Development of (*Z*)-Alkenylsilane Coupling Methodology and Application Towards the Synthesis of Incednine

A thesis submitted to the
Board of the Faculty of Physical Sciences
In partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Christian J. Kuper

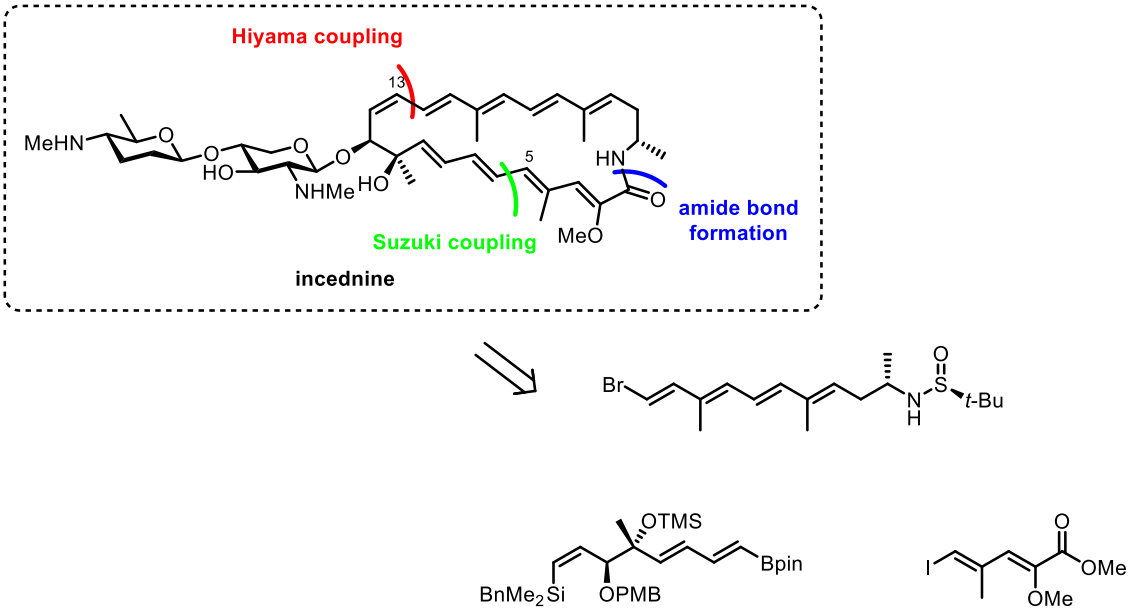
Jesus College, University of Oxford, Hilary Term 2017

Development of (*Z*)-Alkenylsilane Coupling Methodology and Application Towards the Synthesis of Incednine

Doctor of Philosophy **Christian Kuper**

Hilary Term, 2017 **Jesus College**

This thesis describes the development of methods for the synthesis of incednam, the aglycon of incednine, *via* Hiyama cross-coupling. An early chapter discusses the efforts to improve upon previous efforts to access major building blocks. This is followed by a chapter focusing on the development of a novel strategy to access more reactive dimethyl alkenylsiloxanes and their applications. Finally, this new strategy is applied to the synthesis and different approaches to assemble incednam are explored.



Scheme 1

Acknowledgements

I would like to extend my thanks to the following people, without whom the completion of this thesis would not have been possible.

Firstly to Ed, for being a fantastic supervisor with a highly contagious enthusiasm. I have learnt a huge amount from him in the past four years and appreciate his kind advice and guidance.

To the EU, for their generous provision of funding.

To the EAA group past and present, for being always supportive and helpful, both in, and also out of the lab. The biggest thanks to Halli, my accomplice in this project, with whom I shared many constructive (and some silly) discussions about chemistry, life, or whatever was on my mind. Thanks to Guilhem, Carlos, Halli, Bryony, Rob, Marius, Dimitri, Steve, Shermin, Yao and my fellow Team Synthesis members, for their scientific know-how and input. Thanks to Guilhem, Carlos, Halli, Bryony, Rob, Marius, Dimitri, Steve, Shermin, Yao, Eddie, Alistair, Joe, and Venky for their friendship and support throughout these endeavours. Special thanks to the F9 crowd, especially Halli, Eddie, Bryony, Tim, and Tarn for making the time in the lab so enjoyable (particularly during Discofridays). Thanks to everyone who agreed to proof read parts of this thesis, Halli, Carlos, Steve, Dimitri, and Eddie.

To the NMR and mass spectrometry staff, for ensuring that everything is running smoothly.

A big thanks to my family, whose continuous support throughout has enabled me to pursue this.

Abbreviations

ACP	acyl carrier protein
AT	acyltransferase
Bn	benzyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BTSH	mercaptobenzothiazole
Bz	benzoyl
ClAc	2-chloroacetyl
CPF	(*R*)-3a-allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan
dba	dibenzylideneacetone
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,5-benzoquinone
DH	dehydratase
DIBALH	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DIT	diisopropyl tartrate
DIT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
dppf	bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-tert-butyl-4-methylpyridine
DVDS	1,1-divinyl-1,1,3,3,-tetramethyldisiloxane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ER	enoylreductase
Fmoc	fluorenylmethyloxycarbonyl
HMDS	hexamethyldisilazane
imid	imidazole
IS	internal standard
KR	ketoreductase
KS	ketosynthase

LDA	lithium diisopropylamide
PAB	para-acetoxybenzyl
PHB	para-hydroxybenzyl
Phth	phthalimide
pin	pinacol
PKS	polyketide synthase
PMBTCA	4-methoxybenzyl-2,2,2-trichloroacetimidate
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
TBDPS	*tert*-butyldiphenylsilane
TBS	*tert*-butyldimethylsilane
TBS	*tert*-butyldimethylsilyl
TDMPP	tris(2,6-dimethoxyphenyl)phosphine
TDS	thexyl dimethyl silane
TE	thioesterase
Teoc	2-(trimethylsilyl)ethyl carbonate
TES	triethylsilyl
THP	1,2,3,4-tetrahydroquinoline
TMB	tetramethylbutane
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPS	2,4,6-triisopropylbenzenesulfonyl
Troc	2,2,2-trichloroethyl carbonate
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Contents

1 Introduction

1.1 Isolation and structure elucidation of incednine

In 2008 Imoto *et. al* reported the isolation and structure elucidation of a novel macrolide natural product from *Streptomyces sp.* ML694-90F3 culture broth, called incednine (**1**). Incednine was isolated as the result of cell-based chemical-genetic screening to identify novel small molecule inhibitors for BcL-2/BcL-xL proteins,[1] and is comprises a 24-membered polyunsaturated macrolactam appended with a heavily deoxygenated disaccharide (Figure 1.1).

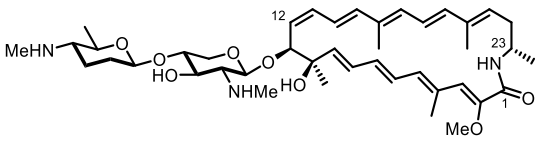


*Figure 1.1 Structure of Incednine (**1**)*

Incednam (**2**), the aglycon of incednine, features two conjugated polyene systems separated by vicinal quaternary *C*10 and tertiary *C*11 hydroxyl-bearing stereocentres, and an amide group adjacent to a third *C*23 stereocentre. The *C*2-*C*9 tetraene contains a *C*2-*C*3 (*Z*)-enol ether, and the *C*12-*C*21 pentaene also contains a single *C*12-*C*13 (*Z*)-alkene in an otherwise all-(*E*) system. Olefin geometries and relative stereochemistry were determined by proton NMR and analysis of the corresponding NOE correlations. Preparation of the *C*11 Mosher esters of incednam enabled the absolute assignment of the *C*10 and *C*11 stereocentres, being R10 and S11 respectively. Stereocentre *S*23 was predicted using *in silico* calculations.

The structure and stereochemistry of the disaccharide was elucidated by ^{1}H NMR and X-ray crystallographic analysis. The aminosugars were identified to be 2-deoxy-2-methylamino-*β*-D-xylopyranose and *N*-monodemethyl-D-forosamine.

In 2012, Schulz *et al.* reported the isolation of the related 24-membered macrolactam aminoglycoside silvalactam (**3**) (Figure 1.2).[2] Silvalactam was isolated from *Streptomyces* strain Tü 6392, and shows a strong structural resemblance to incednine. Key differences are the side chain of the macrolactam at *C*2, which is an isobutyl group instead of the methyl enol ether present in **1**. Further differences are the methylation pattern of the saccharide (2-deoxy-2-methylamino-*β*-D-xylopyranose) attached to *C*11, and the lack of a second sugar. Silvalactam displays potent antiproliferative activity against various cancerous and non-cancerous cell lines.

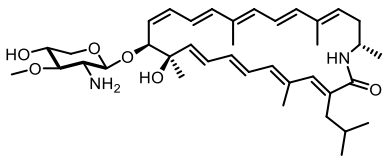


*Figure 1.2 Structure of Silvalactam (**3**)*

1.2 Bioactivity of incednine

Consideration of DNA mutation rates in an average human (1 in 2×10^7 per gene cell division, 10^{14} target cells in the average human) highlights the efficiency of the body's mechanisms to prevent cancer cell development.[3,4] However, if these systems fail, there are six cell-intrinsic hallmarks of cancer that can be observed:[5,6] provision of autonomous growth factors, insensitivity to antiproliferative signals, disabled apoptosis, limitless replication, production of angiogenic modulators, and tissue invasion with metastasis.

Impaired apoptosis is both critical in cancer development and a problem in its treatment.[7] Apoptosis is caused by intracellular cysteine proteases (caspases) that are largely inactive until triggered by activating proteins (e.g. cytochrome C) to cleave cellular proteins leading to destruction of the cell (Figure 1.3).[7,8] The evolutionary older (stress) pathway

is triggered by inter- and intracellular cues and is regulated by members of the Bcl-2 family of proteins.[7]

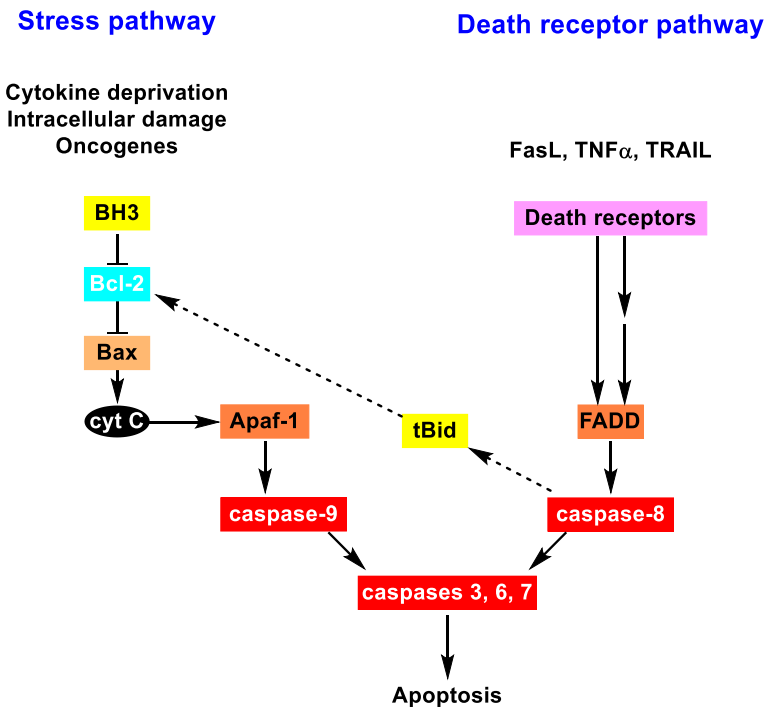


Figure 1.3 Pathways to cell death.[7]

The interaction of proteins of three subfamilies determine if the stress apoptosis pathway is switched on. Subfamilies are grouped based on the number of shared domains (Bcl-2 homology, BH). Anti-apoptotic proteins (BH1-4), such as Bcl-2, Bcl-xL, protect cells from diverse cytotoxic conditions. Pro-apoptotic proteins (BH1-3), such as Bax, Bak and Bok, are very similar to BcL-2 in sequence, in contrast to BH3-only proteins, such as Bid and Bim.[9-13] For cell death to occur both pro-apoptotic families are required; the anti-apoptotic proteins must be inhibited by pro-apoptotic or BH3-only proteins, and pro-apoptotic proteins Bak or Bax need to be activated by BH3-only proteins.[14,15] This leads to permeabilisation of the outer membrane of the mitochondrion (a process known as MOMP).[16] Intermembrane space proteins such as cytochrome C are released, activating caspases to ultimately kill the cell. It seems plausible that overexpression of anti-apoptotic proteins in cancer cells will sequester pro-apoptotic and BH3-only proteins. This will not

only prevent MOMP and cell death, but also provide immunity to chemotherapeutic drugs and radiotherapy.[7,17-19] Many human cancer types show an overexpression of Bcl-2, Bcl-xL, or both, making these proteins an appealing target for inhibition by therapeutics.[20]

The first such small molecule inhibitor, HA14-1, was reported in 2000 by Huang *et al.* (Figure 1.4).[21] HA14-1 was discovered through a combination of *in silico* screening and cell-based assays, and was shown to interact with Bcl-2 proteins and induce apoptosis in human myeloid leukaemia (HL-60). This discovery led to many more inhibitors of survival enzymes, such as ABT-737, antimycin A, navitoclax, obatoclax, maritoclax and sabutoclax, which are currently in preclinical and clinical development (Figure 1.4).[22-29]

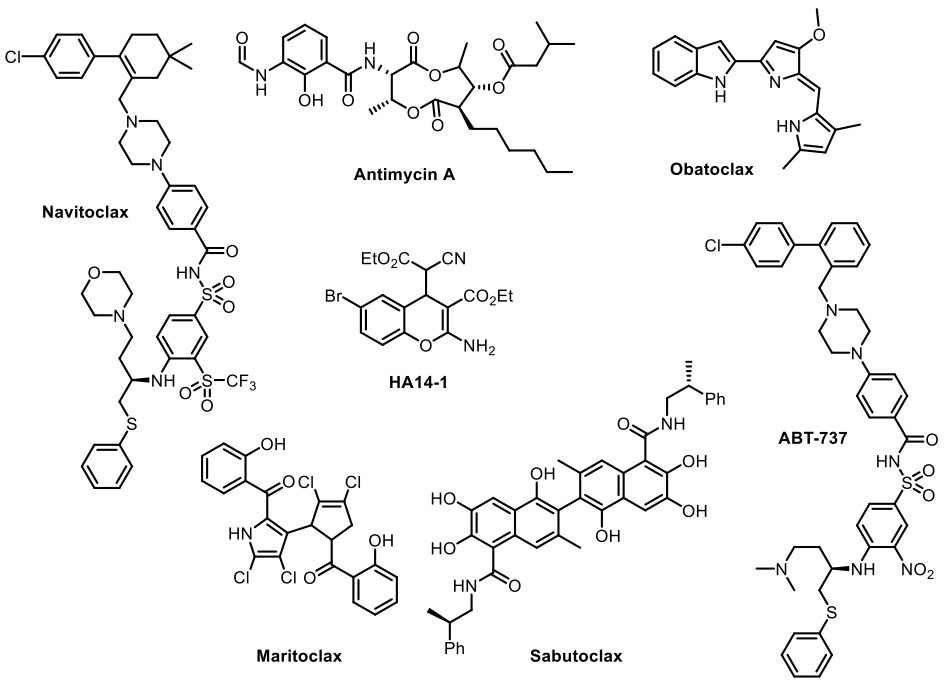


Figure 1.4 Inhibitors of anti-apoptotic enzymes

Incednine, in combination with anti-tumour drugs, is able to induce apoptosis in Bcl-xL overexpressing human small cell lung carcinoma Ms-1 cells. Interestingly, the anti-apoptotic function of Bcl-2/Bcl-xL is inhibited without disrupting its binding to pro-apoptotic Bcl-2 family proteins, as many other small molecule inhibitors do.[21,30] Sakakibara *et al.* set out to identify incednine's actual target.[31] After showing that none of the proteins identified to interact with affinity-tagged incednine were incednine's

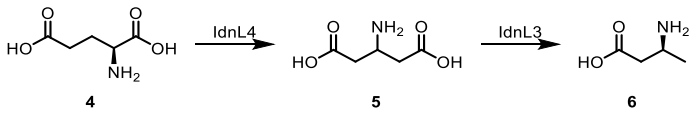
actual target, a different approach was required. *In silico* screening was used to predict candidate proteins that could bind to the ligand;[32] experimental verification by *in vitro* biotinylated incednine pull-down experiments revealed three proteins related to cancer cell survival interacting with incednine.[31] Of these, ACACA (acetyl-CoA carboxylase-α) was determined to be the most likely protein target of incednine. It catalyses the ATP-dependent carboxylation of acetyl-CoA to malonyl-CoA in long-chain fatty acid synthesis. Cancer cell proliferation and survival are believed to be strongly dependent on *de novo* fatty acid synthesis,[33,34] and ACACA is upregulated in several types of cancers.[35] Therefore, survival of Bcl-xL overexpressing cells might be reliant on ACACA. To confirm this hypothesis, TOFA (5-tetradecycloxy-2-furoic acid) and RNA-mediated silencing was used to inhibit ACACA in human small cell lung carcinoma Ms-1 cells. When used in combination with anti-tumour drugs, apoptosis is induced, as is observed when using incednine.[31]

1.3 Biosynthesis of incednine

Polyketide synthases (PKSs) are responsible for the biosynthesis of polyketides, secondary metabolites that show a range of biological activities. PKSs are generally organised into modules, each module being responsible for two carbon homologation, and consisting of several domains with defined functions, such as acyltransferase (AT), acyl carrier protein (ACP), ketosynthase (KS), ketoreductase (KR) dehydratase (DH), enoylreductase (ER), and thioesterase (TE).

The biosynthetic pathway for incednine has been extensively investigated by Eguchi *et al.*, who proposed a probable biosynthesis based on feeding experiments with ^{13}C labelled supplementation culture, as well as the isolation of the biosynthetic gene cluster.[36-38]

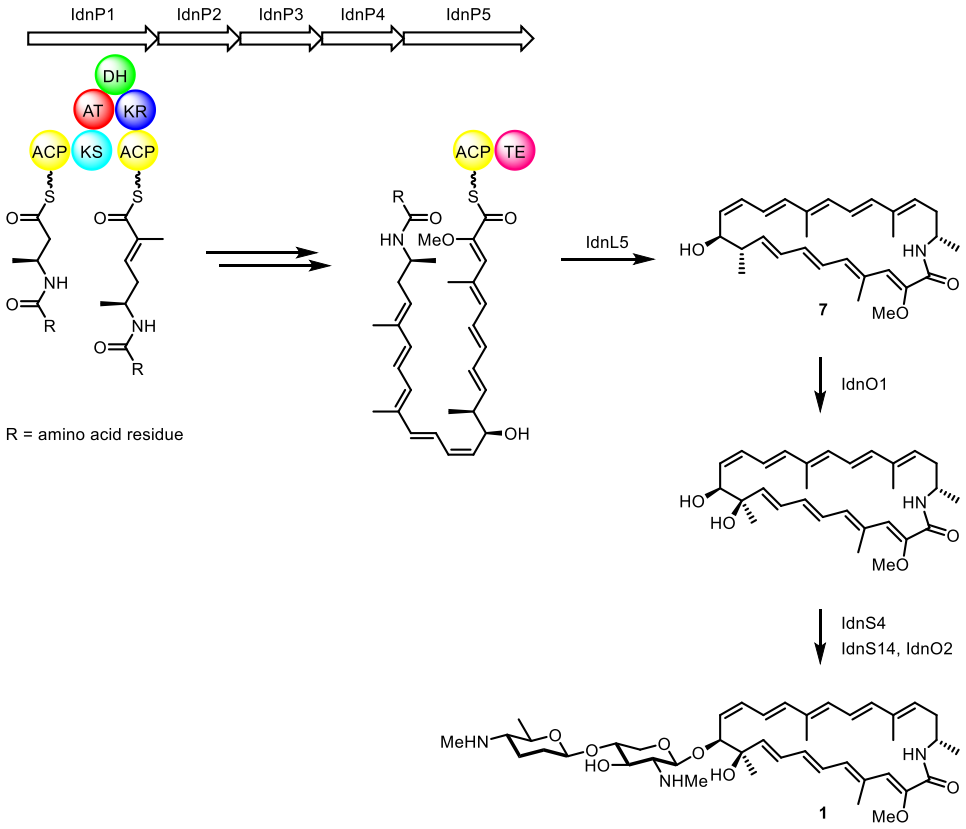
Feeding experiments revealed that incednam is biosynthesised using a unique starter unit, 3-aminobutyrate **6**, which is derived from L-glutamate **4**. Isolation of the biosynthetic gene cluster revealed enzymes *IdnL3* and *IdnL4*, which are conserved in the salinilactam biosynthetic gene cluster, and show homology to aminotransferase genes and amino acid aminomutase genes that convert L-glutamate **4** into 3-aminobutyrate **6** (Scheme 1.1).[39,40]



Scheme 1.1 Biosynthesis of 3-aminobutyrate from L-glutamate

6 is then transferred onto ACP *IdnL6*, where an amino acid is coupled onto the amine moiety to protect the amine and prevent cyclisation at an undesired stage.[41] Polyketide synthesis is then initiated by loading onto the ACP domain (Scheme 1.2).

Five PKSs (IdnP1-5) consisting of a total of 10 modules are responsible for the biosynthesis of the macrolactam. Each module mediates one extender unit condensation cycle from the starter unit overall using five malonate, four methylmalonate and one methoxymalonate extender units. After completion, thioesterase and cleavage of the amino acid residue results in cyclisation to form macrolactam **7**. Post-PKS modification by IdnO1 then introduces the *C*10 hydroxyl, followed by glycosidases IdnS4, IdnS14 and coenzyme IdnO2, which transfers the two saccharides onto the *C*9 position, thereby completing the biosynthesis of incednine (Scheme 1.2). The aminosugars 2-deoxy-2-methylamino-β-D-xylopyranose and *N*-monodemethyl-D-forosamine are both biosynthetically derived from glucose before being transferred onto the macrolactam.



Scheme 1.2 Incednine polyketide synthases (PKSs)

1.4 Previous work towards incednine

To date, the total synthesis of incednine **1** has yet to be achieved. However, there are two syntheses of the aglycon incednam, by Toshima *et al.* from 2010 and 2013.[42,43] The disaccharide also has two reported routes, one by Toshima *et al.* in 2011,[44] and one by Roush *et al.* in 2013.[45]

1.4.1 Toshima's first generation synthesis of Incednam

In Toshima's first generation synthesis of the aglycon incednam, key disconnections *N*-*C*1 amide bond and *C*13-*C*14 bond were identified, providing key building blocks tetraenyl stannane **8** and tetraenoate **9** (Figure 1.5).

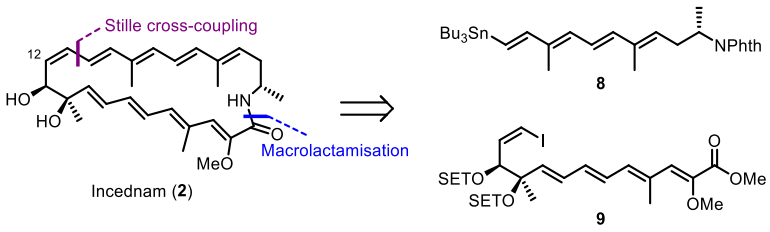
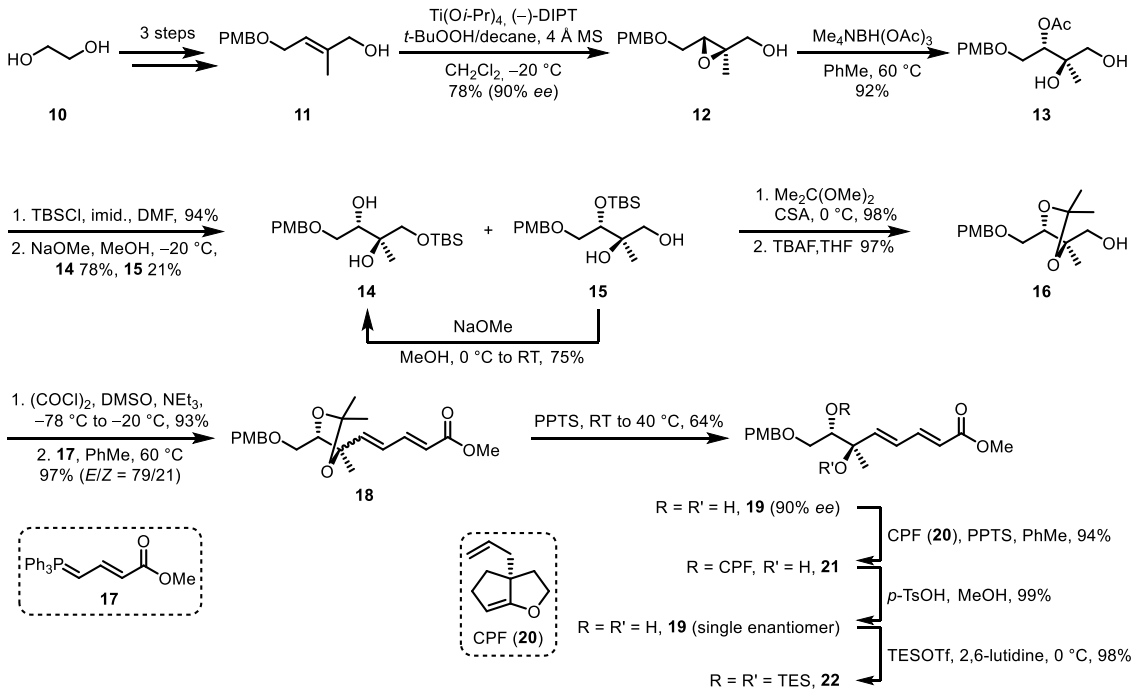


Figure 1.5 First generation synthesis retrosynthetic approach by Toshima et al.

1.4.1.1 Synthesis of *C*1-*C*13 fragment

Toshima *et al.* reported a synthesis of the *C*1-*C*13 subunit in 2009.[46] The synthesis commenced with monoprotection of ethylene glycol (**10**), one-pot Swern-oxidation Wittig reaction and DIBALH reduction to afford **11** in three steps (Scheme 1.3).[47]

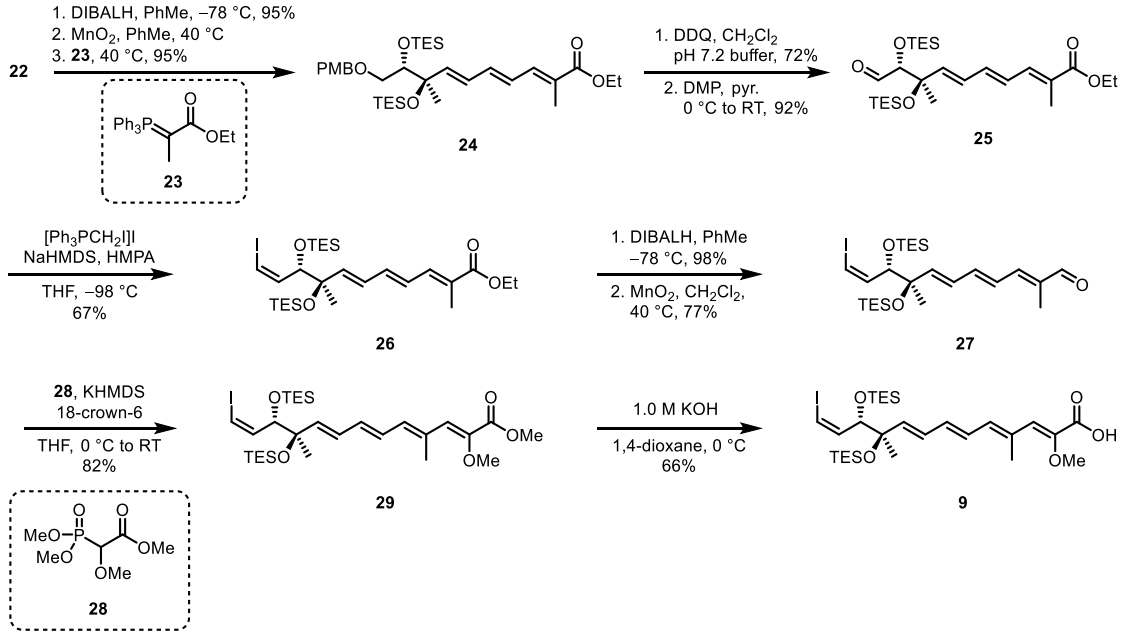


*Scheme 1.3 Toshima's synthesis of C5-C12 fragment **22***

Allylic alcohol **11** was then subjected to Sharpless asymmetric epoxidation, followed by regioselective opening of epoxide **12** using $Me_4NBH(OAc)_3$, to introduce the *C*10 and *C*11 stereocenters, affording diol **13**.[48] Next, several protection/deprotection steps followed by an oxidation/Wittig olefination sequence of alcohol **13** gave dienoate **18** as a *E,E* / *E,Z*-mixture of 79:21. After acetal cleavage and separation of geometric isomers,

the enantiopurity of **19** was enhanced by resolution with CPF (**20**).[49,50] The corresponding acetal **20** was obtained in excellent 94% yield, along with 5% of its diastereomer. Acetal cleavage using p-TsOH proceeded in 99% yield to give diol **19** as effectively a single enantiomer, which was TES-protected to give **22** in 98% (Scheme 1.3).

Dienoate **22** was subjected to a reduction/oxidation/Wittig homologation sequence, after which (*Z*)-vinyl iodide was installed by deprotection of the PMB ether using DDQ, Dess-Martin oxidation, and Stork-Zhao olefination.

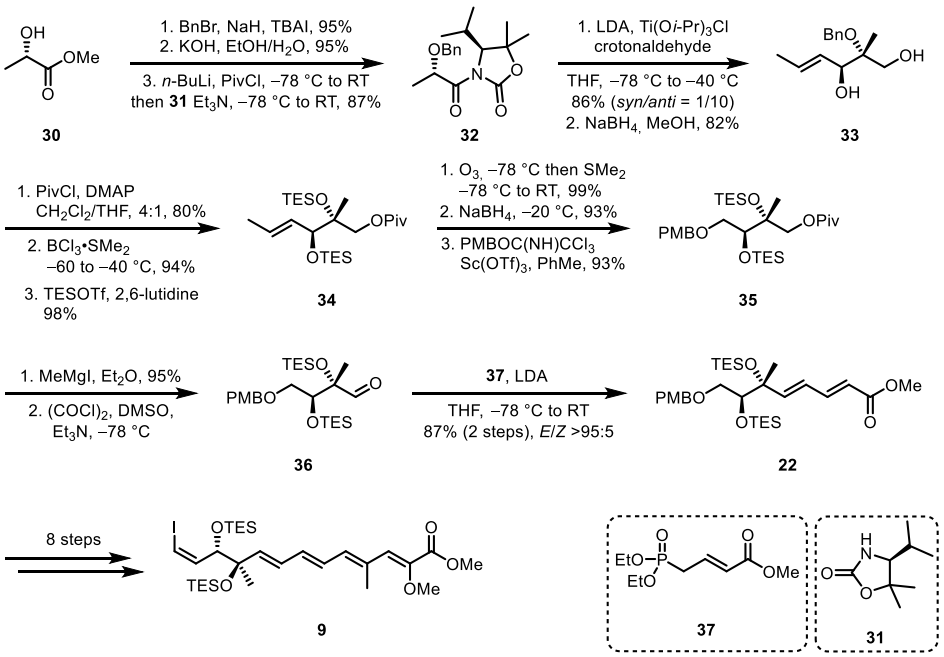


Scheme 1.4 Toshima's synthesis of C1-C13 fragment ***9***

Trienoate **26** was then subjected to a similar reduction/oxidation/HWE-olefination sequence to install the remaining carbon atoms, and afford the first major building block **30** towards incednine in 23 linear steps, with an overall yield of 6.9% (Scheme 1.4).

This first generation synthesis of the *C*1-*C*13 fragment **9** suffers from a number of drawbacks, such that only 5 steps are necessary to install all carbon atoms needed in this fragment, while the remaining 18 steps are mostly protecting group manipulations or oxidation state changes. At the same time, the necessity to separate enantiomers from the

Sharpless epoxidation by chemical modification using CPF (**20**) hampers this synthesis. Some of these challenges were addressed in a revised synthesis of subunit **9**.[44]

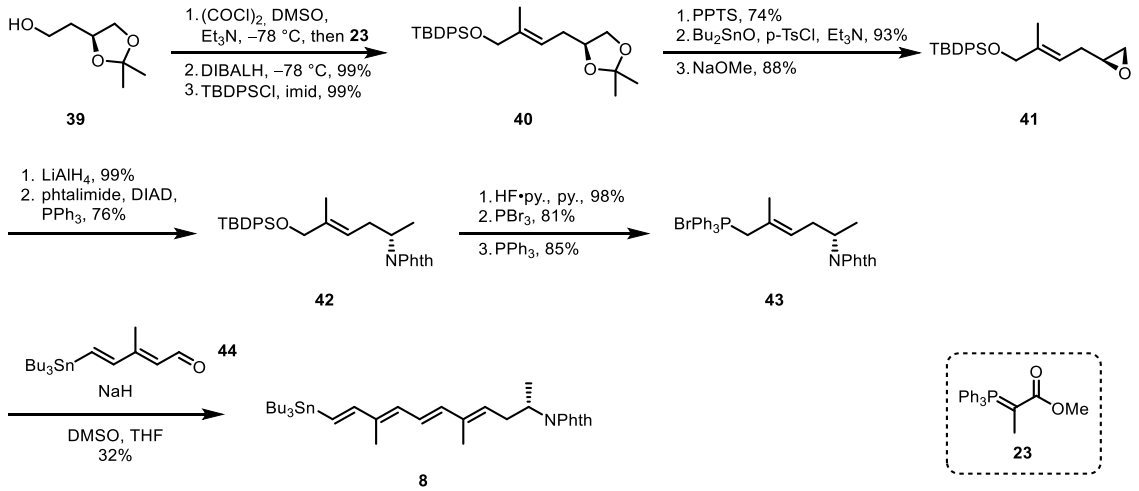


*Scheme 1.5 Toshima's revised synthesis of C1-C13 fragment **9***

In this revised route, methyl L-lactate (**30**) was transformed into oxazolidinone derivative **32** in three steps, followed by a titanium-mediated Evans aldol reaction, which gave the desired *anti* product with high diastereoselectivity.[51,52] Reductive removal of the auxiliary followed by a sequence of protecting group manipulations gave **34**. Ozonolysis, reduction and PMB protection afforded the fully-protected tetraol **35**. Pivaloyl ester-deprotection, Swern oxidation and HWE-olefination afforded dienoate **22**, intersecting the original synthesis (Scheme 1.5).[53,54] While, the second generation synthesis addresses issues from the first generation synthesis, such as the use of chiral reagent to separate enantiomers, and low *E*/*Z* selectivity in the formation of dienoate **18**, both syntheses still suffer from multiple refunctionalisation and protecting group manipulation steps, and are of similar length.

1.4.1.2 Synthesis of *C*14-*C*23 fragment

The synthesis of the *C*14-*C*23 subunit **8** is summarised in Scheme 1.6, and commenced with a one-pot Swern oxidation/Wittig olefination of commercially available alcohol **39**,[55] reduction and TBDPS protection of the resulting alcohol to give protected triol **40**. Acetal cleavage, followed by tin-promoted tosylation of the primary alcohol,[56] and subsequent treatment with sodium methoxide, afforded epoxide **41**. Regioselective epoxide opening gave secondary alcohol, which upon Mitsunobu reaction was converted into protected amine **42**. TBDPS ether deprotection, followed by bromination and treatment of the resulting allyl bromide with triphenyl phosphine, afforded phosphonium salt **43**. Aldehyde **44**, which was prepared from ethyl 2-butynoate in 5 steps, was subjected to Wittig olefination with **43** to afford tetraenylstannane fragment **8** in a modest yield of 32%.[57-59] This stannane was found to be prone to oxidation and photochemical decomposition, and therefore had to be used immediately.

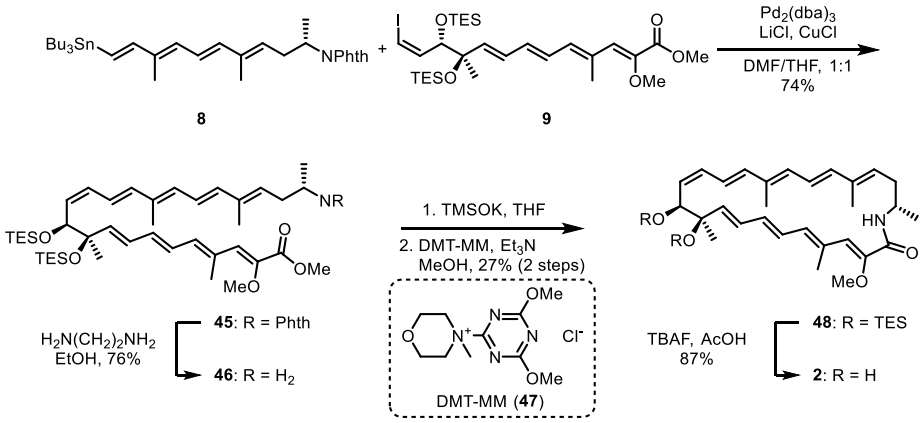


Scheme 1.6 Toshima's synthesis of the C14-C23 fragment

1.4.1.3 Assembly of incednam

The synthesis endgame, summarised in Scheme 1.7, commenced with Stille cross-coupling of stannane **8** and iodide **9**, utilising Corey's conditions with Pd(0), LiCl,

and CuCl, to give **45** in an excellent 74% yield.[60] After phthalimide deprotection and ester demethylation, macrocyclisation of acyclic precursor **46** was achieved using DMTMM (**47**) in 27% yield. Finally, global TES-deprotection afforded incednam in 27 steps longest linear sequence. Synthetic incednam (**2**) was used to confirm the previously only predicted *S*23 stereochemical configuration.[1]



*Scheme 1.7 Endgame of Toshima's first generation synthesis of incednam (**2**)*

1.4.2 Toshima's second generation synthesis of incednam

In Toshima's second generation synthesis, two major limitations from the previous synthesis were addressed. Firstly, the use of unstable tetraenyl stannane **8** was avoided, and secondly macrocyclisation was envisaged to take place *via* ring-closing metathesis (RCM) with the aim to improve the low yield of 27% for the macrocyclisation step. Toshima's new retrosynthetic approach splits the former tetraenyl stannane building block into two shorter polyene systems **48** and **49** that are separately introduced into the synthesis, followed by connecting both ends *via* ring-closing metathesis to reveal the incednam pentaene moiety (Figure 1.6).[43]

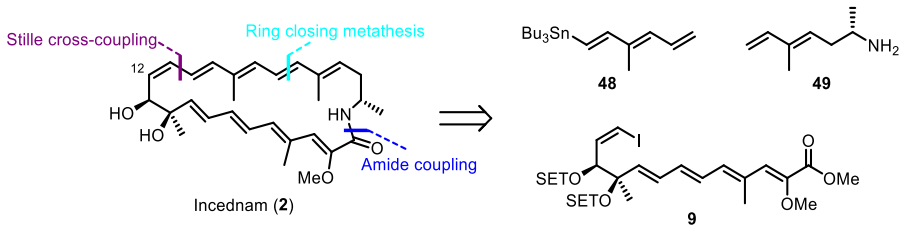
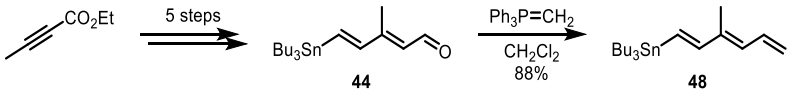


Figure 1.6 Toshima's second generation retrosynthetic approach

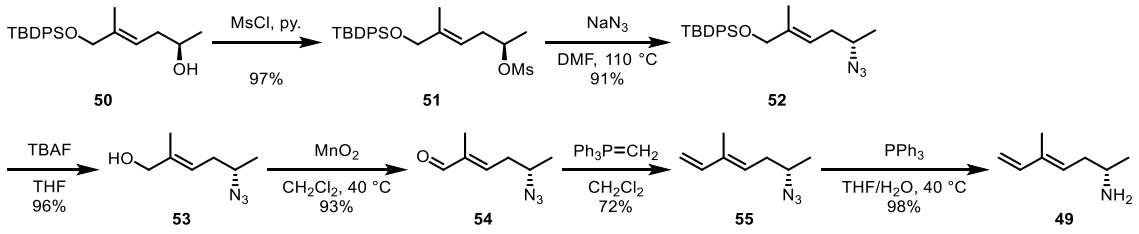
1.4.2.1 Synthesis of *C*14-*C*18 and *C*19-*C*23 fragments

Synthesis of *C*14-*C*18 subunit **48** was achieved by use of previously attained aldehyde **44**, which was subjected to Wittig olefination, affording **48** (Scheme 1.8).[44,57,59]



Scheme 1.8 Synthesis of C14-C18 fragment

Similarly, the required *C*19-*C*23 amine **49** was obtained in six steps from previously established alcohol **50**.[44] Mesylation followed by nucleophilic azide substitution afforded **52**, which upon silyl ether deprotection, oxidation of the resulting alcohol, Wittig olefination and Staudinger reaction gave amine **49** (Scheme 1.9).

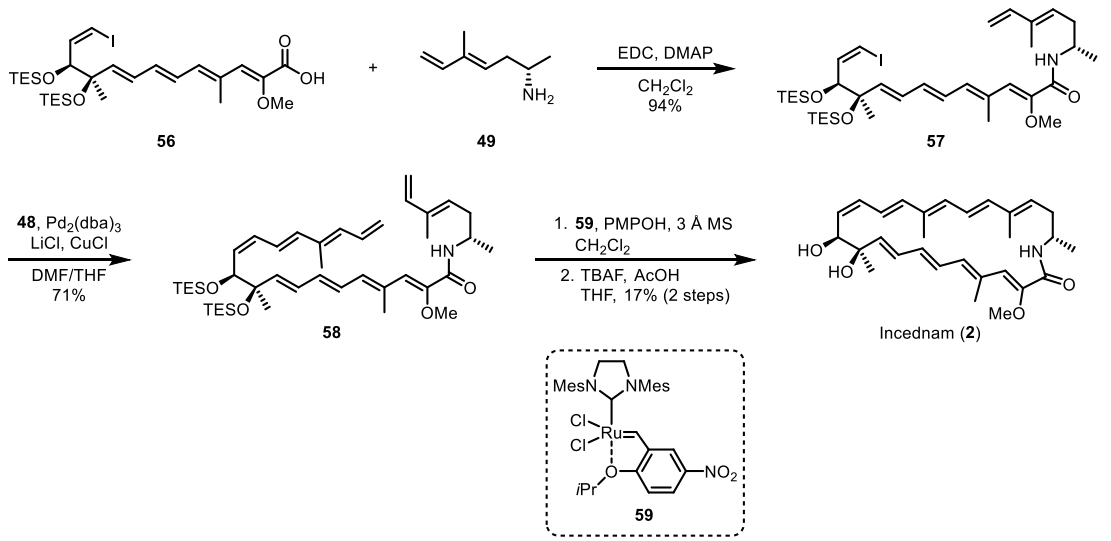


Scheme 1.9 Synthesis of C19-C23 fragment

1.4.2.2 Second generation approach to assemble incednam

Tetraene carboxylic acid **56** was coupled with amine **49** using EDC and DMAP, which gave **57** in an excellent 94% yield. Stille cross-coupling of the resulting iodide **57** with stannane **48** afforded **58** in 71% yield.[60] At this stage, acyclic precursor **58** was subjected to a number of conditions[61-64] to affect the required RCM, of which the use of Grela's

catalyst **59** in the presence of *p*-methoxyphenol proved to be the best.[65,66] However, after TES-deprotection, incednam was only obtained in a rather low 17% yield over two steps. The low yield obtained might be a result of acyclic precursor **58** not being able to adopt a favourable conformation in the macrocyclisation step, possibly due to steric effects of the triethylsilylether groups, or of course the challenge of this RCM reaction.[67,68]



*Scheme 1.10 Endgame of Toshima's second generation synthesis of incednam (**2**)*

1.4.3 Conclusion

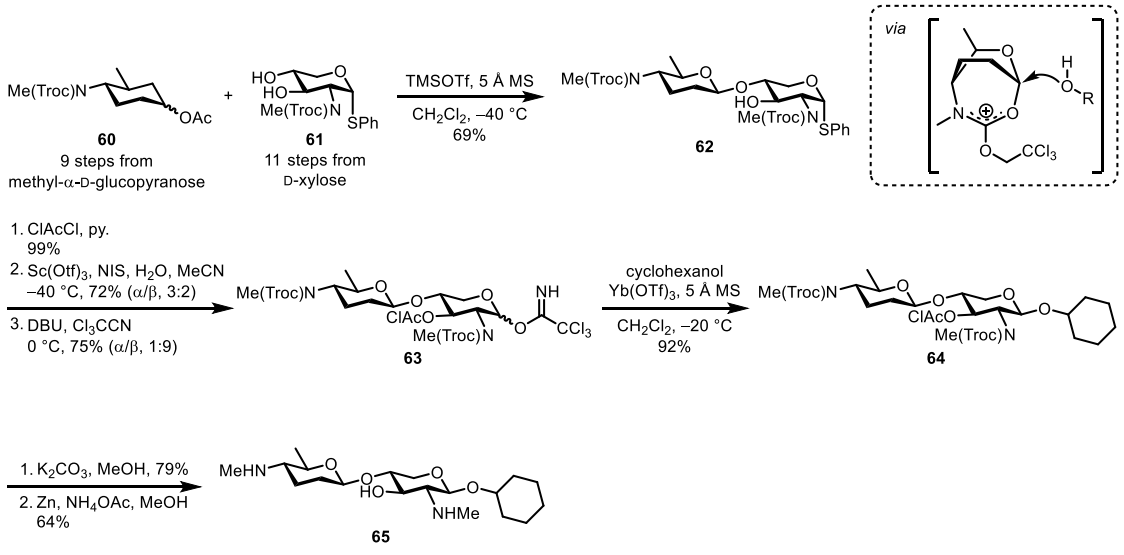
Toshima reported the first total synthesis of incednam, with 27 steps in the longest linear sequence and 0.9% overall yield. The synthesis is highly convergent, using Stille cross-coupling to join two advanced intermediates, followed by macrolactamisation to afford the cyclised product. In the second generation synthesis, some limitations of the first synthesis are addressed, such as the use of highly unstable tetraenyl stannane **8**, and the formation of the amide bond macrocyclisation. Incednam was thus accessed in 26 steps in the longest linear sequence, with an overall yield of 0.5%. Similar to before, macrocyclisation proved unsatisfactory.

Although several issues were addressed in the second synthesis, both approaches suffer from multiple protecting group manipulations and oxidation state adjustments. In addition, both syntheses rely on toxic Stille cross-couplings to form the *C*13-*C*14 bond.

1.4.4 Disaccharide synthesis

1.4.4.1 Toshima's disaccharide synthesis

Toshima's approach to the disaccharide anticipated the use of two monosaccharides **60** and **61** to form the glycosidic bond. The glycosyl donor **60** was prepared in 9 steps from methyl-α-D-glucopyranose, largely based on a synthesis developed by Hashimoto *et al.*[69] The glycosyl acceptor **61** was prepared in 11 steps from D-xylose based on a route developed by Baer *et al.*[70] It was anticipated that β-selective glycosidation could be achieved *via* remote *N*-Troc neighbouring group participation of glycosyl donor **60**, through a chair ring flip and attack of the Troc-carbonyl oxygen at the anomeric position (Scheme 1.11).[71] A screening of various conditions led to the use of TMSOTf in CH_2Cl_2 at −40 °C, which afforded the desired β-1,4 disaccharide **62** in 69% yield along with undesired β-1,3 and α-1,4 products.

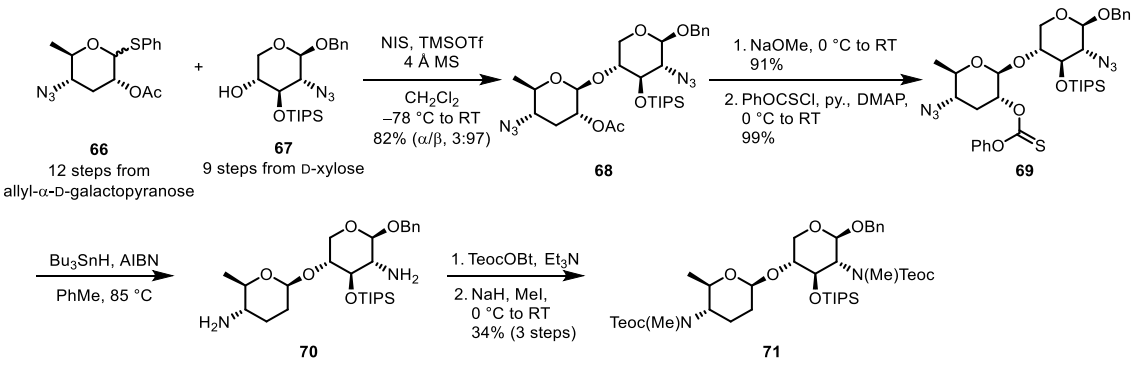


Scheme 1.11 Toshima's disaccharide synthesis

With disaccharide **62** in hand, the *C*3 hydroxyl was protected, followed by hydrolysis of the thiophenyl group and further transformation into the trichloroacetimidate **63** in readiness for the second glycosylation (Scheme 1.11). The stereoselectivity in this glycosylation is controlled by participation of *C*2 *N*-Troc group, forming the β-glycoside **64** in 92% using $Yb(OTf)_3$ as Lewis acid promoter in CH_2Cl_2 at −20 °C. Deprotection of the resulting disaccharide **64** afforded the model incednine disaccharide **65** using cyclohexanol as the aglycon (Scheme 1.11).

1.4.4.2 Roush's disaccharide synthesis

In contrast to Toshima's approach, the Roush group used a temporary substituent at the *C*2 position to control the stereoselectivity of the required β-glycosylation. Glycoside donor **66** was prepared in 12 steps from allyl-α-D-galactopyranose based on a route developed by Tietze *et al.* (Scheme 1.12)[72] Glycoside acceptor **67** was prepared from D-xylose in 9 steps.[45]



Scheme 1.12 Roush's disaccharide synthesis

With both saccharides **66** and **67** in hand, β-selective glycosylation was achieved by deploying NIS in conjunction with TMSOTf, to afford the desired disaccharide **68** in 82% yield with an anomeric ratio of 3:97, α/β. Now that the *C*2 *O*-acetate group had served its purpose, it was removed by acetate deprotection using NaOMe; acylation of the resulting

hydroxyl using phenyl chlorothioformate afforded **69**. Upon treatment of this thiocarbamate with tributyltinhydride and AIBN, both the thiocarbonate and azide functionality were reduced to give **70**. Finally, amine protection and subsequent methylation afforded the fully protected incednine disaccharide **71** in 18 steps with an overall yield of 4.7% (Scheme 1.12).

1.4.5 Previous work towards incednine within the Anderson group

Polyketide natural products containing *Z*-allylic or homoallylic polyene systems have been of great interest in the Anderson group. Work towards incednam, the aglycon of incednine, was started by Diane Lim and continued by Haraldur G. Gudmundsson, and are reported in their DPhil theses of 2013 and 2016 respectively.[73,74] Incednam was envisaged to be built by modular assembly of three major building blocks (Figure 1.7). Cyclic siloxane **73** would contain both hydroxyl-bearing stereocenters and control double bond geometry both in preceding synthetic steps, as well as in the construction of the *Z*/*E*-pentaene unit. The remaining building blocks were identified as dienoate **74** and tetraenyl iodide **72**.

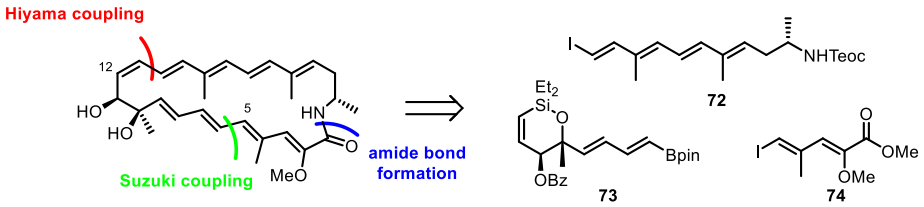
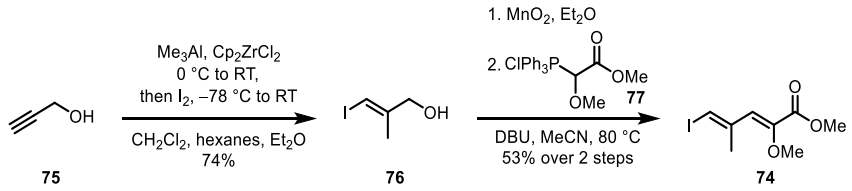


Figure 1.7 Lim's and Gudmundsson's retrosynthetic approach

1.4.5.1 *C*1-*C*5 dienoate fragment synthesis

Dienoate **74** was prepared in three steps from propargyl alcohol (Scheme 1.13). Zirconium-catalysed methylalumination/iodination of **75** afforded vinyl iodide **76**,[75-77]

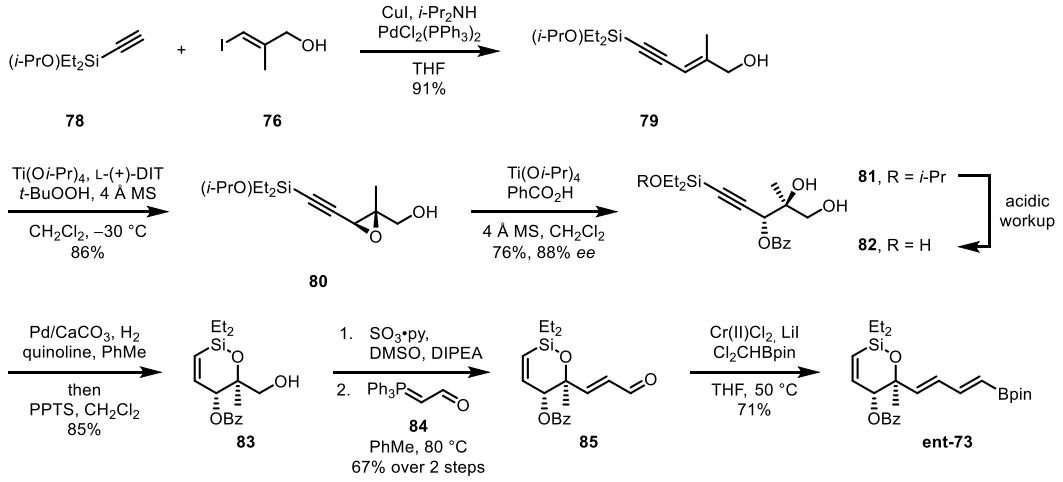
which upon MnO_2 mediated oxidation, and subsequent Wittig olefination of the resulting aldehyde with α-methoxyphosphonium salt **77**, afforded the *C*1-*C*5 fragment **74** in an overall yield of 39%.[78]



Scheme 1.13 C1-C5 fragment synthesis

1.4.5.2 *C*6-*C*13 cyclic alkenylsiloxane fragment synthesis

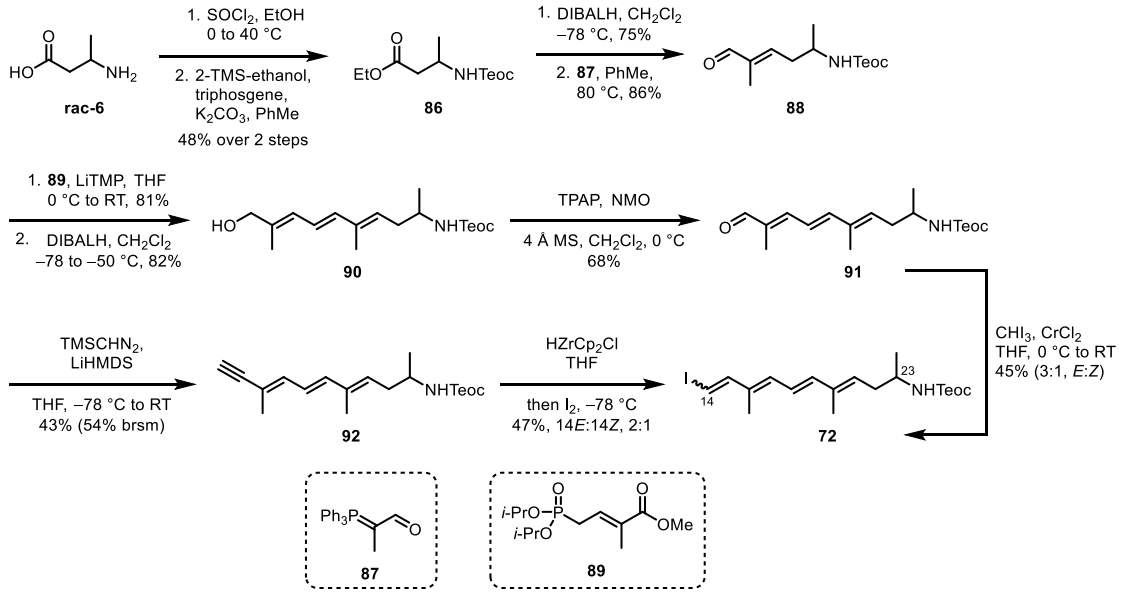
The synthesis of the *C*6-*C*13 alkenylsiloxane fragment **73** commenced with coupling of common intermediate **76** and ethynyl silane **78** in a Sonogashira reaction to give enyne **79** in excellent yield (Scheme 1.14). Next, the *C*10/*C*11 oxygenation was installed by a Sharpless asymmetric epoxidation, which afforded propargylic epoxide **80**.[79,80] It was later discovered that the tartrate employed afforded the incorrect enantiomer. Due to the lack of UV absorption of epoxide **80**, its *ee* could only be assessed after ring opening with benzoic acid.[81] The isopropoxy silane **81** proved very sensitive at this stage and while isopropanol cleavage could be minimised, the use of silanol **82** was found to greatly simplify this step without sacrificing efficiency in the following hydrogenation. The resulting alkene then cyclised under mildly acidic conditions to give the desired alkenylsiloxane **83**. Next, Parikh-Doering oxidation of **83** followed by Wittig olefination of the resulting aldehyde installed the α,β-unsaturated aldehyde to give **85**. Finally, Takai borylation converted the aldehyde into vinylic boronic ester, affording key fragment **73** in 8 steps from propargyl alcohol with an overall yield of 18%.



Scheme 1.14 C6-C13 fragment synthesis

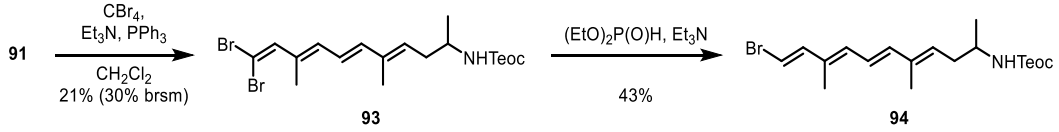
1.4.5.3 *C*14-*C*23 tetraenyl halide fragment synthesis

The synthesis of the racemic *C*14-*C*23 fragment **72** commenced with esterification and amine protection of 3-aminobutanoic acid (**rac-6**) (Scheme 1.15). DIBALH reduction of ester **86** followed by Wittig olefination of the resulting aldehyde gave α,β-unsaturated aldehyde **88**. This was followed by a Horner-Wadsworth-Emmons olefination, and reduction of the resulting trienoate gave trienol **90**. Next, Ley-Griffith oxidation afforded trienal **91** in 68% yield, which was converted into vinyl iodide **72** *via* Takai olefination in 45% yield. Unfortunately, the iodide was received as a 2:1 *E*/*Z* mixture of geometric isomers, presumed to be at the *C*14 iodine bearing carbon atom, which could not be separated. Alternatively, aldehyde **91** was converted into alkyne **92** using trimethylsilyl diazomethane in 43% yield. Hydroziconation with an iodine quench installed the terminal vinyl iodide in 47% yield, but still afforded a similar mixture of isomers.



*Scheme 1.15 C14-C23 tetraenyl iodide fragment **72** synthesis*

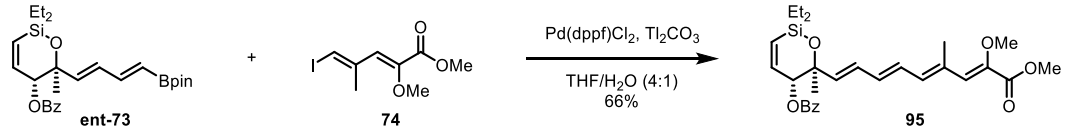
In light of these problems with the synthesis of tetraenyl vinyl iodide **72**, the synthesis of the equivalent bromide was considered (Scheme 1.16). Therefore, aldehyde **91** was subjected to Ramirez dibromination conditions to afford dibromide **93** in 21% yield. Diethyl phosphite and triethylamine were then used to stereoselectively *cis*-debrominate **93** to afford tetraenyl vinyl bromide **94** in 43% yield as a single diastereomer.



*Scheme 1.16 C14-C23 tetraenyl bromide fragment **94** synthesis*

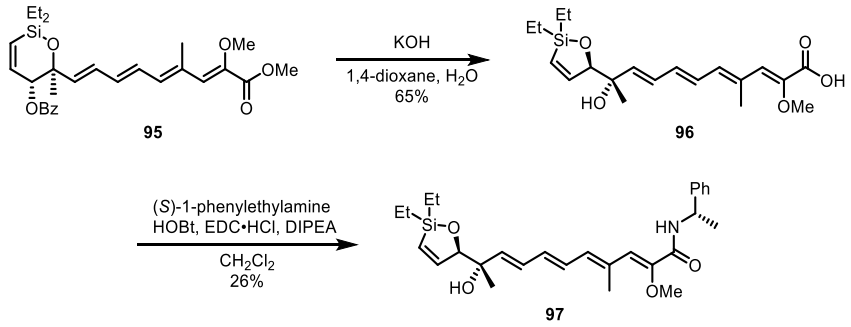
1.4.5.4 Towards the assembly of incednam

While the total synthesis of incednam has yet to be achieved, major advances towards this goal were made in previous work.[73,74] Selective activation of alkenylboronic ester in **73** under Suzuki cross-coupling conditions with dienoate **74** afforded tetraenoate **95** in 66% yield, without affecting the cyclic alkenylsiloxane (Scheme 1.17). This completes the synthesis of the *C*1-*C*13 fragment of incednam with only 9 steps in the longest linear sequence.



*Scheme 1.17 Synthesis of the C1-C13 fragment **95** via Suzuki cross-coupling*

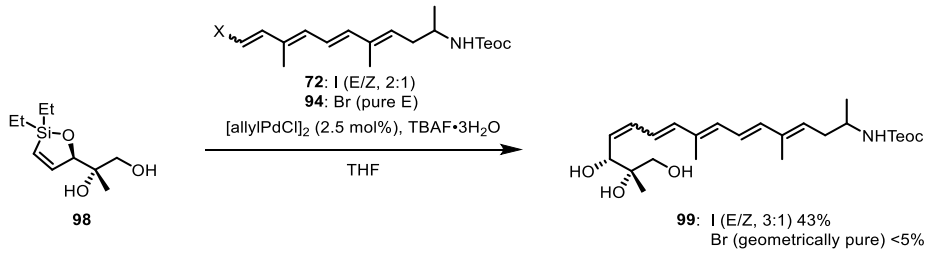
With the *C*1-*C*13 fragment **95** in hand, Lim set out to investigate the amide bond formation. Hydrolysis of the ester to the carboxylic acid using KOH simultaneously cleaved the benzoate group, triggering the rearrangement of the 6-membered cyclic alkenylsiloxane to the five-membered cyclic alkenylsiloxane **96**. The carboxylic acid **96** was then coupled to (*S*)-1-phenylethylamine with EDC·HCl, HOBt and Hünig's base (Scheme 1.18).



Scheme 1.18 Model amide bond formation

While the yield of 26% is not ideal, this reaction is unoptimised and might also be explained through the inherent instability of 5-membered alkenylsiloxanes towards silica.

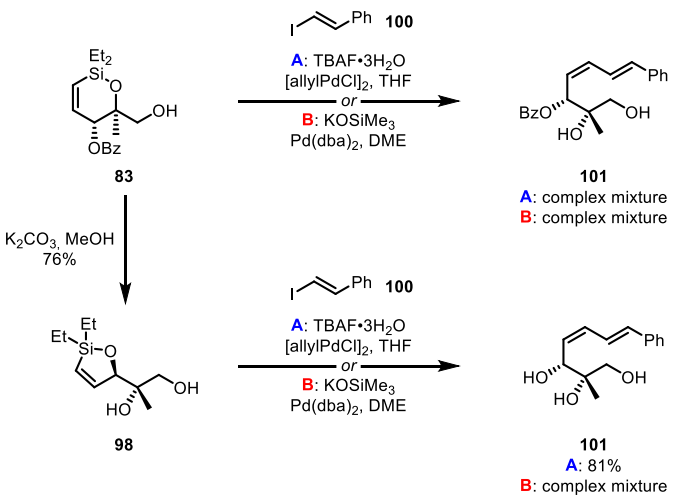
Finally, construction of the *Z,E*-*C*13-*C*14 bond *via* the key Hiyama cross-coupling was investigated by Lim using 5-membered alkenylsiloxane **98** and racemic tetraenyl halides **72** and **94** as a model system (Scheme 1.19). Coupling the geometrically pure tetraenyl bromide **94** only provided the product pentaene **99** in trace amounts. In contrast, coupling of the equivalent iodide **72** afforded the coupling product **99** in 43%, but as a mixture of isomers at what was presumed to be the new *C*13-*C*14 linkage.



*Scheme 1.19 Model Hiyama cross coupling with tetraenyl halides **72** and **94***

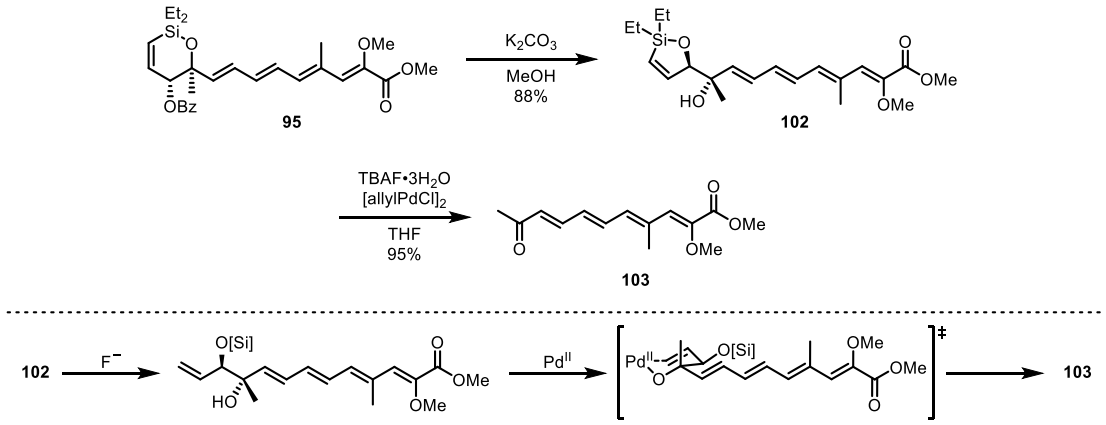
Building on Lim's preliminary results the construction of the *C*13-*C*14 bond was further investigated by Gudmundsson employing several cyclic alkenylsiloxanes. Previous studies within the Anderson group revealed interesting features and key reactivity differences between six- and five-membered diethyl alkenylsiloxanes (see Chapter 3).[82,83] While five-membered diethyl alkenylsiloxanes can undergo cross-coupling both under fluoride and base activation (generally KOTMS), six-membered alkenylsiloxanes only couple under fluoride activation, and are inert to coupling under the alternative base-promoted conditions.

Considering the differences cyclic alkenylsiloxanes display depending on ring-size, Gudmundsson investigated cross-couplings of both six- and five-membered siloxanes with β-iodostyrene (**100**) (Scheme 1.20).[74] The only cross-coupling to show satisfactory yields was that using five-membered siloxane **98**, which was derived from its six-membered precursor **83**, under fluoride promoted cross-coupling conditions. The use of six-membered siloxane **83** only returned a complex mixture, regardless of the mode of activation employed. Surprisingly, when potassium trimethylsilanolate was used to activate five-membered siloxane **98** again a complex mixture was returned, despite this mode of activation having been shown to be an efficient alternative for other five-membered cyclic siloxanes.[82,83]



Scheme 1.20 Gudmundsson's model Hiyama cross-couplings to determine the optimal siloxane substrate

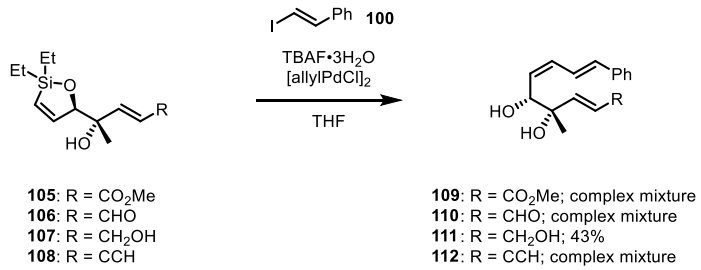
These results suggested that the coupling to construct the *C*13-*C*14 bond is most efficient when the cyclic siloxane employed is a five-membered ring. Gudmundsson also showed that *C*1-*C*13 fragment **95** could easily be rearranged to its equivalent five-membered cyclic siloxane in high yields by treatment with K_2CO_3 in methanol (Scheme 1.21).[74] Unfortunately, the subsequent cross-coupling afforded an unanticipated ketone **103** in high yield, which derives from a fragmentation of the 1,2-diol (Scheme 1.21). It is hypothesised that **103** is formed by protodesilylation followed by palladium-catalysed retro-allylation (Scheme 1.21).[84]



Scheme 1.21 Gudmundsson's six- to five-membered siloxane rearrangement and attempted Hiyama cross-coupling with proposed mechanism for retro-allylation

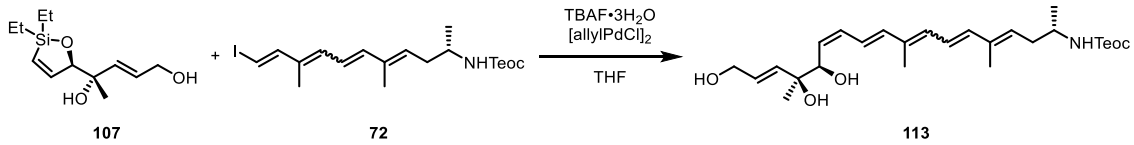
In light of these problems, several different five-membered cyclic siloxanes were prepared by Gudmundsson and subjected to fluoride promoted Hiyama cross-coupling

conditions (Scheme 1.22).[74] Out of these, only substrate **107** bearing an allylic alcohol as the side chain, afforded the corresponding product **111**. With the side chain as an ester, aldehyde or terminal alkyne, the reactions were sluggish and no observable product was formed.



Scheme 1.22 Gudmundsson's attempted Hiyama cross-coupling on different cyclic siloxanes

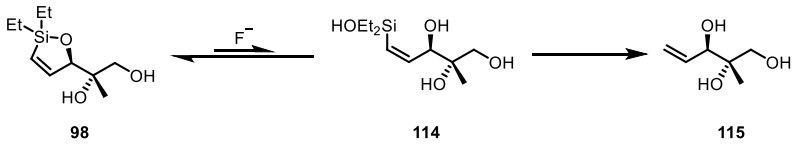
Having identified **107** as the optimal and furthest advanced cyclic siloxane that does undergo Hiyama cross-coupling, fluoride promoted coupling was attempted with *C*14-*C*23 tetraenyl idodide fragment **72** (Scheme 1.23). While there was evidence in the ^{1}H NMR spectrum for product formation in low amounts, the purification proved challenging and any variation to the conditions (slow addition of TBAF or additional water to prevent desilylation) furnished no improvements.[74]



Scheme 1.23 Gudmundsson's attempted Hiyama cross-coupling of C7-C13 silane and C14-C23 iodide

Considering the issues regarding the Hiyama cross-coupling, which was intended to be used to couple the two most advanced intermediates and form the full carbon skeleton of incednam, Gudmundsson performed several NMR-studies to shed light on some of the key questions, such as why does the five-membered siloxane couple whereas its six-membered analogue does not, and the rate of desilylation.[74] Five-membered diethylsiloxane **98** was treated with TBAF·3H$_2$O and the reaction followed by ^{1}H NMR (Scheme 1.24). This revealed a mixture of cyclic siloxane and acyclic silanol

(**98**:**114**, 5.9:1.0), which is in stark contrast to the findings of Elbert studying differently substituted five-membered siloxanes (cyclic:acyclic, 1.8:1.0). Furthermore there is only limited protodesilylation within the first two hours of the reaction.[82]

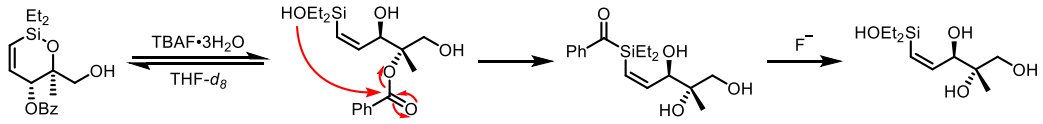


98 114 115

*Scheme 1.24 Treatment of siloxane **98** with TBAF*

Low amounts of protodesilylation, which is believed to arise from relief of ring strain of a five-membered cyclic 'ate' complex, are suggestive of said 'ate' complex being formed in small amounts only. This 'ate' complex is hypothesised to be key for transmetalation in cross-couplings using five-membered cyclic siloxanes. This is consistent with the limited reactivity observed when using siloxane **98** and its derivatives.

When similar studies for six-membered cyclic diethylsiloxane **83** were carried out, the benzoyl group surprisingly was cleaved almost instantaneously accompanied by formation of acyclic silanol **114**, which decomposed over time. Opening of the cyclic siloxane to form a silanol may be key in this transformation as the silanol is believed to assist the de-benzoylation under the conditions applied (Scheme 1.25).[74]



83 114

*Scheme 1.25 Proposed mechanism for the de-benzoylation of **83** with TBAF·3H_2O by Gudmundsson*

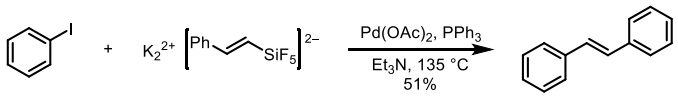
1.5 Organosilicon based cross-coupling reactions

The discovery of cross-coupling reactions in 1972 by Kumada and Corriu resulted in a paradigm shift in the formation of *C-C* bonds.[85,86] This initiated the development of various methodologies using organoboron, organozinc, and organotin coupling

partners.[87-90] Among the last branches of cross-coupling reactions to emerge was the use of organosilicon coupling partners.[91] In contrast to the aformentioned organometallics, organosilanes are typically inert to cross coupling without an activator due to the low polarity and high strength of the *C-Si* bond. However, silicon's capability to expand its valence allows activation for transmetalation by silaphilic Lewis bases such as fluoride, enabling organosilanes to be viable substrates for cross-coupling.[92] Hiyama reactions offer a compelling alternative to the more traditional methods.[91,93] Organosilanes and their byproducts are generally non-toxic and environmentally benign, are easily accessible by a wide variety of methods, and show great chemical stability allowing them to be carried through several synthetic steps, tolerating a range of functional groups while being easy to handle, cheap, and widely commercially available.

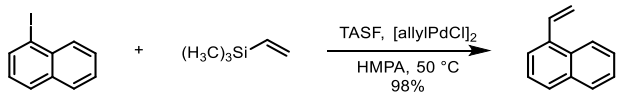
1.5.1 The mechanism of the Hiyama cross-coupling

The generally accepted mechanism for cross-coupling reactions involve oxidative addition of the transition metal to an electrophile (pseudo) halide, followed by transmetalation of an organometallic donor and reductive elimination, which regenerates the metal catalyst while forming a new *C-X* or *C-C* bond. The oxidative addition step is common to most coupling reactions, while the transmetalation step can differ depending on the organometallic donor.[94] One of the first successful reports of silicon cross-coupling made use of a potassium pentafluorosilicate to form stilbene (Scheme 1.26).[95] This provided early evidence for the viability of higher-valent silanes being viable in palladium-catalysed cross-coupling.



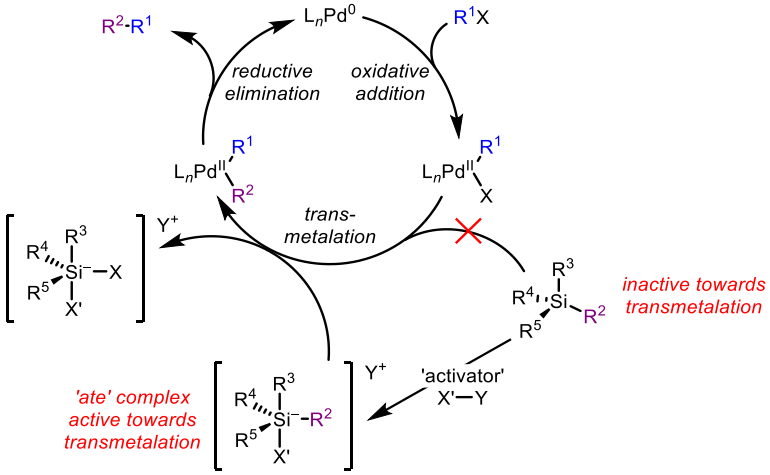
Scheme 1.26 Cross-coupling of pentafluorosilicates

However, the use of these preformed silicates comes with very limited substrate scope and reaction efficiency. These drawbacks could be overcome by using an additive to generate pentacoordinated siliconates *in situ*, as reported by Hiyama and Hatanaka in 1988 (Scheme 1.27).[96]



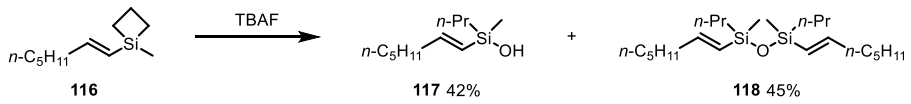
Scheme 1.27 Early example of Hiyama cross-coupling using a fluoride additive

These findings, paired with the previously mentioned ability of silicon to expand its valence, allow for the proposal of a more accurate catalytic cycle for the Hiyama cross-coupling, in which tetracoordinated silicon species need to be activated by silaphilic Lewis bases to form pentacoordinate siliconate complexes (‘ate’ complex) in order for cross-coupling to proceed (Scheme 1.28).



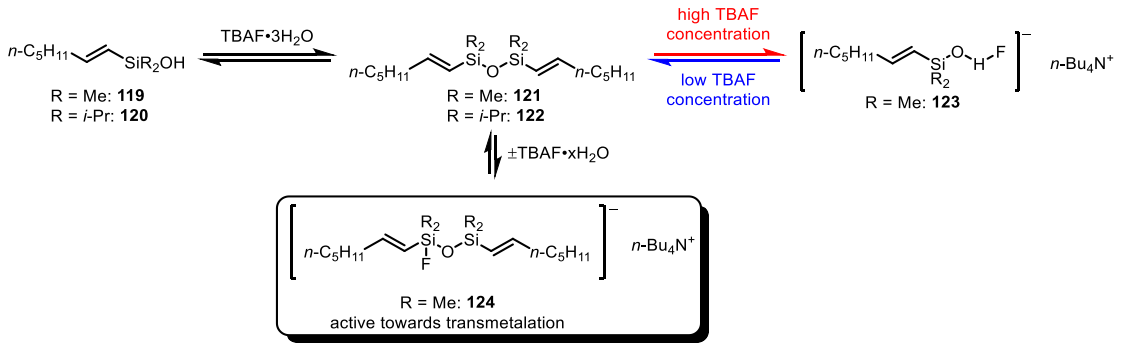
Scheme 1.28 Proposed catalytic cycle via pentacoordinate siliconate (‘ate’) complex for transmetalation

The transmetalation step of oranosilanes can either be fluoride-promoted or fluoride-free processes, which are mechanistically different and have been the subject to several detailed mechanistic studies. An early key observation was that treatment of siletanes (**116**) with TBAF leads to four-membered ring opening to form a silanol (**117**) and disiloxane (**118**), instead of the expected ate complex (Scheme 1.29).[97]



Scheme 1.29 Siletanes discovered to form silanols and disiloxanes in combination with TBAF

This is suggestive of a common mechanistic pathway between silanols, disiloxanes and masked silanols, which is revealed by fluoride *in situ*. Studies by Denmark *et al.* that compared authentic synthetic samples with reaction mixtures using NMR techniques, which revealed the formation of several silane-derived species.[97,98] They concluded that disiloxanes and silanols are in an equilibrium that is influenced by the amount of fluoride present. It was also found that depending on the concentration of fluoride, a third species - a complex of the silanol hydrogenbonded to fluoride (**123**) - becomes the predominant component. Compared to the rapid and almost quantitative formation of disiloxanes for dimethyl silanols, sterically much more demanding diisopropyl silanols are much less prone to dimerisation.

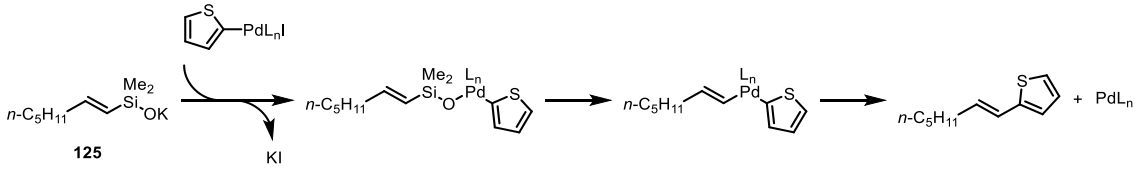


Scheme 1.30 Denmark's proposal for silanol activation by fluoride

The kinetic profile shed further light on the mechanism. The reaction proceeds with a zeroth-order dependency on the organohalide electrophile employed, which is consistent with a fast, irreversible oxidative addition of the palladium catalyst.[99] First-order dependence on palladium was interpreted as a rate-limiting transmetalation step rather than a turnover-limiting fluoride activation. Furthermore, second-order dependence of silanol and first-order behaviour of disiloxane was thought to be in support of a disiloxane, rather than a silanol, being the species that precedes the rate-limiting

transmetalation step. For the TBAF dependence experiments two distinct behaviours were observed. At two or fewer equivalents, the reaction shows a first-order dependence on TBAF. At higher concentrations the reaction rate was inhibited, and an inverse order dependence on TBAF was observed. These different behaviours were rationalised by two different resting states (Scheme 1.30). As the activation of disiloxane **121** by fluoride is required for the reaction to proceed, removal of **121** in favour of silanol-TBAF complex **123** will in turn reduce the concentration of active **124**.

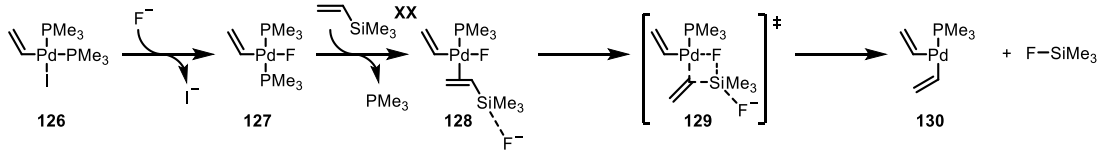
Following their investigation of the fluoride-promoted Hiyama cross-coupling, Denmark *et al.* next studied the mechanism of a fluoride-free silicon-based cross-coupling.[100] The reaction of potassium silanolate salt **125** with 2-iodothiophene and its kinetic profile were investigated (Scheme 1.31). It was found that a silanolate oxygen can coordinate to the palladium centre, forming a Si-O-Pd linkage, preceding *intramolecular* transfer of the vinylgroup without further activation of the silicon centre. The authors stated, that this was an unanticipated result, which contradicts the previously commonly held belief of the need to form a pentacoordinate silicate to effect transmetalation.



Scheme 1.31 Denmark's proposal for the fluoride-free transmetalation of silanols

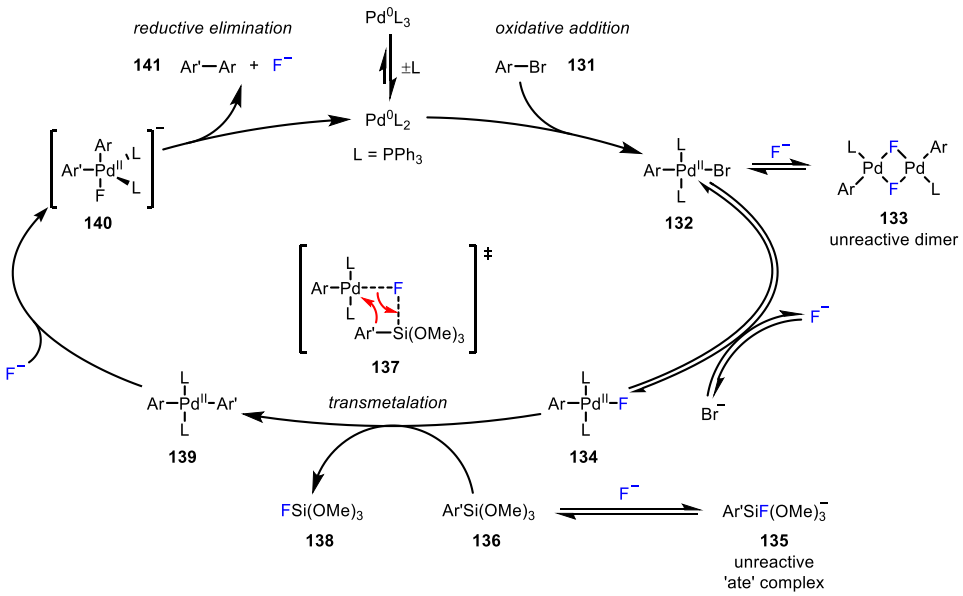
In 2008, Hiyama *et al.* reported a theoretical study on the mechanism of the silicon based cross-coupling, and especially the role of fluoride.[101] DFT calculations were used to simulate three possible reaction courses of the reaction of vinyl trimethylsilane with vinyl iodide in the presence of fluoride and palladium. The first case investigated was a formation of a vinylsilicate anion prior to the transmetalation. Theoretical calculations suggested this not being being the case for vinyl trimethylsilane. Secondly, when the iodo

ligand in complex **126** is substituted with a fluoro ligand at the palladium centre, the transmetalation proceeds with a considerably lower activation barrier of 25.3 kcal/mol compared to 48.7 kcal/mol. Thirdly, fluoride accelerates the reaction by a nucleophilic attack at the silicon centre, weakening the silicon-vinyl bond and leading to transfer of the vinyl-group to palladium. Additionally, the simultaneous formation of a strong *Si-F* bond is, compared to the *Si-I* bond, another important enthalpic driving force. Calculations show another decrease of the activation barrier of transmetalation by 16.5 kcal/mol when taking this second beneficial fluoride interaction into account. In summary, out of the three considered roles of fluoride, only fluoride substitution at the palladium centre and fluoride attack concomitant to the transmetalation were identified to aid the reaction, while prior fluorosilicate formation was suggested not to occur.



Scheme 1.32 Hiyama's proposed mechanism for transmetalation and role of fluoride

A more recent study by Jutand and Amatore *et al.* aimed to investigate the role of fluoride in Hiyama cross-couplings experimentally.[102] The authors used cyclic voltammetry to monitor the cross-coupling between phenyl trimethoxysilane (**136**) and *para*-cyanophenyl bromide (**131**) (Scheme 1.33).



Scheme 1.33 Jutand's proposed catalytic cycle for fluoride activated Hiyama coupling

No reaction of palladium(II) complex **132** with arylsilane **136** was observed in the absence of fluoride. Jutand *et al.* state that previous studies examining Suzuki cross-couplings found the formation of arylpalladium(II) fluoride complex **134** to be crucial before transmetalation.[103] The formation of the same palladium(II) fluoride complex **134** seems to be of similar importance in silicon-based cross-couplings. After fluoride addition, the cross-coupling product **141** was formed at elevated temperatures (70 °C), whereas at 25 °C the catalyst was found to form an inactive off-cycle intermediate **133**. The authors did not observe dimerization of **134**, but only of complex **132** in the presence of fluoride. They reason this as being due to low thermodynamic concentration of palladium(II) fluoride complex **134**, when starting from **132**, not allowing for fast transmetalation leading to the accumulation of the unreactive dimer **133**. When silane **136** was reacted with **134** at room temperature, **139** was formed, however fluoride is necessary to promote the reductive elimination, as also established in the previous study on the Suzuki-Miyaura coupling.[103,104] Additionally, it was found that using fluorosiliconate **135** did afford product **141**, albeit in lower yields and with a drastically reduced reaction rate. Similar results were observed with high concentrations

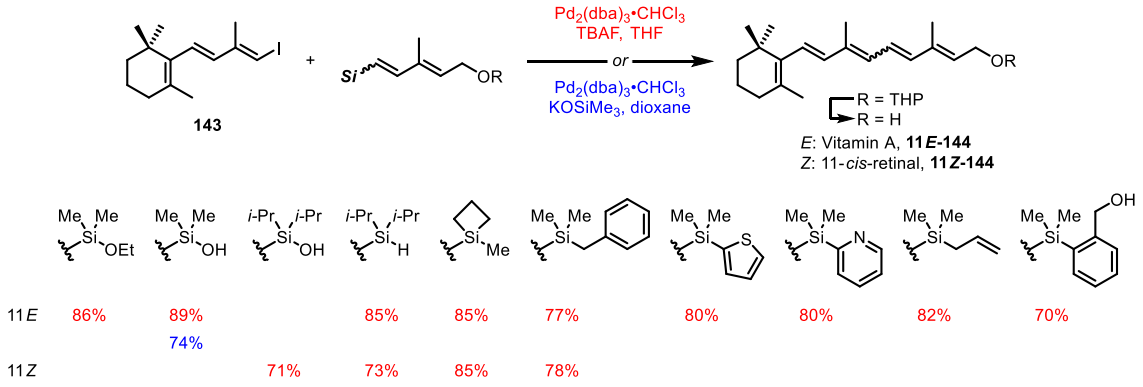
of TBAF and silane **136**, suggesting that 'ate' complex **135** is unreactive towards transmetalation, and fluoride dissociation from the 'ate' complex is necessary for a productive reaction course.

Both the computational studies by Hiyama *et al.* and the experimental studies by Jutand *et al.* provided evidence that an activated pentacoordinate siliconate does not form prior to transmetalation. The key role of fluoride was suggested to be the substitution of other (pseudo)halides to form a palladium(II) fluoride complex, which is then responsible for the rate-determining transmetalation step. This directly contradicts Denmark's findings where a pentacoordinated fluoride activated disiloxane is believed to be the species that transmetalates. However, the possibility of two distinct mechanistic pathways differentiating organosilanes and silanols cannot be ruled out; similar transition states could conceivably be accessed from either the palladium(II) fluoride complex, or *Si-F* 'ate' complex.

1.5.2 Hiyama cross-coupling in total synthesis

The importance of the Hiyama cross-coupling is best demonstrated by its use in the total synthesis of natural products. In such endeavours, efficient synthetic planning and selective and rapid assembly of the carbon skeleton is of great importance.[105] Transition metal-catalysed cross-couplings have been extensively used, and comprise some of the most efficient strategies towards a variety of target molecules.[106] However, while silicon-based cross-couplings have not received the same attention as more traditional methods, the unique traits and advantages of the Hiyama cross-coupling, such as high silane stability and low toxicity, have contributed to its recognition and development.

In 2012, López *et al.* demonstrated the use of Hiyama cross-coupling in the synthesis of both vitamin A (**11*E*-144**) and related 11-*cis*-retinol (**11*Z*-144**). A wide variety of organosilanols and masked organosilanols were employed under different conditions for the construction of the C10-C11 bond (Scheme 1.34).[107]

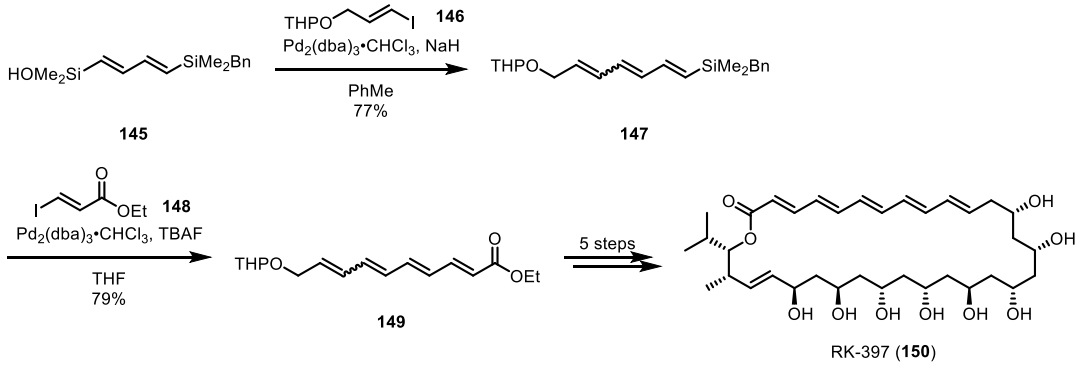


*Scheme 1.34 López's Hiyama cross-coupling approach for the synthesis of retinols **11E-144** and **11Z-144***

While other cross-coupling approaches have been used for the synthesis of retinols, these show a number of drawbacks mostly related to the nature of the organometallic donor. Organostannanes for instance suffer, apart from their inherent toxicity, from the need to use large excesses and forcing conditions to avoid homodimerisation, while boronic acids and esters display problems, due to the challenge of their synthesis and potential air and moisture sensitivity.[108] The high yields and mild conditions reported by López *et al.* nicely illustrate the advantages of silicon-based cross-couplings in the construction of highly conjugated polyenes.

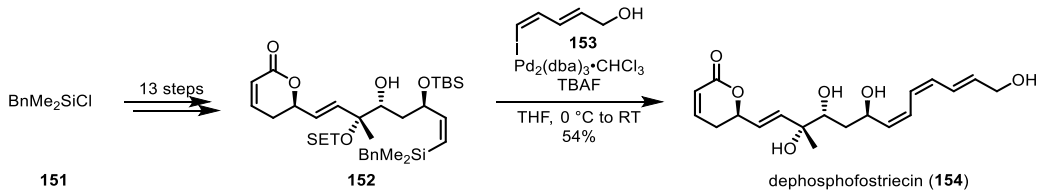
Denmark *et al.* demonstrated orthogonality between organosilanols and organosilanes in their elegant synthesis of RK-397 (**150**) (Scheme 1.35).[109] Diene **145**, bearing a dimethyl silanol at one end, could be coupled selectively with vinyl iodide **146** under fluoride-free conditions to afford **147** in the presence of a benzyldimethyl silane group at the other end. The latter was coupled *via* fluoride promoted cross-coupling conditions to vinyl iodide

148 affording tetraene **149**, which was then converted into a phosphonate, used to introduce the pentaene system in RK-397 (**150**).



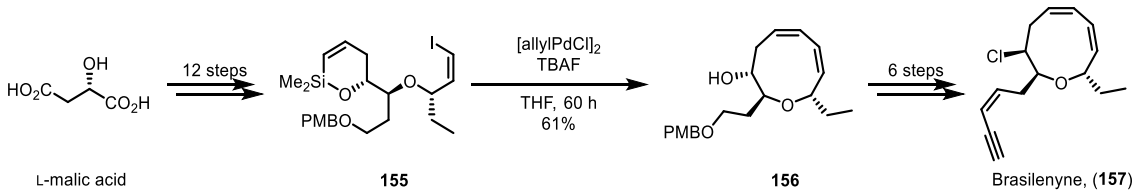
*Scheme 1.35 Denmark's orthogonal silicon-based cross-couplings towards RK-39 (**150**)*

An additional example for the use of a benzyldimethyl silane group is shown in the synthesis of dephosphofostriecin (**154**) by Trost *et al.* to construct the *Z,Z,E*-triene system in 54% yield (Scheme 1.36).[110]



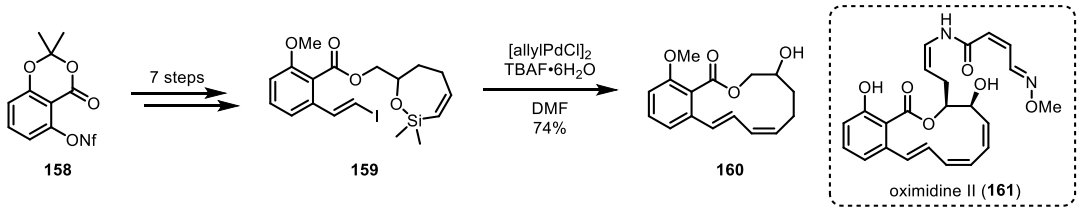
*Scheme 1.36 Trost's synthesis of dephosphofostriecin (**154**)*

Cyclic silanes can be employed in addition to their acyclic counterparts providing useful control over position and geometry of constructed products. Denmark *et al.* reported the first enantioselective total synthesis of brasilenyne (**157**) (Scheme 1.37).[111] **157** is a halogenated medium-ring ether and was isolated from *Aplysia brasiliana*. The substrate for cross-coupling **155** was synthesised from L-malic acid in 12 steps. The six-membered cyclic alkenyl siloxane was installed using molybdenum-catalysed RCM. Intramolecular Hiyama cross-coupling then constructed the *Z,Z*-diene system, and furnished the 9-membered ether core of brasilenyne **156** in 61%.



*Scheme 1.37 Denmark's total synthesis of brasilenyne (**157**)*

The use of differently sized cyclic siloxanes were demonstrated in the context of a model system for the 12-membered macrocycle oximidine II (**161**) by Denmark *et al.* (Scheme 1.38).[112] Seven-membered alkenylsiloxane **159** was accessed in 7 steps from **158**, and successfully employed to prepare 12-membered macrolactone **160**, modelling a ring-closing Hiyama cross-coupling for a potential synthesis of oximidine II.



Scheme 1.38 Denmark's intramolecular Hiyama cross-coupling for a model of oximidine II

1.6 Project aims and retrosynthetic approach

Incednine represents an enticing molecular target due to its interesting and potentially valuable ability to restore susceptibility to anti-cancer drugs in formerly drug-resistant cancer cells.[1] The development of new therapeutic leads *via* the natural product or non-natural analogues would ideally be based on a short and modular synthetic route. Although Toshima *et al.* have reported two syntheses of the incednine aglycon, both are prohibitively long for such applications.[43,44,46]

Analogous to Lim's proposal, our retrosynthetic approach begins with a disconnection at the glycosidic bond, separating incednine into its aglycon incednam and disaccharide **162** (Figure 1.7). Macrolactam **2** is further disconnected at the amide, the *C*5-*C*6, and the *C*13-*C*14 bonds, identifying three building blocks: dienoate **74**, cyclic siloxane **73** and

tetraenyl iodide **72**. However, considering the difficulties in the synthesis of tetraenyl iodide **72**, a further scission at the *C*18-*C*19 bond was proposed, which was envisaged to be constructed by Julia-Kocienski olefination or Ramberg-Bäcklund reaction. We envisaged uniting the major building blocks via cross-coupling methods, with Hiyama cross-coupling to construct the *C*13-*C*14 bond being a key step. While the endgame of this approach is similar to the strategy followed by Toshima et al., we hoped that the lack of the sterically demanding silyl ethers would result in a favourable conformation to enable efficient macrolactamisation.[67,68]

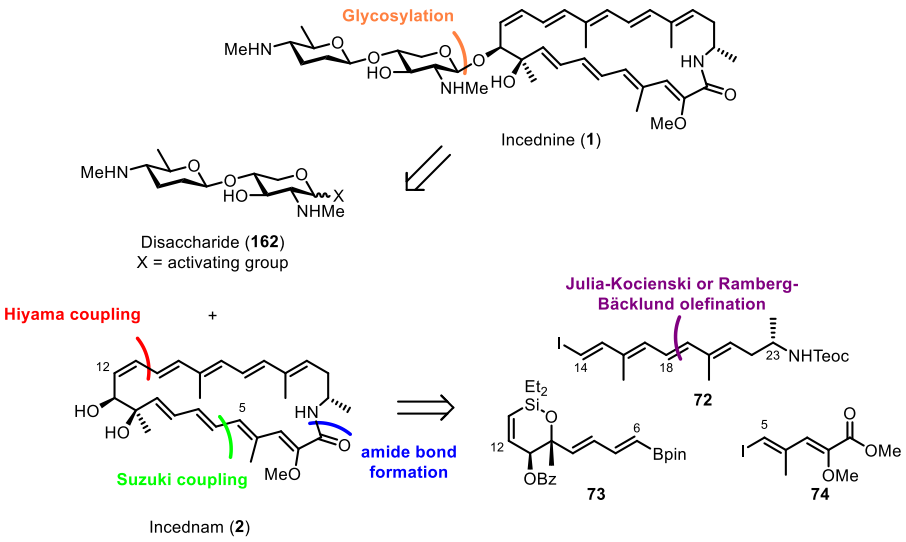


*Figure 1.8 Retrosynthetic approach towards incednine (**1**)*

Building on Lim's and Gudmundsson's work, Chapter 2 will discuss our progress to access major building blocks as well as studies regarding potential improvements in their synthesis. Chapter 3 will discuss the development of cyclic dimethyl alkenylsiloxane coupling methodology, and Chapter 4 its application towards incednam, as well as a revised synthetic strategy. Finally, Chapter 5 will contain a summary of the progress made, and proposals for future work.

2 Towards Incednam – Fragment Synthesis

2.1 *C*14-*C*23 Fragment

The asymmetric synthesis of *C*14-*C*23 tetraenyl vinyl iodide **72** can be achieved in 10 steps from L-alanine methyl ester hydrochloride. However, the desired fragment **72** could so far only be obtained as a mixture of geometric isomers. Initially, the isomeric mixture was believed to consist of 14*E*:14*Z* isomers, as this can often be observed in Takai olefinations.[73,113] However, it was later discovered that iodide **72** had instead isomerised at an internal double bond to give a 18*E*:18*Z* mixture. A similar mixture is obtained when **72** is constructed *via* hydrozirconation/iodination of the corresponding enyne. Although these methods operate by two distinct mechanisms, the observation of comparable isomeric mixture is suggestive of post-iodination isomerisation to establish a thermodynamic ratio, which is potentially iodine-induced.[74,114] Therefore, a new approach to the construction of the tetraenyl iodide **72** was devised. By splitting the fragment into two building blocks, a Julia-Kocienski olefination might afford either the tetraene as a single isomer, or allow construction of the pentaene at a later stage. Alternatively, a Ramberg-Bäcklund olefination of sulfone **165** could reveal the tetraene or pentaene before or after coupling respectively (Figure 2.1)

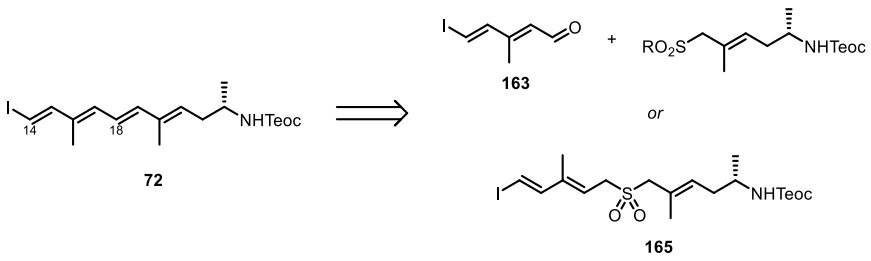
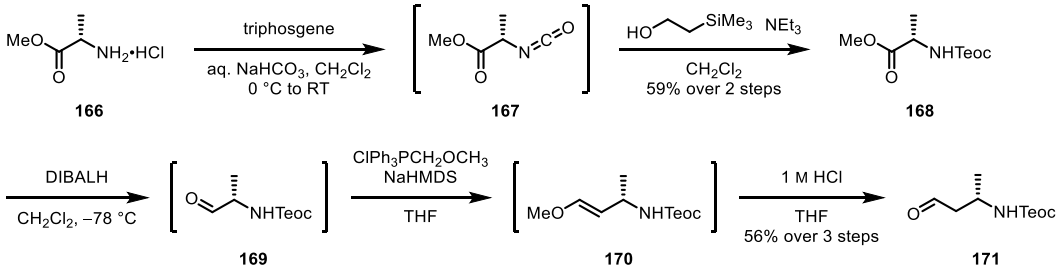


Figure 2.1 Julia-Kocienski and Ramberg-Bäcklund approach for tetraene 72

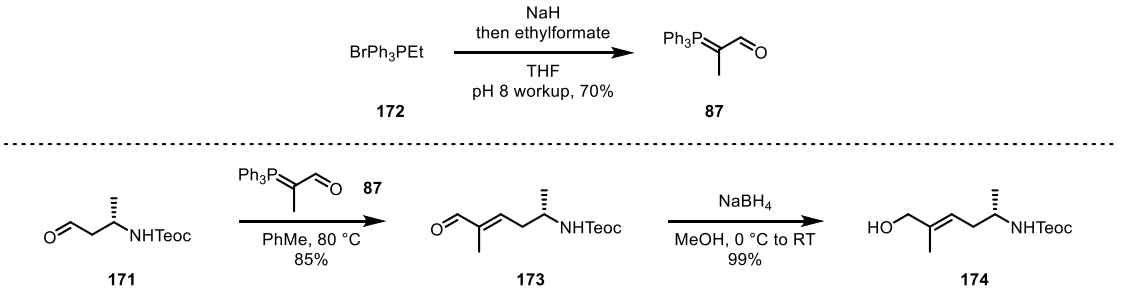
The synthesis for both strategies intersects with the previous chemistry to form tetraenyl iodide **72**. L-Alanine methyl ester hydrochloride was treated with triphosgene to form isocyanate **167**, which afforded *N*-Teoc protected amino ester **168** upon treatment with

2-trimethylsilylethanol in 59% yield over two steps (Scheme 2.1). Then, a sequence of DIBALH reduction to aldehyde **169**, immediately followed by Wittig olefination, to minimise epimerisation of aldehyde **169**, gave enol ether **170**, which upon hydrolysis formed aldehyde **171** in 56% yield over three steps (Scheme 2.1).



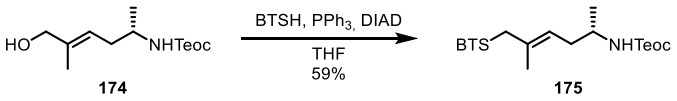
Scheme 2.1 N-Teoc protection of L-alanine methyl ester

Aldehyde **171** was subjected to a second Wittig olefination using phosphorane **87**, which is synthesised in one step from ethyl triphenylphosphonium bromide (Scheme 2.2, top). α,β-Unsaturated aldehyde **173** was obtained in a pleasing 85% yield, and was reduced with sodium borohydride to form allylic alcohol **174** in an excellent 99% yield (Scheme 2.2).



*Scheme 2.2 Synthesis of ylid **87** and alcohol **174** from aldehyde **171***

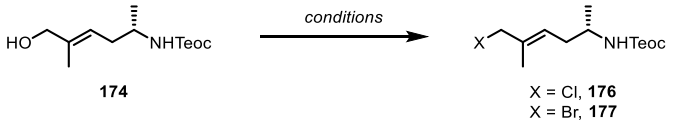
While alcohol **174** could easily be converted into the desired sulfide **175** by a Mitsunobu reaction, as shown in Scheme 2.3, the moderate yield of 59% along with the inherent poor atom economy and prolonged reaction times made us consider a two step approach instead.



*Scheme 2.3 Mitsunobu reaction with allylic alcohol **174***

Attempted conversion of allylic alcohol **174** into a tosylate or mesylate only afforded the corresponding chloride **176** (Table 2.1, entry 1).[115] Use of methanesulfonic anhydride should circumvent this problem, but only a complex mixture was obtained and no product could be isolated (Table 2.1, entry 2). It was therefore decided to prepare the corresponding bromide **177**, as this should be a superior electrophile for the subsequent introduction of sulphur than chloride **176**. Several conditions were explored, of which the Appel reaction afforded bromide **177** in the highest yield of 76% (Table 2.1, entry 5).[116]

*Table 2.1 Conversion of allylic alcohol **174** into allylic halides*

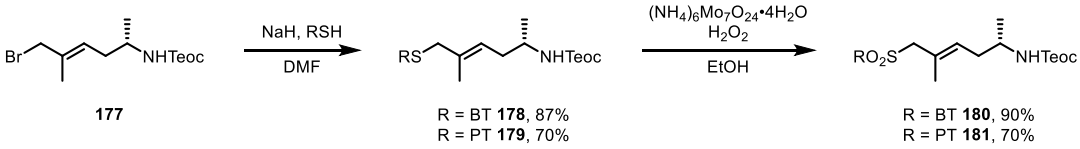


Entry	Conditions	Product	Yield [%][a]
1	$TsCl$, NEt_3, DMAP	**176**	69
2	$MsOMs$, NEt_3	n.d.	n.d.[b]
3	Br_2, PPh_3, pyridine	**177**	23
4	NBS, DMS	**177**	30
5	CBr_4, PPh_3	**177**	76
6	PBr_3	**177**	48

[a] isolated yield; [b] not determined.

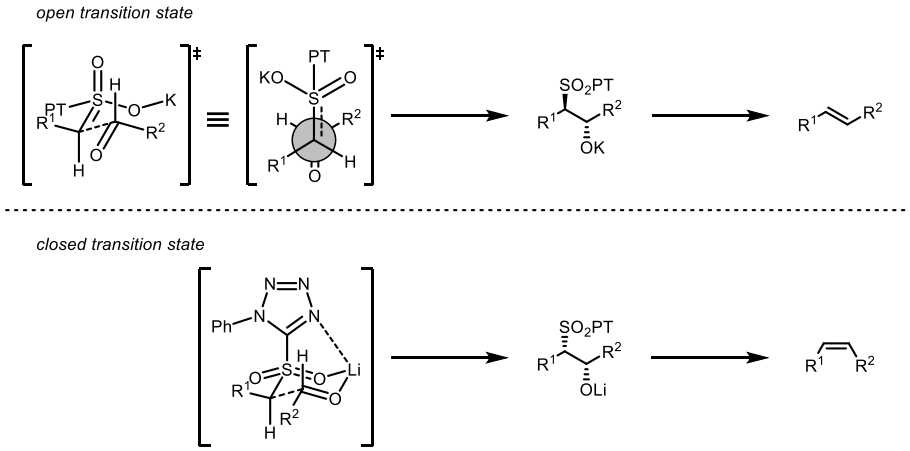
With allylic bromide **177** in hand, we could introduce the sulfone required for the Julia-Kocienski olefination. Deprotonation of 2-mercaptobenzothiazol (BTSH) or 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) using sodium hydride, followed by addition of bromide **177** afforded sulfides **178** and **179** in 87% and 70% yield, respectively (Scheme

2.4). After oxidation of the sulfides with ammonium molybdate and hydrogen peroxide, sulfones **180** and **181** were obtained in 90% and 70% yield, respectively.



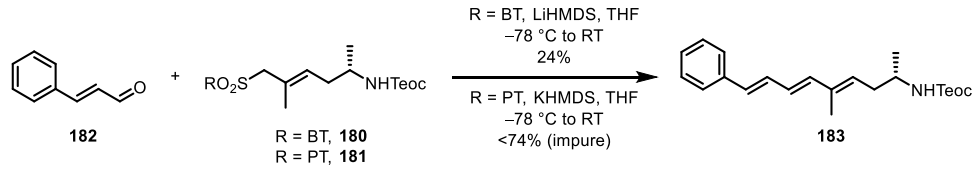
Scheme 2.4 Introduction of the Julia-Kocienski olefination sulfones

Having obtained two different sulfones **180** and **181**, we set out to model the Julia-Kocienski reaction. Mechanistically, the reaction can proceed *via* an open or a closed transition state (Scheme 2.5), which can be influenced by variation of counter ions and solvent polarity.[117-120] As such, the stereochemical outcome of Julia-Kocienski reactions is highly substrate dependent, and not easily predicted.



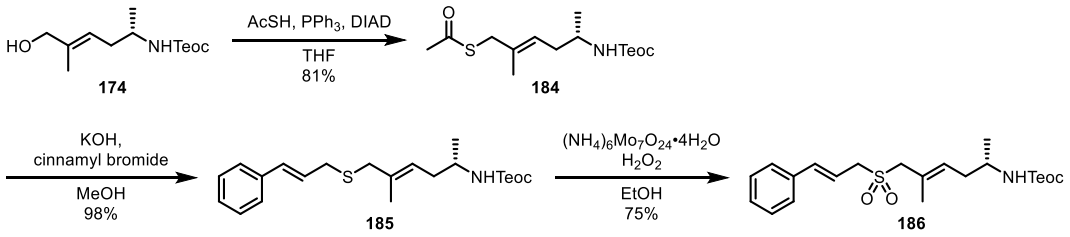
Scheme 2.5 Possible transition states for the Julia-Kocienski olefination

Pleasingly, the reaction of both the benzothiazole derivative **180** and phenyltetrazole derivative **181** with cinnamyl aldehyde afforded the triene **183** with all *E* configuration, regardless of the counter ion employed (Scheme 2.6). Unfortunately, these reactions were plagued by low yields, and in addition an unknown impurity that was inseparable from the product was observed when tetrazole derivative **181** was employed.



Scheme 2.6 Model Julia-Kocienski olefination

To overcome these issues, it was decided to explore the use of the more atom-economical Ramberg-Bäcklund reaction to construct this *C*18-*C*19 bond. A Mitsunobu reaction with thioacetic acid and allylic alcohol **174** afforded thioester **184** in high yields. Saponification followed by nucleophilic substitution of the *in situ* formed thiol with cinnamyl bromide gave the desired sulfide **185** in an excellent yield of 98%. Oxidation of sulfide **185** afforded sulfone **186** in 75% yield (Scheme 2.7).

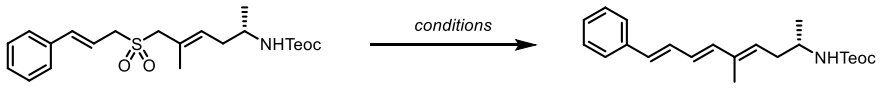


*Scheme 2.7 Synthesis of Ramberg-Bäcklund precursor **186***

Sulfone **186** enabled us to probe commonly used conditions for the Ramberg-Bäcklund rearrangement on a model system, which affords the same triene **183** as was isolated from our previous efforts using the Julia-Kocienski olefination. The original Ramberg-Bäcklund conditions use α-halogenated sulfones that form olefins upon heating with aqueous KOH.[121,122] While α-halogenated sulfones can often easily be accessed, Myers' modification, using CCl_4 and KOH, greatly simplifies this reaction by introducing the halide *in situ* rather than relying on a separate synthetic step.[123] A refinement of this method uses CBr_2F_2 rather than CCl_4, due to observations of higher efficiency in the Ramberg-Bäcklund process.[124] The use of KOH adsorbed onto alumina as the base, which increases the surface area as well as the basicity of KOH represents a further refinement.

The classic conditions of the Myers' modification (Table 2.2, entry 2),[125] were found to be inferior to the more frequently employed conditions using CBr_2F_2 and KOH on alumina (Table 2.2, entry 1).[126] However, since CBr_2F_2 is a class I ozone depleting substance we also investigated other halogen sources that have been used in Ramberg-Bäcklund reactions. Both C_2Cl_6 and $C_2Br_2Cl_4$ did not improve yields, and only afforded the triene **183** in 23% and 11% yield, respectively (Table 2.2, entries 3 & 4).[127,128]

*Table 2.2 Condition optimisation of Ramberg-Bäcklund reaction using model sulfone **186***

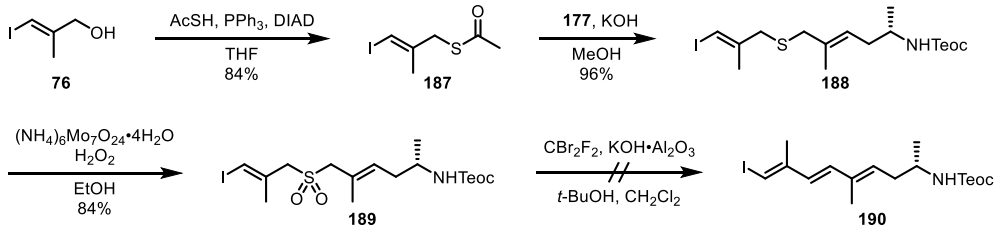


186 **183**

Entry	**Conditions**	**Yield** [%][a]
1	CBr_2F_2, KOH·Al_2O_3, *t*-BuOH	53
2	CCl_4, KOH, *t*-BuOH/CH_2Cl_2	31
3	C_2Cl_6, KOH, *t*-BuOH/CH_2Cl_2	23
4	$C_2Br_2Cl_4$, KOH·Al_2O_3, *t*-BuOH/THF	11

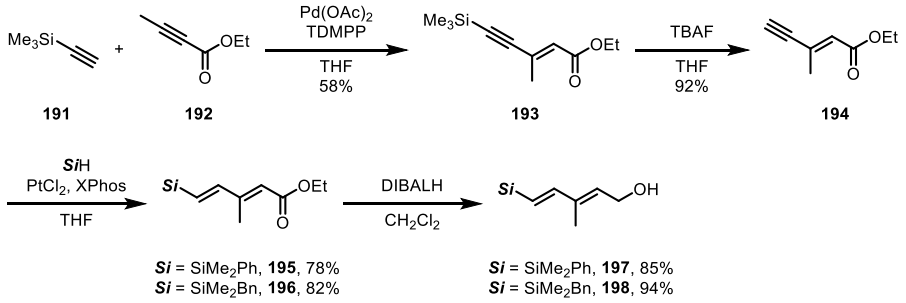
[a] isolated yield.

With reasonable conditions for the model system in hand, we set out to investigate substrates that are closer related to the real system. Allylic alcohol **76** was subjected to Mitsunobu conditions to furnish thioester **187**. As before, one-pot saponification and nucleophilic substitution gave the resulting thioether **188** in excellent yield, followed by high yielding oxidation to sulfone **189**. Unfortunately, when the previous best conditions were used on this substrate, only a complex mixture was obtained and no product **190** was observed (Scheme 2.8).



*Scheme 2.8 Synthesis of sulfone **189** and attempted Ramberg-Bäcklund reaction*

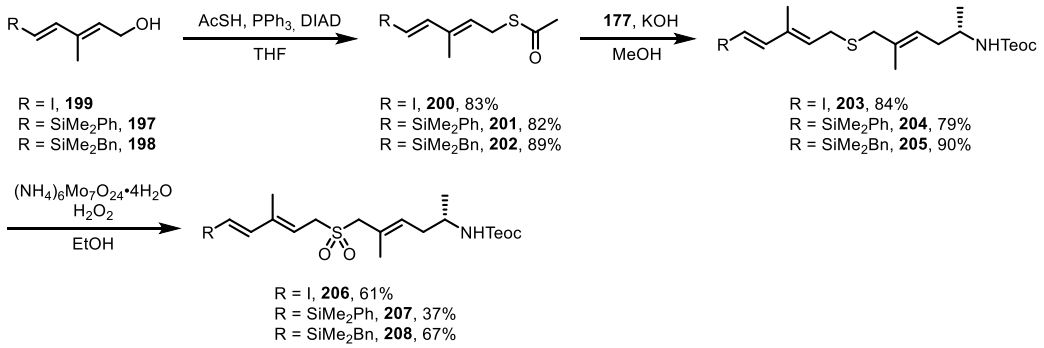
Although the Ramberg-Bäcklund reaction of sulfone **189** bearing a vinyl iodide had not afforded the desired triene **190**, it was decided to synthesise different *C*14-*C*23 polyenes. The synthesis of the *C*14-*C*18 parts of the fragments commenced with a palladium-catalysed alkyne addition to an acceptor alkyne developed by Trost *et al.*[129] This furnished enyne **193**, which after TMS deprotection, was hydrosilylated using platinum(II) chloride and XPhos to afford silanes **195** and **196** in high yields.[130] Interestingly, TMS deprotection of enyne **193** requires substoichiometric amounts of TBAF, namely 0.25 equivalents. After attack of fluoride at the silane and cleavage of the *Si*-alkyne bond, water can presumably substitute the fluoride and ultimately form trimethyl silanol, thus recycling the fluoride ion. Both esters **195** and **196** were then reduced to the corresponding allylic alcohols **197** and **198** using DIBALH (Scheme 2.9).



Scheme 2.9 Synthesis of C14-C18 silane fragments from TMS-alkyne and ethyl but-2-ynoate

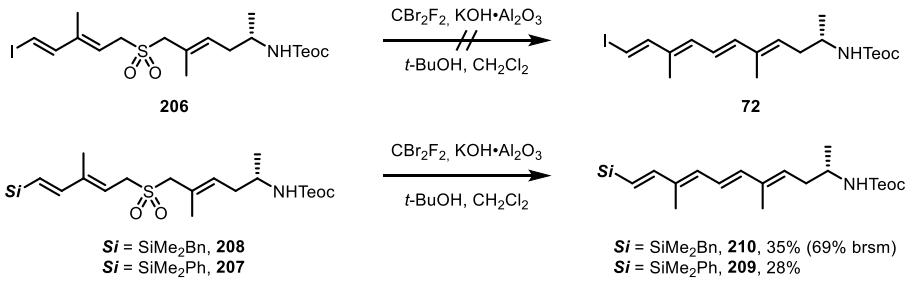
To probe the efficiency of the Ramberg-Bäcklund reaction we set out to synthesise three different C14-C23 fragment derivatives. For this we used both silanes **197** and **198**, as well as dienyl iodide **199**, which was synthesised by Gudmundsson in two steps from silane **195**, by iododesylilation and subsequent ester reduction.[74,131] These building blocks were converted into the desired sulfones by our previously developed sequence and is

summarised in Scheme 2.10. The Mitsunobu reaction to introduce sulphur followed by one-pot saponification, and nucleophilic substitution with bromide **177**, were generally high yielding and provided the desired sulfides **203**, **204**, and **205**. Oxidation to furnish the corresponding sulfones proceeds in good yields, with the phenyldimethyl silane derivative being the exception, where the oxidation provided the product **207** in only 37% yield.



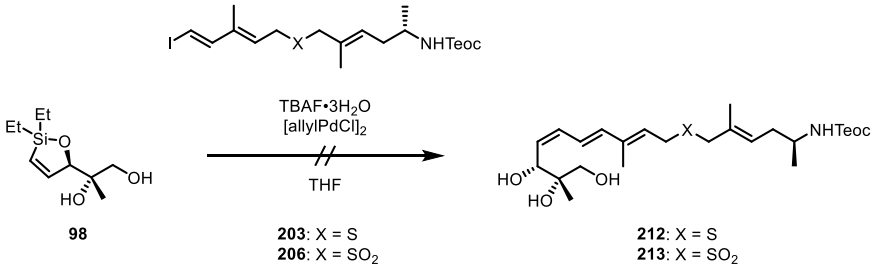
Scheme 2.10 Synthesis of various C14-C23 sulfone fragments

Attention now returned to the Ramberg-Bäcklund reaction. Use of vinyl iodide **206** again only returned a complex mixture without any formation of the desired tetraenyl iodide **72**, however, both silanes formed the targeted tetraene products **209** and **210**, albeit in low yields (Scheme 2.11). Disappointingly, this olefination strategy does not seem to tolerate vinyl iodides, which may reflect the lack of publications featuring this functional group in the Ramberg-Bäcklund olefination. Notably, silanes **209** and **210** were both formed as single geometric isomers, which is an encouraging result for further studies for this strategy.



Scheme 2.11 Ramberg-Bäcklund reaction to form C14-C23 fragments

One variation of our plan involving the Ramberg-Bäcklund reaction was to mask the pentaene of incednam by maintaining the sulfone, then revealing the pentaene at a later stage to avoid potential problems regarding isomerisation of intermediates. Thus, Gudmundsson attempted the Hiyama cross-coupling using sulfides and sulfones containing vinyl iodides (Scheme 2.12).[74] Both sulfone **206** and sulfide **203** were consumed during these reactions, but only a complex mixture was returned without any observable product formation. To the best of our knowledge, there are no examples of allylic sulfides or sulfones being subjected to palladium-catalysed cross-couplings, indicating that these structural features might not be tolerated.



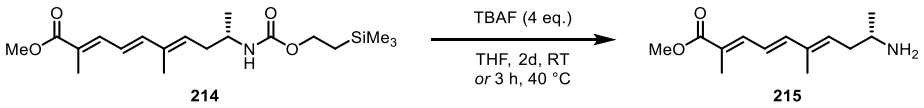
98 **203**: X = S **206**: X = SO_2 **212**: X = S **213**: X = SO_2

*Scheme 2.12 Gudmundsson's attempted Hiyama cross-coupling of sulfide **203** and sulfone **206***

2.2 *N*-Teoc deprotection modelling

While our efforts to improve the synthesis of the *C*14-*C*23 fragment were largely unsuccessful, we were also keen to investigate conditions to deprotect the *N*-Teoc group. The choice of this group over a carbamate such as Boc was made, since we had previously found the latter could not be cleaved without polyene degradation.[73] It was anticipated that the Teoc-group might be removed during the Hiyama cross-coupling, considering the excess of fluoride used, or at the least would require less harsh conditions than Boc. Although this is a feasible strategy, it was surprisingly not observed in any Hiyama cross-couplings carried out by Lim and Gudmundsson that featured this protecting group.[73,74] We therefore decided to model this deprotection on trienoate **214** (provided by

Gudmundsson). For the reaction to go to completion, four equivalents of TBAF were necessary, as well as extended reaction times (namely two days at ambient temperature), or three hours at 40 °C (Scheme 2.13). Although the need for prolonged reaction times or elevated temperatures was not exptected, the real issue was the challenging purification of the resulting free amine **215**, which could not be obtained free from tetrabutylammonium derivatives.



*Scheme 2.13 Deprotection of trienoate **214***

2.3 *C*14-*C*23 Fragment – Improved Synthesis

In order to address the aforementioned issues and improve the current synthesis of the *C*14-*C*23 fragment, we revised our strategy for its synthesis. The use of the Ellman auxiliary[132] to install the nitrogen and set the *C*23 stereocentre would avoid the need to go *via* an aldehyde with an α-stereocentre and potential epimerisation risk (Figure 2.2). Also, the Ellman-auxiliary is easily cleaved, often without the need of further purification, due to the volatility of the byproducts formed. We decided to have the Ellman-auxiliary pose as both the source of stereochemistry as well as probe its viability as a nitrogen-protecting group in our synthesis.

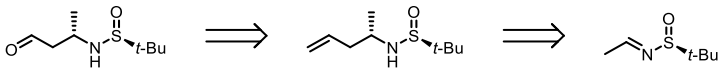
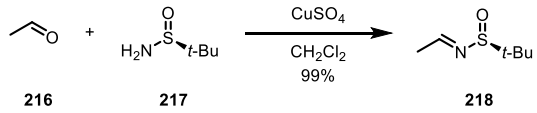


Figure 2.2 Retrosynthetic approach to avoid an epimerisable aldehyde via Ellman auxiliary

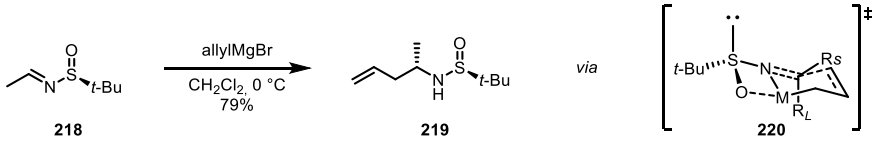
The use of a chiral auxiliary, as opposed to a chiral pool starting material, also enables us to easily change the stereochemistry. This allows us to test the potentially different biological activity of different diastereomers of incednam and incednine.[133-137]

The forward synthesis commenced with the copper mediated condensation of acetaldehyde (**216**) and (*S*)-*tert*-butyl sulfinamide (**217**) (Scheme 2.14).[138,139] from which imine **218** was isolated in an excellent 99% yield.



*Scheme 2.14 Synthesis of imine **218***

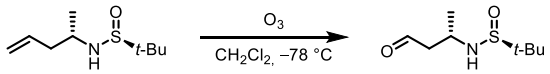
The 1,2-addition of allylmagnesium bromide to imine **218** proceeded in 79% yield (Scheme 2.15). Pleasingly, only one diastereomer was observed in the crude ^{1}H NMR spectrum (>20:1 d.r.). Generally, allylations of Ellman-auxiliary imines using allylic Grignard reagents show higher diastereoselectivity compared to other Grignard reagents; this is thought to arise from a slightly different, more stable transition state. In contrast to a six-membered transition state proposed for most additions of Grignard reagents, allyl-Grignard reagents are thought to form a Lewis-acid coordinated [4.2.0] bicyclic transition state **220**.[140-142]



*Scheme 2.15 Addition of allyl magnesium bromide to imine **218***

Next, we examined the oxidative cleavage of the double bond. First, this was attempted using ozonolysis, but to our dismay, only low yields were obtained. Changing the reducing agent from dimethyl sulfide to triphenylphosphine increased the yield to 45% (Table 2.3, entry 2). Scaling up of this reaction resulted in a drop of the yield to 36% (Table 2.3, entry 3).

*Table 2.3 Ozonolysis of terminal alkene **219***



219 **221**

Entry	Quench	Scale	Yield [%][a]
1	SMe_2	100 mg	27
2	PPh_3	100 mg	45
3	PPh_3	500 mg	36

[a] isolated yield

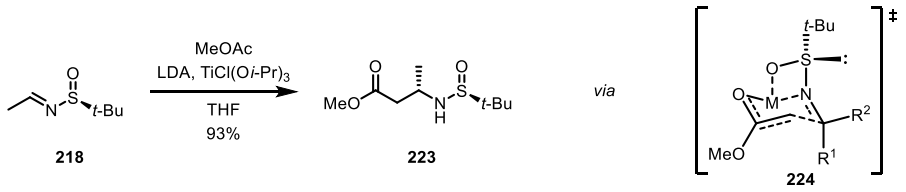
It is not clear why the yield is so low, but during the ozonolysis, the sulfoxamine may be oxidised or the ozonide that is formed may be too stable to break up and reveal the desired aldehyde.[143,144] A solution to the low yields may be a two step approach of an Upjohn dihydroxylation followed by oxidative cleavage. Unfortunately, the dihydroxylation only returned a complex mixture (Scheme 2.16).

219 **222**

*Scheme 2.16 Upjohn dihydroxylation of alkene **219***

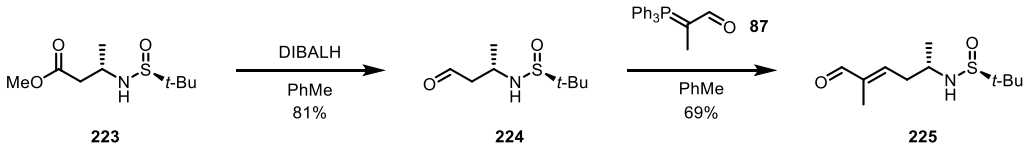
An alternative approach, circumventing this issue, is the addition of an ester enolate into the imine followed by a reduction of the resulting ester. Early examples show the addition of lithium enolates into sulfinamide imines, however with poor diastereoselectivities unless additional coordinative sites are present in the substrates employed.[145-147] Ellman *et al.* later reported the addition of titanium enolates into sulfinamide imines,[148,149] which greatly increased diastereoselectivity.[38,39] The reaction is proposed to proceed *via* a six-membered transition state that is only stable at low temperatures (Scheme 2.17). In our hands, the resulting β-amino acid derivative **223** was obtained in excellent 93% yield without any of the other diastereomer being observable in the ^{1}H NMR spectrum (>20:1 d.r.). Ellman *et al.* investigated the diastereoselectivity for this product in particular

(among others), by cleavage of the auxiliary followed by derivatising the amine and HPLC analysis.[149] This converts the possible four diastereomers into only two possible products and revealed the excellent diastereoselectivity through an *ee* of 98%.



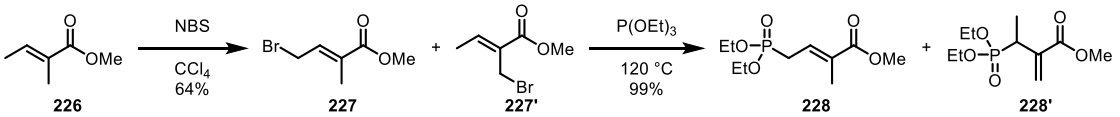
*Scheme 2.17 Enolate addition into imine **218***

The following reduction of **223** with DIBALH afforded aldehyde **224** in 82% yield. The correct number of equivalents of DIBALH as well as close monitoring of the reaction time, was necessary to limit overreduction. **224** was then subjected to a Wittig olefination using phosphorane **87** as in the previous synthesis of this fragement, to afford α,β-unsaturated aldehyde **225** in 69% yield.



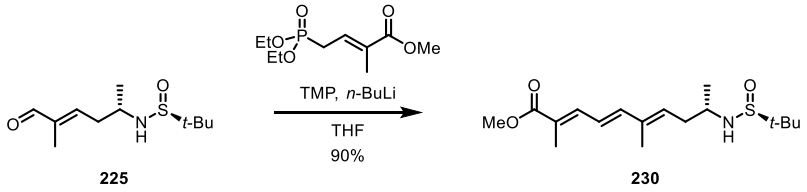
*Scheme 2.18 Reduction of ester **223** and subsequent Wittig olefination*

As before, the next step in the synthesis, the extended HWE reaction to install two further double bonds (Scheme 1.15). The literature known procedure starts by bromination of methyl tiglate (**226**) in carbon tetrachloride, which afforded two inseparable brominated products in a ratio of 1.5:1.0.[150,151] A subsequent Arbuzov reaction gave the desired phosphonate **228** along with an inseperable byproduct derived from the undesired brominated product (Scheme 2.19).[152,153] However, this byproduct does not react or interfere in an HWE reaction.



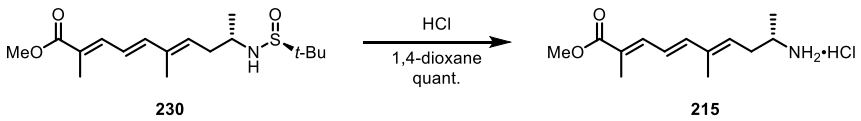
*Scheme 2.19 Synthesis of phosphonate **228***

Aldehyde **225** coincidentally has the same R_f value as triphenylphosphine oxide, and could not be separated by conventional means of purification. As Ph_3PO is the major byproduct in the Wittig olefination that forms aldehyde **225** this impurity might pose a problem in subsequent steps. Fortunately, when a mixture of **225** and triphenylphosphine oxide were subjected to HWE reaction using phosphonate **228** and lithium tetramethylpiperidide, the trienoate **230** was formed in 90% yield and now could be separated from the Ph_3PO byproduct of the previous reaction (Scheme 2.20).



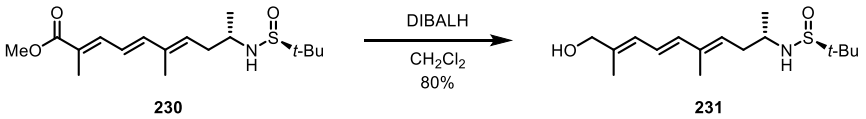
*Scheme 2.20 HWE reaction of aldehyde **225** to form trienoate **230***

At this stage we could probe whether our new strategy of using the Ellman-auxiliary as a protecting group provided any advantages over the formerly used protecting groups. The commonly used conditions to cleave the Ellman-auxiliary are HCl in 1,4-dioxane, followed by removal of volatiles.[132] Often no further purification is necessary. When treating the sulfinamide **230** with HCl in 1,4-dioxane, the reaction seems to be complete almost instantly and it was concentrated *in vacuo* after 30 s stirring. After all volatiles were removed, the free amine was obtained as the hydrochloric salt **215** in quantitative yield (Scheme 2.21). This is a huge improvement over the use of Boc or Teoc groups, as the sulfinamide is easy to cleave and the amine is received in excellent purity without the necessity of further purification.



*Scheme 2.21 Deprotection of the Ellman auxiliary of trienoate **230***

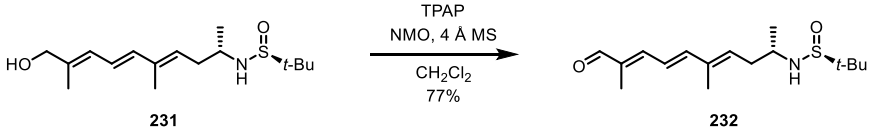
The synthesis continued by reduction of trienoate **230** using DIBALH to allylic alcohol **231** (Scheme 2.22). Alcohol **231** was obtained in 80% yield and serves as the resting state for the bulk of the material.



230 231

*Scheme 2.22 Reduction of trienoate **230***

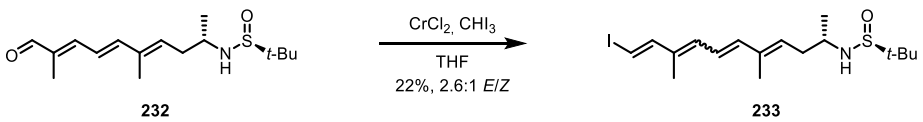
Allylic alcohol **231** can be smoothly converted into trienal **232** by employing the Ley-Griffith oxidation (Scheme 2.23).[154] Trienal **232** was obtained in 77% yield, however it is not very stable towards light and can only be stored up to 2 days in a matrix of frozen benzene before it is mostly decomposed.



231 232

*Scheme 2.23 Ley-Griffith oxidation of allylic alcohol **231***

With aldehyde **232** in hand instalment of the vinyl iodide was attempted by a Takai olefination. Unfortunately, vinyl iodide **233** was obtained in only 22% yield (Scheme 2.24). Unsurprisingly, it was obtained as a mixture of geometric isomers, similar to the previously synthesised tetraene **72**. The low yield may be explained by the sulfinamide present in the substrate, as with other protecting groups the reaction provides the product in satisfactory yields.



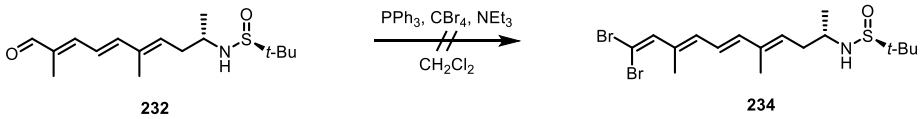
232 233

*Scheme 2.24 Takai olefination to form vinyl iodide **233***

Although the coupling of a previous tetraenyl bromide with a model silane, performed by Lim, had not afforded the product in satisfactory amounts (Scheme 1.19),[73] we nonetheless investigated the synthesis of a tetraenyl bromide. Studies regarding the

Hiyama cross-coupling suggested that we may infact be able to use vinyl bromides efficiently (see chapter 3).

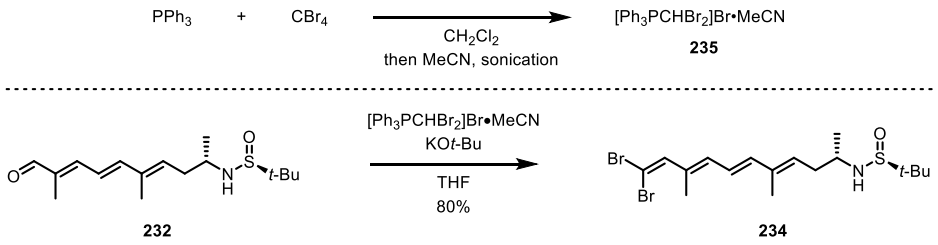
Conversion of aldehyde **232** into a gem-dibromide **234** proved challenging. Standard conditions for the dibromination of aldehydes proceeded sluggishly, and although some signals observed in the crude ^{1}H NMR looked promising, the desired compound was not obtained. We hypothesised that the Ellman-auxiliary does not stand up to the reaction conditions and is degraded or cleaved during its course, greatly increasing the polarity of the product and making purification by column chromatography highly challenging.



232 **234**

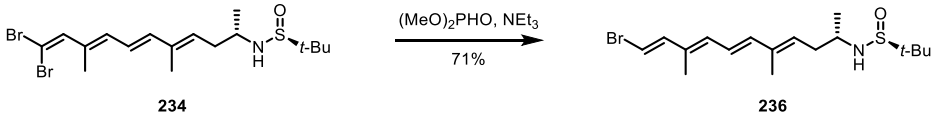
*Scheme 2.25 Attempted dibromination of aldehyde **232***

It was hypothesised that degradation/cleavage of the auxiliary may be due to reaction with an intermediate or byproduct that is formed in the Ramirez dibromination. The bromotriphenylphosphonium ion itself may be Lewis acidic enough to cleave the Ellman auxiliary. Preforming the needed phosphorus olefinating reagent may solve this issue, as reported by Wolkoff (Scheme 2.26).[155,156] Pleasingly, reagent **235** indeed allowed the preparation of the desired dibromide **234** without loss of the auxiliary in the course of reaction (Scheme 2.26). Dibromide **234** was isolated in 80% yield, but unfortunately proved itself to be even more unstable than its precursor, such that it always needed to be used immediately, and storage is only viable for a few hours in the dark either under vacuum or in a matrix of frozen benzene.



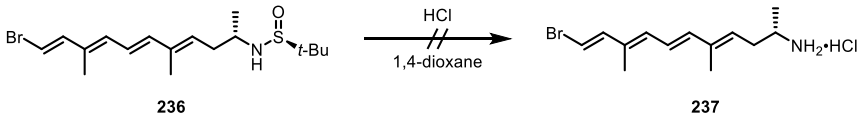
*Scheme 2.26 Dibromination of aldehyde **232***

However, we were delighted to find that, selective monodebromination by Hirao reduction afforded tetraenyl bromide **236** in 71% yield (Scheme 2.27).[157,158] Compound **236** represents the full *C*14-*C*23 fragment, and was accessed in 9 steps from acetaldehyde and (*S*)-2-methylpropane-2-sulfinamide with an overall yield of 16.2%. The Ellman auxiliary therefore indeed acts as both the source of *C*23 stereochemistry, as well as serving as an efficient *N*-protecting group. The *E*/*Z* configuration of **236** was confirmed both by the *J*-values of respective coupling constants, as well as NOE correlations.



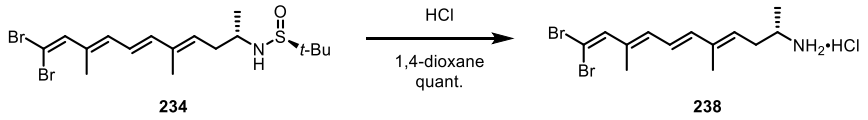
*Scheme 2.27 Hirao reduction to selectively monodebrominate **234***

To ensure the efficiency of the deprotection of the chiral auxiliary, tetraenyl bromide **236** was submitted to previous conditions using HCl in 1,4-dioxane. To our dismay, these conditions seemed too harsh and only led to decomposition of the compound (Scheme 2.28).



*Scheme 2.28 Attempted cleavage of chiral auxiliary of tetraenyl bromide **236***

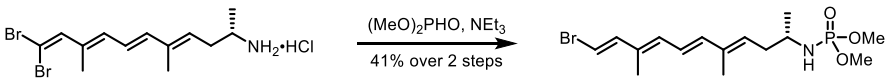
Interestingly, dibromide **234** was better-behaved under these conditions, and could be obtained reasonably pure with some decomposition visible by ^{1}H NMR (Scheme 2.29).



234 238

*Scheme 2.29 Cleavage of chiral auxiliary of tetraenyl dibromide **236***

With reasonably pure hydrochloric salt **238** in hand, it was hypothesised whether **238** would be a viable substrate for the monodebromination. Attempted Hirao reduction of **238** revealed an unexpected problem when a free amine is employed. The monodebromination proceeds efficiently, but dimethyl phosphorobromidate, derived from dimethyl phosphite, reacts with the free amine forming a *N*-*P* bond. Purification afforded product **239** in 41% yield over two steps (Scheme 2.30). While it may be possible to use this compound in further studies, we decided to investigate alternative methods to trigger the deprotection, without causing decomposition in tetraenyl bromide **236**.

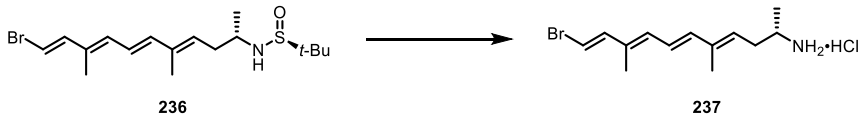


238 239

*Scheme 2.30 Hirao reduction on hydrochloric amine salt **238***

Zhang *et al.* reported an iodine-mediated cleavage of *tert*-butanesulfinyl groups under non-acidic conditions.[159] This method works efficiently and acid sensitive functional groups now remain untouched, while the sulfinyl group is selectively cleaved. Unfortunately, Zhang's conditions are not compatible with our substrate (Table 2.4, entry 2). However, the use of dry HCl in methanol (6% solution) rather than 4 M HCl in 1,4-dioxane afforded the hydrochloric amine salt **237** without decomposition. Amine **237** could not be stored neat for a prolonged period; as it seems that decomposition is greatly accelerated when **237** is not in solution.

Table 2.4 Cleavage of the tert-butanesulfinyl group



236 237

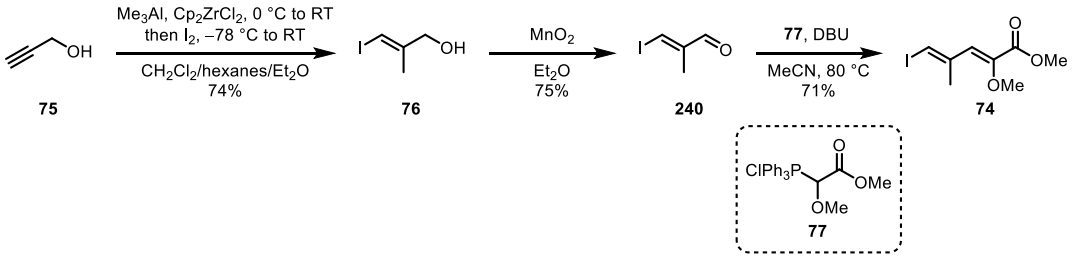
Entry	Conditions	Yield [%][a]
1	4 M HCl in 1,4-dioxane	decomposition
2	Na_2CO_3, DMAP, I_2, THF/H_2O	decomposition
3	AcCl, MeOH	quantitative

[a] crude yield.

2.4 *C*1-*C*13 fragment synthesis and construction of the *C*13-*C*14 bond

2.4.1 *C*1-*C*5 dienoate synthesis

The synthesis of dienoate **74** was achieved by Lim in a three step sequence from propargyl alcohol.[73] First, zirconium catalysed methyl alumination, and quenching with iodine, formed vinyl iodide **76**, which after allylic oxidation with MnO_2 gave aldehyde **240**. This was submitted to a Wittig olefination using phosphonium salt **77** to afford dienoate **74**.

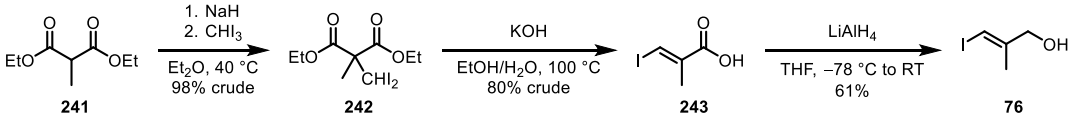


75 76 240 74 77

Scheme 2.31 Lim's synthesis of dienoate 74

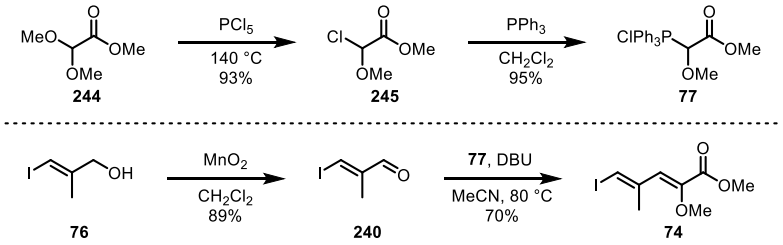
In this work, the synthesis of vinyl iodide **76** was changed to a procedure reported by Brückner *et al.* (Scheme 2.32).[160] This procedure is much more scalable and allowed the synthesis of vinyl iodide **76** on multigram scale, albeit requiring three steps. Alkylation of diethyl methylmalonate (**241**) with iodoform, then saponification of the ester groups, decarboxylation and elimination gave vinyl iodide carboxylic acid **243**. Reduction then

afforded the desired alcohol **76**. All steps were carried out using crude materials, and pure **76** was collected by distillation.



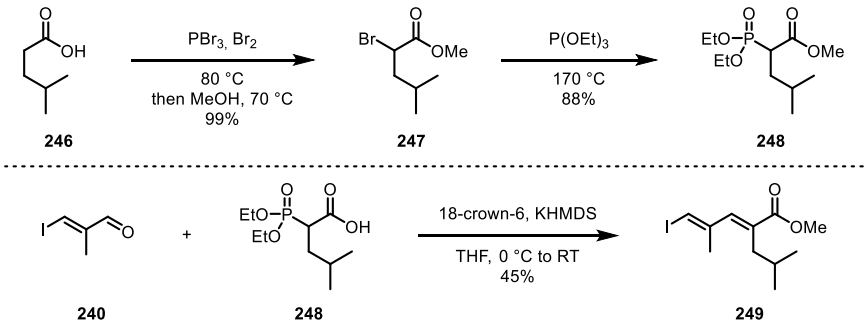
*Scheme 2.32 Synthesis of vinyl iodide **76** according to Brückner's procedure*

The following allylic oxidation with MnO_2 was found to proceed more efficient when performed in dichloromethane instead of diethyl ether; the conditions for the subsequent Wittig olefination with **77**[161-163] were kept as before, and similar yields were obtained (Scheme 2.33). By comparison with data of a mixture of geometric isomers obtained by Gudmundsson the geometry of **74** was confirmed to be as shown.[74]



*Scheme 2.33 Synthesis of dienoate **74***

Alongside the *C*1-*C*5 fragment of incednine, we also wanted to prepare the corresponding fragment for silvalactam **3**. Firstly, phosphonate ester **248** was synthesised by one-pot bromination and esterification of 4-methylvaleric acid (**246**), which gave bromide **247** in 99% yield. (Scheme 2.34). Arbuzov reaction with triethyl phosphite gave the desired phosphonate **248** in 88% yield.[164,165] Attempts to prepare an equivalent phosphorane were unsuccessful. The unoptimised HWE reaction of aldehyde **240** with **248** afforded the silvalactam *C*1-*C*5 fragment in 45% yield (Scheme 2.34). Access to this fragment should enable preparation of the aglycon of silvalactam by following the same strategy as for incednam.



*Scheme 2.34 Synthesis of phosphonate **248** and its application to prepare **249***

2.4.2 Synthesis of an alternative *C*1-*C*6 fragment

While the synthesis of the *C*1-*C*5 dienoate **74** is reliable and scalable, an alternative *C*1-*C*6 fragment was also envisaged that would rely on an HWE or Julia-Kocienski olefination rather than a Suzuki cross-coupling to assemble the *C*1-*C*9 tetraene of incednam. This could improve and simplify the endgame of the synthesis, especially considering the most advanced siloxane that was successfully coupled (Scheme 1.22). Our efforts to the synthesis of a phosphonate requiring a HWE reaction to assemble the C1-C13 fragment and a sulfone requiring a Julia-Kocienski reaction will be discussed below.

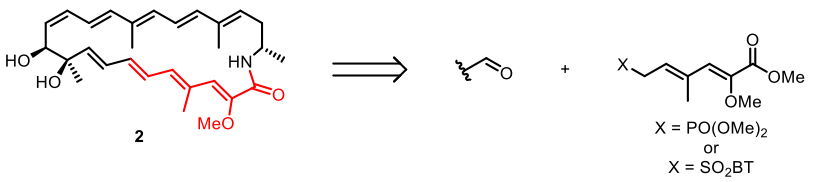


Figure 2.3 Alternative C1-C6 fragment

2.4.2.1 *C*1-*C*6 phosphonate fragment

So-called "extended" phosphonates have seen successful use in a multitude of cases, to install polyene systems of two or more double bonds in one step.[166-168] A phosphonate that constructs the *C*1-*C*6 segment of incednam in one step is an appealing strategy.

Retrosynthetically, an Arbuzov reaction of bromide **251**, was envisaged (Figure 2.4); we hoped to form diene **251** from a Wittig type reaction with aldehyde **252**.

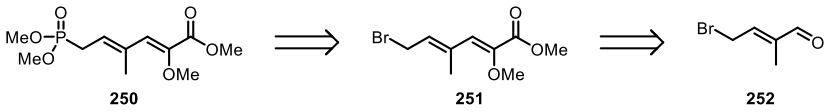
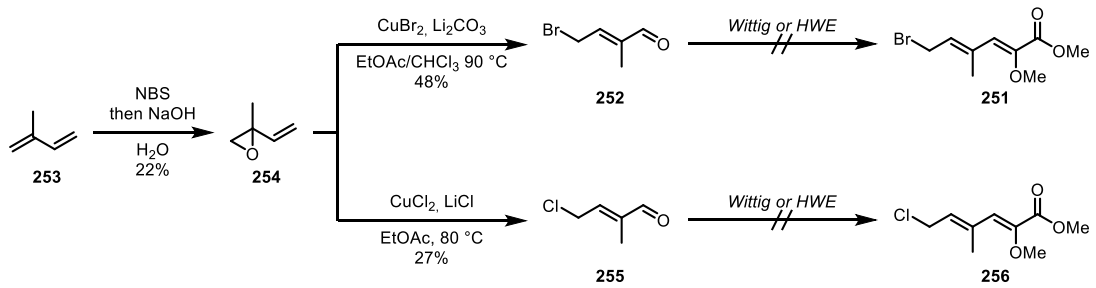


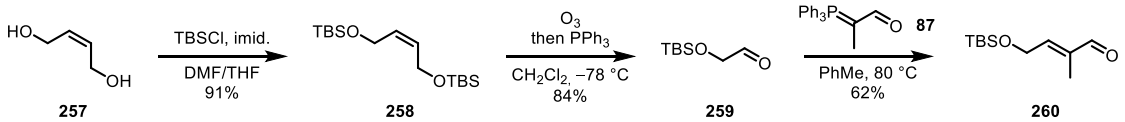
*Figure 2.4 Retrosynthetic approach for C1-C6 phosphonate **250***

The forward synthesis commenced with the epoxidation of isoprene.[169] Epoxide **254** was obtained in low yields, which was in part attributed to the small scale of the reaction as well as the volatility of substrates and products. Reaction of **254** with copper(II) bromide and lithium carbonate triggers an S_N2' reaction, with oxidation thus affording aldehyde **252** in 48% yield.[170] A similar reaction afforded the corresponding chloride in 27% yield.[171] Unfortunately, any olefination conditions employed that had worked on other aldehydes failed for these substrates (Scheme 2.35).



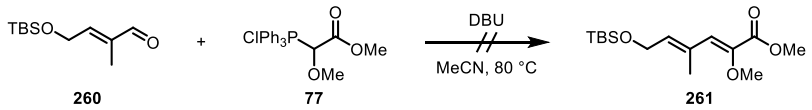
*Scheme 2.35 Attempted synthesis of Arbuzov precursors **251** and **256***

A revised strategy forms the six-carbon skeleton first, upon which functional group interconversions should afford the Arbuzov precursor. Thus, double TBS protection of butenediol **257** followed by ozonolysis and Wittig olefination afforded aldehyde **260** in 47% yield over three steps (Scheme 2.36).[172,173]



*Scheme 2.36 Synthesis of aldehyde **260***

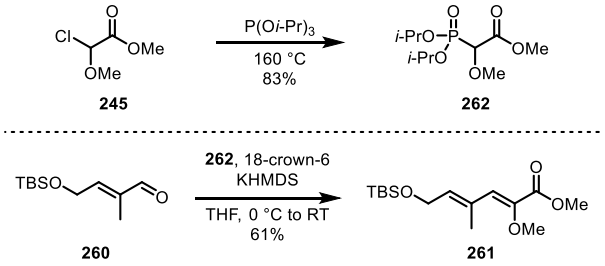
When aldehyde **260** and phosphonium salt **77** were then reacted according to the previous conditions, only a complex mixture was obtained, and no product could be isolated (Scheme 2.37).



*Scheme 2.37 Attempted Wittig olefination on aldehyde **260***

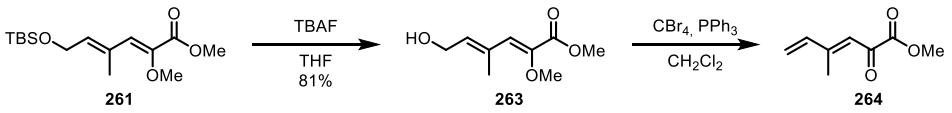
An obvious alternative is to prepare the equivalent HWE reagent. The HWE reaction should not need elevated temperatures, which could be harmful to the potentially sentitive diene **261**. The previously synthesised chloride **245** was therefore reacted with triisopropyl phosphite at 160 °C to give phosphonate **262** in 83% yield (Scheme 2.38).[174]

Pleasingly, aldehyde **260** reacted smoothly with phosphonate **262** using KHMDS/18-crown-6, and dienoate **261** was obtained in a moderate 61% yield. If the reaction time was extended beyond 6 h, the yield dropped, illustrating the delicate nature of **261** (Scheme 2.38**)**.



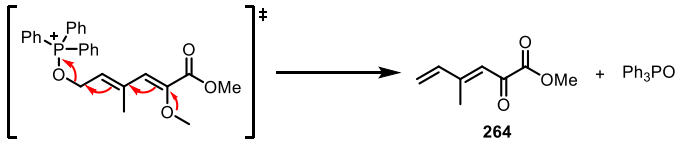
*Scheme 2.38 HWE reaction of aldehyde **260** to form dienoate **261***

TBS deprotection using TBAF provided alcohol **263** in high yields, as expected. The following Appel reaction however, revealed a rather unexpected product: instead of substitution of the allylic alcohol by bromide, a terminal alkene was observed (Scheme 2.40).



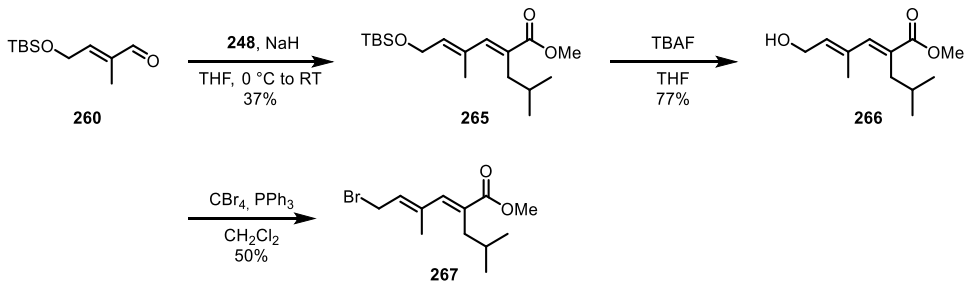
Scheme 2.39 TBS deprotection and attempted Appel reaction

The reason for the formation of this surprising compound likely lies in the enol ether of the starting material (Scheme 2.40): When the alcohol is converted into a leaving group during the reaction, an elimination is triggered that converts the enol ether into a ketone with concomitant double bond migration, forming product **264** along with triphenylphosphine oxide.



*Scheme 2.40 Proposed mechanism for the formation of **264***

This problem derived from the enol ether clearly hampers the strategy for this fragment. However, the related polyketide silvalactam lacks this problematic feature. Thus, it should be possible to prepare the equivalent fragment by applying this synthetic strategy (Scheme 2.41). Unfortunately, most commonly employed conditions with previously synthesised phosphonate **248** afforded diene **266** in low yields.[175,176] Due to time constraints and prioritisation of the synthesis of incednam no further optimisation was carried out. The subsequent deprotection and Appel reaction afforded the desired products, albeit in lower yields than anticipated. The small amounts of material did not allow for the exploration of the subsequent Arbuzov and HWE reaction.



Scheme 2.41 Synthesis of C1-C6 silvalactam building block precursor

2.4.2.2 *C*1-*C*6 sulfone fragment

Alternative to a HWE strategy for installation of the *C*1-*C*6 fragment is a Julia-Kocienski reaction. Our strategy for the synthesis of the phosphonate **250** had failed due to an unanticipated reaction when the allylic alcohol of **263** was transformed into a leaving group in the course of an Appel reaction. The mechanistically related Mitsunobu reaction that might be planned for sulfide introduction would therefore most likely produce similar results. We hypothesised that installation of the Julia-Kocienski sulfide prior to the enol ether would be key (Figure 2.5).

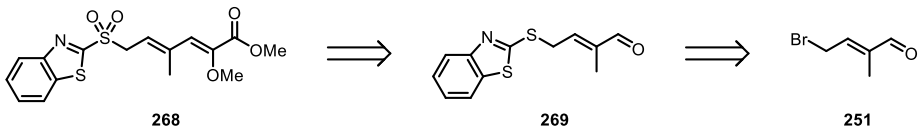
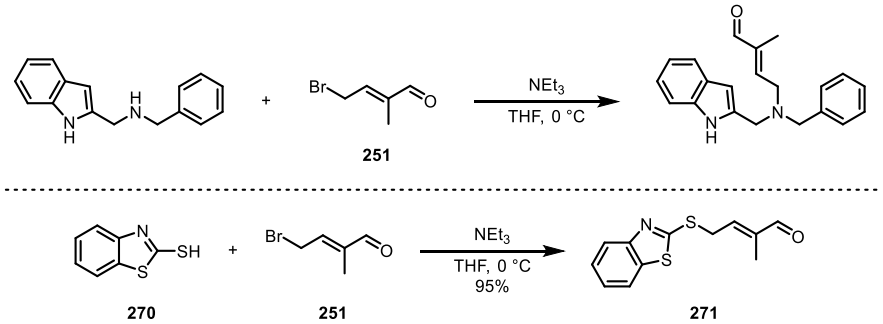


Figure 2.5 Retrosynthetic approach for the C1-C6 sulfone fragment synthesis

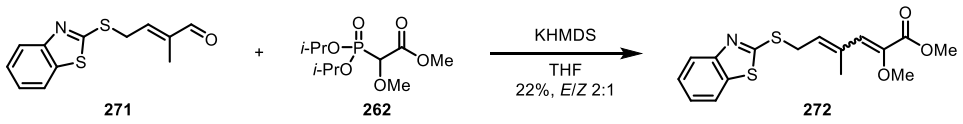
A literature search revealed only one example where aldehyde **251** was used in a nucleophilic substitution reaction to replace the bromine atom with (in this case) an amine is reported, with no yield stated (Scheme 2.42).[177] Pleasingly, when we attempted this reaction with 2-mercaptobenzothiazole (**270**) and aldehyde **251**, product **271** could be isolated in an excellent 95% yield (Scheme 2.42).



*Scheme 2.42 Nucelophilic substitution with thiol **270** and bromide **251***

With this encouraging result in hand, we were disappointed by the low yield and selectivity of the following HWE reaction (Scheme 2.43). While the previously employed conditions used 18-crown-6, product **272** could only be obtained when this was left out.

The low yield of 22% and poor *E*/*Z*-selectivity were discouraging regarding this approach, and we deemed pursuing this fragment would not actually add value compared to the previous fragment synthesis.



*Scheme 2.43 HWE reaction of aldehyde **271***

2.5 Conclusion

While our approach of introducing a further disconnection into tetraenyl iodide **72** to reveal the *C*12-*C*21 polyene system by a Julia-Kocienski or Ramberg Bäcklund reaction was largely unsuccessful, we could improve the synthesis of the *C*14-*C*23 fragment by employing an Ellman auxiliary both as the source of stereochemistry as well as a protecting group that is easily cleaved to afford the respective amine in high purity. Unfortunately, the synthesis of an alternative *C*1-*C*6 fragment to assemble the *C*1-*C*9 polyene in a streamlined way, could not be achieved due to an unforeseen elimination reaction involving the enol-ether.

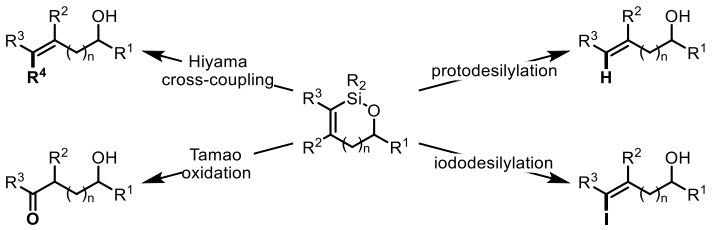
3 Development of Cyclic Dimethyl Alkenylsiloxanes for Cross-Coupling

In light of the challenges we faced with the previously employed cyclic diethyl alkenylsiloxanes, we decided to explore the use of more reactive dimethylalkenylsiloxanes instead to enhance efficiency in the Hiyama cross-coupling.

3.1 Introduction

3.1.1 Previous syntheses of cyclic alkenylsiloxanes

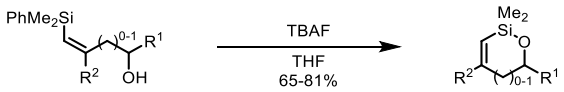
Cyclic siloxanes are somewhat underdeveloped building blocks in organic synthesis despite the number of different synthetically useful transformations they can be employed in, such as cross-couplings, protodesilylation, iododesilylation, and Tamao oxidation (Scheme 3.1). In Hiyama cross-coupling, they enable the stereospecific generation of olefins containing *Z*-allylic or homoallylic alcohols. Through protodesilylation they give access to alkenes with well-defined geometries;[178-180] similarly, iododesilylation affords vinyl iodides often with retention of geometry;[181] and, they can be used as aldol surrogates to prepare β-, γ- or δ-hydroxyl carbonyl compounds *via* Tamao oxidation.[182]



Scheme 3.1 Synthetically useful transformations of cyclic alkenylsiloxanes

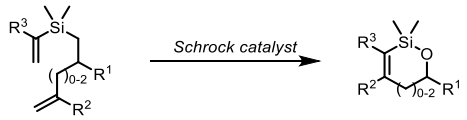
Prior to the pioneering work of Denmark *et al.* in 2001, there were few reports describing the synthesis and applications of cyclic alkenylsiloxanes.[183,184] One of the first examples was reported by Oshima *et al.*, in which five- and six-membered siloxanes were prepared

by treatment of vinylphenylsilanes with fluoride. Subsequent Tamao oxidation enabled access to hydroxyl aldehydes (Scheme 3.2).[178]



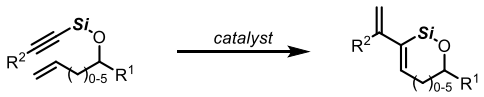
Scheme 3.2 Synthesis of cyclic alkenylsiloxanes by Oshima et al.

To date, metathesis and hydrosilylation are the most commonly applied methods to prepare cyclic alkenylsiloxanes. First demonstrated in 1997, Grubbs' 1st generation catalyst is effective for the construction of these siloxanes, however in the case of more sterically crowded substrates, the Schrock catalyst was required.[185] Building on these results, Denmark *et al.* expanded the use of RCM to access different sizes of cyclic alkenylsiloxanes and demonstrated their use in total synthesis (Scheme 3.3).[111,183,186-188]



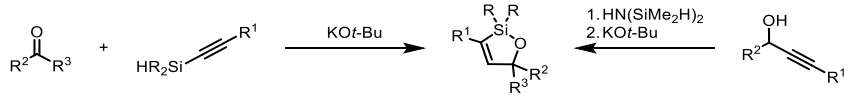
Scheme 3.3 Synthesis of cyclic alkenylsiloxanes via ring-closing metathesis by Denmark

In addition, Lee *et al.* have used ring-closing enyne methathesis to access a wide variety of differently sized cyclic alkenylsiloxanes, using various catalytic systems, such as Grubbs II, Schrock or gold-based catalysts, to effect cyclisation (Scheme 3.4).[189-193]



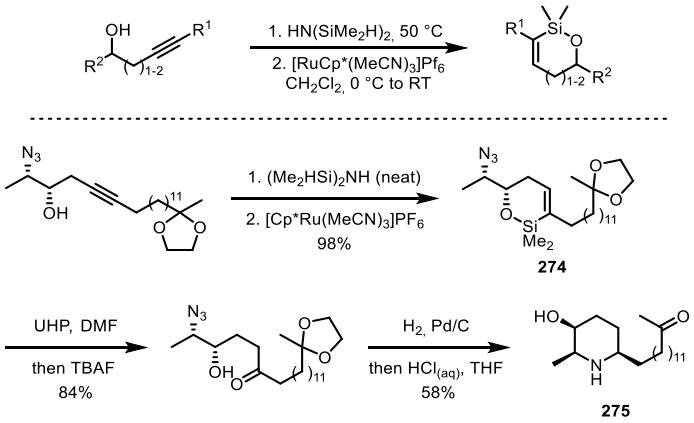
Scheme 3.4 Synthesis of cyclic alkenylsiloxanes via enyne metathesis by Lee et al.

A number of hydrosilylation strategies have been developed for the synthesis of cyclic alkenylsiloxanes. For example, the treatment of carbonyls and alkynylsilanes with substoichiometric potassium *tert*-butoxide affords five-membered siloxanes. The analogous transformation can also be effected using propargylic silyl ethers with catalytic potassium *tert*-butoxide (Scheme 3.5).[194-196] Subsequently, nickel catalysts have been shown to trigger this transformation from similar precursors.[197]



Scheme 3.5 Synthesis of cyclic siloxanes via hydrosilylation

Trost *et al.* developed the intramolecular ruthenium-catalysed hydrosilylation of alkynes, a powerful tool for the synthesis of cyclic siloxanes, albeit this method is limited to internal homo- and bishomopropargylic alcohols. Its use was demonstrated in the total synthesis of spectaline (Scheme 3.6).[182,198-200]

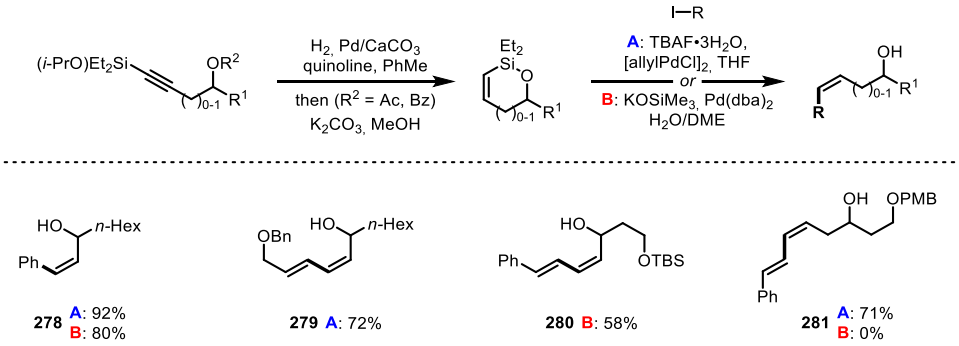


*Scheme 3.6 Synthesis of cyclic alkenylsiloxanes via hydrosilylation and its use in the synthesis of spectaline **275***

Less commonly employed conditions include silacyclopropanation, followed by copper-catalysed ring expansion, reported by Woerpel *et al.*,[201-204] and migration of exocyclic alkenes to endocyclic alkenylsiloxanes.[205,206]

Our approach relies on the semihydrogenation of alkynylsilanes, followed by an intramolecular cyclisation to access five- and six-membered cyclic alkenylsiloxanes (Scheme 3.7).[83] Subsequently, the siloxanes obtained readily undergo cross-coupling reactions under both by fluoride- and base-activated conditions, while displaying an interesting orthogonality between five- and six-membered siloxanes. While five-membered siloxanes coupled effectively under either fluoride- or base-promoted conditions, the six-membered siloxanes were inert towards base activation, enabling the possibility to couple a five-membered alkenylsiloxane in the presence of a six-membered

siloxane. Furthermore, cyclic siloxanes undergo different decomposition pathways and display different stabilities dependent on ring-size. While a common side-reaction for the five-membered silane is protodesilylation to afford terminal alkenes, this has not been observed for the six-membered analogues under cross-coupling conditions. Thus, the latter are somewhat less reactive, but also less prone to undergo decomposition. This chapter will focus on our efforts to improve upon this methodology, and thereby solve the issues encountered in the synthesis of incednam.

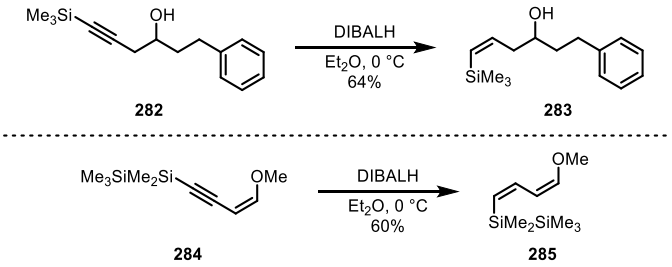


Scheme 3.7 Synthesis of cyclic alkenylsiloxanes via semi-hydrogenation and subsequent cross-coupling

3.1.2 Stereoselective reduction of alkynylsilanes

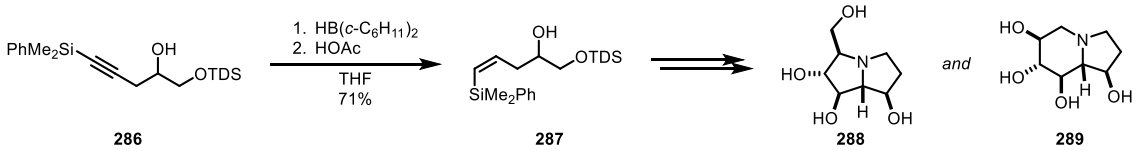
The efficient preparation molecules containing double bonds with well-defined configurations is of great interest, due to their prevalence in natural products and drug molecules.[207] Thus, development of reagents to form geometrically pure (*Z*)-alkenes has received considerable attention. A commonly employed strategy involves hydrometalation and subsequent protodemetalation.[207] This has been demonstrated using several metals, including aluminium, boron, titanium and zirconium. Hydroalumination of alkynylsilanes, typically using DIBALH, has been shown to efficiently afford (*Z*)-alkenylsilanes (Scheme 3.8).[208-210] However, the use of DIBALH and related reagents is often limited by its functional group tolerance: these reagents are destroyed by protic

functionalities and react readily with carbonyls, thus necessitating either the use of protecting groups or superstoichiometric amounts of reagent.



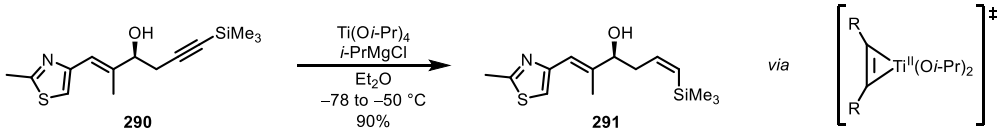
Scheme 3.8 Examples of alkynylsilane reductions using DIBALH

Denmark *et al.* reported the hydroboration and protodeborylation of alkynylsilane **286** to afford (*Z*)-vinylsilane **287** in good yield as a single geometrical isomer, as determined by ^{1}H NMR spectroscopic analysis, in their synthesis of 7-epi-australine (**288**) and 1-epi-castanospermine (**289**) (Scheme 3.9).[211-213]



*Scheme 3.9 Reduction of alkynylsilane **286** via hydroboration by Denmark et al.*

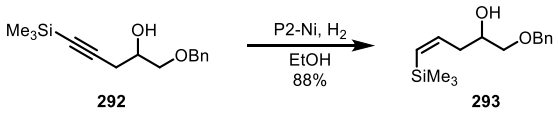
Another efficient method is the titanium(II)-mediated reduction of alkynes reported by Hungerford and Kitching.[214,215] Titanium(II) is generated *in situ* by treatment of Ti(O*i*-Pr)$_4$ with Grignard reagent *i*-PrMgCl and is thought to form a three-membered titanocycle with alkynes, which is then quenched (by protonation) to form (*Z*)-alkenes. This method was successfully used in the total synthesis of epothilone A by Shibasaki *et al.*, affording intermediate **291** in an excellent 90% yield (Scheme 3.10).[216]



*Scheme 3.10 Titanium mediated reduction of akynylsilane **290** in the total synthesis of epothilone A*

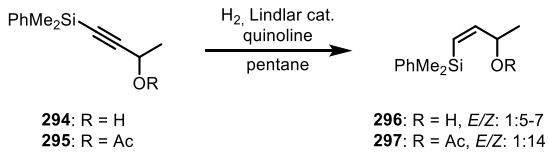
A different approach is the heterogeneous hydrogenation of alkynes. Several different catalysts, often deriving from nickel or palladium deposited onto various materials, are

known to aid in this transformation. There are several examples of alkynylsilanes hydrogenated to afford the corresponding vinylsilanes with the use of nickel-based catalysts, such as Raney-nickel or P2-Ni, as exemplified in the hydrogenation of alkyne **292** (Scheme 3.11).[217-221]



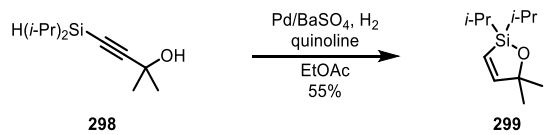
*Scheme 3.11 Semihydrogenation of alkyne **292** using Brown catalyst*

The use of heterogeneous catalysts, for example the Lindlar catalysts, is operationally simple and can often be favoured over expensive, air-sensitive, homogeneous catalysts. The drawbacks can be inconsistent reaction times (which is likely a factor of particle size and surface area), and potential over-reduction and/or sub-optimal stereoselectivity.[222] The Lindlar catalyst has been reported to afford (*Z*)-vinylsilanes in good selectivities and yields, however, propargylic alcohols are notoriously troubled by poor selectivites.[223-225] Studies by Panek and Clark discovered that this problem can be overcome by protection of the hydroxyl with an electron-withdrawing group (Scheme 3.12).[225]



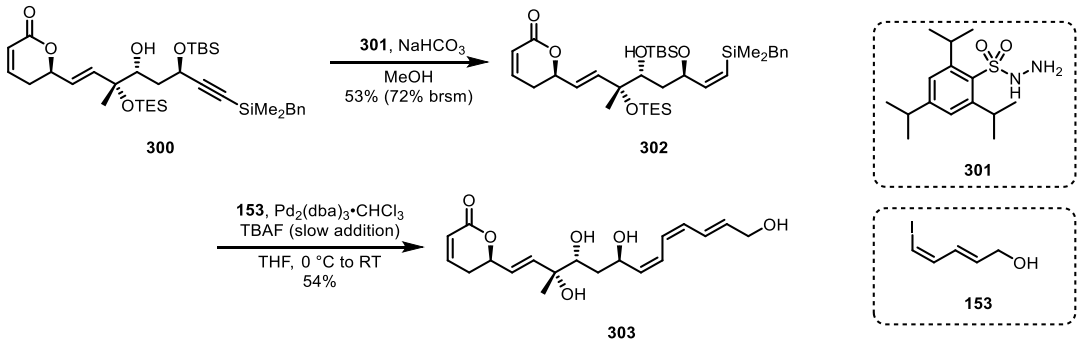
*Scheme 3.12 Comparison of selectivities in semihydrogenation of alkynes **294** and **295***

Similarly, the Rosenmund catalyst has been widely employed in the semihydrogenation of various alkynylysilanes.[226-228] Furthermore, its use provided the first example of semihydrogenation to afford cyclic alkenylsiloxanes (Scheme 3.11).[229]



*Scheme 3.13 Semihydrogenation of alkynylsilane **298** to afford cyclic alkenylsiloxane **299***

Alternatively to hydrometalation and transition metal-catalysed hydrogenations, the use of *in situ* generated diimide provides a metal-free method to reduce alkynes that tolerates a number of functional groups not stable under other reducing conditions.[230] There are several different reagents used to generate the required diimide *in situ*, but many require harsh conditions, which was overcome by the development of 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (**301**).[231] Reactions using **301** generally proceed at ambient temperature, and this approach was successfully employed by Trost *et al.* to reduce alkynylsilane **300** in their synthesis of dephosphofostriecin (**303**) (Scheme 3.14).[110]



*Scheme 3.14 Diimide reduction of alkynylsilane **300** in Trost's synthesis of dephosphofostriecin **303***

3.2 Synthesis of cyclic dimethyl alkenylsiloxanes

3.2.1 Previous efforts and revised strategy

Our previous strategy to access cyclic diethylsiloxanes relied on the palladium-catalysed semi-hydrogenation of diethyl ethynyl isopropoxysilane (**304**) (Figure 3.1).[83] Unfortunately, the same strategy to access equivalent dimethyl siloxanes proved difficult due to issues regarding volatility, purification and stability of intermediates, particularly the alkoxydimethylalkynylsilane **305** (Figure 3.1).[82]

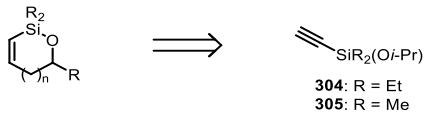
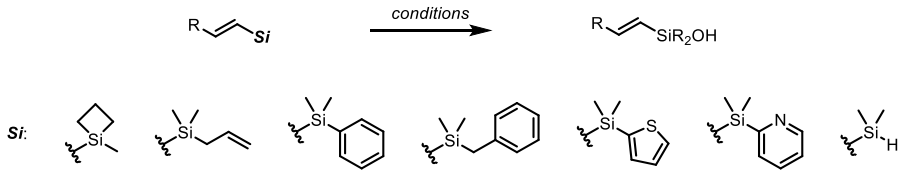


Figure 3.1 Previous strategy to access diethyl- or dimethylsiloxanes

These problems could potentially be overcome by using 'masked' silanols that show increased stability.[93] It has been shown that siletanes, phenyl-, 2-pyridyl, 2-thienyl- and benzylsilanes all reveal a silanol on treatment with fluoride (Scheme 3.15).

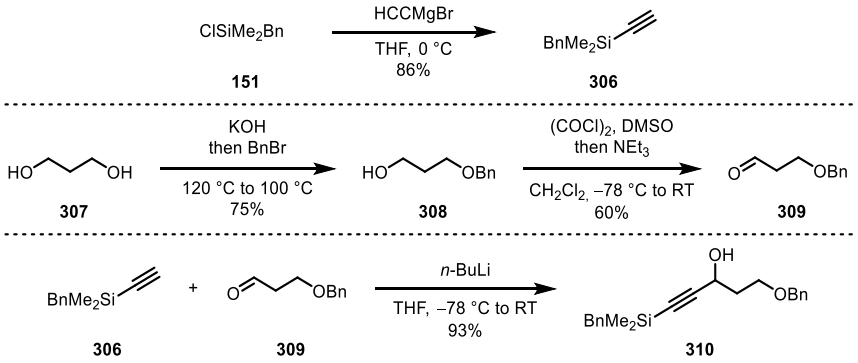


Scheme 3.15 Examples of 'masked' silanols

We therefore opted to try and apply our former strategy to benzyldimethylsilanes, which have been employed in Hiyama cross-couplings in several examples.[91,93,109,110]

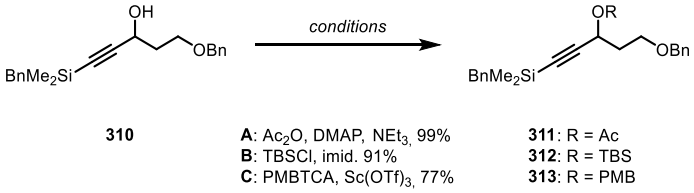
3.2.2 Synthesis of five-membered cyclic alkenylsiloxanes

We targeted the synthesis of the desired five-membered cyclic siloxanes in four steps from alkyne **306** and aldehyde **309** (Scheme 3.16). Alkynyl silane **306** was accessed by a Grignard-reaction with ethynylmagnesium bromide and benzyldimethylchlorosilane in high yields.[232] Aldehyde **309** was prepared in two steps from 1,3-propanediol to serve as our model system, followed by addition of alkyne **306** into aldehyde **309** to afford propargylic alcohol **310** in excellent 93% yield.



*Scheme 3.16 Synthesis of alkyne **306** and aldehyde **309** to access propargylic alcohol **310***

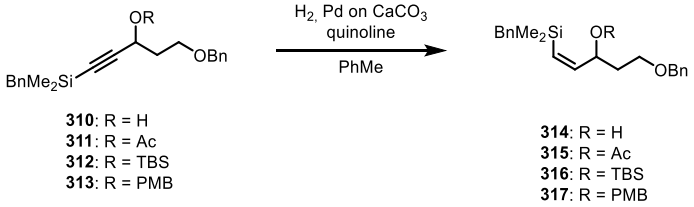
While we were interested to see how compound **310** would behave in the Lindlar hydrogenation (considering previously reported stereoselectivity issues), we also decided to explore the influence of different protecting groups, including the previously beneficial acetate (Scheme 3.17).[83,225]



*Scheme 3.17 Protection of propargylic alcohol **310***

Interestingly, the influence of the protecting group of the progargylic alcohol seemed to have a less drastic influence during the hydrogenation compared to diethylisopropoxy silanes (Table 3.1). Gudmundsson observed that hydrogenation of acetate **311** provided a similarly good yield and *Z*/*E*-selectivity as with the diethyl silane (Table 3.1, Entry 1).[74] Pleasingly, both the free hydroxyl[233] and the *p*-methoxybenzyl ether also seemed to be well-tolerated, with only the (*Z*)-isomer observed in the crude ^{1}H NMR spectrum (Table 3.1, Entries 1 and 4). Only TBS ether **312** showed formation of a considerable amount of the undesired (*E*)-isomer (Table 3.1, Entry 3). All alkenes were isolated in good to excellent yields.

Table 3.1 Hydrogenation of alkynylsilane derivatives



310: R = H
311: R = Ac
312: R = TBS
313: R = PMB

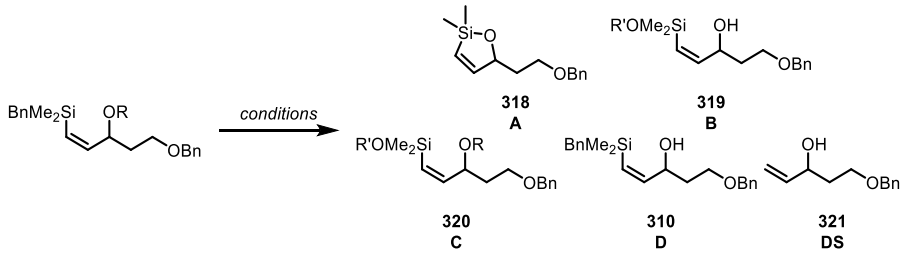
314: R = H
315: R = Ac
316: R = TBS
317: R = PMB

Entry	Substrate / R	*Z*/*E*-ratio[c]	Yield [%][b]
1	**310**: R = H	>20:1	77
2	**311**: R = Ac	>20:1	85
3	**312**: R = TBS	5.3:1.0	67
4	**313**: R = PMB	>20:1	89

[a] H_2, Pd on $CaCO_3$ (5 mol%), quinolone (0.2 eq.), PhMe; [b] isolated yield; [c] determined by crude ^{1}H NMR

With several vinyl silanes in hand, we next investigated a range of conditions to enable deprotection and subsequent cyclisation to afford the cyclic alkenylsiloxane. Preliminary results by Gudmundsson, showed that treatment of allylic hydroxyacetates with fluoride result in debenzylation of the silane, and immediate formation of a five-membered alkenylsiloxane.[74]

Table 3.2 Conditions for formation of five-membered cyclic alkenysiloxane



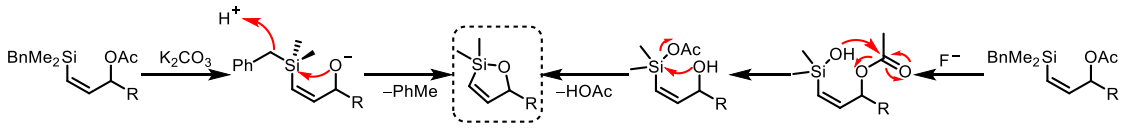
Entry	Substrate	Conditions	Product[a]
1		TBAF (0.25 eq.) in THF	A[c]
2	**314**	K_2CO_3 (1.5 eq.) in MeOH	n.R.[c,d]
3	R = H	$KOSiMe_3$ (1.3 eq.) in THF	A[c]
4		TBAF (0.25 eq.) in THF	A[b]
5	**315**	K_2CO_3 (1.5 eq.) in MeOH	A[b]
6	R = Ac	$KOSiMe_3$ (1.3 eq.) in THF	A + DS (slow)[b]
7		TBAF (1.0 eq.) in THF	A
8	**316**	K_2CO_3 (1.5 eq.) in MeOH	n.R.[d]
9	R = TBS	$KOSiMe_3$ (1.3 eq.) in THF	n.R.[d]
10		TBAF (1.0 eq.) in THF	C
11	**317**	K_2CO_3 (1.5 eq.) in MeOH	n.R.[d]
12	R = PMB	$KOSiMe_3$ (1.3 eq.) in THF	n.R.[d]

[a] determined from crude ^{1}H NMR spectrum; [b] performed by Gudmundsson; [c] performed by Cornut;[233]

[d] no reaction.

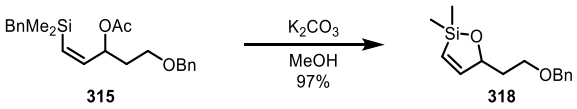
Cyclic siloxane **318** was formed exclusively upon treatment of acetate **315** with K_2CO_3 in methanol (Table 3.2, Entry 5).[74] The other derivatives, including alcohol **314**, do not react under these conditions (Table 3.2, Entries 2, 8, and 11). The lack of reactivity of alcohol **314** under potassium carbonate/MeOH conditions is notable, considering the quick and ready formation of five-membered alkenylsiloxanes when acetate **315** is employed. For all substrates, TBAF serves to cleave the benzyl group from the silane,

leading to cyclisation and formation of the desired siloxane **318** for alcohol **314**, acetate **315** and TBS ether **316** (Table 3.2, Entries 1, 4 and 7); in the case of PMB-derivative **317**, TBAF is unsurprisingly unable to facilitate hydroxyl deprotection, and silanol or disiloxane **PMB-320** was obtained instead (Table 3.2, Entry 10). It is probable that acetate cleavage upon fluoride treatment follows a similar mechanism to that previously discussed; while for the debenzylation with potassium carbonate an attack of the oxygen anion is proposed before protonation occurs (Scheme 3.18).



Scheme 3.18 Proposed mechanism for the formation of five-membered alkenylsiloxanes under fluoride or basic conditions

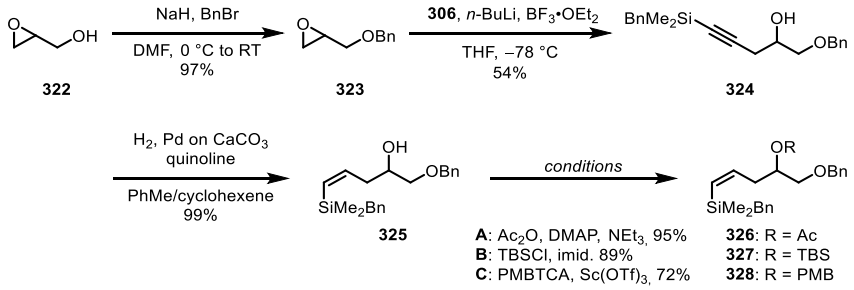
Whilst the secondary TBS ether deprotection with fluoride is unsurprising, the 5 min timescale is remarkable, and we hypothesised that the vinylic silanol assits in the deprotection. Additionally, we investigated how the substrates behave when treated with potassium timethylsilanolate, as this could enable a fluoride free *in situ* formation of an 'active' silanol with a proven activator for cross-couplings. Both alcohol **314** and acetate **315** form the desired cyclic siloxane (Table 3.2, Entries 3, 6),[233] however, in the case of the reaction with the acetate, protodesilylation **321** was observed.[74] TBS and PMB derivatives **316** and **317** do not react under these conditions (Table 3.2, Entries 9, 12). In all, this provides us with several different ways of forming five-membered alkenylsiloxanes either for isolation or use *in situ*. For larger scale syntheses of **318**, we opted to use K_2CO_3/MeOH, since all non-volatile reagents and byproducts are removed by an aqueous workup to afford pure **318** in almost quantitative yields (Scheme 3.19).



*Scheme 3.19 Synthesis of cyclic alkenylsiloxane **318***

3.2.3 Synthesis of six-membered cyclic alkenylsiloxanes

The analogous six-membered alkenylsiloxanes were next investigated. The synthesis of a model six-membered ring commenced with the benzylation of glycidol (**322**), followed by regioselective opening of the epoxide with alkynylsilane **306** to give homopropargylic alcohol **324** (Scheme 3.20). Unlike for propargylic alchols, the hydrogenation of homopropargylic alcohols is typically less stereochemically troublesome, and so a thorough protecting group investigation was unnecessary.[74,82] Hydrogenation of **324** gave the desired alkene **325** in 99% yield as a single isomer. Subsequent protection of homoallylic alcohol **325** afforded either acetate **326**, TBS ether **327** or PMB ether **328**, for comparison of cyclisation conditions (Scheme 3.20).

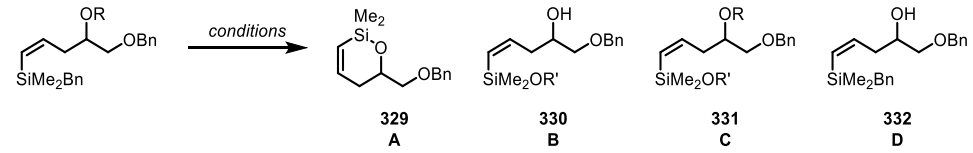


Scheme 3.20 Synthesis of intermediates towards a model for six-membered dimethyl alkenylsiloxanes

With these different precursors in hand, treatment under the aforementioned cyclisation conditions revealed some key differences in the formation of the six-membered alkenylsiloxanes compared to the five-membered analogues. While five-membered siloxane **318** is formed immediately under several conditions, and the silanol also seems to aid in the deprotection of proximal protecting groups, this was not observed for the homoallylic analogues (Table 3.3). Cyclic siloxane **329** was formed when **325** (with a free hydroxyl group) was treated with TBAF (Table 3.3, Entry 1). However, for acetate **326** and PMB ether **328** only debenzylation to reveal a silanol or disiloxane was observed (Table 3.3, Entries 4 and 10). TBS ether **327** gave a mixture of both cyclised **329** and uncyclised hydroxy silanol **330** (Table 3.3, Entry 7). Potassium carbonate only triggered

the acetate deprotection, with the benzyldimethylsilane group remaining intact (Table 3.3, Entry 5); the other substrates only returned the starting material under these conditions (Table 3.3, Entries 2, 8, and 11). Potassium trimethylsilanolate effected the cyclisation for both the free hydroxyl derivative **325** as well as acetate **326**, albeit very slowly in the latter case (Table 3.3, Entries 3 and 6). Unsurprisingly, both the PMB and TBS ether substrates **327** and **328** did not react under these conditions (Table 3.3, Entries 9 and 12).

Table 3.3 Formation of six-membered cyclic alkenysiloxane

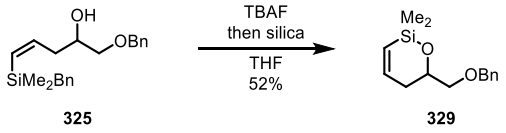


329 **A** | **330** **B** | **331** **C** | **332** **D**

Entry	Substrate	Conditions	Product[a]
1		TBAF (0.25 eq.) in THF	A[c]
2	**325** R = H	K_2CO_3 (1.5 eq.) in MeOH	n.R.[c,d]
3		$KOSiMe_3$ (1.3 eq.) in THF	A[c]
4		TBAF (0.25 eq.) in THF	C[b]
5	**326** R = Ac	K_2CO_3 (1.5 eq.) in MeOH	D[b]
6		$KOSiMe_3$ (1.3 eq.) in THF	A (slow)[b]
7		TBAF (1.0 eq.) in THF	A + B
8	**327** R = TBS	K_2CO_3 (1.5 eq.) in MeOH	n.R.[d]
9		$KOSiMe_3$ (1.3 eq.) in THF	n.R.[d]
10		TBAF (1.0 eq.) in THF	C
11	**328** R = PMB	K_2CO_3 (1.5 eq.) in MeOH	n.R.[d]
12		$KOSiMe_3$ (1.3 eq.) in THF	n.R.[d]

[a] determined from crude ^{1}H NMR spectrum; [b] performed by Gudmundsson; [c] performed by Cornut; [d] no reaction.

For larger scale syntheses of siloxane **329**, treatment of homoallylic alcohol **325** with TBAF, followed by filtration over silica to trigger cyclisation, was the preferred method (Scheme 3.21).



325 **329**

*Scheme 3.21 Synthesis of six-membered cyclic alkenylsiloxane **329***

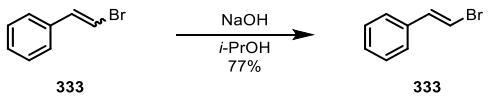
3.2.4 Conclusion

In conclusion, an efficient synthesis was devised of both five- and six-membered alkenylsiloxanes from benzyldimethyl alkynylsilane. We discovered that the substituent on propargylic alcohols has a lesser impact on the *Z*/*E*-selectivity of the Lindlar hydrogenation with a benzyldimethylsilane substituent than on different previsouly reported alkoxysilane substrates. Finally, we discovered that the five- and six-membered ring siloxanes form under different conditions, and can be selectively activated depending on proximity to the hydroxyl group. The formation of a five-membered ring seems to also result concomitant deprotection of a proximal hydroxyl under rather unusual conditions in the case of fluoride-activation. In comparison, the deprotection of an allylic alcohol triggers an concomitant debenzylation of the silane without the need of fluoride.

3.3 Synthesis of vinyl halide substrates for cross-coupling

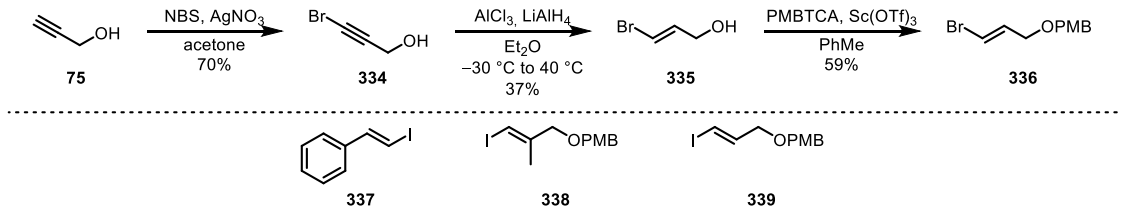
To test the efficacy of dimethyl siloxanes in cross-coupling, a range of different vinyl halide coupling partners were prepared. This included a variety of vinyl and dienyl iodide and bromide substrates to mimic the polyene system we intended to prepare using this method.

Commercially available β-bromostyrene comes as an isomeric mixture of (*Z*)- and (*E*)-alkenes. Treatment of this mixture with NaOH causes E2 elimination of the (*Z*)-bromostyrene and affords only (*E*)-bromostyrene. (Scheme 3.22).[234]



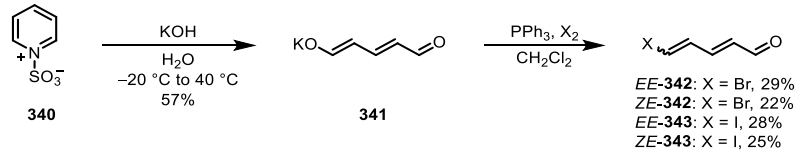
Scheme 3.22 Elimination of undesired (Z)-β-bromostyrene to afford pure (E)-β-bromostyrene

Vinyl bromide **336** was prepared in three steps from propargyl alcohol **75**. Firstly, **75** was converted into the bromoalkyne **334**, followed by reduction to the (*E*)-alkene **335**.[235] Protection of the free alcohol using PMBTCA and scandium(III) triflate afforded the desired vinyl bromide **336** in 59% yield (Scheme 3.23).[83] Vinyl iodides **337**, **338**, and **339** were provided by Gudmundsson/Lim.



*Scheme 3.23 Synthesis of vinyl bromide **336**; vinyl iodides **337**, **338**, and **339** prepared by Gudmundsson/Lim*

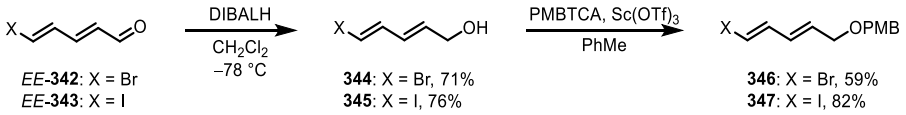
Our synthesis of diene halides commenced with the hydrolysis of the pyridine-SO_3 complex **340** to afford the potassium salt of glutaconaldehyde (**341**), which was treated with triphenylphosphine and either bromine or iodine to afford the respective vinyl halide aldehydes as *E,E*/*Z,E*-mixtures (~1.2:1). These are separable by column chromatography, or recrystallization (Scheme 3.24).[236-238]



Scheme 3.24 Synthesis of vinyl halide aldehydes from pyridine-SO_3 complex

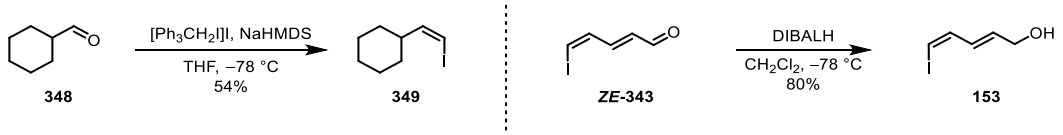
Reduction of both dienals ***EE*-342** and ***EE*-343** was performed using DIBALH, affording allylic alcohols **344** and **345** in good yields. The use of $LiAlH_4$ results in mostly

decomposition and the product was only be observed in small amounts. Alcohols **344** and **345** were protected using PMBTCA and scandium(III) triflate to afford the desired vinyl halides **346** and **347** in good yields (Scheme 3.25).[83] The alternative, deprotonation with sodium hydride followed by alkylation with PMBCl resulted in a poorer yield.



*Scheme 3.25 Reduction and protection of vinyl halide aldehydes **EE-342** and **EE-343***

Finally, vinyl iodides **349** and **153** were prepared, as they represent building blocks for polyenes found in various natural products, and their cross-coupling models the construction of the respective bonds.[83,110,239] Vinyl iodide **349** was prepared by a Stork-Wittig olefination on aldehyde **348** to give the product in 54% yield (Scheme 3.26).[240] Vinyl iodide **153** was easily accessed by reduction of the previously obtained ***Z,E*-343** using DIBALH (Scheme 3.26).



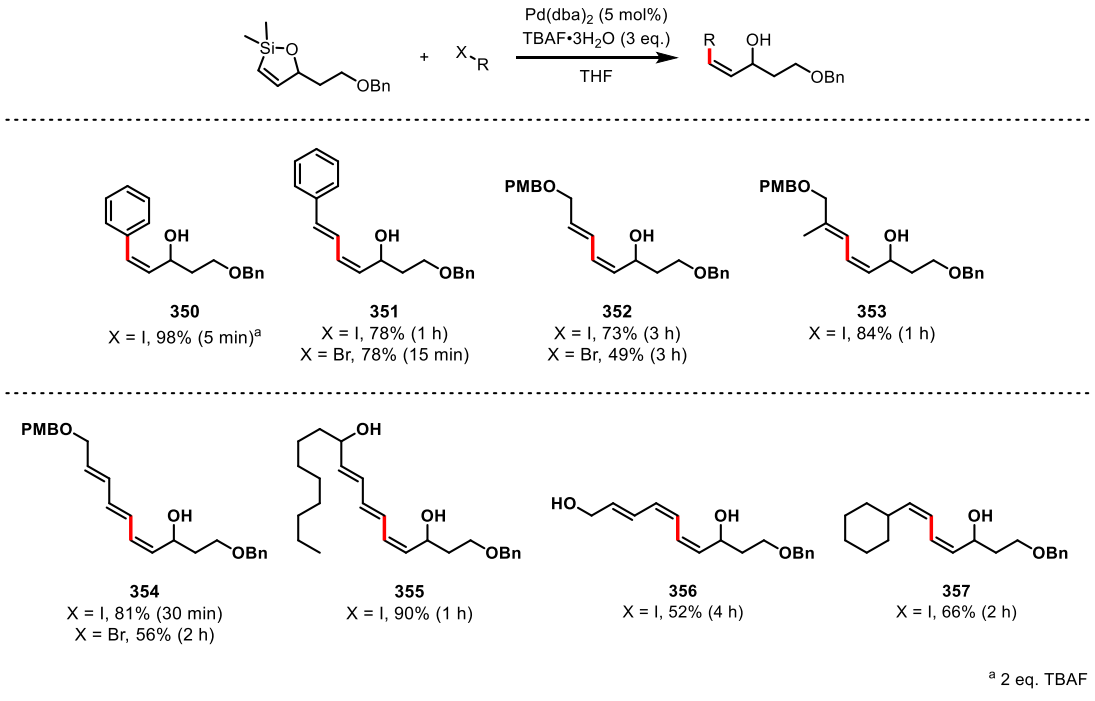
*Scheme 3.26 Synthesis of vinyl iodides **349** and **153***

3.4 Cross-coupling of cyclic dimethyl alkenylsiloxanes

3.4.1 Fluoride promoted Hiyama cross-couplings

The optimisation of the cross-coupling reaction between five-membered cyclic siloxane **318** and β-iodostyrene (**337**) was carried out by Gudmundsson.[74] Building on conditions used by Denmark *et al.* for the coupling of cyclic siloxanes, the influence of different palladium sources with and without ligands was examined for our system;[183,188] $Pd(dba)_2$ (5 mol%) and three equivalents of TBAF were found to be the optimal conditions. When strongly coordinating phosphine ligands were employed, only desilylation or no reaction

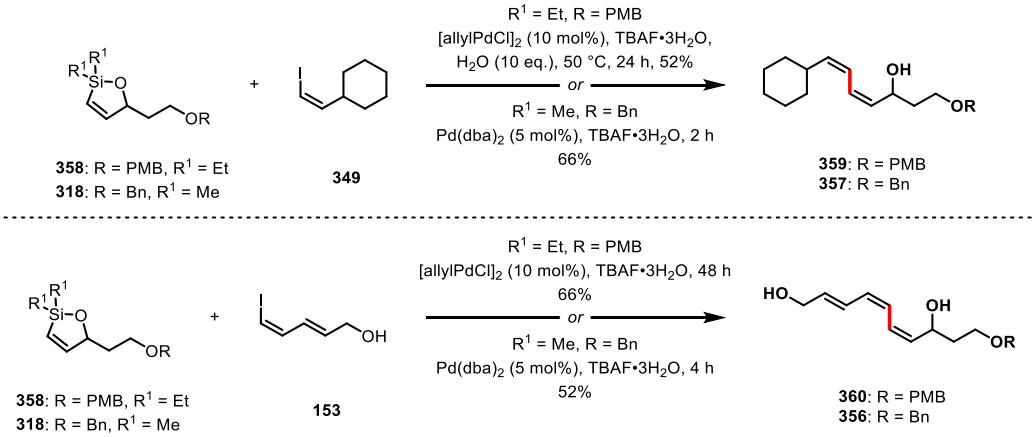
could be observed, which is consistent with Denmark's suggestions that a coordinatively unsaturated palladium species is required prior to the transmetalation step.[241,242] The scope of the cross-coupling of alkenylsiloxane **318** was explored in collaboration with Gudmundsson and is summarised in Scheme 3.27.[74] Coupling with iodobenzene affords the product in excellent 98% yield in only 5 min reaction time, which is a considerably shorter reaction time than observed in the diethyl siloxane analogues. This trend continued for the more challenging coupling with vinyl and dienyl halides. It is of note that whilst vinyl iodides are typically more reactive than analogous bromides in these couplings, we observed that β-bromostyrene (**333**) reacted faster than β-iodostyrene (**337**). Generally, all couplings show moderate to excellent yields and reach completion with short reaction times.



*Scheme 3.27 Scope of the Hiyama cross-coupling of five-membered alkenylsiloxane **318***

These highly successful couplings, especially using the formerly challenging vinyl iodide partners **349** and **153**, clearly display the utility of this methodology for the synthesis of natural product fragments, such as fostriecin and phoslactomycin B.[243-245] Additionally, they allow us to directly compare the efficiency of our previous diethyl siloxanes to the

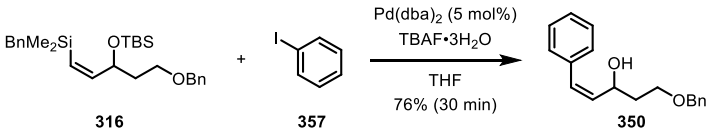
dimethyl analogues (Scheme 3.28).[83] For example, the cross-coupling to afford phoslactomycin B fragment with **349** required the addition of water to inhibit desilylation, and elevated temperatures to give product **360** in satisfactory yields. When dimethyl analogue **318** is used, the reaction proceeds smoothly at ambient temperature without the need for additional water to form product **357** in 66% in only 2 h, compared to 52% in 24 h (at 50 °C) before. In the case of fostriecin fragment **153** however, the reaction with the dimethylsiloxane **318** was slightly lower yielding than the diethyl analogue **358**, albeit again with a significant decrease in reaction time (4 h compared to 48 h). In both cases, a decreased loading of palladium could be employed to effect coupling ($Pd(dba)_2$, 5 mol% Pd, compared to $[allylPdCl]_2$, 10 mol% Pd).



Scheme 3.28 Comparison of efficiency in cross-coupling of diethyl- and dimethylsiloxanes

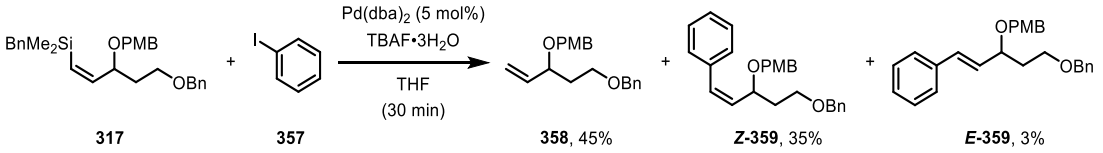
We next compared the reaction of the cyclic dimethylsiloxanes to the acyclic analogues, and explored the influence of the protecting group on the allylic alcohol. We had shown, that an allylic TBS ether does form five-membered alkenylsiloxanes *in situ*, and is thus expected to behave similarly to couplings using preformed cyclic siloxanes. However, cross-coupling of vinylsilane **316** with iodobenzene (**357**) provided product **350** in 76% yield, a drop compared to the coupling using **318** (Scheme 3.29). Additionally, the reaction requires 30 min to reach completion, compared to 5 min with the cyclic siloxane. Clearly, this approach seems inferior to preformation of cyclic siloxane, however it still

provides a valuable alternative in circumstances where the formation of the cyclic siloxanes is not desired.



*Scheme 3.29 Hiyama cross-coupling of OTBS ether **316** with iodobenzene*

Next, we wanted to investigate the outcome of a cross-coupling where no five-membered cyclic siloxane can be formed. Having shown previously that a PMB ether is not cleaved under fluoride conditions, we found that while the coupling of vinylsilane **317** does provide coupled product ***Z*-359** (Scheme 3.30), it is quite inefficient as alongside the desired compound ***Z*-359** (35% yield), desilylated alkene **388** (45%), and ***E*-359** (3%) were also isolated. ***E*-359** likely results from a Heck coupling of **358**, rather than an isomerisation of ***Z*-359**.

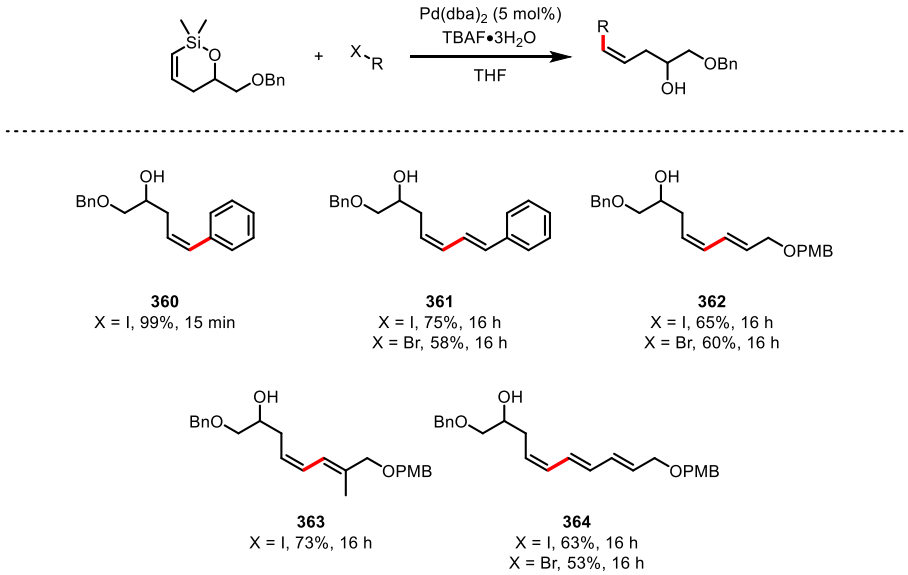


*Scheme 3.30 Hiyama cross-coupling of OPMB´ether **317** with iodobenzene*

This suggests than in the previous cases involving cleavable hydroxyl protecting groups, a cyclic siloxane is likely involved in the cross-coupling mechanism. However, in the case of an "uncleavable" group, the desired reaction is retarded and possibly requires an alternative pathway for the coupling, as well as opening up side reactions.

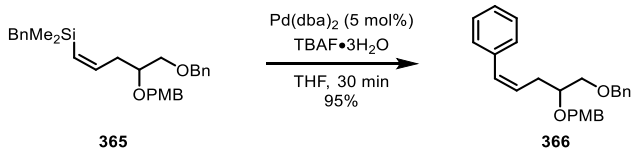
The scope of the Hiyama cross-coupling using six-membered cyclic alkenylsiloxanes is summarised in Scheme 3.31, and was carried out by Gudmundsson.[74] The most notable difference compared to the five-membered alkenylsiloxanes is the extended reaction times necessary for the reaction to reach completion. Only the coupling with iodobenzene furnishes product **360** in 15 min. The yields range from 53 to 99% depending on the

coupling partner, with more challenging polyene substrates affording the products in lower yields. Unsurprisingly, iodides were observed to be more efficient than the equivalent bromides in these cross-couplings.



*Scheme 3.31 Scope of the Hiyama cross-coupling of six-membered alkenylsiloxane **329***

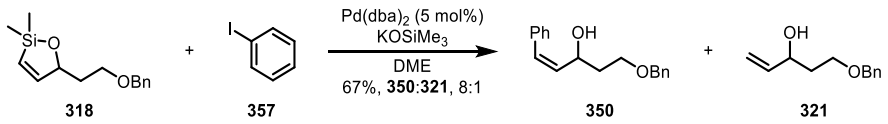
To further understand the differences between the reactions of the five- and six-membered cyclic siloxanes, PMB ether **365** was coupled to iododbenzene (**357**) to probe if the homoallylic alcohol is of similar importance to ensure an efficient cross-coupling (Scheme 3.32). Interestingly, the yield of 95% for this cross-coupling lies in the same range as the cross-coupling of the cyclised version **329**. We therefore questioned whether both acyclic silane **365** and cyclic siloxane **329** couple *via* a common mechanistic pathway that does not require a cyclic species, and is more consistent with the formation of a disiloxane prior to cross-coupling as proposed by Denmark *et al.*[98]



*Scheme 3.32 Cross-coupling of homoallylic PMB ether **365** with iodobenzene*

3.4.2 Base promoted Hiyama cross-couplings

Encouraged by the results obtained in the fluoride promoted Hiyama cross-couplings with cyclic dimethylalkenylsiloxanes, we investigated the viability of the fluoride-free, base promoted cross-couplings, which allows for the use of fluoride sensitive functionalities as well as orthogonality to coupling reactions requiring fluoride. Preliminary results obtained by Gudmundsson showed that five-membered alkenylsiloxane **318** couples effectively with potassium trimethylsilanolate as activator, albeit giving an inseparable mixture with the protodesilylated product **321** (Scheme 3.33).[74]

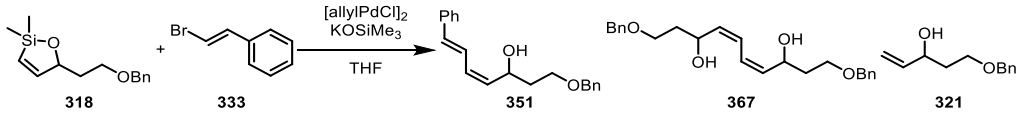


*Scheme 3.33 Base promoted Hiyama cross-coupling of five-membered alkenylsiloxane **318** by Gudmundsson.*

We thus set about optimising the reaction using β-bromostyrene and siloxane **318** as model substrates (Table 3.4). On the basis of preliminary results, THF was selected as the preferred solvent for these studies to ensure a consistently low water content; previous work on the base-promoted coupling of cyclic diethyl alkenylsiloxanes developed by Elbert, showed little difference between DME, THF and 1,4-dioxane, and preliminary results using iodobenzene as halide coupling partner confirmed this.[82,83]

Throughout our optimisation study, the desilylated product **321** was a persistant contaminant, alongside the formation of an additional byproduct, proposed to be homodimer **367**. We were unable to confirm its identity as it could not be obtained as a pure sample for analysis.

*Table 3.4 Optimisation of base promoted cross-coupling of five-membered alkenylsiloxane **318***



318 333 351 367 321

Entry	Concentration	$KOSiMe_3$ [eq.]	Additive	351:367:321[b]	Yield[%][c]
1	0.1 M	3.0	--	84 : 8 : 8	59
2	0.33 M	3.0	--	84 : 16 : 0	61
3	0.5 M	3.0	--	88 : 12 : 0	57
4	1.0 M	3.0	--	87 : 13 : 0	58
5	0.33 M	2.5	--	85 : 15 : 0	52
6	0.33 M	3.5	--	84 : 14 : 2	53
7	0.33 M	4.0	--	81 : 10 : 9	47
8	0.33 M	3.0	H_2O (1.5 eq)	67 : 14 : 19	42
9	0.33 M	3.0	H_2O (3.0 eq)	80 : 20 : 0	43
10	0.33 M	3.0	H_2O (6.0 eq)	72 : 28 : 0	43
11	0.33 M	3.0	H_2O (9.0 eq)	71 : 29 : 0	45
12	0.33 M	3.0	$dppp(O)_2$	86 : 9 : 5	51

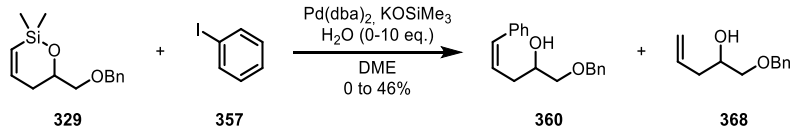
[a] reaction performed on 0.1 mmol scale, 1.2 eq. halide, 5 mol% APC; [b] determined by ^1H NMR; [c] combined yield.

An increased reaction concentration afforded the product mixture in comparable yields, but afforded a higher proportion of the suspected dimer **367**; however, desilylation was suppressed at higher concentrations (Table 3.4, Entries 1 to 4). Variation of the amount of potassium trimethylsilanolate shows a large effect, and three equivalents was determined to be optimal (Table 3.4, Entries 2, 5 to 7). Thirdly, unlike the cases using the cyclic diethylsiloxane, the addition of water resulted in lower yields and a higher proportion of **367** (Table 3.4, Entries 8 to 11). This led us to postulate that the inconsistent product:byproduct ratios are related to residual water in the solvent. Finally, Denmark

has shown that weakly coordinating bidentate phosphine oxide ligands can improve the efficiency of cross-coupling by stabilizing the palladium species and increasing turnover number.[241,246] However, addition of a phosphine oxide ligand did not show improvements in this reaction.

However, the results do show that base-promoted cross-coupling is viable for five-membered alkenylsiloxanes, albeit further optimisation is needed to reach satisfactory yields when alkenyl halides are employed.

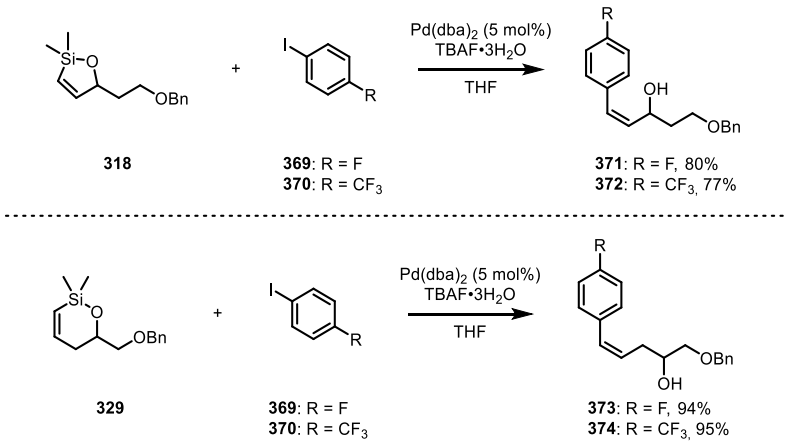
To our surprise, and in contrast to their six-membered diethyl analogues, the six-membered dimethylsiloxanes were found to be reactive under base-promoted coupling conditions. Preliminary results by Gudmundsson showed the formation of product **360** along with the desilylation product **368** as an inseparable mixture in low yields. However, investigation of the effect of additional water revealed that the reaction rate drops on increasing water concentration, and the reaction shuts down completely when ten equivalents are added; under these conditions, cyclic dimethyl alkenylsiloxane **329** can be reisolated in 50% yield with some loss of material.



329 **357** **360** **368**

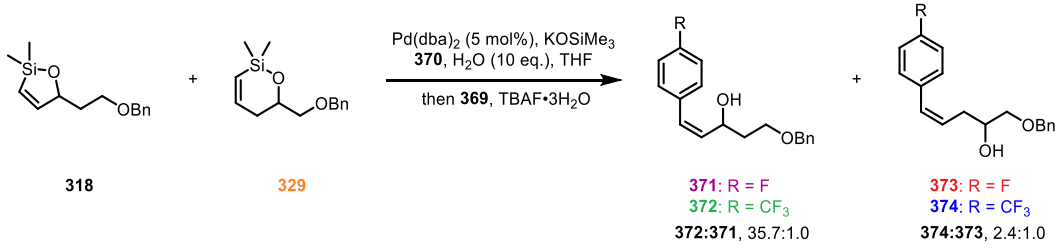
*Scheme 3.34 Base promoted cross-coupling of six-membered alkenylsiloxane **329***

We were interested to see if this result would enable us to restore the orthogonality between five- and six-membered alkenylsiloxanes depending on the conditions employed, as was observed for the cyclic diethyl alkenylsiloxanes.[82,83] Considering the low yields for couplings with alkenyl halides we decided to test this in a competition experiment using aryl iodides. Firstly, all possible products were prepared and characterised to be able to properly analyse the competition experiment (Scheme 3.35).



Scheme 3.35 Synthesis of all anticipated products of subsequent competition experiment

A mixture of five- and six-membered alkenylsiloxanes **318** and **329** were subjected to the base promoted coupling conditions with 10 equivalents of water and aryliodide **370**. After 1 h, a second aryliodide **369** and TBAF were added to effect cross-coupling of the six-membered alkenylsiloxane **329**. Analysis of the ^{1}H and ^{19}F NMR spectra showed that allylic alcohol **372** is formed as the major product, indicating that the five-membered alkenylsiloxane **318** was mostly consumed before addition of the second aryl iodide **369**. Unfortunately, coupling of the six-membered siloxane **329** is considerably slowed down under these conditions, as large quantities of unconsumed **329** are still visible in the proton NMR spectrum. The products derived from **329** seem to be a mixture of both possible homoallylic alcohols **373** and **374**, which reflect the yield of 67% of **350** in the base-promoted cross-coupling (Scheme 3.33). Importantly, allylic alcohol **372** is by far the major product, indicating that selectivity between five- and six-membered siloxanes is feasible.



Scheme 3.36 Competition experiment between five- and six-membered alkenylsiloxanes

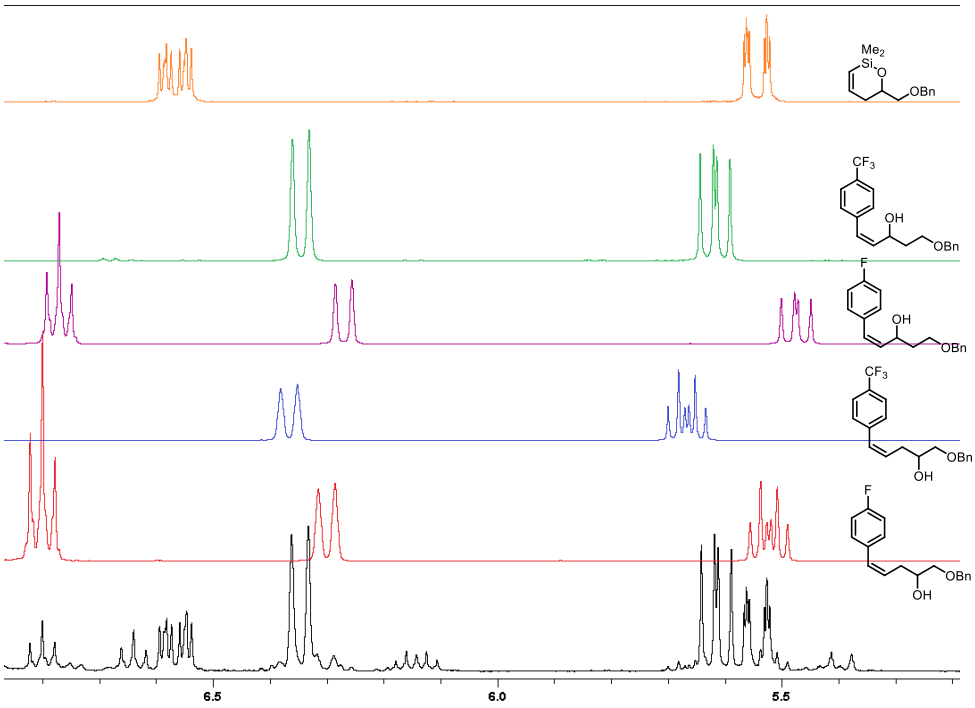


Figure 3.2 Crude ^{1}H NMR spectrum of competition experiment compared to pure samples of possible products and six-membered alkenylsiloxane

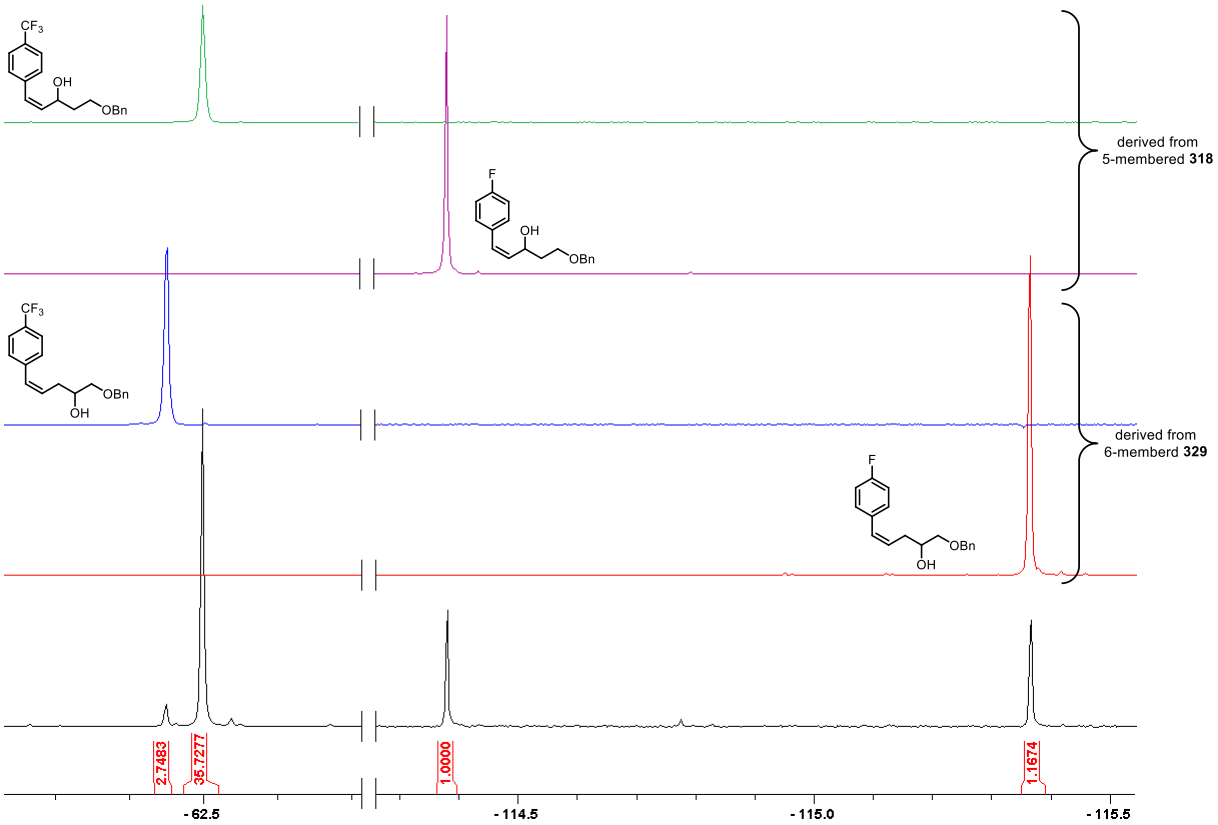
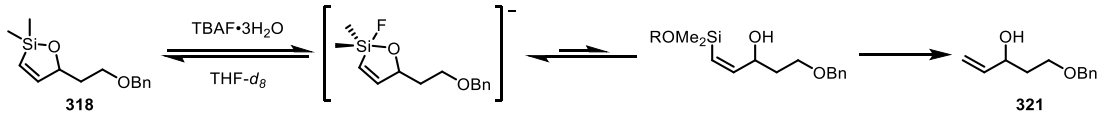


Figure 3.3 Crude ^{19}F NMR spectrum of competition experiment compared to pure samples of possible products

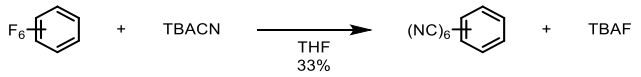
3.5 Mechanistic studies

Building on mechanistic studies by Gudmundsson, further experiments were carried out to gain insight into the processes involved in the fluoride promoted cross-couplings. Gudmundsson showed that when five-membered alkenylsiloxane **318** is treated with TBAF in THF-d_8, a rapid equilibrium between cyclic siloxane and an acyclic silane species was established, which slowly decomposed to protodesilylated product **321** (Scheme 3.37).



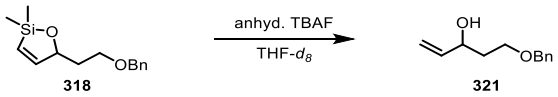
*Scheme 3.37 Treatment of five-membered alkenylsiloxane **318** with TBAF trihydrate*

Water seems to play a delicate role in this reaction. While it was added to certain couplings that employed diethyl siloxanes to suppress desilylation, it seems likely that water also acts as a proton source for the desilylation. Thus we wondered if anhydrous TBAF may form the 'ate' complex necessary for transmetalation with limited desilylation. Anhydrous TBAF was prepared according to a procedure reported by DiMagno *et al.* (Scheme 3.38).[247]



Scheme 3.38 Preparation of anhydrous TBAF after DiMagno

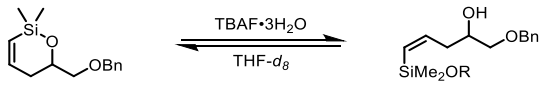
However, use of anhydrous TBAF in THF-d_8 resulted in protodesilylation with greatly increased rate compared to the use of hydrated TBAF (5 minutes *vs.* several hours). Compared to hydrated TBAF, the fluoride in anhydrous TBAF displays an enhanced Lewis basicity, which leads to the 'ate' complex falling apart due to stronger *F-Si* bonds. In this case the proton source for the protodesilylation may stem from tetrabutylammonium decomposition by Hofmann elimination, as anhydrous TBAF is particularly prone to decompose this way (Scheme 3.39).[248]



318 321

*Scheme 3.39 Treatment of alkenylsiloxane **318** with anhydrous TBAF*

Similar to five-membered siloxanes, the six-membered cyclic alkenylsiloxane also equilibrates with TBAF to partially form an acyclic silane species, however no protodesilylation is observed (Scheme 3.40).



329 330

*Scheme 3.40 Treatment of six-membered alkenylsiloxane **329** with TBAF trihydrate*

The equilibrium is instated almost instantly, but the acyclic form could either be a silanol or a disiloxane, which is challenging to assign due to the similar shifts these compounds display in the ^{1}H NMR spectrum. Therefore, the use of a DOSY experiment was considered, as this may provide information concerning the molecular weight of the species formed in solution upon treatment of siloxanes with TBAF.[249] Stalke *et al.* recently reported the development of ECC-DOSY NMR-spectroscopy (External Calibration Curve Diffusion Ordered SpectroscopY) being used on the elucidation of the aggregation of alkalimetal-Cp complexes in solution.[250,251] The use of one internal standard enables the estimation of molecular weight and shape, by correlation of the experimentally obtained diffusion coefficient of the internal standard to the diffusion coefficients of the species of interest. While five-membered alkenylsiloxane **318** cannot be examined in this fashion as protodesilylation occurs at a relatively high rate compared to the timescale of the experiment, six-membered alkenylsiloxane **329** does not decompose on the DOSY NMR timescale.

The estimated molecular weights of **329** in THF-d_8 and species derived from **329** upon addition of TBAF·3H$_2$O, are summarised in Table 3.5. Each signal in the NMR spectrum can be used to estimate a diffusion coefficient, however only signals with enough data

points, showing regular decay were selected (Figure 3.4) and the resulting molecular weight calculated, and some signals were disregarded due to overlap of different species. Determination whether the observed species corresponds to an acyclic or cyclic form is possible due to changes in coupling patterns, *J*-values and chemical shift. For a complete list of calculated molecular weights and diffusion coefficients see the experimental section (Table 6.1, Table 6.2).

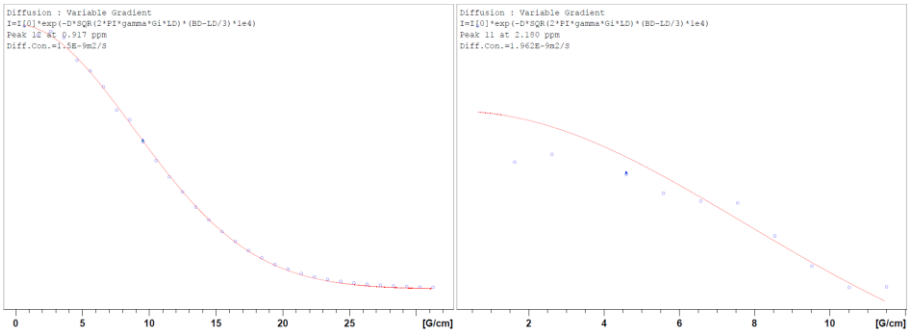
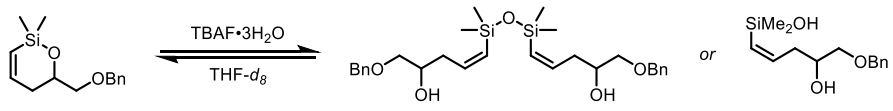


Figure 3.4 Comparison of good (left) and bad (right) experimentally determined curves for determination of diffusioncoefficients

Table 3.5 Estimated molecular weights of cyclic and acyclic siloxane species by ECC-DOSY NMR



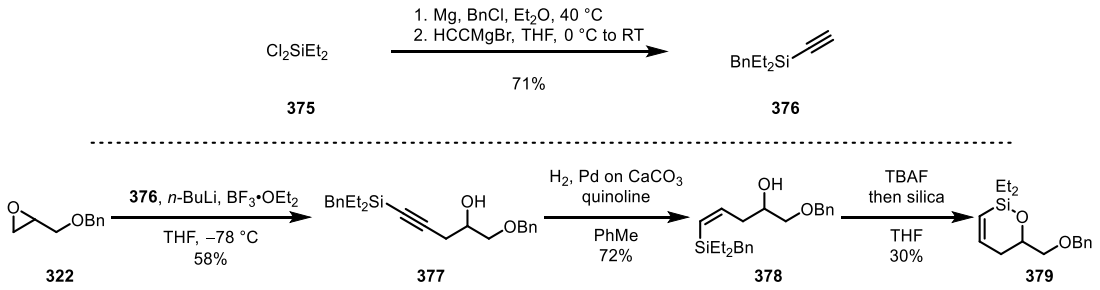
329 248.40 g/mol | **330** 514.81 g/mol | **330a** 266.41 g/mol

Entry	**signal** [ppm][a]	**species**[a]	**MW** [g/mol][b]	**MW$_{det}$** [g/mol][c]	**MW$_{dif}$(ED)**
1	6.30	acyclic	515	671	−23%
2	5.48	acyclic	515	723	−29%
3	4.56	acyclic	515	577	−11%
4	3.76	acyclic	515	735	−30%
5	2.81	acyclic	515	635	−19%
6	2.48	acyclic	515	612	−15%
7	0.06	acyclic	515	675	−24%
8	0.16	cyclic	248	270	−8%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] ECC_{THF}^{ED}

While the calculated molecular weights based on diffusion coefficients for cyclic alkenylsiloxanes are close to the theoretical MW of **329**, even when in equilibrium with an acyclic silane species (Table 3.5, Entry 8, Table 6.3, Table 6.4), the molecular weights for the acyclic species are consistently higher: they are close in value to the molecular weight of the hypothetical disiloxane **330**, suggesting that this dimeric species is indeed predominant when **329** is treated with TBAF.

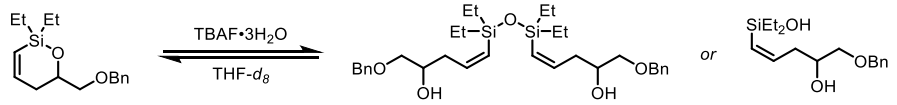
We were keen to investigate if the diethyl siloxanes would behave similarly or form a disiloxane in only minor amounts, as Denmark observed for (*E*)-vinyldiisopropylsilanols.[98] Cyclic diethyl alkenylsiloxane **379** was synthesised by analogy to its dimethyl equivalent **329** as shown in Scheme 3.41. The yields were generally comparable to the synthesis of **329**, with the exception of the cyclisation step, which only provided **379** in 30% yield.



*Scheme 3.41 Synthesis of cyclic diethyl alkenylsiloxane **379***

The molecular weights of the species observed in solution when **379** was treated with TBAF are summarised in Table 3.6 (for a complete list see experimental, Table 6.3, Table 6.4).

Table 3.6 Estimated molecular weights of cyclic and acyclic siloxane species by ECC-DOSY NMR



379 276.45 g/mol | **380** 570.92 g/mol | **380a** 294.47 g/mol

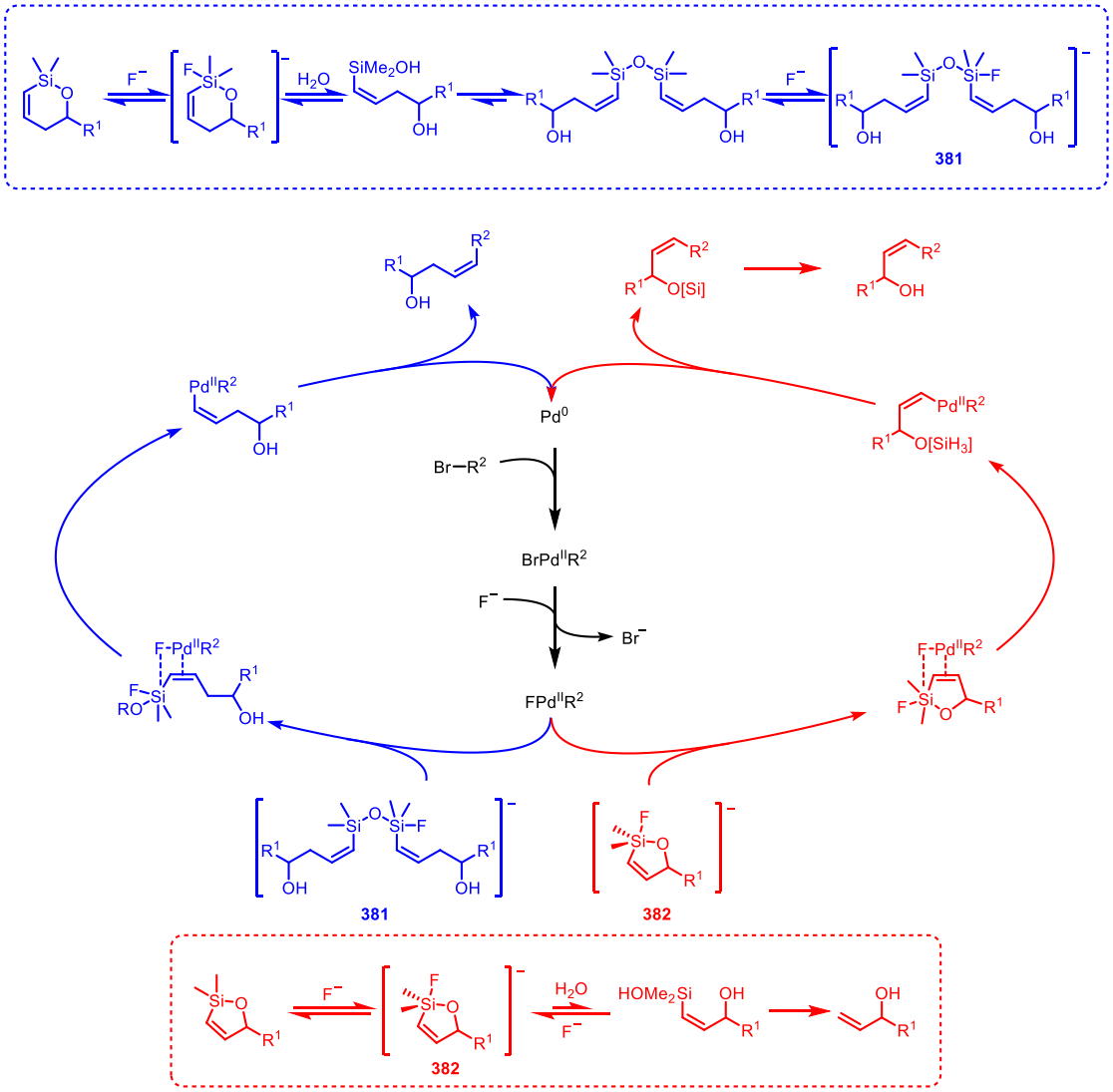
Entry	**signal** [ppm][a]	**species**[a]	**MW** [g/mol][b]	**MW$_{det}$** [g/mol][c]	**MW$_{dif}$(ED)**
1	6.94	cyclic	276	246	12%
2	6.38	acyclic	571	652	−12%
3	5.48	acyclic	571	725	−21%
4	4.56	acyclic	571	517	10%
5	3.76	acyclic	571	669	−15%
6	3.46	acyclic	571	699	−18%
7	2.82	acyclic	571	599	−5%
8	2.49	acyclic	571	626	−9%
9	1.75	acyclic	571	655	−13%
10	1.02	acyclic	571	668	−15%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] ECC_{THF}^{ED}

Similar to the dimethylsiloxane **329**, diethylsiloxane **379** displays estimated molecular weights consistent with a cyclic species (**379**, Table 3.6, Entry 1), and an acyclic disiloxane **380** (Table 3.6, Entries 2-10). This suggests that although coupling of cyclic diethyl siloxanes is slow compared to their dimethyl analogues, the disiloxane - proposed to be necessary for the transmetalation - is formed just as readily. Still, the steric environment clearly has a strong influence on the efficiency of the cross-coupling, and more sterically-demanding substituents on silicon seem to inhibit transmetalation.

Scheme 3.42 shows our proposed mechanisms for the cross-coupling of five- and six-membered alkenylsiloxanes under fluoride promotion. We propose that the observed enhanced reactivity of the dimethyl siloxanes compared to their diethyl analouges stems

from the lower steric demand of the silicon moiety during transmetalation (**381** and **382**), and as such facilitating the formation of the necessary palladium complex.



Scheme 3.42 Proposed mechanism for the cross-coupling of five- and six-membered alkenylsiloxanes

3.6 Total synthesis of Leukotriene B_3

To exemplify the use of this methodology, we targeted a suitable and useful natural product. Leukotriene B_3 (LTB_3) has received attention with respect to its functions in inflammatory states.[252,253] Several syntheses for LTB_3 are reported,[254-259] however, our approach would provide a highly modular method for the assembly, and avoids the use of toxic reagents. Retrosynthetically, the triene system could be constructed by Hiyama

cross-coupling between five-membered alkenylsiloxane **384** and vinyl iodide **385** (Figure 3.5).

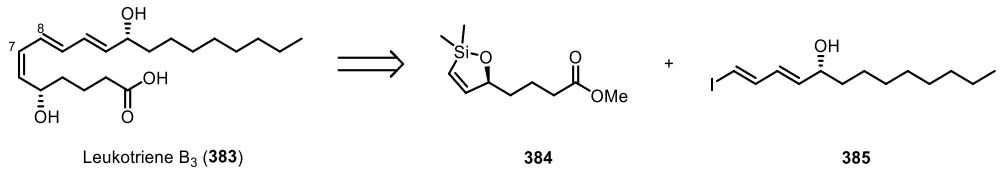
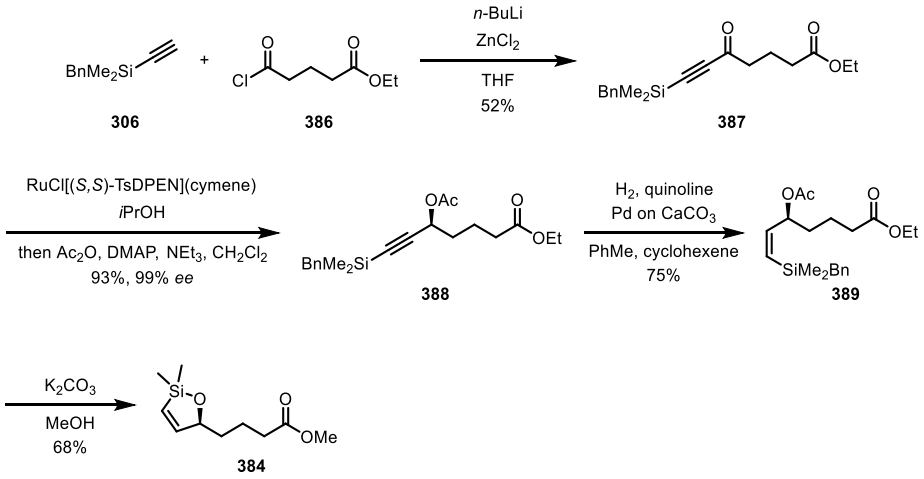


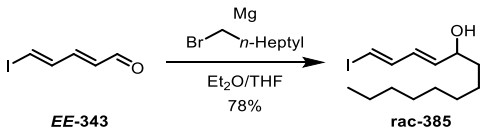
Figure 3.5 Retrosynthetic approach for leukotriene B_3

The synthesis of the cyclic alkenylsiloxane fragment **384** was carried out by Urbitsch and is summarised in Scheme 3.43.[260] The synthesis commenced with the addition of alkyne **306** into acid chloride **386** to provide ynone **387**. Noyori transfer hydrogenation reduces the ynone and sets the alcohol stereochemistry with excellent *ee*.[261] The intermediate alcohol is acetylated and the alkyne hydrogenated to give (*Z*)-vinylsilane **389**. Cyclisation is then effected by treatment with potassium carbonate in methanol to form cyclic alkenylsiloxane **384**.



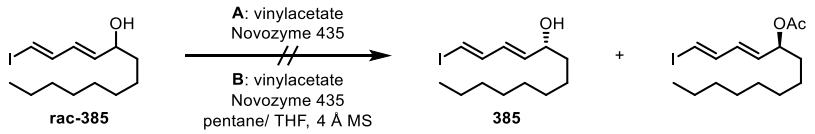
*Scheme 3.43 Synthesis of cyclic alkenylsiloxane **384** by Urbitsch*

The synthesis of the second fragment utilised previously synthesised dienal iodide ***EE*-343**. While addition of freshly prepared octyllithium to ***EE*-343** only returned a complex mixture, a Grignard addition formed product **rac-385** in good yields.[262,263]



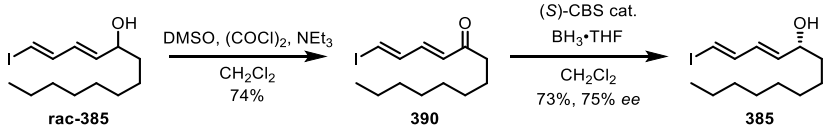
*Scheme 3.44 Grignard reaction for the octyladdition to dienal **EE-343***

To separate the enantiomers of racemic **rac-385**, a kinetic resolution using *Candida antarctica lipase B* (Novozyme435) was attempted. Kinetic resolutions of secondary alcohols are well known with these conditions and often proceed with high efficiency and selectivity to give products with high enantiomeric purity.[264] Unfortunately, no conversion of alcohol **rac-385** to the corresponding acetate could be observed, even after prolonged reaction times (Scheme 3.45).



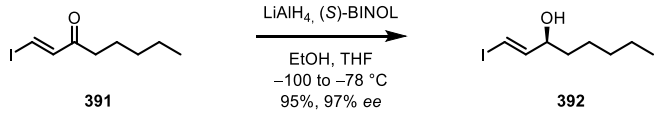
*Scheme 3.45 Attempted kinetic resolution of secondary alcohol **rac-385***

Instead of the kinetic resolution, a two step approach of oxidation and enantioselective reduction would give enantioenriched **385** (Scheme 3.46). Swern oxidation gave ketone **390** in 74% yield, followed by CBS-reduction to set the stereocentre and afford secondary alcohol **385** in 73% yield and 75% *ee*.[265]



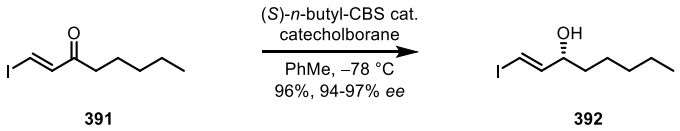
*Scheme 3.46 Oxidation/Reduction-sequence to prepare enantioenriched **385***

The disappointing and unexpected *ee* for **385** from the CBS reduction could be improved in a number of ways. Noyori *et al.* showed that BINOL-modified $LiAlH_4$ reagents are able to enantioselectively reduce ketones with high enantioselectivity, and the structurally similar enone **391** was reduced by this method in high yields and excellent *ee* of 97% (Scheme 3.47).[266]



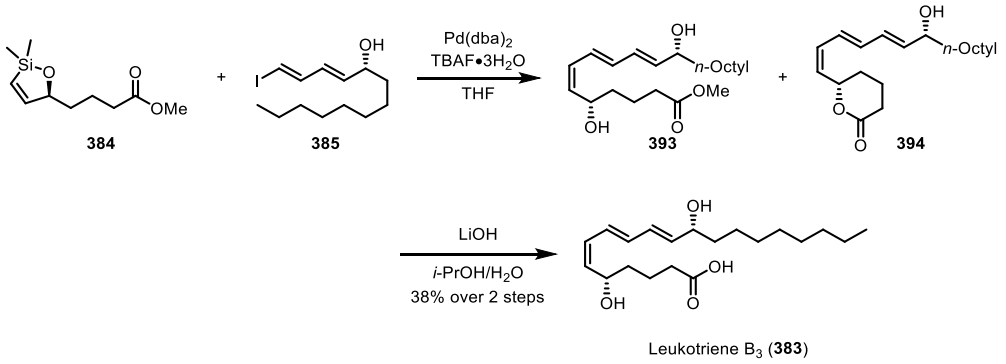
*Scheme 3.47 Enantioselective reduction of enone **393** by Noyori and coworkers*

Additionally, the same enone **391** could be reduced efficiciently and with high enantioselectivites by using a different CBS catalyst, namely the *n*-butyl-derivative, and catecholborane as reducing agent (Scheme 3.48).[267,268]



*Scheme 3.48 Enantioselective reduction of enone **393** using alternative CBS reduction conditions*

Cross-coupling of cyclic alkenylsiloxane **384** with vinyl iodide **385** afforded a mixture of the desired product **393** and lactone **394** (which results from cyclisation of **393**). This mixture was not separated, as hydrolysis using lithium hydroxide afforded leukotriene B_3 from either compound. The natural product was thus obtained in 38% over 2 steps (Scheme 3.49).



Scheme 3.49 Synthesis of leukotriene B_3 via Hiyama cross-coupling

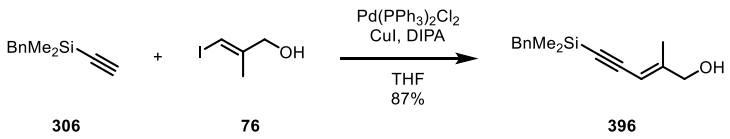
In summary, we have developed a short and concise route to access leukotriene B_3 in only seven steps from commercially available starting materials. However, the low *ee* of iodide **385** translated into the isolation of LTB_3 with poor d.r. (~7:1) We hope to address this problem by applying the methods previously outlined.

4 Towards Incednam - Revised Fragment Synthesis and Union

In light of the great improvement cyclic dimethyl siloxanes offer compared to their diethyl analogues, we were keen to apply them towards our synthesis of incednam. Furthermore, the cleavage of the *C*11 benzoate under cross-coupling conditions, leading to an unanticipated oxidative cleavage product forced us to reconsider our protecting group strategy (Scheme 1.21).

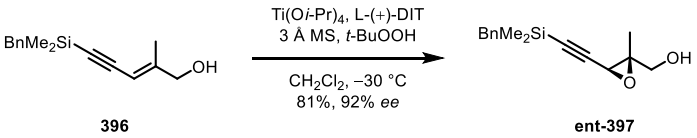
4.1 Synthesis of the *C*1-*C*13 Dimethyl Alkenylsiloxane Fragment

The revised synthesis again commenced with common intermediate **76**, which was coupled with benzyldimethyl ethynylsilane (**306**) under Sonogashira conditions to afford enyne **396** in excellent yields (Scheme 4.1).[269]



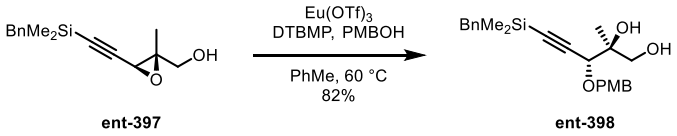
*Scheme 4.1 Synthesis of enyne **396** via Sonogashira cross-coupling*

Next, asymmetric epoxidation under the Sharpless conditions provided epoxide **ent-397** in good yield (Scheme 4.2).[79,80] However, it was realised that the use of L-(+)-diisopropyl tartrate as ligand would afford the incorrect enantiomer of incednine, in contrast to the results previously stated by Lim (Scheme 1.14).[73,74] Accordingly, the synthesis was repeated, now with the correct enantiomer of the stereocontrolling tartrate ligand (see further discussion in section 4.4). However, simply for the purpose of establishing a viable route towards the key *C*1-*C*13 siloxane fragment, epoxide **ent-397** was used.



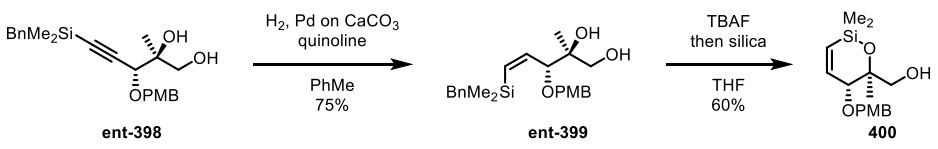
*Scheme 4.2 Asymmetric Sharpless epoxidation of enyne **396***

Following the epoxidation, a regioselective opening of epoxide **ent-397** was needed. The aforementioned issues with the former protecting group strategy now led us to choose a *p*-methoxybenzyl ether (PMB) at *C*11 due to its stability to a variety of reaction conditions. This ether should enable the selective formation of the more stable six-membered siloxane while providing control over the timing of formation of a five-membered siloxane upon cleavage of the PMB group. The regioselective opening with PMB alcohol under conditions developed by Iwabuchi *et al.*, and further optimised for our system by Gudmundsson, afforded PMB ether **ent-398** in good yield (Scheme 4.3).[74,270]



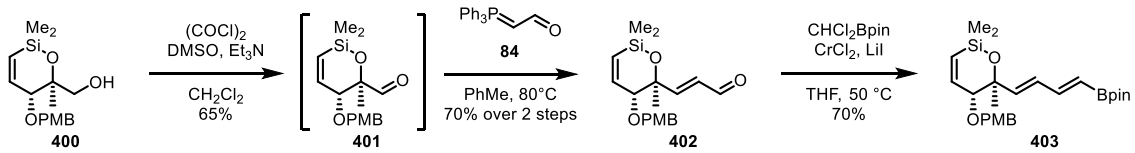
*Scheme 4.3 Regioselective opening of epoxide **ent-398** with PMB alcohol*

Benzyldimethyl alkynylsilane **ent-398** was then subjected to the standard stereoselective semi-hydrogenation conditions to form the desired (*Z*)-alkenylsilane **ent-399** in good yield (Scheme 4.4). This compares well with the equivalent alkynylsilanol, where use of allylic alcohols needed protection with an electron withdrawing group to ensure good selectivities.[73,74,82] Upon debenzylation of alkenylsilane **ent-399** with TBAF, an intermediate silanol was formed, which under slightly acidic conditions cyclised to form **400** (Scheme 4.4).



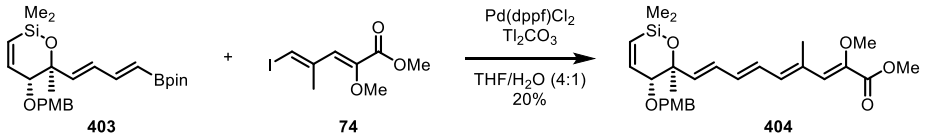
*Scheme 4.4 Semi-hydrogenation of alkynylsilane **ent-398** and subsequent cyclisation to form siloxane **400***

With cyclic alkenylsiloxane **401** in hand, the *C*6-*C*13 fragment was synthesised by Gudmundsson in accordance to our previously developed strategy (Scheme 4.5).[74] First, Swern oxidation followed by Wittig olefination using ylid **84** afforded α,β-unsaturated aldehyde **403**, which upon chromium mediated borylation afforded the *C*6-*C*13 fragment **404** in good overall yields.



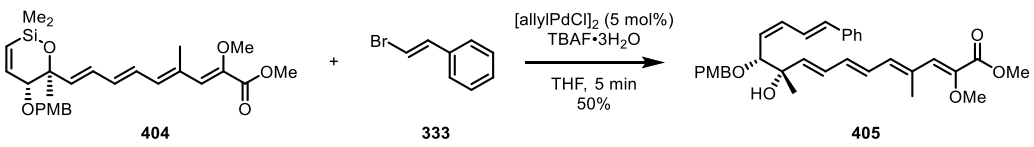
Scheme 4.5 Synthesis of C6-C13 fragment by Gudmundsson

The construction of the *C*1-*C*13 fragment **404** was attempted by Gudmundsson *via* Suzuki cross-coupling (Scheme 4.6).[74] Under the previously optimised conditions using Pd(dppf)Cl_2 and thallium(I) carbonate, tetraenoate **404** was afforded in 20% yield. However, the reaction did not give reproducible results and seemed unreliable.



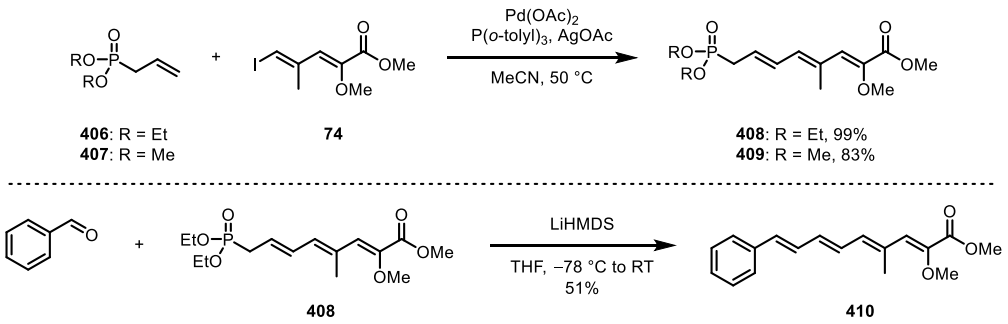
Scheme 4.6 Construction of C5-C6 bond via Suzuki cross coupling by Gudmundsson

The synthesis of **404**, albeit in low yields, enabled us to test the construction of the *C*13-*C*14 bond using the cyclic dimethylsiloxane. Pleasingly, cross-coupling with β-bromostyrene (**333**) under fluoride promoted conditions afforded the coupled product **405** in 50% yield (Scheme 4.7). Notably, the use of the six-membered siloxane seemed to suppress the formation of the previously observed oxidative cleavage product, and no desilylation was seen (Scheme 1.21).



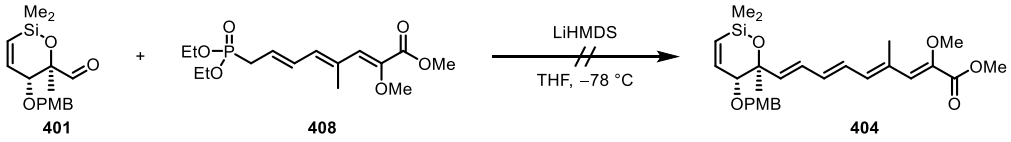
Scheme 4.7 Model Hiyama cross-coupling for the formation of C13-C14 bond by Gudmundsson

To address the issue of the preparation of tetraenoate **404** we reconsidered our previously discarded strategy to form the *C*1-*C*13 fragment *via* HWE olefination. In contrast to our previous strategies for a suitable phosphonate, we wanted to investigate an approach to use an extended phosphonate **408/409** that could be synthesised by Heck coupling of previously employed dienoate **74** and allyl phosphonates **406** and **407** (Scheme 4.8). Using conditions developed by Whiting *et al.*, **408** and **409** were prepared in excellent yields.[74,271] In order to investigate the viability of this strategy, lithiated **408** was reacted with an excess benzaldehyde to form tetraenoate **410** in moderate 51% yield (Scheme 4.8).



Scheme 4.8 Synthesis of C1-C8 phosphonate fragment

Unfortunately, translation of this encouraging result to the cyclic siloxane proved largely unsuccessful. Use of LiHMDS as base, as well as other typical HWE conditions did not afford the desired product **404** and only returned complex mixtures (Scheme 4.9).[74,272-274]



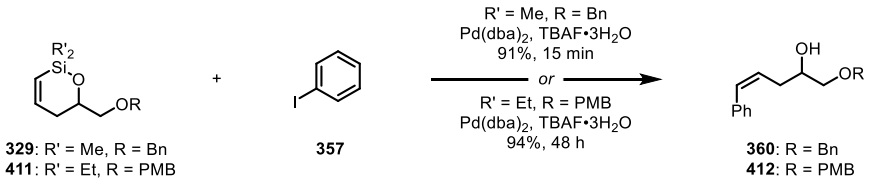
*Scheme 4.9 Attempted HWE reaction using cyclic siloxane **401** and phosphonate **408***

These results, as well as the irreproducibility in the Suzuki coupling, were attributed to the instability of the cyclic dimethyl alkenylsiloxane moiety under basic conditions. While dimethyl siloxanes display a huge improvement in the efficiency of Hiyama

cross-couplings compared to diethyl siloxanes, they also appear to show increased sensitivity to a variety of general reaction conditions and decompose more easily.

4.2 Synthesis of the *C*1-*C*13 Diethyl Alkenylsiloxane Fragment

The higher stability of diethyl alkenylsiloxanes makes them more attractive to be carried through several synthetic steps, but their reactivity in Hiyama cross-couplings is considerably lower. However, while requiring longer reaction times, they do provide the corresponding products in similar yields, exemplified in the two couplings with iodobenzene with diethylsiloxane **411** and dimethylsiloxane **329** (Scheme 4.10), therefore we hypothesised the use of a six-membered diethyl alkenylsilane might yet be a viable strategy for the formation of the *C*13-*C*14 bond in incednam (Scheme 4.10).



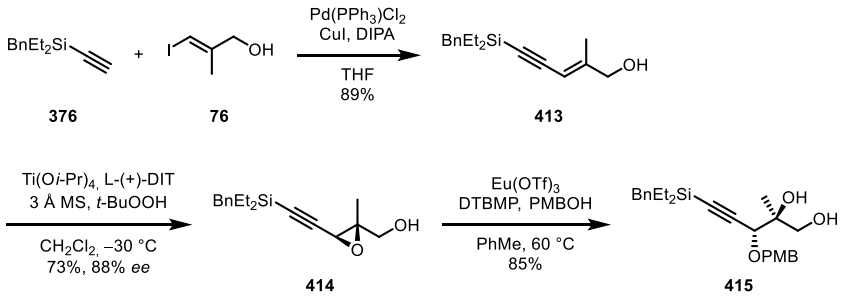
329: R' = Me, R = Bn
411: R' = Et, R = PMB

357

360: R = Bn
412: R = PMB

Scheme 4.10 Comparison of diethyl- and dimethyl alkenylsiloxanes in cross-coupling

The use of benzyldiethyl ethynylsilane **376** mimicked our previous synthesis with the equivalent dimethylsilane, and ensured high yields in the epoxide opening with PMB alcohol. The remaining steps are similarly high yielding and summarised in Scheme 4.11.



376

76

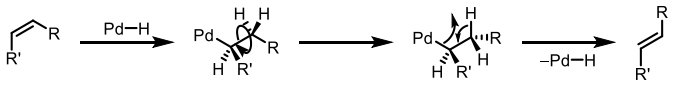
413

414

415

*Scheme 4.11 Synthesis of diol **415** from common intermediate **76** and alkynylsilane **376***

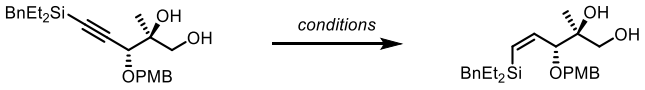
Next, the key semi-hydrogenation of alkynylsilane **415** was investigated. The previously optimised conditions (0.5 equivalents of quinoline, and cyclohexene as cosolvent), surprisingly provided the desired alkenylsilane **416** in a low yield and with poor *Z*/*E*-selectivity (Table 4.1, Entry 1). Reducing the amount of quinoline without additional cyclohexene improved the *Z*/*E*-selectivity (Table 4.1, Entries 2-4). Surprisingly, the highest yield of the desired alkene **416** was obtained when the semi-hydrogenation was carried out any without additives, albeit with slightly lower *Z*/*E*-selectivity (Table 4.1, Entry 5). Changing the solvent to EtOAc did not seem to have a striking effect on the reaction, while the use of cyclohexene or cyclopentene as cosolvent and sacrificial alkene only resulted in lower *Z*/*E*-selectivity. Cyclopentene was suggested to be a superior sacrificial alkene due to the higher ring strain that would be relieved upon hydrogenation. The undesired *E*-isomer most likely arises from post-hydrogenation isomerisation, which is reported to need both the Pd catalyst and hydrogen atmosphere to occur.[275] While isomerisation is often observed towards completion of the reaction, when the product competes for coordination sites, it seems in the case of benzyldiethyl alkynylsilanes that isomerisation takes place throughout the reaction, accounting for the poor observed *Z*/*E*-selectivities.



Scheme 4.12 Isomerisation of (Z)-alkenes in palladium-catalysed hydrogenations

Therefore, alternative methods for the stereoselective reduction of alkynylsilanes were investigated. Diimide reduction, shown by Trost *et al.* to be compatible with benzyldimethyl alkynylsilanes, afforded the desired product in 47% yield but with low *Z*/*E*-selectivity (Table 4.1, Entry 9).[110] Reduction with DIBALH, which has also been shown to be viable in the reduction of alkynylsilanes, only returned starting materials with no product formation observed (Table 4.1, Entry 10).[276]

*Table 4.1 Semi-hydrogenation of diethyl alkynylsilane **415***



415 **416**

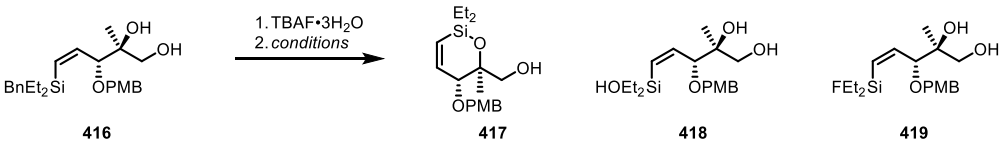
Entry	Conditions	Additive	*Z*/*E*[a]	Yield [%][b]
1	Pd on $CaCO_3$, H_2, PhMe	quinoline (0.5 eq.), cyclohexene	2.3:1	41
2	Pd on $CaCO_3$, H_2, PhMe	quinoline (0.2 eq.)	3.8:1	n.d.[c]
3	Pd on $CaCO_3$, H_2, PhMe	quinoline (0.1 eq.)	5.4:1	n.d.[c]
4	Pd on $CaCO_3$, H_2, PhMe	quinoline (0.05 eq.)	4.3:1	53
5	Pd on $CaCO_3$, H_2, PhMe	--	3.5:1	63
6	Pd on $CaCO_3$, H_2, EtOAc	quinoline (0.2 eq.)	4.1:1	n.d.[c]
7	Pd on $CaCO_3$, H_2, PhMe	cyclohexene	2.6:1	n.d.[c]
8	Pd on $CaCO_3$, H_2, PhMe	cyclopentene	2.8:1	n.d.[c]
9	$TPSNHNH_2$, $NaHCO_3$		2.8:1	47
10	DIBALH, Et_2O		--	--

[a] determined by crude ^{1}H NMR; [b] isolated yield; [c] incomplete conversion.

With alkenylsilane **416** in hand, from conditions in Table 4.1, Entry 5, the cyclisation to afford cyclic diethylalkenylsiloxane **417** was investigated (Table 4.2). Similar to the cyclisation in our previous strategy with diethyl siloxanes, several acidic conditions were employed after debenzylation using TBAF (Table 4.2, Entries 1-7).[73,74] The highest yield was obtained when the mixture was stirred with silica, and then filtered to afford **417** (61%, Table 4.2, Entry 2). Other acidic methods led to the formation of fluorosilane **419** (as determined by coupling constants and multiplicities in the ^{1}H NMR spectrum, and confirmed by mass spectrometry) along with the desired cyclic species **417**, in varying amounts (Table 4.2, Entries 1, 3, 4, 7). Only silica with adsorbed boric acid afforded both the cyclic siloxane **417**, along with the corresponding silanol **418** (Table 4.2, Entry 5).

The use of HCl in 1,4-dioxane only resulted in decomposition to a complex mixture (Table 4.2, Entry 6). Basic conditions, in contrast, formed cyclic siloxane **417** along with silanol **418** (Table 4.2, Entries 8, 9). Potassium carbonate in methanol was observed to be superior to any other conditions employed (Table 4.2, Entry 8), as silanol **418** could also be isolated in 23% in this case (along with 61% of the cyclic siloxane **417**), which is a significant improvement in mass recovery compared to treatment with silica alone.

*Table 4.2 Debenzylation and subsequent cyclisation of alkenylsilane **416***

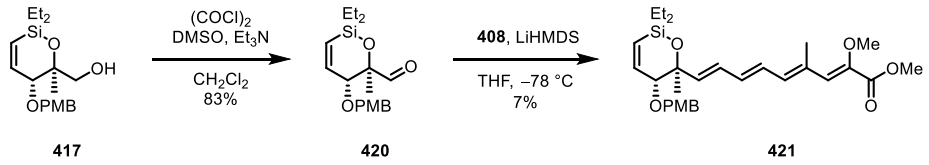


416 **417** **418** **419**

Entry	conditions	417:418:419[a]	Yield [%][b]
1	TFA	1.5:0:1	n.d.
2	silica	1:0:0	61
3	1 M $HCl_{(aq)}$	1:0:1.3	n.d.
4	10 mol% PPTS[d]	1:0:1.8	n.d.
5	silica·$B(OH)_3$	1:4.3:0	n.d.
6	4 M HCl in dioxane[d]	--	--[c]
7	filter over DOWEX with MeOH[d]	0:0:1	n.d.
8	filter over K_2CO_3 with MeOH[d]	2.7:1:0	61
9	Ag_2CO_3[d]	1.4:1:0	n.d.

[a] determined by crude ^{1}H NMR; [b] isolated yield; [c] decomposition; [d] after aqueous workup.

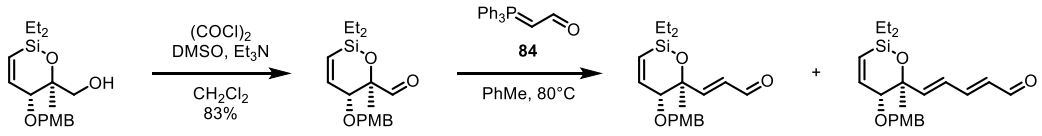
Next, oxidation of alcohol **417** and HWE olefination of aldehyde **420** using the previously prepared extended phosphonate **408** was attempted (Scheme 4.13). Unfortunately, tetraenoate **421** was only obtained in a very poor 7% yield, despite a screening of HWE reaction conditions.



417 **420** **421**

*Scheme 4.13 Oxidation of alcohol **417** and subsequent HWE olefination*

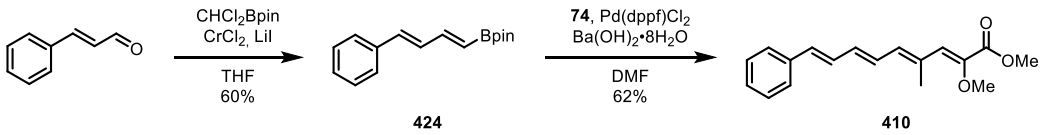
Alternatively, aldehyde **420** was subjected to a Wittig olefination with ylid **84** to afford α,β-unsaturated aldehyde **422**, with a small amount of byproduct **423**, formed due to a competing second Wittig olefination of product **422** (Scheme 4.14).



417 **420** **422**: 73% **423**: 5%

*Scheme 4.14 Oxidation of alcohol **417** and subsequent Wittig olefination*

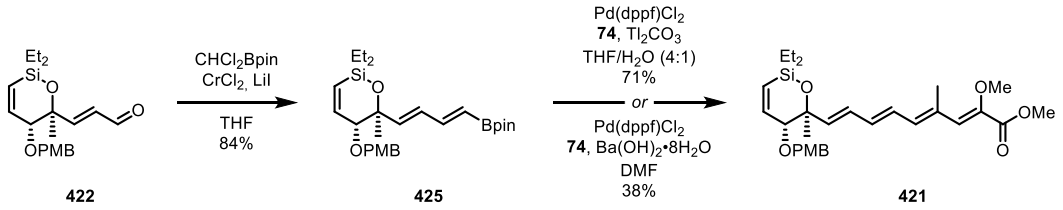
The following Takai olefination and Suzuki cross-coupling were first tested on a model substrate to probe the feasibility of an alternative procedure for the Suzuki coupling, in an attempt to avoid the highly toxic thallium(I) carbonate previously deployed. As such, Takai olefination of cinnamaldehyde to give **424**, and subsequent Suzuki cross-coupling with vinyl iodide **74** using $Ba(OH)_2 \cdot 8H_2O$ as base, afforded tetraene **410** in 62% yield (Scheme 4.15).[277,278]



424 **410**

Scheme 4.15 Boron Takai olefination and Suzuki cross-coupling of cinnamaldehyde as model

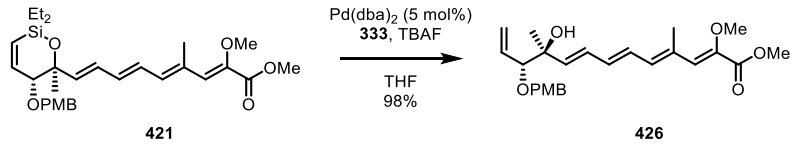
Similarly, Takai olefination of α,β-unsaturated aldehyde **422** to form alkenylboronic ester **425** proceeded smoothly (Scheme 4.16). However, when the Suzuki cross-coupling using the above-mentioned $Ba(OH)_2 \cdot 8H_2O$ instead of thallium(I) carbonate was attempted, *C*1-*C*13 diethyl fragment **421** was afforded in only 38% yield. In comparison, the use of previously optimised conditions employing thallium(I) carbonate formed **421** in a pleasing 71% yield (Scheme 4.16).



*Scheme 4.16 Takai olefination and Suzuki cross-coupling to form C1-C13 fragment **421***

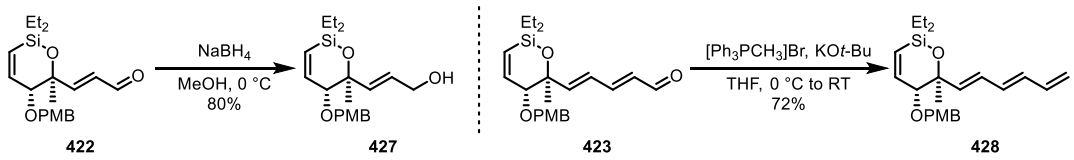
4.3 Modelling the Construction of the *C*13-*C*14 Bond

Formation of the key *C*13-*C*14 bond *via* Hiyama cross-coupling was explored by Gudmundsson, who showed that *C*13-*C*14 dimethylsiloxane **405** indeed couples with β-bromostyrene (**333**) to construct the *C*13-*C*14 bond (Scheme 4.7).[74] In order to test the hypothesis that diethyl- and dimethylsiloxanes provide the respective products in similar yields, but at hugely different rates, *C*1-*C*13 diethylsiloxane fragment **421** was subjected to the fluoride promoted Hiyama cross-coupling with β-bromostyrene (**333**) as a model (Scheme 4.17). Much to our dismay, the only product obtained was the protodesilylated alkene **426** (98% yield). Notably, this is the first time we have observed protodesilylation when employing a six-membered diethyl alkenylsiloxane.[82,83]



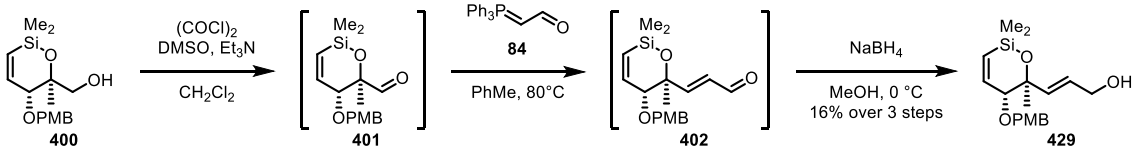
*Scheme 4.17 Attempted Hiyama cross-coupling with cyclic alkenylsiloxane **421***

This result led us to test other related substrates bearing a cyclic diethylsiloxane to further investigate the Hiyama cross-coupling. Reduction of intermediate **422** afforded allylic alcohol **427** in 80% yield (Scheme 4.18). In addition, byproduct **423** was converted to tetraene **428** (Scheme 4.18).



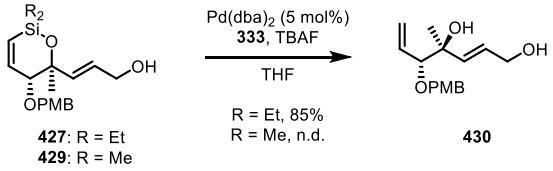
Scheme 4.18 Preparation of cyclic diethyl siloxane substrates for Hiyama cross-coupling

The equivalent dimethyl siloxane **429** was prepared to compare the influence of the substituents on silicon in the Hiyama cross-coupling. Due to the inherent instability of dimethyl siloxanes, intermediates in this sequence were carried through without purification (Scheme 4.19).



*Scheme 4.19 Synthesis of dimethyl siloxane allylic alcohol **429***

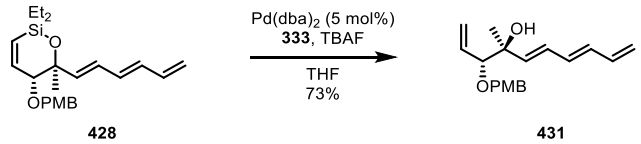
Considering the previously attempted cross-coupling with a cyclic diethylsiloxane, it is perhaps now no surprise that the use of **427** also resulted in protodesilylation (Scheme 4.20). The analogous cyclic dimethylsiloxane **429** also underwent protodesilylation (Scheme 4.20); which may indicate that allylic alcohols **427** and **429** represent special substrates that more easily desilylate, especially considering that the *C*1-*C*13 diethyl fragment **421** undergoes protodesilylation under fluoride promoted Hiyama cross-coupling conditions, while the *C*1-*C*13 dimethyl fragment **404** successfully undergoes cross-coupling with β-bromostyrene.



*Scheme 4.20 Comparison of diethyl- and dimethyl siloxanes **427** and **429** in Hiyama cross-couplings*

When cyclic siloxane triene **428** was subjected to the same cross-coupling conditions, the only product observed was again that of protodesilylation (**431**, Scheme 4.21). This may suggest that protodesilylation can also compete in the slower couplings of diethyl

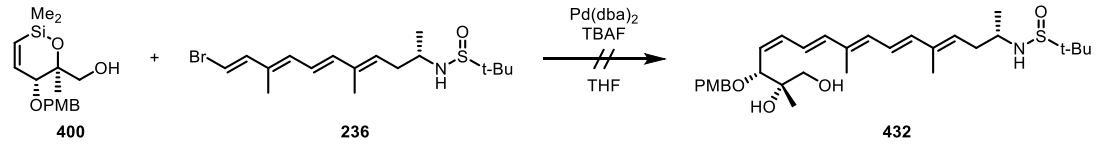
siloxanes. The observed protodesilylation of six-membered diethyl alkenylsiloxanes seems to be unique to this specific system, as other six-membered alkenylsiloxanes were proved viable in a number of Hiyama cross-couplings with no protodesilylation.[82,83]



428 431

*Scheme 4.21 Attempted cross-coupling of cyclic diethyl siloxane **428***

Finally, we also wanted to probe the *C*14-*C*23 bromide fragment **236** in its viability in the Hiyama cross-coupling. Due to the positive result with dimethyl siloxane **404** obtained by Gudmundsson (Scheme 4.7), the coupling of sulfinamide protected tetraenyl bromide **236** was attempted with six-membered siloxane **400** (Scheme 4.22). Disappointingly, no reaction was observed even at extended reaction times. While only speculative it is possible that, the sulfinamide moiety could compete for coordination sites at the palladium centre, rendering the coupling unsuccessful.[279]



400 236 432

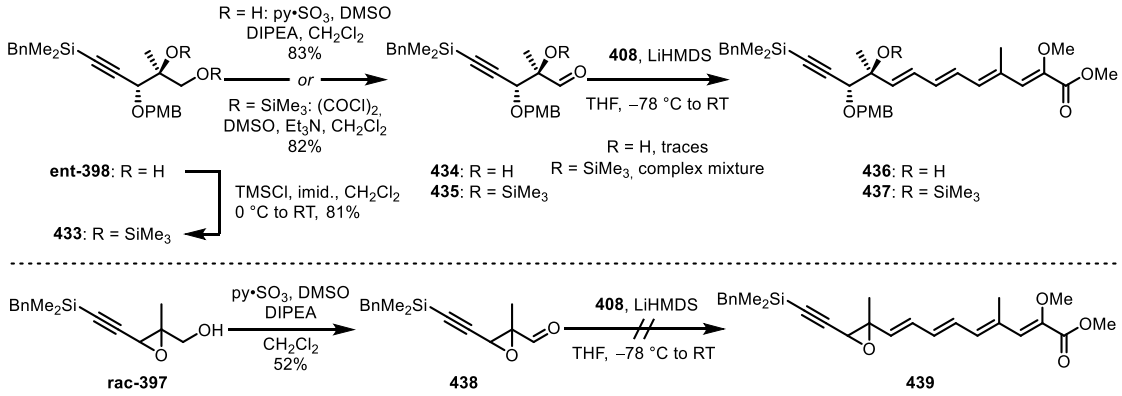
*Scheme 4.22 Attempted Hiyama cross-coupling with C14-C23 fragment **236***

4.4 Synthesis of a Revised *C*1-*C*13 Fragment

In light of the problems encountered with the construction of the *C*13-*C*14 bond, the identity and synthesis of the *C*1-*C*13 fragment had to be addressed. While diethyl siloxane fragment **421** proved ineffective for the key Hiyama cross-coupling, the synthesis of the dimethyl siloxane cousin **404** was plagued by stability issues which prevented scale-up. We now hoped to avoid these issues by carrying the acyclic (*Z*)-alkenylbenzyldimethyl silane through the synthesis, revealing the cyclic siloxane only under coupling conditions,

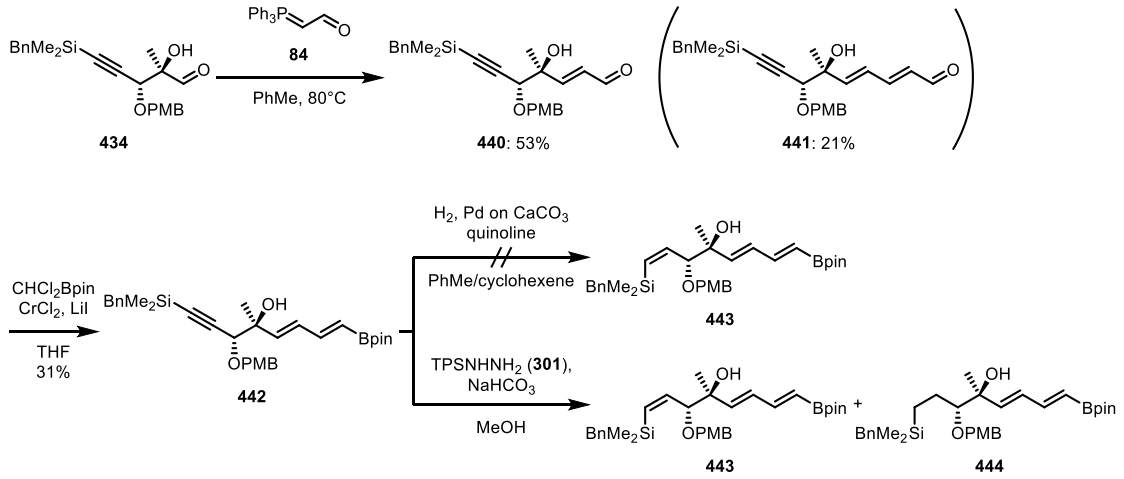
similar to the strategy employed by Trost *et al.* in their synthesis of dephosphofostriecin.[110]

First, efforts were directed to use the previously prepared extended phosphonates **408/409**, via the HWE olefination of aldehyde **434**, however this only provided the desired product **436** in minor quantities (Scheme 4.23). This could be explained by the α-hydroxy group quenching the reaction, but protection of this hydroxyl group as a silyl ether equally rendered the HWE olefination unsuccessful, potentially due to the steric encumbrance of the aldehyde **435** (Scheme 4.23). This led us to attempt the HWE olefination on aldehyde **438** with an epoxide in the α,β-position, which has been shown by Lim to be tolerated in HWE olefinations.[73] However, HWE reaction of aldehyde **438** only returned a complex mixture with no observed formation of the desired product **439** (Scheme 4.23).



*Scheme 4.23 Attempted HWE reactions with extended phosphonate **408***

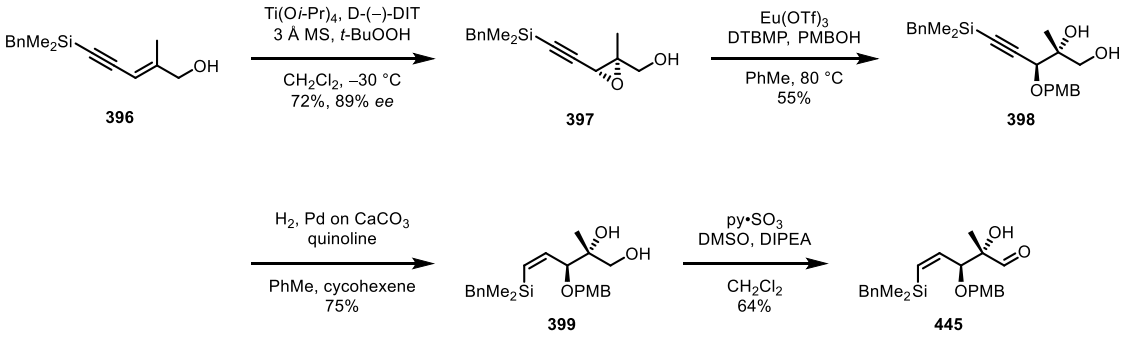
An alternative route to access fragment **436** was considered. Aldehyde **434** was subjected to a Wittig olefination with ylid **84**, followed by Takai olefination to afford vinyl boronic ester **442** (Scheme 4.24). Surprisingly, undesired dienal byproduct **441** was formed in much greater quantities in this case. The poor yield in the Takai olefination may again be due to the allylic alcohol quenching the reaction, albeit alcohols usually being tolerated in this process.



*Scheme 4.24 Synthesis of boronic ester **442** and attempted reduction of the alkynylsilane motif*

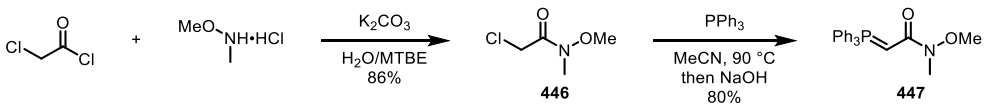
When alkyne **442** was subjected to Lindlar semi-hydrogenation no reduction was observed. However, upon diimide reduction, formation of the desired product **443** was observed, along with inseparable overreduction product **444** and starting material **442**.

To address these problems, the introduction of the (*Z*)-vinyl silane at an earlier stage was considered. Thus, controlled semi-hydrogenation of diol **398** afforded the requisite (*Z*)-vinyl silane **399** in good yield, and subsequent oxidation then gave aldehyde **445** (Scheme 4.25).



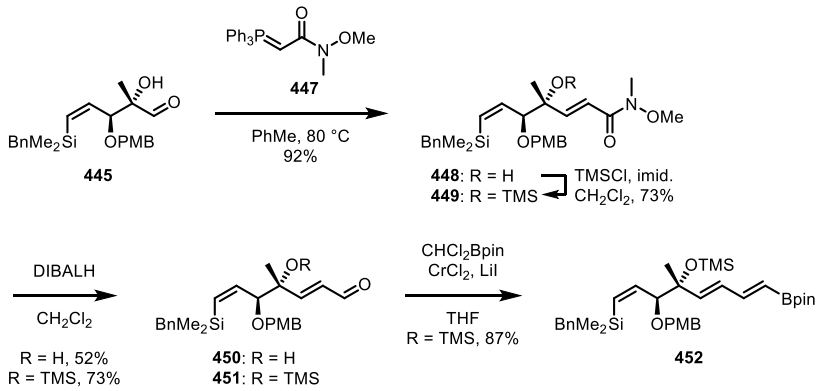
*Scheme 4.25 Synthesis of aldehyde **445** from enyne **396***

Due to previously encountered problems related to the over-olefination when ylid **84** was deployed, Weinreb amide **447** was instead prepared (Scheme 4.26).[280]



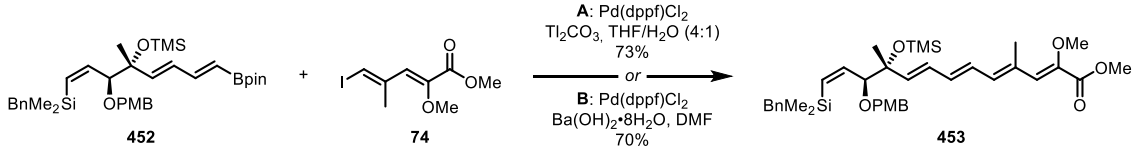
*Scheme 4.26 Synthesis of phosphorane **447***

Wittig olefination with phosphorane **447** afforded product **448** in excellent yield (Scheme 4.27). The following DIBALH reduction afforded aldehyde **450** in moderate yield. However, after protection of alcohol **448** as a trimethylsilyl ether **449**, aldehyde **451** was obtained with improved yield. Similarly, Takai borylation of aldehyde **451** afforded vinyl boronic ester **452** in 87% yield, a huge improvement upon the low yielding Takai olefination on substrate **440** bearing a free allylic hydroxyl (Scheme 4.27, Scheme 4.24).[277] Compound **452** was confirmed to be in the geometry shown by measurement of *J*-values of the coupling constants of the respective double bonds.



*Scheme 4.27 Synthesis of boronic ester **452** from aldehyde **445***

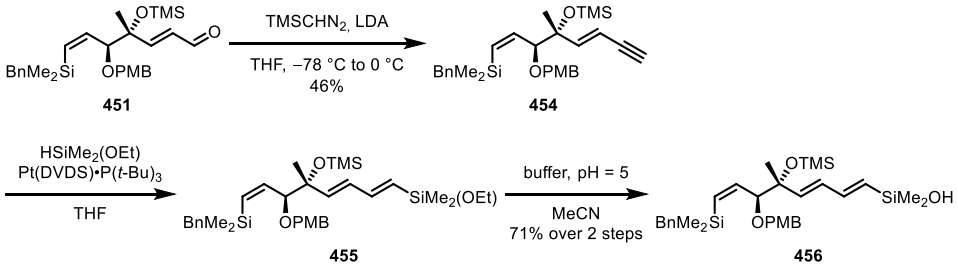
With *C*6-*C*13 boronic ester fragment **452** in hand cross-coupling with iodide **74** under Suzuki conditions was attempted. When thallium(I) carbonate was employed as above the *C*1-*C*13 fragment **453** was afforded in 73% yield. However to our delight, when barium hydroxide was employed instead **453** was obtained in similar yields (70%, Scheme 4.28).



*Scheme 4.28 Suzuki cross-coupling of boronic ester **452** and vinyl iodide **74***

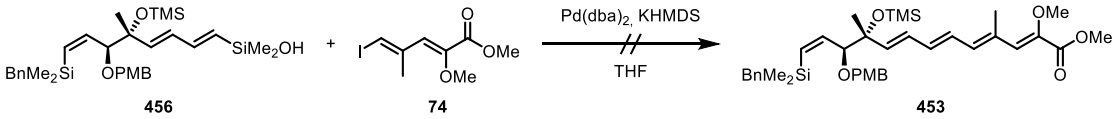
Construction of the *C*5-*C*6 bond by Hiyama cross-coupling can also be considered. For such a strategy, fluoride free conditions would need to be used, which would allow the

activation of a silanol in the presence of the (*Z*)-vinyl benzyldimethyl silane. As such, trimethylsilyl diazomethane was used to convert aldehyde **451** into enyne **454**, which upon platinum-mediated hydrosilylation and subsequent hydrolysis afforded the *C*6-*C*13 silanol **456** (Scheme 4.29).[281-283]



*Scheme 4.29 Synthesis of C6-C13 silanol fragment **456***

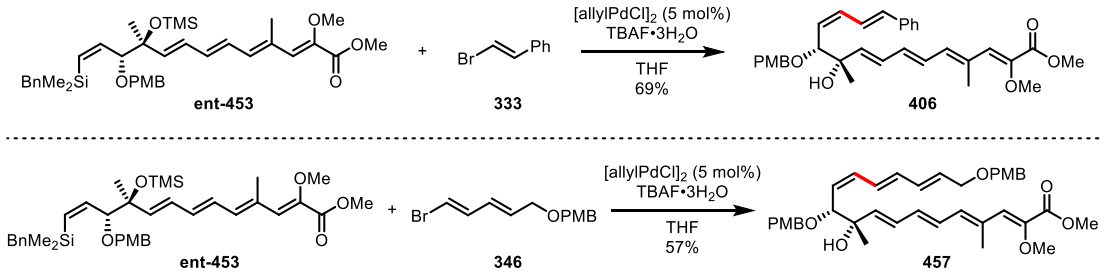
When the Hiyama cross-coupling of the silanolate derived from **456** with iodide **74** was attempted using KHMDS, as previously optimised by Gudmundsson on a model system, no product formation was observed with only 50% of starting material **456** reisolated (Scheme 4.30).[74] Due to time restraints, no further attempts were carried out, however the use of KOTMS promoter may yet prove efficient.



*Scheme 4.30 Attempted Hiyama cross-coupling to form C1-C13 fragment **453***

With *C*1-*C*13 dimethyl silane fragment **453** in hand, cross-coupling with β-bromostyrene was attempted under the fluoride-promoted Hiyama conditions. Product **406** was obtained in 67% yield, slightly improving upon the previously obtained yield when the equivalent six-membered dimethylsiloxane **404** was employed (Scheme 4.7, Scheme 4.31). Even more pleasingly, when the Hiyama cross-coupling of **ent-453** was attempted with the more challenging dienyl bromide **346**, polyene **457** was obtained in 57% yield (Scheme 4.31). These results demonstrate the viability of the *C*1-*C*13 fragment **453** as a coupling partner for the construction of the *C*13-*C*14 bond *via* Hiyama cross-coupling, and in

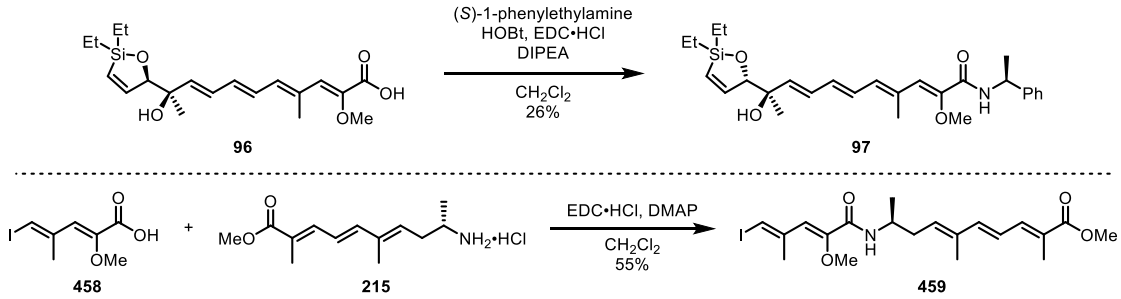
particular with vinyl bromides. In addition, the *C*1-*C*13 fragment **453** can finally be prepared reliably and reproducibly in 10 steps (longest linear sequence) from common iodide **76** and alkyne **306**.



Scheme 4.31 Model Hiyama cross-couplings of C1-C13 fragment ***ent-435***

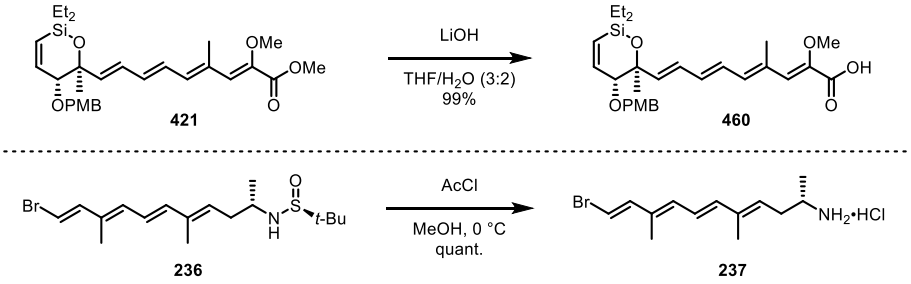
4.5 Construction of the Amide Bond

The first steps in modelling the amide bond formation were carried out by Lim and Gudmundsson.[73,74] While Lim modelled the amide bond using a *C*1-*C*13 siloxane fragment that provided the product **97** in low yield, Gudmundsson carried out the amide coupling using a less advanced acid **458**, but a more representative amine **215** (Scheme 4.32).



Scheme 4.32 Amide couplings carried out by Lim and Gudmundsson.

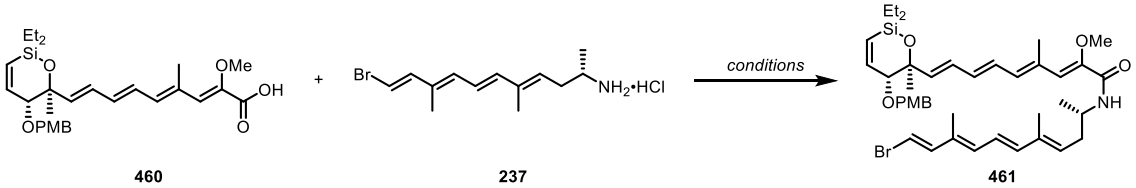
To further investigate this amide bond formation, coupling of the *C*1-*C*13 diethyl siloxane fragment **460** with tetraenyl bromide amine **237** was explored. Hydrolysis of ester **421** and deprotection of sulfinamide **236** proceeded smoothly, affording carboxylic acid **460** and free amine **237** in excellent yields (Scheme 4.33).



*Scheme 4.33 Hydrolysis of ester **421** and deprotection of sulfinamide **236***

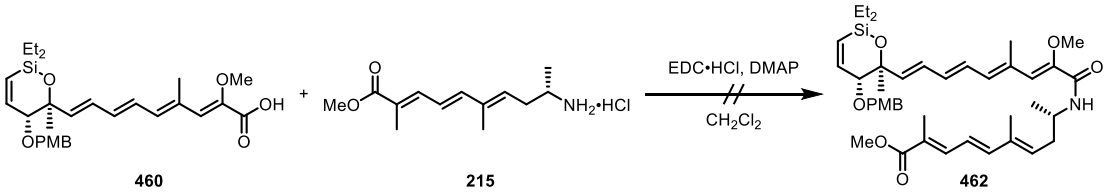
A small selection of different activators to effect amide coupling were selected from the plethora of available conditions (Table 4.3).[284-289] While HATU and EDC·HCl provided trace amounts of product **461** (Table 4.3, Entries 3 and 5), the remaining activators only returned complex mixtures (Table 4.3, Entries 1, 2, and 4).

*Table 4.3 Screening of amide bond formation conditions using carboxylic acid **460***



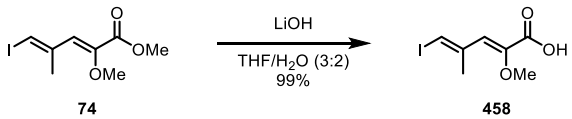
Entry	Conditions	Yield [%]
1	DCC, HOBt, CH_2Cl_2	complex mixture
2	CDI, CH_2Cl_2	complex mixture
3	HATU, DIPEA, CH_2Cl_2	traces
4	BOPCl, Et_3N, CH_2Cl_2	complex mixture
5	EDC·HCl, DMAP, CH_2Cl_2	traces

In order to rule out that the cyclic siloxane motif present in **460** is the source of these problematic results, **460** was coupled with amine **215**, which was previously shown by Gudmundsson to react with carboxylic acid **458** under the same reaction conditions (Scheme 4.32, Scheme 4.34). Unfortunately, the reaction did not form product **462**, and only formed a complex mixture. This indicates that the somewhat delicate cyclic alkenylsiloxane motif may indeed be the reason for the failure of all conditions used.



Scheme 4.34 Attempted amide coupling under conditions previously used by Gudmundsson

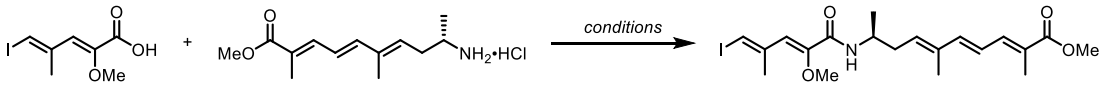
These complications led us to consider testing amide bond formation with a less advanced carboxylic acid and amine. Thus, the carboxylic acid **458** previously employed by Gudmundsson was prepared in quantitative yield from dienoate **74** (Scheme 4.35).



*Scheme 4.35 Saponification of dienoate **74***

Use of EDC·HCl in combination with DMAP afforded amide **459** in 36% yield (Table 4.4, Entry 1). These conditions were previously employed by Gudmundsson as well as Toshima in the synthesis of incednam.[43,74] To our delight, when HATU was used as the activator in combination with DIPEA, **459** was afforded in an improved 75% yield (Table 4.4, Entry 2).[290] Another activator, frequently used with polyunsaturated systems is BOP-Cl; [291,292] when freshly recrystallised BOP-Cl was deployed as the activating agent, amide **459** was obtained in 57% yield (Table 4.4, Entry 3). In contrast, use of an acid chloride prepared from carboxylic acid **458** by treatment with oxalyl chloride gave only minor amounts of coupled product (18%, Table 4.4, Entry 4). It was also discovered that amide **459** is extremely sensitive to acidic conditions: Even $CDCl_3$ that had been stored over K_2CO_3 was found to promote isomerisation of amide **459**. Thus, acidic conditions needed to be stringently avoided in going forward.

*Table 4.4 Screening of amide bond forming conditions using carboxylic acid **458***



Entry	Conditions	Yield [%][a]
1	EDC·HCl, DMAP, CH_2Cl_2	36
2	HATU, DIPEA, DMF	75
3	BOP-Cl, DIPEA, DMAP, THF	57
4	1. $(COCl)_2$, cat. DMF, CH_2Cl_2; 2. DMAP, Et_3N, THF	18

[a] isolated yield.

When stored neat, hydrochloride salt **237** was also found to decompose rather rapidly, and therefore, a procedure was devised whereby after sulfinamide deprotection the solvent was switched to that required for amide bond formation, without **237** being stored neat at any point. This procedure, in combination with the aforementioned optimal conditions for the amide bond formation, now afforded *C*14-*C*5 fragment **463** in 79% yield (Scheme 4.36).

*Scheme 4.36 HATU mediated amide bond formation of carboxylic acid **458** and hydrochloride salt **237***

4.6 Endgame

4.6.1 Ring-closing Hiyama cross-coupling approach

In light of the great efficiency of the amide bond formation as an inter- rather than intramolecular process, an intramolecular Hiyama cross-coupling to form the macrocycle

was considered (Figure 4.1).[111,187] This strategy would involve the coupling of a vinyl iodide in the presence a vinyl bromide, to enable the use of amide **463**.

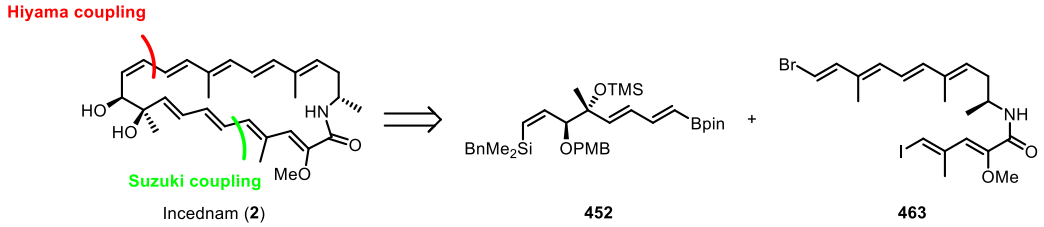
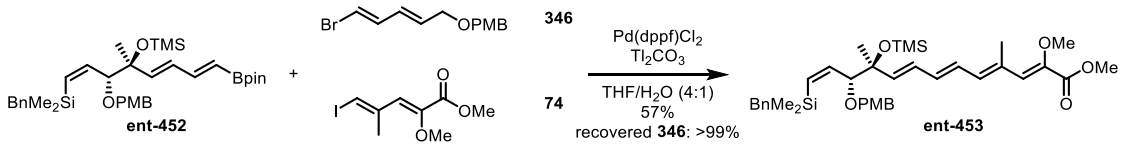


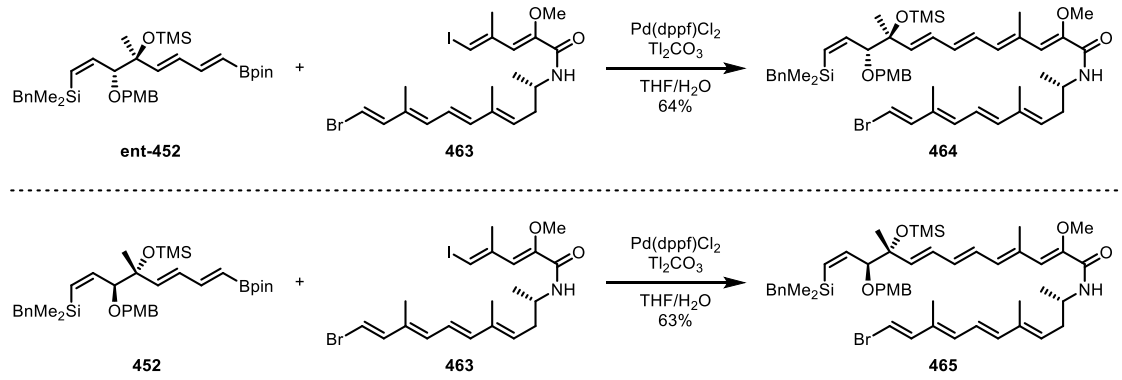
Figure 4.1 Retrosynthetic approach for the Ring-closing Hiyama cross-coupling approach

To investigate the validity of this strategy, a competition experiment was designed where the coupling of vinyl iodide **74** to vinyl boronic ester **ent-452** in the presence of vinyl bromide **346** was attempted (Scheme 4.37). To our delight, exclusive coupling of the vinyl iodide **74** was observed to give polyene **ent-453**, whereas bromide **346** was fully recovered post coupling.



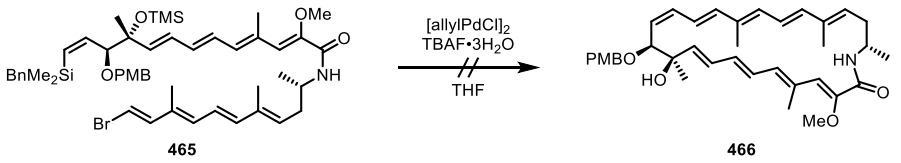
*Scheme 4.37 Competition experiment of Suzuki cross-coupling between iodide **74** and bromide **346***

Encouraged by these results the coupling of the *C*6-*C*13 vinyl boronic ester fragment **ent-452** with *C*14-*C*5 fragment was attempted (Scheme 4.38). Due to the availability of the opposite enantiomer of **452**, two diastereomers **464** and **465** were prepared in similarly good yields.



Scheme 4.38 Suzuki cross-coupling to form a full acyclic incednam carbon skeleton

These different diastereomers could adopt different conformations, which might lead to different efficiencies in the construction of the macrocycle due to spatial separation of both ends. For example, this has been shown by Kakeya *et al.* in their synthesis of heronamide C.[68] Much to our dismay, neither compound **464** nor **465** underwent ring-closing Hiyama cross-coupling, and only returned a complex mixture. Some evidence from crude ^{1}H NMR spectra suggested protodesilylation of the vinylsilane being at least one decomposition pathway. Even mimicking conditions employed by Denmark *et al.* in his studies of intramolecular Hiyama cross-coupling, which involves slow addition of starting material to a TBAF solution with Pd catalyst did not improve the reaction. While the failure of the ring-closing Hiyama cross-coupling could be explained by an unfavourable conformation of the starting material, other reasons cannot be ruled out. The proposed mechanism in place requires the intermolecular dimerisation of two silanols derived from **464** or **465**, followed by transmetalation of the correct vinyl residue. The low concentration of the corresponding silane may have favoured alternative decomposition pathways rather than the cross-coupling pathway.



*Scheme 4.39 Attempted synthesis of PMB-appended incednam **466** via Hiyama cross-coupling*

4.6.2 Macrolactamisation approach

In parallel to our efforts to explore a ring-closing Hiyama cross-coupling approach, a different order of events was investigated. In regard of the successful intermolecular Hiyama cross-coupling of the *C*1-*C*13 fragment **ent-453** with different vinyl bromides, an approach involving cross-coupling followed by macrolactamisation was considered

(Figure 4.2). However, due to the limited success of the Hiyama cross-coupling using molecules with an sulfinamide present, the *N*-protecting group needed to be changed.

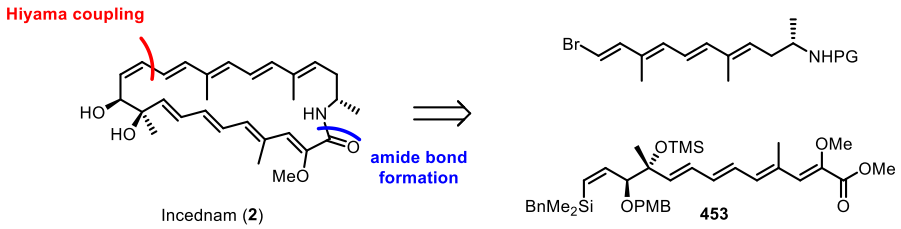
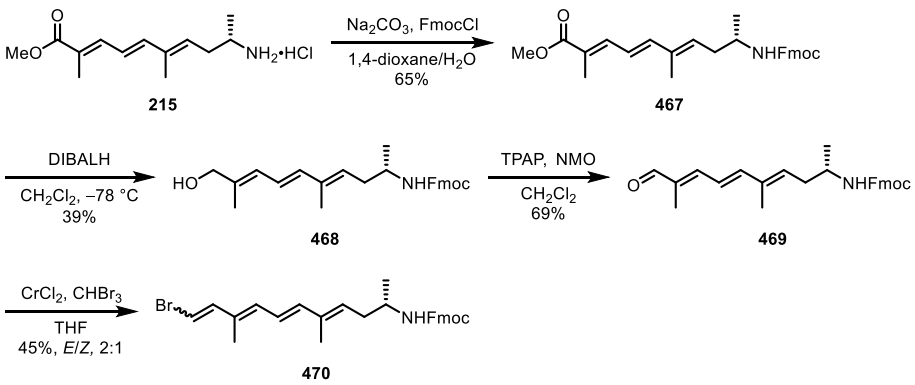


Figure 4.2 Retrosynthetic approach for the intermolecular Hiyama cross-coupling and subsequent macrolactamisation

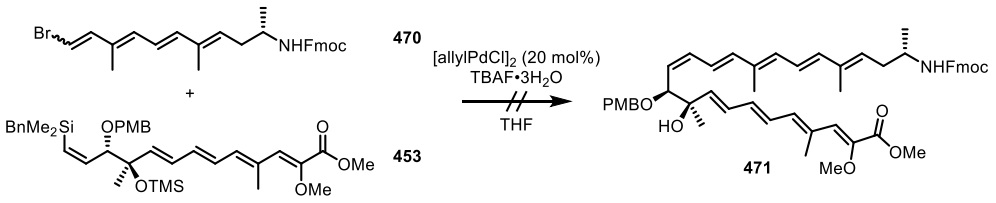
Fmoc was considered due to its easy removal under basic conditions. Protecting groups removed by acidic conditions were avoided, as these were deemed likely to promote unwanted isomerisation of the delicate polyene system. Fmoc protected vinyl bromide **470** was synthesised from hydrochloride salt **215** in 4 steps (Scheme 4.40). After installing the Fmoc group, trienoate **467** was reduced to allylic alcohol **468**, followed by Ley-Griffith oxidation to afford trienal **469**. Our previous strategy to prepare a vinyl bromide, namely dibromination and Hirao-reduction, was not thought to be applicable due to the need for triethylamine in the Hirao reduction, which could cleave the Fmoc group.[293] Therefore, vinyl bromide **470** was prepared by a Takai olefination using chromium(II) chloride and bromoform.[113,294]



*Scheme 4.40 Synthesis of Fmoc protected vinyl bromide **470***

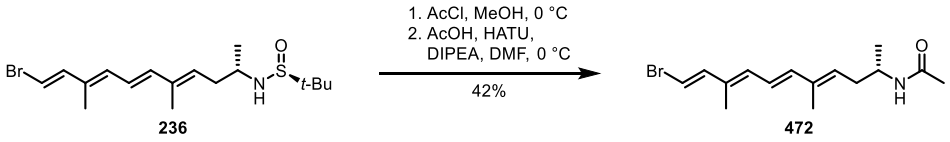
With Fmoc protected tetrenyl bromide **470** in hand, the Hiyama cross-coupling with **453** was attempted, but unfortunately no formation of product **471** was observed (Scheme

4.41). It seems quite possible that the Fmoc group is cleaved under the coupling conditions, which may lead to palladium amine complexes sequester the catalyst and prevent coupling.[295,296]



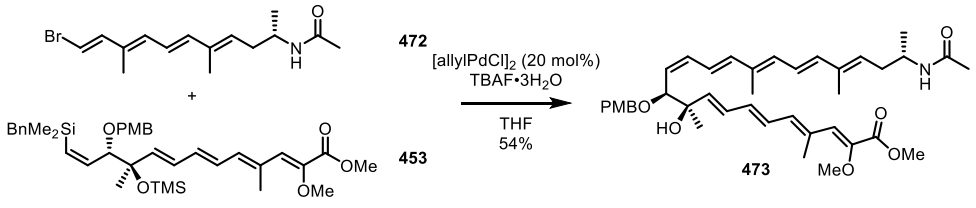
*Scheme 4.41 Attempted Hiyama cross-coupling of C1-C13 fragment **453** and C14-C23 fragment **470***

It is clear that the protecting group strategy is crucial, and also that there are no strongly coordinating groups within the molecule, which could hamper the cross-coupling. An acetate group as *N*-protecting group was therefore considered at the least as a model, as it should both be stable and tolerated under the coupling conditions. Thus, sulfinamide **236** was converted to acetate **472** in 42% yield over two steps (Scheme 4.42).



*Scheme 4.42 Reprotection of sulfinamide **236** as acetate **472***

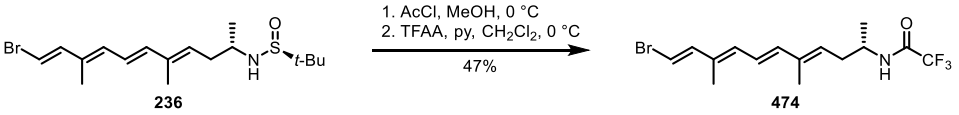
To our delight, when the coupling of *C*14-*C*23 tetraenyl vinyl bromide **472** was attempted with *C*1-*C*13 vinyl silane fragment **453**, acyclic precursor **473** was afforded in 54% yield (Scheme 4.43).



*Scheme 4.43 Hiyama cross-coupling to form acyclic incednam precursor **473***

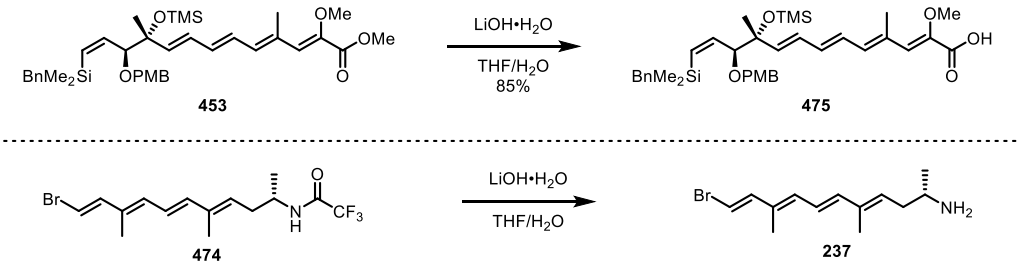
Unfortunately, the stability of amides towards hydrolysis often requires reducing conditions for their cleavage, which are not likely to be compatible with esters or other

carbonyl groups. Thus, trifluoroacetate **474**, which is more readily hydrolysed than other amides, was prepared from sulfinamide **236** in 47% over two steps (Scheme 4.44).



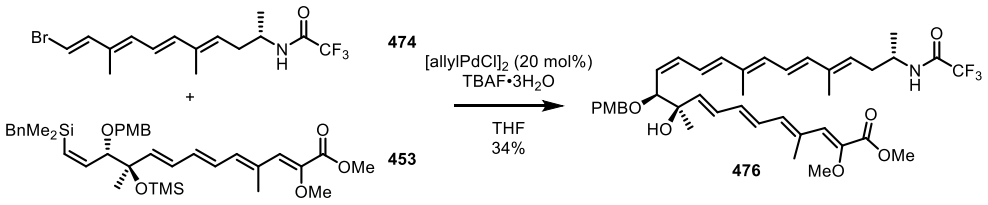
*Scheme 4.44 Reprotection of sulfinamide **236** as trifluoroacetate **474***

When subjecting amide **474** to the same conditions employed to hydrolyse ester **453**, the trifluoroacetate was cleaved, however, due to previous issues in the isolation of **237**, the reaction mixture was analysed solely by UPLC/MS to confirm formation of **237** (Scheme 4.45).



*Scheme 4.45 Saponification of ester **453** and deprotection of trifluoroacetate **474***

We were again pleased to find that cross-coupling of this trifluoroacetate-protected vinyl bromide **474** with silane **453** afforded product **476**, albeit with lower efficiency (34%, Scheme 4.46).

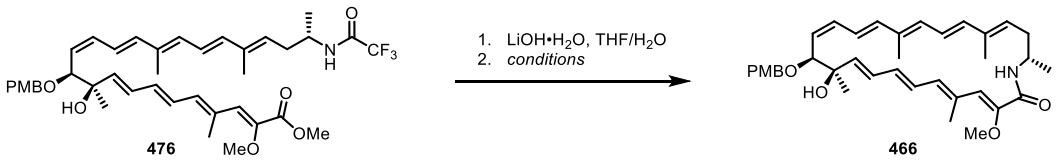


*Scheme 4.46 Hiyama cross-coupling to form acyclic incednam precursor **476***

With polyene **476** in hand, the key macrolactamisation by amide bond formation was attempted using several different conditions (Table 4.5). The first to be explored was DMTMM as coupling agent in combination with triethylamine in methanol (Table 4.5, Entry 1). These conditions were previously deployed by Toshima *et al.* to effect

macrolactamisation of the *O*-triethylsilyl-protected incednam (**48**).[42] We had previously hypothesised that Toshima's cyclisation precursor adopts an unfavourable conformation for cyclisation, explaining the low yield obtained.[67,68] Similarly, the PMB ether may enforce a conformation unfavourable for the macrolactamisation. Apart from Toshima's macrolactamisation conditions, the best conditions applied for our previous intermolecular amide bond formation, which have also been shown to be viable in macrolactamisation, were tested to form macrolactam **466** (HATU, BOP-Cl, Table 4.5, Entries 2 and 3).[297-307] Although a hit by UPLC/MS for **466** was observed for all conditions, and the corresponding peak was attempted to be isolated by semipreparative HPLC, the formation of **466** could not be confirmed.

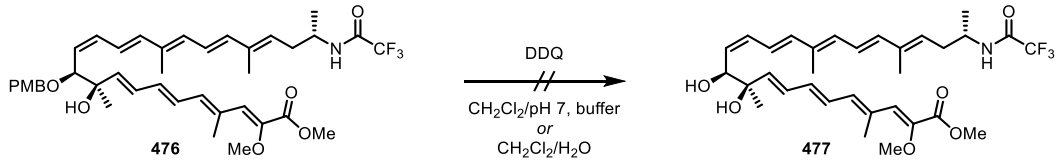
Table 4.5 Attempted macrocyclisations via amide bond formation



Entry	Conditions	Yield [%][a]
1	DMT-MM, Et_3N, MeOH (0.002 M)	--[b]
2	HATU, DIPEA, CH_2Cl_2 (0.002 M)	--[b]
3	BOP-Cl, CH_2Cl_2 (0.0001 M)	--[b]

[a] isolated yield; [b] complex mixture

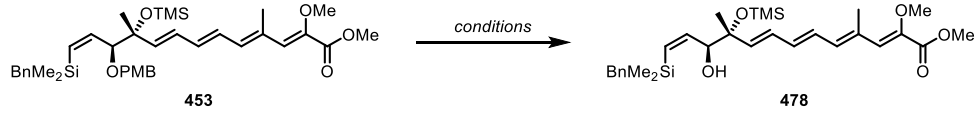
The deprotection of the PMB ether prior to the macrolactamisation was therefore considered, which would afford a compound that is presumably very similar to the natural incednam cyclisation precursor, albeit not the same, as the macrolactam initially formed in nature lacks the *C*10-hydroxy group, which is installed post-cyclisation.[38] However, attempted deprotection of the PMB group of **476** only resulted in a complex mixture (Scheme 4.47).



*Scheme 4.47 Attempted PMB deprotection of **476***

Similarly, PMB-deprotection on *C*1-*C*13 fragment **453** resulted in a complex mixture, regardless of the conditions employed (Table 4.6). Aside from DDQ, acidic conditions using TFA were employed, as well as a procedure involving chromium(II) chloride and lithium iodide, which cleaves PMB ethers by nucleophilic substitution.[293,308,309] All led to decomposition

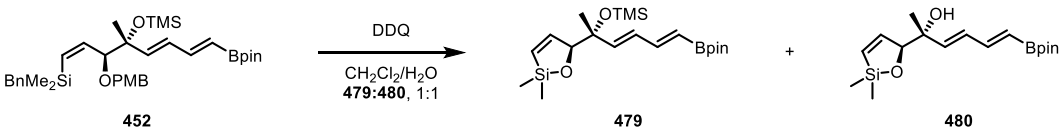
*Table 4.6 Attempted deprotection of PMB ether **453***



Entry	Conditions	Yield [%][a]
1	DDQ, CH_2Cl_2/H_2O	--[b]
2	DDQ, CH_2Cl_2/pH 7 buffer	--[b]
3	TFA, CH_2Cl_2	--[b]
4	$CrCl_2$, LiI, EtOAc/H_2O, 40 °C	--[b]

[a] isolated yield; [b] complex mixture

In fact, the most advanced compound not observed to decompose during the PMB cleavage was diene **452** (Scheme 4.48). However, this reaction results in a concomitant cyclisation to form a five-membered siloxane, which is not stable enough to be carried through further synthetic steps.



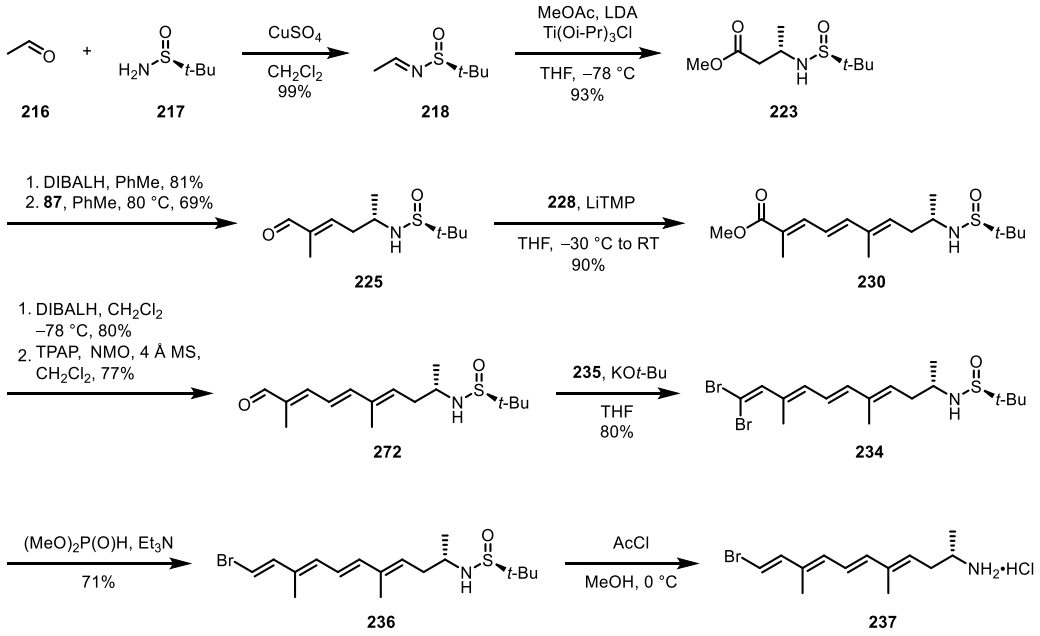
*Scheme 4.48 PMB deprotection of ether **452***

4.7 Conclusion

Significant advances towards the total synthesis of incednam have been achieved. Our previous strategy involving cyclic diethyl siloxanes failed due to issues relating to the efficacy of the Hiyama cross-coupling and unwanted side reactions. However, the use of an acyclic (*Z*)-benzyldimethyl alkenylsilane enabled a reliable and scalable synthesis of a *C*1-*C*13 fragment, which underwent Hiyama cross-coupling with different vinyl bromides in moderate to good yields to construct the key *C*13-*C*14 bond of incednam. Furthermore, we could show that the *C*11-hydroxyl protecting group strategy employed is crucial. This group needs to be both under fluoride promoted Hiyama cross-coupling conditions, but also cleavable under conditions mild enough to not affect delicate polyene systems. Our synthetic studies also enabled us to devise two different strategies, both of which succeeded in the construction of two advanced compounds representing acyclic full carbon skeletons of incednam. Unfortunately, due to time constraints as well as limited amounts of material, neither the intramolecular ring-closing Hiyma cross-coupling nor the macrolactamisation strategy has yet come to fruition to furnish the much desired macrocycles.

5 Conclusion and Future Work

We have developed a reliable synthesis of various key fragments *en route* to incednam. The *C*14-*C*23 fragment **236** was synthesised in 9 steps from acetaldehyde and sulfinamide **217** with an overall yield of 16.2% (Scheme 5.1).

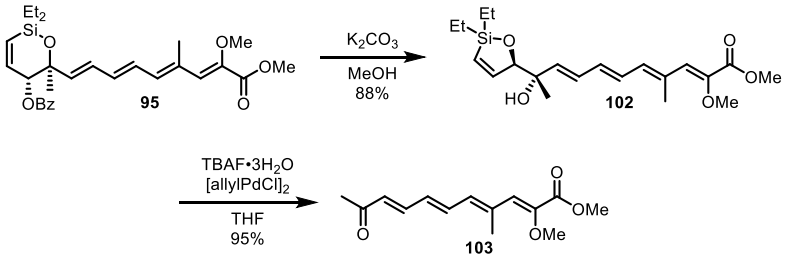


*Scheme 5.1 Synthesis of C14-C23 fragment **236** and subsequent sulfinamide deprotection*

This synthesis addresses several issues in our previous strategy to access equivalent building blocks: firstly, erosion of the *ee* of compounds due to the synthetic route proceeding *via* an epimerisable aldehyde, which is avoided in this route; secondly, identifying appropriate *N*-protecting groups that can provide a free amine in satisfactory yields and purity. The sulfinamide, which plays the dual role of controlling the stereocentre adjacent to the nitrogen, as well as *N*-protecting group for most of the remaining steps, is easily cleavable under acidic conditions and affords hydrochloric amine salt **237** in excellent purity, without the need for further purification, and primed for temporary protection in order to survive the cross-coupling

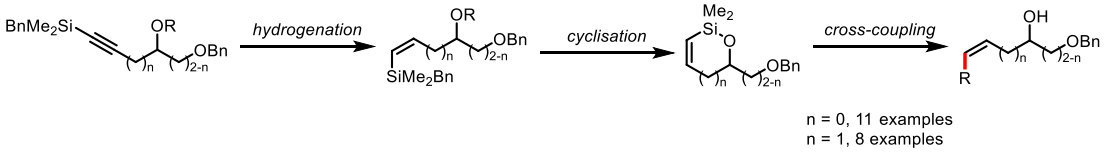
While a synthesis of a *C*1-*C*13 fragment **102** had been achieved by Lim and Gudmundsson, it was not possible to successfully couple this fragment under Hiyama

cross-coupling conditions (Scheme 5.2);[73,74] rather, a retroallylation process was observed to afford ketone **103**. A key observation in regard of this process was benzoyl deprotection and rearrangement of the six- to a five-membered alkenylsiloxane upon treatment with TBAF. This uncontrollable reactivity made it impossible to study the equivalent cross-coupling of the six-membered alkenylsiloxane **95**.



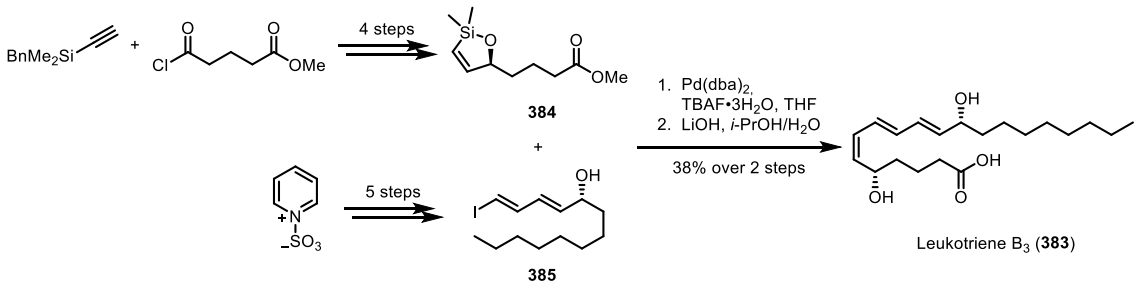
*Scheme 5.2 Attempted model Hiyama cross-coupling of C1-C13 fragment **102** with prior siloxane rearrangement*

Due to this problem, an alternative route was developed to access more reactive dimethyl siloxanes. The synthesis of model five- and six-membered siloxanes allowed for the investigation of a benzyl dimethylsilane in the key semi-hydrogenation reaction, as well as its behaviour in Hiyama cross-couplings after late stage cyclisation (Scheme 5.3).



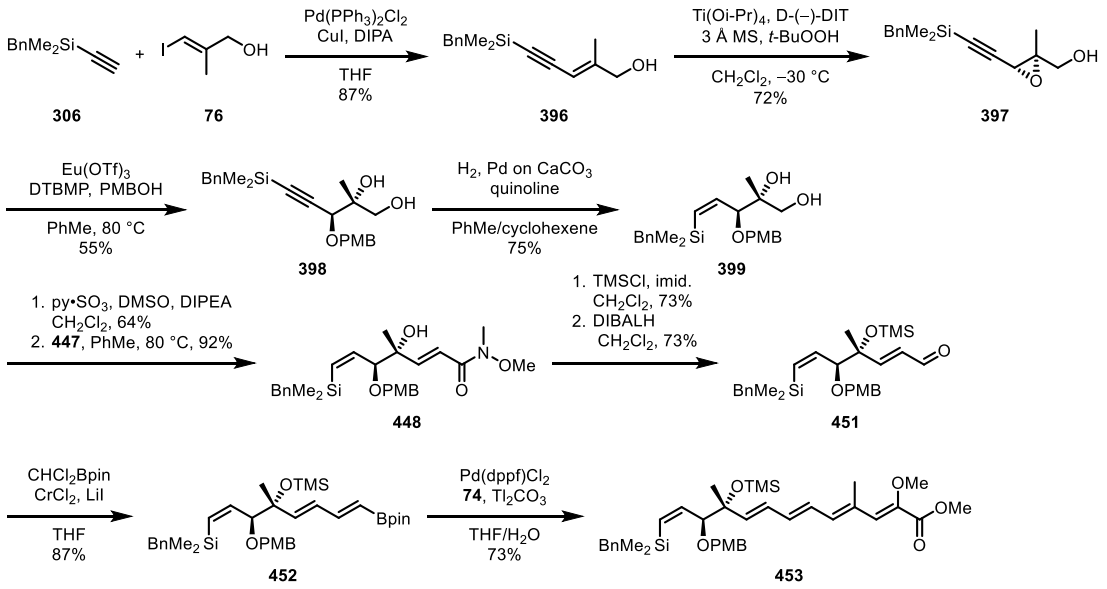
Scheme 5.3 Synthesis of cyclic diemthylsiloxanes and their application in Hiyama cross-couplings

This methodology project culminated in the synthesis of leukotriene B_3 in 7 steps longest linear sequence with a highly modular approach (Scheme 5.4).



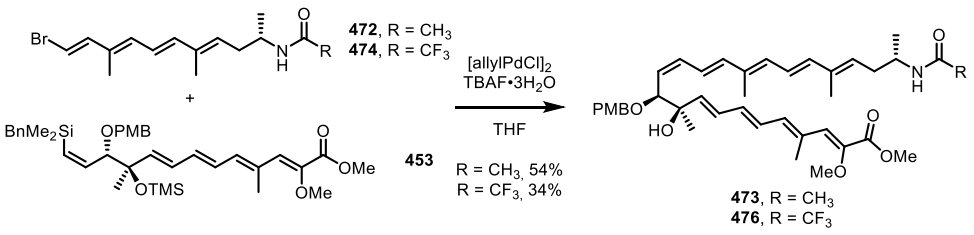
Scheme 5.4 Synthesis of leukotriene B_3

To solve previously encountered synthesis issues, several iterations of improvements on the original synthesis of the *C*1-*C*13 fragment led to the preparation of acyclic (*Z*)-alkenylsilane **453**, which can be accessed in 10 steps with an overall yield of 5.1% (Scheme 5.5).



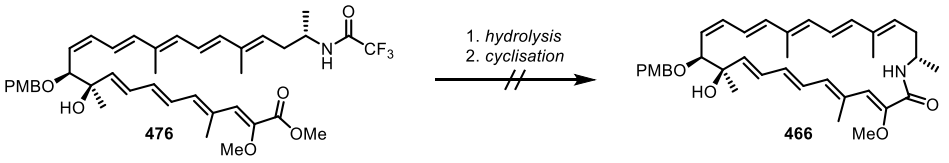
*Scheme 5.5 Synthesis of C1-C13 fragment **453***

It was shown that this *C*1-*C*13 fragment undergoes efficient cross-coupling with the *C*14-*C*23 fragment. However, to ensure a productive coupling the sulfinamide protecting group in this fragment had to be replaced by an amide protecting group (Scheme 5.6).



*Scheme 5.6 Union of C1-C13 fragment **453** and C14-C23 fragments **472** and **474** via Hiyama cross-coupling*

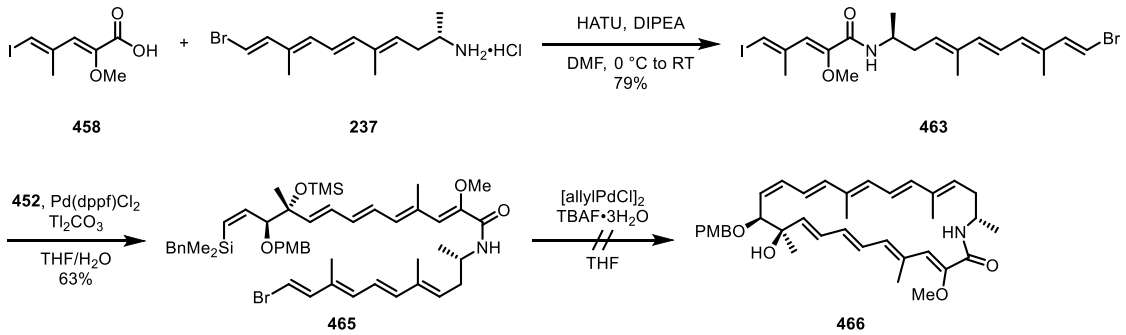
Unfortunately, all efforts to effect cyclisation of **476** after ester saponification and concomitant trifluoroacetate deprotection did not furnish the desired macrocycle, which could in part be due to the small scale of these reactions making purification very challenging (Scheme 5.7).



*Scheme 5.7 Unsuccessful cyclisation to form PMB appended incednam (**466**)*

However, this failure could also be due to a non-favourable conformation of the cyclisation compound. This could in future be addressed by deprotection of the *C*11 PMB ether, which would provide a compound closer to the natural compound. Unfortunately, all conditions tested to cleave the PMB ether resulted only in decomposition.

At the same time, we investigated an alternative exciting approach that changes the order of events and relies on a Hiyama cross-coupling to form the macrocycle (Scheme 5.8). Amide **463** bearing both a vinyl bromide and vinyl iodide was prepared in good yield, and could be selectively coupled with vinyl boronic ester **452**. However, cyclisation again failed, potentially due to an unfavourable conformation, but it could also be due to the Hiyama cross-coupling itself. The proposed mechanism for the coupling of six-membered alkenylsiloxanes requires the dimerisation of silanols to form a disiloxane, which upon fluoride activation becomes active towards transmetalation. This results in an interesting dynamic where the concentration needs to be dilute enough to effect macrocyclisation, but also concentrated enough to efficiently form disiloxanes.



Scheme 5.8 Alternative approach relying on a ring-closing Hiyama cross-coupling

While the ring closing Hiyama cross-coupling was unsuccessful, employing a five-membered alkenylsiloxane in this case might prove successful. Five-membered

alkenylsiloxanes undergo cross-coupling *via* a distinct proposed mechanism without the need of prior dimerisation before transmetalation occurs. The fragmentation mentioned above may, of course, still be a risk.

In light of these challenges, a different protecting group strategy should be employed. While the new protecting group should be cleavable under conditions mild enough not to decompose the polyene, it should be stable throughout the Hiyama cross-coupling, thereby allowing control of either five- or six-membered alkenylsiloxane formation (or their acyclic analogues), and cross-couplings. A *para*-substituted benzyl ether such as **481** or **482** could assume this role (Figure 5.1).

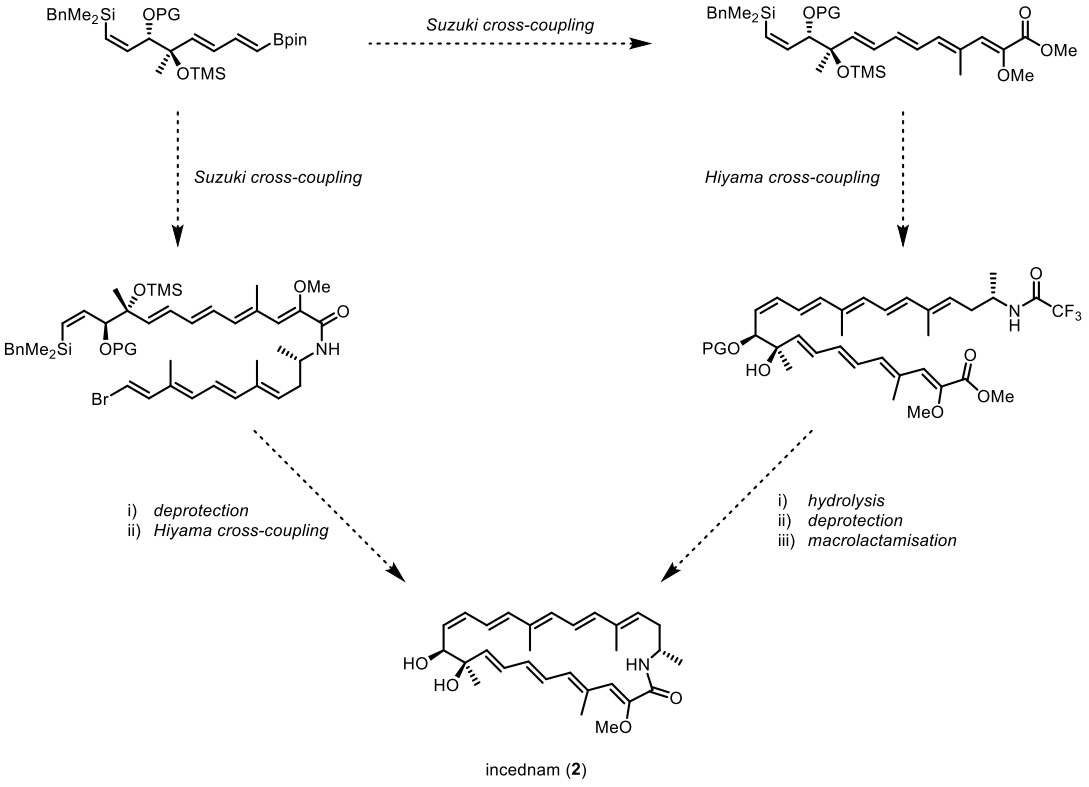
*Figure 5.1 Proposed benzyl ethers **481** and **482** as new protecting group strategy*

While the use of *p*-acetoxybenzyl ether (PAB) would require a different synthesis for the *C*1-*C*13 fragment avoiding a Weinreb amide intermediate, which would probably result in a lower overall yield, it should be stable towards both the base in the Suzuki cross-coupling and towards Hiyama cross-coupling conditions.[310-314] The cleavage of a PAB group can be effected by a mild enzymatic ester hydrolysis followed by a rearrangement to form *para*-quinone methide revealing the hydroxyl group.[315-319] Alternatively it can be cleaved under basic conditions, using sodium methoxide, or mildly oxidising conditions, using iron(III) chloride or silver(I) carbonate.[320-322] Similar methods can be employed for the cleavage of a *p*-hydroxybenzyl ether (PHB), obtained after ester hydrolysis.

Similarly, the use of a *para*-methanesulfonate benzyl ether as a protecting group should stand up to all transformations in our synthesis, but it can easily be converted into a

p-hydroxybenzyl ether by treatment with hydroxide.[323-332] The PHB ether could then be cleaved as outlined above.

Both of these protecting group strategies, should not only enable us to control when deprotection takes place, but also to control whether an acyclic five- or six-membered siloxane analogue undergoes cross-coupling, and further to be cleaved under mild enough conditions to limit decomposition of the respective polyene compound. We remain hopeful of completing the incednam macrolactam.



Scheme 5.9 Proposed endgames with new protecting group strategy

6 Experimental

6.1 General Experimental

Reactions: Unless otherwise stated, all reactions were carried out in oven-dried glassware und an inert gas atmosphere.

Solvents and reagents: Solvents and commercially available reagents were dried and purified before use where appropriate using standard procedures. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), methanol (MeOH), acetonitrile (MeCN) and toluene (PhMe) were obtained dry and oxygen free from solvent dispenser units having passed through an activated alumina column under nitrogen. DIPEA, DIPA, DMSO, and DMF were distilled over CaH_2 under reduced pressure and stored over CaH_2 or 4 Å molecular sieves and under nitrogen. Unless otherwise noted, petroleum ether refers to the fraction of light petroleum ether boiling at 40-60 °C.

Chromatography: Thin layer chromatography was performed using Merck DC Kieselgel 60 F_{254} plates and visualised by either UV fluorescence (λ 254 nm) or stained and heated using vanillin, phosphomolybdic acid (PMA) or potassium permanganate. Flash column chromatography was carried out on Macherey-Nagel Kieselgel 60M (230-400 mesh) under positive pressure.

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

Enantiomeric excess: Enantiomeric excess (*ee*) was determined by HPLC on an Agilent 1200 series running in normal phase under UV (210-254 nm) detection using a ZORBAX RX-SIL (150 mm × 4.6 mm ID) as the analytical column. Chiral analysis was carried out on a DAICEL CHIRALPAK-IA or IB (250 mm × 4.6 mm ID).

Infrared Spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier FT-IR spectrometer, and the samples were prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Absorption maxima ($\tilde{\nu}_{max}$) are quoted in wavenumbers (cm^{-1}). Only selected, characteristic IR absorption data are reported for each compound

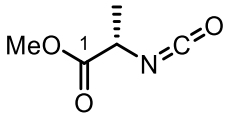
NMR spectra: Proton (^{1}H), carbon (^{13}C), fluorine (^{19}F) and phosphorus (^{31}P) spectra were recorded on a Bruker DPX200 (^{1}H: 200 MHz, ^{13}C: 50 MHz), Bruker AVIII400 (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F: 376 MHz, ^{31}P: 162 MHz), or a Bruker AVIII500 (^{1}H: 500 MHz, ^{13}C: 126 MHz). Chemical shifts (δ_H, δ_C, δ_F and δ_P) are reported in parts per million (ppm), referenced to the residual peak stated ($CDCl_3$: $\delta = 7.26/77.2$; C_6D_6: $\delta = 7.16/128.1$; THF-d_8: $\delta = 1.71/67.2$; DMSO-d_6: $\delta = 2.50/39.5$) with signal splitting recorded as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (p), sextet (sex), septet (hept) and multiplet (m).

Mass spectra: High resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford using a Bruker Daltonics microTOF spectrometer (resolution = 5000 FWHM), a Bruker μTOF spectrometer (resolution = 10000 FWHM) or a Waters MALDI Micro MX TOF spectrometer (resolution = 5000 FWHM). High resolution values are calculated to 4 or 5 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Atom numbering: While the atoms of the compounds in the main body of this thesis were numbered according to their position in incednine for easier recognition of positions, the experimental section uses IUPAC numbers in the names of the compounds. For ease and clarity the IUPAC numbering did not always seem sensible for the assignment of signals in the recorded spectra. For this reason the molecules might be numbered differently, as indicated in the respective figure.

6.2 Experimental Procedures

Methyl (*S*)-2-isocyanatopropanoate, 167

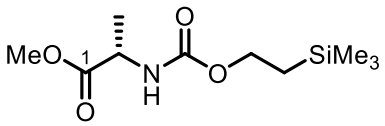


L-Alanine methyl ester hydrochloride (3.53 g, 25.3 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (85 mL). A saturated aqueous solution of $NaHCO_3$ (91 mL) was added, and the mixture was stirred vigorously for 10 min. The mixture was cooled to 0 °C, triphosgene (2.98 g, 10.0 mmol, 0.40 eq.) was added, and the mixture was stirred vigorously for 1 h. The mixture was separated and extracted with CH_2Cl_2 (3 × 60 mL), The combined organics dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product **167**, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.07 (q, J = 7.2 Hz, 1H, 2-H), 3.80 (s, 3H, OCH_3), 1.48 (d, J = 7.2 Hz, 3H, 2-CH_3).

The spectroscopic data is in agreement with that reported by Maia and coworkers.[333]

Methyl ((2-(trimethylsilyl)ethoxy)carbonyl)-L-alaninate, 168



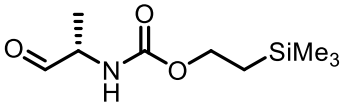
2-(Trimethylsilyl)ethan-1-ol (1.1 mL, 7.7 mmol, 1.0 eq.) and triethylamine (1.1 mL, 7.9 mmol, 1.03 eq.) were dissolved in CH_2Cl_2 (20 mL) at 0 °C. After 30 min, the crude isocyanate **167** (1.71 g, 13.2 mmol 1.7 eq.) in CH_2Cl_2 (5 mL) was added slowly, and the resulting mixture stirred at ambient temperature for 1 h, before being concentrated *in vacuo*, the residue was dissolved in EtOAc (20 mL), washed with aqueous HCl (1 M, 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column

chromatography (petroleum ether / Et_2O, 3:2) afforded the title compound **168** as a colourless oil (1.58 g, 81%).

***R*$_f$** 0.32 (petroleum ether / Et_2O, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.12 (bs, 1H, NH), 4.35 (dq, J = 7.2, 6.9 Hz, 1H, 2-H), 4.13 (t, J = 8.5 Hz, 2H, $OCH_2CH_2Si(CH_3)_3$), 3.73 (s, 3H, CO_2CH_3), 1.38 (d, J = 7.2 Hz, 3H, 2-CH_3), 0.96 (t, J = 8.5 Hz, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.01 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.6, 155.9, 63.3, 52.3, 49.4, 18.6, 17.6, −1.6.

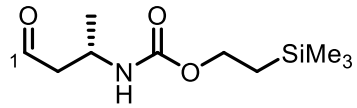
The spectroscopic data is in agreement with that reported by Stanway and Thomas.[334]

2-(Trimethylsilyl)ethyl (*S*)-(1-oxopropan-2-yl)carbamate, 169



A solution of DIBALH (23.6 mL, 1.0 M solution in hexanes, 23.6 mmol, 2.0 eq.) was added dropwise to a solution of amino ester **168** (2.93 g, 11.8 mmol, 1.0 eq.) in CH_2Cl_2 (36 mL). After stirring at −78 °C for 1 h the reaction was quenched with an aqueous solution of Rochelle's salt (40 mL) and diluted with Et_2O. The cooling bath was removed and the reaction was allowed to reach ambient temperature. The layers were separated and the aqueous was extracted with Et_2O (3 × 50 mL). The combined organics were dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound **169** as a colourless oil that was immediately used in the next reaction.

2-(Trimethylsilyl)ethyl (*S*)-(4-oxobutan-2-yl)carbamate, 171

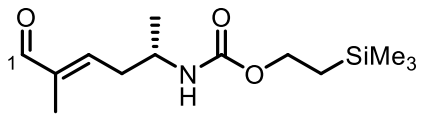


(Methoxymethyl)triphenylphosphonium chloride (7.20 g, 21.0 mmol, 2.0 eq.) was dissolved in THF (64 mL). NaHMDS (9.2 mL, 2.0 M solution in THF, 18 mmol, 1.7 eq.) was added dropwise at −78 °C. The resulting mixture was stirred for 30 min followed by dropwise addition of α-amino aldehyde **169** (2.30 g, 10.8 mmol, 1.0 eq.) in THF (8 mL). The mixture was allowed to reach ambient temperature. After stirring at ambient temperature for 2 h, the reaction was quenched with water, and extracted with EtOAc(3 × 50 mL). The combined organics dried over $MgSO_4$, and concentrated *in vacuo*. The residue was redissolved in THF (55 mL), 1 M HCl (11 mL) added and the resulting solution stirred vigorously at ambient temperature overnight. The reaction mixture was quenched with aqueous $NaHCO_3$ solution, extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 7:3) afforded the title compound **171** as a colourless oil (1.25 g, 56% over three steps).

***R**f* 0.25 (petroleum ether /EtOAc, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, C*H*O), 4.75 (s, 1H, N*H*), 4.25 – 4.06 (m, 1H, 3-H), 4.12 (t, J = 8.2 Hz, 2H, OCH_2CH$_2$Si(CH$_3$)$_3$), 2.70 – 2.54 (m, 2H, 2-H$_2$), 1.23 (d, J = 6.7 Hz, 3H, 3-CH$_3$), 0.94 (t, J = 8.2 Hz, 2H, OCH$_2$CH_2Si(CH$_3$)$_3$), 0.01 (s, 9H, Si(CH_3)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 200.9, 155.9, 63.1, 50.3, 42.7, 20.9, 17.7, −1.5.

The spectroscopic data is in agreement with that reported by H. Gudmundsson and D. Lim.[73,74]

2-(Trimethylsilyl)ethyl (*S*,*E*)-(5-methyl-6-oxohex-4-en-2-yl)carbamate, 173

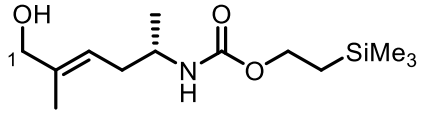


A solution of aldehyde **171** (1.00 g, 4.32 mmol, 1.0 eq.) and ylid **87** (2.06 g, 6.27 mmol, 1.5 eq.) in toluene (30 mL) was stirred at 80 °C overnight. The resulting solution was concentrated *in vacuo* and redissolved in cold Et_2O, filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 9:1 → 4:1) to afforded the title compound **173** as a colourless oil(0.94 g, 80%, 84% *ee* CHIRALPAK IB, 2% IPA /hexane, 1.3 mL/min, t_R (*R*) 11.0 min, t_R (*S*) 14.4 min).

***R*$_f$** 0.29 (petroleum ether / Et_2O, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.40 (s, 1H, C*H*O), 6.49 (t, *J* = 7.1 Hz, 1H, 3-H), 4.47 (s, 1H, N*H*), 4.19 – 4.05 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.91 (m, 1H, 5-H), 2.52 (t, *J* = 5.8 Hz, 2H, 4-H$_2$), 1.73 (s, 3H, 2-C*H*$_3$), 1.18 (d, *J* = 6.7 Hz, 3H, 5-C*H*$_3$), 1.00 – 0.91 (m, 2H, CH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.0, 156.0, 149.7, 141.1, 63.0, 46.3, 36.3, 20.8, 17.7, 9.4, −1.5.

The spectroscopic data is in agreement with that reported by Gudmundsson and Lim.[73,74]

2-(Trimethylsilyl)ethyl (*S*,*E*)-(6-hydroxy-5-methylhex-4-en-2-yl)carbamate, 174

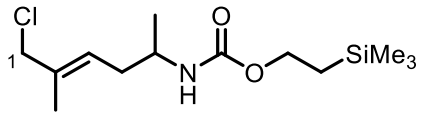


Aldehyde **173** (1.00 g, 3.68 mmol, 1.0 eq.) was dissolved in methanol (19 mL) at 0 °C. $NaBH_4$ (140 mg, 3.70 mmol, 1.0 eq.) was added and the mixture was stirred at 0 °C for 30 min, and stirred for further 30 min at ambient temperature. Water (20 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification

by column chromatography (petroleum ether / Et_2O, 1:1) yielded the title compound **173** (920 mg, 91%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −3.1 (*c* 1.0, $CHCl_3$); $\boldsymbol{R_f}$ 0.07 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3321, 2953, 1689, 1533, 1455, 1333, 1250, 1060, 937, 858, 835, 770, 694. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.41 (t, *J* = 7.1 Hz, 1H, 3-H), 4.46 (s, 1H, N*H*), 4.10 (t, *J* = 8.3 Hz, 2H, $OCH_2CH_2Si(CH_3)_3$), 3.99 (d, *J* = 4.0 Hz, 2H, 1-H_2), 3.74 (m, 1H, 5-H), 2.18 (t, *J* = 6.8 Hz, 2H, 4-H_2), 1.64 (s, 4H, 2-CH_3, O*H*), 1.11 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 0.94 (t, *J* = 8.3 Hz, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.00 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.2, 137.6, 121.1, 68.5, 62.7, 46.9, 34.8, 20.6, 17.7, 13.8, −1.5; **HRMS** (ESI+) calc. for $C_{13}H_{27}NO_3SiNa$ $[M+Na]^+$ 296.1652, found 296.1653.

2-(Trimethylsilyl)ethyl (*E*)-(6-chloro-5-methylhex-4-en-2-yl)carbamate, 176

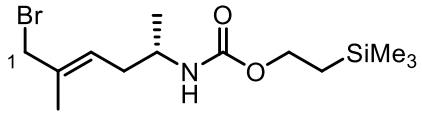


Alcohol **174** (44 mg, 0.16 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.4 mL) and cooled to 0 °C. DMAP (2 mg, 16 µmol, 0.1 eq.), tosylchloride (32 mg, 0.17 mmol, 1.05 eq.) and NEt_3 (23 µL, 0.17 mmol, 1.0 eq.) were sequentially added. The mixture was stirred at 0 °C for 16 h and additional 4 h at ambient temperature. Et_2O (1 mL) was added, and the mixture was washed with an saturated aqueous solution of NH_4Cl (1 mL), and extracted with Et_2O (3 × 1 mL). The combined organics dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:1) afforded title compound **176** as a colouless oil (32 mg, 69%).

$\boldsymbol{R_f}$ 0.40 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 1689, 1530, 1453, 1334, 1258, 1063, 859, 836, 764, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.52 (t, *J* = 7.1 Hz, 1H,

3-H), 4.40 (s, 1H, N*H*), 4.11 (t, *J* = 8.4 Hz, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 4.00 (s, 2H, 1-H$_2$), 3.75 (s, 1H, 5-H), 2.27 – 2.12 (m, 2H, 4-H$_2$), 1.73 (s, 3H, 2-CH$_3$), 1.12 (d, *J* = 6.7 Hz, 3H, 5-CH$_3$), 0.95 (t, *J* = 8.4 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 156.5, 134.5, 126.2, 62.8, 52.05, 46.7, 35.2, 20.6, 17.7, 14.4, −1.5. **HRMS** (ESI+) calc. for $C_{13}H_{26}ClNO_2SiNa$ $[M+Na]^+$ 314.1319, found 314.1326.

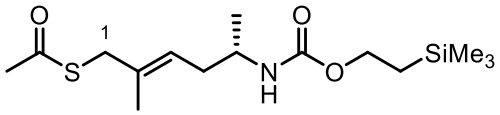
2-(Trimethylsilyl)ethyl (*E*)-(6-bromo-5-methylhex-4-en-2-yl) carbamate, 177



Alcohol **174** (25 mg, 91 µmol, 1.0 eq.) and CBr_4 (38 mg, 0.12 mmol, 1.25 eq.) were dissolved in CH_2Cl_2 (0.25 mL). The mixture was cooled to 0 °C, and PPh_3 (43 mg, 0.16 µmol, 1.8 eq.) was added. The ice bath was removed and the mixture was stirred at ambient temperature for 5.5 h. Purification by column chromatography (solid load, petroleum ether / Et_2O, 4:1, 200 mL) afforded title compound **177** as a colourless oil (27 mg, 87%).

***R*$_f$** 0.33 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 1690, 1530, 1453, 1332, 1249, 1060, 859, 836, 768, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.58 (t, *J* = 7.3 Hz, 1H, 3-H), 4.41 (s, 1H, N*H*), 4.11 (t, *J* = 8.4 Hz, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.94 (s, 2H, 1-H$_2$), 3.75 (m, 1H, 5-H), 2.18 (dd, *J* = 12.1, 6.4 Hz, 2H, 4-H$_2$), 1.74 (s, 3H, 2-CH$_3$), 1.11 (d, *J* = 6.7 Hz, 3H, 5-CH$_3$), 0.94 (t, *J* = 8.4 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.0, 134.7, 126.7, 62.8, 46.7, 41.1, 35.4, 20.6, 17.7, 14.9, −1.5; **HRMS** (ESI+) calc. for $C_{13}H_{26}BrNO_2SiNa$ $[M+Na]^+$ 358.0808, found 358.0813.

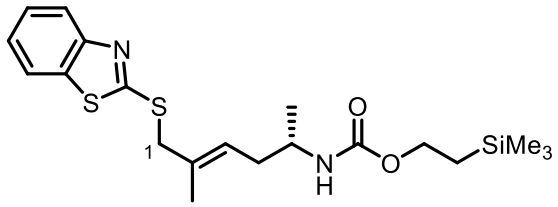
(*E*)-*S*-(2-Methyl-5-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)hex-2-en-1-yl) ethanethioate, 184



Triphenylphosphine (189 mg, 721 µmol) and DBAD (147 mg, 638 µmol) were dissolved in THF (1.0 mL) at 0 °C. A cooled solution of alcohol **174** and thioacetic acid in THF (3.0 mL) were added. The ice bath was removed and the mixture was stirred for 72 h. After concentration *in vacuo* purification by column chromatography (petroleum ether / Et_2O, 3:1) afforded the title compound **184** as a colourless oil (181 mg, 81%).

***R**f* 0.65 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 1689, 1453, 1332, 1250, 1060, 858, 835, 770, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.40 (t, *J* = 7.1 Hz, 1H, 3-H), 4.41 (s, 1H, N*H*), 4.11 (t, *J* = 8.3 Hz, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.78 – 3.67 (m, 1H, 5-H), 3.52 (s, 2H, 1-H$_2$), 2.31 (s, 3H, COC*H*$_3$), 2.18 – 2.11 (m, 2H, 4-H$_2$), 1.62 (s, 3H, 2-CH$_3$), 1.09 (d, *J* = 6.6 Hz, 3H, 5-CH$_3$), 0.95 (t, *J* = 8.3 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.7, 134.7, 133.5, 124.5, 62.9, 38.3, 35.3, 30.7, 30.6, 20.6, 17.9, 15.5, −1.3; **HRMS** (ESI+) calc. for $C_{15}H_{29}NO_3SSiNa$ $[M+Na]^+$ 354.1535, found 354.1240.

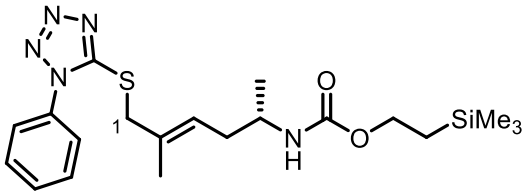
2-(Trimethylsilyl)ethyl (*E*)-(6-(benzo[d]thiazol-2-ylthio)-5-methylhex-4-en-2-yl)carbamate, 178



Triphenylphosphine (49 mg, 0.19 mmol, 1.15 eq.), mercaptobenzothiazole (30 mg, 0.18 mmol, 1.1 eq.) and alcohol **174** (45 mg, 0.17 mmol, 1.0 eq.) were dissolved in THF (1.0 mL) under argon atmosphere. After stirring for 20 min DIAD (36 mg, 178 µmol, 1.1 eq.) in THF (0.5 mL) was added, and the mixture was heated at 40 °C for 48 h. Concentration *in vacuo* and purification by column chromatography (petroleum ether / Et_2O, 7:3 → 3:7) afforded the title compound **178** as a colourless oil (40 mg, 59%).

***R*$_f$** 0.22 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3326, 2953, 1695, 1528, 1457, 1427, 1331, 1249, 1060, 992, 936, 859, 837, 756, 727, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.85 (dd, *J* = 8.1, 0.5 Hz, 1H, Ar*H*), 7.73 (dd, *J* = 8.0, 0.6 Hz, 1H, Ar*H*), 7.39 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H, Ar*H*), 7.27 (ddd, *J* = 8.4, 7.4, 1.2 Hz, 1H, Ar*H*), 5.56 (t, *J* = 7.1 Hz, 1H, 3-H), 4.42 (d, *J* = 6.5 Hz, 1H, NH), 4.08 (t, *J* = 8.3 Hz, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_2$), 3.96 (d, *J* = 2.4 Hz, 2H, 4-H$_2$), 3.72 (m, 1H, 5-H), 2.18 (t, *J* = 6.6 Hz, 2H, 1-H$_2$), 1.76 (s, 3H, 2-CH$_3$), 1.01 (d, *J* = 6.7 Hz, 3H, 5-CH$_3$), 0.92 (t, *J* = 8.3 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_2$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.6, 156.0, 153.1, 135.2, 132.4, 126.0, 125.8, 124.2, 121.5, 120.9, 62.7, 46.7, 42.9, 35.1, 20.3, 17.7, 15.5, −1.5; **HRMS** (ESI+) calc. for $C_{20}H_{30}N_2O_2S_2SiNa$ $[M+Na]^+$ 445.1416, found 445.1419.

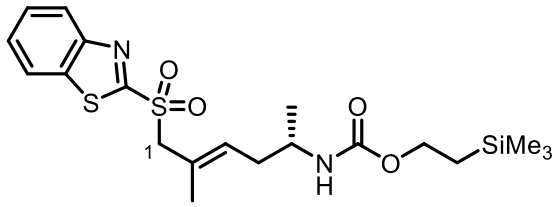
2-(Trimethylsilyl)ethyl (*S*,*E*)-(5-methyl-6-((1-phenyl-1*H*-tetrazol-5-yl)thio)hex-4-en-2-yl)carbamate, 179



Sodium hydride (25 mg, 60% w/w in mineral oil, 0.63 mmol, 2.1 eq.) and 1-phenyl-1*H*-tetrazole-5-thiole (106 mg, 0.60 mmol, 2.0 eq.) were dissolved in DMF (0.2 mL) at 0 °C and stirred for 30 min. Bromide **177** (100 mg, 0.30 mmol, 1.0 eq.) in DMF (0.2 mL) was added and the resulting mixture was stirred for 1 h. Water (20 mL) was added and the mixture was extracted with Et_2O (4 × 15 mL). The combined organics were washed with saturated aqueous NH_4Cl (20 mL), brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **179** as a colourless oil (90 mg, 70%).

***R*$_f$** 0.35 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3328, 2953, 1700, 1597, 1500, 1385, 1331, 1249, 1059, 860, 837, 762, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58 – 7.47 (m, 5H, Ar*H*), 5.57 (t, *J* = 7.0 Hz, 1H, 3-H), 4.44 (s, 1H, N*H*), 4.17 – 4.04 (m, 2H, C*H*$_2$CH$_2$Si(CH$_3$)$_3$), 4.01 (s, 2H, 1-H$_2$), 3.71 (m, 1H, 5-H), 2.19 – 2.10 (m, 2H, 4-H$_2$), 1.71 (s, 3H, 2-C*H*$_3$), 1.06 (d, *J* = 6.7 Hz, 3H, 5-C*H*$_3$), 0.98 – 0.88 (m, 2H, CH$_2$C*H*$_2$Si(CH$_3$)$_3$), −0.01 (s, 9H, Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.0, 154.0, 133.7, 131.5, 130.1, 129.7, 126.9, 123.9, 62.8, 46.7, 42.7, 35.1, 20.3, 17.7, 15.4, −1.5. **HRMS** (ESI+) calc. for $C_{20}H_{31}N_5O_2SSiNa$ $[M+Na]^+$ 456.1860, found 456.1863.

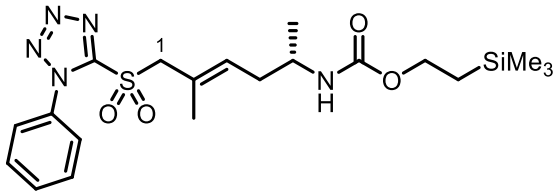
2-(Trimethylsilyl)ethyl (*S*,*E*)-(6-(benzo[d]thiazol-2-ylsulfonyl)-5-methylhex-4-en-2-yl)carbamate, 180



A solution of $(NH_4)_6Mo_7O_{24}$•4 H_2O (13 mg, 11 µmol, 0.20 eq.) in H_2O_2 (48 µL 30%, 0.47 mmol, 10.0 eq.) was added to a stirred solution of sulfide **177** (20 mg, 47 µmol, 1.0 eq.) in ethanol (0.3 mL) and stirred at ambient temperature overnight. Water (2 mL) was added and the mixture was extracted with Et_2O (4 × 2 mL). The combined organics were washed with aqueous $NaHCO_3$ (2 mL), dried over $MgSO_4$, concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **180** as a colourless oil (20 mg, 91%).

***R*$_f$** 0.10 (petroleum ether / Et_2O, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.24 – 8.18 (m, 1H, Ar*H*), 8.02 – 7.96 (m, 1H, Ar*H*), 7.65 – 7.53 (m, 2H, Ar*H*), 5.40 (t, *J* = 7.2 Hz, 1H, 3-H), 4.33 (s, 1H, N*H*), 4.16 (s, 2H, 1-H_2), 4.11 – 4.02 (m, 2H, O*C*$H_2$$CH_2Si(CH_3)_3$), 3.59 (m, 1H, 5-H), 2.15 (dd, *J* = 7.5, 4.8 Hz, 2H, 4-H_2), 1.82 (s, 3H, 2-CH_3), 0.96 – 0.89 (m, 2H, OCH_2C*H*$_2$$Si(CH_3)_3$), 0.85 (d, *J* = 6.7 Hz, 3H, 5-C*H*$_3$), 0.00 (s, 9H, $Si(CH_3)_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.7, 155.9, 152.7, 136.8, 133.1, 128.0, 127.7, 125.4, 124.9, 122.3, 64.4, 62.8, 46.4, 35.2, 19.9, 17.7, 17.1, −1.5. **HRMS** (ESI+) calc. for $C_{20}H_{30}N_2O_4S_2SiNa$ $[M+Na]^+$ 477.1314, found 477.1307.

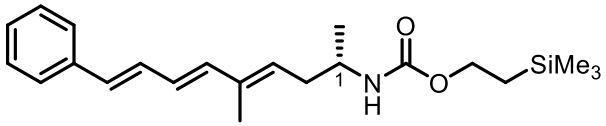
2-(Trimethylsilyl)ethyl (*S*,*E*)-(5-methyl-6-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)hex-4-en-2-yl)carbamate, 181



Sulfide **179** (86 mg, 0.20 mmol, 1.0 eq) was dissolved in ethanol (1.2 mL). A solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (49 mg, 40 µmol, 0.2 eq) and H_2O_2 (60 µL, 2.0 mmol, 10 eq., 30% in water) was added and the resulting mixture was stirred at ambient temperature for 36 h. The mixture was partitioned between water (20 mL) and Et_2O (20 mL). The aqueous layer was acidified to pH ≈ 3 with 1 M HCl / aq. sat. NH_4Cl (1:1) and extracted with Et_2O (3 × 20 mL). The combined organics were washed with aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:1→2:1→1:1) afforded the title compound **181** as a colourless oil (65 mg, 70%).

***R*$_f$** 0.42 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3334, 2954, 1700, 1499, 1458, 1343, 1250, 1153, 1061, 860, 838, 763, 690, 643; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.65 – 7.54 (m, 5H, Ar*H*), 5.64 (t, *J* = 7.1 Hz, 1H, 3-H), 4.42 (s, 1H, N*H*), 4.38 (s, 2H, 1-H_2), 4.14 – 4.05 (m, 2H, OC*H*$_2$$CH_2Si(CH_3)_3$), 3.73 (m, 1H, 5-H), 2.25 (t, *J* = 6.1 Hz, 2H, 4-H_2), 1.82 (s, 3H, 2-CH_3), 1.06 (d, *J* = 6.7 Hz, 3H, 5-CH_3), 0.93 (t, *J* = 8.3 Hz, 2H, OCH_2C*H*$_2$$Si(CH_3)_3$), 0.00 (s, 9H, Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.0, 153.5, 134.9, 133.0, 131.4, 129.6, 125.2, 123.0, 65.5, 62.9, 46.5, 35.5, 20.3, 17.7, 17.4, −1.5. **HRMS** (ESI+) calc. for $C_{20}H_{31}O_4N_5SSiNa$ ($[M+Na]^+$): 488.1758; found: 488.1749.

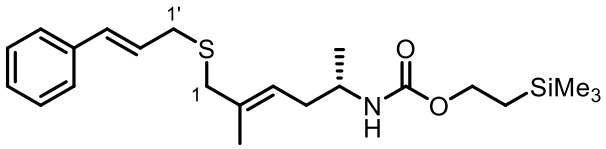
2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*)-5-methyl-9-phenylnona-4,6,8-trien-2-yl)carbamate, 183



An oven dried flask under argon was charged with a solution of sulfone **180** (20 mg, 44 µmol, 1.0 eq.) and cinnamaldehyde (6 µL, 48 µmol, 1.1 eq.) in THF (1.8 mL). The mixture was cooled to −78 °C and LiHMDS (138 µL, 1 M in THF, 3.0 eq.) was added. The mixture was stirred for 2 h at this temperature and for 45 min at ambient temperature. Another portion of LiHMDS (46 µL, 1 m in THF, 1.0 eq.) was added and the reaction stirred at ambient temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (3 mL), extracted with CH_2Cl_2 (3 × 6 mL), and the combined organics dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O 5:1) afforded the title compound **183** as a yellowish liquid (4 mg, 27%).

$\boldsymbol{R_f}$ = 0.67 (petroleum ether / Et_2O, 1:1). **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3328, 2955, 2926, 1695, 1529, 1450, 1334, 1250, 1178, 1063, 986, 860, 837, 748, 692. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.29 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.18 (t, *J* = 7.0 Hz, 1H, Ar*H*), 6.81 (dd, *J* = 15.5, 8.5 Hz, 1H, 6-H), 6.54 (d, *J* = 15.5 Hz, 1H, 5-H), 6.39–6.27 (m, 2H, 7-H, 8-H), 5.53 (t, *J* = 7.5 Hz, 1H, 3-H), 4.42 (s, 1H, NH), 4.17–4.08 (m, 2H, OC$H_2$$CH_2Si(CH_3)_3$), 3.79 (s, 1H, 1-H), 2.38–2.29 (m, 2H, 2-H_2), 1.80 (s, 3H, 4-CH_3), 1.14 (d, *J* = 6.6 Hz, 3H, 1-CH_3), 0.99–0.92 (m, 2H, OCH_2C$H_2Si(CH_3)_3$), 0.02 (s, 9H, Si(CH_3)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.1, 137.9, 137.6, 136.4, 131.7, 129.6, 128.7, 128.6, 127.3, 127.3, 126.3, 126.2, 62.9, 47.1, 20.7, 17.8, 12.6, −1.5. **HRMS** (ESI+) calc. for $C_{22}H_{33}NO_2SiNa$ $[M+Na]^+$ 394.2178, found 394.2186.

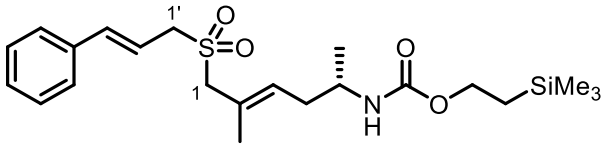
2-(Trimethylsilyl)ethyl ((*E*)-6-(cinnamylthio)-5-methylhex-4-en-2-yl)carbamate, 185



Thioester **184** (20 mg, 60 µmol, 1.0 eq.), cinnamyl bromide (14 µL, 95 µmol, 1.6 eq.) and KOH (17 mg, 0.30 mmol, 5.0 eq.) were dissolved in degassed MeOH (0.3 mL) and stirred at ambient temperature for 1 h. Water (2 mL) was added and the mixture was extracted with EtOAc (3 × 3 mL). The combined organics were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 15:1) afforded the title compound **185** as a colourless oil (24 mg, 98%).

***R**f* 0.23 (petroleum ether / EtOAc, 15:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3329, 2953, 1693, 1450, 1331, 1249, 1059, 963, 859, 836, 751, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 – 7.33 (m, 2H, Ar*H*), 7.31 – 7.26 (m, 2H, Ar*H*), 7.20 (tt, *J* = 7.1, 1.6 Hz, 1H, Ar*H*), 6.39 (d, *J* = 15.7 Hz, 1H, 3'-H), 6.14 (dt, *J* = 15.7, 7.3 Hz, 1H, 2'-H), 5.27 (t, *J* = 7.2 Hz, 1H, 3-H), 4.42 (s, 1H, N*H*), 4.17 – 4.05 (m, 2H, C*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.80 – 3.69 (m, 1H, 5-H), 3.16 (dd, *J* = 7.3, 1.1 Hz, 2H, 1'-H$_2$), 3.08 (s, 2H, 1-H$_2$), 2.28–2.10 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 1.72 (s, 3H, 2-C*H*$_3$), 1.13 (d, *J* = 6.6 Hz, 3H, 5-C*H*$_3$), −0.01 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.1, 136.8, 133.9, 132.3, 128.5, 127.5, 126.2, 125.9, 123.9, 62.8, 47.0, 40.1, 35.4, 33.1, 20.8, 17.7, 15.4, −1.5; **HRMS** (ESI+) calc. for $C_{22}H_{35}NO_2SSiNa$ $[M+Na]^+$ 428.2050, found 428.2057.

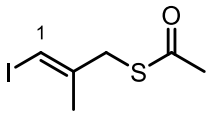
2-(Trimethylsilyl)ethyl ((*E*)-6-(cinnamylsulfonyl)-5-methylhex-4-en-2-yl)carbamate, 186



A solution of $(NH_4)_6Mo_7O_{24}$•4 H_2O (14 mg, 11 µmol, 0.20 eq.) in H_2O_2 (53 µL, 30%, 0.52 mmol, 10 eq.) was added to a solution of sulfide **185** (21 mg, 52 µmol, 1.0 eq.) in ethanol (0.3 mL) and the mixture was stirred for 22 h. Water (8 mL) and Et_2O (8 mL) were added, and extracted with Et_2O (3 × 8 mL); the aqueous layer was acidified with aqueous NH_4Cl to pH 6.5 and then extracted with EtOAc (4 × 10 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 1:1) afforded the title compound **186** as a colourless oil (13 mg, 57%).

***R*$_f$** 0.18 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 1726, 1713, 1688, 1380, 1351, 1250, 1225, 1211; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44 – 7.25 (m, 5H, Ar*H*), 6.68 (d, *J* = 16.0 Hz, 1H, 3'-H), 6.27 – 6.17 (m, 1H, 2'-H), 5.54 (t, *J* = 7.1 Hz, 1H, 3-H), 4.46 (m, 1H, 5-H), 4.17 – 3.99 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.89 – 3.75 (m, 2H, 1'-H$_2$), 3.64 (d, *J* = 4.7 Hz, 2H, 1-H$_2$), 2.27 (t, *J* = 7.1 Hz, 2H, 4-H$_2$), 1.87 (s, 3H, 2-C*H*$_3$), 1.15 (d, *J* = 6.6 Hz, 3H, 5-C*H*$_3$), 0.93 (t, *J* = 8.4 Hz, 2H, CH$_2$C*H*$_2$Si(CH$_3$)$_3$), −0.01 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.1, 139.1, 135.6, 131.8, 128.7, 128.7, 126.7, 126.4, 115.4, 62.9, 61.4, 56.1, 46.8, 35.7, 20.9, 17.7, 17.2, −1.5; **HRMS** (ESI+) calc. for $C_{22}H_{35}NO_4SSiNa$ $[M+Na]^+$ 460.1948, found 460.1953.

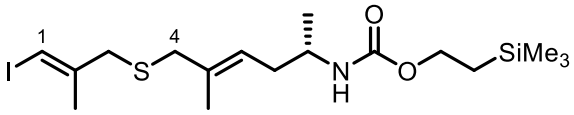
(*E*)-(3-Iodo-2-methylallyl) ethanethioate, 187



Triphenylphosphine (318 mg, 1.21 mmol, 1.2 eq.) and DIAD (238 µL, 1.21 mmol, 1.3 eq.) were dissolved in THF (1.5 mL) at 0 °C. A solution of alcohol **76** (105 µL, 1.01 mmol, 1.0 eq.) and thioacetic acid (95 µL, 1.31 mmol, 1.3 eq.) in THF (3.5 mL) was added dropwise and the mixture was stirred at ambient temperature overnight, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O 9:1) afforded the title compound **187** as a colourless oil (217 mg, 84%).

$\boldsymbol{R_f}$ 0.80 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 1692, 1353, 1276, 1129, 956, 790, 704, 659, 630; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 5.98 (app dd, J = 2.0, 1.1 Hz, 1H, 1-H), 3.32 (d, J = 0.8 Hz, 2H, 3-H_2), 1.74 (s, 3H, COCH_3), 1.65 (d, J = 1.1 Hz, 3H, 2-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 193.5, 143.4, 80.1, 36.6, 30.2, 23.0; **HRMS** (ESI+) calc. for C_6H_9IOSNa $[M+Na]^+$ 278.9317, not found.

2-(Trimethylsilyl)ethyl ((*E*)-6-(((*E*)-3-iodo-2-methylallyl)thio)-5-methylhex-4-en-2-yl)carbamate, 188

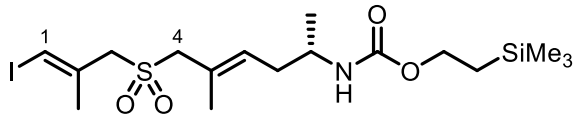


Thioester **187** (90 mg, 0.35 mmol, 1.0 eq.), bromide **177** (142 mg, 422 µmol, 1.2 eq.) and KOH (99 mg, 1.8 mmol, 5.0 eq.) were dissolved in methanol (1.5 mL), and stirred at ambient temperature for 1 h. The mixture was partitioned between water (20 mL) and ethyl acetate (20 mL), extracted with EtOAc (3 × 30 mL), and the combined organics were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by column chromatography (petroleum ether / ethyl acetate, 15:1) afforded the title compound **188** as a light green oil (158 mg, 96%).

***R*$_f$** 0.12 (petroleum ether / ethyl acetate, 15:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2952, 1691, 1511, 1452, 1330, 1249, 1059, 936, 859, 836, 776, 694, 656; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.01 (app d, *J* = 0.9 Hz, 1H, 1-H), 5.21 (t, *J* = 6.9 Hz, 1H, 6-H), 4.37 (s, 1H, N*H*), 4.15 – 4.05 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.71 (m, 1H, 8-H), 3.11 (d, *J* = 0.8 Hz, 2H, 3-H$_2$), 2.96 (s, 2H, 4-H$_2$), 2.17 (t, *J* = 6.8 Hz, 2H, 7-H$_2$), 1.89 (d, *J* = 1.0 Hz, 3H, 2-CH$_3$), 1.67 (s, 3H, 5-CH$_3$), 1.11 (d, *J* = 6.6 Hz, 3H, 8-CH$_3$), 0.93 (t, *J* = 8.3 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.00 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 143.8, 133.6, 124.1, 77.5, 47.0, 40.4, 38.7, 35.4, 22.9, 20.9, 17.8, 15.3, −1.5;[1] **HRMS** (ESI$^+$) calc. for $C_{17}H_{32}O_2NISSiNa$ ([M+Na]$^+$): 492.0860; found: 492.0845.

2-(Trimethylsilyl)ethyl ((*S*,*E*)-6-(((*E*)-3-iodo-2-methylallyl)sulfonyl)-5-methylhex-4-en-2-yl)carbamate, 189



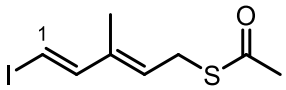
Sulfide **188** (140 mg, 298 µmol, 1.0 eq) was dissolved in ethanol (1.8 mL). A solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (74 mg, 64 µmol, 0.2 eq) and H_2O_2 (89 µL, 3.0 mmol, 10 eq., 30% in water) was added and the resulting mixture was stirred at ambient temperature for 36 h. The mixture was partitioned between water (20 mL) and Et_2O (20 mL). The aqueous layer was acidified to pH ≈ 3 with 1 M HCl / aq. sat. NH_4Cl (1:1) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography

[1] Signals for quarternary carbons C2 and C5 are not visible.

(petroleum ether / Et_2O, 1:1) afforded the title compound **189** as a colourless oil (125 mg, 84%).

***R**f* 0.10 (petroleum ether / ethyl acetate, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3301, 2953, 1697, 1533, 1453, 1331, 1250, 1177, 1052, 860, 837, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.34 (d, *J* = 0.9 Hz, 1H, 1-H), 5.45 (t, *J* = 7.2 Hz, 1H, 6-H), 4.50 (s, 1H, N*H*), 3.13 – 4.03 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.76 (m, 1H, 8-H), 3.49 (d, *J* = 5.6 Hz, 2H, 3-H$_2$), 3.34 (s, 2H, 4-H$_2$), 2.23 (t, *J* = 6.7 Hz, 2H, 7-H$_2$), 1.98 (d, *J* = 1.1 Hz, 3H, 2-CH$_3$), 1.76 (d, *J* = 4.4 Hz, 3H, 5-CH$_3$), 1.12 (d, *J* = 6.7 Hz, 3H, 8-CH$_3$), 0.97 – 0.90 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.00 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 156.1, 138.1, 129.5, 128.0, 82.7, 63.7, 63.4, 61.9, 46.8, 35.4, 24.5, 20.7, 17.8, 17.3, −1.5; **HRMS** (ESI+) calc. for $C_{17}H_{32}INO_4SSiNa$ $[M+Na]^+$ 524.0764, not found.

S-((2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-dien-1-yl) ethanethioate, 200

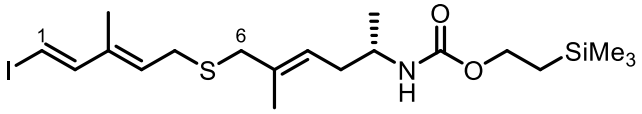


Triphenylphosphine (311 mg, 1.19 mmol, 1.4 eq.) and DIAD (233 µL, 1.19 mmol, 1.4 eq.) were dissolved in THF (2.0 mL) at 0 °C. A solution of alcohol **199** (190 mg, 848 µmol, 1.0 eq.) and thioacetic acid (85 µL, 1.19 mmol, 1.4 eq.) in THF (6.5 mL) was added dropwise. The mixture was allowed to warm to ambient temperature overnight, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 20:1) afforded the title compound **200** as a colourless oil (198 mg, 83%).

***R**f* 0.76 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 1688, 1389, 1353, 1181, 1132, 949, 758, 698, 626; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.80 (d, *J* = 14.7 Hz, 1H, 2-H), 5.90 (d, *J* = 14.7 Hz, 1H, 1-H), 5.16 (t, *J* = 8.1 Hz, 1H, 4-H), 3.34 (d, *J* = 8.1 Hz, 2H, 5-H$_2$),

1.82 (s, 3H, 3-CH_3), 1.32 (s, 3H, COC*H*$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 194.1, 149.2, 137.7, 133.1, 76.5, 30.2, 27.4, 11.9. **HRMS** (FI^+) calc. for $C_8H_{11}IOS$ ($[M]^+$): 281.9575; found: 281.9578.

2-(Trimethylsilyl)ethyl ((*E*)-6-(((2*E*,4*E*)-5-iodo-3-methylpenta-2,4-dien-1-yl)thio)-5-methylhex-4-en-2-yl)carbamate, 203

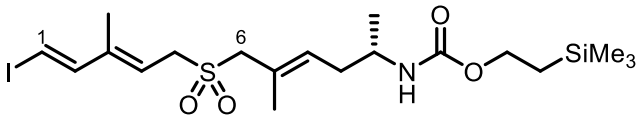


Thioester **200** (198 mg, 702 µmol, 1.0 eq.), bromide **177** (236 mg, 702 µmol, 1.0 eq.) and KOH (197 mg, 3.51 mmol, 5.0 eq.) were dissolved in degassed methanol (3.5 mL) and stirred at ambient temperature for 1 h. The mixture was partitioned between water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), the combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / ethyl acetate, 15:1) afforded the title compound **203** as a light green oil (292 mg, 84%).

***R**$_f$* 0.17 (petroleum ether / EtOAc, 15:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2952, 1701, 1509, 1452, 1330, 1249, 1180, 1059, 949, 858, 836, 759, 695; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.95 (d, *J* = 14.6 Hz, 1H, 2-H), 5.96 (d, *J* = 14.6 Hz, 1H, 1-H), 5.33 (t, *J* = 7.9 Hz, 1H, 4-H), 5.11 (t, *J* = 7.0 Hz, 1H, 8-H), 4.27 (t, *J* = 8.4 Hz, 2H, OC*H*$_2$$CH_2Si(CH_3)_3$), 4.16 (s, 1H, N*H*), 3.80 (m, 1H, 10-H), 2.87 (d, *J* = 7.8 Hz, 2H, 5-H_2), 2.85 (s, 2H, 6-H_2), 2.06 – 1.85 (m, 2H, 9-H_2), 1.62 (s, 3H, 3-CH_3), 1.39 (s, 3H, 7-CH_3), 0.99 (t, *J* = 8.4 Hz, 2H, OCH_2C*H*$_2$$Si(CH_3)_3$), 0.88 (d, *J* = 6.6 Hz, 3H, 10-CH_3), −0.05 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 156.3, 149.6, 137.0, 134.3, 130.4, 124.6, 75.8, 63.1, 47.6,

41.5, 36.0, 28.7, 21.0, 18.5, 15.6, 12.1, −1.1; **HRMS** (ESI+) calc. for $C_{19}H_{34}INO_2SSiNa$ $[M+Na]^+$ 518.1022, not found.

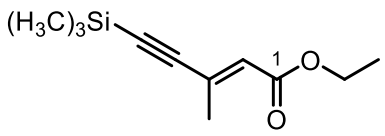
2-(Trimethylsilyl)ethyl ((*E*)-6-(((2*E*,4*E*)-5-iodo-3-methylpenta-2,4-dien-1-yl)sulfonyl)-5-methylhex-4-en-2-yl)carbamate, 206



Sulfide **203** (276 mg, 557 µmol, 1.0 eq) was dissolved in ethanol (3.6 mL) and a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (153 mg, 124 µmol, 0.2 eq) and H_2O_2 (0.62 mL, 5.6 mmol, 10 eq., 30% in water) was added and the resulting mixture was stirred at ambient temperature for 36 h. The mixture was separated between water (50 mL) and Et_2O (50 mL). The aqueous layer was acidified to pH ≈ 3 with 1 M HCl / aq. sat. NH_4Cl (1:1) and extracted with Et_2O (3 × 50 mL). The combined organics were washed with aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 1:1) afforded title compound **206** as a colourless oil (204 mg, 61%).

***R**f* 0.26 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 1700, 1519, 1479, 1310, 1249, 1118, 1060, 950, 836, 759, 678; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.92 (d, J = 14.7 Hz, 1H, 2-H), 6.10 (d, J = 14.7 Hz, 1H, 1-H), 5.29 (t, J = 7.9 Hz, 1H, 4-H), 5.24 (t, J = 7.1 Hz, 1H, 8-H), 4.42 – 4.14 (m, 3H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$, N*H*), 3.84 (m, 1H, 10-H), 3.37 (t, J = 6.2 Hz, 2H, 5-H$_2$), 3.16 (s, 2H, 6-H$_2$), 1.94 (t, J = 6.8 Hz, 2H, 9-H$_2$), 1.75 (s, 3H, 3-CH$_3$), 1.38 (s, 3H, 7-CH$_3$), 1.04 (t, J = 8.4 Hz, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.89 (d, J = 6.6 Hz, 3H, 10-CH$_3$), 0.00 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 156.0, 149.2, 136.7, 134.0, 130.0, 124.3, 75.5, 62.8, 47.3, 41.1, 35.7, 28.4, 20.7, 18.2, 15.3, 11.8, −1.5; **HRMS** (ESI^+) calc. for $C_{19}H_{34}O_4NISSiNa$ ($[M+Na]^+$): 550.0915; found: 550.0903.

Ethyl (*E*)-3-methyl-5-(trimethylsilyl)pent-2-en-4-ynoate, 193

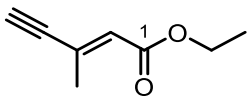


$Pd(OAc)_2$ (210 mg, 935 µmol, 3.5 mol%), and TDMPP (405 mg, 915 µmol, 3.5 mol%) were dissolved in THF (30 mL) and stirred at ambient temperature for 15 min, before ethyl but-2-ynoate (3.00 g, 26.8 mmol) was added, stirred for 5 min, followed by addition of ethynyl trimethylsilane (2.95 g, 30.0 mmol, 1.1 eq.). After stirring for 1 h, the mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 100:2) afforded title compound **193** as a yellow oil (3.27 g, 58%).

R*f* 0.68 (petroleum ether / EtOAc, 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.09 (q, J = 1.5 Hz, 1H, 2-H), 4.16 (q, J = 7.1 Hz, 3H, OCH_2CH_3), 2.27 (d, J = 1.5 Hz, 3H, 3-CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.20 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.2, 137.6, 125.2, 106.6, 99.3, 60.2, 19.8, 14.4, −0.2.

The spectroscopic data is in agreement with that reported by Waser.[335]

Ethyl (*E*)-3-methylpent-2-en-4-ynoate, 194



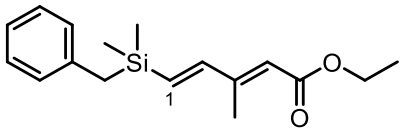
A solution of TMS-protected enyne **193** (1.29 g, 6.13 mmol, 1.0 eq.) in CH_2Cl_2 (19 mL) was added to TBAF·$3H_2O$ (450 mg, 1.43 mmol, 0.25 eq.). This mixture was stirred for 20 min at ambient temperature. It was quenched with water (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column

chromatography (petroleum ether / Et_2O 24:1) afforded the title compound **194** as a colourless oil (783 mg, 92%).

***R**f* 0.39 (petroleum ether / Et_2O, 24:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_C 6.11 (d, J = 1.0 Hz, 1H, 2-H), 4.16 (q, J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.16 (s, 1H, 5-H), 2.27 (d, J = 1.0 Hz, 3H, 3-C*H*$_3$), 1.26 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.7, 136.5, 126.0, 85.2, 81.1, 60.2, 19.5, 14.2.

The spectroscopic data is in agreement with that reported by Diaz and Bernardon.[336]

Ethyl (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dienoate, 196

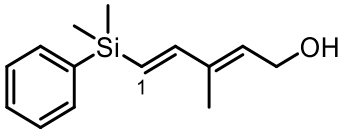


$PtCl_2$ (5 mg, 18 µmol, 5 mol%) and XPhos (17 mg, 36 µmol, 10 mol%) were dissolved in THF (0.1 mL) and stirred at 60 °C for 15 min. To enyne **194** (40 mg, 0.29 mmol, 1.0 eq.) in THF (0.1 mL) was added. Subsequently, benzyldimethylsilane (86 µL, 0.54 mmol, 1.5 eq.) was added dropwise, and the mixture stirred at 60 °C for 1 h, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1) afforded title compound **196** as a colourless oil (68 mg, 82%).

***R**f* 0.21 (petroleum ether / Et_2O, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 1713, 1618, 1493, 1451, 1233, 1207, 1150, 10445, 986, 831, 760, 698, 624; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20 (t, J = 7.4 Hz, 2H, Ar*H*), 7.07 (t, J = 7.4 Hz, 1H, Ar*H*), 6.98 (d, J = 7.4 Hz, 2H, Ar*H*), 6.51 (d, J = 18.9 Hz, 1H, 2-H), 6.28 (d, J = 18.9 Hz, 1H, 1-H), 5.79 (s, 1H, 4-H), 4.18 (q, J = 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 2.24 (d, J = 0.6 Hz, 3H, 3-CH$_3$), 2.17 (s, 2H, SiC*H*$_2$Ph), 1.28 (t, J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.10 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C

167.1, 152.3, 147.6, 139.4, 134.2, 128.2, 128.2, 124.1, 120.5, 59.7, 25.8, 14.3, 13.2, −3.6; **HRMS** (ESI+) calc. for $C_{17}H_{25}O_2Si^+$ $[M+H]^+$ 289.1618, found 289.1612.

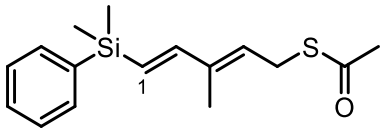
(2*E*,4*E*)-5-(Dimethyl(phenyl)silyl)-3-methylpenta-2,4-dien-1-ol, 197



DIBALH (0.77 mL, 1.0 M in hexanes, 770 µmol, 2.1 eq.) was added dropwise to a solution of ester **195** (100 mg, 364 µmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) at 0 °C. The mixture was allowed to warm to ambient temperature. After stirring for 30 min, the mixture was cooled to 0 °C, and was quenched by subsequent addition of water (0.03 mL), aq. NaOH (15 wt%, 0.03 mL) and water (0.08 mL). The mixture was stirred for 30 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **197** as a colourless oil (72 mg, 82%).

***R*$_f$** 0.43 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3328, 2955, 1582, 1493, 1452, 1247, 1206, 1153, 1058, 986, 833, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 – 7.39 (m, 2H, Ar*H*), 7.30 – 7.22 (m, 3H, Ar*H*), 6.53 (d, *J* = 18.9 Hz, 1H, 2-H), 5.90 (d, *J* = 18.9 Hz, 1H, 1-H), 5.63 (t, *J* = 6.7 Hz, 1H, 4-H), 4.21 (d, *J* = 6.7 Hz, 2H, 5-H_2), 1.71 (s, 3H, 3-CH_3), 0.29 (s, 6H, Si(C*H*$_3$)$_2$Ph). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 149.2, 138.7, 137.3, 133.8, 131.7, 128.9, 127.7, 126.2, 59.5, 12.0, −2.5. **HRMS** (ESI+) calc. for $C_{14}H_{20}OSiNa$ $[M+Na]^+$ 255.1181, found 255.1185.

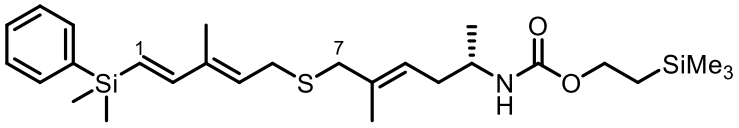
_S_-((2_E_,4_E_)-5-(Dimethyl(phenyl)silyl)-3-methylpenta-2,4-dien-1-yl) ethanethioate, 201



Under inert gas atmosphere, PPh_3 (66 mg, 0.25 mmol, 1.3 eq.) was dissolved in THF (0.6 mL), cooled to 0 °C and DIAD (50 µL, 0.25 mmol, 1.3 eq.) added dropwise. A solution of alcohol **198** (45 mg, 0.19 mmol, 1.0 eq.) and AcSH (20 µL, 0.28 mmol, 1.4 eq.) in THF (1.4 mL) was added dropwise, and the resulting was mixture stirred at ambient temperature overnight, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 100:1) afforded title compound **201** as a colourless oil (47 mg, 82%, 5:1 mixture of *E,E* / *E,Z*).

Analytical data for the major isomer. $\boldsymbol{R_f}$ 0.68 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 1691, 1580, 1492, 1451, 1357, 1250, 1206, 1132, 985, 957, 832, 762, 699, 626; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46 – 7.40 (m, 3H, Ar*H*), 7.27 (d, *J* = 2.0 Hz, 2H, Ar*H*), 6.49 (d, *J* = 18.9 Hz, 1H, 2-H), 5.87 (d, *J* = 18.9 Hz, 1H, 1-H), 5.50 (t, *J* = 8.0 Hz, 1H, 4-H), 3.59 (d, *J* = 8.0 Hz, 2H, 5-H_2), 2.24 (s, 3H, COC*H*$_3$), 1.74 (s, 3H, 3-CH_3), 0.28 (s, 6H, Si(C*H*$_3$)$_2$Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 195.4, 149.0, 138.5, 133.9, 129.0, 127.8, 127.8, 127.4, 126.1, 30.4, 27.5, 11.9, −2.5; **HRMS** (ESI+) calc. for $C_{16}H_{22}OSSiNa$ $[M+Na]^+$ 313.1058, found 313.1055.

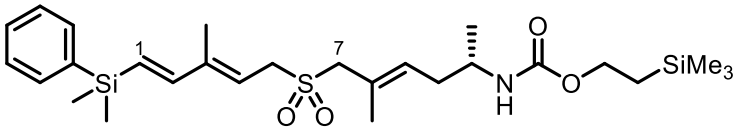
2-(Trimethylsilyl)ethyl ((*S*,*E*)-6-(((2*E*,4*E*)-5-(dimethyl(phenyl)silyl)-3-methylpenta-2,4-dien-1-yl)thio)-5-methylhex-4-en-2-yl)carbamate, 204



Thioester **201** (46 mg, 158 µmol, 1.0 eq.), bromide **177** (53 mg, 158 µmol, 1.0 eq.) and KOH (44 mg, 784 µmol, 5.0 eq.) were dissolved in degassed methanol (0.8 mL) and stirred at ambient temperature for 1 h. The mixture was partitioned between water (10 mL) and EtOAc (10 mL), and extracted with EtOAc (3 × 10 mL).The combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 15:1) afforded title compound **204** as a colourless oil (62 mg, 79%).

R_f 0.20 (petroleum ether / EtOAc, 15:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 1701, 1509, 1427, 1331, 1249, 1114, 1060, 986, 838, 733, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49 (s, 2H, $Si(CH_3)_2Ph$), 7.32 (d, J = 2.1 Hz, 3H, $Si(CH_3)_2Ph$), 6.57 (d, J = 18.9 Hz, 1H, 2-H), 5.88 (d, J = 18.9 Hz, 1H, 1-H), 5.57 (t, J = 7.9 Hz, 1H, 4-H), 5.25 (t, J = 7.0 Hz, 1H, 9-H), 4.40 (s, 1H, N*H*), 4.14 – 4.06 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 3.71 (m, 1H, 11-H), 3.12 (d, J = 7.9 Hz, 2H, 5-H_2), 3.06 (s, 2H, 7-H_2), 2.21 – 2.10 (m, 2H; 10-H_2), 1.75 (s, 3H, 3-CH_3), 1.70 (s, 3H, 8-CH_3), 1.10 (d, J = 6.6 Hz, 3H, 11-CH_3), 0.97 – 0.90 (m, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.34 (s, 6H; $Si(CH_3)_2Ph$), 0.00 (s, 9H; $OCH_2CH_2Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.0, 149.3, 141.1, 138.8, 137.5, 133.8, 129.5, 128.9, 127.7, 125.2, 123.6, 62.7, 46.9, 41.0, 35.4, 28.8, 20.7, 17.7, 15.3, 11.9, −1.5, −2.5; **HRMS** (ESI+) calc. for $C_{27}H_{45}NO_2SSi_2Na$ $[M+Na]^+$ 526.2602, found 526.2593.

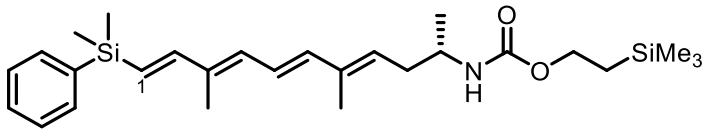
2-(Trimethylsilyl)ethyl ((*E*)-6-(((2*E*,4*E*)-5-(dimethyl(phenyl)silyl)-3-methylpenta-2,4-dien-1-yl)sulfonyl)-5-methylhex-4-en-2-yl)carbamate, 207



Sulfide **204** (29 mg, 57.6 µmol, 1.0 eq.) was dissolved in ethanol (0.34 mL). A solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (13 mg, 10.5 µmol, 0.20 eq.) in aqueous hydrogen peroxide solution (30%, 57 µL, 58.0 mmol, 10.0 eq.) was added to this mixture and stirred for 36 h at ambient temperature. The mixture was partitioned between EtOAc (5 mL) and water (5 mL). The aqueous layer was acidified to pH=3 with 1 M HCl solution, and extracted with EtOAc (3 ×5 mL). The combined organics were washed with aqueous $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / diethyl ether, 1:1) afforded the title compound **207** as a colourless oil (11 mg, 37%).

***R**f* 0.29 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 1726, 1713, 1688, 1380, 1351, 1250, 1225, 1211; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.56 – 7.50 (m, 2H, $Si(CH_3)_2$*Ph*), 7.26 – 7.20 (m, 3H, $Si(CH_3)_2$*Ph*), 6.73 (d, *J* = 18.9 Hz, 1H, 2-H), 6.06 (d, *J* = 18.9 Hz, 1H, 1-H), 5.58 (t, *J* = 7.8 Hz, 1H, 4-H), 5.19 (t, *J* = 7.2 Hz, 1H, 9-H), 4.33 – 4.15 (m, 3H, $OCH_2CH_2Si(CH_3)_3$, N*H*), 3.81 (m, 1H, 11-H), 3.54 – 3.42 (m, 2H, 5-H_2), 3.14 (d, *J* = 3.2 Hz, 2H, 7-H_2), 1.90 (dd, *J* = 6.8, 6.8 Hz, 2H, 10-H_2), 1.70 (s, 3H, 3-CH_3), 1.64 (s, 3H, 8-CH_3), 0.99 (t, *J* = 8.3 Hz, 2H, $OCH_2CH_2Si(CH_3)_3$), 0.85 (d, *J* = 6.6 Hz, 3H, 11-CH_3), 0.35 (s, 6H, $Si(CH_3)_2Ph$), −0.06 (s, 9H, $OCH_2CH_2Si(CH_3)_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 156.1, 148.8, 143.0, 138.5, 134.3, 134.3. 131.4, 129.5, 126.8, 119.3, 62.8, 62.2, 52.6, 46.9, 35.7, 30.5, 20.6, 18.2, 17.1, 12.7, −1.5, −2.4; **HRMS** (ESI+) calc. for $C_{27}H_{45}NO_4SSi_2Na$ $[M+Na]^+$ 558.2511, found 558.2494.

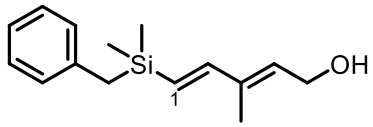
2-(Trimethylsilyl)ethyl ((4*E*,6*E*,8*E*,10*E*)-11-(dimethyl(phenyl)silyl)-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 209



Sulfone **207** (9 mg, 17 µmol, 1.0 eq.) and KOH·Al_2O_3 (1:3, 35 mg, 0.15 mmol, 9.0 eq) were suspended in CH_2Cl_2 (35 µL) and *t*-BuOH (35 µL). The mixture was cooled to 0 °C and CBr_2F_2 (7 µL, 77 µmol, 4.5 eq.) was added to the stirred suspension. After 1.5 h of stirring at 0 °C the mixture was diluted with EtOAc, filtered over silica, and the solvent removed *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 10:1) afforded title compound **209** as a yellowish oil (2 mg, 28%).

***R**f* 0.76 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3324, 2955, 2360, 1702, 1509, 1428, 1331, 1249, 1113, 1060, 983, 960, 843, 734, 699; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.64 – 7.55 (m, 2H, Si(CH$_3$)$_2$*Ph*), 7.29 – 7.20 (m, 3H, Si(CH$_3$)$_2$*Ph*), 6.88 (d, *J* = 18.9 Hz, 1H, 2-H), 6.57 (dd, *J* = 14.9, 11.3 Hz, 1H, 5-H), 6.31 (d, *J* = 15.1 Hz, 1H, 6-H), 6.23 (d, *J* = 11.1 Hz, 1H, 4-H), 6.08 (d, *J* = 18.9 Hz, 1H, 1-H), 5.45 (t, *J* = 7.8 Hz, 1H, 8-H), 4.33 – 4.27 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 4.10 (s, 1H, N*H*), 3.87 (m, 1H, 10-H), 2.19 – 1.99 (m, 2H, 9-H$_2$), 1.85 (s, 3H, 3-CH$_3$), 1.68 (s, 3H, 7-CH$_3$), 1.03 – 0.96 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.85 (d, *J* = 6.4 Hz, 3H, 10-CH$_3$), 0.42 (d, *J* = 5.7 Hz, 6H, Si(C*H*$_3$)$_2$Ph), −0.06 (s, 9H, OCH$_2$CH$_2$Si(C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, C_6D_6) δ_C 157.7, 152.4, 141.3, 140.9, 138.5, 137.8, 136.1, 135.9, 131.1, 127.1, 125.5, 64.5, 49.1, 32.2, 32.0, 22.3, 19.9, 14.4, 14.2, 0.2, −0.4. **HRMS** (ESI+) calc. for $C_{27}H_{43}NO_2Si_2Na$ $[M+Na]^+$ 492.2725, found 492.2722.

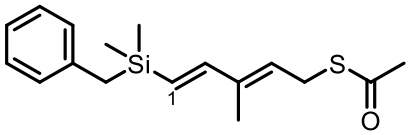
(2*E*,4*E*)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-ol, 198



Ester **196** (64 mg, 0.22 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.6 mL) and the mixture cooled to 0 °C. To this DIBALH (0.47 mL, 1.0 M in hexanes, 0.47 mmol, 2.1 eq.) was added dropwise. After stirring for 20 min. the mixture was diluted with Et_2O (3 mL) and quenched with an aqueous saturated solution of Rochelle's salt (3 mL). This mixture was stirred at ambient temperature for 2 h. The mixture was extracted with Et_2O (3 × 7 mL), the combined organics, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:2) afforded title compound **198** as a colourless oil (48 mg, 88%).

***R**f* 0.12 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3328, 2955, 1581, 1493, 1451, 1247, 1206, 1153, 1056, 987, 832, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.18 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.05 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.98 (d, *J* = 7.4 Hz, 2H, Ar*H*), 6.51 (d, *J* = 19.0 Hz, 1H, 2-H), 5.81 (d, *J* = 19.0 Hz, 1H, 1-H), 5.68 (t, *J* = 6.6 Hz, 1H, 4-H), 4.29 (d, *J* = 6.1 Hz, 2H, 5-H), 2.14 (s, 2H, SiC*H*$_2$Ph), 1.76 (s, 3H, 3-C*H*$_3$), 1.23 (s, 1H, O*H*), 0.05 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 148.6, 139.9, 137.5, 131.4, 128.2, 128.1, 126.6, 124.0, 59.6, 26.2, 12.0, −3.3; **HRMS** (ESI+) calc. for $C_{15}H_{22}OSiNa$ $[M+Na]^+$ 269.1332, found 269.1332.

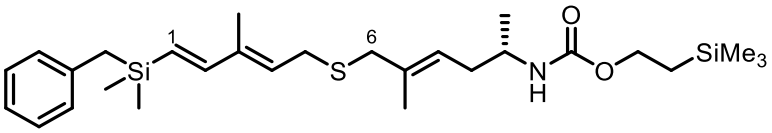
_S_-((2_E_,4_E_)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-yl) ethanethioate, 202



Under inert gas atmosphere, PPh_3 (60 mg, 0.23 mmol, 1.3 eq.) was dissolved in THF (0.5 mL). The solution was cooled to 0 °C and DIAD (45 µL, 0.23 mmol, 1.3 eq.) was added dropwise. To this a solution of alcohol **198** (43 mg, 0.19 mmol, 1.0 eq.) and AcSH (18 µL, 0.25 mmol, 1.4 eq.) in THF (1.3 mL) was added dropwise. The mixture was stirred overnight and allowed to reach ambient temperature, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 100:1) afforded the title compound **202** as a colourless oil (47 mg, 83%).

R_f_ 0.72 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 1692, 1580, 1493, 1451, 1354, 1248, 1206, 1132, 985, 956, 832, 761, 699, 626; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.18 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.05 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.97 (d, *J* = 7.4 Hz, 2H, Ar*H*), 6.47 (d, *J* = 19.0 Hz, 1H, 2-H), 5.78 (d, *J* = 19.0 Hz, 1H, 1-H), 5.54 (t, *J* = 8.0 Hz, 1H, 4-H), 3.65 (d, *J* = 8.0 Hz, 2H, 5-H), 2.32 (s, 3H, COC*H3*), 2.12 (s, 2H, SiC*H*$_2$Ph), 1.78 (s, 3H, 3-C*H3*), 0.04 (s, 6H, Si(C*H3*)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.5, 148.4, 140.0, 138.5, 128.2, 128.1, 127.1, 126.4, 124.0, 30.4, 27.5, 26.2, 11.9, −3.4; **HRMS** (ESI+) calc. for $C_{17}H_{24}OSSiNa$ $[M+Na]^+$ 327.1209, found 327.1207.

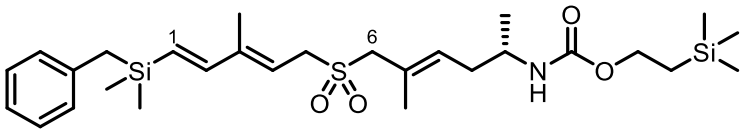
2-(Trimethylsilyl)ethyl ((*E*)-6-(((2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-yl)thio)-5-methylhex-4-en-2-yl)carbamate, 205



Thioester **202** (41 mg, 0.14 mmol, 1.0 eq.), bromide **177** (46 mg, 0.14 mmol, 1.0 eq.) and KOH (38 mg, 0.68 mmol, 4.9 eq.) were dissolved in degassed methanol (0.7 mL) and stirred at ambient temperature for 1 h. The mixture was partitioned between water (10 mL) and EtOAc (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 15:1) afforded title compound **205** as a colourless oil (63 mg, 90%).

***R*$_f$** 0.28 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 1696, 1494, 1452, 1331, 1248, 1057, 985, 833, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.16 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.03 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.96 (d, *J* = 7.3 Hz, 2H, Ar*H*), 6.49 (d, *J* = 18.9 Hz, 1H, 2-H), 5.71 (t, *J* = 18.9 Hz, 1H, 1-H), 5.55 (t, *J* = 7.8 Hz, 1H, 4-H), 5.25 (t, *J* = 7.0 Hz, 1H, 8-H), 4.41 (d, *J* = 6.8 Hz, 1H, N*H*), 4.16 – 4.07 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 3.72 (m, 1H, 10-H), 3.12 (d, *J* = 7.9 Hz, 2H, 5-H$_2$), 3.06 (s, 2H, 6-H$_2$), 2.23 – 2.15 (m, 2H, 9-H$_2$), 2.12 (s, 2H, SiC*H*$_2$Ph), 1.72 (s, 3H, 3-CH$_3$), 1.71 (s, 3H, 7-CH$_3$), 1.11 (d, *J* = 6.6 Hz, 3H, 10-CH$_3$), 0.98 – 0.89 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.03 (s, 6H, Si(C*H*$_3$)$_2$), 0.00 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.0, 148.7, 140.0, 137.5, 134.1, 129.2, 128.2, 128.0125.5, 123.9, 123.6, 62.7, 47.0, 41.0, 35.4, 28.8, 26.2, 20.7, 17.7, 15.3, 11.9, −1.5, −3.3; **HRMS** (ESI+) calc. for $C_{28}H_{47}NO_2SSi_2Na$ $[M+Na]^+$ 540.2758, found 540.2745.

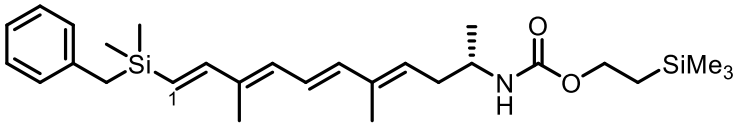
2-(Trimethylsilyl)ethyl ((*E*)-6-(((2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-yl)sulfonyl)-5-methylhex-4-en-2-yl)carbamate, 208



Sulfide **205** (63 mg, 0.12 mmol, 1.0 eq.) was dissolved in ethanol (0.72 mL). A solution of ammonium heptamolybdate tetrahydrate (30 mg, 24 µmol, 0.20 eq.) in aqueous hydrogen peroxide solution (30%, 122 µL, 1.22 mmol, 10.0 eq.) was added to this mixture and stirred for 44 h at ambient temperature. The mixture was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was acidified to pH = 3 with 1 M HCl solution, and extracted with EtOAc (3 ×15 mL), the combined organics washed with $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 1:1) afforded title compound **208** as a colourless oil (35 mg, 52%).

***R*$_f$** 0.29 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3357, 2955, 1702, 1524, 1452, 1309, 1249, 1120, 1058, 986, 836, 699; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.16 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.03 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.98 (d, *J* = 7.3 Hz, 2H, Ar*H*), 6.60 (d, *J* = 19.0 Hz, 1H, 2-H), 5.89 (d, *J* = 19.0 Hz, 1H, 1-H), 5.59 (t, *J* = 7.8 Hz, 1H, 4-H), 5.21 (t, *J* = 7.1 Hz, 1H, 8-H), 4.32 – 4.24 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 4.16 (d, *J* = 8.5 Hz, 1H, N*H*), 3.81 (m, 1H, 10-H), 3.53 – 3.44 (m, 2H, 5-H$_2$), 3.16 (d, *J* = 4.0 Hz, 2H, 6-H$_2$), 2.07 (s, 2H, Si(CH$_3$)C*H*$_2$Ph), 1.90 (dd, *J* = 6.7, 6.7 Hz, 2H, 9-H$_2$), 1.71 (s, 3H, 3-CH$_3$), 1.65 (s, 3H, 7-CH$_3$), 1.03 – 0.97 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.84 (d, *J* = 6.6 Hz, 3H, 10-CH$_3$), 0.06 (s, 6H, Si(C*H*$_3$)CH$_2$Ph), −0.05 (s, 9H, OCH$_2$CH$_2$Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 157.8, 150.0, 144.7, 141.7, 130.3, 130.3, 128.6, 126.3, 120.8, 64.5, 63.9, 55.0, 54.3, 37.4, 27.9, 22.4, 19.9, 18.9, 14.4, 0.2, −1.6; **HRMS** (ESI+) calc. for $C_{28}H_{46}NO_4SSi_2$ $[M-H]^-$ 548.2692, found 548.2698.

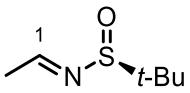
2-(Trimethylsilyl)ethyl ((4*E*,6*E*,8*E*,10*E*)-11-(benzyldimethylsilyl)-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 210



Sulfone **208** (30 mg, 55 µmol, 1.0 eq.), KOH·Al_2O_3 (1:3, 110 mg, 491 mmol, 9.0 eq) were suspended in CH_2Cl_2 (0.11 mL) and *t*-BuOH (0.11 mL). The mixture was cooled to 0 °C and CBr_2F_2 (20 µL, 0.22 mmol, 4.0 eq.) was added to the stirred suspension. After 1.5 h of stirring at 0 °C a second portion of CBr_2F_2 (20 µL, 0.22 mmol, 4.0 eq.) was added and the mixture was stirred overnight and warmed to ambient temperature. The mixture was diluted with EtOAc, filtered over silica, and the solvent removed under reduced pressure. Purification by column chromatography (petroleum ether / Et_2O, 10:1) afforded title compound **210** as a colourless oil (9 mg, 35%).

***R*$_f$** 0.77 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 1698, 1494, 1452, 1332, 1249, 1207, 1058, 983, 960, 855; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.16 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.06 – 6.98 (m, 3H, Ar*H*), 6.76 (d, *J* = 18.9 Hz, 1H, 2-H), 6.58 (dd, *J* = 15.1, 11.3 Hz, 1H, 5-H), 6.36 (d, *J* = 15.1 Hz, 1H, 6-H), 6.25 (d, *J* = 11.0 Hz, 1H, 4-H), 5.91 (d, *J* = 18.9 Hz, 1H, 1-H), 5.46 (t, *J* = 7.4 Hz, 1H, 8-H), 4.34 – 4.26 (m, 2H, OC*H*$_2$CH$_2$Si(CH$_3$)$_3$), 4.14 (d, *J* = 8.2 Hz, 1H, N*H*), 3.87 (m, 1H, 10-H), 2.19 – 2.04 (m, 4H, Si(CH$_3$)$_2$C*H*$_2$Ph, 9-H$_2$), 1.85 (s, 3H, 3-CH$_3$), 1.69 (s, 3H, 7-CH$_3$), 1.04 – 0.97 (m, 2H, OCH$_2$C*H*$_2$Si(CH$_3$)$_3$), 0.86 (d, *J* = 6.6 Hz, 3H, 10-CH$_3$), 0.12 (s, 6H, Si(C*H*$_3$)$_2$CH$_2$Ph), −0.06 (s, 9H, OCH$_2$CH$_2$Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 156.0, 150.1, 140.3, 139.5, 136.8, 136.1, 133.9, 129.9, 128.7, 128.5, 125.5, 124.5, 123.8, 62.7, 35.9, 30.5, 26.6, 20.5, 18.2, 12.6, 12.4, −1.5, −3.0; **HRMS** (ESI+) calc. for $C_{28}H_{45}NO_2Si_2Na$ $[M+Na]^+$ 506.2881, found 506.2873.

(*S*,*E*)-*N*-Ethylidene-2-methylpropane-2-sulfinamide, 218

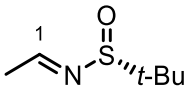


(*S*)-2-Methyl-propane-2-sulfinamide (3.00 g, 24.8 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (41 mL) and anhydrous $CuSO_4$ (11.85 g, 74.2 mmol, 3.0 eq.) was added. Acetaldehyde (2 × 2.8 mL, 2 × 50 mmol, 2 × 2.0 eq.) was added and the mixture stirred at ambient temperature for 12 h, after which the second portion of acetaldehyde was added, and the mixture stirred for further 12 h. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 2:1) afforded the title compound **218** as a colourless oil (3.64 g, 99%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +332.8 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.54 (petroleum ether / EtOAc, 1:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.08 (q, *J* = 5.1 Hz, 1H, 1-H), 2.24 (d, *J* = 5.1 Hz, 3H, 1-CH_3), 1.19 (s, 9H, SOC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.1, 56.7, 22.6, 22.5.

The spectroscopic data is in agreement with that reported by Kells and Chong.[337]

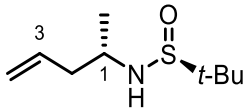
(*R*,*E*)-*N*-ethylidene-2-methylpropane-2-sulfinamide, ent-218



(*R*)-2-Methyl-propane-2-sulfinamide (532 mg, 4.37 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (7.3 mL) and anhydrous $CuSO_4$ (2.10 g, 13.2 mmol, 3.0 eq.) was added. Acetaldehyde (2 × 0.50 mL, 2 × 8.9 mmol, 2 × 2.0 eq.) was added and the mixture stirred at ambient temperature for 12 h, after which the second portion of acetaldehyde was added, and the mixture stirred for further 12 h. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 2:1) afforded the title compound **ent-218** as a colourless oil (539 mg, 83%).

$[\alpha]_D^{25}$ −256.1 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **218**, and in agreement with that reported by Ruan and coworkers.[138]

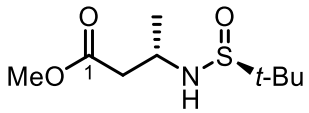
(*S*)-2-Methyl-*N*-((*S*)-pent-4-en-2-yl)propane-2-sulfinamide, 219



Imine **218** (500 mg, 3.40 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (17 mL) and cooled to 0 °C. Allyl magnesium bromide (6.8 mL, 1.0 M in Et_2O, 6.8 mmol, 2.0 eq.) was added dropwise and the resulting mixture was stirred at 0 °C for 3 h. The mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with Et_2O (3 × 25 mL), the combined organics washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:2) afforded the title compound **219** as a colourless oil (507 mg, 79%).

$[\alpha]_D^{25}$ +89.3 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.08 (CH_2Cl_2 / MeOH, 100:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3210, 2977, 1456, 1364, 1217, 1054, 996, 914, 871, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.84 – 5.71 (m, 1H, 3-H), 5.17 – 5.14 (m, 1H, 4-H), 5.14 – 5.11 (m, 1H, 4-H), 3.51 – 3.41 (m, 1H, 1-H), 3.27 (d, *J* = 4.0 Hz, 1H, N*H*), 2.37 – 2.28 (m, 1H, 2-H_2), 2.27 – 2.18 (m, 1H, 2-H_2), 1.22 – 1.14 (m, 12H, 1-CH_3, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.5, 118.8, 55.5, 49.5, 42.8, 22.7, 21.1; **HRMS** (ESI+) calc. for $C_9H_{19}ON^{32}S^{23}Na$ $[M+Na]^+$ 212.10796, found 212.10821.

Methyl (*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)butanoate, 223

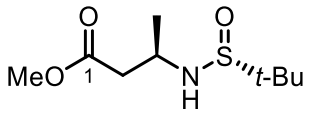


n-Butyllithium (17.3 mL, 2.5 M in hexanes, 43.3 mmol, 1.3 eq.) was added dropwise to a solution of DIPA (5.8 mL, 41 mmol, 1.25 eq.) in THF (60 mL) at 0 °C, and stirred for 15 min, before cooling to −78 °C. MeOAc (3.2 mL, 40 mmol, 1.2 eq.) was added dropwise, and the mixture stirred for 30 min, before adding $TiCl(OiPr)_3$ (20.7 mL, 86.7 mmol, 2.6 eq.) in THF (20 mL) and stirring for further 45 min. To the resulting mixture was added dropwise a solution of imine **218** (4.90 g, 33.3 mmol, 1.0 eq.) in THF (10 mL) and stirring was continued at −78 °C for 3 h, after which it was quenched by addition of aqueous NH_4Cl (60 mL) and allowed to warm to ambient temperature. The mixture was diluted with water (60 mL), extracted with EtOAc (3 × 100 mL), the combined organics washed with brine (60 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1) afforded the title compound **223** as a white solid (6.88 g, 93%).

M.p. 60 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +108.2 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.19 (petroleum ether / EtOAc, 1:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 1735, 1437, 1363, 1286, 1175, 1134, 1047; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.10 (d, *J* = 6.6 Hz, 1H, N*H*), 3.74 (hd, *J* = 6.6, 5.2 Hz, 1H, 3-H), 3.66 (s, 3H, OC*H*$_3$), 2.63 (dd, *J* = 16.0, 5.2 Hz, 1H, 2-H), 2.53 (dd, *J* = 16.0, 6.6 Hz, 1H, 2-H), 1.24 (d, *J* = 6.6 Hz, 3H, 3-CH_3), 1.17 (s, 9H, SOC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.2, 55.5, 51.8, 48.6, 42.0, 22.7, 21.6; **HRMS** (ESI+) calc. for $C_9H_{19}O_3N^{23}Na$ $[M+Na]^+$ 244.09779, found 244.09758.

The spectroscopic data is in agreement with that reported by Tang and Ellman.[148]

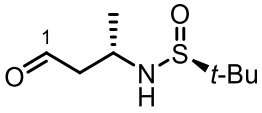
Methyl (*R*)-3-(((*R*)-*tert*-butylsulfinyl)amino)butanoate, ent-223



n-Butyllithium (1.41 mL, 2.5 M in hexanes, 3.53 mmol, 1.3 eq.) was added dropwise to a solution of DIPA (0.48 mL, 3.4 mmol, 1.25 eq.) in THF (5.0 mL) at 0 °C, and stirred for 15 min, before cooling to −78 °C. MeOAc (0.26 mL, 3.3 mmol, 1.2 eq.) was added dropwise, and the mixture stirred for 30 min, before adding $TiCl(OiPr)_3$ (1.7 mL, 7.1 mmol, 2.6 eq.) in THF (1.5 mL) and stirring for further 45 min. To the resulting mixture was added dropwise a solution of imine **ent-218** (400 mg, 2.72 mmol, 1.0 eq.) in THF (1.0 mL) and stirring was continued at −78 °C for 3 h, after which It was quenched by addition of aqueous NH_4Cl (10 mL) and allowed to warm to ambient temperature. The mixture was diluted with water (5 mL), extracted with EtOAc (3 × 20 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1) afforded the title compound **ent-223** as a white solid (494 mg, 82%).

$[\alpha]_D^{25}$ −104.3 (*c* 1.0, $CHCl_3$). The remaining data is identical to that of **223**.

(*S*)-2-Methyl-*N*-((*S*)-4-oxobutan-2-yl)propane-2-sulfinamide, 224

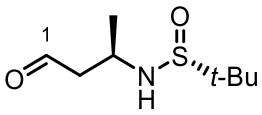


Ester **223** (5.00 g, 22.6 mmol, 1.0 eq.) was dissolved in toluene (226 mL) and cooled to −78 °C. DIBALH (40.7 mL, 1.0 M in cyclohexane, 40.7 mmol, 1.8 eq.) was added dropwise over 20 min, and stirred for further 20 min before the resulting reaction mixture was quenched by subsequent addition of water (1.6 mL), aqueous NaOH (1.6 mL, 15%),

and water (4.1 mL). After allowing to reach ambient temperature $MgSO_4$ was added and the resulting suspension stirred for 15 min, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:4) afforded the title compound **224** as a colourless oil (3.522 g, 81%).

$[\alpha]_D^{25}$ +116.8 (*c* 1.0, $CHCl_3$); R_f 0.14 (petroleum ether / EtOAc, 1:4); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3224, 2977, 1722, 1457, 1364, 1049, 982, 752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.79 – 9.77 (m, 1H, C*H*O), 3.85 (hept, *J* = 6.3 Hz, 1H, 3-H), 3.73 (d, *J* = 6.8 Hz, 1H, N*H*), 2.80 (dd, *J* = 5.8, 1.2 Hz, 2H, 2-H_2), 1.30 (d, *J* = 6.6 Hz, 3H, 3-CH_3), 1.19 (s, 9H, SOC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.0, 55.7, 51.5, 47.5, 22.7, 21.8; **HRMS** (ESI+) calc. for $C_8H_{18}O_2N^{32}S$ 192.10528 $[M+Na]^+$, found 192.10530.

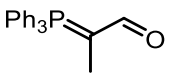
(*R*)-2-Methyl-N-((R)-4-oxobutan-2-yl)propane-2-sulfinamide, ent-224



Ester **ent-223** (100 mg, 452 µmol, 1.0 eq.) was dissolved in toluene (4.5 mL) and cooled to −78 °C. DIBALH (0.81 mL, 1.0 M in cyclohexane, 0.81 mmol, 1.8 eq.) was added dropwise over 5 min, and stirred for further 20 min before the resulting reaction mixture was quenched by subsequent addition of water (0.03 mL), aqueous NaOH (0.03 mL, 15%), and water (0.08 mL). After allowing to reach ambient temperature $MgSO_4$ was added and stirred for 15 min, filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 19:1) afforded the title compound **ent-224** as a colourless oil (52 mg, 60%).

$[\alpha]_D^{25}$ −108.7 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **224**.

2-(Triphenylphosphanylidene)propanal, 87

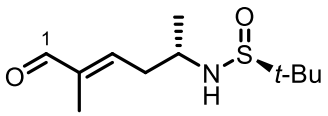


Sodium hydride (3.24 g, 60% *w/w* in mineral oil, 81.0 mmol, 3.0 eq.) under inert gas atmosphere, was washed with pentane (2 × 10 mL) before addition of THF (80 mL). Ethyltriphenylphosphonium bromide (10.0 g, 26.9 mmol, 1.0 eq.) was added and the mixture was stirred at ambient temperature overnight. After cooling to 0 °C ethyl formate (5.4 mL, 67.3 mmol, 2.5 eq.) was added dropwise, and the resulting solution stirred at this temperature for 2 h, followed by further 2 h at ambient temperature. It was quenched by slow addition of aqueous HCl (80 mL, 1 M) at 0 °C. The pH level was adjusted to pH 8 by dropwise addition of aqueous NaOH-solution (10% w/v) followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with water (2 × 100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by dissolving in minimum amount of CH_2Cl_2 followed by dilution with Et_2O to precipitate title compound **87** as a white solid (5.93 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.06 (d, J = 4.6 Hz, 1H, C*H*O), 7.63 – 7.45 (m, 15H, Ar*H*), 1.84 (d, J = 13.5 Hz, 3H, CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.4 (s).

The spectroscopic data is in agreement with that reported by Kiyooka and Hena.[338]

(*S*)-2-Methyl-*N*-((*S*,*E*)-5-methyl-6-oxohex-4-en-2-yl)propane-2-sulfinamide, 225

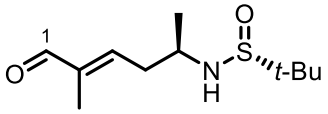


Aldehyde **224** (3.522 g, 18.4 mmol, 1.0 eq.) and phosphorylid (8.792 g, 27.6 mmol, 1.5 eq.) were dissolved in toluene (132 mL), and stirred overnight at 80 °C. The mixture was concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH,

40:1) afforded the title compound **225** as a mixture with triphenylphosphine oxide (8.640 g, 34 wt%, 69%).

R_f 0.59 (CH_2Cl_2 / MeOH, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.41 (s, 1H, C*H*O), 6.51 (app. tq, J = 7.5, 1.5 Hz, 1H, 3-H), 3.58 (app. hept, J = 6.4 Hz, 1H, 5-H), 3.21 (d, J = 5.7 Hz, 1H, N*H*), 2.74 – 2.60 (m, 1H, 4-H_2), 2.60 – 2.49 (m, 1H, 4-H_2), 1.74 (d, J = 1.5 Hz, 3H, 2-CH_3), 1.23 (d, J = 6.5 Hz, 3H, 5-CH_3), 1.17 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.9, 149.2, 141.5, 55.7, 51.0, 37.8, 22.6, 21.6, 9.7; **HRMS** (ESI+) calc. for $C_{11}H_{22}O_2NS$ $[M+H]^+$ 232.13658, found 232.13690.

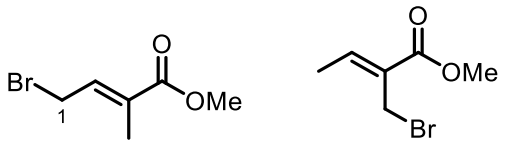
(*R*)-2-Methyl-*N*-((*R*,*E*)-5-methyl-6-oxohex-4-en-2-yl)propane-2-sulfinamide, ent-225



Aldehyde **ent-224** (50 mg, 0.26 mmol, 1.0 eq.) and phosphorylid (125 mg, 393 µmol, 1.5 eq.) were dissolved in toluene (1.9 mL), and stirred overnight at 80 °C. The mixture was concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 40:1) afforded the title compound **ent-225** as a mixture with triphenylphosphine oxide (78 mg, 60 wt%, 78%).

The analytical data is identical to that of **225**.

Methyl (*E*)-4-bromo-2-methylbut-2-enoate, 227

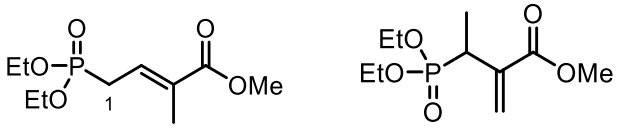


A solution of NBS (15.59 g, 87.6 mmol, 1.0 eq.) and methyl tiglate (9.5 mL, 88 mmol, 1.0 eq.) in CCl_4 (44 mL) was stirred at 100 °C overnight. The mixture was filtered through Celite, after cooling to ambient temperature, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 19:1) afforded an inseparable mixture of title compounds **227** and **227′** (11.13 g, 64%) in 1.5:1.0 ratio.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.92 (tq, J = 8.5, 1.5 Hz, 1H, 2-H), 4.03 (d, J = 8.5 Hz, 2H, 1-H_2), 3.76 (s, 3H, CO_2CH_3), 1.92 (s, 3H, 3-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.8, 143.5, 135.2, 52.3, 26.1, 12.3.

The spectroscopic data is in agreement with that reported by Wolff and coworkers.[339]

Methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate, 228



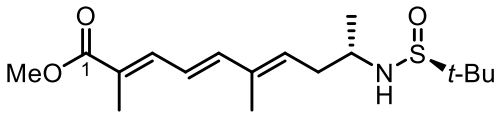
Bromide **227** (10.42 g, 52.6 mmol, 1.0 eq.) and triethyl phosphite (10.2 mL, 59.5 mmol, 1.1 eq.) were stirred at 120 °C overnight. It was cooled to ambient temperature and then concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 49:1) afforded an inseperable mixture of title compounds **228** and **228′** (13.14 g, 99%) in a 2.7:1.0 ratio.

R_f 0.35 (CH_2Cl_2 / MeOH, 25:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.75 (tdt, J = 8.2, 6.7, 1.4 Hz, 1H, 2-H), 4.16 – 4.03 (m, 4H, OCH_2CH_3), 3.74 (s, 3H, CO_2CH_3), 2.73 (dd,

J = 23.4, 8.3 Hz, 2H, 1-H_2), 1.93 – 1.83 (m, 3H, 3-CH_3), 1.37 – 1.23 (m, 6H, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.9, 131.7 (d, J = 13.7 0Hz), 130.6 (d, J = 11.2 Hz), 62.30 (d, J = 6.8 Hz), 52.1, 27.7 (d, J = 139.1 Hz), 16.6 (d, J = 5.7 Hz), 12.7 (d, J = 2.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 25.5.

The spectroscopic data is in agreement with that reported by Wang and coworkers.[340]

Methyl (*S*,2*E*,4*E*,6*E*)-9-(((*S*)-tert-butylsulfinyl)amino)-2,6-dimethyldeca-2,4,6-trienoate, 230

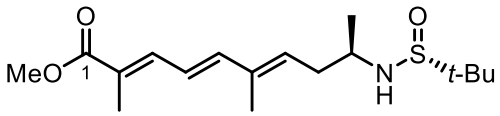


n-Butyllithium (1.7 mL, 2.5 M, 4.3 mmol, 1.3 eq.) was added dropwise to neat 2,2,6,6-tetramethylpiperidine (0.73 mL, 4.3 mmol, 1.3 eq.) and stirred for 20 min. The mixture was cooled to −30 °C and a solution of phosphonate **228** (1.54 g, purity 70 wt%, 4.31 mmol, 1.3 eq.) in THF (13 mL) was added dropwise, and the mixture stirred for 30 min, followed by addition of a solution of aldehyde **225** (1.67 g, purity 46 wt%, mixture with triphenylphosphine oxide, 3.32 mmol, 1.0 eq.) in THF (12 mL). The mixture was warmed to ambient temperature and stirred overnight. It was quenched by addition of aqueous NH_4Cl (20 mL), extracted with EtOAc (3 × 25 mL), the combined organics washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1 →3:2) afforded the title compound **230** as a yellow oil (975 mg, 90%).

$[\alpha]_D^{25}$ +49.2 (*c* 1.0, $CHCl_3$); R_f 0.49 (petroleum ether / EtOAc, 1:4); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2952, 1703, 1611, 1435, 1288, 1229, 1111, 1050, 968; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (dq, J = 11.2, 1.4 Hz, 1H, 3-H), 6.55 (d, J = 15.2 Hz, 1H, 5-H), 6.42 (dd,

J = 15.2, 11.2 Hz, 1H, 4-H), 5.67 (t, *J* = 7.7 Hz, 1H, 7-H), 3.75 (s, 3H, OC*H*$_3$), 3.49 (app hept, *J* = 6.5 Hz, 1H, 9-H), 3.16 (d, *J* = 4.7 Hz, 1H, N*H*), 2.49 (dt, *J* = 14.5, 7.4 Hz, 1H, 8-H$_2$), 2.39 (dt, *J* = 14.5, 6.9 Hz, 1H, 8-H$_2$), 1.97 (d, *J* = 1.4 Hz, 3H, 2-CH$_3$), 1.85 (d, *J* = 1.2 Hz, 3H, 6-CH$_3$), 1.20 (d, *J* = 6.4 Hz, 3H, 9-CH$_3$), 1.18 (s, 9H, SOC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 169.1, 143.9, 139.0, 137.0, 132.0, 126.3, 122.5, 55.5, 51.9, 51.0, 37.7, 22.7, 21.3, 12.9, 12.8; **HRMS** (ESI+) calc. for $C_{17}H_{29}O_3N^{32}S^{23}Na$ 350.17604 $[M+Na]^+$, found 350.17547.

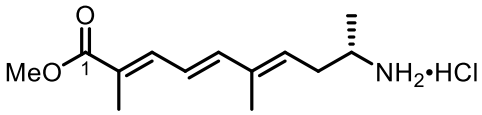
Methyl (*R*,2*E*,4*E*,6*E*)-9-(((*R*)-tert-butylsulfinyl)amino)-2,6-dimethyldeca-2,4,6-trienoate, ent-230



n-Butyllithium (0.12 mL, 1.6 M, 0.19 mmol, 1.3 eq.) was added dropwise to neat 2,2,6,6-tetramethylpiperidine (32 µL, 0.19 mmol, 1.3 eq.) and stirred for 20 min. The mixture was cooled to −30 °C and a solution of phosphonate **228** (68 mg, purity 70 wt%, 0.19 µmol, 1.3 eq.) in THF (0.8 mL) was added dropwise, and the mixture stirred for 30 min, followed by addition of a solution of aldehyde **ent-225** (56 mg, purity 60 wt%, mixture with triphenylphosphine oxide, 0.15 µmol, 1.0 eq.) in THF (0.4 mL). The mixture was warmed to ambient temperature and stirred overnight. It was quenched by addition of aqueous NH_4Cl (8 mL), extracted with EtOAc (3 × 10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1 →1:2) afforded the title compound **ent-230** as a yellow oil (32 mg, 66%).

$[\alpha]_D^{25}$ −39.7 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **230**.

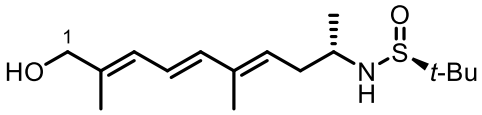
Methyl (*S*,2*E*,4*E*,6*E*)-9-amino-2,6-dimethyldeca-2,4,6-trienoate hydrochloric salt, 215



HCl in 1,4-dioxane (0.16 mL, 4.0 M, 0.64 mmol, 2.1 eq.) was added to sulfinamide **230** (100 mg, 305 µmol, 1.0 eq.), stirred for 2 min, and the volatiles removed *in vacuo* to afford the title compound as a yellow waxy solid (79 mg, 99%), that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.42 (bs, 3H, NH_3), 7.23 (d, J = 11.2 Hz, 1H, 3-H), 6.57 (d, J = 15.2 Hz, 1H, 5-H), 6.43 (dd, J = 15.2, 11.2 Hz, 1H, 4-H), 5.68 (t, J = 7.5 Hz, 1H, 7-H), 3.75 (s, 3H, CO_2CH_3), 3.45 – 3.34 (m, 1H, 9-H), 2.75 – 2.64 (m, 1H, 8-H_2), 2.62 – 2.47 (m, 1H, 8-H_2), 1.96 (s, 3H, 2-CH_3), 1.86 (s, 3H, 6-CH_3), 1.41 (d, J = 6.3 Hz, 3H, 9-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.0, 143.5, 138.8, 138.2, 128.9, 126.8, 123.2, 52.0, 48.5, 34.1, 21.7, 18.8, 13.0; **HRMS** (ESI+) calc. for $C_{13}H_{22}O_2{}^{23}Na$ $[M-Cl]^+$ 224.16451, found 224.16460

(*S*)-*N*-((*S*,4*E*,6*E*,8*E*)-10-Hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, 231

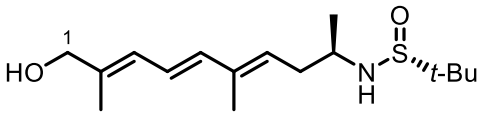


DIBALH (15.5 mL, 1.0 M in cyclohexane, 15.5 mmol, 3.0 eq.) was added dropwise to a solution of trienoate **230** (1.691 g, 5.16 mmol, 1.0 eq.) in CH_2Cl_2 (13 mL) at −78 °C, and the mixture stirred for 1 h. Upon completion it was quenched by subsequent addition of water (0.62 mL), aqueous NaOH (0.62 mL, 15 wt%), and water (1.6 mL). The mixture

was warmed to ambient temperature, $MgSO_4$ was added, stirred for 15 min, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:4) afforded the title compound **231** as a white solid (1.241 g, 80%).

M.p. 80-84 °C; $[\alpha]_D^{25}$ +67.8 (*c* 1.0, $CHCl_3$); R_f 0.35 (petroleum ether / EtOAc, 1:4); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3273, 2976, 1455, 1364, 1131, 1044, 966, 885, 754; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.39 (dd, *J* = 15.2, 10.7 Hz, 1H, 4-H), 6.26 (d, *J* = 15.3 Hz, 1H, 5-H), 6.10 (dq, *J* = 10.7, 1.4 Hz, 1H, 3-H), 5.49 (t, *J* = 7.7 Hz, 1H, 7-H), 4.09 (s, 2H, 1-H_2), 3.46 (app hept, *J* = 6.4 Hz, 1H, 9-H), 3.19 (d, *J* = 4.3 Hz, 1H, N*H*), 2.51 – 2.29 (m, 2H, 8-H_2), 1.82 (s, 6H, 2-CH_3, 6-CH_3), 1.19 (d, *J* = 6.5 Hz, 3H, 9-CH_3), 1.18 (s, 9H, SOC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.3, 137.2, 137.2, 127.9, 125.6, 123.0, 68.8, 55.4, 50.8, 37.5, 22.7, 21.2, 14.5, 12.9; **HRMS** (ESI+) calc. for $C_{16}H_{29}O_2N^{32}S^{23}Na$ 322.18112 $[M+Na]^+$, found 322.18078.

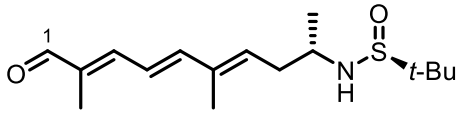
(*R*)-*N*-((*R*,4*E*,6*E*,8*E*)-10-Hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, ent-231



DIBALH (6.4 mL, 1.0 M in cyclohexane, 6.4 mmol, 3.0 eq.) was added dropwise to a solution of trienoate **ent-230** (700 g, 2.14 mmol, 1.0 eq.) in CH_2Cl_2 (5.3 mL) at −78 °C, and the mixture was stirred for 1 h. Upon completion, it was quenched by subsequent addition of water (0.26 mL), aqueous NaOH (0.26 mL, 15 wt%), and water (0.64 mL). The mixture was warmed to ambient temperature, $MgSO_4$ was added, stirred for 15 min, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:4) afforded the title compound **ent-231** as a white solid (235 mg, 37%).

$[\alpha]_D^{25}$ −52.7 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **230**.

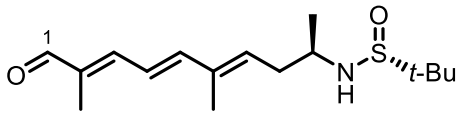
(*S*)-*N*-((*S*,4*E*,6*E*,8*E*)-5,9-Dimethyl-10-oxodeca-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, 232



Alcohol **231** (500 mg, 1.67 mmol, 1.0 eq.), 3 Å molecular sieves, NMO (782 mg, 6.68 mmol, 4.0 eq.), and TPAP (30 mg, 85 µmol, 5 mol%), were dissolved in CH_2Cl_2 (16.7 mL) and the mixture stirred in the dark, at ambient temperature overnight, and then concentrated *in vacuo*. Purification by column chromatography (petroleum ether, 1:4) afforded the title compound **232** as a yellow oil (382 mg, 77%).

$[\alpha]_D^{25}$ +32.4 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.30 (petroleum ether / EtOAc, 1:4); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2967, 2280, 1672, 1607, 1406, 1362, 1192, 1057, 996, 965, 813; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 9.44 (s, 1H, C*H*O), 6.53 – 6.30 (m, 3H, 3-H, 4-H, 5-H), 5.63 (td, *J* = 7.7, 1.4 Hz, 1H, 7-H), 3.34 (app. hept, *J* = 6.3 Hz, 1H, 9-H), 3.17 (d, *J* = 5.7 Hz, 1H, N*H*), 2.28 (dt, *J* = 14.4, 7.1 Hz, 1H, 8-H_2), 2.16 (dt, *J* = 14.5, 6.9 Hz, 1H, 8-H_2), 1.80 (d, *J* = 1.3 Hz, 3H, 2-CH_3), 1.60 (d, *J* = 1.2 Hz, 3H, 6-CH_3), 1.05 (s, 9H, S(O)C(C*H*$_3$)$_3$), 1.03 (d, *J* = 6.4 Hz, 3H, 9-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 193.6, 148.3, 145.5, 137.5, 136.8, 134.2, 122.1, 55.0, 51.5, 37.7, 22.5, 21.6, 12.5, 9.6; **HRMS** (ESI+) calc. for $C_{16}H_{27}O_2N^{32}S^{23}Na$ $[M+Na]^+$ 320.16547, found 320.16525.

(*R*)-*N*-((*R*,4*E*,6*E*,8*E*)-5,9-Dimethyl-10-oxodeca-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, ent-232



Alcohol **ent-231** (190 mg, 634 µmol, 1.0 eq.), 3 Å molecular sieves, NMO (312 mg, 2.66 mmol, 4.0 eq.), and TPAP (12 mg, 34 µmol, 5 mol%), were dissolved in CH_2Cl_2 (6.8 mL) and the mixture stirred in the dark, at ambient temperature overnight, and then concentrated *in vacuo*. Purification by column chromatography (petroleum ether, 1:4) afforded the title compound **232** as a yellow oil (125 mg, 66%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −46.3 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **232**.

(Dibromomethyl)triphenylphosphonium bromide, 235

$[Ph_3PCHBr_2]Br{\cdot}CH_3CN$

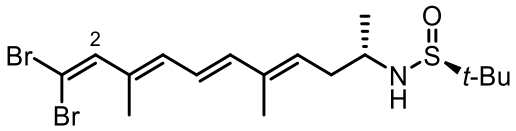
Triphenylphosphine (17.0 g, 64.8 mmol, 2.0 eq.) and tetrabromomethane (10.0 g, 30.2 mmol, 1.0 eq.) were dissolved in CH_2Cl_2 (160 mL) and stirred at ambient temperature for 30 min. Water (50 mL) was added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (1 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in acetonitrile (100 mL) and sonicated for 30 min. The mixture was filtered, and the solids washed with acetonitrile to afford the title compound **235** as a white solid (12.65 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.37 (d, J = 2.4 Hz, 1H, C*H*Br_2), 8.20 – 8.09 (m, 6H, Ar*H*), 7.84 – 7.77 (m, 3H, Ar*H*), 7.74 – 7.65 (m, 6H, Ar*H*), 1.99 (s, 3H, CH_3CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 135.7 (d, J = 3.1 Hz), 135.1 (d, J = 9.7 Hz), 130.4 (d,

J = 12.8 Hz), 116.5 (d, J = 88.8 Hz), 29.84 (d, J = 47.5 Hz), 2.06; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 32.8.

The spectroscopic data is in agreement with that reported by Tosic and Mattay.[156]

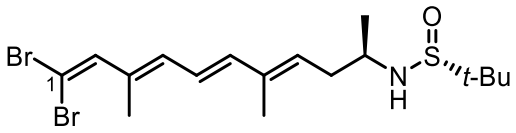
(*S*)-*N*-((*S*,4*E*,6*E*,8*E*)-11,11-Dibromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methylpropane-2-sulfinamide, 234



A solution of potassium *tert*-butoxide (2.5 mL, 1.0 M in THF, 2.5 mmol, 2.0 eq.) was added to a suspension of phosphonium salt **235** (1.521 g, 2.74 mmol, 2.2 eq.) in THF (6.0 mL), and stirred at ambient temperature for 30 min. A solution of aldehyde **232** (370 mg, 1.24 mmol, 1.0 eq.) in THF (6.5 mL) was added, and the mixture stirred for further 30 min. The resulting mixture was put directly onto silica and was purified by column chromatography (petroleum ether / EtOAc, 2:3) to afford the title compound **234** as a brown oil (449 mg, 80%).

$[\alpha]_D^{25}$ +38.2 (c 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.48 (petroleum ether / EtOAc, 1:4); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2970, 2364, 1702, 1606, 1456, 1391, 1365, 1157, 1026, 964, 781; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.89 (s, 1H, 2-H), 6.45 – 6.27 (m, 2H, 5-H, 6-H), 6.10 (dt, J = 9.9, 1.3 Hz, 1H, 4-H), 5.49 (t, J = 7.4 Hz, 1H, 8-H), 3.34 (app. hept, J = 6.4 Hz, 1H, 10-H), 3.01 (d, J = 5.3 Hz, 1H, N*H*), 2.24 (dt, J = 14.4, 7.2 Hz, 1H, 9-H_2), 2.13 (dt, J = 14.4, 7.0 Hz, 1H, 9-H_2), 1.84 (d, J = 1.2 Hz, 1H, 3-CH_3), 1.67 (d, J = 1.1 Hz, 1H, 7-CH_3), 1.04 – 1.00 (m, 12H, $C(CH_3)_3$, 10-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 141.3, 140.4, 137.2, 135.5, 132.2 130.5, 122.9, 86.3, 54.9, 51.3, 37.6, 22.5, 21.5, 15.4, 12.7; **HRMS** (ESI+) calc. for $C_{17}H_{27}ON^{79}Br_2{}^{32}S^{23}Na$ $[M+Na]^+$ 474.00723, found 474.00656.

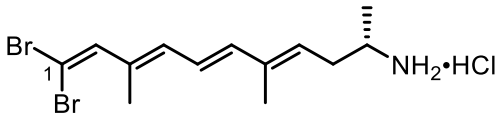
(*R*)-*N*-((*R*,4*E*,6*E*,8*E*)-11,11-Dibromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methylpropane-2-sulfinamide, ent-234



A solution of potassium *tert*-butoxide (0.71 mL, 1.0 M in THF, 0.71 mmol, 2.0 eq.) was added to a suspension of phosphonium salt **235** (432 mg, 777 µmol, 2.2 eq.) in THF (1.5 mL), and stirred at ambient temperature for 30 min. A solution of aldehyde **ent-232** (105 mg, 353 µmol, 1.0 eq.) in THF (2.0 mL) was added, and the mixture stirred for further 30 min. The resulting mixture was put directly onto silica and was purified by column chromatography (petroleum ether / EtOAc, 2:3) to afford the title compound **ent-234** as a brown oil (151 mg, 94%).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −30.8 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **234**.

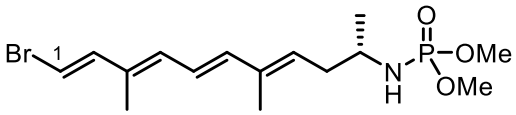
(*S*,4*E*,6*E*,8*E*)-11,11-Dibromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-amine hydrochloric salt, 238



Acetyl chloride (10 µL, 0.14 mmol, 1.4 eq.) was dissolved in MeOH (0.1 mL), stirred for 5 min, before adding vinyl dibromide **234** (45 mg, 99.3 µmol, 1.0 eq.) in MeOH (0.2 mL) at 0 °C and stirring at ambient temperature for 10 min. Another portion of acetyl chloride (9 µL, 0.13 mmol, 1.2 eq.) was added and stirring was continued for further 10 min. Concentration *in vacuo* afforded the crude title compound **238** as a yellowish, brownish substance. The crude product was used immediately without further purification.

^{1}H NMR (200 MHz, Methanol-d_4) δ_H 7.08 (s, 1H, 2-H), 6.58 – 6.18 (m, 3H, 4-H, 5-H, 6-H), 5.54 (t, J = 7.7 Hz, 1H, 8-H), 3.40 – 3.18 (m, 2H, 10-H, NH_3), 2.43 (app. hept, J = 7.8 Hz, 2H, 9-H_2), 2.04 (s, 3H, 3-CH_3), 1.83 (s, 3H, 7-CH_3), 1.25 (d, J = 6.6 Hz, 3H, 10-CH_3).

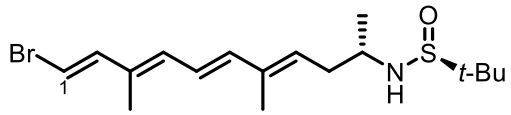
Dimethyl ((*S*,4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl) phosphoramidate, 239



Crude hydrochloric amine salt **238** was dissolved in dimethyl phosphite (0.25 mL, 2.8 mmol, 28.0 eq.) and triethyl amine (0.08 mL, 0.6 mmol, 6.0 eq.) was added. The mixture was stirred at ambient temperature overnight. Purification by column chromatography (basic alumina, CH_2Cl_2 / MeOH / NEt3, 100:1:1→80:20:1) afforded the title compound **239** as a brownish oil (16 mg, 41% over 2 steps).

$[\alpha]_D^{25}$ −17.4 (c 1.0, $CHCl_3$); **R$_f$** 0.15 (CH_2Cl_2 / MeOH, 10:1, neutral alumina); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.78 (d, J = 13.7 Hz, 1H, 2-H), 6.46 – 6.31 (m, 2H, 4-H, 5-H), 6.25 (d, J = 13.6 Hz, 1H, 1-H), 6.09 (d, J = 10.6 Hz, 1H, 6 H), 5.57 (t, J = 7.6 Hz, 1H, 8-H), 3.71 (d, J = 1.2 Hz, 3H, P(OCH_3)$_2$), 3.68 (d, J = 1.2 Hz, 3H, P(OCH_3)$_2$), 3.35 – 3.23 (m, 1H, 10-H), 2.47 (t, J = 10.1 Hz, 1H, NH), 2.38 – 2.25 (m, 2H, 9-H_2), 1.87 (s, 3H, 7-CH_3), 1.81 (s, 3H, 3-CH_3), 1.16 (d, J = 6.5 Hz, 3H, 10-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 142.0, 139.4, 136.8, 133.0, 132.7, 129.7, 122.9, 104.8, 53.2, 48.1, 37.8, 37.8, 23.0, 12.8, 12.7; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 10.5 (tt, J = 21.6, 10.7 Hz); **HRMS** (ESI+) calc. for $C_{15}H_{25}NO_3{}^{79}BrP$ $[M+H]^+$ 378.0828, found 378.0820.

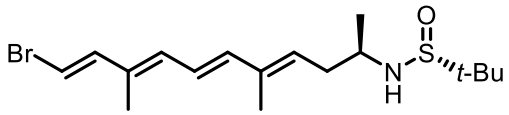
(*S*)-*N*-((*S*,4*E*,6*E*,8*E*,10*E*)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methylpropane-2-sulfinamide, 236



To dibromide **234** (449 mg, 991 µmol, 1.0 eq.) was added dimethylphosphite (2.5 mL, 27 mmol, 28 eq.), and triethylamine (0.69 mL, 5,0 mmol, 7.0 eq.) subsequently. The mixture was stirred at ambient temperature in the dark overnight. Purification by column chromatography (petroleum ether / EtOAc, 2:3) afforded the title compound **236** (267 mg, 71%) as an orange oil.

$[\alpha]_D^{25}$ +40.8 (*c* 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.27 (petroleum ether / EtOAc, 2:3); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2961, 1437, 1184, 1119, 1049, 997, 967, 750, 721, 695; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.76 (d, *J* = 13.7, 0.8 Hz, 1H, 2-H), 6.39 (dd, *J* = 15.2, 10.8 Hz, 1H, 5-H), 6.28 (d, *J* = 15.2 Hz, 1H, 6-H), 6.00 (d, *J* = 13.7 Hz, 1H, 1-H), 5.93 (d, *J* = 10.8 Hz, 1H, 4-H), 5.49 (t, *J* = 7.7 Hz, 1H, 8-H), 3.43 – 3.29 (m, 1H, 10-H), 3.20 (d, *J* = 5.3 Hz, 1H, N*H*), 2.29 (dt, *J* = 14.4, 7.1 Hz, 1H, 9-H_2), 2.18 (dt, *J* = 14.3, 6.9 Hz, 1H, 9-H_2), 1.69 (d, *J* = 1.2 Hz, 3H, 7-CH_3), 1.50 (d, *J* = 1.1 Hz, 3H, 3-CH_3), 1.07 – 1.02 (m, 12H, C(C*H*$_3$)$_3$, 10-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 142.1, 139.7, 137.2, 133.1, 133.1, 129.9, 123.1, 105.2, 55.0, 51.4, 37.6, 22.5, 21.4, 12.7, 12.3; **HRMS** (ESI+) calc. for $C_{17}H_{28}N^{79}Br^{32}S^{23}Na$ $[M+Na]^+$ 396.09672, found 396.09662.

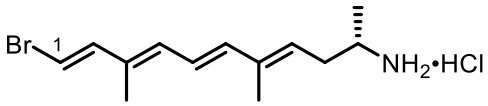
(*R*)-*N*-((*R*,4*E*,6*E*,8*E*,10*E*)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methylpropane-2-sulfinamide, ent-236



To dibromide **ent-234** (80 mg, 0.18 µmol, 1.0 eq.) was added dimethylphosphite (0.64 mL, 4.3 mmol, 25 eq.), and triethylamine (0.12 mL, 1.6 mmol, 9.0 eq.) subsequently. The mixture was stirred at ambient temperature in the dark overnight. Purification by column chromatography (petroleum ether / EtOAc, 2:3) afforded the title compound **ent-236** (30 mg, 45%) as an orange oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −32.5 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to **236**.

(*S*,4*E*,6*E*,8*E*,10*E*)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-amine hydrochloric salt, 237

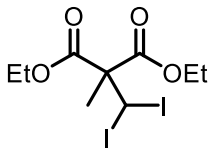


Acetylchloride (8 µL, 0.11 µmol, 2.2 eq.) was dissolved in MeOH (1.0 mL), stirred for 5 min, before adding vinyl bromide (19 mg, 51 µmol, 1.0 eq.) in MeOH (1.0 mL) at 0 °C and stirring at ambient temperature for 15 min. Concentration *in vacuo* afforded the crude title compound **237** as a yellowish, brownish waxy substance (17 mg, quant.).

^{1}H NMR (400 MHz, Methanol-d_4) δ_H 6.82 (d, J = 13.6 Hz, 1H, 2-H), 6.57 (dd, J = 15.2, 11.1 Hz, 2H, 5-H), 6.45 (d, J = 13.7 Hz, 1H, 1-H), 6.43 (d, J = 15.2 Hz, 1H, 6-H), 6.17 (d, J = 10.9 Hz, 1H, 4-H), 5.57 (t, J = 7.4 Hz, 1H, 8-H), 3.42 – 3.31 (m, 1H, 10-H), 2.62 – 2.40 (m, 2H, 9-H_2), 1.89 (s, 3H, 3-CH_3), 1.88 (s, 3H, 7-CH_3), 1.30 (d, J = 6.6 Hz,

3H, 10-CH_3); **^{13}C NMR** (101 MHz, Methanol-d_4) δ_C 143.0, 139.9, 139.7, 134.9, 133.6, 127.4, 125.0, 106.1, 34.7, 21.7, 18.7, 12.9, 12.6.

Diethyl 2-(diiodomethyl)-2-methylmalonate, 242

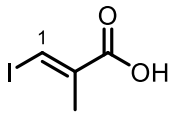


Diethyl methylmalonate (30.0 mL, 176 mmol, 1.0 eq.) was added over 30 min to a suspension of NaH (8.44 g, 60 wt% dispersion in mineral oil, 211 mmol, 1.2 eq.) in Et_2O (110 mL). The mixture was stirred at reflux for 4 h before CHI_3 (69.30 g, 176 mmol, 1.0 eq.) was added. Stirring was continued at reflux for 48 h. The mixture was cooled to 0 °C and quenched with HCl (100 mL, 1 M). After stirring for 30 min, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 120 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **242** as a brown reddish oil (76.00 g, 98%) which was used without further purification.

R_f 0.53 (petroleum ether / Et_2O, 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.77 (q, J = 0.6 Hz, 1H, C*H*I_2), 4.22 (dq, J = 7.1, 1.7 Hz, 4H, OC*H*$_2$$CH_3$), 1.80 (d, J = 0.6 Hz, 3H, C*H*$_3$), 1.29 (t, J = 7.1 Hz, 6H, OCH_2C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.2, 62.9, 62.3, 20.5, 14.1, −25.8.

The spectroscopic data is in agreement with that reported by Fürstner *et al.*[341]

(*E*)-3-Iodo-2-methylacrylic acid, 243

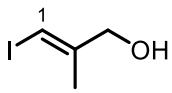


Crude malonate **242** (76.00 g, 173 mmol, 1.0 eq.) was dissolved in ethanol (320 mL) and a solution of KOH (25.20 g, 450 mmol, 2.6 eq.) in water (110 mL) was added. The resulting mixture was stirred at 100 °C overnight. After cooling, volatile materials were removed *in vacuo*, the residue was dissolved in aqueous. K_2CO_3 (10% *w/w*, 200 mL), filtered and acidified with concentrated HCl (80 mL) at 0 °C. Extraction with CH_2Cl_2 (8 × 80 mL), drying over $MgSO_4$ and concentration *in vacuo* afforded the title compound **243** as a reddish oil (28.18 g, 80%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.72 (s, 1H, COO*H*), 8.03 (q, J = 1.3 Hz, 1H, 1-H), 2.06 (d, J = 1.3 Hz, 3H, 2-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.0, 139.1, 102.1, 20.0.

The spectroscopic data is in agreement with that reported by Fürstner *et al.*[341]

(*E*)-3-iodo-2-methylprop-2-en-1-ol, 76



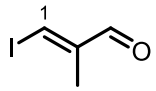
To a suspension of $LiAlH_4$ (5.12 g, 135 mmol, 1.0 eq.) in THF (200 mL) at −78 °C was added dropwise a solution of **243** (28.60 g, 135 mmol, 1.0 eq.), in THF (70 mL). The mixture was allowed to warm to ambient temperature, and stirred for 1 h. It was cooled to 0 °C, and quenched by addition of water (5.1 mL), aqueous NaOH (5.1 mL, 15% w/v) and water (15.3 mL). The mixture was then stirred at ambient temperature for 15 min, $MgSO_4$ was added, and stirred for further 15 min, filtered and concentrated *in vacuo*. The

crude product was purified by distillation (58 °C, 0.3 mbar) to afford the title compound **76** as a colourless oil (12.69 g, 47%).

B.p. 58 °C, 0.3 mbar (Lit.[342] 91 – 91 °C, 0.75 Torr); $\mathbf{R_f}$ 0.35 (petroleum ether / EtOAc, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.28 (p, J = 1.3 Hz, 1H, 1-H), 4.13 (d, J = 6.0 Hz, 2H, 3-H_2), 1.85 (d, J = 1.3 Hz, 3H, 2-CH_3), 1.62 (br s, 1H, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.3, 77.5, 67.3, 21.5.

The spectroscopic data is in agreement with that reported by Carreira *et al.*[342]

(*E*)-3-iodo-2-methylacrylaldehyde, 240

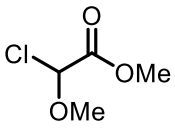


Alcohol **76** (1.00 g, 5.05 mmol, 1.0 eq.) was added to a suspension of MnO_2 (4.40 g, 50.6 mmol, 10.0 eq.) in CH_2Cl_2 (50 mL). The mixture was stirred at ambient temperature for 3 h. It was filtered over celite and concentrated *in vacuo* to afford the title compound **249** as a yellowish oil (883 mg, 89%), and was used without further purification.

$\mathbf{R_f}$ 0.48 (petroleum ether / Et_2O, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.53 (s, 1H, C*H*O), 7.81 (q, J = 1.2 Hz, 1H, 1-H), 1.92 (d, J = 1.2 Hz, 3H, 2-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 189.6, 151.0, 109.7, 16.6.

The spectroscopic data is in agreement with that reported by Kotora *et al.*[343]

Methyl 2-chloro-2-methoxyacetate, 245

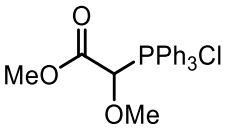


PCl_5 (9.37 g, 45.0 mmol, 1.1 eq.) was placed in a round-bottomed flask fitted with a reflux condenser, under an inert gas atmosphere. Methyl dimethoxyacetate (5.0 mL, 40.9 mmol, 1.0 eq.) was added dropwise, very slowly. After complete addition, the mixture was stirred at 140 °C for 2.5 h, then cooled to ambient temperature, and the reflux condenser replaced by a distillation bridge. Distillation afforded the title compound **245** as a colourless oil (72 °C, 20 mbar, 5.24 g, 93%).

B.p. 72 °C, 20 mbar (Lit.[344]: 60 °C, 0.1 Torr; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.75 (s, 1H, 2-H), 3.86 (s, 3H, OC*H*$_3$), 3.62 (s, 3H, CO_2C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.8, 89.6, 57.7, 53.4.

The spectroscopic data is in agreement with that reported by Crimmins and coworkers.[163,344]

(1,2-Dimethoxy-2-oxoethyl)triphenylphosphonium chloride, 77

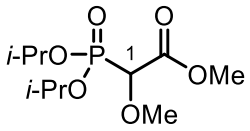


Chloride **245** (12.00 g, 86.6 mmol, 1.0 eq.) and triphenyl phosphine (22.72 g, 86.7 mmol, 1.0 eq.) were dissolved in CH_2Cl_2 (26 mL) and stirred at ambient temperature for 16 h. The mixture was concentrated until it gave a thick oil. The oil was washed with Et_2O and the solvent decanted after each wash (4 × 100 mL). The oil was dried on the high-vacuum for 48 h to afford the title compound **77** as a yellow foamy solid (33.00 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.42 (d, J = 13.4 Hz, 1H, 2-H), 8.09 – 7.29 (m, 15H, Ar*H*), 3.86 (s, 3H, OC*H*$_3$), 3.57 (s, 3H, CO_2C*H*$_3$).

The spectroscopic data is in agreement with that reported by Crimmins and coworkers.[344]

Methyl 2-(di-*iso*-propoxyphosphoryl)-2-methoxyacetate, 262

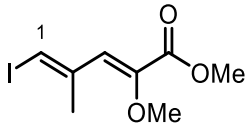


Chloride **245** (2.10 g, 15.2 mmol, 1.0 eq.) and triisopropyl phosphite (3.8 mL, 15.4 mmol, 1.0 eq.) stirred at 160 °C for 24 h. It was concentrated *in vacuo*. Purification by Kugelrohr distillation afforded the title compound **262** as a colourless oil (150 °C, 0.5 mbar, 3.38 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.84 – 4.71 (m, 2H, OC*H*$(CH_3)_2$), 4.16 (dd, J = 18.5, 1.5 Hz, 1H, 1-H), 3.81 (d, J = 1.6 Hz, 3H, OC*H*$_3$), 3.50 (d, J = 1.6 Hz, 3H, OC*H*$_3$), 1.34 (dp, J = 5.2, 1.9 Hz, 12H, OCH(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.9, 78.8 (d, J = 158.8 Hz), 72.6 (d, J = 4.6 Hz), 72.5 (d, J = 4.7 Hz), 60.4 (d, J = 12.8 Hz), 52.5, 24.1 (d, J = 2.3 Hz), 24.1 (d, J = 1.8 Hz), 23.7 (d, J = 1.2 Hz), 23.7 (d, J = 1.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 12.0.

The spectroscopic data is in agreement with that reported by Taft and coworkers.[345]

Methyl (2*Z*,4*E*)-5-iodo-2-methoxy-4-methylpenta-2,4-dienoate, 74

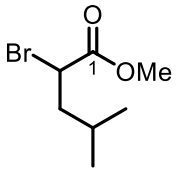


DBU (3.8 mL, 24.7 mmol, 5.0 eq.) was added dropwise to a solution of phosphonium chloride **77** (10.53 g, 26.3 mmol, 5.2 eq.) in acetonitrile (15 mL) and stirred for 30 min. A solution of aldehyde **240** (883 mg, 4.51 mmol, 1.0 eq.) in acetonitrile (5 mL) was added, and the mixture was stirred at 80 °C overnight. The mixture was put directly onto silica to purify by column chromatography (petroleum ether / Et_2O, 1:0 →19:1), and afforded the title compound **74** as an orange oil (890 mg, 70%).

R_f 0.41 (petroleum ether / Et_2O, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.86 (p, J = 1.1 Hz, 1H, 1-H), 6.58 (d, J = 0.8 Hz, 1H, 3-H), 3.80 (s, 3H, OC*H*$_3$), 3.70 (s, 3H, COOC*H*$_3$), 2.12 (d, J = 1.1 Hz, 3H, 2-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.8, 144.0, 142.0, 124.1, 90.5, 60.0, 52.4, 23.4.

The spectroscopic data is in agreement with that reported by Lim.[73]

Methyl 2-bromo-4-methylpentanoate, 247

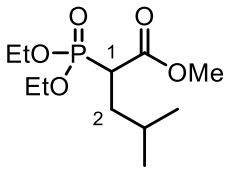


4-Methylvaleric acid (2.5 mL, 20 mmol, 1.0 eq.) was dissolved in PBr_3 (1.95 mL, 20.8 mmol, 1.04 eq.) and bromine (2.6 mL, 50 mmol, 2.5 eq.). The mixture was stirred at 80 °C overnight. It was cooled to 0 °C and methanol (8 mL) was added dropwise and then stirred at 70 °C for 2 h. After cooling to ambient temperature it was quenched with water (40 mL) and aqueous $Na_2S_2O_3$ (10 mL), extracted with Et_2O (3 × 50 mL), the combined organics were dried over $MgSO_4$, and concentrated *in vacuo* to afford crude **247** (4.11 g, 99%) as a yellow oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.29 (t, J = 7.7 Hz, 1H, 2-H), 3.78 (s, 3H, OCH_3), 1.94 – 1.88 (m, 2H, 3-H_2), 1.76 (hept, J = 6.6 Hz, 1H, 4-H), 0.95 (d, J = 6.6 Hz, 3H, 4-CH_3), 0.91 (d, J = 6.6 Hz, 3H, 4-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.8, 53.1, 44.5, 43.6, 26.5, 22.5, 21.7.

The spectroscopic data is in agreement with that reported by Géant and coworkers.[164]

Methyl 2-(diethoxyphosphoryl)-4-methylpentanoate, 248

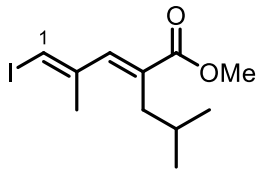


Methyl 2-bromo-4-methylpentanoate (1.00 g, 4.78 mmol, 1.0 eq.) and triethyl phosphite (1.64 mL, 9.56 mmol, 2.0 eq.) were stirred at 170 °C overnight. Purification by Kugelrohr distillation (80 °C, 0.5 mbar to remove most impurities, 120 °C, 0.5 mbar to get the pure product) afforded the title compound **248** as a colourless oil (1.12 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.20 – 4.08 (m, 4H, P(OC$H_2$$CH_3$)$_2$), 3.75 (d, J = 0.7 Hz, 3H, OCH_3), 3.06 (ddd, J = 23.2, 11.6, 3.1 Hz, 1H, 1-H), 2.06 – 1.91 (m, 1H, 3-H), 1.67 – 1.51 (m, 2H, 2-H_2), 1.33 (tt, J = 7.1, 0.9 Hz, 6H, P(OCH$_2$CH_3)$_2$), 0.91 (d, J = 6.3 Hz, 3H, 4-H_3), 0.89 (d, J = 6.3 Hz, 3H, 4′-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.1 (d, J = 4.7 Hz), 62.9 (d J = 7.9 Hz), 62.8 (d, J = 7.9 Hz), 52.5, 44.0 (d, J = 131.1 Hz), 35.7 (d, J = 4.9 Hz), 27.1 (d, J = 14.4 Hz), 23.0, 21.4, 16.6 (d, J = 3.3 Hz), 16.5 (d, J = 3.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 23.2.

The spectroscopic data is in agreement with that reported by Donald and coworkers.[165]

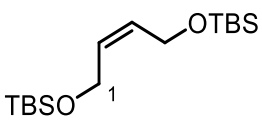
Methyl (2*E*,4*E*)-5-iodo-2-isobutyl-4-methylpenta-2,4-dienoate, 249



Phosphonate **248** (105 mg, 394 µmol, 2.2 eq.) and 18-crown-6 (104 mg, 393 µmol, 2.15 eq.) were dissolved in THF (1.0 mL). A solution of KHMDS in toluene (0.72 mL, 0.5 M, 0.36 mmol, 2.0 eq.) was added dropwise at 0 °C, and stirred for 30 min before aldehyde **240** (35 mg, 0.18 µmol, 1.0 eq.) in THF (0.8 mL) was added. The mixture was stirred at ambient temperature overnight. It was quenched with a phosphate buffer (pH = 7, 3 mL) and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organics were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 15:1) afforded the title compound **249** (25 mg, 45%) as a colourless oil.

IR (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 2361, 2280, 1716, 1435, 1263, 1246, 1222, 1134; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.98 (s, 1H, 3-H), 6.31 (s, 1H, 1-H), 3.68 (s, 3H, CO_2CH_3), 2.24 (d, J = 7.2 Hz, 2H, 4-CH_2CH(CH_3)$_2$), 1.92 (s, 3H, 2-CH_3), 1.75 – 1.62 (m, 1H, 4-CH_2CH(CH_3)$_2$), 0.79 (d, J = 6.7 Hz, 6H, 4-CH_2CH(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.8, 143.6, 139.5, 132.5, 84.1, 51.9, 36.0, 28.3, 24.4, 22.4.

(*Z*)-buten-1,4-di-*tert*-butyldiemthyl silyl ether, 258



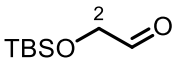
To a solution of TBS chloride (10.4 g, 69.0 mmol, 2.3 eq.) and imidazole (3.21 g, 47.2 mmol, 1.6 eq.) in DMF (50 mL) at 0 °C, was added *Z*-buten-1,4-diol (2.5 mL,

30 mmol, 1.0 eq.) in THF (10 mL). The resulting mixture was stirred at ambient temperature overnight, before being quenched by addition of water (200 mL). It was extracted with EtOAc (3 × 50 mL), the combined organics were washed with aqueous NaOH (5 wt. %, 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound **258** (8.76 g, 91%) as a colourless oil, which was used without further purification.

R_f 0.88 (petroleum ether / Et_2O, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.55 (ddd, J = 4.2, 3.1, 0.8 Hz, 2H, 2-H), 4.30 – 4.18 (m, 4H, 1-H_2), 0.90 (s, 18H, Si(C(CH_3)$_3$), 0.07 (s, 12H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 130.3, 59.8, 26.1, 18.5, −5.0.

The spectroscopic data is in agreement with that reported by Tran and Woerpel.[346]

2-((*tert*-Butyldimethylsilyl)oxy)acetaldehyde, 259

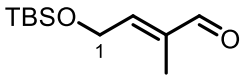


Alkene **258** (8.76 g, 27.7 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (150 mL) and cooled to −78 °C. Oxygen was passed through the solution for 5 min, before ozone was passed through the solution until it turned blue. Then oxygen was passed through it until it turned colourless again, followed by degassing the mixture with nitrogen for 10 min. Triphenylphosphine (8.71 g, 33.2 mmol, 1.2 eq.) was added and the mixture was stirred at ambient temperature for 2.5 h. It was concentrated *in vacuo*, the residue taken up with petroleum ether and filtered. Concentration *in vacuo* followed by purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **259** (8.06 g, 84%) as a colourless oil.

R_f 0.36 (petroleum ether / Et_2O, 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.70 (t, J = 0.9 Hz, 1H, C*H*O), 4.21 (d, J = 0.9 Hz, 2H, 2-H_2), 0.92 (s, 9H, Si(C(C*H*$_3$)$_3$)), 0.10 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.4, 69.8, 25.9, 18.5, −5.3.

The spectroscopic data is in agreement with that reported by Vanier and coworkers.[347]

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbut-2-enal, 260

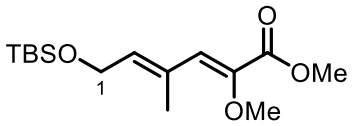


Aldehyde **259** (1.80 g, 10.3 mmol, 1.0 eq.) and ylid **87** (4.93 g, 15.5 mmol, 1.5 eq.) were dissolved in PhMe (74 mL) and stirred at 80 °C overnight. After cooling to ambient temperature, the mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 30:1→20:1→15:1) afforded the title compound **260** (1.37 g, 62%) as a colourless oil.

R_f 0.52 (petroleum ether / Et_2O, 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.43 (s, 1H, C*H*O), 6.53 (tq, J = 5.4, 1.3 Hz, 1H, 2-H), 4.51 (dq, J = 5.4, 1.2 Hz, 2H, 1-H_2), 1.73 (d, J = 1.3 Hz, 3H, 3-CH_3), 0.92 (s, 9H, Si(C(C*H*$_3$)$_3$)), 0.11 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.8, 153.3, 137.9, 60.7, 26.0, 18.5, 9.5, −5.1.

The spectroscopic data is in agreement with that reported by Lafontaine and coworkers.[348]

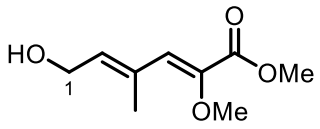
Methyl (2*Z*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-4-methylhexa-2,4-dienoate, 261



To a solution of phosphonate **262** (413 mg, 1.54 mmol, 2.2 eq.) and 18-crown-6 (399 mg, 1.51 mmol, 2.15 eq.) in THF (4 mL) at 0 °C, was added dropwise a solution of KHMDS in toluene (2.8 mL, 0.5 M, 1.4 mmol, 2.0 eq.), and the resulting mixture was stirred for 30 min. Aldehyde **260** (150 mg, 700 μmol, 1.0 eq.) in THF (1.4 mL) was added and the mixture stirred at ambient temperature for 6 h. It was quenched by addition of phosphate buffer (10 mL, pH = 7), extracted with EtOAc (3 × 15 mL), the combined organics washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 30:1→15:1) afforded the title compound **261** as a colourless oil (129 mg, 61%).

R_f 0.42 (petroleum ether / Et_2O, 20:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 2930, 2856, 1722, 1251, 1106, 1069, 1020, 837, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.57 (s, 1H, 4-H), 5.89 (t, J = 6.1 Hz, 1H, 2-H), 4.33 (d, J = 6.0 Hz, 2H, 1-H_2), 3.79 (s, 3H, 5-OCH_3), 3.66 (s, 3H, OCH_3), 1.94 (d, J = 1.5 Hz, 3H, 3-CH_3), 0.90 (s, 9H, Si(C(CH_3)$_3$)), 0.08 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.3, 144.1, 137.9, 131.6, 128.6, 60.4, 60.3, 52.1, 26.1, 18.5, 15.3, −5.0; **HRMS** (ESI+) calc. for $C_{15}H_{28}O_3{}^{28}Si^{23}Na$ $[M+Na]^+$ 323.166491, found 323.16484.

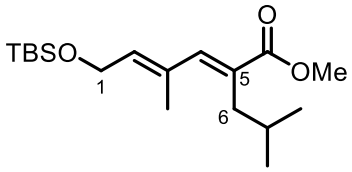
Methyl (2*Z*,4*E*)-6-hydroxy-2-methoxy-4-methylhexa-2,4-dienoate, 263



Silylether **261** (28 mg, 93 µmol, 1.0 eq.) was dissolved in THF (1.2 mL) and TBAF (0.11 mL, 1.0 M in THF, 0.11 mmol, 1.2 eq.) was added. After stirring for 1 h, brine (5 mL) and water (8 mL) were added, it was extracted with Et_2O (3 × 15 mL), the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 7:3→1:1) afforded the title compound **263** as a colourless oil (14 mg, 81%).

R*f* 0.32 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3398, 2953, 2851, 1718, 1436, 1348, 1254, 1199, 1103, 1014, 775; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.56 (s, 1H, 4-H), 5.95 (t, *J* = 6.6 Hz, 1H, 2-H), 4.29 (d, *J* = 6.6 Hz, 2H, 1-H_2), 3.79 (s, 3H, 5-OCH_3), 3.66 (s, 3H, OC*H*$_3$), 1.97 (s, 3H, 3-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.2, 144.5, 136.0, 133.3, 128.1, 60.3, 59.5, 52.2, 15.3; **HRMS** (ESI+) calc. for $C_9H_{14}O_4{}^{23}Na$ $[M+Na]^+$ 209.07843, found 209.07854.

Methyl (2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-2-*iso*-butyl-4-methylhexa-2,4-dienoate, 265

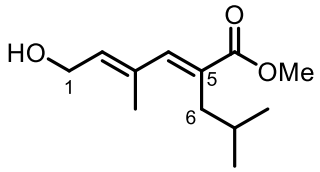


Phosphonate **248** (62 mg, 0.23 mmol, 1.0 eq.) was dissolved in THF (0.4 mL) at 0 °C and NaH (60% dispersion in mineral oil, 10 mg, 0.25 mmol, 1.1 eq.) was added and the mixture was stirred for 30 min. Aldehyde **260** (50 mg, 0.23 mmol, 1.0 eq.) in THF

(0.2 mL) was added, the mixture stirred at ambient temperature overnight, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 15:1) afforded the title compound **265** (28 mg, 37%) as a colourless oil.

R_f 0.78 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 2928, 2857, 1713, 1258, 1227, 1109, 1059, 909, 836, 777, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.10 (s, 1H, 4-H), 5.68 (t, J = 6.2 Hz, 1H, 2-H), 4.30 (d, J = 6.2 Hz, 2H, 1-H_2), 3.74 (s, 3H, OCH_3), 2.39 (d, J = 7.2 Hz, 2H, 6-H_2), 1.80 (s, 3H, 3-CH_3), 1.36 – 1.21 (m, 1H, 7-H), 0.90 (s, 9H, Si(C(CH_3)$_3$)), 0.86 (d, J = 6.8 Hz, 6H, 8-H_3, 8′-CH_3), 0.08 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.7, 142.9, 134.4, 132.5, 131.0, 60.3, 51.9, 35.8, 29.9, 28.7, 26.1, 22.6, 18.5, 16.7, −5.0; **HRMS** (ESI+) calc. for $C_{18}H_{34}O_3{}^{28}Si^{23}Na$ $[M+Na]^+$ 349.21694, found 349.21696.

Methyl (2*E*,4*E*)-6-hydroxy-2-*iso*-butyl-4-methylhexa-2,4-dienoate, 266

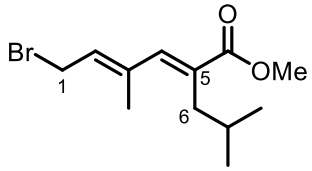


A TBAF solution (0.37 mL, 1.0 M in THF, 0.37 mmol, 1.0 eq.) was added to a solution of silyl ether **265** (120 mg, 367 µmol, 1.0 eq.) in THF (3.7 mL) and stirred for 30 min. The reaction was quenched with water (10 mL), extracted with Et_2O (3 × 15 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:2) afforded the title compound **266** as a colourless oil (60 mg, 77%).

R_f 0.24 (petroleum ether / Et_2O, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.12 (s, 1H, 4-H), 5.74 (tq, J = 6.6, 1.4 Hz, 1H, 2-H), 4.29 (d, J = 6.6 Hz, 2H, 1-H_2), 3.75 (s, 3H, $CO_2C$$H_3$),

2.38 (d, J = 7.2 Hz, 2H, 6-H_2), 1.85 (s, 3H, 3-CH_3), 1.76 (t of hept, J = 13.7, 6.9 Hz, 1H, 7-H), 0.87 (d, J = 6.7 Hz, 6H, 8-H_3, 8′-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.6, 142.6, 134.6, 132.6, 131.6, 59.6, 52.0, 35.8, 28.7, 22.6, 16.6.

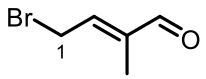
Methyl (2*E*,4*E*)-6-bromo-2-*iso*-butyl-4-methylhexa-2,4-dienoate, 267



A mixture of alcohol **266** (14 mg, 66 µmol, 1.0 eq.), CBr_4 (27 mg, 81 µmol, 1.25 eq.), and triphenylphosphine (31 mg, 0.12 mmol, 1.8 eq.) was dissolved in CH_2Cl_2 (0.2 mL), and the resulting mixture stirred at ambient temperature for 1 h, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **267** as a colourless oil (9 mg, 50%) as a inseparable mixture with an unidentified byproduct.

R_f 0.75 (petroleum ether / Et_2O, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 (s, 1H, 4-H), 5.84 (t, J = 8.6 Hz, 1H, 2-H), 4.08 (d, J = 8.6 Hz, 2H, 1-H_2), 3.75 (s, 3H, $CO_2C\mathit{H_3}$), 2.38 (d, J = 7.2 Hz, 2H, 6-H_2), 1.89 (s, 3H, 3-CH_3), 1.76 (t, J = 6.7 Hz, 1H, 7-H), 0.87 (d, J = 6.7 Hz, 6H, 8-H_3, 8'-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.3, 141.8, 138.1, 132.9, 128.0, 52.0, 35.9, 28.1, 22.6, 16.2.

(*E*)-4-bromo-2-methylbut-2-enal, 252

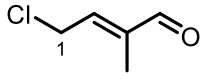


A mixture of epoxide **254** (500 mg, 5.94 mmol, 1.0 eq.), copper(II) bromide (2.788 g, 12.5 mmol, 2.1 eq.), and lithium carbonate (593 mg, 8.03 mmol, 1.35 eq.), in EtOAc (6.0 mL) and chloroform (6.0 mL) was heated to 90 °C for 20 min. After cooling to 10 °C, water (10 mL) was added, stirred for 15 min, and filtered. The filtrate was extracted with petroleum ether (2 × 20 mL), the combined organics washed with water (2 × 20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **252** as a yellow oil (468 mg, 48%).

R_f 0.33 (petroleum ether / Et_2O, 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.48 (d, J = 0.7 Hz, 1H, C*H*O), 6.65 (tq, J = 8.2, 1.5 Hz, 1H, 2-H), 4.17 (d, J = 8.2 Hz, 2H, 1-H_2), 1.82 (s, 3H, 3-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.4, 145.6, 141.5, 25.2, 9.1.

The spectroscopic data is in agreement with that reported by Gray.[170]

(*E*)-4-Chloro-2-methylbut-2-enal, 255

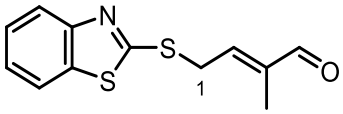


A mixture of epoxide **254** (500 mg, 5.94 mmol, 1.0 eq.), copper(II) chloride (799 mg, 5.94 mmol, 1.0 eq.), and lithium chloride (252 mg, 5.94 mmol, 1.0 eq.) in EtOAc (5.0 mL) was heated at 80 °C for 30 min. Ice was added to the mixture, and then filtered, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by cholumn chromatography (CH_2Cl_2, 100%) afforded the title compound **255** as a yellow oil (188 mg, 27%).

R_f 0.62 (CH_2Cl_2, 100%); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.49 (s, 1H, C*H*O), 6.56 (tq, *J* = 7.5, 1.5 Hz, 1H, 2-H), 4.31 (dq, *J* = 7.5, 0.7 Hz, 2H, 1-H_2), 1.83 (dt, *J* = 1.5, 0.7 Hz, 3H, 3-CH_3).

The spectroscopic data is in agreement with that reported by Hecht and coworkers.[171]

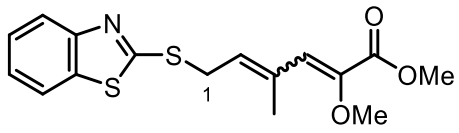
(*E*)-4-(Benzo[*d*]thiazol-2-ylthio)-2-methylbut-2-enal, 271



Procedure adapted from literature procedure.[177] Aldehyde **251** (102 mg, 626 µmol, 1.05 eq.), 2-mercaptobenzothiazole (100 mg, 598 µmol, 1.0 eq.) and triethylamine (0.1 mL, 717 µmol, 1.2 eq.) were dissolved in THF (7.5 mL) at 0 °C and stirred at this temperature for 36 h. Water (10 mL) was added, the volatiles were removed *in vacuo* and extracted with CH_2Cl_2 (3 × 20 mL), the combined organics dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1 →10:1) afforded the title compound **271** as a yellowish oil (142 mg, 95%).

R_f 0.26 (petroleum ether / Et_2O, 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.44 (s, 1H, C*H*O), 7.87 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.77 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.7 Hz, 1H, Ar*H*), 7.32 (t, *J* = 7.7 Hz, 1H, Ar*H*), 6.68 (t, *J* = 7.7 Hz, 1H, 2-H), 4.27 (d, *J* = 7.7 Hz, 2H, 1-H_2), 1.91 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 194.8, 164.7, 153.1, 146.6, 141.5, 135.7, 126.4, 124.7, 121.8, 121.3, 30.8, 9.6; **HRMS** (ESI+) calc. for $C_{12}H_{12}NOS_2$ $[M+H]^+$ 250.03548, found 250.03559.

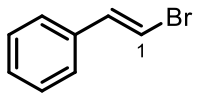
Methyl 6-(benzo[*d*]thiazol-2-ylthio)-2-methoxy-4-methylhexa-2,4-dienoate, 272



KHMDS (0.42 mL, 0.5 M in toluene) was added dropwise to a solution of phosphonate **262** (65 mg, 262 µmol, 1.2 eq.) in THF (1.0 mL) and stirred at ambient temperature for 30 min. Aldehyde **271** (50 mg, 201 µmol, 1.0 eq.) in THF (0.6 mL) was added and the mixture was stirred at ambient temperature for 6 h. The reaction was quenched by addition of phosphate buffer (3 mL, pH = 7), diluted with EtOAc (8 mL), separated and the aqueous layer extracted with EtOAc (3 × 4 mL), the combined organics washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 10:1) afforded the title compound **272** as a colourless oil (15 mg, 22%) as an *E*/*Z*-mixture, 2:1. The analytical data shown corresponds to the major isomer.

R*f* 0.35 (petroleum ether / Et_2O, 5:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 1681, 1459, 1426, 1240, 993, 756, 727; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.87 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.75 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.42 (t, *J* = 7.2 Hz, 2 H, Ar*H*), 7.30 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.57 (s, 1H, 4-H), 6.06 (t, *J* = 8.0 Hz, 1H, 2-H), 4.13 (d, *J* = 8.0 Hz, 2H, 1-H_2), 3.78 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 2.11 (s, 3H, 3-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.9, 164.9, 153.2, 144.5, 135.8, 130.3, 127.6, 126.1, 124.3, 121.6, 121.0, 60.2, 52.1, 31.4, 22.8, 15.1.

β-Bromostyrene, 333

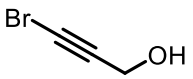


Prepared according to literature procedure.[234] NaOH (3.40 g, 85.0 mmol, 0.85 eq.) and an *E*/*Z*-mixture of β-bromostyrene (12.8 mL, 100 mmol, 1.0 eq.) were dissolved in isopropanol (100 mL) and heated at reflux for 2 h. After cooling to ambient temperature, the mixture was diluted with water (50 mL) and pentane (50 mL), and the organics were washed with water (2 × 25 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Distillation afforded the title compound **333** (14.13 g, 77%) as a yellowish oil and *E*-isomer only.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.24 (m, 5H, Ar*H*), 7.11 (d, J = 14.0 Hz, 1H, 2-H), 6.78 (d, J = 14.0 Hz, 1H, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.3, 136.1, 128.9, 128.4, 126.2, 106.7.

The spectroscopic data is in agreement with that reported by Müller and Alexakis.[234]

3-Bromoprop-2-yn-1-ol, 334

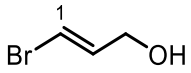


NBS (5.04 g, 28.3 mmol, 1.1 eq.), and $AgNO_3$ (438 mg, 2.58 mmol, 0.1 eq.) were added to a solution of propargyl alcohol (1.5 mL, 26 mmol, 1.0 eq.) in acetone (130 mL) and stirred at ambient temperature for 3 h. It was diluted with pentane, filtered, and the filtrate concentrated *in vacuo*. The residue was taken up in water and extracted with Et_2O (3 × 20 mL), the combined organics washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford crude title compound **334** (2.66 g, 70%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.30 (s, 2H, 3-H_2), 2.37 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 78.3, 52.1, 46.1.

The spectroscopic data is in agreement with that reported by Ouyang and coworkers.[349]

(*E*)-3-bromoprop-2-en-1-ol, 335

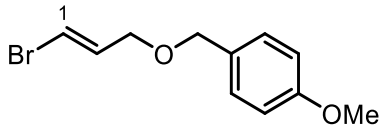


Prepared according to a literature procedure.[235] A solution of $AlCl_3$ (3.42 g, 25.6 mmol, 1.3 eq.) in Et_2O (11 mL) was added dropwise to a suspension of $LiAlH_4$ (1.35 g, 35.6 mmol, 1.8 eq.) in Et_2O (11 mL) at −30 °C, followed by dropwise addition of crude bromoalkyne **334** (2.66 g, 19.7 mmol, 1.0 eq.) in Et_2O (11 mL). The mixture was heated to 40 °C, stirred for 4 h, followed by allowing it to cool to ambient temperature and stirred overnight. The reaction was cooled to −10 °C and quenched by subsequent addition of Et_2O (11 mL), water (1.1 mL) and aqueous NaOH (5%, 1.1 mL). The resulting suspension was filtered over Celite, the filtercake washed with Et_2O. The combined filtrates were separated, and the organics dried over K_2CO_3, and concentrated *in vacuo*. Purification by distillation (74 °C, 20 mbar) afforded the title compound **335** (1.01 g, 37%) as a colourless oil.

B.p. 74 °C, 20 mbar, (Lit.[235]: 75 °C, 25 mbar); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.38 – 6.35 (m, 2H, 1-H, 2-H), 4.15 – 4.09 (m, 2H, 3-H_2), 1.65 – 1.60 (m, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.5, 107.9, 63.0.

The spectroscopic data is in agreement with that reported by Brückner *et al.*[235]

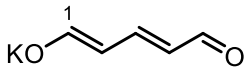
(*E*)-1-(((3-Bromoallyl)oxy)methyl)-4-methoxybenzene, 336



p-(Methoxybenzyl)-trichloroacetimidate (2.3 mL, 11 mmol, 1.5 eq.) and scandium (III) triflate (539 mg, 1.10 mmol, 0.15 eq.) were added to a solution of alcohol **335** (1.00 g, 7.30 mmol, 1.0 eq.) in toluene (46 mL). The reaction was stirred for 2 h, then quenched with $NaHCO_3$ solution, extracted with Et_2O (3 × 30 mL), the combined organics washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 50:1 →25:1) afforded the title compound **336** (1.10 g, 59%) as a colourless oil.

R*f* 0.56 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2837, 1613, 1513, 1302, 1248, 1174, 1103, 1035, 930, 820; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.22 (m, 2H, Ar*H*), 6.93 – 6.84 (m, 2H, Ar*H*), 6.40 – 6.27 (m, 2H, 1-H, 2-H), 4.45 (s, 2H, OC*H*$_2$Ar), 3.95 (d, *J* = 4.9 Hz, 2H, 3-H_2), 3.81 (s, 3H, ArOC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 134.4, 129.9, 129.6, 114.0, 108.7, 72.1, 69.5, 55.4; **HRMS** (CI+) calc. for $C_{11}H_{17}BrNO_2$ $[M+NH_4]^+$ 274.0435, found 274.0443.

Glutaconaldehyde potassium salt, 341



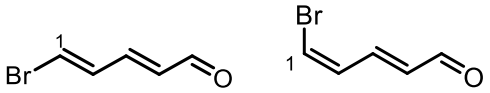
Prepared according to a literature procedure.[236,237] Pyridine·SO_3 complex (20.0 g, 126 mmol, 1.0 eq.) was added to a solution of potassium hydroxide (26.1 g, 465 mmol, 3.7 eq.) in water (70 mL) at −20 °C and stirred at this temperature for 1 h, before being warmed to ambient temperature and stirred for 4 h. The mixture was heated to 40 °C for 30 min, then cooled to 5 °C. The precipitate was collected by filtration and washed with

acetone (2 × 20 mL), and dried in air. The crude material was redissolved in methanol (460 mL), heated to reflux, activated carbon (1 g) added, and stirred for 10 min. The mixture was filtered over Celite, and the filtrate concentrated *in vacuo* to ~20 mL volume. It was cooled to 0 °C and the precipitate collected by filtration, followed by washing with cold acetone, and dried *in vacuo* to give title compound **341** (9.81 g, 57%) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.66 (d, J = 9.1 Hz, 2H, 1-H, 5-H), 7.04 (t, J = 13.1 Hz, 1H, 3-H), 5.11 (dd, J = 13.1, 9.2 Hz, 2H, 2-H, 4-H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C 184.4, 159.9, 106.3.

The spectroscopic data is in agreement with that reported by Becher.[236,237]

(2*E*,4*E*)-5-Bromopenta-2,4-dienal, *EE*-342 and (2*E*,4*Z*)-5-Bromopenta-2,4-dienal, *ZE*-342



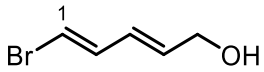
To a solution of triphenylphosphine (4.29 g, 16.4 mmol, 1.1 eq.) in CH_2Cl_2 (80 mL) at 0 °C, was added bromine (0.82 mL, 16 mmol, 1.1 eq.), followed by glutaconaldehyde potassium salt (2.00 g, 14.7 mmol, 1.0 eq.). The resulting mixture was stirred in the dark at ambient temperature for 16 h. $NaHCO_3$ (50 mL, 5% w/v) was added and the mixture was extracted with Et_2O (70 mL), the combined organics washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O 7:3, 2nd column petroleum ether / Et_2O, 49:1) afforded the title compounds ***ZE*-342** (520 mg, 22%), and ***EE*-342** (690 mg, 29%) as brown solids.

***ZE*-342: R_f** 0.55 (petroleum ether / Et_2O, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.69 (d, J = 7.9 Hz, 1H, C*H*O), 7.46 (ddd, J = 15.5, 10.6, 1.0 Hz, 1H, 3-H), 6.92 (dd, J = 10.6, 7.3 Hz, 1H, 2-H), 6.74 (d, J = 7.3 Hz, 1H, 1-H), 6.32 (dd, J = 15.5, 7.9 Hz, 1H, 4-H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.7, 145.8, 134.6, 13097, 119.2.

***EE*-342: R_f** 0.45 (petroleum ether / Et_2O, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.58 (d, J = 7.8 Hz, 1H, C*H*O), 7.06 – 6.93 (m, 3H), 6.25 – 6.11 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.3, 147.9, 135.7, 132.0, 120.0.

The spectroscopic data is in agreement with that reported by Duhamel *et al*.[238]

(2*E*,4*E*)-5-Bromopenta-2,4-dien-1-ol, 344

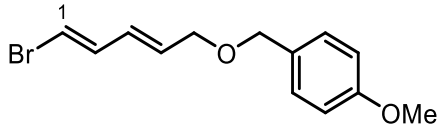


DIBALH (6.4 mL, 1.0 M in cyclohexane, 6.4 mmol, 1.5 eq.) was added dropwise to a solution of aldehyde ***EE*-342** (680 mg, 4.22 mmol, 1.0 eq.) in CH_2Cl_2 (11.0 mL) at −78 °C. After stirring at this temperature for 1 h, the reaction was quenched by subsequent addition of water (0.26 mL), aqueous NaOH (0.26 mL, 15%), and water (0.64 mL), followed by warming it to ambient temperature. $MgSO_4$ was added, the mixture stirred for 15 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1) afforded the title compound **344** as a light yellow oil (492 mg, 71%).

R_f 0.28 (petroleum ether / Et_2O, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.73 (dd, J = 13.5, 10.8 Hz, 1H, 2-H), 6.33 (dt, J = 13.5, 0.8 Hz, 1H, 1-H), 6.20 (ddt, J = 15.3, 10.7, 1.7 Hz, 1H, 3-H), 5.87 (dtt, J = 15.3, 5.4, 0.8 Hz, 1H, 4-H), 4.17 (t, J = 4.1 Hz, 2H, 5-H_2), 1.49 (t, J = 4.9 Hz, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.8, 133.4, 128.3, 109.2, 63.0.

The spectroscopic data is in agreement with that reported by Petasis.[350]

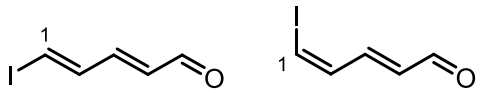
1-((((2*E*,4*E*)-5-Bromopenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene, 346



p-(Methoxybenzyl)-trichloroacetimidate (0.91 mL, 4.4 mmol, 1.5 eq.) and scandium (III) triflate (215 mg, 437 μmol, 0.15 eq.) were added to a solution of alcohol **344** (468 mg, 2.87 mmol, 1.0 eq.) in toluene (19 mL). The reaction was stirred for 2 h, then quenched with $NaHCO_3$ solution, extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 50:1 →25:1) afforded the title compound **346** (1.10 g, 59%) as a yellow oil.

R*f* 0.19 (petroleum ether / Et_2O, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2836, 1612, 1585, 1512, 1463, 1359, 1302, 1247, 1174, 1107, 1035, 979, 820, 736; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (m, 2H, Ar*H*), 6.91 – 6.85 (m, 2H, Ar*H*), 6.72 (ddd, *J* = 13.6, 10.8, 0.8 Hz, 1H, 2-H), 6.31 (dt, *J* = 13.5, 0.7 Hz, 1H, 1-H), 6.19 (ddtd, *J* = 15.4, 10.9, 1.6, 0.6 Hz, 1H, 3-H), 5.82 (dtt, *J* = 15.4, 5.8, 0.8 Hz, 1H, 4-H), 4.44 (s, 2H, OC*H*$_2$Ar), 4.03 – 3.96 (m, 2H, 5-H_2), 3.80 (s, 3H, ArOC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 137.0, 131.2, 130.2, 129.5, 114.0, 109.1, 72.2, 69.7, 55.4; **HRMS** (CI+) calc. for $C_{13}H_{15}O_2{}^{79}Br$ $[M+H]^+$ 283.0331, found 283.0326.

(2*E*,4*E*)-5-Iodopenta-2,4-dienal, *EE*-343 and (2*E*,4*Z*)-5-Iodopenta-2,4-dienal, *ZE*-343



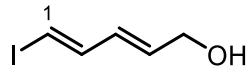
To a solution of triphenylphosphine (10.59 g, 40.4 mmol, 1.1 eq.) in CH_2Cl_2 (200 mL) at 0 °C, was added iodine (10.25 g, 41.7 mmol, 1.1 eq.), followed by glutaconaldehyde potassium salt (5.00 g, 36.7 mmol, 1.0 eq.). The resulting mixture was stirred in the dark at ambient temperature for 72 h. $NaHCO_3$ (100 mL, 5% w/v) was added and the mixture was extracted with Et_2O (3 × 150 mL), the combined organics washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography twice (petroleum ether / Et_2O 7:3, 2nd column petroleum ether / Et_2O, 49:1) afforded the title compounds ***ZE*-343** (1.923 g, 25%), and ***EE*-343** (2.175 g, 28%) as orange solids.

***ZE*-343: R_f** 0.32 (petroleum ether / Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.70 (d, J = 7.9 Hz, 1H, C*H*O), 7.33 – 7.18 (m, 1H, 3-H), 7.08 – 6.99 (m, 2H, 1-H, 2-H), 6.37 (dd, J = 15.3, 7.9 Hz, 1H, 4-H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.7, 150.0, 136.8, 135.1, 95.2.

***EE*-343: R_f** 0.24 (petroleum ether / Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_C 9.58 (d, J = 7.8 Hz, 1H, C*H*O), 7.31 (ddd, J = 14.5, 10.9, 0.7 Hz, 1H, 2-H), 7.15 (dt, J = 14.5, 0.6 Hz, 1H, 1-H), 6.97 (ddd, J = 15.4, 10.9, 0.5 Hz, 1H, 3-H), 6.14 (ddt, J = 15.3, 7.8, 0.7 Hz, 1H, 4-H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.4, 149.7, 143.3, 131.3, 92.3.

The spectroscopic data is in agreement with that reported by Duhamel *et al*.[238]

(2*E*,4*E*)-5-Iodopenta-2,4-dien-1-ol, 345

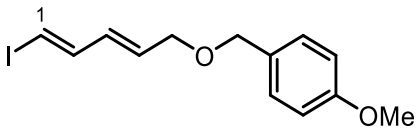


DIBALH (3.6 mL, 1.0 M in cyclohexane, 3.6 mmol, 1.5 eq.) was added dropwise to a solution of aldehyde ***EE*-343** (500 mg, 2.40 mmol, 1.0 eq.) in CH_2Cl_2 (6.0 mL) at −78 °C. After stirring at this temperature for 1 h, the reaction was quenched by subsequent addition of water (0.15 mL), aqueous NaOH (0.15 mL, 15%), and water (0.36 mL), followed by warming it to ambient temperature. $MgSO_4$ was added, the mixture stirred for 15 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 3:1) afforded the title compound **345** as a light yellow oil (382 mg, 76%).

R*f* 0.20 (petroleum ether / Et_2O, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.05 (dd, J = 14.4, 10.6 Hz, 1H, 2-H), 6.35 (d, J = 14.4 Hz, 1H, 1-H), 6.20 (ddt, J = 15.4, 10.6, 1.7 Hz, 1H, 3-H), 5.86 (dt, J = 15.3, 5.5 Hz, 1H, 4-H), 4.16 (t, J = 5.1 Hz, 2H, 5-H_2), 1.43 (t, J = 5.8 Hz, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.6, 133.2, 130.7, 79.6, 62.9.

The spectroscopic data is in agreement with that reported by Li and coworkers.[351]

1-((((2*E*,4*E*)-5-Iodopenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene, 347



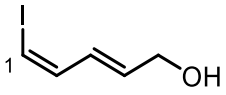
Procedure 1: Alcohol **345** (280 mg, 1.33 mmol, 1.0 eq.) was dissolved in THF (6.7 mL) at 0 °C and NaH (60% dispersion in mineral oil, 53 mg, 1.3 mmol, 1.0 eq.) was added. The mixture was stirred at 0 °C for 20 min, before *p*-methoxybenzyl chloride (0.27 mL, 2.0 mmol, 1.5 eq.) was added and the mixture was stirred overnight and slowly warmed

to ambient temperature. Water (15 mL) was added, the mixture extracted with Et_2O (3 × 15 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 15:1) afforded the title compound **347** (183 mg, 42%) as a yellowish oil.

Procedure 2: *p*-(Methoxybenzyl)-trichloroacetimidate (0.55 mL, 2.7 mmol, 1.5 eq.) and scandium (III) triflate (130 mg, 264 µmol, 0.15 eq.) were added to a solution of alcohol **345** (370 mg, 1.76 mmol, 1.0 eq.) in toluene (11 mL). The reaction was stirred for 2 h, then quenched with $NaHCO_3$ solution, extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 15:1) afforded the title compound **347** (476 mg, 82%) as a colourless oil.

R$_f$ 0.70 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2836, 1612, 1512, 1302, 1247, 1174, 1109, 1034, 980, 820; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 – 7.24 (m, 2H, Ar*H*), 7.04 (dt, *J* = 14.4, 10.7 Hz, 1H, 2-H), 6.92 – 6.86 (m, 2H, Ar*H*), 6.34 (d, *J* = 14.4 Hz, 1H, 1-H), 6.20 (dd, *J* = 15.3, 10.7 Hz, 1H, 3-H), 5.81 (dt, *J* = 15.3, 5.7 Hz, 1H, 4-H), 4.45 (s, 2H, OC*H*$_2$Ar), 3.99 (dd, *J* = 5.6, 0.9 Hz, 2H, 5-H$_2$), 3.81 (s, 3H, ArOC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 144.7, 132.0, 131.0, 130.3, 129.5, 114.0, 79.5, 72.2, 69.6, 55.4; **HRMS** (ESI+) calc. for $C_{13}H_{15}O_2{}^{127}I^{23}Na$ $[M+Na]^+$ 353.00089, found 353.26625.

(2*E*,4*Z*)-5-Iodopenta-2,4-dien-1-ol, 153



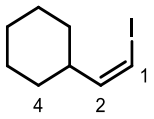
DIBALH (0.72 mL, 1.0 M in cyclohexane, 0.72 mmol, 1.5 eq.) was added dropwise to a solution of aldehyde ***ZE*-343** (100 mg, 481 µmol, 1.0 eq.) in CH_2Cl_2 (1.2 mL) at −78 °C.

After stirring at this temperature for 1 h, the reaction was quenched by subsequent addition of water (0.03 mL), aqueous NaOH (0.03 mL, 15%), and water (0.07 mL), followed by warming it to ambient temperature. $MgSO_4$ was added, the mixture stirred for 15 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 3:1) afforded the title compound **153** as a light yellow oil (81 mg, 80%).

R_f 0.17 (petroleum ether / EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.76 (dd, J = 9.9, 7.7 Hz, 1H, 2-H), 6.45 (ddq, J = 15.3, 9.9, 1.5 Hz, 1H, 3-H), 6.30 (d, J = 7.7 Hz, 1H, 1-H), 6.12 (dt, J = 15.3, 5.5 Hz, 1H, 4-H), 4.25 (d, J = 5.1 Hz, 2H, 5-H_2), 1.52 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.7, 137.2, 130.9, 82.9, 63.3.

The spectroscopic data is in agreement with that reported by Trost *et al.*[110]

(*Z*)-(2-Iodovinyl)cyclohexane, 349

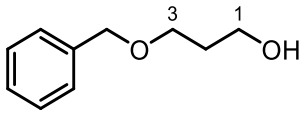


Sodium bis(trimethylsilyl)amide (0.91 mL, 2.0 M in THF, 1.8 mmol, 1.1 eq.) was added dropwise at ambient temperature to a suspension of Stork-Wittig reagent $[Ph_3CH_2I]^+[I]^-$ (960 mg, 1.82 mmol, 1.1 eq.) in THF (8.0 mL) and stirred for 10 min. After cooling to −78 °C, cyclohexanecarboxaldehyde (0.20 mL, 1.7 mmol, 1.0 eq.) was added dropwise. The mixture was stirred at −78 °C in the dark for 4 h, quenched with aqueous $NaHCO_3$, diluted with petrol, and filtered through a pad of Celite. The biphasic mixture was separated, the organics dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether, 100%) afforded the title compound **349** as a colourless oil (210 mg, 54%).

R_f 0.76 (petroleum ether, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.06 (d, J = 7.4 Hz, 1H, 1-H), 5.98 (t, J = 7.9 Hz, 1H, 2-H), 2.40 – 2.24 (m, 1H, 3-H), 1.77 – 1.60 (m, 6H, 4-H_2, 5-H_2), 1.41 – 1.04 (m, 6H, 5-H_2, 6-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_H 146.5, 79.7, 43.8, 31.5, 26.0, 25.7.

The spectroscopic data is in agreement with that reported by Beshai and coworkers.[240]

3-(Benzyloxy)propan-1-ol, 308

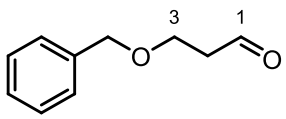


A mixture of propane-1,3-diol (9.1 mL, 0.13 mol, 2.5 eq.) and potassium hydroxide (3.40 g, 60.6 mmol, 1.2 eq.) was heated to 120 °C under reduced pressure for 1 h. After cooling to 100 °C, benzyl bromide (6.0 mL, 50 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at this temperature for 2 h. After cooling to ambient temperature, water (20 mL) was added and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the mixture was concentrated *in vacuo*. Distillation afforded the title compound **308** as a colourless oil (6.32 g, 75%).[352]

b.p. 135 °C, 5 mbar (Lit.: 129-131 °C, 5 Torr[353]); **R_f** 0.26 (petroleum ether / EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.26 (m, 5H, *Ph*), 4.53 (s, 1H, PhCH_2O), 3.79 (t, J = 5.3 Hz, 2H, 1-H_2), 3.67 (t, J = 5.8 Hz, 2H, 3-H_2), 2.33 (s, 1H, OH), 1.87 (p, J = 11.4, 5.7 Hz, 2H, 2-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 128.6, 127.9, 127.8, 73.4, 69.6, 62.1, 32.2.

The spectroscopic data is in agreement with that reported by Szpilman and co-workers.[354]

3-(Benzyloxy)propanal, 309

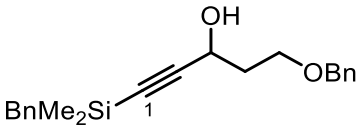


Oxalyl chloride (6.4 mL, 76 mmol, 2.0 eq.) was dissolved in dry DCM (380 mL) and cooled to −78 °C. DMSO (5.9 mL, 83 mmol, 2.2 eq.) was added dropwise, and the mixture was stirred for 30 min, followed by dropwise addition of alcohol **308** (6.30 g, 37.9 mmol, 1.0 eq.) and 2 h further stirring. NEt_3 (32.7 mL, 235 mmol, 6.0 eq.) was added dropwise, and the mixture was allowed to warm to ambient temperature before being quenched with water (150 mL). The mixturewas extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 5:1) afforded the title compound **309** as a yellowish oil (3.75 g, 60%).

$\mathbf{R}_f$ 0.70 (petroleum ether / EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.80 (t, J = 1.8 Hz, 1H, C*H*O), 7.42 – 7.24 (m, 5H, *Ph*), 4.54 (s, 2H, PhCH_2O), 3.82 (t, J = 6.1 Hz, 2H, 3-H_2), 2.70 (td, J = 6.1, 1.8 Hz, 2H, 2-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.3, 138.0, 128.6, 127.9, 127.8, 73.4, 64.0, 44.0.

The spectroscopic data is in agreement with that reported by Fürstner and co-workers.[355]

1-(Benzyldimethylsilyl)-5-(benzyloxy)pent-1-yn-3-ol, 310



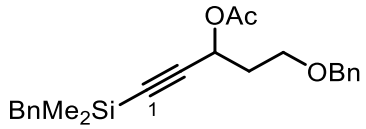
To a solution of alkyne **306** (530 mg, 3.04 mmol, 1.0 eq.) in THF (4.0 mL) at −78 °C was added dropwise *n*-butyllithium (1.2 mL, 2.5 M in hexanes, 3.0 mmol, 1.0 eq.), and the mixture stirred at this temperature for 30 min. A solution of aldehyde **309** (500 mg,

3.05 mmol, 1.0 eq.) in THF (2.0 mL) was added dropwise, the mixture stirred for 20 min, before it was allowed to warm to ambient temperature for 1 h. The reaction was quenched with aqueous NH_4Cl (10 mL), extracted with EtOAc (3 × 10 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **310** as a colourless oil (957 mg, 93%).

R$_f$ 0.36 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.28 (m, 5H, *Ph*), 7.25 – 7.18 (m, 2H, *Ph*), 7.13 – 7.04 (m, 3H, *Ph*), 4.60 (td, J = 6.5, 4.5 Hz, 1H, 3-H), 4.56 – 4.48 (m, 2H, OCH_2Ph), 3.82 (ddd, J = 9.4, 8.2, 4.1 Hz, 1H, 5-H_2), 3.66 (ddd, J = 9.4, 5.9, 4.5 Hz, 1H, 5-H_2), 3.01 (d, J = 6.4 Hz, 1H, OH), 2.20 (s, 2H, SiCH_2Ph), 2.12 – 2.03 (m, 1H, 4-H_2), 1.98 – 1.88 (m, 1H, 4-H_2), 0.13 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.0, 138.0, 128.6, 128.5, 128.3, 127.9, 127.8, 125.5, 107.6, 88.0, 73.5, 67.8, 62.0, 36.7, 26.3, −2.0.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

1-(benzyldimethylsilyl)-5-(benzyloxy)pent-1-yn-3-yl acetate, 311



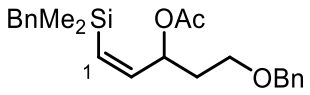
To a mixture of alcohol **310** (950 mg, 2.81 mmol, 1.0 eq.), acetic anhydride (0.53 mL, 5.6 mmol, 2.0 eq.), and triethylamine (1.2 mL, 8.6 mmol, 3.0 eq.) in CH_2Cl_2 (19 mL) was added a single crystal of 4-dimethylaminopyridine (DMAP). The mixture was stirred at ambient temperature for 2 h, quenched with water (15 mL), extracted with Et_2O (3 × 20 mL), the combined organic layers washed with brine (15 mL), dried over $MgSO_4$,

and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 19:1 →9:1) afforded the title compound **311** as a colourless oil (1.070 g, 99%).

R_f 0.08 (petroleum ether / Et_2O, 25:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 – 7.17 (m, 8H, *Ph*), 7.12 – 7.02 (m, 3H, *Ph*), 5.55 (t, *J* = 6.8 Hz, 1H, 3-H), 4.50 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ar), 4.47 (d, *J* = 12.0 Hz, 1H, OC*H*$_2$Ar), 3.61 – 3.49 (m, 2H, 5-H_2), 2.18 (s, 2H, SiC*H*$_2$Ph), 2.14 – 1.96 (m, 6H, 4-H_2, COC*H*$_3$), 0.12 (s, 3H, Si(C*H*$_3$)$_2$), 0.11 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.8, 138.9, 138.3, 128.5, 128.5, 128.3, 127.8, 127.8, 124.5, 103.8, 89.1, 73.2, 65.9, 61.9, 35.2, 26.1, 21.2, −2.1.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

(*Z*)-1-(Benzyldimethylsilyl)-5-(benzyloxy)pent-1-en-3-yl acetate, 315



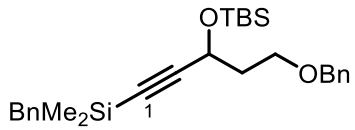
Palldium on calcium carbonate (700 mg, 5 wt%, 329 μmol, 0.05 eq.) was suspended in toluene (60 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **311** (2.50 g, 6.54 mmol, 1.0 eq.) and quinoline (0.16 mL, 1.4 mmol, 0.2 eq.) in toluene (6 mL). The mixture was stirred for 3 h (reaction did not reach completion). It was filtered over Celite and the solids were washed with EtOAc (100 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1 →9:1) afforded the title compound **315** as a colourless oil (1.17 g, 47%).

R_f 0.53 (petroleum ether / Et_2O, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.25 (m, 5H, Ar*H*), 7.22 – 7.16 (m, 2H, SiCH$_2$*Ph*), 7.09 – 6.97 (m, 3H, SiCH$_2$*Ph*), 6.20 (dd, *J* = 14.4, 9.3 Hz, 1H, 2-H), 5.69 (dd, *J* = 14.4, 0.8 Hz, 1H, 1-H), 5.55 (td, *J* = 8.7, 4.8 Hz,

1H, 3-H), 4.50 (d, J = 11.9 Hz, 1H, OCH_2Ar), 4.44 (d, J = 11.9 Hz, 1H, OCH_2Ar), 3.49 – 3.45 (m, 2H, 5-H_2), 2.23 (d, J = 13.5 Hz, 1H, SiCH_2Ph), 2.18 (d, J = 13.5 Hz, 1H, SiCH_2Ph), 2.00 (s, 3H, COCH_3), 1.98 – 1.88 (m, 1H, 4-H_2), 1.85 – 1.74 (m, 1H, 4-H_2), 0.16 (s, 3H, Si(CH_3)$_2$), 0.15 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.3, 145.9, 139.9, 138.5, 131.6, 128.5, 128.4, 128.3, 127.8, 127.7, 124.2, 73.1, 72.2, 66.2, 35.3, 26.5, 21.4, −1.8, −1.8.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

Benzyl(5-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)dimethylsilane, 312

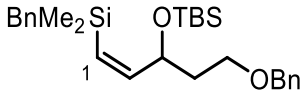


Imidazole (221 mg, 3.25 mmol, 2.2 eq.) was added to a solution of TBS chloride (468 mg, 3.11 mmol, 2.1 eq.) in CH_2Cl_2 (3.0 mL) and stirred for 10 min. Alcohol **310** (500 mg, 1.48 mmol, 1.0 eq.) was added and the mixture was stirred at ambient temperature overnight. The mixture was quenched with aqueous NH_4Cl (5 mL) and water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL), the combined organics were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 50:1) afforded the title compound **312** as a colourless oil (610 mg, 91%).

R_f 0.79 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 2928, 2856, 2173, 1494, 1250, 1096, 1020, 833, 798, 778, 763, 734, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 – 7.25 (m, 5H, ArH), 7.23 – 7.18 (m, 2H, SiCH$_2$$Ph$), 7.11 – 7.03 (m, 3H, SiCH$_2$$Ph$), 4.57 (t, J = 6.7 Hz, 1H, 3-H), 4.53 – 4.44 (m, 2H, OCH$_2$Ar), 3.65 – 3.53 (m, 2H, 5-H_2), 2.17 (s, 2H, SiCH_2Ph), 1.96 (q, J = 6.2 Hz, 2H, 4-H_2), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.12 (s,

3H, Si(C*H*$_3$)$_2$), 0.10 (s, 6H, Si(C*H*$_3$)$_2$'), 0.09 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.1, 138.6, 128.5, 128.3, 127.8, 127.7, 124.5, 108.9, 73.2, 66.4, 60.5, 38.8, 26.2, 25.9, 18.4, −2.1, −2.1, −4.4, −4.9; **HRMS** (ESI+) calc. for $C_{27}H_{40}O_2{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 475.24590, found 475.24531.

(*Z*)-Benzyl(5-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)pent-1-en-1-yl)dimethylsilane, 316

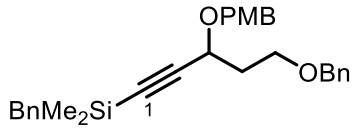


Palldium on calcium carbonate (5 wt%, 35 mg, 17 µmol, 0.05 eq.) was suspended in toluene (1.5 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **312** (150 mg, 331 µmol, 1.0 eq.) and quinoline (8 µL, 68 µmol, 0.2 eq.) in toluene (1.8 mL). The mixture was stirred until TLC showed complete consumption of starting material (1.5 h). It was filtered over Celite and the solids were washed with EtOAc (30 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 75:1) afforded the title compound **316** (101 mg, 67%) as a colourless oil.

R$_f$ 0.34 (petroleum ether / Et_2O, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 2928, 2856, 1494, 1250, 1092, 1048, 1030, 1005, 832, 796, 776, 733, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 – 7.25 (m, 5H, OCH$_2$*Ph*), 7.19 (t, *J* = 7.5 Hz, 2H, Si(CH$_3$)$_2$CH$_2$*Ph*), 7.07 (t, *J* = 7.4 Hz, 1H, Si(CH$_3$)$_2$CH$_2$*Ph*), 6.98 (d, *J* = 7.1 Hz, 2H, Si(CH$_3$)$_2$CH$_2$*Ph*), 6.29 (dd, *J* = 14.6, 8.6 Hz, 1H, 2-H), 5.45 (d, *J* = 14.6 Hz, 1H, 1-H), 4.53 – 4.43 (m, 3H, 3-H, OC*H*$_2$Ph), 3.64 – 3.46 (m, 2H, 5-H$_2$), 2.16 (s, 2H, Si(CH$_3$)$_2$C*H*$_2$Ph), 1.76 – 1.65 (m, 2H, 4-H$_2$), 0.87 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.10 (d, *J* = 1.4 Hz, 6H, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.03 (s, 3H, Si(C*H*$_3$)$_2$CH$_2$Ph), 0.02 (s, 3H, Si(C*H*$_3$)$_2$CH$_2$Ph); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C

153.2, 139.9, 138.8, 128.4, 128.4, 128.3, 127.6, 127.5, 125.9, 124.2, 73.0, 70.2, 66.7, 39.0, 26.8, 26.0, 18.3, −1.5, −1.7, −3.9, −4.5; **HRMS** (ESI+) calc. for $C_{27}H_{42}O_2{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 477.26155, found: 477.26135.

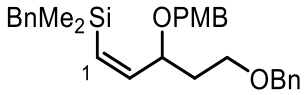
Benzyl(5-(benzyloxy)-3-((4-methoxybenzyl)oxy)pent-1-yn-1-yl)dimethylsilane, 313



p-(Methoxybenzyl)-trichloroacetimidate (616 mg, 2.22 mmol, 1.5 eq.) and scandium (III) triflate (109 mg, 221 µmol, 0.15 eq.) were added to a solution of alcohol **310** (500 mg, 1.48 mmol, 1.0 eq.) in toluene (9.5 mL). The reaction was stirred for 2 h, then quenched with $NaHCO_3$ solution, extracted with Et_2O (3 × 20 mL), the combined organics were washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **313** (521 mg, 77%) as a colourless oil.

R_f 0.45 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3027, 2958, 2862, 2361, 2169, 1513, 1248, 1095, 1034, 833, 762, 738, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 – 7.18 (m, 9H, Ar*H*), 7.12 – 7.05 (m, 3H, Ar*H*), 6.87 (t, *J* = 9.5 Hz, 2H, Ar*H*), 4.68 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.49 – 4.42 (m, 2H, OC*H*$_2$Ph), 4.39 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.27 (dd, *J* = 7.2, 6.4 Hz, 1H, 3-H), 3.79 (s, 3H, ArOC*H*$_3$), 3.64 – 3.55 (m, 2H, 5-H$_2$), 2.21 (s, 2H, SiC*H*$_2$Ph), 2.11 – 1.93 (m, 2H, 4-H$_2$), 0.15 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 139.1, 138.6, 130.1, 129.9, 128.5, 128.5, 128.3, 127.8, 127.7, 124.5, 113.9, 106.1, 89.2, 73.1, 70.5, 66.5, 66.0, 55.4, 36.1, 26.3, −1.9; **HRMS** (ESI+) calc. for $C_{29}H_{34}O_3{}^{28}Si^{23}Na$ $[M+Na]^+$ 481.21694, found 481.21667.

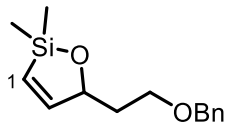
(*Z*)-Benzyl(5-(benzyloxy)-3-((4-methoxybenzyl)oxy)pent-1-en-1-yl)dimethylsilane, 317



Palldium on Calcium carbonate (23 mg, 5 wt%, 11 µmol, 0.05 eq.) was suspended in dry toluene (1.0 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **313** (100 mg, 218 µmol, 1.0 eq.) and quinoline (5.2 µL, 42 µmol, 0.2 eq.) in toluene (1.2 mL). The mixture was stirred until TLC showed complete consumption of starting material. It was filtered over Celite and the solids were washed with EtOAc (30 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **317** (89 mg, ~89%) as a colourless oil and with a small inseparable amount of starting material.

R_f 0.45 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 2858, 1613, 1513, 1494, 1453, 1247, 1207, 1173, 1094, 1058, 1036, 830, 797, 765, 736, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 – 7.16 (m, 9H, Ar*H*), 7.10 – 7.04 (m, 1H, $Si(CH_3)_2CH_2$*Ph*), 6.99 (t, *J* = 7.1 Hz, 2H, $Si(CH_3)_2CH_2$*Ph*), 6.86 – 6.80 (m, 2H, Ar*H*), 6.28 (dd, *J* = 14.5, 9.3 Hz, 1H, 2-H), 5.74 (d, *J* = 14.5 Hz, 1H, 1-H), 4.54 – 4.42 (m, 3H, Ar*H*, 3-H), 3.77 (s, 3H, ArOC*H*$_3$), 3.68 – 3.51 (m, 2H, 5-H_2), 2.15 (s, 2H, $Si(CH_3)_2CH_2$Ph), 1.94 – 1.82 (m, 1H, 4-H_2), 1.80 – 1.67 (m, 1H, 4-H_2), 0.09 (s, 3H, $Si(CH_3)_2CH_2$Ph), 0.08 (s, 3H, $Si(CH_3)_2CH_2$Ph); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.2, 150.3, 139.9, 138.8, 130.7, 129.3, 128.5, 128.4, 128.4, 128.3, 127.7, 127.6, 124.3, 113.9, 77.0, 73.0, 70.1, 66.6, 55.4, 36.3, 26.8, −1.4, −1.5; **HRMS** (ESI+) calc. for $C_{29}H_{36}O_3{}^{28}Si^{23}Na$ $[M+Na]^+$ 483.23259, found: 483.23236.

5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-2,5-dihydro-1,2-oxasilole, 318

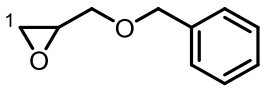


To a solution of silane **315** (1.17 g, 3.06 mmol, 1.0 eq.) in MeOH (15 mL) was added K_2CO_3 (1.27 g, 9.19 mmol, 3.0 eq.), and the mixture stirred at ambient temperature for 3 h. The reaction was quenched with aqueous NH_4Cl (30 mL), extracted with Et_2O (3 × 30 mL), the combined organics washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford title compound **318** as a colourless oil (736 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.25 (m, 5H, Ar*H*), 6.85 (dd, *J* = 10.5, 1.5 Hz, 1H, 2-H), 6.02 (dd, *J* = 10.6, 2.3 Hz, 1H, 1-H), 4.83 (ddt, *J* = 8.0, 4.0, 1.9 Hz, 1H, 3-H), 4.54 (d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ar), 4.49 (d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ar), 3.70 – 3.58 (m, 2H, 5-H_2), 2.01 – 1.91 (m, 1H, 4-H_2), 1.76 – 1.66 (m, 1H, 4-H_2), 0.24 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.6, 138.7, 128.5, 127.8, 127.7, 126.8, 80.4, 73.2, 67.3, 37.7, 1.7, 0.7.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

2-((benzyloxy)methyl)oxirane, 322



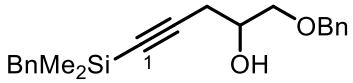
Glycidol (3.0 mL, 45 mmol, 1.0 eq.) and benzyl bromide (7.0 mL, 59 mmol, 1.3 eq.) were dissolved in dry DMF (113 mL) and cooled to 0 °C. To this was added NaH (1.81 g, 60 wt% dispersion in mineral oil, 45.3 mmol, 1.0 eq.) and the mixture was allowed to warm to ambient temperature and stirred overnight. Water (300 mL) was added to the mixture and it was extracted with DCM (5 × 60 mL). The combined organics were dried

over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 5:1) afforded the title compound **322** as a colourless oil (7.23 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.24 (m, 5H, Ar*H*), 4.59 (dd, *J* = 23.8, 11.9 Hz, 2H, OC*H*$_2$Ar), 3.78 (dd, *J* = 11.4, 3.0 Hz, 1H, 1-H), 3.44 (dd, *J* = 11.4, 5.9 Hz, 1H, 1-H), 3.23 – 3.16 (m, 1H, 2-H), 2.81 (dd, *J* = 5.0, 4.2 Hz, 1H, 3-H), 2.63 (dd, *J* = 5.0, 2.7 Hz, 1H, 3-H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.0, 128.6, 127.9, 73.4, 70.9, 51.0, 44.4.

The spectroscopic data is in agreement with that reported by Pal and coworkers.[356]

5-(Benzyldimethylsilyl)-1-(benzyloxy)pent-4-yn-2-ol, 324

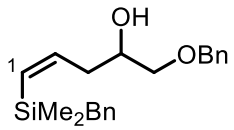


n-Butyllithium (10.1 mL, 25.3 mmol, 1.1 eq.) was added dropwise to a solution of alkyne **306** (4.00 g, 22.9 mmol, 1.0 eq.) in THF (174 mL) at −78 °C and stirred for 1 h. $BF_3{\cdot}OEt_2$ (4.3 mL, 34 mmol, 1.5 eq.) was added dropwise, followed by dropwise addition of epoxide **322** (4.91 g, 29.9 mmol, 1.3 eq.) in THF (10 mL). After stirring at −78 °C for 1.5 h, the mixture was quenched with aqueous NH_4Cl (150 mL) and allowed to warm to ambient temperature. It was extracted with EtOAc (3 × 150 mL), the combined organics washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (Combiflash, gradient) afforded the title compound **324** as a colourless oil (4.15 g, 54%).

R$_f$ 0.30 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3419, 3026, 3958, 2898, 2864, 2176, 1600, 1494, 1453, 1410, 1249, 1207, 1156, 1097, 1057, 1028, 943, 905, 832, 796, 762, 749, 698, 647, 612; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.17 (m, 7H, Ar*H*,

SiCH$_2$*Ph*), 7.12 – 7.02 (m, 3H, SiCH$_2$*Ph*), 4.57 (s, 2H, OC*H*$_2$Ar), 3.93 (qdd, *J* = 6.4, 4.9, 4.1 Hz, 1H, 4-H), 3.56 (dd, *J* = 9.5, 4.0 Hz, 1H, 5-H$_2$), 3.47 (dd, *J* = 9.5, 6.4 Hz, 1H, 5-H$_2$), 2.49 (dd, *J* = 6.4, 3.5 Hz, 2H, 3-H$_2$), 2.35 (d, *J* = 4.9 Hz, 1H, O*H*), 2.16 (s, 2H, SiC*H*$_2$Ph), 0.11 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.2, 138.0, 128.6, 128.4, 128.3, 128.0, 127.9, 124.5, 104.1, 85.8, 73.6, 72.8, 68.9, 26.5, 25.2, −1.8; **HRMS** (ESI+) calc. for $C_{21}H_{26}O_2{}^{28}Si^{23}Na$ $[M+Na]^+$ 361.15943, found 361.15957.

(*Z*)-5-(Benzyldimethylsilyl)-1-(benzyloxy)pent-4-en-2-ol, 325



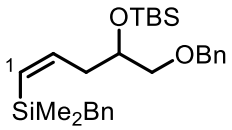
Palldium on calcium carbonate (1.158 g, 5 wt%, 544 µmol, 0.05 eq.) was suspended in dry toluene (100 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **324** (3.669 g, 10.8 mmol, 1.0 eq.), and quinoline (0.64 mL, 5.4 mmol, 0.5 eq.) in cyclohexene (10 mL). The mixture was stirred until TLC showed complete consumption of starting material (1.5 h). It was filtered over Celite and the solids were washed with EtOAc (100 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 7:3) afforded the title compound **325** (3.789 g, quant.) as a colourless oil.

R$_f$ 0.27 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 – 7.28 (m, 5H, Ar*H*), 7.09 – 7.04 (m, 2H, Ar*H*), 7.03 – 6.98 (m, 3H, Ar*H*), 6.38 (dt, *J* = 14.4, 7.3 Hz, 1H, 2-H), 5.62 (dt, *J* = 14.2, 1.5 Hz, 1H, 1-H), 4.55 (s, 2H, OC*H*$_2$Ar), 3.89 – 3.78 (m, 1H, 4-H), 3.47 (dd, *J* = 9.4, 3.4 Hz, 1H, 5-H$_2$), 3.33 (dd, *J* = 9.5, 7.3 Hz, 1H, 5-H$_2$), 2.36 (s, 1H, O*H*), 2.34 – 2.18 (m, 2H, 3-H$_2$), 2.16 (s, 2H, SiC*H*$_2$Ph), 0.11 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C**

NMR (101 MHz, $CDCl_3$) δ_C 146.5, 141.6, 139.6, 131.7, 130.1, 129.9, 129.8, 129.5, 129.4, 125.7, 75.6, 75.0, 71.8, 38.9, 28.3, 0.0, −0.01.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

(*Z*)-Benzyl(5-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-1-yl)dimethylsilane, 327

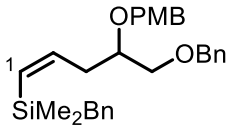


Imidazole (88 mg, 1.3 mmol, 2.2 eq.) was added to a solution of TBS chloride (186 mg, 1.23 mmol, 2.1 eq.) in CH_2Cl_2 (1.2 mL) and stirred for 10 min. Alcohol **325** (200 mg, 587 µmol, 1.0 eq.) was added and the mixture was stirred at ambient temperature overnight. The mixture was quenched with aqueous NH_4Cl (5 mL) and water (5 mL), and extracted with CH_2Cl_2 (3 × 15 mL), the combined organics were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 50:1) afforded the title compound **327** as a colourless oil (239 mg, 89%).

R*f* 0.63 (petroleum ether / Et_2O, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 2929, 2856, 1602, 1494, 1453, 1250, 1116, 834, 776, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 – 7.25 (m, 5H, OCH_2Ph), 7.19 (t, J = 7.5 Hz, 2H, $SiCH_2Ph$), 7.06 (t, J = 6.9 Hz, 1H, $SiCH_2Ph$), 7.02 – 6.96 (m, 2H, $SiCH_2Ph$), 6.40 (dt, J = 14.3, 7.2 Hz, 1H, 2-H), 5.55 (dd, J = 14.2, 1.1 Hz, 1H, 1-H), 4.51 (s, 2H, OCH_2Ph), 3.89 – 3.82 (m, 1H, 4-H), 3.41 – 3.31 (m, 2H, 5-H_2), 2.41 – 2.18 (m, 2H, 3-H_2), 2.16 (s, 2H, $SiCH_2$Ph), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, $Si(CH_3)_2$'), 0.04 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.3, 140.3, 128.9, 128.4, 128.4, 128.2, 127.7, 127.7, 127.6, 74.7, 73.4, 71.6, 38.9, 26.8, 26.0, −1.6,

−4.3, −4.5; **HRMS** (ESI+) calc. for $C_{27}H_{42}O_2{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 477.26155, found 477.26136.

(*Z*)-Benzyl(5-(benzyloxy)-4-((4-methoxybenzyl)oxy)pent-1-en-1-yl)dimethylsilane, 328

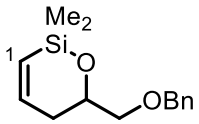


p-(Methoxybenzyl)-trichloroacetimidate (249 mg, 881 µmol, 1.5 eq.) and scandium (III) triflate (43 mg, 87 µmol, 0.15 eq.) were added to a solution of alcohol **325** (200 mg, 587 µmol, 1.0 eq.) in toluene (3.7 mL). The reaction was stirred for 2 h, then quenched with $NaHCO_3$ solution, extracted with Et_2O (3 × 10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **328** (105 mg, 72%) as a colourless oil.

R*f* 0.73 (petroleum ether / Et_2O, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2953, 2897, 1611, 1512, 1493, 1246, 1207, 1090, 1035, 829, 795, 764, 736, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.16 (m, 7H, Ar'*H*, Ar*H*), 7.15 – 7.09 (m, 2H, $SiCH_2$*Ph*), 7.02 – 6.89 (m, 3H, $SiCH_2$*Ph*), 6.81 – 6.76 (m, 2H, Ar*H*), 6.31 (dt, *J* = 14.3, 7.2 Hz, 1H, 2-H), 5.49 (dt, *J* = 14.3, 1.5 Hz, 1H, 1-H), 4.52 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.46 (s, 2H, OC*H*$_2$Ar'), 4.44 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 3.72 (s, 3H, ArOC*H*$_3$), 3.56 – 3.49 (m, 1H, 4-H), 3.47 – 3.37 (m, 2H, 5-H_2), 2.28 (ddd, *J* = 7.5, 6.2, 1.5 Hz, 2H, 3-H_2), 2.08 (s, 2H, SiC*H*$_2$Ph), 0.01 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.2, 145.6, 140.2, 138.5, 130.9, 129.5, 129.3, 128.5, 128.4, 128.2, 127.7, 127.7, 124.1, 113.8, 77.8, 73.5,

72.5, 71.8, 55.4, 36.1, 26.7, −1.6, −1.6; **HRMS** (ESI+) calc. for $C_{29}H_{36}O_3{}^{28}Si^{23}Na$ $[M+Na]^+$ 483.23259, found 483.23261.

6-((Benzyloxy)methyl)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasiline, 329

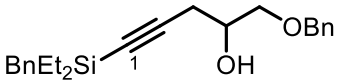


A TBAF solution (3.6 mL, 1.0 M in THF, 3.6 mmol, 1.1 eq.) was added to vinylsilane **325** (1.50 mg, 4.41 µmol, 1.0 eq.), and the mixture was stirred at ambient temperature for 4 h. The mixture was directly applied onto silica and purification by column chromatography (petroleum ether / EtOAc, 9:1) afforded the title compound **329** as a colourless oil (570 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 – 7.13 (m, 5H, Ar*H*), 6.72 – 6.65 (m, 1H, 2-H), 5.66 (ddd, J = 14.2, 2.2, 1.5 Hz, 1H, 1-H), 4.52 (d, J = 12.1 Hz, 1H, OCH_2Ph), 4.47 (d, J = 12.1 Hz, 1H, OCH_2Ph), 4.10 – 4.00 (m, 1H, 4-H), 3.46 (dd, J = 9.7, 5.4 Hz, 1H, 5-H_2), 3.34 (dd, J = 9.7, 5.6 Hz, 1H, 5-H_2), 2.26 – 1.99 (m, 2H, 3-H_2), 0.11 (s, 3H, Si(CH_3)$_2$), 0.10 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.8, 138.5, 128.5, 127.8, 127.7, 127.3, 74.6, 73.5, 70.5, 33.4, −0.1, −0.4.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

5-(Benzyldiethylsilyl)-1-(benzyloxy)pent-4-yn-2-ol, 377

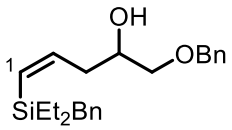


n-Butyllithium (1.5 mL, 3.8 mmol, 1.1 eq.) was added dropwise to a solution of alkyne **376** (700 mg, 3.46 mmol, 1.0 eq.) in THF (30 mL) at −78 °C and stirred for 1 h. $BF_3{\cdot}OEt_2$

(0.64 mL, 5.2 mmol, 1.5 eq.) was added dropwise, followed by dropwise addition of epoxide **322** (738 mg, 4.49 mmol, 1.3 eq.) in THF (5 mL). The resulting mixture was stirred at −78 °C for 1.5 h. It was quenched with aqueous NH_4Cl (30 mL) and allowed to warm to ambient temperature. It was extracted with EtOAc (3 × 40 mL), the combined organics washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (Combiflash, gradient) afforded the title compound **377** as a colourless oil (735 mg, 58%).

R_f 0.34 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3450, 3027, 2954, 2933, 2911, 2874, 2361, 2342, 2174, 1601, 1494, 1453, 1414, 1235, 1208, 1156, 1116, 1098, 1058, 1028, 1016, 960, 946, 805, 770, 729, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H, Ar*H*), 7.23 – 7.18 (m, 2H, $SiCH_2$*Ph*), 7.10 – 7.05 (m, 3H, $SiCH_2$*Ph*), 4.56 (s, 2H, OCH_2Ar), 3.98 – 3.89 (m, 1H, 4-H), 3.58 (dd, J = 9.5, 4.1 Hz, 1H, 5-H_2), 3.48 (dd, J = 9.5, 6.4 Hz, 1H, 5-H_2), 2.58 – 2.45 (m, 2H, 3-H_2), 2.33 (d, J = 5.0 Hz, 1H, O*H*), 2.16 (s, 2H, $SiCH_2$Ph), 0.95 (t, J = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$), 0.55 (q, J = 7.9 Hz, 4H, $Si(CH_2CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4, 138.0, 128.6, 128.5, 128.3, 128.0, 127.9, 124.4, 104.8, 84.0, 73.6, 72.9, 69.0, 25.3, 22.9, 7.5, 4.6; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_2{}^{28}Si^{23}Na$ $[M+Na]^+$ 389.19073, found 389.19111.

(*Z*)-5-(benzyldiethylsilyl)-1-(benzyloxy)pent-4-en-2-ol, 378

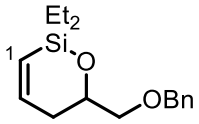


Palldium on calcium carbonate (5 wt%, 58 mg, 27 µmol, 0.05 eq.) was suspended in dry toluene (4.5 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **376** (200 mg, 546 µmol, 1.0 eq.) and

quinoline (13 µL, 0.11 mmol, 0.2 eq.) in toluene (1.0 mL). The mixture was stirred until TLC showed complete consumption of starting material (1 h). It was filtered over Celite and the solids were washed with EtOAc (20 mL), followed by concentration *in vacuo*. Purification by column chromatography (Combiflash, gradient) afforded the title compound **378** as a colourless oil (145 mg, 72%).

R*f* 0.44 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3435, 2953, 2933, 2909, 2874, 1601, 1493, 1453, 1207, 1096, 1058, 1028, 1010, 769, 734, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.41 – 7.28 (m, 5H, Ar*H*), 7.22 – 7.14 (m, 2H, SiCH$_2$*Ph*), 7.09 – 6.97 (m, 3H, SiCH$_2$*Ph*), 6.43 (dt, *J* = 14.3, 7.2 Hz, 1H, 2-H), 5.55 (dt, *J* = 14.3, 1.5 Hz, 1H, 1-H), 4.54 (s, 2H, OC*H*$_2$Ph), 3.81 (tdd, *J* = 7.4, 5.7, 3.3 Hz, 1H, 4-H), 3.45 (dd, *J* = 9.4, 3.3 Hz, 1H, 5-H$_2$), 3.31 (dd, *J* = 9.4, 7.5 Hz, 1H, 5-H$_2$), 2.30 – 2.04 (m, 4H, SiC*H*$_2$Ph, 3-H$_2$), 0.93 (t, *J* = 7.8 Hz, 6H, Si(CH$_2$C*H*$_3$)$_2$), 0.67 – 0.47 (m, 4H, Si(C*H*$_2$CH$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.7, 140.2, 138.0, 128.6, 128.4, 128.3, 127.9, 127.9, 127.6, 124.1, 74.1, 73.5, 70.3, 37.7, 23.0, 7.5, 4.8, 4.7; **HRMS** (ESI+) calc. for $C_{23}H_{32}O_2{}^{28}Si^{23}Na$ $[M+Na]^+$ 391.20638, found 391.20861.

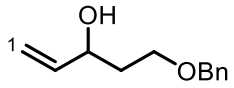
6-((Benzyloxy)methyl)-2,2-diethyl-5,6-dihydro-2*H*-1,2-oxasiline, 379



A TBAF solution (0.42 mL, 1.0 M in THF, 0.42 mmol, 1.2 eq.) was added to vinylsilane **378** (178 mg, 483 µmol, 1.0 eq.), and the mixture was stirred at ambient temperature for 4 h. The mixture was directly applied onto silica and purification by column chromatography (petroleum ether / EtOAc, 9:1) afforded the title compound **379** as a colourless oil (40 mg, 30%).

R_f 0.55 (petroleum ether / Et_2O, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2954, 2912, 2875, 1692, 1598, 1455, 1414, 1364, 1236, 1205, 1161, 1129, 1099, 1057, 1004, 965, 926, 867, 766, 733, 697, 636; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.22 (m, 5H, Ar*H*), 6.88 (ddd, *J* = 14.2, 5.9, 2.6 Hz, 1H, 2-H), 5.75 (ddd, *J* = 14.2, 2.7, 0.9 Hz, 1H, 1-H), 4.60 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$Ar), 4.56 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$Ar), 4.15 (dtd, *J* = 9.8, 5.6, 3.0 Hz, 1H, 4-H), 3.56 (dd, *J* = 9.7, 5.3 Hz, 1H, 5-H_2), 3.42 (dd, *J* = 9.8, 5.9 Hz, 1H, 5-H_2), 2.27 (dddd, *J* = 17.6, 6.0, 3.0, 0.9 Hz, 1H, 3-H_2), 2.17 (ddt, *J* = 17.6, 9.9, 2.7 Hz, 1H, 3-H_2), 0.99 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.94 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.72 – 0.52 (m, 4H, Si(C*H*$_2$$CH_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 148.1, 138.6, 128.5, 127.8, 127.7, 125.1, 74.8, 73.5, 71.0, 33.6, 7.0, 7.0, 6.6, 6.2; **HRMS** (ESI+) calc. for $C_{16}H_{25}O_2{}^{28}Si$ $[M+H]^+$ 277.16183, found 277.16190.

5-(Benzyloxy)pent-1-en-3-ol, 321

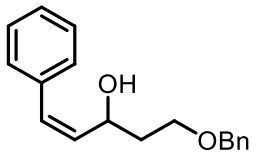


Cyclic siloxane **318** (25 mg, 0.10 mmol, 1.0 eq.) and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) were dissolved in a TBAF solution (0.30 mL, 0.30 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 2 h, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **321** as a colourless oil (12 mg, 62%).

R_f 0.36 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42 – 7.23 (m, 5H, Ar*H*), 5.88 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H, 2-H), 5.27 (dt, *J* = 17.2, 1.6 Hz, 1H, 1-H_2), 5.11 (dt, *J* = 10.5, 1.5 Hz, 1H, 1-H_2), 4.52 (s, 2H, OC*H*$_2$Ar), 4.39 – 4.31 (m, 1H, 3-H), 3.72 (ddd, *J* = 9.3, 6.4, 4.8 Hz, 1H, 5-H_2), 3.65 (ddd, *J* = 9.4, 7.2, 4.8 Hz, 1H, 5-H_2),

2.82 (d, J = 3.7 Hz, 1H, O*H*), 1.95 – 1.77 (m, 2H, 4-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.7, 138.1, 128.6, 127.9, 127.8, 114.5, 73.5, 72.1, 68.5, 36.5.

(*Z*)-5-(Benzyloxy)-1-phenylpent-1-en-3-ol, 350



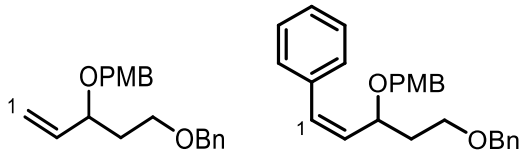
To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), phenyl iodide (13.5 µL, 121 µmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.2 mL, 1.0 M in THF, 200 µmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 5 min. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **350** as a colourless oil (26.5 mg, 98%).

To alkenylsilane **316** (46 mg, 0.10 mmol, 1.0 eq.), phenyl iodide (13.5 µL, 121 µmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 30 min. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **350** as a colourless oil (20.5 mg, 76%).

R_f 0.36 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3351, 2970, 1307, 1160, 1127, 1107, 951, 816, 736, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.23 (m, 10H, Ar*H*), 6.54 (dd, J = 11.7, 0.7 Hz, 1H, 1-H), 5.72 (dd, J = 11.7, 9.2 Hz, 1H, 2-H), 4.84 (td, J = 8.8, 3.2 Hz, 1H, 3-H), 4.55 – 4.48 (m, 2H, OCH_2Ph), 3.75 (ddd, J = 9.5, 6.1, 4.6 Hz, 1H, 5-H_2), 3.67 (ddd, J = 9.4, 8.0, 4.3 Hz, 1H, 5-H_2), 2.80 (s, 1H, O*H*), 2.07 – 1.95 (m,

1H, 4-H_2), 1.92 – 1.83 (m, 1H, 4-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 136.8, 134.1, 130.9, 129.0, 128.6, 128.4, 127.9, 127.8, 127.3, 73.5, 68.6, 67.3, 37.0; **HRMS** (ESI+) calc. for $C_{18}H_{20}O_2{}^{23}Na$ $[M+Na]^+$ 291.13555, found: 291.13563.

1-(((5-(Benzyloxy)pent-1-en-3-yl)oxy)methyl)-4-methoxybenzene, 358 and (*Z*)-1-(((5-(Benzyloxy)-1-phenylpent-1-en-3-yl)oxy)methyl)-4-methoxybenzene, *Z*-359

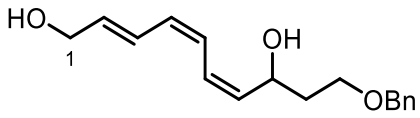


To alkenylsilane **317** (46 mg, 0.10 mmol, 1.0 eq.), phenyl iodide (13.5 µL, 121 µmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 30 min. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compounds **358** and ***Z*-359** as a colourless oils (15 mg, 45%, and 15 mg, 36%).

Data for **358**: $\mathbf{R}_f$ 0.70 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2933, 2860, 1613, 1513, 1247, 1094, 1036, 821, 737, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.18 (m, 4H, Ar*H*), 6.90 – 6.83 (m, 5H, Ar*H*), 5.80 – 5.70 (m, 1H, 2-H), 5.26 – 5.20 (m, 2H, 1-H_2), 4.52 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 4.27 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 4.01 – 3.90 (m, 1H, 3-H), 3.79 (s, 3H, OCH_3), 3.64 – 3.48 (m, 2H, 5-H_2), 1.97 – 1.87 (m, 1H, 4-H_2), 1.86 – 1.76 (m, 1H, 4-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.0, 131.9, 131.0, 129.9, 129.5, 128.5, 127.8, 127.7, 117.2, 113.9, 77.3, 73.1, 70.1, 66.8, 55.4, 36.0; **HRMS** (ESI+) calc. for $C_{20}H_{24}O_3{}^{23}Na$ $[M+Na]^+$ 335.16177, found: 335.16173.

Data for ***Z*-359**: $\mathbf{R}_f$ 0.39 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2925, 2859, 1612, 1513, 1454, 1248, 1174, 1097, 1035, 821, 738, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H (E/Z-mixture, major isomer) 7.41 – 7.21 (m, 10H, OCH_2*Ph*, Ar*H*), 7.04 – 6.98 (m, 2H, Ar*H*), 6.76 – 6.67 (m, 3H, Ar*H*, 1-H), 5.64 (dd, *J* = 11.8, 9.7 Hz, 1H, 2-H), 4.64 (td, *J* = 8.9, 4.6 Hz, 1H, 3-H), 4.48 – 4.37 (m, 3H, OC*H*$_2$Ph, OC*H*$_2$Ar), 4.09 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$Ar), 3.73 (s, 3H, OC*H*$_3$), 3.69 – 3.52 (m, 2H, 5-H_2), 2.08 – 1.84 (m, 2H, 4-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.5, 132.4, 130.8, 129.8, 129.6, 129.1, 128.8, 128.4, 127.9, 127.7, 127.5, 127.2, 126.7, 113.7, 73.1, 70.8, 69.9, 67.0, 55.3, 35.9; **HRMS** (ESI+) calc. for $C_{26}H_{28}O_3{}^{23}Na$ $[M+Na]^+$ 411.19307, found 411.19301.

(2*E*,4*Z*,6*Z*)-10-(Benzyloxy)deca-2,4,6-triene-1,8-diol, 356

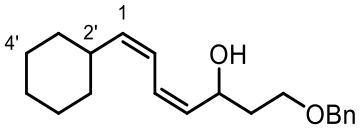


To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **153** (25 mg, 0.12 mmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.30 mL, 1.0 M in THF, 0.30 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 4 h. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1) afforded the title compound **356** as a yellowish oil (14 mg, 51%).

$\mathbf{R}_f$ 0.22 (petroleum ether / EtOAc, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3383, 2923, 2866, 1679, 1617, 1573, 1454, 1365, 1096, 1076, 1028, 999, 739, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.11 (m, 5H, Ar*H*), 6.58 (ddq, *J* = 15.3, 11.3, 1.5 Hz, 1H, 3-H), 6.35 (ddt, *J* = 12.2, 11.0, 1.2 Hz, 1H, 6-H), 6.17 – 6.04 (m, 1H, 5-H), 5.96 – 5.85 (m, 1H, 4-H), 5.75 (dt, *J* = 15.1, 5.7 Hz, 1H, 2-H), 5.38 (ddt, *J* = 11.2, 8.5, 1.4 Hz, 1H, 7-H), 4.70 (tdd, *J* = 8.2,

4.5, 1.3 Hz, 1H, 8-H), 4.36 (s, 2H, OC*H*$_2$Ph), 4.08 (dd, *J* = 5.7, 1.5 Hz, 2H, 1-H$_2$), 3.58 – 3.42 (m, 2H, 10-H$_2$), 2.62 (s, 1H, O*H*), 1.86 – 1.73 (m, 1H, 9-H$_2$), 1.70 – 1.40 (m, 2H, 9-H$_2$, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 134.6, 134.3, 130.1, 128.6, 127.9, 127.8, 125.9, 124.4, 124.2, 73.5, 68.4, 67.1, 63.5, 37.0; **HRMS** (ESI+) calc. for $C_{17}H_{22}O_3{}^{23}Na$ $[M+Na]^+$ 297.14612, found 297.14609.

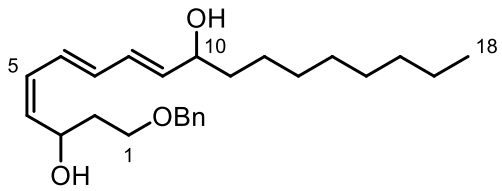
(4*Z*,6*Z*)-1-(Benzyloxy)-7-cyclohexylhepta-4,6-dien-3-ol, 357



To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **349** (27 mg, 0.11 mmol, 1.2 eq.), and Pd(dba)$_2$ (3 mg, 5 mmol, 5 mol%) was added a TBAF solution (0.30 mL, 1.0 M in THF, 0.30 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 2 h. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **357** as a colourless oil (14 mg, 51%).

R$_f$ 0.27 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3398, 2922, 2850, 1449, 1363, 1259, 1098, 1075, 1027, 890, 736, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 – 7.22 (m, 5H, Ar*H*), 6.33 (t, *J* = 11.4 Hz, 1H, 3-H), 6.15 (t, *J* = 11.4 Hz, 1H, 2-H), 5.44 (ddt, *J* = 11.1, 8.5, 1.3 Hz, 1H, 4-H), 5.37 (tt, *J* = 10.7, 1.3 Hz, 1H, 1-H), 4.84 (td, *J* = 8.2, 4.4 Hz, 1H, 5-H), 4.51 (s, 2H, OC*H*$_2$Ph), 3.72 – 3.58 (m, 2H, 7-H$_2$), 2.60 (s, 1H, O*H*), 2.52 – 2.35 (m, 1H, 2'-H), 1.99 – 1.87 (m, 1H, 6-H$_2$), 1.82 – 1.56 (m, 5H, 6-H$_2$, 3'-H$_2$), 1.37 – 1.01 (m, 6H, 4'-H$_2$, 5'-H$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.3, 138.2, 133.0, 128.6, 127.8, 127.8, 125.0, 121.3, 73.4, 68.4, 67.0, 37.0, 36.6, 33.3, 33.2, 26.1, 26.0, 25.9; **HRMS** (ESI+) calc. for $C_{20}H_{28}O_2{}^{23}Na$ $[M+Na]^+$ 323.19815, found 323.19814.

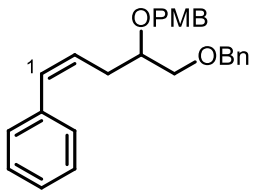
(4*Z*,6*E*,8*E*)-1-(Benzyloxy)octadeca-4,6,8-triene-3,10-diol, 354



To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **rac-385** (39 mg, 0.12 mmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.30 mL, 1.0 M in THF, 0.30 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 1 h. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 3:2) afforded the title compound **354** as a colourless oil (35 mg, 90%, 1:1 d.r.).

R*f* 0.40 and 0.28 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3359, 2925, 2855, 1455, 1363, 1099, 995, 968, 736; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.27 (m, 5H, Ar*H*), 6.51 (dt, *J* = 10.9, 5.0 Hz, 1H, 6-H), 6.29 – 6.15 (m, 2H, 7-H, 8-H), 6.07 (t, *J* = 11.3 Hz, 1H, 5-H), 5.78 – 5.67 (m, 1H, 9-H), 5.46 (dd, *J* = 10.6, 9.0 Hz, 1H, 4-H), 4.87 – 4.77 (m, 1H, 3-H), 4.52 (s, 2H, OCH_2Ar), 4.16 – 4.06 (m, 1H, 10-H), 3.73 – 3.65 (m, 1H, 1-H_2), 3.65 – 3.57 (m, 1H, 1-H_2), 2.56 (d, *J* = 2.7 Hz, 1H, O*H*), 1.99 – 1.88 (m, 1H, 2-H_2), 1.80 – 1.72 (m, 1H, 2-H_2), 1.60 – 1.45 (m, 2H, 11-H_2), 1.45 – 1.19 (m, 13H, O*H*, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2), 0.88 (t, *J* = 6.7 Hz, 3H, 18-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.5, 137.5, 133.8, 133.8, 130.4, 130.4, 129.8, 128.6, 127.9, 127.9, 127.8, 73.5, 72.8, 68.4, 67.4, 60.5, 53.6, 37.5, 37.1, 32.0, 29.7, 29.4, 25.6, 22.8, 21.2, 14.4, 14.3; **HRMS** (CI+) calc. for $C_{25}H_{42}O_3N$ $[M+NH_4]^+$ 404.3159, found 404.3160.

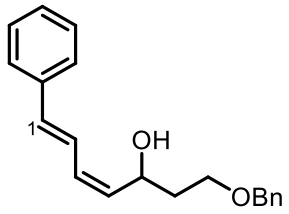
(*Z*)-1-(((1-(Benzyloxy)-5-phenylpent-4-en-2-yl)oxy)methyl)-4-methoxybenzene, 366



To alkenylsilane **318** (24 mg, 0.52 mmol, 1.0 eq.), iodobenzene (7 µL, 63 µmol, 1.2 eq.), and $Pd(dba)_2$ (1.5 mg, 2.6 µmol, 5 mol%) was added a TBAF solution (0.10 mL, 1.0 M in THF, 0.10 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 30 min (however, no change in reaction was observed from 10 to 30 min). The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 9:1) afforded the title compound **366** as a colourless oil (19 mg, 96%).

R_f 0.38 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2902, 2860, 1613, 1586, 1513, 1495, 1453, 1365, 1342, 1302, 1247, 1208, 1173, 1091, 1034, 915, 821, 769, 737, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 – 7.16 (m, 12H, Ar*H*), 6.85 – 6.80 (m, 2H, Ar*H*), 6.47 (dt, *J* = 11.7, 1.9 Hz, 1H, 1-H), 5.70 (dt, *J* = 11.7, 7.3 Hz, 1H, 2-H), 4.57 (d, *J* = 11.4 Hz, 1H, OCH_2Ar), 4.51 (d, *J* = 11.4 Hz, 1H, OCH_2Ar), 4.48 (s, 2H, OCH_2Ph), 3.76 (s, 3H, ArOCH_3), 3.68 (p, *J* = 5.6 Hz, 1H, 4-H), 3.55 – 3.46 (m, 2H, 5-H_2), 2.65 – 2.56 (m, 2H, 3-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 138.5, 137.5, 130.9, 130.8, 129.5, 128.9, 128.5, 128.3, 128.3, 127.7, 127.7, 126.8, 113.9, 77.7, 73.5, 72.5, 71.7, 55.4, 31.1; **HRMS** (ESI+) calc. for $C_{26}H_{28}O_3{}^{23}Na$ $[M+Na]^+$ 411.19307, found 411.19334.

(4*Z*,6*E*)-1-(Benzyloxy)-7-phenylhepta-4,6-dien-3-ol, 351

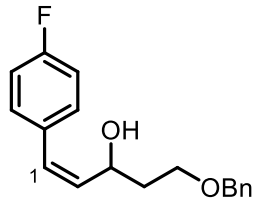


To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), β-bromostyrene (16 µL, 0.12 mmol, 1.2 eq.), and allylpalladium chloride dimer (2 mg, 5 µmol, 0.05 eq.) in THF (0.3 mL), was added KOTMS (39 mg, 0.30 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 3 h, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title **351** compound as a colourless oil (18 mg, 58%).

R*f* 0.25 (petroleum ether / Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 – 7.12 (m, 10H, Ar*H*), 7.02 (ddd, *J* = 15.5, 11.3, 1.2 Hz, 1H, 2-H), 6.50 (d, *J* = 15.5 Hz, 1H, 1-H), 6.15 (ddt, *J* = 11.3, 10.8 1.0 Hz, 1H, 3-H), 5.45 (ddt, *J* = 10.8, 8.6, 1.0 Hz, 1H, 4-H), 4.94 – 4.85 (m, 1H, 5-H), 4.46 (s, 2H, OC*H*$_2$Ph), 3.72 – 3.53 (m, 2H, 7-H_2), 2.61 (bs, 1H, OH), 2.02 – 1.88 (m, 1H, 6-H_2), 1.82 – 1.68 (m, 1H, 6-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 137.2, 134.3, 133.8, 130.2, 128.7, 128.6, 127.9, 127.8, 127.8, 126.7, 123.9, 73.4, 68.3, 67.4, 37.1.

The spectroscopic data is in agreement with that reporded by Gudmundsson.[74]

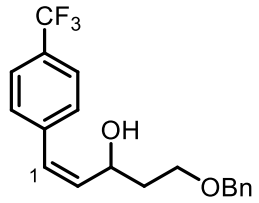
(*Z*)-5-(Benzyloxy)-1-(4-fluorophenyl)pent-1-en-3-ol, 371



To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), 4-fluoroiodobenzene (14 µL, 0.12 mmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 µmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 5 min. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **371** as a colourless oil (23 mg, 80%).

R*f* 0.15 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3385, 2921, 2861, 1602, 1508, 1454, 1401, 1362, 1312, 1224, 1159, 1096, 1075, 1013, 968, 909, 849, 737, 698, 671, 624; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 – 7.18 (m, 7H, Ar*H*, OCH_2*Ph*), 6.95 – 6.87 (m, 2H, Ar*H*), 6.41 (d, *J* = 11.6 Hz, 1H, 1-H), 5.62 (dd, *J* = 11.6, 9.2 Hz, 1H, 2-H), 4.70 (td, *J* = 8.8, 3.4 Hz, 1H, 3-H), 4.44 (s, 2H, OC*H*$_2$Ph), 3.67 (ddd, *J* = 9.2, 6.1, 4.4 Hz, 1H, 5-H_2), 3.58 (ddd, *J* = 9.3, 8.1, 4.1 Hz, 1H, 5-H_2), 2.82 (s, 1H, O*H*), 1.98 – 1.87 (m, 1H, 4-H_2), 1.82 – 1.73 (m, 1H, 4-H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.76 (tt, *J* = 8.8, 5.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.1 (d, *J* = 246.5 Hz), 138.0, 133.9, 132.8 (d, *J* = 3.2 Hz), 130.7 (d, *J* = 7.9 Hz), 129.9, 128.6, 127.9, 127.7, 115.3 (d, *J* = 21.4 Hz), 73.4, 68.6, 67.1, 37.0; **HRMS** (ESI+) calc. for $C_{18}H_{19}O_2F^{23}Na$ $[M+Na]^+$ 309.12613, found 309.12613.

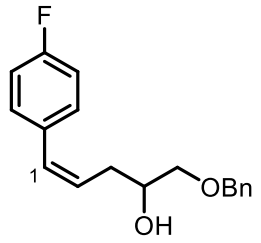
(*Z*)-5-(Benzyloxy)-1-(4-(trifluoromethyl)phenyl)pent-1-en-3-ol, 372



To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), 4-iodobenzotrifluoride (18 µL, 0.12 mmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 5 min. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **372** as a colourless oil (26 mg, 77%).

R*f* 0.16 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3388, 2923, 2863, 1616, 1324, 1164, 1117, 1067, 1016, 856, 736, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.55 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.43 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.40 – 7.28 (m, 5H, OCH_2*Ph*), 6.55 (d, *J* = 11.7 Hz, 1H, 1-H), 5.82 (dd, *J* = 11.7, 9.2 Hz, 1H, 2-H), 4.77 (td, *J* = 8.9, 3.4 Hz, 1H, 3-H), 4.52 (s, 2H, OCH_2Ph), 3.76 (ddd, *J* = 10.0, 6.2, 4.2 Hz, 1H, 5-H_2), 3.66 (ddd, *J* = 9.4, 8.1, 3.9 Hz, 1H, 5-H_2), 2.98 (s, 1H, O*H*), 2.01 (dtd, *J* = 14.7, 8.3, 4.2 Hz, 1H, 4-H_2), 1.85 (ddt, *J* = 14.3, 6.2, 3.7 Hz, 1H, 4-H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F −62.48 (s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.3, 137.9, 136.0, 129.6, 129.2, 129.2 (q, *J* = 32.8 Hz), 128.6, 128.0, 127.8, 125.3 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.9 Hz), 73.5, 68.5, 67.2, 36.9; **HRMS** (ESI+) calc. for $C_{19}H_{19}O_2F_3{}^{23}Na$ $[M+Na]^+$ 359.12294, found 359.12295.

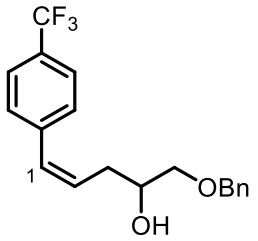
(*Z*)-1-(Benzyloxy)-5-(4-fluorophenyl)pent-4-en-2-ol, 373



To alkenylsiloxane **318** (25 mg, 0.10 mmol, 1.0 eq.), 4-fluoroiodobenzene (14 µL, 0.12 mmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 5 min. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **373** as a colourless oil (27 mg, 94%).

R*f* 0.37 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3427, 2902, 2861, 1602, 1508, 1454, 1398, 1365, 1222, 1158, 1096, 1028, 1014, 843, 737, 699, 613; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.20 (m, 5H, OCH_2*Ph*, Ar*H*), 7.03 – 6.96 (m, 2H, Ar*H*), 6.50 (d, *J* = 11.7 Hz, 1H, 1-H), 5.72 (dt, *J* = 11.7, 7.3 Hz, 1H, 2-H), 4.53 (s, 2H, O*C*H_2Ph), 3.92 (qd, *J* = 6.8, 3.1 Hz, 1H, 4-H), 3.52 (dd, *J* = 9.5, 3.3 Hz, 1H, 5-H_2), 3.36 (dd, *J* = 9.5, 7.4 Hz, 1H, 5-H_2), 2.57 – 2.41 (m, 3H, O*H*, 3-H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F −115.35 (td, *J* = 9.5, 4.8 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_F 161.7 (d, *J* = 245.7 Hz), 137.9, 133.3 (d, *J* = 3.4 Hz), 130.4 (d, *J* = 7.9 Hz), 130.2, 128.6, 128.0, 127.9, 127.7, 115.2 (d, *J* = 21.2 Hz), 74.0, 73.5, 70.5, 32.4; **HRMS** (ESI+) calc. for $C_{18}H_{19}O_2F^{23}Na$ $[M+Na]^+$ 309.12613, found 309.12614.

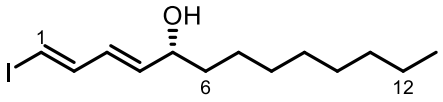
(*Z*)-1-(Benzyloxy)-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-ol, 374



To alkenylsiloxane **318** (25 mg, 0.10 µmol, 1.0 eq.), 4-iodobenzotrifluoride (18 µL, 0.12 µmol, 1.2 eq.), and $Pd(dba)_2$ (3 mg, 5 µmol, 5 mol%) was added a TBAF solution (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq.), and the resulting mixture stirred at ambient temperature for 20 min. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **374** as a colourless oil (32 mg, 95%).

R_f 0.30 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3427, 2862, 1616, 1454, 1323, 1163, 1115, 1067, 1028, 1016, 853, 743, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.57 (d, J = 8.1 Hz, 2H, Ar*H*), 7.42 – 7.28 (m, 7H, Ar*H*, OCH_2*Ph*), 6.58 (d, J = 11.7 Hz, 1H, 1-H), 5.88 (dt, J = 11.7, 7.3 Hz, 1H, 2-H), 4.54 (s, 2H, OCH_2Ph), 3.95 (dt, J = 9.6, 4.8 Hz, 1H, 4-H), 3.53 (dd, J = 9.4, 3.3 Hz, 1H, 5-H_2), 3.38 (dd, J = 9.4, 7.4 Hz, 1H, 5-H_2), 2.59 – 2.45 (m, 3H, O*H*, 3-H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F −62.42 (s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.9, 137.9, 130.1, 130.0, 129.1, 128.8 (q, J = 33.0 Hz), 128.6, 128.0, 127.9, 125.3 (q, J = 3.9 Hz), 124.3 (q, J = 271.8 Hz), 74.0, 73.6, 70.4, 32.5; **HRMS** (ESI+) calc. for $C_{19}H_{19}O_2F_3{}^{23}Na$ $[M+Na]^+$ 359.12294, found 359.12305.

(1*E*,3*E*)-1-Iodotrideca-1,3-dien-5-ol, 385



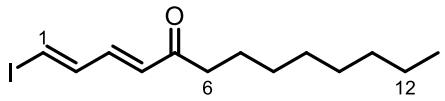
Racemic preparation: To a suspension of Mg (120 mg, 4.94 mmol, 1.8 eq.) in Et_2O (6.0 mL) was added dropwise 1-bromooctane (0.50 mL, 2.9 mmol, 1.2 eq.) so that the mixture refluxed in its own. After addition, the Grignard reagent was cooled to −40 °C and a solution of aldehyde ***EE*-343** (500 mg, 2.04 mmol, 1.0 eq.) in THF (6.0 mL) was added dropwise. The mixture was stirred for 1 h before being quenched with an aqueous solution of NH_4Cl. After extraction with Et_2O (3 × 20 mL), the organic layers were washed with brine (20 mL), dried over MgSO4, concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **rac-385** as an orange solid (604 mg, 78%).

Asymmetric preparation: To a solution of ketone **390** (15 mg, 47 µmol, 1.0 eq.), and (*S*)-(−)-2-Methyl-CBS-oxazaborolidine (6 mg, 22 µmol, 0.5 eq.) in THF at −40 °C was added dropwise BH_3·THF complex (0.06 mL, 60 µmol, 1.2 eq.), and the mixture stirred at −10 °C for 1 h. The reaction was quenched by addition of methanol (1 mL) and allowed to warm to ambient temperature. Aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (3 × 5 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **385** as an orange solid (11 mg, 73%, 75% *ee* CHIRALPAK IC, 10% IPA/hexane, 0.7 mL/min, t_R (*R*) 6.1 min, t_R (*S*) 6.3 min).

R_f 0.51 (petroleum ether / Et_2O, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.02(ddd, J = 14.4, 3.8, 0.5 Hz, 1H, 2-H), 6.33 (d, J = 14.4 Hz, 1H, 1-H), 6.19 – 6.11 (ddd, J = 15.3, 4.6, 0.6 Hz, 1H, 3-H), 5.73 (dd, J = 15.3, 6.4 Hz, 1H, 4-H), 4.15 – 4.08 (m, 1H, 5-H),

1.60 – 1.49 (m, 2H, 6-H_2), 1.43 – 1.19 (m, 12H, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2), 0.91 – 0.85 (m, 3H, 13-H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.7, 137.4, 129.9, 79.4, 72.3, 37.3, 32.0, 29.7, 29.4, 25.5, 22.8, 14.3.

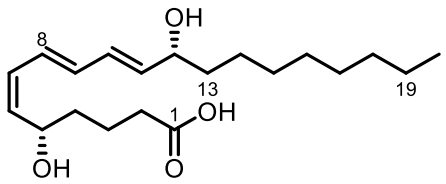
(1*E*,3*E*)-1-Iodotrideca-1,3-dien-5-one, 390



DMSO (88 µL, 1.2 mmol, 4.0 eq.) was added dropwise to a solution of oxalyl chloride (53 µL, 0.63 mmol, 2.0 eq.) in CH_2Cl_2 (1.0 mL) at −78 °C and stirred for 30 min. A solution of alcohol **rac-385** (100 mg, 310 µmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) was added dropwise and the mixture stirred for further 30 min. Triethylamine (0.26 mL, 1.9 mmol, 6.0 eq.) was added dropwise and the mixture was allowed to warm to ambient temperature over 1 h. The reaction was quenched with water (10 mL), extracted with Et_2O (3 × 10 mL), the combined organics were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1) afforded the title compound **390** (74 mg, 74%) as a white waxy solid.

R_f 0.48 (petroleum ether / Et_2O, 9:1); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.75 – 6.58 (m, 2H, 2-H, 3-H), 6.19 – 6.08 (m, 1H, 1-H), 5.74 – 5.62 (m, 1H, 4-H), 2.14 (t, J = 7.3 Hz, 2H, 6-H_2), 1.66 – 1.54 (m, 2H, 7-H_2), 1.34 – 1.18 (m, 10H, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2), 0.90 (t, J = 6.9 Hz, 3H, 13-H_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 198.5, 143.7, 139.6, 129.5, 89.6, 41.5, 32.3, 29.9, 29.7, 29.6, 24.4, 23.1, 14.4.

Leukotriene B_3, 383

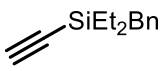


Cyclic siloxane **384** (8 mg, 37 µmol, 1.2 eq.) vinyl iodide **385** (10 mg, 31 µmol, 1.0 eq.) and $Pd(dba)_2$ (1 mg, 2 µmol, 5 mol%) were dissolved in a TBAF solution (0.10 mL, 0.10 mmol, 3.0 eq.), and the resulting mixture stirred at ambient temperature for 3 h, before being concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded a mixture of ester **393** and lactone **394**, which was directly used in the next step. The mixture was dissolved in *i*-PrOH (1.0 mL) and water (0.3 mL) and LiOH (6 mg, 0.14 mmol, 4.0 eq.) was added. The mixture was stirred for 2 h, before being acidified with 1 M HCl, and extracted with EtOAc (3 × 5 mL). The combined organics were dried over Na2SO4, and concentrated *in vacuo* to afford leukotriene B_3 as a colourless oil (3.8 mg, 38% over 2 steps). The NMR contains some aliphatic impurities, as well as an unwanted diastereomer of LTB_3 (d.r. ~7:1).

R_f 0.36 (CH_2Cl_2 / MeOH, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3408, 2925, 2854, 2361, 2340, 1734, 1459, 1438, 1364, 1241, 1166, 1036, 997, 970; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 – 6.42 (m, 1H, 9-H), 6.34 – 6.16 (m, 2H, 8-H, 10-H), 6.09 (t, *J* = 11.2 Hz, 1H, 7-H), 5.83 – 5.66 (m, 1H, 11-H), 5.42 (dd, *J* = 10.9, 8.8 Hz, 1H, 6-H), 4.66 – 4.57 (m, 1H, 5-H), 4.17 (q, *J* = 6.6 Hz, 1H, 12-H), 2.35 (t, *J* = 6.9 Hz, 2H, 2-H_2), 1.81 – 1.12 (m, H, 3-H_2, 4-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2, 19-H_2), 0.95 – 0.78 (m, 3H, 20-H_3); **HRMS** (ESI+) calc. for $C_{20}H_{34}O_4{}^{23}Na$ $[M+Na]^+$ 361.23493, found 361.23504.

The spectroscopic data is in agreement with that reported by Kobayashi and coworkers.[256]

Benzyldiethyl(ethynyl)silane, 376

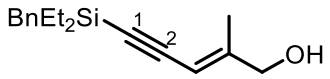


A three-neck flask equipped with reflux condenser was charged with magnesium (4.74 mg, 195 mmol, 1.4 eq.) and flame-dried *in vacuo*. After flushing the apparatus with nitrogen, Et_2O was added (20 mL). To this was added dropwise benzyl chloride (16.0 mL, 139 mmol, 1.0 eq.) and Et_2O (120 mL) with such a speed that the reaction would sustain reflux without additional heating. The mixture was heated at reflux for 2 h, allowed to warm to ambient temperature followed by dropwise addition of dichlorodiethylsilane (29.0 mL, 194 mmol, 1.4 eq.) and heating at reflux for further 2 h. The mixture was filtered under nitrogen over Celite and concentrated *in vacuo*, following removal of excess dichlorodiethylsilane *in vacuo* to afford crude benzyldiethylchlorosilane.

To a solution of benzyldiethylchlorosilane in THF (240 mL) at 0 °C was added dropwise a solution of ethynyl magnesium bromide (360 mL, 0.5 M in THF, 180 mmol, 1.3 eq.). The mixture was warmed to ambient temperature and stirred overnight. The reaction was quenched at 0 °C by addition of saturated aqueous NH_4Cl (300 mL), and extracted with Et_2O (3 ×250 mL). The combined organics were washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1) afforded the title compound **376** (19.99 g, 71%) as a colourless oil.

IR (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 2913, 2877, 2033, 1601, 1494, 1453, 1412, 1237, 1208, 1158, 1058, 1009, 962, 817, 805, 769, 723, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.20 (m, 2H), 7.12 – 7.09 (m, 3H), 2.42 (s, 1H), 2.23 (s, 2H), 0.99 (t, J = 7.9 Hz, 6H), 0.60 (q, J = 7.9 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.9, 128.5, 128.4, 124.6, 95.3, 87.0, 22.6, 7.3, 4.2; **HRMS** (EI+) calc. for $C_{13}H_{18}{}^{28}Si$ 202.1190 $[M]^+$, found 202.1181.

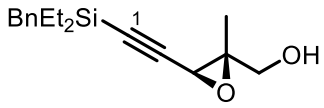
(*E*)-5-(Benzyldiethylsilyl)-2-methylpent-2-en-4-yn-1-ol, 413



To a degassed solution of alkyne **376** (3.58 g, 17.7 mmol, 1.0 eq.) and vinyl iodide **76** (3.50 g, 17.7 mmol, 1.0 eq.) in THF (70 mL) was added $Pd(PPh_3)_2Cl_2$ (124 mg, 177 µmol, 1.0 mol%), and copper(I) iodide (337 mg, 1.77 mmol, 10 mol%). The mixture was further degassed for 15 min during which DIPA (20.0 mL, 143 mmol, 8.0 eq.) was added dropwise. The mixture was sonicated for 1 h followed by stirring at ambient temperature overnight. The reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (80 mL). The mixture was extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **413** (4.12 g, 86%) as a yellowish oil.

R_f 0.30 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3332, 2955, 2912, 2874, 2133, 1600, 1493, 1453, 1412, 1377, 1234, 1208, 1156, 1014, 962, 819, 804, 767, 719, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 – 7.18 (m, 2H, Ar*H*), 7.13 – 7.05 (m, 3H, Ar), 5.63 (tq, *J* = 1.3 Hz, 1H, 3-H), 4.12 (d, *J* = 5.7 Hz, 2H, 5-H_2), 2.23 (s, 2H, SiCH_2Ph), 1.90 (dt, *J* = 1.3, 0.7 Hz, 3H, 4-CH_3), 1.46 (br s, 1H, OH), 0.99 (t, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$), 0.60 (q, *J* = 7.9 Hz, 4H, $Si(CH_2CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.9, 139.4, 128.6, 128.3, 124.4, 104.9, 104.6, 95.2, 66.9, 23.0, 16.8, 7.5, 4.6; **HRMS** (ESI+) calc. for $C_{17}H_{25}O^{28}Si$ $[M+H]^+$ 273.16692, found 273.16702.

((2*S*,3*S*)-3-((Benzyldiethylsilyl)ethynyl)-2-methyloxiran-2-yl)methanol, 414



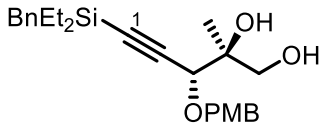
Racemic Preparation. Enyne **413** (87 mg, 0.32 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.7 mL) and cooled to 0 °C. *m*-CPBA (160 mg, 70 wt%, 649 µmol, 2.0 eq.) was added and the mixture was stirred at ambient temperature for 3 h. The mixture was cooled to 0 °C, and quenched with aqueous $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), the combined organics were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound **414** as a colourless oil (51 mg, 55%).

Asymmetric Preparation. Activated molecular sieves (3 Å) were suspended in CH_2Cl_2 (54 mL) and cooled to −30 °C. Ti(O*i*-Pr)$_4$ (2.1 mL, 7.09 mmol, 0.5 eq.) was added and the mixture stirred for 20 min, before adding L-(+)-diisopropyl tartrate (1.9 mL, 9.04 mmol, 0.6 eq.) and stirring further 20 min. A solution of enyne **413** (4.00 g, 14.7 mmol, 1.0 eq.) in CH_2Cl_2 (19 mL) was added followed by stirring for additional 20 min, before *tert*-butyl hydroperoxide (5.4 mL, 5.5 M in decane (stored over 4 Å molecular sieves), 29.7 mmol, 2.0 eq.) was added slowly. After storing the reaction at −30 °C (freezer) overnight, the reaction was quenched by addition of a saturated aqueous solution of Na_2SO_4 (7.1 mL, 1 mL/mmol[Ti]) and vigorous stirring at ambient temperature for 3 h. The mixture was diluted with Et_2O (100 mL) and filtered through Celite. The solid residue was suspended in EtOAc (100 mL), refluxed for 15 min, before being filtered through the same Celite-plug. After concentration *in vacuo* the residue was redissolved in Et_2O (50 mL) and NaOH (30 mL, 30% w/v in brine) was added and the biphasic mixture stirred at ambient temperature for 3 h. It was diluted with water (30 mL), extracted with Et_2O (3 ×80 mL) and the combined organics were washed with brine

(50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound **414** (3.105 g, 73%n 90% *ee* CHIRALPAK IA, 2.5% IPA/hexane, 1.3 mL/min, t_R (*R*) 7.6 min, t_R (*S*) 6.3 min) as a yellowish oil.

$[\alpha]_D^{25}$ +1.5 (*c* 1.0, $CHCl_3$); R_f 0.11 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3422, 2956, 2934, 2876, 2178, 1494, 1453, 1410, 1208, 1057, 1016, 770, 718, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 – 7.18 (m, 2H, $SiCH_2Ph$), 7.12 – 7.06 (m, 3H, $SiCH_2Ph$), 3.75 (dd, *J* = 12.6, 4.1 Hz, 1H, 5-H_2), 3.65 (dd, *J* = 12.6, 9.4 Hz, 1H, 5-H_2), 3.60 (s, 1H, 3-H), 2.22 (s, 2H, $SiCH_2Ph$), 1.67 – 1.58 (m, 1H, OH), 1.43 (s, 3H, 4-CH_3), 0.98 (t, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$), 0.59 (q, J = 7.9 Hz, 4H, $Si(CH_2CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.8, 128.5, 128.4, 124.6, 102.5, 88.8, 63.6, 63.2, 48.2, 22.6, 15.6, 7.4, 4.3; **HRMS** (ESI+) calc. for $C_{17}H_{24}O_2{}^{28}Si^{23}Na$ $[M+Na]^+$ 311.1438, found 311.1435.

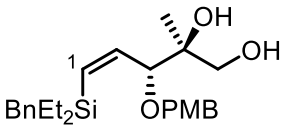
(2*S*,3*R*)-5-(Benzyldiethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-yne-1,2-diol, 415



To a suspension of epoxide **414** (3.00 g, 10.4 mmol, 1.0 eq.), Europium(III) triflate (1.25 g, 2.09 mmol, 0.20 eq.) and DTBMP (430 mg, 2.09 mmol, 0.20 eq.) in toluene (50 mL) was added 4-methoxybenzyl alcohol (2.0 mL, 16.1 mmol, 1.5 eq.) and the resulting mixture was stirred at 60 °C overnight. It was concentrated *in vacuo* followed by purification by column chromatography (petroleum ether / Et_2O, 2:1 →1:1 →1:2) to afford the title compound **415** (3.771 g, 85%) as a colourless oil.

$[\alpha]_D^{25}$ −80.6 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.11 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3441, 2955, 2935, 2875, 2171, 1613, 1514, 1494, 1454, 1303, 1249, 1209, 1174, 1156, 1058, 1034, 821, 770, 723, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.17 (m, 4H, OCH_2ArH, $SiCH_2ArH$), 7.13 – 7.06 (m, 3H, Ar*H*), 6.92 – 6.86 (m, 2H, OCH_2ArH), 4.73 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.39 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.09 (s, 1H, 3-H), 3.90 (dd, *J* = 11.4, 4.0 Hz, 1H, 5-H), 3.81 (s, 3H, $ArOCH_3$), 3.40 (dd, *J* = 11.4, 9.4 Hz, 1H, 5-H), 2.88 (s, 1H, OH), 2.32 (dd, *J* = 9.4, 4.0 Hz, 1H, OH), 2.23 (s, 2H, $SiCH_2Ar$), 1.19 (s, 3H, 4-CH_3), 1.01 (t, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$), 0.64 (q, *J* = 7.9 Hz, 4H, $Si(CH_2CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 138.9, 130.0, 129.1, 128.5, 128.4, 124.6, 114.1, 103.9, 90.5, 76.0, 73.7, 71.3, 67.3, 55.4, 22.6, 20.9, 7.6, 4.5; **HRMS** (ESI+) calc. for $C_{25}H_{34}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 449.21186, found 449.21152.

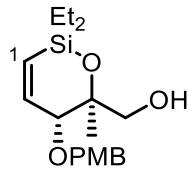
(2*S*,3*R*,*Z*)-5-(Benzyldiethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ene-1,2-diol, 416



Palldium on Calcium carbonate (5 wt%, 125 mg, 59.6 µmol, 0.05 eq.) was suspended in dry toluene (10 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **415** (500 mg, 1.17 mmol, 1.0 eq.) in toluene (2 mL). The mixture was stirred until TLC showed complete consumption of starting material (2.5 h). It was filtered over Celite and the solids were washed with EtOAc (50 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:2) afforded the title compound **416** (315 mg, 63%) as a colourless oil.

$[\alpha]_D^{25}$ +38.3 (*c* 0.5, $CHCl_3$); $\mathbf{R}_f$ 0.18 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3437, 2955, 2909, 2875, 1613, 1514, 1493, 1454, 1374, 1302, 1248, 1207, 1173, 1154, 1158, 1037, 1012, 820, 769, 735, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 – 7.13 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.07 – 7.00 (m, 3H, $SiCH_2$*Ph*), 6.89 – 6.83 (m, 2H, Ar*H*), 6.30 (dd, *J* = 14.8, 10.1 Hz, 1H, 2-H), 5.95 (dd, *J* = 14.8, 0.7 Hz, 1H, 1-H), 4.37 (d, *J* = 10.9 Hz, 1H, OCH_2Ar), 4.09 (d, *J* = 10.9 Hz, 1H, OCH_2Ar), 3.89 (dd, *J* = 10.1, 0.7 Hz, 1H, 3-H), 3.80 (s, 3H, $ArOCH_3$), 3.74 (dd, *J* = 11.3, 4.0 Hz, 1H, 5-H), 3.34 (dd, *J* = 11.3, 8.6 Hz, 1H, 5-H), 2.66 (s, 1H, OH), 2.38 (dd, *J* = 8.6, 4.0 Hz, 1H, OH), 2.26 – 2.16 (m, 2H, $SiCH_2$Ph), 1.05 (s, 3H, 4-CH_3), 0.97 (app. q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_2$), 0.77 – 0.56 (m, 4H, $Si(CH_2CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 145.1, 139.6, 134.6, 130.2, 129.3, 128.4, 124.4, 114.0, 84.7, 73.6, 70.5, 67.7, 55.4, 22.8, 20.8, 7.6, 4.9, 4.8; **HRMS** (ESI+) calc. for $C_{25}H_{34}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 449.21186, found 449, 21207.

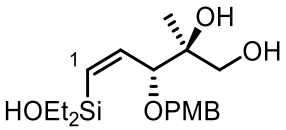
((5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)methanol, 417



Alkene **416** (266 mg, 621 µmol, 1.0 eq.) was dissolved in a solution of TBAF (0.70 mL, 1.0 M in THF, 0.70 mmol, 1.1 eq.) and stirred until TLC showed complete consumption of starting material (~2 h). The mixture was directly applied onto silica, and purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **417** as a colourless oil (124 mg, 60%). In some instances **418** could be isolated alongside.

$[\alpha]_D^{25}$ −97.6 (*c* 1.0, $CHCl_3$); **R_f** 0.10 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3477, 2869, 1613, 1587, 1514, 1394, 1302, 1248, 1205, 1174, 1114, 1083, 1036, 984, 969, 845, 823, 789, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.23 (m, 2H, Ar*H*), 6.91 – 6.84 (m, 2H, Ar*H*), 6.78 (dd, *J* = 14.8, 1.7 Hz, 1H, 2-H), 5.88 (dd, *J* = 14.8, 2.7 Hz, 1H, 1-H), 4.64 (d, *J* = 11.2 Hz, 1H, OC*H*$_2$Ar), 4.51 (d, *J* = 11.2 Hz, 1H, OC*H*$_2$Ar), 4.17 (dd, *J* = 2.7, 1.7 Hz, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 3.61 (dd, *J* = 10.8, 9.8 Hz, 1H, 5-H_2), 3.41 (dd, *J* = 10.8, 3.5 Hz, 1H, 5-H_2), 2.14 (dd, *J* = 9.8, 3.5 Hz, 1H, OH), 1.15 (s, 3H, 4-CH_3), 0.97 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.92 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.69 – 0.48 (m, 4H, Si(C*H*$_2$$CH_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 150.6, 130.5, 129.5, 125.0, 113.9, 77.7, 77.0, 72.4, 68.7, 55.4, 18.8, 7.4, 6.9, 6.7, 6.5; **HRMS** (ESI+) calc. for $C_{18}H_{28}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 359.16489, found 359.16514.

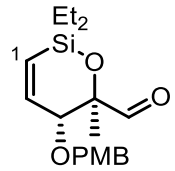
(2*S*,3*R*,*Z*)-5-(Diethyl(hydroxy)silyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ene-1,2-diol, 418



$[\alpha]_D^{25}$ +17.4 (*c* 1.0, $CHCl_3$); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3332, 2954, 2912, 2875, 1613, 1514, 1461, 1302, 1248, 1174, 1078, 1037, 849, 738; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 – 7.19 (m, 2H, Ar*H*), 6.92 – 6.83 (m, 2H, Ar*H*), 6.42 (dd, *J* = 14.9, 9.3 Hz, 1H, 2-H), 5.94 (dd, *J* = 14.8, 0.9 Hz, 1H, 1-H), 4.54 (d, *J* = 11.0 Hz, 1H, OC*H*$_2$Ar), 4.33 – 4.28 (m, 2H, OC*H*$_2$Ar, 3-H), 3.80 (s, 3H, ArOC*H*$_3$), 3.62 (d, *J* = 11.2 Hz, 1H, 5-H_2), 3.52 (d, *J* = 11.2 Hz, 1H, 5-H_2), 1.19 (s, 3H, 4-CH_3), 1.03 – 0.95 (m, 6H, Si(CH_2C*H*$_3$)$_2$), 0.73 – 0.61 (m, 4H, Si(C*H*$_2$$CH_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 147.2, 133.4,

130.5, 129.3, 113.9, 82.2, 74.5, 70.9, 68.3, 55.4, 19.9, 7.5, 7.5, 7.0, 6.6; **HRMS** (ESI+) calc. for $C_{18}H_{30}O_5{}^{28}Si^{23}Na$ $[M+Na]^+$ 377.17547, found 377.17565.

(5*R*,6*R*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasiline-6-carbaldehyde, 420

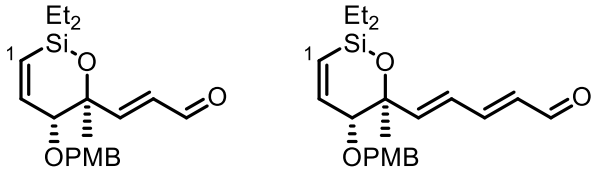


DMSO (0.38 mL, 5.4 mmol, 4.0 eq.) was added dropwise to a solution of oxalyl chloride (0.23 mL, 2.7 mmol, 2.0 eq.) in CH_2Cl_2 (4.5 mL) at −78 °C and stirred for 30 min. A solution of alcohol **417** (450 mg, 1.34 mmol, 1.0 eq.) in CH_2Cl_2 (4.5 mL) was added dropwise and the mixture stirred for further 30 min. Triethylamine (1.12 mL, 8.04 mmol, 6.0 eq.) was added dropwise and the mixture was allowed to warm to ambient temperature over 1 h. The reaction was quenched with water (30 mL), extracted with Et_2O (3 × 50 mL), the combined organics washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **420** (373 mg, 83%) as a colourless oil.

$[\alpha]_D^{25}$ −84.9 (*c* 1.0, $CHCl_3$); R_f 0.18 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 2876, 1744, 1613, 1586, 1514, 1462, 1302, 1249, 1174, 1131, 1084, 1036, 1004, 834, 820, 758, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.45 (s, 1H, C*H*O), 7.25 – 7.19 (m, 2H, Ar*H*), 6.90 – 6.85 (m, 2H, Ar*H*), 6.82 (dd, *J* = 14.7, 3.0 Hz, 1H, 1-H), 6.02 (dd, *J* = 14.7, 1.7 Hz, 1H, 2-H), 4.60 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.43 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.08 (dd, *J* = 3.0, 1.7 Hz, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 1.34 (s, 3H, 4-CH_3), 0.96 (app. q, *J* = 8.0 Hz, 6H, Si(CH_2CH_3)$_2$), 0.74 – 0.55 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.7, 159.5, 148.4, 130.0, 129.6, 128.1, 113.9, 81.0, 74.6, 71.4, 55.4,

18.0, 7.2, 6.8, 6.7, 6.6; **HRMS** (ESI+) calc. for $C_{18}H_{26}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 357.14926, found 357.14911.

(*E*)-3-((5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)acrylaldehyde, 422 and (2*E*,4*E*)-5-((5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)penta-2,4-dienal, 423



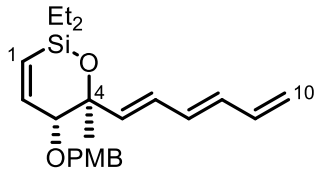
Aldehyde **420** (132 mg, 395 µmol, 1.0 eq.) and phosphorus ylid **84** (156 mg, 513 µmol, 1.3 eq.) were dissolved in toluene (4 mL). The mixture stirred at 80 °C overnight, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **422** (104 mg, 73%) and byproduct **423** (7 mg, 5%) both as yellowish oils.

Data for **422**: $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −119.9 (*c* 0.5, $CHCl_3$); $\mathbf{R}_f$ 0.36 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 2875, 1690, 1613, 1586, 1514, 1460, 1303, 1249, 1174, 1130, 1084, 1035, 1005, 982, 821, 763, 733; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.49 (d, *J* = 8.1 Hz, 1H, C*H*O), 7.26 – 7.21 (m, 2H, Ar*H*), 6.95 (d, *J* = 15.4 Hz, 1H, 5-H), 6.90 – 6.85 (m, 2H, Ar*H*), 6.74 (dd, *J* = 14.8, 1.8 Hz, 1H, 2-H), 6.35 (dd, *J* = 15.4, 8.1 Hz, 1H, 6-H), 5.99 (dd, *J* = 14.8, 2.6 Hz, 1H, 1-H), 4.66 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.39 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 3.83 (dd, *J* = 2.6, 1.8 Hz, 1H, 3-H), 3.81 (s, 3H, OC*H*$_3$), 1.34 (s, 3H, 4-CH_3), 0.97 (t, *J* = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.92 (t, *J* = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.70 – 0.48 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.3, 163.1, 159.6, 148.8,

130.0, 129.8, 129.7, 126.7, 114.0, 80.2, 76.8, 72.2, 55.5, 21.2, 7.2, 6.8, 6.6, 6.6; **HRMS** (ESI+) calc. for $C_{20}H_{28}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 383.16491, found 383.16513.

Data for **423**: $[\alpha]_D^{25}$ −98.1 (*c* 1.0, $CHCl_3$); R_f 0.28 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 2934, 2875, 1684, 1641, 1613, 1585, 1513, 1461, 1302, 1249, 1213, 1175, 1161, 1113, 1086, 1036, 1013, 988, 822, 765, 734, 714; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.56 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.28 – 7.21 (m, 2H, Ar*H*), 7.04 (dd, *J* = 15.3, 10.9 Hz, 1H, 7-H), 6.91 – 6.84 (m, 2H, Ar*H*), 6.74 (dd, *J* = 14.8, 1.9 Hz, 1H, 2-H), 6.57 (ddd, *J* = 15.1, 10.9, 0.6 Hz, 1H, 6-H), 6.43 (d, *J* = 15.1 Hz, 1H, 5-H), 6.14 (dd, *J* = 15.3, 8.0 Hz, 1H, 8-H), 5.97 (dd, *J* = 14.8, 2.5 Hz, 1H, 1-H), 4.64 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.39 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 3.81 (app t, *J* = 2.2 Hz, 1H, 3-H), 3.80 (s, 3H, ArOC*H*$_3$), 1.31 (s, 3H, 4-CH_3), 0.98 (t, *J* = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.95 (t, *J* = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.74 – 0.51 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.1, 159.4, 152.7, 151.8, 149.2, 131.5, 130.0, 129.7, 126.5, 125.7, 113.9, 81.0, 76.8, 72.3, 55.4, 21.6, 7.3, 6.9, 6.7, 6.7; **HRMS** (ESI+) calc. for $C_{22}H_{30}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 409.18056, found 409.18051.

(5*R*,6*S*)-2,2-Diethyl-6-((1*E*,3*E*)-hexa-1,3,5-trien-1-yl)-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasiline, 428

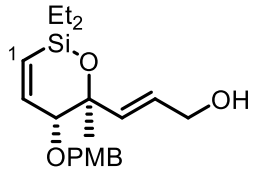


Methyltriphenylphosphonium bromide (41 mg, 0.12 mmol, 2.1 eq.) was suspended in THF (0.1 mL) and cooled to 0 °C. Potassium *tert*-butoxide (0.11 mL, 1 M in THF, 0.11 mmol, 2.0 eq.) was added dropwise and the mixture stirred for 30 min. Aldehyde

423 (21 mg, 54 µmol, 1.0 eq.) in THF (0.4 mL) was added, the mixture was warmed to ambient temperature and stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with water (3 mL), extracted with Et_2O (3 × 7 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1) afforded the title compound **428** (15 mg, 72%) as a colourless oil.

$[\alpha]_D^{25}$ −86.8 (*c* 1.0, $CHCl_3$); R_f 0.66 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 2934, 2912, 2875, 1613, 1586, 1514, 1461, 1302, 1248, 1209, 1173, 1085, 1036, 1006, 895, 823, 765, 733; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.19 (m, 2H, Ar*H*), 6.93 – 6.82 (m, 2H, Ar*H*), 6.73 (dd, *J* = 14.8, 2.0 Hz, 1H, 2-H), 6.45 – 6.30 (m, 2H, 6-H, 9-H), 6.26 – 6.20 (m, 2H, 7-H, 8-H), 6.00 – 5.91 (m, 2H, 1-H, 5-H), 5.21 (dd, *J* = 16.8, 1.8 Hz, 1H, 10-H_2), 5.07 (dd, *J* = 9.9, 1.8 Hz, 1H, 10-H_2), 4.59 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 4.43 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 3.87 – 3.71 (m, 4H, ArOCH_3, 3-H), 1.30 (s, 3H, 4-CH_3), 0.96 (app q, *J* = 7.8 Hz, 6H, Si(CH_2CH_3)$_2$), 0.71 – 0.49 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 149.8, 141.3, 137.3, 133.4, 132.9, 130.4, 129.5, 127.9, 126.4, 116.9, 113.8, 81.8, 76.8, 72.4, 55.4, 22.0, 7.4, 6.9, 6.8; **HRMS** (ESI+) calc. for $C_{23}H_{33}O_3{}^{28}Si$ $[M+H]^+$ 385.21935, found 385.21933.

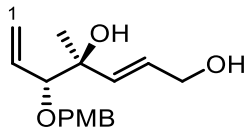
(*E*)-3-((5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)prop-2-en-1-ol, 427



$NaBH_4$ (6 mg, 0.16 mmol, 1.0 eq.) was added to a solution of aldehyde **422** (57 mg, 0.16 mmol, 1.0 eq.) in methanol (1.6 mL) at 0 °C and stirred at this temperature for 1 h. The reaction was quenched by addition of aqueous NH_4Cl. The mixture was diluted with water and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **427** (46 mg, 80%) as a colourless oil.

$[\alpha]_D^{25}$ −90.0 (*c* 0.67, $CHCl_3$); $\mathbf{R}_f$ 0.59 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3386, 2954, 2935, 2874, 1613, 1586, 1514, 1459, 1302, 1248, 1209, 1174, 1080, 1006, 823, 763, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 – 7.22 (m, 2H, Ar*H*), 6.93 – 6.83 (m, 2H, Ar*H*), 6.74 (dd, *J* = 14.8, 2.0 Hz, 1H, 2-H), 5.95 (dd, *J* = 14.9, 2.5 Hz, 1H, 1-H), 5.93 – 5.90 (m, 2H, 5-H, 6-H), 4.62 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.42 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.16 – 4.08 (m, 2H, 7-H$_2$), 3.81 (s, 3H, ArOC*H*$_3$), 3.77 (t, *J* = 2.2 Hz, 1H, 3-H), 1.28 (s, 3H, 4-CH_3), 0.96 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.93 (t, *J* = 7.9 Hz, 3H, Si(CH_2C*H*$_3$)$_2$), 0.69 – 0.48 (m, 4H, Si(C*H*$_2$$CH_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 149.8, 138.4, 130.4, 129.7, 127.3, 126.3, 113.8, 81.6, 76.4, 72.2, 63.6, 55.4, 21.8, 7.4, 6.9, 6.8, 6.7; **HRMS** (ESI+) calc. for $C_{20}H_{30}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 385.18056, found 385.18011.

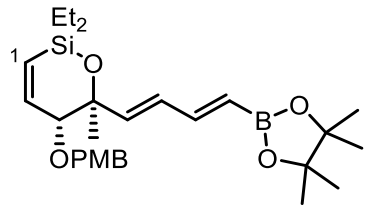
(4*S*,5*R*,*E*)-5-((4-Methoxybenzyl)oxy)-4-methylhepta-2,6-diene-1,4-diol, 430



To alcohol **427** (10 mg, 28 µmol, 1.0 eq.), β-bromostyrene (4.5 µL, 3.5 µmol, 1.2 eq.) and $Pd(dba)_2$ (1 mg, 2 µmol, 5 mol%) was added a TBAF-solution (0.09 mL, 1.0 M in THF, 90 µmol, 3.0 eq.). The resulting mixture was stirred at ambient temperature for 15 min. Purification by column chromatography (petroleum ether / EtOAc, 1:1) afforded the title compound **430** (6.5 mg, 85%) as a colourless oil.

$[\alpha]_D^{25}$ −38.3 (*c* 0.67, $CHCl_3$); $\mathbf{R}_f$ 0.08 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3406, 2931, 2862, 1613, 1514, 1456, 1302, 1248, 1175, 1073, 1034, 979, 931, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.19 (m, 2H, Ar*H*), 6.91 – 6.85 (m, 2H, Ar*H*), 5.92 – 5.80 (m, 2H, 5-H, 6-H), 5.79 – 5.68 (m, 1H, 2-H), 5.38 (ddd, *J* = 10.4, 1.8, 0.8 Hz, 1H, 1-H_2), 5.30 (ddd, *J* = 17.2, 1.8, 0.8 Hz, 1H, 1-H_2), 4.58 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.26 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.15 (d, *J* = 4.9 Hz, 2H, 7-H_2), 3.81 (s, 3H, ArOCH_3), 3.61 (d, *J* = 8.2 Hz, 1H, 3-H), 2.72 (s, 1H, OH), 1.24 (s, 3H, 4-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6, 134.5, 130.1, 129.7, 128.7, 120.7, 114.0, 100.1, 86.8, 73.8, 70.4, 63.5, 55.4, 24.3; **HRMS** (ESI+) calc. for $C_{16}H_{22}O_4{}^{23}Na$ $[M+Na]^+$ 301.14103, found 301.14107.

(5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-6-((1*E*,3*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-1-yl)-5,6-dihydro-2*H*-1,2-oxasiline, 425

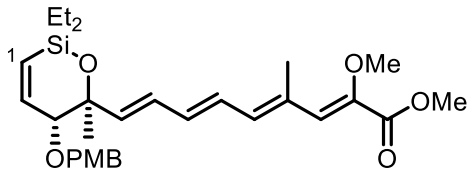


The procedure was adapted from a literature procedure.[277] Chromium(II) chloride (840 mg, 6.83 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (9.0 mL) was added and the suspension stirred at ambient temperature for 30 min to give a minty green mixture. A solution of aldehyde **422** (308 mg, 854 µmol, 1.0 eq.) and $CHCl_2Bpin$ (360 mg, 1.71 mmol, 2.0 eq.) in THF (4.0 mL) was added, followed by dropwise addition of a solution of lithium iodide (457 mg, 3.41 mmol, 4.0 eq.) in THF (4.0 mL). The mixture was stirred in the dark at ambient temperature overnight, poured into water and extracted with Et_2O (3 × 60 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **425** (349 mg, 84%) as a colourless oil.

$[\alpha]_D^{25}$ −67.6 (*c* 1.0, $CHCl_3$); R_f 0.32 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2978, 2956, 1606, 1586, 1514, 1460, 1390, 1357, 1322, 1250, 1213, 1168, 1145, 1084, 1037, 1010, 971, 849, 764, 733; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 – 7.22 (m, 2H, Ar*H*), 7.03 (dd, *J* = 17.7, 10.6 Hz, 1H, 7-H), 6.93 – 6.82 (m, 2H, Ar*H*), 6.71 (dd, *J* = 14.8, 2.1 Hz, 1H, 2-H), 6.41 (ddd, *J* = 15.2, 10.6, 0.8 Hz, 1H, 6-H), 6.14 (d, *J* = 15.2 Hz, 1H, 5-H), 5.93 (dd, *J* = 14.8, 2.4 Hz, 1H, 1-H), 5.55 (d, *J* = 17.7 Hz, 1H, 8-H), 4.56 (d, *J* = 11.2 Hz, 1H, OC*H*$_2$Ar), 4.42 (d, *J* = 11.2 Hz, 1H, OC*H*$_2$Ar), 3.81 (s, 3H, ArOC*H*$_3$), 3.77 (t, *J* = 2.3 Hz,

1H, 3-H), 1.29 (s, 3H, 4-CH_3), 1.28 (s, 12H, OC(CH_3)$_2$), 0.96 (t, J = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.93 (t, J = 7.9 Hz, 3H, Si(CH_2CH_3)$_2$), 0.70 – 0.49 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 150.2, 149.7, 144.7, 130.4, 129.7, 129.5, 126.5, 113.9, 83.3, 81.6, 76.7, 72.5, 55.4, 25.0, 24.9, 22.0, 7.3, 6.9, 6.8, 6.7; **HRMS** (ESI+) calc. for $C_{27}H_{41}O_5{}^{10}B^{28}Si^{23}Na$ $[M+Na]^+$ 507.27085, found 507.27109.

Methyl (2*Z*,4*E*,6*E*,8*E*)-9-((5*R*,6*S*)-2,2-diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-2-methoxy-4-methylnona-2,4,6,8-tetraenoate, 421



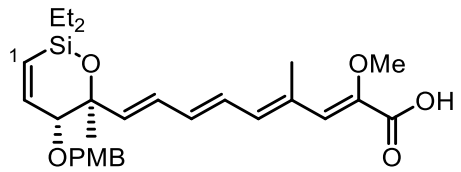
To a solution of dienoate **74** (191 mg, 677 µmol, 1.0 eq.), siloxane **425** (328 mg, 677 µmol, 1.0 eq.) and Tl_2CO_3 (635 mg, 1.35 mmol, 2.0 eq.) in THF (5.4 mL) and water (1.4 mL) was added Pd(dppf)Cl_2 (50 mg, 68 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h, then diluted with Et_2O, filtered over Celite, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **421** (247 mg, 71%) as a yellow oil.

This procedure was adapted from a literature procedure.[357] To a mixture of dienoate **74** (12 mg, 43 µmol, 1.0 eq.), siloxane **425** (20 mg, 41 µmol, 1.0 eq.) in DMF (0.4 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (20 mg, 63 µmol, 1.5 eq.) and Pd(dppf)Cl_2 (3 mg, 4.1 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h. The reaction was quenched with brine. The mixture was diluted with water and extracted with Et_2O (3 × 5 mL). The combined organics were washed with brine (5 mL), dried over

$MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **421** (8 mg, 38%) as a yellow oil.

$[\alpha]_D^{25}$ −55.6 (*c* 1.0, $CHCl_3$); R_f 0.16 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2932, 1716, 1614, 1584, 1514, 1459, 1350, 1251, 1194, 1101, 1035, 1017, 992, 761, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 – 7.22 (m, 2H, Ar*H*), 6.90 – 6.83 (m, 2H, Ar*H*), 6.73 (dd, *J* = 14.8, 2.0 Hz, 1H, 2-H), 6.67 (s, 1H, 11-H), 6.55 (dd, *J* = 14.4, 11.4 Hz, 1H, 8-H), 6.45 (dd, *J* = 14.9, 10.9 Hz, 1H, 6-H), 6.40 (d, *J* = 11.4 Hz, 1H, 9-H), 6.34 (dd, *J* = 14.4, 10.9 Hz, 1H, 7-H), 6.03 (d, *J* = 14.9 Hz, 1H, 5-H), 5.94 (dd, *J* = 14.8, 2.4 Hz, 1H, 1-H), 4.60 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.43 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 3.82 – 3.78 (m, 7H, ArOC*H*$_3$, 12-OC*H*$_3$, 3-H), 3.69 (s, 3H, COOC*H*$_3$), 2.12 (s, 3H, 10-CH_3), 1.30 (s, 3H, 4-CH_3), 1.01 – 0.91 (m, 6H, Si(CH_2CH_3)$_2$), 0.72 – 0.50 (m, 4H, Si(CH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.4, 159.3, 149.8, 143.9, 142.5, 136.9, 136.3, 132.6, 130.4, 129.5, 129.5, 128.3, 128.3, 126.4, 113.9, 81.7, 76.8,[2] 72.4, 60.5, 55.4, 52.1, 21.9, 15.1, 7.4, 6.9, 6.8, 6.8; **HRMS** (ESI+) calc. for $C_{29}H_{40}O_6{}^{28}Si^{23}Na$ $[M+Na]^+$ 535.24864, found 535.24841.

(2*Z*,4*E*,6*E*,8*E*)-9-((5*R*,6*S*)-2,2-Diethyl-5-((4-methoxybenzyl)oxy)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-2-methoxy-4-methylnona-2,4,6,8-tetraenoic acid, 460



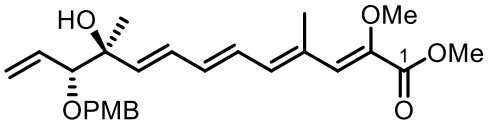
Alkenylsiloxane **421** (22 mg, 43 µmol, 1.0 eq.) and LiOH (4 mg, 95 µmol, 2.0 eq.) were dissolved in THF (0.25 mL) and water (0.2 mL) and stirred at ambient temperature

[2] Determined by HMBC.

overnight. The mixture was poured into 1 M citric acid and extracted with CH_2Cl_2 (3 × 8 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 25:1) afforded the title compound **460** (10 mg, 47%) as a yellow oil.

$[\alpha]_D^{25}$ −50.7 (*c* 1.0, $CHCl_3$); R_f 0.26 (CH_2Cl_2 / MeOH, 25:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 2930, 2874, 1684, 1613, 1583, 1514, 1452, 1352, 1302, 1250, 1087, 1033, 993, 766, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.21 (m, 2H, Ar*H*), 6.90 – 6.84 (m, 2H, Ar*H*), 6.80 (s, 1H, 11-H), 6.73 (dd, *J* = 14.8, 2.0 Hz, 1H, 2-H), 6.56 (dd, *J* = 14.1, 11.4 Hz, 1H, 8-H), 6.50 – 6.42 (m, 2H, 6-H, 9-H), 6.37 (dd, *J* = 14.1, 10.9 Hz, 1H, 7-H), 6.05 (d, *J* = 14.8 Hz, 1H, 5-H), 5.95 (dd, *J* = 14.8, 2.5 Hz, 1H, 1-H), 4.60 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.43 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 3.83 – 3.77 (m, 4H, ArOC*H*$_3$, 3-H), 3.72 (s, 3H, OC*H*$_3$), 2.14 (s, 3H, 10-CH_3), 1.31 (s, 3H, 4-CH_3), 0.97 (app td, *J* = 7.9, 6.3 Hz, 6H, Si(CH_2C*H*$_3$)$_2$), 0.72 – 0.51 (m, 4H, Si(C*H*$_2$CH$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.4, 159.4, 149.8, 143.0, 143.0, 138.1, 137.0, 132.4, 131.6, 130.4, 129.6, 128.3, 128.2, 126.4, 113.9, 81.7, 76.9,[3] 72.5, 60.8, 55.4, 21.9, 14.9, 7.4, 6.9, 6.8, 6.8; **HRMS** (ESI−) calc. for $C_{28}H_{37}O_6{}^{28}Si$ $[M-H]^-$ 497.23649, found 497.23659.

Methyl (2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*)-10-hydroxy-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyltrideca-2,4,6,8,12-pentaenoate, 426



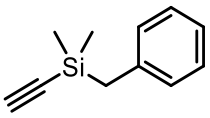
To cyclic siloxane **421** (10 mg, 20 µmol, 1.0 eq.), β-bromostyrene (3 µL, 23 µmol, 1.2 eq.), and $Pd(dba)_2$ (0.6 mg, 1 µmol, 5 mol%) was added a solution of TBAF in THF

[3] Determined by HMBC.

(0.06 mL, 1.0 M, 60 µmol, 3.0 eq.). The resulting mixture was stirred at ambient temperature for 6 h. Purification by column chromatography afforded the title compound **426** (8.2 mg, ~98%) as an inseperable mixture with an unidentified byproduct. The purity proved insufficient to obtain a qualitative ^{13}C NMR spectrum.

R$_f$ 0.26 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.21 (m, 2H, Ar*H*), 6.91 – 6.85 (m, 2H, Ar*H*), 6.65 (d, *J* = 0.7 Hz, 1H, 3-H), 6.54 (dd, *J* = 14.0, 11.5 Hz, 1H, 6-H), 6.44 – 6.32 (m, 3H, 5-H, 7-H, 8-H), 5.87 (d, *J* = 14.5 Hz, 1H, 9-H), 5.73 (ddd, *J* = 17.2, 10.4, 8.1 Hz, 1H, 12-H), 5.38 (dd, *J* = 10.4, 1.8 Hz, 1H, 13-H), 5.31 (ddd, *J* = 17.2, 1.9, 0.8 Hz, 1H, 13-H), 4.58 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.26 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 3.81 (s, 3H, ArOC*H*$_3$), 3.80 (d, *J* = 1.5 Hz, 3H, OC*H*$_3$), 3.68 (s, 3H, CO_2C*H*$_3$), 3.63 (d, *J* = 8.2 Hz, 1H, 11-H), 2.75 (s, 1H, O*H*), 2.10 (d, *J* = 1.2 Hz, 3H, 4-CH_3), 1.26 (d, *J* = 1.0 Hz, 3H, 10-CH_3); **HRMS** (ESI+) calc. for $C_{25}H_{32}O_6{}^{23}Na$ $[M+Na]^+$ 451.20911, found 451.20898.

Benzyl(ethynyl)dimethylsilane, 306

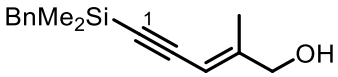


Ethynylmagnesium bromide (160 mL, 0.5 M in THF, 80.0 mmol, 1.3 eq.) was added at 0 °C, to a solution of benzyldimethylchlorosilane (11.1 mL, 61.2 mmol, 1.0 eq.) in THF (200 mL). The resulting mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (150 mL), extracted with Et_2O (3 × 150 mL), the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 25:1) afforded the title compound **306** (9.14 g, 86%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24 (t, J = 7.5 Hz, 2H, Ar*H*), 7.14 – 7.05 (m, 3H, Ar*H*), 2.42 (s, 1H, CC*H*), 2.23 (s, 2H, SiCH_2Ph), 0.16 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.7, 128.5, 128.4, 124.6, 94.5, 88.7, 26.0, −2.2.

The spectroscopic data is in agreement with that reported by Feldman and coworkers.[232]

(*E*)-5-(Benzyldimethylsilyl)-2-methylpent-2-en-4-yn-1-ol, 396



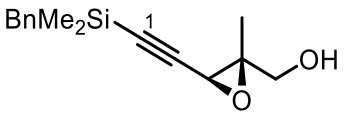
To a degassed solution of alkyne **306** (4.40 g, 25.2 mmol, 1.0 eq.) and vinyl iodide **76** (5.00 g, 25.3 mmol, 1.0 eq.) in THF (100 mL) was added $Pd(PPh_3)_2Cl_2$ (177 mg, 252 µmol, 1.0 mol%), and copper(I) iodide (481 mg, 2.53 mmol, 10 mol%). The mixture was further degassed for 15 min during which DIPA (28.3 mL, 202 mmol, 8.0 eq.) was added dropwise. The mixture was sonicated for 1 h followed by stirring at ambient temperature overnight. The reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (150 mL), and extracted with Et_2O (3 × 150 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **396** (5.34 g, 87%) as a yellowish oil.

R$_f$ 0.21 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3333, 2959, 2133, 1493, 1452, 1249, 1207, 1155, 1099, 1057, 1015, 992, 843, 832, 820, 795, 762, 718, 698, 626; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.19 (m, 2H, SiCH$_2$*Ph*), 7.12 – 7.06 (m, 3H, SiCH$_2$*Ph*), 5.61 (q, J = 1.5 Hz, 1H, 3-H), 4.12 (ddd, J = 6.2, 1.5, 0.8 Hz, 2H, 5-H$_2$), 2.23 (s, 2H, SiCH_2Ph), 1.89 (dt, J = 1.5, 0.8 Hz, 3H, 4-CH$_3$), 1.47 (t, J = 6.2 Hz, 1H, OH), 0.16 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 152.1, 139.2, 128.5, 128.3, 124.5,

104.7, 103.8, 96.9, 66.9, 26.5, 16.8, −1.8; **HRMS** (ESI+) calc. for $C_{15}H_{21}O^{28}Si$ $[M+H]^+$ 245.1356, found 245.1358.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

((2*S*,3*S*)-3-((Benzyldimethylsilyl)ethynyl)-2-methyloxiran-2-yl)methanol, ent-397



Racemic Preparation. Enyne **396** (100 mg, 409 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.3 mL) and cooled to 0 °C. *m*-CPBA (138 mg, 560 µmol, 1.4 eq.) was added and the mixture was stirred at ambient temperature for 3 h, then cooled to 0 °C, quenched with aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title **397** compound as a colourless oil (32 mg, 30%).

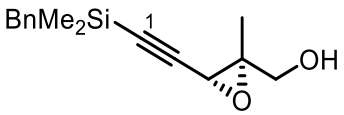
Asymmetric Preparation. Activated molecular sieves (3 Å) were suspended in CH_2Cl_2 (78 mL) and cooled to −30 °C. Ti(O*i*-Pr)$_4$ (3.2 mL, 11 mmol, 0.5 eq.) was added and the mixture stirred for 20 min, before adding L-(+)-diisopropyl tartrate (2.7 mL, 13 mmol, 0.6 eq.) and stirring further 20 min. A solution of enyne **396** (5.20 g, 21.3 mmol, 1.0 eq.) in CH_2Cl_2 (28 mL) was added followed by stirring for additional 20 min, before *tert*-butyl hydroperoxide (7.7 mL, 5.5 M in decane (stored over 4 Å molecular sieves), 42 mmol, 2.0 eq.) was added slowly. After storing the reaction at −30 °C (freezer) overnight, the reaction was quenched by addition of a saturated aqueous solution of Na_2SO_4 (10.8 mL, 1 mL/mmol[Ti]) and vigorous stirring at ambient temperature for 3 h. The mixture was diluted with Et_2O (100 mL) and filtered through Celite. The solid residue was suspended

in EtOAc (100 mL), refluxed for 15 min, before being filtered through the same Celite-plug. After concentration *in vacuo* the residue was redissolved in Et_2O (50 mL) and NaOH (30 mL, 30% w/v in brine) was added and the biphasic mixture stirred at ambient temperature for 3 h. Water (30 mL) was added, the mixture extracted with Et_2O (3 ×80 mL), and the combined organics were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 100:0 →20:1 →9:1 →17:3 →4:1) afforded the title compound **ent-397** (4.49 g, 81%, 92% *ee* CHIRALPAK IA, 2.5% IPA/hexane, 1.3 mL/min, t_R (*R*) 8.2 min, t_R (*S*) 10.0 min) as a yellowish oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +3.4 (*c* 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.65 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3423, 2962, 2929, 2178, 1600, 1494, 1452, 1409, 1383, 1251, 1208, 1158, 1101, 1076, 1057, 1032, 879, 845, 796, 764, 719, 699, 662; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.19 (m, 2H, $SiCH_2$*Ph*), 7.13 – 7.03 (m, 3H, $SiCH_2$*Ph*), 3.75 (dd, *J* = 12.7, 4.0 Hz, 1H, 5-H_2), 3.64 (dd, *J* = 12.7, 9.4 Hz, 1H, 5-H_2), 3.58 (s, 1H, 3-H), 2.22 (s, 2H, $SiCH_2$Ph), 1.60 (dd, *J* = 9.4, 4.1 Hz, 1H, OH), 1.42 (s, 3H, 4-CH_3), 0.15 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.7, 128.5, 128.4, 124.6, 101.7, 90.5, 63.6, 63.2, 48.2, 26.1, 15.6, −2.1; **HRMS** (ESI+) calc. for $C_{15}H_{20}O_2{}^{28}Si^{23}Na$ $[M+Na]^+$ 283.1125, found 283.1125.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

((2*R*,3*R*)-3-((Benzyldimethylsilyl)ethynyl)-2-methyloxiran-2-yl)methanol, 397

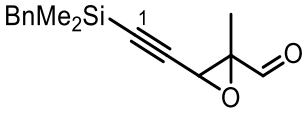


Asymmetric Preparation. Activated molecular sieves (3 Å) were suspended in CH_2Cl_2 (22.5 mL) and cooled to −30 °C. Ti(O*i*-Pr)$_4$ (0.67 mL, 2.3 mmol, 0.5 eq.) was added and

the mixture stirred for 20 min, before adding D-(−)-diisopropyl tartrate (0.57 mL, 2.7 mmol, 0.6 eq.) and stirring further 20 min. A solution of enyne **396** (1.10 g, 4.50 mmol, 1.0 eq.) in CH_2Cl_2 (28 mL) was added followed by stirring for additional 20 min, before *tert*-butyl hydroperoxide (1.64 mL, 5.5 M in decane (stored over 4 Å molecular sieves), 9.02 mmol, 2.0 eq.) was added slowly. After storing the reaction at −30 °C (freezer) overnight, the reaction was quenched by addition of a saturated aqueous solution of Na_2SO_4 (2.3 mL, 1 mL/mmol[Ti]) and vigorous stirring at ambient temperature for 3 h. The mixture was diluted with Et_2O (40 mL) and filtered through Celite. The solid residue was suspended in EtOAc (40 mL), refluxed for 15 min, before being filtered through the same Celite-plug. After concentration *in vacuo* the residue was redissolved in Et_2O (30 mL) and NaOH (15 mL, 30% w/v in brine) was added and the biphasic mixture stirred at ambient temperature for 3 h. Water (15 mL) was added, the mixture extracted with Et_2O (3 ×30 mL), and the combined organics washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 100:0 →20:1 →9:1 →17:3 →4:1) afforded the title compound **397** (844 mg, 72%, 89% *ee* CHIRALPAK IA, 2.5% IPA/hexane, 1.3 mL/min, t_R (*R*) 7.6 min, t_R (*S*) 9.9 min) as a yellowish oil.

$[\alpha]_D^{25}$ +2.8 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-397**.

3-((Benzyldimethylsilyl)ethynyl)-2-methyloxirane-2-carbaldehyde, 438

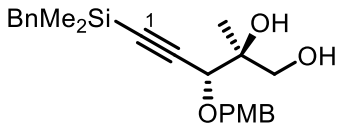


DMSO (77 µL, 1.1 mmol, 10.5 eq.) was added dropwise to pyridine·SO_3-complex (51 mg, 0.32 mmol, 3.1 eq.) and stirred at ambient temperature for 15 min. A solution of

alcohol **397** (27 mg, 0.10 mmol, 1.0 eq.), and DIPEA (94 µL, 0.54 mmol, 5.2 eq.) in CH_2Cl_2 (0.6 mL) was added and stirred for 1 h. The reaction was quenched with aqueous HCl (1 M, 5 mL), extracted with Et_2O (3 × 5 mL), the combined organics washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound **438** (14 mg, 52%) as a colourless oil.

R*f* 0.48 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2059, 3025, 2962, 2182, 1638, 1600, 1494, 1453, 1404, 1250, 1209, 1158, 1108, 1058, 1023, 991, 905, 883, 835, 797, 764, 700, 661, 636; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.88 (s, 1H, C*H*O), 7.25 – 7.20 (m, 2H, $SiCH_2$*Ph*), 7.14 – 7.03 (m, 3H, $SiCH_2$*Ph*), 3.67 (s, 1H, 3-H), 2.22 (s, 2H, $SiCH_2$Ph), 1.54 (s, 3H, 4-CH_3), 0.17 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 197.7, 138.4, 128.4, 124.8, 98.4, 92.7, 64.0, 48.8, 25.8, 11.4, −2.2; **HRMS** (ESI+) calc. for $C_{15}H_{19}O_2{}^{28}Si$ $[M+H]^+$ 259.11488, found 259.11490.

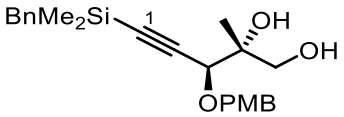
(2*S*,3*R*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-yne-1,2-diol, ent-398



To a suspension of epoxide **ent-497** (4.450 g, 17.1 mmol, 1.0 eq.), Europium(III) triflate (2.048 g, 3.42 mmol, 0.20 eq.) and DTBMP (702 mg, 3.42 mmol, 0.20 eq.) in toluene (85 mL) was added 4-methoxybenzyl alcohol (3.2 mL, 25.8 mmol, 1.5 eq.) and the resulting mixture was stirred at 60 °C overnight, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1 →1:1 →1:2) to afford the title compound **ent-398** (5.605 g, 82%) as a colourless oil.

$[\alpha]_D^{25}$ −82.4 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.34 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3430, 2958, 2169, 1613, 1514, 1493, 1453, 1302, 1249, 1208, 1175, 1155, 1112, 1076, 1057, 1033, 845, 836, 824, 796, 763, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 – 7.19 (m, 4H, $SiCH_2Ph$, Ar*H*), 7.14 – 7.05 (m, 3H, $SiCH_2Ph$), 6.92 – 6.84 (m, 2H, Ar*H*), 4.72 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.38 (d, *J* = 11.2 Hz, 1H, OCH_2Ar), 4.07 (s, 1H, 3-H), 3.87 (dd, *J* = 11.5, 4.2 Hz, 1H, 5-H_2), 3.81 (s, 3H, $ArOCH_3$), 3.39 (dd, *J* = 11.3, 9.1 Hz, 1H, 5-H_2), 2.84 (s, 1H, OH), 2.27 (dd, *J* = 9.1, 4.2 Hz, 1H, OH), 2.23 (s, 2H, $SiCH_2Ph$), 1.18 (s, 3H, 4-CH_3), 0.20 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 138.8, 130.0, 129.2, 128.5, 128.4, 124.7, 114.0, 103.0, 92.1, 75.9, 73.7, 71.3, 67.3, 55.4, 26.2, 20.8, −1.9; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 421.18056, found 421.18057.

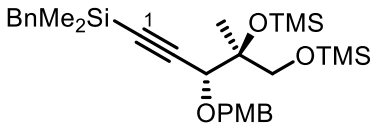
(2*R*,3*S*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-yne-1,2-diol, 398



To a suspension of epoxide **397** (1.750 g, 6.72 mmol, 1.0 eq.), Europium(III) triflate (805 mg, 1.34 mmol, 0.20 eq.) and DTBMP (276 mg, 1.34 mmol, 0.20 eq.) in toluene (33 mL) was added 4-methoxybenzyl alcohol (1.3 mL, 11 mmol, 1.5 eq.) and the resulting mixture was stirred at 80 °C overnight (Temperature this high due to stirrer overheating), and was concentrated *in vacuo*.Purification by column chromatography (petroleum ether / Et_2O, 2:1 →1:1 →1:2) to afford the title compound **398** (1.486 g, 55%) as a colourless oil.

$[\alpha]_D^{25}$ +81.6 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-398**.

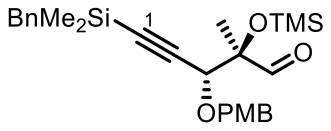
(*S*)-4-((*R*)-3-(Benzyldimethylsilyl)-1-((4-methoxybenzyl)oxy)prop-2-yn-1-yl)-2,2,4,7,7-pentamethyl-3,6-dioxa-2,7-disilaoctane, 433



Imidazole (60 mg, 0.88 mmol, 4.4 eq.) was added to a solution of TMS chloride (0.10 mL, 0.77 mmol, 4.2 eq.) in CH_2Cl_2 (1.0 mL) at 0 °C, and stirred for 5 min. A solution of diol **ent-398** (80 mg, 0.20 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) was added, and the mixture stirred at ambiemt temperature overnight. The mixture was diluted with water (10 mL), extracted with Et_2O (3 × 10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford crude title compound **433** as a colourless oil (88 mg, 81%).

IR (cm^{-1}) $\tilde{\nu}_{max}$ = 2959, 2935, 2360, 2341, 2172, 1613, 1514, 1494, 1453, 1321, 1303, 1250, 1209, 1174, 1155, 1058, 1034, 905, 835, 763, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 – 7.17 (m, 4H, SiCH$_2$*Ph*, Ar*H*), 7.13 – 7.05 (m, 3H, SiCH$_2$*Ph*), 6.89 – 6.83 (m, 2H, Ar*H*), 4.69 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.38 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.13 (s, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 3.55 – 3.45 (m, 2H, 5-H$_2$), 2.23 (s, 2H, SiC*H*$_2$Ph), 1.23 (s, 3H, 4-CH$_3$), 0.15 (s, 6H, Si(C*H*$_3$)$_2$), 0.10 (s, 9H, OSi(C*H*$_3$)$_3$), 0.07 (s, 9H, OSi(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.2, 139.2, 135.2, 130.4, 129.7, 128.5, 128.3, 124.5, 113.7, 105.1, 89.8, 78.0, 73.3, 70.9, 67.6, 55.4, 26.4, 20.5, 2.7, −0.4, −1.9; **HRMS** (ESI+) calc. for $C_{29}H_{46}O_4{}^{28}Si_3{}^{23}Na$ $[M+Na]^+$ 565.25961, found 565.25851.

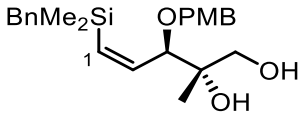
(2*R*,3*R*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methyl-2-((trimethylsilyl)oxy)pent-4-ynal, 435



DMSO (0.06 mL, 0.85 mmol, 5.0 eq.) was added dropwise to a solution of oxalyl chloride (0.06 mL, 0.71 mmol, 4.2 eq.) in CH_2Cl_2 (1.5 mL) at −78 °C and stirred for 30 min. A solution of silyl ether **433** (85 mg, 0.16 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added dropwise and the mixture stirred for further 30 min. DIPEA (0.27 mL, 1.6 mmol, 10.0 eq.) was added dropwise and the mixture was stirred at this temperature for 10 min and then allowed to warm to ambient temperature over 30 min. The reaction was quenched with water (15 mL), extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **435** (60 mg, 82%) as a colourless oil.

R_f 0.35 (petroleum ether / Et_2O, 25:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.44 (s, 1H, C*H*O), 7.30 – 7.17 (m, 4H, SiCH$_2$*Ph*), 7.13 – 7.05 (m, 3H, Ar*H*, SiCH$_2$*Ph*), 6.90 – 6.83 (m, 2H, Ar*H*), 4.68 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.39 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.09 (s, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 2.23 (s, 2H, SiC*H*$_2$Ph), 1.39 (s, 3H, 4-CH$_3$), 0.18 (s, 3H, Si(C*H*$_3$)$_2$), 0.17 (s, 3H, Si(C*H*$_3$)$_2$), 0.11 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.2, 159.5, 130.0, 129.8, 129.2, 128.5, 128.4, 124.6, 113.9, 72.9, 70.5, 55.4, 26.2, 18.5, 2.4, −1.9; **HRMS** (ESI+) calc. for $C_{26}H_{36}O_4{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 491.20443, found 491.20447.

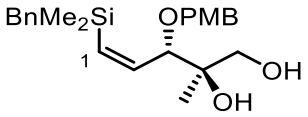
(2*S*,3*R*,*Z*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ene-1,2-diol, ent-399



Palldium on calcium carbonate (5 wt%, 147 mg, 69.0 µmol, 0.05 eq.) was suspended in dry toluene (13.8 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **ent-398** (552 mg, 1.38 mmol, 1.0 eq.) and quinoline (0.08 mL, 0.68 µmol, 0.5 eq.) in cyclohexene (1.4 mL). The mixture was stirred until TLC showed complete consumption of starting material (3 h). It was filtered over Celite and the solids were washed with EtOAc (50 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:2) afforded the title compound **ent-399** (414 mg, 75%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +39.5 (*c* 0.35, $CHCl_3$); $\mathbf{R}_f$ 0.52 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3468, 3021, 2956, 1612, 1514, 1493, 1453, 1302, 1249, 1216, 1174, 1155, 1037, 931, 756, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 – 7.14 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.10 – 7.05 (m, 1H, $SiCH_2$*Ph*), 7.03 – 6.98 (m, 2H, $SiCH_2$*Ph*), 6.89 – 6.83 (m, 2H, Ar*H*), 6.26 (dd, *J* = 14.7, 10.1 Hz, 1H, 2-H), 5.98 (dd, *J* = 14.7, 0.9 Hz, 1H, 1-H), 4.44 (d, *J* = 11.1 Hz, 1H, OCH_2Ar), 4.15 (d, *J* = 11.1 Hz, 1H, OCH_2Ar), 3.98 (d, *J* = 10.3 Hz, 1H, 3-H), 3.80 (s, 3H, $ArOCH_3$), 3.75 (dd, *J* = 11.2, 3.4 Hz, 1H, 5-H_2), 3.35 (dd, *J* = 11.2, 8.4 Hz, 1H, 5-H_2), 2.71 (s, 1H, OH), 2.39 (dd, *J* = 8.8, 3.8 Hz, 1H, OH), 2.24 – 2.10 (m, 2H, $SiCH_2$Ph), 1.07 (s, 3H, 4-CH_3), 0.14 (s, 3H, $Si(CH_3)_2$), 0.12 (s, 3H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 144.3, 139.5, 136.1, 130.1, 129.3, 128.4, 128.4, 124.5, 114.0, 84.1, 73.6, 70.5, 67.7, 55.4, 26.8, 20.8, −1.1, −1.2; **HRMS** (ESI+) calc. for $C_{23}H_{32}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 423.19621, found 423.19596.

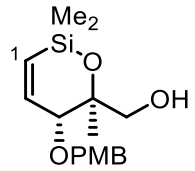
(2*R*,3*S*,*Z*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ene-1,2-diol, 399



Palldium on calcium carbonate (5 wt%, 362 mg, 200 µmol, 0.05 eq.) was suspended in dry toluene (34 mL). The mixture was flushed with hydrogen (evacuated and back filled with H_2 three times), followed by addition of alkyne **398** (1.355 mg, 4.00 mmol, 1.0 eq.) and quinoline (0.20 mL, 1.69 mmol, 0.5 eq.) in cyclohexene (3.4 mL). The mixture was stirred until TLC showed complete consumption of starting material (3 h). It was filtered over Celite and the solids were washed with EtOAc (100 mL), followed by concentration *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:2) afforded the title compound **399** (1.023 mg, 75%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −24.8 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-399**.

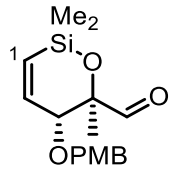
((5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)methanol, 400



TBAF (2.2 mL, 1.0 M in THF, 2.2 mmol, 1.0 eq.) was added to silane **ent-399** (887 mg, 2.21 mmol, 1.0 eq.) and the mixture stirred at ambient temperature until TLC showed completion of reaction (~3 h). The mixture was applied directly onto silica, and purification by column chromatography (petroleum ether / EtOAc, 3:2) afforded the title compound **400** as a colourless oil (413 mg, 60%).

$[\alpha]_D^{25}$ −94.9 (*c* 1.0, $CHCl_3$); R_f 0.45 (petroleum ether / EtOAc, 3:2); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3477, 2869, 1613, 1587, 1514, 1394, 1302, 1248, 1205, 1174, 1114, 1083, 1036, 984, 969, 845, 823, 789, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.24 (m, 2H, Ar*H*), 6.92 – 6.84 (m, 2H, Ar*H*), 6.70 (dd, *J* = 14.8, 1.7 Hz, 1H, 1-H), 5.87 (dd, *J* = 14.8, 2.7 Hz, 1H, 2-H), 4.63 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.51 (d, *J* = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.19 (dd, *J* = 2.7, 1.7 Hz, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 3.60 (dd, *J* = 11.0, 9.9 Hz, 1H, 5-H$_2$), 3.40 (dd, *J* = 11.0, 3.4 Hz, 1H, 5-H$_2$), 2.13 (dd, *J* = 9.9, 3.4 Hz, 1H, OH), 1.16 (s, 3H, 4-CH$_3$), 0.20 (s, 3H, Si(C*H*$_3$)$_2$), 0.14 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 149.2, 130.4, 129.5, 127.1, 113.9, 78.0, 76.5, 72.3, 68.6, 55.4, 18.5, 1.0, 0.4; **HRMS** (ESI+) calc. for $C_{16}H_{24}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 331.13361, found 331.13354.

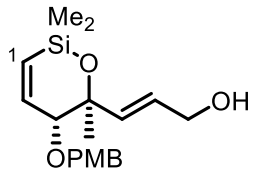
(5*R*,6*R*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2*H*-1,2-oxasiline-6-carbaldehyde, 401



DMSO (0.11 mL, 1.6 mmol, 4.0 eq.) was added dropwise to a solution of oxalyl chloride (0.07 mL, 0.83 µmol, 2.0 eq.) in CH_2Cl_2 (1.3 mL) at −78 °C and stirred for 30 min. A solution of alcohol **400** (117 mg, 379 µmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) was added dropwise and the mixture stirred for further 30 min. Triethylamine (0.32 mL, 2.3 mmol, 6.0 eq.) was added dropwise and the mixture was allowed to warm to ambient temperature over 1 h. The reaction was quenched with water (10 mL), extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude title compound **401** (76 mg, 65%) as a colourless oil. **401** was used without further purification due to its stability towards silica.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.43 (s, 1H, C*H*O), 7.23 – 7.17 (m, 2H, Ar*H*), 6.87 – 6.81 (m, 2H, Ar*H*), 6.72 (dd, *J* = 14.6, 3.2 Hz, 1H, 2-H), 6.00 (dd, *J* = 14.6, 1.4 Hz, 1H, 1-H), 4.57 (d, *J* = 11.4 Hz, 1H, C*H*$_2$Ar), 4.40 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.05 (dd, *J* = 3.2, 1.4 Hz, 1H, 3-H), 3.77 (s, 3H, ArOC*H*$_3$), 1.32 (s, 3H, 4-CH_3), 0.21 (s, 3H, Si(C*H*$_3$)$_2$), 0.19 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.8, 159.3, 146.8, 130.6, 129.8, 129.5, 113.8, 81.5, 74.0, 71.0, 55.3, 18.0, 0.9, 0.5.

(*E*)-3-((5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)prop-2-en-1-ol, 429

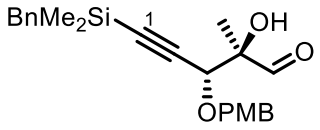


DMSO (0.10 mL, 1.4 mmol, 4.0 eq.) was added dropwise to a solution of oxalyl chloride (0.06 mL, 0.71 mmol, 2.0 eq.) in CH_2Cl_2 (1.8 mL) at −78 °C and stirred for 30 min. A solution of alcohol **400** (113 mg, 366 µmol, 1.0 eq.) in CH_2Cl_2 (1.8 mL) was added dropwise and the mixture stirred for further 30 min. Triethylamine (0.20 mL, 1.44 mmol, 4.0 eq.) was added dropwise and the mixture was allowed to warm to ambient temperature over 1 h. The reaction was quenched with water (10 mL), extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude aldehyde **401** as a colourless oil. Aldehyde **410** and phosphorus ylid **84** (167 mg, 549 µmol, 1.5 eq.) were dissolved in toluene (3.7 mL) and stirred at 80 °C overnight. After cooling to ambient temperature, the mixture was concentrated *in vacuo*, and the residue redissolved in methanol (3.7 mL). $NaBH_4$ (35 mg, 0.93 mmol, 2.5 eq.) was added at 0 °C, and the resulting mixture stirred for 30 min, before being warmed to ambient temperature and stirred for further 30 min. It was quenched

with aqueous NH_4Cl (8 mL), extracted with Et_2O (3 × 10 mL), the combined organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O 4:1) afforded the title compound **429** (20 mg, 16% over 3 steps) as a colourless oil.

$[\alpha]_D^{25}$ −66.2 (*c* 1.0, $CHCl_3$); R_f 0.19 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3400, 2934, 2837, 1613, 1586, 1514, 1465, 1365, 1302, 1249, 1210, 1174, 1079, 1034, 890, 846, 827, 790, 709; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 – 7.22 (m, 2H, Ar*H*), 6.91 – 6.85 (m, 2H, Ar*H*), 6.67 (dd, *J* = 14.7, 2.1 Hz, 1H, 1-H), 5.94 (dd, *J* = 14.7, 2.3 Hz, 1H, 2-H), 5.89 (app t, *J* = 1.3 Hz, 2H, 5-H, 6-H), 4.61 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.42 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.14 – 4.09 (m, 2H, 7-H_2), 3.80 (s, 3H, ArOC*H*$_3$), 3.79 (app t, *J* = 2.2 Hz, 1H, 3-H), 1.31 (s, 3H, 4-CH_3), 0.20 (s, 3H, Si(C*H*$_3$)$_2$), 0.15 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 148.3, 138.1, 130.4, 129.7, 128.7, 127.5, 113.8, 80.8, 76.8, 72.0, 63.5, 55.4, 21.7, 1.1, 0.5; **HRMS** (ESI+) calc. for $C_{18}H_{26}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 357.14926, found 357.15975.

(2*R*,3*R*)-5-(Benzyldimethylsilyl)-2-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ynal, 434

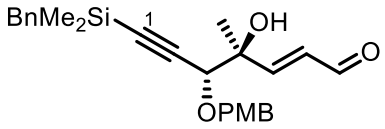


Pyridine·SO_3 complex (248 mg, 1.56 mmol, 3.1 eq.) and DMSO (0.38 mL, 54 mmol, 10.5 eq.) were stirred together at ambient temperature for 15 min. A solution of alcohol **ent-398** (200 mg, 502 µmol, 1.0 eq.) and DIPEA (0.46 mL, 2.6 mmol, 5.2 eq.) in CH_2Cl_2 (2.5 mL) was added and the resulting mixture was stirred at ambient temperature for 1 h. The reaction was diluted with Et_2O and quenched with 1 M HCl. The mixture was

extracted with Et_2O (3 × 30 mL), and the combined organics were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **434** (165 mg, 83%) as a colourless oil.

$[\alpha]_D^{25}$ −132.9 (*c* 1.0, $CHCl_3$); R_f 0.40 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3471, 2958, 2837, 2172, 1738, 1612, 1514, 1494, 1303, 1249, 1209, 1175, 1073, 1034, 833, 763, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.70 (s, 1H, C*H*O), 7.27 – 7.18 (m, 4H, $SiCH_2$*Ph*, Ar*H*), 7.14 – 7.07 (m, 3H, $SiCH_2$*Ph*), 6.91 – 6.84 (m, 2H, Ar*H*), 4.70 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.41 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.06 (s, 1H, 3-H), 3.81 (s, 3H, ArOCH_3), 3.39 (s, 1H, OH), 2.24 (s, 2H, SiCH_2Ph), 1.38 (s, 3H, 4-CH_3), 0.21 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.9, 159.6, 138.7, 129.9, 128.9, 128.5, 128.4, 124.7, 114.0, 101.4, 93.7, 78.9, 73.4, 70.9, 55.4, 26.1, 18.8, −1.9; **HRMS** (ESI+) calc. for $C_{23}H_{28}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 419.16491, found 419.16452.

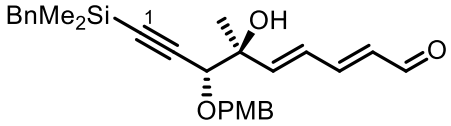
(4*S*,5*R*,*E*)-7-(Benzyldimethylsilyl)-4-hydroxy-5-((4-methoxybenzyl)oxy)-4-methylhept-2-en-6-ynal, 440



Aldehyde **434** (155 mg, 391 µmol, 1.0 eq.) and phosphorus ylid **84** (131 mg, 430 µmol, 1.1 eq.) were dissolved in toluene (4 mL) and the mixture stirred at 80 °C overnight. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1 →4:3) afforded the title compound **440** (88 mg, 53%) and byproduct **441** (36 mg, 21%) both as yellowish oils.

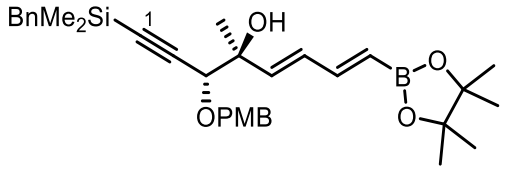
$[\alpha]_D^{25}$ −154.3 (*c* 0.5, $CHCl_3$); $\mathbf{R}_f$ 0.35 (petroleum ether / Et_2O, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, *J* = 7.9 Hz, 1H, C*H*O), 7.26 – 7.18 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.13 – 7.06 (m, 3H, $SiCH_2$*Ph*), 6.98 (d, *J* = 15.7 Hz, 1H, 5-H), 6.91 – 6.86 (m, 2H, Ar*H*), 6.35 (dd, *J* = 15.7, 7.9 Hz, 1H, 6-H), 4.73 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.40 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 3.97 (s, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 2.70 (d, *J* = 0.8 Hz, 1H, OH), 2.23 (s, 2H, SiC*H*$_2$Ph), 1.35 (d, *J* = 0.8 Hz, 3H, 4-CH_3), 0.21 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.7, 159.8, 159.0, 138.7, 131.5, 130.1, 128.8, 128.5, 128.5, 124.8, 114.1, 102.0, 93.2, 75.4, 74.9, 71.1, 55.4, 26.1, 23.6, −1.9, −1.9; **HRMS** (ESI+) calc. for $C_{25}H_{30}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 445.18056, found 445.18004.

(2E,4E,6S,7R)-9-(benzyldimethylsilyl)-6-hydroxy-7-((4-methoxybenzyl)oxy)-6-methylnona-2,4-dien-8-ynal, 441



$[\alpha]_D^{25}$ −117.5 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.28 (petroleum ether / Et_2O, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.57 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.27 – 7.20 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.15 – 7.06 (m, 4H, $SiCH_2$*Ph*, 7-H), 6.93 – 6.85 (m, 2H, Ar*H*), 6.59 (ddd, *J* = 15.3, 10.8, 0.6 Hz, 1H, 6-H), 6.45 (d, *J* = 15.3 Hz, 1H, 5-H), 6.14 (ddd, *J* = 15.3, 8.0, 0.8 Hz, 1H, 8-H), 4.73 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.41 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 3.94 (s, 1H, 3-H), 3.81 (s, 3H, ArOC*H*$_3$), 2.68 (s, 1H, OH), 2.24 (s, 2H, SiC*H*$_2$Ph), 1.34 (s, 3H, 4-CH_3), 0.21 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.0, 159.7, 151.9, 147.5, 138.8, 131.8, 130.1, 128.9, 128.5, 128.4, 127.5, 124.7, 114.0, 102.4, 92.6, 75.7, 74.8, 71.0, 55.4, 26.1, 24.1, −1.9, −1.9; **HRMS** (ESI+) calc. for $C_{27}H_{32}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 471.19621, found 471.19619.

(3R,4S,5E,7E)-1-(benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-4-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-5,7-dien-1-yn-4-ol, 442

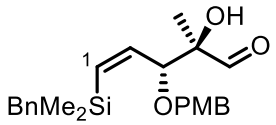


The procedure was adapted from a literature procedure.[277] Chromium(II) chloride (156 mg, 1.27 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (1.6 mL) was added and the suspension stirred at ambient temperature for 30 min to give a minty green mixture. A solution of aldehyde **440** (67 mg, 0.16 µmol, 1.0 eq.) and $CHCl_2Bpin$ (67 mg, 0.32 µmol, 2.0 eq.) in THF (0.8 mL) was added, followed by dropwise addition of a solution of lithium iodide (85 mg, 0.64 µmol, 4.0 eq.) in THF (0.8 mL). The mixture was stirred in the dark at ambient temperature overnight. It was poured into water and the mixture was extracted with Et_2O (3 × 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **442** (27 mg, 31%) as a colourless oil.

$[\alpha]_D^{25}$ −76.4 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.26 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2977, 2171, 1605, 1514, 1494, 1453, 1392, 1359, 1323, 1302, 1250, 1209, 1173, 1144, 1072, 1059, 1034, 1011, 970, 848, 832, 796, 763, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 – 7.17 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.15 – 6.99 (m, 4H, $SiCH_2$*Ph*, 7-H), 6.90 – 6.83 (m, 2H, Ar*H*), 6.41 (ddd, *J* = 15.4, 10.5, 0.8 Hz, 1H, 6-H), 6.14 (d, *J* = 15.4 Hz, 1H, 5-H), 5.55 (d, *J* = 17.7 Hz, 1H, 8-H), 4.71 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.39 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 3.90 (s, 1H, 3-H), 3.81 (s, 3H, $ArOCH_3$), 2.57 (s, 1H, OH), 2.23 (s, 2H, $SiCH_2$Ph), 1.30 (s, 3H, 4-CH_3), 1.28 (s, 12H, $OC(CH_3)_2$), 0.19 (s, 6H, $Si(CH_3)_2$); **^{13}C**

NMR (101 MHz, $CDCl_3$) δ_C 159.5, 149.6, 140.5, 138.9, 131.2, 130.0, 129.3, 128.5, 128.4, 124.7, 120.6,[4] 113.9, 102.9, 92.1, 83.3, 76.1, 74.6, 70.8, 55.4, 26.2, 24.9, 24.3, −1.9; **HRMS** (ESI+) calc. for $C_{32}H_{43}O_5{}^{10}B^{28}Si^{23}Na$ $[M+Na]^+$ 568.29013, found 568.28992.

(2*R*,3*R*,*Z*)-5-(Benzyldimethylsilyl)-2-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enal, ent-445



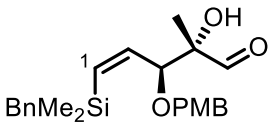
Pyridine·SO_3 complex (493 mg, 3.22 mmol, 3.1 eq.) and DMSO (0.74 mL, 10.4 mmol, 10.5 eq.) were stirred together at ambient temperature for 15 min. A solution of alcohol **ent-399** (400 mg, 999 μmol, 1.0 eq.) and DIPEA (0.90 mL, 5.17 mmol, 5.2 eq.) in CH_2Cl_2 (5.0 mL) was added and the resulting mixture was stirred at ambient temperature for 1 h. The reaction was diluted with Et_2O and quenched with 1 M HCl. The mixture was extracted with Et_2O (3 × 30 mL), and the combined organics were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **ent-445** (303 mg, 76%) as a colourless oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +1.5 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.39 (petroleum ether / Et_2O, 1:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3489, 2956, 1735, 1613, 1514, 1493, 1453, 1302, 1248, 1207, 1174, 1074, 1036, 831, 796, 766, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.68 (s, 1H, C*H*O), 7.23 – 7.16 (m, 2H, $SiCH_2$*Ph*), 7.16 – 7.09 (m, 2H, Ar*H*), 7.09 – 7.03 (m, 1H, $SiCH_2$*Ph*), 7.03 – 6.97 (m, 2H, $SiCH_2$*Ph*), 6.89 – 6.83 (m, 2H, Ar*H*), 6.29 (dd, *J* = 14.6, 10.1 Hz, 1H, 2-H), 5.99 (dd, *J* = 14.6, 0.6 Hz, 1H, 1-H), 4.45 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar), 4.13 (d, *J* = 11.4 Hz, 1H, OC*H*$_2$Ar),

[4] Determined by HSQC.

3.96 (dd, J = 10.1, 0.6 Hz, 1H, 3-H), 3.80 (s, 3H, ArOCH_3), 3.44 (s, 1H, OH), 2.24 – 2.09 (m, 2H, SiCH_2Ph), 1.25 (s, 3H, 4-CH_3), 0.09 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 203.7, 159.4, 142.8, 139.5, 136.5, 129.8, 129.2, 128.4, 128.4, 124.5, 114.0, 83.2, 79.2, 70.1, 55.4, 26.7, 18.7, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 421.18056, found 421.18057.

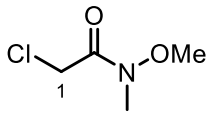
(2*S*,3*S*,*Z*)-5-(Benzyldimethylsilyl)-2-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpent-4-enal, 445



Pyridine·SO_3 complex (1.23 g, 7.73 mmol, 3.1 eq.) and DMSO (1.9 mL, 26.8 mmol, 10.5 eq.) were stirred together at ambient temperature for 15 min. A solution of alcohol **399** (1.00 g, 2.50 mmol, 1.0 eq.) and DIPEA (2.3 mL, 13 mmol, 5.2 eq.) in CH_2Cl_2 (12.5 mL) was added and the resulting mixture was stirred at ambient temperature for 1 h. The reaction was diluted with Et_2O and quenched with 1 M HCl. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organics were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **445** (640 mg, 64%) as a colourless oil.

$[\alpha]_D^{25}$ −0.8 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-445**.

_N_-methoxy-_N_-methylchloroacetamide, 446

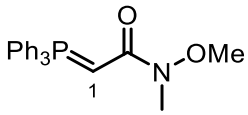


To a solution of potassium carbonate (15.59 g, 113 mmol, 2.2 eq.) in water (63 mL) at 0 °C, was added *N*,*O*-dimethylhydroxylamine hydrochloride (5.00 g, 51.3 mmol, 1.0 eq.) and MTBE (63 mL). Chloroacetyl chloride (4.9 mL, 61.5 mmol, 1.2 eq.) was added over 5 min, and the mixture was stirred vigorously at ambient temperature for 30 min. The mixture was extracted with Et_2O (3 × 30 mL), the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound **446** (6.09 g, 86%) as a white solid. **446** was used without further purification.[358]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.22 (s, 2H, 1-H_2), 3.72 (s, 3H, N(OC*H*$_3$)), 3.20 (s, 3H, N(C*H*$_3$)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.5, 61.7, 40.9, 32.7.

The spectroscopic data is in agreement with that reported by Weidner and coworkers.[359]

_N_-methoxy-_N_-methyl-2-(triphenylphosphoranylidene)acetamide, 447

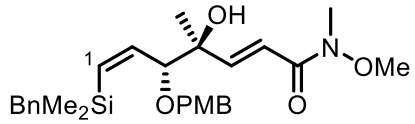


To a solution of chloroacetamide **446** (4.00 g, 29.0 mmol, 1.0 eq) in acetonitrile (39 mL) was added triphenylphosphine (7.78 g, 29.7 mmol, 1.02 eq.). The resulting solution was stirred at 90 °C for 16 h, cooled to ambient temperature, and concentrated *in vacuo*. The viscous residue was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous NaOH (2 M, 2 × 50 mL), and brine (50 mL). The organics were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallised twice (cyclohexane / EtOAc, 1:1) to afford the title compound **447** (8.47 g, 80%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 – 7.63 (m, 6H, Ar*H*), 7.56 – 7.49 (m, 3H, Ar*H*), 7.48 – 7.40 (m, 6H, Ar*H*), 3.73 (s, 3H, N(OC*H*$_3$)), 3.53 (d, J = 23.8 Hz, 1H, 1-H), 3.08 (d, J = 0.7 Hz, 3H, NC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.8 (d, J = 11.0 Hz), 133.2 (d, J = 9.8 Hz), 131.8 (d, J = 2.6 Hz), 128.8 (d, J = 12.4 Hz), 128.3 (d, J = 91.3 Hz), 61.3, 35.9, 33.6 (d, J = 127.0 Hz); **^{31}P NMR** (162 MHz, Chloroform-d) δ_P 18.1.

The spectroscopic data is in agreement with that reported by Evans and coworkers.[360]

(2*E*,4*S*,5*R*,6*Z*)-7-(Benzyldimethylsilyl)-4-hydroxy-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,4-dimethylhepta-2,6-dienamide, ent-448

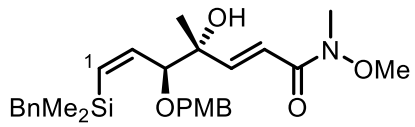


Aldehyde **ent-445** (150 mg, 376 µmol, 1.0 eq.) and ylid **447** (342 mg, 941 µmol, 2.5 eq.) were dissolved in toluene (3.8 mL), and the resulting mixture was stirred at 80 °C overnight. The mixture was concentrated *in vacuo* after cooling to ambient temperature. Purification by column chromatography (petroleum ether / EtOAc, 2:1) afforded the title compound **ent-448** (181 mg, 99%) as a colourless oil.

$[\alpha]_D^{25}$ −26.4 (*c* 1.0, $CHCl_3$); **R$_f$** 0.13 (petroleum ether / EtOAc, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3443, 2934, 1663, 1614, 1514, 1493, 1453, 1417, 1381, 1302, 1248, 1207, 1175, 1073, 1036, 1004, 731, 764, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 – 7.18 (m, 2H, SiCH$_2$*Ph*), 7.17 – 7.13 (m, 2H, Ar*H*), 7.09 – 6.97 (m, 4H, SiCH$_2$*Ph*, 5-H), 6.87 – 6.82 (m, 2H, Ar*H*), 6.63 (d, J = 15.4 Hz, 1H, 6-H), 6.24 (dd, J = 14.7, 10.1 Hz, 1H, 2-H), 5.95 (dd, J = 14.7, 0.8 Hz, 1H, 1-H), 4.44 (d, J = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.14 (d, J = 11.3 Hz, 1H, OC*H*$_2$Ar), 3.86 (dd, J = 10.1, 0.8 Hz, 1H, 3-H), 3.79 (s, 3H, ArOC*H*$_3$), 3.65 (s, 3H, NOC*H*$_3$), 3.24 (s, 3H, NC*H*$_3$), 2.91 (s, 1H, OH), 2.19 (d, J = 13.6 Hz, 1H, SiC*H*$_2$Ph), 2.13

(d, J = 13.6 Hz, 1H, SiCH_2Ph), 1.25 (s, 3H, 4-CH_3), 0.11 (s, 3H, Si(CH_3)$_2$), 0.11 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 149.1, 144.3, 139.5, 135.9, 130.2, 129.3, 128.4, 124.4, 117.8, 113.9, 84.4, 74.8, 70.1, 61.9, 55.4, 26.7, 24.2, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{27}H_{37}O_5N^{28}Si^{23}Na$ $[M+Na]^+$ 506.23332, found 506.23314.

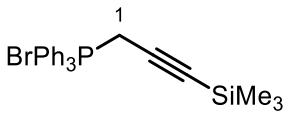
(2*E*,4*R*,5*S*,6*Z*)-7-(Benzyldimethylsilyl)-4-hydroxy-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,4-dimethylhepta-2,6-dienamide, 448



Aldehyde **445** (629 mg, 1.58 mmol, 1.0 eq.) and ylid **447** (1.434 g, 3.95 µmol, 2.5 eq.) were dissolved in toluene (16 mL), and the resulting mixture was stirred at 80 °C overnight. The mixture was concentrated *in vacuo* after cooling to ambient temperature. Purification by column chromatography (petroleum ether / EtOAc, 2:1) afforded the title compound **448** (700 mg, 92%) as a colourless oil.

$[\alpha]_D^{25}$ +26.8 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-448**.

Triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide



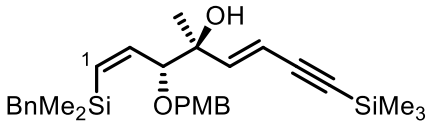
To a solution of triphenyl phosphine (3.57 g, 13.6 mmol, 1.3 eq.) in toluene (10 mL) was added TMS-propargyl bromide (2.00 g, 10.5 mmol, 1.0 eq.). The resulting mixture was stirred at ambient temperature for 24 h. The precipitate was collected by filtration, washed

with cold hexanes, and dried *in vacuo* to afford the title compound (3.07 g, 77%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.02 – 7.74 (m, 15H, Ar*H*), 5.13 (d, J = 16.5 Hz, 2H, 1-H_2), −0.03 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C 135.4 (d, J = 3.2 Hz), 133.8 (d, J = 9.9 Hz), 130.2 (d, J = 12.7 Hz), 117.6 (d, J = 87.3 Hz), 94.9 (d, J = 12.8 Hz), 93.0 (d, J = 8.7 Hz), 16.30 (d, J = 54.3 Hz), −0.8; **^{31}P NMR** (162 MHz, DMSO-d_6) δ_P 22.2.

The spectroscopic data is in agreement with that reported by Zürcher and coworkers.[361]

(1*Z*,3*R*,4*S*,5*E*)-1-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-4-methyl-8-(trimethylsilyl)octa-1,5-dien-7-yn-4-ol

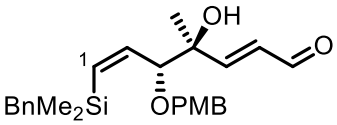


To a solution of phosphonium bromide (74 mg, 0.19 μmol, 3.1 eq.) in THF (0.6 mL) at −78 °C, was added dropwise *n*-butyllithium (0.12 mL, 1.6 M in hexanes, 0.19 μmol, 3.0 eq.), and the resulting mixture stirred for 30 min. A solution of aldehyde **ent-445** (25 mg, 63 μmol, 1.0 eq.) in THF (0.6 mL) was added dropwise. The solution was stirred at −78 °C for 2 h, and subsequently at ambient temperature for further 2 h. The reaction was quenched with aqueous NH_4Cl (3 mL), diluted with water (2 mL), and extracted with EtOAc (3 × 8 mL). The combined organics were washed with brine (7 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound (5 mg, 16%) as a colourless oil.

$[\alpha]_D^{25}$ −18.2 (*c* 0.5, $CHCl_3$); R_f 0.20 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 1612, 1514, 1493, 1453, 1302, 1249, 1207, 1174, 1067, 1037, 842, 796, 764, 723, 699;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 – 7.13 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.09 – 6.94 (m, 3H, $SiCH_2$*Ph*), 6.91 – 6.82 (m, 2H, Ar*H*), 6.28 (d, *J* = 16.1 Hz, 1H, 5-H), 6.20 (dd, *J* = 14.7, 10.0 Hz, 1H, 2-H), 5.93 (d, *J* = 14.7 Hz, 1H, 1-H), 5.76 (d, *J* = 16.1 Hz, 1H, 6-H), 4.45 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 4.15 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 3.84 – 3.74 (m, 4H, $ArOCH_3$, 3-H), 2.69 (s, 1H, O*H*), 2.17 (s, 2H, $SiCH_2$Ph), 1.20 (s, 3H, 4-CH_3), 0.17 (s, 9H, $Si(CH_3)_3$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 147.3, 144.5, 139.5, 135.6, 130.3, 129.3, 128.4, 128.4, 124.4, 114.0, 109.4, 103.8, 95.1, 84.4, 74.6, 70.2, 55.4, 26.8, 24.0, 0.1, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{29}H_{40}O_3{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 515.24082, found 515.24060.

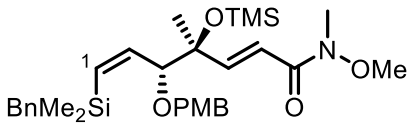
(2E,4S,5R,6Z)-7-(benzyldimethylsilyl)-4-hydroxy-5-((4-methoxybenzyl)oxy)-4-methylhepta-2,6-dienal, ent-450



Amide **ent-448** (21 mg, 43 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.45 mL) and cooled to −78 °C. DIBALH (1.0 M in hexanes, 0.05 mL, 50 µmol, 1.1 eq.) was added dropwise and the mixture stirred for 1 h. Another portion of DIBALH (1.0 M in hexanes, 0.05 mL, 50 µmol, 1.1 eq.) was added, and the mixture stirred for a further hour. The reaction was quenched by addition of an aqueous saturated solution of Rochelles salt, extracted with EtOAc (3 × 3 mL), the combined organics were washed with brine (3 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 2:1) afforded the title compound **ent-450** (9.5 mg, 52%) as a colourless oil.$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −3.7 (*c* 0.33, $CHCl_3$); $\mathbf{R}_f$ 0.25 (petroleum ether / Et_2O, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2929, 2854, 1613, 1514, 1463, 1248, 1208, 1172, 1074, 1038, 987, 830, 796, 760,

700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.55 (d, J = 7.8 Hz, 1H, C*H*O), 7.25 – 7.18 (m, 2H, SiCH$_2$*Ph*), 7.16 – 7.12 (m, 2H, Ar*H*), 7.10 – 7.05 (m, 1H, SiCH$_2$*Ph*), 7.02 – 6.98 (m, 2H, SiCH$_2$*Ph*), 6.89 – 6.81 (m, 3H, Ar*H*, 5-H), 6.29 (dd, J = 15.6, 7.8 Hz, 1H, 6-H), 6.19 (dd, J = 14.7, 10.0 Hz, 1H, 2-H), 6.01 (d, J = 14.7 Hz, 1H, 1-H), 4.46 (d, J = 11.3 Hz, 1H, OC*H*$_2$Ar), 4.14 (d, J = 11.3 Hz, 1H, OC*H*$_2$Ar), 3.87 (d, J = 10.0 Hz, 1H, 3-H), 3.80 (s, 3H, ArOC*H*$_3$), 2.81 (s, 1H, OH), 2.19 (d, J = 13.6 Hz, 1H, SiC*H*$_2$Ph), 2.14 (d, J = 13.6 Hz, 1H, SiC*H*$_2$Ph), 1.27 (s, 3H, 4-CH$_3$), 0.13 (s, 3H, Si(C*H*$_3$)$_2$), 0.11 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 193.8, 159.5, 143.7, 139.3, 136.9, 131.1, 129.8, 129.3, 128.5, 128.4, 124.6, 114.0, 84.1, 74.6, 70.3, 55.5, 29.9, 26.7, 23.4, −1.1, −1.2; **HRMS** (ESI+) calc. for $C_{25}H_{32}O_4{}^{28}Si^{23}Na$ $[M+Na]^+$ 447.19620, found 447.19645.

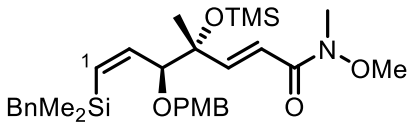
(2*E*,4*S*,5*R*,6*Z*)-7-(Benzyldimethylsilyl)-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,4-dimethyl-4-((trimethylsilyl)oxy)hepta-2,6-dienamide, ent-449



TMS chloride (0.10 mL, 0.83 mmol, 2.2 eq.) and triethylamine (0.16 mL, 1.2 mmol, 3.0 eq.) were added to a solution of tertiary alcohol **ent-448** (185 mg, 382 µmol, 1.0 eq.) in CH_2Cl_2 (0.8 mL). The mixture was stirred for 16 h and a further portion of TMS chloride (0.05 mL, 0.41 mmol, 1.1 eq.) and triethylamine (0.08 mL, 0.57 µmol, 1.5 eq.) were added, and the mixture stirred for further 8 h. The reaction was diluted with water (10 mL), extracted with Et_2O (3 × 20 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 3:1) afforded the title compound **ent-449** (186 mg, 87%) as a yellowish oil.

$[\alpha]_D^{25}$ −3.5 (*c* 0.85, $CHCl_3$); $\mathbf{R}_f$ 0.31 (petroleum ether / EtOAc, 3:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 2929, 1666, 1638, 1613, 1514, 1453, 1411, 1374, 1249, 1207, 1173, 1153, 1115, 1075, 1034, 1003, 839, 796, 765, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 – 7.14 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.09 (d, *J* = 15.5 Hz, 1H, 5-H), 7.07 – 7.03 (m, 1H, $SiCH_2$*Ph*), 7.02 – 6.97 (m, 2H, $SiCH_2$*Ph*), 6.86 – 6.80 (m, 2H, Ar*H*), 6.54 (d, *J* = 15.5 Hz, 1H, 6-H), 6.24 (dd, *J* = 14.6, 9.9 Hz, 1H, 2-H), 5.85 (dd, *J* = 14.6, 0.7 Hz, 1H, 1-H), 4.40 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.14 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 3.79 (s, 3H, ArOC*H*$_3$), 3.72 (dd, *J* = 9.9, 0.7 Hz, 1H, 3-H), 3.63 (s, 3H, NOC*H*$_3$), 3.25 (s, 3H, NC*H*$_3$), 2.17 (d, *J* = 13.6 Hz, 1H, SiC*H*$_2$Ph), 2.10 (d, *J* = 13.6 Hz, 1H, SiC*H*$_2$Ph), 1.41 (s, 3H, 4-CH_3), 0.11 (s, 9H, OSi(C*H*$_3$)$_2$), 0.07 (s, 3H, Si(CH_3)$_2$), 0.07 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.1, 159.1, 152.5, 144.7, 139.9, 134.3, 130.9, 129.2, 128.4, 128.3, 124.2, 117.3, 113.7, 84.2, 78.0, 70.2, 61.8, 55.4, 32.6[5], 26.9, 22.5, 2.8, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{30}H_{45}O_5N^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 578.27285, found 578.27274.

(2*E*,4*R*,5*S*,6*Z*)-7-(Benzyldimethylsilyl)-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,4-dimethyl-4-((trimethylsilyl)oxy)hepta-2,6-dienamide, 449



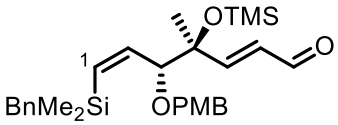
TMS chloride (0.54 mL, 4.2 mmol, 3.0 eq.) was added dropwise to a solution of imidazole (333 mg, 4.88 mmol, 3.5 eq.) in CH_2Cl_2 (10 mL) at 0 °C and stirred for 5 min. A solution of alcohol **448** (680 mg, 1.41 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) was added, and the mixture stirred at ambient temperature for 16 h. It was diluted with water (15 mL), extracted with Et_2O (3 × 25 mL), the combined organics were washed with brine

[5] Determined by HSQC.

(15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 3:1) afforded the title compound **449** (573 mg, 73%) as a yellowish oil.

$[\alpha]_D^{25}$ +11.7 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-449**.

(2*E*,4*S*,5*R*,6*Z*)-7-(Benzyldimethylsilyl)-5-((4-methoxybenzyl)oxy)-4-methyl-4-((trimethylsilyl)oxy)hepta-2,6-dienal, ent-451

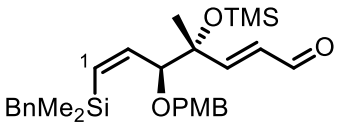


Weinreb amide **ent-449** (175 mg, 315 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.8 mL) and cooled to −78 °C. DIBALH (0.38 mL, 1.0 M in hexanes, 380 µmol, 1.2 eq.) was added dropwise, and the mixture stirred for 1 h. Water (0.02 mL), aqueous NaOH (0.02 mL, 15 wt%), and water (0.04 mL) were added subsequently, before allowing the mixture to warm to ambient temperature, and stirring for 30 min. $MgSO_4$ was added, and the suspension was stirred for further 15 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **ent-451** (106 mg, 68%) as a yellowish oil.

$[\alpha]_D^{25}$ −22.4 (*c* 0.5, $CHCl_3$); $\mathbf{R}_f$ 0.21 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 1693, 1613, 1514, 1493, 1302, 1249, 1208, 1172, 1134, 1099, 1034, 840, 796, 765, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.55 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.23 – 7.15 (m, 2H, $SiCH_2$*Ph*), 7.15 – 7.09 (m, 2H, Ar*H*), 7.09 – 7.02 (m, 1H, $SiCH_2$*Ph*), 7.01 – 6.96 (m, 2H, $SiCH_2$*Ph*), 6.93 (d, *J* = 15.6 Hz, 1H, 5-H), 6.87 – 6.81 (m, 2H, Ar*H*), 6.24 – 6.17 (m, 2H, 2-H, 6-H), 5.90 (d, *J* = 14.6 Hz, 1H, 1-H), 4.41 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.10 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 3.80 (s, 3H, ArOCH_3), 3.75 (dd, *J* = 9.9, 0.7 Hz, 1H, 3-H),

2.17 (d, J = 13.6 Hz, 1H, SiCH_2Ph), 2.11 (d, J = 13.6 Hz, 1H, SiCH_2Ph), 1.41 (s, 3H, 4-CH_3), 0.10 (s, 9H, OSi(CH_3)$_3$), 0.09 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.1, 163.5, 159.2, 144.0, 139.7, 135.2, 130.5, 130.3, 129.2, 128.4, 128.4, 124.4, 113.8, 84.0, 77.7, 70.2, 55.4, 26.9, 22.0, 2.8, −1.1, −1.2; **HRMS** (ESI+) calc. for $C_{28}H_{40}O_4{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 519.23573, found 519.23561.

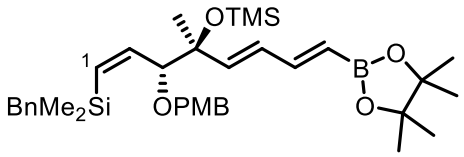
(2*E*,4*R*,5*S*,6*Z*)-7-(Benzyldimethylsilyl)-5-((4-methoxybenzyl)oxy)-4-methyl-4-((trimethylsilyl)oxy)hepta-2,6-dienal, 451



Weinreb amide **449** (550 mg, 989 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to −78 °C. DIBALH (1.2 mL, 1.0 M in cyclohexanes, 1.2 mmol, 1.2 eq.) was added dropwise, and the mixture stirred for 1 h. Water (0.05 mL), aqueous NaOH (0.05 mL, 15 wt%), and water (0.12 mL) were added subsequently, before allowing the mixture to warm to ambient temperature, and stirring for 30 min. $MgSO_4$ was added, and the suspension was stirred for further 15 min, filtered, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **451** (370 mg, 75%) as a yellowish oil.

$[\alpha]_D^{25}$ +28.4 (*c* 0.5, $CHCl_3$). The remaining analytical data is identical to that of **ent-451.**

Benzyl((1*Z*,3*R*,4*S*,5*E*,7*E*)-3-((4-methoxybenzyl)oxy)-4-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((trimethylsilyl)oxy)octa-1,5,7-trien-1-yl)dimethylsilane, ent-452

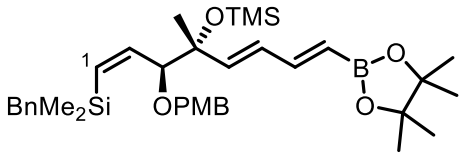


The procedure was adapted from a literature procedure.[277] Chromium(II) chloride (198 mg, 1.61 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (2.0 mL) was added and the suspension stirred at ambient temperature for 30 min to give a minty green mixture. A solution of aldehyde **ent-451** (100 mg, 201 µmol, 1.0 eq.) and $CHCl_2Bpin$ (85 mg, 0.40 mmol, 2.0 eq.) in THF (1.0 mL) was added, followed by dropwise addition of a solution of Lithium iodide (108 mg, 807 µmol, 4.0 eq.) in THF (1.0 mL). The mixture was stirred in the dark at ambient temperature overnight. The mixture was poured into water and extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **ent-452** (101 mg, 81%) as a colourless oil.

$[\alpha]_D^{25}$ −9.6 (*c* 0.8, $CHCl_3$); R_f 0.32 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2977, 1604, 1514, 1390, 1357, 1324, 1250, 1209, 1145, 1110, 1097, 1035, 1010, 840, 763, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 – 7.13 (m, 4H, $SiCH_2$*Ph*, Ar*H*), 7.08 – 6.96 (m, 4H, $SiCH_2$*Ph*, 7-H), 6.86 – 6.81 (m, 2H, Ar*H*), 6.26 – 6.15 (m, 2H, 2-H, 6-H), 6.05 (d, *J* = 15.5 Hz, 1H, 5-H), 5.80 (d, *J* = 14.6 Hz, 1H, 1-H), 5.54 (d, *J* = 17.7 Hz, 1H, 8-H), 4.41 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.17 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 3.80 (s, 3H, $ArOCH_3$), 3.68 (d, *J* = 9.9 Hz, 1H, 3-H), 2.15 (d, *J* = 13.5 Hz, 1H, $SiCH_2$Ph), 2.09 (d,

J = 13.5 Hz, 1H, SiCH_2Ph), 1.34 (s, 3H, 4-CH_3), 1.27 (s, 12H, OC(CH_3)$_2$), 0.07 (s, 9H, OSi(CH_3)$_3$), 0.05 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.0, 149.9, 145.2, 144.1, 140.0, 133.5, 131.2, 130.7, 129.1, 128.4, 128.3, 124.2, 113.7, 84.8, 83.3, 70.2, 55.4, 27.0, 25.0, 24.9, 22.7, 2.8, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{35}H_{53}O_5{}^{10}B^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 643.34168, found 643.34147.

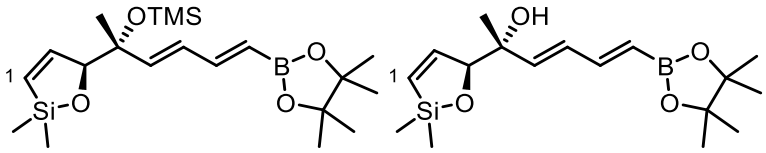
Benzyl((1*Z*,3*S*,4*R*,5*E*,7*E*)-3-((4-methoxybenzyl)oxy)-4-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((trimethylsilyl)oxy)octa-1,5,7-trien-1-yl)dimethylsilane, 452



The procedure was adapted from a literature procedure.[277] Chromium(II) chloride (495 mg, 4.03 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (5.0 mL) was added and the suspension stirred at ambient temperature for 30 min to give a minty green mixture. A solution of aldehyde **451** (250 mg, 503 µmol, 1.0 eq.) and $CHCl_2Bpin$ (212 mg, 1.01 µmol, 2.0 eq.) in THF (2.5 mL) was added, followed by dropwise addition of a solution of Lithium iodide (269 mg, 2.01 µmol, 4.0 eq.) in THF (2.5 mL). The mixture was stirred in the dark at ambient temperature overnight. The mixture was poured into water and extracted with Et_2O (3 × 30 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **452** (272 mg, 87%) as a colourless oil.

$[\alpha]_D^{25}$ +14.3 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-452**.

(*S*)-2,2-Dimethyl-5-((*R*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-((trimethylsilyl)oxy)hexa-3,5-dien-2-yl)-2,5-dihydro-1,2-oxasilole, 479 and (*R*,3*E*,5*E*)-2-((*S*)-2,2-Dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-3,5-dien-2-ol, 480



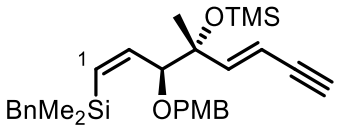
PMB-ether **452** (30 mg, 48 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.45 mL) and water (0.05 mL), and DDQ (12 mg, 53 µmol, 1.1 eq.) was added. The mixture was stirred at ambient temperature for 2.5 h, before another portion of DDQ (11 mg, 49 µmol, 1.0 eq.) was added, and the mixture was stirred for a further 1 h. It was quenched with aqueous $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), the combined organics dried over $MgSO_4$, and concentrated *in vacuo* to afford a mixture of **479**, **480**, and *p*-methoxybenzaldheyde. This mixture could not be purified, due to the instability of 5-membered siloxanes towards silica.

Data for **479**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.07 – 7.00 (m, 1H, 7-H), 6.89 (dd, *J* = 10.7, 1.6 Hz, 1H, 2-H), 6.26 (ddd, *J* = 15.5, 10.5, 0.8 Hz, 1H, 6-H), 6.12 (dd, *J* = 10.7, 2.2 Hz, 1H, 1-H), 6.02 (d, *J* = 15.4 Hz, 1H, 5-H), 5.54 (d, *J* = 17.7 Hz, 1H, 8-H), 4.45 (app. t, *J* = 1.9 Hz, 1Hm 3-H), 1.26 (s, 12H, Bpin*H*), 1.23 (s, 3H, 4-CH_3), 0.21 (s, 3H, Si(CH_3)$_2$), 0.20 (s, 3H, Si(CH_3)$_2$), 0.09 (s, 9H, Si(CH_3)$_3$); **HRMS** (ESI+) calc. for $C_{20}H_{37}O_4{}^{10}B^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 431.22156, found 431.22153.

Data for **480**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.02 – 6.95 (m, 1H, 7-H), 6.80 (dd, *J* = 10.6, 1.5 Hz, 1H, 2-H), 6.37 (dd, *J* = 15.1, 10.6 Hz, 1H, 6-H), 6.16 (dd, *J* = 10.6, 2.3 Hz, 1H, 1-H), 5.82 (d, *J* = 15.3 Hz, 1H, 5-H), 5.54 (d, *J* = 17.7 Hz, 1H, 8-H), 4.57 (t, *J* = 1.9 Hz, 1H, 3-H), 2.51 (s, 1H, O*H*), 1.33 (s, 3H, 4-CH_3), 1.26 (s, 12H, Bpin*H*), 0.25

(s, 3H, Si(C*H*$_3$)$_2$), 0.22 (s, 3H, Si(C*H*$_3$)$_2$); **HRMS** (ESI+) calc. for $C_{17}H_{29}O_4{}^{10}B^{28}Si^{23}Na$ $[M+Na]^+$ 359.18204, found 359.18208.

Benzyl((1*Z*,3*S*,4*R*,5*E*)-3-((4-methoxybenzyl)oxy)-4-methyl-4-((trimethylsilyl)oxy)octa-1,5-dien-7-yn-1-yl)dimethylsilane, 454



To a solution of DIPA (0.15 mL, 1.1 mmol, 10.5 eq.) in THF (2.0 mL) at 0 °C, was added *n*-butyllithium (0.40 mL, 2.5 M in hexane, 1.0 mmol, 10.0 eq.) dropwise, and stirred for 15 min, before being cooled to −78 °C. Trimethylsilyldiazomethane (0.50 mL, 2.0 M in hexane, 1.0 mmol, 10.0 eq.) was added dropwise, and the mixture stirred at this temperature for 30 min. A solution of aldehyde **451** (50 mg, 0.10 µmol, 1.0 eq.) in THF (2.0 mL) was added dropwise, the mixture stirred for 1 h at −78 °C, followed by stirring another hour at 0 °C. The reaction was quenched by addition of aqueous NH_4Cl (10 mL), extracted with EtOAc (3 × 10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 50:1) afforded the title compound **454** (23 mg, 46%) as a colourless oil.

$[\alpha]_D^{25}$ +16.5 (*c* 1.0, $CHCl_3$); R_f 0.57 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2956, 1613, 1514, 1493, 1249, 1207, 1172, 1155, 1117, 1075, 1033, 960, 839, 796, 762, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 – 7.15 (m, 4H, Ar*H*, SiCH$_2$*Ph*), 7.09 – 6.98 (m, 3H, SiCH$_2$*Ph*), 6.88 – 6.82 (m, 2H, Ar*H*), 6.39 (d, *J* = 16.0 Hz, 1H, 5-H), 6.20 (dd, *J* = 14.6, 9.9 Hz, 1H, 2-H), 5.84 (d, *J* = 14.6 Hz, 1H, 1-H), 5.64 (dd, *J* = 16.0, 2.3 Hz, 1H, 6-H), 4.42 (d, *J* = 11.6 Hz, 1H, OC*H*$_2$Ar), 4.16 (d, *J* = 11.6 Hz, 1H, OC*H*$_2$Ar), 3.80 (s, 3H,

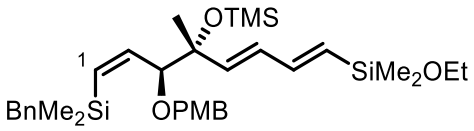
ArOC*H*$_3$), 3.66 (d, J = 9.9 Hz, 1H, 3-H), 2.89 (d, J = 2.3 Hz, 1H, 8-H), 2.17 (d, J = 13.6 Hz, 1H, SiC*H*$_2$Ph), 2.10 (d, J = 13.6 Hz, 1H, SiC*H*$_2$Ph), 1.34 (s, 3H, 4-CH$_3$), 0.11 (s, 9H, Si(C*H*$_3$)$_3$), 0.07 (s, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.1, 151.3, 144.8, 139.9, 134.1, 130.9, 129.1, 128.4, 128.3, 124.3, 113.8, 107.5, 84.3, 82.5, 77.8, 77.7, 70.1, 55.4, 26.9, 22.5, 2.8, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{29}H_{40}O_3{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 515.24082, found 515.24059.

Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane tri-(*tert*-butyl) phosphine complex

Pt(DVDS)•P(*t*-Bu)$_3$

Prepared according to literature procedure.[281,282] P(*t*-Bu)$_3$ (16 mg, 79 µmol, 1.0 eq.) was dissolved in platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Pt(DVDS)) complex (0.75 mL, 0.11 M solution in xylene, 79 µmol, 1.0 eq.). The mixture was stirred at 65 °C for 5 min, and then was cooled to ambient temperature. The solution was stored under nitrogen and stored in the freezer, and used as is.

(*R*,5*E*,7*E*)-4-((*S*,*Z*)-3-(Benzyldimethylsilyl)-1-((4-methoxybenzyl)oxy)allyl)-2,2,4,9,9-pentamethyl-3,10-dioxa-2,9-disiladodeca-5,7-diene, 455

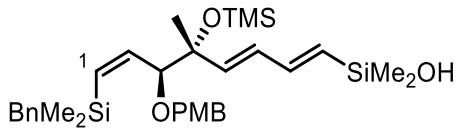


This procedure was adapted from a literature procedure.[283] To Pt(DVDS)·P(*t*-Bu)$_3$ (5 µL, 0.1 M in xylene, 0.5 µmol, 1 mol%) in THF was added ethoxy dimethyl silane (13 µL, 94 µmol, 2.0 eq.) and the mixture stirred at ambient temperature for 30 min. A solution of alkyne **454** (22 mg, 45 µmol, 1.0 eq.) in THF (0.35 mL) was added, stirred for 1.5 h,

before being concentrated *in vacuo* to afford crude title compound **455**, which was used without further purification.

R*f* 0.72 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2958, 2361, 1613, 1514, 1494, 1453, 1369, 1249, 1208, 1172, 1078, 1005, 946, 836, 796, 763, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 – 7.15 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.09 – 6.97 (m, 3H, $SiCH_2$*Ph*), 6.88 – 6.80 (m, 2H, Ar*H*), 6.62 (dd, *J* = 18.5, 10.0 Hz, 1H, 7-H), 6.19 (app. ddd, *J* = 18.9, 15.0, 9.9 Hz, 2H, 2-H, 8-H), 5.93 (d, *J* = 15.5 Hz, 1H, 5-H), 5.85 – 5.77 (m, 2H, 1-H, 6-H), 4.45 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.21 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 3.80 (s, 3H, OCH_3), 3.72 – 3.63 (m, 3H, $Si(OCH_2CH_3)$, 3-H), 2.16 (d, *J* = 13.8 Hz, 1H, $SiCH_2$Ph), 2.09 (d, *J* = 13.5 Hz, 1H, $SiCH_2$Ph), 1.35 (s, 3H, 4-CH_3), 1.19 (t, *J* = 7.0 Hz, 3H, $Si(OCH_2CH_3)$), 0.20 (s, 6H, $Si(CH_3)_2(OCH_2CH_3)$), 0.10 (s, 9H, $Si(CH_3)_3$), 0.05 (app. d, *J* = 1.3 Hz, 6H, $Si(CH_3)_2CH_2$Ph); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.0, 146.0, 145.4, 141.6, 140.0, 133.4, 131.4, 131.2, 130.5, 129.1, 128.4, 128.3, 124.2, 113.7, 84.8, 77.5, 70.2, 58.6, 55.4, 27.0, 23.0, 18.7, 2.8, −1.2, −1.3, −1.6; **HRMS** (ESI+) calc. for $C_{33}H_{52}O_4{}^{28}Si_3{}^{23}Na$ $[M+Na]^+$ 619.30656, found 619.30626.

((1*E*,3*E*,5*R*,6*S*,7*Z*)-8-(Benzyldimethylsilyl)-6-((4-methoxybenzyl)oxy)-5-methyl-5-((trimethylsilyl)oxy)octa-1,3,7-trien-1-yl)dimethylsilanol, 456

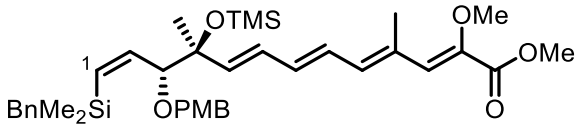


Crude silane **455** obtained in previous step in acetonitrile (0.5 mL) was added acetate buffer (pH = 5, 0,5 mL), and the resulting mixture stirred at ambient temperature overnight. It was diluted with water (5 mL), extracted with Et_2O (3 × 10 mL), the combined organics washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated

in vacuo. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound **456** (18 mg, 71% over 2 steps) as a colourless oil.

$[\alpha]_D^{25}$ +10.5 (*c* 1.0, $CHCl_3$); R_f 0.19 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3352, 2956, 1613, 1514, 1249, 1083, 1035, 1004, 837, 796, 763, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 – 7.14 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.09 – 6.95 (m, 3H, $SiCH_2$*Ph*), 6.86 – 6.81 (m, 2H, Ar*H*), 6.62 (dd, *J* = 18.5, 10.0 Hz, 1H, 7-H), 6.25 – 6.11 (m, 2H, 2-H, 6-H), 5.93 (d, *J* = 15.4 Hz, 1H, 1-H), 5.85 – 5.78 (m, 2H, 5-H, 8-H), 4.44 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.19 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 3.80 (s, 3H, OC*H*$_3$), 3.67 (d, *J* = 9.9 Hz, 1H, 3-H), 2.16 (d, *J* = 13.6 Hz, 1H, SiC*H*$_2$Ph), 2.09 (d, *J* = 13.5 Hz, 1H, SiC*H*$_2$Ph), 1.35 (s, 3H, 4-CH_3), 0.23 (s, 6H, Si(C*H*$_3$)$_2$OH), 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 0.05 (app. d, *J* = 1.1 Hz, 6H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.0, 145.6, 145.3, 141.9, 140.0, 133.4, 131.4, 131.2, 129.1, 128.4, 128.3, 124.3, 113.7, 84.8, 77.2,[6] 70.2, 55.4, 41.0, 27.0, 2.8, 0.2, 0.1, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{31}H_{48}O_4{}^{28}Si_3{}^{23}Na$ $[M+Na]^+$ 591.27526, found 591.27496.

Methyl (2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*)-13-(benzyldimethylsilyl)-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-10-((trimethylsilyl)oxy)trideca-2,4,6,8,12-pentaenoate, ent-453



To a mixture of dienoate **74** (5 mg, 18 µmol, 1.1 eq.), boronic ester **ent-452** (10 mg, 16 µmol, 1.0 eq.) and Tl_2CO_3 (15 mg, 32 µmol, 2.0 eq.) in THF (0.13 mL) and water (0.03 mL) was added Pd(dppf)Cl_2 (1.2 mg, 1.6 µmol, 10 mol%). The mixture was stirred

[6] Determined by HMBC.

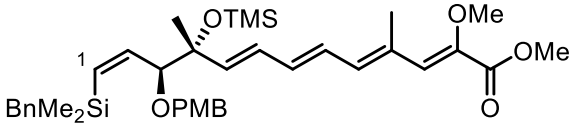
in the dark at ambient temperature for 16 h, then diluted with Et_2O, filtered over Celite, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **ent-453** (6 mg, 57%) as a yellow oil.

This procedure was adapted from a literature procedure.[357] To a mixture of dienoate **74** (5 mg, 18 µmol, 1.1 eq.), boronic ester **ent-452** (10 mg, 16 µmol, 1.0 eq.) in DMF (0.16 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (8 mg, 25 µmol, 1.5 eq.) and $Pd(dppf)Cl_2$ (1.2 mg, 1.6 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h. The reaction was quenched with brine (3 mL). The mixture was diluted with water and extracted with Et_2O (3 × 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **ent-453** (6.4 mg, 61%) as a yellow oil.

$[\alpha]_D^{25}$ −12.7 (*c* 0.6, $CHCl_3$); $\mathbf{R}_f$ 0.16 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2955, 1717, 1613, 1514, 1450, 1435, 1351, 1249, 1206, 1186, 1172, 1154, 1103, 1035, 1018, 992, 839, 796, 762, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 – 7.13 (m, 4H, $SiCH_2$*Ph*, Ar*H*), 7.09 – 7.02 (m, 1H, $SiCH_2$*Ph*), 7.02 – 6.96 (m, 2H, $SiCH_2$*Ph*), 6.86 – 6.80 (m, 2H, Ar*H*), 6.66 (s, 1H, 11-H), 6.55 (dd, *J* = 14.1, 11.4 Hz, 1H, 8-H), 6.43 – 6.17 (m, 4H, 2-H, 6-H, 7-H, 9-H), 5.93 (d, *J* = 14.8 Hz, 1H, 5-H), 5.81 (d, *J* = 14.6 Hz, 1H, 1-H), 4.44 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.19 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 3.80 (s, 3H, $ArOCH_3$), 3.79 (s, 3H, 12-OCH_3), 3.70 – 3.66 (m, 4H, $COOCH_3$, 3-H), 2.15 (d, *J* = 13.6 Hz, 1H, $SiCH_2$Ph), 2.13 (s, 3H, 10-CH_3), 2.09 (d, *J* = 13.5 Hz, 1H, $SiCH_2$Ph), 1.36 (s, 3H, 4-CH_3), 0.09 (s, 9H, $OSi(CH_3)_3$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.4, 159.0, 145.3, 144.1, 141.8, 140.0, 136.7, 136.0, 133.5, 132.9, 131.1, 129.4, 129.1, 129.1, 128.5, 128.4, 128.3, 124.3, 113.7, 84.8, 77.6, 70.2, 60.5, 55.4,

52.2, 27.0, 22.9, 15.1, 2.8, −1.2, −1.3; **HRMS** (ESI+) calc. for $C_{37}H_{52}O_6{}^{28}Si_2{}^{23}Na$ $[M+Na]^+$ 671.31946, found 671.31929.

Methyl (2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*)-13-(benzyldimethylsilyl)-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-10-((trimethylsilyl)oxy)trideca-2,4,6,8,12-pentaenoate, 453

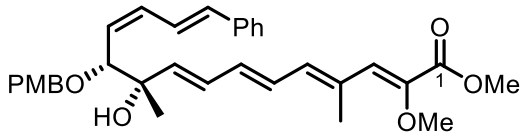


To a mixture of dienoate **74** (21 mg, 74 µmol, 1.0 eq.), boronic ester **452** (50 mg, 81 µmol, 1.1 eq.) and Tl_2CO_3 (70 mg, 0.15 mmol, 2.0 eq.) in THF (0.64 mL) and water (0.16 mL) was added $Pd(dppf)Cl_2$ (5.5 mg, 7.5 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h, then diluted with Et_2O, filtered over Celite, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **453** (35.5 mg, 73%) as a yellow oil.

This procedure was adapted from a literature procedure.[357] To a mixture of dienoate **74** (10 mg, 35.5 µmol, 1.0 eq.), boronic ester **452** (26 mg, 41.9 µmol, 1.2 eq.) in DMF (0.36 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (17 mg, 53.9 µmol, 1.5 eq.) and $Pd(dppf)Cl_2$ (2.6 mg, 3.55 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h. The reaction was quenched with brine. The mixture was diluted with water and extracted with Et_2O (3 × 7 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **453** (16 mg, 70%) as a yellow oil.

$[\alpha]_D^{25}$ +16.1 (*c* 1.0, $CHCl_3$). The remaining analytical data is identical to that of **ent-453**.

Methyl (2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*,14*E*)-10-hydroxy-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-15-phenylpentadeca-2,4,6,8,12,14-hexaenoate, 406

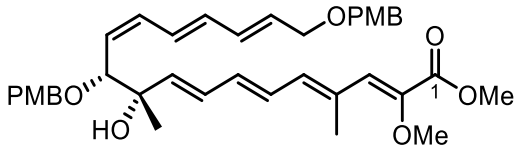


To alkenylsilane **ent-453** (6 mg, 9.3 µmol, 1.0 eq.), β-bromostyrene (1.5 µL, 12 µmol, 1.2 eq.), and APC (0.1 mg, 0.3 µmol, 3 mol%) was added a TBAF solution (0.04 mL, 1.0 M in THF, 0.2 mmol, 4.0 eq.), and the resulting mixture stirred at ambient temperature for 5 min. Purification by column chromatography (petroleum ether / EtOAc, 9:1 →4:1) afforded the title compound **406** as a yellow oil (3.4 mg, 69%).

R_f 0.15 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3524, 2926, 2851, 1715, 1613, 1513, 1449, 1350, 1301, 1250, 1174, 1102, 1071, 1034, 992, 950, 743; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.19 (m, 7H, Ar*H*, 14-H), 6.95 – 6.83 (m, 4H, Ar*H*, 3-H), 6.66 – 6.29 (m, 6H, 5-H, 6-H, 7-H, 8-H, 13-H, 15-H), 5.92 (d, *J* = 14.8 Hz, 1H, 9-H), 5.41 (t, *J* = 10.5 Hz, 1H, 12-H), 4.62 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.30 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ar), 4.22 (d, *J* = 10.0 Hz, 1H, 11-H), 3.79 (s, 7H, ArOC*H*$_3$, OC*H*$_3$), 3.68 (s, 3H, CO_2CH_3), 2.85 (s, 1H, O*H*), 2.10 (s, 3H, 4-CH_3), 1.28 (s, 3H, 10-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.4, 159.5, 144.1, 138.3, 137.0, 136.6, 135.8, 135.4, 134.9, 133.0, 130.0, 129.9, 129.4, 128.8, 128.7, 128.3, 128.2, 127.7, 126.8, 123.8, 114.0, 80.1, 75.0, 70.0, 60.5, 55.4, 52.1, 24.4, 15.1; **HRMS** (ESI+) calc. for $C_{33}H_{38}O_6{}^{23}Na$ $[M+Na]^+$ 553.25606, found 553.25592.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

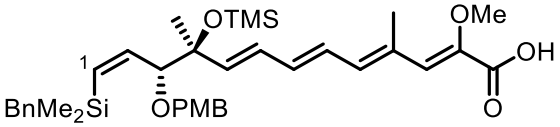
Methyl (2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*,14*E*,16*E*)-10-hydroxy-2-methoxy-11,18-bis((4-methoxybenzyl)oxy)-4,10-dimethyloctadeca-2,4,6,8,12,14,16-heptaenoate, 457



To alkenylsilane **ent-453** (6 mg, 9.3 µmol, 1.0 eq.), vinyl bromide **346** (3.2 mg, 11 µmol, 1.2 eq.), andAPC (0.1 mg, 0.3 µmol, 3 mol%) was added a TBAF solution (0.04 mL, 1.0 M in THF, 0.2 mmol, 4.0 eq.), and the resulting mixture stirred at ambient temperature for 15 min. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **457** as a colourless oil (3.3 mg, 57%).

R*f* 0.09 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 – 7.15 (m, 4H, Ar*H*), 6.93 – 6.81 (m, 4H, Ar*H*), 6.64 (s, 1H, 3-H), 6.54 (dd, *J* = 13.8, 11.3 Hz, 1H, 13-H), 6.43 – 6.24 (m, 7H, 5-H, 6-H, 7-H, 8-H, 9-H, 14-H, 16-H), 5.87 (dd, *J* = 14.8, 6.6 Hz, 2H, 15-H, 17-H), 5.39 – 5.32 (m, 1H, 12-H), 4.55 (d, *J* = 11.6 Hz, 1H, OC*H*$_2$Ar), 4.47 (s, 2H, OC*H*$_2$Ar), 4.24 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$Ar), 4.13 (d, *J* = 10.5 Hz, 1H, 11-H), 4.07 (d, *J* = 5.9 Hz, 2H, 18-H$_2$), 3.81 (s, 3H, ArOC*H*$_3$), 3.80 (s, 3H, ArOC*H*$_3$), 3.80 (s, 4H, OC*H*$_3$), 3.68 (s, 3H, CO_2C*H*$_3$), 2.81 (s, 1H, O*H*), 2.10 (d, *J* = 1.2 Hz, 3H, 4-CH_3), 1.26 (s, 3H, 10-CH_3); **HRMS** (ESI+) calc. for $C_{38}H_{46}O_8{}^{23}Na$ $[M+Na]^+$ 653.30849, found 653.30828.

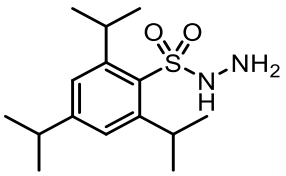
(2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*)-13-(Benzyldimethylsilyl)-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-10-((trimethylsilyl)oxy)trideca-2,4,6,8,12-pentaenoic acid, 475



Ester **ent-453** (6 mg, 9.3 µmol, 1.0 eq.) and LiOH·H_2O (1 mg, 24 µmol, 2.0 eq.) were dissolved in THF (0.08 mL) and water (0.02 mL) and stirred at ambient temperature overnight. The mixture was poured into 1 M citric acid (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 19:1) afforded the title compound **475** (5 mg, 85%) as a yellow oil.

$[\alpha]_D^{25}$ −8.8 (*c* 0.5, $CHCl_3$); R_f 0.34 (CH_2Cl_2 / MeOH, 19:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3024, 2926, 2853, 2361, 1687, 1613, 1584, 1513, 1493, 1451, 1354, 1249, 1207, 1107, 1034, 993, 839, 764, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_C 7.22 – 7.12 (m, 4H, Ar*H*, $SiCH_2$*Ph*), 7.06 (t, *J* = 7.4 Hz, 1H, $SiCH_2$*Ph*), 7.01 – 6.95 (m, 2H, $SiCH_2$*Ph*), 6.90 – 6.80 (m, 2H, Ar*H*), 6.78 (s, 1H, 11-H), 6.55 (dd, *J* = 14.2, 11.4 Hz, 1H, 8-H), 6.47 – 6.32 (m, 2H, 9-H, 6-H), 6.24 (ddd, *J* = 24.3, 14.8, 10.3 Hz, 2H, 2-H, 7-H), 5.95 (d, *J* = 15.0 Hz, 1H, 5-H), 5.82 (d, *J* = 14.6 Hz, 1H, 1-H), 4.44 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.19 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 3.79 (s, 3H, $ArOCH_3$), 3.72 (s, 3H, OCH_3), 3.68 (d, *J* = 9.8 Hz, 1H, 3-H), 2.16 – 2.09 (s, 5H, $SiCH_2$Ph, 10-CH_3), 1.36 (s, 3H, 4-CH_3), 0.09 (s, 9H, $OSi(CH_3)_3$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 158.9, 145.2, 142.1, 141.3, 139.8, 137.7, 136.5, 133.4, 132.4, 131.0, 130.2, 129.0, 128.3, 128.2, 128.2, 128.2, 124.1, 113.6, 110.8, 70.0, 60.4, 55.3, 29.7, 26.8, 22.7, 21.1, 14.2, 2.7, −1.3, −1.4; **HRMS** (ESI−) calc. for $C_{36}H_{49}O_6{}^{28}Si_2$ $[M-H]^-$ 633.30732, found 633.30719.

2,4,6-tri-*iso*-propylbenzenesulfonohydrazide, 301

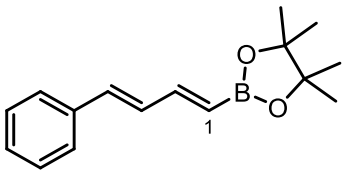


Prepared according literature procedure.[362] Hydrazine hydrate (0.9 mL, 15 mmol, 2.2 eq.) was added dropwise over 10 min to a solution of 2,4,6-tri-*iso*-propylbenzenesulfonyl chloride (2.00 g, 6.60 mmol, 1.0 eq.) in THF (10 mL) at −10 °C. The reaction mixture was warmed to 0 °C and stirred for 3 h. Water was added until the precipitate was dissolved and extracted with Et_2O (50 mL). The organic layer was washed with brine (3 × 10 mL), dried over Na_2SO_4 and filtered through Celite. The filtrate was concentrated *in vacuo*. Petroleum ether (30 mL) was added and the precipitate formed was collected by filtration and washed with petroleum ether and ice-cold water. Drying *in vacuo* afforded the title compound **301** (1.66 g, 84%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 (s, 2H, Ar*H*), 5.45 (s, 1H, N*H*), 4.15 (hept, J = 6.7 Hz, 2H, *o*-C*H*$(CH_3)_2$), 3.57 (s, 2H, N*H*$_2$), 2.91 (hept, J = 6.9 Hz, 1H, *p*-C*H*$(CH_3)_2$), 1.27 (d, J = 6.8 Hz, 12H, *o*-CH(C*H*$_3)_2$), 1.26 (d, J = 6.8 Hz, 6H, *p*-CH(C*H*$_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.0, 151.9, 128.8, 124.2, 34.4, 30.0, 25.1, 23.7.

The spectroscopic data is in agreement with that reported by Pattabiraman and coworkers.[362]

4,4,5,5-Tetramethyl-2-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane

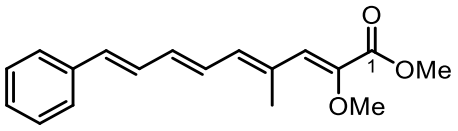


The procedure was adapted from a literature procedure.[277] Chromium(II) chloride (186 mg, 1.51 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (1.8 mL) was added and the suspension stirred at ambient temperature for 30 min to show a minty green colour. A solution of cinnamaldehyde (25 mg, 0.19 mmol, 1.0 eq.) and $CHCl_2Bpin$ (80 mg, 0.38 mmol, 2.0 eq.) in THF (1.0 mL) was added, followed by dropwise addition of a solution of lithium iodide (101 mg, 755 µmol, 4.0 eq.) in THF (1.0 mL). The mixture was stirred in the dark at ambient temperature overnight. It was poured into water and the mixture was extracted with Et_2O (3 × 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 20:1) afforded the title compound **424** (29 mg, 60%) as a colourless oil.

R_f 0.47 (petroleum ether / Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 – 7.40 (m, 2H, Ar*H*), 7.36 – 7.29 (m, 2H, Ar*H*), 7.27 – 7.22 (m, 1H, Ar*H*), 7.18 (dd, *J* = 17.6, 10.3 Hz, 1H, 2-H), 6.86 (ddd, *J* = 15.7, 10.3, 0.7 Hz, 1H, 3-H), 6.70 (d, *J* = 15.7 Hz, 1H, 4-H), 5.68 (dt, *J* = 17.6, 0.7 Hz, 1H, 1-H), 1.30 (s, 12H, OC(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.9, 136.9, 136.2, 130.7, 128.8, 128.3, 127.0, 83.4, 24.9.

The spectroscopic data is in agreement with that reported by Morken and coworkers.[363]

Methyl (2*Z*,4*E*,6*E*,8*E*)-2-methoxy-4-methyl-9-phenylnona-2,4,6,8-tetraenoate, 410



Condition 1. This procedure was adapted from a literature procedure.[357] To a mixture of dienoate **74** (29 mg, 0.10 mmol, 1.0 eq.), diene **424** (20 mg, 0.11 mmol, 1.1 eq.) in DMF (1.0 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (49 mg, 0.16 mmol, 1.5 eq.) and $Pd(dppf)Cl_2$ (8 mg, 11 μmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 48 h. The reaction was quenched with brine. The mixture was diluted with water and extracted with Et_2O (3 × 15 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **410** (18 mg, 62%) as a yellow solid.

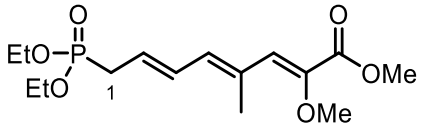
Condition 2. Bis(trimethylsilyl)amine (35 μL, 0.17 mmol, 1.1 eq.) was dissolved in THF (0.5 mL), cooled to 0 °C, *n*-butyllithium (95 μL, 1.6 M in hexanes, 0.15 mmol, 1.0 eq.) added, dropwise and the mixture stirred for 15 min. It was cooled to −78 °C and a solution of phosphonate **409** (50 mg, 0.15 mmol, 1.0 eq.) in THF (1.0 mL) was added dropwise, followed by stirring for 30 min. Benzaldehyde (18 μL, 0.18 mmol, 1.2 eq.) was added and the mixture warmed to ambient temperature overnight. The mixture was quenched with aqueous NH_4Cl, extracted with Et_2O (3 × 15 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 9:1) afforded the title compound **410** (22 mg, 51%) as a yellow solid.

M.p. 96 – 100 °C; **R_f** 0.31 (petroleum ether / Et_2O, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2951, 2930, 1714, 1448, 1434, 1351, 1260, 1247, 1228, 1191, 1102, 1016, 986, 749, 691; **^{1}H NMR**

(400 MHz, $CDCl_3$) δ_H 7.45 – 7.40 (m, 2H, Ar*H*), 7.37 – 7.30 (m, 2H, Ar*H*), 7.27 – 7.21 (m, 1H, Ar*H*), 6.93 (dd, *J* = 15.5, 10.8 Hz, 1H, 8-H), 6.77 – 6.65 (m, 2H, 3-H, 6-H), 6.63 (d, *J* = 15.5 Hz, 1H, 9-H), 6.53 (dd, *J* = 14.5, 10.8 Hz, 1H, 7-H), 6.46 (dq, *J* = 11.5, 1.2 Hz, 1H, 5-H), 3.81 (s, 3H, 2-OC*H*$_3$), 3.70 (s, 3H, COOC*H*$_3$), 2.16 (d, *J* = 1.2 Hz, 3H, 4-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.3, 144.2, 137.3, 136.7, 136.3, 134.0, 133.4, 129.3, 129.3, 129.3, 128.8, 127.9, 126.6, 60.6, 52.2, 15.2; **HRMS** (ESI+) calc. for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.14852, found 285.14868.

The spectroscopic data is in agreement with that reported by Gudmundsson.[74]

Methyl (2*Z*,4*E*,6*E*)-8-(diethoxyphosphoryl)-2-methoxy-4-methylocta-2,4,6-trienoate, 408

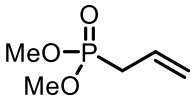


Vinyl iodide **74** (400 mg, 1.42 mmol, 1.0 eq.) in acetonitrile (4.0 mL) and diethyl allyl phosphate (0.37 mL, 2.1 mmol, 1.5 eq.) were added to a mixture of $Pd(OAc)_2$ (32 mg, 0.14 mmol, 10 mol%), P(*o*-tolyl)$_3$ (86 mg, 0.28 mmol, 20 mol%) and silver acetate (355 mg, 2.13 mmol, 1.5 eq.) in acetonitrile (10.0 mL). After stirring at 50 °C overnight, the mixture was diluted with Et_2O (40 mL), filtered through Celite, the filtrate washed with water (20 mL), the filtrate dried over $MgSO_4$, and concentrated *in vacuo*. Excess phosphonate **406** was removed by Kugelrohr distillation (90 °C, 0.5 mbar). Purification of the residue by column chromatography (EtOAc, 100%) afforded the title compound **408** as a yellow oil (470 mg, 99%).

R$_f$ 0.32 (EtOAc, 100%); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2985, 1756, 1722, 1441, 1393, 1217, 1163, 1099, 1053, 1022, 972; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60 (d, *J* = 0.9 Hz, 1H, 6-H),

6.52 (dd, J = 14.9, 11.2 Hz, 1H, 3-H), 6.33 (d, J = 11.2 Hz, 1H, 4-H), 5.78 (dt, J = 15.4, 7.9 Hz, 1H, 2-H), 4.17 – 4.05 (m, 4H, P(OC*H*$_2$CH$_3$)$_2$), 3.79 (s, 3H, OC*H*$_3$), 3.68 (s, 3H, CO$_2$C*H*$_3$), 2.72 (dd, J = 23.1, 7.9 Hz, 2H, 1-H$_2$), 2.08 (s, 3H, 5-CH$_3$), 1.32 (t, J = 7.1 Hz, 6H, P(OCH$_2$C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.1, 135.5, 135.4, 131.1 (d, J = 15.1 Hz), 129.1, 129.1, 125.8 (d, J = 13.3 Hz), 62.2 (d, J = 6.4 Hz), 60.5, 52.2, 31.5 (d, J = 139.5 Hz), 16.6 (d, J = 6.2 Hz), 15.1; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 26.3; **HRMS** (ESI+) calc. for $C_{15}H_{25}O_6P^{23}Na$ $[M+Na]^+$ 355.12810, found 355.12787.

Dimethyl allylphosphonate, 407

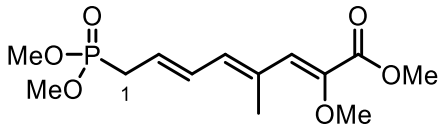


Trimethyl phosphite (5.0 mL, 42.4 mmol, 1.0 eq.) and allyl bromide (4.0 mL, 46.2 mmol, 1.1 eq.) were stirred at 90 °C overnight. After cooling to ambient temperature, the crude products was purified by Kugelrohr distillation (60 °C, 1.0 mbar) to afford the pure title compound **407** (1.92 g, 30%) along with title compound **407**, that contains minor impurities (2.59 g, 37%).

B.p. 60 °C, 1.0 mbar (Kugelrohr); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.80 (ddtd, J = 17.4, 10.1, 7.4, 6.5 Hz, 1H, P(O)CH$_2$C*H*CH$_2$), 5.29 – 5.17 (m, 2H, P(O)CH$_2$CHC*H*$_2$), 3.75 (d, J = 10.8 Hz, 6H, P(O)(OC*H*$_3$)$_2$), 2.63 (ddt, J = 22.0, 7.4, 1.3 Hz, 2H, P(O)C*H*$_2$CHCH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 127.3 (d, J = 11.5 Hz), 120.3 (d, J = 14.4 Hz), 52.9 (d, J = 6.6 Hz), 30.9 (d, J = 139.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 29.6.

The spectroscopic data is in agreement with that reported by Boutevin and coworkers.[364]

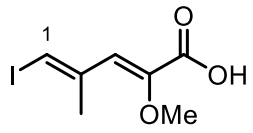
Methyl (2*Z*,4*E*,6*E*)-8-(dimethoxyphosphoryl)-2-methoxy-4-methylocta-2,4,6-trienoate, 409



Vinyl iodide **74** (200 mg, 709 µmol, 1.0 eq.) in acetonitrile (2.0 mL) and allyl phosphonate **407** (160 mg, 1.07 mmol, 1.5 eq.) were added to a mixture of $Pd(OAc)_2$ (16 mg, 71.3 µmol, 10 mol%), P(*o*-tolyl)$_3$ (43 mg, 141 µmol, 20 mol%) and silver acetate (178 mg, 1.07 mmol, 1.5 eq.) in acetonitrile (5.0 mL). After stirring at 50 °C overnight, the mixture was diluted with Et_2O (20 mL), filtered through Celite, the filtrate washed with water (10 mL), the filtrate dried over $MgSO_4$, and concentrated *in vacuo*. Excess phosphonate **407** was removed by Kugelrohr distillation (90 °C, 0.5 mbar). Purification of the residue by column chromatography (EtOAc, 100%) afforded the title compound **409** as a yellow oil (180 mg, 83%).

R$_f$ 0.32 (EtOAc, 100%); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2957, 1751, 1720, 1438, 1255, 1220, 1158, 1103, 1058, 1026, 975, 851, 822; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60 (d, *J* = 0.9 Hz, 1H, 6-H), 6.58 – 6.48 (m, 1H, 3-H), 6.33 (d, *J* = 11.2 Hz, 1H, 4-H), 5.77 (app. dq, *J* = 15.4, 7.8 Hz, 1H, 2-H), 3.79 (s, 1H, 7-OC*H$_3$*), 3.75 (d, *J* = 10.9 Hz, 6H, P(O)(OC*H$_3$*)$_2$), 3.67 (s, 3H, COOC*H$_3$*), 2.73 (dd, *J* = 23.0, 7.8 Hz, 2H, 1-H$_2$), 2.08 (s, 3H, 5-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.2, 135.3 (d, *J* = 5.6 Hz), 132.7, 131.4, 131.2, 129.0 (d, *J* = 2.9 Hz), 125.2 (d, *J* = 13.0 Hz), 60.5, 53.0 (d, *J* = 7.0 Hz), 52.2, 30.6 (d, *J* = 140.0 Hz), 15.2; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 28.8; **HRMS** (ESI+) calc. for $C_{13}H_{21}O_6P^{23}Na$ $[M+Na]^+$ 327.09680, found 327.09677.

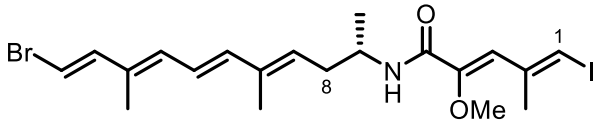
(2*Z*,4*E*)-5-Iodo-2-methoxy-4-methylpenta-2,4-dienoic acid, 458



$LiOH \cdot H_2O$ (89 mg, 2.1 mmol, 2.0 eq.) was added to a solution of ester **74** (300 mg, 1.06 mmol, 1.0 eq.) in THF (8.5 mL) and water (2.1 mL). The mixture was stirred at ambient temperature overnight. The mixture was acidified with aqueous citric acid (15 mL, 1 M), extracted with CH_2Cl_2 (3 × 15 mL), the combined organics dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH, 19:1 →9:1) to afford the title compound **458** as an off white solid (285 mg, 99%).

M.p. 90 °C; **R_f** 0.24 (CH_2Cl_2 / MeOH, 9:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2935, 1681, 1267, 1107, 784; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.96 (app. p, J = 0.9 Hz, 1H, 1-H), 6.73 (app. d, J = 0.8 Hz, 1H, 3-H), 3.73 (s, 3H, OC*H*$_3$), 2.15 (d, J = 1.1 Hz, 3H, 2-CH_3); **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C 171.3, 164.8, 141.6, 122.5, 91.8, 59.2, 22.7; **HRMS** (ESI−) calc. for $C_7H_8O_3{}^{127}I$ $[M-H]^-$ 266.95255, found 266.95236.

(2*Z*,4*E*)-*N*-((*S*,4*E*,6*E*,8*E*,10*E*)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-5-iodo-2-methoxy-4-methylpenta-2,4-dienamide, 463

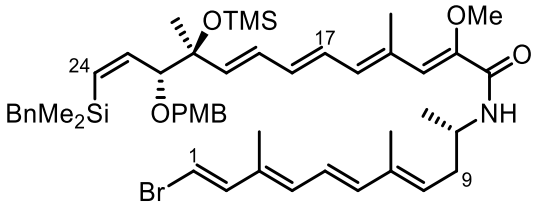


Vinylbromide **236** (267 mg, 713 µmol, 1.1 eq.) was dissolved in methanol (1.8 mL) and cooled to 0 °C. A solution of acetyl chloride (0.10 mL, 1.4 mmol, 2.2 eq.) in methanol (1.8 mL) was added and stirred at 0 °C for 15 min. The mixture was slowly concentrated *in vacuo* to about 1.0 mL volume. DMF (8 mL) was added and the mixture was concentrated *in vacuo* and kept under high vacuum for 30 min. In a separate flask,

carboxylic acid **458** (174 mg, 649 µmol, 1.0 eq.) and HATU (296 mg, 778 µmol, 1.2 eq.) were dissolved in DMF (8 mL), cooled to 0 °C, DIPEA (0.45 mL, 2.6 mmol, 4.0 eq.) added, and the mixture stirred at this temperature for 30 min. Then, amine solution was added dropwise at 0 °C, warmed to ambient temperature and stirred for 14 h. The mixture was quenched by addition of pH 7 phosphate buffer (20 mL) and diluted with water (40 mL). It was extracted with EtOAc (3 × 60 mL) and the combined organics were washed with LiCl solution (30 mL, 10 wt%) and brine (40 mL), dried over $MgSO_4$ and the mixture concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 9:1+1% NEt_3) afforded the title compound **463** as a yellow solid (268 mg, 79%).

M.p. Decomposition above 120 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +11.2 (*c* 0.91, EtOAc); $\mathbf{R}_f$ 0.33 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3304, 2967, 2935, 2360, 2342, 1657, 1621, 1509, 1447, 1328, 1114, 962, 756; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ_H 7.99 (d, *J* = 8.6 Hz, 1H, N*H*), 6.87 (t, *J* = 1.1 Hz, 1H, 3-H), 6.84 (d, *J* = 13.7 Hz, 1H, 15-H), 6.57 (d, *J* = 13.6 Hz, 1H, 16-H), 6.43 (dd, *J* = 15.1, 10.4 Hz, 1H, 12-H), 6.36 (d, *J* = 15.1 Hz, 1H, 11-H), 6.29 (d, *J* = 0.8 Hz, 1H, 1-H), 6.22 (d, *J* = 10.4 Hz, 1H, 13-H), 5.58 (t, *J* = 7.5 Hz, 1H, 9-H), 3.98 – 3.89 (m, 1H, 7-H), 3.52 (s, 3H, OC*H*$_3$), 2.42 – 2.25 (m, 2H, 8-H$_2$), 2.05 (d, *J* = 1.1 Hz, 3H, 2-CH$_3$), 1.85 (s, 3H, 14-CH$_3$), 1.78 (s, 3H, 10-CH$_3$), 1.11 (d, *J* = 6.7 Hz, 3H, 7-CH$_3$); **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ_C 162.1, 148.2, 141.5, 141.4, 139.5, 135.5, 132.7, 132.6, 131.2, 122.5, 117.5, 105.8, 89.2, 59.6, 45.0, 34.9, 22.8, 20.1, 12.4, 12.4; **HRMS** (ESI+) calc. for $C_{20}H_{27}O_2N^{79}Br^{127}I^{23}Na$ $[M+Na]^+$ 542.01621, found 542.01599.

(2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*)-13-(Benzyldimethylsilyl)-N-((*S*,4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-10-((trimethylsilyl)oxy)trideca-2,4,6,8,12-pentaenamide, 464

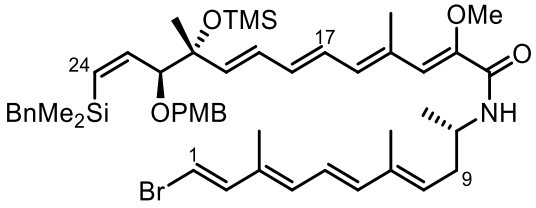


To a mixture of iodide **463** (29 mg, 56 µmol, 1.0 eq.), boronic ester **ent-452** (41 mg, 66 µmol, 1.2 eq.) and Tl_2CO_3 (52 mg, 0.11 mmol, 2.0 eq.) in THF (4.4 mL) and water (1.1 mL) was added Pd(dppf)Cl_2 (4 mg, 5 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h, then diluted with Et_2O, filtered over Celite, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1 →2:1 + 1% NEt_3) afforded the title compound **464** (33 mg, 64%) as a yellow oil.

$[\alpha]_D^{25}$ −92.5 (*c* 1.0, C_6D_6); R_f 0.10 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2961, 2934, 2360, 1651, 1514, 1487, 1462, 1382, 1247, 1029, 882, 732; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.30 – 7.23 (m, 2H, Ar*H*), 7.20 – 7.09 (m, 2H, $SiCH_2$*Ph*), 7.04 – 6.95 (m, 3H, $SiCH_2$*Ph*), 6.87 – 6.81 (m, 2H, Ar*H*), 6.75 (app. dd, *J* = 13.7, 0.7 Hz, 1H, 2-H), 6.54 (dd, *J* = 14.6, 11.5 Hz, 1H, 17-H), 6.48 – 6.38 (m, 2H, 23-H, 19-H), 6.38 – 6.31 (m, 2H, 16-H, 5-H), 6.24 (dt, *J* = 14.6, 5.1 Hz, 2H, 18-H, 6-H), 6.14 – 6.04 (m, 2H, 20-H, 14-H), 5.99 (d, *J* = 13.7 Hz, 1H, 1-H), 5.92 (d, *J* = 11.0 Hz, 1H, 4-H), 5.86 (d, *J* = 14.6 Hz, 1H, 24-H), 5.49 (t, *J* = 7.6 Hz, 1H, 8-H), 4.60 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.34 – 4.21 (m, 2H, OCH_2Ar, 10-H), 3.91 (d, *J* = 9.9 Hz, 1H, 22-H), 3.31 (s, 3H, $ArOCH_3$), 3.20 (s, 3H, 13-OCH_3), 2.23 – 2.04 (m, 4H, $SiCH_2$Ph, 9-H_2), 1.97 (d, *J* = 1.3 Hz, 3H, 15-CH_3), 1.66 (d, *J* = 1.2 Hz, 3H, 7-CH_3), 1.51 (s, 3H, 21-CH_3), 1.50 (s, 3H, 3-CH_3), 0.95 (d, *J* = 6.6 Hz,

3H, 10-CH_3), 0.23 (s, 9H, Si(CH_3)$_3$), 0.13 (s, 3H, Si(CH_3)$_2$), 0.12 (s, 3H, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 163.2, 159.7, 148.5, 145.9, 142.2, 141.5, 140.0, 139.8, 136.7, 135.9, 135.4, 133.7, 133.1, 132.9, 132.3, 131.3, 130.4, 129.7, 129.5, 129.1, 128.7, 128.6, 124.7, 124.6, 122.9, 114.1, 105.2, 85.0, 78.1, 70.5, 60.6, 54.8, 45.5, 35.7, 27.1, 23.3, 20.4, 15.0, 12.6, 12.3, 2.9, −1.0, −1.2; **HRMS** (ESI+) calc. for $C_{49}H_{69}O_5N^{79}Br^{28}Si_2$ $[M+H]^+$ 886.38922, found 886.38968.

(2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*)-13-(Benzyldimethylsilyl)-*N*-((*S*,4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-10-((trimethylsilyl)oxy)trideca-2,4,6,8,12-pentaenamide, 465

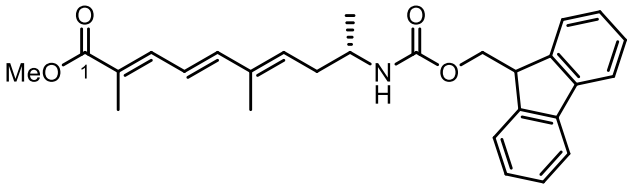


To a mixture of iodide **463** (50 mg, 96 µmol, 1.0 eq.), boronic ester **452** (72 mg, 0.12 mmol, 1.2 eq.) and Tl_2CO_3 (90 mg, 0.19 mmol, 2.0 eq.) in THF (0.8 mL) and water (0.2 mL) was added Pd(dppf)Cl_2 (7 mg, 9 µmol, 10 mol%). The mixture was stirred in the dark at ambient temperature for 16 h, then diluted with Et_2O, filtered over Celite, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1 →2:1 + 1% NEt_3) afforded the title compound **465** (54 mg, 63%) as a yellow oil.

$[\alpha]_D^{25}$ +69.3 (*c* 0.5, C_6D_6); R_f 0.10 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2961, 2934, 2360, 1651, 1514, 1487, 1462, 1382, 1247, 1029, 882, 732; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.31 – 7.24 (m, 2H, Ar*H*), 7.20 – 7.12 (m, 2H, SiCH$_2$*Ph*), 7.05 – 6.96 (m, 3H,

SiCH$_2$*Ph*), 6.89 – 6.81 (m, 2H, Ar*H*), 6.76 (d, *J* = 13.7 Hz, 1H, 2-H), 6.54 (dd, *J* = 14.6, 11.4 Hz, 1H, 17-H), 6.49 – 6.39 (m, 2H, 23-H, 19-H), 6.39 – 6.31 (m, 2H, 16-H, 5-H), 6.30 – 6.19 (m, 2H, 6-H, 18-H), 6.15 – 6.06 (m, 2H, 20-H, 14-H), 5.99 (d, *J* = 13.7 Hz, 1H, 1-H), 5.92 (d, *J* = 11.0 Hz, 1H, 4-H), 5.87 (d, *J* = 14.6 Hz, 1H, 24-H), 5.50 (t, *J* = 7.6 Hz, 1H, 8-H), 4.61 (d, *J* = 11.6 Hz, 1H, OC*H*$_2$Ar), 4.36 – 4.22 (m, 2H, OC*H*$_2$Ar, 10-H), 3.92 (d, *J* = 9.8 Hz, 1H, 22-H), 3.31 (s, 3H, ArOC*H*$_3$), 3.20 (s, 3H, 13-OCH$_3$), 2.24 – 2.03 (m, 4H, SiC*H*$_2$Ph, 9-H$_2$), 1.98 (d, *J* = 1.2 Hz, 3H, 15-CH$_3$), 1.67 (s, 3H, 7-CH$_3$), 1.51 (s, 3H, 21-CH$_3$), 1.50 (s, 3H, 3-CH$_3$), 0.95 (d, *J* = 6.6 Hz, 3H, 10-CH$_3$), 0.24 (s, 9H, Si(C*H*$_3$)$_3$), 0.14 (s, 3H, Si(C*H*$_3$)$_2$), 0.13 (s, 3H, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, C$_6$D$_6$) δ_C 163.5, 160.1, 148.8, 146.3, 142.5, 141.8, 140.4, 140.2, 137.1, 136.2, 135.8, 134.1, 133.4, 133.3, 132.7, 131.7, 130.7, 130.1, 129.8, 129.4, 129.0, 128.9, 125.0, 125.0, 123.2, 114.4, 105.5, 85.4, 78.4, 70.8, 60.9, 55.1, 45.9, 36.1, 27.4, 23.6, 20.7, 15.4, 13.0, 12.6, 3.3, −0.7, −0.8; **HRMS** (ESI+) calc. for C$_{49}$H$_{69}$O$_5$N^{79}Br^{28}Si$_2$ $[M+H]^+$ 886.38922, found 886.38968.

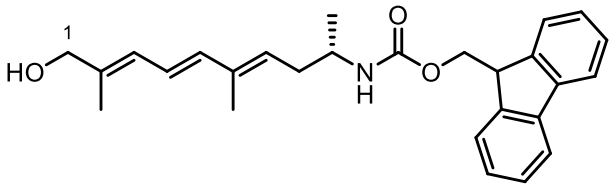
Methyl (*S*,2*E*,4*E*,6*E*)-9-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2,6-dimethyldeca-2,4,6-trienoate, 467



A mixture of crude hydrochloric amine salt **215** (140 mg, 525 µmol, 1.0 eq.), and Na_2CO_3 (167 mg, 1.58 mmol, 3.0 eq.) in 1,4-dioxane (5.3 mL) and water (5.3 mL) at 0 °C, was added FmocCl (204 mg, 789 µmol, 1.5 eq.), and the mixture stirred at ambient temperature for 3 h. The mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 15 mL), the combined organics dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1) afforded the title compound **467** as a white solid (152 mg, 65%).

M.p. 68 °C; $\mathbf{R_f}$ 0.15 (petroleum ether / EtOAc, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2949, 1703, 1611, 1529, 1450, 1332, 1287, 1233, 1109, 1056, 971, 758, 740; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.81 – 7.73 (m, 2H, Ar*H*), 7.64 – 7.55 (m, 2H, Ar*H*), 7.44 – 7.22 (m, 5H, Ar*H*, 3-H), 6.55 (d, *J* = 15.2 Hz, 1H, 5-H), 6.40 (dd, *J* = 15.2, 11.2 Hz, 1H, 4-H), 5.66 (t, *J* = 6.8 Hz, 1H, 7-H), 4.61 (d, *J* = 8.3 Hz, 1H, N*H*), 4.47 – 4.35 (m, 2H, Fmoc*H*), 4.21 (t, *J* = 6.7 Hz, 1H, Fmoc*H*), 4.06 (t, *J* = 6.0 Hz, 1H, 9-H), 3.76 (s, 3H, CO_2CH_3), 2.45 – 2.30 (m, 2H, 8-H_2), 1.98 (d, *J* = 1.4 Hz, 3H, 2-CH_3), 1.81 (s, 3H, 6-CH_3), 1.17 (d, *J* = 6.5 Hz, 3H, 9-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.1, 144.5, 144.2, 144.1, 141.5, 139.1, 136.6, 132.2, 127.8, 127.7, 127.2, 125.1, 124.8, 122.3, 120.2, 120.1, 100.1, 66.6, 65.3, 51.9, 50.5, 47.5, 12.9, 12.7; **HRMS** (ESI+) calc. for $C_{28}H_{32}O_4N$ $[M+H]^+$ 446.23258, found 446.23243.

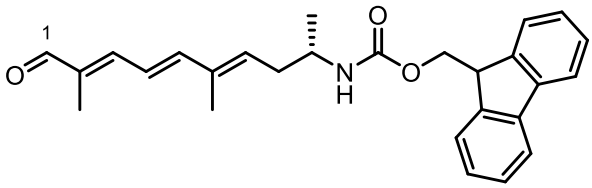
(9*H*-Fluoren-9-yl)methyl ((*S*,4*E*,6*E*,8*E*)-10-hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl)carbamate, 468



A solution of DIBALH (0.91 mL, 1.0 M in cyclohexane, 0.91 mmol, 3.0 eq.) was added dropwise to a solution of trienoate **467** (135 mg, 303 μmol, 1.0 eq.) in CH_2Cl_2 (0.8 mL) at −78 °C, and the mixture was stirred for 1 h. It was quenched by subsequent addition of water (0.04 mL), aqueous NaOH (0.04 mL, 15%), and water (0.09 mL). The mixture was warmed to ambient temperature, $MgSO_4$ was added, stirred for 15 min, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 9:1 →4:1) afforded the title compound **468** as a white solid (49 mg, 39%).

M.p. 98 – 102 °C; $\mathbf{R_f}$ 0.11 (petroleum ether / EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.76 (d, J = 7.6 Hz, 2H, Ar*H*), 7.58 (d, J = 7.5 Hz, 2H, Ar*H*), 7.40 (t, J = 7.4 Hz, 2H, Ar*H*), 7.31 (t, J = 7.4 Hz, 2H, Ar*H*), 6.37 (dd, J = 15.3, 10.6 Hz, 1H, 4-H), 6.26 (d, J = 15.3 Hz, 1H, 5-H), 6.10 (dq, J = 10.6, 0.8 Hz, 1H, 3-H), 5.50 (t, J = 6.6 Hz, 1H, 7-H), 4.60 (d, J = 8.6 Hz, 1H, N*H*), 4.51 – 4.32 (m, 2H, Fmoc*H*), 4.21 (t, J = 6.7 Hz, 1H, Fmoc*H*), 4.09 (d, J = 3.5 Hz, 2H, 1-H_2), 3.90 –3.75 (s, 1H, 9-H), 2.40 – 2.30 (m, 2H, 8-H_2), 1.82 (d, J = 1.2 Hz, 3H, 6-CH_3), 1.79 (s, 3H, 2-CH_3), 1.16 (d, J = 6.0 Hz, 3H, 9-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_H 144.2, 144.2, 141.5, 137.5, 137.0, 136.8, 128.1, 127.8, 127.2, 125.7, 125.2, 122.8, 120.1, 68.9, 68.7, 66.6, 47.5, 35.6, 20.7, 14.5, 12.8; **HRMS** (ESI+) calc. for $C_{27}H_{31}O_3N^{23}Na$ $[M+Na]^+$ 440.21962, found 440.21954.

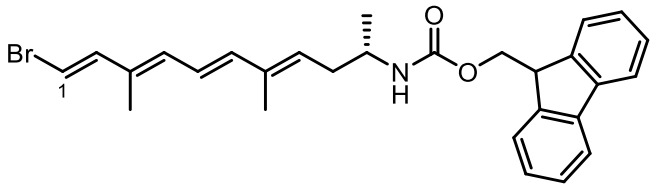
(9*H*-Fluoren-9-yl)methyl ((*S*,4*E*,6*E*,8*E*)-5,9-dimethyl-10-oxodeca-4,6,8-trien-2-yl)carbamate, 469



Alcohol **468** (44 mg, 0.11 mmol, 1.0 eq.), 3 Å molecular sieves, NMO (49 mg, 0.42 μmol, 4.0 eq.), and TPAP (2 mg, 6 μmol, 5 mol%), were dissolved in CH_2Cl_2 (1.1 mL) and the mixture stirred in the dark, at ambient temperature overnight, and then concentrated *in vacuo*. Purification by column chromatography (petroleum ether, 1:4) afforded the title compound **469** as an off white solid (30 mg, 69%).

M.p. 86 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −30.6 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.18 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3330, 2970, 2362, 1699, 1668, 1606, 1530, 1450, 1406, 1357, 1330, 1245, 1192, 1105, 1054, 996, 964; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.43 (s, 1H, C*H*O), 7.76 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.61 – 7.55 (m, 2H, Ar*H*), 7.43 – 7.36 (m, 2H, Ar*H*), 7.34 – 7.28 (m, 2H, Ar*H*), 6.87 (dd, *J* = 10.9, 1.5 Hz, 1H, 3-H), 6.66 (d, *J* = 14.9 Hz, 1H, 5-H), 6.55 (dd, *J* = 15.1, 10.9 Hz, 1H, 4-H), 5.76 (t, *J* = 7.8 Hz, 1H, 7-H), 4.68 (d, *J* = 8.2 Hz, 1H, N*H*), 4.40 (t, *J* = 9.5 Hz, 2H, Fmoc*H*), 4.21 (t, *J* = 6.7 Hz, 1H, Fmoc*H*), 3.95 – 3.79 (m, 1H, 9-H), 2.48 – 2.35 (m, 2H, 8-H_2), 1.88 (d, *J* = 1.2 Hz, 3H, 2-CH_3), 1.84 (s, 3H, 6-CH_3), 1.19 (d, *J* = 6.5 Hz, 3H, 9-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.8, 155.8, 149.4, 146.1, 144.1, 144.0, 141.4, 137.1, 136.5, 127.8, 127.1, 125.1, 121.9, 120.1, 66.6, 47.4, 36.1, 20.8, 20.5, 12.7, 9.7; **HRMS** (ESI+) calc. for $C_{27}H_{29}O_3N^{23}Na$ $[M+Na]^+$ 438.20396, found 438.20370.

(9*H*-Fluoren-9-yl)methyl ((*S*,4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 470

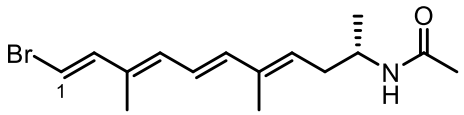


Chromium(II) chloride (71 mg, 0.58 mmol, 8.0 eq.) in a Schlenk tube was activated *in vacuo* by heat. The flask was allowed to reach ambient temperature and purged with nitrogen. THF (0.9 mL) was added and the suspension stirred at ambient temperature for 30 min to give a minty green mixture. A solution of aldehyde **469** (30 mg, 72 µmol, 1.0 eq.) in THF (0.5 mL) was added, followed by dropwise addition of a solution of bromoform (37 mg, 0.14 mmol, 2.0 eq.) in THF (0.4 mL). The mixture was stirred in the dark at ambient temperature overnight. The reaction was quenched by pouring into water and the mixture was extracted with Et_2O (3 × 7 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petroleum ether / Et_2O, 4:1) afforded the title compound **470** (16 mg, 45%) as an *E*/*Z*-mixture of 2:1.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −35.6 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.15 (petroleum ether / Et_2O, 4:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 3316, 2923, 1683, 1539, 1449, 1265, 1110, 1046, 968, 759, 738; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.59 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.44 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.28 – 7.11 (m, 4H, Ar*H*), 6.50 (d, *J* = 13.4 Hz, 1H, 2-H), 6.41 – 6.30 (m, 1H, 5-H), 6.21 (d, *J* = 15.1 Hz, 1H, 6-H), 5.93 (d, *J* = 11.0 Hz, 1H, 4-H), 5.88 (d, *J* = 13.4 Hz, 1H, 1-H), 5.33 (t, *J* = 8.0 Hz, 1H, 8-H), 4.59 – 4.44 (m, 2H, Fmoc*H*), 4.00 (t, *J* = 6.0 Hz, 1H, Fmoc*H*), 3.95 (d, *J* = 8.4 Hz, 1H, N*H*), 3.79 – 3.65 (m, 1H, 10-H), 2.08 – 1.87 (m, 2H, 9-H_2), 1.59 (s, 3H, 3-CH_3), 1.51 (s, 3H, 7-CH_3), 0.70 (d, *J* = 6.7 Hz, 3H, 10-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 155.6, 144.7, 144.7, 141.9, 139.7, 138.4, 136.5, 132.9, 130.1, 127.4, 127.3, 125.2, 125.2, 120.3,

117.2, 65.9, 48.0, 47.2, 35.7, 20.2, 12.6, 12.5; **HRMS** (ESI+) calc. for $C_{28}H_{30}O_2N^{79}Br^{23}Na$ $[M+Na]^+$ 514.13521, found 514.13513.

_N_-((_S_,4_E_,6_E_,8_E_,10_E_)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)acetamide, 472

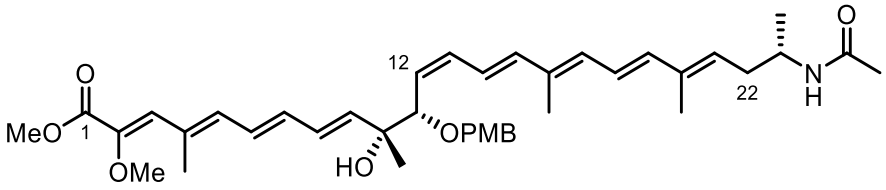


Vinylbromide **236** (99 mg, 0.26 mmol, 1.0 eq.) was dissolved in methanol (0.3 mL) and cooled to 0 °C. A solution of acetyl chloride (0.04 mL, 0.6 mmol, 2.1 eq.) in methanol (0.4 mL) was added and stirred at 0 °C for 15 min. The mixture was slowly concentrated *in vacuo* to about 0.2 mL volume. DMF (3.3 mL) was added and the mixture was concentrated *in vacuo* and kept under high vacuum for 30 min. In a separate flask, acetic acid (17 µL, 0.27 mmol, 1.1 eq.) and HATU (121 mg, 318 µmol, 1.2 eq.) were dissolved in DMF (3.3 mL), cooled to 0 °C, DIPEA (0.18 mL, 1.0 mmol, 4.0 eq.) added, and the mixture stirred at this temperature for 30 min. Then, amine solution was added dropwise at 0 °C, warmed to ambient temperature and stirred for 12 h. The mixture was quenched by addition of pH 7 phosphate buffer (10 mL) and diluted with water (20 mL). It was extracted with EtOAc (3 × 30 mL) and the combined organics were washed with LiCl solution (20 mL, 10 w%) and brine (20 mL), dried over $MgSO_4$ and the mixture concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1+1% NEt_3) afforded the title compound **472** as a yellow solid (35 mg, 42%).

M.p. Decomposition above 128 °C; $\mathbf{R_f}$ 0.12 (petroleum ether / EtOAc, 1:1); **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H 7.73 (d, J = 8.0 Hz, 1H, N*H*), 6.85 (d, J = 13.6 Hz, 1H, 2-H), 6.57 (d, J = 13.6 Hz, 1H, 1-H), 6.44 (dd, J = 15.1, 10.4 Hz, 1H, 5-H), 6.37 (d, J = 15.1 Hz,

1H, 6-H), 6.23 (d, J = 10.3 Hz, 1H, 4-H), 5.58 (t, J = 7.5 Hz, 1H, 8-H), 3.79 (app hept, J = 6.4 Hz, 1H, 10-H), 2.23 (dq, J = 19.0, 7.5 Hz, 2H, 9-H_2), 1.85 (d, J = 1.1 Hz, 3H, C(O)CH_3), 1.77 (s, 6H, 3-CH_3, 7-CH_3), 1.02 (d, J = 6.7 Hz, 3H, 10-CH_3); **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C 168.3, 141.5, 139.5, 135.5, 132.7, 131.0, 122.4, 105.8, 44.5, 35.0, 22.7, 20.1, 12.4; **HRMS** (ESI+) calc. for $C_{15}H_{23}ON^{79}Br$ $[M+H]^+$ 312.09575, found 312.09585.

Methyl (2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*,14*E*,16*E*,18*E*,20*E*,23*S*)-23-acetamido-10-hydroxy-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10,16,20-tetramethyltetracosa-2,4,6,8,12,14,16,18,20-nonaenoate, 473

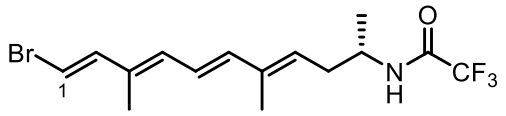


To alkenylsilane **453** (5.5 mg, 8.5 µmol, 1.0 eq.), vinyl bromide **472** (3.2 mg, 10 µmol, 1.2 eq.), and APC (0.6 mg, 1.6 µmol, 20 mol%) was added a TBAF solution (0.1 mL, 1.0 M in THF, 0.10 mmol, 11.8 eq.), and the resulting mixture stirred at ambient temperature for 30 min. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 1:1 →4:1 +1% NEt_3) afforded the title compound **473** as a yellow oil (3.0 mg, 54%).

$[\alpha]_D^{25}$ +90.0 (*c* 0.6, benzene); $\mathbf{R}_f$ 0.17 (petroleum ether / EtOAc, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2925, 2853, 2361, 2341, 1716, 1653, 1541, 1514, 1447, 1350, 1250, 1102, 1033, 992, 700; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.26 – 7.18 (m, 2H, Ar*H*), 6.88 – 6.77 (m, 3H, Ar*H*, 3-H), 6.70 – 6.23 (m, 10H, 5-H, 6-H, 7-H, 8-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H), 6.06 (d, J = 15.5 Hz, 1H, 9-H), 5.50 – 5.46 (m, 2H, 12-H, 21-H), 4.64 (d,

J = 11.8 Hz, 1H, OC*H*$_2$Ar), 4.39 (dd, *J* = 15.5, 9.0 Hz, 2H, 11-H, 23-H), 4.33 – 4.07 (m, 1H, OC*H*$_2$Ar), 3.51 (s, 3H, OC*H*$_3$), 3.41 (s, 3H, OC*H*$_3$), 3.31 (s, 3H, CO$_2$C*H*$_3$), 2.17 – 2.07 (m, 2H, 22-H$_2$), 2.06 (d, *J* = 1.1 Hz, 3H, 16-CH$_3$), 1.85 (s, 3H, C(O)C*H*$_3$), 1.72 (s, 3H, 20-CH$_3$), 1.53 (d, *J* = 1.5 Hz, 3H, 4-CH$_3$), 1.43 (s, 3H, 10-CH$_3$), 0.85 (d, *J* = 6.7 Hz, 3H, 23-CH$_3$); **^{13}C NMR** (101 MHz, C_6D_6) δ_H 168.1, 164.9, 160.0, 144.8, 140.8, 139.5, 139.3, 136.7, 136.7, 136.2, 135.5, 134.9, 134.2, 133.2, 130.5, 130.3, 130.1, 130.0, 129.1, 128.9, 128.6, 123.6, 114.2, 80.7, 75.3, 70.1, 60.0, 54.8, 51.4, 35.7, 30.2, 23.1, 20.2, 15.2, 13.0, 12.7, 1.4; **HRMS** (ESI+) calc. for $C_{40}H_{53}O_7N^{23}Na$ $[M+Na]^+$ 682.37142, found 682.37119.

***N*-((*S*,4*E*,6*E*,8*E*,10*E*)-11-Bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)-2,2,2-trifluoroacetamide, 474**

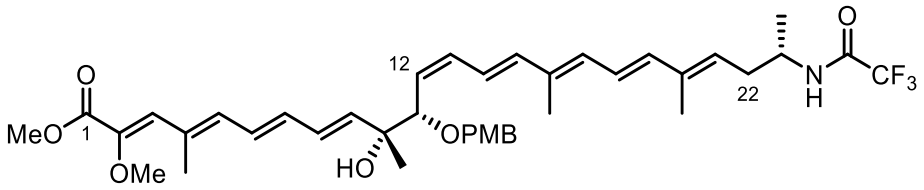


Vinylbromide **236** (92 mg, 0.25 mmol, 1.0 eq.) was dissolved in methanol (0.5 mL) and cooled to 0 °C. A solution of acetyl chloride (13 µL, 0.49 mmol, 2.0 eq.) in methanol (0.5 mL) was added and stirred at 0 °C for 15 min. The mixture was slowly concentrated *in vacuo* to about 0.1 mL volume. CH_2Cl_2 (2.0 mL) was added, and the mixture concentrated *in vacuo* to almost dryness, this was repeated three times. CH_2Cl_2 (1.0 mL) was added, the mixture cooled to 0 °C and pyridine (0.08 mL, 989 µmol, 4.0 eq.) was added, followed by dropwise addition of TFAA (0.05 mL, 0.4 mmol, 1.5 eq.). The reaction was stirred at warmed to ambient temperature, and stirred for 2 h, before being quenched by addition of aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organics, washed with brine (20 mL), dried over $MgSO_4$, and

concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 25:1 →9:1) afforded the title compound **474** as an offwhite solid (42 mg, 47%).

M.p. Decomposition above 50 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −124.1 (*c* 1.0, C_6D_6); $\mathbf{R}_f$ 0.53 (petroleum ether / EtOAc, 4:1); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.50 (d, *J* = 13.7 Hz, 1H, 2-H), 6.12 (dd, *J* = 15.1, 11.1 Hz, 1H, 5-H), 5.92 (d, *J* = 15.2 Hz, 1H, 6-H), 5.74 (d, *J* = 13.7 Hz, 1H, 1-H), 5.65 (d, *J* = 11.2 Hz, 1H, 4-H), 5.08 (d, *J* = 7.0 Hz, 1H, N*H*), 4.92 (t, *J* = 7.7 Hz, 1H, 8-H), 3.51 (app hept, *J* = 6.9 Hz, 1H, 10-H), 1.67 – 1.51 (m, 2H, 9-H_2), 1.30 (d, *J* = 1.1 Hz, 3H, 7-CH_3), 1.24 (d, *J* = 1.1 Hz, 3H, 3-CH_3), 0.33 (d, *J* = 6.7 Hz, 3H, 10-CH_3); **^{19}F NMR** (376 MHz, C_6D_6) δ_F −75.8; **HRMS** (ESI+) calc. for $C_{15}H_{20}ON^{79}BrF_3$ $[M+H]^+$ 366.06749, found 366.06756.

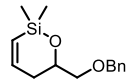
Methyl (2*Z*,4*E*,6*E*,8*E*,10*R*,11*S*,12*Z*,14*E*,16*E*,18*E*,20*E*,23*S*)-10-hydroxy-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10,16,20-tetramethyl-23-(2,2,2-trifluoroacetamido)tetracosa-2,4,6,8,12,14,16,18,20-nonaenoate, 476



To alkenylsilane **453** (35 mg, 54 µmol, 1.0 eq.), vinyl bromide **474** (24 mg, 66 µmol, 1.2 eq.), and APC (5 mg, 7 µmol, 10 mol%) was added a TBAF solution (0.54 mL, 1.0 M in THF, 0.54 mmol, 10.0 eq.), and the resulting mixture stirred at ambient temperature for 30 min. The mixture was concentrated *in vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 4:1 →2:1 → +1% NEt_3) afforded the title compound **476** as a yellow oil (13.1 mg, 34%).

$[\alpha]_D^{25}$ +9.8 (*c* 0.4, benzene); $\mathbf{R}_f$ 0.27 (petroleum ether / EtOAc, 2:1); **IR** (cm^{-1}) $\tilde{\nu}_{max}$ = 2933, 2360, 2341, 1716, 1515, 1260, 1207, 1103, 1021, 798, 669, 656; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.23 – 7.18 (m, 2H, Ar*H*), 6.89 – 6.75 (m, 3H, Ar*H*, 3-H), 6.70 – 6.20 (m, 10H, 5-H, 6-H, 7-H, 8-H, 13-H, 14-H, 15-H, 16-H, 17-H, 18-H), 6.06 (d, *J* = 15.5 Hz, 1H, 9-H), 5.56 (d, *J* = 8.6 Hz, 1H, N*H*), 5.48 (t, *J* = 10.4 Hz, 1H, 12-H), 5.25 (t, *J* = 7.6 Hz, 1H, 21-H), 4.63 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.36 (d, *J* = 9.6 Hz, 1H, 11-H), 4.29 (d, *J* = 11.7 Hz, 1H,. OCH_2Ar), 3.82(app. hept, *J* = 6.8 Hz, 1H, 23-H), 3.50 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.30 (s, 3H, CO_2CH_3), 2.05 (s, 3H, 16-CH_3), 1.96 – 1.85 (m, 2H, 22-H_2), 1.84 (s, 3H, 20-CH_3), 1.61 (s, 3H, 4-CH_3), 1.43 (s, 3H, 10-CH_3), 0.64 (d, *J* = 6.7 Hz, 3H, 23-CH_3); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 164.9, 160.0, 156.3 (q, *J* = 36.2 Hz), 144.8, 140.7, 139.2, 138.8, 137.5, 136.7, 136.1, 136.1, 135.4, 135.3, 133.9, 133.2, 130.5, 130.1, 130.0, 129.8, 129.1, 128.9, 124.2, 123.3, 114.2, 80.7, 75.3, 70.1, 60.0, 54.8, 51.4, 46.5, 34.6, 31.0 (q, *J* = 277.3 Hz), 24.8, 19.1, 15.2, 13.0, 12.6; **HRMS** (ESI+) calc. for $C_{40}H_{50}O_7NF_3{}^{23}Na$ $[M+Na]^+$ 736.34316, found 736.34304.

Table 6.1 Estimated molecular weights of cyclic siloxane species by ECC-DOSY NMR



329
248.40 g/mol

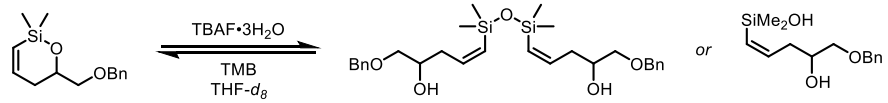
TMB, IS

in THF-d_8

Entry	signal [ppm][a]	Diff.Coeff. [m^2/s][a]	species[a]	MW [g/mol][b]	shape	MW_{det} [g/mol]	MW_{dif}
1	7.34	$1.458 \cdot 10^{-9}$	**329**	248	CS	192	29%
					Merge	196	27%
					DSE	191	30%
					ED	211	18%
2	4.56	$1.222 \cdot 10^{-9}$	**329**	248	CS	275	−10%
					Merge	271	−8%
					DSE	260	−5%
					ED	268	−7%
3	3.62	$2.835 \cdot 10^{-9}$	**329**	248	CS	250	−1%
					Merge	248	0%
					DSE	239	4%
					ED	251	−1%
4	0.18	$1.430 \cdot 10^{-9}$	**329**	248	CS	201	23%
					Merge	204	22%
					DSE	199	25%
					ED	217	14%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] molecular shape: CS: compact spheres, DSE: dissipated spheres and ellipsoids, ED: expanded discs, Merge: merged calibration curves.

Table 6.2 Estimated molecular weights of cyclic and acyclic siloxane species by ECC-DOSY NMR

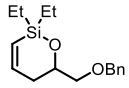


xx 248.40 g/mol | **xx** 514.81 g/mol | **xx** 266.41 g/mol

Entry	signal [ppm][a]	Diff.Coeff. [m²/s][a]	species[a]	MW [g/mol][b]	shape	MW_{det} [g/mol]	MW_{dif}
1	7.34	$5.073 \cdot 10^{-10}$	acyclic	515	CS	1117	−54%
					Merge	946	−46%
					DSE	853	−40%
					ED	671	−23%
2	6.94	$4.795 \cdot 10^{-10}$	acyclic	515	CS	1252	−59%
					Merge	1048	−51%
					DSE	939	−45%
					ED	723	−29%
3	4.57	$5.686 \cdot 10^{-10}$	acyclic	515	CS	887	−42%
					Merge	770	−33%
					DSE	701	−27%
					ED	577	−11%
4	3.55	$4.738 \cdot 10^{-10}$	acyclic	515	CS	1283	−60%
					Merge	1071	−52%
					DSE	959	−45%
					ED	735	−30%
5	3.41	$5.284 \cdot 10^{-10}$	acyclic	515	CS	1029	−50%
					Merge	879	−41%
					DSE	795	−35%
					ED	635	−19%
6	2.50	$5.439 \cdot 10^{-10}$	acyclic	515	CS	970	−47%
					Merge	834	−38%
					DSE	757	−32%
					ED	612	−15%
7	0.06	$5.053 \cdot 10^{-10}$	acyclic	515	CS	1126	−54%
					Merge	953	−46%
					DSE	859	−40%
					ED	675	−24%
8	0.16	$1.006 \cdot 10^{-9}$	cyclic	248	CS	279	−11%
					Merge	274	−9%
					DSE	263	−6%
					ED	270	−8%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] molecular shape: CS: compact spheres, DSE: dissipated spheres and ellipsoids, ED: expanded discs, Merge: merged calibration curves.

Table 6.3 Estimated molecular weights of cyclic siloxane species by ECC-DOSY NMR

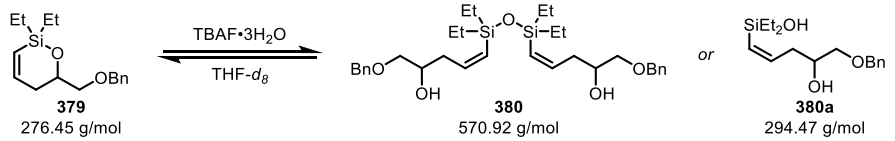


380
276.45 g/mol

Entry	signal [ppm][a]	Diff.Coeff. [m²/s][a]	species[a]	MW [g/mol][b]	shape	MW_{det} [g/mol]	MW_{dif}
1	7.34	$1.334 \cdot 10^{-9}$	**380**	276	CS	201	37%
					Merge	204	35%
					DSE	199	39%
					ED	218	27%
2	6.94	$1.170 \cdot 10^{-9}$	**380**	276	CS	262	5%
					Merge	259	7%
					DSE	249	11%
					ED	259	7%
3	4.57	$4.328 \cdot 10^{-9}$	**380**	276	CS	282	−2%
					Merge	277	0%
					DSE	265	4%
					ED	272	1%
4	3.55	$1.215 \cdot 10^{-9}$	**380**	276	CS	243	14%
					Merge	242	14%
					DSE	234	18%
					ED	246	12%
5	3.41	$1.222 \cdot 10^{-9}$	**380**	276	CS	240	15%
					Merge	240	15%
					DSE	231	19%
					ED	244	13%
6	0.97	$1.187 \cdot 10^{-9}$	**380**	276	CS	255	8%
					Merge	253	9%
					DSE	243	14%
					ED	254	9%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] molecular shape: CS: compact spheres, DSE: dissipated spheres and ellipsoids, ED: expanded discs, Merge: merged calibration curves.

Table 6.4 Estimated molecular weights of cyclic and acyclic siloxane species by ECC-DOSY NMR



Entry	signal [ppm][a]	Diff.Coeff. [m²/s][a]	species[a]	MW [g/mol][b]	shape	MW_{det} [g/mol]	MW_{dif}
1	6.94	$9.916 \cdot 10^{-10}$	cyclic	276	CS	242	14%
					Merge	242	14%
					DSE	233	18%
					ED	246	12%
2	6.38	$4.761 \cdot 10^{-10}$	acyclic	571	CS	1069	−47%
					Merge	910	−37%
					DSE	822	−31%
					ED	652	−12%
3	5.48	$4.398 \cdot 10^{-10}$	acyclic	571	CS	1255	−55%
					Merge	1050	−46%
					DSE	942	−39%
					ED	725	−21%
4	4.56	$5.673 \cdot 10^{-10}$	acyclic	571	CS	750	−24%
					Merge	663	−14%
					DSE	608	−6%
					ED	517	10%
5	3.76	$4.672 \cdot 10^{-10}$	acyclic	571	CS	1111	−49%
					Merge	942	−39%
					DSE	849	−33%
					ED	669	−15%
6	3.46	$4.518 \cdot 10^{-10}$	acyclic	571	CS	1189	−52%
					Merge	1001	−43%
					DSE	899	−36%
					ED	699	−18%
7	2.82	$5.074 \cdot 10^{-10}$	acyclic	571	CS	940	−39%
					Merge	811	−30%
					DSE	737	−23%
					ED	599	−5%
8	2.49	$4.910 \cdot 10^{-10}$	acyclic	571	CS	1005	−43%
					Merge	861	−34%
					DSE	779	−27%
					ED	626	−9%
9	1.75	$4.743 \cdot 10^{-10}$	acyclic	571	CS	1077	−47%
					Merge	916	−38%
					DSE	827	−31%
					ED	655	−13%
10	1.02	$4.680 \cdot 10^{-10}$	acyclic	571	CS	1109	−49%
					Merge	940	−39%
					DSE	848	−33%
					ED	668	−15%

[a] determined from DOSY NMR; [b] calculated molecular weight; [c] molecular shape: CS: compact spheres, DSE: dissipated spheres and ellipsoids, ED: expanded discs, Merge: merged calibration curves.

7 References

(1) Futamura, Y.; Sawa, R.; Umezawa, Y.; Igarashi, M.; Nakamura, H.; Hasegawa, K.; Yamasaki, M.; Tashiro, E.; Takahashi, Y.; Akamatsu, Y.; Imoto, M. *J. Am. Chem. Soc.* **2008**, *130*, 1822.

(2) Schulz, D.; Nachtigall, J.; Geisen, U.; Kalthoff, H.; Imhoff, J. F.; Fiedler, H.-P.; Suessmuth, R. D. *J. Antibiot.* **2012**, *65*, 369.

(3) Oller, A. R.; Rastogi, P.; Morgenthaler, S.; Thilly, W. G. *Mutation research* **1989**, *216*, 149.

(4) Evan, G. I.; Vousden, K. H. *Nature* **2001**, *411*, 342.

(5) Hanahan, D.; Weinberg, R. A. *Cell* **2000**, *100*, 57.

(6) Galluzzi, L.; Morselli, E.; Kepp, O.; Tajeddine, N.; Kroemer, G. *Cell Cycle* **2008**, *7*, 1949.

(7) Adams, J. M.; Cory, S. *Oncogene* **2007**, *26*, 1324.

(8) Adams, J. M. *Genes Dev.* **2003**, *17*, 2481.

(9) Certo, M.; Moore, V. D. G.; Nishino, M.; Wei, G.; Korsmeyer, S.; Armstrong, S. A.; Letai, A. *Cancer Cell*, *9*, 351.

(10) Moldoveanu, T.; Liu, Q.; Tocilj, A.; Watson, M.; Shore, G.; Gehring, K. *Mol. Cell*, *24*, 677.

(11) Suzuki, M.; Youle, R. J.; Tjandra, N. *Cell*, *103*, 645.

(12) Huang, D. C. S.; Strasser, A. *Cell*, *103*, 839.

(13) Willis, S. N.; Adams, J. M. *Curr. Opin. Cell Biol.* **2005**, *17*, 617.

(14) Reed, J. C. *Blood* **2008**, *111*, 3322.

(15) Gillies, L. A.; Kuwana, T. *J. Cell. Biochem.* **2014**, *115*, 632.

(16) Tait, S. W. G.; Green, D. R. *Nat. Rev. Mol. Cell. Biol.* **2010**, *11*, 621.

(17) Yip, K. W.; Reed, J. C. *Oncogene* **2008**, *27*, 6398.

(18) Campos, L.; Rouault, J.; Sabido, O.; Oriol, P.; Roubi, N.; Vasselon, C.; Archimbaud, E.; Magaud, J.; Guyotat, D. *Blood* **1993**, *81*, 3091.

(19) Weller, M.; Malipiero, U.; Aguzzi, A.; Reed, J. C.; Fontana, A. *J. Clin. Invest.* **1995**, *95*, 2633.

(20) Pandey, M. K.; Prasad, S.; Tyagi, A. K.; Deb, L.; Huang, J.; Karelia, D. N.; Amin, S. G.; Aggarwal, B. B. *Pharmaceuticals (Basel)* **2016**, *9*.

(21) Wang, J. L.; Liu, D.; Zhang, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci.* **2000**, *97*, 7124.

(22) Witham, J.; Valenti, M. R.; De-Haven-Brandon, A. K.; Vidot, S.; Eccles, S. A.; Kaye, S. B.; Richardson, A. *Clin. Cancer Res.* **2007**, *13*, 7191.

(23) Tzung, S. P.; Kim, K. M.; Basanez, G.; Giedt, C. D.; Simon, J.; Zimmerberg, J.; Zhang, K. Y.; Hockenbery, D. M. *Nat. Cell Biol.* **2001**, *3*, 183.

(24) Chauhan, D.; Velankar, M.; Brahmandam, M.; Hideshima, T.; Podar, K.; Richardson, P.; Schlossman, R.; Ghobrial, I.; Raje, N.; Munshi, N.; Anderson, K. C. *Oncogene* **2007**, *26*, 2374.

(25) Wilson, W. H.; O'Connor, O. A.; Czuczman, M. S.; LaCasce, A. S.; Gerecitano, J. F.; Leonard, J. P.; Tulpule, A.; Dunleavy, K.; Xiong, H.; Chiu, Y.-L.; Cui, Y.; Busman, T.; Elmore, S. W.; Rosenberg, S. H.; Krivoshik, A. P.; Enschede, S. H.; Humerickhouse, R. A. *Lancet Oncol.* **2010**, *11*, 1149.

(26) Rudin, C. M.; Hann, C. L.; Garon, E. B.; Ribeiro de Oliveira, M.; Bonomi, P. D.; Camidge, D. R.; Chu, Q.; Giaccone, G.; Khaira, D.; Ramalingam, S. S.; Ranson, M. R.; Dive, C.; McKeegan, E. M.; Chyla, B. J.; Dowell, B. L.; Chakravartty, A.; Nolan, C. E.; Rudersdorf, N.; Busman, T. A.; Mabry, M. H.; Krivoshik, A. P.; Humerickhouse, R. A.; Shapiro, G. I.; Gandhi, L. *Clin. Cancer Res.* **2012**, *18*, 3163.

(27) Konopleva, M.; Watt, J.; Contractor, R.; Tsao, T.; Harris, D.; Estrov, Z.; Bornmann, W.; Kantarjian, H.; Viallet, J.; Samudio, I.; Andreeff, M. *Cancer Res.* **2008**, *68*, 3413.

(28) Doi, K.; Li, R.; Sung, S. S.; Wu, H.; Liu, Y.; Manieri, W.; Krishnegowda, G.; Awwad, A.; Dewey, A.; Liu, X.; Amin, S.; Cheng, C.; Qin, Y.; Schonbrunn, E.; Daughdrill, G.; Loughran, T. P., Jr.; Sebti, S.; Wang, H. G. *J. Biol. Chem.* **2012**, *287*, 10224.

(29) Wei, J.; Stebbins, J. L.; Kitada, S.; Dash, R.; Placzek, W.; Rega, M. F.; Wu, B.; Cellitti, J.; Zhai, D.; Yang, L.; Dahl, R.; Fisher, P. B.; Reed, J. C.; Pellecchia, M. *J. Med. Chem.* **2010**, *53*, 4166.

(30) Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; Ng, S.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. *Nature* **2005**, *435*, 677.

(31) Kobayashi, H.; Harada, H.; Nakamura, M.; Futamura, Y.; Ito, A.; Yoshida, M.; Iemura, S.-i.; Shin-ya, K.; Doi, T.; Takahashi, T.; Natsume, T.; Imoto, M.; Sakakibara, Y. *BMC Chem. Biol.* **2012**, *12*, 2.

(32) Nagamine, N.; Sakakibara, Y. *Bioinformatics* **2007**, *23*, 2004.

(33) Chajes, V.; Cambot, M.; Moreau, K.; Lenoir, G. M.; Joulin, V. *Cancer Res.* **2006**, *66*, 5287.

(34) Brusselmans, K.; De Schrijver, E.; Verhoeven, G.; Swinnen, J. V. *Cancer Res.* **2005**, *65*, 6719.

(35) Milgraum, L. Z.; Witters, L. A.; Pasternack, G. R.; Kuhajda, F. P. *Clin. Cancer Res.* **1997**, *3*, 2115.

(36) Takaishi, M.; Kudo, F.; Eguchi, T. *Tetrahedron* **2008**, *64*, 6651.

(37) Takaishi, M.; Kudo, F.; Eguchi, T. *Org. Lett.* **2012**, *14*, 4591.

(38) Takaishi, M.; Kudo, F.; Eguchi, T. *J. Antibiot.* **2013**, *66*, 691.

(39) Pummill, P. E.; Kane, T. A.; Kempner, E. S.; DeAngelis, P. L. *Biochim. Biophys. Acta* **2007**, *1770*, 286.

(40) Udwary, D. W.; Zeigler, L.; Asolkar, R. N.; Singan, V.; Lapidus, A.; Fenical, W.; Jensen, P. R.; Moore, B. S. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 10376.

(41) Shinohara, Y.; Kudo, F.; Eguchi, T. *J. Am. Chem. Soc.* **2011**, *133*, 18134.

(42) Ohtani, T.; Tsukamoto, S.; Kanda, H.; Misawa, K.; Urakawa, Y.; Fujimaki, T.; Imoto, M.; Takahashi, Y.; Takahashi, D.; Toshima, K. *Org. Lett.* **2010**, *12*, 5068.

(43) Takada, A.; Uda, K.; Ohtani, T.; Tsukamoto, S.; Takahashi, D.; Toshima, K. *J. Antibiot.* **2013**, *66*, 155.

(44) Ohtani, T.; Sakai, S.; Takada, A.; Takahashi, D.; Toshima, K. *Org. Lett.* **2011**, *13*, 6126.

(45) Abbott, J. R.; Roush, W. R. *Org. Lett.* **2013**, *15*, 62.

(46) Ohtani, T.; Kanda, H.; Misawa, K.; Urakawa, Y.; Toshima, K. *Tetrahedron Lett.* **2009**, *50*, 2270.

(47) Shimizu, T.; Kusaka, J.; Ishiyama, H.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 4965.

(48) Honda, T.; Mizutani, H. *Heterocycles* **1998**, *48*, 1753.

(49) Nemoto, H. *Tetrahedron Lett.* **1994**, *35*, 7785.

(50) Nemoto, H.; Tsutsumi, H.; Yuzawa, S.; Peng, X.; Zhong, W.; Xie, J.; Miyoshi, N.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2004**, *45*, 1667.

(51) Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2002**, *43*, 8121.

(52) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(53) Heys, R. *J. Chem. Soc., Chem. Commun.* **1992**, 680.

(54) Barth, R.; Mulzer, J. *Tetrahedron* **2008**, *64*, 4718.

(55) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.

(56) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447.

(57) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

(58) Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 1479.

(59) Michels, T. D.; Rhee, J. U.; Vanderwal, C. D. *Org. Lett.* **2008**, *10*, 4787.

(60) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(61) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039.

(62) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(63) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

(64) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(65) Bieniek, M.; Michrowska, A.; Gułajski, Ł.; Grela, K. *Organometallics* **2007**, *26*, 1096.

(66) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038.

(67) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P. *Org. Biomol. Chem.* **2012**, *10*, 5873.

(68) Kanoh, N.; Itoh, S.; Fujita, K.; Sakanishi, K.; Sugiyama, R.; Terajima, Y.; Iwabuchi, Y.; Nishimura, S.; Kakeya, H. *Chem. Eur. J.* **2016**, *22*, 8586.

(69) Hashimoto, H.; Araki, K.; Saito, Y.; Kawa, M.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3131.

(70) Baer, H. H.; Hanna, Z. S. *Carbohydr. Res.* **1981**, *94*, 43.

(71) Nagai, H.; Sasaki, K.; Matsumura, S.; Toshima, K. *Carbohydr. Res.* **2005**, *340*, 337.

(72) Tietze, L. F.; Böhnke, N.; Brasche, G. *ARKIVOC* **2007**, 12.

(73) Lim, D. S. W., University of Oxford, 2013.

(74) Gudmundsson, H. G., University of Oxford, 2016.

(75) Negishi, E.-i.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, *1979*, 501.

(76) Wang, G.; Negishi, E.-i. *Eur. J. Org. Chem.* **2009**, *2009*, 1679.

(77) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750.

(78) Crimmins, M. T.; Stauffer, C. S.; Mans, M. C. *Org. Lett.* **2011**, *13*, 4890.

(79) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(80) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(81) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(82) Elbert, B. L., University of Oxford, 2014.

(83) Elbert, B. L.; Lim, D. S. W.; Gudmundsson, H. G.; O'Hanlon, J. A.; Anderson, E. A. *Chem. Eur. J.* **2014**, *20*, 8594.

(84) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463.

(85) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(86) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144a.

(87) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.

(88) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1977**, 683.

(89) Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55.

(90) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

(91) Chang, W.-T. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. In *Organic Reactions*; Wiley, Hoboken: 2011, p 213.

(92) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.

(93) Sore, H. F.; Galloway, W. R.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 1845.

(94) Echavarren, A. M.; Cardenas, D. J. *Metal-Catalyzed Cross-Coupling Reactions*; 2nd ed. ed.; Wiley-VCH: Weinheim, 2004; Vol. 1.

(95) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

(96) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

(97) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491.

(98) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865.

(99) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(100) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876.

(101) Sugiyama, A.; Ohnishi, Y. Y.; Nakaoka, M.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 12975.

(102) Amatore, C.; Grimaud, L.; Le Duc, G.; Jutand, A. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 6982.

(103) Amatore, C.; Jutand, A.; Le Duc, G. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 1379.

(104) Amatore, C.; Le Duc, G.; Jutand, A. *Chem. Eur. J.* **2013**, *19*, 10082.

(105) Denmark, S. E.; Liu, J. H. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 2978.

(106) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 4442.

(107) Bergueiro, J.; Montenegro, J.; Cambeiro, F.; Saa, C.; Lopez, S. *Chem. Eur. J.* **2012**, *18*, 4401.

(108) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435.

(109) Denmark, S. E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971.

(110) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666.

(111) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 12432.

(112) Denmark, S. E.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 11768.

(113) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(114) Domínguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071.

(115) Clough, J. M.; Pattenden, G. *Tetrahedron* **1981**, *37*, 3911.

(116) Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801.

(117) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, *1998*, 26.

(118) Aïssa, C. *Eur. J. Org. Chem.* **2009**, *2009*, 1831.

(119) Pospíšil, J. *Tetrahedron Lett.* **2011**, *52*, 2348.

(120) Billard, F.; Robiette, R.; Pospisil, J. *J. Org. Chem.* **2012**, *77*, 6358.

(121) Ramberg, L.; Bäcklund, B. *Arkiv Kemi, Mineral. Geol.* **1940**, *13A*, 50.

(122) Taylor, R. J. K.; Casy, G. *The Ramberg-Bäcklund Reaction*; Wiley VCH, 2004.

(123) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

(124) Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *J. Chem. Soc., Chem. Commun.* **1994**, 1771.

(125) Baird, L. J.; Timmer, M. S.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271.

(126) Cao, X.-P. *Tetrahedron* **2002**, *58*, 1301.

(127) Soderman, S. C.; Schwan, A. L. *J. Org. Chem.* **2012**, *77*, 10978.

(128) Oh, E. T.; Kim, Y. H.; Jin, J.; Su, L.; Seo, J. A.; Koo, S. *J. Org. Chem.* **2014**, *79*, 4712.

(129) Trost, B. M.; Sorum, M. T.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.

(130) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Organomet. Chem.* **2008**, *693*, 2789.

(131) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

(132) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(133) Drayer, D. E. *Clin. Pharmacol. Ther.* **1986**, *40*, 125.

(134) Jamali, F.; Mehvar, R.; Pasutto, F. M. *J. Pharm. Sci.* **1989**, *78*, 695.

(135) Blaschke, G.; Hempel, G.; Muller, W. E. *Chirality* **1993**, *5*, 419.

(136) McConathy, J.; Owens, M. J. *Primary Care Companion to The Journal of Clinical Psychiatry* **2003**, *5*, 70.

(137) Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, *2*, 85.

(138) Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q. *Org. Lett.* **2011**, *13*, 4938.

(139) Yao, Q.; Yuan, C. *J. Org. Chem.* **2013**, *78*, 6962.

(140) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.

(141) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349.

(142) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

(143) DenBesten, I. E.; Kinstle, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 5968.

(144) Schaap, A. P.; Siddiqui, S.; Prasad, G.; Rahman, A. F. M.; Oliver, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 6087.

(145) García Ruano, J. L.; Fernández, I.; del Prado Catalina, M.; Hermoso, J. A.; Sanz-Aparicio, J.; Martínez-Ripoll, M. *J. Org. Chem.* **1998**, *63*, 7157.

(146) Viso, A.; de la Pradilla, R. F.; García, A.; Alonso, M.; Guerrero-Strachan, C.; Fonseca, I. *Synlett* **1999**, *1999*, 1543.

(147) Davis, F. A.; Reddy, R. E. *Tetrahedron: Asymmetry* **1994**, *5*, 955.

(148) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.

(149) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.

(150) Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984.

(151) Orsini, F.; Pelizzoni, F. *Synth. Commun.* **2006**, *14*, 169.

(152) Kitahara, T.; Horiguchi, A.; Mori, K. *Tetrahedron* **1988**, *44*, 4713.

(153) Chakor, N. S.; Musso, L.; Dallavalle, S. *J. Org. Chem.* **2009**, *74*, 844.

(154) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(155) Wolkoff, P. *Can. J. Chem.* **1975**, *53*, 1333.

(156) Tosic, O.; Mattay, J. *Eur. J. Org. Chem.* **2011**, *2011*, 371.

(157) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745.

(158) Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215.

(159) Chen, W.; Ren, J.; Wang, M.; Dang, L.; Shen, X.; Yang, X.; Zhang, H. *Chem. Commun.* **2014**, *50*, 6259.

(160) von der Ohe, F.; Brückner, R. *New J. Chem.* **2000**, *24*, 659.

(161) Queron, E.; Lett, R. *Tetrahedron Lett.* **2004**, *45*, 4527.

(162) Puentener, K.; Scalone, M.; Hoffman-La Roche Inc., USA . 2005, p 17 pp.

(163) Groß, H.; Freiberg, J. *Chem. Ber.* **1966**, *99*, 3260.

(164) Géant, P.-Y.; Martínez, J.; Salom-Roig, X. J. *Eur. J. Org. Chem.* **2011**, *2011*, 1300.

(165) Donald, D. K.; Hann, M. M.; Saunders, J.; Wadsworth, H. J.; G.D. Searle and Co., USA . 1986, p 17 pp. Cont.

(166) Kinoshita, M.; Takami, H.; Taniguchi, M.; Tamai, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2151.

(167) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4207.

(168) Srinivasarao, M.; Kim, Y.; Li, X. H.; Robbins, D. W.; Fuchs, P. L. *J. Org. Chem.* **2011**, *76*, 7834.

(169) Smith, P. A. S.; Chou, S.-S. P. *J. Org. Chem.* **1981**, *46*, 3970.

(170) Gray, G. M. *Synthesis* **1983**, *1983*, 488.

(171) Hecht, S.; Amslinger, S.; Jauch, J.; Kis, K.; Trentinaglia, V.; Adam, P.; Eisenreich, W.; Bacher, A.; Rohdich, F. *Tetrahedron Lett.* **2002**, *43*, 8929.

(172) Vanier, S. F.; Larouche, G.; Wurz, R. P.; Charette, A. B. *Org. Lett.* **2010**, *12*, 672.

(173) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 231.

(174) Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1997**, *38*, 4183.

(175) Thiede, S.; Wosniok, P. R.; Herkommer, D.; Debnar, T.; Tian, M.; Wang, T.; Schrempp, M.; Menche, D. *Chem. Eur. J.* **2017**, *23*, 3300.

(176) Llinares, M.; Devin, C.; Azay, J.; Bergé, G.; Fehrentz, J. A.; Martinez, J. *Eur. J. Med. Chem.* **1997**, *32*, 767.

(177) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424.

(178) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257.

(179) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Christopher Braddock, D.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219.

(180) Kumar, R. N.; Meshram, H. M. *Tetrahedron* **2015**, *71*, 5669.

(181) Shan, M.; Kishi, Y. *Org. Lett.* **2012**, *14*, 660.

(182) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028.

(183) Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749.

(184) Corriu, R. J. P.; Masse, J. P. *J. Organomet. Chem.* **1970**, *22*, 321.

(185) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757.

(186) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196.

(187) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102.

(188) Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695.

(189) Maifeld, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228.

(190) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180.

(191) Kim, M.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 12818.

(192) Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664.

(193) Lee, Y. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10652.

(194) Maifeld, S. V.; Lee, D. *Org. Lett.* **2005**, *7*, 4995.

(195) Halvorsen, G. T.; Roush, W. R. *Org. Lett.* **2008**, *10*, 5313.

(196) Halvorsen, G. T.; Roush, W. R. *Tetrahedron Lett.* **2011**, *52*, 2072.

(197) Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662.

(198) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30.

(199) Trost, B. M.; Ball, Z. T.; Joge, T. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3415.

(200) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

(201) Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522.

(202) Clark, T. B.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 4109.

(203) Bourque, L. E.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 5257.

(204) Anderson, L. L.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 425.

(205) Murakami, M.; Oike, H.; Sugawara, M.; Suginome, M.; Ito, Y. *Tetrahedron* **1993**, *49*, 3933.

(206) Bonafoux, D.; Ojima, I. *Org. Lett.* **2001**, *3*, 2333.

(207) Oger, C.; Balas, L.; Durand, T.; Galano, J. M. *Chem. Rev.* **2013**, *113*, 1313.

(208) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520.

(209) Hussman, G.; Wulff, W. D.; Barton, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 1263.

(210) Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063.

(211) Denmark, S. E.; Seierstad, M.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 884.

(212) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887.

(213) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357.

(214) Hungerford, N. L.; Kitching, W. *Chem. Commun.* **1996**, 1697.

(215) Hungerford, N. L.; Kitching, W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1839.

(216) Sawada, D.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 209.

(217) Benkeser, R. A.; Hickner, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5298.

(218) Rehders, F.; Hoppe, D. *Synthesis* **1992**, *1992*, 859.

(219) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426.

(220) Sammtleben, F.; Noltemeyer, M.; Brückner, R. *Tetrahedron Lett.* **1997**, *38*, 3893.

(221) Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 1411.

(222) Anderson, E.; Clark, R. W.; Dagousset, G.; Demchuk, O. M.; Harsanyi, A. *Science of Synthesis Knowledge Updates: 2015/1*; Thieme, 2015.

(223) Robins, M. J.; Manfredini, S.; Wood, S. G.; Wanklin, R. J.; Rennie, B. A.; Sacks, S. L. *J. Med. Chem.* **1991**, *34*, 2275.

(224) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.

(225) Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323.

(226) Bulman-Page, P. C.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1847.

(227) Peters, R. H.; Crowe, D. F.; Tanabe, M.; Avery, M. A.; Chong, W. K. M. *J. Med. Chem.* **1987**, *30*, 646.

(228) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823.

(229) Murthi, K. K.; Salomon, R. G. *Tetrahedron Lett.* **1994**, *35*, 517.

(230) Pasto, D. J.; Taylor, R. T. **2004**, 91.

(231) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozepeikar, B. *Tetrahedron* **1976**, *32*, 2157.

(232) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096.

(233) Cornut, D. *unpublished results*.

(234) Müller, D.; Alexakis, A. *Org. Lett.* **2012**, *14*, 1842.

(235) Kamptmann, S. B.; Brückner, R. *Eur. J. Org. Chem.* **2013**, *2013*, 6584.

(236) Becher, J. *Organic Syntheses* **1979**, *59*, 79.

(237) Becher, J. *Synthesis* **1980**, *1980*, 589.

(238) Soullez, D.; Ple, G.; Duhamel, L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1639.

(239) Shibahara, S.; Fujino, M.; Tashiro, Y.; Okamoto, N.; Esumi, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Synthesis* **2009**, *2009*, 2935.

(240) Beshai, M.; Dhudshia, B.; Mills, R.; Thadani, A. N. *Tetrahedron Lett.* **2008**, *49*, 6794.

(241) Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 6192.

(242) Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Ober, M. H.; Wang, H.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 6200.

(243) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601.

(244) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot.* **1983**, *36*, 1595.

(245) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019.

(246) Denmark, S. E.; Smith, R. C.; Tymonko, S. A. *Tetrahedron* **2007**, *63*, 5730.

(247) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(248) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.

(249) Grushka, E.; Kikta, E. J. *J. Am. Chem. Soc.* **1976**, *98*, 643.

(250) Bachmann, S.; Gernert, B.; Stalke, D. *Chemical Communications (Cambridge)* **2016**, *52*, 12861.

(251) Bachmann, S.; Neufeld, R.; Dzemski, M.; Stalke, D. *Chem. Eur. J.* **2016**, *22*, 8462.

(252) Lee, T. H.; Sethi, T.; Crea, A. E. G.; Peters, W.; Arm, J. P.; Horton, C. E.; Walport, M. J.; Spur, B. W. *Clin. Sci.* **1988**, *74*, 467.

(253) Shimazaki, T.; Kobayashi, Y.; Sato, F.; Iwama, T.; Shikada, K. *Prostaglandins* **1990**, *39*, 459.

(254) Spur, B.; Crea, A.; Peters, W.; König, W. *Arch. Pharm.* **1985**, *318*, 225.

(255) Nakamura, T.; Namiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635.

(256) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324.

(257) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J. H. *J. Org. Chem.* **1990**, *55*, 6203.

(258) Babudri, F.; Fiandanese, V.; Naso, F. *J. Org. Chem.* **1991**, *56*, 6245.

(259) Babudri, F.; Fiandanese, V.; Hassan, O.; Punzi, A.; Naso, F. *Tetrahedron* **1998**, *54*, 4327.

(260) Urbitsch, F. *Unpublished results*.

(261) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

(262) Mladenova, M.; Alami, M.; Linstrumelle, G. *Synth. Commun.* **1996**, *26*, 2831.

(263) Lingam Manthati, V.; Grée, D.; Grée, R. *Eur. J. Org. Chem.* **2005**, *2005*, 3825.

(264) Paravidino, M.; Böhm, P.; Gröger, H.; Hanefeld, U. In *Enzyme Catalysis in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2012, p 249.

(265) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

(266) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

(267) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(268) Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J.-J. *Eur. J. Org. Chem.* **1999**, *1999*, 2655.

(269) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 6703.

(270) Uesugi, S.; Watanabe, T.; Imaizumi, T.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2014**, *16*, 4408.

(271) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525.

(272) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(273) Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281.

(274) Claridge, T. D.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.

(275) Dobson, N. A.; Eglinton, G.; Krishnamurti, M.; Raphael, R. A.; Willis, R. G. *Tetrahedron* **1961**, *16*, 16.

(276) Lowe, J. T.; Youngsaye, W.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 3639.

(277) Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T.; Utimoto, K. *Synlett* **1995**, *1995*, 963.

(278) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367.

(279) Mistico, L.; Ay, E.; Huynh, V.; Bourderioux, A.; Chemla, F.; Ferreira, F.; Oble, J.; Perez-Luna, A.; Poli, G.; Prestat, G. *J. Organomet. Chem.* **2014**, *760*, 124.

(280) Evans; Kaldor; Jones; Clardy; Stout *J. Am. Chem. Soc.* **1990**, *112*, 7001

(281) Chandra, G.; Lo, P. Y.; Hitchcock, P. B.; Lappert, M. F. *Organometallics* **1987**, *6*, 191.

(282) Denmak, S. E.; Wang, Z. *Organic Syntheses* **2005**, *81*, 54.

(283) Montenegro, J.; Bergueiro, J.; Saá, C.; López, S. *Org. Lett.* **2009**, *11*, 141.

(284) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.

(285) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.

(286) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

(287) Joullié, M. M. L., Kenneth M. *ARKIVOC* **2010**, *2010*, 189.

(288) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557.

(289) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. *Org. Process Res. Dev.* **2016**, *20*, 140.

(290) Goto, R.; Okura, K.; Sakazaki, H.; Sugawara, T.; Matsuoka, S.; Inoue, M. *Tetrahedron* **2011**, *67*, 6659.

(291) Van der Auwera, C.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1986**, *95*, 203.

(292) Nazaré, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363.

(293) Wuts, P. G. M.; Greene, T. W. **2006**.

(294) Kuntiyong, P.; Lee, T. H.; Kranemann, C. L.; White, J. D. *Org. Biomol. Chem.* **2012**, *10*, 7884.

(295) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

(296) McNally, A.; Haffemayer, B.; Collins, B. S.; Gaunt, M. J. *Nature* **2014**, *510*, 129.

(297) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657.

(298) Butler, S. J.; Jolliffe, K. A.; Lee, W. Y. G.; McDonough, M. J.; Reynolds, A. J. *Tetrahedron* **2011**, *67*, 1019.

(299) Seiser, T.; Kamena, F.; Cramer, N. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 6483.

(300) Bates, R. B.; Caldera, S.; Ruane, M. D. *J. Nat. Prod.* **1998**, *61*, 405.

(301) Shute, R. E.; Dunlap, B.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 71.

(302) Panek, J. S.; Xu, F.; Rondón, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 4113.

(303) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587.

(304) Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378.

(305) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471.

(306) Canova, S.; Bellosta, V.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 145.

(307) Jeso, V.; Cherry, L.; Macklin, T. K.; Pan, S. C.; LoGrasso, P. V.; Micalizio, G. C. *Org. Lett.* **2011**, *13*, 5108.

(308) Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 1281.

(309) Yu, J.; Lai, J.-Y.; Ye, J.; Balu, N.; Reddy, L. M.; Duan, W.; Fogel, E. R.; Capdevila, J. H.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 3939.

(310) Doria, F.; Gallati, C. M.; Freccero, M. *Org. Biomol. Chem.* **2013**, *11*, 7838.

(311) Rouxel, C.; Charlot, M.; Mongin, O.; Krishna, T. R.; Caminade, A. M.; Majoral, J. P.; Blanchard-Desce, M. *Chem. Eur. J.* **2012**, *18*, 16450.

(312) Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **2003**, *46*, 2436.

(313) Tassano, E.; Alama, A.; Basso, A.; Dondo, G.; Galatini, A.; Riva, R.; Banfi, L. *Eur. J. Org. Chem.* **2015**, *2015*, 6710.

(314) Mathai, M.; D., H. A.; C07C233/56; A61K31/216; A61K31/42; A61K31/4245; A61K45/06; C07D261/18; C07D271/04; C07D413/12","A61K31/216; A61K31/42; A61K31/4245; C07D413/12; C07C233/56; C07D261/18; C07D271/04; C07D271/08; C07C243/28; A61K45/06; C07C235/80 ed. 2013.

(315) Freeman, S.; Irwin, W. J.; Mitchell, A. G.; Nicholls, D.; Thomson, W. *J. Chem. Soc., Chem. Commun.* **1991**, 875.

(316) Waldmann, H.; Nägele, E. *Angew. Chem.* **1995**, *107*, 2425.

(317) Chen, G.; Ren, C.; Wang, L.; Xu, B.; Yang, Z. *Chin. J. Chem* . **2012**, *30*, 53.

(318) Nakata, E.; Yukimachi, Y.; Nazumi, Y.; Uwate, M.; Maseda, H.; Uto, Y.; Hashimoto, T.; Okamoto, Y.; Hori, H.; Morii, T. *RSC Adv.* **2014**, *4*, 348.

(319) Chen, W.; Deng, Z.; Chen, K.; Dou, D.; Song, F.; Li, L.; Xi, Z. *Eur. J. Med. Chem.* **2015**, *93*, 172.

(320) Jobron, L.; Hindsgaul, O. *J. Am. Chem. Soc.* **1999**, *121*, 5835.

(321) Tlais, S. F.; Lam, H.; House, S. E.; Dudley, G. B. *J. Org. Chem.* **2009**, *74*, 1876.

(322) Lam, H.; House, S. E.; Dudley, G. B. *Tetrahedron Lett.* **2005**, *46*, 3283.

(323) Bhuniya, D.; Kumar, D. S.; Ranga, M. G.; Javed, I.; Ranjan, C.; Kannimel, V. R.; US20020306898 ed.; DR, R. L. L., Ed. 2003.

(324) Kvaerno, L.; Werder, M.; Hauser, H.; Carreira, E. M. *J. Med. Chem.* **2005**, *48*, 6035.

(325) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 6402.

(326) Hu, D. X.; Shibuya, G. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2013**, *135*, 12960.

(327) Yonezawa, S.; Komurasaki, T.; Kawada, K.; Tsuri, T.; Fuji, M.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Ohtani, M. *J. Org. Chem.* **1998**, *63*, 5831.

(328) Kawada, K.; Arimura, A.; Tsuri, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 973.

(329) Chapman, D. R.; Bauer, L.; Waller, D. P.; Zaneveld, L. J. D. *J. Heterocycl. Chem.* **1990**, *27*, 2063.

(330) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4336.

(331) Takahashi, S.; Suda, Y.; Nakamura, T.; Matsuoka, K.; Koshino, H. *Synth. Commun.* **2016**, *47*, 22.

(332) Jackson, T.; Woo, L. W.; Trusselle, M. N.; Chander, S. K.; Purohit, A.; Reed, M. J.; Potter, B. V. *Org. Biomol. Chem.* **2007**, *5*, 2940.

(333) Maia, H. L.; Ridge, B.; Rydon, H. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 98.

(334) Stanway, S. J.; Thomas, E. J. *Tetrahedron* **2012**, *68*, 5998.

(335) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

(336) Diaz, P.; Bernardon, J.-m.; Galderma Research & Development, S.N.C., Fr. . 1999, p 79 pp.

(337) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215.

(338) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511.

(339) Wolff, M.; Seemann, M.; Grosdemange-Billiard, C.; Tritsch, D.; Campos, N.; Rodríguez-Concepción, M.; Boronat, A.; Rohmer, M. *Tetrahedron Lett.* **2002**, *43*, 2555.

(340) Wang, J.; Boyarskikh, V.; Rainier, J. D. *Org. Lett.* **2011**, *13*, 700.

(341) Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. *J. Am. Chem. Soc.* **2014**, *136*, 15719.

(342) Kleinbeck, F.; Fettes, G. J.; Fader, L. D.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 3598.

(343) Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. *Eur. J. Org. Chem.* **2016**, *2016*, 2110.

(344) Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. *Org. Lett.* **2010**, *12*, 5028.

(345) Taft, F.; Brünjes, M.; Knobloch, T.; Floss, H. G.; Kirschning, A. *J. Am. Chem. Soc.* **2009**, *131*, 3812.

(346) Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609.

(347) Vanier, S. F.; Larouche, G.; Wurz, R. P.; Charette, A. B. *Org. Lett.* **2010**, *12*, 672.

(348) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.

(349) Ouyang, X.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 12400.

(350) Petasis, N. A.; University of Southern California, USA . 2003, p 43 pp.

(351) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429.

(352) Ma, D.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1703.

(353) Mittendorf, J.; Hiemstra, H.; Nico Speckamp, W. *Tetrahedron* **1990**, *46*, 4049.

(354) Targel, T. A.; Kumar, J. N.; Shneider, O. S.; Bar, S.; Fridman, N.; Maximenko, S.; Szpilman, A. M. *Org. Biomol. Chem.* **2015**, *13*, 2546.

(355) Willwacher, J.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 4217.

(356) Pal, T. K.; Dey, S.; Pathak, T. *J. Org. Chem.* **2011**, *76*, 3034.

(357) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367.

(358) Dolling, U., H.; Frey, L., F.; Tillyer, R., D.; Tschaen, D., M.; Merck & Co., I., Avenue, E. L., Rahway, N. J. U., Eds.; Vol. WO9710195, EP0851850.

(359) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511.

(360) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(361) Zürcher, M.; Hof, F.; Barandun, L.; Schütz, A.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F. *Eur. J. Org. Chem.* **2009**, *2009*, 1707.

(362) Pattabiraman, V. R.; Stymiest, J. L.; Derksen, D. J.; Martin, N. I.; Vederas, J. C. *Org. Lett.* **2007**, *9*, 699.

(363) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708.

(364) Boutevin, B.; Hervaud, Y.; Jeanmaire, T.; Boulahna, A.; Elasri, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *174*, 1.