The Total Synthesis of Furanocembrane Natural Products

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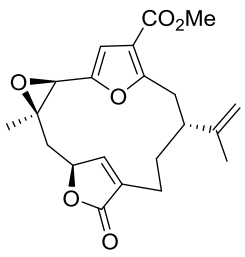
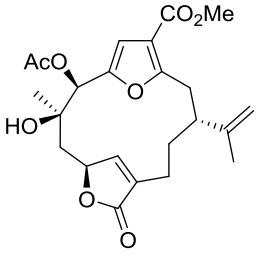
Abstract

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-acetylsinumaxmol 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.



7-*epi*-pukalide



7-acetylsinumaximol B

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 Knovenagel 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

Ac	Acetyl
ACDC	asymmetric counterion directed catalysis
ADD	1,1'-(azodicarbonyl)dipiperidine
aq	aqueous
Ar	aryl
Bn	benzyl
BQ	1,4-benzoquinone
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
CI	chemical ionisation
COX-2	cyclooxygenase-2
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E	electrophile
EDDA	ethylene diammonium diacetate
ee	enantiomeric excess
EMA	European Medicines Agency
equiv	equivalents
ERK1/2	extracellular signal–regulated kinases 1/2
ESI	electrospray ionisation

Et	ethyl
EWG	electron withdrawing group
FDA	U.S. Food and Drug Administration
Grubbs II	Grubbs second generation catalyst
HG II	Hoveyda-Grubbs second generation catalyst
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectometry
HWE	Horner-Wadsworth Emmons
i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
iNOS	inducible nitric oxide synthetase
IR	infrared
L	ligand
LA	Lewis acid
LDA	lithium diisopropyl amide
LRMS	low resolution mass spectometry
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*p*-chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl ether
Mes	mesityl (2,4,6-trimethyllphenyl)
MMTr	4-methoxytrityl (4-methoxytriphenylmethyl)
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n	normal
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NHK	Nozaki-Hiyama-Kishi
NMO	*N*-methylmorpholine-*N*-oxide
Nu	nucleophile
OPP	diphosphate
pet	petroleum
Ph	phenyl

Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pr	propyl
pTSA	*p*-toluenesulfonic acid
pyr	pyridine
quant.	quantitative
R	generalised group
RCM	ring-closing metathesis
rt	room temperature
SAR	structure-activity relationship
SM	starting material
S_N	nucleophilic substitution
T	temperature
t	tert
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
THT	tetrahydrothiophene
TIPP	triisopropylphenyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
TRIP-H	3,3’-bis(2,4,6-triisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl hydrogenphosphate
Ts	tosyl (toluenesulfonyl)
TsOH	toluenesulfonic acid
UV	ultraviolet

Contents

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.[2–4] 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.

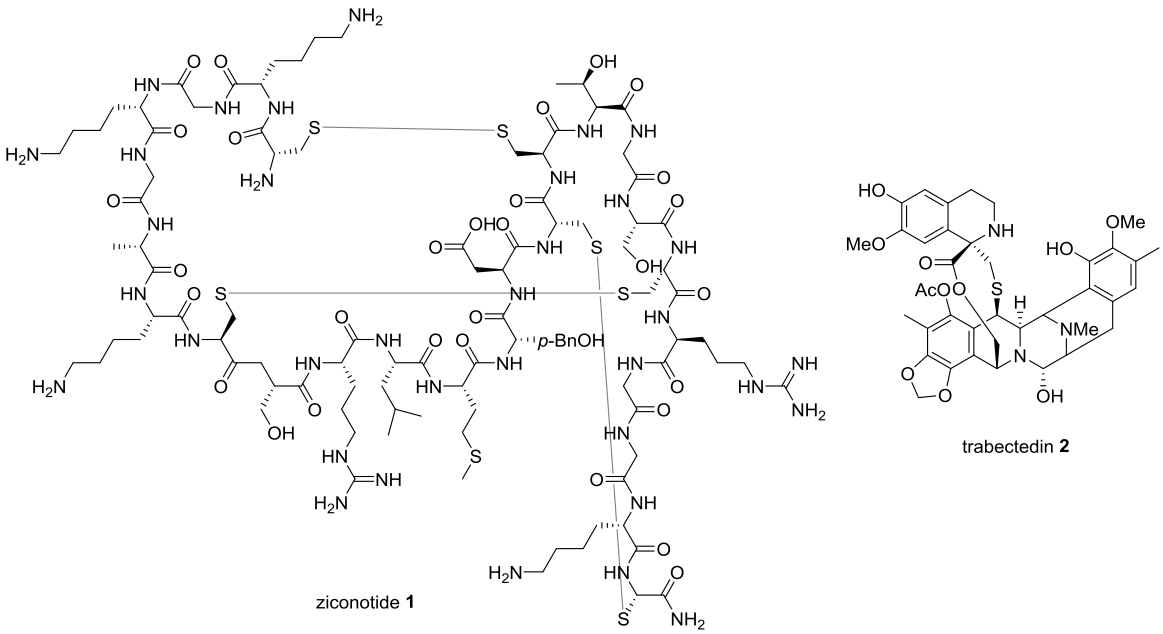


Figure 1 Structures of ziconotide and trabectedin

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]

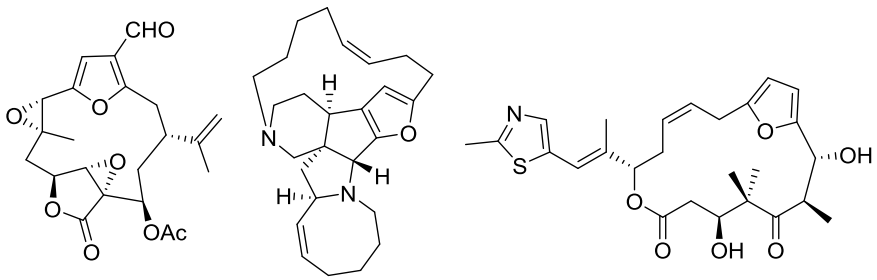


Figure 2 Examples of furan-containing natural products and analogues

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**).

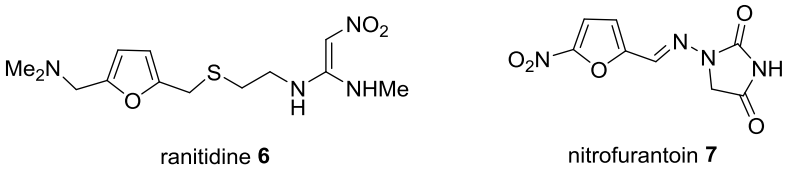


Figure 3 Examples of furan-containing drug molecules

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.[19,20]

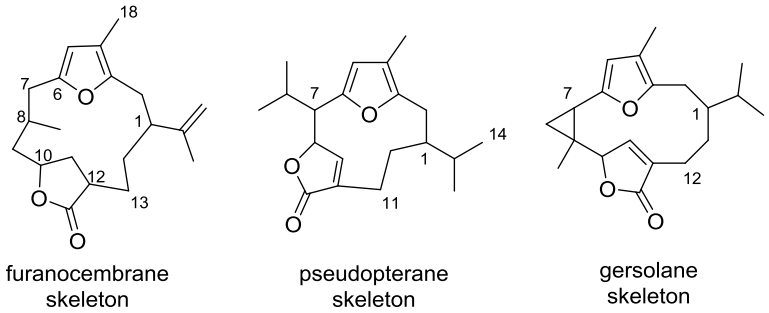


Figure 4 Skeletons of the furanocembrane, pseudopterane and gersolane natural products

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 *R* configuration; however, some furanocembranoids have been found to exhibit the opposite.[21] Lophotoxin (**3**), pukalide (**8**) and bipinnatin G (**9**), along with their various oxygenated and deoxygenated congeners, are representative of the family (**Figure 5**).

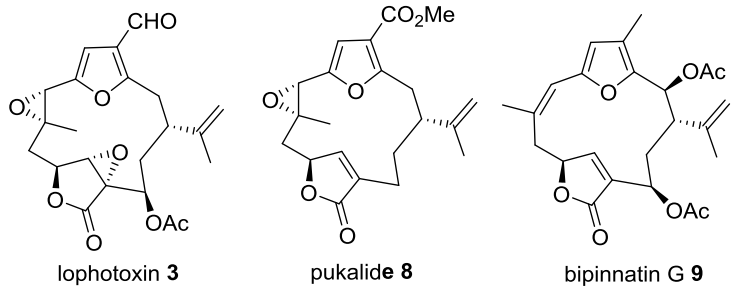
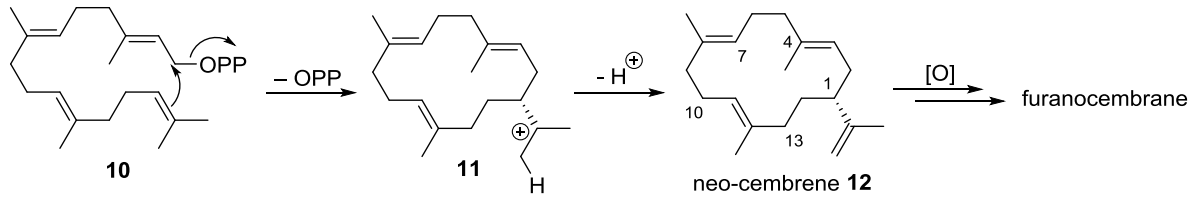


Figure 5 Representative members of the furanocembrane family

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.[22]



Scheme 1 Biosynthetic pathway to the furanocembranoids

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.[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.[13] Other compounds isolated alongside lophotoxin from the gorgorian coral *Lophorgorgia peruana* have also exhibited some cytotoxic activity against breast, lung and colon tumor cell lines.[24]

1.1.3.2 Pukalide and 7-Acetylsinumaximol 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.[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*.[26] Reportedly it is most abundant in the egg-bearing colonies and recently released eggs of *Sinularia* species.[27]

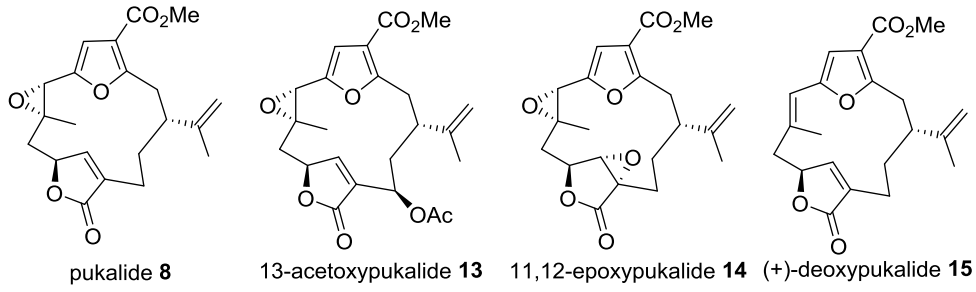


Figure 6 Structure of the natural product pukalide and its biological derivatives

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.[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 analagous 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-carbomethoxyl-10-epigyrosanoldie E (**17**), and several other related known metabolites; including pukalide and sinumaximol B. The absolute configurations of carbomethoxyl-10-epigyrosanoldie 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 Alcyonacean soft corals and Gorgonacean 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.

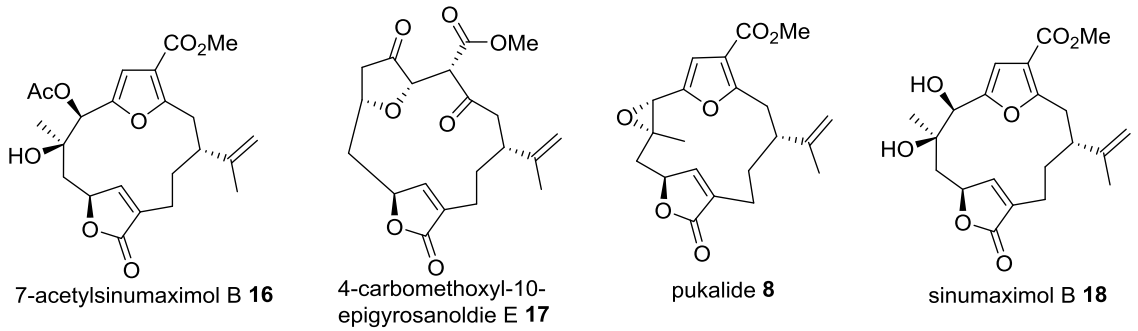


Figure 7 Metabolites isolated from *Sinularia sandensis*.

1.2 Total Syntheses of Furanocembranoids

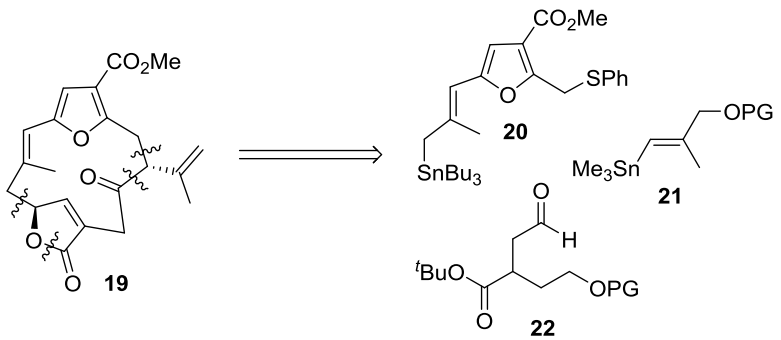
To date numerous syntheses of octocoral diterpene natural products have been reported. One of the earliest publications by Paquette *et al.* in 1992 reported the total synthesis of the pseudopterane derivative gorgiacerone.[33] The Paquette group also completed the first total synthesis of the furanocembranoid 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.

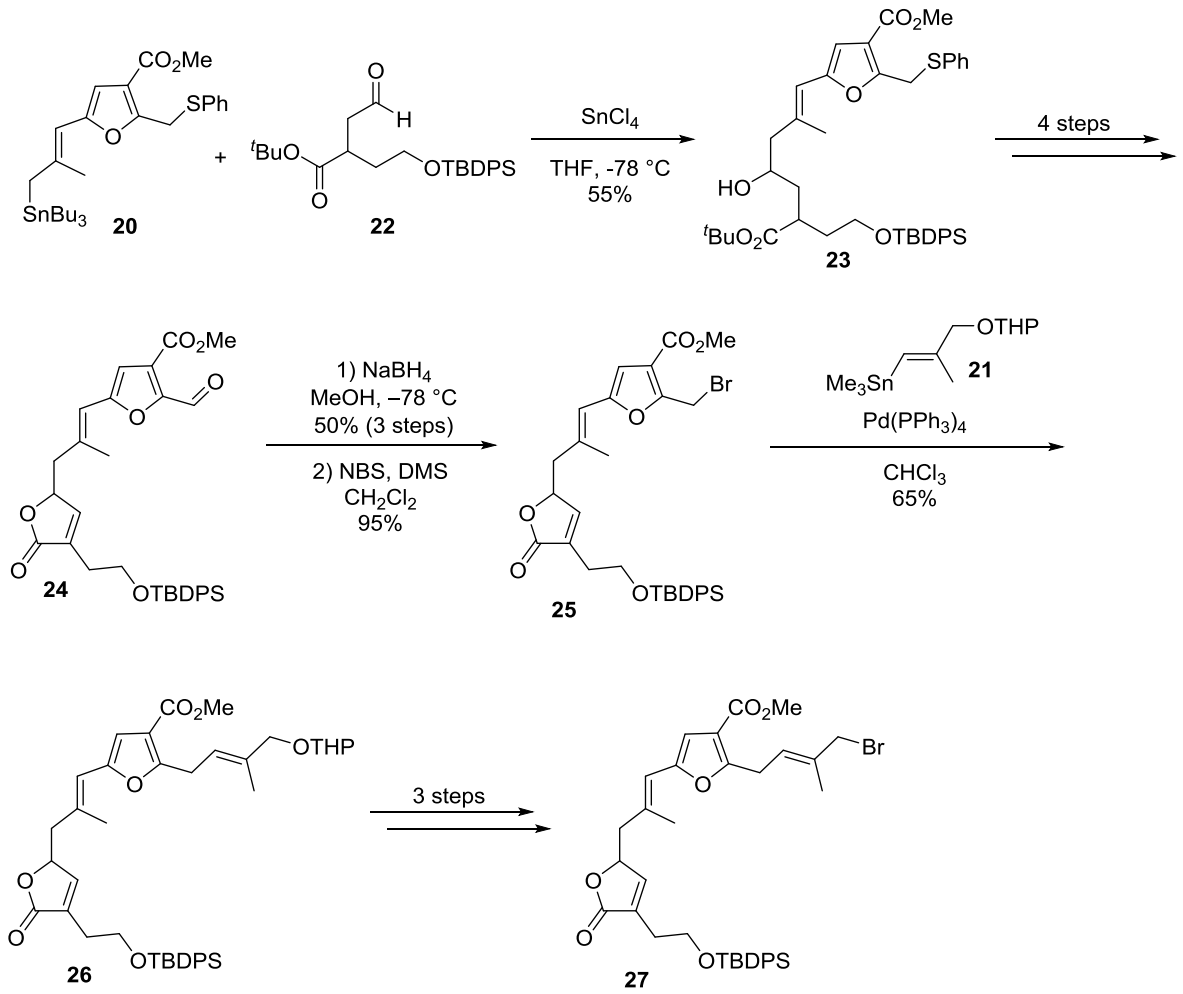
Following previous work reported by the group, for the synthesis of the pseudopterane gorgiacerone, key disconnections were made alpha to the butenolide, ketone and isoprene groups of acerosolide to give three fragments (**20**, **21** and **22**) (**Scheme 2**); the synthesis of which had been reported 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

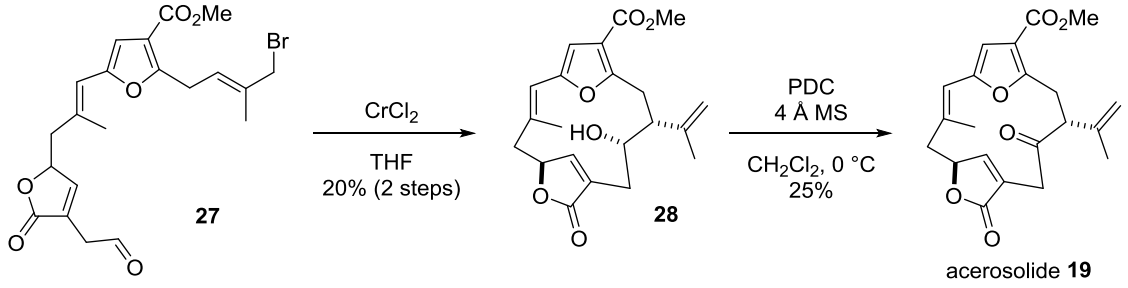
The forward synthesis began with the $SnCl_4$ promoted reaction of aldehyde **22** with allylic stannane **20**, to give homoallylic alcohol **23**. Acid-catalysed lactone formation, followed by an oxidative sequence *via* the bis-selenide afforded the butenolide **24** in four steps. The

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

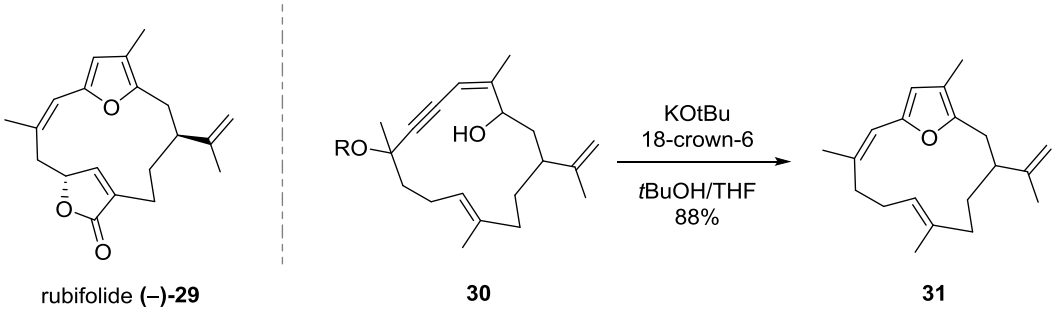
Following the elaboration of *seco*-cembrane **26** into bromo aldehyde **27**, in a three-step sequence, cyclisation was effected using $CrCl_2$ to afford a single homoallylic alcohol **28**. Finally, oxidation of the hydroxyl group gave (±)-acerosolide (**19**), as confirmed by comparison with the natural product spectra.



Scheme 4 Final steps in the total synthesis of acerosolide

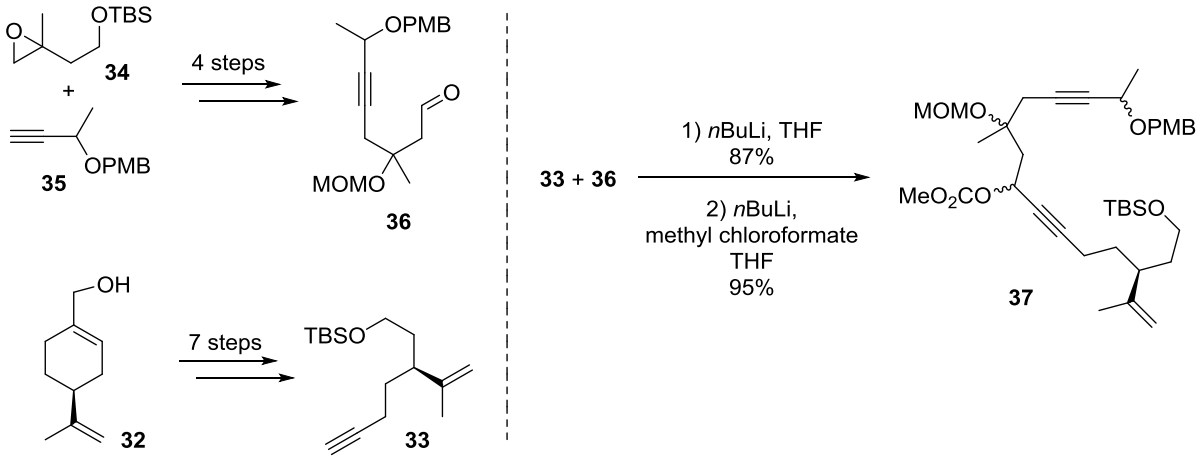
1.2.1.2 The Total Synthesis of (−)-Rubifolide

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]



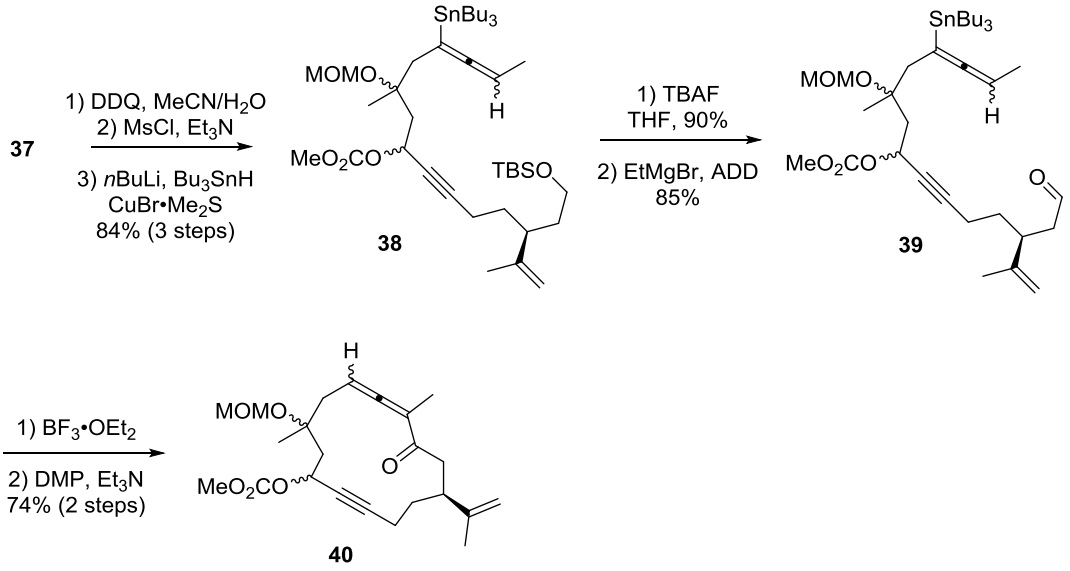
Scheme 5 Model studies for the formation of the rubifolide skeleton

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.



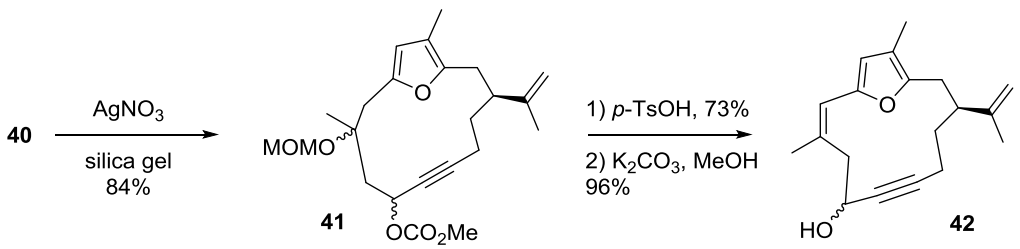
Scheme 6 Initial steps in the synthesis of (−)-rubifolide

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.



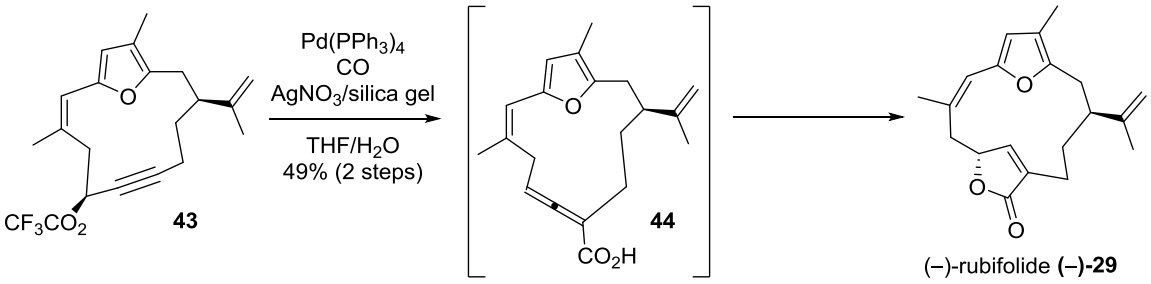
Scheme 7 Formation of a cyclised intermediate in the synthesis of rubifolide

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.

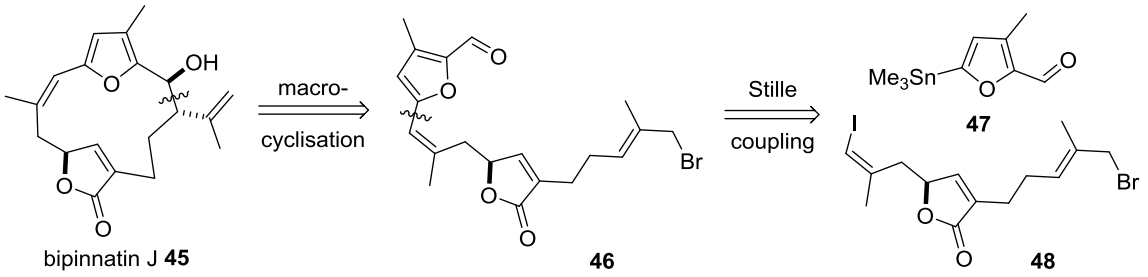


Scheme 9 Completion of the total synthesis of rubifolide

1.2.1.3 The Total Synthesis of Bipinnatin J

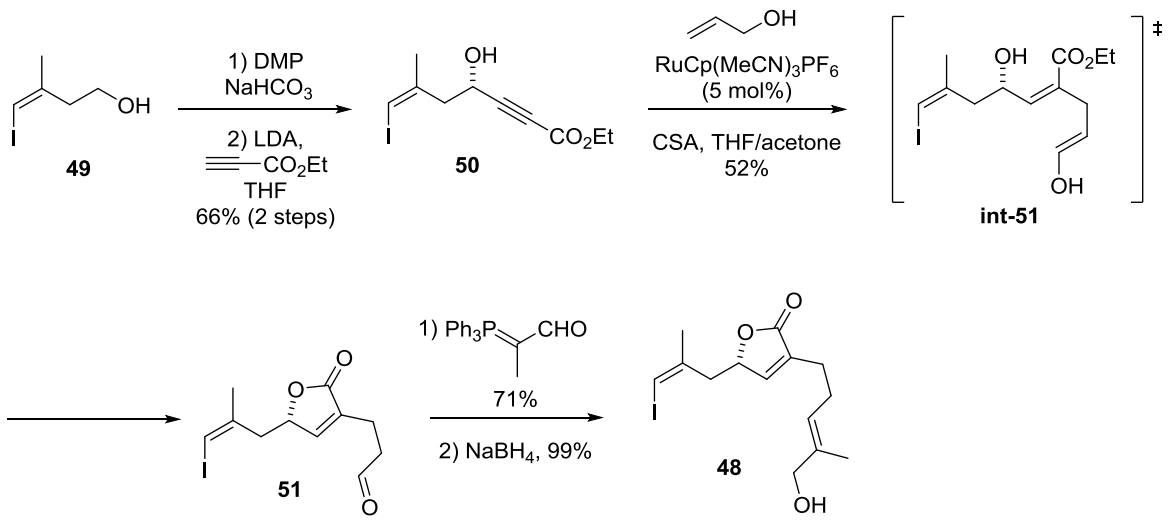
1.2.1.3.1 Trauner's Approach

In 2006, Trauner *et al.* described the first total synthesis of bipinnatin J (**45**) as a racemate.[37] Following a similar strategy to Paquette *et al*. for the synthesis of acerosolide,[34] key disconnections were made between C1-C2 and C6-C7 to allow $CrCl_2$ catalysed macrocyclisation and Stille coupling as the key synthetic steps from proposed fragments **47** and **48**.



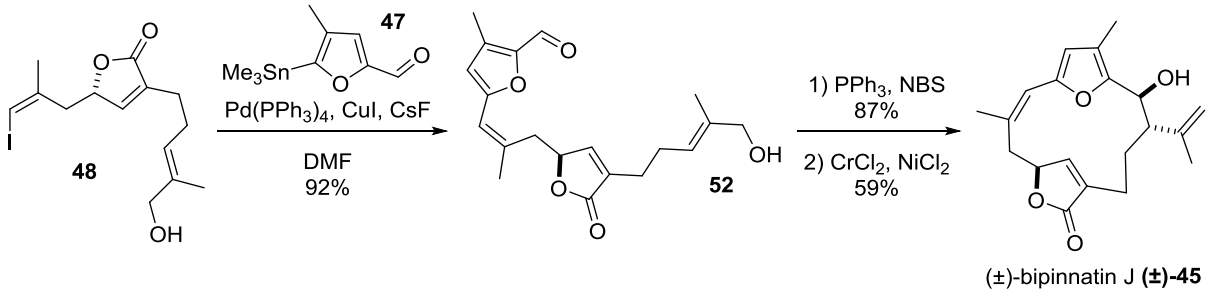
Scheme 10 Retrosynthetic analysis of bipinnatin J by Trauner

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,[41] 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**.



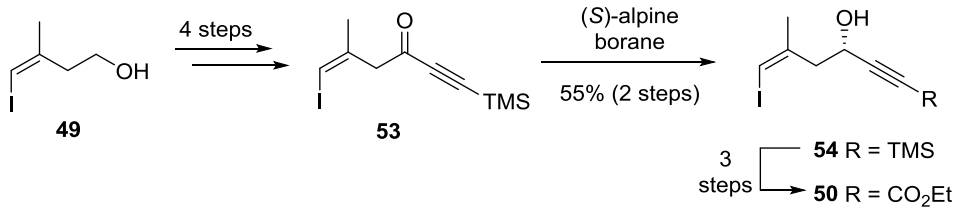
Scheme 11 Formation of the butenolide fragment in bipinnatin J

Following preparation of the vinylic 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**.



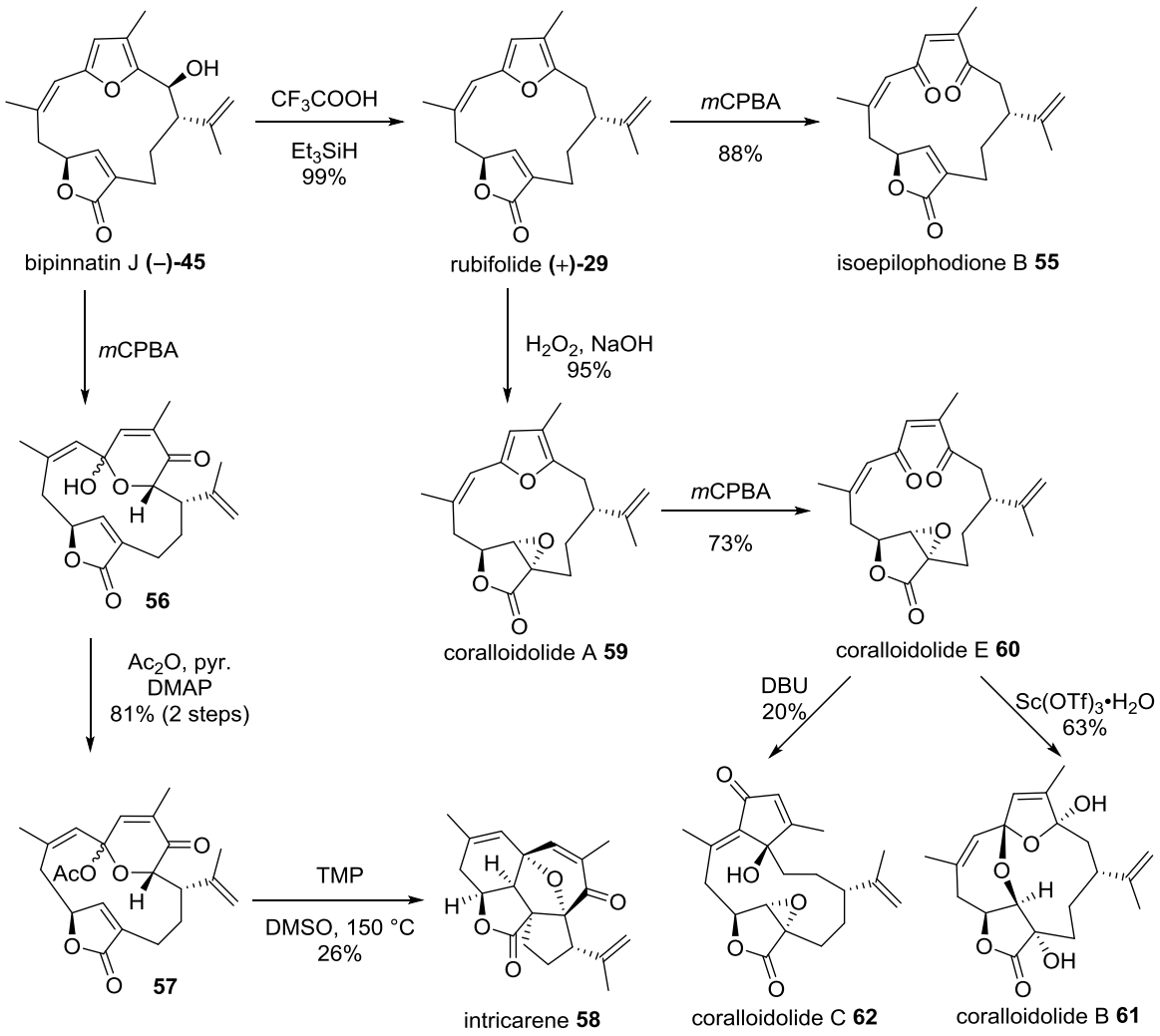
Scheme 12 Completion of the racemic synthesis of (±)-bipinnatin J

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**.[42] 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

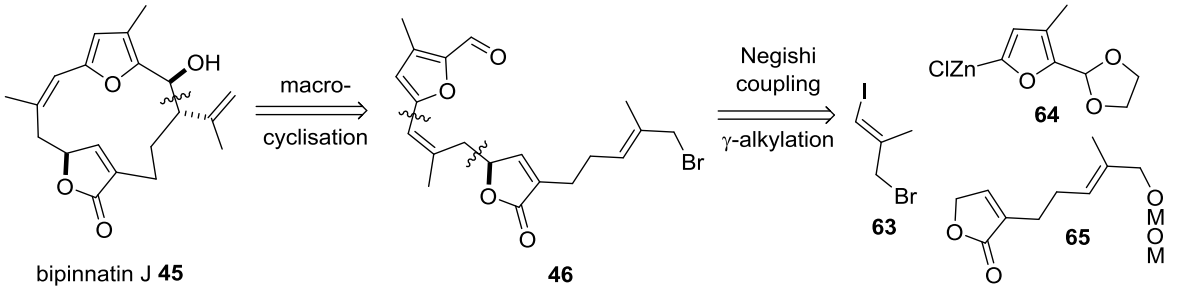
With (−)-bipnnatin J in hand, the group was able to exploit a biosynthetic approach for the synthesis of other family members (**Scheme 14**). An S_N1 deoxygenation reaction of (−)-bipinnatin J (**(−)-45**) with triethylsilane and trifluoroacetic acid gave (+)-rubifolide (**(+)-29**) in almost quantitative yield.[42] Oxidation of the furan with *m*CPBA 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 (+)-rubifolide in a series of oxidation and rearrangement steps to furnish coralloidolides A, B, C and E (**59**, **61**, **62** and **60** respectively).[44]



Scheme 14 Synthesis of multiple family members from (−) bipinnatin J

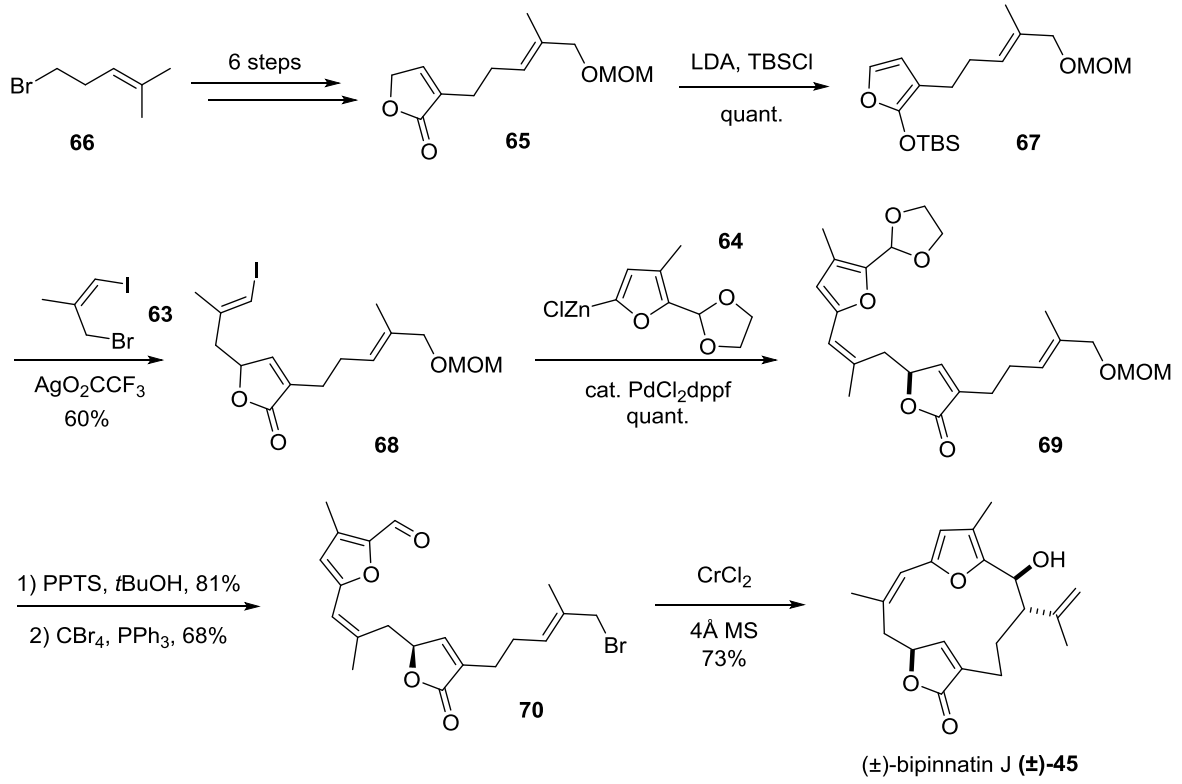
1.2.1.3.2 Rawal's Approach

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**).



Scheme 15 Retrosynthetic analysis of (±)-bipinnatin J by Rawal *et al*.

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 in to 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.



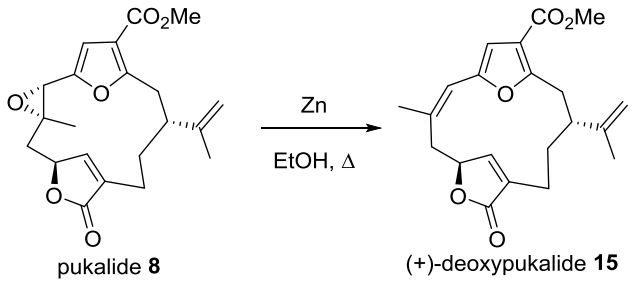
Scheme 16 Racemic synthesis of bipinnatin J by Rawal *et al.*

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]

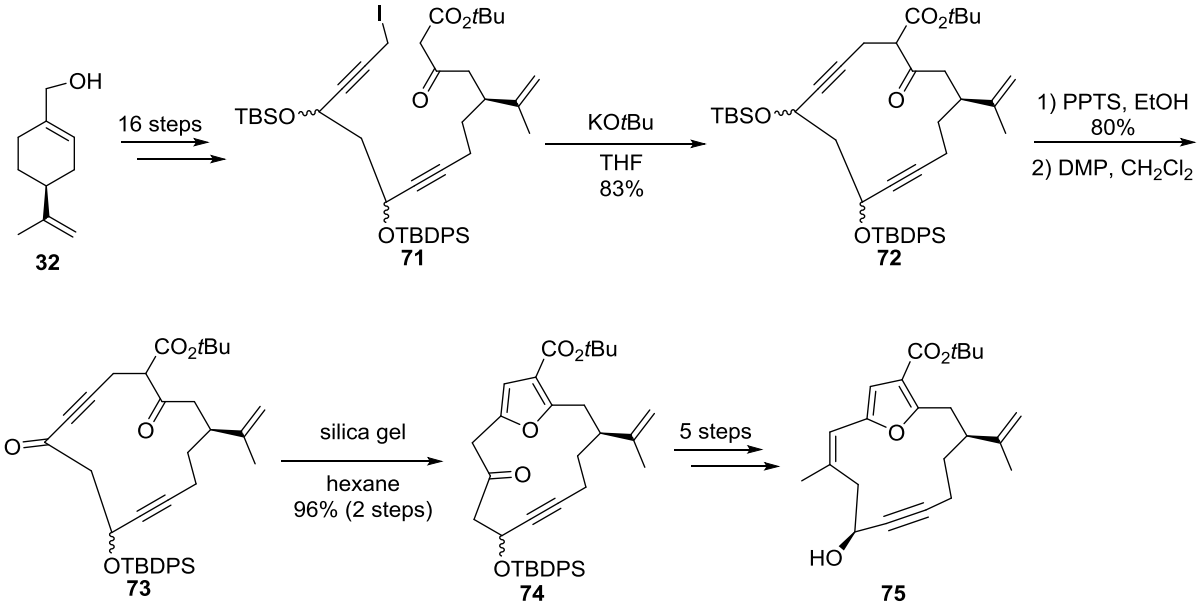


Scheme 17 Experimental formation of deoxypukalide from pukalide

1.2.2.1.1 Marshall and Van Devander's Approach

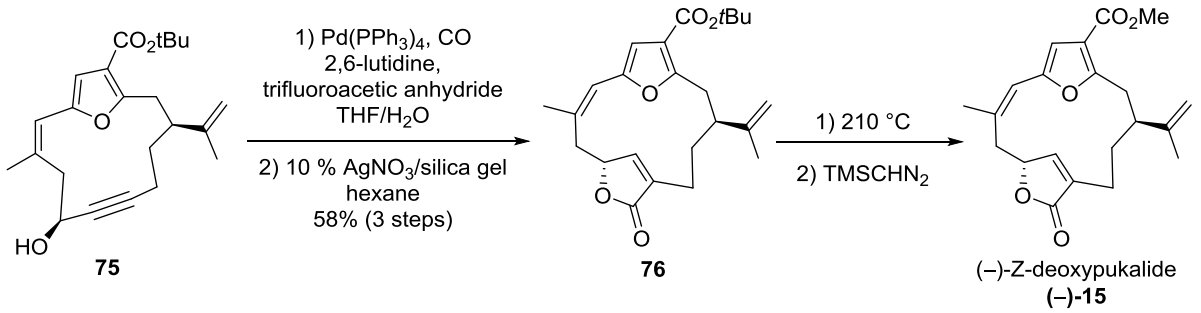
In 2001 Marshall and Van Devander reported the synthesis of the unnatural enantiomer, (−)-*Z*-deoxypukalide (**(−)-15**).[46] Starting from (*S*)-perillyl alcohol (**32**) the group described the total synthesis in 27 linear steps (**Scheme 21**). Based on their earlier work on the total synthesis of 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 KO*t*Bu 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.

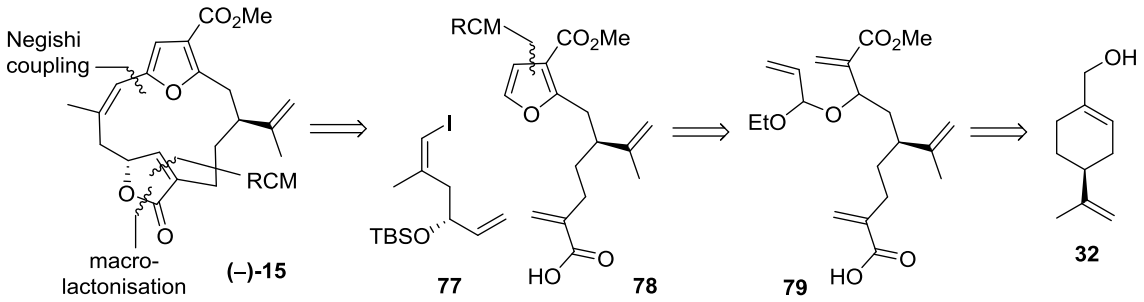


Scheme 22 Final steps in Marshall's synthesis of (−)-Z-deoxypukalide

1.2.2.1.2 Donohoe's Approach

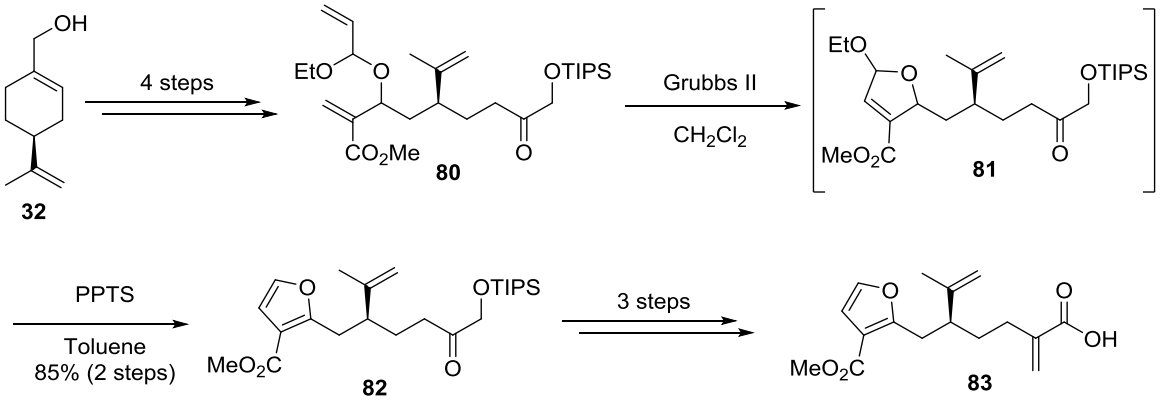
In 2008, Donohoe *et al.* also reported the total synthesis of the unnatural enantiomer, (−)-Z-deoxypukalide (**(−)-15**), from the same chiral pool starting material, (*S*)-perillyl alcohol **32**.[47] Donohoe *et al.* proposed that the furan-alkene bond could be formed by Negishi cross coupling as shown by Rawal *et al.* in the synthesis of bipinnatin J.[45] 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**.



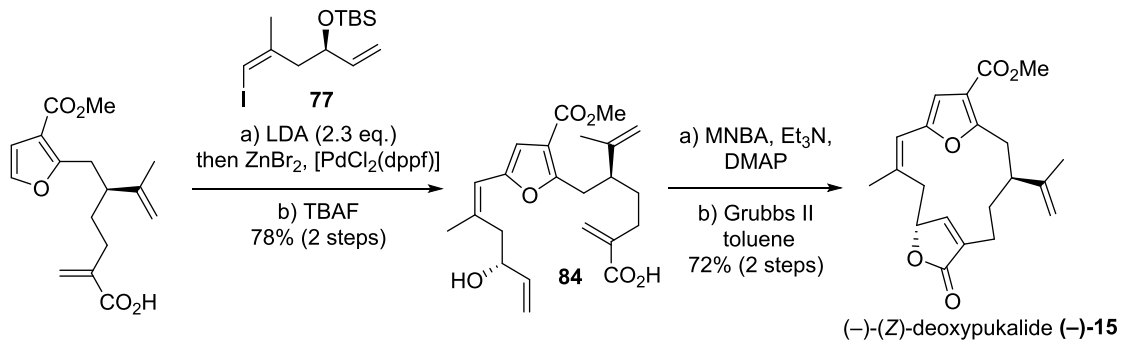
Scheme 23 Retrosynthetic analysis of (−)-Z-deoxypukalide by Donohoe *et al*.

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_2Cl_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.*

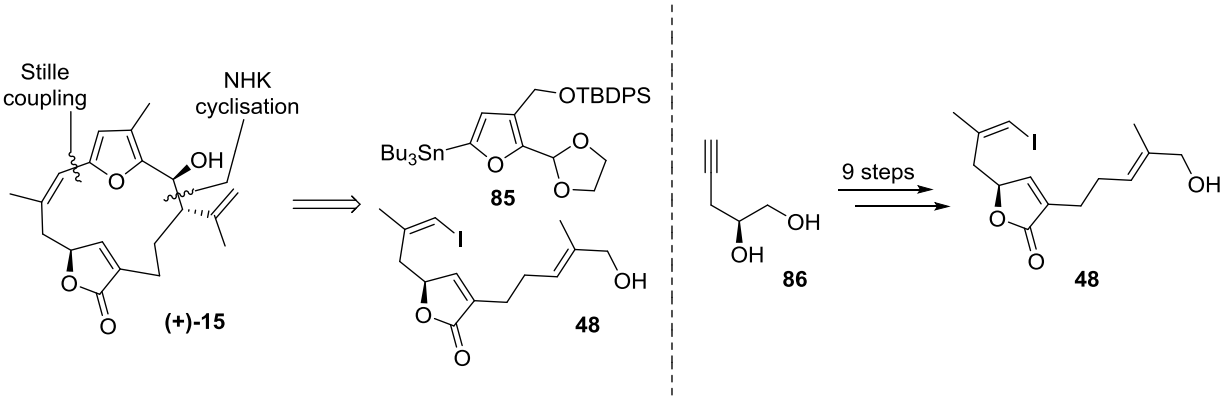
The side-chain on the furan ring was installed by a Negishi cross-coupling reaction with the vinylic iodide **77**, which was synthesised in a four-step sequence previously reported by Pattenden.[49] Double deprotonation of **83** with LDA and *in situ* transmetalation with zinc bromide was followed 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%.



Scheme 25 Final steps in the synthesis of (−)-*Z*-deoxypukalide by Donohoe *et al*.

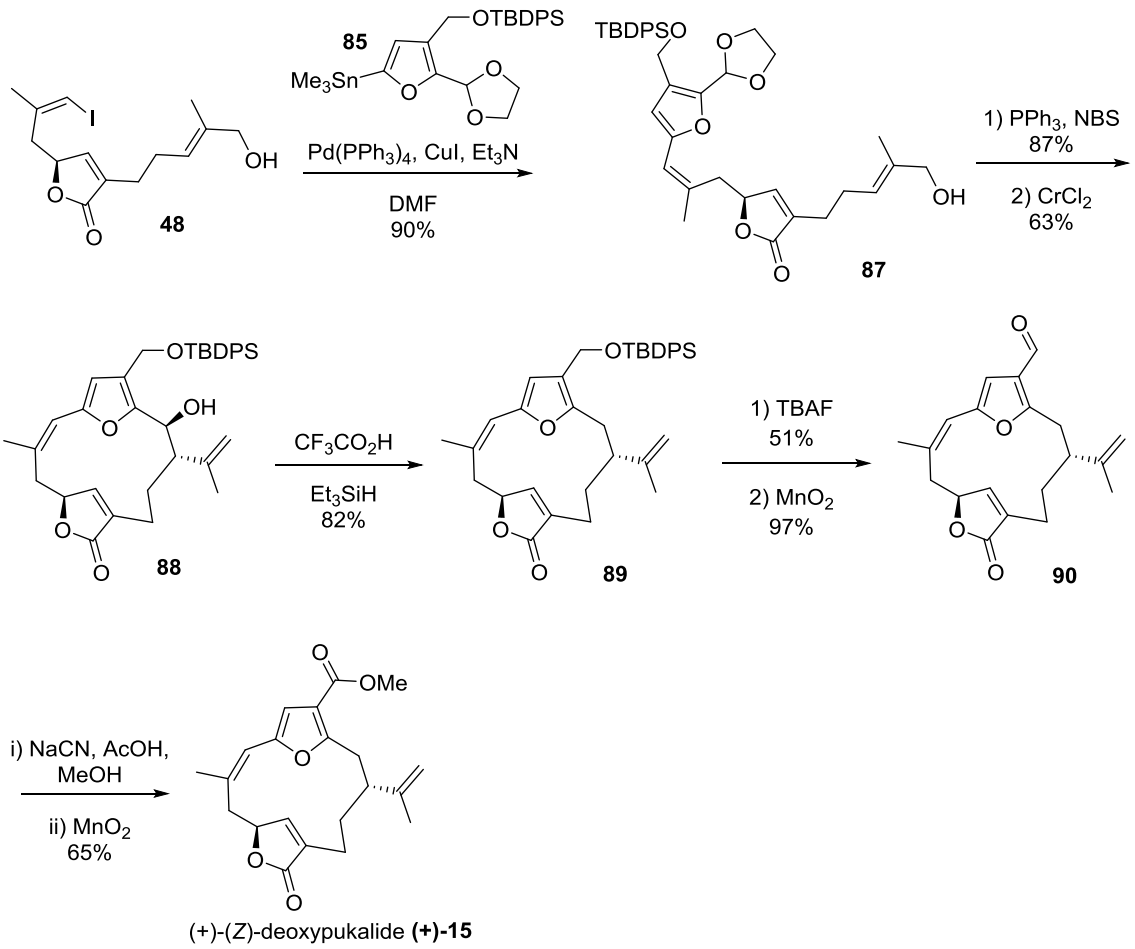
1.2.2.1.3 Pattenden's Approach

A further total synthesis of (+)-*Z*-deoxypukalide (**(+)-15**) was reported by Pattenden *et al*. in 2010.[35] Disconnections were made as in Trauner's synthesis of bipinnatin J;[42] between C6-C7 and C1-C2. The same vinylic 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

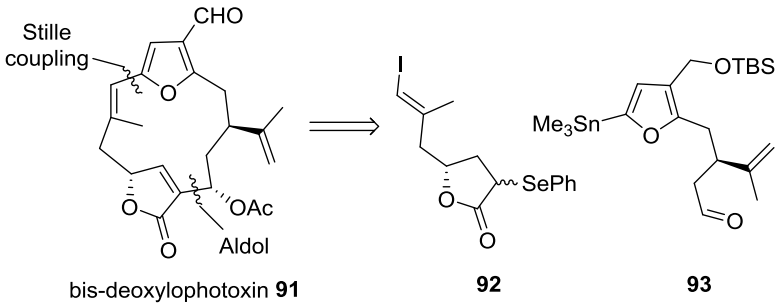
Having established a route to vinylic iodide fragment **48**, Stille coupling with furylstannane **85** afforded the cyclisation precursor **87**. Formation of the corresponding bromide using NBS and PPh_3, followed by NHK macrocyclisation furnished the macrocycle **88** in good yield. Deoxygenation 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.



Scheme 27 Pattenden's synthesis of (+)-*Z*-deoxypukalide

1.2.2.2 Synthesis of Bis-deoxylophotoxin

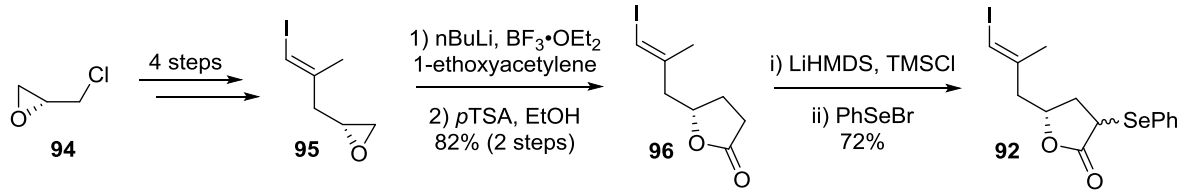
In 2005, Pattenden *et al*. reported the synthesis of bis-deoxylophotoxin (**91**); a lophotoxin analogue with alkenes in place of the epoxides across C7-C8 and C11-C12.[51] Disconnections between C6-C7 and C12-C13 led to the proposal of Stille coupling and an aldol-type reaction as the key steps for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



Scheme 28 Retrosynthetic analysis of bis-deoxylophotoxin (**91**)

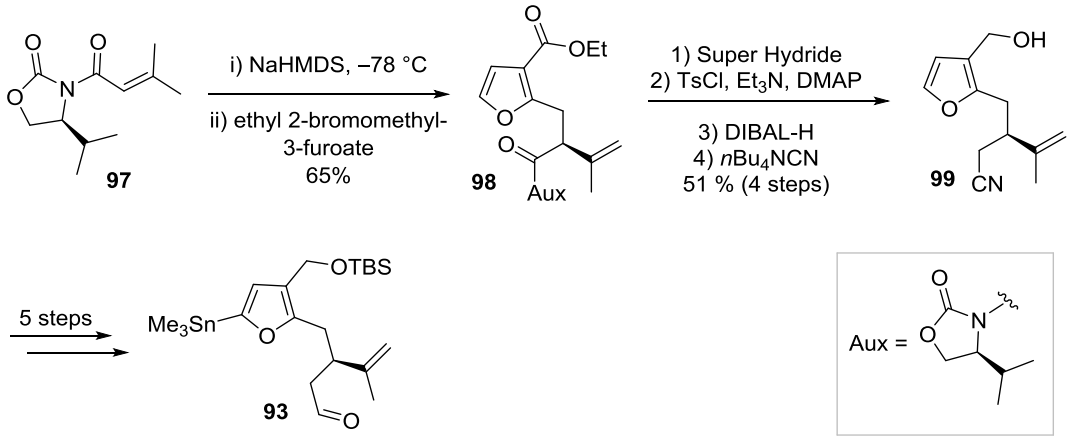
Formation of lactone fragment **92** was achieved from chiral epoxide **95,** which was obtained from (*R*)-epichlorohydrin (**94**) in four steps and with high *ee*. Treatment of epoxide **95** with

the lithium salt of 1-ethoxyacetylene, followed by reaction with *p*TSA 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

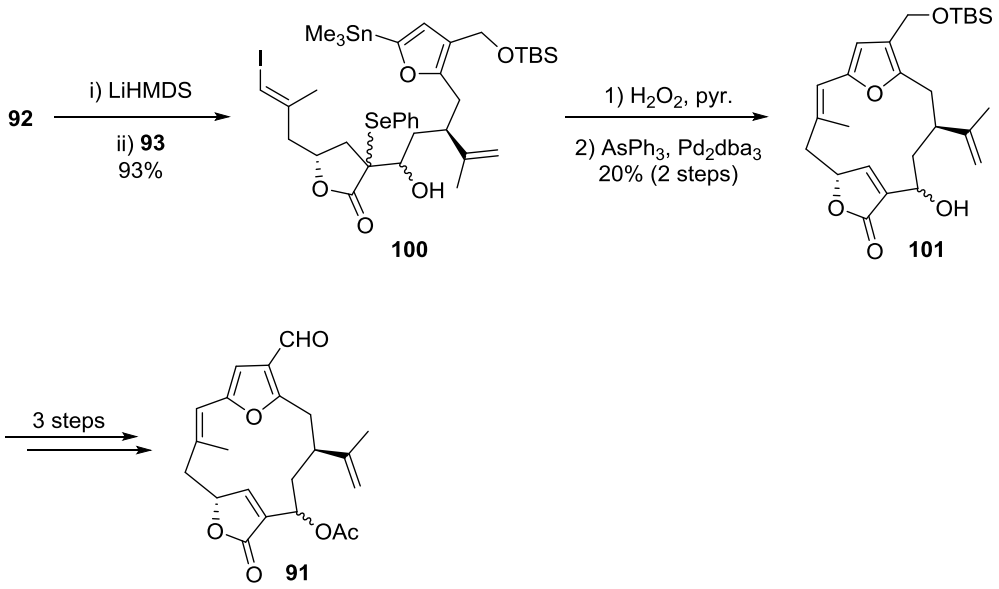
Furan-aldehyde fragment **93** was prepared from oxazolidinone **97** in 10 steps. Deconjugative alkylation through deprotonation of oxazolidinone imide **97** and treatment with ethyl-2-bromomethyl-3-furoate furnished the furan adduct **98**. Reduction of the imide to the corresponding alcohol using two equivalents of Super Hydride was followed by tosylate formation, reduction of the ethyl ester using DIBAL-H and subsequent S_N2 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 H_2O_2 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

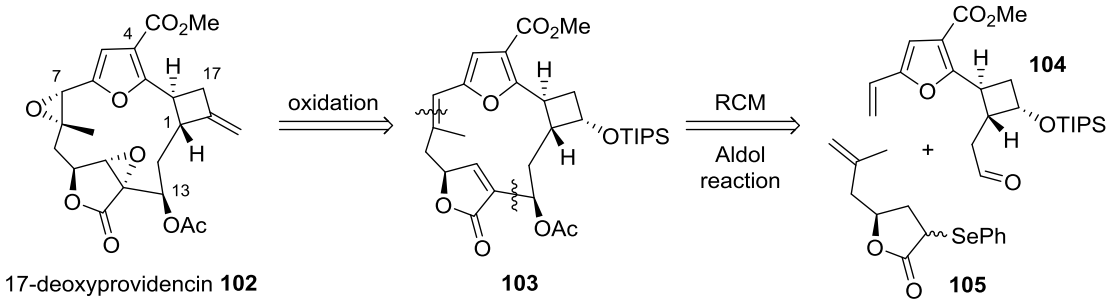
sequence furnished both epimers of bis-deoxylophotoxin (**91**) from the corresponding isomeric alcohols **101**.



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

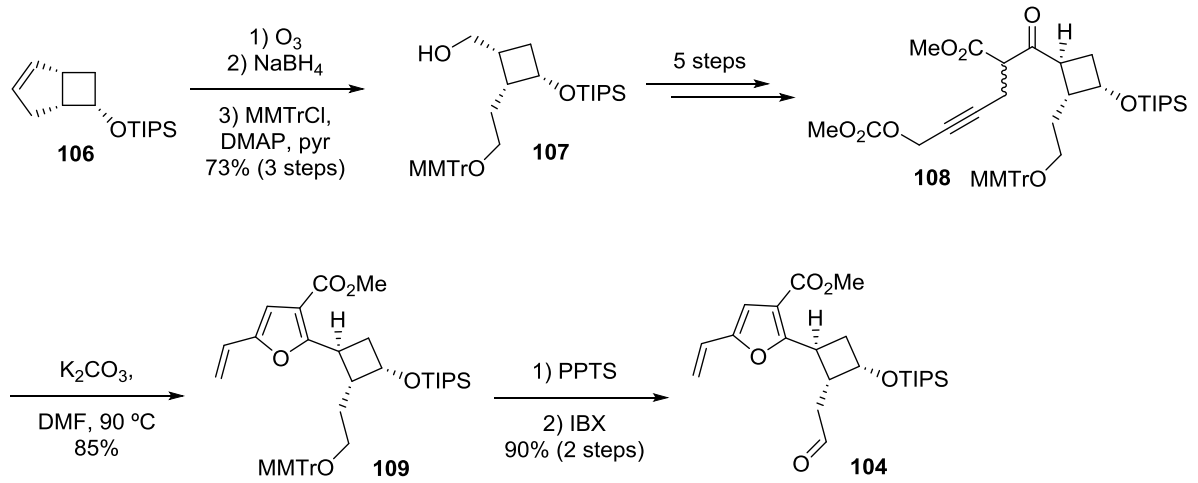
1.2.2.3 Synthesis of Deoxyprovidencin

One of the most recent publications by Mulzer *et al.* detailed the total synthesis of 17-deoxyprovidencin (**102**).[52] 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**.



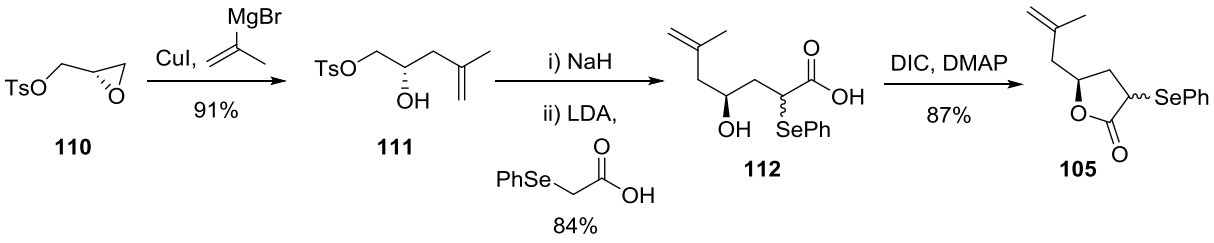
Scheme 32 Retrosynthetic analysis of deoxyprovidencin by Mulzer *et al.*

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**

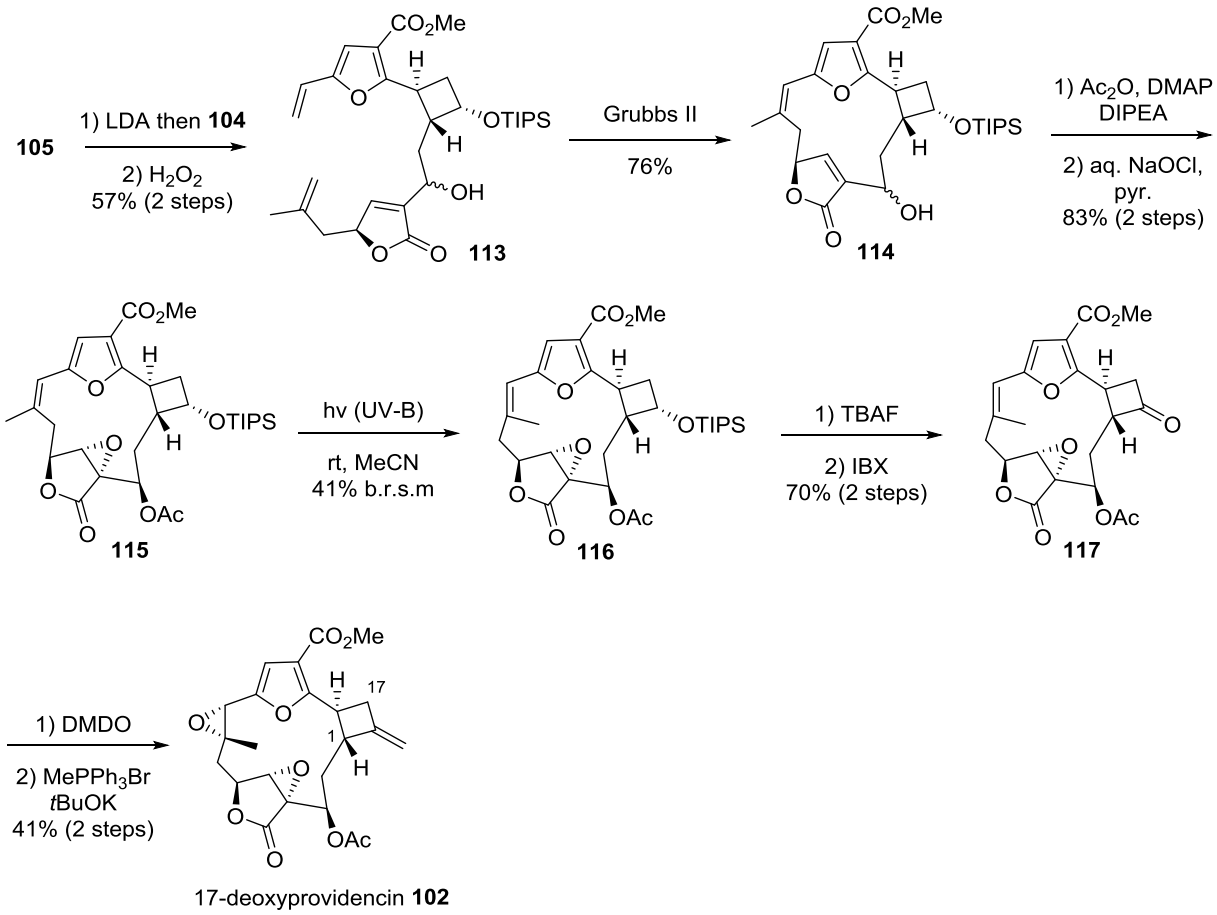
Selenolactone fragment **105** was prepared from (*R*)-glycidyl tosylate (**110**) in three steps. Cuprate mediated addition of isoprenyl magnesium bromide afforded alcohol **111** which was converted into selenide **112** through NaH promoted epoxide formation and treatment with the dianion of phenylselenyl 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 H_2O_2 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.*

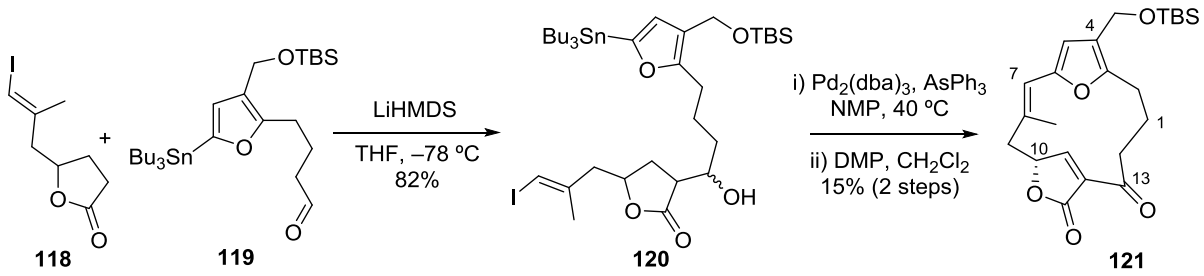
1.2.3 Synthetic Approaches Towards the Furanocembrane Skeleton

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

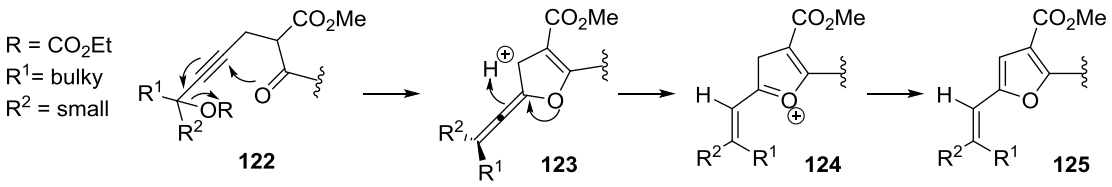
and then coupled using an intermolecular aldol reaction with LiHMDS as the base to afford the alcohol **120** in high yield. However, this strategy proved to be unsuitable as the intramolecular Stille coupling-oxidation sequence afforded the macrocycle **121** in very low yield (15%). Despite the limitations 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

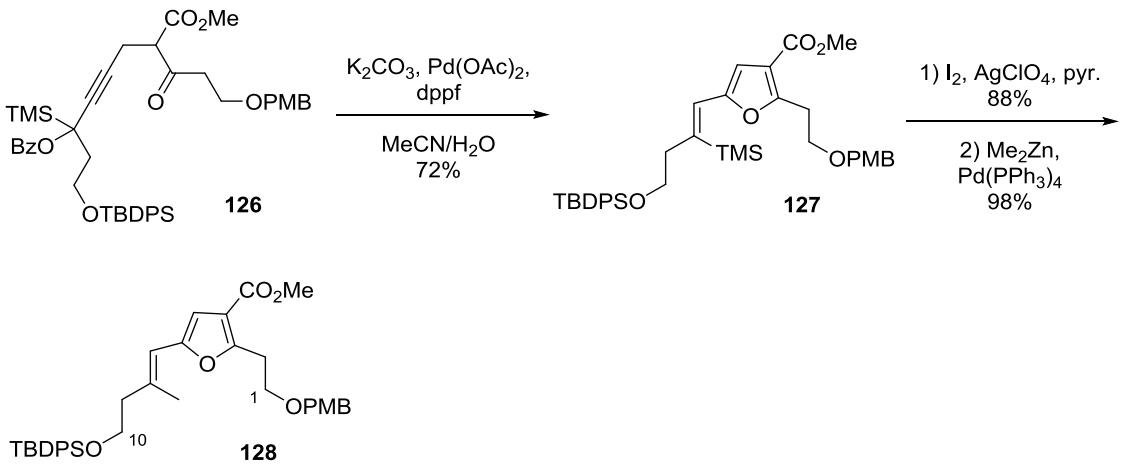
1.2.3.2 Wipf's Approach to the Furanocembrane Skeleton

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.



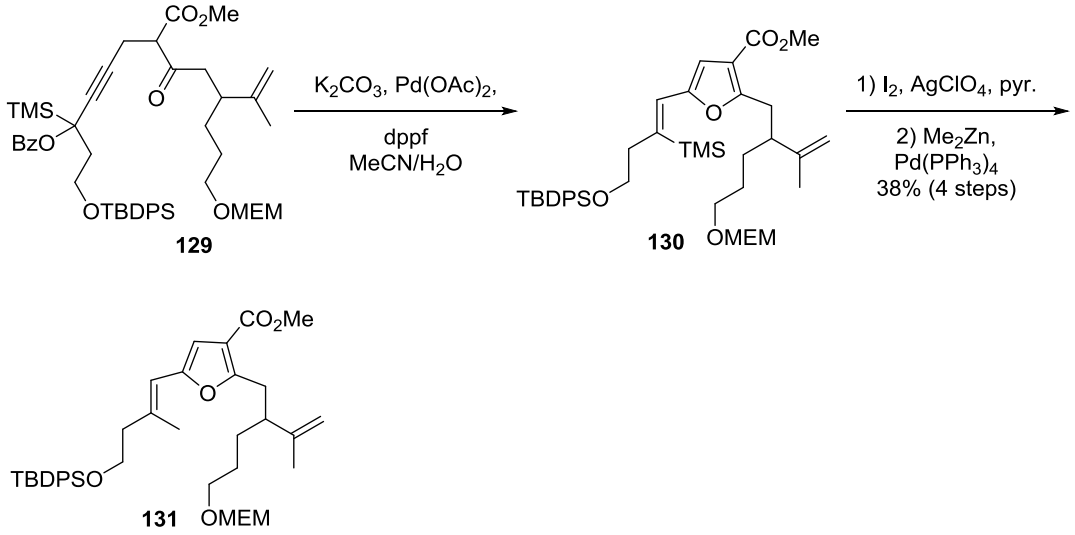
Scheme 37 Facial selectivity in Wipf and Soth's furan formation

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

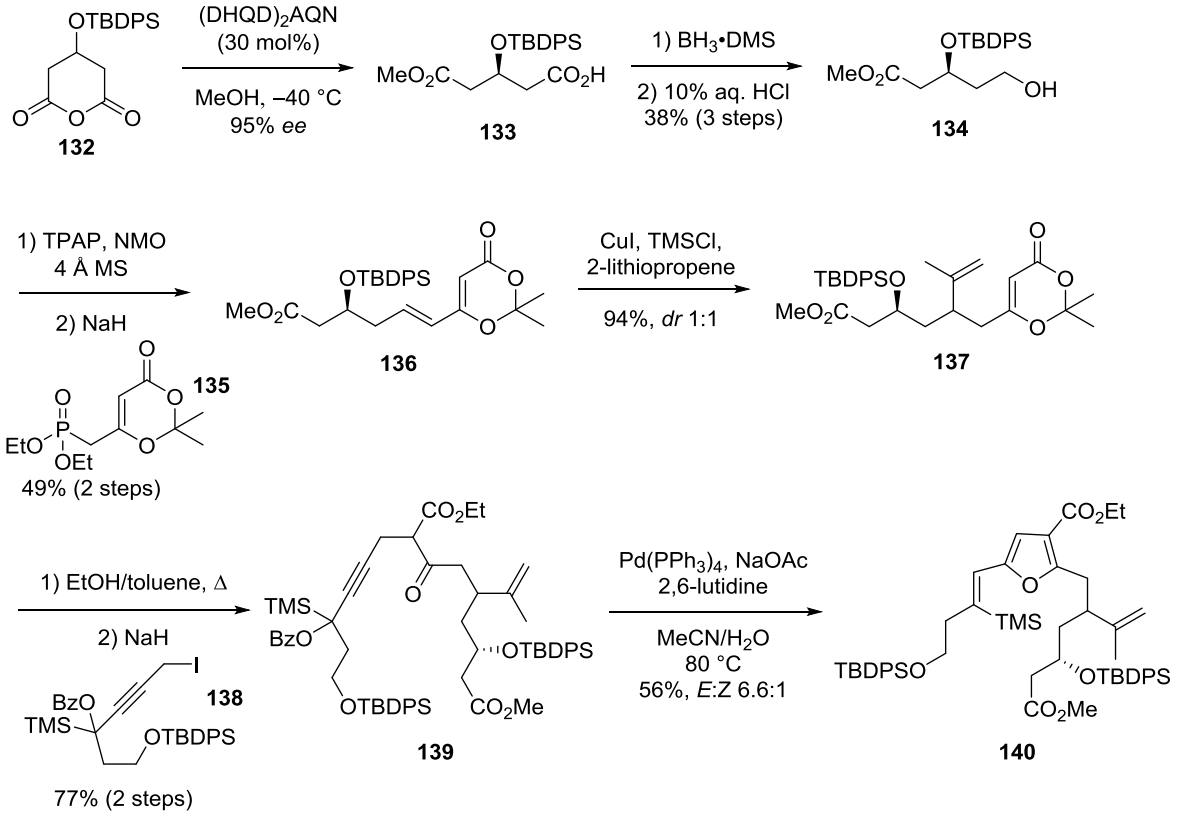
Preparation of an advanced racemic intermediate **131** was achieved subsequently following the same protocol. From intermediate **129** cyclisation, silyl-iodine exchange and Negishi coupling proceeded as before, in moderate yield, to give furan **131**. Overall the fragment was synthesised in a total 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.[56] 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,

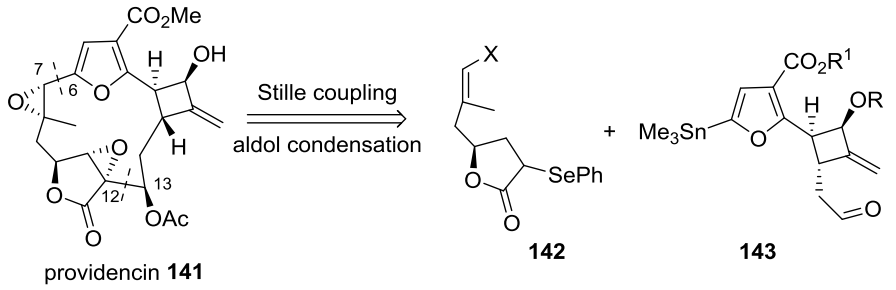
delivering moderate yields and low *dr*. Thermolysis of the dioxin-4-one ring afforded the corresponding β-keto ester which was alkylated with iodide **138** to afford alkyne **139**. Palladium catalysed furan formation was then effected as described previously, albeit with an alternative catalyst and base, to afford furan **140**. Despite preparing this late stage intermediate, Wipf reported no further progress towards the targets of interest.



Scheme 40 Lophotoxin fragment synthesis reported by Wipf

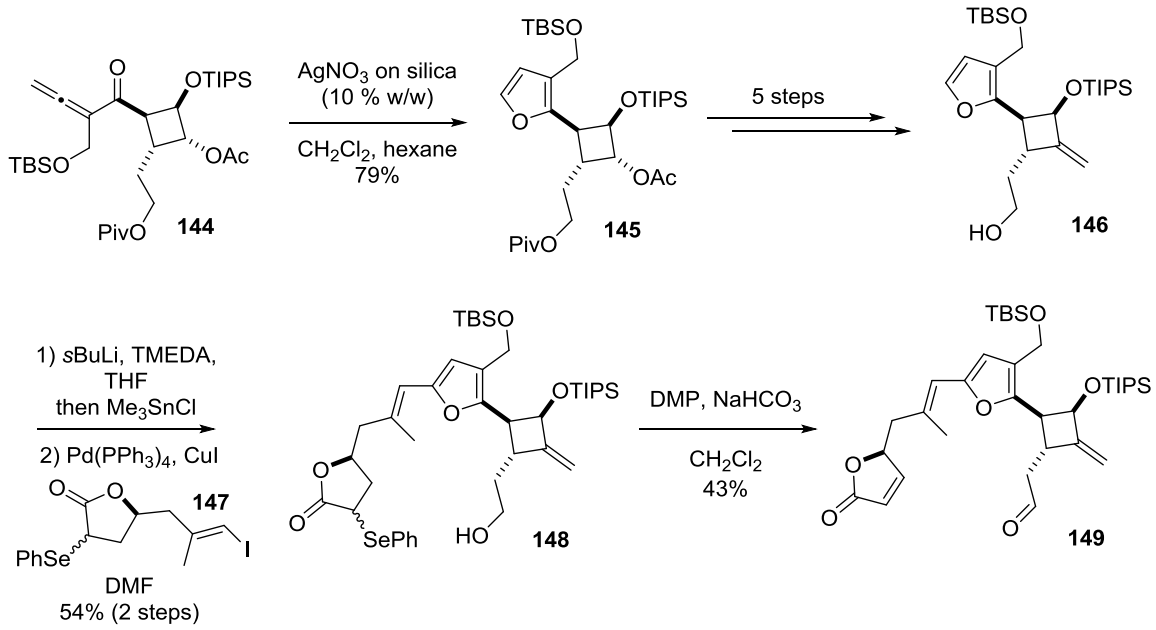
1.2.3.3 White's Approach to the Furanocembrane Skeleton

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

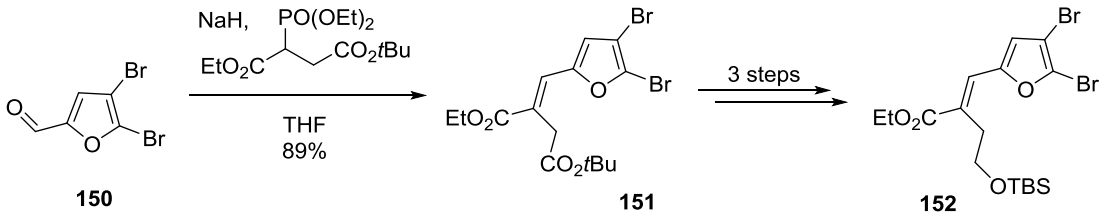
The furan moiety **145** was synthesised by a silver nitrate/silica mediated cyclisation of the keto-allene **144** under conditions similar to those described by Marshall (**Scheme 21**).[46] Subsequent functionalisation of **145**, over five further steps, led to the formation of furan **146** with 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

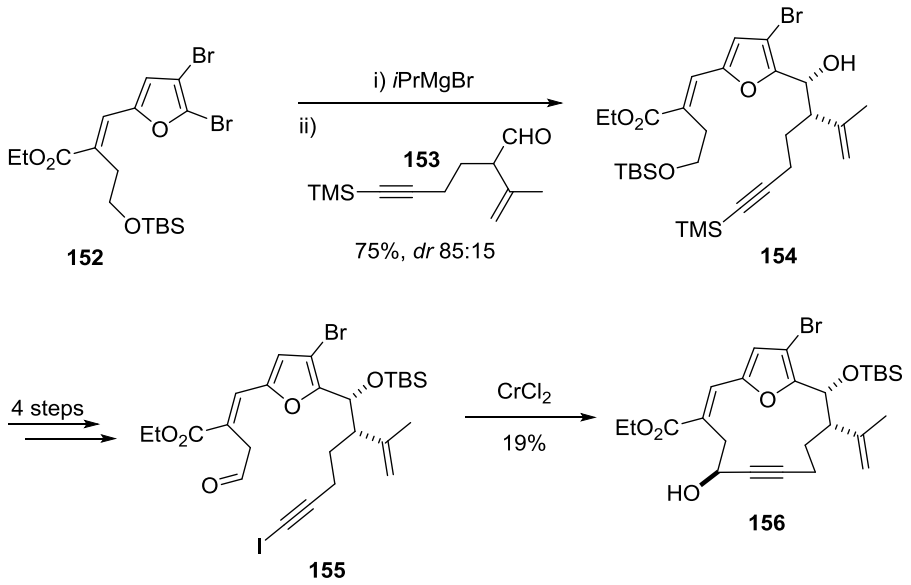
1.2.3.4 Bach's Approach to the Furanocembrane Skeleton

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**

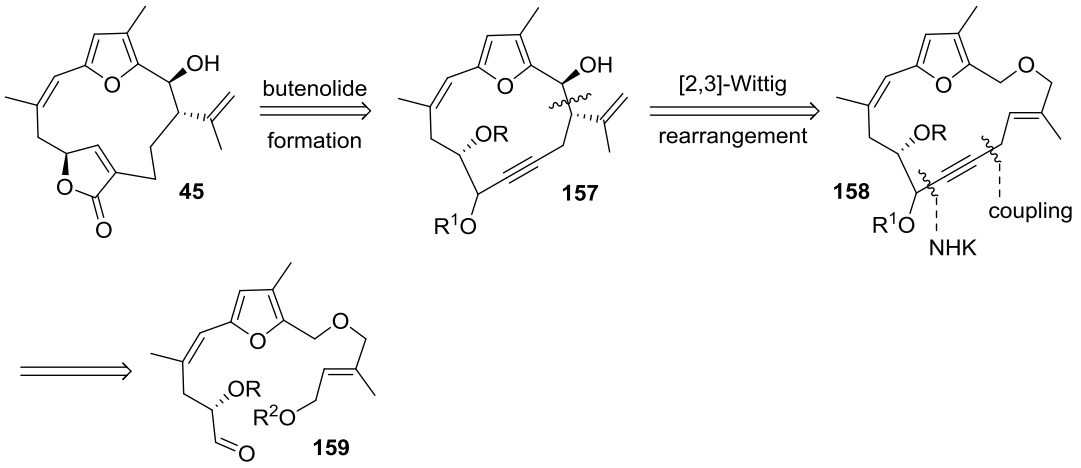
Formation of the furfuryl-Grignard reagent from **152** occurred readily and reaction with vinyl aldehyde **153** occurred cleanly and regioselectively to give alcohol **154**. Attempts to form the C2-C3 carbon bond in other ways were unsuccessful; cross-coupling failed and the use of lithium-halogen 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

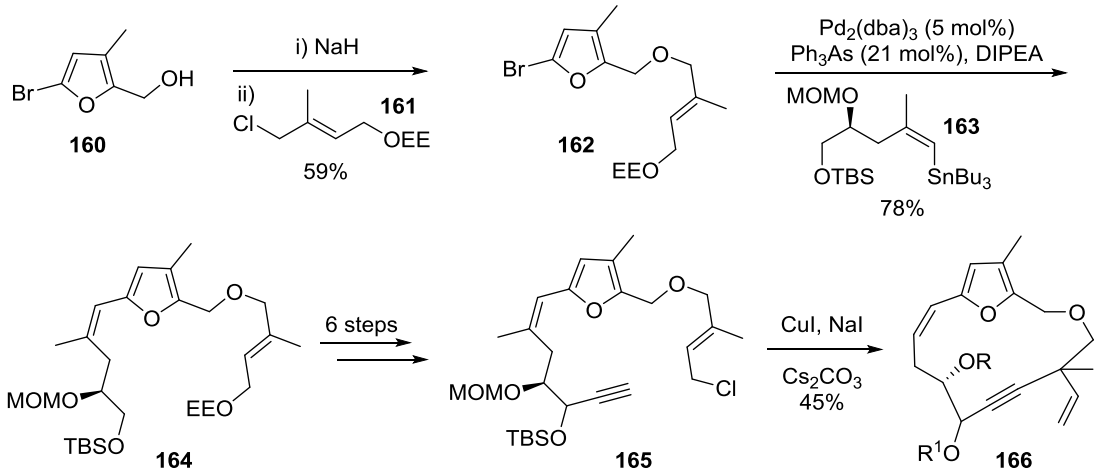
1.2.3.5 Honda's Approach to the Furanocembrane Skeleton

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**).[59] 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.



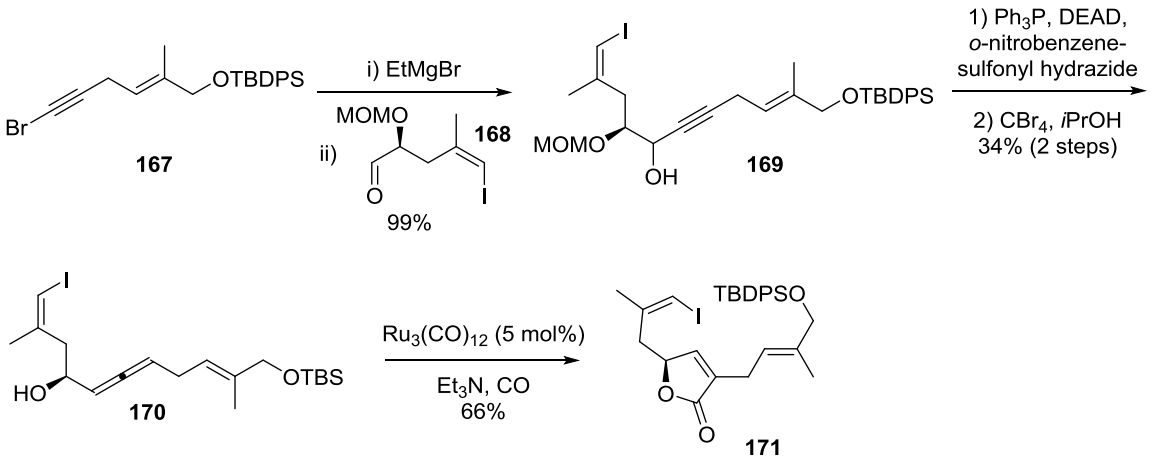
Scheme 45 Retrosynthetic analysis of bipinnatin J by Honda *et al*.

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_2CO_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.*[60] utilising Mitsunobu elimination and subsequent removal of the MOM protecting group with CBr_4 in *i*PrOH. 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 lophotoxin and pukalide has proven to be particularly challenging, with only Mulzer *et al*. having established a successful strategy for its incorporation.[52] 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.

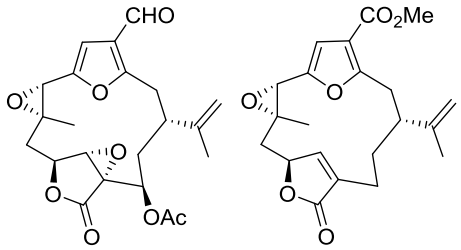
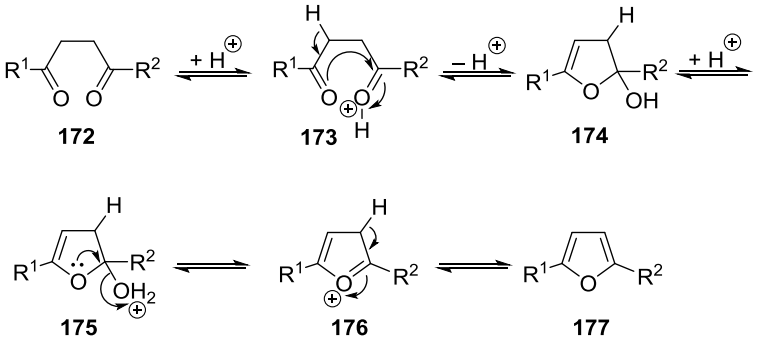


Figure 8 Structures of lophotoxin and pukalide

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.

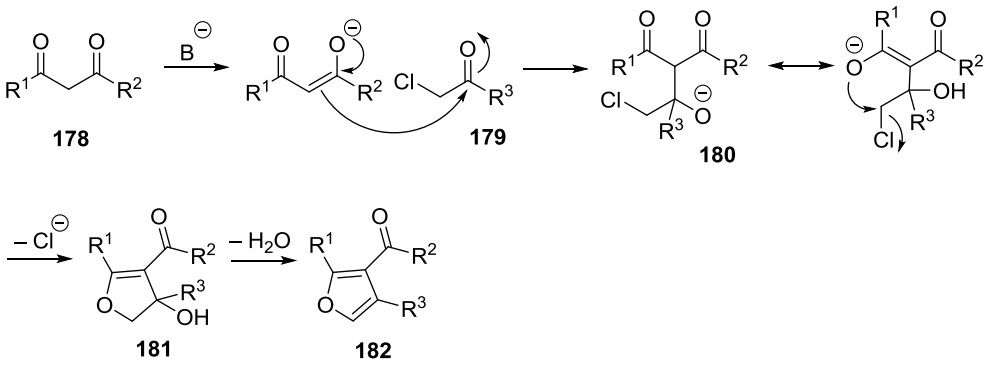
1.3.2 Classical Synthesis of Furan Molecules

The two most important traditional methods for the formation of furans are the Paal-Knorr and Feist-Benary syntheses, first reported in the late 19th and early 20th 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 *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 **174**. Subsequent dehydration promoted by a strong acid, Lewis acid or dehydrating agent, such as acetic anhydride, followed by enolisation, delivers the desired furan **177**.



Scheme 47 Paal-Knorr synthesis of furans

The Feist-Benary synthesis, originally reported by Feist in 1902, also proceeds *via* a condensation type reaction.[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**.



Scheme 48 Feist-Benary synthesis of furans

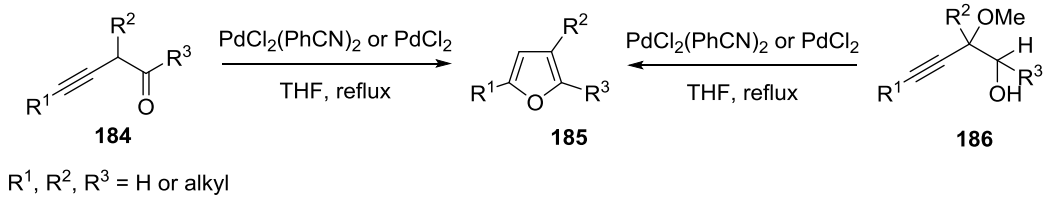
Although these classical methods are useful, they have two major disadvantages: their incompatibility with acid or base sensitive functional groups and the fact that they do not allow for the introduction of a great amount of complexity on the furan ring. As a result of these limitations, many other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

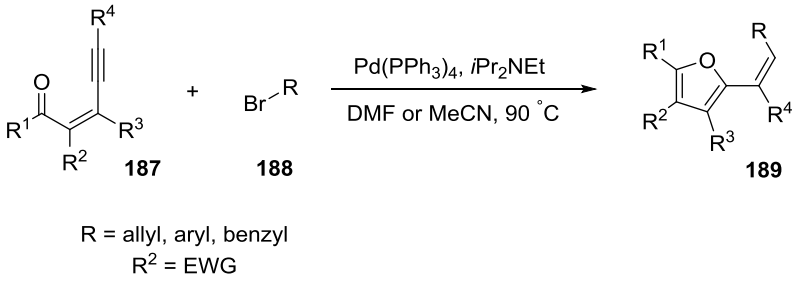
1.3.3.1 Palladium Catalysis

To date, palladium catalysis, along with gold catalysis, has become one of the most commonly used methods for the synthesis of substituted furans.[71] Utimoto reported some of the first examples of Pd(II)-catalysed furan formation in 1983.[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**).



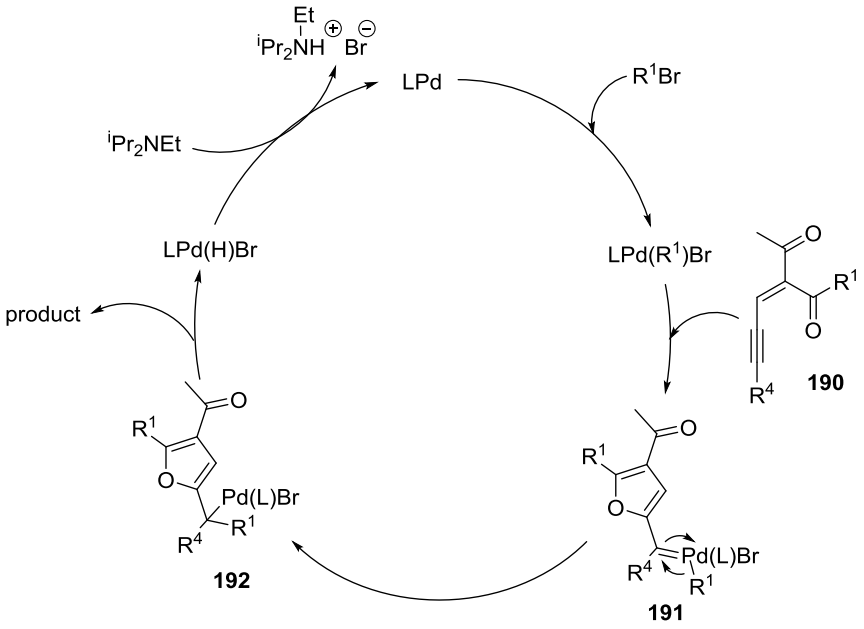
Scheme 49 Pd-catalysed furan formation reported by Utimoto

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.[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**).[74]



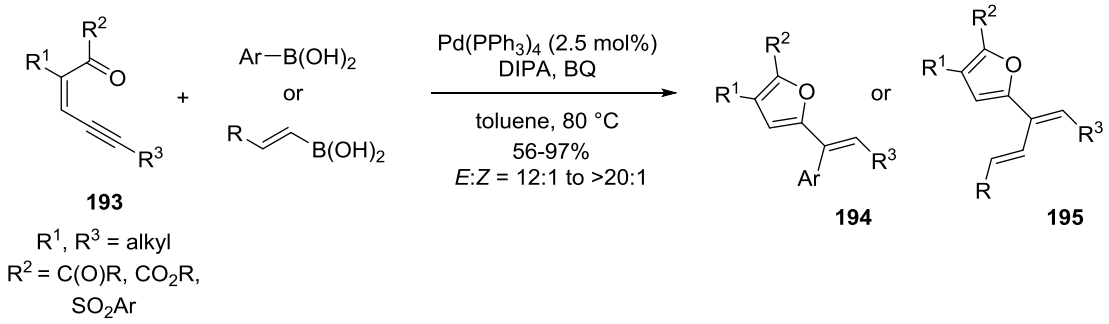
Scheme 50 Palladium catalysed furan formation described by Wang

The reaction proceeds in good yields; however, the nature of the R^4 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**).



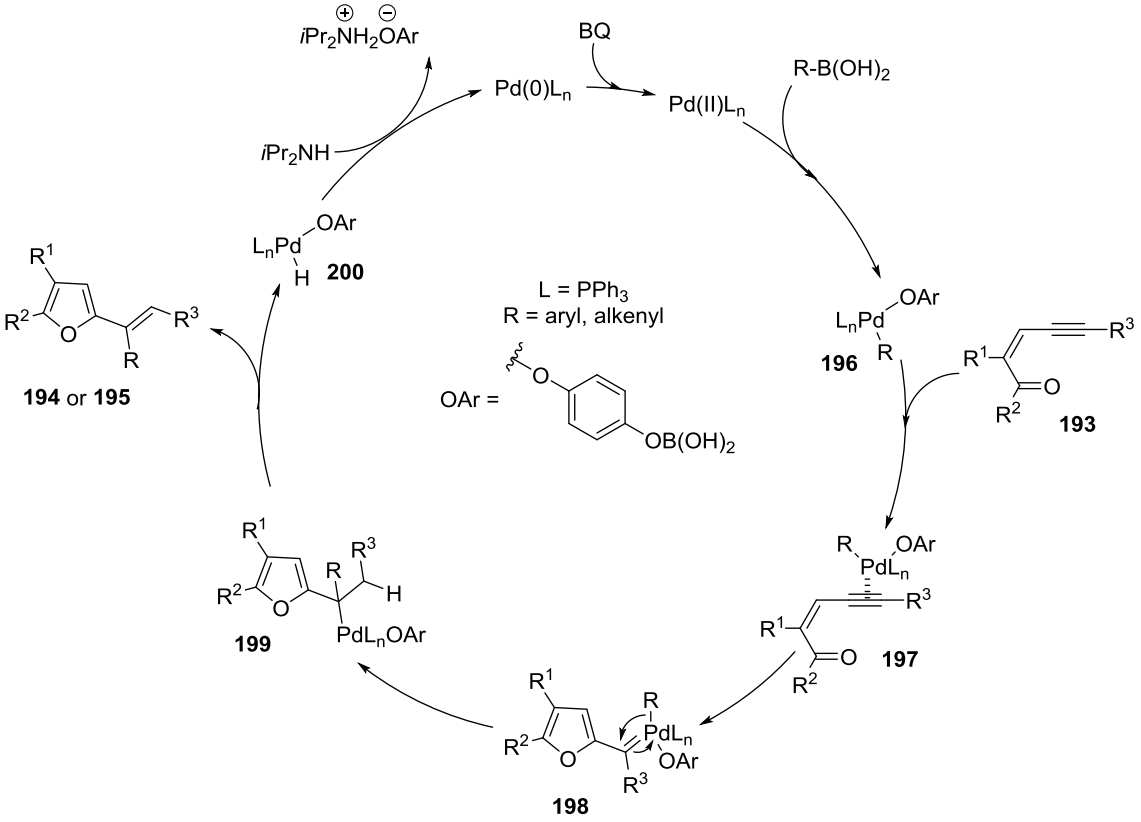
Scheme 51 Catalytic cycle proposed by Wang

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.[75] Oxidative cross-coupling of enynone **193** with either an aryl or a vinyl boronic acid occurs in good yield and with excellent stereoselectivity.



Scheme 52 Synthesis of 2-alkenyl substituted furans by Wang

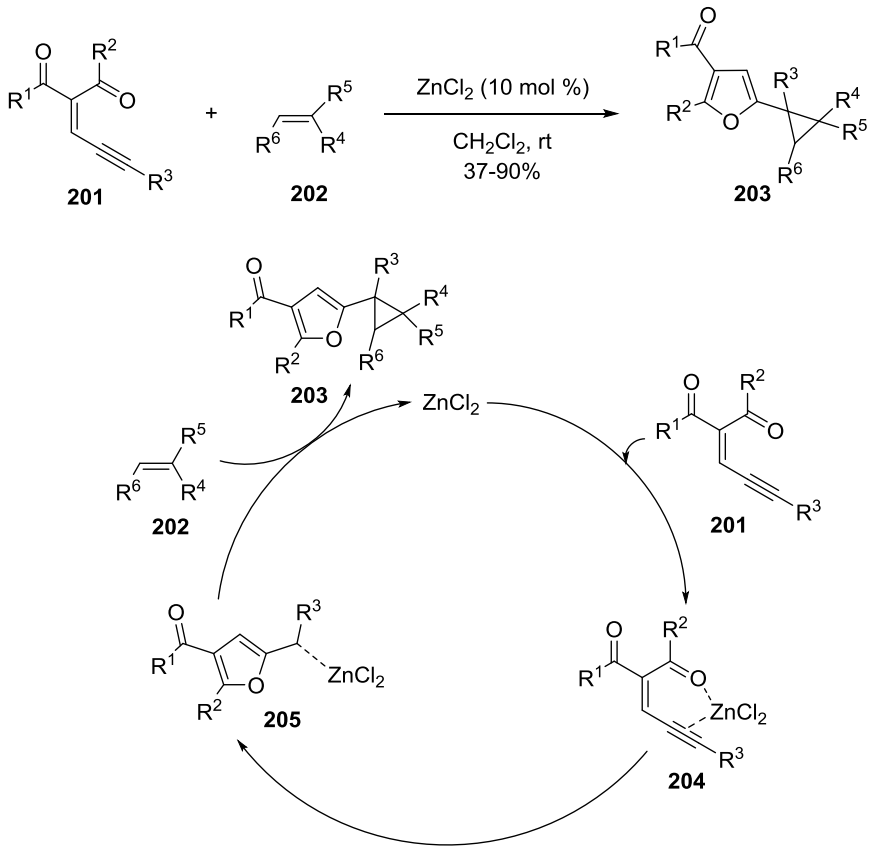
The reaction is proposed to proceed through initial oxidation of Pd(0) to Pd(II) using benzoquinone; consequent oxidative addition of the boronic acid generates the intermediate palladium species **196**. The alkyne **193** is then activated by the newly formed palladium species **197** and nucleophilic 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.



Scheme 53 Catalytic cycle for formation of 2-alkenyl furans

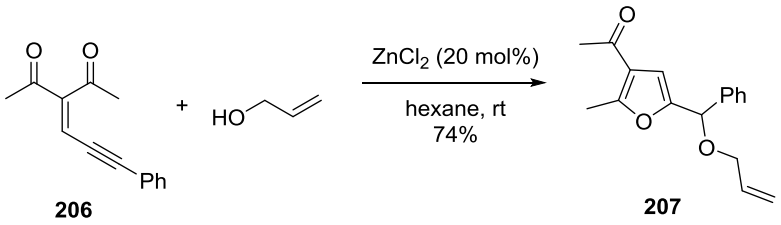
1.3.3.2 Zinc Catalysis

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**).[76] 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

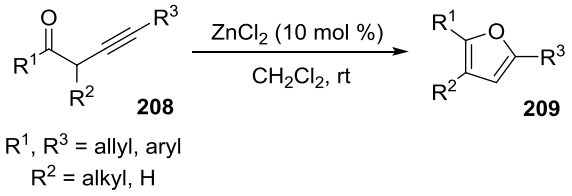
Vicente *et al*. reported an extension of this work in 2013 wherein they described a zinc-catalysed cyclisation, followed by C-O or C-N bond formation through reaction with primary or secondary alcohols or with an azole, such as a pyrazole, imidazole or triazole (**Scheme 55**).[77] Unlike their earlier 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**).[78] The zinc chloride catalysed reaction proceeds *via* a 5-*endo-dig* cycloisomerisation of 1,4-di- and

1,2,4-trisubstituted but-3-yn-1-ones **208** in CH_2Cl_2 at room temperature to give 2,5-di- and 2,3,5-trisubstituted furans **209**.

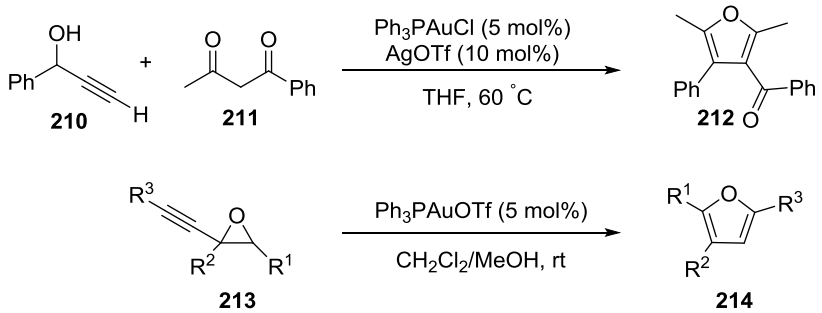


Scheme 56 Zinc catalysed furan formation described by Dembinski

1.3.3.3 Gold Catalysis

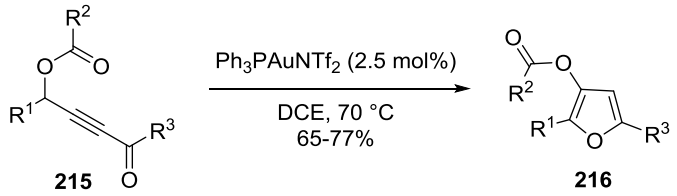
Gold catalysts have proven to be particularly useful for the synthesis of functionalised furans due to the bifunctional properties of the metal. Gold species are adept at activating alkynes and allenes through complexation; cationic gold species also possess strong Lewis acidic properties.

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 tri-substituted furans **214** in good yields. In this case an external nucleophile, namely MeOH, is required to promote the gold-catalysed isomerisation reaction



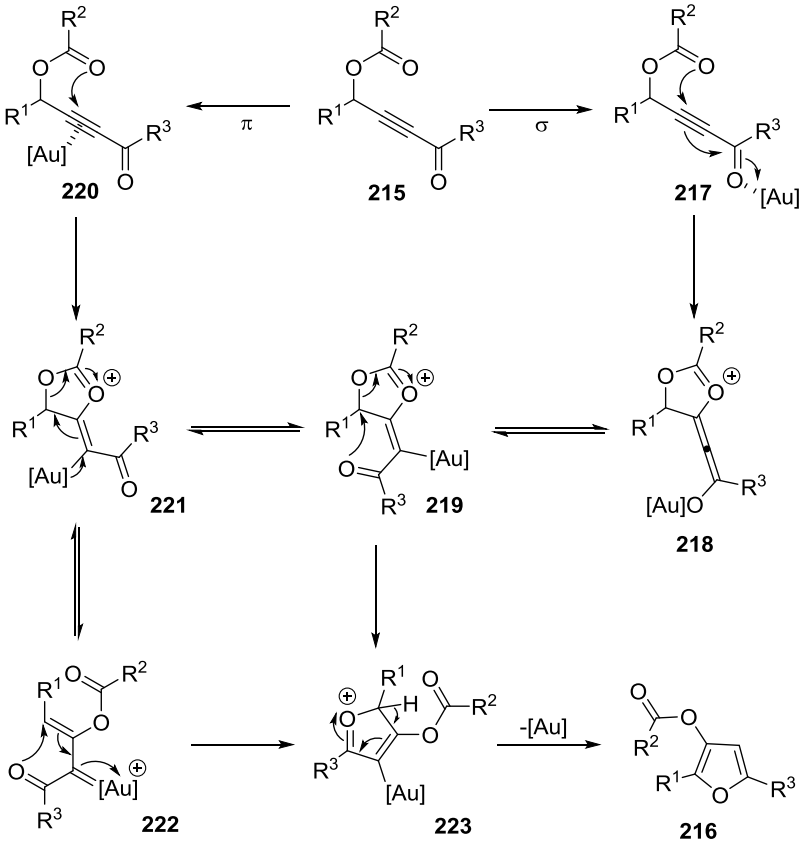
Scheme 57 Examples of gold-catalysed furan formation

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 R^1 and R^2 were alkyl substituents and R^3 was either an alkyl substituent or an electron-rich aryl group (**Scheme 58**).



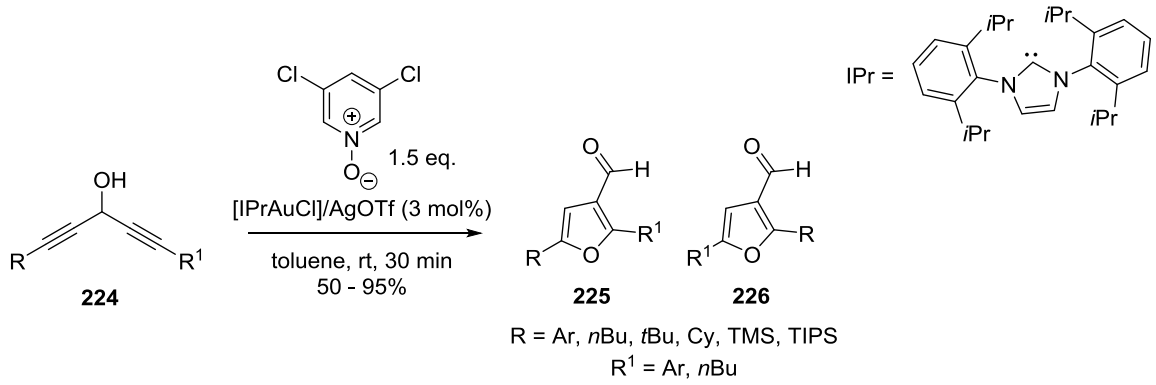
Scheme 58 Gold catalysed furan formation from γ-acyloxyalkynyl ketones

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**.



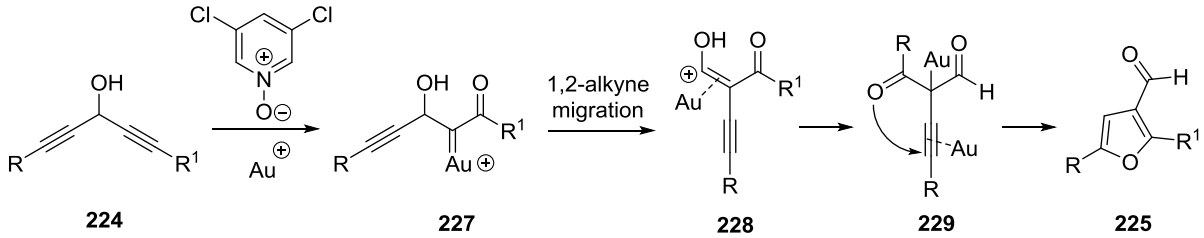
Scheme 59 Mechanism of Pale's gold-catalysed furan formation

In 2014, Hashmi *et al.* reported a gold-catalysed cyclisation cascade reaction for the synthesis of tri-substituted formylfurans **225** and **226** (**Scheme 60**).[82] 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 R^1 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 ^{18}O and ^{13}C, 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**).[83] 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 cycisation to form the desired furan product **225**.

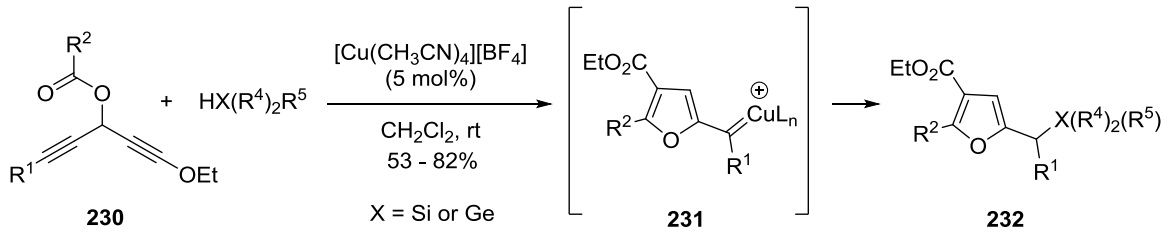


Scheme 61 Mechanism of the gold(I) catalysed furan formation

1.3.3.4 Copper Catalysis

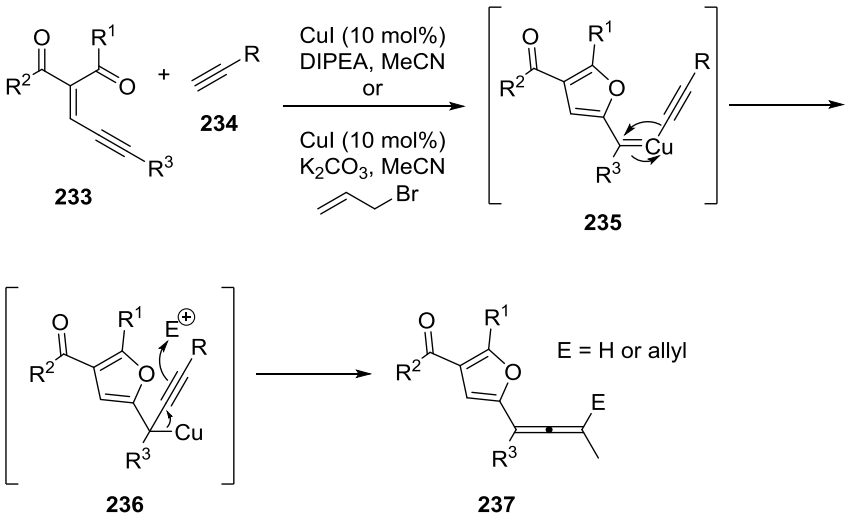
Copper catalysts have been employed instead of transition metal catalysts for the synthesis of substituted furans. In 2008, Barluenga *et al*. reported regioselective methodology for the

synthesis of tri-substituted furans **232** from bis-propargylic esters **230** using copper(I) complexes.[84] 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 = alkyl, vinyl, allyl, aryl or silyl and R^2 = 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.[75] The reaction between eneynedione **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 alkynes **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

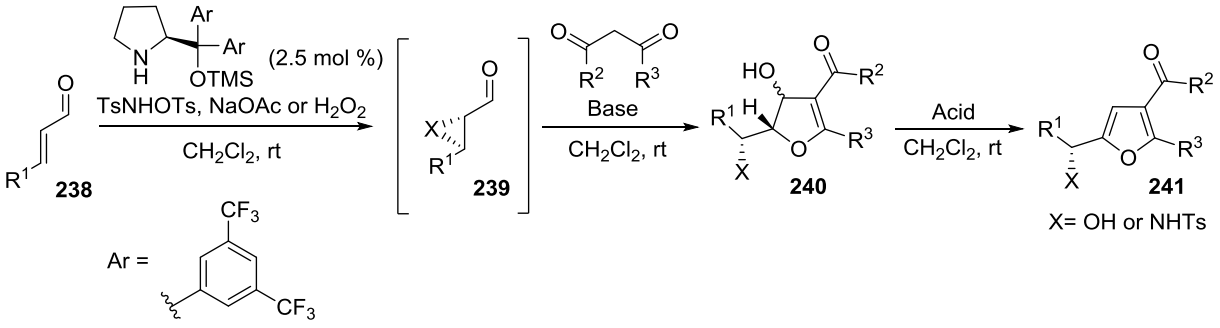
1.3.4 Organocatalytic and Acid/Base Methods

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.[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.[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.[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 aziridation 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**.



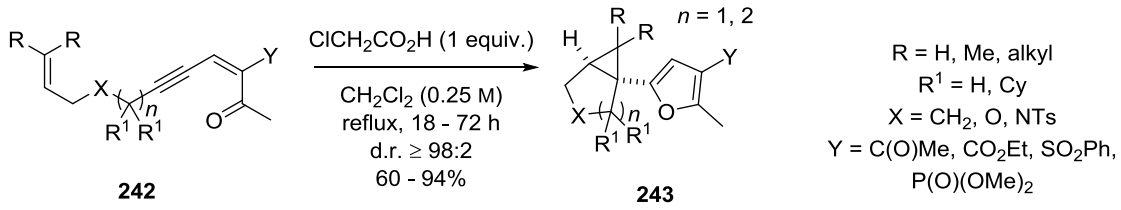
Scheme 64 Synthetic approach towards 2-aminoalkylfurans and 2-hydroxyalkylfurans

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_2CO_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

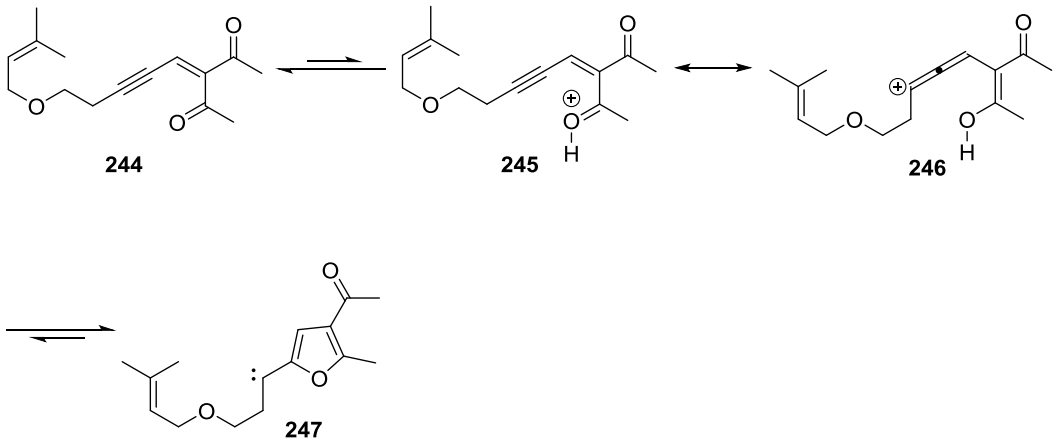
Recently, in 2015, the Clark group reported the synthesis of cyclopropyl-substituted furans using a Brønsted acid promoted cascade reaction.[89] In the reaction, chloroacetic acid is used to promote an efficient and diastereoselective intramolecular cascade reaction of electron-deficient enynones **242** 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.



242 **243**

Scheme 65 Brønsted acid promoted formation of cyclopropyl-substituted furans

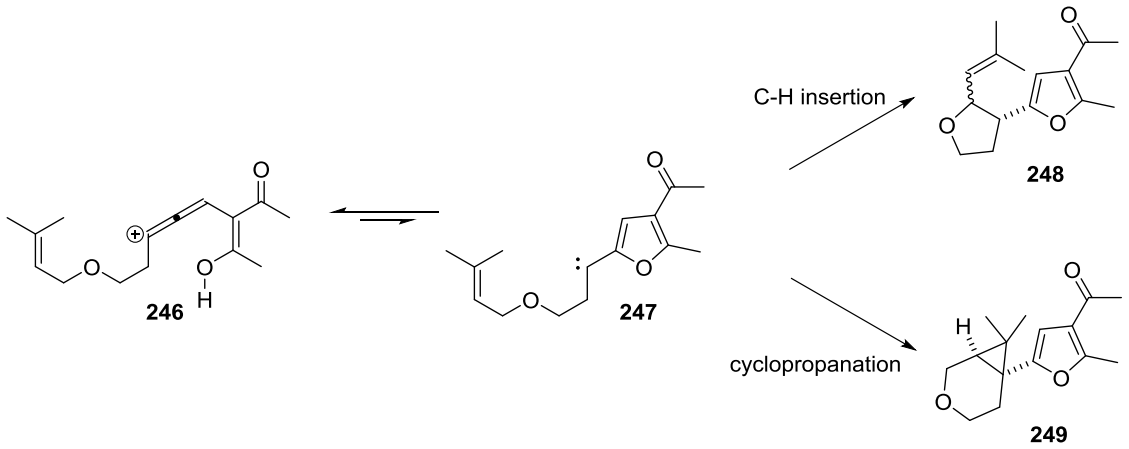
It has been proposed that the acid-catalysed reaction proceeds by an unusual mechanism in which a free carbene is generated under acidic conditions. Initially, an allene **246** is formed through protonation and isomerisation. The allene is then converted into a carbene **247** by attack of the enol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



244 **245** **246** **247**

Scheme 66 Proposed mechanism for the formation of carbene **247**

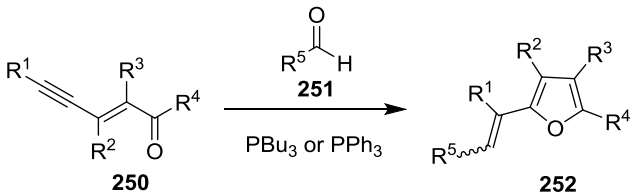
It was found that in cases where an allylic ether was present, the free carbene underwent competitive C-H insertion and intramolecular cyclopropanation to give **248** and **249** respectively (**Scheme 67**). Intermolecular cyclopropanation and intramolecular C-H insertion reactions of less activated 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

1.3.4.3 Phosphine Promoted Synthesis of Furans from Enynes

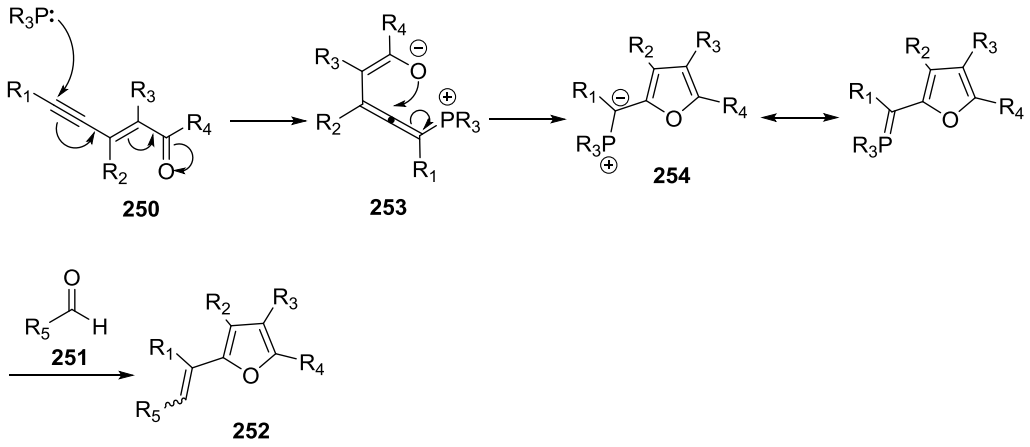
In 1999, Kuroda *et al.* published a phosphine-initiated method for the preparation of furans from substituted enynes.[90] The group went on to further investigate the method and in 2004 published work outlining the formation of tri- and tetra-substituted furans from more highly substituted enynes under 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

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

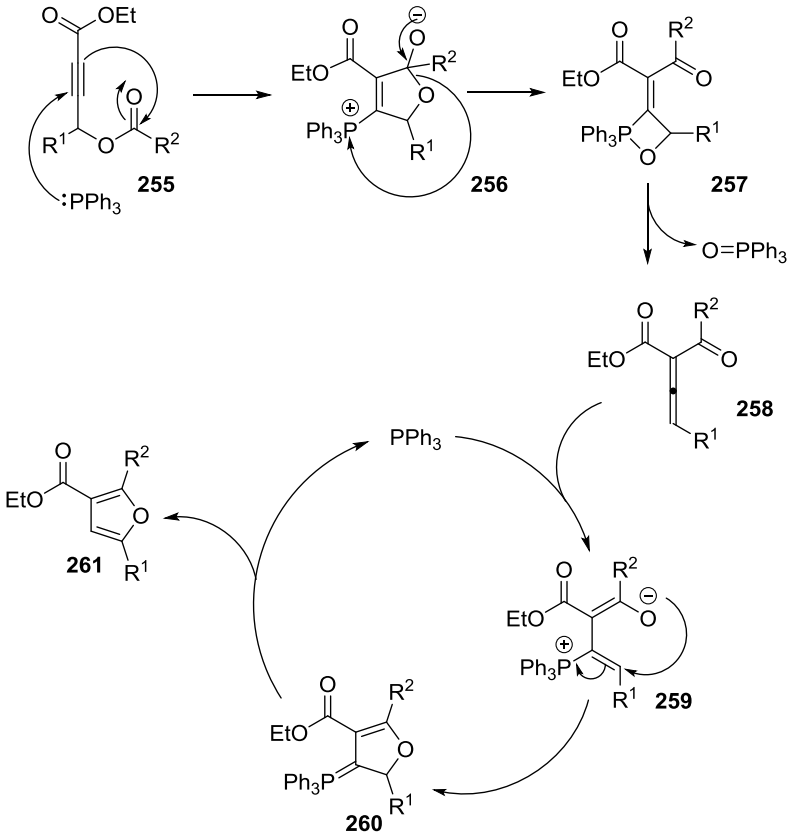
desired unsaturated furan product (**Scheme 69**). Kuroda's work showed that organic compounds could be used to promote furan formation, moving away from the more conventional metal-catalysed approach.



Scheme 69 Proposed reaction mechanism for phosphine mediated furan formation

1.3.4.4 Condensation of γ-acyloxy Butynoates

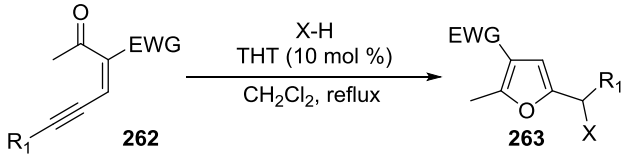
An additional strategy for the construction of substituted furans promoted by a phosphine was described by Krische *et al.* in 2004.[92] γ-Acyloxy butynoates were exposed to an excess of triphenylphosphine resulting in the formation of substituted furans by an intramolecular reductive condensation. The 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.



Scheme 70 Proposed mechanism for Krische *et al.*'s furan synthesis

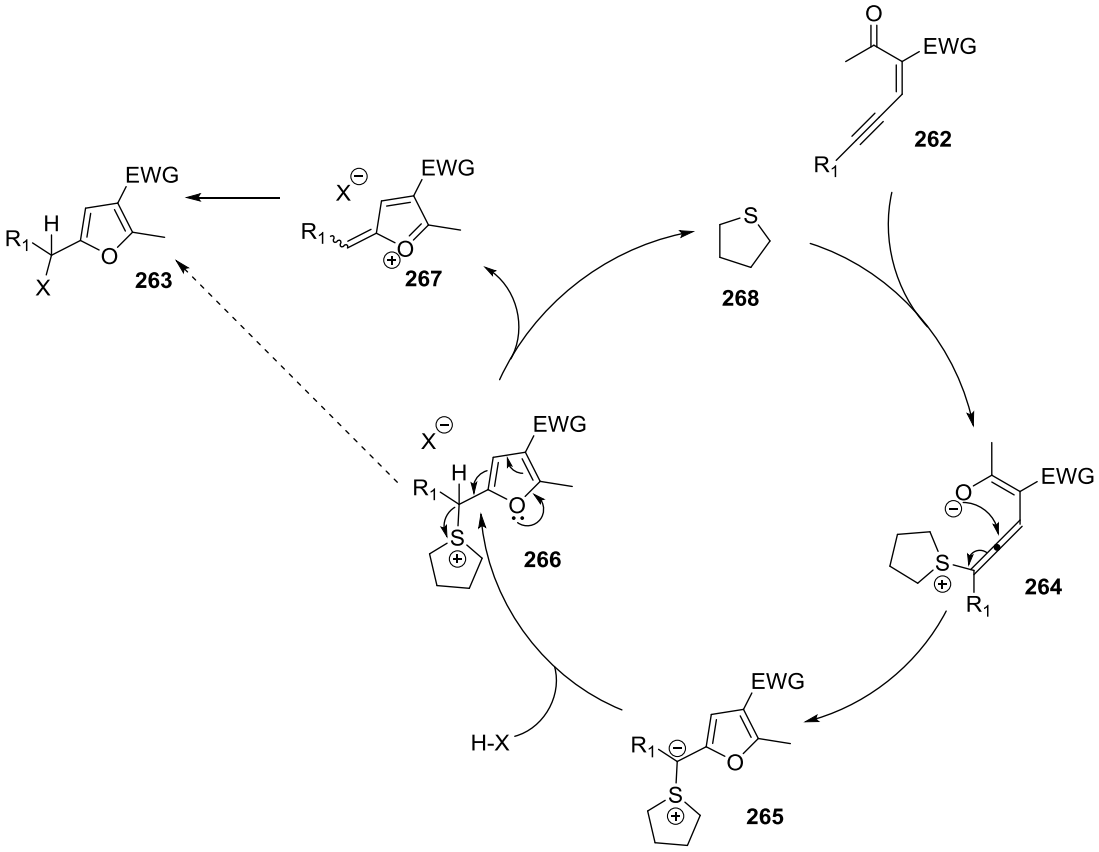
1.3.4.5 Organosulfur Catalysed Synthesis

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 R^1 group could be alkyl, aryl or silyl.



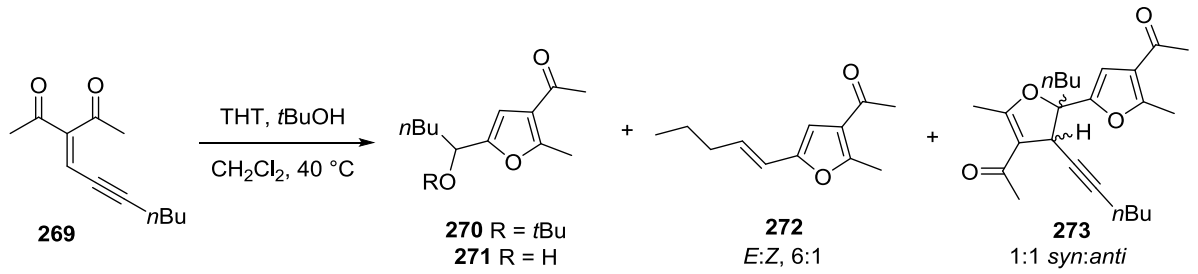
Scheme 71 THT catalysed furan formation

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_N1 pathway rather than through a direct S_N2 displacement of THT.



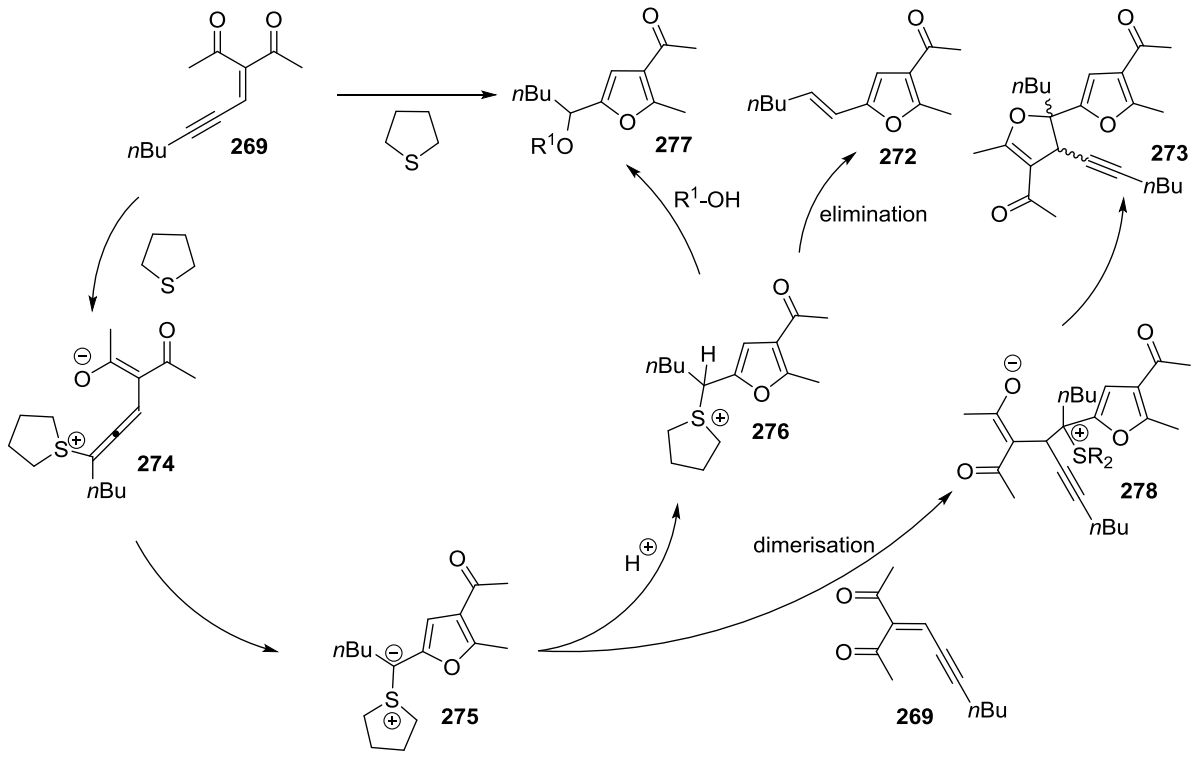
Scheme 72 Mechanism for the THT promoted furan formation

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**.



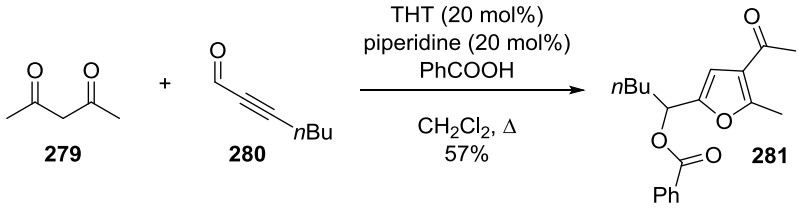
Scheme 73 Formation of side-products in the THT catalysed furan formation

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.



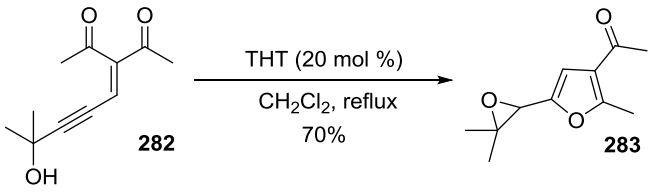
Scheme 74 Mechanism of formation of furan by-products

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.



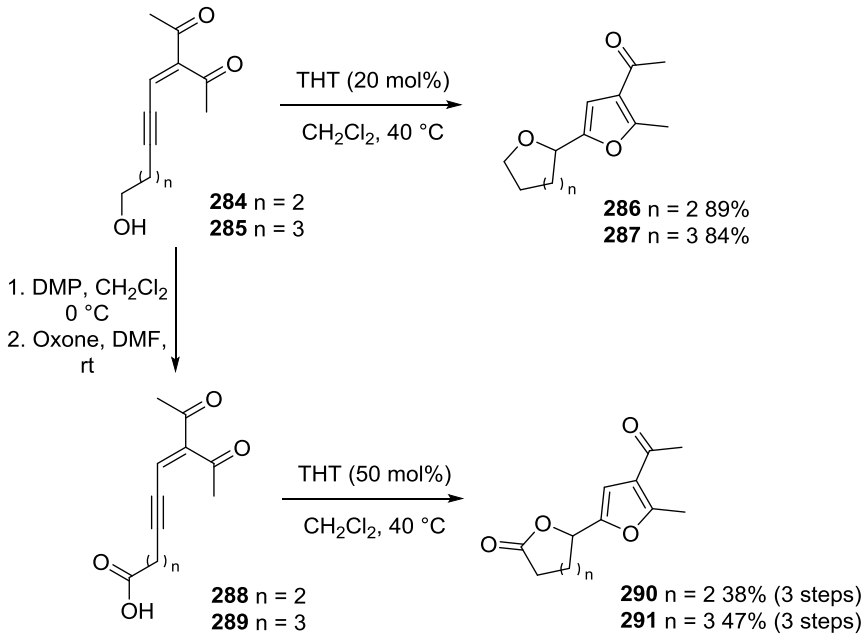
Scheme 75 One-pot condensation furan formation

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**

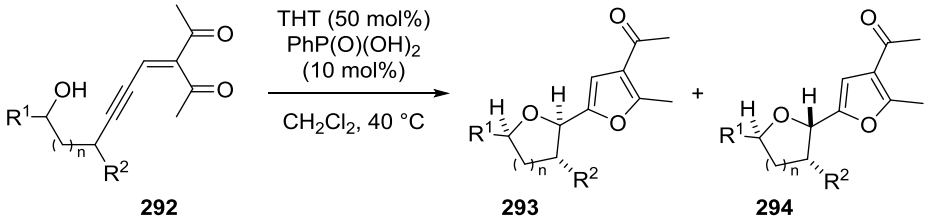
More recent work has also shown that tethered tetrahydropyrans and tetrahydrofurans can be synthesised in the same manner (**Scheme 77**).[94] Starting from acyclic enynediones **284** and **285**, which contain a tethered primary alcohol, tetrahydrofuran and pyran products **286** and **287** were obtained 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.



Scheme 77 Synthesis of bicyclic furan species

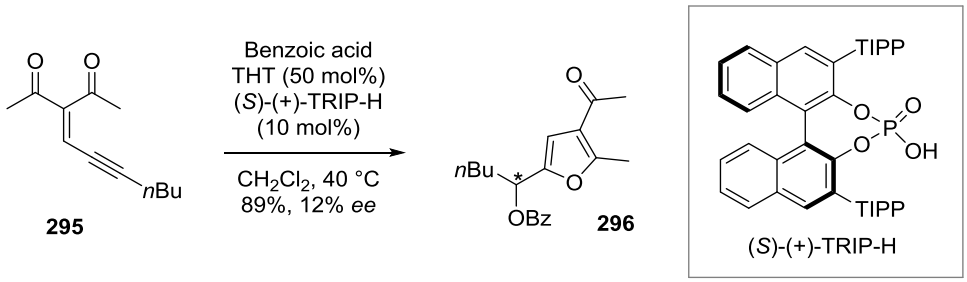
Cyclisation reactions of enynediones **292** possessing tethered secondary alcohols and branched chains were also found to proceed well in the presence of a higher catalytic loading of THT (50 mol%). In this case, phenylphosphonic acid was also required as a co-catalyst to effect tandem cyclisation. Little to no stereocontrol was observed for the formation of the tetrahydrofuran ring when R^1 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 R^1 also resulted in a reasonable level of diastereocontrol during tetrahydropyran formation (entry 5).

Table 1 Diastereoselective formation of bicyclic furans



Entry	n	R^1	R^2	Ratio (293:294)	Yield (%)
1	1	Me	H	1:1.2	79
2	1	Et	H	1:1.1	77
3	1	*i*Pr	H	1.2:1	71
4	1	H	Me	4.3:1	73
5	2	*t*Bu	H	2.7:1	80

Studies were also performed to determine whether cyclisation could be effected in an enantioselective manner.[95] 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*)-(+)-TRIP-H was employed as the catalyst, afforded the product **296** in high yield but with just 12% *ee*.

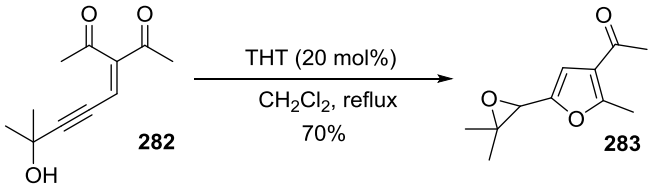


Scheme 78 Attempted enantioselective synthesis of trisubstituted furans

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.[93] 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.

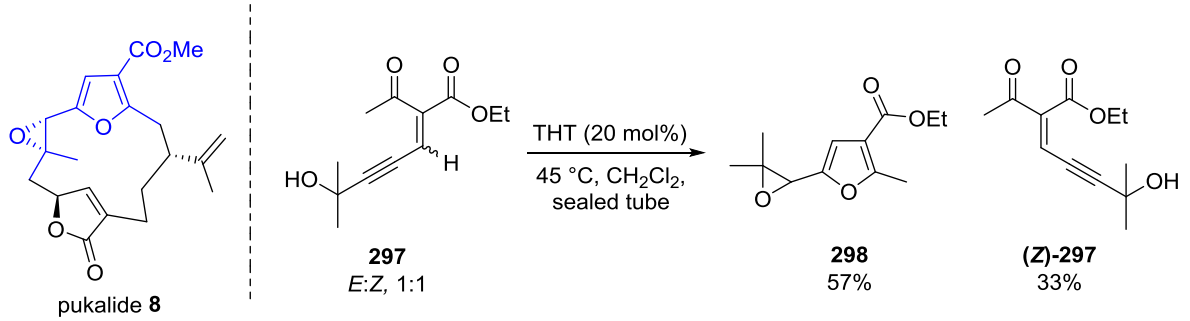


Scheme 79 Epoxyfuran formation using organocatalytic THT

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 *et al*. addressed this by performing a late stage epoxidation of a conjugated alkene using DMDO in their synthesis of deoxyprovidencin;[52] however, in substrates where the butenolide is present, selective epoxidation of the C7-C8 bond is not possible.

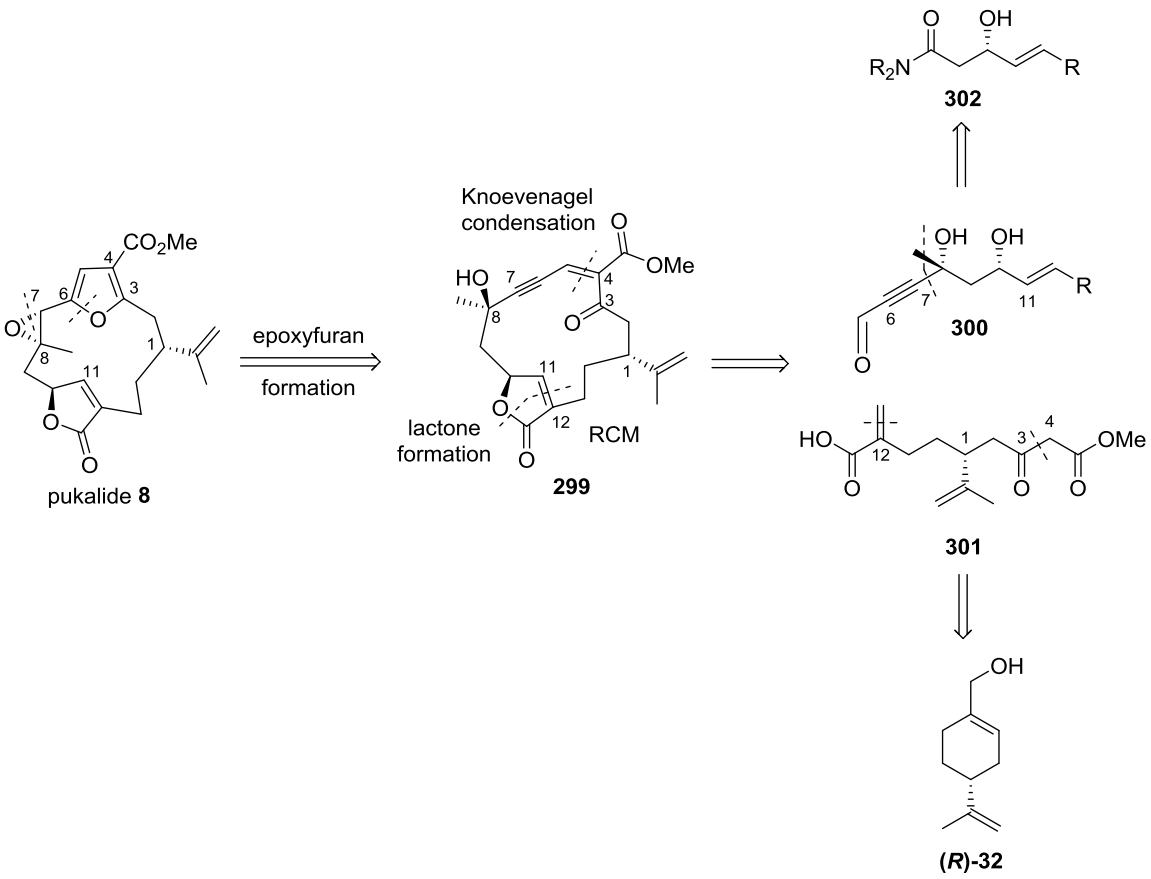
Pukalide, an interesting family member which had so far eluded synthesis, was chosen as the initial target. Previously, epoxyfuran formation under the THT conditions had only been accomplished using the ynenone **282** as the substrate. However, pukalide possesses an ester group at C18 and so an ynenone 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 macrolactone **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.



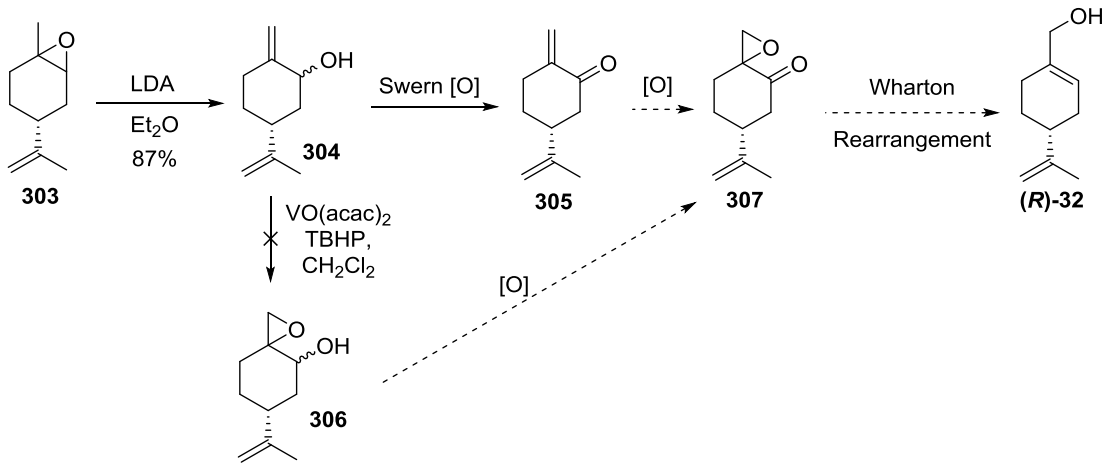
Scheme 81 Retrosynthetic analysis of pukalide

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.[96] 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.[38,47] 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.[97]

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

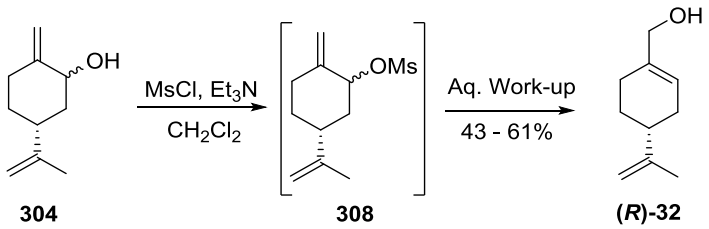
of (+)-limonene oxide (**303**) afforded allylic alcohol **304** as a 1:1 mixture of diastereoisomers in good yield.[98] However, manipulation of the allylic alcohol proved to be problematic. Attempts to oxidise the allylic alcohol **304** resulted in dimerisation of the highly unstable product **305**, 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

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_N2' rearrangement to afford (*R*)-perillyl alcohol (**(*R*)-32**) in good yield upon aqueous work-up. The effect of pH and temperature on the S_N2' 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



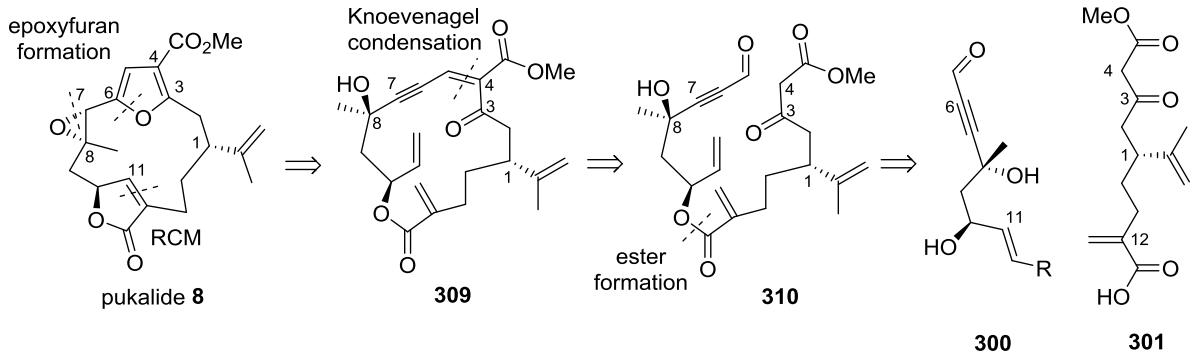
304 **308** **(*R*)-32**

Aq. solution	Temperature	Scale (mmol)	Yield (%)
aq. $NaHCO_3$*	rt	0.66	47
aq. $NaHCO_3$	rt	0.66	61
aq. $NaHCO_3$	rt	170.8	44
H_2O	rt	0.17	-
H_2O	40 °C	1.36	48
1M HCl	rt	0.17	-
1M HCl	40 °C	1.36	43
NaOAc (2 eq.)	rt	0.17	degradation
NaOAc (2 eq.)	40 °C	0.17	degradation

* Wet Et_3N used

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

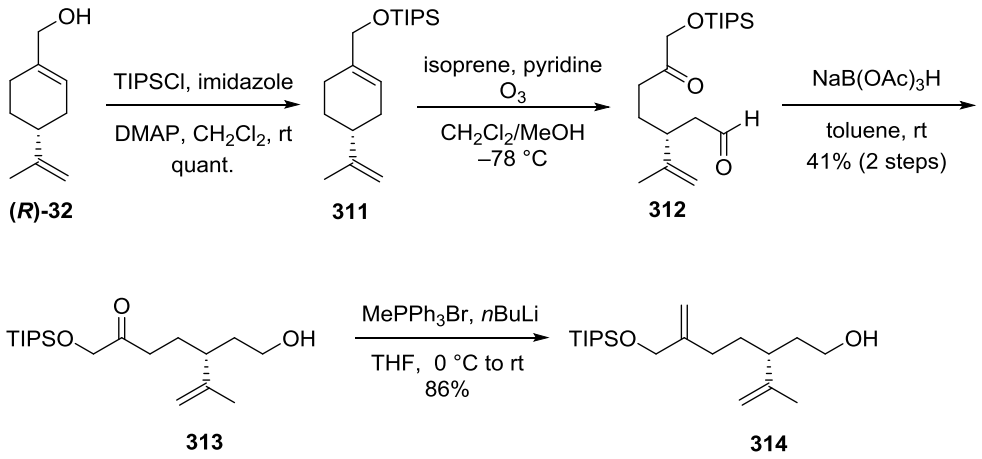
In the first synthetic strategy it was anticipated that the epoxy furan and butenolide functionality would be introduced in the final steps of the synthesis through THT catalysed furan formation and ring-closing metathesis. These ideas led to the proposal of macrocycle **309** as the key intermediate. 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.



Scheme 83 Retrosynthetic analysis through intramolecular Knoevenagel condensation

2.3.1 Synthesis of the C12-C14/C1-C4 Fragment

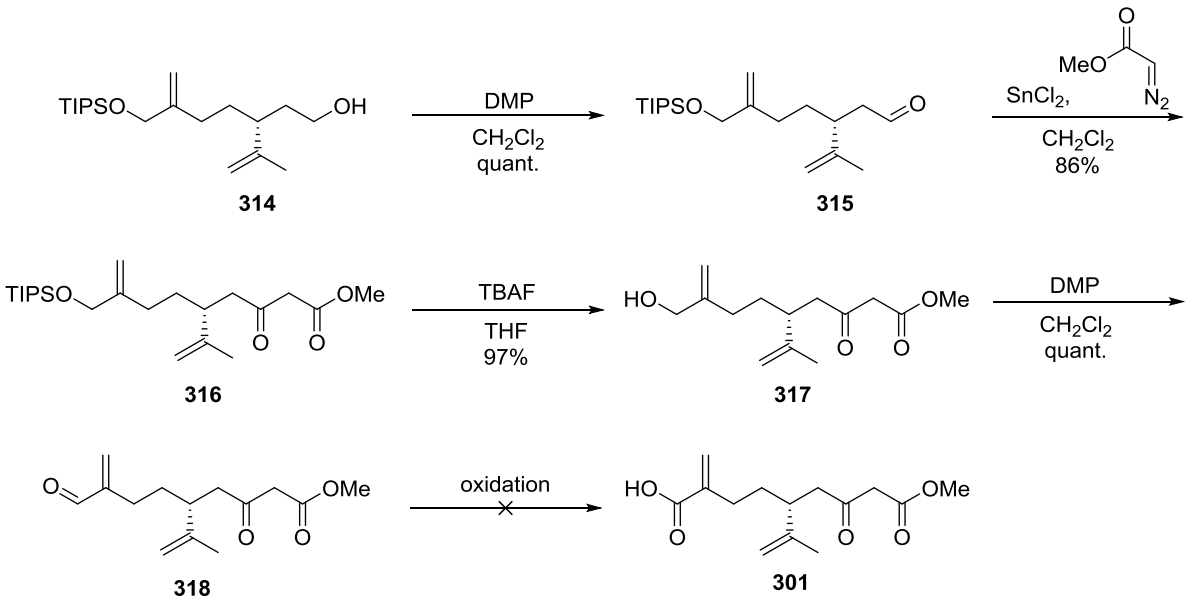
After a viable method for the synthesis of (*R*)-perillyl alcohol had been established, efforts were focused on the synthesis of fragment **301**, C12-C14/C1-C6. (*R*)-Perillyl alcohol (**(*R*)-32**) was protected as its triisopropylsilyl (TIPS) ether **311** and then subjected to selective ozonolysis, 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 methylenation followed, to furnish alkene **314** in high yield.



Scheme 84 Synthesis of alkene **314**

Following the synthesis of alcohol **314**, subsequent steps for the formation of the β-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 β-ketoester **316** under conditions reported by Roskamp,[100] occurred without full conversion and the desired

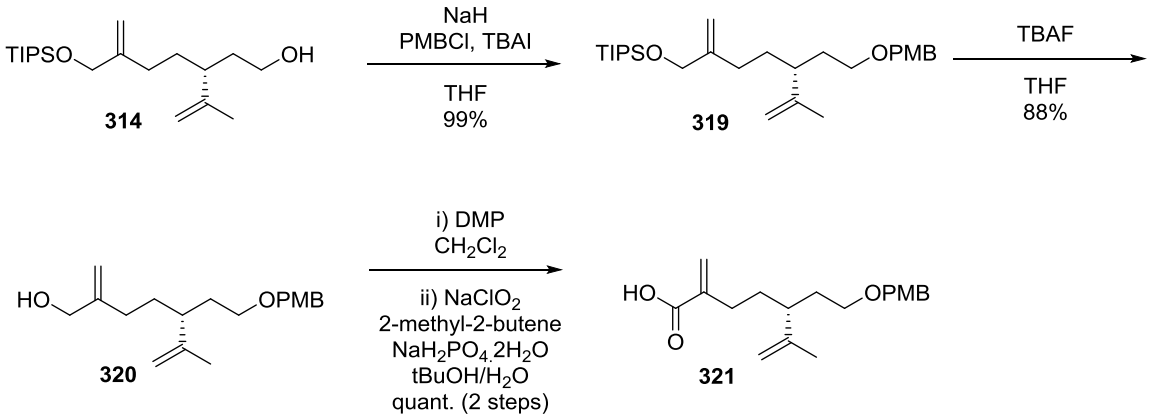
product **316** was obtained in a moderate 57% yield alongside recovered aldehyde (28%). Increasing the number of equivalents of methyl diazoacetate as well as changes to the concentration of the reaction mixture were found to have no effect on the yield. However, the yield could be improved by increasing 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.

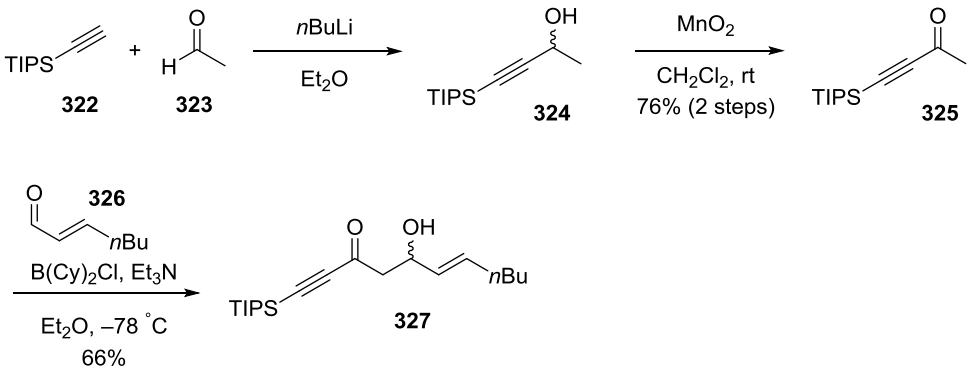
Subsequent oxidation with Dess-Martin periodinane, followed by Pinnick oxidation, afforded the desired carboxylic acid **321** in quantitative yield.



Scheme 86 Synthesis of acid analogue **321**

2.3.2 Synthesis of a Racemic C5-C11 Fragment

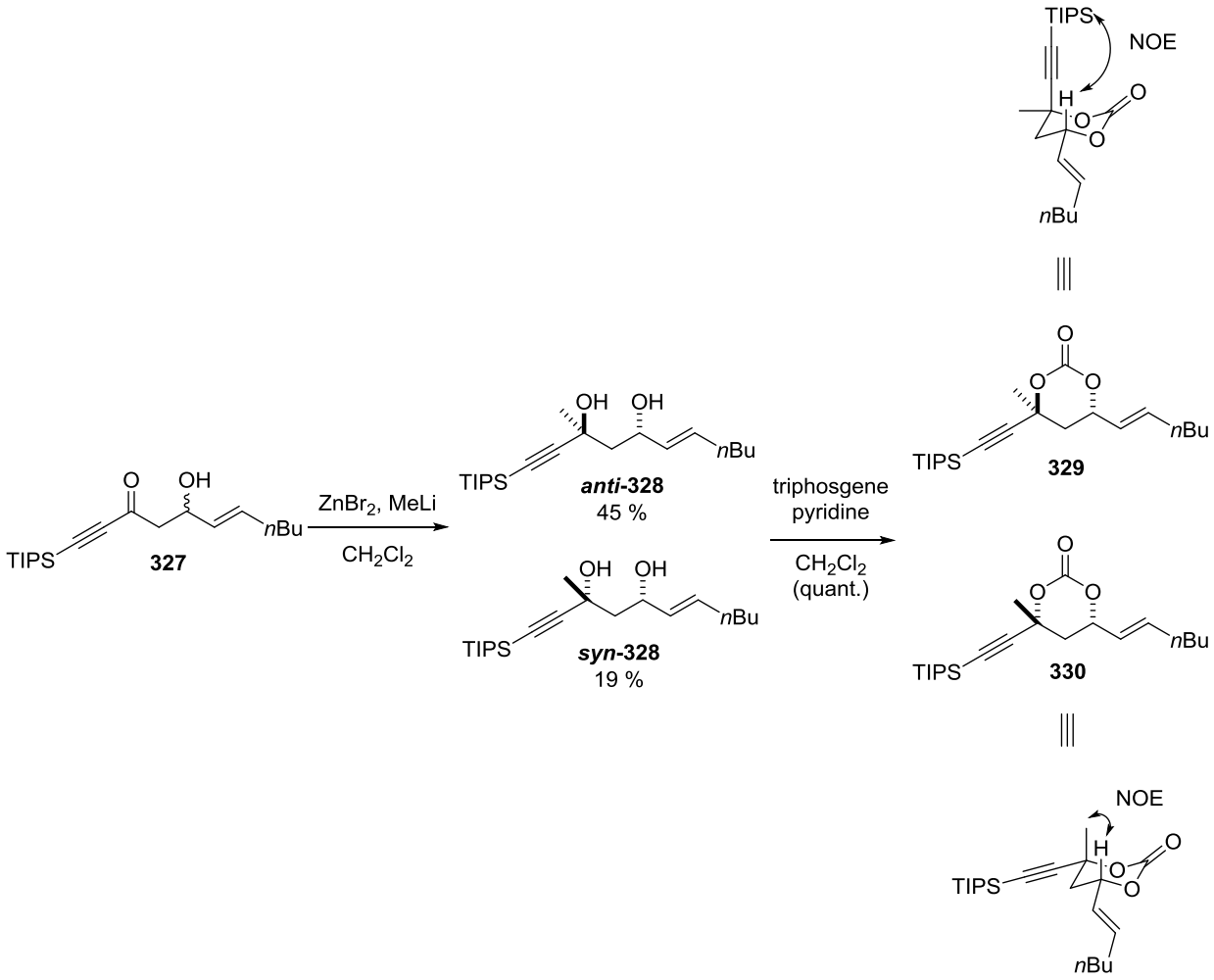
A route for the synthesis of the C5-C11 aldehyde fragment as a racemate was initially pursued to allow optimisation of reaction conditions and exploration of the diastereoselective methylation reaction. Starting from triisopropylsilyl acetylene (**322**) and acetaldehyde (**323**) addition of the lithiated acetylene to the aldehyde gave alkynyl alcohol **324**. Oxidation of the resulting propargylic alcohol in the presence of MnO_2 subsequently delivered ynone **325**.[101] 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 $ZnBr_2$. 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.

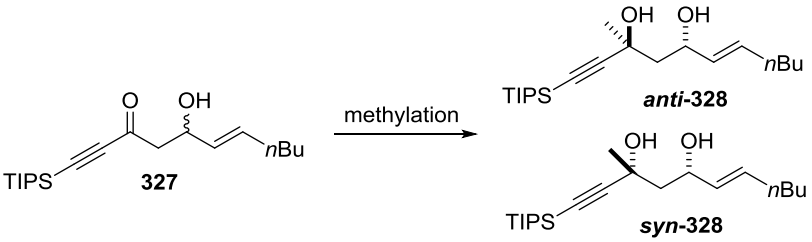


Scheme 88 Determination of the configuration of diol methylation products

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 $MeTi(O\textit{i}Pr)_3$ (formed in the presence of excess $TiCl(O\textit{i}Pr)_3$) was employed as the reagent (entry 8). Determination of the *dr* was conducted on a small scale using ^{1}H 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, $ZnBr_2$ 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



Entry	Methylating Reagents	Solvent	*syn:anti*[a]	Conversion[a]
1	$ZnBr_2$, MeLi	CH_2Cl_2	1:2.4	100 %
2	$ZnBr_2$, MeMgCl	Et_2O	2.8:1	100 %
3	MeMgCl	Et_2O	2:1	10 %
4	$ZnBr_2$, $AlMe_3$	CH_2Cl_2	1.8:1	100 %
5	$AlMe_3$	PhMe	1.5:1	100 %
6	$MeCeCl_2$[b]	THF	1.5:1	100 %
7	$MeTi(OiPr)_3$[c,d]	Et_2O	1.6:1	100 %
8	$MeTi(OiPr)_3$[c,e]	Et_2O	5.9;1	100 %
9	Me_2TiCl_2[f]	CH_2Cl_2	decomposition	100 %
10	$MeTiCl_3$[g]	CH_2Cl_2	decomposition	100 %

[a] Established through ^1H NMR, [b] formed *in situ* from $CeCl_3$/MeMgCl 1:1 [c] formed *in situ* from $TiCl_4$/$Ti(OiPr)_4$ 1:3 and MeLi, [d] 4 eq. MeLi used with respect to $TiCl_4$, [e] 3 eq. of MeLi used with respect to $TiCl_4$, [f] formed *in situ* from $TiCl_4$/Me_2Zn 1:1, [g] formed *in situ* from $TiCl_4$/Me_2Zn 2:1,

The opposite diastereoselectivities obtained using MeLi/$ZnBr_2$ 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.

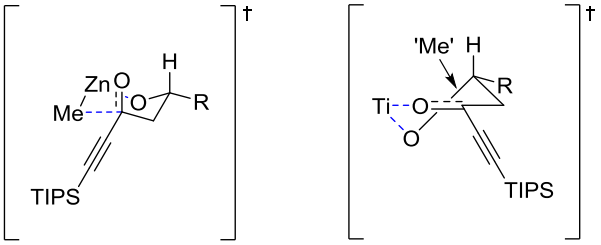
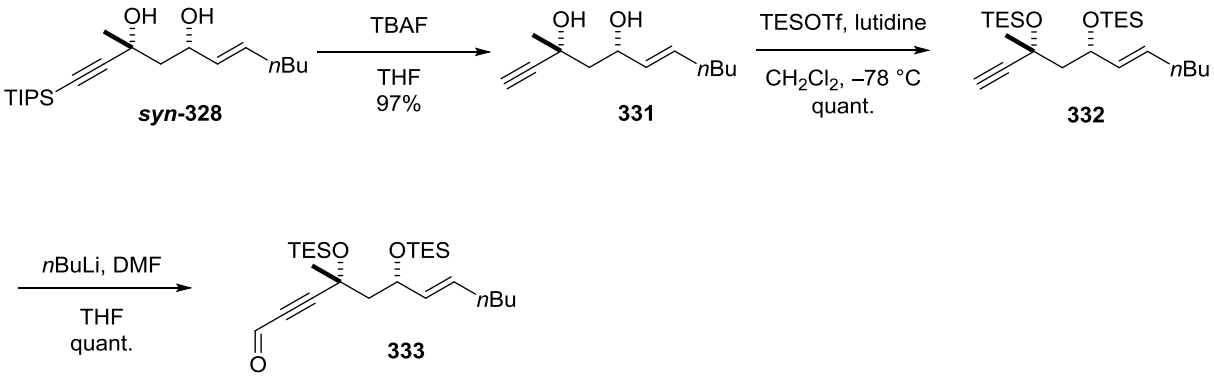


Figure 9 Methylation transition states

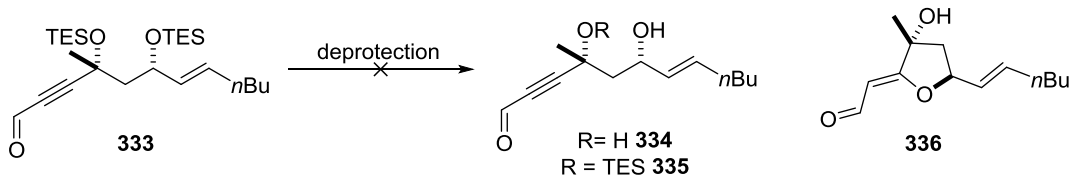
With a route to ***syn*-328** having been established, attention was turned to manipulation of the protecting groups and introduction of the formyl group (**Scheme 89**). Deprotection of the acetylene to afford **331**, followed by protection of both the allylic and tertiary alcohols as silyl ethers, 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**

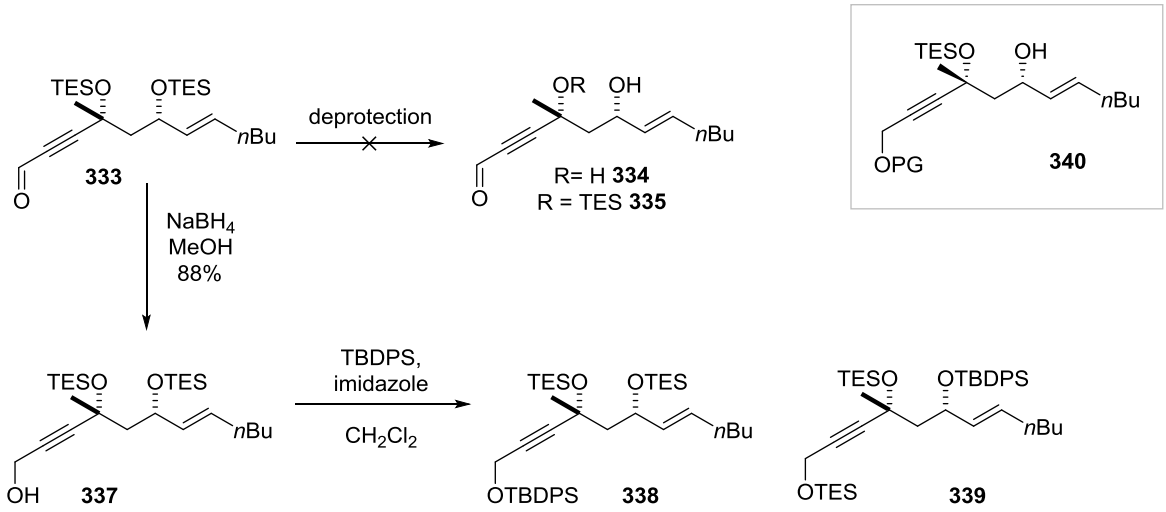
Deprotection conditions were investigated for the selective cleavage of the secondary silyl ether (**Table 4**), but in all cases either a mixture of products was observed or degradation dominated. In most cases multiple products were observed, indicative of silyl migration occurring after initial deprotection. 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.

Table 4 Attempted selective deprotection conditions



Entry	Reagent	Solvent	T (ºC)	Time (h)	Result
1	AcOH	THF/H_2O	−20	30	complex mixture
2	AcOH	THF/H_2O	0	2.5	complex mixture
3	PPTS	THF	0 - rt	4.5	degradation at rt
4	PPTS	THF/MeOH	0	3	complex mixture
5	HF•pyridine	THF	−10	18	complex mixture
6	(+)-CSA	MeOH	0	3	degradation
7	TBAF	THF	rt	1.5	**336** exclusively formed

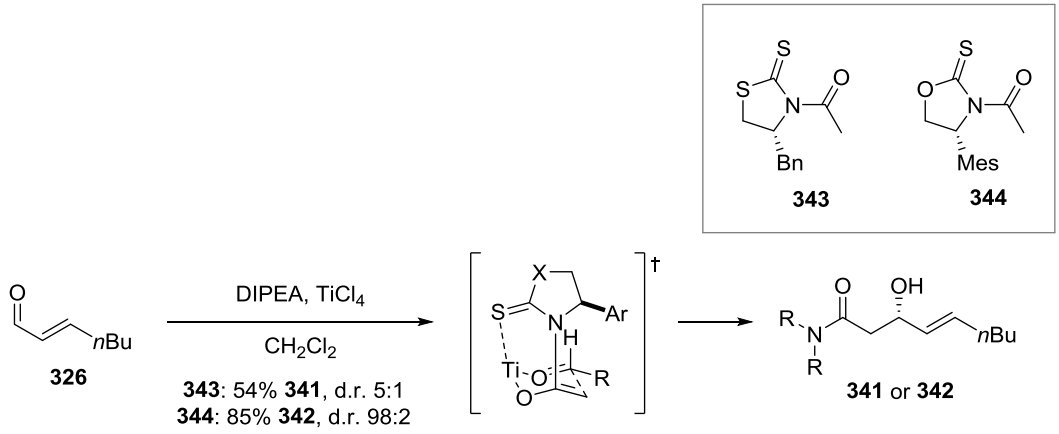
Following these disappointing results, it was envisioned that a protected version of the aldehdye **340** could be used for fragment coupling. Reduction of the aldehyde **333** with sodium borohydride occurred in a high yield (88%) to afford alcohol **337** (**Scheme 90**). However, attempts to protect 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.



Scheme 90 Attempted synthesis of protected aldehyde fragment

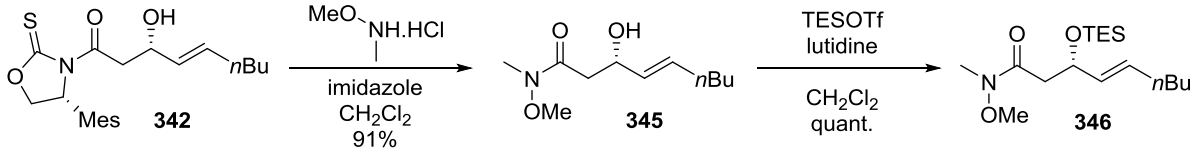
2.3.3 Synthesis of an Enantiopure C5-C11 Fragment

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**).

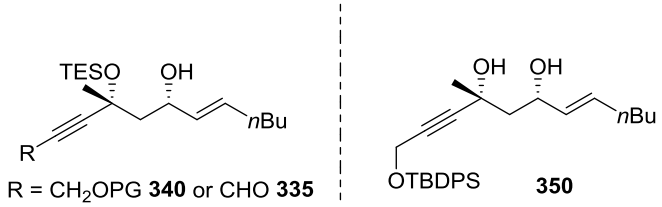
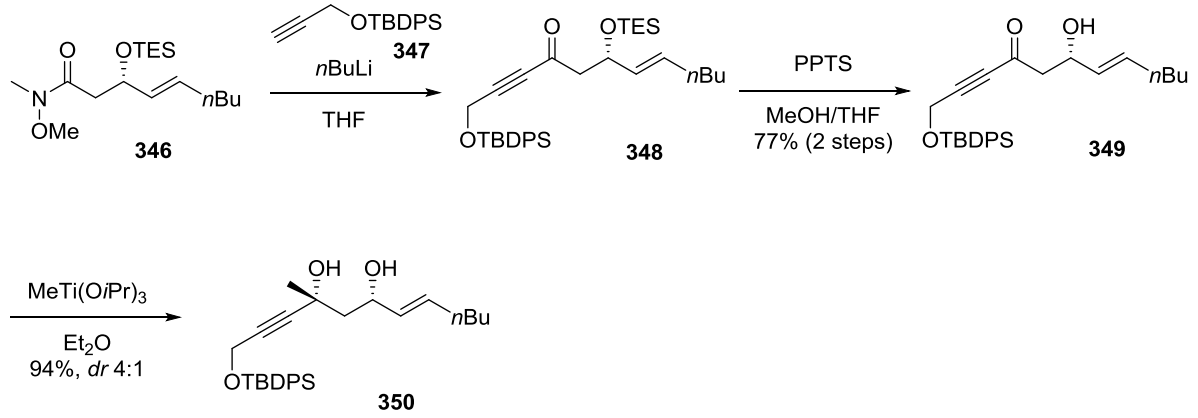


Figure 10 Originally targeted western fragments vs. revised strategy

Known TBDPS ether **347** was formed in one step from propargyl alcohol.[104] 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 MeTiO*i*Pr$_3$, 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.



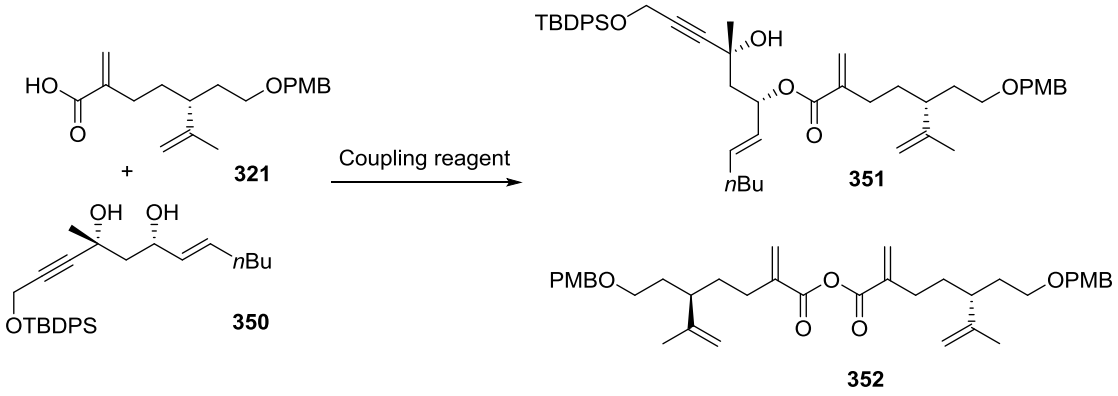
Scheme 93 Synthesis of *syn* diol **350**

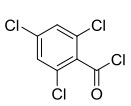
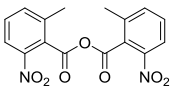
2.3.4 Fragment Coupling and Functionalisation

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**

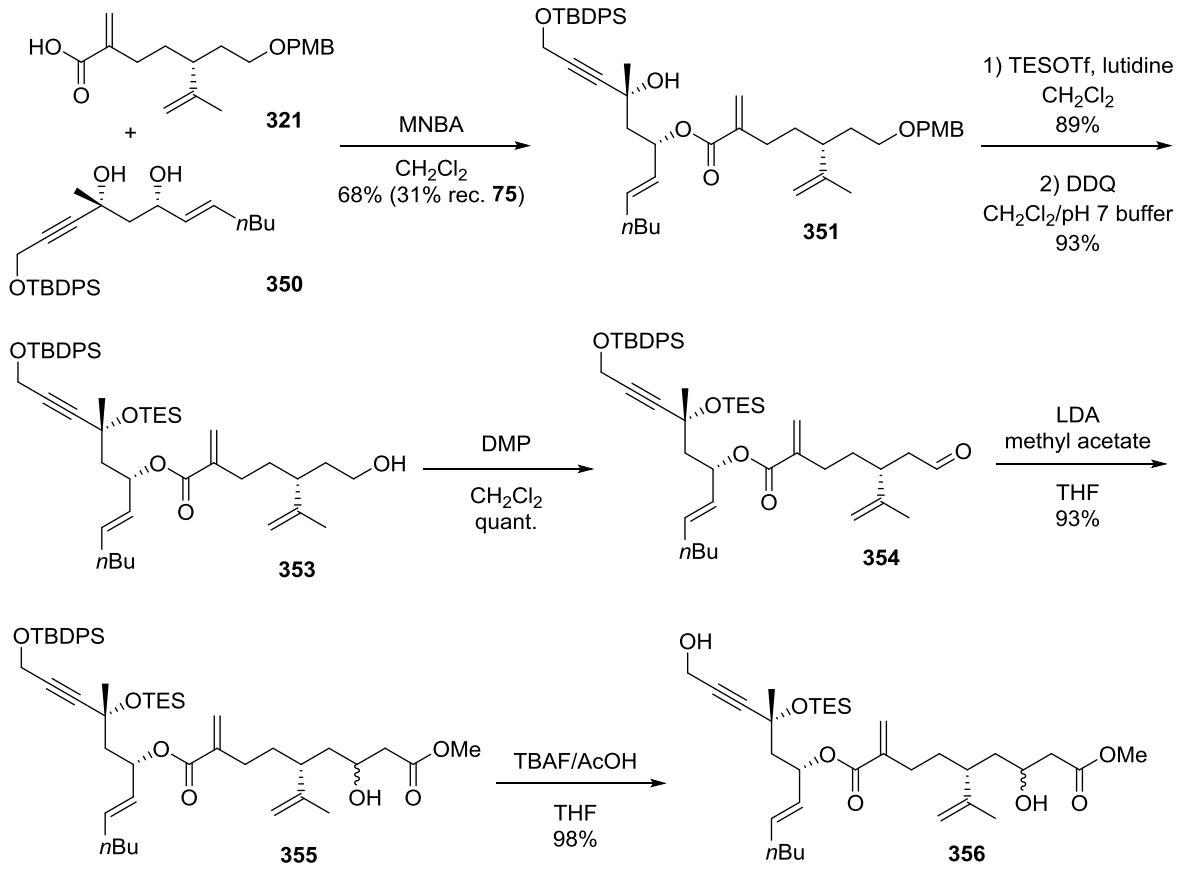


Entry	Conditions	T	Ratio 351:352[a]	Isolated yield (%) of 351
1	DCC, Et_3N, DMAP	rt	1:3	-
2	 , Et_3N, DMAP	rt	1:3	8
3	 , Et_3N, DMAP	rt	3:1	68
4	$SOCl_2$, DMF	rt	degradation	-

[a] determined by ^1H NMR

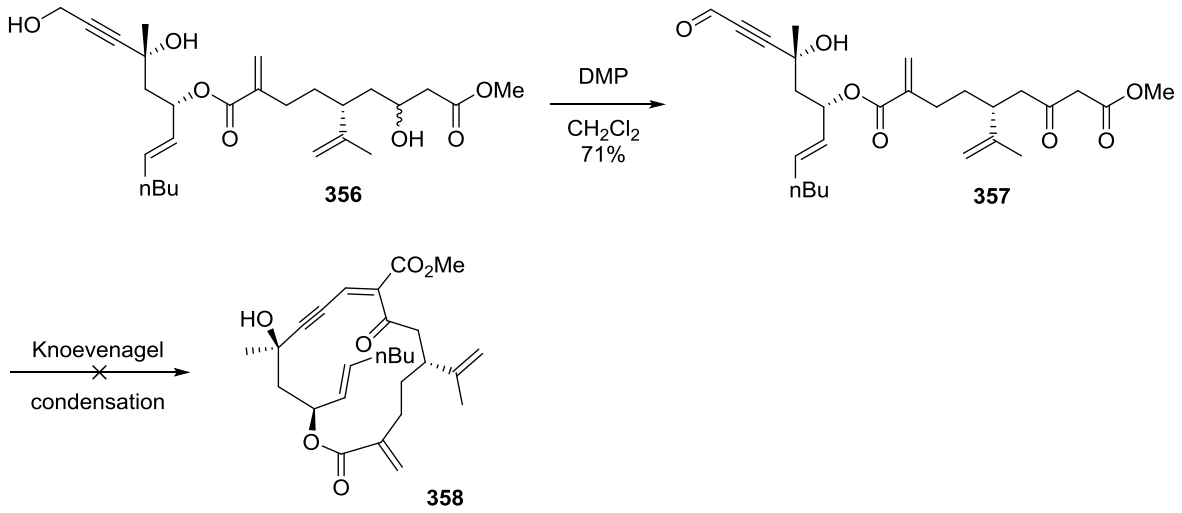
Following formation of the ester **351**, protection of the tertiary alcohol as a silyl ether proceeded in high yield and subsequent benzyl ether cleavage with DDQ afforded the primary alcohol **353** in 93% yield. When cerium ammonium nitrate was used for debenzylation, complete decomposition was observed. 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.



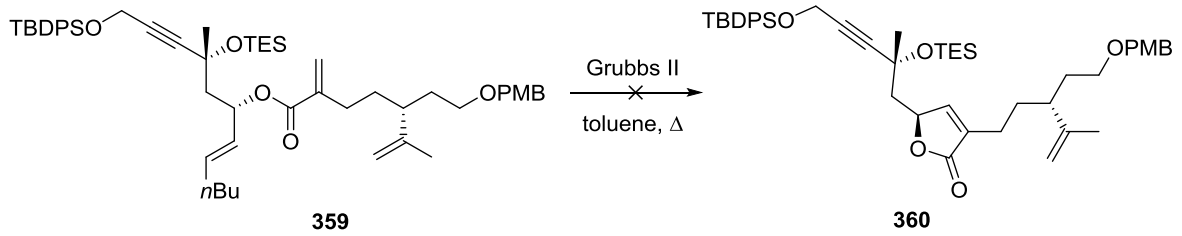
Scheme 94 Formation of intermediate **356**

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.



Scheme 95 Failed intramolecular Knoevenagel condensation

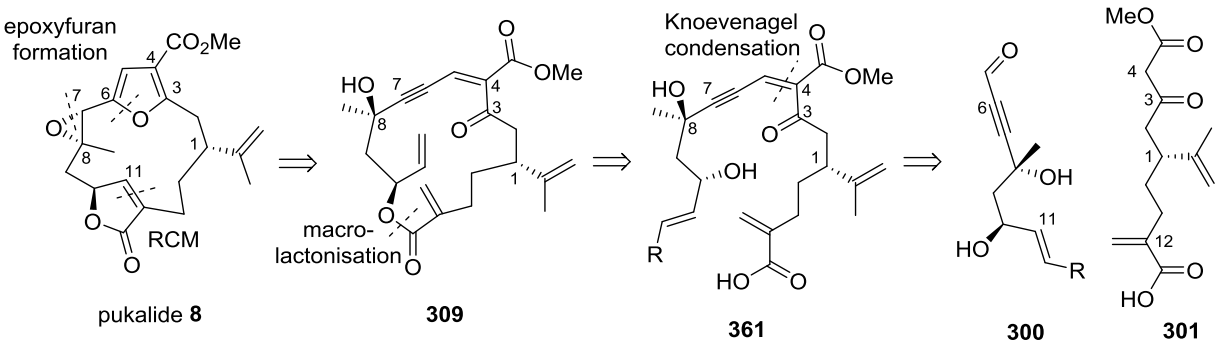
As a last resort, an attempt was made to perform ring-closing metathesis between the methylene and trans-substituted alkene to install the butenolide at an earlier stage in the synthesis (**Scheme 96**). However, the desired product **360** was not obtained. Following this unsuccessful result a revision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



Scheme 96 Attempt to effect ring-closing metathesis at an early stage

2.4 Approach 2: An Intermolecular Knoevenagel Condensation Approach

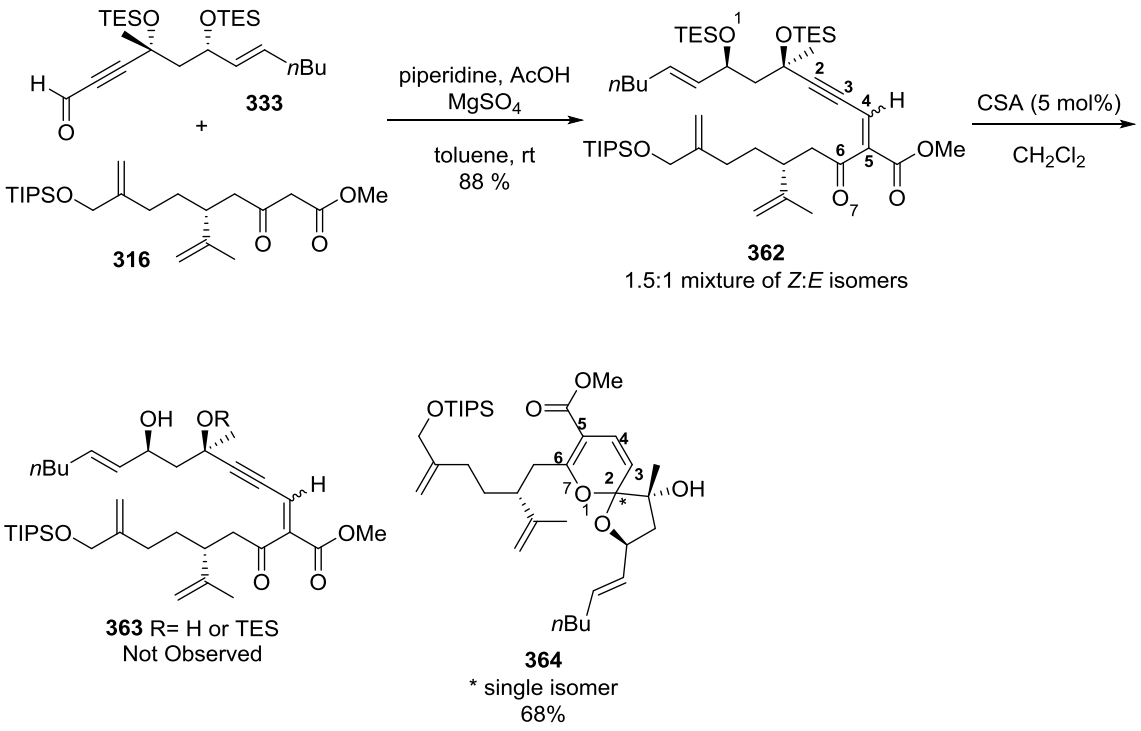
The discovery that macrocycle formation through Knoevenagel condensation was not viable meant that another approach was required. Following the same initial disconnections through the epoxyfuran and butenolide rings gave the same retrosynthetic lactone (**309**) as before. However, it was envisioned 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

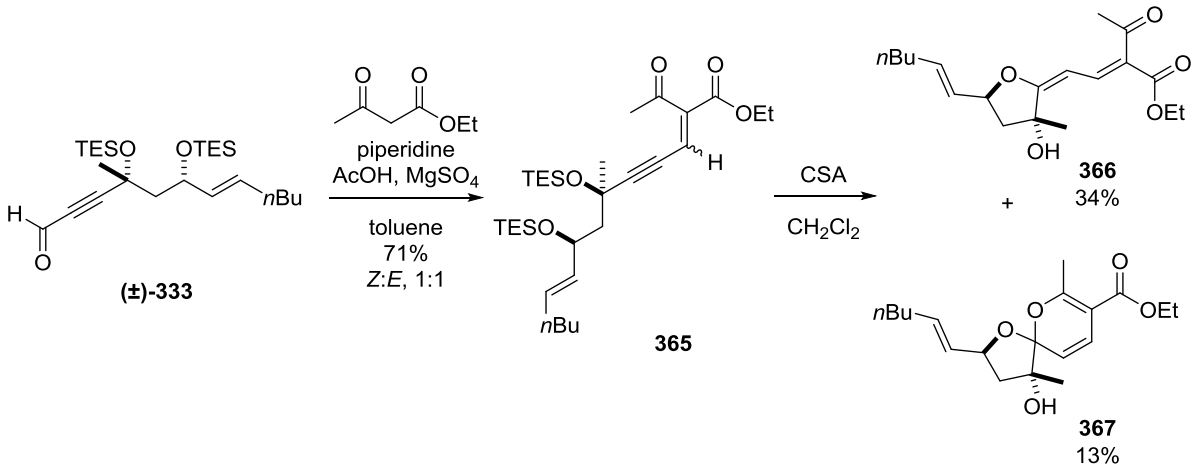
2.4.1 Exploration of Knoevenagel Condensation as the Fragment Coupling Step

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 β-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 β-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.



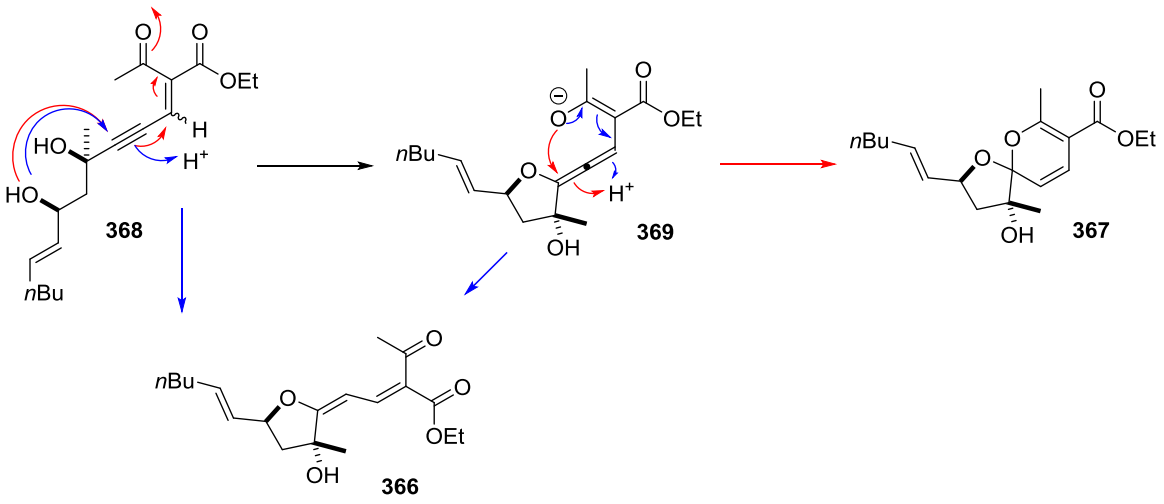
Scheme 98 Formation of a spirocyclic by-product

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**.



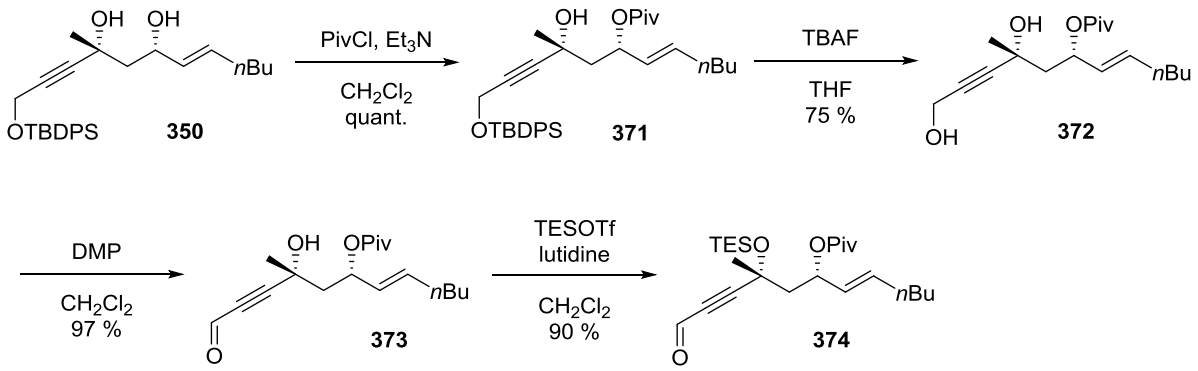
Scheme 99 Investigation into Spirocycle Formation

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

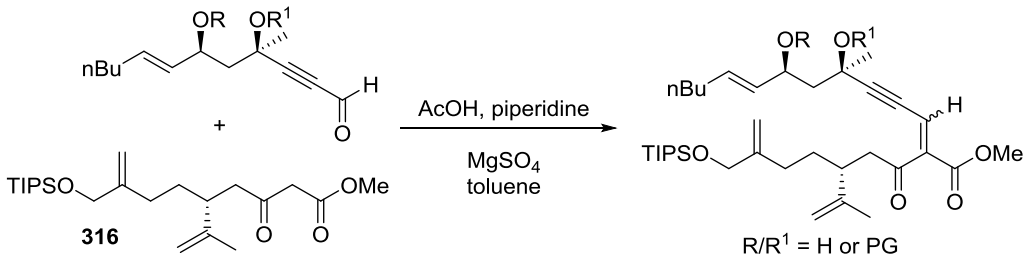
To prevent formation of the undesired spirocycle, protection of the secondary alcohol was necessary. Starting from previously synthesised diol **350**, the secondary alcohol was protected as its pivalate ester **371** to allow easy differentiation between the hydroxyl groups. Silyl ether cleavage with 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

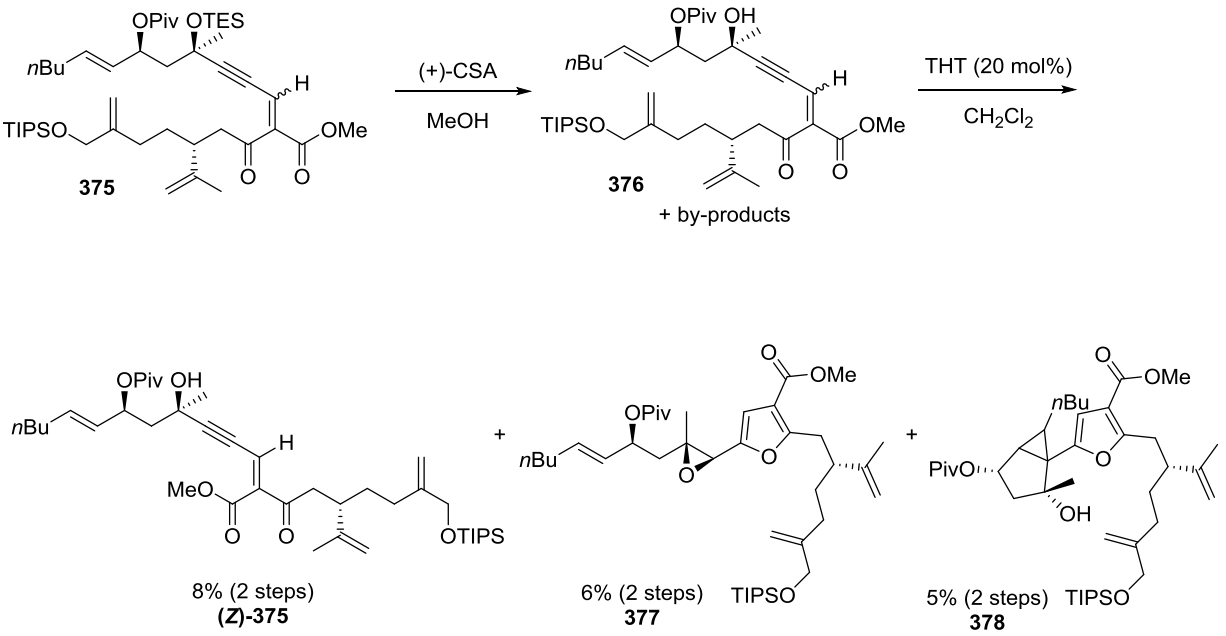
Both of the aldehydes **373** and **374** were coupled with the β-keto ester **316** to explore the Knoevenagel condensation reaction further. Both reactions gave a more favourable isomeric product ratio (1.2:1, *Z*:*E*) than the reaction of the di-TES analogue **362** (entry 3), but lower yields were 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^1) 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



Entry	Product	R	R^1	*E*:*Z* ratio	Yield (%)
1	**375**	Piv	TES	1:1.2	57
2	**376**	Piv	H	1:1.2	69 (brsm)
3	**362**	TES	TES	1:1.5	88

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.

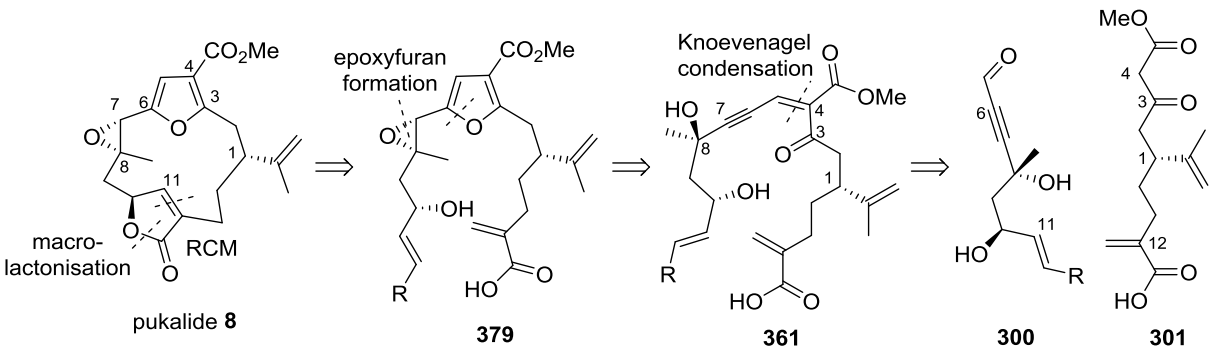


Scheme 102 Exploration of epoxyfuran formation

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

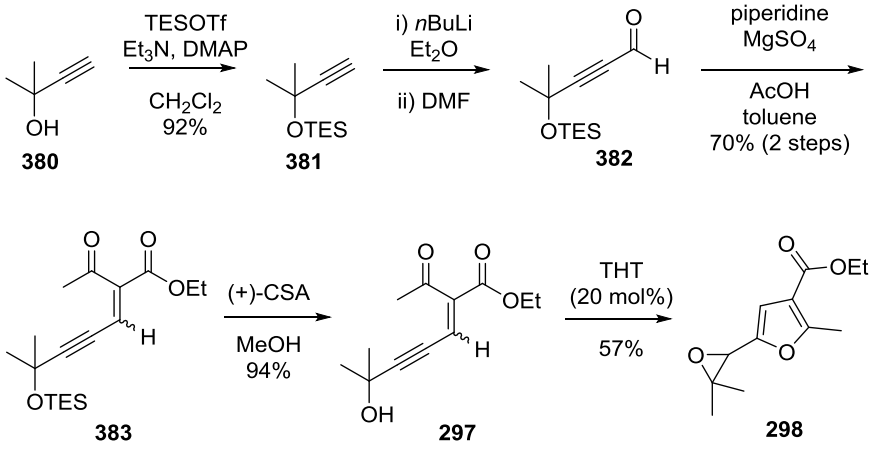
Results of initial Knoevenagel condensation studies showed that furan formation would need to be effected earlier in the synthesis than had been intended. The new strategy was therefore devised so that ring-closing metathesis and macrolactonisation would be used to install the butenolide and macrolactone 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.



Scheme 103 Revised synthetic Strategy

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

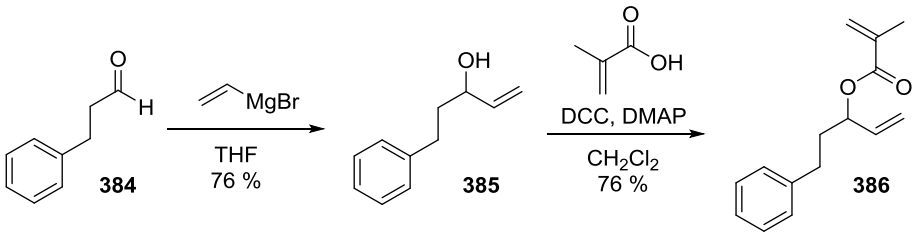
Ring-closing metathesis had been proposed as the final synthetic step and so initial studies focussed on the stability of the epoxyfuran in the presence of Grubbs catalyst and under prolonged heating (**Table 7**). The epoxyfuran **298** was treated with Grubbs II catalyst in two different solvents at 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

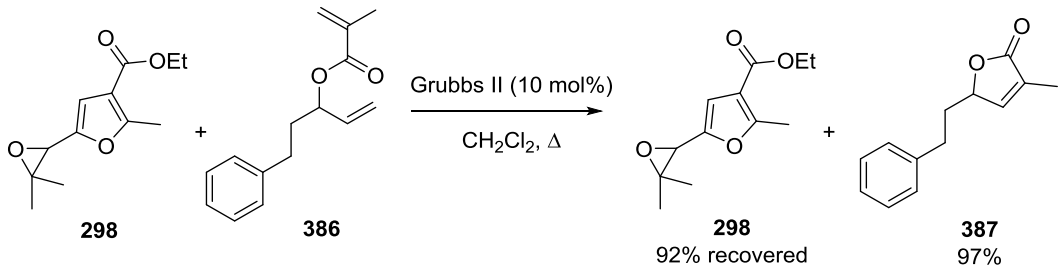
Solvent	Temperature (°C)	Reagent	Time (h)
Toluene	80	-	24
Toluene	rt	Grubbs II	24
Toluene	80	Grubbs II	24
DCM	45	Grubbs II	24

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

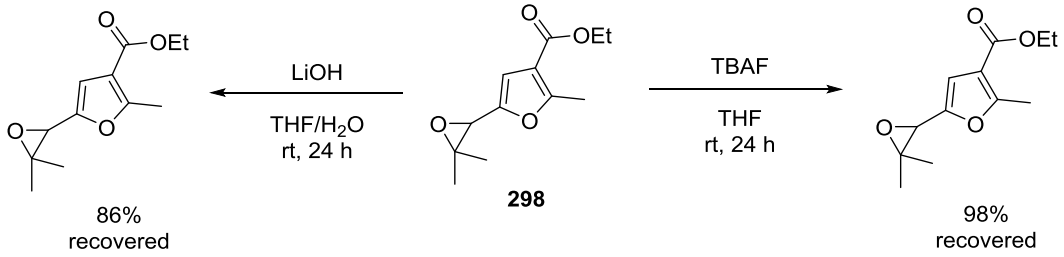
Butenolide formation in the presence of epoxyfuran **298** proceeded well and the butenolide **387** was obtained in 97% yield. Although some degradation of the epoxyfuran was observed, 92% of the epoxyfuran **298** was recovered after column chromatography. These results demonstrated the viability of using a ring-closing metathesis reaction at a very late stage in the synthetic route.



298 **386** **298** 92% recovered **387** 97%

Scheme 106 Butenolide formation in the presence of epoxyfuran

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.



86% recovered **298** 98% recovered

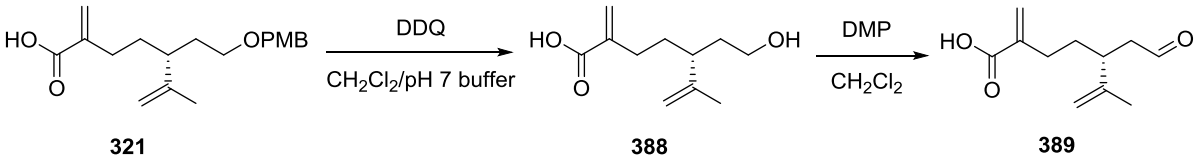
Scheme 107 epoxyfuran stability under basic conditions

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.

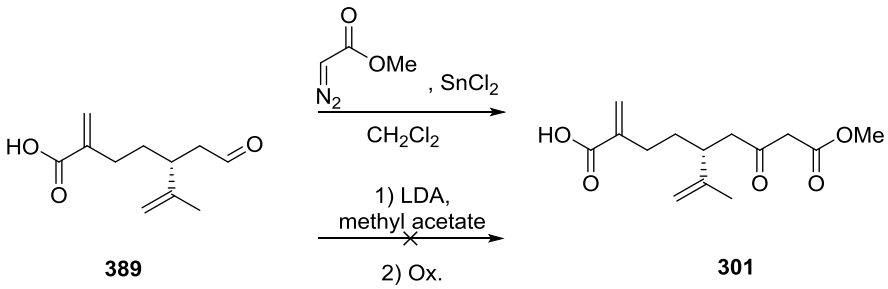
Starting from the carboxylic acid **321**, cleavage of the *p*-methoxy benzyl ether occurred quantitatively in the presence of DDQ. However, due to the polarity of the resulting hydroxy acid **388** it could not be separated from reagent residues and the alcohol **388** was carried forward crude to the 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.



321 **388** **389**

Scheme 108 Formation of crude aldehyde

Aldehyde **389** was carried forward crude to investigate whether the β-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.



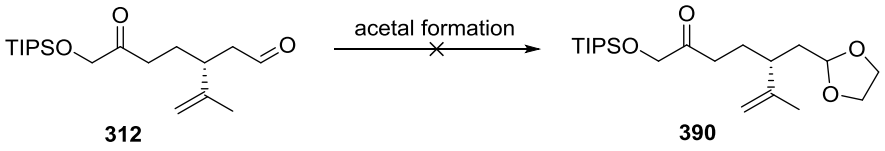
389 **301**

Scheme 109 Installation of the β-keto ester

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

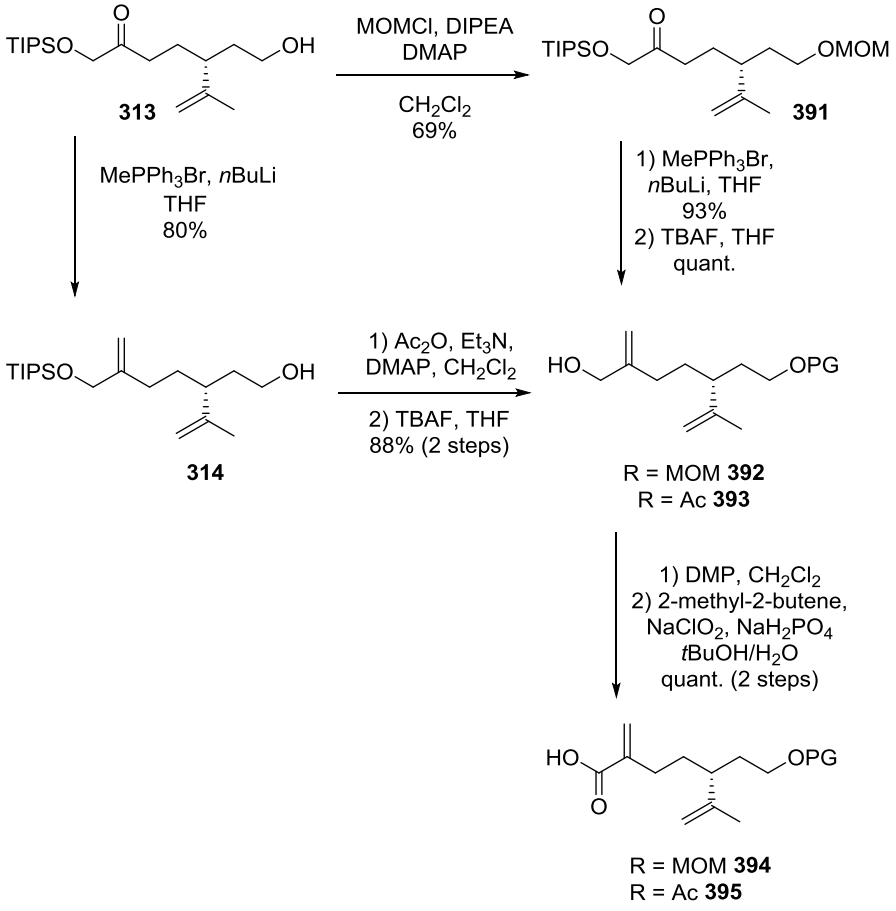
Attempts to synthesise the PMB analogue **321** had been unsuccessful and so a new protecting group strategy was devised for the synthesis of the β-keto ester fragment. Problems with purification had arisen because of the presence of inseparable reagent residues and so the use of an acid/base labile 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 β-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**).



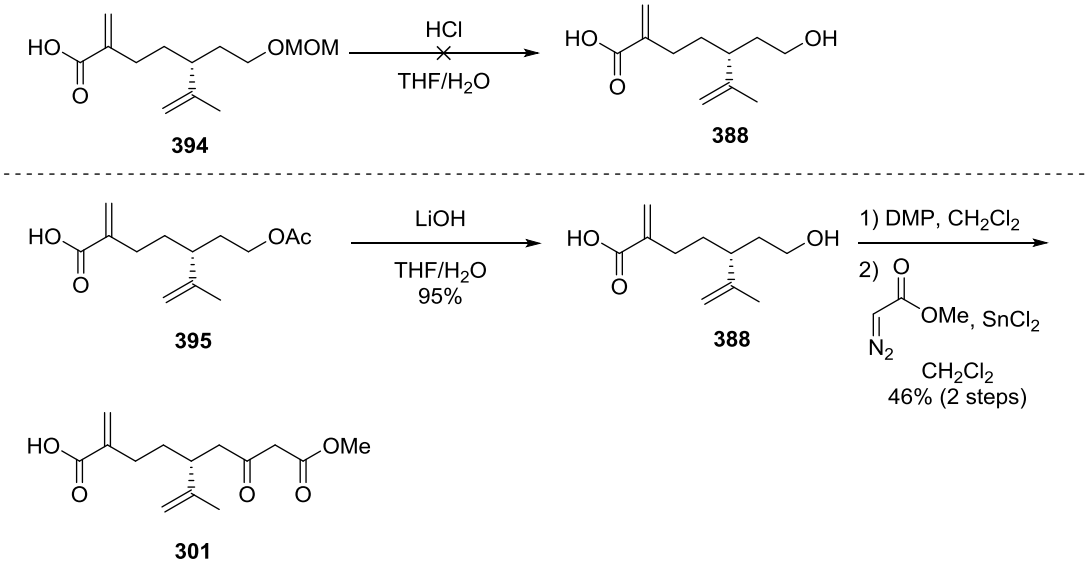
Scheme 110 Attempted acetal formation

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.

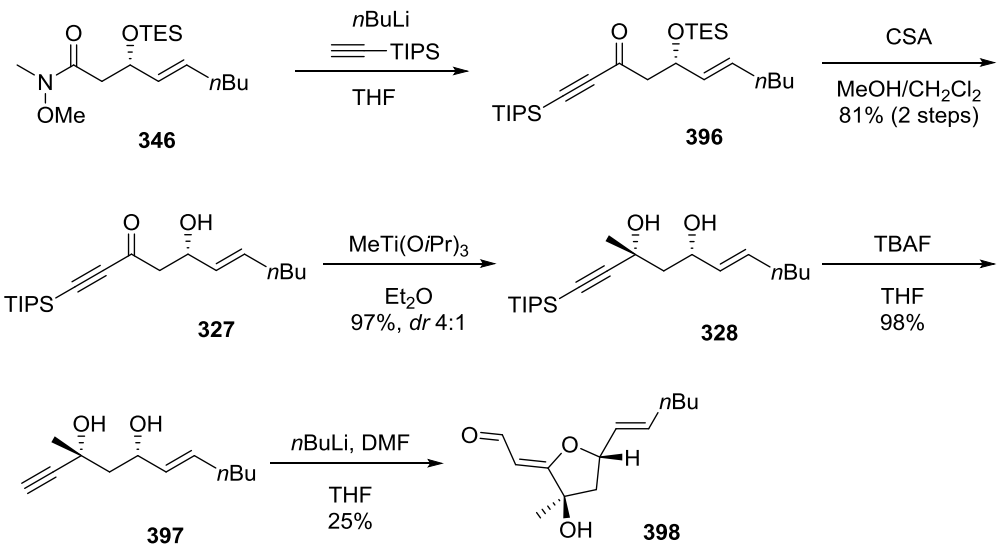


Scheme 112 Formation of the β-keto ester fragment

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.

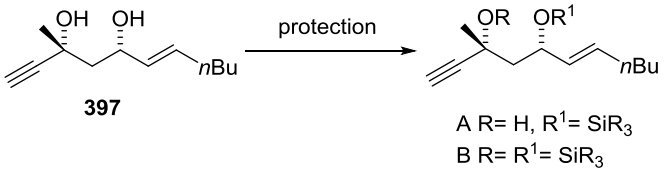
Starting from previously discussed Weinreb amide **346**, addition of lithiated TIPS acetylene followed by triethylsilyl ether cleavage afforded allylic alcohol **327** in high yield (**Scheme 113**). Stereoselective methylation under previously described conditions gave diol **328** with a high *dr* 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

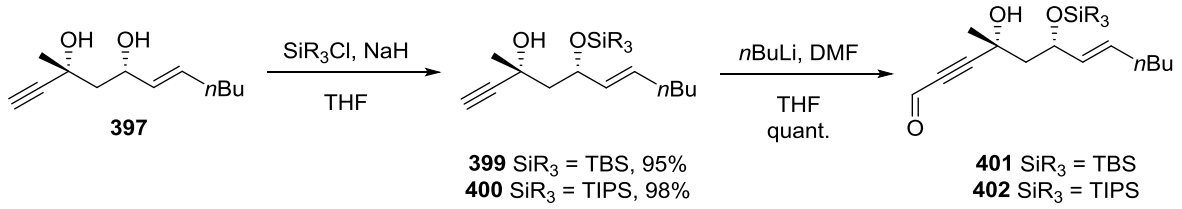
Selective protection of the secondary hydroxyl group as a silyl ether was performed using various silylating reagents and reaction conditions to give substrates that could be tested in the coupling reaction (**Table 8**). Ultimately, a less bulky group was required to minimize formation of the undesired *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



Entry	Reagent	Base	Solvent	Temperature	Product Ratio (SM:A:B)	Isolated Yield A (%)
1	TESCl	imidazole	DCM	rt	0.25:1:0.4	57
2	TBSCl	imidazole	DMF	rt → Δ	1:0:0	-
3	TBSOTf	lutidine	DCM	0 °C	2:1:5	13
4	TBSCl	NaH	THF	0 °C → rt	0:1:0	95
5	TIPSCl	NaH	THF	0 °C → rt	0:1:0	98

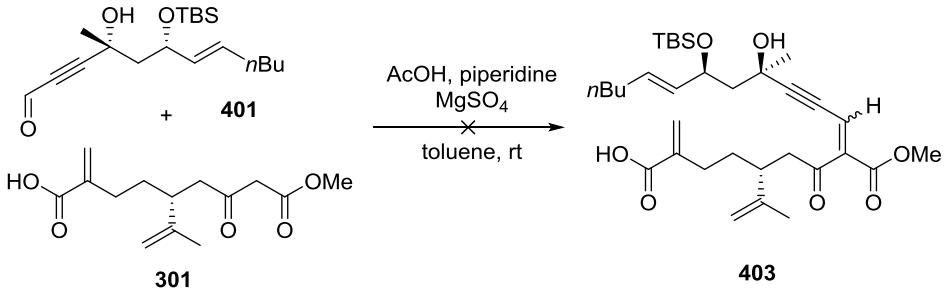
Formylation of both the TBS and TIPS analogues **399** and **400** resulted in quantitative formation of the corresponding aldehydes **401** and **402** (**Scheme 114**). However, when the TES analogue was treated under the same conditions, multiple products were observed. Scrambling of the silyl ether 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

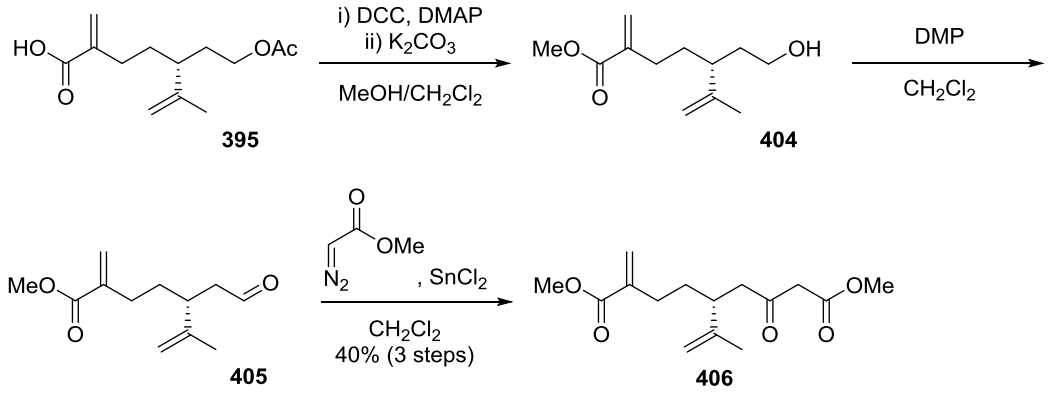
Completion of the aldehyde **401** and β-keto ester **301** meant that attention could be turned to the Knoevenagel coupling of the two fragments (**Scheme 115**). However, all attempts to perform Knoevenagel coupling were unsuccessful and ynenone **403** was not isolated. It was proposed that salt formation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



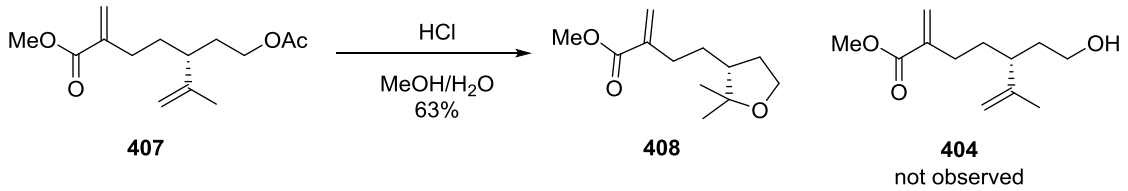
Scheme 115 Failed Knoevenagel coupling

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**).

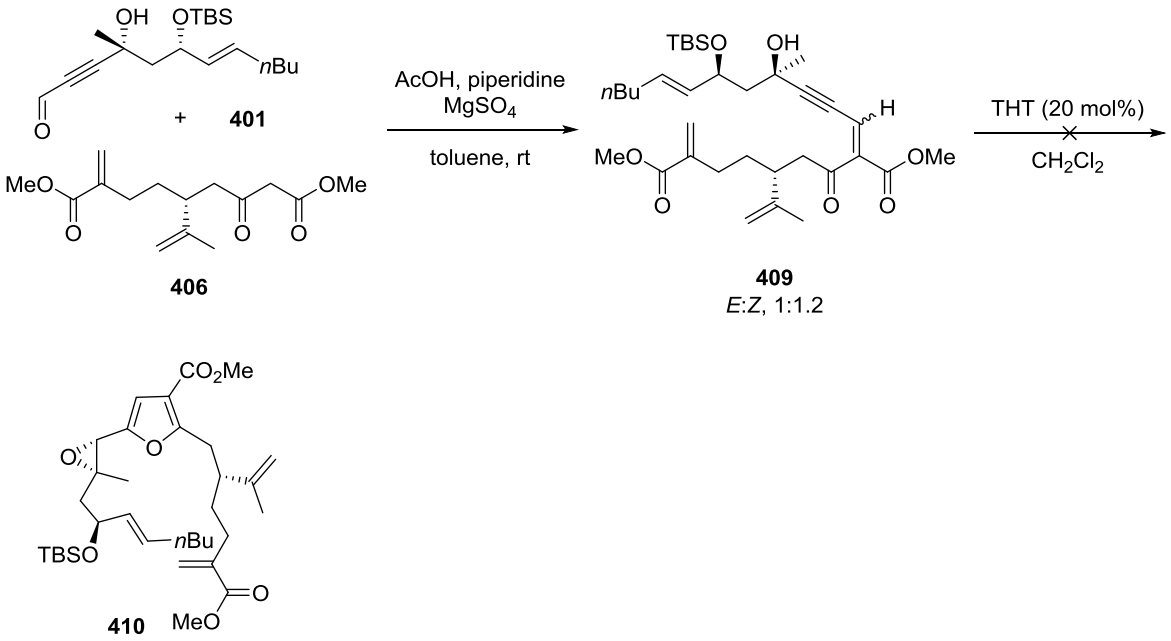


Scheme 116 Formation of a methyl ester coupling partner



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 β-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.



Scheme 118 Knoevenagel condensation

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 $CDCl_3$ 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 furan **411** but isolation was not performed and so full characterisation data were not obtained.

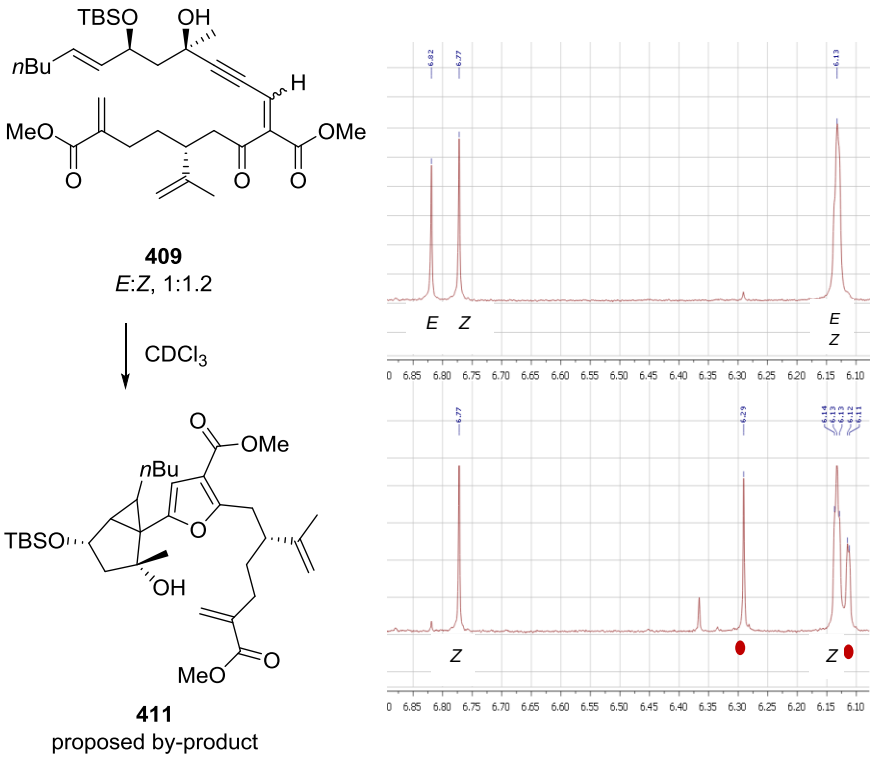


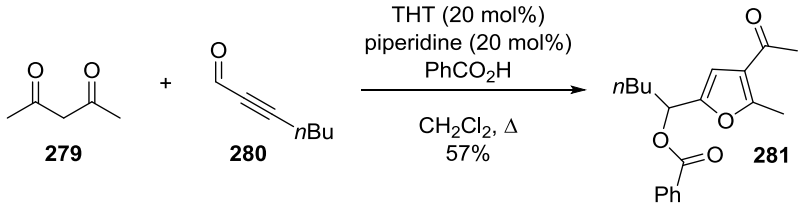
Figure 11 Consumption of the *E* ynenone in $CDCl_3$

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

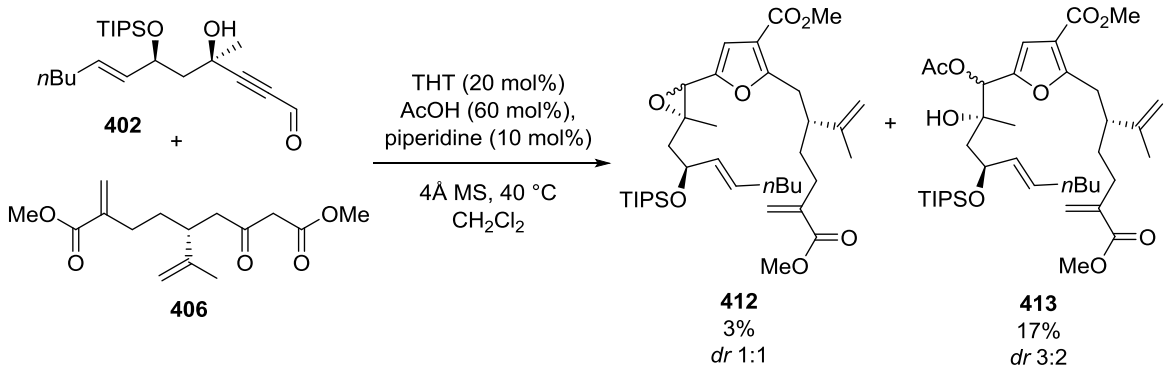
2.5.1 Initial One-Pot Furan Formation Studies

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 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.



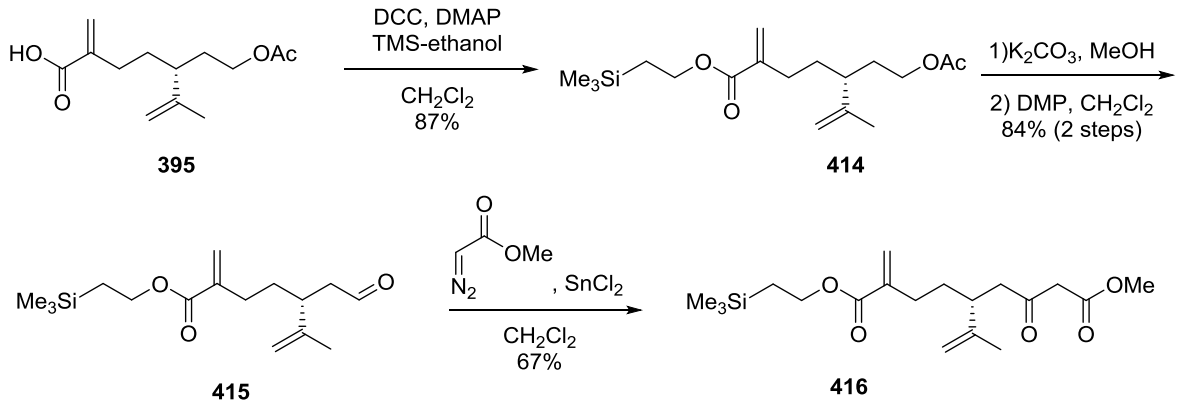
Scheme 120 Initial strategy for one-pot furan formation

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 phenylphoshonic 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.

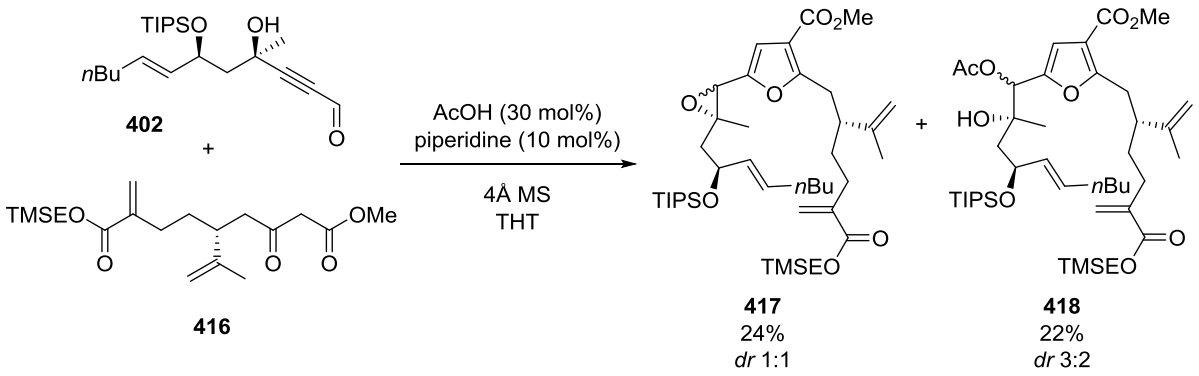
Starting from the acid **395**, which had been synthesised previously, the TMSE ester **414** was prepared by DCC mediated esterification with trimethylsilyl ethanol (**Scheme 121**). Hydrolysis of the acetate group under basic conditions was followed by oxidation with Dess-Martin periodinane to furnish the aldehyde **415** in high yield. The synthesis of the β-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**

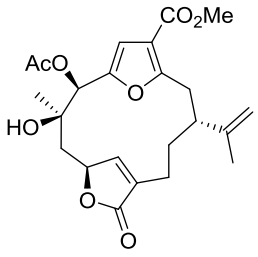
2.5.3 One-Pot Furan Formation and Cyclisation Studies

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.

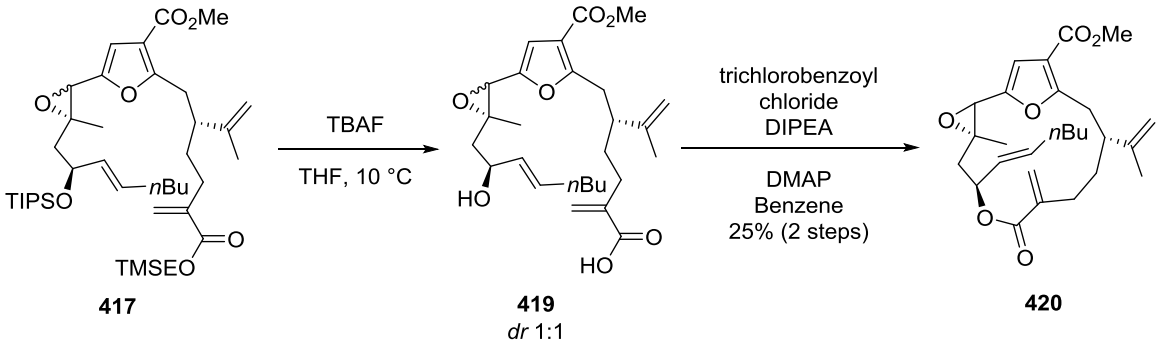


7-acetylsinumaximol B **16**

Figure 12 Structure of 7-acetylsinumaximol B

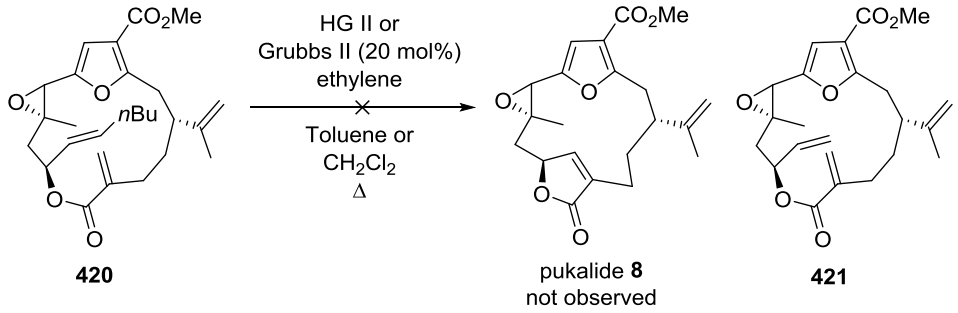
Both **417** and **418** were now readily available and so methods for their deprotection and macrocyclisation were explored. The epoxy furan **417** was treated with a cooled solution of TBAF to afford the seco-acid **419** and this compound was subjected to macrolactonisation

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.



Scheme 123 Macrocycle formation

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.



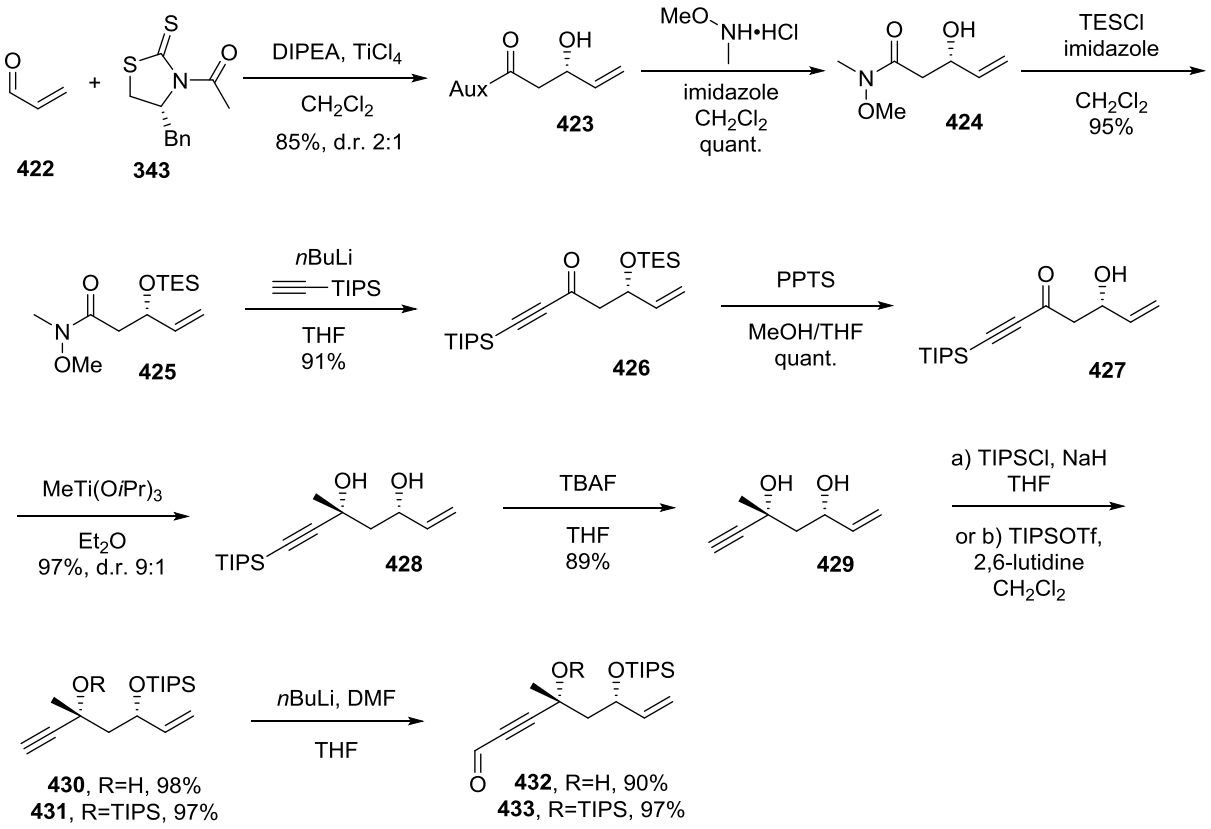
Scheme 124 Attempted ring-closing metathesis

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

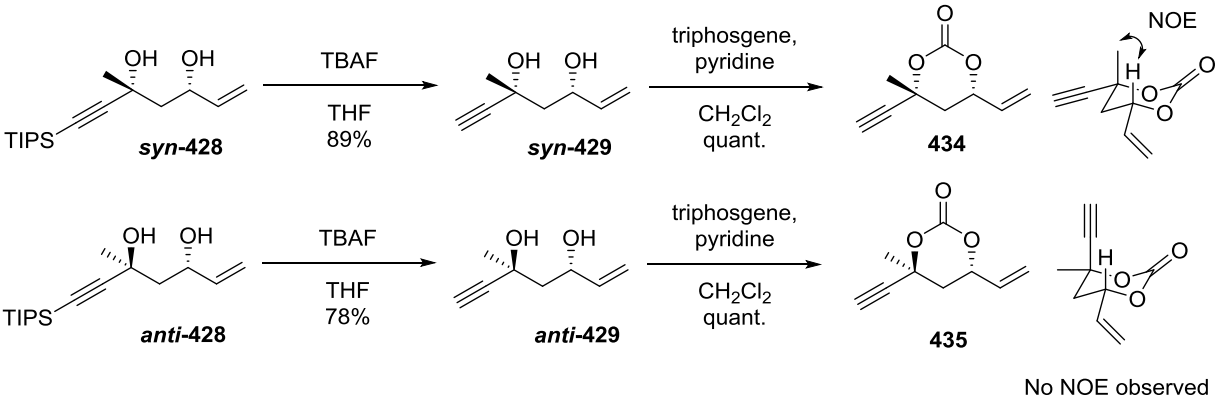
route was redesigned to exclude the *n*-butyl side chain and a terminal alkene was targeted as the RCM substrate.

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**).[105] 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

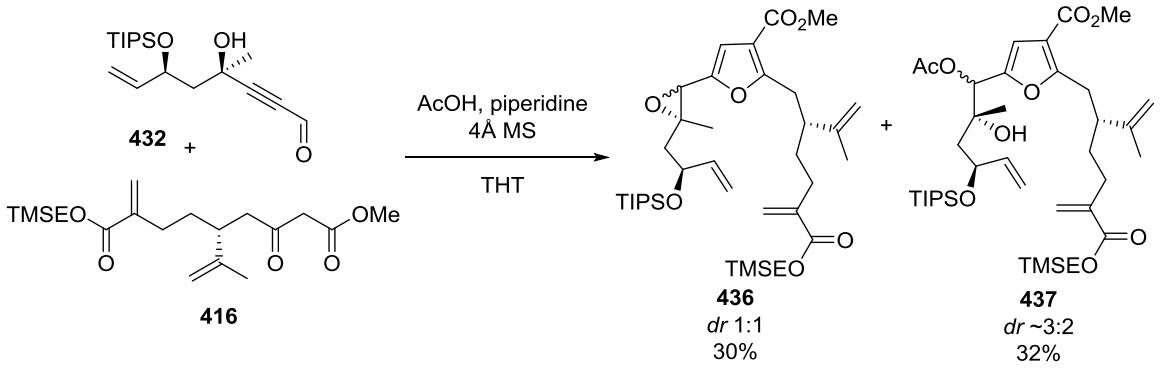
The relative stereochemistry of the *syn* and *anti* diols was confirmed by formation of carbonates **434** and **435** and subsequent NOE experiments (**Scheme 126**). The carbonates were prepared by silyl cleavage of ***syn-*** and ***anti*-428** to form the terminal alkynes ***syn-*** and ***anti*-429**, 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 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

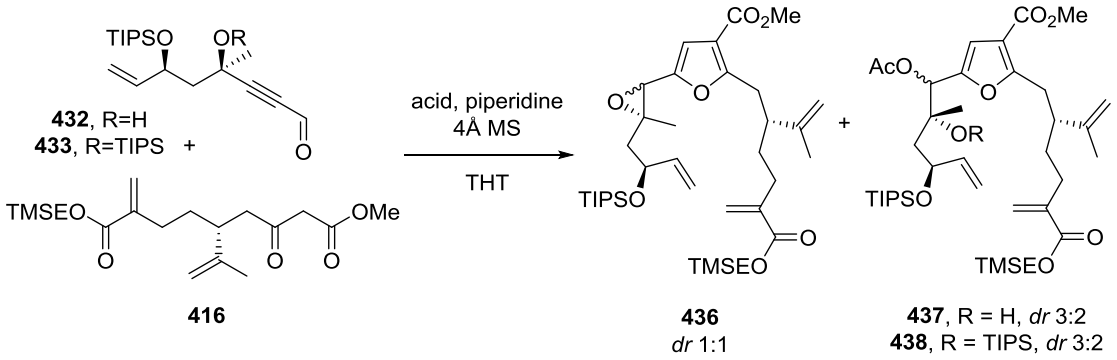
The synthesis of the aldehyde **432** allowed the coupling reaction with the β-keto ester **416** to be performed as described previously to afford a *ca*. 1:1 separable mixture of epoxy furan **436** and acetate **437** (**Scheme 127**). It was envisioned that these compounds would be used for the synthesis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



Scheme 127 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



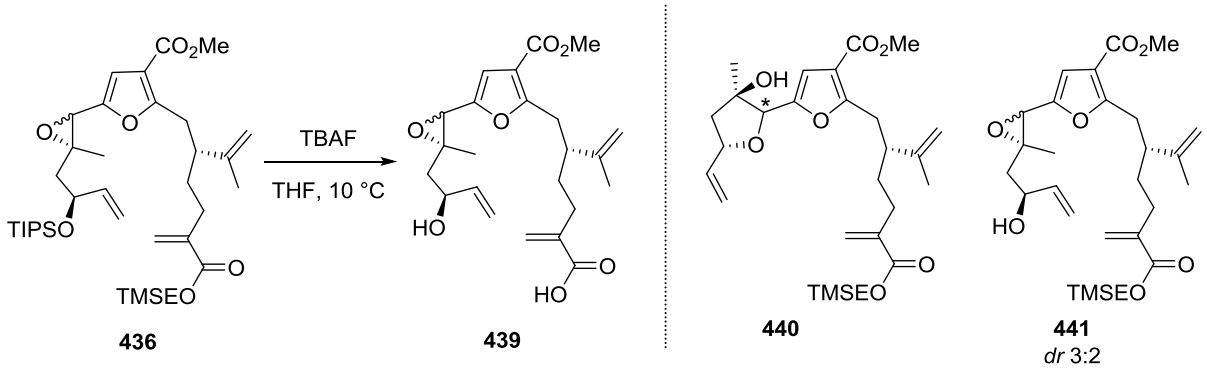
Entry	Aldehyde	Acid	Equiv. RCO_2H	Yield 436 (%)[a]	Yield 437 (%)[a]	Yield 438 (%)[a]
1	**432**	$MeCO_2H$	0.3	36	24	-
2	**432**	$MeCO_2H$	0.6	30	32	-
3	**432**	$MeCO_2H$	1.0	16	50	-
4	**432**	EDDA[b]	0.1	23	10	-
5	**432**	MeCOSH	0.1	-	-	-
6	**432**	Ph_3CO_2H	0.1	-[c]	-	-
7	**432**	1-adamantane-CO_2H	0.1	23	-	-
8	**432**	*t*$BuCO_2H$	0.1	39	-	-
9	**432**	*t*$BuCO_2H$	0.6	62	-	-
10	**432**	*t*$BuCO_2H$	1.2	54	-	-
11	**433**	$MeCO_2H$	1.2	-	-	85
12	**432**	-[d]	-	-	-	-

[a] isolated yield; [b] used without piperidine present; [c] trace observed in NMR; [d] no acid added - control experiment

2.5.6 Completion of 7-*epi*-Pukalide

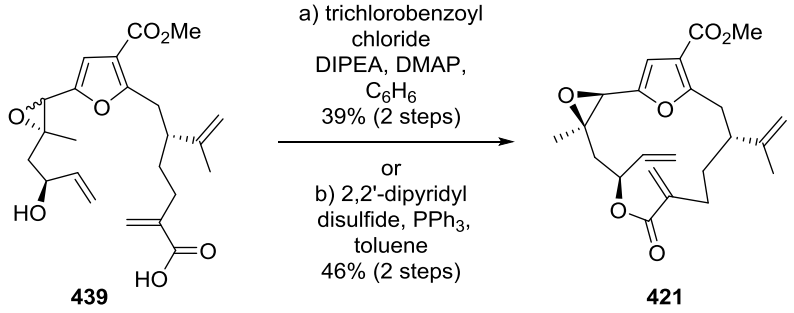
Conditions for the selective formation of epoxyfuran **436** had now been established and so attention was turned to the formation of the macrocycle and installation of the butenolide. Simultaneous cleavage of the silyl ether and the ester was accomplished by treatment of the epoxyfuran **436** with 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

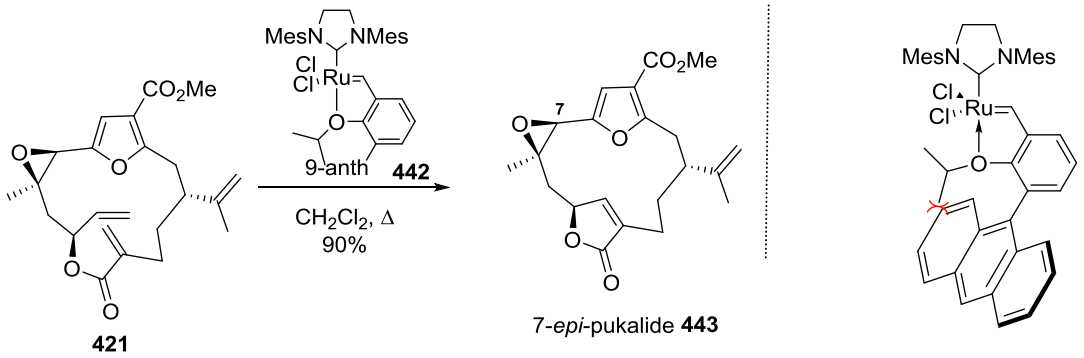
The hydroxy-acid **439** was then subjected to Yamaguchi macrolactonisation conditions to afford the lactone **421** as a single isomer in 39% yield over two steps; the other diastereoisomer failed to undergo cyclisation under the reaction conditions (**Scheme 129**). Cyclisation of the hydroxy-acid 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 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.

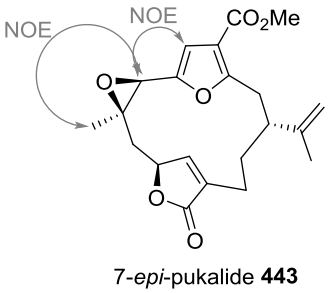
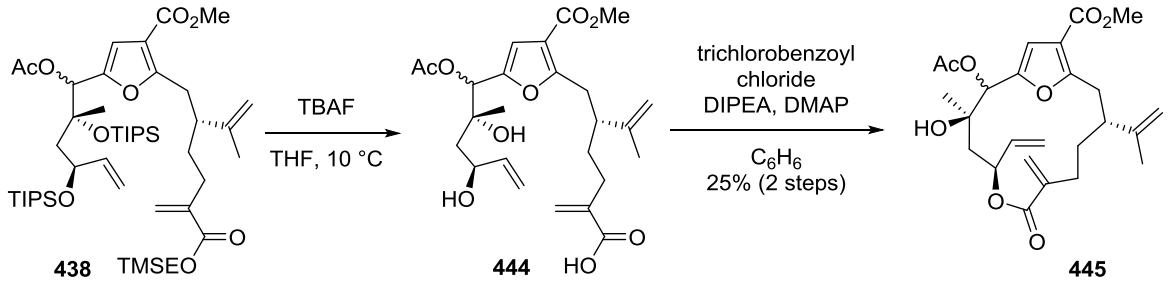


Figure 13 Observed NOEs for 7-*epi*-pukalide

2.5.7 Completion of 7-Acetylsinumaximol B

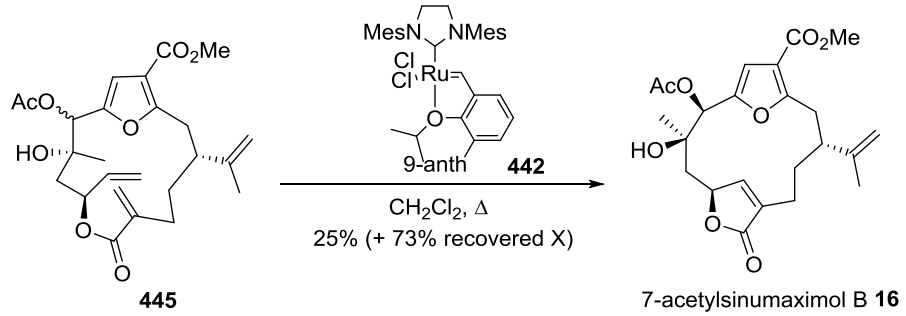
Completion of 7-acetylsinumaximol B was envisioned to occur analogously to the synthesis of 7-*epi*-pukalide. Thus, the acetate product **438** was subjected to the same three step sequence: deprotection, macrolactonisation and RCM. Treatment of acetate **438** with TBAF

effected cleavage of both silyl ethers and the trimethyl silyl ethyl ester to afford hydroxy acid **444** which was used directly in the macrolactonisation reaction. In this case, both diastereoisomers underwent Yamaguchi macrolactonisation, but the macrolactone **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 **445**

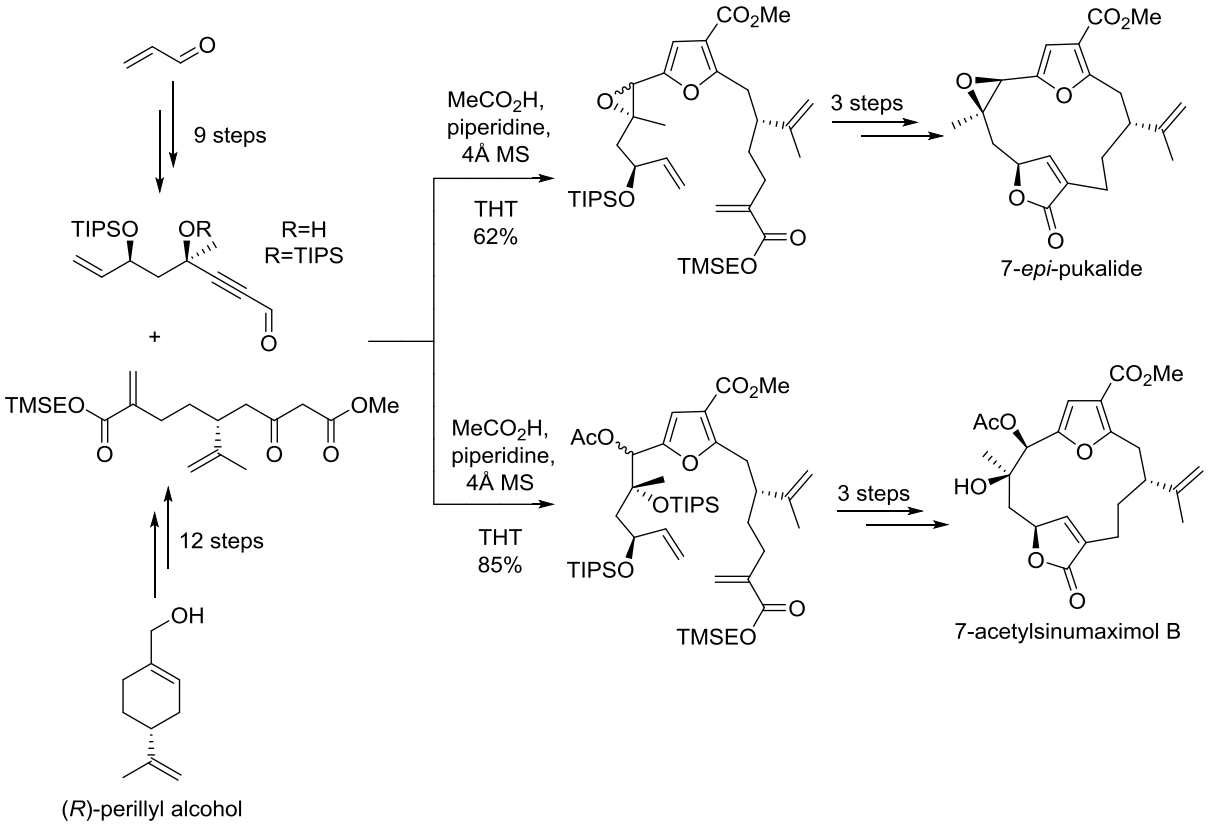
As was previously observed for 7-*epi*-pukalide, the transannular ring-closing metathesis reaction to effect butenolide formation was not successful when either the Grubbs 2nd generation catalyst or the Hoveyda-Grubbs 2nd generation catalyst was used. Only one diastereoisomer of the triene **445** underwent RCM to produce the butenolide when treated with the anthracene modified catalyst **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 **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

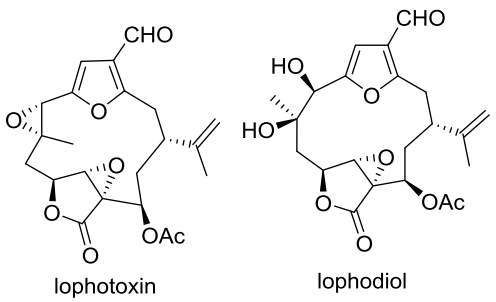
2.6 Conclusions and Future Work

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

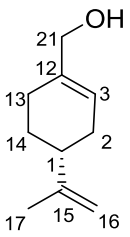
Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Tetrahydrofuran, toluene, dichloromethane, acetonitrile and diethyl ether were purified using a Pure-SolvTM 500 Solvent Purification System. Other dry organic solvents and starting materials 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 ºC fraction.

IR spectra were recorded at rt using a Shimadzu FTIR-8400S spectrometer by ATR and selected frequencies (ν_{max}) are reported. All ^{1}H spectra were recorded on Bruker 400 MHz or 500 MHz spectrometers at rt. ^{1}H NMR data are reported as follows: chemical shifts in ppm relative to $CDCl_3$ (7.26) or C_6D_6 (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 ^{13}C 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 $CHCl_3$ (77.16) or C_6D_6 (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 spectometry 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

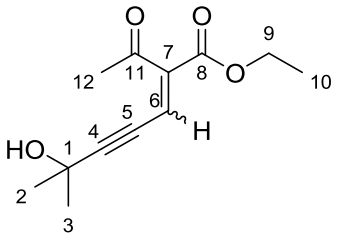


Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.2370

To a solution of allylic alcohol **304** (25.9 g, 171 mmol) in CH_2Cl_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_2O (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_2O, 7:3) to afford (*R*)-perillyl alcohol (**(*R*)-32**) as a colourless oil (11.3 g, 44%)[a]. $[\alpha]_D^{24}$ +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

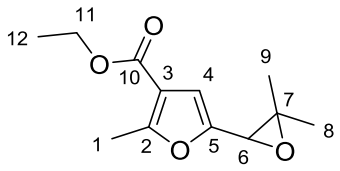


Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224.2560

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_2O, 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, $CDCl_3$) 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, $CDCl_3$) δ 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, $CDCl_3$) 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, $CDCl_3$) δ, 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 $C_{12}H_{16}O_4Na$ $[M+Na]^+$ 247.0941, found 247.0931; IR ν_{max} 3447, 2983, 2937, 1712, 1697, 1599, 1585, 1371, 1136 cm^{-1}.

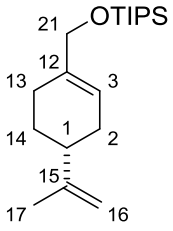
Ethyl 5-(3,3-dimethyloxiran-2-yl)-2-methylfuran-3-carboxylate 298



Chemical 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_2Cl_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_2O, 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, $CDCl_3$) δ 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* = 7.0Hz, CH_3-C12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 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_2-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 $C_{12}H_{16}O_4Na$ $[M+Na]^+$ 247.0941, found 247.0931; IR ν_{max} 1714, 1617, 1420 cm^{-1}

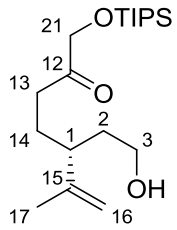
(4*R*)-4-(Prop-1-en-2-yl)-1-((triisopropylsilyloxy)methyl)cyclohex-1-ene 311



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 CH_2Cl_2 (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 CH_2Cl_2 (2 × 100 mL). The combined organic extracts washed with saturated aq. NH_4Cl (300 mL), dried over $MgSO_4$ 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.). $[\alpha]_D^{23}$ +50 (*c* = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (1H, dd, *J* = 3.0, 1.5 Hz, CH-C3), 4.71 (2H, s, CH_2-C21), 4.19–4.00 (2H, m, CH_2-C16), 2.20–2.09 (2H, m, CH_2-C2, CH_2-C13), 2.09–2.01 (2H, m, CH_2-C2, CH_2-C13), 2.01–1.90 (1H, m, CH_2-C14), 1.87–1.80 (1H, m, CH-C1), 1.74 (3H, s, CH_3-C17), 1.53–1.42 (1H, m, CH_2-C14), 1.22–0.97 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3 (C-C15), 137.2 (C-C12), 120.4 (CH-C3), 108.6 (CH_2-C16), 67.3 (CH_2-C21), 41.6 (CH-C1), 30.5 (CH_2-C2), 27.7 (CH_2-C13), 26.1 (CH_2-C14), 21.0 (CH_3-C17), 18.2 (CH(<u>C</u>H$_3$)$_2$), 12.2 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{19}H_{36}OSiNa$ $[M+Na]^+$ 331.2428, found 331.2412; IR ν_{max} 2941, 2866, 1645, 1464 cm^{-1}

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



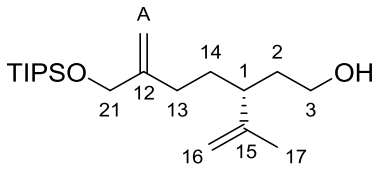
Chemical Formula: $C_{19}H_{38}O_3Si$
Molecular Weight: 342.5950

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 CH_2Cl_2 and MeOH (225 mL) at −78 °C was subjected to ozonolysis and monitored by TLC. After 1 h the mixture was flushed with O_2 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 Et_2O (1 L). The solution was washed with H_2O (2 × 400 mL) and brine (400 mL), then dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was passed through a short pad of silica gel (pet ether:Et_2O, 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. $NaHCO_3$ (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 $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 7:3 → 1:1) to afford the alcohol **313** as a colourless oil (8.64 g, 38% over 2 steps). $[\alpha]_D^{23}$ −1.4 (*c* = 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (1H, dq, *J* = 2.6, 1.4Hz, CH_2-C16), 4.75–4.73 (1H, m, CH_2-C16), 4.20 (2H, s, CH_2-C21), 3.68–3.55 (2H, m, CH_2-C3), 2.53 (2H, dd, *J* = 7.9, 7.1Hz, CH_2-C13), 2.27–2.19 (1H, m, CH-C1), 1.80–1.53 (4H, m, CH_2-C2, CH_2-C14), 1.61 (3H, dd, *J* = 1.4, 0.8Hz, CH_3-C17), 1.23–0.97 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.0 (C-C12), 146.8 (C-C15), 113.0 (CH_2-C16), 69.9 (CH_2-C21), 61.5 (CH_2-C3), 43.9 (CH-C1), 36.4 (CH_2-C13), 36.3 (CH_2-C2), 26.1 (CH_2-C14), 18.0 (CH_3-C17), 17.7 (<u>C</u>H(CH$_3$)$_2$), 12.0 (CH(<u>C</u>H$_3$)$_2$)$_3$); HRMS (ESI$^+$) calcd for $C_{19}H_{38}O_3SiNa$ $[M+Na]^+$ 365.2482, found 365.2467; IR ν_{max} 3402, 2941, 2866, 1719, 1643, 1464, 1369 cm^{-1}

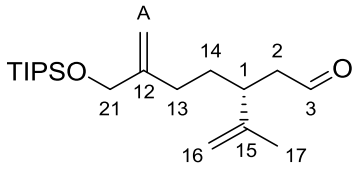
(3*R*)-3-(Prop-1-en-2-yl)-6-((triisopropylsilyloxy)methyl)hept-6-en-1-ol 314



Chemical Formula: $C_{20}H_{40}O_2Si$
Molecular Weight: 340.6230

To a solution of methyl triphenylphosphonium bromide (13.8 g, 38.7 mmol) in THF (80 mL) at 0 °C was added *n*BuLi (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 H_2O (100 mL) and the biphasic mixture was separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:EtOAc, 9:1) to afford the diene **314** as a colourless oil (4.51 g, 86%). $[\alpha]_D^{24}$ −3.5 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09–5.06 (1H, m, CH_2-C^A), 4.83–4.78 (2H, m, CH_2-C^A, CH_2-C16), 4.77–4.75 (1H, m, CH_2-C16), 4.13 (2H, s, CH_2-C21), 3.71–3.48 (2H, m, CH_2-C3), 2.27–2.19 (1H, m, CH-C1), 2.02–1.84 (2H, m, CH_2-C13), 1.66–1.60 (5H, m, CH_2-C2, CH_3-C17), 1.54–1.47 (2H, m, CH_2-C14), 1.24–0.89 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8 (C-C12), 147.4 (C-C15), 112.6 (CH_2-C^A), 108.1 (CH_2-C16), 66.2 (CH_2-C21), 61.8 (CH_2-C3), 44.4 (CH-C1), 36.3 (CH_2-C2), 31.6 (CH_2-C13), 30.5 (CH_2-C14), 18.2 (CH_3-C17), 17.8 (<u>C</u>H(CH$_3$)$_2$), 12.2 (CH(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{20}H_{40}O_2SiNa$ $[M+Na]^+$ 363.2690, found 363.2673; IR ν_{max} 3329, 2941, 2866, 1645, 1462 cm^{-1}

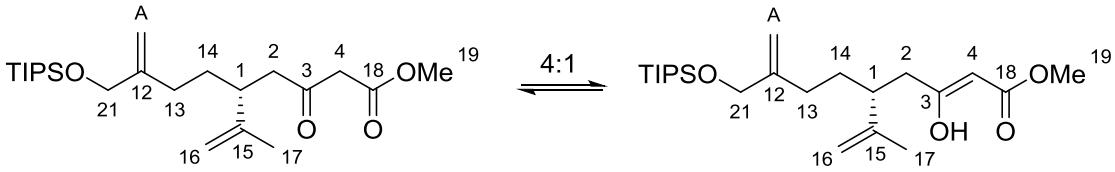
(*R*)-3-(Prop-1-en-2-yl)-6-(((triisopropylsilyl)oxy)methyl)hept-6-enal 315



Chemical Formula: $C_{20}H_{38}O_2Si$
Molecular Weight: 338.6070

To a solution of alcohol **314** (50.0 mg, 0.15 mmol) in CH_2Cl_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. $Na_2S_2O_3$ (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. $[\alpha]_D^{31}$ −1.2 (*c* = 0.250, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (1H, t, *J* = 2.4Hz, CHO-C3), 5.15–5.05 (1H, m, CH_2-C^A), 4.84–4.80 (2H, m, CH_2-C16), 4.80–4.76 (1H, m, CH_2-C^A), 4.13 (2H, s, CH_2-C21), 2.69 (1H, app p, *J* = 7.3 Hz, CH-C1), 2.52–2.38 (2H, m, CH_2-C2), 2.08–1.87 (2H, m, CH_2-C13), 1.59–1.55 (2H, m, CH_2-C14), 1.54 (3H, s, CH_3-C17) 1.18–0.96 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 (CHO-C3), 148.2 (C-C15), 145.6 (C-C12), 112.8 (CH_2-C16), 108.4 (CH_2-C^A), 66.1 (CH_2-C21), 47.5 (CH_2-C2), 41.3 (CH-C1), 31.1 (CH_2-C14), 30.0 (CH_2-C13), 18.7 (CH_3-C17), 18.0 (C<u>H</u>(CH_3)$_2$), 12.0 (CH(C<u>H</u>$_3$)$_2$); IR ν_{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



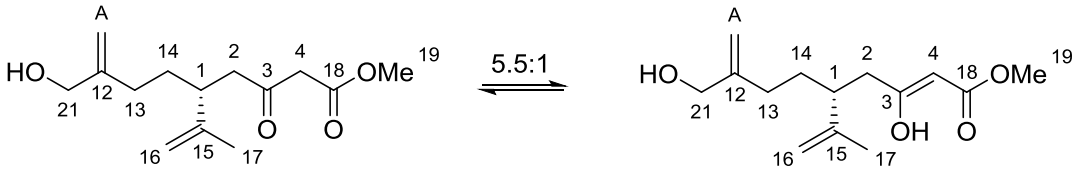
Chemical Formula: $C_{23}H_{42}O_4Si$
Molecular Weight: 410.6700

Methylglycine hydrochloride (300 mg, 2.39 mmol) and $NaNO_2$ (198 mg, 2.87 mmol) were dissolved in a ≈3:1 mixture of CH_2Cl_2 (0.8 mL) and H_2O (0.3 mL) and the resulting mixture was stirred for 1.5 h. Saturated aq. $NaHCO_3$ (2 mL) and CH_2Cl_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_2Cl_2, ~2.4 mmol) and aldehyde **315** (210 mg, 0.62 mmol) in CH_2Cl_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_2O, 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, $CDCl_3$) δ 11.98 (0.2H, s, OH-C3, enol), 5.10-5.06 (1H, m, CH_2-C^A), 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^A), 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_2-C2), 2.24 (0.4H, d, *J* = 7.5 Hz, CH_2-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, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 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^A), 108.2 (CH_2-C^A 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 (<u>C</u>H(CH_3)$_2$), 12.0 (CH(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) calcd. for $C_{23}H_{43}O_4Si$ $[M+H]^+$ 411.2931 found 411.2930; IR ν_{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

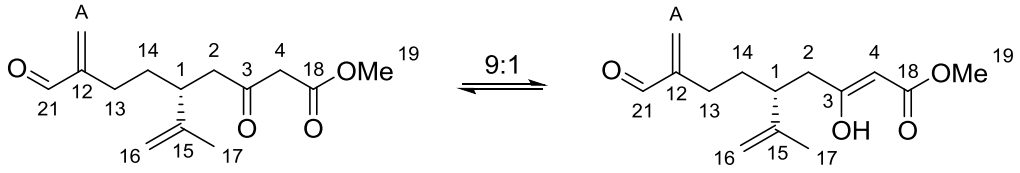


Chemical Formula: $C_{14}H_{22}O_4$
Molecular Weight: 254.3260

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_2O (10 mL) and Et_2O (10 mL) were added and the biphasic mixture was separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts dried over Na_2SO_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

mg, 97%). $[\alpha]_D^{24}$ −5.0 (*c* = 0.66, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (0.15H, s, OH-C3, enol), 5.06–5.00 (1H, m, CH_2-C^A), 4.96 (0.15H, s, CH-C4, enol), 4.88–4.86 (1H, m, CH_2-C16), 4.82–4.80 (1H, m, CH_2-C16), 4.78–4.73 (1H, m, CH_2-C^A), 4.07 (2H, d, *J* = 5.8 Hz, CH_2-C21), 3.73 (2.55H, s, CH_3-C19), 3.72 (0.45H, s, CH_3-C19, enol), 3.45 (0.85H, d, *J* = 15.4 Hz, CH_2-C4), 3.43 (0.85H, d, *J* = 15.4 Hz, CH_2-C4), 2.71–2.55 (3H, m, CH-C1, CH_2-C2), 2.09–1.91 (2H, m, CH_2-C13), 1.66 (2.55H, dd, *J* = 1.5, 0.9 Hz, CH_3-C17), 1.64 (0.45H, dd, *J* = 1.5, 0.8 Hz, CH_3-C17, enol), 1.62–1.45 (2H, m, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8 (C-C3), 167.7 (C-C18), 148.6 (C-C15), 145.9 (C-C12), 113.0 (CH_2-C16 enol), 112.7 (CH_2-C16), 109.8 (CH_2-C^A), 109.5 (CH_2-C^A enol), 90.1 (CH-C4 enol), 66.1 (CH_2-C21), 52.5 (CH_3-C19), 49.4 (CH_2-C4), 47.6 (CH_2-C2), 44.2 (CH_2-C2 enol), 41.9 (CH-C1), 39.9 (CH-C1 enol), 30.9 (CH_2-C14), 30.7 (CH_2-C14 enol), 30.5 (CH_2-C13 enol), 30.5 (CH_2-C13), 19.1 (CH_3-C17), 18.4 (CH_3-C17 enol); IR ν_{max} 3430, 3075, 2926, 2859, 1743, 1713, 1645, 1632, 1437, 1406 cm^{-1}.

Methyl (*R*)-8-formyl-3-oxo-5-(prop-1-en-2-yl)non-8-enoate 318

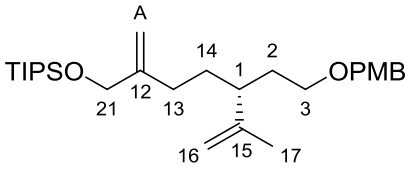


Chemical Formula: $C_{14}H_{20}O_4$
Molecular Weight: 252.3100

To a solution of alcohol **317** (20 mg, 0.08 mmol) in CH_2Cl_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.). $[\alpha]_D^{24}$ −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-C4 enol), 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), 3.72 (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), 167.6 (C-C18), 149.9 (C-C15), 145.6 (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 (CH_2-C13 enol), 25.7 (CH_2-C13), 19.0 (CH_3-C17), 18.3 (CH_3-C17 enol); HRMS (ESI^+) calcd. for $C_{14}H_{20}O_4Na$ $[M+Na]^+$ 275.1254 found 275.1249; IR ν_{max} 2953, 2928, 2856, 1748, 1717, 1686, 1645, 1628, 1437, 1406 cm^{-1}

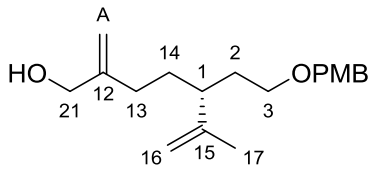
(*R*)-Triisopropyl(5-2-4-methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-en-1-yloxy)silane **319**



Chemical Formula: $C_{28}H_{48}O_3Si$
Molecular Weight: 460.7740

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. NH_4Cl (10 mL) and Et_2O (10 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts dried over $MgSO_4$, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:EtOAc, 95:5) afforded the title compound **319** (590 mg, 99%) as a colourless oil. $[\alpha]_D^{24}$ −4.7 (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-C^A), 4.80 (1H, d, *J* = 1.8 Hz, CH_2-C^A), 4.75 (1H, dq, *J* = 2.6, 1.4 Hz, CH_2-C16), 4.69 (1H, dq, *J* = 2.6, 0.7 Hz, CH_2-C16), 4.40 (2H, s, CH_2-PMB), 4.12 (2H, s, CH_2-C21), 3.80 (3H, s, CH_3-PMB), 3.45–3.32 (2H, m, CH_2-C3), 2.21 (1H, tt, *J* = 9.6, 5.4 Hz, CH-C1), 2.02–1.83 (2H, m, CH_2-C13), 1.75–1.61 (2H, m, CH_2-C2), 1.59 (3H, dd, *J* = 1.4, 0.7 Hz, CH_3-C17), 1.54–1.41 (2H, m, CH_2-C14), 1.19–0.95 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$; ^{13}C NMR (101 MHz, $CDCl_3$) 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 (CH_2-C^A), 108.2 (CH_2-C16), 73.1 (CH_2-PMB), 68.9 (CH_2-C3), 66.6 (CH_2-C21), 55.8 (CH_3-PMB), 44.4 (CH-C1), 33.8 (CH_2-C2), 32.0 (CH_2-C13), 30.9 (CH_2-C14), 18.5 (CH_3-C17), 18.3 (<u>C</u>H(CH_3)$_2$), 12.5 (CH(<u>C</u>H$_3$)$_2$); HRMS (EI^+) calcd for $C_{28}H_{48}O_3Si$ 460.3373, found 460.3376; IR ν_{max} 2970, 2891, 2864, 1612, 1512, 1464 cm^{-1}.

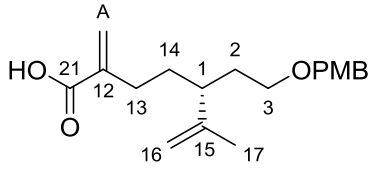
(*R*)-5-(2-4-Methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-en-1-ol 320



Chemical Formula: $C_{19}H_{28}O_3$
Molecular Weight: 304.4300

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 H_2O (10 mL) and Et_2O (15 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et_2O (2 × 15 mL) and the combined organic extracts dried over $MgSO_4$, 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. $[\alpha]_D^{23}$ −8.8 (c = 0.500, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (2H, m, Ar-PMB), 6.89–6.85 (2H, m, CH Ar-PMB), 5.02–4.99 (1H, m, CH_2-C^A), 4.85 (1H, d, *J* = 1.3 Hz, CH_2-C^A), 4.77 (1H, dq, *J* = 2.9, 1.0 Hz, CH_2-C16), 4.71–4.68 (1H, m, CH_2-C16), 4.40 (2H, s, CH_2-PMB), 4.05 (2H, d, *J* = 6.2 Hz, CH_2-C21), 3.80 (3H, s, CH_3-PMB), 3.44–3.33 (2H, m, CH_2-C3). 2.23 (1H, tt, *J* = 9.4, 5.5 Hz, CH-C1), 2.03–1.88 (1H, m, CH_2-C13), 1.73–1.60 (2H, m, CH_2-C2), 1.60 (3H, q, *J* = 1.0 Hz, CH_3-C17), 1.52–1.45 (2H, m, CH_2-C14), 1.37 (1H, t, *J* = 6.2 Hz, OH-C21); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C^A), 109.5 (CH_2-C16), 73.1 (CH_2-PMB), 68.8 (CH_2-C3), 66.5 (CH_2-C21), 55.7 (CH_3-PMB), 44.2 (CH-C1), 33.7 (CH_2-C2), 31.8 (CH_2-C13), 31.1 (CH_2-C14), 18.2 (CH_3-C17); HRMS (EI$^+$) calcd for $C_{19}H_{28}O_3$ 304.2038, found 304.2035; IR ν_{max} 3424, 2934, 2859, 2837, 1613, 1512 cm^{-1}.

(*R*)-5-(2-4-Methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-enoic acid 321

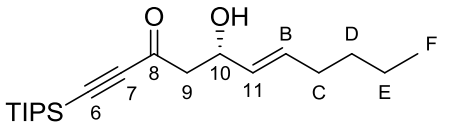


Chemical Formula: $C_{19}H_{26}O_4$
Molecular Weight: 318.4130

To a solution of alcohol **320** (240 mg, 0.79 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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-methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-enal (~0.79 mmol) and 2-methyl-2-butene (0.67 mL, 6.3 mmol) in *t*BuOH (4.75 mL) was added a solution of $NaH_2PO_4 \cdot 2H_2O$ (800 mg, 5.14 mmol) and $NaClO_2$ (239 mg, 4.74 mmol) in H_2O (9.5 mL). The resulting mixture was stirred at rt for 7 h before addition of CH_2Cl_2 (30 mL). The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over Na_2SO_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, 4:1 → 3:2) afforded the title compound **321** (251 mg, quant. over 2 steps) as a yellow oil. $[\alpha]_D^{24}$ −6.6 (*c* = 0.875, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-C^A), 5.68–5.59 (1H, m, CH_2-C^A), 4.81–4.74 (1H, m, CH_2-C16), 4.74–4.67 (1H, m, CH_2-C16), 4.40 (2H, s, CH_2-PMB), 3.80 (3H, s, CH_3-PMB), 3.47–3.31 (2H, m, CH_2-C3), 2.32–2.20 (2H, m, CH_2-C13), 2.20–2.11 (1H, m, CH-C1), 1.75–1.58 (2H, m, CH_2-C2), 1.61 (3H, s, CH_3-C17), 1.57–1.41 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C^A), 114.1 (CH_2-C16), 112.9 (Ar-PMB), 73.0 (CH_2-PMB), 68.7 (CH_2-C3), 55.7 (CH_3-PMB), 44.2 (CH-C1), 33.6 (CH_2-C2), 32.4 (CH_2-C13), 30.0 (CH_2-C14), 18.1 (CH_3-C17); HRMS (ESI$^+$) calcd. for $C_{19}H_{26}O_4Na$ $[M+Na]^+$ 341.1723 found 341.1709; IR ν_{max} 2926, 2854, 1694, 1512 cm^{-1}.

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



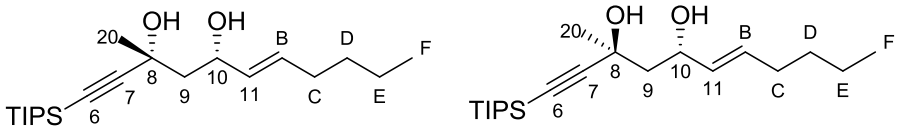
Chemical Formula: $C_{20}H_{36}O_2Si$
Molecular Weight: 336.5910

Racemic: To a solution of triethylamine (0.50 mL, 3.6 mmol) in Et_2O (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-heptenal (0.58 mL, 4.5 mmol). After 4 h stirring at −78 °C The reaction was quenched with H_2O (10 mL) and the phases separated. The aq. phase was extracted with Et_2O (20 mL) and the combined organic extracts washed with saturated aq. NH_4Cl (20 mL) before being dried over $MgSO_4$, filtered and the solvent removed under vacuum to yield the crude product. Purification of the residue by silica gel column chromatography (pet ether: Et_2O, 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 CH_2Cl_2 (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, $CDCl_3$) δ 5.66 (1H, dtd, *J* = 15.3, 6.7, 1.0 Hz, CH-C^B), 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, CH_2-C9), 2.46 (1H, d, *J* = 3.9 Hz, OH-C10), 1.96 (2H, app. q, *J* = 6.7 Hz, CH_2-C^C), 1.39–1.16 (4H, m, CH_2-C^D, CH_2-C^E), 1.16–0.91 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.82 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.2 (C-C8), 133.0 (CH-C^B), 130.3 (CH-C11), 104.2 (C-C7), 97.0 (C-C6), 68.6 (CH-C10), 52.6 (CH_2-C9), 31.8 (CH_2-C^C), 31.2 (CH_2-C^D), 22.2 (CH_2-C^E), 18.5 (CH(<u>C</u>H$_3$)$_2$), 13.9 (CH_3-C^F), 11.0 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd. for $C_{20}H_{36}O_2SiNa$ [M+Na] 359.2377 found 359.2378; IR ν_{max} 3414, 2943, 2866, 2149, 1672, 1464, 1385 cm^{-1}

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



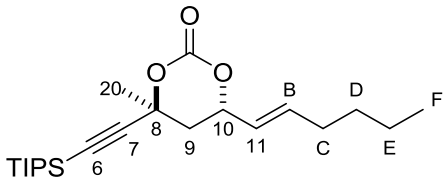
Chemical Formula: $C_{21}H_{40}O_2Si$
Molecular Weight: 352.6340

Racemic: To a stirred solution of $ZnBr_2$ (99.3 mg, 0.44 mmol) in CH_2Cl_2 (1 mL) at rt was added a solution of β-hydroxy ketone **327** (75.8 mg, 0.22 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at rt for 1 h before cooing to 0 °C and addition of MeLi (0.55 mL of a 1.6 M solution in Et_2O, 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_2O (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:Et_2O, 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%).

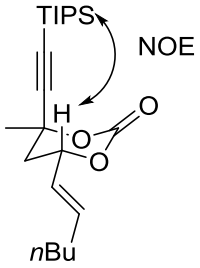
Enantiopure: To a solution of Ti(O*i*Pr)$_4$ (4.5 mL, 15 mmol) in Et_2O (22.5 mL) at 0 °C was added $TiCl_4$ (0.5 mL, 5 mmol). The resulting solution was warmed to rt for 30 min and then cooled to 0 °C. MeLi (12.5 mL of a 1.6 M solution in Et_2O, 20 mmol) was added and the mixture was stirred for 1 h. A portion of the solution (15.9 mL) was added to a solution of β-hydroxy ketone **327** (180 mg, 7.97 mmol) in Et_2O (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_2O (2 × 15 mL). The combined organic extracts were

washed with brine (30 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 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** $[\alpha]_D^{23}$ +17 (*c* = 1.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (1H, dtd, *J* = 15.2, 6.9, 0.8 Hz, CH-C^B), 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, CH_2-C9), 1.79–1.72 (2H, m, CH_2-C^C), 1.55 (3H, s, CH_3-C20), 1.40–1.23 (4H, m, CH_2-C^D, CH_2-C^E), 1.16–0.93 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.90 (3H, t, *J* = 7.1 Hz, CH_3-C^F);^{13}C NMR (126 MHz, $CDCl_3$) δ 132.2 (CH-C^B), 132.1 (CH-C11) 111.1 (C-C7), 83.8 (C-C6), 72.4 (C-C8), 68.6 (CH-C10), 48.6 (CH_2-C9), 31.8 (CH_2-C^C), 31.3 (CH_2-C^D), 31.2 (CH_3-C20), 22.2 (CH_2-C^E), 18.6 (CH(<u>C</u>H$_3$)$_2$), 13.9 (<u>C</u>H(CH$_3$)$_2$), 11.2 (CH_3-C^F); HRMS (ESI+) calcd. for $C_{21}H_{40}O_2Si$ $[M+Na]^+$ 375.2690 found 375.2669; IR ν_{max} 3329, 2928, 2866, 2361, 2342, 1462 cm^{-1}. ***Syn*-328** $[\alpha]_D^{25}$ +6.3 (*c* = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.67 (1H, m, CH-C^B), 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, CH_2-C^C, CH_2-C9), 1.86 (1H, dd, *J* = 14.5, 3.6 Hz, CH_2-C9), 1.55 (3H, s, CH_3-C20), 1.42–1.18 (4H, m, CH_2-C^D, CH_2-C^E), 1.15–0.94 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.7 (CH-C^B), 132.3 (CH-C11), 111.8 (C-C7), 84.5 (C-C6), 70.3 (C-C8), 67.4 (CH-C10), 49.3 (CH_2-C9), 31.9 (CH_2-C^C), 31.2 (CH_2-C^D), 30.1 (CH_3-C20), 22.2 (CH_2-C^E), 18.6 (CH(<u>C</u>H$_3$)$_2$), 13.9 (<u>C</u>H(CH$_3$)$_2$), 11.1 (CH_3-C^F); HRMS (ESI+) calcd. for $C_{21}H_{40}O_2Si$ $[M+Na]^+$ 375.2690 found 375.2672; IR ν_{max} 3356, 2928, 2866, 2361, 2342, 1462 cm^{-1}

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



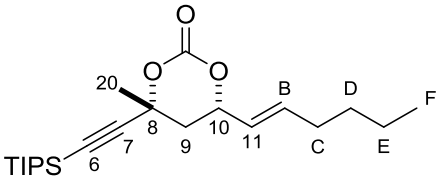
Chemical Formula: $C_{22}H_{38}O_3Si$
Molecular Weight: 378.6280



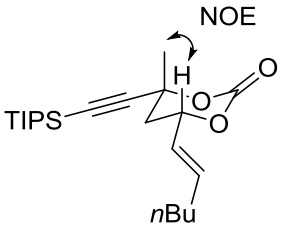
To a solution of racemic 1,3-diol ***anti*-328** (32.0 mg, 0.085 mmol) in CH_2Cl_2 (1 mL) was added pyridine (70 µL, 0.90 mmol) and the solution cooled to −78 °C. Triphosgene (53.4 mg, 0.18 mmol) was added and the reaction stirred for 40 min before being warmed to rt and stirred for a further 35 min. The reaction was quenched by addition of saturated aq. NH_4Cl (3 mL). The biphasic mixture was separated and the aq. phase washed with CH_2Cl_2 (2 × 3 mL).

The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and the solvent removed under vacuum to 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-C^B), 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-C^C), 1.98–1.86 (1H, m, CH_2-C9), 1.70 (3H, s, CH_3-C20), 1.44–1.22 (4H, m, CH_2-C^D, CH_2-C^E), 1.18–0.96 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (O<u>C</u>(O)O), 136.8 (CH-C^B), 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-C^C), 30.8 (CH_3-C20), 28.9 (CH_2-CH^D), 22.2 (CH_2-C^E), 18.5 (CH(<u>C</u>H$_3$)$_2$), 13.9 (<u>C</u>H(CH$_3$)$_2$), 11.0 (CH_3-C^F); HRMS (ESI+) calcd for $C_{22}H_{38}O_3Si$ [M+Na]$^+$ 401.2482 found 41.2450; IR ν_{max} 2941, 2866, 1761, 1464 cm^{-1}.

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

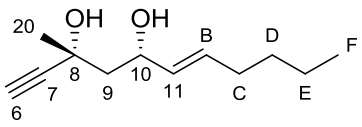


Chemical Formula: $C_{22}H_{38}O_3Si$
Molecular Weight: 378.6280



To a solution of racemic 1,3-diol ***syn*-328** (14.0 mg, 0.043 mmol) in CH_2Cl_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_4Cl (2 mL). The biphasic mixture was separated and the aqueous phase washed with CH_2Cl_2 (2 × 3 mL). Combined organic extracts were washed with brine (5 mL), dried over Na_2SO_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, dtd, *J* = 15.3, 6.7, 0.5 Hz, CH-C^B), 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-C^C), 1.76 (3H, s, CH_3-C20), 1.47–1.21 (4H, m, CH$_2$-C^D, CH_2-C^E), 1.21–0.97 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4 (O<u>C</u>(O)O), 137.2 (CH-C^B), 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-C^C), 30.8 (CH_3-C20), 28.3 (CH_2-C^D), 22.2 (CH_2-C^E), 18.5 (CH(<u>C</u>H$_3$)$_2$), 13.9 (<u>C</u>H(CH$_3$)$_2$), 11.0 (CH_3-C^F); HRMS (ESI+) calcd for $C_{22}H_{38}O_3Si$ [M+Na]$^+$ 401.2482 found 41.2470; IR ν_{max} 2942, 2866, 1753, 1464, 1381, 1234 cm^{-1}.

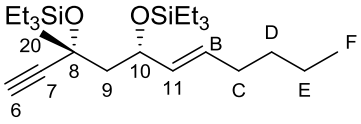
(*E*)-3-Methylundec-6-en-1-yne-3,5-diol 331



Chemical Formula: $C_{12}H_{20}O_2$
Molecular Weight: 196.2900

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. NH_4Cl (70 mL) and Et_2O (70 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et_2O (2 × 70 mL) and the combined organic extracts dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 3:2) afforded title compound **331** (1.10 g, 97%) as a yellow oil. $[\alpha]_D^{24}$ −10.7 (*c* = 0.600, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (1H, dtd, *J* = 15.4, 6.7, 1.0 Hz, CH-C^B), 5.54 (1H, ddt, *J* = 15.4, 7.0, 1.5 Hz, CH-C11), 4.52 (1H, dddd, *J* = 9.4, 7.0, 3.3, 2.8 Hz, CH-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^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^D, CH_2-C^E), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8 (CH-C^B), 132.2 (CH-C11), 88.0 (C-C7), 71.5 (C-C6), 70.3 (CH-C10), 67.1 (C-C8), 48.6 (CH_2-C9), 31.8 (CH_2-C^C), 31.2 (CH_2-C^D), 29.5 (CH_3-C20), 22.2 (CH_2-C^E), 13.9 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1356, found 219.1345; IR ν_{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

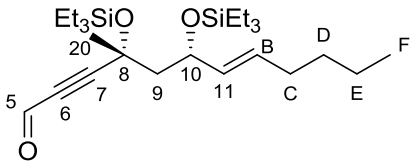


Chemical Formula: $C_{24}H_{48}O_2Si_2$
Molecular Weight: 424.8160

To a solution of 1,3-diol **331** (1.10 g, 5.60 mmol) in CH_2Cl_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_2Cl_2 (2 × 50 mL). The combined organic extracts dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 100:0 → 95:5) afforded title compound **332** (2.38 g, quant.) as a colourless oil. $[\alpha]_D^{25}$ +4.1 (*c* = 0.945, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.43 (2H, m, CH-C^B, 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, CH_2-C^C), 1.91 (1H, dd, *J* = 13.8, 6.2 Hz, CH_2-C9), 1.87 (1H, dd, *J* = 13.8, 6.0 Hz, CH_2-C9), 1.50 (3H, s, CH_3-C20), 1.42–1.23 (4H, m, CH_2-C^D, CH_2-C^E), 0.96 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.94 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.72–0.61 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.65–0.54 (6H, m, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 (CH-C^B), 130.1 (CH-C11), 88.3 (C-C7), 72.2 (CH-C6), 71.2 (CH-C10), 68.4 (C-C8), 53.4 (CH_2-C9), 31.8 (CH_2-C^C), 31.7 (CH_3-C20), 31.3 (CH_2-C^D), 22.3 (CH_2-C^E), 13.9 (CH_3-C^F), 7.0 ($Si(CH_2\underline{C}H_3)_3$), 6.9 ($Si(CH_2\underline{C}H_3)_3$), 6.2 ($Si(\underline{C}H_2CH_3)_3$), 5.2 ($Si(\underline{C}H_2CH_3)_3$); HRMS ($ESI^+$) calcd. for $C_{24}H_{48}O_2Si_2Na$ $[M+Na]^+$ 447.3085, found 447.3053; IR ν_{max} 3310, 2954, 2936, 2914, 2876, 1458, 1414 cm^{-1}.

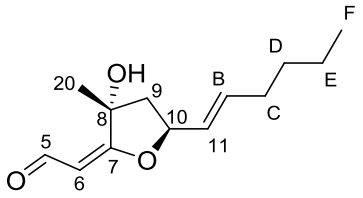
(*E*)-4-Methyl-4,6-bis(triethylsilyloxy)dodec-7-en-2-ynal 333



Chemical Formula: $C_{25}H_{48}O_3Si_2$
Molecular Weight: 452.8260

To a solution of alkyne **332** (2.37 g, 5.58 mmol) in THF (100 mL) at −78 °C under argon was added *n*BuLi (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. KH_2PO_4 (100 mL) and Et_2O (100 mL) were added and the biphasic mixture separated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with 5% aq. KH_2PO_4 (100 mL) before being dried over Na_2SO_4, 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. $[\alpha]_D^{20}$ +8.5 (*c* = 0.770, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (1H, s, CHO-C5), 5.56 (1H, dt, *J* = 15.4, 6.5 Hz, CH-C^B), 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, CH_2-C9, CH_2-C^C), 1.89 (1H, dd, *J* = 13.9, 5.2 Hz, CH_2-C9), 1.57 (3H, s, CH_3-C20), 1.42–1.21 (4H, m, CH_2-C^D, CH_2-C^E), 0.97 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.93 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.90 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.74–0.62 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.58 (6H, q, *J* = 7.9 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (CHO-C5), 133.8 (CH-C^B), 131.2 (CH-C11), 101.0 (C-C7), 83.8 (C-C6), 71.1 (CH-C10), 68.6 (C-C8), 53.0 (CH_2-C9), 32.0 (CH_2-C^C), 31.3 (CH_2-C^D), 31.2 (CH_3-C20), 22.5 (CH_2-C^E), 14.1 (CH_3-C^F), 7.1 ($Si(CH_2\underline{C}H_3)_3$), 7.0 ($Si(CH_2\underline{C}H_3)_3$), 6.3 ($Si(\underline{C}H_2CH_3)_3$), 5.3 ($Si(\underline{C}H_2CH_3)_3$); IR ν_{max} 2955, 2936, 2915, 2876, 2209, 1458, 1414 cm^{-1}.

2-[(2*E*,3*R*,5*S*)-5-[(1*E*)-hex-1-en-1-yl]-3-Hydroxy-3-methyloxolan-2-ylidene]acetaldehyde 336

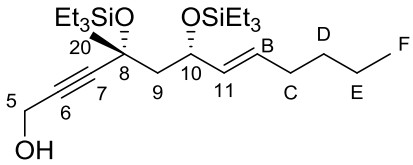


Chemical Formula: $C_{13}H_{20}O_3$
Molecular Weight: 224.3000

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. H_2O (10 mL) and Et_2O (10 mL) were added and the biphasic mixture separated. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 1:4) afforded title compound **336** (69 mg, 58%) as a yellow oil. $[\alpha]_D^{22}$ +6.3 (c = 0.07, $CHCl_3$)[a]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (1H, d, *J* = 8.5 Hz, CHO-C5), 5.85 (1H, dtd, *J* = 15.3, 6.8, 0.9 Hz, CH-C^B), 5.45 (1H, ddt, *J* = 15.3, 7.9, 1.5 Hz, CH-C11), 5.17 (1H, d, *J* = 8.5 Hz, CH-C6), 5.14–5.07 (1H, m, CH-C10), 3.89 (1H, br s, OH-C8) 2.32 (1H, dd, *J* = 13.2, 5.4 Hz, CH_2-C9), 2.10–2.03 (2H, m, CH_2-C^C), 1.75 (1H, dd, *J* = 13.2, 9.7 Hz, CH_2-C9), 1.50 (3H, s, CH_3-C20) 1.42–1.26 (4H, m, CH_2-C^D, CH_2-C^E), 0.88 (3H, t, *J* = 7.2 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2 (CHO-C5), 180.8 (C-C7), 137.3 (CH-C^B), 126.9 (CH-C11), 98.6 (CH-C6), 85.1 (CH-C10), 78.7 (C-C8), 44.8 (CH_2-C9), 32.0 (CH_2-C^C), 30.9 (CH_2-C^D), 24.9 (CH_3-C20), 22.3 (CH_2-C^E), 14.0 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ 247.1305, found 247.1296; IR ν_{max} 3407, 2958, 2926, 2852, 1648, 1637, 1619, 1457 cm^{-1}.

[a]Optical rotation data were obtained from enantiopure material; although only the racemic procedure is reported

(*E*)-4-Methyl-4,6-bis(triethylsilyloxy)dodec-7-en-2-yn-1-ol 337



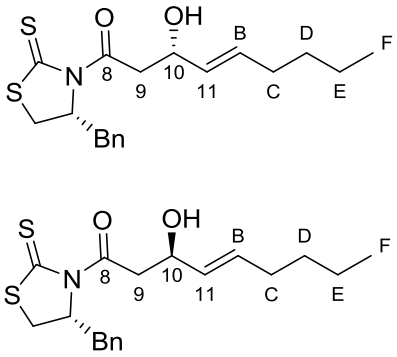
Chemical Formula: $C_{25}H_{50}O_3Si_2$
Molecular Weight: 454.8420

To a solution of aldehyde **333** (~1.65 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (95 mg, 2.48 mmol) and the resulting solution stirred for 1.5 h. Saturated aq. NH_4Cl (20 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford

the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 85:15) afforded title compound **337** (660 mg, 88%) as a yellow oil. $[\alpha]_D^{23}$ +5.6 (c = 0.590, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59–5.46 (2H, m, CH-C^B, CH-C11), 4.39 (1H, ddd, *J* = 6.1, 6.1, 6.0 Hz, CH-C10), 4.29 (2H, d, *J* = 6.3 Hz, CH_2-C5), 2.00 (2H, dt, *J* = 6.7, 6.4 Hz, CH_2-C^C), 1.91 (1H, dd, *J* = 13.7, 6.1 Hz, CH_2-C9), 1.87 (1H, dd, *J* = 13.7, 6.0 Hz, CH_2-C9), 1.49 (3H, s, CH_3-C20), 1.37 (1H, t, *J* = 6.3 Hz, OH-C5), 1.36–1.28 (4H, m, CH_2-C^D, CH_2-C^E), 0.96 (9H, t, *J* = 7.9 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.95 (9H, t, *J* = 7.9 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.70–0.62 (6H, m, Si($C\underline{H}_2CH_3$)$_3$), 0.59 (6H, q, *J* = 7.9 Hz, Si($C\underline{H}_2CH_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (CH-C^B), 130.3 (CH-C^{11}), 90.7 (C-C7), 82.0 (C-C6), 71.4 (CH-C10), 68.7 (C-C8), 53.5 (CH_2-C9), 51.5 (CH_2-C5), 32.0 (CH_2-C^C), 31.8 (CH_2-C^D), 31.4 (CH_3-C20), 22.5 (CH_2-C^E), 14.1 (CH_3-C^F), 7.2 (Si($CH_2\underline{C}H_3$)$_3$), 7.0 (Si($CH_2\underline{C}H_3$)$_3$), 6.4 (Si($\underline{C}H_2CH_3$)$_3$), 5.3 (Si($\underline{C}H_2CH_3$)$_3$); HRMS (ESI$^+$) calcd. for $C_{25}H_{50}O_3Si_2Na$ [M+Na]$^+$ 477.3191, found 477.3164; IR ν_{max} 3375, 2955, 2928, 2876, 1458, 1413 cm^{-1}.

[a]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

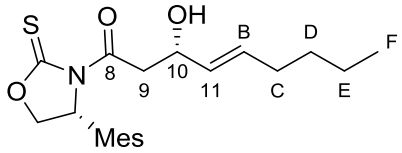


Chemical Formula: $C_{19}H_{25}NO_2S_2$
Molecular Weight: 363.5340

To a solution of thiazolidine-2-thione **343** (1.31 g, 5.21 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added $TiCl_4$ (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. NH_4Cl (40 mL). After further warming to rt the biphasic mixture was separated and the aqueous phase washed with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (2H, m, Ph), 7.31–7.27 (3H, m, Ph), 5.74 (1H, dtd, *J* = 15.1, 7.0, 1.2 Hz, CH-C^B), 5.54 (1H, ddt, *J* = 15.1, 6.4, 1.5 Hz, CH-C11), 5.40 (1H, ddd, *J* = 10.6, 7.1, 3.8 Hz, CH-Aux), 4.60–4.53 (1H, m, CH-C10), 3.61 (1H, dd, *J* = 17.4, 9.0 Hz, CH_2-C9), 3.42–3.37 (2H, m, CH_2-C9, C$\underline{H}_2$Ph), 3.23 (1H, dd, *J* = 13.3, 3.8 Hz, CH_2-Aux), 3.05 (1H, dd, *J* = 13.3, 10.6 Hz, CH_2-Aux), 3.01 (1H, d, *J* = 3.6 Hz, OH-C10), 2.91 (1H, d, *J* = 11.5 Hz, C$\underline{H}_2$Ph), 2.05 (2H, dt, *J* = 7.0, 6.9 Hz, CH_2-C^C), 1.42–1.27 (4H, m, CH_2-C^D, CH_2-C^E), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C=S), 173.2 (C-C8), 136.5 (Ph), 133.0 (CH-C^B), 130.7 (CH-C11), 129.6 (Ph), 129.1 (Ph), 127.4 (Ph), 69.4 (CH-C10), 68.4 (CH-Aux), 45.8 (CH_2-C9), 37.0 (CH_2-Aux), 32.2 (CH_2-Bn), 32.0 (CH_2-C^C), 31.3 (CH_2-C^D), 22.4 (CH_2-C^E), 14.1 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{19}H_{25}NO_2S_2Na$ $[M+Na]^+$ 330.0593, found 330.0588; IR ν_{max} 3565, 2953, 2924, 2855, 1694, 1674, 1497, 1437 cm^{-1}. **Major:** $[\alpha]_D^{24}$ −167 (*c* = 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (2H, m, Ph), 7.31–7.27 (3H, m, Ph), 5.76 (1H, dtd, *J* = 15.1, 6.9, 1.2 Hz, CH-C^B), 5.55 (1H, ddt, *J* = 15.1, 6.5, 1.5 Hz, CH-C11), 5.39 (1H, ddd, *J* = 10.6, 7.1, 3.9 Hz, CH-Aux), 4.68–4.62 (1H, m, CH-C10), 3.61 (1H, dd, *J* = 17.6, 2.9 Hz, CH_2-C9), 3.40 (1H, ddd, *J* = 11.5, 7.1, 0.8 Hz, C$\underline{H}_2$Ph), 3.32 (1H, dd, *J* = 17.6, 9.0 Hz, CH_2-C9), 3.23 (1H, dd, *J* = 13.2, 3.9 Hz, CH_2-Aux), 3.05 (1H, dd, *J* = 13.2, 10.6 Hz, CH_2-Aux), 2.90 (1H, d, *J* = 11.5 Hz, C$\underline{H}_2$Ph), 2.65 (1H, br s, OH-C10), 2.05 (2H, dt, *J* = 6.9, 6.8 Hz, CH_2-C^C), 1.42–1.25 (4H, m, CH_2-C^D, CH_2-C^E), 0.90 (3H, t, *J* = 7.2 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5 (C=S), 172.8 (C-C8), 136.6 (Ph), 132.9 (CH-C^B), 130.5 (CH-C11), 129.6 (Ph), 129.1 (Ph), 127.4 (Ph), 68.9 (CH-C10), 68.5 (CH-Aux), 46.0 (CH_2-C9), 37.0 (CH_2-Aux), 32.3 (CH_2-Bn), 32.0 (CH_2-C^C), 31.4 (CH_2-C^D), 22.4 (CH_2-C^E), 14.1 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{19}H_{25}NO_2S_2Na$ $[M+Na]^+$ 330.0593, found 330.0592; IR ν_{max} 3439, 2955, 2924, 2856, 2690, 1497, 1437 cm^{-1}.

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

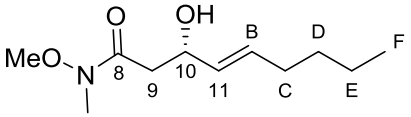


Chemical Formula: $C_{21}H_{29}NO_3S$
Molecular Weight: 375.5270

To a solution of oxazolidinethione **344** (1.01 g, 3.80 mmol) in CH_2Cl_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_4Cl (30 mL) was added and the mixture was warmed to rt. The biphasic mixture was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts

were dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 7:3 → 5:5) afforded title compound **342** (1.21 g, 85%) as a yellow oil. $[\alpha]_D^{26}$ +44 (*c* = +0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, dtd, *J* = 15.1, 6.7, 1.2 Hz, CH-C^B), 5.49 (1H, ddt, *J* = 15.1, 6.2, 1.5 Hz, CH-C11), 4.87 (1H, dd, *J* = 11.0, 9.3 Hz, CH_2-Aux), 4.52–4.46 (1H, m, CH-C10), 4.40 (1H, dd, *J* = 9.3, 7.2 Hz, CH_2-Aux), 3.66 (1H, dd, *J* = 17.8, 9.1 Hz, CH_2-C9), 3.39 (1H, dd, *J* = 17.8, 2.9 Hz, CH_2-C9), 2.45 (3H, s, CH_3-Mes), 2.25 (6H, s, CH_3-Mes), 2.01 (2H, dt, *J* = 7.0, 6.7 Hz, CH_2-C^C), 1.38–1.25 (4H, m, CH_2-C^D, CH_2-C^E), 0.88 (3H t, *J* = 7.2 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.1 (C=S), 173.1 (C-C8), 138.5 (Ar), 135.0 (Ar) 133.0 (CH-C^B), 132.0 (Ar), 130.5 (Ar), 130.4 (CH-C11), 130.0 (Ar), 72.0 (CH_2-Aux), 68.8 (CH-C10), 58.4 (CH-Aux), 45.3 (CH_2-C9), 32.0 (CH_2-C^C), 31.3 (CH_2-C^D), 22.4 (CH_2-C^E), 20.9 (CH_3-Mes), 20.8 (CH_3-Mes), 14.1 (CH_3-C^F); HRMS (EI$^+$) calcd for $C_{21}H_{29}NO_3S$ 375.1868, found 375.1864; IR ν_{max} 3451, 2959, 2926, 2859, 1705, 1613, 1483 cm^{-1}.

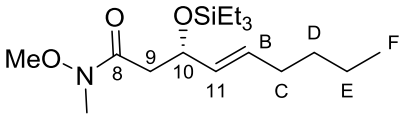
(*S,E*)-3-Hydroxy-*N*-methoxy-*N*-methylnon-4-enamide 345



Chemical Formula: $C_{11}H_{21}NO_3$
Molecular Weight: 215.2930

To a solution of aldol adduct **342** (1.15 g, 3.06 mmol) in CH_2Cl_2 (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. NH_4Cl (50 mL) was added and the biphasic mixture separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried over Na_2SO_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, 8:2 → 1:1) afforded recovered oxazolidinethione auxiliary (657 mg, 99%) followed by the title compound **345** (599 mg, 91%) as a yellow oil. $[\alpha]_D^{26}$ −32 (*c* = 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, dtd, *J* = 15.4, 6.6, 1.2 Hz, CH-C^B), 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, NC$\underline{H}_3$), 3.19 (3H, s, OC$\underline{H}_3$), 2.74–2.53 (2H, m, CH_2-C9), 2.04 (2H, dt, *J* = 6.7, 6.6 Hz, CH_2-C^C), 1.45–1.23 (4H, m, CH_2-C^D, CH_2-C^E), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C-C8), 132.4 (CH-C11), 131.0 (CH-C^B), 69.0 (CH-C10), 61.4 (N$\underline{C}H_3$), 38.7 (CH_2-C9), 32.0 (CH_2-C^C, O$\underline{C}H_3$), 31.4 (CH_2-C^D), 22.4 (CH_2-C^E), 14.1 (CH_3-C^F); HRMS (EI$^+$) calcd. for $C_{11}H_{21}NO_3$ 215.1521, found 215.1519; IR ν_{max} 3435, 2957, 2926, 2872, 2859, 1640, 1464, 1437 cm^{-1}.

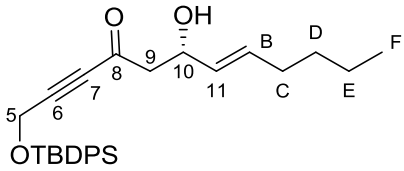
(*S,E*)-*N*-Methoxy-*N*-methyl-3-(triethylsilyloxy)non-4-enamide 346



Chemical Formula: $C_{17}H_{35}NO_3Si$
Molecular Weight: 329.5560

To a solution of allylic alcohol **345** (50.4 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) at −78 °C under argon was added 2,6-lutidine (0.07 mL, 0.6 mmol) followed by TESOTf (0.06 mL, 0.3 mmol). The resulting solution was stirred for 1 h before addition of saturated aq. $NaHCO_3$ (2 mL) and warming to rt. The biphasic mixture was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4, 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. $[\alpha]_D^{23}$ −17 (*c* = 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (1H, dtd, *J* = 15.3, 6.7, 1.0 Hz, CH-C^B), 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, NC$\underline{H}_3$), 3.17 (3H, s, OC$\underline{H}_3$), 2.80 (1H dd, *J* = 14.2, 7.4 Hz, CH_2-C9), 2.43 (1H, dd, *J* = 14.2, 5.6 Hz, CH_2-C9), 2.00 (2H, dt, *J* = 6.7, 6.6 Hz, CH_2-C^C), 1.42–1.22 (4H, m, CH_2-C^D, CH_2-C^E), 0.93 (9H, t, *J* = 7.9 Hz, Si($CH_2C\underline{H}_3)_3$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3-C^F), 0.58 (6H, q, *J* = 7.9 Hz, Si($C\underline{H}_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C-C8), 132.6 (CH-C11), 131.3 (CH-C^B), 70.7 (CH-C10), 61.5 (N$\underline{C}H_3$), 40.9 (CH_2-C9), 31.9 (CH_2-C^C, O$\underline{C}H_3$), 31.4 (CH_2-C^D), 22.4 (CH_2-C^E), 14.1 (CH_3-C^F), 6.9 (Si($CH_2C\underline{H}_3)_3$), 5.0 (Si($C\underline{H}_2CH_3)_3$); HRMS (EI$^+$) calcd. for $C_{17}H_{35}NO_3Si$ 330.2464, found 330.2463; IR ν_{max} 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



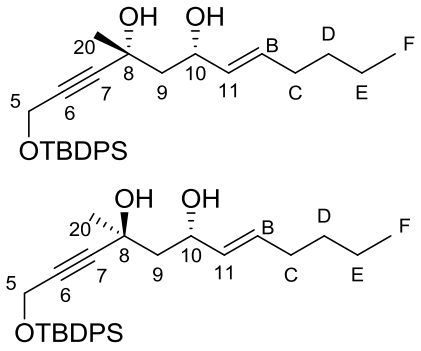
Chemical Formula: $C_{28}H_{36}O_3Si$
Molecular Weight: 448.6780

To a solution of protected propargylic alcohol **347** (187 mg, 0.64 mmol) in THF (3 mL) at rt was added *n*BuLi (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. NH_4Cl (5 mL) was added and the biphasic mixture separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts dried over Na_2SO_4, filtered and the

solvent removed under vacuum to afford the crude product. Filtration through silica (pet. ether:Et_2O, 100:0 → 95:5) afforded an inseparable mixture (347 mg) of alkynone **348** and excess protected propargylic aldehyde **347** which was carried forward directly to the next reaction.

To a solution of crude alkynone **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. $NaHCO_3$ (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 Na_2SO_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, 90:10 → 85:15) afforded title compound **349** (2.27 g, 77% over 2 steps) as a yellow oil. $[\alpha]_D^{22}$ −8.8 (*c* = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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-C^B), 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, CH_2-C5), 2.74–2.62 (2H, m, CH_2-C9), 2.40 (1H, d, *J* = 4.0 Hz, OH-C10), 2.04 (2H, dt, *J* = 6.9, 6.7 Hz, CH_2-C^C), 1.44–1.28 (4H, m, CH_2-C^D, CH_2-C^E), 1.07 (9H, s, C(CH_3)$_3$), 0.90 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.4 (C-C8), 135.7 (Ph), 133.1 (CH-C11), 132.6 (Ph), 130.4 (CH-C^B), 130.2 (Ph), 128.0 (Ph), 91.4 (C-C6), 84.2 (C-C7), 68.6 (CH-C10), 52.6 (CH_2-C5), 52.2 (CH_2-C9), 32.0 (CH_2-C^C), 31.3 (CH_2-C^D), 26.8 (C(<u>C</u>H_3)$_3$), 22.3 (CH_2-C^E), 19.3 (<u>C</u>(CH_3)$_3$), 14.1 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{28}H_{36}O_3SiNa$ $[M+Na]^+$ 471.2304, found 471.2326; IR ν_{max} 3437, 2957, 2930, 2859, 2214, 1709, 1676, 1464 cm^{-1}.

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

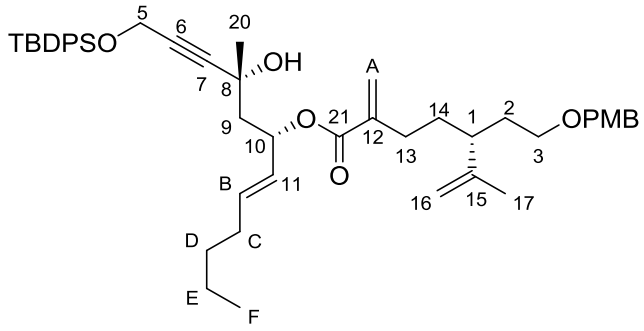


Chemical Formula: $C_{29}H_{40}O_3Si$
Molecular Weight: 464.7210

To a solution of Ti(O*i*Pr)$_4$ (0.9 mL, 3 mmol) in Et_2O (4.5 mL) at 0 °C was added $TiCl_4$ (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 Et_2O, 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 Et_2O (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 Et_2O (2 × 10 mL) and the combined organic extracts washed with brine (10 mL) before being dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the crude product. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 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*****:** $[\alpha]_D^{29}$ +6.6 (*c* = 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.68 (4H, m, Ph), 7.48–7.34 (6H, m, Ph), 5.62 (1H, dtd, *J* = 15.4, 6.7, 1.0 Hz, CH-C^B), 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, CH_2-C5), 4.41 (1H, d, *J* = 16.0 Hz, CH_2-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, CH_2-C^C), 1.75 (1H, dd, *J* = 14.4, 10.7 Hz, CH_2-C9), 1.63 (1H, ddd, *J* = 14.4, 2.3, 1.0, CH_2-C9), 1.40 (3H, s, CH_3-C20), 1.38–1.27 (4H, m, CH_2-C^D, CH_2-C^E), 1.06 (9H, s, C(CH_3)$_3$), 0.90 (3H, t, *J* = 7.0 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (Ph), 133.4 (Ph), 132.2 (CH-C11), 132.1 (CH-C^B), 129.9 (Ph), 127.8 (Ph), 88.3 (C-C7), 82.2 (C-C6), 72.2 (CH-C10), 68.3 (C-C8), 52.9 (CH_2-C5), 48.1 (CH_2-C9), 31.9 (CH-C^C), 31.4 (CH_2-C^D), 30.9 (CH_3-C20), 26.8 (C($\underline{C}H_3$)$_3$), 22.3 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 14.1 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{29}H_{40}O_3Na$ [M+Na]$^+$ 487.2639, found 487.2616; IR ν_{max} 3343, 3073, 3048, 2955, 2930, 2859, 1474, 1462, 1427 cm^{-1}. ***Syn*****:** $[\alpha]_D^{29}$ +2.7 (*c* = 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.68 (4H, m, Ph), 7.48–7.36 (6H, m, Ph), 5.69 (1H, dtd, *J* = 15.4, 6.8, 1.1 Hz, CH-C^B), 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, CH_2-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, CH_2-C^C), 1.92 (1H, dd, *J* = 14.5, 9.3 Hz, CH_2-C9), 1.72 (1H, dd, *J* = 14.5, 3.5 Hz, CH_2-C9), 1.45 (3H, s, CH_3-C20), 1.41–1.24 (4H, m, CH_2-C^D, CH_2-C^E), 1.05 (9H, s, C(CH_3)$_3$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (Ph), 133.4 (Ph), 132.6 (CH-C11), 132.4 (CH-C^B), 129.9 (Ph), 127.8 (Ph), 89.1 (C-C7), 82.2 (C-C6), 70.2 (CH-C10), 67.4 (C-C8), 52.8 (CH_2-C5), 48.7 (CH_2-C9), 32.0 (CH_2-C^C), 31.4 (CH_2-C^D), 29.3 (CH_3-C20), 26.9 (C($\underline{C}H_3$)$_3$), 22.4 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 14.1 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{29}H_{40}O_3Na$ [M+Na]$^+$ 487.2639, found 487.2616; IR ν_{max} 3358, 3073, 3048, 2957, 2859, 1472, 1464, 1427 cm^{-1}.

(4*R*,6*S*,*E*)-1-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-4-methyldodec-7-en-2-yn-6-yl (*R*)-5-(2-(4-methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-enoate 351

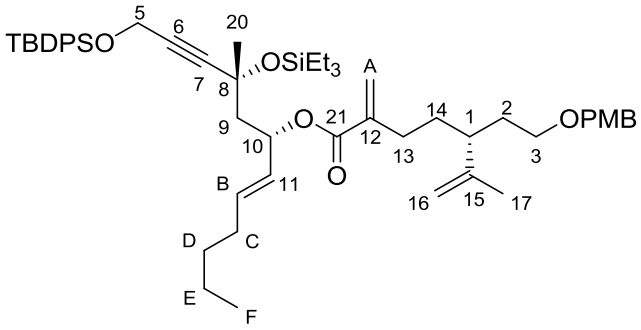


Chemical Formula: $C_{48}H_{64}O_6Si$
Molecular Weight: 765.1190

To a solution of Et_3N (0.42 mL, 1.9 mmol), DMAP (77 mg, 0.63 mmol) and MNBA (227 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) was added a solution of carboxylic acid **321** (201 mg, 0.63 mmol) in CH_2Cl_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_2Cl_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_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_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. $[\alpha]_D^{23}$ −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* = 2.6 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^F); ^{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_3-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($\underline{C}H_3$)$_3$), 22.3 (CH_2-

C^E), 19.3 ($\underline{C}(CH_3)_3$), 17.9 (CH_3-C17), 14.1 (CH_3-C^F); HRMS (ESI^+) calcd. for $C_{48}H_{64}O_6SiNa$ $[M+Na]^+$ 787.4364 found 787.4318; IR ν_{max} 3453, 3071, 2955, 2857, 1715, 1612, 1587, 1512, 1464, 1443, 1429 cm^{-1}.

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

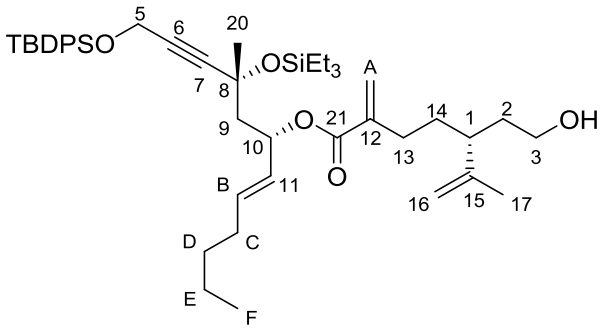


Chemical Formula: $C_{54}H_{78}O_6Si_2$
Molecular Weight: 879.3820

To a solution of ester **351** (300 mg, 0.39 mmol) in CH_2Cl_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. $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_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. $[\alpha]_D^{26}$ −10.2 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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_2-C^A), 5.71–5.61 (1H, m, CH-C^B), 5.55 (1H, ddd, *J* = 7.5, 7.4, 3.9 Hz, CH-C10), 5.48–5.40 (2H, m, CH-C11, CH_2-C^A), 4.76 (1H, dq, J = 2.6, 1.3 Hz, CH_2-C16), 4.69 (1H, d, *J* = 2.6 Hz, CH_2-C16), 4.39 (2H, s, CH_2-PMB), 4.28 (2H, s, CH_2-C5), 3.80 (3H, s, CH_3-PMB), 3.43–3.31 (2H, m, CH_2-C3), 2.28–2.03 (4H, m, CH_2-C9, CH_2-C13, CH-C1), 1.99 (2H, dt, *J* = 6.7, 6.6 Hz, CH_2-C^C), 1.92 (1H, dd, *J* = 14.3, 3.9 Hz, CH_2-C9), 1.73–1.54 (2H, m, CH_2-C2) 1.59 (3H, d, *J* = 1.3 Hz, CH_3-C17), 1.50–1.42 (2H, m, CH_2-C14), 1.42 (3H, s, CH_3-C20), 1.37–1.22 (4H, m, CH_2-C^D, CH_2-C^E), 1.05 (9H, s, $C(CH_3)_3$), 0.94 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.86 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.67 (6H, app qd, *J* = 7.9, 2.2 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 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^B), 130.9 (Ar-PMB), 129.9 (Ph), 129.4 (Ar-PMB), 129.2 (CH-C11), 127.9 (Ph), 124.1 (CH_2-C^A), 113.9 (Ar-PMB), 112.5 (CH_2-C16), 88.6 (C-C7), 82.6 (C-C6), 72.8 (CH_2-PMB), 72.1 (CH-C10), 68.6 (CH_2-C3), 67.7 (C-C8), 55.4 (CH_3-PMB), 52.8 (CH_2-C5), 49.7 (CH_2-C9), 44.0 (CH-C1), 33.3 (CH_2-C2), 32.4 (CH_2-C14), 32.0 (CH_2-C^C), 31.7

(CH_3-C20), 31.2 (CH_2-C^D), 30.1 (CH_2-13), 26.8 ($C(\underline{C}H_3)_3$), 22.3 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 17.9 (CH_3-C17), 14.1 (CH_3-C^F), 7.2 ($Si(CH_2\underline{C}H_3)_3$), 6.2 ($Si(\underline{C}H_2CH_3)_3$); HRMS ($ESI^+$) calcd. for $C_{54}H_{78}O_6Si_2Na$ $[M+Na]^+$ 901.5234 found 901.5208; IR ν_{max} 3071, 2955, 2930, 2874, 2859, 1717, 1643, 1630, 1613, 1514, 1464 cm^{-1}.

(4*R*,6*S,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

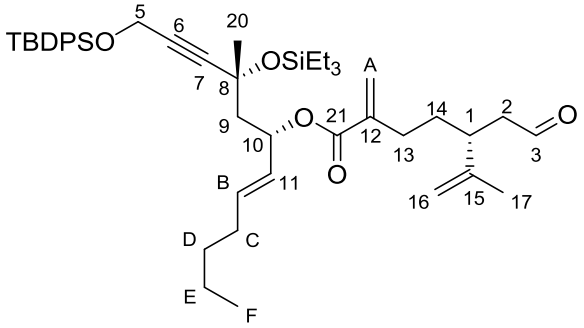


Chemical Formula: $C_{46}H_{70}O_5Si_2$
Molecular Weight: 759.2310

To a solution of (4*R*,6*S,E*)-1-(*tert*-butyldiphenylsilyloxy)-4-methyl-4-(triethylsilyloxy)dodec-7-en-2-yn-6-yl (*R*)-5-(2-4-methoxybenzyloxyethyl)-6-methyl-2-methylenehept-6-enoate (295 mg, 0.34 mmol) in a 9:1 mixture of CH_2Cl_2 (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. $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added and the biphasic mixture separated. The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts dried over Na_2SO_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 → 8:2) afforded the title compound **353** (240 mg, 93%) as a yellow oil. $[\alpha]_D^{23}$ −5.15 (*c* = 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.66 (4H, m, Ph), 7.47–7.35 (6H, m, Ph), 6.08 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.66 (1H, dtd, *J* = 15.3, 6.7, 1.0 Hz, CH-C^B), 5.55 (1H, ddd, *J* = 7.7, 7.4, 3.7 Hz, CH-C10), 5.48–5.39 (2H, m, CH-C11, CH_2-C^A), 4.78 (1H, dq, *J* = 2.4, 1.2 Hz, CH_2-C16), 4.75 (1H, d, *J* = 2.4 Hz, CH_2-C16), 4.26 (1H, d, *J* = 15.8 Hz, CH_2-C5), 4.29 (1H, d, *J* = 15.8 Hz, CH_2-C5), 3.65–3.51 (2H, m, CH_2-C3), 2.26–2.15 (2H, m, CH-C1, CH_2-C13), 2.18–2.09 (1H, m, CH_2-C13), 2.08 (1H, dd, *J* = 14.3, 7.7 Hz, CH_2-C9), 1.99 (2H, dt, *J* = 6.7, 6.6 Hz, CH_2-C^C), 1.92 (1H, dd, *J* = 14.3, 3.7 Hz, CH_2-C9), 1.62 (3H, d, *J* = 1.2 Hz, CH_3-C17), 1.61–1.56 (2H, m, CH_2-C2), 1.47 (2H, dt, *J* = 7.8, 7.6 Hz, CH_2-C14), 1.42 (3H, s, CH_3-C20), 1.36–1.24 (4H, m, CH_2-C^D, CH_2-C^E), 1.04 (9H, s, $C(CH_3)_3$), 0.94 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.86 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.66 (6H, app qd, *J* = 7.9, 3.4 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1 (C-C21), 147.2 (C-C12), 141.4 (C-C15), 135.7 (Ph), 133.3 (Ph), 133.2 (CH-C^B), 129.9 (Ph), 129.1 (CH-C11), 127.9 (Ph), 124.3 (CH_2-

C^A), 112.7 (CH_2-C16), 88.6 (C-C7), 82.6 (C-C6), 72.1 (CH-C10), 67.7 (C-C8), 61.7 (CH_2-C3), 52.8 (CH_2-C5), 49.6 (CH_2-C9), 44.3 (CH-C1), 36.2 (CH_2-C2), 32.4 (CH_2-C14), 32.0 (CH_2-C^C), 31.7 (CH_3-C20), 31.2 (CH_2-C^D), 30.1 (CH_2-C13), 26.8 (C($\underline{C}H_3)_3$), 22.3 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 17.8 (CH_3-C17), 14.1 (CH_3-C^F), 7.2 (Si($CH_2\underline{C}H_3)_3$), 6.2 (Si($\underline{C}H_2CH_3)_3$); HRMS (ESI^+) calcd. for $C_{46}H_{70}O_5Si_2Na$ $[M+Na]^+$ 781.4654 found 781.4597; IR ν_{max} 3412, 3072, 2955, 2932, 2874, 2859, 1717, 1643, 1630, 1462, 1429 cm^{-1}.

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

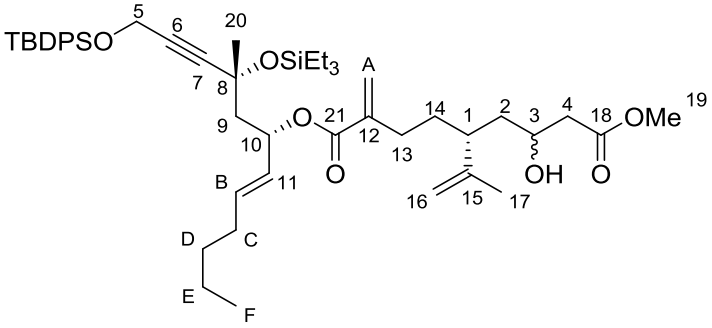


Chemical Formula: $C_{46}H_{68}O_5Si_2$
Molecular Weight: 757.2150

To a solution of alcohol **353** (220 mg, 0.29 mmol) in CH_2Cl_2 (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. $[\alpha]_D^{26}$ −1.65 (*c* = 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-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, CH_2-C^A), 4.82 (1H, dq, *J* = 1.6, 1.5 Hz, CH_2-C16), 4.78 (1H, dq, *J* = 1.6, 0.8 Hz, CH_2-C16), 4.28 (2H, s, CH_2-C5), 2.68 (1H, app p, *J* = 7.2 Hz, CH-C1), 2.51–2.33 (2H, m, CH_2-C2), 2.30–2.13 (2H, m, CH_2-C13), 2.09 (1H, dd, *J* = 14.3, 7.7 Hz, CH_2-C9), 2.00 (2H, dt, *J* = 6.9, 6.7 Hz, CH_2-C^C), 1.93 (1H, dd, *J* = 14.3, 3.8 Hz, CH_2-C9), 1.66 (3H, dd, *J* = 1.5, 0.8 Hz, CH_3-C17), 1.56–1.49 (2H, m, CH_2-C14), 1.43 (3H, s, CH_3-C20), 1.38–1.22 (4H, m, CH_2-C^D, CH_2-C^E), 1.06 (9H, s, C($CH_3)_3$), 0.95 (9H, t, *J* = 7.9 Hz, Si($CH_2\underline{C}H_3)_3$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3-C^F), 0.67 (6H, app qd, *J* = 7.9, 2.2 Hz, Si($C\underline{H}_2CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C^A), 113.1 (CH_2-C16), 88.6 (C-C7), 82.6 (C-C6), 72.2 (CH-C10), 67.7 (C-C8), 52.8 (CH_2-C5), 49.6 (CH_2-C9), 47.4 (CH_2-C2), 41.5 (CH-C1), 32.1 (CH_2-C14), 32.0 (CH_2-C^C), 31.7 (CH_3-C20), 31.2 (CH_2-C^D), 29.8 (CH_2-C13), 26.8 (C($\underline{C}H_3)_3$), 22.3 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 18.8 (CH_3-

C17), 14.1 (CH_3-C^F), 7.2 ($Si(CH_2\underline{C}H_3)_3$), 6.2 ($Si(\underline{C}H_2CH_3)_3$); HRMS ($ESI^+$) calcd. for $C_{46}H_{68}O_5Si_2Na$ $[M+Na]^+$ 779.4497 found 779.4441; IR ν_{max} 3072, 2955, 2930, 2874, 2859, 2716, 1721, 1643, 1630, 1462, 1429 cm^{-1}.

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

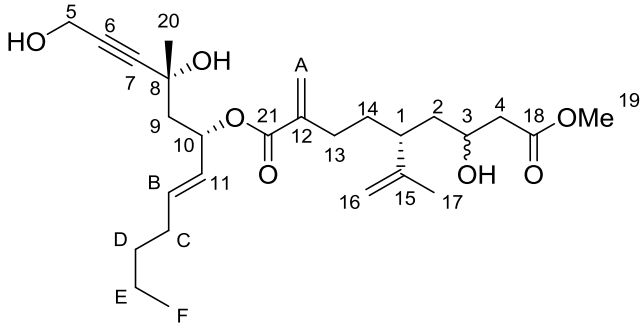


Chemical Formula: $C_{49}H_{74}O_7Si_2$
Molecular Weight: 831.2940

To a solution of diisopropylamine (0.08 mL, 0.6 mmol) in THF (3 mL) at −78 °C was added *n*BuLi (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. NH_4Cl (5 mL) and warming to rt. The biphasic mixture was separated and the aqueous phase extracted with Et_2O (3 × 6 mL). The combined organic extracts were dried over Na_2SO_4, 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, $CDCl_3$) δ 7.74–7.66 (4H, m, $Ph^{a,b}$), 7.47–7.35 (6H, m, $Ph^{a,b}$), 6.08 (1H, dd, *J* = 4.0, 1.6 Hz, CH_2-$C^{Aa,b}$), 5.71–5.62 (1H, m, CH-$C^{Ba,b}$), 5.55 (1H, ddd, *J* = 7.7, 3.8, 3.6 Hz, CH-$C10^{a,b}$), 5.48–5.39 (2H, m, CH-C11, CH_2-$C^{Aa,b}$), 4.84–4.82 (0.5H, m, CH_2-$C16^a$), 4.81–4.76 (1H, m, CH_2-$C16^{a,b}$), 4.75 (0.5H, d, *J* = 2.1 Hz, CH_2-$C16^b$), 4.28 (2H, s, CH_2-$C5^{a,b}$), 4.04–3.90 (1H, m, CH-$C3^{a,b}$), 3.70 (1.5H, s, CH_3-$C19^a$), 3.70 (1.5H, s, CH_3-$C19^b$), 2.94 (0.5H, d, *J* = 3.8 Hz, OH-$C3^a$), 2.70 (0.5H, d, *J* = 4.2 Hz, OH-$C3^b$), 2.51 (0.5H, dd, *J* = 16.2, 3.2 Hz, CH_2-$C4^a$), 2.43 (1H, d, *J* = 6.1 Hz, CH_2-$C4^b$), 2.38–2.30 (0.5H, m, CH-$C1^a$), 2.37 (0.5H, dd, *J* = 16.2, 9.0 Hz, CH_2-$C4^a$), 2.25–2.10 (2.5H, m, CH_2-$C13^{a,b}$, CH-$C1^b$), 2.08 (1H, ddd, *J* = 14.3, 7.7, 1.7 Hz, CH_2-$C9^{a,b}$), 1.99 (2H, dt, *J* = 6.6, 6.5 Hz, CH_2-$C^{Ca,b}$), 1.92 (1H, ddd, *J* = 14.3, 3.8, 1.7 Hz, CH_2-$C9^{a,b}$), 1.71–1.64 (1H, m, CH_2-$C2^a$), 1.64 (1.5H, s, CH_3-$C17^a$), 1.60 (1.5H, s, CH_3-$C17^b$), 1.52–1.43 (3H, m, CH_2-$C2^{b,}$ CH_2-$C14^{a,b}$), 1.43 (1.5H, s, CH_3-$C20^a$), 1.42 (1.5H, s, CH_3-$C20^b$), 1.36–1.24 (4H, m, CH_2-$C^{Da,b}$, CH_2-$C^{Ea,b}$), 1.05 (9H, s, $C(CH_3)_3{}^{a,b}$), 0.94 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3{}^{a,b}$), 0.86

(3H, t, *J* = 7.1 Hz, CH_3-$C^{Fa,b}$), 0.67 (6H, app qd, *J* = 7.9, 3.3 Hz, Si($C\underline{H}_2CH_3)_3^{a,b}$); ^{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($\underline{C}H_3)_3$), 22.3 (CH_2-C^E), 19.3 ($\underline{C}(CH_3)_3$), 17.8 (CH_3-C17), 17.7 (CH_3-C17), 14.1 (CH_3-C^F), 7.2 (Si($CH_2\underline{C}H_3)_3$), 6.2 (Si($\underline{C}H_2CH_3)_3$); HRMS (ESI^+) calcd. for $C_{49}H_{74}O_7Si_2Na$ $[M+Na]^+$ 853.4865 found 853.4826; IR ν_{max} 3508, 3071, 2955, 2930, 2874, 2859, 1717, 1643, 1630, 1458, 1429 cm^{-1}

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

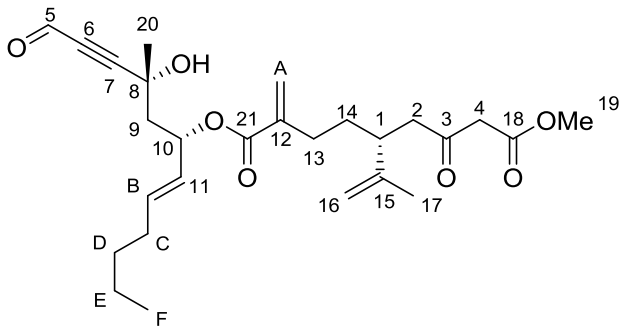


Chemical Formula: $C_{27}H_{42}O_7$
Molecular Weight: 478.6260

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_4Cl (10 mL) and Et_2O (10 mL). The biphasic mixture was separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_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, dtd, *J* = 15.3, 7.2, 1.7 Hz, CH-$C^{Ba,b}$), 5.70 (1H, app tt, *J* = 8.5, 4.3 Hz, CH-C10^{a,b}), 5.56 (1H, dd, *J* = 1.5, 1.4 Hz, CH_2-$C^{Aa,b}$), 5.50 (1H, app ddq, *J* = 15.3, 7.3, 1.6 Hz, CH-C11^{a,b}), 4.85 (0.5H, dq, *J* = 2.9, 1.5 Hz, CH_2-C16^a), 4.82–4.79 (1H, m, CH_2-C16^{a,b}), 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^a),

4.01–3.92 (1H, m, CH-C3[b]), 3.70 (1.5H, s, CH_3-C19[a]), 3.69 (1.5H, s, CH_3-C19[b]), 3.30 (0.5H, s, OH-C8[a]), 3.26 (0.5H, s, OH-C8[b]), 3.06 (0.5H, br s, OH-C3[a]), 2.89 (0.5H, br s, OH-C3[b]), 2.51 (0.5H, dd, *J* = 16.3, 3.3 Hz, CH_2-C4[a]), 2.44 (1H, d, *J* = 6.3 Hz, CH_2-C4[b]), 2.39 (0.5H, dd, *J* = 16.3, 8.9 Hz, CH_2-C4[a]), 2.33–2.13 (3H, m, CH-C1[a,b], CH_2-C13[a,b]), 2.11 (1H, app ddd, *J* = 14.5, 8.5, 2.2 Hz, CH_2-C9[a,b]), 2.03 (2H, ddd, *J* = 7.9, 7.4, 7.2 Hz, CH_2-C[Ca,b]), 1.94 (1H, app ddd, *J* = 14.5, 5.7, 4.3 Hz, CH_2-C9[a,b]), 1.66 (1.5H, br s, CH_3-C17[a]), 1.61 (1.5H, br s, CH_3-C17[b]), 1.59–1.42 (4H, m, CH_2-C2[a,b], CH_2-C14[a,b]), 1.49 (3H, s, CH_3-C20[a,b]) 1.39–1.23 (4H, m, CH_2-C[Da,b], CH_2-C[Ea,b]), 0.88 (3H, t, *J* = 7.1 Hz, CH_3-C[Fa,b]); ^{13}C NMR (126 MHz, $CDCl_3$) 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-C[B]), 134.9 (CH-C[B]), 128.3 (CH-C11), 128.3 (CH-C11), 125.5 (CH_2-C[A]), 125.4 (CH_2-C[A]), 113.6 (CH_2-C16), 112.8 (CH_2-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 (CH_3-C19), 51.9 (CH_3-C19), 51.1 (CH_2-C5), 51.1 (CH_2-C5), 48.0 (CH_2-C9), 44.0 (CH-C1), 43.4 (CH-C1), 41.9 (CH_2-C4), 41.0 (CH_2-C4), 40.3 (CH_2-C2), 40.1 (CH_2-C2), 32.7 (CH_2-C14), 32.0 (CH_2-C[C]), 31.8 (CH_2-C14), 31.2 (CH_2-C[D]), 31.1 (CH_3-C20), 30.0 (CH_2-C13), 29.9 (CH_2-C13), 22.3 (CH_2-C[E]), 18.0 (CH_3-C17), 17.8 (CH_3-C17), 14.0 (CH_3-C[F]); HRMS (ESI$^+$) calcd. for $C_{27}H_{42}O_7Na$ $[M+Na]^+$ 501.2823 found 501.2799; IR ν_{max} 3428, 3071, 2955, 2928, 2858, 1714, 1643, 1630, 1439 cm^{-1}.

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

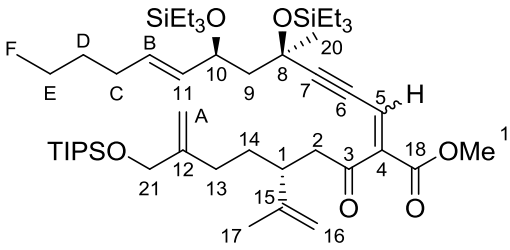


Chemical Formula: $C_{27}H_{38}O_7$
Molecular Weight: 474.5940

To a solution of alcohol **356** (15 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (33 mg, 0.08 mmol) and the resulting mixture stirred at rt for 6 h. Aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts dried over Na_2SO_4, 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. $[\alpha]_D^{27}$ −7.8 (*c* = 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09

(1H, s, CHO-C5), 6.19 (1H, s, CH_2-C^A), 5.84–5.76 (1H, m, CH-C^B), 5.65 (1H, ddd, *J* = 10.1, 7.2, 3.4 Hz, CH-C10), 5.58 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.50 (1H, ddt, *J* = 15.4, 7.2, 1.6 Hz, CH-C11), 4.93 (2H, s, CH_2-C4), 4.82–4.80 (1H, m, CH_2-C16), 4.76 (1H, s, CH_2-C16), 3.85 (3H, s, CH_3-C19), 2.77–2.62 (3H, m, CH-C1, CH_2-C2), 2.28–2.09 (3H, m, CH_2-C9, CH_2-C13), 2.05 (2H, app q, *J* = 6.7 Hz, CH_2-C^C), 1.98 (1H, dd, *J* = 14.7, 3.4 Hz, CH_2-C9), 1.66 (3H, s, CH_3-C17), 1.57 (3H, s, CH_3-C20), 1.54–1.47 (2H, m, CH_2-C14), 1.38–1.26 (4H, m, CH_2-C^D, CH_2-C^E), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) 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-C^B), 127.5 (CH-C11), 126.4 (CH_2-C^A), 112.9 (CH_2-C16), 99.3 (C-C7), 92.7 (CH_2-C4), 82.6 (C-C6), 71.7 (CH-C10), 65.2 (C-C8), 54.0 (CH_3-C19), 47.9 (CH_2-C9), 41.4 (CH-C1), 40.2 (CH_2-C2), 32.0 (CH_2-C^C), 31.6 (CH_2-C14), 31.1 (CH_2-C^D), 30.4 (CH_3-C20), 29.6 (CH_2-C13), 22.3 (CH_2-C^E), 19.1 (CH_3-C17), 14.0 (CH_3-C^F); HRMS (ESI^+) calcd. for $C_{27}H_{38}O_7Na$ $[M+Na]^+$ 497.2510 found 497.2503.

Methyl (6*R*,8*S*,9*E*)-6-methyl-2-[(3*R*)-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



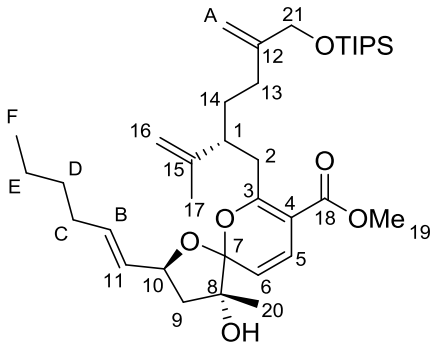
Chemical Formula: $C_{48}H_{88}O_6Si_3$
Molecular Weight: 845.4810

E:*Z*, 1:1.5

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 $MgSO_4$. 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:Et_2O, 95:5) afforded title compound **362** (1:1.5 mixture of *E*:*Z* isomers, 25 mg, 88%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (0.4H, s, CH-$C5_E$), 6.77 (0.6H, s, CH-$C5_Z$), 5.58 (0.4H, app t, *J* = 6.6 Hz, CH-$C^B{}_E$), 5.55 (0.6H, app t, *J* = 6.6 Hz, CH-$C^B{}_Z$), 5.51–5.43 (1H, m, CH-$C11_{E,Z}$), 5.11–5.05 (1H, m, CH_2-$C^A{}_{E,Z}$), 4.83–4.79 (1H, m, CH_2-$C^A{}_{E,Z}$), 4.79–4.76 (1H, m, CH_2-$C16_{E,Z}$), 4.76–4.74 (0.4H, m, CH_2-$C16_E$), 4.73–4.69 (0.6H, m, CH_2-$C16_Z$), 4.39–4.32 (1H, m, CH-$C10_{E,Z}$), 4.12 (2H, s, CH_2-$C21_{E,Z}$), 3.84 (1.8H, s, CH_3-$C19_Z$), 3.78 (1.2H, s, CH_3-$C19_E$), 2.89–2.76 (1H, m, CH_2-$C2_{E,Z}$), 2.76–2.69 (1.4H, CH_2-$C2_{E,Z}$, CH-$C1_E$), 2.69–2.61 (0.6H, m, CH-$C1_Z$), 2.02–1.83 (6H, CH_2-$C^C{}_{E,Z}$, CH_2-$C9_{E,Z}$, CH_2-$C13_{E,Z}$), 1.66–1.65 (1.2H, m, CH_3-$C17_E$), 1.64 (1.8H, dd, *J* = 1.2, 0.7 Hz, CH_3-$C17_Z$), 1.56–1.46 (2H,

m, CH_2-C14$_{E,Z}$), 1.53 (1.8H, s, CH_3-C20$_Z$), 1.50 (1.2H, s, CH_3-C20$_E$), 1.36–1.28 (4H, m, CH_2-C$^D{}_{E,Z}$, CH_2-C$^E{}_{E,Z}$), 1.16–1.08 (3H, m, C<u>H</u>$(CH_3)_{2\ E,Z}$), 1.07 (10.8H, s, CH(C<u>H</u>$_3)_{2\ Z}$), 1.05 (7.2H, s, CH(C<u>H</u>$_3)_{2\ E}$), 0.97–0.91 (18H, m, Si(CH_2C<u>H</u>$_3)_{3\ E,Z}$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C$^F{}_{E,Z}$), 0.66–0.60 (6H, m, Si(C<u>H</u>$_2$CH$_3)_{3\ E,Z}$), 0.57 (6H, q, *J* = 7.8 Hz, Si(C<u>H</u>$_2$CH$_3)_{3\ E,Z}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6 (C-C3$_E$), 195.5 (C-C3$_Z$), 165.8 (C-C18$_Z$), 164.6 (C-C18$_E$), 148.5 (C-C12$_E$), 148.5 (C-C12$_Z$), 146.1 (C-C15$_E$), 146.1 (C-C15$_Z$), 142.5 (CH-C$^B{}_E$), 141.6 (CH-C$^B{}_Z$), 134.1 (CH-C11$_{E,Z}$), 130.9 (C-C4$_E$), 130.8 (C-C4$_Z$), 124.2 (CH-C5$_Z$), 122.8 (CH-C5$_E$), 112.5 (CH_2-C16$_Z$), 112.5 (CH_2-C16$_E$), 111.5 (C-C7$_Z$), 110.4 (C-C7$_E$), 108.2 (CH_2-C$^A{}_Z$), 108.0 (CH_2-C$^A{}_E$), 80.0 (C-C6$_Z$), 79.3 (C-C6$_E$), 71.2 (CH-C10$_Z$), 71.1 (CH-C10$_E$), 69.2 (C-C8$_Z$), 69.2 (C-C8$_E$), 66.2 (CH_2-C21$_{E,Z}$), 53.4 (CH_3-C19$_Z$), 53.3 (CH_3-C19$_E$), 52.6 (CH_2-C9$_E$), 52.4 (CH_2-C9$_Z$), 47.6 (CH_2-C2$_E$), 44.6 (CH_2-C2$_Z$), 42.6 (CH-C1$_Z$), 41.8 (CH-C1$_E$), 32.0 (CH_2-C$^C{}_{E,Z}$), 31.4 (CH_2-C$^D{}_E$), 31.4 (CH_2-C$^D{}_Z$), 31.3 (CH_2-C14$_E$), 31.2 (CH_2-C14$_Z$), 31.0 (CH_2-C13$_E$), 30.5 (CH_2-C13$_Z$), 30.3 (CH_2-C$^E{}_Z$), 30.2 (CH_2-C$^E{}_E$), 22.5 (CH_3-C20$_E$), 22.5 (CH_3-C20$_Z$), 19.2 (CH_3-C17$_E$), 19.1 (CH_3-C17$_Z$), 18.2 (CH(<u>C</u>H$_3)_{2\ E,Z}$), 14.1 (CH_3-C$^F{}_{E,Z}$), 12.2 (<u>C</u>H$(CH_3)_{2\ E,Z}$), 7.1 (Si(CH_2<u>C</u>H$_3)_{3\ E}$), 7.1 (Si(CH_2<u>C</u>H$_3)_{3\ Z}$), 7.1 (Si(CH_2<u>C</u>H$_3)_{3\ E}$), 7.0 (Si(CH_2<u>C</u>H$_3)_{3\ Z}$), 6.3 (Si(<u>C</u>H$_2$CH$_3)_{3\ E}$), 6.2 (Si(<u>C</u>H$_2$CH$_3)_{3\ Z}$), 5.3 (Si(<u>C</u>H$_2$CH$_3)_{3\ E}$), 5.3 (Si(<u>C</u>H$_2$CH$_3)_{3\ Z}$); HRMS (ESI$^+$) calcd. for $C_{48}H_{88}O_6Si_3Na$ $[M+Na]^+$ 867.5781 found 867.5774; IR ν_{max} 2953, 2938, 2874, 1722, 1695, 1584, 1460, 1437 cm^{-1}.

Methyl (2*S*,4*R*)-2-[(1*E*)-hex-1-en-1-yl]-4-hydroxy-4-methyl-7-[(2*R*)-2-(prop-1-en-2-yl)-5-({[tris(propan-2-yl)silyl]oxy}methyl)hex-5-en-1-yl]-1,6-dioxaspiro[4.5]deca-7,9-diene-8-carboxylate 364

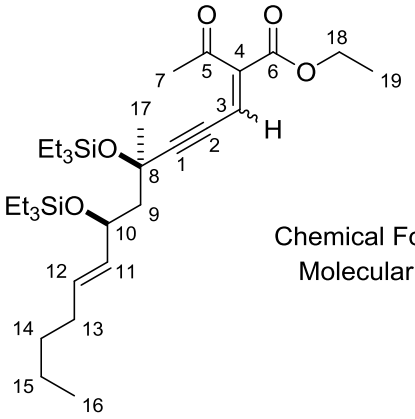


Chemical Formula: $C_{36}H_{60}O_6Si$
Molecular Weight: 616.9550

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_2O, 1:1) afforded the title compound **364** (73 mg, 68%) as a pale yellow oil. ^{1}H NMR (400 MHz, C_6D_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-C^B), 5.32–5.27 (1H, m, CH_2-C^A), 4.99–4.97 (1H, m, CH_2-C^A),

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^C), 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^D, CH_2-C^E), 1.20 (3H, s, CH_3-C20), 1.14–1.10 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.84 (3H, t, *J* = 7.1 Hz, CH_3-C^F);^{13}C NMR (101 MHz, C_6D_6) δ 166.2 (C-C18), 166.1 (C-C3), 148.8 (C-C12), 146.7 (C-C15), 133.3 (CH-C11), 132.3 (CH-C^B), 126.6 (CH-C5), 113.0 (CH_2-C16), 110.2 (C-C7), 109.6 (CH-C6), 108.7 (CH_2-C^A), 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^C), 31.6 (CH_2-C^D), 31.5 (CH_2-C14), 30.8 (CH_2-C13), 22.6 (CH_2-C^E), 22.0 (CH_3-C20), 18.6 (CH_3-C17), 18.3 (CH(<u>C</u>H$_3$)$_2$), 14.1 (CH_3-C^F), 12.4 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI^+) calcd. for $C_{36}H_{60}O_6SiNa$ $[M+Na]^+$ 639.4051 found 639.4008; IR ν_{max} 3473, 2941, 2928, 2866, 1713, 1645, 1578, 1462, 1437 cm^{-1}.

(±)-Ethyl (9*E*)-2-acetyl-6-methyl-6,8-bis[(triethylsilyl)oxy]tetradeca-2,9-dien-4-ynoate 365

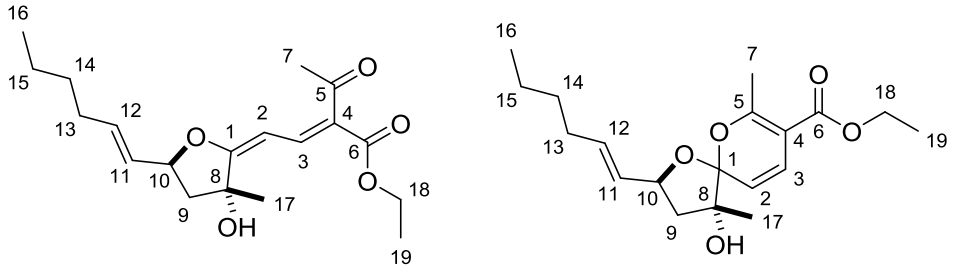


Chemical Formula: $C_{31}H_{56}O_5Si_2$
Molecular Weight: 564.9540

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_2O, 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, $CDCl_3$) δ 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_2C<u>H</u>$_3$)$_3$), 0.87 (3H, t, *J* = 7.0 Hz, CH_2-C16), 0.65–0.52 (12H, m, (Si(C<u>H</u>$_2$CH$_3$)$_3$); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 198.3 (C-C5), 193.9 (C-C5), 165.2 (C-C6), 163.9 (C-C6), 143.0 (CH-C12), 141.8 (CH-C12), 134.1 (CH-C11), 134.0 (CH-C11), 130.8 (C-C4), 130.8 (C-C4), 124.0 (CH-C3), 122.5 (CH-C3), 111.7 (C-C1), 110.3 (C-C1), 79.8 (C-C2), 79.4 (C-C2), 71.2 (CH-C10), 71.1 (CH-C10), 69.2 (C-C8), 69.2 (C-C8), 61.8 (CH_2-C18), 61.6 (CH_2-C18), 53.3 (CH_2-C9), 53.3 (CH_2-C9), 31.9 (CH_2-C13), 31.3 (CH_2-C14), 31.3 (CH_3-C17), 31.2 (CH_3-C17), 30.5 (CH_3-C7), 27.7 (CH_3-C7), 22.4 (CH_2-C15), 14.3 (CH_3-C19), 14.2 (CH_3-C19), 14.0 (CH_3-C16), 7.1 ($Si(CH_2\underline{C}H_3)_3$), 7.0 ($Si(CH_2\underline{C}H_3)_3$), 6.2 ($Si(\underline{C}H_2CH_3)_3$), 5.2 ($Si(\underline{C}H_2CH_3)_3$). HRMS ($ESI^+$) calcd. for $C_{31}H_{56}O_5Si_2Na$ $[M+Na]^+$ 587.3558 found 587.3530; IR ν_{max} 2955, 2936, 2914, 2876, 2209, 1717, 1699, 1587, 1458, 1413 cm^{-1}.

Ethyl (2*E*)-2-acetyl-4-[(2*E*)-5-[(1*E*)-hex-1-en-1-yl]-3-hydroxy-3-methyloxolan-2-ylidene] but-2-enoate 366 and ethyl 2-[(1*E*)-hex-1-en-1-yl]-4-hydroxy-4,7-dimethyl-1,6-dioxaspiro[4.5]deca-7,9-diene-8-carboxylate 367

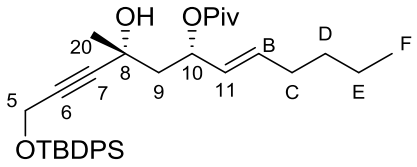


Chemical Formula: $C_{19}H_{28}O_5$
Molecular Weight: 336.4280

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. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added and the biphasic mixture separated. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 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, $CDCl_3$) 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, CH_2-C18), 2.36 (3H, s, CH_3-C7), 2.20 (1H, dd, *J* = 13.1, 6.7 Hz, CH_2-C9), 2.15 (1H, dd, *J* = 13.1, 9.4 Hz, CH_2-C9), 2.05–1.96 (2H, m, CH_2-C13), 1.40–1.23 (10H, m, CH_2-C14, CH_2-C15, CH_3-C17, CH_3-C19), 0.87 (3H, *J* = 7.1 Hz, CH_3-C16); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C18), 44.0 (CH_2-C9), 31.9 (CH_2-C13), 31.2 (CH_2-C14) , 22.3 (CH_3-C17), 21.7 (CH_2-C15), 20.5 (CH_3-C7), 14.5 (CH_3-C19), 14.0 (CH_3-C16); HRMS (ESI^+) calcd. for $C_{19}H_{28}O_5Na$ $[M+Na]^+$ 359.1829 found 359.1810.

Diene 366: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 12.1 Hz, CH-C3), 5.85 (1H, dt, *J* = 15.3, 6.7 Hz, CH-C12), 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, $CDCl_3$) δ 196.2 (C-C5), 173.5 (C-C6), 167.2 (C-C1), 141.1 (CH-C3), 137.1 (CH-C12), 128.2 (C-C4), 127.2 (CH-C11), 92.6 (CH-C2), 83.8 (CH-C10), 78.1 (C-C8) 61.0 (CH_2-C18), 45.7 (CH_2-C9), 32.0 (CH_2-C13), 31.0 (CH_2-C14), 28.0 (CH_3-C17), 25.0 (CH_3-C7) 22.4 (CH_2-C15), 14.4 (CH_3-C19), 14.0 (CH_3-C16); HRMS (ESI$^+$) calcd. for $C_{19}H_{28}O_5Na$ [M+Na]$^+$ 359.1829 found 359.1805.

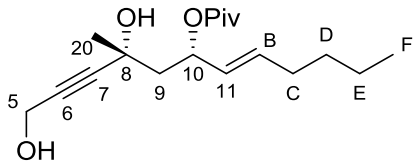
(4*R*,6*S*,7*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-4-hydroxy-4-methyldodec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 371



Chemical Formula: $C_{34}H_{48}O_4Si$
Molecular Weight: 548.8390

To a solution of diol **350** (51 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (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_4Cl (1 mL) and the phases were separated. The organic phase was washed with brine (2 mL) before being dried over Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 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, $CDCl_3$) δ 7.79–7.68 (4H, m, Ph), 7.49–7.33 (6H, m, Ph), 5.76 (1H, dt, *J* = 13.7, 6.8 Hz, CH-C^B), 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^C, 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^D, CH_2-C^E), 1.17 (9H, s, Piv-C(C$\underline{H}_3$)$_3$), 1.06 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.88 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (C=O), 135.8 (Ph), 134.9 (Ph), 133.4 (CH-C^B), 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-$\underline{C}$(CH$_3$)$_3$), 31.9 (CH_2-C^C), 31.1 (CH_2-C^D), 30.5 (CH_3-C20), 27.2 (SiC($\underline{C}$H$_3$)$_3$), 26.8 (SiC($\underline{C}$H$_3$)$_3$), 22.2 (CH_2-C^E), 19.3 (Si$\underline{C}$(CH$_3$)$_3$), 14.0 (CH_3-C^F); HRMS (ESI$^+$) calcd. for $C_{34}H_{48}O_4SiNa$ [M+Na]$^+$ 571.3214 found 571.3187; IR ν_{max} 3451, 2958, 2930, 2858, 1428 cm^{-1}.

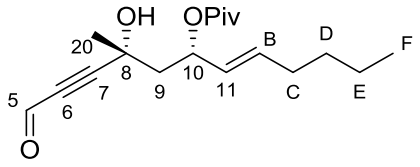
(4*R*,6*S*,7*E*)-1,4-Dihydroxy-4-methyldodec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 372



Chemical Formula: $C_{18}H_{30}O_4$
Molecular Weight: 310.4340

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. NH_4Cl (5 mL) and Et_2O (5 mL) were added and the biphasic mixture separated. The organic extract was washed with brine (5 mL) before being dried over Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 25:75) afforded the title compound **372** (37.2 mg, quant) as a colourless oil. $[\alpha]_D^{27}$ −29 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, dt, *J* = 14.7, 6.8 Hz, CH-C^B), 5.61–5.52 (1H, m, CH-C10), 5.46 (1H, ddt, *J* = 14.7, 7.2, 1.3 Hz, CH-C11), 4.25 (2H, s, CH_2-C5), 2.07 (1H, dd, *J* = 14.3, 7.5 Hz, CH_2-C9), 2.05–1.99 (2H, m, CH_2-C^C), 1.96 (1H, dd, *J* = 14.3, 5.3 Hz, CH_2-C9), 1.49 (3H, s, CH_3-C20), 1.37–1.23 (4H, m, CH_2-C^D, CH_2-C^E), 1.18 (9H, s, C(C$\underline{H}_3$)$_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4 (C=O), 135.0 (CH-C^B), 128.7 (CH-C11), 88.8 (C-C7), 82.4 (C-C6), 72.4 (CH-C10), 66.4 (C-C8), 51.0 (CH_2-C5), 47.8 (CH_2-C9), 38.9 ($\underline{C}(CH_3)_3$), 31.9 (CH_2-C^C), 31.1 (CH_2-C^D), 30.8 (CH_3-C20), 27.2 (C($\underline{C}H_3$)$_3$), 22.2 (CH_2-C^E), 14.0 (CH_3-C^F); HRMS (ESI^+) calcd. for $C_{18}H_{30}O_4Na$ $[M+Na]^+$ 333.2036 found 333.2020; IR ν_{max} 3392, 2958, 2929, 2872, 1727, 1708, 1480, 1459 cm^{-1}.

(4*R*,6*S*,7*E*)-4-Hydroxy-4-methyl-1-oxododec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 373

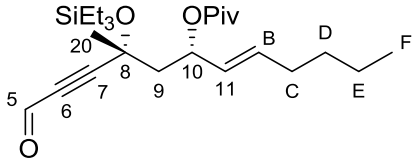


Chemical Formula: $C_{18}H_{28}O_4$
Molecular Weight: 308.4180

To a solution of primary alcohol **372** (32 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (66 mg, 0.15 mmol) and the resulting mixture stirred at rt for 3 h. Saturated aq. $Na_2S_2O_3$ (2 mL) was added and the phases were separated. The organic phase was washed with brine (2 mL) before being dried over Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 3:7) afforded the title compound **373** (30 mg, 97%) as a colourless oil. $[\alpha]_D^{27}$ −9.4 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (1H, s, CHO-

C5), 5.78 (1H, dt, *J* = 13.8, 6.8 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 Hz, CH_2-C9), 2.06–1.97 (3H, m, CH_2-C9, CH_2-C^{C}), 1.57 (3H, s, CH_3-C20), 1.38–1.21 (4H, CH_2-C^{D}, CH_2-C^{E}), 1.18 (9H, s, C(C$\underline{H}_3$)$_3$), 0.88 (3H, t, *J* = 7.2 Hz, CH_3-C^{F}); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9 (C=O), 176.6 (CHO-C5), 135.5 (CH-C^{B}), 128.0 (CH-C11), 99.3 (C-C7), 82.6 (C-C6), 71.8 (CH-C10), 65.8 (C-C8), 47.3 (CH_2-C9), 39.0 (C(CH$_3$)$_3$), 31.9 (CH_2-C^{C}), 31.1 (CH_2-C^{D}), 30.3 (CH_3-C20), 27.1 (C(C$\underline{H}_3$)$_3$), 22.2 (CH_2-C^{E}), 14.0 (CH_3-C^{F}); HRMS (ESI^{+}) calcd. for $C_{18}H_{28}O_4Na$ [M+Na]$^{+}$ 331.1880 found 331.1799; IR ν_{max} 3447, 2959, 2928, 2872, 2857, 2214, 1728, 1707, 1670, 1460 cm^{-1}.

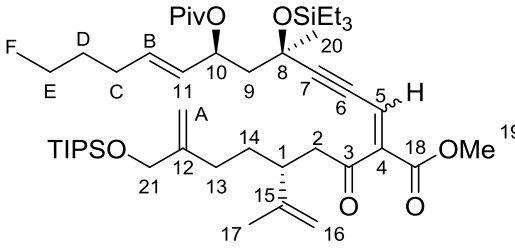
(4*R*,6*S*,7*E*)-4-Methyl-1-oxo-4-[(triethylsilyl)oxy]dodec-7-en-2-yn-6-yl 2,2-dimethylpropanoate 374



Chemical Formula: $C_{24}H_{42}O_4Si$
Molecular Weight: 422.6810

To a solution of aldehyde **373** (27 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added 2,6-lutidine (30 µL, 0.23 mmol) and triethylsilyl triflate (20 µL, 0.11 mmol) and the resulting mixture stirred for 2 h. The reaction was quenched with saturated aq. NH_4Cl (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 Na_2SO_4, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 95:5) afforded the title compound **374** (34 mg, 90%) as a colourless oil. $[\alpha]_D^{24}$ −29.8 (C = 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (1H, s, CHO-C5), 5.73–5.63 (1H, m, CH-C^{B}), 5.47 (1H, td, *J* = 7.5, 4.0 Hz, CH-C10), 5.39 (1H, ddt, *J* = 15.3, 7.3, 1.4 Hz, CH-C11), 2.13 (1H, dd, *J* = 14.4, 7.5 Hz, CH_2-C9), 2.04–1.95 (3H, m, CH_2-C9, CH_2-C^{C}), 1.54 (3H, s, CH_3-C20), 1.37–1.24 (4H, m, CH_2-C^{D}, CH_2-C^{E}), 1.17 (9H, s, C(C$\underline{H}_3$)$_3$), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH_2C$\underline{H}_3$)$_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_3-C^{F}), 0.68 (6H, app qd, *J* = 8.0, 2.2 Hz, Si(C$\underline{H}_2$CH$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3 (C=O), 176.4 (CHO-C5), 134.0 (CH-C^{B}), 128.8 (CH-C11), 99.9 (C-C7), 83.7 (C-C6), 71.1 (CH-C10), 67.8 (C-C8), 49.2 (CH_2-C9), 38.8 (C(CH$_3$)$_3$), 31.9 (CH_2-C^{C}), 31.3 (CH_2-C^{D}), 31.1 (CH_3-C20), 27.2 (C(C$\underline{H}_3$)$_3$), 22.2 (CH_2-C^{E}), 14.0 (CH_3-C^{F}), 7.0 (Si(CH_2C$\underline{H}_3$)$_3$), 6.2 (Si(C$\underline{H}_2$CH$_3$)$_3$); HRMS (ESI^{+}) calcd. for $C_{24}H_{42}O_4Na$ [M+Na]$^{+}$ 445.2744 found 445.2664; IR ν_{max} 2957, 2931, 2876, 2209, 1729, 1673, 1458 cm^{-1}.

Methyl (6*R*,8*S*,9*E*)-8-[(2,2-dimethylpropanoyl)oxy]-6-methyl-2-[(3*R*)-3-(prop-1-en-2-yl)-6-({[tris(propan-2-yl)silyl]oxy}methyl)hept-6-enoyl]-6-[(triethylsilyl)oxy]tetradeca-2,9-dien-4-ynoate 375



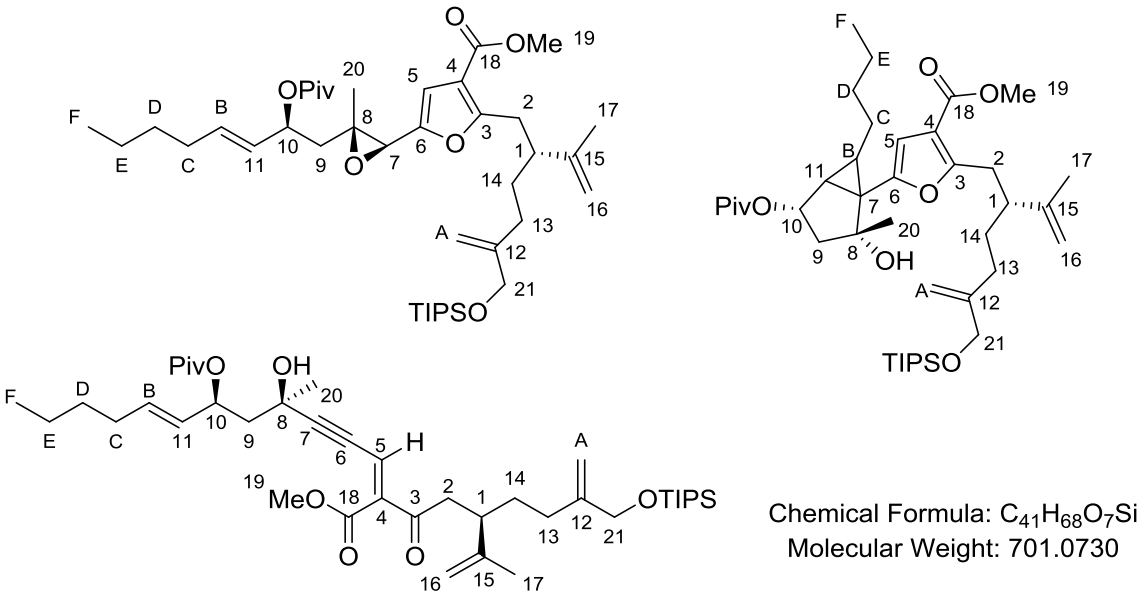
Chemical Formula: $C_{47}H_{82}O_7Si_2$
Molecular Weight: 815.3360

E:*Z*, 1:1.2

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 $MgSO_4$. 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:Et_2O, 95:5 → 90:10) afforded title compound **375** (1:1.2 mixture of *E*:*Z* isomers, 25 mg, 88%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (0.55H, s, CH-C5$_Z$), 6.75 (0.45H, s, CH-C5$_E$), 5.72–5.61 (1H, m, CH-C^B $_{E,Z}$), 5.49–5.35 (2H, m, CH-C11$_{E,Z}$, CH-C10$_{E,Z}$), 5.12–5.03 (1H, m, CH_2-C^A $_{E,Z}$), 4.84–4.69 (3H, m, CH_2-C^A $_{E,Z}$, CH_2-C16$_{E,Z}$), 4.12 (2H, s, CH_2-C21$_{E,Z}$), 3.87 (1.35H, s, CH_3-C19$_E$), 3.78 (1.65H, s, CH_3-C19$_Z$), 2.90–2.60 (3H, m, CH_2-C2$_{E,Z}$, CH-C1$_{E,Z}$), 2.16–1.84 (6H, m, CH_2-C$^C{}_{E,Z}$, CH_2-C9$_{E,Z}$, CH_2-C13$_{E,Z}$), 1.65 (1.65H, s, CH_3-C17$_Z$), 1.64 (1.35H, s, CH_3-C17$_E$), 1.62–1.51 (2H, m, CH_2-C14$_{E,Z}$), 1.49 (1.35H, s, CH_3-C20$_E$), 1.47 (1.65H, s, CH_3-C20$_Z$), 1.38–1.25 (4H, m, CH_2-C$^D{}_{E,Z}$, CH_2-C$^E{}_{E,Z}$), 1.16 (4.05H, s, C(C$\underline{H}_3$)$_{3\ E}$), 1.15 (4.95H, s, C(C$\underline{H}_3$)$_{3\ Z}$), 1.13–1.03 (21H, m, C$\underline{H}$(C$\underline{H}_3$)$_{2\ E,Z}$) 0.97–0.92 (9H, m, Si(CH$_2$C$\underline{H}_3$)$_{3\ E,Z}$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3-C$^F{}_{E,Z}$), 0.68–0.59 (6H, m, Si(C$\underline{H}_2$CH$_3$)$_{3\ E,Z}$); ^{13}C NMR (101 MHz, $CDCl_3$) 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-C^B), 141.7 (CH-C^B), 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 (CH_2-C16), 112.4 (CH_2-C16), 110.5 (CH_2-C7), 109.4 (CH_2-C7), 108.2 (CH_2-C^A), 108.0 (CH_2-C^A), 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 (CH_2-C21), 52.6 (CH_3-C19), 52.5 (CH_3-C19), 49.7 (CH_2-C9), 49.5 (CH_2-C9), 47.5 (CH_2-C2), 44.6 (CH_2-C2), 42.5 (CH-C1), 41.8 (CH-C1), 38.8 (C$\underline{C}$(CH$_3$)$_3$), 32.0 (CH_2-C^C), 32.0 (CH_2-C^C), 31.4 (CH_2-C^D), 31.2 (CH_2-C14), 31.1 (CH_2-C13), 30.5 (CH_2-C13), 30.3 (CH_2-C^E), 30.2 (CH_2-C^E), 27.3 (C(C$\underline{H}_3$)$_3$), 27.2 (C(C$\underline{H}_3$)$_3$), 22.2 (CH_3-C20), 19.2 (CH_3-C17), 19.1 (CH_3-C17), 18.2 (CH(C$\underline{H}_3$)$_2$), 14.0 (CH_3-C^F), 12.2 (C$\underline{H}$(CH$_3$)$_2$), 7.1 (Si(CH$_2$C$\underline{H}_3$)$_3$), 6.2 (Si(C$\underline{H}_2$CH$_3$)$_3$), 6.1

(Si(C$H_2$$CH_3$)$_3$); HRMS (ESI$^+$) calcd. for $C_{47}H_{82}O_7Si_2Na$ $[M+Na]^+$ 837.5491 found 837.5495; IR ν_{max} 2957, 2932, 2866, 2211, 1728, 1586, 1460, 1437 cm^{-1}.

Methyl 5-[(2*S*,3*R*)-3-[(2*S*,3*E*)-2-[(2,2-dimethylpropanoyl)oxy]oct-3-en-1-yl]-3-methyl-oxiran-2-yl]-2-[(2*R*)-2-(prop-1-en-2-yl)-5-({[tris(propan-2-yl)silyl]oxy}methyl)hex-5-en-1-yl]furan-3-carboxylate 377, methyl (2*Z*,6*R*,8*S*,9*E*)-8-[(2,2-dimethylpropanoyl)oxy]-6-hydroxy-6-methyl-2-[(3*R*)-3-(prop-1-en-2-yl)-6-({[tris(propan-2-yl)silyl]oxy}methyl)hept-6-enoyl]tetradeca-2,9-dien-4-ynoate (*Z*)-375 and methyl 5-[(2*R*,4*S*)-6-butyl-4-[(2,2-dimethyl-propanoyl)oxy]-2-hydroxy-2-methylbicyclo[31.0]hexan-1-yl]-2-[(2*R*)-2-(prop-1-en-2-yl)-5-({[tris(propan-2-yl)silyl]oxy}methyl)hex-5-en1-yl]furan-3-carboxylate 378



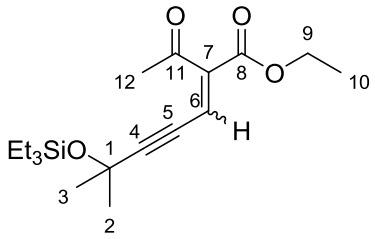
Chemical Formula: $C_{41}H_{68}O_7Si$
Molecular Weight: 701.0730

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:Et_2O, 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 CH_2Cl_2 (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: Et_2O, 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**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (1H, s, CH-C5), 5.64 (1H, dt, J = 15.7, 6.8 Hz, CH-C^B), 5.40–5.30 (1H, m, CH-C10), 5.17–5.09 (1H, m, CH-C11), 5.07 (1H, d, *J* = 1.9 Hz, CH_2-C^A), 4.79 (1H, d, *J* = 1.9 Hz, CH_2-C^A), 4.69 (1H, q, *J* = 1.4 Hz, CH_2-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^C), 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($C\underline{H}_3$)$_3$), 1.15–1.01 (21H, m, C$\underline{H}$($C\underline{H}_3$)$_2$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3-C^F); HRMS (ESI^+) calcd. for $C_{41}H_{68}O_7SiNa$ $[M+Na]^+$ 723.4627 found 723.4578; IR ν_{max} 3467, 2957, 2929, 2866, 1725, 1581, 1480, 1462, 1438 cm^{-1}. **Ynenone (*Z*)-375**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, s, CH-C5), 5.87–5.76 (CH-C^B), 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^C), 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($C\underline{H}_3$)$_3$), 1.15–1.03 (21H, m, C$\underline{H}$($C\underline{H}_3$)$_2$), 0.88 (3H, t, *J* = 7.1 Hz, CH_3-C^F); HRMS (ESI^+) calcd. for $C_{41}H_{68}O_7SiNa$ $[M+Na]^+$ 723.4627 found 723.4587; IR ν_{max} 3467, 2957, 2929, 2866, 1725, 1581, 1480, 1462, 1438 cm^{-1}. **Cyclopropylfuran 378**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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^C CH_2-C^D, CH_2-C^E), 1.20 (9H, s, C($C\underline{H}_3$)$_3$), 1.11–1.03 (21H, m, C$\underline{H}$($C\underline{H}_3$)$_2$), 0.83 (3H, t, *J* = 7.0 Hz, CH_3-C^F); HRMS (ESI^+) calcd. for $C_{41}H_{68}O_7SiNa$ $[M+Na]^+$ 723.4627 found 723.4586.

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



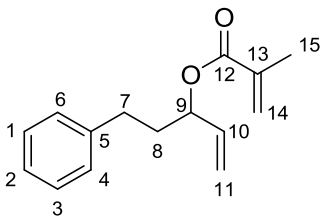
Chemical Formula: $C_{18}H_{30}O_4Si$
Molecular Weight: 338.5190

To a solution of triethyl((2-methylbut-3-yn-2-yl)oxy)silane (1.09 g, 5.49 mmol) in Et_2O (10 mL) at −78 °C was added *n*BuLi (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_2PO_4 (20 mL). Following vigorous stirring

for 30 min the biphasic mixture was separated and the organic phase was washed with 10% aq. KH_2PO_4 (2 × 10mL). The combined organic extracts were dried over $MgSO_4$, 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 $MgSO_4$ (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 H_2O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under vacuum to yield the crude product. Purification of the residue by silica gel column chromatography (pet ether:Et_2O, 10:1) afforded the title compound **383** as a 1:1 mix of *E* and *Z* isomers (560 mg, 75%). **Isomeric mixture**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (0.5H, s, CH-C6), δ 6.79 (0.5H, s, CH-C6), 4.33 (1H, q, *J* = 7.1 Hz, CH_2-C9), 4.26 (1H, q, *J* = 7.1 Hz, CH_2-C9), 2.44 (1.5H, s, CH_3-C12), 2.36 (1.5H, s, CH_3-C12), 1.51 (3H, s, CH_3-C2, CH_3-C3), 1.50 (3H, s, CH_3-C2, CH_3-C3), 1.36 (1.5H, t, *J* = 7.1 Hz, CH_3-C10),1.30 (1.5H, t, *J* = 7.1 Hz, CH_3-C10), 0.94 (4.5H, t, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.94 (4.5H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.63 (3H, q, *J* = 7.8 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.63 (3H, q, *J* = 7.9 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) 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 (CH_2-C9), 61.6 (CH_2-C9), 32.5 (2C, CH_3-C2, CH_3-C3), 32.5 (2C, CH_3-C2, CH_3-C3), 30.4 (CH_3-C12), 27.5 (CH_3-C12), 14.2 (CH_3-C10), 14.1 (CH_3-C10), 6.9 ($Si(CH_2C\underline{H}_3)_3$), 5.97 ($Si(\underline{C}H_2CH_3)_3$); HRMS (ESI$^+$) calcd. for $C_{18}H_{30}O_4SiNa$ $[M+Na]^+$ 361.1806, found 361.1793; IR ν_{max} 2955, 2876, 1727, 1697, 1600, 1585, 1459, 1360, 1225 cm^{-1}

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

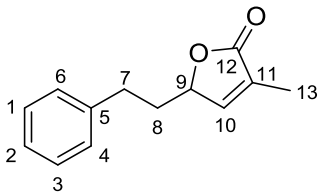


Chemical Formula: $C_{15}H_{18}O_2$
Molecular Weight: 230.3070

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 CH_2Cl_2 (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:Et_2O, 4:1) afforded the title compound **386** as a colourless oil (575 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-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, CH_2-C14), 5.42–5.37 (1H, m, CH-C9), 5.34 (1H, dt, *J* = 17.1, 1.4 Hz, CH_2-C11), 5.27 (1H, dt, *J* = 10.6, 1.4 Hz, CH_2-C11), 2.80–2.66 (2H, m, CH_2-C7), 2.16–1.97 (5H, m, CH_2-C8, CH_3-C15); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C14), 117.0 (CH_2-C11), 74.6 (CH-C9), 36.0 (CH_2-C8), 31.5 (CH_2-C7), 18.5 (CH_3-C15); HRMS (ESI$^+$) Calcd. for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1194; IR ν_{max} 3028, 2953, 2928, 1717, 1638, 1497, 1454 cm^{-1}.

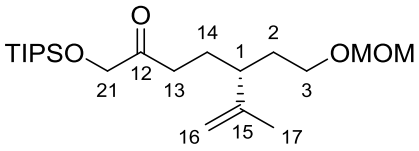
3-Methyl-5-(2-phenylethyl)-2,5-dihydrofuran-2-one 387



Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.2530

To a solution of ester **386** (100 mg, 0.43 mmol) and epoxyfuran **298** (97 mg, 0.43 mmol) in CH_2Cl_2 (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: Et_2O, 4:1 → 3:2) to afford the title compound **387** as a colourless oil (84 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-C7), 2.03 (1H, dddd, *J* = 13.9, 9.2, 7.3, 4.6 Hz, CH_2-C8), 1.95–1.85 (5H, m, CH_2-C8, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C7), 31.6 (CH_2-C8), 10.8 (CH_3-C13); HRMS (ESI$^+$) calcd. for $C_{13}H_{14}O_2Na$ $[M+Na]^+$ 225.0886, found 225.0882; IR ν_{max} 3063, 2924, 1751, 1658, 1497, 1451 cm^{-1}.

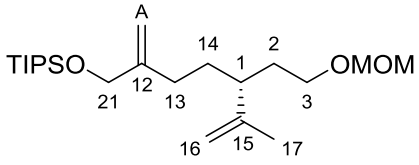
(7*R*)-14-Methyl-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecan-10-one 391



Chemical Formula: $C_{21}H_{42}O_4Si$
Molecular Weight: 386.6480

To a solution of alcohol **313** (200 mg, 0.58 mmol) in CH_2Cl_2 (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 $MgSO_4$, filtered and the solvent removed under vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 9:1) afforded the title compound **391** as a colourless oil (155 mg, 69%). $[\alpha]_D^{20}$ −7.9 (*c* = 0.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (1H, dq, *J* = 2.9, 1.8 Hz, CH_2-C16), 4.70 (1H, d, *J* = 1.8 Hz, CH_2-C16), 4.60 (1H, d, *J* = 6.5 Hz, MOM-CH_2), 4.58 (1H, d, *J* = 6.5 Hz, MOM-CH_2), 4.20 (2H, s, CH_2-C21), 3.49–3.42 (2H, m, CH_2-C3), 3.34 (3H, s, MOM-CH_3), 2.58–2.45 (2H, m, CH_2-C13), 2.21 (1H, tt, *J* = 10.1, 5.0 Hz, CH-C1), 1.75–1.55 (7H, m, CH_2-C2, CH_2-C14, CH_3-C17), 1.16–1.00 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9 (C-C12), 146.0 (C-C15), 113.1 (CH_2-C16), 96.6 (MOM-CH_2), 69.9 (CH_2-C21), 66.1 (CH_2-C3), 55.3 (MOM-CH_3), 43.8 (CH-C1), 36.5 (CH_2-C13), 33.4 (CH_2-C2), 26.3 (CH_2-C14), 18.0 (<u>C</u>H(CH$_3$)$_2$), 17.7 (CH_3-C17), 12.0 (CH(<u>C</u>H$_3$)$_2$); HRMS (ESI$^+$) calcd. for $C_{21}H_{42}O_4SiNa$ $[M+Na]^+$ 409.2745, found 409.2724; IR ν_{max} 2942, 2867, 1734, 1721, 1644, 1464 cm^{-1}.

(7*R*)-14-Methyl-10-methylidene-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-silapentadecane

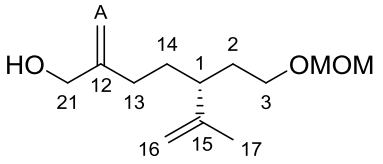


Chemical Formula: $C_{22}H_{44}O_3Si$
Molecular Weight: 384.6760

To a solution of methyltriphenylphosphonium bromide (296 mg, 0.83 mmol) in THF (4 mL) at 0 °C was added *n*BuLi (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 H_2O (10 mL) and Et_2O (10 mL) added. The biphasic mixture was separated and the organic extract was washed with brine (15 mL), dried over $MgSO_4$, filtered and the solvent removed under

vacuum. Purification of the residue by silica gel column chromatography (pet. ether:Et_2O, 95:5 → 90:10) afforded the title compound as a colourless oil (148 mg, quant.). $[\alpha]_D^{23}$ −2.7 (*c* = 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (1H, d, *J* = 1.7 Hz, CH_2-C^A), 4.81 (1H, dq, *J* = 2.1, 1.4 Hz, CH_2-C16), 4.78 (1H, dq, *J* = 2.9, 1.4 Hz, CH_2-C16), 4.72–4.69 (1H, m, CH_2-C^A), 4.60 (1H, d, *J* = 6.6 Hz, MOM-CH_2), 4.58 (1H, d, *J* = 6.6 Hz, MOM-CH_2), 4.13 (2H, s, CH_2-C21), 3.54–3.39 (m, 2H, CH_2-C3), 3.35 (3H, s, MOM-CH_3), 2.22 (1H, tt, *J* = 9.3, 5.5 Hz, CH-C1), 2.02–1.82 (2H, m, CH_2-C13), 1.73–1.58 (5H, m, CH_2-C2, CH_3-C17), 1.55–1.45 (2H, m, CH_2-C14), 1.19–1.00 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9 (C-C12), 146.6 (C-C15), 112.6 (CH_2-C^A), 108.0 (CH_2-C16), 96.7 (MOM-CH_2), 66.3 (CH_2-C21), 66.2 (CH_2-C3), 55.3 (MOM-CH_3), 44.1 (CH-C1), 33.4 (CH_2-C2), 31.7 (CH_2-C13), 30.6 (CH_2-C14), 18.2 (<u>C</u>H(CH$_3$)$_2$), 17.8 (CH_3-C17), 12.2 (CH(<u>C</u>H$_3$)$_2$); HRMS (ESI^+) calcd. for $C_{22}H_{44}O_3SiNa$ $[M+Na]^+$ 407.2952, found 407.2936; IR ν_{max} 2940, 2866, 1644, 1463, 1441 cm^{-1}.

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

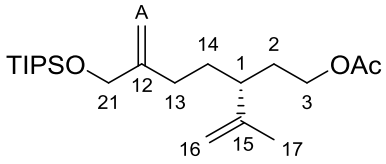


Chemical Formula: $C_{13}H_{24}O_3$
Molecular Weight: 228.3320

To a solution of (7*R*)-14-Methyl-10-methylidene-7-(prop-1-en-2-yl)-13,13-bis(propan-2-yl)-2,4,12-trioxa-13-sil apentadecane (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. NH_4Cl (5 mL) and Et_2O (5 mL) added. The phases were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (pet. ether:Et_2O, 1:1) to afford the allylic alcohol **392** as a pale yellow oil (85 mg, quant.); $[\alpha]_D^{21}$ −13.6 (*c* = 0.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (1H, d, *J* = 1.8 Hz, CH_2-C^A), 4.81 (1H, d, *J* = 1.4 Hz, CH_2-C16), 4.75 (1H, dq, *J* = 2.8, 1.4 Hz, CH_2-C16), 4.69–4.67 (1H, m, CH_2-C^A), 4.56 (1H, d, *J* = 6.6 Hz, MOM-CH_2), 4.54 (1H, d, *J* = 6.6 Hz, MOM-CH_2), 4.00 (2H, s, CH_2-C21), 3.47–3.37 (2H, m, CH_2-C3), 3.31 (3H, s, MOM-CH_3), 2.24–2.15 (1H, m, CH-C1), 2.01–1.85 (2H, m, CH_2-C13), 1.69–1.54 (5H, m, CH_2-C2, CH_3-C17), 1.51–1.42 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2 (C-C12), 146.3 (C-C15), 112.7 (CH_2-C^A), 109.0 (CH_2-C16), 96.5 (MOM-CH_2), 66.1 (CH_2-C21), 65.8 (CH_2-C3), 55.2 (MOM-CH_3), 43.8 (CH-C1), 33.2 (CH_2-

C2), 31.4 (CH_2-C13), 30.7 (CH_2-C14), 17.7 (CH_3-C17); HRMS (ESI^+) calcd. for $C_{13}H_{24}O_3Na$ $[M+Na]^+$ 251.1617, found 251.1598; IR ν_{max} 3408, 2929, 2882, 1645, 1442 cm^{-1}.

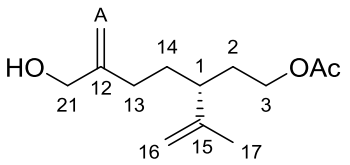
(3*R*)-3-(Prop-1-en-2-yl)-6-((trisisopropylsilyloxy)methyl)hept-6-en-1-yl acetate



Chemical Formula: $C_{22}H_{42}O_3Si$
Molecular Weight: 382.6600

To a solution of alcohol **314** (4.50 g, 13.2 mmol) and DMAP (161 mg, 1.32 mmol) in CH_2Cl_2 (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. NH_4Cl (100 mL) and the phases were separated. The organic phase was washed with brine (50 mL), 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_2O, 19:1) to deliver the title acetate as a colourless oil (4.74 g, 94%). $[\alpha]_D^{24}$ −6.1 (*c* = 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09–5.07 (1H, d, *J* = 1.7 Hz, CH_2-C^A), 4.82–4.78 (2H, m, CH_2-$C^{A,}$ CH_2-C16), 4.72–4.70 (1H, m, CH_2-C16), 4.13 (2H, s, CH_2-C21), 4.07–3.92 (2H, m, CH_2-C3), 2.22–2.14 (1H, m, CH-C1), 2.03 (3H, s, OAc-CH_3), 2.01–1.83 (2H, m, CH_2-C13), 1.77–1.63 (2H, m, CH_2-C2), 1.61 (3H, dd, *J* = 1.3, 0.8 Hz, CH_3-C17), 1.55–1.47 (2H, m, CH_2-C14), 1.17–1.03 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (Ac-<u>C</u>(O)), 148.7 (C-C12), 146.0 (C-C15), 113.0 (CH_2-C^A), 108.1 (CH_2-C16), 66.2 (CH_2-C21), 63.2 (CH_2-C3), 44.0 (CH-C1), 32.1 (CH_2-C2), 31.5 (CH_2-C13), 30.5 (CH_2-C14), 21.1 (Ac-<u>C</u>H_3), 18.2 (<u>C</u>H(CH_3)$_2$), 17.8 (CH_3-C17), 12.2 (CH(<u>C</u>H_3)$_2$); HRMS (ESI^+) calcd for $C_{22}H_{42}O_3SiNa$ $[M+Na]^+$ 405.2796, found 405.2777; IR ν_{max} 2941, 2893, 2866, 1744, 1645, 1464 cm^{-1}.

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

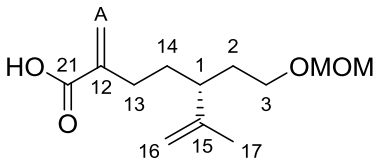


Chemical Formula: $C_{13}H_{22}O_3$
Molecular Weight: 226.3160

To a solution of (3*R*)-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. NH_4Cl (100 mL) and Et_2O (100 mL) added. The phases were separated

and the aqueous phase was extracted with Et_2O (100 mL). The combined organic extracts were dried over $MgSO_4$, 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.). $[\alpha]_D^{21}$ −12 (*c* = 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96–4.94 (1H, m, CH_2-C^A), 4.80–4.77 (1H, m, CH_2-C16), 4.75–4.73 (1H, m, CH_2-C16), 4.67–4.64 (1H, m, CH_2-C^A), 4.01–3.95 (3H, m, CH_2-C21, CH_2-C3), 3.89 (1H, ddd, *J* = 11.0, 7.4, 7.3 Hz, CH_2-C3), 2.40 (1H, br s, OH-C21), 2.16–2.09 (1H, m, CH-C1), 1.97 (3H, s, Ac-CH_3), 1.96–1.84 (2H, m, CH_2-C13), 1.69–1.58 (2H, m, CH_2-C2), 1.56 (3H, dd, *J* = 1.2, 0.7 Hz, CH_3-C17), 1.48–1.42 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (Ac-C(O)), 148.9 (C-C12), 145.7 (C-C15), 112.9 (CH_2-C^A), 109.0 (CH_2-C16), 65.7 (CH_2-C21), 63.0 (CH_2-C3), 43.7 (CH-C1), 31.9 (CH_2-C2), 31.2 (CH_2-C13), 30.5 (CH_2-C14), 21.0 (Ac-CH_3), 17.6 (CH_3-C17); HRMS (ESI$^+$) calcd for C13H22O3Na $[M+Na]^+$ 249.1461, found 249.1456; IR ν_{max} 3431, 3072, 2934, 2901, 2862, 1739, 1720, 1645, 1447 cm^{-1}.

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



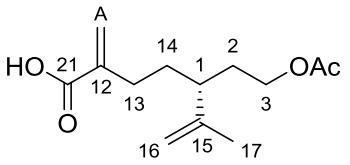
Chemical Formula: $C_{13}H_{22}O_4$
Molecular Weight: 242.3150

To a solution of the allylic alcohol **392** (80 mg, 0.35 mmol) in CH_2Cl_2 (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. $Na_2S_2O_3$ (5 mL) and the phases were separated. The organic phase was washed with saturated aq. $Na_2S_2O_3$ (2 × 5 mL), dried over $MgSO_4$ 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 *t*BuOH (5.35 mL) was added 2-methyl-2-butene (0.76 mL, 7.12 mmol). A solution of NaH_2PO_4 (896 mg, 5.78 mmol) and $NaClO_2$ (483 g, 5.34 mmol) in H_2O (10.7 mL) was then added and the biphasic mixture stirred at rt for 16 h. CH_2Cl_2 (20 mL) was added and the phases separated. The aqueous phase was washed with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford the carboxylic acid **394** as a colourless oil (85 mg, quant.). $[\alpha]_D^{26}$ −14 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.61 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 4.78 (1H, dq, *J* = 2.5, 1.4 Hz, CH_2-C16), 4.71 (1H, d, *J* = 2.5 Hz, CH_2-C16), 4.59 (1H, d, J = 6.6 Hz, MOM-CH_2), 4.57 (1H, d, J = 6.6 Hz, MOM-CH_2), 3.49–3.39 (2H, m, CH_2-C3), 3.33 (3H, s, MOM-CH_3), 2.29–2.19 (2H, m, CH_2-C13),

2.19–2.10 (1H, m, CH-C1), 1.71–1.58 (5H, m, CH_2-C2, CH_3-C17), 1.55–1.47 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (C-C21), 146.1 (C-C15), 140.3 (C-C12), 127.0 (CH_2-C^A), 112.9 (CH_2-C16), 96.5 (MOM-CH_2), 66.2 (CH_2-C3), 55.2 (MOM-CH_3), 43.9 (CH-C1), 33.2 (CH_2-C2), 32.1 (CH_2-C13), 29.7 (CH_2-C14), 17.7 (CH_3-C17); HRMS (ESI$^+$) calcd. for $C_{13}H_{22}O_4Na$ [M+Na]$^+$ 265.1410, found 265.1412; IR ν_{max} 3071, 2930, 2882, 1719, 1694, 1645, 1628, 1441 cm^{-1}.

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

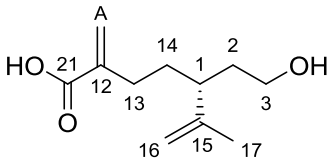


Chemical Formula: $C_{13}H_{20}O_4$
Molecular Weight: 240.2990

To a solution of the allylic alcohol **393** (3.7 g, 16 mmol) in CH_2Cl_2 (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. $Na_2S_2O_3$ (100 mL) and the phases were separated. The organic phase was washed with saturated aq. $Na_2S_2O_3$ (2 × 100 mL), dried over $MgSO_4$ 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 *t*BuOH (120 mL) was added 2-methyl-2-butene (13.1 mL, 123 mmol). A solution of NaH_2PO_4 (15.5 g, 100 mmol) and $NaClO_2$ (8.35 g, 92.3 mmol) in H_2O (240 mL) was then added and the biphasic mixture stirred at rt for 17 h. CH_2Cl_2 (200 mL) was added and the phases separated. The aqueous phase was washed with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford the carboxylic acid **395** as a colourless oil (3.91 g, quant.). $[\alpha]_D^{24}$ −11 (*c* = 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.56 (1H, br, $CO_2\underline{H}$), 6.23 (1H, d, *J* = 0.9 Hz, CH_2-C^A), 5.60–5.58 (1H, m, CH_2-C^A), 4.78–4.75 (1H, m, CH_2-C16), 4.68 (1H, d, *J* = 1.8 Hz, CH_2-C16), 3.99 (1H, ddd, *J* = 11.0, 7.3, 5.7 Hz, CH_2-C3), 3.92 (1H, ddd, *J* = 11.0, 7.3, 7.3 Hz, CH_2-C3), 2.27–2.08 (3H, m, CH_2-C13, CH-C1), 1.99 (3H, s, Ac-CH_3), 1.71–1.59 (2H, m, CH_2-C2), 1.58 (3H, d, *J* = 1.3 Hz, CH_3-C17), 1.53–1.46 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 (C-C21), 171.4 (Ac-$\underline{C}$(O)), 145.5 (C-C15), 140.1 (C-C12), 127.1 (CH_2-C^A), 113.2 (CH_2-C16), 63.0 (CH_2-C3), 43.8 (CH-C1), 32.0 (CH_2-C2), 31.8 (CH_2-C13), 29.5 (CH_2-C14), 21.0 (Ac-$\underline{C}H_3$), 17.5 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{13}H_{20}O_4Na$ [M+Na]$^+$ 263.1254, found 263.1254; IR ν_{max} 3171, 3072, 2936, 1738, 1724, 1693, 1645, 1628, 1440 cm^{-1}

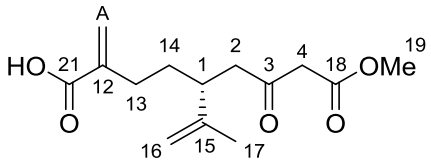
(5*R*)-5-(2-Hydroxyethyl)-6-methyl-2-methylidenehept-6-enoic acid 388



Chemical Formula: $C_{11}H_{18}O_3$
Molecular Weight: 198.2620

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 H_2O (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. CH_2Cl_2 (10 mL) was added and the biphasic mixture separated. The aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under vacuum to afford the alcohol **388** as a colourless oil (168 mg, 95%). $[\alpha]_D^{23}$ −27 (*c* = 0.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.65 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 4.82 (1H, dq, *J* = 2.6, 1.5 Hz, CH_2-C16), 4.78 (1H, d, *J* = 2.6 Hz, CH_2-C16), 3.67–3.56 (2H, m, CH_2-C3), 2.33–2.23 (2H, m, CH_2-C13), 2.22–2.13 (1H, m, CH-C1), 1.67–1.60 (5H, CH_2-C2, CH_3-C17), 1.58–1.51 (2H, m, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C-C21), 147.0 (C-C15), 140.1 (C-C12), 127.2 (CH_2-C^A), 112.9 (CH_2-C16), 61.6 (CH_2-C3), 44.2 (CH-C1), 36.2 (CH_2-C2), 32.3 (CH_2-C13), 29.8 (CH_2-C14), 17.8 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1148, found 221.1145; IR ν_{max} 3284, 3071, 2938, 2879, 1690, 1627, 1443 cm^{-1}.

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



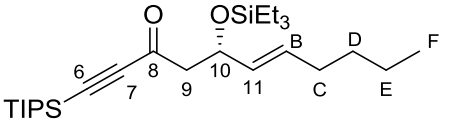
Chemical Formula: $C_{14}H_{20}O_5$
Molecular Weight: 268.3090

To a solution of alcohol **388** (73 mg, 0.37 mmol) in CH_2Cl_2 (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. $Na_2S_2O_3$ (2 mL). The phases were separated and the organic phase washed with saturated aq. $Na_2S_2O_3$ (2 × 2 mL), then dried over Na_2SO_4 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 CH_2Cl_2 (1.8 mL) was added a solution of $NaNO_2$ (459 mg, 6.66 mmol) in H_2O (0.6 mL). The biphasic mixture was stirred for 1.5 h at rt and then saturated aq. $NaHCO_3$ (0.5 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 crude aldehyde and $SnCl_2$ (148 mg, 0.74 mmol) in CH_2Cl_2 (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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, s, CH_2-C^A), 5.66 (1H, s, CH_2-C^A), 4.81 (1H, q, *J* = 1.3 Hz, CH_2-C16), 4.76 (1H, s, CH_2-C16), 3.72 (3H, s, CH_2-C19), 3.43 (2H, s, CH_2-C4), 2.73–2.52 (3H, m, CH_2-C13, CH-C1), 2.33–2.20 (1H, m, CH_2-C2), 2.23–2.08 (1H, m, CH_2-C2), 1.67 (3H, d, *J* = 1.3 Hz, CH_3-C17), 1.60–1.49 (2H, m, CH_2-C14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7 (C-C3), 172.5 (C-C21), 167.7 (C-C18), 145.7 (C-C15), 139.8 (C-C12), 127.5 (CH_2-C^A), 112.9 (CH_2-C16), 52.5 (CH_3-C19), 49.4 (CH_2-C4), 47.5 (CH_2-C2), 42.0 (CH-C1), 31.7 (CH_2-C13), 29.3 (CH_2-C14), 18.9 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{14}H_{20}O_5Na$ [M+Na]$^+$ 291.1203, found 291.1196; IR ν_{max} 3070, 2930, 1742, 1718, 1694, 1628, 1438 cm^{-1}.

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

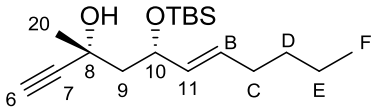


Chemical Formula: $C_{26}H_{50}O_2Si_2$
Molecular Weight: 450.8540

To a solution of triisopropylsilylacetylene (1.23 mL, 5.47 mmol) in THF (9 mL) at 0 °C was added *n*BuLi (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. NH_4Cl (20 mL) and Et_2O (20 mL) added. The phases were separated and the organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 98:2) to afford the propargylic ketone **396** as a colourless oil (1.55 g, 94%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ −4.8 (*c* = 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67–5.58 (1H, m, CH-C^B), 5.43 (1H, ddt, *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, CH_2-C9), 2.65 (1H, dd, *J* = 14.5, 5.8 Hz, CH_2-C9), 2.00 (1H, app q, *J* = 6.8 Hz, CH_2-C^C), 1.38–1.24 (4H, m, CH_2-C^D, CH_2-C^E), 1.18–1.05 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.93 (9H, t, *J* = 7.8 Hz, Si(CH_2C<u>H</u>$_3$)$_2$), 0.88 (3H, t, *J* = 7.1 Hz, CH_3-C^F), 0.58 (6H, q, *J* = 7.8

Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2 (C-C8), 132.0 (CH-C^B), 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^C), 31.3 (CH_2-C^D), 22.3 (CH_2-C^E), 18.6 (CH(<u>C</u>H$_3$)$_2$), 14.1 (CH_3-C^F), 11.2 (<u>C</u>H(CH$_3$)$_2$), 6.9 (Si(CH$_2$<u>C</u>H$_3$)$_3$), 5.0 (Si(<u>C</u>H$_2$CH$_3$)$_3$); HRMS (ESI$^+$) calcd for $C_{26}H_{50}O_2Si_2Na$ $[M+Na]^+$ 473.3242, found 473.3208; IR ν_{max} 2955, 2947, 2868, 2147, 1678, 1628, 1462, 1414 cm^{-1}.

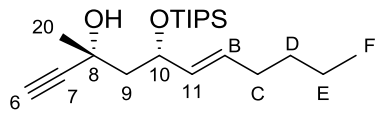
(3*R*,5*S*,6*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methylundec-6-en-1-yn-3-ol 399



Chemical Formula: $C_{18}H_{34}O_2Si$
Molecular Weight: 310.5530

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_2O (10 mL) were added and the phases separated. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 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^F, Si(CH$_3$)$_2$C(C<u>H</u>$_3$)$_3$), 0.10 (3H, s, Si(C<u>H</u>$_3$)$_2$C(CH$_3$)$_3$), 0.06 (3H, s, Si(C<u>H</u>$_3$)$_2$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(<u>C</u>H$_3$)$_3$), 22.4 (CH_2-C^E), 18.1(Si(CH$_3$)$_2$<u>C</u>(CH$_3$)$_3$), 14.1 (CH_3-C^F), −3.4 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$), −4.6 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$); HRMS (ESI$^+$) calcd for $C_{18}H_{34}O_2SiNa$ $[M+Na]^+$ 333.2220, found 333.2210; IR ν_{max} 3470, 3312, 2957, 2930, 2857, 1668, 1472, 1464 cm^{-1}

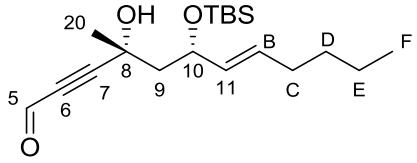
(3*R*,5*S*,6*E*)-3-Methyl-5-{[tris(propan-2-yl)silyl]oxy}undec-6-en-1-yn-3-ol 400



Chemical Formula: $C_{21}H_{40}O_2Si$
Molecular Weight: 352.6340

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. Triisopropylsilyl chloride (0.11 mL, 0.50 mmol) was then added and the mixture was stirred at rt for 14 h. Brine (5 mL) and Et_2O (5 mL) were added and the phases separated. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 8:2) to afford the alkyne **400** as a colourless oil (166 mg, 98%). $[\alpha]_D^{27}$ −12 (*c* = 0.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76–5.63 (2H, m, CH-C11, CH-C^B), 4.66 (1H, td, *J* = 6.9, 5.4 Hz, CH-C10), 4.09 (1H, s, OH-C8), 2.46 (1H, s, CH-C6), 2.11–2.00 (3H, m, CH_2-C9, CH_2-C^C), 1.94 (1H, dd, *J* = 14.2, 6.9 Hz, CH_2-C9), 1.52 (3H, s, CH_3-C20), 1.41–1.28 (4H, m, CH_2-C^D, CH_2-C^E), 1.14–1.00 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.89 (3H, t, *J* = 7.1 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8 (CH-C^B), 132.8 (CH-C11), 88.4 (C-C7), 73.5 (CH-C6), 71.5 (CH-C10), 66.8 (C-C8), 49.8 (CH_2-C9), 31.9 (CH_2-C^C), 31.2 (CH_2-C^D), 30.9 (CH_3-C20), 22.5 (CH_2-C^E), 18.3 (CH(<u>C</u>H$_3$)$_2$), 18.2 (CH(<u>C</u>H$_3$)$_2$), 14.0 (CH_3-C^F), 12.6 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{21}H_{40}O_2SiNa$ $[M+Na]^+$ 375.2690, found 375.2673; IR ν_{max} 3466, 3312, 2943, 2930, 2866, 1464 cm^{-1}

(4*R*,6*S*,7*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxy-4-methyldodec-7-en-2-ynal 401

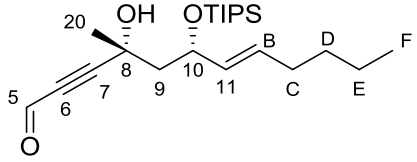


Chemical Formula: $C_{19}H_{34}O_3Si$
Molecular Weight: 338.5630

To a solution of alkyne **399** (170 mg, 0.55 mmol) in THF (15 mL) at −78 °C was added *n*BuLi (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. KH_2PO_4 (20 mL) and Et_2O (20 mL) was added. The phases were separated and the organic phase washed wth brine (20 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 7:3) to deliver the

propargylic aldehyde **401** as a colourless oil (186 mg, quant.). $[\alpha]_D^{26}$ −7.5 (*c* = 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (1H, s, CHO-C5), 5.70–5.53 (2H, m, CH-C11, CH-C^B), 4.79 (1H, s, OH-C8), 4.54 (1H, td, *J* = 7.0, 4.5 Hz, CH-C10), 2.12 (1H, dd, *J* = 14.5, 7.0 Hz, CH_2-C9), 2.06–1.99 (2H, m, CH_2-C^C), 1.94 (1H, dd, *J* = 14.5, 4.5 Hz, CH_2-C9), 1.58 (3H, s, CH_2-C20), 1.43–1.27 (4H, m, CH_2-C^D, CH_2-C^E), 0.98–0.85 (12H, m, CH_3-C^F, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.10 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.07 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9 (CHO-C5), 133.0 (CH-C^B), 132.2 (CH-C11), 100.5 (C-C7), 82.9 (C-C6), 73.3 (CH-C10), 67.5 (C-C8), 47.9 (CH_2-C9), 31.9 (CH_2-C^C), 31.2 (CH_2-C^D), 29.6 (CH_3-C20), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 22.4 ($CH_2$-C^E), 18.1 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.1 ($CH_3$-C^F), −3.5 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −4.7 ($Si(\underline{C}H_3)_2C(CH_3)_3$); HRMS (ESI$^+$) calcd for $C_{19}H_{34}O_3SiNa$ $[M+Na]^+$ 361.2169, found 361.2122; IR ν_{max} 3451, 2957, 2930, 2859, 2210, 1672, 1472, 1646 cm^{-1}.

(4*R*,6*S*,7*E*)-4-Hydroxy-4-methyl-6-{[tris(propan-2-yl)silyl]oxy}dodec-7-en-2-ynal 402

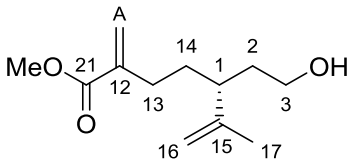


Chemical Formula: $C_{22}H_{40}O_3Si$
Molecular Weight: 380.6440

To a solution of alkyne **400** (122 mg, 0.35 mmol) in THF (2.5 mL) at −78 °C was added *n*BuLi (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. KH_2PO_4 (5 mL) and Et_2O (5 mL) was added. The phases were separated and the organic phase washed wth brine (5 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 8:2) to deliver the propargylic aldehyde **402** as a colourless oil (133 mg, quant.). $[\alpha]_D^{31}$ −20 (*c* = 0.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (1H, s, CHO-C5), 5.78–5.63 (2H, m, CH-C11, CH-C^B), 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, CH_2-C9), 2.06–2.00 (2H, m, CH_2-C^C), 1.57 (3H, s, CH_3-C20), 1.39–1.29 (4H, m, CH_2-C^D, CH_2-C^E), 1.13–1.04 (21H, m, $C\underline{H}(C\underline{H}_3)_2$), 0.89 (3H, t, *J* = 7.0 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7 (CHO-C5), 132.9 (CH-C^B), 132.5 (CH-C11), 100.7 (C-C7), 83.5 (C-C6), 73.7 (CH-C10), 67.3 (C-C8), 48.6 (CH_2-C9), 31.9 (CH_2-C^C), 31.1 (CH_2-C^D), 30.5 (CH_3-C20), 22.5 (CH_2-C^E), 18.2 ($CH(\underline{C}H_3)_2$), 18.1 ($CH(\underline{C}H_3)_2$), 14.0 (CH_3-C^F), 12.5 ($\underline{C}H(CH_3)_2$); HRMS

(ESI$^+$) calcd. for $C_{22}H_{40}O_3SiNa$ $[M+Na]^+$ 403.2639, found 403.2614; IR ν_{max} 3441, 2943, 2932, 2866, 2209, 1672, 1464 cm^{-1}.

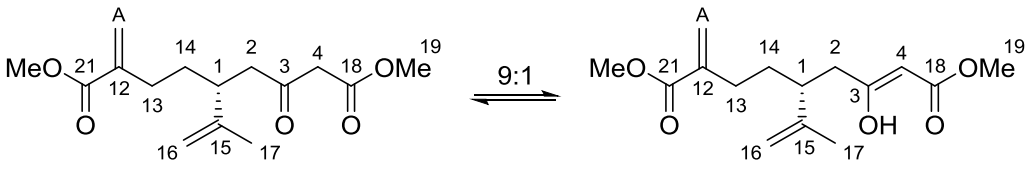
Methyl (5*R*)-5-(2-hydroxyethyl)-6-methyl-2-methylidenehept-6-enoate 404



Chemical Formula: $C_{12}H_{20}O_3$
Molecular Weight: 212.2890

To a solution of carboxylic acid **395** (200 mg, 0.83 mmol) and DMAP (10 mg, 0.08 mmol) in CH_2Cl_2 (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. K_2CO_3 (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. NH_4Cl (5 mL) and AcOH (2 drops) and CH_2Cl_2 (5 mL) added. The phases were separated and the organic phase dried over Na_2SO_4 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.). $[\alpha]_D^{31}$ +4.0 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.52 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 4.80 (1H, dq, *J* = 2.6, 1.4 Hz, CH_2-C16), 4.76 (1H, dq, *J* = 2.6, 0.7 Hz, CH_2-C16), 3.74 (3H, s, O$\underline{C}H_3$), 3.65–3.54 (2H, m, CH_2-C3), 2.31–2.21 (2H, m, CH_2-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, CH_3-C17), 1.64–1.59 (2H, m, CH_2-C2), 1.54–1.47 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8 (C-C21), 147.0 (C-C15), 140.8 (C-C12), 124.9 (CH_2-C^A), 112.7 (CH_2-C16), 61.5 (CH_2-C3), 51.9 (O$\underline{C}H_3$), 44.1 (CH-C1), 36.2 (CH_2-C2), 32.3 (CH_2-C13), 30.1 (CH_2-C14), 17.7 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{12}H_{20}O_3Na$ $[M+Na]^+$ 235.1305, found 235.1299; IR ν_{max} 3392, 3076, 2935, 2860, 1721, 1644, 1628, 1440 cm^{-1}

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



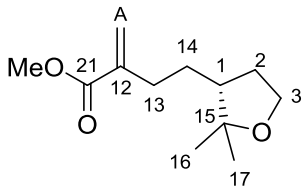
Chemical Formula: $C_{15}H_{22}O_5$
Molecular Weight: 282.3360

To a solution of alcohol **404** (176 mg, 0.83 mmol) in CH_2Cl_2 (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. $Na_2S_2O_3$ (10 mL). The phases were separated and the organic phase washed with saturated aq. $Na_2S_2O_3$ (2 × 10 mL), then dried over Na_2SO_4 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 CH_2Cl_2 (1.7 mL) was added a solution of $NaNO_2$ (414 mg, 5.98 mmol) in H_2O (0.6 mL). The biphasic mixture was stirred for 1.5 h at rt and then saturated aq. $NaHCO_3$ (0.5 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 crude aldehyde **405** and $SnCl_2$ (166 mg, 0.83 mmol) in CH_2Cl_2 (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 15 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%). $[\alpha]_D^{28}$ +28 (*c* = 0.007, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.98 (0.1H, s, OH-C3 enol), 6.13 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.54 (0.9H, d, *J* = 1.4 Hz, CH_2-C^A), 5.53 (0.1H, d, *J* = 1.7 Hz, CH_2-C^A enol), 4.95 (0.1H, s, CH-C4 enol), 4.83–4.81 (1H, m CH_2-C16), 4.76 (1H, s, CH_2-C16), 3.74 (3H, s, O$\underline{C}H_3$), 3.73 (2.7H, s, CH_3-C19), 3.72 (0.3H, s, CH_3-C19 enol), 3.43 (1.8H, d, *J* = 1.3 Hz, CH_2-C4), 2.70–2.56 (3H, m, CH-C1, CH_2-C2), 2.30–2.23 (1H, m, CH_2-C13), 2.20–2.12 (1H, m, CH_2-C13), 1.68–1.66 (2.7H, m, CH_3-C17), 1.66–1.65 (0.3H, s, CH_3-C17 enol), 1.59–1.50 (2H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7 (C-C3), 167.7 (C-C21), 167.7 (C-C18), 145.8 (C-C15), 140.3 (C-C12), 125.2 (CH_2-C^A), 112.9 (CH_2-C16), 52.5 (CH_3-C19), 51.9 (O$\underline{C}H_3$), 49.5 (CH_2-C4), 47.5 (CH_2-C2), 42.1 (CH-C1), 31.8 (CH_2-C13), 29.8 (CH_2-C14), 18.9 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{15}H_{22}O_5Na$ $[M+Na]^+$ 305.1359, found 305.1350; IR ν_{max} 2953, 2926, 2857, 2361, 2336, 1749, 1719, 1645, 1630, 1437 cm^{-1}.

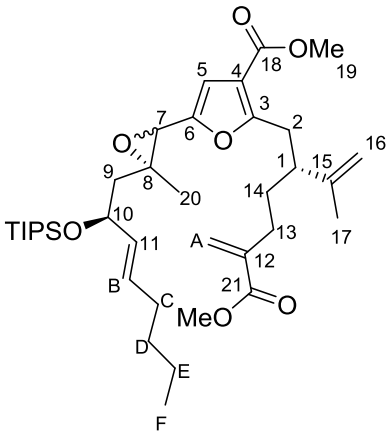
Methyl 4-[(3*R*)-2,2-dimethyloxolan-3-yl]-2-methylidenebutanoate 408



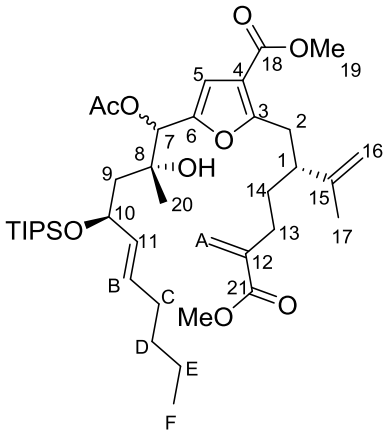
Chemical Formula: $C_{12}H_{20}O_3$
Molecular Weight: 212.2890

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 aqueoous solution, 7.5 mmol) and the resultant stirred at rt for 72 h. Et_2O (10 mL) was added and the phases separated. The organic phase was dried over Na_2SO_4, 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%). $[\alpha]_D^{31}$ −14 (*c* = 0.055, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16–6.13 (1H, m, CH_2-C^A), 5.55 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 3.83 (1H, td, *J* = 8.7, 3.2 Hz, CH_2-C3), 3.78–3.71 (4H, m, O$C\underline{H}_3$, CH_2-C3), 2.44–2.34 (1H, m, CH_2-C13), 2.32–2.22 (1H, m, CH_2-C13), 2.13 (1H, dtd, *J* = 11.9, 7.4, 3.2 Hz, CH_2-C2), 1.80–1.69 (1H, m, CH-C1), 1.68–1.50 (2H, m, CH_2-C2, CH_2-C14), 1.38–1.26 (1H, m, CH_2-C14), 1.23 (3H, s, CH_3-C16), 0.99 (3H, s, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C-C21), 140.6 (C-C12), 124.9 (CH_2-C^A), 81.7 (C-C15), 64.9 (CH_2-C3), 51.9 (O$\underline{C}H_3$), 48.4 (CH-C1), 32.1 (CH_2-C2), 31.5 (CH_2-C13), 29.5 (CH_2-C14), 27.7 (CH_3-C16), 22.1 (CH_3-C17); HRMS (ESI^+) calcd. for $C_{12}H_{20}O_3Na$ $[M+Na]^+$ 235.1305, found 235.1302; IR ν_{max} 2969, 2934, 2873, 1721, 1631, 1438 cm^{-1}.

Methyl 2-[(2*R*)-6-methoxy-5-methylidene-6-oxo-2-(prop-1-en-2-yl)hexyl]-5-[(3*R*)-3-methyl-3-[(2*S*,3*E*)-2-{[tris(propan-2-yl)silyl]oxy}oct-3-en-1-yl]oxiran-2-yl]furan-3-carboxylate 412 and Methyl 5-[(2*R*,4*S*,5*E*)-1-(acetyloxy)-2-hydroxy-2-methyl-4-{[tris(propan-2-yl)silyl]oxy}dec-5-en-1-yl]-2-[(2*R*)-6-methoxy-5-methylidene-6-oxo-2-(prop-1-en-2-yl)hexyl]furan-3-carboxylate 413



Chemical Formula: $C_{37}H_{60}O_7Si$
Molecular Weight: 644.9650

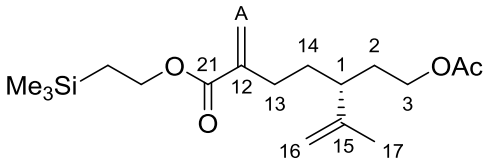


Chemical Formula: $C_{39}H_{64}O_9Si$
Molecular Weight: 705.0170

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 CH_2Cl_2 (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:Et_2O, 80:20 → 75:25) to afford the epoxyfuran **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%). **Epoxyfuran 412:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (0.5H, s, CH-C5), 6.81 (0.5H, s, CH-C5), 6.26 (0.5H, d, *J* = 1.6 Hz, CH_2-C^A), 6.25 (0.5H, d, *J* = 1.6 Hz, CH_2-C^A), 5.72–5.54 (1.5H, m, CH-C11, CH-C^B), 5.49–5.42 (0.5H, m, CH-C11), 5.40 (0.5H, d, *J* = 1.6 Hz, CH_2-C^A), 5.37 (0.5H, d, *J* = 1.6 Hz, CH_2-C^A), 4.92–4.89 (1H, m, CH_2-C16), 4.87–4.84 (1H, m, CH_2-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, CH_3-C19), 3.53 (1.5H, s, CH_3-C19), 3.46 (1.5H, s, O$C\underline{H}_3$), 3.46 (1.5H, s, O$C\underline{H}_3$), 3.43–3.31 (1H, m, CH_2-C2), 3.23 (0.5H, dd, *J* = 14.3, 8.5 Hz, CH_2-C2), 3.11 (0.5H, dd, *J* = 14.3, 6.5 Hz, CH_2-C2), 2.96–2.83 (1H, m, CH-C1), 2.41 (0.5H, dd, *J* = 13.5, 4.8 Hz, CH_2-C13), 2.35–2.24 (1.5H, m, CH_2-C13), 2.18–2.01 (3H, m, CH_2-C9, CH_2-C^C), 1.83 (1.5H, s, CH_3-C17), 1.80 (1.5H, s, CH_3-C17), 1.79–1.63 (3H, m, CH_2-C9, CH_2-C14), 1.48 (3H, s, CH_3-C20), 1.45–1.36 (4H, m, CH_2-C^D, CH_2-C^E), 1.31–1.17 (21H, m, C$\underline{H}$($C\underline{H}_3$)$_2$), 0.99 (3H, t, *J* = 7.0 Hz, CH_3-C^F); HRMS (ESI$^+$) calcd for $C_{37}H_{60}O_7SiNa$ $[M+Na]^+$ 667.4000, found 667.3889; IR ν_{max} 2950, 2926, 2866, 1719, 1645, 1630, 1617, 1579, 1462, 1439 cm^{-1}. **Acetate 413:** ^{1}H NMR (500 MHz, C_6D_6) δ 6.90 (0.4H, s, CH-C5), 6.86 (0.6H, s, CH-C5), 6.17 (0.4H, d, *J* = 1.6 Hz, CH_2-C^A), 6.16 (0.6H, d, *J* = 1.6 Hz, CH_2-C^A), 6.11 (0.4H, s, CH-C7), 6.09 (0.6H, s, CH-C7), 5.62–5.48 (2H, m, CH-C11, CH-C^B), 5.30 (0.4H, d, *J* = 1.6 Hz, CH_2-C^A), 5.29 (0.6H, d, *J* = 1.6 Hz, CH_2-C^A), 4.78–4.70 (3H, m, CH_2-C16, CH-C10), 4.25 (0.6H, s, OH-C8), 4.10 (0.4H, s, OH-C8), 3.41 (1.8H, s, CH_3-C19), 3.41 (1.2H, s, CH_3-C19), 3.37 (1.2H, s, O$C\underline{H}_3$), 3.36 (1.8H, s, O$C\underline{H}_3$), 3.16–3.05 (2H, m, CH_2-C2), 2.75 (1H, dtd, *J* = 14.8, 9.2, 5.7 Hz, CH-C1), 2.43–2.30 (2H, m, CH_2-C9, CH_2-C13), 2.24–2.10 (2H, m, CH_2-C9, CH_2-C13), 1.96–1.85 (3H, m, CH_2-C14, CH_2-C^C), 1.72 (4.8H, s, CH_3-C17, CH_3-C20), 1.69 (1.2H, s, CH_3-C17), 1.64–1.53 (2.2H, m, CH_2-C14, Ac-$C\underline{H}_3$), 1.46 (1.8H, s, Ac-$C\underline{H}_3$), 1.34–1.19 (4H, m, CH_2-C^D, CH_2-C^E), 1.18–1.07 (21H, m, C$\underline{H}$($C\underline{H}_3$)$_2$), 0.90–0.83 (3H, m, CH_3-C^F); ^{13}C NMR (126 MHz, C_6D_6) 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-C^B), 133.8 (CH-C^B), 132.4 (CH-C11), 132.3 (CH-C11), 124.5 (CH_2-C^A), 124.5 (CH_2-C^A), 115.0 (C-C4), 114.9 (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), 73.7 (C-C8), 73.5 (C-C8), 51.3 (O$C\underline{H}_3$), 50.8 (CH_3-C19), 47.0 (CH-C1), 32.2 (CH_2-C2), 32.2 (CH_2-C2), 32.1 (CH_2-C^C), 32.0 (CH_2-C14), 32.0 (CH_2-C14), 31.3 (CH_2-C^D), 31.3 (CH_2-C^D), 30.5 (CH_2-C13), 30.4 (CH_2-C9), 24.0 (Ac-$\underline{C}H_3$), 23.5 (Ac-$\underline{C}H_3$), 22.7 (CH_2-C^E), 22.7 (CH_2-C^E), 20.5 (CH_3-C20), 18.5 (CH($\underline{C}H_3$)$_2$), 18.4 (CH($\underline{C}H_3$)$_2$), 18.1 (CH_3-C17), 18.0 (CH_3-C17), 14.1 (CH_3-C^F), 14.1 (CH_3-C^F), 13.2 ($\underline{C}H(CH_3)_2$); IR ν_{max} 3486, 2950, 2929, 2867, 1747, 1722, 1646, 1629, 1612, 1576, 1458, 1438 cm^{-1}

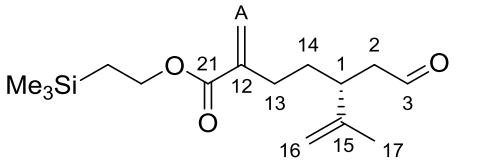
2-(Trimethylsilyl)ethyl (5*R*)-5-(2-acetoxyethyl)-6-methyl-2-methylidenehept-6-enoate 414



Chemical Formula: $C_{18}H_{32}O_4Si$
Molecular Weight: 340.5350

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, 0.021 mmol) in CH_2Cl_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_2O (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_2O, 93:7 → 9:1) afforded the ester **414** as a colourless oil (62.5 mg, 87%). $[\alpha]_D^{25}$ −3.4 (*c* = 1.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.50 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 4.83–4.80 (1H, m, CH_2-C16), 4.74–4.72 (1H, m, CH_2-C16), 4.27–4.21 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 4.08–3.92 (2H, m, CH_2-C3), 2.31–2.10 (3H, m, CH-C1, CH_2-C2), 2.03 (3H, s, Ac-C$\underline{H}_3$), 1.76–1.64 (2H, m, CH_2-C13), 1.64 (3H, dd, *J* = 1.4, 0.8 Hz, CH_3-C17), 1.56–1.48 (2H, m, CH_2-C14), 1.07–0.99 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), 0.05 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (Ac-$\underline{C}$(O)), 167.5 (C-C21), 145.7 (C-C15), 141.2 (C-C12), 124.5 (CH_2-C^A), 113.2 (CH_2-C16), 63.1 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 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-$\underline{C}H_3$), 17.8 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), −1.3 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS (ESI$^+$) calcd for $C_{18}H_{32}O_4SiNa$ $[M+Na]^+$ 363.1962, found 363.1946; IR ν_{max} 2953, 2899, 2350, 2310, 1742, 1713, 1645, 1630, 1452, 1440 cm^{-1}

2-(Trimethylsilyl)ethyl (5*R*)-6-methyl-5-(2-oxoethyl)-2-methylidenehept-6-enoate 415



Chemical Formula: $C_{16}H_{28}O_3Si$
Molecular Weight: 296.4820

To a solution of the acetate **414** (1.70 g, 4.99 mmol) in MeOH (43 mL) was added K_2CO_3 (138 mg, 0.998 mmol) and the resulting mixture was stirred at rt for 3 h. Saturated aq. NH_4Cl (50 mL) and CH_2Cl_2 (100 mL) were added and the phases were separated. The organic

phase was dried over Na_2SO_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_2Cl_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. $Na_2S_2O_3$ (25 mL). The phases were separated and the organic phase washed with saturated aq. $Na_2S_2O_3$ (2 × 25 mL), then dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purificed by silica gel column chromatography (pet. ether:EtOAc, 9:1) to deliver the aldehyde **415** as a colourless oil (1.24 g, 84%). $[\alpha]_D^{28}$ −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, $(CH_3)_3SiCH_2C\underline{H}_2O$), 2.75–2.67 (1H, m, CH-C1), 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, $(CH_3)_3SiC\underline{H}_2CH_2O$), 0.05 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{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 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 47.5 (CH-C1), 41.4 ($CH_2$-C2), 32.0 ($CH_2$-C13), 29.8 ($CH_2$-C14), 18.7 ($CH_3$-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), −1.3 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS (ESI$^+$) calcd for $C_{16}H_{28}O_3SiNa$ $[M+Na]^+$ 319.1700, found 319.1690; IR ν_{max} 2953, 2918, 2723, 1714, 1646, 1630, 1440, 1406 cm^{-1}

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

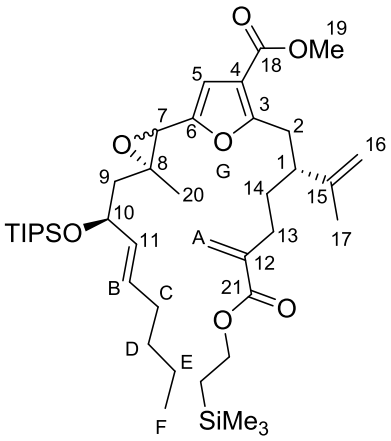
Chemical Formula: $C_{19}H_{32}O_5Si$
Molecular Weight: 368.5450

To a solution of glycine methyl ester hydrochloride (10.5 g, 83.8 mmol) in CH_2Cl_2 (28 mL) was added a solution of $NaNO_2$ (6.94 g, 101 mmol) in H_2O (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.

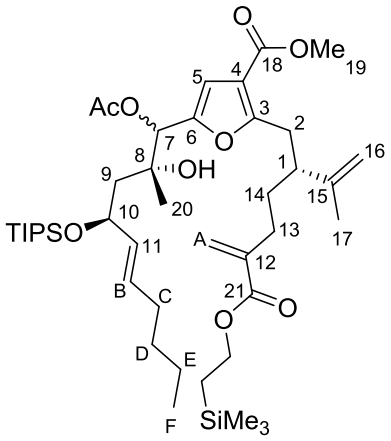
To a solution of the aldehyde **415** (1.24 g, 4.19 mmol) and $SnCl_2$ (945 mg, 4.98 mmol) in CH_2Cl_2 (40 mL) was added the freshly prepared solution of methyl diazoacetate (14 mL, 42

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** (tautomeric mixture by NMR) as a yellow oil (1.03 g, 67%). $[\alpha]_D^{29}$ +2.2 (*c* = 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.98 (0.1H, s, (OH-C3 enol), 6.11 (1H, d, *J* = 1.4 Hz, CH_2-C^A), 5.52 (0.9H, app q, *J* = 1.4 Hz, CH_2-C^A), 5.50 (0.1H, app q, *J* = 1.4 Hz, CH_2-C^A enol), 4.95 (0.1H, s, CH-C4 enol), 4.81 (1H, dq, *J* = 1.5, 1.4 Hz, CH_2-C16), 4.77–4.75 (1H, m, CH_2-C16), 4.28–4.19 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 3.73 (2.7H, s, CH_3-C19), 3.71 (0.3H, s, CH_3-C19 enol), 3.42 (1.8H, app d, *J* = 1.3 Hz, CH_2-C4), 2.71–2.55 (3H, m, CH-C1, CH_2-C2), 2.31–2.22 (1H, m, CH_2-C13), 2.19–2.10 (1H, m, CH_2-C13), 1.68–1.67 (2.7H, m, CH_3-C17), 1.66–1.64 (0.3H, m, CH_3-C17 enol), 1.57–1.49 (2H, m, CH_2-C14), 1.06–1.00 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), 0.05 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7 (C-C3), 167.7 (C-C21), 167.4 (C-C18), 145.8 (C-C15), 140.8 (C-C12), 124.7 (CH_2-C^A), 112.8 (CH_2-C16), 63.0 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 52.5 ($CH_3$-C19), 49.5 ($CH_2$-C4), 47.5 ($CH_2$-C2), 42.1 (CH-C1), 31.9 (CH_2-C13), 29.8 (CH_2-C14), 19.0 (CH_3-C17), 17.4 ($(CH_3)_3Si\underline{C}H_2CH_2O$), −1.3 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS ($ESI^+$) calcd for $C_{19}H_{32}O_5SiNa$ $[M+Na]^+$ 391.1911, found 391.1911; IR ν_{max} 2954, 2925, 2899, 2861, 1750, 1714, 1646, 1630, 1449, 1437, 1406 cm^{-1}

Methyl 5-[(3*R*)-3-methyl-3-[(2*S*,3*E*)-2-{[tris(propan-2-yl)silyl]oxy}oct-3-en-1-yl]oxiran-2-yl]-2-[(2*R*)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 417 and Methyl 5-[(2*R*,4*S*,5*E*)-1-(acetyloxy)-2-hydroxy-2-methyl-4-{[tris(propan-2-yl)silyl]oxy}dec-5-en-1-yl]-2-[(2*R*)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 418



Chemical Formula: $C_{41}H_{70}O_7Si_2$
Molecular Weight: 731.1740

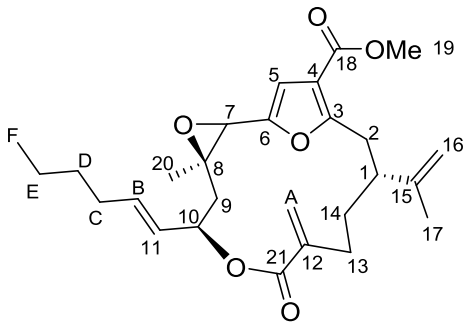


Chemical Formula: $C_{43}H_{74}O_9Si_2$
Molecular Weight: 791.2260

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 seives. 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:Et_2O, 9:1 → 8:2) to afford the epoxyfuran **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%). **Epoxyfuran 417:** ^{1}H NMR (400 MHz, C_6D_6) δ 6.71 (0.5H, s, CH-C5), 6.70 (0.5H, s, CH-C5), 6.26 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 6.25 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.62–5.44 (2H, m, CH-C11, CH-C^B), 5.36 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.33 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 4.84–4.82 (1H, m, CH_2-C16), 4.80–4.78 (0.5H, m, CH_2-C16), 4.76 (0.5H, dq, *J* = 2.9, 1.4 Hz, CH_2-C16), 4.42–4.32 (1H, m, CH-C10), 4.25–4.19 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 3.72 (0.5H, s, CH-C7), 3.50 (0.5H, s, CH-C7), 3.44 (1.5H, s, CH_3-C19), 3.43 (1.5H, s, CH_3-C19), 3.33–3.24 (1H, m, CH_2-C2), 3.14 (0.5H, dd, *J* = 14.3, 8.4 Hz, CH_2-C2), 3.03 (0.5H, dd, *J* = 14.3, 6.6 Hz, CH_2-C2), 2.88–2.75 (1H, m, CH-C1), 2.57–2.42 (1.5H, m, CH_2-C13), 2.36–2.23 (2H, m, CH_2-C^C), 2.17 (0.5H, dd, *J* = 13.7, 5.2 Hz, CH_2-C13), 2.06–1.91 (3H, m, CH_2-C9, CH_2-C14), 1.75 (1.5H, s, CH_3-C17), 1.74–1.64 (2.5H, s, CH_3-C17, CH_2-C14), 1.39 (1.5H, s, CH_3-C20), 1.38 (1.5H, s, CH_3-C20), 1.36–1.26 (4H, m, CH_2-C^D, CH_2-C^E), 1.17–1.06 (21H, m, $C\underline{H}(C\underline{H}_3)_2$), 0.92–0.86 (5H, s, CH_3-C^F, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.08 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (126 MHz, C_6D_6) 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-C^B), 131.7 (CH-C11), 131.5 (CH-C11), 124.2 (CH_2-C^A), 124.1 (CH_2-C^A), 115.2 (C-C4), 115.1 (C-C4), 113.1 (CH_2-C16), 112.9 (CH_2-C16), 109.6 (CH-C5), 72.9 (CH-C10), 72.2 (CH-C10), 62.7 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 62.2 (C-C8), 61.4 (C-C8), 58.6 (CH-C7), 58.1 (CH-C7), 50.9 (CH_3-C19), 46.9 (CH-C1), 46.8 (CH-C1), 41.4 (CH_2-C9), 32.5 (CH_2-C2), 32.4 (CH_2-C2), 32.3 (CH_2-C^C), 32.2 (CH_2-C^C), 32.1 (CH_2-C14), 31.9 (CH_2-C14), 31.7 (CH_2-C^D), 30.5 (CH_2-C13), 30.4 (CH_2-C13), 23.2 (CH_2-C^E) 22.8 (CH_3-C20), 22.7 (CH_3-C20), 18.5 ($CH(\underline{C}H_3)_2$) 18.4 ($CH(\underline{C}H_3)_2$), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 14.2 ($CH_3$-$C^F$), 12.8 ($\underline{C}H(CH_3)_2$), −1.6 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS ($ESI^+$) calcd for $C_{41}H_{70}O_7Si_2Na$ $[M+Na]^+$ 753.4552, found 753.4517; IR ν_{max} 2953, 2924, 2866, 1719, 1645, 1631, 1580, 1462, 1438 cm^{-1}. **Acetate 418:** ^{1}H NMR (500 MHz, C_6D_6) δ 6.89 (0.4H, s, CH-C5), 6.85 (0.6H, s, CH-C5), 6.27 (0.4H, d, *J* = 1.8 Hz, CH_2-C^A), 6.25 (0.6H, d, *J* = 1.7 Hz, CH_2-C^A), 6.11 (0.4H, s, CH-C7), 6.08 (0.6H, s, CH-C7), 5.61–5.48 (2H, m, CH-C11, CH-C^B), 5.37–5.34 (1H, m, CH_2-C^A), 4.80–4.70 (3H, m, CH_2-C16, CH-C10), 4.27–4.19 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 3.42 (1.8H, s, CH_3-C19), 3.42 (1.2H, s, CH_3-C19), 3.17–3.08 (1.6H, m, CH_2-C2), 3.02 (0.4H, dd, *J* = 14.2, 5.8 Hz, CH_2-C2), 2.83–2.74 (1H, m, CH-C1), 2.51–2.43 (1H, m, CH_2-C9), 2.34 (0.6H, dd, *J* = 14.5, 9.1 Hz, CH_2-C13), 2.31–2.23 (2H, m, CH_2-C9, CH_2-C13), 2.13 (0.4H, dd, *J* = 14.3, 8.9 Hz, CH_2-C13),

1.96–1.89 (2H, m, CH_2-C^C), 1.78–1.59 (8H, m, CH_2-C14, CH_3-C17, CH_3-C20), 1.55 (1.2H, s, Ac-C$\underline{H}_3$), 1.46 (1.8H, s, Ac-C$\underline{H}_3$), 1.34–1.21 (4H, m, CH_2-C^D, CH_2-C^E), 1.19–1.05 (21H, m, C$\underline{H}$(C$\underline{H}_3$)$_2$), 0.93–0.80 (5H, m, CH_3-C^F, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.08 (3.6H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$), −0.08 (5.4H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (126 MHz, C_6D_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), 150.2 (C-C6), 150.1 (C-C6), 146.4 (C-C15), 146.3 (C-C15), 141.7 (C-C12), 133.9 (CH-C^B), 133.9 (CH-C^B), 132.4 (CH-C11), 132.3 (CH-C11), 124.1 (CH_2-C^A), 114.9 (C-C4), 113.1 (CH_2-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 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 50.8 ($CH_3$-C19), 47.0 (CH-C1), 32.2 (CH_2-C2), 32.2 (CH_2-C2), 32.1 (CH_2-C^C), 32.1 (CH_2-C14), 31.3 (CH_2-C^D), 31.3 (CH_2-C^D), 30.5 (CH_2-C13), 30.5 (CH_2-C9), 24.1 (OAc-$\underline{C}H_3$), 22.7 (CH_2-C^E), 22.7 (CH_2-C^E), 20.6 (CH_3-C20), 18.5 (CH($\underline{C}H_3$)$_2$), 18.4 (CH($\underline{C}H_3$)$_2$), 18.1 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 14.1 ($CH_3$-$C^F$), 13.2 ($\underline{C}H(CH_3)_2$), −1.5 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS (ESI$^+$) calcd for $C_{43}H_{74}O_9Si_2Na$ $[M+Na]^+$ 813.4764, found 813.4727; IR ν_{max} 3489, 2952, 2925, 2867, 1745, 1716, 1644, 1630, 1613, 1573, 1462, 1439 cm^{-1}.

Methyl (4*R*,6*R*,12*R*)-6-[(1*E*)-hex-1-en-1-yl]-4-methyl-9-methylidene-8-oxo-12-(prop-1-en-2-yl)-3,7,17-trioxatricyclo[12.2.1.0^{2,4}]heptadeca-1(16),14-diene-15-carboxylate 420



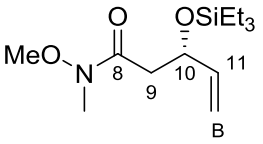
Chemical Formula: $C_{27}H_{36}O_6$
Molecular Weight: 456.5790

To a solution of the epoxyfuran **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. H_2O (0.5 mL) and Et_2O (2 mL) were added and the phases were separated. The aqueous phase was washed with Et_2O (2 × 2 mL) and the combined organic extracts were dried over Na_2SO_4 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. H_2O (30 mL) and Et_2O (20 mL) were added and the phases separated. The organic phase was washed with brine (30 mL), dried

over Na_2SO_4 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%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26}}$ −17.8 (*c* = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 6.70 (1H, s, CH-C5), 6.28 (1H, d, *J* = 1.8 Hz, CH_2-C^A), 5.69–5.62 (2H, m, CH-C10, CH-C^B), 5.29 (1H, ddt, *J* = 15.4, 7.7, 1.5 Hz, CH-C11), 5.12 (1H, d, *J* = 1.8 Hz, CH_2-C^A), 4.78 (1H, dq, *J* = 1.7 Hz, CH_2-C16), 4.75 (1H, d, *J* = 1.7 Hz, CH_2-C16), 3.45 (3H, s, CH_3-C19), 3.37 (1H, s, CH-C7), 3.33 (1H, dd, *J* = 15.3, 12.2 Hz, CH_2-C2), 3.00 (1H, dd, *J* = 15.3, 3.6 Hz, CH_2-C2), 2.74 (1H, ddt, *J* = 12.2, 8.2, 3.6 Hz, CH-C1), 2.33–2.25 (2H, m, CH_2-C9, CH_2-C13), 2.18–2.11 (2H, m, CH_2-C9, CH_2-C13), 1.87–1.81 (2H, m, CH_2-C^C), 1.78–1.70 (1H, m, CH_2-C14), 1.58–1.56 (3H, m, CH_3-C17), 1.56–1.47 (1H, m, CH_2-C14), 1.21–1.16 (4H, m, CH_2-C^D, CH_2-C^E), 1.13 (3H, s, CH_3-C20), 0.82 (3H, t, *J* = 7.0 Hz, CH_3-C^F); ^{13}C NMR (126 MHz, C_6D6) 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-C^B), 128.6 (CH-C11), 126.2 (CH_2-C^A), 115.7 (C-C4), 111.8 (CH_2-C16), 111.1 (CH-C5), 73.3 (CH-C10), 61.9 (C-C8), 58.8 (CH-C7), 51.0 (CH_3-C19), 43.9 (CH-C1), 37.6 (CH_2-C9), 32.4 (CH_2-C2), 32.1 (CH_2-C^C), 31.3 (CH_2-C^D), 30.2 (CH_2-C13), 30.0 (CH_2-C14), 23.5 (CH_3-C20), 22.5 (CH_2-C^E), 19.8 (CH_3-C17), 14.0 (CH_3-C^F); HRMS (ESI^+) calcd for $C_{27}H_{36}O_6Na$ $[M+Na]^+$ 479.2404, found 479.2386; IR ν_{max} 2952, 2925, 2860, 1719, 1644, 1630, 1610, 1577, 1440 cm^{-1}.

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

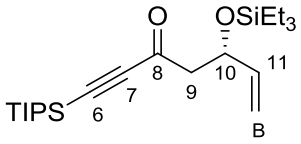


Chemical Formula: $C_{13}H_{27}NO_3Si$
Molecular Weight: 273.4480

To a solution of (3*S*)-3-hydroxy-*N*-methoxy-*N*-methylpent-4-enamide **424** (400 mg, 2.51 mmol) in CH_2Cl_2 (25 mL) was added chlorotriethylsilane (0.51 mL, 3.01 mmol) and the resulting solution was stirred at rt for 14 h. Saturated aq. NH_4Cl (30 mL) was added and the phases were separated. The organic phase was dried over Na_2SO_4 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%). $[\alpha]_D^{24}$ −16 (*c* = 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-C^B), 5.00 (1H, ddd, *J* = 10.4, 1.5, 1.5 Hz, CH_2-C^B), 4.66–4.60 (1H, m, CH-C10), 3.62 (3H, s, $NC\underline{H}_3$), 3.11 (3H, s, $OC\underline{H}_3$), 2.75 (1H, dd, *J* = 14.7, 7.8 Hz, CH_2-C9), 2.38 (1H, dd, *J* = 14.7, 5.5 Hz, CH_2-C9), 0.87 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.53 (6H, q, *J* = 7.9 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C-C8), 141.0 (CH-C11), 114.3 (CH_2-C^B), 70.7 (CH-C10), 61.5 ($OC\underline{C}H_3$)

40.8 (N<u>C</u>H$_3$), 32.1 (CH$_2$-C9), 6.9 (Si(CH$_2$<u>C</u>H$_3$)$_3$), 4.9 (Si(<u>C</u>H$_2$CH$_3$)$_3$); HRMS (ESI$^+$) calcd for $C_{13}H_{27}NO_3SiNa$ [M+Na]$^+$ 296.1652, found 296.1648; IR ν_{max} 3078, 2955, 2941, 2913, 2878, 2822, 1663, 1460, 1414 cm^{-1}

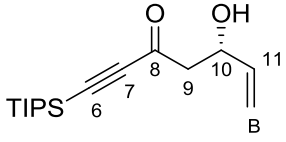
(5*S*)-5-(Triethylsilyloxy)-1-(trisisopropylsilyl)hept-6-en-1-yn-3-one 426



Chemical Formula: $C_{22}H_{42}O_2Si_2$
Molecular Weight: 394.7460

To a solution of triisopropylsilylacetylene (1.97 mL, 8.78 mmol) in THF (20 mL) at 0 °C was added *n*BuLi (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. NH_4Cl (40 mL) and Et_2O (20 mL) added. The phases were separated and the organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 100:0 → 95:5) to afford the propargylic ketone **426** as a colourless oil (2.10 g, 91%). $[\alpha]_D^{25}$ +2.8 (*c* = 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH$_2$-C^B), 5.08 (1H, ddd, *J* = 10.3, 1.4, 1.4 Hz, CH$_2$-C^B), 4.78–4.72 (1H, m, CH-C10), 2.85 (1H, dd, *J* = 14.8, 7.6 Hz, CH$_2$-C9), 2.68 (1H, dd, *J* = 14.8, 5.6 Hz, CH$_2$-C9), 1.16–1.08 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.94 (9H, t, *J* = 7.9 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 0.60 (6H, q, *J* = 7.9 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.0 (C-C8), 140.2 (CH-C11), 114.9 (CH$_2$-C^B), 104.8 (C-C6), 96.2 (C-C7), 70.3 (CH-C10), 54.4 (CH$_2$-C9), 18.6 (CH(<u>C</u>H$_3$)$_2$), 11.2 (<u>C</u>H(CH$_3$)$_2$), 6.9 (Si(CH$_2$<u>C</u>H$_3$)$_3$), 5.0 (Si(<u>C</u>H$_2$CH$_3$)$_3$); HRMS (ESI$^+$) calcd for $C_{22}H_{42}O_2Si_2Na$ [M+Na]$^+$ 417.2616, found 417.2616; IR ν_{max} 2947, 2868, 2147, 1678, 1462, 1416 cm^{-1}

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

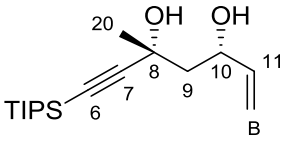


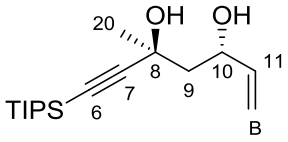
Chemical Formula: $C_{16}H_{28}O_2Si$
Molecular Weight: 280.4830

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. $NaHCO_3$ (40 mL) and EtOAc (50 mL) was then added. The phases were separated and the organic phase dried

over Na_2SO_4 and filtered. The solvent was removed under vacuum ansd the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 85:15 → 3:1) to deliver the β-hydroxy ketone **427** as a colourless oil (1.42 g, quant.). $[\alpha]_D^{26}$ −5.8 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-C^B), 5.17 (1H, ddd, *J* = 10.5, 1.4, 1.4 Hz, CH_2-C^B), 4.71–4.65 (1H, m, CH-C10), 2.85 (2H, d, *J* = 6.1 Hz, CH_2-C9), 2.57 (1H, d, *J* = 4.2 Hz, OH-C10), 1.19–1.07 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.1 (C-C8), 138.7 (CH-C11), 115.7 (CH_2-C^B), 104.2 (C-C6), 97.5 (C-C7), 68.7 (CH-C10), 52.3 (CH_2-C9), 18.6 (CH(<u>C</u>H$_3$)$_2$), 11.1 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{16}H_{28}O_2SiNa$ $[M+Na]^+$ 303.1751, found 303.1751; IR ν_{max} 3443, 2945, 2893, 2866, 2147, 1672, 1464, 1424 cm^{-1}

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



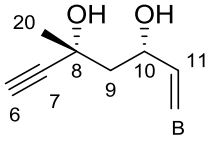


Chemical Formula: $C_{17}H_{32}O_2Si$
Molecular Weight: 296.5260

To a solution of Ti(O*i*Pr)$_4$ (27 mL, 91 mmol) in Et_2O (135 mL) at 0 °C was added $TiCl_4$ (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 Et_2O, 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 Et_2O (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 Et_2O (2 × 150 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 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**: $[\alpha]_D^{25}$ +7.0 (*c* = 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-C^B), 5.13 (1H, ddd, *J* = 10.4, 1.4, 1.4 Hz, CH_2-C^B), 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, CH_2-C9), 1.90 (1H, dd, *J* = 14.5, 3.1 Hz, CH_2-C9), 1.60 (3H, s, CH_3-C20), 1.12–0.97 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (CH-C11), 114.9, (CH_2-C^B), 111.8 (C-C6), 85.0 (C-C7), 70.3 (CH-C10), 67.6 (C-C8), 49.1 (CH_2-C9), 30.4 (CH_3-C20), 18.7 (CH(<u>C</u>H$_3$)$_2$), 11.2 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for

$C_{17}H_{32}O_2SiNa$ $[M+Na]^+$ 319.2064, found 319.2056; IR ν_{max} 3352, 2943, 2893, 2866, 2166, 1464 cm^{-1}. ***anti*-428**: $[\alpha]_D^{25}$ +8.2 (*c* = 0.11, $CHCl_3$); ^1H 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^B), 5.15 (1H, ddd, *J* = 10.4, 1.4, 1.4 Hz, CH_2-C^B), 4.92–4.86 (1H, m, CH-C10), 3.88 (1H, s, OH-C8), 2.57 (1H, d, *J* = 2.8Hz, OH-C10), 1.95–1.73 (2H, m, CH_2-C9), 1.56 (3H, s, CH_3-C20), 1.12–1.08 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4 (CH-C11), 114.6 (CH_2-C^B), 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(<u>C</u>H$_3$)$_2$), 11.2 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI^+) calcd for $C_{17}H_{32}O_2SiNa$ $[M+Na]^+$ 319.2064, found 319.2055; IR ν_{max} 3345, 2943, 2893, 2866, 2166, 1464, 1422 cm^{-1}

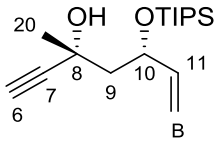
(3*S*,5*R*)-5-Methylhept-1-en-6-yne-3,5-diol *syn*-429



Chemical Formula: $C_8H_{12}O_2$
Molecular Weight: 140.1820

To a solution of the1,3-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_4Cl (50 mL) and Et_2O (50 mL) were added and the phases were separated. The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 1:1 → 55:45) to give the 1,3-diol ***syn*-429** as a yellow oil (585 mg, 89%). $[\alpha]_D^{26}$ +4.6 (*c* = 0.24, $CHCl_3$); ^1H 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^B), 5.15 (1H, ddd, *J* = 10.4, 1.4, 1.4 Hz, CH_2-C^B), 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^B), 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 $C_8H_{12}O_2Na$ $[M+Na]^+$ 163.0730, found 163.0722; IR ν_{max} 3356, 3300, 3082, 2983, 2922, 2876, 2110, 1645, 1450, 1419, 1406 cm^{-1}

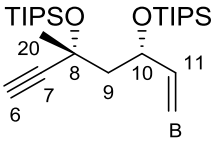
(3*S*,5*R*)-5-Methyl-3-(trisisopropylsilyloxy)hept-1-en-6-yn-5-ol 430



Chemical Formula: $C_{17}H_{32}O_2Si$
Molecular Weight: 296.5260

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 Et_2O (10 mL) were added and the phases separated. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 7:3) to afford the alkyne **430** as a yellow oil (520 mg, 98%). $[\alpha]_D^{27}$ −7.2 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (1H, ddd, *J* = 17.2, 10.3, 7.9 Hz, CH-C11), 5.27 (1H, ddd, *J* = 17.2, 1.2, 1.1 Hz, CH_2-C^B), 5.15 (1H, ddd, *J* = 10.3, 1.1, 1.0 Hz, CH_2-C^B), 4.72–4.66 (1H, m, CH-C10), 4.04 (1H, s, OH-C8), 2.48 (1H, s, CH-C6), 2.09 (1H, dd, *J* = 14.3, 5.2 Hz, CH_2-C9), 1.99 (1H, dd, *J* = 14.3, 6.7 Hz, CH_2-C9), 1.53 (3H, s, CH_3-C20), 1.13–1.03 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (CH-C11), 115.9 (CH_2-C^B), 88.2 (C-C7), 74.0 (CH-C10), 71.9 (CH-C6), 66.8 (C-C8), 49.4 (CH_2-C9), 31.1 (CH_3-C20), 18.2 (CH(<u>C</u>H$_3$)$_2$), 18.2 (CH(<u>C</u>H$_3$)$_2$), 12.5 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{17}H_{32}O_2SiNa$ $[M+Na]^+$ 319.2064, found 319.2052; IR ν_{max} 3456, 3312, 2943, 2893, 2866, 1464, 1419 cm^{-1}

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

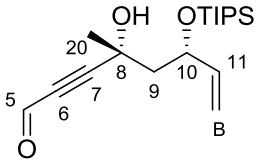


Chemical Formula: $C_{26}H_{52}O_2Si_2$
Molecular Weight: 452.8700

To a solution of 1,3-diol ***syn*-429** (39 mg, 0.28 mmol) in CH_2Cl_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 Et_2O (5 mL) were added and the phases separated. The organic phase was dried over Na_2SO_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%). $[\alpha]_D^{24}$ +25 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (1H, ddd, *J* = 17.2, 10.3, 6.9 Hz, CH-C11), 5.20 (1H, ddd, *J* = 17.2, 1.7, 1.1 Hz, CH_2-C^B), 5.01 (1H, ddd, *J* = 10.3, 1.7, 0.8 Hz, CH_2-C^B), 4.62–4.55 (1H, m, CH-C10),

2.43 (1H, s, CH-C6), 2.07 (1H, dd, *J* = 13.7, 5.5 Hz, CH_2-C9), 1.97 (1H, dd, *J* = 13.7, 6.7 Hz, CH_2-C9), 1.57 (3H, s, CH_3-C20), 1.26–0.98 (42H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (CH-C11), 113.7 (CH_2-C^B), 88.6 (C-C7), 72.5 (CH-C10), 72.2 (CH-C6), 68.5 (C-C8), 54.0 (CH_2-C9), 31.8 (CH_3-C20), 18.6 (CH(<u>C</u>H$_3$)$_2$), 18.5 (CH(<u>C</u>H$_3$)$_2$), 18.4 (CH(<u>C</u>H$_3$)$_2$), 18.3 (CH(<u>C</u>H$_3$)$_2$), 13.3 (<u>C</u>H(CH$_3$)$_2$), 12.8 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{26}H_{52}O_2Si_2Na$ [M+Na]$^+$ 475.3398, found 475.3380; IR ν_{max} 3310, 2960, 2943, 2926, 2866, 2892, 2866, 1464, 1419 cm^{-1}

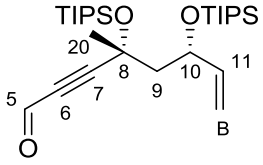
(4*R*,6*S*)-4-Hydroxy-4-methyl-6-(trisisopropylsilyloxy)oct-7-en-2-ynal 432



Chemical Formula: $C_{18}H_{32}O_3Si$
Molecular Weight: 324.5360

To a solution of alkyne **430** (100 mg, 0.337 mmol) in THF (9 mL) at −78 °C was added *n*BuLi (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. KH_2PO_4 (10 mL) and Et_2O (10 mL) was added. The phases were separated and the organic phase washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 7:3) to deliver the propargylic aldehyde **432** as a colourless oil (99 mg, 90%). $[\alpha]_D^{27}$ +8.6 (*c* = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-C^B), 5.18 (1H, ddd, *J* = 10.3, 1.2, 1.2 Hz, CH_2-C^B), 4.73 (1H, s, OH-C8), 4.72–4.67 (1H, m, CH-C10), 2.12 (2H, d, *J* = 5.2 Hz, CH_2-C9), 1.58 (3H, s, CH_3-C20), 1.11–1.04 (21H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (CHO-C5), 140.6 (CH-C11), 116.1 (CH_2-C^B), 100.3 (C-C7), 83.4 (C-C6), 74.0 (CH-C10), 67.1 (C-C8), 47.9 (CH_2-C9), 30.6 (CH_3-C20), 18.1 (CH(<u>C</u>H$_3$)$_2$), 18.0 (CH(<u>C</u>H$_3$)$_2$), 12.3 (<u>C</u>H(CH$_3$)$_2$); HRMS (ESI$^+$) calcd for $C_{18}H_{32}O_3SiNa$ [M+Na]$^+$ 347.2013, found 347.1903; IR ν_{max} 3446, 2943, 2893, 2866, 2206, 1670, 1464, 1419 cm^{-1}

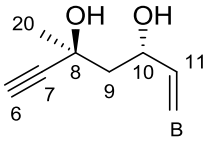
(4*R*,6*S*)-4,6-Bis(trisisopropylsilyloxy)-4-methyloct-7-en-2-ynal 433



Chemical Formula: $C_{27}H_{52}O_3Si_2$
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 *n*BuLi (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. KH_2PO_4 (2 mL) and Et_2O (2 mL) was added. The phases were separated and the organic phase washed with brine (5 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 95:5) to give the propargylic aldehyde **433** as a colourless oil (91 mg, 97%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{27}}$ −21 (*c* = 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2-C^B), 5.05 (1H, ddd, *J* = 10.2, 1.5, 0.8 Hz, CH_2-C^B), 4.56–4.49 (1H, m, CH-C10), 2.13 (1H, dd, *J* = 13.8, 5.6 Hz, CH_2-C9), 2.04 (1H, dd, *J* = 13.8, 6.6 Hz, CH_2-C9), 1.64 (3H, s, CH_3-C20), 1.20–1.02 (42H, m, C<u>H</u>(C<u>H</u>$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4 (CHO-C5), 142.1 (CH-C11), 114.7 (CH_2-C^B), 100.8 (C-C7), 83.9 (C-C6), 72.0 (CH-C10), 68.5 (C-C8), 53.4 (CH_2-C9), 31.0 (CH_3-C20), 18.5 (CH(<u>C</u>H$_3$)$_2$), 18.4 (CH(<u>C</u>H$_3$)$_2$), 18.3 (CH(<u>C</u>H$_3$)$_2$), 18.3 (CH(<u>C</u>H$_3$)$_2$), 13.3 (<u>C</u>H(CH$_3$)$_2$), 12.8 (<u>C</u>H(CH$_3$)$_2$); IR ν_{max} 2945, 2893, 2868, 2210, 1674, 1464, 1421 cm^{-1}

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

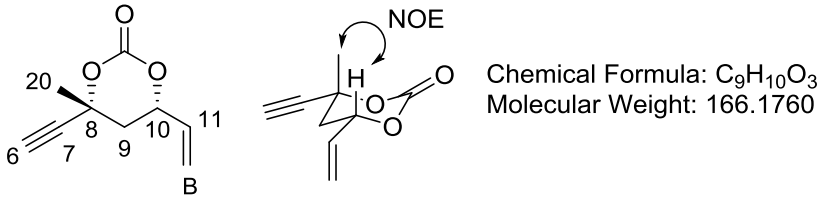


Chemical Formula: $C_8H_{12}O_2$
Molecular Weight: 140.1820

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. NH_4Cl (5 mL) and Et_2O (5 mL) were added and the phases were separated. The organic phase was washed with brine (5 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether:Et_2O, 1:1) to give the corresponding *anti* 1,3-diol ***anti*-429** as a colourless oil (37 mg, 78%). $[\alpha]_D^{31}$ +16 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-C^B), 5.11 (1H, ddd, *J* = 10.4, 1.4, 1.3 Hz, CH_2-C^B), 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, CH_2-C9), 1.50 (3H, s, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (CH-C11), 114.9 (CH_2-C^B), 87.0 (C-C7), 72.1 (CH-C6), 72.1 (CH-C10), 68.3 (C-C8), 47.5 (CH_2-C9), 31.0 (CH_2-C20); HRMS

(ESI$^+$) calcd for $C_8H_{12}O_2Na$ $[M+Na]^+$ 163.0730, found 163.0736; IR ν_{max} 3358, 3294, 3078, 2983, 2915, 2874, 2110, 1653, 1423, 1419 cm^{-1}

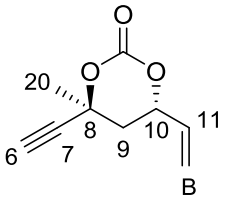
(4*R*,6*S*)-4-Ethynyl-4-methyl-6-vinyl-1,3-dioxan-2-one 434



Chemical Formula: $C_9H_{10}O_3$
Molecular Weight: 166.1760

To a solution of diol ***syn*-429** (27 mg, 0.19 mmol) in CH_2Cl_2 (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_2Cl_2 (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_4Cl (5 mL) was added and the mixture stirred vigorously for 10 min. The biphasic mixture was separated and the aq. phase washed with CH_2Cl_2 (5 mL). Combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent removed under vacuum to yield the cyclic carbonate **434** as a pale yellow oil (31.5 mg, 98%). $[\alpha]_D^{30}$ +40 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, ddd, *J* = 17.2, 10.6, 6.1 Hz, CH-C11), 5.44 (1H, ddd, *J* = 17.2, 1.4, 0.7 Hz, CH_2-C^B), 5.36–5.32 (1H, m, CH_2-C^B), 4.96–4.89 (1H, m, CH-C10), 2.69 (1H, s, CH-C6), 2.35–2.24 (2H, m, CH_2-C9), 1.77 (3H, s, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (O<u>C</u>(O)O), 133.8 (CH-C11), 119.1 (CH_2-C^B), 82.7 (C-C7), 75.9 (CH-C6), 75.1 (C-C8), 74.8 (CH-C10), 38.7 (CH_2-C9), 28.0 (CH_3-C20); HRMS (ESI$^+$) calcd for $C_9H_{10}O_3Na$ $[M+Na]^+$ 189.0522, found 189.0523; IR ν_{max} 3287, 2994, 2916, 2847, 1751, 1736, 1651, 1543, 1435 cm^{-1}

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

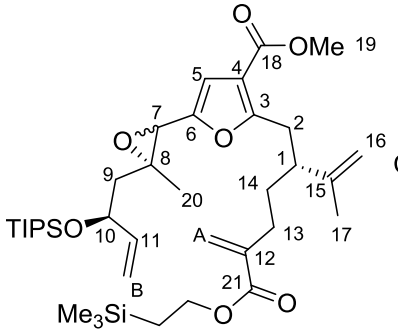


Chemical Formula: $C_9H_{10}O_3$
Molecular Weight: 166.1760

To a solution of diol ***anti*-429** (37 mg, 0.26 mmol) in CH_2Cl_2 (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_2Cl_2 (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_4Cl (6 mL) was added and the mixture stirred vigorously for 10 min. The biphasic mixture was separated and the aq. phase washed with CH_2Cl_2 (5 mL). Combined organic extracts were washed with brine (10 mL),

dried over Na_2SO_4, filtered and the solvent removed under vacuum to yield the cyclic carbonate **435** as a pale yellow oil (43.3 mg, 99%). $[\alpha]_D^{30}$ +25 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_2-C^B), 5.34–5.30 (1H, m, CH_2-C^B), 5.28–5.21 (1H, m, CH-C10), 2.73 (1H, s ,CH-C6), 2.25 (1H, dd, *J* = 14.2, 3.2 Hz, CH_2-C9), 1.91 (1H, dd, *J* = 14.2, 12.0 Hz, CH_2-C9), 1.70 (3H, s, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (O<u>C</u>(O)O), 133.9 (CH-C11), 118.8 (CH_2-C^B), 81.6 (C-C7), 77.5 (CH-C6), 75.9 (C-C8), 74.8 (CH-C10), 39.3 (CH_2-C9), 28.8 (CH_3-C20); HRMS (ESI$^+$) calcd for $C_9H_{10}O_3Na$ $[M+Na]^+$ 189.0522, found 189.0529; IR ν_{max} 3256, 2994, 2916, 2847, 2121, 1751, 1736, 1651, 1535, 1427 cm^{-1}

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

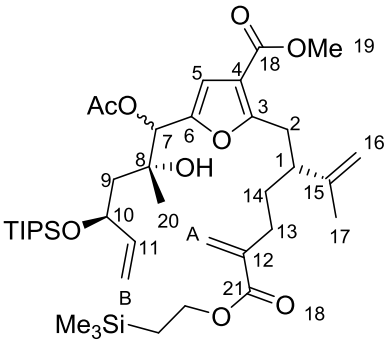


Chemical Formula: $C_{37}H_{62}O_7Si_2$
Molecular Weight: 675.0660

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 seives. 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:Et_2O, 9:1) to afford the epoxyfuran **436** (1:1 mixture of diastereoisomers) as a colourless oil (84 mg, 62%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.69 (1H, s, CH-C5), 6.26 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 6.24 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.88–5.67 (1H, m, CH-C11), 5.35 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.32 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.15 (0.5H, d, *J* = 17.3 Hz, CH_2-C^B), 5.10 (0.5H, d, *J* = 17.3 Hz, CH_2-C^B), 5.01 (0.5H, d, *J* = 10.0 Hz, CH_2-C^B), 4.94 (0.5H, d, *J* = 10.0 Hz, CH_2-C^B), 4.81 (1H, s, CH_2-C16), 4.75 (0.5H, s, CH_2-C16), 4.74 (0.5H, s, CH_2-C16), 4.41–4.28 (1H, m, CH-C10), 4.24–4.18 (2H, m, $(CH_3)_3SiCH_2C\underline{H_2}O$), 3.70 (0.5H, s, CH-C7), 3.49 (0.5H, s, CH-C7), 3.43 (1.5H, s, CH_3-C19), 3.42 (1.5H, s, CH_3-C19), 3.26–3.16 (1.5H, m, CH_2-C2), 3.08 (0.5H, dd, *J* = 14.3, 6.4 Hz, CH_2-C2), 2.87–2.73 (1H, m, CH-C1), 2.54–2.41 (1H, m, CH_2-C13), 2.34–2.22 (1.5H, m, CH_2-C13, CH_2-C9), 2.12 (0.5H, dd, *J* = 13.8, 5.1 Hz, CH_2-C9), 1.96 (0.5H, dd, *J* = 13.8, 8.3 Hz, CH_2-C9), 1.74 (1.5H, s, CH_3-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, C<u>H</u>(C<u>H</u>$_3$)$_2$), 0.91–0.85 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.09 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (101 MHz, C_6D_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^A), 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 ($(CH_3)_3SiCH_2C\underline{H}_2O$), 62.0 (C-C8), 61.2 (C-C8), 58.6 (CH-C7), 58.0 (CH-C7), 50.9 (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(<u>C</u>H$_3$)$_2$), 18.4 (CH(<u>C</u>H$_3$)$_2$), 18.2 (CH_3-C17), 18.2 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 12.7 (<u>C</u>H(CH$_3$)$_2$), −1.6 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS (ESI$^+$) calcd for $C_{37}H_{62}O_7Si_2Na$ $[M+Na]^+$ 697.3926, found 697.3898; IR ν_{max} 2947, 2928, 2894, 2866, 1717, 1645, 1630, 1617, 1579, 1439 cm^{-1}

Methyl 5-[(2*R*,4*S*)-1-(acetyloxy)-2-hydroxy-2-methyl-4-{[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 437

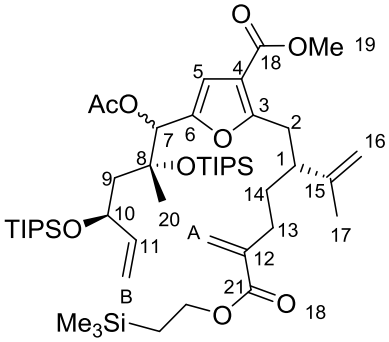


Chemical Formula: $C_{39}H_{66}O_9Si_2$
Molecular Weight: 735.1180

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 THT (1 mL) in the presence of 4 Å molecular seives. 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_6D_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^A), 5.34 (0.6H, d, *J* = 1.7 Hz, CH_2-C^A), 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^B), 4.74 (2H, m, CH_2-C16), 4.72–4.63 (1H, m, CH-C10), 4.25–4.18 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 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-$C\underline{H}_3$), 1.71 (1.8H, s, Ac-$C\underline{H}_3$), 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, $C\underline{H}(C\underline{H}_3)_2$), 0.91– 0.85 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.09 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (101 MHz, C_6D_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^A), 115.4 (CH_2-C^B), 115.3 (CH_2-C^B), 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 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 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_3-C20), 24.1 (CH_3-C20), 20.5 (Ac-$\underline{C}H_3$), 18.4 ($CH(\underline{C}H_3)_2$), 18.4 ($CH(\underline{C}H_3)_2$), 18.1 (CH_3-C17), 18.1 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 13.1 ($\underline{C}H(CH_3)_2$), −1.5 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS (ESI$^+$) calcd for $C_{39}H_{66}O_9Si_2Na$ $[M+Na]^+$ 757.4138, found 757.4108; IR ν_{max} 3485, 3074, 2948, 2894, 2867, 1748, 1718, 1645, 1630, 1613, 1573, 1456, 1439 cm^{-1}

Methyl 5-[(2*R*,4*S*)-1-(acetyloxy)-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

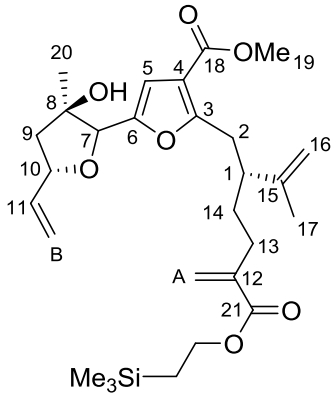


Chemical Formula: $C_{48}H_{86}O_9Si_3$
Molecular Weight: 891.4620

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%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.92 (0.6H, s, CH-C5), 6.92 (0.4H, s, CH-C5), 6.30–6.26 (1H, m, CH_2-C^A), 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, CH_2-C^A), 5.27 (0.6H, dd, *J* = 17.3, 1.5 Hz, CH_2-C^B), 5.16 (0.4H, dd, *J* = 17.3, 1.4 Hz, CH_2-C^B), 5.08 (0.6H, dd, *J* = 10.2, 1.5 Hz, CH_2-C^B), 4.98 (0.4H, dd, *J* = 10.1, 1.4 Hz, CH_2-C^B), 4.85 (0.6H, d, *J* = 2.2 Hz, CH_2-C16), 4.83 (0.4H, d, *J* = 2.2 Hz, CH_2-C16), 4.83–4.79 (0.6H, m, CH_2-C16), 4.81–4.76 (0.4H, m, CH_2-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, $(CH_3)_3SiCH_2C\underline{H}_2O$), 3.46 (1.2H, s, CH_3-C19), 3.43 (1.8H, s, CH_3-C19), 3.33 (0.6H, dd, *J* = 14.3, 9.1 Hz, CH_2-C2), 3.24 (0.4H, dd, *J* = 14.3, 6.4 Hz, CH_2-C2), 3.15 (0.4H, dd, *J* = 14.3, 8.8 Hz, CH_2-C2), 3.05 (0.6H, dd, *J* = 14.3, 6.2 Hz, CH_2-C2), 2.88–2.80 (1H, m, CH-C1), 2.55–2.47 (1H, m, CH_2-C13), 2.37 (0.6H, dd, *J* = 14.3, 5.7 Hz, CH_2-C9), 2.34–2.25 (1.4H, m, CH_2-C9, CH_2-C13), 2.25–2.16 (1H, m, CH_2-C9), 1.78 (1.2H, s, Ac-C$\underline{H}_3$), 1.77 (1.8H, s, Ac-C$\underline{H}_3$), 1.75 (3H, s, CH_3-C17), 1.74–1.59 (2H, m, CH_2-C14), 1.55 (1.2H, s, CH_3-C20), 1.53 (1.8H, s, CH_3-C20), 1.25–1.07 (42H, s, $C\underline{H}(C\underline{H}_3)_2$), 0.93–0.86 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.08 (5.4H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$), −0.08 (3.6H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (126 MHz, C_6D_6) 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 (CH_2-C^A), 115.6 (CH_2-C^B), 115.2 (CH_2-C^B), 115.0 (C-C4), (CH-C7), 115.0 (C-C4), 113.2 (CH_2-C16), 113.2 (CH_2-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 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 62.7 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 50.9 ($CH_3$-C19), 49.6 (CH-C1) 49.5 (CH-C1), 47.2 (CH_2-C9), 47.0 (CH_2-C9), 32.4 (CH_2-C2), 32.4 (CH_2-C2), 32.2 (CH_2-C14), 32.2 (CH_2-C14), 30.5 (CH_2-C13), 26.2 (CH_3-C20), 26.0 (CH_3-C20), 20.6 (Ac-$\underline{C}H_3$), 20.6 (Ac-$\underline{C}H_3$), 18.7 ($CH(\underline{C}H_3)_2$), 18.7 ($CH(\underline{C}H_3)_2$), 18.6 ($CH(\underline{C}H_3)_2$), 18.6 ($CH(\underline{C}H_3)_2$), 18.6 ($CH(\underline{C}H_3)_2$), 18.6 ($CH(\underline{C}H_3)_2$), 18.5 ($CH(\underline{C}H_3)_2$), 18.5 ($CH(\underline{C}H_3)_2$), 18.2 (CH_3-C17), 18.1 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), 14.1 ($\underline{C}H(CH_3)_2$), 14.0 ($\underline{C}H(CH_3)_2$), 13.2 ($\underline{C}H(CH_3)_2$), 13.1 ($\underline{C}H(CH_3)_2$), −1.6 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS ($ESI^+$) calcd for $C_{48}H_{86}O_9Si_3Na$ $[M+Na]^+$ 913.5467, found 913.5427; IR ν_{max} 2945, 2893, 2866, 1749, 1720, 1645, 1631, 1612, 1574, 1464, 1441 cm^{-1}

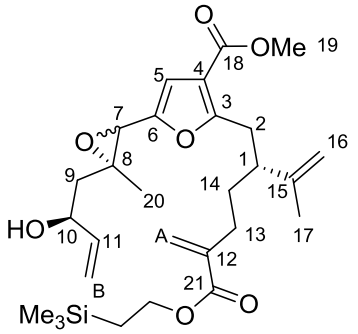
Methyl 5-[(3*R*,5*S*)-5-ethenyl-3-hydroxy-3-methyloxolan-2-yl]-2-[(2*R*)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 440



Chemical Formula: $C_{28}H_{42}O_7Si$
Molecular Weight: 518.7220

^{1}H NMR (400 MHz, C_6D_6) δ 6.63 (1H, s, CH-C5), 6.26 (1H, s, CH_2-C^A), 5.99 (1H, ddd, *J* = 17.0, 10.4, 6.5 Hz, CH-C11), 5.34 (1H, s, CH_2-C^A), 5.29 (1H, dd, *J* = 17.0, 1.6 Hz, CH_2-C^B), 5.05 (1H, dd, *J* = 10.4, 1.6 Hz, CH_2-C^B), 4.82–4.70 (4H, m, CH_2-C16, CH-C7, CH-C10), 4.28–4.19 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 3.45 (3H, s, CH_3-C19), 3.19–3.05 (2H, m, CH_2-C2), 2.81–2.69 (1H, m, CH-C1), 2.54–2.43 (1H, m, CH_2-C13), 2.34–2.24 (1H, CH_2-C13), 1.81–1.60 (7H, m, CH_2-C9, CH_2-C14, CH_3-C17), 1.38 (3H, s, CH_3-C20), 0.96–0.86 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.09 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (101 MHz, C_6D6) δ 167.0 (C-C21), 164.1 (C-C18), 161.7 (C-C3), 153.0 (C-C6), 146.3 (C-C15), 141.7 (C-C12), 139.2 (CH-C11), 124.3 (CH_2-C^A), 115.7 (CH_2-C^B), 114.7 (C-C4), 113.1 (CH_2-C16), 108.6 (CH-C5), 85.2 (CH-C7), 81.3 (C-C8), 79.8 (CH-C10), 62.8 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 50.9 ($CH_3$-C19), 47.1 (CH-C1), 46.3 (CH_2-C9), 32.3 (CH_2-C2), 32.2 (CH_2-C14), 30.5 (CH_3-C20), 30.2 (CH_2-C13), 18.2 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), −1.6 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS ($ESI^+$) calcd for $C_{28}H_{42}O_7SiNa$ $[M+Na]^+$ 541.2592, found 541.2574; IR ν_{max} 3481, 3078, 2949, 2926, 2856, 1719, 1647, 1629, 1613, 1577, 1457, 1437 cm^{-1}

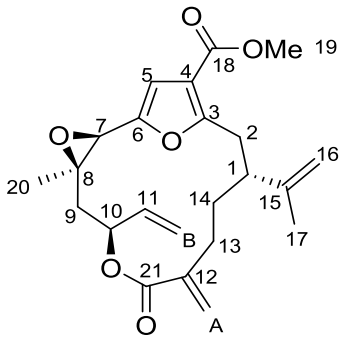
Methyl 5-[(3*R*)-3-[(2*S*)-2-hydroxybut-3-en-1-yl]-3-methyloxiran-2-yl]-2-[(2*R*)-5-methylidene-6-oxo-2-(prop-1-en-2-yl)-6-[2-(trimethylsilyl)ethoxy]hexyl]furan-3-carboxylate 441



Chemical Formula: $C_{28}H_{42}O_7Si$
Molecular Weight: 518.7220

^{1}H NMR (500 MHz,C_6D_6) δ 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^A), 6.24 (0.5H, d, *J* = 1.7 Hz, CH_2-C^A), 5.71–5.62 (1H, m, CH-C11), 5.34–5.32 (1H, m , CH_2-C^A), 5.19 (0.5H, dt, *J* = 17.2, 1.6 Hz, CH_2-C^B), 5.18 (0.5H, dt, *J* = 17.2, 1.6 Hz, CH_2-C^B), 4.96 (0.5H, dt, *J* = 10.4, 1.5 Hz, CH_2-C^B), 4.93 (0.5H, dt, *J* = 10.4, 1.5 Hz, CH_2-C^B), 4.80–4.74 (3H, CH_2-C16, CH-C10) 4.24–4.18 (2H, m, $(CH_3)_3SiCH_2C\underline{H}_2O$), 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), 2.52–2.40 (1H, m, CH_2-C13), 2.34–2.24 (1H, m, CH_2-C13), 1.86 (0.5H, dd, *J* = 14.2, 9.0 Hz, CH_2-C9), 1.75–1.60 (6H, m, CH_2-C9, CH_2-C14, CH_3-C17), 1.53 (0.5H, dd, *J* = 14.2, 4.3 Hz, CH_2-9), 1.25 (1.5H, s, CH_3-C20), 1.19 (1.5H, s, CH_3-C20), 0.92–0.84 (2H, m, $(CH_3)_3SiC\underline{H}_2CH_2O$), −0.09 (9H, s, $(C\underline{H}_3)_3SiCH_2CH_2O$); ^{13}C NMR (126 MHz, C_6D6) δ 167.0 (C-C21), 166.9 (C-C21), 163.9 (C-C18), 163.8 (C-C18), 162.1 (C-C3), 162.0 (C-C3), 149.3 (C-C6), 149.1 (C-C6), 146.4 (C-C15), 146.4 (C-C15), 141.7 (C-C12), 141.7 (C-C12), 141.3 (CH-C11), 141.2 (CH-C11), 124.4 (CH_2-C^A), 124.2 (CH_2-C^A), 115.2 (C-C4), 115.1 (C-C4), 114.1 (CH_2-C^B), 114.1 (CH_2-C^B), 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 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 62.8 ($(CH_3)_3SiCH_2\underline{C}H_2O$), 62.8 (C-C8), 62.4 (C-C8), 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_2-C2), 32.0 (CH_2-C14), 31.9 (CH_2-C14), 30.5 (CH_2-C13), 30.5 (CH_2-C13), 22.4 (CH_3-C20), 18.3 (CH_3-C17), 18.2 (CH_3-C17), 17.5 ($(CH_3)_3Si\underline{C}H_2CH_2O$), −1.56 ($(\underline{C}H_3)_3SiCH_2CH_2O$); HRMS ($ESI^+$) calcd for $C_{28}H_{42}O_7SiNa$ $[M+Na]^+$ 541.2592, found 541.2575; IR ν_{max} 3493, 2953, 2928, 2857, 1717, 1645, 1631, 1614, 1578, 1441 cm^{-1}

Methyl (2*R*,4*R*,6*S*,12*R*)-6-ethenyl-4-methyl-9-methylidene-8-oxo-12-(prop-1-en-2-yl)-3,7,17-trioxatricyclo[12.2.1.$0^{2,4}$]heptadeca-1(16),14-diene-15-carboxylate 421



Chemical Formula:
$C_{23}H_{28}O_6$
Molecular Weight:
400.4710

Macrolactonisation under Yamaguchi conditions

To a solution of the epoxyfuran **438** (35 mg, 50 µmol) in THF (0.25 mL) at 10 °C 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. H_2O (0.5 mL) and Et_2O (2 mL) were added and the phases were separated. The aqueous phase was washed with Et_2O (2 × 2 mL) and the combined organic extracts were dried over Na_2SO_4 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. H_2O (30 mL) and EtOAc (20 mL) were added and the phases separated. The organic phase was washed with brine (30 mL), dried over Na_2SO_4 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%).

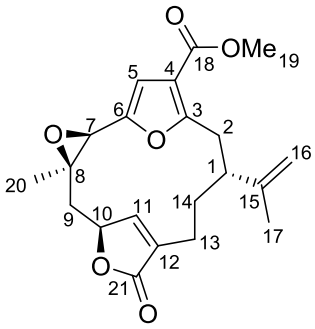
Macrolactonisation under Corey-Nicolaou conditions

To a solution of epoxy-furan **438** (16.5 mg, 24 µmol) in THF (0.1 mL) at 10 °C was added TBAF (0.05 mL of a 1 M solution in THF, 50 µmol) and the resulting solution was stirred for 3 h. H_2O (0.2 mL) and Et_2O (2 mL) were added and the phases separated. The aqueous phase was washed with Et_2O (2 × 1 mL) and the combined organic extracts dried over Na_2SO_4, 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%). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ −15 (*c* = 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 6.65 (1H, s, CH-C5), 6.25 (1H, d, *J* = 1.9 Hz, CH_2-C^A), 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_2-C^B) 5.13–5.11 (1H, m, CH_2-C^A), 4.92 (1H, ddd, *J* = 10.4, 1.3, 1.3 Hz, CH_2-C^B), 4.79 (1H, dq, *J* = 1.8, 1.5 Hz, CH_2-C16), 4.77–4.75 (1H, m, CH_2-C16), 3.44 (3H, s, CH_3-C19), 3.33 (1H, s, CH-C7), 3.20 (1H, dd, *J* = 15.1, 11.9 Hz, CH_2-C2), 3.06 (1H, dd, *J* = 15.1, 3.7 Hz, CH_2-C2), 2.71 (1H, dddd, *J* = 11.9, 8.2, 4.2, 3.7 Hz, CH-C1), 2.32–2.24 (1H, m, CH_2-C13), 2.17–2.07 (2H, m, CH_2-C9, CH_2-C13), 1.98 (1H, dd, *J* = 14.9, 5.0 Hz, CH_2-C9), 1.71–1.68 (1H, m, CH_2-C14), 1.58 (3H, s, CH_3-C17), 1.57–1.49 (1H, m, CH_2-C14), 1.07 (3H, s, CH_3-C20); ^{13}C NMR (101 MHz, C_6D_6) δ 166.0 (C-C21), 163.7 (C-C18), 161.8 (C-C3), 148.7 (C-C6), 147.1 (C-C15), 140.8 (C-C12), 137.0 (CH-C11), 126.3 (CH_2-C^A), 116.4 (CH_2-C^B), 115.5 (C-C4), 111.6 (CH_2-C16), 110.9 (CH-C5), 72.6 (CH-C10), 61.8 (C-C8), 58.7 (CH-C7), 51.0 (CH_3-C19), 43.6 (CH-C1), 37.0 (CH_2-C9), 32.3 (CH_2-C2), 30.2 (CH_2-C14), 29.6 (CH_2-C13), 23.6 (CH_3-C20), 20.0 (CH_3-C17); HRMS (ESI^+) calcd for $C_{23}H_{28}O_6Na$ $[M+Na]^+$ 423.1778, found 423.1766; IR ν_{max} 2953, 2924, 2852, 1720, 1643, 1631, 1609, 1578, 1441 cm^{-1}

7-*epi*-Pukalide 443

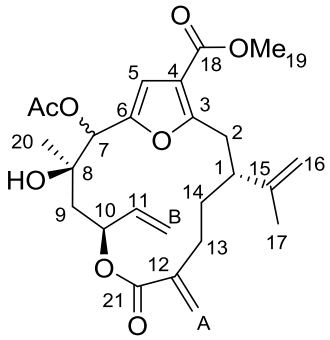


Chemical Formula: $C_{21}H_{24}O_6$
Molecular Weight: 372.4170

The macrolactone **421** (5.0 mg, 12 µmol) and the ruthenium catalyst **442** (1.0 mg, 1.2 µmol) were dissolved in degassed CH_2Cl_2 (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%). $[\alpha]_D^{27}$ +31 (*c* = 0.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (1H, s, CH-C5), 6.42 (1H, d, *J* = 1.8 Hz, CH-C11), 5.00 (1H, br d, *J* = 12.2 Hz, CH-C10), 4.86 (1H, q, *J* = 1.6 Hz, CH_2-C16), 4.79 (1H, s, CH_2-C16), 3.85 (3H, s, CH_3-C19), 3.72 (1H, s, CH-C7), 3.47 (1H, dd, *J* = 14.8, 12.6 Hz, CH_2-C2), 2.87 (1H, dd, *J* = 12.6, 3.4 Hz, CH_2-C9), 2.69 (1H, dd, *J* = 14.8, 3.5 Hz, CH_2-C2), 2.37 (1H, ddd, *J* = 15.5, 13.2, 3.4 Hz, CH_2-C13), 2.17–2.04 (2H, m, CH-C1, CH_2-C13), 2.01 (1H, app t, *J* = 12.6 Hz, CH_2-C9), 1.79–1.74 (1H, m, CH_2-C14), 1.74 (3H, s,

CH_3-C17), 1.58 (3H, s, CH_2-C20), 1.30–1.22 (1H, m, CH_2-C14); ^{13}C NMR (126 MHz, $CDCl_3$) 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 (CH_2-C16), 77.9 (CH-C10), 60.9 (C-C8), 57.8 (CH-C7), 51.8 (CH_3-C19), 43.7 (CH-C1), 40.5 (CH_2-C9), 31.7 (CH_2-C2), 30.0 (CH_2-C14), 23.3 (CH_3-C20), 20.6 (CH_2-C13), 19.3 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{21}H_{24}O_6Na$ $[M+Na]^+$ 395.1465, found 395.1448; IR ν_{max} 2953, 2924, 1757, 1718, 1647, 1612, 1578, 1443 cm^{-1}

Methyl (3*R*,5*S*,11*R*)-2-(acetyloxy)-5-ethenyl-3-hydroxy-3-methyl-8-methylidene-7-oxo-11-(prop-1-en-2-yl)-6,16-dioxabicyclo[11.2.1]hexadeca-1(15),13-diene-14-carboxylate 445



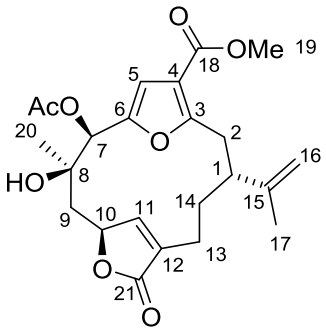
Chemical Formula: $C_{25}H_{32}O_8$
Molecular Weight: 460.5230

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. NH_4Cl were added and the mixture stirred for 10 min. The solution was diluted with Et_2O (10 mL), dried over Na_2SO_4 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 Na_2SO_4 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%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.77 (0.35H, s, CH-C5), 6.74 (0.65H, s, CH-C5), 6.27 (0.35H, d, *J* = 2.1 Hz, CH_2-C^A), 6.19 (0.65H, d, *J* = 1.9 Hz, CH_2-C^A), 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

(0.7H, m, CH-C7, CH-C11), 5.21 (0.65H, dt, *J* = 17.1, 1.4 Hz, CH_2-C^B), 5.17 (0.35H, dt, *J* = 17.1, 1.4 Hz, CH_2-C^B), 5.18–5.16 (0.35H, m, CH_2-C^A), 5.14–5.12 (0.65H, m, CH_2-C^A), 4.98–4.92 (1H, m, CH_2-C^B), 4.78–4.76 (1H, m, CH_2-C16), 4.70–4.68 (0.65H, m, CH_2-C16), 4.68–4.66 (0.35H, m, CH_2-C16), 3.42 (1.95H, s, CH_3-C19), 3.42 (1.05H, s, CH_3-C19), 3.16 (1H, dd, *J* = 15.1, 11.5 Hz, CH_2-C2), 3.04 (1H, dd, *J* = 15.1, 3.6 Hz, CH_2-C2), 2.68–2.61 (1.65H, m, CH-C1, OH-C8), 2.58 (0.35H, s, OH-C8), 2.31–2.22 (1H, m, CH_2-C13), 2.19 (1H, dd, *J* = 15.7, 6.2 Hz, CH_2-C9), 2.12–1.98 (1H, m, CH_2-C13), 1.86 (1H, dd, *J* = 15.7, 3.4 Hz, CH_2-C9), 1.73–1.69 (0.65H, m, CH_2-C14) 1.67 (1.05H, s, OAc-C$\underline{H}_3$), 1.66–1.63 (0.35H, m, CH_2-C14), 1.56–1.55 (5.95H, m, CH_2-C14, CH_3-C17, OAc-C$\underline{H}_3$), 1.20 (1.95H, s, CH_3-C20), 1.09 (1.05H, s, CH_3-C20); ^{13}C NMR (126 MHz, C_6D_6) δ 169.7 (Ac-C=O), 169.0 (Ac-C=O), 167.0 (C-C21), 166.5 (C-C21), 163.7 (C-C18), 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-C15), 140.6 (C-C12), 140.3 (C-C12), 138.0 (CH-C11), 137.8 (CH-C11), 127.4 (CH_2-C^A), 126.6 (CH_2-C^A), 115.6 (CH_2-C^B), 115.4 (CH_2-C^B), 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), 73.2 (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-$\underline{C}H_3$), 20.2 (Ac-$\underline{C}H_3$), 19.6 (CH_3-C17), 19.5 (CH_3-C17); HRMS (ESI$^+$) calcd for $C_{25}H_{32}O_8Na$ $[M+Na]^+$ 483.1989, found 483.1979; IR ν_{max} 3487, 2953, 2924, 2855, 2365, 2343, 2328, 1725, 1719, 1647, 1611, 1570, 1439 cm^{-1}

7-Acetylsinumaximol B 16



Chemical Formula: $C_{23}H_{28}O_8$
Molecular Weight: 432.4690

To a solution of macrolactone **445** (4.5 mg, 9.8 µmol) in degassed CH_2Cl_2 (0.5 mL) was added a solution of the ruthenium catalyst **442** (0.8 mg, 1.0 µmol) in degassed CH_2Cl_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

7-acetylsinumaximol B (**16**) as a white solid (1.1 mg, 25%). $[\alpha]_D^{27}$ −38 (*c* = 0.080, $CHCl_3$) {lit. $[\alpha]_D^{25}$ −56.0 (*c* = 0.6, $CHCl_3$)}[1]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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), 2.17–2.06 (4H, m, CH_2-C13, Ac-C<u>H</u>$_3$), 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, $CDCl_3$) δ 173.3 (Ac-C=O), 169.6 (C-C21), 163.8 (C-C18), 161.3 (C-C3), 149.5 (C-C6), 148.3 (CH-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-<u>C</u>H_3), 21.2 (CH_3-C20), 19.2 (CH_3-C17); HRMS (ESI^+) calcd for $C_{23}H_{28}O_8Na$ $[M+Na]^+$ 455.1676, found 455.1664; IR ν_{max} 3464, 2924, 1755, 1722, 1610, 1572, 1443 cm^{-1}

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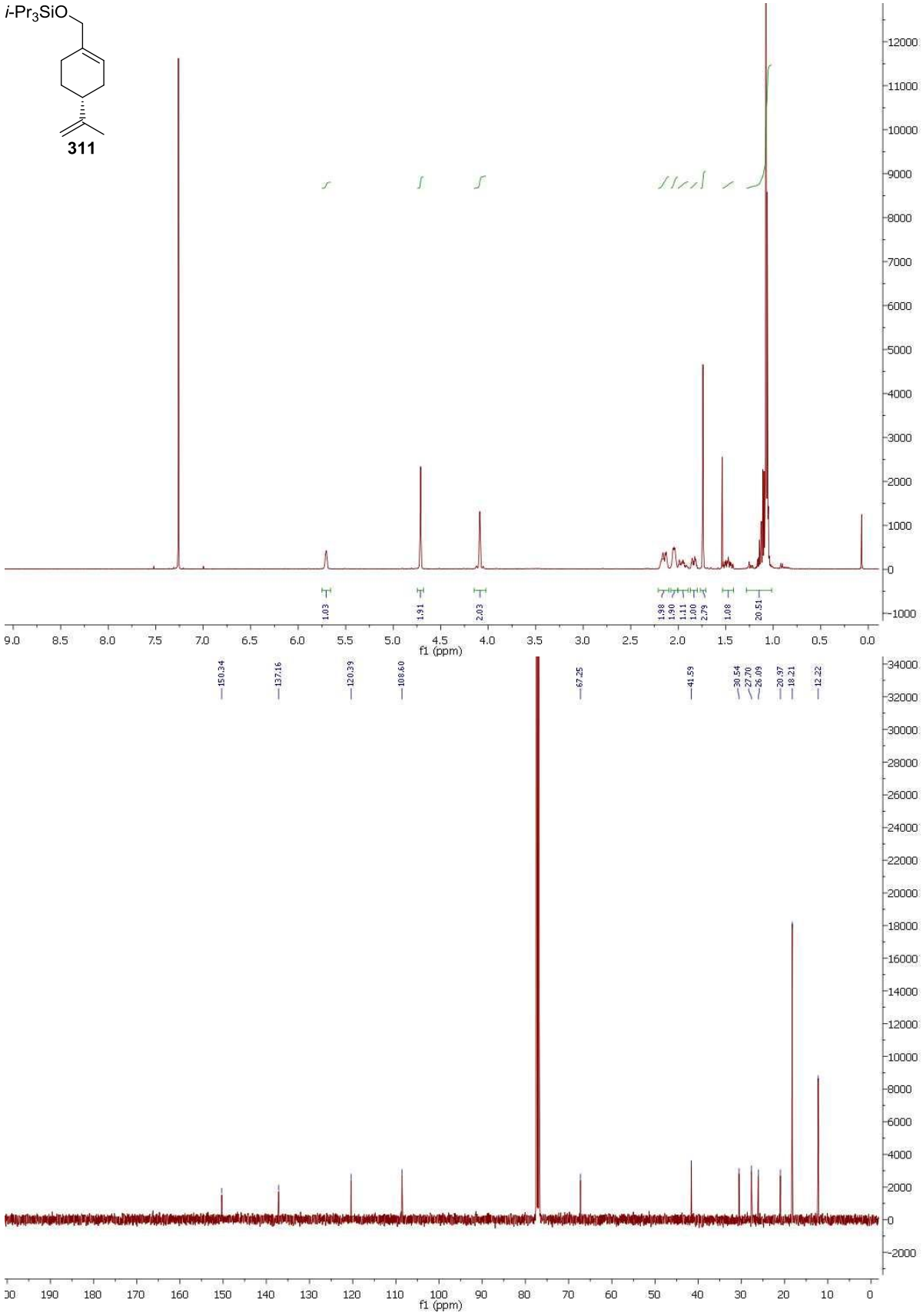
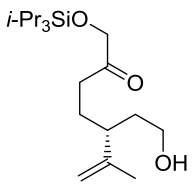
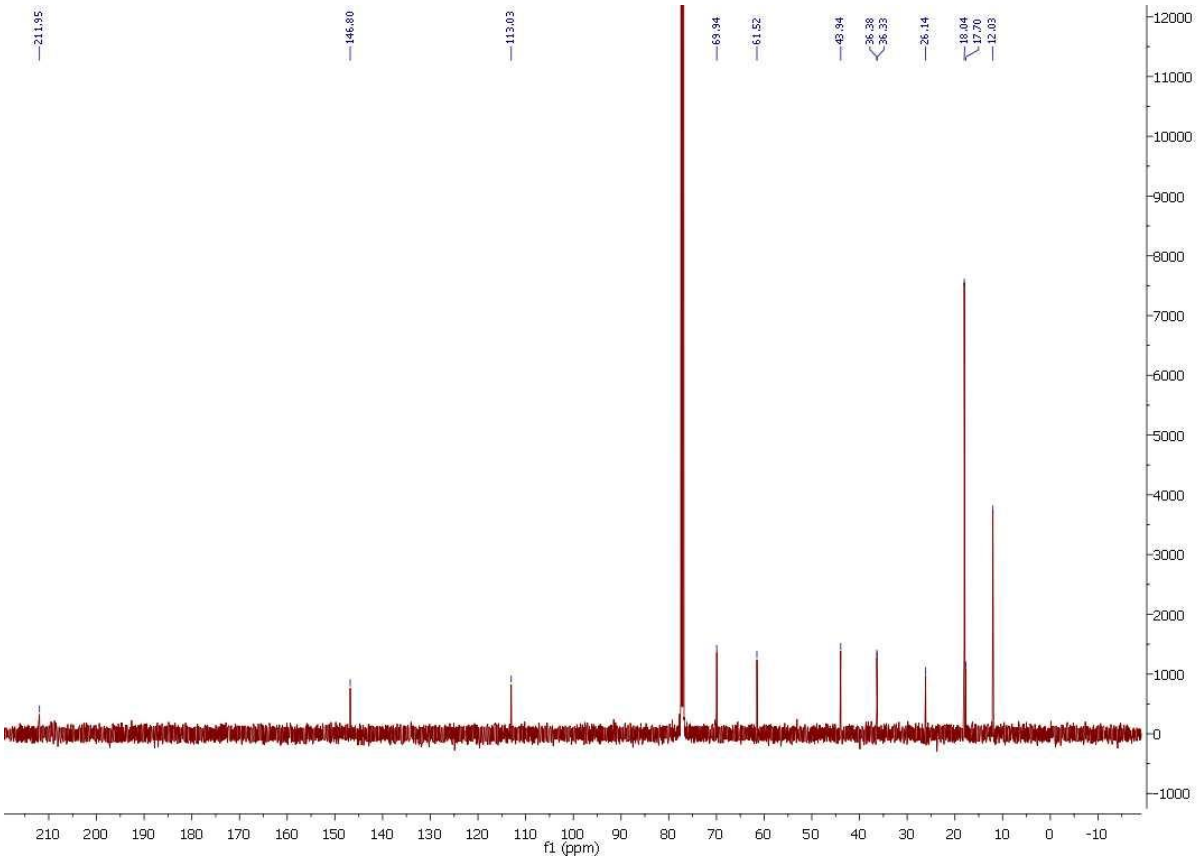
5. Appendix - Relevant NMR Spectra and Published Manuscript

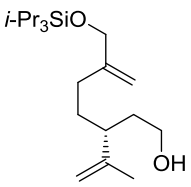



i-Pr3SiO
O
OH

313

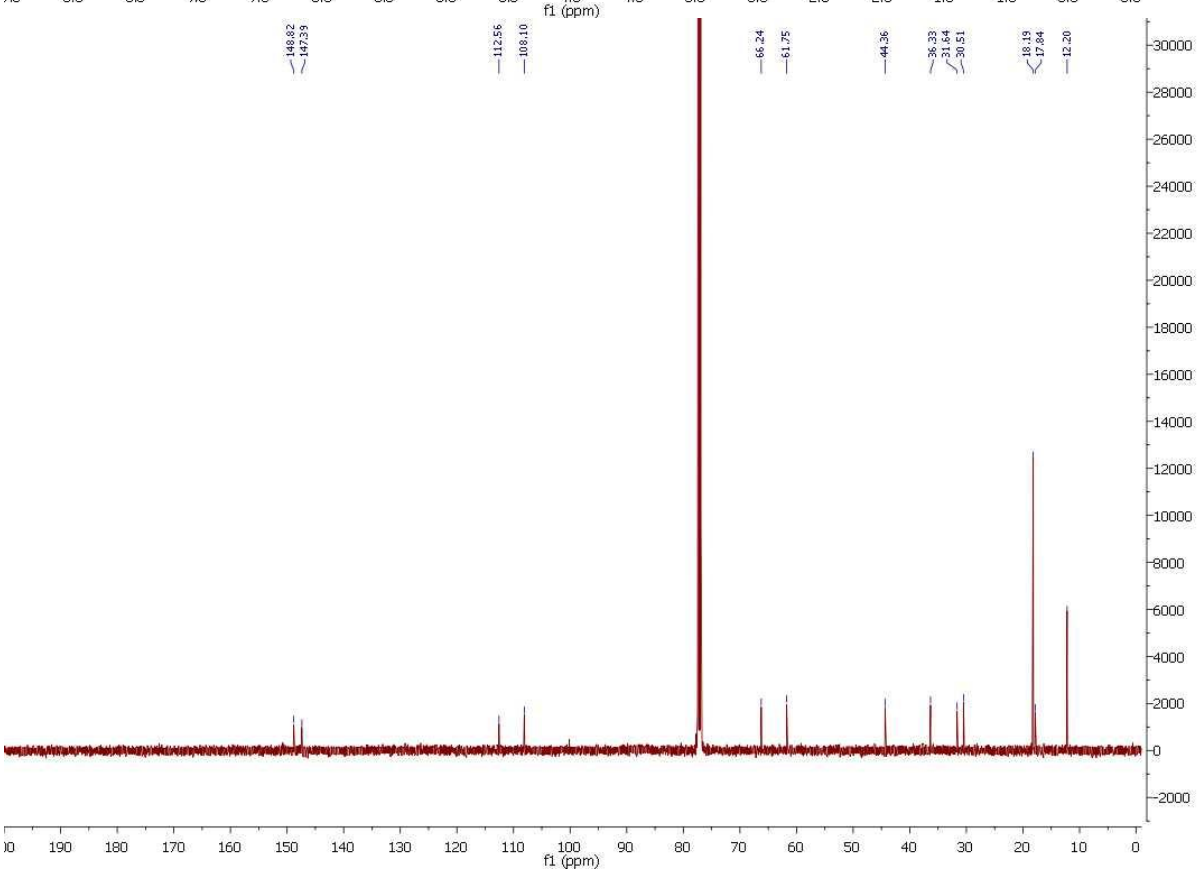
0.95
0.97
1.97
2.00
1.95
1.06
1.16
5.26
0.93
21.08
f1 (ppm)

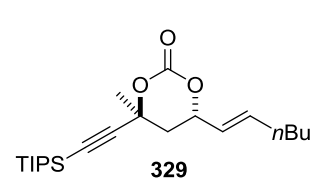

211.95
146.80
113.03
69.94
61.52
43.94
36.38
36.33
26.14
18.04
17.70
12.03
f1 (ppm)


i-Pr3SiO
OH

314

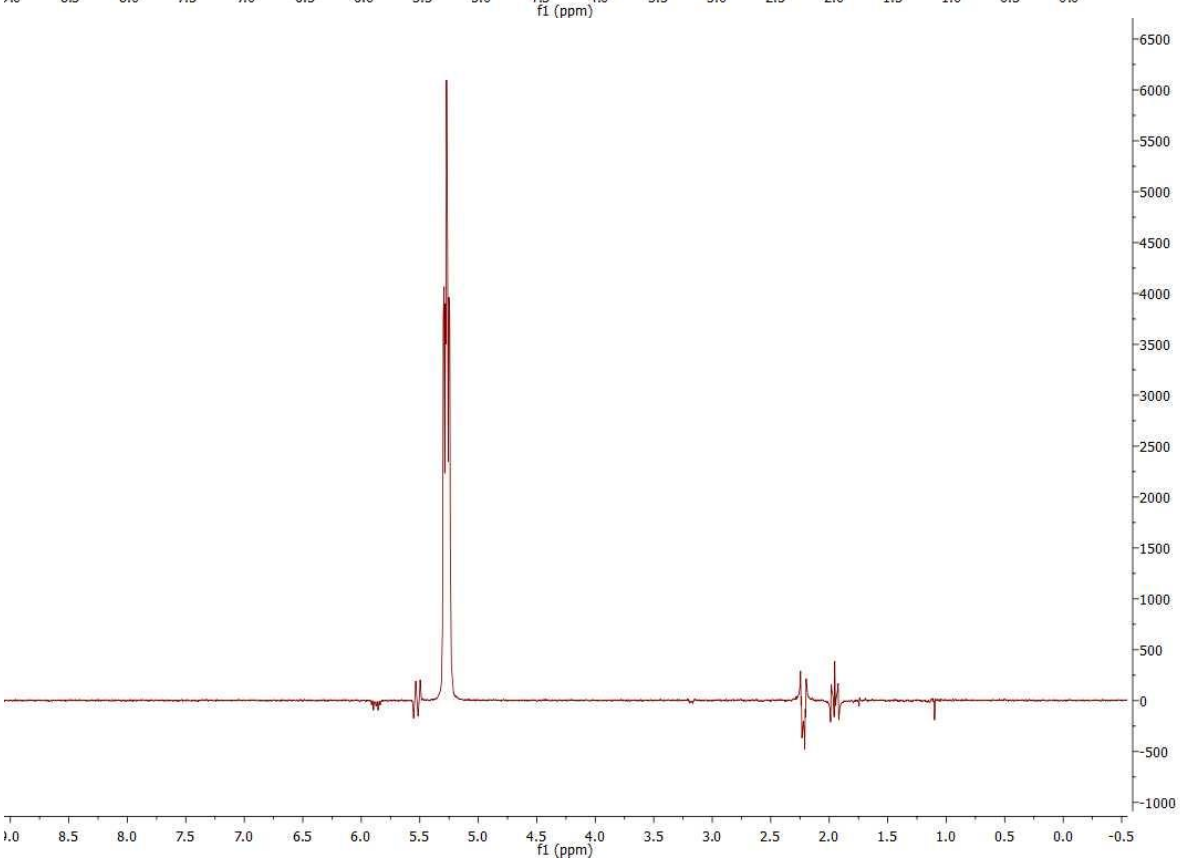
1.00
1.98
1.03
1.97
2.12
1.05
2.16
5.02
2.04
1.01
21.46
f1 (ppm)

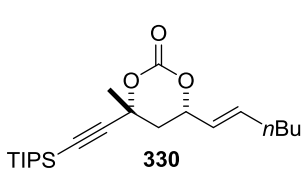

148.82
147.39
112.56
108.10
66.24
61.75
44.36
36.33
31.64
30.51
18.19
17.84
12.20
f1 (ppm)


O
O
O
TIPS
nBu

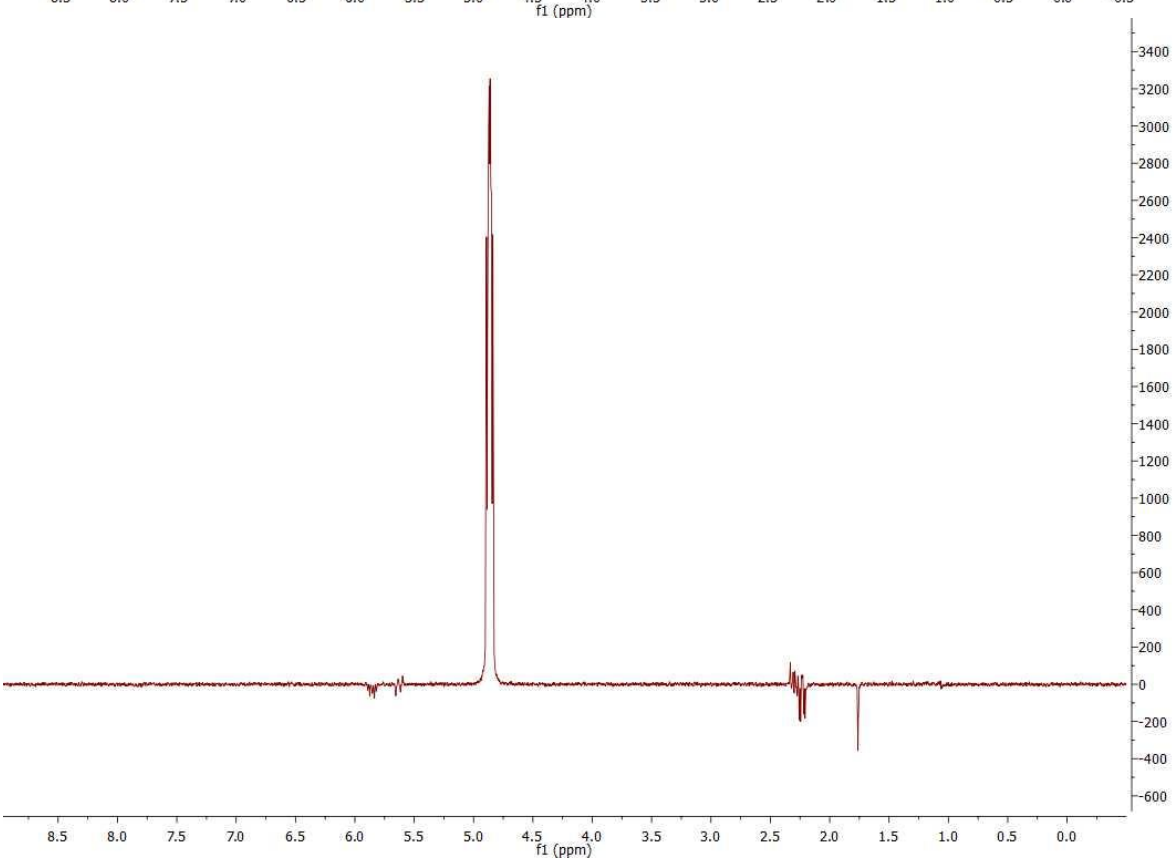
329

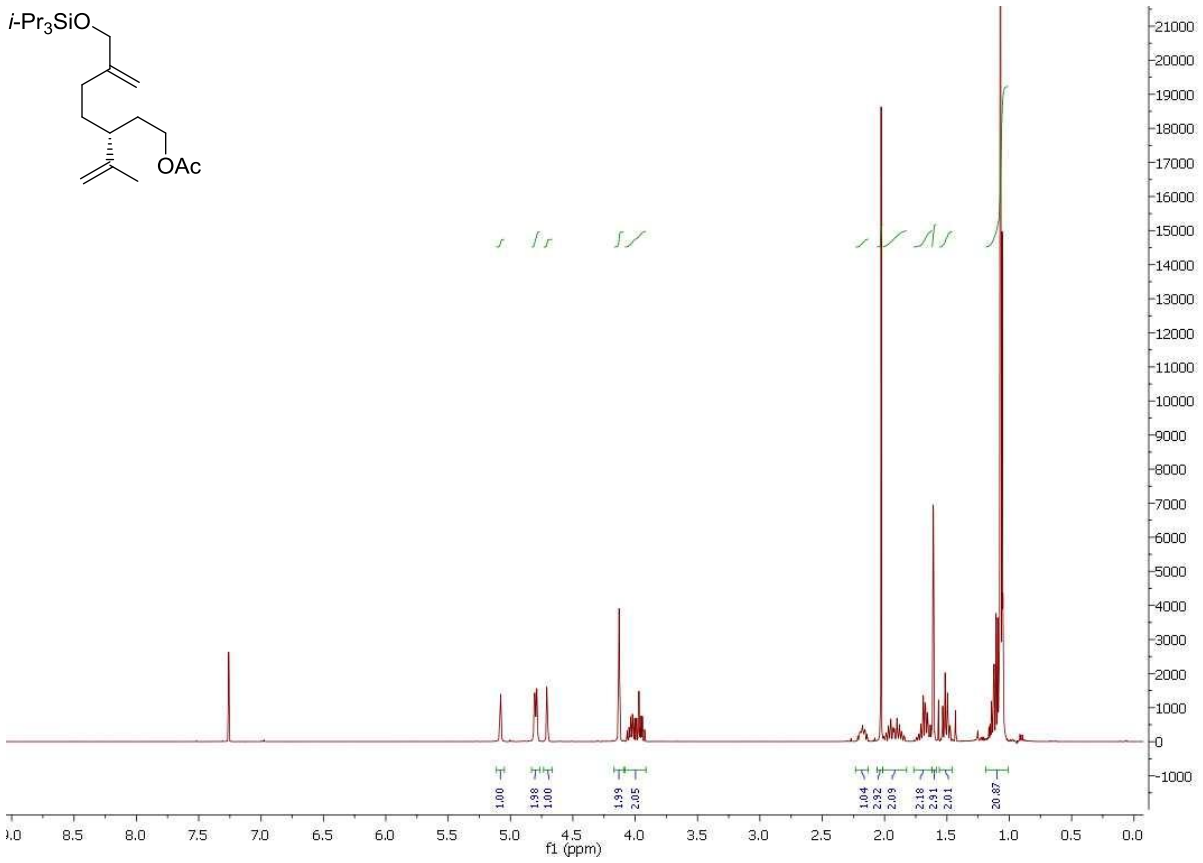
1.00
0.97
1.01
0.96
2.04
1.15
2.82
4.51
22.59
2.98
f1 (ppm)

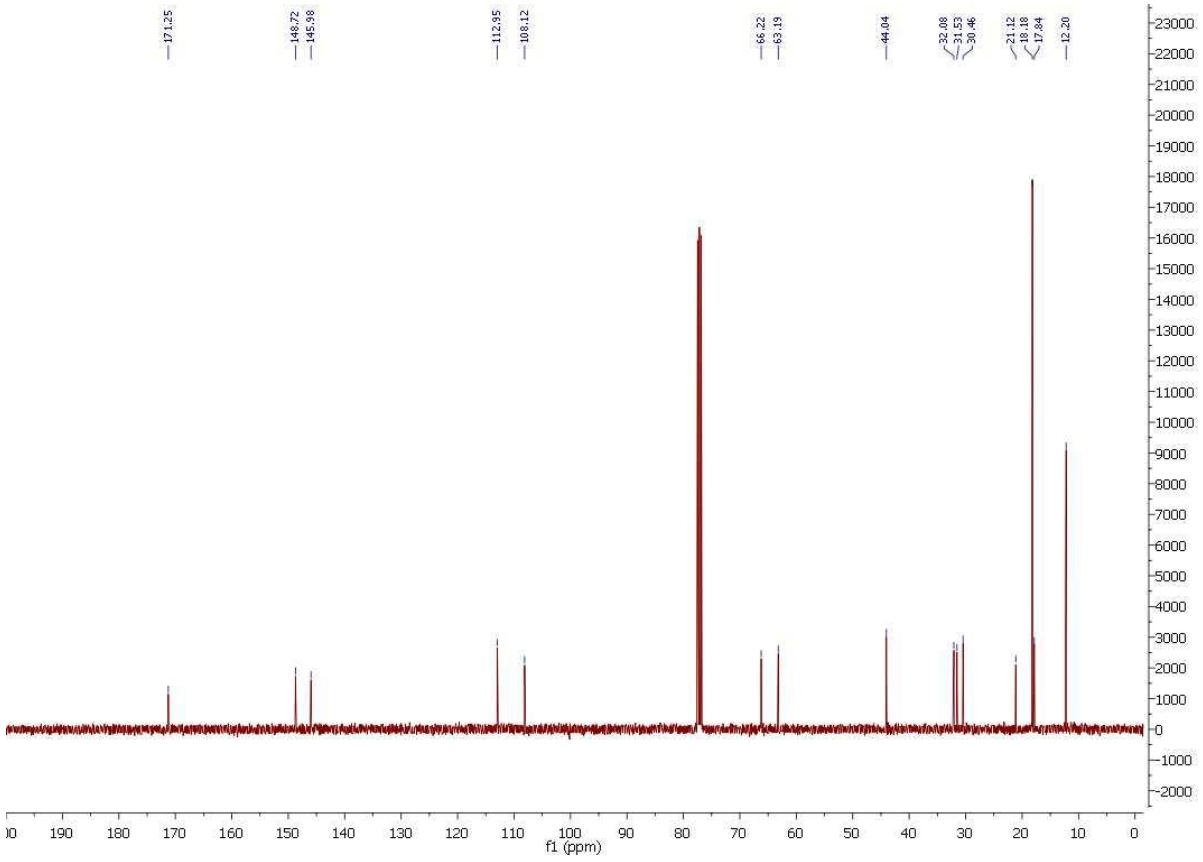

f1 (ppm)

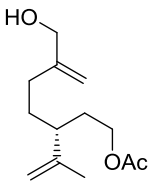


330



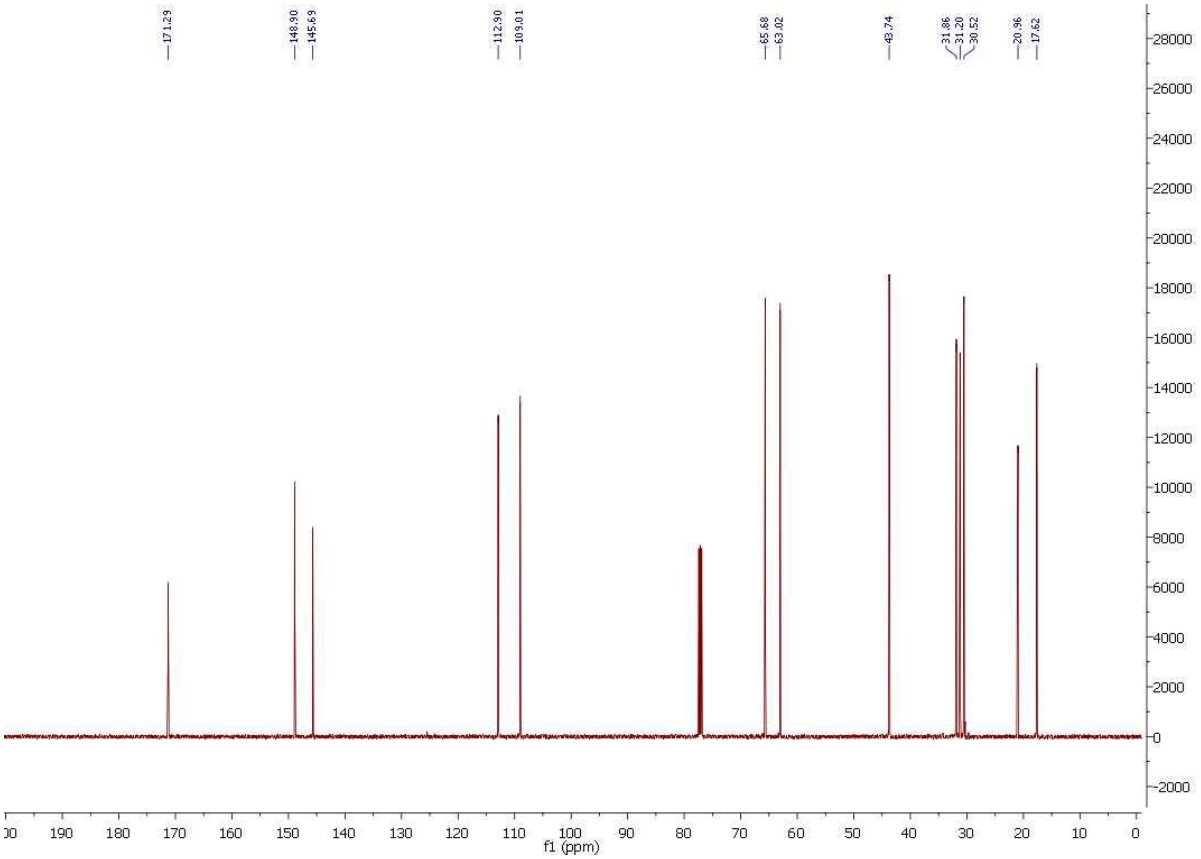

i-Pr3SiO
OAc
1.00
1.98
1.00
1.99
2.05
1.04
2.92
2.09
2.18
2.91
2.01
20.87
f1 (ppm)

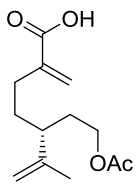

171.25
148.72
145.98
112.95
108.12
66.22
63.19
44.04
32.08
31.53
30.46
21.12
18.18
17.84
12.20
f1 (ppm)


HO
OAc

393

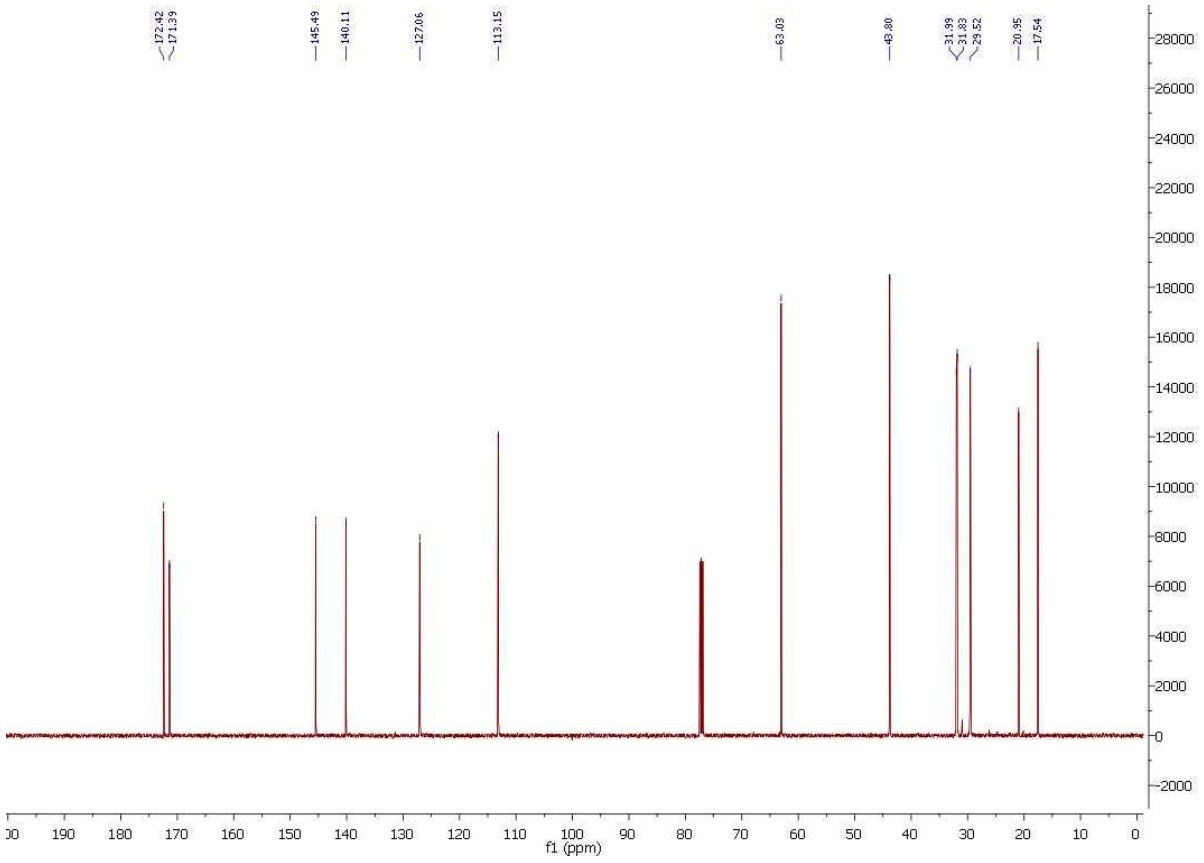
1.00
1.01
1.03
1.04
3.02
1.13
0.95
1.05
3.06
2.15
2.04
3.13
2.12
f1 (ppm)

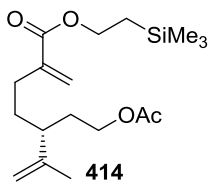

171.29
148.30
145.69
112.90
109.01
65.68
63.02
43.74
31.86
31.20
30.52
20.96
17.62
f1 (ppm)


O
OH
OAc

395

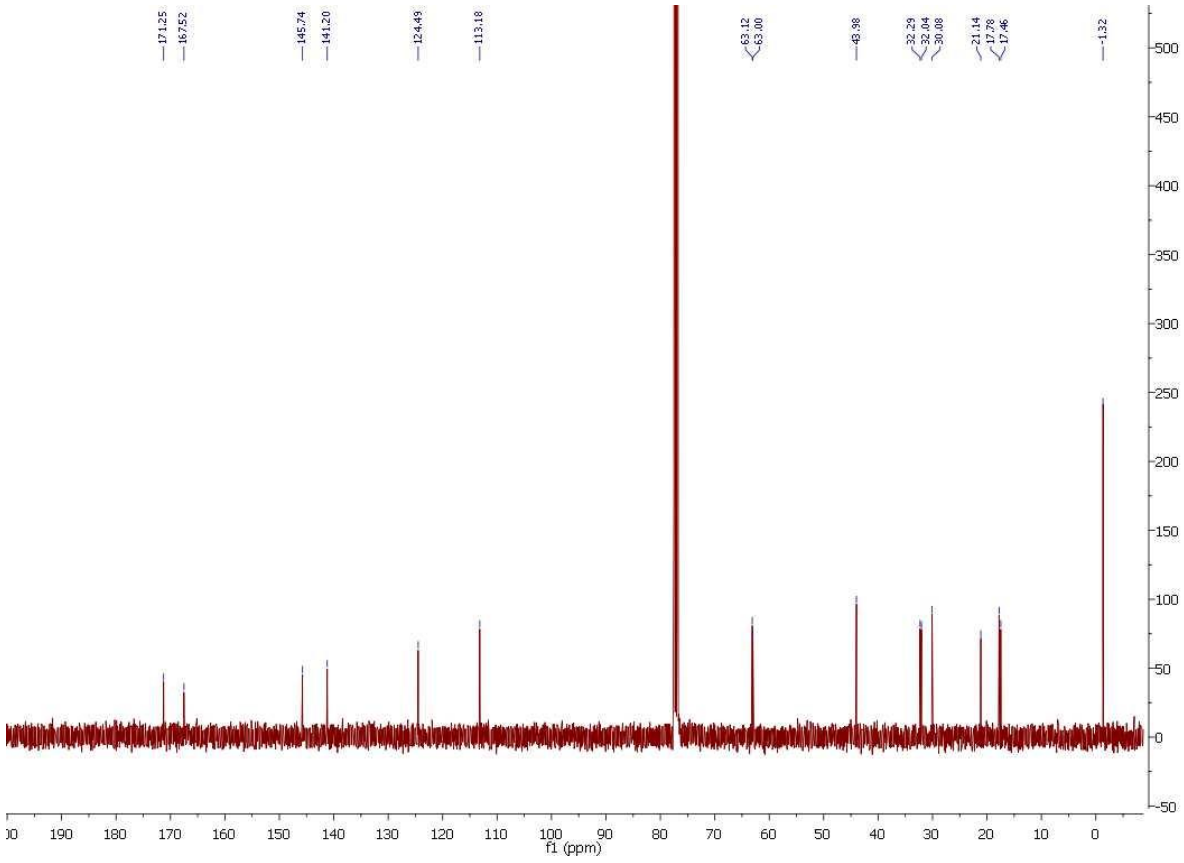
0.95
1.00
0.98
0.98
0.98
0.99
1.04
2.98
2.98
1.99
2.32
2.01
f1 (ppm)

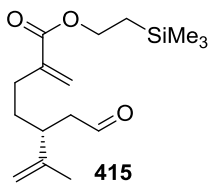

172.42
171.39
145.49
140.11
127.06
113.15
63.03
43.80
31.99
31.83
29.52
20.95
17.54
f1 (ppm)


O
O
SiMe3
OAc

414

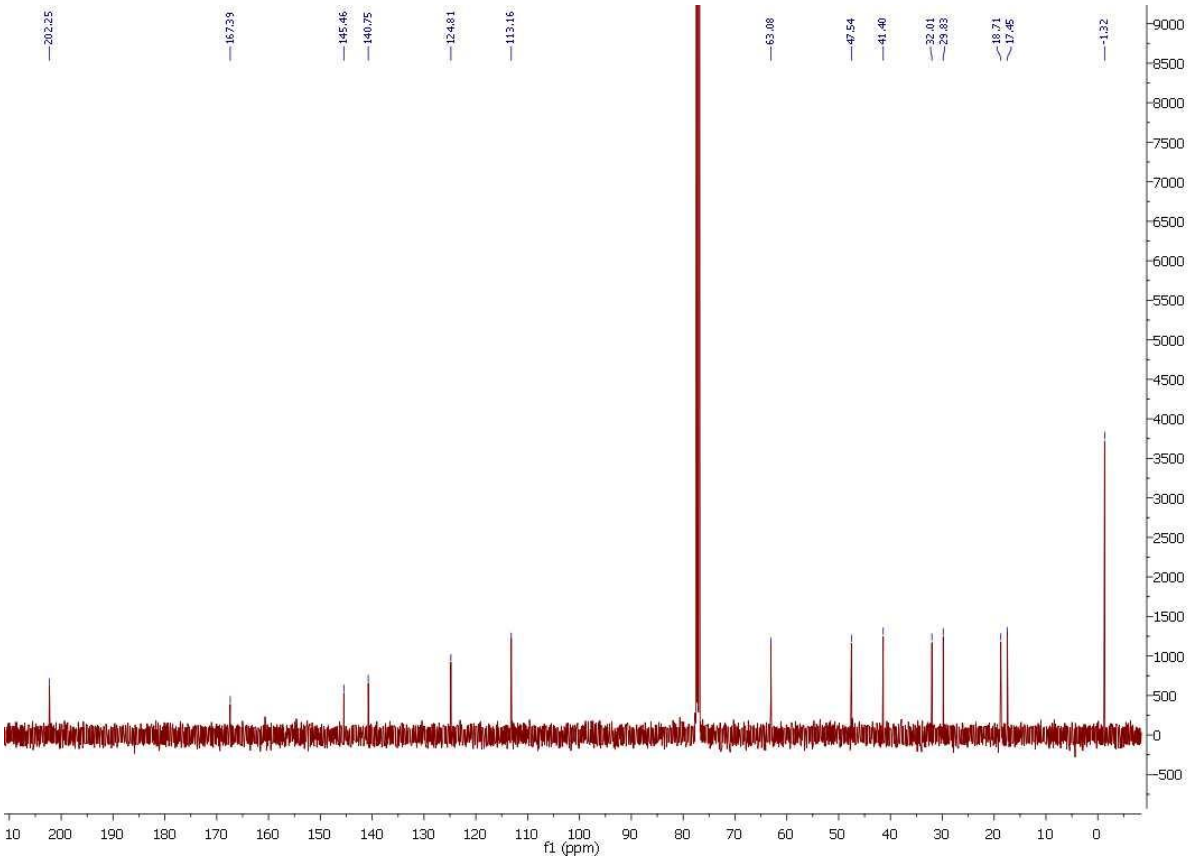
f1 (ppm)

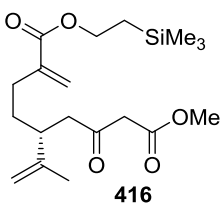

171.25
167.52
145.74
141.20
124.49
113.18
63.12
63.00
43.98
32.29
32.04
30.08
21.14
17.78
17.46
-1.32
f1 (ppm)


O
O
SiMe3
O

415

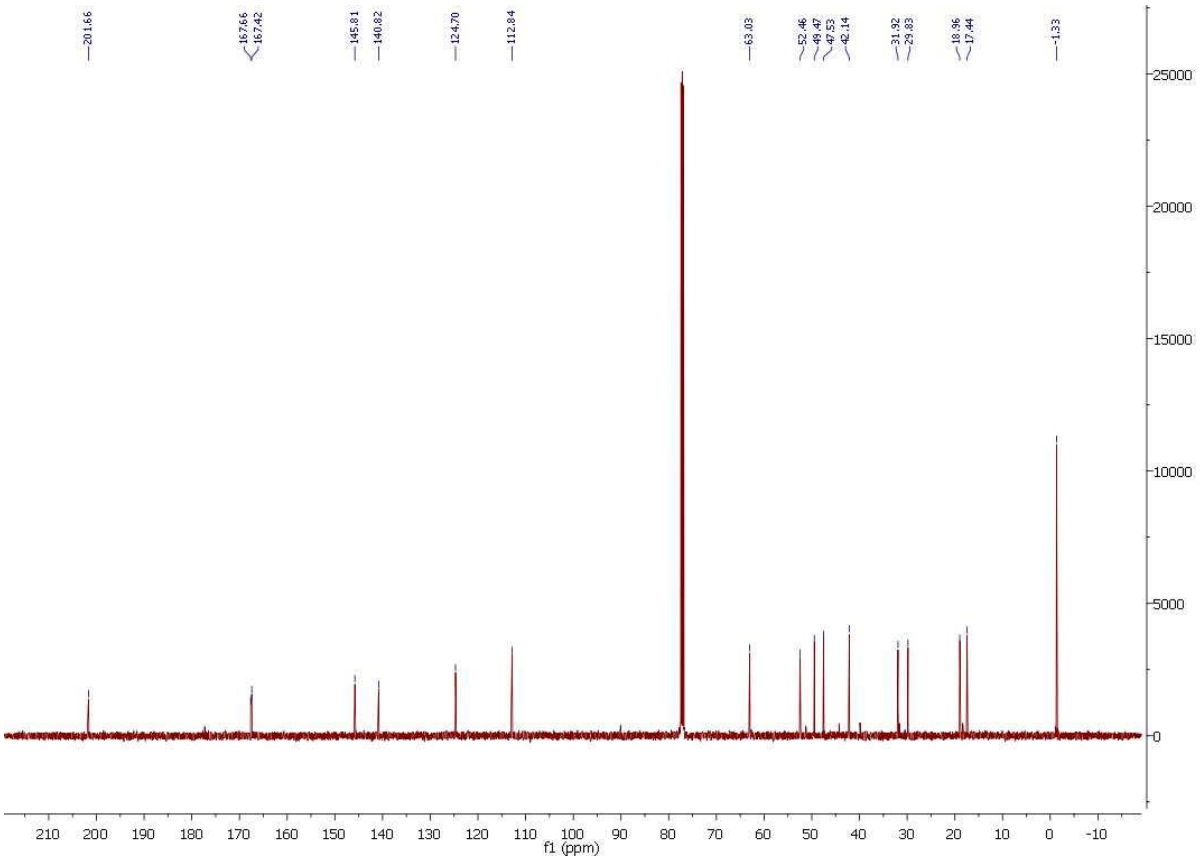
0.90
1.06
1.07
0.99
1.04
1.95
1.16
2.12
2.27
2.87
1.79
2.05
9.05
f1 (ppm)

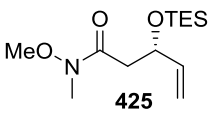

202.25
167.39
145.46
140.75
124.81
113.16
63.08
47.54
41.40
32.01
29.83
18.71
17.45
-1.32
f1 (ppm)


O
O
SiMe3
OMe
O
O

416

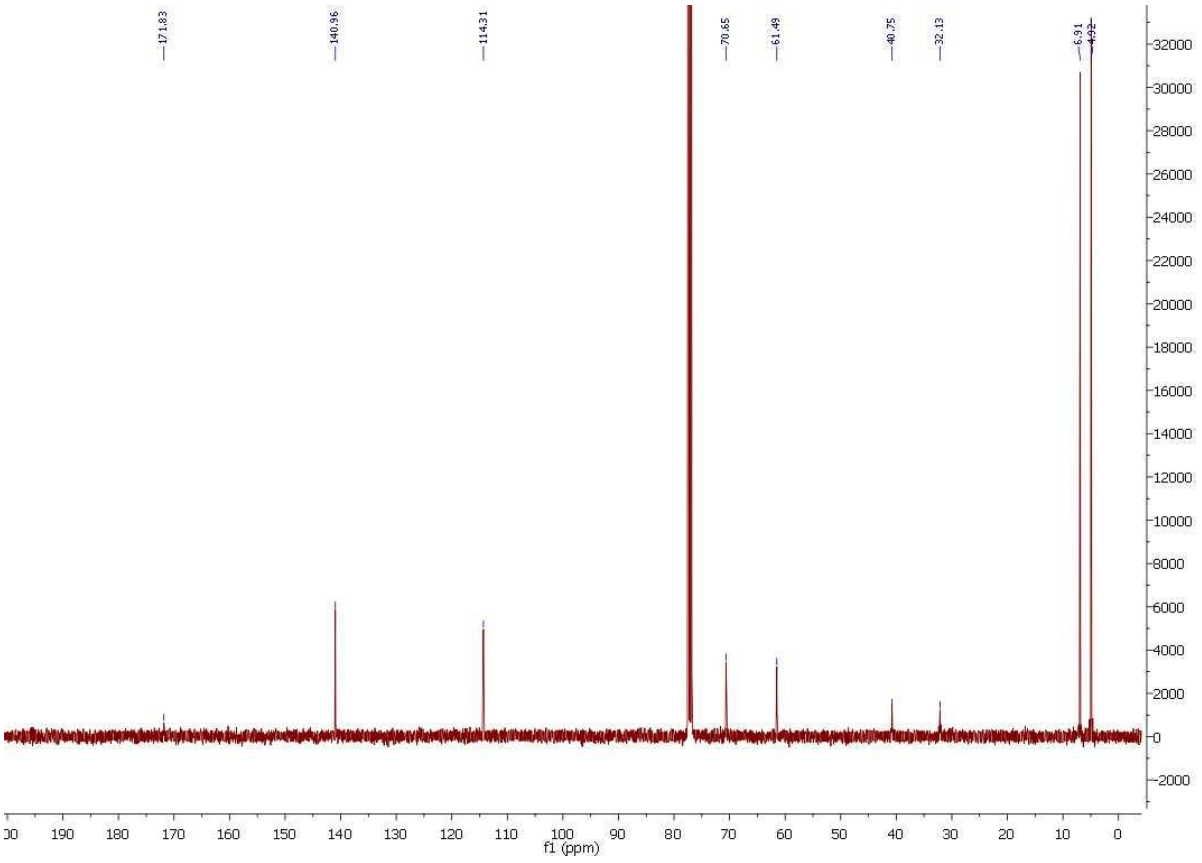
35000
30000
25000
20000
15000
10000
5000
0
0.11
1.00
0.99
0.11
0.99
0.99
2.01
2.59
1.71
2.59
1.25
1.08
2.88
2.01
2.04
8.99
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


201.66
167.66
167.42
145.81
140.82
124.70
112.84
63.03
52.46
49.47
47.53
42.14
31.92
29.83
18.36
17.44
-1.33
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OTES
MeO
N

425

1.00
1.02
0.99
1.00
2.89
2.86
0.95
1.00
8.59
5.71
f1 (ppm)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114.31
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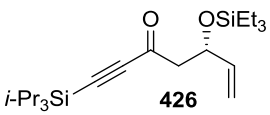
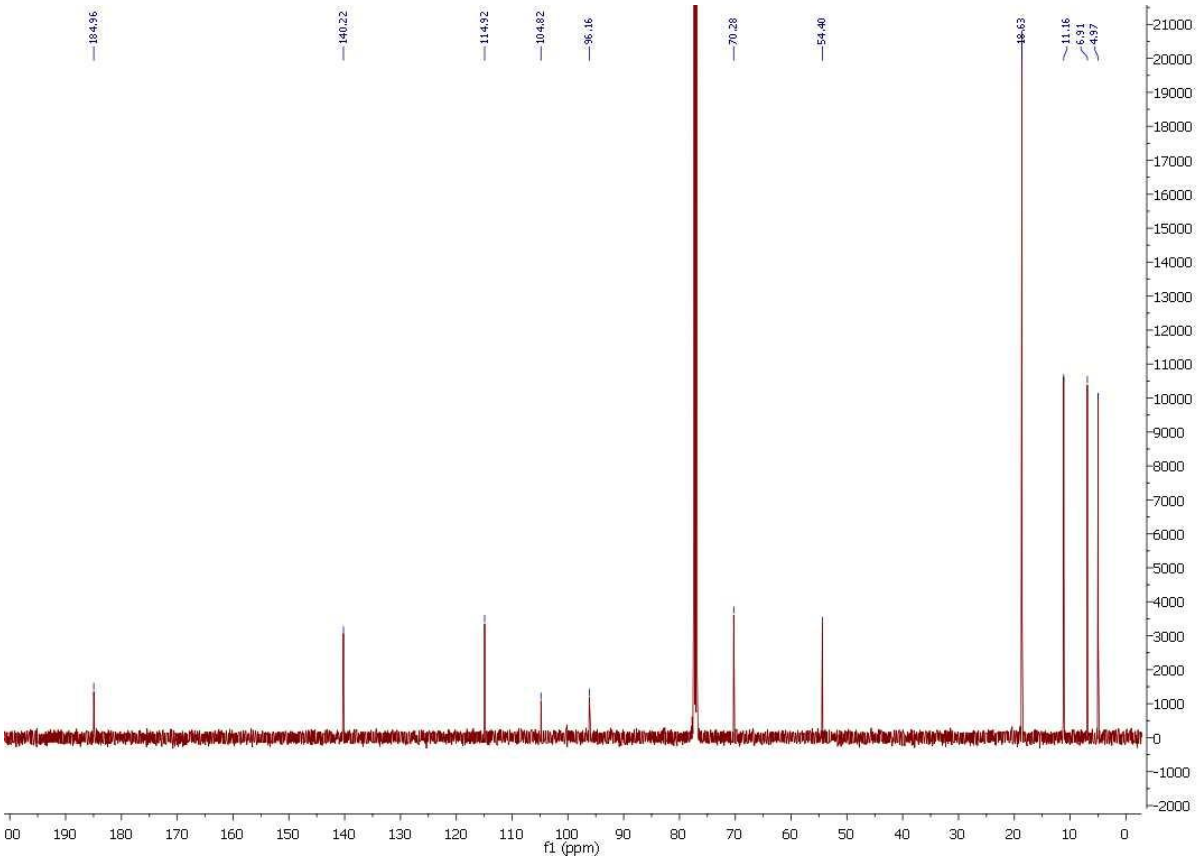
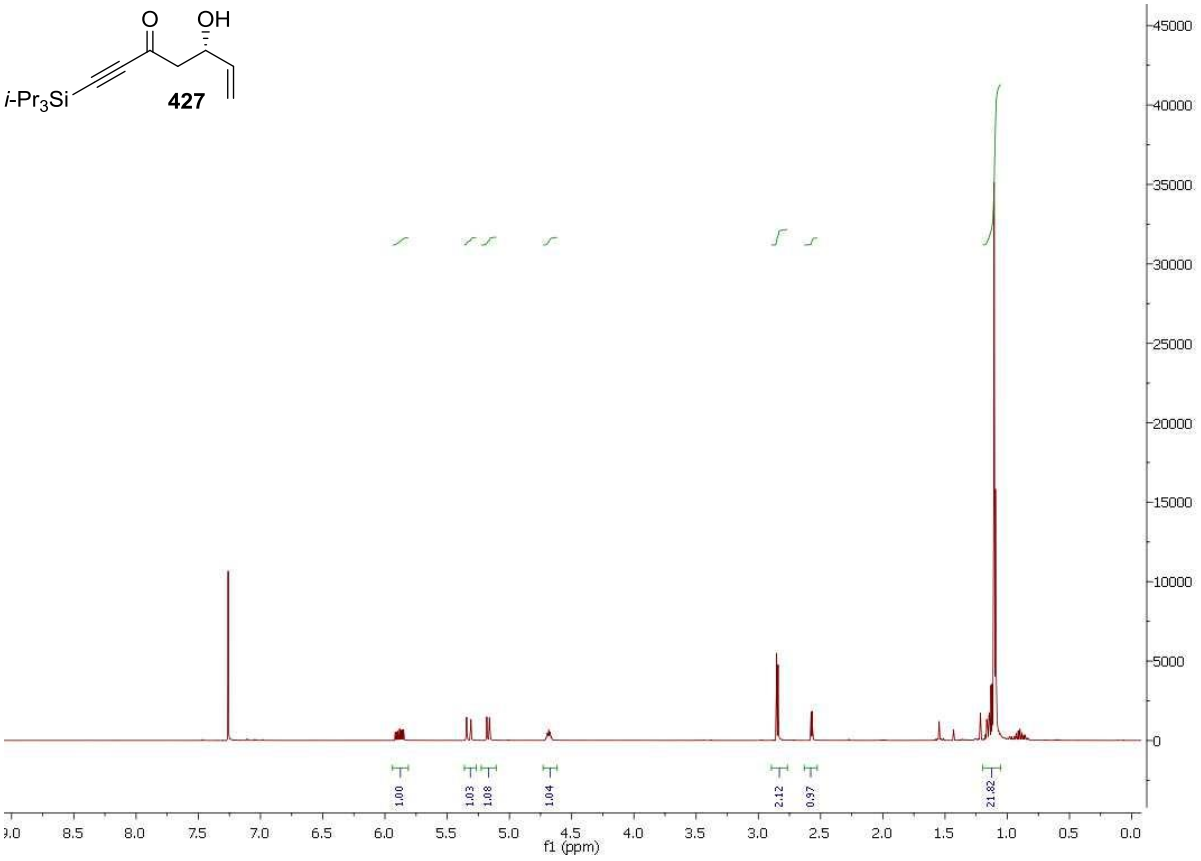
61.49
40.75
32.13
6.91
4.32
f1 (ppm)

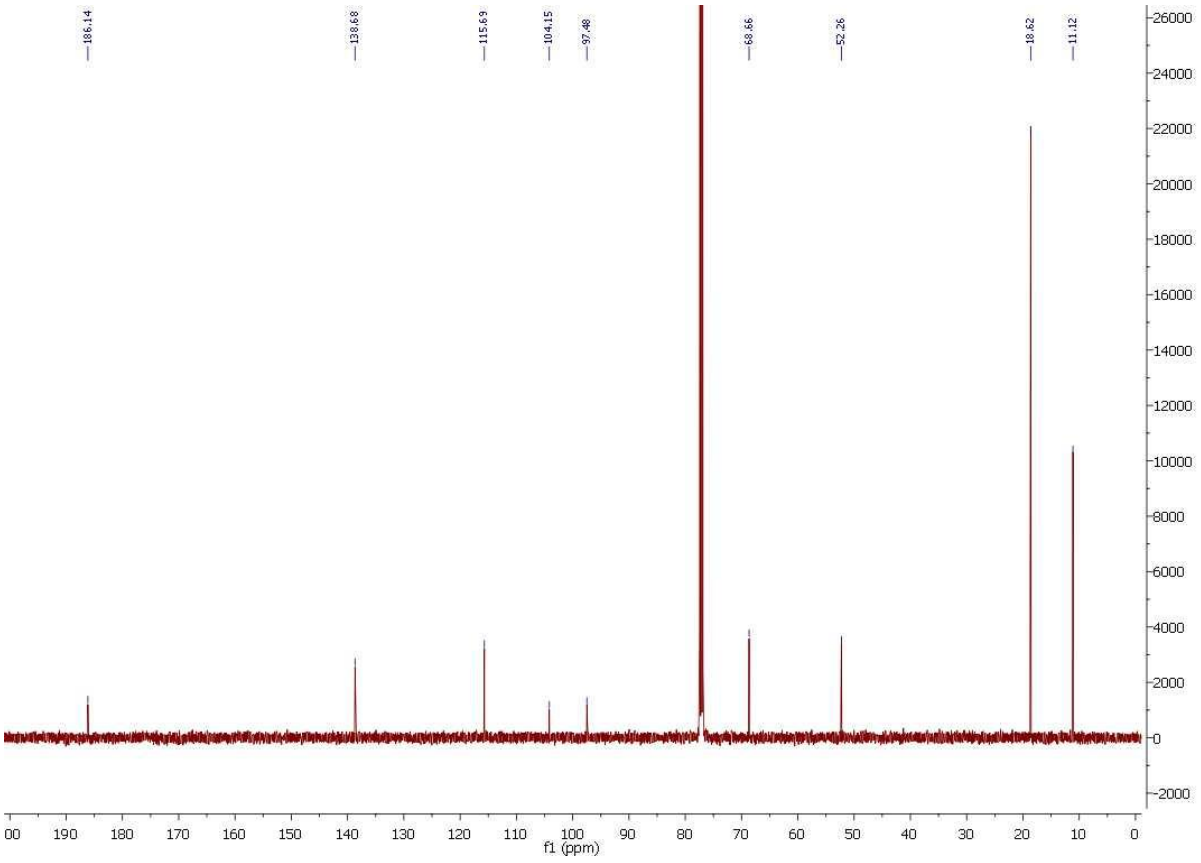

O
OSiEt3
i-Pr3Si

426

1.00
1.04
1.02
0.98
1.07
1.09
21.38
8.95
6.19
f1 (ppm)


184.96
140.22
114.92
104.82
96.16
70.28
54.40
18.63
11.16
6.91
4.97
f1 (ppm)


O
OH
i-Pr3Si
427
1.00
1.03
1.08
1.04
2.12
0.97
21.82
f1 (ppm)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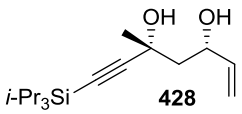
138.68
115.69
104.15
97.48
68.66
52.26
18.62
11.12
f1 (ppm)


OH
OH
i-Pr3Si

428

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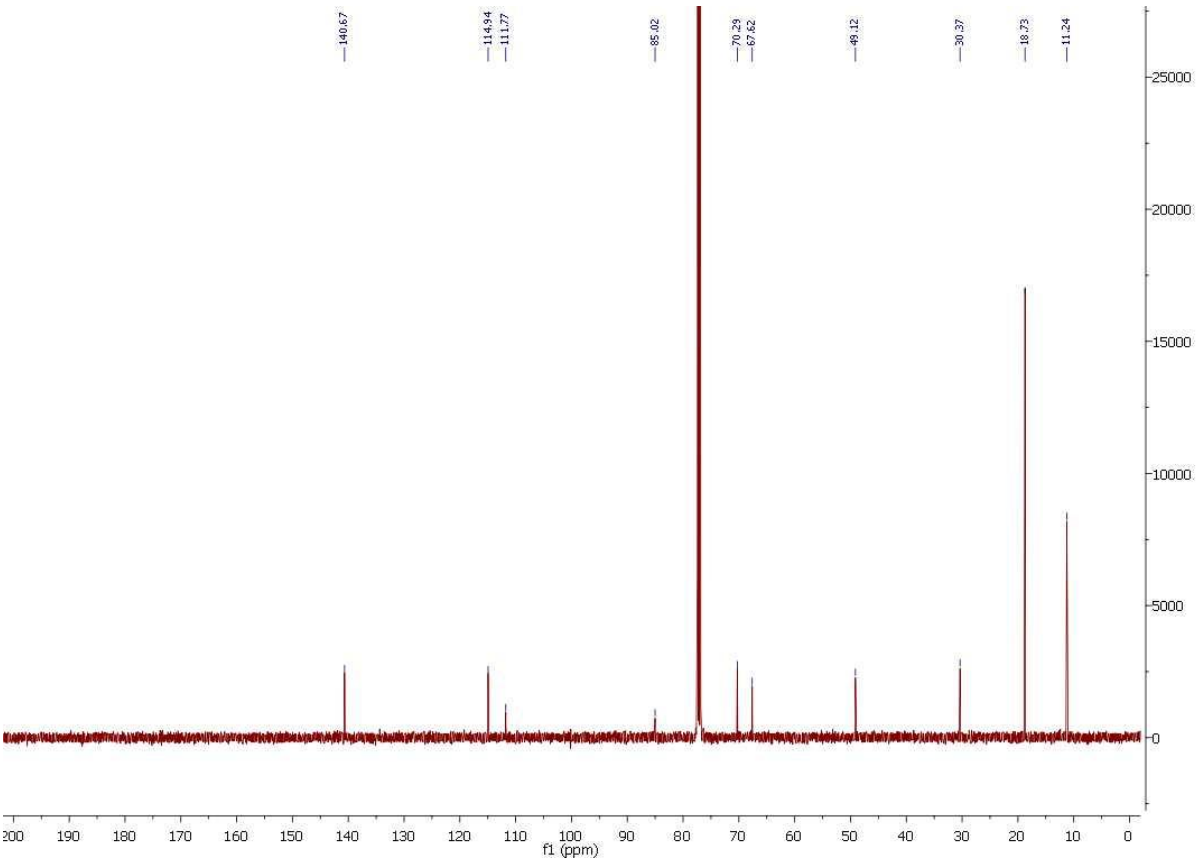
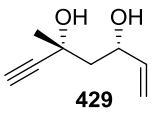
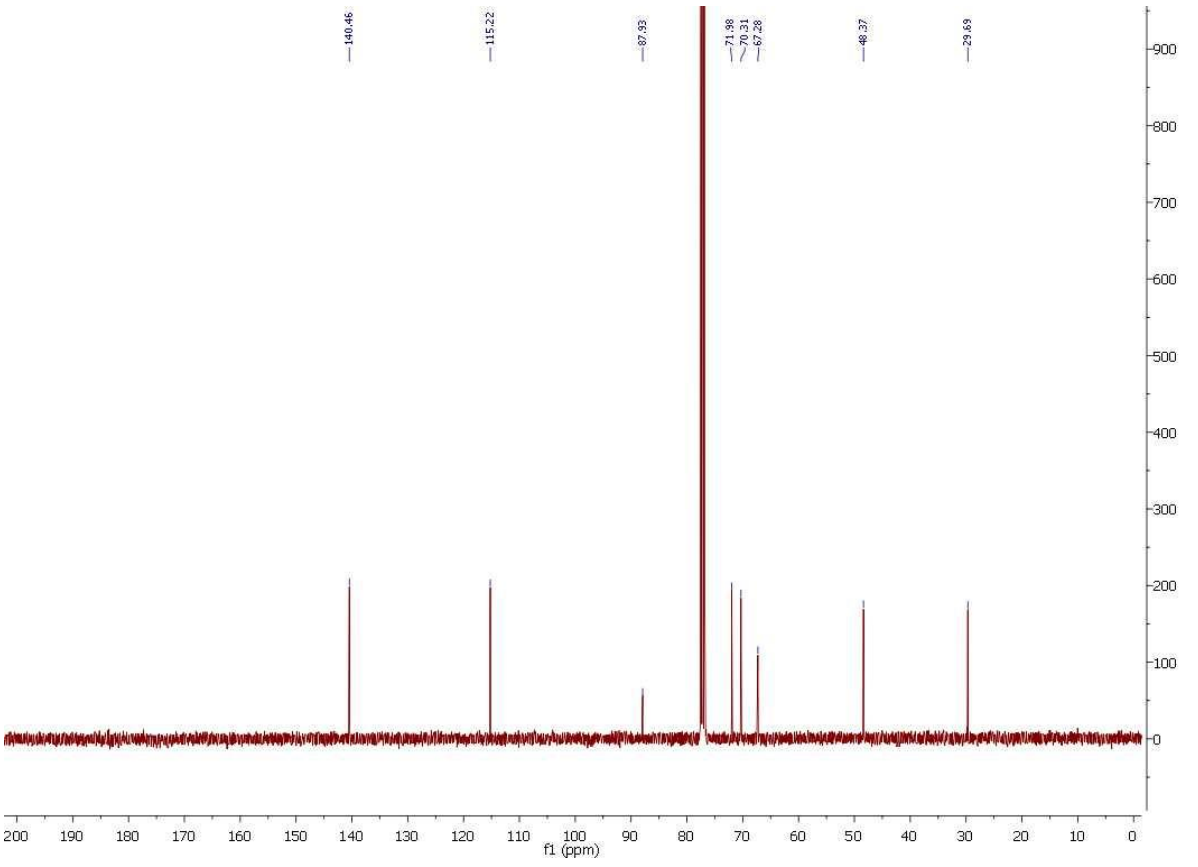
1.02
1.06
1.06
0.97
0.98
1.08
1.06
3.14
21.80
f1 (ppm)

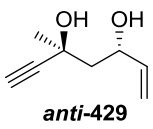

140.67
114.94
111.77
85.02
70.29
67.62
49.12
30.37
18.73
11.24
f1 (ppm)


OH
OH

429

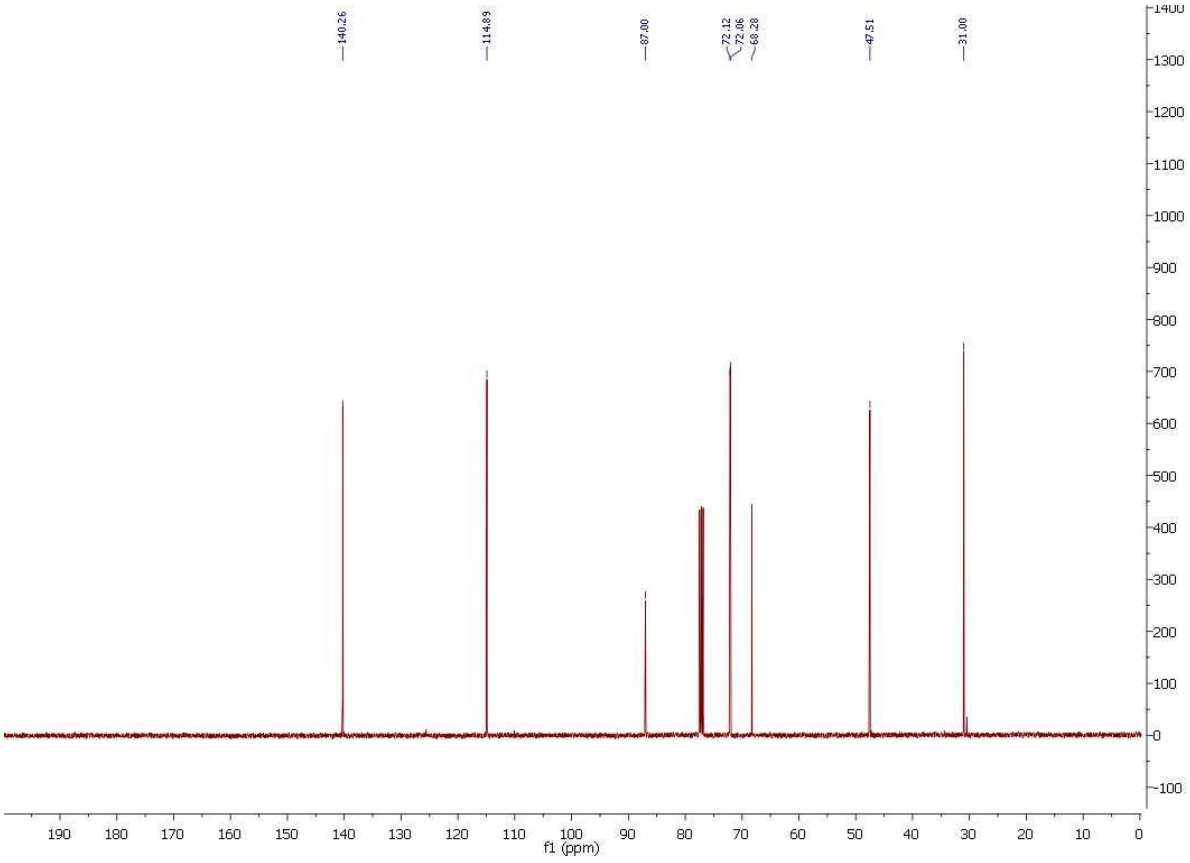
1.00
1.00
0.97
1.00
0.90
0.90
0.92
1.04
1.09
2.38
f1 (ppm)

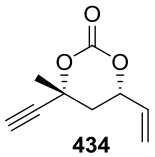

140.46
115.22
87.93
71.98
70.31
67.28
48.37
29.69
f1 (ppm)


OH
OH

***anti*-429**

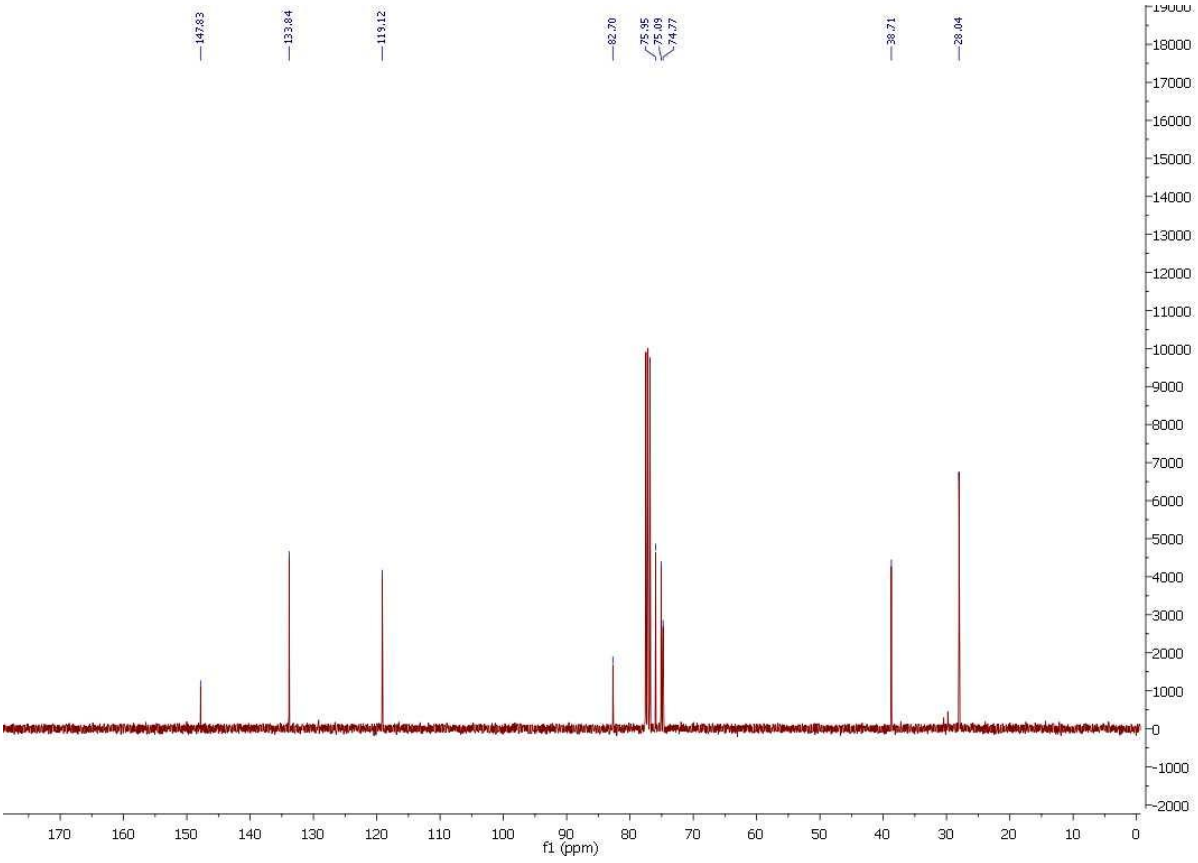
1.00
1.03
1.03
1.01
1.01
1.02
0.97
2.13
3.14
f1 (ppm)

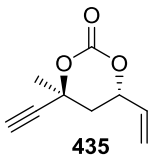

140.26
114.89
87.00
72.12
72.06
68.28
47.51
31.00
f1 (ppm)



434

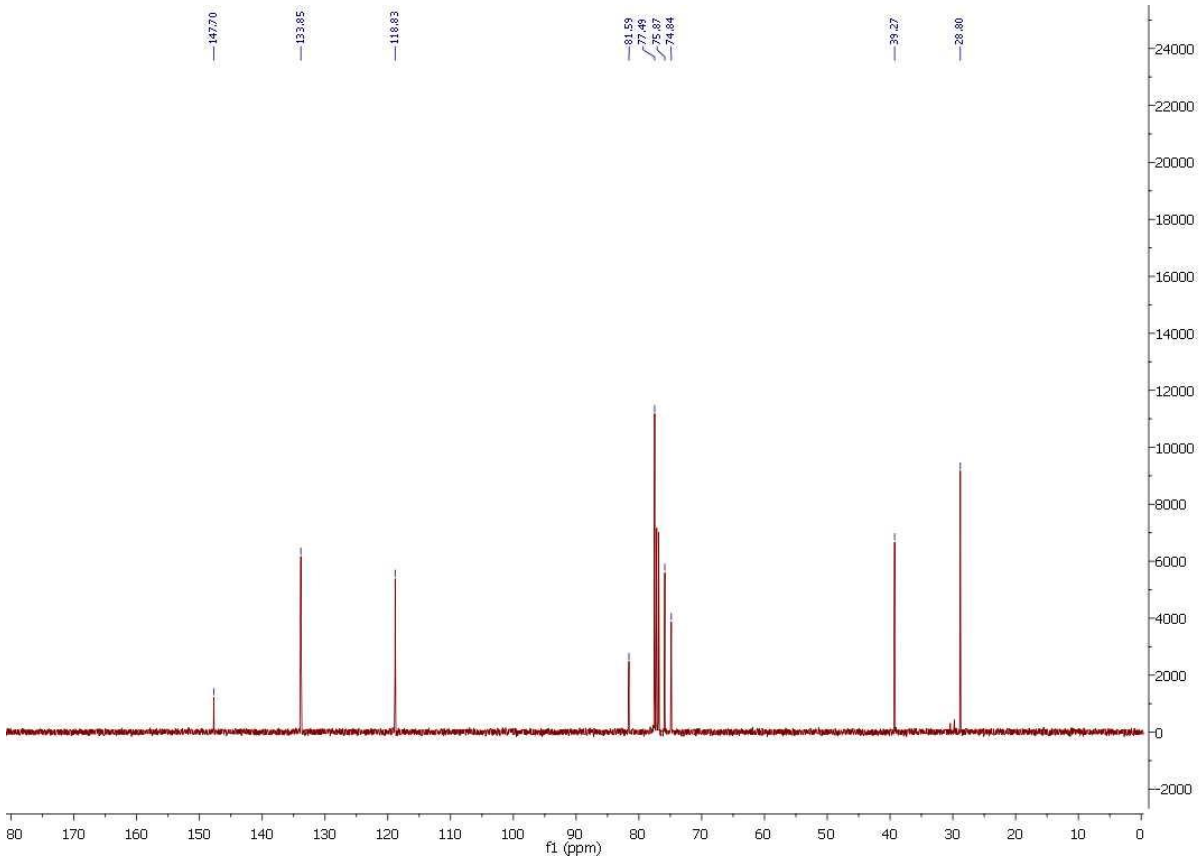
1.00
1.00
0.99
0.99
1.00
2.08
3.12
f1 (ppm)

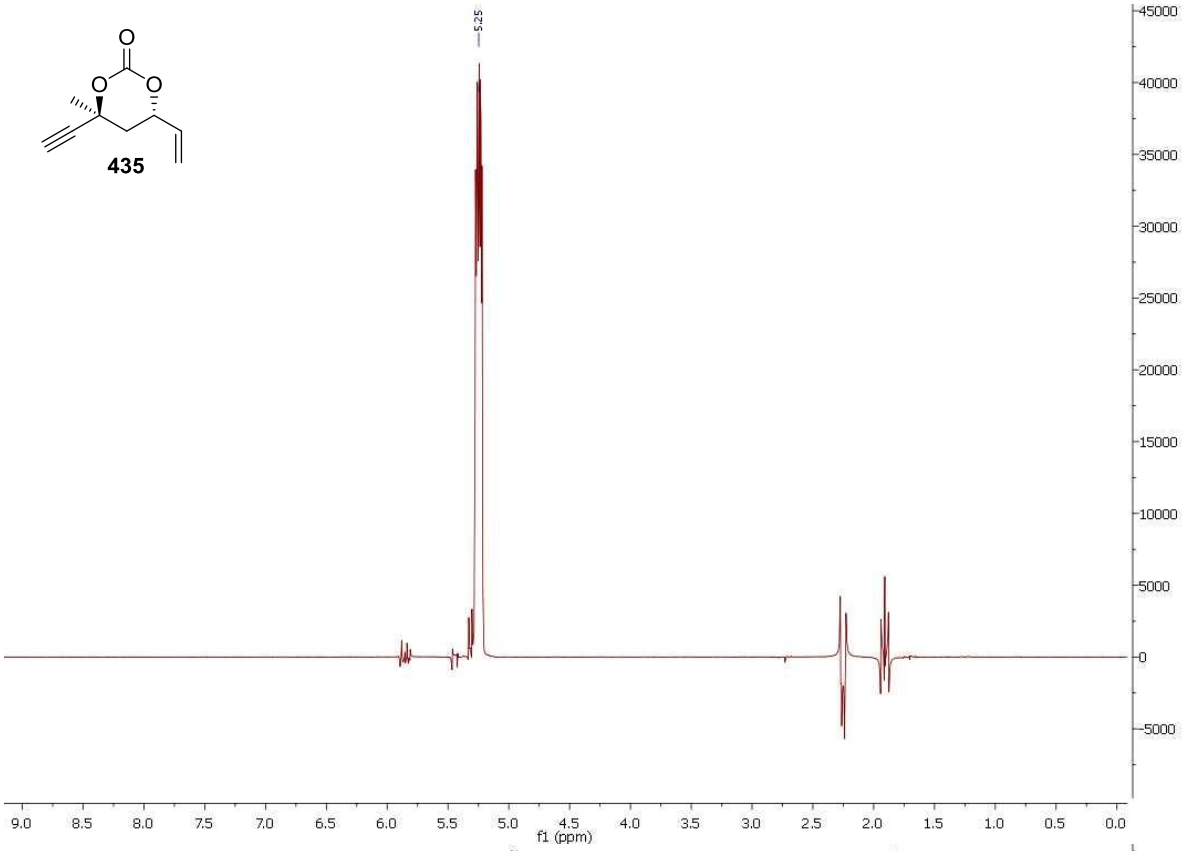

147.83
133.84
119.12
82.70
75.95
75.09
74.77
38.71
28.04
f1 (ppm)

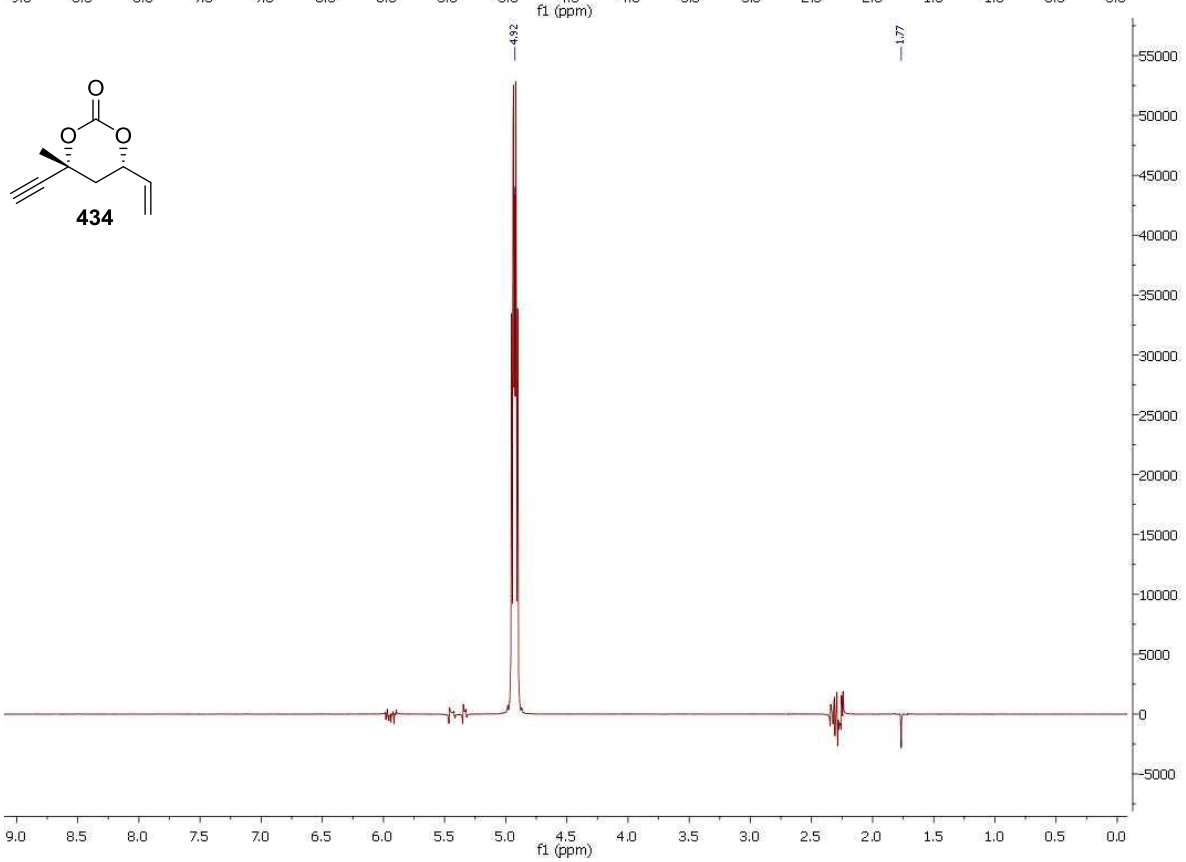


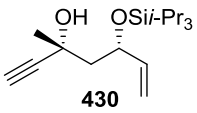
435

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1.00
1.03
0.58
0.57
0.95
1.03
1.02
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


147.70
133.85
118.83
81.59
77.49
75.87
74.84
39.27
28.80
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

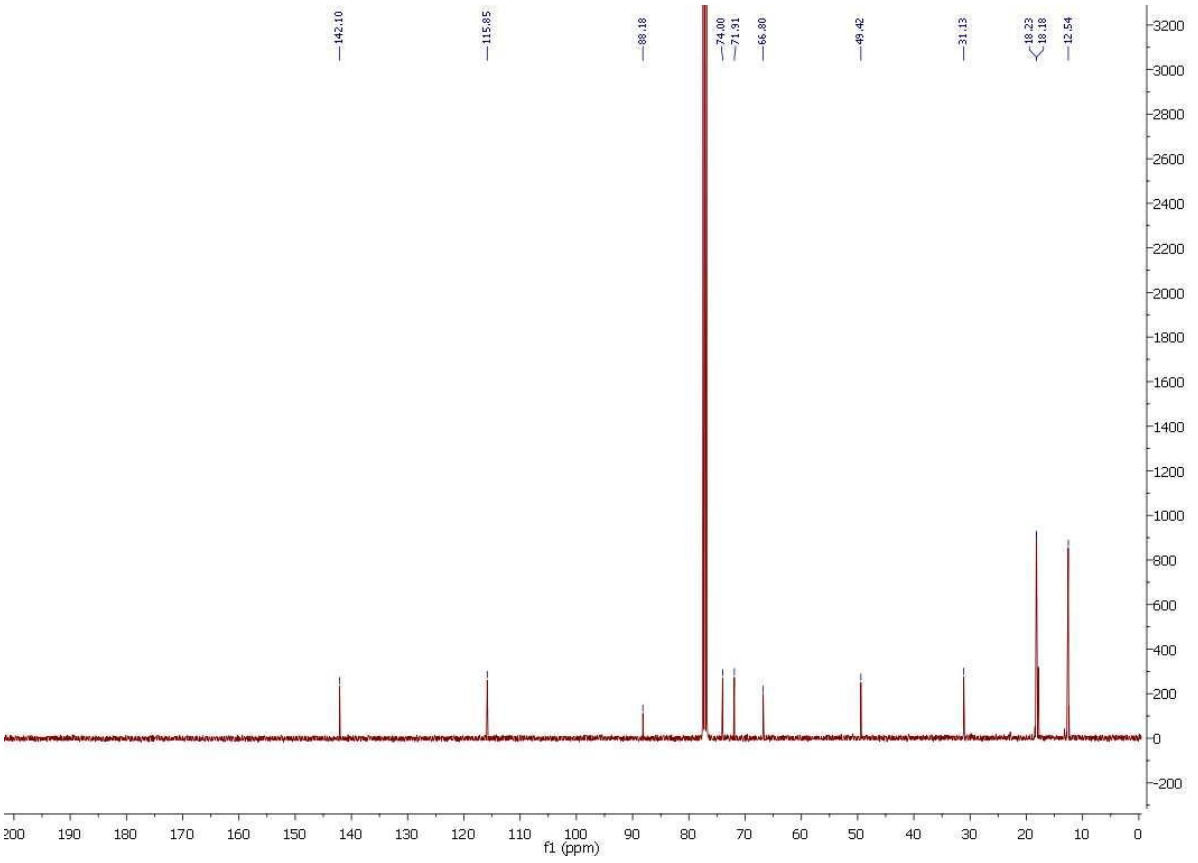

435
5.25
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

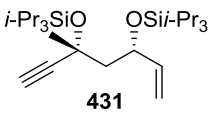

434
4.92
1.77
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


OH
OSi-Pr3

430

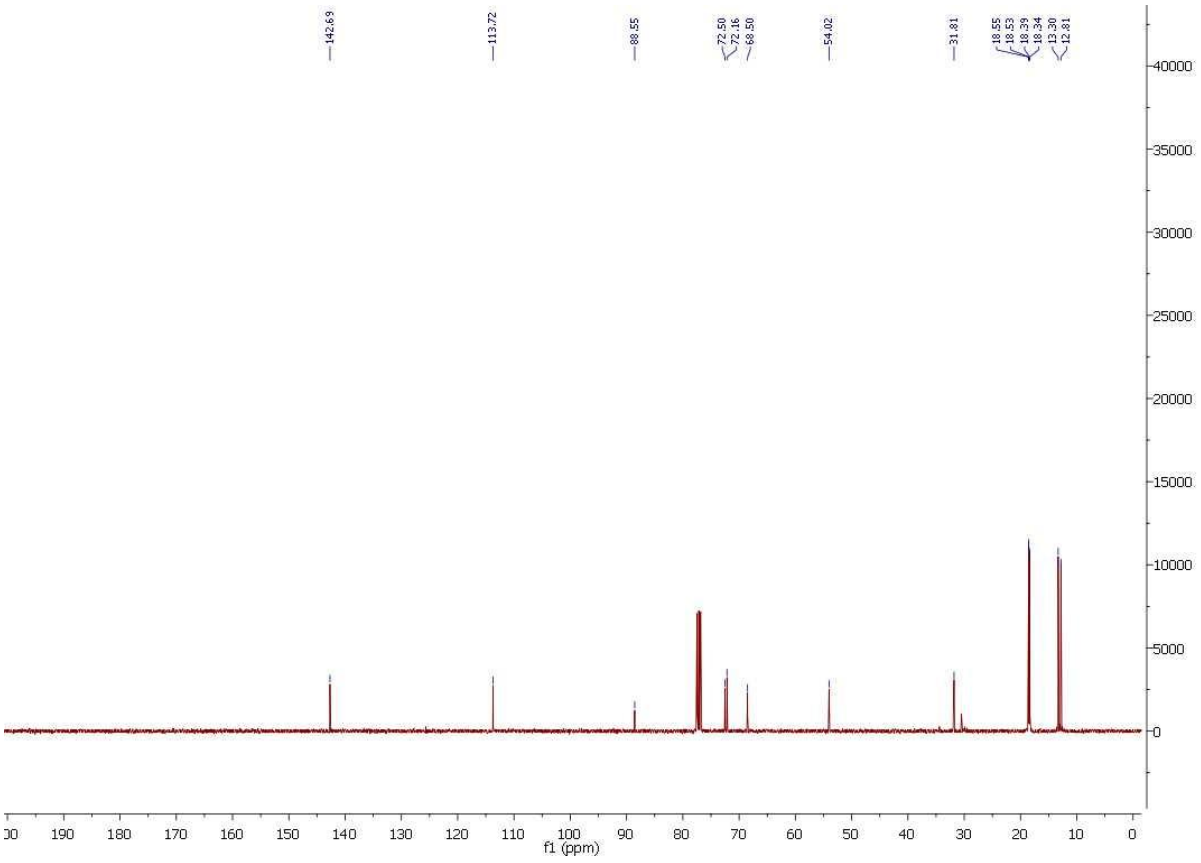
f1 (ppm)

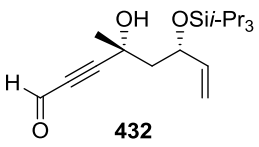

142.10
115.85
88.18
74.00
71.91
66.80
49.42
31.13
18.23
18.18
12.54
f1 (ppm)


i-Pr3SiO
OSii-Pr3

431

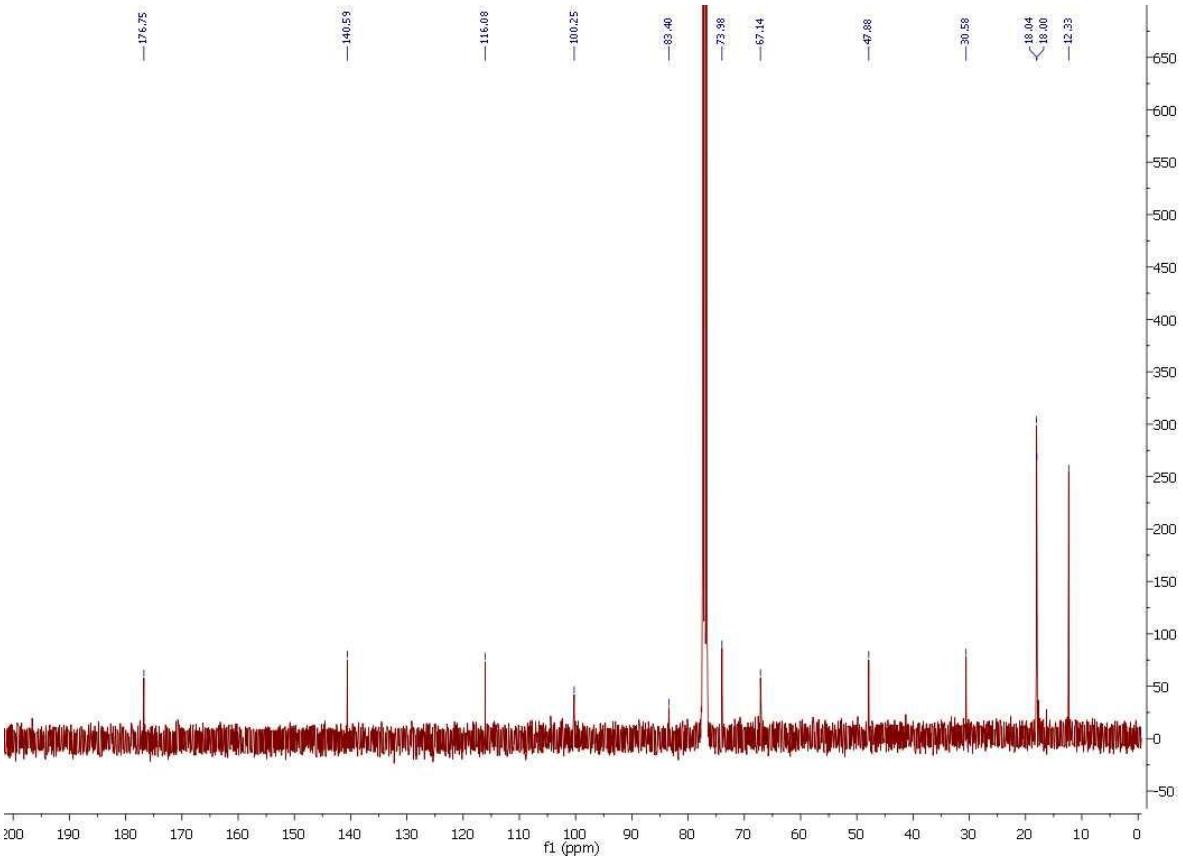
1.00
1.02
1.05
0.99
0.93
1.02
1.02
3.28
42.02
f1 (ppm)

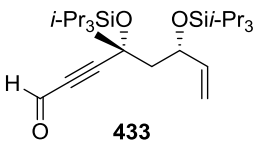

142.69
113.72
88.55
72.50
72.16
68.50
54.02
31.81
18.55
18.53
18.39
18.34
13.30
12.81
f1 (ppm)


OH
OSi-Pr3
H
O

432

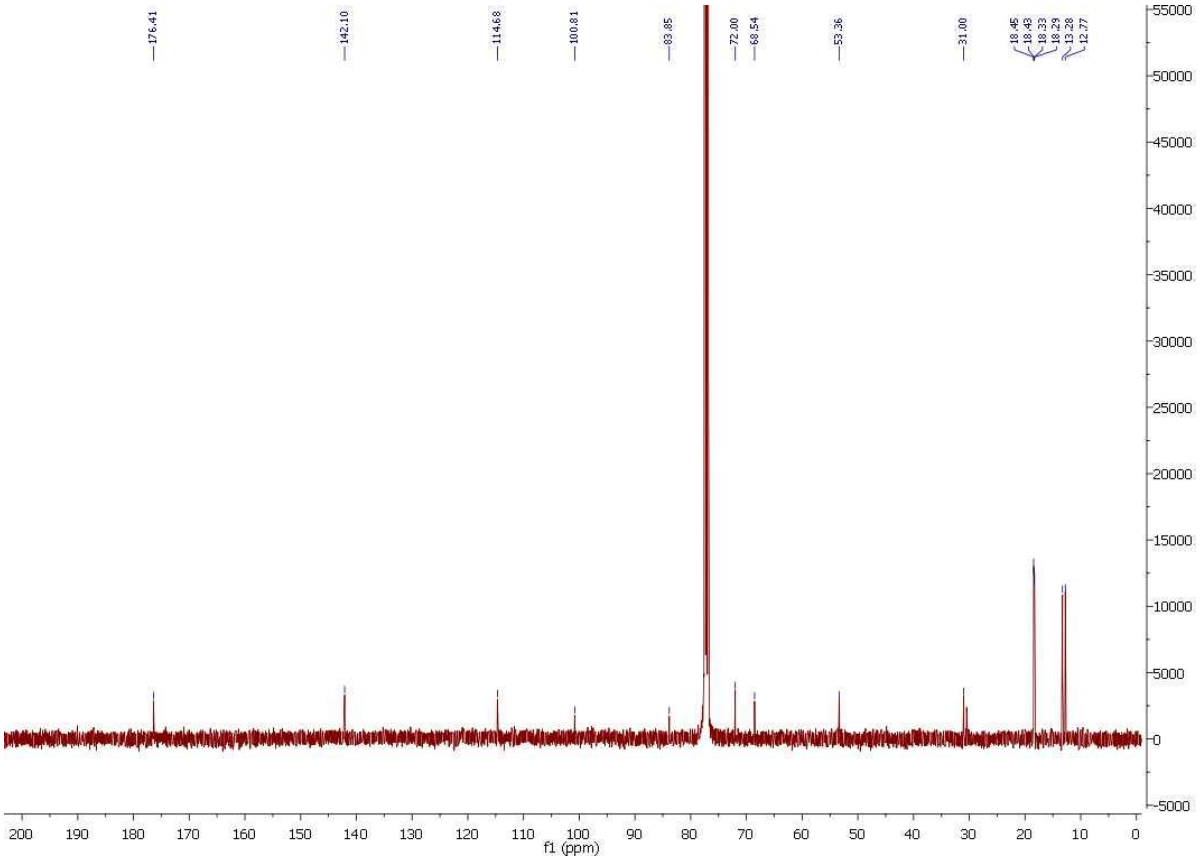
0.77
1.16
1.05
0.97
2.00
1.80
2.74
21.32
f1 (ppm)

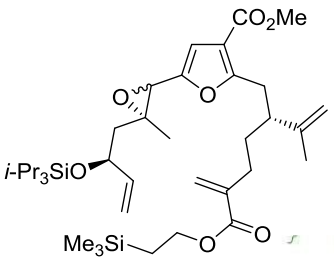

176.75
140.59
116.08
100.25
83.40
73.98
67.14
47.88
30.58
18.04
18.00
12.33
f1 (ppm)


i-Pr3SiO
OSii-Pr3
H
O

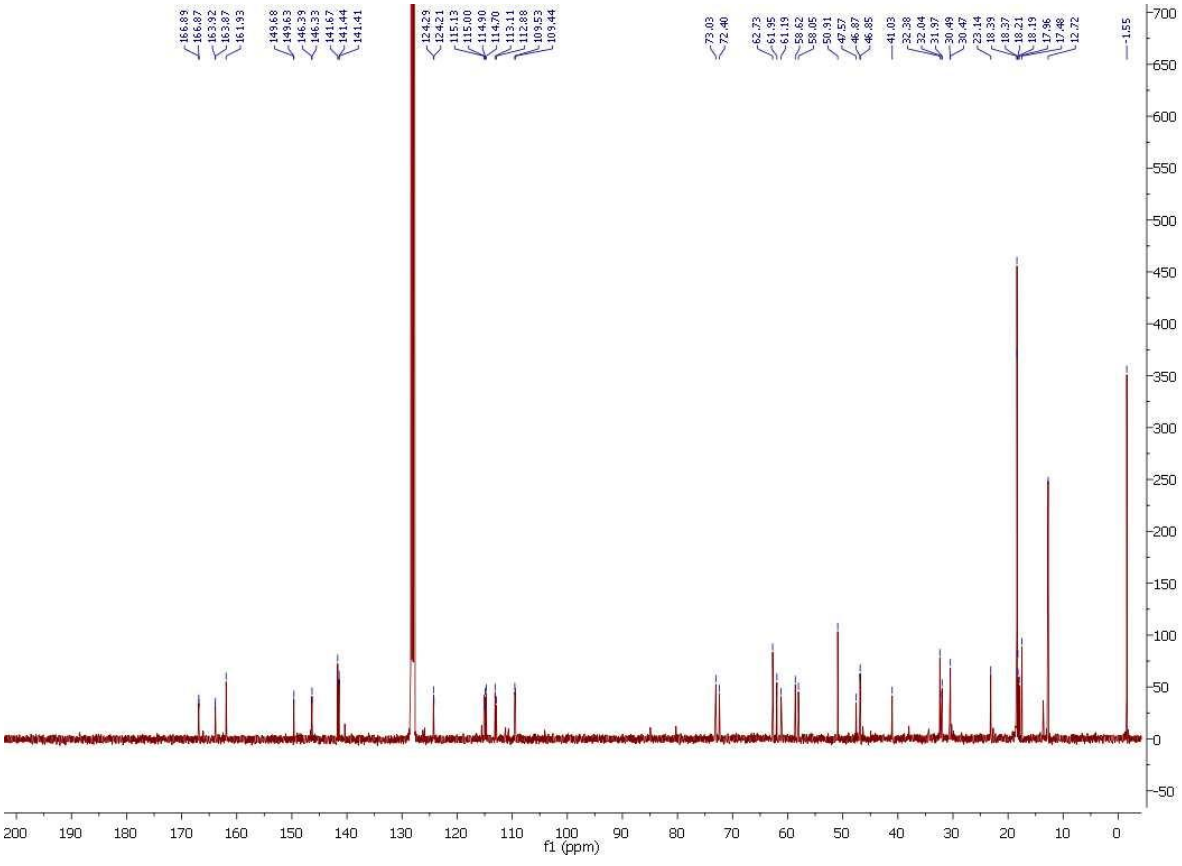
433

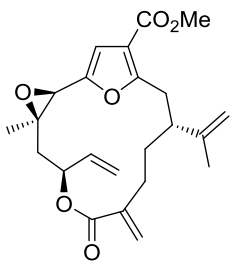
0.87
1.07
1.12
1.04
1.06
1.00
1.25
2.98
41.73
f1 (ppm)


176.41
142.10
114.68
100.81
83.85
72.00
68.54
53.36
31.00
18.45
18.43
18.33
18.29
13.28
12.77
f1 (ppm)



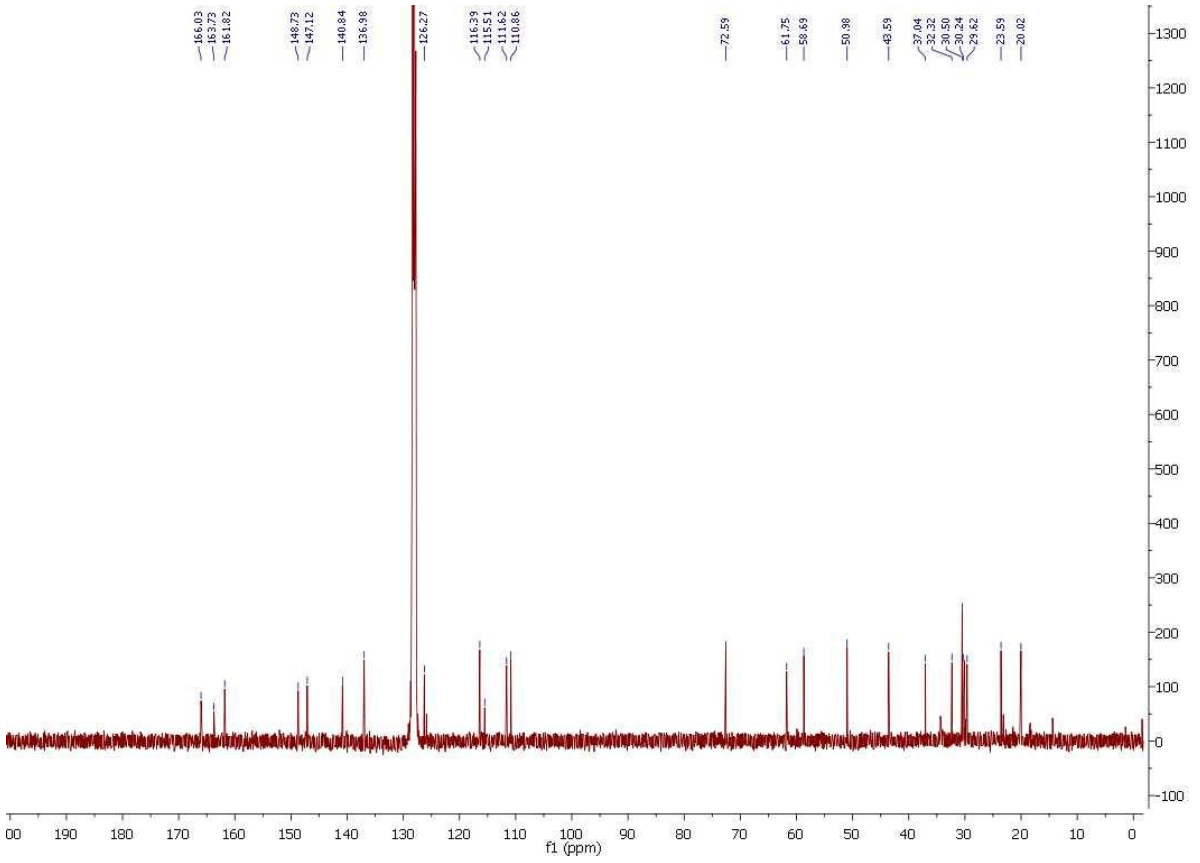
436

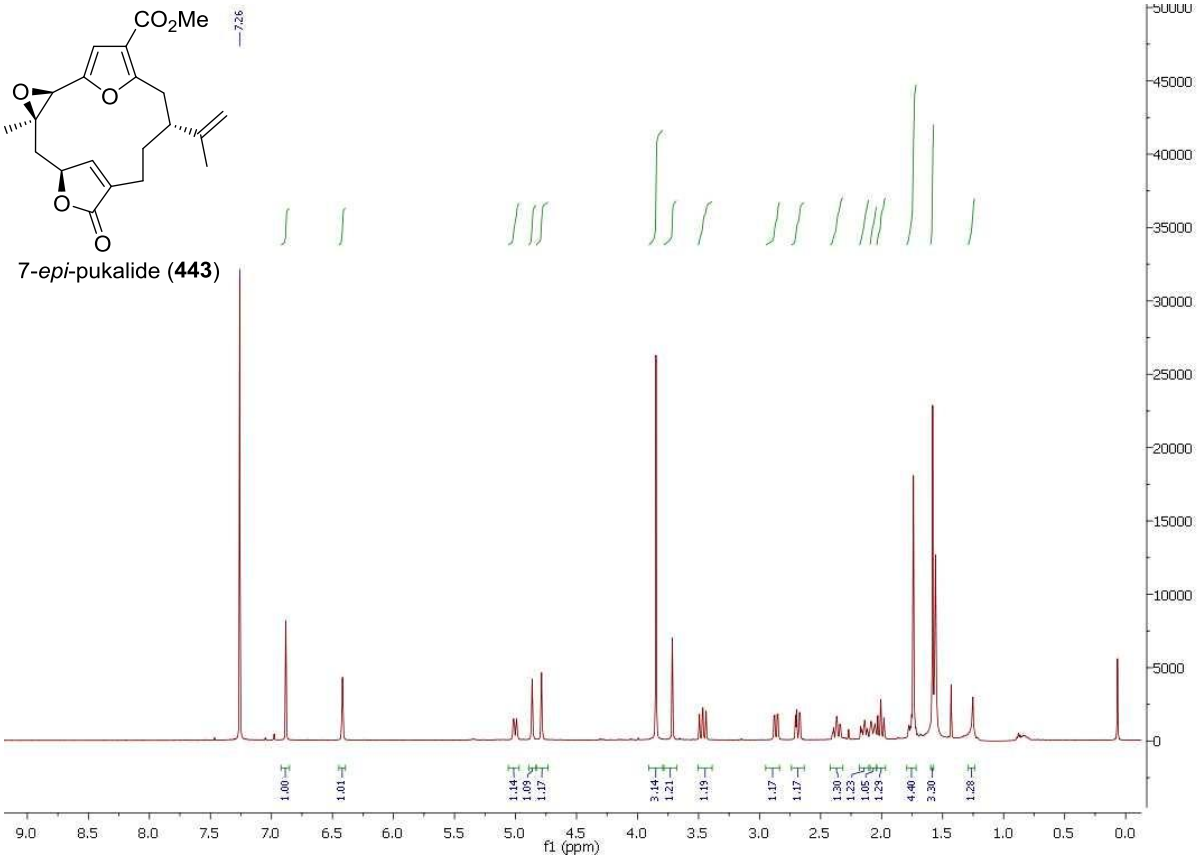



CO2Me
O
O
O
O

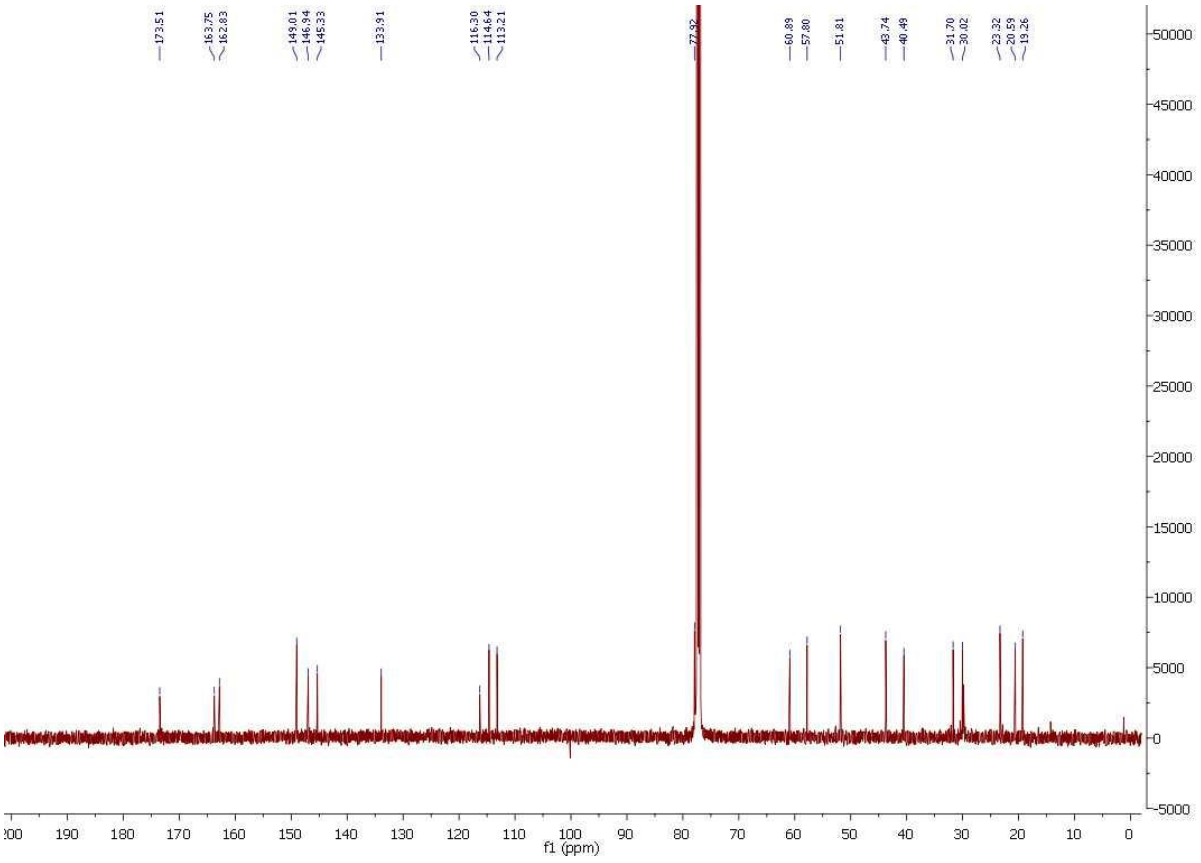
421

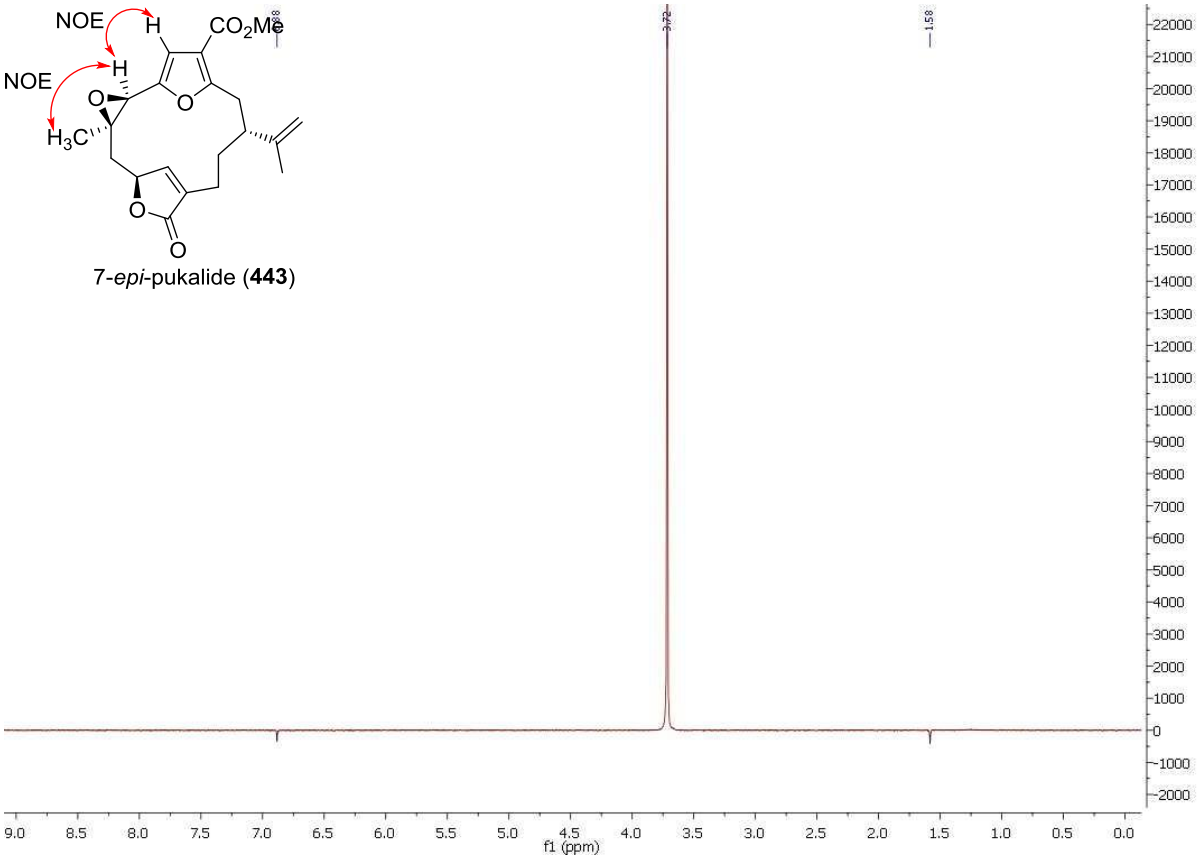
1.00
1.03
1.15
1.22
1.97
0.97
2.26
3.21
0.92
1.15
1.08
1.13
1.16
2.22
1.21
1.18
2.95
2.10
2.98
f1 (ppm)


166.03
163.73
161.82
148.73
147.12
140.84
136.98
126.27
116.39
115.51
111.62
110.86
72.59
61.75
58.69
50.98
43.59
37.04
32.32
30.50
30.24
29.62
23.59
20.02
f1 (ppm)

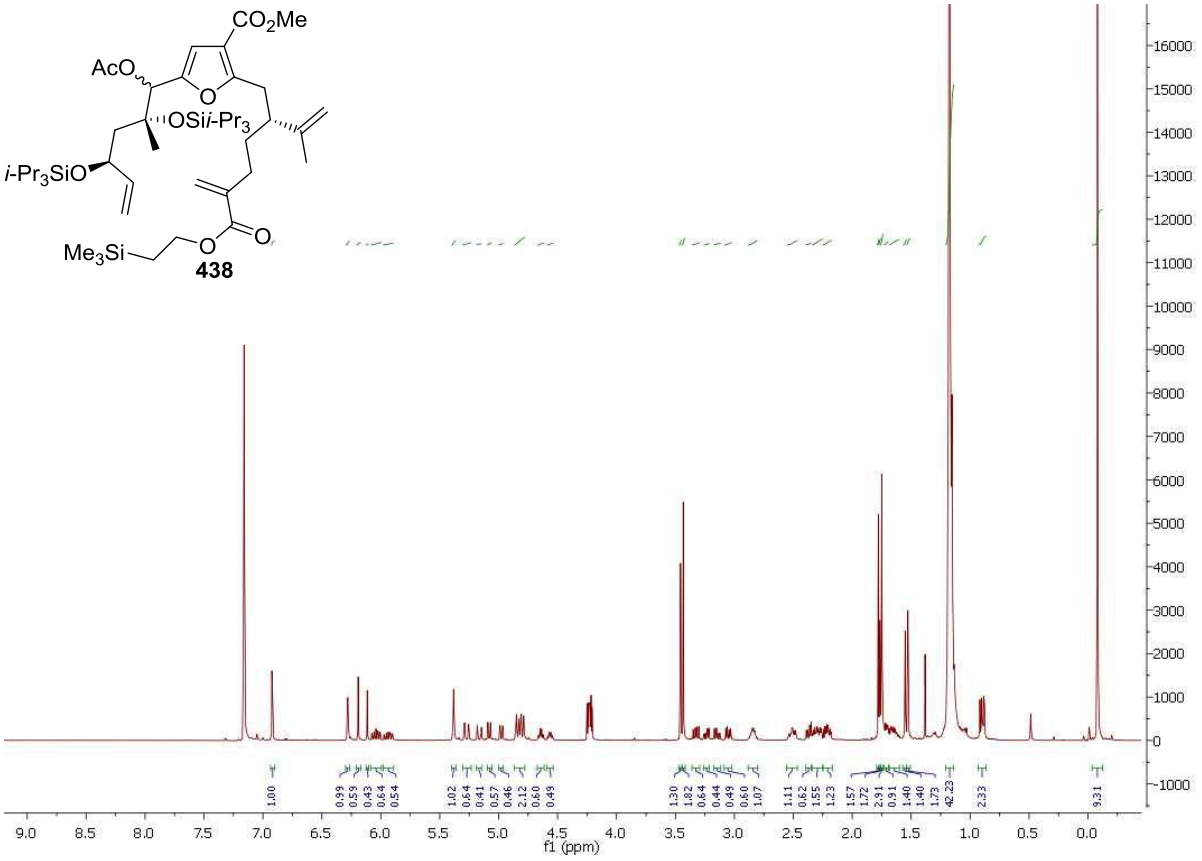


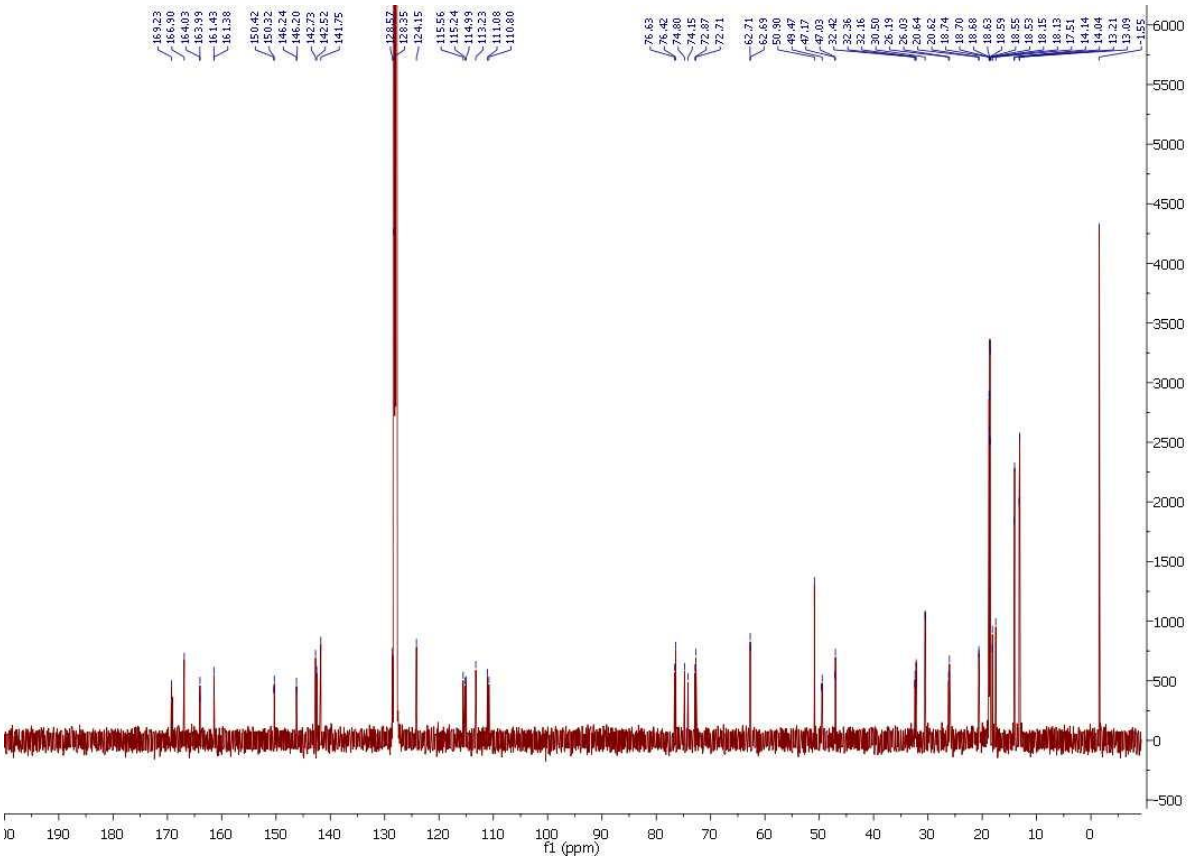
7-*epi*-pukalide (**443**)

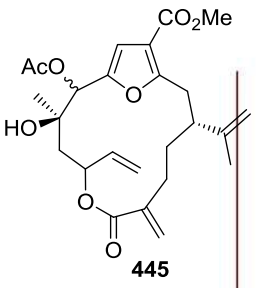




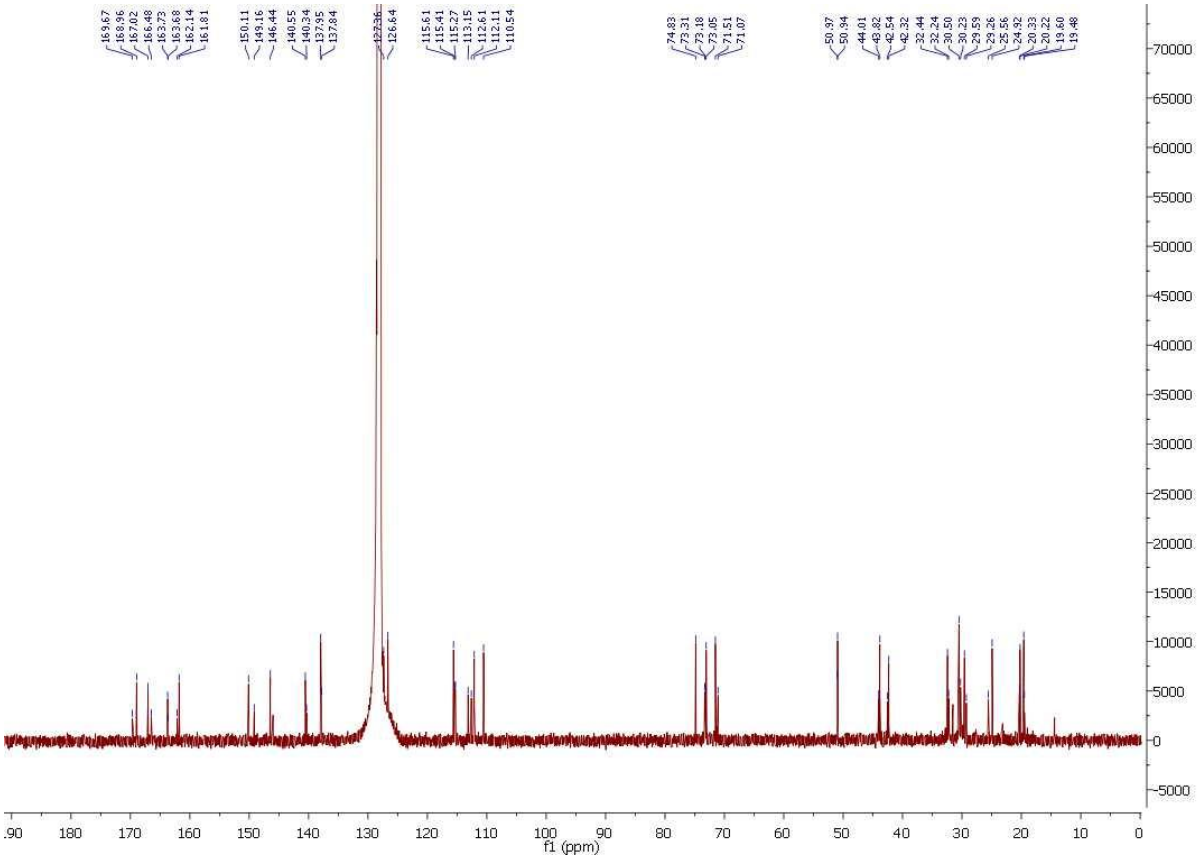
7-*epi*-pukalide (**443**)

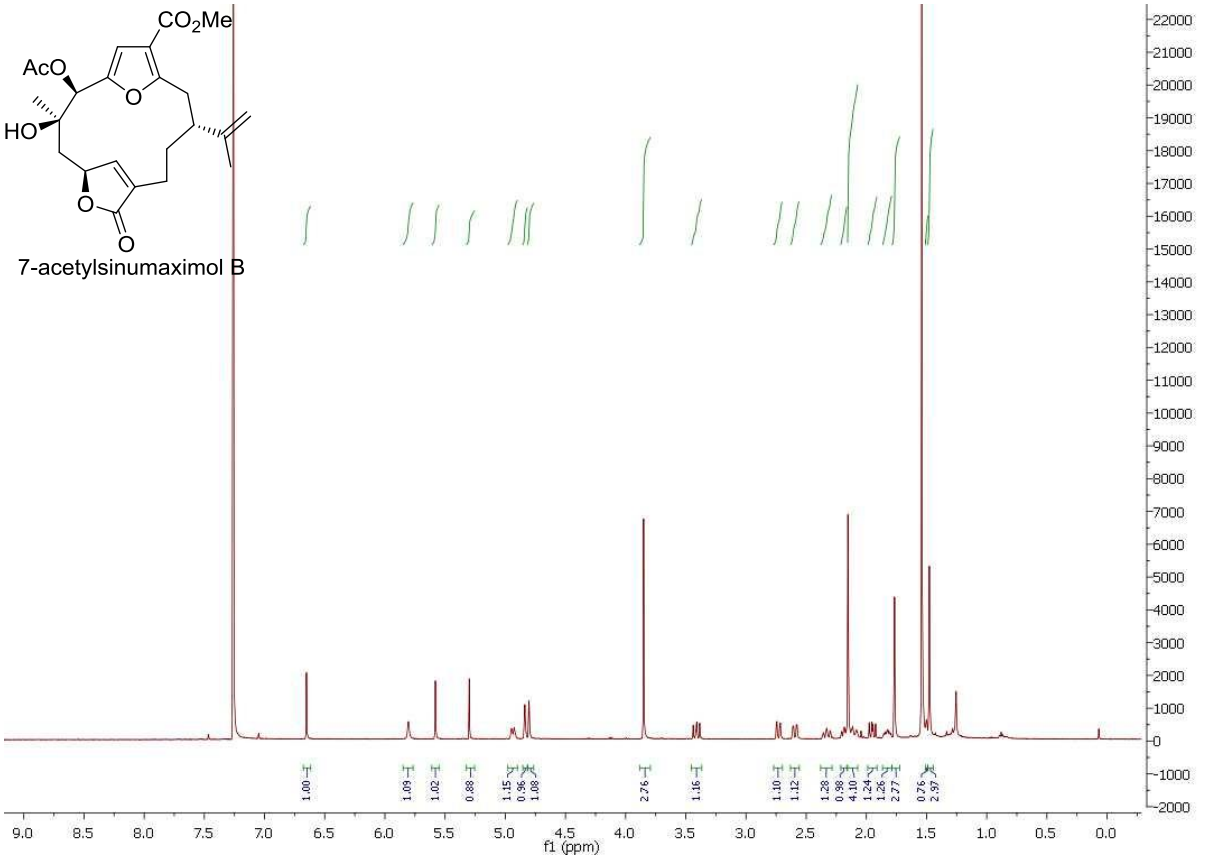

CO2Me
AcO
OSi-Pr3
i-Pr3SiO
Me3Si
O
O
O
438
f1 (ppm)

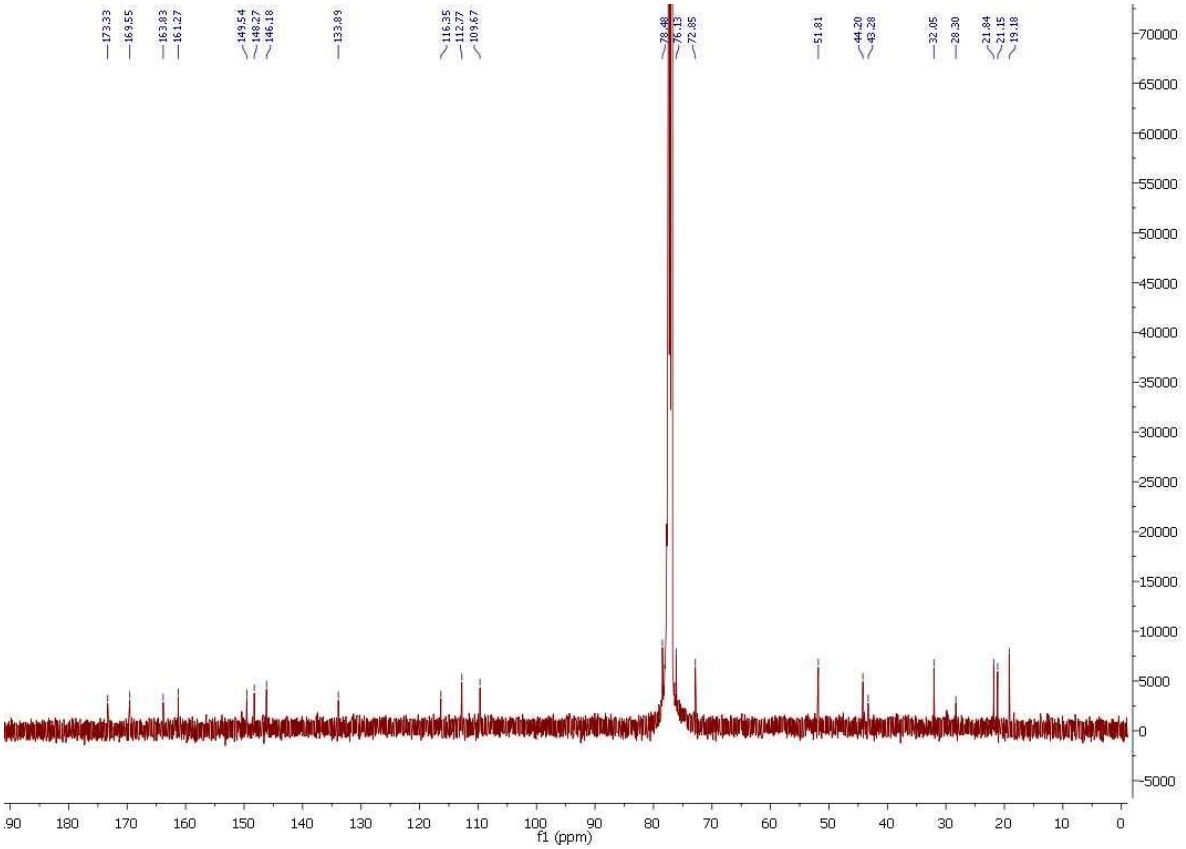

f1 (ppm)



445




CO2Me
AcO
HO
O
O
O
7-acetylsinumaximol B
f1 (ppm)


f1 (ppm)