Cyclic Alkenylsiloxanes: Synthesis and Application Towards Incednam

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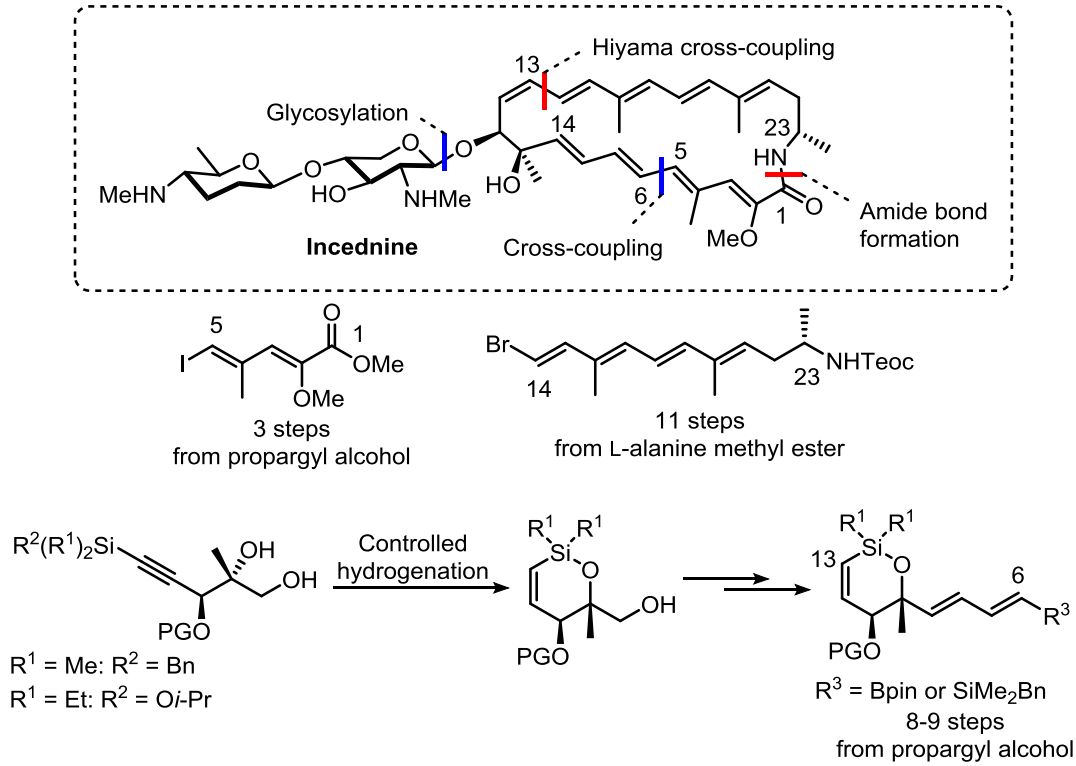
Michaelmas Term, 2016 **Wolfson College**

This thesis explores the use of cyclic alkenylsiloxanes in Hiyama cross-coupling reactions for the stereospecific construction of the *Z*-pentaenyl system of incednam, the aglycon of incednine. The early chapters continue the investigation of the previously developed C6-C13 lynchpin cyclic diethyl alkenylsiloxane, accessed by controlled semi-hydrogenation of alkynylsiloxane (Scheme 1). Later chapters discuss the development of a novel strategy to access the more reactive cyclic dimethyl alkenylsiloxanes and their application towards the synthesis of incednam (Scheme 1).



Scheme 1

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Abbreviations

18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Å	Angstrom
Ac	Acetate
ACP	Acyl carrier protein
AIBN	Azobisisobutyronitrile
AT	Acyltransferase
b.p.	Boiling point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bt	Benzotriazole
Bz	Benzoyl
COD	1,5-Cyclooctadiene
CPF	(*R*)-3a-allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1.4-benzoquinone
DEIPS	Diethylisopropylsilyl
DH	Dehydratase
DIAD	Diisopropyl azodicarboxylate
DIBALH	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DIT	Diisopropyl tartrate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane

DMSO	dimethyl sulfoxide
DMT-MM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
dppf	Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
DTBP	Di-*tert*-butylphenol
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid
eq.	Equivalents
ESI	Electrospray ionisation
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Idn	Identified gene cluster
Imid.	Imidazole
IPA	Isopropyl alcohol
IR	Infrared
KR	Ketoreductase
KS	Ketosynthase
LDA	Lithium diisopropylamine
LN_2	Liquid nitrogen
MCPBA	*m*-Chloroperoxybenzoic acid
MS	Molecular sieves
NBS	*N*-bromosuccinimde
NIS	*N*-Iodosuccinimde

NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Phth	Phthalimide
pin	Pinacol
Piv	Pivaloyl
PKS	Polyketide synthase
PMB	*para*-Methoxybenzyl
PMPOH	*p*-Methoxyphenol
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
RBO	Ramberg-Bäcklund olefination
RCM	Ring closing metathesis
R_f	Retention factor
RT	Room temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TDMPP	Tris(2,6-dimethoxyphenyl)phosphine
TDP	Thymidine diphosphate
TDS	(2,3-Dimethylbutan-2-yl)dimethylsilyl
TE	Thiolesterase
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
TES	Triethylsilyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran

THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Troc	2,2,2-Trichloroethoxycarbonyl
UDP	Uridine diphosphate
w/v	Weight/volume
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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Chapter 1: Introduction

Incednine (**1**) is a bioactive polyketide natural product identified through a cell-based chemical genetic screening targeting the restoration of apoptosis in multidrug-resistant human small cell lung carcinoma Ms-1 cells overexpressing the anti-apoptotic oncoproteins Bcl-2 and Bcl-xL.[1] This bioactivity was exhibited when incednine was used in combination with anti-cancer agents such as adriamycin, cisplatin, camptothecin, inostamycin, taxol and vinblastine.

1.1 Isolation and structural elucidation of incednine

In the course of screening for novel Bcl-2/Bcl-xL inhibitors, Imoto *et al*. isolated a structurally and functionally unique compound from the *Streptomyces sp*. ML694-90F3 culture broth.[1] As a result of its ability to inhibit CED-9, a Bcl-2/Bcl-xL homologue found in the nematode *Caenorhabitis elegans*, it was named incednine.[2] Structurally, incednine was found to consist of a heavily deoxygenated amino disaccharide appended to a 24-membered polyene macrolactam (Figure 1.1).

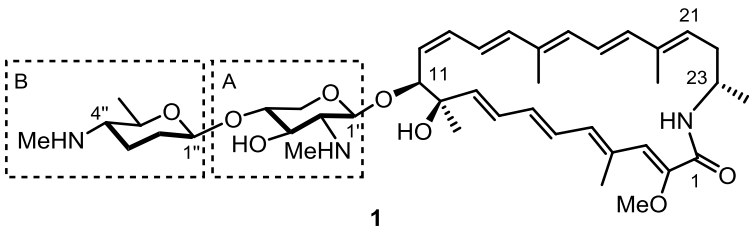


Figure 1.1: Incednine

Incednam (**2**), the aglycon of incednine, consists of two conjugated polyene systems: a C2-C9 tetraene containing a C2-C3 *Z*-enol ether and a C12-C21 pentaene containing a single C12-C13 *Z*-olefin in an otherwise all *E*-environment. The two polyene systems are separated by neighbouring quaternary C10 and secondary C11 hydroxyl-bearing stereocentres and a lactam containing an adjacent C23 stereocentre. The absolute stereochemistry of the C10 and C11 stereocentres was determined to be *R* and *S*,

respectively, by ^{1}H NMR spectroscopic analysis of the C11 Mosher ester derivative of incednam, and NOEs of the surrounding protons. The final stereogenic centre, C23, was concluded to be *S* by observed NOEs and *in silico* simulations. Thus, the three stereogenic centres of incednam were determined as *R*10, *S*11 and *S*23. The stereochemistry and structural elucidation of the two aminosugars was achieved by NMR analysis and X-ray crystallography of aminosugar B derivative obtained from glycoside methanolysis, which allowed assignment of the bridging aminosugar A and aminosugar B as 2-deoxy-2-methylamino-*β*-D-xylopyranose and *N*-monodemethyl-D-forosamine, respectively.

1.2 Bioactivity of incednine

Mitochondria play a central role in inducing apoptosis in cells by releasing caspase activating proteins, such as cytochrome c, along with other cell death mediators.[3–5] This process, known as mitochondrial outer membrane permeabilisation (MOMP), is controlled by proteins of the Bcl-2 family and is an important process in multicelled organisms to prevent the proliferation of malignantly transformed cells.[6–10] This family of proteins is grouped into three subfamilies based on the number of BH (Bcl-2 Homology) domains they share. These subfamilies consist of anti-apoptotic proteins (BH1-4), such as Bcl-2 and Bcl-xL, pro-apoptotic proteins (BH1-3), such as Bak and Bax, and BH3-only proteins, such as Bid and Bim.[11] In order for MOMP to occur two processes must take place. Firstly, all the members of the anti-apoptotic family must be inhibited by either pro-apoptotic and/or BH3-only proteins. Secondly, pro-apoptotic proteins Bak or Bax need to be activated by the BH3-only proteins.[12,13] Overexpression of anti-apoptotic proteins in cancer cells not only prevents MOMP by sequestering pro-apoptotic and BH3-only proteins, thus contributing to the overall cancer progression, but also renders them immune to chemotherapeutic drugs and radioactive

therapy.[14,15] Not surprisingly, most human cancers are found to overexpress Bcl-2, Bcl-xL, or both, and therefore targeted inhibition of these proteins has become an attractive strategy for novel therapeutic drug design.[16] The first of such inhibitors, HA14-1, was discovered by Wang *et al*. in 2000 by using an *in silico* screening strategy based on the predicted structure of the Bcl-2 protein (Figure 1.2).[17]

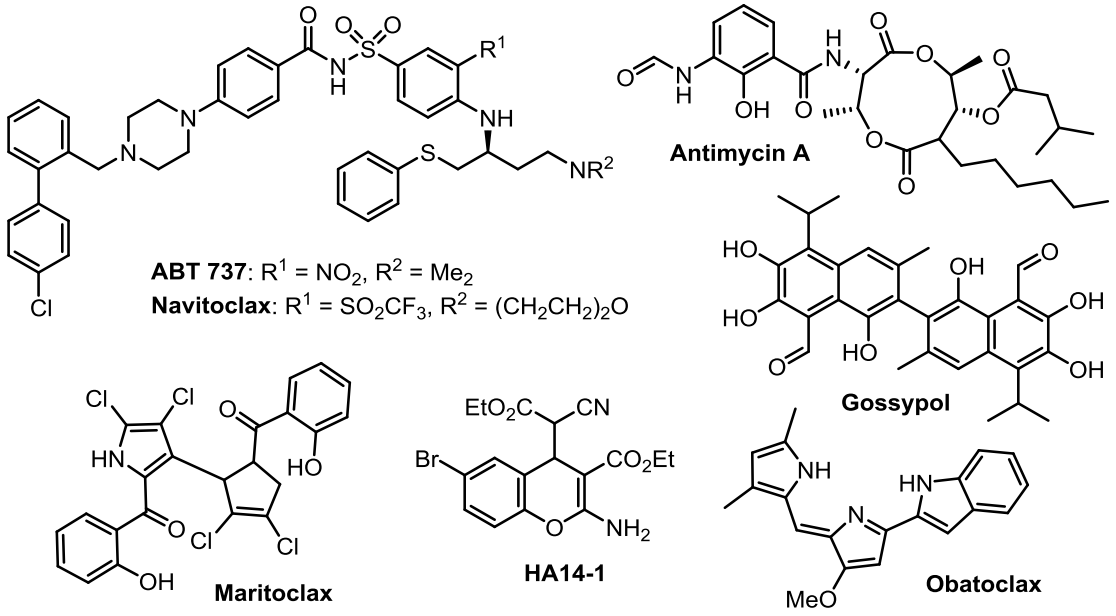


Figure 1.2 Pro-apoptotic inhibitors

HA14-1 was shown to effectively induce apoptosis of human acute myeloid leukaemia HL-60 cells overexpressing the Bcl-2 protein. Following this discovery, many pro-apoptotic inhibitors such as ABT-737, antimycin A, gossypol, maritoclax, navitoclax and obatoclax are currently in the preclinical and clinical phases of development.[18–23] Furthermore, ABT-737 and its orally active analogue navitoclax are among the most potent Bcl-2/Bcl-xL inhibitors to date.

Although incednine was able to overcome the anti-apoptotic function of Bcl-2 and Bcl-xL in overexpressed Ms-1 cells against various kinds of anti-cancer agents, it was found to do so without inhibiting the Bcl-2/Bcl-xL binding capacity. In addition, incednine did not reduce the expression levels of Bcl-xL of which antisense

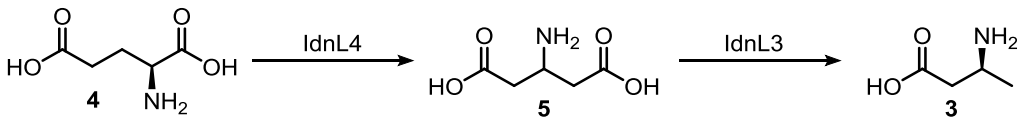
oligonucleotides target.[1,24] These results suggest that incednine inactivates the anti-apoptotic function of Bcl-2 and Bcl-xL by a different mode of action than other oncoprotein inhibitors and could therefore play an important role for the development of novel therapeutic drugs. To elucidate by which mechanism the anti-apoptotic function inhibition of incednine operates, Sakakibara *et al*. employed a combination of *in silico* screening and *in vitro* verification to predict the target protein of incednine.[25] Among the 182 proteins predicted to bind to incednine *in silico*, only three were found to bind incednine by *in vitro* biotinylated incednine pull-down experiments. Of those three, apoptosis was induced only when acetyl-CoA carboxylase-α (ACACA) was chemically inhibited or silenced by siRNA in Bcl-xL overexpressed Ms-1 cells when in combination with anti-tumour agents, suggesting that it might be a target of incednine. ACACA is a rate-limiting enzyme for the long-chain fatty acid synthesis, which is key to maintain the constant supply of lipids required for cancer cell proliferation.[26,27] Additionally, ACACA has been shown to be overexpressed in multiple types of human cancer.[28]

1.3 Biosynthesis of incednine

Polyketides represent a group of secondary metabolite natural products that display structurally diverse and unique features, and a range of biological activities. Many of these compounds have found their use as important pharmaceutical agents such as doxycycline, erythromycin, lovastatin and rapamycin.[29–32] Their biosynthetic pathway consists of multifunctional enzymes, known as the polyketide synthases (PKSs), which are organised into modules responsible for the sequential elongation of the polyketide intermediates. Each module consists of functionally specific domains which, collectively, represent one cycle of the two carbon elongation sequence. These domains include acyl carrier protein (ACP), ketosynthase (KS), ketoreductase (KR), dehydratase

(DH), acyltransferase (AT), and thiolesterase (TE) which governs the polyketide release by either hydrolysis or cyclisation.[33,34]

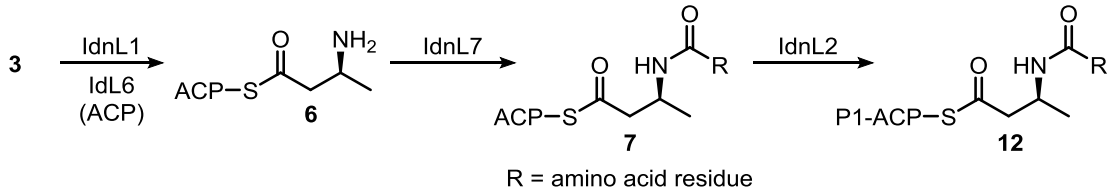
The biosynthetic pathway of incednine has been extensively investigated by Eguchi *et al.* Through both ^{13}C incorporation studies as well as recent isolation of the biosynthetic gene cluster from the *Streptomyces* producer strain, a plausible biosynthesis of incednine has been proposed.[35–37] Feeding experiments had suggested 3-aminobutyrate **3**, derived from L-glutamate (**4**) by an unknown process, as a unique amino acid starter unit of the incednine PKSs. From the biosynthetic gene cluster, two genes encoding for enzymes idnL3 and idnL4 showed homology to a family of aminotransferase genes and amino acid aminomutase genes, respectively.[38–40] While idnL4 was presumed to catalyse the L-glutamate-2,3-aminomutase rearrangement to **5**, an unprecedented β-glutamate decarboxylation catalysed by idnL3 was proposed to give the putative aminobutyrate **3** (Scheme 1.1). Further attestation by isolation of the presumed aminotransferase idnL3 followed by *in vivo* studies indeed showed the formation of (*S*)-3-aminobutyrate from L-glutamate. No other amino acid tested was converted by this novel substrate- and stereospecific β-glutamate-β-decarboxylase.



Scheme 1.1: Biosynthesis of (S)-3-aminobutyrate starter unit from L-glutamate

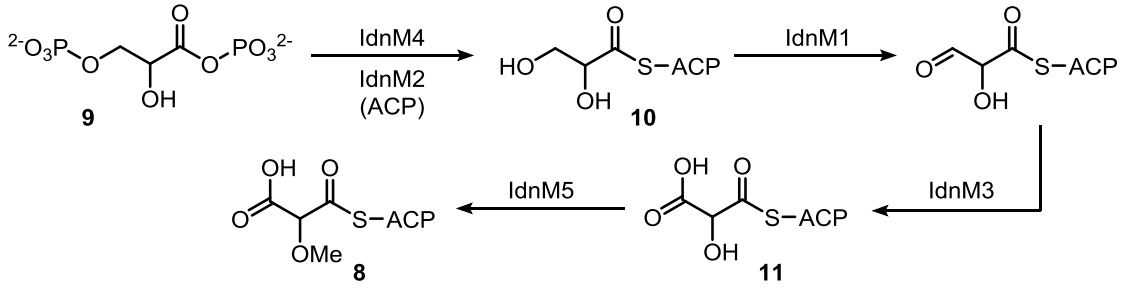
Four genes encoding for characteristic β-amino-acid-carrying enzymes were conserved in the incednine gene cluster (Scheme 1.2). IdnL1 ligase serves as an aminobutyrate **3** carrier onto ACP idnL6. Another ligase, idnL7, recognises amino acids and transfers them onto aminobutyryl-ACP **6** in a type of protecting group strategy that prevents untimely cyclisation in the incednine PKSs.[41] Finally idnL2, an acyltransferase, initiates

the PKSs by transferring the amino starter unit moiety **7**, appended to and recognised by idnL6, to the loading ACP domain.



Scheme 1.2: (S)-Aminobutyryl-ACP starter unit biosynthetic pathway

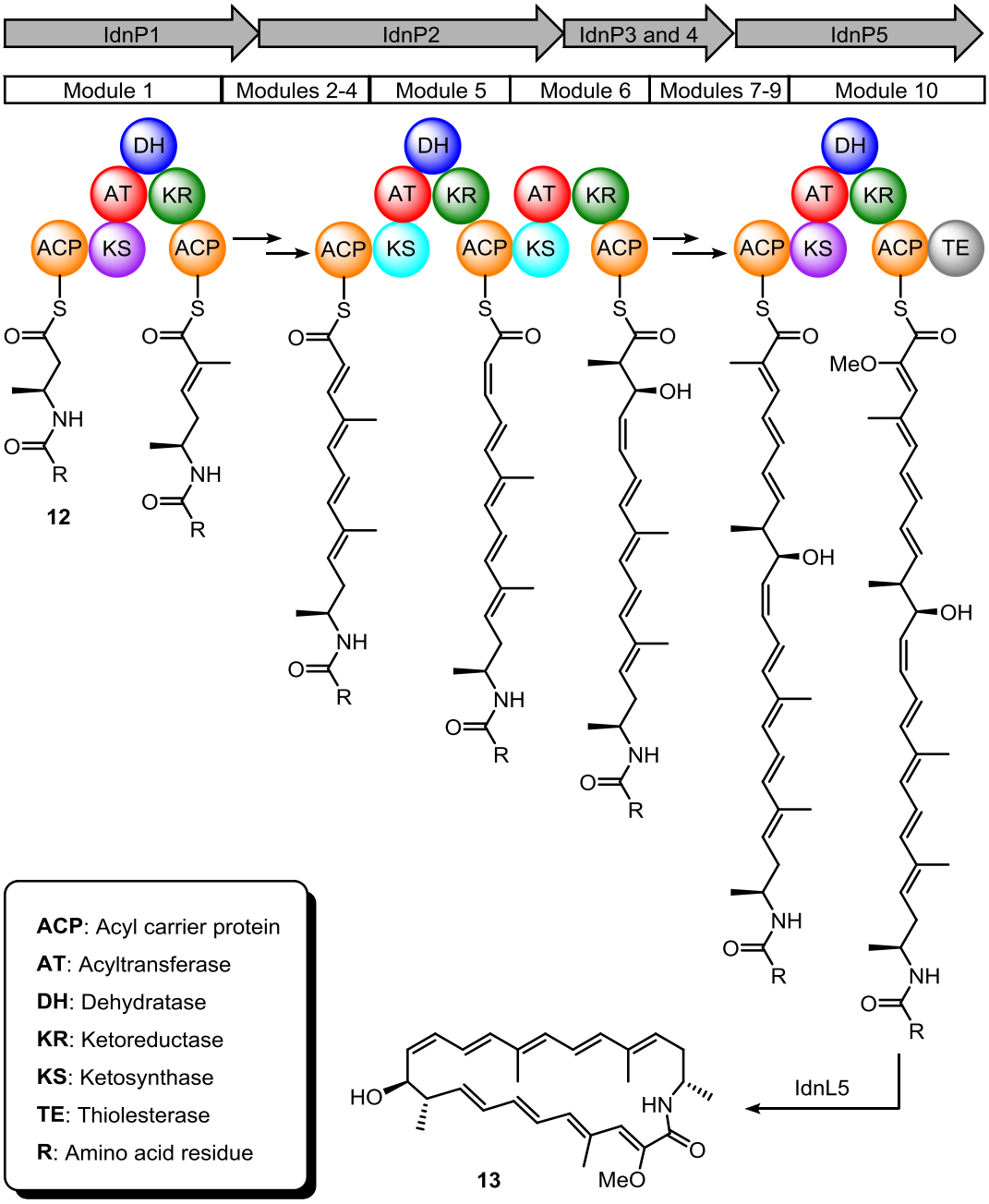
^{13}C incorporation experiments had suggested that the glycolate unit of incednine (C1 and C2) originates from glycerol. In support of this, five characteristic genes translating to enzymes directly involved in methoxymalonyl-ACP **8** formation from glycerol derived phosphoglycerate **9**, were found in the biosynthetic gene cluster (Scheme 1.3).[42] Thus, IdnM4 ligase serves as a phosphoglycerate **9** carrier onto ACP idnM2. The resulting glyceryl **10** is then oxidised by idnM1 and idnM3 to give the hydroxymalonyl **11**. Finally idnM5, an *O*-methyltransferase, affords the methoxymalonyl-ACP C1-C2 extender unit **8** of the incednine PKSs.



Scheme 1.3: Methoxymalonyl-ACP extender unit biosynthetic pathway

Genes encoding for five PKSs (IdnP1-P5) enzymes containing a total of 10 modules were found to be conserved in the incednine gene cluster. The numbers of modules correlate well to the five malonate, four methylmalonate and one methoxymalonate **8** extender unit condensation cycles from aminobutyryl **12** starter unit required for the macrolactam polyketide chain (Scheme 1.4). The PKS is terminated by TE followed by

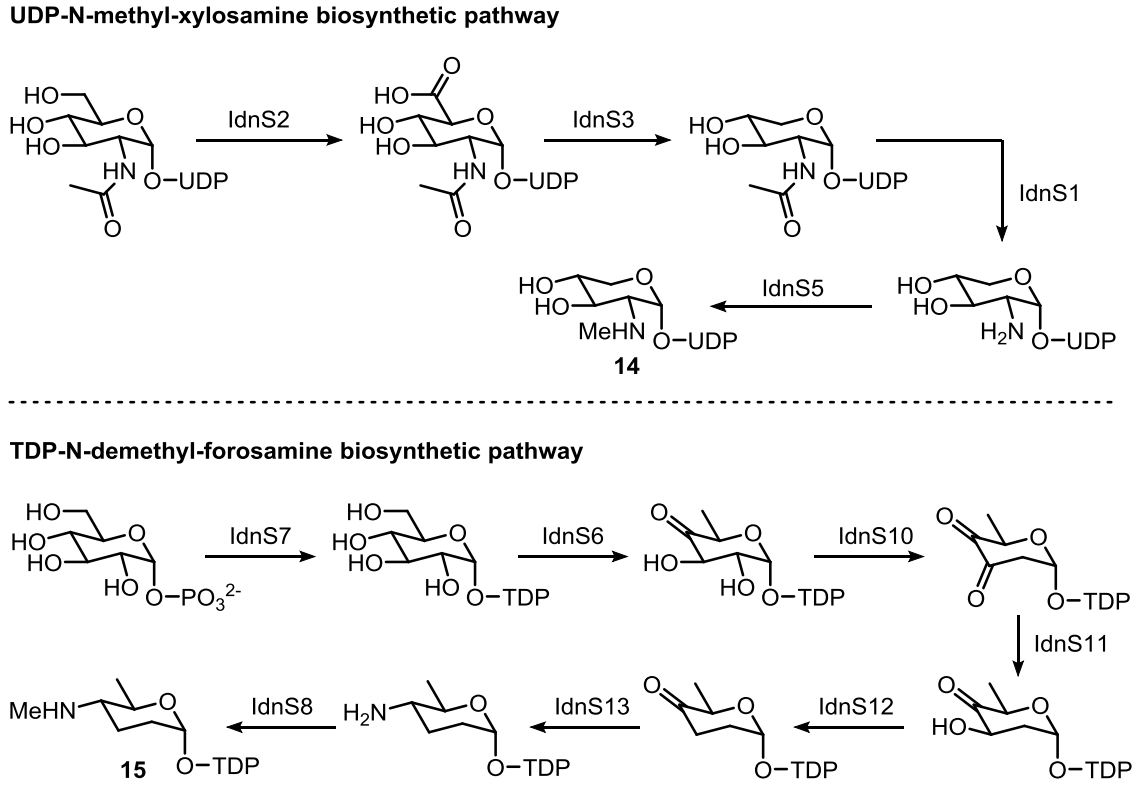
dipeptide amino acid residue cleavage by protease idnL5 resulting in cyclisation forming macrolactam **13**.



Scheme 1.4: Incednine polyketide synthases (PKSs)

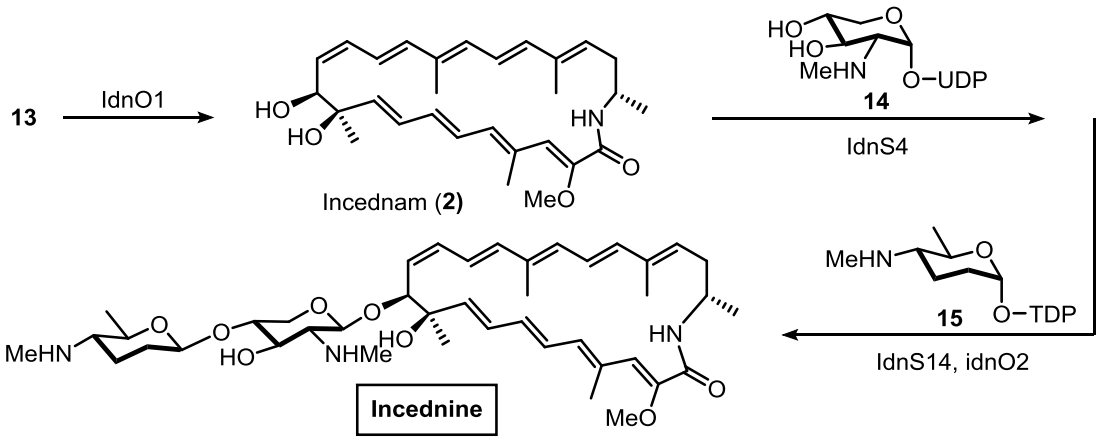
A total of 10 genes encoding for characteristic enzymes involved in the aminosugar biosynthetic pathway were identified in the incednine gene cluster. IdnS1, S2, S3 and S5 were predicted to be involved in the construction of the UDP appended aminosugar

A (**14**) while idnS6, S7, S8, S10, S11 and S12 were predicted to be involved in the synthesis of the TDP appended aminosugar B (**15**) (Scheme 1.5).



Scheme 1.5: UDP-aminosugar A and TDP-aminosugar B biosynthetic pathway

Four genes encoding for two glycosyltransferases, idnS4 and idnS14, along with two P450 type enzymes were thought to be involved in the post-PKS macrolactam **13** modifications (Scheme 1.6).



Scheme 1.6: Post-PKS modifications, the biosynthesis of incednine

While idnO1, an oxygenase, was predicted to catalyse the C11 oxidation of **13**, idnO2 lacked an active site and was presumed to act as an auxiliary protein for the idnS14 glycosyltransferase.

1.4 Previous synthesis of incednine

Although the total synthesis of incednine itself has yet to be accomplished, two syntheses of incednam were reported by Toshima *et al.* in 2010 and 2013.[43,44] In addition, two syntheses of the disaccharide unit were realised by the Toshima and Roush groups, in 2011 and 2013, respectively.[45,46]

1.4.1 Toshima's first synthesis of incednam

Toshima and co-workers first generation retrosynthetic approach recognised the C1-C13 tetraenoate **16** and the C14-C23 tetraenyl stannane **17** as key building blocks (Figure 1.3).

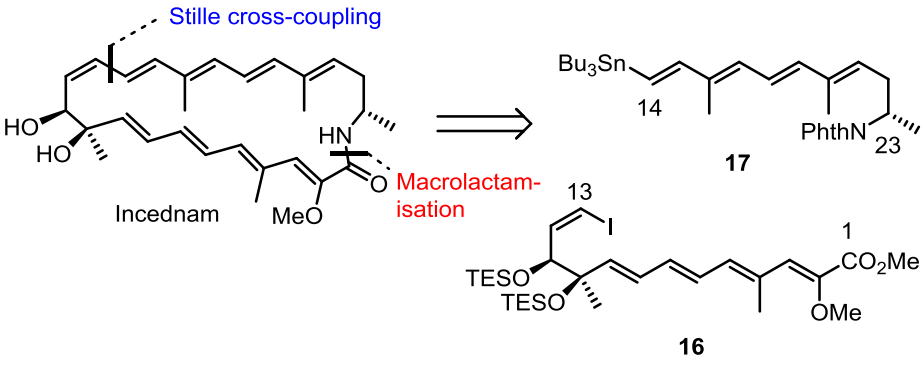
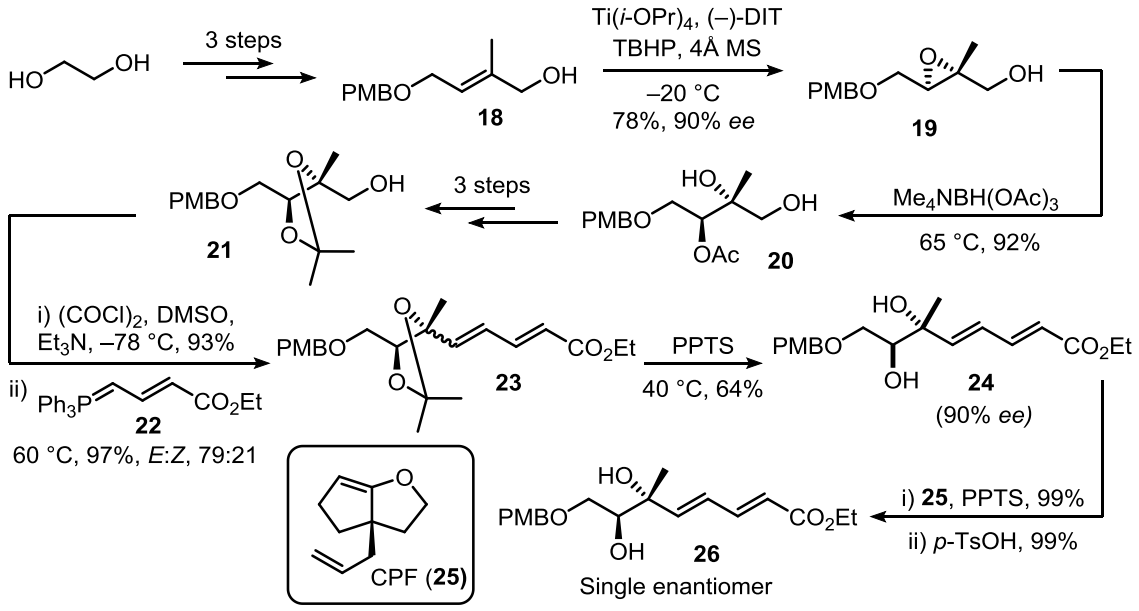


Figure 1.3: Toshima's first generation retrosynthetic approach

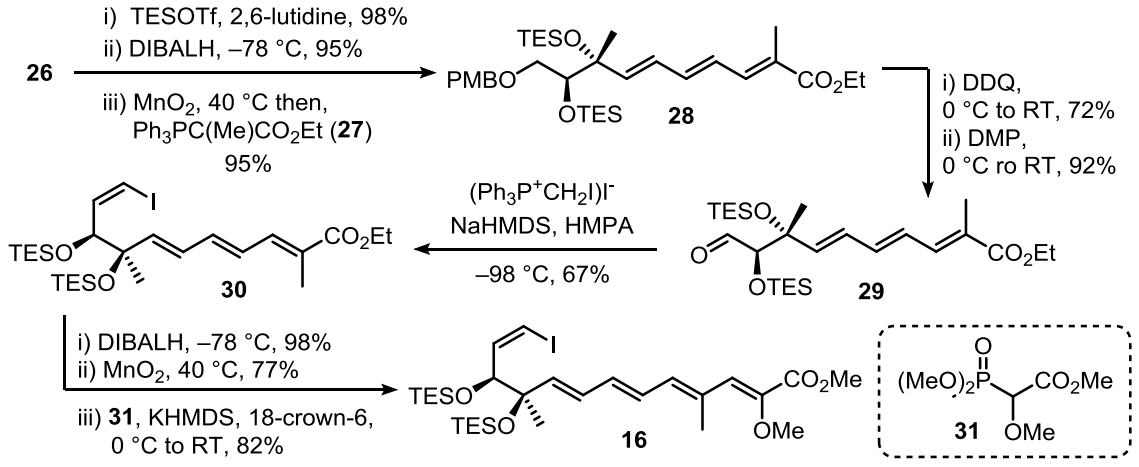
1.4.1.1 C1-C13 Tetraenoate fragment synthesis

The synthesis of the C1-C13 vinyl iodide **16** fragment is summarised in Scheme 1.7 and 1.8.[47] This sequence commenced from ethylene glycol affording allylic alcohol **18** in three steps (Scheme 1.7). The C10 and C11 stereocenters were introduced *via* Sharpless asymmetric epoxidation of **18**, affording epoxide **19** with 90% *ee*, followed by a regioselective ring-opening with $Me_4NBH(OAc)_3$ to give diol **20**.[48]



Scheme 1.7: Toshima's first generation C5-C12 fragment synthesis

Next, a series of protection-deprotection manipulations afforded alcohol **21** in three steps. This was followed by oxidation and subsequent Wittig olefination with extended phosphorane **22** to give dienoate **23** as a mixture of isomers (*E*:*Z*, 79:21), which could be separated after removal of the acetonide to give diol **24**. At this stage, enantiomeric enrichment of **24** was performed by optical resolution using chiral resolving reagent CPF (**25**) to give diol **26** as a single enantiomer in 93% yield after removal of CPF.[49,50] Re-protection of the resolved diol **26** followed by a reduction-oxidation-olefination sequence was carried out with phosphorane **27** to give trienoate **28** (Scheme 1.8).

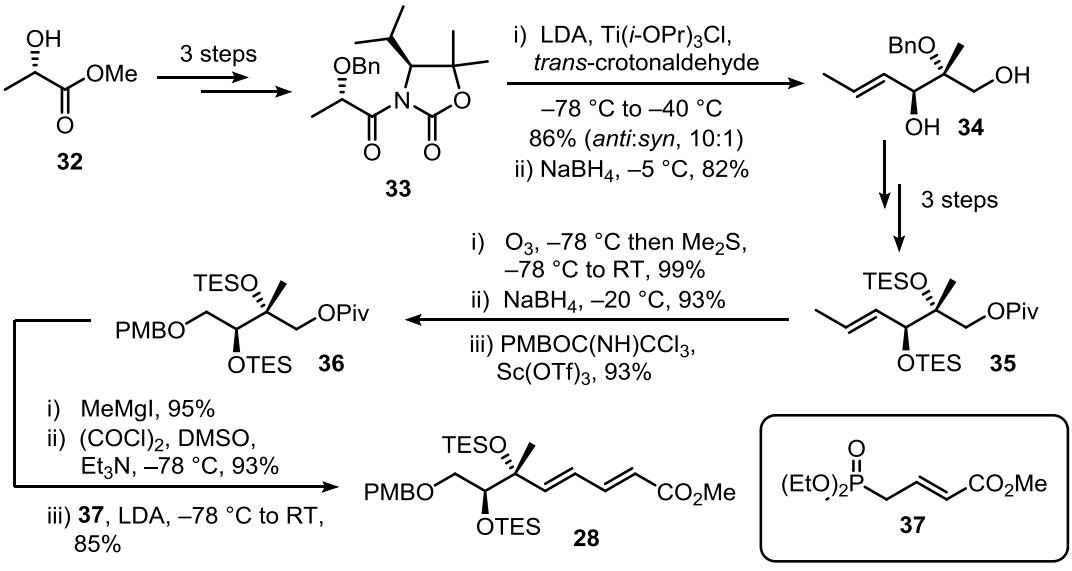


Scheme 1.8: Toshima's C1-C13 tetraenoate fragment synthesis

At this stage, the PMB protecting group was removed followed by oxidation of the resulting alcohol to give aldehyde **29** setting the stage for a Stork-Wittig olefination affording *Z*-vinyl iodide **30**. Finally, reduction-oxidation of trienoate **30** followed by a Horner-Wadsworth-Emmons (HWE) olefination of the resulting aldehyde with phosphonate **31** gave the C1-C13 pentaenoate **16** fragment in total of 23 linear steps with an overall yield of 6.9%.

1.4.1.2 Revised C1-C13 tetraenoate fragment synthesis

There are a number of drawbacks to Toshima and co-workers first reported C1-C13 **16** fragment synthesis, such as that only 5 of the 23 steps are skeletal bond-forming steps whereas the remaining steps involve refunctionalisations and protecting group manipulations. Furthermore, isomeric mixtures obtained from the Sharpless epoxidation necessitates optical resolution involving the stoichiometric use of chiral resolution agent CPF (**25**). To address these challenges Toshima *et al*. reported a second approach towards the C1-C13 **16** fragment, now relying on a diastereoselective Evans aldol addition to establish the C10 and C11 stereocentres and a HWE olefination to construct the C6-C9 diene (Scheme 1.9).[43]



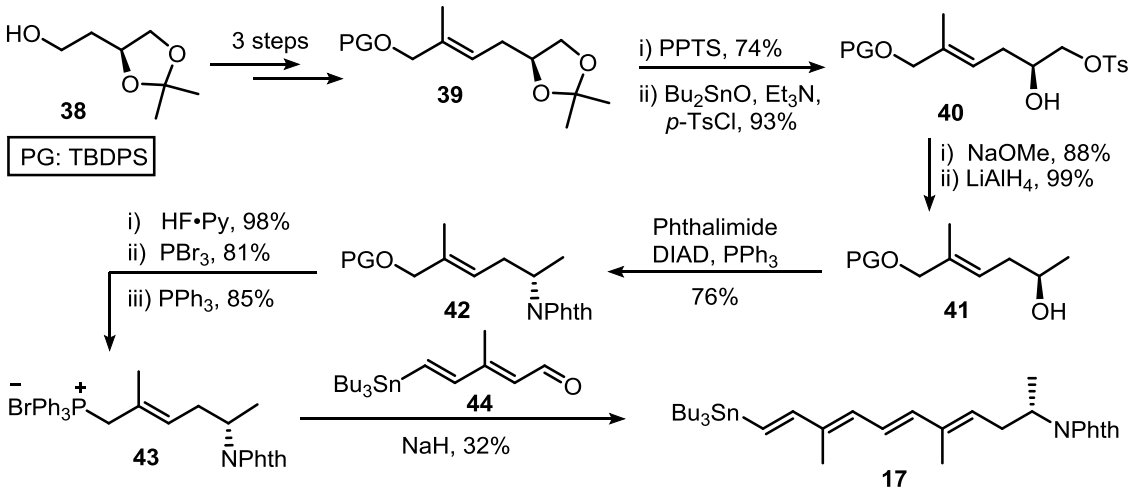
Scheme 1.9: Toshima's revised C5-C12 fragment synthesis

The synthesis commenced from methyl L-lactate (**32**) affording oxazolidinone derivative **33** in three steps, setting the stage for an auxiliary-controlled Evans aldol addition. The desired *anti* product was afforded with high diastereoselectivity (*dr* = 10:1) upon titanium-mediated addition with *trans*-crotonaldehyde using conditions developed by Kobayashi *et al*.[51,52] Reductive removal of the chiral auxiliary then gave diol **34**. Next, a series of protections to afford **35** was followed by ozonolysis, which upon reduction and subsequent protection gave fully protected **36**. At this stage, the pivaloyl group was removed followed by oxidation and subsequent HWE olefination with phosphonate **37** to give dienoate **28** (*E*:*Z*, >95:5), which converges with the previously established C1-C13 pentaenoate **16** fragment synthesis (Scheme 1.8). Thus, **16** was prepared in a total of 22 linear steps with an overall yield of 6.5%. Although both syntheses are of comparable length and overall yield, Toshima and co-workers second approach does manage to address several problems identified in their initial synthesis. However, it still suffers from the excessive use of refunctionalisation and protecting group manipulation.

1.4.1.3 C14-C23 Tetraenyl stannane fragment synthesis

Toshima and co-workers synthesis of the C14-C23 tetraenyl stannane **17** fragment commenced from commercially available alcohol **38** affording acetonide **39** in three steps (Scheme 1.10). Next, deprotection of the acetonide was followed by a regioselective tin-mediated tosylation of the resulting primary alcohol using conditions developed by Martinelli *et* al. to give **40**.[53] This set the stage for an intramolecular epoxidation and a subsequent regioselective ring-opening with $LiAlH_4$ to afford **41**. The secondary alcohol of **41** was converted to a phthalimide under Mitsunobu conditions to give protected amine **42**. Deprotection of the TBDPS ether of **42** followed by

bromination gave the corresponding allyl bromide, which upon treatment with triphenylphosphine afforded the phosphonium salt **43**.



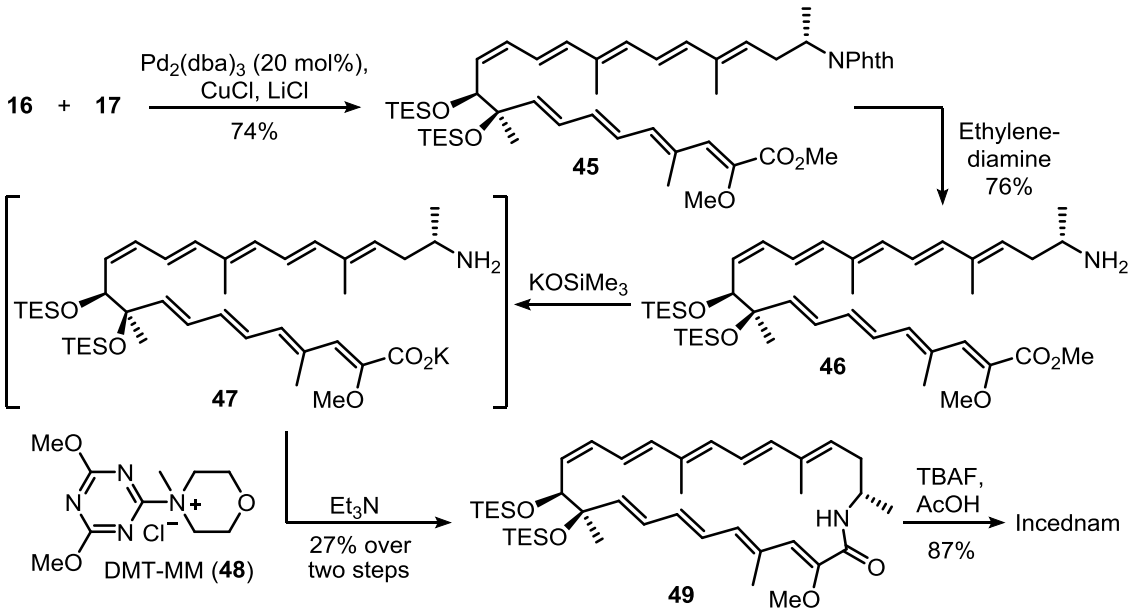
Scheme 1.10: Toshima's C14-C23 tetraenyl stannane fragment synthesis

Finally, Wittig olefination of aldehyde **44**, prepared from ethyl 2-butynoate in 5 steps, with phosphonium salt **43** afforded the C14-C23 tetraenyl stannane **17** fragment in 12 linear steps as the longest linear sequence with an overall yield of 8.9%.[54] Due to its instability towards oxidation and/or photochemical decomposition, **17** had to be used immediately after isolation.

1.4.1.4 Assembly of incednam

Completion of the incednine aglycon is summarised in Scheme 1.11. The Stille cross-coupling of vinyl iodide **16** and tetraenyl stannane **17** to give **45** was accomplished using conditions developed by Corey *et al*. using palladium catalysis in conjunction with LiCl and CuCl as accelerants.[55] At this stage, the phthalimide deprotection revealed the free amine **46** and ester hydrolysis provided the requisite carboxylate **47**. The challenging macrocyclisation, using DMT-MM (**48**) as the activating agent, provided TES-protected macrolactam **49**, albeit in poor yield.[56] Finally, global TES-deprotection of **49** afforded incednam in a total of 27 steps as the

longest linear sequence. Furthermore, the putative *S*23 stereochemical configuration was found to be in support with that previously predicted.[1]



Scheme 1.11: Toshima's first generation assembly of incednam

1.4.2 Toshima second generation synthesis of incednam

A second synthesis of incednam was reported by Toshima *et al*. in 2013.[44] As before, the retrosynthetic analysis recognises disconnection at the amide and C13-C14 bond. However, Toshima and co-workers now envisaged macrocyclisation by olefin metathesis at the C18-C19 bond, which would avoid the use of the unstable tetraenyl stannane **17** previously deployed. As outlined in Figure 1.4, the retrosynthetic analysis identifies C1-C13 vinyl iodide **16**, C14-C18 trienyl stannane **50** and C19-C23 diene **51** as the key building blocks.

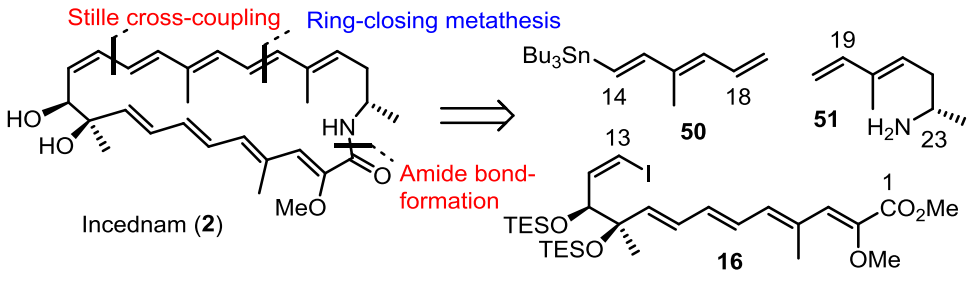
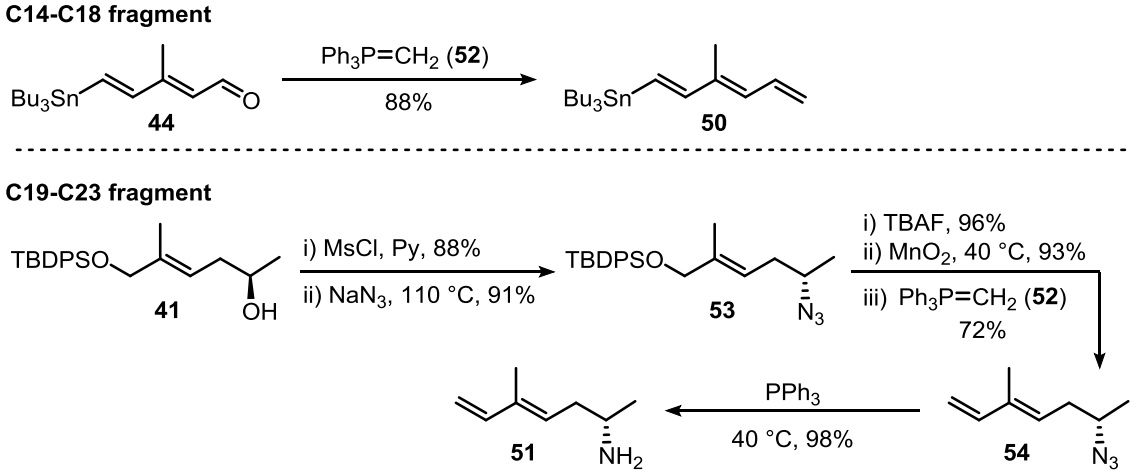


Figure 1.4: Toshima's revised second retrosynthetic approach

1.4.2.1 Synthesis of the C14-C18 and C19-C23 fragments

The synthesis of the C14-C18 trienyl stannane **50** fragment was accomplished by a Wittig olefination of aldehyde **44** (employed in the previous route) with phosphorane **52**, in a total of 6 linear steps (Scheme 1.10 and 1.12).

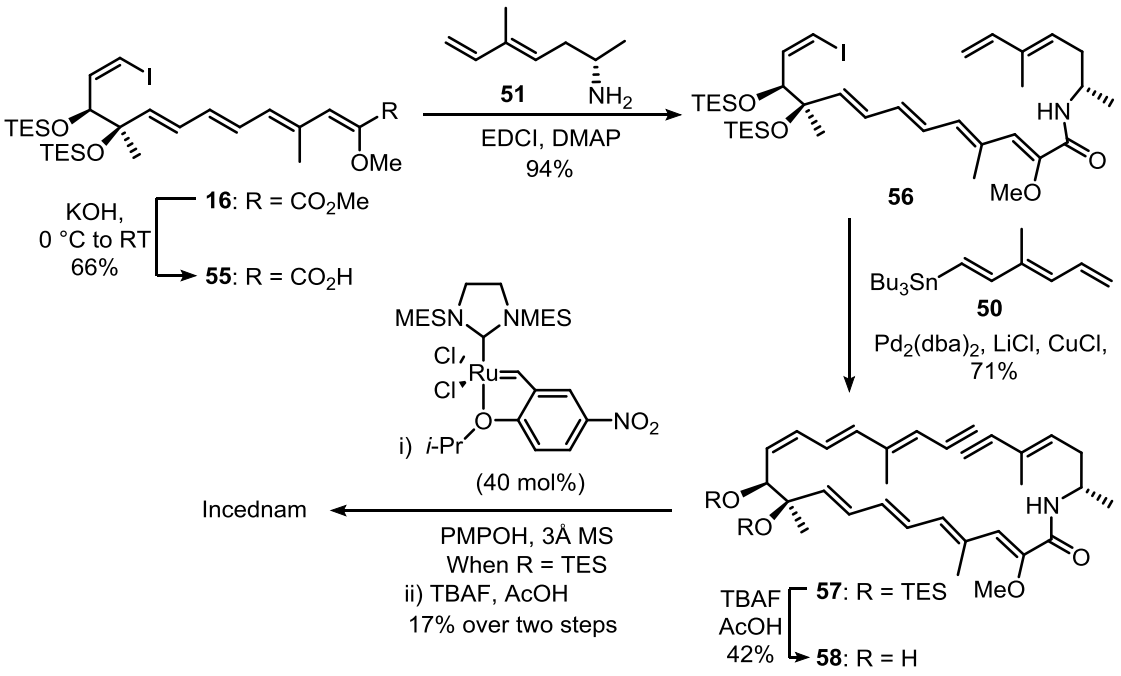


Scheme 1.12: Syntheses of the C14-C18 trienyl stannane and C19-C23 diene fragments

The C19-C23 diene **51** fragment synthesis commenced from allylic alcohol **41**, also an intermediate in the previously established route. Mesylation of the secondary alcohol followed by nucleophilic substitution by azide gave **53**. Silyl ether deprotection of **53** was followed by oxidation and subsequent Wittig olefination with phosphorane **52** to afford diene **54**. Finally a Staudinger reaction converted the azide group of **54** to the C19-C23 diene **51** fragment in a total of 13 linear steps with an overall yield of 30%.

1.4.2.2 Assembly of incednam

The incednine aglycon was accomplished as follows and is summarised in Scheme 1.13. Ester hydrolysis of pentaenoate **16** gave the requisite pentaenoic acid **55** for the subsequent amidation with **51** to give amide **56** using EDCI as the activating agent.



Scheme 1.13: Toshima's second assembly of incednam

Next, the previously established Stille cross-coupling of **56** and trienyl stannane **50** gave **57**. At this stage the TES groups were removed to give diol **58** but ring-closing metathesis, after rigorous screening of catalysts, proved unsuccessful on such a substrate. However, macrocyclisation was accomplished with TES-protected **57** under conditions employing the Grela catalyst, which after global deprotection gave incednam, although in low yield. This low yielding ring-closing metathesis of TES-protected **57** may be suggestive of inhibitory effects by the sterically encumbering TES groups, preventing the acyclic precursor from adopting a favourable conformation required for the macrocyclisation.[57] Overall, the revised synthesis of incednam was completed in total of 26 steps as the longest linear sequence with an overall yield of 0.5%.

1.4.3 Conclusion

Toshima and co-workers reported the first total synthesis of incednam, the aglycon of incednine. The synthesis consisted of 27 steps as the longest linear sequence and an

overall yield of 0.9% featuring a convergent assembly of the macrolactam *via* Stille cross-coupling and macrolactamisation as key steps. In order to avoid the use of unstable tetraenyl stannane **17** as well as to circumvent the disappointing macrolactamisation step, Toshima and co-workers reported a revised total synthesis of incednam featuring macrocyclisation *via* C18-C19 ring-closing olefin metathesis. The synthesis consisted of 26 steps as the longest linear sequence affording incednam in an overall yield of 0.5%. Again, unsatisfactory results were obtained in the macrocyclisation step, perhaps suggesting that the presence of bulky TES groups prevents the acyclic precursor from adopting a favourable conformational pre-organisation.[57] Although Toshima and co-workers addressed several problems identified in their initial synthesis of the C1-C13 tetraenoate **16** fragment, it still suffers from the excessive use of refunctionalisation and protecting group manipulation. Furthermore, both strategies rely on the use of highly toxic Stille cross-coupling for the construction of the C13-C14 bond.

1.4.4 Disaccharide synthesis

Two syntheses of the incednine disaccharide unit have been reported by the Toshima and Roush groups, in 2011 and 2013, respectively.[45,46] Both strategies envisaged construction of the disaccharide unit *via* stereoselective β-glycosylation between forosamine glycosyl donor and xylosamine acceptor (Figure 1.5). Toshima relies on a remote C4 participation-assisted glycosylation *via* a boat oxocarbenium intermediate **59**, which results in blocking the α-face of the donor. Roush, however, depends on a temporary C2 neighbouring group assisted glycosylation *via* a bicyclic acyloxonium intermediate **60**, again directing the nucleophilic attack to the β-face of the donor.

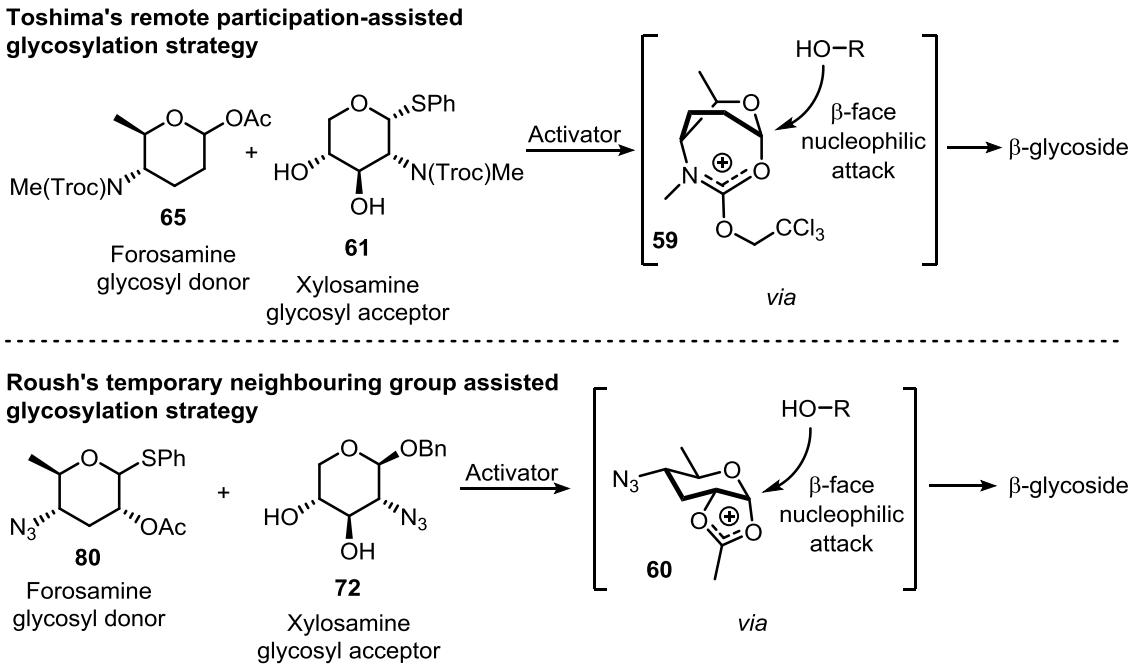
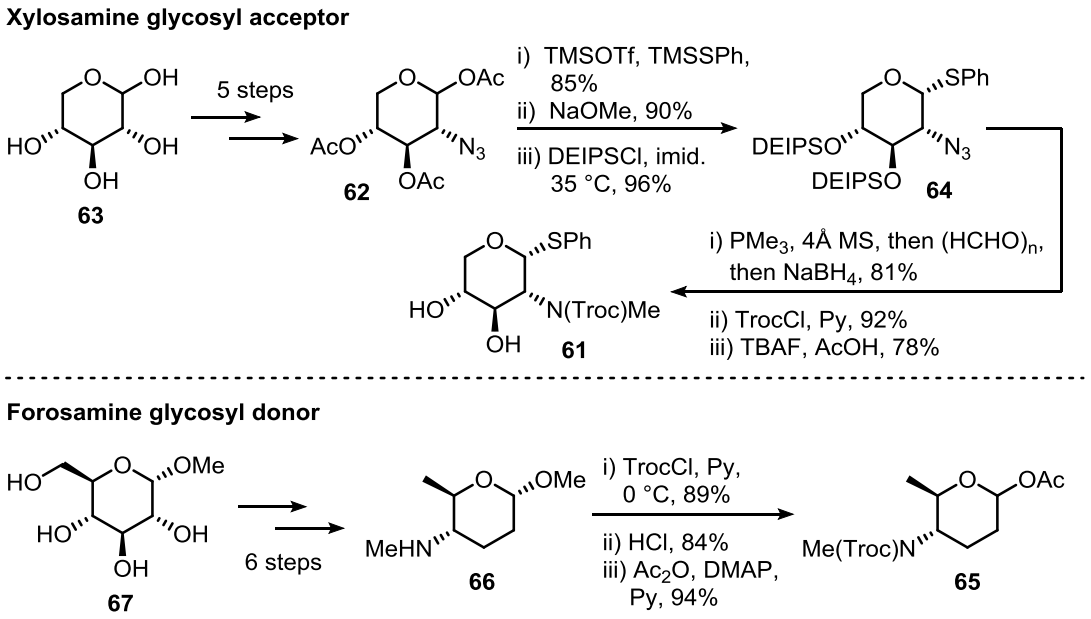


Figure 1.5: Toshima's and Roush's β-glycosylation strategies

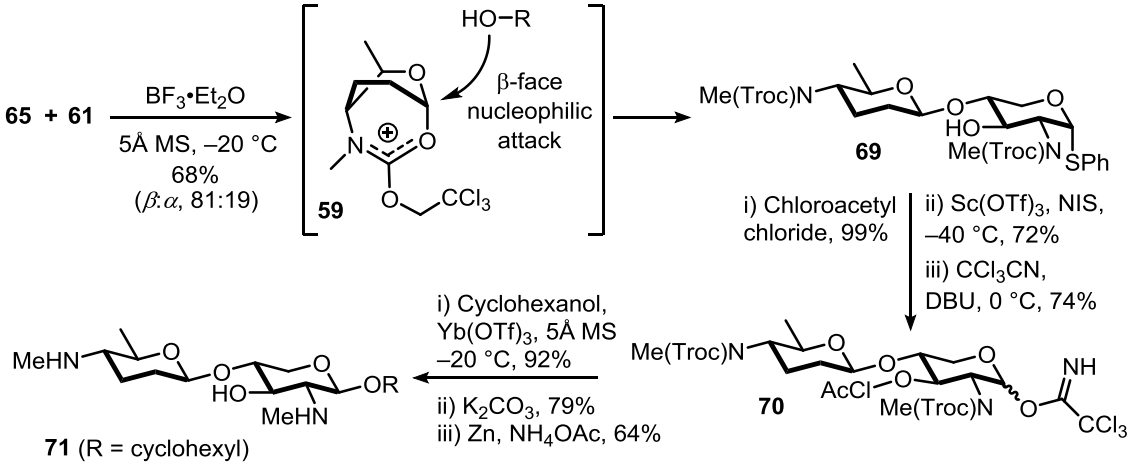
1.4.4.1 Toshima's disaccharide synthesis

The synthesis of xylosamine glycosyl acceptor **61** commenced from known glycoside **62**, which was prepared in 5 steps from D-xylose (**63**) according to literature procedures by Hashimoto *et al*. (Scheme 1.14).[58] Thiolation followed by protecting group switch gave thioglycoside **64**. Next, the azide of **64** was converted to *N*-methylamine followed by *N*-Troc protection and subsequent deprotection of the DEIPS groups to give glycosyl acceptor **61**. The synthesis of forosamine glycosyl donor **65** originated from known methyl-glycoside **66**, which was prepared in 6 steps from α-D-glucopyranoside (**67**) according to literature procedures by Baer *et al*.[59] The *N*-methylamino group of **66** was Troc-protected, followed by acetal hydrolysis and subsequent acetylation of the lactol to give glycosyl donor **65** (Scheme 1.14).



Scheme 1.14: Toshima's synthesis of the glycosyl acceptor and the glycosyl donor

Completion of the disaccharide fragment **70** of incednine is summarised in Scheme 1.15. It was anticipated that β-selective glycosylation of glycosyl acceptor **61** and donor **65** would arise from remote *N*-Troc neighbouring group assistance by forming a boat-like oxocarbenium intermediate **59** that would block the α-face of the glycosyl donor. After extensive screening of conditions it was found that the best results were obtained using $BF_3{\cdot}Et_2O$ as the activator at −20 °C, which provided the disaccharide **69** in high yield and with good β-stereoselectivity (*β*:*α*, 81:19).



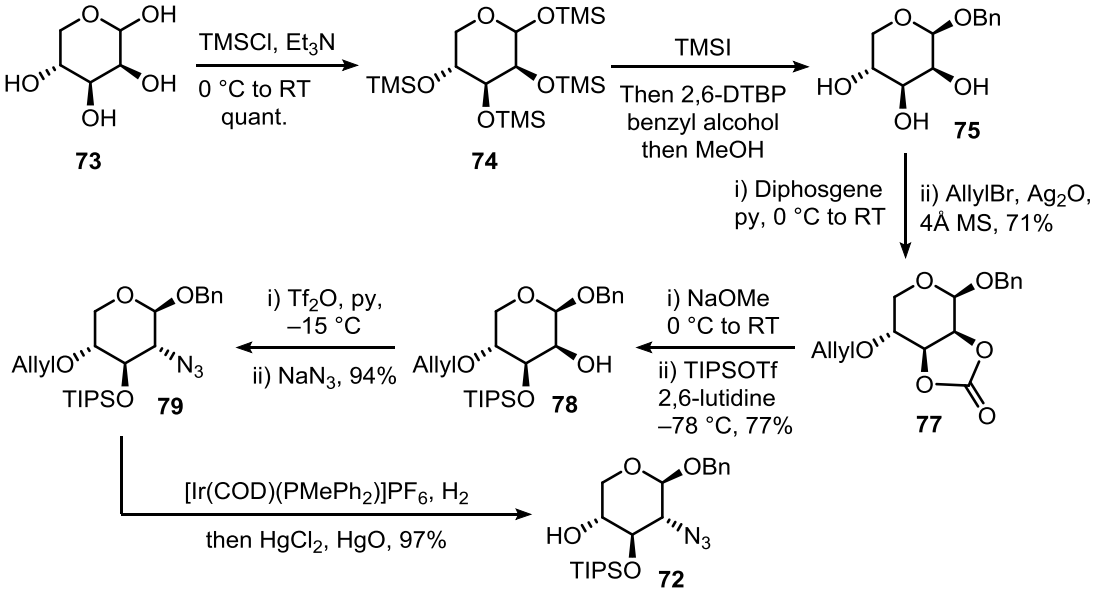
Scheme 1.15: Toshima's synthesis of the disaccharide unit

Next, the C3 alcohol of **69** was protected followed by hydrolysis of the thiophenyl

group and subsequent trichloroacetimidate formation of the resulting lactol to give the key disaccharide donor **70**. Finally, the glycosylation of **70** with cyclohexanol, as a model aglycon, was demonstrated. β-Glycoside **71**, through *N*-Troc neighbouring group participation, and subsequent chloroacetyl and *N*-Troc deprotection, afforded the fully constructed disaccharide fragment of incednine.

1.4.4.2 Roush's disaccharide synthesis

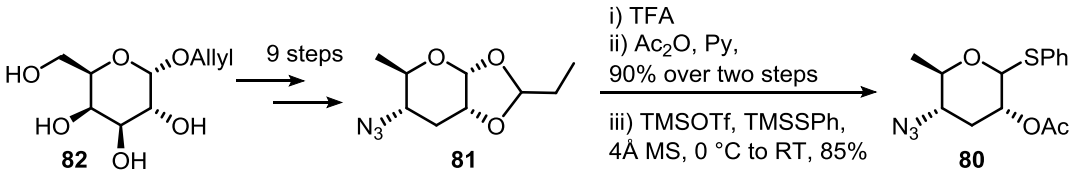
The synthesis of xylosamine glycosyl acceptor **72** commenced with TMS protection of D-lyxose (**73**) affording **74** (Scheme 1.16). Treatment of **74** with TMSI followed by trapping of the *in situ* generated glycopyranosyl iodide with benzyl alcohol and subsequent methanolic removal of the TMS protecting groups gave benzyl glycoside **75** as a single anomer after purification. Next, selective *cis* 2,3-diol protection followed by 4-*O*-allylation provided **77**. Removal of the carbonate protecting group and selective equatorial 3-*O*-silylation gave alcohol **78**, which upon triflation and nucleophilic azide substitution provided **79**, with stereochemical inversion.



Scheme 1.16: Roush's synthesis of the xylosamine glycosyl acceptor

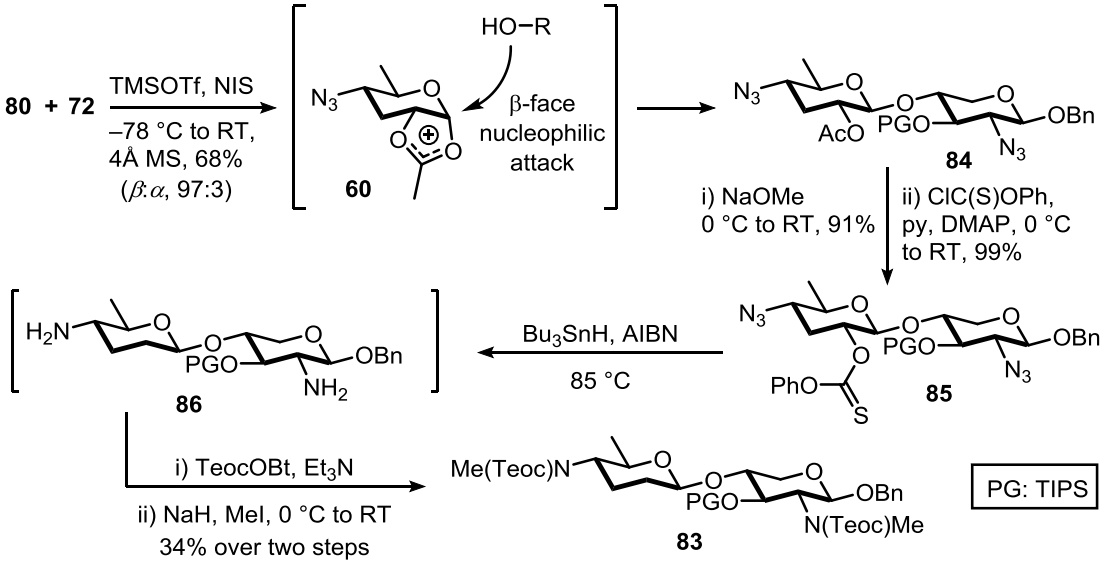
Finally, removal of the allyl group of **79** proved to be challenging but was accomplished

by a two-step deallylation protocol. First, iridium catalysed allyl ether isomerisation provided the corresponding propenyl ether, which upon mercury mediated hydrolysis gave glycosyl acceptor **72**. The synthesis of forosamine glycosyl donor **80** originated from known azido glycoside **81**, which was prepared in 9 steps from allyl-α-D-galactopyranoside (**82**) according to literature procedure by Brasche *et al.* (Scheme 1.17).[60] Removal of the acetal protecting group followed by acetate protections of the resulting lactol and subsequent thiolation gave thioglycosyl donor **80**.



Scheme 1.17: Roush's synthesis of the forosamine glycosyl donor

The synthesis of the fully protected disaccharide unit **83** of incednine commenced with C-2 neighbouring group assisted glycosylation of glycosyl donor **80** with acceptor **72** providing disaccharide **84** with excellent stereoselectivity (*β*:*α*, 97:3) (Scheme 1.18).



Scheme 1.18: Roush's synthesis of the disaccharide unit

Having served its purpose, the deoxygenative removal of the C-2' acetate group of **84** was accomplished by a three step procedure. First, ester hydrolysis of **84** provided the

corresponding alcohol which was converted to thiocarbonyl derivative **85**. Upon treatment with excess Bu_3SnH, both the thiocarbonate and azide functionalities were reduced, providing diamine **86**. Finally, *N*-Teoc protections followed by subsequent bis-*N*-methylation furnished the fully protected disaccharide **83** unit of incednine.

In summary, Toshima and co-workers reported the first synthesis of the disaccharide unit **70** of incednine. The synthesis consisted of 18 steps as the longest linear sequence and featured a remote neighbouring group assisted glycosylation to form the key β-glycosidic bond. Additionally, construction of the full disaccharide unit **71** of incednine was demonstrated using cyclohexanol as a model aglycon. Complementary to Toshima, Roush and co-workers reported a synthesis of fully protected disaccharide **83** unit. The synthesis consisted of 18 steps as the longest linear sequence with an overall yield of 4.7% where the key β-glycosidic bond was effectively constructed *via* neighbouring group assisted participation of the C-2' acetate group.

1.5 Previous work within the group

Polyketide natural products, especially those containing a *Z*-allylic or homoallylic polyene systems such as heronamides, leukotrienes and resolvins have been of much interest in the Anderson group.[61–63] As such, work towards incednam, the aglycon of incedenine, was commenced by Diane Lim, and is reported in her DPhil thesis in 2013.[64] A modular assembly was envisaged *via* C6-C13 cyclic alkenylsiloxane lynchpin **87** to simultaneously incorporate both hydroxyl-bearing stereocenters and stereospecifically construct the C12-C13 *cis*-pentaene system (Figure 1.5). Furthermore, the use of silicon-based Hiyama cross-coupling reaction would avoid the use of highly toxic organotin reagents employed in Toshima syntheses of incednam. The remaining fragments were identified as C1-C5 dienoate **88** and C14-C23 tetraenyl iodide **89**.

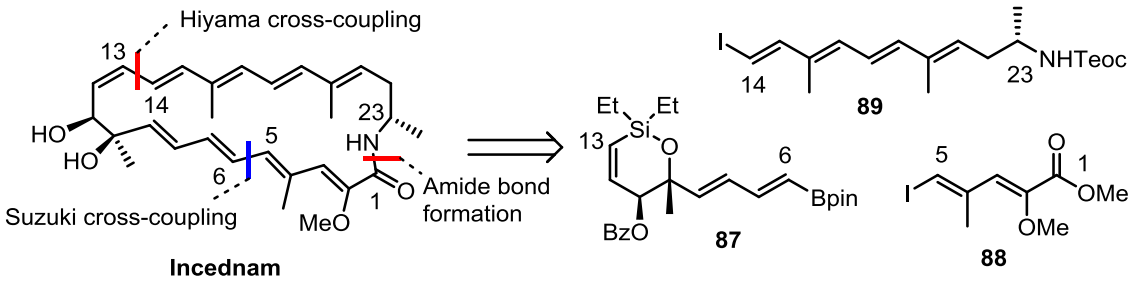
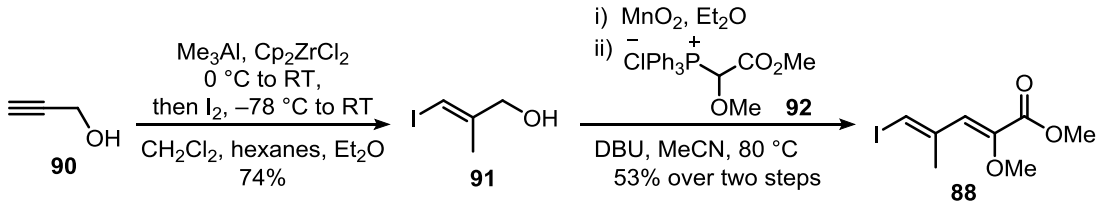


Figure 1.5: Lim's retrosynthetic approach

1.5.1 Lim's C1-C5 dienoate fragment synthesis

The synthesis of the C1-C5 dienoate **87** fragment commenced with a regioselective zirconium-catalysed methylalumination-iodination of propargyl alcohol (**90)** to give vinyl iodide **91** (Scheme 1.19).[65,66] This was followed by a MnO_2 mediated allylic oxidation of **91** and subsequent Wittig olefination of the resulting aldehyde with α-methoxyphosphonium salt **92** to afford the C1-C5 dienoate fragment **88** in a total of 3 linear steps with an overall yield of 39%.[67]

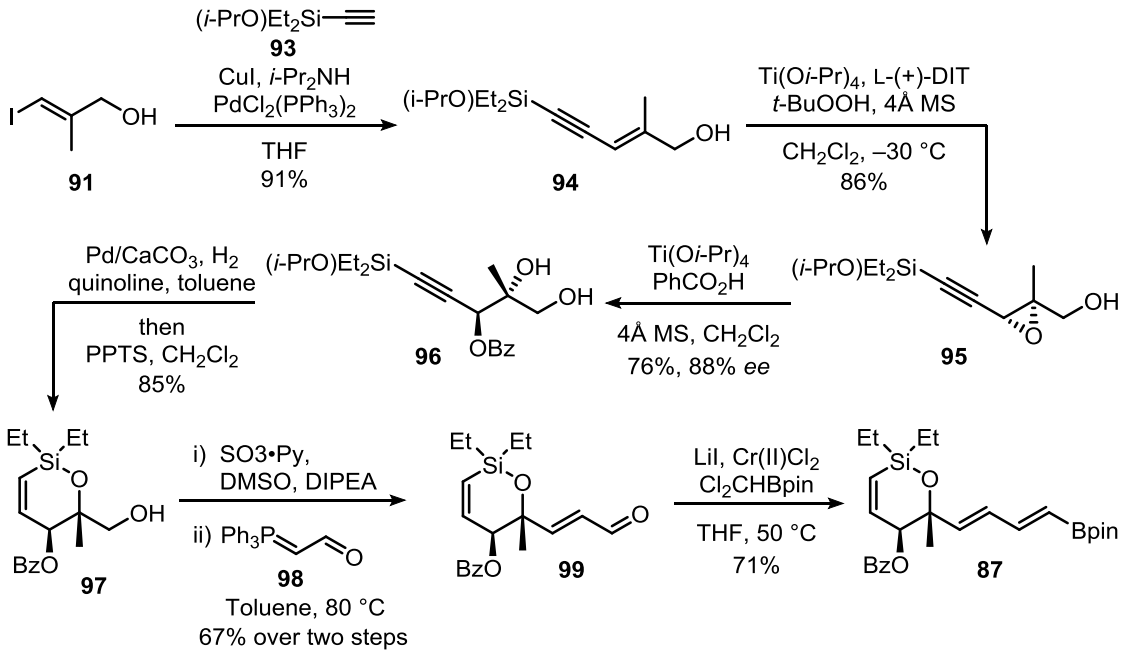


Scheme 1.19: Lim's C1-C5 dienoate fragment synthesis

1.5.2 Lim's C6-C13 cyclic alkenylsiloxane fragment synthesis

The synthesis of the C6-C13 cyclic alkenylsiloxane **87** fragment commenced from common intermediate vinyl iodide **91** and is summarised in Scheme 1.20. This was followed by Sonogashira coupling of **91** with alkynyl isopropoxysilane **93** providing enyne **94**, which upon asymmetric epoxidation under the Sharpless conditions afforded propargylic epoxide **95**.[68,69] Next, titanium-mediated regioselective ring-opening of 2,3-epoxy alcohol **95** with benzoic acid afforded benzoylated triol **96**.[70] At this stage the enantiomeric excess was determined to be 89%. Isolation of **96** proved difficult, due to

the sensitive nature of the alkynyl siloxane motif towards workup conditions typically associated with titanium. However, silanol formation could be limited to trace amounts by the use of a (wet) acetone workup, allowing the reaction to be performed at up to 1 mmol scale.



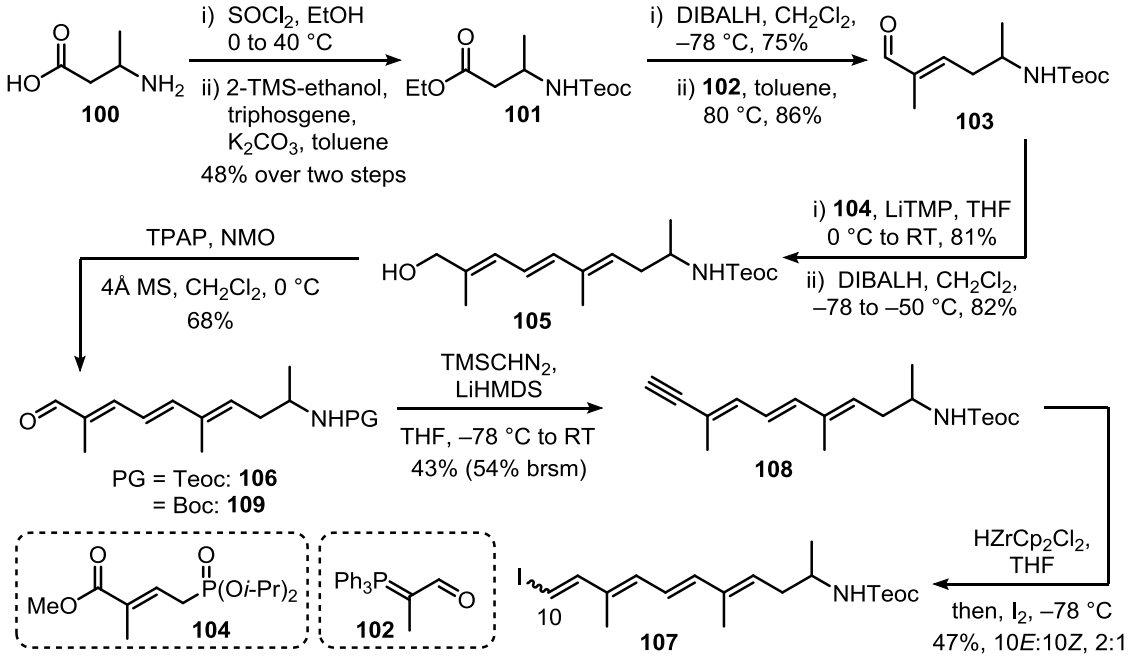
Scheme 1.20: Lim's C6-C13 cyclic alkenylsiloxane fragment synthesis

Next, 6-membered cyclic siloxane **97** was afforded *via* stereoselective controlled semi-hydrogenation of alkynylsilane **96** followed by cyclisation under mildly acidic conditions. This novel strategy for the construction of such motifs represents the key step of the synthesis and will be further discussed in the following chapter. Parikh-Doering oxidation of **97** followed by subsequent Wittig olefination of the resulting aldehyde with phosphorane **98** gave α,β-unsaturated aldehyde **99**. Finally, Takai borylation afforded the C6-C13 cyclic alkenylsiloxane fragment **87** in a total of 8 steps from propargyl alcohol (**90**), as the longest linear sequence with an overall yield of 18%.

1.5.3 Lim's C14-C23 tetraenyl halide fragment synthesis

The racemic synthesis of the C14-C23 tetraenyl iodide **89** fragment commenced with

esterification of 3-aminobutyric acid (**100**) followed by *N*-Teoc protection to give ethyl ester **101** (Scheme 1.21).

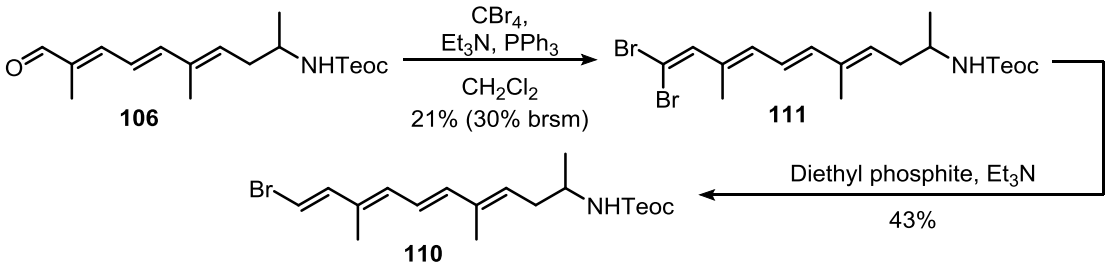


Scheme 1.21: Lim's C14-C23 tetraenyl iodide fragment synthesis

Next, reduction of **101** and subsequent Wittig olefination of the resulting aldehyde with phosphorane **102** gave α,β-unsaturated aldehyde **103**. This was followed by a HWE olefination with extended phosphonate **104** and subsequent reduction of the resulting trienoate gave trienol **105**, which upon oxidation under the Ley-Griffith conditions provided trienal **106**. The C14-C23 tetraenyl iodide fragment **107** was prepared in two steps from **106**. First, Colvin rearrangement gave trienyne **108** which upon hydrozirconation followed by iodine quench, afforded tetraenyl iodide **107** in a total of 9 linear steps with an overall yield of 3.8%, albeit as a 10*E*:10*Z* isomeric mixture (2:1). Similar isomeric mixtures were obtained from Takai olefination of *N*-Boc protected trienal analogue **109**.

In light of these difficulties, tetraenyl bromide **110** was prepared in two steps from trienal **106** (Scheme 1.22). First, Ramirez olefination gave tetraenyl dibromide **111** which upon stereoselective *cis*-monodebromination, using conditions developed by

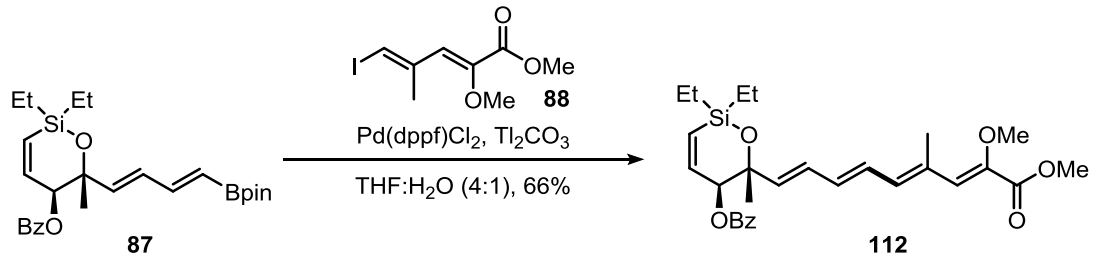
Hirao *et al*., afforded the C14-C23 tetraenyl bromide, as a single geometrical isomer.[71,72]



Scheme 1.22: Lim's C14-C23 tetraenyl bromide fragment synthesis

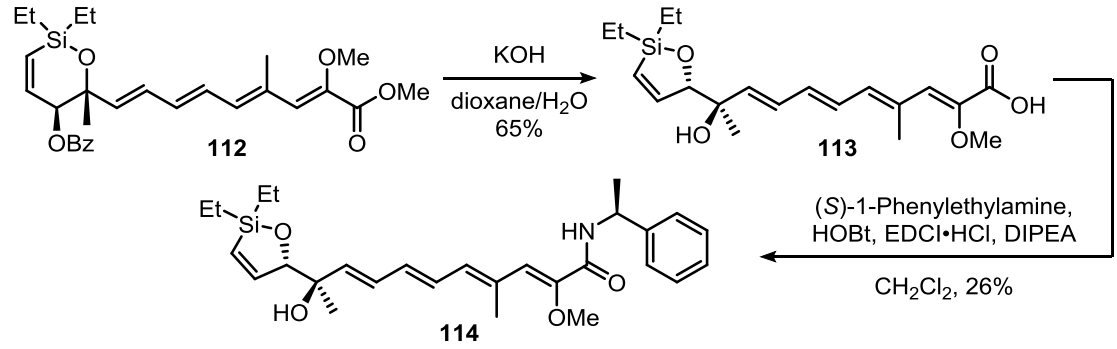
1.5.4 Towards assembling incednam

Although the total synthesis of incednam was not achieved, important advances towards its completion were made. Selective activation of an alkenylboronic ester in the presence of a cyclic akenylsiloxane, allowed the construction of the C1-C13 pentaenoic ester fragment **112** in a total of 9 steps as the longest linear sequence with an overall yield of 12%, *via* C5-C6 Suzuki cross-coupling reaction of boronate **87** and dienyl iodide **88** (Scheme 1.23). Compared to Toshima and co-workers 22 step synthesis of a similar C1-C13 fragment, this is a significant improvement.



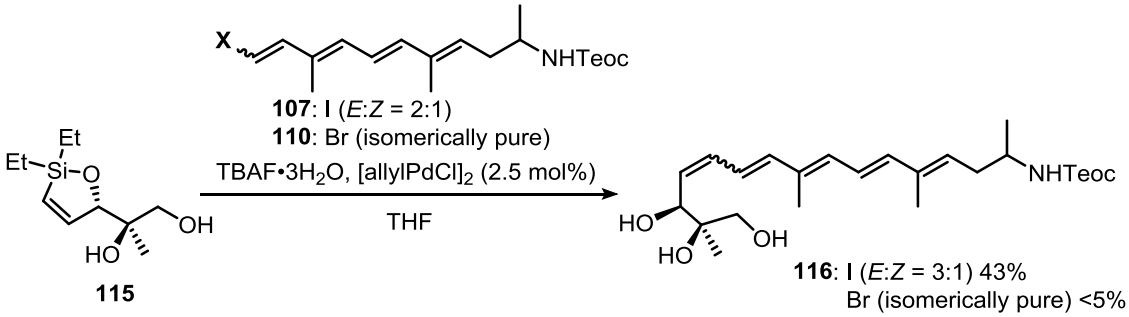
Scheme 1.23: Synthesis of the C1-C13 pentaenoic ester intermediate

Further manipulations of pentaenoic ester **112** provided C1-C13 pentaenoic acid **113** upon ester hydrolysis which was accompanied by benzoyl removal and concomitant rearrangement to the 5-membered cyclic siloxane (Scheme 1.24). This advanced intermediate served as a platform for a model amide bond formation with (*S*)-1-phenylethylamine to give amide **114**.



Scheme 1.24: Model amide bond formation

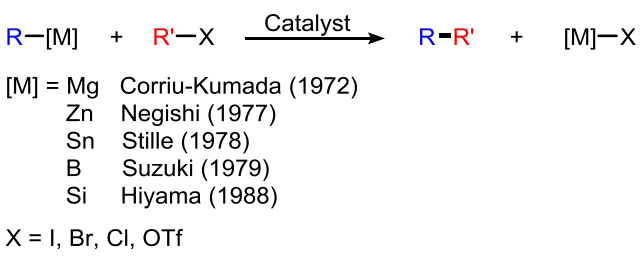
Finally, construction of the key C13-C14 bond *via* Hiyama cross-coupling was demonstrated with model cyclic alkenylsiloxane **115** (Scheme 1.25). While the stereoisomeric tetraenyl iodide **107** provided pentaene **116** in modest yield, only traces were obtained when geometrically pure bromide **110** was employed.



Scheme 1.25: Model C13-C14 bond formation

1.6 Organosilicon reagents in cross-coupling reactions

The first transition-metal-catalysed cross-coupling reaction reported by Corriu and Kumada in 1972 revolutionised the field of organic chemistry in the way chemists conceptually think about constructing C-C bonds (Scheme 1.26).[73,74]



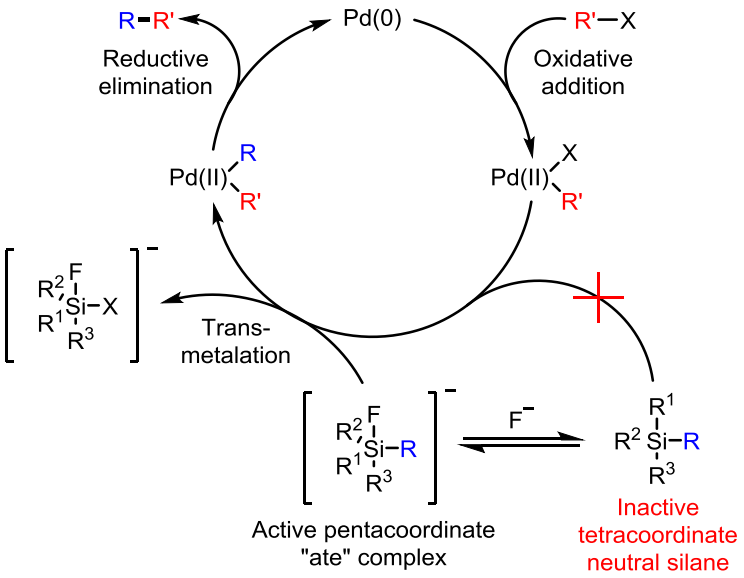
Scheme 1.26: Organometallics in transition-metal-catalysed cross-coupling reactions

Pioneering work by Negishi (1977, organozinc), Stille (1978, organotin) and Suzuki (1979, organoboron), among others, have since then contributed to its development into one of the most important classes of reactions in modern chemistry. Despite many ideal properties, silicon was one of the last organometallic reagents to emerge. The general stability of organosilanes, owing to low polarisation of the Si-C bond, appears to render them relatively unreactive toward cross-coupling compared to other organometallic reagents such as organotin compounds. However, the fluorophilicity of silicon, and its ability to expand its valency is well documented; in 1988, Hiyama *et al*. reported the use of fluoride as an activator to facilitate the palladium-catalysed coupling of organosilanes.[75,76]

Since Hiyama and co-workers breakthrough discovery, a plethora of silicon-based coupling reagents have been reported that undergo successful cross-coupling under activation by fluoride, such as alkylsilanes, halosilanes, silanols and silyl ethers.[77] In addition, other promoters such as silver oxide and potassium trimethylsilanolate, as well as "self-activating" alkali metal silanolates, have been shown to be effective activators, thus greatly expanding the applicability of the Hiyama cross-coupling.[78–80] There are a number of distinct advantages of using organosilicon in transition-metal-catalysed cross-coupling reactions: 1) the silicon motifs can be easily incorporated by a variety of methods from inexpensive commercially available starting materials; 2) due to their chemical stability, organosilanes are easy-to-handle, air- and moisture-stable compounds that can be carried through several synthetic steps; 3) organosilanes are compatible with many functional groups and can be activated towards cross-coupling under mild conditions; 4) compared in particular to organotin, they are relatively non-toxic and environmentally benign.

1.6.1 The mechanism of the Hiyama cross-coupling

The traditionally accepted mechanism of the palladium catalysed Hiyama cross-coupling reaction begins with oxidative addition of a carbon-halide or pseudo halide electrophile to the Pd(0) catalyst (Scheme 1.27). Due to the inert nature of organosilanes, Hiyama *et al*. proposed that through the addition of a silophilic fluoride ion an *in situ* generated pentacoordinated silicon "ate" complex would effectively deliver one of its organic substituents, due to the enhanced polarisation of the Si-C bond, to the transition metal centre. Thus, transmetalation *via* the pentacoordinate silicon species provides the bis-organopalladium complex, which upon reductive elimination constructs the new C-C bond with consequent regeneration of the Pd(0) catalyst.

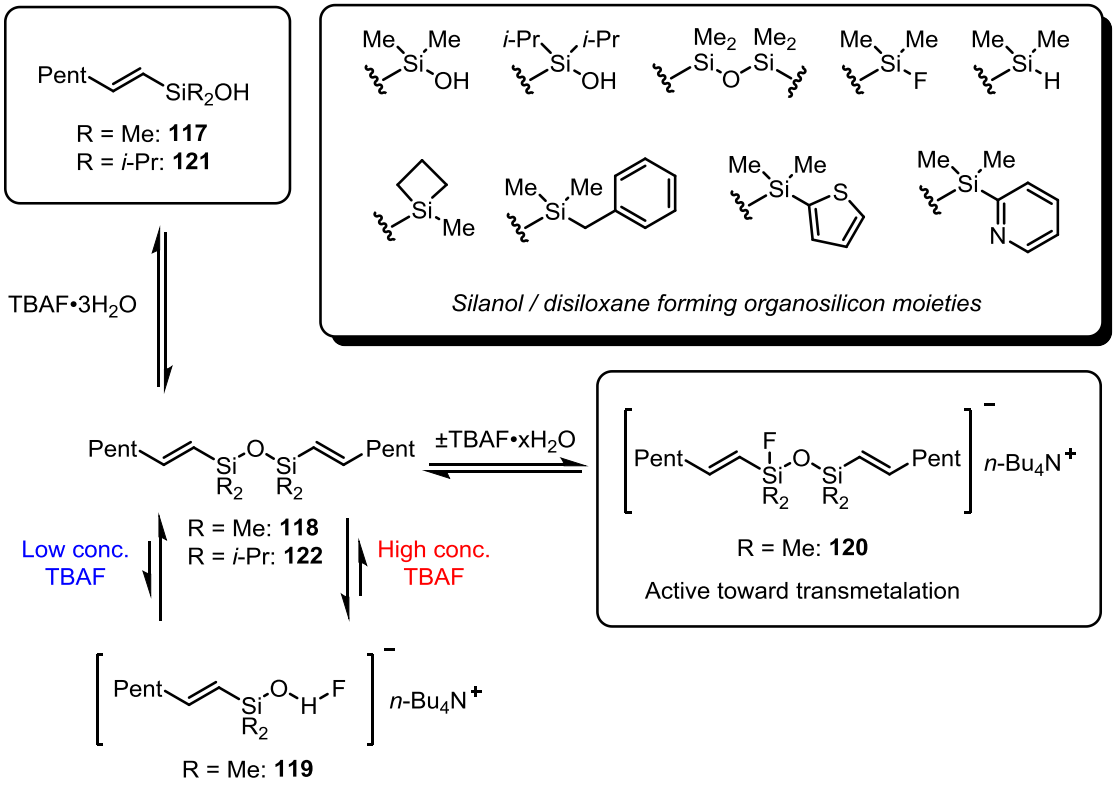


Scheme 1.27: Proposed catalytic cycle via fluorosiliconate

As the transmetalation step involving organosilanes can be either a fluoride-promoted or fluoride-free process, these two mechanistically distinct modes of action have been the subject of spectroscopic, kinetic and computational studies and will be discussed in further detail separately.

1.6.1.1 Fluoride promoted Hiyama cross-coupling

The first comprehensive mechanistic study by Denmark *et al*. effectively used spectroscopic analysis for the identification of reaction intermediates in combination with kinetic profiling to build up a mechanistic picture of the fluoride activated cross-coupling reaction.[81] Upon treatment with TBAF, silanol **117** was found to form disiloxane **118** in equilibrium with hydrogen-bonded silanol-TBAF complex **119** and pentacoordinate fluoride-activated disiloxane **120** (Scheme 1.28).



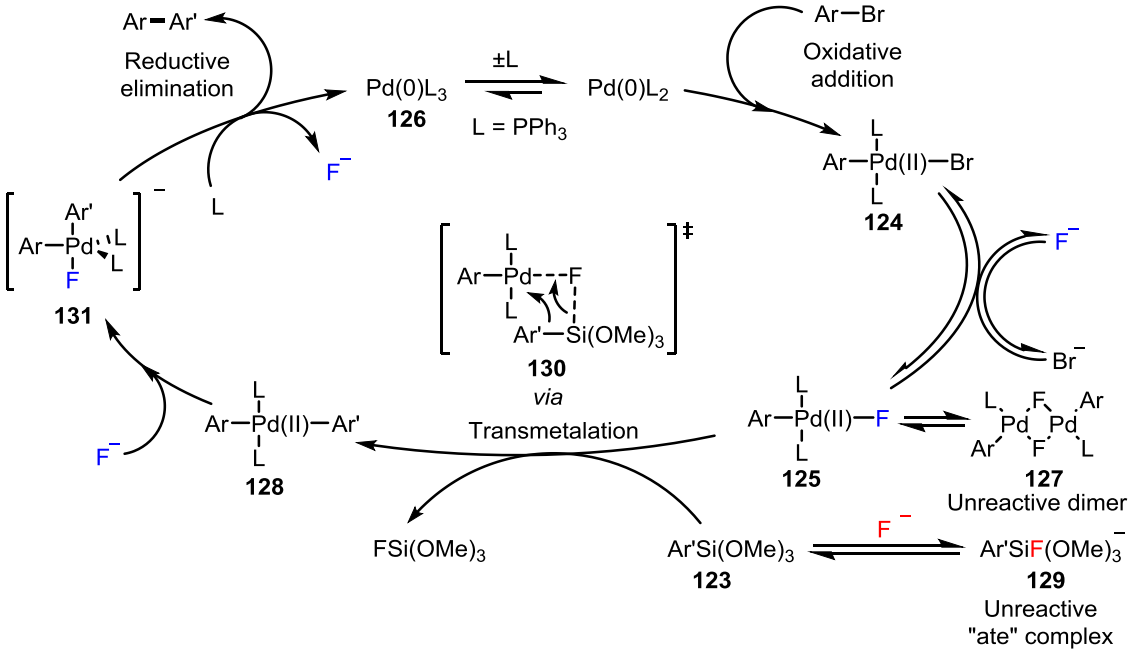
Scheme 1.28: Denmark's proposed fluoride activation of silanols

The ability of many common organosilicon moieties to form these common intermediates, in conjunction with TBAF, suggests a common mechanistic pathway which was further elucidated with kinetic studies. A zeroth-order dependency on organohalide electrophile was found to be consistent with a fast and irreversible oxidative insertion step of the palladium catalyst.[82] Similarly, a first-order dependence on palladium concentration indicated a rate-determining transmetalation step rather than

a turnover-limiting fluoride activation of the silanol. Second-order behaviour of silanol **117** and first-order behaviour of disiloxane **118** suggested that a disiloxane, rather than a silanol, is the species that precedes the rate-limiting transmetalation step. The order dependence of TBAF showed two distinctive behaviours. At two equivalents or below, a first-order dependence was established. However, with increased concentrations an inverse order was found. This divergence in the rate dependence of fluoride was attributed to different resting states established in the pre-equilibrium towards fluoride-activated disiloxane **120** (Scheme 1.28). Thus, at low concentrations, the direct formation of **120** was consistent with the second-order behaviour in silanol (first-order dependence in disiloxane) and first-order behaviour in TBAF. However, at high fluoride concentrations the equilibrium was found to shift from disiloxane **118** towards silanol-TBAF complex **119**. Consequently, the requisite formation of fluoride-activated disiloxane **120** would result in the release of one molecule of TBAF for every two molecules of **119** leading to the observed inverse first-order dependence on TBAF. It should be noted that when the more sterically demanding diisopropylsilanol **121** was employed the inverse first-order dependence on TBAF was found, even at low concentration. Despite the reluctance of **121** to form dimer **122** it still exhibited second-order dependence which, according to the authors, provides further evidence that fluoride-activated disiloxane **120** is the key intermediate involved in the rate-determining transmetalation step.

A more recent mechanistic study by Amatore and Jutand *et al*. utilised cyclic voltammetry for the monitoring of reactive species directly involved in the fluoride promoted cross-coupling of trimethoxysilane **123** (Scheme 1.29).[83] In absence of fluoride, no reaction was observed between arylpalladium(II) bromide complex **124** and trimethoxysilane **123**. Previous fluoride-activation studies with arylboronic acids had

revealed the importance of arylpalladium(II) fluoride complex **125**, generated *in situ* from **124**, preceding the transmetalation.[84] Upon addition of fluoride, the cross-coupling reaction was effected at elevated temperature (70 °C), delivering the product as well as **126**. However, when conducted at room temperature another reaction took place, resulting in the formation of unreactive dimer **127**. This difference was presumed to be derived from the low thermodynamic concentration of **125**, when starting from **124**, which did not allow fast transmetalation at room temperature, resulting in the build-up of **127**.

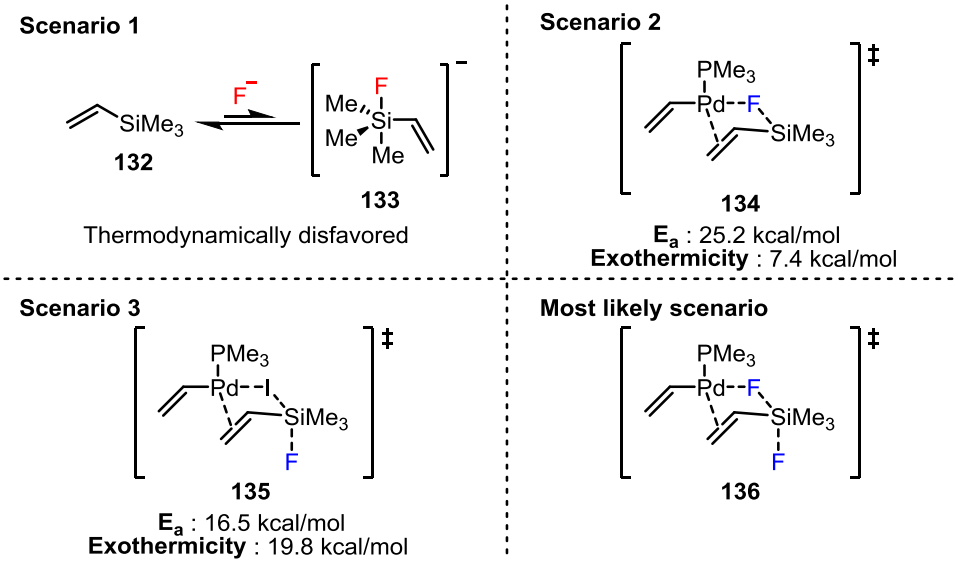


Scheme 1.29: Amatore and Jutand's proposed fluoride activated catalytic cycle

When **125** was reacted with trimethoxysilane **123** at room temperature, organopalladium(II) intermediate **128** was formed. Reductive elimination of this stable intermediate was not promoted until after addition of TBAF which resulted in product formation and **126**, as had previously been established.[84,85] In addition, it was found that the rate of the reaction became significantly slower at either high concentrations of TBAF, or silane **123**, which was interpreted as the formation of unreactive "ate" complex **129**. To test this theory, preformed siliconate **129** was submitted to the reaction

conditions with arylpalladium(II) bromide complex **124**. Although no product was formed, the formation of unreactive dimer **127** was detected, presumably *via* the release of fluoride from siliconate **129** in its equilibrium with **123**. However, when **129** was reacted with arylpalladium(II) fluoride complex **125** the cross-coupled product was obtained, albeit in low yield and at a much slower rate. This, according to the authors, provided further evidence for the reaction proceeding *via* **123**, generated in low concentration in its equilibrium with silanoate **129**. To conclude, Amatore and Jutland *et al*. revealed three mechanistic roles of the fluoride in the palladium-catalysed Hiyama cross-coupling of aryltrimethoxysilanes. Firstly, it is involved in the formation of arylpalladium(II) fluoride complex **125** which then undergoes the rate-determining transmetalation with **123** *via* four-membered transition state **130** as a result of the fluorophilicity of the silicon atom. Secondly, fluoride promotes fast reductive elimination of the stable *trans*-**128** *via* an anionic pentacoordinate species **131**, presumable due to slow *trans*-*cis* isomerisation. Finally, fluoride reacts with trimethoxysilane **123** generating an unreactive pentacoordinated siliconate **129** complex.

The role of fluoride in the rate-determining transmetalation step has been the subject of a computational study by Hiyama *et al*.[86] In the absence of fluoride the transmetalation between [vinylPd(II)I(PMe_3)$_2$] complex and vinylsilane(**132**) was found to occur with a large activation barrier (45.8 kcal/mol) and a large endothermicity (25.6 kcal/mol) which was in agreement with experimental results. Three possible roles of the fluoride were investigated (Scheme 1.30). In the first case fluoride activation of **132** preceding the transmetalation was considered. However, theoretical calculations suggested that a pentacoordinate siliconate **133** species is not formed in the case of **132**.



Scheme 1.30: Hiyama's proposed role of fluoride in the transmetalation step

In the second case, an iodo ligand is substituted for fluoride, which then proceeds in the transmetalation *via* transition state **134**. This process was found to occur with a moderate activation barrier (25.2 kcal/mol) and exothermicity (7.4 kcal/mol). Finally, fluoride activation of the vinylsilane in the transmetalation transition state **135** was considered. This process was found to operate with a small activation barrier (16.5 kcal/mol) and a large exothermicity (19.8 kcal/mol). Thus it was concluded that the involvement of fluoride in the transmetalation process occurs through a combination of both the second and third case *via* the formation of strong Si-F bond and fluoride induced stabilisation of the transmetalation transition state **136** facilitated by the expanded valency of the silicon atom.

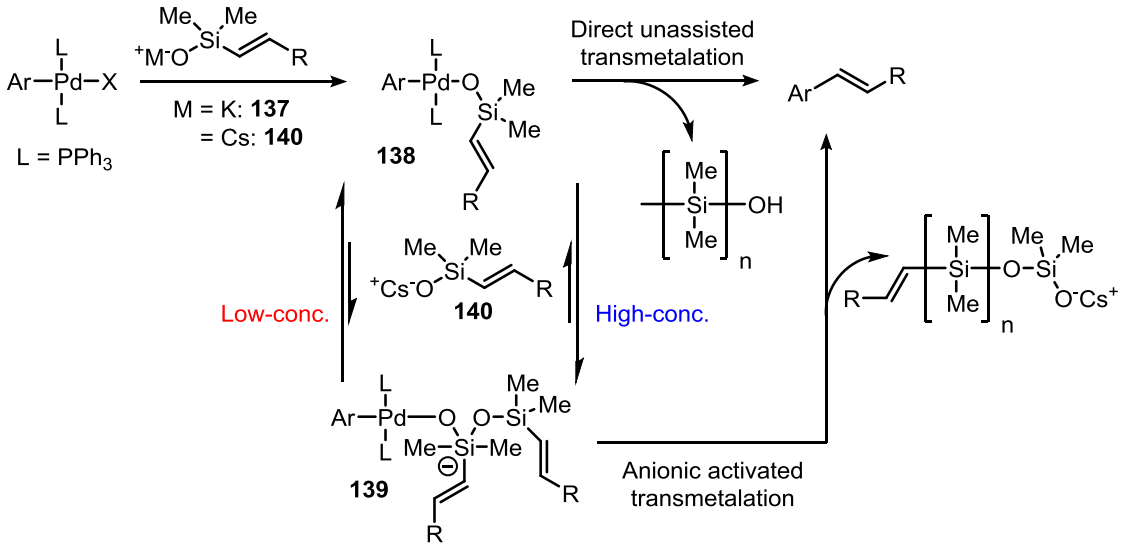
Both the experimental studies by Amatore and Jutand *et al*., and the computational studies by Hiyama *et al*. concluded that the generation of an "activated" pentacoordinated fluorosiliconate is not involved prior to the transmetalation step of aryltrimethoxysilanes or vinyltrimethylsilanes. Rather the role of the fluoride is to generate an organopalladium(II) fluoride complex which then undergoes the rate-determining transmetalation step. This proposal is in contradiction with Denmark's

studies where a pentacoordinated fluoride-activated disiloxane was thought to be the active species involved in the transmetalation step. However, the direct involvement of a disiloxane could result in a favourable formation of pentacoordinated species. Given the number of different silanes capable of participating in the fluoride promoted Hiyama cross-coupling reaction it may not be reasonable to generalise a single mechanistic pathway by which the transmetalation operates.

1.6.1.2 Base promoted Hiyama cross-coupling

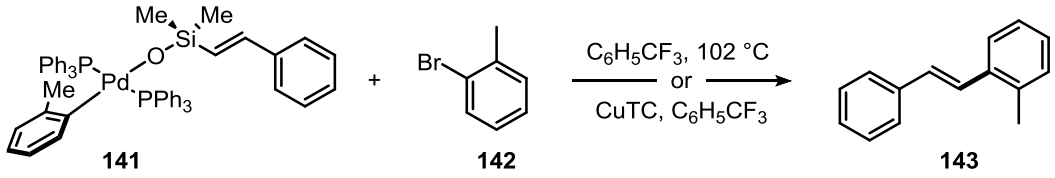
Due to the incompatibility of silicon-based protecting groups to fluoride, which are commonly found in multistep synthesis, the development of base-promoted coupling conditions greatly expands the versatility of the Hiyama cross-coupling.[78–80] Extensive studies on the mechanistic aspects of the fluoride-free palladium-catalysed cross-coupling of organosilanols and their conjugate bases have been carried out by Denmark *et al*.[87–90] The alkali metal silanolate is the active species in the cross-coupling and can be generated *in situ* using a number of bases such as silver oxide, potassium trimethylsilanolate, caesium carbonate and sodium hydride. As a result of kinetic analysis and isolation of putative pre-transmetalation intermediates for the direct validation of their role in the transmetalation step, the base-promoted cross-coupling is now substantially understood. The kinetic study of potassium alkenylsilanolate **137** revealed a zeroth-order rate dependence of both **137** and the aryl halide. Additionally, a first-order dependence on the palladium catalyst suggested a rate-determining transmetalation involving either an unactivated direct transmetalation *via* intermediate **138** or an anionic activation pathway *via* **139** (Scheme 1.31). When the more nucleophilic caesium alkenylsilanolate **140** was employed, a fractional-order rate dependence of **140** was revealed. The partial order suggested that the two putative mechanistic pathways were simultaneously in operation. As the concentration of

silanolate **140** was increased a zeroth-order dependence was established indicating that the rate-determining transmetalation step now operated *via* anionic activated intermediate **140** as a consequence of saturation.



Scheme 1.31: Denmark's proposed base activation of alkenylsilanolates

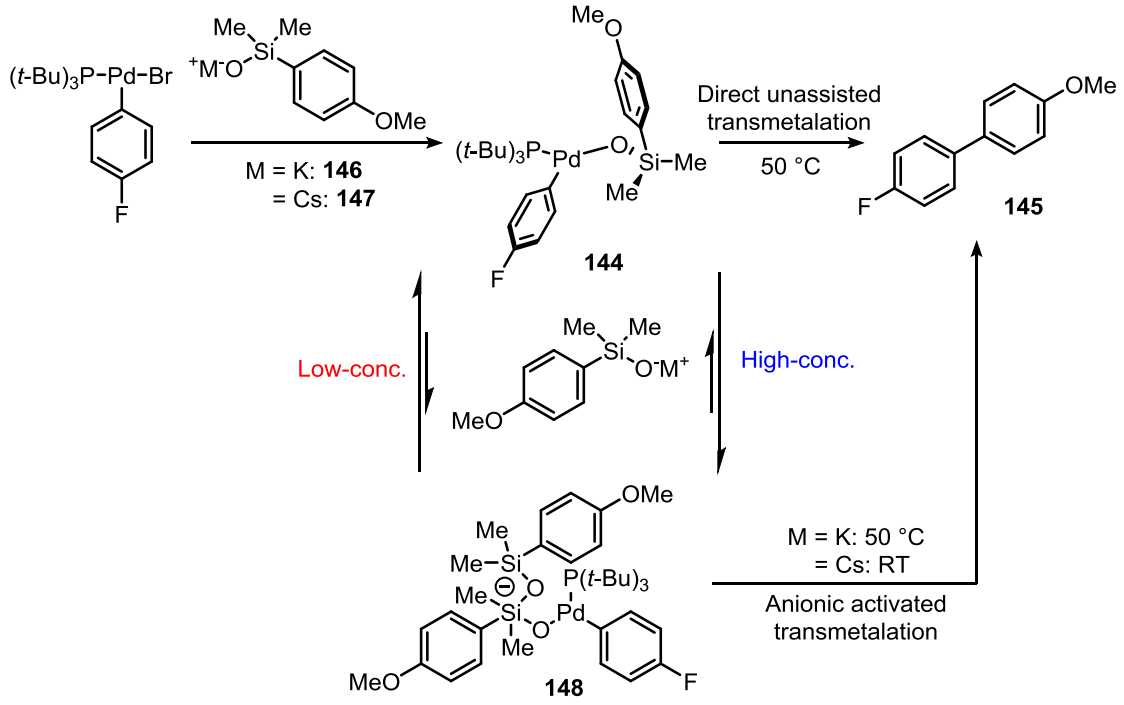
When preformed arylpalladium(II) alkenylsilanolate complex **141** was treated with 2-bromo-toluene (**142**), the formation of **143** was observed, albeit at elevated temperatures (Scheme 1.32).



Scheme 1.32: Hiyama cross-coupling via unassisted transmetalation

Addition of CuTC, which facilitates the dissociation of the strongly binding triphenylphosphine ligand allowing the requisite formation of a 14-electron species from which transmetalation occurs, enabled the formation of **143** at room temperature. This result demonstrated the ability of alkenylsilanolates to undergo direct transmetalation under mild conditions *via* an unactivated pathway. Further evidence of the unactivated transmetalation pathway was obtained with the isolation of

arylpalladium(II) arylsilanolate complex **144**, which upon heating (50 °C) resulted in the direct formation of **145** (Scheme 1.33).



Scheme 1.33: Denmark's proposed base activation of arylsilanolates

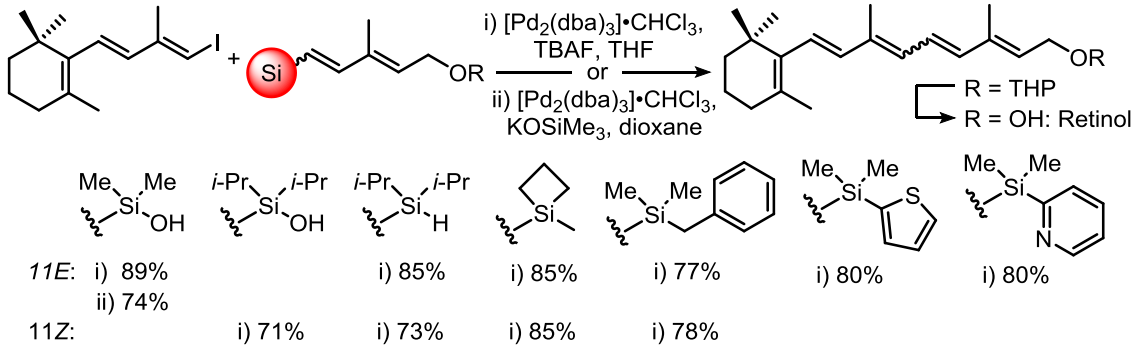
The isolation of **144** allowed the direct analysis of the mechanistic pathway in operation under catalytic conditions. With increased concentration of potassium arylsilanolate **146**, a first-order rate dependence was established. When caesium arylsilanolate **147** was deployed the transmetalation was found to occur at much faster rates, even at room temperature. Rather than being the result of increased nucleophilicity of the caesium silanolate, the rate enhancement was attributed to weaker coordination of the caesium anion associated with anionic intermediate **148**. Thus anionic complex **148** carries a greater localised charge when paired with the larger and weaker coordinating caesium anion which results in faster transmetalation. These results indicate that the anionic activated pathway is primarily in operation under catalytic conditions when arylsilanolates are used. To summarise, potassium alkenylsilanolates were found to react *via* an unactivated transmetalation pathway, while caesium alkenylsilanolates, due

to their increased nucleophilicity, were found to operate primarily *via* an anionic activated pathway. However, in the case of arylsilanolates, where the direct transmetalation is slower, the cross-coupling is most likely to proceed *via* the anionic activated transmetalation pathway although both pathways may simultaneously be in operation.

1.6.2 Application of Hiyama cross-coupling in total synthesis

The chemical stability and ease of introduction, among other unique traits previously stated, make organosilicon compounds attractive and important tools for the construction of C-C bonds in the synthesis of natural products. Although not as widely deployed as other cross-coupling processes such as the Negishi, Suzuki and Stille reactions, recent advancements, such as the development of base-promoted cross-coupling of silanols, have seen them emerge as a viable alternative to the more conventional methods.

In the synthesis of both all-*trans* and 11-*cis*-retinol, López *et al*. demonstrated the use of Hiyama cross-coupling for the construction of the key C10-C11 bond, deploying a wide variety of organosilanols and their surrogates under both fluoride-promoted and fluoride-free conditions (Scheme 1.34).[91]

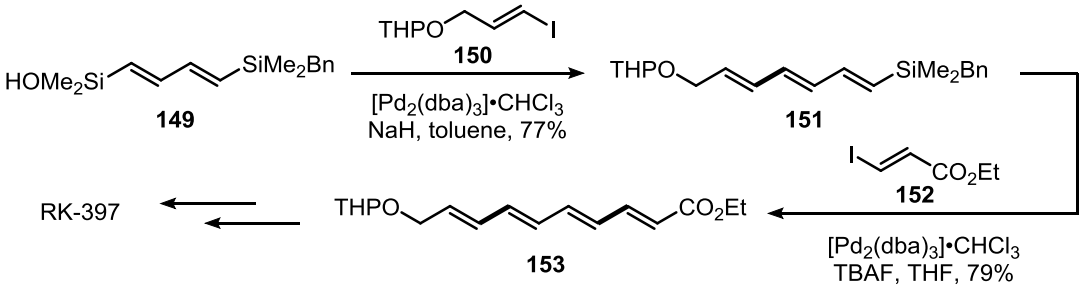


Scheme 1.34: López's Hiyama cross-coupling approach towards retinol

While the Negishi, Suzuki and Stille reactions have all been extensively used for the synthesis of both all-*trans* and 11-*cis*-retinol they do suffer from a number of drawbacks

related to the nature of the organometallic used. These include air and moisture sensitivity of the organozinc, homodimerisation and the general toxicity of organotin compounds, and the instability and somewhat difficult introduction of alkenyl boronic acids.[92] The mild conditions employed and uniformly high yields achieved by the silicon-based couplings demonstrated the advantages for the generation of highly conjugated polyene systems.

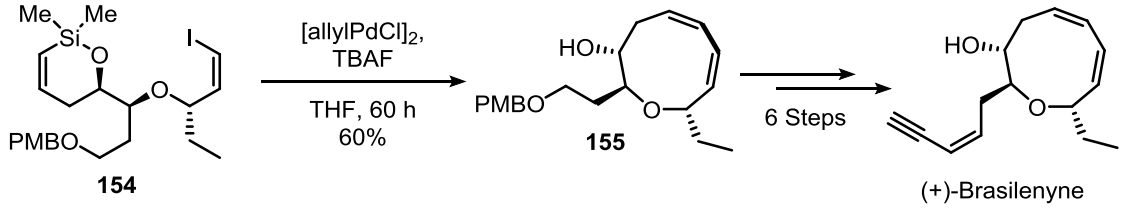
In the total synthesis of RK-397, a polyene macrolide antifungal agent, Denmark *et al*. elegantly demonstrated the orthogonal modes of activation in the construction of the C1-C10 polyene fragment *via* bifunctional diene **149**.[93] First the silanol of **149** was coupled with alkenyl iodide **150** under base-promoted conditions to give triene **151** (Scheme 1.35).



Scheme 1.35: Denmark's C1-C10 polyene fragment of RK-397

The benzyldimethylsilane is inert under these conditions. The second cross-coupling with alkenyl iodide **152** could then be performed upon treatment with TBAF, revealing the silanol, which then participates in the coupling affording unsymmetrical tetraene **153**. Yet another elegant use of the silicon-based cross-coupling reaction is found in the total synthesis of brasilenyne by Denmark *et al* (Scheme 1.36).[94] Brasilenyne, an antifeedant isolated from the digestive gland of the *Aplysia brasiliana* sea slug, features a nine-membered cyclic ether containing a 1,3-*cis*,*cis*-diene unit. A fluoride-promoted intramolecular cross-coupling of six-membered cyclic alkenylsiloxane **154** ensures the

stereospecific construction of the *Z,Z*-conjugated homoallylic alcohol affording **155**.[95–97]



Scheme 1.36: Denmark's key intramolecular cyclisation towards (+)-brasilenyne

1.7 Project goals and retrosynthetic approach

As discussed above, incednine is an important molecular target due to its ability to restore chemotherapeutic activity in drug-resistant cancer cells *via* a novel mechanism.[1] In addition, incednine could represent an important biological tool for the elucidation of its target protein, thus providing valuable insight into this distinctive mode of cancer cell survival. Furthermore, it could serve as a platform for the development of novel therapeutic leads *via* the natural product, or non-natural analogues. Although Toshima *et al*. have previously reported the synthesis of the incednine aglycon, the sheer length of the route prevents development of such applications.[43,44]

Similar to Lim's proposal (Figure 1.5), our retrosynthetic approach begins with scission at the glycosidic bond, separating incednine into its aglycon **2** and disaccharide **157** (Figure 1.6). Further disconnections of the macrolactam at the amide, the C5-C6, and the C13-C14 bonds identify three building blocks: dienoate **88**, cyclic alkenylsiloxanes **87** or **158**, and tetraenyl iodide **89**. In light of the difficulties experienced with the stereoselective synthesis of the tetraenyl iodide fragment **107**, a modular assembly of the C12-C21 pentaene *via* sequential Hiyama and Suzuki cross-couplings with C14-C17 boronate **159** and C18-C23 iododiene **160** is proposed. Another alternative is the latent construction of the C12-C21 pentane *via* Ramberg-Bäcklund olefination, introduced *via*

Hiyama cross-coupling of sulfide **161** (or sulfone **162**). Furthermore, due to the flexible nature of our approach, polyene construction *via* the lynchpin cyclic alkenylsiloxane **87-164** could be achieved in any order; ideally, this would be accomplished *via* orthogonal manipulations of bis-silanes **158** or **164**. However, the C2-C9 tetraene could equally be constructed *via* Suzuki cross-coupling of pinacolborane **88**, as was previously established by Lim. Finally, macrocyclisation is envisioned *via* amide bond formation of the polyene precursor. Although Toshima *et al*. obtained less than satisfactory yields from such an approach, it is hoped that the lack of sterically encumbering TES groups in our strategy will result in a favourable conformational pre-organisation of the acyclic precursor required for the macrolactamisation.[57]

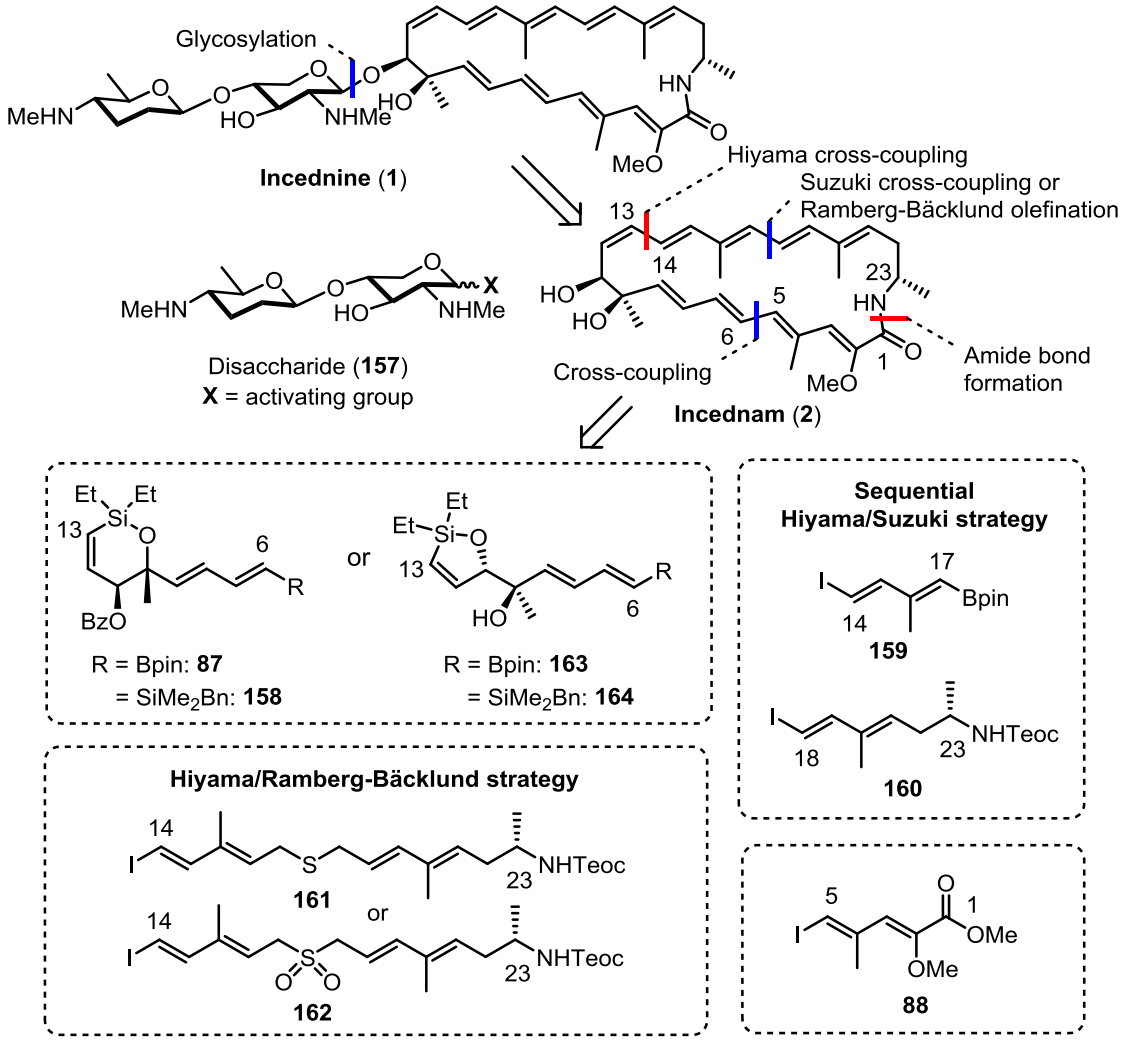


Figure 1.6: Our retrosynthetic approach towards incednine

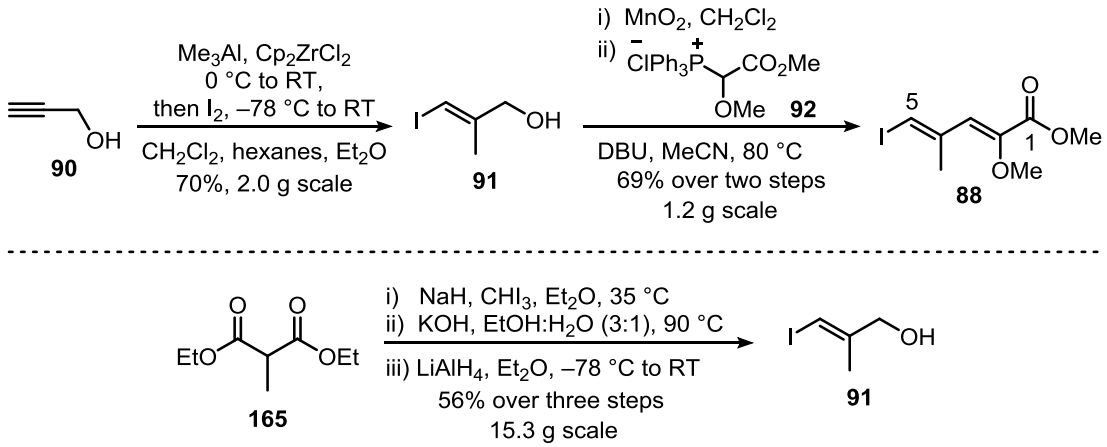
Continuing from Lim's work, the following chapter of this thesis will discuss the progress made towards the total synthesis of incednam (Chapter 2). In chapter 3 the development of dimethyl cyclic alkenylsiloxane methodology will be discussed followed by its application towards incednam in Chapter 4. Finally, summary of the progress made and future work will be dedicated to Chapter 5.

Chapter 2: Towards incednam – Fragment synthesis and union

Continuing from the work of Lim, the following chapter will discuss the synthesis of key fragments carried out by the author, as well as attempts towards a stereoselective construction of the C12-C21 pentaene system. In addition, work towards the incednam assembly will be discussed.

2.1 C1-C5 Dienoate synthesis

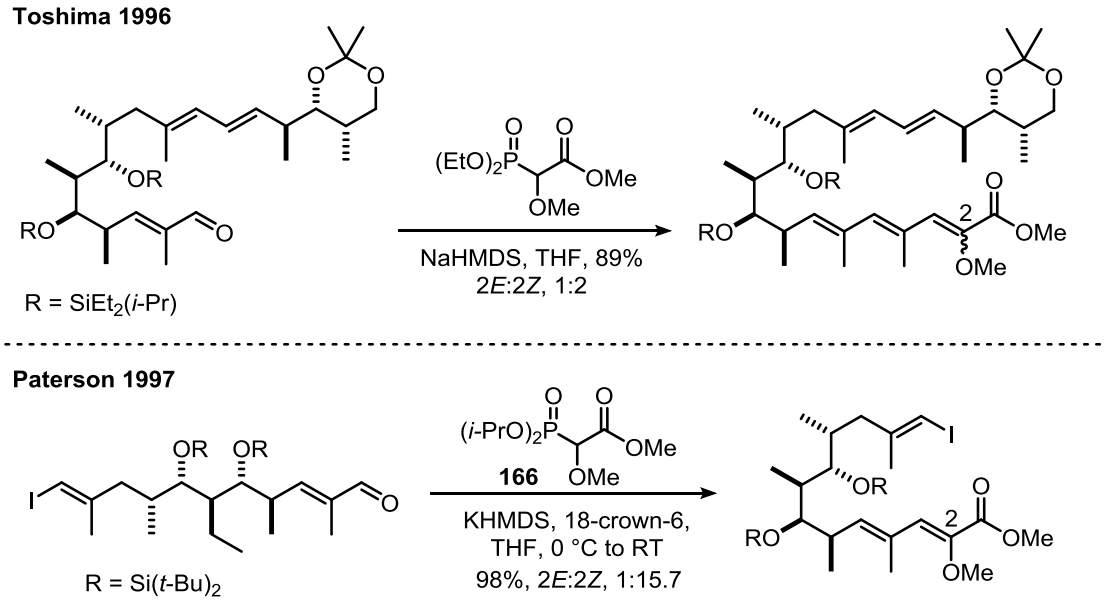
The synthesis of the C1-C5 dienoate **88** fragment develops from a route previously developed by Lim (Scheme 2.1).[64]



Scheme 2.1: Synthesis of C1-C5 dienoate fragment

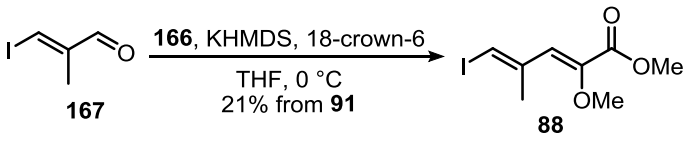
The synthesis commenced with a regioselective zirconium-catalysed methylalumination-iodination of propargyl alcohol (**90**) to give vinyl iodide **91**.[65,66] Although this carboalumination strategy affords **91** in a single step, a more practical three step procedure starting from diethyl methylmalonate (**165**) was employed, which provided multigram quantities of **91**.[98] Next, MnO_2 mediated allylic oxidation of **91** followed by Wittig olefination of the resulting aldehyde with α-methoxyphosphonium salt **92** afforded dienoate **88** as a single geometrical isomer.[67] Although the Wittig olefination provided the desired dienoate **88** it required a large excess of phosphonium

salt **92** (5.2 eq.). To address this problem a HWE olefination strategy was considered for the construction of the (2*Z*,4*E*)-dienoate product. This transformation was studied by Toshima *et al*. in the total synthesis of bafilomycin A1, using a number of phosphonates and conditions, albeit proceeding with poor stereoselectivity, obtaining the desired (2*Z*,4*E*)-dienoate product as a mixture of isomers (1:2, 2*E*:2*Z*) (Scheme 2.2).[99,100]



Scheme 2.2: HWE olefination strategies towards (2Z,4E)-dienoate product

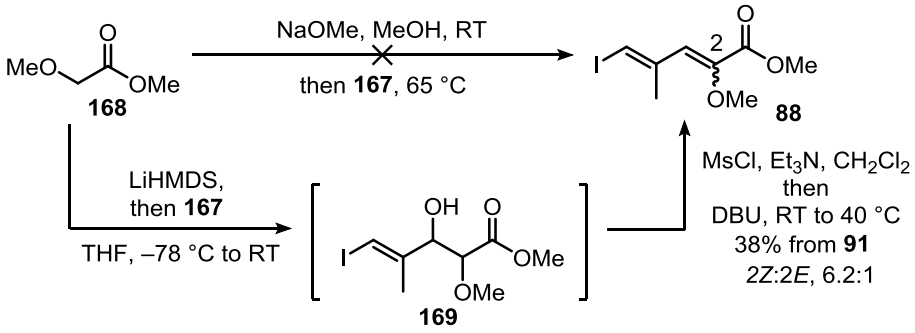
In a related study by Paterson *et al*., the use of isopropyl substituted phosphonate **166** and KHMDS/18-crown-6, afforded the desired (2*Z*,4*E*)-dienoate in excellent yield (98%) and stereoselectivity (2*E*:2*Z*, 6:94).[101,102] Disappointingly, application of these conditions to aldehyde **167**, gave dienoate **88** in poor yield (21% from allylic alcohol **91**), albeit as a single geometrical isomer (Scheme 2.3).



Scheme 2.3: HWE approach to the C1-C5 dienoate fragment

Inspired by a further total synthesis of bafilomycin A1 by Hanessian *et al*., the construction of the required α-methoxy ester motif was attempted *via* an aldol

condensation.[103] First, a one-pot approach was attempted by treatment of methyl methoxyacetate (**168**) with sodium methoxide in methanol, followed by addition of aldehyde **167** under reflux (Scheme 2.4).[104] Although **167** was fully consumed during the reaction, no formation of the desired product was observed.



Scheme 2.4: Aldol approach to the C1-C5 dienoate fragment

Next, a stepwise approach was attempted by first generating the β-hydroxy ester **169**, followed by mesylation and β-elimination.[103] β-hydroxy ester **169** was successfully generated and due to instability towards silica gel chromatography, crude β-hydroxide **169** was used as such. Mesylation of crude **169**, followed by treatment with DBU at elevated temperatures, provided the desired (2*Z*,4*E*)-dienoate **88** in moderate yield (38% from allylic alcohol **91**) as a mixture of isomers (2*E*:2*Z*, 1:6.2). Given the success of the previously established Wittig approach and the unsatisfactory results obtained from both the HWE and aldol condensation strategy, no further attempts were made for a refined approach towards dienoate fragment **88**.

Overall the synthesis of the C1-C5 dienoate fragment **88** was accomplished in total of 3 steps as the longest linear sequence with an overall yield of 48%.

2.2 Cyclic alkenylsiloxanes – Introduction

Cyclic alkenylsiloxanes are highly effective coupling partners for the stereospecific generation of polyenes containing *Z*-allylic or homoallylic alcohols, a prominent feature found in many natural products, *via* palladium-catalysed Hiyama cross-coupling. The

versatility of these building blocks is demonstrated by their ability to undergo a number of other synthetically useful transformations; they can act as aldol surrogates for the preparation of β-, γ- or δ-hydroxyl carbonyl compounds *via* Tamao oxidation, while protodesilylation gives access to alkenes with well-defined geometry (Figure 2.1).

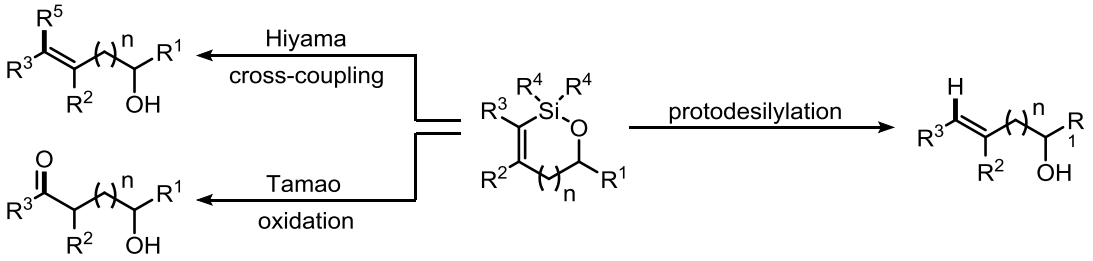
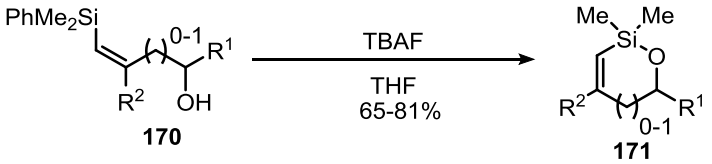


Figure 2.1: Synthetically useful transformations of cyclic alkenylsiloxanes

2.2.1 Previous syntheses of cyclic alkenylsiloxanes

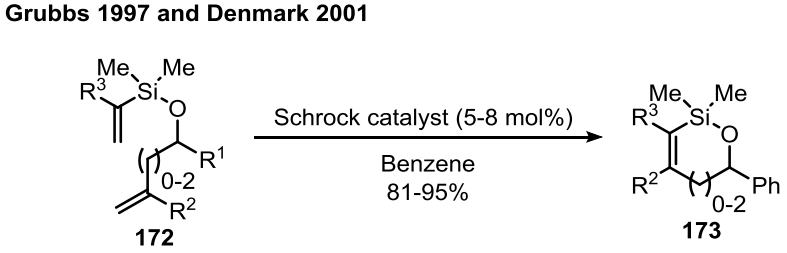
Until their popularisation by Denmark *et al*. from 2001, few examples of cyclic alkenylsiloxanes had been reported in the literature.[95] In one of the earliest examples, Oshima *et al*. demonstrated that *Z*-vinylsilane **170**, containing an allylic or homoallylic alcohol, could generate 5- and 6-membered cyclic siloxane **171**, respectively, in the presence of fluoride (Scheme 2.5).[105] Furthermore, they reported the first example of these motifs in Tamao oxidation.[105]



Scheme 2.5: Oshima's synthesis of cyclic alkenylsiloxanes (1985)

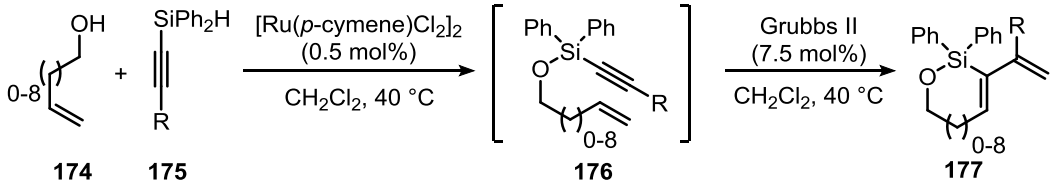
Ring-closing metathesis (RCM) and intramolecular hydrosilylation are the two principal methods that have been employed for the preparation of cyclic alkenyl siloxanes. Ring-closing metathesis is one of the most utilised methods for the preparation of cyclic alkenylsiloxanes, as reported by Grubbs *et al*.[106] The use of the more reactive, air- and moisture sensitive, Schrock catalyst was found to be critical. Building on these results

Denmark *et al*. expanded the use of RCM to mono- and disubstituted dienyl silyl ethers **172** for the preparation of 5-, 6- and 7-membered cyclic siloxanes **173**, and pioneered their use as coupling partners in the Hiyama cross-coupling reaction which culminated in the total synthesis of brasilenyne (Scheme 1.34, Section 1.6.2), amongst other natural products (Scheme 2.6).[95,97,107,108]



Scheme 2.6: Use of ring-closing metathesis for the generation of cyclic siloxanes

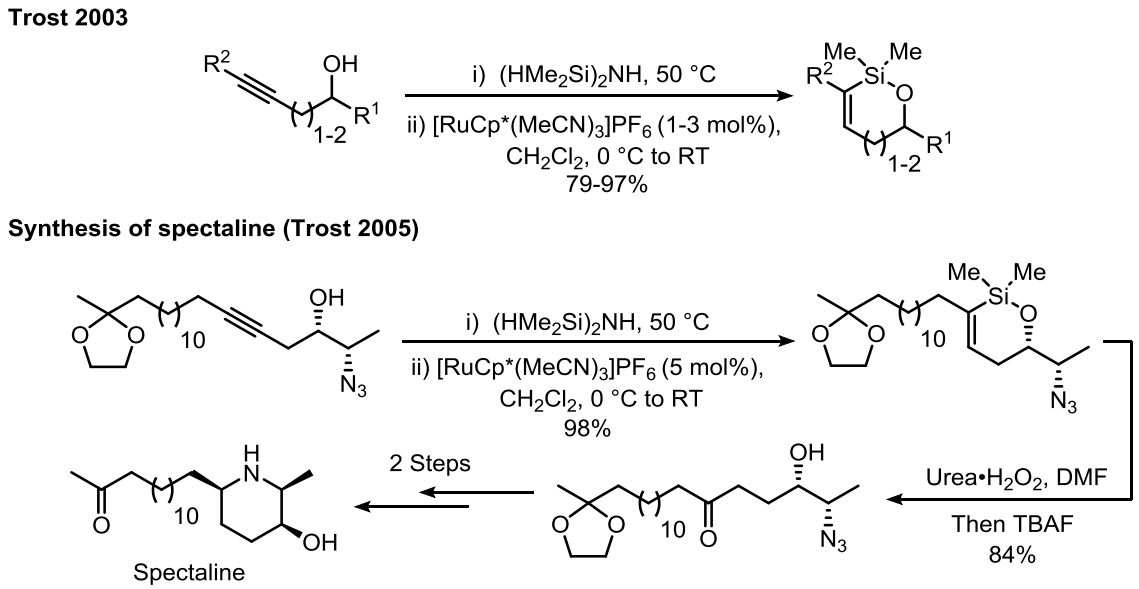
Complementary to the work of Grubbs and Denmark, Lee *et al*. reported the use of ring-closing enyne metathesis allowing the construction of alkenylsiloxanes of various ring sizes (Scheme 2.7).[109]



Scheme 2.7: Use of enyne metathesis for the generation of cyclic siloxanes (Lee, 2005)

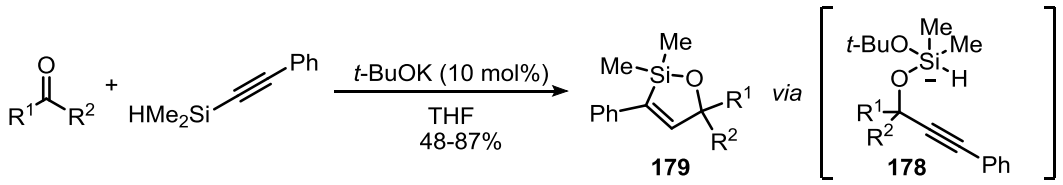
Thus, ruthenium-catalysed dehydrogenative coupling of alcohol **174** and alkynylsilane **175** affords enyne **176**, which then undergoes enyne metathesis using the Grubbs second generation catalyst to give **177**.

Another powerful method for the construction of cyclic alkenylsiloxanes is the use of ruthenium-catalysed intramolecular *endo*-selective *trans*-hydrosilylation of alkynes developed by Trost *et al*. (Scheme 2.8).[110,111] Although limited to internal homo- and bis-homopropargylic alcohols, its synthetic utility was demonstrated in the total synthesis of the piperidine alkaloid, spectaline.[112]



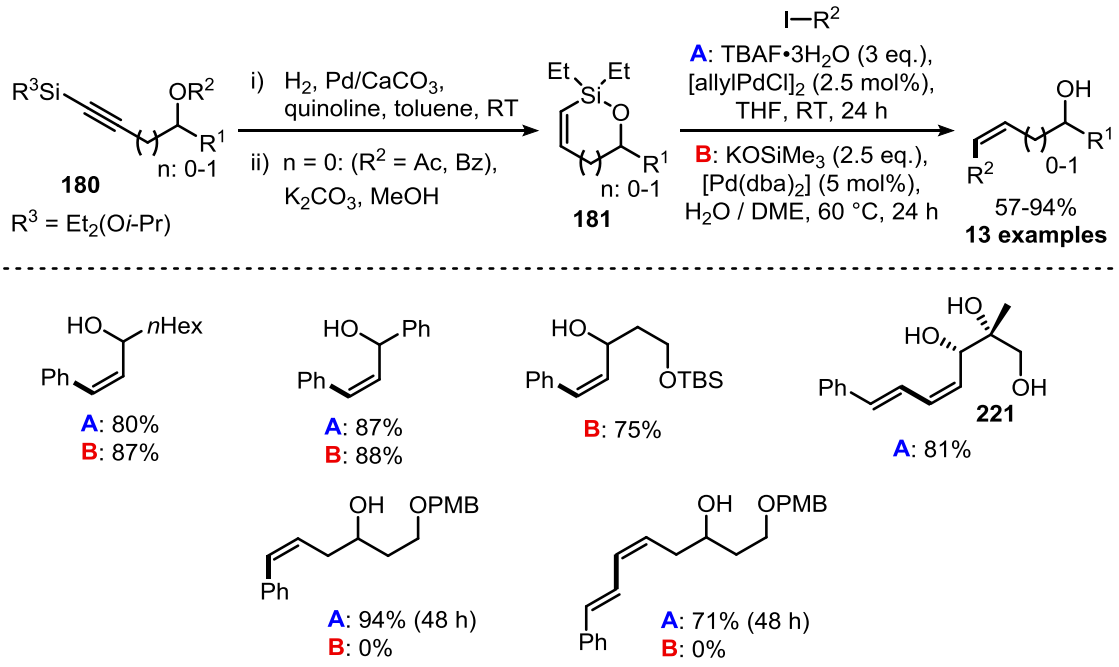
Scheme 2.8: Intramolecular hydrosilylation for the generation of cyclic siloxanes

Complementary to Trost, Lee *et al*. showed that the intramolecular hydrosilylation, *via* alkynyl silyl ether **178**, could be effected in the presence of potassium *tert*-butoxide which gives access to 5-membered siloxanes **179** (Scheme 2.9).[113]



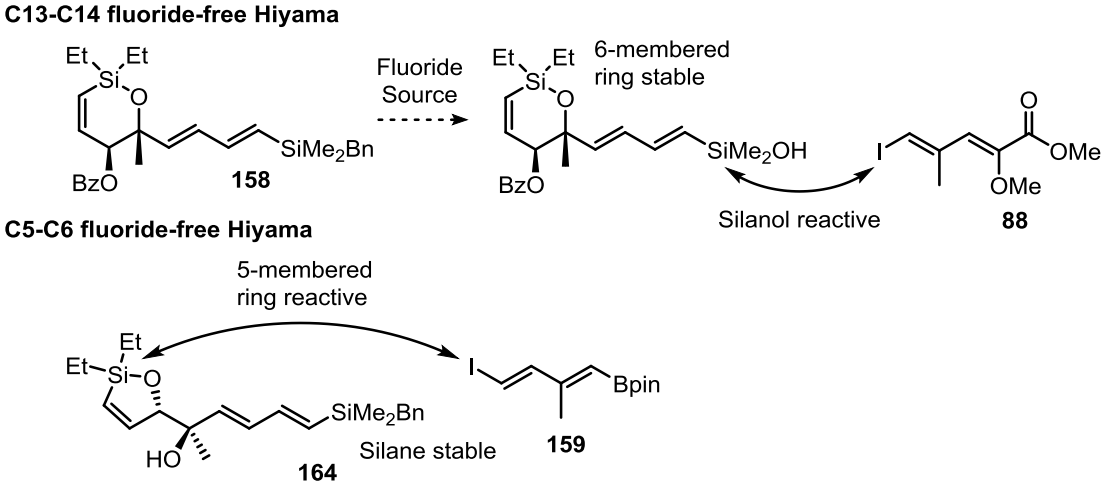
Scheme 2.9: Base promoted intramolecular hydrosilylation (Lee, 2005)

Our strategy relies on the operationally simple, yet powerful, semi-hydrogenation of alkynylsiloxanes **180**. The resulting *Z*-alkenylsiloxanes undergo intramolecular cyclisation to afford 5- and 6-membered cyclic alkenylsiloxanes **181** (Scheme 2.10). In addition, their subsequent cross-coupling was demonstrated as a stereospecific route to *Z*-alkenyl polyenes. This work was published in *Chem. Eur. J.* in 2014.[114]



Scheme 2.10: Preparation of cyclic diethyl alkenylsiloxanes and their coupling

An intriguing ring-size dependent orthogonality was discovered during the course of this study. While 5-membered cyclic alkenylsiloxanes couple under both fluoride- and base-promoted conditions, the cross-coupling of their 6-membered homologues could only be effected by fluoride activation. In the context of incednam, this could be important, allowing the orthogonal manipulations of bis-silanes **158** or **164** (Scheme 2.11).

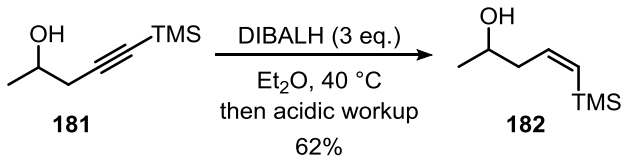


Scheme 2.11: Orthogonal manipulations of bis-silanes

Other methods for the generation of di-, tri- and polysubstituted cyclic alkenylsiloxanes include work by Takeda, Woerpel, Montgomery *et al*.[115–123]

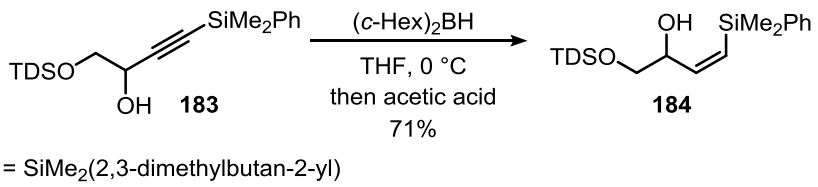
2.2.2 Stereoselective reduction of alkynylsilanes

Perhaps one of the most employed methods for the *cis*-reduction of alkynylsilanes is the two step sequence involving a hydrometalation followed by protodemetalation.[124] Reported examples include the use of aluminum, boron, titanium and zirconium. For example, in synthetic studies towards the antifungal agent ambruticine, *Z*-alkenylsilane **182** was required; while the use of Lindlar hydrogenation gave a mixture of isomers (*E*:*Z*, 1:8) it was found that hydroalumination of alkynylsilane **181** followed by acidic workup afforded the desired *Z*-vinylsilane **182** (Scheme 2.12).[125]



Scheme 2.12: Hydralumination/protodemetalation sequence (Markó, 1994)

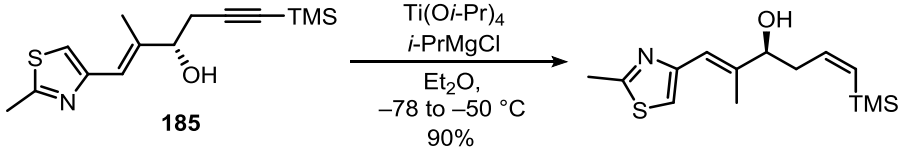
The use of aluminium hydrides as hydrometalating agents is often limited due to poor functional group tolerance, such as carbonyls. In addition, any protic functionalities must be protected, or a large excess of hydroalumination agents is required. Denmark *et al*. found that hydroboration of alkynylsilane **183** with dicyclohexylborane, followed by treatment with acetic acid, resulted in clean conversion to the *cis*-alkene **184** (Scheme 2.13).[126] Other methods, including hydroalumination and Lindlar hydrogenation resulted in poor diastereoselectivity and/or overreduction.



TDS = $SiMe_2$(2,3-dimethylbutan-2-yl)

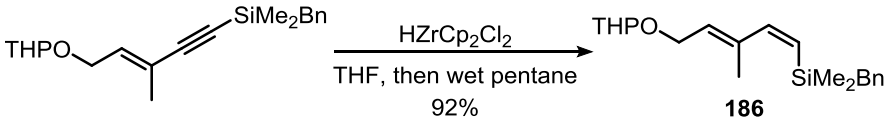
Scheme 2.13: Hydroboration/protodemetalation sequence (Denmark, 2000)

The use of low valent titanium (generated *in situ* by treatment of $Ti(O\textit{i}\text{-}Pr)_4$ with *i*-PrMgCl) for the *cis*-reduction of alkynylsilane **185** was demonstrated by Shibasaki *et al*. in the total synthesis of epothilone A (Scheme 2.14).[127]



Scheme 2.14: Hydrotitanation/protodemetalation sequence (Shibasaki, 2000)

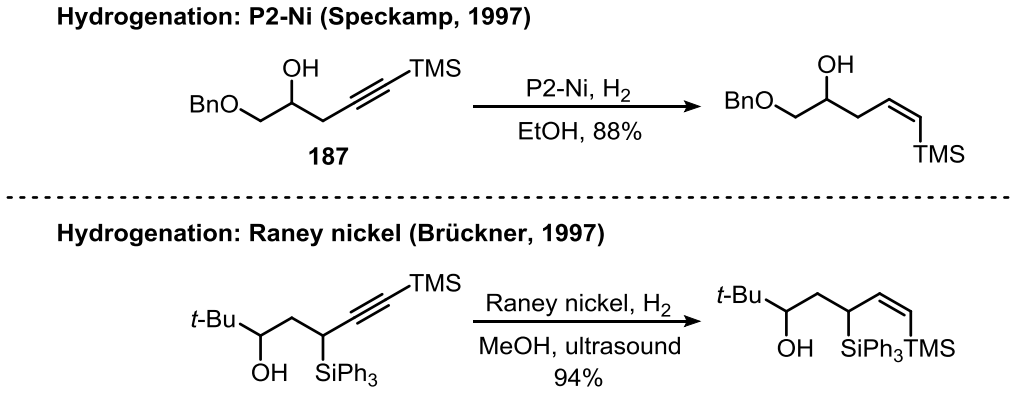
In the synthesis of 11-*cis*-retinol, López *et al*. demonstrated the use hydrozirconation followed by protodemetalation for the stereoselective preparation of *Z*-vinylsilane **186** (Scheme 2.15).[91] Initial attempts at *cis*-reduction using the Lindlar hydrogenation, hydroalumination, and various other procedures, all gave poor yields and/or overreduction.



Scheme 2.15: Hydrozirconation/protodemetalation sequence (López, 2012)

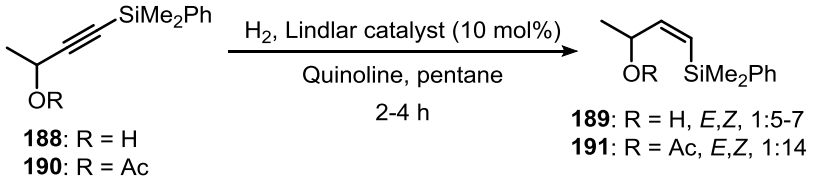
As is discussed in the above examples, hydrogenation in the presence of heterogeneous catalysts, such as the Lindlar catalyst, can be plagued with inconsistency, unreliable stereoselectivity and overreduction. However, the broad functional group tolerance displayed by such systems and their operational simplicity suggests them as an attractive option for the *cis*-selective semi-reduction of alkynes. In the context of alkynylsilanes, numerous heterogeneous systems have been deployed, such as P2-Ni (Brown catalyst), Raney nickel, Lindlar catalyst (Pd deposited on $CaCO_3$ with or without lead acetate) and Rosenmund catalyst (Pd deposited on $BaSO_4$). Speckamp *et al*. found the use of P2-Ni gave exclusive *cis*-reduction of alkynylsilane **187**

(Scheme 2.16).[128] Similar *cis*-selectivities have been reported by Brückner *et al*. using Raney nickel as catalyst.[129]



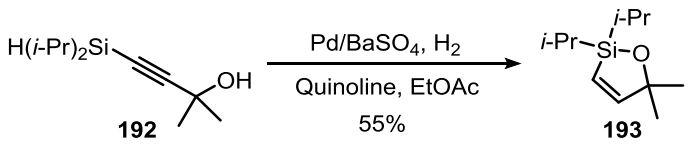
Scheme 2.16: Hydrogenation in presence of heterogeneous nickel catalysts

Since its discovery, the Lindlar catalyst has been widely employed in total synthesis due to impressive tolerance of functional groups including esters, carboxylic acids, hydroxyls, halides, many protecting groups, etc. Although good stereoselectivity is generally obtained, Panek *et al*. found that the presence of a free propargylic alcohol can affect the diastereoselectivity (Scheme 2.17).[130] When free propargyl alcohol **188** was submitted to the Lindlar hydrogenation, vinylsilane **189** was obtained with poor *cis*-selectivity (*E*,*Z*, 1:5-7). However, when acetate **190** was subjected to the same conditions vinylsilane **191** was afforded with much improved *cis*-selectivity (*E*,*Z*, 1:14).



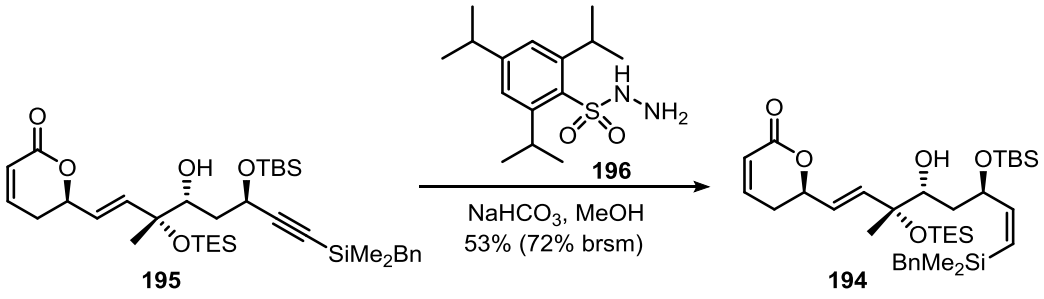
Scheme 2.17: Hydrogenation in presence of Lindlar catalyst (Panek, 1992)

Salomon *et al*. reported the use of Rosenmund catalyst for the semi-hydrogenation of propargyl alcohol **192** followed by *in situ* dehydrogenative cyclisation to generate 5-membered cyclic alkenylsiloxane **193** (Scheme 2.18). Although the *cis*-selectivity is not reported, this single example represents the first use of semi-hydrogenation of an alkynylsilane for the preparation of cyclic alkenylsiloxanes.



Scheme 2.18: Hydrogenation in presence of Rosenmund catalyst (Salomon, 1994)

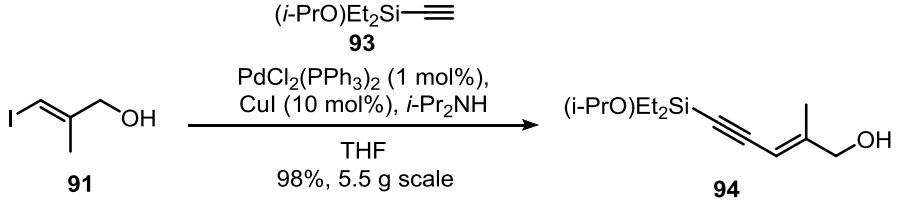
Other methods for the stereoselective reduction of alkynylsilanes include the use of diimide as reducing agent. Towards the synthesis of fostriecin, reported by Trost *et al*., vinylsilane **194** was required (Scheme 2.19).[131] Where other methods to effect the *cis*-reduction of **195** were hampered by low yield and/or overreduction, diimide precursor **196** afforded the *cis* vinylsilane **194** in moderate yield (incomplete conversion) under mild conditions and in the presence of both free hydroxyl and *O*-silylated protecting groups.



Scheme 2.19: Diimide cis-reduction of alkynylsilanes (Trost, 2005)

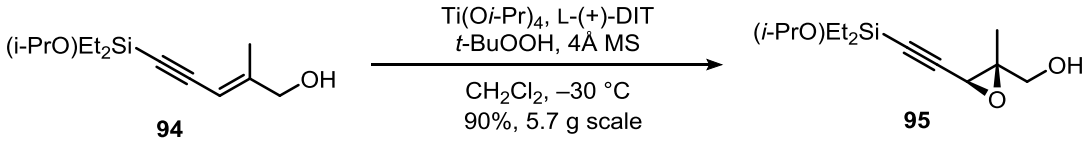
2.2.3 C6-C14 Cyclic alkenylsiloxane synthesis

The synthesis of the C6-C14 cyclic alkenylsiloxane fragments builds on a route developed previously by Lim. This commenced with Sonogashira coupling of common intermediate vinyl iodide **91** with diethylisopropoxysilylacetylene **93**, to provide multi-gram quantities of enyne **94** in excellent yield (Scheme 2.20).[132]



Scheme 2.20: Sonogashira reaction on multi-gram scale

With enyne **94** in hand, asymmetric epoxidation was carried out under the Sharpless conditions, providing epoxide **95** in very good yield and on multi-gram scale (Scheme 2.21).[68,69] However, during the completion of this work it was discovered that the previously established Sharpless epoxidation, using conditions deploying L-(+)-diisopropyl tartrate as the ligand, affords the incorrect enantiomer of epoxide **95**, in contrast with the results stated by Lim (Scheme 1.20).[64] As such, and from this point onwards, the synthesis of the opposite enantiomeric series of incednam, with regards to the C10, C11-diol, will be described. Isolation of **95** had proved difficult due to the sensitive nature of the isopropoxysilane motif, as neither acidic nor basic workup conditions, typically associated with titanium, are tolerated. However, the use of a sodium sulfate workup, which is especially suited for acid sensitive epoxides, was found to exclusively afford the desired epoxide.[64,133]

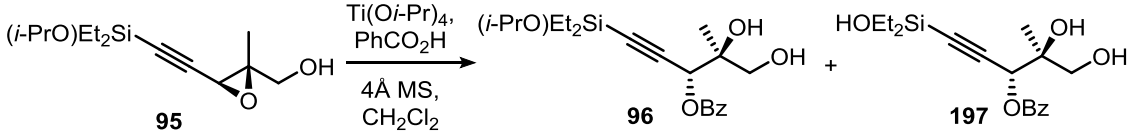


*Scheme 2.21: Asymmetric epoxidation of **94** on multi-gram scale*

Next, a titanium-mediated regioselective ring-opening of 2,3-epoxy alcohol **95** with benzoic acid to yield **96** was required (Table 2.1). The choice of benzoic acid is important as the presence of a propargylic acetyl ester not only improves the stereoselectivity of the key hydrogenation step but also enables the selective formation of the 6-membered ring by protecting the favoured 5-membered cyclisation site. Furthermore, facile removal with concomitant rearrangement, allows the formation of the 5-membered ring when required. As was previously discussed, isolation of benzoyl triol **96** had proved difficult (see section 1.5.2). While an (wet) acetone workup allowed the reaction to be performed at up to 1 mmol scale (Entries 1 to 3, Table 2.1), any increase met with failure. At this stage, having installed the benzoate chromophore, the

enantiomeric excess of **96** was determined to be 88% by chiral HPLC. Attempts were made to fine-tune the workup conditions so that the titanium could be fully hydrolysed while retaining the somewhat delicate isopropoxysilane functionality. Workup conditions involving pH 7 phosphate buffer (Entry 4) and aqueous NH_4Cl (Entry 6) showed promise on small scale, but as before failed on a larger reaction scale (Entry 5). Use of a solution of EDTA to act as a metal scavenger was also ineffective (Entry 7). More conventional acidic workup conditions provided silanol **197** (Entry 8), which also applied to a multi-gram scale (Entry 9).[70]

Table 2.1: Titanium-mediated regioselective ring-opening

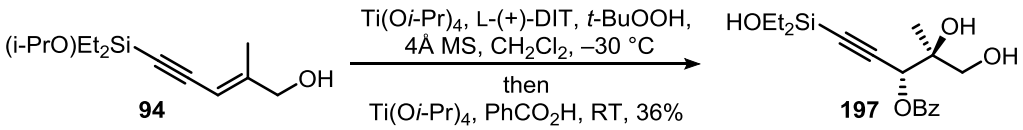


Entry[a]	mmol	workup conditions	**96**:**197**	Yield [%][b]
1[c]	0.098	acetone/H_2O	1:0	76
2[d]	2.52	acetone/H_2O	1:0	38
3[c]	9.90	acetone/H_2O	1:0	33
4	0.32	pH 7 buffer[e]	1:0	57
5	3.34	pH 7 buffer[e]	n.d.[f]	n.d.[f,g]
6	0.32	aq. NH_4Cl	1:0	54
7	0.20	aq. EDTA[h]	n.d.[f]	n.d.[f]
8	0.34	aq. H_2SO_4[i]	1:3	56[j]
9	21.6	aq. H_2SO_4[i]	0:1	75[j]

[a] Reaction stirred for 1 h at RT before quenching. [b] Yield of **96** unless otherwise noted. [c] Results obtained by Diane Lim. [d] 88% *ee*. [e] Phosphate buffer. [f] Not determined. [g] Product not isolated due to difficulties during column chromatography in presence of titanium. [h] 0.4 M solution of EDTA. [i] 5% aqueous solution of H_2SO_4. [j] Yield of silanol **197**.

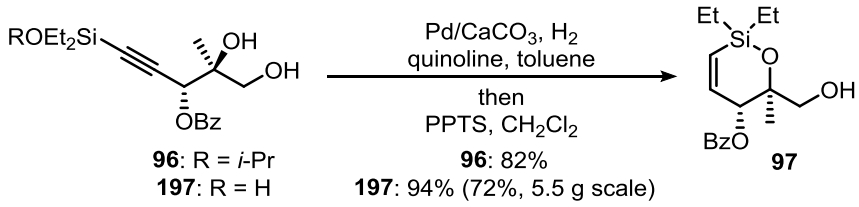
As Ti(O*i*-Pr)$_4$ is used to promote both the epoxidation as well as the epoxide opening, attempts were made to combine both processes in a one-pot fashion. First, the asymmetric epoxidation was carried out with sub-stoichiometric Ti(O*i*-Pr)$_4$ followed by further addition of Ti(O*i*-Pr)$_4$ and benzoic acid to give silanol **197**, after acidic workup,

in moderate yield (Scheme 2.22). However, given the success of the stepwise approach, no further attempts were made to improve this one-pot procedure.



Scheme 2.22: One-pot titanium-mediated epoxidation/epoxide opening

Stereoselective semi-hydrogenation of alkynylsilane **96** afforded the *Z*-alkenylsilane which then underwent intramolecular cyclisation under mildly acidic conditions to give the key 6-membered cyclic alkenylsiloxane **97** (Scheme 2.23). Much to our delight, when silanol **197** was subjected to the same conditions cyclic siloxane **97** was readily obtained, thus enabling access to this key intermediate towards incednam on a synthetically useful scale *via* silanol **197**.

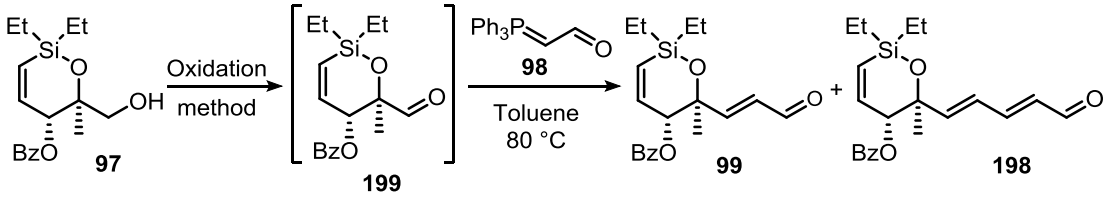


Scheme 2.23: The key hydrogenation step

Further manipulations of siloxane **97** had involved Parikh-Doering oxidation followed by Wittig olefination of the resulting aldehyde with phosphorane **98** to give α,β-unsaturated aldehyde **99** (Table 2.2). Although the desired aldehyde could be obtained in good yield, this sequence was plagued with inconsistency due to the ability of **99** to undergo a competing second olefination, resulting in varying product distributions of **99** and **198** (Entry 1). In an attempt to limit the formation of **198**, the stoichiometry of phosphorane **98** was investigated. While full conversion of the aldehyde starting material was still maintained, no effect was observed on the product distribution (Entry 2). Next, different methods of oxidation were examined (Entries 3 and 4). While both Dess-Martin and Swern oxidations saw improvements in the

formation of aldehyde **199**, similar results were obtained from the olefination step. However, upon purification of the intermediate aldehyde **199** prior to the olefination, near exclusive formation of the desired product **99** was obtained (Entries 5 and 6). Furthermore, this successful modification was found to be consistent on multi-gram scale (Entry 7).

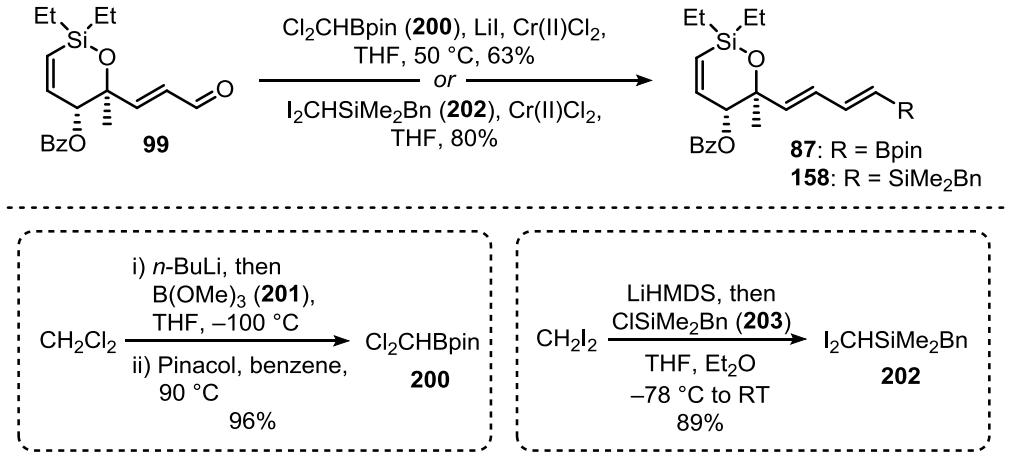
Table 2.2: Sequential oxidation-olefination strategy



Entry	**98** [eq.]	Oxidation method	**199** [%][a]	**99**:**198**[b]	Yield [%][c]
1[d]	1.5	SO_3•py, DMSO, DIPEA, CH_2Cl_2	n.d.	3-4.5:1	46-67
2	1.1	SO_3•py, DMSO, DIPEA, CH_2Cl_2	71	4.2:1	62
3	1.1	DMP, CH_2Cl_2	quant.	2:1	40
4	1.1	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	quant.	4.1:1	66
5	1.05	DMP, CH_2Cl_2	88[e]	35:1	70
6	1.05	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	91[e]	27:1	75
7[f]	1.05	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	87[e]	n.d.	78

[a] Yield of crude **199** unless otherwise noted. [b] Determined by quantified isolation. [c] Isolated yield of **99** after chromatography. [d] Results obtained by Diane Lim. [e] Isolated yield of **199** after chromatography. [f] Reaction performed on a 3.1 g scale.

Finally, a variation of the Takai reaction, using dichloromethylboronic ester **200** afforded the C6-C13 dienyl boronic ester fragment **87** in 63% yield (Scheme 2.24).[134,135] Boronic ester **200** was generated from trimethylborate (**201**) using a modified procedure reported by Jacobsen *et al.*[136] Similarly, the C6-C13 dienyl benzyldimethylsilane fragment **158** was afforded in 80% yield using benzyl(diiodomethyl)dimethylsilane **202**, a novel reagent developed by Lim which was prepared in one step from benzylchlorodimethylsilane (**203**).[137]

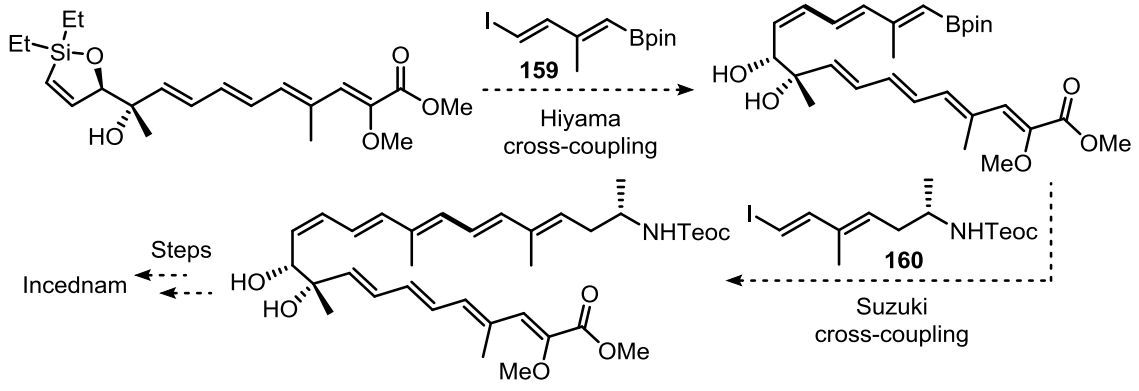


Scheme 2.24: Takai borylolefination for the construction of alkenylboronic ester

Overall the key fragments **87** and **158** were achieved from propargyl alcohol (**90**) in a total of 8 steps as the longest linear sequence with an overall yield of 19% and 23%, respectively.

2.3 Towards incednam ─ Sequential Hiyama-Suzuki strategy

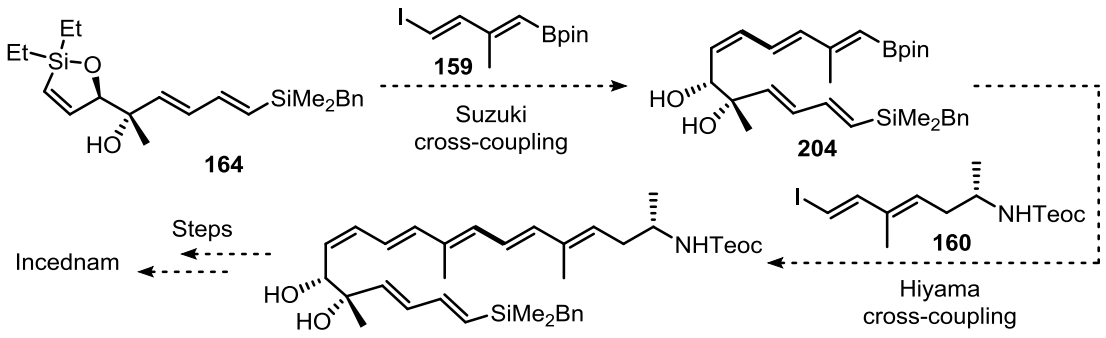
In light of the difficulties experienced by Lim in the stereoselective preparation of the tetraenyl iodide fragment **107**, a stepwise assembly of the C12-C21 pentaene *via* sequential Hiyama and Suzuki cross-couplings with C14-C17 boronate **159** and C18-C23 dienyl iodide **160** was envisaged (Scheme 2.25).



Scheme 2.25: Sequential Hiyama-Suzuki cross-coupling of full length tetraenoate

Alternatively, this could take place *via* base-promoted Hiyama cross-coupling of bis-silane **164** with boronate **159** to give **204** (Scheme 2.26). Orthogonal activation of the boron would then deliver the full length C12-C21 pentaene system *via* Suzuki

cross-coupling of **204** with dienyl iodide **160**.



Scheme 2.26: Orthogonal modes of activation: Sequential Hiyama-Suzuki coupling

2.3.1 C14-C17 Boronate fragment synthesis

The synthesis of the C14-C17 boronate fragment **159** was envisaged to take place *via* boronate **205**, obtained by Miyaura borylation of common intermediate **91** (Figure 2.2). Takai olefination would then deliver the desired vinyl iodide **159** *via* aldehyde **206**.

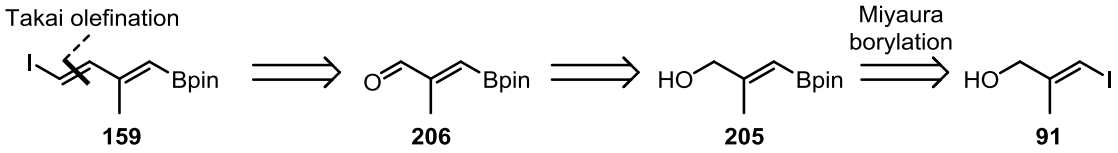


Figure 2.2: Retrosynthetic analysis of the C14-C17 boronate fragment

Borylation of vinyl iodide **91** with bis(pinacolato)diboron was attempted in the presence of $Pd(dppf)Cl_2$ and potassium acetate as the base, using conditions reported by Miyaura *et al*. (Table 2.3, Entry 1).[138,139] Under these conditions vinyl boronate **205** was afforded in moderate yield (26%). However, when **207**, the TBS protected analogue of allylic alcohol **91**, was subjected to the same conditions, boronate **208** was achieved with an increase in yield (39%, Entry 2). The use of a strong base has been reported to accelerate the transmetallation process in the Miyaura borylation reaction, where the formation of byproducts can be ascribed to a slow rate of transmetallation.[140] When **91** and B_2pin_2 were subjected to a combination of $PdCl_2(PPh_3)_2$ and KOPh in toluene,

boronate **205** was afforded in 51% yield (Entry 3).[141] Pleasingly, under the same conditions, boronate **208** was achieved in 76% yield from TBS protected **207** (Entry 4).

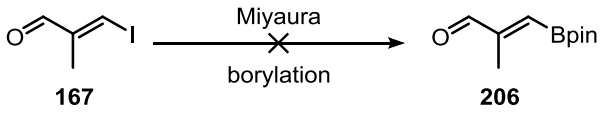
Table 2.3: Miyaura borylation of vinyl iodide



Entry	Iodide	Condition	Boronate	Yield[%][a]
1	**91**	Method A	**205**	26
2	**207**	Method A	**208**	39
3	**91**	Method B	**205**	51
4	**207**	Method B	**208**	76
5	**91**	Method C	**205**	11
6	**207**	Method C	**208**	45

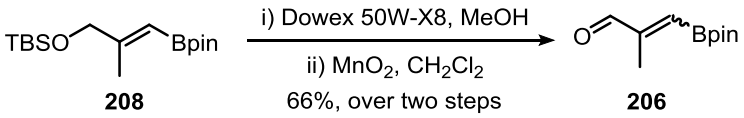
[a] Isolated yield after chromatography. Conditon: Method A: $Pd(dppf)Cl_2$ (3 mol%), B_2pin_2, KOAc, DMSO, 80°C; Method B: $PdCl_2(PPh_3)_2$ (3 mol%), B_2pin_2, KOPh, toluene, 50 °C; Method C: *n*-BuLi, $B(Oi\text{-}Pr)_3$, pinacol, toluene, THF, −78 °C.

For comparison, lithium-halide exchange of both **91** and **207** with subsequent quenching of the vinyl lithium species with triisopropylborate, followed by addition of pinacol, afforded boronate **205** (Entry 5) and **208** (Entry 6) in 11% and 45% yield respectively.[142] In contrast, when enal **167** was subjected to the Miyaura borylation conditions no formation of boronate **206** was observed (Scheme 2.27).



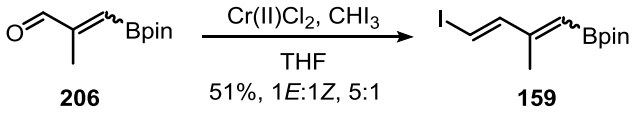
*Scheme 2.27: Attempted Miyaura borylation of enal **167***

With boronate **208** in hand, the required desilylation was accomplished with Dowex 50W-X8 (carboxylic acid resin) which, after filtration and removal of volatiles, was followed by allylic oxidation of the resulting free alcohol using MnO_2 to give enal **206** in good yield over two steps (Scheme 2.28).



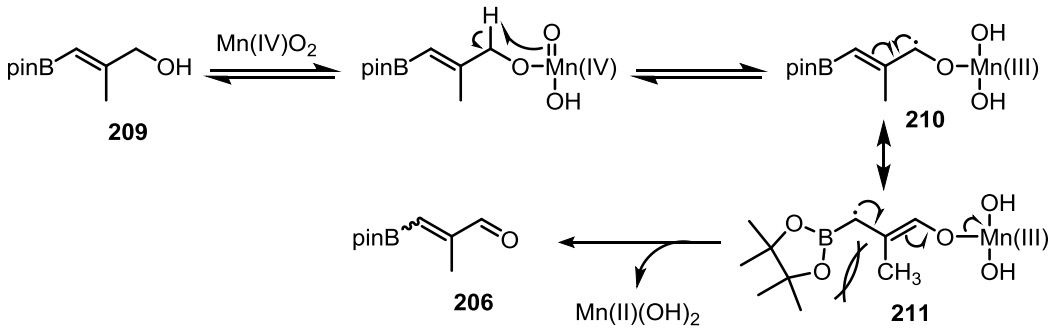
*Scheme 2.28: Preparation of aldehyde **206** by desilylation and oxidation*

Finally, Takai olefination afforded the C14-C17 boronate fragment **159** in 51% yield and as a mixture of isomers (1*E*:1*Z*, 5:1) (Scheme 2.29).



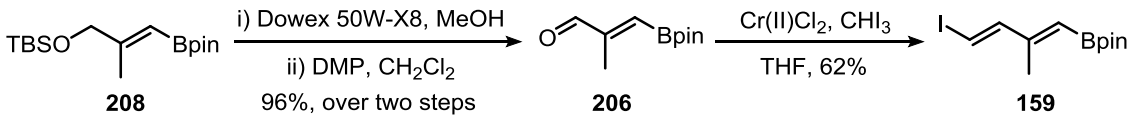
Scheme 2.29: Takai olefination for the preparation of C14-C17 boronate fragment

Rather than being the result of the Takai olefination, this unexpected isomerisation is thought to have arisen from the oxidation of **205**. The mechanism of the MnO_2 oxidation is not entirely known, it has however been proposed to proceed by a radical pathway.[143] This suggests that *cis*/*trans* isomerisation of **206** proceeds *via* a resonance-stabilised allylic radical **210** formed in the MnO_2 oxidation, and is driven by relief of 1,2-allylic strain in **211** (Scheme 2.30).



Scheme 2.30: Proposed mechanism of MnO_2 mediated allylic oxidation

In support of this, geometrically pure dienyl boronate **159** was obtained, after Takai olefination, when a Dess-Martin oxidation was performed instead (Scheme 2.31).

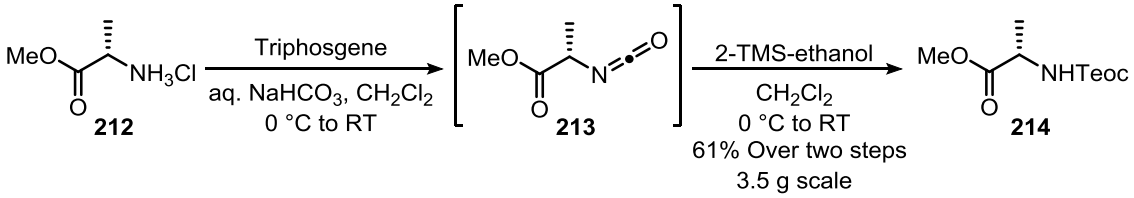


Scheme 2.31: Stereoselective preparation of C14-C17 boronate fragment

Overall the C14-C17 boronate fragment **159** was achieved in total of 6 linear steps, from propargyl alcohol (**90**), with an overall yield of 25%.

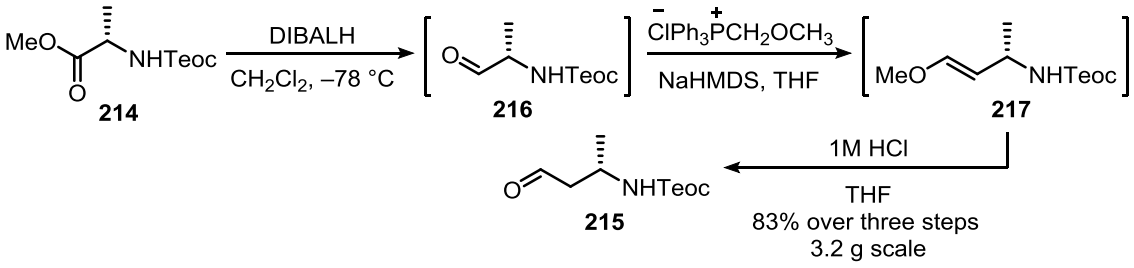
2.3.2 C18-C23 Dienyl iodide fragment synthesis

The asymmetric synthesis of the C14-C23 dienyl iodide fragment **160** builds on work previously described by Lim and commenced with *N*-Teoc carbamate protection of commercially available L-alanine methyl ester hydrochloride (**212**) (Scheme 2.32).[64] First **212** was treated with triphosgene to afford isocyanide **213**, which upon treatment with 2-TMS-ethanol afforded the *N*-Teoc protected amino ester **214** in good yield.



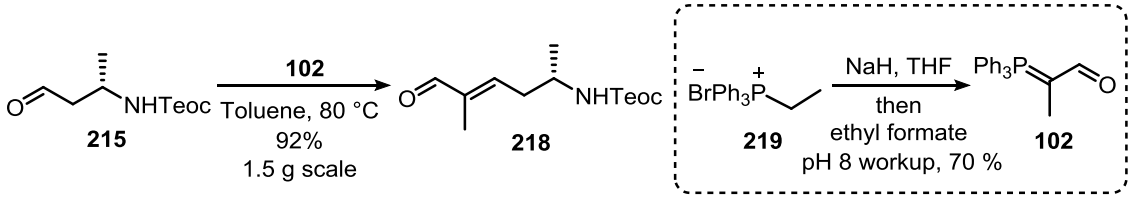
*Scheme 2.32: N-Teoc protection of hydrochloride salt **212***

Aldehyde **215** was prepared in three sequential steps from **214**: first, a DIBALH reduction afforded the α-amino aldehyde **216**, which upon Wittig olefination and subsequent acidic hydrolysis of the resulting enol ether **217** afforded aldehyde **215** in 83% yield over three steps (Scheme 2.33).



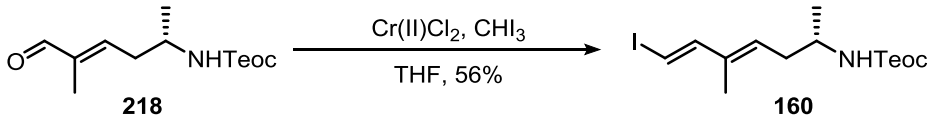
*Scheme 2.33: Three step procedure for the preparation of aldehyde **215***

The required α,β-unsaturated aldehyde **218** was afforded *via* Wittig olefination with phosphorane **102** in 92% yield (Scheme 2.34). Phosphorane **102** was prepared by deprotonation of phosphonium salt **219** with sodium hydride followed by quenching of the resulting phosphorane with ethyl formate to give **102** upon basic workup.



*Scheme 2.34: Preparation of α,β-unsaturated aldehyde **218***

At this stage the enantiomeric excess was determined to be 84% by chiral HPLC. Having commenced the synthesis from enantiopure L-alanine methyl ester hydrochloride (**212**), it is likely that this loss of enantiopurity is due to epimerisation of α-amino aldehyde **216**. Finally, Takai olefination of aldehyde **218** afforded the dienyl iodide **160** (Scheme 2.35).

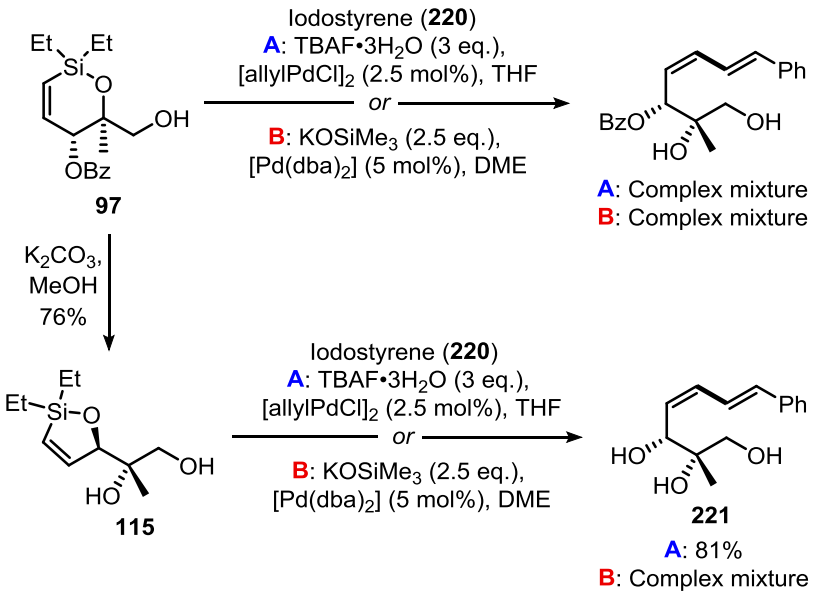


Scheme 2.35: Preparation of the C18-C23 dienyl iodide fragment by Takai olefination

Overall the asymmetric synthesis of the C18-C23 dienyl iodide fragment **160** was achieved in total of 7 linear steps, from L-alanine methyl ester hydrochloride (**212**), with an overall yield of 26%.

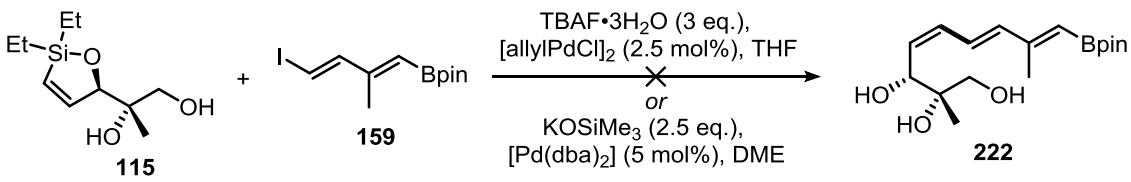
2.3.3 Fragment union ─ Sequential Hiyama-Suzuki cross-coupling

Having successfully prepared the required building blocks to assemble incednam, work towards its assembly was undertaken. First, the cross-coupling of 5- and 6-membered cyclic alkenylsiloxanes **97** and **115** with iodostyrene (**220**), under both fluoride-promoted and fluoride-free conditions was investigated (Scheme 2.36). Disappointingly, when 6-membered cyclic siloxane **97** was subjected to our standard fluoride-promoted Hiyama coupling conditions, only a complex mixture was returned. While expecting siloxane **97** to remain unreactive, a similar complex mixture was returned when performed under the fluoride-free coupling conditions.



Scheme 2.36: Model fluoride-promoted and fluoride-free Hiyama cross-coupling

Gratifyingly, 5-membered cyclic siloxane **115**, generated from **97** by benzoyl removal and concomitant trans-etherification, was found to give the desired allylic diene **221** in 81% yield under fluoride activation. In contrast, only a complex mixture was obtained upon base-promoted coupling of **115**. These results suggest the necessity of fluoride-activation of 5-membered cyclic siloxane precursor in order for successful construction of the key C12-C13 bond to take place *via* the Hiyama cross-coupling reaction. Encouraged by the high yield obtained in the coupling of siloxane **115** with model iodostyrene (**220**), the fluoride-promoted Hiyama cross-coupling of boronate **159** with 5-membered **115** was attempted (Scheme 2.37). To our disappointment no formation of the desired allylic triene **222** was observed and only a complex mixture was returned. Similar results were obtained when the base-promoted conditions were employed.

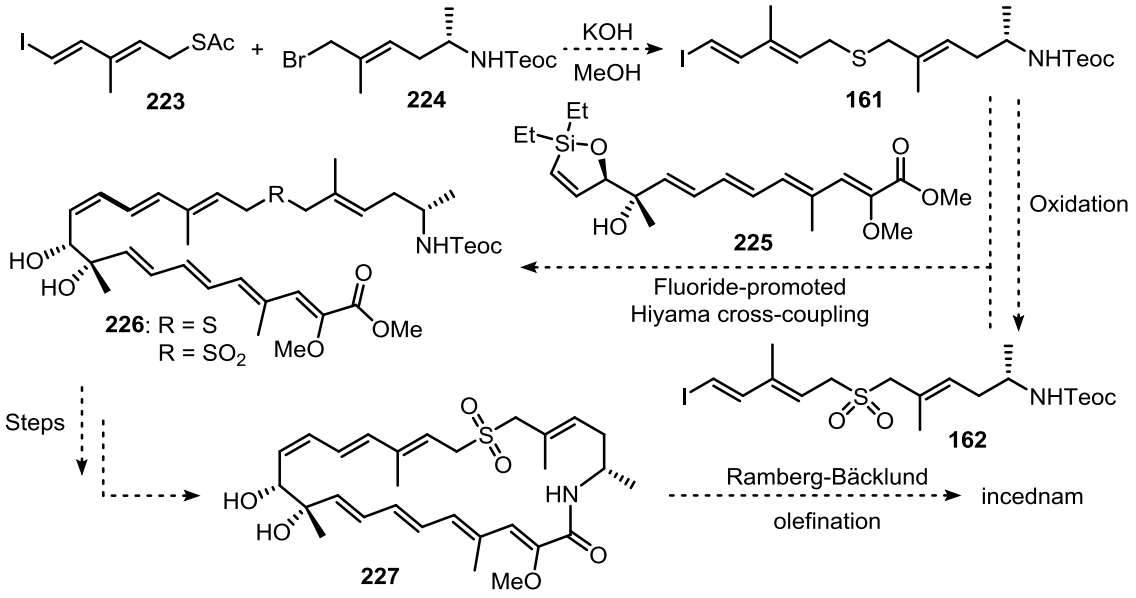


*Scheme 2.37: Hiyama cross-coupling with boronate **159***

While the fluoro- and oxophilicity of boron is well known, no decomposition was observed upon treatment of boronate **159** with TBAF (3 eq.) in THF or $KOSiMe_3$ (3 eq.) in dimethoxyethane (DME), with full recovery of the starting material even after two days.

2.4 Towards incednam – Ramberg-Bäcklund strategy

An alternative approach involves the latent construction of the C12-C21 pentaene *via* Ramberg-Bäcklund olefination (RBO), introduced *via* Hiyama cross-coupling of sulfide **161** (or sulfone **162**) (Scheme 2.38). This would commence with coupling of allylic precursors **223** and **224** followed by Hiyama cross-coupling of the resulting sulfide **161** (or sulfone **162**) with tetraenoate **225** to give **226** (or the analogous sulfone).



Scheme 2.38: Latent construction of the C12-C21 pentaene via RBO strategy

One possibility at this stage would be macrocyclisation to give **227**, which upon RBO would deliver the sensitive pentaene as the last step of the incednam synthesis.

2.4.1 C14-C17 Sulfone precursor synthesis

We envisaged the synthesis of the C14-C17 sulfone precursor **223** would arise from thiolation of allylic alcohol **228** obtained from dienoate **229**, itself the result of Takai

olefination of α,β-unsaturated aldehyde **230** prepared *via* Wittig olefination of aldehyde such as **231** (Figure 2.3).

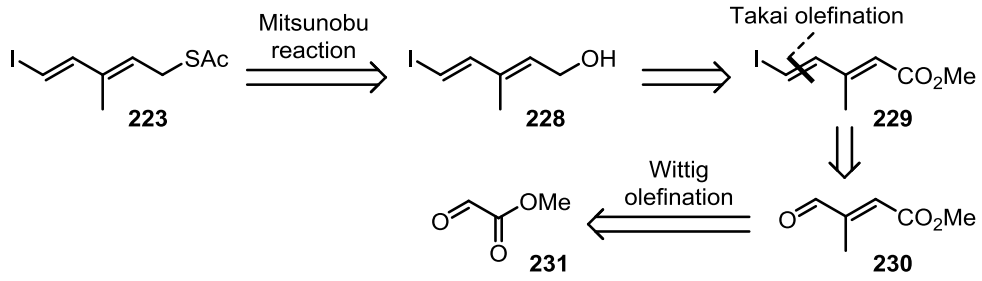
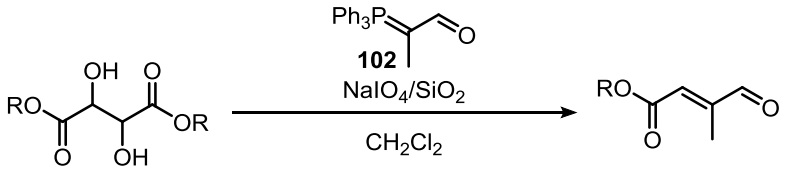


Figure 2.3: Retrosynthetic analysis of the C14-C17 sulfone precursor

The synthesis of sulfone **223** commenced with one-pot oxidative cleavage of dimethyl tartrate (**232**) with sodium periodate on silica gel and *in situ* olefination with phosphorane **102** using a one-pot procedure reported by Dunlap *et al*. (Table 2.4, Entry 1).[144]

Table 2.4: One-pot oxidative cleavage/olefination of tartrates

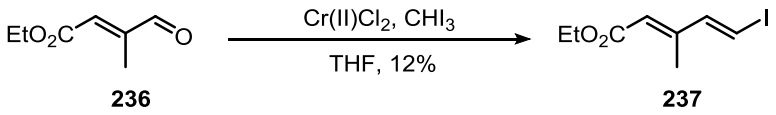


Entry	Tartrate	Product	Yield [%]	*E*:*Z*[a]
1	**232**	**230**	42	3:1
2	**234**	**236**	69	10:1
3	**235**	**303**	79	15:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

While dimethyl tartrate (**232**) provided the desired α,β-unsaturated aldehyde **230**, moderate yield were obtained and as a mixture of isomers, However, an increase in both yield and stereoselectivity was obtained when more sterically demanding tartrates **234** and **235** were employed (Entries 2 and 3).

Next, Takai olefination of aldehyde **236** afforded the desired iodo dienoate **237** in 12% yield (Scheme 2.39).

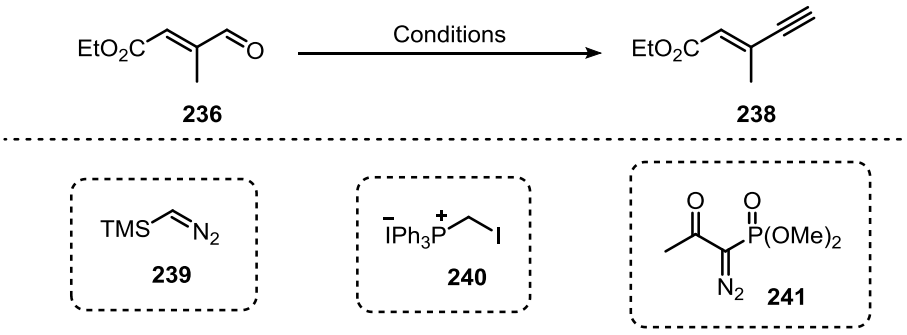


236 **237**

*Scheme 2.39: Low yielding Takai olefination of **236***

The disappointing yield obtained led us to consider a hydrozirconation/iodination as an alternative strategy toward dienyl iodide **237**. This would require the preparation of enyne **238** from aldehyde **236**. When **236** was submitted to TMS-diazomethane (**239**) promoted Colvin alkynylation conditions only decomposition of **236** was observed (Table 2.5, Entry 1).[145]

*Table 2.4: Attempted alkynylation of aldehyde **237***



236 **238**

239 **240** **241**

Entry	Conditions	Conv. [%][a]	Yield [%][b]
1	**239**, LiHMDS, THF, −78 °C to RT	100	—
2	PPh_3, CBr_4, CH_2Cl_2, 0 °C	100	—
3	**240**, NaHMDS, THF then *t*-BuOK	100	—
4	**240**, NaHMDS, THF then TBAF	100	—
5	**241**, K_2CO_3, MeOH	100	—

[a] Determined by TLC analysis of the reaction mixture. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Attempts to apply the Corey-Fuchs procedure (Entry 2) or the Stork-Zhao olefination/elimination alkynylation protocol using potassium *tert*-butoxide (Entry 3) or TBAF (Entry 4) as base were also unsuccessful.[146–148] Even mild conditions employing

the Ohira-Bestmann diazophosphonate **241** did not deliver any trace of the desired enyne **238** (Entry 5).[149] The delicate nature of aldehyde **236** led us to contemplate a revised strategy towards the elusive C14-C17 sulfone precursor **223** *via* iododesilylation of **242** obtained from hydrosilylation of enyne **238** (Figure 2.4).

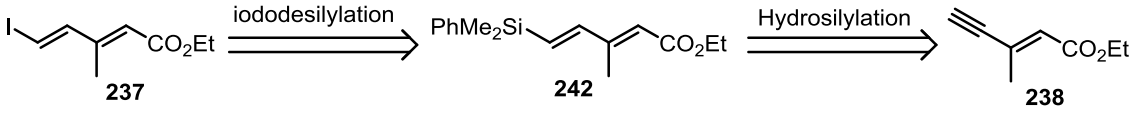
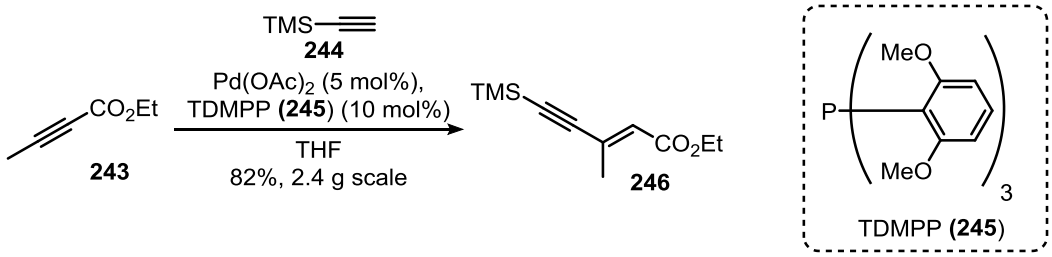


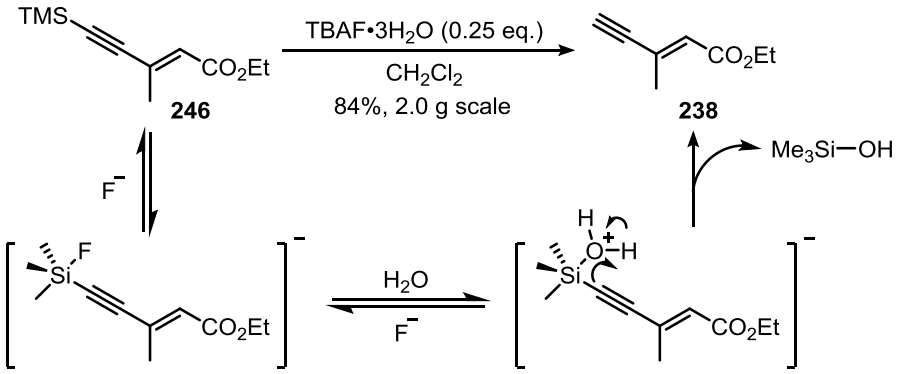
Figure 2.4: Retrosynthetic analysis of the C14-C17 sulfone precursor

This sequence commenced with cross-coupling of ethyl-2-butynoate (**243**) and trimethylsilylacetylene (**244**) in the presence of $Pd(OAc)_2$ and phosphine ligand **245**, using conditions developed by Trost *et al.* (Scheme 2.40).[150] The use of the electron rich sterically encumbered ligand **245** is critical to prevent side reactions, such as competing cycloisomerisations, and promote the diyne coupling.



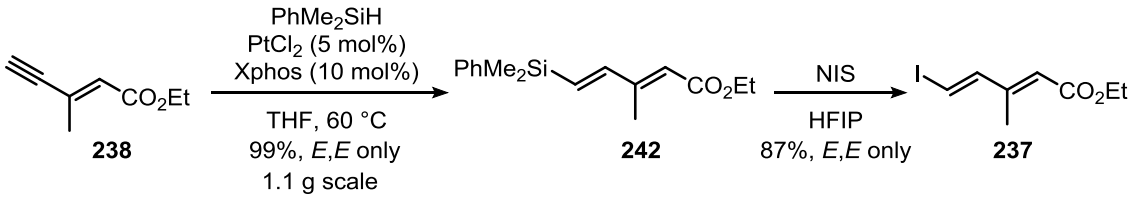
*Scheme 2.40: Preparation of enyne **246** via diyne cross-coupling*

Next, desilylation of TMS protected enyne **246** was required. While the desired enyne **238** was afforded using potassium carbonate in ethanol, removal of volatiles proved difficult due to the low molecular mass of product **238**. We therefore tested TBAF•$3H_2O$, and speculated whether the reaction could proceed in the presence of catalytic amounts of fluoride (Scheme 2.41). To our delight, instantaneous desilylation was observed employing just 0.25 equivalents of TBAF•$3H_2O$ in CH_2Cl_2, affording enyne **238** in very good yield. Upon lowering the amount of TBAF•$3H_2O$ the reaction proceeded sluggishly.



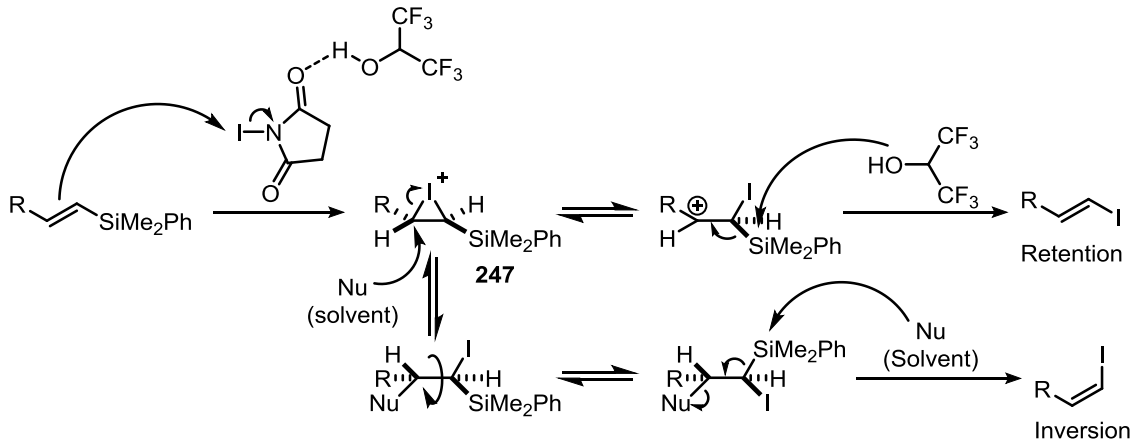
*Scheme 2.41: Preparation of enyne **238** by catalytic fluoride promoted desilylation*

Next, a regio- and stereoselective *syn*-hydrosilylation of enyne **238** with phenyldimethylsilane catalysed by $PtCl_2$ and Xphos afforded *E*,*E*-dienyl silane **242** in quantitative yield, using conditions developed by Alami *et al*. (Scheme 2.42).[151] The key iododesilylation of **242** was achieved using NIS and hexafluoroisopropanol (HFIP) as the solvent to give dienyl iodide **237** in excellent yield and with complete retention of configuration.[152]



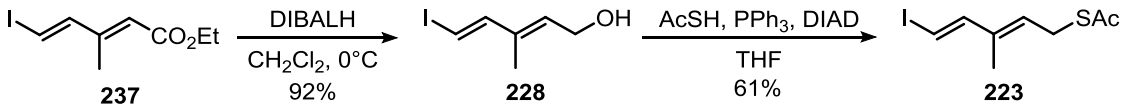
*Scheme 2.42: Preparation of dienyl iodide **237** from enyne **238***

Zakarian *et al*. found the use of HFIP plays a critical role in this transformation due to its low nucleophilicity and strong hydrogen-bond donating power *via* electrophilic activation of NIS resulting in significant rate acceleration (Scheme 2.43). As a result, nucleophilic addition at the β carbon of iodonium intermediate **247**, which results in vinyl iodide with inverted stereochemistry *via* antiperiplanar elimination, is largely prevented thus favouring the product with retention of stereochemistry.



Scheme 2.43: Proposed iododesilylation mechanism

Finally, the C14-C17 sulfone precursor **223** was afforded *via* DIBALH reduction of dienoate **237** to give allylic alcohol **228**, which was converted to a thioacetate under Mitsunobu conditions to afford sulfone **223** (Scheme 2.44).

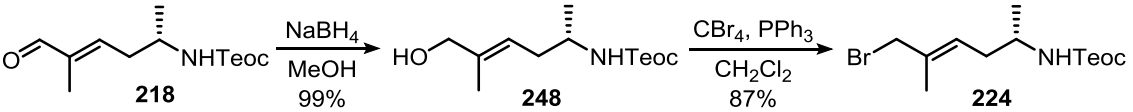


Scheme 2.44: Preparation of the C14-C17 sulfone precursor

Overall the synthesis of the elusive C14-C17 sulfone precursor **223** was achieved in a total of 6 linear steps from ethyl-2-butynoate (**243**), with an overall yield of 33%.

2.4.2 C18-C23 Allyl bromide precursor synthesis

The synthesis of the C18-C23 allyl bromide precursor **224** is reported by Christian Kuper and commenced with reduction of common intermediate **218** to give allylic alcohol **248** (Scheme 2.45).[153]



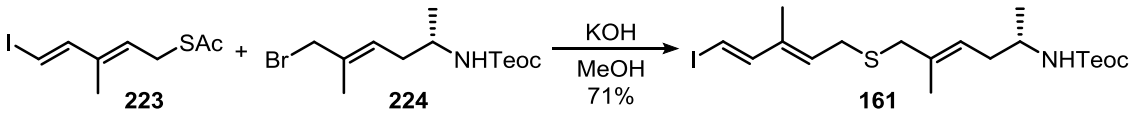
Scheme 2.45: Preparation of C18-C23 allyl bromide precursor by Kuper

Bromination of allylic alcohol **248** was then achieved under the Appel conditions to give the C18-C23 allyl bromide precursor **224** in total of 8 linear steps, from L-alanine

methyl ester hydrochloride (**212**), with an overall yield of 36%.

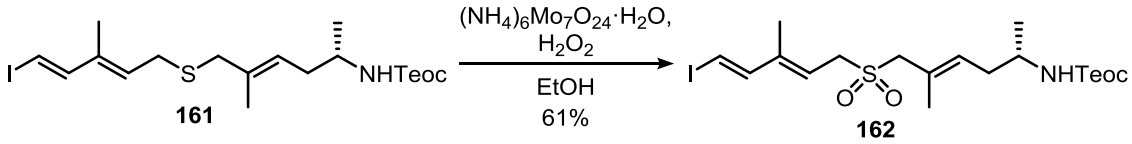
2.4.3 Fragment union – Ramberg-Bäcklund strategy

With allylic precursors **223** and **224** in hand, their union was achieved using potassium hydroxide in methanol to give sulfide **161** in good yield (Scheme 2.46).[154]



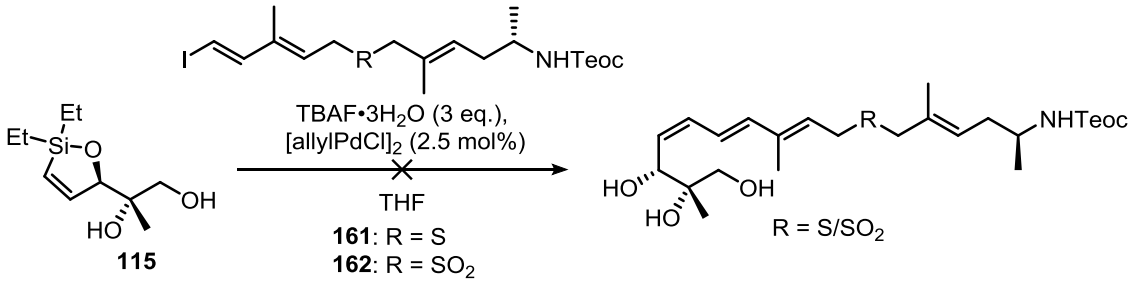
*Scheme 2.46: Preparation of sulfide **161** fragment*

In addition, Kuper demonstrated that sulfide **161** undergoes mild oxidation to give sulfone **162** (Scheme 2.47).[153]



*Scheme 2.47: Oxidation of sulfide **161** to give sulfone **162** fragment by Kuper*

Next, the fluoride-promoted coupling of sulfide **161** with 5-membered cyclic alkenylsiloxane **115** was attempted (Scheme 2.48).



*Scheme 2.48: Fluoride promoted Hiyama cross-coupling of sulfide **161** and sulfone **162***

Although sulfide **161** was consumed during the course of the reaction, much to our disappointment, only a complex mixture was returned. Similarly, cross-coupling of sulfone **162** with cyclic siloxane **115** proved unsuccessful under the standard fluoride-promoted Hiyama conditions. To the best of our knowledge, there are no reported examples in the literature of allylic sulfides or sulfones that participate in

palladium-catalysed cross-coupling reactions, we can only speculate whether such motifs are tolerated.

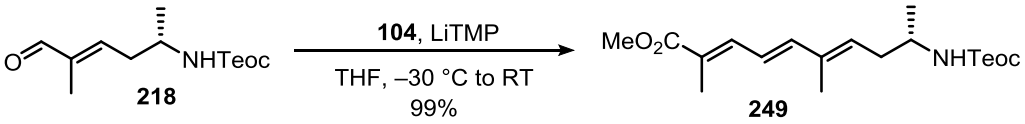
2.5 Towards incednam ─ Revisiting the tetraenyl iodide

While previous work by Lim had successfully demonstrated the cross-coupling of tetraenyl iodides **107** (10*E*:10*Z,* 2:1) with model 5-membered cyclic alkenylsiloxane **115**, we had thus far been unsuccessful in our attempts towards a refined synthesis of the C12-C21 pentaene. In hope that the less hindered *E*-vinyl iodide would preferentially couple in presence of the more sterically demanding *Z*-isomer, the synthesis of the C14-C23 tetraenyl iodide fragment **89** was undertaken.

2.5.1 C14-C23 Tetraenyl iodide fragment synthesis

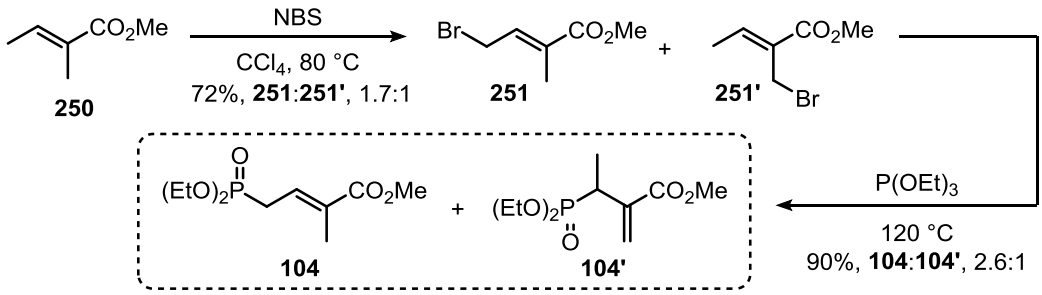
Work towards the tetraenyl fragment commenced with preparation of racemic trienol **105** and is summarised in Scheme 1.21.[64]

The asymmetric synthesis of the C14-C23 tetraenyl fragment **89** builds on this work and commenced with HWE olefination of common intermediate α,β-unsaturated aldehyde **218** with extended phosphonate **104** to give trienoate **249** in quantitative yield (Scheme 2.49).[64]



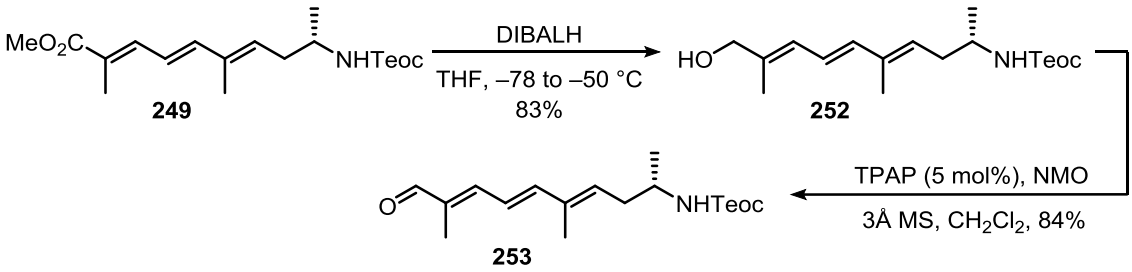
*Scheme 2.49: Preparation of trienoate **249** by HWE olefination of **218***

The known phosphonate **104** was prepared in two steps from methyl tiglate (**250**) according to literature procedure by Prestwich *et al*. (Scheme 2.50).[155]



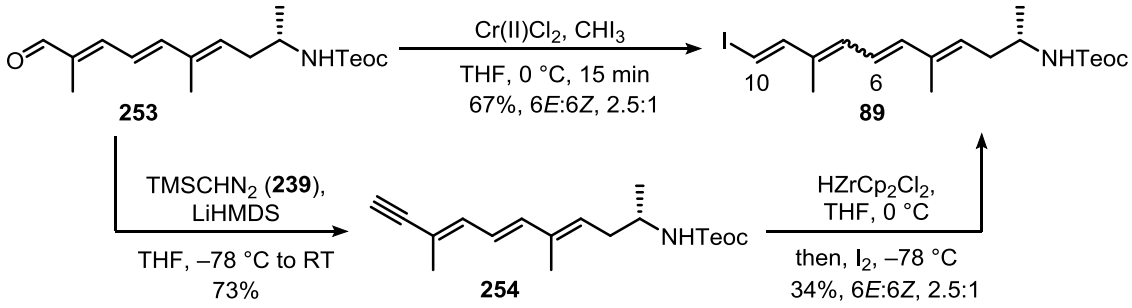
*Scheme 2.50: Preparation of phosphonate **104***

The ester functionality was reduced using DIBALH to obtain trienol **252** in 83% yield which upon oxidation under the Ley-Griffith conditions gave trienal **253** in 84% yield (Scheme 2.51).



*Scheme 2.51: Oxidation – reduction sequence for the preparation of trienal **253***

Finally, Takai olefination of trienal **253** afforded tetraenyl iodide **89** in good yield (67%) and as a mixture of geometrical isomers (Scheme 2.52). To our dismay ^{1}H NMR spectroscopic analysis revealed that iodide **89** consisted of 6*E*:6*Z* stereoisomers rather than the previously suggested 10*E*:10*Z* by Lim.



*Scheme 2.52: Preparation of tetraenyl iodide **89***

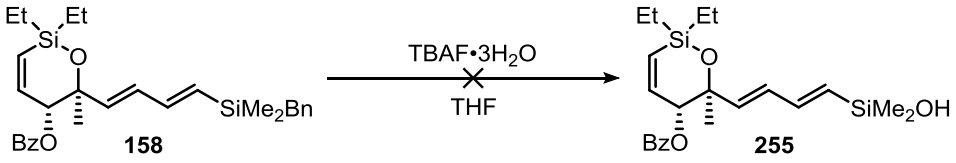
Iodide **89** was found to be highly unstable but could however be stored in the dark in a frozen benzene matrix at −20 °C for several months showing limited degradation.

Interestingly, a comparable ratio of geometrical isomers was obtained *via* hydrozirconation/iodination of enyne **254**, prepared by Colvin rearrangement from trienal **253**. Despite the chromium-mediated Takai olefination and the hydrozirconation/iodination operating by two distinctive mechanisms, tetraenyl iodide **89** was obtained as comparable isomeric mixtures. While only speculative, this deterioration of the geometric purity of tetraenyl iodide **89** may be the result of iodine-induced isomerisation of **89** establishing a thermodynamic ratio.[156]

Overall the synthesis of the C14-C23 tetraenyl iodide **89** was achieved in a total of 10 linear steps from L-alanine methyl ester hydrochloride (**212**), with an overall yield of 22%.

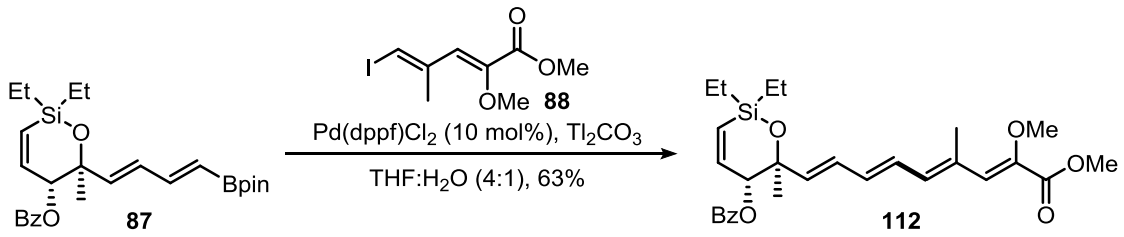
2.5.2 Towards incednam ─ Fragment union

With the required building blocks in hand, construction of the C5-C6 bond *via* Hiyama cross-coupling of silane **158** and dienoate **88** was attempted (Scheme 2.53). It was anticipated that treatment of bis-silane **158** with TBAF•3H_2O would reveal silanol **255**, to which the 6-membered siloxane is inert. Silanol **255** would then proceed to couple with dienoate **88** under fluoride-free Hiyama conditions. To our disappointment, when **158** was exposed to TBAF•3H_2O only a complex mixture was returned.



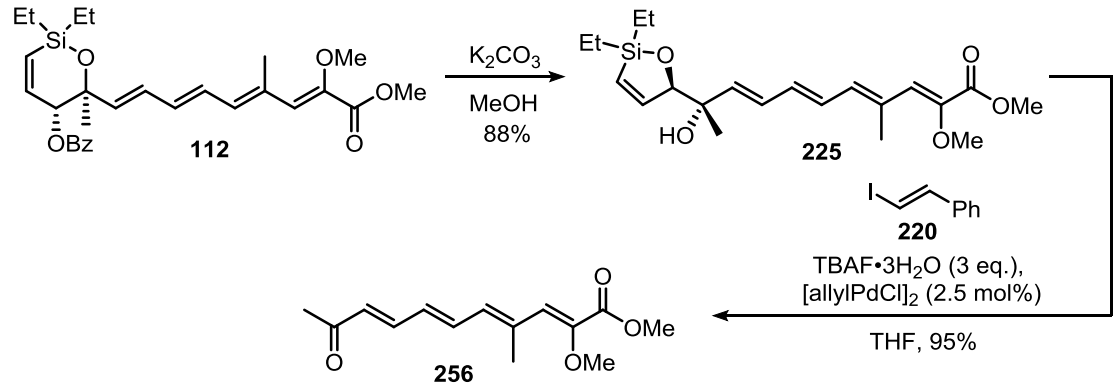
*Scheme 2.53: Treatment of bis-silane **158** with TBAF•3H_2O*

However, construction of the C5-C6 bond *via* Suzuki cross-coupling of boronic ester **87** and dienoate **88** was accomplished in presence of Pd(dppf)Cl_2 and thallium carbonate as base, using conditions previously optimised by Lim (Scheme 2.54).[64] Under these conditions the full length C1-C13 tetraenoate **112** was afforded in 63% yield.



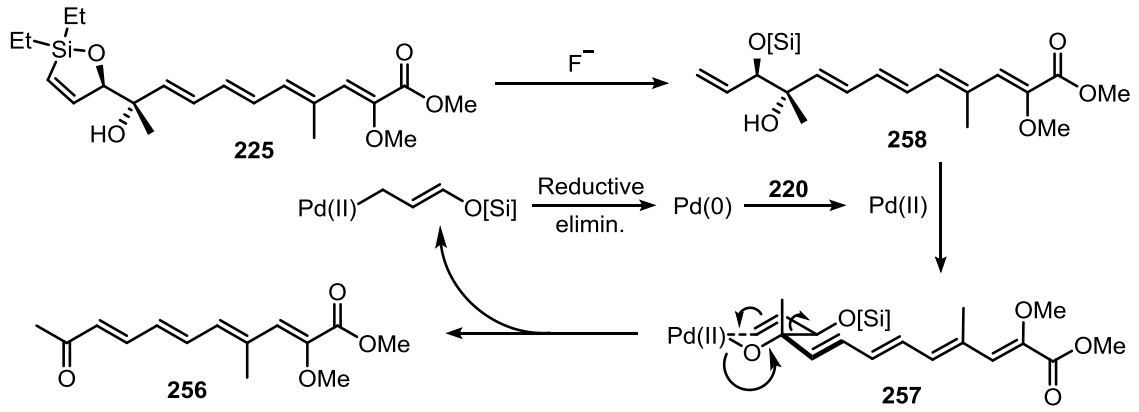
Scheme 2.54: Construction of full length tetraene via C5-C6 Suzuki cross-coupling

Next, the construction of the key C13-C14 bond *via* fluoride promoted Hiyama cross-coupling was attempted with 5-membered cyclic alkenylsiloxane **225** and iodostyrene (**220**) as a model coupling handle (Scheme 2.55). Siloxane **225** was obtained from **112** as a result of benzoyl removal and concomitant trans-etherification under mild conditions using potassium carbonate in methanol.



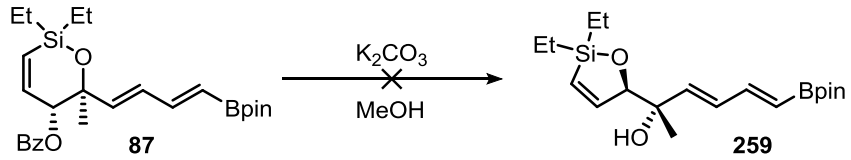
Scheme 2.55: Model C13-C14 Hiyama cross-coupling of full length tetraene

Rather than obtaining the desired coupled product, we were surprised to find near exclusive formation of tetraenone **256**. Although it is not understood by which process **256** is obtained, it may be the result of palladium-catalysed retro-allylation of oxo-palladium species **257** *via* protodesilylated product **258** (Scheme 2.56).[157] The facility by which this putative retro-allylation affords **256** may be driven by the formation of a highly conjugated enol ether system.



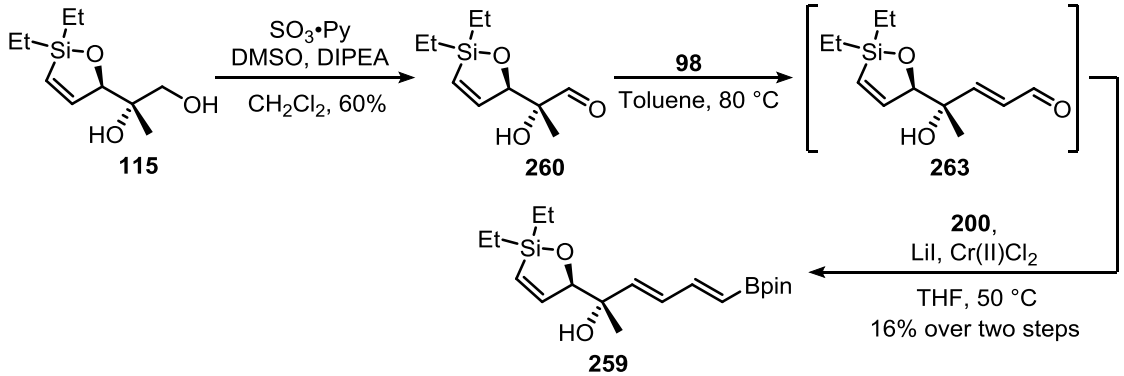
*Scheme 2.56: Palladium mediated oxidative cleavage of **256***

An alternative approach would be to construct the C13-C14 bond first before assembling the C5-C6 bond *via* Suzuki cross-coupling. This would require 5-membered cyclic alkenylsiloxane **259**, generated by de-benzoylation of **87**. However, upon methanolysis only a complex mixture was returned (Scheme 2.57).



*Scheme 2.57: Attempted de-benzoylation of **87***

Boronic ester **259** was obtained, albeit in low yield, in three steps from **115** (Scheme 2.58).

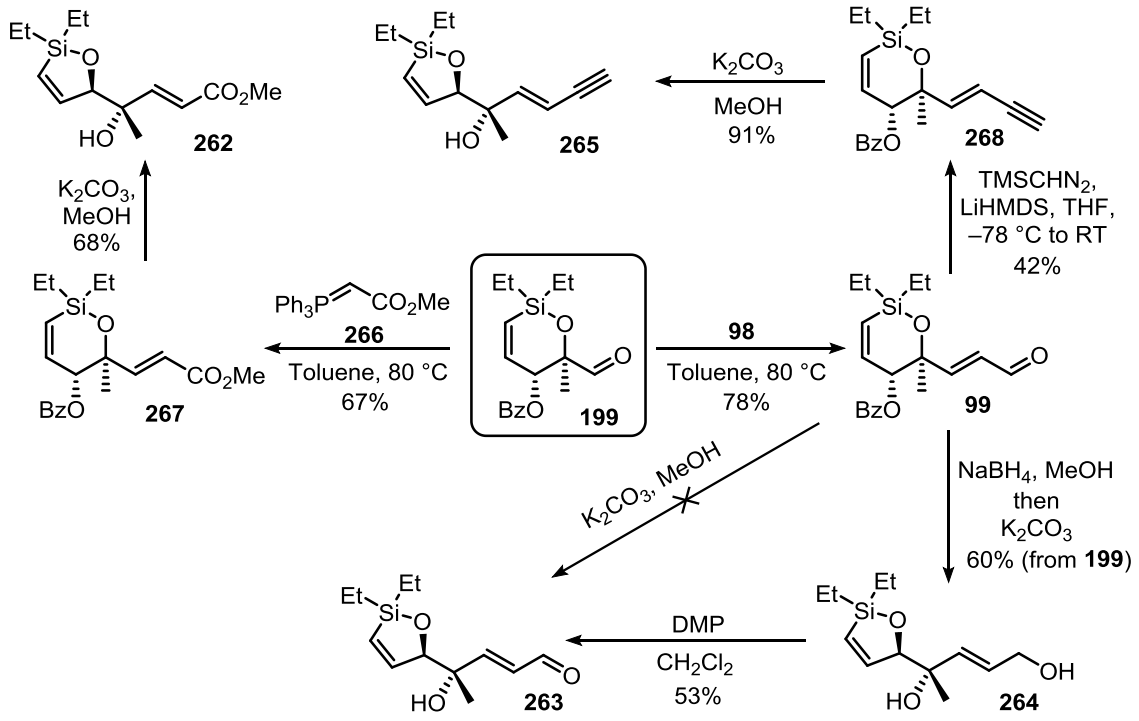


*Scheme 2.58: Preparation of boronic ester **259***

Parikh-Doering oxidation provided aldehyde **260**, which upon Wittig olefination with phosphorane **98** and subsequent Takai borylolefination of the resulting α,β-unsaturated

aldehyde **263** afforded the desired product **259**. These 5-membered cyclic siloxane intermediates were found to be extremely sensitive to silica gel chromatography and difficult to isolate.

The failure of the full length tetraenoate **225** to couple under the fluoride-promoted Hiyama coupling conditions and the difficulties encountered with the synthesis of boronic ester **259** led us to investigate 5-membered cyclic siloxanes containing functional groups which we could further manipulate for the construction of the C2-C9 tetraene. As such, the synthesis of siloxanes containing ester (**262**), aldehyde (**263**), alcohol (**264**) and alkyne (**265**) functionalities were commenced from 6-membered cyclic siloxane **199** (Scheme 2.59).

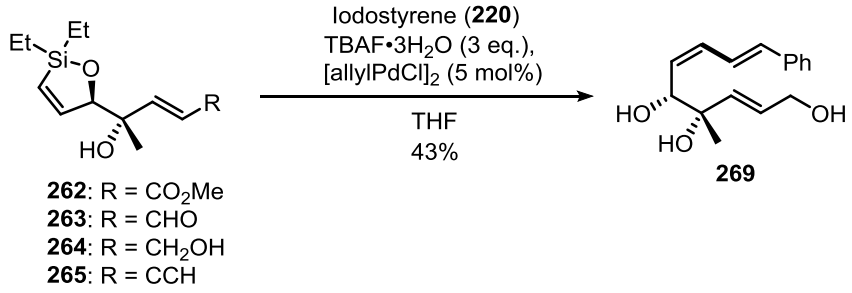


*Scheme 2.59: Synthesis of siloxanes **262-265***

Dienoate **262** was prepared in two steps from **199**. Wittig olefination with phosphorane **266** led to ester **267**, which upon benzoyl removal afforded **262**. Dienal **263** was obtained in two steps from **99**. While de-benzoylation of **99** did not lead to **263**, the desired compound was afforded by Dess-Martin oxidation of allylic alcohol **264**, itself

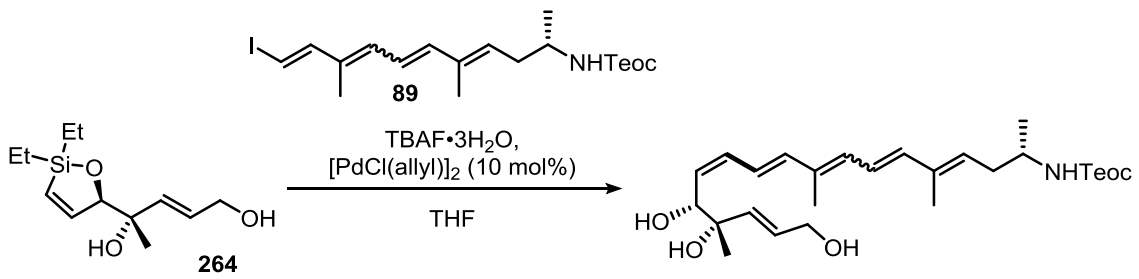
the result of reduction and *in situ* methanolysis of **99**. Enyne **265** was prepared in two steps from **99**. Colvin rearrangement afforded enyne **268** which upon benzoyl removal and concomitant trans-etherification gave crude **265**, which was found to be unstable towards silica gel chromatography and was used as such. The Ohira-Bestmann and Stork-Zhao olefination/elimination alkynylation protocols were unsuccessful for the preparation of enyne **268**.

With siloxanes **262-265** in hand their coupling under the standard fluoride-promoted Hiyama conditions was attempted with iodostyrene (**220**) as a model coupling handle (Scheme 260). Under these conditions, only allylic alcohol **264** provided the desired allylic diene **269** in 43% yield.



Scheme 2.60: Model fluoride promoted Hiyama cross-coupling

Having identified 5-membered cyclic alkenylsiloxane **264**, its coupling with tetraenyl iodide **89** for the construction of the key C12-C13 bond under the fluoride-promoted Hiyama conditions was attempted (Scheme 2.61).



Scheme 2.61: Construction of the key C12-C21 pentaene via Hiyama cross-coupling

While initially encouraged by ^{1}H NMR analysis to see evidence of the desired coupled

product, albeit in modest quantities at best and as a mixture of isomers (6*E*:6*Z*, 2.5:1), its quantitative analysis proved challenging where isolation by column chromatography was only partially effective due to comparable polarity of contaminant tetrabutylammonium ions. Furthermore, as a result of prolonged reaction time (due to the inherent reactivity of cyclic diethylsiloxanes) it is likely that both competing homocoupling of **89** and desilylation of siloxane **264** are of potential significance. In an attempt to prevent this, tetraenyl iodide **89** and TBAF•3H_2O were added *via* syringe pump over 12 h as a solution in THF. This did not result in any notable improvement. Similarly, addition of water (10 eq.) to prevent desilylation of **264** did not result in any improvement other than prolonging the reaction time (72 h).

2.6 ^{1}H NMR studies – Cyclic diethyl alkenylsiloxanes

In light of the problems experienced with the many attempted Hiyama couplings, 5- and 6-membered cyclic alkenylsiloxanes **115** and **97** were treated with nucleophilic activator TBAF•3H_2O in d_8-THF, and their behaviour monitored periodically by ^{1}H NMR spectroscopy. We hoped to answer a few key questions such as why does the 5-membered siloxane couple while its 6-membered analogue does not, and what is the rate of desilylation.

2.6.1 ^{1}H NMR studies – 5-Membered diethyl siloxane

Upon treatment of 5-membered siloxane **115** with TBAF•3H_2O (3 eq.) in d_8-THF, a rapid equilibrium was established between siloxane **115** and acyclic silanol **270** which are slowly converted to protodesilylated product **271** over the course of the experiment (Figure 2.5).

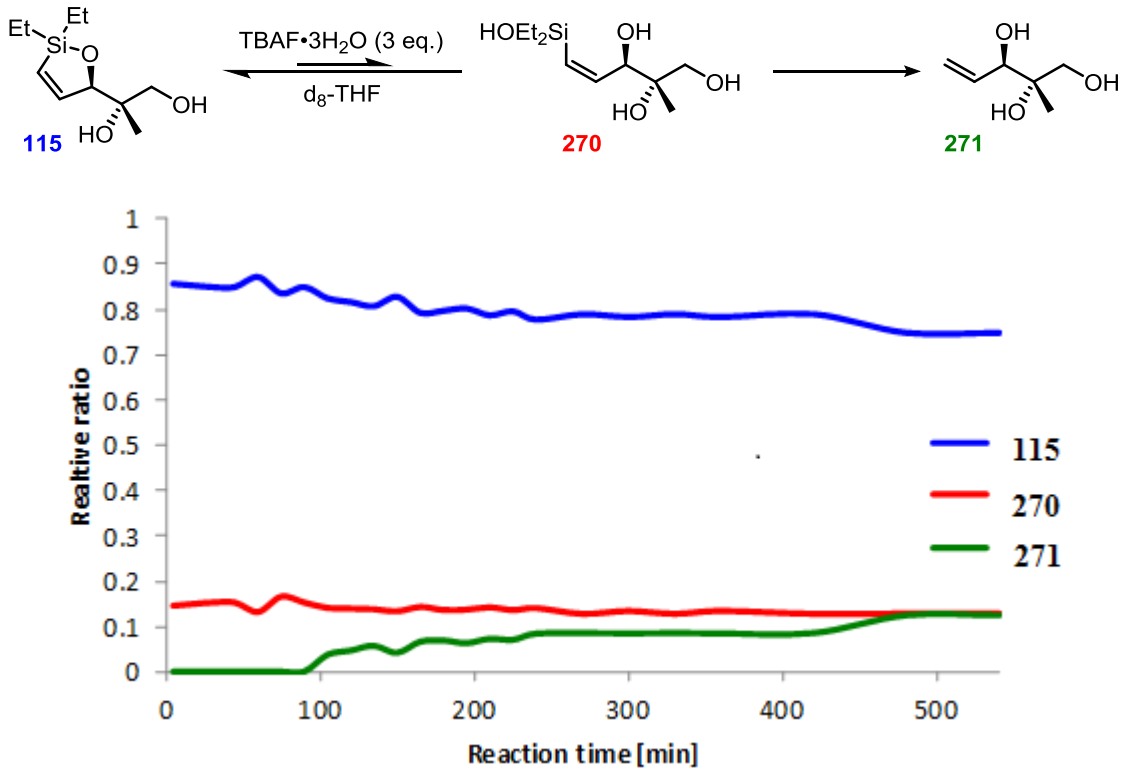


*Figure 2.5: Treatment of 5-membered cyclic siloxane **115** with TBAF•3H$_2$O (3 eq.) monitored periodically by ^{1}H NMR spectroscopy*

When compared to a previous study of diethyl siloxane **272** by Elbert (reported in her DPhil thesis in 2014), it is interesting that the ratio of cyclic siloxane **115** and acyclic silanol **270** (**115**:**270**, 5.9:1) is much higher than that observed by Elbert (**272**:**273**, 1:1.8) (Figure 2.6).[158] Furthermore, almost no protodesilylation is observed in the first 2 h where the previous studies had found the opposite.

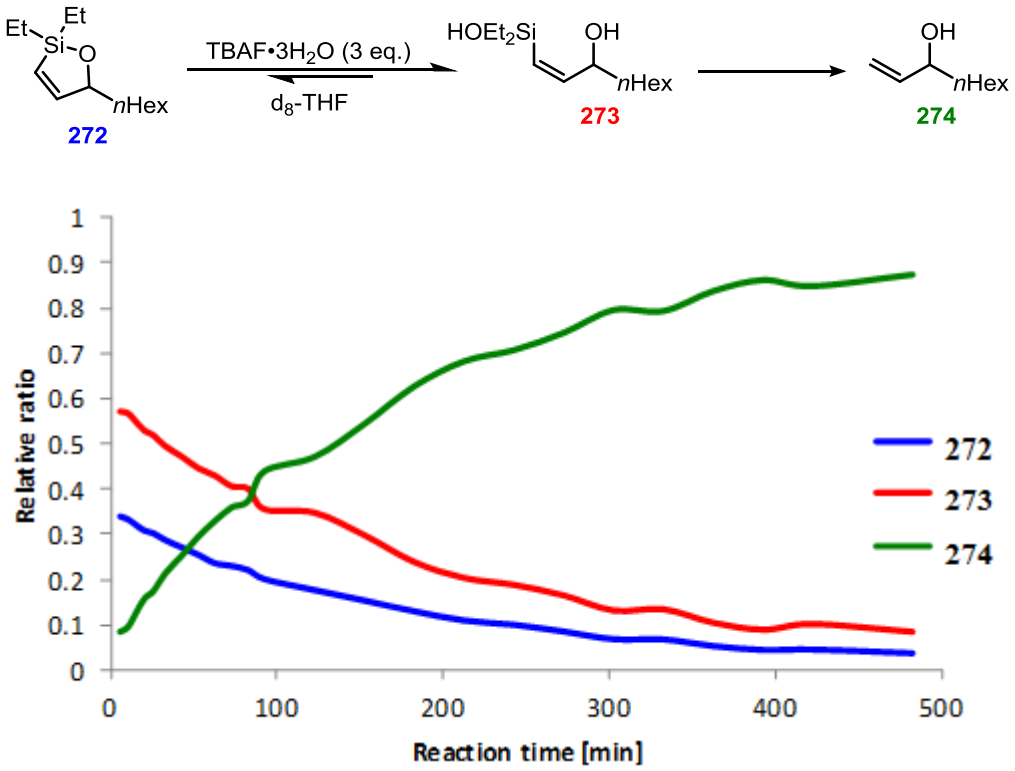
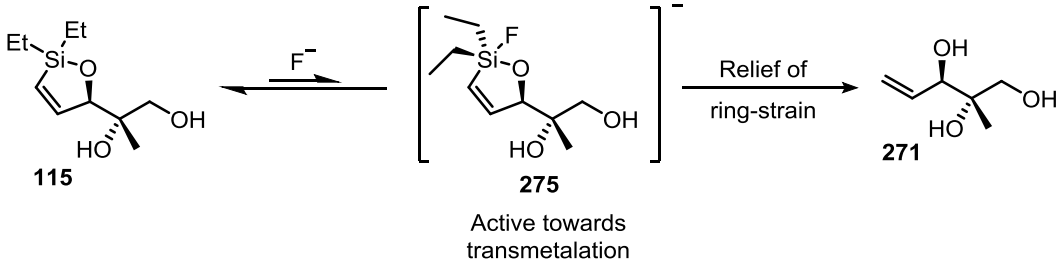


*Figure 2.6: Treatment of 5-membered cyclic siloxane **272** with TBAF•3H$_2$O (3 eq.) monitored periodically by ^{1}H NMR spectroscopy as obtained by Elbert*

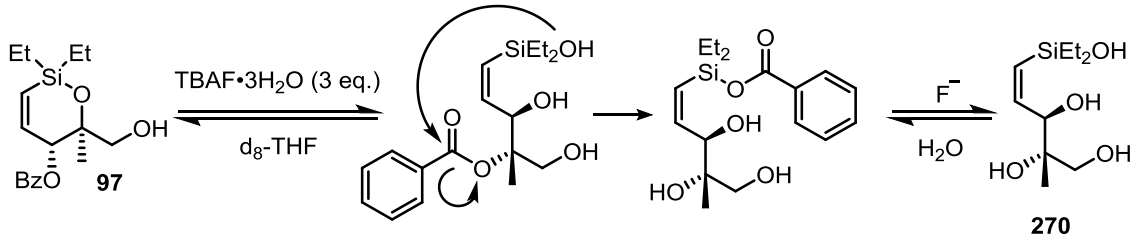
This lack of protodesilylation, which is thought to arise from the relief of ring strain of 5-membered cyclic "ate" complex **275**, might indicate the absence of **275**, which is believed to be the key species from which transmetalation occurs in the cross-coupling of 5-membered cyclic siloxanes (see Section 4.6.1 for further discussion). This reluctance of **115** to form the required "ate" complex could therefore explain the somewhat limited reactivity experienced with siloxane **115** (Scheme 2.62).



*Scheme 2.62: The event of protodesilylation via cyclic "ate" complex **275***

2.6.2 ^{1}H NMR studies – 6-membered diethyl siloxane

Upon treatment of 6-membered siloxane **97** with TBAF•3H_2O (3 eq.) in d_8-THF we were surprised to see almost instantaneous removal of the benzoyl group accompanied by what is believed to be acyclic species **270**, which gradually disappeared resulting in full degradation of **97** (Scheme 2.63).



*Scheme 2.63: Plausible scenario for the de-benzoylation of **97** with TBAF•3H_2O*

2.7 Conclusion

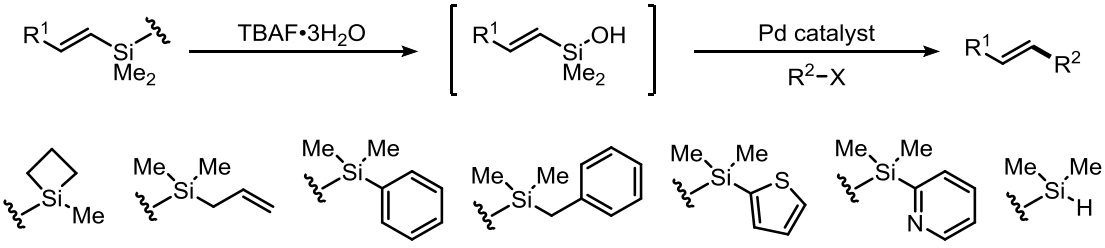
While we have successfully developed robust and reliable synthesis of key fragments *en route* to incednam, we have been largely unsuccessful in the stereoselective construction of the delicate C12-C21 pentaene system *via* the sequential Hiyama-Suzuki cross-coupling or the Ramberg-Bäcklund olefination strategies. In addition, the failure of the full length tetraenoate fragment **225** to couple and the unfavourable geometrical mixture of the key tetraenyl iodide fragment **89** seriously hampered progress towards the synthesis of incednam. Furthermore, the instability of the benzoate protected 6-membered cyclic siloxane **97**, as revealed by the ^{1}H NMR studies, represents a serious flaw in our strategy which needs to be addressed.

Chapter 3: Development of the cross-coupling of cyclic dimethyl alkenylsiloxanes

The lack of reactivity experienced with cyclic diethyl alkenylsiloxanes towards the synthesis of incednam led us to contemplate the use of the more reactive dimethyl analogue. The following chapter will discuss the development of a novel methodology to access such compounds, their applications and studies.

3.1 Masked silanols

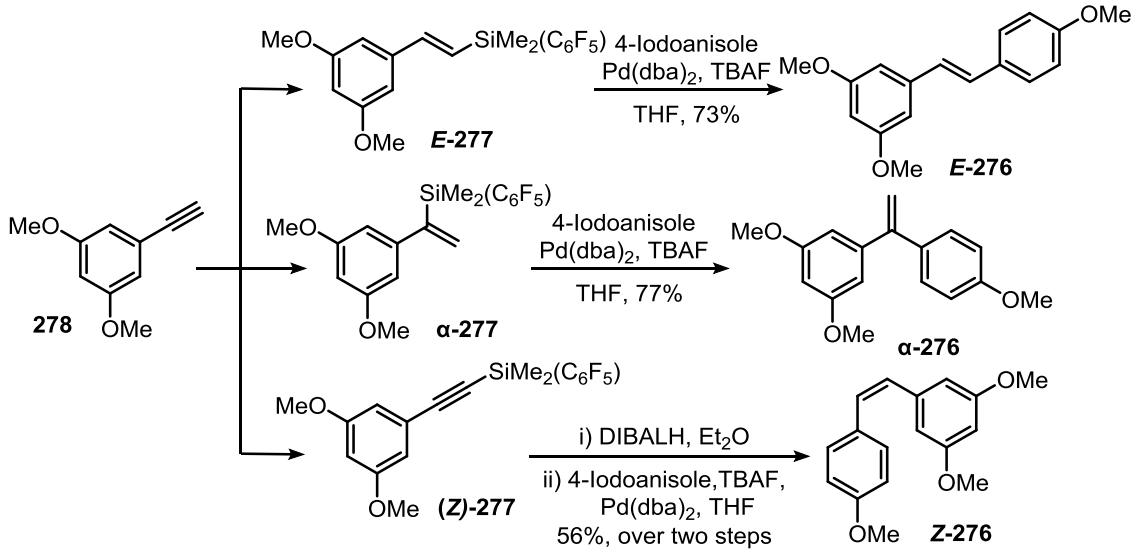
Organosilanes such as siletanes, allyl-, phenyl-, benzyl-, 2-thienyl-, 2-pyridyl- and hydrosilanes that can be converted to silanols upon treatment with hydrated fluoride source are referred to as masked silanol or "safety-catch" silanols (Scheme 3.1).



Scheme 3.1: Examples of masked "safety-catch" silanols

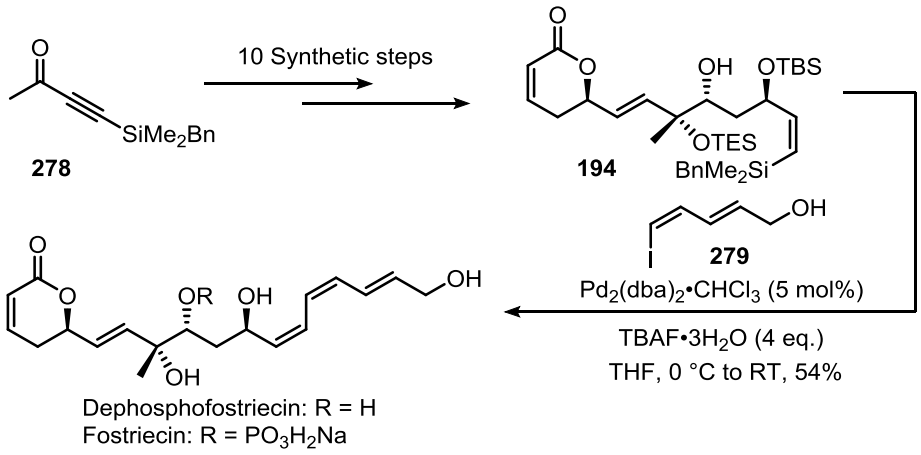
These silanol surrogates offer the advantage of being chemically robust and can thus be carried through several synthetic steps until the active silanol is required. There are a number of examples found in the literature that demonstrate their synthetic utility. For example, Spring *et al*. reported an expeditious diversity-oriented synthesis (DOS) of all geometric isomers of trimethoxyresveratrol **276** utilising pentafluorophenyldi-methylsilanes **277** as masked silanol intermediates (Scheme 3.2).[159] Vinylsilanes **277** were generated from alkyne **278** *via* hydrosilylation, for the selective generation of ***E*-277** and **α-277**, or nucleophilic substitution of the chlorosilane followed by *cis*-selective hydroalumination/protodemetalation. Subsequent fluoride activated

Hiyama cross-coupling afforded the corresponding disubstituted alkenes **276** without loss of selectivity.



Scheme 3.2: Diversity-oriented synthesis (DOS) of trimethoxyresveratrol

In the synthesis towards fostriecin, a cytotoxic phosphate ester isolated from *Streptomyces pulveraceus*, Trost *et al*. demonstrated the robustness of the benzyldimethylsilyl group by carrying it through 10 synthetic steps from **278** to give dephosphofostriecin, a fostriecin precursor (Scheme 3.3).[131]

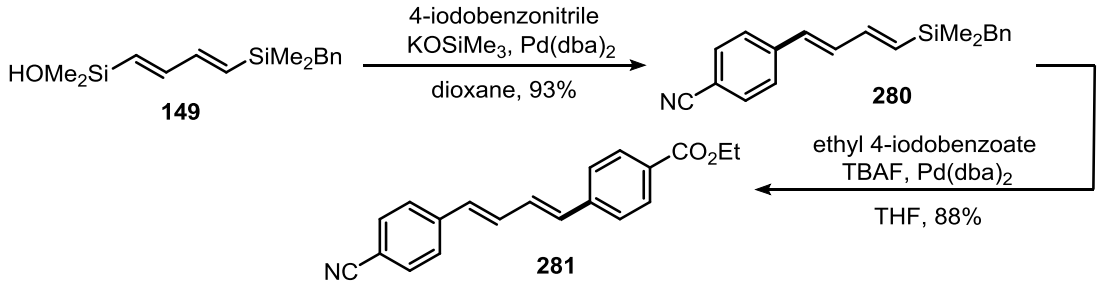


Scheme 3.3: Synthesis of dephosphofostriecin by Trost

These include a Zinc-mediated aldol reaction, ruthenium-catalysed hydrogenation, acid hydrolysis, organomagnesiate coupling, RCM and finally a diimide reduction to give *Z*-vinylbenzyldimethylsilane **194** as a masked silanol intermediate. Subsequent

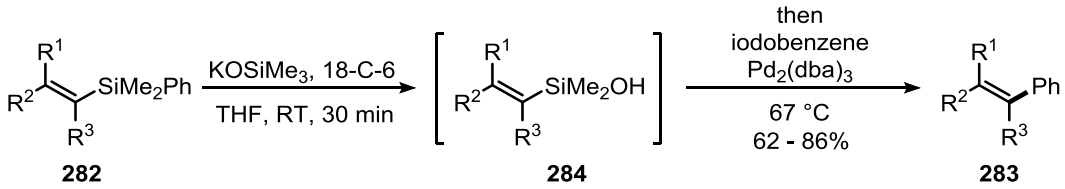
fluoride-promoted cross-coupling with vinyl iodide **279**, and concomitant deprotection of the silicon protecting groups, gave fostriecin in good yield.

Denmark *et al*. reported the sequential cross-coupling of 1,4-bissilylbutadienes for the synthesis of unsymmetrical 1,4-butadienes (Scheme 3.4).[160] First, silanol **149** was coupled under base-promoted conditions to give **280** which upon fluoride activation delivered **281**. These complementary modes of activation were aptly demonstrated in the total synthesis of the polyene macrolide antifungal agent RK-397 (Scheme 1.33).[93]



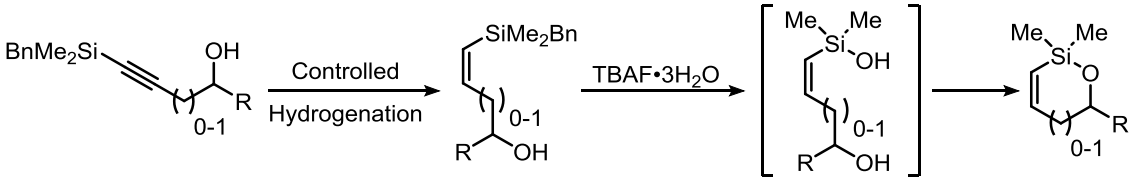
Scheme 3.4: Complementary modes of activation, synthesis of unsymmetrical dienes

Fluoride-free activation of masked silanols has also been reported. Anderson *et al*. reported that dimethylphenylvinylsilanes **282** are able to undergo cross-coupling with iodobenzene to give **283** *via* silanol intermediate **284** under fluoride-free conditions (Scheme 3.5).[161]



Scheme 3.5: Fluoride-free activation of masked silanols (Anderson, 2004)

While our current strategy offers a robust and a general route to cyclic alkenylsiloxanes *via* semi-hydrogenation, we are limited to diethyl isopropoxy alkynylsilanes due to the inherent instability of their dimethyl analogues. Inspired by the work of Oshima *et al*. (Scheme 2.5, Section 2.2.1) we considered the use of masked silanol to give access to 5- and 6-membered cyclic dimethyl alkenylsiloxanes (Scheme 3.6).[105]



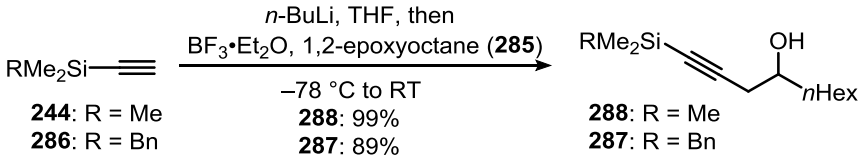
Scheme 3.6: Synthesis of cyclic siloxanes via the use of masked silanol

For this we intend to use benzyldimethylsilane due to their stability towards a variety of reaction conditions.[131,162]

3.2 Synthesis and application of cyclic dimethyl alkenylsiloxanes

3.2.1 Synthesis of 6-membered cyclic dimethyl siloxane

The synthesis of a model 6-membered dimethyl cyclic alkenylsiloxane commenced with a regioselective boron trifluoride-mediated ring-opening of the arbitrarily selected 1,2-epoxyoctane (**285**) with lithium benzyldimethylsilylacetylide **286** to give alkynylsilane **287** in excellent yield (Scheme 3.7).[163] Alkynyl trimethylsilane **288** was obtained by a similar procedure from trimethylsilylacetylene (**244**). **286** was obtained in 85% yield by addition of ethynylmagnesium bromide to commercially available benzyldimethylchlorosilane **203**.[131]

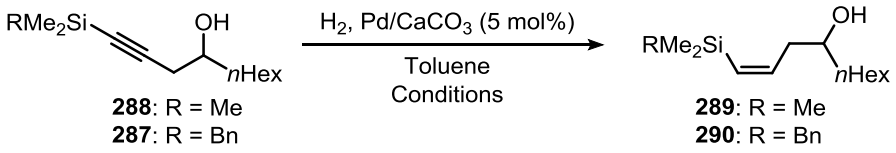


Scheme 3.7: Regioselective ring-opening, synthesis of homopropargylic alkynylsilanes

The key semi-hydrogenation was first explored on a model alkynyl trimethylsilane **288** (Table 3.1). When **288** was subjected to our standard semi-hydrogenation conditions, *Z*-vinylsilane **289** was obtained with poor diastereoselectivity (*dr* = 3.7:1, Entry 1).[114] An increase in selectivity was observed with higher loading of quinoline (*dr* = 6.7:1, Entry 2). While the use of cyclohexene as a sacrificial co-solvent resulted in increased reaction time, the desired *Z*-vinylsilane **289** was obtained with good diastereoselectivity

(*dr* = 8.3:1, Entry 3).[164] We anticipated that the sterically encumbering benzyl group would result in better stereoselectivity. Indeed when **287** was submitted to these conditions, *Z*-vinylbenzyldimethylsilane **290** was afforded in excellent yield (95%) and diastereoselectivity (*dr* = 11.0:1, Entry 4).

Table 3.1: Stereoselective semi-hydrogenation of homopropargylic alkynylsilanes



288: R = Me
287: R = Bn

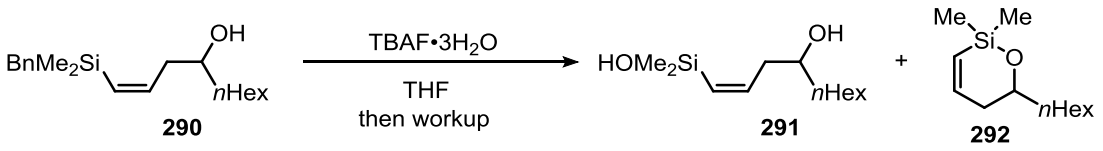
289: R = Me
290: R = Bn

Entry[a]	R	Conditions		Time [min][c]	diastero-selectivity (*dr*)[d]	Yield [%][e]
		QN [mol%][b]	Additive			
1	Me	20	none	20	3.7:1	n.d.[f]
2	Me	50	none	20	6.7:1	n.d.[f]
3	Me	50	cyclohexene[g]	30	8.3:1	n.d.[f]
4[h]	Bn	50	cyclohexene[g]	30	11.0:1	95

[a] Reaction performed on a 0.23 mmol scale. [b] QN stands for quinoline. [c] Monitored by TLC. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] Isolated yield of **290**. [f] Not determined. [g] Cyclohexene used in a 1:10 ratio with toluene. [h] Reaction performed on a 4.39 mmol scale.

With *Z*-vinylsilane **290** in hand, the use of TBAF•3H$_2$O to effect the required de-benzylation was investigated (Table 3.2).

*Table 3.2: De-benzylation of vinylsilane **290***



290 **291** **292**

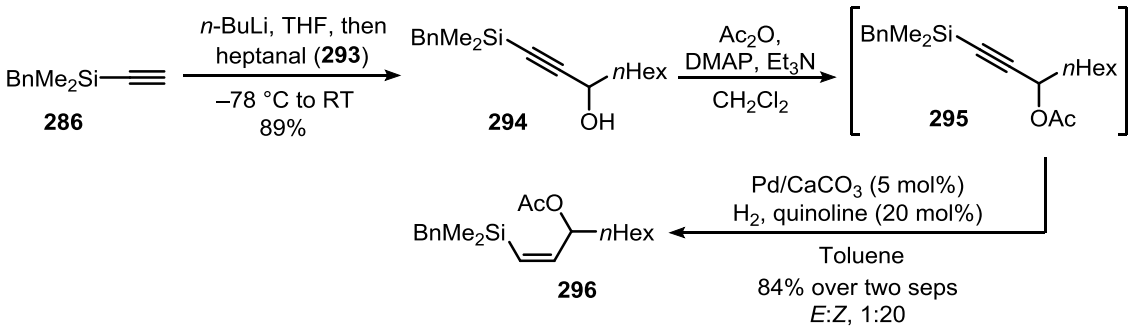
Entry	TBAF•3H$_2$O [eq.]	Time [min]	Workup	**291**:**292**[a]	Yield [%][b]
1	3.0	5	H_2O	1.7:1	n.d.[c]
2	1.0	5	1M HCl	0:1	69
3	0.5	30	1M NaOH	0:1	n.d.[c]
4	0.25	30	1M HCl	0:1	71

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] Isolated yield of **292**. [c] Not determined.

Upon treatment of **290** with TBAF (3 eq.) near instantaneous formation of silanol **291** was observed, as well as the desired cyclic siloxane **292** (Entry 1). The de-benzylation was retained at lower amounts of TBAF•$3H_2O$ (as low as 0.25 eq.) with exclusive formation of cyclic siloxane **292** upon either basic or acidic workup conditions (Entries 2,3 and 4).

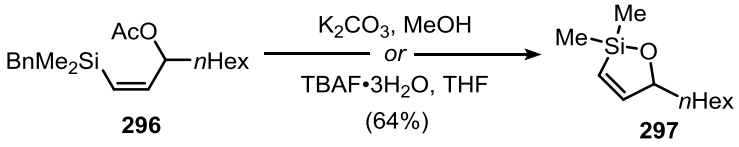
3.2.2 Synthesis of 5-membered cyclic dimethyl siloxane

The synthesis of a model 5-membered dimethyl cyclic alkenylsiloxane commenced with addition of benzyldimethylsilylacetylene **286** to heptanal (**293**), affording alkynylsilane **294** in 89% yield (Scheme 3.8). At this stage, the propargyl alcohol **294** was converted to acetate derivative **295**, followed by semi-hydrogenation to give *Z*-vinylsilane **296** in high yield (84%, *dr* = 20:1).



*Scheme 3.8: preparation of vinylsilane **296***

Next, acetyl removal was required. However, under standard methanolysis conditions, using potassium carbonate in methanol, exclusive formation of cyclic siloxane **297** with concomitant loss of toluene was observed (Scheme 3.9).

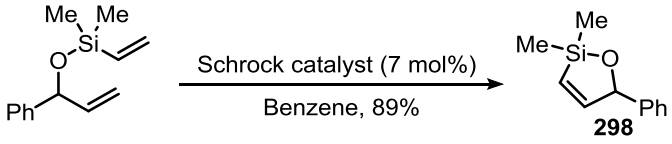


Scheme 3.9: Synthesis of 5-membered cyclic silanes

The moderate yield is due to the difficulty in removal of volatiles due to the low molecular mass of product **297**. Similarly, cyclic siloxane **297** was afforded upon

treatment of **296** with TBAF•3H_2O. For full conversion, equimolar amounts of fluoride were required, presumably due to loss of acetic acid which moderates the reactivity of the fluoride.

5-Membered cyclic dimethyl siloxanes such as **297** are unstable towards column chromatography and can thus be challenging to isolate. Denmark *et al*. have only reported one example *via* RCM, using the air- and moisture sensitive Schrock catalyst, which necessitated the use of a dry box (Scheme 3.10).[95,97]

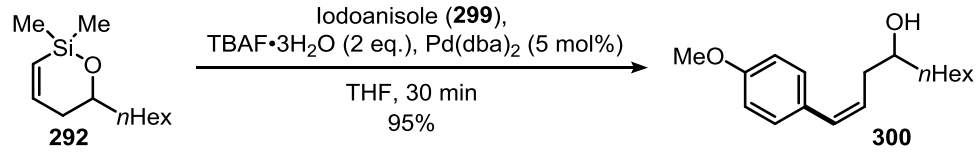


Scheme 3.10: Synthesis of 5-membered cyclic siloxanes via RCM

Siloxane **298** was afforded in 89% yield after filtration through Celite and purification by Kugelrohr distillation under reduced pressure, likely highlighting its chromatographic sensitivity. Our method offers the advantage of being operationally simple and requires no further purification than an aqueous workup, where the only side products are ascribed to the loss of toluene and acetate derivatives.

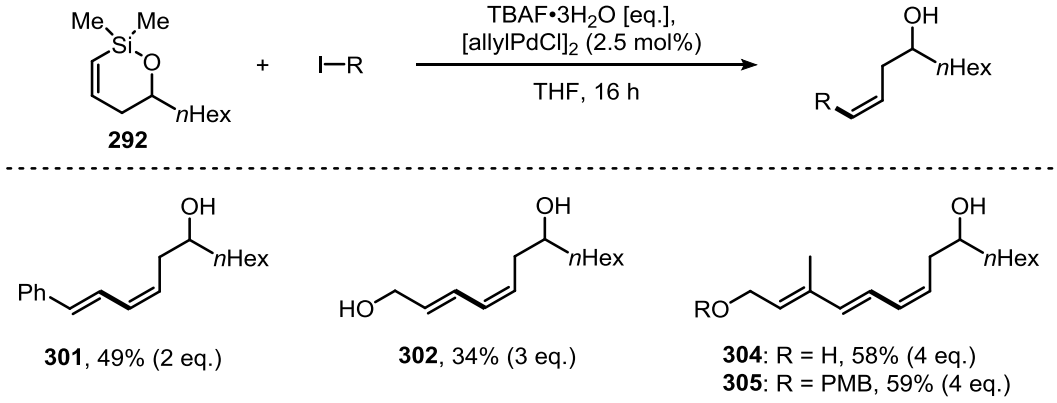
3.2.3 Cross-coupling: Preliminary results

With both 5- and 6-membered cyclic siloxanes **297** and **292** in hand we were keen to investigate their participation in the Hiyama cross-coupling. Using conditions reported by Denmark *et al*., the coupling of 6-membered siloxane **292** with iodoanisole (**299**) afforded homoallylic alcohol **300** in excellent yield (95%) in 30 min (Scheme 3.11).[95,97] Notably, the diethyl analogue required 48 h to achieve a similar yield (Scheme 2.10).[114]



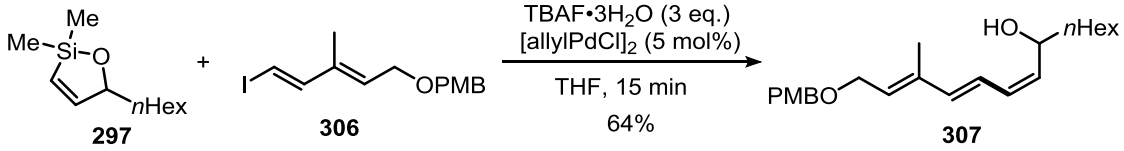
Scheme 3.11: Fluoride-promoted Hiyama reaction with iodoanisole

While Denmark's studies have primarily involved aryl iodides, there is one reported example of a bromostyrene cross-coupling.[95,97] Applying those conditions, the cross-coupling of siloxane **292** with iodostyrene (**220**) was found to progress sluggishly to give homoallylic diene **301** in modest yield over 16 h (Scheme 3.12). Similar results were obtained with polyenes **302**-**305**.



Scheme 3.12: Fluoride-promoted Hiyama reaction with vinyl iodides

When *O*-PMB protected dienyl iodide **306** was submitted to the coupling with 5-membered siloxane **297**, allylic triene **307** (64 %) was obtained in a significant shorter reaction time (15 min, Scheme 3.13).



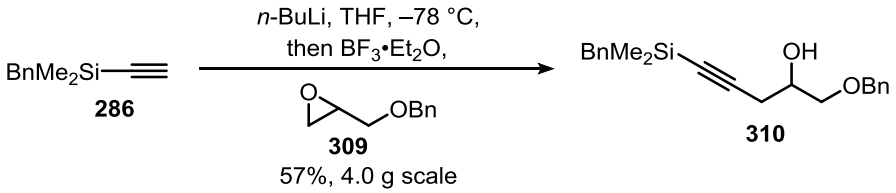
Scheme 3.13: Fluoride-promoted Hiyama reaction with dienyl iodide

While these results are encouraging, there is a clear need for optimisation. For this we intended the use 5- and 6-membered cyclic alkenylsiloxanes **297** and **292**, discussed in the following section, while exploring the cross-coupling of complex bromo- and iodo-polyenes. The mechanism of the various cyclisations will also be discussed.

3.3 Optimisation – Synthesis of cyclic alkenyl siloxanes

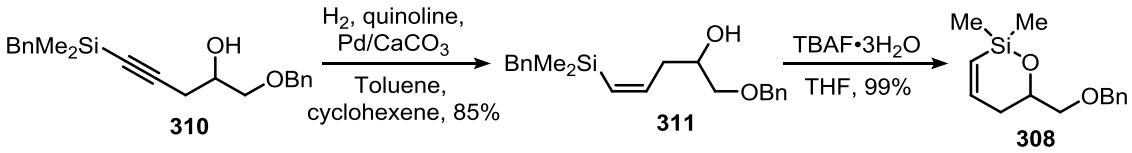
3.3.1 Synthesis of 6-membered cyclic dimethyl siloxane

The synthesis of the 6-membered cyclic alkenylsiloxane **308** commenced with a regioselective ring-opening of epoxide **309** with **286** to give alkynylsilane **310** in good yield (Scheme 3.14). Benzyl protected glycidol **309** was prepared by Kuper.[153]



*Scheme 3.14: Synthesis of homopropargylic alkynylsilane **310***

Cyclic siloxane **308** was prepared by Cornut *via* the previously established semi-hydrogenation of alkyne **310** to give *Z*-vinylsilane **311**, which upon treatment with TBAF•3H$_2$O gave the desired cyclised compound (Scheme 3.15).[165]

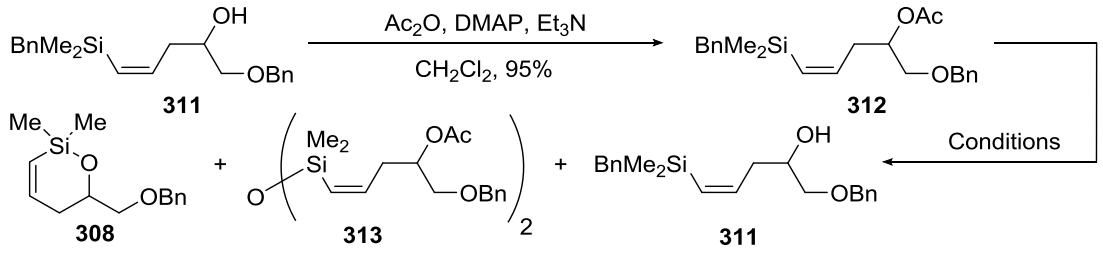


*Scheme 3.15: Semi-hydrogenation/de-benzylation sequence, synthesis of **308** by Cornut*

To further explore the effect of the neighbouring acetate observed with **296**, homoallylic alcohol **311** was converted to acetate derivative **312** followed by treatment with previously established conditions (Table 3.3). In contrast to acetate derivative **296**, upon methanolysis of **312**, using potassium carbonate in methanol, no cyclisation was observed, with vinylsilane **311** returned (Entry 1). When **312** was submitted to the fluoride conditions, disiloxane **313** was obtained, again with no cyclisation observed (Entry 2). While these results suggest the importance of proximal allylic acetate, we were surprised to find that upon treatment of **312** with potassium trimethylsilanolate,

cyclic siloxane **308** was formed, albeit in moderate yield over an extended reaction time (Entry 3).

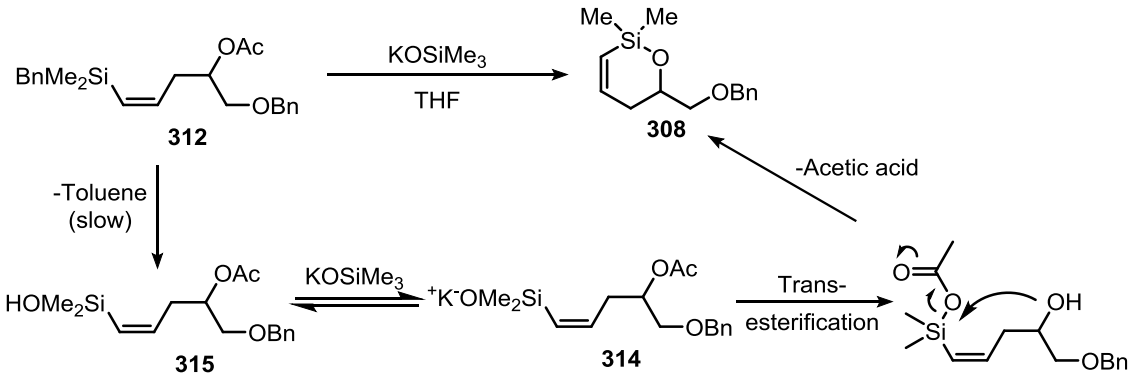
Table 3.3: Exploring the effect of homoallylic acetate



Entry[a]	Conditions	**308**:**313**:**311**	Time [h]	Yield [%][b]
1	K_2CO_3 (1.5 eq.) in MeOH	0:0:1	3	93
2	TBAF•$3H_2O$ (0.25 eq.) in THF	0:1:0	0.5	62
3	$KOSiMe_3$ (1.3 eq.) in THF	1:0:0	24	34

[a] Reaction performed on a 0.13 mmol scale. [b] Isolated yield.

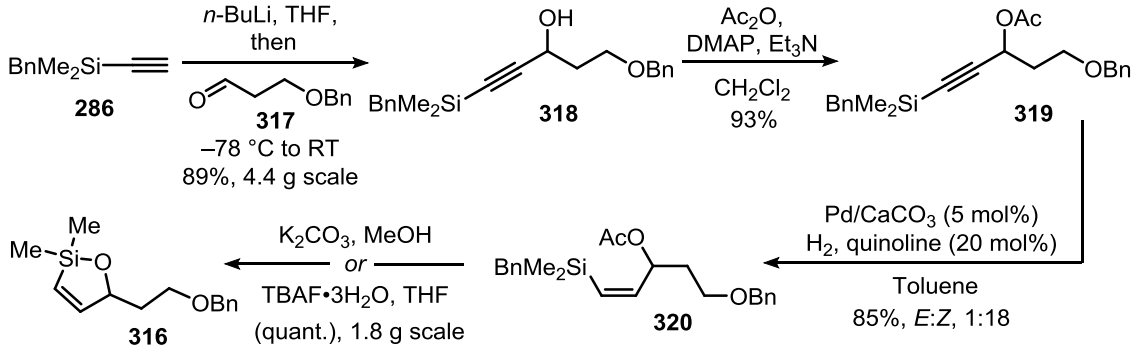
This latter reaction most likely proceeds *via* nucleophilic silanolate **314** in its equilibrium with silanol **315** (Scheme 3.16).



*Scheme 3.16: A likely scenario for the formation of cyclic siloxanes via silanolate **314***

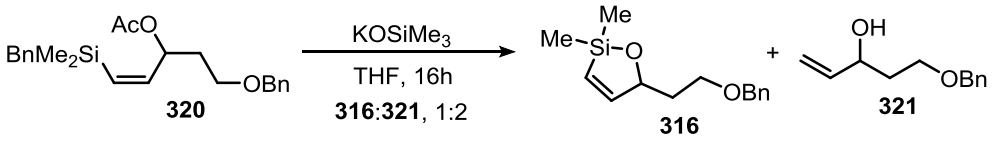
3.3.2 Synthesis of 5-membered cyclic dimethyl siloxane

The synthesis of 5-membered dimethyl cyclic alkenylsiloxane **316** is summarised in Scheme 3.17 and commenced with addition of benzyldimethylsilylacetylene **286** to 3-(benzyloxy)propanal (**317**), affording propargylic alkynylsilane **318** in 89% yield. **317** was prepared by Kuper in two steps from 3-hexene-1,6-diol.[153]



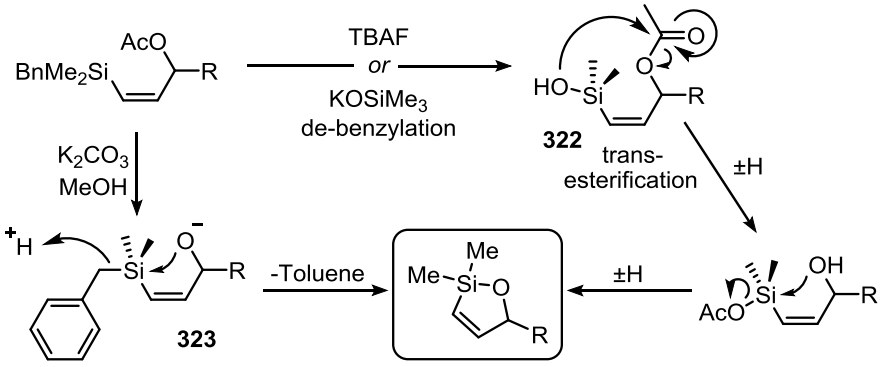
*Scheme 3.17: Synthesis of 5-membered cyclic siloxane **316***

Acetylation of propargylic alcohol **318** gave **319**, which upon semi-hydrogenation gave *Z*-vinylsilane **320** in excellent yield (85%, *dr* = 18:1). Finally, under either methanolysis or treatment with fluoride, cyclic siloxane **316** was afforded in quantitative yield. However, when acetate **320** was treated with potassium trimethylsilanolate (1.3 eq.), siloxane **316** was obtained along with desilylated product **321**, as a result of prolonged reaction time (Scheme 3.18).



Scheme 3.18: Preparation of cyclic siloxane by use of $KOSiMe_3$

The mechanism of the fluoride- and silanolate-promoted cyclisations is likely to proceed *via* silanol intermediate **322** followed by proximity enhanced intramolecular transesterification/cyclisation (Scheme 3.19).

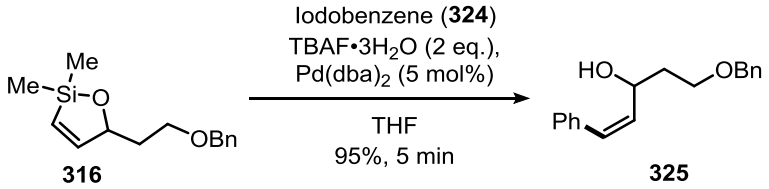


Scheme 3.19: Proposed mechanism for the generation of 5-membered cyclic siloxane

Similarly, upon methanolysis, nucleophilic activation of the silicon *via* the resulting hydroxide **323** results in Si-benzyl cleavage to give the cyclised product. Such activation is not possible for homoallylic acetates, such as **312**, and therefore methanolysis in such cases will only result in cleavage of the acetate group.

3.3.2 Optimisation – Fluoride-promoted cross-coupling

Using conditions reported by Denmark *et al*. near instantaneous cross-coupling of 5-membered siloxane **316** with iodobenzene (**324**) afforded allylic alcohol **325** in excellent yield (95%) (Scheme 3.20).[95,97]

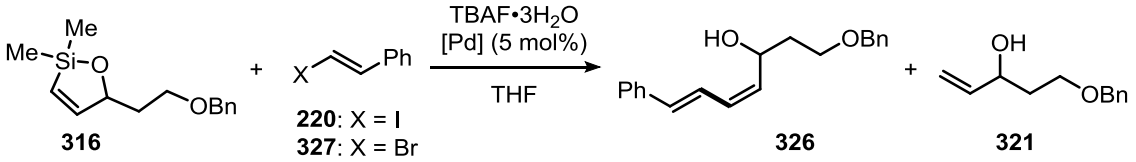


Scheme 3.20: Fluoride-promoted Hiyama reaction with iodobenzene

When Denmark's previously reported conditions were applied with iodostyrene (**220**), the cross-coupling was found to progress sluggishly with incomplete conversion after 1.5 h (Entry 1, Table 3.4). Addition of an extra equivalent of fluoride enabled full conversion of **220**, affording diene **326** in 63% yield (Entry 2). When siloxane **316** was used as the limiting reagent, the coupled product **326** was obtained in higher yield (68%, Entry 3). Next, different palladium sources were surveyed; both Pd(0) and Pd(II) were explored with and without phosphine ligands (Entries 4 to 11). Of the Pd(0) catalysts, the best results were obtained with $Pd(dba)_2$, a commonly used catalyst in the Hiyama reaction, affording the desired allylic diene **326** in 78% yield (Entries 4 to 6). In case of the ligandless Pd(II) sources, $[allylPdCl]_2$ and $Pd(OAc)_2$ gave similar results, while the use of $PdCl_2$ gave rise to protodesilylated product **321** (Entry 3, 7 and 8). However, in the presence of strongly binding triphenylphosphine ligands, either no reaction took place or protodesilylation occurred (Entries 9 to 11). This observed ligand

inhibitory effect finds analogy with Denmark's previous suggestions that formation of a coordinatively unsaturated palladium species, from which the transmetallation proceeds, is required.[89,90]

Table 3.4: Fluoride-promoted Hiyama coupling with styrenyl halides, an optimisation



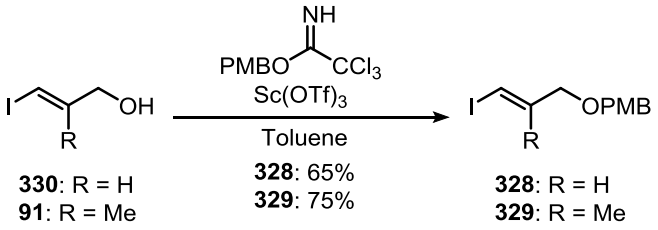
Entry[a]	X	TBAF [eq.]	[Pd]	**326**:**321**[b]	Time [h][c]	Yield [%][d]
1[e]	I	2	$[allylPdCl]_2$	1:0	1.5[f]	n.d.[g]
2[e]	I	3	$[allylPdCl]_2$	1:0	0.75	63
3	I	3	$[allylPdCl]_2$	1:0	0.75	68
4	**I**	**3**	**$Pd(dba)_2$**	**1:0**	**0.75**	**78**
5	I	3	$Pd_2(dba)_3$	1:0	0.75	68
6	I	3	$Pd_2(dba)_3•CHCl_3$	1:0	0.75	75
7	I	3	$Pd(OAc)_2$	1:0	0.75	68
8	I	3	$PdCl_2$	1.6:1	o.n.[h]	n.d.[g]
9	I	3	$Pd(OAc)_2/2PPh_3$	0:1	o.n.[h]	n.d.[g]
10	I	3	$(PPh_3)_2PdCl_2$	0:0	o.n.[h]	n.d.[g]
11	I	3	$Pd(PPh_3)_4$	0:1	o.n.[h]	n.d.[g]
12	Br	3	$[allylPdCl]_2$	1:0	0.25	65
13	**Br**	**3**	**$Pd(dba)_2$**	**1:0**	**0.25**	**78**

[a] Reaction performed with an excess of halide (1.2 eq.). [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Monitored by TLC. [d] Yield of isolated **326** by column chromatography. [e] Reaction performed with excess siloxane (1.1 eq.). [f] Reaction disconnected after 1.5 h. [g] Not determined. [h] Over night.

Having identified the optimal conditions (Entry 4), the cross-coupling was performed with bromostyrene (**327**) to give the coupled product **326** (78%) in significantly shorter reaction time (15 min, Entry 13). This dependence on styrenyl halide suggests a faster oxidative addition step of the palladium when bromostyrene (**327**) is employed.

3.3.3 Fluoride-promoted cross-coupling – Substrate scope

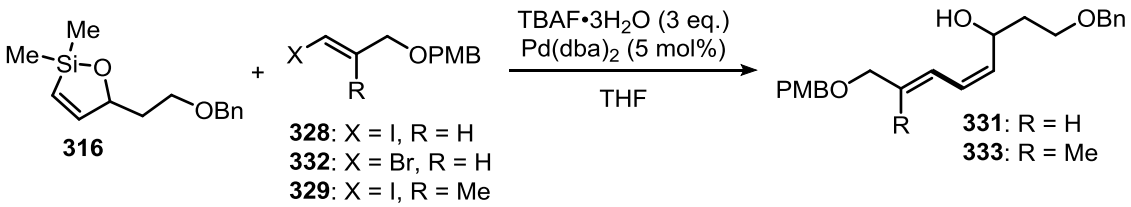
The halide coupling partners used in the following substrate scope were prepared by Kuper, aside from vinyl iodides **328** and **329** which were obtained by PMB protection of their corresponding alcohol (Scheme 3.21).[153]



Scheme 3.21: Preparation of PMB protected vinyl iodides

Other than aryl iodide cross-couplings reported by Denmark, there have only been few reported examples of the cross-coupling of cyclic alkenylsiloxanes, especially that concerning alkene-alkene coupling.[95] We were thus keen to apply our newly developed methodology to a range of challenging bromo- and iodo-alkenes with varying degree of unsaturation which would, hopefully, culminate in the synthesis of incednam among other natural products. Thus, the substrate scope initiated with the cross-coupling of siloxane **316** with vinyl iodide **328** (Table 3.5). Under our optimised standard conditions, allylic diene **331** was obtained in 73% yield (Entry 1). Interestingly, when siloxane **316** was employed in excess, a dramatic reduction in reaction time was observed (Entry 2). When the coupling was performed with vinyl bromide **332**, the desired product **331** was afforded in moderate yield (35%, Entry 3). While an excess of siloxane **316** saw an increase in yield, the reaction time remained the same (entry 4). However, when $[allylPdCl]_2$ was employed as the catalyst the desired product **331** was obtained in 57% yield (Entry 5). The coupling of siloxane **316** with the more sterically demanding vinyl iodide **329** afforded allylic diene **333** in excellent yield, independent of the stoichiometry used (Entries 6 and 7).

Table 3.5: Fluoride-promoted Hiyama reaction with PMB-protected vinyl halides

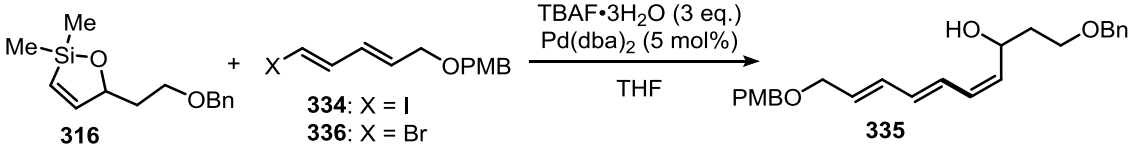


Entry[a]	X	R	Siloxane **316** [eq.]	Halide [eq.]	Time [h][b]	Yield [%][c]
1	I	H	1.0	1.2	3	73
2	**I**	**H**	**1.2**	**1.0**	**0.25**	**73**
3	Br	H	1.0	1.2	3	35
4	Br	H	1.2	1.0	3	49
5[d]	**Br**	**H**	**1.2**	**1.0**	**3**	**57**
6	**I**	**Me**	**1.0**	**1.2**	**1**	**84**
7	I	Me	1.2	1.0	1	81

[a] Reaction performed on a 0.10 mmol scale. [b] Monitored by TLC. [c] Yield of isolated dienes by column chromatography. [d] Reaction performed with $[allylPdCl]_2$ (2.5 mol%) as the catalyst.

When the more complex dienyl iodide **334** was submitted to the coupling conditions with siloxane **316**, allylic triene **335** was obtained in excellent yield (Entry 1, Table 3.6).

Table 3.6: Fluoride-promoted Hiyama reaction with PMB protected dienyl halides



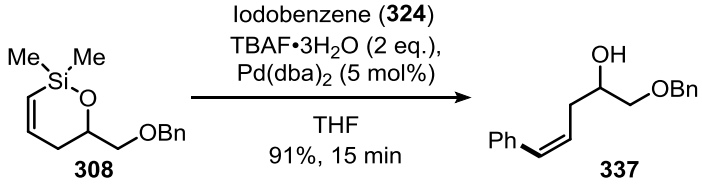
Entry[a]	X	Siloxane **316** [eq.]	Halide [eq.]	Time [h][b]	Yield [%][c]
1	**I**	**1.0**	**1.2**	**0.5**	**81**
2	I	1.2	1.0	1	63
3	Br	1.0	1.2	2	56
4[d]	**Br**	**1.0**	**1.2**	**2**	**58**

[a] Reaction performed on a 0.10 mmol scale. [b] Monitored by TLC. [c] Yield of isolated **335** by column chromatography. [d] Reaction performed with $[allylPdCl]_2$ (2.5 mol%) as the catalyst.

In excess of siloxane **316**, the desired product was afforded in lower yield and with

increased reaction time (Entry 2). Under the standard conditions, when dienyl bromide **336** was employed, allylic triene **335** was obtained in 56% yield (Entry 3). No significant improvement was observed when $[allylPdCl]_2$ was used as the catalyst (Entry 4).

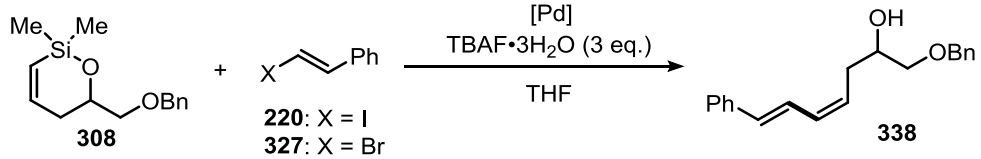
We next turned our attention to the 6-membered cyclic alkenylsiloxane **308**; using conditions reported by Denmark *et al*. the coupling with iodobenzene (**324**) afforded homoallylic alcohol **337** in excellent yield (91%) in 15 min (Scheme 3.22).[95,97]



Scheme 3.22: Fluoride-promoted Hiyama reaction with iodobenzene

While significantly slower than that of 5-membered siloxane **316**, the cross-coupling of iodostyrene (**220**) with siloxane **308** afforded homoallylic diene **338** in good yield (Entry 1, Table 3.7).

Table 3.7: Fluoride-promoted Hiyama reaction with styrenyl halides



Entry[a]	X	[Pd][b]	**308** [eq.]	Halide [eq.]	Time [h][c]	Yield [%][d]
1	**I**	**$Pd(dba)_2$**	**1.0**	**1.2**	**16**	**75**
2	I	$[allylPdCl]_2$	1.0	1.2	16	71
3	Br	$Pd(dba)_2$	1.0	1.2	5	58
4	Br	$[allylPdCl]_2$	1.0	1.2	5	61
5	**Br**	**$[allylPdCl]_2$**	**1.2**	**1.0**	**5**	**68**

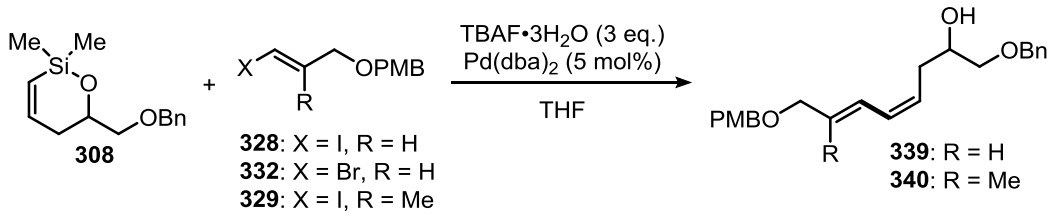
[a] Reaction performed on a 0.10 mmol scale. [b] Reaction was performed using $Pd(dba)_2$ (5 mol%) or $[allylPdCl]_2$ (2.5 mol%) as catalyst. [c] Monitored by TLC. [d] Yield of isolated **338** by column chromatography.

No notable difference was observed when $[allylPdCl]_2$ was employed as the catalyst

(Entry 2). Again, bromostyrene (**327**) was found to react faster than its iodide analogue, affording the coupled product **338** in 58% yield under our standard coupling conditions (Entry 3). While the use of $[allylPdCl]_2$ catalyst gave similar yield, the best results were obtained when excess of siloxane **308** was employed (Entry 4 and 5).

Next, the cross-coupling of vinyl halides **328**-**332** was examined (Table 3.8). Under our standard conditions, the coupling of vinyl iodide **328** afforded homoallylic diene **339** in moderate yield (43%, Entry 1). When performed with excess of siloxane **308**, the desired product **339** was achieved in 65% yield (Entry 2).

Table 3.8: Fluoride-promoted Hiyama reaction with vinyl halides



Entry[a]	X	R	Siloxane **308** [eq.]	Halide [eq.]	Time [h][b]	Yield [%][c]
1	I	H	1.0	1.2	16	43
2	**I**	**H**	**1.2**	**1.0**	**16**	**65**
3	Br	H	1.0	1.2	16	57
4[d]	Br	H	1.0	1.2	16	41
5[d]	**Br**	**H**	**1.2**	**1.0**	**16**	**60**
6	**I**	**Me**	**1.0**	**1.2**	**16**	**73**

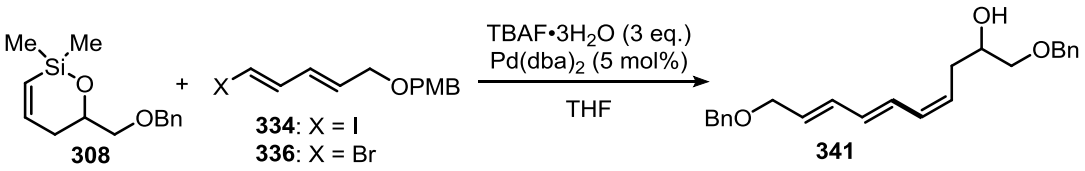
[a] Reaction performed on a 0.10 mmol scale. [b] Monitored by TLC. [c] Yield of isolated dienes by column chromatography. [d] Reaction performed with $[allylPdCl]_2$ (2.5 mol%) as the catalyst.

Similar results were obtained when vinyl bromide **332** was employed (Entries 3 to 5). The coupling of siloxane **308** with the more sterically demanding vinyl iodide **329** afforded diene **340** in 73% yield (Entry 6).

When the more complex dienyl iodide **334** was submitted to the standard coupling conditions with siloxane **308**, allylic triene **341** was obtained in 63% yield (Entry 1, Table 3.9). The desired triene **341** was afforded in 53% yield when dienyl bromide **336**

was employed (Entry 2). No improvement was observed when $[allylPdCl]_2$ was used as the catalyst (Entry 3).

Table 3.9: Fluoride-promoted Hiyama reaction with dienyl halides



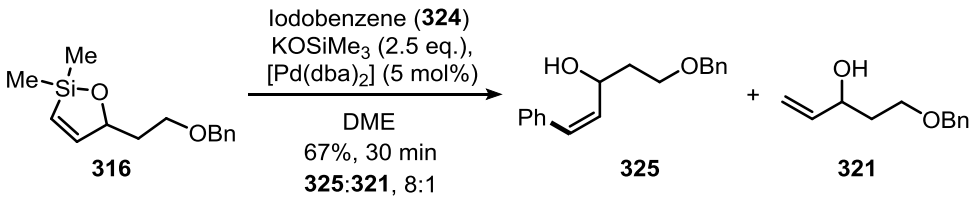
Entry[a]	X	Siloxane **308** [eq.]	Halide [eq.]	Time [h][b]	Yield [%][c]
1	I	1.0	1.2	16	63
2	Br	1.0	1.2	16	53
3	Br[d]	1.0	1.2	16	53

[a] Reaction performed on a 0.10 mmol scale. [b] Monitored by TLC. [c] Yield of isolated **341** by column chromatography. [d] Reaction performed with $[allylPdCl]_2$ (2.5 mol%) as the catalyst.

In summary, we have demonstrated that 5- and 6-membered cyclic alkenylsiloxanes are effective coupling partners in the fluoride-promoted Hiyama cross-coupling with polyenyl iodides and bromides for the stereospecific construction of conjugated *Z*-alkenyl polyenes.

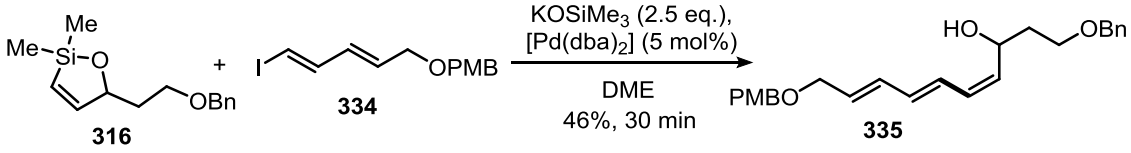
3.3.4 Base-promoted cross-coupling

We were highly encouraged by the results obtained under the fluoride-promoted conditions and were thus keen to see whether the same could be achieved under fluoride-free coupling conditions. While such base-promoted cross-coupling of cyclic dimethyl siloxanes has yet to be reported, allylic alcohol **325** was afforded in 67% yield along with protodesilylated product **321** as an inseparable mixture (**325**:**321**, 8:1) when coupled to iodobenzene (**324**), under the previously optimised diethyl analogue conditions (Scheme 3.23).[114]



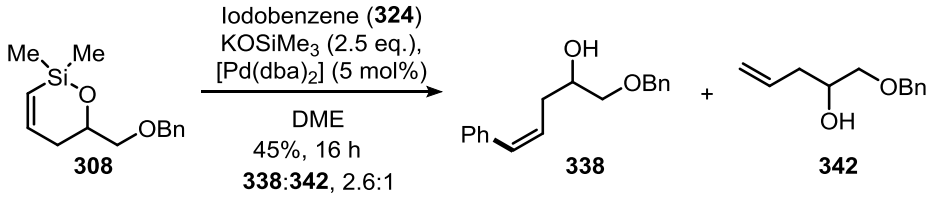
Scheme 3.23: Fluoride-free Hiyama reaction with iodobenzene

Under the same conditions, allylic triene **335** was afforded in 46% yield when coupled with dienyl iodide **334** (Scheme 3.24).



Scheme 3.24: Fluoride-free Hiyama reaction with PMB protected dienyl iodide

The previous study of cyclic diethyl siloxanes had revealed an intriguing ring-size dependency where 5-membered cyclic siloxanes are activated by base and fluoride, their 6-membered homologues are inert to base.[114] We were therefore surprised to find that when 6-membered cyclic siloxane **308** was submitted to the base-promoted conditions with iodobenzene (**324**), homoallylic alcohol **338** was obtained in 45% yield along with protodesilylated product **342** as an inseparable mixture (**338**:**342**, 2.6:1, Scheme 3.25). Importantly, protodesilylation is not observed under fluoride-promoted conditions.



Scheme 3.25: Fluoride-free Hiyama reaction with iodobenzene

This reactivity perhaps highlights the importance of sterics around the silicon, where the diethyl analogue was found to be inert under base activation.

Optimisation of the base-promoted Hiyama coupling, with further application and substrate scope, is currently being investigated in the Anderson group. Preliminary

results have shown that the previously established ring-size dependent orthogonality can be regained upon addition of water.[153]

3.4 ^{1}H NMR studies – Cyclic dimethyl alkenylsiloxanes

To further probe the interaction of the cyclic dimethyl siloxanes with fluoride activator both 5- and 6-membered siloxanes **316** and **308** were treated with TBAF•3H_2O in d_8-THF and their behaviour monitored periodically by ^{1}H NMR spectroscopy. For clarification, these results will be directly compared to a similar study of 5- and 6-membered diethyl siloxanes **272** and **343** reported by Elbert.[158]

3.4.1 ^{1}H NMR studies – 5-Membered dimethyl siloxane

Upon treatment of 5-membered siloxane **316** with TBAF•3H$_2$O (3 eq.) in d$_8$-THF a rapid equilibrium was established between cyclic siloxane **316** and acyclic silanol **344**, which are slowly converted to protodesilylated product **321** over the course of the experiment (Figure 3.1).

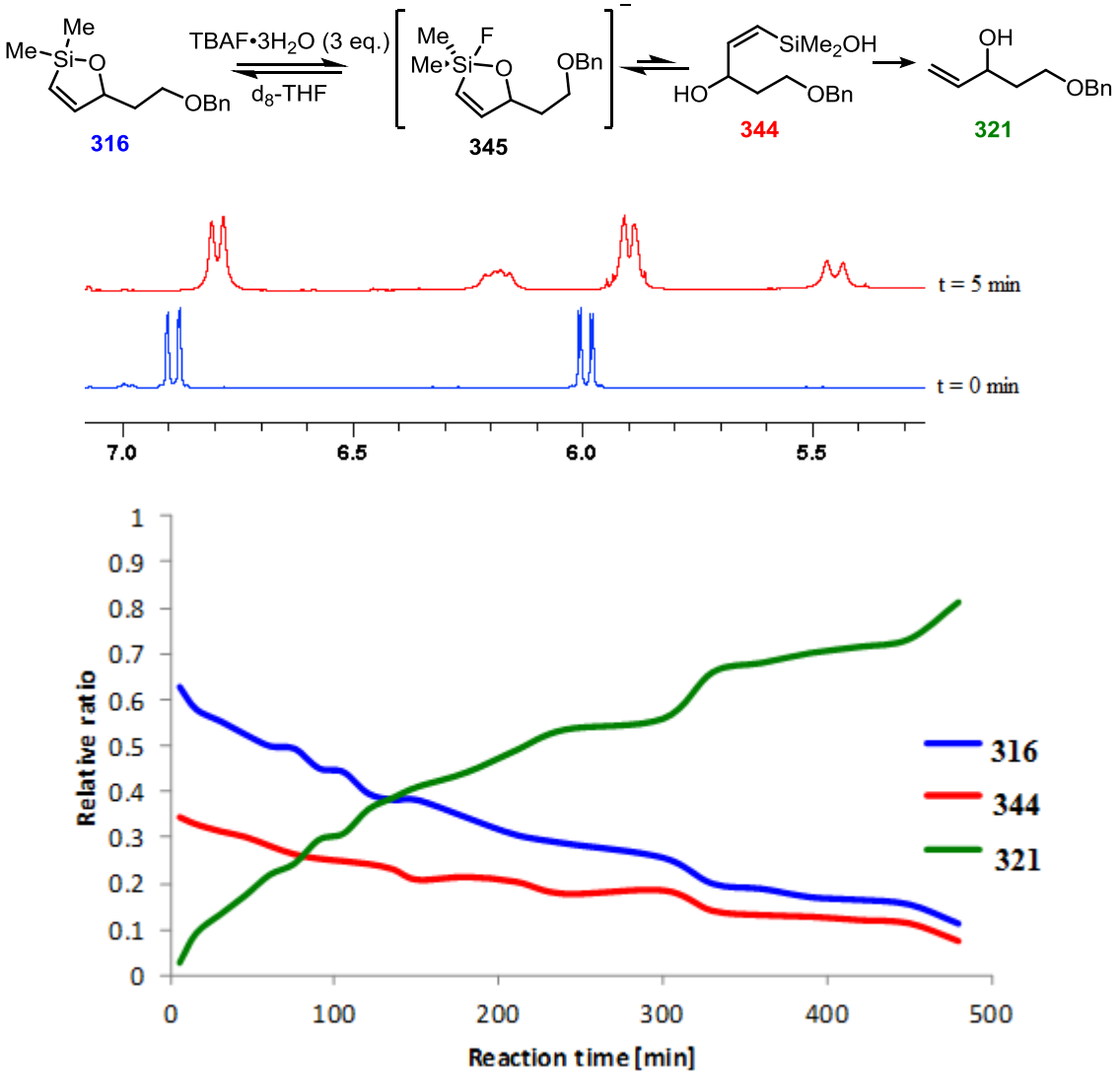


*Figure 3.1: Treatment of 5-membered dimethyl siloxane **316** with TBAF•3H$_2$O (3 eq.) in d$_8$-THF, monitored periodically by ^{1}H NMR spectroscopy*

When compared to the previous study of diethyl siloxane **272** by Elbert (**272**:**273**, 1:1.8), an inverted ratio of cyclic siloxane **316** and acyclic species **344** is observed (**316**:**344**, 1.7:1) (Figure 3.2).[158] This might be interpreted that in the case of dimethyl

siloxane **316** a higher proportion of cyclic "ate" complex **345**, in its equilibrium with siloxane **316** and acyclic **344**, is involved than for diethyl siloxane **272** (Scheme 3.26).

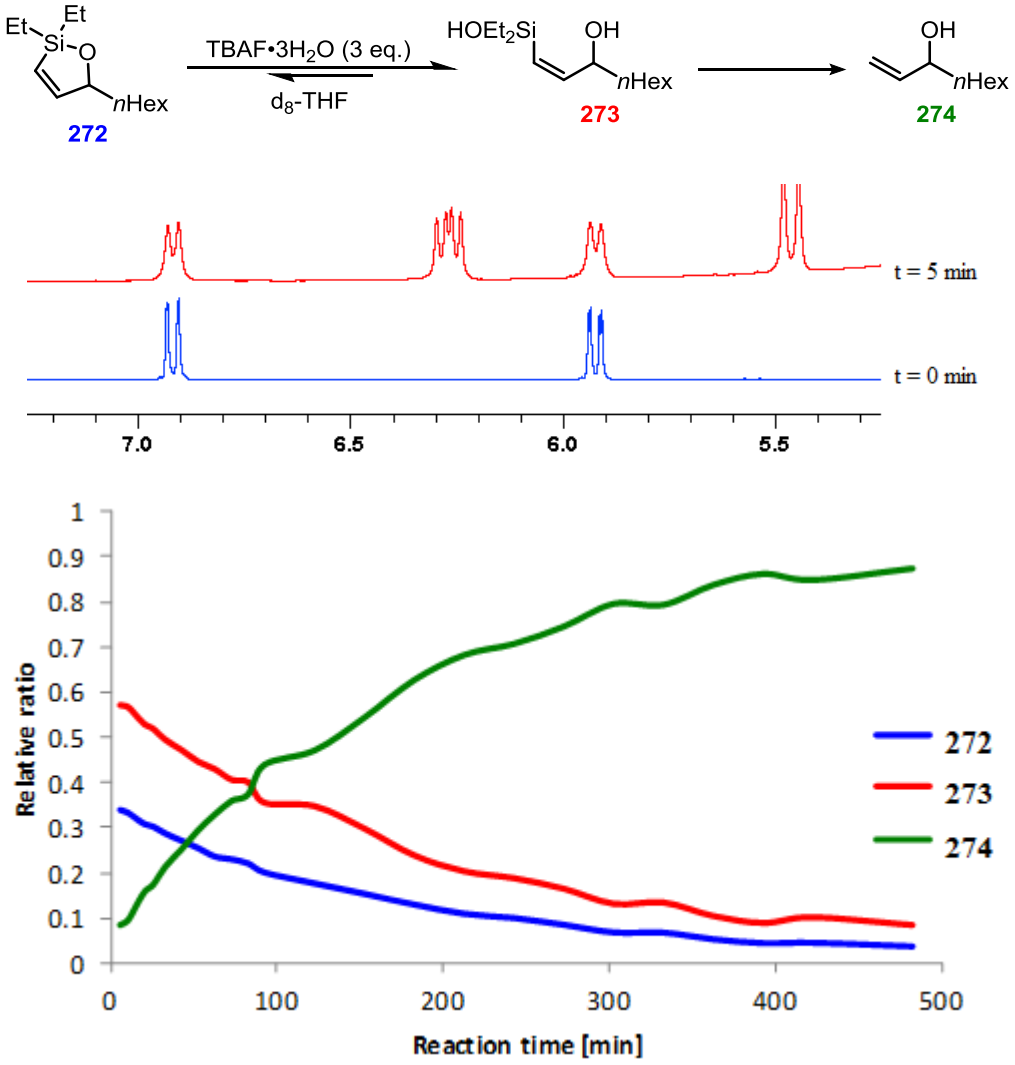
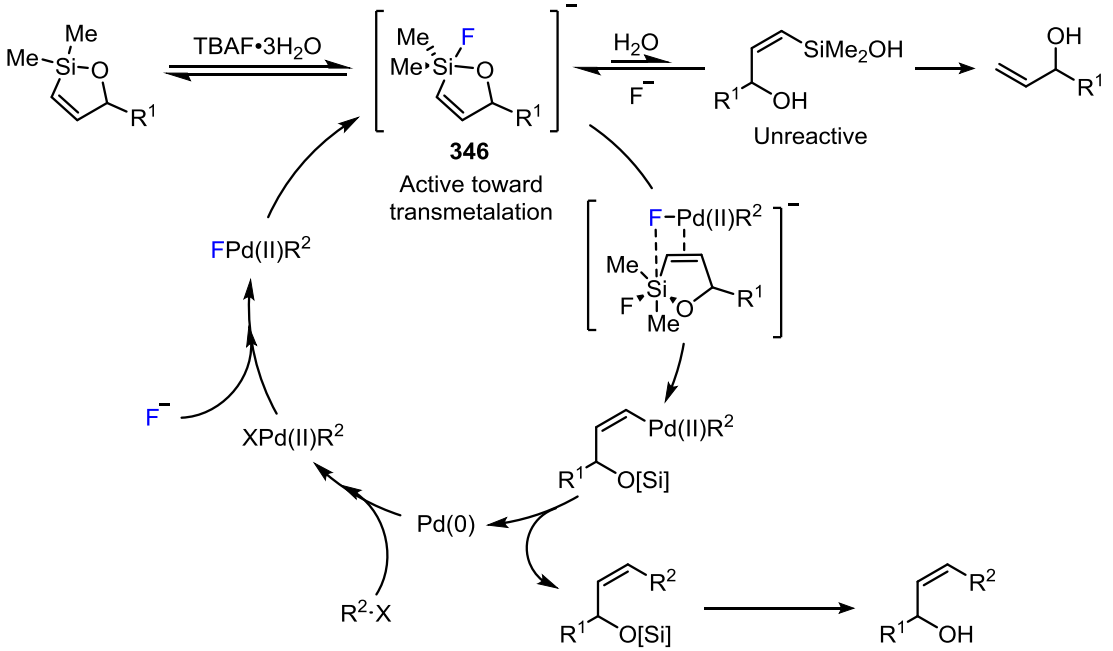


*Figure 3.2: Treatment of 5-membered diethyl siloxane **272** with TBAF•3H$_2$O (3 eq.) in d$_8$-THF, monitored periodically by ^{1}H NMR spectroscopy as obtained by Elbert*

Furthermore, upon addition of the nucleophilic activator TBAF•3H$_2$O, the distinct alkene signals of cyclic siloxanes **316** and **272** and acyclic silanols **344** and **273** are significantly broadened (Figures 3.1 and 3.2). However, in the case of cyclic dimethyl siloxane **316**, this is accompanied by a shift in their signals which could be interpreted as a rapid interconversion of cyclic **316** and cyclic "ate" complex **345**, only showing an average spectrum due to the NMR timescale. This is not observed with cyclic diethyl siloxane **272** and may provide further evidence that 5-membered dimethyl siloxanes are

able to form cyclic "ate" complex **346** more readily than their diethyl analogues. This is important because the "ate" complex **346** is believed to be the active species toward transmetalation involved with 5-membered cyclic siloxanes, thus explaining the difference in reactivity observed with diethyl and dimethyl siloxanes (Scheme 3.26).



Scheme 3.26: Proposed mechanism for the cross-coupling of 5-membered siloxanes

3.4.2 ^{1}H NMR studies – 6-Membered dimethyl siloxane

Upon treatment of 6-membered siloxane **308** with TBAF•3H_2O (3 eq.) in d_8-THF rapid equilibrium is established between siloxane **308** and acyclic silanol **347** which remained at constant ratio (**308**:**347**, 1:1.3) throughout the course of the experiment (Figure 3.3).

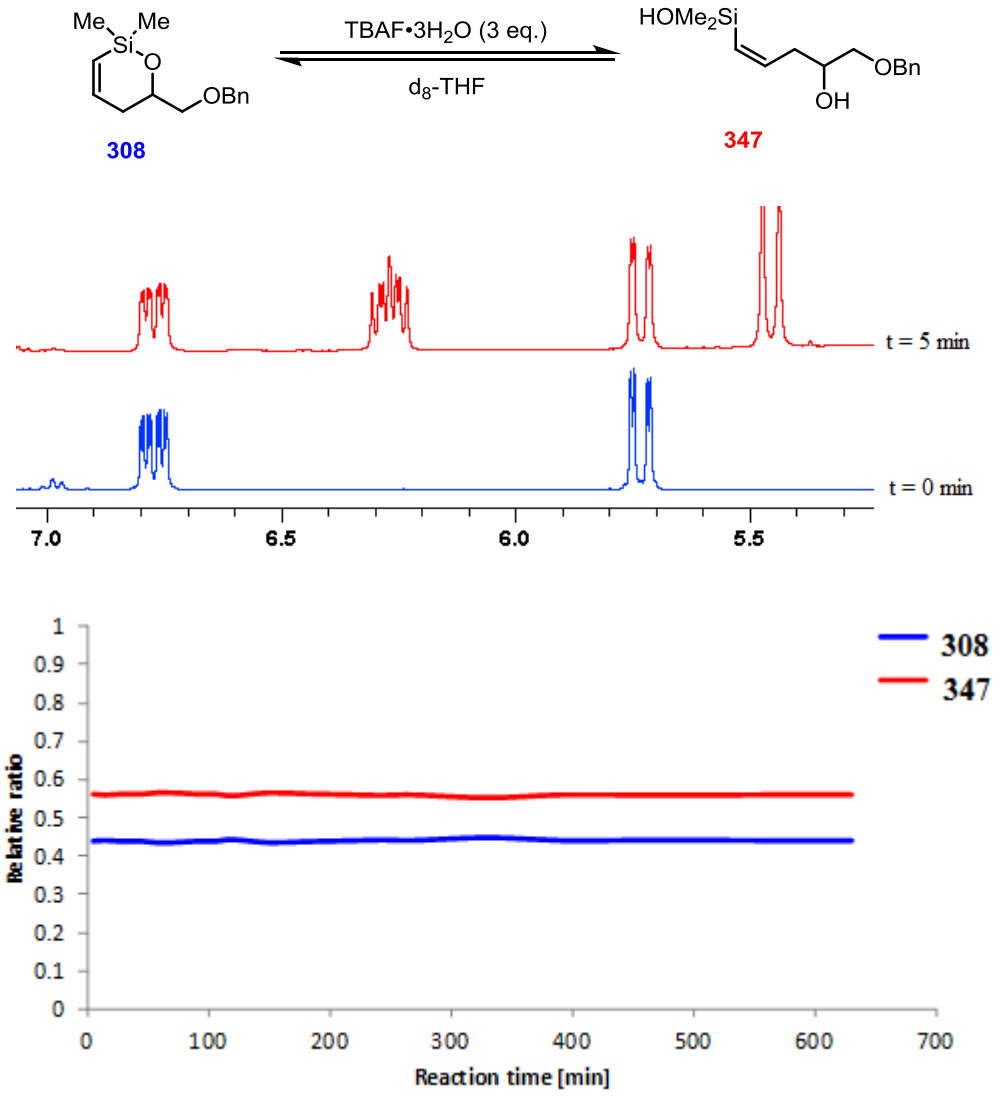


*Figure 3.3: Treatment of 6-membered dimethyl siloxane **308** with TBAF•3H_2O (3 eq.) in d_8-THF, monitored periodically by ^{1}H NMR spectroscopy*

In this case, unlike the 5-membered analogue, the same behaviour is observed when compared to the previous study of diethyl siloxane **348** by Elbert (**348**:**349**, 1:1.3, Figure 3.4).[158]

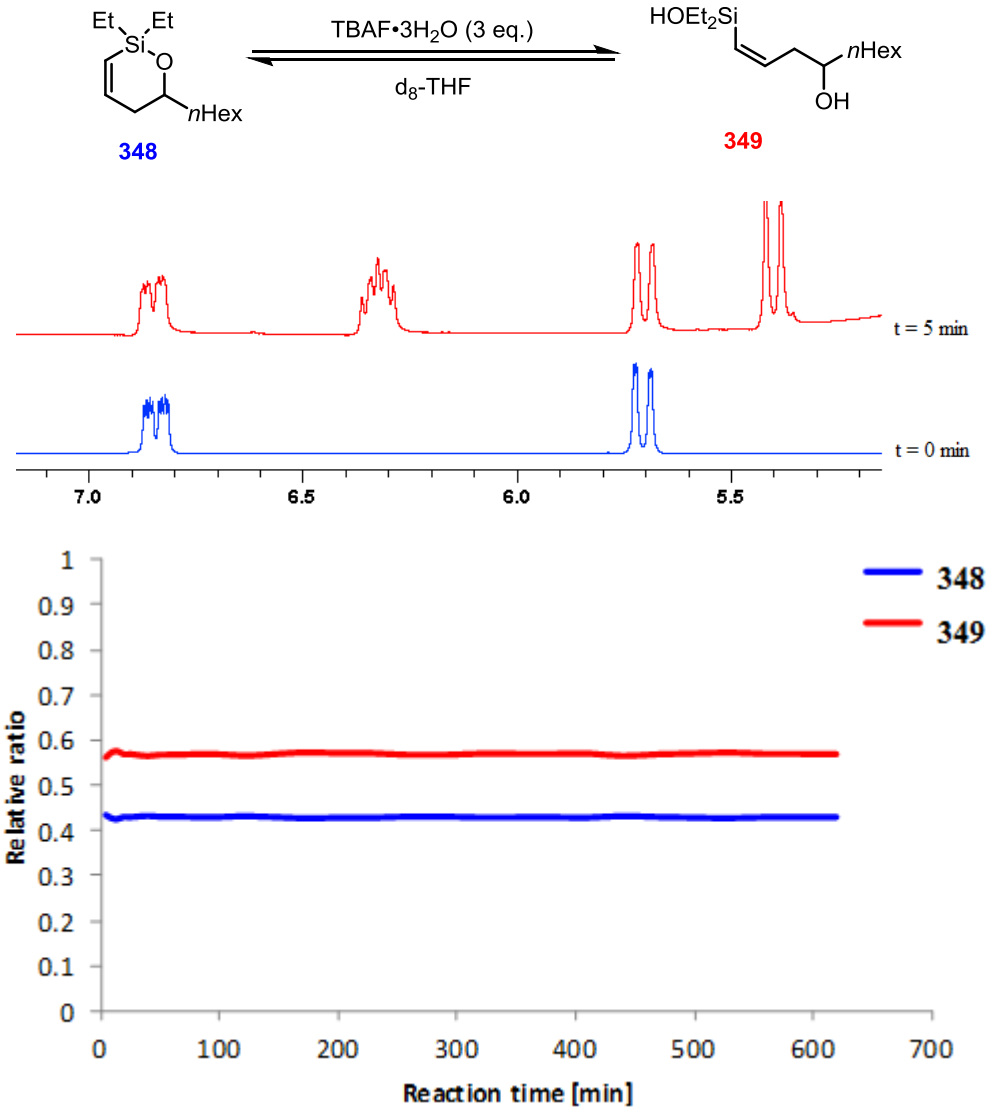
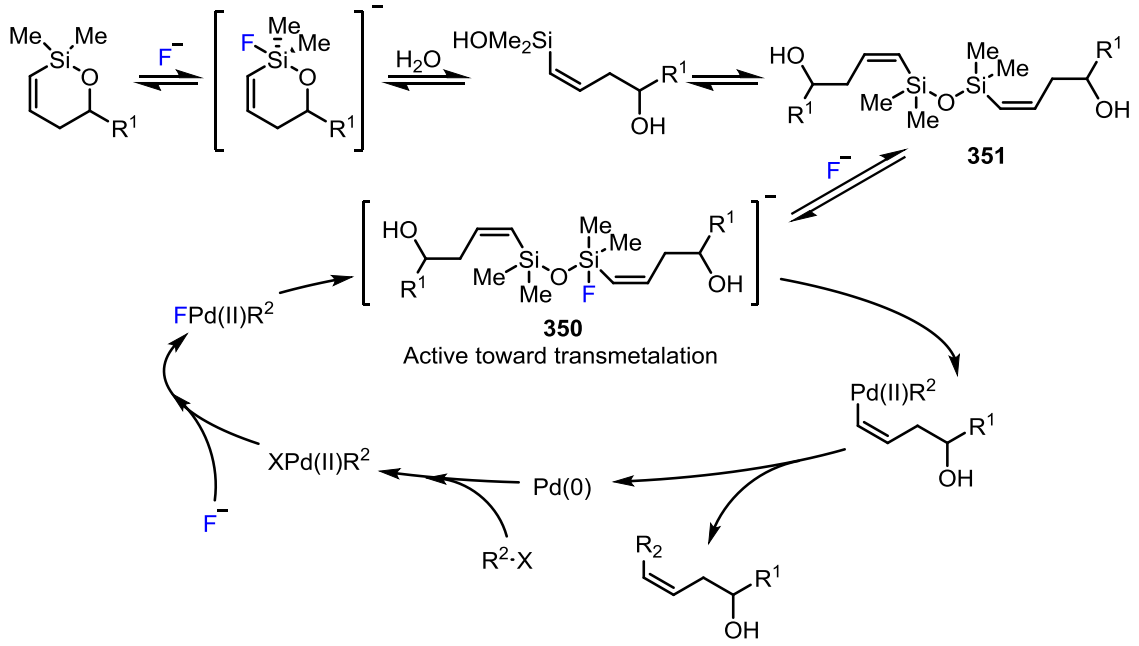


*Figure 3.4: Treatment of 6-membered diethyl siloxane **348** with TBAF•3H$_2$O (3 eq.) in d$_8$-THF, monitored periodically by ^{1}H NMR spectroscopy as obtained by Elbert*

This suggests that both 6-membered siloxanes share a common mechanistic pathway *via* the formation of fluoride-activated disiloxane **350** as proposed by Denmark *et al.* (Scheme 3.27).[81]

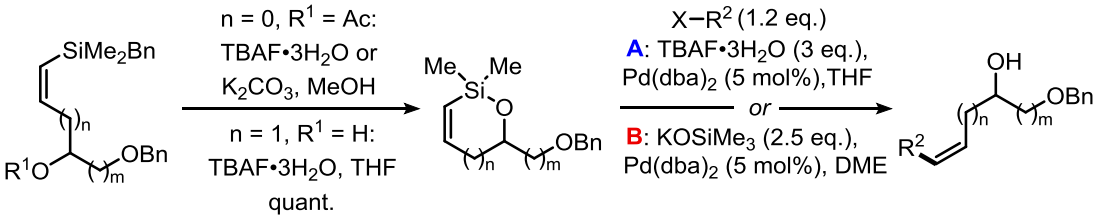


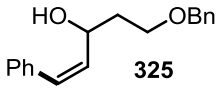
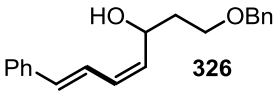
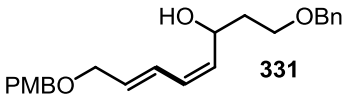
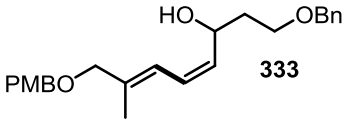
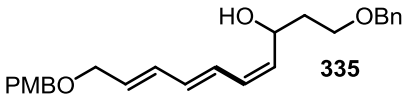
Scheme 3.27: Formation of activated disiloxane

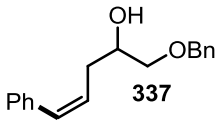
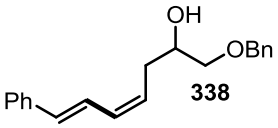
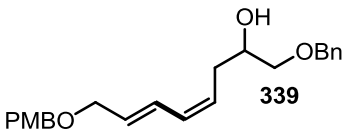
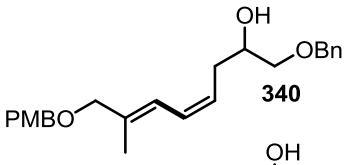
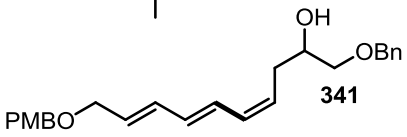
Dimethylsilanols would be expected to have a greater propensity to form the requisite fluoride-activated *Z*-vinyldisiloxane **350**, *via* disiloxane **351**, than the more sterically demanding diethylsilanols, thus explaining their enhanced reactivity.

3.5 Conclusion

We have developed a novel methodology for the preparation of 5- and 6-membered cyclic dimethyl alkenylsiloxanes utilising *Z*-vinylbenzyldimethylsilanes as masked silanol intermediates (Scheme 3.28). While 6-membered precursors require activation by hydrated fluoride source prior to their generation, 5-membered precursors display a unique mode of activation under mildly basic conditions. Furthermore, we have demonstrated their subsequent cross-coupling with a range of challenging polyenyl iodides and bromides as a stereospecific route to conjugated *Z*-alkenyl polyenes. While ^{1}H NMR spectroscopic studies proved insightful, further kinetic profiling is required for a more complete mechanistic picture.



Product (n = 0, m = 2)	A: (X = I)	A:(X = Br)	B: (X = I)
 **325**	95%, 5 min*		67%, 30 min
 **326**	78%, 45 min	78%, 15 min	
 **331**	73%, 15 min***	57%, 3 h**	
 **333**	84%, 1 h		
 **335**	81%, 30 min	56%, 2 h****	46%, 30 min

Product (n = 1, m = 1)	A: (X = I)	A:(X = Br)	B: (X = I)
 **337**	91%, 15 min*		45%, 30 min
 **338**	75%, 16 h	68%, 5 h**	
 **339**	65%, 16 h	60%, 16 h**	
 **340**	73%, 16 h		
 **341**	63%, 30 min	53%, 16 h	

* TBAF•3H$_2$O (2 eq.),** [allylPdCl]$_2$ (2.5 mol%) 1.2 eq. siloxane,*** 1.2 eq. siloxane,
**** [allylPdCl]$_2$ (2.5 mol%)

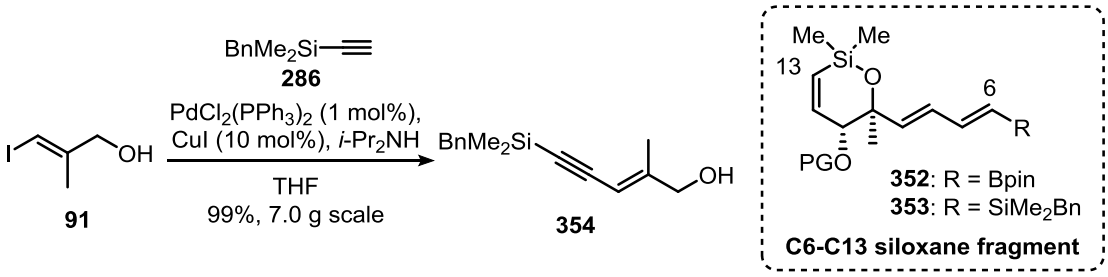
Scheme 3.28: Overview of methodology and subsequent cross-coupling

Chapter 4: Towards incednam – A revised synthesis

Having developed a novel method for the generation of 5- and 6-membered cyclic dimethyl siloxanes we were keen to adapt this new strategy to the incednam siloxane fragment. In addition, the instability of the C11 benzoate protecting group under cross-coupling conditions led us to contemplate a new protecting group strategy. The following chapter will describe this work, along with progress towards the completion of incednam.

4.1 C6-C13 Cyclic dimethyl alkenylsiloxane synthesis

The revised synthesis of the C6-C13 cyclic dimethyl alkenylsiloxane fragment commenced with Sonogashira coupling of common intermediate vinyl iodide **91** with benzyldimethylsilylacetylene **286**, which provided multi-gram quantities of enyne **354** in excellent yield (Scheme 4.1).[132]

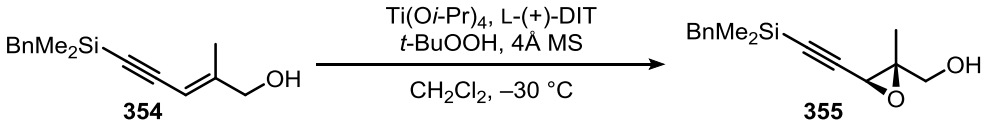


*Scheme 4.1: Preparation of enyne **354** by Sonogashira reaction*

Under the previously employed Sharpless asymmetric epoxidation conditions, using substoichiometric amounts of Ti(O*i*-Pr)$_4$ (0.5 eq.) and L-(+)-diisopropyl tartrate ligand (0.6 eq.), epoxide **355** was afforded in 78% yield with 90% *ee* (Entry 1, Table 4.1). In Sharpless seminal work, trisubstituted allylic alcohols were reported to give best selectivities (*ee* > 98%) when stoichiometric reaction conditions were employed.[68,69] However, under those conditions, epoxide **355** was obtained with disappointing 66% *ee* (Entry 2). Similar reports by Sharpless employing 10 mol% of Ti(O*i*-Pr)$_4$ afforded **355** with 86% *ee* (Entry 3).[69] In stark contrast to the delicate isopropoxysilane, the stability

of the benzyldimethylsilane greatly facilitated product isolation and purification, allowing conventional workup procedures typically associated with Ti(O*i*-Pr)$_4$.

Table 4.1: Exploring conditions for the Sharpless asymmetric epoxidation reaction



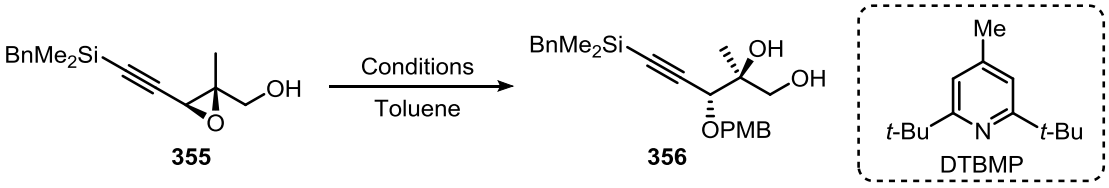
Entry	Ti(O*i*-Pr)$_4$ [eq.]	L-(+)-DIT [eq.]	*ee* [%][a]	Yield [%][b]
1	0.5	0.6	90	78
2	1.0	1.2	66	n.d.[c]
3	0.10	0.12	86	n.d.[c]

[a] Determined by HPLC analysis of the crude reaction mixture. [b] Yield of isolated **355** by column chromatography. [c] Not determined.

Next, regioselective ring-opening of 2,3-epoxy alcohol **355** was required (Table 4.2). For this a *p*-methoxybenzyl (PMB) alcohol was chosen due to its stability towards a variety of reaction conditions, and potential to undergo selective cleavage using single electron oxidants such as DDQ. The choice of a PMB ether is very important, as this will not only allow the selective formation of the more stable 6-membered ring, but give us the predictability required to precisely control the formation of the less stable but more reactive 5-membered ring, which was found lacking with the previously employed benzoate analogue. However, when epoxy alcohol **355** was submitted to titanium-mediated ring-opening with PMB alcohol in refluxing toluene, only degradation of the starting material was observed (Entry 1).[70] Similar reports using Ti(OPMB)$_4$, generated from Ti(O*i*-Pr)$_4$ and PMB alcohol, were not successful (Entry 2).[166] Gratifyingly, conditions developed by Iwabuchi *et al*. employing catalytic amounts of Eu(OTf)$_3$ and DTBMP as a proton scavenger enabled the required ring-opening to take place (Entry 3).[167] While the reported conditions generally employ the intended nucleophile as the solvent, we were unable to separate the desired product

from the excess PMB alcohol. However, using 1.5 equivalents of PMB alcohol in toluene, albeit at the expense of reaction time, 1,2-diol **356** was obtained in good yield (Entry 4). Upon gentle heating (60 °C), the desired diol was obtained in good yield with reduced reaction time (Entry 5).

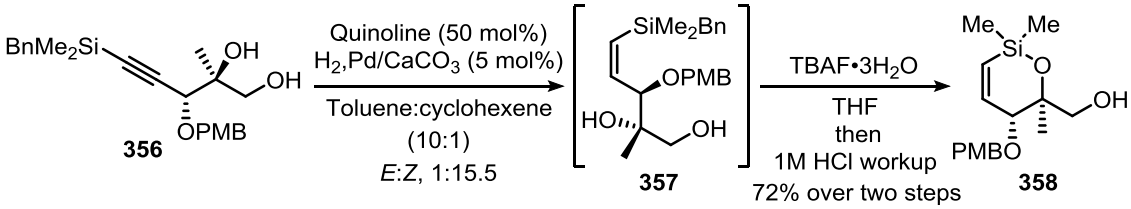
Table 4.2: Regioselective epoxide opening with PMB alcohol



Entry	Conditions	PMBOH [eq.]	T [°C]	t [h]	Yield [%][a]
1	$Ti(O\textit{i}\text{-}Pr)_4$ (1.5 eq.)	3.0	110	1	—
2	$Ti(OPMB)_4$ (1.5 eq.)	—	85	1	—
3	$Eu(OTf)_3$ (20 mol%), DTBMP (20 mol%)	0.2 M	RT	16	n.d.[b]
4	$Eu(OTf)_3$ (20 mol%), DTBMP (20 mol%)	1.5	RT	72	77
5	$Eu(OTf)_3$ (20 mol%), DTBMP (20 mol%)	1.5	60	16	77

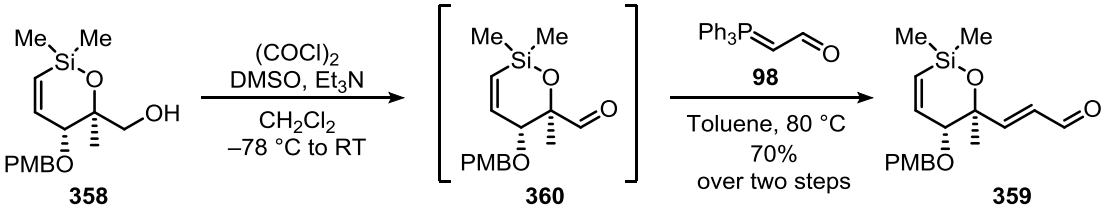
[a] Yield of isolated **356** by column chromatography. [b] Not determined.

Under our standard conditions, the key stereoselective semi-hydrogenation of alkynylsilane **356** afforded the desired *Z*-alkenylsilane **357** with good diastereoselectivity (*dr* = 10:1). However, with increased quinoline loading and the use of cyclohexene as sacrificial co-solvent, **357** was obtained with excellent *cis*-selectivity (*dr* = 15.5:1) which upon fluoride mediated benzyl cleavage and subsequent acidic workup afforded the key 6-membered cyclic alkenylsiloxane **358** in 72% yield over two steps (Scheme 4.2)



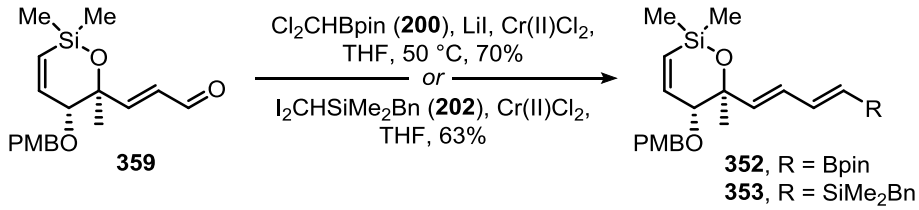
Scheme 4.2: The key stereoselective semi-hydrogenation/cyclisation sequence

α,β-Unsaturated aldehyde **359** was prepared in two steps from alcohol **358** (Scheme 4.3). First, Swern oxidation gave aldehyde **360** which upon Wittig olefination with phosphorane **98** afforded the desired **359** in 70% yield over two steps. Aldehyde **360** was found to be unstable towards silica gel column chromatography and was thus used crude. In contrast to the benzoate analogue **199**, no over addition was observed in the subsequent Wittig reaction, even though two equivalents of phosphorane **98** were required in order for full conversion.



*Scheme 4.3: Two step preparation of α,β-unsaturated aldehyde **359***

Finally, Takai borylolefination using boronate **200** afforded the C6-C13 dienyl boronic ester fragment **352** in 70% yield (Scheme 4.4). Similarly, Takai silylolefination with diiodomethylsilane **202** afforded the C6-C13 dienyl benzyldimethylsilane fragment **353** in 63% yield.



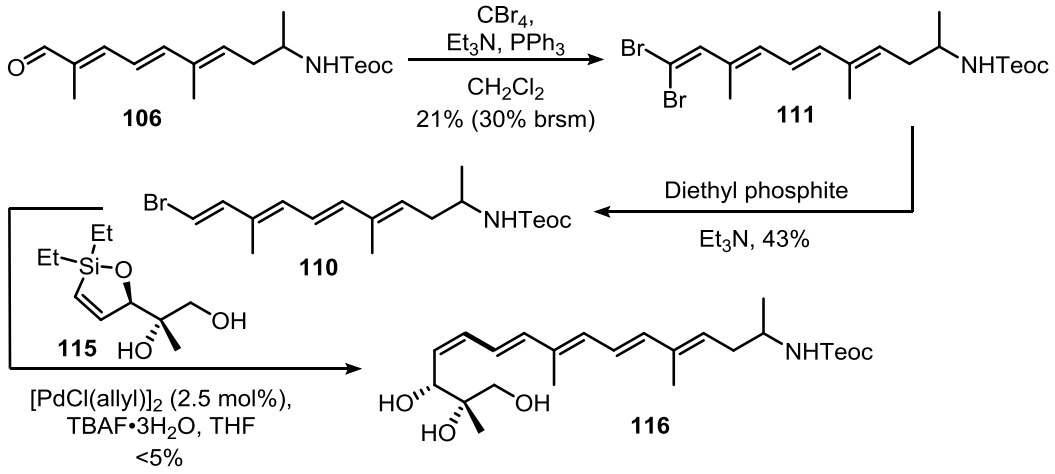
Scheme 4.4: Takai olefination for the preparation of vinyl organometallic species

Overall the key fragments **352** and **353** were achieved in total of 9 steps from propargyl alcohol (**90**), with an overall yield of 15% and 14%, respectively.

4.2 C14-C23 Tetraenyl bromide fragment synthesis

Previous work by Lim had demonstrated that tetraenyl bromide **110** could be prepared as a single geometrical isomer in two steps from trienal **106** (Scheme 4.5). However,

only traces of the desired pentaene **116** were obtained under the fluoride-promoted Hiyama cross-coupling with model 5-membered diethyl siloxane **115**. In contrast, the stereoisomeric tetraenyl iodide **107** had provided pentaene **116** in modest yield (Scheme 1.25).



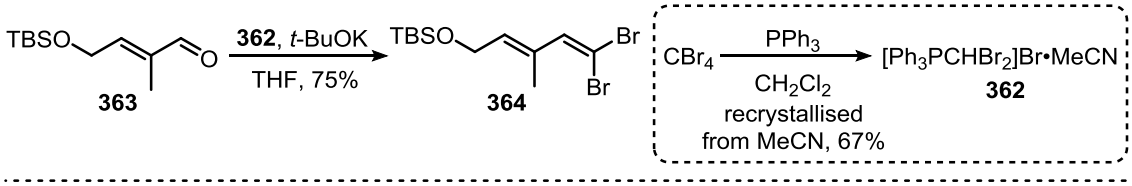
*Scheme 4.5: Preparation of tetraenyl bromide **110** by Lim and its subsequent coupling*

Given the enhanced reactivity of the cyclic dimethyl alkenylsiloxanes, as was demonstrated in the previous chapter, we were hopeful that this modification would allow the coupling of tetraenyl bromide **361** for the stereoselective construction of the C12-C21 pentane system of incednam. Thus, the asymmetric synthesis of the C14-C23 tetraenyl bromide fragment **361** commenced with dibromoolefination of trienal **253** (Table 4.3). The previously employed Ramirez olefination had proved low yielding, and therefore the mild conditions afforded by the Wolkoff reagent **362** were explored.[168] With model α,β-unsaturated aldehyde **363** (provided by Kuper), containing an acid labile silyl ether, dibromide **364** was obtained in good yield (75%) by this Wittig-type olefination.[153,169] However, when trienal **253** was submitted to these conditions, the intended transformation was not observed, with full recovery of **253** (Entry 1). Using conditions developed by Lièvre *et al*. the desired dibromide **365** was obtained in 10% yield (13% brsm) in presence of zinc in refluxing 1,4-dioxane (Entry 2).[170] Ironically,

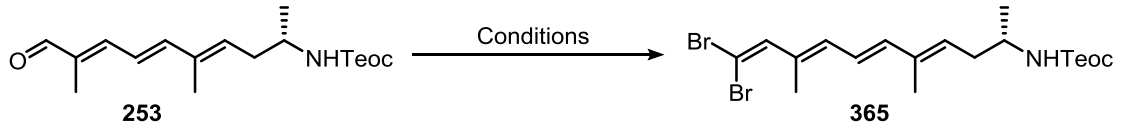
with few modifications of the previously employed Ramirez olefination, most importantly omitting an aqueous workup, dibromide **365** was obtained in 77% yield (Entries 3 and 4).

*Table 4.3: Exploring the dibromoolefination for the preparation of **365***

Model system:



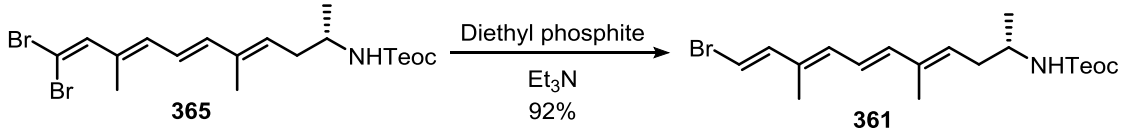
C14-C23 trienal fragment:



Entry	Conditions	Yield [%][a]
1	**362** (2.0 eq.), *t*-BuOK (1.9 eq.), THF, RT to 40 °C	–
2	**362** (4.0 eq.), Zn (4.4 eq.), 1,4-dioxane, 100 °C	10
3	CBr_4 (2.8 eq.), Ph_3P (5.5 eq.), Et_3N (13.8 eq.), CH_2Cl_2, 0 °C	23
4[b]	CBr_4 (3.0 eq.), Ph_3P (6.0 eq.), Et_3N (15.0 eq.), CH_2Cl_2, 0 °C	77

[a] Yield of isolated **365** by column chromatography. [b] No aqueous workup performed prior to isolation of **365** by column chromatography.

Similar modifications afforded tetraenyl bromide **361** from dibromide **364** in 92% yield under the Hirao-Hayes monodebromination conditions, when an aqueous workup was excluded (Scheme 4.6).[71,72]

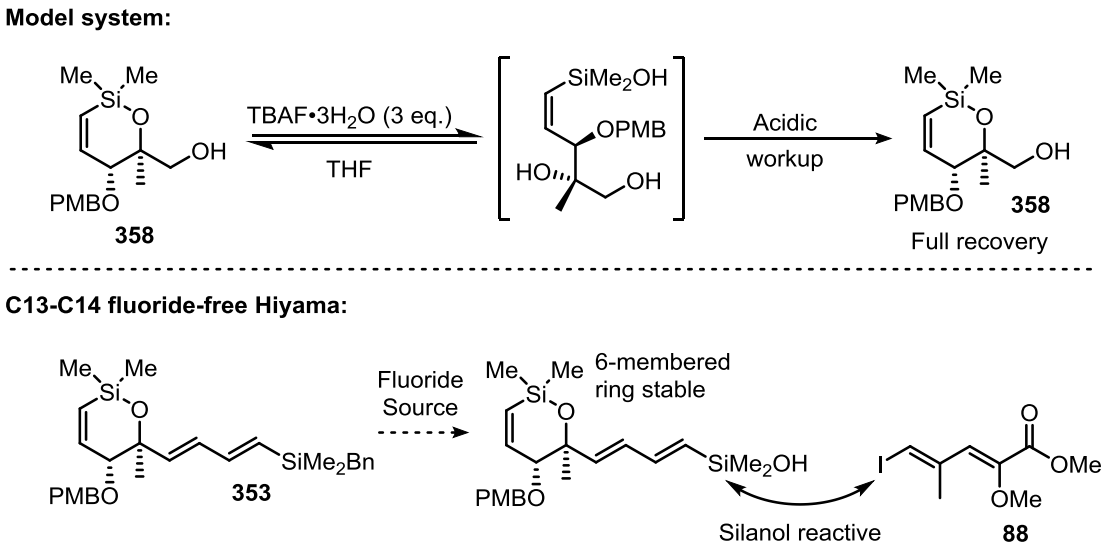


*Scheme 4.6: Monodebromination of dibromide **365***

Overall the C14-C23 tetraenyl bromide fragment **361** was obtained in total of 11 steps, starting from L-alanine methyl ester hydrochloride (**212**), with an overall yield of 23%.

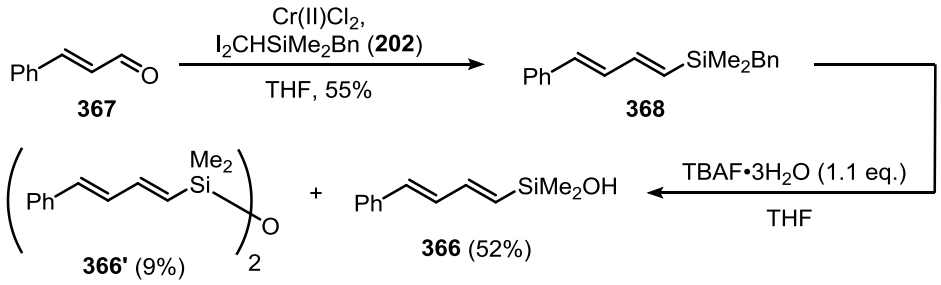
4.3 Towards incednam ─ C1-C13 Pentaenoate fragment

In stark contrast to the benzoate analogue **97**, when *O*-PMB appended 6-membered siloxane **358** was treated with TBAF•3H_2O (3 eq.), full recovery of the starting material was obtained (Scheme 4.7). This is important as this gives us the opportunity to construct the C2-C9 tetraene system *via* orthogonal Hiyama cross-coupling of bis-silane **353** and dienoate **88**.



Scheme 4.7: Activation of benzyldimethylsilane in presence of 6-membered siloxane

Before embarking on this ambitious strategy, dienyl silanol **366** was chosen as a representative system to study the required fluoride-free Hiyama cross-coupling. Silanol **366** was obtained in two steps from cinnamaldehyde (**367**) (Scheme 4.8).

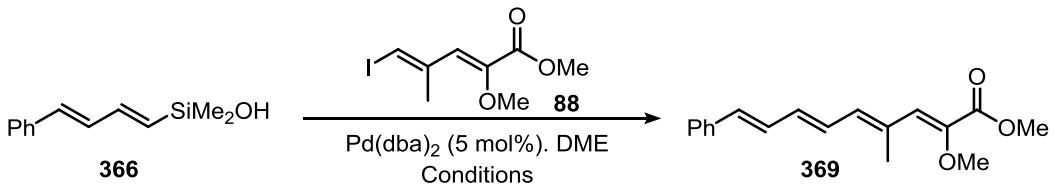


*Scheme 4.8: Preparation of dienyl silanol **366** from cinnamaldehyde*

Takai silylolefination of **367** using diiodomethylsilane **202** afforded dienyl silane **368**, which upon fluoride promoted de-benzylation gave silanol **366** in 52% yield. With

silanol **366** in hand the fluoride-free cross-coupling with dienoate **88** was explored under Brønsted base activation (Table 4.4). The sodium alkenylsilanolate salt, generated *in situ* with sodium hydride, underwent cross-coupling with dienoate **88** in presence of $Pd(dba)_2$ to give tetraenoate **369** in 39% yield (Entry 1). The use of sodium hexamethyldisilazide resulted in extended reaction time with comparable yield obtained (Entry 2).

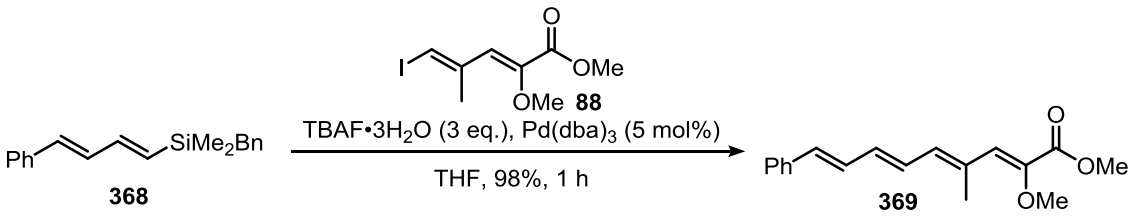
*Table 4.4: Base-promoted Hiyama cross-coupling of silanol **366***



Entry[a]	Conditions	Time [h]	Yield [%][b]
1	NaH (1.0 eq.)	0.5	39
2	NaHMDS (1.0 eq.)	16	39
3[c]	$KOSiMe_3$ (2.0 eq.)	0.5	59
4	KHMDS (1.0 eq.)	0.5	60

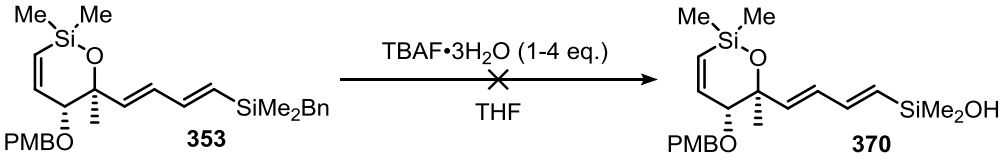
[a] Solution of silanol **366** treated with base prior to addition of **88** and catalyst. [b] Yield of isolated **369** by column chromatography. [c] Activator added to a stirred solution containing silanol **366**, dienoate **88** and catalyst.

Better results were obtained with the more nucleophilic potassium alkenylsilanolate salt, generated *in situ* with potassium trimethylsilanoate or potassium hexamethyldisilazide, which afforded the desired tetraenoate **369** in 60% yield (Entries 3 and 4). For comparison, tetraenoate **369** was obtained in near quantitative yield under fluoride-promoted coupling of dienyl silane **368** with dienoate **88** (Scheme 4.9).



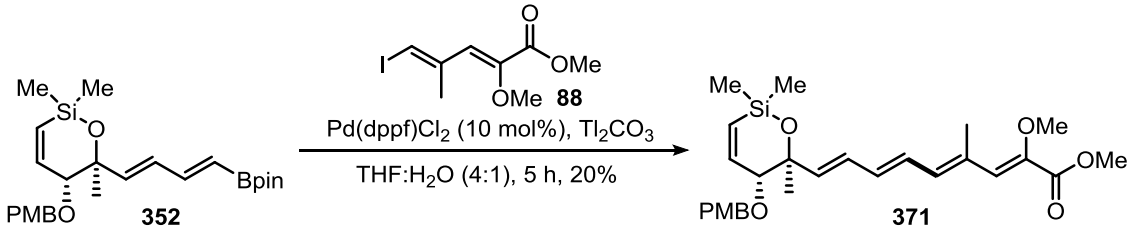
*Scheme 4.9: Fluoride-promoted Hiyama cross-coupling of vinylsilane **368***

Encouraged by these results, the de-benzylation of bis-silane **353** was thus attempted (Scheme 4.10). Upon addition of TBAF•3H_2O (1 eq.), only partial consumption of benzylsilane **353** was observed, as suggested by TLC, with formation of a new spot presumed to be silanol **370**. While further addition of fluoride (portionwise addition up to 4 eq.) resulted in full consumption of benzylsilane **353**, the putative silanol **370** was consumed as well, only to return a complex mixture.



*Scheme 4.10: Attempted fluoride mediated de-benzylation of bis-silane **353***

While disappointed in this result, the construction of the C1-C13 tetraenoate fragment **371** was attempted *via* the previously established C5-C6 Suzuki reaction (Scheme 4.11). In presence of Pd(dppf)Cl_2 and thallium carbonate as base, the cross-coupling of dienyl boronic ester **352** and dienoate **88** afforded tetraenoate **371** in 20% yield.



Scheme 4.11: C5-C6 bond formation via previously established Suzuki reaction

When left over an extended period of time under the reaction conditions (16 h), no product could be obtained suggesting that the dimethyl siloxane functionality is not tolerated under the reaction conditions employed.

In light of this problem, we contemplated the use of C8-C9 HWE olefination for the construction of the C2-C9 tetraene system. This would involve the use of extended phosphonate **372**, derived from dienoate **88** by Heck cross-coupling (Figure 4.1).

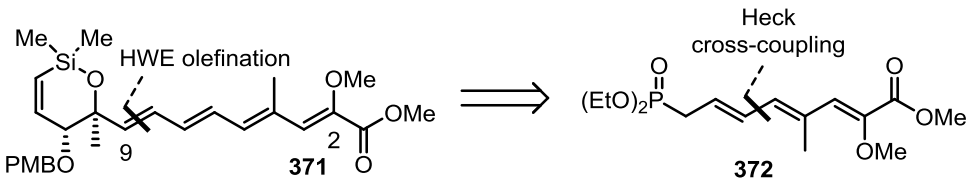
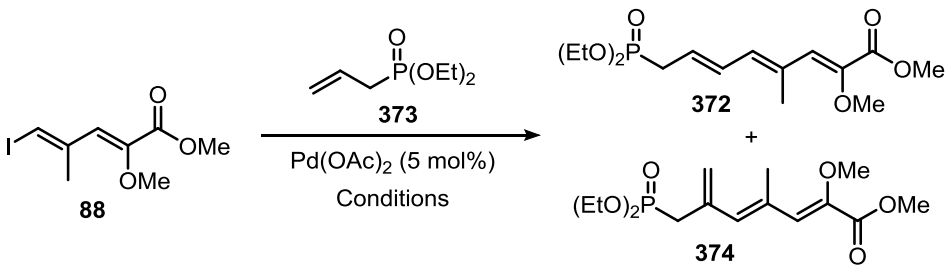


Figure 4.1: Construction of the C2-C9 tetraenoate by HWE olefination

After a short literature search, we were surprised that such an approach towards extended stabilised phosphonates has not been exploited (Table 4.5). Under Jeffery conditions, using potassium carbonate in combination with tetrabutylammonium bromide as phase transfer catalyst, no cross-coupling between dienoate **88** and allyl phosphonate **373** was observed (Entries 1 and 2).[171,172] However, when silver acetate was used as base, phosphonate **372** was obtained along with regioisomer **374** (**372**:**374**, 2.7:1, 79%, Entry 3). When performed in combination with tri(*o*-tolyl)phosphine, a common ligand employed in Heck reactions, almost exclusive formation of the desired phosphonate **372** was obtained in 87% yield (entry 4).

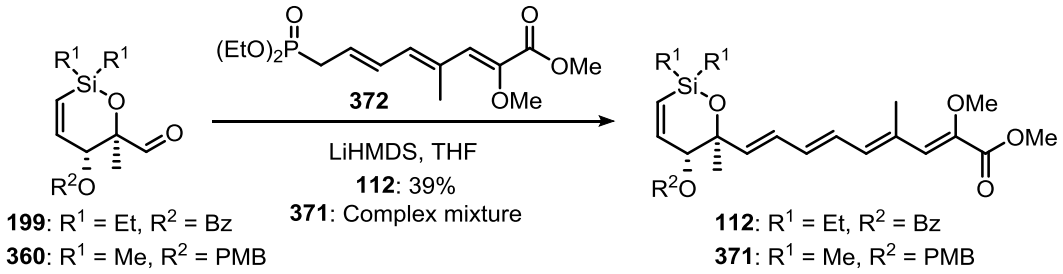
Table 4.5: Preparation of extended stabilised phosphonates by Heck reaction



Entry	Conditions	**372**:**374**[a]	Yield [%][b]
1	K_2CO_3 (2.0 eq.), TBAB (1.0 eq.), DMF, 50 °C	—	—
2	K_2CO_3 (2.5 eq.), TBAB (1.0 eq.), PPh_3 (10 mol%), DMF:H_2O (10:1), 80 °C	—	—
3	$Ag(OAc)_2$ (1.5 eq.), MeCN, 80 °C	2.7:1	79
4[c]	$Ag(OAc)_2$ (1.5 eq.), P(*o*-tol)$_3$ (20 mol%), MeCN, 80 °C	10.6:1	87

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] Yield of isolated **372** by column chromatography. [c] 10 mol% of $Pd(OAc)_2$ used.

Applying the extended phosphonate **372** to model diethyl siloxane **199**, tetraenoate **112** was afforded in 39% yield upon deprotonation of **372** with lithium hexamethyldisilazide, followed by addition of aldehyde **199** to the resulting deep red solution (Scheme 4.12). However, when dimethyl siloxane **360** was submitted to these conditions only a complex mixture was returned, again highlighting the delicate nature of the dimethyl siloxane functionality compared to its diethyl analogue.

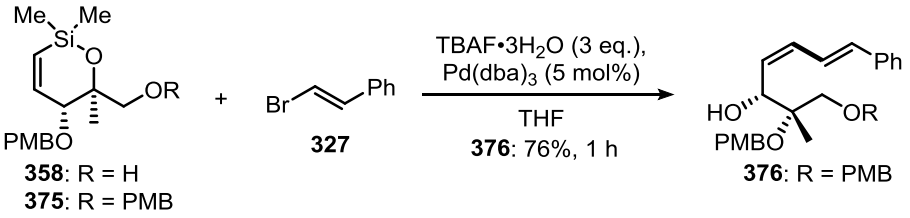


*Scheme 4.12: HWE olefination with extended phosphonate **372***

In addition, milder HWE olefination conditions as reported by Masamune and Roush, Myers, and Davies were unsuccessful.[173–175]

4.4 Towards incednam – Modelling the C13-C14 bond construction *via* Hiyama cross-coupling

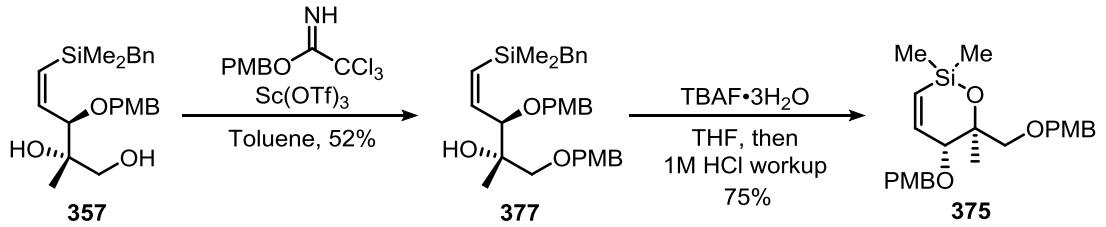
The key C13-C14 bond formation *via* Hiyama cross-coupling was first explored on model 6-membered siloxane **358**. When **358** was submitted to the fluoride-promoted coupling conditions with bromostyrene (**327**), no formation of coupled product with recovery of siloxane starting material **358** was observed (Scheme 4.13).



Scheme 4.13: Fluoride-promoted Hiyama cross-coupling of 6-membered siloxane

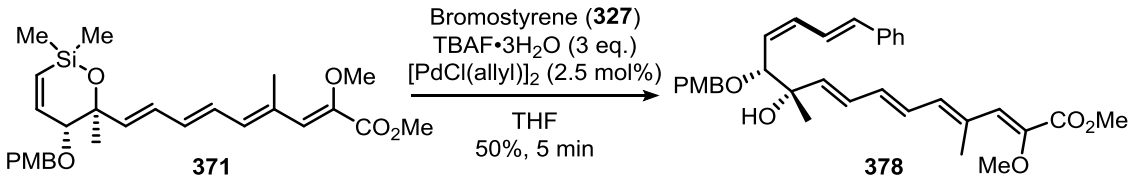
However, when PMB protected **375** was submitted to the same conditions, diene **376**

was obtained in 76% yield. Diprotected siloxane **375** was prepared in two steps from diol **357**: first, the primary alcohol of **357** was protected as the PMB ether to give **377**, which upon fluoride mediated cyclisation afforded siloxane **375** (Scheme 4.14). Direct protection of siloxane **358** proved unsuccessful as **358** was not tolerant under the conditions employed.



*Scheme 4.14: Two step preparation of PMB protected siloxane **375***

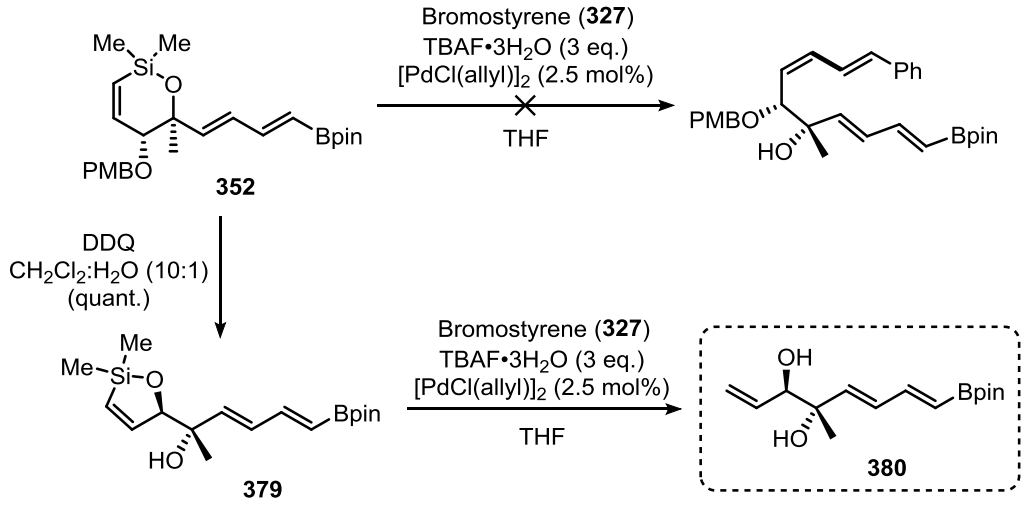
When the full length tetraenoate **371** was submitted to the fluoride-promoted coupling conditions with bromostyrene (**327**) we were delighted to find that the desired product **378** was obtained in 50% yield with full consumption of siloxane **371** in just 5 min (Scheme 4.15).



*Scheme 4.15: Fluoride-promoted Hiyama cross-coupling of tetraenoate **371***

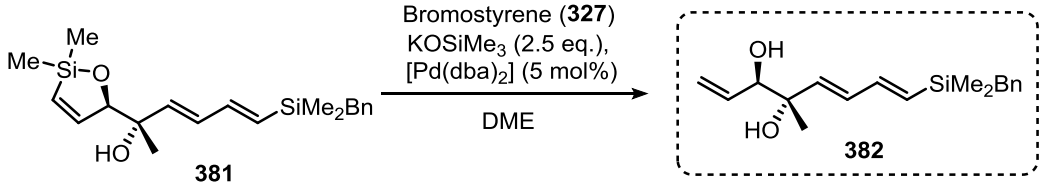
In light of the difficulties encountered with construction of the full length C2-C9 tetraene system in presence of the cyclic dimethyl siloxane functionality, the fluoride-promoted cross-coupling of siloxane **352** with bromostyrene (**327**) was attempted. While consumption of the siloxane **352** was observed, only a complex mixture was returned (Scheme 4.16). When 5-membered cyclic siloxane **379**, generated by oxidative removal of the PMB ether with concomitant rearrangement, was submitted to the fluoride-promoted coupling with bromostyrene (**327**), only protodesilylation of

siloxane **379** was observed (identified by the characteristic terminal alkene of **380** by ^{1}H NMR spectroscopy of the crude reaction mixture).



*Scheme 4.16: Attempted fluoride-promoted cross-couplings of siloxanes **352** and **379***

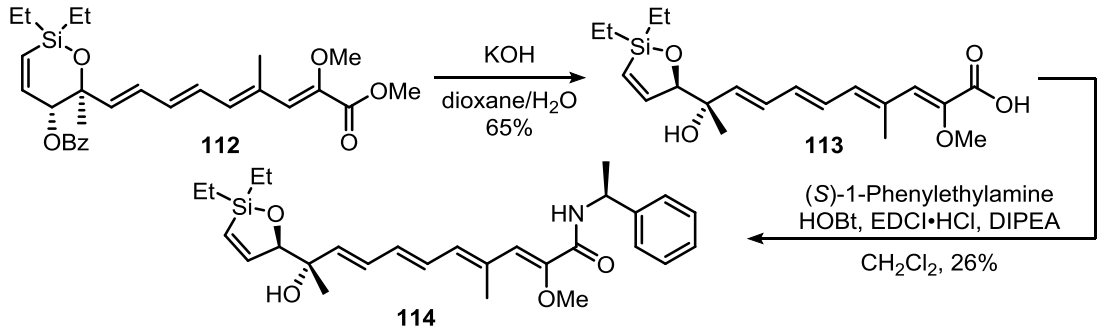
Similarly, under base-promoted coupling conditions of 5-membered siloxane **381**, afforded *via* PMB removal of bis-silane **353**, with bromostyrene (**327**), the protodesilylation of **381** was primarily observed (identified by the characteristic terminal alkene of **382** by ^{1}H NMR spectroscopy of the crude reaction mixture) (Scheme 4.17).



*Scheme 4.17: Attempted base-promoted cross-coupling of bis-silane **381***

4.5 Towards incednam – Modelling the amide bond formation

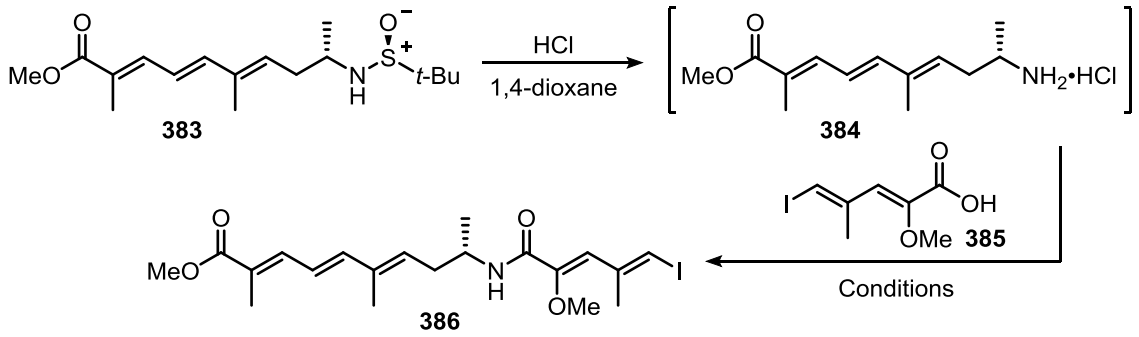
Lim had carried out ester hydrolysis of the full length C1-C13 tetraenoate fragment **112**, which was accompanied by benzoyl removal and consequent rearrangement to the 5-membered cyclic siloxane **113**. Model amide bond formation with (*S*)-1-phenylethylamine gave amide **114** in modest yield (26%, Scheme 4.18).[64]



*Scheme 4.18: Model amide bond of **113** formation by Lim*

We were keen to further explore this key amide coupling from the perspective of the C12-C21 pentaene. While not covered by the context of this thesis, due to problems encountered by Kuper with removal of the *N*-Teoc protecting group, a refined synthesis finds the use of chiral *tert*-butylsulfinamide for the asymmetric synthesis of the C14-C23 tetraenyl halide fragment which can be removed under mildly acidic conditions.[153] Thus, solvolysis of sulfinamide **383** (provided by Kuper), under acidic conditions gave amine salt **384** (Table 4.6).

*Table 4.6: Model amide formation of dienoic acid **385** and amine salt **384***



Entry	Conditions	Yield [%][a]
1	HOBt (1.2 eq.), EDCI•HCl (1.2 eq.), DIPEA (2.5 eq.)	–
2	EDCI•HCl (2.0 eq.), DMAP (4.0 eq.)	55

[a] Yield of **386**, isolated by column chromatography.

Similarly, ester hydrolysis of dienoate **88** with potassium trimethylsilanolate afforded dienoic acid **385** in quantitative yield, which provided the platform for our amidation studies. When the amide coupling of dienoic acid **385** and amine salt **384** was attempted

under the previously employed conditions using EDCI in presence of HOBt and DIPEA, only a complex mixture was returned (Entry 1). However, when the same coupling was performed in the presence of DMAP the desired amide **386** was afforded in 55% yield (Entry 2).

4.6 ^{1}H NMR studies – Cyclic dimethyl alkenylsiloxanes

In light of the heightened reactivity observed with the 6-membered cyclic dimethyl siloxane, and the somewhat variable desilylation experienced with the 5-membered dimethyl siloxane, their behaviour was studied by ^{1}H NMR spectroscopic analysis in the presence of the nucleophilic activator TBAF•3H$_2$O, in d$_8$-THF.

4.6.1 ^{1}H NMR studies – 5-Membered cyclic dimethyl siloxane

When 5-membered siloxane precursor **387** in d$_8$-THF was treated with TBAF•3H$_2$O (3 eq.) rapid and complete conversion to acyclic silanol **388** was observed which remained as such throughout the course of the experiment (Figure 4.1).

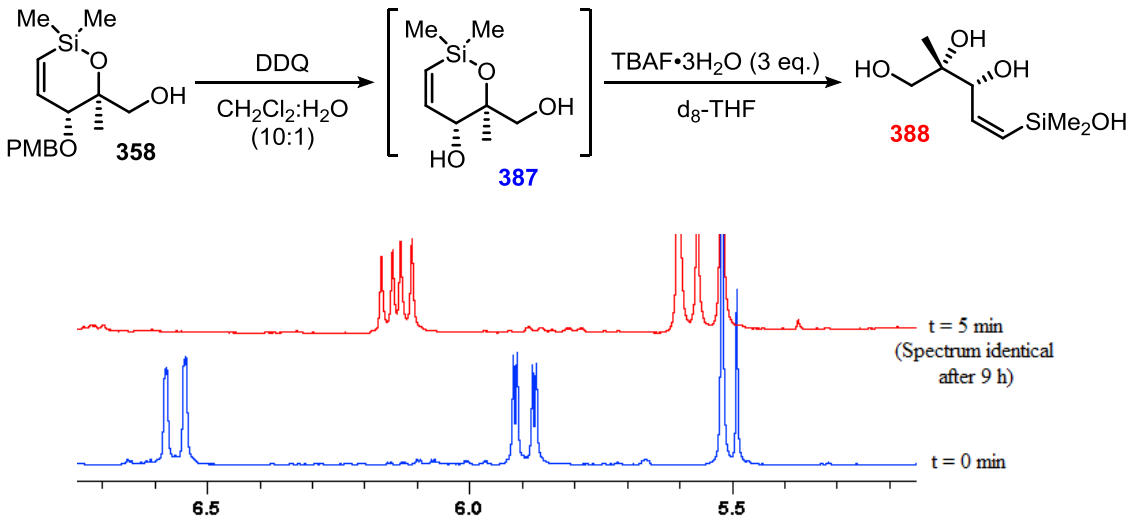


*Figure 4.1: Treatment of 5-membered siloxane precursor **387** with TBAF•3H$_2$O, analysed by ^{1}H NMR spectroscopy*

While it is not understood why the acyclic form is so strongly favoured compared to the previously studied 5-membered siloxane **316** (Figure 4.2), it is interesting that *no protodesilylation was observed*, which may suggest that desilylation occurs primarily

via the cyclic "ate" complex **345** (in its equilibrium with **316** and **344**) where as the acyclic species **344** (and **388**) is inert toward desilylation under these conditions.

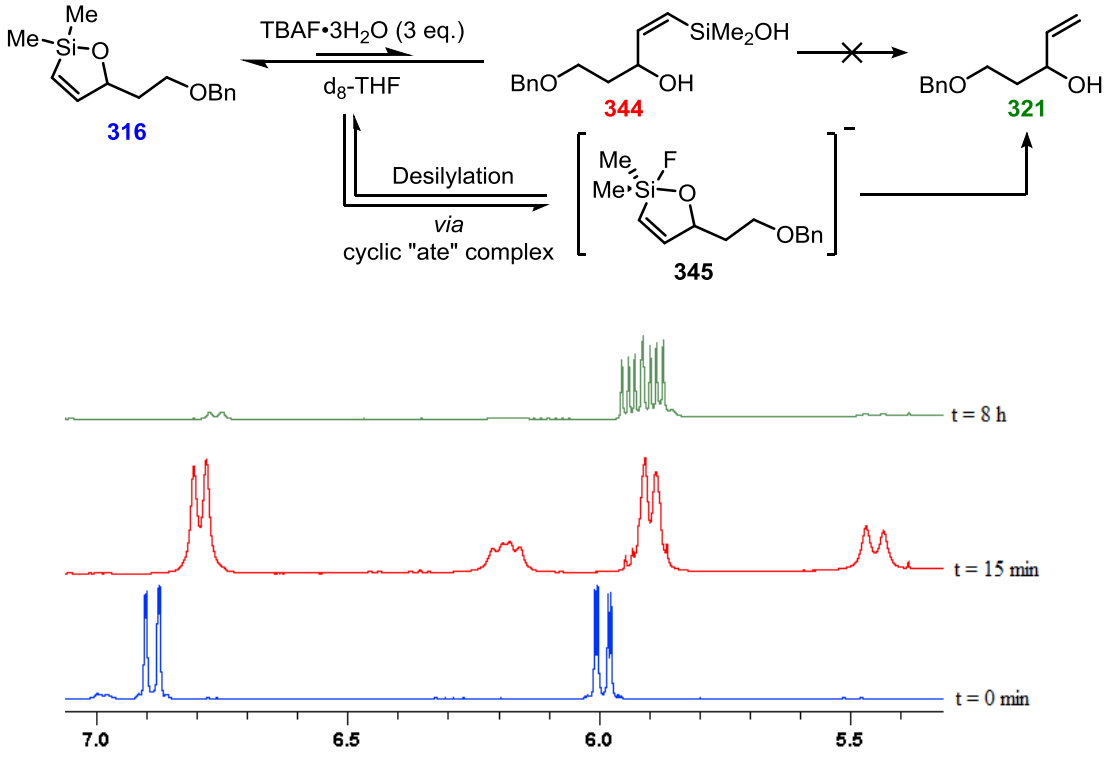
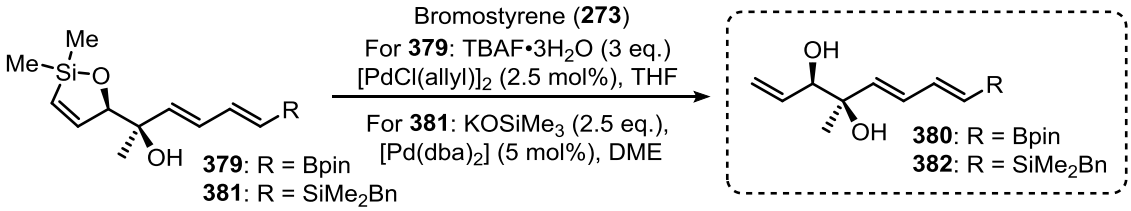


*Figure 4.2: Treatment of 5-membered siloxane **316** with TBAF•3H$_2$O (3 eq.), analysed by ^{1}H NMR spectroscopy*

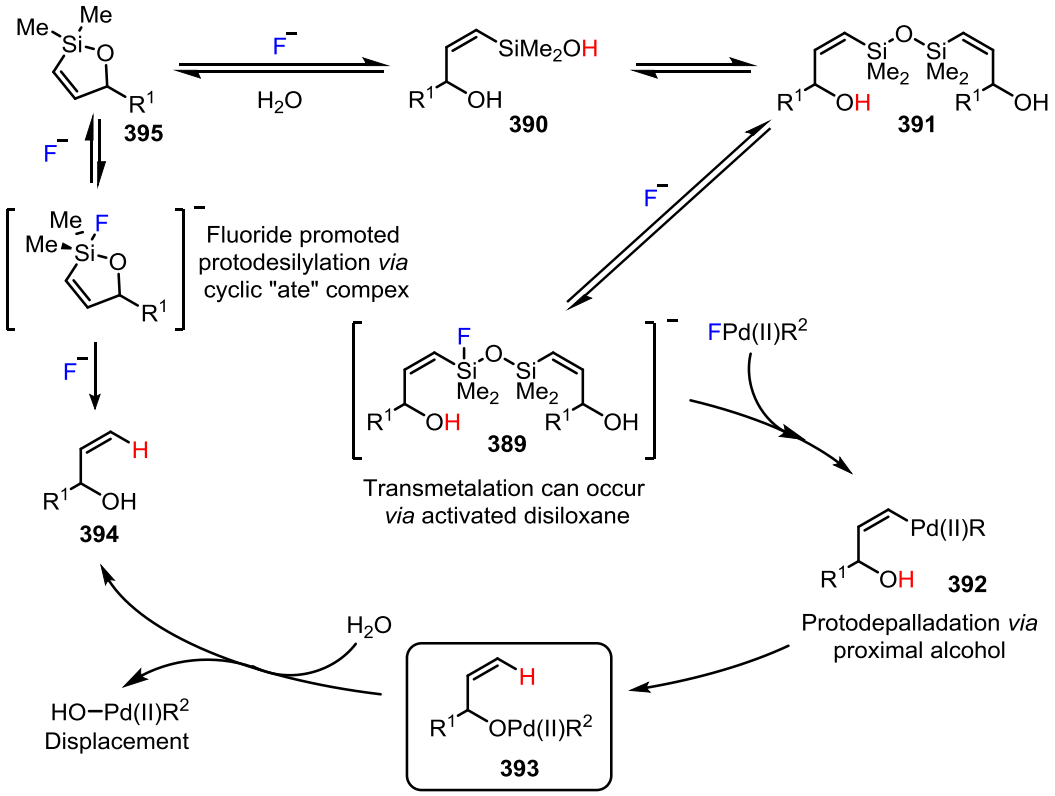
The related reactions of Schemes 4.16 and 4.17 (reproduced in Scheme 4.19) likely also form exclusively the acyclic silanol, and do not access the cyclic "ate" complex believed to be required for the coupling of a 5-membered cyclic siloxane, which could therefore explain the poor yields in cross-coupling.



Scheme 4.19: Attempted cross-coupling of 5-membered dimethyl siloxane

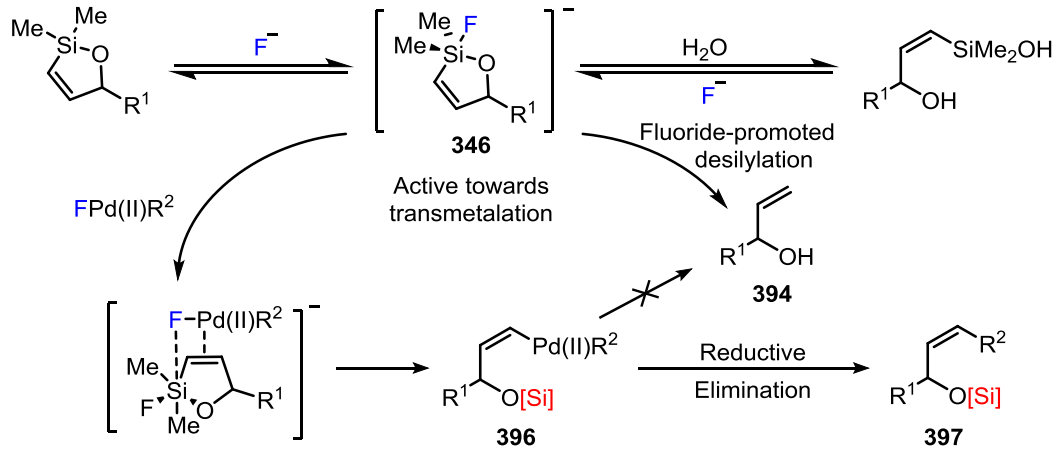
The sole observation of protodesilylation in those reactions could therefore indicate that desilylation may occur *via* a different mechanism under cross-coupling conditions (Scheme 4.20). A metal-promoted desilylation could take place *via* transmetalation of

activated disiloxane **389**, formed from acyclic silanol **390** *via* disiloxane **391** under fluoride-promoted coupling conditions, to give organopalladium complex **392**. Protodepalladation of **392** could then be mediated by the proximal allylic alcohol, which would then give oxo-palladium complex **393** and, upon displacement of Pd(II), the protodesilylated product **394**. Certainly, desilylation is much more rapid under coupling conditions than when isolated **395** is treated with fluoride.



Scheme 4.20: Proposed metal-catalysed protodesilylation of 5-membered siloxane

When transmetalation takes place *via* the more reactive cyclic "ate" complex **346** to give organopalladium complex **396**, the presence of the silyl ether (which masks the alcohol as a proton source), and the action of a presumably fast reductive elimination, ensures the formation of the desired cross-coupled product **397** (Scheme 4.21).



Scheme 4.21: Proposed metal-mediated protodesilylation of acyclic silanol

This study has thus revealed that the cross-coupling of 5-membered cyclic siloxanes can be highly substrate dependent with regards to whether the cyclic and/or acyclic form is favoured upon nucleophilic activation. Thus, in order for successful cross-coupling to take place, the cyclic siloxane needs to be readily accessed for the requisite formation of its activated "ate" complex under the coupling conditions. This can be easily discovered by ^{1}H NMR spectroscopic analysis prior to coupling, as described above.

4.6.2 ^{1}H NMR studies – 6-Membered cyclic dimethyl siloxane

Upon treatment with TBAF•3H_2O (3 eq.), 6-membered siloxane **358** in d_8-THF was also rapidly and completely converted to acyclic **398** (and disiloxane), and remained as such throughout the course of the experiment (Figure 4.3).

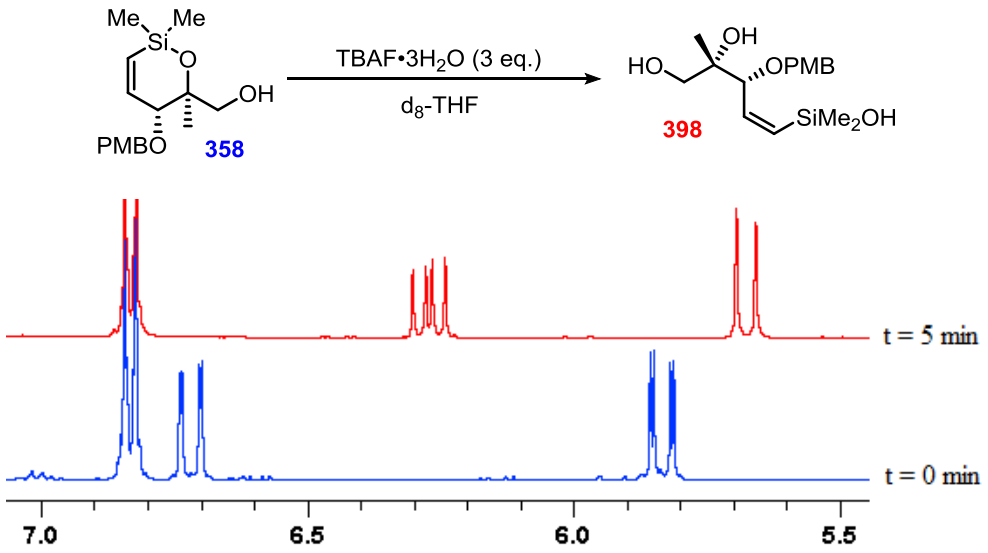


*Figure 4.3: Treatment of 6-membered siloxane **358** with TBAF•3H$_2$O (3 eq.), analysed by ^{1}H NMR spectroscopy*

Compared to the previously studied 6-membered siloxane **308** (Figure 4.4), which upon activation established an equilibrium between **308** and acyclic silanol **347**, it is likely that the presence of bulky substituents on the siloxacycle **358** results in favourable formation of the acyclic siloxane **398** due to 1,3-diaxial interaction.

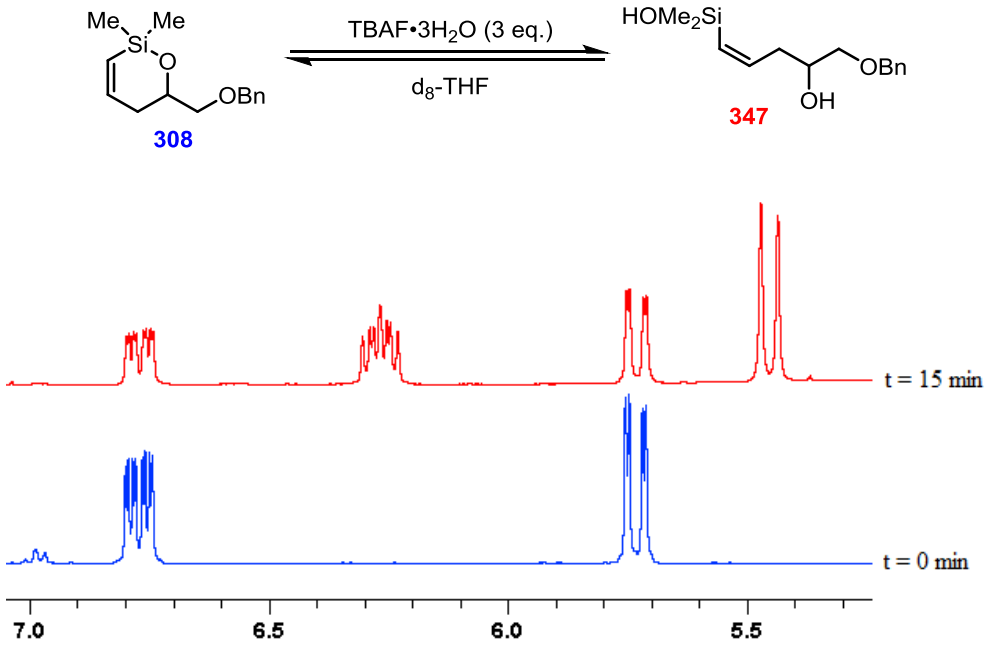
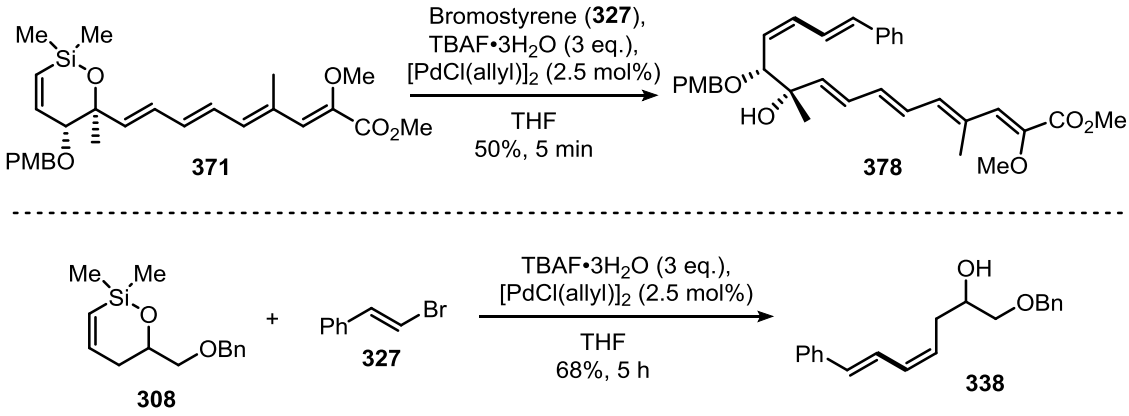


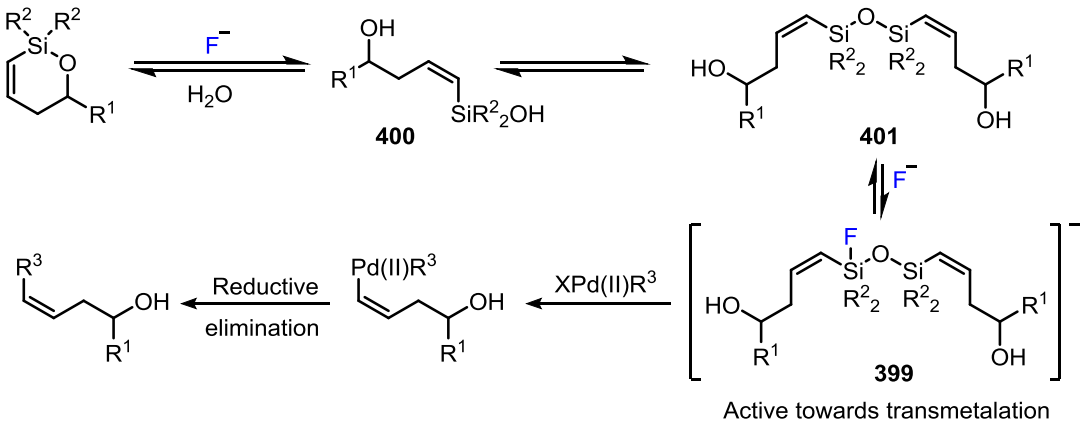
*Figure 4.4: Treatment of 6-membered siloxane **308** with TBAF•3H$_2$O, analysed by ^{1}H NMR spectroscopy*

As a consequence, the requisite fluoride-activated disiloxane **399** (Scheme 4.23) is more readily formed, resulting in rapid cross-coupling as was demonstrated using the full length tetraenoate **371** (Scheme 4.22)



Scheme 4.22: Hiyama cross-coupling of 6-membered cyclic dimethyl siloxanes

Similar to the 5-membered siloxanes, this study has revealed that the cross-coupling of 6-membered cyclic siloxanes can also be highly substrate dependent with regards to whether the cyclic and/or acyclic form is favoured upon nucleophilic activation. In addition, the propensity with which the resulting acyclic siloxane **400** forms disiloxane **401** which upon fluoride activation delivers the active transmetalating species **399**, is important (Scheme 4.23). This can vary with substitution on the silicon (i.e. ethyl vs methyl), where the more sterically demanding substituents are more reluctant to form the dimer, which results in a longer reaction time.



Scheme 4.23: Proposed mechanism of the 6-membered cyclic siloxane

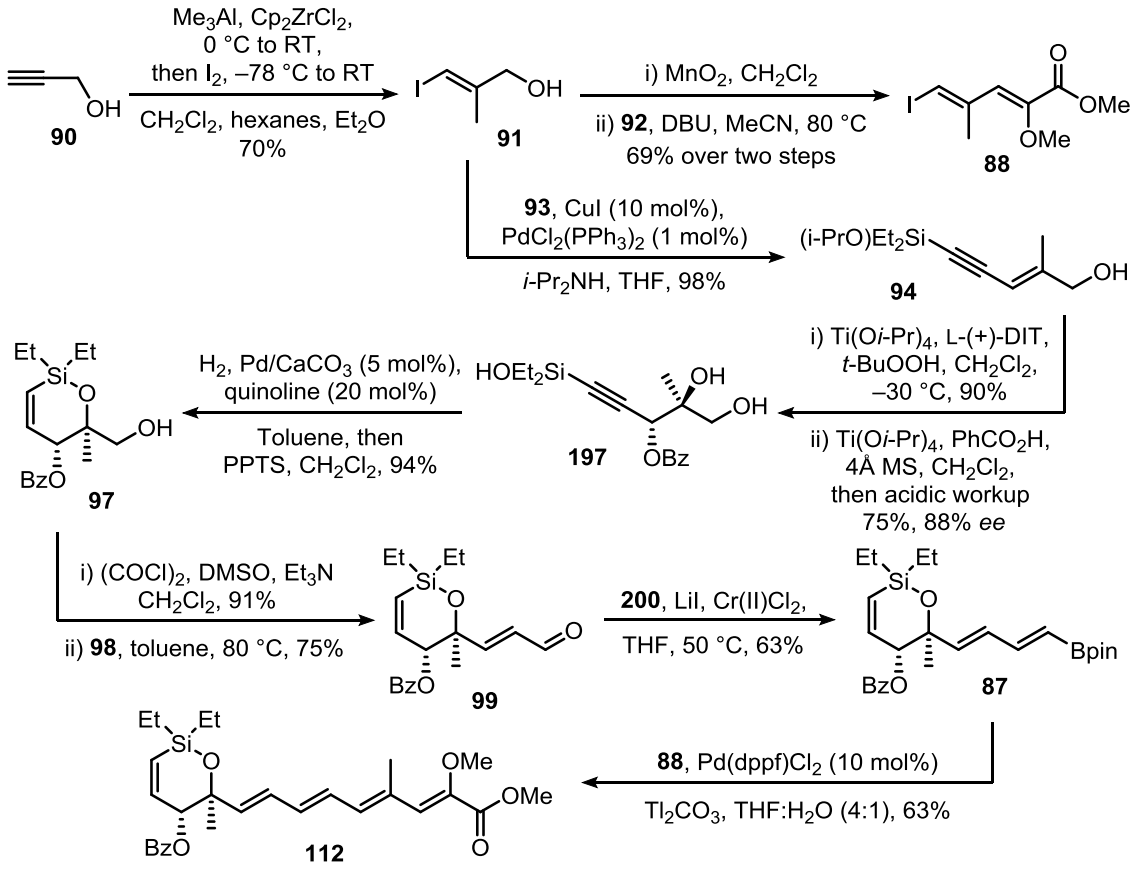
In contrast to its 5-membered analogue, due to the more distant nature of the homoallylic alcohol and perhaps a reduced tendency towards the cyclic "ate" complex, no protodesilylation is experienced with the 6-membered cyclic siloxane.

4.7 Conclusion

Our progress towards completing the synthesis of incednam has thus far been seriously hampered by the delicate nature of the cyclic dimethyl siloxane. However, important advances have been made such as the introduction of the C11 PMB ether. This modification allowed the construction of the key C13-C14 bond *via* fluoride-promoted Hiyama cross-coupling to be modelled using the full-length C1-C13 tetraenoate fragment **371**. The heightened reactivity experienced with the 6-membered dimethyl siloxane, compared to that of previously studied 6-membered dimethyl siloxane **308** led us to study its behaviour in the presence of TBAF•3H_2O by ^{1}H NMR spectroscopy. This revealed a rapid and complete conversion to the acyclic silanol **398** (and disiloxane), and therefore insight into the fluoride-activated disiloxane **399** required for the rate-determining transmetalation. Related studies on the 5-membered siloxane revealed similar behaviour, which was found to be consistent with experimental results, wherein the active species towards transmetalation is thought to require the formation of a cyclic "ate" complex for the coupling of a 5-membered cyclic siloxane. Furthermore, the key amide bond formation was explored with model dienoic acid **385** and amine salt **384** with good results, suggesting its viability as an endgame strategy. Finally, a novel approach towards the synthesis of extended stabilised phosphonate **372** *via* a Heck reaction was developed. While this saw the construction of the C1-C13 pentaenoate fragment **112** with diethyl siloxane **199** shortened by two synthetic steps, we were as yet unable to apply the same strategy to dimethyl siloxane **360**.

Chapter 5: Conclusion and future work

We have successfully developed a robust and reliable synthesis of key fragments *en route* to incednam. The synthesis of the C1-C13 tetraenoate fragment **112** was achieved in 9 steps in the longest linear sequence from propargyl alcohol (**90**), with an overall yield of 13% (Scheme 5.1).

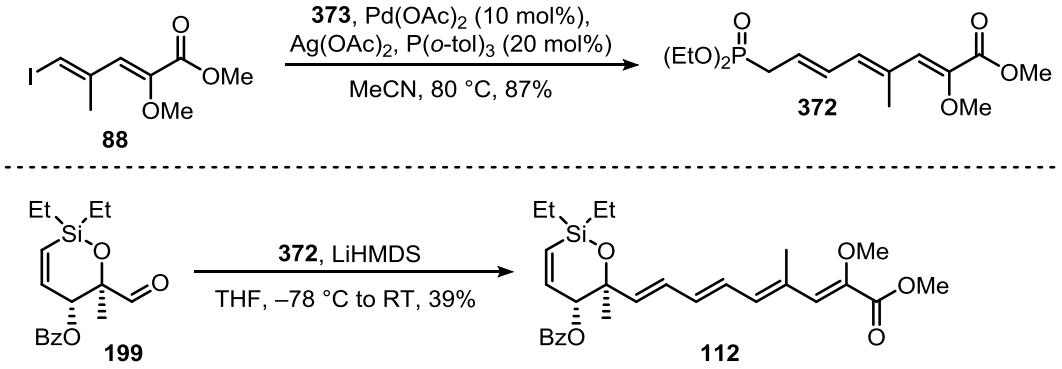


*Scheme 5.1: Preparation of the tetraenoate fragment **112***

The key feature of the synthesis of **112** is the use of controlled semi-hydrogenation followed by acid-promoted cyclisation for the stereoselective construction of the key cyclic diethyl siloxane **97**. The two stereogenic centres were introduced *via* Sharpless asymmetric epoxidation/regio-selective ring opening sequence. The C2-C9 tetraene was assembled by C5-C6 Suzuki cross-coupling of boronic ester **87** and dienoate **88** *via* orthogonal activation of the boronate in presence of the cyclic siloxane functionality.

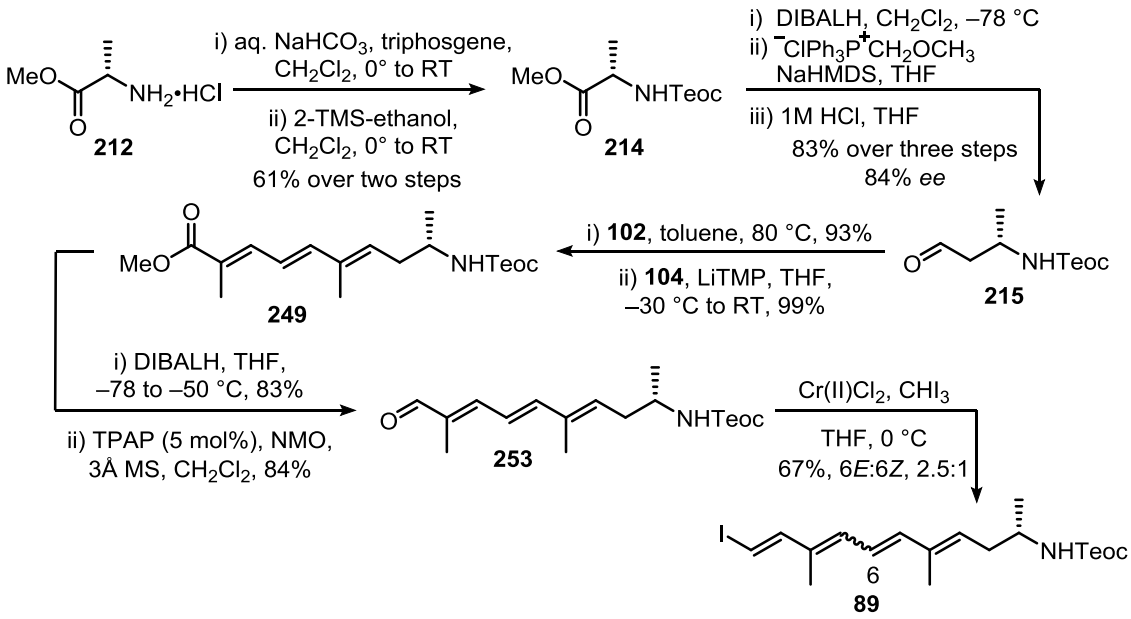
The development of a novel strategy for the synthesis of extended stabilised

phosphonate **372** by Heck reaction was successfully applied to the synthesis of the C1-C13 fragment **112** *via* C8-C9 HWE olefination, thus achieving this key fragment towards incednam in total of 7 steps in the longest linear sequence with an overall yield of 16% (Scheme 5.2).



*Scheme 5.2: Preparation of the tetraenoate fragment **112** by HWE olefination*

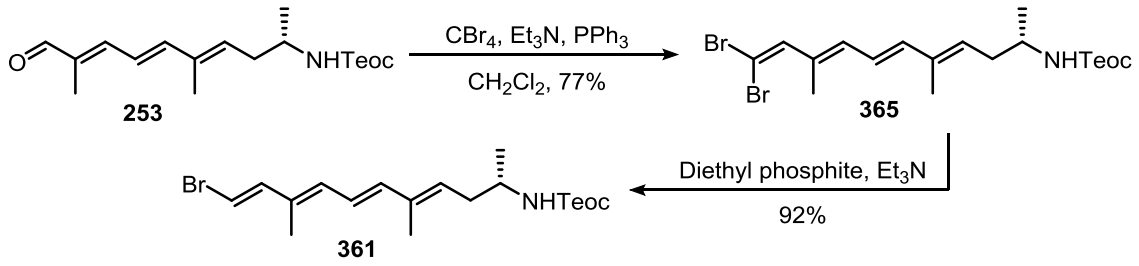
The synthesis of the C14-C23 tetraenyl iodide fragment **89** commenced from L-alanine methyl ester hydrochloride (**212**), and was achieved in total of 10 linear steps with an overall yield of 22% (Scheme 5.3).



*Scheme 5.3: Preparation of the tetraenyl iodide fragment **89***

While tetraenyl iodide **89** was obtained as a geometrical mixture of isomers (6*E*:6*Z*, 2.5:1), its bromide analogue **361** was obtained as single geometrical isomer *via*

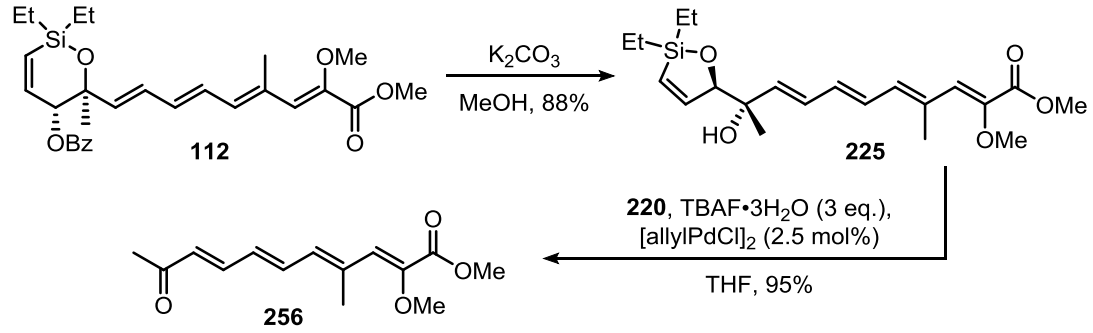
Ramirez olefination of trienal **253** followed by a stereoselective Hirao-Hayes monodebromination of the dibromide **365** (Scheme 5.4).



*Scheme 5.4: Stereoselective preparation of the tetraenyl bromide fragment **361***

Overall the synthesis of the C14-C23 tetraenyl bromide fragment **361** was achieved in total of 11 linear steps with an overall yield of 23%.

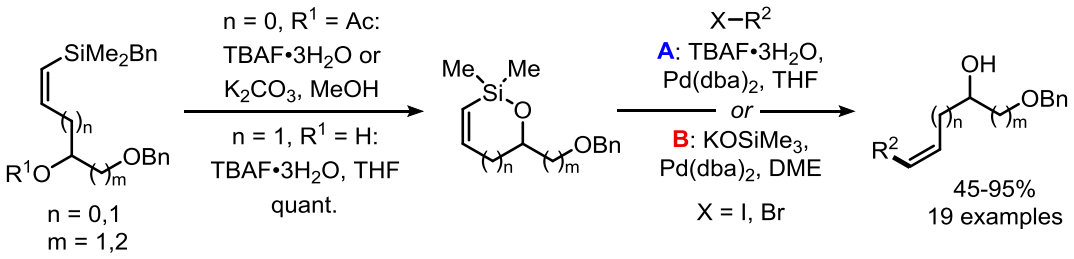
We had thus far been unable to effect the cross-coupling of the 6-membered siloxane, as removal of the benzoate of **112** led to concomitant rearrangement to afford 5-membered siloxane **225** (Scheme 5.5). However, when submitted to the fluoride-promoted Hiyama coupling conditions with iodostyrene (**220**), only the product of retro-allylation was returned.



Scheme 5.5: Model C13-C14 Hiyama cross-coupling of full length tetraene

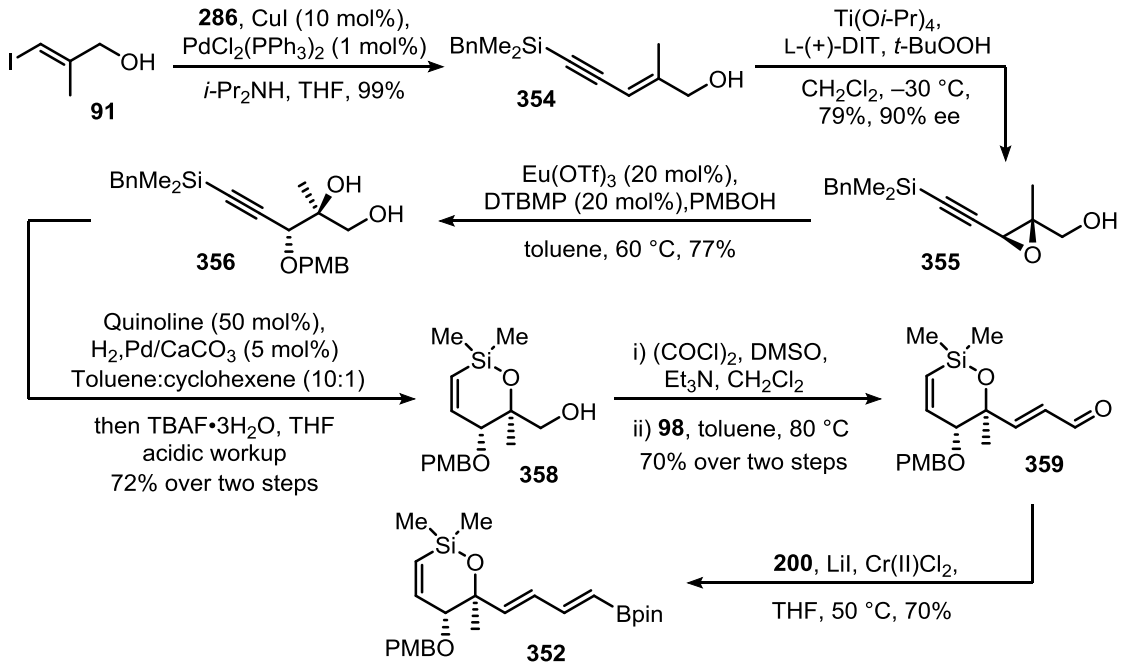
The failure of the full length tetraenoate **225** to couple under the fluoride-promoted Hiyama coupling conditions led us to investigate the behaviour of the 6-membered diethyl siloxane **97** in presence of TBAF•$3H_2O$ by ^1H NMR spectroscopy. This study identified a serious flaw in our strategy where the benzoate group was found to be unstable under the nucleophilic activation conditions.

To address the lack of reactivity experienced with the cyclic diethyl alkenylsiloxane a novel methodology was developed for the synthesis of the more reactive dimethyl analogue. This work saw the use of *Z*-vinylbenzyldimethylsilane, generated by stereoselective semi-hydrogenation of the corresponding alkynyl benzyl silane, as a masked silanol intermediate for the preparation of 5- and 6-membered cyclic dimethyl alkenylsiloxanes (Scheme 5.6). While 6-membered precursors require activation by hydrated fluoride source prior to their generation, 5-membered precursors displayed a unique mode of activation under mildly basic conditions. Furthermore, their subsequent cross-coupling was demonstrated with a range of complex polyenyl iodides and bromides as a stereospecific route to conjugated *Z*-alkenyl polyenes.



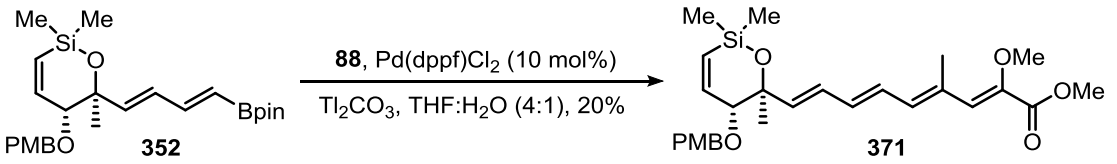
Scheme 5.6: Synthesis and application of 5- and 6-membered dimethyl siloxanes

Applying this novel strategy to the incednam synthesis, the preparation of the C16-C13 6-membered dimethyl siloxane fragment **352** was achieved in total of 9 steps from propargyl alcohol (**90**), with an overall yield of 15% (Scheme 5.7). Furthermore, and perhaps most importantly, in light of the difficulties identified with the benzoate protecting group, the PMB protected analogue was prepared *via* europium-catalysed regioselective ring-opening of epoxide **355** with PMB alcohol.



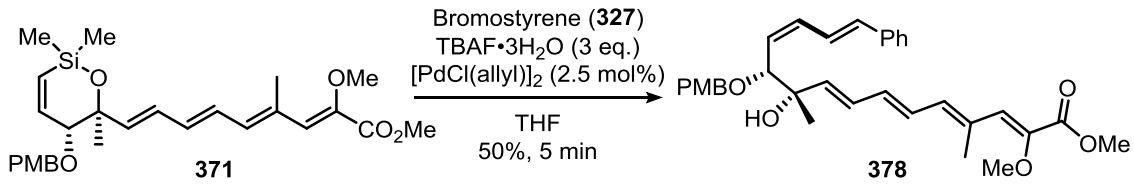
*Scheme 5.7: Preparation of the C6-C13 6-membered dimethyl siloxane fragment **352***

The construction of the C1-C13 tetraenoate fragment **371** was attempted *via* the previously established C5-C6 Suzuki reaction (Scheme 5.8). Disappointingly, and in contrast to the diethyl analogue, in the presence of $Pd(dppf)Cl_2$ and thallium carbonate as base, the cross-coupling of dienyl boronic ester **352** and dienoate **88** afforded tetraenoate **371** in 20% yield.



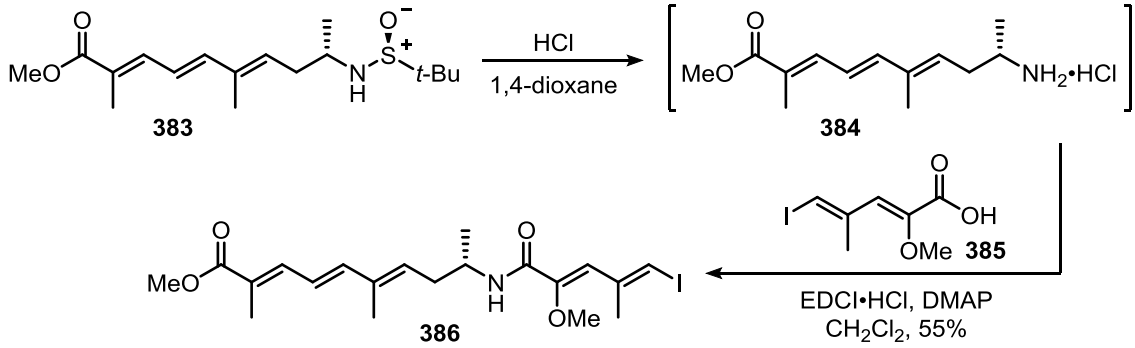
Scheme 5.8: C5-C6 bond formation via previously established Suzuki reaction

When dimethyl siloxane **360** was submitted to the HWE olefination with phosphonate **372**, a complex mixture was returned, further highlighting the delicate nature of the dimethyl siloxane functionality compared to its diethyl analogue. However, with the PMB protected tetraenoate **371** in hand the key C13-C14 Hiyama cross-coupling was modelled with bromostyrene (**327**) (Scheme 5.9). To our delight, the coupled product **378** was obtained in 50% yield with consumption of siloxane **371** in just 5 minutes.



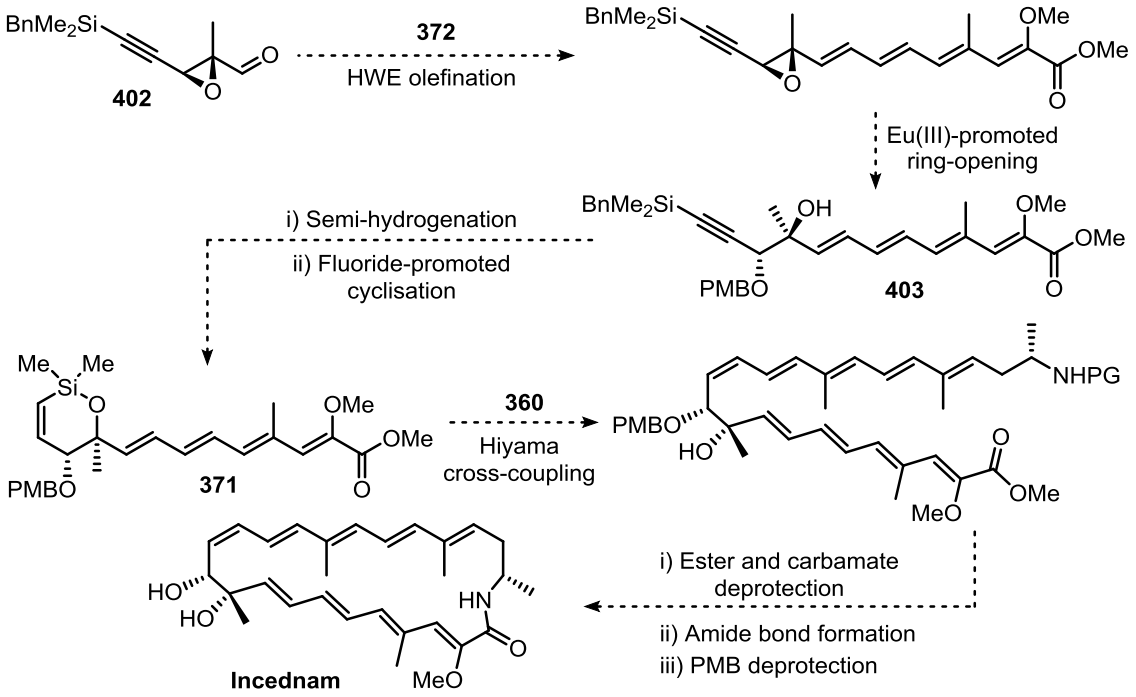
Scheme 5.9: Modelling the key C13-C14 Hiyama cross-coupling

In addition, the key amide bond formation of model dienoic acid **385** and C12-C21 pentaene representative amine salt **384**, afforded amide **386** in good yield, suggesting its viability as a possible endgame strategy (Scheme 5.10).



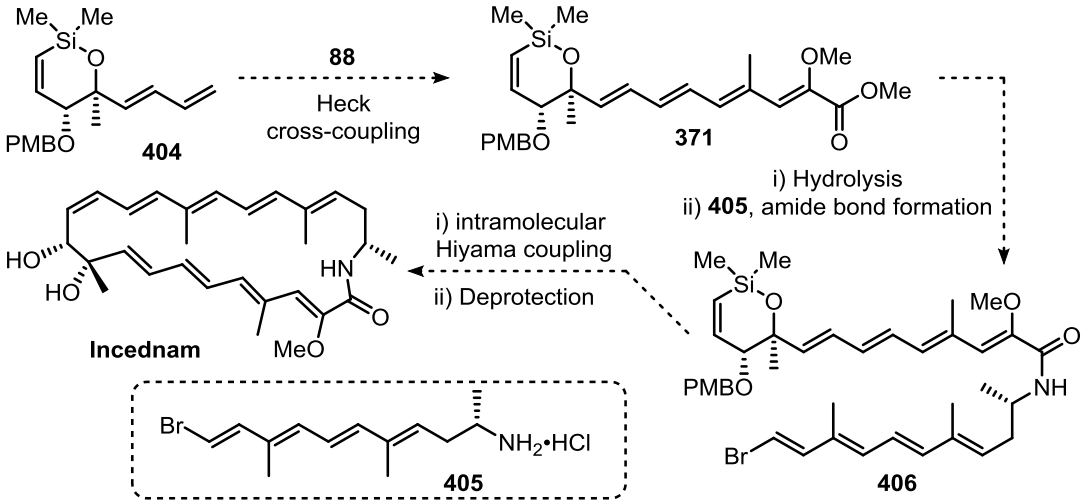
Scheme 5.10: Modelling the key amide bond formation

In light of the difficulties experienced with the instability of the 6-membered dimethyl siloxane, introduction of the C2-C9 tetraene at an earlier stage *via* C8-C9 HWE olefination of aldehyde **402** and phosphonate **372** is proposed (Scheme 5.11). This would be followed by regioselective ring-opening with PMB alcohol to give **403** followed by semi-hydrogenation and fluoride-promoted de-benzylation/cyclisation to give tetraenoate **371**. At this stage, the Hiyama cross-coupling of 6-membered dimethyl siloxane **371** could be attempted with the geometrically pure tetraenyl bromide **360**. Given our previous studies with the coupling of polyenyl bromides and the heightened reactivity of the incednam 6-membered cyclic siloxane, we are optimistic that the cross-coupling will be successful. Ester and carbamate deprotection of the resulting coupled product could then be followed by macrocyclisation *via* amide bond formation. Finally, removal of the PMB protecting group affords incednam.



Scheme 5.11: Proposed synthetic scheme towards the completion of incednam

Alternatively, the C2-C9 tetraene system could be constructed by the mild reaction conditions afforded by the Heck cross-coupling between diene **404** and dienoate **88** (Scheme 5.12).

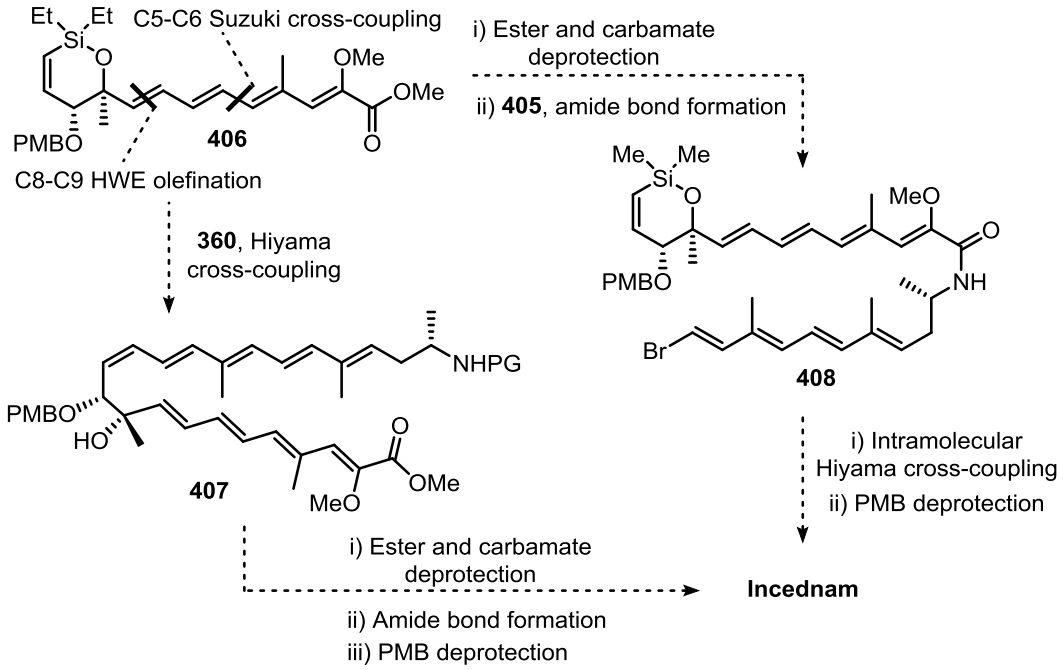


Scheme 5.12: Proposed synthetic scheme towards the completion of incednam

An exciting order of events could take place at this stage; hydrolysis of the resulting tetraenoate **371** followed by amide bond formation with amine salt **405** would afford

amide **406** which upon intramolecular Hiyama cross-coupling and subsequent removal of the PMB ether, delivers incednam.

The ^{1}H NMR spectroscopic studies of the 6-membered dimethyl siloxane **358** revealed an important ability of the incednam 6-membered siloxane to fully convert to its acyclic form in the presence of the nucleophilic activator TBAF•3H_2O. It is anticipated that the diethyl analogue, with the added benefit of inherent stability, will exhibit a similar propensity under nucleophilic activation. This would allow the construction the C2-C9 tetraene under the previously established C8-C9 HWE olefination or C5-C6 Suzuki cross-coupling to give tetraenoate **406** (Scheme 5.13).



Scheme 5.13: Proposed synthetic scheme towards the completion of incednam

From there the completion of incednam could proceed from either macrolactamisation *via* amide bond formation of acyclic precursor **407** or cyclication *via* intramolecular Hiyama cross-coupling of **408**. Current studies in the Anderson group aim to explore both courses.

Chapter 6: Experimental

6.1 General experimental

Reactions: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen.

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 were obtained dry and oxygen free from solvent dispenser units having passed through an activated alumina column under nitrogen. DIPEA, DIPA and DMSO were distilled over CaH_2 under reduced pressure and stored over CaH_2 or 4Å molecular sieves and under N_2. 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).

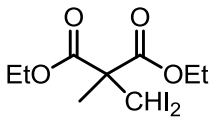
Infrared spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier FT-IR spectrometer, and the samples were prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). Only selected, characteristic IR absorption data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

NMR spectra: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on a Bruker DPX200 (200/50 MHz), Bruker AVIII400 (400/100 MHz), or a Bruker AVIII500 (500/125 MHz). Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm), referenced to the residual peak stated ($CDCl_3$ (δ = 7.26/77.2), C_6D_6 (δ = 7.16/128.1), d_8-THF (δ = 1.72/67.2), DMSO (δ = 2.50/39.5)) with signal splitting recorded as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept) and multiplet (m). Coupling constants (*J*) are reported to the nearest 0.5 Hz.

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). High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

6.2 C1-C5 Dienoate synthesis

Diethyl 2-(diiodomethyl)-2-methylmalonate, 409

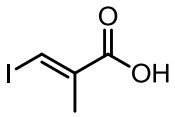


To a stirred suspension of NaH (4.20 g, 60% w/w in mineral oil, 105.4 mmol, 1.2 eq.) in Et_2O (55 mL) was added, *via* syringe pump over a period of 30 min, diethyl methylmalonate (**165**) (15 mL, 87.8 mmol, 1.0 eq.). The resulting solution was refluxed for 4 h, allowed to reach RT and iodoform (34.6 g, 88 mmol, 1.0 eq.) added in one portion. After refluxing for 48 h the reaction mixture was cooled to 0 °C and 1 M aqueous HCl solution (65 mL) added followed by vigorous stirring for 20 min. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product **409** as a brown-red oil (38.0 g, 86.4 mmol, 98%) which was used in the next step without any further purification;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.77 (1H, s, C*H*I_2), 4.22 (2H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 4.21 (2H, q, *J* = 7.0 Hz, OC*H*$_2$'CH$_3$), 1.79 (3H, s, C*H*$_3$), 1.29 (6H, app t, *J* = 7.0 Hz, OCH_2CH_3 and OCH_2CH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.1, 62.7, 62.1, 20.3, 14.0, −26.0.

The physical and spectroscopic data was found to be in agreement with that reported by Fürstner *et al*.[176]

(*E*)-3-Iodo-2-methylacrylic acid, 410

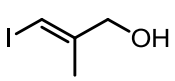


To a stirred solution of **409** (38.0 g, 86.4 mmol, 1.0 eq.) in a mixture of EtOH and water (3:1, 220 mL) was added KOH (12.8 g, 228 mmol, 2.6 eq.). After stirring at reflux overnight the reaction mixture was concentrated and an aqueous layer solution of K_2CO_3 (10% w/v, 200 mL) added, the resulting suspension was filtered and the filtrate carefully acidified using conc. HCl (40 mL). After extraction with CH_2Cl_2 (8 × 50 mL) the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product **410** as a red oil (12.6 g, 59.6 mmol, 68%) which was used without further purification;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.1 (1H, bs, COO*H*), 8.03 (1H, q, *J* = 1.0 Hz, IC*H*), 2.06 (3H, d, *J* = 1.0 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.9, 139.0, 101.8, 19.8.

The physical and spectroscopic data was found to be in agreement with that reported by Fürstner *et al*.[176]

(*E*)-3-Iodo-2-methylprop-2-en-1-ol, 91



Procedure A: To a stirred suspension of $LiAlH_4$ (2.26 g, 59.5 mmol, 1.0 eq.) in Et_2O (100 mL) at −78 °C was added slowly *via* syringe a solution of **410** (12.6 g, 59.6 mmol, 1.0 eq.) in Et_2O (19 mL). The cooling bath was removed and the reaction mixture allowed to reach RT. After stirring at RT for 1 h, the reaction was cooled to 0 °C and

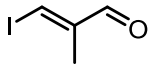
quenched by slow addition of water (2.3 mL) followed by addition of an aqueous layer NaOH solution (2.3 mL, 15% w/v) and water (6.8 mL). The cooling bath was removed and the resulting mixture stirred for 15 min, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by vacuum distillation (75 °C, 2.1 mbar) to give the title compound **91** as a colourless oil (9.78 g, 49.4 mmol, 83%);

Procedure B: To bis(cyclopentadienyl)zirconium(IV) dichloride (2.09 g, 7.14 mmol, 0.2 eq.) in a round-bottom flask at 0 °C and under nitrogen atmosphere was added *via* syringe trimethylaluminum (44.7 mL, 2.0 M solution in hexanes, 89.3 mmol, 2.5 eq.). After the resulting white fumes had settled, a solution of propargylic alcohol **90** (2.11 mL, 35.7 mmol, 1.0 eq.) in CH_2Cl_2 (7 mL) was added by the same method to give a yellow solution which was stirred at RT overnight. The resulting brown reaction mixture was cooled to −78 °C and a solution of iodine (10.9 g, 42.8 mmol, 1.2 eq.) in Et_2O (40 mL) was added dropwise *via* syringe. After stirring for 30 min at −78 °C, the cooling bath was removed and the brown reaction mixture allowed to reach RT followed by further stirring for 2 h to give a clear yellow solution. The reaction mixture was quenched by slow portionwise addition to a vigorously stirred biphasic mixture of pentane (100 mL) and a saturated aqueous Rochelle's salt solution (100 mL) at 0 °C. After stirring at RT overnight the organic layer was decanted and the aqueous layer passed through Celite. The filtrate was extracted with Et_2O (3 × 20 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%) → petroleum ether / EtOAc (30%)) to give title compound **91** as a greenish brown oil (4.96 g, 25.1 mmol, 70%);

b.p. 75 °C, 2.1 mbar (lit. 92 °C, 0.75 mmHg); $\mathbf{R_f}$ 0.35 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.27-6.23 (1H, m, CI*H*), 4.09 (3H, s, C*H*$_3$), 2.25 (1H, bs, O*H*), 1.82 (3H, s, CH_2OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.2, 77.4, 67.1, 21.4.

The physical and spectroscopic data was found to be in agreement with that reported by Carreira *et al*.[177]

(*E*)-3-Iodo-2-methylacrylaldehyde, 167

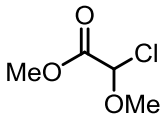


To a solution of vinyl iodide **91** (1.20 g, 6.06 mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) was added activated manganese dioxide (5.30 g, 60.6 mmol, 10.0 eq.). After stirring vigorously at RT overnight, the reaction mixture was filtered through Celite and the filtrate carefully concentrated *in vacuo* to give title compound **167** (1.12 g, 5.69 mmol, 94%) as a yellow oil, which was used in the next step without further purification;

$\mathbf{R_f}$ 0.65 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.53 (1H, s, *H*1), 7.81 (1H, q, *J* = 1.0 Hz, *H*3), 1.91 (3H, d, *J* = 1.0 Hz, C2C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 189.4, 150.9, 109.5, 16.5.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

Methyl 2-chloro-2-methoxyacetate, 411

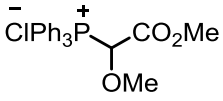


To a round-bottom flask containing phosphorus pentachloride (9.37 g, 45.0 mmol, 1.5 eq.) and equipped with a reflux condenser, was added methyl dimethoxyacetate (4.0 mL, 33 mmol, 1.0 eq.) dropwise *via* syringe. After stirring at 140 °C for 2 h, the reaction was cooled to RT and the reflux condenser exchanged for a short path distillation condenser. Purification *via* vacuum distillation (70 °C, 20-23 mbar) gave title compound **411** (4.41 g, 31.8 mmol, 97%) as a clear oil, which was used immediately in the following reactions;

b.p. 70 °C, 20-23 mbar (lit. 60 °C, 0.1 mmHg); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.75 (1H, s, *H*2), 3.87 (3H, s, CO_2CH_3), 3.63 (3H, s, OCH_3).

The physical and spectroscopic data was found to be in agreement with that reported by Crimmins *et al*.[67]

(1,2-Dimethoxy-2-oxoethyl)triphenylphosphonium chloride, 92



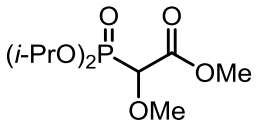
To a solution of chloroacetate **411** (4.41 g, 31.8 mmol, 1.0 eq.) in CH_2Cl_2 (9.5 mL) was added triphenylphosphine (8.34 g, 31.8 mmol, 1.0 eq.). The reaction mixture was stirred at RT overnight to give a yellow solution which was concentrated *in vacuo* to give a thick oil that was triturated with Et_2O (3 × 50 mL). The Et_2O was discarded, and the resulting yellow taffy-like material dried *in vacuo* to give a foamy solid which was

crushed with a spatula and dried *in vacuo* for 24 h to give title compound **92** (12.0 g, 29.9 mmol, 94%) as a yellow solid;

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 8.52 (1H, d, *J* = 13.5 Hz, *H*2), 8.18-7.56 (15H, m, P(Ar*H*)$_3$), 3.87 (3H, s, CO2C*H*$_3$), 3.57 (3H, s, OC*H*$_3$).

The physical and spectroscopic data was found to be in agreement with that reported by Crimmins *et al*.[67]

Methyl 2-(diisopropoxyphosphoryl)-2-methoxyacetate, 166

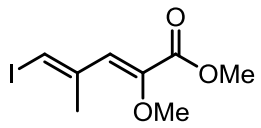


A mixture of chloroacetate **411** (2.29 g, 16.5 mmol, 1.0 eq.) and triisopropyl phosphite (4.1 mL, 17 mmol, 1.0 eq.) was stirred at reflux (100 °C) for 24 h, then cooled to RT and the reflux condenser exchanged for a short path distillation condenser. Volatiles were removed by heating to 200 °C at 15 mbar, to give title compound **166** (2.84 g, 10.6 mmol, 64%) as the residue;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.85-4.71 (2H, m, C*H*(CH$_3$)$_2$), 4.16 (1H, d, *J* = 18.5 Hz, *H*2), 3.81 (3H, s, OC*H*$_3$), 3.50 (3H, s, CO_2C*H*$_3$), 1.39-1.26 (12H, m, CH(C*H*$_3$)$_2$).

The physical and spectroscopic data was found to be in agreement with that reported by Paterson *et al*.[101]

(2*Z*,4*E*)-Methyl 5-iodo-2-methoxy-4-methylpenta-2,4-dienoate, 88



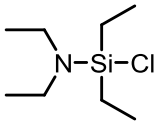
To a stirred solution of phosphonium chloride **93** (11.6 g, 29.6 mmol, 5.2 eq.) in acetonitrile (10 mL) was added dropwise *via* syringe DBU (4.2 mL, 2.2 mmol, 5.0 eq.). The resulting dark yellow suspension was stirred for 30 min followed by addition of a solution of aldehyde **167** (1.12 g, 5.69 mmol, 1.0 eq.) in acetonitrile (3 mL). After stirring at 80 °C overnight, the reaction mixture was concentrated *in vacuo* and the crude product redissolved in EtOAc (100 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (50 mL) then brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* column chromatography (petroleum ether / Et_2O (0%) → petroleum ether / Et_2O (5%)) to give title compound **88** (1.18 g, 4.17 mmol, 73%) as an amber oil;

R_f 0.36 (petroleum ether / EtOAc (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.87 (1H, s, *H*5), 6.58 (1H, s, *H*3), 3.80 (3H, C2OCH_3), 3.70 (3H, s, CO_2CH_3), 2.13 (3H, s, C4CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 164.6, 143.9, 141.9, 123.9, 90.3, 59.9, 52.2, 23.3.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

6.3 C6-C13 Cyclic diethyl alkenylsiloxane synthesis

1-Chloro-*N*,*N*,1,1-tetraethylsilanamine, 412

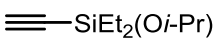


To a solution of dichlorodiethylsilane (20.0 mL, 134 mmol, 1.0 eq.) and Et_3N (20.6 mL, 148 mmol, 1.1 eq.) in THF (50 mL) at 0 °C was added a solution of Et_2NH (13.8 mL, 134 mmol, 1.0 eq.) in THF (6 mL) dropwise *via* syringe over a 2 h period. The resulting mixture was vigorously stirred at RT for 24 h after which it was filtered through Celite under nitrogen atmosphere and washed with anhydrous pentane. The filtrate was concentrated *in vacuo* to give the crude product as an orange oil, which was purified by vacuum distillation (90 °C, 36 mbar) to give the title compound **412** as a colourless oil (22.0 g, 114 mmol, 85%);

b.p. 90 °C, 36 mbar (lit. 104-106 °C, 56 mmHg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.87 (4H, q, J = 7.0 Hz, $N(CH_2CH_3)_2$), 1.07-0.97 (12H, m, $Si(CH_2CH_3)_2$ and $N(CH_2CH_3)_2$), 0.92-0.83 (4H, m, $Si(CH_2CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 39.5, 15.1, 7.4, 6.9.

The physical and spectroscopic data was found to be in agreement with that reported by Cox *et al*.[121]

Diethyl(ethynyl)(isopropoxy)silane, 93



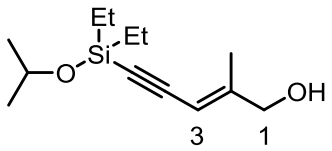
To chloroaminosilane **412** (22.0 g, 114 mmol, 1.0 eq.) was added *via* syringe ethynylmagnesium bromide (250 mL, 0.5 M solution in THF, 125 mmol, 1.1 eq.) at −78 °C. The resulting mixture was warmed to RT, then refluxed for 3 h and cooled to

RT whereupon isopropanol (17.3 mL, 227 mmol, 2.0 eq.) and a single crystal of 4 dimethylaminopyridine (DMAP) were added. After stirring at RT overnight, the resulting mixture was concentrated *in vacuo*, the residue redissolved in petroleum and filtered through Celite. The filtrate was concentrated *in vacuo* and the crude product purified by vacuum distillation (50-54 °C, 20 mbar) to give a 10:1 mixture of the title compound **93** and diethyldiisopropoxysilane as a colourless oil (11.0 g, 57.4 mmol, 89% purity by weight, 51%);

b.p. 50-54 °C, 20 mbar (lit. 104-106 °C, 56 mmHg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.16 (1H, sept, J = 6.0 Hz, OC*H*$(CH_3)_2$), 2.42 (1H, s, CC*H*), 1.20 (6H, d, J = 6.0 Hz, OCH$(CH_3)_2$), 1.01 (6H, t, J = 8.0 Hz, Si$(CH_2CH_3)_2$), 0.67 (4H, q, J = 8.0 Hz, Si$(CH_2CH_3)_2$).

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(*E*)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-2-en-4-yn-1-ol, 94



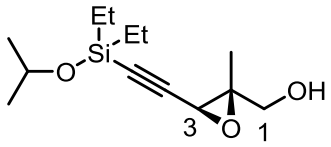
To a degassed (N_2 bubbling, 15 min) solution of vinyl iodide **91** (5.54 g, 28.0 mmol, 1.0 eq.) and alkyne **93** (5.36 g, 89% purity by weight, 28.0 mmol, 1.0 eq.) in THF (112 mL) was added copper(I) iodide (533 mg, 2.80 mmol, 10 mol%) and $PdCl_2(PPh_3)_2$ (197 mg, 0.28 mmol, 1 mol%). The mixture was further degassed (N_2 bubbling) for 15 min, during which diisopropylamine (31.5 mL, 224 mmol, 8.0 eq.) was added dropwise *via* syringe. After stirring at RT overnight, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (120 mL), the organic layer separated and

the aqueous layer further extracted with Et_2O (2 × 150 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (40%) → petroleum ether / Et_2O (50%)) to give title compound **94** (6.56 g, 27.3 mmol, 98%) as a dark brown oil;

$\mathbf{R_f}$ 0.38 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.66-5.63 (1H, m, *H*3), 4.17 (1H, sept, *J* = 6.0 Hz, C*H*(CH_3)$_2$), 4.12 (2H, d, *J* = 6.0 Hz, *H*1), 1.91 (3H, s, C2C*H*$_3$), 1.61 (1H, t, *J* = 6.0 Hz, O*H*), 1.20 (6H, d, *J* = 6.0 Hz, CH(C*H*$_3$)$_2$), 1.02 (6H, t, *J* = 8.0 Hz, Si(CH_2C*H*$_3$)$_2$), 0.67 (4H, q, *J* = 8.0 Hz, Si(C*H*$_2$$CH_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.2, 104.6, 103.0, 94.8, 66.7, 66.1, 25.5, 16.6, 6.9, 6.7.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

((2*R*,3*R*)-3-((Diethyl(isopropoxy)silyl)ethynyl)-2-methyloxiran-2-yl)methanol, 95



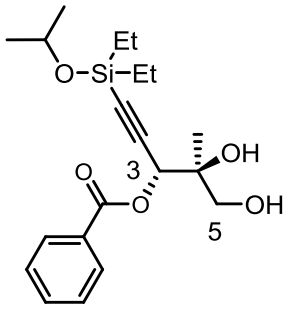
4Å Molecular sieves (1.70 g, 30% w/w) were added to a Schlenk tube, evacuated and the sieves activated by heat. The tube was allowed to reach RT, filled with nitrogen and CH_2Cl_2 (80 mL) was added. The flask was then cooled to −30 °C and titanium(IV) isopropoxide (3.61 mL, 12.0 mmol, 0.5 eq.) was added while stirring. Next, L-(+)-diisopropyl tartrate (3.02 mL, 14.3 mmol, 0.6 eq.) was added and the resulting mixture stirred for 30 min. Subsequently, a solution of enyne **94** (5.74 g, 23.9 mmol, 1.0 eq.) in CH_2Cl_2 (24 mL) was added and stirred for further 30 min after which *t*-butyl hydroperoxide (8.70 mL, 5.5 M solution in decane (over 4Å molecular sieves),

47.8 mmol, 2.0 eq.) was added slowly. The resulting reaction mixture was stirred at −30 °C overnight, then diluted with Et_2O (12 mL) followed by addition of a saturated aqueous solution of Na_2SO_4 (12.0 mL, 1 mL / mmol of titanium(IV) isopropoxide). The resulting biphasic mixture was stirred at RT for 4 h before filtering through Celite, washing several times with Et_2O. The solid residue was then transferred to an Erlenmeyer flask, diluted with EtOAc (50 mL), refluxed for 15 min followed by filtration through the same Celite filter. The filtrate was concentrated *in vacuo* and purified *via* column chromatography (petroleum ether / EtOAc (5%) → petroleum ether / EtOAc (15%)) to give title compound **95** as a yellow oil (5.55 g, 21.6 mmol, 90%);

R_f 0.37 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.12 (1H, sept, *J* = 6.0 Hz, C*H*$(CH_3)_2$), 3.76 (1H, dd, *J* = 12.5 and 9.0 Hz, *H*1), 3.65 (1H, dd, *J* = 12.5 and 9.5 Hz, *H*1'), 3.58 (1H, s, *H*3), 1.62 (1H, dd, *J* = 9.5 and 4.0 Hz, O*H*), 1.45 (3H, s, C2CH_3), 1.17 (6H, d, *J* = 6.0 Hz, CH(C$H_3)_2$), 0.98 (6H, t, *J* = 8.0 Hz, Si($CH_2CH_3)_2$), 0.65 (4H, q, *J* = 8.0 Hz, Si($CH_2CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 100.9, 88.4, 66.3, 63.4, 63.1, 48.0, 25.5, 15.5, 6.7, 6.5.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(3*R*,4*S*)-1-(Diethyl(isopropoxy)silyl)-4,5-dihydroxy-4-methylpent-1-yn-3-yl benzoate, 96



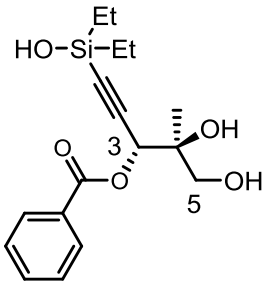
4Å Molecular sieves (200 mg, 30% w/w) were added to a round-bottom flask containing a stirrer bar, the flask evacuated and the sieves activated by heat. The flask was allowed to reach RT, filled with nitrogen, followed by addition of benzoic acid (462 mg, 3.78 mmol, 1.5 eq.), titanium(IV) isopropoxide (1.12 mL, 3.78 mmol, 1.5 eq.) and CH_2Cl_2 (22 mL). After stirring at RT for 15 min, a solution of epoxide **95** (646 mg, 2.52 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) was added slowly and the resulting reaction mixture stirred for 1 h. Upon completion, monitored by TLC, the reaction was quenched by addition of a 5:1 mixture of acetone and water (25 ml) followed by vigorous stirring for 2 h. The resulting clear mixture was diluted with Et_2O (15 mL) and washed quickly with a 1 M aqueous HCl solution (10 mL), the organic layer separated and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%) → petroleum ether / EtOAc (30%)) to give title compound **96** (367 mg, 0.97 mmol, 38%) as a yellow oil;

$[\alpha]_D^{20}$ +2.0 (*c* 1.0, $CHCl_3$); 88% *ee* (CHIRALPAK IA, 5% IPA / hexane, 1.25 mL/min, t_R (3*S*, 4*R*) 7.50 min, t_R (3*R*, 4*S*) 8.61 min); $\mathbf{R}_f$ 0.42 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15-7.37 (5H, m, Ar*H*), 5.75 (1H, s, *H*3), 4.13 (1H,

sept, J = 6.0 Hz, C*H*$(CH_3)_2$), 3.70 (1H, d, J = 12.0 Hz, *H*5), 3.55 (1H, d, J = 12.0 Hz, *H*5'), 2.58 (1H, bs, O*H*), 2.42 (1H, bs, O*H*)), 1.39 (3H, s, C4CH_3), 1.19 (3H, d, J = 6.0 Hz, CHCH_3), 1.17 (3H, d, J = 6.0 Hz, CHCH_3'), 1.00 (6H, t, J = 8.0 Hz, Si$(CH_2CH_3)_2$), 0.72-0.63 (4H, m, Si$(CH_2CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.6, 133.6, 129.9, 129.2, 128.6, 100.4, 89.8, 73.8, 68.1, 66.5, 66.2, 25.4, 19.9, 6.6, 6.5.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(3*R*,4*S*)-1-(Diethyl(hydroxy)silyl)-4,5-dihydroxy-4-methylpent-1-yn-3-yl benzoate, 197

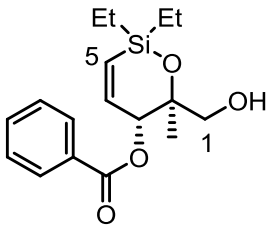


4Å Molecular sieves (1.67 g, 30% w/w) were added to a round-bottom flask containing a stirrer bar, the flask evacuated and the sieves activated by heat. The flask was allowed to reach RT, filled with nitrogen, followed by addition of benzoic acid (3.96 g, 32.4 mmol, 1.5 eq.), titanium(IV) isopropoxide (9.80 mL, 32.4 mmol, 1.5 eq.) and CH_2Cl_2 (210 mL). After stirring at RT for 15 min a solution of epoxide **95** (5.55 g, 21.6 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) was added and the resulting reaction mixture stirred for 1 h. Upon completion, monitored by TLC, the reaction mixture was concentrated *in vacuo* and the residue redissolved in Et_2O (50 mL) and a 5% aqueous solution of H_2SO_4 (50 mL) added. The resulting biphasic mixture was stirred vigorously (5 h) until two clear layers formed. The organic layer was separated and the aqueous layer further extracted

with Et_2O (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* and the crude product purified *via* column chromatography (petroleum ether / EtOAc (20%) → petroleum ether / EtOAc (60%)) to give title compound **197** (5.49 g, 16.3 mmol, 75%) as a clear oil;

$[\alpha]_D^{20}$ −12.8 (*c* 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.16 (petroleum ether / EtOAc (50%)); **IR (**thin film, ν_{max} / cm^{-1}) 3430, 2958, 1708, 1453, 1273, 1057; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.10-8.00 (2H, m, Ar*H*), 7.65-7.56 (1H, m, Ar*H*), 7.50-7.43 (2H, m, Ar*H*), 5.74 (1H, s, *H*3), 3.68 (1H, d, *J* = 12.0 Hz, *H*5), 3.56 (1H, d, *J* = 12.0 Hz, *H*5'), 2.94 (3H, bs, SiO*H*, O*H* and O*H*), 1.34 (3H, s, C4CH_3), 1.03 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 1.02 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.74-0.67 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 165.6, 133.6, 129.9, 129.1, 128.6, 100.3, 90.1, 74.0, 67.7, 66.2, 19.6, 7.3, 7.2, 6.4, 6.3; **HRMS** (ESI+) calc. for $C_{17}H_{24}O_5SiNa$ $[M+Na]^+$ 359.1285, found 359.1281.

(5*R*,6*S*)-2,2-Diethyl-6-[hydroxymethyl]-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 97



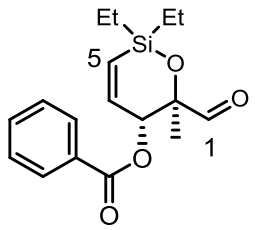
To a round-bottom flask was added Pd on $CaCO_3$ (1.73 g, 5 w% Pd, 0.815 mmol, 5.0 mol%). The flask was evacuated, filled with nitrogen, toluene (150 mL) added and the flask purged with hydrogen. Subsequently a solution of silanol **197** (5.49 g, 16.3 mmol, 1.0 eq.) and quinoline (0.38 mL, 3.26 mmol, 0.2 eq.) in toluene (16 mL) was added *via* syringe and hydrogenation continued until completion (1 h, monitored by TLC (visualised with vanillin)). The reaction mixture was filtered through Celite and

the filtrate concentrated *in vacuo*, the residue redissolved in CH_2Cl_2 (163 mL) and pyridinium *p*-toluenesulfonate (PPTS) (410 mg, 1.63 mmol, 0.1 eq.) added. After stirring at RT overnight, the resulting reaction mixture was concentrated *in vacuo* and the crude product purified *via* column chromatography (petroleum ether / Et_2O (40%)) to give title compound **97** (3.74 g, 11.7 mmol, 72%) as a colourless oil;

$\mathbf{R}_f$ 0.19 (petroleum ether / Et_2O (40%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.08-7.37 (5H, m, Ar*H*), 6.64 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*4), 6.00 (1H, dd, *J* = 14.5 and 2.5, *H*5), 5.78 (1H, app t, *J* = 2.5 Hz, *H*3), 3.48 (1H, dd, *J* = 11.5 and 7.5 Hz, *H*1), 3.43 (1H, dd, *J* = 11.5 and 4.5 Hz, *H*1'), 2.32-2.23 (1H, m, O*H*), 1.34 (1H, s, C2CH_3), 1.01 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.99 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.78-0.55 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.7, 148.1, 133.2, 129.9, 129.7, 129.5, 128.5, 126.5, 71.5, 68.2, 19.3, 7.3, 6.7, 6.5, 6.3.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(5*R*,6*R*)-2,2-Diethyl-6-formyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 199



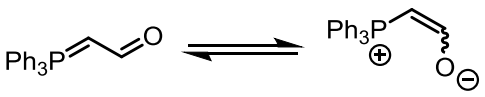
To a solution of oxalyl chloride (0.17 mL, 2.0 mmol, 2.0 eq.) in CH_2Cl_2 (7.0 mL) was added *via* syringe DMSO (0.28 mL, 3.9 mmol, 4.0 eq.) at −78 °C. After stirring for 15 min, a solution of **97** (314 mg, 0.980 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL) was added *via* syringe and the resulting mixture stirred for 1 h. Next, Et_3N (0.54 mmol, 3.9 mmol, 4.0 eq.) was added, the cooling bath removed and the reaction mixture allowed to reach

RT. After stirring at RT for 1 h, the reaction was quenched with water (10 mL), the organic layer separated followed by further extraction of the aqueous layer with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (20%)) to give title compound **199** (284 mg, 0.89 mmol, 91%) as a yellow oil;

$[\alpha]_D^{25}$ −140 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.31 (petroleum ether / Et_2O (15%)); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 1722, 1600, 1266, 1108, 710; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.59 (1H, s, *H*1) 8.08-7.42 (5H, m, Ar*H*), 6.83 (1H, dd, *J* = 14.5 and 4.0 Hz, *H*4), 6.13 (1H, dd, *J* = 14.5 and 1.0 Hz, *H*5), 5.72 (1H, dd, *J* = 4.0 and 1.0 Hz, *H*3), 1.42 (3H, s, C2C*H*$_3$), 1.03 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.97 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.79-0.70 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.0 165.6, 145.7, 133.3, 130.3, 129.8, 129.6, 128.5, 80.8, 69.5, 19.3, 6.9, 6.8, 5.6, 6.4; **HRMS** (ESI+) calc. for $C_{18}H_{26}O_5NaSi$ $[M+Na+MeOH]^+$ 373.1442, found 373.1443.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

2-(Triphenylphosphanylidene)acetaldehyde, 98



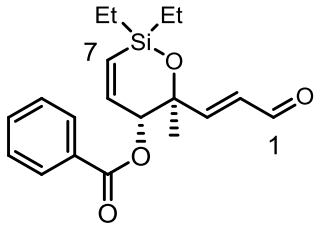
To a separatory funnel containing a solution of (formylmethyl)triphenylphosphonium chloride (1.50 g, 4.40 mmol, 1.0 eq.) in CH_2Cl_2 (22 mL) was added a 1 M aqueous NaOH solution (5 mL, 5.0 mmol, 1.1 eq.). After vigorous shaking, the organic layer was

separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **98** (1.27 g, 4.20 mmol, 95%) as a light brown solid, which was used without further purification;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.00 (1H, d, *J* = 3.5 Hz, *cis* C*H*O), 8.26 (1H, d, *J* = 11.0 Hz, *trans* C*H*O), 7.83-7.34 (30H, m, ArH), 4.03 (1H, d, *J* = 11.0 Hz, *trans* PC*H*), 3.65 (1H, d, *J* = 3.5 Hz, *cis* PC*H*).

The physical and spectroscopic data was found to be in agreement with that reported by Kayser *et al*.[178]

(5*R*,6*S*)-2,2-Diethyl-6-methyl-6-[(*E*)-3-oxoprop-1-en-1-yl]-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 99



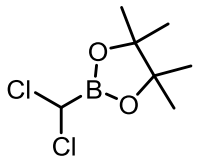
To a round-bottom flask, equipped with a stirrer bar and a reflux condenser was added aldehyde **199** (2.65 g, 8.31 mmol, 1.0 eq.), **98** (2.66 mg, 8.73 mmol, 1.05 eq.) and toluene (83 mL). After stirring at 80 °C overnight, the resulting mixture was concentrated *in vacuo* and the residue purified *via* column chromatography (petroleum ether / Et_2O (15%)) to give title compound **99** (2.24 g, 6.50 mmol, 78%) as a bright yellow oil;

R_f 0.27 (petroleum ether / EtOAc (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.56-9.50 (1H, d, *J* = 8.0 Hz, *H*1), 8.12-7.43 (5H, m, Ar*H*), 6.85 (1H, d, *J* = 15.5 Hz, *H*3), 6.63 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*6), 6.41 (1H, dd, *J* = 15.5 and 8.0 Hz, *H*2), 6.10 (1H, dd,

J = 14.5 and 2.5 Hz, *H*7), 5.54 (1H, t, *J* = 2.5 Hz, *H*5), 1.55 (3H, s, C4CH_3), 1.02 (3H, t, *J* = 8.0 Hz, SiCH$_2$CH_3), 0.99 (3H, t, *J* = 8.0 Hz, SiCH$_2$CH_3'), 0.82-0.67 (4H, m, SiCH_2CH$_3$ and SiCH_2'CH$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.8, 165.5, 160.1, 146.5, 133.5, 130.7, 129.7, 129.6, 128.6, 128.4, 75.9, 74.1, 22.3, 7.1, 6.6, 6.4, 6.3.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

2-(Dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 200

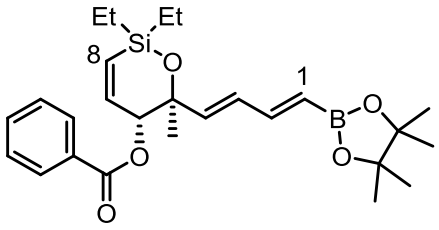


To solution of CH_2Cl_2 (3.60 mL, 56.0 mmol, 1.12 eq.) in THF (100 mL) at −100 °C (MeOH/LN_2) was added a solution of *n*-BuLi (20.0 mL, 2.5 M in hexanes, 50.0 mmol, 1.0 eq.) *via* syringe over a period of 40 min. The resulting suspension was stirred for 30 min before trimethylborate (**201**) (6.23 mL, 56.0 mmol, 1.12 eq.) was added. After stirring for 30 min at −100 °C, the reaction mixture was quenched with a 5 M aqueous HCl solution (10 mL), the cooling bath removed and the resulting mixture allowed to reach RT. The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 25 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting viscous pale yellow oil was redissolved in benzene (100 mL) and pinacol added (6.5 g, 55 mmol, 1.1 eq.) and the biphasic mixture stirred at reflux for 48 h. The resulting homogeneous yellow solution was allowed to reach RT and fractionally distilled (68 °C, 1.5 mbar) to give boronate **200** (10.1 g, 48 mmol, 96%) as a colourless oil;

b.p. 68 °C, 1.5 mbar (lit. 103 °C, 20 mmHg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.35 (1H, s, C*H*), 1.33 (12H, s, Bpin*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 85.8, 83.2, 24.5.

The physical and spectroscopic data was found to be in agreement with that reported by Jacobsen *et al*.[136]

(5*R*,6*S*)-2,2-Diethyl-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-2H-1,2-oxasilin-5-yl benzoate, 87



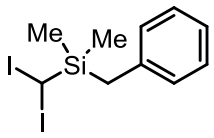
Chromium(II) chloride (144 mg, 1.17 mmol, 8.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The flask was allowed to reach RT, filled with nitrogen and THF (1.0 mL) was added. The resulting grey suspension was stirred for 30 min at 50 °C after which a solution of **99** (52 mg, 0.15 mmol, 1.0 eq.) and boronate **200** (62 mg, 0.29 mmol, 2.0 eq.) in THF (1 mL) was added *via* syringe, followed by addition of a solution of LiI (78 mg, 0.58 mmol, 4.0 eq.) in THF (1.0 mL) by a similar method. After stirring at 50 °C for 16 h, the resulting brown suspension was diluted with Et_2O (5 mL) and filtered through Celite. The filtrate was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (5%) $\rightarrow$ petroleum ether / Et_2O (20%) + 1% Et_3N) to give title compound **87** as a bright yellow oil (43 mg, 0.092 mmol, 63%);

R_f 0.58 (petroleum ether / Et_2O (20%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 8.17-8.13 (2H, m, Ar*H*), 7.32 (1H, dd, *J* = 17.5 and 10.5 Hz, *H*2), 7.14-7.03 (3H, m, Ar*H*), 6.72 (1H, dd, *J* = 14.5 and 3.5 Hz, *H*7), 6.62 (1H, dd, *J* = 15.5 and 10.5 Hz, *H*3), 5.97 (1H, d,

J = 15.5 Hz, *H*4), 5.86 (1H, d, *J* = 17.5 Hz, *H*1), 5.84 (1H, dd, *J* = 14.5 and 1.5 Hz, *H*8), 5.66 (1H, dd, *J* = 3.5 and 1.5 Hz, *H*6), 1.45 (3H, s, C5CH_3), 1.06 (12H, s, Bpin*H*), 1.00-0.89 (6H, m, *J* = 8.0 Hz, $SiCH_2CH_3$ and $SiCH_2CH_3$'), 0.68-0.45 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 165.3, 149.8, 146.9, 142.2, 132.8, 131.1, 130.5, 129.7, 128.9, 128.4, 82.8, 76.0, 74.7, 24.7, 24.6, 23.8, 7.1, 6.7, 6.6, 6.4.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

Benzyl(diiodomethyl)dimethylsilane, 202



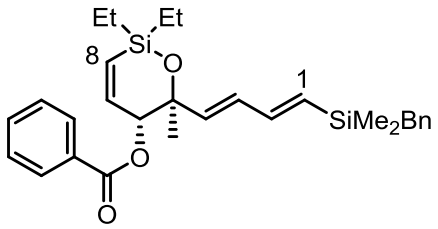
To a solution of hexamethyldisilazane (1.70 mL, 8.12 mmol, 1.5 eq.) in Et_2O (6 mL) at 0 °C was added a solution of *n*-BuLi (3.20 mL, 2.5 M in hexanes, 8.12 mmol, 1.5 eq.) dropwise *via* syringe. After stirring at 0 °C for 15 min, the resulting suspension was diluted with Et_2O (10 mL) and THF (4 mL) and cooled to −78 °C. Subsequently, a solution of diiodomethane (0.66 mL, 8.12 mmol, 1.5 eq.) in Et_2O (2 mL) was added dropwise *via* syringe and the resulting mixture stirred for 20 min before a solution of benzylchlorodimethylsilane (**203**) (0.98 mL, 5.4 mmol, 1.0 eq.) in Et_2O (1.2 mL) was added by a similar method. After stirring at −78 °C for 3 h, the cooling bath was removed and the reaction mixture stirred at RT overnight. The resulting mixture was quenched with water (20 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via*

column chromatography (petroleum ether) to give title compound **202** as an orange oil (2.01 g, 4.83 mmol, 89%);

R$_f$ 0.20 (petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28-7.04 (5H, m, Ar*H*), 4.37 (1H, s, C*H*), 2.25 (2H, s, SiCH_2Ar), 0.24 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.3, 128.5, 128.2, 124.7, 65.9, 23.9, −3.87.

The physical and spectroscopic data was found to be in agreement with that reported by Anderson and Lim.[137]

(5*R*,6*S*)-6-[(1*E*,3*E*)-4-(Benzyldimethylsilyl)buta-1,3-dien-1-yl]-2,2-diethyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 158

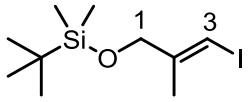


Chromium(II) chloride (107 mg, 0.870 mmol, 6.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The flask was allowed to reach RT, filled with nitrogen and THF (1.8 mL) was added. The resulting grey suspension was stirred for 30 min after which a solution of **202** (50 mg, 0.15 mmol, 1.0 eq.) and silane **99** (79 mg, 0.19 mmol, 1.3 eq.) in THF (2 mL) was added *via* syringe. After stirring at RT for 16 h, the resulting purple suspension was diluted with Et_2O (5 mL) and filtered through Celite. The filtrate was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (0%) → petroleum ether / EtOAc (2.5%)) to give title compound **158** as a pale yellow oil (57 mg, 0.12 mmol, 80%);

$[\alpha]_D^{25}$ –120 (*c* 0.73, $CHCl_3$); $\mathbf{R}_f$ 0.47 (petroleum ether / EtOAc (5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 1723, 1601, 1583, 1247, 1110, 1001, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.08 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.61 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.49 (2H, t, *J* = 7.5 Hz, Ar*H*), 7.19 (2H, t, *J* = 7.5 Hz, Ar*H*), 7.06 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.99 (2H, d, *J* = 7.5 Hz, Ar*H*), 6.72 (1H, dd, *J* = 14.5 and 3.0 Hz, *H*7), 6.45 (1H, dd, *J* = 18.0 and 10.0 Hz, *H*2), 6.36 (1H, dd, *J* = 15.0 and 10.0 Hz, *H*3), 6.11 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*8), 5.86 (1H, d, *J* = 15.0 Hz, *H*4), 5.82 (1H, d, *J* = 18.0 Hz, *H*1), 5.48 (1H, dd, *J* = 3.0 and 2.0 Hz, *H*6), 2.13 (2H, s, SiCH_2Ar), 1.50 (3H, s, C5CH_3), 1.04 (6H, t, *J* = 8.0 Hz, Si(CH_2CH_3)$_2$), 0.77-0.65 (4H, m, SiC$H_2$$CH_3$ and SiCH_2'CH_3), –0.04 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 164.7, 145.7, 143.7, 138.8, 138.0, 132.1, 131.2, 130.7, 129.1, 128.6, 127.7, 127.4, 127.2, 127.0, 122.9, 74.7, 74.1, 24.9, 22.4, 6.0, 5.7, 5.6, 5.5, −4.4, −4.5; **HRMS** (ESI+) calc. for $C_{29}H_{38}O_3Si_2Na$ $[M+Na]^+$ 513.2252, found 513.2248.

6.4 C14-C17 Boronate synthesis

(*E*)-*tert*-Butyl((3-iodo-2-methylallyl)oxy)dimethylsilane, 207



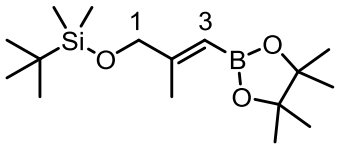
To a stirred solution of vinyl iodide **91** (605 mg, 3.06 mmol, 1.0 eq.) and imidazole (229 mg, 3.37 mmol, 1.1 eq.) in CH_2Cl_2 (8 mL) was added *tert*-butyldimethylsilyl chloride (553 mg, 3.67 mmol, 1.2 eq.) at 0 °C. After stirring overnight at RT, the reaction mixture was quenched with brine (5 mL), the organic layer separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude

product which was purified *via* column chromatography (petroleum ether) to give title compound **207** (766 mg, 2.45 mmol, 80%) as an orange oil;

$\mathbf{R_f}$ 0.37 (petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.20 (1H, s, *H*3), 4.10 (2H, s, *H1*), 1.77 (3H, s, C2CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.07 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 146.8, 75.9, 67.1, 25.8, 21.1, 18.3, −5.5.

The physical and spectroscopic data was found to be in agreement with that reported by Lipshutz *et al*.[179]

(*E*)-*tert*-Butyldimethyl((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane, 208

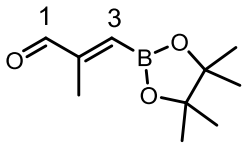


A solution of TBS-protected vinyl iodide **207** (60 mg, 0.19 mmol, 1.0 eq.) in toluene (1 mL) was added *via* syringe to a vial containing potassium phenoxide (77 mg, 0.58 mmol, 3.0 eq.), bis(pinacolato)diboron (96 mg, 0.38 mmol, 2.0 eq.) and bis(triphenylphosphine) palladium(II) dichloride (4 mg, 0.006 mmol, 3 mol%). After stirring for 2.5 h at 50 °C, the resulting reaction mixture was diluted with Et_2O (5 mL), washed with brine (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (2%)) to give title compound **208** (45 mg, 0.15 mmol, 76%);

$\mathbf{R_f}$ 0.19 (petroleum ether / EtOAc (2%)); **IR (**thin film, ν_{max} / cm^{-1}) 2956, 1650, 1257, 1115; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.48 (1H, s, *H*3), 4.04 (2H, s, *H*1), 1.90 (3H, s, C2CH_3), 1.26 (12H, s, Bpin*H*); 0.90 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$);

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 159.9, 109.9, 82.6, 68.3, 25.9, 24.8, 18.4, 17.5, −5.4; **HRMS** (ESI+) calc. for $C_{16}H_{33}BO_3SiNa$ $[M+Na]^+$ 335.2187, found 335.2177.

2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylaldehyde, 206

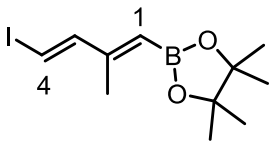


To a solution of TBS-protected boronate **208** (162 mg, 0.52 mmol) in methanol (2 mL) was added activated Dowex 50W-X8 (230 mg, in excess) resin. After stirring vigorously at RT for 2 h, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was redissolved in CH_2Cl_2 (2.6 mL) followed by addition of Dess-Martin periodinane (DMP) (265 mg, 0.620 mmol, 1.2 eq.). After stirring at 0 °C for 1.5 h, the reaction mixture was concentrated *in vacuo* and the resulting crude product redissolved in petroleum ether / EtOAc (10%) and filtered through Celite. The resulting filtrate was concentrated *in vacuo* to give aldehyde **206** (98 mg, 0.50 mmol, 96% over two steps), which was pure enough to use in the next reaction;

R_f 0.25 (petroleum ether / EtOAc (20%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.49 (1H, s, *H*1), 6.31 (1H, q, *J* = 1.0 Hz, *H*3), 2.01 (3H, d, *J* = 1.0 Hz, C2C*H*$_3$), 1.31 (12H, s, Bpin*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 196.5, 155.4, 84.0, 24.9, 13.1 [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus].[180]

The physical and spectroscopic data was found to be in agreement with that reported by Tortosa *et al*.[181]

2-((1*E*,3*E*)-4-Iodo-2-methylbuta-1,3-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 159

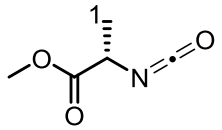


Chromium(II) chloride (374 mg, 3.04 mmol, 8.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The tube was allowed to reach RT, filled with nitrogen and THF (7.5 mL) was added. The resulting grey suspension was stirred for 10 min after which a solution of iodoform (299 mg, 0.760 mmol, 2.0 eq.) in THF (1 mL) was added *via* syringe and the resulting dark red suspension stirred for 20 min, after which a solution of **206** (75 mg, 0.38 mmol, 1.0 eq.) in THF (1 mL) was added by a similar method. After stirring at RT for 1 h, the reaction mixture was diluted with Et_2O (10 mL) and filtered through Celite. The filtrate washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (2%)) to give title compound **159** (75 mg, 0.23 mmol, 62%);

R_f 0.37 (petroleum ether / Et_2O (5%)); **IR (**thin film, ν_{max} / cm^{-1}) 2978, 1609, 1445, 1143, 762; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.08 (1H, d, *J* = 14.5 Hz, *H*4), 6.18 (1H, d, *J* = 14.5 Hz, *H*3), 5.43 (1H, s, *H*1), 1.98 (3H, s, C2C*H*$_3$), 1.04 (12H, s, Bpin*H*); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 155.3, 151.5, 83.2, 81.3, 25.1, 16.4 [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus];[180] **HRMS** (ESI+) calc. for $C_{11}H_{18}BIO_2Na$ $[M+Na]^+$ 343.0339, found 343.0336.

6.5 C18-C23 Dienyl iodide synthesis

(*S*)-Methyl 2-isocyanatopropanoate, 213

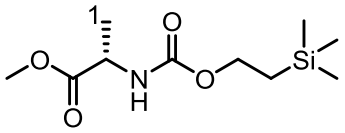


To a biphasic mixture of L-alanine methyl ester hydrochloride **212** (3.50 g, 25.1 mmol, 1.0 eq.), saturated aqueous $NaHCO_3$ solution (91 mL), and CH_2Cl_2 (84 mL) was added triphosgene (2.97 g, 10.0 mmol, 0.4 eq.) at 0 °C. After stirring vigorously for 15 min, the organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give crude product isocyanate **213** (2.53 g, 19.6 mmol, 78%) which could be used without further purification. Purification *via* vacuum distillation (60-61 °C, 20-23 mmbar) provided isocyanate **213** (1.99 g, 15.4 mmol, 61%) as a clear oil;

b.p. 60-61 °C, 20-23 mbar (lit. 60-61 °C, 15 mmHg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.09 (1H, q, *J* = 7.0 Hz, *H*2), 3.81 (3H, s, CO_2CH_3), 1.50 (3H, d, *J* = 7.0 Hz, *H*1); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.4, 53.2, 52.8, 20.4.

The physical and spectroscopic data was found to be in agreement with that reported by Hlavacek *et al*.[182]

(*S*)-Methyl 2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanoate, 214

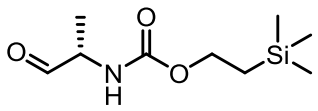


To a solution of 2-(trimethylsilyl)ethanol (2.1 mL, 15, mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) was added triethylamine (1.6 mL, 12 mmol, 0.8 eq.) at 0 °C. After stirring for 15 min, a solution of isocyanate **213** (2.53 g, 19.6 mmol, 1.3 eq.) in CH_2Cl_2 (5 mL) was added slowly *via* syringe. After stirring at RT for 1 h, the reaction mixture was concentrated *in vacuo*, the crude residue redissolved in EtOAc (20 mL), washed sequentially with a 1 M aqueous HCl (20 mL) solution and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (40%)) to give title compound **214** (3.18 g, 11.4 mmol, 78%) as a clear oil;

$[\alpha]_D^{25}$ −7.6 (*c* 0.10, $CHCl_3$); **R_f** 0.32 (petroleum ether / Et_2O (40%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.15 (1H, bd, *J* = 5.5 Hz, N*H*), 4.43-4.29 (1H, m, *H*2), 4.15 (2H, t, *J* = 8.5 Hz, O*CH*$_2$CH$_2$Si), 3.74 (3H, s, CO$_2$C*H*$_3$), 1.40 (3H, d, *J* = 7.0 Hz, *H*1), 1.02-0.93 (2H, m, OCH$_2$C*H*$_2$Si), 0.03 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.2, 157.5, 64.9, 53.9, 50.9, 20.2, 19.2, 0.0.

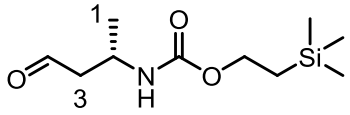
The physical and spectroscopic data was found to be in agreement with that reported by Stanway and Thomas.[183]

(*S*)-2-(Trimethylsilyl)ethyl (1-oxopropan-2-yl)carbamate, 216



To a solution of Teoc-protected amino ester **214** (3.18 g, 11.6 mmol, 1.0 eq.) in CH_2Cl_2 (39 mL) was added a solution of DIBALH (23.2 mL, 1.0 M solution in hexanes, 23.2 mmol, 2.0 eq.) dropwise *via* syringe at −78 °C. After stirring at −78 °C for 15 min, monitored by TLC, the reaction was quenched with a saturated aqueous solution of Rochelle's salt (30 mL) and diluted with Et_2O (10 mL), the cooling bath removed and the reaction allowed to reach RT. The organic layer was separated and the aqueous layer further extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the α-amino aldehyde **216** (2.79 g) as a colourless oil which was used immediately in the next reaction.

(*S*)-2-(Trimethylsilyl)ethyl (4-oxobutan-2-yl)carbamate, 215

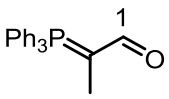


To a solution of (methoxymethyl)triphenylphosphonium chloride (7.95 g, 23.2 mmol, 2.0 eq.) in THF (67 mL) was added a solution of NaHMDS (9.9 mL, 2.0 M solution in THF, 20 mmol, 1.7 eq.) dropwise *via* syringe at −78 °C. The resulting red mixture was stirred at −78 °C for 30 min followed by addition of the α-amino aldehyde **216** (2.79 g, 11.6 mmol, 1.0 eq.) in THF (10 mL) *via* syringe. Subsequently, the cooling bath was removed and the reaction mixture allowed to reach RT. After stirring at RT for 2 h, the reaction was quenched with water (50 mL), the organic layer separated and the aqueous layer further extracted with EtOAc (3 × 50 mL). The combined organic layers were

dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was redissolved in THF (55 mL), 1 M aqueous HCl solution (11 mL) added and the resulting solution stirred vigorously at RT overnight. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **215** (2.23 g, 9.63 mmol, 83% over three steps) as a clear oil;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −18 (*c* 0.1, $CHCl_3$); $\mathbf{R}_f$ 0.25 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3325, 1690, 1529, 1249, 1067; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.76 (1H, t, *J* = 2.0 Hz, *H*4), 4.78 (1H, bs, N*H*), 4.25-4.06 (3H, m, *H*2 and OCH_2CH_2Si), 2.67 (2H, ddd, *J* = 17.0, 6.0 and 2.0 Hz, *H*3), 2.60 (2H, app dd, *J* = 17.0 and 6.0 Hz, *H*3'), 1.25 (3H, d, *J* = 7.0 Hz, C2CH_3), 0.96-0.91 (2H, m, OCH$_2$CH_2Si), 0.02 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.8, 155.9, 63.1, 50.2, 42.7, 20.9, 17.7, −1.5; **HRMS** (ESI+) calc. for $C_{11}H_{25}NO_4SiNa$ [M+Na+MeOH]$^+$ 286.1445, found 286.1458.

2-(Triphenylphosphoranylidene)propanal, 102



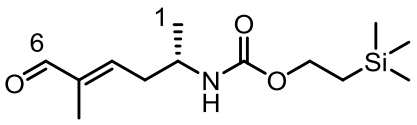
To a stirred suspension of Sodium hydride (3.24 g, 60% w/w in mineral oil, 81.0 mmol, 1.0 eq.) in THF (80 mL) was added ethyltriphenylphosphonium bromide (**219**) (10.0 g, 26.9 mmol, 1.0 eq.). After stirring at RT overnight, the reaction mixture was cooled to 0 °C and ethyl formate (5.4 mL, 67.3 mmol, 2.5 eq.) added dropwise *via* syringe. The resulting solution was stirred at 0 °C for 2 h and then at RT for further 2 h. The reaction

was quenched by portionwise addition of a 1 M aqueous HCl solution (80 mL) at 0 °C. The resulting mixture was adjusted to pH 8 by a dropwise addition of aqueous NaOH (10% w/v) solution followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by dissolving in minimum amount of CH_2Cl_2 followed by dilution with Et_2O until precipitation of product occurred giving, after filtration, title product **102** (6.03 g, 18.9 mmol, 70%) as a beige coloured solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (1H, d, *J* = 5.5 Hz, *H*1), 7.70-7.48 (15H, m, ArH), 1.86 (3H, d, *J* = 13.5 Hz, C2C*H*$_3$).

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

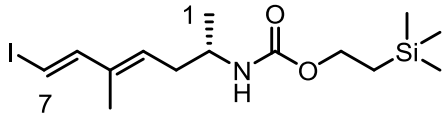
(*S*,*E*)-2-(Trimethylsilyl)ethyl (5-methyl-6-oxohex-4-en-2-yl)carbamate, 218



A stirred suspension of aldehyde **215** (1.47 g, 6.35 mmol, 1.0 eq.) and phosphorane **102** (3.03 g, 9.54 mmol, 1.5 eq.) in toluene (45 mL) was heated at 80 °C overnight. The resulting orange solution was concentrated *in vacuo* and redissolved in cold Et_2O, filtered and the filtrate concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (40%)) to give title compound **218** (1.59 g, 5.84 mmol, 92%) as a clear oil;

$[\alpha]_D^{25}$ −42 (*c* 0.1, $CHCl_3$); 84% *ee* (CHIRALPAK IB, 2% IPA / hexane, 1.3 mL/min, t_R (*R*) 11.4 min, t_R (*S*) 13.7 min); $\mathbf{R}_f$ 0.29 (petroleum ether / Et_2O (40%)); **IR (**thin film, ν_{max} / cm^{-1}) 3326, 1687, 1529, 1250, 1061; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.42 (1H, s, *H*6), 6.50 (1H, t, *J* = 7.0 Hz, *H*4), 4.5 (1H, bs, N*H*), 4.18-4,08 (2H, m, OCH_2CH_2Si), 4.02-3.84 (1H, m, *H*2), 2.61-2.47 (2H, m, *H*3), 1.75 (3H, s, C5CH_3), 1.20 (3H, d, *J* = 7.0 Hz, C1CH_3), 1.02-0,92 (2H, m, OCH_2CH_2Si), 0.03 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 195.0, 156.0, 149.6, 141.2, 63.1, 46.3, 36.3, 20.9, 17.7, 9.4, −1.5; **HRMS** (ESI+) calc. for $C_{13}H_{25}NO_3SiNa$ $[M+Na]^+$ 294.1496, found 294.1498.

2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*)-7-iodo-5-methylhepta-4,6-dien-2-yl)carbamate, 160

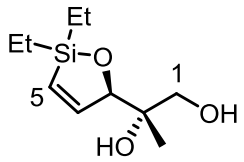


Chromium(II) chloride (246 mg, 2.0 mmol, 8.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The tube was allowed to reach RT, filled with nitrogen and THF (4.5 mL) was added. The resulting grey suspension was stirred for 10 min, after which a solution of iodoform (197 mg, 0.50 mmol, 2.0 eq.) in THF (1 mL) was added *via* syringe. The resulting dark red suspension stirred for 20 min, followed by addition of a solution of aldehyde **218** (67 mg, 0.25 mmol, 1.0 eq.) in THF (1 mL) *via* syringe. After stirring at RT for 1 h, the reaction mixture was diluted with Et_2O (5 mL) and filtered through Celite. The filtrate was washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (0%) → petroleum ether / Et_2O (20%)) to give title compound **160** (55 mg, 0.14 mmol, 56%) as a yellow oil;

$[\alpha]_D^{25}$ –26 (*c* 0.1, $CHCl_3$); $\mathbf{R}_f$ 0.54 (petroleum ether / Et_2O (40%)); **IR (**thin film, ν_{max} / cm^{-1}) 3323, 1690, 1531, 1250, 1050, 837; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 6.92 (1H, d, *J* = 14.5 Hz, *H*7), 5.89 (1H, d, *J* = 14.5 Hz, *H*6), 5.08 (1H, t, *J* = 7.5 Hz, *H*4), 4.33-4.26 (2H, m, CH_2CH_2Si), 4.07 (1H, bd, *J* = 7.0 Hz, N*H*), 4.83-3.65 (1H, m, *H*2), 2.02-1.90 (1H, m, *H*3), 1.90-1.77 (2H, m, *H*3'), 2.00 (3H, d, *J* = 1.0 Hz, C2CH_3), 1.33 (3H, s, C5CH_3), 1,02-0,96 (2H, m, CH$_2$CH_2Si), 0.77 (3H, d, *J* = 7.0 Hz, C1H_3), −0.06 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 157.4, 152.2, 138.2, 131.4, 75.9, 64.3, 48.4, 36.7, 21.8, 19.7, 13.3, 0.0; **HRMS** (ESI+) calc. for $C_{14}H_{26}INO_2SiNa$ $[M+Na]^+$ 418.0670, found 418.0669.

6.6 Sequential Hiyama-Suzuki cross-coupling

(*S*)-2-((*R*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)propane-1,2-diol, 115



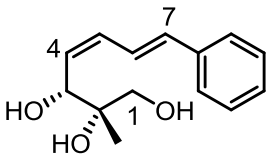
To a stirred solution of **97** (53 mg, 0.17 mmol, 1.0 eq.) in MeOH (1.7 mL) was added K_2CO_3 (30 mg, 0.22 mmol, 1.3 eq.) and the resulting suspension stirred vigorously overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (5 ml) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **115** (27 mg, 0.13 mmol, 76%) as a colourless oil;

$\mathbf{R}_f$ 0.24 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.99 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*4), 6.15 (1H, dd, *J* = 10.5 and 2.5, *H*5), 4.66 (1H, app t, *J* = 2.0 Hz, *H*3), 3.64 (1H, dd, *J* = 11.0 and 4.0 Hz, *H*1), 3.39 (1H, dd, *J* = 11.0 and 6.5

Hz, *H*1'), 2.66-2.54 (1H, m, O*H*), 2.44 (1H, bs, *J* = 6.5 Hz, O*H*), 1.10 (3H, s, C2CH_3), 0.99 (3H, t, *J* = 8.0 Hz, SiCH$_2$CH_3), 0.90 (3H, t, *J* = 8.0 Hz, SiCH$_2$CH_3'*),* 0.79-0.50 (4H, m, SiCH_2CH$_3$ and SiCH_2'CH$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 150.2, 127.4, 87.7, 74.0, 67.8, 19.5, 7.2, 6.8, 6.7, 6.3.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

((2*S*,3*R*,4*Z*,6*E*)-2-Methyl-7-phenylhepta-4,6-diene-1,2,3-triol, 221



To a vial containing siloxane **115** (20 mg, 0.09 mmol, 1.0 eq.), iodostyrene (**220**) (21 mg, 0.09 mmol, 1.0 eq.) and [allylPdCl]$_2$ (0.8 mg, 0.0023 mmol, 2.5 mol%) was added TBAF•3H$_2$O (0.27 mL, 1 M in THF, 0.27 mmol, 3.0 eq.). After stirring at RT overnight, the crude product mixture was purified *via* column chromatography (petroleum ether / EtOAc (80%)) to give diene **221** (17 mg, 0.38 mmol, 81%) as a yellow oil;

$[\alpha]_D^{25}$ +46 (*c* 0.73, $CHCl_3$); $\mathbf{R}_f$ 0.28 (petroleum ether / EtOAc (80%)); **IR (**thin film, ν_{max} / cm^{-1}) 3368, 2927, 1450, 1043, 1002; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.42-6.98 (5H, m, Ar*H*), 7.23 (1H, dd, *J* = 15.5 and 11.5 Hz, *H*6), 6.41 (1H, d, *J* = 15.5 Hz, *H*7), 6.18 (1H, app t, *J* = 11.5 Hz, *H*5), 5.57 (1H, app t, *J* = 10.5 Hz, *H*4), 4.82 (1H, d, *J* = 10.5 Hz, *H*3), 3.94 (1H, bs, O*H*), 3.87 (1H, d, *J* = 11.5 Hz, *H*1), 3.77 (1H, bs, O*H*), 3.59 (1H, bs, O*H*), 3.52 (1H, d, *J* = 11.5 Hz, *H*1'), 1.14 (3H, s, C2CH_3); **^{13}C NMR** (100 MHz, C_6D_6)

δ_C 137.1, 135.0, 132.3, 129.6, 128.6, 127.8, 126.7, 123.9, 74.5, 74.0, 67.5, 20.8; **HRMS** (ESI+) calc. for $C_{14}H_{18}O_3Na$ $[M+Na]^+$ 257.1148, found 257.1151.

6.7 C14-C23 Sulfide synthesis

Preparation of sodium periodate adsorbed on silica[184]

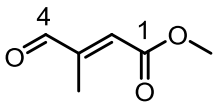
$NaIO_4/SiO_2$

$NaIO_4$ (2.57 g, 12.0 mmol) was dissolved in water (10 mL) at 70 °C followed by addition of silica (10 g). The resulting slurry was vigorously shaken after which water was removed *in vacuo*.

General procedure for diol cleavage/olefination

To a suspension of $NaIO_4/SiO_2$ (3.0 eq., 10% by weight) and tartrate (1.0 eq.) in CH_2Cl_2 (0.1 M) was added phosphorane **102** (1.0 or 2.0 eq.). The resulting mixture was stirred at RT overnight after which it was filtered, and washing several times with CH_2Cl_2. The filtrate was concentrated *in vacuo* and purified *via* column chromatography (petroleum ether / Et_2O) to give *α,β*-unsaturated aldehyde.

(*E*)-Methyl 3-methyl-4-oxobut-2-enoate, 230

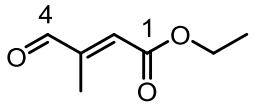


Following the aforementioned procedure, **102** (159 mg, 0.50 mmol, 1.0 eq.) was added to a suspension of $NaIO_4/SiO_2$ (3.20 g, 1.50 mmol, 3.0 eq., 10% by weight) and L-(+)-dimethyl tartrate (**232**) (89 mg, 0.5 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL). Purification *via* column chromatography (petroleum ether / Et_2O (20%)) gave *α,β*-unsaturated aldehyde **230** (27 mg, 0.21 mmol, 42%) as a 3:1 mixture of isomers;

R_f 0.20 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.55 (1H, S, *H*4), 6.50 (1H, q, *J* = 1.5 Hz, *H*2), 3.82 (3H, s, CO_2CH_3), 2.16 (3H, d, *J* = 1.5 Hz, C3CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 194.5, 166.0, 150.7, 135.0, 52.0, 10.9.

The physical and spectroscopic data was found to be in agreement with that reported by Yoshi *et al*.[115]

(*E*)-Ethyl 3-methyl-4-oxobut-2-enoate, 236

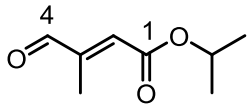


Following the aforementioned procedure, **102** (4.09 g, 12.8 mmol, 2.0 eq.) was added to a suspension of $NaIO_4/SiO_2$ (41.3 g, 19.3 mmol, 3.0 eq., 10% by weight) and L-(+)-diethyl tartrate (**234**) (1.10 mL, 6.42 mmol, 1.0 eq.) in CH_2Cl_2 (64 mL). Purification *via* column chromatography (petroleum ether / Et_2O (10%)) gave *α,β*-unsaturated aldehyde **236** (1.01 g, 7.88 mmol, 62%) as a 10:1 mixture of isomers;

R_f 0.24 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.55 (1H, s, *H*4), 6.55 (1H, q, *J* = 1.5 Hz, *H*2), 4.28 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 2.16 (3H, d, *J* = 1.5 Hz, C3CH_3), 1.34 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 194.6, 165.5, 150.4, 135.6, 61.1, 14.2, 10.8.

The physical and spectroscopic data was found to be in agreement with that reported by Papaioannou *et al*.[185]

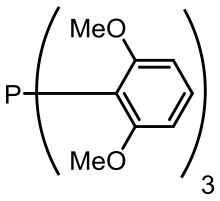
(*E*)-Isopropyl 3-methyl-4-oxobut-2-enoate, 303



Following the aforementioned procedure, **102** (153 mg, 0.48 mmol, 2.0 eq.) was added to a suspension of $NaIO_4/SiO_2$ (1.54 g, 0.72 mmol, 3.0 eq., 10% by weight) and L-(+)-diisopropyl tartrate (**235**) (0.050 mL, 0.24 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL). Purification *via* column chromatography (petroleum ether / Et_2O (10%)) gave title compound **303** (60 mg, 0.38 mmol, 79%) as a 15:1 mixture of isomers;

R_f 0.25 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2917, 1788, 1739, 1267, 1069; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.54 (1H, s, *H*4), 6.48 (1H, q, *J* = 1.5 Hz, *H*2), 5.48 (1H, sept, *J* = 6.5 Hz, C*H*$(CH_3)_2$), 2.15 (3H, d, *J* = 1.5 Hz, C3C*H*$_3$), 1.32 (6H, d, *J* = 6.5 Hz, CH(C*H*$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 194.7, 165.1, 150.0, 136.2, 68.8, 21.8, 10.8; **HRMS** (ESI+) calc. for $C_9H_{16}NaO_4$ $[M+MeOH+Na]^+$ 211.0941, found 211.0939.

Tris(2,6-dimethoxyphenyl)phosphine, 245



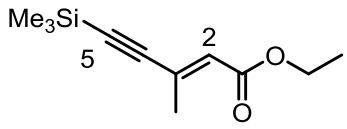
To a stirred solution of 1,3-dimethoxybenzene (2.50 mL, 19.2 mmol, 3.0 eq.) in Et_2O (4.0 mL) was added a solution of *n*-BuLi (7.68 mL, 2.5 M in hexanes, 19.2 mmol, 3.0 eq.) *via* syringe, at −78 °C. The resulting suspension was stirred overnight, and allowed to reach RT. Next, phosphorus trichloride (0.56 mL, 6.4 mmol, 1.0 eq.) was added

dropwise *via* syringe at 0 °C, after which the cooling bath was removed and the reaction flask fitted with a reflux condenser. After stirring for 2 h at 40 °C, the reaction was allowed to reach RT, then quenched with a 5 M aqueous NaOH solution (20 mL) and extracted with chloroform (3 × 20 mL). The combined organic layers were dried over K_2CO_3, filtered and concentrated *in vacuo* to give the crude product which was purified by recrystallisation from boiling ethanol affording title compound **245** (1.16 g, 2.62 mmol, 41%) as colourless crystals;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.12 (3H, t, J = 8.0 Hz, *p*-Ar*H*), 6.43 (6H, dd, J = 8.0 and 3.0 Hz, *m*-Ar*H*), 3.47 (18H, s, OCH_3),

The physical and spectroscopic data was found to be in agreement with that reported by Horner and Simons.[186]

(*E*)-Ethyl 3-methyl-5-(trimethylsilyl)pent-2-en-4-ynoate, 246

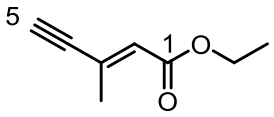


A round-bottom flask containing $Pd(OAc)_2$ (240 mg, 1.07 mmol, 5.0 mol%) and phosphine **245** (947 mg, 2.14 mmol, 10.0 mol%) was evacuated and refilled with argon, THF (54 mL) was then added and the resulting mixture stirred at RT for 15 min. Subsequently, ethyl butynoate (**243**) (2.50 mL, 21.4 mmol, 1.0 eq.) was added *via* syringe, followed by trimethylsilylacetylene (**244**) (3.0 mL, 21.4 mmol, 1.0 eq.) by a similar method. After stirring for 2 h, the reaction mixture was concentrated *in vacuo* and the crude product purified *via* column chromatography (petroleum ether / Et_2O (2%)) to give title compound **246** (3.68 g, 17.5 mmol, 82%);

R_f 0.33 (petroleum ether / Et_2O (2%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.09 (1H, q, *J* = 1.5 Hz, *H*2), 4.16 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 2.27 (3H, d, *J* = 1.5 Hz, $C3CH_3$), 1.27 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 0.20 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.3, 137.7, 125.3, 106.8, 99.4, 60.3, 19.9, 14.5, 0.0.

The physical and spectroscopic data was found to be in agreement with that reported by Carreira *et al*.[187]

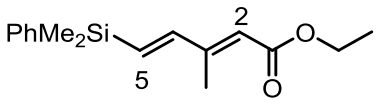
(*E*)-Ethyl 3-methylpent-2-en-4-ynoate, 238



To a stirred solution of $TBAF{\bullet}3H_2O$ (760 mg, 2.41 mmol, 0.25 eq.) in CH_2Cl_2 (22 mL) was added a solution of **246** (2.03 g, 9.63 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) *via* syringe. After stirring vigorously for 10 min, the resulting dark red mixture was quenched with water (30 mL), the organic layer separated and the aqueous layer further extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and carefully concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether (b.p. 30-40) / Et_2O (4%)) to give title compound **238** (1.12 g, 8.09 mmol, 84%) as a yellow volatile oil;

R_f 0.33 (petroleum ether / Et_2O (4%)); **IR** (thin film, ν_{max} / cm^{-1}) 2362, 1716, 1621, 1225, 1147; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.13 (1H, q, *J* = 1.5 Hz, *H*2), 4.17 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 3.18 (1H, s, *H*5), 2.29 (3H, d, *J* = 1.5 Hz, $C3CH_3$), 1.28 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.8, 136.5, 126.0, 85.2, 81.1, 60.2, 19.6, 14.2; **HRMS** (ESI+) calc. for $C_9H_{10}O_2$ $[M+H]^+$ 139.0754, found 139.0753.

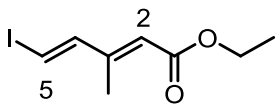
(2*E*,4*E*)-Ethyl 5-(dimethyl(phenyl)silyl)-3-methylpenta-2,4-dienoate, 242



A round-bottom flask containing $PtCl_2$ (105 mg, 0.40 mmol, 5.0 mol%) and Xphos (378 mg, 0.79 mmol, 10.0 mol%) was evacuated and refilled with argon, THF (2 mL) was then added and the resulting mixture stirred at 60 °C for 30 min, until a yellow homogenous mixture formed. Subsequently, a solution of enyne **238** (1.10 g, 7.92 mmol, 1.0 eq.) in THF (2 mL) was added *via* syringe followed by phenyldimethylsilane (1.8 mL, 12 mmol, 1.5 eq.). After stirring at 60 °C overnight, the reaction mixture was concentrated *in vacuo* and the crude product purified *via* column chromatography (petroleum ether / Et_2O (4%)) to give title compound **242** (2.15 g, 7.83 mmol, 99%) as a yellow oil;

R_f 0.36 (petroleum ether / Et_2O (4%)); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 1714, 1619, 1234, 1153, 827; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56-7.35 (5H, m, Ar*H*), 6.61 (1H, d, *J* = 19.0 Hz, *H*4), 6.46 (1H, d, *J* = 19.0 Hz, *H*5), 5.82 (1H, app s, *H*2), 4.18 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 2.29 (3H, d, *J* = 1.0 Hz, C3CH_3), 1.29 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 0.41 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.1, 152.4, 148.2, 137.8, 134.1, 133.9, 133.8, 129.3, 127.9, 120.7, 59.8, 14.3, 13.3, −2.7; **HRMS** (ESI+) calc. for $C_{16}H_{22}O_2NaSi$ $[M+Na]^+$ 297.1281, found 297.1279.

(2*E*,4*E*)-Ethyl 5-iodo-3-methylpenta-2,4-dienoate, 237

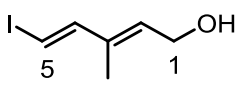


To a stirred solution of vinyl silane **242** (407 mg, 1.48 mmol, 1.0 eq.) in hexafluoroisopropanol (HFIP) (6.0 mL) was added NIS (500 mg, 2.22 mmol, 1.5 eq.) in one portion. After stirring at 0 °C for 2 h, the reaction was diluted with CH_2Cl_2 (20 mL) and washed sequentially with saturated aqueous $Na_2S_2O_3$ (20 mL) and $NaHCO_3$ (20 mL) solutions. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (3%)) to afford title compound **237** (343 mg, 1.29 mmol, 87%) as a bright yellow oil;

R_f 0.29 (petroleum ether / Et_2O (3%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.82 (1H, d, *J* = 14.5 Hz, *H*4), 6.35 (1H, d, *J* = 14.5 Hz, *H*5), 5.60 (1H, app s, *H*2), 4.06 (2H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 2.08 (3H, d, *J* = 1.0 Hz, $C3CH_3$), 1.06 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 0.41 (6H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 165.9, 150.7, 148.0, 120.4, 84.3, 59.5, 13.9, 12.7.

The physical and spectroscopic data was found to be in agreement with that reported by de Lera *et al.*[188]

(2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-dien-1-ol, 228



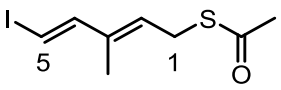
To a solution of dienoate **237** (340 mg, 1.28 mmol, 1.0 eq.) in CH_2Cl_2 (3.2 mL) was added a solution of DIBALH (2.68 mL, 1.0 M solution in hexanes, 2.68 mmol, 2.1 eq.)

dropwise *via* syringe, at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched by slow addition of water (0.11 mL) followed by addition of an aqueous NaOH solution (0.11 mL, 15% w/v) and then water (0.3 mL). The cooling bath was removed and the resulting mixture stirred for 15 min, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (40%)) to give title compound **228** (265 mg, 1.18 mmol, 92%) as a yellow to green oil;

R_f 0.22 (petroleum ether / Et_2O (40%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.99 (1H, d, *J* = 14.5 Hz, *H*4), 6.03 (1H, d, *J* = 14.5 Hz, *H*5), 5.31 (1H, t, *J* = 6.5 Hz, *H*2), 3.85 (2H, d, *J* = 6.5 Hz, *H*1), 1.31 (3H, s, C3CH_3), 0.61 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 148.8, 141.9, 132.5, 75.5, 58.5, 11.3.

The physical and spectroscopic data was found to be in agreement with that reported by de Lera *et al*.[147]

_S_-((2_E_,4_E_)-5-Iodo-3-methylpenta-2,4-dien-1-yl) ethanethioate, 223



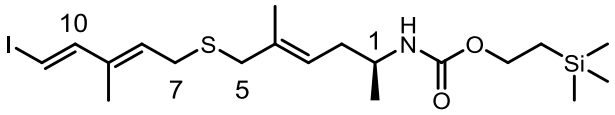
To a stirred solution of triphenylphosphine (320 mg, 1.22 mmol, 1.2 eq.) and DIAD (0.24 mL, 1.22 mmol, 1.2 eq.) in THF (3.4 mL) was added a solution of dienol **228** (229 mg, 1.02 mmol, 1.0 eq.) and freshly distilled AcSH (0.10 mL, 1.33 mmol, 1.3 eq.) in THF (4.0 mL) dropwise *via* syringe, at 0 °C. The cooling bath was removed and the reaction mixture allowed to reach RT. After stirring at RT overnight, the reaction mixture was concentrated *in vacuo* and the crude product purified *via* column

chromatography (petroleum ether / Et_2O (1%)) to give title compound **223** (176 mg, 0.62 mmol, 61%) as a yellow oil;

R_f 0.18 (petroleum ether / Et_2O (2%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.80 (1H, d, *J* = 14.5 Hz, *H*4), 5.90 (1H, d, *J* = 14.5 Hz, *H*5), 5.16 (1H, t, *J* = 8.0 Hz, *H*2), 3.34 (2H, d, *J* = 8.0 Hz, *H*1), 1.81 (3H, s, $COCH_3$), 1.31 (3H, s, $C3CH_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 194.1, 149.2, 137.7, 133.1, 76.5, 30.2, 27.4, 11.9.

The physical and spectroscopic data was found to be in agreement with that reported by Christian Kuper.[153]

2-(Trimethylsilyl)ethyl ((*S*,*E*)-6-(((2*E*,4*E*)-5-iodo-3-methylpenta-2,4-dien-1-yl)thio)-5-methylhex-4-en-2-yl) carbamate, 161



A solution of sulfone **223** (46 mg, 0.16 mmol, 1.0 eq.) and bromide **224** (55 mg, 0.16 mmol, 1.0 eq.) in MeOH (0.8 mL) was degassed (N_2 bubbling, 15 min) before KOH (46 mg, 0.82 mmol, 5.0 eq.) was added. After stirring vigourously for 1 h, the resulting mixture was quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (10%) → petroleum ether / Et_2O (15%)) to give the title compound **161** (57 mg, 0.12 mmol, 71%) as a red oil;

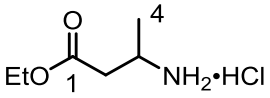
R_f 0.30 (petroleum ether / Et_2O (20%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.95 (1H, d, *J* = 14.5 Hz, *H*10), 5.95 (1H, d, *J* = 14.5 Hz, *H*11), 5.32 (1H, t, *J* = 8.0 Hz, *H*8), 5.09 (1H, t, *J* = 8.0 Hz, *H*3), 4.33-4.24 (2H, m, OCH_2CH_2Si), 4.08 (1H, d, *J* = 7.5 Hz, N*H*),

3.87-3.73 (1H, m, *H*1), 2.88-2.82 (4H, m, *H*7 and *H*5), 2.04-1.84 (2H, m, *H*2 and *H*2'), 1.62 (3H, s, C4CH_3), 1.38 (3H, s, C9CH_3), 1.03-0.96 (2H, m, OCH_2CH_2Si), −0.05 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 156.1, 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.

The physical and spectroscopic data was found to be in agreement with that reported by Christian Kuper.[153]

6.8 C14-C23 Tetraenyl iodide synthesis

Ethyl 3-aminobutanoate hydrochloride, 413

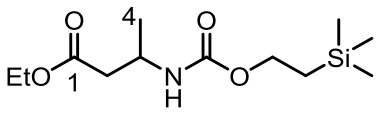


To ethanol (100 mL) was added thionyl chloride (7.8 mL, 107 mmol, 1.1 eq.) slowly, at 0 °C. After stirring for 30 min, 3-aminobutanoic acid **100** (10.0 g, 97 mmol, 1.0 eq.) was added and the resulting mixture stirred for 1 h at 0 °C, then 3 h at 40 °C. The resulting reaction mixture was allowed to reach RT and concentrated *in vacuo* to give the title compound **413** (16.2 g, 97.0 mmol, quant.) as a dark red oil, which was used in the next step without further purification;

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 8.45 (3H, bs, NH_3), 4.18 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 3.94-3.72 (1H, m, *H3*), 3.11-2.56 (2H, m, *H2*), 1.60-1.41 (3H, m, *H*4), 1.25 (3H, q, J = 7.0 Hz, $CO_2CH_2CH_3$).

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

Ethyl 3-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)butanoate, 101

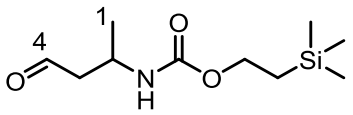


To a suspension of potassium carbonate (19.2 g, 139 mmol, 4.3 eq.) and 2-(trimethylsilyl)-ethanol (5.1 mL, 36 mmol, 1.1 eq.) in toluene (100 mL) was added slowly *via* syringe a solution of triphosgene (3.56 g, 120 mmol, 0.37 eq.) in toluene (50 mL) at 0 °C. After addition, the cooling bath was removed and the reaction allowed to reach RT followed by stirring for 1 h. Next, the reaction mixture was cooled to −20 °C and a solution of hydrochloride salt **413** (5.4 g, 33mmol, 1.0 eq.) in toluene (50 mL) added *via* syringe. After stirring at RT overnight, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL), the organic layer separated and the aqueous layer further extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (15%) → petroleum ether / EtOAc (30%)) to give title compound **101** (4.82 g, 17.5 mmol, 54%) as a clear oil;

R_f 0.46 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.06 (1H, bs, N*H*), 4.22-3.99 (5H, m, $CO_2CH_2CH_3$, *H*3 and OCH_2CH_2Si), 2.50 (2H, d, *J* = 5.5 Hz, *H*2), 1.26 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 1.23 (3H, d, *J* = 7.0 Hz, *H*4), 1.03-0.91 (2H, m, OCH_2CH_2Si), 0.03 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.5, 157.4, 64.7, 62.0, 45.6, 42.4, 21.9, 19.2, 15.7, 0.0.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

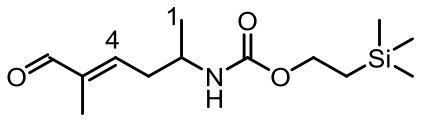
2-(Trimethylsilyl)ethyl (4-oxobutan-2-yl)carbamate, 414



To a solution of Teoc-protected amino ester **101** (4.82 g, 17.5 mmol, 1.0 eq.) in CH_2Cl_2 (145 mL) was added a solution of DIBALH (35.0 mL, 1.0 M solution in hexanes, 35.0 mmol, 2.0 eq.) dropwise *via* syringe, at −78 °C. After stirring at −78 °C for 1 h, the reaction was quenched with a saturated aqueous solution of Rochelle's salt (30 mL) and diluted with Et_2O (30 mL), the cooling bath removed and the reaction allowed to reach RT. The organic layer was separated and the aqueous layer further extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (15%) → petroleum ether / EtOAc (20%)) to give title compound **414** (3.65 g, 15.8 mmol, 90%) as a colourless oil;

R_f 0.25 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3326, 2954, 1690, 1528, 1249, 1067; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* = 2.0 Hz, *H*4), 4.78 (1H, d, *J* = 7.5 Hz, N*H*), 4.25-4.01 (3H, m, *H*2 and OCH_2CH_2Si), 2.67 (1H, ddd, *J* = 17.0, 6.0 and 2.0 Hz, *H*3), 2.60 (1H, app dd, *J* = 17.0, and 5.5 Hz, *H*3'), 1.25 (3H, d, *J* = 7.0 Hz, *H*1), 1.02-0.90 (2H, m, OCH$_2$CH_2Si), 0.02 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.8, 155.9, 63.1, 50.2, 42.7, 20.9, 17.7, −1.7; **HRMS** (ESI+) calc. for $C_{10}H_{21}NO_3SiNa$ $[M+Na]^+$ 254.1183, found 254.1187.

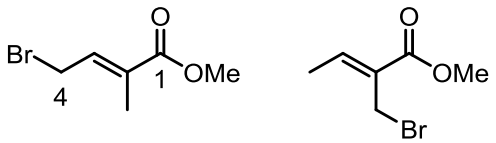
(*E*)-2-(Trimethylsilyl)ethyl (5-methyl-6-oxohex-4-en-2-yl)carbamate, 103



A stirred solution of aldehyde **414** (2.92 g, 12.5 mmol, 1.0 eq.) and phosphorane **102** (6.0 g, 18.8 mmol, 1.5 eq.) in toluene (84 mL) in an oven dried round-bottom flask, was heated at 80 °C overnight. The resulting orange solution was concentrated *in vacuo* and redissolved in cold Et_2O, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%) → petroleum ether / EtOAc (20%)) to give title compound **103** (3.09 g, 11.4 mmol, 91%);

R_f 0.41 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3324, 2954, 1686, 1529, 1249, 1061; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.42 (1H, s, *H*6), 6.50 (1H, t, *J* = 7.0 Hz, *H*4), 4.52 (1H, bd, *J* = 8.0 Hz, N*H*), 4.17-4.07 (2H, t, m, OCH_2CH_2Si), 3.94 (1H, m, *H*2), 2.62-2.45 (2H, m, *H*3), 1.75 (3H, s, C5CH_3), 1.20 (3H, d, *J* = 7.0 Hz, *H*1), 1.03-0.90 (2H, m, OCH_2CH_2Si), 0.02 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 194.9, 156.0, 149.7, 141.2, 63.0, 46.3, 36.3, 20.8, 17.7, 9.4, −1.5; **HRMS** (ESI+) calc. for $C_{13}H_{25}NO_3SiNa$ $[M+Na]^+$ 294.1496, found 294.1495.

(*E*)-Methyl 4-bromo-2-methylbut-2-enoate, 251



251 **251'**

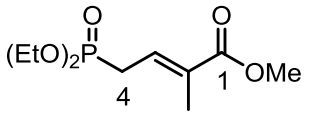
A stirred solution of NBS (7.41 g, 41.6 mmol, 1.0 eq.) and methyl tiglate (**250**) (5.40 mL, 41.6 mmol, 1.0 eq.) in CCl_4 (21 mL) was heated at reflux overnight. Next, the reaction was cooled to RT, filtered through Celite and concentrated *in vacuo*. The crude

product was purified *via* column chromatography (petroleum ether / EtOAc (5%)) to give an inseparable mixture of title compound **251** and **251'** (5.79 g, 30.0 mmol, 72%) in a 1.7:1 ratio;

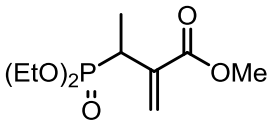
R_f 0.33 (petroleum ether / EtOAc (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.93 (1H, tq, *J* = 8.5 and 1.5 Hz, *H*3), 4.03 (2H, d, *J* = 8.5 Hz, *H*4), 3.77 (3H, s, CO_2CH_3), 1.92 (3H, m, C2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.7, 135.1, 131.9, 52.1, 25.9, 12.2.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(*E*)-Methyl 4-(diethoxyphosphoryl)-2-methylbut-2-enoate, 104



104



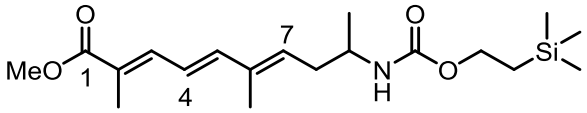
104'

A mixture of allyl bromide **251** (5.79 g, 30.0 mmol, 1.0 eq.) and triethyl phosphite (5.6 mL, 31.5 mmol, 1.05 eq.) were stirred at 120 °C overnight. Next, the reaction was cooled to RT and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (2%)) to give inseparable mixture of phosphonates **104** and **104'** (6.76 g, 27.0 mmol, 90%) in a 2.6:1 ratio;

R_f 0.21 (CH_2Cl_2 / MeOH (2%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.80-6.70 (1H, m, *H*3), 4.16-4.00 (4H, m, P(O)O(CH_2CH$_3$)$_2$), 3.74 (3H, s, CO_2CH_3), 2.73 (2H, ddd, *J* = 23.5, 8.5 and 0.5 Hz, *H*4), 1.93-1.84 (3H, m, C2CH_3), 1.31 (6H, t, *J* = 7.0 Hz, P(O)(OCH$_2$CH_3)$_2$).

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

(2*E*,4*E*,6*E*)-Methyl 2,6–dimethyl-9-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)deca-2,4,6-trienoate, 415

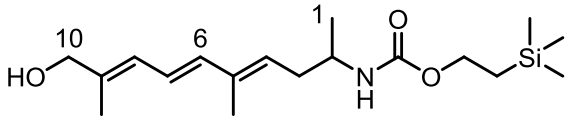


To neat 2.2.6.6-tetramethylpiperidine (TMP) (0.90 mL, 5.30 mmol, 2.3 eq.) was added a solution of *n*-BuLi (2.1 mL, 2.5 M in hexanes, 5.3 mmol, 2.3 eq.) dropwise *via* syringe, at 0 °C. The resulting mixture was stirred for 30 min before cooling to −30 °C followed by addition of a solution of phosphonate **104** (1.91 g, 70% purity by weight, 5.30 mmol, 2.3 eq.) in THF (13 mL) *via* syringe. After stirring for 30 min, a solution of aldehyde **103** (624 mg, 2.30 mmol, 1.0 eq.) in THF (5 mL) was added *via* syringe and the resulting mixture stirred at RT overnight. The reaction mixture was concentrated *in vacuo* and the crude residue purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **415** (797 mg, 2.17 mmol, 94%) as a bright yellow oil;

R*f* 0.52 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3340, 2952, 1706, 1528, 1249; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.63 (1H, dd, *J* = 10.5 and 1.0 Hz, *H*3), 6.42-6.28 (2H, m, *H*4 and *H*5), 5.41 (1H, t, *J* = 7.0 Hz, *H*7), 4.34-4.27 (2H, m, OC*H*$_2$CH$_2$Si), 4.12 (1H, d, *J* = 8.0 Hz, N*H*), 3.91-3.78 (1H, m, *H*9), 3.49 (3H, s, CO$_2$C*H*$_3$), 2.16-1.92 (2H, m, *H*8), 2.00 (3H, d, *J* = 1.0 Hz, C2C*H*$_3$), 1.57 (3H, s, C6C*H*$_3$), 1.03-0.97 (2H, m, OCH$_2$C*H*$_2$Si), 0.83 (3H, d, *J* = 7.0 Hz, C9C*H*$_3$), −0.06 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 168.4, 155.9, 144.3, 139.2, 136.3, 132.9,

126.5, 122.3, 62.8, 51.4, 47.1, 35.9, 20.5, 18.1, 12.9, 12.4, −1.6; **HRMS** (ESI+) calc. for $C_{19}H_{33}NO_4SiNa$ $[M+Na]^+$ 390.2071, found 390.2066.

2-(Trimethylsilyl)ethyl ((4*E*,6*E*,8*E*)-10-hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl)carbamate, 105

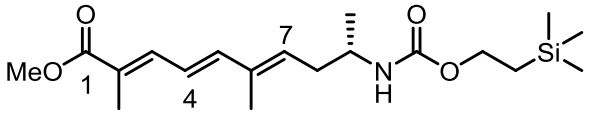


To a stirred solution of trienoate **415** (780 mg, 2.12 mmol, 1.0 eq.) in CH_2Cl_2 (5.3 mL) was added a solution of DIBALH (6.40 mL, 1.0 M solution in hexanes, 6.40 mmol, 3.0 eq.) dropwise *via* syringe, at −78 °C. After stirring at −78 °C for 1 h, the reaction was allowed to warm up to −50 °C then quenched with a saturated aqueous solution of Rochelle's salt (5 mL), diluted with Et_2O (5 mL) and the reaction allowed to reach RT. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (20%) → petroleum ether / EtOAc (30%)) to give title compound **105** (516 mg, 1.52 mmol, 72%) as a clear oil;

R_f 0.25 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3328, 2953, 1690, 1531, 1250, 1063; **^{1}H NMR** (500 MHz C_6D_6) δ_H 6.48 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*7), 6.31 (1H, d, *J* = 15.5 Hz, *H*6), 6.17 (1H, d, *J* = 11.0 Hz, *H*8), 5.44 (1H, t, *J* = 7.0 Hz, *H*4), 4.43-4.36 (2H, m, OCH_2CH_2Si), 4.19 (1H, bd, *J* = 8.0 Hz, N*H*), 3.94-3.85 (1H, m, *H*2), 3.83 (2H, d, *J* = 5.5 Hz, *H*10), 2.22-2.11 (1H, m, *H*3), 2.11-2.01 (1H, m, *H*3'), 1.72 (3H, s, C5CH_3), 1.66 (3H, s, C9CH_3), 1.12-1.06 (2H, m, OCH_2CH_2Si), 0.92 (1H, t, *J* = 5.5 Hz, O*H*), 0.88 (3H, d, *J* = 7.0 Hz, C1H_3) −0.06 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 157.6, 139.0, 138.8, 138.1, 129.9, 127.0,

124.6, 69.9, 64.2, 48.8, 37.3, 22.0, 19.7, 15.7, 14.2, 0.0; **HRMS** (ESI+) calc. for $C_{18}H_{33}NO_3SiNa$ $[M+Na]^+$ 362.2122, found 362.2109.

(*S*,2*E*,4*E*,6*E*)-Methyl 2,6-dimethyl-9-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)deca-2,4,6-trienoate, 249

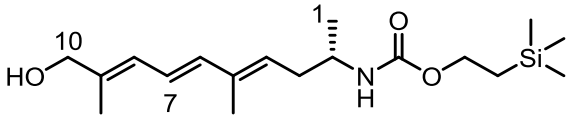


To neat 2.2.6.6-tetramethylpiperidine (TMP) (1.24 mL, 7.27 mmol, 2.3 eq.) was added a solution of *n*-BuLi (2.90 mL, 2.5 M in hexanes, 7.27 mmol, 2.3 eq.) dropwise *via* syringe, at 0 °C. The resulting mixture was stirred for 30 min before cooling to −30 °C followed by addition of a solution of phosphonate **104** (2.60 g, 70% purity by weight, 7.27 mmol, 2.3 eq.) in THF (20 mL) *via* syringe. After stirring for 30 min a solution of aldehyde **218** (860 mg, 3.16 mmol, 1.0 eq.) in THF (4 mL) was added *via* syringe and the resulting mixture stirred at RT overnight. The reaction mixture was concentrated *in vacuo* and the resulting crude residue purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **249** (1.16 g, 3.15 mmol, 99%) as a bright yellow oil;

$[\alpha]_D^{25}$ −33 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.52 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3340, 2952, 1706, 1528, 1249; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.63 (1H, dd, *J* = 10.5 and 1.0 Hz, *H*3), 6.42-6.28 (2H, m, *H*4 and *H*5), 5.41 (1H, t, *J* = 7.0 Hz, *H*7), 4.34-4.27 (2H, m, OCH_2CH_2Si), 4.12 (1H, bd, *J* = 8.0 Hz, N*H*), 3.91-3.78 (1H, m, *H*9), 3.49 (3H, s, CO_2CH_3), 2.16-1.92 (2H, m, *H*8), 2.00 (3H, d, *J* = 1.0 Hz, C2CH_3), 1.57 (3H, s, C6CH_3), 1.03-0.97 (2H, m, OCH_2CH_2Si), 0.83 (3H, d, *J* = 7.0 Hz, *H*9), −0.06 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 168.4, 155.9, 144.3, 139.2, 136.3,

132.9, 126.5, 122.3, 62.8, 51.4, 47.1, 35.9, 20.5, 18.1, 12.9, 12.4, −1.6; **HRMS** (ESI+) calc. for $C_{19}H_{33}O_4NNaSi$ $[M+Na]^+$ 390.2071, found 390.2072.

2-(Trimethylsilyl)ethyl ((*S*,4E,6*E*,8*E*)-10-hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl)carbamate, 252

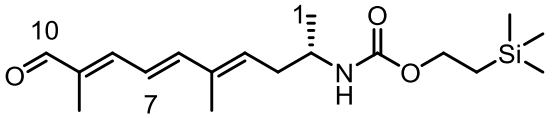


To a stirred solution of trienoate **249** (538 mg, 1.42 mmol, 1.0 eq.) in CH_2Cl_2 (3.7 mL) was added a solution of DIBALH (4.38 mL, 1.0 M solution in hexanes, 8.76 mmol, 3.0 eq.) dropwise *via* syringe, at −78 °C. After stirring at −78 °C for 1 h, the reaction was allowed to warm up to −50 °C then quenched with a saturated aqueous solution of Rochelle's salt (10 mL), diluted with Et_2O (10 mL) and the reaction allowed to reach RT. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the crude product purified *via* column chromatography (petroleum ether / EtOAc (20%) → petroleum ether / EtOAc (30%)) to give title compound **252** (402 mg, 1.80 mmol, 83%) as a clear oil;

$[\alpha]_D^{25}$ −29 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.25 (petroleum ether / EtOAc (30%)); **IR (**thin film, ν_{max} / cm^{-1}) 3328, 2953, 1690, 1531, 1250, 1063; **^{1}H NMR** (500 MHz C_6D_6) δ_H 6.48 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*7), 6.31 (1H, d, *J* = 15.5 Hz, *H*6), 6.17 (1H, d, *J* = 11.0 Hz, *H*8), 5.44 (1H, t, *J* = 7.0 Hz, *H*4), 4.43-4.36 (2H, m, OCH_2CH_2Si), 4.19 (1H, bd, *J* = 8.0 Hz, N*H*), 3.94-3.85 (1H, m, *H*2), 3.83 (2H, d, *J* = 5.5 Hz, *H*10), 2.22-2.11 (1H, m, *H*3), 2.11-2.01 (1H, m, *H*3'), 1.72 (3H, s, C5CH_3), 1.66 (3H, s, C9CH_3), 1.12-1.06 (2H, t, *J* = 8.5 Hz, OCH_2CH_2Si), 0.92 (1H, t, *J* = 5.5 Hz, O*H*), 0.88 (3H, d, *J* = 7.0 Hz, *H*1), −0.06 (9H, s, $Si(CH_3)_3$)**;** **^{13}C NMR** (125 MHz, C_6D_6) δ_C 157.6, 139.0, 138.8, 138.1,

129.9, 127.0, 124.6, 69.9, 64.2, 48.8, 37.3, 22.0, 19.7, 15.7, 14.2, 0.0; **HRMS** (ESI+) calc. for $C_{18}H_{33}O_3NNaSi$ $[M+Na]^+$ 362.2122, found 362.2121.

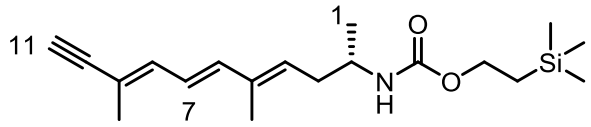
2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*)-5,9-dimethyl-10-oxodeca-4,6,8-trien-2-yl)carbamate, 253



A solution of **252** (432 mg, 1.18 mmol, 1.0 eq.) in CH_2Cl_2 (13 mL) was added to a round-bottom flask containing tetrapropylammonium perruthenate (TPAP) (223 mg, 0.63 mmol, 0.05 eq.), 4-methylmorpholine *N*-oxide (NMO) (597 mg, 5.09 mmol, 4.0 eq.) and 3Å molecular sieves (130 mg, 30% w/w). After stirring in the dark for 5 h, the reaction mixture was concentrated *in vacuo* and the crude residue purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **253** (333 mg, 0.99 mmol, 84%) as a bright yellow oil;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −38 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.26 (petroleum ether / EtOAc (20%)); **IR (**thin film, ν_{max} / cm^{-1}) 3327, 2953, 1671, 1607, 1250; **^{1}H NMR** (400 MHz C_6D_6) δ_H 9.43 (1H, s, *H*10), 6.46 (1H, d, *J* = 10.0 Hz, *H*8), 6.40-6.25 (2H, m, *H*7 and *H*6), 5.56 (1H, t, *J* = 7.5 Hz, *H*4), 4.36-4.27 (2H, m, OCH_2CH_2Si), 4.22 (1H, bs, N*H*), 3.96-3.75 (1H, m, *H*2), 2.19-2.08 (1H, m, *H*3), 2.08-1.98 (1H, m, *H*3'), 1.80 (3H, s, C9CH_3), 1.57 (3H, s, C5CH_3), 1.04-0.96 (2H, m, OCH_2CH_2Si), 0.86 (3H, d, *J* = 6.5 Hz, *H*1) −0.06 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 195.2, 157.8, 150.0, 147.3, 139.2, 138.0, 136.3, 123.6, 64.6, 48.9, 38.0, 22.4, 19.9, 14.1, 11.4, −0.2; **HRMS** (ESI+) calc. for $C_{18}H_{31}O_3NNaSi$ $[M+Na]^+$ 360.1965, found 360.1970.

2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*)-5,9-dimethylundeca-4,6,8-trien-10-yn-2-yl)carbamate, 254

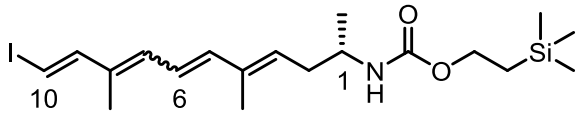


To a solution of LiHMDS (0.28 mL, 1 M in THF, 0.28 mmol, 2.0 eq.) in THF (1.4 mL) was added a solution of (trimethylsilyl)diazomethane (**239**) (0.15 mL, 2 M in Et_2O, 0.30 mmol, 2.0 eq.) dropwise *via* syringe, at −78 °C. After stirring for 1 h, a solution of trienal **253** (48 mg, 0.14 mmol, 1.0 eq.) in THF (0.7 mL) was added *via* syringe. After stirring for 2.5 h, the cooling bath was removed and the reaction mixture allowed to reach RT followed by additional stirring for 1.5 h. Subsequently, the reaction was diluted with Et_2O (5 mL) and quenched with a saturated aqueous solution of NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (15%)) to give title compound **254** (14 mg, 0.042 mmol, 30%) as a yellow oil;

$[\alpha]_D^{25}$ −37 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.12 (petroleum ether / EtOAc (15%)); **IR (**thin film, ν_{max} / cm^{-1}) 2954, 1694, 1530, 1250, 1096, 860; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.66 (1H, d, *J* = 10.0 Hz, *H*8), 6.31 (1H, dd, *J* = 15.5 and 11.5 Hz, *H*7), 6.14 (1H, d, *J* = 15.5 Hz, *H*6), 5.36 (1H, t, *J* = 7.5 Hz, *H*4), 4.33-4.25 (2H, m, OCH_2CH$_2$Si), 4.15 (1H, bs, N*H*), 3.91-3.78 (1H, m, *H*2), 2.78 (1H, s, *H*11), 2.18-2.06 (1H, m, *H*3), 2.06-1.96 (1H, m, *H*3'), 1.81 (3H, s, C9CH_3), 1.54 (3H, s, C5CH_3), 1.04-0.96 (2H, m, OCH$_2$CH_2Si), 0.84 (3H, d, *J* = 7.0 Hz, *H*1) −0.06 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 157.7, 141.6, 139.8, 138.1, 132.7, 124.1, 118.9, 89.7, 79.3, 64.5, 48.9, 37.6, 22.2, 19.9, 19.2,

14.2, −0.2; **HRMS** (ESI+) calc. for $C_{19}H_{31}O_2NNaSi$ $[M+Na]^+$ 356.2016, found 356.2017.

2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*,10*E*)-11-Iodo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 89



Takai olefination: Chromium(II) chloride (309 mg, 2.51 mmol, 8.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The tube was allowed to reach RT, filled with nitrogen and THF (4 mL) was added. The resulting grey suspension was stirred for 10 min after which a solution of iodoform (248 mg, 0.63 mmol, 2.0 eq.) in THF (2 mL) was added *via* syringe and the resulting dark red suspension stirred for 20 min. Next, the mixture was cooled to 0 °C followed by a dropwise addition of a solution of **253** (106 mg, 0.31 mmol, 1.0 eq.) in THF (2 mL) *via* syringe. After stirring at RT for 15 min, the reaction mixture was diluted with Et_2O (10 mL) and washed with brine (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (10%) → petroleum ether / Et_2O (20%)) to give title compound **89** (101 mg, 0.23 mmol, 74%) as a 2.5:1 mixture of isomers (*E*6:*Z*6);

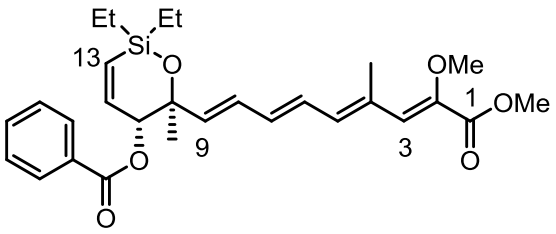
Schwartz hydrozirconation/iodination: To a stirred suspension of bis(cyclopentadienyl)zirconium(IV) chloride hydride (Schwartz's reagent) (57 mg, 0.22 mmol, 2.0 eq.) in CH_2Cl_2 (1 mL) was added a solution of alkyne **254** (36 mg, 0.108 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) dropwise *via* syringe, at 0 °C. The resulting mixture was stirred for 2 h, until a clear homogeneous solution was formed, after which

it was cooled to −78 °C followed by addition of a solution of iodine (69 mg, 0.27 mmol, 2.5 eq.) in CH_2Cl_2 (1 mL). Subsequently the cooling bath was removed and the reaction mixture allowed to reach RT. The reaction was diluted with Et_2O (5 mL) and quenched with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL), the organic layer separated and the aqueous layer was further extracted with E_2O (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (10%) → petroleum ether / Et_2O (20%)) to give title compound **89** (16 mg, 0.037 mmol, 34%) as a 2.5:1 mixture of isomers (*E*6:*Z*6);

$[\alpha]_D^{25}$ −11 (*c* 1.0, $CHCl_3$); **IR (**thin film, ν_{max} / cm^{-1}) 2954, 1695, 1530, 1250, 837; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.06 (1H, d, *J* = 14.5 Hz, *H*9), 6.36 (1H, dd, *J* = 15.5 and 11.0, Hz, *H*6), 6.26 (1H, d, *J* = 15.5 Hz, *H*5), 6.00 (1H, d, *J* = 14.5 Hz, *H*10), 5.91 (1H, d, *J* = 11.0 Hz, *H*7), 5.46 (1H, t, *J* = 7.5 Hz, *H*3), 4.33-4.25 (2H, m, OCH_2CH_2Si), 4.19 (1H, bs, N*H*), 3.93-3.77 (1H, m, *H*1), 2.20-2.09 (1H, m, *H*2), 2.09-1.99 (1H, m, *H*2'), 1.65 (3H, s, C4CH_3), 1.50 (3H, s, C8CH_3), 1.03-0.96 (2H, m, OCH_2CH_2Si), 0.89 (3H, d, *J* = 7.0 Hz, C1CH_3) −0.06 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 157.7, 151.5, 141.9, 138.4, 136.5, 135.0, 132.1, 124.5, 76.7, 65.5, 48.9, 37.7, 22.3, 19.9, 14.3, 13.7, 0.2; **HRMS** (ESI+) calc. for $C_{19}H_{32}O_2NINaSi$ $[M+Na]^+$ 484.1139, found 484.1139.

6.9 C1-C13 Cyclic diethyl siloxane and beyond

(5*R*,6*S*)-6-((1*E*,3*E*,5*E*,7*Z*)-8,9-Dimethoxy-6-methyl-9-oxonona-1,3,5,7-tetraen-1-yl)-2,2-diethyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 112



Suzuki cross-coupling: To a mixture of dienoate **88** (50 mg, 0.18 mmol, 1.0 eq.), siloxane **87** (92 mg, 0.20 mmol, 1.1 eq.) and Tl_2CO_3 (169 mg, 0.360 mmol, 2.0 eq.) in THF (1.4 mL) and water (0.35 mL) was added Pd(dppf)Cl_2 (15 mg, 0.018 mmol, 10 mol%). The biphasic mixture was stirred in the dark at RT over 5 h. The reaction mixture was diluted with Et_2O and filtered through Celite, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification *via* column chromatography (petroleum ether / Et_2O (5%) → petroleum ether / Et_2O (15%) + 1% Et_3N) gave the title compound **112** (56 mg, 0.11 mmol, 63%) as a yellow oil;

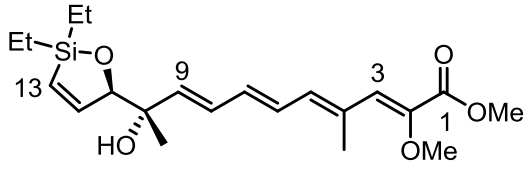
HWE olefination: To a solution of phosphonate **372** (54 mg, 0.16 mmol, 2.5 eq.) in THF (5.5 mL) was added a solution of LiHMDS (0.18 mL, 0.86 M in THF, 0.15 mmol, 2.3 eq.) dropwise *via* syringe, at −78 °C. The resulting deep red solution was stirred for 15 min followed by addition of a solution of aldehyde **199** (21 mg, 0.066 mmol, 1.0 eq.) in THF (1.0 mL) dropwise *via* syringe. Subsequently, the cooling bath was removed and the resulting mixture allowed to reach RT. After stirring at RT for 1 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which

was purified *via* column chromatography (petroleum ether / Et_2O (15%)) to give the title compound **112** (13 mg, 0.026 mmol, 39%) as a yellow oil;

R_f 0.23 (petroleum ether / Et_2O (20%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 8.20 (2H, d, *J* = 7.0 Hz, Ar*H*), 7.15-7.04 (3H, m, Ar*H*), 6.81 (1H, s, *H*3), 6.73 (1H, dd, *J* = 14.5 and 3.0 Hz, *H*12), 6.64 (1H, dd, *J* = 15.0 and 11.0 Hz, *H*8), 6.45 (1H, dd, *J* = 14.5 and 11.5 Hz, *H*6), 6.23 (1H, d, *J* = 11.5 Hz, *H*5), 6.11 (1H, dd, *J* = 14.5 and 11.5 Hz, *H*7), 5.97 (1H, d, *J* = 15.0 Hz, *H*9), 5.87 (1H, d, *J* = 14.5 Hz, *H*13), 5.82 (1H, s, *H*11), 3.49 (3H, s, C2OCH_3), 3.40 (3H, s, CO_2CH_3), 2.00 (3H, s, C4CH_3), 1.57 (3H, s, C10CH_3), 1.03 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 1.01 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.74-0.52 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 165.2, 164.4, 147.2, 144.5, 139.7, 136.1, 135.3, 133.0, 132.8, 130.4, 129.4, 129.5, 128.9 (2), 128.4, 128.4, 76.1, 75.0, 59.5, 51.0, 23.6, 14.8, 7.1, 6.6, 6.5, 6.4.

The physical and spectroscopic data was found to be in agreement with that reported by Lim. [64]

Methyl (*S*,2*Z*,4*E*,6*E*,8*E*)-10-((*R*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-10-hydroxy-2-methoxy-4-methylundeca-2,4,6,8-tetraenoate, 225



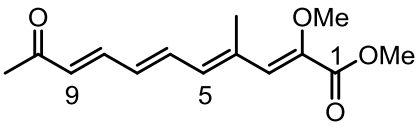
To a stirred solution of **112** (10 mg, 0.021 mmol, 1.0 eq.) in MeOH (0.21 mL) was added K_2CO_3 (4 mg, 0.027 mmol, 1.3 eq.). After stirring vigorously for 3 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (3 mL), extracted with Et_2O (3 × 3 mL), the combined organic layers dried over anhydrous Na_2SO_4,

filtered and concentrated *in vacuo* to give title compound **225** and methyl benzoate (8 mg, 0.018 mmol, 88% purity by weight, 85%) as a yellow oil;

R_f 0.33 (petroleum ether / Et_2O (40%)); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.84 (1H, s, *H*3), 6.75 (1H, d, *J* = 10.5 Hz, *H*12), 6.57 (1H, dd, *J* = 15.0 and 11.0 Hz, *H*8), 6.49 (1H, dd, *J* = 14.5 and 11.5 Hz, *H*6), 6.29 (1H, d, *J* = 11.5 Hz, *H*5), 6.23 (1H, dd, *J* = 14.5 and 11.5 Hz, *H*7), 5.96 (1H, d, *J* = 14.5 Hz, *H*13), 5.73 (1H, d, *J* = 15.0 Hz, *H*9), 5.55 (1H, s, *H*11), 3.50 (3H, s, C2OCH_3), 3.49 (3H, s, CO_2CH_3), 2.37 (1H, bs, O*H*), 2.06 (3H, s, C4CH_3), 1.32 (3H, s, C10CH_3), 0.94 (6H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_2$), 0.74-0.48 (4H, m, $Si(CH_2CH_3)_2$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 164.5, 150.3, 144.5, 139.0, 136.2, 135.3, 133.0, 129.6, 129.5, 128.5, 128.4, 90.0, 74.7, 59.6, 51.0, 29.8, 14.8, 7.2, 6.8, 6.6, 6.3.

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

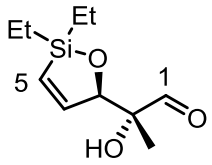
Methyl (2Z,4E,6E,8E)-2-methoxy-4-methyl-10-oxoundeca-2,4,6,8-tetraenoate, 256



To an oven-dried vial containing siloxane **225** (8 mg, 0.018 mmol, 1.0 eq.), iodostyrene (**220**) (4.8 mg, 0.021 mmol, 1.2 eq.) and $[PdCl(allyl)]_2$ (0.2 mg, 0.5 μmol, 2.5 mol%) was added TBAF•$3H_2O$ (63 μL, 1 M in THF, 0.063 mmol, 3.5 eq.). After stirring at RT overnight, the crude product mixture was purified *via* column chromatography (petroleum ether / Et_2O (10%) → petroleum ether / Et_2O (20%) + 1% Et_3N) to give tetraenoate **256** (4.3 mg, 0.017 mmol, 95%);

R_f 0.28 (petroleum ether / Et_2O (20%)); **IR (**thin film, ν_{max} / cm^{-1}) 2955, 1715, 1665, 1257, 1002; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.98 (1H, dd, *J* = 15.5 and 11.5 Hz, *H*8), 6.75 (1H, s, *H*3), 6.53 (1H, dd, *J* = 12.0 and 14.5 Hz, *H*6), 6.16 (1H, d, *J* = 12.0 Hz, *H*5), 6.05-5.94 (2H, m, *H*7 and *H*9), 3.50 (3H, s, OCH_3), 3.40 (3H, s, CO_2CH_3), 2.00 (3H, s, C4CH_3), 1.91 (3H, s, *H*11); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C [Material proved insufficient to obtain a qualitative ^{13}C spectrum]; **HRMS** (ESI+) calc. for $C_{14}H_{18}O_4Na$ $[M+Na]^+$ 273.1097, found 273.1098.

(*R*)-2-((*R*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-2-hydroxypropanal, 260

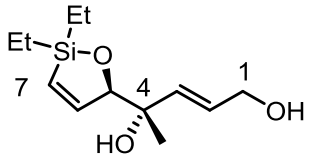


To a vial containing SO_3·pyridine complex (62 mg, 0.39 mmol, 3.1 eq.) was added DMSO (0.21 mL, 1.31 mmol, 10.5 eq.) and the resulting mixture stirred for 15 min at RT. Subsequently, siloxane **115** (27 mg, 0.13 mmol, 1.0 eq.) and *N*,*N*-diisopropylethylamine (DIPEA) (0.12 mL, 0.65 mmol, 5.2 eq.) dissolved in CH_2Cl_2 (0.65 mL) was added. After stirring for 1 h, the resulting mixture was diluted with Et_2O (5 mL) and quenched with a 1 M aqueous HCl solution (5 mL). After stirring for 15 min, the organic layer was separated and the aqueous layer was further extracted with Et_2O (2 × 5 mL), the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), then brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (40%)) to give title compound **260** (16 mg, 0.075 mmol, 60%);

R_f 0.65 (petroleum ether / EtOAc (40%)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.69 (1H, s, *H*1), 6.98 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*4), 6.25 (1H, dd, *J* = 10.5 and 2.5 Hz, *H*5), 4.62 (1H, dd, *J* = 2.5 and 1.5 Hz, *H*3), 1.28 (3H, s, C2C*H*$_3$), 1.03-0.83 (6H, m, *J* = 8.0 Hz, Si(CH_2CH_3)$_2$), 0.74-0.54 (4H, m, Si(CH_2CH_3)$_2$).

The physical and spectroscopic data was found to be in agreement with that reported by Lim.[64]

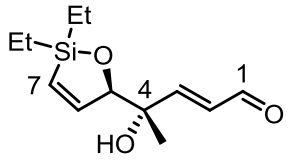
(*S*,*E*)-4-((*R*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)pent-2-ene-1,4-diol, 264



A solution of siloxane **199** (114 mg, 0.36 mmol, 1.0 eq.) and phosphorane **98** (120 mg, 0.39 mmol, 1.1 eq.) in toluene (3.6 mL) was stirred overnight at 80 °C. The resulting mixture was concentrated *in vacuo* and the crude product redissolved in MeOH (1.8 mL) and $NaBH_4$ (14 mg, 0.36 mmol, 1.0 eq.) added. After stirring vigorously for 1h, the reaction was quenched with water (5 mL), extracted with Et_2O (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was redissolved in MeOH (3.6 mL) and K_2CO_3 (65 mg, 0.47 mmol, 1.3 eq.) added. After stirring vigorously for 3 h, the reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL), extracted with Et_2O (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification *via* column chromatography (petroleum ether / EtOAc (40%) → petroleum ether / EtOAc (50%)) afforded title compound **264** (52 mg, 0.21 mmol, 60% over three steps) as a yellow oil;

$[\alpha]_D^{25}$ +52 (*c* 1.1, $CHCl_3$); $\mathbf{R}_f$ 0.13 (petroleum ether / EtOAc (40%)); **IR** (thin film, ν_{max} / cm^{-1}) 3368, 2956, 1030, 802, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.90 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*6), 6.15 (1H, dd, *J* = 10.5 and 2.5 Hz, *H*7), 5.91 (1H, dd, *J* = 15.5 and 5.5 Hz, *H*2), 5.70 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*3), 4.56 (1H, dd, *J* = 2.5 and 1.5 Hz, *H*5), 4.16-4.13 (1H, m, *H*1), 1.95 (2H, bs, O*H*), 1.32 (3H, s, C4CH_3), 0.96 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.89 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.78-0.57 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.6, 134.4, 128.6, 128.2, 89.8, 74.4, 63.2, 24.4, 7.2, 6.8, 6.7, 6.4; **HRMS** (ESI+) calc. for $C_{12}H_{22}O_3SiNa$ $[M+Na]^+$ 265.1225, found 265.1230.

(*S*,*E*)-4-((*R*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-4-hydroxypent-2-enal, 263

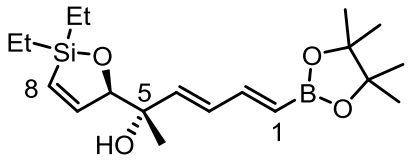


A solution of siloxane **264** (11.5 mg, 0.047 mmol, 1.0 eq.) in CH_2Cl_2 (0.25 mL) was added to a dry vial containing DMP (24 mg, 0.057 mmol, 1.2 eq.) at 0 °C. After stirring at RT overnight, the resulting mixture was diluted with Et_2O (5 mL) and washed sequentially with saturated aqueous $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL) solutions. The aqueous layer was further extracted with Et_2O (2 × 10 mL), the combined organic layer dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give aldehyde **263** (10 mg, 0.042 mmol, 88%), which was used without further purification;

$\mathbf{R}_f$ 0.23 (petroleum ether / Et_2O (40%)); **IR** (thin film, ν_{max} / cm^{-1}) 3451, 2957, 1688, 1033, 816; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.54 (1H, d, *J* = 8.0 Hz, *H*1), 6.92 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*6), 6.76 (1H, d, *J* = 15.5 Hz, *H*3), 6.38 (1H, dd, *J* = 15.5 and 8.0 Hz, *H*2), 6.24 (1H, dd, *J* = 10.5 and 2.5 Hz, *H*7), 4.65 (1H, dd, *J* = 2.5 and 1.5 Hz,

*H*5), 1.40 (3H, s, C*H*$_3$), 0.92 (3H, t, *J* = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.90 (3H, t, *J* = 8.0 Hz, SiCH$_2$C*H*$_3$'), 0.78-0.59 (4H, m, SiC*H*$_2$CH$_3$ and SiC*H*$_2$'CH$_3$); **HRMS** (ESI+) calc. for $C_{12}H_{20}O_3SiNa$ $[M+Na]^+$ 263.1071, found 263.1074.

(*S*,3*E*,5*E*)-2-((*R*)-2,2-Diethyl-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, 259

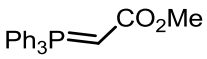


A solution of aldehyde **260** (18 mg, 0.083 mmol, 1.0 eq.) and phosphorane **98** (28 mg, 0.092 mmol, 1.1 eq.) in toluene (1 mL) was stirred overnight at 80 °C. The resulting mixture was concentrated *in vacuo* and the crude product redissolved in THF (0.5 mL) followed by addition of boronate **200** (35 mg, 0.17 mmol, 2.0 eq.). The resulting solution was then added, *via* syringe, to a stirred suspension of dry chromium(II) chloride (82 mg, 0.67 mmol, 8.0 eq.) in THF (0.7 mL) at 50 °C, followed by a solution of LiI (45 mg, 0.34 mmol, 4.0 eq.) in THF (0.5 mL). After stirring at overnight at 50 °C and under nitrogen atmosphere, the resulting mixture was diluted with Et_2O (5 mL), washed with water (2 × 5 mL), then brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (20%) → petroleum ether / Et_2O (30%)) to give title compound **259** (5 mg, 0.014 mmol, 16% over two steps) as a yellow oil;

$[\alpha]_D^{25}$ +14 (*c* 0.5, $CHCl_3$); $\mathbf{R}_f$ 0.30 (petroleum ether / Et_2O (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 2922, 1595, 1345, 1165, 732; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.97 (1H, dd, *J* = 17.5 and 10.5 Hz, *H*3), 6.87 (1H, dd, *J* = 10.5 and 1.0 Hz, *H*7), 6.38 (1H, dd, *J* = 15.0 and 10.5 Hz, *H*2), 6.14 (1H, dd, *J* = 10.5 and 2.5 Hz, *H*8), 5.84 (1H, d,

J = 15.0 Hz, *H*1), 5.54 (1H, dd, *J* = 17.5 Hz, *H*4), 5.56 (1H, dd, *J* = 2.5 and 1.0 Hz, *H*6), 1.34 (3H, s, C5CH_3), 1.27 (12H, s, Bpin*H*), 0.95 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.90 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.78-0.56 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C [Material proved insufficient to obtain a qualitative ^{13}C spectrum]; **HRMS** (ESI+) calc. for $C_{19}H_{33}O_4BSiNa$ $[M+Na]^+$ 387.2133, found 387.2129.

Methyl 2-(triphenylphosphoranylidene)acetate, 266

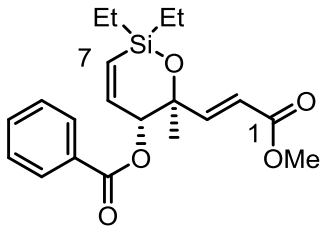


To a stirred solution of (methoxycarbonyl)triphenylphosphonium bromide (5.0 g, 12.0 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) was added an aqueous solution of NaOH (25 mL, 1 M, 24.0 mmol, 2.0 eq.). After stirring vigorously for 30 min, the organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give phosphorane **266** (4.0 g, 12.0 mmol, quant.) as a colourless solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80-7.39 (15H, m, Ar*H*), 3.57 (2.3H, bs, CO_2CH_{3A}), 3.12 (0.8H, bs, PCH_A), 2.94 (0.7H, bs, CO_2CH_{3B}), 2.74 (0.2H, bs, PCH_B). Rotameric mixture

The physical and spectroscopic data was found to be in agreement with that reported by Lugtenburg *et al*.[189]

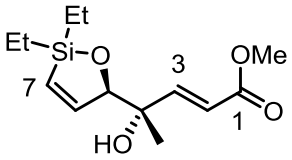
(5*R*,6*S*)-2,2-Diethyl-6-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 267



A solution of siloxane **199** (17 mg, 0.054 mmol, 1.0 eq.) and phosphorane **266** (20 mg, 0.059 mmol, 1.1 eq.) in toluene (0.54 mL) was stirred overnight at 80 °C. The resulting mixture was concentrated *in vacuo* and the residue purified *via* column chromatography (petroleum ether / Et_2O (10%)) to give title compound **267** (10 mg, 0.027 mmol, 49%) as a yellow oil;

$[\alpha]_D^{25}$ −117 (*c* 0.9, $CHCl_3$); $\mathbf{R}_f$ 0.12 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 1724, 1263, 1109, 711; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.11-7.44 (5H, m, Ar*H*), 7.02 (1H, d, *J* = 15.5 Hz, *H*2), 6.63 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*6), 6.17 (1H, d, *J* = 15.5, *H*3), 6.08 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*7), 5.45 (1H, dd, *J* = 2.5 and 2.0 Hz, *H*5), 3.71 (3H, s, CO_2CH_3), 1.50 (3H, s, C4C*H*$_3$), 1.01 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 1.00 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.77-0.59 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.1, 165.6, 151.7, 146.6, 133.4, 129.8, 129.7, 128.5, 128.4, 119.8, 75.7, 74.5, 51.6, 22.7, 7.1, 6.6, 6.5, 6.4; **HRMS** (ESI+) calc. for $C_{20}H_{26}O_5SiNa$ $[M+Na]^+$ 397.1442, found 397.1431.

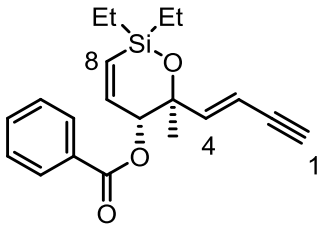
Methyl (*S*,*E*)-4-((*R*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-4-hydroxypent-2-enoate, 262



To a stirred solution of **267** (10 mg, 0.027 mmol, 1.0 eq.) in MeOH (0.3 mL) was added K_2CO_3 (5 mg, 0.035 mmol, 1.3 eq.). After stirring vigorously overnight, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (3 mL), extracted with Et_2O (3 × 3 mL), the combined organic layer dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (20%)) to give title comound **262** (5 mg, 0.018 mmol, 68%);

$[\alpha]_D^{20}$ 132 (*c* 1.0, $CHCl_3$); R_f 0.36 (petroleum ether / Et_2O (40%)); **IR** (thin film, ν_{max} / cm^{-1}) 3467, 2956, 1725, 1272, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.89 (1H, d, *J* = 15.5 Hz, *H*3), 6.88 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*6), 6.19 (1H, dd, *J* = 10.5 and 2.5 Hz, *H*7), 6.12 (1H, d, *J* = 15.5 Hz, *H*2), 4.59 (1H, dd, *J* = 2.5 and 1.5 Hz, *H*5), 3.71 (3H, s, CO_2CH_3), 2.67 (1H, s, O*H*), 1.35 (3H, s, C4CH_3), 0.92 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.89 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.77-0.55 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.8, 151.1, 148.6, 129.1, 120.5, 89.4, 75.0, 51.5, 23.7, 7.0, 6.7, 6.6, 6.3; **HRMS** (ESI+) calc. for $C_{13}H_{22}O_4KSi$ $[M+K]^+$ 309.0919, found 309.0916.

(5*R*,6*S*)-6-((*E*)-But-1-en-3-yn-1-yl)-2,2-diethyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate, 268

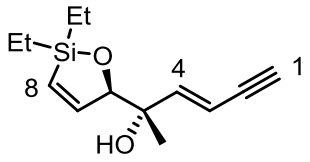


To a solution of LiHMDS (148 μL, 1 M in THF, 0.148 mmol, 1.0 eq.) in THF (0.8 mL) was added a solution of (trimethylsilyl)diazomethane (**239**) (82 μL, 2 M in Et_2O, 0.163 mmol, 1.1 eq.) dropwise *via* syringe, at −78 °C. After stirring for 1 h at −78 °C, a solution of aldehyde **99** (51 mg, 0.148 mmol, 1.0 eq.) in THF (0.7 mL) was added *via* syringe. After stirring for 5 h, the cooling bath was removed and the reaction mixture allowed to reach RT followed by additional stirring for 1.5 h. Subsequently, the reaction was diluted with Et_2O (5 mL) and quenched with a saturated aqueous NH_4Cl solution (5 mL), the organic layer was separated followed by further extraction of the aqueous layer with Et_2O (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give the crude product which was purified *via* filtration through a short plug of silica (petroleum ether / Et_2O (1%)) to give title compound **268** (21 mg, 0.062 mmol, 42%) as a brown oil;

$[\alpha]_D^{20}$ −123 (*c* 0.7, $CHCl_3$); $\mathbf{R}_f$ 0.47 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3297, 2958, 2361, 1723, 1267; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.09-7.43 (5H, m, Ar*H*), 6.63 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*7), 6.37 (1H, d, *J* = 16.0 Hz, *H*4), 6.07 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*8), 5.87 (1H, dd, *J* = 16.0 and 2.5 Hz, *H*3), 5.43 (1H, dd, *J* = 2.5 and 2.0 Hz, *H*6), 2.86 (1H, d, *J* = 2.5 Hz, *H*1), 1.46 (3H, s, C5CH_3), 1.01 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 1.00 (3H, t, *J* = 8.0 Hz, $SiCH_2CH_3$'), 0.77-0.58 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.5, 149.1, 146.8,

133.3, 129.9, 129.7, 128.5, 128.3, 108.1, 81.9, 78.2, 75.7, 75.0, 22.9, 7.1, 6.6, 6.4(2); **HRMS** (ESI+) calc. for $C_{20}H_{24}O_3NaSi$ $[M+Na]^+$ 363.1387, found 363.1387.

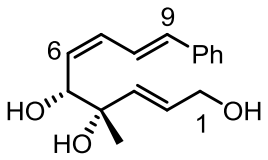
(*S*,E)-2-((*R*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)hex-3-en-5-yn-2-ol, 265



To a stirred solution of **268** (21 mg, 0.062 mmol, 1.0 eq.) in MeOH (0.6 mL) was added K_2CO_3 (11 mg, 0.080 mmol, 1.3 eq.). After stirring vigorously overnight, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (3 mL) and extracted with Et_2O (3 × 3 mL). The combined organic layer dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude title compound **265** along with methyl benzoate (18 mg, 0.057 mmol, 75% purity by weight, 91%) which was used without further purification;

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 6.89 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*7), 6.25-6.11 (1H, m, *H*8 and *H*4), 5.79 (1H, dd, *J* = 15.5 and 2.5 Hz, *H*3), 4.55 (1H, dd, *J* = 2.5 and 1.5 Hz, *H*6), 2.86 (1H, d, *J* = 2,5 Hz, *H*1), 2.60 (1H, s, O*H*), 1.32 (3H, s, C5CH_3), 1.04-0.81 (6H, m, $SiCH_2CH_3$ and $SiCH_2CH_3$'), 0.77-0.54 (4H, m, $SiCH_2CH_3$ and $SiCH_2'CH_3$);

(2*E*,4*S*,5*R*,6*Z*,8*E*)-4-Methyl-9-phenylnona-2,6,8-triene-1,4,5-triol, 269



To a vial containing siloxane **264** (56 mg, 0.23 mmol, 1.0 eq.), iodostyrene (**220**) (80 mg, 0.35 mmol, 1.5 eq.) and [allylPdCl]$_2$ (4 mg, 0.012 mmol, 5.0 mol%) was added TBAF•3H$_2$O (0.69 mL, 1 M in THF, 0.69 mmol, 3.0 eq.). After stirring at RT overnight, the crude product mixture was purified *via* column chromatography (CH_2Cl_2 / MeOH (5%)) to give title compound **269** (26 mg, 0.10 mmol, 43%);

$[\alpha]_D^{25}$ −46 (*c* 1.0, $CHCl_3$); **R$_f$** 0.18 (CH_2Cl_2 / MeOH (5%)); **IR (**thin film, ν_{max} / cm^{-1}) 3364, 2929, 1041, 1000, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.20 (5H, m, Ar*H*), 7.08 (1H, dd, *J* = 15.5 and 11.5 Hz, *H*8), 6.60 (1H, d, *J* = 15.5 Hz, *H*9), 6.33 (1H, app t, *J* = 11.0 Hz, *H*7), 5.95 (1H, dt, *J* = 15.5 and 5.5 Hz, *H*2), 5.85 (1H, d, *J* = 15.5 Hz, *H*3), 5.54 (1H, app t, *J* = 10.0 Hz, *H*6), 4.55 (1H, d, *J* = 9.5 Hz, *H*5), 4.23-4.67 (2H, m, *H*1), 3.32-3.00 (2H, m, O*H*), 2.99 (1H, bs, O*H*), 1.28 (3H, s, C4CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.9, 135.3, 133.7, 132.9, 129.8, 128.8, 128.7, 128.1, 126.7, 123.6, 75.2, 74.7, 62.9, 24.2; **HRMS** (ESI+) calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305, found 283.1305.

6.10 Synthesis of 6-membered cyclic dimethyl siloxane

Benzyl(ethynyl)dimethylsilane, 286



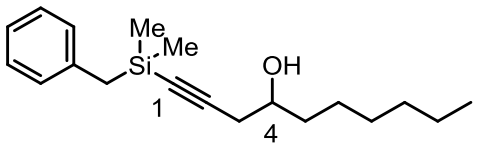
To a solution of benzyldimethylchlorosilane (**203**) (5.0 mL, 27.6 mmol, 1.0 eq.) in THF (92 mL) was added ethynylmagnesium bromide (72 mL, 0.5 M in THF, 35.9 mmol, 1.3

eq.) dropwise, at 0 °C. The cooling bath was subsequently removed, the reaction allowed to reach RT and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (160 mL), the organic layer separated and the aqueous layer was further extracted with Et_2O (2 × 160 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (5%)) to give title compound **286** (4.09 g, 23.5 mmol, 85%) as a pale yellow oil;

R_f 0.73 (petroleum ether / EtOAc (5%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27-7.21 (2H, m, Ar*H*), 7.14-7.0 (3H, m, Ar*H*), 2.42 (1H, s, CC*H*), 2.23 (2H, s, ArCH_2Si), 0.16 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 140.9, 130.7, 130.6, 126.8, 96.7, 90.9, 28.2, 0.0.

The physical and spectroscopic data was found to be in agreement with that reported by Trost *et al*.[131]

1-(Benzyldimethylsilyl)dec-1-yn-4-ol, 287

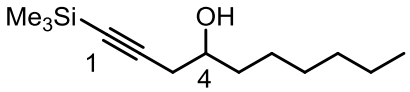


To a solution of alkyne **286** (1.00 g, 5.73 mmol, 1.0 eq.) in THF (46 mL) was added a solution of *n*-BuLi (2.50 mL, 2.5 M in hexanes, 6.31 mmol, 1.1 eq.) dropwise *via* syringe, at −78 °C. The resulting mixture stirred for 1 h, after which BF_3•Et_2O (1.10 mL, 8.61 mmol, 1.5 eq.) was added followed by 1.2-epoxyoctane (**285)** (1.14 mL, 7.46 mmol, 1.3 eq.). After stirring at −78 °C for 1 h, the resulting mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL), the cooling bath removed and the

resulting biphasic mixture allowed to reach RT. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 mL), the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (5%)) to give title compound **287** (1.55 g, 5.12 mmol, 89%) as a clear oil;

R_f 0.13 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3328, 2929, 2175, 1249, 839; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, Ar*H*), 7.14-7.04 (3H, m, Ar*H*), 3.74-3.64 (1H, m, *H*4), 2.45 (1H, dd, *J* = 17.0 and 4.5 Hz, *H*3), 2.32 (1H, dd, *J* = 17.0 and 7.0 Hz, *H*3'), 2.19 (2H, s, ArCH_2Si), 1.68 (1H, app d, *J* = 5.0 Hz, O*H*), 1.40-1.31 (2H, m, *H*5), 1.30-1.21 (8H, m, *H*6-*H*9), 0.89 (3H, t, *J* = 7.0 Hz, *H*10), 0.14 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 141.0, 130.2, 130.1, 126.3, 106.8, 87.7, 71.7, 38.1, 33.7, 31.1, 30.8, 28.3, 27.4, 24.5, 15.9, 0.0; **HRMS** (ESI+) calc. for $C_{19}H_{30}ONaSi$ $[M+Na]^+$ 325.1959, found 325.1958.

1-(trimethylsilyl)dec-1-yn-4-ol, 288



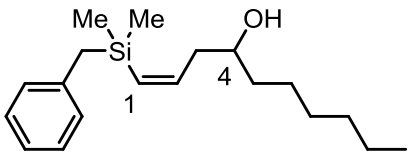
To a solution of alkyne **244** (0.20 mL, 1.42 mmol, 1.0 eq.) in THF (11 mL) was added a solution of *n*-BuLi (0.62 mL, 2.5 M in hexanes, 1.56 mmol, 1.1 eq.) dropwise *via* syringe, at −78 °C. The resulting mixture stirred for 1 h, after which BF_3•Et_2O (0.23 mL, 2.14 mmol, 1.5 eq.) was added followed by 1.2-epoxyoctane (**285)** (0.28 mL, 1.86 mmol, 1.3 eq.). After stirring at −78 °C for 1 h, the resulting mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), the cooling bath removed and the resulting biphasic mixture allowed to reach RT. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 10 mL), the combined organic layers dried over

anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (5%)) to give title compound **288** (335 mg, 1.40 mmol, 99%) as a clear oil;

R_f 0.18 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.77-3.67 (1H, m, *H*4), 2.45 (1H, dd, *J* = 17.0 and 4.5 Hz, *H*3), 2.32 (1H, dd, *J* = 17.0 and 7.0 Hz, *H*3'), 1.92 (1H, app d, *J* = 5.0 Hz, O*H*), 1.55-1.47 (2H, m, *H*5), 1.39-1.21 (8H, m, *H*6-*H*9), 0.88 (3H, t, *J* = 7.0 Hz, *H*10), 0.16 (H, s, Si(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 103.2, 87.5, 69.8, 36.1, 31.7, 29.1, 28.8, 25.4, 22.5, 14.0, −0.0.

The physical and spectroscopic data was found to be in agreement with that reported by Huang *et al*.[190]

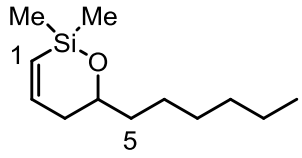
(*Z*)-1-(Benzyldimethylsilyl)dec-1-en-4-ol, 290



To an oven dried round-bottom flask, equipped with a stirrer bar, was added Pd on $CaCO_3$ (467mg, 5 w% Pd, 0.22 mmol, 5.0 mol%). The flask was evacuated, filled with nitrogen, toluene (34 mL) added and the flask purged with hydrogen. Subsequently, a solution of alkyne **287** (1.33 g, 4.39 mmol, 1.0 eq.), quinoline (0.26 mL, 2.19 mmol, 50 mol%) and cyclohexene (4 mL) in toluene (6 mL) was added *via* syringe and hydrogenation continued until completion (2.5 h, monitored by TLC (visualised with vanillin)). The reaction mixture was then filtered through Celite and the filtrate concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (2.5%)) to give vinylsilane **290** (1.28 g, 4.20 mmol, 95%);

R_f 0.33 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3450, 2927, 1493, 1248, 831; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24-7.17(2H, m, Ar*H*), 7.10-6.96 (3H, m, Ar*H*), 6.38 (1H, ddd, *J* = 14.5, 8.0 and 7.0 Hz, *H*2), 5.64 (1H, dt, *J* = 14.5 and 1.5 Hz, *H*1), 3.65-3.55 (1H, m, *H*4), 2.28-2.19 (1H, m, *H*3), 2.17 (2H, s, ArCH_2Si), 2.16-2.08 (1H, m, *H*3'), 1.47-1.22 (10H, m, *H*5-*H*9), 0.89 (3H, t, *J* = 7.0 Hz, *H*10), 0.12 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.3, 141.5, 132.0, 129.8, 129.7, 125.6, 72.8, 42.9, 38.6, 33.4, 30.9, 28.2, 27.2, 24.2, 15.6, 0.0; **HRMS** (CI+) calc. for $C_{19}H_{36}NOSi$ $[M+NH_4]^+$ 322.2566, found 322.2556.

6-Hexyl-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline, 292

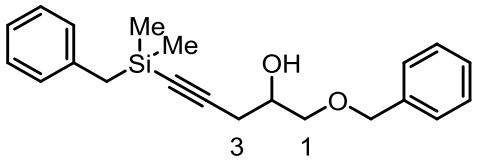


To a solution of vinylsilane **290** (1.00 g, 3.29 mmol, 1.0 eq.) in THF (16.5 mL) was added TBAF•3H_2O (0.82 mL, 1 M in THF, 0.82 mmol, 0.25 eq.). After stirring at RT for 2 h, the resulting mixture was diluted with Et_2O (20 mL) and quenched with a 1 M aqueous HCl solution (20 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title product **292** (466 mg, 2.19 mmol, 67%) as a clear oil;

R_f 0.71 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2927, 1249, 842; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.75 (1H, dt, *J* = 14.0 and 4.5 Hz, *H*2), 5.73 (1H, dt, *J* = 14.0 and 1.5 Hz, *H*1), 3.92-3.84 (1H, m, *H*4), 2.17-2.10 (2H, m, *H*3), 1.62-1.19 (10H, m, *H*5-*H*9), 0.88 (3H, t, *J* = 7.0 Hz, *H*10), 0.18 (3H, s, SiCH_3), 0.17 (3H, s,

SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.3, 127.1, 71.4, 37.9, 36.4, 31.9, 29.2, 25.5, 22.7, 14.1, −0.4, −0.5; **HRMS** (Cl+) calc. for $C_{12}H_{25}OSi$ $[M+H]^+$ 213.1675, found 213.1678.

5-(Benzyldimethylsilyl)-1-(benzyloxy)pent-4-yn-2-ol, 310

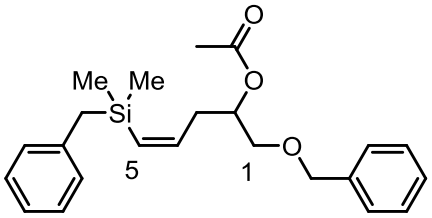


To a solution of alkyne **286** (4.01 g, 23.0 mmol, 1.0 eq.) in THF (184 mL) was added a solution of *n*-BuLi (10.1 mL, 2.5 M in hexanes, 25.3 mmol, 1.1 eq.) dropwise *via* syringe, at −78 °C. After stirring at −78 °C for 1 h, BF_3•Et_2O (4.26 mL, 34.5 mmol, 1.5 eq.) was added followed by epoxide **309** (4.92 g, 30.0 mmol, 1.3 eq.). After stirring at −78 °C for 1 h, the resulting mixture was quenched with a saturated aqueous solution of NH_4Cl (180 mL), the cooling bath removed and the resulting biphasic mixture allowed to reach RT. The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 × 180 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (30%)) to give title compound **310** (4.45 g, 13.1 mmol, 57%) as a clear oil;

R_f 0.19 (petroleum ether / Et_2O (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3410, 2981, 1383, 1152, 954; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.02 (10H, m, Ar*H*), 4.57 (2H, s, OCH_2Ar), 3.98-3.3.89 (1H, m, *H*2), 3.57 (1H, dd, *J* = 9.5 and 4.0 Hz, *H*1), 3.47 (1H, dd, *J* = 9.5 and 6.5 Hz, *H*1'), 2.49 (2H, dd, *J* = 6.5 and 4.0 Hz, *H*3), 2.35 (1H, bs, O*H*), 2.16 (2H, s, ArCH_2Si), 0.11 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 141.1, 139.8,

130.5, 130.3, 130.1, 129.8, 129.7, 126.3, 105.9, 87.7, 75.4, 74.7, 70.8, 28.3, 27.0, 0.0; **HRMS** (ESI+) calc. for $C_{21}H_{26}O_2NaSi$ $[M+Na]^+$ 361.1594, found 361.1592.

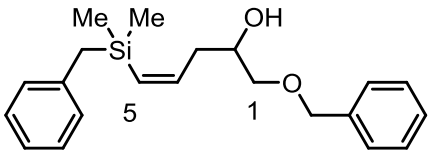
(*Z*)-5-(Benzyldimethylsilyl)-1-(benzyloxy)pent-4-en-2-yl acetate, 312



To a solution of homoallylic alcohol **311** (205 mg, 0.61 mmol, 1.0 eq.), acetic anhydride (0.12 mL, 1.22 mmol, 2.0 eq.) and Et_3N (0.25 mL, 1.83 mmol, 3.0 eq.) in CH_2Cl_2 (4 mL) was added a single crystal of 4-dimethylaminopyridine (DMAP). After stirring at RT for 30 min, the resulting mixture was quenched with water (10 mL), the organic layer separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (10%)) to give title compound **312** (219 mg, 0.58 mmol, 95%) as a clear oil;

R_f 0.40 (petroleum ether / Et_2O (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3026, 1738, 1236, 905, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39-6.95 (10H, m, Ar*H*), 6.27 (1H, dt, *J* = 14.0 and 7.5 Hz, *H*4), 5.60 (1H, dt, *J* = 14.0 and 1.5 Hz, *H*5), 5.13-5.03 (1H, m, *H*2), 4.56 (1H, d, *J* = 12.0 Hz, OCH_2Ar), 4.50 (1H, d, *J* = 12.0 Hz, OCH_2'Ar), 3.52-3.48 (2H, m, *H*1), 2.41-2.35 (2H, m, *H*3), 2.16 (2H, s, ArCH_2Si), 2.05 (3H, s, CO_2CH_3), 0.11 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.3, 145.5, 141.6, 139.7, 132.1, 130.1, 130.0, 129.9, 129.4, 129.3, 125.8, 74.9, 73.8, 72.4, 36.7, 28.3, 22.9, 0.0, −0.04; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_3NaSi$ $[M+Na]^+$ 405.1856, found 405.1863.

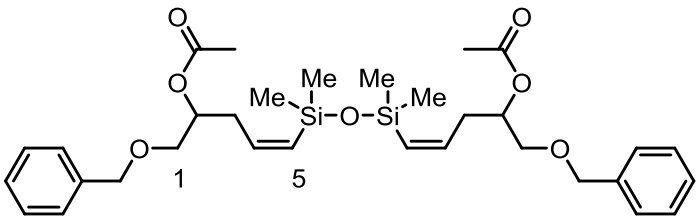
(*Z*)-5-(Benzyldimethylsilyl)-1-(benzyloxy)pent-4-en-2-ol, 311



To a solution of acetate **312** (50 mg, 0.13 mmol, 1.0 eq.) in MeOH (0.43 mL) was added K_2CO_3 (27 mg, 0.20 mmol, 1.5 eq.) and the resulting mixture stirred vigorously at RT for 3 h. Next, the reaction was diluted with Et_2O (2 mL) and quenched with a saturated aqueous solution of NH_4Cl (2 mL), the organic layer separated and the aqueous layer extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (30%)) to give title compound **311** (41 mg, 0.12 mmol, 92%) as a clear oil;

R_f 0.40 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3444, 2895, 1493, 1095, 830; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42-6.98 (10H, m, Ar*H*), 6.39 (1H, dt, *J* = 14.0 and 7.5 Hz, *H*4), 5.63 (1H, dt, *J* = 14.0 and 1.0 Hz, *H*5), 4.56 (2H, s, OCH_2Ar), 3.92-3.79 (1H, m, *H*2), 3.48 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.34 (1H, dd, *J* = 9.5 and 7.5 Hz, *H*1'), 2.41-2.19 (2H, m, *H*3), 2.36 (1H, d, *J* = 3.5 Hz, O*H*), 2.18 (2H, s, ArCH_2Si), 0.13 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 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; **HRMS** (ESI+) calc. for $C_{21}H_{28}O_2NaSi$ $[M+Na]^+$ 363.1751, found 363.1756.

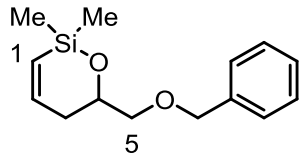
(4*Z*,4'*Z*)-(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(1-(benzyloxy)pent-4-ene-5,2-diyl) diacetate, 313



To a solution of vinylsilane **312** (50 mg, 0.13 mmol, 1.0 eq.) in THF (0.65 mL) was added TBAF•3H_2O (0.13 mL, 1 M in THF, 0.13 mmol, 1.0 eq.). After stirring at RT for 30 min, the resulting mixture was diluted with Et_2O (2 mL) and quenched with water (2 mL), the organic layer separated and the aqueous layer was further extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **313** (41 mg, 0.12 mmol, 92%) as a clear oil;

R_f 0.40 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 1739, 1372, 1237, 1047; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-7.27 (10H, m, Ar*H*), 6.27-6.17 (2H, m, *H*4), 5.61-5.52 (2H, m, *H*5), 5.15-5.08 (2H, m, *H*2), 4.59-4.47 (4H, m, OCH_2Ar), 3.56-3.48 (4H, m, *H*1), 2.54-2.47 (4H, m, *H*3), 2.05 (6H, s, CO_2CH_3), 0.21-0.14 (6H, m, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.2, 140.8, 135.6, 129.7, 126.0, 125.3, 125.2, 70.7, 69.7, 68.4, 32.4, 18.8, 0.0 −0.01; **HRMS** (ESI+) calc. for $C_{32}H_{46}NaO_7Si_2$ $[M+Na]^+$ 621.2674, found 621.2664.

6-((Benzyloxy)methyl)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasiline, 308

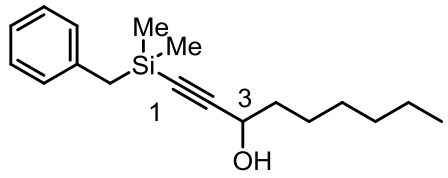


To a solution of vinylsilane **312** (50 mg, 0.13 mmol, 1.0 eq.) in THF (0.7 mL) was added $KOSiMe_3$ (20 mg, 0.17 mmol, 1.3 eq.). After stirring at RT for 9 h, the resulting mixture was diluted with Et_2O (2 mL) and quenched with a saturated aqueous solution of NH_4Cl (2 mL), the organic layer was separated and the aqueous layer further extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (5%)) to give title compound **308** (11 mg, 0.044 mmol, 34%) as a clear oil;

R_f 0.29 (petroleum ether / Et_2O (5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2859, 1355, 1129, 843, 789; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.26 (5H, m, Ar*H*), 6.82-6.73 (1H, m, *H*2), 5.80-5.71 (1H, m, *H*1), 4.61 (1H, d, *J* = 12.0 Hz, OC*H*$_2$Ar), 4.56 (1H, d, *J* = 12.0 Hz, OC*H*$_2$'Ar), 4.19-4.10 (1H, m, *H*4), 3.56 (1H, dd, *J* = 9.5 and 5.5 Hz, *H*5), 3.43 (1H, dd, *J* = 9.5 and 5.5 Hz, *H*5'), 2.56-2.19 (2H, m, *H*3), 2.36 (1H, d, *J* = 3.5 Hz, O*H*), 0.21 (3H, s, SiC*H*$_3$), 0.20 (3H, s, SiC*H*$_3$'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.1, 138.9, 128.8, 128.2, 128.1, 127.6, 75.0, 73.8, 70.8, 33.8, 0.2, 0.0; **HRMS** (ESI+) calc. for $C_{14}H_{21}O_2Si$ $[M+H]^+$ 249.1305, found 249.1307.

6.11 Synthesis of 5-membered cyclic dimethyl siloxane

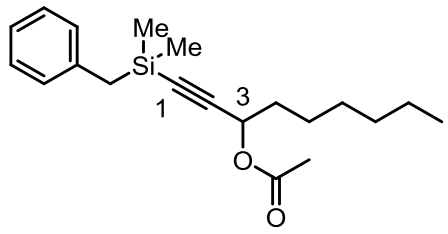
1-(Benzyldimethylsilyl)non-1-yn-3-ol, 294



To a solution of alkyne **286** (500 mg, 2.87 mmol, 1.1 eq.) in THF (8.7 mL) was added a solution of *n*-BuLi (1.1 mL, 2.5 M in hexanes, 2.74 mmol, 1.05 eq.) dropwise *via* syringe, at −78 °C. The resulting mixture was stirred for 1 h, after which heptanal (**293**) (0.36 mL, 2.61 mmol, 1.0 eq.) was added. After stirring at −78 °C for 30 min, the cooling bath was removed and the reaction allowed to reach RT and stirred for further 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer was further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **294** (684 mg, 2.32 mmol, 89%) as a clear oil;

R_f 0.23 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3329, 2928, 2173, 1250, 839; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, Ar*H*), 7.14-7.04 (3H, m, Ar*H*), 4.38-4.29 (1H, m, *H*3), 2.20 (2H, s, ArCH_2Si), 1.75-1.22 (10H, m, *H*4-*H*8), 0.90 (3H, t, *J* = 7.0 Hz, *H*9), 0.14 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 141.0, 130.5, 130.3, 126.5, 110.5, 89.9, 65.1 39.8, 33.9, 31.0, 28.3, 27.2, 24.7, 16.2, 0.0; **HRMS** (ESI+) calc. for $C_{18}H_{28}ONaSi$ $[M+Na]^+$ 311.1802, found 311.1802.

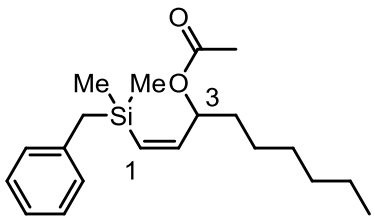
1-(Benzyldimethylsilyl)non-1-yn-3-yl acetate, 295



To a solution of propargylic alcohol **294** (200 mg, 0.69 mmol, 1.0 eq.), acetic anhydride (0.13 mL, 1.38 mmol, 2.0 eq.) and Et_3N (0.29 mL, 2.07 mmol, 3.0 eq.) in CH_2Cl_2 (4.6 mL) was added a single crystal of 4-dimethylaminopyridine (DMAP). After stirring at RT for 2 h, the resulting mixture was quenched with water (10 mL), the organic layer separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **295** (239 mg, 0.69 mmol, quant.) as a yellow oil which was used without further purification;

R_f 0.51 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 1745, 1234, 840, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, Ar*H*), 7.14-7.04 (3H, m, Ar*H*), 5.36 (1H, t, *J* = 6.5 Hz, *H*3), 2.20 (2H, s, ArCH_2Si), 2.09 (3H, s, CO_2CH_3), 1.78-1.66 (2H, m, *H*4), 1.46-1.22 (8H, m, *H*5-*H*8), 0.89 (3H, t, *J* = 7.0 Hz, *H*9), 0.13 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.1, 141.0, 130.6, 130.4, 126.6, 106.4, 90.9, 66.6, 36.9, 33.9, 31.0, 28.3, 27.1, 24.8, 23.3, 16.3, 0.0; **HRMS** (ESI+) calc. for $C_{20}H_{30}O_2NaSi$ $[M+Na]^+$ 353.1907, found 353.1906.

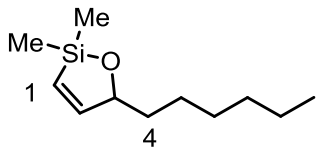
(*Z*)-1-(Benzyldimethylsilyl)non-1-en-3-yl acetate, 296



To an oven dried round-bottom flask, equipped with a stirrer bar, was added Pd on $CaCO_3$ (85 mg, 5 w% Pd, 0.040 mmol, 5.0 mol%). The flask was evacuated, filled with nitrogen, toluene (6 mL) added and the flask purged with hydrogen. Subsequently, a solution of acetate **295** (231 mg, 0.70 mmol, 1.0 eq.) and quinoline (19 µL, 0.16 mmol, 20 mol%) in toluene (2 mL) was added *via* syringe and hydrogenation continued until completion (3 h, monitored by TLC (visualised with vanillin)). The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (2.5%)) to give title compound **296** (195 mg, 0.59 mmol, 84%) as a clear oil;

R_f 0.26 (petroleum ether / EtOAc (2.5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2927, 1737, 1238, 1019, 833; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, Ar*H*), 7.11-6.96 (3H, m, Ar*H*), 6.19 (1H, dd, *J* = 14.5 and 9.5 Hz, *H*2), 5.67 (1H, d, *J* = 14.5 Hz, *H*1), 5.38-5.29 (1H, m, *H*3), 2.20 (1H, s, ArCH_2Si), 2.19 (1H, s, ArCH_2'Si), 2.04 (3H, s, CO_2CH_3), 1.69-1.57 (1H, m, *H*4), 1.51-1.37 (1H, m, *H*4'), 1.35-1.18 (8H, m, *H*5-*H*8), 0.88 (3H, t, *J* = 7.0 Hz, *H*9), 0.16 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.1, 148.2, 141.6, 133.0, 130.1, 130.0, 125.9, 76.5, 36.7, 33.5, 31.0, 28.3, 26.9, 24.4, 23.2, 15.9, 0.1, 0.0; **HRMS** (ESI+) calc. for $C_{20}H_{32}O_2NaSi$ $[M+Na]^+$ 355.2064, found 355.2064.

5-Hexyl-2,2-dimethyl-2,5-dihydro-1,2-oxasilole, 297



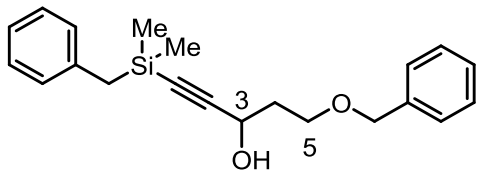
Condition A: To a solution of vinylsilane **296** (50 mg, 0.15 mmol, 1.0 eq.) in MeOH (0.3 mL) was added K_2CO_3 (31 mg, 0.23 mmol, 1.5 eq.) and the resulting mixture stirred vigorously at RT. Upon completion (2 h, monitored by TLC) the reaction was diluted with Et_2O (2 mL) and quenched with a saturated aqueous solution of NH_4Cl (2 mL), the organic layer separated and the aqueous layer was further extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and carefully concentrated *in vacuo* to give title compound **297** (19 mg, 0.096 mmol, 64%) as a clear oil;

Condition B: To a solution of vinylsilane **296** (21 mg, 0.063 mmol, 1.0 eq.) in THF (0.3 mL) was added TBAF•$3H_2O$ (63 μL, 1 M in THF, 0.063 mmol, 1.0 eq.). After stirring at RT for 2 h, the resulting mixture was diluted with Et_2O (2 mL) and quenched with a 1 M aqueous HCl solution (2 mL), the organic layer separated and the aqueous layer was further extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and carefully concentrated *in vacuo* to give title compound **297** (8 mg, 0.040 mmol, 64%) as a clear oil;

IR (thin film, ν_{max} / cm^{-1}) 2928, 1741, 1252, 1022, 851; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.84 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*2), 6.01 (1H, dd, *J* = 10.5 and 2.0 Hz, *H*1), 4.72-4.66 (1H, m, *H*3), 1.74-1.17 (10H, m, *H*4-*H*8), 0.87 (3H, t, *J* = 7.0 Hz, *H*9), 0.25 (3H, s, SiCH_3), 0.24 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.1, 125.2,

81.5, 35.8, 30.4, 28.0, 23.7, 21.2, 12.7, 0.0, −0.9; **HRMS** (ESI+) calc. for $C_{11}H_{23}OSi$ $[M+H]^+$ 199.1513, found 199.1516.

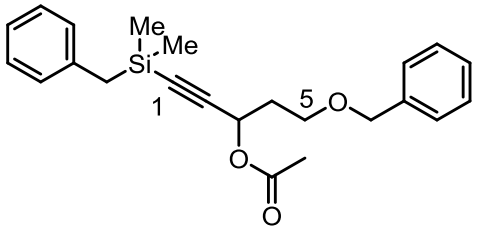
1-(Benzyldimethylsilyl)-5-(benzyloxy)pent-1-yn-3-ol, 318



To a solution of alkyne **286** (4.37 g, 25.1 mmol, 1.1 eq.) in THF (76 mL) was added a solution of *n*-BuLi (9.6 mL, 2.5 M in hexanes, 23.9 mmol, 1.05 eq.) dropwise *via* syringe, at −78 °C. The resulting mixture was stirred for 1 h, after which aldehyde **317** (3.74 g, 22.8 mmol, 1.0 eq.) was added. After stirring at −78 °C for 30 min, the cooling bath was removed and the reaction allowed to reach RT and stirred for further 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (80 mL) the organic layer separated and the aqueous layer further extracted with Et_2O (3 × 80 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **318** (6.88 g, 2.32 mmol, 89%) as a clear oil;

$\mathbf{R}_f$ 0.17 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3410, 2958, 2100, 832, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32-6.95 (10H, m, Ar*H*), 4.56-4.48 (1H, m, *H*3), 4.48-4.38 (2H, m, OCH_2Ar), 3.79-3.69 (1H, m, *H*5), 3.63-3.52 (1H, m, *H*5'), 2.99-2.92 (1H, m, O*H*), 2.12 (2H, s, ArCH_2Si), 2.06-1.93 (1H, m, *H*4), 1.93-1.80 (1H, m, *H*4'), 0.056 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 141.0, 139.9, 130.6, 130.5, 130.3, 129.9, 129.8, 126.5, 109.6, 90.0, 75.5, 69.8, 64.0, 38.7, 28.3, 0.0; **HRMS** (ESI+) calc. for $C_{21}H_{26}O_2NaSi$ $[M+Na]^+$ 361.1594, found 361.1595.

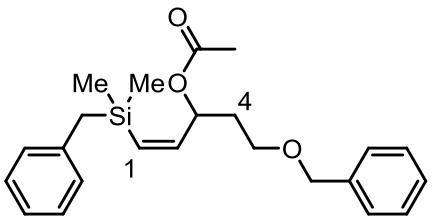
1-(Benzyldimethylsilyl)-5-(benzyloxy)pent-1-yn-3-yl acetate, 319



To a solution of propargylic alcohol **318** (563 mg, 1.66 mmol, 1.0 eq.), acetic anhydride (0.31 mL, 3.33 mmol, 2.0 eq.) and Et_3N (0.69 mL, 4.98 mmol, 3.0 eq.) in CH_2Cl_2 (11 mL) was added a single crystal of 4-dimethylaminopyridine (DMAP). After stirring at RT for 2 h, the resulting mixture was quenched with water (10 mL), the organic layer separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give acetate **319** (685 mg, 1.66 mmol, quant.) as a yellow oil which was used without further purification. Purification *via* column chromatography (petroleum ether / Et_2O (10%)) gave an analytically pure sample (588 mg, 1.54 mmol, 93%) as a clear oil;

$\mathbf{R}_f$ 0.37 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2961, 2180, 1745, 1229, 837; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39-7.02 (10H, m, Ar*H*), 5.56 (1H, t, J = 7.0 Hz, *H*3), 4.53-4.45 (2H, m, OCH_2Ar), 3.62-3.50 (2H, m, *H*5), 2.18 (2H, s, ArCH_2Si), 2.15-1.97 (2H, m, *H*4), 2.06 (3H, s, CO_2CH_3), 0.12 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.9, 141.0, 140.4, 130.7, 130.6, 130.4, 130.0, 129.9, 126.7, 105.9, 91.2, 75.3, 68.1, 64.0, 37.3, 28.3, 23.3, 0,0, −0.02; **HRMS** (ESI+) calc. for $C_{23}H_{28}O_3NaSi$ $[M+Na]^+$ 403.1700, found 403.1692.

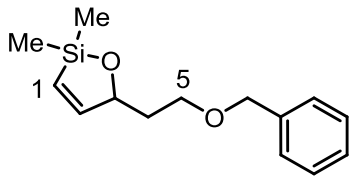
(*Z*)-1-(Benzyldimethylsilyl)-5-(benzyloxy)pent-1-en-3-yl acetate, 320



To an oven dried round-bottom flask, equipped with a stirrer bar, was added Pd on $CaCO_3$ (839 mg, 5 w% Pd, 0.39 mmol, 5.0 mol%). The flask was evacuated, filled with nitrogen, toluene (70 mL) added and the flask purged with hydrogen. Subsequently a solution of acetate **319** (3.00 g, 7.89 mmol, 1.0 eq.) and quinoline (0.185 mL, 1.58 mmol, 20 mol%) in toluene (10 mL) was added *via* syringe and hydrogenation continued until completion (2 h, monitored by TLC (visualised with vanillin)). The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (5%)) to give title compound **320** (2.26 g, 5.91 mmol, 75%) as a clear oil;

R_f 0.39 (petroleum ether / Et_2O (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 1737, 1239, 832, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-6.94 (10H, m, Ar*H*), 6.20 (1H, dd, *J* = 14.5 and 9.5 Hz, *H*2), 5.69 (1H, d, *J* = 14.5 Hz, *H*1), 5.58-5.50 (1H, m, *H*3), 4.50 (1H, d, *J* = 12.0 Hz, OCH_2Ar), 4.44 (1H, d, *J* = 12.0 Hz, OCH_2'Ar), 3.50-3.44 (2H, m, *H*5), 2.22 (1H, d, *J* = 13.5 Hz, ArCH_2Si), 2.18 (1H, d, *J* = 13.5 Hz, ArCH_2'Si), 2.00 (3H, s, CO_2CH_3), 1.97-1.88 (1H, m, *H*4), 1.84-1.74 (1H, m, *H*4'), 0.16 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.1, 147.7, 141.7, 140.3, 133.4, 130.3, 130.2, 130.1, 129.6, 129.5, 126.0, 74.9, 74.0, 68.0, 37.1, 28.3, 23.2, 0.0 −0.05; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_3NaSi$ $[M+Na]^+$ 405.1856, found 405.1856.

5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-2,5-dihydro-1,2-oxasilole, 316



Condition A: To a solution of vinylsilane **320** (534 mg, 1.34 mmol, 1.0 eq.) in MeOH (4.5 mL) was added K_2CO_3 (278 mg, 2.01 mmol, 1.5 eq.) and the resulting mixture stirred vigorously at RT. Upon completion (3 h, monitored by TLC) the reaction was diluted with Et_2O (10 mL) and quenched with a saturated aqueous solution of NH_4Cl (10 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **316** (334 mg, 1.34 mmol, quant.) as a clear oil;

Condition B: To a solution of vinylsilane **320** (22 mg, 0.060 mmol, 1.0 eq.) in THF (0.3 mL) was added TBAF•$3H_2O$ (60 µL, 1 M in THF, 0.060 mmol, 1.0 eq.). After stirring at RT for 15 min, the resulting mixture was diluted with Et_2O (2 mL) and quenched with a 1 M aqueous HCl solution (2 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **316** (14 mg, 0.060 mmol, quant.) as a clear oil;

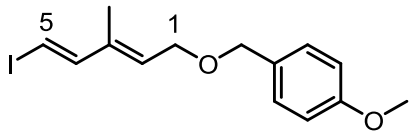
Condition C: To a solution of vinylsilane **320** (50 mg, 0.14 mmol, 1.0 eq.) in THF (0.7 mL) was added $KOSiMe_3$ (23 mg, 0.18 mmol, 1.3 eq.). After stirring at RT for overnight, the resulting mixture was diluted with Et_2O (2 mL) and quenched with a saturated aqueous solution of NH_4Cl (2 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 2 mL). The combined organic layers

were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a 1:2 mixture of siloxane **316** and proteodesilylated product **321** (23 mg, 0.030 mmol, 38% purity by weight, 21%);

IR (thin film, ν_{max} / cm^{-1}) 2858, 1251, 1097, 853, 788; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-7.25 (5H, m, Ar*H*), 6.86 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*2), 6.03 (1H, dd, *J* = 10.5 and 2.0 Hz, *H*1), 4.87-4.80 (1H, m, *H*3), 4.54 (1H, d, *J* = 12.0 Hz, OCH_2Ar), 4.49 (1H, d, *J* = 12.0 Hz, OCH_2'Ar), 3.70-3.58 (2H, m, *H*5), 2.02-1.91 (1H, m, *H*4), 1.76-1.66 (1H, m, *H*4'), 0.25 (3H, s, SiCH_3), 0.24 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.9, 137.9, 127.8, 127.1, 126.9, 126.1, 79.7, 72.5, 66.6, 37.0, 0.9, 0.0; **HRMS** (ESI+) calc. for $C_{14}H_{21}O_2Si$ $[M+H]^+$ 249.1305, found 249.1306.

6.12 Cross-coupling of 5-membered cyclic dimethyl siloxane

1-((((2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene, 306

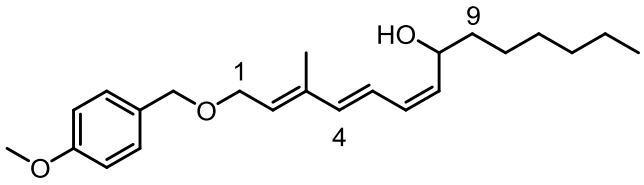


To a stirred suspension of NaH (50 mg, 60% w/w in mineral oil, 1.2 mmol, 2.0 eq.) in THF (1.0 mL) was added a solution of dienol **228** (138 mg, 0.62 mmol, 1.0 eq.) in THF (1 mL) dropwise *via* syringe, at 0 °C. After stirring for 30 min, PMBCl (92 µL, 0.68 mmol, 1.1 eq.) was added *via* syringe followed by an addition of a single crystal of TBAI. After stirring overnight at RT, the reaction was quenched with MeOH (2 mL), diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified *via* column chromatography

(petroleum ether / Et_2O (10%)) to afford title compound **306** (181 mg, 0.53 mmol, 85%);

R_f 0.49 (petroleum ether / Et_2O (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 2932, 2361, 1585, 1247, 1035; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.24-6.77 (4H, m, Ar*H*), 6.95 (1H, d, *J* = 14.5 Hz, *H*4), 5.96 (1H, d, *J* = 14.5 Hz, *H*5), 5.47 (1H, t, *J* = 7.0 Hz, *H*2), 4.28 (2H, s, OC*H*$_2$Ar), 3.85 (2H, d, *J* = 7.0, *H*1), 3.32 (3H, s, ArOMe), 1.28 (3H, s, C3CH_3); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 159.3, 148.8, 136.4, 130.6, 130.2, 129.1, 113.8, 75.6, 71.6, 65.6, 54.4, 11.6; **HRMS** (ES+) calc. for $C_{14}H_{17}O_2INa$ $[M+H]^+$ 367.0165, found 367.0165.

(2*E*,4*E*,6*Z*)-1-((4-Methoxybenzyl)oxy)-3-methylpentadeca-2,4,6-trien-8-ol, 307

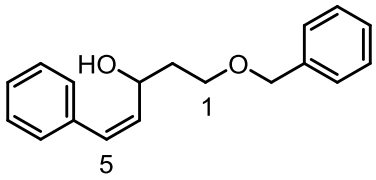


To vial containing siloxane **297** (20 mg, 0.10 mmol, 1.5 eq.), **306** (23 mg, 0.067 mmol, 1.0 eq.) and $[allylPdCl]_2$ (1.8 mg, 0.0051 mmol, 6.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 4.5 eq.). After stirring at RT for 15 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **307** (16 mg, 0.043 mmol, 64%) as a yellow oil;

R_f 0.53 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3431, 2928, 1514, 1248, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, J = 8.5 Hz, ArH), 6.86 (2H, d, J = 8.5 Hz, ArH), 6.48 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*5), 6.27 (1H, d, *J* = 15.5Hz, *H*4), 6.09 (1H, t, *J* = 11.0 Hz, *H*6), 5.69 (1H, *J* = 6.5 Hz, *H*2), 5.42-5.35 (1H, m, *H*7), 4.64-4.54 (1H, m, *H*8), 4.43 (2H, s, OC*H*$_2$Ar), 4.12 (2H, d, *J* = 6.5 Hz, *H*1), 3.78 (3H, s,

ArOC*H*$_3$), 1.77 (3H, s, C3C*H*$_3$), 1.67-1.17 (11H, m, *H*9-*H*13 and O*H*), 0.86 (3H, t, *J* = 7.0 Hz, *H*14); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.6, 137.0, 136.7, 136.2, 133.7, 130.5, 129.5, 122.9, 113.8, 72.0, 68.1, 66.3, 55.3, 37.5, 31.8, 29.3, 25.3, 22.6, 14.1, 12.8; **HRMS** (ESI+) calc. for $C_{23}H_{34}O_3Na$ $[M+Na]^+$ 381.2400, found 381,2419.

(*Z*)-5-(Benzyloxy)-1-phenylpent-1-en-3-ol, 325



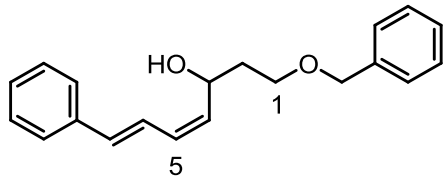
Condition A: To a vial containing siloxane **316** (58 mg, 0.23 mmol, 1.1 eq.), iodobenzene (**324**) (43 mg, 0.21 mmol, 1.0 eq.) and $Pd(dba)_2$ (6 mg, 0.010 mmol, 5.0 mol%) was added TBAF•3H_2O (0.42 mL, 1 M in THF, 0.42 mmol, 2.0 eq.). After stirring at RT for 15 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **325** (54 mg, 0.20 mmol, 95%) as a yellow oil;

Condition B: To solution of siloxane **316** (50 mg, 0.20 mmol, 1.0 eq.), iodobenzene (**324**) (49 mg, 0.24 mmol, 1.2 eq.) and $Pd(dba)_2$ (6 mg, 0.010 mmol, 5.0 mol%) in DME (0.48 mL) was added $KOSiMe_3$ (64 mg, 0.50 mmol, 2.5 eq.). After stirring at RT for 30 min, the crude product mixture was purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **325** (39 mg, 0.15 mmol, 73%) as a yellow oil;

R$_f$ 0.27 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3432, 2860, 1452, 1028, 697; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.13 (10H, m, Ar*H*), 6.48 (1H, d, *J* = 11.5 Hz, *H*1), 5.66 (1H, dd, *J* = 11.5 and 9.0 Hz, *H*2), 4.83-4.74 (1H, m, *H*3), 4.46

(2H, s, OC*H*$_2$Ar), 3.73-3.64 (1H, m, *H*5), 3.64-3.55 (1H, m, *H*5'), 2.76 (1H, bs, O*H*), 2.01-1.89 (1H, m, *H*4), 1.87-1.77 (1H, m, *H*4'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.0, 136.6, 134.0, 130.8, 128.9, 128.5, 128.3, 127.7, 127.6, 127.2, 73.3, 68.5, 67.2, 36.9; **HRMS** (ESI+) calc. for $C_{18}H_{20}O_2Na$ $[M+Na]^+$ 291.1356, found 291.1356.

(4*Z*,6*E*)-1-(Benzyloxy)-7-phenylhepta-4,6-dien-3-ol, 326



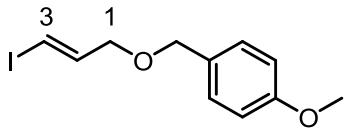
Condition A: To a vial containing siloxane **316** (25 mg, 0.10 mmol, 1.0 eq.), iodostyrene (**220**) (28 mg, 0.12 mmol, 1.2 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•3H_2O (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 45 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **326** (23 mg, 0.078 mmol, 78%) as a yellow oil;

Condition B: To a vial containing siloxane **316** (50 mg, 0.20 mmol, 1.0 eq.), bromostyrene (**327**) (44 mg, 0.24 mmol, 1.2 eq.) and $Pd(dba)_2$ (6.0 mg, 0.010 mmol, 5.0 mol%) was added TBAF•3H_2O (0.60 mL, 1 M in THF, 0.60 mmol, 3.0 eq.). After stirring at RT for 15 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **326** (46 mg, 0.16 mmol, 78%) as a yellow oil;

$\mathbf{R}_f$ 0.25 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3403, 2861, 1453, 1094, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.12 (10H, m, Ar*H*), 7.03 (1H, ddd, *J* = 15.5, 11.5 and 1.0 Hz, *H*6), 6.50 (1H, d, *J* = 15.5 Hz, *H*7), 6.19-6.11 (1H, m, *H*5),

5.50-5.40 (1H, m, *H*4), 4.96-4.85 (1H, m, *H*3), 4.45 (2H, s, OCH_2Ar), 3.69-3.61 (1H, m, *H*1), 3.61-3.52 (1H, m, *H*1'), 2.70 (1H, bs, O*H*), 2.01-1.88 (1H, m, *H*2), 1.78-1.69 (1H, m, *H*2'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.0, 137.1, 134.2, 133.7, 130.0, 128.6, 128.5, 127.8, 127.7, 127.6, 126.6, 123.8, 73.3, 68.1, 67.2, 37.1; **HRMS** (ESI+) calc. for $C_{20}H_{22}O_2Na$ $[M+Na]^+$ 317.1512, found 317.1512.

(*E*)-1-(((3-Iodoallyl)oxy)methyl)-4-methoxybenzene, 328



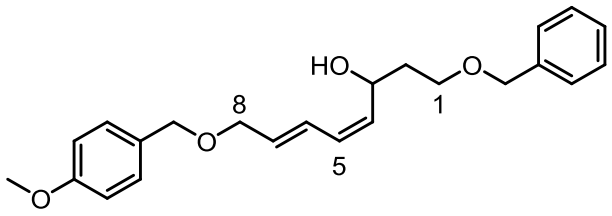
To a solution of allylic alcohol **330** (320 mg, 1.74 mmol, 1.0 eq.) and scandium(III) triflate (128 mg, 0.26 mmol, 0.15 eq.) in toluene (9 mL) was added *via* syringe 4-Methoxybenzyl-2,2,2-trichloroacetimidate (0.54 mL, 2.61 mmol, 1.5 eq.). After stirring at RT for 1 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (2.5%) → petroleum / Et_2O (5%)) to give title compound **328** (346 mg, 1.14 mmol, 65%) as a clear oil;

R_f 0.35 (petroleum ether / Et_2O (5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2836, 1612, 1312, 1247, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.65 (1H, dt, *J* = 14.5 and 5.5 Hz, *H*2), 6.39 (1H, dt, *J* = 14.5 and 1.5 Hz, *H*3), 4.45 (2H, s, OCH_2Ar), 3.92 (2H, dd, *J* = 5.5 and 1.5 Hz, *H*1), 3.81 (3H, s, ArOCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.3, 142.5, 129.8, 129.4, 113.9, 78.8,

72.0, 71.5, 55.3; **HRMS** (Cl+) calc. for $C_{11}H_{17}INO_2$ $[M+NH_4]^+$ 322.0304, found 322.0303.

The physical and spectroscopic data was found to be in agreement with that reported by Raghavan and Kumar.[191]

(4*Z*,6*E*)-1-(Benzyloxy)-8-((4-methoxybenzyl)oxy)octa-4,6-dien-3-ol, 331



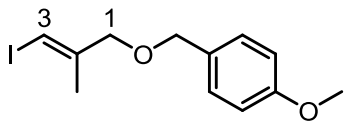
Condition A: To a vial containing siloxane **316** (30 mg, 0.12 mmol, 1.2 eq.), vinyl iodide **328** (30 mg, 0.10 mmol, 1.0 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 15 min, the crude mixture was purified *via* column chromatography (petroleum / EtOAc (30%)) to give title compound **331** (27 mg, 0.073 mmol, 73%) as a yellow oil;

Condition B: To a vial containing siloxane **316** (30 mg, 0.12 mmol, 1.2 eq.), vinyl bromide **332** (26 mg, 0.10 mmol, 1.0 eq.) and $[allylPdCl]_2$ (0.9 mg, 0.0025 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 3 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **331** (21 mg, 0.057 mmol, 57%) as a yellow oil;

$\mathbf{R}_f$ 0.15 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3430, 2854, 1513, 1247, 1096, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32-7.16 (7H, m, Ar*H*), 6.80 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.50-6.45 (1H, m, *H*6), 5.98 (1H, t, *J* = 11.0 Hz, *H*5), 5.75 (1H, dt,

J = 15.0 and 6.0 Hz, *H*7), 5.38 (1H, dd, *J* = 11.0 and 9.0 Hz, *H*4), 4.80-4.71 (1H, m, *H*3), 4.44 (2H, s, OCH_2Ar), 4.36 (2H, s, OCH_2ArOCH_3), 3.95 (2H, dd, *J* = 6.0 and 1.0 Hz, *H*8), 3.73 (3H, s, ArOCH_3), 3.66-3.59 (1H, m, *H*1), 3.58-3.50 (1H, m, *H*1'), 2.64 (1H, bs, O*H*), 1.93-1.81 (1H, m, *H*2), 1.74-1.65 (1H, m, *H*2'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.0, 133.6, 131.8, 130.3, 129.5, 129.1, 128.4, 127.7, 127.6, 127.4, 113.8, 73.3, 72.0, 70.1, 68.2, 67.1, 55.3, 36.9; **HRMS** (ESI+) calc. for $C_{23}H_{28}O_4Na$ $[M+Na]^+$ 391.1880, found 391.1867.

(*E*)-1-(((3-Iodo-2-methylallyl)oxy)methyl)-4-methoxybenzene, 329



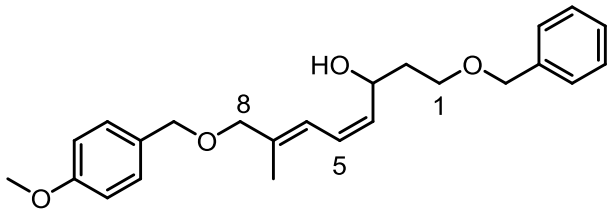
To a solution of vinyl silane **91** (352 mg, 1.78 mmol, 1.0 eq.) and scandium(III) triflate (131 mg, 0.26 mmol, 0.15 eq.) in toluene (9 mL) was added *via* syringe 4-Methoxybenzyl-2,2,2-trichloroacetimidate (0.55 mL, 2.67 mmol, 1.5 eq.). After stirring at RT for 1 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (2.5%) → petroleum ether / Et_2O (5%)) to give title compound **329** (420 mg, 1.32 mmol, 74%) as a clear oil;

R_f 0.35 (petroleum ether / Et_2O (5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2835, 1612, 1513, 1247, 1035; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.28-6.25 (1H, m, *H*3), 4.41 (2H, s, OCH_2Ar), 3.97 (2H, d,

J = 1.0 Hz, *H*3), 3.81 (3H, s, ArOCH_3) 1.85 (3H, d, *J* = 1.0 Hz, C2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.3, 145.0, 130.0, 129.4, 113.9, 78.6, 73.7, 71.7, 55.3, 21.6; **HRMS** (Cl+) calc. for $C_{12}H_{19}INO_2$ $[M+NH_4]^+$ 336.0460, found 336.0459.

The physical and spectroscopic data was found to be in agreement with that reported by Organ *et al*.[192]

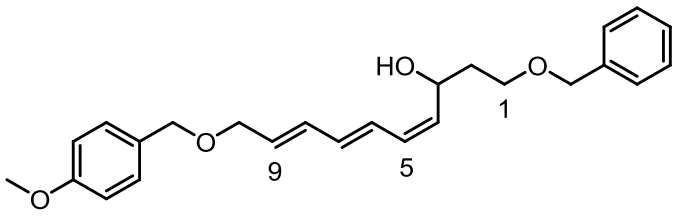
(4*Z*,6*E*)-1-(Benzyloxy)-8-((4-methoxybenzyl)oxy)-7-methylocta-4,6-dien-3-ol, 333



To a vial containing siloxane **316** (25 mg, 0.12 mmol, 1.0 eq.), vinyl iodide **329** (38 mg, 0.12 mmol, 1.0 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 1 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **333** (32mg, 0.084 mmol, 84%) as a yellow oil;

R_f 0.20 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3425, 2856, 1513, 1247, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.23 (7H, m, Ar*H*), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.38-6.25 (2H, m, *H*5 and *H*6), 5.48 (1H, dd, *J* = 10.5, and 8.5 Hz, *H*4), 4.89-4.81 (1H, m, *H*3), 4.52 (2H, s, OCH_2Ar), 4.39 (2H, s, OCH_2ArOCH_3), 3.93 (2H, s, *H*8), 3.80 (3H, s, ArOCH_3), 3.73-3.66 (1H, m, *H*1), 3.66-3.58 (1H, m, *H*1'), 2.73 (1H, bs, O*H*), 1.99-1.89 (1H, m, *H*2), 1.82-1.70 (1H, m, *H*2'), 1.79 (3H, s,C7CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.0, 137.0, 133.2, 130.4, 129.4, 128.5, 127.7, 127.6, 125.0, 121.3, 113.8, 75.5, 73.3, 71.6, 68.3, 67.0, 55.3, 36.9, 14.2; **HRMS** (ESI+) calc. for $C_{24}H_{30}O_4Na$ $[M+Na]^+$ 405.1946, found 405.1927.

(4*Z*,6*E*,8*E*)-1-(Benzyloxy)-10-((4-methoxybenzyl)oxy)deca-4,6,8-trien-3-ol, 335



Condition A: To a vial containing siloxane **316** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **334** (40 mg, 0.10 mmol, 1.2 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 30 min, the crude mixture was purified *via* column chromatography (petroleum / EtOAc (30%)) to give title compound **335** (32 mg, 0.081 mmol, 81%) as a yellow oil;

Condition B: To a vial containing siloxane **316** (25 mg, 0.10 mmol, 1.0 eq.), vinyl bromide **336** (34 mg, 0.12 mmol, 1.2 eq.) and $[allylPdCl]_2$ (0.9 mg, 0.0025 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 2 h, the crude product mixture was purified *via* column chromatography (petroleum / EtOAc (30%)) to give title compound **335** (23 mg, 0.058 mmol, 58%) as a yellow oil;

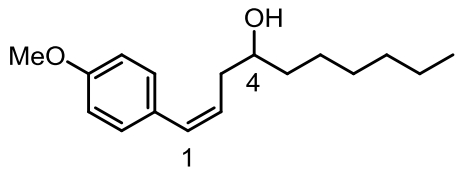
Condition C: To solution of siloxane **316** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **334** (40 mg, 0.12 mmol, 1.2 eq.) and $Pd(dba)_2$ (3.0 mg, 0.0050 mmol, 5.0 mol%) in DME (0.24 mL) was added $KOSiMe_3$ (32 mg, 0.25 mmol, 2.5 eq.). After stirring at RT for 30 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **335** (18 mg, 0.046 mmol, 46%) as a yellow oil;

R_f 0.20 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3428, 2861, 151, 1248, 1095; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-7.20 (7H, m, Ar*H*), 6.89 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.89-6,44 (1H, m, *H*6), 6.30-6.19 (2H, m, *H*7 and *H*8), 6,10-6,01 (1H,

m, *H*5), 5.81 (1H, dt, *J* = 14.0 and 6.0 Hz, *H*9), 5.44 (1H, dd, *J* = 10.5 and 9,0 Hz, *H*4), 4.88-4.77 (1H, m, *H*3), 4.50 (2H, s, OCH_2Ar), 4.43 (2H, s, OCH_2ArOCH_3), 4.03 (2H, d, *J* = 6,0 Hz, *H*10), 3.79 (3H, s, ArOCH_3), 3.71-3.65 (1H, m, *H*1), 3.63-3.55 (1H, m, *H*1'), 2.65 (1H, bs, O*H*), 1.99-1.88 (1H, m, *H*2), 1.80-1.70 (1H, m, *H*2'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.0, 133.8, 133.7, 132.5, 130.8 130.3, 129.6, 129.4, 128.5, 127.8, 127.7, 127.6, 113.8, 73.3, 71.8, 70.1, 68.2, 67.2, 55.3, 36.9; **HRMS** (ESI+) calc. for $C_{25}H_{30}O_4Na$ $[M+Na]^+$ 417.19105, found 417.19272.

6.13 Cross-coupling of 6-membered cyclic dimethyl siloxane

(*Z*)-1-(4-Methoxyphenyl)dec-1-en-4-ol, 300

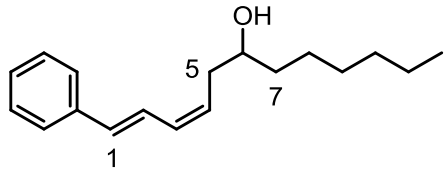


To a vial containing siloxane **292** (24 mg, 0.11 mmol, 1.1 eq.) was added TBAF•$3H_2O$ (0.2 mL, 1 M in THF, 0.20 mmol, 2.0 eq.) and the resulting mixture stirred for 5 min before iodoanisole (**299**) (24 mg, 0.10 mmol, 1.0 eq.) and $Pd(dba)_2$ (3.0 mg, 0.050 mmol, 5.0 mol%) were added sequentially. After stirring at RT for 30 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (5%) → petroleum ether / EtOAc (10%)) to give title compound **300** (25 mg, 0.95 mmol, 95%) as a yellow oil;

R_f 0.19 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3378, 2927, 1510, 1249, 816; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.10 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.72 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.37 (1H, d, *J* = 11.5 Hz, *H*1), 5.50 (1H, dt, *J* = 11.5 and 7.0 Hz, *H*2), 3.66 (3H, s, ArOCH_3), 3.57 (1H, quint, *J* = 12.5 and 6.0 Hz, *H*4), 2.39-2.30 (2H, m,

*H*3), 1.42 (1H, bs, O*H*), 1.38-1.04 (10H, m, *H*5-*H*9), 0.73 (3H, t, *J* = 7.0 Hz, *H*10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.4, 131.0, 130.0, 129.9, 126.8, 113.6, 71.9, 55.3, 37.1, 36.5, 31.8, 29.3, 25.7, 22.6, 14.1; **HRMS** (ESI+) calc. for $C_{17}H_{27}O_2Si$ $[M+H]^+$ 263.2006, found 263.2002.

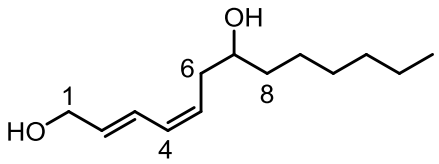
(*1E,3Z*)-1-Phenyldodeca-1,3-dien-6-ol, 301



To an oven-dried vial containing siloxane **292** (45 mg, 0.21 mmol, 1.1 eq.), iodostyrene (**220**) (44 mg, 0.19 mmol, 1.0 eq.) and $[allylPdCl]_2$ (1.7 mg, 0.0048 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.38 mL, 1 M in THF, 0.38 mmol, 2.0 eq.). After stirring at RT overnight, the crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **301** (24 mg, 0.093 mmol, 49%) as a yellow oil;

R_f 0.20 (petroleum Et_2O / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3355, 2954, 946, 691; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.18 (5H, m, Ar*H*), 7.06 (1H, ddd, *J* = 15.5, 11.0 and 1.0 Hz, *H*2), 6.58 (1H, d, *J* = 15.5 Hz, *H*1), 6.33 (1H, dd, *J* = 11.0 and 1.0 Hz, *H*3), 5.63-5.53 (1H, m, *H*4), 3.72 (1H, app. quint., *J* = 6.0 Hz, *H*6), 2.51-2.44 (2H, m, *H*5), 1.71-1.21 (10H, m, *H*7-*H*11), 0.83 (3H, t, *J* = 7.0 Hz, *H*12); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.4, 133.2, 131.6, 128.6, 128.2, 127.6, 126.5, 124.0, 71.6, 37.0, 36.1, 31.9, 29.3, 25.7, 22.6, 14.1; **HRMS** (ESI+) calc. for $C_{18}H_{27}O$ $[M+H]^+$ 259.2056, found 259.2058.

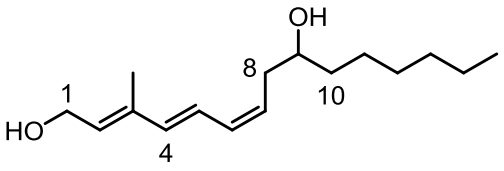
(2*E*,4*Z*)-Trideca-2,4-diene-1,7-diol, 302



To an oven-dried vial containing siloxane **292** (40 mg, 0.19 mmol, 1.0 eq.), vinyl iodide **330** (44 mg, 0.24 mmol, 1.3 eq.) and $[allylPdCl]_2$ (3.5 mg, 0.0096 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.57 mL, 1 M in THF, 0.57 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (40%)) to give title compound **302** (13 mg, 0.066 mmol, 34%) as a yellow oil;

R$_f$ 0.25 (petroleum ether / EtOAc (40%)); **IR** (thin film, ν_{max} / cm^{-1}) 3333, 2926, 1459, 986; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60-6.49 (1H, m, *H*3), 6.23-6.13 (1H, m, *H*4), 5.86 (1H, dt, *J* = 15.0 and 5.5 Hz, *H*2), 5.55-5.46 (1H, m, *H*5), 4.21 (1H, d, *J* = 5.5 Hz, *H*1), 3.66 (1H, app. quint., *J* = 6.0 Hz, *H*7), 2.40-2.31 (2H, m, *H*6), 1.69-1.18 (10H, m, *H*8-*H*12), 0.88 (3H, t, *J* = 7.0 Hz, *H*13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 133.0, 130.7, 128.1, 126.3, 71.5, 63.4, 37.0, 35.8, 31.8, 29.3, 25.7, 22.6, 14.1; **HRMS** (ESI+) calc. for $C_{13}H_{24}O_2Na$ $[M+Na]^+$ 235.1669, found 235.1670.

((2*E*,4*E*,6*Z*)-3-Methylpentadeca-2,4,6-triene-1,9-diol, 304

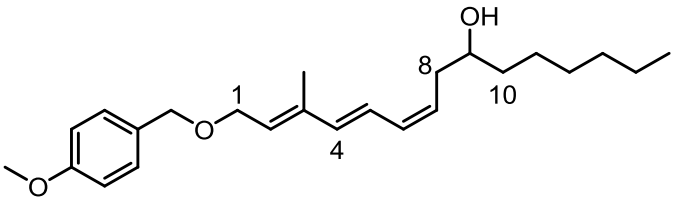


To a vial containing siloxane **292** (40 mg, 0.19 mmol, 1.0 eq.), vinyl iodide **228** (73 mg, 0.21 mmol, 1.1 eq.) and $[allylPdCl]_2$ (3.5 mg, 0.0096 mmol, 5.0 mol%) was added

TBAF•3H_2O (0.19 mL, 1 M in THF, 0.19 mmol, 1.0 eq.) followed by another batch of TBAF•3H_2O (0.57 mL, 1 M in THF, 0.57 mmol, 3.0 eq.) *via* syringe pump over 3 h. After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **304** (42 mg, 0.11 mmol, 58%) as a yellow oil;

R_f 0.16 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3333, 2927, 2856, 1456, 946; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.50 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*5), 6.26 (1H, d, *J* = 15.5 Hz, *H*4), 6.25-6.16 (1H, m, *H*6), 5.68 (1H, t, *J* = 7.0, *H*2), 5.55-5.44 (1H, m, *H*7), 4.29 (1H, d, *J* = 7.0 Hz, *H*1), 3.67 (1H, app. quint., *J* = 6.5 Hz, *H*9), 2.43-2.35 (2H, m, *H*8), 1.82 (3H, s, C3C*H*$_3$), 1.64 (2H, bs, O*H*), 1.55-1.18 (10H, m, *H*10-*H*14), 0.87 (3H, t, *J* = 7.0 Hz, *H*15); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.5, 136.3, 131.7, 130.8, 127.7, 123.5, 71.6, 59.4, 36.9, 26.0, 31.8, 29.3, 25.7, 22.6, 14.1, 12.6; **HRMS** (ESI+) calc. for $C_{16}H_{28}O_2Na$ $[M+Na]^+$ 275.1982, found 275.1984.

(9*Z*,11*E*,13*E*)-15-((4-Methoxybenzyl)oxy)-13-methylpentadeca-9,11,13-trien-7-ol, 305

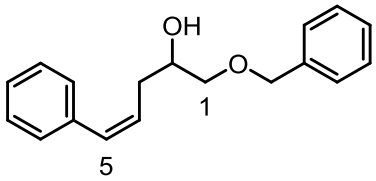


To an oven-dried vial containing siloxane **292** (40 mg, 0.19 mmol, 1.0 eq.), vinyl iodide **306** (73 mg, 0.21 mmol, 1.1 eq.) and $[allylPdCl]_2$ (3.5 mg, 0.0096 mmol, 5.0 mol%) was added TBAF•3H_2O (0.19 mL, 1 M in THF, 0.19 mmol, 1.0 eq.) followed by another batch of TBAF•3H_2O (0.57 mL, 1 M in THF, 0.57 mmol, 3.0 eq.) *via* syringe pump over 3 h. After stirring at RT overnight, the crude product was

purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **305** (42 mg, 0.11 mmol, 59%) as a yellow oil;

R$_f$ 0.24 (petroleum ether / EtOAc (15%)); **IR** (thin film, ν_{max} / cm^{-1}) 3434, 2927, 1513, 1247, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (2H, d, J = 8.5 Hz, ArH), 6.88 (2H, d, J = 8.5 Hz, ArH), 6.49 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*5), 6.29 (1H, d, *J* = 15.5 Hz, *H*4), 6.26-6.16 (1H, m, *H*6), 5.73-5.64 (1H, m, *H*2), 5.54-5.44 (1H, m, *H*7), 4.45 (2H, s, OC*H*$_2$Ar), 4.14 (1H, d, *J* = 6.5 Hz, *H*1), 3.81 (3H, s, ArOC*H*$_3$), 3.74-3.61 (1H, m, *H*9), 2.43-2.36 (2H, m, *H*8), 1.79 (3H, s, C3C*H*$_3$), 1.56-1.23 (11H, m, *H*10-*H*14 and O*H*), 0.88 (3H, t, *J* = 7.0 Hz, *H*15); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 137.7, 137.0, 131.8, 129.5, 129.4, 128.9, 127.5, 123.2, 113.8, 71.9, 71.6, 66.3, 55.3, 36.9, 36.0, 31.8, 29.3, 25.7, 22.6, 14.1, 12.8; **HRMS** (ESI+) calc. for $C_{24}H_{36}O_3Na$ $[M+Na]^+$ 395.2557, found 398.2556.

(*Z*)-1-(Benzyloxy)-5-phenylpent-4-en-2-ol, 337

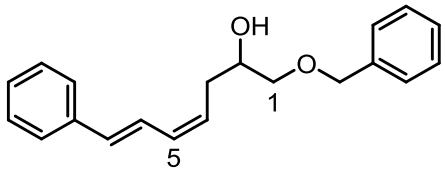


Condition A: To a vial containing siloxane **308** (50 mg, 0.20 mmol, 1.0 eq.), iodobenzene (**324**) (49 mg, 0.24 mmol, 1.2 eq.) and $Pd(dba)_2$ (6.0 mg, 0.010 mmol, 5.0 mol%) was added TBAF•3H_2O (0.4 mL, 1 M in THF, 0.40 mmol, 2.0 eq.). After stirring at RT for 5 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **337** (49 mg, 0.18 mmol, 91%) as a yellow oil;

Condition B: To solution of siloxane **308** (50 mg, 0.20 mmol, 1.0 eq.), iodobenzene (**324**) (49 mg, 0.24 mmol, 1.2 eq.) and $Pd(dba)_2$ (6.0 mg, 0.010 mmol, 5.0 mol%) in DME (0.48 mL) was added $KOSiMe_3$ (64 mg, 0.50 mmol, 2.5 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (15%)) to give title compound **337** (31 mg, 0.12 mmol, 60%) as a yellow oil;

$\mathbf{R}_f$ 0.25 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3405, 2862, 1099, 737, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.41-7.22 (10H, m, Ar*H*) 6.58 (1H, dt, *J* = 11.5 and 1.5 Hz, *H*5), 5.77 (1H, dt, *J* = 11.5 and 7.5 Hz, *H*4), 4.55 (2H, s, OCH_2Ar), 4.02-3.91 (1H, m, *H*2), 3.54 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.40 (1H, dd, *J* = 9.5 and 7.5 Hz, *H*1'), 2.61-2.51 (3H, m, *H*3 and O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.9, 137.3, 131.2, 128.8, 128.5, 128.3, 127.9, 127.8, 127.7, 126.8, 74.0, 73.4, 70.5, 32.5; **HRMS** (ESI+) calc. for $C_{18}H_{20}O_2Na$ $[M+Na]^+$ 291.1356, found 291.1355.

(4*Z*,6*E*)-1-(Benzyloxy)-7-phenylhepta-4,6-dien-2-ol, 338

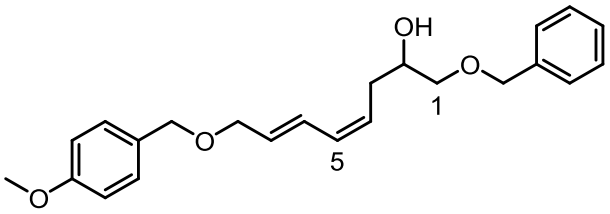


Condition A: To a vial containing siloxane **308** (25 mg, 0.10 mmol, 1.0 eq.), iodostyrene (**220)** (28 mg, 0.12 mmol, 1.2 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 8 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **338** (22 mg, 0.075 mmol, 75%) as a yellow oil;

Condition B: To a vial containing siloxane **308** (25 mg, 0.11 mmol, 1.1 eq.), bromostyrene (**327**) (18 mg, 0.10 mmol, 1.0 eq.) and $[allylPdCl]_2$ (0.9 mg, 0.0025 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT for 5 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **338** (20 mg, 0.068 mmol, 68%) as a yellow oil;

R_f 0.19 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3437, 2859, 1595, 1092, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.19 (10H, m, Ar*H*), 7.06(1H, dd, *J* = 15.5 and 11.0 Hz, *H*6), 6.57 (1H, d, *J* = 15.5 Hz, *H*7), 6.50 (1H, t, *J* = 11.0 Hz, *H*5), 5.56 (1H, dt, *J* = 11.0 and 8.0 Hz, *H*4), 4.57 (2H, s, OCH_2Ar), 3.99-3.89 (1H, m, *H*2), 3.57 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.44 (1H, dd, *J* = 9.5 and 7.5 Hz, *H*1'), 2.58-2.50 (2H, m, *H*3), 2.41 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.9, 137.4, 133.2, 131.4, 128.6, 128.5, 127.8, 127.7, 127.6, 127.4, 126.5, 124.0, 73.7, 73.5, 70.3, 32.1; **HRMS** (ESI+) calc. for $C_{20}H_{22}O_2Na$ $[M+Na]^+$ 317.1512, found 317.1501.

(4*Z*,6*E*)-1-(benzyloxy)-8-((4-methoxybenzyl)oxy)octa-4,6-dien-2-ol, 339



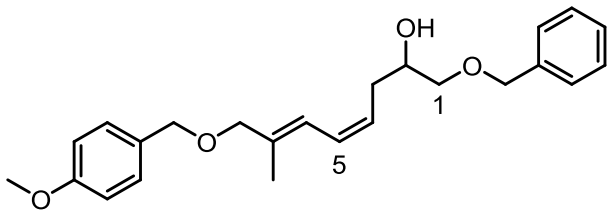
Condition A: To a vial containing siloxane **308** (30 mg, 0.12 mmol, 1.2 eq.), vinyl iodide **328** (30 mg, 0.10, 1.0 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether

/ EtOAc (20%) → petroleum ether / EtOAc (30%)) to give title compound **339** (24 mg, 0.065 mmol, 65%) as a yellow oil;

Condition B: To a vial containing siloxane **308** (30 mg, 0.12 mmol, 1.2 eq.), vinyl bromide **332** (26 mg, 0.10, 1.0 eq.) $[allylPdCl]_2$ (0.90 mg, 0.0025 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%) → petroleum ether / EtOAc (30%)) to give title compound **339** (22 mg, 0.060 mmol, 60%) as a yellow oil;

$\mathbf{R_f}$ 0.19 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3433, 2856, 1513, 1247, 989; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39-7.25 (7H, m, Ar*H*), 6.87 (2H, d, *J* = 8,5 Hz, Ar*H*), 6.56-6.47 (1H, m, *H*6), 6.11 (1H, t, *J* = 11.0 Hz, *H*5), 5.80 (1H, dt, *J* = 12.5 and 6.0 Hz, *H*7), 5.47 (1H, dt, *J* = 11.0 and 7.5 Hz, *H*4), 4.54 (2H, s, OCH_2Ar), 4.43 (2H, s, OCH_2ArOCH_3), 4.03 (2H, d, *J* = 6.0 Hz, *H*8), 3.91-3.83 (1H, m, *H*2), 3.78 (3H, s, ArOCH_3), 3.51 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.37 (1H, dd, *J* = 9.5 and 7.5 Hz, *H*1'), 2.45-2.33 (3H, m, *H*3 and O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.0, 130.7, 130.4, 130.3, 129.5, 128.5, 127.8, 127.7, 127.6, 127.1, 113.8, 73.8, 73.4, 71.9, 70.3, 70.2, 55.3, 31.8; **HRMS** (ESI+) calc. for $C_{23}H_{28}O_4Na$ $[M+Na]^+$ 319.1880, found 391.1873.

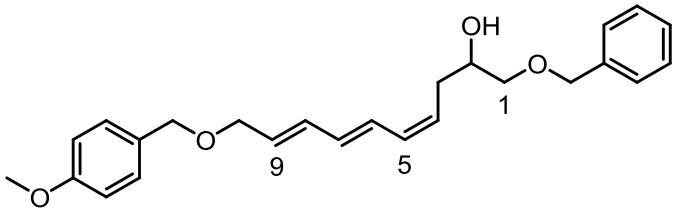
(4*Z*,6*E*)-1-(Benzyloxy)-8-((4-methoxybenzyl)oxy)-7-methylocta-4,6-dien-2-ol, 340



To a vial containing siloxane **308** (25 mg, 0.12 mmol, 1.0 eq.), vinyl iodide **329** (38 mg, 0.12, 1.0 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%) → petroleum ether / EtOAc (30%)) to give title compound **340** (27 mg, 0.073 mmol, 73%) as a yellow oil;

R_f 0.23 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3446, 2856, 1513, 1247, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.28 (7H, m, Ar*H*), 6.87 (2H, d, *J* = 8,5 Hz, Ar*H*), 6.40-6.26 (1H, m, *H*5 and *H*6), 5.55-5.45 (1H, m, *H*4), 4.54 (2H, s, OCH_2Ar), 4.39 (2H, s, OCH_2ArOCH_3), 3.93 (2H, s, *H*8), 3.93-3.83 (1H, m, *H*2), 3.79 (3H, s, ArOCH_3), 3.52 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.38 (1H, dd, *J* = 9.5 and 7.5 Hz, *H*1'), 2.44-2.38 (2H, m, *H*3), 2.37 (1H, d, *J* = 3.5 Hz, O*H*), 1.78 (3H, s, C7CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 138.0, 135.8, 130.5, 129.4, 128.5, 127.8, 127.7, 126.6, 126.5, 121.7, 113.8, 75.7, 73.9, 73.4, 71.5, 70.3, 55.3, 31.7, 14.3; **HRMS** (ESI+) calc. for $C_{24}H_{30}O_4Na$ $[M+Na]^+$ 405.2036, found 405.2028.

(4*Z*,6*E*,8*E*)-1-(Benzyloxy)-10-((4-methoxybenzyl)oxy)deca-4,6,8-trien-2-ol, 341



Condition A: To a vial containing siloxane **308** (25 mg, 0.10 mmol, 1.0 eq.), vinyl iodide **334** (40 mg, 0.12, 1.2 eq.) and $Pd(dba)_2$ (2.9 mg, 0.0050 mmol, 5.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **341** (25 mg, 0.063 mmol, 63%) as a yellow oil;

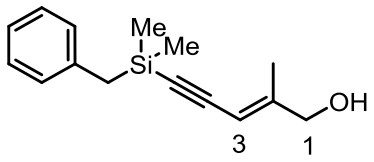
Condition B: To a vial containing siloxane **308** (25 mg, 0.10 mmol, 1.0 eq.), vinyl bromide **336** (34 mg, 0.12, 1.2 eq.) and $[allylPdCl]_2$ (0.90 mg, 0.0025 mmol, 2.5 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 3.0 eq.). After stirring at RT overnight, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **341** (21 mg, 0.053 mmol, 53%) as a yellow oil;

R_f 0.17 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3443, 2856, 1513, 1247, 944; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39-7.25 (7H, m, Ar*H*), 6.89 (2H, d, *J* = 8,5 Hz, Ar*H*), 6.89 (1H, dd, *J* = 14.0 and 11.5 Hz, *H*6), 6.35-6.10 (3H, m, *H*5, *H*7 and *H*8), 5.82 (1H, dt, *J* = 14.5 and 6.0 Hz, *H*9), 5.50 (1H, dt, *J* = 10.5 and 8.0 Hz, *H*4), 4.55 (2H, s, O*CH*$_2$Ar), 4.45 (2H, s, O*CH*$_2$ArOCH$_3$), 4.05 (2H, d, *J* = 6.0 Hz, *H*10), 3.93-3.85 (1H, m, *H*2), 3.81 (3H, s, ArOC*H*$_3$), 3.53 (1H, dd, *J* = 9.5 and 3.5 Hz, *H*1), 3.39 (1H, dd, *J* = 9.5 and 7.0 Hz, *H*1'), 2.47-2.40 (2H, m, *H*3), 2.37 (1H, d, *J* = 4.0 Hz, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 137.9, 132.8, 132.7, 131.0, 130.4, 130.2,

129.4, 128.5, 128.0, 127.8, 127.7, 127.4, 113.8, 73.7, 73.4, 71.8, 70.2, 70.1, 55.3, 31.9; **HRMS** (ESI+) calc. for $C_{25}H_{30}O_4Na$ $[M+Na]^+$ 417.2036, found 417.2045.

6.14 C6-C13 Cyclic dimethyl alkenylsiloxane synthesis

(*E*)-5-(Benzyldimethylsilyl)-2-methylpent-2-en-4-yn-1-ol, 354

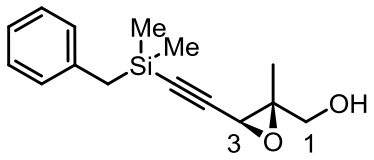


To a degassed (N_2 bubbling, 15 min) solution of vinyl iodide **91** (7.01 g, 35.4 mmol, 1.0 eq.) and alkyne **286** (6.47 g, 37.1 mmol, 1.05 eq.) in THF (142 mL) was added copper(I) iodide (674 mg, 3.54 mmol, 10.0 mol%) and $PdCl_2(PPh_3)_2$ (248 mg, 0.354 mmol, 1.0 mol%). The mixture was further degassed (N_2 bubbling) for 15 min, during which diisopropylamine (40.0 mL, 283 mmol, 8.0 eq.) was added dropwise *via* syringe. The resulting suspension was sonicated for 1h followed by further stirring at RT overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (150 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 150 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **354** as a dark reddish oil (8.52 g, 34.9 mmol, 99%);

R_f 0.27 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3321, 2960, 2134, 1494, 833; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26-7.19 (2H, m, Ar*H*), 7.13-7.06 (3H, m, Ar*H*), 5.63-5.59 (1H, m, *H*3), 2.23 (2H, s, CH_2Ar), 1.89 (3H, s, C2CH_3), 1.53 (1H, t, *J* = 6.5 Hz, O*H*), 0.16 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 153.9, 141.0,

130.3, 130.1, 126.3, 106.5, 105.7, 98.7, 68.7, 28.3, 15.6, 0.0; **HRMS** (ESI+) calc. for $C_{15}H_{21}OSi$ $[M+H]^+$ 245.1356, found 245.1358.

((2*S*,3*S*)-3-((Benzyldimethylsilyl)ethynyl)-2-methyloxiran-2-yl)methanol, 355



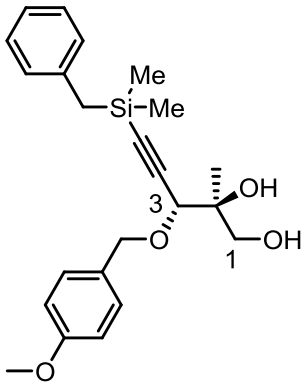
Racemic preparation: To a solution of enyne **354** (100 mg, 0.41 mmol, 1.0 eq.) in CH_2Cl_2 (1.6 mL) was added MCPBA (139 mg, 0.62 mmol, 1.5 eq.). After stirring at RT overnight, the reaction mixture was quenched with a saturated aqueous solution of Na_2SO_3 (20 mL) and diluted with Et_2O (20 mL), the organic layer separated and washed sequentially with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum / EtOAc (20%)) to give racemic epoxide **355** (71 mg, 0.27 mmol, 67%) as a clear oil;

Asymmetric preparation: 4Å Molecular sieves (932 mg, 30% w/w) were added to a Schlenk tube, evacuated and the sieves activated by heat. The tube was allowed to reach RT, filled with nitrogen and CH_2Cl_2 (42 mL) added. The flask was then cooled to −30 °C and titanium tetraisopropoxide (1.9 mL, 6.35 mmol, 0.5 eq.) and L-(+)-diisopropyl tartrate (1.60 mL, 7.62 mmol, 0.6 eq.) were added and the resulting mixture stirred for 30 min. Subsequently, a solution of enyne **354** (3.11 g, 12.1 mmol, 1.0 eq.) in CH_2Cl_2 (13 mL) was added and stirred for further 30 min after which *t*-butyl hydroperoxide (4.60 mL, 5.5 M solution in decane (over 4Å molecular sieves), 25.4 mmol, 2.0 eq.) was added slowly. After stirring at −30 °C overnight, the reaction

was quenched by slow addition to a freshly prepared solution of Iron(II) sulfate hydrate (17.4 g, 114.3 mmol, 9.0 eq.) and tartaric acid (5.70 g, 38.1 mmol, 3.0 eq.) in water (40 mL) at 0 °C. After vigorous stirring for 1 h, the organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 40 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was redissolved in Et_2O (50 mL) followed by slow addition of asolution of NaOH (30 mL, 30% w/v) in brine, at 0 °C. After stirring vigorously for 1 h, the organic layer was separated and the aqueous layer further extracted with Et_2O (2 × 30 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **355** as an yellowish oil (2.56 g, 9.90 mmol, 78%);

$\boldsymbol{[\alpha]_D^{25}}$ +2.8 (*c* 0.82, $CHCl_3$); 90% *ee* (CHIRALPAK 1A, 2.5% IPA / hexane, 1.0 mL/min, t_R (2*S*, 3*S*) 9.65 min, t_R (2*R*, 3*R*) 12.48 min); $\mathbf{R}_f$ 0.23 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3414, 2961, 2180, 1250, 835; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, ArH), 7.13-7.04 (3H, m, Ar*H*), 3.75 (1H, dd, *J* = 12.5 and 4.0 Hz, *H*1), 3.64 (1H, dd, *J* = 12.5 and 9.5 Hz, *H*1'), 3.58 (1H, s, *H*3), 2.21 (2H, s, SiCH_2Ar), 1.63 (1H, dd, *J* = 9.5 and 4.0 Hz, O*H*), 1.42 (3H, s, CH_3), 0.15 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 140.8, 130.6, 130.5, 126.8, 103.8, 92.6, 65.7, 65.4, 50.3, 28.2, 17.7, 0.0; **HRMS** (ESI+) calc. for $C_{15}H_{20}O_2NaSi$ $[M+Na]^+$ 283.1125, found 283.1125.

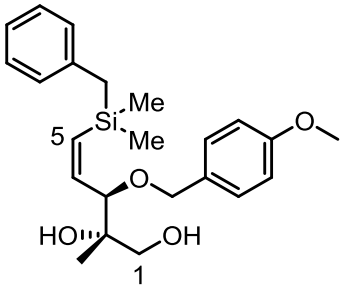
(2*S*,3*R*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-yne-1,2-diol, 356



To a stirred suspension of epoxide **355** (1.66 g, 6.36 mmol, 1.0 eq.), europium(III) triflate (761 mg, 1.27 mmol, 0.2 eq.) and 2,6-di-tert-butyl-4-methylpyridine (DTBMP) (261 mg, 1.27 mmol, 0.2 eq.) in toluene (37 mL) was added 4-methoxybenxyl alcohol (1.2 mL, 9.54 mmol, 1.5 eq.). After stirring at 60 °C overnight, the reaction mixture was allowed to reach RT then concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (50%)) to give title compound **356** as an yellowish oil (1.92 g, 5.00 mmol, 79%);

$[\alpha]_D^{25}$ +82 (*c* 1.0, $CHCl_3$); **R_f** 0.12 (petroleum ether / Et_2O (50%)); **IR** (thin film, ν_{max} / cm^{-1}) 3429, 2958, 2170, 1514, 1249, 1034, 834; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.20 (4H, m, Ar*H*), 7.13-7.06 (3H, m, ArH), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 4.72 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.38 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 4.07 (1H, s, *H*3), 3.87 (1H, dd, *J* = 11.5 and 4.0 Hz, *H*1), 3.81 (3H, s, ArOCH_3), 3.39 (1H, dd, *J* = 11.5 and 9.5 Hz, *H*1'), 2.84 (1H, s, C2O*H*), 2.28 (1H, dd, *J* = 9.5 and 4.0 Hz, C1O*H*), 2.23 (2H, s, SiCH_2Ar), 1.18 (3H, s, C2CH_3), 0.19 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.8, 129.9, 129.2, 128.4, 28.4, 124.7, 114.0, 103.0, 92.1, 75.8, 73.7, 71.3, 67.3, 55.4, 31.1, 26.1, 20.8, −1.9; **HRMS** (ESI+) calc. for $C_{23}H_{30}O_4NaSi$ $[M+Na]^+$ 421.1806, found 421.1797.

(2*S*,3*R*,*Z*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)-2-methylpent-4-ene-1,2-diol, 357

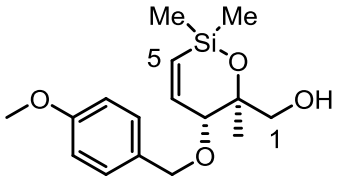


To an oven dried round-bottom flask, equipped with a stirrer bar, was added Pd on $CaCO_3$ (85 mg, 5 w% Pd, 0.040 mmol, 5.0 mol%). The flask was evacuated, filled with nitrogen, toluene (6 mL) added and the flask purged with hydrogen. Subsequently a solution of alkyne **356** (308 mg, 0.80 mmol, 1.0 eq.), quinoline (47 µL, 0.40 mmol, 50 mol%) and cyclohexene (0.8 mL) in toluene (1.2 mL) was added *via* syringe and hydrogenation continued until completion (1 h, monitored by TLC (visualised with vanillin)). The reaction mixture was then filtered through Celite and the filtrate concentrated *in vacuo* to give title compound **357** (322 mg, 0.80 mmol, quant.) which could be used without further purification. Purification *via* column chromatography (petroleum ether / Et_2O (70%)) gave an analytically pure sample of **357** (34 mg, 0.088 mmol, 70%) as a clear oil;

$\boldsymbol{[\alpha]_D^{25}}$ +30 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.25 (petroleum ether / Et_2O (70%)); **IR** (thin film, ν_{max} / cm^{-1}) 3437, 2955, 1514, 1248, 830; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24-7.13 (4H, m, Ar*H*), 7.10-6.97 (3H, m, ArH), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.26 (1H, dd, *J* = 14.5 and 10.0 Hz, *H*4), 5.98 (1H, d, *J* = 14.5 Hz, *H*5), 4.44 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.15 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 3.98 (1H, d, *J* = 10.0 Hz, *H*3), 3.81 (3H, s, ArOCH_3), 3.75 (1H, dd, *J* = 11.5 and 4.0 Hz, *H*1), 3.35 (1H, dd, *J* = 11.5 and 9.0 Hz, *H*1'), 2.72 (1H, s, C2O*H*), 2.39 (1H, dd, *J* = 9.0 and 4.0 Hz, C1O*H*), 2.23-2.10 (2H, m,

SiCH_2Ar), 1.07 (3H, s, C2CH_3), 0.13 (3H, s, SiCH_3), 0.13 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.2, 139.4, 136.0, 130.0, 129.2, 128.3, 128.2, 128.1, 124.3, 113.9, 84.0, 73.4, 70.4, 67.5, 55.3, 26.6, 20.7, −1.3, −1.4 ; **HRMS** (ESI+) calc. for $C_{23}H_{32}O_4NaSi$ $[M+Na]^+$ 423.1962, found 423.1942.

((5*R*,6*S*)-5-((4-methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methanol, 358

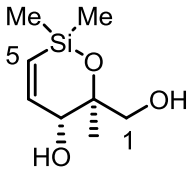


To a solution of vinylsilane **357** (322 mg, 0.80 mmol, 1.0 eq.) in THF (4.0 mL) was added TBAF•3H_2O (0.8 mL, 1 M in THF, 0.80 mmol, 1.0 eq.). After stirring at RT for 1 h, the resulting mixture was diluted with Et_2O (10 mL) and quenched with a 1 M aqueous HCl solution (10 mL), the organic layer was separated and the aqueous layer further extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **358** as a clear oil (177 mg, 0.57 mmol, 72%);

$[\alpha]_D^{25}$ −75 (*c* 1.0, $CHCl_3$); R_f 0.57 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 3475, 2956, 1514, 1248, 845; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.70 (1H, dd, *J* = 15.0 and 1.5 Hz, *H*4), 5.88 (1H, dd, *J* = 15.0 and 2.5 Hz, *H*5), 4.63 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.51 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 4.19 (1H, dd, *J* = 2.5 and 1.5 Hz, *H*3), 3.80 (3H, s, ArOCH_3), 3.60 (1H, dd, *J* = 11.0 and 10.0 Hz, *H*1), 3.40 (1H, dd, *J* = 11.0 and 3.5 Hz, *H*1'), 2.14 (1H, dd, *J* = 10.0 and 3.5 Hz, C1O*H*), 1.16 (3H, s, C2CH_3), 0.20 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.0, 148.8, 130.0, 129.1, 126.7,

113.5, 77.7, 76.1, 71.9, 68.2, 55.0, 18.1, 0.6, 0.0; **HRMS** (ESI+) calc. for $C_{16}H_{24}O_4NaSi$ $[M+Na]^+$ 331.1336, found 331.1325.

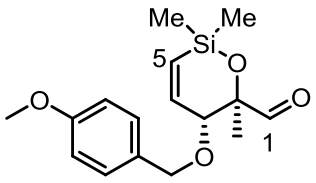
(5*R*,6*S*)-6-(Hydroxymethyl)-2,2,6-trimethyl-5,6-dihydro-2H-1,2-oxasilin-5-ol, 387



To a solution of siloxane **358** (35 mg, 0.11 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) and water (0.1 mL) was added DDQ (27 mg, 0.12 mmol, 1.1 eq.). After stirring at RT for 2 h, the resulting mixture was diluted with water (10 mL) and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **387** along with 4-methoxybenzaldehyde which was used directly for ^{1}H NMR spectroscopic studies.

^{1}H NMR (400 MHz, d_8-THF) δ_H 6.56 (1H, dd, *J* = 14.5 and 1.5 Hz, *H*4), 5.90 (1H, dd, *J* = 14.5 and 3.0 Hz, *H*5), 4.32-4.28 (1H, m, *H*3), 3.79 (1H, d, *J* = 10.5 Hz, *H*1), 3.61 (1H, d, *J* = 10.5 Hz, *H*1'), 1.40 (3H, s, C2CH_3), 1.29 (1H, bs, O*H*), 0.20 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3').

(5*R*,6*R*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2H-1,2-oxasiline-6-carbaldehyde, 360

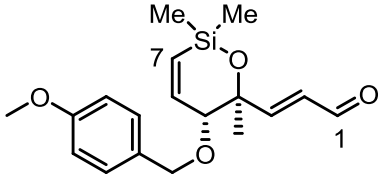


To a solution of oxalyl chloride (0.26 mL, 3.04 mmol, 2.0 eq.) in CH_2Cl_2 (12 mL) was added DMSO (0.43 mL, 6.08 mmol, 4.0 eq.) *via* syringe, at −78 °C. After stirring for

15 min, a solution of **358** (470 mg, 1.52 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL) was added *via* syringe and the resulting mixture stirred for 1 h. Next, Et_3N (0.84 mL, 6.08 mmol, 4.0 eq.) was added, the cooling bath removed and the reaction mixture allowed to reach RT. After stirring at RT for 1 h, the reaction was quenched with water (20 mL), the organic layer separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give aldehyde **360** (512 mg, 1.52 mmol, quant.) which was used without further purification. Purification *via* column chromatography (petroleum ether / EtOAc (20%)) gave an analytical sample (60 mg, 0.20 mmol, 75%) as a clear oil;

$[\alpha]_D^{25}$ −104 (*c* 1.0, $CHCl_3$); R_f 0.27 (petroleum ether / EtOAc (10%); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 1744, 1514, 1249, 847; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.47 (1H, s, *H*1), 7.23 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.75 (1H, dd, *J* = 14.5 and 3.5 Hz, *H*4), 6.03 (1H, dd, *J* = 14.5 and 1.5 Hz, *H*5), 4.60 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.44 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 4.08 (1H, dd, *J* = 3.5 and 1.5 Hz, *H*3), 3.81 (3H, s, ArOCH_3), 1.36 (3H, s, C2CH_3), 0.25 (3H, s, SiCH_3), 0.22 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.0, 125.5, 145.9, 129.7, 128.9, 128.6, 112.9, 80.7, 73.1, 70.2, 54.4, 17.1, 0.0, −0.4; **HRMS** (ESI+) calc. for $C_{16}H_{22}O_4NaSi$ $[M+Na]^+$ 329.1180, found 329.1181.

(*E*)-3-((5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)acrylaldehyde, 359

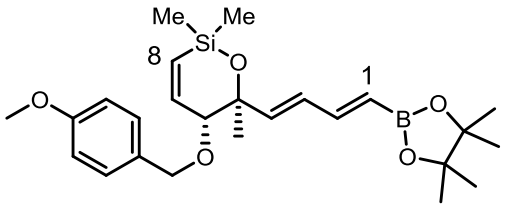


A solution of aldehyde **360** (466 mg, 1.52 mmol, 1.0 eq.) and phosphorane **98** (925 mg, 3.04 mmol, 2.0 eq.) in toluene (15 mL) was stirred at 80 °C overnight. The resulting

mixture was concentrated *in vacuo* and the crude residue purified *via* column chromatography (petroleum ether / Et_2O (15%)) to give title compound **359** (355 mg, 1.07 mmol, 70% over two steps) as a bright yellow oil;

$[\alpha]_D^{25}$ −86 (*c* 1.0, $CHCl_3$); R_f 0.29 (petroleum ether / Et_2O (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 1689, 1514, 1250, 1083; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.48 (1H, d, J = 8.0 Hz, *H*1), 7.24 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.91 (1H, d, *J* = 15.5 Hz, *H*3), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.78 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*6), 6.33 (1H, dd, *J* = 15,5 and 8.0 Hz, *H*2), 5.98 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*7), 4.65 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.39 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 3.85 (1H, app t, *J* = 2.0 Hz, *H*5), 3.81 (3H, s, ArOCH_3), 1.36 (3H, s, C4CH_3), 0.22 (3H, s, SiCH_3), 0.16 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.3, 161.9, 158.7, 146.5, 129.2, 128.9, 128.8, 128.0, 113.1, 78.6, 71.1, 54.5, 20.2, 0.0, −0.7; **HRMS** (ESI+) calc. for $C_{19}H_{28}O_5NaSi$ $[M+Na+MeOH]^+$ 387.1598, found 387.1598.

(5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2,6-trimethyl-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-2H-1,2-oxasiline, 352

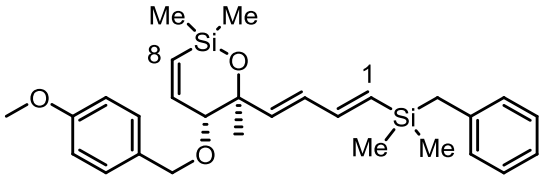


Chromium(II) chloride (787 mg, 6.40 mmol, 8.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The flask was allowed to reach RT, filled with nitrogen and THF (10.0 mL) was added. The resulting grey suspension was stirred for 30 min at 50 °C after which a solution of aldehyde **359** (266 mg, 0.81 mmol, 1.0 eq.) and boronate **200** (337 mg, 1.60 mmol, 2.0 eq.) in THF (3 mL) was added *via* syringe, followed by addition of a solution of LiI (428 mg, 3.20 mmol, 4.0 eq.) in THF (3.0 mL)

by a similar method. After stirring at 50 °C for 16 h, the resulting brown suspension was diluted with Et_2O (10 mL) and filtered through Celite. The filtrate was washed with water (25 mL) then brine (2 × 25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **352** as a bright yellow oil (255 mg, 0.56 mmol, 70%);

$[\alpha]_D^{25}$ −41 (*c* 1.0, $CHCl_3$); **R$_f$** 0.33 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2978, 1606, 1356, 1250, 826; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.01 (1H, dd, *J* = 17.5 and 10.5 Hz, *H*2), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.65 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*7), 6.39 (1H, dd, *J* = 15,0 and 10.5 Hz, *H*3), 6.10 (1H, d, *J* = 15.0 Hz, *H*4), 5.93 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*8), 5.55 (1H, d, *J* = 17.5 Hz, *H*1), 4.56 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.23 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 3.81 (3H, s, ArOCH_3), 3.81 (1H, app t, *J* = 2.0 Hz, *H*6), 1.31 (3H, s, C5CH_3), 1.28 (12H, s, Bpin*H*), 0.21 (3H, s, SiCH_3), 0.16 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.9, 148.1, 144.3, 130.3, 129.8, 129.4, 128.8, 119.3, 113.8, 83.1, 80.6, 72.1, 55.3, 24.8, 24.7, 24.4, 21.9, 0.9, 0.3; **HRMS** (ESI+) calc. for $C_{25}H_{37}BO_5NaSi$ $[M+Na]^+$ 479.2396, found 479.2396.

(5*R*,6*S*)-6-((1*E*,3*E*)-4-(Benzyldimethylsilyl)buta-1,3-dien-1-yl)-5-((4-methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2H-1,2-oxasiline, 353



Chromium(II) chloride (398 mg, 3.24 mmol, 6.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The flask was allowed to reach RT, filled with nitrogen and THF (10 mL) was added. The resulting grey suspension was stirred for

30 min after which a solution of aldehyde **359** (180 mg, 0.54 mmol, 1.0 eq.) and silane **202** (292 mg, 0.70 mmol, 1.3 eq.) in THF (4 mL) was added *via* syringe. After stirring at RT overnight, the resulting purple suspension was diluted with Et_2O (15 mL) and filtered through Celite. The filtrate was washed with water (20 mL) then brine (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether / Et_2O (0%) → petroleum ether / Et_2O (10%)) to give title compound **353** as a pale yellow oil (164 mg, 0.34 mmol, 63%);

$[\alpha]_D^{25}$ −45 (*c* 1.0, $CHCl_3$); R_f 0.51 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2955, 1514, 1249, 1083, 826; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.20-7.10 (4H, m, Ar*H*), 7.05-6.62 (3H, m, Ar*H*), 6.78 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.76-6.62 (3H, m, *H*2, *H*3 and *H*7), 6.16 (1H, d, *J* = 14.5 Hz, *H*4), 5.91-5.82 (2H, m, *H*1 and *H*8), 4.45 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.29 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 3.90 (1H, app t, *J* = 2.0 Hz, *H*6), 3.30 (3H, s, ArOCH_3), 2.06 (2H, s, SiCH_2Ar), 1.55 (3H, s, C5CH_3), 0.21 (3H, s, SiCH_3), 0.20 (3H, s SiCH_3'), 0.05 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 159.6, 148.7, 145.6, 141.4, 39.9, 130.9, 130.5, 129.5, 128.4, 128.3, 128.2, 124.2, 113.8, 80.9, 77.2, 71.9, 54.5, 26.0, 22.3, 0.8, 0.2, −3.5, −3.6; **HRMS** (ESI+) calc. for $C_{28}H_{38}O_3NaSi_2$ $[M+Na]^+$ 501.2252, found 501.2276.

6.15 C14-C23 tetraenyl bromide fragment synthesis

(Dibromomethyl)triphenylphosphonium bromide, 362

$[Ph_3PCHBr_2]Br•MeCN$

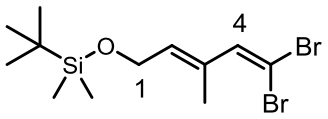
To a stirred suspension of PPh_3 (5.25 g, 20.0 mmol, 2.0 eq.) in CH_2Cl_2 (50 mL) was added CBr_4 (3.32 g, 10.0 mmol, 1.0 eq.). After stirring for 30 min, the reaction was

quenched with water (50 mL), the organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was redissolved in MeCN (30 mL) and sonicated for 30 min. The resulting solid was filtered, washing several times with MeCN, and dried *in vacuo* to give the title compound **362** (3.74 g, 6.72 mmol, 67%) as a white solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.2-10.1 (1H, m, C*H*Br_2), 8.18-8.07 (6H, m, Ar*H*), 7.84-7.77 (3H, m, Ar*H*), 7.74-7.64 (6H, m, Ar*H*), 1.99 (3H, s, CH_3CN).

The physical and spectroscopic data was found to be in agreement with that reported by Tosic and Mattay.[193]

(*E*)-*tert*-Butyl((5,5-dibromo-3-methylpenta-2,4-dien-1-yl)oxy)dimethylsilane, 364



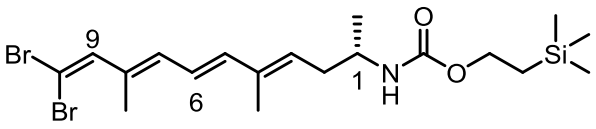
To a stirred suspension of phosphonium salt **362** (534 mg, 0.96 mmol, 2.0 eq.) in THF (2.9 mL) was added a solution of *t*-BuOK (0.91 mL, 1.0 M in THF, 0.91 mmol, 1.9 eq.) *via* syringe. The resulting brown to yellow solution was stirred for 5 min, followed by addition of aldehyde **363** (102 mg, 0.48 mmol, 1.0 eq.) in THF (1 mL). After 10 min the reaction was quenched with brine (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (5%)) to give title compound **364** (135 mg, 0.36 mmol, 75%);

R_f 0.67 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.94 (1H, s, *H*4), 5.76-5.71 (1H, m, *H*2), 4.26-4.23 (2H, m, *H*1), 1.83 (3H, d, *J* = 1.0 Hz, C3CH_3)

0.90 (9H, s, SiC(CH_3)$_3$), 0.075 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 140.1, 134.7, 131.9, 87.2, 60.0, 25.9, 18.4, 15.7, −5.1.

The physical and spectroscopic data was found to be in agreement with that reported by Satake *et al*.[194]

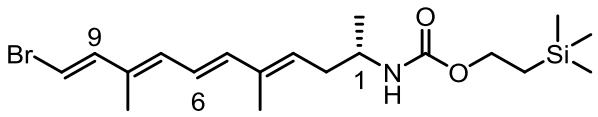
2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*)-11,11-dibromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 365



To a solution of PPh_3 (472 mg, 0.30 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) was added CBr_4 (140 mg, 0.91 mmol, 3.0 eq.). The resulting bright yellow mixture was stirred at 0 °C for 10 min before a solution of Et_3N (0.62 mL, 4.50 mmol, 15.0 eq.) and aldehyde **253** (102 mg, 0.30 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) was added. After stirring at 0 °C for 2 h, the reaction mixture was concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **365** (112 mg, 0.23 mmol, 77%);

$[\alpha]_D^{25}$ −15 (*c* 1.3, $CHCl_3$); $\mathbf{R}_f$ 0.28 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3331, 2954, 1694, 1250, 837; **^{1}H NMR** (400 MHz C_6D_6) δ_H 6.82 (1H, s, *H*9), 6.33-6.18 (2H, m, *H*5 and *H*6), 6.03 (1H, d, *J* = 10.0 Hz, *H*7), 5.41 (1H, t, *J* = 7.5 Hz, *H*3), 4.28-4.19 (2H, m, OCH_2CH_2Si), 4.07 (1H, bs, N*H*), 3.87-3.74 (1H, m, *H*1), 2.11-2.01 (1H, m, *H2*), 2.01-1.90 (1H, m, *H*2'), 1.79 (3H, s, C8CH_3), 1.57 (3H, s, C4CH_3), 0.97-0.89 (2H, m, OCH_2CH_2Si), 0.78 (3H, d, *J* = 6.5 Hz, C1CH_3), −0.13 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 156.0, 141.2, 140.6, 136.6, 135.5, 131.9, 130.8, 128.6, 122.4, 62.7, 47.1, 35.9, 20.5, 18.1, 15.3, 12.5, −1.5; **HRMS** (ESI+) calc. for $C_{19}H_{31}O_2NBr_2NaSi$ $[M+Na]^+$ 514.0383, found 514.0381.

2-(Trimethylsilyl)ethyl ((*S*,4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl)carbamate, 361

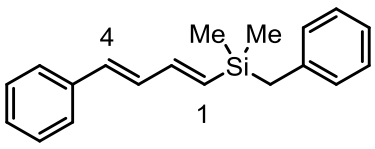


To a mixture of dibromide **365** (53 mg, 0.10 mmol, 1.0 eq.) and diethyl phosphite (0.37 mL, 2.86 mmol, 28.0 eq.) was added Et_3N (64 µL, 0.50 mmol, 5.0 eq.). After stirring at RT overnight, the crude reaction mixture was purified *via* column chromatography (petroleum ether / EtOAc (0%) → petroleum ether / EtOAc (10%)) to give title compound **361** (38 mg, 0.092 mmol, 92%);

$\boldsymbol{[\alpha]_D^{25}}$ −23 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.18 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3323, 2953, 1693, 1250, 837; **^{1}H NMR** (400 MHz C_6D_6) δ_H 6.77 (1H, d, *J* = 13.5 Hz, *H*9), 6.37 (1H, dd, *J* = 15.0 and 11.0 Hz, *H*6), 6.25 (1H, d, *J* = 15.0 Hz, *H*5), 5.99 (1H, d, *J* = 13.5 Hz, *H*10), 5.93 (1H, d, *J* = 11.0 Hz, *H*7), 5.46 (1H, t, *J* = 7.5 Hz, *H*3), 4.34-4.26 (2H, m, OC*H*$_2$CH$_2$Si), 4.15 (1H, bs, N*H*), 3.93-3.79 (1H, m, *H*1), 2.20-2.09 (1H, m, *H2*), 2.09-1.99 (1H, m, *H*2'), 1.65 (3H, s, C8C*H*$_3$*),* 1.50 (3H, s, C4C*H*$_3$), 1.03-1.00 (2H, m, OCH$_2$C*H*$_2$Si), 0.87 (3H, d, *J* = 6.5 Hz, C1C*H*$_3$), −0.06 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 157.7, 143.9, 141.6, 138.4, 134.9, 134.6, 132.0, 124.6, 106.8, 64.5, 49.0, 37.7, 22.3, 19.9, 14.3, 14.0, 0.2; **HRMS** (ESI+) calc. for $C_{19}H_{32}O_2NBrNaSi$ $[M+Na]^+$ 436.1278, found 436.1270.

6.16 C1-C13 Cyclic diethyl siloxane and beyond

Benzyldimethyl((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)silane, 368

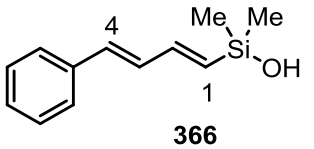


Chromium(II) chloride (737 mg, 6.00 mmol, 6.0 eq.) was added to a Schlenk tube followed by activation *in vacuo* by heat. The flask was allowed to reach RT, filled with nitrogen and THF (20 mL) was added. The resulting grey suspension was stirred for 30 min after which a solution of cinnamaldehyde **367** (0.13 mL, 1.00 mmol, 1.0 eq.) and silane **202** (541 mg, 1.30 mmol, 1.3 eq.) in THF (5 mL) was added *via* syringe. After stirring at RT overnight, the resulting purple suspension was diluted with Et_2O (30 mL) and filtered through Celite. The filtrate was washed with water (20 mL), then brine (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (petroleum ether) to give title compound **368** (152 mg, 0.55 mmol, 55%);

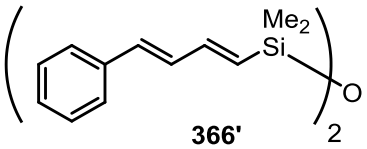
R_f 0.19 (petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45-6.95 (10H, m, Ar*H*), 6.79 (1H, dd, *J* = 15.5 and 10.0 Hz, *H*3), 6.66 (3H, dd, *J* = 18.0 and 10,0 Hz, *H*2), 6.57 (1H, d, *J* = 15.5 Hz, *H*4), 5.93 (1H, d, *J* = 18.0 Hz, *H*1), 2.18 (2H, s, SiCH_2Ar), 0.10 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 145.3, 140.0, 139.5, 133.3, 132.7, 131.6, 128.7, 128.3 (2), 127.8, 126.7, 124.1, 26.2, −3.3;

The physical and spectroscopic data was found to be in agreement with that reported by Anderson and Lim.[137]

Dimethyl((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)silanol, 366 & 1,1,3,3-tetramethyl-1,3-bis((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)disiloxane, 366'



366



366'

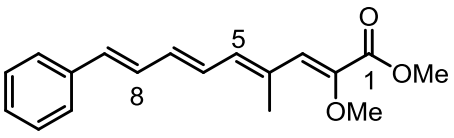
To a solution of vinyl silane **368** (50 mg, 0.18 mmol, 1.0 eq.) in THF (0.18 mL) was added TBAF•3H_2O (0.19 mL, 1 M in THF, 0.19 mmol, 1.05 eq.). After stirring at RT for 5 h, the resulting mixture was diluted with Et_2O (5 mL) and quenched with water

(5 mL), the organic layer was separated and the aqueous layer further extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (10%) → petroleum ether / EtOAc (15%)) to give silanol **366** (19 mg, 0.093 mmol, 52%) and disiloxane **366'** (6.0 mg, 0.015 mmol, 9%);

366: $\mathbf{R_f}$ 0.15 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 3316, 2957, 1496, 1187, 1042, 801; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28-7.04 (5H, m, Ar*H*), 6.69-6.57 (2H, m, *H*2 and *H*3), 6.52-6.41 (1H, m, *H*4), 5.86-5.76 (1H, m, *H*1), 1.63 (1H, bs, SiO*H*), 0.10 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 145.5, 136.9, 134.2, 132.4, 131.2, 128.6, 127.9, 126.6, −0.0; **HRMS** (ESI+) calc. for $C_{12}H_{17}OSi$ $[M+H]^+$ 205.1049, found 205.1047.

366': $\mathbf{R_f}$ 0.60 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 1583, 1254, 1044, 802; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47-7.18 (10H, m, Ar*H*), 6.85-6.69 (4H, m, *H*2 and *H*3), 6.61 (2H, d, *J* = 15.0 Hz, *H*4), 5.96 (2H, d, *J* = 18.0 Hz, *H*1), 0.21 (12H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.9, 136.3, 133.0, 132.9, 130.7, 127.8, 126.9, 125.8, −0.0; **HRMS** (ESI+) calc. for $C_{24}H_{31}O_2Si$ $[M+H]^+$ 319.1913, found 391.1914.

Methyl (2*Z*,4*E*,6*E*,8*E*)-2-methoxy-4-methyl-9-phenylnona-2,4,6,8-tetraenoate, 369



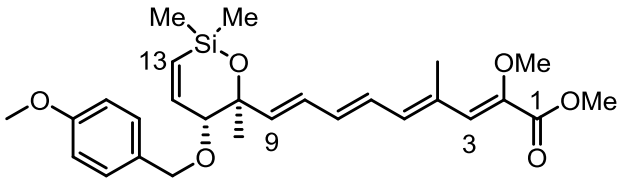
Condition A: To a vial containing vinyl iodide **368** (10 mg, 0.036 mmol, 1.0 eq.), dienoate **88** (11 mg, 0.040 mmol, 1.1 eq.) and $Pd(dba)_2$ (1.0 mg, 0.0017 mmol,

5.0 mol%) was added TBAF•$3H_2O$ (0.11 mL, 1 M in THF, 0.11 mmol, 3.0 eq.). After stirring at RT for 1 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **369** (10 mg, 0.035 mmol, 98%) as a yellow oil;

Condition B: To a vial containing silanol **366** (8.0 mg, 0.039 mmol, 1.1 eq.) was added a solution of KHMDS (39 μL, 0.91 M in THF, 0.035 mmol, 1.0 eq.) *via* syringe. The resulting mixture was stirred for 5 min followed by addition of a solution of dienoate **88** (10 mg, 0.035 mmol, 1.0 eq.) in THF (0.1 mL) and $Pd(dba)_2$ (1.0 mg, 0.0017 mmol, 5.0 mol%). After stirring at RT for 30 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (10%)) to give title compound **369** (6.0 mg, 0.021 mmol, 60%) as a yellow oil;

$\mathbf{R_f}$ 0.15 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2950, 1712, 1349, 1250, 1101; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45-7.20 (5H, m, Ar*H*), 6.92 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*8), 6.71-6.65 (2H, m, *H*3 and *H*6), 6.63 (1H, d, *J* = 15.5 Hz, *H*9), 6.53 (1H, dd, *J* = 14.5 and 11.0 Hz, *H*7), 6.46 (1H, d, *J* = 11.5 Hz, *H*5), 3.81 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 2.16 (3H, s, C4CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.2, 144.1, 137.2, 136.6, 136.2, 133.8, 133.2, 129.2, 129.1, 129.0, 128.7, 127.8, 126.5, 60.4, 52.0, 15.1; **HRMS** (ESI+) calc. for $C_{18}H_{21}O_3$ $[M+H]^+$ 284.1492, found 205.285.1489.

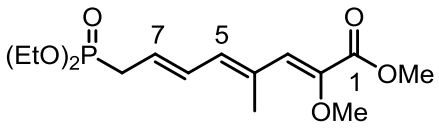
Methyl (2*Z*,4*E*,6*E*,8*E*)-2-methoxy-9-((5*R*,6*S*)-5-((4-methoxybenzyl)oxy)-2,2,6-trimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-4-methylnona-2,4,6,8-tetraenoate, 371



To a mixture of dienoate **88** (42 mg, 0.15 mmol, 1.0 eq.), siloxane **352** (55 mg, 0.17 mmol, 1.1 eq.) and Tl_2CO_3 (141 mg, 0.30 mmol, 2.0 eq.) in THF (1.2 mL) and water (0.3 mL) was added Pd(dppf)Cl_2 (12 mg, 0.015 mmol, 10 mol%). The biphasic mixture was stirred in the dark at RT over 5 h. The reaction mixture was diluted with Et_2O (5 mL) and filtered through a Celite, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification *via* column chromatography (petroleum ether / Et_2O (5%) → petroleum ether / Et_2O (15%)) afforded title compound **371** (14 mg, 0.030 mmol, 20%);

$[\alpha]_D^{25}$ −33 (*c* 1.0, $CHCl_3$); R_f 0.23 (petroleum ether / Et_2O (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 2951, 1716, 1249, 1101, 1350; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.19 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.89 (1H, s, *H*3), 6.80 (3H, d, *J* = 8.5 Hz, Ar*H*), 6.78 (1H, dd, *J* = 15.0 and 11.0 Hz, *H*8), 6.72 (1H, dd, *J* = 14.5 and 2.0 Hz, *H*12), 6.53 (1H, dd, *J* = 14.0 and 10.5 Hz, *H*6), 6.36-6.26 (2H, m, *H*5 and *H*7), 6.19 (1H, d, *J* = 15.0 Hz, *H*9), 5.87 (1H, dd, *J* = 14.5 and 2.5 Hz, *H*13), 4.49 (1H, d, *J* = 11.5 Hz, ArCH_2O), 4.30 (1H, d, *J* = 11.5 Hz, ArCH_2'O), 3.92 (1H, app t, *J* = 2.0 Hz, *H*11), 3.50 (3H, s, OCH_3), 3.40 (3H, s, CO_2CH_3), 3.20 (3H, s, ArOCH_3), 2.04 (3H, s, C4CH_3), 1.56 (3H, s, C10CH_3), 0.22 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 164.6, 159.6, 148.8, 144.5, 141.9, 136.5, 136.0, 132.7, 130.4, 129.5, 128.7, 128.5, 128.4, 128.3, 113.9, 81.0, 77.5, 72.1, 59.6, 54.5, 51.1, 22.2, 14.9, 0.8, 0.2; **HRMS** (ESI+) calc. for $C_{27}H_{36}O_6NaSi$ $[M+Na]^+$ 507.2173, found 507.2175.

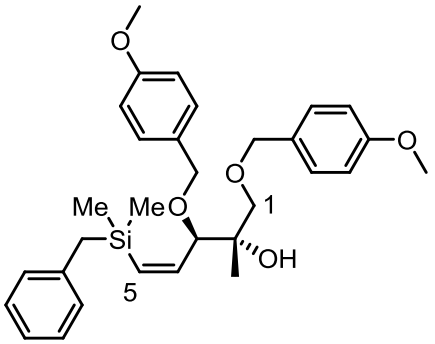
Methyl (2*Z*,4*E*,6*E*)-8-(diethoxyphosphoryl)-2-methoxy-4-methylocta-2,4,6-trienoate, 372



To a mixture of $Pd(OAc)_2$ (24 mg, 0.11 mmol, 10 mol%), P(*o*-tolyl)$_3$ (65 mg, 0.21 mmol, 20 mol%) and silver acetate (269 mg, 1.61 mmol, 1.5 eq.) in MeCN (8 mL) was added a solution of dienoate **88** (303 mg, 1.07 mmol, 1.0 eq.) in MeCN (3 mL) followed by allyl phosphonate **373** (0.28 mL, 1.61 mmol, 1.5 eq.) *via* syringe. After stirring at 80 °C overnight, the resulting reaction mixture was diluted with Et_2O (15 mL) and filtered through Celite and the resulting filtrate washed with water (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. After removal of excess allyl phosphonate **373** by Kugelrohr distillation under reduced pressure (100 °C, 0.5 mbar), the crude product was purified *via* column chromatography (petroleum ether / EtOAc (10%)) affording title compound **372** (308 mg, 0.93 mmol, 87%) as a yellow oil;

R$_f$ 0.31 (petroleum ether / EtOAc (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2983, 1716, 1248, 1023, 963; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60 (1H, s, *H*3), 6.52 (1H, dd, *J* = 15.0 and 11.0 Hz, *H*6), 6.33 (1H, d, *J* = 11.0 Hz, *H*5), 5.78 (1H, dt, *J* = 15.0 and 8.0 Hz, *H*7), 4.17-4.04 (4H, m, PO(CH_2CH_3)$_2$), 3.79 (3H, s, OCH_3), 3.67 (3H, s, CO_2CH_3), 2.71 (2H, d, *J* = 8.0 Hz, *H*8), 2.08 (3H, s, C4CH_3), 1.31 (6H, t, *J* = 7.0 Hz, PO(CH_2CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.1, 144.3, 135.3 (d, *J* = 5.5 Hz), 132.3 (d, *J* = 4.5 Hz), 131.0 (d, *J* = 15.5 Hz), 128.9 (d, *J* = 3.0 Hz), 125.6 (d, *J* = 13.0 Hz), 62.1 (d, *J* = 6.5 Hz), 60.3, 52.0, 31.4 (d, *J* = 139.5 Hz), 16.5 (d, *J* = 6.0 Hz), 14.9; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 26.3; **HRMS** (ESI+) calc. for $C_{15}H_{25}O_6NaP$ $[M+Na]^+$ 355.1281, found 355.1278.

(2*S*,3*R*,*Z*)-5-(Benzyldimethylsilyl)-1,3-bis((4-methoxybenzyl)oxy)-2-methylpent-4-en-2-ol, 377

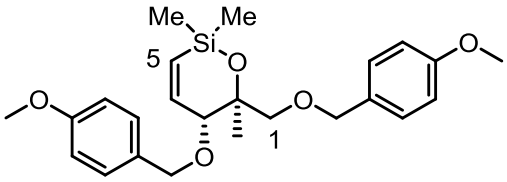


To a solution of vinylsilane **357** (109 mg, 0.27 mmol, 1.0 eq.) and 4-Methoxybenzyl-2,2,2 trichloroacetimidate (85 μL, 0.41 mmol, 1.5 eq.) in CH_2Cl_2 (0.5 mL) was added CSA (7 mg, 0.03 mmol, 0.10 eq.). After stirring at RT for 4.5 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and diluted with Et_2O (5 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / Et_2O (20%)) to give title compound **377** (73 mg, 0.14 mmol, 52%) as a clear oil;

$\boldsymbol{[\alpha]_D^{25}}$ +14 (*c* 1.0, $CHCl_3$); $\mathbf{R_f}$ 0.51 (petroleum ether / Et_2O (10%)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 1312, 1513, 1247, 830; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-6.79 (13H, m, Ar*H*), 6.33 (1H, dd, *J* = 14.5 and 10.0 Hz, *H*4), 5.94 (1H, d, *J* = 14.5 Hz, *H*5), 4.52-4.39 (3H, m, OCH_2Ar, OCH_2'Ar and OCH_2Ar), 4.14 (1H, d, *J* = 11.0 Hz, OCH_2'Ar), 4.00 (1H, d, *J* = 10.0 Hz, *H*3), 3.79 (3H, s, ArOCH_3), 3.78 (3H, s, ArOCH_3), 3.58 (1H, d, *J* = 9.0 Hz, *H*1), 3.31 (1H, d, *J* = 9.0 Hz, *H*1'), 2.45 (1H, bs, O*H*), 2.18 (1H, d, *J* = 13.5 Hz, SiCH_2Ar), 2.12 (1H, d, *J* = 13.5 Hz, SiCH_2'Ar), 1.17 (3H, s, C2CH_3), 0.08 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.9, 139.7, 134.8, 130.7, 130.3, 129.2, 129.0, 128.3, 128.2, 124.1, 113.7, 113.7, 81.1, 74.2, 73.8, 73.1, 70.0, 55.3, 55.2,

26.8, 20.0, −1.3, −1.4; **HRMS** (ESI+) calc. for $C_{31}H_{40}O_5NaSi$ $[M+Na]^+$ 343.2537, found 543.2537.

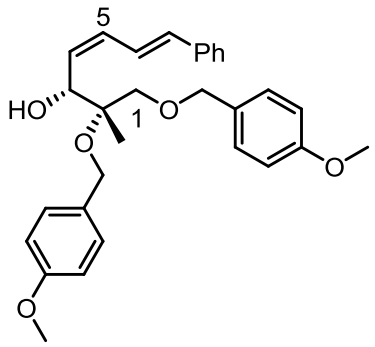
(5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-6-(((4-methoxybenzyl)oxy)methyl)-2,2,6-trimethyl-5,6-dihydro-2*H*-1,2-oxasiline, 375



To vinylsilane **377** (59 mg, 0.11 mmol, 1.0 eq.) was added TBAF•$3H_2O$ (0.11 mL, 1 M in THF, 0.11 mmol, 1.0 eq.). After stirring at RT for 5 h, the crude mixture was purified *via* column chromatography (petroleum ether / Et_2O (20%)) to give title compound **375** (35 mg, 0.082 mmol, 75%);

$[\alpha]_D^{25}$ −70 (*c* 1.00, $CHCl_3$); R_f 0.34 (petroleum ether / Et_2O (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 1613, 1514, 1248, 1092; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.16 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.88-6.80 (4H, m, ArH), 6.67 (1H, dd, *J* = 14.5 and 3.0 Hz, *H*4), 5.89 (1H, d, *J* = 14.5 and 2.5 Hz, *H*5), 4.62 (1H, d, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.56 (1H, d, *J* = 11.0 Hz, OC*H*$_2$Ar), 4.45 (1H, d, *J* = 11.5 Hz, OC*H*$_2$'Ar), 4.40 (1H, d, *J* = 11.0 Hz, OC*H*$_2$'Ar), 4.24 (1H, app t, *J* = 2.5 Hz, *H*3), 3.79 (3H, s, ArOC*H*$_3$), 3.78 (3H, s, ArOC*H*$_3$), 3.58 (1H, d, *J* = 10.0 Hz, *H*1), 3.31 (1H, d, *J* = 10.0 Hz, *H*1'), 1.17 (1H, s, C2C*H*$_3$), 0.19 (3H, s, SiC*H*$_3$), 0.16 (3H, s, SiC*H*$_3$'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.1, 158.0, 147.6, 130.0, 129.6, 128.3, 128.2, 126.8, 112.7, 112.6, 77.1, 75.3, 74.7, 72.0, 70.8, 54.3, 54.2, 18.2, −0.0, −0.5; **HRMS** (ESI+) calc. for $C_{24}H_{32}O_5NaSi$ $[M+Na]^+$ 451.1911, found 451.1907.

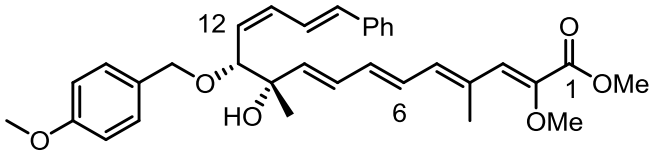
(2*S*,3*R*,4*Z*,6*E*)-1,2-bis((4-methoxybenzyl)oxy)-2-methyl-7-phenylhepta-4,6-dien-3-ol, 376



To a vial containing siloxane **375** (26 mg, 0.061 mmol, 1.0 eq.), bromostyrene (**327)** (23 mg, 0.12 mmol, 2.0 eq.) and $[allylPdCl]_2$ (0.9 mg, 0.0025 mmol, 4.0 mol%) was added TBAF•$3H_2O$ (0.30 mL, 1 M in THF, 0.30 mmol, 5.0 eq.). After stirring at RT for 1 h, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **376** (22 mg, 0.046 mmol, 75%);

$\boldsymbol{[\alpha]_D^{25}}$ +13 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.17 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3492, 2933, 1612, 1513, 1247; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35-7.14 (9H, m, Ar*H*), 6.95 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*6), 6.89-6.76 (4H, m, Ar*H*), 6.61 (1H, d, *J* = 15.5 Hz, *H*7), 6.89-6.76 (1H, m, *H*5), 5.60-5.51 (1H, m, *H*4), 4.58 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.42-4.35 (1H, m, *H*3), 4.40 (2H, s, OCH_2Ar), 4.28 (1H, d, *J* = 11.5 Hz, OCH_2'Ar), 3.77 (3H, s, ArOCH_3), 3.76 (3H, s, ArOCH_3), 3.48 (1H, d, *J* = 9.0 Hz, *H*1), 3.36 (1H, d, *J* = 9.0 Hz, *H*1'), 2.50 (1H, s, O*H*), 1.27 (1H, s, C2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.2, 159.1, 137.1, 134.6, 134.4, 130.3, 130.2, 129.7, 129.2, 128.6, 127.9, 127.8, 126.6, 124.1, 113.7 (4), 74.5, 74.3, 73.1, 69.8, 55.2, 21.3; **HRMS** (ESI+) calc. for $C_{30}H_{34}O_3Na$ $[M+Na]^+$ 497.2299, found 497.2294.

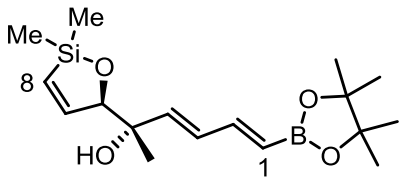
Methyl (2*Z*,4*E*,6*E*,8*E*,10*S*,11*R*,12*Z*,14*E*)-10-hydroxy-2-methoxy-11-((4-methoxybenzyl)oxy)-4,10-dimethyl-15-phenylpentadeca-2,4,6,8,12,14-hexaenoate, 378



To a vial containing siloxane **371** (11 mg, 0.023 mmol, 1.0 eq.), bromostyrene (**273)** (5 mg, 0.028 mmol, 1.2 eq.) and $[allylPdCl]_2$ (0.2 mg, 0.55 µmol, 2.5 mol%) was added TBAF•$3H_2O$ (69 µL, 1 M in THF, 0.069 mmol, 3.0 eq.). After stirring at RT for 5 min, the crude mixture was purified *via* column chromatography (petroleum ether / EtOAc (20%)) to give title compound **378** (6.1 mg, 0.012 mmol, 50%) as an yellow oil;

$\boldsymbol{[\alpha]_D^{25}}$ −129 (*c* 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.15 (petroleum ether / EtOAc (20%)); **IR** (thin film, ν_{max} / cm^{-1}) 3496, 1715, 1494, 1250; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28-7.01 (8H, m, Ar*H* and *H*14), 6.84 (1H, s, *H*3), 6.78 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.63 (1H, dd, *J* = 15.5 and 11.0 Hz, *H*8), 6.89-6.76 (5H, m, *H*5, *H*6, *H*7, *H*13 and *H*15), 6.00 (1H, d, *J* = 15.5 Hz, *H*9), 5.51 (1H, app t, *J* = 10.5 Hz, *H*12), 4.61 (1H, d, *J* = 12.0 Hz, OCH_2Ar), 4.34 (1H, d, *J* = 10.0 Hz, *H*11), 4.26 (1H, d, *J* = 12.0 Hz, OCH_2'Ar), 3.50 (3H, s, C2OCH_3), 3.40 (3H, s, CO_2CH_3), 3.29 (3H, s, ArOCH_3), 2.04 (3H, s, C4CH_3), 1.40 (3H, s, C10CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.6, 159.6, 144.4, 138.7, 137.0, 136.3, 135.7, 135.2, 134.5, 132.9, 130.0, 129.7, 129.6, 128.7, 128.6, 128.5, 128.3, 128.2, 126.7, 123.7, 113.9, 80.0, 74.8, 69.7, 59.6, 54.4, 51.0, 24.5, 14.8; **HRMS** (ESI+) calc. for $C_{33}H_{38}O_6$ $[M+NH_4]^+$ 548.3012, found 548.3014.

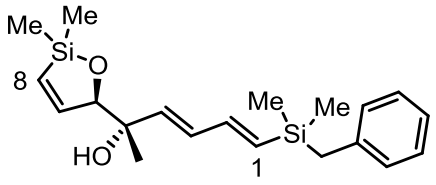
(*S*,3*E*,5*E*)-2-((*R*)-2,2-Dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-3,5-dien-2-ol, 379



To a solution of siloxane **352** (51 mg, 0.11 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) and water (0.1 mL) was added DDQ (27 mg, 0.12 mmol, 1.1 eq.). After stirring at RT for 3 h, the resulting mixture was diluted with water (10 mL) and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **379** and 4-methoxybenzaldehyde (55 mg, 0.11 mmol, 71% purity by weight, quant.) which was used without further purification;

IR (thin film, ν_{max} / cm^{-1}) 3026, 1239, 833; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.97 (1H, dd, *J* = 17.5 and 10.5 Hz, *H*2), 6.80 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*7), 6.37 (1H, dd, *J* = 15.5 and 10.5 Hz, *H*3), 6.16 (1H, dd, *J* = 10.5 and 2.0 Hz, *H*8), 5.82 (1H, d, *J* = 15.5 Hz, *H*4), 5.54 (1H, d, *J* = 17.5 Hz, *H*1), 4.58 (1H, dd, *J* = 2.0 and 1.5 Hz, *H*6), 2.51 (1H, bs, O*H*), 1.33 (3H, s, C5CH_3), 1.28 (12H, s, Bpin*H*), 0.23 (3H, s, SiCH_3), 0.21(3H, s, SiCH_3'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.1, 148.5, 140.6, 132.0, 131.3, 130.3, 114.3, 89.5, 83.2, 24.8, 24.7, 0.9, 0.6; **HRMS** (ESI+) calc. for $C_{17}H_{29}BO_4NaSi$ $[M+Na]^+$ 359.1820, found 359.1819.

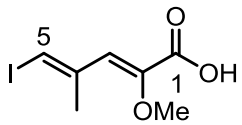
(*S*,3*E*,5*E*)-6-(Benzyldimethylsilyl)-2-((*R*)-2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)hexa-3,5-dien-2-ol, 381



To a solution of siloxane **353** (50 mg, 0.10 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) and water (0.1 mL) was added DDQ (26 mg, 0.11 mmol, 1.1 eq.). After stirring at RT for 3 h, the resulting mixture was diluted with water (10 mL) and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give title compound **381** and 4-methoxybenzaldehyde (53 mg, 0.096 mmol, 65% purity by weight, 96%);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24-6.95 (5H, m, Ar*H*), 6.85 (1H, dd, *J* = 10.5 and 1.5 Hz, *H*7), 6.45 (1H, dd, *J* = 18.0 and 10.0 Hz, *H*3), 6.31 (1H, dd, *J* = 15.0 and 10.0 Hz, *H*2), 6.19 (1H, dd, *J* = 10.5 and 2.0 Hz, *H*8), 5.80 (1H, d, *J* = 18.0 Hz, *H*4), 5.68 (1H, d, *J* = 15.0 Hz, *H*1), 4.58 (1H, dd, *J* = 2.0 and 1.5 Hz, *H*6), 2.13 (2H, s, SiC*H*$_2$Ar), 1.33 (3H, s, C5C*H*$_3$), 0.22 (6H, s, Si(C*H*$_3$)$_2$), 0.04 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$').

(2*Z*,4*E*)-5-Iodo-2-methoxy-4-methylpenta-2,4-dienoic acid, 385

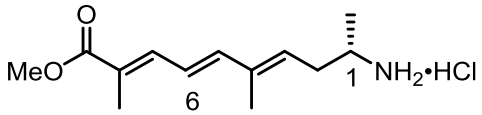


To a solution of dienoate **88** (77 mg, 0.27 mmol, 1.0 eq.) in Et_2O (13.5 mL) was added $KOSiMe_3$ (175 mg, 1.36 mmol, 5.0 eq.). After stirring at RT for 1 h, the resulting reaction mixture was quenched with 1 M aqueous HCl solution (15 mL), the organic layer separated and the aqueous layer further extracted with Et_2O (2 × 10 mL). The

combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (5%) → CH_2Cl_2 / MeOH (10%)) to give title compound **385** (72 mg, 0.27 mmol, quant.);

R_f 0.15 (CH_2Cl_2 / MeOH (5%)); **IR** (thin film, ν_{max} / cm^{-1}) 2935, 1681, 1267, 1107, 784; **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ_H 13.1 (1H, bs, CO_2H), 7.04 (1H, s, *H*3), 6.58 (1H, s, *H*5), 3.62 (3H, s, C2OCH_3), 2.06 (3H, s, C4CH_3); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ_C 171.3, 164.8, 141.6, 122.5, 91.8, 59.2, 22.7; **HRMS** (ESI+) calc. for $C_7H_{10}IO_3$ $[M+H]^+$ 268.9675, found 268.9670.

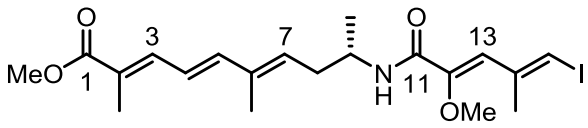
Methyl (*S*,2E,4*E*,6*E*)-9-amino-2,6-dimethyldeca-2,4,6-trienoate hydrochloride salt, 384



To a vial containing sulfonamide **383** (106 mg, 0.32 mmol, 1.0 eq.) was added a solution of HCl (0.16 mL, 4 M in dioxane, 0.65 mmol, 2.0 eq.). After stirring at RT for 5 min, the resulting reaction mixture was concentrated *in vacuo* to give title compound **384** which was used directly in the next reaction;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.35 (3H, bs, NH_3Cl), 7.23 (1H, dq, *J* = 11.0 and 1.0 Hz, *H*7), 6.56 (1H, d, *J* = 15.0 Hz, *H*5), 6.43 (1H, dd, *J* = 15.0 and 11.0, *H*6), 5.67 (1H, t, *J* = 7.5 Hz, *H*3), 3.75 (3H, s, CO_2CH_3), 3.45-3.33 (1H, m, *H*1), 2.77-2.66 (1H, m, *H*2), 2.60-2.49 (1H, m, *H*2'), 1.96 (3H, d, *J* = 1.0 Hz, C8CH_3), 1.85 (3H, s, C4CH_3), 1.40 (3H, d, *J* = 6.5 Hz, C1CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.9, 143.4, 138.7, 137.9, 129.0, 126.6, 122.9, 51.8, 48.3, 33.9, 25.2, 18.5, 12.8.

Methyl (*S*,2*E*,4*E*,6*E*)-9-((2*Z*,4*E*)-5-iodo-2-methoxy-4-methylpenta-2,4-dienamido)-2,6-dimethyldeca-2,4,6-trienoate, 386



To a mixture of dienoic acid **385** (50 mg, 0.19 mmol, 1.0 eq.), EDCI hydrochloride (71 mg, 0.37 mmol, 2.0 eq.) and DMAP (90 mg, 0.74 mmol, 4.0 eq.) in CH_2Cl_2 (1.5 mL) was added a solution of amine salt **386** (56 mg, 0.22 mmol, 1.2 eq.) in CH_2Cl_2 (0.5 mL). After stirring at RT overnight, the resulting reaction mixture was diluted with EtOAc (5 mL) and quenched with water (5 mL), the organic layer was separated and the aqueous was layer further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (petroleum ether / EtOAc (30%)) to give title compound **386** (48 mg, 0.10 mmol, 55%);

$[\alpha]_D^{25}$ −23 (*c* 1.4, $CHCl_3$); R_f 0.25 (petroleum ether / EtOAc (30%)); **IR** (thin film, ν_{max} / cm^{-1}) 1703, 1614, 1513, 1232, 1113; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (1H, dq, *J* = 11.0 and 1.0 Hz, *H*3), 6.72 (1H, *s, H*13), 6.58 (1H, s, *H*15), 6.53 (1H, d, *J* = 15.5 Hz, *H*5), 6.44-6.34 (1H, m, *H*10), 5.66 (1H, t, *J* = 7.5 Hz, *H*7), 4.21-4.07 (1H, m, *H*9), 3.75 (3H, s, C12CH_3), 3.57 (3H, s, CO_2CH_3), 2.48-2.35 (2H, m, *H*8), 2.07 (3H, s, C14CH_3), 1.96 (3H, d, *J* = 1.0 Hz, C2CH_3), 1.83 (3H, s, C6CH_3), 1.21 (3H, d, *J* = 6.5 Hz, C9CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.9, 162.9, 147.3, 143.9, 141.3, 138.9, 136.6, 131.9, 126.1, 122.2, 119.7, 88.4, 60.8, 51.8, 45.4, 35.5, 23.3, 20.4, 12.8, 12.6; **HRMS** (ESI+) calc. for $C_{20}H_{29}INO_4$ $[M+H]^+$ 474.1141, found 474.1137.

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