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The Total Synthesis of Furanocembrane Natural Products

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MChem (Hons) Chemistry with Medicinal Chemistry

Thesis submitted in the fulfilment of the requirements for the degree of Doctor of Philosophy

University of Glasgow
School of Chemistry
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Abstract

The furanocembranes are a family of marine diterpenoids isolated from octocoral invertebrates. These macrocyclic natural products possess interesting molecular structures including a furan ring at C3-C6 and a butenolide moiety encompassing C10-C12. As well as their unique structures, family members have shown promising biological activities, and thus they represent attractive synthetic targets.

This thesis describes the synthetic efforts towards two of these family members: pukalide and 7-acetylsinumaximol B. In particular, focus has been directed towards the investigation of different synthetic strategies and the synthesis of key fragments; culminating in the total synthesis of 7-epi-pukalide and 7-acetylsinumaximol B. The key synthetic approach undertaken was designed to take advantage of new methodology developed by our group for the synthesis of highly functionalised furans, including epoxy-furans, in which tetrahydrothiophene (THT) was used as an organocatalyst. The reaction promotes the formation of both a furan and an epoxide in one step from a Knoevenagel condensation product.

In the first approach described herein, an intramolecular Knoevenagel condensation strategy for macrocycle formation was explored. The C12-C14/C1-C4 and C5-C11 were initially coupled through esterification; however, after further functionalisation, macrocyclisation could not be effected under Knoevenagel conditions. The second approach focused on the use of an intermolecular Knoevenagel condensation reaction for fragment coupling. Although fragment coupling was successful further functionalisation proved to be difficult because of the reactive nature of the ynenone intermediates. The third and final approach investigated the development of a one-pot condensation and furan formation; combining the Knoevenagel condensation with organocatalytic tetrahydrothiophene to produce the furan directly from two separate fragments. This approach was successful, allowing completion of the full skeleton to be effected through macrolactonisation and ring-closing metathesis. Following this strategy both 7-epi-pukalide and 7-acetylsinumaximol B were accessed in 16 steps from the chiral pool starting material (R)-perillyl alcohol.
Declaration

I hereby declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted, nor is being concurrently submitted, in candidature for any other degree at the University of Glasgow or any other institution.

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Kirsten McAulay

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Prof. J. Stephen Clark
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'These days are all gone now but some things remain'
### Abbreviations

<table>
<thead>
<tr>
<th>Ac</th>
<th>Acetyl</th>
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<tbody>
<tr>
<td>ACDC</td>
<td>asymmetric counterion directed catalysis</td>
</tr>
<tr>
<td>ADD</td>
<td>1,1′-(azodicarbonyl)dipiperidine</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BQ</td>
<td>1,4-benzoquinone</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
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<td>cyclooxygenase-2</td>
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<td>camphorsulfonic acid</td>
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</tr>
<tr>
<td>DCE</td>
<td>dichloroethane</td>
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<td>diisopropylamine</td>
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<td>DIPEA</td>
<td>diisopropylethylamine</td>
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<td>dimethyldioxirane</td>
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<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
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<tr>
<td>EDDA</td>
<td>ethylene diammonium diacetate</td>
</tr>
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<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
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<tr>
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<td>extracellular signal–regulated kinases 1/2</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>-----------</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawng group</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
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<td>Grubbs II</td>
<td>Grubbs second generation catalyst</td>
</tr>
<tr>
<td>HG II</td>
<td>Hoveyda-Grubbs second generation catalyst</td>
</tr>
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<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
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<td>high resolution mass spectrometry</td>
</tr>
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</tr>
<tr>
<td>i</td>
<td>iso</td>
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<td>IBX</td>
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<td>IR</td>
<td>infrared</td>
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<td>ligand</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrometry</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
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<tr>
<td>mCPBA</td>
<td>p-chloroperbenzoic acid</td>
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<td>methyl</td>
</tr>
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<td>MEM</td>
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<td>MMTr</td>
<td>4-methoxytrityl (4-methoxytriphenylmethyl)</td>
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<td>MNBA</td>
<td>2-methyl-6-nitrobenzoic anhydride</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl (methanesulfonyle)</td>
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<td>MTBD</td>
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<tr>
<td>n</td>
<td>normal</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<td>NHC</td>
<td>N-heterocyclic carbene</td>
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<td>NHK</td>
<td>Nozaki-Hiyama-Kishi</td>
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<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<td>pet</td>
<td>petroleum</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
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1 Introduction

1.1 Furan Containing Natural Products and Bioactivity

1.1.1 Drug Discovery from Natural Products

Natural products can be defined as structurally diverse substances which are created by living organisms. Their varying structural nature means that they cover a wide area of chemical space relevant to biology.\(^1\) This inherent diversity allows molecules to spatially complement biological targets, often resulting in greater substrate selectivity. As a result, many natural products have acted as a source of inspiration for drug discovery and, to date, they remain one of the best sources of drug leads, with some of the biggest selling pharmaceuticals being natural product derivatives.

Natural products represent a rich source of novel molecular scaffolds. Subsequently, the discovery of new natural products holds significant promise for advances in chemistry, biochemistry and medicine.\(^2\) Most currently available medicines derived from nature come from terrestrial species; however, the marine world has also proven to be a rich source of biological and chemical diversity.\(^5\) Marine organisms produce a range of structurally interesting secondary metabolites as protection against predation and the extreme conditions of their surroundings. These secondary metabolites often have interesting biological properties and unusual modes of action.\(^6\) Ziconotide (1) was the first marine natural product approved for use by the FDA in 2004.\(^7\) Isolated from a marine cone snail, this peptide was approved for the treatment of chronic pain resulting from spinal chord injury. A second natural product, trabectedin (2), originally isolated from a sea squirt, was the first anti-cancer agent of marine origin to be approved.\(^8\) In 2007, it was approved by the EMA for the treatment of soft tissue sarcoma.
The enormous structural and chemical diversity associated with natural products is unsurpassed by any synthetic library. However, despite this, there are many challenges associated with the transition from drug discovery to pharmaceutical product; limited supply, low yield and limited possibility for structural modification all detract from the appeal of natural products as drug candidates. For this reason, total synthesis is often required to provide sufficient quantities for biological testing and to allow modifications for SAR studies.\(^9\)

### 1.1.2 Furans in Biologically Active Molecules

The furan system is a common motif in natural products, biologically active molecules and pharmaceuticals. Members of many natural product families, including acetogenins, terpenes and complex alkaloids, contain a furan within their structure.\(^{10}\) Bioactive marine natural products such as lophotoxin (3) and nakadomarin A (4) possess a tri-substituted furan as part of their macrocyclic core (Figure 2) and exhibit potent biological activity.\(^{11,12}\) Lophotoxin, acts as a neurotoxin by inhibiting nicotinic acetylcholine receptors, and nakadomarin A displays cytotoxicity against specific lymphoma cell lines, as well as some anti-microbial activity.\(^{13,14}\) Furano epothilone C (5) is a biologically active natural product analogue, shown to be an inhibitor of cancer cell growth *in vitro*.\(^{15}\)
Many marketed drugs also contain a furan moiety. The anti-ulcer drug ranitidine (6), which acts as an H$_2$-receptor antagonist, as well as the common urinary-tract infection antibiotic nitrofurantoin (7), both contain a di-substituted furan (Figure 3).

The prevalence of the furan motif within biologically active molecules and natural products has meant that the development of new, mild and efficient protocols for the synthesis of highly substituted furans has become an important goal for synthetic chemists. Thus, in recent years many metal-mediated as well as a few organocatalytic methods for the synthesis of substituted furans have been developed, in addition to classical protocols.

1.1.3 The Furanocembranoid Natural Product Family

1.1.3.1 Isolation, Structure and Biological Activity of the Furanocembranes

The furanocembrane natural products are a family of diterpenoids isolated from octocorals; a group of marine invertebrates which include species of sea fans, sea whips and soft corals.$^{[11,16–18]}$ From within this group the vast majority of compounds have been isolated from gorgonian corals. As a result of their interesting molecular structures and promising biological activities, the furanocembranes have received the attention of many synthetic chemists. Studies concerning these natural products have led to many discoveries regarding their pharmacological activities as well as some advances in synthetic methodology.$^{[16–18]}$

The furanocembranoids feature a 14-membered carbocyclic skeleton which includes a furan ring at C3-C6 and a butenolide moiety encompassing C10-C12 (Figure 4). Pseudopterane and gersolane natural products have similar structures but the carbocyclic skeletons are comprised of only 12 and 13 carbons respectively and they have different substitution at the
C7 and C8 positions. They are thought to be biosynthetically derived from furanocembrane type compounds through photochemical and enzymatic transformations.\textsuperscript{[19,20]}

**Figure 4** Skeletons of the furanocembrane, pseudopterane and gersolane natural products

Oxidation patterns and saturation levels vary greatly amongst the natural products within the furanocembranolide family, whilst the basic backbone always remains the same. Oxidation typically occurs at C2, C13 and C18 and across the double bonds at C7-C8 and C11-C12. In most furanocembranes, the stereocentre at C1 has the \textit{R} configuration; however, some furanocembranoids have been found to exhibit the opposite.\textsuperscript{[21]} Lophotoxin (3), pukalide (8) and bipinnatin G (9), along with their various oxygenated and deoxygenated congeners, are representative of the family (**Figure 5**).

**Figure 5** Representative members of the furanocembrane family

The biosynthesis of the cembrane skeleton begins with the cyclisation of geranyl-geranyl diphosphate (10) to give a 14-membered macrocycle 11 as a carbocationic species (**Scheme 1**). Loss of a proton from the isopropyl side chain subsequently affords the natural product neo-cembrene (12). A series of oxidation and reduction reactions, and the closure of the furan ring, occur subsequently to afford the furanocembrane products. Despite a significant number of family members having been isolated, the full enzymatic pathway from neo-cembrene has yet to be elucidated.\textsuperscript{[22]}
Many of the natural products within the furanocembrane family have been found to be biologically active. Several studies have delivered promising results, with new compounds still being recently isolated.\cite{23} Lophotoxin (3) is the most recognized biologically active family member and is found in multiple species of *Lophogorgia*. It is a potent irreversible inhibitor of the nicotinic acetylcholine receptor, making it an effective neurotoxin.\cite{13} Other compounds isolated alongside lophotoxin from the gorgonian coral *Lophorgorgia peruana* have also exhibited some cytotoxic activity against breast, lung and colon tumor cell lines.\cite{24}

### 1.1.3.2 Pukalide and 7-Acetylisinumaximol B

In 1975, pukalide (8), was the first furanocembranoid to be isolated and identified, after extraction from the alcynacean octocoral *Sinularia abrupta*. Subsequently, this natural product has been isolated from several other coral species. Scheuer and Missakian published the original structure; of which the stereochemistry has now been revised.\cite{25} Pukalide, along with its derivatives (13-15) and other structurally related compounds are found in a variety of octocorals in the orders *Gorgonacea* and *Alcyonacea*.\cite{26} Reportedly it is most abundant in the egg-bearing colonies and recently released eggs of *Sinularia* species.\cite{27}

Studies based around the ecological activity of pukalide within *Leptogorgia virgulata*, a sea whip of the order *Gorgonocea* found on North-western Atlantic coastlines, have shown that ingestion of pukalide by fish induces vomiting episodes.\cite{28} Therefore, the terpenoid is partially or completely responsible for the emetic properties of the *Leptogorgia* species skeletal tissues.
Although little is known about the pharmacological activity of pukalide, studies have shown promising results for closely related family members. Cozar-Castellano et al. reported that epoxypukalide activates the ERK1/2 pathway to induce β-cell proliferation, making it a potential treatment for diabetes.\[29\] The epoxide at C11-C12, along with the ester group, was found to be essential for activity. SAR studies focusing on the activity of the analogous molecule lophotoxin also revealed the importance of the epoxide.\[30\] The results suggested that the pharmacophore necessary for irreversible inhibition of the nicotinic acetylcholine receptor retains the γ-lactone and the trisubstituted epoxide, which are also present in pukalide, and which are thought to mimic the acetate oxygens and cationic ammonium group in acetylcholine.

7-acetylsinumaximol B (16) was recently isolated in 2015 by Su et al. from the cultured soft coral *Sinularia sandensis*.\[23\] It was found alongside another new cembranoid, 4-carbomethoxy-10-epigyrosoanoldie E (17), and several other related known metabolites; including pukalide and sinumaximol B. The absolute configurations of carbomethoxy-10-epigyrosoanoldie E (17) and pukalide (8) were determined by single crystal X-ray crystallography. The determined absolute configurations, and comparison with known analogues, showed the hypothesis that cembrane diterpenes obtained from Alcyonaceaen soft corals and Gorgonaceaen corals belong to different series with respect to their C1 stereochemistry does not apply to some cembranoids.\[31,32\] All compounds isolated were tested for anti-inflammatory activity resulting from inhibition of protein expression of inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX-2). Several metabolites were found to be active; however, pukalide (8), sinumaximol B (18) and 7-acetylsinumaximol B (16) were shown to be inactive.

![Figure 7 Metabolites isolated from Sinularia sandensis.](image-url)
1.2 Total Syntheses of Furanocembranoids

To date numerous syntheses of octocoral diterpene natural products have been reported. One of the earliest publications by Paquette et al. in 1992 reported the total synthesis of the pseudopterane derivative gorgiacerone.[33] The Paquette group also completed the first total synthesis of the furanocembranoid acerosolide in 1993.[34] Since then, numerous groups, including those of Pattenden, Trauner and Marshall, have reported total syntheses of and synthetic studies directed toward the furanocembranoid family of natural products.[35–37] The majority of completed total syntheses pertain to deoxygenated members or enantiomers of the natural compounds.

1.2.1 Total Synthesis of Natural Furanocembranoids

1.2.1.1 The Total Synthesis of Acerosolide

In 1993, Paquette et al. reported the first total synthesis of a 14-membered furanocembranolide, acerosolide (19).[34] Acerosolide contains 2-stereogenic centres at C1 and C10 and a double bond at C7-C8; total synthesis allowed the relative and absolute configuration of the two stereogenic centres to be determined.

Following previous work reported by the group, for the synthesis of the pseudopterane gorgiacerone, key disconnections were made alpha to the butenolide, ketone and isoprene groups of acerosolide to give three fragments (20, 21 and 22) (Scheme 2); the synthesis of which had been reported previously. The two stereocentres could therefore be installed by a Lewis acid promoted addition reaction between the allylic stannane (21) and aldehyde (22) and an intramolecular Cr(II) promoted reductive coupling reaction, following previous methodology.

![Scheme 2 Retrosynthetic analysis of acerosolide](image)

The forward synthesis began with the SnCl₄ promoted reaction of aldehyde 22 with allylic stannane 20, to give homoallylic alcohol 23. Acid-catalysed lactone formation, followed by an oxidative sequence via the bis-selenide afforded the butenolide 24 in four steps. The
aldehyde 24 was then converted to the bromide 25 and this compound coupled with vinylstannane 21 to afford seco-cembrane 26. A further three steps afforded aldehyde 27.

Scheme 3 Forward synthesis of acerosolide

Following the elaboration of seco-cembrane 26 into bromo aldehyde 27, in a three-step sequence, cyclisation was effected using CrCl₂ to afford a single homoallylic alcohol 28. Finally, oxidation of the hydroxyl group gave (±)-acerosolide (19), as confirmed by comparison with the natural product spectra.

Scheme 4 Final steps in the total synthesis of acerosolide
1.2.1.2 The Total Synthesis of (-)-Rubifolide

Marshall et al. reported the first total synthesis of (-)-rubifolide ((-)-29), the non-natural enantiomer of the natural product, in 1997.[38] The group earlier reported the synthesis of 2-vinylfurans through base mediated rearrangement of 2-hexen-4-yn-1-ols possessing a leaving group (OR) at the 6-position.[39] With this methodology in mind they proposed to use the reaction for the synthesis of the rubifolide skeleton. Model studies showed that formation of furan 31 could be effected from a mixture of four diastereoisomers 30.[40]

![Scheme 5 Model studies for the formation of the rubifolide skeleton](image)

At the onset of the synthesis the absolute stereochemistry of rubifolide was unknown. (S)-Perillyl alcohol (32) was therefore utilised due to its economic viability; however, this ultimately resulted in the formation of the natural product enantiomer. The key building blocks were formed in 6 and 4 steps respectively from simple building blocks; alkyne 33 was formed in 6 steps from (S)-perillyl alcohol (32) and aldehyde 36 was formed in 4 steps from epoxide 34 and alkyne 35. Fragment coupling was accomplished by attack of the alkyne anion of 33 onto aldehyde 36. Subsequent carbonate formation afforded diyne intermediate 37 in high yield.

![Scheme 6 Initial steps in the synthesis of (-)-rubifolide](image)
Deprotection of the propargylic alcohol 37 using DDQ, followed by mesylate formation and addition of the cuprate of lithiated tributyltin afforded allenylstannane 38 in 84% yield over the 3 steps. Deprotection of the primary alcohol followed by oxidation, as the magnesium alkoxide, with ADD (1,1’-(azodicarbonyl)dipiperidine) furnished aldehyde 39, which underwent ring closure upon treatment with boron trifluoride etherate to form the corresponding homopropargylic alcohol. Oxidation with Dess-Martin periodinane and in situ isomerisation of the resulting ketone gave allenone 40 as a mixture of eight diastereoisomers.

Scheme 7 Formation of a cyclised intermediate in the synthesis of rubifolide

Furan formation was effected in 84% yield by treatment of allenone 40 with silver nitrate impregnated silica gel to afford furan 41. Highly Z-selective elimination of the protected tertiary hydroxyl group in the presence of tosylic acid, followed by carbonate cleavage afforded propargylic alcohol 42 in good yield. Despite the results of earlier model studies, attempts to effect elimination using the originally reported base-mediated conditions led to decomposition.

Scheme 8 Furan formation in the synthesis of rubifolide
Following separation of the two hydroxyl isomers 42 and formation of the trifluoracetate 43, a one-pot Pd(0)-catalysed hydrocarbonylation and silver nitrate catalysed cyclisation reaction furnished (-)-rubifolide ((-)-29), via the allenic acid 44. The reaction proceeds with inversion of configuration at the C-O bond. Marshall et al. therefore achieved the synthesis in 19 steps (longest linear sequence) from (S)-perillyl alcohol.

Scheme 9 Completion of the total synthesis of rubifolide

1.2.1.3 The Total Synthesis of Bipinnatin J

1.2.1.3.1 Trauner’s Approach

In 2006, Trauner et al. described the first total synthesis of bipinnatin J (45) as a racemate. Following a similar strategy to Paquette et al. for the synthesis of acerosolide, key disconnections were made between C1-C2 and C6-C7 to allow CrCl2 catalysed macrocyclisation and Stille coupling as the key synthetic steps from proposed fragments 47 and 48.

Scheme 10 Retrosynthetic analysis of bipinnatin J by Trauner

Synthesis of the targeted butenolide fragment 48 was achieved in 5 steps starting from known vinyl iodide 49. Oxidation of alcohol 49 with DMP gave the corresponding aldehyde before addition of lithiated ethyl propiolate to afford propargylic alcohol 50. A ruthenium(II)-catalysed enyne reaction, initially reported by Trost, gave a 7:1 mixture of butenolide 51 and its corresponding regioisomer. The key ruthenium catalysed reaction is thought to proceed through formation of the equivalent enol intermediate int-51, followed by tautomerisation and intramolecular transesterification. A further two step Wittig olefination and reduction sequence yielded butenolide 48.
Scheme 11 Formation of the butenolide fragment in bipinnatin J

Following preparation of the vinylc iodide 48, coupling of this compound with furyl stannane 47 under Stille conditions afforded allylic alcohol 52. Subsequent closure of the macrocycle was achieved through formation of the corresponding allylic bromide and cyclisation using Nozaki-Hiyama-Kishi conditions to afford (±)-bipinnatin J with a dr of > 9:1 in a total of 8 steps from the alcohol 49.

Scheme 12 Completion of the racemic synthesis of (±)-bipinnatin J

Following this success, Trauner et al. went on to report the enantiomeric synthesis of (−)-bipinnatin J in a slightly longer 16 step sequence from vinyl iodide 49. The initial stereochemistry was set through reduction of propargylic ketone 53 using (S)-alpine borane. A further 3-step sequence from alcohol 54 gave the common intermediate 50 which was transformed into (−)-bipinnatin J in 8 steps using a similar sequence to that described previously.
Scheme 13 Formation of the butenolide stereocentre for (−)-bipinnatin J

With (−)-bipinnatin J in hand, the group was able to exploit a biosynthetic approach for the synthesis of other family members (Scheme 14). An S_N1 deoxygenation reaction of (−)-bipinnatin J ((−)-45) with triethylsilane and trifluoroacetic acid gave (+)-rubifolid ((+)-29) in almost quantitative yield.\(^{42}\) Oxidation of the furan with mCPBA resulted in the formation of (+)-isoepilophodione 55. The group also reported the synthesis of intracarene 58 in 3 steps from (−)-bipinnatin J; an initial Achmatowicz rearrangement gave 56 which was acetylated to afford 57. Subsequently a one-pot elimination and 1,3-dipolar cycloaddition occurred to afford intracarene (58). It was also found that selective addition of singlet oxygen followed by reduction also gave 58; giving insight into the potential biosynthesis of this compound. Later, in 2014, a photochemical method for the formation of intricarene from (−)-bipinnatin J was also reported.\(^{43}\) In 2010, Trauner et al. reported the further manipulation of (+)-rubifolid in a series of oxidation and rearrangement steps to furnish coralloidolides A, B, C and E (59, 61, 62 and 60 respectively).\(^{44}\)
1.2.1.3.2 Rawal’s Approach

In 2006, Rawal et al. reported a second synthesis of bipinnatin J in racemic form using similar disconnections to those reported by Trauner.\[45\] Rawal proposed to use the same precursor 46 and final macrocyclisation step as Trauner et al. but expected to form the precursor through a γ-alkylation reaction of a butenolide fragment and subsequent Negishi cross-coupling (Scheme 15).
In the forward synthesis, the butenolide fragment 65 was formed in 6 steps from 5-bromo-2-methylpent-2-ene 66 (Scheme 16). Alkylation of the butenolide was achieved through formation of siloxyfuran 67 and subsequent treatment with allylic bromide 63 in the presence of silver trifluoroacetate. Negishi coupling with organozinc compound 64, prepared in situ, furnished the completed carbon scaffold 69. Deprotection of both the primary alcohol and aldehyde was carried out under acidic conditions and the corresponding alcohol was transformed into the bromide 70 using the Appel reaction. The Nozaki-Hiyama macrocyclisation reaction was then carried out, as described by Trauner, to afford (±)-bipinnatin J in a total of 12 steps.

Scheme 16 Racemic synthesis of bipinnatin J by Rawal et al.

1.2.2 Total Synthesis of Deoxygenated Furanocembranoids

1.2.2.1 Synthesis of Deoxypukalide

Deoxypukalide is the degradation product of pukalide and exists in nature solely as the Z-alkene isomer. There have been two enantiomeric syntheses and one synthesis of the natural enantiomer of this natural product: Marshall (2001),[46] Donohoe (2008)[47] and Pattenden (2010).[35] The original synthesis, completed by Marshall and van Devander was published before deoxypukalide had been isolated as a natural product. The isolation of deoxypukalide was first reported by Darias et al. in 2007 from the Pacific octocoral Leptogorgia spp.[48] The formation of deoxypukalide by deoxygenation of pukalide has also
been established experimentally by treatment of pukalide with zinc in refluxing ethanol (Scheme 17).[^46]

![Scheme 17 Experimental formation of deoxypukalide from pukalide](image)

### 1.2.2.1.1 Marshall and Van Devander’s Approach

In 2001 Marshall and Van Devander reported the synthesis of the unnatural enantiomer, (−)-Z-deoxypukalide (−)-15.[^46] Starting from (S)-perillyl alcohol (32) the group described the total synthesis in 27 linear steps (Scheme 21). Based on their earlier work on the total synthesis of rubifolide the group proposed the same key disconnections and a similar late stage furan formation from a cyclic precursor.

The synthesis of iodo-compound 71 was achieved in 16 steps from (S)-perillyl alcohol (32). Cyclisation was effected by treatment of β-keto ester 71 with KOtBu under high dilution conditions to furnish macrocycle 72 in 83% yield. Selective cleavage of the TBS-silyl ether followed by oxidation with Dess-Martin periodinane furnished ynone 73. The furan was subsequently installed by a mild acid-catalysed process using silica to afford 74; analogous to the method used for the synthesis of rubifolide. Ketone 74 was converted to the corresponding Z-alkene 75 in a five step sequence involving enol triflate formation, Pd-catalysed methylation and deprotection of the propargylic alcohol.
Scheme 21 Formation of the furan macrocycle in the synthesis of (−)-Z-deoxypukalide by Marshall

With alkyne 75 in hand attention was turned to formation of the butenolide 76. A Pd-catalysed carbohydroxylation from the in situ formed trifluoroacetate of propargylic alcohol 75 and subsequent cyclisation upon treatment with silver nitrate impregnated silica gel afforded butenolide 76. Pyrolysis of the tert-butyl ester followed by methylation of the corresponding acid with TMS-diazomethane installed the methyl ester, furnishing (−)-Z-deoxypukalide.

Scheme 22 Final steps in Marshall's synthesis of (−)-Z-deoxypukalide

1.2.2.1.2 Donohoe's Approach

In 2008, Donohoe et al. also reported the total synthesis of the unnatural enantiomer, (−)-Z-deoxypukalide ((−)-15), from the same chiral pool starting material, (S)-perillyl alcohol 32. Donohoe et al. proposed that the furan-alkene bond could be formed by Negishi cross coupling as shown by Rawal et al. in the synthesis of bipinnatin J. Disconnections through the butenolide ring were also envisioned to allow ring closure through macrolactonisation and RCM; leading to two key fragments 77 and 78. It was anticipated that the furan ring
could also be formed through RCM and that the resulting fragment 79 could in turn be formed from the chiral pool starting material (S)-perillyl alcohol 32.

Scheme 23 Retrosynthetic analysis of (−)-Z-deoxypukalide by Donohoe et al.

The forward synthesis began with the four-step synthesis of ring-closing metathesis precursor 80 from (S)-perillyl alcohol 32 (Scheme 24). Treatment of 80 with Grubbs II in refluxing CH$_2$Cl$_2$ furnished the cyclic olefin 81 which was immediately aromatised in situ under acidic conditions to afford the furan 82 in 85% yield. This was followed by a three-step functional group manipulation to give the furan fragment 83.

Scheme 24 Furan formation in the total synthesis of (−)-Z-deoxypukalide by Donohoe et al.

The side-chain on the furan ring was installed by a Negishi cross-coupling reaction with the vinylic iodide 77, which was synthesised in a four-step sequence previously reported by Pattenden.$^{[49]}$ Double deprotonation of 83 with LDA and in situ transmetalation with zinc bromide was followed by Pd-catalysed coupling to furnish 84. Following this, deprotection, macrolactonisation under Shiina conditions$^{[50]}$ and a second ring-closing metathesis reaction afforded (−)-Z-deoxypukalide (−)-15 (Scheme 25). Following this route, synthesis of (−)-Z-deoxypukalide was completed in 12 steps (longest linear sequence) with an overall yield of 15%.
1.2.2.1.3 Pattenden’s Approach

A further total synthesis of (+)-Z-deoxypukalide ((+)-15) was reported by Pattenden et al. in 2010. Disconnections were made as in Trauner’s synthesis of bipinnatin J; between C6-C7 and C1-C2. The same vinyllic iodide fragment 48 was used; although synthesised in an alternative manner in 9 steps from diol 86.

Scheme 26 Key disconnections and initial steps in Pattenden’s synthesis of (+)-Z-deoxypukalide

Having established a route to vinyllic iodide fragment 48, Stille coupling with furylstannane 85 afforded the cyclisation precursor 87. Formation of the corresponding bromide using NBS and PPh₃, followed by NHK macrocyclisation furnished the macrocycle 88 in good yield. Deoxygenation was carried out in high yield using TFA and triethylsilane to afford 89. Subsequent deprotection of the primary alcohol, followed by oxidation with manganese dioxide, gave the corresponding aldehyde 90, which was further converted into the methyl ester in two steps to complete the synthesis of (+)-Z-deoxypukalide.
1.2.2.2 Synthesis of Bis-deoxylophotoxin

In 2005, Pattenden et al. reported the synthesis of bis-deoxylophotoxin (91); a lophotoxin analogue with alkenes in place of the epoxides across C7-C8 and C11-C12.\textsuperscript{[51]} Disconnections between C6-C7 and C12-C13 led to the proposal of Stille coupling and an aldol-type reaction as the key steps for fragment coupling of the iodide 92 to the stannane 93.

Formation of lactone fragment 92 was achieved from chiral epoxide 95, which was obtained from \((R)\)-epichlorohydrin (94) in four steps and with high ee. Treatment of epoxide 95 with
the lithium salt of 1-ethoxyacetylene, followed by reaction with pTSA afforded lactone 96 in high yield. α-Phenylselenolactone 92 was subsequently formed through formation of the silyl enol ether and trapping with phenylselenium bromide; direct trapping of the lithium enolate resulted in formation of the bis-selenated lactone.

Scheme 29 Formation of the lactone fragment for the formation of bis-deoxylophotoxin

Furan-aldehyde fragment 93 was prepared from oxazolidinone 97 in 10 steps. Deconjugative alkylation through deprotonation of oxazolidinone imide 97 and treatment with ethyl-2-bromomethyl-3-furoate furnished the furan adduct 98. Reduction of the imide to the corresponding alcohol using two equivalents of Super Hydride was followed by tosylate formation, reduction of the ethyl ester using DIBAL-H and subsequent SN2 nitrile formation to afford alcohol 99. A further five-step sequence furnished furan-aldehyde 93 required for the coupling reaction.

Scheme 30 formation of furan fragment 93 in the synthesis of bis-deoxylophotoxin

Formation of the macrocycle 101 was achieved in three steps from fragments 92 and 93. Intermolecular alkylation proceeded in high yield, furnishing alcohol 100 as a mixture of diastereoisomers. Oxidative elimination of the phenylselenide using H2O2 delivered the butenolide whilst a subsequent intramolecular Stille reaction completed formation of the macrocycle to furnish 101 as a ~2:1 mixture of diastereoisomers in low yield. Intermolecular Stille coupling followed by an intramolecular aldol reaction was also explored; however, macrocycle formation was not observed. A three-step acetylation, deprotection and oxidation
sequence furnished both epimers of bis-deoxylophotoxin (91) from the corresponding isomeric alcohols 101.

Scheme 31 Completion of the synthesis of the bis-deoxylophotoxin (91)

1.2.2.3 Synthesis of Deoxyprovidencin

One of the most recent publications by Mulzer et al. detailed the total synthesis of 17-deoxyprovidencin (102). The synthesis was completed in a longest linear sequence of 17 steps, from a known compound, in an overall yield of 1.6%. The key furan motif was constructed using a base-mediated cyclisation reaction whilst the desired alkene geometry was obtained by isomerisation under UV-B light; a method previously unseen in the synthesis of these natural products. Retrosynthetic analysis suggested that both epoxides could be installed at a late stage in the synthesis after completion of the macrocycle 103 using RCM of an intermediate generated by intermolecular aldol coupling of the two key fragments 104 and 105.

Scheme 32 Retrosynthetic analysis of deoxyprovidencin by Mulzer et al.
Synthesis of furan fragment 104 began from the known cyclobutane 106, which was converted into the corresponding diol through ozonolysis and reduction. Differentiation of the two primary alcohols was achieved by selective tritylation of the less hindered alcohol to afford alcohol 107. A five-step sequence subsequently yielded alkyne 108 which underwent base-mediated cyclisation to install the furan functionality, affording vinylfuran 109. The final furan fragment 104 was obtained after a two-step hydroxyl deprotection-oxidation sequence.

Scheme 33 Key steps in the synthesis of fragment 104

Selenolactone fragment 105 was prepared from (R)-glycidyl tosylate (110) in three steps. Cuprate mediated addition of isoprenyl magnesium bromide afforded alcohol 111 which was converted into selenide 112 through NaNH promoted epoxide formation and treatment with the dianion of phenylselenyl acetic acid. The seco-acid 112 was subsequently cyclised under Steglich conditions too afford selenolactone 105.

Scheme 34 Formation of selenolactone fragment 105

An intermolecular aldol reaction between fragments 104 and 105 furnished the aldol adduct as a mixture of four diastereoisomers. Subsequent treatment with H2O2 promoted oxidative elimination of the selenide to afford the butenolide 113 as a mixture of alcohol epimers. Ring-closing metathesis using Grubbs second generation catalyst resulted in the formation of the readily separable Z-olefin diastereoisomers 114 in a 1.5:1 ratio. Acetylation of the (S)-alcohol ((S)-114) was followed by treatment with sodium hypochlorite, under conditions...
reported by Node et al.,[53] to form the C11-C12 epoxide diastereoselectively and afford 115. Irradiation of 115 with UV-B light resulted in Z/E isomerisation to give desired E-olefin 116. Ketone 117 was generated though TBAF mediated silyl ether cleavage and subsequent oxidation with IBX. Stereoselective epoxidation of the C7-C8 olefin was then conducted using DMDO before a final Wittig methylenation reaction afforded 17-deoxyprovidencin (102).

Scheme 35 Final steps in the synthesis of 17-deoxyprovidencin by Mulzer et al.

1.2.3 Synthetic Approaches Towards the Furanocembrane Skeleton

In addition to the total syntheses discussed previously, other studies directed toward furanocembranoid natural products have been reported by several groups. These studies have either largely focused on the construction of the furanocembrane skeleton or more highly oxygenated family members such as lophotoxin, pukalide and providencin.

1.2.3.1 Paterson’s Approach to the Furanocembrane Skeleton

In 1999, Paterson et al. reported studies towards the synthesis of the skeleton of lophotoxin and pukalide; an intermolecular aldol reaction was used to join the key fragments and an intramolecular Stille coupling reaction was employed to close the model macrocycle.[36] Model fragments 118 and 119 were both formed in three steps from known starting materials
and then coupled using an intermolecular aldol reaction with LiHMDS as the base to afford the alcohol 120 in high yield. However, this strategy proved to be unsuitable as the intramolecular Stille coupling-oxidation sequence afforded the macrocycle 121 in very low yield (15%). Despite the limitations of this approach it was later adopted by Pattenden et al. for the synthesis of bis-deoxylophotoxin.

**Scheme 36** Synthesis of the furanocembranoid backbone by Paterson

### 1.2.3.2 Wipf’s Approach to the Furanocembrene Skeleton

In 2002, Wipf and Soth reported a synthesis of the C1-C10 fragment of lophotoxin and pukalide using Pd catalysis to assemble the furan ring through intramolecular reaction of an alkyne with a ketone.\[^{54}\] They had earlier reported the formation of tri-substituted furans 125 in this manner from β keto esters 122 but reported little selectivity with respect to the E/Z ratio of the alkene product.\[^{55}\] They proposed that the E/Z ratio could be tuned depending on the facial selectivity of the allene protonation step; if one face was blocked by a bulky group then one alkene isomer would predominate because the proton would approach from the opposite face.

**Scheme 37** Facial selectivity in Wipf and Soth's furan formation

After a five-step synthesis of furan precursor 126 had been achieved, formation of the C1-C10 fragment was explored. As proposed, cyclisation proceeded with a high level of stereocontrol to give (Z)-alkenylfuran 127 in a ca. 15:1 ratio in high yield. The TMS group was converted into the desired methyl substituent using a silane-iodine exchange reaction followed by Negishi cross-coupling to give the desired (E)-isomer 128.
Scheme 38 Furan formation described by Wipf and Soth

Preparation of an advanced racemic intermediate 131 was achieved subsequently following the same protocol. From intermediate 129 cyclisation, silyl-iodine exchange and Negishi coupling proceeded as before, in moderate yield, to give furan 131. Overall the fragment was synthesised in a total of 11 steps and with an overall yield of 10% from 1,4-butanediol.

Scheme 39 Synthesis of an advanced intermediate 131 of the furanocembranes

In 2006, Wipf and Grenon reported further advances in their synthesis of lophotoxin fragments. Starting from cyclic meso-anhydride 132 the C13 stereocentre was installed by catalytic desymmetrisation to afford carboxylic acid 133. Reduction of the free carboxylic acid furnished alcohol 134, which was converted to the [1,3]dioxin-4-one 136 through oxidation and a Horner-Wadsworth-Emmons reaction with phosphonate 135. A novel 1,6-addition of an organocuprate bearing the isoprene functionality ensued to give ester 137 as a 1:1 mixture of diastereoisomers. Attempts to improve the stereoselectivity of the reaction using a rhodium catalyst and potassium isoprenyltrifluoroborate were largely unsuccessful,
delivering moderate yields and low \( dr \). Thermolysis of the dioxin-4-one ring afforded the corresponding \( \beta \)-keto ester which was alkylated with iodide \( 138 \) to afford alkyne \( 139 \). Palladium catalysed furan formation was then effected as described previously, albeit with an alternative catalyst and base, to afford furan \( 140 \). Despite preparing this late stage intermediate, Wipf reported no further progress towards the targets of interest.

\[ \text{Scheme 40 Lophotoxin fragment synthesis reported by Wipf} \]

**1.2.3.3 White's Approach to the Furanocembrane Skeleton**

Recently, White et al. published studies concerning the total synthesis of providencin (141).\(^{[57]}\) They envisioned that the macrocyclic structure could be constructed by use of Stille coupling between a vinyl iodide \( 142 \) and the furylstannane \( 143 \) to construct the C6-C7 bond and intermolecular aldol condensation of the enolate of the selenyl lactone to construct the C12-C13 bond (Scheme 9).
Scheme 41 Retrosynthetic strategy adopted by White et al. for the synthesis of Providencin

The furan moiety 145 was synthesised by a silver nitrate/silica mediated cyclisation of the keto-allene 144 under conditions similar to those described by Marshall (Scheme 21).\[46]\] Subsequent functionalisation of 145, over five further steps, led to the formation of furan 146 with the desired exocyclic alkene. Stannylation of the furan and coupling with vinyl iodide 147 resulted in the formation of the trisubstituted furan 148. However, all attempts accomplish cyclisation to form the full natural product were unsuccessful. Oxidation of the primary alcohol also resulted in oxidation of the phenylselenyl functionality, which underwent thermal elimination to produce butenolide 149. Therefore, the envisioned aldol reaction could not be carried out and the macrocyclic skeleton of the natural product could not be completed.

Scheme 42 Key steps reported by White et al. towards the synthesis of Providencin
1.2.3.4 Bach’s Approach to the Furanocembrane Skeleton

In 2005, Bach et al. reported studies towards the furanocembrane skeleton using a regioselective bromine-magnesium exchange reaction.\[^{58}\] Starting from 4,5-dibromofurfural (150), dibromofuran 151 was prepared in high yield using a Horner-Wadsworth-Emmons reaction. A subsequent three-step deprotection, reduction and protection sequence afforded furan 152.

**Scheme 43 Formation of dibromofuran 152**

Formation of the furfuryl-Grignard reagent from 152 occurred readily and reaction with vinyl aldehyde 153 occurred cleanly and regioselectively to give alcohol 154. Attempts to form the C2-C3 carbon bond in other ways were unsuccessful; cross-coupling failed and the use of lithium-halogen exchange gave yields of less than 30%. A further four steps were required to convert furan 154 into aldehyde 155 which underwent subsequent intramolecular Nozaki-Hiyama coupling in low yield to afford propargylic alcohol 156. The alkyne 156 represents a similar intermediate to those described in previous furanocembrane syntheses by Marshall;\[^{38,46}\] however, completion of the synthesis was not reported in this case.

**Scheme 44 Synthesis of an advanced furanocembrane skeleton intermediate 156 by Bach**
1.2.3.5 Honda’s Approach to the Furanocembrane Skeleton

Honda et al. reported the synthesis of two potentially useful intermediates, furfuryl ether 165 and butenolide 171 in a synthetic approach to bipinnatin J (45).\(^{[50]}\) The group postulated that the butenolide could be installed stereoselectively at a late stage in the synthesis, giving 157 as the proposed intermediate. In turn, they proposed that the homoallylic alcohol 157 could be formed by [2.3]-Wittig rearrangement of furfuryl ether 158. Disconnections adjacent to the alkyne led to the proposal of aldehyde 159 as the key fragment.

Scheme 45 Retrosynthetic analysis of bipinnatin J by Honda et al.

Starting from furfuryl alcohol 160, etherification with allyl chloride 161 gave furfuryl ether 162 in moderate yield. Stille coupling of furyl bromide 162 and stannane 163 subsequently furnished vinylfurfuryl ether 164, which underwent a further six-step sequence to afford the alkyne cyclisation precursor 165. However, treatment of 165 with CuI, NaI and Cs\(_2\)CO\(_3\) in DMF at 80 °C resulted in S\(_{N2}'\) substitution, instead of the expected S\(_{N2}\) substitution, giving 15-membered macrocycle 166 instead of the desired 17-membered macrocycle.

Scheme 46 Studies towards bipinnatin J by Honda et al.
The group also examined construction of the butenolide using a model system. Propargylic alcohol 169 reaction of the aldehyde 168 with the alkynyl Grignard reagent derived from bromide 167. The propargylic alcohol 169 was then converted into allenic alcohol 170 through a procedure originally reported by Myers et al.\textsuperscript{[60]} utilising Mitsunobu elimination and subsequent removal of the MOM protecting group with CBr\textsubscript{4} in iPrOH. The butenolide was finally installed by ruthenium catalysed cyclocarbonylation to afford γ-butenolide 171 in 66% yield.

Scheme 46 Synthetic studies towards the butenolide moiety in the furanocembrane skeleton

1.2.4 Conclusion

Despite numerous studies and total syntheses there are still many difficulties associated with the synthesis of furanocembranes due to their complex structures and reactive functionality. Notably, all of the previously reported total syntheses have been of family members possessing low oxidation levels. Introduction of the C7–C8 epoxide that is present in lophtoxin and pukalide has proven to be particularly challenging, with only Mulzer et al.\textsuperscript{[52]} having established a successful strategy for its incorporation. Consequently, a total synthesis of pukalide, as well as other oxygenated members, has yet to be achieved. This fact, coupled with the interesting associated biological activity, makes furanocembrane natural products highly attractive total synthesis targets.
1.3 Furan Synthesis

1.3.1 Furan Formation

Polysubstituted furans have received a great deal of attention as they are not only common motifs in natural products and pharmaceuticals, but are also useful building blocks for the construction of highly complex structures. For example, members of the furanocembrane natural product family include a trisubstituted furan within their core structure.

![Figure 8 Structures of lophotoxin and pukalide](image)

In the past 30 years many new reactions have been discovered for the synthesis of furans; these approaches employ a range of both inter- and intramolecular processes encompassing many transition metal catalysed reactions as well as some involving acid/base catalysed reactions and a small number involving organocatalytic processes.\(^{[61-64]}\)

This section comprises a brief overview of furan synthesis with particular focus on the synthesis of tri-substituted furans.

1.3.2 Classical Synthesis of Furan Molecules

The two most important traditional methods for the formation of furans are the Paal-Knorr and Feist-Benary syntheses, first reported in the late 19\(^{th}\) and early 20\(^{th}\) centuries.\(^{[65-68]}\) In 1884, C. Paal and L. Knorr independently reported the formation of substituted furans by dehydration of 1,4-diketones; this reaction is now known as the Paal-Knorr synthesis (Scheme 47). Although the reaction was discovered more than a century ago the mechanism was only fully elucidated in 1995 by Amarnath \textit{et al.}\(^{[69]}\) The mechanism of this transformation involves protonation of one of the carbonyl groups, which is then attacked by the enol of the second carbonyl to generate the dihydrofuran intermediate \textit{174}. Subsequent dehydration promoted by a strong acid, Lewis acid or dehydrating agent, such as acetic anhydride, followed by enolisation, delivers the desired furan \textit{177}. 

![Scheme 47 Paal-Knorr synthesis](image)
The Feist-Benary synthesis, originally reported by Feist in 1902, also proceeds via a condensation type reaction.\textsuperscript{[67,68]} The process involves the reaction of a β-dicarbonyl compound 178 with an α-haloketone 179 in the presence of a base. The reaction proceeds through the formation of the aldol adduct 180 and subsequent intramolecular nucleophilic displacement of the chloride by the enolate; upon dehydration, the reaction affords the desired furan 182.

Although these classical methods are useful, they have two major disadvantages: their incompatibility with acid or base sensitive functional groups and the fact that they do not allow for the introduction of a great amount of complexity on the furan ring. As a result of these limitations, many other furan-forming reactions have since been developed.

### 1.3.3 Metal-catalysed Furan Synthesis

Developments in the field of transition-metal chemistry have led to many new efficient and selective synthetic reactions.\textsuperscript{[70]} The construction of furans under mild metal-catalysed conditions has been reported using a wide range of metals such as copper, gold, zinc, platinum, palladium and silver. Herein, representative examples of metal-mediated procedures for the synthesis of tri-substituted furans are discussed.
1.3.3.1 Palladium Catalysis

To date, palladium catalysis, along with gold catalysis, has become one of the most commonly used methods for the synthesis of substituted furans.\(^\text{[71]}\) Utimoto reported some of the first examples of Pd(II)-catalysed furan formation in 1983.\(^\text{[72]}\) The use of β,γ-acetylenic ketones 184 and 2-methoxy-3-alkyn-1-ols 186 for the formation of furans 185 by an intramolecular cyclisation process was described, utilising either palladium(II) chloride or bis(benzonitrile)palladium(II) chloride (Scheme 49).

Scheme 49 Pd-catalysed furan formation reported by Utimoto

Since then, numerous groups have reported the use of alkenynols and alkenynones for the formation of a variety of tri- and tetra-substituted furans under similar Pd(II)-catalysed reaction conditions.\(^\text{[73]}\) Recently, in 2013, Wang and co-workers reported a palladium-catalysed reaction using conjugated enynones 187 as carbene precursors for the formation of furans 189 by a migratory insertion process (Scheme 50).\(^\text{[74]}\)

Scheme 50 Palladium catalysed furan formation described by Wang

The reaction proceeds in good yields; however, the nature of the R⁴ group affects the E/Z selectivity. It was found that a bulky substituent at this position gave the Z isomer with high selectivity, whereas smaller substituents, such as TMS, resulted in the production of a mixture of E and Z isomers. The catalytic cycle is proposed to begin with oxidative addition of Pd(0) into the halo compound, followed by activation of the alkyne 190 and cyclisation of the oxygen atom onto it to generate a palladium (2-furyl)carbene intermediate 191. Subsequent migratory insertion and β-hydride elimination affords the product; the catalyst is regenerated by treatment trapping of HBr with base (Scheme 51).
In subsequent work, Wang et al. described the formation of 2-alkenyl substituted furans 194 and 195 with high (E)-selectivity using a combination of carbene chemistry and palladium cross-coupling. Oxidative cross-coupling of enynone 193 with either an aryl or a vinyl boronic acid occurs in good yield and with excellent stereoselectivity.

The reaction is proposed to proceed through initial oxidation of Pd(0) to Pd(II) using benzoquinone; consequent oxidative addition of the boronic acid generates the intermediate palladium species 196. The alkyne 193 is then activated by the newly formed palladium species 197 and nucleophilic attack of the carbonyl oxygen onto the alkyne ensues. The resulting (2-furyl)carbene species 198 undergoes migratory insertion to give the final intermediate 199, before β-hydride elimination occurs to afford the 2-alkenyl furan 194/195. The reactive palladium(0) species is then regenerated upon reaction of the palladium hydride 200 with base.
In 2012, Vicente and Lopez reported the formation of cyclopropyl-furans as a result of the zinc chloride catalysed intermolecular reaction between an enynone and alkene. (Scheme 54). The method described generates a zinc carbenoid species 205 from enynone 201 and the zinc salt. Initially, the zinc is proposed to co-ordinate to the carbonyl and alkyne of the enynone 201 to give a zinc complex 204. Attack of the carbonyl onto the alkyne results in 5-exo-dig cyclisation and subsequent tautomerisation. The alkene can then trap the carbene intermediate to form the cyclopropane product 203. Using this methodology a wide range of highly functionalised cyclopropyl-furans was synthesised with moderate to high stereocontrol, depending on the nature of the substituents on the cyclopropane ring.
Scheme 54 The zinc chloride catalysed formation of cyclopropyl-furans as described by Vicente and Lopez

Vicente et al. reported an extension of this work in 2013 wherein they described a zinc-catalysed cyclisation, followed by C-O or C-N bond formation through reaction with primary or secondary alcohols or with an azole, such as a pyrazole, imidazole or triazole (Scheme 55). Unlike their earlier work, it was found that an electron-rich aryl group was required for the reaction to proceed. A higher catalyst loading of 20 mol% zinc chloride was also required.

Scheme 55 Representative example of the zinc-catalysed cyclisation reported by Vicente

Intramolecular Zn-mediated processes, such as that described by Dembinski et al. in 2007, have also been employed for the synthesis of substituted furans (Scheme 56). The zinc chloride catalysed reaction proceeds via a 5-endo-dig cycloisomerisation of 1,4-di-
1,2,4-trisubstituted but-3-yn-1-ones 208 in CH₂Cl₂ at room temperature to give 2,5-di- and 2,3,5-trisubstituted furans 209.

Scheme 56 Zinc catalysed furan formation described by Dembinski

1.3.3.3 Gold Catalysis

Gold catalysts have proven to be particularly useful for the synthesis of functionalised furans due to the bifunctional properties of the metal. Gold species are adept at activating alkynes and allenes through complexation; cationic gold species also possess strong Lewis acidic properties.

Two interesting examples of gold-catalysed furan-formation are denoted in the works published by Arcadi et al. and Pale et al. (Scheme 57).[79,80] Arcadi’s group described the coupling of a 1,3-dicarbonyl compound 211 with a propargylic alcohol 210 in a tandem cascade process to form tetra-substituted furans 212. Pale et al. reported the rearrangement of alkynyloxiranes 213 upon treatment with triphenylphosphine gold triflate; giving trisubstituted furans 214 in good yields. In this case an external nucleophile, namely MeOH, is required to promote the gold-catalysed isomerisation reaction

Scheme 57 Examples of gold-catalysed furan formation

In 2013, Pale et al. went on to report the formation of tri-substituted furans 216 using a gold(I) complex from γ-acyloxyalkynyl ketone precursors 215.[81] Furan formation was found to proceed with moderate yield when both R¹ and R² were alkyl substituents and R³ was either an alkyl substituent or an electron-rich aryl group (Scheme 58).
Pale proposed a mechanism for the reaction based on the ability of the gold catalyst to function as both a π and σ Lewis acid. He hypothesised that, when acting as a σ Lewis acid, the gold cation would complex to the oxygen of the ketone 217, acting as an oxophilic activator. This would be followed by 1,4-addition of the nucleophilic acyloxy group to the alkyne to form allene 218, which would in turn be in equilibrium with E and Z vinyl intermediates 219 and 221. The π Lewis acidic pathway leads to the same intermediate via gold complexation to the alkyne 220 and nucleophilic attack of the acyloxy carbonyl. Rearrangement of 221 produces the carbenoid species 222 which undergoes intramolecular attack of the carbonyl onto the alkene to generate the cyclic oxocarbenium ion 223. Tautomerisation with regeneration of the gold catalyst then furnishes the furan product 216.
In 2014, Hashmi et al. reported a gold-catalysed cyclisation cascade reaction for the synthesis of tri-substituted formylfurans 225 and 226 (Scheme 60). These motifs, or higher oxidation state analogues thereof, are found in the furanocembrane natural products. The group reported that treatment of diynol 224 with IPrAuCl, in combination with silver triflate and an oxidant, resulted in the formation of the formylfurans. When substituents R and R¹ were identical, high yields of desired product were reported. However, reactions of diynols that lacked symmetry gave lower yields and produced mixtures of regioisomers, 225 and 226.

Scheme 60 Gold(I) catalysed cascade reaction for tri-substituted formylfuran formation

Mechanistic studies, using isotopic ¹⁸O and ¹³C, led to the elucidation of the reaction mechanism. Initially, in an established process, α-oxo gold carbenoid 227 is generated from the diyne 224 in the presence of gold(I) and the pyridine N-oxide (Scheme 61). A 1,2-alkyne shift onto the gold carbenoid then occurs instead of a potential 1,2-hydride shift, to give intermediate 228, which subsequently isomerised to give aldehyde 229 before cyclisation to form the desired furan product 225.

Scheme 61 Mechanism of the gold(I) catalysed furan formation

1.3.3.4 Copper Catalysis
Copper catalysts have been employed instead of transition metal catalysts for the synthesis of substituted furans. In 2008, Barluenga et al. reported regioselective methodology for the
The reaction proceeds through the formation of a furyl-copper carbene complex 231, which allows functionalisation through the creation of a carbon-heteroatom bond; in the absence of a suitable reaction partner, furyl alkene dimers are isolated (Scheme 62). The reaction tolerates a wide range of functionality and the reaction proceeds in good yield when $R^1 = \text{alkyl, vinyl, allyl, aryl or silyl and } R^2 = \text{alkyl or vinyl}$.

Scheme 62 Furan formation described by Barluenga et al.

In 2016, a new approach to the synthesis of furan-substituted allenes was reported by Wang et al (Scheme 63). In this case, furan formation occurs through a copper-catalysed carbene migratory insertion reaction. The reaction between ene-yne-dione 233 and an alkyne 234 in the presence of catalytic amounts of copper(I) gives carbene complex 235, which then undergoes migratory insertion to furnish the desired allene product 237. A wide range of alkyynes 234 are tolerated under the reaction conditions; electron-rich, electron-poor, aryl and alkyl substituted systems were all found to give moderate yields.

Scheme 63 Synthesis of furan-substituted allenes
1.3.4 Organocatalytic and Acid/Base Methods

Interest in organocatalysis has increased greatly in recent years and many enantioselective organocatalytic reactions have been developed. As a result, many synthetic transformations can now be carried out organocatalytically.\cite{85,86} Organocatalysed and acid/base catalysed reactions have great potential in synthesis and possess particular advantages when compared to their metal-catalysed counterparts; namely that small molecules are generally stable to air and water and have a low toxicity. In addition, small organic molecules are often cheaper than transition metals and more readily available.\cite{87} Despite their growing popularity, organocatalysts have been used less frequently than metal catalysis in the field of furan synthesis.

1.3.4.1 Synthesis of 2-Hydroxyalkylfurans and 2-Aminoalkylfurans

In 2010, Jørgensen et al. reported an organocatalytic and enantioselective method for the synthesis of trisubstituted furans, and specifically 2-hydroxyalkyl and 2-aminoalkyl furans, based on the Feist-Benary synthesis.\cite{88} The method allows furans to be synthesised in a highly enantioselective fashion (ee >90%) under mild conditions and with low catalyst loadings (Scheme 64).

In the Jørgensen protocol, a proline derivative is employed as a catalyst for the epoxidation or aziridination of an α,β-unstaurated trans alkenal 238, to afford an enantioenriched 2,3-epoxyaldehyde or 2,3-aziridinyl aldehyde 239. These compounds were then used in the Feist-Benary type reaction to give an electron-poor 2-hydroxyalkyl furan or furfuryl amine 241.

\[ 238 + \text{TsNHOtS, NaOAc or H}_2\text{O}_2 \rightarrow 239 \]

\[ 239 + \text{Base} \rightarrow 240 \]

\[ 240 + \text{Acid} \rightarrow 241 \]

Scheme 64 Synthetic approach towards 2-aminoalkylfurans and 2-hydroxyalkylfurans

The methodology allows for the use of both γ-branched aliphatic and aromatic α,β-unsaturated aldehydes as substrates as well as a variety of 1,3-diketones, which provides scope to change the functionality of the trisubstituted furan products. Numerous acids and bases were screened to promote the furan formation and it was found that using a milder base such as K$_2$CO$_3$ or Hünig’s base allowed for the isolation of the hydroxyl/tosylamide
intermediate 240. However, use of MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) with either CSA or TFA proved to be optimal for preparation of the hydroxy and amino products 241 in a one-pot procedure.

1.3.4.2 Acid Catalysed Synthesis of Cyclopropyl-substituted Furans

Recently, in 2015, the Clark group reported the synthesis of cyclopropyl-substituted furans using a Brønsted acid promoted cascade reaction.[89] In the reaction, chloroacetic acid is used to promote an efficient and diastereoselective intramolecular cascade reaction of electron-deficient enynes 242 to deliver products that feature a 2,3,5-trisubstituted furan bearing a fused cyclopropyl substituent at the 5-position 243 (Scheme 65). This method allowed for the synthesis of polycyclic building blocks featuring rings of various sizes and featuring various heteroatoms.

![Scheme 65 Brønsted acid promoted formation of cyclopropyl-substituted furans](image)

It has been proposed that the acid-catalysed reaction proceeds by an unusual mechanism in which a free carbene is generated under acidic conditions. Initially, an allene 246 is formed through protonation and isomerisation. The allene is then converted into a carbene 247 by attack of the enol onto the allene (Scheme 66).

![Scheme 66 Proposed mechanism for the formation of carbene 247](image)
It was found that in cases where an allylic ether was present, the free carbene underwent competitive C-H insertion and intramolecular cyclopropanation to give 248 and 249 respectively (Scheme 67). Intermolecular cyclopropanation and intramolecular C-H insertion reactions of less activated substrates were found to be disfavoured, suggesting that cyclisation to give the furan and carbene is reversible in the absence of a reactive group able to trap the carbene. It was also suggested that a low concentration of carbene intermediate 247 is present within the reaction mixture as a result of the equilibrium between the carbene and cationic species 246.

![Scheme 67 Formation of C-H insertion and cyclopropanation products](image)

### 1.3.4.3 Phosphine Promoted Synthesis of Furans from Enynes

In 1999, Kuroda et al. published a phosphine-initiated method for the preparation of furans from substituted enynes.[90] The group went on to further investigate the method and in 2004 published work outlining the formation of tri- and tetra-substituted furans from more highly substituted enynes under these conditions (Scheme 68).[91] The reactions were performed in the presence of a stoichiometric amount of phosphine.

![Scheme 68 Phosphine promoted formation of tetrasubstituted furans](image)

Investigations in to the reaction mechanism led to the proposal of the formation of an ylide as an intermediate as using triethylamine as a catalyst did not deliver the furan product. Kuroda suggested that the phosphine acted as a reaction initiator through 1,6-addition to the enyne and that this reaction was followed by cyclisation to give the phosphonium intermediate 254. A Wittig reaction of an aldehyde with the ylide would therefore give the
desired unsaturated furan product (Scheme 69). Kuroda's work showed that organic compounds could be used to promote furan formation, moving away from the more conventional metal-catalysed approach.

**Scheme 69** Proposed reaction mechanism for phosphine mediated furan formation

### 1.3.4.4 Condensation of γ-acyloxy Butynoates

An additional strategy for the construction of substituted furans promoted by a phosphine was described by Krische et al. in 2004.[92] γ-Acyloxy butynoates were exposed to an excess of triphenylphosphine resulting in the formation of substituted furans by an intramolecular reductive condensation. The proposed mechanism for this transformation involves the conjugate addition of triphenylphosphine into the butynoate 255 and attack of the resulting enolate onto the ester carbonyl group to generate the five-membered oxacycle 256 (Scheme 70). This is followed by rearrangement to the oxaphosphetane 257 and extrusion of triphenylphosphine oxide to produce the allenic ester 258. Nucleophilic attack by a second equivalent of triphenylphosphine onto the allenic ester and cyclisation of the resulting zwitterionic intermediate 259 results in the formation of phosphonium ylide 260 which undergoes enolisation with elimination of triphenylphosphine to generate the furan product 261. Studies into the efficiency of the method revealed that the reaction is most proficient when $R^2$ of the butynoate is electron-deficient; thus, making the carbonyl group more reactive towards nucleophilic attack in the initial step.
1.3.4.5 Organosulfur Catalysed Synthesis

Inspired by the methodology published by Kuroda, Clark et al. proposed that an analogous reaction could be promoted by a thioether. In 2012, the Clark group published novel methodology for the organocatalytic formation of highly substituted furans from ynenones using tetrahydrothiophene (THT) (Scheme 71).\[93] Treatment of the enyne 262 with 10 mol% of THT in the presence of a suitable nucleophile, such as a carboxylic acid, alcohol or sulfonamide, gave the resulting highly functionalised furfuryl product 263. Various electron withdrawing groups (EWGs) were found to be well-tolerated (ketones, esters, nitriles, sulfones and phosphonates) and it was shown that the R¹ group could be alkyl, aryl or silyl.

Scheme 71 THT catalysed furan formation
The proposed reaction mechanism begins with conjugate addition of the tetrahydrothiophene (268) into the enyne 262 followed by formation of ylide 265 through intramolecular cyclisation of the resulting enolate onto the allene. In the presence of a proton donor, the sulfonium ylide is protonated to form the sulfonium ion 266 and the corresponding nucleophile. The THT is released back into the catalytic cycle through formation of the oxonium intermediate 267 which is then trapped by the nucleophile to form the product (Scheme 72). It is likely that this transformation proceeds through the described S_{N}1 pathway rather than through a direct S_{N}2 displacement of THT.

Scheme 72 Mechanism for the THT promoted furan formation

Further investigation of the reaction mechanism revealed that three side products are formed when the reaction is performed using an electrophilic ynenone and tert-butyl alcohol. In this case, alcohol 271, alkene 272 and dimer 273 were all found to be produced alongside the desired product 270.
Formation of the three side-products is proposed to arise at different points in the catalytic cycle (Scheme 74). Dimer 273 is thought to arise through nucleophilic attack of the sulfur ylide 275 onto a second enynone compound, giving intermediate 278. Cyclisation is then thought to arise through an $S_N2$ type mechanism, eliminating THT to furnish the dimer 273. Vinyl furan 272 is proposed to result from proton abstraction and elimination of THT from cationic intermediate 276. Alcohol by-product 271 arises from competing nucleophilic addition of water to the cationic sulfur intermediate 276; this by-product is not observed when there is rigorous exclusion of water from the reaction.
An example of a tandem one-pot condensation and furan-forming reaction was also reported by the Clark group as an extension to this methodology (Scheme 75). One-pot transformations have the added advantage that they significantly reduce chemical waste and improve synthetic efficiency. The reaction of acetylacetone (279) and the alkynyl aldehyde 280 in the presence of benzoic acid, THT and piperidine afforded the furan 281 in 57% yield, which was comparable to the overall yield obtained when the reactions were performed separately.

Scheme 75 One-pot condensation furan formation

Alongside the intermolecular trapping of the sulfonium ion intermediates with a nucleophile, it was also demonstrated that nucleophilic attack can occur by an intramolecular process (Scheme 76). Treatment of enyne 282 with THT resulted in the formation of the epoxyfuran species 283. Epoxyfurans can be unstable and thus the formation of 283 in good yield demonstrates the mild nature of the reaction conditions. This result suggested a potential application of the reaction in the total synthesis of complex natural products which possess an epoxyfuran motif, such as the marine furanocembranoids.

Scheme 76 Organocatalytic formation of an epoxyfuran 283

More recent work has also shown that tethered tetrahydropyrans and tetrahydrofurans can be synthesised in the same manner (Scheme 77). Starting from acyclic enynediones 284 and 285, which contain a tethered primary alcohol, tetrahydrofuran and pyran products 286 and 287 were obtained in good yield using 20 mol% of THT as the catalyst. The reaction was also extended to systems containing a carboxylic acid nucleophile. Treatment of alcohols 284 and 285 with DMP, followed by oxone, afforded the corresponding carboxylic acids 288 and 289. Cyclisation of these enynedione substrates bearing ω-carboxylic acids afforded bicyclic γ-butyrolactone 290 and δ-valerolactone 291 products.
Cyclisation reactions of enynediones 292 possessing tethered secondary alcohols and branched chains were also found to proceed well in the presence of a higher catalytic loading of THT (50 mol%). In this case, phenylphosphonic acid was also required as a co-catalyst to effect tandem cyclisation. Little to no stereocontrol was observed for the formation of the tetrahydrofuran ring when R₁ was a small group (Me, Et etc.) (entries 1-3, Table 1). However, diastereoselectivity was observed when a branched chain primary alcohol was used (entry 4). The use of a tert-butyl group at R₁ also resulted in a reasonable level of diastereocontrol during tetrahydropyran formation (entry 5).

Scheme 77 Synthesis of bicyclic furan species
Studies were also performed to determine whether cyclisation could be effected in an enantioselective manner.\[^{[99]}\] Having established that an acidic co-catalyst helps promote furan formation, it was hypothesised that the new stereocentre could be introduced using a chiral acid through asymmetric counterion directed catalysis (ACDC). However, the best cases, in which \((S)-(\text{+})-\text{TRIP-H}\) was employed as the catalyst, afforded the product 296 in high yield but with just 12% ee.

\[
\text{Scheme 78 Attempted enantioselective synthesis of trisubstituted furans}
\]
2 Results and Discussion

2.1 Background and Retrosynthetic Strategy

In 2012 the Clark group reported a novel organocatalytic method for the synthesis of trisubstituted furans from ynenones, which are easily obtainable through Knoevenagel condensation of propargylic aldehydes.\(^9\) This new methodology has been used to prepare a wide range of substrates, including the epoxyfuran \(283\), through treatment of the ynenone \(282\) with a sub-stoichiometric amount of tetrahydrothiophene (THT) (Scheme 79). The formation of epoxyfuran \(283\) in good yield highlights the mild nature of the reaction conditions. Moreover, it represents a strategy for the formation of such an epoxide in the presence of other reactive alkenes present in the substrate. These observations suggested a potential application of the reaction in the total synthesis of complex natural products that possess an epoxyfuran unit.

![Scheme 79](image)

Scheme 79 Epoxyfuran formation using organocatalytic THT

With the THT methodology in mind, we became interested in exploring whether the transformation could be used as the furan-forming reaction in the total synthesis of members of the furanocembrane natural product family. Construction of the epoxyfuran unit that is present in many of the family members has so far proven to be very challenging. Mulzer \textit{et al.} addressed this by performing a late stage epoxidation of a conjugated alkene using DMDO in their synthesis of deoxyprovidencin;\(^5\) however, in substrates where the butenolide is present, selective epoxidation of the C7-C8 bond is not possible.

Pukalide, an interesting family member which had so far eluded synthesis, was chosen as the initial target. Previously, epoxyfuran formation under the THT conditions had only been accomplished using the ynenone \(282\) as the substrate. However, pukalide possesses an ester group at C18 and so an ynenone possessing non-equivalent carbonyl groups would be required for the synthesis. To examine whether cyclisation of this type of substrate would be feasible, a reaction was performed using a mixture of \(E/Z\) ynenones \(297\) under the THT catalysed conditions (Scheme 80). Complete conversion of the \(E\)-alkene occurred within 19 hours to give the desired epoxyfuran product \(298\); however, most of the \(Z\) isomer was recovered. The difference in reactivity between the two isomers suggested implications for
the total synthesis; during the late-stage Knoevenagel condensation the product with the desired *E* geometry would have to be formed in order to complete the target in good yield. Slow isomerisation of *Z* to *E* was observed; however, after 48 hours 66% of the *Z* isomer was still present.

**Scheme 80** Formation of epoxyfuran 298

The synthesis of pukalide was envisioned to include the THT-mediated reaction as a mild and efficient way to install the C7-C8 epoxide and furan, simultaneously, at a late stage. Retrosynthetic analysis led to disconnection of the furan and epoxide to give macroactone 299 as a late stage intermediate. It was anticipated that this could in turn be formed from two key fragments: aldehyde 300 and β-ketoester 301. In a forward sense, it was envisioned that the ynenone would be constructed through Knoevenagel condensation of a propargylic aldehyde and a β-ketoester. The butenolide would be assembled through esterification and ring-closing metathesis. However, a decision as to which order these reactions would be utilised was to be made at a later stage. Disconnection of the methyl and alkyne groups in fragment 300 led to amide 302 as the key intermediate, whilst for fragment 301 cleavage of the β-keto ester by retro-Claisen condensation, removal of the methylene group and reconnection of C3 to C12 revealed (*R*)-perillyl alcohol (*R*-32) as the starting material.
2.2 Synthesis of (R)-Perillyl Alcohol

Retrosynthetic analysis of pukalide and the subsequently proposed fragments led to the proposal of (R)-perillyl alcohol as a starting material. However, (R)-perillyl is not commercially available and at the outset of this study, a synthetic protocol for its preparation had not been described in the literature; although, bio-catalytic methods were known. For this reason, in several previous syntheses of furanocembrane natural products, (S)-perillyl alcohol had been utilised as the starting material, resulting in the formation of the natural products in antipodal form. At the beginning of this project it was therefore necessary to establish a synthetic route for the synthesis of (R)-perillyl alcohol. In the course of the project, Evans et al. reported the synthesis of (R)-perillyl alcohol in which a palladium-mediated rearrangement reaction was employed.

It was thought that the desired (R)-perillyl alcohol ((R)-32) could be prepared from the commercially available and relatively cheap starting material (+)-limonene oxide (303) (Scheme 82). It was proposed that (R)-perillyl alcohol could be formed by Wharton rearrangement of epoxy ketone 307, which could in turn be synthesised through rearrangement and oxidation of (+)-limonene oxide. Base-mediated epoxide rearrangement
of (+)-limonene oxide (303) afforded allylic alcohol 304 as a 1:1 mixture of diastereoisomers in good yield. However, manipulation of the allylic alcohol proved to be problematic. Attempts to oxidise the allylic alcohol 304 resulted in dimerisation of the highly unstable product 305, and epoxidation with VO(acac)$_2$ led to the formation of a complex mixture which could not be separated.

![Scheme 82 Attempted synthesis of (R)-perillyl alcohol](image)

Following these disappointing results, a new strategy was sought. It was found that treatment of allylic alcohols 304 with methanesulfonyl chloride in the presence of triethylamine resulted in the formation of the corresponding mixture of mesylates 308, which underwent S$_\text{N}$$^2$ rearrangement to afford (R)-perillyl alcohol ((R)-32) in good yield upon aqueous work-up. The effect of pH and temperature on the S$_\text{N}$$^2$ rearrangement was investigated. Both acidic and mildly basic work-up conditions afforded the desired product, but treatment with saturated aq. NaHCO$_3$ was found to be optimal for product formation. However, use of a stronger base, such as sodium acetate caused degradation of the starting material.
Table 2 Formation of (R)-perillyl alcohol

<table>
<thead>
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<th>Temperature</th>
<th>Scale (mmol)</th>
<th>Yield (%)</th>
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<td>0.66</td>
<td>47</td>
</tr>
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<td>1.36</td>
<td>48</td>
</tr>
<tr>
<td>1M HCl</td>
<td>rt</td>
<td>0.17</td>
<td>-</td>
</tr>
<tr>
<td>1M HCl</td>
<td>40 °C</td>
<td>1.36</td>
<td>43</td>
</tr>
<tr>
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<td>NaOAc (2 eq.)</td>
<td>40 °C</td>
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<td>degradation</td>
</tr>
</tbody>
</table>

* Wet Et₃N used

2.3 Approach 1: An Intramolecular Knoevenagel Condensation Strategy for Macrocycle Formation

In the first synthetic strategy it was anticipated that the epoxy furan and butenolide functionality would be introduced in the final steps of the synthesis through THT catalysed furan formation and ring-closing metathesis. These ideas led to the proposal of macrocycle 309 as the key intermediate. Earlier proof of concept studies for the formation of epoxyfuran 297 from the ynenone 298 had shown that furan formation was only effected from the corresponding E isomer. It was therefore envisioned that macrocyclisation through Knoevenagel condensation would result in sole formation of the E isomer, due to ring strain, and as such would allow for full conversion to the desired furan. Disconnection of the macrocycle 309 through the ynenone subsequently gave aldehyde 310 as the precursor. In the forward direction it was proposed that this intermediate could be formed by fragment coupling of 300 and 301 through esterification. Macrocyclisation by the proposed method was unprecedented for rings of this size and consequently, this initial strategy was risky.
2.3.1 Synthesis of the C12-C14/C1-C4 Fragment

After a viable method for the synthesis of \((R)\)-perillyl alcohol had been established, efforts were focused on the synthesis of fragment 301, C12-C14/C1-C6. \((R)\)-Perillyl alcohol \((R)-32\) was protected as its triisopropylsilyl (TIPS) ether 311 and then subjected to selective ozonolysis, under conditions reported by Donohoe et al.\(^{[47]}\) Chemoselective reduction of the aldehyde 312 using sodium triacetoxyborohydride afforded hydroxyketone 313 in 41% yield over three steps.\(^{[99]}\) Wittig methylation followed, to furnish alkene 314 in high yield.

Following the synthesis of alcohol 314, subsequent steps for the formation of the \(\beta\)-keto ester fragment 301 were explored (Scheme 85). Oxidation of alcohol 314 with Dess-Martin periodinane afforded aldehyde 315 in quantitative yield. Formation of the \(\beta\)-ketoester 316 under conditions reported by Roskamp,\(^{[100]}\) occurred without full conversion and the desired
product 316 was obtained in a moderate 57% yield alongside recovered aldehyde (28%). Increasing the number of equivalents of methyl diazoacetate as well as changes to the concentration of the reaction mixture were found to have no effect on the yield. However, the yield could be improved by increasing the quantity of tin(II) dichloride; use of a stoichiometric amount resulted in full conversion and afforded the desired β-keto ester in 86% yield. Following this, silyl ether cleavage using TBAF occurred cleanly in high yield to give primary alcohol 317. Initially, one-pot oxidation procedures for the conversion of alcohol 317 to carboxylic acid 301 were investigated, but in all cases the desired product was not observed. Therefore, aldehyde 318 was accessed through oxidation with DMP and it was envisioned that acid 301 could be obtained through a second oxidation step. Unfortunately, all conditions tested resulted in oxidation of the methylene group of the α,β-dicarbonyl system and so desired product 301 was not observed. After these disappointing results it was decided that an alternative route would be required and a masked analogue of fragment 301 was targeted.

Scheme 85 Failed synthesis of β-keto ester fragment 301

Given that synthesis of carboxylic acid 301 with the β-ketoester present was unsuccessful, due to over-oxidation, it was decided that the carboxylic acid analogue 321 would be synthesised and functionalisation to form the β-ketoester would be carried out after fragment coupling. Starting from previously formed primary alcohol 314, the synthesis of the acid fragment 321 was completed in four steps; eight steps from (R)-perillyl alcohol (Scheme 86). Protection of the primary hydroxyl group of 314 as a PMB ether, followed by silyl ether cleavage resulted in the formation of alcohol 320 in 87% yield over the two steps.
Subsequent oxidation with Dess–Martin periodinane, followed by Pinnick oxidation, afforded the desired carboxylic acid 321 in quantitative yield.

Scheme 86 Synthesis of acid analogue 321

2.3.2 Synthesis of a Racemic C5-C11 Fragment

A route for the synthesis of the C5-C11 aldehyde fragment as a racemate was initially pursued to allow optimisation of reaction conditions and exploration of the diastereoselective methylation reaction. Starting from triisopropylsilyl acetylene (322) and acetaldehyde (323) addition of the lithiated acetylene to the aldehyde gave alkynyl alcohol 324. Oxidation of the resulting propargyl alcohol in the presence of MnO₂ subsequently delivered ynone 325. An aldol reaction with trans-2-heptenal (326) resulted in the formation of the alcohol 327 in good yield. Trans-2-heptenal was chosen as a readily available aldehyde to facilitate handling and purification.

Scheme 87 Formation of the racemic alcohol intermediate 327

Following the synthesis of alcohol 327 in three steps, conditions for the diastereoselective methylation of the ketone were explored. Initially, methylation was effected by treatment of
ketone 327 with MeLi and ZnBr₂. Under these conditions a 2.4:1 anti: syn mixture of the diols 328 was obtained. Assignment of the relative stereochemistry was carried out through formation of the six-membered carbonates 329 and 330 and subsequent NOE studies (Scheme 88). Relevant NOEs were observed between the axial allylic proton and methyl group in the desired syn isomer, whilst a weak NOE was observed between the axial allylic proton and the TIPS group in the undesired anti isomer.

Scheme 88 Determination of the configuration of diol methylation products

After the preliminary methylation result and determination of the relative stereochemistries, screening of further methylation conditions was carried out. Several conditions were screened with the objective of improving the diastereomeric ratio in favour of the desired syn isomer (Table 3). The most favourable diastereomeric ratio (syn:anti 5.9:1) was obtained when MeTi(OiPr)₃ (formed in the presence of excess TiCl(OiPr)₃) was employed as the reagent (entry 8). Determination of the dr was conducted on a small scale using ¹H NMR.
analysis and the isolated yield was not obtained. However, degradation with resultant by-product formation was not observed. With the exception of the initial MeLi, ZnBr₂ conditions, all of the reaction conditions explored resulted in the formation of the desired syn diastereoisomer as the major product. It is also notable that although full conversion was observed in most cases, unknown by-product/decomposition peaks were also observed by NMR.

Table 3 Methylation conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methylating Reagents</th>
<th>Solvent</th>
<th>syn:anti</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnBr₂, MeLi</td>
<td>CH₂Cl₂</td>
<td>1:2.4</td>
<td>100 %</td>
</tr>
<tr>
<td>2</td>
<td>ZnBr₂, MeMgCl</td>
<td>Et₂O</td>
<td>2.8:1</td>
<td>100 %</td>
</tr>
<tr>
<td>3</td>
<td>MeMgCl</td>
<td>Et₂O</td>
<td>2:1</td>
<td>10 %</td>
</tr>
<tr>
<td>4</td>
<td>ZnBr₂, AlMe₃</td>
<td>CH₂Cl₂</td>
<td>1.8:1</td>
<td>100 %</td>
</tr>
<tr>
<td>5</td>
<td>AlMe₃</td>
<td>PhMe</td>
<td>1.5:1</td>
<td>100 %</td>
</tr>
<tr>
<td>6</td>
<td>MeCeCl₂</td>
<td>THF</td>
<td>1.5:1</td>
<td>100 %</td>
</tr>
<tr>
<td>7</td>
<td>MeTi(OiPr)₃</td>
<td>Et₂O</td>
<td>1.6:1</td>
<td>100 %</td>
</tr>
<tr>
<td>8</td>
<td>MeTi(OiPr)₃</td>
<td>Et₂O</td>
<td>5.9:1</td>
<td>100 %</td>
</tr>
<tr>
<td>9</td>
<td>Me₂TiCl₂</td>
<td>CH₂Cl₂</td>
<td></td>
<td>decomposition</td>
</tr>
<tr>
<td>10</td>
<td>MeTiCl₃</td>
<td>CH₂Cl₂</td>
<td></td>
<td>decomposition</td>
</tr>
</tbody>
</table>

*a Established through ¹H NMR. b formed in situ from CeCl₃/MeMgCl 1:1 c formed in situ from TiCl₄/Ti(OiPr)₄ 1:3 and MeLi, d 4 eq. MeLi used with respect to TiCl₄. e 3 eq. of MeLi used with respect to TiCl₄. f formed in situ from TiCl₄/Me₂Zn 1:1, g formed in situ from TiCl₄/Me₂Zn 2:1.

The opposite diastereoselectivities obtained using MeLi/ZnBr₂ and MeTi(OiPr)₃ can be explained by consideration of the corresponding transition states (Figure 9). In the case of the zinc procedure, co-ordination of zinc to the hydroxyl group produces a chair transition state including the methyl group. Internal methyl addition therefore occurs on the Re face of the carbonyl to produce the anti diol. When MeTi(OiPr)₃ is employed as the reagent, co-
ordination of titanium to both the carbonyl and hydroxyl group occurs, producing a half-chair transition state. External methyl addition, from a separate titanium species, occurs subsequently from the least hindered face of the ketone to afford the syn diol through a chair-like transition state.

![Figure 9 Methylation transition states](image)

With a route to syn-328 having been established, attention was turned to manipulation of the protecting groups and introduction of the formyl group (Scheme 89). Deprotection of the acetylene to afford 331, followed by protection of both the allylic and tertiary alcohols as silyl ethers, resulted in the formation of alkyne 332 in a high yield (97% over 2 steps). Subsequent formylation of the alkyne 332 proceeded in quantitative yield to afford aldehyde 333.

![Scheme 89 Synthesis of aldehyde 333](image)

Deprotection conditions were investigated for the selective cleavage of the secondary silyl ether (Table 4), but in all cases either a mixture of products was observed or degradation dominated. In most cases multiple products were observed, indicative of silyl migration occurring after initial deprotection. Product mixtures were found to be inseparable and characterisation to confirm formation of specific by-products was not possible. Given that selective deprotection could not be effected, aldehyde 333 was treated with TBAF to try and promote cleavage of both silyl ethers simultaneously; in this case, the desired diol was not observed. Instead, the conjugate addition product 336 was obtained in 58% yield.
Following these disappointing results, it was envisioned that a protected version of the aldehyde 340 could be used for fragment coupling. Reduction of the aldehyde 333 with sodium borohydride occurred in a high yield (88%) to afford alcohol 337 (Scheme 90). However, attempts to protect the primary alcohol as its TBDPS ether resulted in the formation of two inseparable products with similar $^1$H NMR shifts. It is proposed that silyl migration occurs under the reaction conditions, resulting in a mixture of both the desired compound 338 and the migration side product 339 being produced. As a consequence of this result, this approach was abandoned.

**Table 4 Attempted selective deprotection conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>THF/H$_2$O</td>
<td>−20</td>
<td>30</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>THF/H$_2$O</td>
<td>0</td>
<td>2.5</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>PPTS</td>
<td>THF</td>
<td>0 - rt</td>
<td>4.5</td>
<td>degradation at rt</td>
</tr>
<tr>
<td>4</td>
<td>PPTS</td>
<td>THF/MeOH</td>
<td>0</td>
<td>3</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>HF•pyridine</td>
<td>THF</td>
<td>−10</td>
<td>18</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>(+)-CSA</td>
<td>MeOH</td>
<td>0</td>
<td>3</td>
<td>degradation</td>
</tr>
<tr>
<td>7</td>
<td>TBAF</td>
<td>THF</td>
<td>rt</td>
<td>1.5</td>
<td>336 exclusively formed</td>
</tr>
</tbody>
</table>
2.3.3 Synthesis of an Enantiopure C5-C11 Fragment

Synthesis of the enantiopure fragment was explored after completion of fragment studies in racemic form. Starting from the same aldehyde, *trans*-2-heptenal (326), a diastereoselective Crimmins aldol reaction was used to set the alcohol stereochemistry at C10. Initially, the readily available thiazolidine-2-thione auxiliary 343 was employed.\(^{[102]}\) However, formation of product 341 occurred in only moderate yield with low diastereoselectivity (Scheme 91). In an attempt to improve both the yield and diastereomeric ratio, the oxazolidinethione auxiliary 344 was synthesised in seven steps from ethylene glycol following a procedure reported by Crimmins in 2006.\(^{[103]}\) The aldol reaction carried out with oxazolidinethione auxiliary 344 resulted in a significantly higher yield with almost exclusive formation of the desired diastereoisomer 342. The bulky mesityl group present in the auxiliary 344 provides a greater degree of facial selectivity during the aldol reaction than its benzyl counterpart as a consequence of its increased bulk and decreased flexibility. Therefore, the chlorotitanium enolate species reacts to primarily give one diastereoisomer.
Scheme 91 Crimmins aldol reaction to set the stereochemistry of the C10 hydroxyl group

The stereochemistry of the allylic alcohol was now established and so attention turned to further functionalisation of the molecule (Scheme 92). Conversion of Crimmins aldol adduct 342 into the Weinreb amide 345 occurred in 91% yield. Subsequent protection of the alcohol 345 as its silyl ether afforded compound 346 in quantitative yield. Protection of the secondary alcohol was essential to prevent a retro-aldol reaction occurring under the basic conditions required for the addition of the acetylene group in the next step.

Scheme 92 Synthesis of Weinreb intermediate 346

Problems had already been experienced when preparing fragments 335 and 340 in racemic form (Section 2.3.2), and so a new strategy was sought for introduction of the acetylene with a protected primary alcohol. It was decided that the reactivity difference between the allylic and tertiary alcohols could be exploited during fragment coupling and so protection of the tertiary alcohol would not be necessary. Consequently, the diol 350 was selected as the target (Figure 10).

Figure 10 Originally targeted western fragments vs. revised strategy
Known TBDPS ether 347 was formed in one step from propargyl alcohol. Addition of the corresponding lithium acetylide species to the amide 346 afforded a mixture of the desired ketone 348 and unreacted protected propargyl alcohol 347. Subsequent cleavage of the triethylsilyl ether under acidic conditions afforded allylic alcohol 349 in 77% yield over the two steps. Treatment of the ketone 349 under the previously established methylation conditions, using MeTi(OiPr)3, afforded the desired syn diol in 72% yield. The observed dr was comparable to that obtained during the synthesis of the racemic TIPS protected ynone 328. The similar dr’s observed for both the formation of 327 and 349 confirm that the outcome of methyl addition reaction is due to the directing effects of the free alcohol; changing the size of the acetylene group has no effect on the diastereomeric ratio of the products. Synthesis of the desired syn diol 350 was therefore completed in six steps and 40% overall yield from trans-2-heptenal (326). As well as overcoming the protection and deprotection issues encountered previously, this new revised route allowed access to the desired coupling fragment in fewer steps.

Scheme 93 Synthesis of syn diol 350

2.3.4 Fragment Coupling and Functionalisation

A synthetic route to both fragments 321 and 350 had been established and so attention was turned to the coupling of the two fragments by ester formation. Multiple conditions for the formation of ester 351 were investigated with varying degrees of success (Table 5). In all cases at least small amounts of the desired product were observed; in two cases the major observed product was the acid anhydride 352. The use of coupling reagents was found to be superior to formation of the acyl chloride, which underwent degradation and delivered only trace amounts of the desired product. When Steglich and Yamaguchi esterification conditions were utilised (entries 1 and 2), the major products were the anhydride 352 and acid-reagent coupled intermediates. Attempts to push these reactions to completion by use
of larger quantities of DMAP, longer reaction times and heat were unsuccessful and it was found that 352 was highly unreactive. The use of MNBA, under conditions reported by Shiina,[50] gave the best results; the product 351 was obtained in 68% yield (Entry 3). The diol starting material 350 was also recovered despite complete consumption of the acid, due to formation of the anhydride by-product 352.

Table 5 Coupling conditions for the formation of ester 351

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>T</th>
<th>Ratio 351:352&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Isolated yield (%) of 351</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCC, Et&lt;sub&gt;3&lt;/sub&gt;N, DMAP</td>
<td>rt</td>
<td>1:3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[51]</td>
<td></td>
<td>1:3</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>SOCl&lt;sub&gt;2&lt;/sub&gt;, DMF</td>
<td>rt</td>
<td>3:1</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>degradation</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined by <sup>1</sup>H NMR

Following formation of the ester 351, protection of the tertiary alcohol as a silyl ether proceeded in high yield and subsequent benzyl ether cleavage with DDQ afforded the primary alcohol 353 in 93% yield. When cerium ammonium nitrate was used for debenzylation, complete decomposition was observed. The alcohol 353 was oxidised to the corresponding aldehyde 354 in quantitative yield using DMP and then subjected to an aldol reaction with methyl acetate to afford the desired β-hydroxy ester intermediate 355 as a 1:1
mixture of inseparable diastereoisomers in excellent yield. The stereochemistry at C3 was inconsequential so the mixture of isomers was carried forward to subsequent reactions. Global deprotection was then performed to afford triol 356 in 98% yield. The addition of AcOH as a buffer was necessary to avoid retro-aldol, but this resulted in a very slow deprotection time of five days.

Scheme 94 Formation of intermediate 356

Oxidation of triol 356 was performed using Dess-Martin periodinane to install both the aldehyde and β-keto ester in a single step and thereby deliver the Knoevenagel condensation precursor 357. Disappointingly, all attempts to effect intramolecular Knoevenagel condensation resulted in either polymerisation or degradation and macrocycle 358 was never obtained.
Failed intramolecular Knoevenagel condensation

As a last resort, an attempt was made to perform ring-closing metathesis between the methylene and trans-substituted alkene to install the butenolide at an earlier stage in the synthesis (Scheme 96). However, the desired product 360 was not obtained. Following this unsuccessful result a revision of the synthetic strategy was required.

Attempt to effect ring-closing metathesis at an early stage
2.4 Approach 2: An Intermolecular Knoevenagel Condensation Approach

The discovery that macrocycle formation through Knoevenagel condensation was not viable meant that another approach was required. Following the same initial disconnections through the epoxyfuran and butenolide rings gave the same retrosynthetic lactone (309) as before. However, it was envisioned that this intermediate would now be formed through macrolactonisation of seco acid 361. Disconnection through the ynenone gave the same key fragments 300 and 301 as before, leading to the proposal that fragment coupling would be carried out by intermolecular Knoevenagel condensation.

Scheme 97 New retrosynthetic strategy

2.4.1 Exploration of Knoevenagel Condensation as the Fragment Coupling Step

Routes to suitable coupling fragments had already been established in the previous strategy and so studies were performed to ascertain the yield and $E/Z$ selectivity of the coupling reactions, as well as the tolerance of products towards further manipulation. Initially aldehyde 333 was utilised in the Knoevenagel condensation reaction with $\beta$-keto ester 316. This reaction proceeded in high yield to afford ynenone 362 as a 1.5:1 ($Z$:$E$) mixture of stereoisomers. The stereochemical outcome is hypothesised to result from steric repulsion between the large triethylsilyl protecting groups and the carbon skeleton of the $\beta$-keto ester chain; favouring the less hindered $Z$ isomer. Despite this, the resultant isomeric mixture 362 was taken forward. Attempts to cleave the triethylsilyl ethers under acidic conditions did not result in the expected ynenone product 363; the spiroacetal 364 was formed instead. Interestingly, the $Z$ isomer also reacted in this case. Only one spiroacetal diastereoisomer was observed. An attempt was made to determine the configuration of the new stereocentre through further functionalisation of the primary alcohol and crystallisation. However, degradation occurred during this process and so the configuration of the new stereocentre remains undetermined.
A further investigation into the formation of the spirocycle was conducted using racemic aldehyde (±)-333. Reaction of (±)-333 with ethyl acetoacetone under Knoevenagel conditions afforded the corresponding ynenone 365 as a 1:1 mixture of $E$:$Z$ isomers. Treatment of the ynenone 365 with CSA in this case afforded two products: the furan 366 and the spirocycle 367.

Scheme 98 Formation of a spirocyclic by-product

Scheme 99 Investigation into Spirocycle Formation
Formation of both the furan 366 and the spirocycle 367 led to the proposal of a mechanism to account for cyclisation. Upon cleavage of the silyl ethers to give the 1,3-diol 368, attack of the secondary alcohol onto the alkyne occurs. Protonation occurs to afford furan 366 (blue arrows) or conjugate addition occurs to produce the allene 369 (red arrows). The enol/ enolate can then react with the allene to form the spirocyclic compound 367.

Scheme 100 Mechanism of spirocycle formation

To prevent formation of the undesired spirocycle, protection of the secondary alcohol was necessary. Starting from previously synthesised diol 350, the secondary alcohol was protected as its pivalate ester 371 to allow easy differentiation between the hydroxyl groups. Silyl ether cleavage with TBAF followed to afford the diol 372 in 75% yield. The propargylic aldehyde was installed using DMP to give tertiary alcohol 372, which was subsequently converted to its triethylsilyl ether 374 upon treatment with TESOTf.

Scheme 101 Formation of aldehyde coupling partners
Both of the aldehydes 373 and 374 were coupled with the β-keto ester 316 to explore the Knoevenagel condensation reaction further. Both reactions gave a more favourable isomeric product ratio (1.2:1, Z:E) than the reaction of the di-TES analogue 362 (entry 3), but lower yields were obtained in both cases. In the case of the substrate bearing the free tertiary hydroxyl group, an inseparable mixture of E:Z isomers was obtained along with unreacted aldehyde (entry 2). The E:Z ratios obtained indicate the tertiary alcohol protecting group (R') has no effect on selectivity of the reaction, whilst the bulkiness of the allylic alcohol protecting group (R) has a profound effect. It is also interesting to note that in the presence of a free tertiary hydroxyl (entry 2), the reaction still proceeds well, albeit with lower conversion. This suggested that a second protection step may not be necessary in this synthetic route.

Table 6 Intermolecular Knoevenagel Condensation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>R'</th>
<th>E:Z ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>375</td>
<td>Piv</td>
<td>TES</td>
<td>1:1.2</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>376</td>
<td>Piv</td>
<td>H</td>
<td>1:1.2</td>
<td>69 (brsm)</td>
</tr>
<tr>
<td>3</td>
<td>362</td>
<td>TES</td>
<td>TES</td>
<td>1:1.5</td>
<td>88</td>
</tr>
</tbody>
</table>

Silyl ether cleavage of ynenone 375 was effected using CSA to give a mixture of compounds which was directly subjected to THT-mediated furan formation (Scheme 102). As expected, the E isomer was converted into the corresponding epoxyfuran 377 whilst the Z isomer remained unreacted. The major by-product, formed under acidic deprotection conditions, was found to be cyclopropylfuran 378. Previous work in the Clark group had shown that cyclopropyl products of this type could be produced by treatment of ynenones bearing a tethered alkene with chloroacetic acid.[89] Other Brønsted acids had been utilised, but CSA had not been previously found to promote cyclopropane formation. Cyclopropyl furan formation is thought to proceed through reversible formation of a carbene as described in Section 1.3.4.2.
The results obtained during these studies led to two conclusions. Firstly, that Knoevenagel condensation needs to be performed with a free tertiary hydroxyl in place to avoid competing side reactions resulting from deprotection and secondly, that furan formation needs to be effected directly after Knoevenagel condensation due to the highly reactive nature of the resultant ynenones. With these considerations in mind a revised strategy was adopted.

**2.4.2 Revision of the Retrosynthetic Strategy**

Results of initial Knoevenagel condensation studies showed that furan formation would need to be effected earlier in the synthesis than had been intended. The new strategy was therefore devised so that ring-closing metathesis and macrolactonisation would be used to install the butenolide and macrolactone from seco acid precursor 379 as the final steps in the synthesis. Prior to this sequence, epoxyfuran formation would be effected directly after Knoevenagel condensation of the two fragments to form 361. This strategy had not been considered previously because epoxyfurans are usually considered to be relatively unstable.
2.4.3 Epoxyfuran Stability Studies

To ascertain whether the epoxyfuran motif would tolerate the reaction conditions required for further functionalisation of the surrounding molecule, a model epoxyfuran system was treated under varying conditions. The synthesis of the model epoxyfuran commenced from the tertiary alcohol 380 (Scheme 104). Protection of the tertiary alcohol as its triethylsilyl ether occurred in high yield to afford alkyne 381. Formylation of the alkyne to give the propargylic aldehyde 382 was then followed by Knoevenagel condensation with ethyl acetoacetate to give 383 as a 1:1 mixture of E:Z isomers. Silyl ether cleavage occurred under acidic conditions to afford tertiary alcohol 297 which, upon treatment with THT, afforded the targeted epoxyfuran 298.

Scheme 104 Formation of a model epoxyfuran system

Ring-closing metathesis had been proposed as the final synthetic step and so initial studies focussed on the stability of the epoxyfuran in the presence of Grubbs catalyst and under prolonged heating (Table 7). The epoxyfuran 298 was treated with Grubbs II catalyst in two different solvents at varying temperatures. A heated control, without the catalyst, was also
studied. Reactions were followed by $^1$H NMR and in all cases minimal signs of epoxyfuran degradation were observed.

Table 7 Stability of the epoxyfuran motif to metathesis conditions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Reagent</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>80</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>Toluene</td>
<td>rt</td>
<td>Grubbs II</td>
<td>24</td>
</tr>
<tr>
<td>Toluene</td>
<td>80</td>
<td>Grubbs II</td>
<td>24</td>
</tr>
<tr>
<td>DCM</td>
<td>45</td>
<td>Grubbs II</td>
<td>24</td>
</tr>
</tbody>
</table>

As well as establishing the stability of the epoxyfuran motif in the presence of Grubbs II catalyst, a full RCM reaction was conducted in its presence to ensure that catalyst activity was not affected. A model substrate (386) for butenolide synthesis was synthesised in two steps from commercially available hydrocinnamaldehyde (384) (Scheme 105). The synthesis involved Grignard addition to afford the allylic alcohol 385, followed by esterification with methacrylic acid to furnish the RCM precursor 386.

![Scheme 105 Synthesis of a ring closing metathesis precursor](image)

Butenolide formation in the presence of epoxyfuran 298 proceeded well and the butenolide 387 was obtained in 97% yield. Although some degradation of the epoxyfuran was observed, 92% of the epoxyfuran 298 was recovered after column chromatography. These results demonstrated the viability of using a ring-closing metathesis reaction at a very late stage in the synthetic route.
The stability of the epoxyfuran was also tested under basic conditions as both deprotection and macrolactonisation conditions would require the presence of base. Both strongly and weakly basic conditions were utilised to determine general stability. When the epoxyfuran 298 was treated with TBAF at room temperature over a 24 hour period, almost no degradation was observed and 98% of the starting material recovered. However, treatment of the model substrate with lithium hydroxide led to a lower recovery of only 86% after 24 hours. Products arising from epoxide opening and ester hydrolysis were identified by high resolution mass spectrometry.

All of the reaction conditions explored gave promising results for the retention of the epoxyfuran motif and these findings suggested that it would be possible to install it at an earlier stage in the synthesis than originally planned. Acidic conditions were not investigated because it was not anticipated that they would be required during the final steps of the synthesis.

2.4.3 Installation of the β-Keto Ester in the C12-C14/C1-C4 Fragment

During the exploration of an intramolecular Knoevenagel condensation route, a viable synthetic strategy for the synthesis of protected alcohol 321 had been established. It was therefore envisioned that this fragment could be converted to the desired β-keto ester fragment 301 following a short synthetic sequence.
Starting from the carboxylic acid 321, cleavage of the $p$-methoxy benzyl ether occurred quantitatively in the presence of DDQ. However, due to the polarity of the resulting hydroxy acid 388 it could not be separated from reagent residues and the alcohol 388 was carried forward crude to the subsequent oxidation step. In this case, a large excess of Dess-Martin periodinane was required to promote full conversion of the alcohol 388 into the corresponding aldehyde 389 and the product could not be separated from reagent residues. Other oxidising reagents, including IBX, were also explored, but clean conversion could not be effected.

\[ \text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{OPMB} \xrightarrow{\text{DDQ, CH}_2\text{Cl}_2/\text{pH 7 buffer}} \text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{OH} \xrightarrow{\text{DMP, CH}_2\text{Cl}_2} \text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{O}\]

**Scheme 108** Formation of crude aldehyde

Aldehyde 389 was carried forward crude to investigate whether the $\beta$-keto ester functionality could be installed. Treatment of the aldehyde with freshly prepared methyl diazoacetate in the presence of tin (II) dichloride led to incomplete conversion and the product 301 could not be separated from oxidation reagent residues. In addition, an aldol approach did not give any of the desired product and resulted in degradation of the starting material.

\[ \begin{align*}
\text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{O} & \xrightarrow{\text{N}_2, \text{SnCl}_2, \text{CH}_2\text{Cl}_2} \text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{OMe} \\
& \xrightarrow{1) \text{LDA, methyl acetate, 2) Ox.}} \text{HO-C=)} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{O}\end{align*}\]

**Scheme 109** Installation of the $\beta$-keto ester

### 2.4.4 A New Protecting Group Strategy for the C12-C14/C1-C4 Fragment

Attempts to synthesise the PMB analogue 321 had been unsuccessful and so a new protecting group strategy was devised for the synthesis of the $\beta$-keto ester fragment. Problems with purification had arisen because of the presence of inseparable reagent residues and so the use of an acid/base labile protecting group and subsequent purification of the hydroxy acid 388 by extraction was explored. MOM and acetate protecting groups were selected and the synthetic routes for preparation of the $\beta$-keto ester 301 were explored.
in parallel. Selective conversion of the keto aldehyde 313 into the acetal 390 was explored as a protection strategy, but only degradation was observed in this case (Scheme 110).

Scheme 110 Attempted acetal formation

The previously synthesised primary alcohol 313 was converted into the MOM ether 392 in 3 steps (Scheme 111). Protection of the primary alcohol 313 as its MOM ether 391 occurred in good yield. This was followed by Wittig methylenation of the ketone and cleavage of the silyl ether to form allylic alcohol 392. A similar three-step sequence was used to furnish acetate 393: Wittig methylenation of the ketone, acetylation of the alcohol 314 and silyl ether cleavage. A two-step oxidation sequence, involving Dess-Martin periodinane and Pinnick oxidation, afforded the carboxylic acids 394 and 395 in quantitative yield.

Scheme 111 Synthesis of the carboxylic acids 394 and 395
Treatment of MOM ether 394 with HCl resulted in complete degradation of the starting material and none of the desired hydroxy acid 388 was obtained (Scheme 112). However, acetate cleavage under basic conditions afforded the desired hydroxy acid 388 in 95% yield upon acidic aqueous work-up. Oxidation of the primary alcohol was followed by β-keto ester installation under Roskamp conditions to afford β-keto ester 301 in moderate yield.

Scheme 112 Formation of the β-keto ester fragment

2.4.5 Synthesis of a Mono-protected C5-C11 Fragment

Previous studies had shown that protection of the secondary hydroxyl group is necessary for effective Knoevenagel condensation to occur. They had also revealed that the tertiary hydroxyl did not require protection during the reaction. An aldehyde substrate possessing a protected secondary hydroxyl group and unprotected tertiary hydroxyl group was therefore targeted.

Starting from previously discussed Weinreb amide 346, addition of lithiated TIPS acetylene followed by triethylsilyl ether cleavage afforded allylic alcohol 327 in high yield (Scheme 113). Stereoselective methylation under previously described conditions gave diol 328 with a high dr and in excellent yield. Deprotection of the acetylene group occurred readily using TBAF to afford terminal alkyne 397. Disappointingly, treatment of the alkyne 397 under formylation conditions did not afford the corresponding aldehyde but instead gave the tetrahydrofuran containing by-product 398.
Scheme 113 Towards the synthesis of the C5-C11 fragment

Selective protection of the secondary hydroxyl group as a silyl ether was performed using various silylating reagents and reaction conditions to give substrates that could be tested in the coupling reaction (Table 8). Ultimately, a less bulky group was required to minimize formation of the undesired Z isomer during Knoevenagel condensation. A mix of both mono- and di-protected products was obtained when TESCl/imidazole and TBSOTf/lutidine were utilised (entries 1 and 3). However, clean conversion was observed when using sodium hydride as a base along with the appropriate silyl chloride (entries 4 and 5).

Table 8 Selective protection of the secondary hydroxyl

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Product Ratio (SM:A:B)</th>
<th>Isolated Yield A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TESCl</td>
<td>imidazole</td>
<td>DCM</td>
<td>rt</td>
<td>0.25:1:0.4</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>TBSCI</td>
<td>imidazole</td>
<td>DMF</td>
<td>rt → Δ</td>
<td>1:0:0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TBSOTf</td>
<td>lutidine</td>
<td>DCM</td>
<td>0 °C</td>
<td>2:1:5</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>TBSCI</td>
<td>NaH</td>
<td>THF</td>
<td>0 °C → rt</td>
<td>0:1:0</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>TIPSCI</td>
<td>NaH</td>
<td>THF</td>
<td>0 °C → rt</td>
<td>0:1:0</td>
<td>98</td>
</tr>
</tbody>
</table>
Formylation of both the TBS and TIPS analogues 399 and 400 resulted in quantitative formation of the corresponding aldehydes 401 and 402 (Scheme 114). However, when the TES analogue was treated under the same conditions, multiple products were observed. Scrambling of the silyl ether appeared to occur and the previously isolated tetrahydrofuran by-product 398 was also observed.

Scheme 114 Synthesis of aldehyde fragments 401 and 402

2.4.6 Intermolecular Knoevenagel Coupling

Completion of the aldehyde 401 and β-keto ester 301 meant that attention could be turned to the Knoevenagel coupling of the two fragments (Scheme 115). However, all attempts to perform Knoevenagel coupling were unsuccessful and ynenone 403 was not isolated. It was proposed that salt formation between the carboxylic acid and the piperidine may be occurring, hampering the reaction.

Scheme 115 Failed Knoevenagel coupling

To prevent unfavourable interactions and explore the Knoevenagel condensation further, masking of the carboxylic acid was necessary. The carboxylic acid 395 was therefore protected as its methyl ester through esterification before cleavage of the acetate was performed under basic conditions to afford the corresponding alcohol 404 (Scheme 116). Primary alcohol 404 was then oxidised to give the aldehyde 405 using Dess-Martin periodinane. Installation of the β-keto ester was performed thereafter to give the methyl ester 406. Interestingly, when acetate cleavage was attempted under acidic conditions, the
tetrahydrofuran 408 was formed in good yield instead of the desired primary alcohol (Scheme 117).

Scheme 116 Formation of a methyl ester coupling partner

Scheme 117 Formation of a furan by-product

Knoevenagel coupling of the aldehyde 401 and the methyl ester 406 afforded a mixture of $E$ and $Z$ ynenones 409 (1:1.2 ratio) along with some unreacted $\beta$-ketoester starting material (Scheme 118). This mixture of isomers was subjected directly to THT-mediated furan formation, but none of the desired product 410 was obtained and the mixture of ynenones 409 was not recovered.
In addition, the mixture of ynenones 409 proved to be highly reactive in the presence of small quantities of acid. When it was left in CDCl₃ for four hours complete consumption of the E isomer was observed and a new product was formed (Figure 11). This product is proposed to be cyclopropyl furyl 411 but isolation was not performed and so full characterisation data were not obtained.

Figure 11 Consumption of the E ynenone in CDCl₃
It became apparent that a two-step procedure for the formation of the desired epoxyfuran was not viable. Attention was therefore turned to a new approach in which one-pot Knoevenagel condensation and THT promoted furan formation would be performed.

### 2.5 Approach 3: A One-Pot Knoevenagel Condensation and Furan Formation Strategy

#### 2.5.1 Initial One-Pot Furan Formation Studies

The two-step Knoevenagel condensation furan formation approach was not feasible and so attention was turned to a one-pot method. Previously, Clark *et al.* had described the one-pot synthesis of the furan 281 by THT-promoted reaction of acetoacetone (279) with the propargylic aldehyde 280 in the presence of benzoic acid as the nucleophile (Scheme 119). However, a one-pot procedure with intramolecular trapping of the sulfur ylide had not been devised.

![Scheme 119](image)

**Scheme 119** Previous one-pot synthesis reported by Clark *et al.*

The conditions reported for the formation of the furan 281 were adapted to include acetic acid, as a proton source, and molecular seives. Reaction of the aldehyde 402 with the β-keto ester 406 produced the epoxyfuran product 412 in a very low yield (3%) along with the acetate addition product 413 in slightly higher yield (Scheme 120). The protected secondary alcohol 402 was chosen, despite the bulky TIPS group, as it was thought to be more stable to prolonged periods of heating in the presence of acid than its TBS counterpart.

![Scheme 120](image)

**Scheme 120** Initial strategy for one-pot furan formation
Increasing the amount of THT present using dichloromethane as a solvent, had little effect on the reaction outcome. However, when THT was used as a solvent, a large increase in conversion to both the epoxyfuran product 412 and the acetate 413 was observed by \(^1\)H NMR. Replacing the acetic acid with phenylphosphonic acid in an attempt to effect sole formation of the epoxyfuran resulted in degradation, as did performing the reaction in the absence of an acid.

### 2.5.2 Introduction of the TMSE Protecting Group

It had become apparent that a one-pot strategy for the synthesis of the furan was possible and so a strategy for the protection of the carboxylic acid functionality was sought. Initially the methyl ester derivative 406 was employed for proof of concept studies, but selective deprotection would not be possible without affecting the furyl ester. Trimethylsilyl ethyl ester was therefore chosen so that deprotection of both the alcohol and acid functionalities could be effected in the same step in the presence of fluoride ion.

Starting from the acid 395, which had been synthesised previously, the TMSE ester 414 was prepared by DCC mediated esterification with trimethylsilyl ethanol (Scheme 121). Hydrolysis of the acetate group under basic conditions was followed by oxidation with Dess-Martin periodinane to furnish the aldehyde 415 in high yield. The synthesis of the \(\beta\)-keto ester 416 was completed by a tin(II) chloride mediated reaction of the aldehyde 415 with methyl diazoacetate.\(^{[100]}\)

![Scheme 121 Formation of TMSE ester 416](image)
2.5.3 One-Pot Furan Formation and Cyclisation Studies

Now that a viable synthetic route to TMSE ester 416 was established, one-pot furan formation was explored again (Scheme 122). Knoevenagel condensation of the aldehyde 402 with the β-keto ester 416 and in situ cyclisation proceeded in moderate yield to afford the epoxyfuran 417 and the corresponding acetate addition product 418. Unreacted β-keto ester 416 (46%) was also recovered. As before, both products were obtained as a mixture of diastereoisomers. A more favourable ratio of the epoxide 417 to the acetate 418 was obtained by decreasing the quantity of acetic acid present in the reaction mixture to 30 mol%.

Scheme 122 One-pot furan formation

The formation of the acetate product 418 suggested that the strategy could also be used for the formation of the natural product 7-acetylsinumaximol B (16) which was isolated in 2015.[23] Therefore, the selectivity of the furan formation reaction was deemed to be less important at this point until investigations for the further development of both compounds had been conducted.

Figure 12 Structure of 7-acetylsinumaximol B

Both 417 and 418 were now readily available and so methods for their deprotection and macrolactisation were explored. The epoxy furan 417 was treated with a cooled solution of TBAF to afford the seco-acid 419 and this compound was subjected to macrolactonisation
without further purification (Scheme 123). Macrolactonisation under Yamaguchi conditions afforded macrocycle 420 in moderate yield as a single diastereoisomer, with unknown stereochemistry at the C7 position. Shiina macrolactonisation conditions, utilising MNBA, were also explored but did not deliver the required product.

Disappointingly, all attempts to effect ring-closing metathesis of the macrolactone 420 were unsuccessful. Treatment of 420 with both Grubbs second generation and Hoveyda-Grubbs second generation catalysts did not result in reaction of the starting material (Scheme 124). Addition of ethylene to the reaction mixture resulted in formation of the terminal alkene 421 but no further reaction was observed. Degradation occurred after addition of further catalyst and prolonged heating.

2.5.4 Synthesis of a Terminal Alkene C5-C11 Fragment

Originally, a C5-C11 propargylic aldehyde fragment 402 containing a trans alkene with an n-butyl side chain was synthesised from trans-2-heptenal. Despite successful coupling through Knoevenagel condensation and furan formation, and subsequent macrolactonisation, ring-closing metathesis reactions could not be effected to install the butenolide. As a result, the
route was redesigned to exclude the n-butyl side chain and a terminal alkene was targeted as the RCM substrate.

Following a procedure reported by Nagaiah et al., the Weinreb amide 424 was synthesised from isoprene (422) and thiazolidinethione 343 in a two-step sequence involving an aldol reaction and subsequent displacement of the auxiliary (Scheme 125). Nagaiah had reported an observed dr of 85:15 for the formation of allylic alcohol 423, but a dr of greater than 2:1 could not be obtained in spite of numerous attempts to perform the reaction. Following this, protection of the alcohol group as its triethylsilyl ether afforded Weinreb amide 425, which was converted to ynone 426 by addition of lithiated TIPS acetylene. Silyl ether cleavage was effected under acidic conditions to afford allylic alcohol 427 in quantitative yield. Diastereoselective methylation was carried out as previously described using methyl titanium isopropoxide to afford a separable 9:1 mixture of syn:anti diols 428. Deprotection of the syn diol afforded acetylene 429 in high yield and the corresponding mono- or di-triisopropylsilyl ethers 430 and 431 were formed through treatment with sodium hydride/triisopropylsilyl chloride and lutidine/triisopropylsilyl triflate respectively. Formylation of both acetylenes 430 and 431 subsequently occurred in high yield to afford the desired aldehyde coupling fragments 432 and 433.

Scheme 125 Synthesis of the C5-C11 aldehyde fragment
The relative stereochemistry of the **syn** and **anti** diols was confirmed by formation of carbonates 434 and 435 and subsequent NOE experiments (Scheme 126). The carbonates were prepared by silyl cleavage of **syn**- and **anti**-428 to form the terminal alkynes **syn**- and **anti**-429, followed by reaction with triphosgene to furnish cyclic carbonates 434 and 435. Selective NOE experiments confirmed the major isomer as the **syn** diol, with an NOE observed between the allylic proton and the methyl substituent. This NOE was absent in the case of the minor isomer, which confirmed this compound as the **anti** diol.

![Scheme 126](image)

**Scheme 126** Confirmation of the relative stereochemistry of the **syn** and **anti** diastereomers of diol 429

### 2.5.5 Optimisation of One-Pot Knoevenagel Condensation and Furan Formation

The synthesis of the aldehyde 432 allowed the coupling reaction with the β-keto ester 416 to be performed as described previously to afford a ca. 1:1 separable mixture of epoxy furan 436 and acetate 437 (Scheme 127). It was envisioned that these compounds would be used for the synthesis of different natural products, namely pukalide and 7-acetylsinumaximol B, and so optimisation for the selective synthesis of each compound was required.

![Scheme 127](image)

**Scheme 127** One-pot Knoevenagel condensation-furan formation
It was proposed that the selectivity of the reaction could be altered by changing the amount and type of carboxylic acid additive or by protecting the tertiary alcohol. Initially, the effect of the quantity of acetic acid present was explored (Entries 1-3, Table 9). It was found that increasing the quantity of acetic acid favoured formation of the acetate adduct 437 and decreasing the quantity reversed that selectivity. However, highly selective formation of neither the epoxy furan 436 nor the acetate 437 could be achieved simply by varying the amount of acetic acid. The use of ethylenediammonium diacetate (EDDA) also resulted in the formation of both compounds but in diminished yield (Entry 4) and the addition of thioacetic acid led to the degradation of both starting materials (Entry 5). Changing the acid source from acetic acid to a bulkier derivative in order to minimise formation of the addition product 437 and allow selective formation of the epoxy adduct 436 was proposed. Several acids were screened (Entries 6-8), with pivalic acid affording the highest yield of epoxy furan. Interestingly, it was found that increasing bulk too much hampered formation of the epoxy furan 436; the reaction involving 1-adamantane carboxylic acid afforded the product in only 23% yield and that involving triphenylacetic acid afforded only trace amounts of product. Epoxide 436 was obtained exclusively in 62% yield when the concentration of pivalic acid was increased to 0.6 equivalents (Entry 9); increasing the quantity of acid further resulted in a diminished yield (Entry 10). Selective formation of the acetate 438 was accomplished in 85% yield (3:2 mixture of diastereoisomers) when the bis-protected aldehyde 433 was used as a substrate and the reaction was performed in the presence of 1.2 equivalents of acetic acid (Entry 11).
Table 9 One-pot Knoevenagel condensation and furan formation

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Acid</th>
<th>Equiv. RCO₂H</th>
<th>Yield 436 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield 437 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield 438 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>432</td>
<td>MeCO₂H</td>
<td>0.3</td>
<td>36</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>432</td>
<td>MeCO₂H</td>
<td>0.6</td>
<td>30</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>432</td>
<td>MeCO₂H</td>
<td>1.0</td>
<td>16</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>432</td>
<td>EDDA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1</td>
<td>23</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>432</td>
<td>MeCOSH</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>432</td>
<td>Ph₃CO₂H</td>
<td>0.1</td>
<td>-&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>432</td>
<td>1-adamantane-CO₂H</td>
<td>0.1</td>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>432</td>
<td>tBuCO₂H</td>
<td>0.1</td>
<td>39</td>
<td>-</td>
<td>-</td>
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<tr>
<td>9</td>
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<td>tBuCO₂H</td>
<td>0.6</td>
<td>62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>432</td>
<td>tBuCO₂H</td>
<td>1.2</td>
<td>54</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>433</td>
<td>MeCO₂H</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>432</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yield; <sup>b</sup> used without piperidine present; <sup>c</sup> trace observed in NMR; <sup>d</sup> no acid added - control experiment

2.5.6 Completion of 7-epi-Pukalide

Conditions for the selective formation of epoxyfuran 436 had now been established and so attention was turned to the formation of the macrocycle and installation of the butenolide. Simultaneous cleavage of the silyl ether and the ester was accomplished by treatment of the epoxyfuran 436 with tetrabutylammonium fluoride (Scheme 128). The crude seco-acid 439 was used without further purification in the macrolactonisation step. Interestingly, when the...
reaction was performed at room temperature, tetrahydrofuran by-product 440 was observed. Similarly, when the temperature or quantity of TBAF present was decreased TMSE ester 441 was isolated.

Scheme 128 Silyl deprotection

The hydroxy-acid 439 was then subjected to Yamaguchi macrolactonisation conditions to afford the lactone 421 as a single isomer in 39% yield over two steps; the other diastereoisomer failed to undergo cyclisation under the reaction conditions (Scheme 129). Cyclisation of the hydroxy-acid using the Corey–Nicolaou method also delivered the lactone 421 in 46% yield as a single isomer. Other macrolactonisation conditions were explored in an attempt to effect cyclisation of the second diastereoisomer; Shiina conditions using MNBA and macrolactonisation utilising DCC gave neither the previously observed macrolactone 421 nor the corresponding diastereoisomer. At this point the stereochemistry of the C7 position was unknown.

Scheme 129 Macrolactonisation of seco acid 421

Attempts to construct the butenolide by ring-closing metathesis (RCM) with either the Grubbs second generation catalyst or the Hoveyda–Grubbs second generation catalyst were unsuccessful. However, the very reactive modified Hoveyda–Grubbs second generation catalyst 442, developed by Matsugi et al.,[106] proved to be highly effective and the butenolide was obtained in 90% yield. The aromatic anthracene at the 3-position of the 2-isopropoxy
styrene ligand results in an intramolecular steric hindrance between the aromatic ring of the ligand and the methyl group of the isopropoxy substituent, which alters the coordination environment between the lone electron pair of the ether oxygen and the ruthenium. As the rate-determining step is thought to be the release of the bidentate ligand the reaction rate is determined by its ligation ability. Due to the steric strain caused by the CH$_3$-π interaction the ligand is released more readily, increasing the activity of the catalyst.

![Scheme 130](image)

Scheme 130 Installation of the butenolide ring and catalyst conformation

$^1$H and $^{13}$C NMR spectra for the final compound were found to be inconsistent with the original data recorded for natural pukalide. NOE analysis of the final compound revealed that it was in fact the C7-epimer 443 (Figure 13). Selective NOE analysis of the C7 proton showed observed NOEs between it and both the C8 methyl substituent and the C5 furan proton. On the basis of this result, it is evident that the epoxide isomer, required for the synthesis of natural pukalide, did not undergo macrolactonisation. The trans epoxide is more sterically strained than its cis counterpart and as such the finding that the cis epoxide isomer of 439 undergoes cyclisation whilst the trans epoxide isomer does not, is not unsurprising.

![Figure 13](image)

Figure 13 Observed NOEs for 7-epi-pukalide

2.5.7 Completion of 7-Acetylisinumaximol B

Completion of 7-acetylisinumaximol B was envisioned to occur analogously to the synthesis of 7-epi-pukalide. Thus, the acetate product 438 was subjected to the same three step sequence: deprotection, macrolactonisation and RCM. Treatment of acetate 438 with TBAF
effected cleavage of both silyl ethers and the trimethyl silyl ethyl ester to afford hydroxy acid \textbf{444} which was used directly in the macrolactonisation reaction. In this case, both diastereoisomers underwent Yamaguchi macrolactonisation, but the macrolactone \textbf{445} was obtained in relatively low yield and attempts to optimise the sequence were unsuccessful (Scheme 131). Corey-Nicolaou, Shiina and Mukaiyama macrolactonisation conditions, along with the Yonemitsu variation of the Yamaguchi reaction, were all tested, but in all cases the product was not observed.

Scheme 131 Formation of the 7-acetylsinumaximol B macrocyclic intermediate \textbf{445}

As was previously observed for 7-\textit{epi}-pukalide, the transannular ring-closing metathesis reaction to effect butenolide formation was not successful when either the Grubbs 2nd generation catalyst or the Hoveyda-Grubbs 2nd generation catalyst was used. Only one diastereoisomer of the triene \textbf{445} underwent RCM to produce the butenolide when treated with the anthracene modified catalyst \textbf{442} and virtually all of the unreacted triene was recovered (Scheme 132). Analysis of the $^1$H and $^{13}$C NMR data confirmed that the diastereoisomer that underwent cyclisation was the one required for preparation of the natural product \textbf{16}. NMR data for the final compound were identical to those reported for 7-acetylsinumaximol B that had been isolated from natural sources.

Scheme 132 Completion of the synthesis of 7-acetylsinumaximol B
2.6 Conclusions and Future Work

In conclusion, convergent total syntheses of both 7-epi-pukalide and 7-acetylsinumaximol B have been completed with longest linear sequences of 16 steps from (R)-perillyl alcohol (Scheme 133). In addition, a new synthesis of the starting material (R)-perillyl alcohol has also been devised. The routes represent the first total syntheses of both 7-epi-pukalide and 7-acetylsinumaximol B and demonstrate an effective strategy for the introduction of oxygen substituents at C7 and C8. The key THT-promoted reaction allowed the rapid and convergent assembly of the complete furan-containing skeleton and permitted completion of the syntheses by a parallel macrolactonisation and ring-closing metathesis sequence.

Scheme 133 Summary of the synthesis of 7-epi-pukalide and 7-acetylsinumaximol B

In future, the above strategy may be adapted for the synthesis of other, more complex, furanocembrane natural products and their epimers. For example, biologically active lophotoxin and its analogue lophodiol B possess an epoxide and diol, respectively, at the C7-C8 position; motifs which may be accessed directly through the one-pot Knoevenagel condensation furan formation strategy.
Scheme 134 Proposed future targets
3. Experimental Section
3.1 General Experimental Information

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Tetrahydrofuran, toluene, dichloromethane, acetonitrile and diethyl ether were purified using a Pure-SolvTM 500 Solvent Purification System. Other dry organic solvents and starting materials were obtained from commercial sources and used as received unless otherwise specified. Triethylamine, diisopropylamine, diisopropylethylamine, titanium tetrachloride, titanium isopropoxide, acetaldehyde and methyl acetate were distilled and stored under argon prior to use. n-Butyllithium and methyllithium solutions were titrated against diphenylacetic acid to obtain accurate molarity. 4 Å molecular sieves were oven-dried prior to use.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered alumina plates F254. Visualisation of TLC plates was carried out under UV light and stained using either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Flash column chromatography was performed using silica gel – Fluorochem 35-70 µm, 60A. Petroleum ether used for column chromatography was the 40–60 °C fraction.

IR spectra were recorded at rt using a Shimadzu FTIR-8400S spectrometer by ATR and selected frequencies (νmax) are reported. All 1H spectra were recorded on Bruker 400 MHz or 500 MHz spectrometers at rt. 1H NMR data are reported as follows: chemical shifts in ppm relative to CDCl3 (7.26) or C6D6 (7.16) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app. = apparent or a combination of thereof), coupling constant(s) J (Hz) and assignment. All 13C NMR spectra were recorded on a Bruker 400 MHz and Bruker 500 MHz spectrometers at 101 MHz and 126 MHz respectively. Data are reported as follows; chemical shifts in ppm relative to CHCl3 (77.16) or C6D6 (128.06) on the δ scale and assignment. HSQC and COSY data were utilised for structural assignments. Mass spectra were recorded by the University of Glasgow mass spectrometry service using positive chemical ionization (CI+), positive ion impact (EI+) and positive ion electrospray (ESI+) techniques on a Jeol MStation JMS-700 instrument. The intensity of each peak is quoted as a percentage of the largest where this information was available. Optical rotations were recorded on an Autopol V polarimeter. Ozonolysis was carried out using a Degremont Technologies Triogen ozone generator.
3.2 Experimental Procedures

(R)-Perillyl alcohol (R)-32

To a solution of allylic alcohol 304 (25.9 g, 171 mmol) in CH$_2$Cl$_2$ (700 mL) at 0 °C was added triethylamine (59.6 mL, 427 mmol) followed by methanesulfonyl chloride (14.1 mL, 188 mmol). The mixture was stirred for 1 h before the addition of H$_2$O (200 mL) and saturated aq. NaHCO$_3$ (200 mL), then stirred at rt for 5.5 h. The resulting mixture biphasic mixture was separated and the organic phase was washed with brine (300 mL) then dried over MgSO$_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et$_2$O, 7:3) to afford (R)-perillyl alcohol (R)-32 as a colourless oil (11.3 g, 44%).$^a$ [α]$^D$$^2$ +86 (c = 1.51, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.73–5.68 (1H, m, CH=C3), 4.81–4.63 (2H, m, CH$_2$-C16), 4.08–3.94 (2H, m, CH$_2$-C21), 2.22–2.03 (4H, m, CH$_2$-C2, CH$_2$-C13), 2.03–1.91 (1H, m, CH$_2$-C14), 1.90–1.83 (1H, m, CH-C1), 1.74 (3H, s, CH$_3$-C17), 1.54–1.43 (1H, m, CH$_2$-C14); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.8 (C-C15), 137.3 (C-C12), 122.5 (CH-C3), 108.7 (CH$_2$-C16), 67.3 (CH$_2$-C21), 41.1 (CH-C1), 30.4 (CH$_2$-C2), 27.5 (CH$_2$-C13), 26.1 (CH$_2$-C14), 20.8 (CH$_3$-C17); LRMS m/z (EI+) [M+H]$^+$ 152.21 (20%), 134.20 (32%), 121.19 (53%), 93.14 (82%), 79.12 (100%), 68.13 (85%), 67.12 (76%), 55.15 (33%).

$^a$Reaction on 0.66 mmol scale delivered a higher yield (61%).

(E/Z)-Ethyl 2-acetyl-6-hydroxy-6-methylhept-2-en-4-ynoate 297

To a solution of ynenone 383 (520 mg, 1.54 mmol) in MeOH (9 mL) at 0 °C was added (+)-CSA (17.9 mg, 0.08 mmol). The reaction was stirred for 45 min before removal of the solvent under vacuum. The resulting residue was purified by silica gel column chromatography (pet. ether: Et$_2$O, 30:70 → 50:50) to afford the title compound 297 as an orange oil (306 mg, 89%)
as a 1:1 mix of \(E\) and \(Z\) isomers. \(E\) isomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.80\) (1H, s, CH-C6), 4.27 (2H, q, \(J = 7.1\) Hz, CH\(_2\)-C9), 2.45 (3H, s, CH\(_3\)-C12), 2.03 (1H, s, OH-C1), 1.56 (6H, s, CH\(_3\)-C2, CH\(_3\)-C3), 1.31 (3H, t, \(J = 7.1\) Hz, CH\(_3\)-C10); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 194.6\) (C-C11), 163.8 (C-C8), 142.3 (C-C7), 122.7 (CH-C6), 110.9 (C-C4), 77.8 (C-C5), 65.8 (C-C1), 61.9 (CH\(_2\)-C9), 31.0 (2C, CH\(_3\)-C2, CH\(_3\)-C3), 24.3 (CH\(_3\)-C12), 14.2 (CH\(_3\)-C10); \(Z\) isomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.78\) (1H, s, CH-C6), 4.35 (2H, q, \(J = 7.1\) Hz, CH\(_2\)-C9), 2.36 (3H, s, CH\(_3\)-C12), 2.05 (1H, s, OH-C1), 1.57 (6H, s, CH\(_3\)-C2, CH\(_3\)-C3), 1.38 (3H, t, \(J = 7.1\) Hz, CH\(_3\)-C10); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 194.0\) (C-C11), 165.4 (C-C8), 142.3 (C-C7), 124.1 (CH-C6), 109.4 (C-C4), 78.1 (C-C5), 65.9 (C-C1), 61.8 (CH\(_2\)-C9), 31.0 (2C, CH\(_3\)-C2, CH\(_3\)-C3), 27.7 (CH\(_3\)-C12), 14.3 (CH\(_3\)-C10); **Isomeric mixture**: HRMS (ESI\(^+\)) calcd. for C\(_{12}\)H\(_{16}\)O\(_4\)Na [M+Na]\(^+\) 247.0941, found 247.0931; IR \(\nu_{\text{max}}\) 3447, 2983, 2937, 1712, 1697, 1599, 1585, 1371, 1136 cm\(^{-1}\).

**Ethyl 5-(3,3-dimethyloxiran-2-yl)-2-methylfuran-3-carboxylate 298**

![Chemical structure of ethyl 5-(3,3-dimethyloxiran-2-yl)-2-methylfuran-3-carboxylate 298](image)

Chemical Formula: C\(_{12}\)H\(_{16}\)O\(_4\)
Molecular Weight: 224.2560

To a sealed tube under argon was added a solution of enyne 297 (100 mg, 0.45 mmol) in CH\(_2\)Cl\(_2\) (1 mL). THT (7 μl, 0.09 mmol) was added and the solution heated to 45 °C for 40.5 h. The solvent was removed under vacuum and the resulting residue purified by silica gel column chromatography (pet ether: Et\(_2\)O, 7:3) to afford the title compound 298 as a colourless oil (57.1 mg, 57%) along with recovered (\(Z\)-297) as a pale yellow oil (32.9 mg, 33%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 6.51\) (1H, s, CH-C4), 4.27 (2H, q, \(J = 7.0\) Hz, CH\(_2\)-C11), 3.67 (1H, s, CH-C6), 2.56 (3H, s, CH\(_3\)-C1), 1.44 (3H, s, CH\(_3\)-C8), 1.35 (3H, s, CH\(_3\)-C9), 1.33 (1H, t, \(J = 7.0\) Hz, CH\(_2\)-C12); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 163.9\) (C-C10), 159.1 (C-C3), 148.5 (CH-C4), 114.4 (C-C2), 109.3 (C-C5), 61.4 (C-C7), 60.2 (CH-C6), 58.3 (CH-C11), 24.2 (CH\(_3\)-C8), 18.8 (CH\(_3\)-C9), 14.3 (CH\(_3\)-C1), 13.8 (CH\(_3\)-C12). HRMS (ESI\(^+\)) calcd. for C\(_{12}\)H\(_{16}\)O\(_4\)Na [M+Na]\(^+\) 247.0941, found 247.0931; IR \(\nu_{\text{max}}\) 1714, 1617, 1420 cm\(^{-1}\).

**\((4R)-4-(Prop-1-en-2-yl)-1-(((triisopropylsilyloxy)methyl)cyclohex-1-ene 311**

![Chemical structure of \((4R)-4-(Prop-1-en-2-yl)-1-(((triisopropylsilyloxy)methyl)cyclohex-1-ene 311](image)

Chemical Formula: C\(_{19}\)H\(_{36}\)OSi
Molecular Weight: 308.5810
To a solution of (R)-perillyl alcohol ((R)-32) (11.0 g, 72.3 mmol) in CH₂Cl₂ (400 ml) was added imidazole (6.40 g, 94.0 mmol) and DMAP (0.88 g, 7.2 mmol) followed by chlorotriisopropylsilane (17.1 mL, 79.6 mmol). The mixture was stirred at rt for 4 h and brine (400 mL) was added. The biphasic mixture separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 100 mL). The combined organic extracts washed with saturated aq. NH₄Cl (300 mL), dried over MgSO₄ and then filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to afford the silyl ether 311 as a pale yellow oil (22.3 g, quant.).

\[ \alpha_\text{D}^3 +50 (c = 0.71, \text{CHCl}_3); ^1\text{H} \text{NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta 5.70 (1\text{H}, \text{dd}, J = 3.0, 1.5 \text{ Hz}, \text{CH}-C_3), 4.71 (2\text{H}, \text{s}, \text{CH}_2-C_2, \text{CH}_2-C_13), 4.19–4.00 (2\text{H}, \text{m}, \text{CH}_2-C_6), 2.20–2.09 (2\text{H}, \text{m}, \text{CH}_2-C_2, \text{CH}_2-C_13), 2.01–1.90 (1\text{H}, \text{m}, \text{CH}_2-C_14), 1.87–1.80 (1\text{H}, \text{m}, \text{CH}-C_1), 1.74 (3\text{H}, \text{s}, \text{CH}_3-C_17), 1.53–1.42 (1\text{H}, \text{m}, \text{CH}_2-C_14), 1.22–0.97 (21\text{H}, \text{m}, \text{CH}_3\text{(CH}_3)_2); ^{13}\text{C} \text{NMR} (126 \text{ MHz}, \text{CDCl}_3) \delta 150.3 (\text{C}-C_15), 137.2 (\text{C}-C_12), 120.4 (\text{CH}-C_3), 108.6 (\text{CH}_2-C_16), 67.3 (\text{CH}_2-C_2), 41.6 (\text{CH}-C_1), 30.5 (\text{CH}_2-C_2), 27.7 (\text{CH}_2-C_13), 26.1 (\text{CH}_2-C_14), 21.0 (\text{CH}_3-C_17), 18.2 (\text{CH}(\text{CH}_3)_2), 12.2 (\text{CH}(\text{CH}_3)_2); \text{HRMS (ESI)}^+ \text{calc} \text{f}or \text{C}_{19}\text{H}_{36}\text{OSiNa [M+Na]}^+ \text{331.2428, found 331.2412; IR } \nu_{\text{max}} \text{2941, 2866, 1645, 1464 cm}^{-1} \text{.}

7-Hydroxy-5-(prop-1-en-2-yl)-1-(triisopropylsilyloxy)heptan-3-one 313

A solution of silyl ether 311 (5.0 g, 16 mmol), pyridine (1.3 mL, 16 mmol) and isoprene (16.2 mL, 162 mmol) in a mixture (1:4) of CH₂Cl₂ and MeOH (225 mL) at −78 °C was subjected to ozonolysis and monitored by TLC. After 1 h the mixture was flushed with O₂ and the reaction was quenched with dimethyl sulfide (50 mL) before being warmed to rt and stirred overnight. This reaction was repeated on three further batches and the solutions were combined. The solvent was removed under vacuum and the residue was dissolved in Et₂O (1 L). The solution was washed with H₂O (2 × 400 mL) and brine (400 mL), then dried over MgSO₄ and filtered. The solvent was removed under vacuum and the residue was passed through a short pad of silica gel (pet ether:Et₂O, 85:15) to afford the crude product 312 as a yellow oil.

To a solution of crude aldehyde 312 in toluene (400 mL) was added NaB(OAc)_3H (7.88 g, 37.2 mmol) and the reaction mixture stirred at rt for 4.5 days. The reaction was quenched by addition of saturated aq. NaHCO₃ (400 mL) and the biphasic mixture separated. The aqueous phase was extracted with EtOAc (3 × 200 mL) and the combined organic extracts...
were dried over MgSO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 7:3 → 1:1) to afford the alcohol 313 as a colourless oil (8.64 g, 38% over 2 steps). [α]₂³⁴° -1.4 (c = 1.16, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.79 (1H, dq, J = 2.6, 1.4Hz, CH₂-C16), 4.75–4.73 (1H, m, CH₂-C16), 4.20 (2H, s, CH₂-C21), 3.68–3.55 (2H, m, CH₂-C3), 2.53 (2H, dd, J = 7.9, 7.1Hz, CH₂-C13), 2.27–2.19 (1H, m, CH-C1), 1.80–1.53 (4H, m, CH₂-C2, CH₂-C14), 1.61 (3H, dd, J = 1.4, 0.8Hz, CH₃-C17), 1.23–0.97 (21H, m, CH(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 212.0 (C-C12), 146.8 (C-C15), 113.0 (CH₂-C16), 69.9 (CH₂-C21), 61.5 (CH₂-C3), 43.9 (CH-C1), 36.4 (CH₂-C13), 36.3 (CH₂-C2), 26.1 (CH₂-C14), 18.0 (CH₃-C17), 17.7 ((CH(CH₃)₂), 12.0 (CH(CH₃)₂)₂); HRMS (ESI⁺) calcd for C₁₉H₃₇O₃SiNa [M+Na]⁺ 365.2482, found 365.2467; IR ν max, 3402, 2941, 2866, 1719, 1643, 1369 cm⁻¹

(3R)-3-(Prop-1-en-2-yl)-6-((triisopropylsilyloxy)methyl)hept-6-en-1-ol 314

To a solution of methyl triphenylphosphonium bromide (13.8 g, 38.7 mmol) in THF (80 mL) at 0 °C was added nBuLi (17.6 mL of a 2.2 M solution in hexane, 39 mmol) and the solution stirred for 45 min. A solution of the alcohol 313 (5.3 g, 15 mmol) in THF (20 mL) was then added and the solution stirred at rt for 18 h. The reaction was quenched with H₂O (100 mL) and the biphasic mixture was separated. The aqueous phase was extracted with Et₂O (3 × 100 mL) and the combined organic extracts were washed with brine (200 mL), dried over MgSO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to afford the diene 314 as a colourless oil (4.51 g, 86%), [α]₂³⁴° -3.5 (c = 0.67, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.09–5.06 (1H, m, CH₂-C¹), 4.83–4.78 (2H, m, CH₂-C², CH₂-C16), 4.77–4.75 (1H, m, CH₂-C16), 4.13 (2H, s, CH₂-C21), 3.71–3.48 (2H, m, CH₂-C3), 2.27–2.19 (1H, m, CH-C1), 2.02–1.84 (2H, m, CH₂-C13), 1.66–1.60 (5H, m, CH₂-C2, CH₂-C17), 1.54–1.47 (2H, m, CH₂-C14), 1.24–0.89 (21H, m, CH(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 148.8 (C-C12), 147.4 (C-C15), 112.6 (CH₂-C¹), 108.1 (CH₂-C16), 66.2 (CH₂-C21), 61.8 (CH₂-C3), 44.4 (CH-C1), 36.3 (CH₂-C2), 31.6 (CH₂-C13), 30.5 (CH₂-C14), 18.2 (CH₃-C17), 17.8 (CH(CH₃)₂), 12.2 (CH(CH₃)₂); HRMS (ESI⁺) calcd for C₂₅H₄₀O₃SiNa [M+Na]⁺ 363.2690, found 363.2673; IR ν max 3329, 2941, 2866, 1645, 1462 cm⁻¹
To a solution of alcohol 314 (50.0 mg, 0.15 mmol) in CH$_2$Cl$_2$ (4 mL) was added Dess-Martin periodinane (97.0 mg, 0.18 mmol) and the resulting solution was stirred at rt for 5 h. Saturated aq. Na$_2$S$_2$O$_3$ (3 mL) was added and the phases separated. The organic phase was washed with saturated aq. NaHCO$_3$ (2 × 2 mL), dried over MgSO$_4$, filtered and the solvent removed under vacuum to afford crude title compound. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 9:1) afforded the title compound 315 (48.6 mg, quant.) as a colourless oil.

$\text{[a]}_{D}^{31}$ = –1.2 (c = 0.250, CHCl$_3$); 1H NMR (500 MHz, CDCl$_3$) δ 9.67 (1H, t, J = 2.4 Hz, CHO-C$_3$), 5.15–5.05 (1H, m, CH$_2$-C$_16$), 4.84–4.80 (2H, m, CH$_2$-C$_{12}$), 4.80–4.76 (1H, m, CH$_2$-C$_{15}$), 4.13 (2H, s, CH$_2$-C$_{21}$), 2.69 (1H, app p, J = 7.3 Hz, CH-C$_1$), 2.52–2.38 (2H, m, CH$_2$-C$_2$), 2.08–1.87 (2H, m, CH$_2$-C$_{13}$), 1.59–1.55 (2H, m, CH$_2$-C$_{14}$), 1.54 (3H, s, CH$_3$-C$_{17}$) 1.18–0.96 (21H, m, CH($\text{C}_3$H$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 202.2 (CHO-C$_3$), 148.2 (C-C$_{15}$), 145.6 (C-C$_{12}$), 112.8 (CH$_2$-C$_{16}$), 108.4 (CH$_2$-C$_{4}$), 66.1 (CH$_2$-C$_{21}$), 47.5 (CH$_2$-C$_2$), 41.3 (CH-C$_1$), 31.1 (CH$_2$-C$_{14}$), 30.0 (CH$_2$-C$_{13}$), 18.7 (CH$_3$-C$_{17}$), 18.0 (CH(CH$_3$)$_2$), 12.0 (CH(CH$_3$)$_2$); IR $\nu_{\text{max}}$ 3075, 2942, 2891, 2866, 2716, 1726, 1647, 1462 cm$^{-1}$.

**Methyl (R)-3-oxo-5-(prop-1-en-2-yl)-8-(triisopropylsilyloxy)methyl)non-8-enoate 316**

Methylglycine hydrochloride (300 mg, 2.39 mmol) and NaNO$_2$ (198 mg, 2.87 mmol) were dissolved in a ≈3:1 mixture of CH$_2$Cl$_2$ (0.8 mL) and H$_2$O (0.3 mL) and the resulting mixture was stirred for 1.5 h. Saturated aq. NaHCO$_3$ (2 mL) and CH$_2$Cl$_2$ (2 mL) were added and the biphasic mixture separated. The organic phase was dried over MgSO$_4$ and filtered to give a solution of methyl diazoacetate which was used directly in the reaction.

To tin(II) chloride (12.2 mg, 0.064 mmol) was added the solution of methyl diazoacetate (4.0 mL, ~0.6 M in CH$_2$Cl$_2$, ~2.4 mmol) and aldehyde 315 (210 mg, 0.62 mmol) in CH$_2$Cl$_2$ (5 mL).
The resulting solution was stirred at rt for 19 h before removal of solvent under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et\(_2\)O, 95:5 → 90:10) afforded recovered aldehyde starting material 315 (59.3 mg, 28%) followed by the title compound 316 (tautomeric mixture by NMR) as a colourless oil (144 mg, 57%). \([\alpha]_D^{22} -0.7\) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.98 (0.2 H, s, OH-C3, enol), 5.10-5.06 (1H, m, CH\(_2\)-C\(^6\)), 4.96 (0.2H, s, CH-C4, enol), 4.84-4.77 (2H, m, CH\(_2\)-C16), 4.76-4.72 (1H, m, CH\(_2\)-C\(^3\)), 4.13 (2H, s, CH\(_2\)-C21), 3.73 (2.4H, s, CH\(_3\)-C19), 3.72 (0.6H, s, CH\(_3\)-C19, enol) 3.44 (0.8H, d, \(J = 15.5\) Hz, CH\(_2\)-C4), 3.40 (0.8H, d, \(J = 15.5\) Hz, CH\(_2\)-C4), 2.69–2.53 (2.6H, m, CH-C1, CH-C2), 2.24 (0.4H, d, \(J = 7.5\) Hz, CH-C2, enol), 2.03–1.81 (2H, m, CH\(_2\)-C13), 1.65 (2.4H, dd, \(J = 1.5, 0.8\) Hz, CH\(_3\)-C17), 1.63 (0.6H, dd, \(J = 1.4, 0.8\) Hz, CH\(_3\)-C17, enol), 1.59–1.43 (2H, m, CH\(_2\)-C14), 1.21–0.95 (21H, m, CH\((\text{CH}_3)_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.5 (C-C3), 177.3 (C-C3 enol), 167.5 (C-C18), 148.4 (C-C15 enol), 148.3 (C-C15), 145.9 (C-C12), 145.6 (C-C12 enol), 112.7 (CH\(_2\)-C16 enol), 112.5 (CH\(_2\)-C16), 108.2 (CH\(_2\)-C\(^\Lambda\) enol), 108.2 (CH\(_2\)-C\(^\Lambda\) enol), 89.9 (CH-C4 enol), 66.1 (CH\(_2\)-C21), 52.3 (CH\(_3\)-C19), 51.0 (CH\(_3\)-C19 enol), 49.3 (CH\(_2\)-C4), 47.5 (CH\(_2\)-C2), 44.2 (CH\(_2\)-C2 enol), 42.1 (CH-C1), 39.8 (CH-C1 enol), 31.1 (CH\(_2\)-C14), 30.7 (CH\(_2\)-C14 enol), 30.2 (CH\(_2\)-C13 enol), 30.1 (CH\(_2\)-C13), 18.9 (CH\(_3\)-C17), 18.3 (CH\(_3\)-C17 enol), 18.0 (CH\((\text{CH}_3)_2\), 12.0 (CH\((\text{CH}_3)_2\)); HRMS (ESI\(^+\)) calcd. for C\(_{23}\)H\(_{44}\)O\(_4\)Si [M+H]\(^+\) 411.2931 found 411.2930; IR \(\nu_{\text{max}}\) 3075, 2943, 2866, 1751, 1719, 1647, 1630, 1449, 1437 cm\(^{-1}\).

**Methyl (R)-8-(hydroxymethyl)-3-oxo-5-(prop-1-en-2-yl)non-8-enoate 317**

\[
\begin{align*}
\text{HO} & \quad \text{A} \\
12 & \quad 13 \\
14 & \quad 15 \\
3 & \quad 4 \quad \text{OMe} \\
1 & \quad 2 \quad 16 \quad 17
\end{align*}
\]

Chemical Formula: C\(_{14}\)H\(_{22}\)O\(_4\)
Molecular Weight: 254.3260

To a solution of silyl ether 316 (130 mg, 0.32 mmol) in THF (3.5 mL) at rt was added TBAF (0.35 mL, 1 M in THF, 0.35 mmol) dropwise. The resulting solution was stirred for 2 h before a second addition of TBAF (0.35 mL, 1 M in THF, 0.35 mmol) and stirring for a further 3 h. H\(_2\)O (10 mL) and Et\(_2\)O (10 mL) were added and the biphasic mixture was separated. The aqueous phase was extracted with Et\(_2\)O (3 × 10 mL) and the combined organic extracts dried over Na\(_2\)SO\(_4\), filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 6:4) afforded the title compound 317 (tautomeric mixture by NMR) as a colourless oil (78.0...
Methyl (R)-8-formyl-3-oxo-5-(prop-1-en-2-yl)non-8-enoate 318

To a solution of alcohol 317 (20 mg, 0.08 mmol) in CH$_2$Cl$_2$ (1 mL) was added Dess-Martin periodinane (40 mg, 0.09 mmol) and the resulting solution stirred at rt for 6 h. The solution was filtered through a silica gel plug and the solvent removed under vacuum to afford the title compound 318 (tautomeric mixture by NMR) as a colourless oil without purification (19.8 mg, quant.). [α]$_D^{24}$ =6.1 (c = 0.21, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 11.97 (0.1H, s, OH-C3, enol), 9.51 (1H, s, CHO-C21), 6.27 (0.9H, app s, CH$_2$-C$^A$, 6.25-6.23 (0.1H, m, CH$_2$-C$^A$, enol), 5.99 (0.9H, app s, CH$_2$-C$^A$), 5.99 (0.1H, app s, CH$_2$-C$^A$, enol), 4.94 (0.1H, s, CH$_2$-C$^A$), 4.86-4.84 (0.1H, m, CH$_2$-C16 enol), 4.81 (0.9H, dq, J = 1.6, 1.5 Hz, CH$_2$-C16), 4.75 (1H, br s, CH$_2$-C16), 4.72 (2.7H, s, CH$_3$-C19), 3.71 (0.3H, s, CH$_3$-C19, enol), 3.44 (0.9H, d, J = 15.8 Hz, CH$_2$-C4), 3.40 (0.9H, d, J = 15.8Hz, CH$_2$-C4), 2.69–2.53 (3H, m, CH-C1, CH$_2$-C2), 2.26–2.16 (1H, m, CH$_2$-C13), 2.14–2.06 (1H, m, CH$_2$-C13), 1.66 (3H, br s, CH$_3$-C17), 1.55–1.45 (2H, m, CH$_2$-C14); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.6 (C-C3), 194.7 (CHO-C21), 187.6 (C-C18), 149.9 (C-C15), 145.7 (C-C12), 145.3 (C-C12 enol), 134.4 (CH$_2$-C$^A$), 113.3 (CH$_2$-C16 enol) 112.9 (CH$_2$-C16), 90.1 (CH$_2$-C4 enol), 52.5 (CH$_3$-C19), 49.5 (CH$_2$-C4), 47.4 (CH$_2$-C2), 44.2 (CH$_2$-C2 enol), 42.0 (CH-C1), 39.8 (CH-C1 enol), 30.9 (CH$_2$-C14), 29.8 (CH$_2$-
C14 enol), 25.9 (CH₂-C13 enol), 25.7 (CH₂-C13), 19.0 (CH₃-C17), 18.3 (CH₃-C17 enol); HRMS (ESI⁺) calcd. for C₁₄H₂₀O₄Na [M+Na]⁺ 275.1254 found 275.1249; IR νmax 2953, 2928, 2856, 1748, 1717, 1686, 1645, 1628, 1437, 1406 cm⁻¹

(R)-Triisopropyl(5-2-4-methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-en-1-yloxy)silane 319

To a solution of alcohol 314 (440 mg, 1.29 mmol) in THF (10 mL) at rt was added NaH (62.0 mg of a 60% dispersion in mineral oil, 1.55 mmol) and the reaction stirred for 30 min. TBAI (48 mg, 0.13 mmol) and PMBCl (0.2 mL, 1.42 mmol) were added and the reaction stirred for 17 h. DMF (1 mL) was added and the reaction was heated to 45 °C for 17 h. After cooling to rt, saturated aq. NH₄Cl (10 mL) and Et₂O (10 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et₂O (2 × 10 mL) and the combined organic extracts dried over MgSO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 95:5) afforded the title compound 319 (590 mg, 99%) as a colourless oil. [α]D⁴ -4.7 (c = 0.64, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.23 (2H, m, Ar-PMB), 6.91–6.82 (2H, m, Ar-PMB), 5.07 (1H, d, J = 1.8 Hz, CH₂-C⁵), 4.80 (1H, d, J = 1.8 Hz, CH₂-C⁵), 4.75 (1H, dq, J = 2.6, 1.4 Hz, CH₂-C₁₆), 4.69 (1H, dq, J = 2.6, 0.7 Hz, CH₂-C₁₆), 4.40 (2H, s, CH₂-PMB), 4.12 (2H, s, CH₂-C₂₁), 3.80 (3H, s, CH₃-PMB), 3.45–3.32 (2H, m, CH₂-C₃), 2.21 (1H, tt, J = 9.6, 5.4 Hz, CH-C₁), 2.02–1.83 (2H, m, CH₂-C₁₃), 1.75–1.61 (2H, m, CH₂-C₂), 1.59 (3H, dd, J = 1.4, 0.7 Hz, CH₃-C₁₇), 1.54–1.41 (2H, m, CH₂-C₁₄), 1.19–0.95 (21H, m, CH(CH₃)₂; ¹³C NMR (101 MHz, CDCl₃) δ 159.6 (Ar-PMB), 149.3 (C-C₁₂), 147.1 (C-C₁₅), 131.3 (Ar-PMB), 129.7 (Ar-PMB), 114.2 (Ar-PMB), 112.7 (CH₂-C⁵), 108.2 (CH₂-C₁₆), 73.1 (CH₂-PMB), 68.9 (CH₂-C₃), 66.6 (CH₂-C₂₁), 55.8 (CH₃-PMB), 44.4 (CH-C₁), 33.8 (CH₂-C₂), 32.0 (CH₂-C₁₃), 30.9 (CH₂-C₁₄), 18.5 (CH₃-C₁₇), 18.3 (CH(CH₃)₂), 12.5 (CH(CH₃)₂); HRMS (EI⁺) calcd for C₂₈H₄₈O₃Si 460.3373, found 460.3376; IR νmax 2970, 2891, 2864, 1612, 1512, 1464 cm⁻¹.
To a solution of silyl ether 319 (500 mg, 1.09 mmol) in THF (20 mL) at rt was added TBAF (2.17 mL, 1 M in THF, 2.17 mmol). The resulting mixture was stirred for 14.5 h before H₂O (10 mL) and Et₂O (15 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et₂O (2 × 15 mL) and the combined organic extracts dried over MgSO₄, filtered and the solvent removed under vacuum to afford the crude title compound.

Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 4:1) afforded title compound 320 (290 mg, 88%) as a colourless oil. [α]D²³⁻⁸.8 (c = 0.500, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.27–7.23 (2H, m, Ar-PMB), 6.89–6.85 (2H, m, CHAr-PMB), 5.02–4.99 (1H, m, CH₂-Ar), 4.85 (1H, d, J = 1.3 Hz, CH₂-C₁), 4.77 (1H, dq, J = 2.9, 1.0 Hz, CH₂-C₁₆), 4.71–4.68 (1H, m, CH₂-C₁₆), 4.40 (2H, s, CH₂-PMB), 4.05 (2H, d, J = 6.2 Hz, CH₂-C₂₁), 3.80 (3H, s, CH₃-PMB), 3.44–3.33 (2H, m, CH₂-C₃), 2.23 (1H, tt, J = 9.4, 5.5 Hz, CH-C₁), 2.03–1.88 (1H, m, CH₂-C₁₃), 1.73–1.60 (2H, m, CH₂-C₂), 1.60 (3H, q, J = 1.0 Hz, CH₃-C₁₇), 1.52–1.45 (2H, m, CH₂-C₁₄), 1.37 (1H, t, J = 6.2 Hz, OH-C₂₁); ¹³C NMR (126 MHz, CDCl₃) δ 159.5 (Ar-PMB), 149.6 (C-C₁₂), 146.9 (C-C₁₅), 131.2 (Ar-PMB), 129.7 (Ar-PMB), 114.2 (Ar-PMB), 112.7 (CH₂-C₄), 109.5 (CH₂-C₁₆), 73.1 (CH₂-PMB), 68.8 (CH₂-C₃), 66.5 (CH₂-C₂₁), 55.7 (CH₃-PMB), 44.2 (CH-C₁), 33.7 (CH₂-C₂), 31.8 (CH₂-C₁₃), 31.1 (CH₂-C₁₄), 18.2 (CH₃-C₁₇); HRMS (EI⁺) calcd for C₁₉H₂₇O₃ 304.2038, found 304.2035; IR νmax 3424, 2934, 2859, 2837, 1613, 1512 cm⁻¹.

(R)-5-(2-4-Methoxybenzylloxyethyl)-6-methyl-2-methylenehept-6-en-1-ol 320

To a solution of alcohol 320 (240 mg, 0.79 mmol) in CH₂Cl₂ (6 mL) at rt was added Dess-Martin periodinane and the resulting mixture stirred for 3 h. The reaction was filtered through a silica plug, washed with CH₂Cl₂ (20 mL) and the solvent removed under vacuum to afford the crude aldehyde (251 mg) which was used directly in the next reaction without further purification.
To a solution of crude (R)-5-(2-4-methoxybenzoyloxyethyl)-6-methyl-2-methylenehept-6-enal (~0.79 mmol) and 2-methyl-2-butene (0.67 mL, 6.3 mmol) in tBuOH (4.75 mL) was added a solution of NaH₂PO₄·2H₂O (800 mg, 5.14 mmol) and NaClO₂ (239 mg, 4.74 mmol) in H₂O (9.5 mL). The resulting mixture was stirred at rt for 7 h before addition of CH₂Cl₂ (30 mL). The biphasic mixture was separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet ether:EtOAc, 4:1 → 3:2) afforded the title compound 321 (251 mg, quant. over 2 steps) as a yellow oil. [α]₀̥²⁴ –6.6 (c = 0.875, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.21 (2H, m, Ar-PMB, CH- Ar-PMB), 6.91–6.81 (2H, m, Ar-PMB), 6.26 (1H, d, J = 1.4 Hz, CH₂-C₇), 5.68–5.59 (1H, m, CH₂-C₇), 4.81–4.74 (1H, m, CH₂-C₁₆), 4.74–4.67 (1H, m, CH₂-C₁₆), 4.40 (2H, s, CH₂-PMB), 3.80 (3H, s, CH₃-PMB), 3.47–3.31 (2H, m, CH₂- C₃), 2.32–2.20 (2H, m, CH₂-C₁₃), 2.20–2.11 (1H, m, CH-C₁), 1.75–1.58 (2H, m, CH₂-C₂), 1.61 (3H, s, CH₃-C₁₇), 1.57–1.41 (2H, m, CH₂-C₁₄); ¹³C NMR (126 MHz, CDCl₃) δ 172.6 (COOH-C₂₁), 159.5 (Ar-PMB), 146.7 (C-C₁₂), 140.6 (C-C₁₅), 131.1 (Ar-PMB), 129.7 (Ar- PMB), 127.3 (CH₂-C₇), 114.1 (CH₂-C₁₆), 112.9 (Ar-PMB), 73.0 (CH₂-PMB), 68.7 (CH₂-C₃), 55.7 (CH₃-PMB), 44.2 (CH-C₁), 33.6 (CH₂-C₂), 32.4 (CH₂-C₁₃), 30.0 (CH₂-C₁₄), 18.1 (CH₃- C₁₇); HRMS (ESI⁺) calcd. for C₁₉H₂₈O₄Na [M+Na]⁺ 341.1723 found 341.1709; IR νmax 2926, 2854, 1694, 1512 cm⁻¹.

(E)-5-Hydroxy-1-(triisopropylsilyl)undec-6-en-1-yn-3-one 327

Racemic: To a solution of triethylamine (0.50 mL, 3.6 mmol) in Et₂O (10 mL) at 0 °C was added chlorodicyclohexylborane (3.35 mL, 1.0 M in hexane, 3.35 mmol) followed by ketone 325 (502 mg, 2.23 mmol). The solution was stirred for 2 h before being cooled to −78 °C and addition of trans-2-hepteninal (0.58 mL, 4.5 mmol). After 4 h stirring at −78 °C The reaction was quenched with H₂O (10 mL) and the phases separated. The aq. phase was extracted with Et₂O (20 mL) and the combined organic extracts washed with saturated aq. NH₄Cl (20 mL) before being dried over MgSO₄, filtered and the solvent removed under vacuum to yield the crude product. Purification of the residue by silica gel column chromatography (pet ether: Et₂O, 9:1) afforded the title compound 327 as a pale yellow oil (498 mg, 66%).

Enantiopure: To a solution of silyl ether 396 (1.01 g, 2.24 mmol) in MeOH (10 mL) and CH₂Cl₂ (10 mL) at 0 °C was added (+)-CSA (52 mg, 0.22 mmol). The resulting mixture was stirred for 2 h before removal of the solvent under vacuum to afford the crude product.
Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 90:10 → 85:15) afforded the title compound 327 (692 mg, 92%) as a yellow oil. \( [\alpha]_D^{23} = -9.1 \) (c = 1.25, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.66 (1H, dtd, \( J = 15.3, 6.7, 1.0 \) Hz, CH-C\(_6\)), 5.41 (1H, ddt, \( J = 15.3, 6.7, 1.4 \) Hz, CH-C11), 4.64–4.46 (1H, m, CH-C10), 2.90–2.75 (2H, m, CH2-C9), 2.46 (1H, d, \( J = 3.9 \) Hz, OH-C10), 1.96 (2H, app. q, \( J = 6.7 \) Hz, CH2-C7), 1.39–1.16 (4H, m, CH2-C8, CH2-C14), 1.16–0.91 (21H, m, CH(CH3)2), 0.82 (3H, t, \( J = 7.1 \) Hz, CH3-C18); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 186.2 (C-C8), 133.0 (CH-CB), 130.3 (CH-C11), 104.2 (C-C7), 97.0 (C-C6), 68.6 (CH-C10), 52.6 (CH2-C9), 31.8 (CH2-C5), 31.2 (CH2-C8), 22.2 (CH2-C5), 18.5 (CH(CH3)2), 13.9 (CH3-CF), 11.0 (CH(CH3)2); HRMS (ESI+) calcd. for C\(_{20}\)H\(_{36}\)O\(_2\)SiNa [M+Na] \( 359.2377 \) found 359.2378; IR \( \nu_{\max} \) 3414, 2943, 2866, 2149, 1672, 1464, 1385 cm\(^{-1}\)

(E)-3-Methyl-1-(triisopropylsilyl)undec-6-en-1-yne-3,5-diol 328

Racemic: To a stirred solution of ZnBr\(_2\) (99.3 mg, 0.44 mmol) in CH\(_2\)Cl\(_2\) (1 mL) at rt was added a solution of \( \beta \)-hydroxy ketone 327 (75.8 mg, 0.22 mmol) in CH\(_2\)Cl\(_2\) (1 mL). The resulting mixture was stirred at rt for 1 h before cooling to 0 °C and addition of MeLi (0.55 mL of a 1.6 M solution in Et\(_2\)O, 0.88 mmol). The reaction was warmed to rt and stirred for 2 h before quenching with 1 M HCl (2 mL). The phases were separated and the aq. phase extracted with Et\(_2\)O (3 × 3 mL). Combined organic extracts were washed with brine (5 mL), dried over MgSO\(_4\), filtered and the solvent removed under vacuum to yield the crude product as pale yellow oil. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 8:2) afforded the anti title compound anti-328 (34.7 mg, 45%) followed by the syn title compound syn-328 (14.4 mg, 19%).

Enantiopure: To a solution of Ti(O\(_i\)Pr)\(_4\) (4.5 mL, 15 mmol) in Et\(_2\)O (22.5 mL) at 0 °C was added TiCl\(_4\) (0.5 mL, 5 mmol). The resulting solution was warmed to rt for 30 min and then cooled to 0 °C. MeLi (12.5 mL of a 1.6 M solution in Et\(_2\)O, 20 mmol) was added and the mixture was stirred for 1 h. A portion of the solution (15.9 mL) was added to a solution of \( \beta \)-hydroxy ketone 327 (180 mg, 7.97 mmol) in Et\(_2\)O (5 mL) at −78 °C. The solution was stirred for 15 minutes, warmed to 0 °C and then stirred for 30 min. 2 M HCl (15 mL) was added dropwise and the biphasic mixture was warmed to rt. The phases were separated and the aqueous phase was extracted with Et\(_2\)O (2 × 15 mL). The combined organic extracts were
washed with brine (30 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 8:2) to deliver the anti 1,3-diol anti-328 (40 mg, 20%) as a colourless oil (less polar isomer) followed by the diastereomeric syn 1,3-diol syn-328 (155 mg, 78%) as a colourless oil (more polar isomer). Anti-328 [α]D²⁵ +17 (c = 1.25, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.67 (1H, ddd, J = 15.2, 6.9, 0.8 Hz, CH-C⁵), 5.51 (1H, ddt, J = 15.2, 6.9, 1.3 Hz, 1H, CH-C₁₁), 4.87–4.78 (1H, CH-C₁₀), 4.07 (1H, s, OH-C₈), 2.33 (1H, d, J = 2.7 Hz, OH-C₁₀), 2.03 (2H, dd, J = 13.8, 6.9 Hz, CH₂-C₉), 1.79–1.72 (2H, m, CH₂-C⁵), 1.55 (3H, s, CH₃-C₂₀), 1.40–1.23 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.16–0.93 (21H, m, CH(CH₃)₂), 0.90 (3H, t, J = 7.1 Hz, CH₃-C⁵);¹³C NMR (126 MHz, CDCl₃) δ 132.2 (CH-C⁹), 132.1 (CH-C₁₁) 111.1 (C-C⁷), 83.8 (C-C₆), 72.4 (C-C₈), 68.6 (CH-C₁₀), 48.6 (CH₂-C₉), 31.8 (CH₂-C⁵), 31.3 (CH₂-C⁰), 31.2 (CH₃-C₂₀), 22.2 (CH₂-C⁵), 18.6 (CH(CH₃)₂), 13.9 (CH(CH₃)₂), 11.2 (CH₃-C⁵); HRMS (ESI+) calcd. for C₂₁H₄₀O₂Si [M+Na]⁺ 375.2690 found 375.2669; IR νmax 3356, 2928, 2866, 2361, 2342, 1462 cm⁻¹. Syn-328 [α]D²⁵ +6.3 (c = 0.71, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.83–5.67 (1H, m, CH-C⁰), 5.53 (1H, ddt, J = 15.3, 7.1, 1.3 Hz, CH-C₁₁), 4.62–4.48 (1H, m, CH-C₁₀), 2.72 (1H, d, J = 2.3 Hz, OH-C₁₀), 2.67 (1H, s, OH-C₈), 2.08–1.99 (3H, m, CH₂-C⁵, CH₂-C₉), 1.86 (1H, dd, J = 14.5, 3.6 Hz, CH₂-C₉), 1.55 (3H, s, CH₃-C₂₀), 1.42–1.18 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.15–0.94 (21H, m, CH(CH₃)₂), 0.89 (3H, t, J = 7.1 Hz, CH₃-C⁵);¹³C NMR (126 MHz, CDCl₃) δ 132.7 (CH-C⁵), 132.3 (CH-C₁₁), 111.8 (C-C⁷), 84.5 (C-C₆), 70.3 (C-C₈), 67.4 (CH-C₁₀), 49.3 (CH₂-C₉), 31.9 (CH₂-C⁵), 31.2 (CH₂-C⁰), 30.1 (CH₃-C₂₀), 22.2 (CH₂-C⁵), 18.6 (CH(CH₃)₂), 13.9 (CH(CH₃)₂), 11.1 (CH₃-C⁵); HRMS (ESI+) calcd. for C₂₁H₄₀O₂Si [M+Na]⁺ 375.2690 found 375.2672; IR νmax 3356, 2928, 2866, 2361, 2342, 1462 cm⁻¹

(±)-(4R,6R)-6-((E)-Hex-1-en-1-yl)-4-methyl-4-((triisopropylsilyl)ethynyl)-1,3-dioxan-2-one 329

To a solution of racemic 1,3-diol anti-328 (32.0 mg, 0.085 mmol) in CH₂Cl₂ (1 mL) was added pyridine (70 μL, 0.90 mmol) and the solution cooled to −78 °C. Triphosgene (53.4 mg, 0.18 mmol) was added and the reaction stirred for 40 min before being warmed to rt and stirred for a further 35 min. The reaction was quenched by addition of saturated aq. NH₄Cl (3 mL). The biphasic mixture was separated and the aq. phase washed with CH₂Cl₂ (2 × 3 mL).
The combined organic extracts were washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and the solvent removed under vacuum to afford the title compound 329 as pale yellow oil (36.5 mg). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.90–5.79 (1H, m, CH-Cb), 5.48 (1H, ddt, $J$ = 15.3, 7.2, 1.3 Hz, CH-C11), 5.31–5.16 (1H, m, CH-C10), 2.18 (1H, dd, $J$ = 14.1, 3.2 Hz, CH$_2$-C9), 2.07 (2H, app q, $J$ = 13.5, 6.7 Hz, CH$_2$-C5), 1.98–1.86 (1H, m, CH$_2$-C9), 1.70 (3H, s, CH$_3$-C20), 1.44–1.22 (4H, m, CH$_2$-C0, CH$_2$-C5); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.2 (OCC(O)O), 136.8 (CH-Cb), 125.9 (CH-C11), 104.9 (C-C7), 89.1 (C-C6), 78.3 (C-C8), 75.2 (CH-C10), 40.2 (CH$_2$-C9), 31.8 (CH$_2$-C5), 30.8 (CH$_3$-C20), 28.9 (CH$_2$-C0), 22.2 (CH$_2$-C5), 18.5 (CH(CH$_3$)$_2$), 13.9 (CH(CH$_3$)$_2$), 11.0 (CH$_3$-C5); HRMS (ESI+) calcd for C$_{22}$H$_{38}$O$_2$Si [M+Na]$^+$ 401.2482 found 41.2450; IR $\nu_{\text{max}}$ 2941, 2866, 1761, 1464 cm$^{-1}$.

(±)-(4S,6R)-6-((E)-Hex-1-en-1-yl)-4-methyl-4-((triisopropylsilyl)ethynyl)-1,3-dioxan-2-one 330

To a solution of racemic 1,3-diol syn-328 (14.0 mg, 0.043 mmol) in CH$_2$Cl$_2$ (1 mL) was added pyridine (30 µL, 0.40 mmol) and the solution cooled to −78 °C. Triphosgene (23.7 mg, 0.08 mmol) was added and the reaction stirred for 40 min before being warmed to rt and stirred for a further 35 min. The reaction was quenched by addition of saturated aq. NH$_4$Cl (2 mL). The biphasic mixture was separated and the aqueous phase washed with CH$_2$Cl$_2$ (2 × 3 mL). Combined organic extracts were washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and the solvent removed under vacuum to yield the title compound 330 as pale yellow oil (15.7 mg). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.85 (1H, ddt, $J$ = 15.3, 6.7, 0.5 Hz, CH-Cb), 5.63 (1H, ddt, $J$ = 15.3, 7.4, 1.4 Hz, CH-C11), 4.92–4.80 (1H, m, CH-C10), 2.34–2.20 (2H, m, CH$_2$-C9), 2.03–2.11 (2H, m, CH$_2$-C5), 1.76 (3H, s, CH$_3$-C20), 1.47–1.21 (4H, m, CH$_2$-C5, CH$_2$-Cb), 1.21–0.97 (21H, m, CH(CH$_3$)$_2$), 0.89 (3H, t, $J$ = 7.1 Hz, CH$_3$-C5); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 148.4 (OCC(O)O), 137.2 (CH-Cb), 125.9 (CH-C11), 106.0 (C-C7), 88.1 (C-C6), 76.6 (C-C8), 75.0 (CH-C10), 39.4 (CH$_2$-C9), 31.8 (CH$_2$-C5), 30.8 (CH$_3$-C20), 28.3 (CH$_2$-C5), 22.2 (CH$_2$-C5), 18.5 (CH(CH$_3$)$_2$), 13.9 (CH(CH$_3$)$_2$), 11.0 (CH$_3$-C5); HRMS (ESI+) calcd for C$_{22}$H$_{38}$O$_2$Si [M+Na]$^+$ 401.2482 found 41.2450; IR $\nu_{\text{max}}$ 2942, 2866, 1753, 1464, 1381, 1234 cm$^{-1}$. 

![Chemical Structure](image)
(E)-3-Methylundec-6-en-1-yne-3,5-diol 331

To a solution of 1,3-diol syn-328 (2.03 g, 5.75 mmol) in THF (100 mL) was added TBAF (6.33 mL of a 1 M solution in THF, 6.33 mmol) and the resulting solution stirred at rt for 2 h. Saturated aq. NH₄Cl (70 mL) and Et₂O (70 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et₂O (2 × 70 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 3:2) afforded title compound 331 (1.10 g, 97%) as a yellow oil. $\left[\alpha\right]_D^{24} +10.7$ (c = 0.600, CHCl₃); $^1$H NMR (500 MHz, CDCl₃) $\delta$ 5.73 (1H, dtd, J = 15.4, 6.7, 1.0 Hz, CH$_2$-C₂), 5.54 (1H, ddt, J = 15.4, 7.0, 1.5 Hz, CH$_2$-C₁₁), 4.52 (1H, dddd, J = 9.4, 7.0, 3.3, 2.8 Hz, CH$_2$-C₁₀), 3.11 (1H, s, OH-C₈), 2.51 (1H, s, CH-C₆), 2.42 (1H, d, J = 2.8 Hz, OH-C₁₀), 2.08 (1H, dd, J = 14.5, 9.4 Hz, CH$_2$-C₉), 2.07–2.00 (2H, m, CH$_2$-C), 1.87 (1H, dd, J = 14.5, 3.3 Hz, CH$_2$-C₉), 1.60 (3H, s, CH$_3$-C₂₀), 1.42–1.25 (4H, m, CH$_2$-C, CH$_2$-C), 0.89 (3H, t, J = 7.1 Hz, CH$_3$-C₂₀); $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 132.8 (CH$_2$-C₂), 132.2 (CH$_2$-C₁₁), 88.0 (CH-C₇), 71.5 (C-C₆), 70.3 (CH-C₁₀), 67.1 (C-C₈), 48.6 (CH₂-C₉), 31.8 (CH$_2$-C), 31.2 (CH$_2$-C), 29.5 (CH$_3$-C₂₀), 22.2 (CH$_2$-C), 13.9 (CH$_3$-C₂₀); HRMS (ESI⁺) calcd. for C$_{12}$H$_{20}$O$_2$Na [M+Na]$^+$ 219.1356, found 219.1345; IR $\nu_{max}$ 3402, 3309, 3300, 2957, 2926, 2860, 1420 cm$^{-1}$.

(E)-3,3,9,9-Tetraethyl-5-ethynyl-7-(hex-1-en-1-yl)-5-methyl-4,8-dioxa-3,9-disilaundecane 332

To a solution of 1,3-diol 331 (1.10 g, 5.60 mmol) in CH$_2$Cl$_2$ (50 mL) at −78 °C was added lutidine (4.24 mL, 36.4 mmol) followed by TESOTf (4.05 mL, 17.9 mmol). The resulting solution was stirred for 1 h before addition of aq. NaHCO$_3$ (50 mL). The biphasic mixture was separated and the aqueous phase extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined organic extracts dried over Na$_2$SO$_4$, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 100:0 → 95:5) afforded title compound 332 (2.38 g, quant.) as a colourless oil. $\left[\alpha\right]_D^{25} +4.1$ (c = 0.945, CHCl₃); $^1$H NMR (400 MHz, CDCl₃) $\delta$ 5.62–5.43 (2H, m, CH-C, CH-...
C11), 4.43 (1H, ddd, J = 6.2, 6.2, 6.0 Hz, CH-C10), 2.43 (1H, s, CH-C6), 2.03–1.96 (2H, m, CH2-C5), 1.91 (1H, dd, J = 13.8, 6.2 Hz, CH2-C9), 1.87 (1H, dd, J = 13.8, 6.0 Hz, CH2-C9), 1.50 (3H, s, CH3-C20), 1.42–1.23 (4H, m, CH2-C20D, CH2-C20E), 0.96 (9H, t, J = 7.9 Hz, Si(CH3)3), 0.94 (9H, t, J = 7.9 Hz, Si(CH2CH3)3), 0.89 (3H, t, J = 7.1 Hz, CH3-C5), 0.72–0.61 (6H, m, Si(CH3)3), 0.65–0.54 (6H, m, Si(CH2CH3)3); 13C NMR (101 MHz, CDCl3) δ 134.3 (CH-C5), 130.1 (CH-C11), 88.3 (C-C7), 72.2 (CH-C6), 71.2 (CH-C10), 68.4 (C-C8), 53.4 (CH2-C9), 31.8 (CH2-C5), 31.7 (CH3-C20), 31.3 (CH2-C9), 22.3 (CH2-C5), 13.9 (CH3-C5), 7.0 (Si(CH2CH3)3), 6.9 (Si(CH2CH3)3), 6.2 (Si(CH2CH3)3), 5.2 (Si(CH2CH3)3); HRMS (ESI+) calcd. for C24H48O2Si2Na [M+Na]+: 447.3085, found: 447.3053; IR νmax 3310, 2954, 2936, 2914, 2876, 2209, 1458, 1414 cm⁻¹.

**(E)-4-Methyl-4,6-bis(triethysilyloxy)dodec-7-en-2-ynal 333**

![Chemical Structure](image)

To a solution of alkyne **332** (2.37 g, 5.58 mmol) in THF (100 mL) at −78 °C under argon was added nBuLi (2.70 mL of a 2.28 M solution in hexane, 6.16 mmol). The resulting solution was stirred for 30 min before warming to 0 °C and addition of DMF (0.87 mL, 11.2 mmol). After 30 min stirring at 0 °C the reaction was warmed to rt and stirred for 1 h. 5% aq. KH2PO4 (100 mL) and Et2O (100 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et2O (2 × 100 mL) and the combined organic extracts were washed with 5% aq. KH2PO4 (100 mL) before being dried over Na2SO4, filtered and the solvent removed under vacuum to afford the title compound **333** (2.48 g, quant.) as a colourless oil which was used directly in the next reaction. [α]D20 +8.5 (c = 0.770, CHCl3); 1H NMR (500 MHz, CDCl3) δ 9.24 (1H, s, CHO-C5), 5.56 (1H, dt, J = 15.4, 6.5 Hz, CH-C5), 5.46 (1H, ddt, J = 15.4, 7.3, 1.4 Hz, CH-C11), 4.38 (1H, app td, J = 7.3, 5.2 Hz, CH-C10), 2.04–1.96 (3H, m, CH2-C9, CH2-C5), 1.89 (1H, dd, J = 13.9, 5.2 Hz, CH2-C9), 1.57 (3H, s, CH3-C20), 1.42–1.21 (4H, m, CH2-C20D, CH2-C20E), 0.97 (9H, t, J = 7.9 Hz, Si(CH2CH3)3), 0.93 (9H, t, J = 7.9 Hz, Si(CH2CH3)3), 0.90 (3H, t, J = 7.1 Hz, CH3-C5), 0.74–0.62 (6H, m, Si(CH2CH3)3), 0.58 (6H, q, J = 7.9 Hz, Si(CH2CH3)3); 13C NMR (126 MHz, CDCl3) δ 176.5 (CHO-C5), 133.8 (CH-C5), 131.2 (CH-C11), 101.0 (C-C7), 83.8 (C-C6), 71.1 (CH-C10), 68.6 (C-C8), 53.0 (CH2-C9), 32.0 (CH2-C5), 31.3 (CH3-C20), 22.5 (CH2-C5), 14.1 (CH3-C5), 7.1 (Si(CH2CH3)3), 7.0 (Si(CH2CH3)3), 6.3 (Si(CH2CH3)3), 5.3 (Si(CH2CH3)3); IR νmax 2955, 2936, 2915, 2876, 2209, 1458, 1414 cm⁻¹.
To a solution of aldehyde 333 (180 mg, 0.40 mmol) in THF (4 mL) was added a solution of TBAF (0.83 mL of a 1 M solution in THF, 0.83 mmol) and the resulting mixture stirred at rt for 1 h. H₂O (10 mL) and Et₂O (10 mL) were added and the biphasic mixture separated. The organic phase was dried over Na₂SO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 1:4) afforded title compound 336 (69 mg, 58%) as a yellow oil.

**[E]**-4-Methyl-4,6-bis(triethylsilyloxy)dodec-(159,811),(599,890)-7-en-2-yn-1-ol 337

To a solution of aldehyde 333 (~1.65 mmol) in MeOH (30 mL) at 0 °C was added NaBH₄ (95 mg, 2.48 mmol) and the resulting solution stirred for 1.5 h. Saturated aq. NH₄Cl (20 mL) was added and the resulting solution extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford...
the crude product. Purification of the residue by silica gel column chromatography (pet.
ether:Et₂O, 85:15) afforded title compound 337 (660 mg, 88%) as a yellow oil. [α]D⁰^²⁺ = 5.6 (c =
0.590, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.59–5.46 (2H, m, CH-C⁸, CH-C¹¹), 4.39 (1H,
ddd, J = 6.1, 6.1, 6.0 Hz, CH-C¹⁰), 4.29 (2H, d, J = 6.3 Hz, CH₂-C⁵), 2.00 (2H, dt, J = 6.7,
6.4 Hz, CH₂-C⁵), 1.91 (1H, dd, J = 13.7, 6.1 Hz, CH₂-C⁹), 1.87 (1H, dd, J = 13.7, 6.0 Hz,
CH₂-C⁹), 1.49 (3H, s, CH₃-C₂₀), 1.37 (1H, t, J = 6.3 Hz, OH-C⁵), 1.36–1.28 (4H, m, CH₂-C⁰,
CH₂-C⁵), 0.96 (9H, t, J = 7.9 Hz, Si(CH₃)₃), 0.95 (9H, t, J = 7.9 Hz, Si(CH₃)₃), 0.89
(3H, t, J = 7.1 Hz, CH₂-C⁵), 0.70–0.62 (6H, m, Si(CH₃)₃), 0.59 (6H, q, J = 7.9 Hz,
Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 134.4 (CH-C⁵), 130.3 (CH-C¹¹), 90.7 (C-C⁷),
82.0 (C-C⁶), 71.4 (CH-C¹⁰), 68.7 (C-C⁸), 53.5 (CH₂-C⁹), 51.5 (CH₂-C⁵), 32.0 (CH₂-C⁵),
31.8 (CH₂-C⁵), 31.4 (CH₂-C₂₀), 22.5 (CH₂-C⁵), 14.1 (CH₂-C⁵), 7.2 (Si(CH₃)₃), 7.0
(Si(CH₃)₃), 6.4 (Si(CH₂)₃), 5.3 (Si(CH₂)₃); HRMS (ESI⁺) calcd. for C₃₅H₅₅O₃Si₂Na
[M+Na]^+ 477.3191, found 477.3164; IR νmax 3375, 2955, 2928, 2876, 1458, 1413 cm⁻¹.

Optical rotation data were obtained from enantiopure material; although only the racemic
synthesis is reported in this document

(S,E)-1-((R)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxynon-4-en-1-one 341-major and
(R,E)-1-((R)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxynon-4-en-1-one 341-minor

Chemical Formula: C₁₉H₂₆NO₂S₂
Molecular Weight: 363.5340

To a solution of thiazolidine-2-thione 343 (1.31 g, 5.21 mmol) in CH₂Cl₂ (50 mL) at 0 °C was
added TiCl₄ (0.57 mL, 5.42 mmol) followed by DIPEA (0.99 mL, 5.68 mmol) and the resulting
solution cooled to −78 °C. The mixture was stirred for 30 min and trans-2-heptenal (0.67 mL,
5.16 mmol) was added. The solution was stirred for a further 1 h before warming to 0 °C and
the addition of saturated aq. NH₄Cl (40 mL). After further warming to rt the biphasic mixture
was separated and the aqueous phase washed with CH₂Cl₂ (2 × 40 mL). The combined
organic extracts were dried over Na₂SO₄, filtered and the solvent removed under vacuum to
afford the crude product. Purification of the residue by silica gel column chromatography
(pet. ether:Et₂O, 75:25 → 60:40) afforded 341-minor (195 mg, 10%) as a yellow oil followed
by 341-major (1.00 g, 54%) as a yellow oil. **Minor:** $[\alpha]_D^{24} = -124 \ (c = 0.87, \text{CHCl}_3)$; $^1\text{H NMR (500 MHz, CDCl}_3\) \delta 7.38–7.33 \ (2H, \text{m, Ph}), 7.31–7.27 \ (3H, \text{m, Ph}), 5.74 \ (1H, \text{dd, J = 15.1, 7.0, 1.2 Hz, CH-}^\beta), 5.54 \ (1H, \text{dtt, J = 15.1, 6.4, 1.5 Hz, CH(C11)), 5.40 \ (1H, \text{ddd, J = 10.6, 7.1, 3.8 Hz, CH-Aux}), 4.60–4.53 \ (1H, \text{m, CH-C10}), 3.61 \ (1H, \text{dd, J = 17.4, 9.0 Hz, CH$_2$C9}), 3.42–3.37 \ (2H, \text{m, CH$_2$C9, CH$_2$Ph}), 3.23 \ (1H, \text{dd, J = 13.3, 3.8 Hz, CH$_2$-Aux}), 3.05 \ (1H, \text{dd, J = 13.3, 10.6 Hz, CH$_2$-Aux}), 3.01 \ (1H, \text{d, J = 3.6 Hz, OH-C10}), 2.91 \ (1H, \text{d, J = 11.5 Hz, CH$_2$-Aux}), 2.05 \ (2H, \text{dt, J = 7.0, 6.9 Hz, CH$_2$C9}), 1.42–1.27 \ (4H, \text{m, CH$_2$C}$^\text{D}, \text{CH$_2$C}$^\text{E}), 0.89 \ (3H, \text{t, J = 7.1 Hz, CH$_3$-F}); $^{13}\text{C NMR (101 MHz, CDCl}_3\) \delta 201.5 \ (\text{C-S}), 173.2 \ (\text{C-C8}), 136.5 \ (\text{Ph}), 133.0 \ (\text{CH-C}$^\text{B}), 130.7 \ (\text{CH-C11}), 129.6 \ (\text{Ph}), 129.1 \ (\text{Ph}), 127.4 \ (\text{Ph}), 69.4 \ (\text{CH-C10}), 68.4 \ (\text{CH-Aux}), 45.8 \ (\text{CH$_2$C9}), 37.0 \ (\text{CH$_2$-Aux}), 32.2 \ (\text{CH$_2$-Bn}), 32.0 \ (\text{CH$_2$C}$^\text{D}), 31.3 \ (\text{CH$_2$-C}$^\text{E}), 22.4 \ (\text{CH$_2$C}$^\text{F}), 14.1 \ (\text{CH$_3$C}$^\text{F}); \text{HRMS (ESI$^+$) calcd. for C$_{19}$H$_{28}$NO$_2$S$_2$Na [M+Na]$^+ 330.0593, found 330.0588; IR $\nu_{\text{max}} 3565, 2953, 2924, 2855, 1694, 1674, 1497, 1437 \text{ cm}^{-1}$.}

**Major:** $[\alpha]_D^{24} = -167 \ (c = 1.16, \text{CHCl}_3)$; $^1\text{H NMR (500 MHz, CDCl}_3\) \delta 7.37–7.33 \ (2H, \text{m, Ph}), 7.31–7.27 \ (3H, \text{m, Ph}), 5.76 \ (1H, \text{dd, J = 15.1, 6.9, 1.2 Hz, CH-}^\beta), 5.55 \ (1H, \text{ddt, J = 15.1, 6.5, 1.5 Hz, CH-C11}), 5.39 \ (1H, \text{dd, J = 10.6, 7.1, 3.9 Hz, CH-Aux}), 4.68–4.62 \ (1H, \text{m, CH-C10}), 3.61 \ (1H, \text{dd, J = 17.6, 2.9 Hz, CH$_2$C9}), 3.40 \ (1H, \text{ddd, J = 11.5, 7.1, 0.8 Hz, CH$_2$Ph}), 3.32 \ (1H, \text{dd, J = 17.6, 9.0 Hz, CH$_2$-C9}), 3.23 \ (1H, \text{dd, J = 13.2, 3.9 Hz, CH$_2$-Aux}), 3.05 \ (1H, \text{dd, J = 13.2, 10.6 Hz, CH$_2$-Aux}), 2.90 \ (1H, \text{d, J = 11.5 Hz, CH$_2$Ph}), 2.65 \ (1H, \text{brs, OH-C10}), 2.05 \ (2H, \text{dt, J = 6.9, 6.8 Hz, CH$_2$C9}), 1.42–1.25 \ (4H, \text{m, CH$_2$C}$^\text{D}, \text{CH$_2$C}$^\text{E}), 0.90 \ (3H, \text{t, J = 7.2 Hz, CH$_3$C}$^\text{F}); $^{13}\text{C NMR (126 MHz, CDCl}_3\) \delta 201.5 \ (\text{C-S}), 172.8 \ (\text{C-C8}), 136.6 \ (\text{Ph}), 132.9 \ (\text{CH-}^\beta), 130.5 \ (\text{CH-C11}), 129.6 \ (\text{Ph}), 129.1 \ (\text{Ph}), 127.4 \ (\text{Ph}), 68.9 \ (\text{CH-C10}), 68.5 \ (\text{CH-Aux}), 46.0 \ (\text{CH$_2$-C9}), 37.0 \ (\text{CH$_2$-Aux}), 32.3 \ (\text{CH$_2$-Bn}), 32.0 \ (\text{CH$_2$C}$^\text{D}), 31.4 \ (\text{CH$_2$-C}$^\text{E}), 22.4 \ (\text{CH$_2$C}$^\text{F}), 14.1 \ (\text{CH$_3$C}$^\text{F}); \text{HRMS (ESI$^+$) calcd. for C$_{19}$H$_{28}$NO$_2$S$_2$Na [M+Na]$^+ 330.0592, found 330.0592; IR $\nu_{\text{max}} 3439, 2955, 2924, 2856, 2690, 1497, 1437 \text{ cm}^{-1}$.}

**(S,E)-3-Hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)non-4-en-1-one 342**

![Chemical Structure of (S,E)-3-Hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)non-4-en-1-one 342](image)

To a solution of oxazolidinethione 344 (1.01 g, 3.80 mmol) in CH$_2$Cl$_2$ (20 mL) at −40 °C was added TiCl$_4$ (0.84 mL, 7.6 mmol). After 5 minutes, DIPEA (1.33 mL, 7.60 mmol) was added and the resulting solution stirred for 2 h. The solution was cooled to −78 °C, trans-2-heptenal (0.60 mL, 4.6 mmol) added and the mixture stirred for a further 5 h. Half-saturated aq. NH$_4$Cl (30 mL) was added and the mixture was warmed to rt. The biphasic mixture was separated and the aqueous phase extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extracts
were dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 7:3 → 5:5) afforded title compound **342** (1.21 g, 85%) as a yellow oil. [α]🎬^20^ +44 (c = +0.51, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.87 (1H, s, CH-Mes), 6.85 (1H, s, CH-Mes), 6.11 (1H, dd, J = 11.0, 7.2 Hz, CH-Aux), 5.68 (1H, ddt, J = 15.1, 6.7, 1.2 Hz, CH-C⁹), 5.49 (1H, ddt, J = 15.1, 6.2, 1.5 Hz, CH-C₁₁), 4.87 (1H, dd, J = 11.0, 9.3 Hz, CH₂-Aux), 4.52–4.46 (1H, m, CH-C₁₀), 4.40 (1H, dd, J = 9.3, 7.2 Hz, CH₂-Aux), 3.66 (1H, dd, J = 17.8, 9.1 Hz, CH₂-C₉), 3.39 (1H, dd, J = 17.8, 2.9 Hz, CH₂-C₉), 2.45 (3H, s, CH₃-Mes), 2.25 (6H, s, CH₃-Mes), 2.01 (2H, dt, J = 7.0, 6.7 Hz, CH₂-Cᵡ), 1.38–1.25 (4H, m, CH₂-Cᵩ, CH₂-Cᵩ), 0.88 (3H t, J = 7.2 Hz, CH₃-Cᵩ); ¹³C NMR (126 MHz, CDCl₃) δ 186.1 (C=S), 173.1 (C-C₈), 138.5 (Ar), 135.0 (Ar), 133.0 (CH-C⁹), 132.0 (Ar), 130.5 (Ar), 130.4 (CH-C₁₁), 130.0 (Ar), 72.0 (CH₂-Aux), 68.8 (CH-C₁₀), 58.4 (CH-Aux), 45.3 (CH₂-C₉), 32.0 (CH₂-Cᵩ), 31.3 (CH₂-Cᵩ), 22.4 (CH₂-Cᵩ), 20.9 (CH₃-Mes), 20.8 (CH₃-Mes), 14.1 (CH₃-Cᵩ); HRMS (EI⁺) calcd for C₂₁H₂₃NO₅S 375.1868, found 375.1864; IR νmax 3451, 2959, 2926, 2859, 1705, 1613, 1483 cm⁻¹.

**(S,E)-3-Hydroxy-N-methoxy-N-methylnon-4-enamide 345**

![Chemical structure](image)

To a solution of aldol adduct **342** (1.15 g, 3.06 mmol) in CH₂Cl₂ (60 mL) was added N,O-dimethylhydroxylamine hydrochloride (1.78 g, 18.4 mmol) and imidazole (2.11 g, 30.6 mmol) and the resulting solution stirred for 21 h at rt. Saturated aq. NH₄Cl (50 mL) was added and the biphasic mixture separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 8:2 → 1:1) afforded recovered oxazolidinethione auxiliary (657 mg, 99%) followed by the title compound **345** (599 mg, 91%) as a yellow oil. [α]🎬^20^ =-32 (c = 0.71, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.74 (1H, ddt, J = 15.4, 6.6, 1.2 Hz, CH-C⁹), 5.51 (1H, ddt, J = 15.4, 6.6, 1.4 Hz, CH-C₁₁), 4.56–4.47 (1H, m, CH-C₁₀), 3.78 (1H, d, J = 3.2 Hz, OH-C₁₀), 3.69 (3H, s, NCH₃), 3.19 (3H, s, OCH₃), 2.74–2.53 (2H, m, CH₂-C₉), 2.04 (2H, dt, J = 6.7, 6.6 Hz, CH₂-Cᵩ), 1.45–1.23 (4H, m, CH₂-Cᵩ, CH₂-Cᵩ), 0.89 (3H t, J = 7.1 Hz, CH₃-Cᵩ); ¹³C NMR (101 MHz, CDCl₃) δ 173.6 (C-C₈), 132.4 (CH-C₁₁), 131.0 (CH-C⁹), 69.0 (CH-C₁₀), 61.4 (NCH₃), 38.7 (CH₂-C₉), 32.0 (CH₂-Cᵩ), 31.4 (CH₂-Cᵩ), 22.4 (CH₂-Cᵩ), 14.1 (CH₃-Cᵩ); HRMS (EI⁺) calcd for Cₑ₁H₂₄NO₅S 215.1521, found 215.1519; IR νmax 3435, 2957, 2926, 2872, 2859, 1640, 1464, 1437 cm⁻¹.
(S,E)-N-Methoxy-N-methyl-3-(triethylsilyloxy)non-4-enamide 346

![Chemical structure of 346]

Chemical Formula: C₁₇H₃₅NO₃Si  
Molecular Weight: 329.5560

To a solution of allylic alcohol 345 (50.4 mg, 0.23 mmol) in CH₂Cl₂ (1 mL) at −78 °C under argon was added 2,6-lutidine (0.07 mL, 0.66 mmol) followed by TESOTf (0.06 mL, 0.3 mmol). The resulting solution was stirred for 1 h before addition of saturated aq. NaHCO₃ (2 mL) and warming to rt. The biphasic mixture was separated and the aqueous phase extracted with CH₂Cl₂ (3 × 3 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude title compound. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 9:1) afforded the title compound 346 (67.4 mg, 89%) as a yellow oil. α − 17 (c = 0.65, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.64 (1H, dtd, J = 15.3, 6.7, 1.0 Hz, CH-C₈), 5.47 (1H, ddt, J = 15.3, 6.7, 1.4 Hz, CH-C₁₁), 4.63 (1H, ddd, J = 7.4, 6.7, 5.6 Hz, CH-C₁₀), 3.69 (3H, s, NC₃H₇), 3.17 (3H, s, OC₃H₇), 2.80 (1H dd, J = 14.2, 7.4 Hz, CH₂-C₉), 2.43 (1H, dd, J = 14.2, 5.6 Hz, CH₂-C₉), 2.00 (2H, dt, J = 6.7, 6.6 Hz, CH₂-C₈), 1.42−1.22 (4H, m, CH₂-C₄, CH₂-C₆), 0.93 (9H, t, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.88 (3H, t, J = 7.0 Hz, CH₃-C⁰), 0.58 (6H, q, J = 7.9 Hz, Si(CH₂CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 167.6 (C-C₈), 132.6 (C-C₁₁), 131.3 (CH-C⁰), 70.7 (CH-C₁₀), 61.5 (NCH₃), 40.9 (CH₂-C₉), 31.9 (CH₂-C⁰, OCH₃), 31.4 (CH₂-C⁰), 22.4 (CH₂-C₆), 14.1 (CH₃-C⁰), 6.9 (Si(CH₂CH₃)₃), 5.0 (Si(CH₂CH₃)₃); HRMS (EI⁺) calcd. for C₁₇H₃₅NO₃Si 330.2464, found 330.2463; IR νmax 2955, 2934, 2916, 2876, 1665, 1460, 1441 cm⁻¹.

(S,E)-3,3-Diethyl-5-(hex-1-en-1-yl)-13,13-dimethyl-12,12-diphenyl-4,11-dioxa-3,12-disilatetradec-8-yn-7-one 349

![Chemical structure of 349]

Chemical Formula: C₂₈H₃₆O₃Si  
Molecular Weight: 448.6780

To a solution of protected propargylic alcohol 347 (187 mg, 0.64 mmol) in THF (3 mL) at rt was added nBuLi (0.30 mL, 2.1 M in hexane, 0.64 mmol) and the resulting solution stirred for 30 min. A solution of amide 346 (140 mg, 0.43 mmol) in THF (2 mL) was added and the solution stirred for 10 min before warming to rt and stirring for 1 h. Saturated aq. NH₄Cl (5 mL) was added and the biphasic mixture separated. The aqueous phase was extracted with Et₂O (2 × 10 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the
solvent removed under vacuum to afford the crude product. Filtration through silica (pet. ether:Et₂O, 100:0 → 95:5) afforded an inseparable mixture (347 mg) of alkyne 348 and excess protected propargylic aldehyde 347 which was carried forward directly to the next reaction.

To a solution of crude alkyne 348 (~6.56 mmol) in MeOH (46 mL) and THF (15 mL) at 0 °C was added PPTS (164 mg, 0.65 mmol). The resulting mixture was stirred for 6 h before addition of saturated aq. NaHCO₃ (40 mL) and warming to rt. EtOAc (40 mL) was added and the biphasic mixture separated. The aqueous phase was extracted with EtOAc (3 × 60 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 90:10 → 85:15) afforded title compound 349 (2.27 g, 77% over 2 steps) as a yellow oil.

−8.8 (c = 0.50, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.71–7.67 (4H, m, Ph), 7.48–7.39 (6H, m, Ph), 5.70 (1H, dtd, J = 15.2, 6.9, 1.2 Hz, CH-C₈), 5.45 (1H, ddt, J = 15.2, 6.6, 1.4 Hz, CH-C₁₁), 4.60–4.52 (1H, m, CH-C₁₀), 4.47 (2H, s, CH₂-C₅), 2.74–2.62 (2H, m, CH₂-C₉), 2.40 (1H, d, J = 4.0 Hz, OH-C₁₀), 2.04 (2H, dt, J = 6.9, 6.7 Hz, CH₂-C⁵), 1.44–1.28 (4H, m, CH₂-C₄), 1.07 (9H, s, C(CH₃)₃), 0.90 (3H, t, J = 7.1 Hz, CH₃-C⁵); ¹³C NMR (126 MHz, CDCl₃) δ 186.4 (C-C₈), 135.7 (Ph), 133.1 (CH-C₁₁), 132.6 (Ph), 130.4 (CH-C⁸), 130.2 (Ph), 128.0 (Ph), 91.4 (C-C⁶), 84.2 (C-C⁷), 68.6 (CH-C₁₀), 52.6 (CH₂-C⁵), 52.2 (CH₂-C⁹), 32.0 (CH₂-C⁵), 31.3 (CH₂-C⁷), 26.8 (C(CH₃)₃), 22.3 (CH₂-C⁵), 19.3 (C(CH₃)₃), 14.1 (CH₃-C⁵); HRMS (ESI⁺) calcd. for C₂₈H₃₆O₃SiNa [M+Na]⁺ 471.2304, found 471.2326; IR νmax 3437, 2957, 2930, 2859, 2214, 1709, 1676, 1464 cm⁻¹.

(4R,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-methyldodec-7-en-2-yne-4,6-diol 350-syn and (4S,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-methyldodec-7-en-2-yne-4,6-diol 350-anti

To a solution of Ti(OiPr)₄ (0.9 mL, 3 mmol) in Et₂O (4.5 mL) at 0 °C was added TiCl₄ (0.1 mL, 0.9 mmol). The resulting solution was warmed to rt for 30 min before cooling to 0 °C and addition of MeLi (2.5 mL of a 1.6 M in Et₂O, 4.0 mmol). After stirring for 1 h a portion of the solution (6.42 mL) was added to a solution of ynone 349 (96 mg, 0.21 mmol) in Et₂O (4 mL)
at −78 °C. The solution was stirred for 15 minutes before warming to 0 °C and stirring for 30 min. 2 M HCl (5 mL) was added dropwise before warming to rt and separation of the biphasic mixture. The aqueous phase was extracted with Et₂O (2 × 10 mL) and the combined organic extracts washed with brine (10 mL) before being dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 6:4) afforded 350-anti (18.9 mg, 19%) as a colourless oil followed by 350-syn (70.2 mg, 72%) as a colourless oil.

**Anti:** [α]₀²⁹⁺+6.6 (c = 0.42, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.76−7.68 (4H, m, Ph), 7.48−7.34 (6H, m, Ph), 5.62 (1H, ddt, J = 15.4, 6.7, 1.0 Hz, CH-C⁵), 5.44 (1H, ddt, J = 15.4, 6.7, 1.4 Hz, CH-C₁₁), 4.67−4.55 (1H, m, CH-C₁₀), 4.43 (1H, d, J = 16.0 Hz, CH₂-C₅), 4.41 (1H, d, J = 16.0 Hz, CH₂-C₅), 4.18 (1H, s, OH-C₈), 2.28 (1H, dd, J = 2.9, 1.0 Hz, OH-C₁₀), 2.02 (2H, dt, J = 6.7, 6.6 Hz, CH₂-C⁴), 1.75 (1H, dd, J = 14.4, 10.7 Hz, CH₂-C⁹), 1.63 (1H, ddd, J = 14.4, 2.3, 1.0, CH₂-C⁹), 1.40 (3H, s, CH₃-C₂₀), 1.38−1.27 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.06 (9H, s, C(CH₃)₃), 0.90 (3H, t, J = 7.0 Hz, CH₃-C⁸); ¹³C NMR (101 MHz, CDCl₃) δ 135.8 (Ph), 133.4 (Ph), 132.2 (CH-C₁₁), 132.1 (CH-C⁵), 129.9 (Ph), 127.8 (Ph), 88.3 (C-C⁷), 82.2 (C-C⁶), 72.2 (CH-C₁₀), 68.3 (C-C⁸), 52.9 (CH₂-C₅), 48.1 (CH₂-C⁹), 31.9 (CH-C⁵), 31.4 (CH₂-C⁰), 30.9 (CH₃-C₂₀), 26.8 (C(CH₃)₃), 22.3 (CH₂-C⁵), 19.3 (C(CH₃)₃), 14.1 (CH₃-C⁵); HRMS (ESI⁺) calcd. for C₂₉H₄₀O₃Na [M+Na]⁺ 487.2639, found 487.2616; IR νₘₐₓ 3358, 3073, 3048, 2957, 2859, 1474, 1462, 1427 cm⁻¹.

**Syn:** [α]₀²⁹⁺+2.7 (c = 0.11, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.75−7.68 (4H, m, Ph), 7.48−7.36 (6H, m, Ph), 5.69 (1H, ddt, J = 15.4, 6.8, 1.1 Hz, CH-C⁵), 5.48 (1H, ddt, J = 15.4, 7.1, 1.3 Hz, CH-C₁₁), 4.46−4.38 (1H, m, CH-C₁₀), 4.36 (2H, s, CH₂-C₅), 2.61 (1H, s, OH-C₈), 2.57 (1H, d, J = 2.5 Hz, OH-C₁₀), 2.02 (2H, dt, J = 7.0, 6.8 Hz, CH₂-C⁴), 1.92 (1H, dd, J = 14.5, 9.3 Hz, CH₂-C⁹), 1.72 (1H, dd, J = 14.5, 3.5 Hz, CH₂-C⁹), 1.45 (3H, s, CH₃-C₂₀), 1.41−1.24 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.05 (9H, s, C(CH₃)₃), 0.89 (3H, t, J = 7.1 Hz, CH₂-C⁵); ¹³C NMR (101 MHz, CDCl₃) δ 135.8 (Ph), 133.4 (Ph), 132.6 (CH-C₁₁), 132.4 (CH-C⁵), 129.9 (Ph), 127.8 (Ph), 89.1 (C-C⁷), 82.2 (C-C⁶), 70.2 (CH-C₁₀), 67.4 (C-C₈), 52.8 (CH₂-C₅), 48.7 (CH₂-C₉), 32.0 (CH₂-C⁵), 31.4 (CH₂-C⁰), 29.3 (CH₃-C₂₀), 26.9 (C(CH₃)₃), 22.4 (CH₂-C⁵), 19.3 (C(CH₃)₃), 14.1 (CH₃-C⁵); HRMS (ESI⁺) calcd. for C₂₉H₄₀O₃Na [M+Na]⁺ 487.2639, found 487.2616; IR νₘₐₓ 3358, 3073, 3048, 2957, 2859, 1472, 1464, 1427 cm⁻¹.
(4R,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-hydroxy-4-methylhept-7-en-2-yn-6-yl (R)-5-(2-(4-methoxybenzoyloxyethyl)-6-methyl-2-methylenehept-6-enoate 351

To a solution of Et$_3$N (0.42 mL, 1.9 mmol), DMAP (77 mg, 0.63 mmol) and MNBA (227 mg, 0.66 mmol) in CH$_2$Cl$_2$ (4 mL) was added a solution of carboxylic acid 321 (201 mg, 0.63 mmol) in CH$_2$Cl$_2$ (4 mL). The resulting solution was stirred at rt for 30 min before addition of a solution of diol 350-syn (293 mg, 0.63 mmol) in CH$_2$Cl$_2$ (4 mL). The resulting solution was stirred for 18 h before addition of saturated aq. NaHCO$_3$ (10 mL). The biphasic mixture was separated and the aqueous phase extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 8:2) afforded recovered diol 350-syn (57 mg, 31%) followed by the title compound 351 (328 mg, 68%) as a yellow oil. [α]$_D^{23}$ $-5.4$ (c = 1.12, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73–7.66 (4H, m, Ph), 7.46–7.35 (6H, m, Ph), 7.26–7.21 (2H, m, Ar-PMB), 6.90–6.84 (2H, m, Ar-PMB), 6.06 (1H, d, J = 1.5 Hz, CH$_2$-C$^A$), 5.76 (1H, dtd, J = 15.3, 6.8, 0.9 Hz, CH-C$^B$), 5.59 (1H, ddd, J = 7.9, 7.7, 4.6 Hz, 1H, CH-C10), 5.46 (1H, ddt, J = 15.3, 7.7, 1.5 Hz, CH-C11), 5.42 (1H, d, J = 1.5 Hz, CH$_2$-C$^A$), 4.75 (1H, dq, J = 2.6, 1.3 Hz, CH$_2$-C16), 4.68 (1H, d, J = 2.0 Hz, CH$_2$-C16), 4.40 (1H, d, J = 11.7 Hz, CH$_2$-PMB), 4.37 (1H, d, J = 11.7 Hz, CH$_2$-PMB), 4.27 (1H, d, J = 15.7 Hz, CH$_2$-C5), 4.25 (1H, d, J = 15.7 Hz, CH$_2$-C5), 3.80 (3H, s, CH$_3$-PMB), 3.42–3.30 (2H, m, CH$_2$-C3), 2.25–2.14 (2H, m, CH$_2$-C13), 2.12–1.97 (4H, m, CH-C1, CH$_2$-C9, CH$_2$-C$^C$), 1.85 (1H, dd, J = 14.3, 4.6 Hz, CH$_2$-C9), 1.70–1.54 (2H, m, CH$_2$-C2), 1.58 (3H, d, J = 1.3 Hz, CH$_3$-C17), 1.48–1.39 (2H, m, CH$_2$-C14), 1.38 (3H, s, CH$_3$-C20), 1.36–1.26 (4H, m, CH$_2$-C$^D$, CH$_2$-C$^E$), 1.04 (9H, s, C(CH$_3$)$_3$), 0.87 (3H, t, J = 7.2 Hz, CH$_3$-C$^E$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.1 (C-C21), 159.2 (Ar-PMB), 146.4 (C-C12), 141.2 (C-C15), 135.8 (Ph), 135.0 (CH-C$^B$), 133.4 (Ph), 130.9 (Ar-PMB), 129.9 (Ph), 129.4 (Ar-PMB), 128.5 (CH-C11), 127.8 (Ph), 124.9 (CH$_2$-C$^A$), 113.9 (Ar-PMB), 112.7 (CH$_2$-C16), 88.3 (C-C7), 82.0 (C-C6), 72.8 (CH$_2$-PMB), 72.2 (CH-C10), 68.5 (CH$_2$-C3), 65.7 (C-C8), 55.4 (CH$_2$-PMB), 52.8 (CH$_2$-C5), 47.7 (CH$_2$-C9), 44.0 (CH-C1), 33.3 (CH$_2$-C2), 32.4 (CH$_2$-C14), 32.0 (CH$_2$-C$^C$), 31.2 (CH$_3$-C20), 30.7 (CH$_2$-C$^D$), 30.0 (CH$_2$-C13), 26.9 (C(CH$_3$)$_3$), 22.3 (CH$_2$-}
C\textsuperscript{5}, 19.3 (C(CH\textsubscript{3})\textsubscript{3}), 17.9 (CH\textsubscript{3}-C17), 14.1 (CH\textsubscript{3}-C\textsuperscript{5}); HRMS (ESI\textsuperscript{+}) calcd. for C\textsubscript{46}H\textsubscript{60}O\textsubscript{6}SiNa [M+Na]\textsuperscript{+} 787.4364 found 787.4318; IR \textit{v}_{\text{max}} 3453, 3071, 2955, 2857, 1715, 1612, 1587, 1512, 1464, 1443, 1429 cm\textsuperscript{-1}.

\((4R,6S,E)-1-(\textit{tert}-Butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yn-6-yl \((R)-5-(2-4-methoxybenzoyloxyethyl)-6-methyl-2-methylenehept-6-enoate 353\)

To a solution of ester 351 (300 mg, 0.39 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (12 mL) at −78 °C was added 2,6-lutidine (0.12 mL, 1.0 mmol) followed by TESOTf (0.11 mL, 0.51 mmol). The resulting solution was stirred for 1.5 h before addition of saturated aq. NaHCO\textsubscript{3} (10 mL). The phases were separated and the aqueous phase extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 15 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 9:1) afforded the title compound (306 mg, 89%) as a colourless oil. [\(\alpha\)]\textsubscript{D}\textsuperscript{6} −10.2 (c = 0.21, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.73–7.67\) (4H, m, Ph), \(7.47–7.35\) (6H, m, Ph), \(7.28–7.23\) (2H, m, Ar-PMB), \(6.90–6.85\) (2H, m, Ar-PMB), \(6.07\) (1H, d, \(J = 1.5\) Hz, CH\textsubscript{2}-C\textsuperscript{A}), \(5.71–5.61\) (1H, m, CH\textsubscript{2}-C\textsuperscript{B}), \(5.55\) (1H, ddd, \(J = 7.5, 7.4, 3.9\) Hz, CH\textsubscript{2}-C10), \(5.48–5.40\) (2H, m, CH-C11, CH-C\textsuperscript{A}), \(4.76\) (1H, dq, \(J = 2.6, 1.3\) Hz, CH\textsubscript{2}-C16), \(4.69\) (1H, d, \(J = 2.6\) Hz, CH\textsubscript{2}-C16), \(4.39\) (2H, s, CH\textsubscript{2}-PMB), \(4.28\) (2H, s, CH\textsubscript{2}-C5), \(3.80\) (3H, s, CH\textsubscript{3}-C17), \(3.43–3.31\) (2H, m, CH\textsubscript{2}-C3), \(2.28–2.03\) (4H, m, CH\textsubscript{2}-C9, CH\textsubscript{2}-C13, CH-C1), \(1.99\) (2H, dt, \(J = 6.7, 6.6\) Hz, CH\textsubscript{2}-C\textsuperscript{C}), \(1.92\) (1H, dd, \(J = 14.3, 3.9\) Hz, CH\textsubscript{2}-C9), \(1.73–1.54\) (2H, m, CH\textsubscript{2}-C2) (3H, d, \(J = 1.3\) Hz, CH\textsubscript{3}-C17), \(1.50–1.42\) (2H, m, CH\textsubscript{2}-C14), \(1.42\) (3H, s, CH\textsubscript{3}-C20), \(1.37–1.22\) (4H, m, CH\textsubscript{2}-C\textsuperscript{D}, CH\textsubscript{2}-C\textsuperscript{E}), \(1.05\) (9H, s, C(CH\textsubscript{3})\textsubscript{3}), \(0.94\) (9H, t, \(J = 7.9\) Hz, Si(CH\textsubscript{3}CH\textsubscript{3})\textsubscript{3}), \(0.86\) (3H, t, \(J = 7.1\) Hz, CH\textsubscript{3}-C\textsuperscript{F}), \(0.67\) (6H, app qd, \(J = 7.9, 2.2\) Hz, SiCH\textsubscript{3}CH\textsubscript{3})\textsubscript{3}; \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta 166.2\) (C-C21), \(159.2\) (Ar-PMB), \(146.5\) (C-C12), \(141.6\) (C-C15), \(135.7\) (Ph), \(133.3\) (Ph), \(133.2\) (CH-C\textsuperscript{B}), \(130.9\) (Ar-PMB), \(129.9\) (Ph), \(129.4\) (Ar-PMB), \(129.2\) (CH-C11), \(127.9\) (Ph), \(124.1\) (CH\textsubscript{2}-C\textsuperscript{A}), \(113.9\) (Ar-PMB), \(112.5\) (CH\textsubscript{2}-C16), \(88.6\) (C-C7), \(82.6\) (C-C6), \(72.8\) (CH\textsubscript{2}-PMB), \(72.1\) (CH-C10), \(68.6\) (CH\textsubscript{2}-C3), \(67.7\) (C-C8), \(55.4\) (CH\textsubscript{3}-PMB), \(52.8\) (CH\textsubscript{2}-C5), \(49.7\) (CH\textsubscript{2}-C9), \(44.0\) (CH-C1), \(33.3\) (CH\textsubscript{2}-C2), \(32.4\) (CH\textsubscript{2}-C14), \(32.0\) (CH\textsubscript{2}-C\textsuperscript{C}), \(31.7\)
(CH₂-C20), 31.2 (CH₂-C₃), 30.1 (CH₂-13), 26.8 (C(CH₃)₃), 22.3 (CH₂-C⁵), 19.3 (C(CH₃)₃), 17.9 (CH₃-C17), 14.1 (CH₃-C⁵), 7.2 (Si(CH₂CH₃)₃), 6.2 (Si(CH₂CH₃)₃); HRMS (ESI⁺) calcd. for C₅₄H₇₀O₆Si₂Na [M+Na]⁺ 901.5234 found 901.5208; IR ν max 3071, 2955, 2930, 2874, 2859, 1717, 1643, 1630, 1613, 1514, 1464 cm⁻¹.

(4R,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yn-6-yl (R)-5-(2-hydroxyethyl)-6-methyl-2-methylenehept-6-enoate 353

To a solution of (4R,6S,E)-1-(tert-butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yn-6-yl (R)-5-(2-methoxybenzylxoyethyl)-6-methyl-2-methylenehept-6-enoate (295 mg, 0.34 mmol) in a 9:1 mixture of CH₂Cl₂ (9 mL) and aqueous pH7 buffer (1 mL) was added DDQ (84 mg, 0.37 mmol) and the resulting solution stirred at rt for 1.5 h. Saturated aq. NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL) were added and the biphasic mixture separated. The aqueous phase was washed with CH₂Cl₂ (2 × 10 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 9:1 → 8:2) afforded the title compound 353 (240 mg, 93%) as a yellow oil. [α]ᵢ²ˡ⁺ = -5.15 (c = 0.68, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.73–7.66 (4H, m, Ph), 7.47–7.35 (6H, m, Ph), 6.08 (1H, d, J = 1.4 Hz, CH₂-C⁶), 5.66 (1H, ddd, J = 15.3, 6.7, 1.0 Hz, CH-C⁶), 5.55 (1H, ddd, J = 7.7, 7.4, 3.7 Hz, CH-C10), 5.48–5.39 (2H, m, CH-C11, CH₂-C⁸), 4.78 (1H, dq, J = 2.4, 1.2 Hz, CH₂-C16), 4.75 (1H, d, J = 2.4 Hz, CH₂-C16), 4.26 (1H, d, J = 15.8 Hz, CH₂-C5), 4.29 (1H, d, J = 15.8 Hz, CH₂-C5), 3.65–3.51 (2H, m, CH₂-C3), 2.26–2.15 (2H, m, CH-C11, CH₂-C13), 2.18–2.09 (1H, m, CH₂-C13), 2.08 (1H, dd, J = 14.3, 7.7 Hz, CH₂-C9), 1.99 (2H, dt, J = 6.7, 6.6 Hz, CH₂-C⁵), 1.92 (1H, dd, J = 14.3, 3.7 Hz, CH₂-C9), 1.62 (3H, d, J = 1.2 Hz, CH₃-C17), 1.61–1.56 (2H, m, CH₂-C2), 1.47 (2H, dt, J = 7.8, 7.6 Hz, CH₂-C14), 1.42 (3H, s, CH₃-C20), 1.36–1.24 (4H, m, CH₂-C⁵, CH₂-C⁶), 1.04 (9H, s, C(CH₃)₃), 0.94 (9H, t, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.86 (3H, t, J = 7.1 Hz, CH₃-C⁶), 0.66 (6H, app qd, J = 7.9, 3.4 Hz, Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 166.1 (C-C21), 147.2 (C-C12), 141.4 (C-C15), 135.7 (Ph), 133.3 (Ph), 133.2 (CH-C⁶), 129.9 (Ph), 129.1 (CH-C11), 127.9 (Ph), 124.3 (CH₂-
C^A), 112.7 (CH2-C16), 88.6 (C-C7), 82.6 (C-C6), 72.1 (CH-C10), 67.7 (C-C8), 61.7 (CH2-C3), 52.8 (CH2-C5), 49.6 (CH2-C9), 44.3 (CH-C1), 36.2 (CH2-C2), 32.4 (CH2-C14), 32.0 (CH2-C^C), 31.7 (CH3-C20), 31.2 (CH2-C^D), 30.1 (CH2-C13), 26.8 (C(CH3)3), 22.3 (CH2-C^E), 19.3 (C(CH3)3), 17.8 (CH3-C17), 14.1 (CH3-C^F), 7.2 (Si(CH2CH3)3), 6.2 (Si(CH2CH3)3); HRMS (ESI^+) calcd. for C_{68}H_{80}O_{3}Si_{2}Na [M+Na]^+ 781.4654 found 781.4597; IR ν_max 3412, 3072, 2955, 2932, 2874, 2859, 1717, 1643, 1630, 1462, 1429 cm^-1.

(4R,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yne-6-yl (R)-6-methyl-2-methylene-5-(2-oxoethyl)hept-6-enoate 354

To a solution of alcohol 353 (220 mg, 0.29 mmol) in CH2Cl2 (10 mL) was added Dess-Martin periodinane (148 mg, 0.35 mmol) and the resulting solution stirred at rt for 4 h. The solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to afford the title compound 354 (219 mg, quant.) as a yellow oil. [α]_D^25 -1.65 (c = 0.61, CHCl3); ^1H NMR (400 MHz, CDCl3) δ 9.65 (1H, dd, J = 2.8, 2.0 Hz, CHO-C3), 7.76–7.66 (4H, m, Ph), 7.49–7.35 (6H, m, Ph), 6.11 (1H, d, J = 1.5 Hz, CH2-C^A), 5.67 (1H, ddd, J = 15.3, 6.9, 6.1 Hz, CH-C^B), 5.56 (1H, ddd, J = 7.7, 7.4, 3.8 Hz, CH-C10), 5.50–5.39 (2H, m, CH-C11, CH2-C^A), 4.82 (1H, dq, J = 1.6, 1.5 Hz, CH2-C16), 4.78 (1H, dq, J = 1.6, 0.8 Hz, CH2-C16), 4.28 (2H, s, CH2-C5), 2.68 (1H, app p, J = 7.2 Hz, CH-C1), 2.51–2.33 (2H, m, CH2-C2), 2.30–2.13 (2H, m, CH2-C13), 2.09 (1H, dd, J = 14.3, 7.7 Hz, CH2-C9), 2.00 (2H, t, J = 6.9, 6.7 Hz, CH2-C^C), 1.93 (1H, dd, J = 14.3, 3.8 Hz, CH2-C9), 1.66 (3H, dd, J = 1.5, 0.8 Hz, CH2-C17), 1.56–1.49 (2H, m, CH2-C14), 1.43 (3H, s, CH3-C20), 1.38–1.22 (4H, m, CH2-C^D, CH2-C^E), 1.06 (9H, s, C(CH3)3), 0.95 (9H, t, J = 7.9 Hz, Si(CH2CH3)3), 0.87 (3H, t, J = 7.0 Hz, CH3-C^F), 0.67 (6H, app qd, J = 7.9, 2.2 Hz, Si(CH2CH3)3); ^13C NMR (126 MHz, CDCl3) δ 202.3 (CHO-C3), 166.0 (C-C21), 145.5 (C-C12), 140.9 (C-C15), 135.7 (Ph), 133.4 (Ph), 133.2 (CH-C^B), 129.9 (Ph), 129.1 (CH-C11), 127.9 (Ph), 124.6 (CH2-C^A), 113.1 (CH2-C16), 88.6 (C-C7), 82.6 (C-C6), 72.2 (CH-C10), 67.7 (C-C8), 52.8 (CH2-C5), 49.6 (CH2-C9), 47.4 (CH2-C2), 41.5 (CH-C1), 32.1 (CH2-C14), 32.0 (CH2-C^C), 31.7 (CH3-C20), 31.2 (CH2-C^D), 29.8 (CH2-C13), 26.8 (C(CH3)3), 22.3 (CH2-C^E), 19.3 (C(CH3)3), 18.8 (CH3-
C17), 14.1 (CH₃-C⁵), 7.2 (Si(CH₂CH₃)₃), 6.2 (Si(CH₂CH₃)₃); HRMS (ESI⁺) calcd. for C₄₆H₆₈O₅SiNa [M+Na⁺] 779.4497 found 779.4441; IR νmax 3072, 2955, 2930, 2874, 2859, 2716, 1721, 1643, 1630, 1462, 1429 cm⁻¹.

1-((4R,6S,E)-1-(tert-Butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yn-6-yl) 9-methyl (5R)-7-hydroxy-2-methylene-5-(prop-1-en-2-yl)nonanedioate 355

To a solution of diisopropylamine (0.08 mL, 0.6 mmol) in THF (3 mL) at −78 °C was added nBuLi (0.35 mL, 1.68 M in hexane, 0.59 mmol). After 30 min stirring, methyl acetate (0.05 mL, 0.64 mmol) was added dropwise and the resulting solution stirred for a further 30 min. A solution of aldehyde 354 (180 mg, 0.24 mmol) in THF (2 mL) was added and the reaction stirred for 3 h before addition of saturated aq. NH₄Cl (5 mL) and warming to rt. The biphasic mixture was separated and the aqueous phase extracted with Et₂O (3 × 6 mL). The combined organic extracts were dried over Na₂SO₄, filtered and the solvent removed under vacuum to afford the crude title compound.

Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 9:1) afforded the title compound 355 (1:1 mixture of diastereoisomers, 185 mg, 93%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.66 (4H, m, Pha,b), 7.47–7.35 (6H, m, Pha,b), 6.08 (1H, dd, J = 4.0, 1.6 Hz, CH₂-C⁴a,b), 5.71–5.62 (1H, m, CH=C⁵a,b), 5.55 (1H, ddd, J = 7.7, 3.8, 3.6 Hz, CH-C₁₀a,b), 5.48–5.39 (2H, m, CH₂-C₁₁, CH₂-C⁵a,b), 4.84–4.82 (0.5H, m, CH₂-C₁₆a), 4.81–4.76 (1H, m, CH₂-C₁₆a,b), 4.75 (0.5H, d, J = 2.1 Hz, CH₂-C₁₆b), 4.28 (2H, s, CH₂-C⁵a,b), 4.04–3.90 (1H, m, CH-C₃a,b), 3.70 (1.5H, s, CH₃-C₁₉a), 3.70 (1.5H, s, CH₃-C₁₉b), 2.94 (0.5H, d, J = 3.8 Hz, OH-C₃b), 2.70 (0.5H, d, J = 4.2 Hz, OH-C₃b), 2.51 (0.5H, dd, J = 16.2, 3.2 Hz, CH₂-C⁴a), 2.43 (1H, d, J = 6.1 Hz, CH₂-C⁴b), 2.38–2.30 (0.5H, m, CH-C₁₉a), 2.37 (0.5H, dd, J = 16.2, 9.0 Hz, CH₂-C⁴a), 2.25–2.10 (2.5H, m, CH₂-C₁₃a,b, CH-C₁₅b), 2.08 (1H, ddd, J = 14.3, 7.7, 1.7 Hz, CH₂-C₉a,b), 1.99 (2H, dt, J = 6.6, 6.5 Hz, CH₂-C⁶a,b), 1.92 (1H, ddd, J = 14.3, 3.8, 1.7 Hz, CH₂-C⁹a,b), 1.71–1.64 (1H, m, CH₂-C₂b), 1.64 (1.5H, s, CH₃-C₁₇a), 1.60 (1.5H, s, CH₃-C₁₇b), 1.52–1.43 (3H, m, CH₂-C₂b, CH₂-C₁₄a,b), 1.43 (1.5H, s, CH₃-C₂₀a), 1.42 (1.5H, s, CH₃-C₂₀b), 1.36–1.24 (4H, m, CH₂-C⁶a,b, CH₂-C⁶b), 1.05 (9H, s, C(CH₃)₃a,b), 0.94 (9H, t, J = 7.9 Hz, Si(CH₂CH₃)₃a,b), 0.86
(3H, t, J = 7.1 Hz, CH$_3$-C$^{ab}$), 0.67 (6H, app qd, J = 7.9, 3.3 Hz, Si(CH$_3$)$_3$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.3 (C-C18), 173.3 (C-C18), 166.1 (C-C21), 166.1 (C-C21), 147.2 (C-C12), 146.2 (C-C12), 141.4 (C-C15), 141.3 (C-C15), 135.7 (Ph), 133.3 (CH-C$^B$), 133.3 (CH-C$^B$), 133.2 (Ph), 129.9 (Ph), 129.2 (CH-C11), 129.1 (CH-C11), 127.9 (Ph), 124.3 (CH$_2$-C$^A$), 124.2 (CH$_2$-C$^A$), 113.4 (CH$_2$-C16), 112.9 (CH$_2$-C16), 88.5 (C-C7), 82.6 (C-C6), 72.2 (CH-C10), 72.1 (CH-C10), 67.7 (C-C8), 67.7 (C-C8), 67.0 (CH-C3), 65.9 (CH-C3), 52.8 (CH$_2$-C5), 51.9 (CH$_3$-C19), 51.8 (CH$_3$-C19), 49.6 (CH$_2$-C9), 44.3 (CH-C1), 43.4 (CH-C1), 41.9 (CH$_2$- C4), 40.9 (CH$_2$-C4), 40.2 (CH$_2$-C2), 40.1 (CH$_2$-C2), 32.8 (CH$_2$-C14), 32.1 (CH$_2$-C14), 32.0 (CH$_2$-C$^C$), 31.7 (CH$_2$-C$^C$), 31.2 (CH$_3$-C20), 30.5 (CH$_3$-C20), 30.2 (CH$_2$-C$^D$), 29.9 (CH$_2$-C$^D$), 29.8 (CH$_2$-C13), 26.8 (C(CH$_3$)$_3$), 22.3 (CH$_2$-C$^E$), 19.3 (C(CH$_3$)$_3$), 17.8 (CH$_3$-C17), 17.7 (CH$_3$-C17), 14.1 (CH$_2$-C$^F$), 7.2 (Si(CH$_2$CH$_3$)$_3$), 6.2 (Si(CH$_2$CH$_3$)$_3$); HRMS (ESI$^+$) calcd. for C$_{49}$H$_{74}$O$_5$Si$_2$Na [M+Na]$^+$ 853.4865 found 853.4826; IR $\nu_{max}$ 3508, 3071, 2955, 2930, 2874, 2859, 1717, 1643, 1630, 1458, 1429 cm$^{-1}$

1-((4R,6S,E)-1,4-Dihydroxy-4-methyldec-7-en-2-yn-6-yl) 9-methyl (5R)-7-hydroxy-2-methylene-5-(prop-1-en-2-yl)nonanedioate 356

To a solution of silyl ether 355 (175 mg, 0.21 mmol) in THF (8 mL) was added AcOH (35 μL, 0.63 mmol) followed by TBAF (0.74 mL, 1 M in THF, 0.74 mmol). The resulting solution was stirred for 120 h at rt before addition of saturated aq. NH$_4$Cl (10 mL) and Et$_2$O (10 mL). The biphasic mixture was separated and the aqueous phase extracted with Et$_2$O (3 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 2:3) afforded the title compound 356 (105 mg, 98%) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.17 (1H, dd, J = 2.6, 1.5 Hz, CH$_2$-C$^{Aa,b}$), 5.78 (1H, dtt, J = 15.3, 7.2, 1.7 Hz, CH-C$^{Bb}$), 5.70 (1H, app tt, J = 8.5, 4.3 Hz, CH-C10$^{ab}$), 5.95 (1H, dd, J = 1.5, 1.4 Hz, CH$_2$-C$^{Aa,b}$), 5.50 (1H, app ddd, J = 15.3, 7.3, 1.6 Hz, CH-C11$^{ab}$), 4.85 (0.5H, dq, J = 2.9, 1.5 Hz, CH$_2$-C16$^a$), 4.82–4.79 (1H, m, CH$_2$-C16$^{ab}$), 4.77 (0.5H, d, J = 2.1 Hz, CH$_2$-C16$^b$), 4.17 (1H, s, CH$_2$-C5$^a$), 4.17 (1H, s, CH$_2$-C5$^b$), 4.06–3.99 (0.5H, m, CH-C3$^b$),
4.01–3.92 (1H, m, CH–C3b), 3.70 (1.5H, s, CH3–C19b), 3.69 (1.5H, s, CH3–C19b), 3.30 (0.5H, s, OH–C8b), 3.26 (0.5H, s, OH–C8b), 3.06 (0.5H, br s, OH–C3b), 2.89 (0.5H, br s, OH–C3b), 2.51 (0.5H, dd, J = 16.3, 3.3 Hz, CH2–C4b), 2.44 (1H, d, J = 6.3 Hz, CH2–C4b), 2.39 (0.5H, dd, J = 16.3, 8.9 Hz, CH2–C4b), 2.33–2.13 (3H, m, CH–C1ab, CH2–C13ab), 2.11 (1H, app ddd, J = 14.5, 8.5, 2.2 Hz, CH2–C9b), 2.03 (2H, ddd, J = 7.9, 7.4, 7.2 Hz, CH2–C13ab), 1.94 (1H, app ddd, J = 14.5, 5.7, 4.3 Hz, CH2–C9ab), 1.66 (1.5H, br s, CH3–C17b), 1.61 (1.5H, br s, CH3–C17b), 1.59–1.42 (4H, m, CH2–C2ab, CH2–C14ab), 1.49 (3H, s, CH3–C20ab) 1.39–1.23 (4H, m, CH2–C3ab, CH2–C13ab), 0.88 (3H, t, J = 7.1 Hz, CH3–Cfa,b); 13C NMR (126 MHz, CDCl3) δ 173.4 (C–C18), 173.3 (C–C18), 167.5 (C–C21), 167.4 (C–C21), 147.2 (C–C12), 146.1 (C–C12), 141.2 (C–C15) 141.2 (C–C15), 135.0 (CH–C8b), 134.9 (CH–C8b), 128.3 (CH–C11), 128.3 (CH–C11), 125.5 (CH2–C9a), 125.4 (CH2–C9a), 113.6 (CH2–C16), 112.8 (CH2–C16), 88.9 (C–C7), 88.8 (C–C7), 82.1 (C–C6), 72.4 (CH–C10), 72.3 (CH–C10), 66.7 (C–C8), 66.0 (C–C8), 65.8 (CH–C3), 65.7 (CH–C3), 51.9 (CH3–C19), 51.9 (CH3–C19), 51.1 (CH2–C5), 51.1 (CH2–C5), 48.0 (CH2–C9a), 44.0 (CH–C1), 43.4 (CH–C1), 41.9 (CH2–C4), 41.0 (CH2–C4), 40.3 (CH2–C2), 40.1 (CH2–C2), 32.7 (CH2–C14), 32.0 (CH2–C14), 31.8 (CH2–C14), 31.2 (CH2–C13), 31.1 (CH2–C13), 30.0 (CH2–C13), 29.9 (CH2–C13), 22.3 (CH2–C13), 18.0 (CH2–C17), 17.8 (CH2–C17), 14.0 (CH3–C6); HRMS (ESI+) calcd. for C27H42O2Na [M+Na]+ 501.2823 found 501.2799; IR νmax 3428, 3071, 2955, 2858, 1714, 1643, 1630, 1439 cm⁻¹.

1-(4R,6S,7E)-4-Hydroxy-4-methyl-1-oxododec-7-en-2-yn-6-yl 9-methyl(5R)-2-methylidene-7-oxo-5-(prop-1-en-2-yl)nonanedioate 357

To a solution of alcohol 356 (15 mg, 0.03 mmol) in CH2Cl2 (1 mL) was added Dess-Martin periodinane (33 mg, 0.08 mmol) and the resulting mixture stirred at rt for 6 h. Aq. NH4Cl (2 mL) and CH2Cl2 (2 mL) were added and the phases were separated. The aqueous phase was extracted with CH2Cl2 (3 x 3 mL) and the combined organic extracts dried over Na2SO4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 7:3 → 1:1) afforded the title compound 357 (10.4 mg, 71%) as a colourless oil. [α]D27 7.8 (c = 0.51, CHCl3); 1H NMR (500 MHz, CDCl3) δ 9.09
(1H, s, CHO-C5), 6.19 (1H, s, CH2-C8), 5.84–5.76 (1H, m, CH-C8), 5.65 (1H, ddd, J = 10.1, 7.2, 3.4 Hz, CH-C10), 5.58 (1H, d, J = 1.4 Hz, CH2-C9), 5.50 (1H, ddt, J = 15.4, 7.2, 1.6 Hz, CH-C11), 4.93 (2H, s, CH2-C4), 4.82–4.80 (1H, m, CH2-C16), 4.76 (1H, s, CH2-C16), 3.85 (3H, s, CH3-C19), 2.77–2.62 (3H, m, CH-C1, CH2-C2), 2.28–2.09 (3H, m, CH2-C9, CH2-C13), 2.05 (2H, app q, J = 6.7 Hz, CH2-C5), 1.98 (1H, dd, J = 14.7, 3.4 Hz, CH2-C9), 1.66 (3H, s, CH3-C17), 1.57 (3H, s, CH3-C20), 1.54–1.47 (2H, m, CH2-C14), 1.38–1.26 (4H, m, CH2-C2, CH2-C18), 0.89 (3H, t, J = 7.1 Hz, CH3-CF3); 13C NMR (126 MHz, CDCl3) δ 202.1 (C-C3), 176.5 (CHO-C5), 169.6 (C-C18), 168.0 (C-C21), 145.5 (C-C12), 140.5 (C-C15), 135.5 (CH-C8), 127.5 (CH-C11), 126.4 (CH2-C9), 112.9 (CH2-C16), 99.3 (C-C7), 92.7 (CH2-C4), 82.6 (C-C6), 71.7 (CH-C10), 65.2 (C-C8), 54.0 (CH3-C19), 47.9 (CH2-C9), 41.4 (CH-C1), 40.2 (CH2-C2), 32.0 (CH2-C5), 31.6 (CH2-C14), 31.1 (CH2-C16), 30.4 (CH2-C20), 29.6 (CH2-C13), 22.3 (CH2-C5), 19.1 (CH2-C17), 14.0 (CH3-C2); HRMS (ESI+) calcd. for C27H38O7Na [M+Na]+ 497.2510 found 497.2503.

Methyl (6R,8S,9E)-6-methyl-2-[(3R)-3-(prop-1-en-2-yl)-6-((tris(propan-2-yl)silyl)oxy)methyl)hept-6-enoyl]-6,8-bis[(triethylsilyl)oxy]tetradeca-2,9-dien-4-ynoate 362

Aldehyde 333 (14 mg, 0.03 mmol) and β-keto ester 316 (15 mg, 0.03 mmol) were dissolved in a stock solution of toluene (0.1 mL) containing AcOH (0.02 mmol) and piperidine (3 μmol) in the presence of MgSO4. The resulting mixture was stirred at rt for 2 h before the solvent was removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et2O, 95:5) afforded title compound 362 (1:1.5 mixture of E:Z isomers, 25 mg, 88%) as a yellow oil. 1H NMR (500 MHz, CDCl3) δ 6.82 (0.4H, s, CH-C5e), 6.77 (0.6H, s, CH-C5d), 5.58 (0.4H, app t, J = 6.6 Hz, CH-C5d), 5.55 (0.6H, app t, J = 6.6 Hz, CH-C5e), 5.51–5.43 (1H, m, CH-C11E,Z), 5.11–5.05 (1H, m, CH2-C4E,Z), 4.83–4.79 (1H, m, CH2-C5A,E,Z), 4.79–4.76 (1H, m, CH2-C16E,Z), 4.76–4.74 (0.4H, m, CH2-C16E), 4.73–4.69 (0.6H, m, CH2-C16d), 4.39–4.32 (1H, m, CH-C10E,Z), 4.12 (2H, s, CH2-C21E,Z), 3.84 (1.8H, s, CH3-C19d), 3.78 (1.2H, s, CH3-C19e), 2.89–2.76 (1H, m, CH2-C2E,Z), 2.76–2.69 (1.4H, CH2-C2E,Z, CH-C1e), 2.69–2.61 (0.6H, m, CH-C1d), 2.02–1.83 (6H, CH2-C2E,Z, CH3-C9E,Z, CH2-C13E,Z), 1.66–1.65 (1.2H, m, CH3-C17d), 1.64 (1.8H, dd, J = 1.2, 0.7 Hz, CH3-C17d), 1.56–1.46 (2H,
To a solution of ynenone $362$ (143 mg, 0.17 mmol) in MeOH (2 mL) at 0 °C was added (±)-CSA (2.2 mg, 8.7 μmol). The resulting mixture was stirred for 1.5 h before removal of the solvent under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et$_2$O, 1:1) afforded the title compound $364$ (73 mg, 68%) as a pale yellow oil. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.00 (1H, d, $J = 10.2$ Hz, CH-C5), 5.66 (1H, d, $J = 10.2$ Hz, CH-C6), 5.63–5.53 (2H, m, CH-C11, CH-C8), 5.32–5.27 (1H, m, CH$_2$-C8), 4.99–4.97 (1H, m, CH$_2$-C7),
4.92–4.91 (1H, m, CH$_2$-C16), 4.82–4.77 (1H, m, CH$_2$-C16), 4.71 (1H, dt, $J = 9.8, 6.5$ Hz, CH-C10), 4.18 (2H, s, CH$_2$-C21), 3.42 (3H, s, CH$_3$-C19), 3.41–3.34 (1H, m, CH$_2$-C2), 2.89–2.73 (2H, m, CH-C1, CH$_2$-C2), 2.18 (1H, ddd, $J = 15.2, 10.0, 5.3$ Hz, CH$_2$-C13), 2.13–2.01 (2H, m, CH$_2$-C9, CH$_2$-C13), 2.01–1.91 (3H, m, CH$_2$-C9, CH$_2$-C$_5^r$), 1.77–1.64 (2H, m, CH$_2$-C14), 1.72 (3H, s, CH$_3$-C17), 1.34–1.22 (4H, m, CH$_2$-C$_5^o$, CH$_2$-C$_5^e$), 1.20 (3H, s, CH$_3$-C20), 1.14–1.10 (21H, m, CH(CH$_3$)$_2$), 0.84 (3H, t, $J = 7.1$ Hz, CH$_3$-C$_5^e$); $^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta$ 166.2 (C-C18), 166.1 (C-C3), 148.8 (C-C12), 146.7 (C-C15), 133.3 (CH-C11), 132.3 (CH-C$_5^o$), 126.6 (CH-C5), 113.0 (CH$_2$-C16), 110.2 (C-C7), 109.6 (CH-C6), 108.7 (CH$_2$-C$_5^o$), 104.3 (C-C4), 82.0 (C-C8), 79.8 (CH-C10), 66.6 (CH$_2$-C21), 50.9 (CH$_3$-C19), 46.3 (CH-C1), 44.5 (CH$_2$-C9), 37.9 (CH$_2$-C2), 32.3 (CH$_2$-C$_5^o$), 31.6 (CH$_2$-C$_5^e$), 31.5 (CH$_2$-C14), 30.8 (CH$_2$-C13), 22.6 (CH$_2$-C$_5^e$), 22.0 (CH$_3$-C20), 18.6 (CH$_3$-C17), 18.3 (CH(CH$_3$)$_2$), 14.1 (CH$_3$-C$_5^o$), 12.4 (CH(CH$_3$)$_2$); HRMS (ESI$^+$) calcld. for C$_{36}$H$_{66}$O$_6$SiNa [M+Na]$^+$ 639.4051 found 639.4008; IR $\nu_{max}$ 3473, 2941, 2928, 2866, 1713, 1645, 1578, 1462, 1462, 1437 cm$^{-1}$.

(±)-Ethyl (9E)-2-acetyl-6-methyl-6,8-bis[(triethylsilyloxy)tetradaea-2,9-dien-4-ynoate

To a solution of racemic aldehyde 333 (300 mg, 0.66 mmol) in toluene (2 mL) was added ethyl acetoacetate (0.1 mL, 0.7 mmol), piperidine (7 μL, 0.1 mmol), AcOH (0.02 mL, 0.4 mmol) and MgSO$_4$ (16 mg, 0.13 mmol). The resulting mixture was stirred at rt for 3 h before the solvent was removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et$_2$O, 9:1) afforded the title compound 365 (1:1 mixture of E:Z isomers, 266 mg, 71%) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.78 (0.5H, s, CH-C3), 6.78 (0.5H, s, CH-C3), 5.60–5.51 (1H, m, CH-C12), 5.49–5.42 (1H, m, CH-C11), 4.38–4.28 (2H, m, CH-C10, CH$_2$-C18), 4.25 (1H, q, $J = 7.1$ Hz, CH$_2$-C18), 2.42 (1.5H, s, CH$_3$-C7), 2.34 (1.5H, CH$_3$-C7), 2.02–1.91 (3H, CH$_2$-C9, CH$_2$-C13), 1.88 (0.5H, app t, $J = 5.7$ Hz, CH$_2$-C9), 1.85 (0.5H, app t, $J = 5.8$ Hz, CH$_2$-C9), 1.51 (1.5H, s, CH$_3$-C17), 1.51 (1.5H, s, CH$_3$-C17), 1.36–1.27 (7H, m, CH$_2$-C14, CH$_2$-C15, CH$_3$-C19), 0.96–0.89 (18H, m, (Si(CH$_3$)$_3$)$_3$, 0.87 (3H, t, $J = 7.0$ Hz, CH$_2$-C16), 0.65–0.52 (12H, m, (Si(CH$_3$)$_3$)$_3$); $^{13}$C NMR (126 MHz,
Ethyl (2E)-2-acetyl-4-[(2E)-5-[(1E)-hex-1-en-1-yl]-3-hydroxy-3-methyloxolan-2-ylidene] but-2-enoate 366 and ethyl 2-[(1E)-hex-1-en-1-yl]-4-hydroxy-4,7-dimethyl-1,6-dioxaspiro[4.5]deca-7,9-diene-8-carboxylate 367

To a solution of ynenone 365 (266 mg, 0.47 mmol) in MeOH (5 mL) was added (+)-CSA (5 mg, 0.02 mmol) and the resulting mixture stirred at rt for 1 hr. Saturated aq. NaHCO₃ (10 mL) and CH₂Cl₂ (10 mL) were added and the biphasic mixture separated. The organic phase was dried over Na₂SO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 1:1) afforded spirocycle 367 (54 mg, 34%) as a pale yellow oil followed by diene 366 (20.4 mg, 13%) as a yellow oil.

**Spirocycle 367**: ¹H NMR (500 MHz, CDCl₃) δ 6.84 (1H, d, J = 10.1 Hz, CH-C3), 5.62 (1H, dt, J = 15.2, 6.8 Hz, CH-C12), 5.57 (1H, d, J = 10.1 Hz, CH-C2), 5.39 (1H, ddt, J = 15.2, 8.1, 1.4 Hz, CH-C11), 4.68–4.62 (1H, m, CH-C10), 4.22–4.15 (2H, m, CH₂-C18), 2.36 (3H, s, CH₃-C7), 2.20 (1H, dd, J = 13.1, 6.7 Hz, CH₂-C9), 2.15 (1H, dd, J = 13.1, 9.4 Hz, CH₂-C9), 2.05–1.96 (2H, m, CH₂-C13), 1.40–1.23 (10H, m, CH₂-C14, CH₂-C15, CH₃-C17, CH₃-C19), 0.87 (3H, J = 7.1 Hz, CH₃-C16); ¹³C NMR (126 MHz, CDCl₃) δ 166.2 (C-C6), 163.8 (C-C5), 134.3 (CH-C2), 131.2 (CH-C11), 126.8 (CH-C3), 109.0 (CH-C12), 108.7 (C-C4), 104.1 (C-C1), 82.0 (C-C8), 79.8 (CH-C10), 60.2 (CH₂-C18), 44.0 (CH₂-C9), 31.9 (CH₂-C13), 31.2 (CH₂-C14), 22.3 (CH₃-C17), 21.7 (CH₂-C15), 20.5 (CH₃-C7), 14.5 (CH₃-C19), 14.0 (CH₃-C16); HRMS (ESI⁺) calcd. for C₁₉H₂₈O₅Na [M+Na]⁺ 359.1829 found 359.1810.
Diene 366: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.79 (1H, d, \(J = 12.1\) Hz, CH-C3), 5.85 (1H, dt, \(J = 15.3, 6.7\) Hz, CH-C11), 5.80 (1H, d, \(J = 12.1\) Hz, CH-C2), 5.45 (1H, ddt, \(J = 15.3, 7.9, 1.6\) Hz, CH-C11), 5.06–4.99 (1H, m, CH-C10), 4.36–4.23 (3H, m, CH\(_2\)-C18, OH-C8) 2.35 (3H, s, CH\(_3\)-C7), 2.30 (1H, dd, \(J = 13.1, 5.2\) Hz, CH\(_2\)-C9), 2.12–1.99 (2H, m, CH\(_2\)-C13), 1.76 (1H, dd, \(J = 13.1, 10.0\) Hz, CH\(_2\)-C9), 1.42 (3H, s, CH\(_3\)-C17), 1.41–1.27 (7H, CH\(_2\)-C14, CH\(_2\)-C15, CH\(_3\)-C19), 0.90 (3H, t, \(J = 7.2\) Hz, CH\(_3\)-C16); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 196.2 (C=O), 135.8 (Ph), 134.9 (Ph), 133.4 (CH-C5), 128.2 (C-C4), 127.2 (CH-C11), 92.6 (CH-C2), 83.8 (CH-C10), 78.1 (C-C8) 61.0 (CH-C7) 22.4 (CH\(_2\)-C15), 14.4 (CH\(_3\)-C19), 14.0 (CH\(_3\)-C16); HRMS (ESI\(^+\)) calcd. for C\(_{19}\)H\(_{28}\)O\(_3\)Na [M+Na]\(^+\) 359.1829 found 359.1805.

(4R,6S,7E)-1-[(tert-Butyldiphenylsilyloxy)-4-hydroxy-4-methyldodec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 371

![Chemical Structure]

To a solution of diol 350 (51 mg, 0.11 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added Et\(_3\)N (20 μL, 0.13 mmol) and pivaloyl chloride (10 μL, 0.11 mmol). The resulting mixture was stirred at rt for 3 h. Saturated aq. NH\(_4\)Cl (1 mL) and the phases were separated. The organic phase was washed with brine (2 mL) before being dried over Na\(_2\)SO\(_4\), filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et\(_2\)O, 7:3) afforded the title compound 371 (67 mg, quant) as a pale yellow oil. \([\alpha]_D^{27}\) = −48 (c = 0.30, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.79–7.68 (4H, m, Ph), 7.49–7.33 (6H, m, Ph), 5.76 (1H, d, \(J = 13.7, 6.8\) Hz, CH-C\(_5\)) 5.53–5.39 (2H, m, CH-C11, CH-C10), 4.35 (2H, s, CH\(_2\)-C5), 2.64 (1H, s, OH-C8), 2.08–1.97 (3H, m, CH\(_2\)-C\(_5\), CH\(_2\)-C9), 1.88 (1H, dd, \(J = 14.3, 5.1\) Hz, CH\(_2\)-C9), 1.40 (3H, s, CH\(_3\)-C20), 1.37–1.29 (4H, m, CH\(_2\)-C\(_5\), CH\(_2\)-C\(_5\)), 1.17 (9H, s, Piv-C(CH\(_3\))\(_3\)), 1.06 (9H, s, SiC(CH\(_3\))\(_3\)), 0.88 (3H, t, \(J = 7.1\) Hz, CH\(_3\)-C\(_5\)); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 177.9 (C=O), 135.8 (Ph), 134.9 (Ph), 133.4 (CH-C\(_5\)), 129.9 (CH-C11), 128.8 (Ph), 127.8 (Ph), 88.5 (C-C7), 82.1 (C-C6), 72.1 (CH-C10), 66.2 (C-C8), 52.8 (CH\(_2\)-C5), 47.5 (CH\(_2\)-C9), 38.8 (Piv-C(CH\(_3\))\(_3\)), 31.9 (CH\(_2\)-C\(_5\)), 31.1 (CH\(_2\)-C\(_5\)), 30.5 (CH\(_3\)-C20), 27.2 (SiC(CH\(_3\))\(_3\)), 26.8 (SiC(CH\(_3\))\(_3\)), 22.2 (CH\(_2\)-C\(_5\)), 19.3 (SiC(CH\(_3\))\(_3\)), 14.0 (CH\(_3\)-C\(_5\)); HRMS (ESI\(^+\)) calcd. for C\(_{34}\)H\(_{48}\)O\(_3\)SiNa [M+Na]\(^+\) 571.3214 found 571.3187; IR \(\nu_{\text{max}}\) 3451, 2958, 2930, 2858, 1428 cm\(^{-1}\).
To a solution of silyl ether 371 (60.5 mg, 0.11 mmol) in THF (2 mL) was added TBAF (0.13 mL, 1 M in THF, 0.13 mmol) and the resulting mixture stirred at rt for 16 h. Saturated aq. NH₄Cl (5 mL) and Et₂O (5 mL) were added and the biphasic mixture separated. The organic extract was washed with brine (5 mL) before being dried over Na₂SO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 25:75) afforded the title compound 372 (37.2 mg, quant) as a colourless oil.

\[
\begin{align*}
\text{OH} & \quad \text{OPiv} \\
5 & \quad 6 \\
7 & \quad 8 \\
9 & \quad 10 \\
11 & \quad B \\
C & \quad D \\
E & \quad F
\end{align*}
\]

chemical formula: C₁₉H₃₀O₄
molecular weight: 310.4340

\[
\text{To a solution of primary alcohol 372 (32 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) was added Dess-Martin periodinane (66 mg, 0.15 mmol) and the resulting mixture stirred at rt for 3 h. Saturated aq. Na₂S₂O₅ (2 mL) was added and the phases were separated. The organic phase was washed with brine (2 mL) before being dried over Na₂SO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 3:7) afforded the title compound 373 (30 mg, 97%) as a colourless oil. [α]₀^2₇ = -9.4 (c = 0.21, CHCl₃); \text{¹H NMR} (500 MHz, CDCl₃) δ 9.21 (1H, s, CHO-}
\]
C5), 5.78 (1H, dt, \( J = 13.8, 6.8 \text{ Hz, C-C}^B \)), 5.51–5.43 (2H, m, CH-C10, CH-C11), 3.67 (1H, s, OH-C8), 2.18 (1H, dd, \( J = 14.6, 8.3 \text{ Hz, CH}-C9), 2.06–1.97 (3H, m, CH2-C9, CH2-C5), 1.57 (3H, s, CH3-C20), 1.38–1.21 (4H, \( \text{CH}_2-\text{C}^D \), \( \text{CH}_2-\text{C}^E \)), 1.18 (9H, s, C(CH3)3), 0.88 (3H, t, \( J = 7.2 \text{ Hz, CH}_3-C^E \)); \(^{13}C\) NMR (126 MHz, CDCl3) δ 178.9 (C=O), 176.6 (CHO-C5), 135.5 (CH-C8), 128.0 (CH-C11), 99.3 (C-C7), 82.6 (C-C6), 71.8 (CH-C10), 65.8 (C-C8), 47.3 (CH2-C9), 39.0 (C(CH3)3), 31.9 (CH2-C5), 31.1 (CH2-C9), 30.3 (CH3-C20), 27.1 (C(CH3)3), 22.2 (CH2-C5), 14.0 (CH3-C5); HRMS (ESI+) calcd. for C18H28O4Na [M+Na]+ 331.1880 found 331.1799; IR \( \nu_{max} \) 3447, 2959, 2872, 2857, 1729, 1707, 1670, 1460 cm\(^{-1}\).

\(4R,6S,7E\)-4-Methyl-1-oxo-4-[(triethyloxysilyl)oxy]dodec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 374

![Chemical Structure of 374](image)

Molecular Weight: 422.6810

To a solution of aldehyde 373 (27 mg, 0.09 mmol) in CH2Cl2 (1 mL) at \(-78^\circ\text{C} \) was added 2,6-lutidine (30 \( \mu\text{L}, 0.23 \text{ mmol}) and triethylsilyl triflate (20 \( \mu\text{L}, 0.11 \text{ mmol}) and the resulting mixture stirred for 2 h. The reaction was quenched with saturated aq. NH4Cl (1 mL) and warmed gradually to rt. The phases were separated and the organic phase was washed with brine (2 mL) before being dried over Na2SO4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et2O, 95:5) afforded the title compound 374 (34 mg, 90%) as a colourless oil. \([\alpha]_D^2 +29.8 \text{ (C = 0.05, CHCl}_3)\); \(^1H\) NMR (500 MHz, CDCl3) δ 9.22 (1H, s, CHO-C5), 5.73–5.63 (1H, m, CH-C8), 5.47 (1H, td, \( J = 7.5, 4.0 \text{ Hz, CH}-C10), 5.39 (1H, ddt, \( J = 15.3, 7.3, 1.4 \text{ Hz, CH}-C11), 2.13 (1H, dd, \( J = 14.4, 7.5 \text{ Hz, CH}_2-C9), 2.04–1.95 (3H, m, CH2-C9, CH2-C5), 1.54 (3H, s, CH3-C20), 1.37–1.24 (4H, m, CH2-C5, CH2-C5), 1.17 (9H, s, C(CH3)3), 0.96 (9H, t, \( J = 8.0 \text{ Hz, Si(CH}_2CH}_3)_3), 0.87 (3H, t, \( J = 7.1 \text{ Hz, CH}_3-C^E), 0.68 (6H, app qd, \( J = 8.0, 2.2 \text{ Hz, Si(CH}_2CH}_3)_3); \(^{13}C\) NMR (126 MHz, CDCl3) δ 177.3 (C=O), 176.4 (CHO-C5), 134.0 (CH-C8), 128.8 (CH-C11), 99.9 (C-C7), 83.7 (C-C6), 71.1 (CH-C10), 67.8 (C-C8), 49.2 (CH2-C9), 38.8 (C(CH3)3), 31.9 (CH2-C5), 31.3 (CH2-C9), 31.1 (CH3-C20), 27.2 (C(CH3)3), 22.2 (CH2-C5), 14.0 (CH3-C5), 7.0 (Si(CH2CH3)_3), 6.2 (Si(CH2CH3)_3); HRMS (ESI+) calcd. for C24H42O4Na [M+Na]+ 445.2744 found 445.2664; IR \( \nu_{max} \) 2957, 2931, 2876, 2209, 1729, 1673, 1458 cm\(^{-1}\).
Methyl (6R,8S,9E)-8-[(2,2-dimethylpropanoyl)oxy]-6-methyl-2-[(3R)-3-(prop-1-en-2-yl)-6-[(tris(propan-2-yl)silyl)oxy]methyl]hept-6-enoyl]-6-[(triethyilsilyloxy)tetradeca-2,9-dien-4-ynoate 375

Aldehyde 374 (33 mg, 0.08 mmol) and β-keto ester 316 (32 mg, 0.08 mmol) were dissolved in a stock solution of toluene (0.25 mL) containing AcOH (0.05 mmol) and piperidine (8 μmol) in the presence of MgSO₄. The resulting mixture was stirred at rt for 2 h before the solvent was removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 95:5 → 90:10) afforded title compound 375 (1:1.2 mixture of E:Z isomers, 25 mg, 88%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.78 (0.55H, s, CH-C₅₂), 6.75 (0.45H, s, CH-C₅₂), 5.72–5.61 (1H, m, CH-C₈₂,E₂), 5.49–5.35 (2H, m, CH-C₁₁₂,E₂, CH-C₁₀₂,E₂), 5.12–5.03 (1H, m, CH₂-C₂⁴₂,A₂,E₂), 4.84–4.69 (3H, m, CH₂-C⁵₂₂,A₂,E₂, CH₂-C₁₆₂,E₂), 4.12 (2H, s, CH₂-C₂₁₂,E₂), 3.87 (1.35H, s, CH₃-C₁₉₂), 3.78 (1.65H, s, CH₃-C₁₉₂), 2.90–2.60 (3H, m, CH₂-C₅₂₂,E₂, CH₁₁₂,E₂), 2.16–1.84 (6H, m, CH₂-C₁₃₂,E₂, CH₂-C₉₂,E₂, CH₂-C₁₃₂,E₂), 1.65 (1.65H, s, CH₃-C₁₇₂), 1.64 (1.35H, s, CH₃-C₁₇₂), 1.62–1.51 (2H, m, CH₂-C₁₄₂,E₂), 1.49 (1.35H, s, CH₃-C₂₀₂), 1.47 (1.65H, s, CH₃-C₂₀₂), 1.38–1.25 (4H, m, CH₂-C₈₂,E₂, CH₂-C₁₃₂,E₂), 1.16 (4.05H, s, C(CH₃)₃₂,E), 1.15 (4.95H, s, C(CH₃)₃₂,Z), 1.13–1.03 (21H, m, CH(CH₃)₂₂₂,E₂, 0.97–0.92 (9H, m, Si(CH₃)₃₂₂,E₂), 0.87 (3H, t, J = 7.0 Hz, CH₃-C₈₂,E₂), 0.68–0.59 (6H, m, Si(CH₃)₃₂₂,E₂); ¹³C NMR (101 MHz, CDCl₃) δ 199.5 (C-C₃), 195.4 (C-C₃), 177.3 (Piv-C=O), 177.2 (Piv-C=O), 165.7 (C-C₁₈), 164.4 (C-C₁₈), 148.6 (C-C₁₂), 148.5 (C-C₁₂), 146.2 (C-C₁₅), 146.1 (C-C₁₅), 142.7 (CH-C⁶₂), 141.7 (CH-C⁵₂), 133.7 (CH-C₁₁), 133.5 (CH-C₁₁), 129.1 (C-C₄), 129.1 (C-C₄), 123.9 (CH-C₅), 122.7 (CH-C₅), 112.5 (CH₂-C₁₆), 112.4 (CH₂-C₁₆), 110.5 (CH₂-C₇), 109.4 (CH₂-C₇), 108.2 (CH₂-C₈), 108.0 (CH₂-C₈), 80.3 (C-C₆), 79.6 (C-C₆), 71.4 (CH-C₁₀), 71.3 (CH-C₁₀), 68.7 (C-C₈), 68.4 (C-C₈), 66.2 (CH₂-C₂₁), 52.6 (CH₃-C₁₉₂), 52.5 (CH₃-C₁₉₂), 49.7 (CH₂-C₉₂), 49.5 (CH₂-C₉₂), 47.5 (CH₂-C₂), 46.6 (CH₂-C₂), 42.5 (CH-C₁₁), 41.8 (CH-C₁₁), 38.8 (C(CH₂)₃₂), 32.0 (CH₂-C₈), 32.0 (CH₂-C₈), 31.4 (CH₂-C₈), 31.2 (CH₂-C₁₄₂), 31.1 (CH₂-C₁₃), 30.5 (CH₂-C₁₃), 30.3 (CH₂-C₈), 30.2 (CH₂-C₈), 27.3 (CH(CH₃)₃₂), 27.2 (CH(CH₃)₃₂), 22.2 (CH₃-C₂₀), 19.2 (CH₃-C₁₇), 19.1 (CH₃-C₁₇), 18.2 (CH(CH₃)₂), 14.0 (CH₃-C₈), 12.2 (CH(CH₃)₂), 7.1 (Si(CH₂CH₃)₃), 6.2 (Si(CH₂CH₃)₃), 6.1
(Si(CH₂CH₃)₃); HRMS (ESI⁺) calcd. for C₄₇H₈₂O₇Si₂Na [M+Na]⁺ 837.5491 found 837.5495; IR ν max 2957, 2932, 2866, 2211, 1728, 1586, 1460, 1437 cm⁻¹.


To a solution of ynenone 375 (33 mg, 0.04 mmol) in MeOH (0.5 mL) at 0 °C was added (+)-CSA and the resulting mixture stirred for 5.5 h. The solvent was removed under vacuum and the residue was passed through a short pad of silica gel (pet ether:Et₂O, 7:3 → 5:5) to afford a crude mixture of ynenone and cyclopropylfuran products as a yellow oil (11.7 mg).

To a sealed tube under argon was added a solution of crude ynenones (11.7 mg) and THT (1 μl, 0.01 mmol) in CH₂Cl₂ (0.1 mL). The resulting solution was heated to 45 °C for 16 h. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet ether: Et₂O, 8:2 → 5:5) to afford epoxyfuran 377 (1.6 mg, 6% 2 steps) followed by Z-enynone (Z)-375 (2.1 mg, 8% 2 steps) and cyclopropyl furan 378 (1.3 mg, 5% 2 steps). Epoxyfuran 377: ¹H NMR (400 MHz, CDCl₃) δ 6.50 (1H, s, CH-C₅), 5.64 (1H, dt, J = 15.7, 6.8 Hz, CH-C⁵), 5.40–5.30 (1H, m, CH-C₁₀), 5.17–5.09 (1H, m, CH-C₁₁), 5.07 (1H, d, J = 1.9 Hz, CH₂-C⁶), 4.79 (1H, d, J = 1.9 Hz, CH₂-C⁶), 4.69 (1H, q, J = 1.4 Hz, CH₂-C₁₆),
4.62 (1H, s, CH$_2$-C16), 4.11 (2H, s, CH$_2$-C21), 3.81 (3H, s, CH$_3$-C19), 3.59 (1H, s, CH-C7), 3.12 (1H, dd, $J = 14.3$, 6.8 Hz, CH$_2$-C2), 2.99 (1H, dd, $J = 14.3$, 8.6 Hz, CH$_2$-C2), 2.64–2.52 (1H, m, CH-C1), 2.08–1.81 (6H, m, CH$_2$-C9, CH$_2$-C13, CH$_2$-C$_3^\delta$), 1.64–1.56 (2H, m, CH$_2$-C14), 1.43 (3H, d, $J = 1.4$ Hz, CH$_3$-C17), 1.37–1.23 (7H, m, CH$_2$-C$^D$, CH$_2$-C$^E$, CH$_3$-C20), 1.20 (9H, s, C(CH$_3$)$_3$), 1.15–1.01 (21H, m, CH(CH$_3$)$_2$), 0.87 (3H, t, $J = 7.0$ Hz, CH$_3$-C$^\delta$); HRMS (ESI$^+$) calcd. for C$_{41}$H$_{68}$O$_2$SiNa [M+Na]$^+$ 723.4627 found 723.4587; IR $\nu_{\max}$ 3467, 2957, 2929, 2866, 1725, 1581, 1480, 1462, 1438 cm$^{-1}$. **Ynnone (Z)-375**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.74 (1H, s, CH-C5), 5.87–5.76 (CH-C$^\delta$), 5.55–5.42 (2H, m, CH-C10, CH-C11), 5.08 (1H, d, $J = 1.8$ Hz, CH$_2$-C$^A$), 4.80 (1H, d, $J = 1.8$ Hz, CH$_2$-C$^A$), 4.78–4.75 (1H, m, CH$_2$-C16), 4.72–4.69 (1H, m, CH$_2$-C16), 4.12 (2H, s, CH$_2$-C21), 3.87 (3H, s, CH$_3$-C19), 2.74 (2H, dd, $J = 7.0$, 4.9 Hz, CH$_2$-C2), 2.71–2.59 (1H, m, CH-C1), 2.27 (1H, s, OH-C8), 2.15 (1H, dd, $J = 14.4$, 7.4 Hz, CH$_2$-C9), 2.08–1.83 (5H, m, CH$_2$-C9, CH$_2$-C13, CH$_2$-C$^\delta$), 1.64–1.63 (3H, m, CH$_3$-C17), 1.55–1.47 (5H, m, CH$_2$-C14, CH$_3$-C20), 1.38–1.23 (4H, m, CH$_2$-C$^D$, CH$_2$-C$^E$), 1.17 (9H, s, C(CH$_3$)$_3$), 1.15–1.03 (21H, m, CH(CH$_3$)$_2$), 0.88 (3H, t, $J = 7.1$ Hz, CH$_3$-C$^\delta$); HRMS (ESI$^+$) calcd. for C$_{41}$H$_{68}$O$_2$SiNa [M+Na]$^+$ 723.4627 found 723.4587; IR $\nu_{\max}$ 3467, 2957, 2929, 2866, 1725, 1581, 1480, 1462, 1438 cm$^{-1}$. **Cyclopropylfuran 378**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.32 (1H, s, CH-C5), 5.18 (1H, td, $J = 8.2$, 4.3 Hz, CH-C10), 5.08 (1H, d, $J = 2.0$ Hz, CH$_2$-C$^A$), 4.79 (1H, d, $J = 2.0$ Hz, CH$_2$-C$^A$), 4.66 (1H, q, $J = 1.2$ Hz, CH$_2$-C16), 4.60 (1H, s, CH$_2$-C16), 4.11 (2H, s, CH$_2$-C21), 3.80 (3H, s, CH$_3$-C19), 3.12 (1H, dd, $J = 14.6$, 9.4 Hz, CH$_2$-C2), 2.99 (1H, dd, $J = 14.6$, 6.1 Hz, CH$_2$-C2), 2.64–2.55 (1H, m, CH-C1), 2.13 (1H, dd, $J = 13.4$, 8.2 Hz, CH-C9), 2.08–1.93 (2H, m, CH$_2$-C9, CH-C$^B$) 1.88 (1H, app t, $J = 4.3$ Hz, CH-C11), 1.65 (3H, d, $J = 1.2$ Hz, CH$_3$-C17), 1.40–1.22 (13H, m, CH$_2$-C13, CH$_2$-C14, CH$_3$-C20, CH$_2$-C$^D$, CH$_2$-C$^E$), 1.20 (9H, s, C(CH$_3$)$_3$), 1.11–1.03 (21H, m, CH(CH$_3$)$_2$), 0.83 (3H, t, $J = 7.0$ Hz, CH$_3$-C$^\delta$); HRMS (ESI$^+$) calcd. for C$_{41}$H$_{68}$O$_2$SiNa [M+Na]$^+$ 723.4627 found 723.4586.

(E/Z)-Ethyl 2-acetyl-6-methyl-6-((triethylsilyl)oxy)hept-2-en-4-ynoate 383

![Chemical Structure](image)

Chemical Formula: C$_{16}$H$_{30}$O$_4$Si
Molecular Weight: 338.5190

To a solution of triethyl((2-methylbut-3-yn-2-yl)oxy)silane (1.09 g, 5.49 mmol) in Et$_2$O (10 mL) at −78 °C was added nBuLi (2.5 m in hexane, 2.19 mL, 6.0 mmol) dropwise and the solution stirred for 15 min before dropwise addition of DMF (0.85 mL, 11 mmol) and further stirring for 30 min. The solution was warmed to 0 °C and stirred for 15 min before the reaction was quenched by addition to 10%aq. KH$_2$PO$_4$ (20 mL). Following vigorous stirring
for 30 min the biphasic mixture was separated and the organic phase was washed with 10% aq. KH₂PO₄ (2 × 10mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed under vacuum to yield the aldehyde 382 as yellow oil (1.12 g) which was used in the next step without further purification.

Anhydrous MgSO₄ (53.0 mg, 0.44 mmol), acetic acid (8 μL, 1.32 mmol) and piperidine (20 μL, 0.22 mmol) were added sequentially to a stirred solution of aldehyde 4-methyl-4-(triethylsilyloxy)pent-2-ynal 382 (500 mg, 2.21 mmol) and ethylacetoacetate (0.28 mL, 2.23 mmol) in toluene (8mL) at rt. The reaction was stirred for 1 h before quenching with H₂O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under vacuum to yield the crude product. Purification of the residue by silica gel column chromatography (pet ether:Et₂O, 10:1) afforded the title compound 383 as a 1:1 mix of E and Z isomers (560 mg, 75%). Isomeric mixture: ¹H NMR (400 MHz, CDCl₃) δ 6.79 (0.5H, s, CH-C₆), δ 6.79 (0.5H, s, CH-C₆), 4.33 (1H, q, J = 7.1 Hz, CH₂-C₉), 4.26 (1H, q, J = 7.1 Hz, CH₂-C₉), 2.44 (1.5H, s, CH₃-C₁₂), 2.36 (1.5H, s, CH₃-C₁₂), 1.51 (3H, s, CH₃-C₂, CH₃-C₃), 1.50 (3H, s, CH₃-C₂, CH₃-C₃), 1.36 (1.5H, t, J = 7.1 Hz, CH₃-C₁₀), 1.30 (1.5H, t, J = 7.1 Hz, CH₃-C₁₀), 0.94 (4.5H, t, J = 7.8 Hz, Si(C₆H₄C₆H₃)₃), 0.63 (3H, q, J = 7.9 Hz, Si(C₆H₄C₆H₃)₃), 0.63 (3H, q, J = 7.9 Hz, Si(C₆H₄C₆H₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 193.9 (C-C₁₁), 165.3 (C-C₈), 163.8 (C-C₈), 143.0 (CH-C₆), 141.9 (CH-C₆), 123.9 (C-C₇), 122.4 (C-C₇), 112.0 (C-C₄), 110.8 (C-C₄), 78.3 (C-C₅), 77.9 (C-C₅), 66.8 (C-C₁), 66.8 (C-C₁), 61.7 (CH₂-C₉), 61.6 (CH₂-C₉), 32.5 (2C, CH₃-C₂, CH₃-C₃), 32.5 (2C, CH₃-C₂, CH₃-C₃), 30.4 (CH₃-C₁₂), 27.5 (CH₃-C₁₂), 14.2 (CH₃-C₁₀), 14.1 (CH₃-C₁₀), 6.9 (Si(CH₃C₆H₃)₃), 5.97 (Si(CH₃C₆H₃)₃); HRMS (ESI⁺) calcd. for C₁₆H₂₈O₄SiNa [M+Na]⁺ 361.1806, found 361.1793; IR νmax 2955, 2876, 1727, 1697, 1600, 1585, 1459, 1360, 1225 cm⁻¹

5-Phenylpent-1-en-3-yl 2-methylprop-2-enoate 386

![Chemical Structure](attachment:image.png)

To a solution of allylic alcohol 385 (510 mg, 3.14 mmol), methacrylic acid (0.27 mL, 3.14 mmol) and DMAP (38 mg, 0.31 mmol) in CH₂Cl₂ (15 mL) was added DCC (712 mg, 3.45 mmol) and the resulting mixture stirred at rt for 24 h. The resulting suspension was filtered and the solvent removed under vacuum. Purification of the residue by silica gel column
chromatography (pet. ether:Et₂O, 4:1) afforded the title compound 386 as a colourless oil (575 mg, 80%). ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.30 (2H, m, CH-C3, CH-C1), 7.27–7.20 (3H, m, CH-C2, CH-C4, CH-C6), 6.22–6.17 (1H, m, CH₂-C14), 5.91 (1H, ddd,  J = 17.1, 10.6, 6.2 Hz, CH-C10), 5.63 (1H, dq,  J = 1.6, 1.6 Hz, CH₂-C14), 5.42–5.37 (1H, m, CH-C9), 5.34 (1H, dt,  J = 17.1, 1.4 Hz, CH₂-C11), 5.27 (1H, dt,  J = 10.6, 1.4 Hz, CH₂-C11), 2.80–2.66 (2H, m, CH₂-C7), 2.16–1.97 (5H, m, CH₂-C8, CH₃-C15); ¹³C NMR (126 MHz, CDCl₃) δ 166.8 (C-C12), 141.5 (C-C5), 136.7 (CH-C10), 136.4 (C-C13), 128.6 (CH-C1, CH-C3), 128.5 (CH-C4, CH-C6), 126.1 (CH-C2), 125.6 (CH₂-C14), 117.0 (CH₂-C11), 116.0 (CH₂-C11), 74.6 (CH-C9), 36.0 (CH₂-C8), 31.5 (CH₂-C7), 18.5 (CH₃-C15); HRMS (ESI⁺) calcd. for C₁₅H₁₈O₂Na [M+Na]⁺ 253.1199, found 253.1194; IR vₘₐₓ 3028, 2953, 2928, 1717, 1638, 1497, 1454 cm⁻¹.

3-Methyl-5-(2-phenylethyl)-2,5-dihydrofuran-2-one 387

To a solution of ester 386 (100 mg, 0.43 mmol) and epoxyfuran 298 (97 mg, 0.43 mmol) in CH₂Cl₂ (11 mL) was added Grubbs II (34 mg, 0.04 mmol) and the resulting mixture heated to 45 °C for 18 h. The solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (pet. ether: Et₂O, 4:1 → 3:2) to afford the title compound 387 as a colourless oil (84 mg, 97%). ¹H NMR (500 MHz, CDCl₃) δ 7.30 (2H, dd,  J = 8.1, 6.9 Hz, CH-C1, CH-C3), 7.24–7.18 (3H, m, CH-C2, CH-C4, CH-C6), 6.99–6.97 (1H, m, CH-C10), 4.90–4.84 (1H, m, CH-C9), 2.87–2.73 (2H, m, CH₂-C7), 2.03 (1H, dddd,  J = 13.9, 9.2, 7.3, 4.6 Hz, CH₂-C8), 1.95–1.85 (5H, m, CH₂-C8, CH₃-C13); ¹³C NMR (126 MHz, CDCl₃) δ 174.4 (C-C12), 148.7 (CH-C10), 140.7 (C-C5), 130.2 (C-C11), 128.7 (CH-C1, CH-C3), 128.7 (CH-C4, CH-C6), 126.4 (CH-C2), 80.3 (CH-C9), 35.4 (CH₂-C7), 31.6 (CH₂-C8), 10.8 (CH₃-C13); HRMS (ESI⁺) calcd. for C₁₃H₁₄O₂Na [M+Na]⁺ 225.0886, found 225.0882; IR vₘₐₓ 3063, 2924, 1751, 1658, 1497, 1451 cm⁻¹.
To a solution of alcohol 313 (200 mg, 0.58 mmol) in CH₂Cl₂ (5 mL) was added DIPEA (0.2 mL, 1.2 mmol) and DMAP (24 mg, 1.2 mmol), followed by MOMCl (0.09 mL, 1.2 mmol) and the resulting mixture stirred at rt for 3 h. Aq. 1 M NaOH (2.5 mL) was added and the mixture stirred for 1 h. The biphasic mixture was separated and the organic extract washed with brine (5 mL), dried over MgSO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 9:1) afforded the title compound 391 as a colourless oil (155 mg, 69%).

$$\text{(7R)-14-Methyl-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecane-10-one 391}$$

To a solution of alcohol 313 (200 mg, 0.58 mmol) in CH₂Cl₂ (5 mL) was added DIPEA (0.2 mL, 1.2 mmol) and DMAP (24 mg, 1.2 mmol), followed by MOMCl (0.09 mL, 1.2 mmol) and the resulting mixture stirred at rt for 3 h. Aq. 1 M NaOH (2.5 mL) was added and the mixture stirred for 1 h. The biphasic mixture was separated and the organic extract washed with brine (5 mL), dried over MgSO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 9:1) afforded the title compound 391 as a colourless oil (155 mg, 69%).

$$\text{(7R)-14-Methyl-10-methylidene-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecane}$$

To a solution of methyltriphenylphosphonium bromide (296 mg, 0.83 mmol) in THF (4 mL) at 0 °C was added nBuLi (0.08 mL of a 11 M solution in hexane, 0.83 mmol). After 1 h at 0 °C a solution of ketone 391 (144 mg, 0.41 mmol) in THF (4 mL) was added and the resulting mixture warmed to rt and stirred for 18 h. The reaction was quenched with H₂O (10 mL) and Et₂O (10 mL) added. The biphasic mixture was separated and the organic extract was washed with brine (15 mL), dried over MgSO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et₂O, 9:1) afforded the title compound 391 as a colourless oil (155 mg, 69%).

$$\text{(7R)-14-Methyl-10-methylidene-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecane}$$
vacuum. Purification of the residue by silica gel column chromatography (pet. ether:EtoO, 95:5 → 90:10) afforded the title compound as a colourless oil (148 mg, quant.). [α]D23 -2.7 (c = 0.33, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.08 (1H, d, J = 1.7 Hz, CH2-C6), 4.81 (1H, dq, J = 2.1, 1.4 Hz, CH2-C16), 4.78 (1H, dq, J = 2.9, 1.4 Hz, CH2-C16), 4.72–4.69 (1H, m, CH2-C6), 4.60 (1H, d, J = 6.6 Hz, MOM-CH2), 4.58 (1H, d, J = 6.6 Hz, MOM-CH2), 4.13 (2H, s, CH2-C21), 3.54–3.39 (m, 2H, CH2-C3), 3.35 (3H, s, MOM-CH3), 2.22 (1H, tt, J = 9.3, 5.5 Hz, CH-C1), 2.02–1.82 (2H, m, CH2-C13), 1.73–1.58 (5H, m, CH2-C2, CH3-C17), 1.55–1.45 (2H, m, CH2-C14), 1.19–1.00 (21H, m, CH(CH3)2); 13C NMR (126 MHz, CDCl3) δ 148.9 (C-C12), 146.6 (C-C15), 112.6 (CH2-C8), 108.0 (CH2-C16), 96.7 (MOM-CH2), 66.3 (CH2-C21), 66.2 (CH2-C3), 55.2 (MOM-CH3), 44.1 (CH-C1), 33.4 (CH2-C2), 31.7 (CH2-C13), 30.6 (CH2-C14), 18.2 (CH(CH3)2), 17.8 (CH3-C17), 12.2 (CH(CH3)2); HRMS (ESI+) calcd. for C22H44O5SiNa [M+Na]+ 407.2952, found 407.2936; IR νmax 2940, 2866, 1644, 1463, 1441 cm⁻¹.

(5R)-5-[2-(Methoxymethoxy)ethyl]-6-methyl-2-methylidenehept-6-en-1-ol 392

\[
\text{HO} \quad \text{A} \quad 12 \quad 13 \quad 14 \quad 15 \quad 16 \quad 17 \quad \text{OMOM}
\]

To a solution of (7R)-14-Methyl-10-methylidene-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecane (135 mg, 0.39 mmol) in THF (3 mL) was added TBAF (0.43 mL of a 1 M solution in THF, 0.43 mmol) and the resulting mixture stirred at rt for 2 h. The reaction was quenched with saturated aq. NH4Cl (5 mL) and EtoO (5 mL) added. The phases were separated and the aqueous phase was extracted with EtoO (5 mL). The combined organic extracts were dried over MgSO4, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (pet. ether:EtoO, 1:1) to afford the allylic alcohol 392 as a pale yellow oil (85 mg, quant.); [α]D21 +13.6 (c = 0.06, CHCl3); 1H NMR (500 MHz, CDCl3) δ 4.97 (1H, d, J = 1.8 Hz, CH2-C6), 4.81 (1H, d, J = 1.4 Hz, CH2-C16), 4.75 (1H, dq, J = 2.8, 1.4 Hz, CH2-C16), 4.69–4.67 (1H, m, CH2-C6), 4.66 (1H, d, J = 6.6 Hz, MOM-CH2), 4.54 (1H, d, J = 6.6 Hz, MOM-CH2), 4.00 (2H, s, CH2-C21), 3.47–3.37 (2H, m, CH2-C3), 3.31 (3H, s, MOM-CH3), 2.24–2.15 (1H, m, CH-C1), 2.01–1.85 (2H, m, CH2-C13), 1.69–1.54 (5H, m, CH2-C2, CH3-C17), 1.51–1.42 (2H, m, CH2-C14); 13C NMR (126 MHz, CDCl3) δ 149.2 (C-C12), 146.3 (C-C15), 112.7 (CH2-C8), 109.0 (CH2-C16), 96.5 (MOM-CH2), 66.1 (CH2-C21), 65.8 (CH2-C3), 55.2 (MOM-CH3), 43.8 (CH-C1), 33.2 (CH2-
C2), 31.4 (CH2-C13), 30.7 (CH2-C14), 17.7 (CH2-C17); HRMS (ESI⁺) calcd. for C13H24O3Na [M+Na]⁺ 251.1617, found 251.1598; IR νmax 3408, 2929, 2882, 1645, 1442 cm⁻¹.

(3R)-3-(Prop-1-en-2-yl)-6-((trisisopropylsilyloxy)methyl)hept-6-en-1-yl acetate

To a solution of alcohol 314 (4.50 g, 13.2 mmol) and DMAP (161 mg, 1.32 mmol) in CH2Cl2 (100 mL) at rt was added triethylamine (5.50 mL, 39.7 mmol) followed by acetic anhydride (1.50 mL, 15.9 mmol) and the solution stirred for 15 h. The reaction was quenched with saturated aq. NH4Cl (100 mL) and the phases were separated. The organic phase was washed with brine (50 mL), dried over MgSO4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et2O, 19:1) to deliver the title acetate as a colourless oil (4.74 g, 94%), [α]D20−6.1 (c = 0.28, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.09–5.07 (1H, d, J = 1.7 Hz, CH2-C2), 4.82–4.78 (2H, m, CH2-C2:CH2-C16), 4.72–4.70 (1H, m, CH2-C16), 4.13 (2H, s, CH2-C21), 4.07–3.92 (2H, m, CH2-C3), 2.22–2.14 (1H, m, CH-C1), 2.03 (3H, s, OAc-CH3), 2.01–1.83 (2H, m, CH2-C13), 1.77–1.63 (2H, m, CH2-C2), 1.61 (3H, dd, J = 1.3, 0.8 Hz, CH3-C17), 1.55–1.47 (2H, m, CH2-C14), 1.17–1.03 (21H, m, CH(CH3)2); 13C NMR (101 MHz, CDCl3) δ 171.3 (Ac-C(O)), 148.7 (C-C12), 146.0 (C-C15), 113.0 (CH2-C4), 108.1 (CH2-C16), 66.2 (CH2-C21), 63.2 (CH2-C3), 44.0 (CH-C1), 32.1 (CH2-C2), 31.5 (CH2-C13), 30.5 (CH2-C14), 21.1 (Ac-CH3), 18.2 (CH(CH3)2), 17.8 (CH3-C17), 12.2 (CH(CH3)2); HRMS (ESI⁺) calcd for C22H42O3SiNa [M+Na]⁺ 405.2796, found 405.2777; IR νmax 2941, 2893, 2866, 1744, 1645, 1464 cm⁻¹.

(3R)-3-(Prop-1-en-2-yl)-6-(hydroxymethyl)hept-6-en-1-yl acetate 393

To a solution of (3R)-3-(Prop-1-en-2-yl)-6-((trisisopropylsilyloxy)methyl)hept-6-en-1-yl acetate (6.30 g, 16.5 mmol) in THF (80 mL) was added TBAF (16.5 mL of a 1 M solution in THF, 16.5 mmol) and the resulting mixture stirred at rt for 18 h. The reaction was quenched with saturated aq. NH4Cl (100 mL) and Et2O (100 mL) added. The phases were separated
and the aqueous phase was extracted with Et₂O (100 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (pet. ether:EtOAc, 1:1) to afford the allylic alcohol 393 as a yellow oil (3.72 g, quant.). [α]D²⁴ -12 (c = 0.22, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.96–4.94 (1H, m, CH₂-C), 4.80–4.77 (1H, m, CH₂-C16), 4.75–4.73 (1H, m, CH₂-C16), 4.67–4.64 (1H, m, CH₂-C2), 4.01–3.95 (3H, m, CH₂-C21, CH₂-C3), 3.89 (1H, ddd, J = 11.0, 7.4, 7.3 Hz, CH₂-C3), 2.40 (1H, br s, OH-C21), 2.16–2.09 (1H, m, CH-C1), 1.97 (3H, s, Ac-CH₃), 1.96–1.84 (2H, m, CH₂-C13), 1.69–1.58 (2H, m, CH₂-C2), 1.56 (3H, dd, J = 1.2, 0.7 Hz, CH₃-C17), 1.48–1.42 (2H, m, CH₂-C14); ¹³C NMR (126 MHz, CDCl₃) δ 171.3 (Ac-C(O)), 148.9 (C-C12), 145.7 (C-C15), 112.9 (CH₂-C), 109.0 (CH₂-C16), 65.7 (CH₂-C21), 63.0 (CH₂-C3), 43.7 (CH-C1), 31.9 (CH₂-C2), 31.2 (CH₂-C13), 30.5 (CH₂-C14), 21.0 (Ac-CH₃), 17.6 (CH₃-C17); HRMS (ESI⁺) calcd for C₁₃H₂₂O₃Na [M+Na]+ 249.1461, found 249.1456; IR νmax 3431, 3072, 2934, 2901, 2862, 1739, 1720, 1645, 1447 cm⁻¹.

(5R)-5-[2-(Methoxymethoxy)ethyl]-6-methyl-2-methylidenehept-6-enoic acid 394

To a solution of the allylic alcohol 392 (80 mg, 0.35 mmol) in CH₂Cl₂ (3.5 mL) was added Dess-Martin periodinane (163 mg, 0.39 mmol) and the resulting mixture was stirred at rt for 2.5 h. The reaction was quenched with saturated aq. Na₂S₂O₃ (5 mL) and the phases were separated. The organic phase was washed with saturated aq. Na₂S₂O₃ (2 × 5 mL), dried over MgSO₄ and filtered. The solvent was removed under vacuum to afford the crude product, which was used directly in the next step.

To a solution of crude aldehyde in tBuOH (5.35 mL) was added 2-methyl-2-buten (0.76 mL, 7.12 mmol). A solution of Na₂H₂PO₄ (896 mg, 5.78 mmol) and NaClO₂ (483 g, 5.34 mmol) in H₂O (10.7 mL) was then added and the biphasic mixture stirred at rt for 16 h. CH₂Cl₂ (20 mL) was added and the phases separated. The aqueous phase was washed with CH₂Cl₂ (2 × 20 mL) and the combined organic extracts were dried over Na₂SO₄ and filtered. The solvent was removed under vacuum to afford the carboxylic acid 394 as a colourless oil (85 mg, quant.). [α]D²⁶ +14 (c = 0.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.24 (1H, d, J = 1.4 Hz, CH₂-C), 5.61 (1H, d, J = 1.4 Hz, CH₂-C), 4.78 (1H, dq, J = 2.5, 1.4 Hz, CH₂-C16), 4.71 (1H, d, J = 2.5 Hz, CH₂-C16), 4.59 (1H, d, J = 6.6 Hz, MOM-CH₂), 4.57 (1H, d, J = 6.6 Hz, MOM-CH₂), 3.49–3.39 (2H, m, CH₂-C3), 3.33 (3H, s, MOM-CH₃), 2.29–2.19 (2H, m, CH₂-C13),
2.19–2.10 (1H, m, CH-C1), 1.71–1.58 (5H, m, CH2-C2, CH3-C17), 1.55–1.47 (2H, m, CH2-C14); 13C NMR (126 MHz, CDCl3) δ 172.5 (C-C21), 146.1 (C-C15), 140.3 (C-C12), 127.0 (CH2-C9), 112.9 (CH2-C16), 96.5 (MOM-CH2), 66.2 (CH2-C3), 55.2 (MOM-CH3), 43.9 (CH-C1), 33.2 (CH2-C2), 32.1 (CH2-C13), 29.7 (CH2-C14), 17.7 (CH3-C17); HRMS (ESI+) calcd. for C13H22O4Na [M+Na]+ 265.1410, found 265.1412; IR νmax 3071, 2930, 2882, 1719, 1694, 1645, 1628, 1441 cm⁻¹.

(5R)-5-(2-Acetoxyethyl)-6-methyl-2-methylidenehept-6-enoic acid 395

To a solution of the allylic alcohol 393 (3.7 g, 16 mmol) in CH2Cl2 (80 mL) was added Dess-Martin periodinane (7.2 g, 17 mmol) and the resulting mixture was stirred at rt for 2.5 h. The reaction was quenched with saturated aq. Na2S2O3 (100 mL) and the phases were separated. The organic phase was washed with saturated aq. Na2S2O3 (2 × 100 mL), dried over MgSO4 and filtered. The solvent was removed under vacuum to afford the crude product, which was used directly in the next step.

To a solution of crude aldehyde in tBuOH (120 mL) was added 2-methyl-2-buten (13.1 mL, 123 mmol). A solution of NaH2PO4 (15.5 g, 100 mmol) and NaClO2 (8.35 g, 92.3 mmol) in H2O (240 mL) was then added and the biphasic mixture stirred at rt for 17 h. CH2Cl2 (200 mL) was added and the phases separated. The aqueous phase was washed with CH2Cl2 (2 × 200 mL) and the combined organic extracts were dried over Na2SO4 and filtered. The solvent was removed under vacuum to afford the carboxylic acid 395 as a colourless oil (3.91 g, quant.). [α]D²⁴ -11 (c = 0.16, CHCl3); 1H NMR (500 MHz, CDCl3) δ 10.56 (1H, br, CO2H), 6.23 (1H, d, J = 0.9 Hz, CH2-C9), 5.60–5.58 (1H, m, CH2-C8), 4.78–4.75 (1H, m, CH2-C16), 4.68 (1H, d, J = 1.8 Hz, CH2-C16), 3.99 (1H, ddd, J = 11.0, 7.3, 5.7 Hz, CH2-C3), 3.92 (1H, ddd, J = 11.0, 7.3, 7.3 Hz, CH2-C3), 2.27–2.08 (3H, m, CH2-C13, CH-C1), 1.99 (3H, s, Ac-CH3), 1.71–1.59 (2H, m, CH2-C2), 1.58 (3H, d, J = 1.3 Hz, CH3-C17), 1.53–1.46 (2H, m, CH2-C14); 13C NMR (126 MHz, CDCl3) δ 172.4 (C-C21), 171.4 (Ac-C(O)), 145.5 (C-C15), 140.1 (C-C12), 127.1 (CH2-C16), 113.2 (CH2-C16), 63.0 (CH2-C3), 43.8 (CH-C1), 32.0 (CH2-C2), 31.8 (CH2-C13), 29.5 (CH2-C14), 21.0 (Ac-CH3), 17.5 (CH3-C17); HRMS (ESI+) calcd. for C13H20O4Na [M+Na]+ 263.1254, found 263.1254; IR νmax 3171, 3072, 2936, 1738, 1724, 1693, 1645, 1628, 1440 cm⁻¹

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(5R)-5-(2-Hydroxyethyl)-6-methyl-2-methylidenehept-6-enoic acid 388

To a solution of acid 395 (214 mg, 0.89 mmol) in THF (2 mL) was added a solution of LiOH (85 mg, 3.56 mmol) in H₂O (1 mL) and the resulting mixture stirred at rt for 3 h. The reaction was quenched with 1M HCl which was added until pH 2 was reached. CH₂Cl₂ (10 mL) was added and the biphasic mixture separated. The aqueous phase was washed with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent removed under vacuum to afford the alcohol 388 as a colourless oil (168 mg, 95%).

−27 (c = 0.09, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.27 (1H, d, J = 1.4 Hz, CH₂-C₆), 5.65 (1H, d, J = 1.4 Hz, CH₂-C₆), 4.82 (1H, dq, J = 2.6, 1.5 Hz, CH₂-C₁₆), 4.78 (1H, d, J = 2.6 Hz, CH₂-C₁₆), 3.67–3.56 (2H, m, CH₂-C₃), 2.33–2.23 (2H, m, CH₂-C₁₃), 2.22–2.13 (1H, m, CH-C₁), 1.67–1.60 (5H, CH₂-C₂, CH₃-C₁₇), 1.58–1.51 (2H, m, CH₂-C₁₄); ¹³C NMR (101 MHz, CDCl₃) δ 171.4 (C-C₂₁), 147.0 (C-C₁₅), 140.1 (C-C₁₂), 127.2 (CH₂-C₆), 112.9 (CH₂-C₁₆), 61.6 (CH₂-C₃), 44.2 (CH-C₁), 36.2 (CH₂-C₂), 32.3 (CH₂-C₁₃), 29.8 (CH₂-C₁₄), 17.8 (CH₃-C₁₇); HRMS (ESI⁺) calcd for C₁₁H₁₈O₃Na [M+Na]⁺ 221.1148, found 221.1145; IR νmax 3284, 3071, 2938, 2879, 1690, 1627, 1443 cm⁻¹.

(5R)-9-Methoxy-2-methylidene-7,9-dioxo-5-(prop-1-en-2-yl)nonanoic acid 301

To a solution of alcohol 388 (73 mg, 0.37 mmol) in CH₂Cl₂ (2 mL) was added Dess-Martin periodinane (2.54 g, 5.99 mmol). The resulting mixture was stirred at rt for 3 h and the reaction was then quenched with saturated aq. Na₂S₂O₃ (2 mL). The phases were separated and the organic phase washed with saturated aq. Na₂S₂O₃ (2 × 2 mL), then dried over Na₂SO₄ and filtered to afford the crude aldehyde which was used without further purification.

To a solution of glycine methyl ester hydrochloride (694 mg, 5.55 mmol) in CH₂Cl₂ (1.8 mL) was added a solution of NaNO₂ (459 mg, 6.66 mmol) in H₂O (0.6 mL). The biphasic mixture was stirred for 1.5 h at rt and then saturated aq. NaHCO₃ (0.5 mL) was added. The phases
were separated and the organic phase was dried over MgSO₄ and filtered. The solution of methyl diazoacetate was then used directly.

To a solution of the crude aldehyde and SnCl₂ (148 mg, 0.74 mmol) in CH₂Cl₂ (2.5 mL) was added the freshly prepared solution of methyl diazoacetate (1.5 mL, 5.55 mmol). The resulting mixture was stirred at rt for 16 h and the excess diazo ester was destroyed by dropwise addition of glacial acetic acid (0.2 mL). The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 1:1 → 2:8) to afford the title compound 301 as a colourless oil (45.2 mg, 46%).

1H NMR (400 MHz, CDCl₃) δ 6.28 (1H, s, CH₂-C₆), 5.66 (1H, s, CH₂-C₆), 4.81 (1H, q, J = 1.3 Hz, CH₂-C₁₆), 4.76 (1H, s, CH₂-C₁₆), 3.72 (3H, s, CH₂-C₁₉), 3.43 (2H, s, CH₂-C₄), 2.73–2.52 (3H, m, CH₂-C₁₃, CH-C₁), 2.33–2.20 (1H, m, CH₂-C₂), 2.23–2.08 (1H, m, CH₂-C₂), 1.67 (3H, d, J = 1.3 Hz, CH₃-C₁₇), 1.60–1.49 (2H, m, CH₂-C₁₄); 13C NMR (101 MHz, CDCl₃) δ 201.7 (C-C₃), 172.5 (C-C₂₁), 167.7 (C-C₁₈), 145.7 (C-C₁₅), 139.8 (C-C₁₂), 127.5 (C-C₆), 112.9 (C-C₁₆), 52.5 (CH₃-C₁₉), 49.4 (CH₂-C₄), 47.5 (CH₂-C₂), 42.0 (CH-C₁), 31.7 (CH₂-C₁₃), 29.3 (CH₂-C₁₄), 18.9 (CH₃-C₁₇); HRMS (ESI⁺) calcd for C₁₄H₂₀O₅Na [M+Na]⁺ 291.1203, found 291.1196; IR νmax 3070, 2930, 1742, 1718, 1694, 1628, 1438 cm⁻¹.

(5S,6E)-5-[(Triethylsilyl)oxy]-1-[(tris(propan-2-yl)silyl)undec-6-en-1-yn-3-one 396

To a solution of triisopropylsilylacetylene (1.23 mL, 5.47 mmol) in THF (9 mL) at 0 °C was added nBuLi (2.18 mL of a 2.5 M solution in hexanes, 5.47 mmol) and the resulting solution was stirred at 0 °C for 30 mins. A solution of the amide 346 (1.20 g, 3.65 mmol) in THF (6 mL) was added and the mixture stirred at 0 °C for 10 min then warmed to rt and stirred for 1 h. The reaction was quenched with saturated aq. NH₄Cl (20 mL) and Et₂O (20 mL) added. The phases were separated and the organic phase was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 98:2) to afford the propargylic ketone 396 as a colourless oil (1.55 g, 94%). [α]D₂⁴ +4.8 (c = 0.56, CHCl₃); 1H NMR (500 MHz, CDCl₃) δ 5.67–5.58 (1H, m, CH-C₇), 5.43 (1H, dd, J = 15.3, 7.0, 1.4 Hz, CH-C₁₁), 4.74–4.67 (1H, m, CH-C₁₀), 2.84 (1H, dd, J = 14.5, 7.5 Hz, CH₂-C₉), 2.65 (1H, dd, J = 14.5, 5.8 Hz, CH₂-C₉), 2.00 (1H, app q, J = 6.8 Hz, CH₂-C₆), 1.38–1.24 (4H, m, CH₂-C⁵, CH₂-C⁶), 1.18–1.05 (21H, m, CH(CH₃)₂), 0.93 (9H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.88 (3H, t, J = 7.1 Hz, CH₃-C⁵), 0.58 (6H, q, J = 7.8 Hz, CH₃-C⁵).
Hz, Si(CH$_2$CH$_3$)$_3$; $^{13}$C NMR (101 MHz, CDCl$_3$) δ 185.2 (C-C8), 132.0 (CH-C$^5$), 131.9 (CH-C11), 104.9 (C-C7), 95.8 (C-C6), 70.3 (CH-C10), 54.8 (CH$_2$-C9), 31.9 (CH$_2$-C$^5$), 31.3 (CH$_2$-C$^D$), 22.3 (CH$_2$-C$^E$), 18.6 (CH(CH$_3$)$_2$), 14.1 (CH$_3$-C$^I$), 11.2 (CH(CH$_3$)$_2$), 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.0 (Si(CH$_2$CH$_3$)$_3$); HRMS (ESI$^+$) calcd for C$_{26}$H$_{50}$O$_2$Si$_2$Na [M+Na]$^+$ 473.3242, found 473.3208; IR $\nu_{max}$ 2955, 2947, 2868, 2147, 1678, 1628, 1462, 1414 cm$^{-1}$.

(3R,5S,6E)-5-[(tert-Butyldimethylsilyl)oxy]-3-methylundec-6-en-1-yn-3-ol 399

![Chemical structure](image)

To a solution of NaH (46 mg of 60% dispersion in mineral oil, 1.16 mmol) in THF (1 mL) at 0 °C was added a solution of 1,3-diol 397 (228 mg, 1.16 mmol) in THF (1.5 mL). The resulting mixture was gradually warmed to rt and stirred for 20 min. A solution of tert-butyldimethylsilyl chloride (175 mg, 1.16 mmol) in THF (1.5 mL) was then added and the mixture was stirred at rt for 17.5 h. Brine (10 mL) and Et$_2$O (10 mL) were added and the phases separated. The organic phase was dried over Na$_2$SO$_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et$_2$O, 8:2) to afford the alkyne 399 as a yellow oil (341 mg, 95%). $[\alpha]_{D}^{26}$ −24 (c = 0.165, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.68–5.52 (2H, m, CH-C11, CH-C$^B$), 4.53 (1H, td, J = 7.4, 5.1 Hz, CH-C10), 4.25 (1H, s, OH-C8), 2.44 (1H, s, CH-C6), 2.09 (1H, dd, J = 14.4, 7.4 Hz, CH$_2$-C9), 2.06–1.99 (2H, m, CH$_2$-C$^C$), 1.86 (1H, dd, J = 14.4, 5.1 Hz, CH$_2$-C9), 1.54 (3H, s, CH$_3$-C20), 1.42–1.28 (4H, m, CH$_2$-C$^D$, CH$_2$-C$^E$), 0.93–0.86 (12H, m, CH$_3$-C$^E$, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.10 (3H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.06 (3H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 133.2 (CH-C$^B$), 132.7 (CH-C11), 88.5 (C-C7), 73.3 (CH-C6), 71.0 (CH-C10), 67.1 (C-C8), 49.1 (CH$_2$-C9), 31.9 (CH$_2$-C$^C$), 31.2 (CH$_2$-C$^D$), 30.0 (CH$_3$-C20), 26.0 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 22.4 (CH$_2$-C$^E$), 18.1(Si(CH$_3$)$_2$C(CH$_3$)$_3$), 14.1 (CH$_3$-C$^E$), −3.4 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), −4.6 (Si(CH$_3$)$_2$C(CH$_3$)$_3$); HRMS (ESI$^+$) calcd for C$_{18}$H$_{34}$O$_2$SiNa [M+Na]$^+$ 333.2220, found 333.2210; IR $\nu_{max}$ 3470, 3312, 2957, 2930, 2857, 1668, 1472, 1464 cm$^{-1}$
To a solution of NaH (19 mg of 60% dispersion in mineral oil, 0.48 mmol) in THF (1 mL) at 0 °C was added a solution of 1,3-diol 397 (94 mg, 0.48 mmol) in THF (1 mL). The resulting mixture was gradually warmed to rt and stirred for 20 min. Trisopropylsilyl chloride (0.11 mL, 0.50 mmol) was then added and the mixture was stirred at rt for 14 h. Brine (5 mL) and Et₂O (5 mL) were added and the phases separated. The organic phase was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 8:2) to afford the alkyne 400 as a colourless oil (166 mg, 98%).

\[\text{[\(4R,5S,6E\)]-3-Methyl-5-{{[\text{tris(propan-2-yl)silyl]oxy}}undec-6-1-yn-3-ol}

\[(3R,5S,6E)-3\text{-Methyl-5-}[\text{tris(propan-2-yl)silyl]oxy}]\text{undec-6-en-1-yn-3-ol} 400

IR \(\nu_{\text{max}}\) 3466, 3312, 2943, 2930, 2866, 1464 cm\(^{-1}\)

To a solution of alkyne 399 (170 mg, 0.55 mmol) in THF (15 mL) at −78 °C was added nBuLi (0.54 mL of a 2.15 M solution in hexane, 1.15 mmol). The resulting solution was stirred for 5 mins and then warmed to 0 °C. DMF (0.11 mL, 1.37 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with 5% aq. KH₂PO₄ (20 mL) and Et₂O (20 mL) was added. The phases were separated and the organic phase was washed with brine (20 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 7:3) to deliver the

\[\text{[\(4R,6S,7E\)]-6-[[\text{tert-Butyldimethylsilyl]oxy}}]-4\text{-hydroxy-4-methylundec-7-en-2-ynal} 401

\[(4R,6S,7E)-6-[[\text{tert-Butyldimethylsilyl]oxy}}]-4\text{-hydroxy-4-methylundec-7-en-2-ynal} 401\]
propargylic aldehyde 401 as a colourless oil (186 mg, quant.). $[\alpha]_D^{26} = -7.5$ (c = 0.10, CHCl₃);

$^1$H NMR (500 MHz, CDCl₃) $\delta$ 9.24 (1H, s, CHO-C5), 5.70–5.53 (2H, m, CH-C11, CH-C5), 4.79 (1H, s, CH-C8), 4.54 (1H, td, $J = 7.0, 4.5$ Hz, CH-C10), 2.12 (1H, dd, $J = 14.5, 7.0$ Hz, CH₂-C9), 2.06–1.99 (2H, m, CH₂-C5), 1.94 (1H, dd, $J = 14.5, 4.5$ Hz, CH₂-C9), 1.58 (3H, s, CH₂-C20), 1.43–1.27 (4H, m, CH₂-C⁵, CH₂-C⁶), 0.98–0.85 (12H, m, CH₃-C⁵, Si(CH₃)₂C(CH₃)₃), 0.10 (3H, s, Si(CH₃)₂C(CH₃)₃), 0.07 (3H, s, Si(CH₃)₂C(CH₃)₃); $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 176.9 (CHO), 133.0 (CH-C⁵), 132.2 (CH-C11), 100.5 (C-C7), 82.9 (C-C6), 73.3 (CH-C10), 47.9 (CH₂-C9), 31.9 (CH₂-C⁵), 31.2 (CH₂-C⁵), 29.6 (CH₃-C20), 25.9 (Si(CH₃)₂C(CH₃)₃), 22.4 (CH₂-C⁵), 18.1 (Si(CH₃)₂C(CH₃)₃), 14.1 (CH₃-C⁵), −3.5 (Si(CH₃)₂C(CH₃)₃), −4.7 (Si(CH₃)₂C(CH₃)₃); HRMS (ESI⁺) calcd for C₁₉H₃₄O₅SiNa [M+Na]$^+$ 361.2169, found 361.2122; IR $\nu_{max}$ 3451, 2957, 2930, 2859, 2210, 1672, 1472, 1646 cm⁻¹.

(4R,6S,7E)-4-Hydroxy-4-methyl-6-[[tris(propan-2-yl)silyloxy]dodec-7-en-2-ynal 402

![Chemical Structure](image)

To a solution of alkyne 400 (122 mg, 0.35 mmol) in THF (2.5 mL) at −78 °C was added nBuLi (0.33 mL of a 2.2 M solution in hexane, 0.73 mmol). The resulting solution was stirred for 5 mins and then warmed to 0 °C. DMF (0.07 mL, 0.86 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with 5% aq. KH₂PO₄ (5 mL) and Et₂O (5 mL) was added. The phases were separated and the organic phase washed with brine (5 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 8:2) to deliver the propargylic aldehyde 402 as a colourless oil (133 mg, quant.). $[\alpha]_D^{31} = -20$ (c = 0.03, CHCl₃);

$^1$H NMR (500 MHz, CDCl₃) $\delta$ 9.24 (1H, s, CHO-C5), 5.78–5.63 (2H, m, CH-C11, CH-C⁵), 4.82 (1H, s, OH-C8), 4.66 (1H, dt, $J = 7.3, 5.3$ Hz, CH-C10), 2.08 (2H, dd, $J = 5.3, 3.7$ Hz, CH₂-C9), 2.06–2.00 (2H, m, CH₂-C⁵), 1.57 (3H, s, CH₃-C20), 1.39–1.29 (4H, m, CH₂-C⁵, CH₂-C⁶), 1.13–1.04 (21H, m, CH(CH₃)₂), 0.89 (3H, t, $J = 7.0$ Hz, CH₃-C⁵); $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 176.7 (CHO-C5), 132.9 (CH-C⁵), 132.5 (CH-C11), 100.7 (C-C7), 83.5 (C-C6), 73.7 (CH-C10), 67.3 (C-C8), 48.6 (CH₂-C9), 31.9 (CH₂-C⁵), 31.1 (CH₂-C⁵), 30.5 (CH₃-C20), 22.5 (CH₂-C⁵), 18.2 (CH(CH₃)₂), 18.1 (CH(CH₃)₂), 14.0 (CH₃-C⁵), 12.5 (CH(CH₃)₂); HRMS
(ESI⁺) calcd. for C₂₂H₄₀O₃SiNa [M+Na]⁺ 403.2639, found 403.2614; IR νₘₐₓ 3441, 2943, 2932, 2866, 2209, 1672, 1464 cm⁻¹.

**Methyl (5R)-5-(2-hydroxyethyl)-6-methyl-2-methylidenehept-6-enoate 404**

![Chemical structure of Methyl (5R)-5-(2-hydroxyethyl)-6-methyl-2-methylidenehept-6-enoate 404]

Chemical Formula: C₁₃H₂₀O₃  
Molecular Weight: 212.2890

To a solution of carboxylic acid 395 (200 mg, 0.83 mmol) and DMAP (10 mg, 0.08 mmol) in CH₂Cl₂ (4 mL) and MeOH (0.2 mL) at 0 °C was added DCC (190 mg, 0.92 mmol). The resulting mixture was warmed to rt and stirred for 17 h. K₂CO₃ (23 mg, 0.17 mmol) and MeOH (4 mL) were added and the reaction stirred at rt for a further 6 hours. The reaction was quenched with saturated aq. NH₄Cl (5 mL) and AcOH (2 drops) and CH₂Cl₂ (5 mL) added. The phases were separated and the organic phase dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 7:3) afforded the methyl ester 404 as a colourless oil (176 mg, quant.). [α]⁺₀³³ +4.0 (c = 0.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.11 (1H, d, J = 1.4 Hz, CH₂-C⁵), 5.52 (1H, d, J = 1.4 Hz, CH₂-C⁴), 4.80 (1H, dq, J = 2.6, 1.4 Hz, CH₂-C₁₆), 4.76 (1H, dq, J = 2.6, 0.7 Hz, CH₂-C₁₆), 3.74 (3H, s, OCH₃), 3.65–3.54 (2H, m, CH₂-C₃), 2.31–2.21 (2H, m, CH₂-C₁₃), 2.15 (1H, dddd, J = 14.6, 9.0, 6.6, 1.2 Hz, CH-C₁), 1.64 (3H, dd, J = 1.4, 0.7 Hz, CH₃-C₁₇), 1.64–1.59 (2H, m, CH₂-C₂), 1.54–1.47 (2H, m, CH₂-C₁₄); ¹³C NMR (126 MHz, CDCl₃) δ 167.8 (C-C₂₁), 147.0 (C-C₂₁), 140.8 (C-C₁₂), 124.9 (CH₂-C⁴), 112.7 (CH₂-C₁₆), 61.5 (CH₂-C₃), 51.9 (OCH₃), 44.1 (CH-C₁), 36.2 (CH₂-C₂), 32.3 (CH₂-C₁₃), 30.1 (CH₂-C₁₄), 17.7 (CH₃-C₁₇); HRMS (ESI⁺) calcd for C₁₂H₂₀O₃Na [M+Na]⁺ 235.1305, found 235.1299; IR νₘₐₓ 3392, 3076, 2936, 2860, 1721, 1644, 1628, 1440 cm⁻¹

**1,9-Dimethyl (5R)-2-methylidene-7-oxo-5-(prop-1-en-2-yl)nonanedioate 406**

![Chemical structure of 1,9-Dimethyl (5R)-2-methylidene-7-oxo-5-(prop-1-en-2-yl)nonanedioate 406]

Chemical Formula: C₁₅H₂₂O₅  
Molecular Weight: 282.3360

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To a solution of alcohol 404 (176 mg, 0.83 mmol) in CH₂Cl₂ (8 mL) was added Dess-Martin periodinane (422 mg, 0.99 mmol). The resulting mixture was stirred at rt for 2.5 h and the reaction was then quenched with saturated aq. Na₂S₂O₃ (10 mL). The phases were separated and the organic phase washed with saturated aq. Na₂S₂O₃ (2 × 10 mL), then dried over Na₂SO₄ and filtered to afford the crude aldehyde 405 which was used without further purification.

To a solution of glycine methyl ester hydrochloride (627 mg, 4.98 mmol) in CH₂Cl₂ (1.7 mL) was added a solution of NaNO₂ (414 mg, 5.98 mmol) in H₂O (0.6 mL). The biphasic mixture was stirred for 1.5 h at rt and then saturated aq. NaHCO₃ (0.5 mL) was added. The phases were separated and the organic phase was dried over MgSO₄ and filtered. The solution of methyl diazoacetate was then used directly.

To a solution of the crude aldehyde 405 and SnCl₂ (166 mg, 0.83 mmol) in CH₂Cl₂ (12.5 mL) was added the freshly prepared solution of methyl diazoacetate (1.7 mL, 4.98 mmol). The resulting mixture was stirred at rt for 1.5 h and the excess diazo ester was destroyed by dropwise addition of glacial acetic acid (0.1 mL). The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 8:2) to afford the title compound 406 (tautomeric mixture by NMR) as a colourless oil (98 mg, 40%).

α+28 (c = 0.007, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 11.98 (0.1H, s, OH-C3 enol), 6.13 (1H, d, J = 1.4 Hz, CH₂-C⁸), 5.54 (0.9H, d, J = 1.4 Hz, CH₂-C⁸), 5.53 (0.1H, d, J = 1.7 Hz, CH₂-C⁸ enol), 4.95 (0.1H, s, CH-C4 enol), 4.83–4.81 (1H, m CH₂-C₁₆), 4.76 (1H, s, CH₂-C₁₆), 3.74 (3H, s, OCH₃), 3.73 (2.7H, s, CH₃-C₁₉), 3.72 (0.3H, s, CH₃-C₁₉ enol), 3.43 (1.8H, d, J = 1.3 Hz, CH₂-C⁴), 2.70–2.56 (3H, m, CH-C₁, CH₂-C₂), 2.30–2.23 (1H, m, CH₂-C₁₃), 2.20–2.12 (1H, m, CH₂-C₁₃), 1.68–1.66 (2.7H, m, CH₃-C₁₇), 1.66–1.65 (0.3H, s, CH₃-C₁₇ enol), 1.59–1.50 (2H, m, CH₂-C₁₄); ¹³C NMR (126 MHz, CDCl₃) δ 201.7 (C-C₃), 167.7 (C-C₂₁), 167.7 (C-C₁₈), 145.8 (C-C₁₅), 140.3 (C-C₁₂), 125.2 (CH₂-C⁸), 112.9 (CH₂-C₁₆), 52.5 (CH₃-C₁₉), 51.9 (OCH₃), 49.5 (CH₂-C₄), 47.5 (CH₂-C₂), 42.1 (CH-C₁), 31.8 (CH₂-C₁₃), 29.8 (CH₂-C₁₄), 18.9 (CH₃-C₁₇); HRMS (ESI⁺) calcd for C₁₅H₂₂O₃Na [M+Na]⁺ 305.1359, found 305.1350; IR νmax 2953, 2926, 2857, 2361, 2336, 1749, 1719, 1645, 1630, 1437 cm⁻¹.

**Methyl 4-[(3R)-2,2-dimethyloxolan-3-yl]-2-methylidenebutanoate 408**

![Chemical Structure](image)
To a solution of acetate 407 (50 mg, 0.21 mmol) in MeOH (3.5 mL) was added HCl (1.5 mL of a 5 M aqueous solution, 7.5 mmol) and the resultant stirred at rt for 72 h. Et₂O (10 mL) was added and the phases separated. The organic phase was dried over Na₂SO₄, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 8:2) afforded methyl ester 408 as a yellow oil (28 mg, 63%). [α]ᵢ₃¹⁻¹⁴ (c = 0.055, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.16–6.13 (1H, m, CH₂-C₅), 5.55 (1H, d, J = 1.4 Hz, CH₂-C₅), 3.83 (1H, td, J = 8.7, 3.2 Hz, CH₂-C₃), 3.78–3.71 (4H, m, OCH₃, CH₂-C₃), 2.44–2.34 (1H, m, CH₂-C₁₃), 2.32–2.22 (1H, m, CH₂-C₁₃), 2.13 (1H, dtd, J = 11.9, 7.4, 3.2 Hz, CH₂-C₂), 1.80–1.69 (1H, m, CH₃-C₁), 1.68–1.50 (2H, m, CH₂-C₂, CH₂-C₁₄), 1.38–1.26 (1H, m, CH₂-C₁₄), 1.23 (3H, s, CH₃-C₁₆), 0.99 (3H, s, CH₃-C₁₇); ¹³C NMR (101 MHz, CDCl₃) δ 167.7 (C-C₂₁), 140.6 (C-C₁₂), 124.9 (CH₂-C₅), 81.7 (C-C₁₅), 64.9 (CH₂-C₃), 51.9 (OCH₃), 48.4 (CH-C¹), 32.1 (CH₂-C₂), 31.5 (CH₂-C₁₃), 29.5 (CH₂-C₁₄), 27.7 (CH₃-C₁₆), 22.1 (CH₃-C₁₇); HRMS (ESI⁺) calcd. for C₁₂H₂₀O₃Na [M+Na]⁺ 235.1305, found 235.1302; IR νmax 2969, 2934, 2873, 1721, 1631, 1438 cm⁻¹.


β-keto ester 406 (18 mg, 0.06 mmol) and propargylic aldehyde 402 (26 mg, 0.08 mmol) were dissolved in a solution of piperidine in CH₂Cl₂ (0.2 mL, 0.03 M, 0.006 mmol) in the presence of 4 Å molecular seives and THT (1 μL, 0.013 mmol) and AcOH (2 μL, 0.038 mmol) were added. The resulting mixture was heated to 35 °C and stirred at this temperature for 15 h. The solvent was removed under vacuum and the residue purified by silica gel column.
chromatography (pet. ether:Et₂O, 80:20 → 75:25) to afford the epoxynuran 412 (1:1 mixture of diastereoisomers) as a colourless oil (1.1 mg, 3%) followed by the acetate 413 (~3:2 mixture of diastereoisomers) as a colourless oil (7.2 mg, 17%). **Epoxyynuran 412:** ¹H NMR (400 MHz, CDCl₃) δ 6.82 (0.5H, s, CH-C5), 6.81 (0.5H, s, CH-C5), 6.26 (0.5H, d, J = 1.6 Hz, CH₂-C⁴), 6.25 (0.5H, d, J = 1.6 Hz, CH₂-C⁴), 5.72–5.54 (1.5H, m, CH-C11, CH-C⁵), 5.49–5.42 (0.5H, m, CH-C11), 5.40 (0.5H, d, J = 1.6 Hz, CH₂-C⁴), 5.37 (0.5H, d, J = 1.6 Hz, CH₂-C⁴), 4.92–4.89 (1H, m, CH₂-C16), 4.87–4.84 (1H, m, CH₂-C16), 4.53–4.42 (1H, m, CH-C10), 3.82 (0.5H, s, CH-C7), 3.59 (0.5H, s, CH-C7), 3.53 (1.5H, s, CH₃-C19), 3.53 (1.5H, s, CH₃-C19), 3.46 (1H, s, OCH₃), 3.46 (1.5H, s, OCH₃), 3.43–3.31 (1H, m, CH₂-C2), 3.23 (0.5H, dd, J = 14.3, 8.5 Hz, CH₂-C16), 3.11 (0.5H, dd, J = 14.3, 6.5 Hz, CH₂-C2), 2.96–2.83 (1H, m, CH-C1), 2.41 (0.5H, dd, J = 13.5, 4.8 Hz, CH₂-C13), 2.35–2.24 (1.5H, m, CH-C13), 2.18–2.01 (3H, m, CH₂-C9, CH₂-C⁷), 1.83 (1.5H, s, CH₃-C17), 1.80 (1.5H, s, CH₃-C17), 1.79–1.63 (3H, m, CH₂-C9, CH₂-C14), 1.48 (3H, s, CH₃-C20), 1.45–1.36 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.31–1.17 (21H, m, CH(CH₃)₂), 0.99 (3H, t, J = 7.0 Hz, CH₃-C⁵); HRMS (ESI⁺) calc'd for C₉H₆O₃SiNa [M+Na]⁺ 667.4000, found 667.3889; IR νmax 2950, 2926, 2866, 1719, 1645, 1630, 1617, 1579, 1462, 1439 cm⁻¹. **Acetate 413:** ¹H NMR (500 MHz, CDCl₃) δ 6.90 (0.4H, s, CH-C5), 6.86 (0.6H, s, CH-C5), 6.17 (0.4H, d, J = 1.6 Hz, CH₂-C⁴), 6.16 (0.6H, d, J = 1.6 Hz, CH₂-C⁴), 6.11 (0.4H, s, CH-C7), 6.09 (0.6H, s, CH-C7), 5.62–5.48 (2H, m, CH-C11, CH-C⁵), 5.30 (0.4H, d, J = 1.6 Hz, CH₂-C⁴), 5.29 (0.6H, d, J = 1.6 Hz, CH₂-C⁴), 4.78–4.70 (3H, m, CH₂-C16, CH-C10), 4.25 (0.6H, s, OH-C8), 4.10 (0.4H, s, OH-C8), 3.41 (1.8H, s, CH₃-C19), 3.41 (1.2H, s, CH₃-C19), 3.37 (1.2H, s, OCH₃), 3.36 (1.8H, s, OCH₃), 3.16–3.05 (2H, m, CH₂-C2), 2.75 (1H, dtd, J = 14.8, 9.2, 5.7 Hz, CH-C1), 2.43–2.30 (2H, m, CH₂-C9, CH₂-C13), 2.24–2.10 (2H, m, CH₂-C9, CH₂-C13), 1.96–1.85 (3H, m, CH₂-C14, CH₂-C⁷), 1.72 (4.8H, s, CH₃-C17, CH₃-C20), 1.69 (1.2H, s, CH₃-C17), 1.64–1.53 (2.2H, m, CH₂-C14, Ac-CH₃), 1.46 (1.8H, s, Ac-CH₃), 1.34–1.19 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.18–1.07 (21H, m, CH(CH₃)₂), 0.90–0.83 (3H, m, CH₃-C⁵); ¹³C NMR (126 MHz, CDCl₃) δ 169.4 (Ac-C=O), 169.3 (Ac-C=O), 167.2 (C-C21), 164.0 (C-C18), 161.7 (C-C3), 161.7 (C-C3), 150.2 (C-C6), 150.2 (C-C6), 146.4 (C-C15), 146.3 (C-C15), 141.2 (C-C12), 141.1 (C-C12), 133.9 (CH-C⁰), 133.8 (CH-C⁰), 132.4 (CH-C11), 132.3 (CH-C11), 124.5 (CH₂-C⁷), 124.5 (CH₂-C⁷), 115.0 (C-C⁴), 114.9 (C-C⁴), 113.1 (CH₂-C16), 113.0 (CH₂-C16), 110.8 (CH-C5), 110.7 (CH-C5), 75.3 (CH-C7), 75.2 (CH-C7), 73.9 (CH-C10), 73.7 (C-C8), 73.5 (C-C8), 51.3 (OCH₃), 50.8 (CH₃-C19), 47.0 (CH-C1), 32.2 (CH₂-C2), 32.2 (CH₂-C2), 32.1 (CH₂-C⁵), 32.0 (CH₂-C14), 32.0 (CH₂-C14), 31.3 (CH₂-C⁰), 31.3 (CH₂-C⁰), 30.5 (CH₂-C13), 30.4 (CH₂-C9), 24.0 (Ac-CH₃), 23.5 (Ac-CH₃), 22.7 (CH₂-C⁷), 22.7 (CH₂-C⁷), 20.5 (CH₂-C20), 18.5 (CH(CH₃)₂), 18.4 (CH(CH₃)₂), 18.1 (CH₂-C17), 18.0 (CH₃-C17), 14.1 (CH₃-C⁵), 14.1 (CH₃-C⁵), 13.2 (CH(CH₃)₂); IR νmax 3486, 2950, 2929, 2867, 1747, 1722, 1646, 1629, 1612, 1576, 1458, 1438 cm⁻¹.
To a solution of carboxylic acid 395 (50 mg, 0.21 mmol), 2-(trimethylsilyl)ethanol (0.06 mL, 0.4 mmol) and DMAP (2.6 mg, 0.02 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added DCC (48 mg, 0.23 mmol). The resulting mixture was warmed to rt and stirred for 17 h. The mixture was filtered and the solid washed with Et$_2$O (5 mL). The filtrate was collected and the solvent removed under vacuum to yield the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et$_2$O, 93:7 → 9:1) afforded the ester 414 as a colourless oil (62.5 mg, 87%).

$\text{1H NMR (400 MHz, CDCl}_3 \delta$ 6.10 (1H, d, $J = 1.4$ Hz, CH$_2$-$C_4$), 5.50 (1H, d, $J = 1.4$ Hz, CH$_2$-$C_4$), 4.83–4.80 (1H, m, CH$_2$-$C_{16}$), 4.74–4.72 (1H, m, CH$_2$-C16), 4.27–4.21 (2H, m, (CH$_3$)$_3$SiCH$_2$C$_3$H$_2$O), 4.08–3.92 (2H, m, CH$_2$-$C_3$), 2.31–2.10 (3H, m, CH$_2$-C1, CH$_2$-C2), 2.03 (3H, s, Ac-$C_3$H$_3$), 1.76–1.64 (2H, m, CH$_2$-$C_{13}$), 1.64 (3H, dd, $J = 1.4$, 0.8 Hz, CH$_2$-C17), 1.56–1.48 (2H, m, CH$_2$-C14), 1.07–0.99 (2H, m, (CH$_3$)$_3$SiCH$_2$CH$_2$O), 0.05 (9H, s, (CH$_3$)$_3$SiCH$_2$CH$_2$O); $\text{13C NMR (101 MHz, CDCl}_3 \delta$ 171.3 (Ac-$C$(O)), 167.5 (C-C21), 145.7 (C-C15), 141.2 (C-C12), 124.5 (CH$_2$-$C^4$), 113.2 (CH$_2$-C16), 63.1 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), 63.0 (CH$_2$-C3), 44.0 (CH-C1), 32.3 (CH$_2$-C2), 32.0 (CH$_2$-C13), 30.1 (CH$_2$-C14), 21.1 (Ac-$C_3$H$_3$), 17.8 (CH$_3$-C17), 17.5 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), −1.3 ((CH$_3$)$_3$SiCH$_2$CH$_2$O); HRMS (ESI$^+$) calcd for C$_{18}$H$_{32}$O$_4$SiNa $[M+Na]^+$ 363.1962, found 363.1946; IR $\nu$$_{\text{max}}$ 2953, 2899, 2350, 2310, 1742, 1713, 1645, 1630, 1452, 1440 cm$^{-1}$

To a solution of the acetate 414 (1.70 g, 4.99 mmol) in MeOH (43 mL) was added K$_2$CO$_3$ (138 mg, 0.998 mmol) and the resulting mixture was stirred at rt for 3 h. Saturated aq. NH$_4$Cl (50 mL) and CH$_2$Cl$_2$ (100 mL) were added and the phases were separated. The organic
phase was dried over Na$_2$SO$_4$ and filtered. Removal of the solvent under vacuum afforded the crude alcohol which was used directly in the next step.

The crude alcohol was dissolved in CH$_2$Cl$_2$ (25 mL) and Dess-Martin periodinane (2.54 g, 5.99 mmol) added. The resulting mixture was stirred at rt for 3 h and the reaction was then quenched with saturated aq. Na$_2$S$_2$O$_3$ (25 mL). The phases were separated and the organic phase washed with saturated aq. Na$_2$S$_2$O$_3$ (2 × 25 mL), then dried over Na$_2$SO$_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to deliver the aldehyde 415 as a colourless oil (1.24 g, 84%).

-3.2 (c = 0.29, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.68 (1H, t, J = 2.2 Hz, CHO-C3), 6.12 (1H, s, CH$_2$-C$^A$), 5.52 (1H, s, CH$_2$-C$^A$), 4.84 (1H, s, CH$_2$-C16), 4.80 (1H, s, CH$_2$-C16), 4.24 (2H, dd, J = 9.3, 7.8 Hz, ((CH$_3$)$_3$SiCH$_2$CH$_2$O)), 2.75 – 2.67 (1H, m, CH-), 2.53 – 2.37 (2H, m, CH$_2$-C2), 2.35 – 2.14 (2H, m, CH$_2$-C13), 1.68 (3H, s, CH$_3$-C17), 1.62 – 1.54 (2H, m, CH$_2$-C14), 1.03 (2H, dd, J = 9.3, 7.8 Hz, ((CH$_3$)$_3$SiCH$_2$CH$_2$O)), 0.05 (9H, s, ((CH$_3$)$_3$SiCH$_2$CH$_2$O)); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.3 (CHO-C3), 167.4 (C-C21), 145.5 (C-C15), 140.8 (C-C12), 124.8 (CH$_2$-C$^A$), 113.2 (CH$_2$-C16), 63.1 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), 47.5 (CH-C1), 41.4 (CH$_2$-C2), 32.0 (CH$_2$-C13), 29.8 (CH$_2$-C14), 18.7 (CH$_2$-C17), 17.5 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), −1.3 ((CH$_3$)$_3$SiCH$_2$CH$_2$O); HRMS (ESI$^+$) calcd for C$_{16}$H$_{28}$O$_3$SiNa [M+Na]$^+$ 319.1700, found 319.1690; IR $\nu$$_{max}$ 2953, 2918, 2723, 1714, 1646, 1630, 1406 cm$^{-1}$

**1-Methyl 9-(trimethylsilyl)ethyl 8-methylidene-3-oxo-5-(prop-1-en-2-yl)nonanedioate 416**

To a solution of glycine methyl ester hydrochloride (10.5 g, 83.8 mmol) in CH$_2$Cl$_2$ (28 mL) was added a solution of NaNO$_2$ (6.94 g, 101 mmol) in H$_2$O (11 mL). The biphasic mixture was stirred for 1.5 h at rt and then saturated aq. NaHCO$_3$ (2 mL) was added. The phases were separated and the organic phase was dried over MgSO$_4$ and filtered. The solution of methyl diazoacetate was then used directly.

To a solution of the aldehyde 415 (1.24 g, 4.19 mmol) and SnCl$_2$ (945 mg, 4.98 mmol) in CH$_2$Cl$_2$ (40 mL) was added the freshly prepared solution of methyl diazoacetate (14 mL, 42
mmol). The resulting mixture was stirred at rt for 16 h and the excess diazo ester was destroyed by dropwise addition of glacial acetic acid (1 mL). The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to afford the title compound 416 (tautemic mixture by NMR) as a yellow oil (1.03 g, 67%). [α]D20 +2.2 (c = 0.51, CHCl3); 1H NMR (500 MHz, CDCl3) δ 11.98 (0.1H, s, (OH-C3 enol), 6.11 (1H, d, J = 1.4 Hz, CH2-C^), 5.52 (0.9H, app q, J = 1.4 Hz, CH2-C^), 5.50 (0.1H, app q, J = 1.4 Hz, CH2-C^ enol), 4.95 (0.1H, s, CH-C4 enol), 4.81 (1H, dq, J = 1.5, 1.4 Hz, CH2-C16), 4.77–4.75 (1H, m, CH2-C16), 4.28–4.19 (2H, m, (CH3)3SiCH2CH2O), 3.73 (2.7H, s, CH3-C19), 3.71 (0.3H, s, CH3-C19 enol), 3.42 (1.8H, app d, J = 1.3 Hz, CH2-C4), 2.71–2.55 (3H, m, CH-C1, CH2-C2), 2.31–2.22 (1H, m, CH2-C13), 2.19–2.10 (1H, m, CH2-C13), 1.68–1.67 (2.7H, m, CH3-C17), 1.66–1.64 (0.3H, m, CH3-C17 enol), 1.57–1.49 (2H, m, CH2-C14), 1.06–1.00 (2H, m, (CH3)3SiCH2CH2O), 0.05 (9H, s, (CH3)3SiCH2CH2O); 13C NMR (126 MHz, CDCl3) δ 201.7 (C-C3), 167.7 (C-C21), 167.4 (C-C18), 145.8 (C-C15), 140.8 (C-C12), 124.7 (CH2-C^), 112.8 (CH2-C16), 63.0 ((CH3)3SiCH2CH2O), 52.5 (CH3-C19), 49.5 (CH2-C4), 47.5 (CH2-C2), 42.1 (CH-C1), 31.9 (CH2-C13), 29.8 (CH2-C14), 19.0 (CH3-C17), 17.4 ((CH3)3SiCH2CH2O), −1.3 ((CH3)3SiCH2CH2O); HRMS (ESI+) calcd for C18H32O8SiNa [M+Na]^+ 391.1911, found 391.1911; IR v max 2954, 2925, 2899, 2861, 1750, 1714, 1646, 1630, 1449, 1437, 1406 cm⁻¹

β-keto ester 416 (53 mg, 0.145 mmol) and propargylic aldehyde 402 (49 mg, 0.145 mmol) were dissolved in a solution of piperidine and AcOH in THT (0.028 M, 0.5 mL, 0.014 mmol) in the presence of 4 Å molecular sieves. The resulting mixture was heated to 43 °C and stirred at this temperature for 15 h. The solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:Et₂O, 9:1 → 8:2) to afford the epoxynuran 417 (1:1 mixture of diastereoisomers) as a colourless oil (25 mg, 24%) followed by the acetate 418 (3:2 mixture of diastereoisomers) as a colourless oil (25.5 mg, 22%).

**Epoxynuran 417:** ¹H NMR (400 MHz, C₆D₆) δ 6.71 (0.5H, s, CH-C5), 6.70 (0.5H, s, CH-C5), 6.26 (0.5H, d, J = 1.7 Hz, CH₂-C⁶), 6.25 (0.5H, d, J = 1.7 Hz, CH₂-C⁶), 5.62–5.44 (2H, m, CH-C11, CH-C⁶), 5.36 (0.5H, d, J = 1.7 Hz, CH₂-C⁶), 5.33 (0.5H, d, J = 1.7 Hz, CH₂-C⁶), 4.84–4.82 (1H, m, CH₂-C16), 4.80–4.78 (0.5H, m, CH₂-C16), 4.76 (0.5H, dq, J = 2.9, 1.4 Hz, CH₂-C16), 4.42–4.32 (1H, m, CH-C10), 4.25–4.19 (2H, m, (CH₃)₃SiCH₂CH₂O), 3.72 (0.5H, s, CH-C7), 3.50 (0.5H, s, CH-C7), 3.44 (1.5H, s, CH₃-C19), 3.43 (1.5H, s, CH₃-C19), 3.33–3.24 (1H, m, CH₂-C2), 3.14 (0.5H, dd, J = 14.3, 8.4 Hz, CH₂-C2), 3.03 (0.5H, dd, J = 14.3, 6.6 Hz, CH₂-C2), 2.88–2.75 (1H, m, CH-C1), 2.57–2.42 (1.5H, m, CH₂-C13), 2.36–2.23 (2H, m, CH₂-C⁵), 2.17 (0.5H, dd, J = 13.7, 5.2 Hz, CH₂-C13), 2.06–1.91 (3H, m, CH₂-C9, CH₂-C14), 1.75 (1.5H, s, CH₃-C17), 1.74–1.64 (2.5H, s, CH₃-C17, CH₂-C14), 1.39 (1.5H, s, CH₃-C20), 1.38 (1.5H, s, CH₃-C20), 1.36–1.26 (4H, m, CH₂-C⁵, CH₂-C⁵), 1.17–1.06 (21H, m, CH(CH₃)₂), 0.92–0.86 (5H, s, CH₃-C⁵, (CH₃)₃SiCH₂CH₂O), −0.09 (8H, s, (CH₃)₃SiCH₂CH₂O); ¹³C NMR (126 MHz, C₆D₆) δ 166.9 (C-C21), 166.9 (C-C21), 163.9 (C-C18), 163.9 (C-C18), 161.9 (C-C3), 161.9 (C-C3), 149.8 (C-C6), 149.8 (C-C6), 146.4 (C-C15), 146.3 (C-C15), 141.7 (C-C12), 133.5 (CH-C⁵), 131.7 (CH-C11), 131.5 (CH-C11), 124.2 (CH₂-C⁶), 124.1 (CH₂-C⁶), 115.2 (C-C4), 115.1 (C-C4), 113.1 (CH₂-C16), 112.9 (CH₂-C16), 109.6 (CH-C5), 72.9 (CH-C10), 72.2 (CH-C10), 62.7 ((CH₃)₃SiCH₂CH₂O), 62.2 (C-C8), 61.4 (C-C8), 58.6 (CH-C7), 58.1 (CH-C7), 50.9 (CH₃-C19), 46.9 (CH-C1), 46.8 (CH-C1), 41.4 (CH₂-C9), 32.5 (CH₂-C2), 32.4 (CH₂-C2), 32.3 (CH₂-C⁵), 32.2 (CH₂-C⁵), 32.1 (CH₂-C14), 31.9 (CH₂-C14), 31.7 (CH₂-C⁵), 30.5 (CH₂-C13), 30.4 (CH₂-C13), 23.2 (CH₂-C⁵) 22.8 (CH₃-C20), 22.7 (CH₃-C20), 18.5 (CH(CH₃)₂) 18.4 (CH(CH₃)₂), 17.5 ((CH₃)₃SiCH₂O), 14.2 (CH₃-C⁵), 12.8 (CH(CH₃)₂), −1.6 ((CH₃)₃SiCH₂O); HRMS (ESI⁺) calcd for C₄₁H₇₀O₇Si₂Na [M+Na]⁺ 753.4552, found 753.4517; IR νmax 2953, 2924, 2866, 1719, 1645, 1631, 1580, 1462, 1438 cm⁻¹. **Acetate 418:** ¹H NMR (500 MHz, C₆D₆) δ 6.89 (0.4H, s, CH-C5), 6.85 (0.6H, s, CH-C5), 6.27 (0.4H, d, J = 1.8 Hz, CH₂-C⁶), 6.25 (0.6H, d, J = 1.7 Hz, CH₂-C⁶), 6.11 (0.4H, s, CH-C7), 6.08 (0.6H, s, CH-C7), 5.61–5.48 (2H, m, CH-C11, CH-C⁵), 5.37–5.34 (1H, m, CH₂-C⁶), 4.80–4.70 (3H, m, CH₂-C16, CH-C10), 4.27–4.19 (2H, m, (CH₃)₃SiCH₂CH₂O), 3.42 (1.8H, s, CH₃-C19), 3.42 (1.2H, s, CH₃-C19), 3.17–3.08 (1.6H, m, CH₂-C2), 3.02 (0.4H, dd, J = 14.2, 5.8 Hz, CH₂-C2), 2.83–2.74 (1H, m, CH-C1), 2.51–2.43 (1H, m, CH₂-C9), 2.34 (0.6H, dd, J = 14.5, 9.1 Hz, CH₂-C13), 2.31–2.23 (2H, m, CH₂-C9, CH₂-C13), 2.13 (0.4H, dd, J = 14.3, 8.9 Hz, CH₂-C13).
1.96–1.89 (2H, m, CH₂–C), 1.78–1.59 (8H, m, CH₃–C₁₄, CH₃–C₁₇, CH₃–C₂₀), 1.55 (1.2H, s, Ac–CH₃), 1.46 (1.8H, s, Ac–CH₃), 1.34–1.21 (4H, m, CH₂–C⁰, CH₂–C⁵), 1.19–1.05 (21H, m, CH(CH₃)₂), 0.93–0.80 (5H, m, CH₃–C⁵, (CH₃)₂SiCH₂CH₂O), −0.08 (3.6H, s, (CH₃)₃SiCH₂CH₂O), −0.08 (5.4H, s, (CH₃)₂SiCH₂CH₂O); ¹³C NMR (126 MHz, C₆D₆) δ 169.4 (Ac–C=O), 169.3 (Ac–C–O), 166.9 (C–C₂₁), 164.0 (C–C₁₈), 161.8 (C–C₃), 161.7 (C–C₃), 150.2 (C–C₆), 150.1 (C–C₆), 146.4 (C–C₁₅), 146.3 (C–C₁₅), 141.7 (C–C₁₂), 133.9 (CH–C⁵), 133.9 (CH–C⁵), 132.4 (CH–C₁₁), 132.3 (CH–C₁₁), 124.1 (CH₂–C⁴), 114.9 (C–C₄), 113.1 (CH₂–C₁₆), 110.9 (CH–C₅), 110.8 (CH–C₅), 75.3 (CH–C₇), 75.2 (CH–C₇), 73.9 (CH–C₁₀), 73.7 (C–C₈), 73.5 (C–C₈), 62.7 ((CH₃)₂SiCH₂CH₂O), 50.8 (CH₃–C₁₉), 47.0 (CH–C₁), 32.2 (CH₂–C₂), 32.2 (CH₂–C₂), 32.1 (CH₂–C⁵), 32.1 (CH₂–C₁₄), 31.3 (CH₂–C⁰), 31.3 (CH₂–C⁵), 30.5 (CH₂–C₁₃), 30.5 (CH₂–C₉), 24.1 (OAc–CH₃), 22.7 (CH₂–C⁵), 22.7 (CH₂–C⁵), 20.6 (CH₃–C₂₀), 18.5 (CH(CH₃)₂), 18.4 (CH(CH₃)₂), 18.1 (CH₃–C₁₇), 17.5 ((CH₃)₂SiCH₂CH₂O), 14.1 (CH₃–C⁵), 13.2 (CH(CH₃)₂), −1.5 ((CH₃)₃SiCH₂CH₂O); HRMS (ESI⁺) calcd for C₄₃H₇₄O₉Si₃Na [M+Na]+ 813.4764, found 813.4727; IR νₘₚₙₐₓ 3489, 2952, 2925, 2867, 1745, 1716, 1644, 1630, 1613, 1573, 1462, 1439 cm⁻¹.


![Chemical Structure](image)

**Chemical Formula:** C₂₂H₃₆O₆

**Molecular Weight:** 456.5790

To a solution of the epoxifuran 417 (30 mg, 0.04 mmol) in THF (0.2 mL) at 10 °C was added TBAF (0.09 mL of a 1 M solution in THF, 0.09 mmol) and the resulting mixture was stirred for 3 h. H₂O (0.5 mL) and Et₂O (2 mL) were added and the phases were separated. The aqueous phase was washed with Et₂O (2 × 2 mL) and the combined organic extracts were dried over Na₂SO₄ and filtered. The solvent was removed under vacuum to yield crude seco-acid 419, which was used directly in the next step.

To a solution of the crude seco-acid 419 in benzene (4 mL) at rt was added DIPEA (0.10 mL, 0.60 mmol) followed by trichlorobenzoyl chloride (0.06 mL, 0.40 mmol) and the resulting mixture was stirred for 4.5 h. A solution of DMAP (195 mg, 1.60 mmol) in benzene (16 mL) was added and the mixture stirred for a further 11.5 h. H₂O (30 mL) and Et₂O (20 mL) were added and the phases separated. The organic phase was washed with brine (30 mL), dried
over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 93:7) to deliver the macrolactone 420 as a single isomer and colourless oil (4.7 mg, 25%). [α]°D −17.8 (c = 0.45, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.70 (1H, s, CH-C5), 6.28 (1H, d, J = 1.8 Hz, CH₂-C¹), 5.69–5.62 (2H, m, CH-C10, CH-C⁵), 5.29 (1H, ddt, J = 15.4, 7.7, 1.5 Hz, CH-C11), 5.12 (1H, d, J = 1.8 Hz, CH₂-C⁴), 4.78 (1H, dq, J = 1.7 Hz, CH₂-C16), 4.75 (1H, d, J = 1.7 Hz, CH₂-C16), 3.45 (3H, s, CH₃-C19), 3.37 (1H, s, CH-C7), 3.33 (1H, dd, J = 15.3, 12.2 Hz, CH₂-C2), 3.00 (1H, dd, J = 15.3, 3.6 Hz, CH₂-C2), 2.74 (1H, ddt, J = 12.2, 8.2, 3.6 Hz, CH-C1), 2.33–2.25 (2H, m, CH₂-C9, CH₂-C13), 2.18–2.11 (2H, m, CH₂-C9, CH₂-C13), 1.87–1.81 (2H, m, CH₂-C⁵), 1.78–1.70 (1H, m, CH₂-C14), 1.58–1.56 (3H, m, CH₃-C17), 1.56–1.47 (1H, m, CH₂-C14), 1.21–1.16 (4H, m, CH₂-C⁰, CH₂-C⁵), 1.13 (3H, s, CH₃-C20), 0.82 (3H, t, J = 7.0 Hz, CH₃-C⁵); ¹³C NMR (126 MHz, CDCl₃) δ 166.1 (C-C21), 163.7 (C-C18), 161.7 (C-C3), 148.9 (C-C6), 146.8 (C-C15), 141.0 (C-C12), 134.7 (CH-C⁵), 128.6 (CH-C11), 126.2 (CH₂-C⁹), 115.7 (C-C4), 111.8 (CH₂-C16), 111.1 (CH-C5), 73.3 (CH-C10), 61.9 (C-C8), 58.8 (CH-C7), 51.0 (CH₃-C19), 43.9 (CH-C1), 37.6 (CH₂-C9), 32.4 (CH₂-C2), 32.1 (CH₂-C⁵), 31.3 (CH₂-C⁵), 30.2 (CH₂-C13), 30.0 (CH₂-C14), 23.5 (CH₃-C20), 22.5 (CH₂-C⁵), 19.8 (CH₃-C17), 14.0 (CH₃-C⁵); HRMS (ESI⁺) calcd for C₂₂H₃₆O₇Na [M+Na]⁺ 479.2404, found 479.2386; IR νmax 2952, 2925, 2860, 1719, 1644, 1630, 1610, 1577, 1440 cm⁻¹.

(3S)-N-Methoxy-N-methyl-3-(triethylsilyloxy)pent-4-enamide 425

![Chemical Structure](image)

To a solution of (3S)-3-hydroxy-N-methoxy-N-methylpent-4-enamide 424 (400 mg, 2.51 mmol) in CH₂Cl₂ (25 mL) was added chlorotriethylsilane (0.51 mL, 3.01 mmol) and the resulting solution was stirred at rt for 14 h. Saturated aq. NH₄Cl (30 mL) was added and the phases were separated. The organic phase was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1 → 7:3) to give the silyl ether 425 as a colourless oil (650 mg, 95%). [α]°D −16 (c = 0.60, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.83 (1H, ddd, J = 17.1, 10.4, 5.9 Hz, CH-C11), 5.19 (1H, ddd, J = 17.1, 1.5, 1.5 Hz, CH₂-C⁵), 5.00 (1H, ddd, J = 10.4, 1.5, 1.5 Hz, CH₂-C⁵), 4.66–4.60 (1H, m, CH-C10), 3.62 (3H, s, NCH₃), 3.11 (3H, s, OCH₃), 2.75 (1H, dd, J = 14.7, 7.8 Hz, CH₂-C9), 2.38 (1H, dd, J = 14.7, 5.5 Hz, CH₂-C9), 0.87 (9H, t, J = 7.9 Hz, Si(CH₃)₃), 0.53 (6H, q, J = 7.9 Hz, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.8 (C-C8), 141.0 (CH-C11), 114.3 (CH₂-C⁵), 70.7 (CH-C10), 61.5 (OCH₃)
40.8 (NCH₃), 32.1 (CH₂-C9), 6.9 (Si(CH₂CH₃)₃), 4.9 (Si(CH₂CH₃)₃); HRMS (ESI⁺) calcd for C₁₃H₂₇NO₃SiNa [M+Na]⁺ 296.1652, found 296.1648; IR ν max 3078, 2955, 2941, 2913, 2878, 2822, 1663, 1460, 1414 cm⁻¹

(5S)-5-(Triethylsilyloxy)-1-(trisisopropylsilyl)hept-6-en-1-yn-3-one 426

To a solution of triisopropylsilylacetylene (1.97 mL, 8.78 mmol) in THF (20 mL) at 0 °C was added nBuLi (3.66 mL of a 2.4 M solution in hexanes, 8.78 mmol) and the resulting solution was stirred at 0 °C for 30 mins. A solution of the amide 425 (1.60 g, 5.85 mmol) in THF (15 mL) was added and the mixture stirred at 0 °C for 10 min then warmed to rt and stirred for 1 h. The reaction was quenched with saturated aq. NH₄Cl (40 mL) and Et₂O (20 mL) added. The phases were separated and the organic phase was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 100:0 → 95:5) to afford the propargylic ketone 426 as a colourless oil (2.10 g, 91%). [α]D²⁵ +2.8 (c = 0.36, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.85 (1H, ddd, J = 17.1, 10.3, 6.2 Hz, CH-C11), 5.24 (1H, ddd, J = 17.1, 1.4, 1.4 Hz, CH₂-C9), 5.08 (1H, ddd, J = 10.3, 1.4, 1.4 Hz, CH₂-C9), 4.78–4.72 (1H, m, CH-C10), 2.85 (1H, dd, J = 14.8, 7.6 Hz, CH₂-C9), 2.68 (1H, dd, J = 14.8, 5.6 Hz, CH₂-C9), 1.16–1.08 (21H, m, CH(CH₃)₂), 0.94 (9H, t, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.60 (6H, q, J = 7.9 Hz, Si(CH₂CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 185.0 (C-C8), 140.2 (CH-C11), 114.9 (CH₂-C9), 104.8 (C-C6), 96.2 (C-C7), 70.3 (CH-C10), 54.4 (CH₂-C9), 18.6 (CH(CH₃)₂), 11.2 (CH(CH₃)₂), 6.9 (Si(CH₂CH₃)₃), 5.0 (Si(CH₂CH₃)₃); HRMS (ESI⁺) calcd for C₂₂H₄₂O₂Si₂Na [M+Na]⁺ 417.2616, found 417.2616; IR ν max 2947, 2868, 2147, 1678, 1462, 1416 cm⁻¹

(5S)-5-(Hydroxy)-1-(trisisopropylsilyl)hept-6-en-1-yn-3-one 427

To a solution of propargylic ketone 426 (2.00 g, 5.05 mmol) in a mixture (3:1) of THF and MeOH (50 mL) at 0 °C was added PPTS (127 mg, 0.505 mmol) and the resulting solution was stirred for 4.5 h. The reaction was quenched with saturated aq. NaHCO₃ (40 mL) and EtOAc (50 mL) was then added. The phases were separated and the organic phase dried
over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 85:15 → 3:1) to deliver the β-hydroxy ketone 427 as a colourless oil (1.42 g, quant.). [α]₂⁰¹⁺⁰ =−5.8 (c = 0.12, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.88 (1H, ddd, J = 17.2, 10.5, 5.7 Hz, CH-C11), 5.33 (1H, ddd, J = 17.2, 1.4, 1.4 Hz, CH₂-C⁵), 5.17 (1H, ddd, J = 10.5, 1.4, 1.4 Hz, CH₂-C⁵), 4.71–4.65 (1H, m, CH-C10), 2.85 (2H, d, J = 6.1 Hz, CH₂-C9), 2.57 (1H, d, J = 4.2 Hz, OH-C10), 1.19–1.07 (21H, m, CH(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 186.1 (C₁), 138.7 (C₈), 115.7 (CH₂-C⁵), 104.2 (C-C₆), 97.5 (C-C₇), 68.7 (CH-C10), 52.3 (CH₂-C₉), 18.6 (CH(CH₃)₂), 11.1 (CH(CH₃)₂); HRMS (ESI⁺) calcd for C₁₆H₂₉O₂SiNa [M+Na]⁺ 303.1751, found 303.1751; IR νmax 3443, 2945, 2893, 2866, 2147, 1672, 1464, 1424 cm⁻¹

(3S,5R)-5-Methyl-7-(trisisopropylsilyl)hept-1-en-6-yne-3,5-diol syn-428 and (3S,5S)-5-Methyl-7-(trisisopropylsilyl)hept-1-en-6-yne-3,5-diol anti-428

To a solution of Ti(OiPr)₄ (27 mL, 91 mmol) in Et₂O (135 mL) at 0 °C was added TiCl₄ (3.0 mL, 27 mmol). The resulting solution was warmed to rt for 30 min and then cooled to 0 °C. MeLi (75 mL of a 1.6 M solution in Et₂O, 120 mmol) was added and the mixture was stirred for 1 h. A portion of the solution (150 mL) was added to a solution of β-hydroxy ketone 427 (1.20 g, 4.30 mmol) in Et₂O (95 mL) at −78 °C. The solution was stirred for 15 minutes, warmed to 0 °C and then stirred for 30 min. 2 M HCl (150 mL) was added dropwise and the biphasic mixture was warmed to rt. The phases were separated and the aqueous phase was extracted with Et₂O (2 × 150 mL). The combined organic extracts were washed with brine (300 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 6:4) to deliver the 1,3-diol anti-428 (172 mg, 9%) as a colourless oil (less polar isomer) followed by the diastereomeric 1,3-diol syn-428 (1.44 g, 88%) as a colourless oil (more polar isomer). syn-428: [α]₂⁰¹⁺⁰ =+7.0 (c = 0.22, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.92 (1H, ddd, J = 17.2, 10.4, 6.0 Hz, CH-C11), 5.31 (1H, ddd, J = 17.2, 1.4, 1.4 Hz, CH₂-C⁵), 5.13 (1H, ddd, J = 10.4, 1.4, 1.4 Hz, CH₂-C⁵), 4.61–4.55 (1H, m, CH-C10), 2.98 (1H, d, J = 2.5 Hz, OH-C10), 2.55 (1H, s, OH-C₈), 2.03 (1H, dd, J = 14.5, 9.3 Hz, CH₂-C₉), 1.90 (1H, dd, J = 14.5, 3.1 Hz, CH₂-C₉), 1.60 (3H, s, CH₃-C20), 1.12–0.97 (21H, m, CH(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 140.7 (CH-C11), 114.9, (CH₂-C⁵), 111.8 (C-C₆), 85.0 (C-C₇), 70.3 (CH-C10), 67.6 (C-C₈), 49.1 (CH₂-C₉), 30.4 (CH₃-C20), 18.7 (CH(CH₃)₂), 11.2 (CH(CH₃)₂); HRMS (ESI⁺) calcd for
C_{17}H_{32}O_{2}SiNa [M+Na]^+ 319.2064, found 319.2056; IR $v_{\text{max}}$ 3352, 2943, 2893, 2866, 2166, 1464 cm$^{-1}$. **anti-428:** [α]$^D_{[0]}$ +8.2 ($c$ = 0.11, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.93 (1H, ddd, $J$ = 17.2, 10.4, 6.0 Hz, CH-C11), 5.29 (1H, ddd, $J$ = 17.2, 1.4, 1.4 Hz, CH$_2$-C$_8$), 5.15 (1H, ddd, $J$ = 10.4, 1.4, 1.4 Hz, CH$_2$-C$_8$), 4.92–4.86 (1H, m, CH-C10), 3.88 (1H, s, OH-C8), 2.57 (1H, d, $J$ = 2.8 Hz, OH-C10), 1.95–1.73 (2H, m, CH$_2$-C9), 1.56 (3H, s, CH$_3$-C20), 1.12–1.08 (21H, m, CH(CH$_3$)$_2$); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 140.4 (CH-C11), 114.6 (CH$_2$-C$_8$), 111.7 (C-C6), 72.4 (C-C7), 69.8 (CH-C10), 68.7 (C-C8), 48.2 (CH$_2$-C9), 31.3 (CH$_3$-C20), 18.6 (CH(CH$_3$)$_2$), 11.2 (CH(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for C$_{17}$H$_{32}$O$_2$SiNa [M+Na]$^+$ 319.2064, found 319.2055; IR $v_{\text{max}}$ 3345, 2943, 2893, 2866, 2166, 1422 cm$^{-1}$

(3S,5R)-5-Methylhept-1-en-6-yne-3,5-diol **syn-429**

![Chemical Structure of syn-429](image)

To a solution of the 1,3-diol **syn-428** (1.40 g, 4.7 mmol) in THF (50 mL) was added TBAF (5.2 mL of a 1 M solution in THF, 5.2 mmol) and the resulting solution was stirred at rt for 1 h. Saturated aq. NH$_4$Cl (50 mL) and Et$_2$O (50 mL) were added and the phases were separated. The organic phase was washed with brine (50 mL), dried over Na$_2$SO$_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et$_2$O, 1:1 → 55:45) to give the 1,3-diol **syn-429** as a yellow oil (585 mg, 89%). [α]$^D_{[0]}$ +4.6 ($c$ = 0.24, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.92 (1H, ddd, $J$ = 17.1, 10.4, 6.0 Hz, CH-C11), 5.31 (1H, ddd, $J$ = 17.1, 1.4, 1.4 Hz, CH$_2$-C$_8$), 5.15 (1H, ddd, $J$ = 10.4, 1.4, 1.4 Hz, CH$_2$-C$_8$), 4.61–4.54 (1H, m, CH-C10), 2.94 (1H, s, OH-C8), 2.67 (1H, d, $J$ = 2.6 Hz, OH-C10), 2.53 (1H, s, CH-C6), 2.07 (1H, dd, $J$ = 14.6, 9.5 Hz, CH$_2$-C9), 1.90 (1H, dd, $J$ = 14.6, 3.1 Hz, CH$_2$-C9), 1.61 (3H, s, CH$_3$-C20); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 140.5 (CH-C11), 115.2 (CH$_2$-C$_8$), 87.9 (C-C7), 72.0 (CH-C6), 70.3 (CH-C10), 67.3 (C-C8), 48.4 (CH$_2$-C9), 29.7 (CH$_3$-C20); HRMS (ESI$^+$) calcd for C$_9$H$_{12}$O$_2$Na [M+Na]$^+$ 163.0730, found 163.0722; IR $v_{\text{max}}$ 3356, 3300, 3082, 2983, 2922, 2876, 2110, 1645, 1450, 1419, 1406 cm$^{-1}$
(3S,5R)-5-Methyl-3-(trisisopropylsilyloxy)hept-1-en-6-yn-5-ol 430

To a solution of NaH (71.6 mg of 60% dispersion in mineral oil, 1.79 mmol) in THF (2 mL) at 0 °C was added a solution of 1,3-diol syn-429 (250 mg, 1.79 mmol) in THF (4 mL). The resulting mixture was gradually warmed to rt and stirred for 20 min. Chlorotriisopropylsilane (0.38 mL, 1.8 mmol) was then added and the mixture was stirred at rt for 17 h. Brine (10 mL) and Et₂O (10 mL) were added and the phases separated. The organic phase was dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 7:3) to afford the alkyne 430 as a yellow oil (520 mg, 98%).

$\alpha$H NMR (400 MHz, CDCl₃) δ 6.15 (1H, ddd, $J = 17.2, 10.3, 7.9$ Hz, CH$_7$C$_1$), 5.27 (1H, ddd, $J = 17.2, 1.2, 1.1$ Hz, CH$_2$C$_6$B), 5.15 (1H, ddd, $J = 10.3, 1.1, 1.0$ Hz, CH$_2$C$_7$B), 4.72–4.66 (1H, m, CH$_3$C$_8$), 4.04 (1H, s, OH-C$_5$), 2.48 (1H, s, CH$_2$C$_6$), 2.09 (1H, dd, $J = 14.3, 5.2$ Hz, CH$_7$C$_8$), 1.99 (1H, dd, $J = 14.3, 6.7$ Hz, CH$_7$C$_9$), 1.53 (3H, s, CH$_3$C$_2$), 1.13–1.03 (21H, m, CH(CH$_3$_)$_2$); $^{13}$C NMR (101 MHz, CDCl₃) δ 142.0 (CH$_7$C$_1$), 115.9 (CH$_2$C$_7$B), 88.2 (C-C$_7$), 74.0 (CH-C$_1$0), 71.9 (CH-C$_6$), 66.8 (C-C$_8$), 49.4 (CH$_2$C$_9$), 31.1 (CH$_3$C$_2$), 18.2 (CH(CH$_3$)$_2$), 18.2 (CH(CH$_3$)$_2$), 12.5 (CH(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for C$_{17}$H$_{32}$O$_2$SiNa [M+Na]$^+$ 319.2064, found 319.2052; IR $\nu_{max}$ 3456, 3312, 2943, 2893, 2866, 1464, 1419 cm$^{-1}$

(3S,5R)-3,5-Bis(trisisopropylsilyloxy)-5-methylhept-1-en-6-yne 431

To a solution of 1,3-diol syn-429 (39 mg, 0.28 mmol) in CH$_2$Cl$_2$ (4 mL) at −78 °C was added 2,6-lutidine (0.14 mL, 1.2 mmol) followed by triisopropylsilyl trifluoromethanesulfonate (0.16 mL, 0.59 mmol). The resulting solution was gradually warmed to rt and then stirred for 24 h. Saturated aq. NaHCO$_3$ (5 mL) and Et₂O (5 mL) were added and the phases separated. The organic phase was dried over Na$_2$SO$_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether) to give the bis-silyl ether 431 as a yellow oil (122 mg, 97%). $\alpha$H NMR (400 MHz, CDCl$_3$) δ 6.00 (1H, ddd, $J = 17.2, 10.3, 6.9$ Hz, CH-C$_1$1), 5.20 (1H, ddd, $J = 17.2, 1.7, 1.1$ Hz, CH$_2$C$_7$B), 5.01 (1H, ddd, $J = 10.3, 1.7, 0.8$ Hz, CH$_2$C$_8$B), 4.62–4.55 (1H, m, CH-C$_1$0), 172
2.43 (1H, s, CH-C6), 2.07 (1H, dd, J = 13.7, 5.5 Hz, CH2-C9), 1.97 (1H, dd, J = 13.7, 6.7 Hz, CH2-C9), 1.57 (3H, s, CH3-C20), 1.26–0.98 (42H, m, CH(CH3)2); 13C NMR (101 MHz, CDCl3) δ 142.7 (CH-C11), 113.7 (CH2-C8), 88.6 (C-C7), 72.5 (CH-C10), 72.2 (CH-C6), 68.5 (C-C8), 54.0 (CH2-C9), 31.8 (CH3-C20), 18.6 (CH(CH3)2), 18.5 (CH(CH3)2), 18.4 (CH(CH3)2), 18.3 (CH(CH3)2), 13.3 (CH(CH3)2), 12.8 (CH(CH3)2); HRMS (ESI+) calcd for C26H32O2Si2Na [M+Na]+ 475.3398, found 475.3380; IR νmax 3310, 2960, 2943, 2926, 2866, 2892, 2866, 2892, 2866, 2866, 2866, 1464, 1419 cm−1

(4R,6S)-4-Hydroxy-4-methyl-6-(trisopropylsilyloxy)oct-7-en-2-ynal 432

To a solution of alkyne 430 (100 mg, 0.337 mmol) in THF (9 mL) at −78 °C was added nBuLi (0.3 mL of a 2.3 M solution in hexane, 0.70 mmol). The resulting solution was stirred for 5 mins and then warmed to 0 °C. DMF (0.06 mL, 0.84 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with 5% aq. KH2PO4 (10 mL) and Et2O (10 mL) was added. The phases were separated and the organic phase washed with brine (10 mL), dried over Na2SO4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et2O, 7:3) to deliver the propargylic aldehyde 432 as a colourless oil (99 mg, 90%). [α]D27 +8.6 (c = 0.04, CHCl3); 1H NMR (400 MHz, CDCl3) δ 9.24 (1H, s, CHO-C5), 6.14 (1H, ddd, J = 17.3, 10.3, 7.3 Hz, CH-C11), 5.28 (1H, ddd, J = 17.3, 1.2, 1.2 Hz, CH2-C8), 5.18 (1H, ddd, J = 10.3, 1.2, 1.2 Hz, CH2-C9), 4.73 (1H, s, OH-C8), 4.72–4.67 (1H, m, CH-C10), 2.12 (2H, d, J = 5.2 Hz, CH2-C9), 1.58 (3H, s, CH3-C20), 1.11–1.04 (21H, m, CH(CH3)2); 13C NMR (101 MHz, CDCl3) δ 176.8 (CHO-C5), 140.6 (CH-C11), 116.1 (CH2-C8), 100.3 (C-C7), 83.4 (C-C6), 74.0 (CH-C10), 67.1 (C-C8), 47.9 (CH2-C9), 30.6 (CH3-C20), 18.1 (CH(CH3)2), 18.0 (CH(CH3)2), 12.3 (CH(CH3)2); HRMS (ESI+) calcd for C18H32O3SiNa [M+Na]+ 347.2013, found 347.1903; IR νmax 3446, 2943, 2893, 2866, 2206, 1670, 1464, 1419 cm−1

(4R,6S)-4,6-Bis(trisopropylsilyloxy)-4-methyloct-7-en-2-ynal 433

Chemical Formula: C18H32O3Si
Molecular Weight: 324.5360

Chemical Formula: C27H52O3Si2
Molecular Weight: 480.8800
To a solution of alkyne 431 (91 mg, 0.20 mmol) in THF (1.5 mL) at −78 °C was added nBuLi (0.10 mL of a 2.3 M solution in hexane, 0.24 mmol). The resulting solution was stirred for 5 mins and then warmed to 0 °C. DMF (0.03 mL, 0.40 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with 5% aq. KH₂PO₄ (2 mL) and Et₂O (2 mL) was added. The phases were separated and the organic phase was washed with brine (5 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 95:5) to give the propargylic aldehyde 433 as a colourless oil (91 mg, 97%). [α]²⁷° −21 (c = 0.28, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.22 (1H, s, CHO-C5), 5.95 (1H, ddd, J = 17.3, 10.2, 7.3 Hz, CH-C11), 5.20 (1H, ddd, J = 17.3, 1.5, 1.2 Hz, CH₂-C⁴), 5.05 (1H, ddd, J = 10.2, 1.5, 0.8 Hz, CH₂-C⁵), 4.56–4.49 (1H, m, CH-C10), 2.13 (1H, dd, J = 13.8, 5.6 Hz, CH₂-C9), 2.04 (1H, dd, J = 13.8, 6.6 Hz, CH₂-C9), 1.64 (3H, s, CH₃-C20), 1.20–1.02 (42H, m, CH(CH₃)₂); ¹³C NMR (126 MHz, CDCl₃) δ 176.4 (CHO-C5), 142.1 (CH-C11), 114.7 (CH₂-C⁴), 100.8 (C-C⁷), 83.9 (C-C⁶), 72.0 (CH-C10), 68.5 (C-C₈), 53.4 (CH₂-C₉), 31.0 (CH₃-C20), 18.5 (CH(CH₃)₂), 18.4 (CH(CH₃)₂), 18.3 (CH(CH₃)₂), 18.3 (CH(CH₃)₂), 13.3 (CH(CH₃)₂), 12.8 (CH(CH₃)₂); IR νmax 2945, 2893, 2868, 2210, 1674, 1464, 1421 cm⁻¹

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\text{(3S,5S)-5-Methylhept-1-en-6-yne-3,5-diol anti-429}
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\begin{align*}
\text{Chemical Formula: C}_{9}\text{H}_{12}\text{O}_2
\end{align*}
\]

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\text{Molecular Weight: 140.1820}
\]

To a solution of the anti 1,3-diol anti-428 (100 mg, 0.34 mmol) in THF (2 mL) was added TBAF (0.37 mL of a 1M solution in THF, 0.37 mmol) and the resulting solution was stirred at rt for 2 h. Saturated aq. NH₄Cl (5 mL) and Et₂O (5 mL) were added and the phases were separated. The organic phase was washed with brine (5 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et₂O, 1:1) to give the corresponding anti 1,3-diol anti-429 as a colourless oil (37 mg, 78%). [α]²¹° +16 (c = 0.12, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.87 (1H, ddd, J = 17.2, 10.4, 5.8 Hz, CH-C11), 5.27 (1H, ddd, J = 17.2, 1.4, 1.4 Hz, CH₂-C⁴), 5.11 (1H, ddd, J = 10.4, 1.4, 1.3 Hz, CH₂-C⁵), 4.84–4.77 (1H, m, CH-C10), 4.73 (1H, s, OH-C₈), 3.19 (1H, d, J = 2.9 Hz, OH-C10), 2.50 (1H, s, CH-C₆), 1.84–1.73 (2H, m, CH₂-C₉), 1.50 (3H, s, CH₃-C20); ¹³C NMR (101 MHz, CDCl₃) δ 140.3 (CH-C11), 114.9 (CH₂-C⁴), 87.0 (C-C⁷), 72.1 (CH-C₆), 72.1 (CH-C10), 68.3 (C-C₈), 47.5 (CH₂-C₉), 31.0 (CH₂-C20); HRMS
(ESI<sup>+</sup>) calcd for C<sub>6</sub>H<sub>12</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 163.0730, found 163.0736; IR ν<sub>max</sub> 3358, 3294, 3078, 2983, 2915, 2874, 2110, 1653, 1423, 1419 cm<sup>-1</sup>

(4R,6S)-4-Ethynyl-4-methyl-6-vinyl-1,3-dioxan-2-one 434

To a solution of diol syn-429 (27 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added pyridine (0.16 mL, 1.9 mmol) and the resultant cooled to −78 °C. A solution of triphosgene (114 mg, 0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added and the reaction stirred for 45 min before being warmed to rt and stirred for a further 40 min. Saturated aq. NH<sub>4</sub>Cl (5 mL) was added and the mixture stirred vigorously for 10 min. The biphasic mixture was separated and the aq. phase washed with CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed under vacuum to yield the cyclic carbonate 434 as a pale yellow oil (31.5 mg, 98%). [α]<sub>D</sub><sup>30</sup> +40 (c = 0.20, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.94 (1H, ddd, <i>J</i> = 17.2, 10.6, 6.1 Hz, CH-C<sub>11</sub>), 5.44 (1H, ddd, <i>J</i> = 17.2, 1.4, 0.7 Hz, CH<sub>2</sub>-C<sub>B</sub>), 5.36–5.32 (1H, m, CH<sub>2</sub>-C<sub>B</sub>), 4.96–4.89 (1H, m, CH-C<sub>10</sub>), 2.69 (1H, s, CH-C<sub>6</sub>), 2.35–2.24 (2H, m, CH<sub>2</sub>-C<sub>9</sub>), 1.77 (3H, s, CH<sub>3</sub>-C<sub>20</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 147.8 (OCC(O)O), 133.8 (CH-C<sub>11</sub>), 119.1 (CH<sub>2</sub>-C<sub>B</sub>), 82.7 (C-C<sub>7</sub>), 75.9 (CH-C<sub>6</sub>), 75.1 (C-C<sub>8</sub>), 74.8 (CH-C<sub>10</sub>), 38.7 (CH<sub>2</sub>-C<sub>9</sub>), 28.0 (CH<sub>3</sub>-C<sub>20</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup> 189.0522, found 189.0523; IR ν<sub>max</sub> 3287, 2994, 2916, 2847, 1751, 1736, 1651, 1543, 1435 cm<sup>-1</sup>

(4S,6S)-4-Ethynyl-4-methyl-6-vinyl-1,3-dioxan-2-one 435

To a solution of diol anti-429 (37 mg, 0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL) was added pyridine (0.21 mL, 2.6 mmol) and the resultant cooled to −78 °C. A solution of triphosgene (157 mg, 0.53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL) was added and the reaction stirred for 45 min before being warmed to rt and stirred for a further 40 min. Saturated aq. NH<sub>4</sub>Cl (6 mL) was added and the mixture stirred vigorously for 10 min. The biphasic mixture was separated and the aq. phase washed with CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Combined organic extracts were washed with brine (10 mL),
dried over Na₂SO₄, filtered and the solvent removed under vacuum to yield the cyclic carbonate 435 as a pale yellow oil (43.3 mg, 99%). [α]ᵢ³⁰ +25 (c = 0.12, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.85 (1H, ddd, J = 17.2, 10.5, 6.0 Hz, CH-C11), 5.44 (1H, ddd, J = 17.2, 1.4, 0.8 Hz, CH₂-C⁵), 5.34–5.30 (1H, m, CH₂-C⁹), 5.28–5.21 (1H, m, CH-C10), 2.73 (1H, s, CH-C6), 2.25 (1H, dd, J = 14.2, 3.2 Hz, CH₂-C9), 1.91 (1H, dd, J = 14.2, 12.0 Hz, CH₂-C9), 1.70 (3H, s, CH₃-C20); ¹³C NMR (101 MHz, CDCl₃) δ 147.7 (C₁₁), 133.9 (CH-C11), 118.8 (CH₂-C⁵), 81.6 (C-C7), 77.5 (CH-C6), 75.9 (C-C8), 74.8 (CH-C10), 39.3 (CH₂-C9), 28.8 (CH₃-C20); HRMS (ESI⁺) calc'd for C₉H₁₅O₂Na [M+Na]⁺ 189.0522, found 189.0529; IR νmax 3256, 2994, 2916, 2847, 2121, 1751, 1535, 1427 cm⁻¹.

**Methyl 5-[(3R)-3-methyl-3-[(2S)-2-[(tris(propan-2-yl)silyl)oxy]but-3-en-1-yl]oxiran-2-yl]-2-[(2R)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[(2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 436**

Pivalic acid (12 mg, 0.12 mmol), the β-keto ester 416 (75 mg, 0.20 mmol) and the propargylic aldehyde 432 (162 mg, 0.499 mmol) were dissolved in a solution of piperidine in THT (0.027 M, 0.75 mL, 0.02 mmol) in the presence of 4 Å molecular sieves. The resulting mixture was heated to 35 °C and stirred at this temperature for 16 h. The solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:Et₂O, 9:1) to afford the epoxyfuran 436 (1:1 mixture of diastereoisomers) as a colourless oil (84 mg, 62%). ¹H NMR (400 MHz, CdCl₃) δ 6.69 (1H, s, CH-C5), 6.26 (0.5H, d, J = 1.7 Hz, CH₂-C⁴), 6.24 (0.5H, d, J = 1.7 Hz, CH₂-C⁴), 5.88–5.67 (1H, m, CH-C11), 5.35 (0.5H, d, J = 1.7 Hz, CH₂-C⁴), 5.32 (0.5H, d, J = 1.7 Hz, CH₂-C⁴), 5.15 (0.5H, d, J = 17.3 Hz, CH₂-C⁵), 5.10 (0.5H, d, J = 17.3 Hz, CH₂-C⁵), 5.01 (0.5H, d, J = 10.0 Hz, CH₂-C⁵), 4.94 (0.5H, d, J = 10.0 Hz, CH₂-C⁵), 4.81 (1H, s, CH₂-C16), 4.75 (0.5H, s, CH₂-C16), 4.74 (0.5H, s, CH₂-C16), 4.41–4.28 (1H, m, CH-C10), 4.24–4.18 (2H, m, (CH₃)₃SiCH₂CH₂O), 3.70 (0.5H, s, CH-C7), 3.49 (0.5H, s, CH-C7), 3.43 (1.5H, s, CH₃-C19), 3.42 (1.5H, s, CH₃-C19), 3.26–3.16 (1.5H, m, CH₂-C₂), 3.08 (0.5H, dd, J = 14.3, 6.4 Hz, CH₂-C2), 2.87–2.73 (1H, m, CH-C1), 2.54–2.41 (1H, m, CH₂-C13), 2.34–2.22 (1.5H, m, CH₂-C13, CH₂-C9), 2.12 (0.5H, dd, J = 13.8, 5.1 Hz, CH₂-C9), 1.96 (0.5H, dd, J = 13.8, 8.3 Hz, CH₂-C9), 1.74 (1.5H, s, CH₃-C17),
1.70 (1.5H, s, CH$_3$-C17), 1.69–1.60 (2.5H, m, CH$_2$-C9, CH$_2$-C14), 1.34 (1.5H, s, CH$_3$-C20), 1.28 (1.5H, s, CH$_3$-C20), 1.12–1.05 (21H, m, CH(CH$_3$)$_2$), 0.91–0.85 (2H, m, (CH$_3$)$_3$SiCH$_2$CH$_2$O), −0.09 (9H, s, (CH$_3$)$_2$SiCH$_2$CH$_2$O); $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 166.9 (C-C21), 166.9 (C-C21), 163.9 (C-C18), 163.9 (C-C18), 161.9 (C-C3), 149.7 (C-C6), 149.6 (C-C6), 146.4 (C-C15), 146.3 (C-C15), 141.7 (CH-C11), 141.4 (CH-C11), 124.3 (CH$_2$-C$^A$), 124.2 (CH$_2$-C$^B$), 115.1 (C-C4), 115.0 (C-C4), 114.9 (CH$_2$-C$^B$), 114.7 (CH$_2$-C$^B$), 113.1 (CH$_2$-C16), 112.9 (CH$_2$-C16), 109.5 (CH-C5), 109.4 (CH-C5), 73.0 (CH-C10), 72.4 (CH-C10), 62.7 ([CH$_3$)$_2$SiCH$_2$CH$_2$O], 62.0 (C-C8), 61.2 (C-C8), 58.6 (CH-C7), 58.0 (CH-C7), 59.9 (CH$_3$-C19), 47.6 (CH$_2$-C9), 46.9 (CH-C1), 46.9 (CH-C1), 41.0 (CH$_2$-C9), 32.4 (CH$_2$-C2), 32.0 (CH$_2$-C14), 32.0 (CH$_2$-C14), 30.5 (CH$_2$-C13), 30.5 (CH$_2$-C13), 23.1 (CH$_3$-C20), 18.4 (CH(CH$_3$)$_2$), 18.4 (CH(CH$_3$)$_2$), 18.2 (CH$_2$-C17), 18.2 (CH$_2$-C17), 17.5 ([CH$_3$)$_2$SiCH$_2$CH$_2$O], 12.7 (CH(CH$_3$)$_2$), −1.6 ([CH$_3$)$_2$SiCH$_2$CH$_2$O]; HRMS (ESI$^+$) calcd for C$_{37}$H$_{62}$O$_7$Si$_2$Na [M+Na]$^+$ 697.3926, found 697.3898; IR $\nu_{\text{max}}$ 2947, 2928, 2894, 2866, 1717, 1645, 1630, 1617, 1579, 1439 cm$^{-1}$


The β-Keto ester 416 (69 mg, 0.187 mmol) and the propargylic aldehyde 432 (82 mg, 0.253 mmol) were dissolved in a solution of acetic acid (2 µL, 0.035 mmol) and piperidine (3 µL, 0.029 mmol) in THF (1 mL) in the presence of 4 Å molecular sieves. The resulting mixture was heated to 40 °C and stirred at this temperature for 16 h. The solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:EtOAc, 9:1 → 7:3) to afford the epoxyfuran 436 (1:1 mixture of diastereoisomers) as a colourless oil (38.3 mg, 30%) followed by the acetate 437 (~3:2 mixture of diastereoisomers) as a colourless oil (44.6 mg, 32%). **Acetate:** $^1$H NMR (400 MHz, C$_6$D$_6$) δ 6.86 (0.4H, s, CH-C5), 6.82 (0.6H, s, CH-C5), 6.26 (0.4H, d, $J$ = 1.7 Hz, CH$_2$-C$^A$), 6.24 (0.6H, d, $J$ = 1.7 Hz, CH$_2$-C$^A$), 6.05 (0.4H, s CH-C7), 6.02 (0.6H, s, CH-C7), 5.91–5.78 (1H, m, CH-C11), 5.35 (0.4H, d, $J$ = 1.7 Hz, CH$_2$-C$^B$), 5.34 (0.6H, d, $J$ = 1.7 Hz, CH$_2$-C$^B$), 5.05 (0.6H, d, $J$ = 6.0 Hz, CH$_2$-C$^B$), 5.01 (0.4H, d, $J$ = 6.0 Hz, CH$_2$-C$^B$), 4.89 (0.6H, dd, $J$ = 4.2, 1.3 Hz, CH$_2$-C$^B$), 4.86
(0.4H, dd, J = 4.2, 1.3 Hz, CH$_2$-C$^8$), 4.74 (2H, m, CH$_2$-C16), 4.72-4.63 (1H, m, CH-C10), 4.25-4.18 (2H, m, (CH$_3$)$_2$SiCH$_2$CH$_2$O), 4.01 (0.6H, s, OH-C8), 3.89 (0.4H, s, OH-C8), 3.42 (3H, s, CH$_3$-C19), 3.28-2.98 (2H, m, CH$_2$-C2), 2.82-2.71 (1H, m, CH-C1), 2.50-2.41 (1H, m, CH$_2$-C13), 2.32-2.21 (1.4H, m, CH$_2$-C9, CH$_2$-C13), 2.07 (0.4H, dd, J = 14.5, 8.6 Hz, CH$_2$-C9), 1.83 (0.6H, dd, J = 14.4, 3.9 Hz, CH$_2$-C9), 1.71 (1.2H, s, Ac-CH$_3$), 1.71 (1.8H, s, Ac-CH$_3$), 1.70 (1.2H, s, CH$_3$-C17), 1.70 (1.8H, s, CH$_3$-C17), 1.68-1.57 (2.6H, CH$_2$-C14, CH$_2$-C9), 1.40 (1.2H, s, CH$_3$-C20), 1.38 (1.8H, s, CH$_3$-C20), 1.18-1.05 (21H, m, CH(CH$_3$)$_2$), 0.91-0.85 (2H, m, (CH$_3$)$_2$SiCH$_2$CH$_2$O), −0.09 (9H, s, (CH$_3$)$_3$SiCH$_2$CH$_2$O); $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 169.4 (Ac-C=O), 169.3 (Ac-C=O), 166.9 (C-C21), 164.0 (C-C18), 161.8 (C-C3), 161.7 (C-C3), 150.1 (C-C6), 150.0 (C-C6), 146.4 (C-C15), 146.3 (C-C15), 142.1 (C-C12), 142.0 (C-C12), 141.7 (CH-C11), 124.2 (CH$_2$-C$^8$), 115.4 (CH$_2$-C$^8$), 115.3 (CH$_2$-C$^8$), 114.9 (C-C4), 114.8 (C-C4), 113.1 (CH$_2$-C16), 113.0 (CH$_2$-C16), 110.8 (CH-C5), 110.7 (CH-C5), 75.3 (CH-C7), 75.2 (CH-C7), 73.9 (CH-C10), 73.9 (CH-C10), 73.7 (C-C8), 62.7 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), 50.8 (CH$_3$- C19), 47.0 (CH-C1), 45.2 (CH$_2$-C9), 44.3 (CH$_2$-C9), 32.3 (CH$_2$-C2), 32.2 (CH$_2$-C2), 32.1 (CH$_2$-C14), 32.0 (CH$_2$-C14), 30.5 (CH$_2$-C13), 30.4 (CH$_2$-C13), 24.2 (CH$_2$-C20), 24.1 (CH$_2$-C20), 20.5 (Ac-CH$_3$), 18.4 (CH(CH$_3$)$_2$), 18.4 (CH(CH$_3$)$_2$), 18.1 (CH$_3$-C17), 18.1 (CH$_3$-C17), 17.5 ((CH$_3$)$_3$SiCH$_2$CH$_2$O), 13.1 (CH(CH$_3$)$_2$), −1.5 ((CH$_3$)$_3$SiCH$_2$CH$_2$O); HRMS (ESI') calc for C$_{39}$H$_{65}$O$_5$Si$_2$Na [M+Na]$^+$ 757.4138, found 757.4108; IR $\nu_{max}$ 3485, 3074, 2948, 2894, 2867, 1748, 1718, 1645, 1630, 1613, 1573, 1456, 1439 cm$^{-1}$

Methyl 5-[(2R,4S)-1-(acyloxy)-2-methyl-2,4-bis([tris(propan-2-yl)silyl]oxy)hex-5-en-1 -yl]-2-[5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 438

The β-Keto ester 416 (53 mg, 0.14 mmol) and the propargylic aldehyde 433 (134 mg, 0.279 mmol) were dissolved in a solution of acetic acid (10 µL, 0.17 mmol) and piperidine (3 µL, 0.029 mmol) in THT (0.5 mL) in the presence of 4 Å molecular seives. The resulting mixture was heated to 35 °C and stirred at this temperature for 18 h. The solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:EtOAc, 7:3) to afford the furan 438 (~3:2 mixture of diastereoisomers) as a colourless
oil (110 mg, 85%). ¹H NMR (500 MHz, C₆D₆) δ 6.92 (0.6H, s, CH-C5), 6.92 (0.4H, s, CH-C5), 6.30–6.26 (1H, m, CH₂-C⁴), 6.19 (0.6H, s, CH-C7), 6.11 (0.4H, s, CH-C7), 6.04 (0.6H, ddd, J = 17.3, 10.2, 7.9 Hz, CH-C11), 5.94 (0.4H, ddd, J = 17.3, 10.1, 8.2 Hz, CH-C11), 5.39–5.37 (1H, m, CH₂-C⁵), 5.27 (0.6H, dd, J = 17.3, 1.5 Hz, CH₂-C⁴), 5.16 (0.4H, dd, J = 17.3, 1.4 Hz, CH₂-C⁴), 5.08 (0.6H, dd, J = 10.2, 1.5 Hz, CH₂-C⁴), 4.98 (0.4H, dd, J = 10.1, 1.4 Hz, CH₂-C⁴), 4.85 (0.6H, d, J = 2.2 Hz, CH₂-C16), 4.83 (0.4H, d, J = 2.2 Hz, CH₂-C16), 4.83–4.79 (0.6H, m, CH₂-C16), 4.81–4.76 (0.4H, m, CH₂-C16), 4.64 (0.6H, ddd, J = 7.9, 7.5, 5.7 Hz, CH-C10), 4.60–4.52 (0.4H, m, CH-C10), 4.27–4.17 (2H, m, (CH₃)₃SiCH₂CH₂O), 3.46 (1.2H, s, CH₃-C19), 3.43 (1.8H, s, CH₃-C19), 3.33 (0.6H, dd, J = 14.3, 9.1 Hz, CH₂-C2), 3.24 (0.4H, dd, J = 14.3, 6.4 Hz, CH₂-C2), 3.15 (0.4H, dd, J = 14.3, 8.8 Hz, CH₂-C2), 3.05 (0.6H, dd, J = 14.3, 6.2 Hz, CH₂-C2), 2.88–2.80 (1H, m, CH-C1), 2.59–2.47 (1H, m, CH₂-C13), 2.37 (0.6H, dd, J = 14.3, 5.7 Hz, CH₂-C9), 2.34–2.25 (1.4H, m, CH₂-C9, CH₂-C13), 2.25–2.16 (1H, m, CH₂-C9), 1.78 (1.2H, s, Ac-CH₃), 1.77 (1.8H, s, Ac-CH₃), 1.75 (3H, s, CH₃-C17), 1.74–1.59 (2H, m, CH₂-C14), 1.55 (1.2H, s, CH₃-C20), 1.53 (1.8H, s, CH₃-C20), 1.25–1.07 (42H, s, CH(CH₃)₂), 0.93–0.86 (2H, m, (CH₃)₃SiCH₂CH₂O), -0.08 (5.4H, s, (CH₃)₃SiCH₂CH₂O), -0.08 (3.6H, s, (CH₃)₂SiCH₂CH₂O); ¹³C NMR (126 MHz, C₆D₆) δ 169.2 (Ac-C=O), 166.9 (C-C21), 164.0 (C-C18), 164.0 (C-C18), 161.4 (C-C3), 161.4 (C-C3), 150.4 (C-C6), 150.3 (C-C6), 146.2 (C-C15), 146.2 (C-C15), 142.7 (C-C12), 142.5 (C-C12), 141.8 (CH-C11), 124.2 (CH₂-C⁴), 115.6 (CH₂-C⁵), 115.2 (CH₂-C⁵), 115.0 (C-C4), (CH-C7), 115.0 (C-C4), 113.2 (CH₂-C16), 113.2 (CH₂-C16), 111.1 (CH-C5), 110.8 (CH-C5), 76.6 (CH-C7), 76.4 (CH-C7), 74.8 (CH-C10), 74.2 (CH-C10), 72.9 (C-C8), 72.7 (C-C8), 62.7 ((CH₃)₃SiCH₂CH₂O), 62.7 ((CH₃)₂SiCH₂CH₂O), 50.9 (CH₃-C19), 49.6 (CH-C1) 49.5 (CH-C1), 47.2 (CH₂-C9), 47.0 (CH₂-C9), 32.4 (CH₂-C2), 32.4 (CH₂-C2), 32.2 (CH₂-C14), 32.2 (CH₂-C14), 30.5 (CH₂-C13), 26.2 (CH₃-C20), 26.0 (CH₃-C20), 20.6 (Ac-CH₃), 20.6 (Ac-CH₃), 18.7 (CH(CH₃)₂), 18.7 (CH(CH₃)₂), 18.1 (CH(CH₃)₂), 18.6 (CH(CH₃)₂), 18.6 (CH(CH₃)₂), 18.6 (CH(CH₃)₂), 18.5 (CH(CH₃)₂), 18.5 (CH(CH₃)₂), 18.2 (CH₃-C17), 18.1 (CH₃-C17), 17.5 ((CH₃)₃SiCH₂CH₂O), 17.5 ((CH₃)₂SiCH₂CH₂O), 14.1 (CH(CH₃)₂), 14.0 (CH(CH₃)₂), 13.2 (CH(CH₃)₂), 13.1 (CH(CH₃)₂), -1.6 ((CH₃)₃SiCH₂CH₂O); HRMS (ESI⁺) calcd for C₄₈H₇₈O₇Si₃Na [M+Na]⁺ 913.5467, found 913.5427; IR v_max 2945, 2893, 2866, 1749, 1720, 1645, 1631, 1612, 1574, 1464, 1441 cm⁻¹
Methyl 5-[(3R,5S)-5-ethenyl-3-hydroxy-3-methyloxolan-2-yl]-2-[(2R)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 440

\[
\text{Chemical Formula: C}_{28}\text{H}_{42}\text{O}_7\text{Si}
\]

Molecular Weight: 518.7220

\(^1\)H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) δ 6.63 (1H, s, CH-C5), 6.26 (1H, s, CH\textsubscript{2}-C\textsubscript{A}), 5.99 (1H, ddd, \(J = 17.0, 10.4, 6.5\) Hz, CH-C11), 5.34 (1H, s, CH\textsubscript{2}-C\textsubscript{A}), 5.29 (1H, dd, \(J = 17.0, 1.6\) Hz, CH\textsubscript{2}-C\textsubscript{B}), 5.05 (1H, ddd, \(J = 10.4, 1.6\) Hz, CH\textsubscript{2}-C\textsubscript{B}), 4.82–4.70 (4H, m, CH\textsubscript{2}-C16, CH\textsubscript{-}C7, CH\textsubscript{-}C10), 4.28–4.19 (2H, m, (CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O), 3.45 (3H, s, CH\textsubscript{3}-C19), 3.19–3.05 (2H, m, CH\textsubscript{2}-C2), 2.81–2.69 (1H, m, CH-C1), 2.54–2.43 (1H, m, CH\textsubscript{2}-C13), 2.34–2.24 (1H, CH\textsubscript{2}-C13), 1.81–1.60 (7H, m, CH\textsubscript{2}-C9, CH\textsubscript{2}-C14, CH\textsubscript{2}-C17), 1.38 (3H, s, CH\textsubscript{3}-C20), 0.96–0.86 (2H, m, (CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O), −0.09 (9H, s, (CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O); \(^{13}\)C NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) δ 167.0 (C\textsubscript{-}C21), 164.1 (C\textsubscript{-}C18), 161.7 (C\textsubscript{-}C3), 153.0 (C\textsubscript{-}C6), 146.3 (C\textsubscript{-}C15), 141.7 (C\textsubscript{-}C12), 139.2 (C\textsubscript{-}C11), 124.3 (CH\textsubscript{2}-C\textsubscript{A}), 115.7 (CH\textsubscript{2}-C\textsubscript{B}), 114.7 (C\textsubscript{-}C4), 113.1 (CH\textsubscript{2}-C16), 108.6 (CH\textsubscript{-}C5), 85.2 (CH\textsubscript{-}C7), 81.3 (C\textsubscript{B}), 79.8 (CH\textsubscript{-}C10), 62.8 ((CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O), 50.9 (CH\textsubscript{3}-C19), 47.1 (CH\textsubscript{-}C1), 46.3 (CH\textsubscript{2}-C9), 32.3 (CH\textsubscript{2}-C2), 32.2 (CH\textsubscript{2}-C14), 30.5 (CH\textsubscript{3}-C20), 30.2 (CH\textsubscript{2}-C13), 18.2 (CH\textsubscript{3}-C17), 17.5 ((CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O), −1.6 ((CH\textsubscript{3})\textsubscript{3}SiCH\textsubscript{2}CH\textsubscript{2}O); HRMS (ESI\textsuperscript{+}) calcd for C\textsubscript{28}H\textsubscript{42}O\textsubscript{7}SiNa [M\textsubscript{+}Na\textsuperscript{+}] 541.2592, found 541.2574; IR \textit{\nu}_{\text{max}} 3481, 3078, 2949, 2926, 2856, 1719, 1647, 1629, 1613, 1577, 1457, 1437 cm\textsuperscript{-1}
Methyl 5-[(3R)-3-[(2S)-2-hydroxybut-3-en-1-yl]-3-methyloxiran-2-yl]-2-[(2R)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 441

\[ \text{Chemical Formula: } C_{28}H_{42}O_7Si \]
\[ \text{Molecular Weight: } 518.7220 \]

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 6.70 (0.5H, s, CH-C5), 6.69 (0.5H, s, CH-C5), 6.25 (0.5H, d, \(J = 1.8\) Hz, CH\(_2\)-C\(^6\)), 6.24 (0.5H, d, \(J = 1.7\) Hz, CH\(_2\)-C\(^6\)), 5.71–5.62 (1H, m, CH-C11), 5.34–5.32 (1H, m, CH\(_2\)-C\(^6\)), 5.19 (0.5H, dt, \(J = 17.2, 1.6\) Hz, CH\(_2\)-C\(^6\)), 5.18 (0.5H, dt, \(J = 17.2, 1.6\) Hz, CH\(_2\)-C\(^6\)), 4.96 (0.5H, dt, \(J = 10.4, 1.5\) Hz, CH\(_2\)-C\(^6\)), 4.93 (0.5H, dt, \(J = 10.4, 1.5\) Hz, CH\(_2\)-C\(^6\)), 4.80–4.74 (3H, CH\(_2\)-C16, CH-C10) 4.24–4.18 (2H, m, (CH\(_3\))\(_3\)SiCH\(_2\)O), 3.66 (0.5H, s, CH-C7), 3.47 (0.5H, s, CH-C7), 3.44 (1.5H, s, CH\(_3\)-C19), 3.40 (1.5H, s, CH\(_3\)-C19), 3.29–3.18 (1H, m, CH\(_2\)-C2), 3.16–3.03 (1H, m, CH\(_2\)-C2), 2.86–2.73 (1H, m, CH-C1), 1.92–1.84 (2H, m, (CH\(_3\))\(_3\)SiCH\(_2\)O), 0.92–0.84 (2H, m, (CH\(_3\))\(_3\)SiCH\(_2\)O), −0.09 (9H, s, (CH\(_3\))\(_3\)SiCH\(_2\)O); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 167.0 (C\(_2\)-C21), 166.9 (C\(_2\)-C21), 163.9 (C\(_2\)-C18), 163.8 (C\(_2\)-C18), 162.1 (C\(_2\)-C3), 162.0 (C\(_2\)-C3), 149.3 (C\(_2\)-C6), 149.1 (C\(_2\)-C6), 146.4 (C\(_2\)-C15), 146.4 (C\(_2\)-C15), 141.7 (C-C12), 141.7 (C-C12), 141.3 (C\(_1\)-C11), 141.2 (C\(_1\)-C11), 124.4 (CH-C\(^4\)), 124.2 (CH-C\(^4\)), 115.2 (C-C4), 115.1 (C-C4), 114.1 (CH\(_2\)-C\(^3\)), 114.1 (CH\(_2\)-C\(^3\)), 112.9 (CH\(_2\)-C16), 112.9 (CH\(_2\)-C16), 109.8 (CH-C5), 109.7 (CH-C5), 70.6 (CH-C10), 70.0 (CH-C10), 63.1 ((CH\(_3\))\(_3\)SiCH\(_2\)CH\(_2\)O), 62.8 ((CH\(_3\))\(_3\)SiCH\(_2\)CH\(_2\)O), 62.8 (C\(_8\)), 62.4 (C\(_8\)), 57.9 (CH-C7), 57.4 (CH-C7), 50.9 (CH\(_3\)-C19), 46.8 (CH\(_2\)-C9), 44.6 (CH-C1), 39.4 (CH\(_2\)-C9), 32.4 (CH-C2), 32.0 (CH-C14), 31.9 (CH\(_2\)-C14), 30.5 (CH\(_2\)-C13), 30.5 (CH\(_2\)-C13), 22.4 (CH\(_3\)-C20), 18.3 (CH-C17), 18.2 (CH\(_3\)-C17), 17.5 ((CH\(_3\))\(_3\)SiCH\(_2\)CH\(_2\)O), −1.56 ((CH\(_3\))\(_3\)SiCH\(_2\)CH\(_2\)O); HRMS (ESI\(^+\)) calcd for C\(_{28}\)H\(_{42}\)O\(_7\)SiNa [M+Na\(^+\)] 541.2592, found 541.2575; IR \(\nu_{\text{max}}\) 3493, 2953, 2928, 2857, 1717, 1645, 1631, 1578, 1441 cm\(^{-1}\)
Macrolactonisation under Yamaguchi conditions

To a solution of the epoxyfuran 438 (35 mg, 50 µmol) in THF (0.25 mL) at 10 ºC was added TBAF (0.11 mL of a 1 M solution in THF, 0.11 mmol) and the resulting mixture was stirred for 3.5 h. H₂O (0.5 mL) and Et₂O (2 mL) were added and the phases were separated. The aqueous phase was washed with Et₂O (2 x 2 mL) and the combined organic extracts were dried over Na₂SO₄ and filtered. The solvent was removed under vacuum to yield crude seco-acid 439, which was used directly in the next step.

To a solution of the crude seco-acid 439 in benzene (6.5 mL) at rt was added DIPEA (0.13 mL, 0.75 mmol) followed by trichlorobenzoyl chloride (0.08 mL, 0.5 mmol) and the resulting mixture was stirred for 4 h. A solution of DMAP (244 mg, 2.00 mmol) in benzene (18.5 mL) was added and the mixture stirred for a further 15.5 h. H₂O (30 mL) and EtOAc (20 mL) were added and the phases separated. The organic phase was washed with brine (30 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 85:15 → 75:25) to deliver the macrolactone 421 as a single isomer and colourless oil (7.8 mg, 39%).

Macrolactonisation under Corey-Nicolaou conditions

To a solution of epoxy-furan 438 (16.5 mg, 24 µmol) in THF (0.1 mL) at 10 ºC was added TBAF (0.05 mL of a 1 M solution in THF, 50 µmol) and the resulting solution was stirred for 3 h. H₂O (0.2 mL) and Et₂O (2 mL) were added and the phases separated. The aqueous phase was washed with Et₂O (2 x 1 mL) and the combined organic extracts dried over Na₂SO₄, filtered and the solvent removed under vacuum to yield the crude seco-acid 439, which was used directly in the next step.

To a solution of crude seco-acid 439 in toluene (1 mL) at rt was added 2,2′-dipyridyl disulfide (7.3 mg, 33 µmol) and triphenylphosphine (8.7 mg, 33 µmol) and the resulting mixture stirred for 7 h. Toluene (26 mL) was added and the solution was heated to reflux for 14 h. The solution was cooled to rt and the solvent removed under vacuum and the residue was
purified by silica gel column chromatography (pet. ether: EtOAc, 85:15 → 80:20) to give the macrolactone 421 as a single isomer and colourless oil (4.5 mg, 46%). [α]D25 +15 (c = 0.36, CHCl3); 1H NMR (500 MHz, C6D6) δ 6.65 (1H, s, CH-C5), 6.25 (1H, d, J = 1.9 Hz, CH-C9), 5.68–5.62 (1H, m, CH-C10), 5.56 (1H, ddd, J = 17.1, 10.4, 6.3 Hz, CH-C11), 5.12 (1H, ddd, J = 17.1, 1.3, 1.3 Hz, CH-C6B) 5.13–5.11 (1H, m, CH-C10), 4.92 (1H, ddd, J = 10.4, 1.3, 1.3 Hz, CH-C6B), 4.79 (1H, dq, J = 1.8, 1.5 Hz, CH2-C16), 4.77–4.75 (1H, m, CH2-C16), 3.44 (3H, s, CH3-C19), 3.33 (1H, s, CH-C7), 3.20 (1H, dd, J = 15.1, 11.9 Hz, CH2-C2), 3.06 (1H, ddd, J = 15.1, 3.7 Hz, CH2-C2), 2.71 (1H, dddd, J = 11.9, 8.2, 4.2, 3.7 Hz, CH-C1), 2.32–2.24 (1H, m, CH2-C13), 1.98 (1H, dd, J = 14.9, 5.0 Hz, CH2-C9), 1.71–1.68 (1H, m, CH2-C14), 1.58 (3H, s, CH3-C17), 1.57–1.49 (1H, m, CH2-C14), 1.07 (3H, s, CH3-C20); 13C NMR (101 MHz, C6D6) δ 166.0 (C21), 163.7 (C18), 161.8 (C3), 148.7 (C6), 147.1 (C15), 140.8 (C12), 137.0 (CH-C11), 126.3 (CH2-C14), 116.4 (CH2-C8), 115.5 (C-C4), 111.6 (CH2-C16), 110.9 (CH-C5), 72.6 (CH-C10), 61.8 (C8), 58.7 (CH-C7), 51.0 (CH3-C19), 43.6 (CH-C1), 37.0 (CH2-C9), 32.3 (CH2-C2), 30.2 (CH2-C14), 29.6 (CH2-C13), 23.6 (CH3-C20), 20.0 (CH3-C17); HRMS (ESI+) calcd for C22H28O6Na [M+Na]+ 423.1778, found 423.1766; IR νmax 2953, 2924, 2852, 1720, 1643, 1631, 1578, 1441 cm−1

7-epi-Pukalide 443

The macrolactone 421 (5.0 mg, 12 µmol) and the ruthenium catalyst 442 (1.0 mg, 1.2 µmol) were dissolved in degassed CH2Cl2 (1.3 mL) and heated at 40 °C for 17 h. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether: EtOAc, 8:2 → 7:3) to give 7-epi-pukalide (443) as a colourless wax (4.6 mg, 90%). [α]D25 +31 (c = 0.13, CHCl3); 1H NMR (500 MHz, CDCl3) δ 6.88 (1H, s, CH-C5), 6.42 (1H, d, J = 18.1 Hz, CH-C11), 5.00 (1H, br d, J = 12.2 Hz, CH-C10), 4.86 (1H, q, J = 1.6 Hz, CH2-C16), 4.79 (1H, s, CH2-C16), 3.85 (3H, s, CH3-C19), 3.72 (1H, s, CH-C7), 3.47 (1H, dd, J = 14.8, 12.6 Hz, CH2-C2), 2.87 (1H, dd, J = 12.6, 3.4 Hz, CH2-C9), 2.69 (1H, dd, J = 14.8, 3.5 Hz, CH2-C2), 2.37 (1H, ddd, J = 15.5, 13.2, 3.4 Hz, CH2-C13), 2.17–2.04 (2H, m, CH-C1, CH2-C13), 2.01 (1H, app t, J = 12.6 Hz, CH2-C9), 1.79–1.74 (1H, m, CH2-C14), 1.74 (3H, s,
CH₃-C17), 1.58 (3H, s, CH₂-C20), 1.30–1.22 (1H, m, CH₂-C14); ¹³C NMR (126 MHz, CDCl₃) δ 173.5 (C-C21), 163.8 (C-C18), 162.8 (C-C3), 149.0 (CH-C11), 146.9 (C-C6), 145.3 (C-C15), 133.9 (C-C12), 116.3 (C-C4), 114.6 (CH-C5), 113.2 (CH₂-C16), 77.9 (CH-C10), 60.9 (C-C8), 57.8 (CH-C7), 51.8 (CH₃-C19), 43.7 (CH-C1), 40.5 (CH₂-C9), 31.7 (CH₂-C13), 23.3 (CH₃-C20), 20.6 (CH₂-C14), 19.3 (CH₃-C17); HRMS (ESI⁺) calcd for C₂₁H₂₄O₈Na [M+Na]⁺ 395.1465, found 395.1448; IR νmax 2953, 2924, 1757, 1718, 1647, 1612, 1578, 1443 cm⁻¹


To a solution of furan 438 (20.1 mg, 22.6 µmol) in THF (0.2 mL) at 10 °C was added TBAF (0.1 mL of a 1 M solution in THF, 0.1 mmol) and the resultant mixture was stirred at 10 °C for 7 h. Three drops of half saturated aq. NH₄Cl were added and the mixture stirred for 10 min. The solution was diluted with Et₂O (10 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum to afford the crude seco-acid 444 which was used directly in the next step.

To a solution of the crude seco-acid 444 in benzene (2.2 mL) at rt was added DIPEA (0.06 mL, 0.3 mmol) followed by trichlorobenzoyl chloride (0.04 mL, 0.3 mmol) and the resulting mixture was stirred for 5 h at rt. A solution of DMAP (108 mg, 0.884 mmol) in benzene (6.6 mL) was added and the mixture stirred for a further 16 h. Half saturated brine (10 mL) and EtOAc (10 mL) were added and the phases separated. The organic phase was washed with brine (2 × 10 mL), dried over Na₂SO₄ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 7:3) to afford the title compound 445 (~2:1 mixture of diastereomers) as a colourless oil (2.6 mg, 25%). ¹H NMR (500 MHz, C₆D₆) δ 6.77 (0.35H, s, CH-C5), 6.74 (0.65H, s, CH-C5), 6.27 (0.35H, d, J = 2.1 Hz, CH₂-C⁴), 6.19 (0.65H, d, J = 1.9 Hz, CH₂-C⁴), 6.06 (0.65H, s, CH-C7), 5.99–5.93 (1H, m, CH-C10), 5.82 (0.65H, ddd, J = 17.1, 10.5, 6.0 Hz, CH-C11), 5.73–5.65
To a solution of macrolactone 445 (4.5 mg, 9.8 µmol) in degassed CH$_2$Cl$_2$ (0.5 mL) was added a solution of the ruthenium catalyst 442 (0.8 mg, 1.0 µmol) in degassed CH$_2$Cl$_2$ (0.6 mL). The resulting solution was heated to 40 °C for 16 h. The solvent was removed under vacuum and residual material was purified by silica gel column chromatography (pet. ether:EtOAc, 8:2 → 1:1) to afford recovered starting material 445 (3.3 mg, 73%) followed by 13C NMR (126 MHz, CD$_2$Cl$_2$) δ 169.7 (C=O), 169.0 (Ac-C=O), 167.0 (C-C21), 166.5 (C-C21), 163.7 (C-C18), 162.1 (C-C3), 161.8 (C-C3), 150.1 (C-C6), 149.2 (C-C6), 146.4 (C-C15), 146.0 (C-C12), 140.3 (C-C12), 138.0 (CH-C11), 137.8 (CH-C11), 127.4 (CH$_2$-C$^5$), 126.6 (CH$_2$-C$^6$), 115.6 (CH$_2$-C$^5$), 115.4 (CH$_2$-C$^6$), 115.3 (C-C4), 113.2 (CH-C5), 112.6 (CH$_2$-C16), 112.1 (CH$_2$-C16), 110.5 (CH-C5), 74.8 (CH-C7), 73.3 (C-C8), 72.3 (C-C8), 73.1 (CH-C7), 71.5 (CH-C10), 71.1 (CH-C10), 51.0 (CH$_3$-C19), 50.9 (CH$_3$-C19), 44.0 (CH-C1), 43.8 (CH-C1), 42.5 (CH$_2$-C9), 42.3 (CH$_2$-C9), 32.4 (CH$_2$-C2), 32.2 (CH$_2$-C2), 30.5 (CH$_2$-C13), 30.2 (CH$_2$-C13), 29.6 (CH$_2$-C14), 29.3 (CH$_2$-C14), 25.6 (CH$_3$-C20), 24.9 (CH$_3$-C20), 20.3 (Ac-CH$_3$), 20.2 (Ac-CH$_3$), 19.6 (CH$_3$-C17), 19.5 (CH$_3$-C17); HRMS (ESI$^+$) calcd for C$_{25}$H$_{52}$O$_{8}$Na [M+Na]$^+$ 483.1989, found 483.1979; IR $\nu_{max}$ 3487, 2953, 2924, 2855, 2365, 2343, 2328, 1725, 1719, 1647, 1611, 1570, 1439 cm$^{-1}$
7-acetylsinunumaximol B (16) as a white solid (1.1 mg, 25%). \([\alpha]_D^{27} = -38 \ (c = 0.080, \text{CHCl}_3)\) \{lit. \([\alpha]_D^{25} = -56.0 \ (c = 0.6, \text{CHCl}_3)\}\[1\]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.65 (1H, s, CH-C5), 5.80 (1H, br s, CH-C11), 5.58 (1H, s, CH-C7), 4.94 (1H, br d, \(J = 11.4\) Hz, CH-C10), 4.85–4.82 (1H, m, CH\(_2\)-C16), 4.80 (1H, s, CH\(_2\)-C16), 3.85 (3H, s, CH\(_3\)-C19), 3.41 (1H, dd, \(J = 14.7, 12.3\) Hz, CH\(_2\)-C2), 2.73 (1H, dd, \(J = 14.7, 2.5\) Hz, CH\(_2\)-C2), 2.60 (1H, dd, \(J = 14.9, 4.0\) Hz, CH\(_2\)-C9), 2.37–2.29 (1H, m, CH\(_2\)-C13), 2.24–2.17 (1H, m, CH-C1), 1.95 (1H, dd, \(J = 14.9, 11.4\) Hz, CH\(_2\)-C9), 1.86–1.79 (1H, m, CH\(_2\)-C14), 1.77 (3H, s, CH\(_3\)-C17), 1.52–1.49 (1H, m, CH\(_2\)-C14), 1.48 (3H, s, CH\(_3\)-C20); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.3 (Ac-C=O), 169.6 (C-C21), 163.8 (C-C18), 161.3 (C-C3), 149.5 (C-C6), 148.3 (C-C11), 146.2 (C-C15), 133.9 (C-C12), 116.4 (C-C4), 112.8 (CH\(_2\)-C16), 109.7 (CH-C5), 78.5 (CH-C10), 76.1 (CH-C7), 72.9 (C-C8), 51.8 (CH\(_3\)-C19), 44.2 (CH-C1), 43.3 (CH\(_2\)-C9), 32.1 (CH\(_2\)-C2), 28.3 (CH\(_2\)-C14), 21.8 (CH\(_2\)-C13), 21.2 (Ac-CH\(_3\)), 21.2 (CH\(_3\)-C20), 19.2 (CH\(_3\)-C17); HRMS (ESI\(^+\)) calcd for C\(_{23}\)H\(_{28}\)O\(_8\)Na [M+Na]\(^+\) 455.1676, found 455.1664; IR \(\nu_{\text{max}}\) 3464, 2924, 1755, 1722, 1572, 1443 cm\(^{-1}\)
4. References


[93] V. Klaus, Novel Synthesis of Highly Functionalised Furans and Investigation into a Cope Rearrangement of Furlyvinylcyclopropanes, University of Glasgow, 2016.


5. Appendix - Relevant NMR Spectra and Published Manuscript
\[ \text{Structural Formula} \]

**415**
7-epi-pukalide (443)