMP acetal are suitable protecting groups for the protection of C33–C51 heptaols.

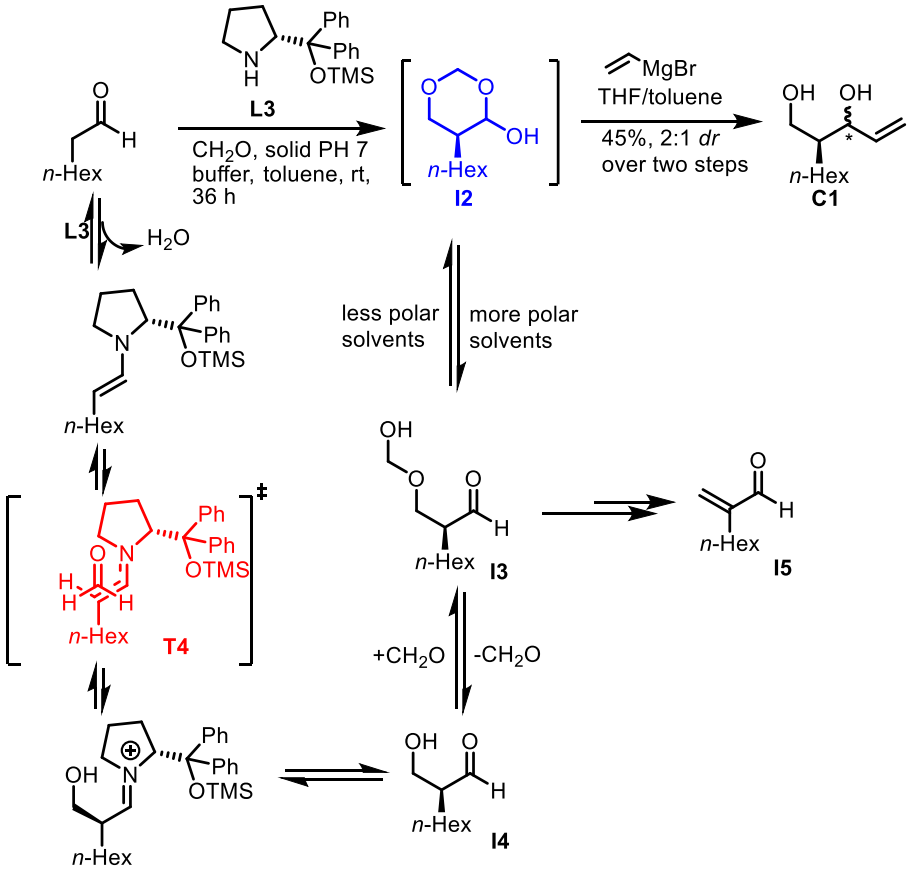
Chapter 3: Synthesis of the C23–C31 (1,2-*anti* diol at C27 and C28) fragment

Among the four diastereomers of stambomycin D, two are originated from the C28 stereogenic center, which should be installed at an early synthetic stage. Previous work in our group illustrated that the 1,2-acetonide at C27 and C28 in the acyclic C1–C51 fragment requires harsh conditions such as strong acid to remove, whereas the C10–C13 diene proved susceptible to degradation under such conditions. As a consequence, selection of a suitable protecting group for the C27 and C28 hydroxyl groups is extremely important. This chapter will introduce the synthetic pathways towards the C23–C31 fragment bearing a 1,2-*anti* diol at C27 and C28, and will also discuss the choice of the protecting group at C27 and C28. More importantly, deprotection tests on the final C23–C31 (1,2-*anti* diol at C27 and C28) fragment will be discussed in this chapter as well.

3.1 Installation of 1,2-*anti* diol at C27 and C28

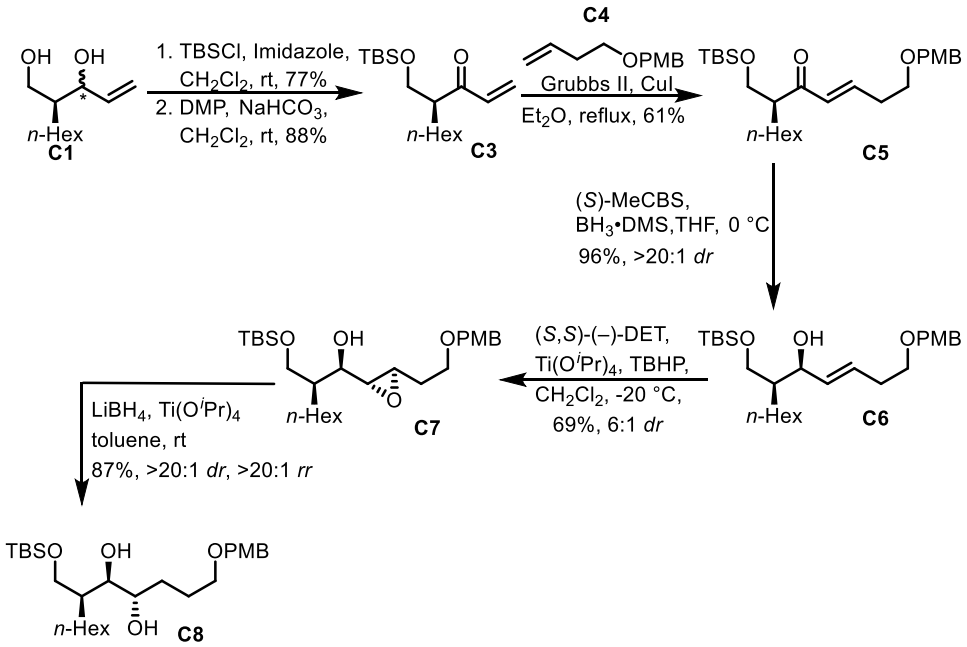
Synthesis of C23–C31 fragment commenced with an asymmetric organocatalytic aldol reaction[60] (Scheme 3.1) catalyzed by Jørgensen−Hayashi diarylprolinol catalyst **L3**, which resulted in the formation of intermediate lactol **I2**. Treatment of **I2** with vinyl magnesium bromide in the presence of THF and toluene (1:1) gave allylic alcohol **C1** in moderate yield and as an inseparable mixture of diastereomers (2:1 *dr*). In the process of forming intermediate **I2**, octanal was condensed with prolinol catalyst **L3** to first produce an enamine. Attack of the enamine on formaldehyde proceeds from the less hindered *re* face of the enamine due to the blocked *si* face resulted from nonbonding steric interactions from the *α*-substituent of the catalyst **L3** (Scheme 3.1, **T4**). The following hydrolysis of the iminium

ion furnishes α-hydroxymethylated compound **I4**, which is in an equilibrium with lactol **I2**. The open form β-hydroxyl aldehyde is more favorable if the more polar solvents are used as reaction solvents, however, less polar solvents prefer the closed form lactol. Previously, we adopted pure THF as reaction solvent for the second step of vinyl magnesium bromide addition but it only offered us around 34% yield. Based on the analysis on the equilibrium between open and closed forms, **I4** and **I2**, we replaced pure THF with co-solvent of THF and toluene in 1:1 ratio, and obtained a higher yield of **C1** (45%). To further improve the reaction yield, purified octanal should be employed to the reaction since a tiny amount of octanoic acid impurity existing in the commercial octanal caused formation of the elimination product **I5**. In light of this, addition of pH 7 buffer is also necessary to suppress the formation of this elimination product.



Scheme 3.1. First step of synthesis of the C23–C31 fragment.

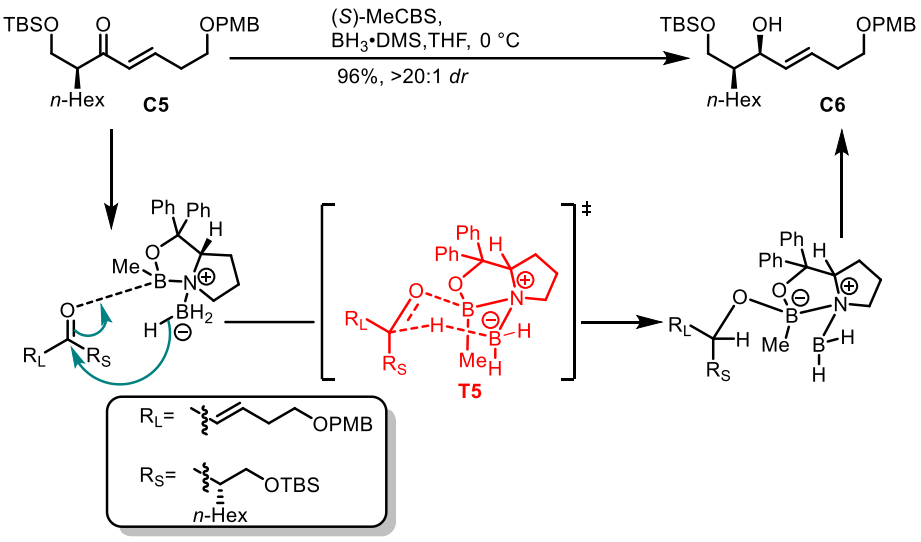
With diol **C1** in hands, we carried out a mono-TBS protection of **C1** (77%), followed by Dess-Martin oxidation to obtain enone **C3** in 88% yield, which is ready for the following cross metathesis to build the C25–C31 skeleton (Scheme 3.2). But-3-en-1-ol was protected as the PMB ether **C4**, and then **C4** was coupled with **C3** *via* cross metathesis reaction[61] using Grubbs II catalyst to produce **C5** in 61% yield. Higher yields could not be acquired on account of the rapid homodimerization of olefinic partner **C4**.



Scheme 3.2. Synthetic routes towards C8 bearing 1,2-*anti* diol.

To install the C27-(*S*) stereocenter, the cross-metathesis product was subjected to an asymmetric reduction with (*S*)-MeCBS catalyst[62] to give enol **C6** with excellent stereoselectivity and yield (96%, >20:1 *dr*). In the process of the reduction, hydride was delivered to carbonyl group *via* a 6-membered ring transition state in which the large group is placed in a psuedoequatorial position, whereas the small group is in an axial position that eclipses the B–Me substituent (Scheme 3.3, **T4**). In enone **C5**, the alkene portion (right part)

was considered as the large group, however the TBS portion (left part) was assumed as small group due to electronic effects[63]. To be specific, the substrate prefers to combine with the catalytic boron center at the carbonyl oxygen lone pair adjacent to the side of TBS portion as opposed to the side of alkene portion, as this enables better conjugation of the alkene group with the electron deficient carbonyl carbon (allowing maximum π-electron donation from this alkene to the carbonyl carbon).



Scheme 3.3. Mechanism for CBS reduction of enone **C5** to enol **C6**.

To install the required stereocenter at C28, a Sharpless epoxidation[64,65] (Scheme 3.2) was carried out on allylic alcohol **C6** in the presence of titanium *iso*-propoxide, tert-butyl hydroperoxide and (*S*/*S*)-diethyl tartrate leading to the *si* face attack directed by the allylic alcohol to afford the desired epoxide **C7** in 69% yield and 6:1 *dr*. The following step involved a titanium *iso*-propoxide mediated nucleophilic ring opening of the 2,3-epoxy alcohol.[66] Treatment of epoxide **C7** with titanium *iso*-propoxide and lithium borohydride

triggered the formation of 1,2-*anti* diol **C8** in pleasing yield, diastereoselectivity and regioselectivity (87%, >20:1 *dr*, >20:1 *rr*). Titanium *iso*-propoxide is proposed to coordinate the two vicinal oxygen atoms at C27 and C28/29, which generates a five-membered ring transition state (Figure 3.1) and also weakens the epoxide bond at C29 more than that at C28. In addition, there is less steric hindrance at C29 than C28. Consequently, the hydride from lithium borohydride is delivered to C29 regioselectively instead of C28 to open the epoxide and produce 1,2-*anti* diol **C8**, which set the scene for the subsequent studies on protection and deprotection.

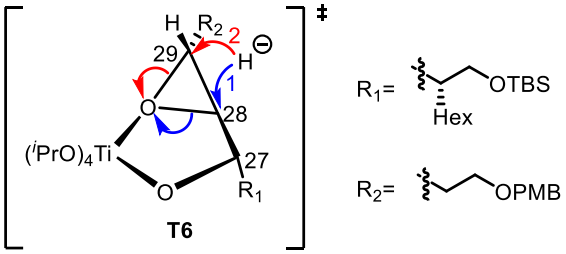
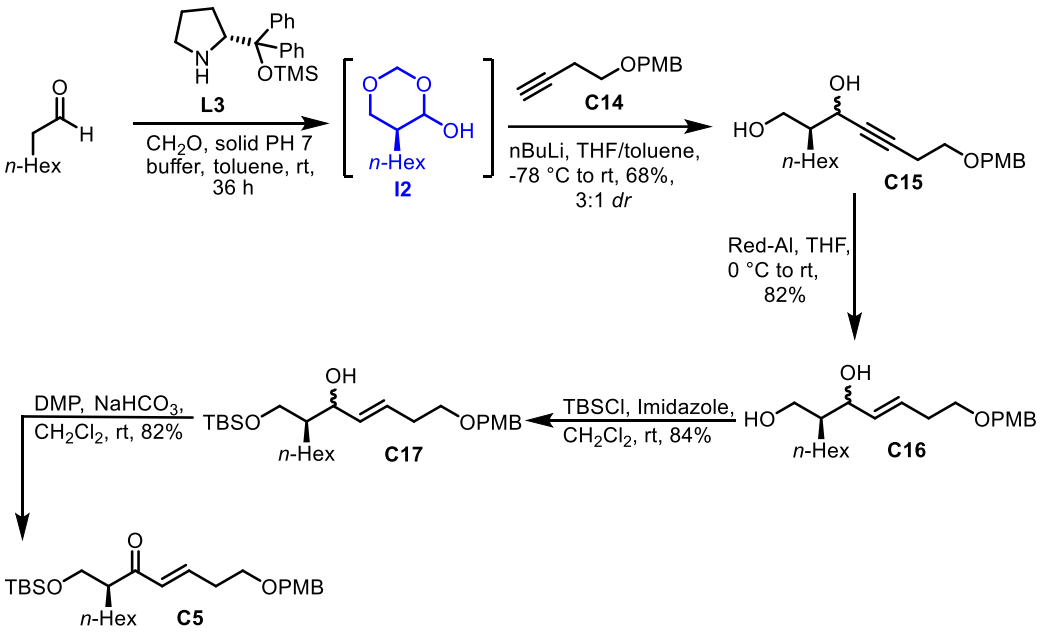


Figure 3.1 Transition state of titanium mediated nucleopilic opening of 2,3-epoxy alcohol **C7**.

As the vinyl magnesium bromide and Grubbs second generation catalyst are costly and the first step of synthesis of C23–C31 fragment requires large amount of vinyl magnesium bromide to produce grams of diol **C1**, we also considered changing the established synthetic route towards 1,2-*anti* diol **C8** from a sustainable point of view. Our new synthetic route (Scheme 3.4) started with addition of PMB protected alkyne **C14** to aldol product **I2**, which gave propargylic alcohol **C15** as an inseparable mixture of diastereomers in 68% yield and 3:1 *dr*. Subsequent Chan alkyne reduction[67] of **C15** with sodium *bis*(2-methoxyethoxy) aluminum hydride (SMEAH or Red-Al®) afforded *trans* allylic alcohol **C16** in good yield

(82%). The primary alcohol in **C16** was protected as a TBS ether (84%), and then oxidized by Dess-Martin reagent to produce enone **C5** in 82% yield, which could undergo the above-mentioned CBS reduction/ Sharpless epoxidation/epoxide opening sequence to generate 1,2-*anti* diol **C8**. Importantly, this new synthetic pathway avoids the use of expensive chemicals (vinyl magnesium bromide and Grubbs second generation catalyst), and it enhanced the yield of preparing enone **C5**.



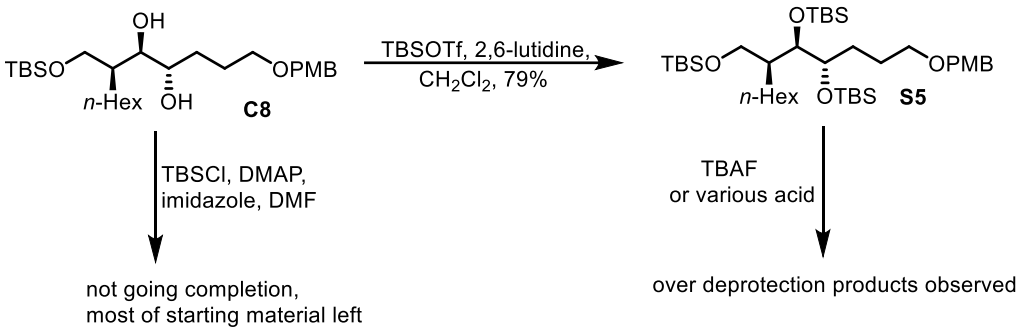
Scheme 3.4 New synthetic route towards enone **C5**.

3.2 Choice of protecting group for the C27 and C28 diol

Previous work in the group protected the 1,2-*anti* diol at C27 and C28 in the C23–C31 fragment as an acetonide, which was found to be difficult to remove in the final stage and required strong acid to deprotect, while the C10–C13 diene is vulnerable to strong acid and degraded. Whereafter, attention turned to TBS protecting group as it is widely used to protect hydroxyl groups and able to tolerate somewhat harsh reaction conditions (organometallics,

etc.) but can be readily removed with a variety of methods. Thus, we planned to protect the diol at C27 and C28 with TBS groups and then attempt to selectively deprotect the TBS of the primary alcohol without affecting the TBS ethers of the secondary alcohols.

To begin with the synthesis of **S5** (Scheme 3.5), **C8** was treated with TBSCl, but the expected product could not be obtained in high yield, even if the Lewis basic solvent DMF was employed as reaction solvent to increase the reactivity.[68] However, when TBS triflate with lutidine[69] was applied to **C8** the reaction proceeded smoothly, giving the desired TBS protected product **S5** in 79% yield. With **S5** in hands, we set about screening mild and efficient selective deprotection conditions. Many literature precdents[70-77] show that selective deprotection of primary TBS groups in the presence of secondary TBS groups is attainable. Several deprotection conditions were employed to compound **S5** such as TBAF, PTSA, HCl, TFA and HF·pyridine on the basis of literature conditions, however all conditions failed to give the desired product, and always more than one TBS group fell off. We speculated this is because of 1,3 relationship between the primary TBS group at C25 and the secondary one at C27. On the one hand, under basic or fluoride conditions, the negative charge formed on the primary oxygen atom probably easily attack the silicon atom of the TBS ether at C27, which results in the C27-TBS group migrating to the primary oxygen and then being deprotected. On the other hand, acid conditions could affect protonation at the C25 alcohol, enabling intramolecular general acid catalysis of deprotection at C27. As a result, this TBS approach was abandoned, and we began to explore other suitable (labile) protecting groups for the 1,2-*anti* diol at C27 and C28.



Scheme 3.5. TBS protection of diol at C27/C28 and selective deprotection attempts in **S5**.

After some consideration of options, a protecting group similar to an acetonide drew our attention. We questioned whether protection of the diol as a cyclopentylidiene acetal might be a good choice as it is more acid labile than an acetonide, yet could stand up to a number of reaction conditions. When the diol is protected as cyclopentylidene acetal **C9**, the envelope conformer of **C9** is more favorable than twist conformer of that due to less torsional strain (Figure 3.2). When the sp^3 center in the cyclopentylidiene acetal turns to a sp^2 center (as in cyclopentanone) in the process of deprotection of the cyclopentylidene acetal in **C9**, strain energy decreases by 10 kJ mol^{-1} (the sp^2 center removes the torsional strain with adjacent CH_2 groups). Therefore, utilization of a cyclopentylidene acetal at C27 and C28 might be a good choice for the protection of C27 and C28 anti diol. We expected this group could survive the whole synthetic journey but be much more labile than a regular acetonide to mild acidic deprotection in the final stage of the synthesis. Deprotection studies on the cyclopentylidene acetal will be discussed later when the synthetic sequence of C23–C31 fragment was completed, and these studies validated this choice of protecting group.

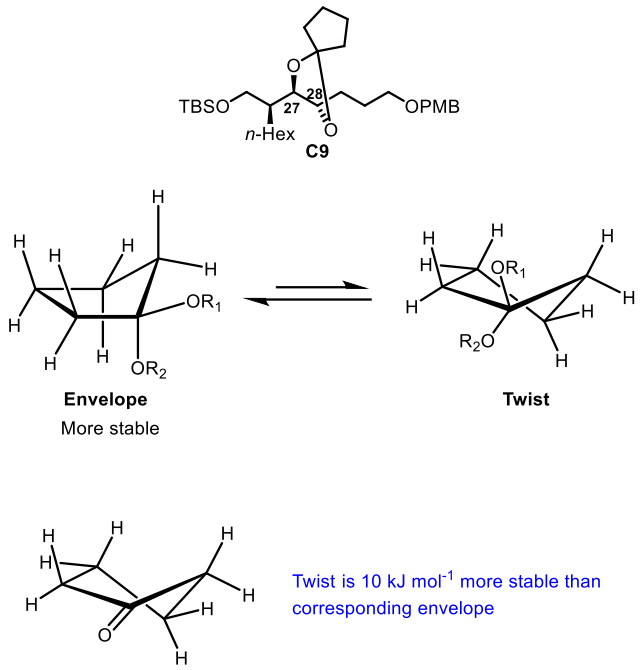
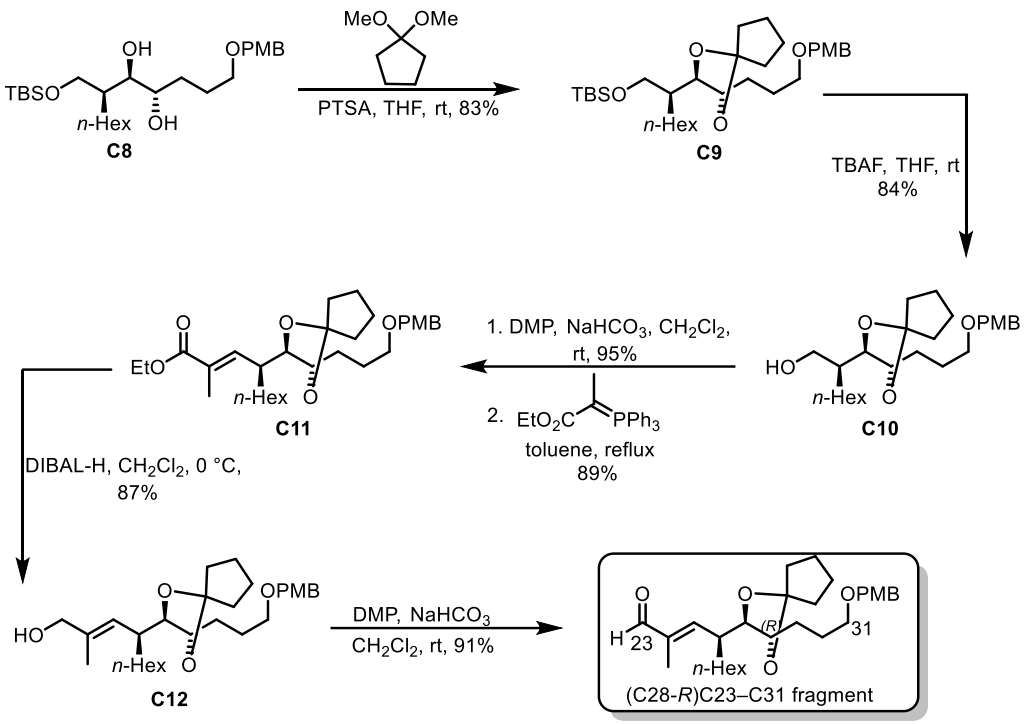


Figure 3.2. Conformational analysis of cyclopentylidene acetal and cyclopentanone.

3.3 Completion of the synthetic sequence of the C23–C31 (1,2-*anti* diol at C27 and C28) fragment

To complete the synthesis of the C23–C31 fragment (Scheme 3.6), diol **C8** was treated with 1,1-dimethoxycyclopentane and catalytic PTSA to afford compound **C9** in good yield (83%). Subsequent addition of TBAF removed the primary TBS group in **C9** with 84% yield. The resulting primary alcohol was oxidized by Dess-Martin reagent to afford the corresponding aldehyde (95%), and the crude residue was submitted to Wittig olefination[78] directly to generate compound **C11** in 89% yield. The ester group in **C11** was then reduced by DIBAL-H to produce primary allylic alcohol **C12** in 87% yield, which is the starting point for the following deprotection studies. Finally, **C12** underwent Dess-Martin oxidation to furnish the C23–C31 (1,2-*anti* diol at C27 and C28) aldehyde fragment, which is one of

the coupling partners to construct C13–C31 skeleton.

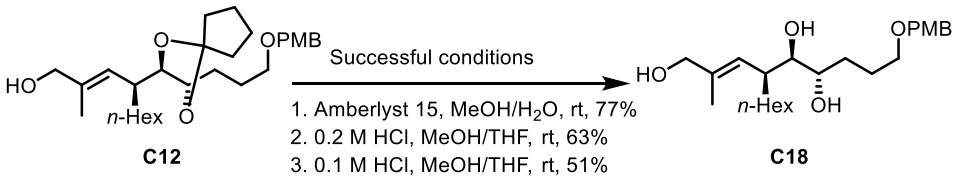


Scheme 3.6. Synthetic routes towards C23–C31 (C28-R) fragment.

3.4 Deprotection study of the C23–C31 (1,2-*anti* diol at C27 and C28) fragment

With compound **C12** in hand, we turned our attention to the crucial deprotection study on this compound (Scheme 3.7). On the basis of the successful deprotection conditions for the C1–C27 fragment and C33–C51 fragment, we commenced with 0.1 M HCl conditions to test the deprotection of C23–C31 (1,2-*anti* diol at C27 and C28) fragment. 0.1 M aq. HCl solution was added to the mixture of compound **C12** and MeOH/THF (1:1) and the resulting mixture was stirred at room temperature. After 24 h, a little of the desired triol product was observed, and thus we decided to leave the reaction mixture for another 24 h. This resulted in more conversion to the desired product and eventually, product **C18** was obtained in 51% yield. In addition, more concentrated 0.2 M HCl was applied to deprotect the C23–C31

fragment in order to shorten the reaction time. To our delight, after 24 h, the desired triol **C18** was generated with better yield (63%). Apart from HCl, we also attempted to deprotect the cyclopentylidene acetal in **C12** with Amberlyst 15 and MeOH/H_2O as solvent and obtained an even higher yield of the desired product **C18** (77%). However, the Amberlyst 15 conditions could not be employed into the deprotection of our northern and southern hemisphere fragments (C1–C27 and C33–C51) without degradation, and therefore this deprotection condition was abandoned and would not be applied to later fragments. Overall, the cyclopentylidene acetal could thus be readily installed using 1,1-dimethoxycyclopentane, and deprotected using HCl (0.1M/0.2 M) conditions. Hence, this protecting groups currently seems the best choice to protect 1,2-*anti* diol at C27 and C28, and is expected to survive the following functional transformations before the final deprotection study.



Scheme 3.7. Deprotection of compound **C12** to triol **C18**.

3.5 Summary

Firstly, we have successfully installed a 1,2-*anti* diol at C27 and C28 in the C23–C31 (1,2-*anti* diol at C27 and C28) fragment. More importantly, we proposed that protecting C27 and C28 hydroxyl groups as cyclopentylidene acetal would make it easier to deprotect the full length C1–C51 fragment bearing the C10–C13 diene. This is because deprotection studies on the C23–C31 (1,2-*anti* diol at C27 and C28) fragment indicate that deprotection

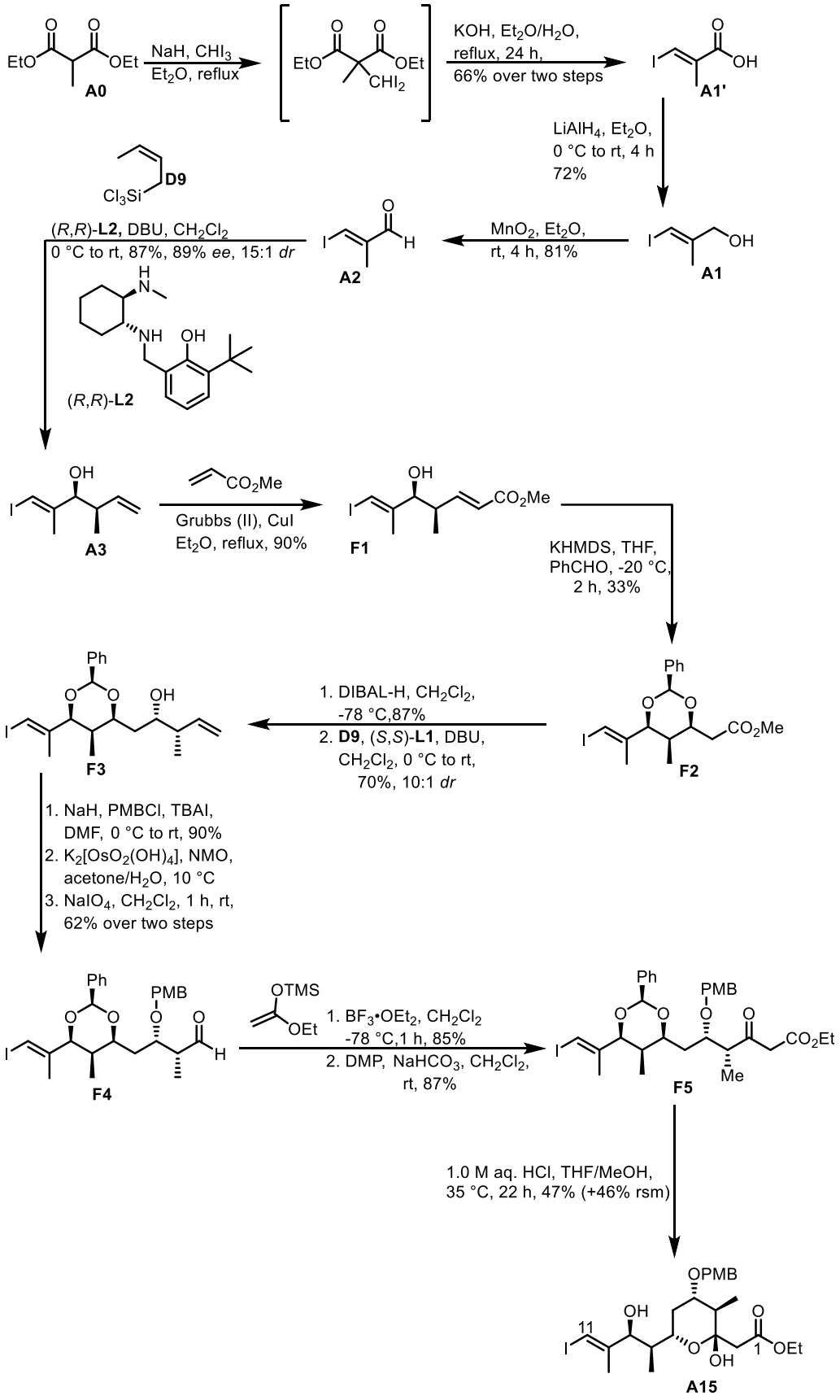
of the cyclopentylidene acetal can proceed smoothly under mild conditions (0.1 M/0.2 M HCl) and harsh conditions are not necessary. What's more, the cyclopentylidene acetal is a protecting group similar to acetonide and thus a relatively stable protecting group. We believe it can withstand numerous harsh reaction conditions and survive the whole synthetic routes before we attempt to deprotect the full-length compound. Moreover, we have identified the consistent deprotection conditions (0.1 M HCl) for our C1–C27, C33–C51 and C23–C31 (1,2-*anti* diol at C27 and C28) fragments, which paved the way for our deprotection studies on the subsequent C13–C31, C13–C48 and C1–C51 fragments.

Chapter 4: Synthesis of the C1–C11 fragment and C13–C22 fragment

The C1–C11 fragment is one of the partners for Suzuki cross coupling to install the C10–C13 diene functionality late in the synthesis. However, synthesis of this tetrahydropyran derivative is non-trivial on account of its complexity (six stereocenters and the potentially unstable hemiacetal). In this chapter, we discuss our synthetic routes towards the C1–C11 fragment as well as the C13–C22 fragment, which will be combined with C23–C31 fragment to construct C13–C31 skeleton.

4.1 Previous synthesis of C1–C11 fragment from our group

Our group's previous synthesis of the C1–C11 alkenyl iodide fragment (Scheme 4.1) began with commercially available methylmalonate **A0**, which was converted into carboxylic acid **A1'** in 66% yield over two consecutive steps. The carboxylic acid was then reduced to allylic alcohol **A1** (72%) by lithium aluminum hydride.[79] Oxidation of alcohol **A1** with manganese dioxide yielded aldehyde **A2** in 81% yield. To install the two adjacent stereocenters, an enantio- and diastereoselective Leighton crotylation was carried out on aldehyde **A2** to afford homoallylic alcohol **A3** in good yield and enantioselectivity as well as diastereoselectivity (87%, 89% *ee*, 15:1 *dr*). Subsequently, cross metathesis between compound **A3** and methyl acrylate catalyzed by Grubbs IIcatalyst gave α,β-unsaturated ester **F1** in excellent yield (90%). Ester **F1** was submitted to Evans-Prunet acetalization[80] reaction in the presence of benzaldehyde and potassium bis(trimethylsilyl) amide to generate benzylidene acetal **F2**, but in only 33% yield. The low yield was attributed to the unfavorable equilibrium with the retro-Michael reaction. The cyclization failed to reach full conversion even with longer reaction time. On top of that, the recovered starting material possessed



Scheme 4.1. Previous synthetic route towards C1–C11 fragment **A15**.

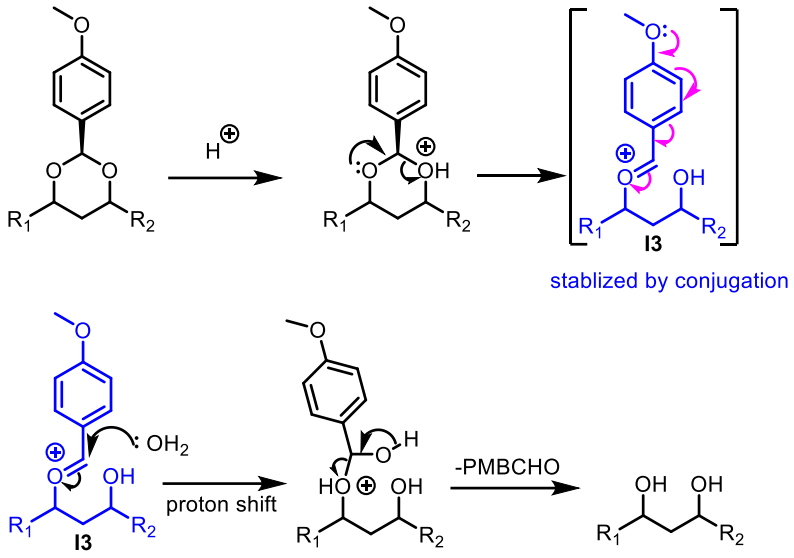
mainly a *cis* alkene instead of the original *trans* alkene and could not55ed to the Evans-Prunet acetalization reaction. The issue is due to the presence of C8 (*R*)-methyl group necessarily occupying an axial position in the six-membered cyclic acetal. Acetal **F2** was treated with DIBAL-H to produce an aldehyde, which underwent Leighton crotylation again to furnish alcohol **F3** in 70% yield and 10:1 *dr*. The homoallylic alcohol **F3** was protected as PMB ether (90%) with PMBCl, where the oxidative cleavage of terminal alkene gave aldehyde **F4** in 62% yield. The next step involved a Mukaiyama aldol reaction;[81-83] treatment of **F4** with ((1-ethoxyvinyl)oxy)trimethylsilane and boron trifluoride diethyl etherate generated *β*-hydroxy ester (85%), which was then oxidized using Dess-Martin reagent to furnish *β*-keto ester **F5** in 87% yield.

It was proposed that the deprotection of benzylidene acetal under acidic conditions would lead to spontaneous cyclization of the C7 hydroxy group onto the C3 ketone to form the expected tetrahydropyran **A15**. However, to our surprise, the benzylidene acetal in **F5** was unexpectedly robust. After exploring numerous deprotection conditions, we found that conditions which led to full consumption of the starting material **F5** caused significant degradation of starting material, and unknown side products which could not be separated from the desired product and thereby be identified. A variety of deprotection conditions were attempted to reach a balance between conversion of compound **F5** and generation of product **A15**, most of which related to different concentrations of aqueous HCl in MeOH and THF. Eventually, it was found that with 1.0 M aqueous HCl in MeOH/THF (1:1) at 35 ºC, the desired product tetrahydropyran **A15** was obtained in 47% yield (still with some inseparable impurities) and recovered starting material **F5** was obtained in 46% yield.

Although this synthetic pathway delivered the desired C1–C11 fragment, there are several problems with it. On one hand, the cross-metathesis step requires relatively large amounts of expensive Grubbs II catalyst (if grams of **F1** need to be prepared). On the other hand, the following Evans-Prunet acetalization after cross metathesis offered low conversion of **F1** to benzylidene acetal **F2**, and the recovered starting material had changed the alkene configuration and could not be resubmitted to the acetalization reaction. Furthermore, the deprotection of the benzylidene acetal in **F5** proved hard, thus the desired product **A15** could not be obtained with high yield and purity. In order to tackle above-mentioned disadvantage, we reexamined our synthetic routes of C1–C11 fragment and developed a new synthetic pathway towards C1–C11 fragment.

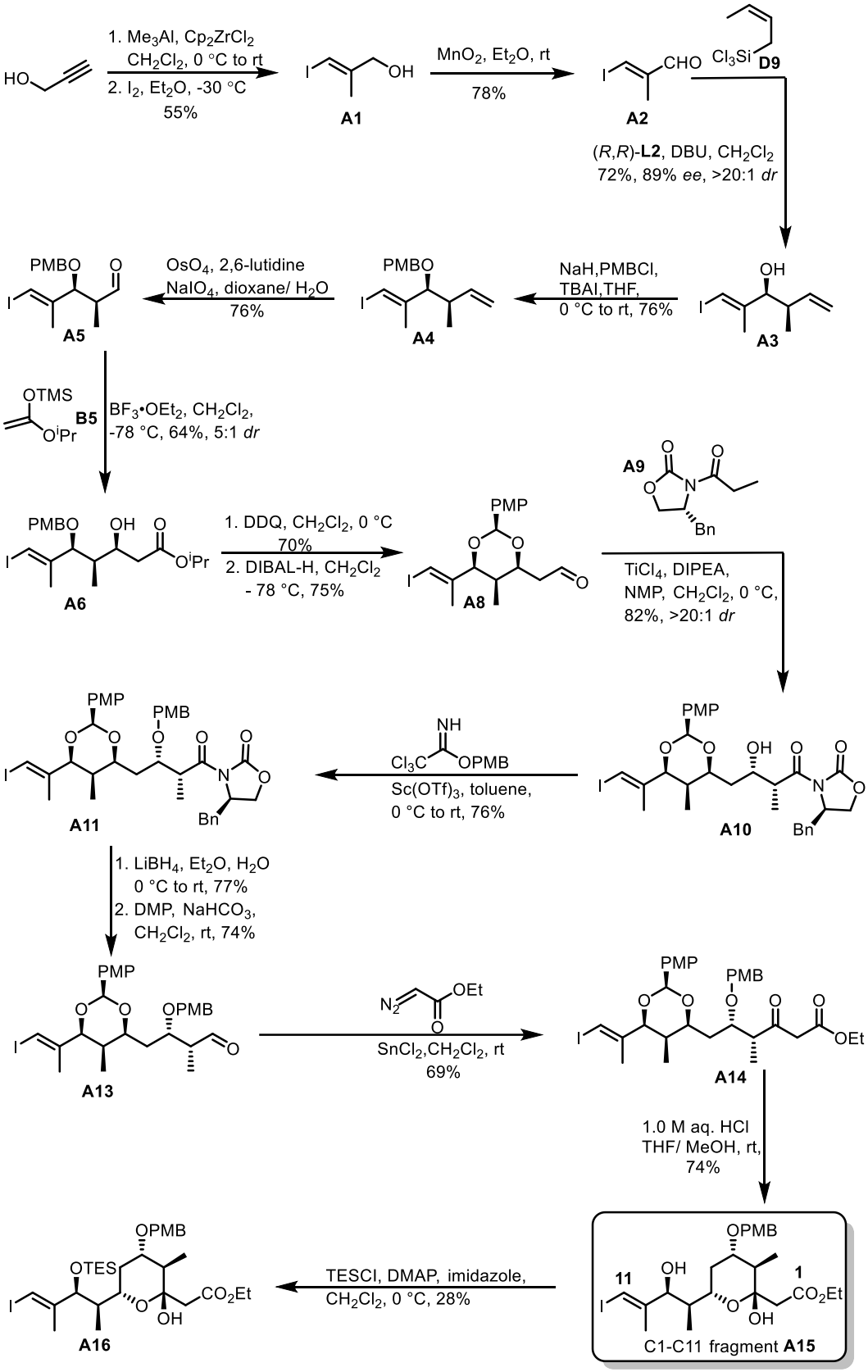
4.2 New synthetic routes towards C1–C11 fragment

As the benzylidene acetal was unexpectedly stable and required harsh conditions to remove, we considered other more labile protecting groups. Substitution of the aryl ring of a benzylidene acetal with a *p*-methoxy substituent increases the rate of hydrolysis by about an order of magnitude.[84] To explain this, in acidic conditions, *p*-methoxyphenyl (PMP) acetal is protonated to generate intermediate **I3**, which could be stabilized by conjugation from the methoxy substituent (Scheme 4.2). Therefore, intermediate **I3** is formed in higher concentration, increasing the rate of hydrolysis. Moreover, the final 4-methoxybenzaldehdye appears to be a better leaving group than benzaldehyde. Based on these analysis, we hoped the installation of PMP acetal would improve the synthetic yield of C1–C11 fragment.



Scheme 4.2. Mechanism of PMP acetal hydrolysis.

Our new synthesis of C1–C11 fragment (Scheme 4.3) started with a Zr–catalyzed carboalumination[85-88] of propargyl alcohol with Me_3Al, followed by iodination to afford *E*-allylic alcohol **A1** in 55% yield. Although the yield of preparation of **A1** requires some improvement, it was already less tedious than our previous synthetic route to compound **A1**. Identically, alcohol **A1** was then oxidized to aldehyde **A2** with MnO_2 in 78% yield. Leighton crotylation was carried out on **A2** to give homoallylic alcohol **A3** with good yield (72%, 89 *ee*, >20:1 *dr*). Alcohol **A3** was protected as PMB ether **A4** (76%) using PMBCl, and subsequent oxidation of the terminal alkene in **A4** produced aldehyde **A5** in 76% yield. A boron trifluoride-mediated Mukaiyama aldol reaction between silyl enol ether **B5** and aldehyde **A5** afforded alcohol **A6** as a mixture of separable diastereomers (5:1 *dr*), with the separated major (desired) diastereomer accounting for 64% yield. The product **A6** is the Felkin-Anh product, and the newly formed stereocenter was confirmed as (*S*) configuration through Mosher ester analysis. Treatment of **A6** with DDQ at 0 ºC for 1 h generated *p*-



Scheme 4.3. New synthetic route towards C1–C11 fragment.

methoxyphenyl acetal (70%), which was then reduced to the aldehyde **A8** in 75% yield using DIBAL-H.

To install two adjacent stereocenters in compound **A10**, we initially adopted a Leighton crotylation, however interestingly, only degradation of starting material was observed and no desired product was observed even under extended reaction time. The problem might be attributed to the acidity of crotyl trichlorosilane **D9**, and the PMP acetal is more sensitive to acid than benzylidene acetal. Thus, we turned to a Crimmins aldol reaction.[89] Aldehyde **A8** was treated with oxazolidinone **A9**, titanium tetrachloride, diisopropylethylamine and *N*-methyl-2-pyrrolidinone to yield **A10** in good yield and diastereoselectivity (82%, >20:1 *dr*). Regarding the stereoselectivity, the addition of *N*-methyl-2-pyrrolidinone promotes the formation of nonchelated transition state **T7** due to the coordination of the *N*-methyl-2-pyrrolidinone to the titanium center, therefore preventing the coordination of imide carbonyl to the titanium center and triggering the formation of Evans *syn* product as major product (Figure 4.1). We also attempted an Evans aldol[90] reaction to construct the two consecutive stereocenters in **A10** but this did not proceed in as a high yield. In addition, the procedure for Evans aldol reaction is much more tedious than Crimmins aldol reaction, which we selected for the preparation of **A10**.

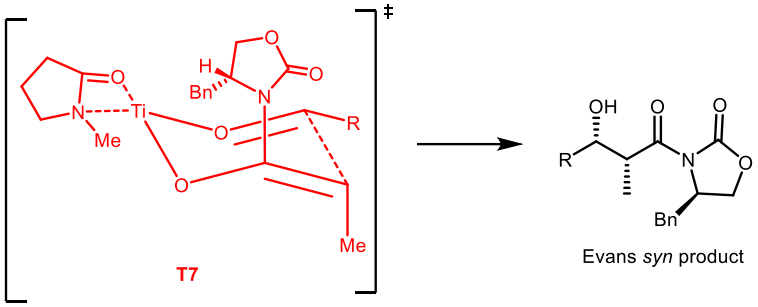


Figure 4.1. Transition state of titanium-mediated aldol reaction.

Protection of the secondary alcohol **A10** using 4-methoxybenzyl-2,2,2-trichloroacetimidate gave PMB ether **A11** in 76% yield. Compound **A11** was reduced using lithium borohydride (77%) and then oxidized by Dess-Martin reagent to generate aldehyde **A13** (74%). Subsequently, **A13** was converted into *β*-keto ester **A14** *via* Roskamp reaction[91] in 69% yield, which is ready for the final deprotection and cyclization. As 1.0 M aqueous HCl had been used for deprotection of the benzylidene acetal in our old synthetic route, we slightly modified the conditions, changing the reaction temperature to ambient temperature, and then applied it to ester **A14**. To our delight, the desired tetrahydropyran **A15** was obtained in high yield (74%) and purity. The relative stereochemistry of the different substituents on the six-membered ring were confirmed by NOESY correlations (OH/H7, OH/H5, H7/H5) and coupling constants analysis (Figure 4.2a and figure 4.2b). **A15** was then protected as TES ether **A16** in an unoptimized 28% yield, which would be coupled with the C13–C48 fragment to construct the C1–C48 skeleton through Suzuki cross coupling.

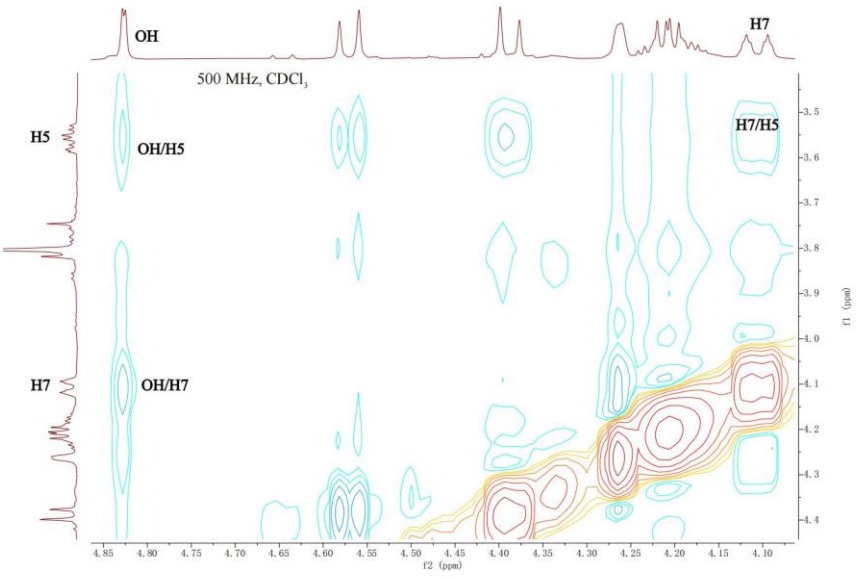


Figure 4.2a. The partial NOSEY spectrum of **A15**.

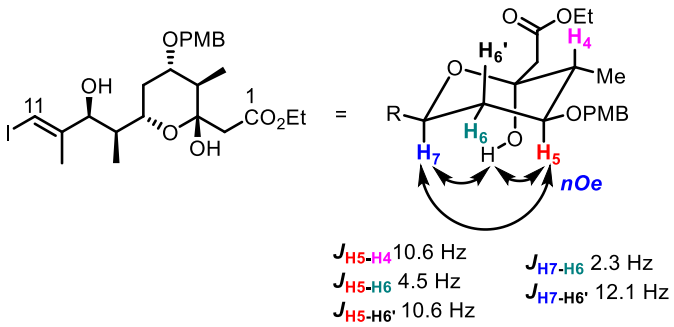
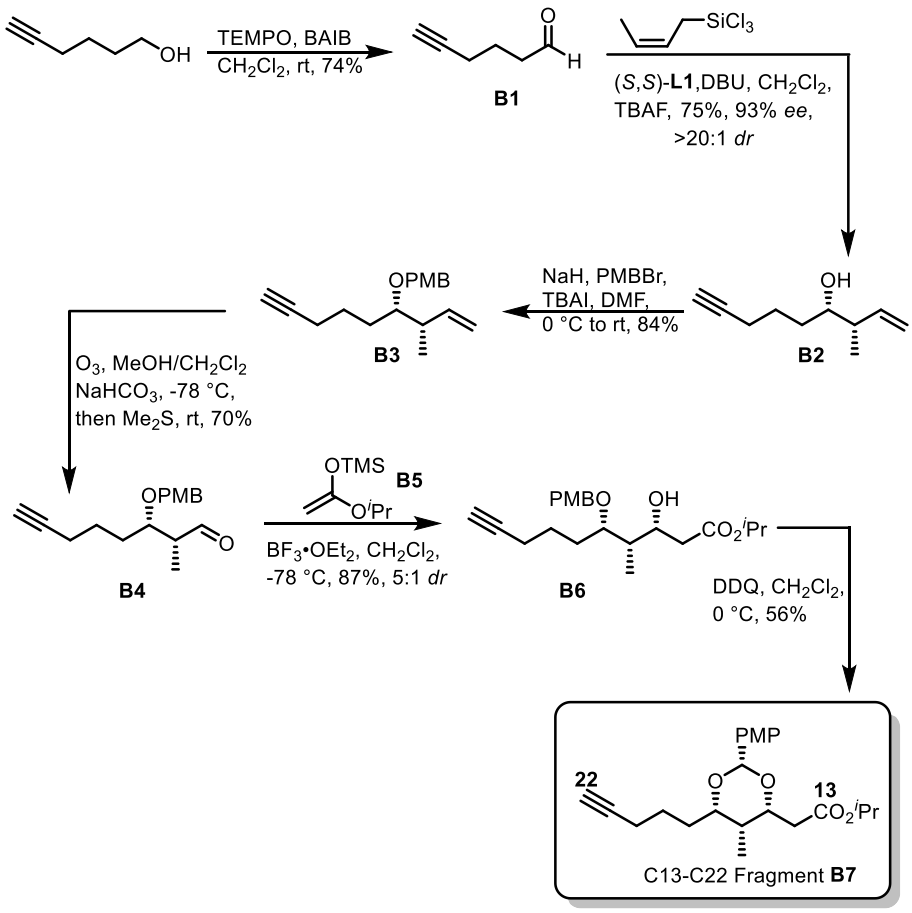


Figure 4.2b. The NOESY correlations of **A15**.

4.3 Synthesis of C13–C22 fragment

Synthesis of the C13–C22 fragment (Scheme 4.4) commenced with the oxidation of 5-hexynol to 5-hexynal **B1** (74%). Employing a similar strategy to that utilized for the C1–C11 fragment, a Leighton crotylation was carried out on **B1** to set two adjacent stereocenters in **B2** with good yield and stereoselectivity (75%, 93% *ee*, >20:1 *dr*). The newly-generated stereocenter of alcohol in **B2** was validated as (*S*) configuration *via* Mosher ester analysis (see experimental section). Protection of **B2** as PMB ether **B3** (84%) and ozonolysis[92,93] of terminal alkene of **B3**, followed by reductive workup with dimethyl sulfide, produced aldehyde **B4** in 70% yield over two steps. A Mukaiyama aldol was again employed to generate *β*-hydroxy ester **B6** as a mixture of inseparable diastereomers in 87% yield and 5:1 *dr*. The stereochemistry of the newly-installed hydroxyl group was confirmed as (*R*) configuration *via* Mosher ester analysis. Finally, alcohol **B6** was treated with DDQ under anhydrous condition to afford the 1,3-PMP acetal, furnishing the pure C13–C22 fragment **B7** as a single diastereomer in 56% yield, which was ready for coupling with the C23–C31 fragment to construct C13–C31 skeleton.



Scheme 4.4. Synthetic route toward C13–C22 fragment **B7**.

Besides, analysis of NOESY correlations of substituents in C13–C22 fragment and coupling constants (Figures 4.3a and 4.3b) further validated the stereochemistry of **B7**.

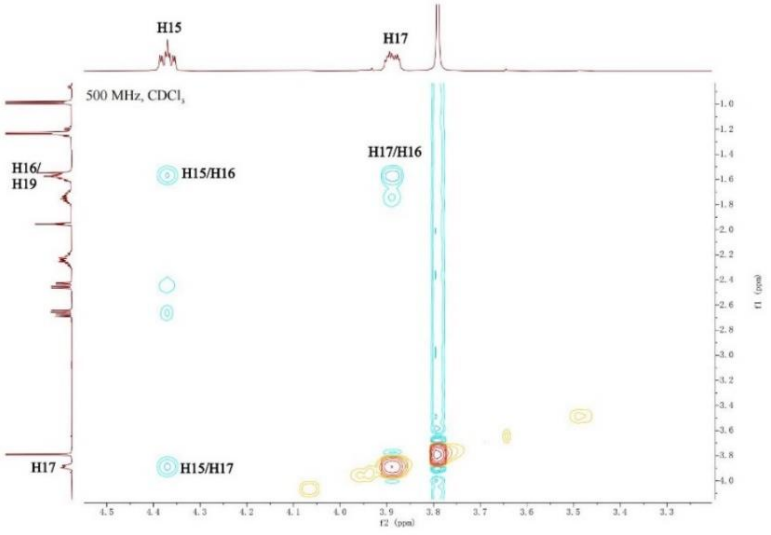


Figure 4.3a. The partial NOSEY spectrum of **B7**.

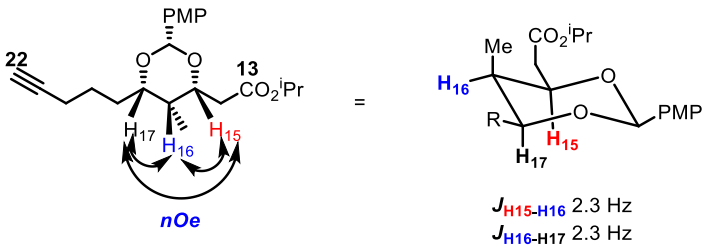


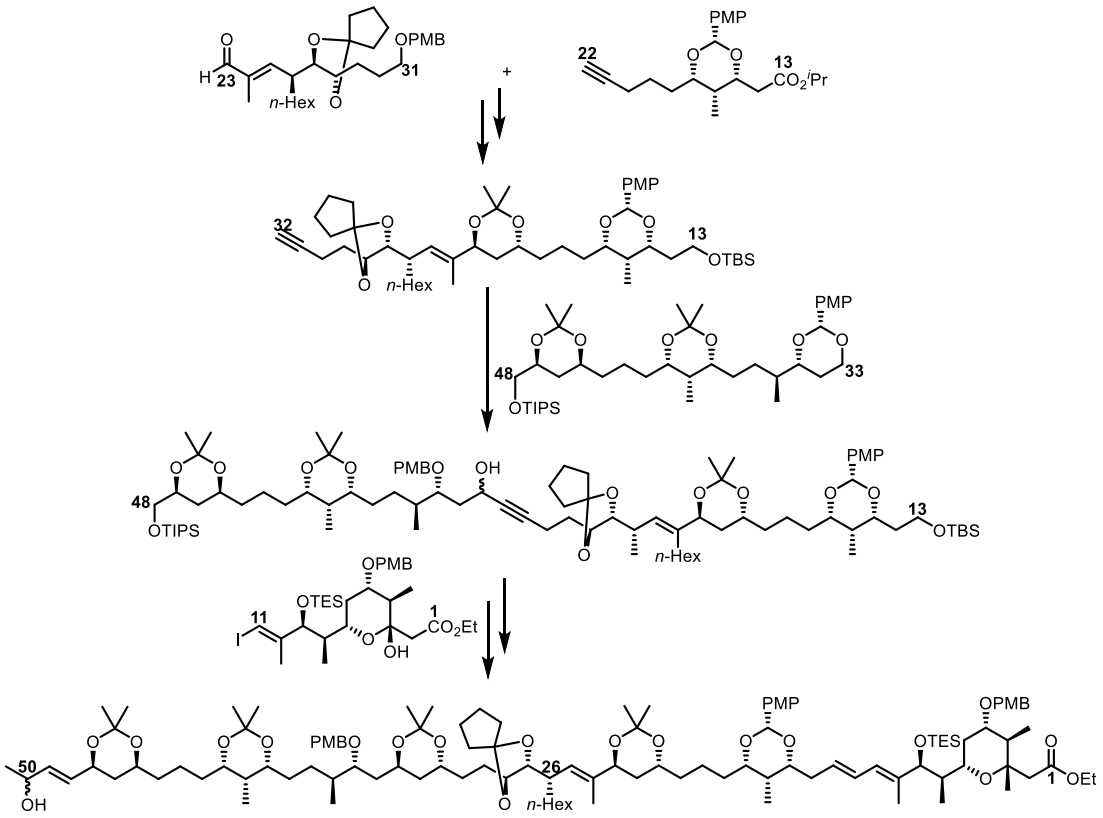
Figure 4.3b. The NOSEY correlations of C13–C22 fragment.

4.4 Summary

We have successfully improved the synthetic route to the C1–C11 fragment which now proceeds with better conversion and yield. In our new synthetic pathway, we avoided the costly cross metathesis with Grubbs II catalyst and the low yielding Evans-Prunet acetalization to form a benzylidene acetal, which proved a problem in the fragment deprotection / cyclization. More importantly, we switched the benzylidene acetal group to *p*-methoxyphenyl acetal group, which proved much more labile than the benzylidene acetal was easily deprotected using 1.0 aqueous HCl at room temperature, thus the C1–C11 fragment **A15** was obtained with higher yield and purity. Moreover, the relative stereochemistry of the substituents in **A15** were validated by nOe analysis. Secondly, we have completed the synthesis of the C13–C22 fragment, the stereochemistry of which was also confirmed by nOe analysis. This completes the synthesis of all the stambomycin fragments, and lifts the curtain on their combination to construct the full C1–C51 chain.

Chapter 5: Synthesis of the acyclic C1–C51 stambomycin chains

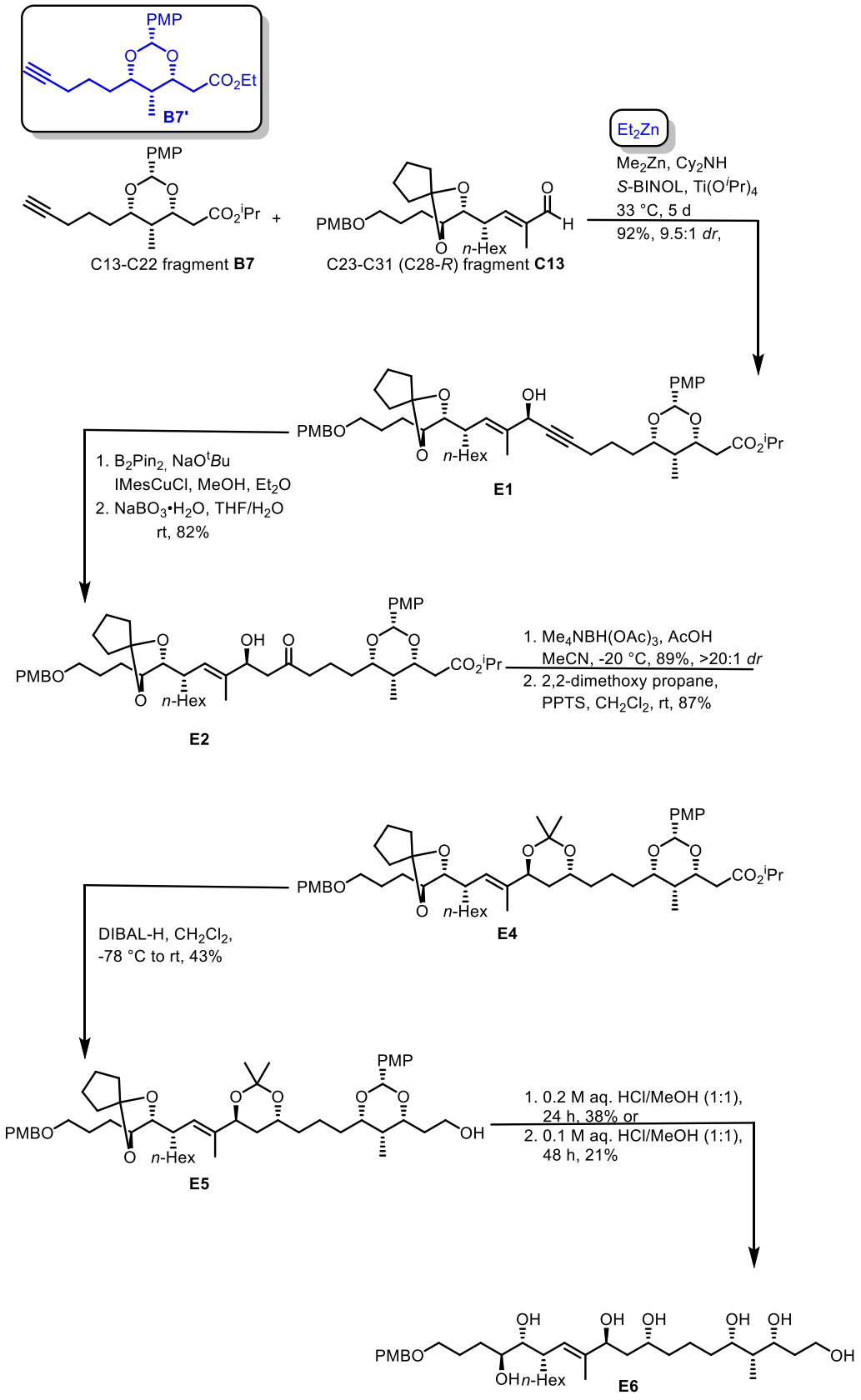
With C1–C11, C13–C22, C23–C31 and C33–C48 fragments in hands, we set about combining these four fragments together to synthesize our desired C1–C51 fragment. After careful consideration, we settled on the order of union of these fragments. To begin with (Scheme 5.1), the C13–C22 fragment was to be coupled with the C23–C31 fragment by an asymmetric alkyne addition to construct the C13–C31 skeleton. After a series of functional group transformations to prepare the C13–C32 fragment, this would be combined with the C33–C48 fragment to generate C13–C48 skeleton. In turn, the C13–C48 fragment was then to be coupled with the C1–C11 fragment *via* Suzuki cross coupling to produce the C1–C48 fragment. Subsequent HWE olefination, followed by *R*/*S*–CBS reduction would give the C1–C51 (C50-*S*) and C1–C51 (C50-*R*) fragments respectively, which are the starting point for the deprotection study on the full-length fragments. In this chapter, we also discuss deprotection studies on the C13–C31 and C13–C48 fragments, which pave the way for the deprotection study of the full 51 carbon chain. More importantly, with the fully deprotected two C13–C48 fragments (C28-*R*/*S*) in hands, we may be able to assign the stereocenter at C28, and could then move the correct diastereomer forward to produce the full-length fragments (C50-*R*/*S*).



Scheme 5.1. Combination sequence of the four small fragments of stambomycin D.

5.1 Synthesis and deprotection study of C13–C31 fragment

Synthesis of the C13–C32 fragment (Scheme 5.2) commenced with an (*S*,*S*)-BINOL/Ti(IV)-catalyzed asymmetric alkyne addition[94-97] between the C13–C22 alkyne and the C23–C31 (C28-*R*) aldehyde to afford propargylic alcohol **E1** with excellent yield and diastereoselectivity (92%, 9.5:1 *dr*). It is noteworthy that use of alkyne **B7'** bearing an ethyl ester group, and diethyl zinc, led to significantly inferior results. Diethyl zinc is always used in the literature instead of dimethyl zinc, however under these conditions the desired product was always obtained in low yield on account of transesterification of **B7'** to **B7** in the presence of $Ti(O^iPr)_4$, accompanied by formation of the 'ethyl addition' side product from



Scheme 5.2. Synthetic routes towards deprotected C13–C31 fragment **E6**.

addition of diethyl zinc to aldehyde **C13**. However, replacing **B7'** with **B7** (*i*-propyl ester), and diethyl zinc with dimethyl zinc, inhibited these side reactions. After fine-tuning the reaction conditions, to our delight, a much higher yield of the product was obtained upon slight heating to 33 ºC and extending the reaction time to 5 days. The proposed transition state of this process is shown in Figure 5.1, where the addition of the bulky secondary amine Cy_2NH increases the basicity of the methyl group of Me_2Zn and accelerates the deprotonation of the alkyne. The newly formed stereocenter of hydroxyl group was confirmed as our desired (*R*) configuration by Mosher ester analysis.

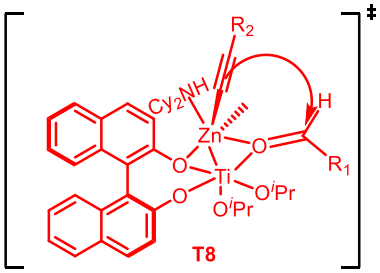


Figure 5.1. The transition state of BINOL/Ti(IV)-catalyzed asymmetric alkyne addition.

A regioselective hydroboration/oxidation[98,99] of the homopropargylic alcohol **E1** gave *β*-hydroxy ketone **E2** in 82% yield. In order to explain the regioselectivity, the transition state of this reaction was proposed in Figure 5.2, where the more Lewis acidic NHC-Cu complex prefers to form the *β*-vinylboronate due to more electron density at *β* position.

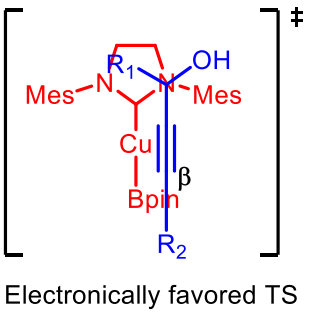
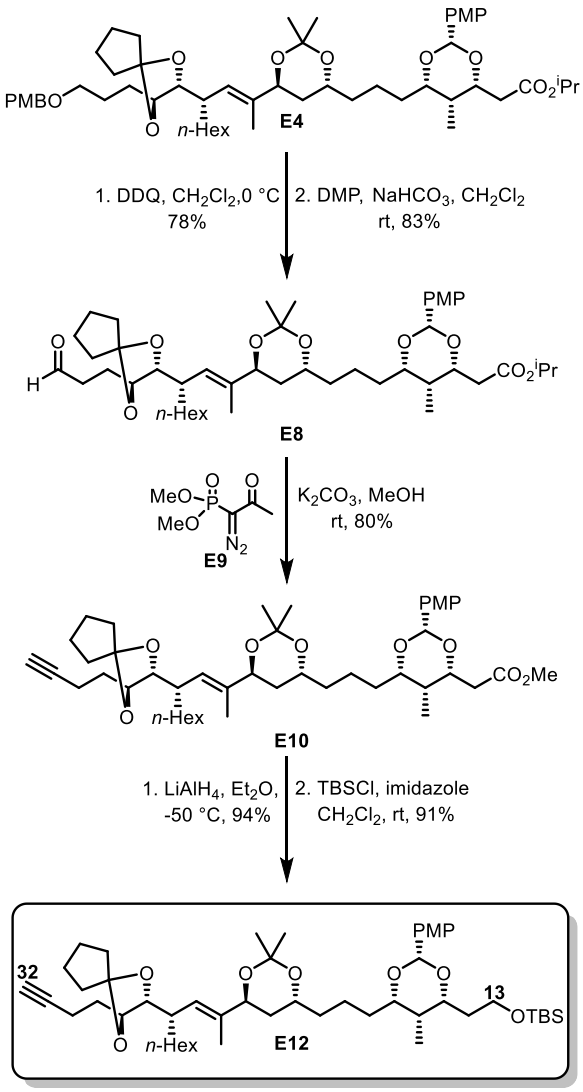


Figure 5.2. Proposed transition state of hydroboration of **E1**.

Subsequent Evans-Saksena reduction[100] was carried out on **E2** to generate the 1,3-*anti* diol (89%, >20:1 *dr*), which was then protected as acetonide **E4** (87%) using 2,2-dimethoxypropane. The relative stereochemistry of the 1,3-*anti* diol was confirmed by analysis of ^{13}C NMR chemical shift of the formed acetonide through the Rychnovsky method (see experimental section). Ester **E4** was then reduced to primary alcohol **E5** (43%) using DIBAL-H, which is the starting point for deprotection studies on C13–C31 fragment. Based on our previous deprotection studies on the C33–C51 fragment and C23–C31 fragment, we employed both 0.2 M aqueous HCl and 0.1 M aqueous HCl / methanol on the C13–C31 fragment. We were pleased to find that 0.2 M aqueous HCl gave the desired product **E6** in 38% yield, while the milder 0.1 M aqueous HCl also offered us product **E6** in 21% yield after an extended reaction time. The successful deprotection study on the C13–C31 fragment further rendered us confidence to achieve deprotection of full-length compound, not least as it contains the potentially troublesome cyclopentylidene acetal.

To complete the synthesis of C13–C32 fragment (Scheme 5.3), which will be coupled with C33–C48 fragment, acetonide **E4** was treated with DDQ to remove the PMB group, followed by Dess-Martin oxidation to afford aldehyde **E8** in 83% yield. Seyferth–Gilbert homologation[101-103] of **E8** with the Ohira-Bestmann reagent **E9** led to the formation of alkyne **E10** in 80% yield. During the alkynylation of **E8**, it was observed that the *iso*-propyl ester group was transesterified to a methyl ester group due to the presence of MeOH and a long reaction time (overnight). This transesterification is of no consequence, as both the *iso*-propyl ester or methyl ester are reduced to the primary alcohol **E10** using $LiAlH_4$ in the next step. Finally, alcohol **E10** was protected as its TBS ether **E11** (91%), which is ready for the

union with C33–C48 fragment.



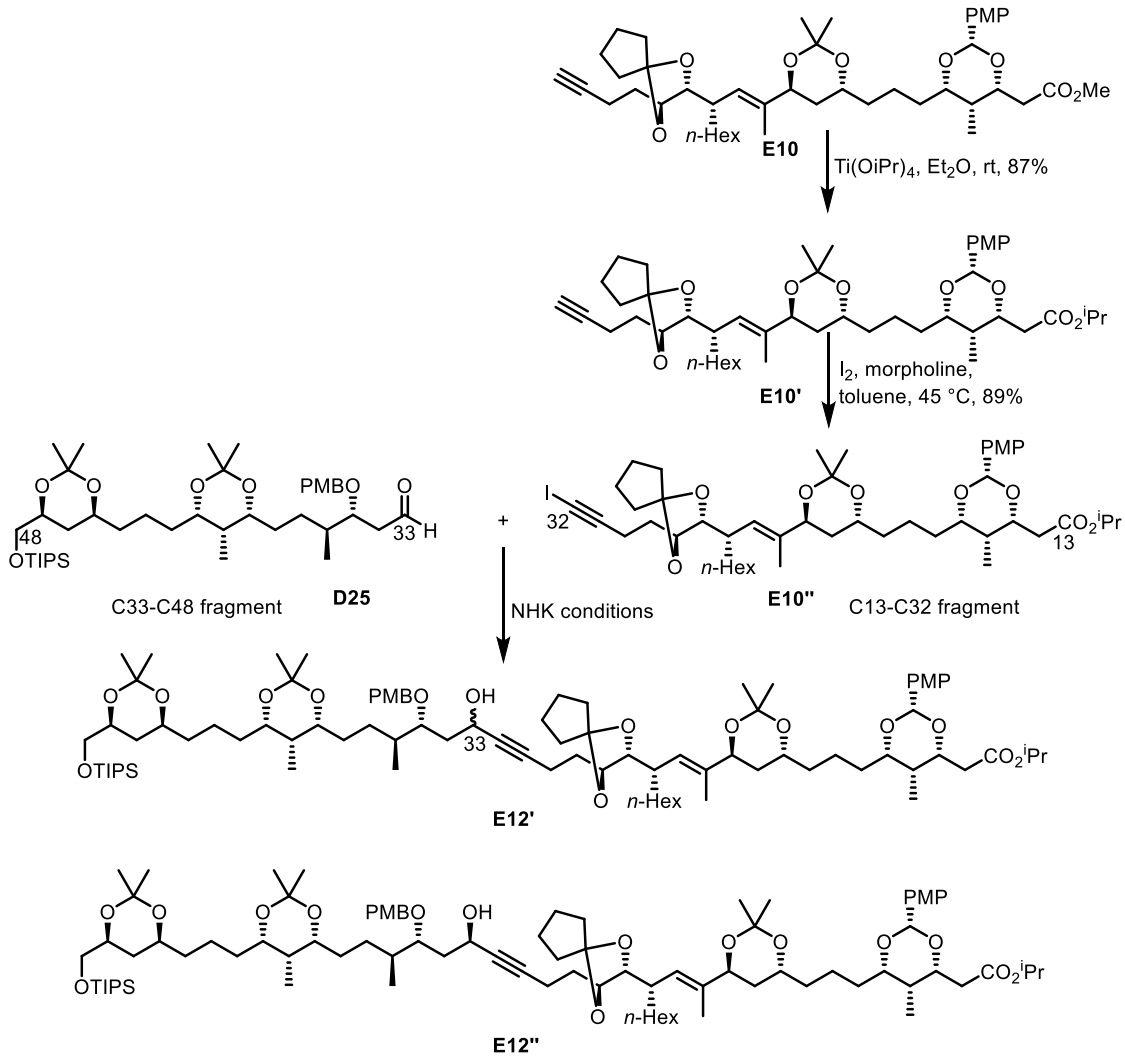
Scheme 5.3. Synthesis of C13–C32 fragment.

5.2 Synthesis and deprotection study of the C13–C48 fragment

The union of the C13–C32 and C33–C48 fragments to construct the C13–C48 skeleton proved challenging. A great number of conditions were explored but most of them failed to render us desired product. First of all, according to our successful application of BINOL/Ti(IV)-catalyzed asymmetric alkyne addition as used for the synthesis of the C13–C31 fragment, we adopted the same strategy to construct the C13–C48 propargylic alcohol

E12'' with the desired stereocenter at C33 in one step (Scheme 5.4). Before doing so, alkyne **E10** with its methyl ester group was transesterified to **E10''** bearing an *iso*-propyl ester group, as $Ti(O^iPr)_4$ would be used in the following asymmetric alkyne addition and would cause a potential transesterification issue as noted above. With the **E10'** alkyne and C33–C48 aldehyde in hands, (*S, S*)-BINOL/Ti(IV)–catalyzed asymmetric alkyne addition was attempted, however no desired product **E12''** was observed even with extended reaction time and higher reaction temperature. After several attempts at this strategy, we realized it appears not to be possible to combine the C13–C32 alkyne with the C33–C48 aldehyde to give the propargylic alcohol **E12''** in one step via asymmetric alkyne addition, perhaps due to the intrinsic complexity of this reaction and typical use of excess alkyne.

As a result, we turned our attention to a Nozaki-Hiyama-Kishi (NHK) reaction[104-109], which is a very useful methodology for the synthesis of natural products because of its mild reaction conditions, good yield and the possibility of performing the reaction with many functional groups. In preparation for this, iodination of alkyne **E10'** afforded iodide **E10''** (89%), which would be coupled with the C33–C48 aldehyde through the NHK reaction. We first adopted 97% $CrCl_2$ and anhydrous THF, which was our first attempt, and obtained propargylic alcohol **E12'** as a mixture of diastereomers (40%, 1:1 *dr*) (Scheme 5.4). In order to further improve the reaction yield, various reaction conditions (Table 5.1) were screened such as additional drying of the THF solvent, changing the reaction solvent, and the ratio of $CrCl_2$ and $NiCl_2$, but all failed to give the desired product. Although a new batch of $CrCl_2$ was utilized, and anhydrous DMF and THF from the solvent dispenser units were dried over 3Å molecular sieves for two days, the reaction yield still could not be improved.



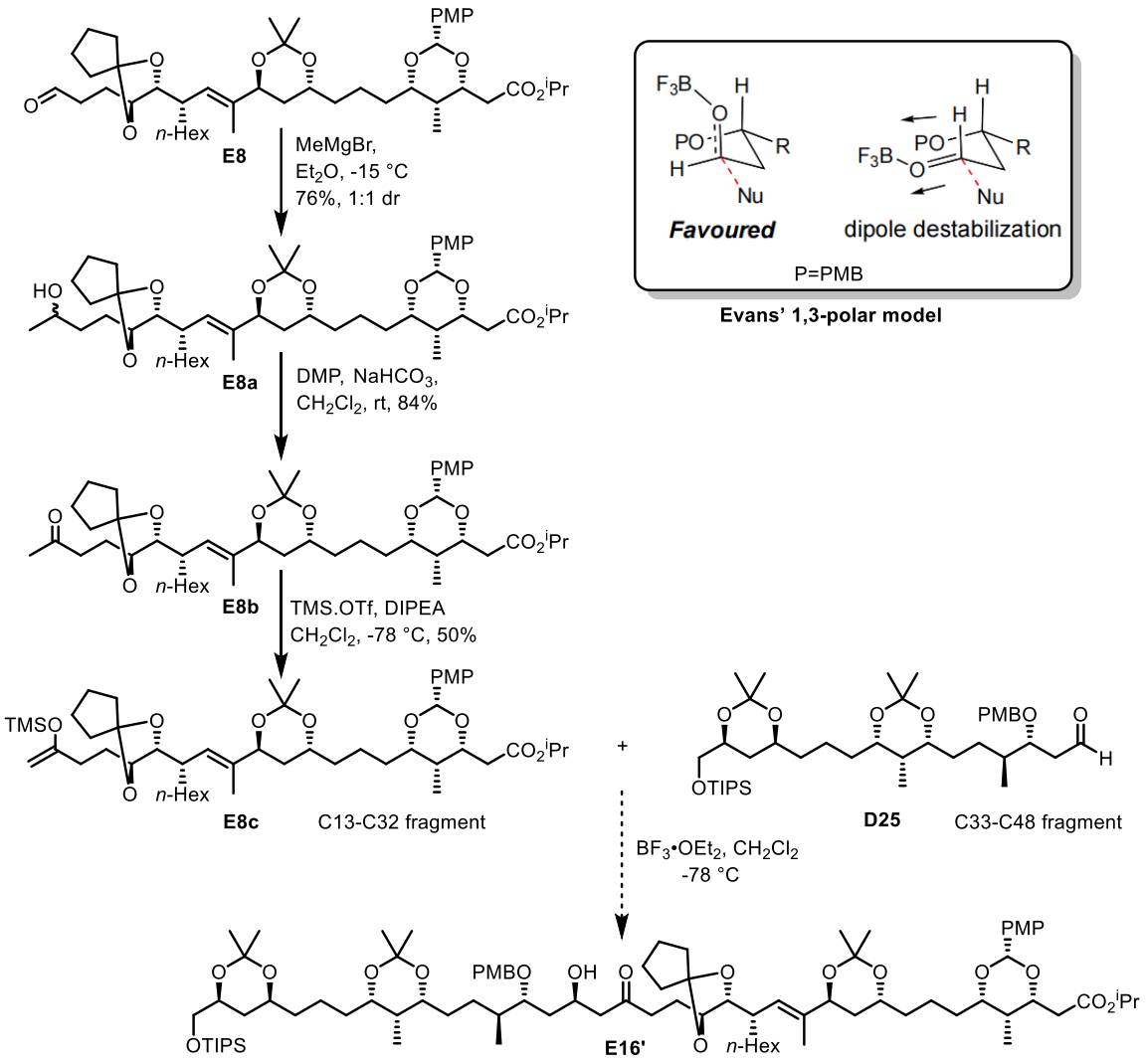
Scheme 5.4. Synthesis of C13–C48 skeleton using NHK strategy.

Table 5.1. Screened reaction conditions for NHK reaction.

Entry	Reagents	Solvent	Yield (%)
1	97% $CrCl_2$ (10.0 equiv.)	THF	40
2	97% $CrCl_2$ (10.0 equiv.)	DMF	0
3	97% $CrCl_2$ (10.0 equiv.)	THF/DMF[a]	0
4	99.9% $CrCl_2$ (10.0 equiv.) and $NiCl_2$ (0.05 equiv.)	THF/DMF[a]	0
5	99.9% $CrCl_2$ (10.0 equiv.) and $NiCl_2$ (1.0 equiv.)	THF	

[a]The ratio of THF and DMF cosolvent is 1:1.

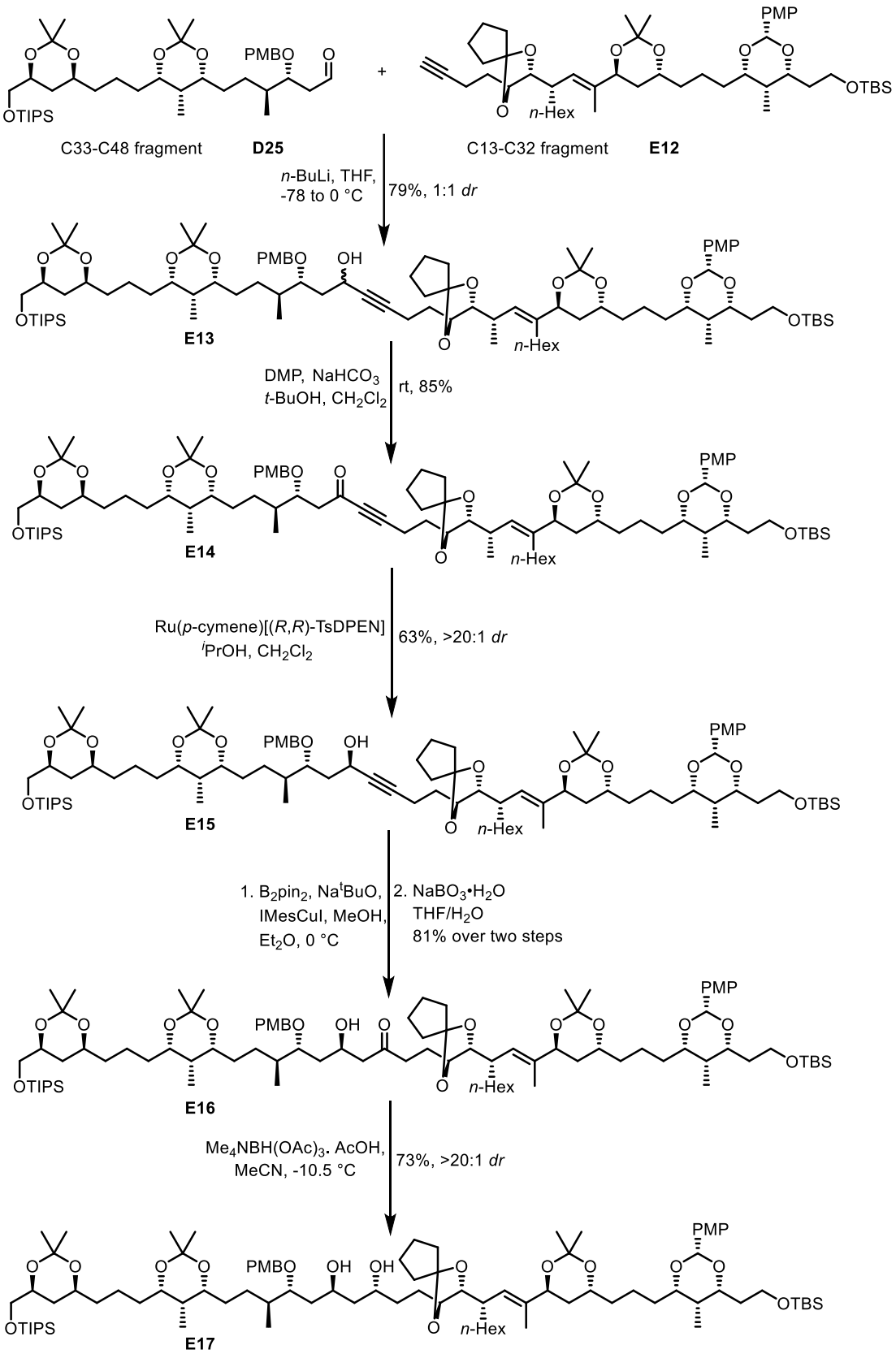
A review of the literature[110,111] suggested that Mukaiyama aldol reactions with *β*-OPMB aldehydes proceed with high levels of 1,3-*anti* induction (also OBn), according to Evans' 1,3-polar model (Scheme 5.5). Based on this, we proposed that a Mukaiyama aldol between the C33–C48 aldehyde bearing a *β*-OPMB, and TMS enol ether **E8c**, was expected to assemble the C13–C48 *β*-hydroxy ketone **E16'** (1,3-*anti* OPMB and OH), due to dipole stabilization. To begin with, aldehyde **E8** was treated with methylmagnesium bromide to produce secondary alcohol **E8a** in 76% yield as a mixture of diastereomers. **E8a** was oxidized by Dess-Martin reagent to yield methyl ketone **E8b** in 84% yield, which was treated with TMS triflate at -78 ºC to produce TMS enol ether **E8c** (50%). The TMS enol ether product is particularly labile and even with careful workup, it is still prone to reverse back to methyl ketone **E8b**. With TMS enol ether **E8c** and aldehyde **D25** in hand, a Mukaiyama aldol was attempted at -78 ºC, however no reaction occurred even with extended reaction time as well as increased reaction temperature, and only degradation of starting material was observed. Additionally, substitution of $BF_3{\cdot}OEt_2$ with $TiCl_4$, and/or increasing the equivalents of TMS enol ether, could not give us the desired product either. We speculated that the main reason is the complexity of the molecule itself.



Scheme 5.5. Synthesis of **E16'** using Mukaiyama aldol.

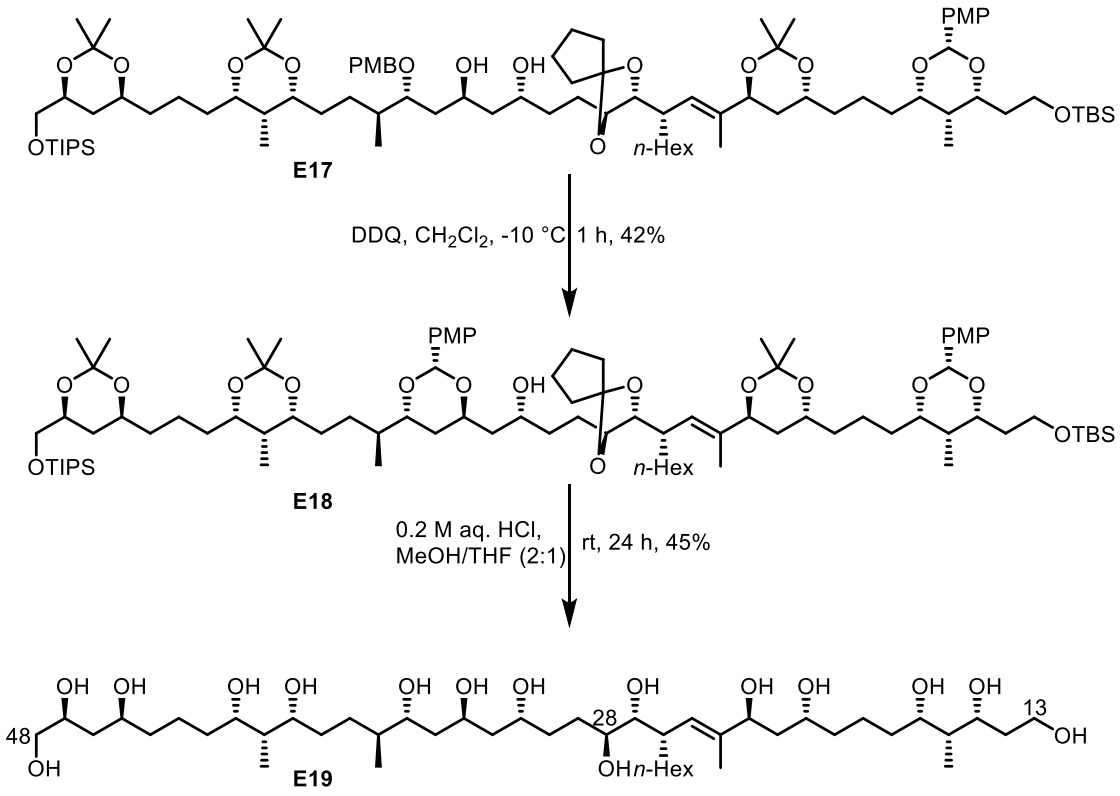
Since neither of these strategies could achieve the C13–C48 fragment, we turned our attention to the 'traditional' strategy of using *n*-BuLi to combine the C13–C32 alkyne and C33–C48 aldehyde (Scheme 5.6). As mentioned in Chapter 5.1, alkyne **E10** was reduced with $LiAlH_4$ and then protected as TBS ether **E12**, which was then coupled with C33–C48 aldehyde using *n*-BuLi to furnish propargylic alcohol **E13** as a mixture of separable diastereomers in pleasing yield (79%, 1:1 *dr*). The undesired diastereomer was then oxidized by Dess-Martin reagent to generate alkynone **E14** in 85% yield. Subsequent Noyori

asymmetric hydrogenation of **E14** gave the desired propargylic alcohol **E15** in 63% yield (>20:1 *dr*). Adopting a similar strategy to that used for C13–C31 fragment, the propargylic alcohol underwent regioselective hydroboration / oxidation to give *β*-hydroxy ketone **E16** in 81% yield over two steps. Evans-Saksena reduction was again employed on **E16** with a slightly higher reaction temperature (-10.5 ºC) to generate 1,3-*anti* diol **E17** in 73% yield (>20:1 *dr*), and the relative stereochemistry of the 1,3-*anti* diol was confirmed after acetonide formation (**E20**, Scheme 5.8) through the Rychnovsky method. With the diol **E20** in hands, we set about exploring deprotection conditions for this big C13–C48 fragment. The PMB group always requires relatively harsh conditions to deprotect, whereas the remaining protecting groups in the C13–C48 fragment demand mild deprotection conditions to avoid degradation. Initially, we attempted to utilize DDQ and water to remove PMB group but unfortunately, degradation products were always obtained even with lower reaction temperatures. As a consequence, the formation of a PMP acetal from the 1,3-*anti* PMB group and hydroxyl group in compound **E17** was considered, as this would be an ideal target for deprotection study of C13–C48 fragment on account of its lability.



Scheme 5.6. Synthesis of 1,3-*anti* diol **E17**.

In the event, treatment of **E17** with DDQ under anhydrous / cold conditions produced the desired PMP acetal **E18** with 42% yield with some unknown side products (Scheme 5.7). Based on our successful deprotection conditions for C1–C27, C33–C48, C23–C31 and C13–C31 fragments, the C13–C48 fragment was then submitted to 0.2 M aqueous HCl in methanol and, to our delight, the desired polyol product **E19** was obtained in 45% yield by reversed phase HPLC purification. In addition, 0.1 M aqueous HCl conditions were applied on **E18** and the desired product was observed with an extended reaction time to two days. However, as the reaction time extends, more elimination products appear to be formed based on mass spectroscopic analysis. Therefore, 0.2 M aqueous HCl gave us the best yield of the fully deprotected C13–C48 fragment **E19**.



Scheme 5.7. Deprotection study of C13–C48 fragment.

COSY correlations analysis (Figure 5.3) shows that isomerization of the C24–C25 double bond to a C23–C24 double bond (which had been observed earlier in the group) did not occur, and this gives us confidence to deprotect the full-length compound.

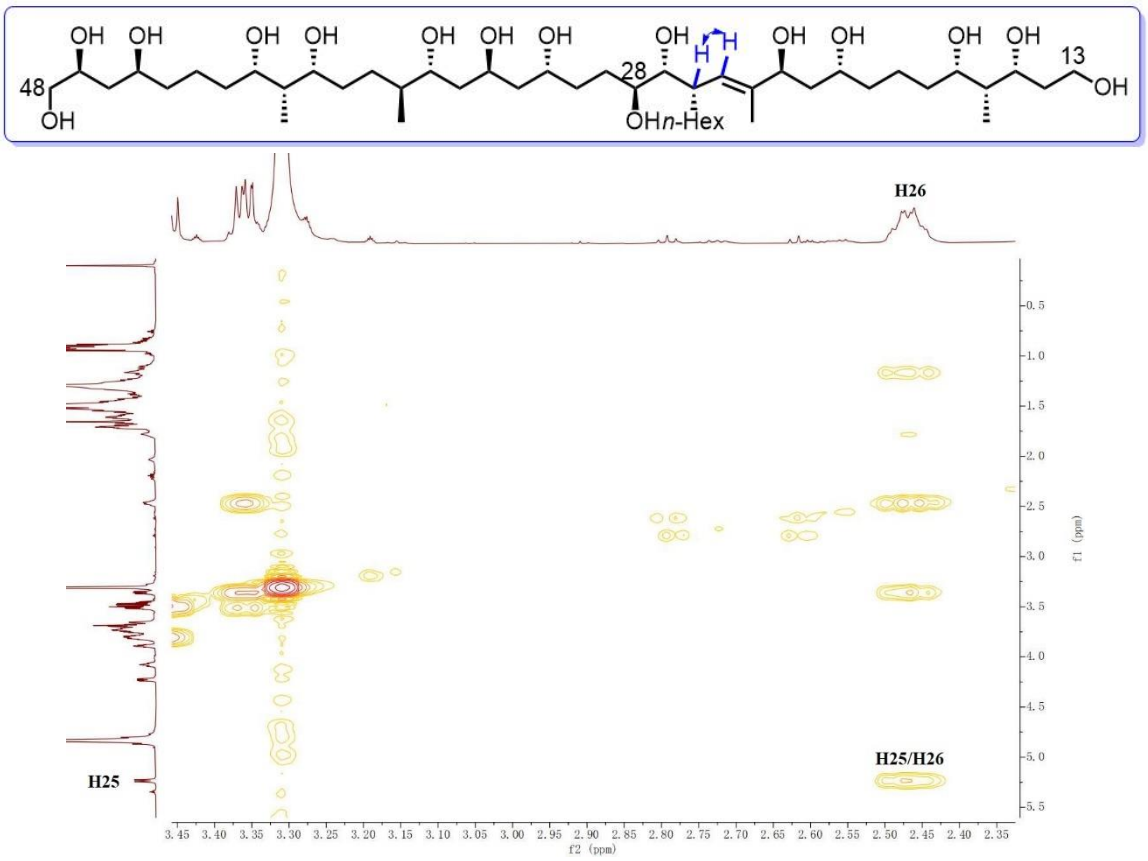


Figure 5.3. COSY correlations of C13–C48 fragment **E19**.

With fully deprotected C13–C48 (1,2-*anti* diol at C27 and C28) fragment in hands, attention now turned to comparison of its NMR data with the corresponding NMR data of stambomycin D (Figures 5.4a, 5.4b, 5.4c and 5.5). To our delight, the ^{1}H and ^{13}C NMR data for **E19** show remarkable agreement with that for stambomycin D, in particular in the central area (C16–C44). Truncation of the acyclic fragment at C13 and C48 can explain the larger discrepancies of ^{1}H and ^{13}C NMR data at C13 and C48. Additionally, another discrepancy was noted at one of the C37 protons, which was already illustrated in Chapter 2.4, suggesting a potential minor reassignment is required. More importantly, we identified the ^{13}C NMR

chemical shift of C28 in our synthesized C13–C48 (1,2-*anti* diol at C27 and C28) fragment is at 73.9 ppm, while that in stambomycin D and stambomycin D aglycon are 74.2 and 73.7 respectively. While a close match, we are currently waiting for the other diastereomer C13–C48 (1,2-*syn* diol at C27 and C28) to be synthesized in the group, which will enable comparison of these two synthesized diastereomers with stambomycin D to assign the correct stereocenter at C28. (Compound **E19** requires to be repurified by reverse phase HPLC as it appeared to degrade during the process of NMR running.)

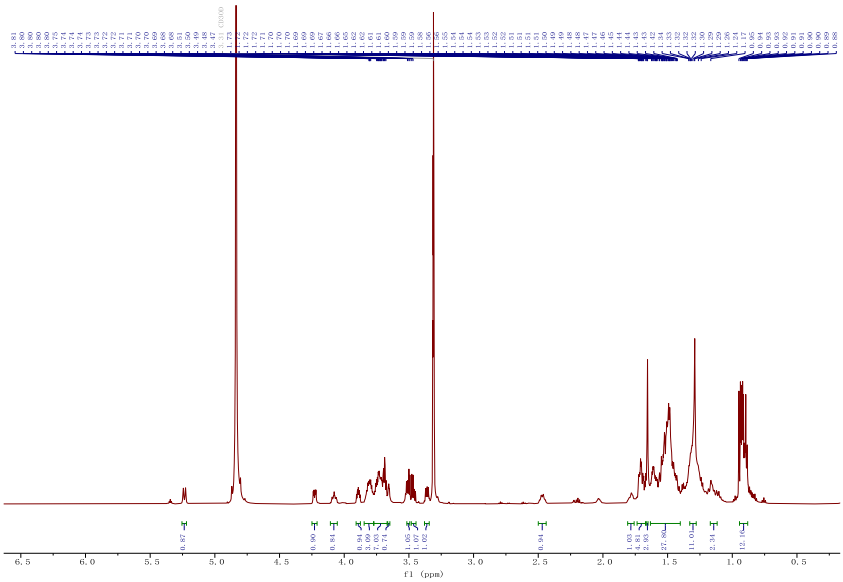


Figure 5.4a. ^{1}H NMR spectrum of compound **E19** (600 MHz, MeOD).

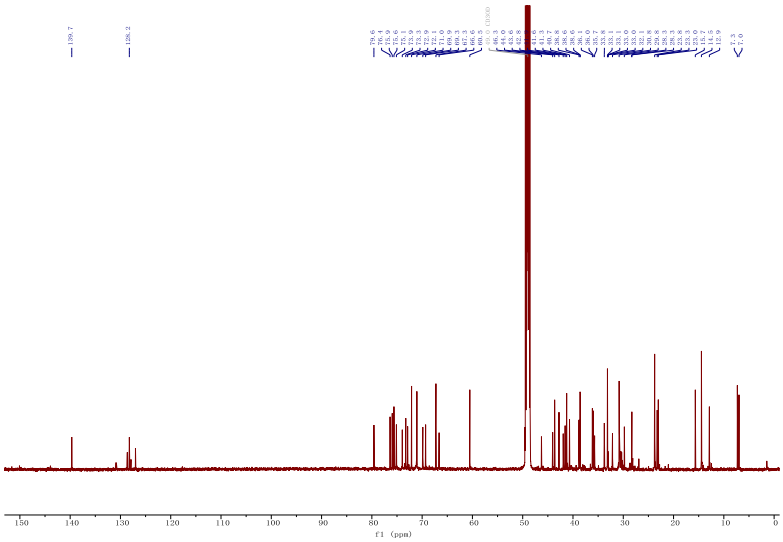


Figure 5.4b. ^{13}C NMR spectrum of compound **E19** (600 MHz, MeOD).

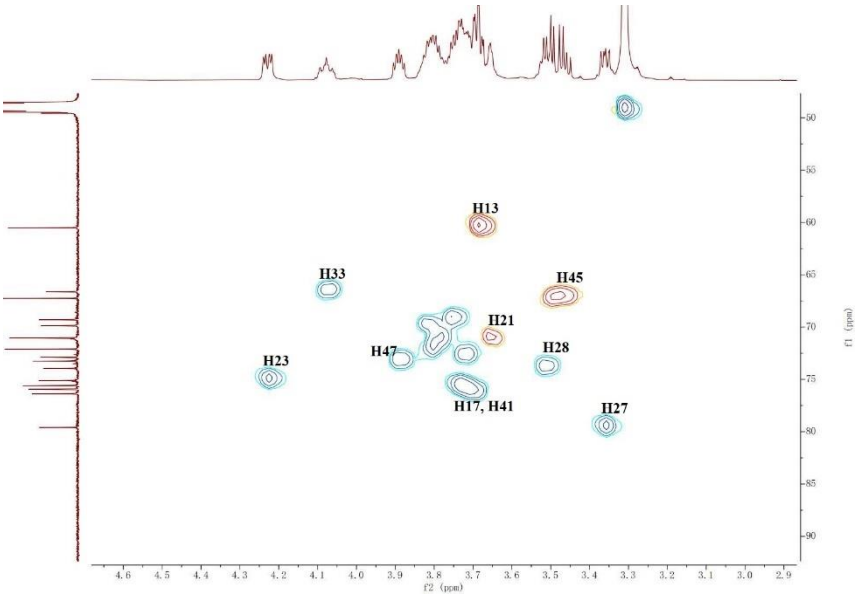
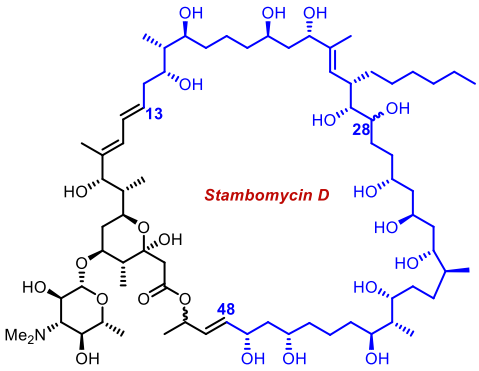
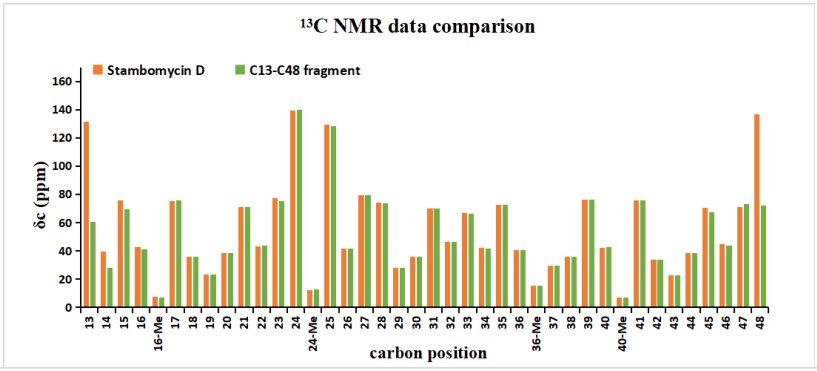


Figure 5.4c. Partial HSQC spectrum of compound **E19** (600 MHz, MeOD).





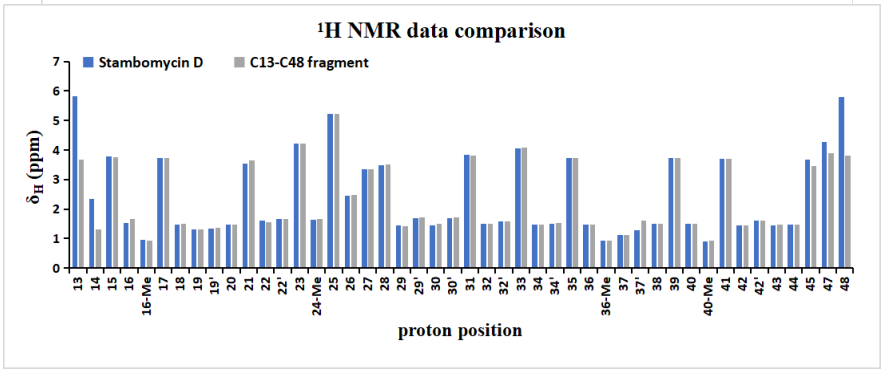
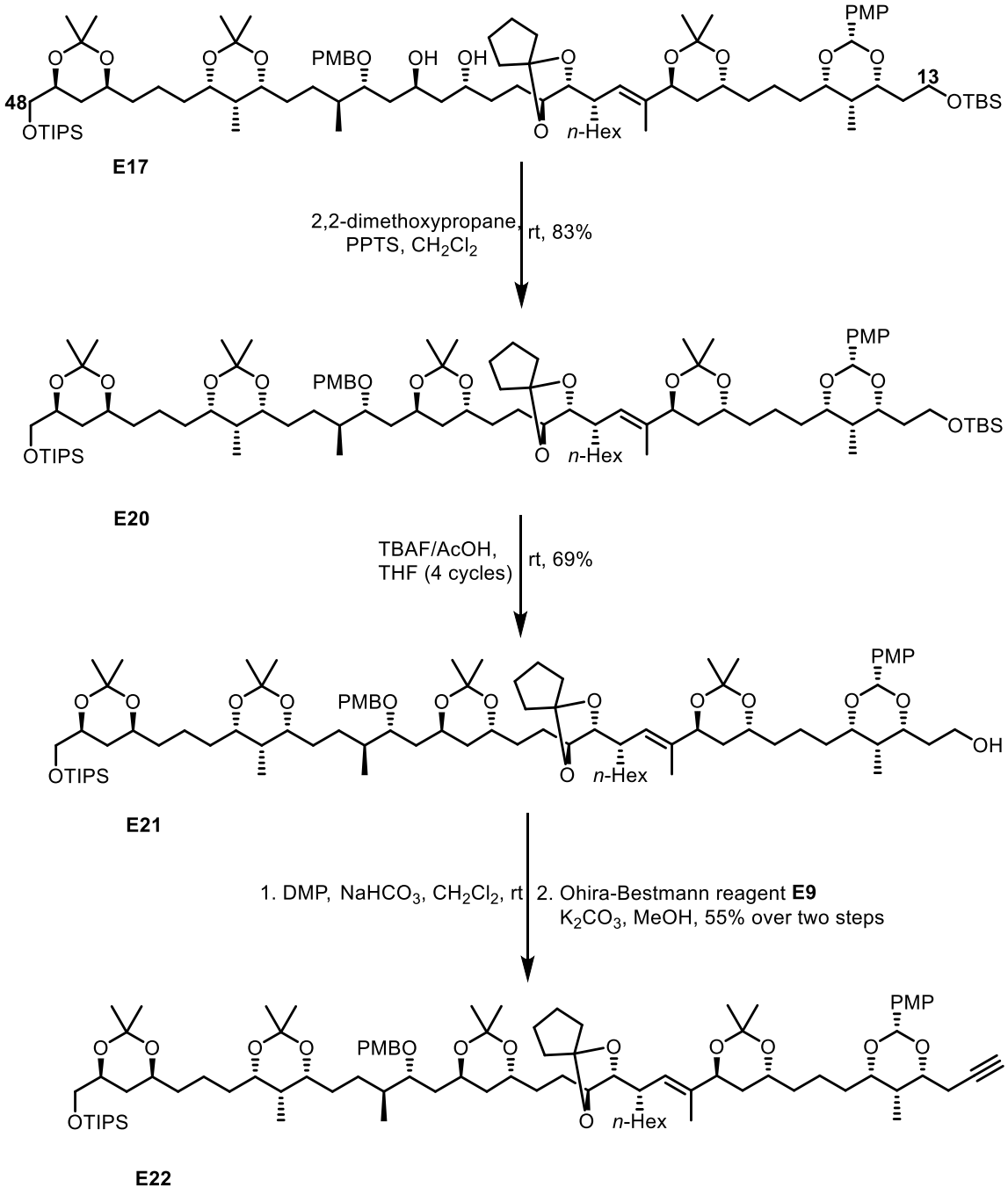


Figure 5.5. Comparison of ^{1}H and ^{13}C NMR data of **E19** with stambomycin D.

5.3 Synthesis of the C1–C48 fragment

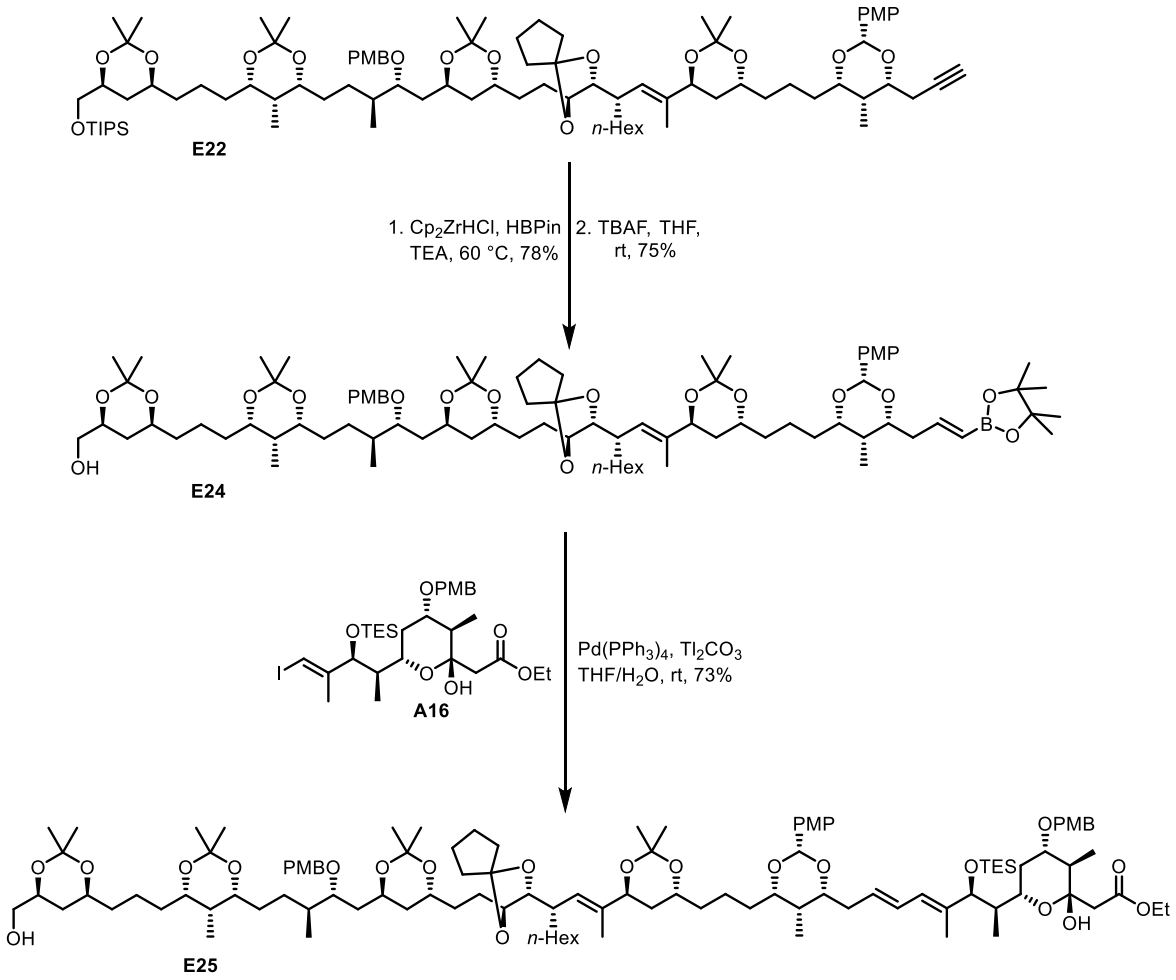
Synthesis of C1–C48 fragment (Scheme 5.8) started with protection of the 1,3-*anti* diol in **E17** as acetonide **E20** (83%), which served to confirm the relative stereochemistry of the 1,3-*anti* diol in **E17** through the Rychnovsky method.[49.50] Selective deprotection of the primary TBS group in the presence of the primary TIPS group was achieved by acetic acid buffered TBAF solution, after exploring numerous other deprotection conditions, and the desired product **E21** was obtained in 69% yield after four cycles (reaction quenched before reaching completion to avoid TIPS removal and the recovered starting material was resubmitted to the deprotection conditions). Dess-Martin oxidation of **E21** afforded the corresponding aldehyde, and the crude residue was alkynylated with Ohira-Bestmann reagent to yield alkyne **E22** in 55% yield over two steps. During the homologation, it was observed that the PMP acetal tended to cleave readily, presumably *via* enolization of the adjacent aldehyde under the basic reaction conditions and E1cb elimination. This gave rise to the formation of a side product which not only caused purification problems of the product but also lowered the yield of alkyne **E22**, which had also proven an issue for our synthesis of the C1–C27 fragment. The problem was addressed by use of excess Ohira-Bestmann reagent during the synthesis of C1–C27 fragment, however this solution did not improve the yield of **E22** significantly. Other conditions were also attempted, such as replacing the base K_2CO_3 with NaOMe, and performing the reaction -78 ºC. Unfortunately, higher yields of the desired product **E22** could not be obtained, therefore, we decided to stick to our original reaction conditions.



Scheme 5.8. Synthesis of alkyne **E22**.

To complete the synthesis of the C1–C48 framework (Scheme 5.9), a Zr-mediated hydroboration[112] of **E22** generated the *trans* vinylboronic ester in 78% yield, which was treated with TBAF to remove the primary TIPS group, forming compound **E24** in 75% yield.

A Suzuki cross coupling[113] was carried out between the alkenyl iodide **A16** and boronic ester **E24** to give the C1–C48 fragment **E25** in 73% yield. Previous exploration of reaction conditions for this coupling suggested that the use of Tl_2CO_3 is of essence for success, giving the C1–C48 fragment in the best yield.

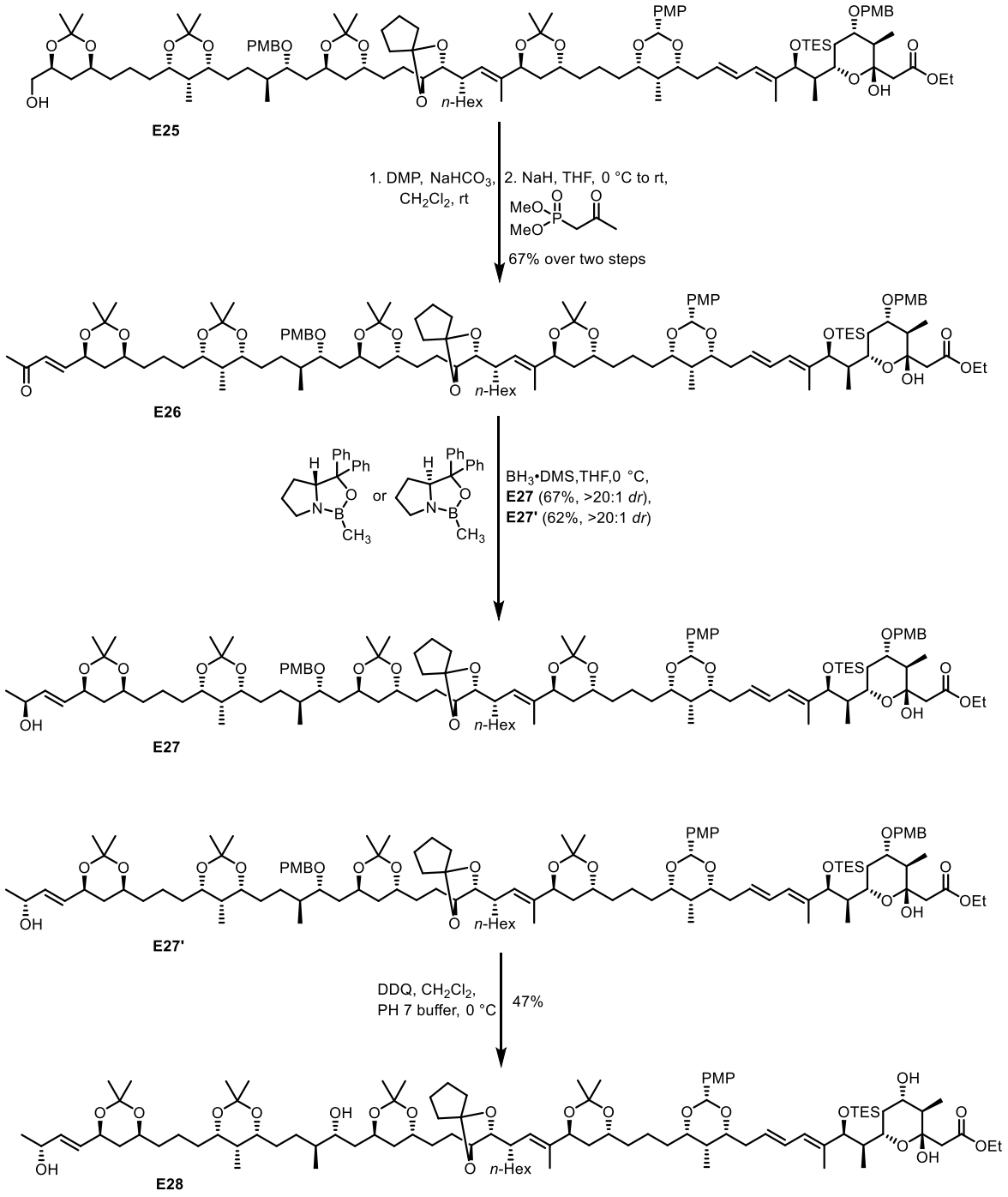


Scheme 5.9. Synthesis of C1–C48 fragment **E25**.

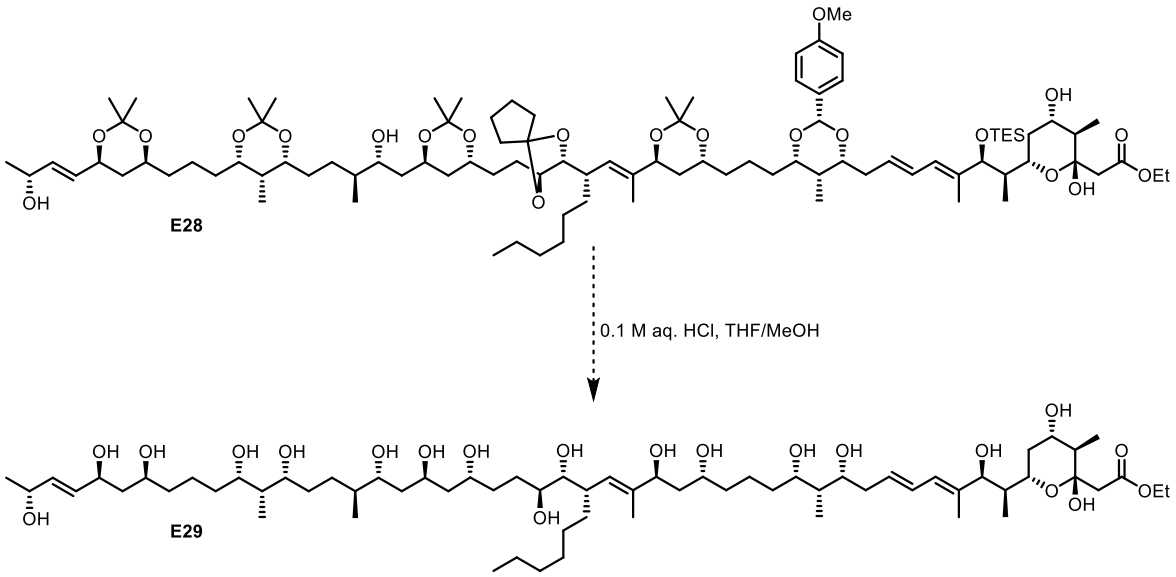
5.4 Synthesis and deprotection study of C1–C51 fragment

To complete the synthesis of C1–C51 acyclic fragment (Scheme 5.10), elongation of C1–C48 fragment commenced with a Dess-Martin oxidation at C48, followed by HWE olefination to afford enone **E26** in 67% yield over two steps. Because of the uncertainty of

the stereocenter at C50, **E26** was treated with (*R*)–CBS and (*S*)–CBS reagents respectively to achieve asymmetric CBS reduction, giving enol **E27** (67%, >20:1 *dr*) and **E27'** (62%, >20:1 *dr*) separately. The following attempt of deprotection of PMB group was carefully carried out on enol **E27'** at 0 ºC with the addition of DDQ and pH 7 buffer, producing the desired product **E28** (47%) with some degradation side products. Having obtained **E28**, we turned our attention to attempt deprotection on it. As we discussed in previous chapters, 0.1 M HCl and 0.2 M HCl are suitable conditions for deprotection of C1–C27, C33–C51, C23–C31, C13–C31 and C13–C48 fragments. Therefore, we first adopted the milder 0.1 M aqueous HCl condition to 1.2 mg of compound **E28** in the presence of THF/MeOH (1:1) (Scheme 5.11). After stirring at room temperature for 24 h, the reaction was quenched and several spots were observed by reversed phase TLC plates. Purification of these spots was very difficult due to very small amount of material and unfortunately no direct conclusions could be drawn. As a result, more compound **E28** are required to explore suitable deprotection condition.



Scheme 5.10. Synthesis of C1–C51 acyclic fragment.



Scheme 5.11. Deprotection attempt on C1–C51 acyclic fragment **E28**.

5.5 Summary

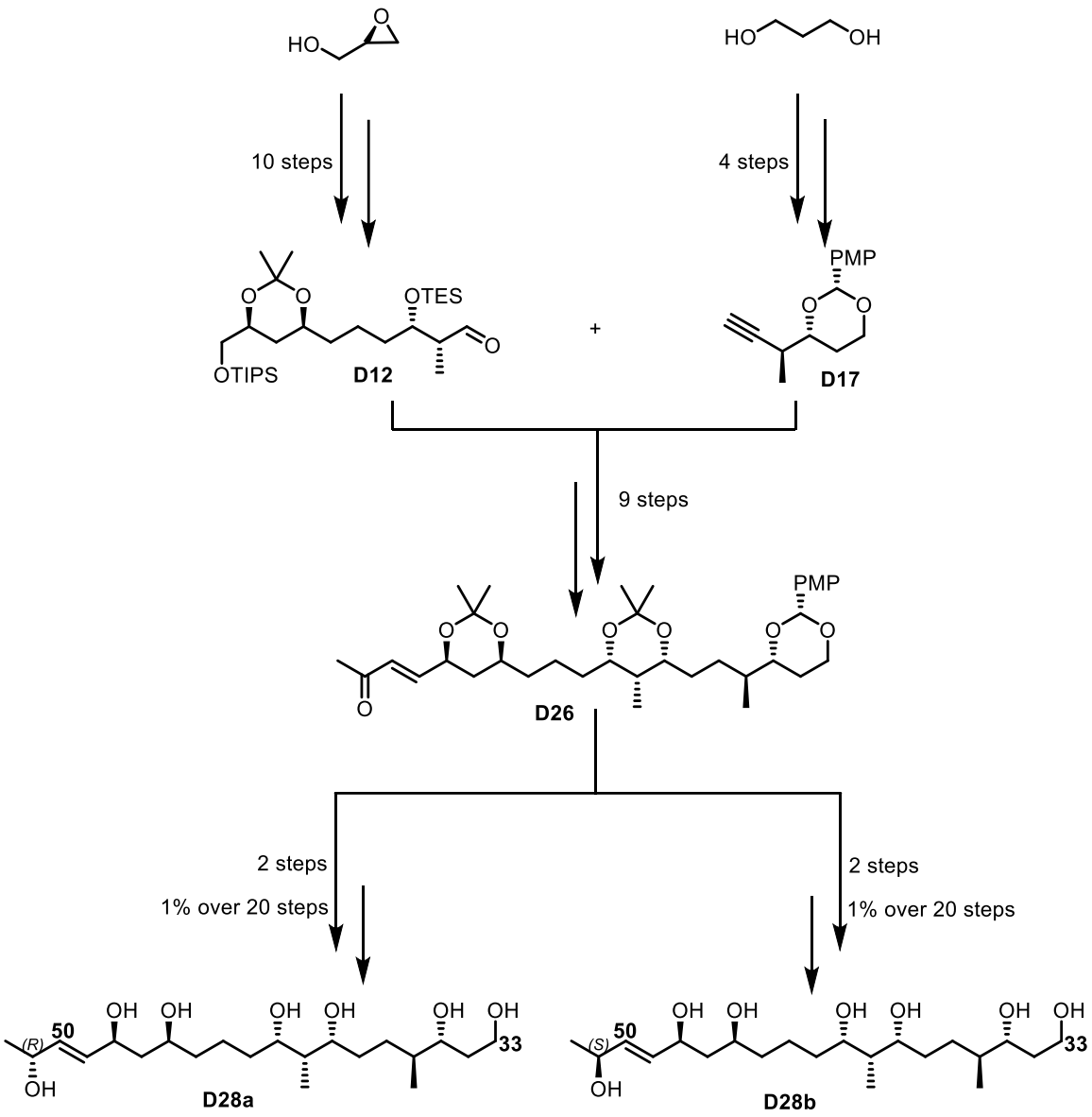
With four key fragments (C1–C11, C13–C22, C23-31and C33–C48) in hand, first of all, we successfully synthesized and deprotected the C1–C31 fragment (the combination of C13–C22 and C23–C31 segments) with 0.1 M aqueous HCl and 0.2 M aqueous HCl conditions. Secondly, synthesis of the C13–C48 (1,2-*anti* diol at C27 and C28) fragment was achieved through union of C13–C32 and C33–C48 segments. The following deprotection study was proceeded smoothly with 0.1 M aqueous HCl and 0.2 M aqueous HCl conditions as well. More importantly, the NMR data of the fully deprotected C13–C48 fragment showed remarkable agreement with that of the stambomycin D, which supports the predicted stereochemistry of the molecule as a whole, and quite possible at C28. Subsequently, two C1–C51 acyclic fragments differing in the stereocenter of C50 were successfully prepared by Suzuki cross coupling, followed by late stage HWE olefination and asymmetric reduction. Disappointingly, the first attempt on deprotection of the C1–C51 acyclic fragment failed due

to little starting material, and more material is being prepared for the final deprotection study of the full-length carbon chain.

Chapter 6: Conclusion and future work

6.1 Conclusion

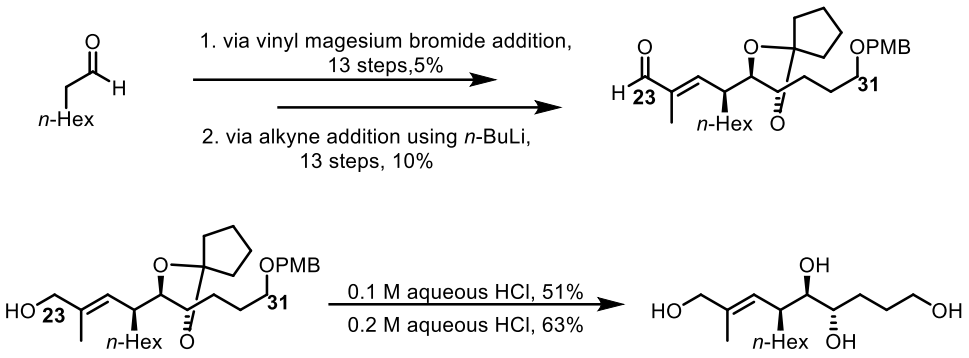
In the first place, we successfully synthesiszed and deprotected our southern hemisphere C33–C51 fragments (Scheme 6.1) of stambomycin D in 21 steps in the longest linear sequence with 1% overall yield for both two C33–C51 fragments (C50-*R*/*S*), which allowed us a preliminary comparison of NMR spectra with stambomycin D. Comparsion of NMR



Scheme 6.1. Synthesis and deprotection of C33–C51 fragments.

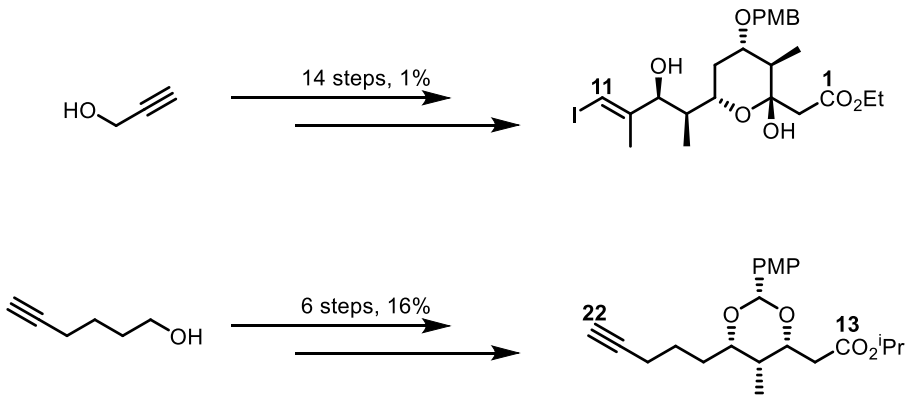
data of C33–C51 fragments with that of stambomycin D show excellent agreement between them, strongly supporting the sequence-based stereochemical assignment of this region of stambomycin D. Additionally, the successful application of mild 0.1 M aqueous HCl conditions on deprotection of C33–C51 fragments laid the groundwork for the following deprotection studies of other fragments.

Secondly, as shown in Scheme 6.2, our old synthetic routes (prolinol catalyst-catalyzed aldol, followed by vinyl magnesium bromide addition) gave the C23–C31 (1,2-*anti* diol at C27 and C28) fragment in 13 steps with an overall yield of 5%. The new synthetic pathyway (prolinol catalyst-catalyzed aldol, followd by alkyne addition using *n*-BuLi) yielded the C23–C31 (1,2-*anti* diol at C27 and C28) fragment in 13 steps as well but higher overall yield (10%). More importantly, the choice of the protecting group for 1,2-*anti* diol at C27 and C28 was determined by testing a variety of protecting groups and finally cyclopentylidene acetal which is similar to acetonide but more labile was adopted as the protecting group for that diol. Subsequently, deprotection of this fragment was successfully achieved with 0.1 M or 0.2 M aqueous HCl conditions, giving the desired product in 51% yield and 63% yield respectively. The successful employment of mild deprotection conditions (0.1 M or 0.2 M aqueous HCl) in C1–C27 fragment, C33–C51 fragment and C23–C31 (1,2-*anti* diol at C27 and C28) fragment rendered us more confidence to test the deprotection of combined fragments (C13–C31, C13–C48 and C1–C51 fragments).



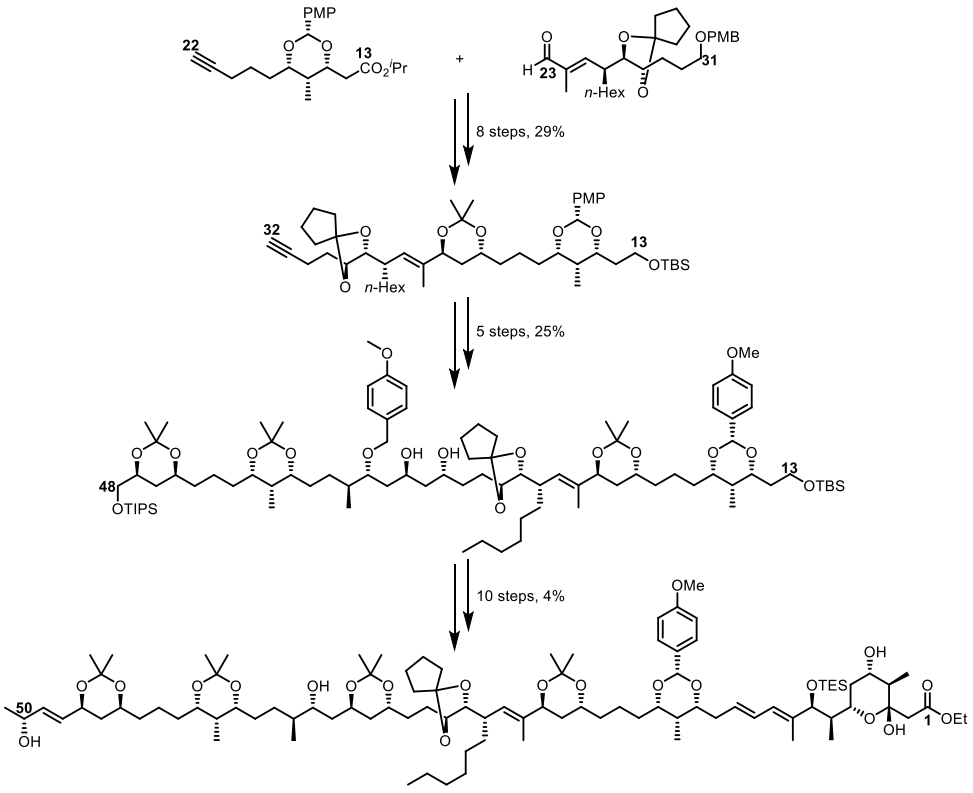
Scheme 6.2. Synthesis and deprotectionof the C23–C31 (1,2-*anti* diol at C27 and C28) fragment.

After that, the C1–C11 fragment was synthesized in 14 steps with 1% overall yield using our new synthetic strategy (Scheme 6.3) and the replacement of benzylidene acetal with *p*-methoxyphenylidene acetal accelerates the final deprotection as well as cyclization. The stereochemistry of the substituents in C1–C11 tetrahydropyran was confirmed through analysis of NOSEY correlations and coupling constants. Moreover, the C13–C22 fragment was smoothly synthesized from commercially available 5-hexnol in 6 steps with 16% overall yield and NOSEY analysis validated the stereochemistry of the C13–C22 PMP acetal.



Scheme 6.3. Synthesis of C1–C11 fragment and C13–C22 fragment.

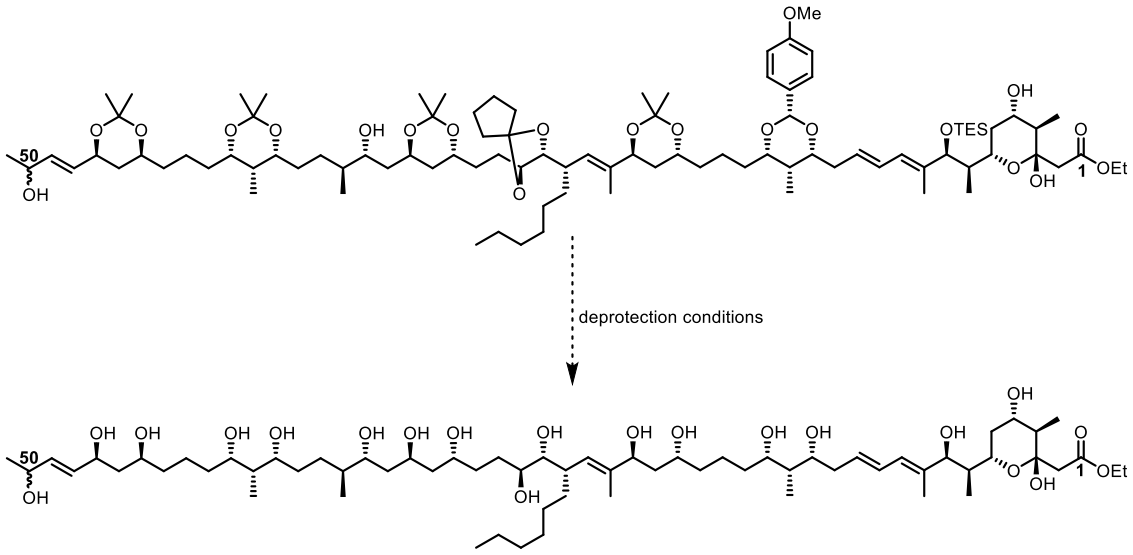
Union of C13–C22 fragment and C23–C31 (C28-*R*) fragment (Scheme 6.4) commenced with (*S*,*S*)-BINOL/Ti(IV)–catalyzed asymmetric alkyne addition, followed by 7 steps to afford C13–C32 fragment in an overall yield of 29%. In addition, deprotection of C13–C31 fragment was achieved with 0.1 M or 0.2 M HCl conditions as well. The following synthesis of C13–C48 fragment was achieved in 5 steps with 25% overall yield. Adopting the similar deprotection conditions (0.1 M or 0.2 M HCl) to above mentioned fragments, the fully deprotected C13–C48 fragment was obtained successfully. Comparison of NMR data of this fragment with that of stambomycin D shows a remarkable match between the two, strongly supporting the predicted stereochemistry in this region. Subsequently, the C1–C51 fragment (C50-*R*) was synthesized *via* an important Suzuki cross coupling in 10 steps with 4% overall yield. The preliminary deprotection attempt on C1–C51 fragment (C50-*R*) was not achieved due to the limited starting material.



Scheme 6.4. Synthesis of C1-C51 acyclic chains.

6.2 Future work

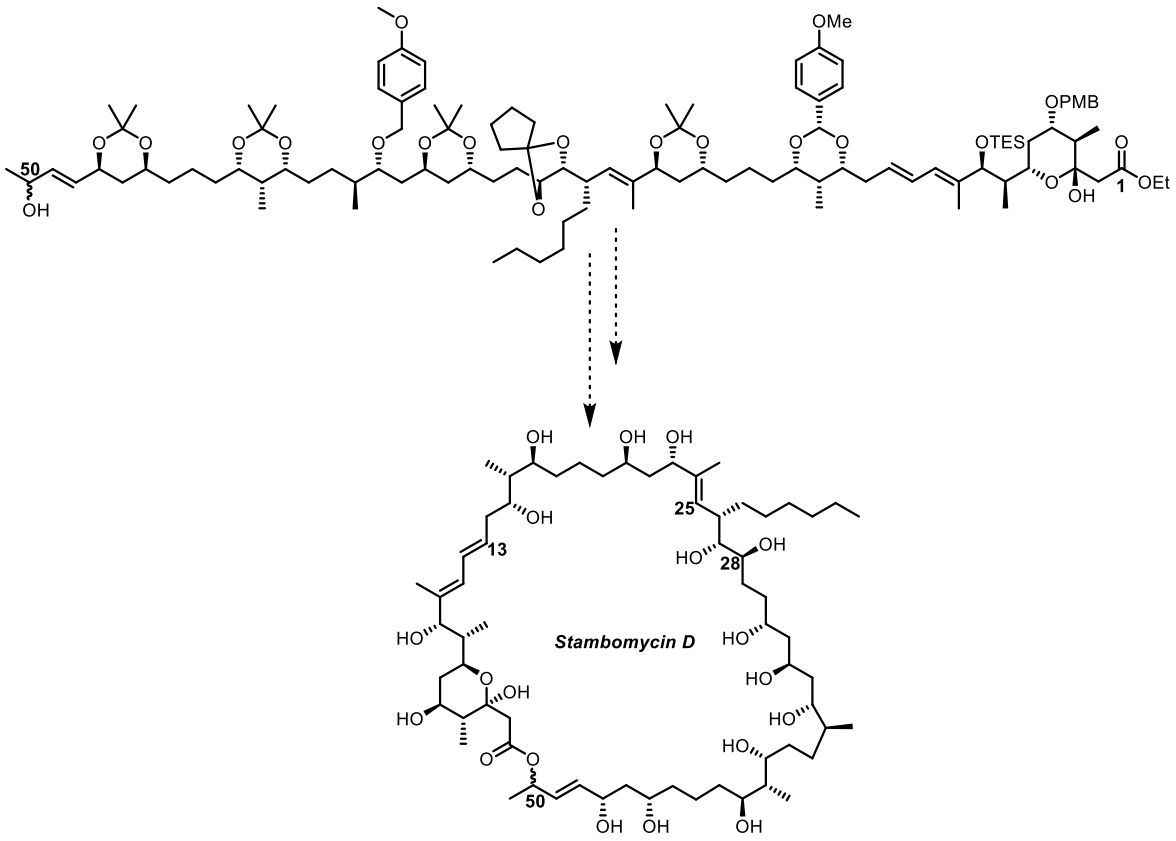
Once the other diastereomer of fully deprotected C13–C48 (1,2-*syn* diol at C27 and C28) fragment is synthesized, we will compare the NMR spectra of this fragment with that of stambomycin D and then the stereochemistry of C28 has a high likelihood to be identified through analysis of NMR data of the diastereomeric C13–C48 fragments and the natural product. If my synthesized diastereomer (1,2-*anti* diol at C27 and C28) proves the correct one, we will move it forward to reach the fully deprotected acyclic C1–C51 fragment (Scheme 6.5) first. On the one hand, the suitable deprotection condition for acyclic C1–C51 fragments under which C12–C13 diene is not affected could be found out, paving the way for the deprotection of final macrolide.



Scheme 6.5. Deprotection of acyclic C1-C51 fragments.

On the other hand, the successful deprotection of acyclic C1–C51 fragments could provide us with opportunity to compare the NMR spectra of this fragment with that of stambomycin D, validating the stereochemical assignment of this region especially in the

central area. However, the configuration of C50 stereogenic center still could not be figured out with the comparison of NMR data between the acyclic C1–C51 fragments and the cyclized stambomycin D. In order to achieve this, if more material is made, we might attempt to synthesize the diastereomers of stambomycin D aglycones (C50-*R*/*S*) (Scheme 6.6) through macrolactonization which presumably may be achieved by Yamaguchi macrolactonization[114,115,] followed by deprotection using the same conditions which are adopted for deprotection of acyclic C1–C51 fragments. If two diastereomeric stambomycin D aglycones are synthesized, we will set about comparing the NMR data of these two chemically synthesized aglycones with that of the stambomycin D aglycone discovered by genome mining. However, if we could not obtain cyclic macrolactone, a further option would be to ring-open the natural macrolactone aglycon to generate acyclic C1-C51 chain and compare the NMR spectroscopic data of it with two chemically synthesized acyclic C1-C51 diastereomers. By then, whether we obtain cyclized or non-cyclized stambomycin D aglycones, the configurations of all the stereocenters of stambomycin D, which were predicted *via* sequence analysis, would be definitely illustrated. Additionally, the stereocenters of C28 and C50 which could not be predicted through such method would be assigned as well. The successful synthesis of stambomycin D will be the first example of a structurally complex polyketide for which the stereochemistry predicted by sequence analysis is confirmed through chemical synthesis, to our best knowledge.



Scheme 6.6. Synthesis of the final macrolides (C50-*R*/*S*).

Chapter 7: Experimental

7.1 General Experimental

Regents, solvents and reaction conditions

All reactions were performed in dry glassware under a nitrogen atmosphere unless otherwise stated. Solvents and commercially available reagents were dried and purified before use where appropriate using standard procedures. Tetrahydrofuran (THF), dichloromethane, dimethylformamide (DMF), dioxane, toluene and triethylamine were obtained anhydrous from solvent dispenser units having been passed through an activated alumina column under nitrogen. Dry methanol and dimethylsulfoxide (DMSO) were obtained commercially and used directly without further purification. Brine refers to a saturated aqueous solution of NaCl.

Chromatography methods

Reactions were monitored by thin layer chromatography using Merck DC Kieselgel 60 F_{254} 0.2 mm precoated plates. Visualisation was carried out under UV light ($\lambda = 254$ nm) or stains such as vanillin, phosphomolybdic acid (PMA) and potassium permanganate ($KMnO_4$). Flash column chromatography was performed on Macherey-Nagel Kieselgel 60 Å (230-400 mesh particle size) as static phase and under increased pressure. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 series under UV-vis detection. The analytical chiral column used was a CHIRALPAK-IC column (250 mm x 4.6 mm, 5µm, Daicel Corporation) and the analytical as well as semi-preparative reverse phase column used was an Eclipse XDB–C18 column (150 mm x 4.6 mm, 5µm, Agilent Technologies).

Instrumental analytical methods

Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a 1 dm path length cell (using the sodium D line, 589 nm). Specific rotations ($[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$) are given in deg dm^2g^{-1}. Concentration (c) is reported in g/100 mL.

Infrared spectra were recorded on a Bruker Tensor 27 Fourier FT-IR spectrometer, and the samples were prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

NMR spectra were recorded on a Bruker AVIII HD 400 (operating at 400 MHz for ^1H and 101 MHz for ^{13}C acquisitions), a Bruker AVIII HD 500 (500 MHz for ^1H acquisitions and 126 MHz for ^{13}C aquisitions), or a Bruker AVIII HD 600 (600 MHz for ^1H and 151 MHz for ^{13}C acquisitions). The analysis of the NMR spectra was carried out with MestReNova®. Chemical shifts δ are given in parts per million (ppm) to the nearest 0.01 ppm for ^1H and 0.1 ppm for ^{13}C spectra, with the solvent resonance as internal standard: chloroform-d_1: 7.26 (^1H NMR) and 77.16 (^{13}C NMR), methanol-d_4: 3.31, 4.87 (^1H NMR) and 49.00 (^{13}C NMR). Coupling constants *J* are reported to the nearest 0.1 Hz. Multiplicities are reported as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets etc., t = triplet, q = quartet, sept = septet, m = multiplet. Assignments of compounds were based on two-dimensional NMR (COSY, HSQC, HMBC).

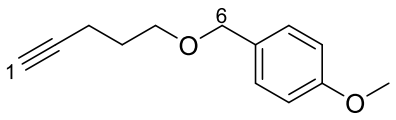
High resolution mass spectra (HRMS) were recorded under ESI conditions on a Bruker MicroTOF (resolution = 5000 FWHM) using tetraoctylammonium bromide as a lock-mass in both positive and negative ion mode. Values are calculated to 4 decimal places from the molecular formula. The parent ion $[M]^+$, $[M+H]^+$or $[M+Na]^+$ are quoted.

Liquid chromatography–mass spectrometry (LC-MS) was performed on a Xevo G2-XS QTof equipped with a high resolution, high stability quadrupole analyzer (MS1), plus pre-filters and a high performance oaTof mass analyzer (MS2) with a mass range up to m/z 100,000 and a resolving power of >40,000 FWHM. The ionization mode used is ESI+ mode and the TOF mass range is *m/z* 20 to 100000.

7.2 Experimental

Note: The numbering of each characterized compound does not completely adopt the IUPAC rule and was renumbered for easier characterization. In addition, proton assignment of some C13-C48 compounds might not be accurate enough due to extremely complicated NMR spectra. Each reaction was done more than once and the best yield was selected for characterization.

1-Methoxy-4-((pent-4-yn-1-yloxy)methyl)benzene (D1)

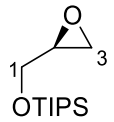


To a suspension of sodium hydride (2.72 g, 60% dispersion in mineral oil, 68.0 mmol, 1.1 equiv.) in THF (88 mL) at 0 °C was added 4-pentyn-1-ol (5.20 g, 61.8 mmol, 1.0 equiv.). After stirring at room temperature for 30 min, the mixture was cooled to 0 °C, then 4-methoxybenzyl chloride (9.2 mL, 68.0 mmol, 1.1 equiv.) and tetrabutylammonium iodide (1.14 g, 3.09 mmol, 0.05 equiv.) were added. The resulting mixture was gradually warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, quenched with water (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et_2O/pentane to 10% Et_2O/pentane) to obtain alkyne **D1** (10.5 g, 51.4 mmol, 83%) as a colourless oil. (The reaction can be scaled up to tens of grams).

R_f 0.45 (10% Et_2O/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3294, 2955, 2861, 1613, 1513, 1246, 1173, 1101, 1035, 819, 640; **^{1}H NMR** (400 MHZ, $CDCl_3$); δ 7.26 (2H, d, J = 8.8 Hz, ArH),

6.88(2H, d, *J* = 8.7 Hz, ArH), 4.44 (2H, s, H6), 3.81 (3H, s, OCH_3), 3.55 (2H, t, *J* = 6.2 Hz, H5), 2.31 (2H, td, *J* = 7.1, 2.7 Hz, H3), 1.94 (1H, t, *J* = 2.6 Hz, H1), 1.83-1.75 (2H, tt, *J* = 7.1, 6.1 Hz, H4); **^{13}C NMR** (101MHz, $CDCl_3$) δ 159.3, 130.7, 129.4, 113.9, 84.2, 72.7, 68.6, 68.5, 55.4, 28.8, 15.5; **HRMS** (ESI^+) calc. for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1053, found 227.1044.

(*S*)-Triisopropyl(oxiran-2-ylmethoxy)silane (D2)

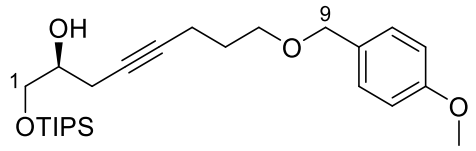


(*R*)-glycidol (3.00 g, 40.5 mmol, 1.0 equiv.) was added to a stirred mixture of triisopropylsilyl chloride (11.3 mL, 52.7 mmol, 1.3 equiv.) and imidazole (4.41 g, 64.8 mmol, 1.6 equiv.) in anhydrous DMF (24 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, during which time a white precipitate formed, then it was allowed to warm to room temperature. After stirring at room temperature for 2 h, the reaction was quenched with water (100 mL). The mixture was stirred for an additional 20 min and then extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with bine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/pentane to 10% Et_2O/pentane) to afford epoxide **D2** as a colourless oil (7.01 g, 30.4 mmol, 75%). (The reaction can be scaled up to tens of grams).

R_f 0.65 (10% Et_2O/pentane); $[\alpha]_D^{25}$ –2.0 (*c* = 0.91, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2867, 1463, 1384, 1253, 1161, 1137, 1099, 882, 681; **^{1}H NMR** (400 MHz, $CDCl_3$); δ 3.91 (1H, dd, *J* = 11.6, 3.3 Hz, H1), 3.75 (1H, dd, *J* = 11.6, 4.7 Hz, H1), 3.11 (1H, tt, *J* = 4.4, 3.0

Hz, H2), 2.77 (1H, dd, *J* = 5.2, 4.0 Hz, H3), 2.67 (1H, dd, *J* = 5.2, 2.7 Hz, H3), 1.15-1.03 (21H, m, TIPS); **^{13}C NMR** (101MHz, $CDCl_3$) δ 64.1, 52.7, 44.6, 18.1, 12.1; **HRMS** (ESI^+) calc. for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 253.1594, found 253.1595.

(*S*)-8-((4-Methoxybenzyl)oxy)-1-((triisopropylsilyl)oxy)oct-4-yn-2-ol (D3)

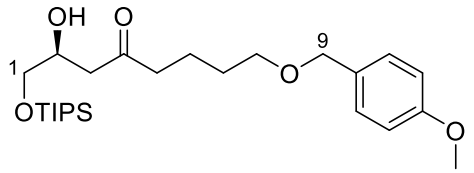


To a solution of PMB alkyne **D1** (6.41 g, 31.4 mmol, 1.3 equiv.) in THF (63 mL) at -78 °C under argon, was added *n*-butyl lithium (11.6 mL, 2.5 M in hexane, 29.0 mmol, 1.2 equiv.) dropwise. The reaction mixture was stirred at -78 °C for 1 h, then warmed gradually to 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was recooled to -78 °C and a solution of epoxide **D2** (5.56 g, 24.1 mmol, 1.0 equiv.) in THF (48 mL) was added, followed by boron trifluoride diethyl etherate (3.0 mL, 24.1 mmol, 1.0 equiv.). The resulting mixture was warmed to -70 °C. After stirring at -70 °C for 3 h, the reaction was quenched with sat. aq. NH_4Cl solution (50 mL) then warmed to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et_2O/pentane to 20% Et_2O/pentane) to afford alkynyl alcohol **D3** (8.5 g, 19.6 mmol, 81%) as a colourless oil. (The reaction can be scaled up to tens of grams).

R_f 0.40 (20% Et_2O/pentane); $[\alpha]_D^{25}$ +10.0 (*c* = 0.69, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3460, 2942, 2865, 1613, 1513, 1463, 1366, 1247, 1102, 1038, 883, 663; **^{1}H NMR** (400 MHz, $CDCl_3$)) δ 7.27 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 4.43 (2H, s, H9),

3.80 (3H, s, OCH_3), 3.78-3.72 (2H, m, H1), 3.71-3.67 (1H, m, H2), 3.52 (2H, t, *J* = 6.2 Hz, H8), 2.40 (2H, dq, *J* = 6.8, 2.4 Hz, H3), 2.28 (2H, tt, *J* = 7.1, 2.4 Hz, H7), 1.81-1.71 (2H, m, H6), 1.15-1.04 (21H, m, TIPS); **^{13}C NMR** (101 MHz, $CDCl_3$) 159.3, 130.7, 129.3, 113.9, 82.0, 76.3, 72.7, 70.8, 68.8, 66.1, 55.4, 29.3, 23.6, 18.1, 15.8, 12.1; **HRMS** (ESI^+) calc. for $C_{25}H_{42}O_4NaSi$ $[M+Na]^+$ 457.2745, found 457.2744.

(*S*)-2-Hydroxy-8-((4-methoxybenzyl)oxy)-1-((triisopropylsilyl)oxy)octan-4-one (D4)

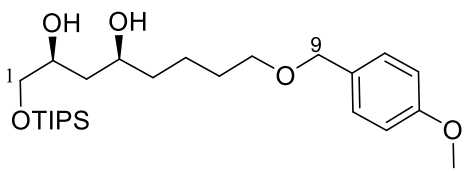


Alkynyl alcohol **D3** (8.50 g, 19.6 mmol, 1.0 equiv.) was dissolved in 1,1,3,3-tetramethyldisilazane (25 mL) and the resulting mixture was heated to 100 °C. After stirring at 100 °C for 16 h, the reaction mixture was cooled to room temperature and the volatiles were removed by rotavap. The residue was dried under high vacuum for 2 h, then dissolved in THF (40 mL). Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex in xylene (1.2 mL, 2% Pt in xylene) was added, and the resulting mixture was stirred at room temperature overnight, producing a cyclic siloxane. EDTA disodium salt dihydrate (100 mg) was added to sequester platinum ions. After filtration of the EDTA salt, the mixture was concentrated and the resulting residue was dissolved in THF/MeOH (1:1, 100 mL), followed by addition of solid $KHCO_3$ (5.49 g, 54.8 mmol, 3.0 equiv.) and KF (3.18 g, 54.8 mmol, 3.0 equiv.). Aqueous hydrogen peroxide (62 g, 30% w/w in water, 548 mmol, 30.0 equiv.) was added dropwise to the mixture dropwise at room temperature, and the mixture was stirred

for 6 h. The reaction was then cooled to 0 °C and precooled sat. aq. Na_2SO_3 solution (100 mL) was added slowly. After gas and heat evolution ceased, the reaction was warmed to room temperature and stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 20% EtOAc/pentane) to afford *β*-hydroxyketone **D4** (5.31 g, 11.7 mmol, 60%) as a colourless oil.

R*f* 0.40 (20% EtOAc /pentane); $[\alpha]_D^{25}$ –4.2 (*c* = 0.38, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3461, 2942, 2865, 1712, 1613, 1513, 1247, 1098, 1037, 883, 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 4.42 (2H, s, H9), 4.14-4.07 (1H, m, H2), 3.80 (3H, s, OCH_3), 3.68 (1H, dd, *J* = 9.7, 5.1 Hz, H1), 3.61 (1H, dd, *J* = 9.8, 6.1 Hz, H1'), 3.44 (2H, t, *J* = 6.2 Hz, H8), 2.92 (1H, d, *J* = 4.2 Hz, OH), 2.60 (2H, d, *J* = 6.1 Hz, H3), 2.48 (2H, t, *J* = 7.1 Hz, H5), 1.70-1.57 (4H, m, H6, H7), 1.14-1.00 (21H, m, TIPS); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.7, 159.3, 130.8, 129.4, 113.9, 72.7, 69.8, 68.6, 66.7, 55.4, 45.7, 43.6, 29.3, 20.5, 18.1, 12.0; **HRMS** (ESI^+) calc. for $C_{25}H_{44}O_5NaSi$ $[M+Na]^+$ 475.2850, found 475.2847.

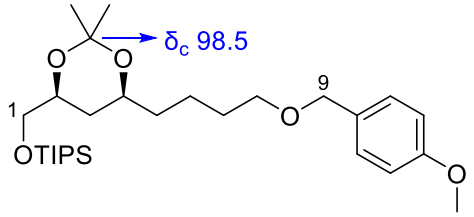
(*2R, 4R*)-8-((4-Methoxybenzyl)oxy)-1-((triisopropylsilyl)oxy)octane-2,4-diol (D5)



To a solution of *β*-hydroxyketone **D4** (3.34 g, 7.38 mmol, 1.0 equiv.) in THF (30 mL) at -70 °C was added anhydrous methanol (7.4 mL), followed by slow addition of diethylmethoxyborane (8.9 mL, 1.0 M in THF, 8.85 mmol, 1.2 equiv.). The resulting mixture was stirred at -70 °C for 2 h and then sodium borohydride (0.59 g, 15.5 mmol, 2.1 equiv.) was added portionwise. After stirring at -70 °C for 5 h, the reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was azeotroped with methanol until the TLC showed hydrolysis of the boronate was complete. The residue was concentrated under reduced pressure and purified by flash chromatography (10% EtOAc/pentane to 30% EtOAc/pentane) to obtain diol **D5** (2.68 g, 5.89 mmol, 80%) as a colourless oil.

R_f 0.35 (20% EtOAc/pentane); **$[\alpha]_D^{25}$** +5.0 (*c* = 0.54, $CHCl_3$); **IR** (thin film, ν_{max} /cm^{-1}) 3396, 2941, 2865, 1613, 1513, 1462, 1247, 1097, 1037, 883. 806, 683; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 4.43 (2H, s, H9), 3.95-3.84 (2H, m, H2 and H4), 3.80 (3H, s, OMe), 3.66 (1H, dd, *J* = 9.8, 3.9 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 7.3 Hz, H1), 3.45 (2H, t, *J* = 6.5 Hz, H8), 1.68-1.38 (8H , m, H3, H5, H6 and H7), 1.19-1.00 (21H, m, TIPS); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 130.9, 129.4, 113.9, 73.2, 72.7, 72.0, 70.2, 67.6, 55.4, 39.1, 37.7, 29.9, 22.3, 18.1, 12.0; **HRMS** (ESI^+) calc. for $C_{25}H_{46}O_5NaSi$ $[M+Na]^+$ 477.3007, found 477.3006.

Triisopropyl(((4*S*,6*S*)-6-(4-((4-methoxybenzyl)oxy)butyl)-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)silane (D6)

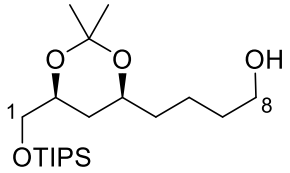


To a solution of diol **D5** (2.68 g, 5.89 mmol, 1.0 equiv.) in CH_2Cl_2 (23 mL) and 2,2-dimethoxypropane (23 mL) was added pyridinium *p*-toluenesulfonate (0.15 g, 0.589 mmol, 0.1 equiv.). After stirring at room temperature for 15 h, the mixture was quenched with sat. aq. $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane) to obtain acetonide **D6** (2.47g, 5.01 mmol, 85%) as a colorless oil. (The reaction can be scaled up to tens of grams).

R$_f$ 0.50 (10% EtOAc/pentane); $[\alpha]_D^{25}$ –2.1 (*c* = 0.42, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2941, 2865, 1613, 1513, 1463, 1379, 1248, 1111, 1039, 882, 820, 683; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 4.43 (2H, s, H9), 3.95-3.88 (1H, m, H4), 3.86-3.81 (1H, m, H2), 3.80 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 3.44 (2H, t, *J* = 6.6 Hz, H8), 1.70-1.56 (4H , m, H3 and H7), 1.55-1.39 (4H, m, H5, H6), 1.43 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.16-0.99

(21H, m, TIPS); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 130.9, 129.4, 113.9, 98.5, 72.7, 70.2, 70.2, 69.0, 67.5, 55.4, 36.5, 34.4, 30.3, 29.9, 21.8, 20.0, 18.1, 12.1; **HRMS** (ESI^+) calc. for $C_{28}H_{50}O_5NaSi$ $[M+Na]^+$ 517.3320, found 517.3318.

4-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)butan-1-ol (D7)

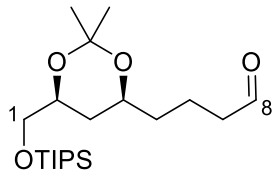


To a stirred solution of the ether **D6** (2.47 g, 5.01 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) and pH 7 phosphate buffer solution (3.8 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (2.26 g, 10.0 mmol, 2.0 equiv.) After stirring vigorously at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (50 mL), diluted with CH_2Cl_2 (100 mL) and filtered through a Büchner funnel to remove solids. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 20% EtOAc/pentane) to afford alcohol **D7** (1.41 g, 3.77 mmol, 75%) as a colorless oil.

R_f 0.45 (30% EtOAc/pentane); $[\alpha]_D^{25}$ –5.4 (*c* = 0.55, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3378, 2941, 2866, 1463, 1380, 1220, 1113, 882, 682; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.93 (1H, dddd, *J* =11.8, 6.9, 5.1, 2.6 Hz, H4), 3.84 (1H, *J* =11.5, 7.0, 4.5, 2.4 Hz, H2), 3.76 (1H, dd,

J = 9.7, 5.1 Hz, H1), 3.65 (2H, q, *J* = 6.0 Hz, H8), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 1.67 (1H, dt, *J* = 13.0, 2.6 Hz, H3), 1.63-1.45 (7H, m, H3, H5, H6 and H7), 1.44 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.18-1.00 (21H, m, TIPS); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 98.6, 70.2, 69.0, 67.4, 63.0, 36.4, 34.4, 32.8, 30.3, 21.4, 20.0, 18.1, 12.1; **HRMS** (ESI^+) calc. for $C_{20}H_{42}O_4NaSi$ $[M+Na]^+$ 397.2745, found 397.2746.

4-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)butanal (D8)

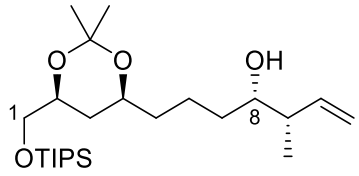


To a solution of alcohol **D7** (1.41 g, 3.77 mmol, 1.0 equiv.) in CH_2Cl_2 (40.0 mL) was added solid sodium bicarbonate (3.17 g, 37.7 mmol, 10.0 equiv.), followed by Dess-Martin periodinane (2.39 g, 5.66 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (20 mL) and dropwise addition of sat. aq. $Na_2S_2O_3$ solution (20 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane) to obtain aldehyde **D8** (1.29 g, 3.46 mmol, 92%) as a colourless oil.

R_f 0.50 (10% EtOAc/pentane); $[\alpha]_D^{25}$ –13.0 (*c* = 0.49, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2865, 1734, 1462, 1379, 1239, 1165, 882, 683; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77

(1H, s, H8), 3.93 (1H, dddd, *J* = 11.6, 6.7, 5.0, 2.6 Hz, H4), 3.85 (1H, dddd, *J* = 11.8, 7.3, 4.9, 2.5 Hz, H2), 3.76 (1H, dd, *J* = 9.7, 5.1 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 2.46 (2H, td, *J* = 7.4, 1.7 Hz, H7), 1.88-1.55 (4H, m, H3 and H6), 1.50 (2H, dtd, *J* = 9.5, 6.7, 5.3 Hz, H5), 1.44 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.19-1.01 (21H, m, TIPS); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.7, 98.6, 70.1, 68.7, 67.4, 43.9, 36.0, 34.4, 30.2, 20.0, 18.1, 18.0, 12.1; **HRMS** (ESI^+) calc. for $C_{20}H_{40}O_4NaSi$ $[M+Na]^+$ 395.2588, found 395.2583.

(3*S*,4*S*)-7-((4S,6S)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-3-methylhept-1-en-4-ol (D10)

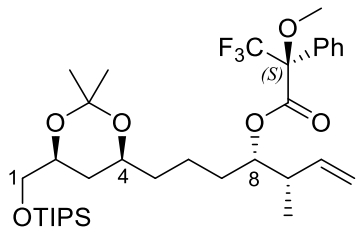


To a solution of (*S*,*S*)-**L1** (1.10 g, 3.81 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.7 mL, 11.4 mmol, 3.3 equiv.), followed by slow addition of *cis*–Crotyl trichlorosilane **D9** (0.8 mL, 4.15 mmol, 1.2 equiv.). The ice/water bath was removed. After stirring at room temperature for 1 h, the mixture was recooled to 0 °C and a solution of aldehyde **D8** (1.29 g, 3.46 mmol, 1.0 equiv.) in CH_2Cl_2 (1.4 mL) was added dropwise. After stirring at 0 °C for 1 h, the mixture was concentrated under reduced pressure and diethyl ether (10 mL) was added. The resulting mixture was stirred vigorously for 30 min to ensure complete precipitation of the DBU·HCl salts. The reaction mixture was filtered through a Büchner funnel to remove solid and subsequently, tetrabutylammonium fluoride solution (3.5 mL, 1.0 M in THF, 3.46 mmol, 1.0 equiv.) was

added to the filtrate. After stirring at room temperature for 30 min, the reaction mixture was quenched with 1 M HCl (5 mL, aq.). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/pentane to 15% EtOAc/pentane) to obtain alcohol **D10** (0.91 g, 2.12 mmol, 61%, 12:1 *dr*) as a colourless oil. (The procedure for the synthesis of known compounds (*S, S*)-**L1**, **D9** and recovery of (*S, S*)-**L1** was described in our published work).[42]

R_f 0.50 (15% EtOAc/pentane); $[\alpha]_D^{25}$ –22.1 (*c* = 0.50, $CHCl_3$); **IR (**thin film, ν_{max}/ cm-1**)** 3421, 2943, 2866, 1463, 1381, 1116, 996, 881, 683; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83-5.74 (1H, m, H10), 5.08 (1H, dt, *J* = 7.3, 1.6 Hz, H11), 5.06 (1H, s, H11), 3.93 (1H, dddd, *J* = 11.7, 7.3, 5.1, 2.5 Hz, H4), 3.83 (1H, ddd, *J* =11.3, 5.9, 3.2 Hz, H2), 3.75 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.54-3.47 (2H, m, H1' and H8), 2.30-2.23 (1H, m, H9), 1.69-1.65 (1H, m, H3), 1.57-1.40 (7H, m, H3, H5, H6, H7), 1.43 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.17-1.04 (21H, m, TIPS), 1.02 (3H, d, *J* = 6.9 Hz, C9-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 115.4, 98.5, 74.7, 70.2, 69.1, 67.4, 43.6, 36.5, 34.5, 33.9, 30.2, 21.9, 20.0, 18.1, 14.3, 12.1; **HRMS** (ESI^+) calc. for $C_{24}H_{48}O_4NaSi$ $[M+Na]^+$ 451.3214, found 451.3216.

(3*S*,4*S*)-7-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-3-methylhept-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (D10-*S*-ester)

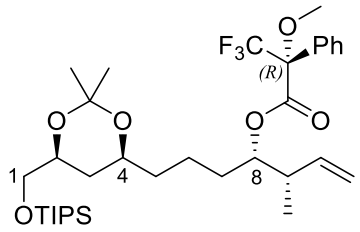


To a solution of alcohol **D10** (13.4 mg, 0.0313 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was added anhydrous pyridine (15.7 µL, 0.194 mmol, 6.2 equiv.), followed by dropwise addition of (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (22.2 µL, 0.119 mmol, 3.8 equiv.) at room temperature. After stirring at ambient temperature for 3 h, the reaction was quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane) to afford **D10-*S*-ester** (15.2 mg, 0.0236 mmol, 76%).

R_f 0.50 (5% EtOAc/pentane); $[\alpha]_D^{25}$ -44.2 (*c* = 3.6, $CHCl_3$); **IR (**thin film, ν_{max}/ cm-1**)** 2948, 2867, 1745, 1453, 1381, 1272, 1171, 1120, 994, 965, 882, 764, 717, 698**; ^{1}H NMR** (500 MHz, $CDCl_3$, ^{19}F decoulped) δ 7.56 (2H, dd, *J* = 6.7, 2.9 Hz, ArH), 7.41-7.36 (3H, m, ArH), 5.76 (ddd, 1H, *J* = 16.9, 10.8, 7.1, H10), 5.08-5.07 (1H, m, H8), 5.07-5.03 (2H, m, H11), 3.91 (1H, dddd, *J* = 11.6, 7.3, 5.0, 2.5 Hz, H4), 3.76-3.69 (2H, m, H1 and H2), 3.54 (3H, s, OCH_3), 3.51 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 2.53 (1H, dtd, *J* = 8.4, 6.8, 1.4 Hz, H9), 1.65-1.52 (4H, m, H3 and H7), 1.50-1.45 (1H, m, H5), 1.42 (3H, s, acetonide), 1.35 (3H, s, acetonide), 1.32-1.27 (3H, m, H5' and H6), 1.10-1.04 (21H, m, TIPS), 1.02 (3H, d, *J* = 6.9 Hz, C9-Me). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 139.4, 132.4, 129.7, 128.4, 127.7, 123.2 (q, *J* = 289 Hz), 115.9, 98.5, 84.2 (q, *J* = 28 Hz), 80.4, 70.2, 68.6, 67.4, 55.6, 40.7, 36.3, 34.3,

30.9 30.2, 20.8, 19.9, 18.1, 14.9, 12.1; **^{19}F NMR** (470 Hz, $CDCl_3$) δ -71.1; **HRMS** (ESI^+) calc. for $C_{34}H_{55}F_3O_6NaSi$ $[M+Na]^+$ 667.3612, found 667.3608.

(3*S*,4*S*)-7-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-3-methylhept-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (D10-*R*-ester)



To a solution of alcohol **D10** (6.1 mg, 0.0142 mmol, 1.0 equiv.) in CH_2Cl_2 (0.15 mL) was added anhydrous pyridine (7.1 μL, 0.0882 mmol, 6.2 equiv.) and (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (10.1 μL, 0.0541 mmol, 3.8 equiv.) at room temperature. The resulting mixture was stirred at ambient temperature for 3 h. The reaction was quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane) to afford **D10-*R*-ester** (7.8 mg, 0.0121 mmol, 85%).

R_f 0.50 (4% EtOAc/pentane); **$[\alpha]_D^{25}$** -2.4 (*c* = 1.2, $CHCl_3$); **IR (**thin film, ν_{max}/ cm-1**)** 2943, 2866, 1745, 1462, 1380, 1259, 1169, 1122, 995, 919, 882, 767, 719, 683; **^{1}H NMR** (500 MHz, $CDCl_3$, ^{19}F decoupled) δ 7.56 (2H, dd, *J* = 6.8, 3.0 Hz, ArH), 7.41-7.36 (3H, m, ArH), 5.64 (ddd, 1H, *J* = 17.5, 10.5, 7.3, H10), 5.04 (1H, dt, *J* = 7.3, 5.3 Hz, H8), 5.01-4.94 (2H, m, H11), 3.91 (1H, dddd, *J* = 11.6, 7.3, 5.0, 2.6 Hz, H4), 3.81-3.74 (2H, m, H1 and H2), 3.55

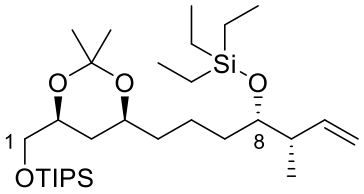
(3H, s, OCH_3), 3.51 (1H, dd, *J* = 9.7, 6.8 Hz, H1'), 2.47 (1H, td, *J* = 7.1, 5.7 Hz, H9), 1.64-1.60 (4H, m, H3 and H7), 1.52-1.48 (1H, m, H5), 1.42 (3H, s, acetonide), 1.40-1.37 (3H, m, H5' and H6), 1.35 (3H, s, acetonide), 1.10-1.04 (21H, m, TIPS), 0.95 (3H, d, *J* = 6.9 Hz, C9-Me). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.4, 139.2, 132.5, 129.7, 128.5, 127.6, 123.6 (q, *J* = 289 Hz), 115.8, 98.5, 84.6 (q, *J* = 28 Hz), 80.3, 70.1, 68.6, 67.4, 55.6, 40.6, 36.4, 34.4, 31.1, 30.2, 21.0, 19.9, 18.1, 14.9, 12.1; **^{19}F NMR** (470 Hz, $CDCl_3$) δ -71.2; **HRMS** (ESI^+) calc. for $C_{34}H_{55}F_3O_6NaSi$ $[M+Na]^+$ 667.3612, found 667.3611.

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

Proton position	**D10-*S*-ester (ppm)**	**D10-*R*-ester (ppm)**	**$\Delta\delta_{SR}$**
H1 and H2	3.74	3.76	-0.02
H3 and H7	1.59	1.62	-0.03
H5	1.47	1.50	-0.03
H5' and H6	1.29	1.38	+0.09
H9	2.53	2.47	+0.06
H9-Me	1.02	0.95	+0.07
H10	5.76	5.64	+0.12
H11	5.05	4.98	+0.07

Negative values obtained for alkene portion and positive values obtained for acetonide portion. Analysis of all the values reveals the C8 centre is of *S* configuration.

(((3*S*,4*S*)-7-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-3-methylhept-1-en-4-yl)oxy)triethylsilane (D11)

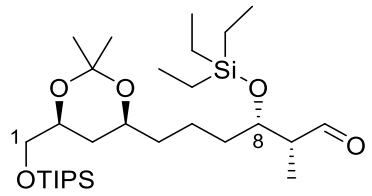


To a solution of alcohol **D10** (0.91g, 2.12 mmol, 1.0 equiv.) in CH_2Cl_2 (4.3 mL) at -78 °C was added anhydrous 2,6-lutidine (0.37 mL, 3.18 mmol, 1.5 equiv.) followed by slow addition of triethylsilyl trifluoromethanesulfonate (0.49 mL 2.33 mmol, 1.1 equiv.). The resulting mixture was stirred at -78 °C for 30 min, then the reaction was gradually warmed to 0 °C and stirred for a further 30 min. The reaction mixture was quenched with water (5 mL), diluted with CH_2Cl_2 (5 mL) and brought back to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane) to obtain TES ether **D11** (1.05 g, 2.00 mmol, 94%) as a colourless oil.

R_f 0.50 (5% Et_2O/pentane); $[\alpha]_D^{25}$ –16.9 (*c* = 0.47 $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2870, 1711, 1512, 1461, 1379, 1248, 1115, 1007, 882, 741, 682; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (1H, ddd, *J* = 17.6, 10.7, 7.1 Hz, H10), 5.01 (1H, dt, *J* = 8.4, 1.7 Hz, H11), 4.97 (1H, s, H11'), 3.93 (1H, dddd, *J* = 11.6, 7.3, 5.0, 2.5 Hz, H4), 3.85-3.80 (1H, m, H2), 3.76 (1H, dd, *J* = 9.6, 5.0 Hz, H1), 3.56-3.47 (2H, m, H1' and H8), 2.28 (1H, qd, *J* = 7.1, 5.4 Hz, H9), 1.68 (1H, dt, *J* = 12.9, 2.5 Hz, H3), 1.58-1.37 (7H, m, H3', H5, H6, H7), 1.43 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.16-1.04 (21H, m, TIPS), 0.98 (3H, d, *J* = 2.5 Hz, C9-Me), 0.95 (9H, t, *J* = 8.0 Hz, TES) 0.60 (6H, q, *J* = 8.1 Hz, TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 114.1, 98.5, 76.2, 70.2, 69.0, 67.4, 43.3, 36.9, 34.6, 34.0, 30.2, 21.1, 20.0,

18.1, 15.3, 12.1, 7.2, 5.4; **HRMS** (ESI$^+$) calc. for $C_{30}H_{62}O_4NaSi_2$ $[M+Na]^+$ 565.4079, found 565.4080.

(2*R*,3*S*)-6-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-2-methyl-3-((triethylsilyl)oxy)hexanal (D12)

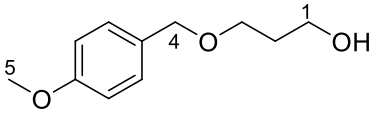


To a solution of TES ether **D11** (1.05 g, 2.00 mmol, 1.0 equiv.) in dioxane/water (20 mL, 3:1) was added 2,6-lutidine (0.47 mL, 4.00 mmol, 2.0 equiv.), osmium tetroxide (0.24 mL, 4% w/w in water, 0.0387 mmol, 0.02 equiv.), and sodium periodate (2.14 g, 10.0 mmol, 5.0 equiv.). The resulting mixture was stirred at room temperature overnight. The reaction was diluted with water (50 mL) and CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% Et_2O/pentane) to afford aldehyde **D12** (0.93 g, 1.71 mmol, 85%) as a colourless oil.

R_f 0.50 (10% Et_2O/pentane); $[\alpha]_D^{25}$ –31.2 (*c* = 0.55 $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2943, 2867, 1727, 1462, 1379, 1112, 1011, 882, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (1H, s, H10), 4.11 (1H, td, *J* = 6.4, 3.6 Hz, H8), 3.93 (1H, dddd, *J* = 11.6, 7.2, 5.0, 2.5 Hz, H4), 3.82 (1H, dddd, *J* = 11.5, 7.2, 4.5, 2.4 Hz, H2), 3.76 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 6.8 Hz, H1), 2.44 (1H, qd, *J* = 6.9, 3.4 Hz, H9), 1.66 (1H, dt, *J* = 12.8, 2.5 Hz, H3),

1.57-1.45 (4H, m, H3, H7 and H5), 1.43 (3H, s, acetonide) 1.43-1.36 (3H, m, H5' and H6), 1.37 (3H, s, acetonide), 1.15-1.02 (24H, m, H9-Me and TIPS), 0.94 (9H, t, *J* = 7.9 Hz, TES), 0.59 (6H, q, *J* = 7.7 Hz, TES); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.5, 98.5, 72.4, 70.2, 68.8, 67.4, 51.5, 36.6, 34.7, 34.5, 30.2, 21.6, 20.0, 18.1, 12.1, 7.9, 7.0, 5.3; **HRMS** (ESI^+) calc. for $C_{29}H_{60}O_5NaSi_2$ $[M+Na]^+$ 567.3871, found 567.3871.

3-((4-Methoxybenzyl)oxy)propan-1-ol (D13)

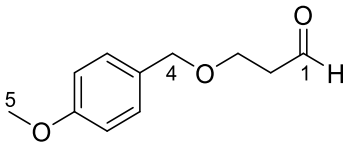


To a solution of propane-1,3-diol (5.48 g, 72.0 mmol, 2.0 equiv.) in DMSO (25 mL) at 0 °C was added potassium hydroxide (4.04 g, 72.0 mmol, 2.0 equiv.) portionwise. The resulting mixture was stirred until the solution turned clear again and then 4-methoxy benzyl chloride (4.9 mL, 36.0 mmol, 1.0 equiv.) was added dropwise. The reaction was warmed to room temperature, stirred for 4 h, then recooled to 0 °C and quenched with water (100 mL). After warming to room temperature, diethyl ether (20 mL) was added and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford alcohol **D13** (5.33 g, 27.2 mmol, 75%) as a colourless oil.

R_f 0.50 (50% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3387, 2936, 2864, 1612, 1512, 1245, 1032, 818; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 6.7 Hz, ArH), 6.88 (2H, d, *J* = 6.7 Hz, ArH), 4.45 (2H, s, H4), 3.81 (3H, s, H5), 3.77 (2H, t, *J* = 6.1 Hz, H3), 3.64 (2H, t,

J = 5.8 Hz, H1), 1.88-1.83 (2H, m, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.3, 129.4, 114.0, 73.1, 69.4, 62.2, 55.4, 32.2. **HRMS** (ESI^+) calculated for $C_{11}H_{16}O_3Na$ $[M+Na]^+$: 219.0992, found: 219.0993.

3-((4-Methoxybenzyl)oxy)propanal (D14)

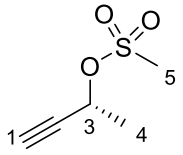


To a solution of alcohol **D13** (2.50 g, 12.7 mmol, 1.0 equiv.) in CH_2Cl_2 (84.9 mL), was added sodium bicarbonate (10.7 g, 12.7 mmol, 10.0 equiv.), followed by Dess-Martin periodinane (8.10 g, 19.1 mmol, 1.5 equiv.). After stirring at room temperature for 2 h, the reaction was cooled to 0 ºC and quenched with sat. aq. $NaHCO_3$ solution (20 mL) and sat. aq. $Na_2S_2O_3$ solution (20 mL). The resulting mixture was warmed to room temperature and stirred until the layers turned clear. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane) to afford alcohol **D14** (2.15 g, 11.1 mmol, 87%) as a colourless oil.

R_f 0.50 (30% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 2860, 2731, 1723, 1613, 1513, 1247, 1092, 1033, 820; **^{1}H NMR** (400 MHz, CDCl3) δ 9.79 (1H, t, *J* = 1.8 Hz, H1), 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 4.46 (2H, s, H4), 3.81 (3H, s, H5), 3.79 (2H, t, *J* = 6.1 Hz, H3), 2.69 (2H, t, *J* = 6.1, 1.8 Hz, H2); **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 201.3, 159.5, 130.1, 129.5, 114.0, 73.1, 63.7, 55.4, 44.0. **HRMS** (ESI^+) calc. for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835, found 217.0837.

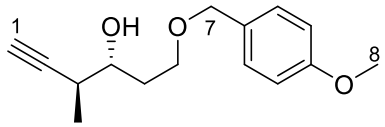
(*S*)-But-3-yn-2-yl methanesulfonate (D15)



To a solution of (*R*)-(+)-3-butyn-2-ol (1.10 g, 15.7 mmol, 1.0 equiv.) in CH_2Cl_2 (105 mL) at -78 °C, was added triethylamine (4.4 mL, 31.4 mmol, 2.0 equiv.) followed by dropwise addition of methanesulfonyl chloride (1.8 mL, 23.5 mmol, 1.5 equiv.). The resulting mixture was stirred at -78 °C for 1 h, then quenched by addition of sat. aq. $NaHCO_3$ solution (50 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane) to afford mesylate **D15** (2.18 g, 14.7 mmol, 94%) as a yellow oil.

R_f 0.40 (20% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3283, 2941, 2124, 1354, 1173, 1089, 1016, 973, 905, 851; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.29 (1H, dq, *J* = 6.7, 2.1 Hz, H3), 3.12 (3H, s, H5), 2.70 (1H, d, *J* = 2.2 Hz, H1), 1.66 (3H, d, *J* = 6.7 Hz, H4); **^{13}C NMR** (101MHz, $CDCl_3$) δ 80.3, 76.4, 67.6, 39.3, 22.6; **HRMS** (ESI^+) calc. for $C_5H_8O_3NaS$ $[M+Na]^+$ 171.0086, found 171.0087.

(3*R*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-yn-3-ol (D16)

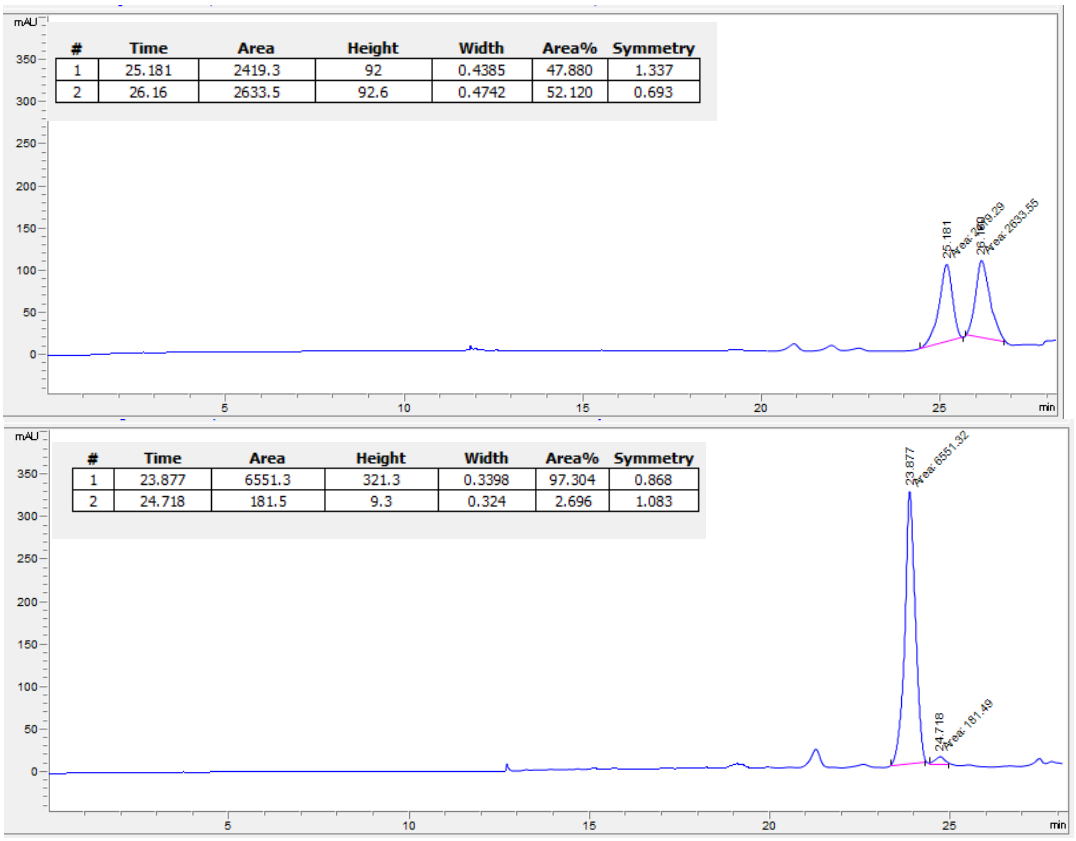


To a solution of $Pd(OAc)_2$ (10.6 mg, 0.474 mmol, 0.05 equiv.) in THF (63.2 mL) at -78 °C, was added PPh_3 (12.4 mg, 0.474 mmol, 0.05 equiv.), and the resulting mixture was stirred for 5 min. A solution of aldehyde **D14** (1.84 g, 9.47 mmol, 1.0 equiv.) and mesylate **D15** (2.18 g, 14.7 mmol, 1.55 equiv.) in THF (3.9 mL) was added. After stirring at -78 °C for 5 min, Et_2Zn (28.4 mL, 1.0 M in hexane, 28.4 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred for another 5 min and then warmed to -20 °C (colour changed to dark brown). After stirring at -20 °C overnight, the reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 20% EtOAc/pentane) to afford alcohol **D16** (1.27 g, 5.11 mmol, 54%, 95% *ee*, 16:1 *dr*) as a yellow oil.

R_f 0.50 (30% EtOAc /pentane); $[\alpha]_D^{25}$ –8.8 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3420, 3288, 2979, 2936, 2871, 1613, 1513, 1248, 1092, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.5 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 4.46 (2H, s, H7), 3.80 (3H, s, H8), 3.78-3.69 (2H, m, H4 and H6), 3.63 (1H, ddd, *J* = 9.4, 7.8, 4.6 Hz, H6'), 2.81 (1H, d, *J* = 4.4 Hz, OH), 2.56 (1H, qdd, *J* = 7.0, 4.4, 2.5 Hz, H3), 2.12 (1H, d, *J* = 2.5 Hz, H1), 1.93-1.78 (2H, m, H5), 1.23 (3H, d, *J* = 7.0 Hz, C3-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4,

130.2, 129.5, 114.0, 85.7, 73.3, 73.1, 70.6, 68.5, 55.4, 34.2, 32.8, 16.9; **HRMS** (ESI^+) calc. for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1305, found 271.1305.

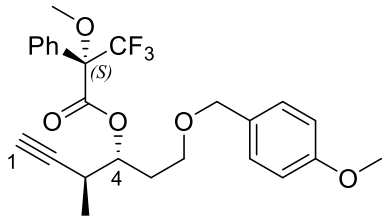
HPLC for compound **D16**: [CHIRALPAK-IC, eluent system: 100% isopropanol-10% isopropanol/*n*-hexane (0-20 min), 10% isopropanol/*n*-hexane-15% isopropanol/*n*-hexane (20-40 min), injection volume: 5μL, flow rate: 1.0 mL/min, λ = 260 nm]: t_R = 23.9 min (major), 24.7 min (minor); 95% *ee*



#	Time	Area	Height	Width	Area%	Symmetry
1	25.181	2419.3	92	0.4385	47.880	1.337
2	26.16	2633.5	92.6	0.4742	52.120	0.693

#	Time	Area	Height	Width	Area%	Symmetry
1	23.877	6551.3	321.3	0.3398	97.304	0.868
2	24.718	181.5	9.3	0.324	2.696	1.083

(3*R*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-yn-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (D16-*S*-ester)

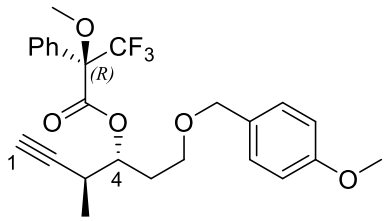


To a solution of alcohol **D16** (5.9 mg, 0.0238 mmol, 1.0 equiv.) in CH_2Cl_2 (0.35 mL) was added anhydrous pyridine (11.9 µL, 0.147 mmol, 6.2 equiv.) and (*R*)-(–)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (16.9 µL, 0.0903 mmol, 3.8 equiv.) at room temperature. After stirring at room temperature overnight, the reaction was quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 10% EtOAc/pentane) to afford alcohol **D16-*S*-ester** (9.0 mg, 0.0194 mmol, 82%) as a yellow oil.

R_f 0.50 (10% EtOAc /pentane); $[\alpha]_D^{25}$ −5.1 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3293, 2954, 2850, 1745, 1612, 1514, 1249, 1170, 1082, 994, 719; **^{1}H NMR** (500 MHz, $CDCl_3$,^{19}F decoupled) δ 7.56 (2H, d, *J* = 6.1 Hz, ArH), 7.41-7.35 (3H, m, ArH), 7.25 (2H, d, *J* = 8.5 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.29 (1H, dt, *J* = 8.4, 4.1 Hz, H4), 4.40 (2H, s, H7), 3.80 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 3.49-3.41 (2H, m, H6), 2.82 (1H, qdd, *J* = 7.0, 4.0, 2.6 Hz, H3), 2.12 (1H, dddd, *J* = 14.2, 7.9, 6.2, 4.2 Hz, H5), 2.05 (1H, d, *J* = 2.5 Hz, H1), 2.04-1.98 (1H, m, H5'), 1.07 (3H, d, *J* = 7.1 Hz, C3-Me); **^{13}C NMR** (126 MHz, $CDCl_3$)

δ 166.3, 159.4, 132.1, 130.3, 129.7, 129.5, 128.5, 127.6, 123.5 (q, *J* = 289 Hz),114.0, 84.7 (q, *J* = 28 Hz), 83.8, 75.7, 72.9, 70.9, 65.9, 55.6, 55.4, 31.4, 29.8, 16.2; **^{19}F NMR** (470 Hz, $CDCl_3$) δ -71.5; **HRMS** (ES^+) calc. for $C_{25}H_{27}O_5F_3Na$ $[M+Na]^+$ 487.1703, found 487.1699.

(3*R*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-yn-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (D16-*R*-ester)



To solution of alcohol **D16** (5.5 mg, 0.0221 mmol, 1.0 equiv.) in CH_2Cl_2 (0.33 mL) was added anhydrous pyridine (11.1 μL, 0.137 mmol, 6.2 equiv.) and (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (15.7 μL, 0.0842 mmol, 3.8 equiv.) at room temperature. After stirring at room temperature overnight, the reaction was quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 10% EtOAc/pentane) to afford alcohol **D16-*R*-ester** (8.1 mg, 0.0174 mmol, 81%) as a yellow oil.

R_f 0.50 (10% EtOAc /pentane); **$[\alpha]_D^{25}$** +43.7 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3291, 2981, 2856, 1746, 1613, 1514, 1249, 1170, 1082, 1018, 717; **^{1}H NMR** (500 MHz, $CDCl_3$,^{19}F decoupled) δ 7.59 (2H, dd, *J* = 8.1 Hz, ArH), 7.42-7.35 (3H, m, ArH), 7.23 (2H,

d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.33 (1H, dt, *J* = 8.5, 4.2 Hz, H4), 4.32 (2H, s, H7), 3.80 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.39-3.33 (1H, m, H6), 3.27 (1H, ddd, *J* = 9.6, 8.1, 5.5 Hz, H6'), 2.83 (1H, qdd, *J* = 7.1, 4.2, 2.5 Hz, H3), 2.09 (1H, d, *J* = 2.5 Hz, H1), 2.07-1.92 (2H, m, H5),1.20 (3H, d, *J* = 7.1 Hz, H3-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3, 159.4, 132.3, 130.4, 129.7, 129.4, 128.5, 127.6, 123.5 (q, *J* = 289 Hz) 114.0, 84.7, 84.0 (q, *J* = 28 Hz), 75.6, 72.8, 71.1, 65.7, 55.8, 55.4, 31.8, 30.4, 16.9; **^{19}F NMR** (470 Hz, $CDCl_3$) δ -71.3; **HRMS** (ES^+) calc. for $C_{25}H_{27}O_5F_3Na$ $[M+Na]^+$ 487.1703, found 487.1697.

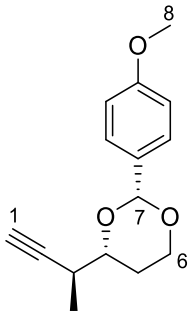
Comparison of ^{1}H NMR data of two Mosher ester derivatives is shown below:

Proton position	**D16-*S*-ester (ppm)**	**D16-*R*-ester (ppm)**	**$\Delta\delta_{SR}$**
H1	2.05	2.09	-0.04
H3	2.82	2.83	-0.01
H3'	1.07	1.02	-0.13
H5	2.02	2.00	+0.02
H6	3.44	3.36	+0.08
H6	3.44	3.27	+0.17
H7	4.40	4.32	+0.08

Negative values obtained for alkyne portion and positive values obtained for PMB portion.

Analysis of all the values reveals the C4 centre is of *R* configuration.

(2*R*,4*R*)-4-((*S*)-But-3-yn-2-yl)-2-(4-methoxyphenyl)-1,3-dioxane (D17)

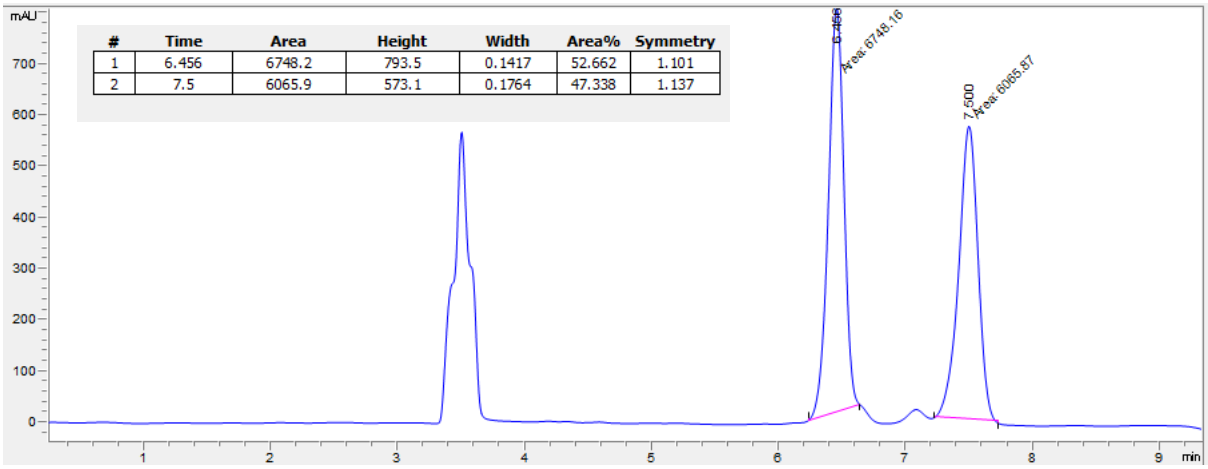


To a solution of alcohol **D16** (1.25 g, 5.03 mmol, 1.0 equiv.) and 3Å molecular sieves (3.7 g) in CH_2Cl_2 (25.0 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (1.48 g, 6.54 mmol, 1.3 equiv.) in three portions at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (50 mL) and filtered through celite. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 10% EtOAc/pentane) to afford title PMP alkyne **D17** (0.81 g, 3.29 mmol, 65%, 95% *ee*, 19:1*dr*) as a white solid.

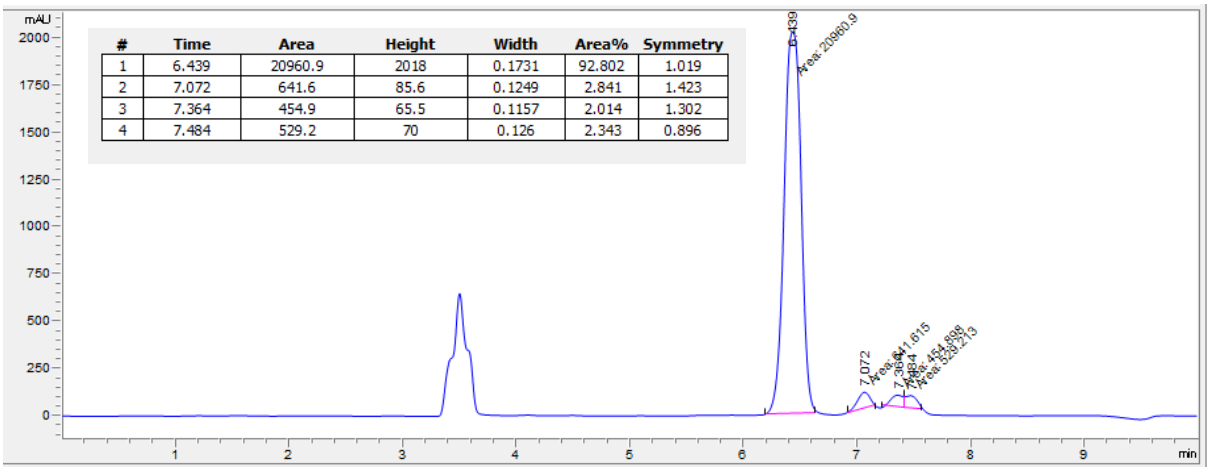
m.p. 67-68 °C; $\mathbf{R_f}$ 0.50 (10% EtOAc /pentane); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –12.3 (*c* = 0.55, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}) 3289, 2979, 2936, 2851, 1615, 1518, 1248, 1102, 1034, 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.4 Hz, ArH), 6.89 (2H, d, *J* = 8.8 Hz, ArH), 5.48 (1H, s, H7), 4.30 (1H, ddd, *J* = 11.4, 5.1, 1.4 Hz, H4), 3.96 (1H, td, *J* = 12.1, 2.5 Hz, H6), 3.91-3.85 (1H, m, H6'), 3.80 (3H, s, H8), 2.77 (1H, qdd, *J* = 7.2, 5.0, 2.5 Hz, H3), 2.10 (1H, d, *J* = 2.5 Hz, H1), 1.99 (1H, dddd, *J* = 13.1, 12.3, 11.3, 5.0 Hz, H5), 1.59 (1H, m, dtd, *J* = 13.2, 2.5, 1.4 Hz, H5'), 1.27 (3H, d, *J* = 7.1 Hz, C3-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 131.4,

127.5, 113.7, 101.3, 85.5, 78.7, 70.0, 67.0, 55.4, 31.1, 27.1, 15.7; **HRMS** (ESI^+) calc. for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ 269.1148, found 269.1146.

HPLC for compound 4 (CHIRALPAK-IC, eluent system: 10% isopropanol/*n*-hexane, injection volume: 5µL, flow rate: 1.0 mL/min, λ = 222 nm): t_R = 6.4 min (product), 7.5 min (enantiomer of product); 95% *ee*, 19:1 *dr*[a])



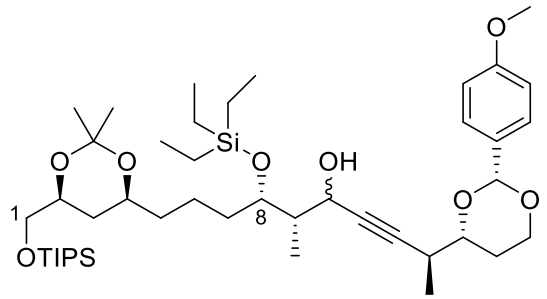
#	Time	Area	Height	Width	Area%	Symmetry
1	6.456	6748.2	793.5	0.1417	52.662	1.101
2	7.5	6065.9	573.1	0.1764	47.338	1.137



#	Time	Area	Height	Width	Area%	Symmetry
1	6.439	20960.9	2018	0.1731	92.802	1.019
2	7.072	641.6	85.6	0.1249	2.841	1.423
3	7.364	454.9	65.5	0.1157	2.014	1.302
4	7.484	529.2	70	0.126	2.343	0.896

[a]Peak at 3.5 min is the residual solvent peak for both graphs. In the second graph, peak 2 and 3 are diastereomers of product. In addition, peak 4 is the enantiomer of product and the enantioselectivity originates from previous allenyl zinc addition step.

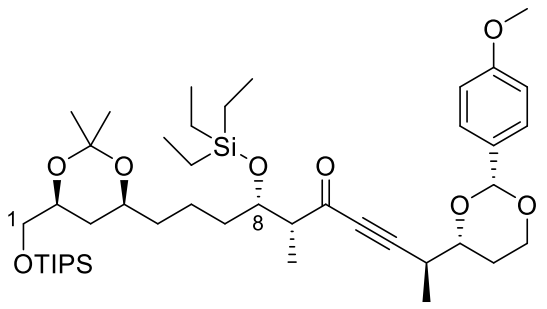
(2*S*,6*S*,7*S*)-10-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-2-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6-methyl-7-((triethylsilyl)oxy)dec-3-yn-5-ol (D18)



To a solution of alkyne **D17** (0.38 g, 1.56 mmol, 1.6 equiv.) in THF (2.1 mL) at -78 °C under argon was added *n*-butyllithium (0.58 mL, 2.5 M in hexanes, 1.46 mmol, 1.4 equiv.) dropwise. After stirring at -78 °C for 1 h, the reaction mixture was warmed to 0 °C and stirred for another 1 h. The reaction mixture was recooled to -78 °C and a solution of aldehyde **D12** (0.53 g, 0.973 mmol, 1.0 equiv.) in THF (0.4 mL) was added dropwise. After stirring at -78 °C for 1 h, the reaction was slowly warmed to 0 °C. After stirring at 0 °C for 1 h, the mixture was warmed to room temperature and stirred for a further 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 30% EtOAc/pentane) to afford title compound **D18** (0.66 g, 0.834 mmol, 86%) as a colourless oil and inseparable mixture of diastereomers (1:1), along with recovered alkyne **D17** (0.12 g, 0.49 mmol).

R_f 0.45 (20% EtOAc /pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3464, 2942, 2867, 1616, 1518, 1463, 1379, 1249, 1109, 1009, 883, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.9 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.46 (1H, s, PMP acetal), 4.48 (0.5H, br s, H10), 4.40-4.35 (0.5H, m, H10), 4.28 (1H, ddd, *J* = 11.3, 5.0, 1.4 Hz, H14), 4.03-3.81 (5H, m, H2, H4, H8 and H16), 3.80 (3H, s, OMe), 3.76 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.63 (0.5H, d, *J* = 4.4 Hz, OH), 3.52 (1H, dd, *J* = 9.7, 6.8 Hz, H1'), 2.88 (0.5H, d, *J* =3.7 Hz, OH), 2.81 (1H, tdd, *J* = 6.9, 5.0, 2.1 Hz, H9),) 2.04-1.91(1H, qd, *J* = 12.4, 5.0 Hz, H13), 1.90-1.72 (1H, m, H3), 1.71-1.44 (7H, m, H3', H5, H7 and H15), 1.43 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.35-1.26 (2H, m, H6), 1.24 (3H, d, *J* = 7.1 Hz, C9-Me), 1.15-0.99 (24H, m, TIPS and C13-Me), 0.95 (9H, t, *J* =7.9 Hz, TES), 0.62 (6H, q, *J* = 8.0 Hz, TES); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 131.4, 127.6, 113.7, 101.3, 98.5, 86.4, 86.3, 82.9, 82.8, 78.9, 78.9, 75.9, 75.0, 70.2, 68.9, 68.8, 67.4, 67.1, 66.6, 65.9, 55.4, 43.4, 42.8, 36.7, 34.9, 34.5, 32.9, 31.3, 31.2, 30.2, 27.1, 26.9, 21.9, 21.4, 20.0, 18.1, 15.7, 15.6, 12.1, 7.9, 7.0, 5.4, 5.3; **HRMS** (ESI^+) calc. for $C_{44}H_{78}O_8NaSi_2$ $[M+Na]^+$ 813.5127, found 813.5120.

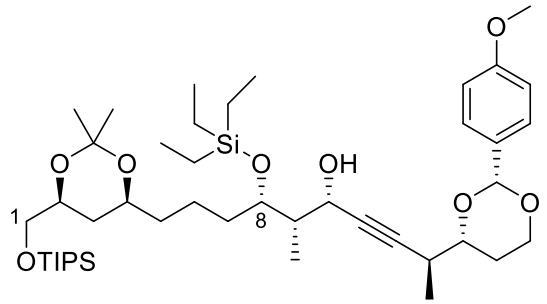
(2*S*,6*R*,7*S*)-10-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-2-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6-methyl-7-((triethylsilyl)oxy)dec-3-yn-5-one (D19)



To a solution of the diastereomers **D18** (0.66 g, 0.834 mmol, 1.0 equiv.) in CH_2Cl_2 (5.6 mL) and *tert*-butanol (70.0 μL), was added solid $NaHCO_3$ (0.70 g, 8.34 mmol, 10.0 equiv.) and Dess-Martin periodinane (0.53 g, 1.25 mmol, 1.5 equiv.). After stirring at room temperature for 2 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and sat. aq. $Na_2S_2O_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane) to afford title compound **D19** (0.59 g, 0.748 mmol, 90%) as a colourless oil.

R_f 0.50 (10% EtOAc/pentane); $[\alpha]_D^{25}$ -9.1 (*c* = 0.27, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2951, 2867, 1676, 1518, 1380, 1250, 1111, 1011, 882, 829, 744; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.48 (1H, s, PMP acetal), 4.33-4.22 (2H, m, H8 and H14), 3.99-3.89 (4H, m, H2, H4 and H16), 3.80 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 2.93 (1H, qd, *J* = 7.1, 5.1 Hz, H9), 2.58 (1H, qd, *J* = 6.9, 4.1 Hz, H13), 2.02-1.92 (1H, m, H7), 1.67-1.45 (7H, m, H3, H5, H7' and H15), 1.43 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.31 (3H, d, *J* = 7.1 Hz, H9-Me), 1.14 (3H, d, *J* = 6.9 Hz, H13-Me), 1.15-1.03 (23H, m, H6 and TIPS), 0.93 (9H, t, *J* = 7.9 Hz, TES), 0.57 (6H, q, *J* = 7.7 Hz, TES); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.8, 160.1, 131.1, 127.5, 113.7, 101.4, 98.5, 95.0, 81.9, 78.2, 72.7, 70.2, 68.8, 67.4, 66.8, 55.4, 53.3, 36.7, 35.8, 34.5, 31.8, 30.2, 27.6, 21.2, 19.9, 18.1, 15.1, 12.1, 9.8, 7.1, 5.3; **HRMS** (ESI^+) calc. for $C_{44}H_{76}O_8NaSi_2$ $[M+Na]^+$ 811.4971, found 811.4966.

(2*S*,5*S*,6*S*,7*S*)-10-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-2-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6-methyl-7-((triethylsilyl)oxy)dec-3-yn-5-ol (D20)

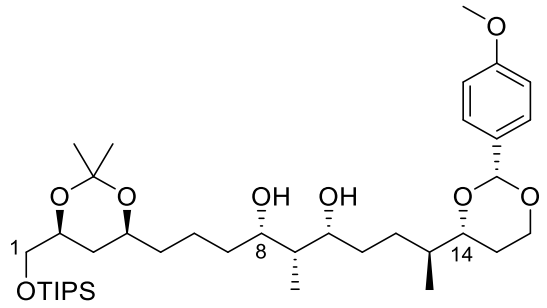


To a solution of ketone **D19** (0.59 g, 0.748 mmol, 1.0 equiv.) in degassed 2-propanol (7.5 mL), was added a solution of Ru[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-*p*–Cymene)[116] (50.0 mg, 0.0748 mmol, 0.1 equiv.) in degassed CH_2Cl_2 (0.65 mL) dropwise. The resulting mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% ethyl acetate/pentane) to afford title compound **D20** (0.54 g, 0.682 mmol, 92%, >20:1 *dr*) as a yellow oil.

R_f 0.45 (20% EtOAc/pentane); $[\alpha]_D^{25}$ –4.7 (*c* = 0.45, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3461, 2943, 2868, 1616, 1518, 1462, 1379, 1249, 1109, 1010, 883, 828, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.8 Hz, ArH), 5.47 (1H, s, PMP acetal), 4.48 (1H, brs, H10), 4.28 (1H, ddd, *J* = 11.3, 5.0, 1.4 Hz, H14), 3.98-3.85 (5H, m, H2, H4, H8 and H16), 3.80 (3H, s, OCH_3), 3.76 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 2.88 (1H, d, *J* =3.7 Hz, OH), 2.82 (1H, ddt, *J* = 10.3, 7.1, 3.1 Hz, H9),) 1.97 (1H, qd, *J* = 12.4, 5.0 Hz, H13), 1.82-1.75 (1H, m, H3), 1.65 (1H, dt, *J* = 12.9,

2.5 Hz, H3'), 1.62-1.46 (6H, m, H5, H7 and H15), 1.43 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.35-1.27 (2H, m, H6), 1.24 (3H, d, *J* =7.0 Hz, H9-Me), 1.15-1.03 (21H, m, TIPS), 1.02 (3H, d, *J* = 6.9 Hz, H13-Me), 0.96 (9H, t, *J* = 7.9 Hz, TES), 0.61 (6H, q, *J* = 8.0 Hz, TES); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 131.4, 127.6, 113.7, 101.3, 98.5, 86.4, 82.8, 78.9, 75.9, 70.2, 68.8, 67.4, 67.1, 66.6, 55.4, 42.8, 36.7, 34.9, 34.5, 31.2, 30.3, 26.9, 21.4, 20.0, 18.1, 15.6, 12.1, 7.9, 7.0, 5.4; **HRMS** (ESI^+) calc. for $C_{44}H_{78}O_8NaSi_2$ $[M+Na]^+$ 813.5127, found 813.5107.

(4*S*,5*R*,6*R*,9*S*)-1-((4*S*,6*S*)-2,2-Dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)-9-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-5-methyldecane-4,6-diol (D22)



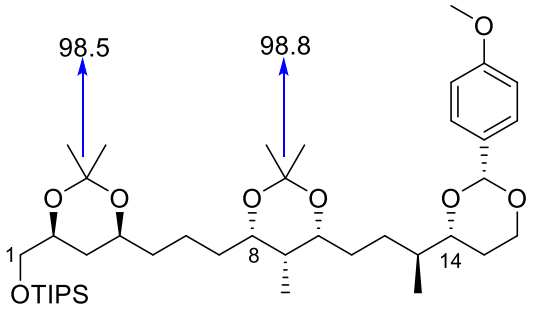
To a solution of alkyne **D20** (0.54 g, 0.682 mmol, 1.0 equiv.) in degassed EtOAc (16 mL), was added degassed Et_3N (0.54 mL, 3.89 mmol, 5.7 equiv.), followed by 20% palladium hydroxide on carbon (43 mg, 0.307 mmol, 0.45 equiv.) The resulting black suspension was stirred under a hydrogen atmosphere (balloon) for 1 h. The mixture was then filtered through celite, washed with ethyl acetate (20 mL), and the solvent was removed under reduced pressure. The crude yellow residue **D21** (0.52 g, 0.654 mmol, 96%) was submitted to next step directly without further purification.

To a solution of the crude residue (0.52 g, 0.654 mmol, 1.0 equiv.) in THF (13 mL) at -30 °C

was added tetra-*n*-butylammonium fluoride (0.65 mL, 1.0 M in THF, 0.654 mmol, 1.0 equiv.) dropwise. After stirring at -30 °C for 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 30% EtOAc/pentane) to afford diol **D22** (0.35 g, 0.514 mmol, 75% over two steps) as a colourless oil.

R_f 0.40 (30% EtOAc/pentane); $[\alpha]_D^{25}$ –3.7 (*c* = 0.32, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3468, 2942, 2865, 1615, 1518, 1463, 1379, 1249, 1111, 882; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.44 (1H, s, PMP acetal), 4.27 (1H, ddd, *J* = 11.3, 5.0, 1.4 Hz, H14), 3.95-3.88 (2H, m, H2, H4), 3.87-3.81 (3H, m, H8 and H16), 3.80 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.61 (1H, ddd, *J* = 11.6, 6.6, 2.2 Hz, H10), 3.52 (1H, dd, *J* = 9.7, 6.6 Hz, H1'), 2.78 (2H, d, *J* = 12.9 Hz, OH), 1.86-1.78 (1H, m, H13), 1.77-1.62 (5H, m, H5, H7 and H9), 1.62-1.45 (10H, m, H3, H6, H11, H12 and H15), 1.44 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.10-1.02 (21H, m, TIPS), 0.95 (3H, d, *J* = 6.8 Hz, H9-Me), 0.88 (3H, d, *J* = 7.0 Hz, H13-Me); δ **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 131.7, 127.5, 113.7, 101.3, 98.6, 81.1, 77.9, 77.3, 70.2, 69.2, 67.4, 67.3, 55.4, 40.5, 38.0, 36.2, 35.2, 34.5, 32.7, 30.2, 28.9, 28.2, 22.0, 20.0, 18.1, 15.1, 12.1, 4.3; **HRMS** (ESI^+) calc. for $C_{38}H_{68}O_8NaSi$ $[M+Na]^+$ 703.4576, found 703.4557.

Triisopropyl(((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*)-3-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)silane (D23)

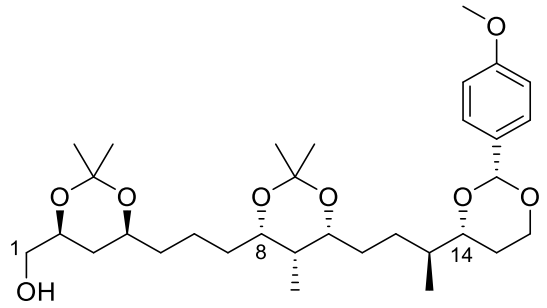


To a solution of diol **D22** (0.35 g, 0.514 mmol, 1.0 equiv.) in CH_2Cl_2 (10.3 mL), was added 2,2-dimethoxypropane (10.3 mL) and pyridinium *p*-toluenesulfonate (25.8 mg, 0.103 mmol, 0.2 equiv.). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane) to afford title compound **D23** (0.33 g, 0.458 mmol, 88%) as a colourless oil.

R_f 0.45 (10% EtOAc/pentane); $[\alpha]_D^{25}$ –6.2 (*c* = 0.70, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2941, 2865, 1615, 1518, 1462, 1379, 1249, 1112, 1010, 882; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.44 (1H, s, PMP acetal), 4.27 (1H, ddd, *J* = 11.4, 5.0, 1.4 Hz, H14), 3.95-3.90 (2H, m, H2 and H4), 3.86-3.81 (3H, m, H8 and H16), 3.80 (3H, s, OCH_3), 3.76 (1H, dd, *J* = 9.7, 5.0 Hz, H1), 3.61 (1H, ddd, *J* = 11.3, 6.8, 2.3 Hz, H10), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1'), 1.85-1.76 (1H, m, H13), 1.76-

1.62 (3H, m, H3 and H9), 1.61-1.45 (8H, m, H5, H7, H11 and H15), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.36-1.30 (4H, m, H6 and H12), 1.16-1.03 (21H, m, TIPS), 0.95 (3H, d, *J* = 6.8 Hz, H9-Me), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 131.7, 127.5, 113.7, 101.2, 98.8, 98.5, 81.1, 73.8, 73.4, 70.2, 69.0, 67.4, 67.3, 55.4, 37.9, 36.7, 34.4, 34.2, 33.0, 30.3, 30.2, 29.9, 28.1, 27.6, 21.1, 20.0, 19.9, 18.1, 15.0, 12.1, 4.6; **HRMS** (ESI^+) calc. for $C_{41}H_{72}O_8NaSi$ $[M+Na]^+$ 743.4889, found 743.4867.

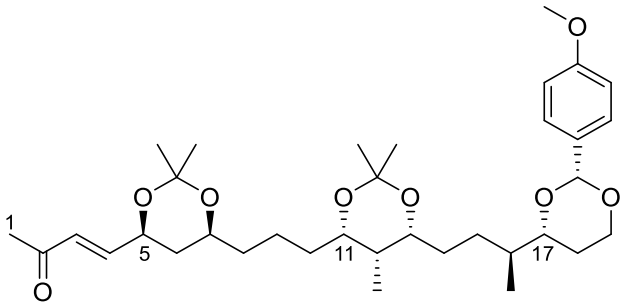
((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*)-3-((4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methanol (D24)



To a solution of acetonide **D23** (97.7 mg, 0.135 mmol, 1.0 equiv.) in THF (2.1 mL) was added tetra-*n*-butylammonium fluoride (0.271 mL, 1.0 M in THF, 0.271 mmol, 2.5 equiv.). After stirring at room temperature overnight, the reaction was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30% EtOAc/pentane) to afford primary alcohol **D24** (67.1 mg, 0.119 mmol, 88%) as a colourless oil.

R_f 0.30 (30% EtOAc/pentane); **$[\alpha]_D^{25}$** –11.6 (*c* = 0.45, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3483, 2981, 2863, 1615, 1518, 1380, 1250, 1170, 1104, 1010, 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.44 (1H, s, PMP acetal), 4.27 (1H, ddd, *J* = 11.3, 5.0, 1.4 Hz, H14), 4.01-3.92 (2H, m, H2, H4), 3.91-3.81 (3H, m, H8, H16), 3.80 (3H, s, OCH_3), 3.63-3.57 (2H, m, H1, H10), 3.51-3.46 (1H, m, H1'), 1.96 (1H, t, *J* = 6.3 Hz, OH), 1.86-1.67 (2H, m, H9 and H13), 1.66-1.47 (6H, m, H3, H5 and H7), 1.45 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.36-1.10 (8H, m, H6, H11, H12 and H15), 0.94 (3H, d, *J* = 6.8 Hz, H9-Me), 0.80 (3H, d, *J* = 6.9 Hz, H13-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 131.7, 127.5, 113.7, 101.2, 98.8, 98.8, 81.0, 73.8, 73.4, 69.8, 68.6, 67.3, 66.3, 55.4, 37.9, 36.6, 34.1, 33.0, 32.5, 30.3, 30.2, 29.8, 28.2, 27.6, 21.1, 20.1, 19.9, 15.0, 4.6; **HRMS** (ESI^+) calc. for $C_{32}H_{52}O_8Na$ $[M+Na]^+$ 587.3554, found 587.3539.

(*E*)-4-((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*)-3-((4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-3-en-2-one (D26)



To a solution of alcohol **D24** (67.1 mg, 0.119 mmol, 1.0 equiv.) in CH_2Cl_2 (0.80 mL), was added solid $NaHCO_3$ (99.8 mg, 1.19 mmol, 10.0 equiv.) and Dess-Martin periodinane (75.6

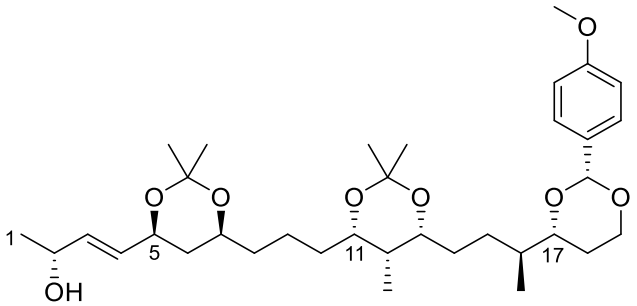
mg, 0.178 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 ºC and quenched with sat. aq. $NaHCO_3$ solution (1 mL) and sat. aq. $Na_2S_2O_3$ solution (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the corresponding aldehyde (61.2 mg, 0.109 mmol, 91%) as a colourless oil. **R_f** 0.50 (10% EtOAc/petane); The crude residue was used for the next step directly without further purification.

To a suspension of sodium hydride (8.7 mg, 60% dispersion in mineral oil, 0.218 mmol, 2.0 equiv.) in THF (2.2 mL) at 0 °C, was slowly added dimethyl (2-oxopropyl) phosphonate (31.6 μL, 0.228 mmol, 2.1 equiv.) and then the resulting mixture was warmed to room temperature. After stirring at room temperature for 1 h, the reaction mixture was cooled to -78 °C and a solution of crude aldehyde (61.2 mg, 0.109 mmol, 1.0 equiv.) in THF (1.1 mL) was added dropwise. The resulting mixture was allowed to warm slowly to room temperature and was stirred for 2 h. The mixture was quenched with water (1 mL) and diluted with Et_2O (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 30% EtOAc/pentane) to afford enone **D26** (45.1 mg, 0.0746 mmol, 63% over two steps) as a colourless oil.

R_f 0.50 (25% EtOAc/pentane); $[\alpha]_D^{25}$ +6.5 (*c* = 0.14, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2940, 2859, 1678, 1615, 1518, 1461, 1379, 1250, 1170, 1104, 1035, 829; **^{1}H NMR** (500

MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 6.68 (1H, dd, *J* = 16.0, 4.6 Hz, H4) (The value of the coupling constant indicates the alkene is in trans configuration.), 6.26 (1H, d, *J* = 16.0 Hz, H3), 5.44 (1H, s, PMP acetal), 4.56-4.52 (1H, m, H5), 4.27 (1H, ddd, *J* = 11.3, 5.1, 1.4 Hz, H17), 3.95-3.85 (3H, m, H11, H19), 3.85-3.81 (1H, m, H7), 3.80 (3H, s, OCH_3), 3.61 (1H, ddd, *J* =11.3, 6.8, 2.3 Hz, H13), 2.27 (3H, s, H1), 1.84-1.69 (3H, m, H6, H12 and H16), 1.65-1.48 (9H, m, H6', H8, H10, H14, H18), 1.47 (3H, s, acetonide), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.35-1.30 (4H, m, H9, H15), 0.94 (3H, d, *J* = 6.8 Hz, H12-Me), 0.80 (3H, d, *J* = 6.8 Hz, H16-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.7, 159.9, 146.1, 131.7, 129.4, 127.5, 113.7, 101.2, 99.0, 98.8, 81.0, 73.8, 73.4, 68.8, 68.5, 67.3, 55.4, 37.9, 36.4, 36.3, 34.2, 33.0, 30.2, 30.2, 29.8, 28.2, 27.6, 27.5, 21.1, 19.9, 19.9, 15.0, 4.6; **HRMS** (ESI^+) calc. for $C_{35}H_{54}O_8Na$ $[M+Na]^+$ 625.3711, found 625.3701.

(2*R*,*E*)-4-((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*)-3-((4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-3-en-2-ol (D27a)

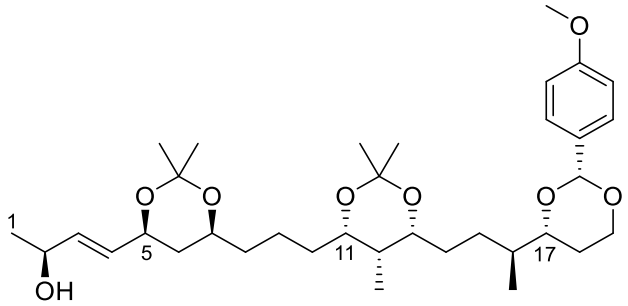


To a solution of (*S*)-(–)-2-methyl–CBS-oxazaborolidine (39.8 μL, 1.0 M in toluene, 0.0398 mmol, 1.0 equiv.) in THF (0.6 mL) at 0 °C was added borane dimethyl sulfide complex

solution (100 µL, 1.0 M in THF, 0.1 mmol, 2.5 equiv.) dropwise. After stirring at 0 °C for 30 min, a solution of enone **D26** (24.1 mg, 0.0398 mmol, 1.0 equiv.) in THF (0.2 mL) was added slowly and stirred for 1 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl solution (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford enol **D27a** (22.0 mg, 0.036 mmol, 91%, >20:1 *dr*) as a colourless oil.

R_f 0.35 (30% EtOAc/pentane); $[\alpha]_D^{25}$ −3.5 (*c* = 0.35, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3415, 2941, 2861, 1615, 1518, 1379, 1258, 1104, 971, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.77 (1H, dd, *J* = 15.6, 6.0 Hz, H3), 5.65 (1H, dd, *J* = 15.6, 6.0 Hz, H4), 5.44 (1H, s, PMP acetal), 4.36-4.25 (3H, m, H2, H5, H17), 3.92 (1H, td, *J* = 11.9, 2.6 Hz, H11), 3.86-3.81 (3H, m, H7, H19), 3.80 (3H, s, OCH_3), 3.61 (1H, ddd, *J* = 11.3, 6.8, 2.3 Hz, H13), 1.84-1.62 (4H, m, H6, H12, H16), 1.61-1.48 (8H, m, H8, H10, H14, H18), 1.46 (3H, s, acetonide), 1.42 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.36-1.31 (4H, m, H9, H15), 1.27 (3H, d, *J* = 6.5 Hz, H1), 0.94 (3H, d, *J* = 6.8 Hz, C12-Me), 0.80 (3H, d, *J* = 6.8 Hz, C16-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 135.4, 131.7, 130.6, 127.5, 113.6, 101.2, 98.8, 98.7, 81.0, 73.8, 73.4, 69.6, 68.8, 68.3, 67.3, 55.4, 37.9, 37.1, 36.5, 34.1, 33.0, 30.4, 30.2, 29.8, 28.1, 27.5, 23.2, 21.1, 20.0, 19.9, 15.0, 4.6; **HRMS** (ESI^+) calc. for $C_{35}H_{56}O_8Na$ $[M+Na]^+$ 627.3867, found 627.3862.

(2*S*,*E*)-4-((4*S*,6*S*)-6-(3-((4*S*,5*R*,6*R*)-6-((3*S*)-3-((4*R*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-3-en-2-ol (D27b)

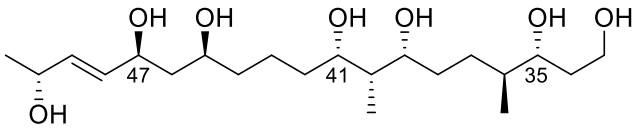


To a solution of (*R*)-(+)-2-methyl–CBS-oxazaborolidine (34.8 μL, 1.0 M in toluene, 0.0348 mmol, 1.0 equiv.) in THF (0.55 mL) at 0 °C was added borane dimethyl sulfide complex solution (87.1 μL, 1.0 M in THF, 0.0871 mmol, 2.5 equiv.) dropwise. After stirring at 0 °C for 30 min, a solution of enone **D26** (21.0 mg, 0.0348 mmol, 1.0 equiv.) in THF (0.15 mL) was added slowly and stirred for 1 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl solution (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford enol **D27b** (19.0 mg, 0.031 mmol, 90%, >20:1 *dr*) as a colourless oil.

R$_f$ 0.35 (30% EtOAc/pentane); $[\alpha]_D^{25}$ −2.5 (*c* = 0.30, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3454, 2938, 2857, 1615, 1518, 1379, 1250, 1104, 969, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.8 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.77 (1H, dd, *J* = 15.6, 6.1 Hz, H3), 5.64 (1H, dd, *J* = 15.6, 6.0 Hz, H4), 5.44 (1H, s, PMP acetal), 4.36-4.25 (3H, m, H2,

H5, H17), 3.92 (1H, td, *J* = 11.9, 2.6 Hz, H11), 3.86-3.81 (3H, m, H7, H19), 3.80 (3H, s, OCH_3), 3.61 (1H, ddd, *J* = 11.3, 6.9, 2.3 Hz, H13), 1.84-1.63 (4H, m, H6, H12, H16), 1.62-1.47 (8H, m, H8, H10, H14, H18), 1.46 (3H, s, acetonide), 1.42 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.36-1.30 (4H, m, H9, H15), 1.27 (3H, d, *J* = 6.4 Hz, H1), 0.94 (3H, d, *J* = 6.8 Hz, H12-Me), 0.80 (3H, d, *J* = 6.8 Hz, H16-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 135.4, 131.7, 130.6, 127.5, 113.7, 101.2, 98.8, 98.8, 81.0, 73.8, 73.4, 69.6, 68.8, 68.4, 67.3, 55.4, 37.9, 37.1, 36.5, 34.1, 33.0, 30.4, 30.2, 29.8, 28.1, 27.6, 23.2, 21.1, 20.0, 19.9, 15.0, 4.6; **HRMS** (ESI^+) calc. for $C_{35}H_{56}O_8Na$ $[M+Na]^+$ 627.3867, found 627.3863.

(3*R*,4*S*,7*R*,8*R*,9*S*,13*S*,15*S*,18*S*,*E*)-4,8-Dimethylnonadec-16-ene-1,3,7,9,13,15,18-heptaol (D28a)

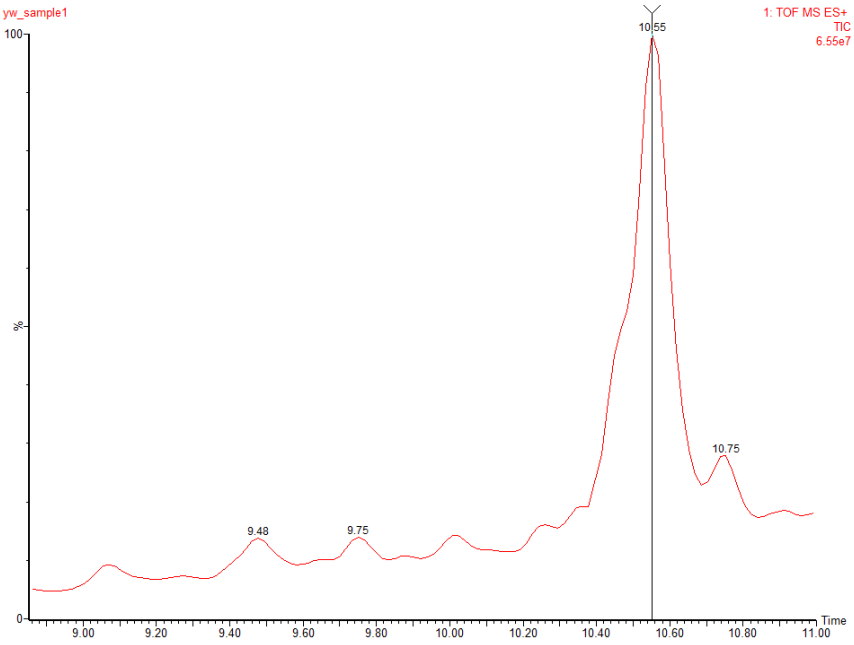


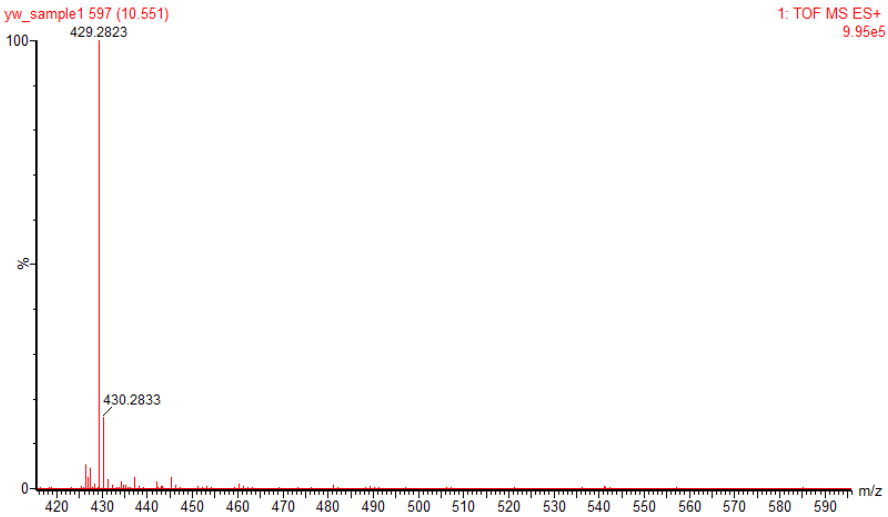
To a solution of enol **D27a** (22.0 mg, 0.0364 mmol, 1.0 equiv.) in methanol (2.4 mL) and THF (1.2 mL), was added aq. HCl solution (2.4 mL, 0.1 M). After stirring at room temperature for 3 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (3 mL) and extracted with chloroform/2-propanol (3:1) (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (100% water to 25% acetonitrile/water gradient over 45 min) to give **D28a** (8.1 mg, 0.0199 mmol, 55%) as a colourless oil. HPLC: Product peak is visible at 210 nm and the retention time is 18.2 min. In addition, other conditions

(TFA, PTSA, CSA and high concentration aqueous HCl) were attempted to achieve deprotection but various byproducts were observed due to the vulnerability of the allylic alcohol.

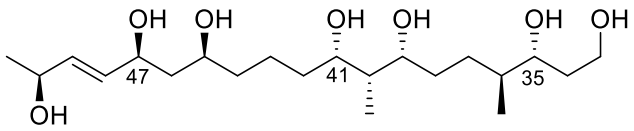
R_f = 0.10 (20% EtOH/CH_2Cl_2); **$[\alpha]_D^{25}$** +3.9 (*c* = 0.69, MeOH); **IR** (thin film, ν_{max} / cm^{-1}) 3366, 2981, 2889, 1647, 1382, 1252, 1151, 1071, 956; **^{1}H NMR** (600 MHz, MeOD) δ 5.72 (1H, ddd, *J* = 15.5, 5.8, 0.9 Hz, H48), 5.61 (1H, ddd, *J* = 15.5, 6.6, 1.1 Hz, H49), 4.28-4.21 (2H, m, H47 and H50), 3.74-3.67 (5H, m, H33, H39, H41, H45), 3.58 (1H, ddd, *J* = 9.9, 5.2, 2.6 Hz, H35), 1.72-1.56 (6H, m, H34, H37, H42 and H46), 1.54-1.39 (9H, m, H36, H38, H40, H42, H43, H44), 1.23 (3H, d, *J* = 6.5 Hz, H51), 1.13-1.09 (1H, m, H37'), 0.93 (3H, d, *J* = 2.5 Hz, 36-Me), 0.92 (3H, d, *J* = 2.7 Hz, C40-Me); **^{13}C NMR** (151 MHz, MeOD) δ 136.1, 133.2, 76.4, 75.9, 73.8, 71.7, 70.6, 68.7, 60.8, 45.3, 42.8, 40.6, 38.7, 36.6, 36.0, 33.8, 29.7, 23.6, 23.0, 15.7, 7.0; **HRMS** (ESI^+) calc. for $C_{21}H_{42}O_7Na$ $[M+Na]^+$ 429.2823, found 429.2822.

LC-MS analysis of crude 1a before purification [LC: XDB–C18 column (150 mm x 4.6 mm, 5μm), 100% (water + 0.1% formic acid)-50% (acetonitrile + 0.1 fomic acid)/(water + 0.1% formic acid) (0-40 min), MS: ESI^+ positive mode, *m/z* range from 100-1000]; calc. for $C_{21}H_{42}O_7Na$ $[M+Na]^+$ 429.2823, found 429.2823. (*t* = 10.55 min)





(3*R*,4*S*,7*R*,8*R*,9*S*,13*S*,15*S*,18*R*,*E*)-4,8-Dimethylnonadec-16-ene-1,3,7,9,13,15,18-heptaol (D28b)



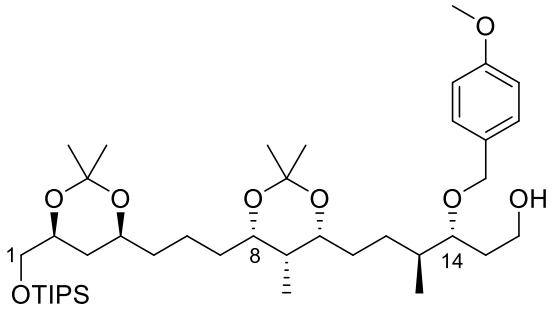
To a solution of enol **D27b** (19.0 mg, 0.0314 mmol, 1.0 equiv.) in methanol (2.0 mL) and THF (1.0 mL) was added aq. HCl solution (2.0 mL, 0.1 M). After stirring at room temperature for 3 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (2 mL) and extracted with chloroform/2-propanol (3:1) (5 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (100% water to 10% acetonitrile/water gradient over 45 min) to give **D28b** (6.6 mg, 0.0162 mmol, 52%) as a colourless oil. HPLC: Product peak is visible at 210 nm and the retention time is 13.0 min.

$\mathbf{R_f}$ = 0.10 (20% EtOH/DCM); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +9.9 (*c* = 0.76, MeOH); **IR** (thin film, ν_{max} / cm^{-1}) 3344, 2981, 2889, 1653, 1382, 1252, 1150, 1071, 955; **^{1}H NMR** (600 MHz, MeOD) δ 5.72 (1H, dd, *J* = 15.5, 5.9 Hz, H48), 5.61 (1H, ddd, *J* = 15.5, 6.6, 1.1 Hz, H49), 4.28-4.21 (2H, m, H47 and H50), 3.74-3.67 (5H, m, H33, H39, H41, H45), 3.58 (1H, ddd, *J* = 10.0, 5.2, 2.6 Hz, H35), 1.72-1.56 (6H, m, H34, H37, H42 and H46), 1.54-1.39 (9H, m, H36, H38, H40, H42, H43, H44), 1.23 (3H, d, *J* = 6.4 Hz, H51), 1.13-1.09 (1H, m, H37'), 0.93 (3H, d, *J* = 3.0 Hz, 36-Me), 0.92 (3H, d, *J* = 3.2 Hz, C40-Me); **^{13}C NMR** (151 MHz, MeOD) δ 136.0, 133.1, 76.4, 75.9, 73.8, 71.7, 70.6, 68.7, 60.8, 45.3, 42.8, 40.6, 38.7, 36.6, 36.0, 33.8, 29.7, 23.7, 23.1, 15.7, 7.0; **HRMS** (ESI^+) calc. for $C_{21}H_{42}O_7Na$ $[M+Na]^+$ 429.2823, found 429.2823.

NMR data comparison of stambomycin D and two diastereomeric C33–C51 fragments D28a and D28b.

	Stambomycin D (MeOD, 700 MHz)		**C50(*R*)–C33–C51 Fragment D28a (MeOD, 600 MHz)**		**C50(*S*)–C33–C51 Fragment D28b (MeOD, 600 MHz)**	
Position	**δ_C (ppm)**	**δ_H (ppm)**	**δ_C (ppm)**	**δ_H (ppm)**	**δ_C (ppm)**	**δ_H (ppm)**
33	66.8	4.06	60.8	3.71	60.8	3.71
34	42.0	1.48, 1.50	36.6	1.57, 1.69,	36.6	1.57, 1.69,
35	72.9	3.74	73.8	3.58	73.8	3.58
36	40.8	1.48	40.6	1.53	40.6	1.53
36-Me	15.6	0.92	15.7	0.93	15.7	0.93
37	29.8	1.12, 1.28	29.7	1.10, 1.62	29.7	1.10, 1.62
38	36.0	1.50	36.0	1.48	36.0	1.48
39	76.3	3.72	76.4	3.71	76.4	3.71
40	42.3	1.51	42.8	1.50	42.8	1.50
40-Me	7.0	0.91	7.0	0.92	7.0	0.92
41	75.9	3.71	75.9	3.71	75.9	3.71
42	33.8	1.43, 1.62	33.8	1.41, 1.60	33.8	1.41, 1.60
43	22.9	1.43	23.0	1.46	23.1	1.46
44	38.8	1.45, 1.46	38.7	1.48	38.7	1.48
45	70.6	3.67	70.6	3.69	70.6	3.69
46	44.8	1.60, 1.65	45.3	1.57, 1.64	45.3	1.57, 1.64
47	71.1	4.28	71.7	4.25	71.7	4.25
48	136.7	5.80	136.1	5.72	136.0	5.72
49	130.8	5.72	133.2	5.63	133.1	5.63
50	72.8	5.43	68.7	4.25	68.7	4.25
51	20.8	1.33	23.6	1.23	23.7	1.23

(3*R*,4*S*)-6-((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-((4-methoxybenzyl)oxy)-4-methylhexan-1-ol (D24')

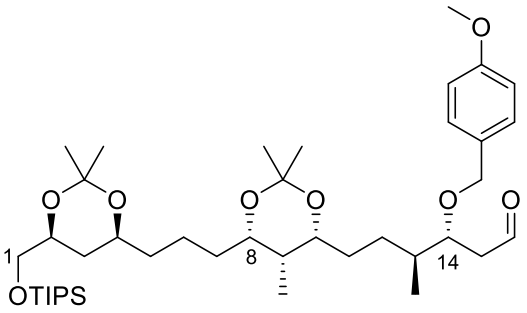


To a solution of acetonide **D23** (0.300 g, 0.416 mmol, 1.0 equiv.) in CH_2Cl_2 (2.8 mL) at -78 °C was added DIBAL-H (0.6 mL, 1.0 M in CH_2Cl_2, 0.624 mmol, 1.5 equiv.) dropwise. After stirring at -78 °C for 1 h, the reaction mixture was warmed to -35 °C and stirred for further 2 h. The reaction mixture was quenched with sat. aq. Rochelle salt (5.0 mL) and stirred for 15 min at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 30% EtOAc/pentane) to afford title compound **D24'** (0.150 g, 0.207 mmol, 50 %) and recovered starting material D (0.125 g, 0.173 mmol) as a colourless oil.

R_f 0.46 (30% EtOAc/pentane); $[\alpha]_D^{25}$ +13.1 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3472, 2942, 2866, 1614, 1514, 1462, 1379, 1249, 1200, 1173, 1116, 1070, 1010, 882, 821, 680; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.5 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 4.54 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.36 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 3.93 (1H, dtt,

J = 9.2, 5.0, 2.5 Hz, H14), 3.85-3.78 (6H, m, H2, H4, H8 and OCH_3), 3,80 (3H, s, OCH_3), 3.78-3.71 (3H, m, H10 and H16), 3.56-3.49 (2H, m, H1), 2.39 (1H, t, *J* = 5.4 Hz, OH), 1.97-1.86 (1H, m, H13), 1.77-1.63 (3H, m, H3 and H9), 1.60-1.28 (20H, m, H5, H7, H11, H15 and acetonide x 4), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.19-1.01 (25H, m, H6, H12 and TIPS), 0.92 (3H, d, *J* = 6.8 Hz, H9-Me), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.6, 129.6, 114.0, 98.9, 98.5, 82.3, 73.9, 73.4, 70.9, 70.2, 69.0, 67.4, 61.6, 55.4, 36.7, 34.8, 34.7, 34.4, 32.9, 31.3, 31.2, 30.3, 30.2, 29.2, 21.1, 20.0, 19.9, 18.1, 13.9, 12.1, 4.8; **HRMS** (ESI^+) calc. for $C_{41}H_{74}O_8NaSi$ $[M+Na]^+$ 745.5045, found 745.5039.

(3*R*,4*S*)-6-((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-((4-methoxybenzyl)oxy)-4-methylhexanal (D25)

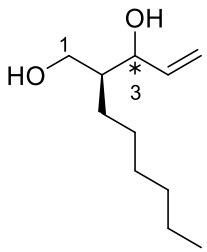


To a solution of alcohol **D24** (0.145 g, 0.201 mmol, 1.0 equiv.) in CH_2Cl_2 (1.4 mL) was added solid sodium bicarbonate (0.168 g, 2.01 mmol, 10.0 equiv.), followed by Dess-Martin periodinane (0.128g, 0.301 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with dropwise addition of sat. aq. $NaHCO_3$ solution (5.0 mL)

and sat. aq. $Na_2S_2O_3$ solution (5.0 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred until the layers turned clear. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane) to afford aldehyde **D25** (0.129 g, 0.179 mmol, 89%) as a colourless oil.

R_f 0.50 (14% EtOAc/pentane); $[\alpha]_D^{25}$ +4.97 (*c* = 0.35, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2889, 1727, 1514, 1462, 1381, 1250, 1151, 1072, 954, 882, 819, 681; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (1H, dd, *J* = 2.7, 1.7 Hz, H16), 7.23 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 4.50 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 4.40 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 3.97-3.81 (4H, m, H14, H8, H4 and H2), 3.80 (3H, s, OCH_3), 3.79-3.73 (2H, m, H10 and H1), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1), 2.61 (1H, ddd, *J* = 16.2, 8.9, 2.7 Hz, H15), 2.42 (1H, ddd, *J* = 16.3, 3.5, 1.8 Hz, H15), 1.95-1.85 (1H, m, H13), 1.71-1.26 (23H, m, H3, H5, H7, H9, H11, H15 and acetonide x 4), 1.44 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.20-0.99 (25H, m, H6, H12 and TIPS), 0.92 (3H, d, *J* = 6.8 Hz, H9-Me), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.4, 159.4, 130.5, 129.5, 114.0, 98.9, 98.5, 77.8, 73.9, 73.4, 71.2, 70.2, 69.0, 67.4, 55.4, 44.6, 36.7, 35.6, 34.7, 34.4, 32.9, 31.0, 30.3, 30.2, 28.9, 21.1, 20.0, 19.9, 18.1, 14.3, 12.1, 4.8; **HRMS** (ESI^+) calc. for $C_{41}H_{72}O_8NaSi$ $[M+Na]^+$ 743.4889, found 743.4881.

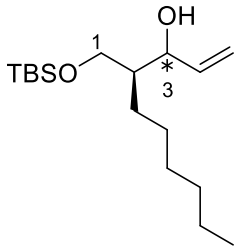
(2*S*)-2-Hexylpent-4-ene-1,3-diol (C1)



To a solution of catalyst **L3**[59] (1.87 g, 5.76 mmol, 0.1 equiv.) in toluene (115 mL) was added solid potassium phosphate PH 7 buffer (5.74 g) and formaldehyde (12.9 mL, 37 % wt. % in H_2O, 173 mmol, 3.0 equiv.). The resulting biphasic mixture was stirred vigorously for 15 min at room temperature, followed by addition of octanal (9.0 mL, 57.6 mmol, 1.0 equiv.). After stirring at room temperature for 36 h, the reaction mixture was diluted with water (50 mL) and the aqueous layer was extracted with toluene (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was dissolved in toluene (150 mL) and cooled to 0 °C, followed by slow addition of vinylmagnesium bromide solution (173 mL, 1.0 M in THF, 173 mmol, 3.0 equiv.) *via* a dropping funnel. After stirring at room temperature for 1 h, the reaction mixture was recooled to 0 °C and quenched by addition of sat. aq. NH_4Cl solution (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 400 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **C1** (4.43 g, 23.8 mmol, 41 %) as a yellow oil and an inseparable mixture of diastereomers (2:1).

R_f 0.40 (40% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3342, 2981, 2928, 1462, 1382, 1252, 1151, 1072, 955, 817; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.00-5.88 (1.5H, m, $H4_{major}$ and $H4_{minor}$), 5.35-5.18 (3H, m, $H5_{major}$ and $H5_{minor}$), 4.40-4.36 (0.5H, m, $H3_{minor}$), 4.19-4.15 (1H, m, $H3_{major}$), 3.88 (1H, ddd, *J* = 11.0, 5.8, 2.9 Hz, $H1_{major}$), 3.75-3.70 (1H, m, $H1_{minor}$ and $H1'_{minor}$), 3.66 (1H, ddd, *J* = 10.9, 6.2, 4.6 Hz, $H1'_{major}$), 2.54-2.35 (3H, OH_{major} and OH_{minor}), 1.89-1.80 (0.5H, m, $H2_{minor}$), 1.61-1.53 (1H, m, $H2_{major}$), 1.45-1.20 (15H, m, $(CH_2)_{5major}$ and $(CH_2)_{5minor}$), 0.90-0.84 (4.5H, m, CH_{3major} and CH_{3minor}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 138.2, 116.1, 116.0, 77.5, 76.3, 64.6, 64.5, 44.9, 44.8, 31.9, 31.9, 29.7, 29.7, 28.2, 27.7, 27.4, 26.2, 22.8, 14.2. **HRMS** (ESI^+) calc. for $C_{11}H_{22}O_2Na$ $[M+Na]^+$ 209.1512, found 209.1513.

(4*S*)-4-(((Tert-butyldimethylsilyl)oxy)methyl)dec-1-en-3-ol (C2)

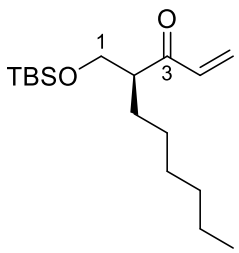


To a solution of diol **C1** (4.43 g, 23.8 mmol, 1.0 equiv.) in CH_2Cl_2 (59.4 mL) was added imidazole (3.24 g, 47.6 mmol, 2.0 equiv.). The resulting mixture was cooled to 0 °C and then *tert*-butyldimethylsilyl chloride (3.58 g, 23.8 mmol, 1.0 equiv.) was added portionwise. After stirring overnight at room temperature, the reaction mixture was quenched with water (20 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (5% Et_2O/pentane to 10% Et_2O/pentane) to afford title compound **C2** (5.50 g, 18.3 mmol, 77%) as a colourless oil and an inseparable mixture of diastereomers (2:1).

R_f 0.45 (10% Et_2O/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3441, 2955, 2928, 2857, 1470, 1255, 1092, 836, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93-5.84 (1.5H, m, $H4_{major}$ and $H4_{minor}$), 5.34-5.13 (3H, m, $H5_{major}$ and $H5_{minor}$), 4.33-4.28 (0.5H, m, $H3_{minor}$), 4.18-4.11 (1H, m, $H3_{major}$), 3.92 (1H, ddd, *J* = 10.0, 3.0, $H1_{major}$), 3.73-3.65 (2H, m, $H1_{minor}$, $H1'_{minor}$, OH_{major} and OH_{minor}), 3.62 (1H, ddd, *J* = 10.0, 4.5Hz, $H1'_{major}$), 1.83-1.77 (0.5H, m, $H2_{minor}$), 1.52-1.46 (1H, m, $H2_{major}$), 1.35-1.21 (15H, m, $(CH_2)_{5major}$ and $(CH_2)_{5minor}$), 0.91-0.86 (18H, m, CH_{3major}, CH_{3minor}, $SiC(CH_3)_{3major}$ and $SiC(CH_3)_{3minor}$), 0.09-0.05 (9H, m, $Si(CH_3)_{2major}$ and $Si(CH_3)_{2minor}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 138.5, 115.3, 115.0, 76.5, 75.9, 65.5, 64.9, 44.7, 44.4, 31.9, 31.9, 29.7, 29.7, 28.3, 27.7, 27.4, 26.0, 26.0, 22.8, 18.2, 14.2, -5.5, -5.5, -5.6; **HRMS** (ESI^+) calc. for $C_{17}H_{36}O_2NaSi$ $[M+Na]^+$ 323.2377, found 323.2377.

(*S*)-4-(((Tert-butyldimethylsilyl)oxy)methyl)dec-1-en-3-one (C3)

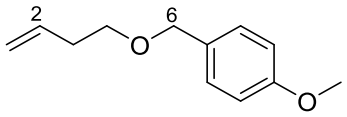


To a solution of alcohol **C2** (5.50 g, 18.3 mmol, 1.0 equiv.) in CH_2Cl_2 (121 mL) was added sodium bicarbonate (15.4 g, 183 mmol, 10 equiv.), followed by Dess-Martin periodinane

(11.6 g, 27.4 mmol, 1.5 equiv.). After stirring at room temperature for 1h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (50 mL) and sat. aq. $Na_2S_2O_3$ solution (50 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/pentane) to obtain aldehyde **C3** (4.81 g, 16.1 mmol, 88%) as a colourless oil.

R_f 0.60 (10% Et_2O/PE); $[\alpha]_D^{25}$ +2.9 (*c* = 1.0, $CHCl_3$); **IR** (thin film, v_{max} / cm^{-1}) 2956, 2929, 2857, 1699, 1679, 1470, 1402, 1254, 1101, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.45 (1H, dd, *J* = 17.5, 10.6 Hz, H4), 6.24 (1H, dd, *J* = 17.5, 1.3 Hz, H5), 5.77 (1H, dd, *J* = 10.5, 1.3 Hz, H5'), 3.77 (1H, dd, *J* = 9.7, 8.0 Hz, H1), 3.65 (1H, dd, *J* = 9.8, 5.5, H1'), 3.09-3.01 (1H, m, H2), 1.64-1.52 (1H, m, H2'), 1.47-1.35 (1H, m, H2'), 1.30-1.20 (8H, m, $(CH_2)_4$), 0.89-0.83 (12H, m, CH_3 and $SiC(CH_3)_3$), 0.02 (3H, s, $Si(CH_3)$), 0.00 (3H, s, $Si(CH_3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.8, 137.1, 128.0, 64.8, 51.6, 31.8, 29.6, 28.6, 27.4, 26.0, 22.7, 18.4, 14.2, -5.4; **HRMS** (ESI^+) calc. for $C_{17}H_{35}O_2Si$ $[M+H]^+$ 299.2401, found 299.2401.

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene (C4)

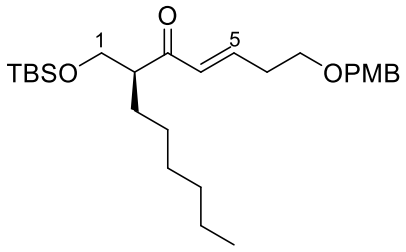


To a suspension solution of sodium hydride (4.09 g, 60% dispersion in mineral oil, 102.3 mmol, 1.1 equiv.) in THF (133 mL) at 0 °C was added 3-buten-1-ol (8.0 mL, 93.0 mmol, 1.0 equiv.). The resulting mixture was stirred for 30 min at 0 °C, followed by dropwise addition of 4-methoxybenzyl bromide (13.4 mL, 93.0 mmol, 1.0 equiv.) and

tetrabutylammonium iodide (1.72 g, 4.65 mmol, 0.05 equiv.). After stirring at room temperature overnight, the reaction mixture was quenched with water (100 mL). The layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (100% pentane to 10% Et_2O/pentane) to obtain PMB alkene **C4** (15.1 g, 78.5 mmol, 84 %) as a colorless oil.

R_f 0.60 (8% Et_2O/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 1613, 1513, 1248, 1173, 1095, 1036, 915, 821; **^{1}H NMR** (400 MH_Z, $CDCl_3$); δ 7.27 (2H, d, *J* = 8.2 Hz, ArH), 6.88 (2H, d, *J* = 8.3 Hz, ArH), 5.84 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H2), 5.14-5.01 (2H, m, H1), 4.45 (2H, s, $PMBCH_2$), 3.80 (3H, s, OCH_3), 3.50 (2H, t, *J* = 6.8 Hz, H4), 2.37 (2H, Td, *J* = 6.8, 1.4 Hz, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 135.5, 130.7, 129.4, 116.4, 113.9, 72.7, 69.5, 55.4, 34.4; **HRMS** (ESI^+) calc. for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1043, found 215.1043.

(*S*,*E*)-6-(((Tert-butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)dodec-3-en-5-one (C5)

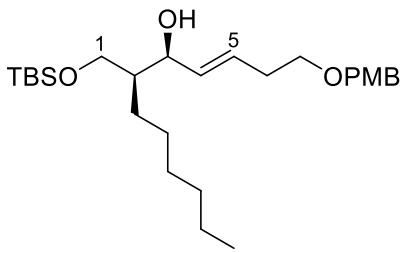


To a solution of Grubbs II catalyst (0.176 g, 0.208 mmol, 0.02 equiv.) and copper iodide (0.0593 g, 0.312 mmol, 0.03 equiv.) in degassed Et_2O (104 mL) under argon was added alkenone **C3** (3.10 g, 10.4 mmol, 1.0 equiv.) and PMB protected alkene **C4** (5.99 g, 31.2

mmol, 3.0 equiv.). The resulting mixture was refluxed at 40 °C overnight and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane to 10% Et_2O/pentane) to afford title compound **C5** (2.92 g, 6.31 mmol, 61 %) as a colourless oil.

R_f 0.31 (10% Et_2O/pentane); $[\alpha]_D^{25}$ +10.4 (*c* = 0.65, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 2929, 2857, 1694, 1668, 1513, 1249, 1098, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 7.8 Hz, ArH), 6.90-6.82 (3H, m, ArH and H4), 6.24 (1H, dt, *J* = 15.8, 1.5 Hz, H5), 4.45 (2H, s, $PMBCH_2$), 3.80 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.8, 7.8 Hz, H1), 3.62 (1H, dd, *J* = 9.7, 5.6, H1'), 3.56 (2H, t, *J* = 6.6 Hz, H7), 2.97 (1H, tt, *J* = 8.0, 5.5 Hz, H2), 2.51 (2H, qd, *J* = 6.6, 1.5 Hz, 2H, H6) 1.63-1.52 (1H, m, H2'), 1.45-1.36 (1H, m, H2'), 1.29-1.18 (8H, m, $(CH_2)_4$), 0.88-0.82 (12H, m, CH_3 and $SiC(CH_3)_3$), 0.01 (3H, s, $Si(CH_3)$), 0.01 (3H, s, $Si(CH_3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.2, 159.4, 143.6, 132.3, 130.4, 129.4, 114.0, 72.9, 68.3, 64.8, 55.4, 52.1, 33.1, 31.8, 29.6, 28.7, 27.4, 26.0, 22.7, 18.3, 14.2, -5.4; **HRMS** (ESI^+) calc. for $C_{27}H_{46}O_4NaSi$ $[M+Na]^+$ 485.3058, found 485.3052.

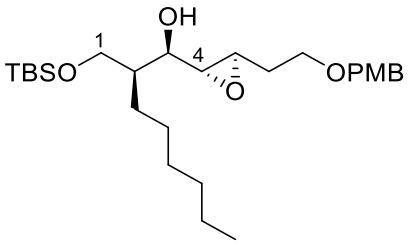
(5*S*,6*S*,*E*)-6-(((Tert-butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)dodec-3-en-5-ol (C6)



To a solution of (S)-MeCBS (5.5 mL, 1.0 M in toluene, 5.51 mmol, 1.0 equiv.) in THF (105 mL) at 0 °C was added BH_3·DMS (13.8 mL, 1.0 M in THF, 13.8 mmol, 2.5 equiv.) dropwise. After stirring for 15 min, a solution of enone **C5** (2.55 g, 5.51 mmol, 1.0 equiv.) in THF (5.0 mL) was added slowly and then the resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl (50 mL) solution and the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 15% EtOAc/pentane) to afford title compound **C6** (2.45 g, 5.27 mmol, 96 %, > 20:1 *dr*) as a colourless oil.

R_f 0.45 (10% EtOAc/pentane); $[\alpha]_D^{25}$ +1.8 (*c* = 0.75, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3465, 2954, 2928, 2856, 1513, 1249, 1095, 836, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 7.8 Hz, ArH), 6.87 (2H, d, *J* = 7.8 Hz, ArH), 5.70 (1H, dtd, *J* = 15.4, 6.7, 1.2 Hz, H4), 5.58 (1H, ddt, *J* = 15.4, 6.0, 1.2 Hz, H5), 4.44 (2H, s, PMBCH_2), 4.28-4.21 (1H, m, H3), 3.80 (3H, s, OCH_3), 3.69 (1H, d, *J* = 5.9 Hz, H1), 3.60 (1H, d, *J* =5.8, H1'), 3.49 (2H, t, *J* = 7.0 Hz, H7), 2.38 (2H, tdd, *J* = 8.1, 6.4, 1.1 Hz, H6), 1.81-1.72 (1H, m, H2), 1.32-1.20 (10H, m, $(CH_2)_5$), 0.91-0.87 (12H, m, CH_3 and $SiC(CH_3)_3$), 0.07 (3H, s, $Si(CH_3)$), 0.07 (3H, s, $Si(CH_3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 132.1, 130.7, 129.4, 128.1, 113.9, 75.7, 72.7, 69.9, 65.5, 55.4, 44.9, 33.1, 31.9, 29.7, 27.7, 26.1, 26.0, 22.8, 18.2, 14.2, -5.5, -5.5; **HRMS** (ESI^+) calc. for $C_{27}H_{48}O_4NaSi$ $[M+Na]^+$ 487.3214, found 487.3207.

(1*R*,2*S*)-2-(((Tert-butyldimethylsilyl)oxy)methyl)-1-((2*R*,3*R*)-3-(2-((4-methoxybenzyl)oxy)ethyl)oxiran-2-yl)octan-1-ol (C7)

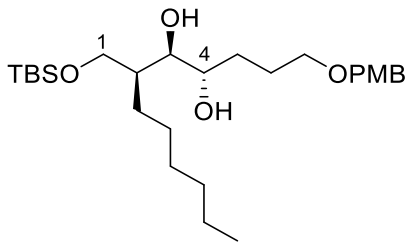


To a solution of squashed 3Å molecular sieves (0.96 g, 40% w/w of starting material) in CH_2Cl_2 (48.0 mL) at -20 °C was added (-)-diethyl D-tartrate (1.1 mL, 6.20 mmol, 1.2 equiv.) and titanium isopropoxide (1.5 mL, 5.16 mmol, 1.0 equiv.). After stirring for 30 min, *tert*-butylhydroperoxide (5.6 mL, 5.5 M in Decan, 31.0 mmol, 6.0 equiv.) was added dropwise. After stirring at -20 °C for 1 h, a solution of alcohol **29** (2.40 g, 5.16 mmol, 1.0 equiv.) in CH_2Cl_2 (4.0 mL) was added dropwise over 15 min. The resulting mixture was stirred at -20 °C for 40 h. The reaction was quenched with water (50 mL) and filtered through celite to remove precipitation. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 15% EtOAc/pentane) to afford title compound **C7** (1.72 g, 3.58 mmol, 69 %, 6:1 *dr*) as a colourless oil.

R_f 0.40 (15% EtOAc/pentane); $[\alpha]_D^{25}$ +3.5 (*c* = 0.28, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3497, 2954, 2929, 2857, 1513, 1465, 1250, 1097, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 7.8 Hz, ArH), 6.87 (2H, d, *J* = 7.8 Hz, ArH), 4.44 (2H, s, $PMBCH_2$), 3.80 (3H, s, OCH_3), 3.80-3.71 (3H, m, H1 and H3), 3.59 (2H, t, *J* =6.5 Hz, H7), 3.20 (1H, d, *J* = 3.5 Hz, OH), 3.12 (1H, tdd, *J* = 7.0, 4.4, 2.3 Hz, H5), 2.85 (1H, dd, *J* = 4.9, 2.2 Hz, H4),

2.04-1.92 (1H, m, H6), 1.83-1.70 (2H, m, H6 and H2), 1.44-1.23 (10H, m, hex-$(CH_2)_5$), 0.90-0.84 (12H, m, hex–CH_3 and $SiC(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 130.5, 129.4, 113.9, 73.3, 72.9, 66.9, 65.2, 59.0, 55.4, 54.3, 43.1, 32.5, 31.9, 29.7, 27.8, 26.0, 25.4, 22.8, 18.3, 14.2, -5.5, -5.5; **HRMS** (ESI^+) calc. for $C_{27}H_{48}O_5NaSi$ $[M+Na]^+$ 503.3163, found 503.3156.

(4*S*,5*R*,6*S*)-6-(((Tert-butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)dodecane-4,5-diol (C8)

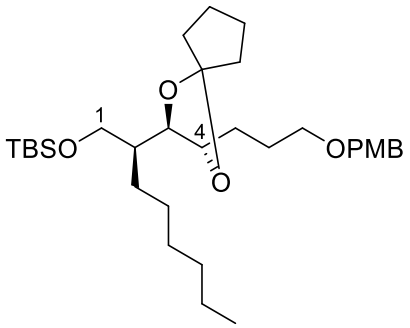


To a solution of epoxide **C7** (1.71 g, 3.56 mmol, 1.0 equiv.) in toluene (35.6 mL) was added titanium isopropoxide (1.8 mL, 6.05 mmol, 1.7 equiv.). The resulting solution was stirred at room temperature for 15 min, followed by slow addition of lithium borohydride (7.1 mL, 2.0 M in THF, 14.2 mmol, 4.0 equiv.). After stirring at room temperature for 1 h, the reaction was quenched with sat. aq. Rochelle salt (50 mL) and the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 20% EtOAc/pentane) to afford title compound **C8** (1.50 g, 3.11 mmol, 87 %, >20:1 *dr*, >20:1 *rr*) as a colourless oil.

R_f 0.30 (20% EtOAc/pentane); $[\alpha]_D^{25}$ +5.3 (*c* = 0.45, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1})

3454, 2928, 2857, 1514, 1249, 1088, 1039, 836, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 7.8 Hz, ArH), 6.87 (2H, d, *J* = 7.8 Hz, ArH), 4.46 (2H, s, $PMBCH_2$), 3.89 (1H, dd, *J* =10.0, 3.7 Hz, H1), 3.80 (3H, s, OCH_3), 3.78-3.75 (1H, m, H1), 3.67-3.57 (2H, m, H3 and H4), 3.55-3.48 (2H, m, H7), 3.15 (1H, d, *J* = 4.2 Hz, OH), 1.96 (1H, dtd, *J* = 14.2, 7.1, 2.4 Hz, H5), 1.86-1.73 (2H, m, H2 and H5), 1.55-1.44 (2H, m, H6), 1.40-1.19 (10H, m, hex-$(CH_2)_5$), 0.89-0.84 (12H, m, hex–CH_3 and $SiC(CH_3)_3$), 0.08 (3H, s, $Si(CH_3)_2$), 0.08 (3H, s, $Si(CH_3)_2$) ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.2, 129.5, 114.0, 78.9, 72.9, 71.9, 70.7, 66.2, 55.4, 40.6, 32.0, 31.4, 29.8, 27.7, 26.4, 26.0, 23.8, 22.8, 18.3, 14.2, -5.5, -5.6; **HRMS** (ESI^+) calc. for $C_{27}H_{50}O_5NaSi$ $[M+Na]^+$ 505.3319, found 505.3318.

Tert-butyl(((2*S*)-2-((3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)octyl)oxy)dimethylsilane (C9)

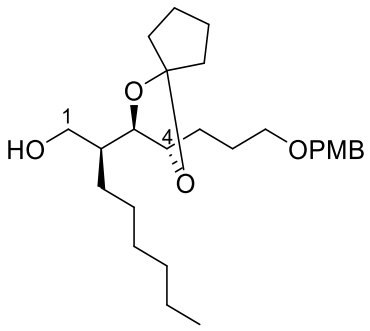


To a solution of diol **C8** (1.40 g, 2.90 mmol, 1.0 equiv.) in THF (4.9 mL) and 1,1-dimethoxycyclopentane (4.0 mL, 29.0 mmol, 10.0 equiv.) at 0 °C was added PTSA (0.0281 g, 0.145 mmol, 98% purity, 0.05equiv.). After stirring at room temperature for 3 h, the reaction was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and diluted with Et_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered

and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane to 10% Et_2O/pentane) to afford title compound **C9** (1.32 g,2.40 mmol, 83%) as a colourless oil.

R_f 0.55 (5% EtOAc/pentane); $[\alpha]_D^{25}$ +6.7 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2928, 2856, 1513, 1464, 1248, 1099, 836, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 7.8 Hz, ArH), 6.87 (2H, d, *J* = 7.8 Hz, ArH), 4.43 (2H, s, PMBCH_2), 4.04-3.96 (1H, m, H3), 3.93-3.87 (1H, m, H4), 3.80 (3H, s, OCH_3), 3.56 (1H, dd, *J* = 10.1, 4.3 Hz, H1), 3.52-3.43 (3H, m, H1 and H7), 1.90-1.77 (3H, m, H2 and H5), 1.73-1.54 (10H, m, H6 and cyclopent–CH_2), 1.36-1.22 (10H, m, hex-$(CH_2)_5$), 0.92-0.85 (12H, m, hex–CH_3 and $SiC(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 131.0, 129.3, 116.8, 113.9, 79.2, 77.7, 72.5, 70.2, 63.6, 55.4, 40.3, 37.8, 37.5, 32.0, 31.1, 29.9, 28.1, 27.0, 26.6, 26.5, 26.1, 23.9, 23.5, 22.8, 18.4, 14.2, -5.4, -5.4; **HRMS** (ESI^+) calc. for $C_{32}H_{56}O_5NaSi$ $[M+Na]^+$ 571.3789, found 571.3790.

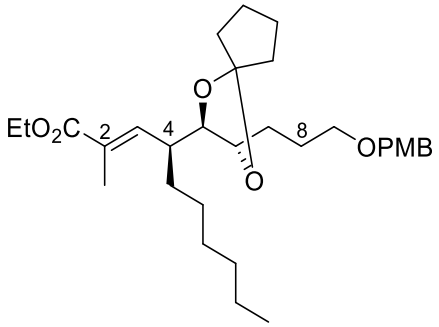
(2*S*)-2-((3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)octan-1-ol (C10)



To a solution of compound **C9** (1.30 g, 2.37 mmol, 1.0 equiv.) in THF (5.9 mL) was added TBAF (2.8 mL, 1.0 M in THF, 2.84 mmol, 1.2 equiv.). After stirring at room temperature overnight, the reaction was quenched with sat. aq. NH_4Cl solution (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 30% EtOAc/pentane) to afford title compound **C10** (0.87 g, 2.00 mmol, 84%) as a colourless oil.

R_f 0.50 (30% EtOAc/PE); $[\alpha]_D^{25}$ +10.1 (*c* = 0.95, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3448, 2955, 2927, 2856, 1613, 1513, 1465, 1248, 1101; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 7.8 Hz, ArH), 6.87 (2H, d, *J* = 7.8 Hz, ArH), 4.43 (2H, s, $PMBCH_2$), 4.06-4.00 (2H, m, H3 and H4), 3.80 (3H, s, OCH_3), 3.67-3.61 (2H, m, H1), 3.55-3.42 (2H, m, H7), 1.90-1.79 (3H, m, H2 and H5), 1.74-1.55 (10H, m, H6 and cyclopent–CH_2), 1.43-1.21 (10H, m, hex-$(CH_2)_5$), 0.88 (3H, t, *J* = 5.6 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 130.8, 129.4, 117.5, 113.9, 79.5, 77.8, 72.6, 69.8, 64.0, 55.4, 40.5, 37.3, 37.2, 32.0, 29.9, 27.2, 26.9, 26.8, 26.2, 24.0, 23.4, 22.8, 14.2; **HRMS** (ESI^+) calc. for $C_{26}H_{42}O_5Na$ $[M+Na]^+$457.2924, found 457.2926.

Ethyl (4*S*,*E*)-4-((3*R*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methyldec-2-enoate (C11)

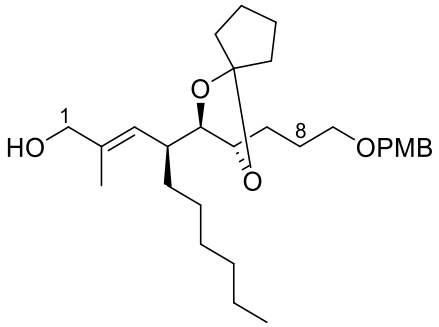


To a solution of alcohol **C10** (0.85 g, 1.96 mmol, 1.0 equiv.) in CH_2Cl_2 (13.0 mL) was added $NaHCO_3$ (1.64 g, 19.6 mmol, 10.0 equiv.) and Dess-Martin periodinane (1.24 g, 2.93 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ solution (10 mL) and sat. aq. $Na_2S_2O_3$ solution (10 mL) at 0 °C and stirred for 10 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The crude residue was dissolved in toluene (6.5 mL), followed by addition of ethyl 2-(triphenyl-phosphaneylidene)propanoate (2.13 g, 5.87 mmol, 3.0 equiv.). After refluxing at 110 °C overnight, the solvent was taken off in vacuo. The residue was dissolved in 20% Et_2O/pentane, filtered through celite and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (4% EtOAc/pentane to 15% EtOAc/pentane) to afford title compound **C11** (0.90 g, 1.74 mmol, 89%) as a colourless oil. $\mathbf{R_f}$ 0.52 (10% EtOAc/pentane); $[\alpha]_D^{25}$ −9.8 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2955, 2929, 2857, 1711, 1513, 1247, 1101, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.4 Hz, ArH), 6.87 (2H, d, *J* = 8.8 Hz, ArH), 6.47 (1H, d, *J* = 11.0 Hz, H3), 4.39 (2H, s,

PMBCH_2), 4.18 (2H, q, *J* = 7.1 Hz, ethyl ester–CH_2), 3.90-3.81 (2H, m, H5 and H6), 3.80 (3H, s, OCH_3), 3.48-3.35 (2H, m, H9), 2.62-2.51 (1H, m, H4), 1.89-1.75 (7H, m, cyclopent–CH2 and methyl-H2'), 1.75-1.51 (8H, m, cyclopent–CH_2, H7 and H8), 1.36-1.16 (13H, m, hex-$(CH_2)_5$ and ethyl ester–CH_3), 0.87 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 159.2, 141.7, 130.9, 129.3, 129.0, 117.6, 113.9, 80.7, 77.6, 72.6, 70.0, 60.8, 55.4, 39.4, 37.9, 37.5, 32.5, 32.0, 29.7, 26.6, 26.5, 26.3, 23.8, 23.5, 22.8, 14.4, 14.2, 13.7; **HRMS** (ESI^+) calc. for $C_{31}H_{48}O_6Na$ $[M+Na]^+$ 539.3343, found 457.3337.

(4*S*,*E*)-4-((3*R*)-3-(3-((4-Methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methyldec-2-en-1-ol (C12)

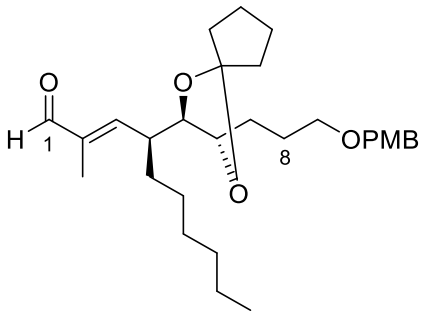


To a solution of ester **C11** (0.89 g, 1.72 mmol, 1.0 equiv.) in CH_2Cl_2 (17.2 mL) at -78 °C was added DIBAL-H (3.6 mL, 1.0 M in CH_2Cl_2, 3.62 mmol, 2.1 equiv.) dropwise. After stirring for 1 h, the cooling bath was removed and the reaction mixture was stirred for further 1 h at room temperature. The reaction was cooled to 0 °C and quenched by slowly adding water (0.14 mL), 15 % wt NaOH solution (0.14 mL), then water (0.36 mL). The resulting mixture was stirred for further 15 min at room temperature, filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on

silica gel (10% EtOAc/pentane to 20% EtOAc/pentane) to afford title compound **C12** (0.71 g, 1.50 mmol, 87 %) as a colourless oil.

R_f 0.17 (20% EtOAc/pentane); $[\alpha]_D^{25}$ −7.3 (*c* = 1.0, $CHCl_3$); **IR** (thin film, v_{max} / cm^{-1}) 3421. 2955, 2927, 2856, 1613, 1514, 1456, 1363, 1248, 1103, 1037, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.4 Hz, ArH), 6.87 (2H, d, *J* = 8.5 Hz, ArH), 5.11 (1H, d, *J* = 10.2 Hz, H3), 4.41 (2H, s, PMBCH_2), 3.96 (2H, d, *J* = 4.9 Hz, H1), 3.88-3.82 (1H, m, H5), 3.80 (3H, s, OCH_3), 3.80-3.74 (1H, m, H6), 3.52-3.37 (2H, m, H9), 2.49-2.40 (1H, m, H4), 1.84-1.42 (16H, m, cyclopent–CH2, methyl-H2', OH, H7 and H8), 1.31-1.13 (10H, m, hex-$(CH_2)_5$), 0.87 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 136.5, 130.7, 129.4, 126.1, 117.4, 113.9, 81.4, 77.7, 72.5, 69.9, 68.9, 55.4, 38.1, 38.0, 37.5, 33.1, 32.1, 29.8, 26.6, 26.3, 26.0, 23.8, 23.5, 22.8, 14.9, 14.2; **HRMS** (ESI^+) calc. for $C_{29}H_{46}O_5Na$ $[M+Na]^+$497.3237, found 497.3238.

(*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 (C13)

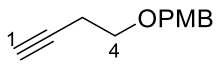


To a solution of alcohol **C12** (0.65 g, 1.37 mmoL, 1.0 equiv.) in CH_2Cl_2 (9.1 mL) was added sodium bicarbonate (1.15 g, 13.7 mmoL, 10.0 equiv.) and Dess-Martin periodinane (0.871

g, 2.05 mmoL, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL) and sat. aq. $Na_2S_2O_3$ solution (10 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (8% EtOAc/pentane to 15% EtOAc/pentane) to afford title compound **C13** (0.59 g, 1.16 mmol, 91%) as a colourless oil.

R_f 0.35 (15% EtOAc/pentane); $[\alpha]_D^{25}$ −17.7 (*c* = 1.3, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2955, 2927, 2856, 2361, 2340, 1690, 1614, 1513, 1333, 1248, 1102, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.41 (1H, s, CHO), 7.21 (2H, d, *J* = 8.5 Hz, ArH), 6.87 (2H, d, *J* = 8.5 Hz, ArH), 6.22 (1H, d, *J* = 10.6 Hz, H3), 4.39 (2H, s, $PMBCH_2$), 3.91-3.87 (2H, m, H5 and H6), 3.81 (3H, s, OCH_3), 3.46-3.37 (2H, m, H9), 2.79-2.73 (1H, m, H4), 1.94-1.47 (15H, m, cyclopent–CH_2, methyl-H2', H7 and H8), 1.37-1.16 (10H, m, hex-$(CH_2)_5$), 0.87 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.3, 159.3, 154.3, 140.2, 130.7, 129.3, 117.8, 113.9, 80.2, 77.6, 72.6, 69.7, 55.4, 39.9, 37.7, 37.4, 32.1, 31.9, 29.6, 26.7, 26.6, 26.3, 23.9, 23.5, 22.7, 14.2, 10.5; **HRMS** (ESI^+) calc. for $C_{29}H_{44}O_5Na$ $[M+Na]^+$ 495.3081, found 495.3081.

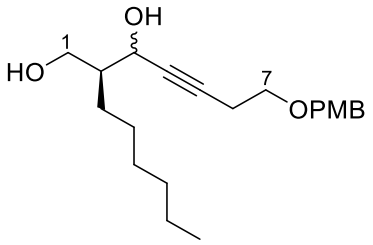
1-((But-3-yn-1-yloxy)methyl)-4-methoxybenzene (C14)



To a solution of but-3-yn-1-ol (1.85 g, 26.4 mmol, 1.0 equiv.) in THF (37.7 mL) at 0 °C was added sodium hydride (1.16 g, 60% dispersion in mineral oil, 29.0 mmol, 1.1 equiv.) portionwise. After 30 min of stirring at 0 °C, PMBBr (5.84 g, 29.0 mmol, 1.1 equiv.) was added dropwise, followed by tetrabutylammonium iodide (0.487 g, 1.32 mmol, 0.05 equiv.) After stirring at room temperature overnight, the reaction mixture was recooled to 0 °C and quenched with water (30 mL) slowly and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et_2O/pentane to 10% Et_2O/pentane) on silica gel to afford title compound **C14** (4.61 g, 24.2 mmol, 92%) as a colourless oil.

R_f 0.48 (10% Et_2O/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 2918, 2864, 2360, 2342, 1613, 1514, 1248, 1098, 1034, 822; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.5 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 4.49 (2H, s, OCH_2Ar), 3.81 (3H, s, OCH_3), 3.58 (2H, t, *J* = 7.0 Hz, H4), 2.49 (2H, td, *J* = 7.0, 2.7 Hz, H3), 1.99 (1H, t, *J* = 2.7 Hz, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.2, 129.5, 114.0, 81.5, 72.8, 69.4, 68.0, 55.4, 20.0; **HRMS** (ESI^+) calc. for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ 213.0886, found 213.0887.

(2*S*)-2-Hexyl-7-((4-methoxybenzyl)oxy)hept-4-yne-1,3-diol (C15)



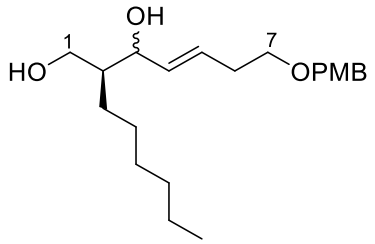
To a solution of catalyst **L3** (1.04 g, 3.20 mmol, 0.1 equiv.) in toluene (64.0 mL) was added solid potassium phosphate PH 7 buffer (3.19 g) and formaldehyde (7.2 mL, 37 wt. % in H_2O, 95.9 mmol, 3.0 equiv.). The resulting biphasic mixture was stirred vigorously for 15 min at room temperature, followed by addition of octanal (5.0 mL, 32.0 mmol, 1.0 equiv.). After stirring at room temperature for 36 h, the reaction mixture was diluted with water (50 mL) and the aqueous layer was extracted with toluene (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude hemiacetal (5.61 g, 29.8 mmol). To a solution of alkyne **C14** (6.80 g, 35.8 mmol, 1.2 equiv.)) in THF (59.0 mL) at -78 °C was added *n*-BuLi (13.1 mL, 2.5 M in hexane, 32.8 mmol, 1.1 equiv.) dropwise. After stirring at -78 °C for 1 h, the reaction mixture was warmed to 0 °C and stirred for another 1 h. The reaction mixture was recooled to -78 °C and a solution of crude hemiacetal (5.61 g, 29.8 mmol, 1.0 equiv.) in toluene (59.0 mL) was added dropwise, followed by dropwise addition of another portion of *n*-BuLi (10.7 mL, 2.5 M in hexane, 26.8 mmol, 0.9 equiv.). After stirring at -78 °C for 1 h, the reaction mixture was warmed to -40 °C and stirred for another 1 h. Then, it was warmed to 0 °C and stirred for further 1 h. After that, the reaction mixture was warmed to room temperature and stirred for 1 h before being quenched with sat. aq. NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were

washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **C15** (7.61 g, 21.8 mmol, 68%) as a colourless oil and an inseparable mixture of diastereomers (3:1).

R_f 0.42 (50% EtOAc/pentane); **IR** (thin film, v_{max} / cm^{-1}) 3384, 2981, 2363, 2340, 1613, 1514, 1463, 1381, 1249, 1091, 1034, 822; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2.7H, d, *J* = 8.6 Hz, $ArH_{major\ and\ minor}$), 6.88 (2.7H, d, *J* = 8.6 Hz, $ArH_{major\ and\ minor}$), 4.48 (2.7H, s, $OCH_2Ar_{major\ and\ minor}$), 4.46-4.42 (1H, m, $H3_{major}$), 4.26-4.22 (0.3H, m, $H3_{minor}$), 4.02-3.96 (1H, m, $H1_{major}$), 3.92-3.85 (0.3H, m, $H1_{minor}$), 3.80 (4H, s, $OCH_{3major\ and\ minor}$), 3.76-3.64 (1.3H, m, $H1_{major\ and\ minor}$), 3.59-3.52 (2.7H, m, $H7_{major\ and\ minor}$), 2.53 (2.7H, tt, *J* = 7.0, 2.0 Hz, $H6_{major\ and\ minor}$), 1.96-1.88 (0.3H, m, $H2_{minor}$)1.74-1.65 (1H, m, $H2_{major}$), 1.59-1.17 (13.3H, m, $Hex–CH_{2major\ and\ minor}$), 0.92-0.83 (4H, m, $Hex–CH_{3major\ and\ minor}$)

; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.2, 129.5, 114.0, 81.7, 72.8, 68.2, 68.1, 66.7, 66.3, 64.7, 64.2, 55.4, 46.1, 45.3, 31.9, 31.9, 29.6, 29.6, 27.7, 27.6, 27.4, 27.3, 22.8, 20.3, 14.2; **HRMS** (ESI^+) calc. for $C_{21}H_{32}O_4Na$ $[M+Na]^+$ 371.2193, found 371.2195.

(2*S*,*E*)-2-Hexyl-7-((4-methoxybenzyl)oxy)hept-4-ene-1,3-diol (C16)

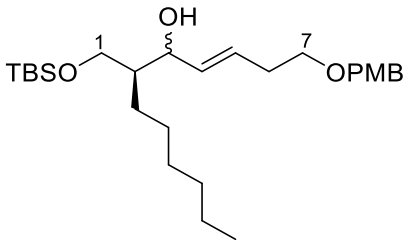


To a solution of compound **C15** (7.49 g, 21.5 mmol, 1.0 equiv.) in THF (107.0 mL) at 0 °C was added sodium bis(2-methoxyethoxy)aluminum hydride solution (8.4 mL, ≥ 60 wt. % in

toluene, 43.0 mmol, 2.0 equiv.) dropwise. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for another 1 h. The reaction mixture was cooled to 0 °C and quenched with sat. aq. Rochelle salt (30 mL) slowly. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **C16** (6.13 g, 17.5 mmol, 82%) as a colourless oil and an inseparable mixture of diastereomers (3:1).

R_f 0.35 (40% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3374, 2926, 2855, 2361, 1613, 1514, 1302, 1248, 1098, 1035, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2.7H, d, *J* = 8.7 Hz, $ArH_{major\ and\ minor}$), 6.88 (2.7H, d, *J* = 8.6 Hz, $ArH_{major\ and\ minor}$), 5.77-5.65 (1.3H, m, $H5_{major\ and\ minor}$), 5.60 (1.3H, dd, *J* = 15.5, 6.9 Hz, $H4_{major\ and\ minor}$), 4.44 (2.7H, s, $OCH_2Ar_{major\ and\ minor}$), 4.31-4.25 (0.3H, m, $H3_{minor}$), 4.13-4.07 (1H, m, $H3_{major}$), 3.87-3.82 (1H, m, $H1_{major}$), 3.80 (4H, s, $OCH_{3major\ and\ minor}$), 3.76-3.60 (1.7H, m, $H1_{major\ and\ minor}$), 3.49 (2.7H, t, *J* = 6.7 Hz, $H7_{major\ and\ minor}$), 2.37 (2.7H, tdd, *J* = 6.5, 4.7, 3.1 Hz, $H6_{major\ and\ minor}$), 1.85-1.77 (0.3H, m, $H2_{minor}$), 1.63-1.50 (1H, m, $H2_{major}$), 1.40-1.17 (13.3H, m, Hex–$CH_{2major\ and\ minor}$), 0.92-0.83 (4H, m, Hex–$CH_{3major\ and\ minor}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 134.0, 130.6, 129.5, 129.4, 113.9, 72.7, 69.4, 64.7, 64.4, 55.4, 45.3, 45.2, 32.9, 32.8, 31.9, 29.7, 29.7, 28.2, 27.6, 27.3, 22.8, 14.2; **HRMS** (ESI^+) calc. for $C_{21}H_{34}O_4Na$ $[M+Na]^+$ 373.2349, found 373.2354.

(6*S*,*E*)-6-(((Tert-butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)dodec-3-en-5-ol (C17)



To a solution of diol **C16** (6.12 g, 17.5 mmol, 1.0 equiv.) in CH_2Cl_2 (43.7 mL) was added imidazole (2.38 g, 34.9 mmol, 2.0 equiv.). The resulting mixture was cooled to 0 °C and then *tert*-butyldimethylsilyl chloride (2.63 g, 17.5 mmol, 1.0 equiv.) was added portionwise. After stirring at room temperature overnight, the reaction mixture was quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 10% EtOAc/pentane) to afford title compound **C17** (6.81 g, 14.7 mmol, 84%) as a colourless oil and an inseparable mixture of diastereomers (3:1).

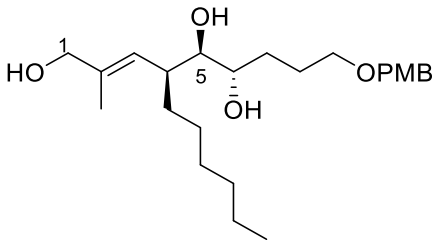
R_f 0.45 (10% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 34615, 2953, 2928, 2856, 1514, 1249, 1095, 836, 777; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (2.7H, d, *J* = 8.7 Hz, $ArH_{major\ and\ minor}$), 6.87 (2.7H, d, *J* = 8.6 Hz, $ArH_{major\ and\ minor}$), 5.70 (1.3H, dtd, *J* = 14.7, 6.8, 1.1 Hz, $H5_{major\ and\ minor}$), 5.56 (1.3H, dd, *J* = 15.4, 6.4 Hz, $H4_{major\ and\ minor}$), 4.44 (2.7H, s, $OCH_2Ar_{major\ and\ minor}$), 4.27-4.23 (0.3H, m, $H3_{minor}$), 3.91 (1H, dd, *J* = 10.0, 3.2 Hz, $H3_{major}$), 3.80 (4H, s, $OCH_{3major\ and\ minor}$), 3.71-3.67 (1.3H, m, $H1_{major\ and\ minor}$), 3.62-3.57 (1.3H, m, $H1_{major\ and\ minor}$),

3.49 (2.7H, td, J = 7.0, 1.5 Hz, $H7_{major\ and\ minor}$), 2.41-2.34 (2.7H, m, $H6_{major\ and\ minor}$), 1.73-1.80 (0.3H, m, $H2_{minor}$), 1.51-1.40 (1H, m, $H2_{major}$), 1.34-1.16 (13.3H, m, Hex–$CH_{2major\ and\ minor}$), 0.91-0.86 (16H, m, Hex–$CH_{3major\ and\ minor}$ and $SiC(CH_3)_{3major\ and\ minor}$), 0.07 (8H, s, $Si(CH_3)_{2major\ and\ minor}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 134.2, 132.1, 130.7, 129.4, 128.1, 128.1, 113.9, 76.5, 75.7, 72.7, 72.7, 69.9, 69.8, 65.5, 65.2, 55.4, 44.9, 44.8, 33.1, 33.0, 31.9, 31.9, 29.7, 29.7, 28.2, 27.6, 27.4, 26.1, 26.0, 26.0, 22.8, 18.2, 14.2, -5.5, -5.5, -5.5; **HRMS** (ESI^+) calc. for $C_{27}H_{48}O_4NaSi$ $[M+Na]^+$ 487.3214, found 487.3221.

The oxidation of **C17** to form **C5** can be achieved by the following DMP oxidation procedure: To a solution of alcohol **C17** (6.72 g, 14.5 mmol, 1.0 equiv.) in CH_2Cl_2 (96.4 mL) was added sodium bicarbonate (12.1 g, 144.6 mmol, 10.0 equiv.) and Dess-Martin periodinane (9.20 g, 21.7 mmoL, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (30 mL) and sat. aq. $Na_2S_2O_3$ solution (30 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane to 10% Et_2O/pentane) to afford title compound **C5** (5.49 g, 11.9 mmol, 82%) as a colourless oil.

The physical and spectroscopic data of compound **C5** were already described beforehand.

(4*S*,5*R*,6*S*,*E*)-4-Hexyl-9-((4-methoxybenzyl)oxy)-2-methylnon-2-ene-1,5,6-triol (C18)

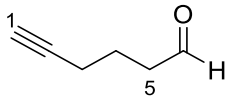


To a solution of alcohol **C12** (10.0 mg, 0.0211 mmol, 1.0 equiv.) in MeOH (0.2 mL) and water (0.01 mL) was added amberlyst 15 (60 mg). The resulting mixture was stirred at room temperature overnight and diluted with chloroform (10.0 mL), filtered through celite. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **C18** (6.6 mg, 0.0162 mmol, 77%) as a colourless oil.

R$_f$ 0.18 (20% EtOAc/pentane); $[\alpha]_D^{25}$ −6.2 (*c* = 0.9, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3384, 2924, 2855, 2360, 1613, 1513, 1362, 1247, 1087, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.13 (1H, d, *J* = 10.4 Hz, H3), 4.44 (2H, s, OCH_2Ar), 3.98 (2H, d, *J* = 2.5 Hz, H1), 3.80 (3H, s, OCH_3), 3.58-3.43 (3H, m, H9 and H5), 3.28-3.24 (1H, m, H6), 2.42-2.31 (1H, m, H4), 2.21 (1H, brs, OH), 1.86 – 1.77 (1H, m, OH), 1.75-1.67 (2H, m, H7), 1.66-1.61 (5H, m, H2-Me and H8), 1.33-1.10 (10H, m, hex-$(CH_2)_5$), 0.85 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 136.1, 129.9, 129.6, 126.5, 114.0, 77.8, 72.9, 72.8, 70.4, 68.9, 55.4, 40.6, 32.1, 31.9, 29.8, 27.8,

27.0, 26.4, 22.8, 14.6, 14.3; **HRMS** (ESI^+) calc. for $C_{24}H_{40}O_5Na$ $[M+Na]^+$431.2768, found 431.2764.

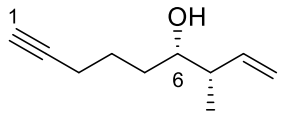
Hex-5-ynal (B1)



Synthesized according to a modified literature procedure.[117] To a solution of TEMPO (0.354 g, 2.27 mmol, 0.1 equiv.) and (diacetoxyiodo)benzene (8.76 g, 27.2 mmol, 1.2 equiv.) in CH_2Cl_2 (64.8 mL) was added hex-5-yn-1-ol (2.5 mL, 22.7 mol, 1.0 equiv.) dropwise. The resulting orange solution was stirred at room temperature for 3 h before quenching with sat. aq. $NaHCO_3$ solution (20 mL) and sat. aq. $Na_2S_2O_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated carefully under reduced pressure (volatile compound, keep the vacuum at around 500 mbar and turn off the heating of the water bath). The crude product was purified by flash chromatography on silica gel (20% CH_2Cl_2/pentane to 80% CH_2Cl_2/pentane) to afford title compound **B1** (1.62 g, 16.9 mmol, 74%) as a colouless oil.

R_f 0.45 (50% CH_2Cl_2/pentane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.3 Hz, ArH), 2.61 (2H, td, *J* =7.2, 1.3Hz, H5), 2.27 (2H, td, *J* =6.9, 2.7Hz, H3), 1.98 (1H, t, *J* =2.7 Hz, H1), 1.85 (2H, quint, *J* =7.0 Hz, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.8, 83.3, 69.5, 42.7, 20.9, 17.9. The physical and spectroscopic data were consistent with the literature reported data.[118]

(3*S*,4*S*)-3-Methylnon-1-en-8-yn-4-ol (B2)

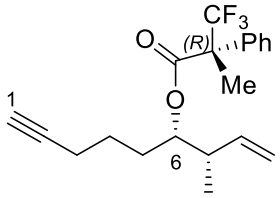


To a solution of (*S*,*S*)-**L1** (5.34 g, 18.4 mmol, 1.1 equiv.) in CH_2Cl_2 (60.8 mL) at 0 °C was added DBU (8.3 mL, 55.3 mol, 3.3 equiv.), followed by slow addition of *cis*–Crotyltrichlorosilane **D9** (3.81 g, 20.1 mmol, 1.2 equiv.). The ice/water bath was removed. After stirring at room temperature for 1 h, the reaction mixture was recooled to 0°C and aldehyde **B1** (1.61 g, 16.7 mmol, 1.0 equiv.) was added dropwise. After stirring at 0°C for 1 h, the reaction mixture was treated with TBAF solution (21.8 mL, 1.0 M in THF, 21.8 mmol, 1.3 equiv.). After stirring at room temperature for 1 h, the reaction mixture was concentrated under *vacuo* carefully and the residue was suspended in Et_2O (50 mL). The resulting mixture was stirred vigorously for 30 min to ensure complete precipitation of the DBU·HCl salts. The mixture was filtered through celite to remove solids and then the filtrate was treated with aq. HCl solution (92.1 mL, 1.0 M, 92.1 mmol, 5.5 equiv.). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 ml) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution (100 mL) and concentrated under reduced pressure carefully. The residue was purified by flash chromatography (10% ethyl acetate/pentane) to obtain alkene **B2** (1.92 g, 12.6 mmol, 75%, 93% *ee*, >20:1 *dr*) as a colourless oil.

R_f 0.50 (20% EtOAc/pentane); $[\alpha]_D^{25}$ −35.8 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3384, 3306, 2935, 2870, 1640, 1456, 1109, 997, 954, 915, 630; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 (1H, ddd, *J* =17.5, 9.6, 7.5 Hz, H8), 5.12-5.07 (2H, m, H1), 3.51 (1H, dtd, *J* = 8.6,

5.2, 2.9 Hz, H6), 2.33-2.25 (1H, m, H7), 2.23 (2H, td, *J* = 6.9, 2.6 Hz, H3), 1.95 (1H, t, *J* =2.7 Hz, H1), 1.79-1.41 (4H, m, H4 and H5), 1.03 (3H, d, *J* = 6.9 Hz, methyl-H7'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 115.7, 84.5, 74.4, 68.6, 43.7, 33.1, 25.2, 18.5, 14.3; **HRMS** not found.

(3*S*,4*S*)-3-Methylnon-1-en-8-yn-4-yl (R)-3,3,3-trifluoro-2-methyl-2-phenylpropanoate (B2-*R*-ester)

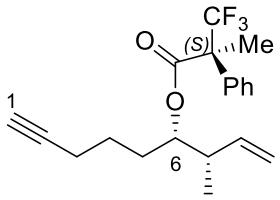


To a solution of alcohol **B2** (10.0 mg, 0.066 mmol, 1.0 equiv.) in CH_2Cl_2 (0.66 mL) was added anhydrous pyridine (32.9 μL, 0.407 mmol, 6.2 equiv.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (46.7 μL, 0.250 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane) to afford title compound **B2-*R*-ester** (21.2 mg, 0.060 mmol, 92%) as a colouless oil.

R_f 0.55 (10% Et_2O/pentane); **$[\alpha]_D^{25}$** +18.3 (*c* = 1.5, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3307, 2921, 1744, 1269, 1170, 1122, 1018, 994; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (1H, dd, *J* =7.0, 3.0 Hz, ArH), 7.41-7.39 (3H, m, ArH), 5.65 (1H, ddd, *J* =17.5, 10.5, 7.4 Hz, H8), 5.07 (1H, ddd, *J* =8.0, 5.7, 4.0 Hz, H6), 5.02-4.95 (2H, m, H9), 3.55 (3H, s, OCH_3), 2.51-2.44

(1H, m, H7), 2.19 (2H, td, *J* = 7.2, 2.8 Hz, H3), 1.95 (1H, t, *J* =2.6 Hz, H1), 1.82-1.69 (2H, m, H5), 1.60-1.47 (2H, m, H4), 0.96 (3H, d, *J* = 6.8 Hz, methyl-H7'); **^{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, 15.0; **^{19}F NMR** (470 MHz, CDCl3): δ –71.1; **HRMS** (ESI^+) calc. for $C_{20}H_{23}F_3O_3Na$ $[M+Na]^+$ 391.1492, found 391.1492.

(3*S*,4*S*)-3-Methylnon-1-en-8-yn-4-yl (S)-3,3,3-trifluoro-2-methyl-2-phenylpropanoate (B2-*S*-ester)



To a solution of alcohol **B2** (10.0 mg, 0.066 mmol, 1.0 equiv.) in CH_2Cl_2 (0.66 mL) was added anhydrous pyridine (32.9 μL, 0.407 mmol, 6.2 equiv.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (46.7 μL, 0.250 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane) to afford title compound **B2-*S*-ester** (22.3 mg, 0.063 mmol, 97%) as a colourless oil.

R_f 0.55 (10% Et_2O/pentane); $[\alpha]_D^{25}$ −45.7 (*c* = 1.3, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3307, 2920, 1744, 1269, 1170, 1122, 1018, 995; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J*

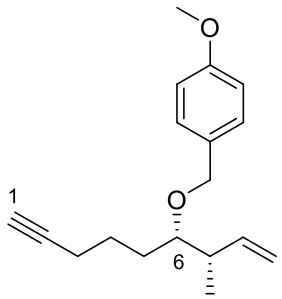
=7.1, 2.8 Hz, ArH), 7.41-7.38 (3H, m, ArH), 5.76 (1H, ddd, *J* =17.4, 10.7, 7.1 Hz, H8), 5.09-5.05 (3H, m, H6 and H9), 3.55 (3H, s, OCH_3), 2.57-2.50 (1H, m, H7), 2.12 (2H, td, *J* = 7.1, 2.6 Hz, H3), 1.93 (1H, t, *J* =2.6 Hz, H1), 1.77-1.63 (2H, m, H5), 1.49-1.33 (2H, m, H4), 1.04 (3H, d, *J* = 6.8 Hz, methyl-H7'); **^{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, 18.3, 15.0; **^{19}F NMR** (470 MHz, CDCl3): δ –71.1; **HRMS** (ESI^+) calc. for $C_{20}H_{23}F_3O_3Na$ $[M+Na]^+$ 391.1492, found 391.1492.

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

Proton position	**B2-*S*-ester (ppm)**	**B2-*R*-ester (ppm)**	**$\Delta\delta_{SR}$**
H1	1.93	1.95	-0.02
H3	2.12	2.19	-0.07
H4	1.41	1.53	-0.12
H5	1.70	1.75	-0.05
H7	2.54	2.48	+0.06
methyl-H7'	1.04	0.96	+0.08
H8	5.76	5.65	+0.11
H9	5.07	4.99	+0.08

Negative values obtained for alkyne portion and positive values obtained for alkene portion. Analysis of all the values reveals the C6 centre is of *S* configuration.

1-Methoxy-4-((((3*S*,4*S*)-3-methylnon-1-en-8-yn-4-yl)oxy)methyl)benzene (B3)

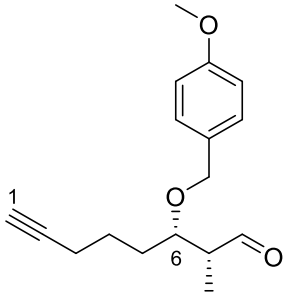


To a solution of alkene **B2** (1.85 g, 12.2 mmol, 1.0 equiv.) in DMF (24.3 mL) at 0 °C was added sodium hydride (0.972 g, 60% dispersion in mineral oil, 24.3 mmol, 2.0 equiv.) portionwise. After stirring at 0 °C for 30 min, the reaction mixture was added PMBBr (4.89 g, 24.3 mmol, 2.0 equiv.) followed by tetrabutylammonium iodide (0.898 g, 2.43 mmol, 0.2 equiv.) The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water (60 mL) at 0 °C and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/pentane) to obtain pmb protected alkene **B3** (2.77 g, 10.2 mmol, 84%) as a colourless oil.

R_f 0.49 (10% Et_2O/pentane); $[\alpha]_D^{25}$ −38.7 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3299, 2954, 2937, 2867, 1613, 1514, 1248, 1173, 1079, 1037, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.84 (1H, ddd, *J* = 17.6, 10.4, 7.4 Hz, H8), 5.08-5.01 (2H, m, H9), 4.50 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.44 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 3.80 (3H, s, OCH_3), 3.26 1H, ddd, *J* = 7.4, 5.7, 3.4 Hz, H6), 2.52-2.45 (1H, m, H7), 2.21-2.14 (m, 2H, H3), 1.94 (1H, t, *J* = 2.6 Hz, H1), 1.73-1.50 (4H, m, H4 and

H5), 1.05 (3H, d, *J* = 6.9 Hz, methyl-H7'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 140.9, 131.1, 129.5, 114.6, 113.9, 84.7, 82.1, 71.5, 68.5, 55.4, 40.8, 30.2, 24.6, 18.6, 15.9; **HRMS** (ESI^+) calc. for $C_{18}H_{24}O_2Na$ $[M+Na]^+$ 295.1669, found 295.1671.

(2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)-2-methyloct-7-ynal (B4)

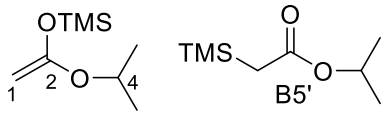


To a solution of pmb alkyne **B3** (2.75 g, 10.1 mmol, 1.0 equiv.) in CH_2Cl_2/MeOH (45.3 mL/ 45.3 mL) was added $NaHCO_3$ (4.24 g, 50.5 mmol, 5.0 equiv.) and Sudan III indicator (a saturated solution of Sudan III in MeOH) (0.05 mL). The resulting mixture was cooled to -78 °C and then ozonolyzed until the pink colour began to fade. The reaction mixture was quenched with dimethyl sulfide (22.6 mL), warmed to room temperature and stirred for 3 h before being diluted with water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/pentane to 10% EtOAc/pentane) to obtain aldehyde **B4** (1.94 g, 7.07 mmol, 70%) as a colourless oil.

R_f 0.45 (10% EtOAc/pentane); $[\alpha]_D^{25}$ −40.2 (*c* = 1.1, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3291, 2939, 2870, 1720, 1613, 1514, 1249, 1174, 1065, 1034, 821; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 9.76 (1H, d, *J* = 1.1 Hz, CHO), 7.23 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 4.45 (2H, s, OCH_2Ar), 3.84-3.81 (1H, m, H6), 3.80 (3H, s, OCH_3), 2.58 (1H, qdd, J = 7.1, 3.9, 1.0 Hz, H7), 2.24-2.18 (2H, m, H3), 1.96 (1H, t, *J* = 2.6 Hz, H1), 1.75-1.51 (4H, m, H4 and H5), 1.13 (3H, d, *J* = 7.0 Hz, methyl-H7'); **^{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^+) calc. for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ 297.1461, found 297.1463.

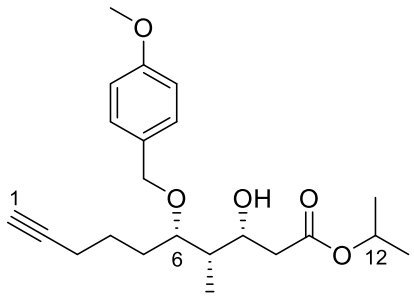
((1-Isopropoxyvinyl)oxy)trimethylsilane (B5)



Synthesized according to a literature modified procedure.[119] To a solution of diisopropylamine (28.7 mL, 204.9 mmol, 1.2 equiv.) in THF (198.6 mL) at 0 °C was added n-BuLi solution (75.1 mL, 2.5 M in hexane, 187.8 mmol, 1.1 equiv.) dropwise. After stirring at 0 °C for 30 min, the reaction was cooled to -78 °C. A mixture of isopropyl acetate (20.0 mL, 170.8 mmol, 1.0 equiv.) and chlorotrimethylsilane (26.0 mL, 204.9 mmol, 1.2 equiv.) in THF (102.3 mL) was added slowly and the resulting mixture was stirred at room temperature for 3 h. Then THF was evaporated under reduced pressure and hexane (50 mL) was added. The resulting precipitate was filtered off through a celite pad, washed with hexane and concentrated under reduced pressure. The residue was purified *via* vacuum distillation (60 °C, 50mbar) to afford a mixture of **B5** as a major product (7.5 g, 43.0 mmol, 25%) and a little amount of **B5'** as a byproduct (similar boiling point to the product **B5**, difficult to obtain pure **B5** enol ether, the ratio of the desired product **B5** and side product **B5'** is 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (1H, p, *J* = 6.1 Hz, H4), 3.26 (1H, d, *J* = 2.5 Hz, ArH), 3.09 (1H, d, *J* = 2.5 Hz, ArH), 1.26 (6H, d, *J* = 6.1 Hz, isopropyl H5 and H5'), 0.23 (9H, s, TMS); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7, 70.1, 61.4, 21.7, 0.3.

Isopropyl (3*R*,4*S*,5*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-4-methyldec-9-ynoate (B6)

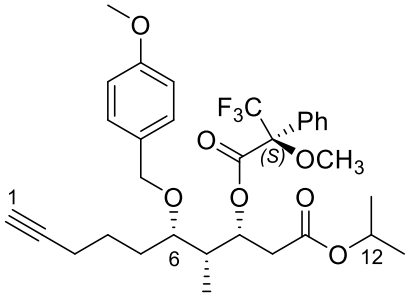


To a solution of aldehyde **B4** (1.92 g, 7.00 mmol, 1.0 equiv.) in CH_2Cl_2 (140.0 mL) was added enol ether **B5** (3.66 g, 21.0 mmol, 3.0 equiv.) and the resulting mixture was cooled to -78 °C. Borontrifluoride etherate (0.86 mL, 7.00 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h before being quenched with sat. aq. $NaHCO_3$ solution (20 mL), The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/pentane to 15% EtOAc/pentane) to obtain alcohol **B6** (2.29 g, 6.08 mmol, 87%, 5:1 *dr*) as a colourless oil and inseparable diastereomers.

R_f 0.24 (10% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3488, 3292, 2981, 2889, 2360, 1725, 1613, 1514, 1249, 1175, 1108, 1035, 957, 822; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.5 Hz, ArH), 6.87 (2H, d, *J* = 8.5 Hz, ArH), 5.03 (1H, p, *J* = 7.1 Hz, H12), 4.55

(1H, d, *J* = 11.0 Hz OCH_2Ar), 4.39 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.21-4.15 (1H, m, H8), 3.80 (3H, s, OCH_3), 3.56 (1H, ddd, *J* = 7.2, 5.8, 3.7 Hz, H6), 3.34 (1H, d, *J* = 2.3 Hz, OH), 2.50 (1H, dd, *J* = 15.9, 8.5 Hz, H9), 2.30 (1H, dd, *J* = 15.9, 4.7 Hz, H9'), 2.22 (2H, tdd, J = 6.9, 2.7, 1.1 Hz, H3), 1.97 (1H, t, *J* = 2.8 Hz, H1), 1.88-1.77 (1H, m, H7), 1.73-1.64 (2H, m, H4), 1.58-1.49 (2H, m, H5), 1.24 (6H, d, *J* = 6.3 Hz, H13 and H13'), 0.97 (3H, d, *J* = 7.1 Hz, methyl-H7'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ172.3, 159.4, 130.4, 129.6, 114.0, 84.2, 82.1, 71.0, 70.9, 68.9, 68.1, 55.4, 40.2, 39.5, 29.6, 24.8, 22.0, 18.7, 7.6; **HRMS** (ESI^+) calc. for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.2142, found 399.2138.

Isopropyl (3*R*,4*R*,5*S*)-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)dec-9-ynoate (B6-*S*-ester)

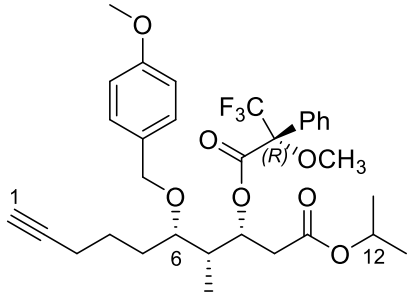


To a solution of alcohol **B6** (4.1 mg, 0.011 mmol, 1.0 equiv.) in CH_2Cl_2 (0.11 mL) was added anhydrous pyridine (5.5 μL, 0.068 mmol, 6.2 equiv.) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7.7 μL, 0.041 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography

on silica gel (10% EtOAc/pentane) to afford title compound **B6-*S*-ester** (4.2 mg, 0.0071 mmol, 65%) as a colourless oil.

R_f 0.15 (8% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3294, 2922, 2340, 1747, 1514, 1248, 1189, 1107, 1017; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57-7.54 (2H, m, ArH), 7.40-7.39 (3H, m, ArH), 7.21 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.53 (1H, dt, *J* =7.7, 4.9 Hz, H8), 4.97 (1H, p, *J* = 6.2 Hz, H12), 4.38 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 4.28 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 3.80 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.19 (1H, q, *J* = 5.6 Hz, H6), 2.71-2.64 (2H, m, H9), 2.16-2.12 (2H, m, H3), 2.03 (1H, dt, *J* = 7.1, 5.1 Hz, H7), 1.96 (1H, t, *J* = 2.7 Hz, H1), 1.64-1.57 (2H, m, H4), 1.48-1.38 (2H, m, H5), 1.20 (6H, d, *J* = 6.2 Hz, H13 and H13'), 0.91 (3H, d, *J* = 7.0 Hz, methyl-H7'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.0, 165.8, 159.3, 132.4, 130.6, 129.7, 129.6, 128.5, 127.5, 123.5 (q, J = 289 Hz), 113.9, 84.5 (q, J = 28 Hz), 84.2, 78.4, 74.9, 71.2, 68.8, 68.6, 55.7, 55.4, 38.8, 37.2, 29.8, 24.3, 21.9, 21.8, 18.6, 10.4; **^{19}F NMR** (470 MHz, CDCl3): δ –71.1; **HRMS** (ESI^+) calc. for $C_{32}H_{39}F_3O_7Na$ $[M+Na]^+$ 615.2540, found 615.2542.

Isopropyl (3*R*,4*R*,5*S*)-5-((4-methoxybenzyl)oxy)-4-methyl-3-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)dec-9-ynoate (B6-*R*-ester)



To a solution of alcohol **B6** (4.1 mg, 0.011 mmol, 1.0 equiv.) in CH_2Cl_2 (0.11 mL) was added anhydrous pyridine (5.5 μL, 0.068 mmol, 6.2 equiv.) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (7.7 μL, 0.041 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane) to afford title compound **B6-*R*-ester** (4.4 mg, 0.0074 mmol, 68%) as a colourless oil.

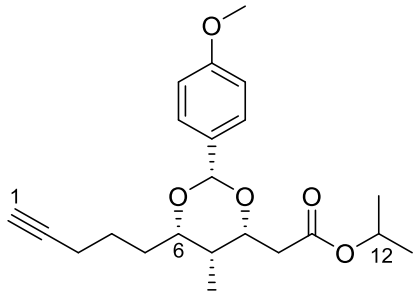
R_f 0.15 (8% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3294, 2981, 2359, 1747, 1514, 1250, 1172, 1108, 964; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.51 (2H, m, ArH), 7.41-7.38 (3H, m, ArH), 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.8 Hz, ArH), 5.53 (1H, dt, *J* =7.3, 5.2 Hz, H8), 4.93 (1H, p, *J* = 6.3 Hz, H12), 4.43 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.35 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 3.80 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.31 (1H, q, *J* = 5.5 Hz, H6), 2.66-2.60 (2H, m, H9), 2.20-2.16 (2H, m, H3), 2.10-2.06 (1H, m, H7), 1.97 (1H, t, *J* = 2.6 Hz, H1), 1.71-1.65 (2H, m, H4), 1.52-1.46 (2H, m, H5), 1.19 (6H, d, *J* = 6.2 Hz, H13 and H13'), 0.98 (3H, d, *J* = 7.0 Hz, methyl-H7'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.8, 165.9, 159.3, 132.0, 130.6, 129.7, 129.6, 128.6, 127.9, 123.5 (q, *J* = 289 Hz), 113.9, 84.6 (q, *J* = 28 Hz), 84.2, 78.6, 75.1, 71.2, 68.6, 68.5, 55.4, 55.4, 38.8, 37.1, 29.8, 24.4, 21.9, 21.8, 18.6, 10.5; **^{19}F NMR** (470 MHz, CDCl3): δ –71.0; **HRMS** (ESI^+) calc. for $C_{32}H_{39}F_3O_7Na$ $[M+Na]^+$ 615.2540, found 615.2541

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

Proton position	**B6-S-ester (ppm)**	**B2-R-ester (ppm)**	**$\Delta\delta_{SR}$**
H1	1.96	1.97	-0.01
H3	2.14	2.18	-0.04
H4	1.61	1.68	-0.07
H5	1.44	1.49	-0.05
H6	3.19	3.31	-0.12
H7	2.03	2.08	-0.05
methyl-H7'	0.91	0.98	-0.07
H9	2.68	2.63	+0.05
H12	4.97	4.93	+0.04
H13 and H13'	1.20	1.19	+0.01

Negative values obtained for alkyne portion and positive values obtained for ester portion. Analysis of all the values reveals the C8 centre is of *R* configuration.

Isopropyl 2-((4*R*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-(pent-4-yn-1-yl)-1,3-dioxan-4-yl)acetate (B7)

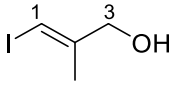


To a solution of alcohol **B6** (1.90 g, 5.05 mmoL, 1.0 equiv.) in CH_2Cl_2 (50.5 mL) at 0 °C was added DDQ (1.48 g, 6.56 mmoL, 1.3 equiv.) portionwise and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution

(30 mL), filtered through a celite pad and washed with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane) to obtain alkyne **B7** (1.05 g, 2.80 mmol, 56%) as a colourless oil.

R_f 0.45 (16% EtOAc/pentane); $[\alpha]_D^{25}$ −5.7 (*c* = 1.0, $CHCl_3$); **IR** (thin film, v_{max} / cm^{-1}) 3289, 2937, 2361, 1730, 1518, 1249, 1184, 1107, 1034, 829; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.52 (1H, s, CHPMP), 5.03 (1H, p, *J* = 6.3 Hz, H12), 4.37 (1H, ddd, *J* = 8.1, 5.9, 2.3 Hz, H8), 3.89 (1H, ddd, *J* = 8.5, 4.6, 2.3 Hz, H6), 3.79 (3H, s, OCH_3), 3 2.67 (1H, dd, *J* = 15.5, 8.0 Hz, H9), 2.44 (1H, dd, *J* = 15.5, 5.8 Hz, H9'), 2.31-2.17 (2H, m, H3), 1.96 (1H, t, *J* = 2.6 Hz, H1), 1.81-1.68 (2H, m, H5), 1.62-1.55 (3H, m, H7 and H4), 1.24 (6H, d, *J* = 6.3 Hz, H13 and H13'), 0.99 (3H, d, *J* = 6.9 Hz, methyl-H7'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 160.0, 131.4, 127.5, 113.7, 101.6, 84.4, 80.5, 77.4, 68.7, 68.1, 55.5, 38.5, 34.6, 31.9, 24.8, 22.0, 22.0, 18.5, 6.1; **HRMS** (ESI^+) calc. for $C_{22}H_{30}O_5Na$ $[M+Na]^+$ 397.1985, found 397.1984.

(*E*)-3-Iodo-2-methylprop-2-en-1-ol (A1)

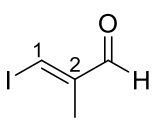


Synthesized according to modified literature procedure.[120] To a solution of Cp_2ZrCl_2 (1.96 g, 6.69 mmol, 0.25 equiv.) in CH_2Cl_2 (205 mL) was added Me_3Al (40.1 mL, 2.0 M in hexane,

80.27 mmol, 3.0 equiv.) dropwise. The resulting mixture was cooled to 0 ºC and a solution of propargyl alcohol (1.50 g, 26.8 mmol, 1.0 equiv.) in CH_2Cl_2 (21.8 mL) was added slowly. After stirring at room temperature for 17 h, the reaction mixture was cooled to – 30 ºC and a solution of I_2 (8.15 g, 32.11 mmol, 1.2 equiv.) in Et_2O (12.7 mL) was added dropwise. After stirring at that temperature for 30 min, it was warmed to 0 ºC and then quenched with saturated sodium potassium tartrate solution (10 mL) carefully (heavy gas and heat development). After gas development ceased, another portion of saturated sodium potassium tartrate solution was added (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure carefully. The crude vinyl iodide was purified by vacuum distillation to afford the pure compound **A1** (2.90 g, 14.7 mmol, 55%) as a light yellow oil.

b.p. 80 ºC (4 mbar); **R_f** 0.40 (20% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3314, 2981, 2889, 1381, 1275, 1150, 1071, 1011, 954, 774, 666; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.28 (1H, q, *J* = 1.3 Hz, H1), 4.13 (2H, d, *J* = 5.4 Hz, H3), 1.85 (3H, s, H2'), 1.65 (1H, s, OH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.3, 77.5, 67.3, 21.5. The physical and spectroscopic data were consistent with the literature reported data.[120]

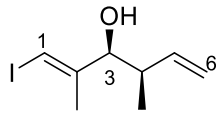
(*E*)-3-Iodo-2-methylacrylaldehyde (A2)



Synthesized according to modified literature procedure.[121] To a solution of alcohol **A1** (2.90 g, 14.7 mmol, 1.0 equiv.) in Et_2O (58.6 mL) at room temperature was added activated manganese (IV) oxide (19.1 g, 219.70 mmol, 15.0 equiv.). The resulting mixture was stirred at room temperature until reaction went completion, as analyzed by TLC (5 h). Afterwards, the reaction mixture was filtered through a short pad of celite and washed with Et_2O. The resulting filtrate was concentrated under reduced pressure to afford the title compound **A2** (2.25 g, 11.5 mmol, 78%) as a volatile yellow oil), which was used for the next step directly without further purification.

R_f 0.50 (10% EtOAc/pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.52 (1H, s, H3), 7.80 (1H, q, *J* = 1.2 Hz, H1), 1.92 (3H, d, *J* = 1.2 Hz, H2'); **^{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.[121]

(3*S*,4*R*, *E*)-1-Iodo-2,4-dimethylhexa-1,5-dien-3-ol (A3)

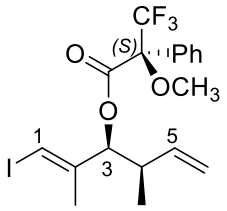


To a solution of (*R*,*R*)-**L2** (3.42 g, 11.79 mmol, 1.1 equiv.) in CH_2Cl_2 (42.9 mL) at 0 °C was added DBU (5.3 mL, 35.36 mmol, 3.3 equiv.). The *cis*–Crotyltrichlorosilane **D9** (2.44 g, 12.86 mmol, 1.2 equiv.) was then added dropwise. The ice/water bath was removed and after stirring at room temperature for 1 h, the reaction mixture was recooled to 0 °C. The aldehyde **A2** (2.10 g, 10.71 mmol, 1.0 equiv.) was added dropwise and the solution was stirred at 0 °C for 1 h. The reaction mixture was treated with TBAF (13.9 mL, 1.0 M in THF, 13.9 mmol,

1.3 equiv.) and stirred for 1 h at room temperature. The mixture was concentrated and the residue was suspended in Et_2O (60 mL). The resulting mixture was stirred vigorously for 20 min to ensure complete precipitation of the DBU•HCl salts. The mixture was then filtered off and the filtrate was treated with 1.0 M aqueous HCl solution (58.9 mL, 58.9 mmol, 5.5 equiv.) and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 130 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution (1 x 80 mL), brine (1 x 80 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 20% EtOA/pentane) to afford the title compound **A3** (1.95 g, 7.74 mmol, 72%, 89% *ee*, >20:1 *dr*) as a colourless oil. (*ee* was determined by fluorine nmr of corresponding mosher ester. The procedure for the synthesis of known compounds (*R*,*R*)-**L2** and recovery of (*R*,*R*)-**L1** was described in our published work)[42]

R_f 0.50 (15% EtOAc/pentane); $[\alpha]_D^{25}$ –8.3 (*c* = 1.9, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3385, 3079 2963, 2919, 1725, 1639, 1616, 1456, 1376, 1267, 1010, 917, 784, 666; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.26 (1H, s, H1), 5.76-5.68 (1H, m, H5), 5.09 (1H, dt, *J* = 9.4, 1.5 Hz, H6), 5.07 (1H, d, *J* = 1.5 Hz, H6'), 4.03 (1H, ddd, *J* = 6.2, 3.5, 1.0 Hz, H3), 2.48-2.40 (1H, m, H4), 1.80 (3H, d, *J* = 1.1 Hz, H2'), 1.01 (3H, d, *J* = 6.8 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 140.1, 115.6, 79.8, 79.1, 41.1, 20.7, 14.0; **HRMS** not found.

(3*S*,4*R*,*E*)-1-Iodo-2,4-dimethylhexa-1,5-dien-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (A3-*S*-ester)

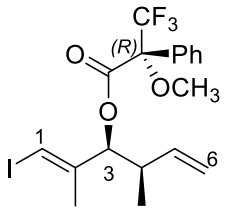


To a solution of alcohol **A3** (6.0 mg, 0.024 mmol, 1.0 equiv.) in CH_2Cl_2 (0.36 mL) was added anhydrous pyridine (11.9 μL, 0.148 mmol, 6.2 equiv.) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (16.9 μL, 0.090 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2% Et_2O/pentane) to afford title compound **A3-*S*-ester** (10.2 mg, 0.018 mmol, 92%) as a colourless oil.

R_f 0.75 (10% Et_2O/pentane); $[\alpha]_D^{25}$ –33.5 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2360, 1746, 1271, 1242, 1170, 1121, 1016, 994; **^{1}H NMR** (400 MHz, $CDCl_3$) δ : δ 7.47 - 7.39 (5H, m, ArH), 6.38 (1H, s, H1), 5.55 (1H, ddd, *J* = 17.0, 10.5, 7.7 Hz, H5), 5.34 (1H, d, *J* = 8.4 Hz, H3), 5.05 (1H, dt, *J* = 7.4, 1.1 Hz, H6), 5.02 (1H, d, *J* = 1.1 Hz, H6'), 3.49 (3H, s, OCH_3), 2.60-2.50 (1H, m, H4), 1.78 (3H, d, *J* = 1.1 Hz, H2'), 0.93 (3H, d, *J* = 6.7 Hz, H4'); **^{13}C NMR** (101 MHz, CDCl3): 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, CDCl3): δ –70.8; **HRMS** (ESI$^+$) calc. for $C_{18}H_{20}F_3IO_3Na$ $[M+Na]^+$ 491.0301, found 491.0301.

(3*S*,4*R*,*E*)-1-Iodo-2,4-dimethylhexa-1,5-dien-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (A3-*R*-ester)



To a solution of alcohol **A3** (6.0 mg, 0.024 mmol, 1.0 equiv.) in CH_2Cl_2 (0.36 mL) was added anhydrous pyridine (11.9 μL, 0.148 mmol, 6.2 equiv.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (16.9 μL, 0.090 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2% Et_2O/pentane) to afford the title compound **A3-*R*-ester** (10.5 mg, 0.022 mmol, 95%) as a colourless oil.

R_f 0.75 (10% Et_2O/pentane); $[\alpha]_D^{25}$ +22.6 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2360, 1747, 1272, 1248, 1170, 1121, 1016, 991; **^{1}H NMR** (400 MHz, $CDCl_3$) δ : δ 7.47 - 7.40 (5H, m, ArH), 6.24 (1H, s, H1), 5.59 (1H, ddd, *J* = 17.1, 10.4, 7.5 Hz, H5), 5.27 (1H, d, *J* = 8.0 Hz, H3), 5.08 (1H, dt, *J* = 7.9, 1.1 Hz, H6), 5.04 (1H, d, *J* = 1.1 Hz, H6'), 3.57 (3H,

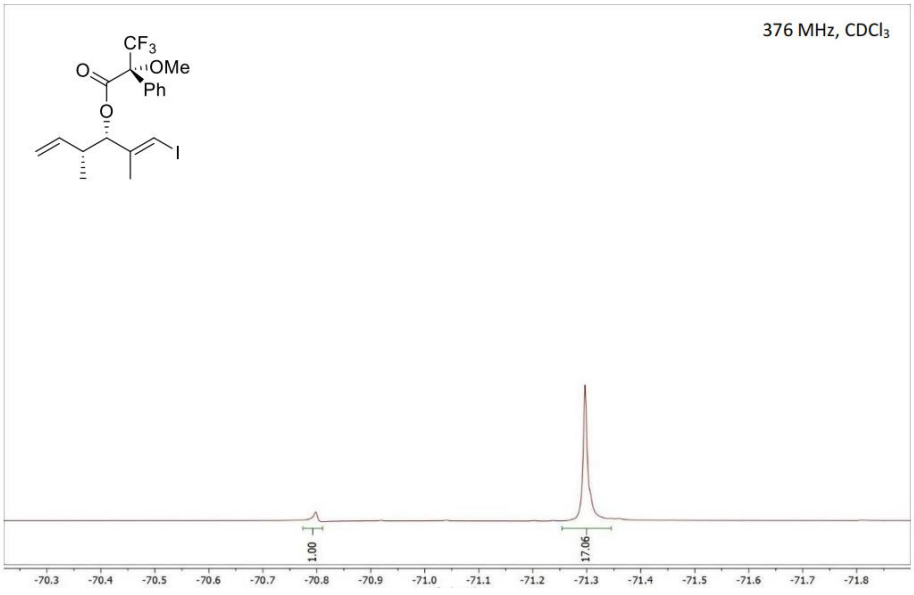
s, OCH_3), 2.60-2.53 (1H, m, H4), 1.62 (3H, d, *J* = 1.1 Hz, H2'), 1.05 (3H, d, *J* = 6.7 Hz, H4'); **^{13}C NMR** (101 MHz, CDCl3): δ 165.9, 143.7, 138.1, 132.2, 129.8, 128.6, 127.3, 123.4 (q, *J* = 290 Hz), 116.4, 84.8 (q, *J* = 28 Hz), 83.2, 83.0, 56.0, 39.7, 20.6, 15.7; **^{19}F NMR** (376 MHz, CDCl3): δ –71.3; **HRMS** (ESI^+) calc. for $C_{18}H_{20}F_3IO_3Na$ $[M+Na]^+$ 491.0301, found 491.0300.

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

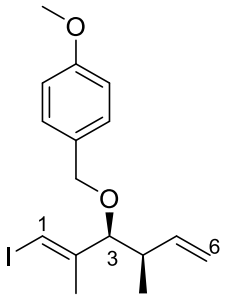
Proton position	**A3-*S*-ester (ppm)**	**A3-*R*-ester (ppm)**	**$\Delta\delta_{SR}$**
H1	6.38	6.24	+0.14
H2'	1.78	1.62	+0.16
H4	2.55	2.57	-0.02
H4'	0.93	1.05	-0.12
H5	5.55	5.59	-0.04
H6	5.05	5.08	-0.03
H6'	5.02	5.04	-0.02

Negative values obtained for terminal alkene portion and positive values obtained for vinyl iodide portion. Analysis of all the values reveals the C3 centre is of *S* configuration.

Determination of *ee* of compound **A3** by ^{19}F NMR of mosher ester: 89% *ee*



1-((((3*S*,4*R*,*E*)-1-Iodo-2,4-dimethylhexa-1,5-dien-3-yl)oxy)methyl)-4 methoxybenzene (A4)

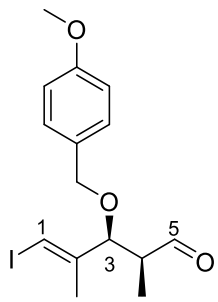


To a solution of NaH (0.762 g, 19.0 mmol, 60% dispersion in mineral oil, 2.5 equiv.) in DMF (15.2 mL) at 0 °C was added alcohol **A3** (1.92 g, 7.62 mmol, 1.0 equiv.) dropwise. After stirring at 0 °C for 1 h, PMBBr(3.83 g, 19.0 mmol, 2.5 equiv.) was added, followed by tetrabutylammonium iodide (0.844 g, 2.28 mmol, 0.3 equiv.) The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water (100 mL) at 0 °C and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (4% Et_2O/pentane) to afford the title compound **A4** (2.15 g, 5.78 mmol, 76%) as a colourless oil.

R_f 0.48 (4% Et_2O/PE); $[\alpha]_D^{25}$ -65.7 (*c* = 0.93, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2889, 2362, , 1613, 1514, 1381, 1248, 1070, 954, 820, 668; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.5 Hz, ArH), 6.10 (1H, s, H1), 5.53 (1H, ddd, *J* = 17.1, 10.3, 7.9 Hz, H5), 4.97 (1H, dt, *J* = 17.2, 1.5 Hz, H6), 4.93 (1H, ddd, *J* = 10.3, 1.8,

0.9 Hz, H6'), 4.42 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.14 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 3.81 (3H, s, OCH_3), 3.52 (1H, d, *J* = 8.7 Hz, H3), 2.43-2.35 (1H, m, H4), 1.76 (3H, d, *J* = 1.1 Hz, H2'), 1.08 (3H, d, *J* = 6.6 Hz, H4'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 147.4, 139.9, 130.4, 129.6, 114.7, 113.9, 87.7, 79.9, 70.3, 55.4, 41.2, 19.5, 16.9; **HRMS** (ESI^+) calc. for $C_{16}H_{21}IO_2Na$ $[M+Na]^+$ 395.0478, found 395.0480.

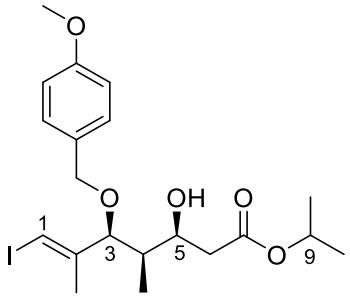
(2*S*,3*S*,*E*)-5-Iodo-3-((4-methoxybenzyl)oxy)-2,4-dimethylpent-4-enal (A5)



To a solution of pmb alkene **A4** (1.86 g, 5.00 mmol, 1.0 equiv.) in dioxane / water (50 mL, 3:1) at room temperature was added 2,6-lutidine (1.2 mL, 9.99 mmol, 2.0 equiv.), followed by osmium tetroxide (0.64 g, 4% wt. in water, 0.10 mmol, 0.02 equiv.) and sodium periodate (4.27 g, 20.0 mmol, 4.0mequiv.). After stirring at room temperature for 3 h, the reaction mixture was quenched with water (100 mL) and then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et_2O/pentane to 20% Et_2O/pentane) to afford the title compound **A5** (1.43 g, 3.82 mmol, 76%) as a colourless oil.

R_f 0.45 (15% Et_2O/pentane); $[\alpha]_D^{25}$ -52.0 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2935, 2836, 1726, 1612, 1514, 1456, 1248, 1035, 821, 756; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.57 (1H, d, *J* = 1.5 Hz, H5), 7.19 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 6.32 (1H, s, H1), 4.48 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.22-4.15 (2H, m, OCH_2Ar and H3), 3.81 (3H, s, OCH_3), 2.61-2.54 (1H, m, H4), 1.81 (3H, d, *J* = 1.2 Hz, H2'), 1.09 (3H, d, *J* = 7.0 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.9, 159.5, 145.2, 129.7, 114.0, 82.0, 80.4, 70.6, 55.4, 49.3, 20.8, 13.3, 9.3; **HRMS** (ESI^+) calc. for $C_{15}H_{19}IO_3Na$ $[M+Na]^+$ 397.0271, found 397.0272.

Isopropyl (3*S*,4*R*,5*S*,*E*)-3-hydroxy-7-iodo-5-((4-methoxybenzyl)oxy)-4,6-dimethylhept-6-enoate (A6)

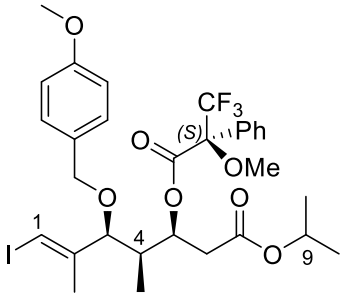


To a stirred solution of aldehyde **A5** (1.41 g, 3.77 mmol, 1.0 equiv.) and ((1-isopropoxyvinyl)oxy)trimethylsilane **B5** (1.97 g, 11.3 mmol, 3.0 equiv.) in CH_2Cl_2 (75.4 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.47 mL, 3.77 mmol, 1.0 eq.) dropwise. After stirring at −78 °C for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography (10% Et_2O/pentane to 25% Et_2O/pentane) to afford the title compound **A6** (1.15 g, 2.41 mmol, 64%, 5:1 *dr*) as a colourless oil.

R_f 0.45 (30% Et_2O/pentane); $[\alpha]_D^{25}$ -39.7 (*c* = 0.95, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3657, 2981, 2888, 1725, 1382, 120, 1151, 1073, 955, 819; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 6.28 (1H, s, H1), 5.03 (1H, p, *J* = 6.3 Hz, H9), 4.43 (1H, *J* = 11.1 Hz, OCH_2Ar), 4.19 (1H, *J* = 11.2 Hz, OCH_2Ar), 4.00-3.95 (2H, m, H3 and H5), 3.80 (3H, s, OCH_3), 2.97 (1H, d, *J* = 2.7 Hz, OH), 2.51 (1H, dd, *J* = 16.2, 9.3 Hz, H6), 2.29 (1H, dd, *J* = 16.2, 3.8 Hz, H6'), 1.78 (3H, d, *J* = 1.1 Hz, H2'), 1.70 (1H, td, *J* =6.9, 2.4 Hz, H4), 1.24 (3H, d, *J* = 2.2 Hz, H10-^{i}pr), 1.23 (3H, d, *J* = 2.1 Hz, H10'-^{i}pr), 0.96 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 159.5, 146.1, 130.0, 129.7, 114.0, 86.0, 79.8, 70.8, 68.9, 68.3, 55.4, 40.1, 39.9, 22.0, 20.5, 8.3; **HRMS** (ESI^+) calc. for $C_{20}H_{29}IO_5Na$ $[M+Na]^+$ 499.0952, found 499.0956.

Isopropyl (3*S*,4*R*,5*S*,*E*)-7-iodo-5-((4-methoxybenzyl)oxy)-4,6-dimethyl-3-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hept-6-enoate (A6-*S*-ester)

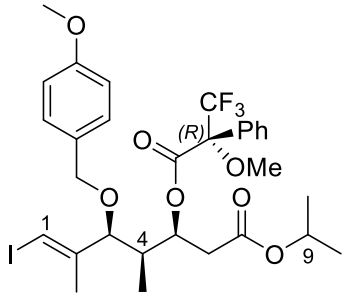


To a solution of alcohol **A6** (4.0 mg, 0.0084 mmol, 1.0 equiv.) in CH_2Cl_2 (0.13 mL) was added anhydrous pyridine (4.2 μL, 0.052 mmol, 6.2 equiv.) and (*R*)-(-)-α-methoxy-α-

(trifluoromethyl)phenylacetyl chloride (6.0 μL, 0.032 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.3 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% Et_2O/pentane) to afford the title compound **A3-*S*-ester** (5.1 mg, 0.0074 mmol, 88%) as a colourless oil.

R_f 0.14 (10% Et_2O/pentane); $[\alpha]_D^{25}$ -22.2 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2888, 1383, 1251, 1156, 1079, 955, 819; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.47 (2H, m, ArH), 7.43-7.37 (3H, m, ArH), 7.18 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.98 (1H, s, H1), 5.22 (1H, td, *J* = 6.8, 2.9 Hz, H5), 4.96 (1H, p, *J* = 6.3 Hz, H9), 4.36 (1H, d, *J* = 11.3 Hz, OCH_2Ar), 4.07 (1H, d, *J* = 11.3 Hz, OCH_2Ar), 3.80 (3H, s, OCH_3), 3.62 (1H, d, *J* = 7.4 Hz, H3), 3.40 (3H, s, OCH_3), 2.65 (1H, dd, *J* = 16.0, 6.5 Hz, H6), 2.53 (1H, dd, *J* = 16.1, 7.1 Hz, H6'), 2.07 (1H, qt, *J* = 7.0, 3.7 Hz, H4), 1.79 (3H, d, *J* = 1.1 Hz, H2'), 1.22-1.18 (6H, m, H10 and H10'-^{i}pr)), 1.00 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.4, 165.6, 159.5, 145.9, 131.7, 129.9, 129.9, 129.7, 128.7, 127.9, 123.5 (q, *J* = 290 Hz), 114.0, 84.7 (q, *J* = 28 Hz), 83.7, 81.0, 74.1, 70.4, 68.6, 55.4, 55.3, 38.5, 36.6, 29.9, 21.9, 21.9, 19.8, 9.9; **^{19}F NMR** (376 MHz, CDCl3): δ –71.0; **HRMS** (ESI^+) calc. for $C_{30}H_{36}F_3IO_7Na$ $[M+Na]^+$ 715.1350, found 715.1345.

Isopropyl (3*S*,4*R*,5*S*,*E*)-7-iodo-5-((4-methoxybenzyl)oxy)-4,6-dimethyl-3-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hept-6-enoate (A6-*R*-ester)



To a solution of alcohol **A6** (4.0 mg, 0.0084 mmol, 1.0 equiv.) in CH_2Cl_2 (0.13 mL) was added anhydrous pyridine (4.2 μL, 0.052 mmol, 6.2 equiv.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (6.0 μL, 0.032 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.3 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% Et_2O/pentane) to afford the title compound **A3-*R*-ester** (5.0 mg, 0.0072 mmol, 86%) as a colourless oil.

R_f 0.14 (10% Et_2O/pentane); **$[\alpha]_D^{25}$** +1.2 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2889, 1383, 1252, 1153, 1073, 955, 816; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54-7.47 (2H, m, ArH), 7.44-7.38 (3H, m, ArH), 7.16 (2H, d, *J* = 8.6 Hz, ArH), 6.85 (2H, d, *J* = 8.6 Hz, ArH), 5.92 (1H, s, H1), 5.20 (1H, td, *J* = 6.8, 2.9 Hz, H5), 4.98 (1H, p, *J* = 6.3 Hz, H9), 4.32 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 4.04 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 3.80 (3H, s, OCH_3), 3.57 (1H, d, *J* = 7.5 Hz, H3), 3.52 (3H, s, OCH_3), 2.71 (1H, dd, *J* = 15.9, 6.5 Hz, H6), 2.59 (1H, dd, *J*

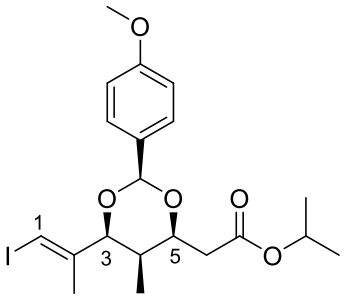
= 16.0, 7.2 Hz, H6'), 2.05 (1H, qt, *J* = 7.1, 2.8 Hz, H4), 1.75 (3H, d, *J* = 1.1 Hz, H2'), 1.21 (6H, dd, *J* = 6.3, 4.7 Hz, H10 and H10'-^{i}pr)), 0.99 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.4, 165.6, 159.4, 146.0, 132.7, 129.9, 129.8, 129.7, 128.6, 127.4, 123.3 (q, *J* = 290 Hz), 114.0, 84.3 (q, *J* = 28 Hz), 83.7, 81.0, 74.0, 70.5, 68.7, 55.6, 55.4, 38.4, 36.5, 29.9, 21.9, 21.9, 19.6, 9.9; **^{19}F NMR** (470 MHz, CDCl3): δ –71.0; **HRMS** (ESI^+) calc. for $C_{30}H_{36}F_3IO_7Na$ $[M+Na]^+$ 715.1350, found 715.1342.

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

Proton position	**A6-S-ester (ppm)**	**A6-R-ester (ppm)**	**$\Delta\delta_{SR}$**
H1	5.98	5.92	+0.06
H2'	1.79	1.75	+0.04
H3	3.62	3.57	+0.05
H4	2.07	2.05	+0.02
H4'	1.00	0.99	+0.01
H6	2.65	2.71	-0.06
H6'	2.53	2.59	-0.06
H9	4.96	4.98	-0.02
H10 and H10'	1.20	1.21	-0.01

Negative values obtained for ester portion and positive values obtained for pmb portion. Analysis of all the values reveals the C5 centre is of *S* configuration.

Isopropyl 2-((4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (A7)

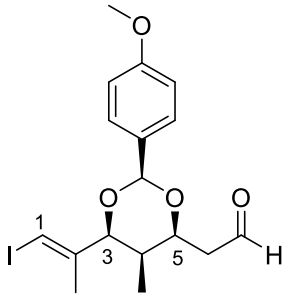


To a solution of ester **A6** (1.13 g, 2.37 mmol, 1.0 equiv.) in CH_2Cl_2 (20.8 mL) at 0 °C was added DDQ (0.697 g, 3.08 mmol, 1.3 equiv.) portionwise. After stirring at 0 °C for 2 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (20 mL). The mixture was filtered through a celite pad and washed with CH_2Cl_2.The filtrate was transferred to a separatory funnel and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% Et_2O/pentane to 20% Et_2O/pentane) to afford the title compound **A7** (0.79 g, 1.67 mmol, 70%) as a colourless oil.

R_f 0.49 (30% Et_2O/pentane); $[\alpha]_D^{25}$ -19.5 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2888, 1730, 1383, 1250, 1153, 956, 828; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.89 (2H, d, *J* = 8.8 Hz, ArH), 6.33 (1H, s, H1), 5.57 (1H, s, PMP acetal), 5.04 (1H, p, *J* = 6.3 Hz, H9), 4.47-4.38 (2H, m, H3 and H5), 3.81 (3H, s, OCH_3), 2.67 (1H, dd, *J* = 15.7, 7.8 Hz, H6), 2.46 (1H, dd, *J* = 15.7, 5.9 Hz, H6'), 1.78 (3H, d, *J* = 1.1 Hz, H2'), 1.24

(6H, dd, *J* = 6.3, 1.2 Hz, H10 and H10'-^{i}pr), 0.85 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 160.2, 144.0, 130.9, 127.6, 113.7, 101.4, 83.6, 78.3, 77.0, 68.2, 55.5, 38.5, 33.2, 22.0, 21.5, 6.3; **HRMS** (ESI^+) calc. for $C_{20}H_{27}IO_5Na$ $[M+Na]^+$ 497.0795, found 497.0795.

2-((4*S*,5*R*,6*S*)-6-((*E*)-1-Iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl) acetaldehyde (A8)

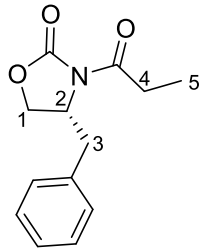


To a solution of pmp acetal **A7** (0.70 g, 1.48 mmol, 1.0 equiv.) in CH_2Cl_2 (14.8 mL) at -78 °C was added precooled (0 °C) diisobutylaluminum hydride solution (1.8 mL, 1.77 mmol, 1.0 M in CH_2Cl_2, 1.2 equiv.) dropwise and stirred until reaction went completion, analyzed by TLC (30 min). The reaction mixture was diluted with EtOAc (1.0 mL) and quenched with sat. aq. potassium sodium tartrate solution (10 mL) at -78 °C and then was allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue

was purified by flash chromatography (10% EtOAc/pentane to 15% EtOAc/pentane) to afford the title compound **A8** (0.55 g, 1.32 mmol, 90%) as a colourless oil.

R_f 0.35 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -37.5 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2888, 1726, 1615, 1518, 1383, 1249, 1032, 954, 831; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.83 (1H, t, *J* = 1.7 Hz, H7), 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.90 (2H, d, *J* = 8.7 Hz, ArH), 6.34 (1H, s, H1), 5.60 (1H, s, PMP acetal), 4.54 (1H, ddd, *J* = 8.4, 4.8, 2.3 Hz, H5), 4.43 (1H, d, *J* = 2.2 Hz, H3), 3.81 (3H, s, OCH_3), 2.86 (1H, ddd, *J* = 17.2, 8.4, 1.7 Hz, H6), 2.53 (1H, ddd, *J* = 17.2, 4.8, 1.7 Hz, H6'), 1.85 (1H, qt, *J* = 6.9, 2.3 Hz, H4), 1.79 (3H, d, *J* = 1.1 Hz, H2'), 0.87 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.2, 160.3, 143.8, 130.6, 127.6, 113.8, 101.5, 83.6, 78.5, 75.3, 55.5, 46.9, 33.4, 21.5, 6.5; **HRMS** (ESI^+) calc. for $C_{17}H_{21}IO_4Na$ $[M+Na]^+$ 439.0377, found 439.0377.

(*R*)-4-Benzyl-3-propionyloxazolidin-2-one (A9)

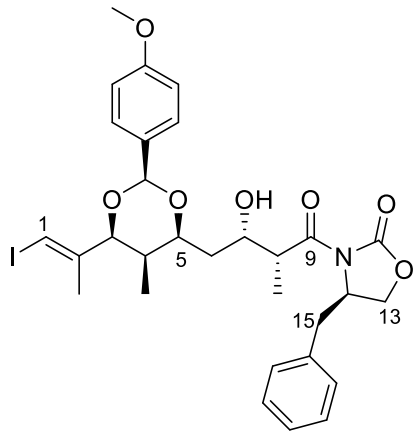


Synthesized according to a literature procedure.[122] To a solution of (*R*)-4-benzyloxazolidine-2-one (4.90 g, 27.7 mmol, 1.0 equiv.) in THF (46.9 mL) at -78 °C was added n-BuLi solution (12.2 mL, 30.4 mmol, 2.5 M in hexane, 1.1 equiv.) dropwise over 10 min. After 30 min of stirring, the propionyl chloride (3.4 mL, 38.7 mmol, 1.4 equiv.) was added. The resulting mixture was stirred at -78 °C for 30 min and then warmed to room temperature and stirred

for further 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/pentane to 20% EtOAc/pentane) to afford the title compound **A9** (6.19 g, 26.5 mmol, 96%) as white needle crystals.

$[\alpha]_D^{25}$ -62.6 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 1781,1703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.37-7.18 (5H, m, ArH), 4.72-4.63 (1H, m, H2), 4.24-4.12 (2H, m, H1), 3.30 (1H, dd, *J* = 13.4, 3.3 Hz, H3), 3.07-2.86 (2H, m, H4), 2.77 (1H, dd, *J* = 13.4, 9.6 Hz, H3'), 1.21 (3H, t, *J* = 7.4 Hz, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2, 153.6, 135.5, 129.5, 129.1, 127.5, 66.3, 55.3, 38.1, 29.3, 8.4; **HRMS** (ESI^+) calc. for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$ 256.0944, found 256.0944.

(4*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-4-((4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-2-methylbutanoyl)oxazolidin-2-one (A10)

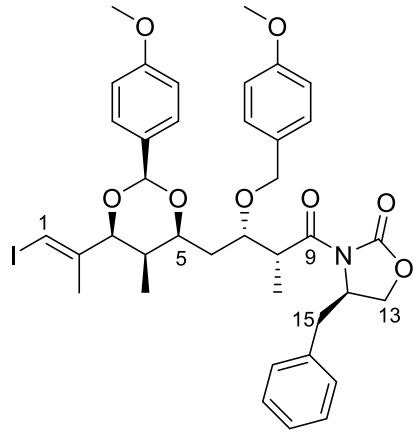


To a solution of N-acyloxazolidinone **A9** (0.303 g, 1.30 mmol, 1.0 equiv.) in CH_2Cl_2 (12.5 mL) at 0 °C was added $TiCl_4$ (0.15 mL, 1.36 mmol, 1.05 equiv.) dropwise. After 15 min of stirring, N,N-diisopropylethylamine (0.27 mL, 1.56 mmol, 1.2 equiv.)was added slowly and the resulting mixture was stirred at 0 °C for 1 h. NMP (0.13 mL, 1.30 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 10 min. A solution of aldehyde **A8** (0.54 g, 1.30 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was added dropwise. After stirring at 0 °C for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 30% EtOAc/pentane) to afford the title compound **A10** (0.69 g, 1.06 mmol, 82%, > 20:1 *dr*) as white solids.

R_f 0.45 (35% EtOAc/pentane); $[\alpha]_D^{25}$ -42.6 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3656, 2981, 2971, 2889, 1382, 1251, 1154, 1073, 953; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.7 Hz, ArH), 7.36 – 7.27 (3H, m, ArH), 7.19 (2H, d, *J* = 6.9 Hz, ArH), 6.89 (2H, d, *J* = 8.8 Hz, ArH), 6.29 (1H, s, H1), 5.58 (1H, s, PMP acetal), 4.68 (1H, ddt, *J* = 10.4, 6.9, 3.3 Hz, H14), 4.39 (1H, brs, H3), 4.28-4.22 (2H, m, H13), 4.22-4.19 (1H, m, H5), 3.80 (3H, s, OCH_3), 3.73-3.67 (1H, m, H7), 3.27 (1H, t, *J* = 2.2 Hz, H8), 3.23 (1H, dd, *J* = 13.4, 3.4 Hz, H15), 2.79 (1H, dd, *J* = 13.4, 9.4 Hz, H15'), 1.77 (3H, d, *J* = 1.8 Hz, H2'), 1.75-1.56 (3H, m, H4 and H6), 1.28 (3H, d, *J* = 7.1 Hz, H8'), 0.85 (3H, d, *J* = 6.8 Hz, H4'); **^{13}C NMR** (121 MHz, $CDCl_3$) δ 178.2, 160.1, 153.0, 144.2, 135.1, 131.3, 129.6, 129.2, 127.8, 127.6, 113.7,

101.4, 83.9, 78.1, 76.7, 67.6, 66.4, 55.5, 55.1, 42.5, 38.0, 37.7, 34.5, 21.5, 10.5, 6.4; **HRMS** (ESI^+) calc. for $C_{30}H_{36}INO_7Na$ $[M+Na]^+$ 672.1429, found 672.1423.

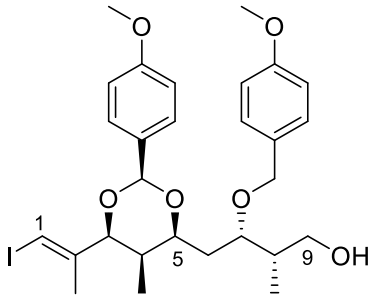
(4*R*)-4-Benzyl-3-((2*R*,3*S*)-4-((4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-((4-methoxybenzyl)oxy)-2-methylbutanoyl)oxazolidin-2-one (A11)



To a solution of alcohol **A10** (0.67 g, 1.03 mmol, 1.0 equiv.) in toluene (10.3 mL) at 0 °C was added $Sc(OTf)_3$ (0.0254 g, 0.052 mmol, 0.05 equiv.) portionwise, followed by addition of 4-methoxybenzyl-2,2,2-trichloroacetimidate (0.54 mL, 2.58 mmol, 2.5 equiv.). After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for further 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution (5 mL) at 0 °C and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc/pentane to 20% EtOAc/pentane) to afford the title compound **A11** (0.60 g, 0.78 mmol, 76%) as yellow solids.

R_f 0.47 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -61.6 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 1777, 1728, 1699, 1613, 1514, 1384, 1211, 1033, 827; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.24 (7H, m, ArH), 7.20 (2H, d, *J* = 6.6 Hz, ArH), 6.90 (2H, d, *J* = 8.7 Hz, ArH), 6.82 (2H, d, *J* = 8.6 Hz, ArH), 6.27 (1H, s, H1), 5.29 (1H, s, PMP acetal), 4.61-4.50 (2H, m, H14 and OCH_2Ar), 4.41 (1H, d, *J* = 11.3 Hz, OCH_2Ar), 4.27 (1H, brs, H3), 4.09 (1H, dd, *J* = 9.0, 2.1 Hz, H5), 4.01-3.95 (2H, m, H13), 3.89-3.84 (1H, m, H7), 3.82 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.28 (1H, dd, *J* = 13.4, 3.3 Hz, H15), 2.75 (1H, dd, *J* = 13.4, 9.7 Hz, H15'), 1.96-1.87 (1H, m, H8), 1.75 (3H, s, H2'), 1.72-1.57 (3H, m, H4 and H6), 1.24 (3H, d, *J* = 7.1 Hz, H8'), 0.82 (3H, d, *J* = 6.8 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1, 160.2, 159.2, 153.0, 144.3, 135.6, 131.3, 130.2, 129.6, 129.1, 127.6, 127.5, 127.5, 113.9, 113.6, 101.1, 83.9, 78.0, 76.6, 72.5, 67.4, 66.1, 55.8, 55.5, 55.4, 40.2, 37.9, 35.3, 34.3, 21.5, 13.0, 6.5 (^{13}C NMR spectrum not very clear); **HRMS** (ESI^+) calc. for $C_{38}H_{44}INO_8Na$ $[M+Na]^+$ 792.2004, found 792.2003.

(2*S*,3*S*)-4-((4*S*,5*R*,6*S*)-6-((*E*)-1-Iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-((4-methoxybenzyl)oxy)-2-methylbutan-1-ol (A12)

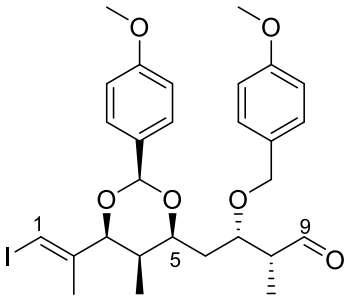


To a solution of compound **A11** (0.59 g, 0.77 mmol, 1.0 equiv.) in Et_2O (15.3 mL) and water (0.041 mL, 2.30 mmol, 3.0 equiv.) at 0 °C was added LiBH4 (1.1 mL, 2.30 mmol, 2.0 M in

THF, 3.0 equiv.) solution dropwise. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for further 1 h at room temperature. The reaction mixture was cooled to 0 °C and quenched with 1N NaOH solution (5 mL). The resulting mixture was stirred at 0 °C for 10 min and at room temperature for another 10 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 25% EtOAc/pentane) to afford the title compound **A12** (0.35 g, 0.59 mmol, 77%) as colourless oil.

R_f 0.35 (30% EtOAc/pentane); $[\alpha]_D^{25}$ -45.9 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3443, 2959, 2836, 1614, 1515, 1248, 1034, 827; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.6 Hz, ArH), 7.29-7.26 (2H, m, ArH), 6.88 (4H, dd, *J* = 16.0, 8.8 Hz, ArH), 6.29 (1H, s, H1), 5.29 (1H, s, PMP acetal), 4.64 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 4.42 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 4.18 (1H, brs, H3), 4.00 (1H, dt, *J* = 10.1, 2.3 Hz, H5), 3.84-3.77 (4H, m, H7 and OCH_3), 3.76-3.68 (4H, m, OCH_3 and H9), 3.59-3.51 (1H, m, H9'), 1.76 (3H, s, H2'), 1.73-1.64 (2H, m, H4 and H8), 1.62-1.51 (2H, m, H6), 0.85 (3H, d, *J* = 7.1 Hz, H8'), 0.81 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 159.6, 144.2, 131.2, 130.4, 130.1, 127.5, 114.1, 113.7, 101.1, 84.0, 78.2, 78.0, 77.4, 72.1, 65.8, 55.5, 55.4, 36.8, 34.4, 33.8, 21.5, 12.8, 6.5 (^{13}C NMR spectrum not very clear); **HRMS** (ESI^+) calc. for $C_{28}H_{37}IO_6Na$ $[M+Na]^+$ 619.1527, found 619.1525.

(2*R*,3*S*)-4-((2*S*,4*S*,5*R*,6*S*)-6-((*E*)-1-Iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-((4-methoxybenzyl)oxy)-2-methylbutanal (A13)

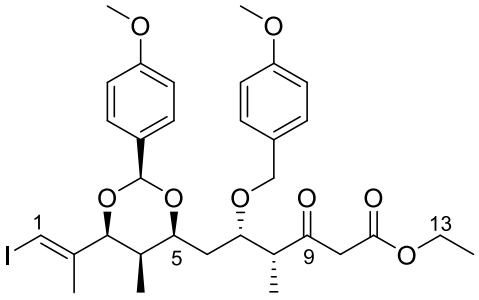


To a solution of alcohol **A12** (0.34 g, 0.57 mmol, 1.0 equiv.) in CH_2Cl_2 (3.8 mL) was added sodium bicarbonate (0.479 g, 5.70 mmoL, 10.0 equiv.) and Dess-Martin periodinane (0.363 g, 0.85 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and sat. aq. $Na_2S_2O_3$ solution (5 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **A13** (0.25 g, 0.42 mmol, 74%) as a colourless oil.

R_f 0.50 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -59.7 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2981, 2886, 1722, 1614, 1514, 1383, 1248, 1155, 1033, 955, 825; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.83 (1H, d, *J* = 0.9 Hz, H9), 7.36 (2H, d, *J* = 8.7 Hz, ArH), 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.91 (2H, d, *J* = 8.7 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 6.29 (1H, s, H1), 5.35 (1H, s, PMP acetal), 4.56 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.39 (1H, d, *J* = 11.3 Hz,

OCH_2Ar), 4.28 (1H, brs, H3), 4.13 (1H, dt, *J* = 10.3, 3.2 Hz, H5), 4.05 (1H, dt, *J* = 10.2, 2.3 Hz, H7), 3.82 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.67-2.59 (1H, m, H8), 1.75 (3H, s, H2'), 1.72-1.56 (3H, m, H4 and H6), 1.12 (3H, d, *J* = 7.1 Hz, H8'), 0.80 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.6, 160.1, 159.6, 144.1, 131.1, 130.2, 129.9, 127.6, 114.1, 113.7, 101.2, 83.9, 78.1, 76.6, 74.7, 72.3, 55.5, 55.4, 50.4, 36.6, 34.3, 21.5, 8.5, 6.5; **HRMS** (ESI^+) calc. for $C_{28}H_{35}IO_6Na$ $[M+Na]^+$ 617.1371, found 617.1367.

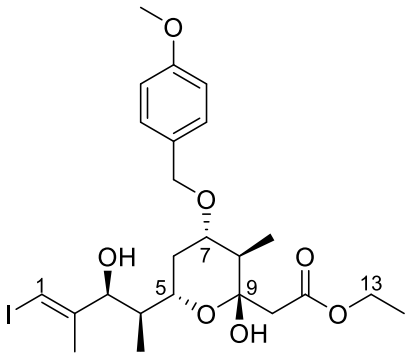
Ethyl (4*R*,5*S*)-6-((2*S*,4*S*,5*R*,6*S*)-6-((*E*)-1-iodoprop-1-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5-((4-methoxybenzyl)oxy)-4-methyl-3-oxohexanoate (A14)



To a solution of aldehyde **A13** (0.24 g, 0.40 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) at room temperature was added $SnCl_2$(0.0459 g, 0.24 mmol, 0.6 equiv.), followed by dropwise addition of ethyl diazoacetate (0.20 mL, 1.61 mmol, contains ≥13 wt. % dichloromethane, 4.0 equiv.). The resulting mixture was stirred at room temperature for 1 h during which the reaction mixture turned cloudy green. It was diluted with CH_2Cl_2 (10 mL), filtered through a short celite pad and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 15% EtOAc/pentane) to afford title compound **A14** (0.19 g, 0.28 mmol, 69%) as a colourless oil.

R_f 0.48 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -66.4 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2917, 2849, 1738, 1614, 1515, 1248, 1033, 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.8 Hz, ArH), 7.28 (2H d, *J* = 8.8 Hz, ArH), 6.88 (4H, dd, *J* = 13.7, 8.6 Hz, ArH), 6.27 (1H, s, H1), 5.27 (1H, s, PMP acetal), 4.65 (1H, d, *J* = 11.2 Hz, OCH_2Ar), 4.41 (1H, d, *J* = 11.4 Hz, OCH_2Ar), 4.26 (1H, brs, H3), 4.18 (2H, qd, *J* = 7.1, 1.1 Hz, H13), 3.97 (1H, dt, *J* = 10.2, 2.3 Hz, H5), 3.87 (1H, dt, *J* = 10.5, 3.2 Hz, H7), 3.82 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.58 (2H, d, *J* = 1.8 Hz, H10), 3.12 (1H, qd, *J* = 7.0, 3.7 Hz, H8), 1.74 (3H, s, H2'), 1.73-1.59 (3H, m, H4 and H6), 1.26 (3H t, *J* = 7.1 Hz, H14), 1.09 (3H, d, *J* = 7.0 Hz, H8'), 0.78 (3H, d, *J* = 6.9 Hz, H4'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.4, 167.6, 160.1, 159.6, 144.1, 131.1, 130.0, 129.9, 127.5, 114.1, 113.7, 101.1, 83.9, 78.1, 76.4, 74.6,72.2, 61.4, 55.5, 55.4, 50.2, 48.8, 35.4, 34.3, 21.5, 14.3, 12.0, 6.5; **HRMS** (ESI^+) calc. for $C_{32}H_{41}IO_8Na$ $[M+Na]^+$ 703.1738, found 703.1732.

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-2H-pyran-2-yl)acetate (A15)

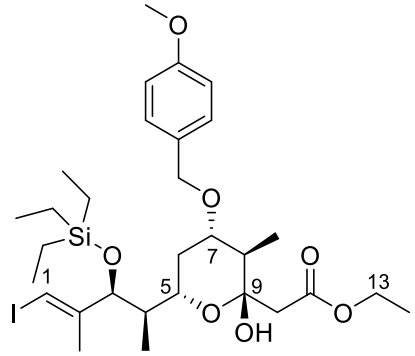


To a solution of ester **A14** (0.18 g, 0.26 mmol, 1.0 equiv.) in THF (1.7 mL) and MeOH (1.7 mL) at room temperature was added 1.0 M aq. HCl solution (1.7 mL) dropwise. The resulting mixture was stirred at room temperature overnight before being quenched with sat. aq.

$NaHCO_3$ solution (3.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 10% EtOAc/pentane) to afford title compound **A15** (0.11 g, 0.196 mmol, 74%) as a colourless oil.

R_f 0.40 (20% EtOAc/pentane); $[\alpha]_D^{25}$ +7.8 (*c* = 1.7, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3443, 2981, 2888, 1711, 1382, 1250, 1153, 1073, 954; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 6.32 (1H, s, H1), 4.83 (1H, d, *J* = 1.9 Hz, OH), 4.57 (1H, d, *J* = 11.0 Hz, OCH_2ArH), 4.39 (1H, d, *J* = 10.9 Hz, OCH_2ArH), 4.26 (1H, d, *J* = 3.3 Hz, H3), 4.20 (2H, qt, *J* = 7.1, 3.4 Hz, H13), 4.11 (1H, dt, *J* = 12.1, 2.3 Hz, H5), 3.80 (3H, s, OCH_3), 3.56 (1H, td, *J* = 10.6, 4.5 Hz, H7), 2.88 (1H, brs, OH), 2.81 (1H, d, *J* = 15.5 Hz, H10), 2.52 (1H, d, *J* = 15.5 Hz, H10'), 1.96 (1H, ddd, *J* = 12.3, 4.6, 2.1 Hz, H6), 1.75 (3H, s, H2'), 1.73-1.69 (1H, m, H4), 1.54-1.43 (2H, m, H8 and H6'), 1.29 (3H, d, *J* = 7.2 Hz, H14), 1.09 (3H, d, *J* = 6.6 Hz, H8-Me), 0.83 (3H, d, *J* = 7.0 Hz, H4'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1, 159.4, 147.0, 130.8, 129.4, 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^+) calc. for $C_{24}H_{35}IO_7Na$ $[M+Na]^+$ 585.1320, found 585.1317.

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-2H-pyran-2-yl)acetate (A16)

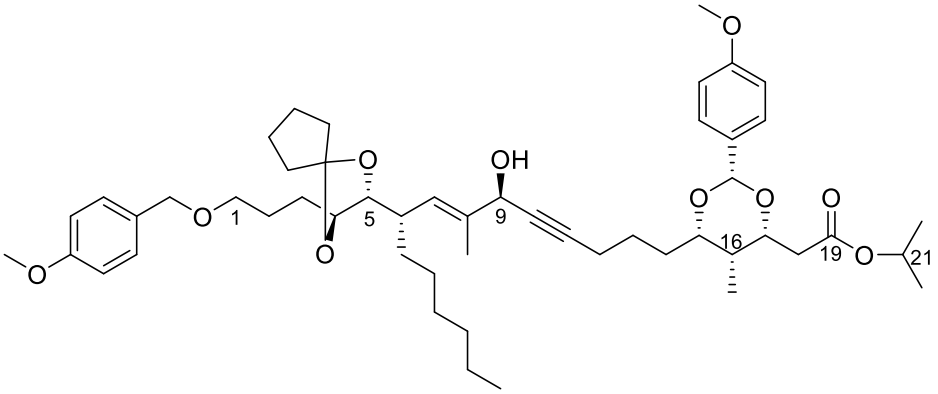


To a solution of compound **A15** (0.095 g, 0.169 mmol, 1.0 equiv.) in CH_2Cl_2 (1.7 mL) at 0 °C was added DMAP (1.4 mg, 0.012 mmol, 0.07 equiv.) and imidazole (0.0264 g, 0.388 mmol, 2.3 equiv.), followed by dropwise addition of chlorotriethylsilane (0.034 mL, 0.203 mmol, 1.2 equiv.). After stirring at 0 °C for 3 h, the reaction mixture was quenched with water (2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% Et_2O/pentane to 10% Et_2O/pentane) to afford title compound **A16** (0.032 g, 0.047 mmol, 28%) as a colourless oil.

R_f 0.50 (10% Et_2O/pentane); $[\alpha]_D^{25}$ +13.1 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2877, 1713, 1514, 1247, 1188, 1078, 1036, 843, 743; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 6.26 (1H, s, H1), 4.62 (1H, d, *J* = 1.9 Hz, OH), 4.56 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.37 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.19 (2H, qt, *J* = 7.0, 3.5 Hz, H13), 4.00 (1H, d, *J* = 8.9 Hz, H3), 3.80 (3H, s, OCH_3), 3.65 (1H,

dt, *J* = 12.3, 2.4 Hz, H5), 3.53 (1H, td, *J* = 10.6, 4.5 Hz, H7), 2.74 (1H, d, *J* = 15.1 Hz, H10), 2.46 (1H, d, *J* = 15.1 Hz, H10'), 1.86 (1H, ddd, *J* = 12.3, 4.6, 2.2 Hz, H6), 1.73 (3H, s, H2'), 1.58-1.53 (1H, m, H6'), 1.45-1.39 (2H, m, H4 and H8), 1.30 (3H, t, *J* = 7.1 Hz, H14), 1.07 (3H, d, *J* = 6.6 Hz, H8'), 0.96-0.89 (12H, m, H4' and TES), 0.54 (6H, q, *J* = 8.0 Hz, TES); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.3, 159.3, 148.9, 131.0, 129.4, 114.0, 98.8, 80.3, 79.6, 77.4, 71.0, 67.2, 61.1, 55.4, 45.5, 42.7, 41.2, 35.0, 19.1, 14.3, 12.4, 9.9, 7.0, 4.9; **HRMS** (ESI^+) calc. for $C_{30}H_{49}IO_7NaSi$ $[M+Na]^+$ 699.2184, found 699.2173.

Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-((6*R*,9*S*,*E*)-6-hydroxy-9-((2*S*,3*S*)-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 (E1)



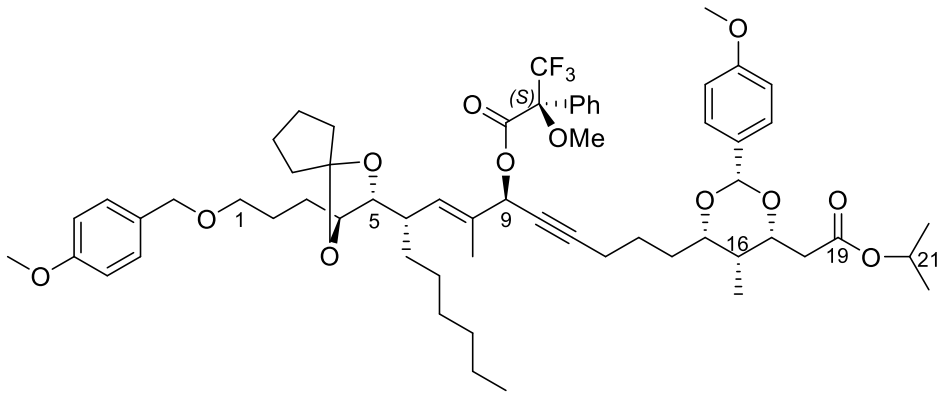
To a solution of alkyne **B7** (1.54 g, 4.13 mmol, 3.0 equiv.) in Et_2O (17.0 mL) at room temperature was added (S)-BINOL (0.157 g, 0.550 mmol, 0.4 equiv.) and dicyclohexylamine (99%) (0.0548 mL, 0.275 mmol, 0.2 equiv.), followed by dropwise addition of dimethylzinc (4.1 mL, 1.0 M in heptane, 4.13 mmol, 3.0 equiv.) The resulting mixture was sealed by parafilm, heated to 34°C and stirred at that temperature for 5 days. The reaction mixture was cooled to room temperature, followed by dropwise addition of

fresh distilled $Ti(O^iPr)_4$ (0.45 mL mL, 1.51 mmol, 1.1 equiv.). After stirring at room temperature for 3 h, a solution of aldehyde **C13** (0.65 g, 1.38 mmol, 1.0 equiv.) in Et_2O (0.5 mL) was added slowly and the resulting mixture was stirred for 2 h before being quenched with sat. aq. NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 25% EtOAc/pentane) to afford title compound **E1** (1.07 g, 1.26 mmol, 92%, 9.5:1 *dr*) as a colourless oil and recovered alkyne **B7** (1.01 g, 2.70 mmol).

R_f 0.40 (30% EtOAc/pentane); $[\alpha]_D^{25}$ -21.8 (*c* = 0.85, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3442, 2935, 2855, 2359, 2336, 1732, 1615, 1516, 1248, 1106, 1035, 826; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz, ArH), 7.23 (2H, d, *J* = 8.6 Hz, ArH), 6.89-6.83 (4H, m, ArH), 5.51 (1H, s, PMP acetal), 5.23 (1H, d, *J* = 10.2 Hz, H7), 5.03 (1H, p, *J* = 6.3 Hz, H21), 4.71 (1H, dd, *J* = 4.7, 2.3 Hz, H9), 4.40 (2H, s, OCH_2Ar), 4.36 (1H, ddd, *J* = 8.0, 5.8, 2.3 Hz, H17), 3.90-3.81 (2H, m, H5 and H15), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.76 (1H, dd, *J* = 9.4, 5.3 Hz, H4), 3.46 (1H, dt, *J* = 9.6, 6.0 Hz, H1), 3.38 (1H, dt, *J* = 9.5, 6.2 Hz, H1'), 2.66 (1H, dd, *J* = 15.6, 7.9 Hz, H18), 2.47-2.40 (2H, m, H18' and H6), 2.30 – 2.19 (2H, m, H12), 1.85-1.41 (20H, m, H2, H3, H13, H14, H16, H8' and cyclopent–CH_2), 1.31-1.19 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.97 (3H, d, *J* = 6.9 Hz, H16'), 0.87 (3H, t, *J* = 6.8 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 160.0, 159.3, 136.9, 131.4, 130.6, 129.5, 127.8, 127.5, 117.4, 113.9, 113.7, 101.6, 86.2, 81.2, 80.5, 79.9, 77.8, 72.4, 69.7, 68.6,

68.1, 55.4, 55.4, 38.5, 38.3, 38.0, 37.5, 34.5, 33.0, 32.1, 32.0, 29.7, 26.5, 26.2, 26.0, 25.0, 23.8, 23.5, 22.8, 22.0, 22.0, 18.9, 14.3, 13.3, 6.1; **HRMS** (ESI^+) calc. for $C_{51}H_{74}O_{10}Na$ $[M+Na]^+$ 869.5174, found 869.5169.

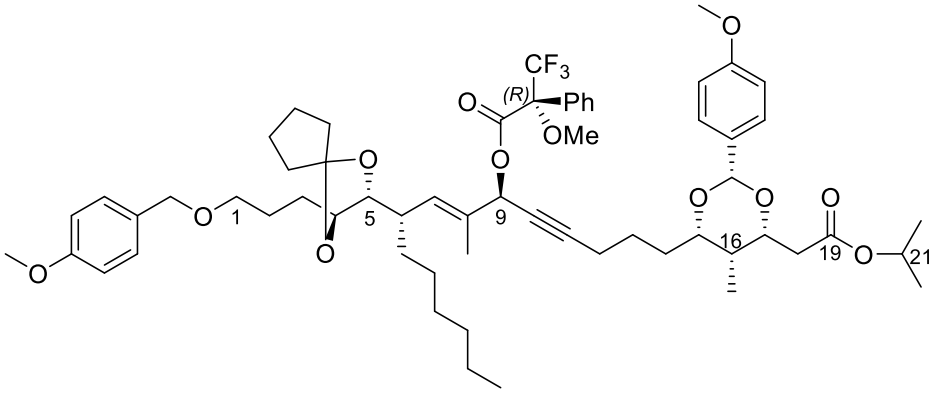
(6*R*,9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-Isopropoxy-2-oxoethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*S*,3*S*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-4-yn-6-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



To a solution of alcohol **E1** (10.0 mg, 0.012 mmol, 1.0 equiv.) in CH_2Cl_2 (0.12 mL) was added anhydrous pyridine (5.9 μL, 0.0732 mmol, 6.2 equiv.) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.4 μL, 0.045 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **E1-*S*-ester** (11.0 mg, 0.010 mmol, 87%) as a colourless oil.

R_f 0.25 (14% EtOAc/pentane); $[\alpha]_D^{25}$ -26.0 (*c* = 1.5, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2924, 2852, 1733, 1516, 1248, 1183, 1171, 1107, 1036, 1014, 826; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 7.8 Hz, ArH), 7.40-7.35 (5H, m, ArH), 7.21 (2H, d, *J* = 8.3 Hz, ArH), 6.86 (4H, dd, *J* = 8.4, 5.8 Hz, ArH), 5.88 (1H, s, H9), 5.51 (1H, s, PMP acetal), 5.45 (1H, d, *J* = 10.3 Hz, H7), 5.03 (1H, p, *J* = 6.2 Hz, H21), 4.38-4.33 (3H, m, OCH_2Ar and H17), 3.85-3.81 (2H, m, H15 and H5), 3.79 (6H, s, OCH_3), 3.77-3.73 (1H, m, H4), 3.48 (3H, s, OCH_3), 3.39 (2H, td, *J* = 6.4, 3.6 Hz, H1), 2.65 (1H, dd, *J* = 15.6, 8.0 Hz, H18), 2.47-2.39 (2H, m, H18' and H6), 2.25 (2H, dq, *J* = 15.6, 8.7, 8.0 Hz, H12), 1.83-1.43 (20H, m, H2, H3, H13, H14, H16, H8' and cyclopent–CH_2), 1.27-1.18 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.96 (3H, d, *J* = 6.8 Hz, H16'), 0.86 (3H, t, *J* = 6.8 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 165.6, 160.0, 159.2, 132.1, 132.1, 132.0, 131.4, 130.9, 129.7, 129.3, 128.5, 127.7, 127.5, 123.4 (q, *J* = 289 Hz), 117.6, 113.9, 113.7, 101.6, 88.6, 84.9 (q, *J* = 28 Hz), 81.1, 80.5, 77.7, 75.4, 72.5, 72.2, 70.1, 68.1, 55.5, 55.4, 55.4, 38.5, 38.4, 37.9, 37.5, 34.7, 32.8, 32.0, 29.8, 29.6, 26.4, 26.3, 24.8, 23.8, 23.5, 22.7, 22.0, 21.9, 18.9, 14.3, 14.0, 6.1; **^{19}F NMR** (470 MHz, CDCl3): δ –71.9 **HRMS** (ESI^+) calc. for $C_{61}H_{81}F_3O_{12}Na$ $[M+Na]^+$ 1085.5572, found 1085.5566.

(6*R*,9*S*,*E*)-1-((2*S*,4*S*,5*R*,6*R*)-6-(2-Isopropoxy-2-oxoethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-9-((2*S*,3*S*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-4-yn-6-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (E1-*R*-ester)



To a solution of alcohol **E1** (10.0 mg, 0.012 mmol, 1.0 equiv.) in CH_2Cl_2 (0.12 mL) was added anhydrous pyridine (5.9 μL, 0.0732 mmol, 6.2 equiv.) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.4 μL, 0.045 mmol, 3.8 equiv.). The resulting mixture was stirred at room temperature overnight. It was quenched with water (0.5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **E1-*R*-ester** (12.0 mg, 0.011 mmol, 95%) as a colourless oil.

R_f 0.25 (14% EtOAc/pentane); $[\alpha]_D^{25}$ -10.4 (*c* = 1.6, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2855, 1732, 1516, 1248, 1182, 1172, 1107, 1036, 1014, 827; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 7.8 Hz, ArH), 7.40-7.34 (5H, m, ArH), 7.23 (2H, d, *J* = 8.3 Hz,

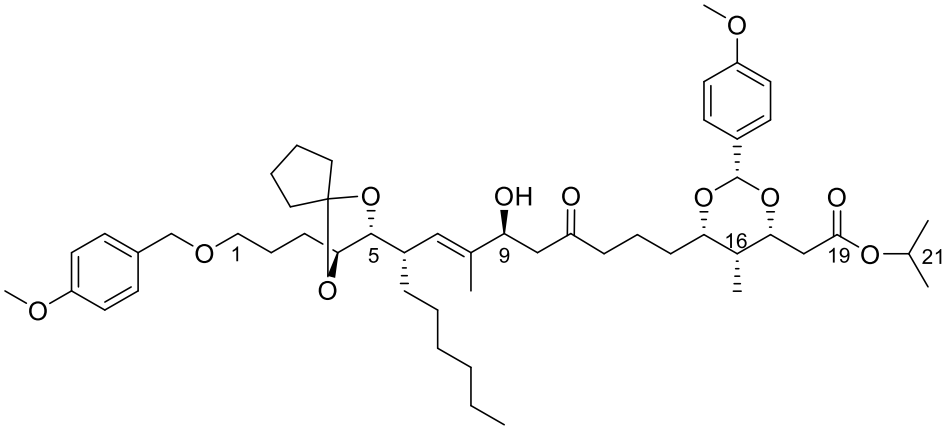
ArH), 6.86 (4H, d, *J* = 8.4 Hz, ArH), 5.92 (1H, s, H9), 5.50 (1H, s, PMP acetal), 5.40 (1H, d, *J* = 10.3 Hz, H7), 5.03 (1H, p, *J* = 6.3 Hz, H21), 4.38 (2H, d, *J* = 4.2 Hz, OCH_2Ar), 4.35 (1H, d, *J* = 5.6 Hz, H17), 3.87-3.82 (1H, m, H15), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.76 (1H, d, *J* = 2.7 Hz, H5), 3.72 (1H, dd, *J* = 9.3, 5.3 Hz, H4), 3.53 (3H, s, OCH_3), 3.39 (2H, t, *J* = 6.4 Hz, H1), 2.65 (1H, dd, *J* = 15.5, 8.0 Hz, H18), 2.46-2.38 (2H, m, H18' and H6), 2.29 (2H, qd, *J* = 7.2, 4.0 Hz, H12), 1.83-1.40 (20H, m, H2, H3, H13, H14, H16, H8' and cyclopent–CH_2), 1.28-1.17 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.95 (3H, d, *J* = 6.8 Hz, H16'), 0.86 (3H, t, *J* = 6.9 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 165.6, 160.0, 159.2, 132.4, 132.0, 131.6, 131.4, 131.0, 129.8, 129.3, 128.5, 127.6, 127.5, 123.5 (q, *J* = 289 Hz), 117.5, 113.9, 113.7, 101.6, 88.8, 84.6 (q, *J* = 28 Hz), 81.1, 80.5, 77.7, 75.5, 72.5, 71.7, 70.2, 68.1, 55.5, 55.4, 55.4, 38.5, 38.3, 38.0, 37.5, 34.6, 32.8, 32.0, 32.0, 29.6, 26.4, 26.2, 24.9, 23.8, 23.5, 22.7, 22.0, 21.9, 18.9, 14.2, 13.9, 6.1; **^{19}F NMR** (470 MHz, CDCl3): δ –71.7 **HRMS** (ESI^+) calc. for $C_{61}H_{81}F_3O_{12}Na$ $[M+Na]^+$ 1085.5572, found 1085.5562.

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

Proton position	**E1-*S*-ester (ppm)**	**E1-*R*-ester (ppm)**	**$\Delta\delta_{SR}$**
H4	3.75	3.72	+0.03
H7	5.45	5.40	+0.05
H8'	1.70	1.64	+0.06
H12	2.25	2.29	-0.04
H15	3.83	3.85	-0.02

Negative values obtained for alkyne portion and positive values obtained for alkene portion. Analysis of all the values reveals the C9 centre is of *R* configuration.

Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-((6*S*,9*S*,*E*)-6-hydroxy-9-((2*S*,3*S*)-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 (E2)

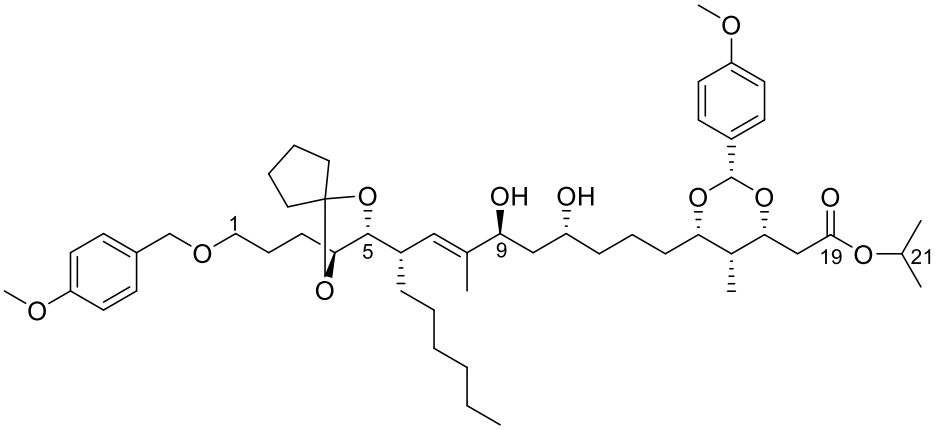


To a solution of propargylic alcohol **E1** (1.04 g, 1.23 mmol, 1.0 equiv.) in Et_2O (6.1 mL) was added bis(pinacolato)diboron (0.748 g, 2.95 mmol, 2.4 equiv.) and sodium *tert*-butoxide (97%) (0.0732 g, 0.737 mmol, 0.6 equiv.). The resulting mixture was cooled to 0°C and IMesCuI (0.0248 g, 0.0614 mmol, 0.05 equiv.) was added, followed by slow addition of anhydrous methanol (0.20 mL, 4.91 mmol, 4.0 equiv.). After stirring at 0°C for 40 min, the resulting dark brown–Coloured mixture was quenched with 2 to 3 drops of triethanolamine and stirred for 10 min at 0°C and another10 min at room temperature. The resulting mixture was diluted with Et_2O and filtered through a celite pad. The filtrate was washed with brine and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in THF (15.3 mL) and water (15.3 mL), followed by addition of sodium perborate monohydrate (0.582 g, 6.14 mmol, 5.0 equiv.) After stirring at room temperature overnight, the reaction mixture was quenched with water (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (10% EtOAc/pentane to 25% EtOAc/pentane) to afford hydroxyketone **E2** (0.872 g, 1.01 mmol, 82%) as a colourless oil.

R_f 0.35 (30% EtOAc/pentane); **$[\alpha]_D^{25}$** -15.3 (*c* = 0.61, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3468, 2980, 2889, 1729, 1615, 1515, 1462, 1382, 1250, 1150, 1072, 955, 827; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.8 Hz, ArH), 7.22 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (4H, dd, *J* = 8.7, 3.1 Hz, ArH), 5.50 (1H, s, PMP acetal), 5.14 (1H, d, *J* = 10.2 Hz, H7), 5.02 (1H, p, *J* = 6.3 Hz, H21), 4.43-4.40 (1H, m, H17), 4.39 (2H, s, OCH_2Ar), 4.36 (1H, ddd, *J* = 8.1, 5.7, 2.2 Hz, H9), 3.87-3.81 (2H, m, H15 and H5), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.5, 5.3 Hz, H4), 3.49 (1H, ddd, *J* = 9.5, 7.1, 5.4 Hz, H1), 3.39 (1H, ddd, *J* = 9.5, 7.2, 5.4 Hz, H1'), 2.92 (1H, d, *J* = 2.9 Hz, OH), 2.65 (1H, dd, *J* = 15.5, 8.0 Hz, H18), 2.57 (1H, dd, *J* = 16.5, 9.3 Hz, H18'), 2.47-2.43 (5H, m, H12, H10 and H6), 1.85-1.40 (20H, m, H2, H3, H13, H14, H16, H8' and cyclopent–CH_2), 1.30-1.18 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.96 (3H, d, *J* = 6.9 Hz, H16'), 0.87 (3H, t, *J* = 6.7 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.9, 170.7, 160.0, 159.3, 137.5, 131.3, 130.6, 129.5, 127.5, 126.5, 117.4, 113.9, 113.7, 101.6, 81.3, 80.8, 77.8, 73.2, 72.5, 69.9, 68.1, 55.4, 55.4, 48.0, 43.6, 38.5, 38.0, 38.0, 37.5, 34.5, 33.0, 32.2, 32.1, 29.8, 26.6, 26.3, 26.1, 25.0, 23.8, 23.5, 22.8, 22.0, 22.0, 19.7, 14.3, 13.2, 6.1; **HRMS** (ESI^+) calc. for $C_{51}H_{76}O_{11}Na$ $[M+Na]^+$ 887.5280, found 887.5270.

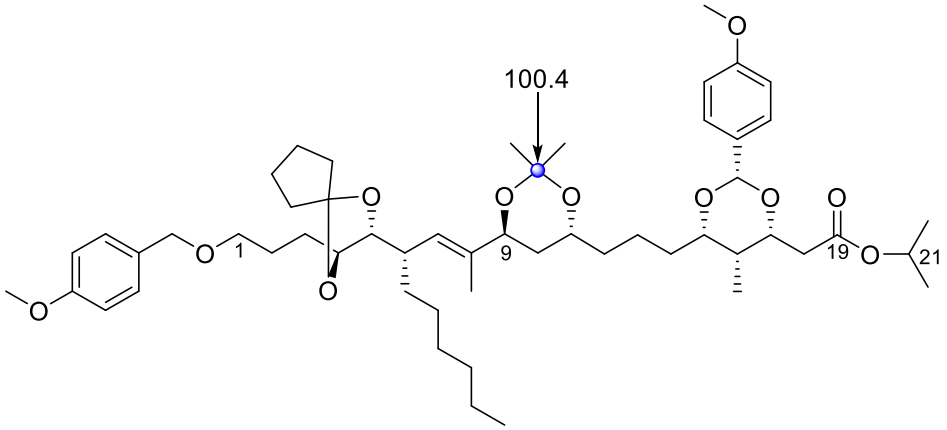
Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-((4*R*,6*S*,9*S*,*E*)-4,6-dihydroxy-9-((2*S*,3*S*)-3-(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylpentadec-7-en-1-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (E3)



To a suspension of tetramethylammonium triacetoxyborohydride (1.52 g, 5.77 mmol, 5.8 equiv.) in anhydrous acetonitrile (26.2 mL) was added acetic acid (5.7 mL). The resulting mixture was cooled to -20 °C and a solution of hydroxyketone **E2** (0.861 g. 0.995 mmol, 1.0 equiv.) in anhydrous acetonitrile (7.1 mL) was added dropwise. After stirring at -20°C overnight, the reaction mixture was quenched with sat. aq. Rochelle salt (10 mL), warmed to room and stirred for 10 min, upon which white precipitate was formed. The reaction mixture was poured over ice, neutralized with sat. aq. $NaHCO_3$ solution (30 mL) and stirred until the layers turned clear. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford diol **E3** (0.764 g, 0.881 mmol, 89%, >20:1 *dr*) as a colourless oil.

R_f 0.30 (50% EtOAc/pentane); **$[\alpha]_D^{25}$** -13.3 (*c* = 0.27, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3475, 2980, 2889, 1731, 1615, 1516, 1463, 1376, 1249, 1215, 1104, 747; **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.39 (2H, d, *J* = 8.7 Hz, ArH), 7.22 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (4H, dd, *J* = 8.6, 1.5 Hz, ArH), 5.51 (1H, s, PMP acetal), 5.16 (1H, d, *J* = 10.2 Hz, H7), 5.03 (1H, p, *J* = 6.3 Hz, H21), 4.39 (2H, s, OCH_2Ar), 4.37-4.34 (1H, m, H17), 4.26 (1H, dd, *J* = 8.3, 3.3 Hz, H9), 3.89-3.81 (2H, m, H15 and H5), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.78-3.75 (2H, m, H11 and H4), 3.50 (1H, ddd, *J* = 9.6, 7.1, 4.9 Hz, H1), 3.38 (1H, ddd, *J* = 9.6, 7.1, 4.9 Hz, H1'), 2.66 (2H, dd, *J* = 15.5, 8.0 Hz, H18), 2.49-2.37 (3H, m, H10 and H6), 1.85-1.41 (22H, m, H2, H3, H12, H13, H14, H16, H8' and cyclopent–CH_2), 1.32-1.19 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.97 (3H, d, *J* = 6.9 Hz, H16'), 0.87 (3H, t, *J* = 6.8 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 160.0, 159.4, 138.9, 131.5, 130.5, 129.6, 127.6, 125.9, 117.4, 113.9, 113.7, 101.6, 81.4, 80.9, 77.8, 74.8, 72.5, 69.7, 69.5, 68.1, 55.5, 55.4, 40.9, 38.6, 38.1, 37.5, 37.5, 34.5, 33.2, 32.8, 32.1, 29.8, 26.6, 26.3, 26.1, 23.8, 23.5, 22.8, 22.0, 22.0, 21.9, 14.3, 13.3, 6.1; **HRMS** (ESI^+) calc. for $C_{51}H_{78}O_{11}Na$ $[M+Na]^+$ 889.5460, found 889.5425.

Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-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 (E4)

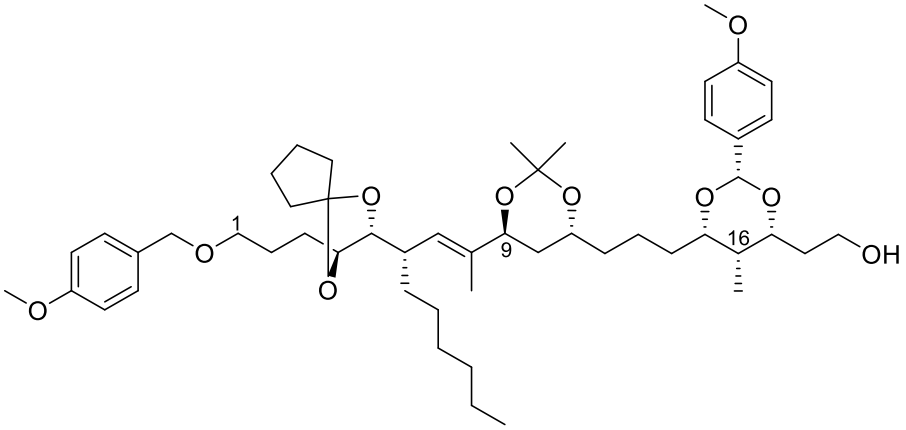


To a solution of diol **E3** (0.755 g, 0.871 mmol, 1.0 equiv.) in CH_2Cl_2 (3.3 mL) and 2,2-dimethoxypropane (3.3 mL) was added pyridinium *p*-toluenesulfonate (0.0175 g, 0.0697 mmol, 0.08 equiv.). After stirring at room temperature for 20 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford acetonide **E4** (0.691g, 0.762 mmol, 87%) as a colourless oil.

R_f 0.49 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -21.1 (*c* = 0.54, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2889, 1732, 1382, 1250, 1151, 1073, 955; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz, ArH), 7.24 (2H, d, *J* = 8.5 Hz, ArH), 6.86 (4H, dd, *J* = 8.8, 2.7 Hz, ArH), 5.51 (1H, s, PMP acetal), 5.08 (1H, d, *J* = 10.2 Hz, H7), 5.03 (1H, p, *J* = 6.2 Hz, H21), 4.40 (2H,

s, OCH_2Ar), 4.35 (1H, ddd, *J* = 8.1, 5.8, 2.3 Hz, H17), 4.14 (1H, dd, *J* = 9.4, 6.1 Hz, H9), 3.88 – 3.82 (2H, m, H15 and H5), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.78-3.71 (2H, m, H11 and H4), 3.50-3.39 (2H, m, H1), 2.66 (1H, dd, *J* = 15.5, 8.0 Hz, H18), 2.48-2.39 (2H, m, H18 and H6), 1.86-1.40 (24H, m, H2, H3, H10, H12, H13, H14, H16, H8' and cyclopent–CH_2), 1.33 (6H, s, acetonide), 1.29-1.13 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.97 (3H, d, *J* = 6.9 Hz, H16'), 0.87 (3H, t, *J* = 6.7 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.8, 160.0, 159.2, 136.8, 131.5, 130.9, 129.3, 127.5, 125.0, 117.4, 113.9, 113.7, 101.6, 100.4, 81.5, 80.8, 77.8, 72.5, 71.1, 70.2, 68.0, 66.6, 55.5, 55.4, 38.6, 37.9, 37.8, 37.5, 37.3, 36.0, 34.3, 33.0, 32.5, 32.0, 29.7, 26.5, 26.5, 26.1, 25.1, 25.0, 23.9, 23.5, 22.8, 22.0, 21.9, 21.3, 14.3, 13.7, 6.0; **HRMS** (ESI^+) calc. for $C_{54}H_{82}O_{11}Na$ $[M+Na]^+$ 929.5749, found 929.5741.

2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-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 (E5)

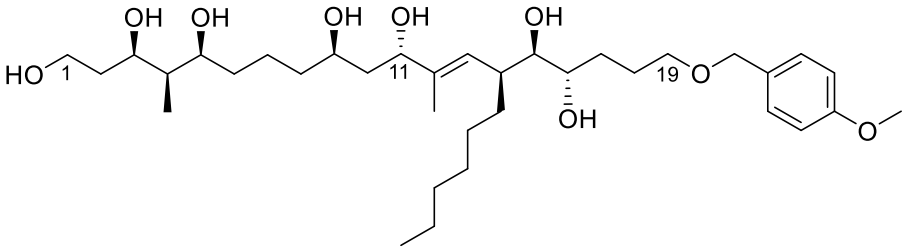


To a solution of acetonide **E4** (32.5 mg, 0.0358 mmol, 1.0 equiv.) in CH_2Cl_2 (0.36 mL) at -78 °C was added DIBAL-H (0.11 mL, 1.0 M in toluene, 0.107 mmol, 3.0 equiv.) dropwise.

After stirring at -78 °C for 1 h, the cooling bath was removed and the reaction mixture was stirred for another 1 h at room temperature. The reaction was quenched with sat. aq. Rochelle salt (1.0 mL) at 0 °C slowly and the resulting mixture was stirred at room temperature for further 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 50% EtOAc/pentane) to afford compound **E5** (13.0 mg, 0.0153 mmol, 43%) as a colourless oil

R_f 0.13 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -16.5 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3384, 2932, 2856, 1614, 1515, 1461, 1331, 1302, 1248, 1172, 1102, 1034, 827; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.7 Hz, ArH), 7.22 (2H, d, *J* = 8.4 Hz, ArH), 6.86 (4H, dd, *J* = 8.7, 3.2 Hz, ArH), 5.51 (1H, s, PMP acetal), 5.21 (1H, d, *J* = 10.1 Hz, H7), 4.42 (2H, s, OCH_2Ar), 4.33-4.26 (1H, m, H17), 4.19-4.12 (2H, m, H9 and H15), 4.11-4.04 (3H, H4, H5 and H11), 3.86-3.81 (2H, m, H19), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.66-3.60 (2H, m, H1), 3.17 (1H, dd, *J* = 15.5, 8.0 Hz, H18), 2.49-2.28 (2H, m, H18 and H6), 1.86-1.40 (24H, m, H2, H3, H10, H12, H13, H14, H16, H8' and cyclopent–CH_2), 1.33 (6H, s, acetonide), 1.30-1.12 (10H, m, hex-$(CH_2)_5$), 0.97 (3H, d, *J* = 6.9 Hz, H16'), 0.87 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 159.0, 136.8, 131.3, 130.8, 129.2, 127.4, 124.9, 117.3, 113.7, 113.6, 101.4, 100.3, 84.5, 81.3, 80.9, 77.6, 72.5, 71.0, 70.0, 69.5, 66.5, 60.7, 55.4, 55.3, 38.0, 37.8, 37.6, 37.4, 37.2, 35.9, 34.1, 32.9, 32.3, 31.9, 29.7, 26.3, 26.0, 25.0, 24.8, 23.7, 23.3, 22.7, 21.2, 15.3, 14.2, 14.1, 13.6, 6.0; **HRMS** (ESI^+) calc. for $C_{51}H_{78}O_{10}Na$ $[M+Na]^+$ 873.5595, found 873.5597.

(3*R*,4*R*,5*S*,9*R*,11*S*,14*S*,15*R*,16*S*,*E*)-14-Hexyl-19-((4-methoxybenzyl)oxy)-4,12-dimethylnonadec-12-ene-1,3,5,9,11,15,16-heptaol (E6)

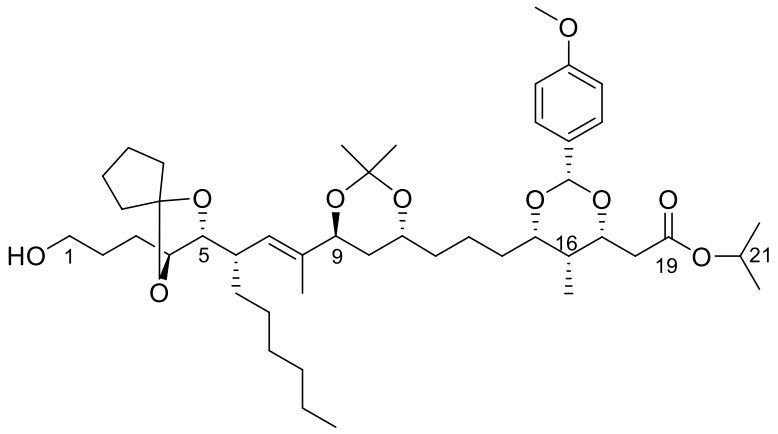


To a solution of alcohol **E5** (12.2 mg, 0.0143 mmol, 1.0 equiv.) in MeOH (0.5 mL) at room temperature was added 0.2 M aq. HCl solution (0.5 mL). After stirring at room temperature overnight, the reaction was quenched with sat. aq. $NaHCO_3$ solution (2.0 mL), extracted with CH_2Cl_2 (10 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2% EtOH/CH_2Cl_2 to 10% EtOH/CH_2Cl_2) to afford fully deprotected alcohol **E6** (3.4 mg, 0.00542 mmol, 38%, not very pure) as a colourless oil.

R_f 0.43 (10% EtOH/CH_2Cl_2); $[\alpha]_D^{25}$ -12.3 (*c* = 0.46, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3386, 2932, 2856, 1614, 1515, 1461, 1331, 1302, 1248, 1172, 1102, 1034, 827; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.4 Hz, ArH), 6.86 (4H, dd, *J* = 8.7, 3.2 Hz, ArH), 5.26 (1H, d, *J* = 10.7 Hz, H13), 4.42 (2H, s, OCH_2Ar), 4.29-4.24 (1H, m, H3), 4.14-4.05 (2H, m, H5 and H9), 4.00-3.90 (1H, m, H15), 3.80 (3H, s, OCH_3), 3.89-3.72 (4H, m, H1, H11 and H16), 3.49-3.44 (2H, m, H19), 2.57-2.15 (3H, m, H2 and H14), 1.86-1.40 (16H, m, H4, H6, H7, H8, H10, H12', H17 and H18), 1.30-1.12 (10H, m, hex-$(CH_2)_5$), 0.93 (3H, d, *J* = 6.9 Hz, H4'), 0.87 (3H, t, *J* = 7.1 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 159.0, 137.7, 129.2, 127.4, 123.8, 113.8, 81.3, 80.9, 77.6, 72.5, 71.0, 69.5, 66.5, 60.7, 55.4, 41.4, 37.6,

37.4, 35.9, 34.1, 32.9, 32.3, 31.9, 29.7, 26.3, 24.8, 23.7, 23.3, 22.7, 21.2, 15.3, 14.2, 13.6, 6.0;

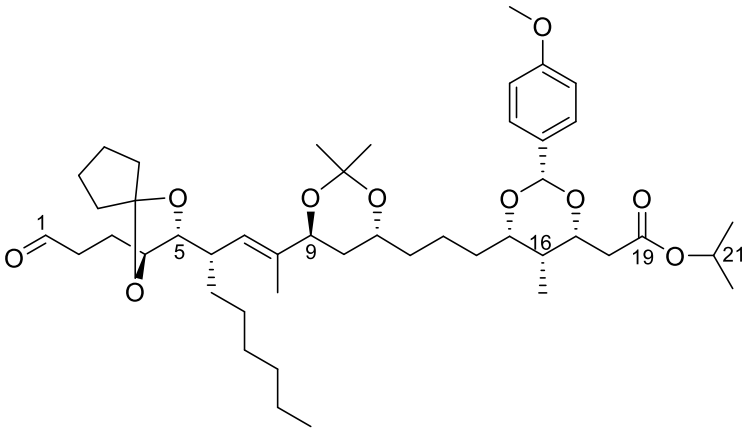
Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-3-(3-hydroxypropyl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)acetate (E7)



To a solution of acetonide **E4** (0.648 g, 0.714 mmol, 1.0 equiv.) in CH_2Cl_2 (23.8 mL) and water (1.3 mL) at 0 °C was added DDQ (0.290 g, 1.29 mmoL, 1.8 equiv.) portionwise. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (30 mL), filtered through a celite pad and washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 30% EtOAc/pentane) to afford title compound **E7** (0.437 g, 0.555 mmol, 78%) as a colourless oil.

R_f 0.29 (30% EtOAc/pentane); $[\alpha]_D^{25}$ –14.5 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3467, 2981, 2889, 1382, 1250, 1151, 1072, 955; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.8 Hz, ArH), 6.87 (2H, d, *J* = 8.8 Hz, ArH), 5.52 (1H, s, PMP acetal), 5.10 (1H, d, *J* = 10.2 Hz, H7), 5.03 (1H, p, *J* = 6.3 Hz, H21), 4.36 (1H, ddd, *J* = 8.3, 6.1, 2.1 Hz, H17), 4.19 (1H, dd, *J* = 9.5, 6.2 Hz, H9), 3.91-3.81 (2H, m, H15 and H5), 3.79 (3H, s, OCH_3), 3.77-3.71 (2H, m, H11 and H4), 3.61-3.54 (2H, m, H1), 2.70-2.62 (1H, m, H18), 2.49 – 2.36 (2H, m, H18 and H6), 1.89-1.42 (24H, m, H2, H3, H10, H12, H13, H14, H16, H8' and cyclopent–CH_2), 1.35 (6H, s, acetonide), 1.30-1.10 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.97 (3H, d, *J* = 6.8 Hz, H16'), 0.87 (3H, t, *J* = 6.7 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 160.0, 136.4, 131.5, 127.6, 126.8, 117.6, 113.7, 101.6, 100.6, 81.4, 80.9, 77.8, 72.4, 68.1, 66.7, 62.1, 55.5, 38.5, 38.1, 38.0, 37.5, 36.8, 36.0, 34.3, 32.9, 32.5, 32.0, 29.7, 29.5, 26.5, 25.7, 25.2, 24.8, 23.8, 23.5, 22.8, 22.0, 21.9, 21.3, 14.3, 13.2, 6.0; **HRMS** (ESI^+) calc. for $C_{46}H_{74}O_{10}Na$ $[M+Na]^+$ 809.5174, found 809.5166.

Isopropyl 2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-2,2-dimethyl-6-((*S*,*E*)-4-((2*S*,3*S*)-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 (E8)

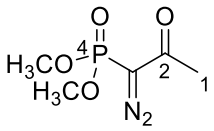


To a solution of alcohol **E7** (0.428 g, 0.544 mmol, 1.0 equiv.) in CH_2Cl_2 (3.6 mL) was added sodium bicarbonate (0.457 g, 5.44 mmol, 10.0 equiv.) and Dess-Martin periodinane (0.346 g, 0.816 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 mL) and sat. aq. $Na_2S_2O_3$ solution (5 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford compound **E8** (0.355 g, 0.452 mmol, 83%) as a colourless oil.

R_f 0.45 (20% EtOAc/pentane); $[\alpha]_D^{25}$ –27.5 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2935, 2364, 1729, 1617, 1518, 1377, 1249, 1171, 1107, 828; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (1H, t, *J* = 1.6 Hz, H1), 7.40 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.52 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.3 Hz, H7), 5.03 (1H, p, *J* = 6.3 Hz, H21), 4.36 (1H, ddd, *J* = 8.1, 5.8, 2.2 Hz, H17), 4.16 (1H, dd, *J* = 9.4, 6.2 Hz, H9), 3.90-3.80 (3H, m, H15, H5 and H4), 3.79 (3H, s, OCH_3), 3.78-3.73 (1H, m, H11), 2.66 (1H, dd, *J* = 15.5, 7.9 Hz, H18), 2.51-2.41 (2H, m, H18 and H6), 1.86-1.40 (24H, m, H2, H3, H10, H12, H13, H14, H16, H8' and cyclopent–CH_2), 1.34 (s, 6H, acetonide), 1.31-1.12 (16H, m, hex-$(CH_2)_5$, H22 and H22'), 0.97 (3H, d, *J* = 6.8 Hz, H16'), 0.87 (3H, t, *J* = 6.7 Hz, hex–CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.5, 170.8, 160.0, 137.4, 131.5, 127.6, 124.3, 117.7, 113.7, 101.6, 100.4, 81.4, 80.8, 71.0, 68.0, 66.6, 55.5, 40.8, 38.6, 37.9, 37.7, 37.4, 36.0, 34.3, 33.3, 32.5, 32.0,

29.7, 26.4, 25.1, 25.0, 23.8, 23.5, 22.8, 22.5, 22.0, 22.0, 21.3, 14.3, 13.7, 6.0; **HRMS** (ESI^+) calc. for $C_{46}H_{72}O_{10}Na$ $[M+Na]^+$ 807.5018, found 807.5016.

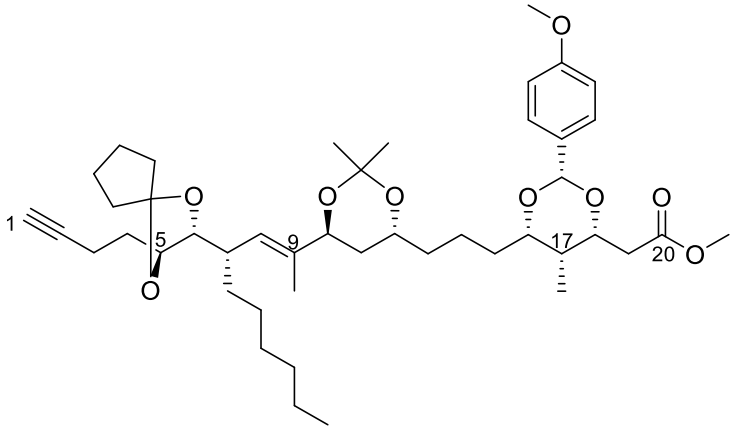
Dimethyl (1-diazo-2-oxopropyl) phosphonate (E9)



Synthesized according to a literature procedure.[123] To a solution of sodium hydride (0.353 g, 60% in mineral oil, 8.81 mmoL, 1.1 equiv.) in THF (25.0 mL) at 0 °C was added a solution of dimethyl 2-oxopropylphosphonate (1.1 mL, 8.01 mmoL, 1.0 equiv.) in THF (14.8 mL) dropwise, upon which white precipitate was formed. The resulting mixture was stirred at 0 °C for 1 h and then p-toluene sulfonyl azide solution (6.5 mL, 30% wt in toluene, 8.57 mmoL, 1.07 equiv.) was added slowly. After stirring at 0 °C for 3 h, the reaction mixture was filtered through celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (40% EtOAc/pentane to 80% EtOAc/pentane) to afford title compound **E9** (1.24 g, 6.45 mmol, 81 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.25 (3H, s, H1); **^{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 the literature reported data.[123]

Methyl 2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-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 (E10)

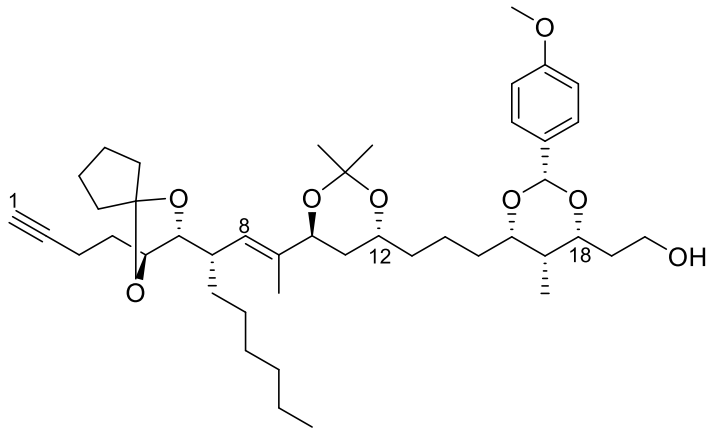


To a solution of phosphonate **E9** (0.217 g, 1.13 mmoL, 3.0 equiv.) in anhydrous methanol (9.4 mL) was added potassium carbonate (0.182 g, 1.32 mmoL, 3.5 equiv.), followed by a solution of aldehyde **E8** (0.295 g, 0.376 mmoL, 1.0 equiv.) in anhydrous methanol (5.6 mL). After stirring at room temperature overnight, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford alkyne **E10** (0.225 g, 0.299 mmol, 80%) as a colourless oil.

R_f 0.50 (18% EtOAc/pentane); $[\alpha]_D^{25}$ –21.3 (*c* = 0.41, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2937, 2858, 2361, 1742, 1617, 1518, 1436, 1379, 1248, 1172, 1106, 1036, 912, 828, 737; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH),

5.52 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.2 Hz, H8), 4.37 (1H, ddd, *J* = 7.9, 5.9, 2.2 Hz, H18), 4.15 (1H, dd, *J* = 9.5, 6.2 Hz, H10), 3.98 (1H, ddd, *J* = 10.7, 5.3, 2.8 Hz, H16), 3.86 (1H, ddd, *J* = 7.6, 5.5, 2.1 Hz, H6), 3.82-3.80 (1H, m, H12), 3.79 (3H, s, OCH_3), 3.78-3.74 (1H, m, H5), 3.69 (3H, s, $COOCH_3$), 2.70 (1H, dd, *J* = 15.8, 7.8 Hz, H19), 2.49 (1H, dd, *J* = 15.8, 5.8 Hz, H19'), 2.41 (1H, qd, *J* = 9.3, 3.0 Hz, H7), 2.37-2.31 (1H, m, H3), 2.26-2.19 (1H, m, H3), 1.89 (1H, t, *J* = 2.5 Hz, H1), 1.84-1.42 (22H, m, H4, H11, H13, H14, H15, H17, H9-Me and cyclopent–CH_2), 1.35 (6H, s, acetonide), 1.30-1.13 (10H, m, hex-$(CH_2)_5$), 0.98 (3H, d, *J* = 6.7 Hz, H17-Me), 0.87 (3H, t, *J* = 6.7 Hz, hex–CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.7, 160.1, 137.1, 131.4, 127.6, 124.1, 117.6, 113.8, 101.7, 100.4, 84.3, 81.4, 80.8, 76.2, 70.8, 68.4, 66.6, 55.5, 51.9, 38.1, 38.0, 37.7, 37.5, 37.5, 36.0, 34.3, 33.2, 32.5, 32.0, 29.7, 28.5, 26.5, 25.1, 25.0, 23.9, 23.5, 22.8, 21.3, 15.2, 14.3, 13.9, 6.0; **HRMS** (ESI^+) calc. for $C_{45}H_{68}O_9Na$ $[M+Na]^+$ 775.4756, found 775.4747.

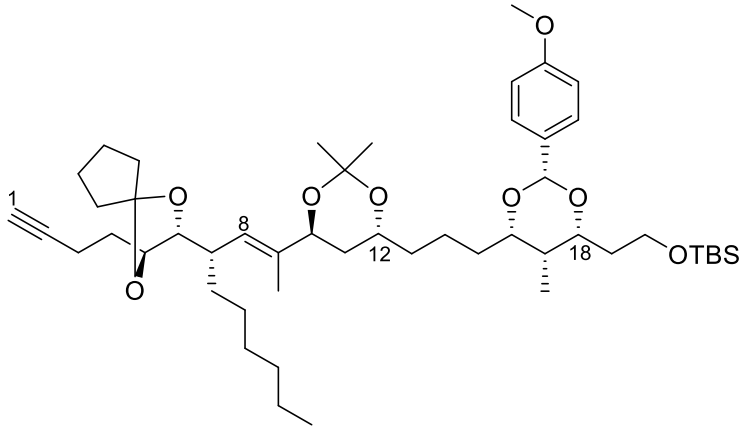
2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-3-(But-3-yn-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)dec-2-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)ethan-1-ol (E11)



To a solution of LiAlH4 (0.0298 g, 0.784 mmol, 2.1 equiv.) in Et_2O (1.9 mL) at -50 °C was added a solution of alkyne **E10** (0.281 g, 0.373 mmol, 1.0 equiv.) in Et_2O (1.9 mL) dropwise. After stirring at -50 °C for 30 min, the reaction mixture was diluted with EtOAc (1.0 mL) and quenched with sat. aq. Rochelle salt solution (5 mL). The resulting mixture was warmed to room temperature and stirred for another 10 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30% EtOAc/pentane) to afford alcohol **E11** (0.254 g, 0.350 mmol, 94%) as a colourless oil.

R_f 0.46 (40% EtOAc/pentane); **$[\alpha]_D^{25}$** –23.7 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3312, 2981, 2889, 1617, 1518, 1462, 1382, 1250, 1151, 1073, 955, 829; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.8 Hz, ArH), 5.52 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.2 Hz, H8), 4.18-4.12 (1H, m, H18), 4.09 (1H, dt, *J* = 9.8, 2.8 Hz, H10), 3.97 (1H, ddd, *J* = 10.7, 5.3, 2.9 Hz, H16), 3.88-3.80 (3H, m, H12, H6 and H5), 3.79 (3H, s, OCH_3), 3.79-3.73 (2H, m, H20), 2.45-2.30 (2H, m, H19), 2.23 (1H, dddd, *J* = 16.7, 8.6, 7.5, 2.7 Hz, H7), 2.07-1.97 (2H, m, H3), 1.88 (1H, t, *J* = 2.6 Hz, H1), 1.84-1.42 (22H, m, H4, H11, H13, H14, H15, H17, H9' and cyclopent–CH_2), 1.35 (6H, s, acetonide), 1.30-1.11 (10H, m, hex-$(CH_2)_5$), 1.00 (3H, d, *J* = 6.9 Hz, H17'), 0.87 (3H, t, *J* = 6.8 Hz, hex–CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.1, 137.1, 131.5, 127.6, 124.1, 117.7, 113.8, 101.7, 100.4, 84.3, 81.4, 81.2, 80.5, 76.2, 70.8, 68.4, 66.6, 61.3, 55.5, 38.1, 37.7, 37.5, 36.0, 35.4, 35.1, 33.2, 32.5, 32.0, 29.7, 28.5, 26.5, 25.1, 25.0, 23.9, 23.5, 22.8, 21.3, 15.2, 14.3, 13.9, 6.2; **HRMS** (ESI^+) calc. for $C_{44}H_{68}O_8Na$ $[M+Na]^+$ 747.4806, found 747.4799.

(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,3*S*)-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 (E12)

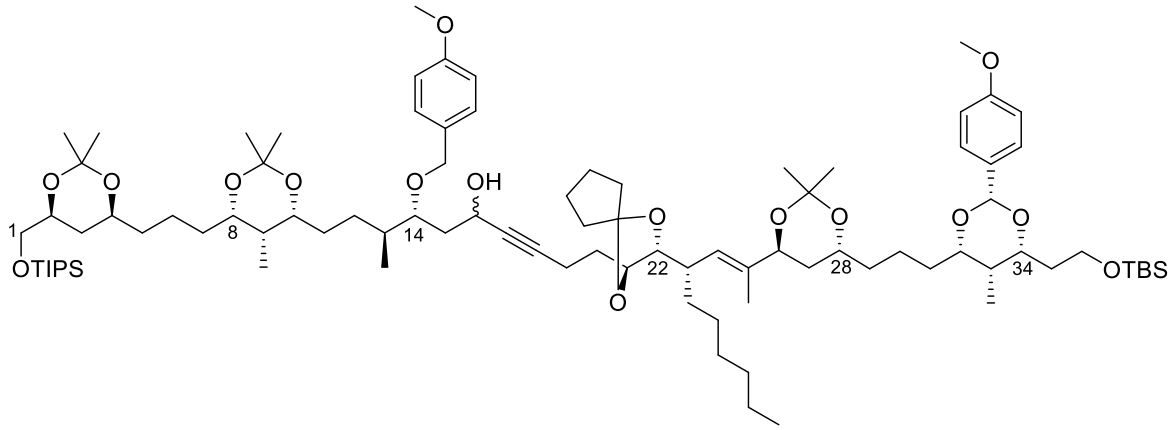


To a solution of alcohol **E11** (0.245 g, 0.338 mmol, 1.0 equiv.) in CH_2Cl_2 (3.4 mL) was added imidazole (0.0690 g, 1.01 mmol, 3.0 equiv.). The resulting mixture was cooled to 0 °C and then *tert*-butyldimethylsilyl chloride (0.0764 g, 0.507 mmol, 1.5 equiv.) was added portionwise. After stirring at room temperature overnight, the reaction mixture was quenched with water (5 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane) to afford title compound **E12** (0.259 g, 0.309 mmol, 91%) as a colourless oil.

R$_f$ 0.65 (12% EtOAc/pentane); $[\alpha]_D^{25}$ –14.6 (*c* = 0.50, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2955, 2931, 2857, 1617, 1518, 1462, 1379, 1249, 1106, 1069, 834, 776; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.46 (1H, s, PMP

actal), 5.09 (1H, d, *J* = 10.2 Hz,), 4.15 (1H, dd, *J* = 9.5, 6.2 Hz, H18), 4.02 (1H, ddd, *J* = 9.0, 4.0, 2.1 Hz, H10), 3.98 (1H, ddd, *J* = 10.7, 5.3, 2.9 Hz, H16), 3.84-3,80 (2H, m, H12 and H6), 3.79 (3H, s, OCH_3), 3.79-3.68 (3H, m, H5 and H20), 2.45-2.30 (2H, m, H19), 2.23 (1H, dtd, *J* = 16.6, 8.2, 2.6 Hz, H7), 1.89 (1H, t, *J* = 2.6 Hz, H1), 1.85-1.80 (2H, m, H3), 1.77-1.40 (22H, m, H4, H11, H13, H14, H15, H17, H9' and cyclopent–CH_2), 1.35 (6H, s, acetonide), 1.30-1.10 (10H, m, hex-$(CH_2)_5$), 0.96 (3H, d, *J* = 6.9 Hz, H17'), 0.91-0.85 (12H, m, $SiC(CH_3)_3$ and hex–CH_3), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 137.1, 131.9, 127.6, 124.1, 117.6, 113.7, 101.7, 100.4, 84.3, 81.4, 81.2, 76.2, 70.9, 68.4, 66.6, 59.5, 55.5, 38.1, 37.7, 37.5, 37.5, 36.0, 34.9, 33.2, 32.6, 32.0, 29.8, 28.5, 26.5, 26.1, 25.8, 25.1, 25.0, 23.9, 23.5, 22.8, 21.3, 18.5, 15.2, 14.3, 13.9, 6.1, -2.8, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{50}H_{82}O_8NaSi$ $[M+Na]^+$ 861.5671, found 861.5664.

(7*R*,8*S*)-1-((2*S*,3*S*)-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 (E13)



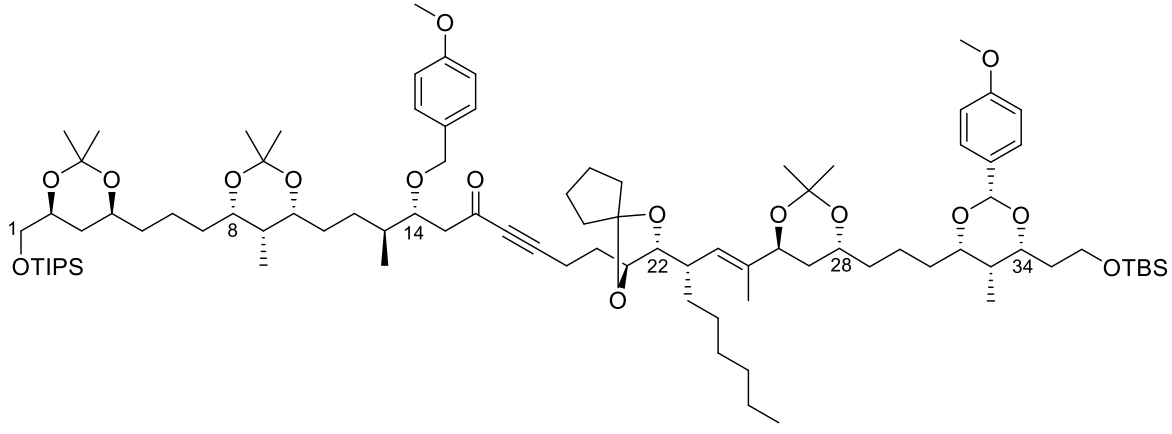
To a solution of alkyne **E12** (0.240 g, 0.286 mmol, 1.5 equiv) in THF (2.6 mL) at -78 °C was added *n*-butyl lithium (0.14 mL, 1.6 M in hexane, 0.229 mmol, 1.2 equiv.) dropwise. After stirring at -78 °C for 1 h, the reaction mixture was warmed to -30 °C and stirred for another 1 h. The reaction mixture was recooled to -78 °C and a solution of aldehyde **D2** (0.137 g, 0.191 mmol, 1.0 equiv) in THF (0.3 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h and warmed to -30 °C. After stirring at -30 °C for 1 h, the reaction mixture was warmed to 0 °C and stirred for 1 h. Then it was warmed to room temperature and stirred for further 1 h. The reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl solution (5.0 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc/pentane to 20% EtOAc/pentane) to afford title compound **E13** (top diastereomer: 0.075 g, 0.0481 mmol, 25%, mixture of top and bottom diastereomers: 0.160 g, 0.103 mmol, 54%, 1:1 *dr*) as a colourless oil.

R_f top diastereomer: 0.46, bottom diastereomer: 0.45 (16% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3463, 2937, 2864, 1615, 1515, 1463, 1379, 1249, 1171, 1110, 1068, 1037, 1010, 833, 776; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.28 – 7.22 (2H, m, ArH), 6.90 – 6.84 (4H, m, ArH), 5.46 (1H, s, PMP acetal), 5.07 (1H, d, *J* = 10.1 Hz, H24), 4.55 – 4.49 (2H, m, H16 and OCH_2Ar), 4.39 (0.5H d, *J* = 10.7 Hz, OCH_2Ar), 4.31 (0.5H d, *J* = 10.8 Hz, OCH_2Ar), 4.16 (1H, dd, *J* = 9.5, 6.1 Hz, H26), 4.02 (1H, ddd, *J* = 9.2, 4.0, 2.2 Hz, H34), 3.96-3.90 (2H, m, H14 and H32), 3.86-3.80 (4H, m, H28, H22, H21 and H2), 3.79 (6H, s, OCH_3), 3.78-3.68 (5.5H, m, H1,H4, H8, H10 and H36), 3.59 (0.5H dt, *J* = 11.1, 3.1 Hz, H36), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, 1H), 3.18 (0.5H, d, *J* = 2.8 Hz, OH), 3.04 (0.5H, d, *J* = 7.0 Hz, OH), 2.45-2.34 (2H, m, H35), 2.22 (1H, dq, *J* = 15.7, 7.3 Hz, H23), 1.94-1.48 (34H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H19, H20, H27, H29, H31 and H33), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.30-1.19 (10H, m, hex–CH_2), 1.17-1.02 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.93-0.85 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.83 (3H, d, *J* = 6.9 Hz, H13-Me), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 159.4, 137.1, 131.9, 130.6, 130.4, 129.7, 129.6, 128.8, 127.6, 124.9, 124.8, 117.6, 117.6, 114.1, 114.0,

114.0, 113.7, 101.6, 100.4, 98.9, 98.9, 98.5, 85.0, 84.9, 82.3, 81.3, 81.3, 81.2, 80.4, 77.5, 76.5, 76.5 73.9, 73.5, 71.3, 71.0, 71.3, 71.3, 70.2, 69.0, 67.4, 66.7, 62.4, 60.6, 59.5, 55.4, 55.4, 38.0, 38.0, 37.7, 37.5, 37.5, 37.4, 36.7, 36.1, 34.9, 34.8, 34.8, 34.7, 34.4, 33.1, 33.0, 33.0, 32.6, 32.0, 31.3, 31.2, 30.3, 30.3, 29.9, 29.7, 29.1, 29.1, 29.0, 28.9, 26.4, 26.1, 25.2, 24.9, 24.9, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 19.9, 18.5, 18.1, 15.7, 14.3, 13.9, 13.7, 13.6, 13.6, 12.1, 6.1, 4.8, 4.8, 1.2, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{154}O_{16}NaSi_2$ $[M+Na]^+$ 1583.0698, found 1583.0647.

(7*R*,8*S*)-1-((2*S*,3*S*)-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-((4R,5R,6S)-6-(3-((4S,6S)-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 (E14)



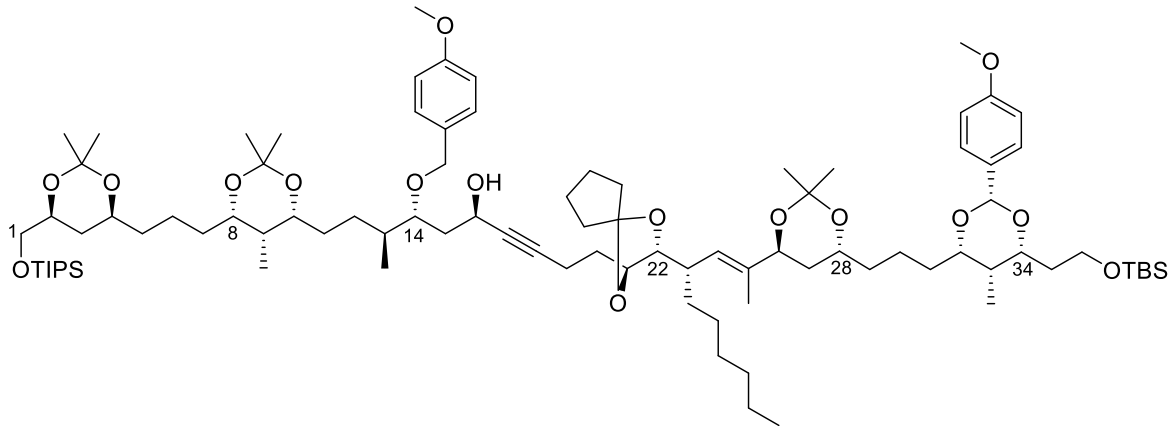
To a solution of alcohol **E13** (0.155 g, 0.0993 mmol, 1.0 equiv.) in CH_2Cl_2 (0.66 mL) and *t*-BuOH (0.5 mL) was added sodium bicarbonate (0.0835 g, 0.993 mmol, 10.0 equiv.) and Dess-Martin periodinane (0.0632 g, 0.149 mmol, 1.5 equiv.). After stirring at room

temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.0 mL) and sat. aq. $Na_2S_2O_3$ solution (1.0 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford compound **E14** (0.131 g, 0.0841 mmol, 85%) as a colourless oil.

R_f 0.53 (16% EtOAc/pentane); $[\alpha]_D^{25}$ +3.4 (*c* = 0.34, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2946, 2867, 1674, 1516, 1462, 1379, 1249, 1170, 1111, 833, 622; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.7 Hz, ArH), 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.92-6.85 (4H, m, ArH), 5.49 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.7 Hz, H24), 4.46 (2H, s, OCH_2Ar), 4.18 (1H, dd, *J* = 9.5, 6.2 Hz, H26), 4.05 (1H, ddd, *J* = 9.0, 4.0, 2.1 Hz, H34), 3.99-3.90 (3H, m, H14, H28 and H32), 3.88-3.82 (4H, m, H2, H4, H21 and H22), 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.80-3.71 (5H, m, H1, H8, H10 and H36), 3.55 (1H, dd, *J* = 9.7, 6.7 Hz, H1), 2.81 (1H, dd, *J* = 16.1, 8.8 Hz, H15), 2.61-2.52 (2H, m, H15 and H35), 2.46-2.34 (2H, m, H23 and H35), 1.92-1.50 (32H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H19, H20, H27, H29, H31 and H33), 1.47 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.36 (6H, s, acetonide), 1.33-1.22 (10H, m, hex–CH_2), 1.19-1.05 (27H, m, H6, H12, H30 and TIPS), 0.98 (3H, d, *J* = 6.8 Hz, H33-Me), 0.95 – 0.88 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.84 (3H, d, *J* = 6.8 Hz, H13-Me), 0.08 (3H, s, $Si(CH_3)_2$), 0.07 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.7, 159.9, 159.3,

137.4, 131.9, 130.8, 129.5, 127.6, 124.5, 117.7, 113.8, 113.7, 101.6, 100.4, 98.9, 98.5, 94.5, 81.5, 81.3, 81.2, 79.0, 76.1, 73.8, 73.5, 71.8, 71.2, 70.2, 69.0, 67.4, 66.7, 59.6, 55.4, 55.4, 47.2, 38.0, 37.7, 37.5, 36.7, 36.2, 36.1, 34.9, 34.7, 34.4, 33.2, 33.0, 32.6, 32.0, 31.0, 30.3, 30.2, 29.9, 29.7, 28.6, 28.1, 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, 15.9, 14.7, 14.3, 13.6, 12.1, 6.1, 4.8, 1.2, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{152}O_{16}NaSi_2$ $[M+Na]^+$ 1580.0511, found 1580.0482.

(5*R*,7*R*,8*S*)-1-((2*S*,3*S*)-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-((4R,5R,6S)-6-(3-((4S,6S)-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 (E15)



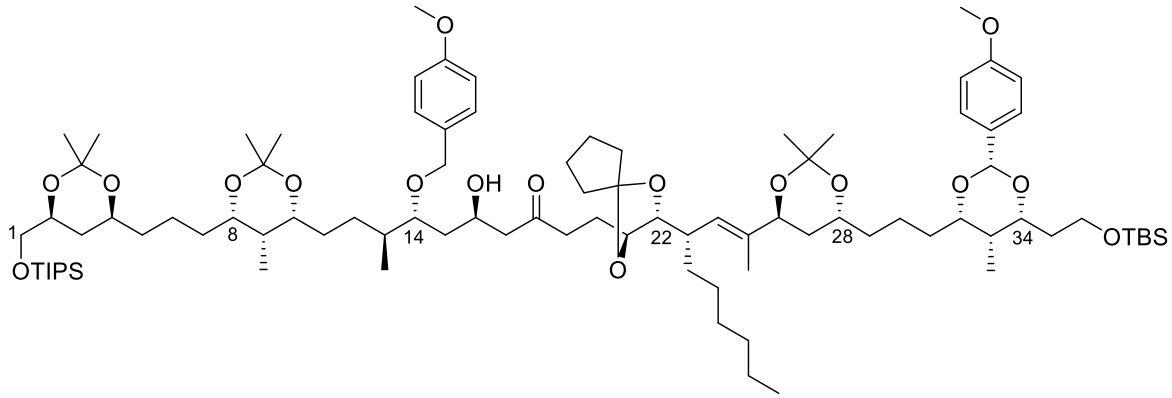
To a solution of ketone **E14** (0.123 g, 0.0789 mmol, 1.0 equiv.) in degassed 2-propanol (0.80 mL), was added a solution of Ru[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-*p*–Cymene)[2] (4.8 mg, 0.00789 mmol, 0.1 equiv.) in degassed CH_2Cl_2 (0.07 mL) dropwise. The resulting mixture was stirred at room temperature for 3 h and then concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane) to afford title compound **E15** (0.0781 g, 0.0500 mmol, 63%, >20:1 *dr*) as a yellow oil and recovered starting material **E14** (0.0392 g, 0.0252 mmol).

R_f 0.46 (16% EtOAc/pentane); $[\alpha]_D^{25}$ +9.3 (*c* = 0.25, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3472, 2938, 2864, 1615, 1516, 1462, 1379, 1248, 1171, 1109, 1067, 1038, 1010, 833, 776; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.26 (2H, d, *J* = 8.7 Hz, ArH), 6.90-6.83 (4H, m, ArH), 5.46 (1H, s, PMP acetal), 5.07 (1H, d, *J* = 10.1 Hz, H24), 4.56 – 4.48 (2H, m, H16 and OCH_2Ar), 4.39 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.16 (1H, dd, *J* = 9.5, 6.1 Hz, H26), 4.02 (1H, ddd, *J* = 9.1, 4.0, 2.1 Hz, H34), 3.96-3.90 (2H, m, H14 and H32), 3.86-3.80 (4H, m, H28, H22, H21 and H2), 3.79 (6H, s, OCH_3), 3.78-3.67 (6H, m, H1,H4, H8, H10 and H36), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1), 3.04 (1H, d, *J* = 7.0 Hz, OH), 2.45-2.36 (2H, m, H35), 2.27-2.17 (1H, m, H23), 1.95-1.48 (34H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H19, H20, H27, H29, H31 and H33), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.34 (6H, s, acetonide), 1.30-1.19 (10H, m, hex–CH_2), 1.17-1.02 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.92-0.84 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 159.4, 137.1, 131.9, 130.6, 129.7, 127.6, 124.9, 117.6, 114.0, 113.7, 101.6, 100.4, 98.9, 98.5, 85.0, 81.6, 81.3, 81.2, 80.4, 77.5, 76.5, 73.9, 73.5, 71.3, 71.3, 70.2, 69.0, 67.4, 66.7, 60.6, 59.6, 55.4, 55.4, 38.0, 37.7, 37.5, 37.4, 36.7, 36.6, 36.1, 34.9, 34.8, 34.7, 34.4, 33.1, 33.0, 32.6, 32.0, 31.2, 30.3, 30.3, 29.9, 29.7, 29.1, 29.0, 26.4, 26.1,

25.2, 24.9, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 15.7, 14.3, 13.9, 13.6, 12.1, 6.1, 4.8, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{154}O_{16}NaSi_2$ $[M+Na]^+$ 1583.0698, found 1583.0675.

(5*R*,7*R*,8*S*)-1-((2*S*,3*S*)-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-((4R,5R,6S)-6-(3-((4S,6S)-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 (E16)



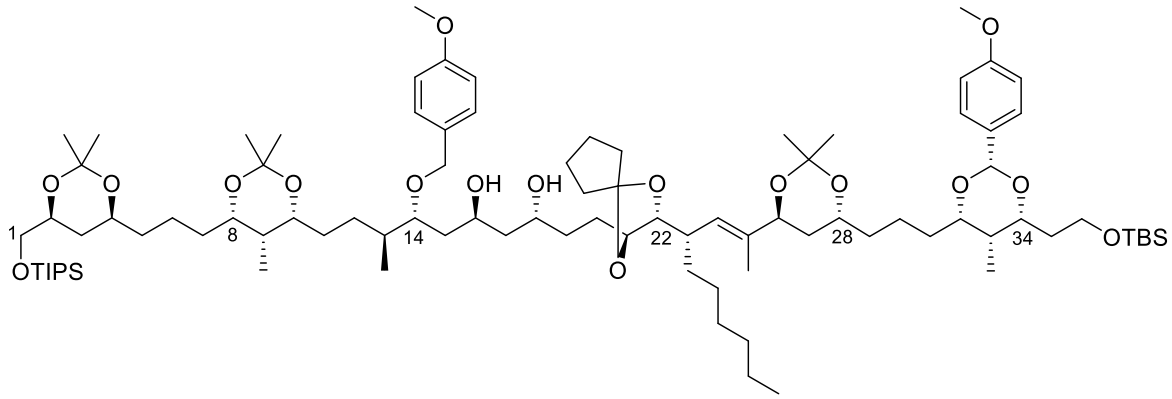
To a solution of propargylic alcohol **E15** (0.0825 g, 0.0529 mmol, 1.0 equiv.) in Et_2O (0.26 mL) was added bis(pinacolato)diboron (0.0322 g, 0.127 mmol, 2.4 equiv.) and sodium *tert*-butoxide (97%) (0.0032 g, 0.0317 mmol, 0.6 equiv.). The resulting mixture was cooled to 0°C and IMesCuI (0.0021 g, 0.00529 mmol, 0.10 equiv.) was added, followed by slow addition of anhydrous methanol (0.0086 mL, 0.211 mmol, 4.0 equiv.). After stirring at 0°C for 40 min, the resulting dark brown–Coloured mixture was quenched with 2 to 3 drops of triethanolamine and stirred for 10 min at 0°C and another10 min at room temperature. The

resulting mixture was diluted with Et_2O and filtered through a celite pad. The filtrate was washed with brine and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in THF (0.66 mL) and water (0.66 mL), followed by addition of sodium perborate monohydrate (0.0264 g, 0.264 mmol, 5.0 equiv.) After stirring at room temperature overnight, the reaction mixture was quenched with water (2.0 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 16% EtOAc/pentane) to afford hydroxyketone **E16** (0.0679 g, 0.0430 mmol, 81%) as a colourless oil.

R_f 0.25 (16% EtOAc/pentane); $[\alpha]_D^{25}$ -3.5 (*c* = 0.35, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3473, 2939, 2864, 1706, 1615, 1516, 1462, 1379, 1249, 1200, 1172, 1110, 1069, 1037, 1010, 833, 777; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.25 (2H, d, *J* = 8.7 Hz, ArH), 6.89-6.84 (4H, m, ArH), 5.46 (1H, s, PMP acetal), 5.06 (1H, d, *J* = 9.9 Hz, H24), 4.50 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.40 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.29-4.23 (1H, m, H16), 4.19-4.14 (1H, m, H26), 4.04-4.00 (1H, m, H34), 3.96-3.90 (1H, m, H14), 3.86-3.80 (4H, m, H32, H28, H22 and H21), 3.79 (6H, s, 6H), 3.78-3.67 (6H, m, H36, H10, H8, H4, H2 and H1), 3.61-3.56 (1H, m, H36), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1), 3.33 (1H, d, *J* = 3.4 Hz, OH), 2.61-2.50 (3H, m, H17 and H35), 2.48-2.38 (2H, m, H35 and H23), 1.91-1.47 (34H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H19, H20, H27, H29, H31 and H33), 1.44 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.34 (6H, s, acetonide), 1.30-1.19 (10H, m, hex–CH_2), 1.16-1.03 (27H, m, H6,

H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.92-0.85 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.81 (3H, d, *J* = 6.8 Hz, H13-Me), 0.05 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.7, 159.9, 159.3, 137.3, 131.9, 131.0, 129.6, 127.6, 124.5, 117.6, 114.0, 113.7, 101.6, 100.4, 98.9, 98.5, 81.4, 81.2, 79.6, 77.5, 76.8, 73.8, 73.5, 71.7, 71.2, 70.2, 69.0, 67.4, 66.7, 65.1, 59.5, 55.4, 55.4, 50.0, 40.1, 37.8, 37.6, 37.4, 37.4, 36.7, 36.6, 36.1, 35.4, 34.9, 34.6, 34.4, 33.2, 33.0, 32.5, 32.0, 31.1, 30.3, 30.3, 29.7, 28.9, 26.4, 26.1, 25.2, 25.0, 25.0, 23.8, 23.6, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.3, 14.2, 13.7, 12.1, 6.1, 4.7, 1.2, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{156}O_{17}NaSi_2$ $[M+Na]^+$ 1600.0773, found 1600.0769.

(3*R*,5*S*,7*R*,8*S*)-1-((2*S*,3*S*)-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-((4R,5R,6S)-6-(3-((4S,6S)-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 (E17)

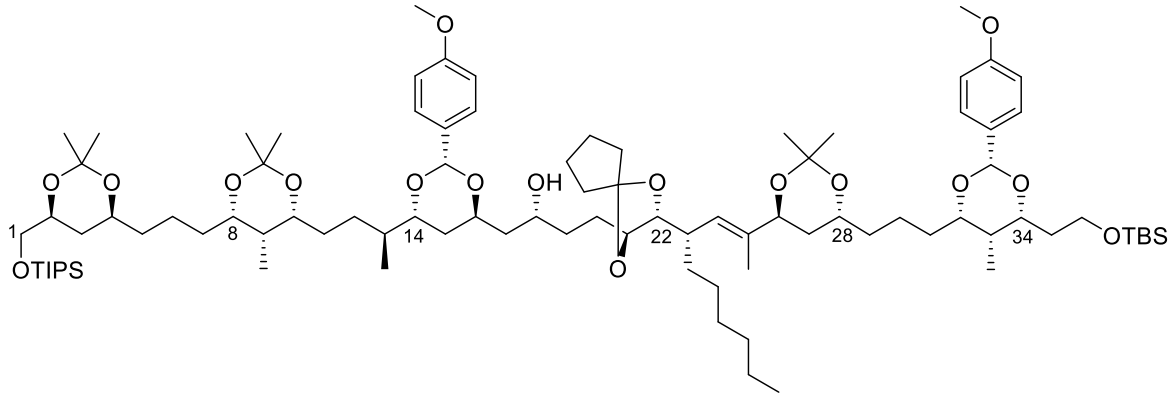


To a suspension of tetramethylammonium triacetoxyborohydride (0.253 g, 0.963 mmol, 8.0 equiv.) in anhydrous acetonitrile (3.0 mL) was added acetic acid (3.0 mL). After stirring at room temperature for 1 h, the reaction mixture was cooled to -10.5 °C and a solution of hydroxyketone **E16** (0.190 g. 0.120 mmol, 1.0 equiv.) in anhydrous acetonitrile (3.0 mL) was added dropwise. After stirring at -10.5 °C for 27 h, the reaction mixture was quenched with sat. aq. Rochelle salt (5.0 mL), warmed to room and stirred for 10 min, upon which white precipitate was formed. The reaction mixture was poured over ice, neutralized with sat. aq. $NaHCO_3$ solution (20 mL) and stirred until the layers turned clear. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane to 30% EtOAc/pentane) to afford diol **E17** (0.139 g, 0.0880 mmol, 73%, >20:1 *dr*) as a colourless oil.

R_f 0.14 (24% EtOAc/pentane); $[\alpha]_D^{25}$ -8.8 (*c* = 1.37, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1})3427, 2981, 2360, 1616, 1516, 1462, 1380, 1250, 1152, 1038,833; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.25 (2H, d, *J* = 8.7 Hz, ArH), 6.90 – 6.84 (4H, m, ArH), 5.46 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.2 Hz, H24), 4.49 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.43 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.20-4.15 (2H, m, H26 and H16), 4.04-4.00 (1H, m, H34), 3.96-3.90 (1H, m, H14), 3.89-3.85 (2H, m, H32 and H18), 3.85-3.80 (4H, m, H28, H22, H21 and H2), 3.79 (6H, s, OCH_3), 3.78-3.69 (5H, m, H36, H10, H8, H4 and H1), 3.56-3.50 (2H, m, H36 and H1), 3.17 (1H, d, *J* = 4.3 Hz, OH), 2.79 (1H, d, *J* = 5.3 Hz, OH), 2.47-

2.41 (1H, m, H23), 1.91-1.49 (38H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31, H33 and H35), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.30-1.20 (10H, m, hex–CH_2), 1.16 – 1.03 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.91 – 0.85 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.9, 159.4, 136.6, 132.0, 130.7, 129.7, 127.6, 126.4, 117.4, 114.0, 113.7, 101.6, 100.5, 98.9, 98.5, 81.3, 81.2, 80.4, 78.5, 77.5, 73.9, 73.5, 72.0, 71.4, 70.2, 69.6, 69.0, 67.4, 66.7, 66.5, 59.6, 55.5, 55.4, 43.4, 38.1, 37.8, 37.4, 37.0, 36.7, 36.2, 36.1, 35.2, 34.9, 34.6, 34.6, 34.4, 33.0, 32.8, 32.6, 32.0, 31.0, 30.3, 30.3, 29.9, 29.7, 29.0, 26.5, 26.1, 25.9, 25.3, 25.0, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 14.5, 14.3, 13.4, 12.1, 6.1, 4.8, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{158}O_{17}NaSi_2$ $[M+Na]^+$ 1602.0930, found 1602.0888.

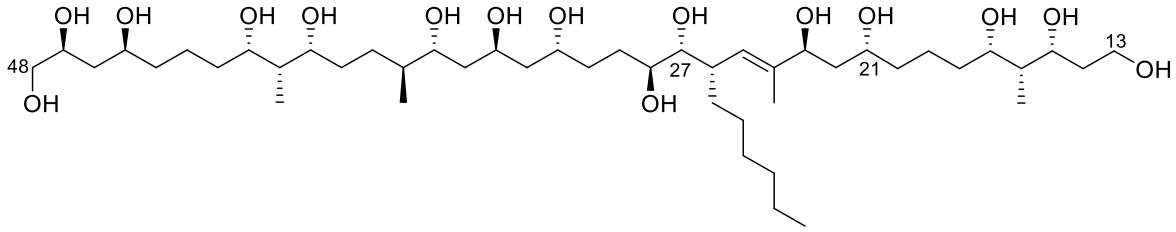
(*R*)-4-((2*S*,3*S*)-3-((*S*,*E*)-2-((4*S*,6*R*)-6-(3-((2*S*,4*S*,5*R*,6*R*)-6-(2-((Tert-butyldimethylsilyl)oxy)ethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)dec-2-en-4-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-1-((2R,4S,6R)-6-((S)-4-((4R,5R,6S)-6-(3-((4S,6S)-2,2-dimethyl-6-(((triisopropylsilyl)oxy)methyl)-1,3-dioxan-4-yl)propyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-yl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)butan-2-ol (E18)



To a solution of diol **E17** (0.0551g, 0.0349 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) was added 3 Å molecular sieves (0.027 g). The reaction mixture was cooled to -10 °C and DDQ (0.0095 g, 0.0418 mmol, 1.2 equiv.) was added slowly. After stirring at -10 °C for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.0 mL), filtered through a celite pad and washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 20% EtOAc/pentane) to afford title compound **E18** (0.0230 g, 0.0146 mmol, 42%) as a colourless oil.

R_f 0.30 (20% EtOAc/pentane); **$[\alpha]_D^{25}$** -13.0 (*c* = 0.96, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3468, 2981, 2889, 1819, 1381, 1250, 1151, 1115, 1072, 954, 830, 775; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44-7.36 (4H, m, ArH), 6.87 (4H, dd, *J* = 8.7, 1.8 Hz, ArH), 5.68 (1H, s, PMP acetal), 5.46 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.2 Hz, H24), 4.57-4.50 (1H, m, H18), 4.17 (1H, dd, *J* = 9.5, 6.2 Hz, H26), 4.04-3.99 (1H, m, H34), 3.96-3.86 (3H, m, H14, H16 and H32), 3.85-3.81 (4H, m, H2, H21, H22 and H28), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.78-3.68 (6H, m, H1, H4, H8, H10 and H36), 3.52 (1H, dd, *J* = 9.7, 6.7 Hz, H1), 2.48-2.39 (1H, m, H23), 2.38-2.30 (2H, m, H17 and H35), 2.02 (1H, td, *J* = 12.8, 6.4 Hz, H17), 1.89-1.49 (35H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H19, H20, H27, H29, H31, H33 and H35), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.32 (3H, s, acetonide), 1.28-1.19 (s, 10H, m, hex–CH_2), 1.17-1.02 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.93-0.84 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.80 (3H, d, *J* = 6.8 Hz, H13-Me), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 136.6, 131.9, 131.9, 127.6, 127.5, 126.3, 117.4, 113.7, 113.7, 101.6, 100.5, 98.8, 98.5, 94.3, 81.3, 81.2, 78.5, 76.3, 73.8, 73.4, 71.9, 70.2, 69.7, 69.0, 69.0, 67.4, 66.7, 59.5, 55.5, 38.2, 38.0, 37.8, 37.3, 37.0, 36.7, 36.1, 35.0, 34.9, 34.4, 34.2, 33.0, 32.8, 32.6, 32.0, 31.6, 30.3, 29.9, 29.8, 29.7, 27.6, 26.5, 26.1, 25.3, 25.0, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.5, 18.1, 15.0, 14.3, 13.4, 12.1, 6.1, 4.6, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{91}H_{156}O_{17}NaSi_2$ $[M+Na]^+$ 1600.0773, found 1600.0734.

(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 (E19)

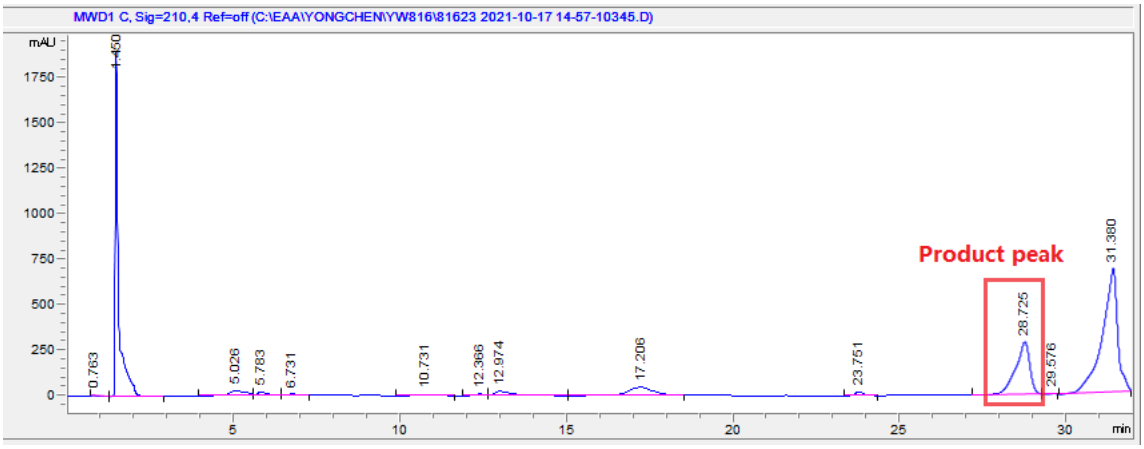


To a solution of compound **E18** (0.0221 mg, 0.0140 mmol, 1.0 equiv.) in methanol (1.4 mL) and THF (0.7 mL), was added aq. HCl solution (1.4 mL, 0.2 M) dropwise. After stirring at room temperature overnight, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.5 mL) and concentrated directly under reduced pressure. The residue was purified by reverse phase HPLC (100% water to 35% acetonitrile/water gradient over 40 min) to give **E19** (5.6 mg, 0.00632 mmol, 45%, not very pure) as a colourless oil. (HPLC: Product peak is obviously visible at 210 nm or 220 nm wavelength and the retention time is 28.7 min.)

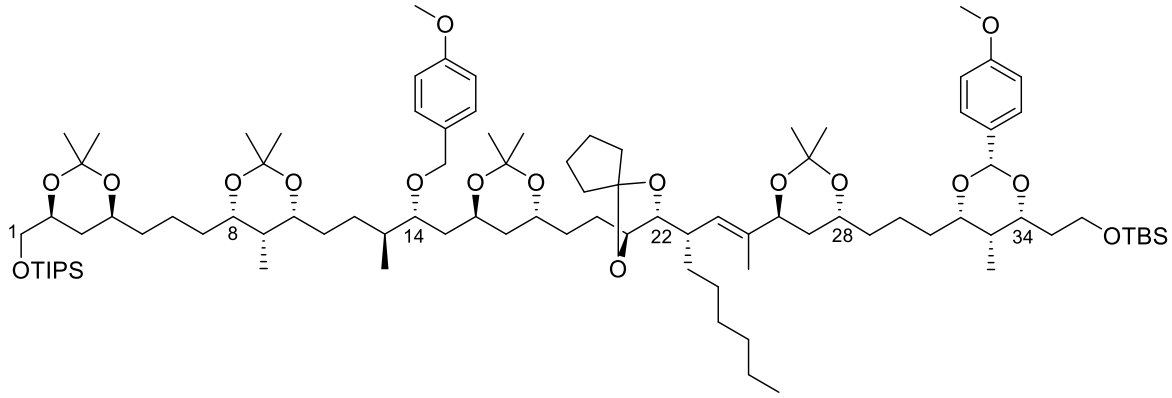
R_f 0.46 (30% MeCN/H_2O, reverse phase TLC plate); $[\alpha]_D^{25}$ -1.4 (*c* = 0.67, MeOH); **IR** (thin film, ν_{max} / cm^{-1}) 3386, 2981, 2889, 2499, 1462, 1383, 1252, 1152, 1120, 1073, 969, 688; **^{1}H NMR** (600 MHz, MeOD) δ 5.23 (1H, d, *J* = 10.5 Hz, H25), 4.23 (1H, dd, *J* = 9.1, 3.7 Hz, H23), 4.08 (1H, tq, *J* = 9.5, 3.2, 2.5 Hz, H33), 3.89 (1H, ddd, *J* = 8.2, 4.9, 3.7 Hz, H47), 3.85-3.77 (3H, m, H31 and H48), 3.77-3.67 (7H, m, H13, H15, H17, H35, H39 and H41), 3.66-3.65 (1H, m, H21), 3.51 (1H, dd, *J* = 11.2, 4.6 Hz, H28), 3.46 (1H, dd, *J* = 11.2, 6.0 Hz, H45), 3.38-3.34 (1H, m, H27), 2.50-2.44 (1H, m, H26), 1.81-1.76 (1H, m, hex–CH_2), 1.74-1.67 (4H, m, H16, H22, H29 and H30), 1.66 (3H, d, *J* = 1.4 Hz, 24-Me), 1.63-1.41 (25H, m,

H14, H20, H22', hex–CH_2, H29', H30', H32, H34, H36, H37, H38, H40, H42, H43 and H44), 1.40-1.21 (9H, m, H19 and hex–CH_2), 1.17-1.10 (2H, m, H37' and hex–CH_2), 0.96-0.87 (12H, m, 16-Me, 36-Me, 40-Me and hex-Me); **^{13}C NMR** (151 MHz, MeOD) δ 139.7, 128.2, 79.6, 76.4, 75.9, 75.6, 75.1, 73.9, 73.3, 72.9, 72.1, 71.0, 69.6, 69.3, 67.3, 66.6, 60.5, 46.3, 44.0, 43.6, 42.8, 41.9, 41.6, 41.3, 40.7, 38.8, 38.6, 38.6, 36.1, 36.0, 35.7, 33.8, 33.1, 32.1, 30.8, 29.8, 28.3, 28.3, 23.8, 23.3, 23.0, 15.7, 14.5, 12.9, 7.3, 7.0; **HRMS** (ESI^+) calc. for $C_{46}H_{92}O_{15}Na$ $[M+Na]^+$ 907.6328, found 907.6317.

HPLC analysis of crude compound E19 before purification by semi-preparative reverse phase HPLC (Eclipse XDB–C18 column, eluent system: 100% water to 35% acetonitrile/water gradient over 40 min, injection volume: 5µL, flow rate: 1.0 mL/min, λ = 210 nm): t_R = 28.7 min (product) (Only product peak is visible in reverse phase TLC plates and other peaks are invisible in reverse phase TLC plates.



Tert-butyl(2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,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 (E20)

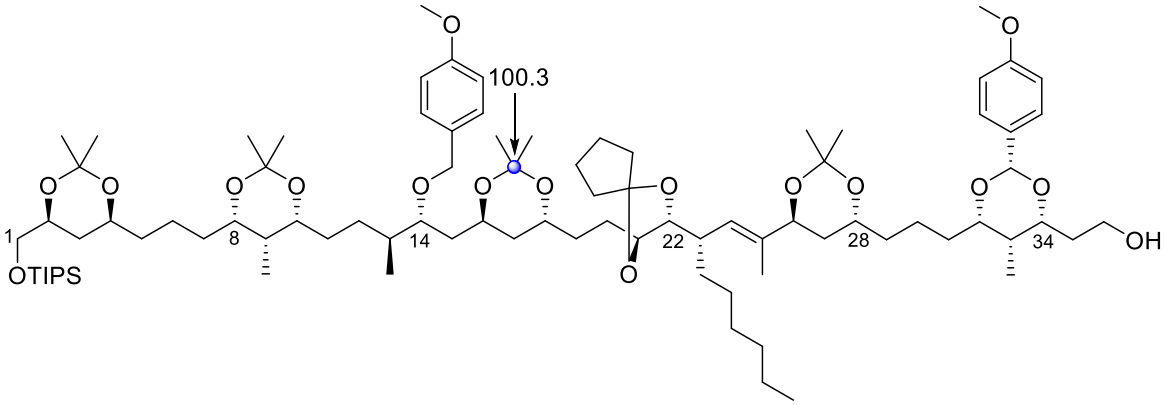


To a solution of diol **E17** (0.121 g, 0.0766 mmol, 1.0 equiv.) in CH_2Cl_2 (0.38 mL) and 2,2-dimethoxypropane (98%) (0.39 mL) was added pyridinium *p*-toluenesulfonate (1.5 mg, 0.00612 mmol, 0.08 equiv.). After stirring at room temperature for 20 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.0 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **E20** (0.103 g, 0.0636 mmol, 83%) as a colourless oil.

R_f 0.63 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -11.9 (*c* = 0.25, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2930, 2862, 2361, 1732, 1616, 1515, 1462, 1378, 1250, 1170, 1110, 1069, 1038, 1010, 833;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.90 – 6.82 (4H, m, ArH), 5.46 (1H, s, PMP acetal), 5.06 (1H, d, *J* = 10.1 Hz, H24), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.33 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.15 (1H, dd, *J* = 9.4, 6.0 Hz, H26), 4.04-4.00 (2H, m, H16 and H34), 3.96-3.90 (1H, m, H14), 3.86 – 3.80 (5H, m, H18, H21, H22, H28 and H32), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.78-3.74 (4H, m, H2, H4, H8 and H10), 3.73-3.68 (2H, m, H1 and H36), 3.55-3.51 (2H, m, H1 and H36), 2.47-2.38 (1H, m, H23), 1.89-1.46 (38H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31, H33 and H35), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.31 (3H, s, acetonide), 1.30 (3H, s, acetonide), 1.28-1.18 (10H, m, hex–CH_2), 1.17-1.01 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.8 Hz, H33-Me), 0.92-0.85 (15H, m, H9-Me, hex–CH_3 and $SiC(CH_3)_3$), 0.82 (3H, d, *J* = 6.9 Hz, H13-Me), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.9, 159.3, 136.9, 132.0, 131.3, 129.4, 127.6, 124.9, 117.4, 114.0, 113.7, 101.6, 100.4, 100.3, 98.9, 98.5, 81.4, 81.2, 79.2, 78.1, 77.5, 73.9, 73.5, 71.6, 71.1, 70.2, 69.0, 67.4, 67.3, 66.7, 63.6, 59.6, 55.5, 55.4, 39.4, 38.0, 37.8, 37.5, 37.3, 36.8, 36.7, 36.1, 36.1, 35.3, 34.9, 34.5, 34.4, 33.0, 33.0, 32.6, 32.0, 31.3, 30.3, 30.3, 29.8, 28.7, 26.5, 26.1, 26.0, 25.2, 25.2, 25.1, 25.0, 23.9, 23.5, 22.8, 21.4, 21.2, 20.0, 19.9, 18.5, 18.1, 14.3, 14.1, 13.7, 12.1, 6.1, 4.7, -5.1, -5.2; **HRMS** (ESI^+) calc. for $C_{94}H_{162}O_{17}NaSi_2$ $[M+Na]^+$ 1642.1243, found 1642.1197.

2-((2*S*,4*R*,5*R*,6*S*)-6-(3-((4*R*,6*S*)-6-((*S*,*E*)-4-((2*S*,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 (E21)

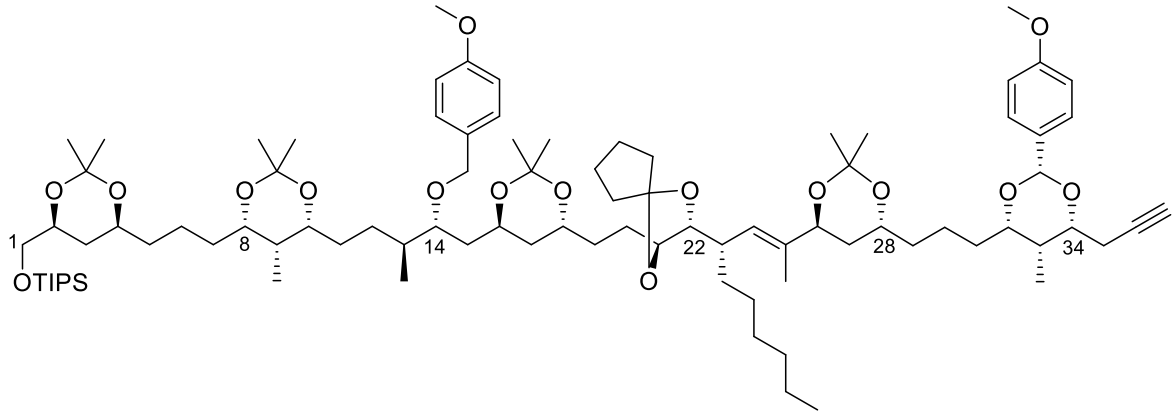


To a solution of **E20** (0.145 g, 0.0895 mmol, 1.0 equiv.) in THF (1.7 mL) was added acetic acid (5.1µL, 0.0895 mmol, 1.0 equiv.) and TBAF (89µL, 0.0895 mmol, 1.0 equiv.). After stirring at room temperature for 12 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (1.0 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **E21** (0.0921 g, 0.0611 mmol, 69%, after 4 recycles) as a colourless oil and recovered starting material **E20** (0.0212g, 0.0131 mmol).

R_f 0.24 (30% EtOAc/pentane); $[\alpha]_D^{25}$ -11.1 (*c* = 0.68, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3483, 2937, 2866, 1615, 1515, 1462, 1379, 1248, 1171, 1111, 1070, 1038, 1010, 827; **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.7 Hz, ArH), 7.27 (2H, d, *J* = 8.6 Hz, ArH), 6.93-6.85 (4H, m, ArH), 5.54 (1H, s, PMP acetal), 5.09 (1H, d, *J* = 10.0 Hz, H24), 4.51 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.34 (1H, d, *J* = 10.8 Hz, OCH_2Ar), 4.17 (1H, dd, *J* = 9.4, 6.0 Hz, H26), 4.13-4.02 (2H, m, H16 and H34), 3.95 (1H, dt, *J* = 7.0, 4.7 Hz, H14), 3.90-3.82 (6H, m, H2, H18, H21, H22, H28, H32), 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.80-3.70 (5H, m, H1, H4, H8, H10, H36), 3.58-3.52 (2H, m, H1 and H36), 2.49-2.41 (1H, m, H23), 2.14-1.97 (2H, m, H35), 1.91-1.49 (36H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31 and H33), 1.47 (3H, s, acetonide), 1.44 (3H, s, acetonide), 1.42 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.37 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.33 (6H, s, acetonide), 1.30-1.22 (10H, m, hex–CH_2)1.19-1.05 (27H, m, H6, H12, H30 and TIPS), 1.01 (3H, d, *J* = 6.9 Hz, H33-Me), 0.93-0.88 (6H, m, H9-Me and hex–CH_3), 0.85 (3H, d, *J* = 6.8 Hz, H13-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.1, 159.3, 136.9, 131.5, 131.2, 129.5, 127.6, 124.7, 117.4, 114.0, 113.8, 101.7, 100.3, 100.3, 98.9, 98.5, 81.4, 81.2, 80.4, 79.2, 78.1, 73.9, 73.5, 71.6, 71.0, 70.2, 69.0, 67.4, 67.3, 66.6, 63.6, 61.2, 55.5, 55.4, 39.5, 38.0, 37.8, 37.5, 37.4, 36.7, 36.0, 35.4, 35.3, 35.1, 34.5, 34.4, 33.1, 33.0, 32.5, 32.0, 31.3, 30.3, 30.3, 29.9, 29.8, 28.7, 26.5, 26.1, 26.0, 25.2, 25.1, 25.0, 23.9, 23.5, 22.8, 21.3, 21.2, 20.0, 19.9, 18.1, 14.3, 14.1, 13.7, 12.1, 6.2, 4.7; **HRMS** (ESI^+) calc. for $C_{88}H_{148}O_{17}NaSi$ $[M+Na]^+$ 1528.0378, found 1528.0336.

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*S*)-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 (E22)



To a solution of alcohol **E21** (0.089 g, 0.0591 mmol, 1.0 equiv.) in CH_2Cl_2 (0.40 mL) was added sodium bicarbonate (0.0596 g, 0.709 mmol, 12.0 equiv.) and Dess-Martin periodinane (0.0752 g, 0.177 mmol, 3.0 equiv.). After stirring at room temperature for 1 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (1.0 mL) and sat. aq. $Na_2S_2O_3$ solution (1.0 mL) at 0 °C, stirring for further 15 min to allow complete quenching. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude aldehyde (0.0705 g, 0.0469 mmol).

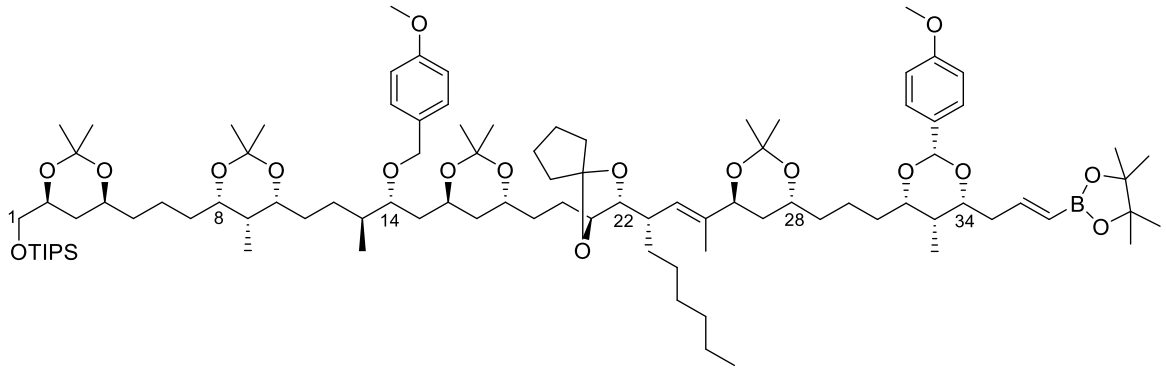
To a solution of Ohira-Bestmann reagent **E9** (0.0810 g, 0.422 mmoL, 9.0 equiv.) in anhydrous methanol (0.65 mL) was added potassium carbonate (0.0596 g, 0.431 mmoL, 9.2 equiv.), followed by a solution of crude aldehyde (0.0705 g, 0.0469 mmoL, 1.0 equiv.) in

anhydrous methanol (0.45 mL). After stirring at room temperature for 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (1.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 20% EtOAc/pentane) to afford alkyne **E22** (0.0384 g, 0.0256 mmol, 55%) as a colourless oil.

R_f 0.70 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -10.0 (*c* = 0.30, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2937, 2866, 2361, 2339, 1615, 1516, 1461, 1379, 1248, 1171, 1110, 1067, 1038, 1012, 824; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.24 (2H, d, *J* = 8.7 Hz, ArH), 6.90 – 6.84 (4H, m, ArH), 5.48 (1H, s, PMP acetal), 5.07 (1H, d, *J* = 9.9 Hz, H24), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.33 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.18-4.12 (1H, m, H26), 4.05-4.00 (2H, m, H34 and H16), 3.96-3.90 (1H, m, H22), 3.88-3.81 (5H, m, H32, H28, H16, H14 and H10), 3.79 (3H, s, acetonide), 3.78 (3H, s, acetonide), 3.77-3.68 (4H, m, H1, H2, H4, H8), 3.55-3.51 (2H, m, H1 and H21), 2.60-2.55 (1H, m, H35), 2.47-2.40 (2H, m, H35 and H23), 1.99 (1H, t, *J* = 2.6 Hz, H37), 1.89-1.46 (36H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31 and H33), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.35 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.31 (3H, s, acetonide), 1.30 (3H, s, acetonide), 1.28-1.19 (10H, m, hex–CH_2), 1.16-1.03 (27H, m, H6, H12, H30 and TIPS), 0.98 (3H, d, *J* = 6.9 Hz, H33-Me), 0.92-0.79 (9H, m, H9-Me, hex–CH_3 and H13-Me); **^{13}C NMR** (151 MHz,

$CDCl_3$) δ 160.1, 159.3, 136.9, 131.4, 131.3, 129.4, 127.7, 124.8, 117.4, 114.0, 113.8, 101.7, 100.4, 100.3, 98.9, 98.5, 81.4, 81.0, 80.1, 79.2, 79.0, 78.1, 73.9, 73.5, 71.6, 71.1, 70.2, 69.0, 67.4, 67.3, 66.6, 63.6, 55.5, 55.4, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.7, 36.1, 35.3, 34.5, 34.4, 33.2, 33.1, 33.0, 32.6, 32.1, 32.0, 31.3, 30.5, 30.3, 30.3, 29.9, 29.8, 29.8, 29.5, 29.4, 28.7, 26.5, 26.1, 26.0, 25.2, 25.2, 25.1, 25.0, 24.9, 23.9, 23.5, 22.8, 22.8, 22.6, 21.4, 21.2, 20.0, 19.9, 18.1, 14.3, 14.1, 13.7, 12.1, 5.4, 4.7; **HRMS** (ESI^+) calc. for $C_{89}H_{146}O_{16}NaSi$ $[M+Na]^+$ 1522.0272, found 1522.0242.

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*S*)-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)methoxy)silane (E23)



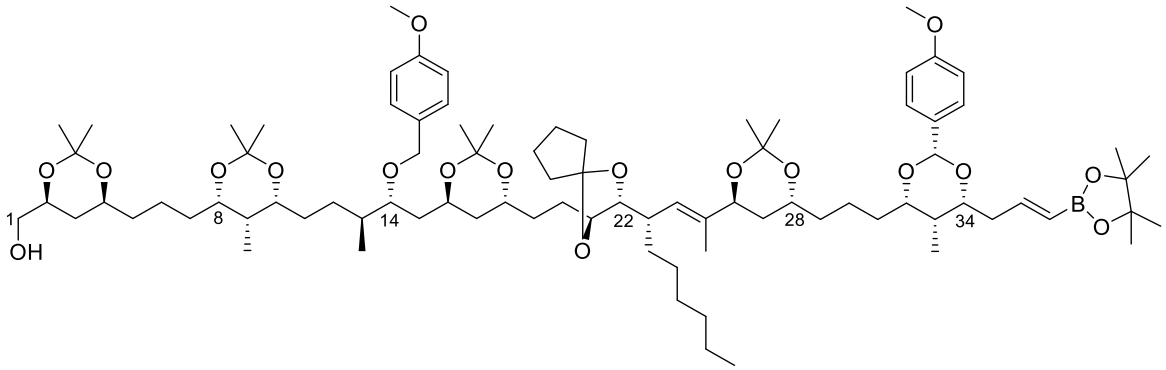
To a solution of alkyne **E22** (0.0351 g, 0.0234 mmol, 1.0 eq.) and pinacolborane (50.9 µL, 1.300 mmol, 15.0 eq.) was added bis(cyclopentadienyl)zirconium chloride hydride (1.2 mg, 0.00468 mmol, 0.2 eq.), followed by anhydrous triethylamine (3.9 µL, 0.0281 mmol, 1.2 eq.). The resulting mixture was heated at 60 °C for 2 h and then cooled to room temperature.

The reaction mixture was diluted with Et_2O (0.5 mL) and quenched with brine (0.5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 1.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/pentane) to afford title compound **E23** (0.0298 g, 0.0183 mmol, 78%) as a colourless oil.

R_f 0.65 (20% EtOAc/pentane); $[\alpha]_D^{25}$ -9.4 (*c* = 0.34, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2932, 2864, 2360, 2341, 1616, 1516, 1461, 1378, 1248, 1171, 1112, 1070, 1038, 1010, 826; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.8 Hz, ArH), 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.90-6.82 (4H, m, ArH), 6.57 (1H, ddd, *J* = 17.9, 7.6, 5.9 Hz, H36), 5.56 (1H, dd, *J* = 18.0, 1.5 Hz, H37), 5.47 (1H, s, PMP acetal), 5.06 (1H, d, *J* = 10.0 Hz, H24), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.32 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.18-4.11 (1H, m, H26), 4.06-3.99 (1H, m, H16), 3.96-3.90 (2H, m, H34 and H22), 3.88-3.80 (4H, m, H32, H28, H18 and H14), 3.79 (3H, s, acetonide), 3.78 (3H, s, acetonide), 3.78-3.67 (5H, m, H1, H2, H4, H8 and H10), 3.55-3.50 (2H, m, H1 and H21), 2.59-2.52 (1H, m, H35), 2.47-2.31 (2H, m, H23 and H35), 1.88-1.46 (36H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31 and H33), 1.44 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.38 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.31 (6H, s, acetonide), 1.28-1.19 (22H, m, Bpin-$(CH_3)_4$ and hex-$(CH_2)_5$), 1.15-1.02 (27H, m, H6, H12, H30 and TIPS), 0.96 (3H, d, *J* = 6.9 Hz, H33-Me), 0.91-0.78 (9H, m, H9-Me, hex–CH_3 and H13-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0, 159.2, 149.5, 136.9, 131.7, 131.3, 131.0,

129.5, 129.0, 127.7, 127.6, 124.8, 117.4, 113.9, 113.7, 101.7, 100.4, 100.3, 98.8, 98.5, 83.3, 81.4, 81.1, 80.1, 79.2, 78.1, 73.9, 73.5, 71.5, 71.1, 70.2, 69.0, 68.3, 67.4, 67.3, 66.6, 63.6, 55.5, 55.4, 39.4, 39.4, 38.9, 38.0, 37.8, 37.5, 37.4, 36.7, 36.1, 35.3, 34.5, 34.4, 34.1, 33.0, 33.0, 32.6, 32.1, 32.0, 31.3, 30.5, 30.3, 30.3, 29.9, 29.7, 29.6, 29.5, 29.1, 28.7, 26.5, 26.1, 26.0, 25.2, 25.1, 25.0, 25.0, 24.9, 24.9, 24.9, 23.9, 23.5, 23.1, 22.8, 22.8, 21.4, 21.2, 20.0, 19.9, 18.1, 14.3, 14.2, 14.1, 13.7, 12.1, 11.1, 5.8, 4.7; **HRMS** (ESI^+) calc. for $C_{95}H_{159}BO_{18}NaSi$ $[M+Na]^+$ 1650.1281, found 1650.1289.

((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*S*)-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 (E24)



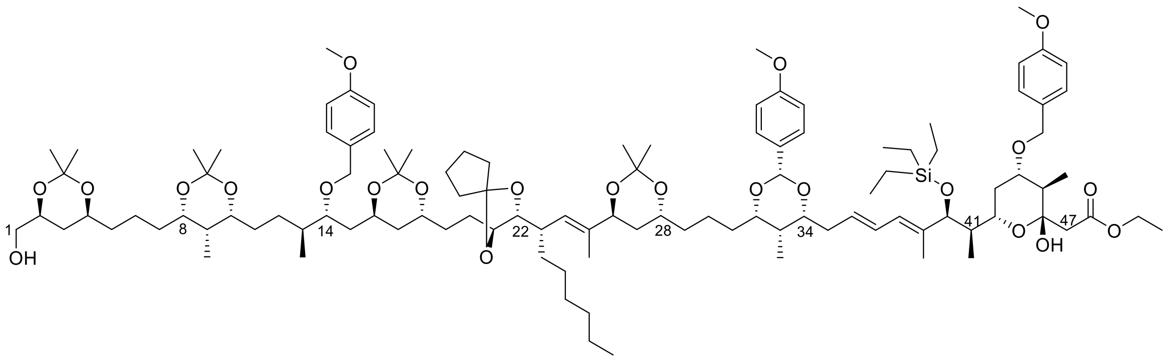
To a solution of compound **E23** (0.0243 g, 0.0149 mmol, 1.0 equiv.) in THF (0.42 mL) at 0 °C was added TBAF (22.4 µL, 22.4 mmol, 1.0 M in THF, 1.5 equiv.). After stirring at 0 °C for 10 min, the reaction mixture was warmed to room temperature and stirred for 5 h before being quenched with sat. aq. NH_4Cl solution (1.0 mL). The organic layer was separated and

the aqueous layer was extracted with Et_2O (3 x 2.0 mL). The combined organic layers were washed with brine (2.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **E24** (0.0166 g, 0.0113 mmol, 75%) as a colourless oil.

R_f 0.23 (30% EtOAc/pentane); $[\alpha]_D^{25}$ -9.4 (*c* = 0.37, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3489, 2937, 2858, 2361, 2337, 1615, 1515, 1461, 1379, 1248, 1224, 1171, 1145, 1112, 1037, 826; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.6 Hz, ArH), 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.90-6.84 (4H, m, ArH), 6.59 (1H, ddd, *J* = 17.9, 7.6, 5.8 Hz, H36), 5.56 (1H, d, *J* = 18.0 Hz, H37), 5.47 (1H, s, PMP acetal), 5.06 (1H, d, *J* = 10.1 Hz, H24), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.33 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.15 (1H, dd, *J* = 9.4, 6.1 Hz, H26), 4.05-3.96 (2H, m, H16 and H2), 3.92 (1H, td, *J* = 7.1, 2.1 Hz, H34), 3.88-3.80 (5H, m, H32, H28, H22, H18 and H14), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.77-3.68 (3H, m, H10, H8 and H4), 3.63-3.58 (1H, m, H1), 3.55-3.48 (2H, m, H1 and H21), 2.55 (1H, dt, *J* = 13.0, 6.4 Hz, H35), 2.47-2.39 (1H, m, H23), 2.36 (1H, dt, *J* = 14.6, 7.3 Hz, H35), 1.88-1.47 (36H, m, cyclopent–CH_2, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31 and H33), 1.46 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.39 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.31 (3H, s, acetonide), 1.30 (3H, s, acetonide), 1.28-1.10 (28H, m, Bpin-$(CH_3)_4$, hex-$(CH_2)_5$, H6, H12 and H30), 0.96 (3H, d, *J* = 6.7 Hz, H33-Me), 0.90 (3H, d, *J* = 6.6 Hz, H9-Me), 0.87 (3H, t, *J* = 7.0 Hz, hex–CH_3), 0.82 (3H, d, *J* = 6.8 Hz, H13-Me); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0, 159.3,

149.5, 136.9, 131.8, 131.3, 129.4, 127.7, 124.9, 117.4, 114.0, 113.8, 101.7, 100.4, 100.3, 98.9, 98.8, 83.3, 81.4, 81.1, 80.1, 79.2, 78.1, 73.9, 73.4, 71.6, 71.1, 69.8, 68.7, 67.3, 66.6, 66.3, 63.6, 55.5, 55.4, 39.4, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.6, 36.1, 35.4, 34.5, 34.1, 33.0, 33.0, 32.6, 32.5, 32.0, 31.3, 30.3, 30.3, 29.8, 29.7, 28.6, 26.5, 26.0, 25.2, 25.2, 25.1, 25.0, 25.0, 24.9, 24.9, 23.9, 23.5, 22.8, 22.8, 21.4, 21.1, 20.1, 19.9, 14.3, 14.2, 13.7, 5.8, 4.7; **HRMS** (ESI$^+$) calc. for $C_{86}H_{139}BO_{18}Na$ [M+Na]$^+$ 1493.9947, found 1493.9934.

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*S*,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-2H-pyran-2-yl)acetate (E25)

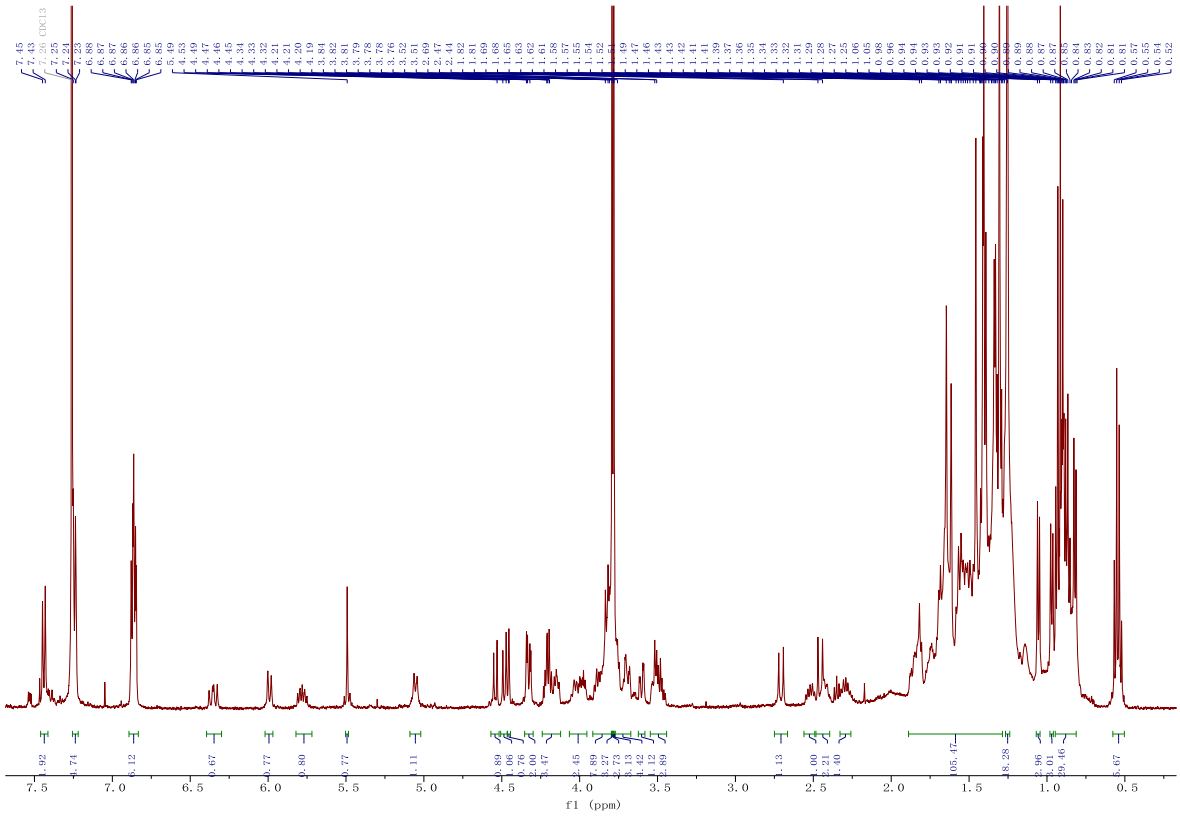


To a mixture of iodide **A16** (7.2 mg, 0.0106 mmol, 1.1 equiv.), boronate **E24** (14.2 mg, 0.00965 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (3.3 mg, 0.00289 mmol, 0.3 equiv.) in degassed THF (1.2 mL) was added a solution of Tl_2CO_3 (8.1 mg, 0.0174 mmol, 1.8 equiv.) in degassed water (0.38 mL) dropwise. (Note: Tl_2CO_3 was dissolved in degassed water under nitrogen

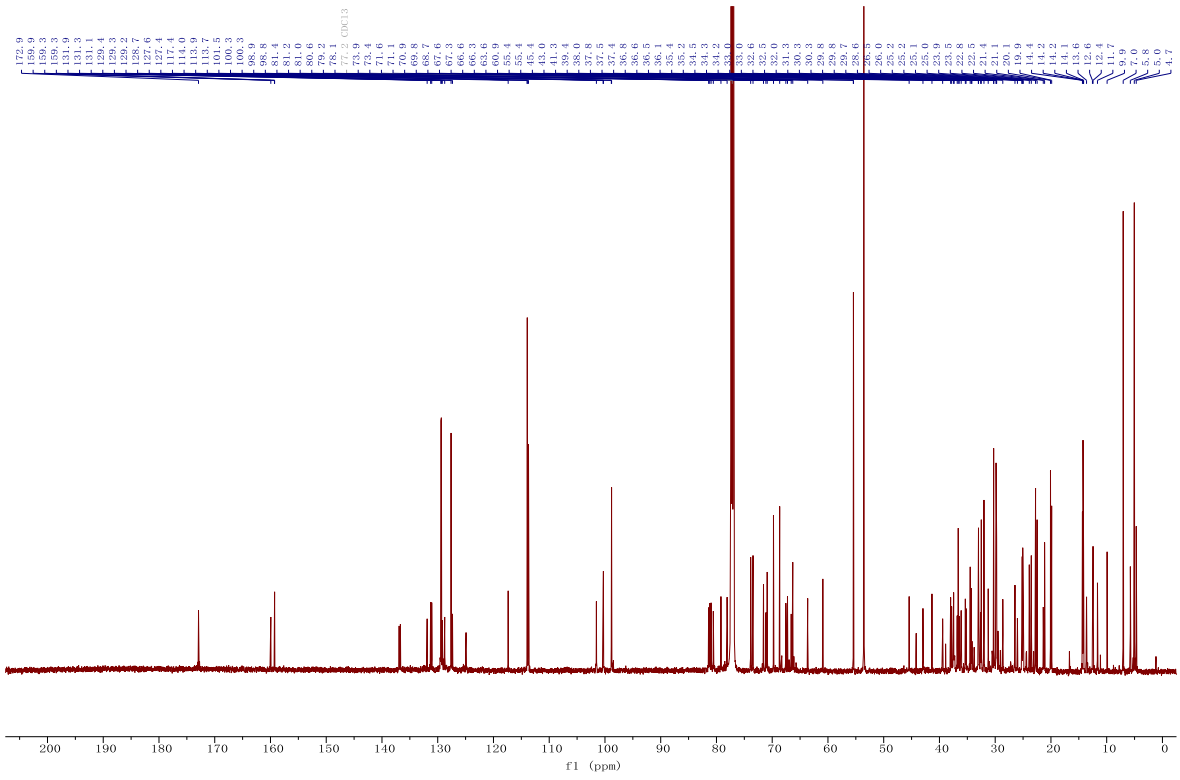
and stirred for 30 min prior to addition to the reaction mixture). After stirring at room temperature overnight, the resulting black solution was diluted with EtOAc (3.0 mL) and quenched with water (3.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 40% EtOAc/pentane) to afford title compound **E25** (13.3 mg, 0.00703 mmol, 73%) as a colourless oil.

R_f 0.24 (30% EtOAc/pentane); $[\alpha]_D^{25}$ +4.1 (*c* = 0.48, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3480, 2934, 2854, 2360, 2342, 1715, 1614, 1515, 1461, 1379, 1248, 1171, 1073, 1037, 829; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.7 Hz, ArH), 7.26-7.22 (4H, m, ArH), 6.89-6.83 (6H, m, ArH), 6.35 (1H, dd, *J* = 15.1, 10.9 Hz, H37), 5.99 (1H, d, *J* = 11.0 Hz, H38), 5.78 (1H, dt, *J* = 15.1, 7.3 Hz, H36), 5.49 (1H, s, PMP acetal), 5.05 (1H, d, *J* = 9.8 Hz, H24), 4.54 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.45 (1H, d, *J* = 1.8 Hz, OH), 4.33 (2H, dd, *J* = 10.8, 3.4 Hz, OCH_2Ar), 4.24-4.12 (3H, m, $CO_2CH_2CH_3$ and H26), 4.07-3.95 (2H, m, H16 and H2), 3.92-3.80 (7H, m, H40, H34, H32, H28, H22, H18 and H14), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.77-3.67 (4H, m, H42, H10, H8 and H4), 3.60 (1H, dd, *J* = 11.3, 3.2 Hz, H1), 3.55-3.44 (3H, m, H44, H21 and H1), 2.71 (1H, d, *J* = 14.7 Hz, H47), 2.56-2.49 (1H, m, H35), 2.48-2.39 (2H, m, H23 and H47), 2.33-2.25 (1H, m, H35), 1.89-1.29 (69H, m, cyclopent–CH_2, H39-Me, H25-Me, H3, H5, H7, H9, H11, H13, H15, H17, H19, H20, H27, H29, H31, H33, H43, H45, acetonide x 8 and

$CO_2CH_2CH_3$), 1.28-1.18 (16H, s, hex-$(CH_2)_5$, H6, H12 and H30), 1.05 (3H, d, J = 6.6 Hz, H45-Me), 0.97 (3H, d, J = 6.8 Hz, H33-Me), 0.95-0.77 (21H, m, H9-Me, hex-Me, H41-Me, H13-Me and TES), 0.54 (6H, q, J = 7.5 Hz, TES); **^{13}C NMR** (126 MHz, $CDCl_3$) δ172.9, 159.9, 159.3, 159.3, 136.9, 136.7, 131.9, 131.3, 131.1, 129.4, 129.3, 129.2, 128.7, 127.6, 127.4, 124.9, 117.4, 114.0, 113.9, 113.8, 113.7, 101.5, 100.3, 100.3, 98.9, 98.8, 81.4, 81.2, 81.0, 80.6, 79.2, 78.1, 73.9, 73.4, 71.6, 71.1, 70.9, 69.8, 68.7, 67.6, 67.3, 66.6, 66.3, 63.6, 60.9, 55.4, 55.4, 45.4, 44.2, 43.0, 41.3, 39.4, 38.9, 38.0, 37.8, 37.5, 37.4, 36.8, 36.6, 36.5, 36.1, 35.4, 35.2, 34.5, 34.3, 34.2, 34.1, 34.1, 33.8, 33.0, 33.0, 32.6, 32.5, 32.1, 32.0, 31.3, 30.3, 30.3, 29.8, 29.8, 29.7, 29.5, 28.6, 26.5, 26.0, 25.2, 25.2, 25.1, 25.0, 23.9, 23.5, 22.8, 22.8, 22.5, 21.4, 21.1, 20.1, 19.9, 14.4, 14.2, 14.2, 14.1, 13.6, 12.6, 12.4, 11.7, 9.9, 7.0, 5.8, 5.0, 4.7; **HRMS** (ESI^+) calc. for $C_{110}H_{176}O_{23}NaSi$ $[M+Na]^+$ 1916.2264, found 1916.2245.

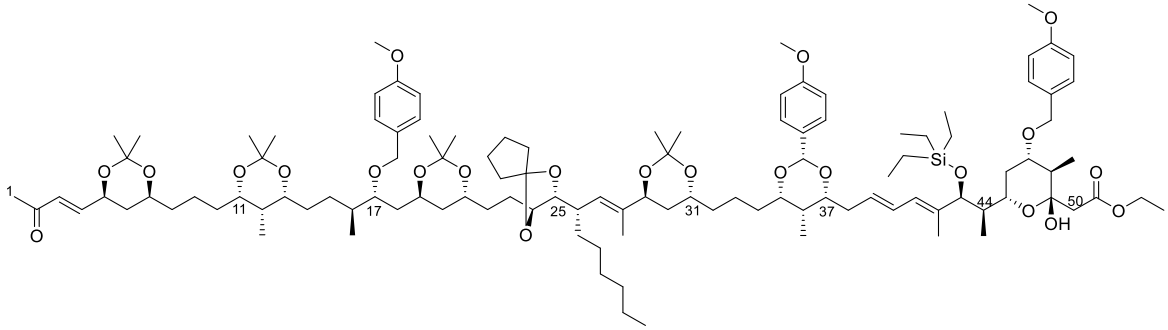


^{1}H NMR spectrum of compound **E25** (500 MHz, $CDCl_3$)



^{13}C NMR spectrum of compound **E25** (126 MHz, $CDCl_3$)

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*S*,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-2H-pyran-2-yl)acetate (E26)



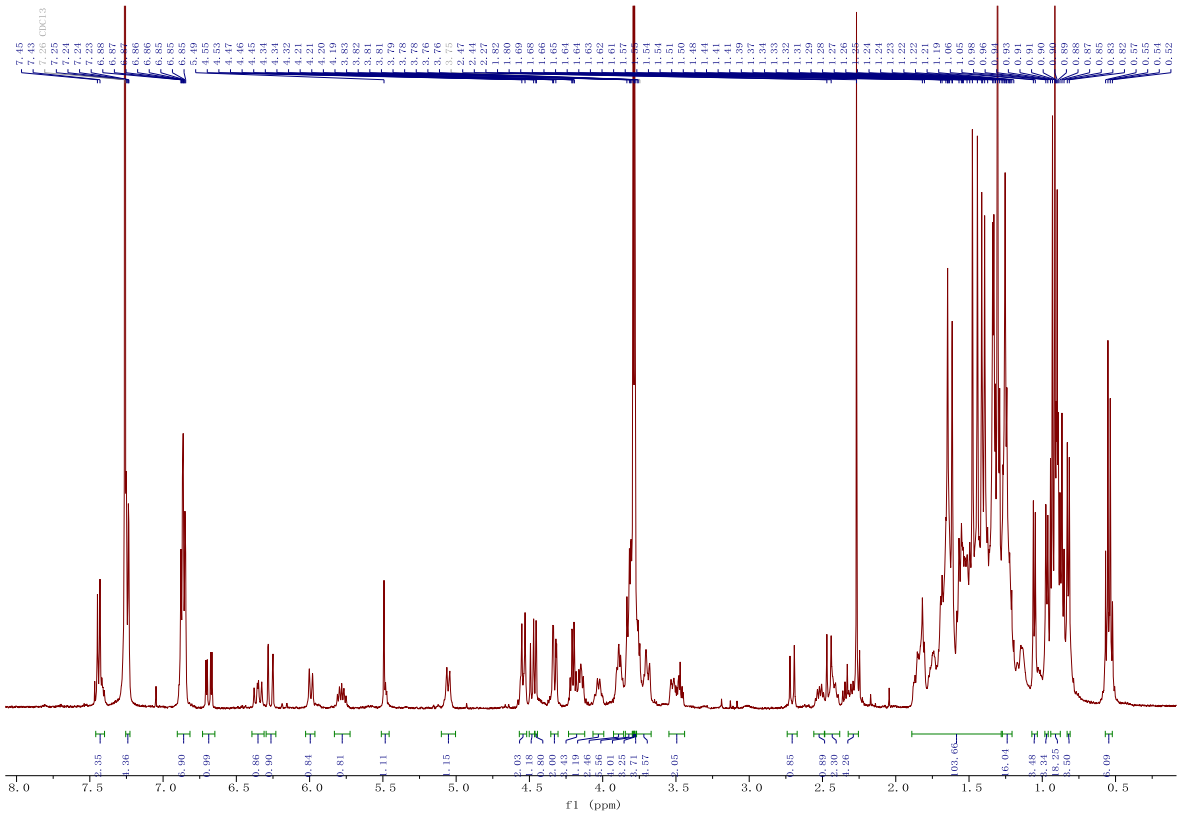
To a solution of alcohol **E25** (12.9 mg, 0.00682 mmol, 1.0 equiv.) in CH_2Cl_2 (0.68 mL) and *tert*-butanol (0.050 mL), was added solid $NaHCO_3$ (14.3 mg, 0.170 mmol, 25.0 equiv.) and Dess-Martin periodinane (23.1 mg, 0.0545 mmol, 8.0 equiv.). After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 ºC and quenched with sat. aq. $NaHCO_3$ solution (1 mL) and sat. aq. $Na_2S_2O_3$ solution (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the corresponding aldehyde (11.1 mg, 0.00587 mmol) as a colourless oil. The crude residue was used for the next step directly without further purification.

To a suspension of sodium hydride (6.8 mg, 60% dispersion in mineral oil, 0.170 mmol, 29.0

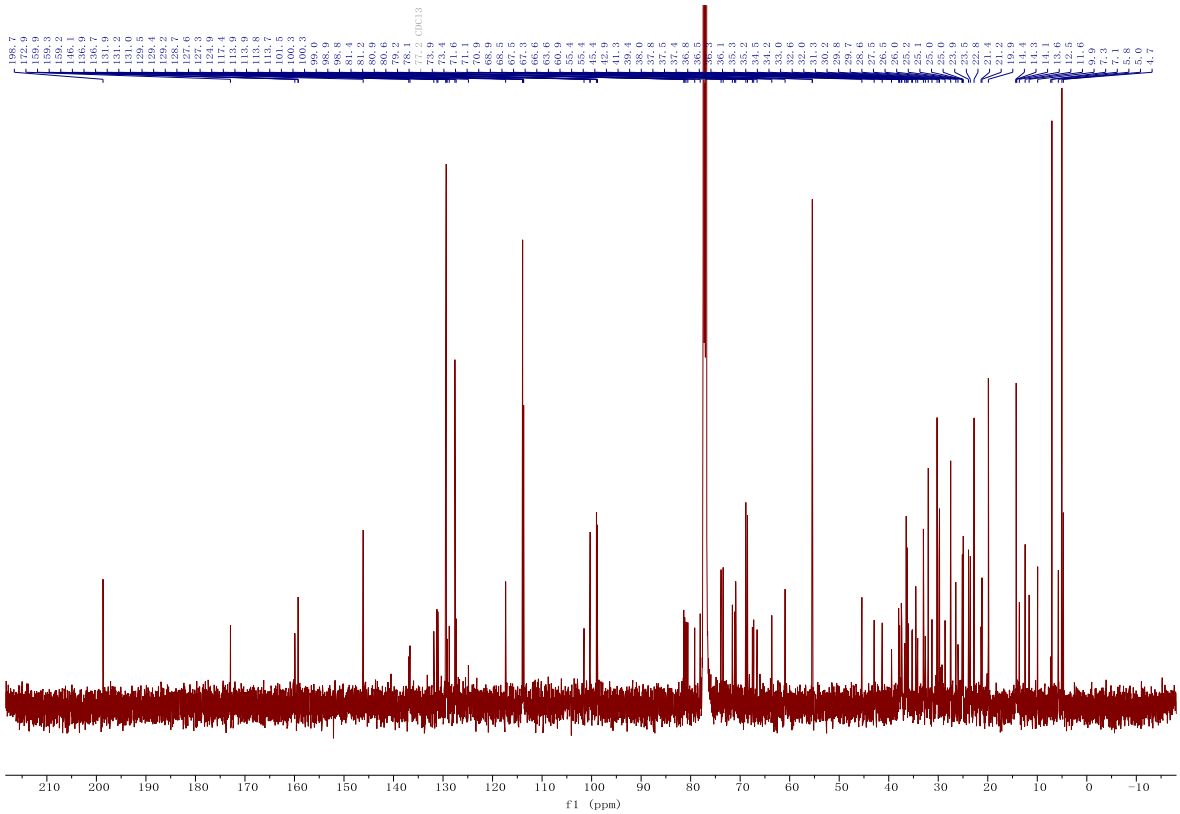
equiv.) in THF (0.78 mL) at 0 °C, was slowly added dimethyl (2-oxopropyl) phosphonate (26.0 μL, 0.188 mmol, 32.0 equiv.) and then the resulting mixture was warmed to room temperature. After stirring at room temperature for 1 h, the reaction mixture was cooled to -78 °C and a solution of crude aldehyde (11.1 mg, 0.00587 mmol, 1.0 equiv.) in THF (0.39 mL) was added dropwise. The resulting mixture was allowed to warm slowly to room temperature and was stirred for 2 h. The reaction mixture was quenched with water (1 mL) and diluted with Et_2O (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/pentane to 30% EtOAc/pentane) to afford enone **E26** (7.6 mg, 0.00394 mmol, 67% over two steps) as a colourless oil.

R_f 0.45 (30% EtOAc/pentane); $[\alpha]_D^{25}$ -5.8 (*c* = 0.68, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2939, 2874, 2360, 2341, 1716, 1615, 1515, 1458, 1248, 1198, 1172, 1037, 824; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.8 Hz, ArH), 7.26-7.23 (4H, m, ArH), 6.89-6.84 (6H, m, ArH), 6.69 (1H, dd, *J* = 16.0, 4.6 Hz, H4), 6.35 (1H, dd, *J* = 15.1, 10.9 Hz, H40), 6.27 (1H, dd, *J* = 16.0, 1.6 Hz, H3), 5.99 (1H, d, *J* = 11.0 Hz, H41), 5.78 (1H, dt, *J* = 14.8, 7.4 Hz, H39), 5.49 (1H, s, PMP acetal), 5.05 (1H, d, *J* = 9.9 Hz, H27), 4.57-4.52 (2H, m, OCH_2Ar and H5), 4.48 (1H, d, *J* = 10.7 Hz, OCH_2Ar), 4.45 (1H, d, *J* = 1.8 Hz, OH), 4.33 (2H, dd, *J* = 10.7, 2.9 Hz, OCH_2Ar), 4.23-4.12 (3H, m, $CO_2CH_2CH_3$ and H29), 4.07-3.99 (1H, m, H19), 3.93-3.86 (2H, H37 and H43), 3.85-3.80 (5H, m, H35, H31, H25, H21 and H17), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.77-3.67 (4H, m, H45,

H13, H11 and H7), 3.55-3.44 (2H, m, H47 and H24), 2.71 (1H, d, *J* = 14.7 Hz, H50), 2.56-2.49 (1H, m, H38), 2.48-2.38 (2H, m, H50 and H26), 2.33-2.23 (4H, m, H38 and H1), 1.89-1.28 (69H, m, cyclopent–CH_2, H42-Me, H28-Me, H6, H8, H10, H12, H14, H16, H18, H20, H22, H23, H30, H32, H34, H36, H46, H48, acetonide x 8 and $CO_2CH_2CH_3$), 1.28-1.18 (16H, s, hex-$(CH_2)_5$, H9, H15 and H33), 1.05 (3H, d, *J* = 6.6 Hz, H48-Me), 0.97 (3H, d, *J* = 6.8 Hz, H36-Me), 0.95-0.84 (18H, m, H12-Me, hex-Me, H44-Me and TES), 0.82 (3H, d, *J* = 6.9 Hz, H16-Me), 0.54 (6H, q, *J* = 7.6 Hz, TES); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.7, 172.9, 159.9, 159.3, 159.2, 146.1, 136.9, 136.7, 131.9, 131.2, 131.0, 129.5, 129.4, 129.2, 128.7, 127.6, 127.3, 124.9, 117.4, 113.9, 113.9, 113.8, 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, 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, 45.4, 42.9, 41.3, 39.4, 38.0, 37.8, 37.5, 37.4, 36.8, 36.5, 36.3, 36.1, 35.3, 35.2, 34.5, 34.2, 33.0, 33.0, 32.6, 32.1, 32.0, 31.3, 30.3, 30.2, 29.8, 29.8, 29.7, 29.3, 28.6, 27.5, 26.5, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 22.8, 22.8, 21.4, 21.2, 19.9, 14.4, 14.3, 14.1, 13.6, 12.5, 11.6, 9.9, 7.3, 7.1, 5.8, 5.0, 4.7; **HRMS** (ESI^+) calc. for $C_{113}H_{178}O_{23}NaSi$ $[M+Na]^+$ 1954.2420, found 1954.2402.

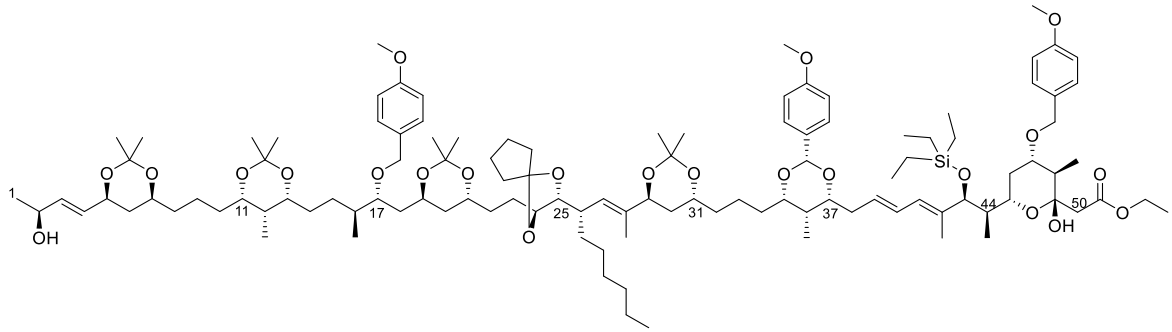


^{1}H NMR spectrum of compound **E26** (500 MHz, $CDCl_3$)



^{13}C NMR spectrum of compound **E26** (126 MHz, $CDCl_3$)

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*S*,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-((*S*,*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 (E27)

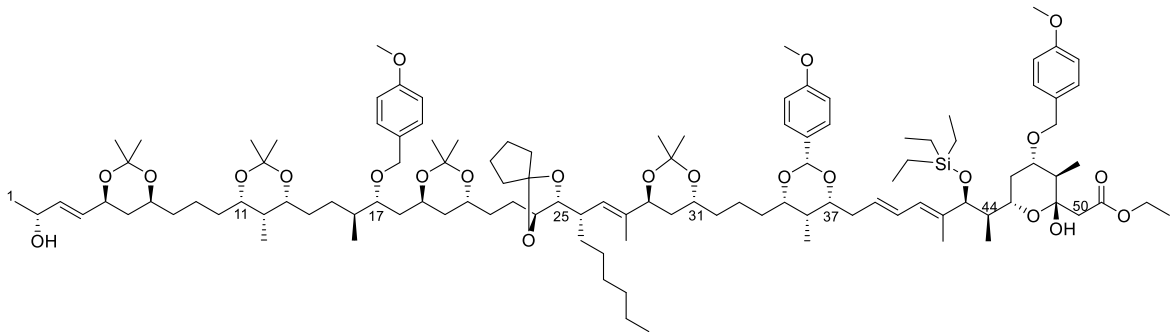


To a solution of (*R*)-(+)-2-methyl–CBS-oxazaborolidine (190 μL, 1.0 M in toluene, 0.190 mmol, 30.0 equiv.) in THF (1.2 mL) at 0 °C was added borane dimethyl sulfide complex solution (126 μL, 1.0 M in THF, 0.126 mmol, 20.0 equiv.) dropwise. After stirring at 0 °C for 15 min, a solution of enone **E26** (12.2 mg, 0.00632 mmol, 1.0 equiv.) in THF (0.63 mL) was added slowly and stirred for 1 h at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2.0 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford enol **E27** (8.2 mg, 0.00424 mmol, 67%, >20:1 *dr*) as a colourless oil.

R_f 0.24 (30% EtOAc/pentane); **$[\alpha]_D^{25}$** +1.4 (*c* = 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3483, 2981, 2954, 2935, 2360, 2341, 1716, 1614, 1515, 1460, 1379, 1248, 1171, 1071, 1038, 827, 739; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.5 Hz, ArH), 7.26-7.22 (4H, m, ArH), 6.90-6.83 (6H, m, ArH), 6.35 (1H, dd, *J* = 15.1, 10.9 Hz, H40), 5.99 (1H, d, *J* = 11.0 Hz, H41), 5.78 (2H, dd, *J* = 15.5, 6.1 Hz, H39 and H3), 5.65 (1H, dd, *J* = 15.5, 6.2 Hz, H4), 5.49 (1H, s, PMP acetal), 5.05 (1H, d, *J* = 10.1 Hz, H27), 4.54 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.50-4.44 (2H, m, OCH_2Ar and OH), 4.38-4.28 (4H, m, OCH_2Ar, H5 and H2), 4.23-4.13 (3H, m, $CO_2CH_2CH_3$ and H29), 4.06-4.00 (1H, m, H19), 3.93-3.80 (7H, m, H43, H37, H35, H31, H25, H21 and H17), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.77-3.67 (4H, m, H45, H13, H11 and H7), 3.55-3.45 (2H, m, H47 and H24), 2.71 (1H, d, *J* = 14.7 Hz, H50), 2.55-2.49 (1H, m, H38), 2.48-2.39 (2H, m, H50 and H26), 2.36-2.25 (1H, m, H38), 1.89-1.29 (69H, m, cyclopent–CH_2, H42-Me, H28-Me, H6, H8, H10, H12, H14, H16, H18, H20, H22, H23, H30, H32, H34, H36, H46, H48, acetonide x 8 and $CO_2CH_2CH_3$), 1.28-1.18 (19H, s, H1, hex-$(CH_2)_5$, H9, H15 and H33), 1.05 (3H, d, *J* = 6.6 Hz, H48-Me), 0.97 (3H, d, *J* = 6.5 Hz, H36-Me), 0.95-0.85 (18H, m, H12-Me, hex-Me, H44-Me and TES), 0.82 (3H, d, *J* = 6.8 Hz, H16-Me), 0.54 (6H, q, *J* = 7.9 Hz, TES); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.9, 159.9, 159.3, 159.3, 136.9, 136.7, 135.4, 131.9, 131.2, 131.1, 130.6, 129.5, 129.4, 129.2, 128.7, 127.6, 127.4, 124.9, 117.4, 113.9, 113.9, 113.8, 113.7, 101.5, 100.3, 100.3, 98.9, 98.8, 98.8, 81.4, 81.2, 80.9, 80.6, 79.2, 78.1, 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, 45.4, 42.9, 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, 32.1, 32.0, 31.3, 30.4, 30.3, 29.9, 29.8, 29.7, 29.5, 28.6, 26.5, 26.0, 25.2, 25.1, 25.0, 25.0, 23.9, 23.5, 23.2,

22.8, 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^+) calc. for $C_{113}H_{180}O_{23}NaSi$ $[M+Na]^+$ 1956.2577, found 1956.2554.

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*S*,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 (E27')

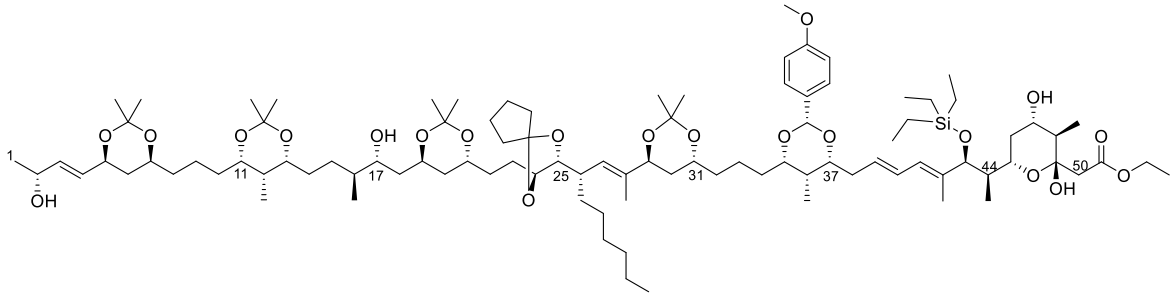


To a solution of (*S*)-(-)-2-methyl–CBS-oxazaborolidine (78 µL, 1.0 M in toluene, 0.077 mmol, 30.0 equiv.) in THF (0.50 mL) at 0 °C was added borane dimethyl sulfide complex solution (52 µL, 1.0 M in THF, 0.052 mmol, 20.0 equiv.) dropwise. After stirring at 0 °C for 15 min, a solution of enone **E26** (5.0 mg, 0.00259 mmol, 1.0 equiv.) in THF (0.26 mL) was added slowly and stirred for 1 h at 0 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2.0 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (20% EtOAc/pentane to 40% EtOAc/pentane) to afford enol **E27'** (3.1 mg, 0.00160 mmol, 62%, >20:1 *dr*) as a colourless oil.

R_f 0.24 (30% EtOAc/pentane); **IR** (thin film, ν_{max} / cm^{-1}) 3656, 2981, 2888, 1514, 1462, 1382, 1250, 1152, 1073, 955, 829, 702; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.5 Hz, ArH), 7.26-7.22 (4H, m, ArH), 6.89-6.84 (6H, m, ArH), 6.35 (1H, dd, *J* = 15.1, 10.9 Hz, H40), 5.99 (1H, d, *J* = 10.9 Hz, H41), 5.78 (2H, dd, *J* = 15.5, 6.1 Hz, H39 and H3), 5.66 (1H, dd, *J* = 15.5, 6.0 Hz, H4), 5.49 (1H, s, PMP acetal), 5.06 (1H, d, *J* = 10.1 Hz, H27), 4.54 (1H, d, *J* = 10.9 Hz, OCH_2Ar), 4.50-4.44 (2H, m, OCH_2Ar and OH), 4.38-4.28 (4H, m, OCH_2Ar, H5 and H2), 4.23-4.13 (3H, m, $CO_2CH_2CH_3$ and H29), 4.06-4.00 (1H, m, H19), 3.91-3.80 (7H, m, H43, H37, H35, H31, H25, H21 and H17), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.77-3.67 (4H, m, H45, H13, H11 and H7), 3.55-3.45 (2H, m, H47 and H24), 2.71 (1H, d, *J* = 14.7 Hz, H50), 2.55-2.49 (1H, m, H38), 2.48-2.39 (2H, m, H50 and H26), 2.36-2.25 (1H, m, H38), 1.89-1.29 (69H, m, cyclopent–CH_2, H42-Me, H28-Me, H6, H8, H10, H12, H14, H16, H18, H20, H22, H23, H30, H32, H34, H36, H46, H48, acetonide x 8 and $CO_2CH_2CH_3$), 1.28-1.19 (19H, s, H1, hex-$(CH_2)_5$, H9, H15 and H33), 1.05 (3H, d, *J* = 6.6 Hz, H48-Me), 0.97 (3H, d, *J* = 6.5 Hz, H36-Me), 0.95-0.85 (18H, m, H12-Me, hex-Me, H44-Me and TES), 0.82 (3H, d, *J* = 6.8 Hz, H16-Me), 0.55 (6H, q, *J* = 7.9 Hz, TES); **HRMS** (ESI^+) calc. for $C_{113}H_{180}O_{23}Na$ $[M+Na]^+$ 1956.2577, found 1956.2565. (The characterization of compound **E27'** might not be accurate enough due to the insufficient data obtained).

Ethyl 2-((2*S*,3*R*,4*S*,6*S*)-2,4-dihydroxy-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*S*,3*S*)-3-(2-((4*R*,6*R*)-6-((2*R*,3*S*)-2-hydroxy-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)-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)-3-methyltetrahydro-2H-pyran-2-yl)acetate (E28)



To a stirred solution of the compound **E27'** (2.9 mg, 0.00150 mmol, 1.0 equiv.) in CH_2Cl_2 (0.1 mL) and pH 7 phosphate buffer solution (0.05 mL) at 0 °C was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (0.8 mg, 0.00375 mmol, 2.5 equiv.) After stirring at 0 °C for 3 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (0.5 mL), diluted with CH_2Cl_2 (1.0 mL) and filtered through a Büchner funnel to remove solids. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 1.0 mL). The combined organic layers were washed with brine (1.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/pentane to 50% EtOAc/pentane) to afford alcohol **E28** (1.2 mg, 0.000708 mmol, 47%) as a colorless oil.

R_f 0.26 (52% EtOAc/pentane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.8 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 6.35 (1H, dd, *J* = 15.1, 10.9 Hz, H40), 5.98 (1H, d, *J* = 10.9 Hz, H41), 5.81-5.73 (2H, m, H39 and H3), 5.66 (1H, dd, *J* = 15.6, 6.0 Hz, H4), 5.49 (1H, s, PMP acetal), 5.07 (1H, d, *J* = 10.3 Hz, H27), 4.42 (1H, d, *J* = 1.8 Hz, OH), 4.37-4.27 (4H, m, H5, H2 and OH x 2), 4.24-4.11 (5H, m, $CO_2CH_2CH_3$, H47, H29 and H17), 3.90-3.80 (6H, m, H43, H37, H35, H31, H25 and H21), 3.79 (3H, s, OCH_3), 3.77-3.62 (5H, m, H45, H24, H13, H11 and H7), 2.70 (1H, d, *J* = 14.7 Hz, H50), 2.48-2.41 (2H, m, H50 and H26), 2.37-2.26 (2H, m, H38), 1.89-1.29 (69H, m, cyclopent–CH_2, H42-Me, H28-Me, H6, H8, H10, H12, H14, H16, H18, H20, H22, H23, H30, H32, H34, H36, H46, H48, acetonide x 8 and $CO_2CH_2CH_3$), 1.28-1.17 (19H, s, H1, hex-$(CH_2)_5$, H9, H15 and H33), 1.05 (3H, d, *J* = 6.6 Hz, H48-Me), 0.97 (3H, d, *J* = 6.5 Hz, H36-Me), 0.95-0.85 (18H, m, H12-Me, hex-Me, H44-Me and TES), 0.83 (3H, d, *J* = 6.8 Hz, H16-Me), 0.54 (6H, q, *J* = 7.9 Hz, TES); **HRMS** (ESI^+) calc. for $C_{97}H_{164}O_{21}NaSi$ $[M+Na]^+$ 1716.1427, found 1716.1412. (The characterization of compound **E28** might not be accurate enough due to the insufficient data obtained).

Chapter 8: References

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