

Organosilicon Reagents in Carbon-Carbon Bond Forming Reactions: Towards the Total Synthesis of Incednine

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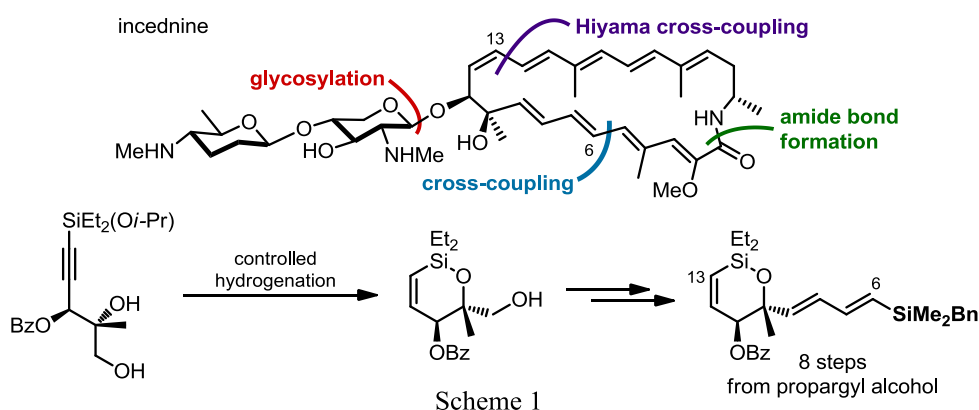
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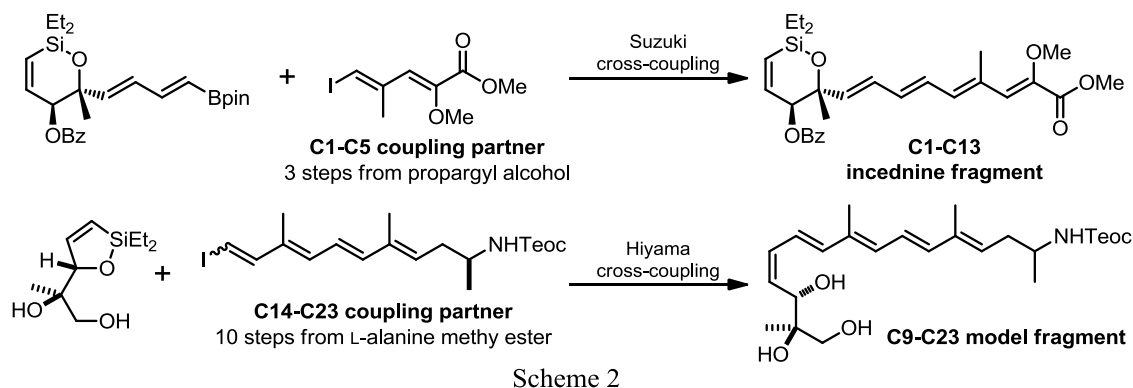
Trinity Term, 2013

Merton College

This thesis investigates a total synthesis of the incednine aglycon by utilising alkenylsilane reagents to assemble the pentaenyl and tetraenyl systems through cross-coupling reactions. The early chapters develop methodology to access both cyclic alkenylsiloxanes and functionalised (*E*)-alkenylsilanes by the controlled hydrogenation of alkynylsiloxanes and silylolefination of aldehydes, respectively, and culminate in the synthesis of a C6-C13 *bis*(alkenylsilane) incednine fragment (Scheme 1).



The C1-C5 and C14-C23 coupling partners are synthesised in three and ten steps from propargyl alcohol and L-alanine methyl ester through phosphorous-based olefination strategies. In the final chapter we describe our first generation approach to incednine which entails orthogonal cross-couplings to construct the C5-C6 and C13-C14 bonds (Scheme 2).



Acknowledgements

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Abbreviations

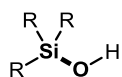
acac	acetylacetonate
aq.	aqueous
BAIB	(diacetoxy)iodobenzene
Boc	<i>tert</i> -butylcarbonate
bp	boiling point
Bt	benzotriazole
^{13}C	carbon 13
cod	cyclooctadiene
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DET	diethyl tartrate
(DHQ) ₂ PHAL	hydroquinine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DIT	diisopropyltartrate
DMAP	4-dimethylaminopyridine
DME	dimethoxy ethane
DMSO	dimethylsulfoxide
DMT-MM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
dppf	bis(diphenylphosphino)ferrocene

DVDS	1,1-divinyl-1,1,3,3-tetramethyldisiloxane
EA	elemental analysis
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
equiv	equivalent(s)
ESI	electrospray ionisation
FI	field ionisation
^1H	proton
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
imid	imidazole
IR	infra red
LDA	lithium diisopropylamide
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
mp	melting point
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Phth	phthalimide
pin	pinacol
Piv	pivaloyl

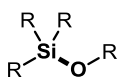
PKS	polyketide synthase
PMB	<i>para</i> -methoxybenzyl
PPTS	pyridinium <i>para</i> -toluenesulfonate
py	pyridine
quant.	quantitative
R _f	retention factor
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBA	tetrabutylammonium
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TCICA	trichloroisocyanuric acid
temp	temperature
Teoc	2-(trimethylsilyl)ethyl carbonate
TES	triethylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
THP	tetrahydropyran
THQ	1,2,3,4-tetrahydroquinoline
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethyl carbonate
w/v	weight/volume

Nomenclature Conventions

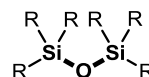
Throughout this report, to aid rapid identification of organosilicon intermediates and products, the following convention is used to refer to Si-O containing functional groups:



silanol



siloxane



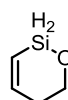
disiloxane

Cyclic alkenylsiloxanes refer to the class of siloxacycles in which silicon, oxygen and both alkene carbon atoms are incorporated within the ring:



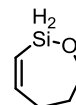
**five-membered
cyclic alkenylsiloxane**

*IUPAC
name:* 2,5-dihydro-
1,2-oxasilole



**six-membered
cyclic alkenylsiloxane**

5,6-dihydro-2*H*-
1,2-oxasiline



**seven-membered
cyclic alkenylsiloxane**

2,5,6,7-tetrahydro-
1,2-oxasilepine

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1 Introduction

Incednine is a bioactive polyketide identified through a cell-based chemical-genetic screen on multidrug-resistant human small cell lung carcinoma Ms-1 cells.¹ Whilst such cells display resistance to various chemotherapeutic drugs, including adriamycin, camptothecin, cisplatin, inostamycin, taxol and vinblastine, administration in combination with incednine restored sensitivity to these anti-tumour drugs, resulting in apoptosis.

1.1 Isolation of incednine

Incednine was isolated as a pale yellow powder from a culture broth of *Streptomyces* sp. ML694-90F3 by centrifugal liquid-liquid partition chromatography. It was determined to have a novel architecture comprising a 24-membered polyunsaturated macrolactam tethered to an amino deoxy disaccharide (Figure 1.1).¹ The disaccharide consists of a 2-deoxy-2-methylamino-D-xylopyranose connected to the C11 position of macrolactam by a β -glycosidic linkage, and a second *N*-monodemethyl-D-forosamine connected to the xylopyranose by a β -1,4-glycosidic bond.

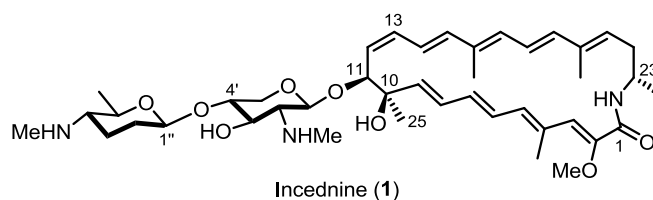


Figure 1.1 Incednine

The aglycon consists of tetra- and pentaene segments separated by neighbouring C10 and C11 quaternary and tertiary hydroxyl-bearing stereocentres and a remote C23 stereocentre adjacent to the amide. The C2-C9 tetraene features an enol ether, and the C12-C21 pentaene a single C12-C13 (*Z*)-olefin in an otherwise all-(*E*)-olefin system.

The relative stereochemistry of the C10 and C11 stereocentres was assigned as 10*R** and 11*S** based on nOes observed between H8 and H25, H25 and H11 and H11 and H14. The absolute configuration of the C11 stereocentre was determined by preparation of both Mosher esters to be *S*. The remaining C23 stereocentre was deduced to be *S* by nOes and the prediction was supported by *in silico* calculations.

Since the isolation of incednine by Imoto and co-workers in 2008, the structurally related secondary metabolite silvalactam (**2**) was isolated in 2012 by Süssmuth and co-workers from *Streptomyces* sp. Tü 6392 (Figure 1.2).² While the absolute configurations of the C10, C11 and C23 stereocentres of the silvalactam aglycon have yet to be assigned, the aglycons of incednine and silvalactam differ only in the C2 sidechains, with silvalactam featuring an isobutyl group in place of the methoxy group in incednine. Silvalactam also contains a single amino deoxysugar which bears marked similarities to the xylopyranose unit found in incednine, differing only in the *O*- and *N*-methylation pattern. Preliminary testing revealed that silvalactam inhibits the growth of a variety of human cancer cell lines including proliferating human skin fibroblasts and pancreatic ductal epithelial cell lines, the latter of which has proved to be resistant to treatment with existing chemotherapeutical agents. Silvalactam also behaves as a selective antibiotic against selected Gram-positive bacteria.

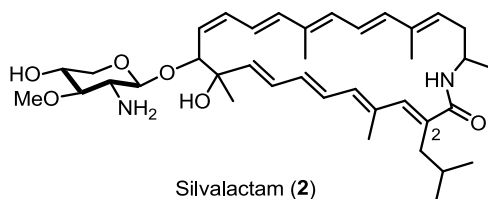


Figure 1.2

1.2 Bioactivity of incednine

Many cancer cell lines, including the human small cell lung carcinoma, have been observed to overexpress the anti-apoptotic oncoproteins Bcl-xL and Bcl-2, members of the Bcl-2 family of proteins which also include the pro-apoptotic oncoproteins Bax and Bak.³ Heterodimerisation between pro- and anti-apoptotic members provides the means by which the Bcl-2 proteins regulate cellular apoptosis. Overexpression of anti-apoptotic Bcl-xL and Bcl-2 results in the sequestering of pro-apoptotic proteins, diverting the normal cellular apoptotic pathway, leading the cell to cancerous proliferation.⁴

Previous efforts to inhibit the growth of Bcl-xL and Bcl-2-overexpressing cancer cell lines with small molecule inhibitors aim to disrupt heterodimerisation with pro-apoptotic family members by targeting the Bcl-xL and Bcl-2 protein binding pocket.^{5,6} Incednine inhibits Bcl-xL neither by disrupting its binding to pro-apoptotic Bcl-2 family proteins, nor by decreasing Bcl-xL expression in the cell.¹ Uncovering the mechanism of Bcl-xL inhibition by incednine thus presents an opportunity to uncover novel mechanisms through which apoptosis is regulated independent of the known pathways of the Bcl-2 family of proteins.

To this end, Sakakibara and co-workers, by employing a new protocol combining *in silico* screening and experimental verification for the prediction of target proteins of bioactive compounds, have identified three incednine-binding proteins which are related to cancer survival and drug resistance.⁷ Of the three, ACACA (acetyl-CoA carboxylase- α) was identified as the most likely target protein of incednine. ACACA is a critical enzyme in long-chain fatty acid synthesis, making it key to cellular energy storage and lipid synthesis, on which cancer cell proliferation and survival is dependent.⁸ Upregulation of ACACA has been observed in multiple types of human

cancers, and treatment of human small cell lung carcinoma Ms-1 cells with ACACA antagonists or silencers in combination with anti-tumour drugs resulted in the induction of apoptosis, as was observed with incednine. Further investigations into the mode of ACACA inhibition by incednine, and the possible inhibitory effects of incednine on PI3KCG and PARP1 – other protein targets identified through the Sakakibara screening protocol – are ongoing.

1.3 Biosynthesis of Incednine

Aliphatic polyketides share a common biosynthetic pathway wherein a carboxylic acid starter unit is elaborated through a series of Claisen condensations with acetate, propionate or butyrate extender units.⁹ Polyketide synthases (PKSs) are modules of enzymes typically consisting of keto-synthases (KS), β -ketoreductases (KR), dehydratases (DH) and enoylreductases (ER). These enzymes are responsible for multiple rounds of chain-elongating condensations which may be followed by reduction of the newly-formed β -keto group, conversion of the resulting β -hydroxyls to α,β -unsaturated carbonyl compounds and reduction of the α,β -double bond. The polyketide may undergo further modifications during post-PKS tailoring, a process governed by post-PKS enzymes including methyltransferases, oxidative enzymes and glycosidases.

The biosynthesis of incednine has been investigated by Eguchi and co-workers through a series of ^{13}C -labelled feedstock experiments employing isotopically-labelled acetate, propionate, glycerol and amino acids as traceable units incorporated into the polyketide during biosynthesis.¹⁰ In keeping with the expected polyketide synthase pathway, the incorporation pattern of ^{13}C -labelled $[1-^{13}\text{C}]$ acetate, $[1,2-^{13}\text{C}_2]$ acetate and $[1-^{13}\text{C}]$ propionate suggested that acetate and propionate extender units account for the polyunsaturated C3-C20 length of the aglycon. Further feeding experiments revealed

that the remaining C1-C2 glycolate unit and C21-C23 amine-containing unit were derived from glycerol and an L-glutamic acid starter unit, respectively (Figure 1.3). L-Methionine was determined to be the source of the O-2 methyl group, which is thought to be transferred from the *S*-adenosyl L-methionine (SAM) intermediate by a SAM-dependent methyltransferase enzyme.

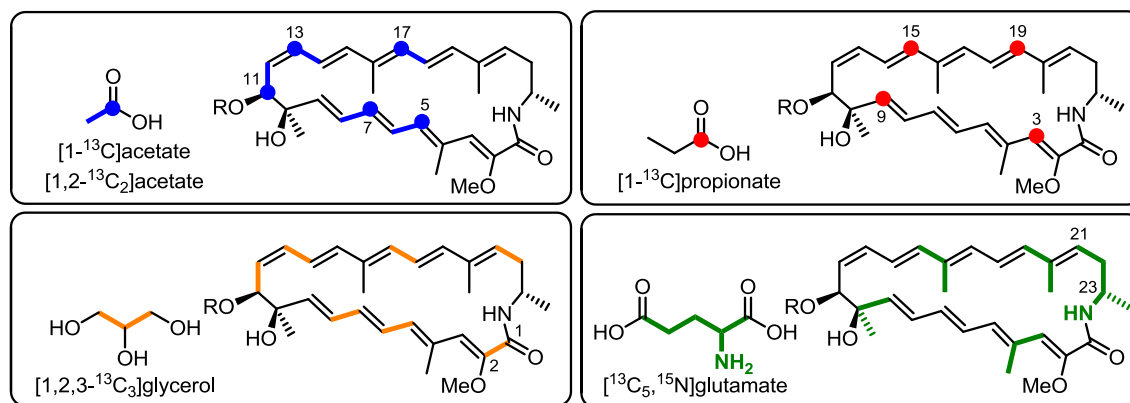
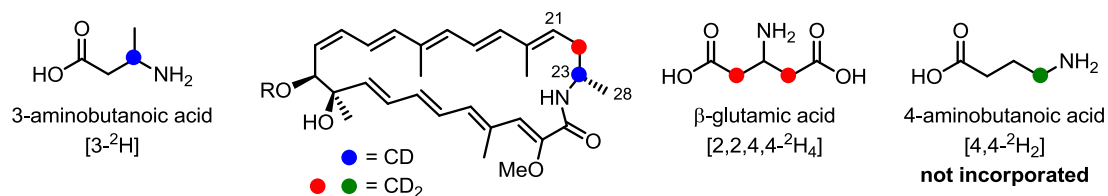


Figure 1.3 Biosynthetic origins of the aglycon determined by ^{13}C -labelled feeding experiments

The pathway by which L-glutamic acid is converted to the requisite 3-aminobutanoic acid starter unit has been studied by the same group.¹¹ Feeding experiments with deuterium-labelled 3-[3- ^2H]aminobutanoic acid confirmed that it was a direct starter unit of incednam (Figure 1.4). Structurally, the conversion of L-glutamic acid to 3-aminobutanoic acid would involve decarboxylation and amino group rearrangement. To elucidate the order in which this occurs, deuterium-labelled β -[2,2,4,4- $^2\text{H}_4$]-glutamic acid and 4-[4,4- $^2\text{H}_2$]-aminobutanoic acid, postulated intermediates of each sequence, were separately fed to the *Streptomyces* culture. Strong incorporation of deuterated β -glutamate, alongside the complete absence of 4-aminobutyrate incorporation, supported the pathway in which amino group-rearrangement precedes β -decarboxylation. Bacterial glutamate-2,3-aminomutase, which converts L-glutamate into β -glutamate, has been reported,¹² as have decarboxylases for other β -amino acids.¹³ However, the

putative enzyme for the decarboxylation of β -glutamate remains elusive. The lack of deuterium incorporation at the C28 position from labelled β -glutamic acid is postulated to be a result of deuterium-protium exchange in enamine-iminium tautomerisation during a proposed PLP-facilitated β -decarboxylation.



Proposed biosynthetic pathway of 3-aminobutyrate

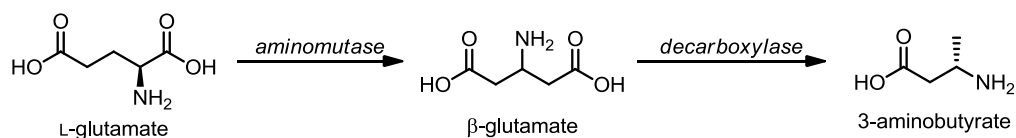
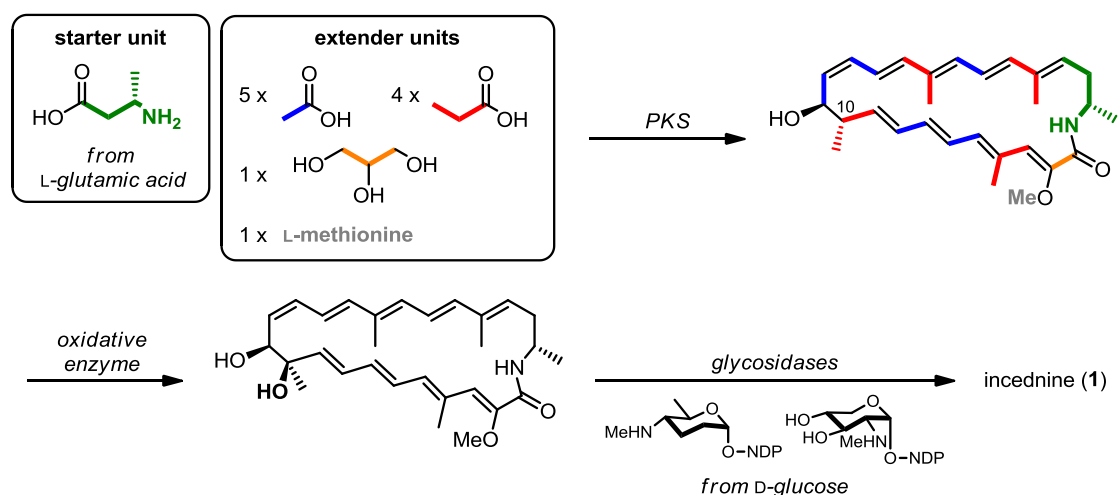


Figure 1.4 Biosynthesis of 3-aminobutyrate determined by ^2H -labelled feeding experiments

Based on these results, the following biosynthetic pathway of incednine was proposed. 3-Aminobutyrate, the starter unit derived from L-glutamic acid, is loaded onto the first module of the PKS and condensed with five malonates, four methylmalonates and one methoxymalonnate extender units derived from acetate, propionate and glycerol respectively (Scheme 1.1). Accompanying β -keto reduction followed by dehydration of all resulting β -hydroxyls, except for that deriving from the C11-C12 acetate unit, results in the distribution of olefins observed in the aglycon. Post-PKS modifications by an oxidative enzyme introduces the C10 hydroxyl, followed by glycosidases, which transfer the two aminodeoxy sugars onto the C9 position, complete the biosynthesis of incednine. The aminodeoxy sugars are postulated to derive from D-glucose *via* the pentose phosphate cycle, as suggested by the incorporation pattern of ^{13}C -labelled glycerol and D-[6,6- $^2\text{H}_2$]glucose in feeding experiments.¹⁰



Scheme 1.1 Proposed biosynthetic pathway of incednine

1.4 Related polyketide macrolactams

To the best of our knowledge, incednine is just the second 24-membered polyunsaturated polyketide macrolactam which has been isolated, with micromonosporin A¹⁴ isolated in 2004, being the only other example (Figure 1.5). In comparison, 20-membered macrolactams have been known since 1992, when researchers from Banyu Pharmaceuticals reported BE-14106 as an antitumour and antibiotic agent.¹⁵ It was subsequently redescribed in 1997 as GT32-A along with its C8-deoxy analogue GT32-B.¹⁶ Vicenistatin and cyclamenol, the most famous of this class of compounds, were reported as potent antitumour agents in 1993 and 1994, respectively: vicenistatin demonstrated growth inhibition against human colon carcinoma cells in a mouse xenograft model,¹⁷ and cyclamenol completely inhibited adhesion of leukocyte to arterioles in hamsters.¹⁸ Aureoverticillactam, a 22-membered macrolactam, was reported in 2004 to also show moderate *in vitro* antitumour activity.¹⁹ The latest additions to the family of 20-membered macrolactams are the structurally related ML-449²⁰ and heronamide C,²¹ isolated from different species of *Streptomyces* bacteria in 2010, which differ only in geometry at the C6-C7 double bond.

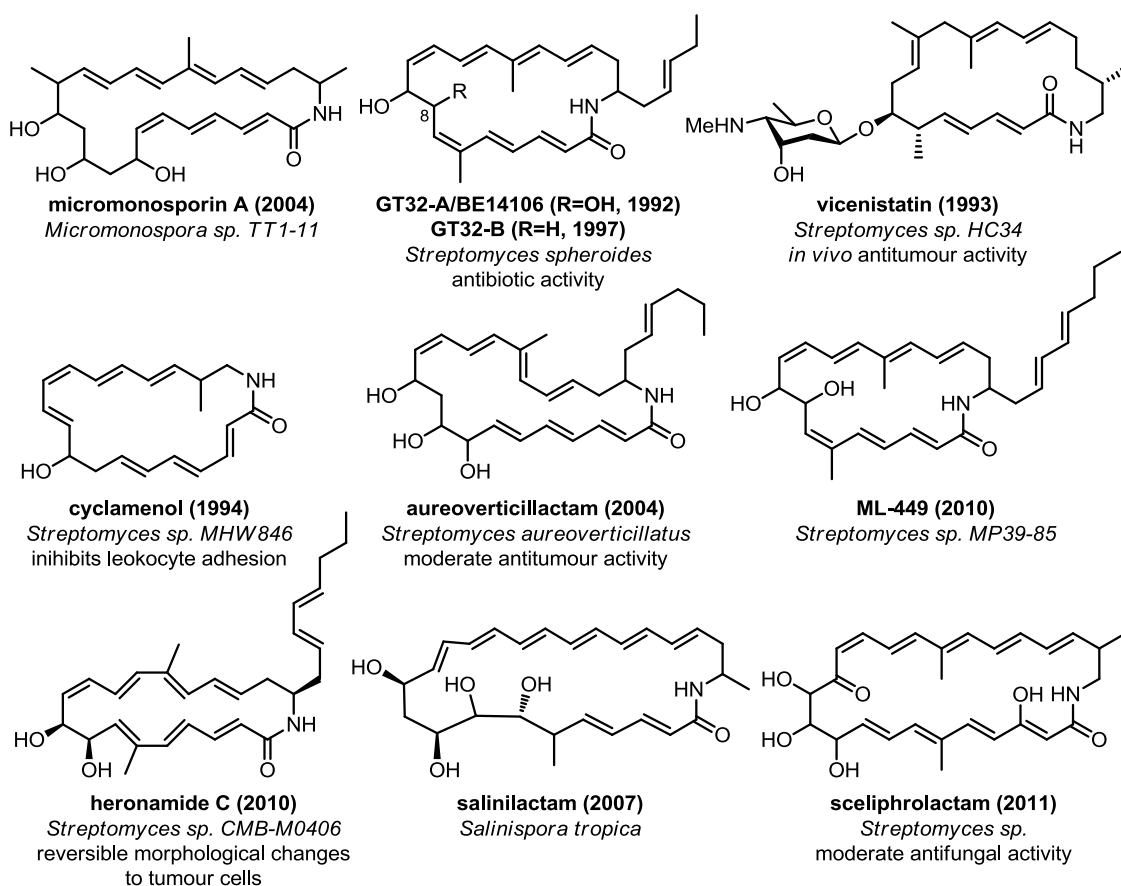


Figure 1.5 Related 20-26-membered polyketide macrolactams

Larger ring systems have only been known since 2007, when salinilactam, a 26-membered macrolactam isolated from marine actinomycete *Salinispora tropica*, was identified and had its structure elucidated by genomic analysis.²² Finally, and most recently, sceliphrolactam was reported in 2011 as an antifungal isolated from a mud dauber-derived strain of *Streptomyces* bacteria.²³

In all cases but vicienistatin, no stereochemical assignment was provided; although predictions based on biosynthetically related metabolites (heronamide C) or homology between known ketoreductase domains (salinilactam) have been reported. The complete absolute stereochemistry of vicienistatin was solved by enantioselective synthesis 10 years after it was first isolated.¹⁷ Like incednine, and silvalactam, vicienistatin comprises a macrolactam aglycon, vicienilactam, tethered to a single deoxyamino sugar,

vicenisamine. The crucial role of vicenisamine in the overall cytotoxic behaviour of vicenistatin was discovered when the related polyketide vicenisamine M, in which vicenisamine is replaced by D-mycarose, failed to inhibit the growth of human cancer cell lines during *in vitro* assays.²⁴

1.5 Previous syntheses of incednine

Although the total synthesis of incednine has yet to be reported, Toshima and co-workers published the first syntheses of the aglycon and disaccharide in 2010 and 2011, respectively. A second synthesis of the disaccharide unit was recently disclosed by Roush and co-workers in 2013.

1.5.1 Incednam Aglycon Synthesis

Toshima and co-workers' initial approach to the aglycon identified the N-C1 amide bond and the C13-C14 bond adjacent to the *cis*-alkene as key retrosynthetic disconnections, providing C1-C13 pentaenyl iodide **4** and C14-C23 tetraenyl stannane **5** which would be united *via* a Stille coupling followed by macrolactamisation (Figure 1.6). In the course of the synthesis, the poor stability of the C14-C23 tetraenyl stannane, which was found to be “extremely prone to oxidation and/or photochemical decomposition”, led the group to develop a second generation approach which utilised alkene metathesis to construct the C18-C19 alkene in the final ring-closing step. This simplified the problematic fragment to stannane **6** and amine **7**, thereby improving the stability of the stannane coupling partner by reducing the length of the conjugated alkene system to which it was attached.

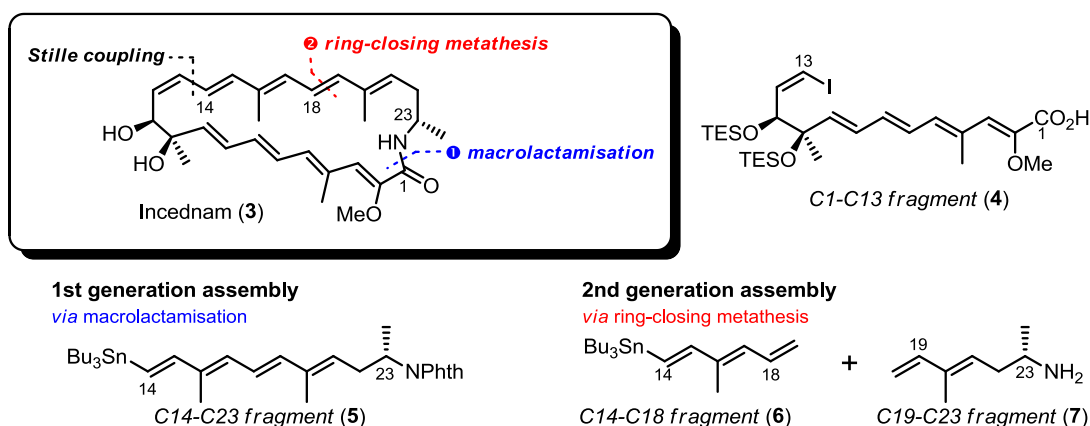


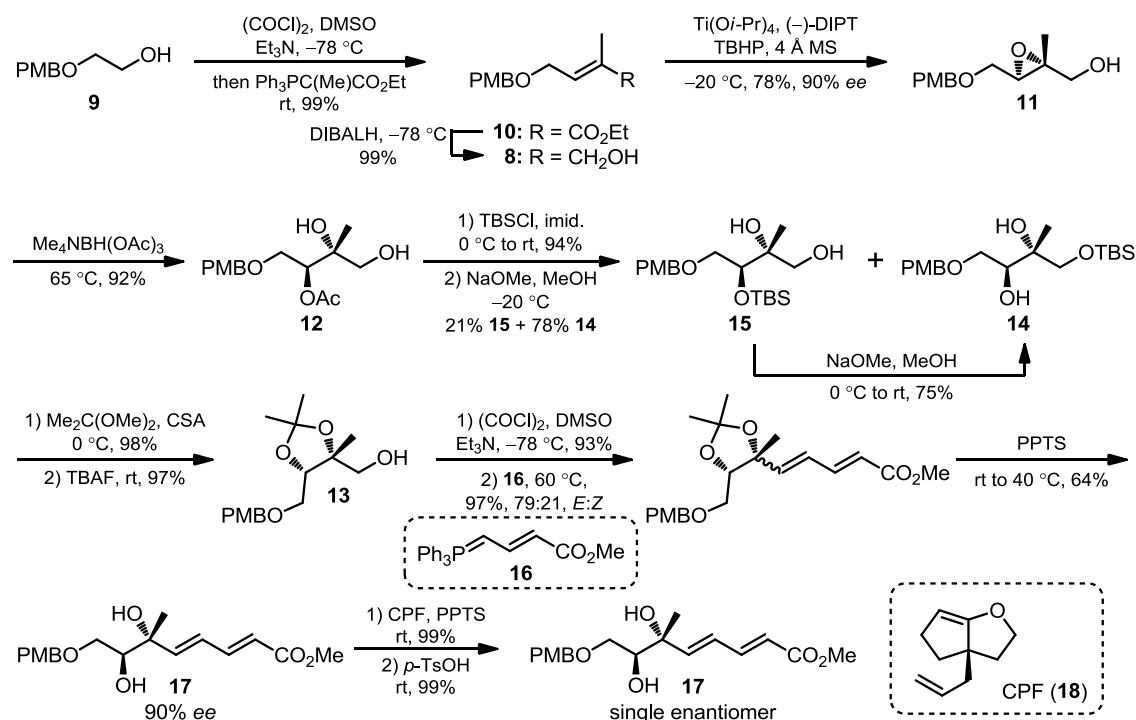
Figure 1.6 Toshima's retrosynthetic disconnection of incednam

An overview of the construction of each subunit and a summary of both the macrolactamisation and ring-closing metathesis approach to assembling the aglycon is found in the following section.

1.5.1.1 C1-C13 Synthesis

The C1-C13 pentaenoic acid subunit **4** was first prepared by Toshima and co-workers in 2009.²⁵ Allylic alcohol **8** was prepared in two steps from mono-PMB protected ethylene glycol **9** by a one-pot Swern oxidation/Wittig reaction, followed by DIBALH reduction of α,β -unsaturated ester **10** (Scheme 1.2). The C10 and C11 hydroxyl-bearing stereocentres were introduced by a Sharpless asymmetric epoxidation which afforded chiral epoxide **11** in 90% *ee*, followed by regioselective epoxide opening using conditions developed by Honda and co-workers employing $\text{Me}_4\text{NBH}(\text{OAc})_3$ as the source of nucleophilic acetate.²⁶ Diol **12** was then converted to 2,3-dimethyl acetonide **13** via the primary TBS-ether **14** following methoxide-mediated acetyl deprotection. This sequence was complicated by migration of the silyl group under the basic conditions employed for acetyl deprotection, which afforded a 78:21 mixture of the desired primary silyl ether **14** and the rearranged secondary silyl ether **15**. The

undesired product could be recovered and, upon further treatment with sodium methoxide, converted into the desired regioisomer **14**.

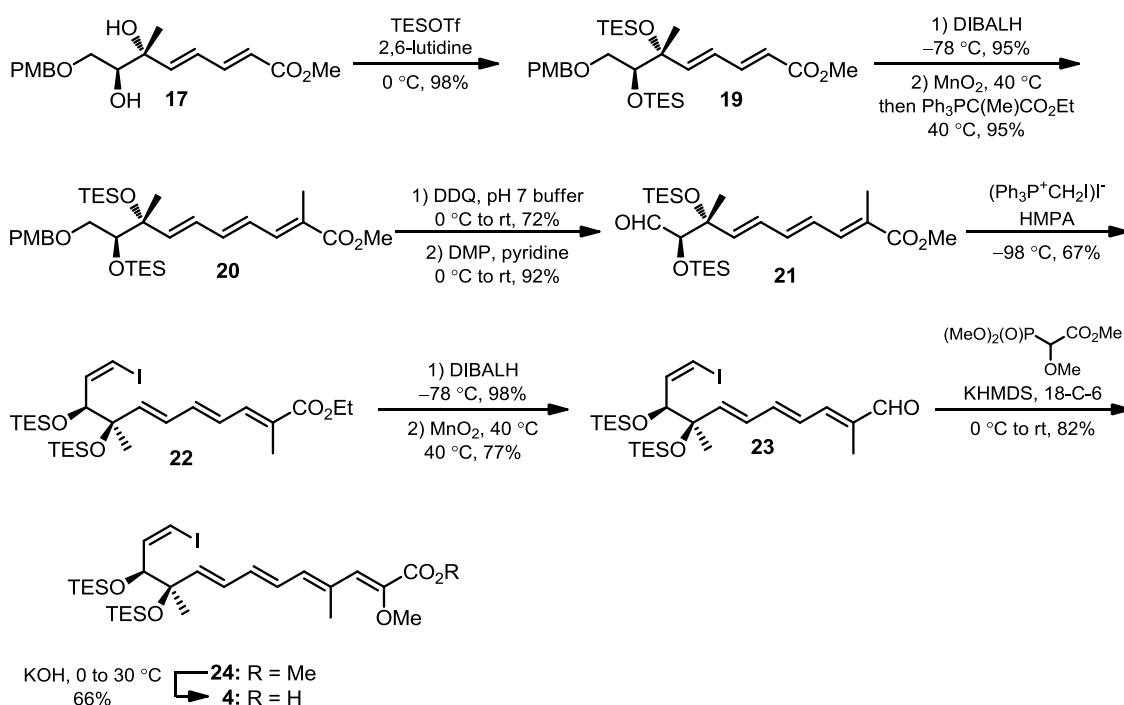


Scheme 1.2

Swern oxidation of acetonide **13** followed by Wittig reaction of the resulting aldehyde with extended phosphorane **16** efficiently introduced the C6-C9 diene structure, albeit in a modest *E:Z* ratio of 79:21 at the C8-C9 alkene. Acetal deprotection under acidic conditions afforded diol **17**, which could undergo an optical enhancement with chiral reagent CPF (**18**) to provide **17** as a single enantiomer in 93% after CPF removal.

Global TES protection of resolved **17**, followed by a reduction-oxidation-Wittig sequence applied to dienyl ester **19** provided the trienoic ester **20**, and introduced the third alkene in the C2-C9 tetraenyl system (Scheme 1.3). At this point, deprotection of the PMB ether, oxidation of the primary alcohol with Dess-Martin periodinane and a Stork-Wittig reaction at the resulting aldehyde **21**, installed the C12-C13 (*Z*)-alkene in the tetraenyl iodide **22**. The final alkene in this fragment, an enol ether, was constructed

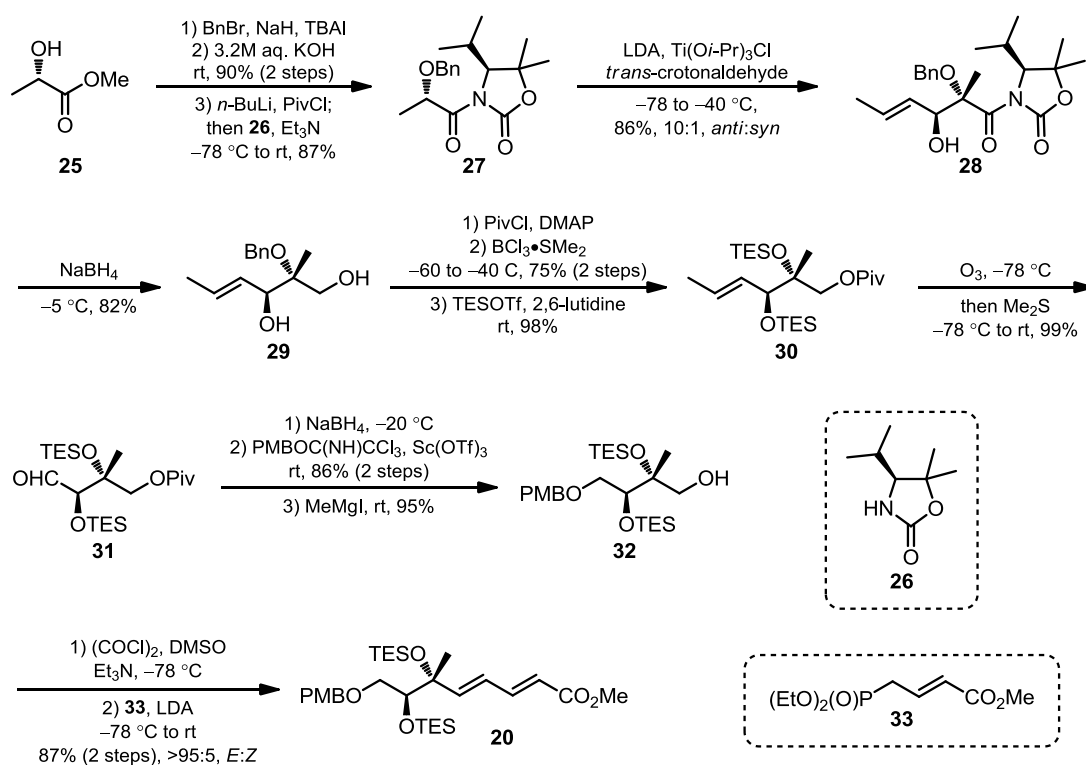
by a two-step oxidation state adjustment of the unsaturated ester to the corresponding aldehyde **23**, which then underwent a Horner-Wadsworth-Emmons olefination with an unusual α -methoxy-methyl ester phosphonate to provide the pentaenyl methyl ester **24**. Ester hydrolysis under aqueous basic conditions gave the C1-C13 pentaenoic acid subunit **4**.



Scheme 1.3

Toshima's maiden synthesis of the C1-C13 was achieved in 23 linear steps with an overall yield of 4.2% from ethylene glycol. The route suffers from a number of drawbacks, including extensive protecting group manipulations (five different protecting groups are employed and 8 of the 23 steps involve protecting group manipulation) further complicated by silyl migration during acetyl deprotection. Furthermore, a modest *E/Z* selectivity in the Wittig olefination with phosphorane **16**, and the use of a stoichiometric amount of chiral resolution reagent, present significant challenges to the scalability of this route and its application to the preparation of the complete natural product.

A second approach to the C1-C13 pentanoic acid subunit published the following year addressed a number of these challenges.²⁷ In the improved synthesis, the hydroxyl-bearing stereocentres were introduced using an Evans aldol reaction instead of a Sharpless asymmetric epoxidation. This strategy began with methyl L-lactate (**25**), which upon benzylation, ester hydrolysis and coupling with the chiral auxiliary **26** provided the oxazolidinone derivative **27** (Scheme 1.4). Regioselective 1,2-addition of the titanium enolate to *trans*-crotonaldehyde was achieved in the presence of Ti(Oi-Pr)₃Cl using methodology developed by Kobayashi and co-workers, which gave the predicted *anti* product **28** with excellent diastereoselectivity.²⁸



Scheme 1.4

Reductive cleavage of the chiral auxiliary with NaBH₄ afforded the primary alcohol **29** which underwent a series of protecting group manipulations comprising pivaloyl protection of the primary alcohol, debenzylation with BCl₃.SMe₂ and a final TES-protection of the secondary and tertiary alcohols. Ozonolysis of the alkene in **30**

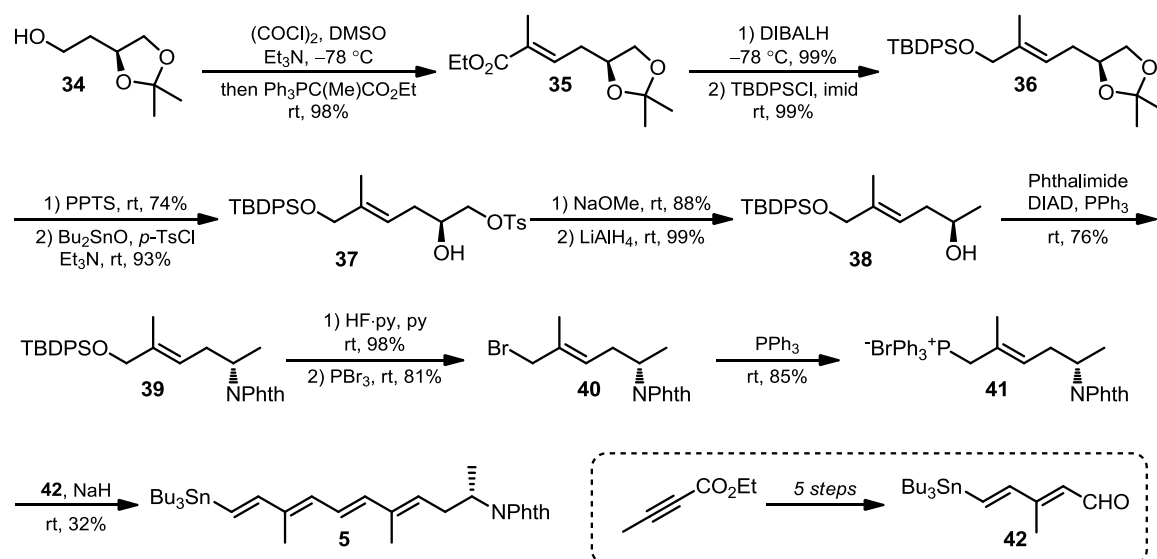
followed by a dimethyl sulfide quench of the ozonide revealed the aldehyde **31**, which was reduced with NaBH₄ and protected as a PMB ether. The pivaloyl ester was removed with methylmagnesium iodide, and the resulting primary alcohol **32**, upon Swern oxidation and Horner-Wadsworth-Emmons olefination with extended phosphonate **33**, provided unsaturated ester **20**, which intersects with the original subunit synthesis.

While comparable in length and overall yield (23 linear steps with an overall yield of 4.7% from methyl L-lactate **25** to pentanoic acid **4**), this route offers significant improvements to the synthesis. The use of a chiral resolution agent was circumvented by employing Evans aldol chemistry to introduce the C10 and C11 stereocentres. In addition, the choice of a pivaloyl ester protecting group to replace the TBS-ether and careful choice of debenzylating conditions avoids the unwelcome rearrangement previously observed. Finally, and perhaps most significantly, the Horner-Wadsworth-Emmons olefination gave the diene **20** with excellent *E/Z* selectivity.

1.5.1.2 First generation aglycon assembly

The requisite tetraenyl stannane coupling partner for the group's first generation Stille-coupling-macrolactamisation strategy was next prepared from the commercially available L-malic acid-derived acetonide **34** (Scheme 1.5).²⁷ A one-pot Swern-oxidation/Wittig olefination provided α,β -unsaturated ester **35**, which was reduced to the allylic alcohol and subsequently protected as the TBDPS ether **36**. Acidic deprotection of the acetonide revealed the 1,2-diol which upon regioselective tosylation in the presence of catalytic amounts of chelating dibutyltin(IV) oxide, afforded the monotosylated product **37** with exclusive selectivity for the primary alcohol. The tosylate was reduced by a two-step intramolecular epoxide formation followed by epoxide opening with LiAlH₄, providing the homoallylic alcohol **38**. At this point,

formation of the C23 stereocentre was achieved with a stereoinvertive substitution of the alcohol with phthalimide under Mitsunobu conditions.

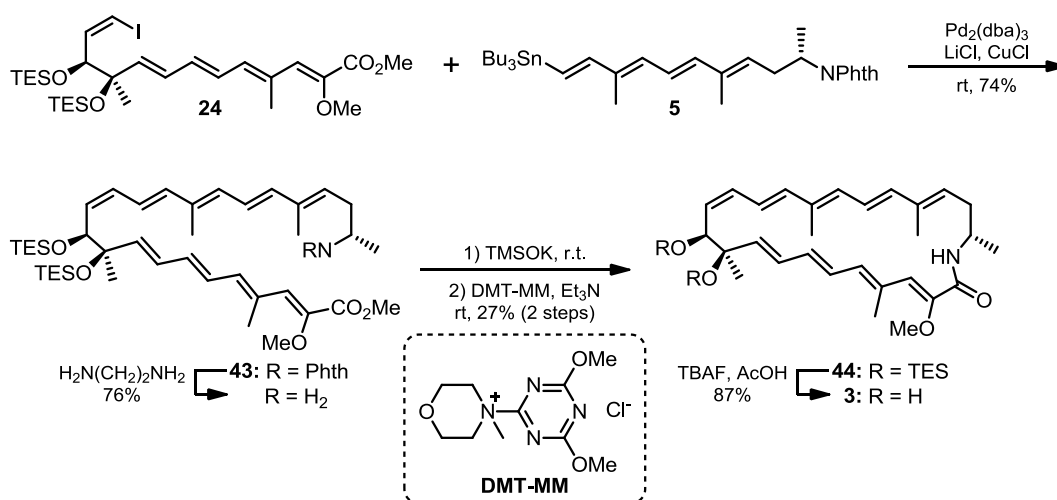


Scheme 1.5

Fluoride-induced deprotection of the TBDPS ether **39** and ensuing bromination with PBr₃ provided bromide **40**, which was converted to phosphonium salt **41** by alkylation of triphenylphosphine. The aldehyde **42** which was required for the Wittig reaction to complete the synthesis of the C14-23 subunit was prepared in five steps from ethyl-2-butyrate, using methodology for the stannylcupration of enynols developed by Prunet and co-workers.²⁹ The stannane can also be prepared in three steps from 4-picoline *via* the Zincke aldehyde using methodology developed by Vanderwal and co-workers.³⁰ The key (*E*)-selective Wittig olefination was performed with NaH in DMSO to afford the C14-C23 subunit **5** in a modest yield of 32%. The tetraenylstannane was found to be extremely prone to decomposition, and had to be used immediately after isolation.

The endgame was executed by first performing a highly efficient Stille cross-coupling between the C1-C13 and C14-23 subunits, **24** and **5** (Scheme 1.6), using conditions developed by Corey and co-workers.³¹ Lithium chloride is thought to play a dual role of generating a more reactive vinylcuprate species *via* transmetalation of vinylstannane **5**

to copper(I) chloride and the coordinatively unsaturated active Pd(0) species. Consecutive phthaloyl deprotection and saponification of the resulting methyl ester **43** revealed the amino-carboxylate macrolactam precursor which was treated with DMT-MM to effect macrolactamisation and provide the TES-protected aglycon **44** in a modest yield of 17% over three steps. A final TES ether deprotection step afforded the free aglycon incednam.



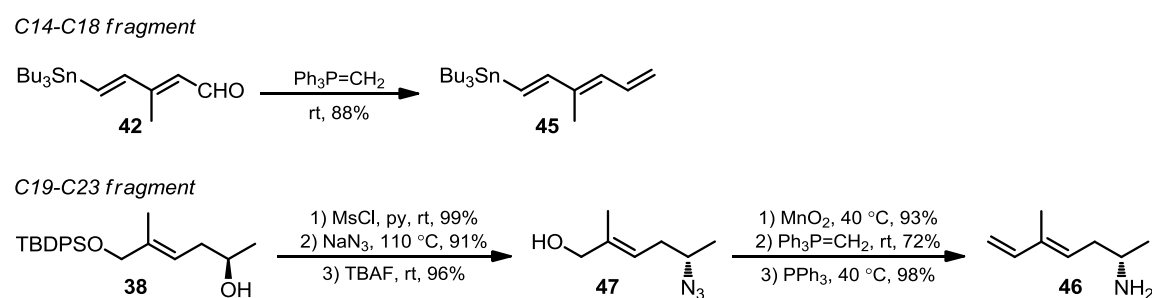
Scheme 1.6

The first generation Toshima synthesis of incednam was executed in an overall yield of 0.5% over 27 linear steps from ethylene glycol. The 44 steps employed across the synthetic campaign feature an Evans aldol addition and HWE olefination with an extended phosphonate ester to construct the C1-C13 methyl ester subunit **24**, a Wittig olefination with an extended phosphorane to construct the C14-C23 stannane **5**, and a Stille coupling-macrolactamisation sequence to unite the fragments. The synthesis is notable for being the first published synthesis of the incednine aglycon, and for supporting the previously predicted stereochemical configuration of the remote stereocentre at C23.

1.5.1.3 Second generation aglycon assembly

A second generation approach to the aglycon, recently published by the Toshima group, circumvents the use of the unstable tetraenyl stannane **5**.³² Instead, the group envisaged a late-stage construction of the C12-C21 pentaene system by a ring-closing metathesis at the C18-C19 alkene, which required the C14-C18 stannane **45** and C19-C23 amine **46** to be separately installed on the C1-C13 pentanoic acid **4** (see Figure 1.6 on page 10).

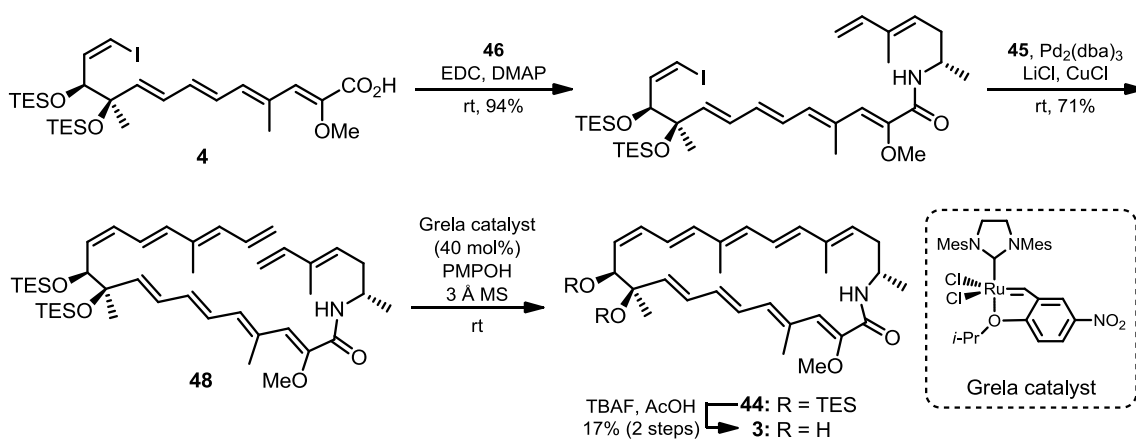
The revised subunits were synthesised from intermediates of the previously established route. Trienyl stannane **45** was obtained in excellent yield from a Wittig methylenation of the known aldehyde **42** (Scheme 1.7). The C19-C23 subunit was prepared from alcohol **38**, itself prepared in seven steps from the L-malic acid-derived acetone **34**. Mesylation of the homoallylic alcohol allowed azide displacement with stereoinversion to introduce the C23 stereocentre. Fluoride deprotection of the TBDPS ether followed by allylic oxidation of **47** with MnO₂ and a Wittig reaction of the resulting α,β -unsaturated aldehyde installed the terminal alkene. A final Staudinger reduction of the azide furnished the desired free amine **46**.



Scheme 1.7

The endgame commenced with the condensation of C1-C13 pentanoic acid **4** with amine **46** using EDC peptide coupling conditions (Scheme 1.8). The remaining C14-C18 containing domain **45** was attached using similar Stille cross-coupling conditions

to those employed previously. At this point, the group attempted to perform ring-closing metathesis on the diol obtained by a global TES-deprotection of **48**, but after a rigorous screen of catalysts and conditions, found that the best results were obtained when the reaction was performed on the TES-protected substrate **48** employing the Grela catalyst,³³ which offers improved reactivity and comparable air-stability to the Hoveyda-Grubbs II catalyst. Subsequent buffered fluoride deprotection of macrolactam **44** afforded incednam in a somewhat disappointing yield of 17% from **48**.



Scheme 1.8

While the ring-closing metathesis approach assembles the macrocycle with a high degree of convergence, and avoids the use of unstable tetraenyl stannane **5** by disconnecting the C12-C21 pentaene system at the C18-C19 olefin, it is plagued by a low yielding cyclisation despite using 40 mol% of Grela catalyst. Notably, the intermolecular amide formation between acid **4** and amine **46** proceeds in an excellent yield of 94%, compared to the modest yield of 27% obtained over the two-step saponification-macrolactamisation sequence in the first generation synthesis, suggesting that the low yielding macrolactamisation of the first generation approach, and potentially the moderate yield of the final two steps of this revised route, is a result of unfavourable conformations adopted by the TES-protected acyclic precursors.

1.5.2 Disaccharide Synthesis

Two syntheses of the disaccharide unit of incednine have been reported by the Toshima and Roush groups in 2010 and 2013 respectively. Both groups have undertaken the strategy of assembling the disaccharide prior to attaching it to the aglycon, and identified respective forosamine glycosyl donors and xylopyranose glycosyl acceptors for the formation of the key β -glycosidic linkage (Figure 1.7).

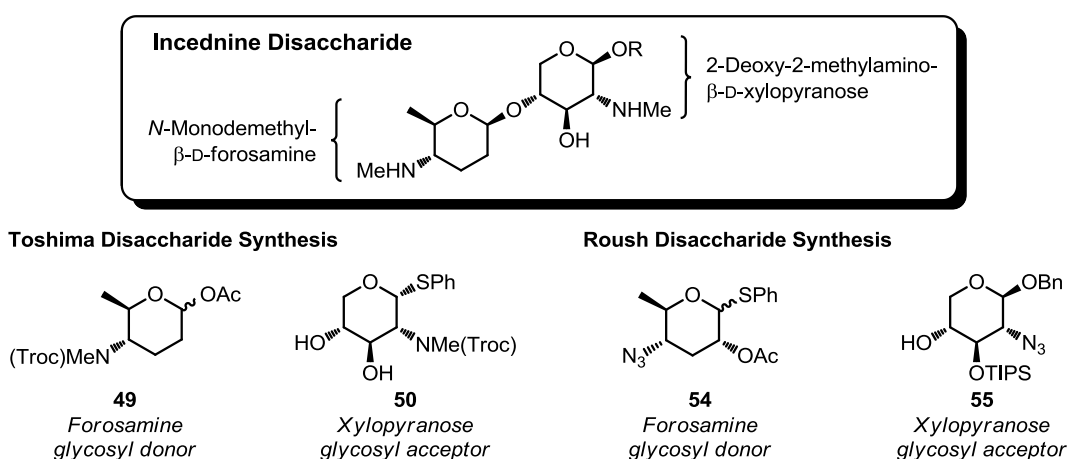
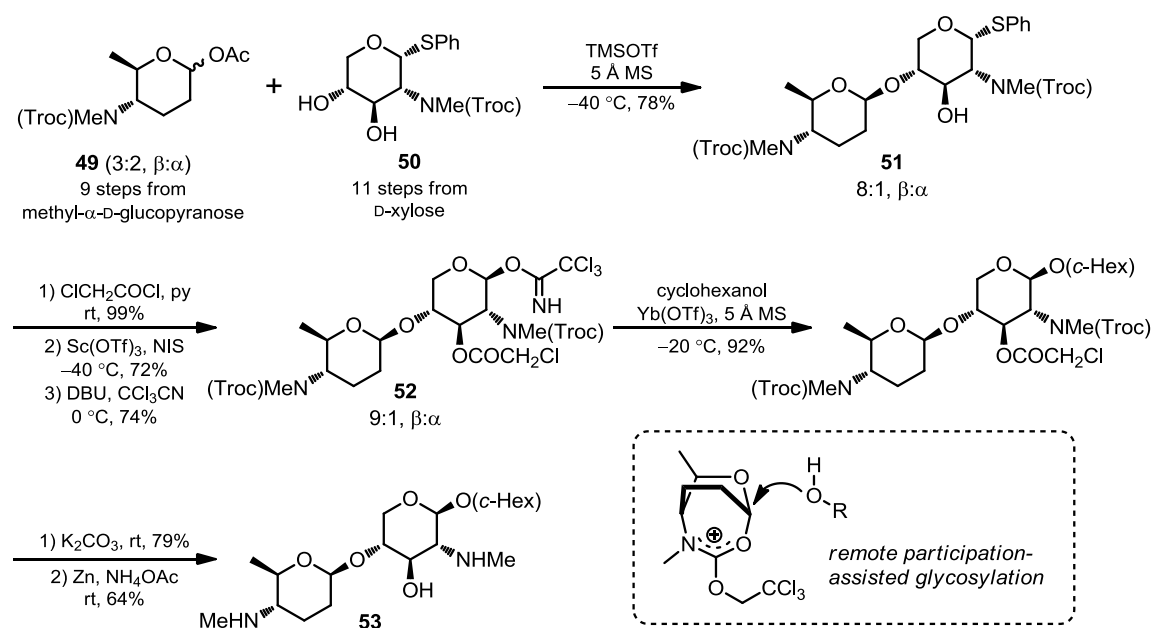


Figure 1.7 Toshima and Roush disaccharide syntheses

The Toshima disaccharide synthesis exploited routes developed by the Hashimoto³⁴ and Baer groups³⁵ to convert methyl- α -D-glucopyranose and D-xylose into the forosamine glycosyl donor **49** and xylopyranose glycosyl acceptor **50** respectively (Scheme 1.9).³⁶ The *N*-Troc protected glycosyl donor **49** was selected in anticipation of the carbamate in the C4 position promoting β -selective glycosidation *via* remote participation-assisted glycosylation, requiring the pyranose to undergo a chair flip for the carbonyl oxygen to attack the anomeric position (see inset, Scheme 1.9). A screen of additives, solvents and reaction temperatures led to the conditions of substoichiometric amounts of TMSOTf at -40 °C which effected a regio- and stereoselective glycosidation, preferentially furnishing the β -1,4 disaccharide **51** over the possible β -1,3 and α -1,4-products.

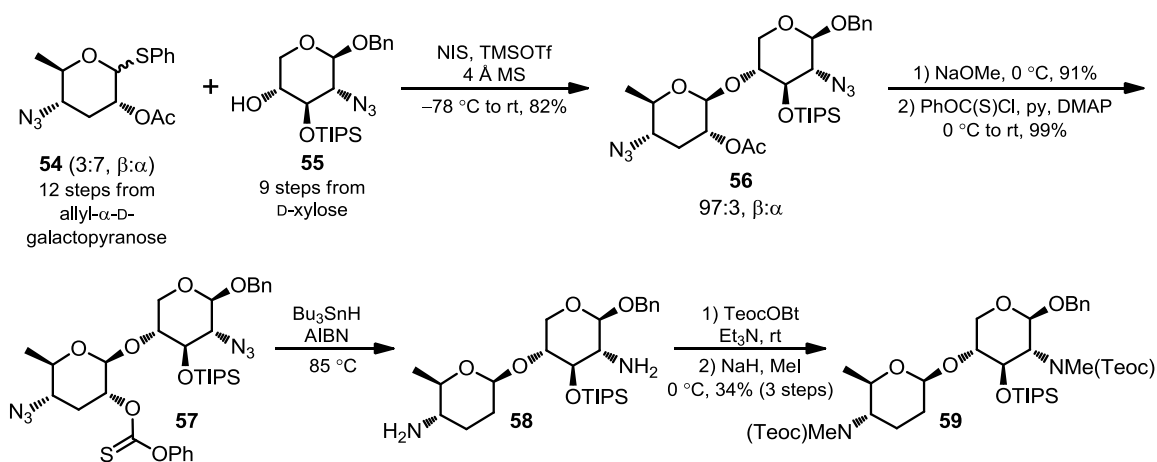


Scheme 1.9

Protection of the C3 hydroxyl as a chloroacetate allowed the thiophenyl group to be hydrolysed under mild conditions and converted to the trichloroacetimidate glycosyl donor **52**, setting up for the second glycosylation reaction. With cyclohexanol serving as a model for the aglycon, a second β -selective glycosylation, this time assisted by neighbouring group participation of the carbamate, was achieved in the presence of $\text{Yb}(\text{OTf})_3$ as a mild Lewis acid promoter without anomerisation at the existing β -glycoside bond. Chloroacetyl and *N*-Troc deprotection provided the incednine disaccharide fragment **53**.

A more recent synthesis of the incednine disaccharide by the Roush group features a complementary approach to the glycosylation reaction between glycosyl donor **54** and glycosyl acceptor **55**, relying on the neighbouring C2 acetate group in the thioglycoside donor **54** to promote β -glycosidation (Scheme 1.10).³⁷ The requisite azido sugar **54** was prepared from allyl- α -D-galactopyranose based on a route developed by Tietze and co-workers,³⁸ while the glycosyl donor **55** was prepared in 9 steps from D-xylose.

Glycosylation was achieved with *N*-iodosuccinimide in the presence of catalytic amounts of TMSOTf, affording the disaccharide **56** with excellent β -selectivity.



Scheme 1.10

The C2' acetate, having served its function in directing β -glycosidic bond formation, was to then be removed in a tandem azide reduction and alcohol deoxygenation sequence. In preparation, the azido disaccharide was converted into thiocarbonate **57** by acetate deprotection followed by thioacylation of the C2' alcohol. AIBN-initiated free radical reduction of the azido thiocarbonate by treatment with tributyltin yielded the diamine **58**. Protection of the diamine with TeocOBt and Et₃N and subsequent bis-*N*-methylation of the carbamates provided the protected incednine disaccharide fragment **59**.

1.6 Project aims and retrosynthetic approach

The challenge of assembling incednine in a concise manner, coupled with its promising bioactivity, drew us to this novel molecular architecture as an enticing target for total synthesis. The Toshima syntheses of incednam suffer from a number of drawbacks, including lengthy routes of 26 and 28 linear steps to prepare the macrolactam from methyl L-lactate, multiple rounds of oxidation state adjustments, and low yielding ring-closing steps. We envisaged a modular synthesis of the macrolactam **3** based upon a

cyclic alkenylsiloxane linchpin (**60**, Figure 1.8) to simultaneously incorporate both hydroxyl-bearing stereocentres and define the geometry of the C12-C13 (*Z*)-olefin. The remaining fragment was naturally disconnected at the amide bond, providing three key building blocks which would be used to construct the macrolactam. We anticipated that the cyclic nature of the alkenylsiloxane would specify the configuration of the (*Z*)-olefin, and maintain this configuration during subsequent manipulations, while doubling as a handle for a Hiyama cross-coupling reaction to append the C14-C23 aminotetraene **61**.

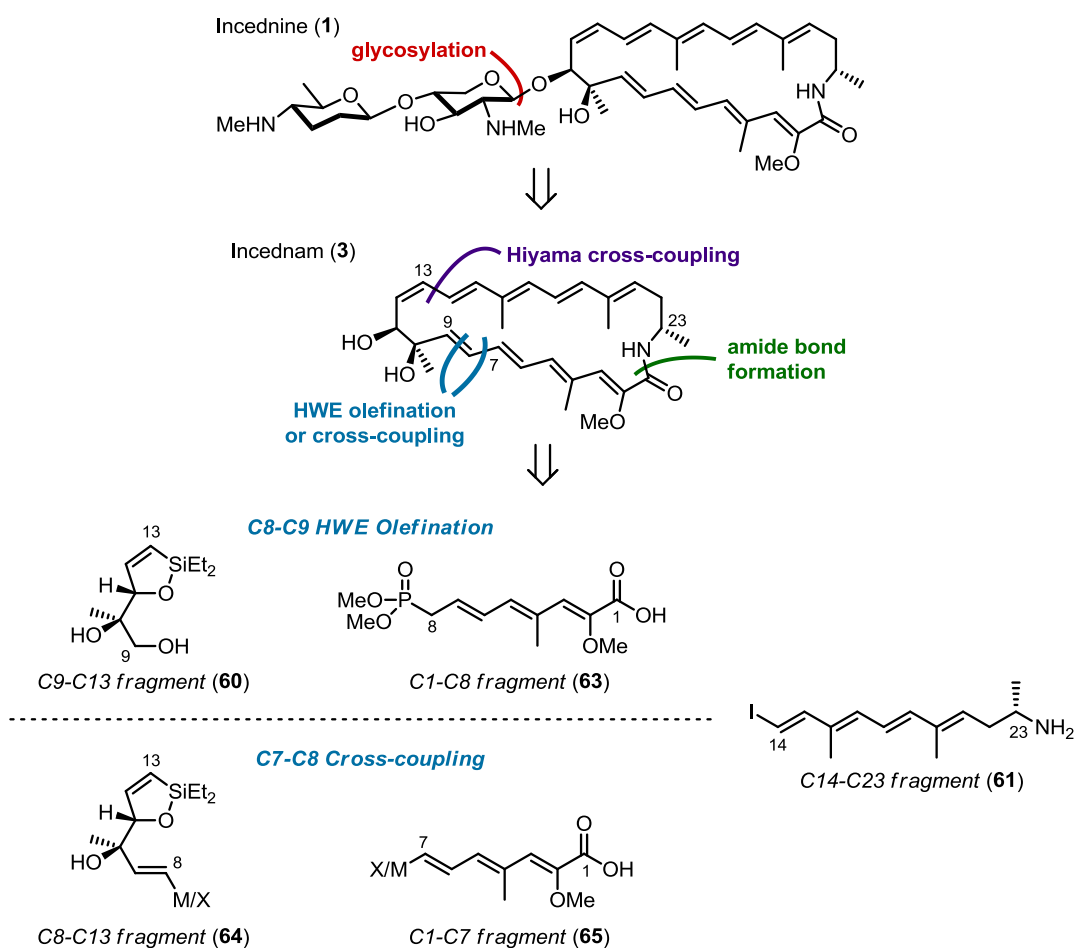
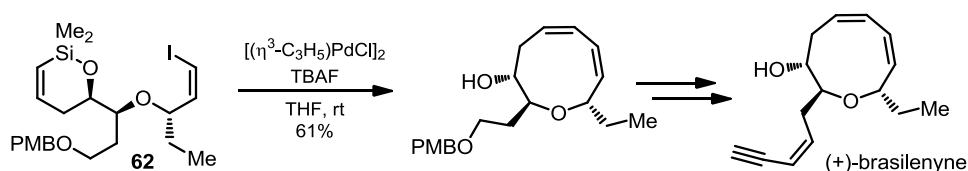


Figure 1.8 Retrosynthesis of incednam via C8-C9 olefination

Developing a convenient method for the preparation of cyclic alkenylsiloxanes and utilising these motifs in cross-coupling with polyene coupling partners stands to offer a

general route of accessing a variety of (*Z*)-containing polyene natural products. This class of compounds includes a number of the 20-26 membered polyketide macrolactams related to incednine, many of which show interesting anticancer and antibacterial activity. Current methods of assembling (*Z*)-containing polyenes often rely on the Stille cross-coupling, as demonstrated in the Toshima syntheses of incednam, which necessitates the use of toxic organotin compounds. Pioneering work on the application of Hiyama cross-coupling reactions to natural product syntheses has been performed by the Denmark group,³⁹ who have also demonstrated that cyclic alkenylsiloxanes are competent donors in this palladium-catalysed reaction.^{40,41} While examples of alkenyl-aryl partner combinations are readily available, alkenyl-alkenyl cross-couplings of cyclic silyl ethers are scarce, with one of the few examples being the intramolecular ring-closing cross-coupling of silacycle **62** to construct the medium-sized ring of brasilenyne (Scheme 1.11).⁴²



Scheme 1.11 Hiyama cross-coupling in the total synthesis of brasilenyne

In addition to amide bond formation, the final key connection would be the construction of the C8-C9 alkene. This could be achieved by olefination of the aldehyde derived from the primary alcohol **60**, utilising classical methods such as the Horner-Wadsworth-Emmons reaction with the extended phosphonate **63** or Julia olefination with an analogous sulfonyl reagent which is not shown (Figure 1.8).

Alternatively, disconnecting the C7-C8 bond provides cross-coupling partners **64** and **65**, with **64** derived from functional group manipulation of the previously identified primary alcohol **60** (Figure 1.8). While the late-stage introduction of the C8 cross-

coupling handle allows significant flexibility in the nature of this organometallic coupling partner, we were drawn to either boron or silicon species, which would provide the opportunity to demonstrate orthogonal palladium-catalysed carbon-carbon bond forming steps in constructing both the C8-C9 and C13-C14 bonds. In the course of our investigations, it became apparent that whereas methods to conveniently prepare (*E*)-alkenyl boronic esters and iodides from aldehydes have been developed, a comparable method for the construction of silane cross-coupling partners was lacking, thus leading to the development of methodology to access functionalised (*E*)-vinylsilanes from aldehydes.

The following chapters of this thesis deal with the construction of the cyclic alkenylsiloxanes **60** and **64** (Chapter 2) and requisite polyene building blocks **61**, **63** and **65** (Chapter 4). A separate chapter is dedicated to the development of aldehyde silylolation methodology (Chapter 3), which was subsequently applied to the incednine system. The final chapter (Chapter 5) charts our investigations towards uniting the building blocks and the endgame to achieve a modular synthesis of the incednine aglycon.

2 Syntheses of Cyclic Alkenylsiloxane Building Blocks

2.1 Introduction

Organosilicon chemistry has enjoyed a renaissance in the last decade, coinciding with advances in Hiyama cross-coupling⁴³⁻⁴⁵ and Tamao oxidation,⁴⁶⁻⁴⁸ which allow carbon-silicon bonds to behave as handles for the construction of carbon-carbon and carbon-oxygen bonds. Organosilanes benefit from being non-toxic, stable to a variety of synthetic transformations, and prepared from relatively inexpensive starting materials, making them attractive synthetic intermediates. The class of cyclic alkenylsiloxanes are particularly attractive precursors to polyenes containing (*Z*)-alkenes,⁴⁹⁻⁵⁰ or latent β -, γ - or δ -hydroxy aldehydes and ketones⁵¹ (Figure 2.1).

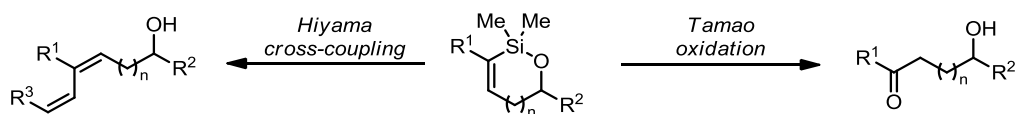


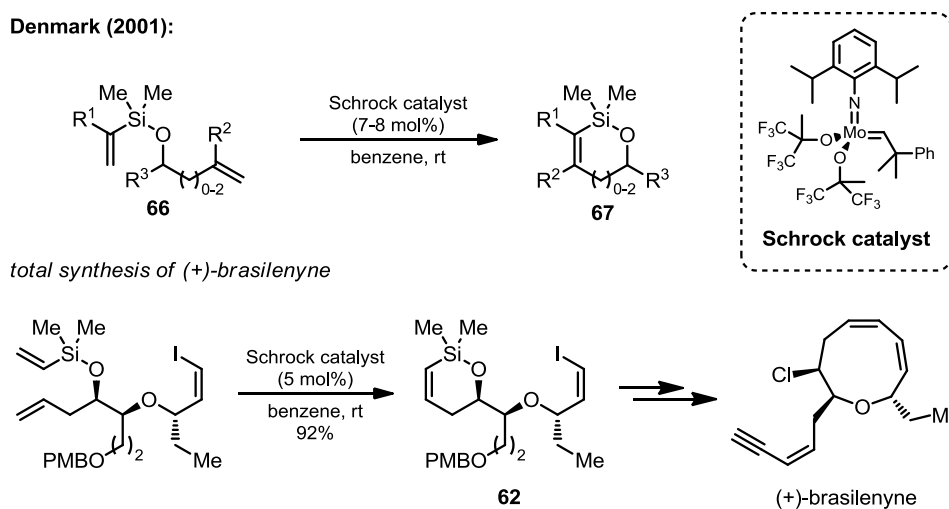
Figure 2.1

2.1.1 Previous syntheses of cyclic alkenylsiloxanes

In one of the first general routes to cyclic alkenylsiloxanes, Denmark and co-workers applied ring-closing metathesis to mono- and disubstituted dienylsiloxane substrates **66** with a range of tether lengths to access cyclic alkenylsiloxanes of various substitutions and ring-sizes (**67**, Scheme 2.1).⁴¹ While the use of Schrock's molybdenum catalyst, which is less sensitive to steric crowding around the reaction centre, is mandatory for these vinylsilane substrates, the olefin metathesis can be performed in the presence of vinyl iodides. This enables the siloxacyclic product to participate in subsequent Hiyama cross-coupling ring expansions into medium rings containing 1,3-dienes, as was

elegantly demonstrated in the total synthesis of (+)-brasilenyne from cyclic alkenylsiloxane **62**.⁴²

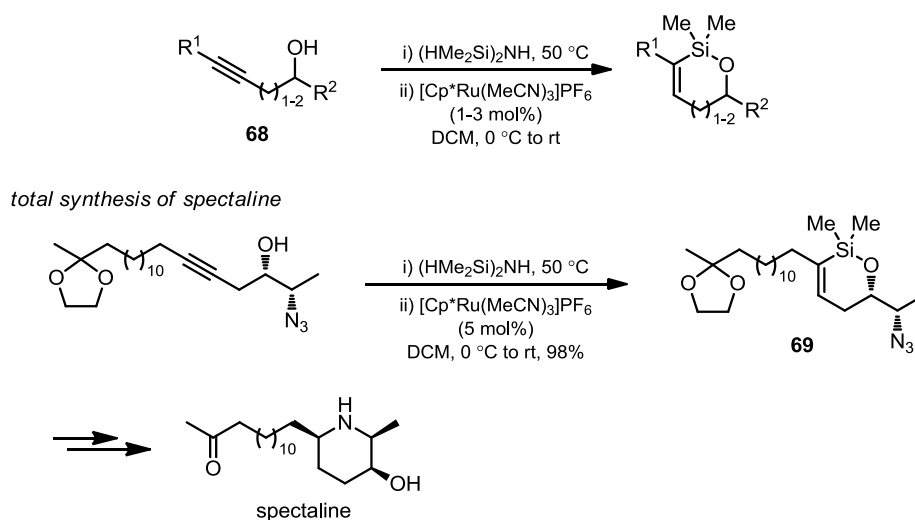
Denmark (2001):



Scheme 2.1 Ring-closing metatheses of dienylsiloxanes

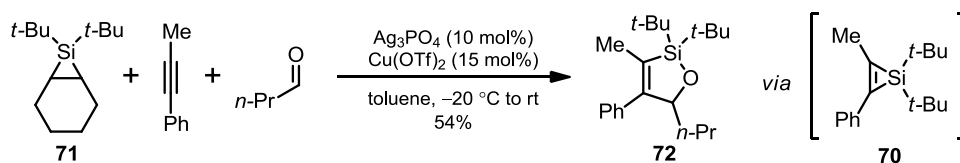
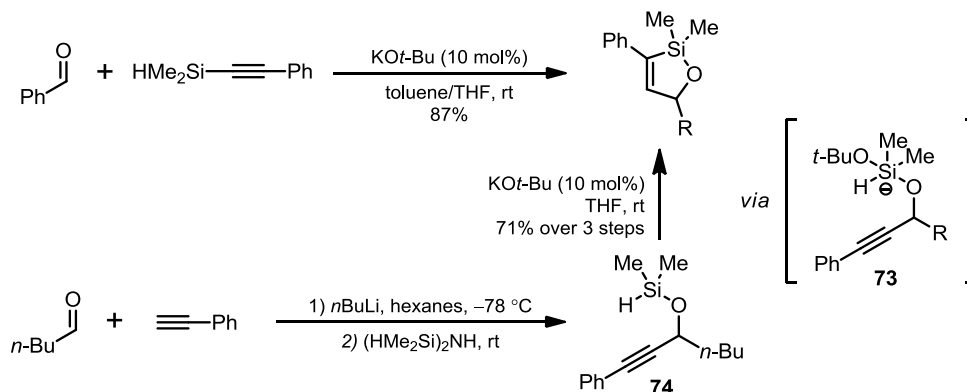
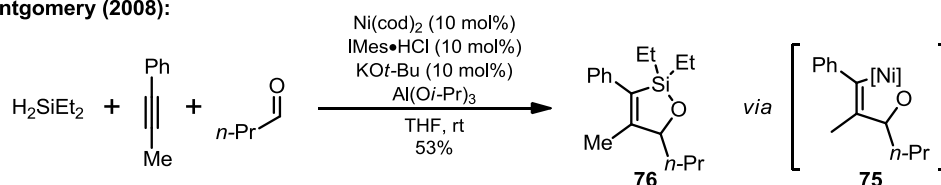
Following on from earlier work on the ruthenium-catalysed intermolecular *trans*-hydrosilylation of alkynes, Trost and co-workers introduced an intramolecular variation with alkyne-substituted siloxanes **68** (Scheme 2.2).⁵² The intramolecular hydrosilylation proceeds with exclusive selectivity for the (*Z*)-alkenylsilane despite substantial steric bulk around the alkyne, and the use of tetramethyldisilazane allows O-silylation and hydrosilylation to be performed in one pot. Although this approach cannot be applied to propargylic siloxanes or terminal alkynes, it continues to be a powerful method of generating six and seven-membered siloxacycles as demonstrated in the total synthesis of the piperidine alkaloid spectraline in three steps from cyclic alkenylsiloxane **69**.⁵¹

Trost (2003):



Scheme 2.2 Intramolecular hydrosilylations of propargylic alkoxy silanes

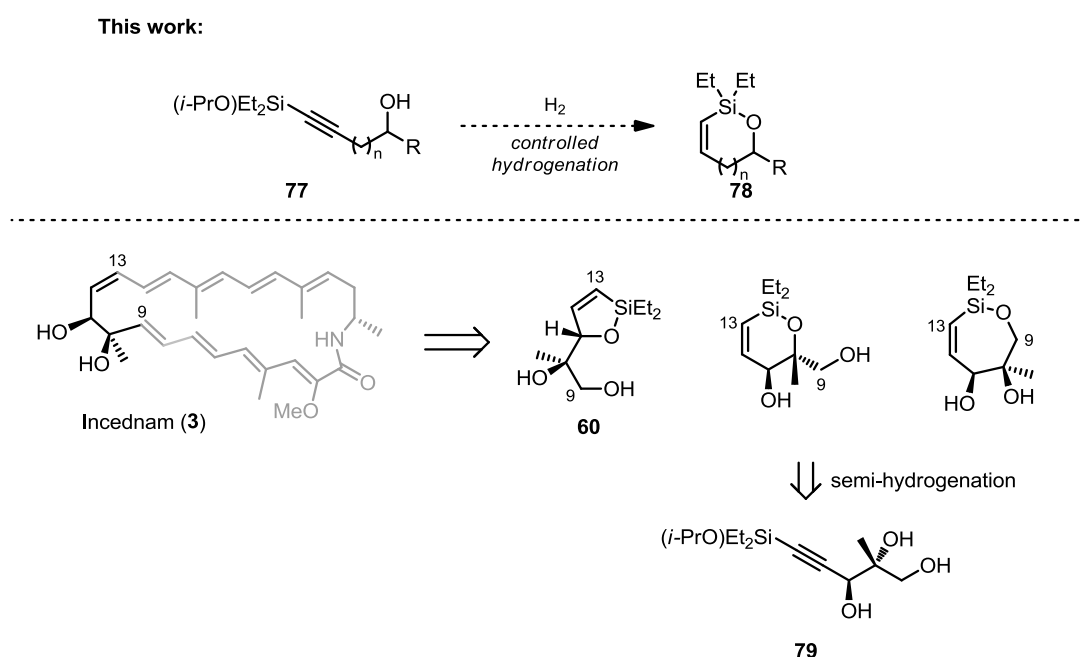
An approach to constructing heavily substituted five-membered silacycles involves the assembly of an alkyne, aldehyde and a silylene equivalent in a multicomponent reaction (Scheme 2.3). Woerpel and co-workers have developed a mild silver-catalysed route to prepare silacyclopentene **70** *in situ* by silicon transfer to an internal alkyne from silacyclopentane **71**.⁵³ Copper-catalysed carbonyl insertion into the silacyclopentene affords the five-membered siloxacycle **72** in a convenient one-pot procedure. Lee and co-workers have reported a two component assembly from the reaction of aldehydes and alkynylsilanes catalysed by potassium *tert*-butoxide catalysed.⁵⁴ Formation of the silacycle is thought to occur *via* intramolecular hydrosilylation of oxasilicate **73**, which may arise from silylalkyne addition across the aldehyde. The findings of Roush and co-workers, who observed the same cyclic alkenylsiloxanes on treating propargylic alkoxy silanes **74** catalytic *tert*-butoxide, support this reaction pathway.⁵⁵

Woerpel (2004):**Lee (2005) & Roush (2008):****Montgomery (2008):**

Scheme 2.3 Multicomponent assembly of five-membered cyclic alkenylsiloxanes

Finally, a nickel-NHC catalysed cyclocondensation developed by the Montgomery group allows dialkylsilanes to be used as silylene components.⁵⁶ Dihydrosilane incorporation is proposed to occur through double Si-H σ -metatheses into the Ni-O and Ni-C bonds of nickel metallocycle **75**, generating the five-membered siloxacycle **76**. It is worth noting that products with complementary substitution patterns can be attained by careful selection of the silylene component, as seen from **72** and **76** prepared from the silacyclopropane and diethylsilane routes, respectively. Although a significant degree of complexity is achieved from simple and readily available starting materials in a single step with this approach, stereochemical control at the allylic position is currently lacking, and the methodology is necessarily limited to five-membered rings.

Our strategy exploits the conceptually straightforward controlled hydrogenation of alkynylsiloxanes **77**, affording a (*Z*)-alkenylsiloxane that could undergo intramolecular trans-etherification to form cyclic siloxane **78** (Scheme 2.4). When compared to existing methods of preparing cyclic alkenylsiloxanes, this approach benefits from the use of low cost, air-stable catalysts (such as the Lindlar system) and versatility in accessing a variety of ring sizes and substituents. In the context of incednine, the required C10 and C11 hydroxylation pattern derives from triol **79**, which upon semi-hydrogenation could conceivably undergo intramolecular capture by one of three hydroxyls to form a five, six or seven-membered siloxacycle. The five-membered siloxacycle **60**, which we anticipated as the kinetic cyclisation product, strategically protects the secondary alcohol, allowing the C9 primary alcohol to be selectively manipulated for elaboration into the aglycon.

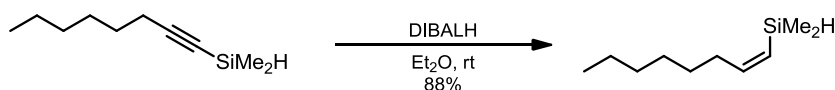


Scheme 2.4 A controlled hydrogenation strategy to the incednam C12-C13 (*Z*)-alkene

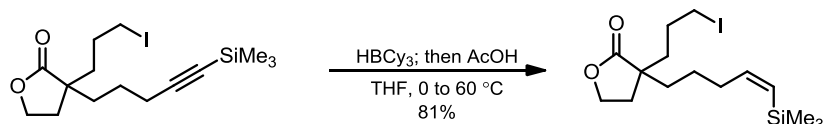
2.1.2 Controlled hydrogenations of alkynylsilanes

Many of the protocols developed for *syn*-hydrogenations of alkynes have been applied to alkynylsilanes with great success. (*Z*)-Alkenylsilane products are usually obtained in excellent stereoselectivity with little over reduction to silylalkanes, although product distribution can be highly substrate and operator dependent when a heterogeneous catalyst is employed.⁵⁷ It is perhaps for this reason that most *cis*-reductions of alkynylsilanes are performed by a hydrometalation/protodemetalation sequence utilising soluble metal hydride or organometallic reagents. Examples of silylalkyne reduction with aluminium, boron, titanium and zirconium complexes have been reported across a wide range of alkynylsilane substrates which showcase an impressive functional group tolerance (Scheme 2.5).⁵⁸⁻⁶¹

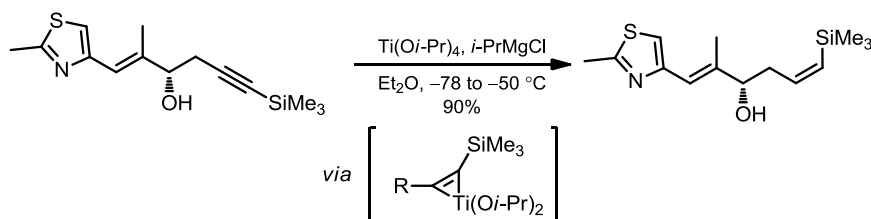
Hydroalumination/protodemetalation (Tamao, 1988):



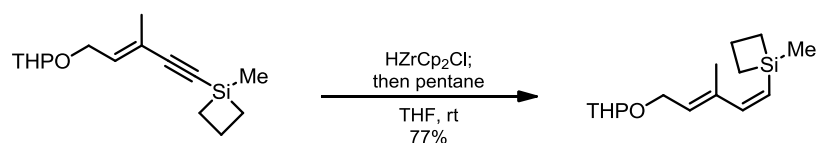
Hydroboration/protodemetalation (Molander, 1996):



Hydrotitanation/protodemetalation (Shibasaki, 2000):



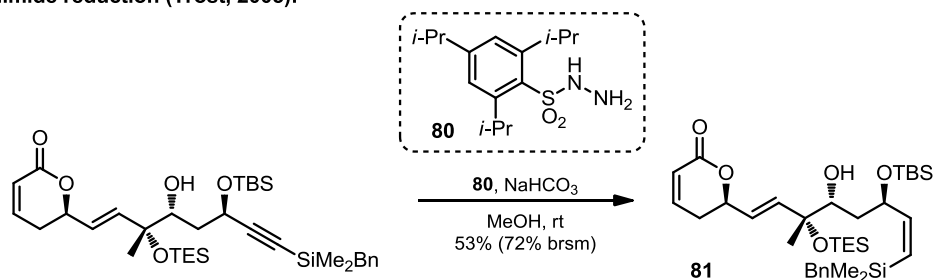
Hydrozirconation/protodemetalation (Lopez, 2009):



Scheme 2.5 Hydrometalation approaches to alkynylsilane reduction

Homogeneous hydrogen transfer can be accomplished with diimide derivatives which produces nitrogen gas as a by-product of the reaction, vastly simplifying product isolation and purification. Although application to acetylene reduction is limited by competing reduction of the (*Z*)-alkene product,⁶² an example of diimide alkynylsilane reduction can be found in Trost and coworkers' synthesis of fostriecin, where diimide was generated *in situ* by treating sulfonamide **80** under mildly basic conditions.⁶³ Notably, the silylalkyne was reduced in the presence of a free hydroxy group, a *trans*-olefin and an α,β -unsaturated lactone, and alkenylsilane **81** could be isolated after partial conversion in a good yield (Scheme 2.6).

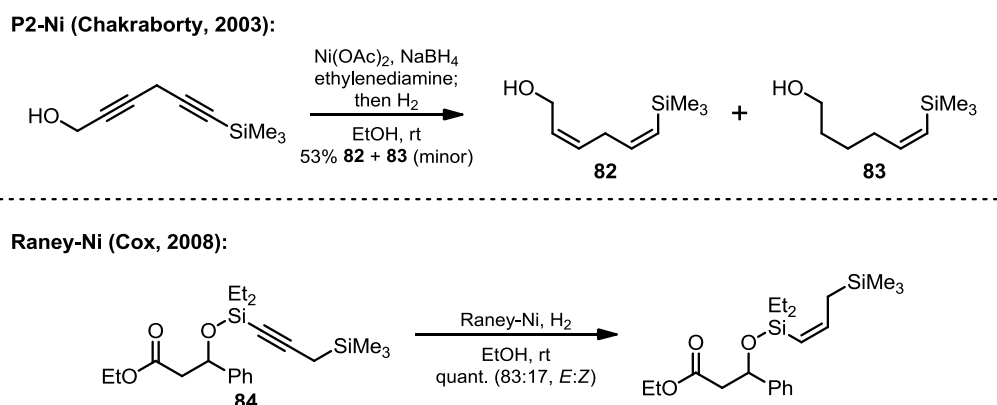
Diimide reduction (Trost, 2005):



Scheme 2.6 Diimide hydrogenation of an alkynylsilane

Heterogeneous metal-catalysed alkynylsilane hydrogenations are reputed for unreliable stereoselectivities and over reduction of the alkenylsilane product, leading to mixtures of alkenylsilane isomers and silylalkane that complicates isolation of the *cis*-olefin. However, these catalytic systems display a wide functional group tolerance and allow direct incorporation of molecular hydrogen, which when coupled with scalability and convenient methods of catalyst removal, continue to make this an attractive method of preparing (*Z*)-alkenylsilanes.⁵⁷ Activated nickel systems such as P2-nickel (Brown's catalyst) and Raney nickel are known to perform the *syn*-hydrogenation of silylalkynes (Scheme 2.7). The P2-nickel reduction has been applied to a skipped alkyne-alkynylsilane by Chakraborty and co-worker in the total synthesis of (+)-crocin A to

prepare the (*Z,Z*)-skipped diene **82**.⁶⁴ The silylalkyne was reduced at a slower rate compared to the internal alkyne, resulting in a mixture of diene **82** and silylalkene **83**. Cox and co-workers have employed Raney nickel to perform a sterically demanding hydrogenation of alkoxy silylalkyne **84**. Although over reduction to the alkylsilane could be avoided by careful reaction monitoring, the alkenylsilane was still obtained as a mixture of (*Z*) and (*E*)-isomers.⁶⁵



Scheme 2.7 Nickel-based hydrogenations of alkynylsilanes

Poisoned palladium catalysts are the stalwarts of alkyne semi-hydrogenation, and since Lindlar's discovery of the eponymous catalyst in 1952, have evolved to include palladium deposited on a variety of surfaces. Although the Lindlar catalyst strictly refers to palladium prepared on calcium carbonate and treated with lead acetate,⁶⁶ the term has been used in the literature to refer to lead-free Pd/CaCO₃ catalysts, as well as palladium deposited on barium sulfate which is more accurately termed the Rosenmund catalyst.⁶⁷ Catalyst poisoning with lead or quinoline is thought to improve *cis/trans* selectivity and reduce further hydrogenation of alkene products by modifying the catalyst's structure and inhibiting alkene interaction with the surface, respectively.⁵⁷

Poisoned palladium catalysts are tolerant of a wide variety of functional groups, including cyclobutenones, free alcohols, carboxylic acids, thioethers, acetonides and

enamides (see first row, Figure 2.2).⁶⁸⁻⁷¹ The hydrogenations usually proceed with high selectivity for the *cis*-silylalkene, although the presence of neighbouring silyl ethers, free carboxylic acids or hydroxyls in the substrate can influence the amount of *trans*-alkene and over-reduced alkylsilane formed (see second row, Figure 2.2).⁷²⁻⁷⁵ The relative rate of silylalkyne hydrogenation appears to be dependent on silicon substitution, allowing trimethylsilylalkynes to be selectively reduced in the presence of bulkier *tert*-butyldiphenylsilylalkynes.⁷⁵

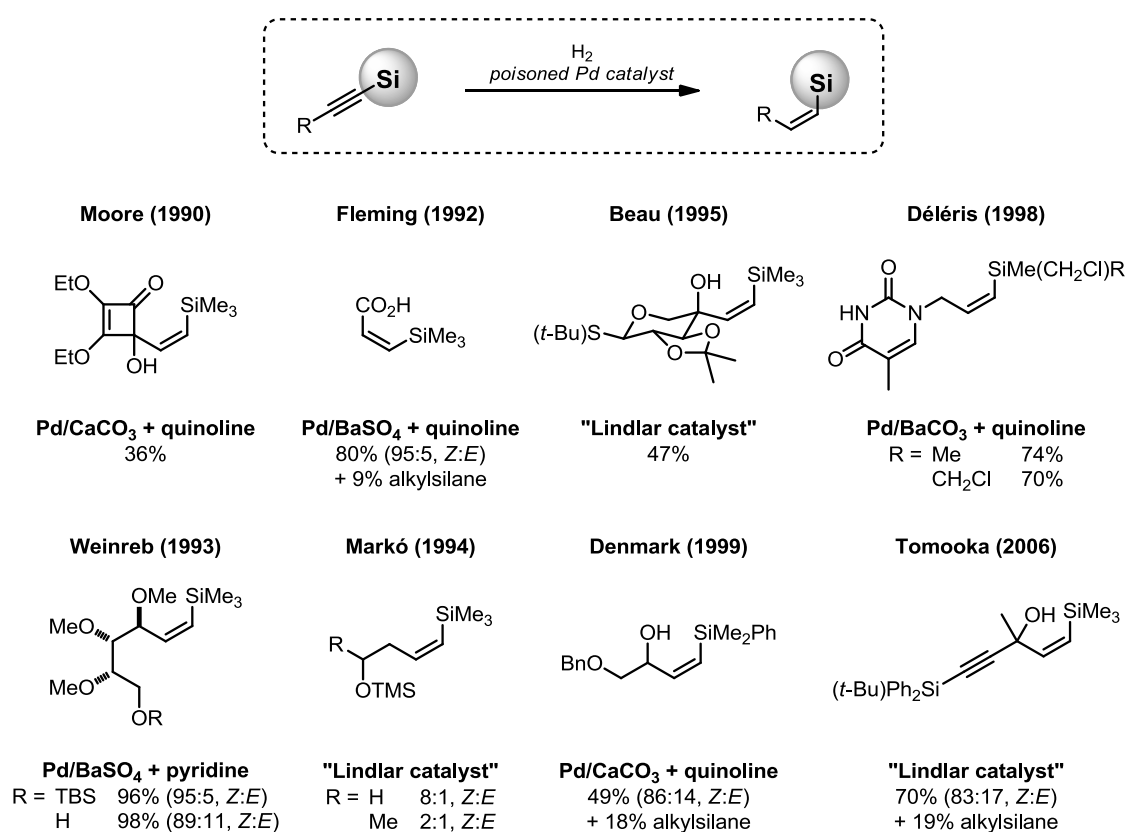
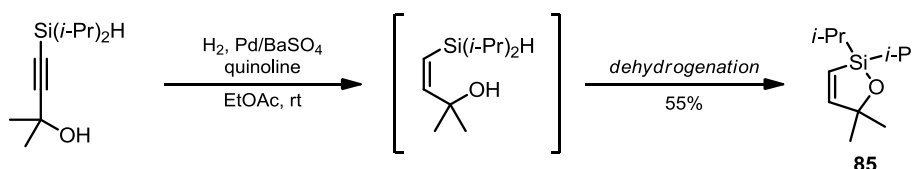


Figure 2.2 Selected hydrogenations of alkynylsilanes with poisoned palladium catalysts

In comparison to hydrometalations and nickel-catalysed hydrogenations, the substrates of Lindlar-derived catalysts display a narrower scope of silicon substitution: apart from standard silicon groups (such as trimethyl and dimethylphenylsilanes), the hydrogenation has been conducted on mono and di(chloromethyl)silylalkyne with a palladium on barium carbonate catalyst by Délérís and co-workers (Figure 2.2). In the

course of our investigations, it came to our attention that a report of the semi-hydrogenation of hydrosilanes by Salomon and co-workers had gone unnoticed. The report contains a single example of hydrogenation with a substrate containing a free propargylic alcohol followed by *in situ* dehydrogenative cyclisation to afford siloxacycle **85** (Scheme 2.8).⁷⁶ Palladium-catalysed formation of silyl ethers from hydrosilanes of this type were first reported by Speier⁷⁷ using Pd/C, and have subsequently been exploited by Yamamoto,⁷⁸ Cox,⁷⁹ and our own group.⁴⁸ The preparation of cyclic alkenylsiloxanes from ring-closing trans-etherification of semi-hydrogenated alkynylsiloxanes allows much greater flexibility in substrate preparation: Hydrosilanes can interfere with palladium-catalysed cross-coupling and are deprotonated by organolithium reagents. This reactivity precludes many modular preparations of alkynylsilanes from silylacetylenes which are available to alkynylsiloxanes, including Sonogashira cross-coupling with aryl and alkenyl halides and deprotonation followed by addition to carbon electrophiles.

Salomon (1994):



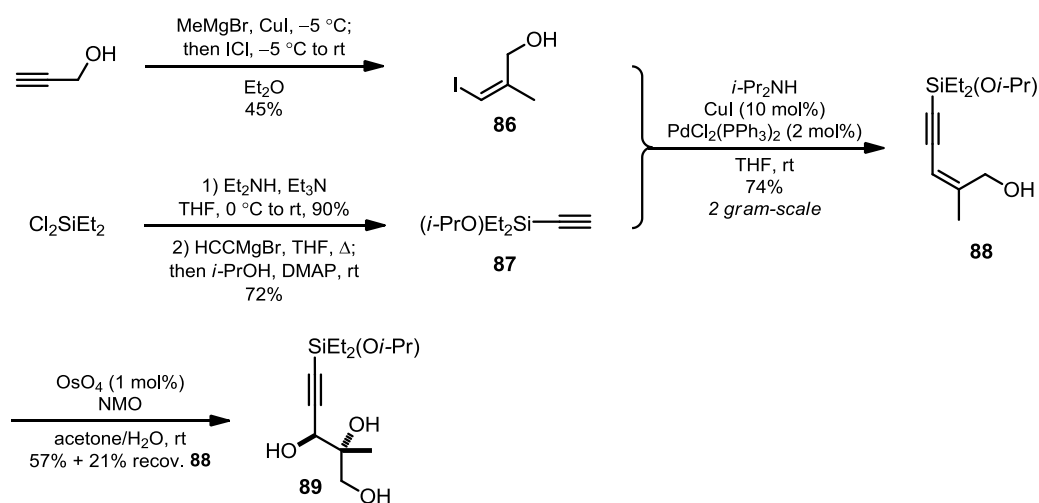
Scheme 2.8

2.2 Racemic synthesis of the cyclic alkenylsiloxane

2.2.1 Establishing the semi-hydrogenation methodology

Preparation of the alkynylsiloxane substrate commenced with commercially available propargyl alcohol, which was converted to the known iodide **86**⁸⁰ by copper-catalysed methylmagnesium followed by quenching of the vinylic metal intermediate with

iodine (Scheme 2.9). Dichlorodiethylsilane was transformed in two steps to ethynylsiloxane **87**,⁸¹ and following Sonogashira coupling with iodide **86** using the procedure of Hatakeyama and co-workers afforded multigram quantities of silyl enyne **88**.⁸⁰ The diethyl silyl ether was selected over its dimethyl analogue (prepared from dichlorodimethylsilane) on the basis of its greater stability towards silica gel chromatography. This is reflected in the known relative stabilities of typical silyl ethers under acidic conditions (TMS < TES < TIPS).⁸²

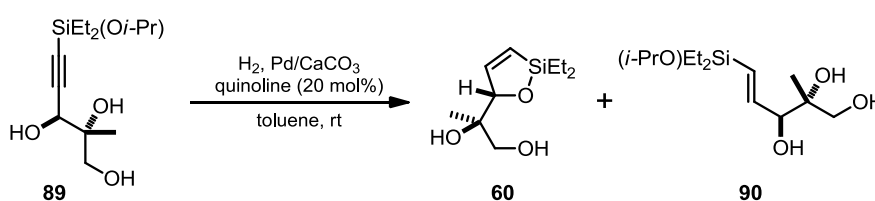


Scheme 2.9

Enyne **88** was then subjected to a *syn*-selective Upjohn dihydroxylation to introduce the secondary and tertiary alcohols. Although sluggish, these conditions afforded triol **89** in 57% yield after 16 hours with 21% recovered starting material. Prolonged reaction times, increased catalyst loading, or addition of citric acid⁸³ failed to improve the yield of the triol. While there are numerous enyne *syn*-dihydroxylation substrates in the literature, there are limited reports of successful silyl enyne substrates (see Section 2.3.1). The reason for this poor reactivity of silylenyne **88** remains unclear.

The *cis*-hydrogenation of **89**, which we anticipated would be followed by *in situ* ring closure of alkenyl siloxane **60**, was next investigated. As had been previously observed

by others in the hydrogenations of silylalkyne substrates containing free hydroxyl groups, a significant amount of the *trans*-isomer **90** was formed when either lead-free or lead-poisoned Lindlar's catalyst was employed. In addition, the reduction was incomplete even after extended reaction times (Entries 1 and 2, Table 2.1). Increasing the ratio of catalyst to quinoline to 1:4 (Entry 3) resulted in complete conversion of the alkyne, affording desired cyclic alkenylsiloxane **60** in good yields, while slightly lowering the *cis*-selectivity of the reaction. Further increasing the catalyst loading increased the formation of the *trans*-isomer (Entry 4), and subsequent increments resulted in significant overreduction of the alkenylsiloxanes to the alkylsilane (Entry 5). Other heterogeneous catalytic systems for semi-hydrogenation, such as P2-nickel⁸⁴ or polymer-bound palladium,⁸⁵ resulted either in a complex mixture of products or no conversion and recovery of the alkynylsiloxane.



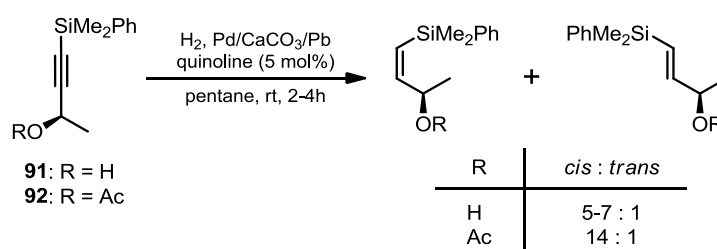
Entry	conditions			60 : 90 ^a	yield (%) ^a (conversion (%) ^b)
	Pd/CaCO ₃ eq.	Quinoline eq.	t / h		
1	0.02	0.20	72	6.5 : 1	n.d. ^c (50)
2 ^d	0.02	0.20	72	2 : 1	n.d. (29)
3	0.05	0.20	5	5 : 1	84 (100)
4	0.10	0.20	2	3 : 1	33 (100)
5	0.20	0.20	2	10 : 1	15 ^e (100)

^a Isolated yields of **60** + **90** after chromatography. ^b Determined by ¹H NMR spectroscopic analysis of crude reaction mixture. ^c Not determined. ^d Pd/Pb/CaCO₃ (Lindlar's) catalyst. ^e Significant alkene reduction observed.

Table 2.1

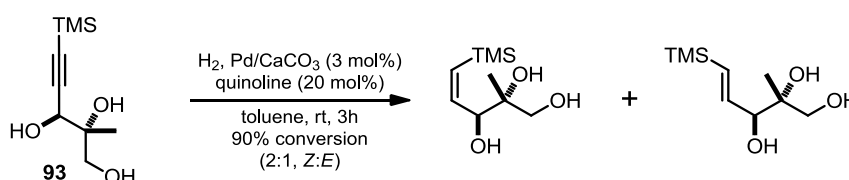
Related semi-hydrogenations by Panek and co-workers have shown that the presence of a free propargylic alcohol in alkynylsilane substrates can increase the formation of the undesired *trans*-alkenylsilane.⁸⁶ Under Lindlar conditions, a *cis:trans* ratio of 5-7:1 was obtained using alcohol **91** (Scheme 2.10). In contrast, protecting the free alcohol with an acetyl group in **92** resulted in an improved *cis:trans* ratio of 14:1. This effect is consistent with some of our later findings, which are discussed in Section 2.3.3.

Panek (1992):



Scheme 2.10

Interestingly, reduction of the related TMS-acetylene **93** reached 90% conversion in just 3 hours at 3 mol% palladium loading, with a 2:1 ratio of *cis:trans* alkenylsilane products (Scheme 2.11). The isopropyl ether thus appears to decrease the reactivity of the system but with the benefit of improving *cis*-selectivity. This is attributed to increased steric hindrance around the alkyne hampering palladium coordination, and the alkoxy silane substituent potentially exerting an electronic influence on the alkyne which increases the *cis:trans* selectivity of the Lindlar reduction.



Scheme 2.11

To confirm the presence of the five-membered cyclic alkenylsiloxane **60** (and not the six- or seven-membered rings **94** or **95**, Figure 2.3), ^1H COSY NMR experiments were conducted which identified the presence of a free primary alcohol from coupling interactions with the H5 signals, thus eliminating seven-membered silyl ether **95**. Formation of the six-membered alkenylsiloxane **94** was also thought unlikely, based on the sharp ^1H NMR peak corresponding to H3, suggesting the absence of a secondary alcohol. Lack of coupling to the non-primary hydroxyl peak in the proton spectrum led to its assignment as a tertiary alcohol, supporting the formation of five-membered alkenylsiloxane **60**. In addition, the formation of a dicarbonyl compound was never observed in later oxidations of the cyclic alkenylsiloxane employing excess oxidant, as would be expected if six-membered ring **94** had formed. Chemical shift comparison to later rearrangement products provided further evidence for the formation of the five-membered cyclic alkenylsiloxane.

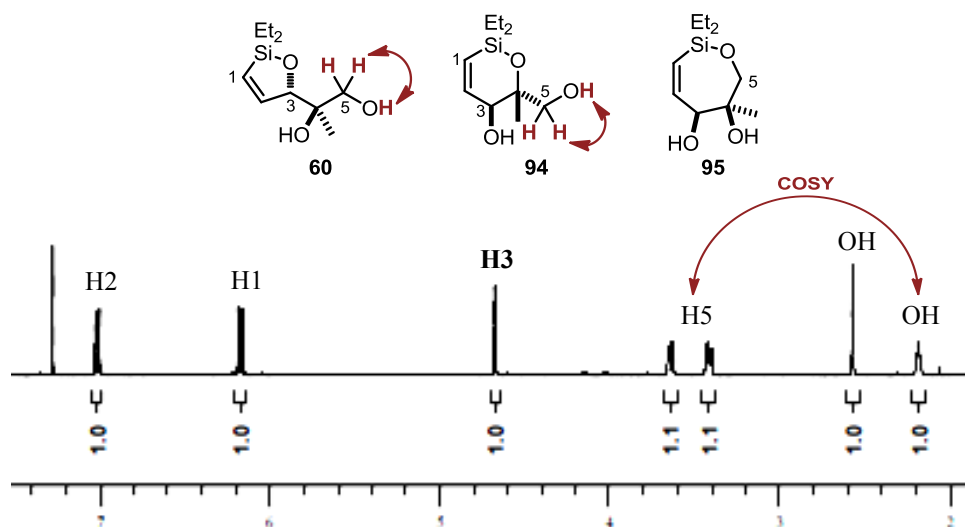


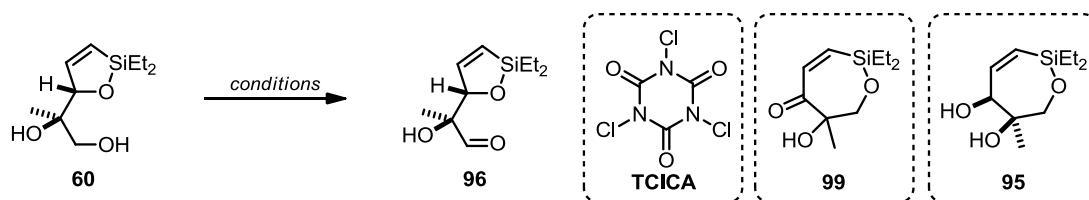
Figure 2.3 ^1H NMR spectrum of cyclic alkenylsiloxane (selected region)

Overall, the racemic synthesis of the cyclic alkenylsiloxane **60** was accomplished in a total of six steps, with the longest linear sequence spanning five steps, and an overall yield of 29%.

2.2.2 Elaborating the cyclic alkenylsiloxane

As a prelude to either the C8-C9 olefination or C7-C8 cross-coupling, we next investigated the oxidation of **60** to aldehyde **96**. The oxidation was found to proceed sluggishly under standard DMP oxidation conditions buffered with sodium bicarbonate, resulting in partial conversion of **60** to a mixture of the desired aldehyde and a side product (Entry 1, Table 2.2). Warming the reaction slightly to 30 °C facilitated complete conversion of **60** with an accompanying increase in the formation of the same side product (Entry 2). The TEMPO/BAIB system⁸⁷ was next attempted (Entry 3). To our surprise, methyl ketone **97** was formed exclusively, presumably *via* the elimination of formaldehyde from the intermediate **98** through participation of the neighbouring tertiary alcohol (Scheme 2.12). Transition metal-based oxidants TPAP⁸⁸ and PCC⁸⁹ also failed to provide **96**, with starting material recovered in the case of TPAP and a complex mixture of products formed from the PCC oxidation (Entries 5 and 6).

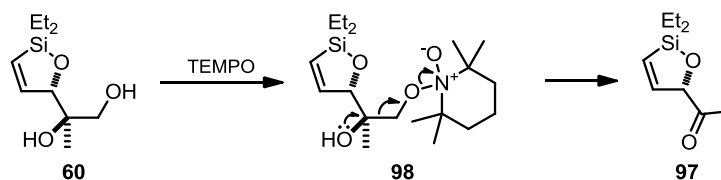
When DMSO was activated with oxalyl chloride under standard Swern oxidation conditions, a 2:1 mixture of aldehyde **96** and the same side product was obtained (Entry 7). Replacing oxalyl chloride with SO₃·pyridine complex under standard Parikh-Doering conditions provided a 1.3:1 mixture of the aldehyde and enone **99** (Entry 8), which suggests an *in situ* rearrangement of the cyclic alkenylsiloxane **60** to its regioisomer **95**, followed by oxidation of the newly unprotected secondary hydroxyl group. By modifying these conditions – using DIPEA instead of triethylamine as the base (Entry 9) and premixing the SO₃·pyridine complex and DMSO (Entry 10) – we were able to suppress side product formation, allowing aldehyde **96**, which was found to degrade on silica, to be carried on to the next step without further purification.



Entry	conditions	T / °C	conv ^a / %	products ^a
1	DMP, NaHCO ₃	20	67	4:1, 96:95 ^b
2	DMP, NaHCO ₃	30	100	3.5:1, 96:95
3	TEMPO, BAIB	20	100	97
4	TEMPO, TCICA ⁹⁰	20	100	Complex mixture
5	TPAP, NMO, 4 Å MS	20	0	-
6	PCC, NaOAc	20	100	Complex mixture
7	(COCl) ₂ , DMSO, Et ₃ N	-78	100	2:1, 96:95
8	SO ₃ ·py, DMSO, Et ₃ N	0	100	1.3:1, 96:99
9	SO ₃ ·py, DMSO, DIPEA	0	100	3:1, 96:95
10 ^c	SO ₃ ·py, DMSO, DIPEA	20	100	>19:1, 96:95

^a Determined by ¹H NMR spectroscopic analysis of crude reaction mixture unless otherwise noted. ^b Unidentified side product. ^c SO₃·py complex and DMSO were premixed for 15 minutes at room temperature before addition of **60** and DIPEA.

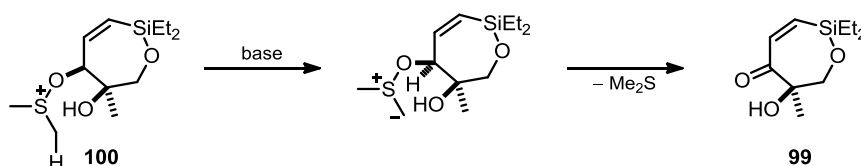
Table 2.2



Scheme 2.12

The side product recovered after DMP, Swern and Parikh-Doering oxidations (Entries 1, 2, 7 and 9) decomposed during any attempt at chromatographic purification, and as

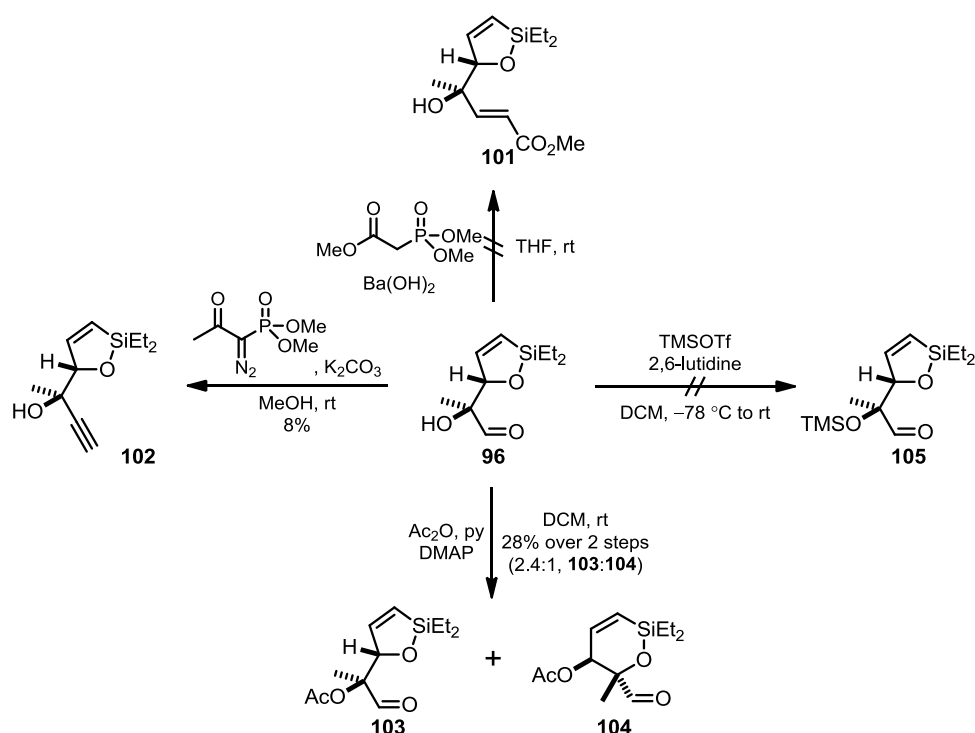
such has eluded characterisation. Based on ^1H NMR analyses of the crude reaction mixtures, the structure contains neither an aldehyde nor a ketone, as evidenced by the presence of a signal corresponding to an allylic proton. The side product is tentatively assigned as seven-membered cyclic alkenylsiloxane **95** (Table 2.2). This assignment is consistent with the formation of enone **99** when triethylamine was used in conjunction with $\text{SO}_3\cdot\text{pyridine}$ complex: a larger base (*i.e.* DIPEA) would encounter significant steric resistance from the neighbouring tertiary carbon centre in the deprotonation of adduct **100** to form a sulfur ylide (Scheme 2.13). Chemical shift comparison of the vinyl proton signals to later rearrangement products supported formation of the seven-membered siloxacycle **95**.



Scheme 2.13

With aldehyde **96** in hand, the C8-C9 bond forming olefination was attempted. When Paterson's conditions for the HWE olefination of base-sensitive compounds were employed (barium hydroxide and wet THF),⁹¹ **101** was not detected, and degraded starting material was recovered instead (Scheme 2.14). Parallel efforts to convert the aldehyde to an alkyne **102** by the Colvin rearrangement or Corey-Fuchs protocol led to decomposition of the starting material. Even mild conditions employing the Ohira-Bestmann reagent afforded no more than a low yield of alkyne **102**.⁹² Based on the belief that quenching of the phosphonate carbanion by the free alcohol present in **96** was occurring, acetate **103** was prepared. At this point, we were intrigued to observe the formation of the six-membered siloxane **104** under basic acetylation conditions. This is the likely result of the secondary silyl ether undergoing an acetylation-promoted

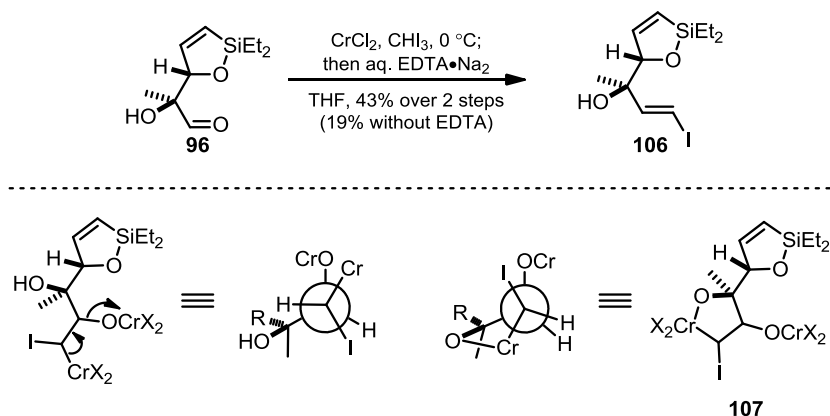
desilylation, accompanied by the tertiary hydroxyl group ring closing to form the six-membered siloxane **94**. Spectroscopic comparison of rearranged product **104** with a sample of **60** agreed with our earlier assignment of **60** as a five-membered cyclic siloxane. Subsequent unsuccessful attempts at olefinating acetates **103** and **104**, in which starting material was recovered, and difficulty in preparing TMS-protected aldehyde **105** led us to focus on the C7-C8 cross-coupling strategy.



Scheme 2.14

Alkenyl iodide **106** was conveniently prepared by a Takai olefination⁹³ of aldehyde **96** albeit in disappointing yields (Scheme 2.15). Unusually broad peaks in the proton NMR spectrum of the crude reaction mixture even after filtering through Celite® and repeated aqueous washes, and poor mass recovery from silica gel chromatography, led us to suspect that the α -hydroxyaldehyde was forming a chromacycle of type **107** during the reaction. Confined in a ring system, the alkyl and the alkoxy chromium moieties would be prevented from aligning in a *syn*-periplanar fashion, and *syn*-elimination of (L_nCr)₂O

to give the alkenyliodide would be impeded (according to the mechanism proposed by Takai).⁹⁴ Formation of the chromacycle **107** could be disrupted by quenching the reaction with metal-chelating agent EDTA·Na₂,⁹⁵ allowing the elimination of chromium (III) oxides to proceed and improving the isolated yield of iodide **106**.

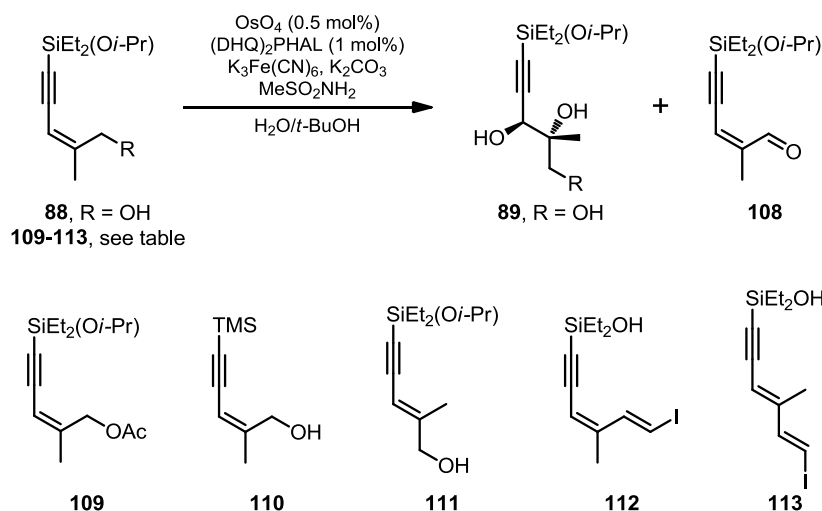


Scheme 2.15

2.3 Asymmetric synthesis of the cyclic alkenylsiloxane

2.3.1 Sharpless asymmetric dihydroxylation

We next aimed to develop an asymmetric synthesis of **60** *via* Sharpless asymmetric dihydroxylation (SAD) of silylenyne **88**, installing both hydroxyl-bearing stereocentres of incednine in one step. Initial attempts under standard conditions for trisubstituted alkenes yielded a mixture of triol **89**, enal **108**, and starting material (Entry 1, Table 2.3). Varying the ligand and temperature of the reaction had little effect on the outcome of the reaction (Entries 2 and 3), and only starting material was recovered when the allylic alcohol was protected as acetate **109** (Entry 4). The best results were obtained when methanesulfonamide was excluded from the reaction, which reduced enal side product formation to less than 5% (Entry 5). However, the reaction proceeded at a much slower rate, most likely owing to the slow hydrolysis of the osmate (VI) ester, and hence lower rate of catalytic turnover in the absence of methanesulfonamide.⁹⁶



Entry	enyne	temp. / °C	t / h	diol : enal : enyne SM ^a
1	88	0	48	29 : 47 : 24
2^b	88	0	24	22 : 14 : 64
3	88	20	24	24 : 42 : 34
4	109	20	24	0 : - : 100
5^c	88	20	24	23 : 3 : 74
6	110	20	24	52 : 24 : 24
7	111	20	24	24 : 18 : 58
8	112	20	48	0 : - : 100
9	113	20	48	0 : - : 100

^a Determined by ¹H NMR spectroscopic analysis of crude reaction mixture. ^b (DHQ)₂PYR replaced (DHQ)₂PHAL as the ligand. ^c MeSO₂NH₂ was excluded from the reaction.

Table 2.3

Typically, successful enyne substrates⁹⁷⁻¹⁰⁵ for SAD bear a large alkyl or aromatic substituent in the position *trans* to the silylalkyne, which fills the ‘southwest (SW) quadrant’ of the Sharpless mnemonic (Figure 2.4).¹⁰⁶ The ‘northwest (NW) quadrant’

which is typically considered mildly repulsive to bulky substituents can accommodate aromatic groups (*e.g.* reversed facial selectivity was observed when α -alkylstyrenes dihydroxylations were performed with the DHQD-PYR ligand)¹⁰⁷ but does not appear to tolerate polar functional groups.¹⁰⁸⁻¹⁰⁹ In our case, a methyl group occupies the SW quadrant and a polar hydroxymethyl group the NW quadrant (*i.e.* $R_L = \text{Me}$, $R_S = \text{CH}_2\text{OH}$) and poor binding to the osmium complex may be expected as a result. Silylenynes **111-113** (Table 2.3) were thus prepared with the hope of improving binding with the complex. Alkenyl iodides **112** and **113** were of particular interest as they contained a handle for coupling the siloxane fragment, in accordance with the orthogonal cross-coupling strategy.

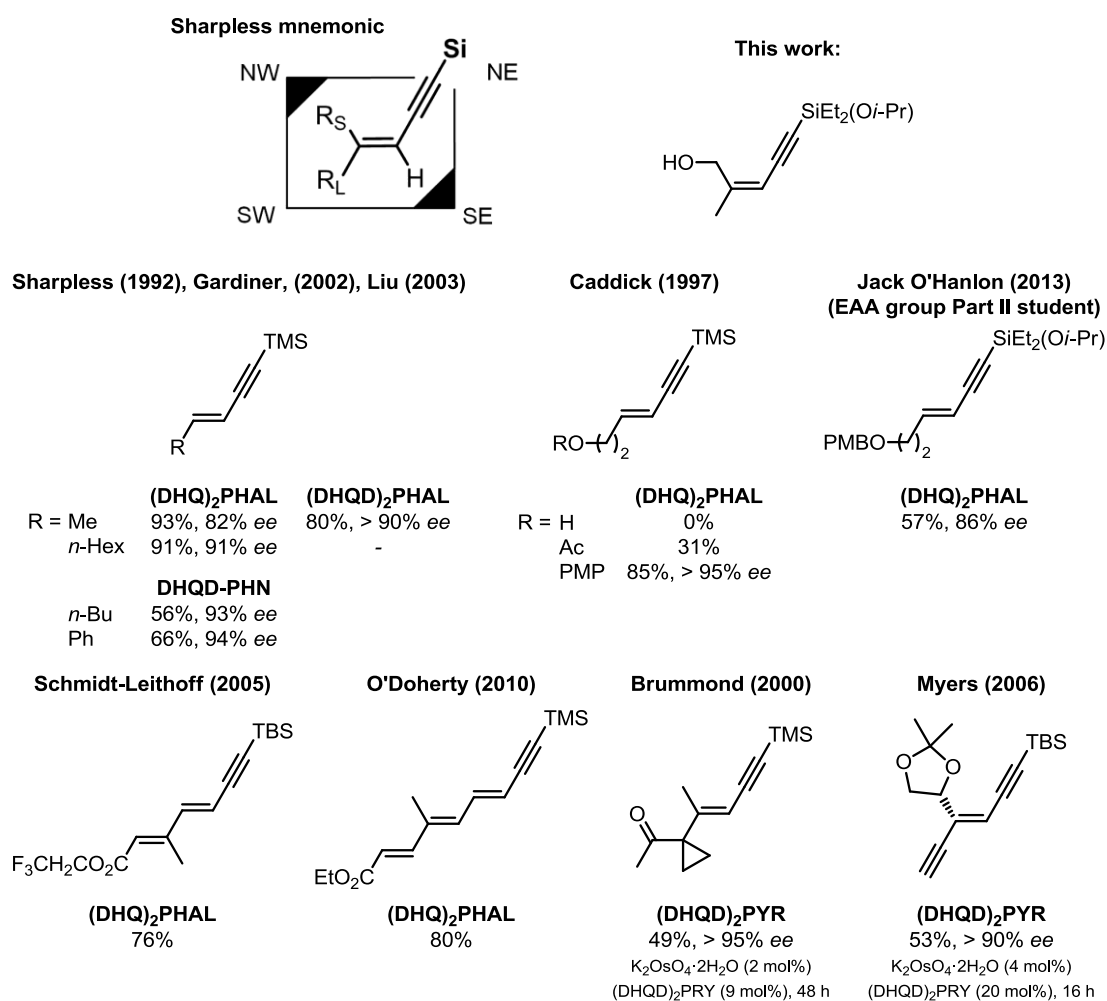
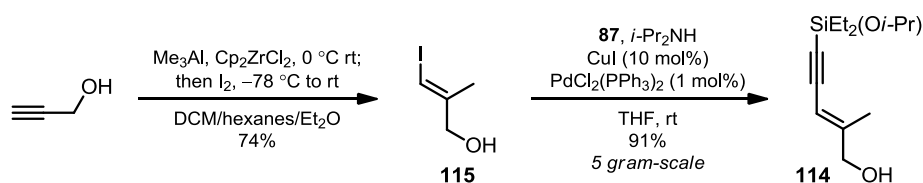


Figure 2.4

Disappointingly, none of these substrates presented any significant improvement over **88** under standard reaction conditions (Entries 6-9, Table 2.3). Considerable enal formation was observed even with the simplified TMS-enyne **110**, supporting the theory that substitution pattern and not the nature of the silyl group was responsible for the poor selectivity. Additionally, no conversion was observed with **112** and **113** even after stirring at room temperature for 48 hours. This is attributed to the trisubstituted olefin's location in a conjugated iodo-dienyne system, for which no precedent exists in SAD chemistry.

2.3.2 Sharpless asymmetric epoxidation

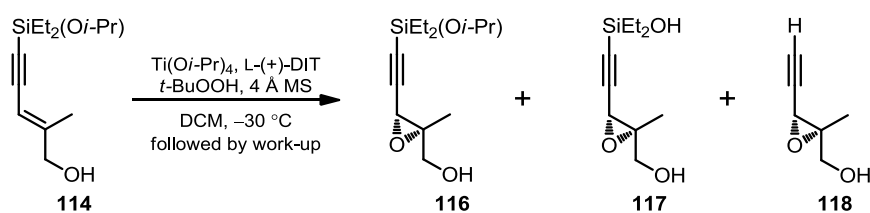
An alternate asymmetric route was therefore explored which utilised regioselective opening of 2,3-epoxy alcohols, which we anticipated could be prepared with high stereoselectivity from (*E*)-silylenyne **114** by the Sharpless asymmetric epoxidation (Scheme 2.16). The enyne was assembled in an analogous manner to its geometrical isomer, with known (*E*)-vinyl iodide **115**¹¹⁰ undergoing Sonogashira coupling with alkynyl siloxane **87** to afford multigram quantities of silylenyne **114** in excellent yield.



Scheme 2.16

Asymmetric epoxidation employing substoichiometric amounts of titanium (IV) isopropoxide and the natural L-(+)-diisopropyl tartrate ligand under the Sharpless conditions resulted in full conversion of silylenyne **114** to 2,3-epoxy alcohol **116**.¹¹¹ Isolation of the product from this reaction proved challenging, as the standard tartaric acid work up was found to be incompatible with the alkynyl siloxane motif, and

resulted in low yields and significant formation of alkynyl silanol **117** from hydrolysis of the silyl ether (Entry 1, Table 2.4). While basic conditions¹¹² effected complete protodesilylation returning only the terminal alkyne **118** (Entry 2), a mild “precipitating” work up with wet acetone, which is typically employed for kinetic resolutions,¹¹³ exclusively afforded the desired epoxide **116** in good yields (Entry 3). The highest product recovery was achieved with a sodium sulfate work up that is especially well-suited to acid-sensitive epoxy alcohols (Entry 4).^{112,114} This involves addition of a saturated sodium sulfate solution (1 mL per mmol of $\text{Ti}(\text{O}i\text{-Pr})_4$) to an ether-diluted reaction mixture. Filtration of the resultant heterogeneous mixture removes most of the titanium species, and any excess *tert*-butyl hydroperoxide (TBHP) and tartrate is separated from the epoxide product by column chromatography.

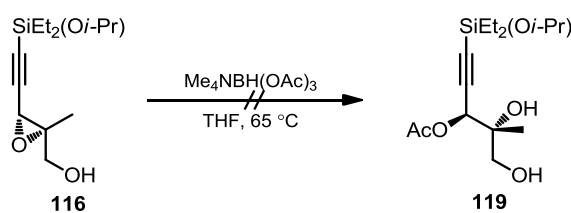


Entry	work-up procedure	116 : 117 : 118 ^a	yield (%) ^b
1	15% w/v aqueous tartaric acid + $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	5.7 : 1 : 0	34
2	NaOH , $\text{Et}_2\text{O}/\text{H}_2\text{O}$	0 : 0 : 1	0
3	acetone/ H_2O (5:1)	1 : 0 : 0	71
4	saturated aqueous Na_2SO_4	1 : 0 : 0	86

^a Based on isolated yields after chromatography. ^b Isolated yield of **116** after chromatography.

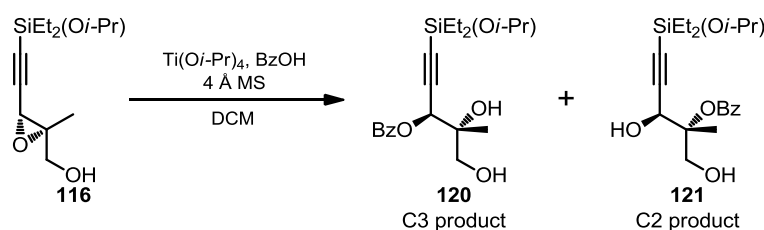
Table 2.4

Regioselective opening of the 2,3-epoxy alcohol **116** was then attempted with $\text{Me}_4\text{NBH}(\text{OAc})_3$ ²⁶ which Toshima and co-workers had employed in their earlier synthesis of the C1-C13 incednine fragment.²⁵ To our disappointment, none of the C3-acetoxy product **119** was observed in the complex mixture that was isolated from the reaction (Scheme 2.17).



Scheme 2.17

However, the Sharpless method for titanium-directed epoxide opening of epoxide **116** with benzoic acid gave promising preliminary results and provided a moderate yield of benzoylated triol **120** with good selectivity for the C3 product (Entry 1, Table 2.5). The high regioselectivity reported by Sharpless and co-workers in such reactions is attributed to coordination of the epoxy alcohol to the metal centre in a rigid, bidentate fashion, forming a five-membered titanocycle which strongly favours external nucleophile attack at the C3 position.¹¹⁵ Extending the reaction time had the unexpected effect of increasing the amount of C2 product (Entry 2), suggesting that the C2 benzoylated product **121** arises from an acid-catalysed rearrangement of the desired C3-opened product **120**, rather than nucleophilic attack at the C2 position. This was confirmed by separately subjecting **120** and **121** to a hydrogenation/benzoyl deprotection sequence which in both cases provided stereo-enriched five-membered cyclic alkenylsiloxane **60** with optical rotation values of the same sign.



Entry	conditions		reaction scale (mmol)	work up	120 : 121 ^a	yield (%) ^b
	T / °C	t / h				
1	20	1	0.098	aq. Na ⁺ /K ⁺ tartrates	9 : 1	51
2	20	2	0.098	aq. Na ⁺ /K ⁺ tartrates	4 : 1	43
3	0	3.5	0.098	aq. Na ⁺ /K ⁺ tartrates	> 20 : 1	23 ^c
4	20	1	1.20	sat. aq. Na ₂ SO ₄	10 : 1	52
5	20	1	2.00	sat. aq. Na ₂ SO ₄	4 : 1	24
6	20	1	3.80	acetone/H ₂ O	9 : 1	76 ^d
7	20	1	6.60	acetone/H ₂ O	n.d. ^e	49
8	20	1	9.90	acetone/H ₂ O	4.5 : 1	33

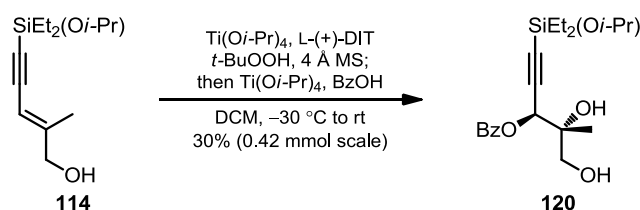
^a Determined by ¹H NMR spectroscopic analysis of crude reaction mixture. ^b Isolated yield of **120**. ^c 46% Recovered starting material. ^d 89% *ee*. ^e Not determined.

Table 2.5

Formation of the C2-benzoylated side product **121** could be suppressed by lowering the temperature at which the reaction was conducted, though this was accompanied by poorer reactivity resulting in incomplete conversion even after extended reaction times (Entry 3, Table 2.5). By switching from a tartrate-based work up to the sodium sulfate work up, silanol formation was limited to trace amounts even when the reaction was scaled up to over 1 mmol (Entry 4). Further increasing the reaction scale led to more of the rearrangement product **121** (Entry 5), largely owing to prolonged exposure of **120** to acidic conditions – a result of slow extraction of the titanium-laden emulsion which

formed on such scales. The extraction efficacy could be improved, to a point, with a wet acetone work up which allowed the reaction to be performed on a synthetically practical scale (Entries 6-8). At this point, the enantiomeric excess of diol **120** was determined to be 89% by HPLC comparison to a racemic specimen obtained from the *m*-CPBA epoxidation/ring opening of silylenyne **114**.

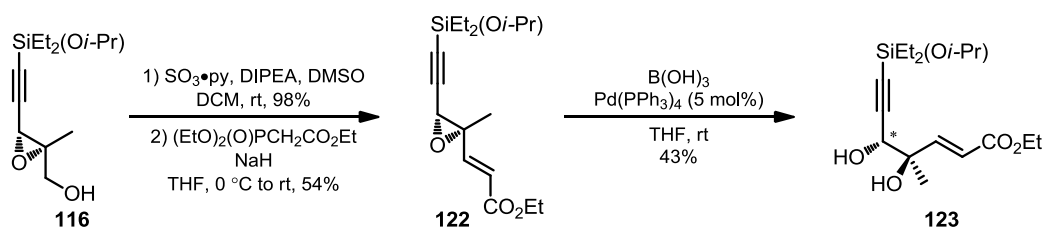
Given the common use of titanium (IV) isopropoxide as a reagent in both the Sharpless epoxidation and subsequent epoxide opening, we attempted to telescope the two steps into a one-pot operation. Sharpless epoxidation of allylic alcohol **114** was followed by the addition of a further equivalent of titanium reagent and benzoic acid, and warming the reaction mixture to room temperature (Scheme 2.18). The sodium sulfate work up furnished diol **120** in a modest yield of 30%, which was inferior to the combined yield of the two-step procedure on a similar scale.



Scheme 2.18

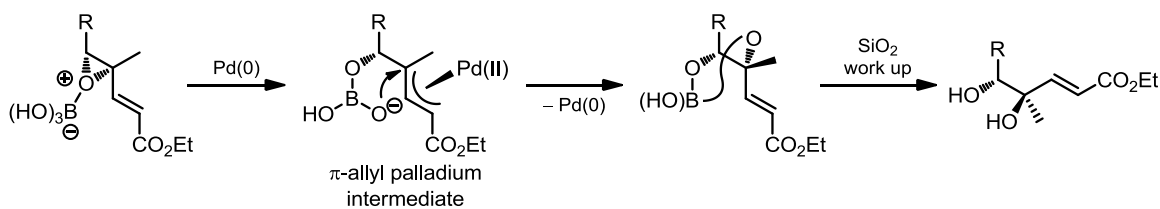
A complementary route of first elaborating the primary alcohol before epoxide opening and siloxane ring formation was also investigated. Epoxy alcohol **116** was oxidised using Parikh-Doering conditions and the resulting aldehyde subjected to Horner-Wadsworth-Emmons olefination to afford the γ,δ -epoxy- α,β -unsaturated ester **122** in modest yields (Scheme 2.19). Such substrates have been reported by Miyashita and co-workers to undergo regiospecific epoxide opening with chelating oxygen nucleophiles in the presence of palladium, leading to γ,δ -diols.¹¹⁶⁻¹¹⁸ Indeed, treating epoxide **122** with a stoichiometric amount of boric acid in the presence of catalytic amounts of

$\text{Pd}(\text{PPh}_3)_4$ at room temperature resulted in complete conversion after just 15 minutes to diol **123**, which was isolated as a single diastereomer in a moderate unoptimized yield. The ester functionality was found to be critical to the success of the reaction; an aldehyde or silane in its place led to a mixture of diastereomeric products in the former case and no reaction in the latter.



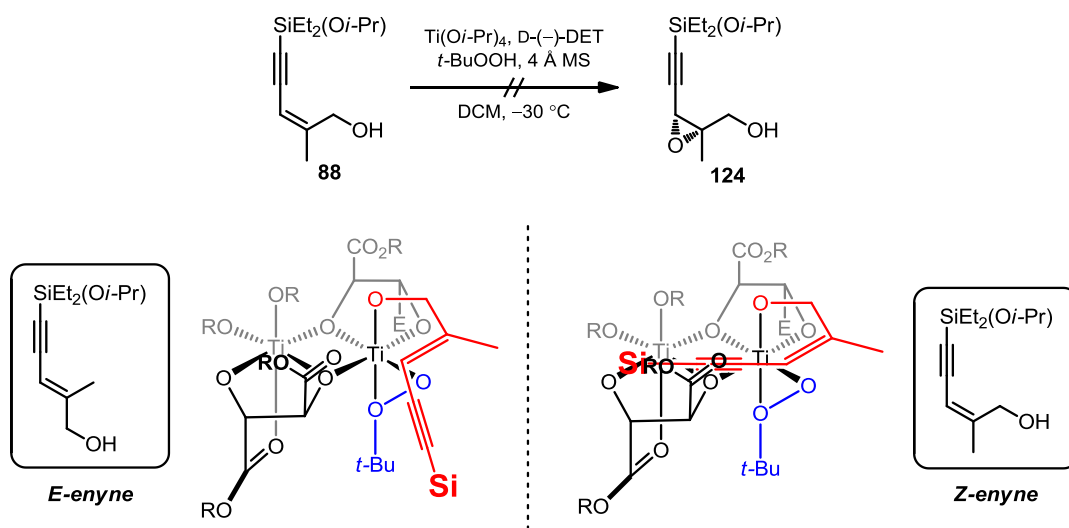
Scheme 2.19

Unlike conventional $\text{S}_{\text{N}}2$ epoxide openings which proceed with inversion of stereochemistry at the point of nucleophilic attack, Miyashita and co-workers have shown that this reaction proceeds with retention of stereochemical configuration.¹¹⁷ Epoxide opening is proposed to occur *via* a π -allyl palladium complex, which subsequently undergoes intramolecular nucleophilic attack at the γ -position by coordinated boronate, expelling palladium (0) and forming the cyclic boronic ester of the γ,δ -diol (Scheme 2.20). The ester appears to be critical for successful reaction, with the stabilising influence of the ester towards the π -allyl system playing a large role in determining both the selectivity and reactivity of the process. Configurational retention is the net result of a double inversion arising from consecutive $\text{S}_{\text{N}}2$ steps, and in the case of diol **123** provided the C9 epimer of incednam configuration (Scheme 2.19).



Scheme 2.20

The correct stereochemistry for incednam would thus be obtained from epoxide **124**, which we anticipated could be derived from the now familiar (*Z*)-silylenyne **88** by a Sharpless asymmetric epoxidation with the unnatural D-(–)-tartrate ligand (Scheme 2.21). To our dismay, the enyne proved resistant to epoxidation even when stoichiometric amounts of titanium and ligand were employed over extended periods of time, and was recovered unchanged from the reaction mixture.



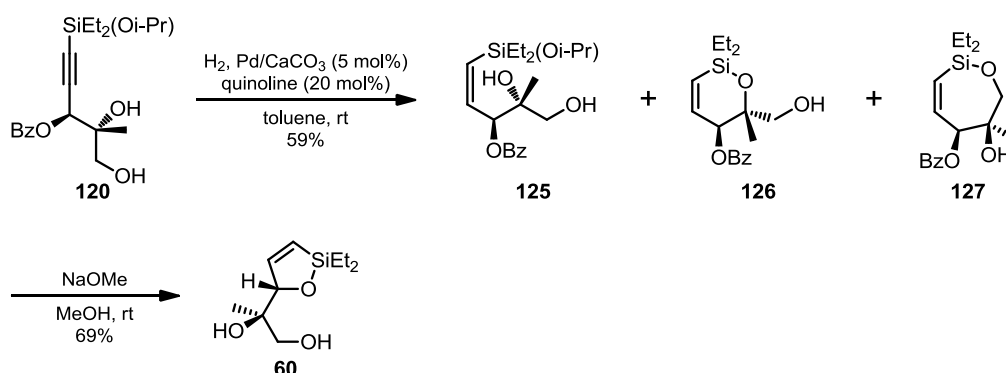
Scheme 2.21

The stark difference in reactivity between (*E*) and (*Z*)-enynes may be rationalised by considering the structure of the catalyst and substrate binding. The active catalyst is proposed to exist as a titanium dimer with two chelated tartrate ligands defining the chiral environment in which the titanium-coordinated allylic alcohol and TBHP react (Scheme 2.21).¹¹⁹ Alkene substituents *syn* to the allylic alcohol project into the catalyst

structure and encounter steric resistance, which may impede the substrate binding in a reactive mode where the olefin is suitably oriented with respect to the peroxide. This phenomena accounts for the lower enantiomeric excesses achieved with disubstituted *cis* olefins and the paucity of successful *Z*-trisubstituted olefin substrates.¹²⁰ In successful cases, the substituent *syn* to the alcohol is small or flexible, capable of twisting away from the steric bulk imposed by the tartrate. This position of the enyne substrate **88** is occupied by a bulky silane at the end of an inflexible alkyne tether, rendering it impossible for the substrate to bind in a reactive orientation.

2.3.3 Revisiting the semi-hydrogenation

With alkynylsiloxane **120** in hand, we were close to assembling the first building block of the synthesis. Standard semi-hydrogenation conditions returned a mixture of acyclic alkenylsilane **125** and cyclic six and seven-membered (*Z*)-alkenylsiloxanes **126** and **127** (Scheme 2.22). The relative composition of the mixture was found to vary significantly each time the reaction was repeated, although notably, no (*E*)-alkenylsiloxane was detected in any of these reactions. Enantioenriched cyclic alkenylsiloxane **60** was obtained as the single product upon methanolysis of the mixture followed by *in situ* cyclisation or rearrangement by the newly revealed secondary alcohol.



Scheme 2.22

Instead of removing the propargylic benzoyl ester, we hoped to exploit its presence to selectively prepare the six and seven membered regioisomers of building block **60**. To elucidate the point at which cyclisation of alicyclic **125** occurred during the semi-hydrogenation, the reduction of alkyne **120** was monitored by ^1H NMR spectroscopic analysis of aliquots removed on an hourly basis (Figure 2.5). Initial formation of traces of seven-membered cyclic siloxane **127** within the first hour of the reaction was not followed by any further cyclisation, and, at complete conversion, the mixture mostly contained the acyclic intermediate **125** (93:7, **125**:**127**). This result has been repeated on multiple occasions since, and our initial experience of varying degrees of cyclisation to

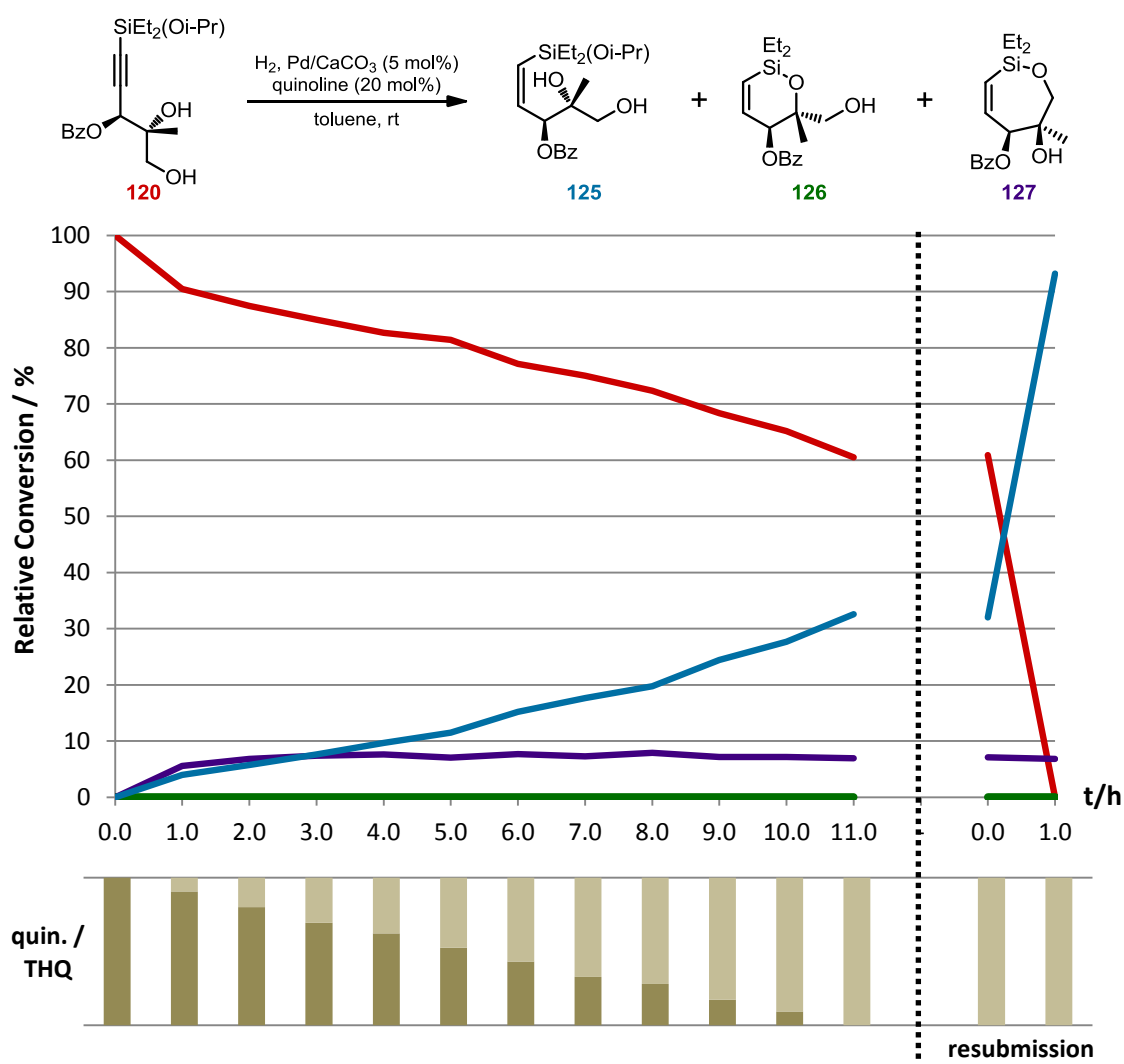
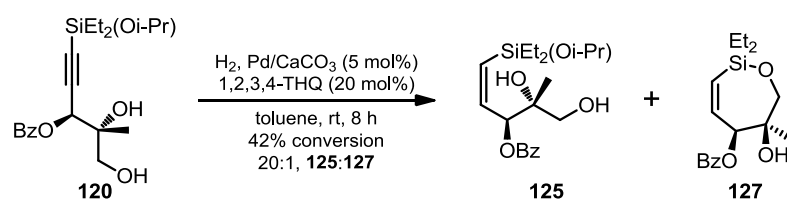


Figure 2.5

both the six and seven membered siloxanes has been avoided by carefully monitoring the reaction mixture by thin layer chromatography (the alkyne starting material and alkene product can be distinguished by retention factor in 30% ethyl acetate-petrol and stain black and blue respectively in vanillin), and by removing the catalyst by filtration once semi-hydrogenation is complete.

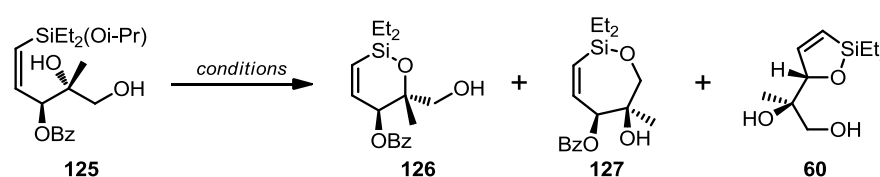
The aliquot studies highlighted an intriguing quirk of the Lindlar hydrogenation, where a sluggish reaction can be dramatically accelerated by replacing the old catalyst with a fresh batch of supported palladium. This is usually achieved by filtering the reaction mixture through Celite®, concentrating *in vacuo*, redissolving the residue in toluene and adding a fresh batch of palladium catalyst. It became apparent that the improved efficacy of the fresh catalyst may coincide with diminishing amounts of quinoline as it was reduced to 1,2,3,4-tetrahydroquinoline (THQ) over the course of the reaction (see quin./THQ bar graph, Figure 2.5). This hypothesis was tested by replacing quinoline with THQ from the very start of the reaction. Disappointingly, little increase in reactivity was observed and the cause of the unpredictable rates of hydrogenation remains elusive (Scheme 2.23).



Scheme 2.23

Having established a reliable method to prepare the alicyclic alkenylsilane intermediate **125**, we turned our attention to discovering cyclisation conditions which were regioselective for either the six or seven-membered cyclic siloxanes **126** or **127**. Treating the alicyclic silane with catalytic amounts of fluoride was completely

unselective, returning almost equal amounts of cyclic siloxanes **126** and **127** (Entry 1, Table 2.6). As previously observed, stoichiometric amounts of alkoxide effected an unwanted deprotection of the benzoyl ester, with *in situ* rearrangement leading to the five-membered cyclic siloxane **60** exclusively (Entry 2). Shortened exposure to alkoxide by filtering a methanolic solution of alkene **125** through a short pad of packed potassium carbonate provided a mixture of siloxanes **60** and **127**, with the seven-membered siloxane **127** as the minor product (Entry 3).



Entry	conditions	126 : 127 : 60 ^a	Yield ^b / %
1	TBAF (10 mol%), THF, rt	52 : 48 : 0	52
2	NaOMe (1.1 equiv.), MeOH, rt	0 : 0 : 100	n.d. ^c
3	K ₂ CO ₃ /MeOH filtration	0 : 25 : 75	n.d.
4	PPTS (10 mol%), DCM/toluene, rt	93 : 7 : 0	75
5	PPTS (10 mol%), DCM/toluene, rt ^d	94 : 6 : 0	85

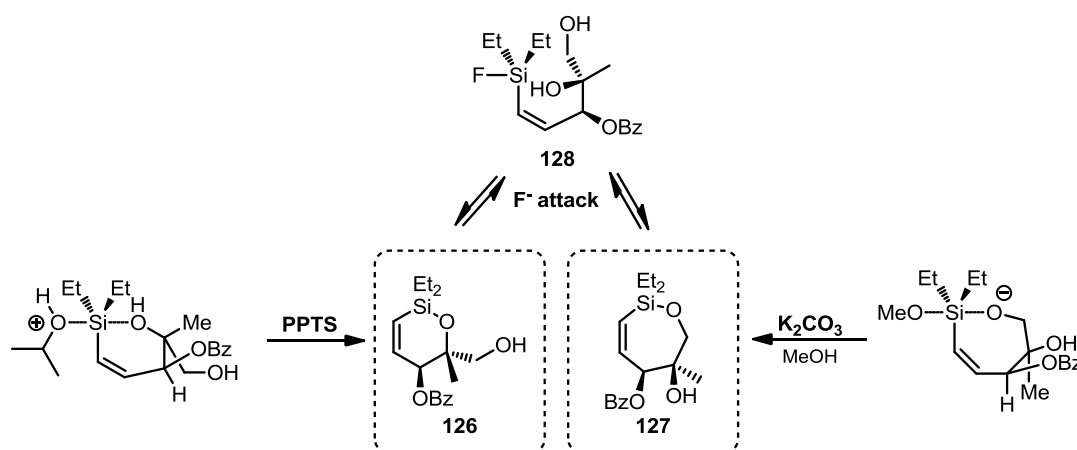
^a Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^b Combined isolated yield of **126**, **127** and/or **60**. ^c Not determined. ^d Without isolation of alkene **125**; the Lindlar hydrogenation reaction mixture was filtered through Celite®, the filter pad rinsed with DCM, and the filtrate directly treated with PPTS.

Table 2.6

A chance observation that NMR samples of alicyclic siloxane **125**, upon standing in mildly acidic CDCl₃, showed some cyclisation to the six-membered siloxane led to testing conditions of catalytic PPTS. These proved to be ideal, and resulted in the cyclisation of alkenylsiloxane **125** entirely to the six-membered silacycle **126** (Entry 4).

The small amount of siloxacycle **127** recovered corresponded to that formed during semi-hydrogenation. Streamlining the hydrogenation-cyclisation steps into a single process with minimal work up – involving filtering the heterogeneous hydrogenation reaction mixture through Celite®, rinsing the filter pad with DCM and immediately treating the filtrate with PPTS – provided the six-membered siloxacycle **126** in excellent yields (Entry 5).

The product distributions observed under nucleophilic fluoride, acidic and basic conditions can be rationalised by considering the mechanism by which cyclisation occurs in each case. In the presence of nucleophilic fluoride, the fluorosilane **128** is presumably formed initially upon cleavage of the isopropoxy silane **125**, and then behaves as a common intermediate for reversible ring closure to the six or seven-membered rings, resulting in a mixture of both siloxacycles (Scheme 2.24). Protonation of isopropoxy silane **125** in the presence of PPTS, on the other hand, results in irreversible cyclisation onto the tertiary alcohol to give six-membered silacycle **126**, the presumed kinetic cyclisation product. No further rearrangement is possible under these conditions due to the absence of external nucleophiles and the inability of the tethered primary alcohol to approach the silicon centre from the opposite face which is required for S_N2-like nucleophilic displacement or, more likely, addition/elimination. Finally, preferential deprotonation of the primary homoallylic alcohol by an alkoxide base in the presence of the tertiary allylic alcohol results in cyclisation to form the seven-membered siloxacycle. Competing benzoyl deprotection by excess methoxide generates the propargylic alkoxide, leading to facile *in situ* rearrangement to five-membered silacycle **60**.

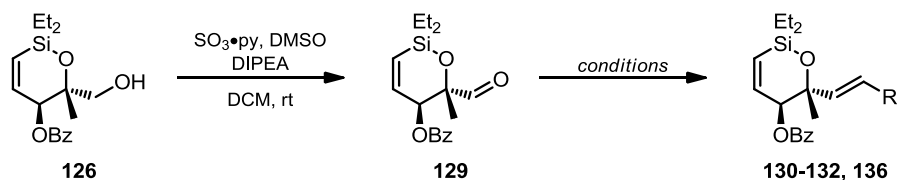


Scheme 2.24

2.3.4 An improved strategy for C9 elaboration

The elaboration of alkenylsiloxane **126** *via* aldehyde **129** was next investigated. Where C8-C9 olefination strategies had failed with α -hydroxyaldehyde **96** (see Scheme 2.14 on page 42), aldehyde **129** was successfully converted into α,β -unsaturated esters **130** and **131** under Wittig or HWE conditions, albeit in modest yields for the two-step oxidation/olefination (Entries 1 and 2, Table 2.7). α,β -Unsaturated aldehyde **132** was prepared from Wittig salt **133** in good yields, but was contaminated with unreacted starting material and aldehyde **134**, the result of the α,β -unsaturated product **132** undergoing a second olefination (Entry 3). Such two-carbon homologations are typically conducted at ambient temperature and are chemoselective for the unconjugated aldehyde substrate. The sterically encumbered aldehyde **129**, bearing a fully substituted α -carbon, required heating to 60 °C for reaction to occur. This allowed the otherwise dormant conjugated aldehyde product **132** to compete with aldehyde **129** for limited reagent. Varying the temperature, reagent stoichiometry and solvent had little positive effect on product distribution (Entries 4 and 5), and it was the use of preformed ylide **135** rather than salt **133** which ultimately allowed the reaction to proceed to completion while limiting formation of **134** to acceptable amounts (Entry 6).

In stark contrast to the difficulties we had encountered with the five-membered aldehyde **96**, the Takai olefination allowed an alkenyl iodide to be smoothly introduced with exclusive (*E*)-selectivity, providing a cross-coupling handle for a C7-C8 disconnection (Entry 7).



Entry	R	conditions	yield (%) ^a
1	CO ₂ Me (130)	137 , THF, 60 °C	34
2	CO ₂ Et (131)	138 , NaHMDS, THF, rt	25
3	CHO (132)	133 , Et ₃ N, PhMe, 80 °C	55 + 7 (134) ^b
4		133 , Et ₃ N, PhMe, 60 °C	41 + 10 (134) ^b
5		133 , Et ₃ N, CHCl ₃ , 60 °C	39 + 7 (134) ^c
6		135 , PhMe, 80 °C	67 + 15 (134)
7	I (136)	CHI ₃ , CrCl ₂ , THF, rt	46

^a Isolated yield over two steps. ^b 9% Recovered starting material. ^c 22% Recovered starting material.

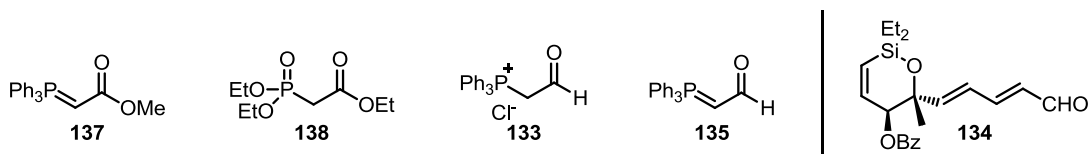
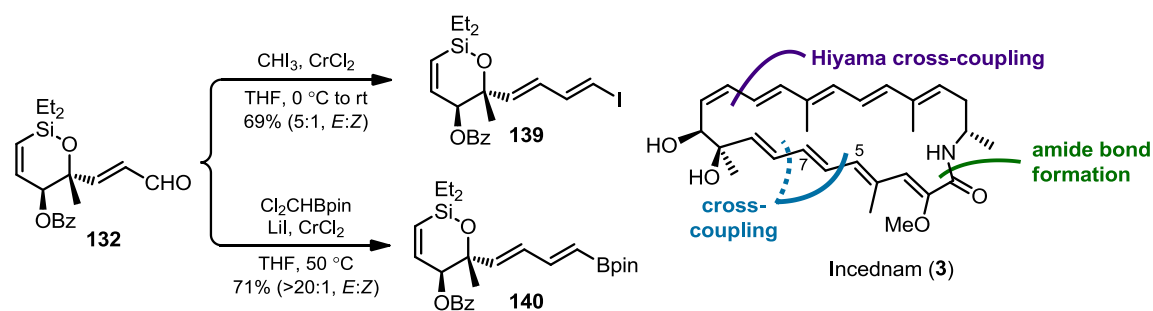


Table 2.7

The successful preparation of aldehyde **132** allowed us to consider the C5-C6 cross-coupling disconnection, which is one alkene unit further along the C2-C9 tetraene (Scheme 2.25). This had the benefit of reducing the conjugated length of the enol ether

cross-coupling partner, which proved critical in devising an efficient route for its synthesis (see Chapter 4). To this end, both alkenyl iodide **139** and boronic ester **140** were prepared by established Takai methodology. The stereoselectivity of the Takai reaction has been reported to erode considerably with α,β -unsaturated aldehyde substrates.¹²¹ This was found to be consistent in the iodoolefination of **132**, which afforded a 5:1 mixture of *E* and *Z* isomers of alkenyl iodide **139**. Gratifyingly, the complementary borylolefination returned the (*E*)-olefin **140** exclusively, which may be attributed to the bulkier *gem*-dichromium organometallic ensuring that addition to the conjugated aldehyde proceeds with high diastereoselectivity.



Scheme 2.25

At this point, inspired by the strategy of orthogonal cross-coupling and Denmark's elegant use of alkenyl silanols in his synthesis of RK-397,¹²² a route exploiting the fluoride free coupling of alkenyl silanols in the presence of cyclic alkenylsiloxanes was conceived. The mixed silanol-cyclic alkenylsiloxanes **141** and **142** were desired as substrates for fluoride-free Hiyama-Denmark cross-couplings (Figure 2.6).¹²³ To this end, we began to consider methods to directly access (*E*)-alkenylsilanes from their corresponding aldehyde precursors which could be applied to aldehydes **129** or **132**. The results of our investigations are reported in the following chapter.

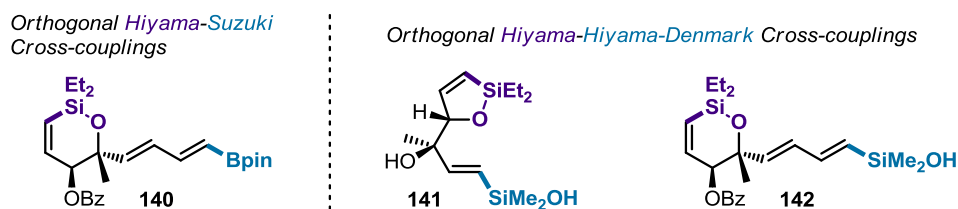


Figure 2.6

2.4 Conclusion

The first of the three building blocks identified from our retrosynthetic disconnection of incednam was prepared enantioselectively using a Sharpless epoxidation/regioselective epoxide opening strategy. The cyclic alkenylsiloxane was introduced by a novel approach involving alkynylsiloxane semi-hydrogenation, followed by alkoxide or acid-promoted cyclisation to selectively provide five or six-membered cyclic alkenylsiloxanes. Parikh-Doering oxidation of the primary hydroxyl afforded aldehydes **96** and **126** (Figure 2.7), which are themselves key intermediates for the C8-C9 olefination, and can be elaborated to the alkenyl iodides **106** and **136**, intermediates of the C7-C8 cross-coupling approach. A third disconnection at the C5-C6 bond has also been identified and the subunits for this strategy, **139** and **140**, have been prepared in two steps from α,β -unsaturated aldehyde **132**.

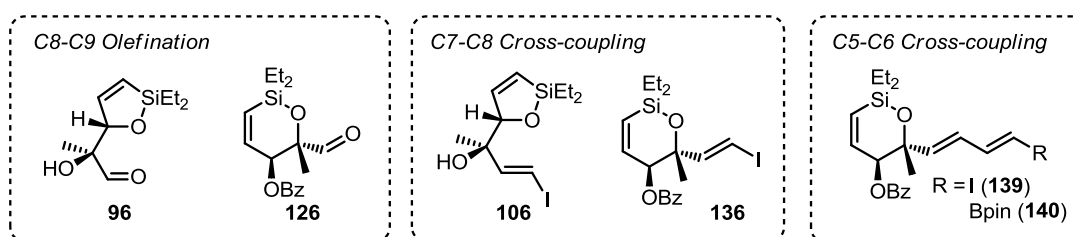


Figure 2.7 Key cyclic alkenylsiloxane building blocks

3 Direct Functionalised Silylolefination of Aldehydes

3.1 Previous syntheses of functionalised (*E*)-alkenylsilanes

As key building blocks for polyene systems in both natural products and materials, (*E*)-disubstituted alkenylsilanes are valuable synthetic intermediates. Their participation in Hiyama cross-couplings depends on suitable functionalisation of the silane which would allow it to be activated toward transmetalation on treatment with a fluoride source or base. Early work in the field focused on halosilanes, siloxanes, silanols and siletanes, which are substituted with electron withdrawing or strained groups, predisposing them to formation of the active pentacoordinate silicate complex.⁴³⁻⁴⁵ While such substitution patterns allow the cross-coupling to proceed under mild conditions, the inherent lability of the silanes make them difficult to handle, limiting any application of the cross-coupling to simple substrates or cases in which the silane can be introduced at a late stage.

Recent advances in Hiyama methodology have uncovered a class of ‘safety-catch silanols’ which show improved stability compared to heteroatom-substituted silanes but can be selectively unmasked to reveal a reactive silanol.⁴³ This subclass of silane reagents include hydrosilanes¹²⁴ and dimethylphenylsilanes,¹²⁵⁻¹²⁶ which benefit from fluoride-free activation, but show limited scope as coupling partners with regards to the olefin substitution and level of selectivity which can be achieved (Figure 3.1). In contrast, triallylsilanes,¹²⁷ benzyl,¹²⁸ 2-thienyl¹²⁹ and 2-pyridyl¹³⁰ dimethylsilanes, which are unmasked in the presence of TBAF, are compatible with a wide range of alkene substitution patterns and halide or pseudohalide coupling partners. Benzyl dimethylsilane, in particular, approaches the ideal safety-catch silanol when its

ready release of silanol (complete conversion within 10 minutes at 0 °C)⁵¹ is considered alongside its stability under basic, mildly acidic and buffered fluoride conditions.

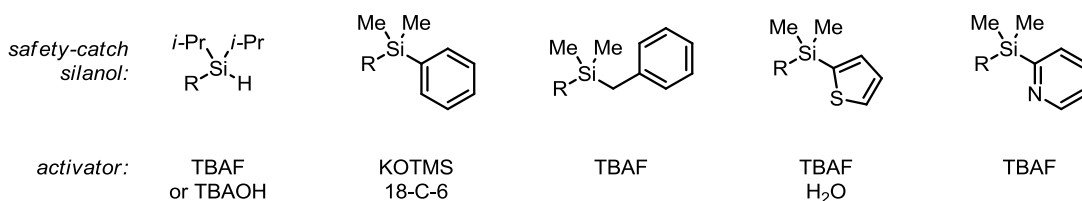
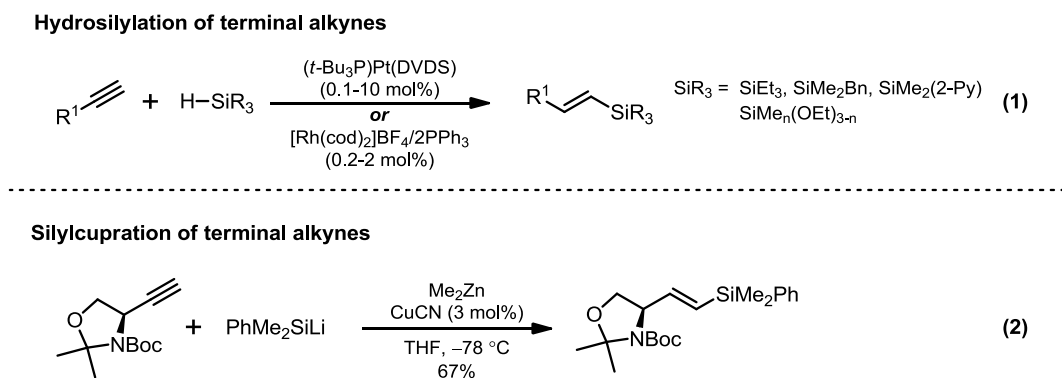


Figure 3.1 Selected safety-catch silanols

The growth of the organosilicon cross-coupling field has been supported by the discovery of new methods to access functionalised alkenylsilanes reagents. Where classical routes to (*E*)-alkenylsilanes were generally limited to metal-halogen exchange/carbanion silylation of vinylhalide substrates and semihydrogenation of alkynylsilanes, recent developments in methodology have considerably expanded the scope of functional groups which can be used to access these motifs.¹³¹

Significant advances in hydrosilylation methodology over the last two decades have made terminal alkynes the most popular entry point to alkenylsilanes, owing to the atom-efficiency of the reaction and exquisite regio and stereocontrol which can be achieved with platinum and cationic rhodium complexes (Equation 1, Scheme 3.1).¹³² The (*t*-Bu₃P)Pt(DVDS) system, in particular, is widely used due to the ready availability of the platinum(0) source and phosphine, and the wide range of silane substitution it tolerates, including siloxanes, benzyldimethylsilanes and (2-pyridyl)dimethylsilanes.¹³³ Cationic rhodium complexes, while limited to trialkylsilanes, offer increased air and moisture stability compared to many platinum(0) catalysts. [Rh(cod)₂]BF₄ has been employed to produce multigram quantities of alkenylsilane intermediates for natural product syntheses.¹³⁴ Terminal alkynes can also be converted into alkenylsilanes *via* silylmetallation with Fleming-Lipshutz silylcuprate

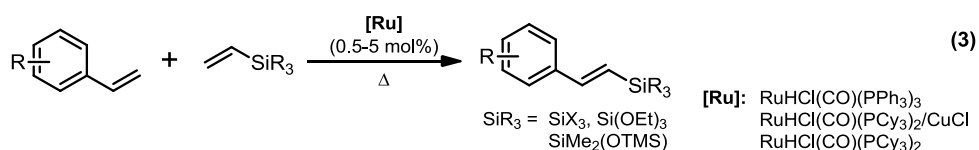
reagents, which perform regioselective *syn*-additions across the carbon-carbon triple bond (Equation 2). An acidic quench of the vinyl metal intermediate provides the alkenylsilane with excellent selectivity for (*E*)-configuration when bulky groups such as dimethylphenylsilane are employed.¹³⁵⁻¹³⁷



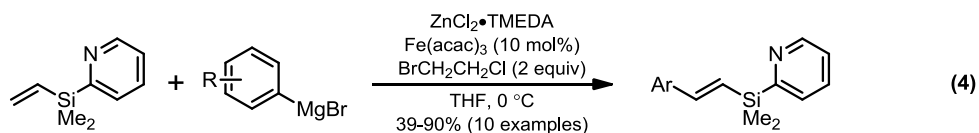
Scheme 3.1

The subclass of β -silylstyrenes can be prepared from terminal vinylsilanes by ruthenium-catalysed silylative couplings with styrenes (Equation 3, Scheme 3.2).¹³⁸ The key silylruthenium intermediate is generated by a hydorruthenation/ β -hydride elimination sequence between the vinylsilane and ruthenium hydride catalyst, extruding ethylene. Halosilanes, siloxanes and disiloxanes are tolerated by the catalyst. Silylruthenation of the styrene followed by β -hydride elimination frees the alkenylsilane product and regenerates ruthenium hydride.¹³⁹⁻¹⁴⁰ Complementary arylmetalation of 2-pyridylvinylsilanes following a Mizoroki-Heck-type mechanism has also been reported (Equation 4). Under iron catalysis, aryl zinc reagents add regioselectively across the terminal vinylsilane.¹⁴¹ The 2-pyridylsilane group was critical to the success of the reaction, presumably by directing carbometalation to proceed through a stabilised five-membered ferracycle intermediate which upon β -hydride elimination then provides the (*E*)-styrenylsilane selectively.

Silylative coupling terminal alkenylsilanes

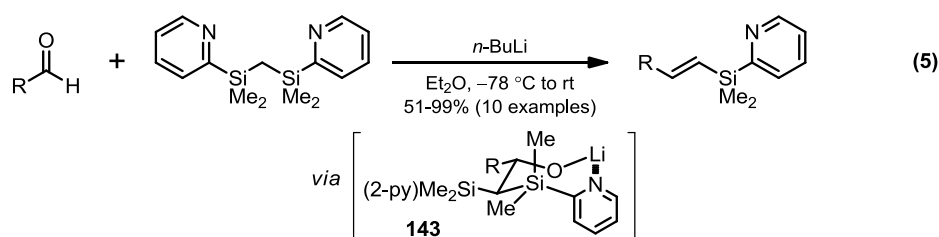
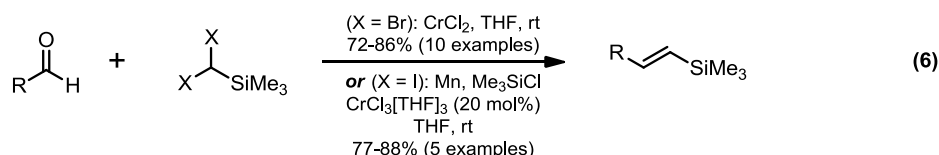


Heck-type coupling of terminal alkenylsilanes



Scheme 3.2

The silylolefination of aldehydes is an appealing mode of entry to functionalised alkenylsilanes, as it can provide a more direct route by avoiding prior conversion of the aldehyde into an alkyne (for hydrosilylation). To our knowledge, the only direct preparation of functionalised alkenylsilanes from aldehydes was reported by Yoshida and co-workers and involves the formation of 2-pyridyldimethylsilyl alkenes through the (*E*)-selective Peterson olefination of a *bis*-pyridyldimethylsilylcarbanion (Equation 5, Scheme 3.3).¹⁴² This is attributed to selective coordination of one of the pyridyl groups to the lithium cation, such that the β -alkoxysilane intermediate adopts a chairlike conformation **143** with the second silyl group and large carbonyl substituent occupying pseudo-equatorial (*anti*) positions, prior to *syn*-elimination.¹⁴³ While a range of aliphatic, aromatic and conjugated aldehydes were converted in good yields and excellent stereoselectivity, functional group tolerance may be limited by the strongly basic conditions required to generate the bisilylcarbanion.

Peterson Olefination**Takai Olefination**

Scheme 3.3

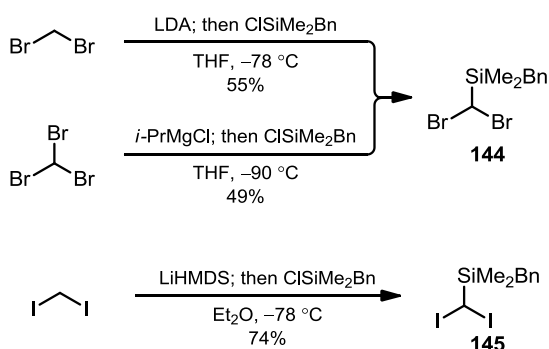
In contrast, aldehydes have been employed for the preparation of nonfunctionalised trimethyl alkenylsilanes with much greater precedent. In particular, the Takai silylolefination of aldehydes with an organochromium nucleophile, generated *in situ* from the reaction of a chromium (II) halide with dihalotrimethylsilane reagents, afford (*E*)-alkenylsilanes with high stereoselectivity (Equation 6, Scheme 3.3).¹⁴⁴ Unlike many carbanions, the organochromium nucleophile adds with complete chemoselectivity to aldehydes in the presence of ketones. Since the original report, the Takai group has developed a variant which is catalytic in chromium, employing manganese as a stoichiometric reductant. For simple aldehydes, this procedure maintains the high stereoselectivity of the original transformation.⁹⁴

The mild, non-basic reaction conditions of the Takai olefination are particularly attractive for sensitive substrates, and suggested that the use of a functionalised silane reagent in this chemistry would offer a convenient method to prepare useful synthetic building blocks, such as the incednine subunits for orthogonal organosilicon cross-coupling reactions discussed in the previous chapter.

3.2 Takai silylolefinations of functionalised silanes

3.2.1 Benzyldimethylsilanes

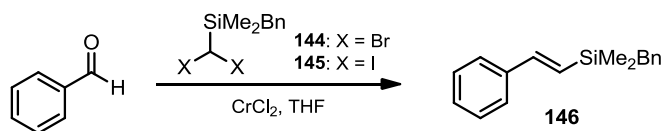
Our investigations began with the selection of the benzyldimethylsilyl group as a representative safety-catch silanol. The dihalomethyl benzyldimethylsilane reagents **144** and **145** (Scheme 3.4) were conveniently prepared on a multigram scale by treating the corresponding dihalomethanes with LDA or LiHMDS, followed by trapping of the lithium carbanion with benzylchlorodimethylsilane.¹⁴⁵⁻¹⁴⁶ Dibromide **144** could also be prepared from the Grignard reagent formed *in situ* from treatment of bromoform with *iso*-propylmagnesium chloride.¹⁴⁷ Although **144** can be stored indefinitely at room temperature without decomposition, diiodide **145** gradually turns from a colourless to brown oil on storage for a month in the dark at 4 °C.



Scheme 3.4

Benzaldehyde was used in reaction optimisation studies (Table 3.1), which commenced with the standard Takai olefination conditions of 2 equivalents of **144** and 8 equivalents of chromium(II) chloride in dry THF.¹⁴⁴ To our delight, this resulted in complete consumption of benzaldehyde after 16 hours and provided the desired alkenylsilane **146** in 74% isolated yield, with exclusive formation of the (*E*)-alkenylsilane (Entry 1). Reducing the equivalents of **144** and CrCl₂ to 1.3 and 6.0 respectively resulted in

complete conversion on the same timescale and a slightly improved yield (Entry 2). Further efforts to lower the stoichiometry of either dibromide **144** or chromium(II) chloride led to incomplete conversion even after 24 hours (Entries 3 and 4).



Entry	silane (equiv)	CrCl ₂ (equiv)	temp (°C)	time (h)	yield (%) ^a (conversion (%)) ^b	<i>E:Z</i>
1	144 (2.0)	8.0	20	16	74 (100)	> 99:1
2	144 (1.3)	6.0	20	16	82 (100)	> 99:1
3	144 (1.2)	6.0	20	24	74 (92)	> 99:1
4	144 (1.3)	4.0	20	24	53 (71)	> 99:1
5	144 (1.3)	6.0	50	2	75 (100)	> 99:1
6	145 (1.3)	6.0	20	6.5	76 (100)	> 99:1
7	145 (1.3)	6.0	50	0.75	77 (100)	> 99:1

^a Isolated yield. ^b Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

Table 3.1

In order to reduce the reaction time scale, we next performed the olefination at elevated temperatures. Pleasingly, complete conversion occurred in just 2 hours when the reaction was conducted at 50 °C, without any loss of stereoselectivity (*E:Z* > 99:1, Entry 5). We anticipated that the more reactive diiodosilane reagent **145** might offer benefits over **144** and indeed found that this reagent maintained both the yield and selectivity of the olefination, as well as significantly reducing the reaction time at room temperature (Entry 6). The most rapid silylolefination could be achieved using **145** at

50 °C, which reduced the reaction time to just 45 minutes (Entry 7). In our subsequent evaluations, conditions corresponding to entries 2, 5 and 7 were employed.

3.2.2 Investigating the aldehyde substrate scope

Having established a set of optimal reaction conditions for the formation of (*E*)-disubstituted alkenyl benzyldimethylsilanes, a range of aldehydes were tested to determine the scope of the silylolefination. Initial screening of aromatic aldehydes (Table 3.2) revealed that *para*-substituted benzaldehydes generally afforded good to excellent yields of the corresponding alkenylsilanes **147-151** when treated with **144** (Entries 1-5). Electron-rich, electron-poor, halogen and boronic ester substituents were all tolerated by the mild reaction conditions. In the latter case, a slightly improved yield could be attained by heating the reaction mixture (Conditions B), and in all instances, complete selectivity for the (*E*)-alkenylsilane was observed. *p*-Nitrobenzaldehyde was the exception to this general functional group tolerance: no product was detected in the crude reaction mixture despite complete consumption of the starting material (Entry 6), likely resulting from reduction of the nitro group by chromium (II).¹⁴⁸

In a manner reminiscent of other Takai olefinations, the reaction proved selective for aldehydes in the presence of ketones, as illustrated by the conversion of 3-acetylbenzaldehyde (Entry 7, Table 3.2). The presence of *ortho* substituents on the arene necessitated the use of heated reaction conditions (Entries 8 and 9), with mesitaldehyde giving a low yield of silane **155**, which intriguingly was formed in a 13:1 (*Z:E*) ratio. The geometry of the alkene was characterised by a $^3J_{\text{HH}}$ value of 15.0 Hz, which is typical for (*Z*)-alkenylsilanes.¹⁴⁹

Entry	alkenylsilane	condition ^a	time (h)	yield (%) ^b (conversion (%)) ^c
1	147	A	16	90 (100)
2	148	A	36	82 (91)
3	149	A	24	65 (100)
4	150	B	4	75 (100)
5	151	A B	24 3	78 (92) 86 (100)
6	152	A	16	0 (100)
7	153	A	24	92 (100)
8	154	B	5	83 (100)
9	155	B	24	29 (40) ^d
10	156	A B	24 2	86 (100) 86 (100)
11	157	A A C	16 16 1	0 (100) 45 (100) ^e 49 (100) ^e

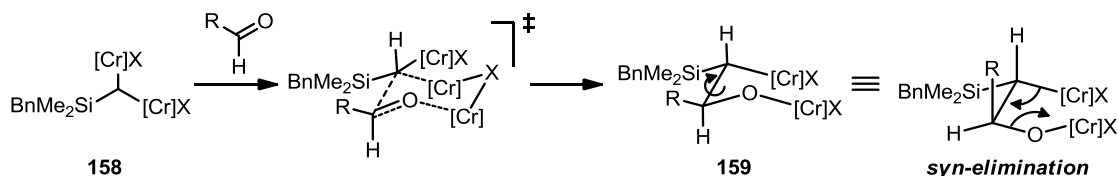
^a Reaction conditions: **A**: BnMe₂SiCHBr₂ (1.3 equiv), CrCl₂ (6.0 equiv), THF, 20 °C; **B**: BnMe₂SiCHBr₂ (1.3 equiv), CrCl₂ (6.0 equiv), THF, 50 °C; **C**: BnMe₂SiCH₂ (1.3 equiv), CrCl₂ (6.0 equiv), THF, 50 °C. ^b Isolated yields. ^c Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^d Z:E = 13:1. ^e Quenched with aqueous EDTA·Na₂.

Table 3.2

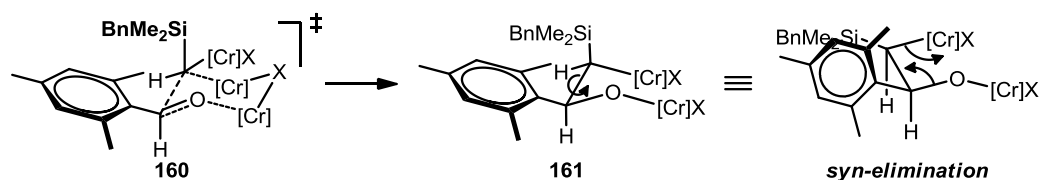
The reaction of heteroaromatic aldehydes proved more challenging; furfural required extended reaction time to achieve a satisfactory yield of **156** (Entry 10, Table 3.2), although this could be improved to two hours by employing Conditions B. In the case of nicotinaldehyde (Entry 11), no product was detected despite complete consumption of starting material. Broadening of signals in the ^1H NMR spectrum of the crude reaction mixture suggested complexation of the pyridine to chromium. Pleasingly, chromium(II) could be sequestered by quenching the reaction mixture with aqueous $\text{EDTA}\cdot\text{Na}_2$, thereby liberating the pyridyl group,⁹⁵ enabling the isolation of **157** in moderate yields.

The high (*E*)-selectivity observed in the formation of alkenylsilanes is attributed to addition of the *gem*-dichromium nucleophile **158** to aldehydes *via* a six-membered chair-like transition state containing two chromium ions bridged by a halide (Scheme 3.5).⁹⁴ The bulky silane and aldehyde substituent are in an *anti*-orientation, occupying pseudo-equatorial positions. Rotation at the newly-formed single bond in adduct **159** followed by *syn*-elimination of $(\text{L}_n\text{Cr})_2\text{O}$ provides the (*E*)-product. In the exceptional case of mesitaldehyde, the aryl system is proposed to rotate out of conjugation with the aldehyde, resulting in an *ortho*-methyl group directed into the neighbouring pseudo-equatorial position typically occupied by the silane. The addition may still proceed, but with the silane in a pseudo-axial position to relieve steric congestion, resulting in the silane and arene occupying *syn*-positions in the closed transition state **160**. Elimination of $(\text{L}_n\text{Cr})_2\text{O}$ from adduct **161** affords the (*Z*)-alkene.

mechanism of the Takai olefination:



mesitaldehyde:



Scheme 3.5

We next screened a range of aliphatic aldehydes under the silylolefination conditions (Table 3.3). Simple aliphatic aldehydes with secondary, tertiary and quaternary α -carbon centres gave excellent yields (Entries 1-3) with pivaldehyde being a particularly notable substrate that underwent complete conversion to **164**. Dienes **165** and **166**, which are valuable building blocks for the synthesis of polyunsaturated compounds, were readily prepared from α,β -unsaturated aldehydes (Entries 4 and 5). Alkenylsilane **168**, bearing a terminal alkyne and which would likely prove challenging to prepare *via* hydrosilylation, was isolated from hex-5-ynal in good yield (Entry 7). Disappointingly, valerolactol was not compatible with the reaction conditions; alcohol **169** was obtained in low yields even after the aqueous $\text{EDTA}\cdot\text{Na}_2$ quench was applied (Entry 8).

To demonstrate the applicability of the reaction in more complex settings, a series of aldehydes containing other functional groups or stereogenic centres were subjected to the olefination. Alkenylsilanes **170** and **171** were both obtained with excellent stereoselectivity ($E/Z > 99:1$) and with little or no epimerisation of the adjacent stereocentre, suggesting the reaction to be well-suited for applications in synthesis. Even configurationally unstable (*R*)-2-(hydroxymethyl)propionaldehyde, which has been reported to spontaneously epimerise during storage at low temperatures,¹⁵⁰ was

converted to the corresponding alkenylsilane with little erosion of stereochemical integrity (Entry 10).

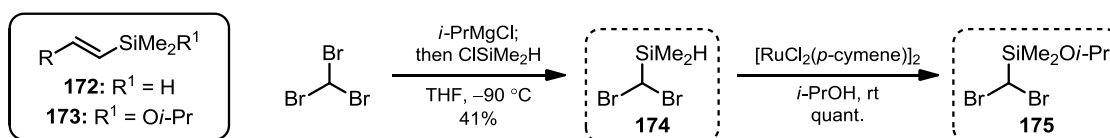
Entry		alkenylsilane	condition ^a	time (h)	yield (%) ^b (conversion (%)) ^c
1	162		A	16	77 (100)
2	163		A B	16 2	80 (100) 78 (100)
3	164		A	24	77 (100)
4	165		A	24	94 (100)
5	166		A	16	82 (100)
6	167		B	3	81 (100)
7	168		A	18	79 (100)
8 ^d	169		A B	24 5	< 5 (11) < 5 (100) ^e
9	170		A	16	61 (100) ^f
10	171		A B	24 3	68 (100) ^g 79 (100) ^h

^a Reaction conditions: **A**: BnMe₂SiCHBr₂ (1.3 equiv), CrCl₂ (6.0 equiv), THF, 20 °C; **B**: BnMe₂SiCHBr₂ (1.3 equiv), CrCl₂ (6.0 equiv), THF, 50 °C. ^b Isolated yields. ^c Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^d Valerolactol was used in place of the aldehyde. ^e Quenched with aqueous EDTA·Na₂. ^f 99% *ee*. ^g 74% *ee*; the aldehyde was prepared in 80% *ee*. ^h 60% *ee*.

Table 3.3

3.2.3 Investigating the silane reagent scope

The range of substitution that would be tolerated on the *gem*-dichromium nucleophile was next investigated. Based on the excellent performance of alkenyl hydrosilanes **172** and siloxanes **173** in Hiyama cross couplings, the equivalent dibromomethyl reagents were prepared in the hope of accessing these silicon substitutions by the Takai silylolefination. Dibromomethyl dimethylsilane **174** was isolated in a modest yield after trapping dibromomethyl Grignard reagent with chlorodimethylsilane. The hydrosilane was then converted to isopropylsiloxane reagent **175** by solvent-free dehydrosilylation, catalysed by dimeric ruthenium complex $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$.¹⁵¹



Scheme 3.6

Trisubstituted alkenes have also been prepared by chromium(II) halide olefinations of aldehydes by employing fully substituted dihalomethane reagents. Some of the earliest work by Hodgson and co-workers accessed simple alkenylbis(silanes) from dibromobis(trimethylsilyl)methane **176** (Figure 3.2).¹⁵² Intriguingly, the same group reported that the reaction of the tribromosilylmethane **177** with benzaldehyde returned only small amounts of the expected 1-bromo-1-trimethylsilyl alkene, with acetophenone isolated as the major product instead.¹⁵³ Falck and co-workers showed dichloromethane reagents **178-181**, bearing electron withdrawing substituents, were reactive with aldehydes under chromium-mediated conditions. The olefinations afforded α,β -unsaturated carbonyl products with high selectivity for the geometrical isomers with the carbonyl derivative and aldehyde group adopting a *trans* orientation.¹⁵⁴⁻¹⁵⁷

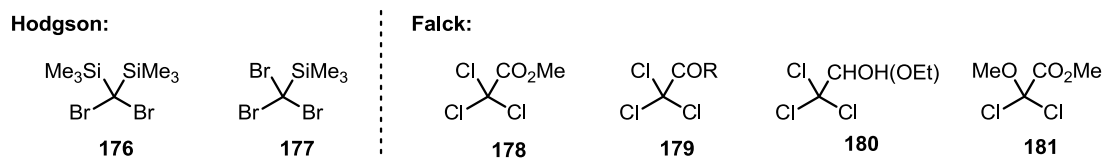
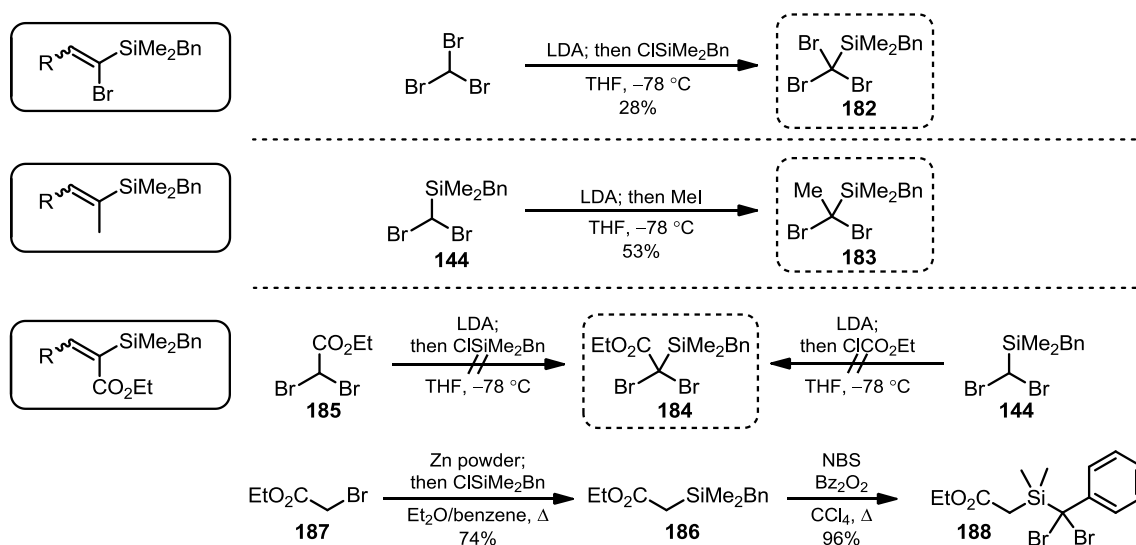


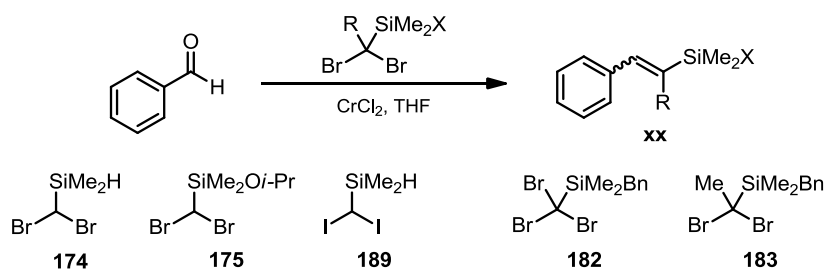
Figure 3.2

We thus set out to prepare the silylolefination reagents **182-184**, which we anticipated would provide trisubstituted alkenylsilanes (Scheme 3.7). Tribromomethylsilane **182** was obtained by deprotonating bromoform with LDA and quenching the lithium carbanion with benzylchlorodimethylsilane. Methyl-substituted **183** was prepared in a similar deprotonation/electrophilic quench sequence from the now-familiar benzyldimethylsilane reagent **144** and methyl iodide. The equivalent ester-substituted reagent proved elusive, with neither α -dibromo ester **185** nor dibromomethylsilane **144** providing the desired reagent **184** under the conditions described above. An alternative approach *via* double radical bromination of α -silyl ester **186**, itself prepared from the Reformatsky enolate of **187** and benzylchlorodimethylsilane, appeared to furnish the fully α -substituted ester. However, closer analysis based on HMBC interactions revealed the bromination had been completely selective for the unwanted benzylic position **188**. Further attempts to trap the enolate of **186** with a variety of electrophilic bromine sources led to complex mixtures of products.



Scheme 3.7

Reagent screening studies were performed on benzaldehyde (Table 3.4), which was subjected to the optimised olefination conditions of 1.3 equivalents of silane reagent and 6 equivalents of chromium (II) chloride in dry THF at 20 or 50 °C. To our disappointment, formation of styrenyl hydrosilane or siloxane was not observed with either of the heteroatom-substituted silane reagents **174** or **175** (Entries 1-2). Heating the reactions to 50 °C returned a complex mixture, while the addition of stoichiometric lithium iodide, which activates dibromomethane reagents by converting them to the more reactive diiodide *in situ*, led to recovery of benzaldehyde only. To fully exploit the reactivity of the diiodomethane reagent, silane **189** was prepared from diiodomethane and chlorodimethylsilane (Entry 3). Unfortunately, an identical outcome was observed when the reaction was carried out at room temperature where only benzaldehyde was recovered. Cooling the reaction led to no conversion of either the silane or aldehyde.



Entry ^a	silane	temp (°C)	additive (equiv)	yield (%)	recovered S.M. ^b	
					aldehyde	silane
1	174	20	-	0	✓	✓
		50	-	0	c.m. ^c	c.m.
		20	LiI (3.0)	0	✓	✗
2	175	20	-	0	✓	✓
		50	-	0	c.m.	c.m.
		20	LiI (3.0)	0	✓	✗
3	189	20	-	0	✓	✗
		0	-	0	✓	✓
4	182	20	-	0	c.m.	c.m.
5	183	20	-	0 ^d	✓	✗

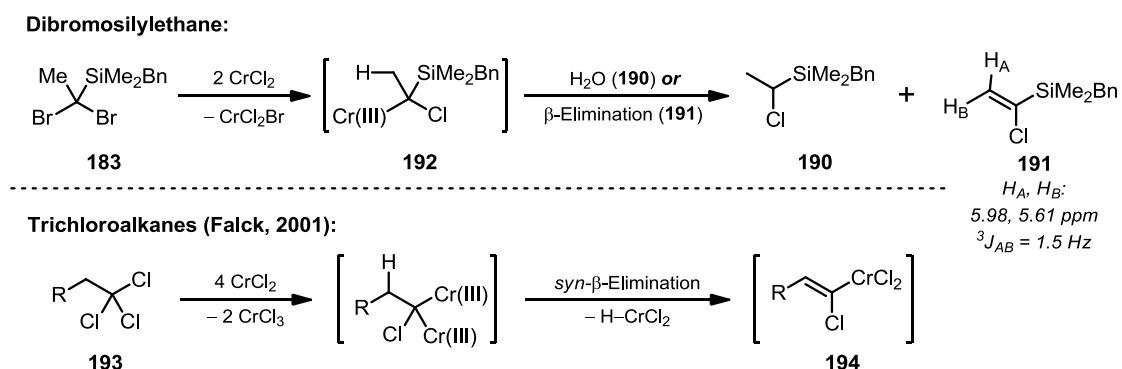
^a Reaction conditions (unless otherwise noted): silane (1.3 equiv), CrCl_2 (6.0 equiv), THF, 24 h.

^b Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. ^c Complex mixture. ^d Recovered a 1:1 mixture of 1-chloro-1-silylethane **190** and 1-chlorovinylsilane **191**.

Table 3.4

Tribromomethylsilane returned a complex mixture of products, none containing olefinic protons (Entry 4, Table 3.4). This result is unsurprising in light of Hodgson's work where aldehydes were converted to methyl ketones using the analogous trimethylsilyl reagent through a proposed carbene rearrangement to the C-silylated chromium enolate.¹⁵³ The reaction of 1,1-dibromo-1-silylethane **183** with benzaldehyde (Entry 5) afforded 1-chloro-1-silylethane **190** and a 1,1-disubstituted alkene which was assigned as 1-chlorovinylsilane (**191**, Scheme 3.8) based on comparison of the chemical shifts of

the geminal olefinic protons to similar compounds in the literature¹⁵⁸⁻¹⁵⁹ and mass spectrometry.

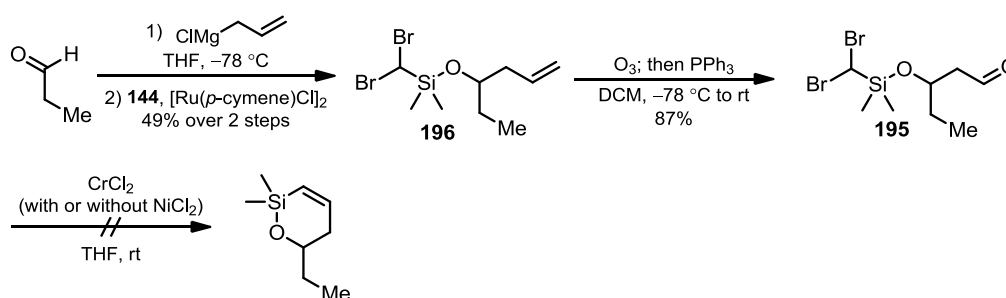


Scheme 3.8

Formation of chlorovinylsilane **191** may proceed *via* a 1-chloro-1-chromium ethane intermediate **192** which arises from the insertion of chromium (II) into one of the carbon-halide bonds by consecutive single electron transfer processes in which two equivalents of CrCl_2 are consumed (Scheme 3.8). Chloride may be introduced by Finkelstein halide exchange which *gem*-dibromoalkane reagents are known to undergo with CrCl_2 .⁹³ Subsequent β -hydride elimination of a chromium (III) hydride species, which Falck and co-workers have observed in trichloroalkane systems **193**, leads to chlorovinylsilane **191**.¹⁶⁰ The same metalloid intermediate **192** could also give rise to chlorosilylethane **190** following proton trapping by adventitious water in the reaction or during the aqueous work up. Falck's chromium vinylidene carbenoids **194** behave as nucleophiles in the presence of aldehydes, affording allylic alcohols. No addition products containing benzaldehyde were observed in the dibromosilylethane reaction.

Our final attempt at varying the silane reagent sought an *intramolecular* variation of the silylolation utilising substrates with a tethered aldehyde and *gem*-dihalomethylsilane. In the case where a siloxane tether is used, the anticipated product would be a cyclic alkenylsiloxane. The synthesis of a model substrate **195** from

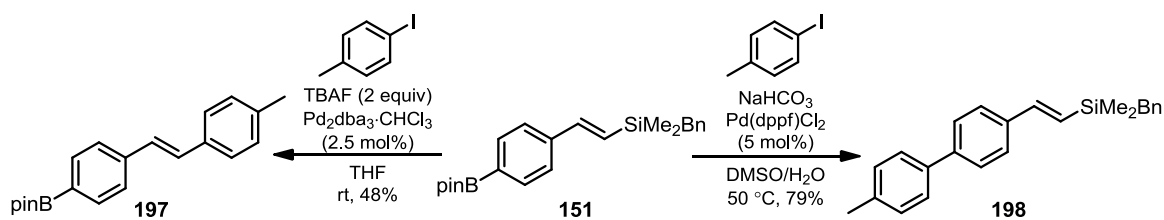
propionaldehyde was achieved in the following manner: Allyl Grignard addition to the aldehyde and ruthenium-catalysed dehydrosilylation of the resulting alcohol with dibromomethylsilane **144** afforded siloxane **196** (Scheme 3.9). Unmasking the terminal alkene by ozonolysis provided the tethered aldehyde reagent **195**. Frustratingly, and in a manner reminiscent of the siloxane reagent **175** (Entry 2, Table 3.4), no reaction was observed when the substrate was treated with chromium (II) chloride. Nickel (II) chloride has been shown to aid formation of the organochromium species by performing the initial oxidative addition to the carbon halide bond, then undergoing transmetallation with chromium.¹⁶¹ Doping the reaction with catalytic nickel (II) chloride led to an identical outcome of almost complete recovery of starting material.



Scheme 3.9

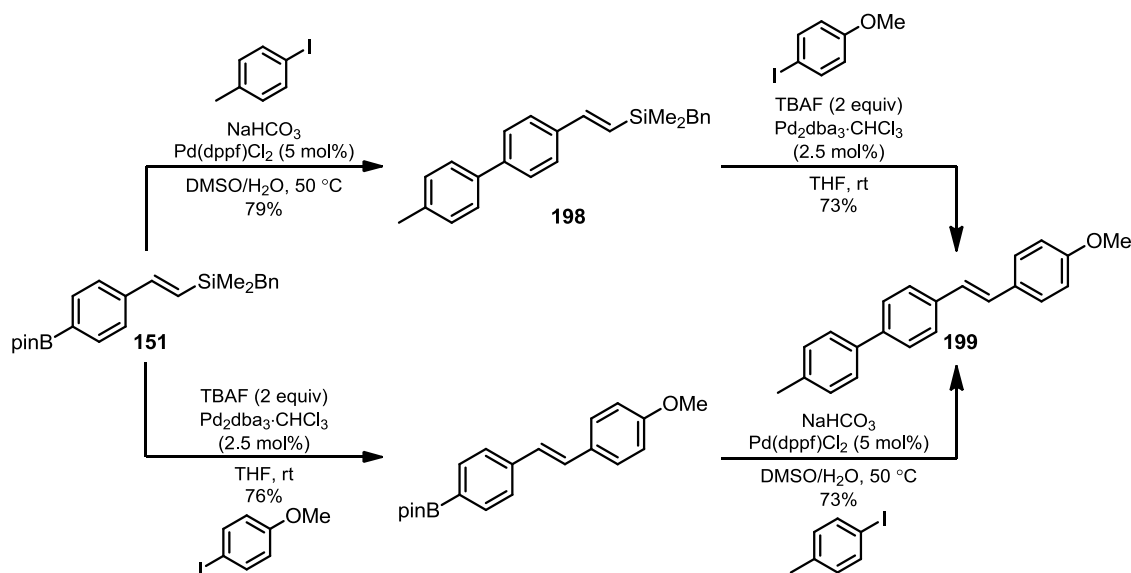
3.3 Orthogonal silicon-boron cross-coupling reactions

We aimed to demonstrate the utility of the silylolefination through selective alkenylsilane cross-coupling. The boronic ester product **151** was selected as we anticipated it could be activated to either Hiyama or Suzuki cross-couplings by a choice of either fluoride or base additives (Scheme 3.10). Indeed, 4-iodotoluene was smoothly coupled at the alkenyl position when two equivalents of fluoride were employed, or at the aryl position when the reaction was carried out in aqueous sodium bicarbonate. The biaryl products **197** and **198** respectively were obtained exclusively in each case.



Scheme 3.10

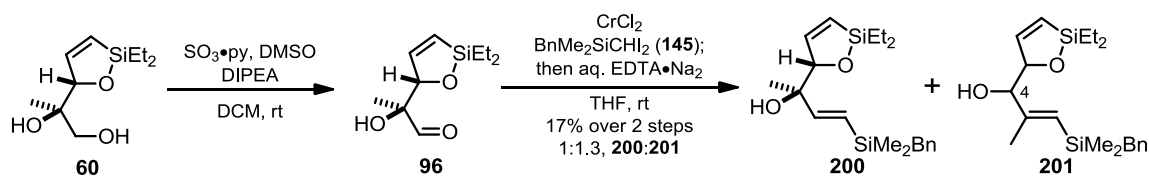
The orthogonal nature of the activation of silicon and boron cross-coupling partners also enabled us to perform these operations in either order to arrive at the same triaryl product (Scheme 3.11). Thus, the silane product of Suzuki coupling of **151** with 4-iodotoluene, **198**, upon subsequent fluoride activation of the benzyldimethylsilyl group and Hiyama coupling with 4-iodoanisole provided the arylated product **199** (73%). An equally efficient synthesis of **199** could be achieved when the order of cross-coupling reactions were exchanged and Hiyama coupling with 4-iodoanisole preceded the Suzuki coupling (76% and 73% for the Hiyama and Suzuki couplings, respectively).



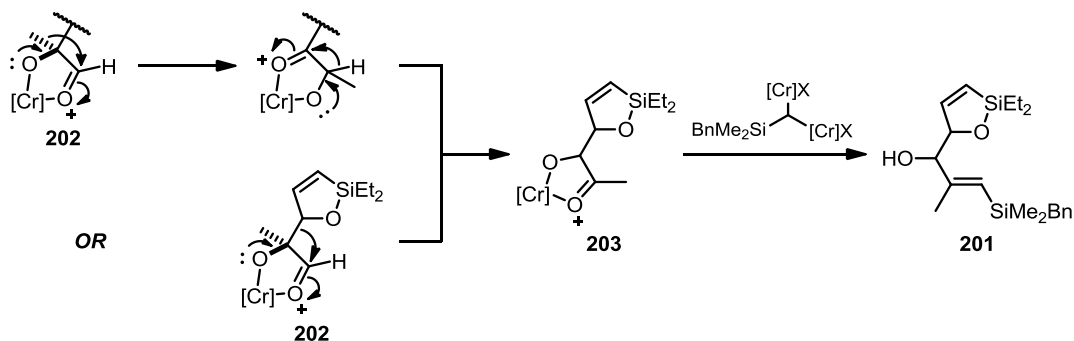
Scheme 3.11

3.4 Application to incednine building blocks

Returning to the original motivation for this methodology, the silylolation was applied to three of the incednine building blocks whose preparations were described in the previous chapter. Silylolation of the five-membered cyclic alkenylsiloxane **96** required the enhanced reactivity of the diiodomethane reagent **145** to proceed, but disappointingly, benzyldimethylsilane **200** was isolated as the minor product in a low yield alongside trisubstituted alkenylsilane **201** (Scheme 3.12). Substitution around the unexpected alkene product **201** was determined by HMBC and nOe interactions. While the exact mechanism by which **201** is formed remains unclear, we tentatively suggest a rearrangement that proceeds through a 1,2-migration of the methyl group in the organochromium chelate **202** followed by a second 1,2-hydride migration from the newly formed secondary alcohol. Alternatively, migration of the five-membered siloxacycle affords the methylketone directly. Silylolation of the methylketone **203** would give rise to the trisubstituted alkenylsilane **201**.

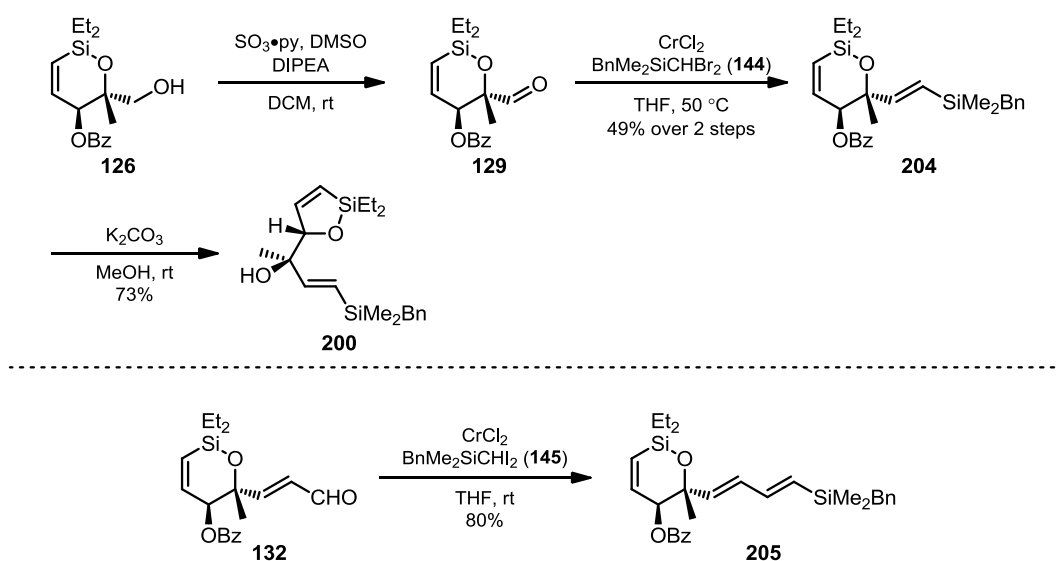


proposed formation of trisubstituted alkenylsilane **201**:



Scheme 3.12

Pleasingly, the six-membered cyclic alkenylsiloxane **129**, lacking a free α -hydroxyl group which could coordinate to chromium, was smoothly converted to (*E*)-alkenylsilane **204** using dibromomethane reagent **144** in a satisfactory two-step yield from alcohol **126** (Scheme 3.13). Five-membered siloxane **200** could now be accessed by a rearrangement triggered by benzoyl deprotection of **204** in basic methanol (a more thorough investigation of this transformation is described in Section 5.1.2). Silylolefination of the α,β -unsaturated aldehyde **132** also required the more reactive diiodomethane reagent **145** to proceed, and provided the C6-C13 incednine fragment **205** in a good yield under these conditions. These *bis*(silane) reagents allowed us to investigate conditions under which orthogonal Hiyama/Hiyama-Denmark cross-couplings might proceed. The preliminary findings of this work are discussed in the penultimate chapter of the thesis.



Scheme 3.13

3.5 Conclusion

Building on the seminal work of Takai and co-workers, we have developed a series of conditions to perform the silylolefination of aldehydes, conveniently accessing

functionalised (*E*)-alkenylsilanes. The chromium(II)-mediated conditions with dibromomethyl benzyldimethylsilane reagent **144** were found to be compatible with a wide range of aromatic and aliphatic aldehydes decorated with synthetically relevant functional groups. Long reaction times can be shortened by warming the reaction or employing the more reactive diiodide reagent **145**, usually with no detriment to stereoselectivity. These conditions do not appear to tolerate heteroatom substituents on silicon or more heavily substituted dihalomethane reagents – no alkenylsilane products were isolated from these reactions. However, the benzyldimethylsilyl alkene products are themselves useful synthetic intermediates, as demonstrated by their ability to participate in orthogonal silicon-boron cross-coupling reactions. Finally, the silylolation has been applied to the cyclic alkenylsiloxanes developed in the previous chapter to prepare *bis*(silane reagents) **200**, **204** and **205** for orthogonal silicon-silicon cross-coupling reactions (Figure 3.3).

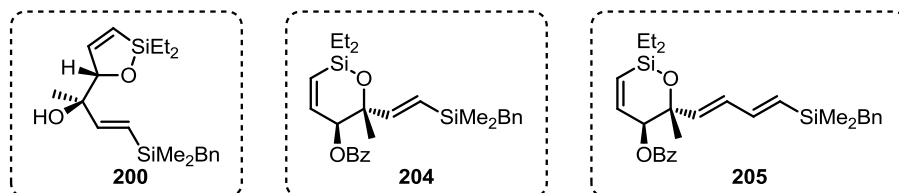


Figure 3.3 Key cyclic alkenylsiloxane building blocks

4 The Enol Ether and Amine Coupling Partners

In the course of our investigations into the cyclic alkenylsiloxane building block (described in Chapter 2), we had synthesised fragments which spanned both the C8-C13 (**136** and **204**, Figure 4.1) and the C6-C13 (**139**, **140** and **205**) portions of incednam. The remaining length of the macrolactam comprised the matching C1-C7 or C1-C5 enol ether coupling partner **206** or **207**, connected by an amide linkage to the C14-C23 amine fragment **62**. This chapter describes the syntheses of each of these building blocks.

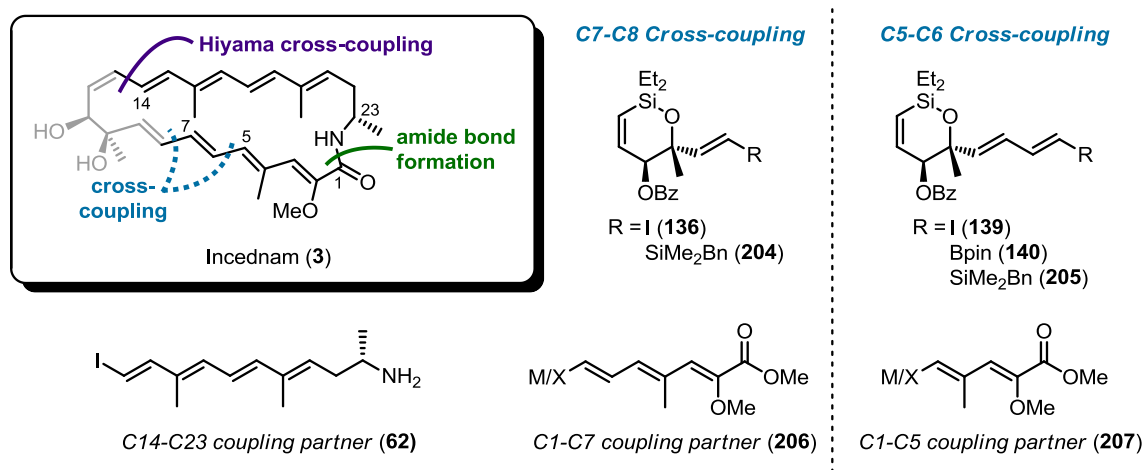


Figure 4.1

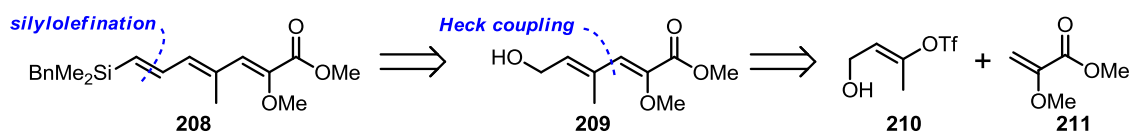
4.1 The enol ether coupling partner

4.1.1 C1-C7 Enol ether synthesis

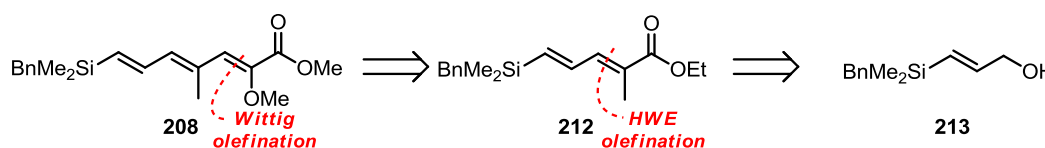
In considering the appropriate halide and metalloid handle for the C1-C7 enol ether coupling partner, the benzyldimethylsilyl group was selected on the basis that it could either be directly coupled with the matching iodide (**136**, Figure 4.1), or converted to the alkenyl iodide at a late stage in the synthesis in order to reverse the coupling partner

combination. Trienyl silane **208** could be disconnected in either of the following two methods (Scheme 4.1): A late stage installation of the alkenylsilane applying the silylolefination methodology described in Chapter 3 requires dienol ether **209**, itself prepared by a Heck coupling between trisubstituted alkene **210** and methyl α -methoxy acrylate **211**. Alternatively, reversing the order of assembly and introducing the enol ether at the very end by Wittig olefination would require the silyl diene **212**, itself the product of HWE olefination of the β -silyl acrolein derived from alcohol **213**. Of the two routes, the former featured a higher degree of convergence as well as fewer oxidation state manipulations, and thus was the route we chose to pursue initially.

① Heck coupling/Silylolefination



② HWE/Wittig Olefination

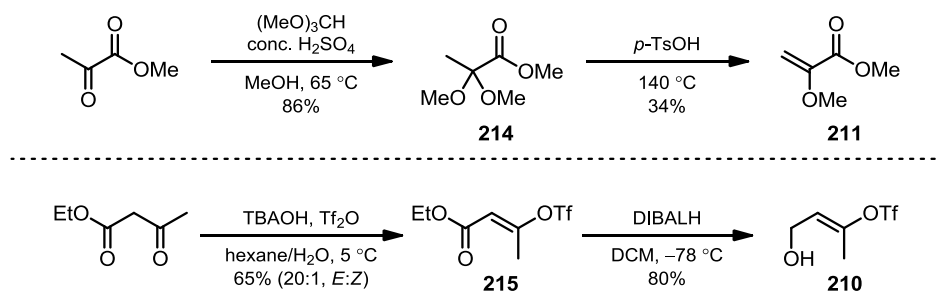


Scheme 4.1

The Heck coupling/silylolefination strategy

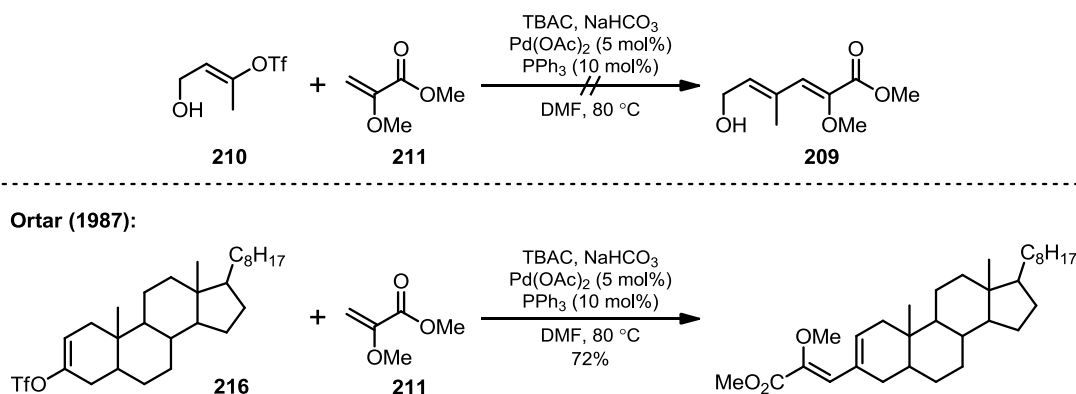
While acrylate esters are archetypal olefins for the Mizoroki-Heck reaction,¹⁶² the behaviour of α -alkoxy acrylates under palladium-catalysed cross-coupling conditions is less well known.¹⁶³⁻¹⁶⁶ In the seminal report on olefins of this type, Ortar and co-workers observed that 1,3-dienol ether products were successfully obtained from alkenyl triflate coupling partners, while poor yields of the diene were noted when alkenyl iodides were employed.¹⁶³ Based on these results, we set out to prepare α -methoxy acrylate **211** and triflate coupling partner **210** (Scheme 4.2). α -Methoxy acrylate was prepared in two steps *via* acetal **214** from methyl pyruvate using the

procedure of Wenkert and co-workers.¹⁶⁷ The triflate coupling partner was synthesised by stereoselective triflation of ethyl acetoacetate with triflic anhydride and tetramethylammonium hydroxide under Schotten-Baumann conditions, affording (*E*)-vinyl triflate **215** with excellent selectivity.¹⁶⁸ Reduction of the ester with DIBALH smoothly afforded allylic alcohol **210**.



Scheme 4.2

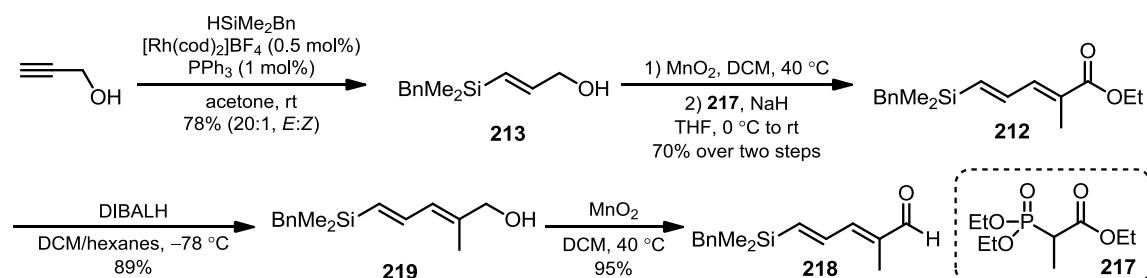
To our disappointment, the Heck coupling between α -methoxy acrylate **211** and triflate **210** failed to provide any diene product using Ortar's original conditions of tetrabutylammonium chloride and excess sodium bicarbonate in the presence of catalytic palladium(II) acetate and triphenylphosphine ligand (Scheme 4.3). Exchanging the base for sodium acetate,¹⁶⁵ increasing the reaction temperature and employing the alkenyl iodide equivalent of triflate **210**¹⁶⁹ had no effect on the outcome of the reaction; α -methoxy acrylate was recovered in every instance. Although there are few precedents for the alkenyl-alkenyl cross coupling of α -methoxy acrylates, Ortar and co-workers reported steroid **216**, which features a similar substitution pattern to triflate coupling partner **210**, undergoing successful cross-coupling with α -methoxy acrylate.¹⁶³ It appeared that the presence of a free alcohol in the vinyl triflate **210** was impeding the reaction, which led us to consider the alternative HWE/Wittig olefination approach to the enol ether coupling partner.



Scheme 4.3

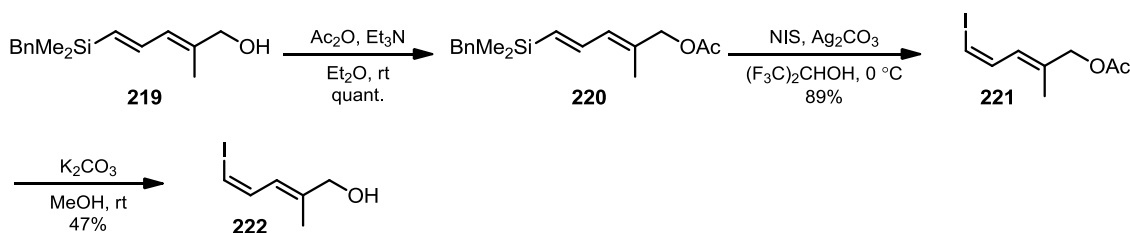
The HWE/Wittig olefination strategy

The known β -silyl acrolein¹⁷⁰ substrate for HWE olefination was prepared *via* alkenylsilane **213** in two steps from propargyl alcohol (Scheme 4.4). Alkyne hydrosilylation with benzyldimethylsilane in the presence of the cationic rhodium catalyst $[\text{Rh}(\text{cod})_2]\text{BF}_4$ afforded silane **213** in good yields with excellent selectivity for the (*E*)-isomer.¹³⁴ Allylic oxidation with manganese (IV) oxide provided the β -silyl enal which was taken on to HWE olefination with commercially available phosphonate **217**. The olefination product, dienyl ester **212**, was smoothly transformed into $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde **218** in a two-step sequence of DIBALH reduction followed by allylic oxidation of the intermediate alcohol **219**.



Scheme 4.4

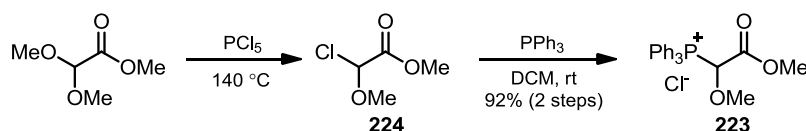
At this stage, we examined the potential of applying an iododesilylation to a late stage intermediate to access the corresponding alkenyl iodide coupling partner. Homoallylic alcohol **219** was identified as a suitable point to effect the functional group conversion, taking into account the decreasing stability of the intermediates as the length of conjugation increased (Scheme 4.5). When Kishi's conditions¹⁷¹ of *N*-iodosuccinimide (NIS) in acetonitrile were applied to alkenylsilane **219**, only aromatic products, and none of the desired iodide, were returned. Ester **212** afforded a complex mixture of products under the same conditions. Pleasingly, protecting the free alcohol as an acetate and subjecting silane **220** to the same conditions did afford alkenyl iodide **221**, albeit in a low yield of 22% and as a mixture of (*E,E*) and (*E,Z*) isomers.



Scheme 4.5

Though unexpected, this result is consistent with the findings of Kishi¹⁷¹ and Costa¹⁷² who observed that substrates with non-TMS alkenylsilanes, *O*-silylated or acylated groups, or other alkenes in conjugation with the alkenyl silane, showed poor retention of olefin geometry during iododesilylation. Zakarian and co-workers have shown that using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), a polar and non-nucleophilic solvent, in place of acetonitrile retained alkene geometry in the iodoalkene products with the added advantage of dramatically shortened reaction times.¹⁷³ Further improvements to the methodology by Costa and co-workers exploited the iodide-trapping ability of silver(I) salts to prevent unwanted side reactions of sensitive polyene products with iodine.¹⁷² To our disappointment, a combination of these modifications afforded a

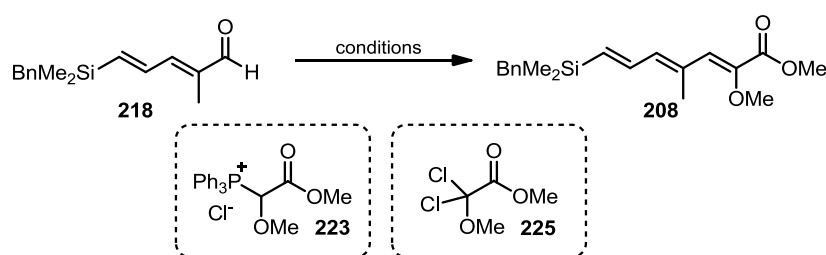
single diene stereoisomer which was assigned as the (*Z,E*)-iodide **221** based on a $^3J_{\text{HH}}$ value of 7.5 Hz for coupling between the vinylic protons across the disubstituted iodoalkene. Deprotection of the allylic acetate with basic methanol provided iodide **222**. All that remained at this point was to install the enol ether using Wittig olefination chemistry. Seneci and co-workers, who were the first to investigate the Wittig reactions of α -alkoxy phosphonium salts with aldehydes, reported high selectivities for the (*Z*)-enol ethers when arylphosphonium salts such as **223** were employed.¹⁷⁴ Phosphonium chloride **223** was prepared on a large scale from methyl dimethoxyacetate using the procedure developed by Crimmins and co-workers (Scheme 4.6).¹⁷⁵ Monochlorination of dimethoxyacetate afforded α -chloroacetate **224** which, on treatment with triphenylphosphine, was converted to the triphenylphosphonium chloride **223**. The Wittig salt was isolated as a foamy hygroscopic solid which gradually evolved into a thick glue when open to air. To facilitate handling, the solid was stored in a glovebox at room temperature, where it remains a solid for months, and manipulated rapidly in air when required.



Scheme 4.6

The Wittig reaction of aldehyde **218** using five equivalents each of phosphonium salt **223** and DBU in refluxing acetonitrile returned a low yield of enol ether **208**, as a single geometrical isomer, along with unreacted aldehyde **218** (Entry 1, Table 4.1). The poor reactivity of aldehyde **218** may be attributed to its conjugation with a diene, reducing the electrophilicity of the carbonyl carbon thereby making it less prone to attack by the phosphonium ylide generated in the reaction. Attempts to improve the conversion of

aldehyde **218** by introducing lithium halide additives (Entries 2 and 3),¹⁷⁶⁻¹⁷⁷ varying the solvent and amine base (Entry 4, others not shown),¹⁷⁸ and pre-forming the ylide (Entry 5) had no positive effect; starting material was recovered in almost every case, except when *n*-butyl lithium was used to generate the ylide. Performing the same transformation with the corresponding phosphonate reagent under HWE conditions typically requires the use of stoichiometric amounts of crown ether in order to obtain good *E/Z* selectivities, and was not explored in these studies.^{25,179-181}



Entry	α -methoxy acetate (equiv.)	base and/or additive (equiv.)	solvent	temp (°C)	yield (%) ^a (conversion (%)) ^b
1	223 (5.0)	DBU (5.2)	MeCN	80	11 (29)
2	223 (1.2)	DBU/LiCl (1.0/1.2)	MeCN	20	n.d. ^c (13)
3	223 (1.2)	DBU/LiCl (1.0/1.2)	MeCN	80	n.d. (5)
4	223 (1.5)	Et ₃ N (2.1)	THF	70	0 (0)
5	223 (2.0)	<i>n</i> -BuLi ^d (2.0)	THF	65	0 (89)
6	225 (1.3)	CrCl ₂ (6.0)	THF	20	16 (82)
7	225 (1.3)	Fe/CrCl ₂ (8.0/0.2)	THF	60	0 (0)
8	225 (1.3)	Zn/CuCl (3.0/0.3)	THF	50	0 (100)

^a Isolated yield. ^b Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

^c Not determined. ^d *n*-BuLi and phosphonium chloride **223** were stirred for 30 minutes at room temperature before aldehyde **218** was added.

Table 4.1

Metal-mediated olefinations employing α,α -dichloroacetate **225** offer another mode of preparing homologated enol ethers from aldehydes. Metal insertion into a carbon-chlorine bond (*via* consecutive single electron transfer steps) generates metal enolates capable of adding to aldehyde substrates. Reductive elimination of the Reformatsky-type adducts affords olefin products. Chromium(II),¹⁵⁷ iron(0)¹⁸² and a zinc(0)-copper(I) couple¹⁸³ have been shown to be selective for the (*Z*)-olefin product when dichloromethoxyacetate or trihaloacetates were employed as the metal enolate precursors. A screen of these systems in search of a more efficient protocol to prepare enol ether **208** was met with moderate success: chromium(II) slightly improved the yield of enol ether **208**, whereas no reaction occurred in the presence of iron(0) (Entries 6 and 7, Table 4.1). The zinc-copper couple returned a complex mixture of products (Entry 8). Ultimately, the inherent instability of the trienol ether system, as well as the inefficient olefinations to access them, led us to favour the C5-C6 cross-coupling which requires on the shorter, and less labile, C1-C5 enol ether.

4.1.2 C1-C5 Enol ether synthesis

In order to avoid another iododesilylation with a conjugated alkenylsilane which could lead to products with unpredictable olefin geometries (as was the case in the iododesilylation of dienyl silane **219**), we opted to prepare the C1-C5 enol ether coupling partner **227** with an iodide coupling handle (Figure 4.2). It was our hope that the iodide coupling partner would be less prone to isomerisation given the shorter conjugated system, and would lend itself more readily to functional group interconversion to access other coupling partners such as boronic ester **228**. Retrosynthetically, installation of the enol ether by Wittig or metal-mediated olefination would require the β -iodo enal derived from trisubstituted (*E*)-iodoalkene **115**.

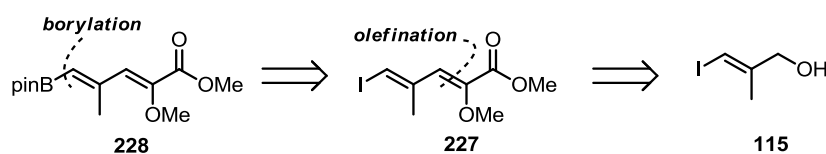
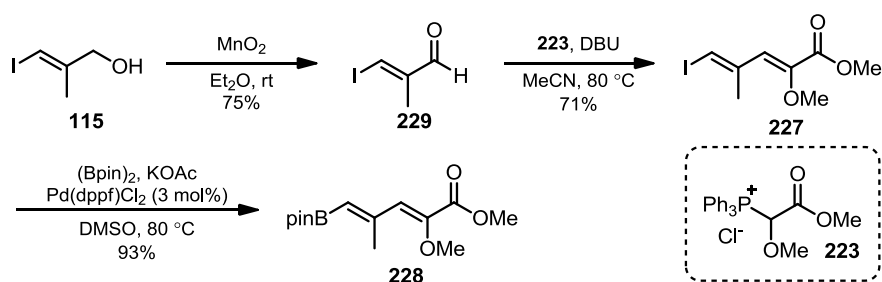


Figure 4.2

Iodoalkene **115** was previously encountered in the synthesis of the cyclic alkenylsiloxane building block, where it was prepared by the zirconium-catalysed methylmagnesiumation of propargyl alcohol followed by quenching of the vinylic metal intermediate with iodine. The allylic alcohol was converted to enal **229** under standard allylic oxidation conditions, and this was immediately followed by a straightforward Wittig olefination with α -methoxy phosphonium salt **223** to rapidly afford the C1-C5 iodide **227** (Scheme 4.7). Iodide **227** was formed as the (2*Z*,4*E*)-diene exclusively, but was prone to isomerisation when exposed to light or stored for extended periods above $-20\text{ }^{\circ}\text{C}$. The ease and efficiency with which enal **229** was converted to the enol ether, in contrast to the difficulties we encountered in the C1-C7 enol ether synthesis, underscores the significant influence which length of conjugation has on aldehyde reactivity.



Scheme 4.7

We next investigated the conversion of alkenyl iodide **227** to other coupling handles. Pleasingly, the standard Miyaura borylation conditions cleanly converted the iodide to boronic ester **228** (Scheme 4.7).¹⁸⁴⁻¹⁸⁵ Purification of the boronic ester product by

column chromatography in a variety of solvent systems was complicated by co-elution of excess bis(pinacolato)diboron. Reducing the amount of diboron reagent to one equivalent (from three equivalents) required extended reaction times for the complete consumption of iodide **227**, and gave rise to the tetraene dimer of the starting iodide, presumably from competing Suzuki cross-coupling between the iodide substrate and boronic ester product. Lithium-halide exchange of iodide **227**, and quenching the vinyl lithium species with triisopropylborate, followed by *in situ* formation of the pinacol ester returned trace amounts of product. Fortunately, the diboron reagent was found to be inert under the Suzuki cross-coupling conditions used to assemble the C2-C9 tetraene and no further attempts were made to optimise the purification of **228**.

4.2 The C14-C23 amine coupling partner

Having established an expeditious route to the C1-C5 enol ether coupling partner, we next turned our attention to the lengthier C14-C23 iodo tetraene partner (**S**)-**230** (Figure 4.3). The decision to install the iodide at a late stage was informed by our previous experience with conjugated polyenyl iodides, and was to be executed by olefination of the aldehyde arising from reduction of trienyl ester (**S**)-**231**. A convergent disconnection at the central olefin of triene (**S**)-**231** pointed to a HWE olefination uniting α,β -unsaturated aldehyde (**S**)-**232** and a phosphonate unit contributing four skeletal carbons. Enal (**S**)-**232** is itself the product of a Wittig homologation of the aldehyde derived from chiral aminobutyrate (**S**)-**233**, which Kanerva and co-workers have prepared from the enzymatic resolution of ethyl 3-aminobutyrate.¹⁸⁶

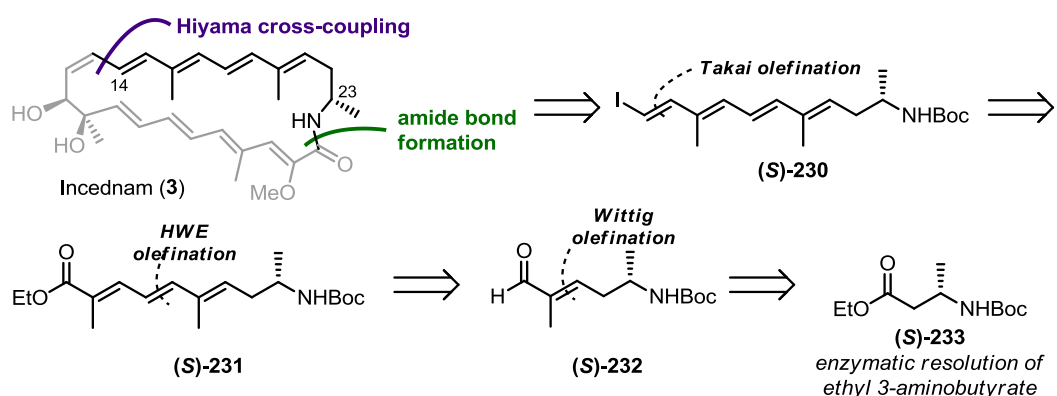


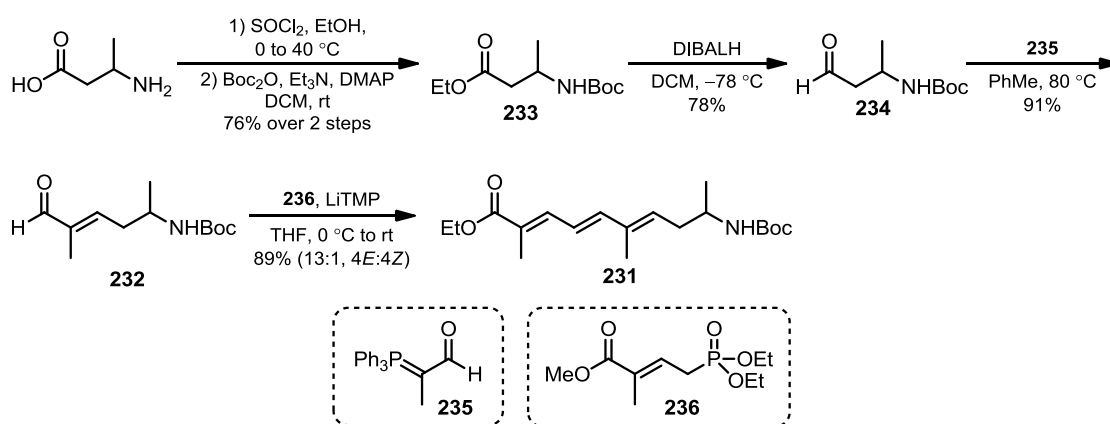
Figure 4.3

The *tert*-butylcarbamate group (Boc) was selected to protect the amine on the basis of its stability to basic conditions and immunity to most of the common methods of ester reduction. Additionally, the ubiquity of the Boc protecting group in natural product syntheses, and its removal from late stage polyene intermediates,¹⁸⁷⁻¹⁸⁹ suggested that suitable conditions for Boc-deprotection in the presence of the tetraene motif might be found. In order to investigate the compatibility of *N*-Boc deprotection with a tetraene,

and establish the viability of the synthetic route outlined above, we embarked on a racemic synthesis of the C14-C23 iodo tetraene **230**.

4.2.1 Racemic synthesis of the C14-C23 amine

The racemic synthesis of the C14-C23 building block commenced with 3-aminobutyric acid which was converted to the known *N*-Boc ethyl ester **233**¹⁹⁰ in two steps (Scheme 4.8). Careful reduction of the ester by the slow addition of cold DIBALH afforded aldehyde **234**, which upon Wittig olefination with phosphorane **235**¹⁹¹ was directly converted to α,β -unsaturated aldehyde **232** in excellent yields. The ensuing convergent HWE olefination was initially plagued by incomplete conversion, low yields and modest *E/Z* selectivity when standard bases (*e.g.* *n*-BuLi, LDA, NaH, LiHMDS and NaHMDS) were employed to deprotonate phosphonate **236**. After an extensive screen of reagent equivalents, bases, solvent and reaction temperature, we were delighted to find that, by adapting the conditions reported by Masamune and co-workers,¹⁹² the use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at 0 °C cleanly afforded trienyl ester **231** with very good selectivity for the desired (*2E,4E,6E*) isomer. In contrast with LiHMDS, in which the aldehyde **232** was returned largely unchanged, it

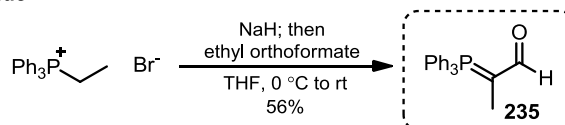


Scheme 4.8

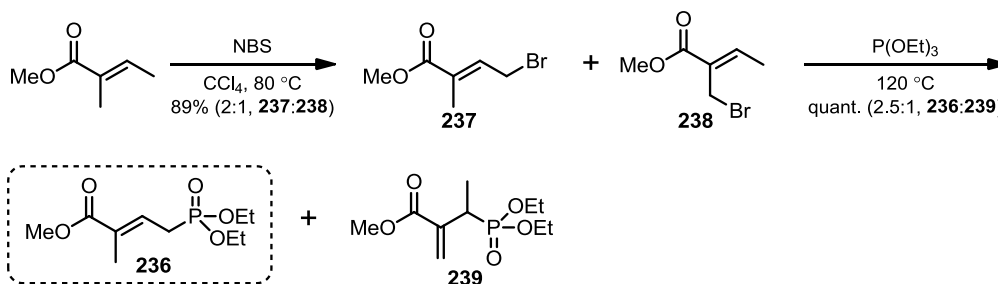
seems that the bulky and rigid frame which encases the amide base in LiTMP is critical for the successful union of the enal with the extended phosphonate **236**.

The Wittig ylide¹⁹³ and HWE phosphonate¹⁹⁴⁻¹⁹⁵ selected to extend the polyene by two and four carbon units, respectively, were prepared by adaptations of previously reported procedures (Scheme 4.9). The Wittig reagent **235** was prepared on a five gram scale by deprotonating ethyltriphenylphosphonium bromide with sodium hydride and quenching the phosphorane with ethyl formate. A second deprotonation of the α -formyl phosphonium salt with excess sodium hydride provided crude phosphorane **235**, which was purified by recrystallization from ether and dichloromethane.¹⁹⁶ Phosphonate **236** was prepared in a two step sequence from methyl tiglate:¹⁹⁷ Initial radical bromination was moderately selective for the γ -position, returning an inseparable 2:1 mixture of regioisomers **237** and **238**.¹⁹⁸ Under Arbuzov conditions, the mixture of bromides afforded the desired phosphonate **236** contaminated with terminal alkene **239**, the product of S_N2' substitution of bromide **238**.¹⁹⁴ The mixture of phosphonates **236** and **239** proved to be suitable for use in HWE olefination: the only products isolated from

Two-carbon Wittig Ylide



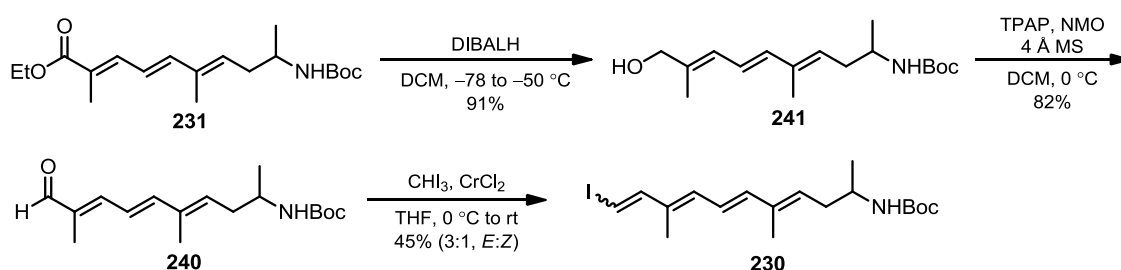
Four-carbon HWE Phosphonate



Scheme 4.9

the reaction were those formed from deprotonation of the more acidic phosphonate **236**, in which the carbanion is stabilised through conjugation with an α,β -unsaturated ester group.

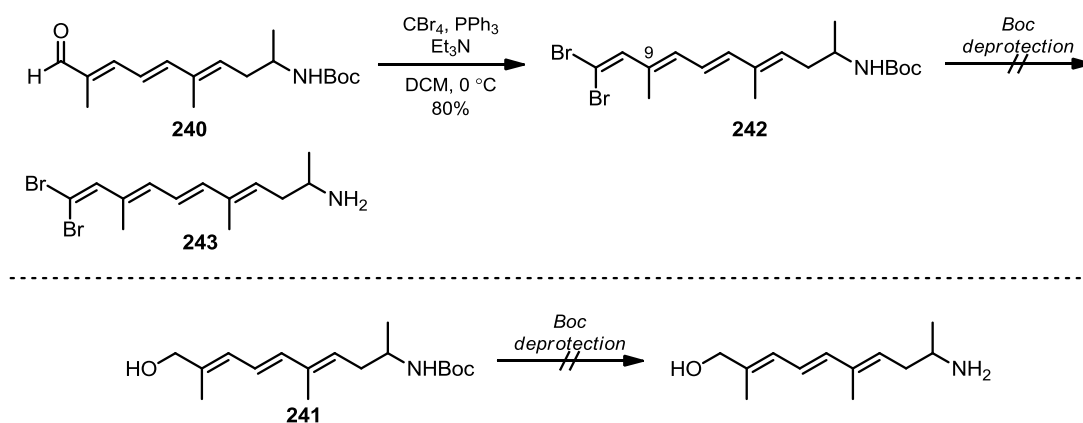
To complete the synthesis of the C14-C23 tetraene, ester **231** was converted through a two-step DIBALH reduction/TPAP oxidation sequence to aldehyde **240** *via* alcohol **241** (Scheme 4.10). Although early attempts to reduce the trienyl ester with DIBALH afforded a mixture of alkene isomers in low yields, further optimisation of the reaction conditions allowed the trienyl alcohol to be isolated with little degradation if the reaction was quenched at $-50\text{ }^{\circ}\text{C}$ rather than being allowed to warm to room temperature. Other common reducing agents, such as lithium borohydride,¹⁹⁹ Superhydride²⁰⁰ and L-Selectride,²⁰¹ resulted in the recovery of ester **231** which had undergone significant isomerisation. Allylic oxidation of alcohol **241** with manganese (IV) oxide promoted isomerisation of the triene, and a brief screen of conditions for the controlled oxidation of alcohols favoured the TPAP/NMO system developed by Ley and co-workers.⁸⁸ The trienal was obtained in good yields with the configuration of the conjugated alkene system preserved during the transformation. Aldehyde **240** was not amenable to storage, and was completely degraded after two days even when stored in the dark as a benzene matrix at $-20\text{ }^{\circ}\text{C}$.



Scheme 4.10

Freshly prepared samples of the aldehyde were used on the day of their preparation in the Takai olefination to install the iodide coupling handle. Disappointingly, the olefination was low yielding and only modestly selective for the (*E*)-iodide **230** (Scheme 4.10). The stereoselectivity of the Takai reaction has been reported to erode considerably with α,β -unsaturated aldehyde substrates,¹²¹ although in some cases (*E*)-selectivity can be improved by the use of a 6:1 dioxane/THF solvent system, albeit with concomitant extension of reaction times.²⁰² Disappointingly, performing the olefination with aldehyde **240** under these conditions led to a worse *E/Z* distribution (2:1, *E:Z*), supporting our suspicion that the tetraene system promotes product isomerisation which is exacerbated by long reaction times. The analogous bromoolefination to prepare (*E*)-alkenylbromides from chromium(II) bromide, generated *in situ* from the reduction of chromium(III) bromide by LiAlH_4 ,⁹³ was not successful in our hands.

At this point, we considered vinyl dibromide **242** as an alternative cross-coupling handle to the unstable (*E*)-iodide (Scheme 4.11). Negishi, Suzuki and Stille cross-couplings have been performed with dibromides and are generally selective for the *trans*-position.²⁰³ Furthermore, the remaining bromide can be removed under conditions which tolerate polyenes.²⁰⁴⁻²⁰⁵ Vinyl dibromide **242** was smoothly prepared by the Ramirez olefination of unsaturated aldehyde **240**,²⁰⁶ and was noted to be more stable than both aldehyde **240** and iodide **230** by showing limited degradation (*c.a.* 20% side products) by ^1H NMR spectroscopy after storage for a week in the dark in a frozen benzene matrix at $-20\text{ }^\circ\text{C}$. The stability of dibromide **242** may be a result of sufficient 1,3-allylic strain between the *cis*-bromide and the C9 methyl substituent to twist the C9-C10 bond, such that the tetraene prefers to adopt a conformation in which conjugation between the C4-C9 alkenes and C10-C11 vinyl dibromide is disrupted to the extent which minimises photo and thermal isomerisation under storage conditions.

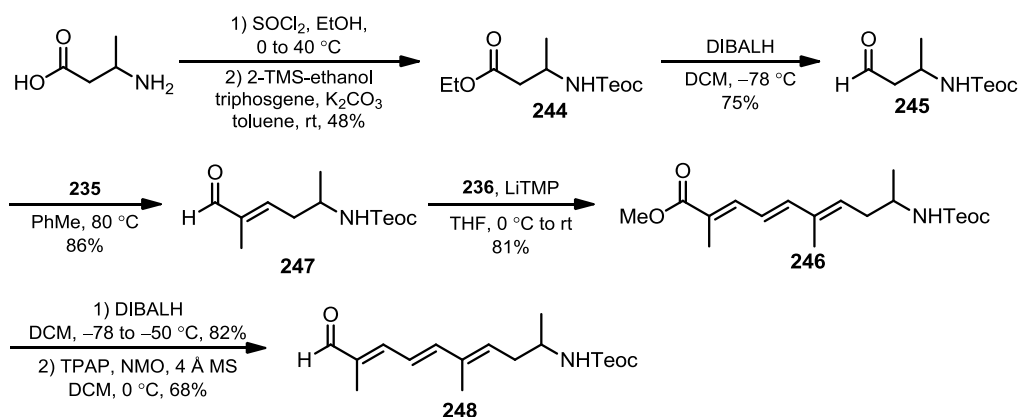


Scheme 4.11

However, to our great dismay, all efforts to perform *N*-Boc deprotection on tetraene **242** were unsuccessful despite the wide range of conditions for deprotection that were investigated. These include treating carbamate **242** with TFA/DCM, HCl in methanol or ethyl acetate, TMS triflate/2,6-lutidine²⁰⁷ and thermal aqueous conditions.²⁰⁸ Either unreacted starting material or a slew of indistinguishable unsaturated products was recovered under these conditions. Conducting the deprotection on alcohol **241**, an intermediate with a shorter polyene system, was similarly unsuccessful (Scheme 4.11).

A new protecting group was required, and the 2-trimethylethylsilyl carbamate (Teoc) group was chosen on the basis of its ready and reliable cleavage under fluoride conditions,⁸² which suggested that its removal might be conveniently promoted under the conditions of the Hiyama cross-coupling with the cyclic alkenylsiloxane fragment. Thus, the synthesis of the C14-C23 coupling partner was revisited. This time, the route commenced with *N*-Teoc protected amino ester **244**, prepared by carbamation of ethyl 3-aminobutyrate with freshly prepared Teoc-Cl (Scheme 4.12).²⁰⁹ Reduction of the ester to an aldehyde in one step proceeded smoothly, affording β -amino aldehyde **245** which was elaborated to trienyl ester **246** following the Wittig/HWE olefination sequence. Ester reduction with DIBALH followed by catalytic TPAP oxidation of the allylic

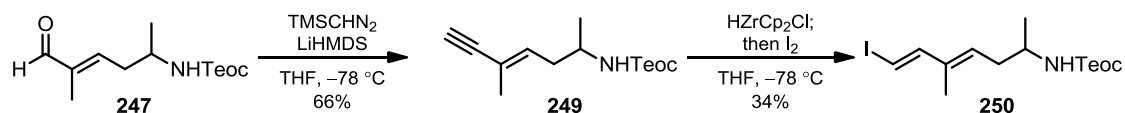
alcohol afforded *N*-Teoc-protected conjugated aldehyde **248** in yields comparable to those obtained with the *N*-Boc compounds.



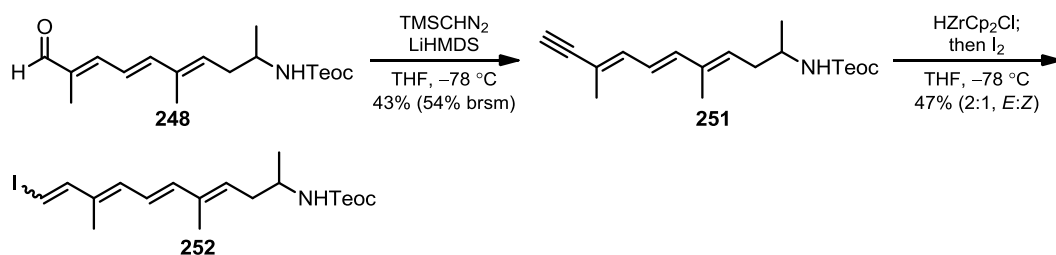
Scheme 4.12

Before embarking on the challenging final olefination of conjugated aldehyde **248**, we elected to use α,β -unsaturated aldehyde **247** as a testing ground for suitable strategies. While the delicate triene motif is omitted in **247**, the readily accessible intermediate replicates both the homoallylic Teoc-protected amine and alkene substitution adjacent to the aldehyde. In order to improve the geometrical purity of the iodide cross-coupling partner we had originally envisaged, the alkenyl iodide was to be introduced in two steps *via* hydrozirconation of an enyne intermediate. Enyne **249** was prepared by the Colvin rearrangement of the model enal **247** (Scheme 4.13), and underwent hydrozirconation followed by quenching of the vinyl organozirconium species with iodine to afford the (*E,E*)-iododiene **250** exclusively. However, when the same sequence was applied to trienal aldehyde **248**, the hydrozirconation/iodine quench of triene-yne **251** returned a comparable mixture of 10*E*:10*Z* isomers as observed in the Takai olefination of *N*-Boc protected aldehyde **240** (*i.e.* 2:1).

Model system:



C14-C23 amine:



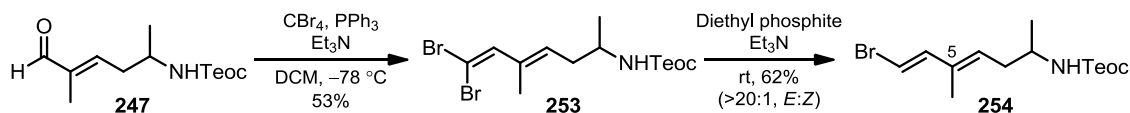
Scheme 4.13

In light of the poor stability of the iodotetraene, we returned to the vinyl dibromide strategy with the intention of converting it to the (*E*)-alkenylbromide coupling partner by a stereoselective monodebromination. A perusal of the literature reveals that while monodebromination of the *trans*-bromide to afford *cis* bromoalkenes is well-established,²¹⁰ a similarly reliable method to perform *cis*-debromination to afford *trans* bromoalkenes is lacking. To the best of our knowledge, the only conditions selective for *cis*-debromination is a little known reduction first published by Hirao and co-workers in 1981,²¹¹ and revisited by Hayes and co-workers in 2000.²¹² The debromination is typically carried out by treating a vinyl dibromide with diethyl (or dimethyl) phosphite and triethylamine in DMF or under solvent-free conditions. Hirao and Hayes both reported the reduction to be highly selective in the case of β,β -dibromostyrene, with selectivity tailing off when less bulky alkyl and alkenyl substituents were present.

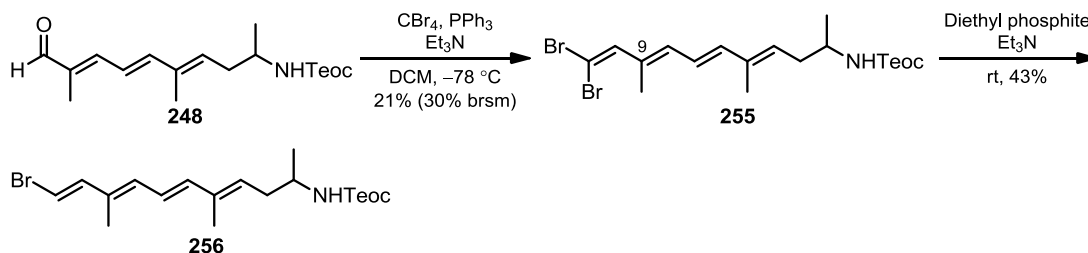
When the Hirao-Hayes conditions (diethyl phosphite, triethylamine, DMF, 70 °C) were auditioned on the model diene **253**, we were delighted to isolate the (*E,E*)-dienylbromide **254** as the exclusive bromoalkene product in a 51% yield (Scheme 4.14). While these conditions resulted in polyene degradation when applied to tetraenyl dibromide **255**, the (*E*)-alkenylbromide **256** was eventually obtained in 43% yield when

the reaction was conducted under solvent-free conditions at room temperature. (The model dienyl bromide **254** was obtained in 62% yield under these conditions.)

Model system:



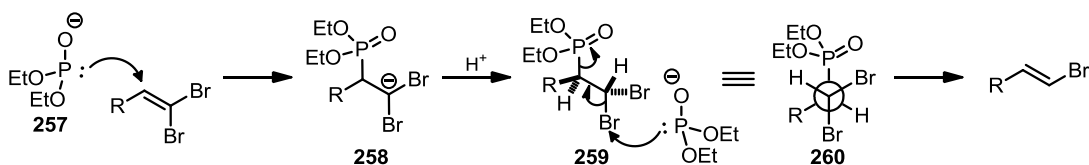
C14-C23 amine:



Scheme 4.14

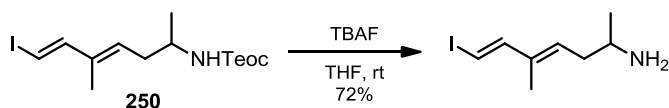
The mechanism of this reaction proposed by Hayes proceeds *via* nucleophilic attack at the vinyl dibromide by diethylphosphite anion **257**, generating carbanion **258** in which the negative charge is stabilised by two adjacent bromides (Scheme 4.15).²¹² Protonation followed by phosphite anion-promoted elimination from **259** provides a plausible route to bromoalkenes. Elimination from the conformation with the departing phosphonate and bromide in an *anti*-periplanar alignment (illustrated in the Newman projection **260**) accounts for the selective formation of *trans* bromoalkenes. The unusually high selectivity observed for diene **253** and tetraene **255** in comparison with those reported by Hayes²¹³ could be due to the methyl substituent adjacent to the vinyl dibromide (at the C5 position of **253** and the C9 position of **255**) allowing the trisubstituted olefin to sterically mimic an aromatic group. This has the result of imparting greater selectivity for the *trans*-bromoalkene product by favouring elimination from the conformation which places hydrogen, the smallest substituent on the dibromomethyl carbon, between the bulky phosphonate and trisubstituted alkene (depicted as R in the Newman projection **260**). An alternative mechanism proposed by

Hirao requires the formation of an extremely basic vinylic anion following halophilic attack at the vinyl dibromide by diethylphosphite anion.²¹¹



Scheme 4.15

In light of the difficulties we encountered when attempting to remove the *N*-Boc group, we were pleased to find that the *N*-Teoc group was successfully removed from model iododiene **250** when the carbamate was treated with an excess of tetrabutylammonium fluoride in THF at room temperature (Scheme 4.16).²¹⁴ Overall, the racemic synthesis of the C14-C23 building block as bromotetraene **256** was achieved in nine linear steps from 3-aminobutyric acid. The route features consecutive two and four-carbon Wittig and HWE olefinations, which allow the rapid construction of the polyene framework, as well as a Ramirez olefination/Hirao reduction sequence that stereoselectively installs the (*E*)-bromoalkene in the final stage of the synthesis.



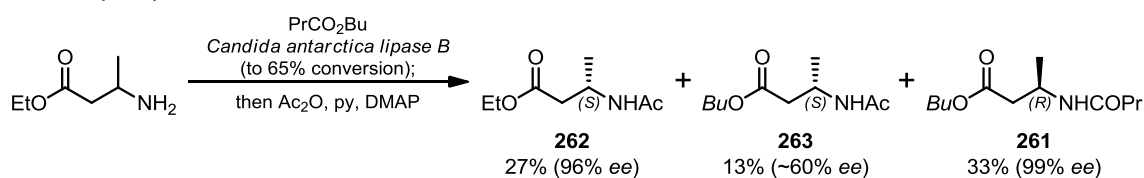
Scheme 4.16

4.2.2 Asymmetric synthesis of the C14-C23 amine

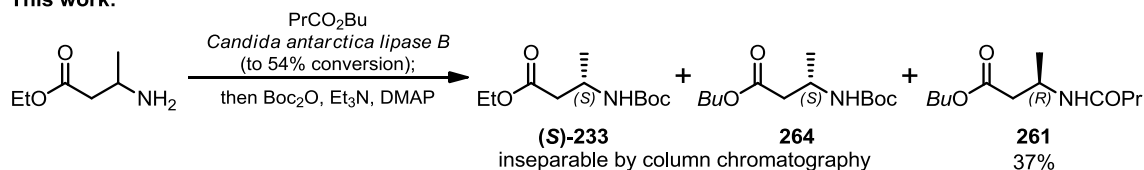
All that remained to complete the synthesis of the C14-C23 building block was to prepare the bromotetraene from enantioenriched (*S*)-3-aminobutanoic acid. The (*R*)-selective enzymatic resolution of ethyl 3-aminobutyrate was reported by Kanerva and co-workers in 1999.¹⁸⁶ *Candida antarctica* lipase B, in the presence of butyl butyrate, was found to perform selective butyratation and transesterification of the (*R*)-

enantiomer, affording highly enantioenriched (*R*)-butyramide **261** when the reaction was stopped at 65% substrate conversion (Scheme 4.17). The (*S*)-enantiomer could be recovered in its acetamide form **262** if the resolved mixture was acetylated before chromatographic purification. A third product, acetylated (*S*)-butyl ester **263**, was also noted to accumulate in significant amounts, albeit in a modest enantiomeric excess. Kanerva and co-workers were able to isolate each of the three products by column chromatography and determine the enantiomeric excesses of each product separately by chiral gas chromatography.

Kanerva (1999):



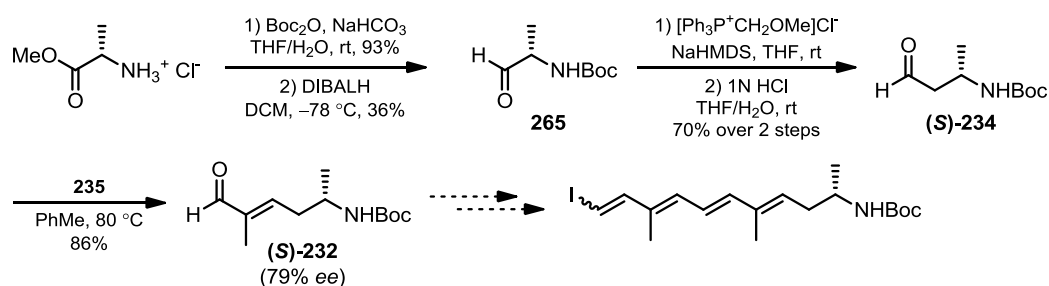
This work:



Scheme 4.17

We attempted to repeat Kanerva's results during our synthesis of the *N*-Boc protected intermediates, and anticipated that the desired (*S*)-*N*-Boc protected amine might be obtained by treating the enzymatically resolved mixture with Boc anhydride prior to chromatographic separation (Scheme 4.17). While we were indeed able to obtain the corresponding (*R*)-butyramide **261** in comparable yields to that reported by Kanerva, separation of the carbamates (*S*)-**233** and **264** was unsuccessful under a variety of chromatographic solvent systems. Given the lower enantiomeric excess of butyl ester **263** reported by Kanerva, we were reluctant to carry the mixture of carbamates through the synthetic sequence.

An alternative method of preparing stereoenriched 3-aminobutanoate derivatives taps the chiral pool of compounds at our disposal. In this case, the chiral β -amino acid can be prepared from L-alanine *via* homologation adjacent to the carbonyl carbon. This strategy was executed based on a procedure developed by Matsuya and co-workers,²¹⁵ in which the *N*-Boc aldehyde **265** derived from L-alanine methyl ester is treated with the Wittig reagent methoxymethyltriphenylphosphine (Scheme 4.18). The enol ether product conveniently yields the homologated aldehyde (**S**)-**234** upon stirring in a dilute solution of hydrochloric acid, which coincides with the previously described route.



Scheme 4.18

To determine how the amine stereocentre had fared during homologation, aldehyde (**S**)-**234** was taken through a Wittig reaction, at which point the enantiomeric excess of the UV-active product, α,β -unsaturated aldehyde (**S**)-**232** was determined by HPLC analysis to be 79%. Although modest, this is perhaps unsurprising in light of the known tendency of α -amino aldehydes to undergo facile racemisation in solution.²¹⁶⁻²¹⁷ The synthetic route has since been repeated by another member of the group with *N*-Teoc-L-alanine methyl ester, during which special care was taken to ensure that the α -amino aldehyde intermediate was used immediately. This has allowed the *N*-Teoc protected α,β -unsaturated aldehyde to be prepared in 84% enantiomeric excess, and the *N*-Teoc iodotetraene can be accessed in its enantioenriched form.

4.3 Conclusion

The polyene coupling partners required to assemble incednam from the cyclic alkenylsiloxane building blocks described in Chapter 2 have been prepared from readily available starting materials by utilising a combination of phosphorous-based olefination strategies. The C1-C7 silane coupling partner (**208**, Figure 4.4) was accessed in six steps from propargyl alcohol, using a rhodium-catalysed *syn*-hydrosilylation to install the (*E*)-alkenylsilane, followed by a HWE olefination and a low-yielding Wittig reaction to introduce the second olefin and enol ether. In contrast, the C1-C5 iodide coupling partner **227** was conveniently prepared in two steps from a common (*E*)-iodoalkene intermediate, formerly employed in the syntheses of the cyclic alkenylsiloxane building blocks. The boronic ester equivalent **228** was obtained by a Miyaura borylation of iododiene **227**. A chiral pool approach to the C14-C23 coupling partner allows *N*-Teoc protected bromotetraene (**S**)-**256** to be prepared in ten linear steps from L-alanine methyl ester. A series of one- and two-carbon Wittig homologations, followed by a convergent HWE olefination with β,γ -unsaturated phosphonate reagent **236** introduces eight carbons, including three stereodefined olefin units, in four transformations without the need for oxidation state manipulations. A late stage Ramirez olefination/Hirao reduction installs the final (*E*)-bromoalkene, completing the tetraene fragment.

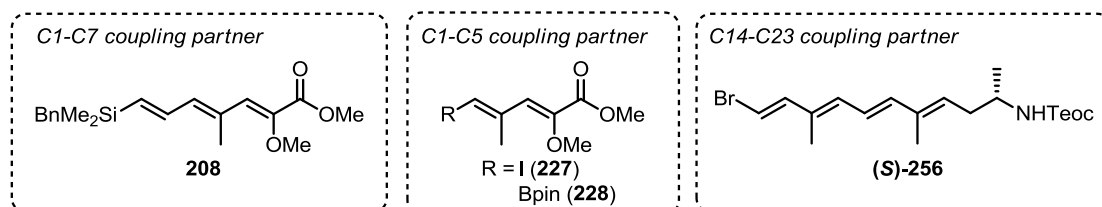


Figure 4.4 Key polyene cross-coupling partners

5 Towards Assembling Incednam by Orthogonal Cross-Couplings

5.1 Investigation of orthogonal Hiyama cross-couplings

With the requisite building blocks to assemble incednam, we approached the final chapter of the synthesis – the construction of an amide linkage and two C_{sp^2} - C_{sp^2} bonds within the polyene systems. The most ambitious of the strategies we had considered was to use a combination of fluoride-free and fluoride-mediated conditions to perform orthogonal Hiyama cross-couplings with the *bis*(alkenylsilane) reagents **204** and **205** (Figure 5.1). This would require the selective activation of one silane group in the presence of another to undergo cross-coupling with the polyene partners prepared in the previous chapter. Our preliminary investigations into the feasibility of such a route are described in this section.

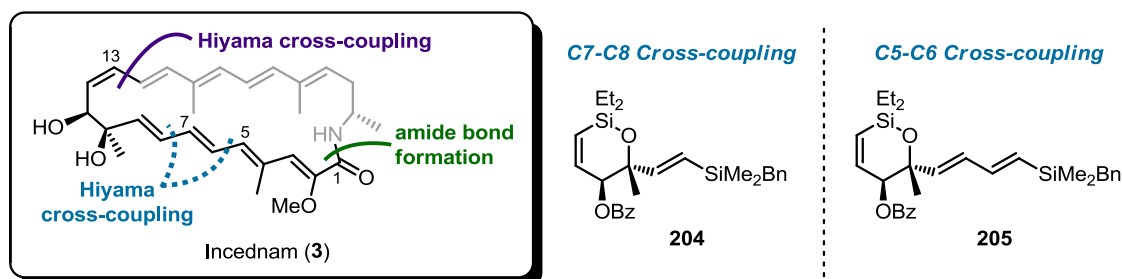
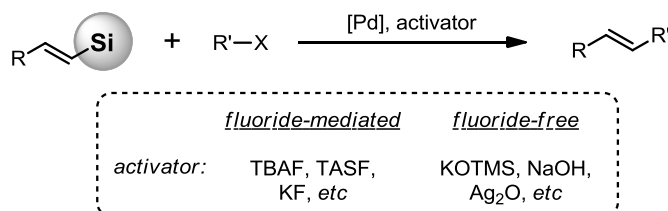


Figure 5.1

5.1.1 Fluoride-activated and free cross-couplings of organosilanes

Since the palladium-catalysed cross-coupling of organosilicon reagents was first reported by Hiyama and co-workers in 1988,²¹⁸ advances in the scope of reactive silane substituents and nature of the fluoride activator have made the Hiyama reaction a competitive, and sometimes superior, method for performing cross-coupling (Scheme

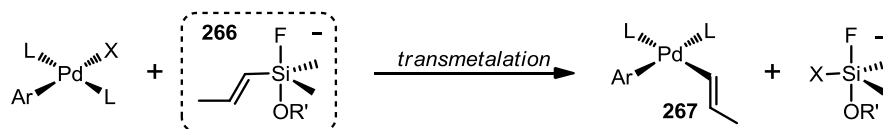
5.1). The subsequent discovery that certain organosilicon reagents may be activated by nucleophiles other than fluoride²¹⁹ has expanded the application of the Hiyama cross-coupling to include substrates bearing silyl ether protecting groups or orthogonally activated silyl groups.



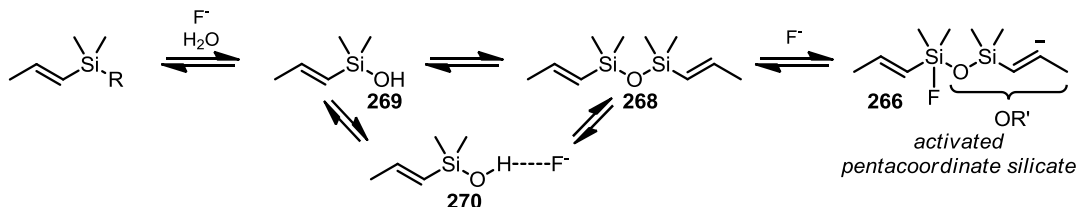
Scheme 5.1 The Hiyama cross-coupling

Mechanistically, the fluoride-activated reaction is proposed to proceed *via* pentacoordinate fluorosilicates **266** which transfer an alkenyl group onto the organopalladium(II) centre in exchange for a halide ligand in the transmetalation step (Scheme 5.2). Reductive elimination from alkenylpalladium complex **267** yields the coupled product and regenerates the palladium(0) catalyst. Based on analyses of the Hiyama reactions of silanols and disiloxanes, including a Hammett study,²²⁰ spectroscopic identification of intermediates, determination of rate equations,²²¹ and evaluation of substituent effects,²²² Denmark and co-workers have suggested that the active pentacoordinate silicate arises from fluoride addition to disiloxane **268**, which is found in equilibrium with silanol **269** and hydrogen-bonded silanol-fluoride complex **270** when either silanols or disiloxanes were treated with TBAF. Given that almost all suitably functionalised silanes known to participate in cross-couplings form silanols with TBAF,⁴³ it seems reasonable to generalise this mechanism to the fluoride-activated Hiyama reaction manifold.

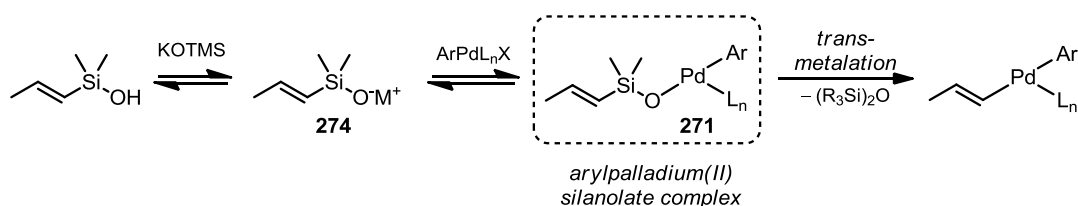
Fluoride activation



proposed formation of pentacoordinate silicates:



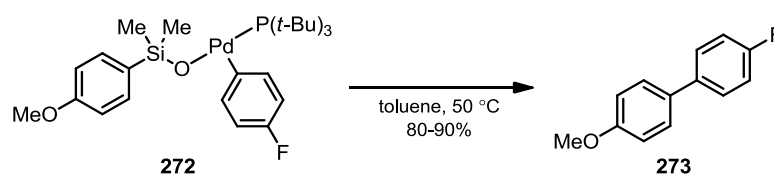
Silanolate activation



Scheme 5.2

In the absence of a fluoride source, transmetalation does not proceed through the sterically hindered pentavalent silicate, and is proposed to proceed *intramolecularly* instead from the palladium silanolate complex **271**, the product of silanolate addition/halide elimination from the organopalladium(II) halide intermediate (Scheme 5.2). A representative complex **272** containing the Si-O-Pd bond has been isolated, and this species has been observed to undergo transmetalation upon gentle warming in the absence of an activator to yield biaryl product **273** (Scheme 5.3).²²³ Silanolates **274** can be isolated from silanols as their alkali metal salts upon treatment with metal hydrides, or generated *in situ* by reversible deprotonation with potassium trimethylsilanolate (KOTMS). Disiloxanes are known to react in a similar manner in the presence of KOTMS: silanolate exchange with trimethylsilanolate generates the silanolate intermediate **274**.²²⁴

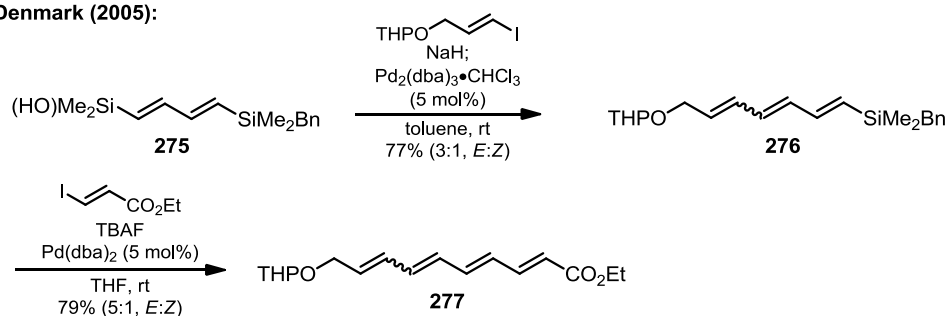
Denmark (2010):



Scheme 5.3

These complementary modes of activating organosilicon reagents have been exploited by Denmark and co-workers to develop an orthogonal cross-coupling strategy in order to access unsymmetrical polyenes from 1,4-bissilylbutadiene reagent **275**,¹²³ and applied to the total synthesis of the polyene macrolide RK-397 (Scheme 5.4).¹²² The first cross-coupling proceeds *via* base-activated silanol transmetalation and yields triene **276**. A second *fluoride*-activated cross-coupling of the remaining benzyldimethylsilyl group introduces a different olefin unit, providing the unsymmetrical tetraene **277** which, in the synthesis of RK-397, was converted to an extended phosphonate reagent for HWE olefination.

Denmark (2005):

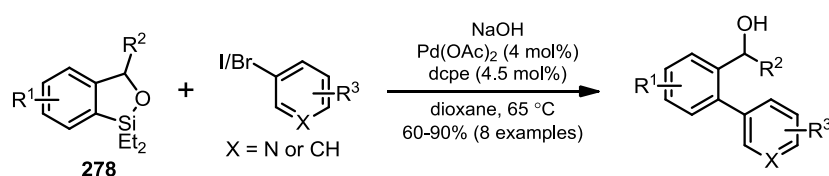


Scheme 5.4

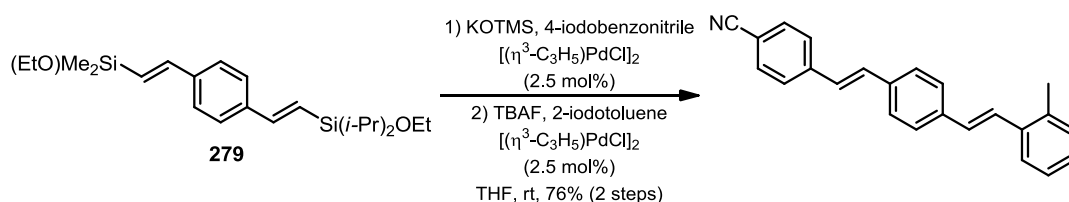
To date, the application of fluoride-free conditions to alkoxyasilanes (*i.e.* siloxanes) as a class of organosilicon reagents remains underexplored. Alkenylsiloxanes, and cyclic alkenylsiloxanes in particular, are valuable synthetic scaffolds. Alkoxyasilanes are stable under a wide range of reaction conditions and to chromatographic purification, as

evinced by the prevalence of silyl ether protecting groups in syntheses. When employed as a tether prior to carbon-silicon bond formation, alkoxyasilanes can also facilitate incorporation of the alkenylsilane handle in a regio and stereodefined manner, providing cyclic alkenylsiloxane products.²²⁵ To the best of our knowledge, the only preparative examples of fluoride-free alkoxyasilane couplings that have been reported are of benzoxasiloles **278**, by Hartwig in 2010,²²⁶ and an isolated example of (*E*)-ethoxysilylalkene **279** by Denmark in 2006²²² (Scheme 5.5). In both these instances, aryl coupling partners are employed and there appear to be no examples of fluoride-free alkoxyasilane coupling applied to the construction of polyenes.

Hartwig (2010):



Denmark (2006):

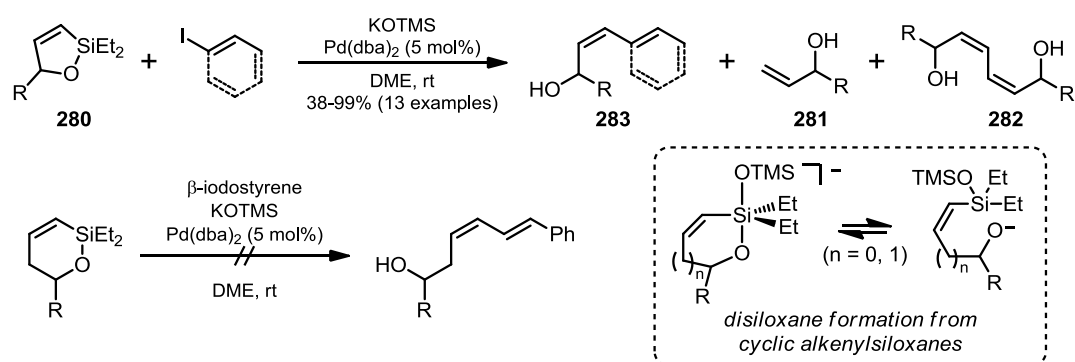


Scheme 5.5

Ongoing work in our group has been geared towards investigating the fluoride-free cross-coupling of cyclic alkenylsiloxanes **280** under silanolate activation. While the reaction has proven to be generally applicable to a wide variety of aryl and alkenyl coupling partners, and particularly robust in the case of aryl iodides and iodostyrenes, the use of less reactive alkenyl iodides can lead to the recovery of desilylated allylic alcohols **281** and homocoupled dienes **282** in addition to the desired polyene product **283** (Scheme 5.6).²²⁷ Importantly, six-membered cyclic alkenylsiloxanes are not

reactive under these conditions, presumably due to six-membered siloxacycles experiencing unfavourable bond compression around the silicon centre when forming pentacoordinate silicate intermediates following trimethylsilanolate attack (see inset, Scheme 5.6). Ring-opening trimethylsilanolate attack is thought to be the first step towards forming disiloxane intermediates *en route* to the reactive alkenylsilanolates.

Elbert and Anderson (unpublished results):

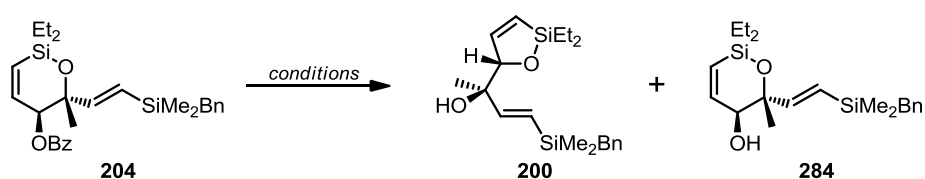


Scheme 5.6

5.1.2 *Bis*(alkenylsilane) building blocks towards incednam

In light of these results, we set out to determine conditions under which benzoyl deprotection of the *bis*(alkenylsilane) **204** would be accompanied by rearrangement of the six-membered alkenylsiloxane to its reactive five-membered regioisomer **200**. Treating the benzoate ester with an excess of alkoxide effected the desired transformations, affording the five-membered siloxane exclusively in a modest yield (Entry 1, Table 5.1). The yield of *bis*(alkenylsilane) **200** could be improved by employing milder conditions of potassium carbonate in methanol (Entry 2). Interestingly, other methods of benzoate ester deprotection such as ester reduction with DIBALH or formation of the phenylketone with methyl lithium allowed the isolation of six-membered siloxane **284**, in which the benzoyl group had been removed with little or no accompanying siloxacycle rearrangement (Entries 3 and 4). Rearrangement of the

cyclic alkenylsiloxane is thought to proceed *via* ring opening with an external nucleophile, such as methoxide, followed by ring closing by the newly revealed secondary alcohol. In the absence of a silaphilic nucleophile, ring opening does not occur and the six-membered siloxacycle is preserved. In the case where DIBALH was employed (Entry 3), limited exposure of the six-membered product **284** to methoxide generated from quenching excess DIBALH with methanol may have resulted in the formation of some five-membered product.



Entry	conditions	200 : 284 ^a	yield (%) ^b
1	NaOMe (4.0 equiv), MeOH, rt, 24 h	1 : 0	43
2	K ₂ CO ₃ (1.1 equiv), MeOH, rt, 24 h	1 : 0	73
3	DIBALH (2.2 equiv), toluene, −78 °C to rt, 1.5 h ^c	1 : 8	47
4	MeLi·LiBr (2.2 equiv), Et ₂ O, −78 to 0 °C, 1 h	0 : 1	71

^a Determined by ¹H NMR spectroscopic analysis of chromatographically purified products.

^b Isolated yields of **200** + **284**. ^c Quenched with MeOH at -78°C and allowed to warm to rt over 30 min.

Table 5.1

With a route to access the five-membered siloxane building block, we now had a small library of compounds to investigate the orthogonal Hiyama couplings of cyclic alkoxy silanes. We envisaged that each building block offered an opportunity to test a unique ordering of fluoride and silanolate-activated cross-couplings with a variety of coupling partner combinations (Figure 5.2). Based on Elbert's results from the silanolate-activated cross-couplings of five-membered cyclic alkenylsiloxanes,

bis(alkenylsilane) **200** might undergo an initial fluoride-free cross-coupling at the (*Z*)-alkenyl alkoxy silane position in the presence of the benzyldimethylsilyl group. In the second case, the *bis*(alkenylsilane) **204** contains a six-membered cyclic alkenylsiloxane and (*E*)-benzyldimethylsilyl alkene. The benzyldimethylsilane might preferentially cross-couple under *fluoride*-activated conditions, given its facile conversion to silanol.⁵¹ In addition, any ring opening *en route* to the activated pentavalent fluorosilicate at the cyclic alkoxy silane (**266**, Scheme 5.2) would be in competition with the reverse ring closing process, thereby disfavoured cross-coupling at that position. Finally, in the third case of 1-iodo-6-siloxydiene **136**, the iodoalkene may be coupled with a silanol partner under silanolate-activation in the presence of the six-membered cyclic alkenylsiloxane. Dimerisation of **136** would require a six-membered cyclic alkenylsiloxane to react in a silanolate-activated cross-coupling, and was thought to be disfavoured based on Elbert's earlier results.

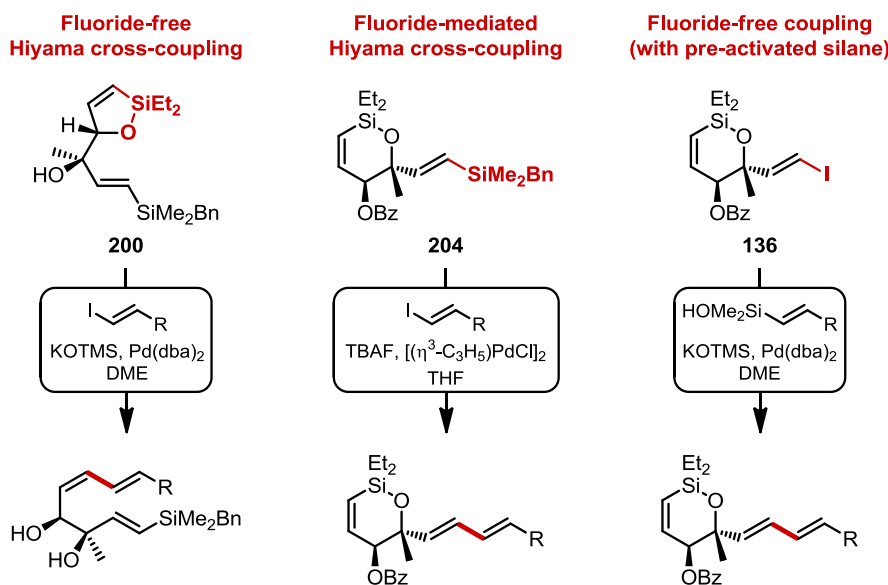
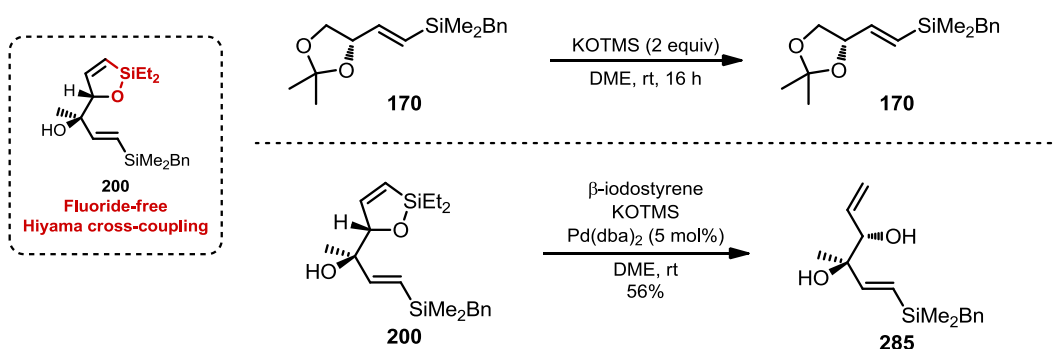


Figure 5.2

In an effort to understand the behaviour of each alkenylsilane (or iodide) group, each strategy was evaluated by treating the silane building blocks with ‘deconstructed

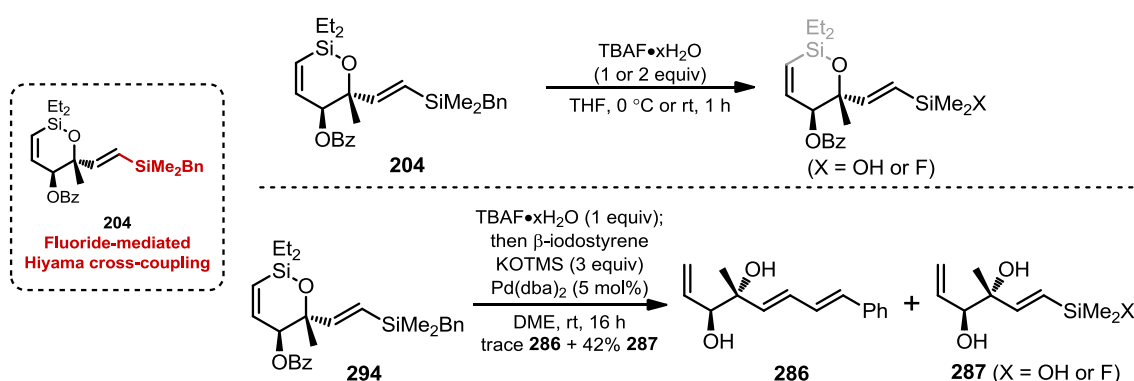
conditions' which consisted of the substrate and fluoride or silanolate activator only; and cross-coupling conditions, with the palladium catalyst and model iodide or silanol coupling partner present as well. In the first case, the stability of the benzyldimethylsilyl group to silanolate was first determined by stirring the simple (*E*)-alkenyl benzyldimethylsilane **170** with KOTMS overnight (Scheme 5.7). Pleasingly, the silane was recovered unchanged. Subjecting *bis*(alkenylsilane) **200** to the standard silanolate-activated cross-coupling conditions, however, led to recovery of the terminal alkene **285** in 56% yield. Alkenylsiloxane desilylation has been noted by Elbert in the case of poorly reactive alkenyl iodide coupling partners, and silanolate-promoted desilylation is believed to take place as a competitive background process to cross-coupling.²²⁷ The mechanism by which desilylation occurs under these dry and aprotic conditions remains unclear.



Scheme 5.7

For the second *bis*(alkenylsilane) candidate **204**, stirring with one or two equivalents of TBAF at 0 °C or at room temperature returned apparently identical mixtures when analysed by ^1H NMR spectroscopy (Scheme 5.8). Signals corresponding to the benzylic and aromatic proton environments of the benzylsilane were conspicuously absent, suggesting that conversion to silanol or a reactive Si-X species had occurred. Recovery of a diethylsilyl species suggested some desilylation of the alkenylsiloxane, which is an

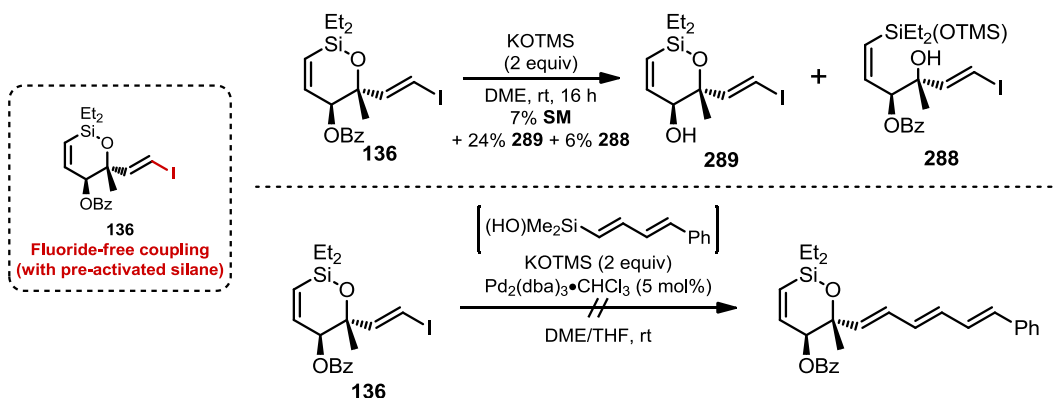
expected outcome in the absence of palladium catalyst and coupling partner. Based on these promising observations, a cross-coupling was attempted with β -iodostyrene by pretreating *bis*(alkenylsilane) **204** with one equivalent of TBAF to unmask the silanol, followed by the addition by of the palladium catalyst, coupling partner and KOTMS in DME. Although traces of the cross-coupled product **286** were recovered along with unreacted silanol **287** following chromatographic purification, we were disappointed to discover that these conditions promoted complete protodesilylation of the alkenylsiloxane. Intriguingly, all the recovered olefinic products bore a free allylic alcohol, suggesting that KOTMS-promoted benzoyl deprotection had occurred: while the reagent is commonly employed for the cleavage of methyl and ethyl esters, a paper by Lovrić and co-workers documents the ability of trimethylsilanolate salts to cleave isopropyl and allyl benzoates with high efficiency.²²⁸



Scheme 5.8

Our final strategy relied on the silanolate-activated cross-coupling of iodide **136** with a silanol partner. The stability of the six-membered siloxacycle to trimethylsilanolate was determined by stirring **136** with two equivalents of KOTMS in DME overnight (Scheme 5.9). Along with starting material and a small amount of ring-opened disiloxane **288**, the main component of the resulting mixture was benzoyl-deprotected

siloxacycle **289** in which the six-membered cyclic alkenylsiloxane had survived intact. Disappointingly, no product was formed when the reaction was carried out with a dienyl silanol and palladium catalyst; only silanol and trace amounts of the alkenyl iodide **136** were recovered at the end of the reaction. This attempt marked an end to our investigations of orthogonal organosilicon cross-couplings in the context of incednine: ongoing work in the group is directed towards uncovering and understanding the mode by which competing pathways occur, in the hope of devising methods to suppress these unproductive modes of reaction.



Scheme 5.9

5.2 Assembling the C2-C9 tetraene by Suzuki cross-coupling

The orthogonal cross-couplings of cyclic alkenylsiloxanes in the presence of another organosilicon group had proven to be unexpectedly complicated, with competing siloxane protodesilylation in the presence of both fluoride and silanolate activators presenting one of the key hurdles to successful couplings of the *bis*(alkenylsilanes). However, by shifting our focus to the cyclic alkenylsiloxane and enol ether building blocks with boronic ester coupling handles (**140** and **228**, Figure 5.3), we were able to continue the campaign to assemble incednam, this time by a Suzuki cross-coupling to construct the C5-C6 bond.

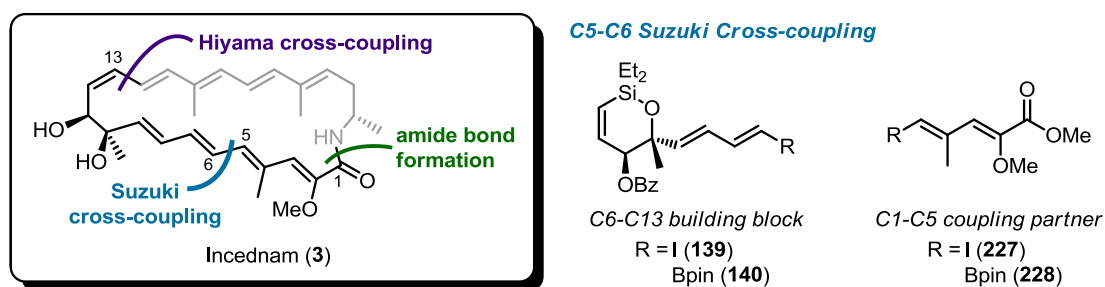


Figure 5.3

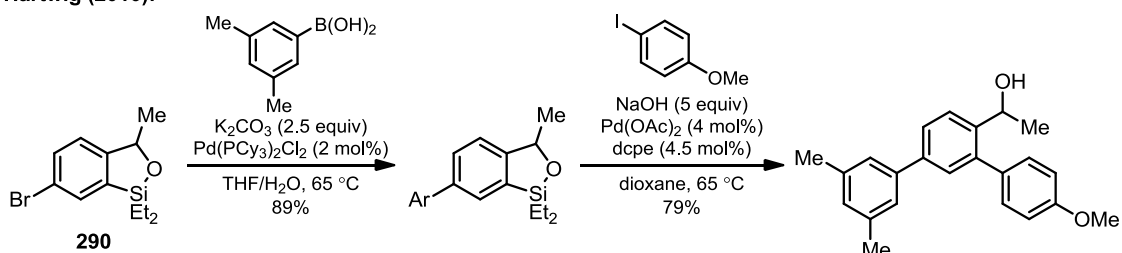
5.2.1 Modelling the C5-C6 construction

In comparison to the Hiyama cross-coupling, the literature is replete with examples of cross-couplings between alkenylboron reagents and alkenyl halides since the seminal work of Suzuki and co-workers three and a half decades ago.²²⁹ Early limitations of the alkenyl-alkenyl coupling included poor regioselectivity (resulting in head-to-tail coupling), protodeboronation of the alkylborane reagents, and palladium hydride-induced olefin isomerisation.²³⁰ Most of these problems have been remedied by the use of bulky phosphine ligands and strong bases,²³¹ and by replacing alkylboranes with boronic acid or ester reagents to avoid palladium hydride formation.²³² Combined with the dramatic coupling rate enhancement brought about by thallium hydroxide,²³³ these improvements have allowed the Suzuki coupling to be applied to the construction of key alkenyl-alkenyl bonds in a growing collection of complex polyene natural products which includes palytoxin,²³⁴ rutamycin²³⁵ and palmerolide.²³⁶

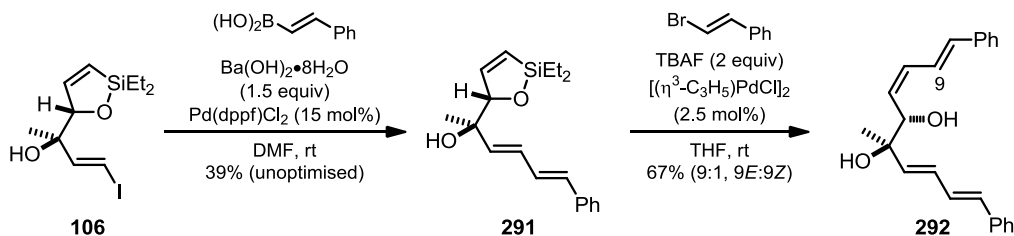
In this projected synthesis of incednam, we anticipated that the C2-C9 tetraene might be assembled by an alkenyl-alkenyl Suzuki cross-coupling between appropriate C1-C5 and C6-C13 coupling partners (**139** and **228**, or **140** and **227**, Figure 5.3). This would require an alkenyl boronic ester to be selectively activated in the presence of a cyclic alkenylsiloxane which, to the best of our knowledge, finds its closest precedent in an isolated report of aryl-aryl cross-coupling between bromo-benzoxasilole **290** and 3,5-

dimethylphenylboronic acid (Scheme 5.10).²²⁶ In preliminary investigations, we were delighted to find that alkenyl iodide **106**, when treated with barium hydroxide in the presence of *trans*- β -styreneboronic acid and catalytic amounts of palladium, afforded the coupled triene **291** in a modest unoptimised yield. The Hiyama product was not detected in the crude reaction mixture. At this point, fluoride-activation of the siloxyl group in the coupling product **291** allowed a Hiyama cross-coupling to be performed with β -bromostyrene, to furnish the (*E,E,Z,E*)-tetraene **292**. The tetraene was obtained as a 9:1 mixture of 9*E*:9*Z* isomers, which reflected the *E/Z* composition of the bromostyrene reagent.

Hartwig (2010):



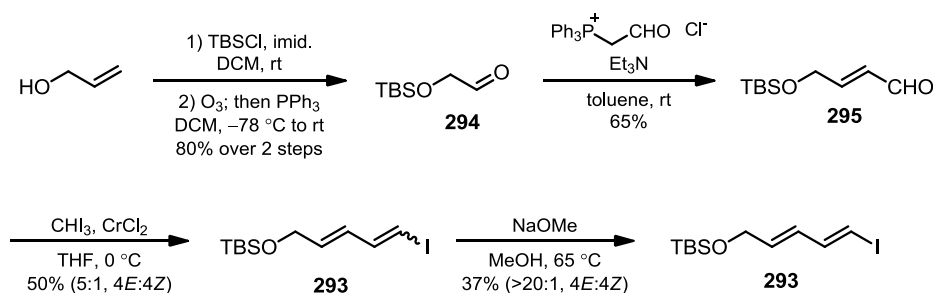
This work:



Scheme 5.10

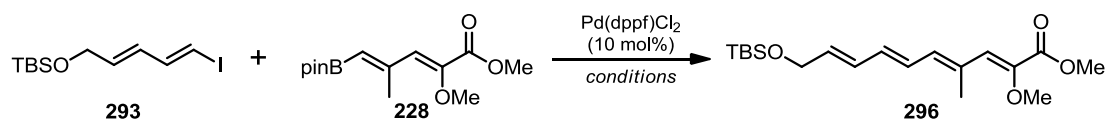
Buoyed by these positive results, a model dienyl iodide partner was prepared to investigate tetraene construction *via* dienyl-dienyl Suzuki cross-coupling with the C1-C5 boronic ester coupling partner **228**. The preparation of iododiene **293** commenced with allyl alcohol, which upon TBS protection and oxidative cleavage was converted to aldehyde **294** in an excellent two-step yield (Scheme 5.11). Wittig olefination with the

α -phosphonium aldehyde reagent smoothly afforded α,β -unsaturated aldehyde **295**, which was transformed by a Takai olefination into iododiene **293** as a 5:1 mixture of inseparable (4*E*) and (4*Z*)-isomers. The unwanted (4*Z*)-isomer was converted to the corresponding enyne by refluxing the mixture of stereoisomers with sodium methoxide in methanol, allowing the all-(*E*) isomer to be separated by column chromatography.



Scheme 5.11

With iododiene **293** in hand, the dienyl-dienyl Suzuki cross-coupling with the C1-C5 boronic ester partner **228** was first attempted with barium hydroxide and Pd(dppf)Cl₂. This system has been noted for its efficiency in coupling hindered boronic acid and halide partners (Entry 1, Table 5.2).²³⁷⁻²³⁸ While we were pleased to note that the reaction proceeded at room temperature (75% conversion over 5 hours), the low yield of tetraene **296** prompted an evaluation of other base systems. A suitable base should not only promote the coupling with minimal heating, so as to avoid degradation of the tetraene product – it also had to be compatible with the methyl ester found in the enol ether coupling partner **228**. So, while caesium carbonate in a biphasic solvent system required heating to 55 °C before consumption of starting material was observed, and even then returned a complex mixture of products (Entry 2),²³⁹ we were pleased to find that potassium phosphate performed the coupling under gentle warming and returned tetraene **296** in a good yield (71% based on recovered starting material) with the methyl ester intact (Entry 3).²⁴⁰



Entry	conditions ^a	time (h)	yield (%) ^b (conversion (%)) ^c
1	$\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$ (1.5 equiv), DMF, rt	5	25 (75)
2	Cs_2CO_3 (6.0 equiv), THF/ H_2O , rt to 55 °C	16	c.m. ^d (100)
3	K_3PO_4 (6.0 equiv), THF/ H_2O , rt to 40 °C	19	59 (83)
4 ^e	Tl_2CO_3 (2.0 equiv), THF/ H_2O , rt	3.5	44 (74)

^a Reactions were conducted with 1.0 equiv of iodide **293** and 1.2 equiv of boronic ester **228** unless otherwise noted. ^b Isolated yields. ^c Based on recovered mass of iodide **293**. ^d Complex mixture. ^e 1.1 equiv of boronic ester **228** was employed.

Table 5.2

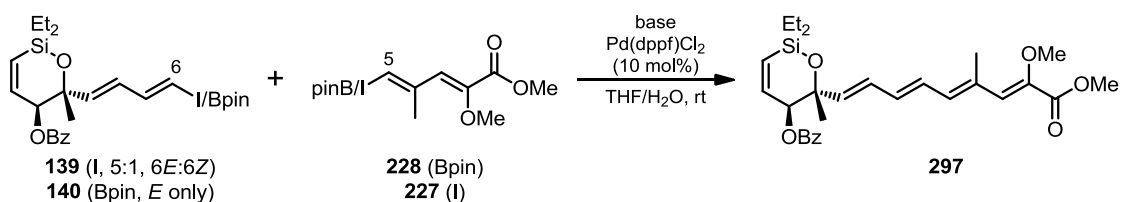
The use of thallium(I) salts, in keeping with Kishi's observations of accelerated coupling rates, allowed the reaction to proceed at room temperature, effecting 74% conversion in just 3.5 hours (Entry 4, Table 5.2). In this system, thallium carbonate offers a distinct advantage over thallium hydroxide, found in Kishi's original report, as it tolerates the presence of esters on either coupling partner.^{236,241} The beneficial effect thallium(I) salts exert on the rate of alkenyl-alkenyl couplings is attributed to the formation of insoluble thallium(I) iodide, observed as a yellowish-green precipitate that accumulates over the course of the reaction. In stripping post-oxidative addition palladium(II) complexes of the halide ligand, a free coordination site is created for hydroxide attack to form a palladium(II) hydroxide species, which is thought to facilitate transmetalation with organoboron reagents.²³³

5.2.2 Constructing the C5-C6 bond

To our delight, applying the best conditions from our brief screen of base systems (potassium phosphate and thallium carbonate) to the C6-C13 iodide partner **139** and C1-C5 boronic ester **228** allowed us to prepare the C1-C13 pentaene segment of incednam (Entries 1 and 2, Table 5.3). In particular, the recovery of 44% of cyclic alkenylsiloxane **139** when thallium carbonate was employed suggested that a clean and highly efficient transformation could be achieved in this challenging dieny-dienyl coupling. Although we hoped to improve the utility of this step by replacing toxic thallium(I) salts with another halide-precipitating base, silver carbonate²⁴² provided an inferior yield of **297** after the iodide coupling partner had been completely consumed in 4 hours at room temperature (Entry 3). This result suggests that thallium may be responsible for more than halide removal, and the possibility of the alkenyl group undergoing transmetalation from boron to thallium to form an organothallium species which participates in the catalytic cycle should not be ruled out.^{230,243} Despite the excellent yield of pentane **297** with this combination of coupling partners, this approach was limited by the stereochemical purity of the iodide partner **139**, which we were only able to prepare as a 5:1 mixture of 6*E*:6*Z* isomers.

Therefore, we also examined the effects of exchanging the coupling handles of the C1-C5 and C6-C13 fragments by performing the reaction with the C6-C13 boronic acid **140** and C1-C5 iodide partner **227**. Although this combination of halide and boronic ester components were less reactive under the potassium phosphate conditions (Entry 4), the thallium and silver carbonate reactions showed improved conversions and yields of pentene **297**, albeit with poorer recovery of unreacted starting material (Entries 5 and 6). Performing the coupling with this set of partners had the advantage of providing the C1-C13 fragment of incednam as a single stereoisomer, as opposed to a mixture of

6*E*:6*Z* isomers as was the case when it was prepared from the C6-C13 iodide **139**. For this reason, the coupling of boronic ester **140** and iodide **227** is our preferred method of preparing the C1-C13 incednam fragment.



Entry	C6-C13 partner	C1-C5 partner	base (equiv)	time (h)	yield (%) ^a (conversion (%)) ^b
1	139	228	K ₃ PO ₄ (6.0)	16	34 (100)
2	139	228	Tl ₂ CO ₃ (2.0)	4	53 (56)
3	139	228	Ag ₂ CO ₃ (2.0)	4	19 (100)
4	140	227	K ₃ PO ₄ (6.0)	16	21 (61)
5	140	227	Tl ₂ CO ₃ (2.0)	5	66 (93)
6	140	227	Ag ₂ CO ₃ (2.0)	4	40 (100) ^c

^a Isolated yields. ^b Based on isolated recovered mass of iodide **139** or **227**. ^c The remnant of iodide **227** was recovered as the tetraene dimer.

Table 5.3

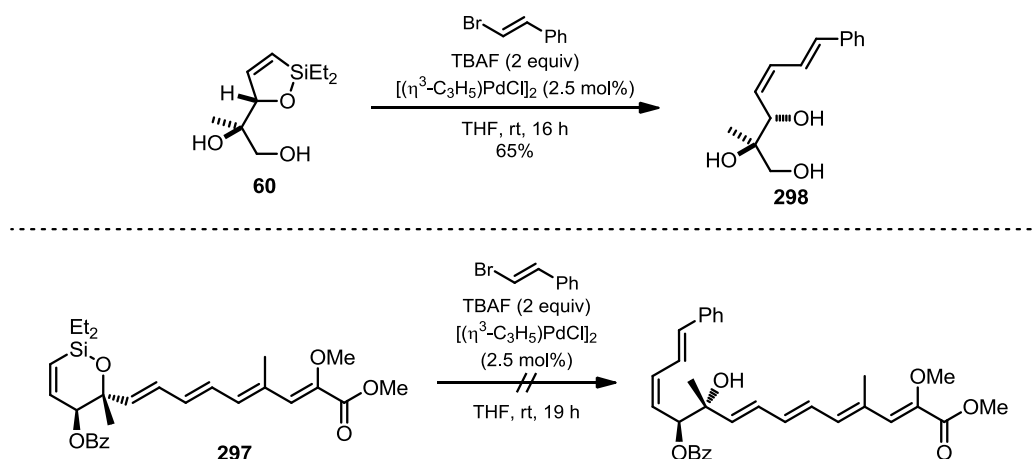
From a mechanistic point of view, these (admittedly somewhat esoteric) results appear to contradict the understanding that thallium salts promote cross-coupling by accelerating transmetalation. As both combinations of coupling partners provide identical products, the rate of reductive elimination from the *bis*-alkenyl palladium(II) complex following transmetalation should be identical. This would suggest that where potassium phosphate is used as the base, oxidative addition is the rate limiting step as a more hindered iodide slows down the coupling rate (Entries 1 and 4). Conversely, in the

thallium carbonate promoted coupling, transmetalation appears to be rate limiting as a less hindered boronic ester allows the reaction to proceed more rapidly (Entries 2 and 5). To further complicate matters, performing the coupling with boronic ester **140** and iodide **227** in the presence of silver carbonate led to the recovery of substantial amounts of a tetraene dimer resulting from homocoupling of iodide **227** (Entry 6). It has been difficult to reconcile these results with the current understanding of the catalytic cycle involved in Suzuki cross-coupling reactions.

5.3 Assembling the C12-C21 pentaene and beyond

5.3.1 Modelling C13-C14 construction by Hiyama cross-coupling

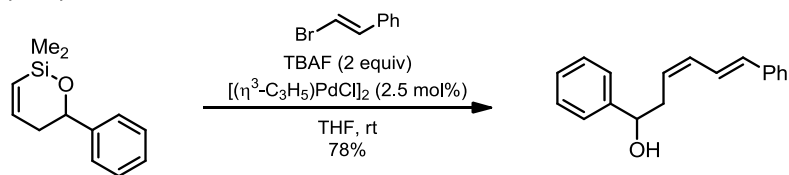
Having successfully constructed the first of three key bonds towards assembling incednam, we next set out to investigate the construction of the C13-C14 bond by Hiyama coupling of the C1-C13 fragment with the C14-C23 amino tetraene partner. Where silanolate-activated cross-couplings of five-membered cyclic alkenylsiloxanes had resulted in substantial protodesilylation, *fluoride*-activation of two model cyclic alkenylsiloxanes (**291** and **60**, Scheme 5.10 and Scheme 5.12) in the palladium-catalysed coupling with β -bromostyrene proceeded smoothly and returned the (*Z,E*) products **292** and **298** with a high degree of stereochemical fidelity. The six-membered cyclic alkenylsiloxane **297** did not afford any of the desired product when treated under identical conditions (Scheme 5.12); a mixture of starting material and desilylation product was recovered along with β -bromostyrene.



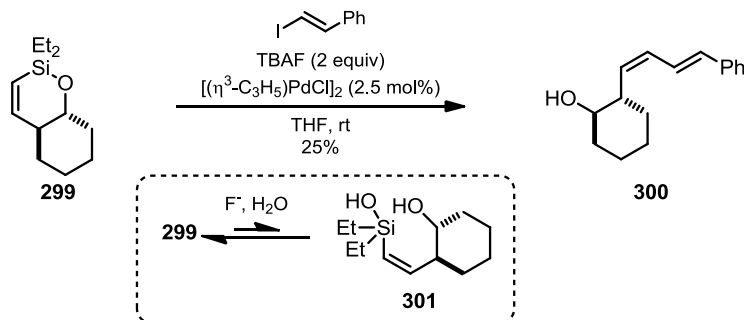
Scheme 5.12

At first glance, this is surprising as the fluoride-promoted Hiyama cross-coupling of a six-membered cyclic siloxane with β -bromostyrene has been reported by Denmark and co-workers (Scheme 5.13).⁴¹ Similar observations have been made by Elbert in her investigations of the fluoride-activated Hiyama reaction. However, Elbert has also observed that increasing the degree of substitution on the siloxacycle, such as in the case of **299**, is detrimental to the coupling reaction, and significantly lowers the yield of (*Z,E*)-diene **300**. The poorer reactivity of **299** may be explained by the alkenylsiloxane being located in a *trans*-decalin-like structure. The structural rigidity enforced by the bicyclic nature of the substrate may disfavour the formation of silanol **301** by favouring the reverse process of ring closing to the cyclic siloxane (see inset in Scheme 5.13). Silanol formation, in the mechanism proposed by Denmark, necessarily precedes the formation of an activated pentacoordinate silicate species which participates in the catalytic cycle.

Denmark (2001):

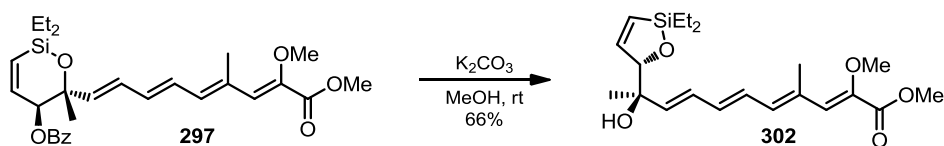


Elbert and Anderson (unpublished):



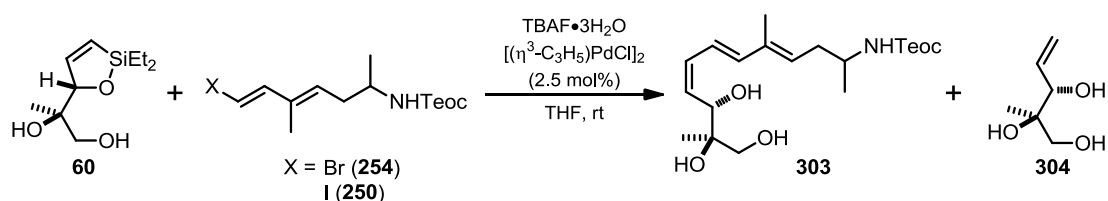
Scheme 5.13

The same argument could be applied to the heavily substituted C1-C13 fragment (**297**, Scheme 5.14), where the Thorpe-Ingold effect created by the C10 substituents favours the ring-closed six-membered siloxacycle over acyclic silanol, thus impeding cross-coupling. However, this limitation of the six-membered siloxacycle could in theory be addressed by performing benzoate deprotection/rearrangement to a five-membered siloxacycle, which we have already demonstrated undergoes cross-coupling with a model styrenyl coupling partner. We were therefore pleased to find that treating pentaene **297** with basic methanol at room temperature cleaved the benzoyl ester and promoted *in situ* rearrangement to **302** in good yields, in the presence of a conjugated tetraenyl enol ether and methyl ester.



Scheme 5.14

With some understanding as to the nature of the siloxane coupling partner, the behaviour of the C14-C23 amino tetraene was considered next. Here, the truncated diene model systems employed in the synthesis of the C14-C13 tetraene proved useful in investigating the cross-coupling of a polyene partner with a simple alkenylsiloxane, as we were able to study the reaction outcomes with somewhat more stable triene products. Bromodiene **254**, when subjected to the standard fluoride-activated conditions, was coupled with racemic cyclic alkenylsiloxane **60** to afford the (*Z,E,E*)-triene **303** in a low yield as a mixture of diastereomers (Entry 1, Table 5.4). The remainder of the recovered material consisted of unreacted bromodiene **254** and desilylation product **304**. Increasing the amount of TBAF from 2 to 3 equivalents, which it was hoped might accelerate cross-coupling over desilylation, had the opposite effect: more than twice the amount of desilylated product **304** was recovered (Entry 2).



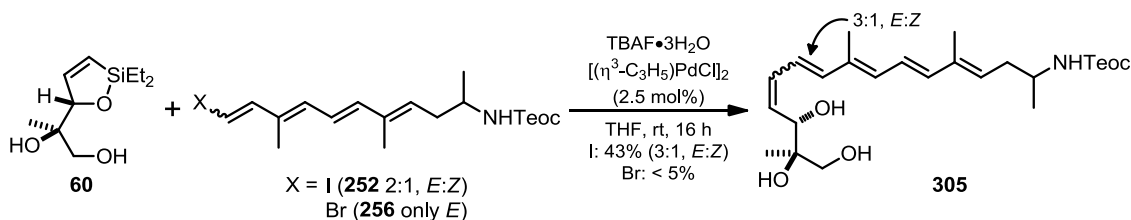
Entry	X	TBAF equiv.	time (h)	yield, 303 (%) ^a (conversion (%)) ^b	yield, 304 (%) ^a
1	Br	2.0	16	21 (100)	10
2	Br	3.0	16	25 (100)	22
3	Br	2.0 ^c	72	15 (51)	< 5
4	I	2.0	24	57 (67)	0

^a Isolated yields. **303** was isolated as an inseparable mixture of diastereomers. ^b Based on the mass of recovered cyclic alkenylsiloxane **60**. ^c 10 equiv. of H₂O and 5 mol% of [(η³-C₃H₅)PdCl]₂ were employed.

Table 5.4

Denmark and co-workers have noted that the hydration level of TBAF can have a dramatic effect on the coupling of sterically hindered partners; higher levels of hydration ostensibly moderate fluoride basicity, thus avoiding catalyst deactivation and substrate decomposition.²⁴⁴ In our hands, these conditions did indeed suppress protodesilylation, although at the cost of overall reactivity as low conversions were observed even after conducting the reaction with higher catalyst loadings and over extended times (Entry 3, Table 5.4). The more reactive iodide coupling partner **250** overcame the problems of protodesilylation and poor reactivity, and was efficiently converted to triene **303** in an excellent yield of 57%, or 85% based on recovered starting material, with no desilylation (Entry 4).

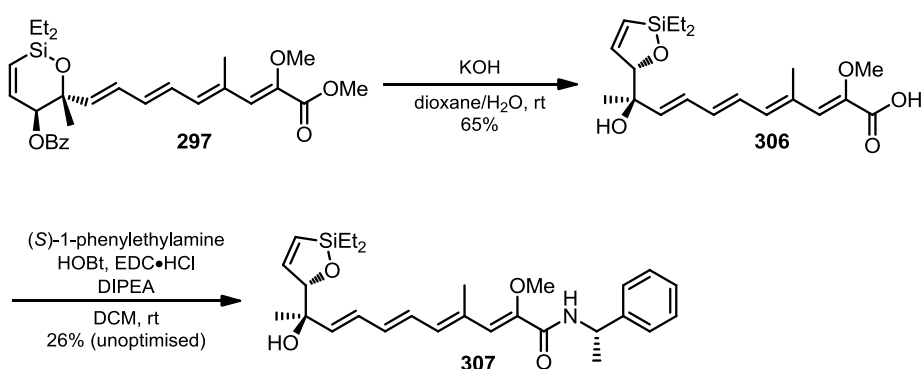
The difference in reactivity between the bromo and iodoalkene coupling partners was magnified when these conditions were translated to the C14-C23 tetraene system (Scheme 5.15): Ironically, iodotetraene **252**, which was available only as a mixture of *E* and *Z* isomers, gave a satisfactory yield of pentaene **305**, with the all-(*E*)-isomer showing a slight preference for coupling over the (*Z*)-alkenyl iodide. Bromotetraene **256**, which could be accessed exclusively as the all-(*E*)-isomer, provided only trace amounts of pentaene **305** along with significant amounts of the desilylation product **304**. This result has led us to revise our strategy to assemble the C12-C21 pentaene, which is briefly discussed in the concluding chapter.



Scheme 5.15

5.3.2 Beyond the C1-C13 pentaenoic fragment

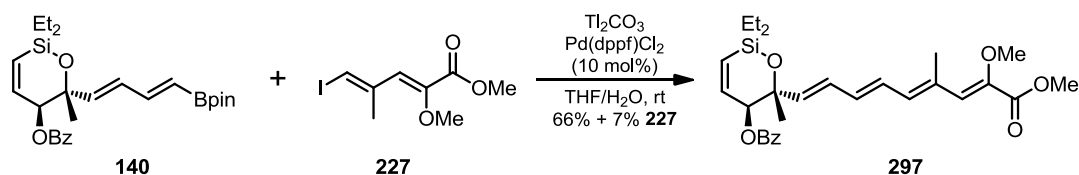
Although our efforts to construct the C12-C21 pentaene by a Hiyama cross-coupling between a cyclic alkenylsiloxane and tetraene partner had thus far been thwarted, we were keen to evaluate the final step of the synthesis by modelling the amide bond formation with the C1-C13 segment. To this end, the saponification of methyl ester **297** was carried out with potassium hydroxide to obtain pentaenoic acid **306** (Scheme 5.16).²⁴⁵ This was conveniently accompanied by benzoate deprotection and *in situ* rearrangement to the five-membered cyclic alkenylsiloxane, which also allows us to consider reversing the order of the final Hiyama coupling/amide formation sequence. Preliminary attempts to perform an amide coupling with a model α -methyl substituted amine suggest that a coupling with α -methoxyacrylic acid **306** can be accomplished by standard carbodiimide coupling reagents with HOBt as an additive.²⁴⁶ Given the plethora of readily available reagents to perform amide bond formations,²⁴⁷ including the triazine salt DMTMM that Toshima and co-workers applied to their macrolactamisation of incednam,²⁷ we are confident that further attempts will allow the amide bond formation to be efficiently performed.



Scheme 5.16

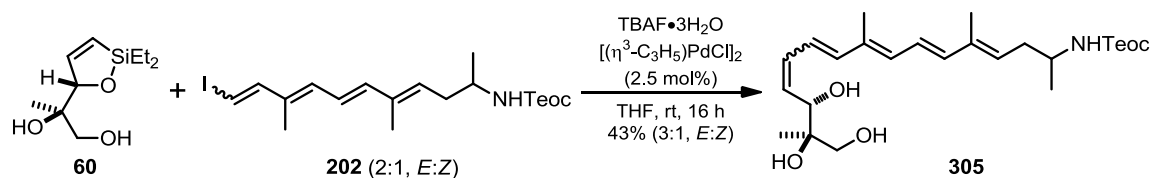
5.4 Conclusion

The assembly of the C1-C13 incednam fragment by orthogonal Hiyama cross-coupling reactions with *bis*(alkenylsilane) intermediates was investigated using a combination of silanolate and fluoride-activated conditions. Competing protodesilylation of the cyclic alkenylsiloxane under fluoride and silanolate activation currently restricts its application to the synthesis of incednam, and ongoing work in the group is geared towards identifying a means of suppressing these non-productive side reactions in order to realise this strategy. However, by selectively activating an alkenylboronic ester in the presence of a cyclic alkenylsiloxane, the dieny-dienyl Suzuki coupling of boronic ester **140** and iodide **227** was successfully executed to provide the C1-C13 pentaenoate **297**, a key intermediate towards assembling incednam.



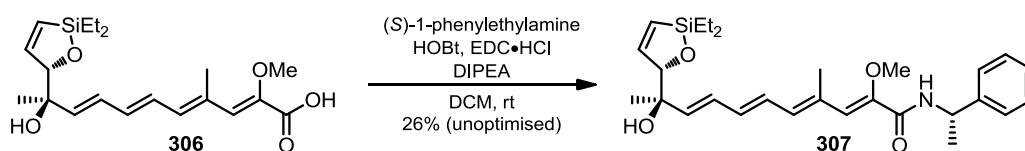
Scheme 5.17

The remaining cross-coupling to construct the C13-C14 bond has been modelled between the C14-C23 tetraene building blocks and a simpler cyclic alkenylsiloxane **60**. Frustratingly, the iodide coupling partner which we were able to prepare only as a mixture of stereoisomers underwent facile coupling, while the stereochemically homogenous bromide partner provided only trace amounts of pentaene product. This has led to a revised approach to assembling the C12-C21 pentaene which avoids the use of configurationally labile polyenyl iodide intermediates, which will be discussed in the following chapter.



Scheme 5.18

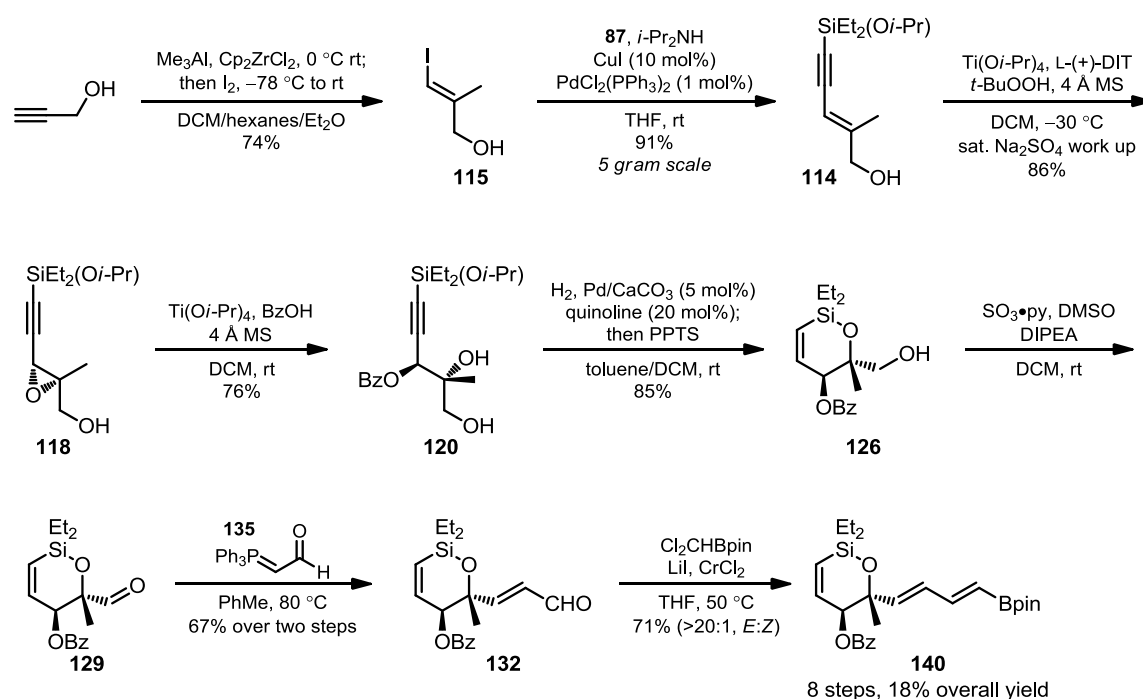
Finally, methyl ester deprotection with concomitant benzoyl removal yielded the C1-C13 pentaenoic acid **306**. The behaviour of this advanced intermediate under amide bond forming conditions was modelled with (*S*)-1-phenylethylamine, and the modest yield of amide **307** isolated from unoptimised reaction conditions suggests this would be a viable step for the endgame of our incednam synthesis.



Scheme 5.19

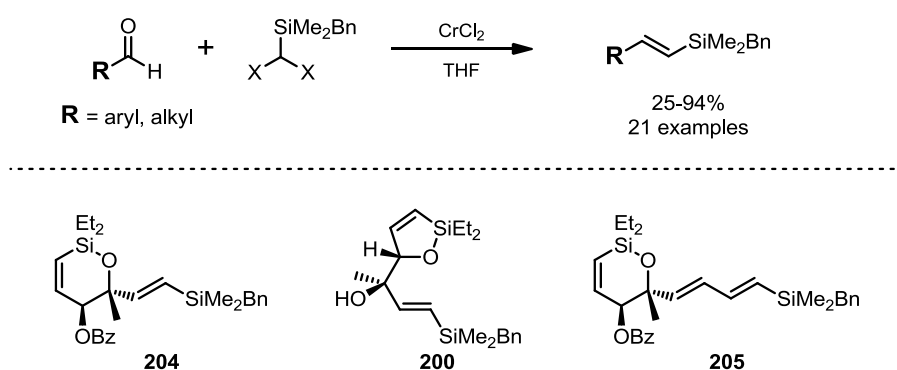
6 Conclusions and Future Work

A new strategy to construct cyclic alkenylsiloxanes by the controlled hydrogenation of alkynylsiloxanes has been used to prepare the key C9-C13 building block of incednam. The carbon framework of alkynylsiloxane **120** was assembled by Sonogashira cross-coupling and the stereogenic hydroxyl centres introduced by a Sharpless asymmetric epoxidation/regioselective opening sequence. Hydrogenation over quinoline-poisoned Pd/CaCO₃ followed by acid-promoted cyclisation afforded cyclic alkenylsiloxane **126** with a primary alcohol conveniently available for further elaboration. Finally, installing a dienyl boronic ester in three steps – an oxidation, a Wittig homologation and Takai borylolation – transforms **126** into the C6-C13 incednine building block **140** in eight linear steps from propargyl alcohol with an overall yield of 18% (Scheme 6.1).



Scheme 6.1

Building on the seminal work of Takai and co-workers, we have developed a new reagent to prepare functionalised (*E*)-alkenylsilanes by direct silylolefination of aldehydes. The reaction has been applied to a range of aryl and alkyl aldehydes, and tolerates a wide variety of functional groups. Substrates with α -stereogenic centres can be olefinated with little epimerisation of the sensitive stereocentre. A series of orthogonal silicon/boron cross couplings of an aryl boronic ester substrate demonstrated the utility of these products in synthesis. This work has been published in *Organic Letters*,²⁴⁸ and the methodology has been applied to a number of cyclic alkenylsiloxane intermediates to prepare the *bis*(silane) incednine building blocks **204**, **200** and **205** (Scheme 6.2).

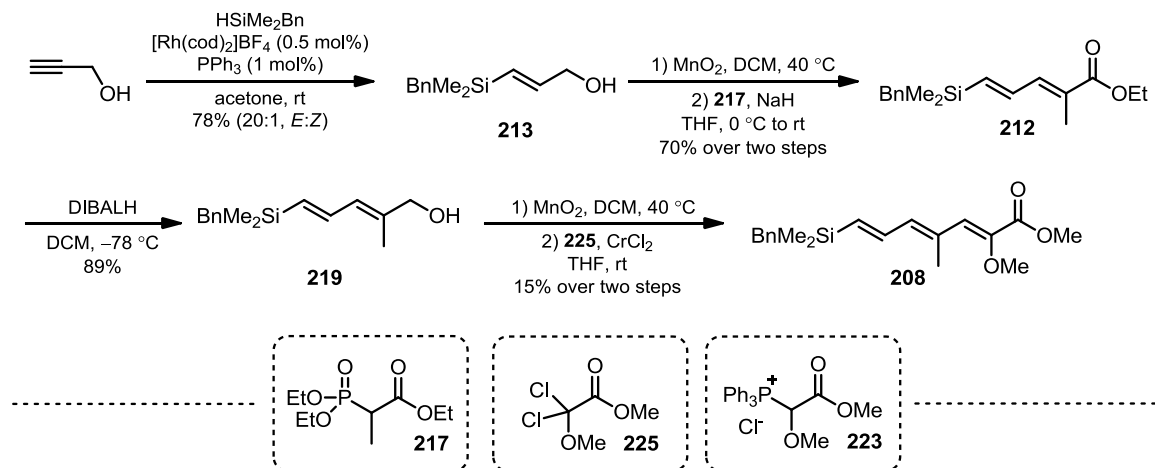


Scheme 6.2

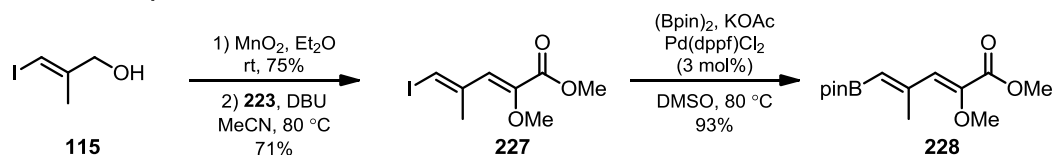
Returning to the synthesis of incednine, the C1-C7 and C1-C5 enol ether building blocks were prepared through a combination of phosphorous-based and metal-mediated olefination strategies. The C1-C7 trienyl silane **208** was prepared in a six-step route from propargyl alcohol which features a hydrosilylation, HWE reaction and chromium-mediated olefination to construct each of the olefin units. A low yielding final step led us to consider a second disconnection which would require a shorter C1-C5 enol ether coupling partner. This was conveniently prepared with an iodide cross coupling handle

(**227**) from the common vinyl iodide intermediate **115** in two steps, or with a boronic ester (**228**) handle in three steps *via* Miyaura borylation (Scheme 6.3).

C1-C7 Enol ether partner:

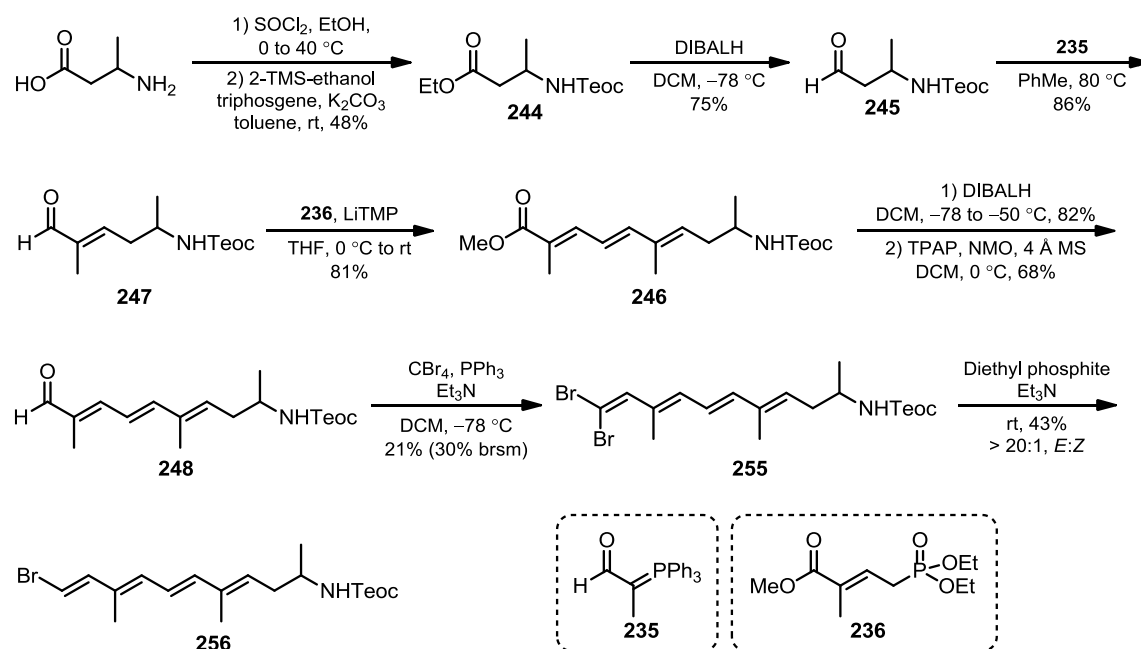


C1-C5 Enol ether partner:



Scheme 6.3

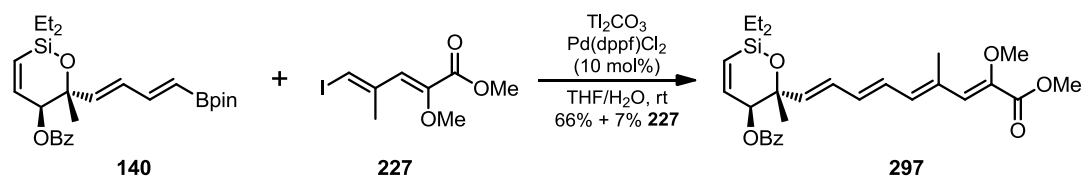
The final incednam building block, the C14-C23 amino tetraene, was prepared as a racemate in nine steps from 3-aminobutanoic acid. The route features a two-carbon Wittig homologation followed by a vinylogous HWE olefination with β,γ -unsaturated phosphonate reagent **236** that introduces three stereodefined olefin units in two steps without the need for oxidation state manipulations. After struggling to stereoselectively install the final (*E*)-iodo olefin by either a Takai olefination or a Colvin rearrangement/Schwartz hydrozirconation sequence, we were able to prepare the bromo tetraene **256** from aldehyde **248** *via* Ramirez olefination followed by a stereoselective Hirao monodebromation. We have also demonstrated that enantioenriched C14-C23 amine can be prepared from L-alanine methyl ester following conversion to aldehyde (*S*)-**245** in three steps (Scheme 6.4).



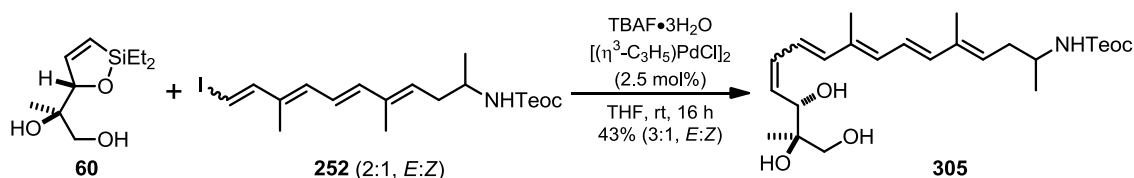
Scheme 6.4

The C1-C5 enol ether and C6-C13 cyclic alkenylsiloxane building blocks **227** and **140** were connected by a challenging dienyl-dienyl Suzuki cross-coupling to construct the C1-C13 pentaenoic ester **297**. A screen of bases revealed that good conversion to product could be attained at room temperature when Ti_2CO_3 was employed in the coupling. We have modelled the Hiyama cross-coupling to construct the C13-C14 bond between a simple cyclic alkenylsiloxane **60** and the C14-C23 amino tetraene coupling partners. Ironically, the iodide coupling partner, which undergoes facile isomerisation to a mixture of (*E*) and (*Z*)-isomers, afforded the coupled product **305** in a modest yield while bromotetraene **256** provided only traces of the desired pentaene. Finally, modelling amide bond formation with the C1-C13 pentaenoic acid fragment **306** and (*S*)-1-phenylethylamine returned the α -methoxy pentaenyl amide **306** in modest yields, suggesting that further optimisation should allow incednam to be prepared by this endgame approach (Scheme 6.5).

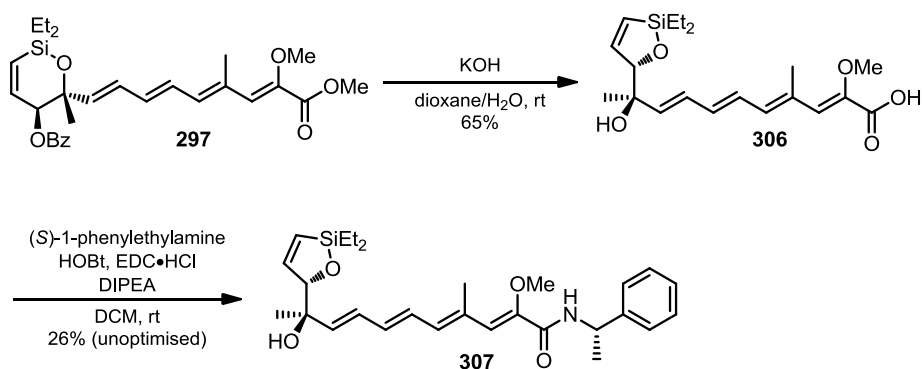
C5-C6 Suzuki cross coupling:
the C1-C13 incednine fragment



C13-C14 Hiyama cross coupling:

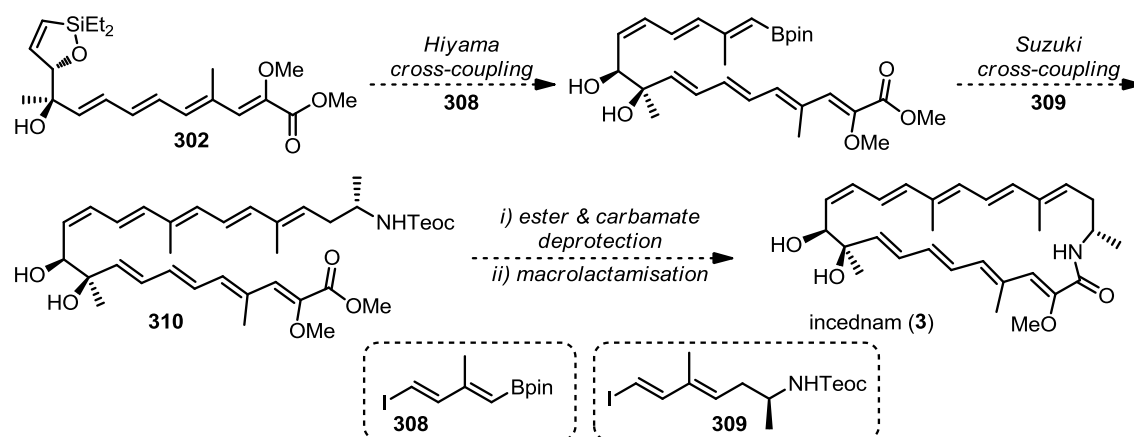


Amide bond formation:



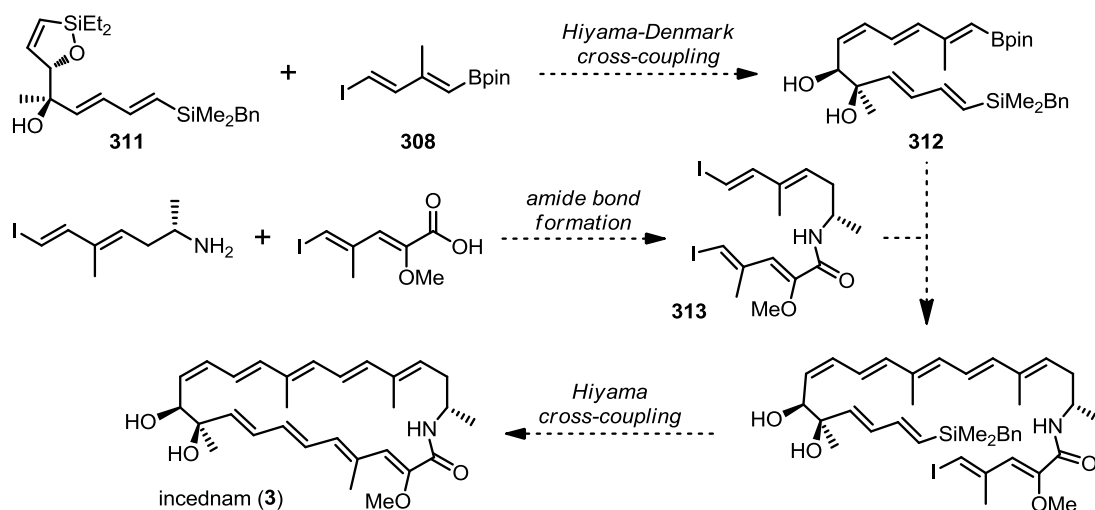
Scheme 6.5

In light of the difficulties we experienced in manipulating the C14-C23 iodo tetraene coupling partner, a modular assembly of the C12-C21 pentaene *via* sequential Hiyama and Suzuki cross-couplings with the C14-C17 and C18-C23 iododiene units **308** and **309** is proposed (Scheme 6.6). Ester and carbamate deprotection of the acyclic product **310** followed by macrolactamisation of the resulting amino acid provides a feasible route to complete our synthesis of incednam (Scheme 6.6).



Scheme 6.6

Looking forward, we hope to implement the orthogonal silicon/silicon cross-coupling discussed in Chapter 5 with *bis*(silylalkene) **311**. The most ambitious strategy entails a silanolate-promoted coupling of the *bis*(silylalkene) with iododiene **308** to first assemble the C6-C15 segment of incednam. Pentaene **312** may participate in a chemoselective Suzuki cross-coupling with *bis*(iodoalkene) **313** – we anticipate selective C17-C18 bond formation to occur at the less hindered disubstituted iodide in the presence of a trisubstituted iodide. Finally, ring-closing *via* fluoride-promoted cross-coupling between the benzyldimethylsilyl alkene and iodoalkene yields incednam.



Scheme 6.7

7 Experimental

7.1 General Experimental

Solvents and reagents: Solvents and commercially available reagents were dried and purified before use where appropriate using standard procedures. Tetrahydrofuran (THF), diethyl ether (ether), dichloromethane (DCM), toluene and methanol (MeOH) 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 4 Å molecular sieves and under N_2 . Petrol refers to the fraction of light petroleum ether which boils in the range 40-60 °C.

Reactions: For reactions requiring anhydrous conditions, experiments were carried out in oven-dried glassware. Unless otherwise stated, all reactions were carried out under argon.

Chromatography: Thin layer chromatography was performed using Merck DC Kieselgel 60 F_{254} plates. Product spots were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) then stained and heated using vanillin, potassium manganate or ammonium molybdenate as appropriate. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was carried out on Macherey-Nagel Kieselgel 60M (230 – 400 mesh) under positive pressure, and the solvent system used recorded in parentheses.

Optical rotation: Optical rotations were recorded Perkin-Elmer 341 polarimeter using a 1 dm path length cell. Specific rotations ($[\alpha]_{\text{D}}^{20}$) are given in $^{\circ}\text{dm}^2\text{g}^{-1}$. Concentration (c) is quoted in $\text{g}/100\text{ cm}^3$.

Enantiomeric excess: Enantiomeric excess (ee) was determined by HPLC on a Agilent 1200 series running in normal phase under UV (210-254 nm) detection using a ZORBAX RX-SIL (5 μm , 150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out on a DAICEL CHIRALPAK-IA, IB or IC (5 μm , 250 mm x 4.6 mm ID).

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

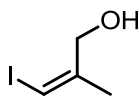
NMR spectra: Proton (^1H) and carbon (^{13}C) spectra were recorded on a Bruker DPX200 (200/50 MHz), Bruker DQX400 (400/100 MHz), Bruker DRX500 (500/125 MHz) or a Bruker AVANCE III 500 (500/125 MHz). Data are presented in the order: chemical shift, integration, multiplicity (br, broad; s, singlet, d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; qu, quintet, sept, septet; m, multiplet), coupling constant and proton assignment. Chemical shifts (δ_{H} or δ_{C}) are quoted in ppm downfield of SiMe_4 with residual solvent as the internal standard. Coupling constants (J) are given in Hz and are rounded to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, analysis of 2D spectra (COSY, HSQC and HMBC) or by analogy to fully interpreted spectra of structurally related compounds.

Mass spectra: High resolution mass spectra (HRMS) were recorded using a Bruker Daltonics microTOF spectrometer by Robin Procter at the Chemistry Research laboratory. High resolution values are calculated to four decimal places from the molecular formula and all obtained values are within a tolerance of 5 ppm.

Elemental analysis: Elemental analysis (EA) was carried out externally by Stephen Boyer at the London Metropolitan University.

7.2 Syntheses of cyclic alkenylsiloxane building blocks

(Z)-3-Iodo-2-methylprop-2-en-1-ol (86)

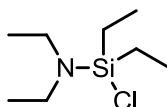


To a suspension of copper(I) iodide (6.78 g, 35.6 mmol, 1.0 eq) in ether (100 mL) at -5°C was added propargyl alcohol (2.1 mL, 35.6 mmol, 1.0 eq) and methylmagnesium bromide in ether (3.0 M, 25 mL, 74.8 mmol, 2.1 eq). The yellow solution was stirred as it warmed to room temperature over 2 h forming a black solution. Iodine monochloride (1.78 mL, 35.6 mmol, 1.0 eq) was added at -5°C , and the mixture stirred as it warmed to room temperature overnight. The mixture was quenched with saturated NH_4Cl at 0°C and filtered through Celite[®]. The filtrate was washed with H_2O and the aqueous layer extracted twice with ether. The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo* as a brown oil. The mixture was purified by flash chromatography (0 $\rightarrow$ 40% ether / petrol) to afford the title compound as a brown oil (3.17 g, 45%).

R_f 0.30 (33% ether / petrol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.99 (1H, s, CH), 4.26 (2H, s, CH_2), 1.99 (3H, s, CH_3).

The spectroscopic data were found to be in agreement with that reported by Hatakeyama and co-workers.⁸⁰

Diethyl(diethylamino)chlorosilane (S1)



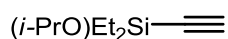
To a solution of dichlorodiethylsilane (20 mL, 133.6 mmol, 1.0 eq) and triethylamine (20.6 mL, 146.7 mmol, 1.1 eq) in THF (20 mL) at 0°C was added a solution of diethylamine (13.8 mL, 133.6 mmol, 1.0 eq) in THF (6 mL) over 2 h. The resulting beige suspension was warmed to room temperature overnight with vigorous stirring maintained. The mixture was filtered through

Celite[®] under N₂, the filter cake washed with pentane and concentrated *in vacuo* as an orange oil. The mixture was purified by vacuum distillation to afford the title compound as a colourless oil (23.3 g, 90%).

bp 92-94 °C, 36 mbar; ¹H NMR (250 MHz, CDCl₃) δ_H 2.88 (4H, q, *J* = 7.0 Hz, (CH₃CH₂)₂N), 1.07-0.99 (12H, m, (CH₃CH₂)₂N + (CH₃CH₂)₂Si), 0.90 (4H, q, *J* = 6.5 Hz, (CH₃CH₂)₂Si).

The physical and spectroscopic data were found to be in agreement with that reported by Cox and co-workers.⁶⁵

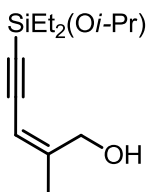
Diethyl(ethynyl)(isopropoxy)silane (87)



To **S1** (10 mL, 46.0 mmol, 1.0 eq) at -78 °C was added ethynylmagnesium bromide in THF (0.5 M, 101 mL, 50.6 mmol, 1.1 eq) *via* canula. The solution was warmed to room temperature over 30 min then stirred under reflux for 3 h. After cooling to room temperature, isopropanol (7.1 mL, 92.1 mmol, 2.0 eq) and DMAP were added and the mixture stirred at room temperature overnight. The reaction mixture was concentrated, redissolved in petrol and filtered through Celite[®]. The filtrate was concentrated *in vacuo* as a yellow oil and purified by vacuum distillation to afford a mixture of the title compound and diethyldiisopropoxysilane as a colourless oil (7.23 g, 78% purity by wt., 72%).

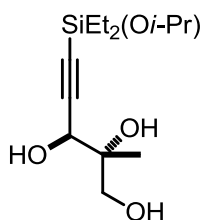
bp 54-56 °C, 20 mbar; ¹H NMR (400 MHz, CDCl₃) δ_H 4.18 (1H, sept, *J* = 6.0 Hz, OCH), 2.43 (1H, s, CH), 1.21 (6H, d, *J* = 6.0 Hz, CH(CH₃)₂), 1.02 (6H, t, *J* = 8.0 Hz, 2 x CH₂CH₃), 0.68 (4H, q, *J* = 8.0 Hz, 2 x CH₂CH₃).

The physical data was found to be in agreement with that reported by Voronkov and co-workers.⁸¹

(Z)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-2-en-4-yn-1-ol (88)

To a solution of **86** (1.2 g, 6.06 mmol, 1.0 eq) and **87** (84% purity by wt., 1.2 g, 6.06 mmol, 1.0 eq) in THF (30 mL) degassed by bubbling through with nitrogen (balloon) was added $\text{PdCl}_2(\text{PPh}_3)_2$ (84 mg, 0.12 mmol, 0.02 eq) and copper(I) iodide (116 mg, 0.61 mmol, 0.1 eq). The mixture was degassed for a further 5 min, diisopropylamine (6.8 mL, 48.5 mmol, 8.0 eq) added and stirred at room temperature. After 5 h, the solution was quenched with saturated NaHCO_3 and stirred at room temperature for a further 1 h. The mixture was extracted three times with DCM and the combined organic layers dried over magnesium sulphate and concentrated *in vacuo* as orange solids. The mixture was purified by flash chromatography (5 → 40% ether / petrol) to afford the title compound as a yellow oil (1.08 g, 74%).

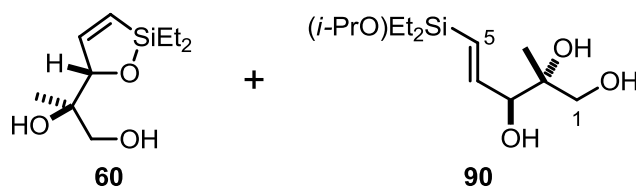
R_f 0.30 (33% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3357, 2961, 2877, 2138, 1750, 1460, 1380, 1122, 1032, 876, 735, 487; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 5.46 (1H, s, CH), 4.39 (2H, d, $J = 6.0$ Hz, CH_2OH), 4.15 (1H, sept, $J = 6.0$ Hz, OCH), 1.91 (3H, s, CH_3), 1.20 (6H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.01 (6H, t, $J = 8.0$ Hz, 2 x CH_2CH_3), 0.68 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 152.4 (CCH_2OH), 106.5 (CH), 101.9 (SiCC), 95.0 (SiC), 66.1 ($\text{OCH}(\text{CH}_3)_2$), 64.1 (CH_2OH), 25.5 ($\text{OCH}(\text{CH}_3)_2$), 20.3 (CCH_3), 6.8 (2 x CH_2CH_3), 6.6 (2 x CH_2CH_3); **HRMS** (ESI+) calc. for $\text{C}_{13}\text{H}_{24}\text{O}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 263.1438 found 263.1445.

***rac*-(2*R*,3*S*)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-4-yne-1,2,3-triol (89)**

To a solution of **88** (1.10 g, 4.63 mmol, 1.0 eq) and 4-methylmorpholine N-oxide (597 mg, 5.09 mmol, 1.1 eq) in acetone/H₂O (32 mL/8 mL) was added osmium tetroxide (350 μ L [2.5% wt. in ^tBuOH], 0.028 mmol, 0.6 mol%). The solution was stirred at room temperature overnight, quenched with sodium metabisulfite (7 g), diluted with H₂O and stirred at room temperature for a further 1 h. The mixture was extracted three times with ethyl acetate, and the combined organic layers dried over Na₂SO₄ and concentrated *in vacuo* as an orange oil. The mixture was purified by flash chromatography (10 $\rightarrow$ 70% ethyl acetate / petrol) to recover the starting material (233 mg, 21%) and afford the title compound as a yellow oil (730 mg, 57%, 73% based on recovered starting material).

R_f 0.21 (50% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3385, 2961, 2933, 2173, 1460, 1381, 1122, 1035, 737, 455; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 4.37 (1H, s, CHOH), 4.14 (1H, sept, *J* = 6.0 Hz, OCH), 4.05 (1H, d, *J* = 11.5 Hz, 1 x CH₂OH), 3.57 (1H, d, *J* = 11.5 Hz, 1 x CH₂OH), 1.24 (3H, s, CH₃), 1.20 (6H, d, *J* = 6.0 Hz, CH(CH₃)₂), 1.01 (6H, t, *J* = 8.0 Hz, 2 x CH₂CH₃), 0.68 (4H, q, *J* = 8.0 Hz, 2 x CH₂CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 104.1 (CCHOH), 88.7 (SiC), 73.7 (C(OH)CH₃), 69.6 (CHOH), 67.4 (CH₂OH), 66.3 (OCH(CH₃)₂), 25.4 (OCH(CH₃)₂), 20.7 (CCH₃), 6.6 (2 x CH₂CH₃), 6.5 (2 x CH₂CH₃); **HRMS** (ESI⁺) calc. for C₁₃H₂₆O₄Si [M+Na]⁺ 297.1493 found 297.1492.

***rac*-(*R*)-2-[(*S*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl]propane-1,2-diol (**60**) & *rac*-(2*R*,3*S*,*E*)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-4-ene-1,2,3-triol (**90**)**



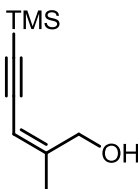
To a solution of **89** (1.21 g, 3.97 mmol, 1.0 eq) and quinoline (94 μ L, 0.794 mmol, 0.2 eq) in toluene (40 mL) was added palladium on calcium carbonate (5% by wt., no lead content, 422 mg, 0.199 mmol, 5 mol%). H₂ was introduced by three vacuum/H₂ (balloon) cycles and subsequently bubbled through the stirred reaction mixture at room temperature for 5 h. The mixture was filtered through Celite[®], the filter cake rinsed with ethyl acetate, and the combined

washings concentrated in vacuo as a pale yellow oil. The mixture was purified by flash chromatography (0 → 2% methanol / DCM + 1% triethylamine) to afford **60** as a pale yellow oil (600 mg, 70%) and **90** as a yellow oil (154 mg, 14%).

60: R_f 0.31 (50% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3396, 2957, 2877, 1557, 1114, 1030, 803, 732, 429; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.00 (1H, dd, $J = 10.5, 1.5$ Hz, SiCHCH), 6.16 (1H, dd, $J = 10.5, 2.5$ Hz, SiCH), 4.67 (1H, dd, $J = 2.5, 1.5$ Hz, CHOSi), 3.64 (1H, d, $J = 11.0$, 1 x CH_2OH), 3.40 (1H, d, $J = 11.0$, 1 x CH_2OH), 1.13 (3H, s, CH_3), 1.00 (3H, t, $J = 8.0$ Hz, CH_2CH_3), 0.87 (3H, t, $J = 8.0$ Hz, CH_2CH_3), 0.74 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 150.1 (SiCHCH), 127.3 (SiCH), 87.6 (CHOH), 73.9 (CCH_2OH), 67.5 (CH_2OH), 19.5, 7.1, 6.7, 6.3; **HRMS** (ESI+) calc. for $\text{C}_{10}\text{H}_{20}\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 239.1074 found 239.1075; **EA** calc. for $\text{C}_{10}\text{H}_{20}\text{O}_3\text{Si}$: C, 55.52; H, 9.32. Found: C, 55.48; H, 9.25.

90: R_f 0.20 (50% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3387, 1624, 1461, 1381, 1236, 1172, 1124, 1030; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 6.27 (1H, dd, $J = 19.0, 5.0$ Hz, H4), 5.98 (1H, dd, $J = 19.0, 1.5$ Hz, H5), 4.11 (1H, d, $J = 5.0, 1.5$ Hz, H3), 3.99 (1H, sept, $J = 6.0$ Hz, OCH), 3.74 (1H, d, $J = 11.0$ Hz, 1 x H1), 3.38 (1H, d, $J = 11.0$ Hz, 1 x H1), 1.14 (6H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.08 (3H, s, CH_3), 0.95 (6H, t, $J = 8.0$ Hz, CH_2CH_3), 0.65 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 146.3 (C4), 127.6 (C5), 80.1 (C3), 73.7 (C2), 67.5 (C1), 65.2 (OCH), 25.8 ($\text{OCH}(\text{CH}_3)_2$), 20.7 (CH_3), 6.7 (2 x CH_2CH_3), 5.3 (2 x CH_2CH_3); **HRMS** (ESI+) calc. for $\text{C}_{13}\text{H}_{28}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$ 299.1649 found 299.1648.

(Z)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (S2)



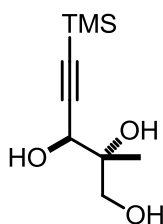
To a solution of **86** (1.3 g, 6.57 mmol, 1.0 eq) and ethynyltrimethylsilane (1.0 mL, 7.22 mmol, 1.1 eq) in THF (35 mL) degassed by bubbling through with N_2 (balloon) was added $\text{PdCl}_2(\text{PPh}_3)_2$ (92 mg, 0.13 mmol, 0.02 eq) and copper(I) iodide (125 mg, 0.66 mmol, 0.1 eq).

The mixture was degassed for a further 5 min, diisopropylamine (7.4 mL, 52.5 mmol, 8.0 eq) added and stirred at room temperature. After 5 h, the solution was quenched with saturated NaHCO₃ and stirred at room temperature for a further 1 h. The mixture was extracted three times with DCM and the combined organic layers dried over MgSO₄ and concentrated *in vacuo* as a red oil. The mixture was purified by flash chromatography (20 → 35% ether / petrol) to afford the title compound as a yellow oil (808 mg, 73%).

R_f 0.36 (20% ether acetate / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.42 (1H, s, CH), 4.37 (2H, s, CH₂), 1.88 (3H, s, CH₃), 0.19 (9H, s, 3 x CH₃).

The spectroscopic data were found to be in agreement with that reported by Hatakeyama and co-workers.⁸⁰

***rac*-(2*R*,3*S*)-2-Methyl-5-(trimethylsilyl)pent-4-yne-1,2,3-triol (93)**

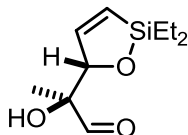


To a solution of **S2** (50 mg, 0.30 mmol, 1.0 eq) and 4-methylmorpholine N-oxide (38 mg, 0.33 mmol, 1.1 eq) in acetone/H₂O (4 mL/1 mL) was added osmium tetroxide (2.5% wt. in *t*-BuOH, 75 μL, 0.006 mmol, 2.0 mol%). The solution was stirred at room temperature overnight, quenched with sodium metabisulfite (450 mg), diluted with H₂O and stirred at room temperature for a further 1 h. The mixture was extracted three times with ethyl acetate, and the combined organic layers dried over Na₂SO₄ and concentrated *in vacuo* as a black oil. The mixture was purified by flash chromatography (30 → 80% ethyl acetate / petrol) to recover the starting material (14 mg, 28%) and afford the title compound as a yellow oil (31 mg, 52%, 72% based on recovered starting material).

R_f 0.13 (40% ether acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3384, 2960, 2361, 2175, 1251, 1053, 844, 761; **¹H NMR** (400 MHz, CDCl₃) δ_H 4.34 (1H, s, CHOH), 4.00 (1H, d, *J* = 11.5 Hz,

1 x CH_2OH), 3.55 (1H, d, $J = 11.5$ Hz, 1 x CH_2OH), 2.99 (1H, br s, OH), 2.87 (1H, br s, OH), 2.35 (1H, br s, OH), 1.23 (3H, s, CH_3), 0.20 (9H, s, 3 x CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 103.5 (SiCC), 92.1 (SiC), 73.9 ($\text{C}(\text{OH})\text{CH}_3$), 69.4 (CHOH), 67.2 (CH_2OH), 14.2 (CH_3), -0.3 ($\text{Si}(\text{CH}_3)_3$); HRMS (ESI+) calc. for $\text{C}_9\text{H}_{18}\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 225.0917 found 225.0919.

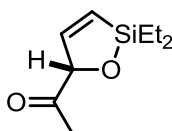
***rac*-(S)-2-[(S)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-2-hydroxypropanal (96)**



SO_3 .pyridine complex (92 mg, 0.58 mmol, 3.1 eq) and DMSO (138 μL , 1.94 mmol, 10.5 eq) were stirred together for 15 min at room temperature. A solution of **60** (40 mg, 0.185 mmol, 1.0 eq) and DIPEA (164 μL , 0.962 mmol, 5.2 eq) in DCM (1 mL) was added and the resulting solution stirred at room temperature for 1 h. The reaction was diluted with DCM, quenched with aqueous 1M HCl and stirred vigorously for 15 min at room temperature, then extracted three times with DCM. The combined organic layers were washed with saturated aqueous NaHCO_3 , dried over MgSO_4 and concentrated *in vacuo* as a light brown oil which was used in the next step without further purification.

R_f 0.55 (50% ethyl acetate / petrol); ^1H NMR (500 MHz, CDCl_3) δ_{H} 9.68 (1H, s, CHO), 6.98 (1H, dd, $J = 10.5, 1.5$ Hz, SiCHCH), 6.25 (1H, dd, $J = 10.5, 2.5$ Hz, SiCH), 4.62 (1H, dd, $J = 2.5, 1.5$ Hz, CHOSi), 1.27 (3H, s, CH_3), 0.97 (3H, t, $J = 8.0$ Hz, 2 x CH_2CH_3), 0.71 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3).

1-(2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)ethanone (97)

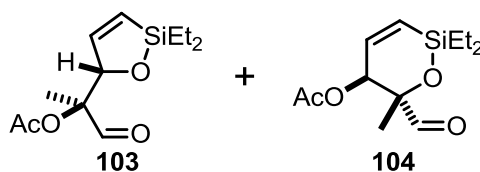


To a solution of **60** (70 mg, 0.32 mmol, 1 eq) and (diacetoxyiodo)benzene (120 mg, 0.37 mmol, 1.15 eq) in DCM (1.5 mL) was added TEMPO (5 mg, 0.03 mmol, 0.1 eq). The resulting yellow

solution was stirred over 16 h at room temperature then quenched saturated NaHCO_3 and saturated sodium thioslphate (1:1, v/v) and stirred for 1 h at room temperature. The mixture was extracted two times with DCM and the combined organic layers dried over MgSO_4 and concentrated *in vacuo* as a yellow oil. The mixture was purified by flash chromatography (10% ether / petrol) to afford the title compound as a yellow oil (37 mg, 53%).

R_f 0.28 (10% ether / petrol); δ_{H} **¹H NMR** (400 MHz, CDCl_3) δ_{H} 6.91 (1H, dd, $J = 10.5, 2.0$ Hz, SiCHCH), 6.18 (1H, dd, $J = 10.5, 3.0$ Hz, SiCH), 5.06 (1H, dd, $J = 3.0, 2.0$ Hz, CHOSi), 2.19 (3H, s, CH_3), 1.02-0.91 (6H, m, 2 x CH_2CH_3), 0.84-0.74 (4H, m, 2 x CH_2CH_3); **¹³C NMR** (100 MHz, CDCl_3) δ_{C} 209.1 (COCH_3), 148.5 (SiCHCH), 127.4 (SiCH), 89.7 (COSi), 25.2 (CH_3), 7.1 (CH_2CH_3), 6.7 (CH_2CH_3), 6.6 (CH_2CH_3), 6.3 (CH_2CH_3).

***rac*-(*S*)-2-[(*S*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-1-oxopropan-2-yl acetate (103) & *rac*-(*5S,6S*)-2,2-Diethyl-6-formyl-6-methyl-5,6-dihydro-2H-1,2-oxasilin-5-yl acetate (104)**

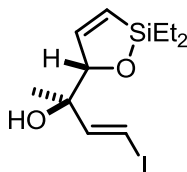


To a solution of **96** (0.139 mmol, 1 eq) and acetic anhydride (33 μL , 0.348 mmol, 2.5 eq) in DCM (1.7 mL) was added pyridine (45 μL , 0.556 mmol, 4 eq) and DMAP. After stirring for 16 h at room temperature, the solution was quenched with aqueous 1M HCl and extracted three times with DCM. The combined organic layers were washed with saturated aqueous NaHCO_3 , dried over MgSO_4 and concentrated *in vacuo* as a light brown oil. The mixture was purified by flash chromatography (0 $\rightarrow$ 20% ethyl acetate / petrol) to afford an inseparable mixture of the title compounds in a 2.4:1 ratio as a colourless oil (13 mg, 28% over two steps).

103: **R_f** 0.41 (20% ethyl acetate / petrol); δ_{H} **¹H NMR** (200 MHz, CDCl_3) δ_{H} 9.60 (1H, s, CHO), 6.88 (1H, dd, $J = 10.5, 1.5$ Hz, SiCHCH), 6.25 (1H, dd, $J = 10.5, 2.5$ Hz, SiCHCH), 4.90 (1H, dd, $J = 2.5, 1.5$ Hz, CHOSi), 2.13 (3H, s, COCH_3), 1.45 (3H, s, CH_3), 1.03-0.85 (6H, m, overlapping 2 x CH_2CH_3), 0.79-0.64 (4H, m, overlapping 2 x CH_2CH_3).

104: R_f 0.41 (20% ethyl acetate / petrol); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ_{H} 9.52 (1H, s, CHO), 6.69 (1H, dd, $J = 14.5, 4.0$ Hz, SiCHCH), 6.07 (1H, dd, $J = 14.5, 1.5$ Hz, SiCHCH), 5.48 (1H, dd, $J = 4.0, 1.5$ Hz, CHOSi), 2.09 (3H, s, COCH_3), 1.32 (3H, s, CH_3), 1.03-0.85 (6H, m, overlapping 2 x CH_2CH_3), 0.79-0.64 (4H, m, overlapping 2 x CH_2CH_3).

***rac*-(*R,E*)-2-[(*S*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-4-iodobut-3-en-2-ol (106)**

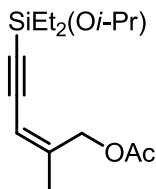


To chromium (II) chloride (171 mg, 1.39 mmol, 10.0 eq) dried under vacuum and heat was added THF (3 mL) and the resulting grey suspension was stirred for 30 min at room temperature. The suspension was cooled to 0 °C and a solution of crude aldehyde **96** (0.139 mmol, 1.0 eq) and iodoform (109 mg, 0.0278 mmol, 2.0 eq) in THF (1 mL) was added *via* syringe. The resulting red suspension was stirred in the dark for 4 h at 0 °C, after which it quenched with a saturated solution of $\text{EDTA}\cdot\text{Na}_2$ in brine and stirred for 30 min at room temperature. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium thiosulfate followed by brine, dried over MgSO_4 and concentrated *in vacuo* as yellow solids. The crude product was purified by flash chromatography (0 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a pale yellow oil (20 mg, 43%).

R_f 0.47 (20% ethyl acetate / petrol); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 6.88 (1H, dd, $J = 10.5, 1.5$ Hz, SiCHCH), 6.49 (1H, d, $J = 14.5$ Hz, CHCHI), 6.38 (1H, d, $J = 14.5$ Hz, CHI), 6.21 (1H, dd, $J = 10.5, 2.5$ Hz, SiCH), 4.52 (1H, dd, $J = 2.5, 1.5$ Hz, CHOSi), 2.72 (1H, s, OH), 1.31 (3H, s, CH_3), 0.99 (3H, t, $J = 8.0$ Hz, CH_2CH_3), 0.91 (3H, t, $J = 8.0$ Hz, CH_2CH_3), 0.74-0.65 (4H, m, 2 x CH_2CH_3); δ_{C} $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ_{C} 148.6 (SiCHCH), 148.5 (CHCHI), 129.0 (SiCH), 89.5 ($\text{C}(\text{OH})\text{CH}_3$), 89.4 (CHOSi), 77.9 (CHI), 23.7 (CH_3), 7.3 (CH_2CH_3), 6.8

(CH₂CH₃), 6.6 (CH₂CH₃), 6.3 (CH₂CH₃); **HRMS** (ESI+) calc. for C₁₁H₁₉IO₂Si [M+Na]⁺ 361.0091 found 361.0088.

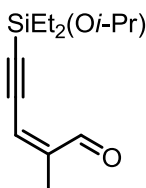
(Z)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-2-en-4-yn-1-yl acetate (109)



To a solution of **88** (100 mg, 0.416 mmol, 1 eq) in DCM (5 mL) was added acetic anhydride (50 μ L, 0.520 mmol, 1.25 eq), triethylamine (116 μ L, 0.832 mmol, 2 eq) and DMAP (5 mg, 0.04 mmol, 0.1 eq). The resulting solution was stirred over 16 h at room temperature then quenched with saturated NaHCO₃. The mixture was extracted three times with ether and the combined organic layers dried over MgSO₄ and concentrated *in vacuo* as a yellow oil which was used in the next step without further purification.

R_f 0.60 (20% ether / petrol); **¹H NMR** (250 MHz, CDCl₃) δ _H 5.54 (1H, s, CH), 4.86 (2H, d, *J* = 6.0 Hz, CH₂OAc), 4.15 (1H, sept, *J* = 6.0 Hz, OCH), 2.10 (3H, s, CH₃), 1.86 (3H, s, CH₃), 1.21 (6H, d, *J* = 6.0 Hz, CH(CH₃)₂), 1.01 (6H, t, *J* = 8.0 Hz, 2 x CH₂CH₃), 0.68 (4H, q, *J* = 8.0 Hz, 2 x CH₂CH₃).

(Z)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-2-en-4-ynal (108)

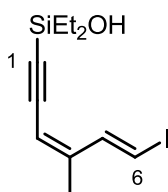


To a solution of **88** (335 mg, 1.39 mmol, 1.0 eq) and NaHCO₃ (117 mg, 1.39 mmol, 1.0 eq) in DCM (7 mL) at 0 °C was added DMP (768 mg, 1.81 mmol, 1.3 eq). The reaction mixture was stirred at 0 °C for 10 min before the ice bath was removed. The colourless solution was stirred at room temperature for 1 h then quenched with saturated aqueous NaHCO₃ and saturated aqueous sodium thiosulfate and stirred vigorously for a further 30 min. The mixture was

extracted three times with DCM and the combined organic layers dried over MgSO_4 and concentrated *in vacuo* to yield the enal as a yellow oil which was used in the next step without further purification.

R_f 0.62 (20% ethyl acetate–petrol); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ_{H} 10.28 (1H, s, CHO), 6.58 (1H, s, CH), 4.15 (1H, sept, $J = 6.0$ Hz, OCH), 1.89 (3H, s, CH_3), 1.21 (6H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.03 (6H, t, $J = 8.0$ Hz, 2 x CH_2CH_3), 0.73 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3).

Diethyl((3*Z*,5*E*)-6-iodo-4-methylhexa-3,5-dien-1-yn-1-yl)silanol (112)

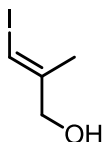


Chromium (II) chloride (1.02 g, 8.34 mmol, 6.0 eq) was stirred in THF (19 mL) for 10 min at room temperature. After the grey suspension formed was cooled to 0 °C, a solution of crude **108** (1.39 mmol, 1.0 eq) and iodoform (1.10 g, 2.78 mmol, 2.0 eq) in THF (4 mL) was added *via* syringe and the mixture stirred for 3 h at 0 °C. The resulting brown suspension was diluted with ether, quenched with distilled H_2O and extracted three times with ether. The combined organic layers were filtered through Celite[®], dried over MgSO_4 and concentrated *in vacuo* as brown solids. The mixture was purified by flash chromatography (0 → 20% ether / petrol) to afford the title compound as a yellow oil (207 mg, 47%) which dimerised on storage at 4 °C.

R_f 0.51 (10% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2133, 1222, 1094, 1006, 952, 826, 736; Silanol **112**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 7.79 (1H, d, $J = 15.0$ Hz, H5), 6.67 (1H, d, $J = 15.0$ Hz, H6), 5.39 (1H, s, H3), 1.89 (3H, s, Me), 1.06 (6H, t, $J = 8.0$ Hz, 2 x CH_2CH_3), 0.75 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ_{C} 147.2 (C4), 144.0 (C5), 108.9 (C3), 102.3 (C2), 97.7 (C1), 82.2 (C6), 18.6 (CH_3), 7.50 (CH_2CH_3), 6.46 (CH_2CH_3); **Disiloxane dimer**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 7.10 (1H, d, $J = 15.0$ Hz, H5), 6.56 (1H, d, $J = 15.0$ Hz, H6), 5.50 (1H, s, H3), 2.01 (3H, s, Me), 1.06 (6H, t, $J = 8.0$ Hz, 2 x

CH_2CH_3), 0.75 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 148.4 (C4), 147.1 (C5), 110.6 (C3), 102.8 (C2), 100.3 (C1), 79.8 (C6), 14.8 (CH_3), 7.50 (CH_2CH_3), 6.46 (CH_2CH_3); m/z (ESI+) 645 **Disiloxane dimer** $[\text{M}+\text{Na}]^+$, 445, 343 Silanol **112** $[\text{M}+\text{Na}]^+$, 289.

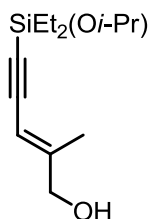
(E)-3-Iodo-2-methylprop-2-en-1-ol (115)



To bis(cyclopentadienyl)zirconium(IV) dichloride (1.04 g, 3.56 mmol, 0.2 eq) at 0 °C was added trimethylaluminum in hexanes (2.0 M, 22.3 mL, 44.6 mmol, 2.5 eq) then a solution of propargyl alcohol (1.06 mL, 17.8 mmol, 1.0 eq) in DCM (3.6 mL). The mixture was warmed to room temperature overnight. The yellow solution was cooled to -78 °C, upon which a solution of iodine (5.42 g, 21.4 mmol, 1.2 eq) in ether (30 mL) was added. The solution was stirred at -78 °C for 30 min, then allowed to warm to room temperature. The reaction was quenched by careful slow addition to a vigorously stirring biphasic mixture of pentane (50 mL) and saturated Na^+/K^+ tartrates solution (50 mL) at 0 °C. The mixture was stirred vigorously at room temperature for 3 h before the organic layer was decanted and the aqueous layer extracted three times with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* as a yellow oil. The mixture was purified by flash chromatography (10 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a pale yellow oil (2.61 g, 74%).

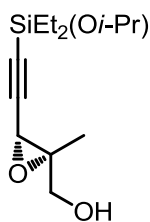
R_f 0.40 (50% ether–petrol); ^1H NMR (200 MHz, CDCl_3) δ_{H} 6.29 (1H, s, CH), 4.15 (2H, d, $J = 6.0$ Hz, CH_2OH), 1.86 (3H, s, CH_3).

The spectroscopic data was found to be in agreement with that reported by Liu and co-workers.²⁴⁹

(E)-5-(Diethyl(isopropoxy)silyl)-2-methylpent-2-en-4-yn-1-ol (114)

To a solution of **115** (4.83 g, 24.4 mmol, 1.0 eq) and **87** (85% purity by wt., 4.89 g, 24.4 mmol, 1.0 eq) in THF (30 mL) degassed by bubbling through with nitrogen (balloon) was added $\text{PdCl}_2(\text{PPh}_3)_2$ (171 mg, 0.244 mmol, 0.01 eq) and copper(I) iodide (465 mg, 2.44 mmol, 0.1 eq). The mixture was degassed for a further 5 min, diisopropylamine (27.3 mL, 195 mmol, 8.0 eq) added and stirred at room temperature. After 16 h, the solution was quenched with saturated NaHCO_3 (50 mL) and diluted with DCM (125 mL). The mixture was extracted three times with DCM and the combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. The residue was redissolved in 30% ethyl acetate / petrol, filtered through Celite® and concentrated *in vacuo* as brown solids. The mixture was purified by flash chromatography (10 → 30% ether / petrol) to afford the title compound as a yellow oil (5.37 g, 91%).

R_f 0.30 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3346, 2969, 2134, 1460, 1236, 1122, 1031, 877, 736, 413; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 5.66 (1H, s, CH), 4.18 (1H, sept, J = 6.0 Hz, OCH), 4.14 (2H, d, J = 6.0 Hz, CH_2OH), 1.93 (3H, s, CH_3), 1.21 (6H, d, J = 6.0 Hz, $\text{CH}(\text{CH}_3)_2$), 1.52 (1H, t, J = 6.0 Hz, OH), 1.03 (6H, t, J = 8.0 Hz, 2 x CH_2CH_3), 0.69 (4H, q, J = 8.0 Hz, 2 x CH_2CH_3); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 152.1 (CCH_2OH), 104.6 (CH), 103.0 (SiCC), 94.8 (SiC), 66.7 (CH_2OH), 66.1 (OCH), 25.5 ($\text{OCH}(\text{CH}_3)_2$), 16.6 (CCH_3), 6.9 (2 x CH_2CH_3), 6.7 (2 x CH_2CH_3); **HRMS** (ESI+) calc. for $\text{C}_{13}\text{H}_{24}\text{O}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 263.1438 found 263.1445.

[(2*R*,3*R*)-3-(Diethylisopropoxysilylethynyl)-2-methyloxiran-2-yl]methanol (116**)**

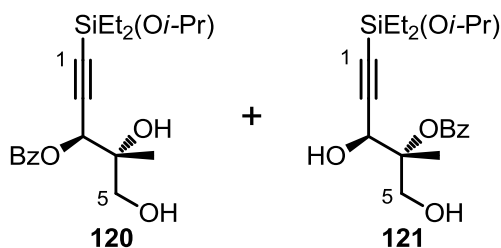
Asymmetric preparation: A solution of $\text{Ti}(\text{O}i\text{-Pr})_4$ (946 μL , 3.12 mmol, 0.5 eq) in DCM (21 mL) over 4 Å molecular sieves (450 mg, 30% w/w) in a Schlenk tube was cooled to $-20\text{ }^\circ\text{C}$. L-(+)-Diisopropyl tartrate (791 μL , 3.74 mmol, 0.6 eq) was added dropwise and the solution was stirred at $-20\text{ }^\circ\text{C}$ for 30 min. A solution of **114** (1.50 g, 6.24 mmol, 1.0 eq) in DCM (6 mL) was added dropwise and the solution was stirred at $-20\text{ }^\circ\text{C}$ for 30 min. TBHP (2.27 mL [5.5 M in decane], 12.5 mmol, 2.0 eq) was added slowly and the solution was stood in the freezer at $-30\text{ }^\circ\text{C}$ for 16 h. After this time, the solution was removed from the freezer, diluted with ether (10 mL) followed immediately by saturated Na_2SO_4 (3.2 mL, 1 mL/mmol of $\text{Ti}(\text{O}i\text{-Pr})_4$). The mixture was stirred vigorously and allowed to warm to room temperature over 2 h. It was then filtered through a Celite[®] pad and the resulting yellow paste was washed with ether until it became granular. The yellow layer was scraped into an Erlenmeyer flask containing ethyl acetate (20 mL) and a stirrer bar and stirred vigorously for 30 min in boiling ethyl acetate. The slurry was filtered through the same Celite[®] pad, and washed with ethyl acetate. The combined organic layers was concentrated *in vacuo* as a pale yellow oil. The mixture was purified by flash chromatography (10 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a pale yellow oil (1.38 g, 86%).

Racemic preparation: To a solution of **114** (50 mg, 0.208 mmol, 1.0 eq) and disodiumhydrogenphosphonate (77 mg, 0.312 mmol, 1.5 eq) in DCM (0.3 mL) at $0\text{ }^\circ\text{C}$ was added *meta*-chloroperbenzoic acid (372 mg, 2.16 mmol, 4.0 eq). The mixture was allowed to warm to room temperature over 16 h, then quenched with saturated sodium carbonate and stirred for a further 3 h. The mixture was extracted with three times with DCM and the

combined organic layers dried over MgSO_4 and concentrated *in vacuo* as a brown oil (34 mg, 64%) which was used without further purification.

R_f 0.24 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3419, 2964, 2179, 1732, 1382, 1173, 1035, 738; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 4.15 (1H, sept, $J = 6.0$ Hz, OCH), 3.76 (1H, d, $J = 12.5$ Hz, 1 x CH_2OH), 3.66 (1H, d, $J = 12.5$ Hz, 1 x CH_2OH), 3.62 (1H, CCH), 1.46 (3H, s, CH_3), 1.20 (6H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.01 (6H, t, $J = 8.0$ Hz, 2 x CH_2CH_3), 0.68 (4H, q, $J = 8.0$ Hz, 2 x CH_2CH_3); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 100.8 (SiCC), 88.3 (SiC), 66.2 (OCH), 63.4 (CH_2OH), 63.0 (CCH_2OH), 47.9 (CHO), 25.4 ($\text{CH}(\text{CH}_3)_2$), 15.5 (CCH_3), 6.6 (2 x CH_2CH_3), 6.5 (2 x CH_2CH_3); **HRMS** (ESI+) calc. for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 279.1387 found 279.1393.

(3*S*,4*R*)-1-(Diethylisopropoxysilyl)-4,5-dihydroxy-4-methylpent-1-yn-3-yl benzoate (120) & (2*R*,3*S*)-5-(Diethylisopropoxysilyl)-1,3-dihydroxy-2-methylpent-4-yn-2-yl benzoate (121)

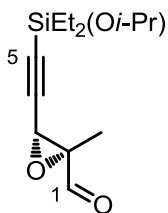


To a solution of benzoic acid (692 mg, 5.67 mmol, 1.5 eq) in DCM (35 mL) over 4 Å molecular sieves (290 mg, 30%w/w) was added $\text{Ti}(\text{O}i\text{-Pr})_4$ (1.68 mL, 5.67 mmol, 1.5 eq). A solution of **116** (970 mg, 3.78 mmol, 1.0 eq) in DCM (3 mL) was added and the mixture was stirred at room temperature for 1 h. The reaction was quenched with acetone/ H_2O (36 mL, 5:1 v/v) and stirred vigorously for 2 h. The mixture was washed successively with 1M aqueous HCl and saturated aqueous NaHCO_3 , dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (2 → 5% methanol / DCM) to afford the title compound as a colourless oil (981 mg, 76%).

120: $[\alpha]_{\text{D}}^{25} +2.0$ (c 1.00, CHCl_3); 89% *ee* (CHIRALPAK IA, 5% IPA / hexane, 1.25 mL/min, t_{R} (3*S*, 4*R*) 7.79 min, t_{R} (3*R*, 4*S*) 8.72 min); R_{f} 0.53 (60% ethyl acetate–petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3438, 2179, 1729, 1602, 1269, 1118, 1028, 711; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 8.53 (2H, d, $J = 7.5$ Hz, ArH), 7.61 (1H, t, $J = 7.5$ Hz, ArH), 7.48 (2H, t, $J = 7.5$ Hz, ArH), 5.76 (1H, s, H3), 4.15 (1H, sept, $J = 6.0$ Hz, OCH), 3.71 (1H, d, $J = 11.5$ Hz, 1 x H5), 3.56 (1H, dd, $J = 11.5$ and 3.5 Hz, 1 x H5), 2.65 (1H, br s, OH), 2.41 (1H, br s, OH), 1.40 (3H, s, CH_3), 1.19 (3H, d, $J = 6.0$ Hz, 1 x $\text{CH}(\text{CH}_3)_2$), 1.18 (3H, d, $J = 6.0$ Hz, 1 x $\text{CH}(\text{CH}_3)_2$), 1.01 (6H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.71-0.66 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 165.5 (CO_2), 133.6 (Ar), 129.8 (Ar), 129.2 (Ar), 128.6 (Ar), 100.4 (C2), 89.7 (C1), 73.8 (C4), 68.1 (C3), 66.3 (OCH), 66.2 (C5), 25.4 ($\text{CH}(\text{CH}_3)_2$), 19.8 (CH_3), 6.6 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.5 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{20}\text{H}_{30}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 401.1755, found 401.1754.

121: $[\alpha]_{\text{D}}^{25} +0.14$ (c 1.77, CHCl_3); R_{f} 0.24 (30% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3435, 2173, 1724, 1603, 1272, 1118, 1028, 1010; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 8.62 (2H, d, $J = 8.0$ Hz, ArH), 7.59 (1H, t, $J = 8.0$ Hz, ArH), 7.46 (2H, t, $J = 8.0$ Hz, ArH), 4.60 (1H, d, $J = 11.5$ Hz, 1 x H5), 4.43 (1H, d, $J = 11.5$ Hz, 1 x H5), 4.44-4.41 (1H, m, H3), 4.12 (1H, sept, $J = 6.0$ Hz, OCH), 2.82 (2H, br s, 2 x OH), 1.41 (3H, s, CH_3), 1.18 (6H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.99 (6H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.68-0.62 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 166.9 (CO_2), 133.3 (Ar), 129.7 (Ar), 129.6 (Ar), 128.5 (Ar), 103.1 (C2), 89.1 (C1), 73.9 (C4), 68.5 (C5), 68.1 (C3), 66.2 (OCH), 25.4 ($\text{CH}(\text{CH}_3)_2$), 20.7 (CH_3), 6.6 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.5 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{20}\text{H}_{30}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 401.1755, found 401.1754.

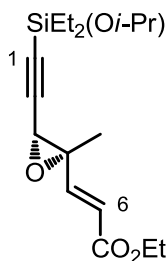
(2*S*,3*R*)-3-[(Diethylisopropoxysilyl)ethynyl]-2-methyloxirane-2-carbaldehyde (S3)



SO₃·pyridine complex (277 mg, 1.74 mmol, 3.1 eq) and DMSO (417 μL, 5.89 mmol, 10.5 eq) were stirred together for 15 min at room temperature. A solution of **116** (144 mg, 0.561 mmol, 1.0 eq) and DIPEA (498 μL, 2.92 mmol, 5.2 eq) in dichloromethane (3 mL) was added and the resulting solution stirred at room temperature for 1 h. The reaction was diluted with ether and quenched with aqueous 1M HCl. The organic layer was washed with saturated aqueous NaHCO₃, dried over MgSO₄ and concentrated *in vacuo* as a yellow oil (140 mg, 98%) which was used in the next step without further purification.

R_f 0.29 (10% ethyl acetate / petrol); ¹H NMR (400 MHz, CDCl₃) δ_H 8.90 (1H, s, H1), 4.14 (1H, sept, *J* = 6.0 Hz, OCH), 3.72 (1H, s, H3), 1.59 (3H, s, CH₃), 1.20 (6H, d, *J* = 6.0 Hz, CH(CH₃)₂), 1.01 (6H, t, *J* = 8.0 Hz, Si(CH₂CH₃)₂), 0.69 (4H, q, *J* = 8.0 Hz, Si(CH₂CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 197.6 (C1), 97.5 (C4), 90.6 (C5), 66.4 (OCH), 63.8 (C2), 48.6 (C3), 25.4 (CH(CH₃)₂), 11.3 (CH₃), 6.5 (Si(CH₂CH₃)₂), 6.4 (Si(CH₂CH₃)₂).

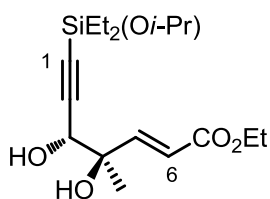
(*E*)-Ethyl 3-[(2*R*,3*R*)-3-((diethylisopropoxysilyl)ethynyl)-2-methyloxiran-2-yl]acrylate (122**)**



A solution of triethylphosphonoacetate (85 mg, 0.378 mmol, 1.6 eq) in THF (1.2 mL) was added to sodium hydride (60% in mineral oil, 14 mg, 0.354 mmol, 1.5 eq) and the cloudy mixture stirred at room temperature for 45 min. To the resulting colourless solution was added a solution of **S3** (60 mg, 0.236 mmol, 1.0 eq) in THF (1.2 mL). The reaction mixture was stirred at room temperature for 30 min and quenched with saturated aqueous ammonium chloride. The reaction mixture was extracted three times with ether. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatograph (0 → 10% ether / petrol) to afford the title compound as a pale yellow oil (41 mg, 54%).

$[\alpha]_{\text{D}}^{20}$ -39.0 (c 0.50, CHCl_3); R_f 0.31 (10% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2181, 1723, 1658, 1368, 1309, 1173, 1032, 978; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 6.72 (1H, d, $J = 15.5$ Hz, H5), 6.07 (1H, d, $J = 15.5$ Hz, H6), 4.21 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.14 (1H, sept, $J = 6.0$ Hz, OCH), 3.38 (1H, s, H3), 1.62 (3H, s, CH_3), 1.30 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.20 (6H, d, $J = 6.0$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.01 (6H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.70-0.65 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 165.7 (C7), 146.6 (C5), 123.1 (C6), 99.7 (C2), 89.1 (C1), 66.3 (OCH), 60.7 (OCH_2CH_3), 60.6 (C4), 53.3 (C3), 25.4 ($\text{OCH}(\text{CH}_3)_2$), 16.8 (CH_3), 14.2 (OCH_2CH_3), 6.6 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.5 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{17}\text{H}_{28}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$ 347.1649, found 347.1645.

(4R,5R,E)-Ethyl 7-(diethylisopropoxysilyl)-4,5-dihydroxy-4-methylhept-2-en-6-ynoate (123)

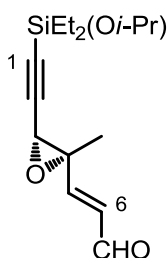


A solution of **122** (6.0 mg, 0.0185 mmol, 1.0 eq) in degassed THF (200 μL) was added to boronic acid (1.5 mg, 0.0240 mmol, 1.3 eq) and $\text{Pd}(\text{PPh}_3)_4$ (1.1 mg, 0.925 μmol , 0.05 eq). The resulting red solution was stirred at room temperature for 15 min, diluted with ethyl acetate and filtered through a pad of silica. The filtrate was concentrated *in vacuo* and purified by column chromatography (10 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a yellow oil (2.7 mg, 43%).

$[\alpha]_{\text{D}}^{20}$ -4.08 (c 0.26, CHCl_3); R_f 0.19 (30% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3434, 2178, 1705, 1659, 1277, 1183, 1062, 1006; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.02 (1H, d, $J = 15.5$ Hz, H5), 6.19 (1H, d, $J = 15.5$ Hz, H6), 4.28 (1H, d, $J = 4.5$ Hz, H3), 4.21 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.14 (1H, sept, $J = 6.0$ Hz, OCH), 2.38-2.37 (2H, m, 2 x OH), 1.45 (3H, s, CH_3), 1.30 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 1.20 (6H, d, $J = 6.0$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.01 (6H, t, $J = 8.0$ Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.71-0.66 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 166.2

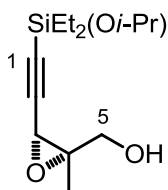
(C7), 149.1 (C5), 121.5 (C6), 102.8 (C2), 89.4 (C1), 75.1 (C4), 69.1 (C3), 66.3 (OCH), 60.5 (OCH₂CH₃), 25.4 (OCH(CH₃)₂), 22.9 (CH₃), 14.2 (OCH₂CH₃), 6.6 (Si(CH₂CH₃)₂), 6.5 (Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₁₇H₃₀O₅Si [M+Na]⁺ 365.1755, found 365.1756.

(E)-3-[(2R,3R)-3-((Diethylisopropoxysilyl)ethynyl)-2-methyloxiran-2-yl]acrylaldehyde (S4)



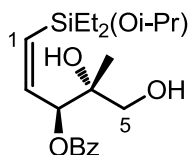
To a solution of **S3** (40 mg, 0.123 mmol, 1.0 eq) in toluene at $-78\text{ }^{\circ}\text{C}$ was added DIBALH (1.0 M in hexanes, 135 μL , 0.135 mmol, 1.1 eq) dropwise. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, quenched with MeOH (100 μL) and allowed to warm to $0\text{ }^{\circ}\text{C}$, upon which saturated aqueous sodium/potassium tartrates was added and the mixture stirred vigorously and warmed to room temperature over 1 h. The reaction mixture was extracted twice with ether and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 30% ether / petrol) to afford the title compound as a colourless oil (29 mg, 85%).

$[\alpha]_{\text{D}}^{20} +11.7$ (*c* 0.22, CHCl₃); **R_f** 0.32 (20% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 2959, 2878, 2180, 1722, 1640, 1063, 1007, 738; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 9.58 (1H, d, *J* = 7.5 Hz, CHO), 6.56 (1H, d, *J* = 16.0 Hz, H5), 6.34 (1H, dd, *J* = 16.0, 7.5 Hz, H6), 4.15 (1H, sept, *J* = 6.0 Hz, OCH), 3.45 (1H, s, H3), 1.68 (3H, s, CH₃), 1.20 (6H, d, *J* = 6.0 Hz, OCH(CH₃)₂), 1.01 (6H, t, *J* = 8.0 Hz, Si(CH₂CH₃)₂), 0.71-0.66 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 192.5 (CHO), 154.8 (C5), 133.1 (C6), 99.1 (C2), 89.8 (C1), 66.3 (OCH), 60.6 (C4), 53.5 (C3), 25.4 (OCH(CH₃)₂), 16.6 (CH₃), 6.6 (Si(CH₂CH₃)₂), 6.5 (Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₁₅H₂₄O₃Si [M+Na]⁺ 303.1387, found 303.1389.

***rac*-[*(2S-3R)*-3-((Diethyl(isopropoxy)silyl)ethynyl)-2-methyloxiran-2-yl]methanol (124)**

To a solution of **88** (520 mg, 2.16 mmol, 1.0 eq) in wet DCM (8.6 mL) was added disodium hydrogen phosphate (1.29 g, 9.08 mmol, 4.2 eq) and *m*-CPBA (70% technical grade, 1.28 g, 5.18 mmol, 2.4 eq). The reaction mixture was stirred at room temperature for 16 h, quenched with saturated aqueous sodium thiosulphate then stirred vigorously at room temperature for 30 min. The mixture was extracted three times with DCM and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 20% ethyl acetate / petrol) to afford the title compound as a colourless oil (134 mg, 24%).

R_f 0.25 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3395, 2180, 1727, 1239, 1094, 1050, 1007, 734; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 4.13 (1H, sept, J = 6.0 Hz, OCH), 3.83 (2H, s, H5), 3.35 (1H, s, H3), 1.45 (3H, s, CH_3), 1.19 (6H, d, J = 6.0 Hz, $\text{OCH}(\text{CH}_3)_2$), 1.00 (6H, t, J = 8.0 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.69-0.65 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 100.3 (C2), 88.6 (C1), 66.3 (OCH), 65.5 (C5), 62.9 (C4), 50.8 (C3), 25.4 ($\text{OCH}(\text{CH}_3)_2$), 18.4 (CH_3), 6.6 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.5 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 279.1387, found 279.1387.

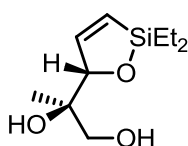
(*3S, 4R, Z*)-1-[Diethyl(isopropoxy)silyl]-4,5-dihydroxy-4-methylpent-1-en-3-yl benzoate (125)

To a solution of **120** (45 mg, 0.119 mmol, 1.0 eq) and quinoline (2.8 μL , 0.024 mmol, 0.2 eq) in toluene (1.2 mL) was added palladium on calcium carbonate (5% wt. no lead content, 13 mg,

0.0059 mmol, 0.05 eq). H₂ purged through the solution with a balloon and subsequently bubbled slowly through the stirred reaction mixture at room temperature for 9 h. The mixture was filtered through Celite®, the filter cake rinsed with ethyl acetate, and the combined washings concentrated *in vacuo* as a pale yellow oil. The mixture was purified by flash column chromatography (5 → 25% ethyl acetate / petrol) afford a mixture of **125** and **127** in a 93:7 ratio as a pale yellow oil.

$[\alpha]_{\text{D}}^{25} +26.9$ (*c* 2.13, CHCl₃); *R_f* 0.25 (30% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3433, 1722, 1614, 1271, 1114, 1026, 1002, 711; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 8.05 (2H, d, *J* = 7.5 Hz, ArH), 7.58 (1H, t, *J* = 7.5 Hz, ArH), 7.46 (2H, d, *J* = 7.5 Hz, ArH), 6.56 (1H, dd, *J* = 15.0 and 9.0 Hz, H2), 5.98 (1H, d, *J* = 9.0 Hz, H3), 5.84 (1H, d, *J* = 15.0 Hz, H1), 4.16-4.12 (1H, m, OCH(CH₃)₂), 3.86 (1H, s, OH), 3.48 (2H, d, *J* = 7.0 Hz, H5), 2.98 (1H, t, *J* = 7.0 Hz, OH), 1.34 (3H, d, *J* = 6.0 Hz, 1 x OCH(CH₃)₂), 1.26 (3H, d, *J* = 6.0 Hz, 1 x OCH(CH₃)₂), 1.25 (3H, s, CH₃), 1.04-0.97 (6H, m, Si(CH₂CH₃)₂), 0.82-0.65 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 165.9 (CO₂), 143.8 (C2), 133.3 (Ar), 131.0 (C1), 129.9 (Ar), 129.7 (Ar), 128.4 (Ar), 75.7 (C3), 73.9 (C4), 68.0 (C5), 66.5 (OCH(CH₃)₂), 25.6 (OCH(CH₃)₂), 18.6 (CH₃), 7.0 (Si(CH₂CH₃)₂), 6.8 (Si(CH₂CH₃)₂), 6.1 (Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₂₀H₃₂O₅Si [M+Na]⁺ 403.1911, found 403.1915.

(*R*)-2-[(*S*)-2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl]propane-1,2-diol (60**)**

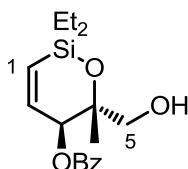


To a mixture of **126** and **127** (8 mg, 0.0251 mmol, 1.0 eq) was added a solution of sodium methoxide in MeOH (0.045 M, 600 μ L, 0.0276 mmol, 1.1 eq) for 4 h. The reaction mixture was quenched with H₂O and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to afford the title compound as a pale yellow oil (3.7 mg, 69%).

$[\alpha]_{\text{D}}^{20} +79.2$ (c 1.0, CHCl_3).

The spectroscopic data was found to be in agreement with the racemic compound whose preparation is described above.

(5*S*,6*R*)-2,2-Diethyl-6-(hydroxymethyl)-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (126)

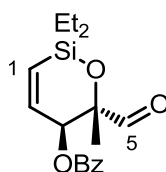


To a solution of **120** (1.22 g, 3.22 mmol, 1.0 eq) and quinoline (76 μL , 0.645 mmol, 0.2 eq) in toluene (32 mL) in a 100 mL round-bottomed flask fitted with a rubber septum was added palladium on calcium carbonate (5% wt. no lead content, 343 mg, 0.161 mmol, 0.05 eq). The flask was fitted with an outlet needle and H_2 was bubbled into the reaction mixture from a balloon. The progress of the reaction was monitored by TLC. After 7 h, the mixture was filtered through Celite[®] and the filter cake rinsed with DCM (64 mL). PPTS (81 mg, 0.322 mmol, 0.1 eq) was added to the filtrate, and the pale yellow solution stirred at room temperature for a further 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatograph (5 $\rightarrow$ 20% ethyl acetate / petrol) to afford the title compound as a colourless oil (914 mg, 85%).

$[\alpha]_{\text{D}}^{20} -4.22$ (c 0.51, CHCl_3); R_f 0.20 (10% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3406, 1606, 1503, 1310, 1269, 1096, 1007, 746; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 8.45 (1H, dd, $J = 8.0, 1.0$ Hz, ArH), 7.59 (1H, t, $J = 8.0$ Hz, ArH), 7.47 (2H, t, $J = 8.0$ Hz, ArH), 6.65 (1H, dd, $J = 14.5, 2.5$ Hz, C2), 6.01 (1H, dd, $J = 14.5, 2.5$ Hz, C1), 5.79 (1H, t, $J = 2.5$ Hz, H3), 3.50 (1H, dd, $J = 11.0, 8.0$ Hz, 1 x H5), 3.44 (1H, dd, $J = 11.0, 4.0$ Hz, 1 x H5), 2.26 (1H, dd, $J = 8.0, 4.0$ Hz, OH), 1.35 (3H, s, CH_3), 1.02 (3H, t, $J = 8.0$ Hz, 1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 1.00 (3H, t, $J = 8.0$ Hz, 1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.74-0.59 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 165.7 (CO_2), 148.1 (C2), 133.3 (Ar), 129.9 (Ar *ipso*), 129.7 (Ar), 128.5 (Ar), 126.5 (C1), 76.5

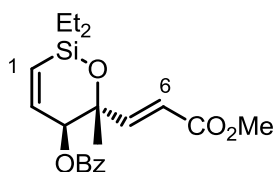
(C4), 71.4 (C3), 68.2 (C5), 19.2 (CH₃), 7.2 (1 x Si(CH₂CH₃)₂), 6.6 (1 x Si(CH₂CH₃)₂), 6.4 (1 x Si(CH₂CH₃)₂), 6.3 (1 x Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₁₇H₂₄O₄Si [M+Na]⁺ 343.1336, found 343.1332.

(5*S*,6*S*)-2,2-Diethyl-6-formyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (129)



SO₃·pyridine complex (231 mg, 1.45 mmol, 3.1 eq) and DMSO (350 μL, 4.91 mmol, 10.5 eq) were stirred together for 15 min at room temperature. A solution of **126** (150 mg, 0.468 mmol, 1.0 eq) and DIPEA (420 μL, 2.43 mmol, 5.2 eq) in DCM (2.4 mL) was added and the resulting solution stirred at room temperature for 1 h. The reaction was diluted with ether and quenched with aqueous 1M HCl. The organic layer was washed with saturated aqueous NaHCO₃, dried over MgSO₄ and concentrated *in vacuo* as a yellow oil (141 mg, 95%) which was used in the next step without further purification.

[α]_D²⁰ -124 (c 0.98, CHCl₃); **R_f** 0.42 (10% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 2958, 1723, 1600, 1493, 1267, 1110, 833, 700; **¹H NMR** (500 MHz, CDCl₃) δ_H 9.60 (1H, s, CHO), 8.05 (2H, d, *J* = 8.0 Hz, ArH), 7.59 (1H, t, *J* = 8.0 Hz, ArH), 7.46 (2H, t, *J* = 8.0 Hz, ArH), 6.84 (1H, dd, *J* = 14.5, 4.0 Hz, H2), 6.14 (1H, dd, *J* = 14.5, 1.0 Hz, H1), 5.72 (1H, dd, *J* = 4.0, 1.0 Hz, H3), 1.43 (CH₃), 1.04 (3H, t, *J* = 8.0 Hz, 1 x Si(CH₂CH₃)₂), 1.03 (3H, t, *J* = 8.0 Hz, 1 x Si(CH₂CH₃)₂), 0.80-0.71 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 201.0 (C5), 165.6 (CO₂), 145.7 (C2), 133.3 (Ar), 130.2 (C1), 129.7 (Ar), 129.6 (Ar *ipso*), 128.5 (Ar), 80.8 (C4), 69.5 (C3), 19.2 (CH₃), 6.9 (1 x Si(CH₂CH₃)₂), 6.8 (1 x Si(CH₂CH₃)₂), 6.5 (1 x Si(CH₂CH₃)₂), 6.4 (1 x Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₁₇H₂₂O₄Si [M+Na+MeOH]⁺ 373.1442, found 373.1436.

(5*S*,6*R*)-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 (130)

To a solution of (methoxycarbonylmethyl)triphenylphosphonium bromide (31 mg, 0.0754 mmol, 1.2 eq) in THF (300 μ L) at 0 $^{\circ}$ C was added NaHMDS (1.0 M in THF, 63 μ L, 0.0628 mmol, 1.0 eq). The mixture was stirred at 0 $^{\circ}$ C for 10 min, then warmed to room temperature. A solution of **129** (20 mg, 0.0628 mmol, 1.0 eq) in THF (300 μ L) was added dropwise at room temperature and the reaction mixture stirred at 60 $^{\circ}$ C for 16 h. The yellow solution was diluted with ether and washed with saturated aqueous ammonium chloride. The organic layer was dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 20% ether / petrol) to afford the title compound as a pale yellow oil (8 mg, 34%).

R_f 0.18 (10% ether / petrol); **¹H NMR** (500 MHz, CDCl_3) δ_{H} 8.06 (2H, d, J = 7.5 Hz, ArH), 7.61 (1H, t, J = 7.5 Hz, ArH), 7.48 (2H, t, J = 7.5 Hz, ArH), 7.02 (1H, d, J = 14.5 Hz, H5), 6.64 (1H, dd, J = 14.5, 2.5 Hz, H2), 6.18 (1H, d, J = 14.5 Hz, H6), 6.08 (1H, dd, J = 14.5, 2.5 Hz, H1), 5.46 (1H, t, J = 2.5 Hz, H3), 3.71 (OCH₃), 1.50 (CH₃), 1.04-0.99 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.77-0.61 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 167.1 (CO₂), 165.5 (CO₂), 151.7 (C5), 146.6 (C2), 133.3 (Ar), 129.7 (Ar), 129.6 (Ar *ipso*), 128.5 (Ar), 128.4 (C1), 119.8 (C6), 75.6 (C4), 74.5 (C3), 51.6 (OCH₃), 22.7 (CH₃), 7.0 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.6 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.4 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.3 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{20}\text{H}_{36}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 397.1442, found 397.1429.

2-(Triphenylphosphoranylidene)acetaldehyde (135)

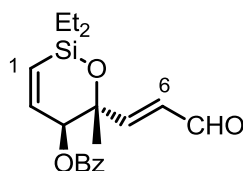
To a solution of (formylmethyl)triphenylphosphonium chloride (2.00 g, 5.87 mmol, 1.0 eq) in wet DCM (29 mL) was added aqueous 1M NaOH (6.5 mL, 6.5 mmol, 1.1 eq). The biphasic

mixture was stirred vigorously at room temperature for 1.5 h. The aqueous layer was extracted with DCM and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo* as light brown solids (1.77 g, 99%) which were used without any further purification.

$^1\text{H NMR}$ (200 MHz, CDCl_3) δ_{H} 9.00 (1H, $J = 38.0, 3.5$ Hz, *cis* CHO), 8.26 (1H, $J = 10.5, 3.5$ Hz, *trans* CHO), 4.07 (1H, $J = 19.5, 10.5$ Hz, *trans* CHP), 3.67 (1H, $J = 24.5, 3.5$ Hz, *cis* CHP).

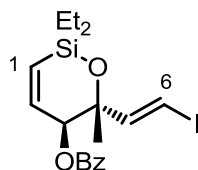
The spectroscopic data was found to be in agreement with that reported by Kayser and co-workers.²⁵⁰

(5*S*,6*R*)-2,2-Diethyl-6-methyl-6-[(*E*)-3-oxoprop-1-en-1-yl]-5,6-dihydro-2H-1,2-oxasilin-5-yl benzoate (132)



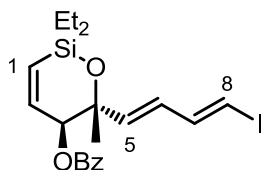
A solution of **129** (96 mg, 0.303 mmol, 1.0 eq) and phosphorous ylide **135** (101 mg, 0.333, 1.1 eq) in toluene (3 mL) was stirred at 80 °C over 16 h, then concentrated *in vacuo*. The residue was purified by column chromatography (10 → 20% ether / petrol) to afford the title compound as a colourless oil (70 mg, 67%).

$[\alpha]_{\text{D}}^{20}$ -166 (*c* 1.0, CHCl_3); R_f 0.12 (10% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2877, 1723, 1692, 1316, 1265, 1108, 712; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 9.54 (1H, d, $J = 8.0$ Hz, CHO), 8.07 (2H, d, $J = 7.5$ Hz, ArH), 7.62 (1H, t, $J = 7.5$ Hz, ArH), 7.49 (2H, t, $J = 7.5$ Hz, ArH), 6.85 (1H, d, $J = 15.5$ Hz, H5), 6.64 (1H, dd, $J = 14.5, 2.5$ Hz, H2), 6.21 (1H, dd, $J = 15.5, 8.0$ Hz, H6), 6.11 (1H, dd, $J = 14.5, 2.5$ Hz, H1), 5.55 (1H, t, $J = 2.5$ Hz, H3), 1.55 (3H, s, CH_3), 1.05-0.99 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.77-0.62 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 193.8 (CHO), 165.5 (CO_2), 160.1 (C5), 146.5 (C2), 133.5 (Ar), 130.6 (C6), 129.7 (Ar), 129.5 (Ar *ipso*), 128.6 (Ar), 128.4 (C1), 75.8 (C4), 74.1 (C3), 22.2 (CH_3), 7.0 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.6 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.4 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.3 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$ 367.1336, found 367.1333.

(5*S*,6*R*)-2,2-Diethyl-6-[(*E*)-2-iodovinyl]-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (136)

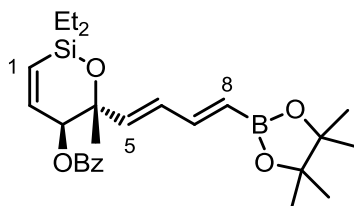
To chromium(II) chloride (77 mg, 0.642 mmol, 8.0 eq) dried under vacuum and heat was added THF (1 mL) and the resulting grey suspension was stirred for 30 min at room temperature. A solution of **129** (25 mg, 0.0780 mmol, 1.0 eq) and iodoform (61 mg, 0.156 mmol, 2.0 eq) in THF (1 mL) was then added *via* syringe and the mixture stirred at room temperature for 4 h. The resulting reddish-brown solution was diluted with ether, filtered through a pad of Celite®, and rinsed with ether. The filtrate was washed twice with distilled H₂O and once with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatograph (0 → 5% ether / petrol) to afford the title compound as a pale yellow oil (15.9 mg, 46%).

$[\alpha]_D^{20}$ -123 (*c* 1.0, CHCl₃); *R_f* 0.41 (5% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm⁻¹) 1724, 1602, 1370, 1315, 1264, 1109, 997, 710; **¹H NMR** (500 MHz, CDCl₃) δ_H 8.06 (2H, d, *J* = 7.5 Hz, ArH), 7.61 (1H, t, *J* = 7.5 Hz, ArH), 7.48 (2H, t, *J* = 7.5 Hz, ArH), 6.68 (1H, d, *J* = 14.5 Hz, H5), 6.63 (1H, dd, *J* = 14.5, 2.5 Hz, H2), 6.48 (1H, d, *J* = 14.5 Hz, H6), 6.07 (1H, dd, *J* = 14.5, 2.5 Hz, H1), 5.44 (1H, t, *J* = 2.5 Hz, H3), 1.45 (3H, s, CH₃), 1.03-0.99 (6H, m, Si(CH₂CH₃)₂), 0.75-0.62 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 165.5 (CO₂), 149.7 (C5), 146.6 (C2), 133.3 (Ar), 129.8 (Ar *ipso*), 129.7 (Ar), 128.5 (Ar), 128.4 (C1), 78.4 (C4), 77.5 (C6), 74.6 (C3), 22.7 (CH₃), 7.0 (1 x Si(CH₂CH₃)₂), 6.6 (1 x Si(CH₂CH₃)₂), 6.5 (1 x Si(CH₂CH₃)₂), 6.4 (1 x Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₁₈H₂₃IO₃Si [M+Na]⁺ 465.0353, found 465.0339.

(5*S*,6*R*)-2,2-Diethyl-6-[(1*E*,3*E*)-4-iodobuta-1,3-dien-1-yl]-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (139)

To chromium(II) chloride (58 mg, 0.474 mmol, 8.0 eq) dried under vacuum and heat was added THF (1 mL) and the resulting grey suspension was stirred for 30 min at room temperature. The suspension was cooled to 0 °C and a solution of **132** (20 mg, 0.059 mmol, 1.0 eq) and iodoform (46 mg, 0.12 mmol, 2.0 eq) in THF (0.5 mL) was added *via* syringe. The resulting red suspension was stirred in the dark for 4.5 h and allowed to warm to room temperature, after which it was diluted with ether and washed twice with distilled H₂O and once with brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 5% ether / petrol) to afford the title compound as a pale yellow oil (19 mg, 69%) as a 5:1 mixture of (1*E*) and (1*Z*)-isomers.

$[\alpha]_{\text{D}}^{20}$ -106 (*c* 1.0, CHCl₃); *R*_f 0.66 (15% ether / petrol + 1% Et₃N); **IR** (thin film, ν_{max} / cm⁻¹) 1721, 1587, 1451, 1266, 1068, 984, 710; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 8.06 (2H, d, *J* = 8.0 Hz, ArH), 7.60 (1H, t, *J* = 8.0 Hz, ArH), 7.48 (2H, t, *J* = 8.0 Hz, ArH), 6.97 (1H, dd, *J* = 14.0, 11.0 Hz, H7), 6.67 (1H, dd, *J* = 14.5, 3.0 Hz, H2), 6.31 (1H, d, *J* = 14.0 Hz, H8), 6.28 (1H, dd, *J* = 15.0, 11.0 Hz, H6), 6.08 (1H, dd, *J* = 14.5, 2.0 Hz, H1), 5.85 (1H, d, *J* = 15.0 Hz, H5), 5.45 (1H, dd, *J* = 3.0, 2.0 Hz, H3), 1.46 (3H, s, CH₃), 1.04-0.99 (6H, m, Si(CH₂CH₃)₂), 0.78-0.63 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 165.6 (CO₂), 146.7 (C2), 144.6 (C7), 139.1 (C5), 133.2 (Ar), 129.9 (Ar *ipso*), 129.6 (Ar), 128.8 (C6), 128.6 (C1), 128.5 (Ar), 79.4 (C8), 75.6 (C4), 75.0 (C3), 23.1 (CH₃), 7.0 (1 x Si(CH₂CH₃)₂), 6.7 (1 x Si(CH₂CH₃)₂), 6.5 (1 x Si(CH₂CH₃)₂), 6.5 (1 x Si(CH₂CH₃)₂); **HRMS** (ESI+) calc. for C₂₀H₂₅IO₃Si [M+Na]⁺ 491.0510, found 491.0522.

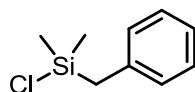
(5*S*,6*R*)-2,2-Diethyl-6-methyl-6-[(1*E*,3*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-1-yl]-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (140)

To chromium(II) chloride (200 mg, 1.63 mmol, 8.0 eq) dried under vacuum and heat was added THF (2 mL) and the resulting grey suspension was stirred for 30 min at room temperature. A solution of **132** (70 mg, 0.20 mmol, 1.0 eq) and pinacol (dichloromethyl)boronate (86 mg, 0.41 mmol, 2.0 eq) in THF (1 mL) was added *via* syringe, followed by a solution of LiI (109 mg, 0.813 mmol, 4.0 eq) in THF (1.0 mL) which was added dropwise in the dark. The resulting brown suspension was stirred in the dark at 50 °C for 16 h, after which it was diluted with ether and washed twice with distilled H₂O and once with brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 20% ether / petrol) to afford the title compound as a colourless oil (67 mg, 71%).

$[\alpha]_{\text{D}}^{20}$ -119 (*c* 1.0, CHCl₃); *R*_f 0.61 (10% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 1723, 1644, 1605, 1265, 1070, 970, 711; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 8.06 (2H, d, *J* = 7.5 Hz, ArH), 7.59 (1H, t, *J* = 7.5 Hz, ArH), 7.47 (2H, t, *J* = 7.5 Hz, ArH), 6.95 (1H, dd, *J* = 17.5, 10.5 Hz, H7), 6.71 (1H, dd, *J* = 14.5, 3.0 Hz, H2), 6.41 (1H, dd, *J* = 15.0, 10.5 Hz, H6), 6.09 (1H, dd, *J* = 14.5, 1.5 Hz, H1), 6.00 (1H, d, *J* = 15.0 Hz, H5), 5.54 (1H, d, *J* = 17.5 Hz, H8), 5.43 (1H, dd, *J* = 3.0, 1.5 Hz, H3), 1.46 (3H, s, CH₃), 1.25 (12H, s, OC(CH₃)₂), 1.04-0.99 (6H, m, Si(CH₂CH₃)₂), 0.75-0.63 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 165.63 (CO₂), 149.3 (C7), 146.4 (C2), 142.3 (C5), 133.2 (Ar), 130.7 (C6), 130.0 (Ar *ipso*), 129.6 (Ar), 129.1 (C1), 128.4 (Ar), 121.0 (C8), 83.1 (OC(CH₃)₂), 75.8 (C4), 74.8 (C3), 24.7 (C(CH₃)₂), 23.6 (CH₃), 7.0 (1 x Si(CH₂CH₃)₂), 6.7 (1 x Si(CH₂CH₃)₂), 6.6 (1 x Si(CH₂CH₃)₂), 6.5 (1 x Si(CH₂CH₃)₂); **HRMS** (FI⁺) calc. for C₂₆H₃₇BO₅Si [M]⁺ 468.2509, found 468.2511.

7.3 Direct functionalised silylolefination of aldehydes

Benzylchlorodimethylsilane

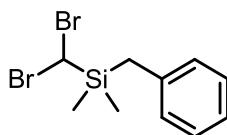


To dichlorodimethylsilane (2.45 mL, 20.3 mmol, 1.2 eq) in a two neck round-bottomed flask fitted with a reflux condenser under argon was added a solution of benzyl magnesium chloride in ether (0.94 M, 18 mL, 16.9 mmol, 1.0 eq). The resulting solution was heated at reflux for 2 h, whereupon it was concentrated *in vacuo*, redissolved in anhydrous pentane, filtered through Celite[®] under nitrogen and concentrated *in vacuo* as a yellow oil. The mixture was purified by vacuum distillation to afford the title compound as a colourless oil (2.88 g, 92%).

bp 97-99 °C, 17 mbar (lit.⁹ 105 °C, 21 mbar); ¹H NMR (400 MHz, CDCl₃) δ_H 7.27 (2H, t, *J* = 7.5 Hz, ArH), 7.15 (1H, t, *J* = 7.5 Hz, ArH), 7.09 (2H, d, *J* = 7.5 Hz, ArH), 2.42 (2H, s, SiCH₂), 0.40 (6H, s, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 137.1, 128.8, 128.5, 124.9, 28.9, 1.1.

The physical and spectroscopic data was found to be in agreement with that reported by Tacke and co-workers.²⁵¹

Benzyl(dibromomethyl)dimethylsilane (144)



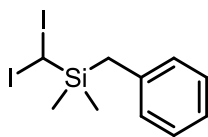
Method A: To a solution of diisopropylamine (1.6 mL, 11.3 mmol, 1.03 eq) in THF (7 mL) at 0 °C under argon was added a solution of *n*-BuLi in hexanes (2.5 M, 4.5 mL, 11.2 mmol, 1.02 eq). The solution was stirred at 0 °C for 15 min, then added dropwise to a solution of dibromomethane (0.78 mL, 11.0 mmol, 1.0 eq) and benzylchlorodimethylsilane (2.0 mL, 11.0 mmol, 1.0 eq) in THF at -78 °C. The resulting pale yellow solution was stirred at -78 °C for 1 h, then quenched by pouring into a 1M aqueous solution of HCl (20 mL). The mixture was extracted with ether (3 x 20 mL), then the combined organic layers were dried over MgSO₄ and

concentrated *in vacuo* to afford the the crude product. The title compound was purified by flash chromatography (petrol) as a colourless oil (1.93 g, 6.00 mmol, 55%).

Method B: To a solution of bromoform (0.48 mL, 5.51 mmol, 1.0 eq) in THF (7 mL) at $-90\text{ }^{\circ}\text{C}$ under argon was added a solution of *i*-PrMgCl in THF (2.0 M, 2.75 mL, 5.51 mmol, 1.0 eq) dropwise, maintaining the temperature of the solution below $-80\text{ }^{\circ}\text{C}$. The resulting yellow solution was stirred at $-90\text{ }^{\circ}\text{C}$ for 15 min. A solution of benzylchlorodimethylsilane (1.00 mL, 5.51 mmol, 1.0 eq) in THF (2.0 mL) was then added, maintaining the temperature of the solution below $-80\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-90\text{ }^{\circ}\text{C}$ for 1 h before being allowed to warm to room temperature, then it was quenched with NH_4Cl (20 mL, sat., aq.) and stirred for a further 1 h at room temperature. The organic layer was separated, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol) to provide silane **144** as a colourless oil (872 mg, 2.71 mmol, 49%)

R_f 0.27 (petrol); **IR** (thin film, $\nu_{\text{max}} / \text{cm}^{-1}$) 3024, 1600, 1452, 1492, 1251, 835, 699, 614; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.25 (2H, t, $J = 7.5\text{ Hz}$, ArH), 7.13 (1H, t, $J = 7.5\text{ Hz}$, ArH), 7.08 (2H, d, $J = 7.5\text{ Hz}$, ArH), 5.11 (1H, s, CHBr_2), 2.36 (2H, s, CH_2Ph), 0.24 (6H, s, $\text{Si}(\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 137.9, 128.5, 128.2, 124.7, 35.1 (CHBr_2), 23.2 (CH_2Ph), -5.2 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (FI+) calc. for $\text{C}_{10}\text{H}_{14}\text{Br}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 319.9232, found 319.9233.

Benzyl(diiodomethyl)dimethylsilane (145)



To a solution of hexamethyldisilazane (850 μL , 4.06 mmol, 1.5 eq) in ether (3 mL) at $0\text{ }^{\circ}\text{C}$ under argon was added a solution of *n*-BuLi in hexanes (2.5 M, 1.60 mL, 4.06 mmol, 1.5 eq) dropwise. The solution was stirred at $0\text{ }^{\circ}\text{C}$ over 15 min, during which time a white precipitate formed. The mixture was diluted with ether (5 mL) and THF (2 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. A solution of diiodomethane (330 μL , 4.06 mmol, 1.5 eq) in ether (1 mL) was added dropwise in

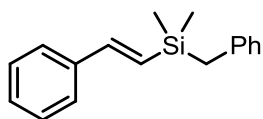
the dark. After 20 min, a solution of benzylchlorodimethylsilane (500 mg, 2.71 mmol, 1 eq) in ether (0.6 mL) was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, then allowed to warm to room temperature overnight. The reaction mixture was quenched with H_2O (15 mL) and the aqueous layer extracted with ether (3 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to give a brown oil. The residue was purified by column chromatography (petrol) to afford the silane **145** as an orange oil (830 mg, 1.99 mmol, 74%)

R_f 0.20 (petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3023, 2956, 1599, 1492, 1249, 1057, 820, 697; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.25 (2H, t, $J = 7.5\text{ Hz}$, ArH), 7.12 (1H, t, $J = 7.5\text{ Hz}$, ArH), 7.09 (2H, d, $J = 7.5\text{ Hz}$, ArH), 4.37 (1H, s, CH_2), 2.36 (1H, s, SiCH_2), 0.24 (6H, s, $\text{Si}(\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 138.3, 128.5, 128.1, 124.7, 23.8 (SiCH_2), -3.9 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (FI+) calc. for $\text{C}_{10}\text{H}_{14}\text{I}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 415.8954, found 415.8954.

General procedure for synthesis of vinylsilanes:

To chromium(II) chloride (176 mg, 1.43 mmol, 6.0 eq, flame dried under vacuum) in a 10 mL round-bottomed flask was added THF (4 mL), and the resulting grey suspension was stirred for 30 min at room temperature. A solution of aldehyde (0.239 mmol, 1.0 eq) and dihalomethylsilane (0.310 mmol, 1.3 eq) in THF (1.5 mL) was then added *via* syringe and the mixture stirred at room temperature or $50\text{ }^{\circ}\text{C}$ and monitored by TLC. After complete consumption of starting material, the resulting purple suspension was diluted with ether (10 mL), filtered through a pad of Celite[®], and washed with additional ether (10 mL). The filtrate was washed with H_2O (2 x 10 mL) and once with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography.

(*E*)-Benzyldimethyl(styryl)silane (**146**)

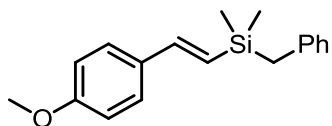


Conditions A: 53 mg, 0.196 mmol, 82%; Conditions B: 45 mg, 0.179 mmol, 75%; Conditions C: 46 mg, 0.184 mmol, 77%.

R_f 0.13 (petrol); **¹H NMR** (500 MHz, CDCl₃) δ_H 7.45 (2H, d, *J* = 7.5 Hz, ArH), 7.37 (2H, t, *J* = 7.5 Hz, ArH), 7.29 (1H, t, *J* = 7.5 Hz, ArH), 7.25 (2H, t, *J* = 7.5 Hz, ArH), 7.12 (1H, t, *J* = 7.5 Hz, ArH), 7.07 (2H, d, *J* = 7.5 Hz, ArH), 6.89 (1H, d, *J* = 19.0 Hz, CHPh), 6.47 (1H, d, *J* = 19.0 Hz, CHSi), 2.25 (2H, s, CH₂Ph), 0.18 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 144.7, 139.9, 138.2, 128.5, 128.3, 128.2, 128.1, 127.4 (CHPh), 126.4, 124.0 (CHSi), 26.1 (CH₂Ph), −3.3 (Si(CH₃)₂).

The spectroscopic data was found to be in agreement with that reported by Oshima and co-workers.²⁵²

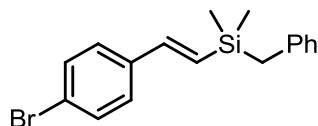
(*E*)-Benzyl(4-methoxystyryl)dimethylsilane (147)



Conditions A: 61 mg, 0.215 mmol, 90%.

R_f 0.43 (10% ether / petrol); **IR** (thin film, ν_{max} / cm^{−1}) 3024, 2361, 1604, 1509, 1251, 1172, 830, 699; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.39 (2H, d, *J* = 8.5 Hz, ArH), 7.24 (2H, t, *J* = 7.5 Hz, ArH), 7.10 (1H, t, *J* = 7.5 Hz, ArH), 7.06 (2H, d, *J* = 7.0 Hz, ArH), 6.89 (2H, d, *J* = 8.5 Hz, ArH), 6.82 (1H, d, *J* = 19.0 Hz, SiCHCH), 6.28 (1H, d, *J* = 19.0 Hz, SiCH), 3.84 (3H, s, OCH₃), 2.23 (2H, s, SiCH₂), 0.15 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 159.6, 144.1 (SiCHCH), 140.0, 131.2, 128.3, 128.1, 127.6, 124.5 (SiCH), 124.0, 113.9, 55.3 (OCH₃), 26.3 (SiCH₂), −3.3 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₀H₁₄I₂Si [M]⁺ 282.1440, found 282.1441.

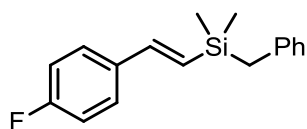
(*E*)-Benzyl(4-bromostyryl)dimethylsilane (148)



Conditions A: 65 mg, 0.196 mmol, 82%.

R_f 0.31 (10% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3024, 2955, 1601, 1248, 987, 904, 829, 796; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.46 (2H, d, $J = 8.5$ Hz, ArH), 7.28 (2H, d, $J = 8.5$ Hz, ArH), 7.23 (2H, t, $J = 7.5$ Hz, SiArH), 7.10 (1H, t, $J = 7.5$ Hz, SiArH), 7.03 (2H, d, $J = 7.0$ Hz, SiArH), 6.78 (1H, d, $J = 19.0$ Hz, SiCHCH), 6.43 (1H, d, $J = 19.0$ Hz, SiCH), 2.23 (2H, s, SiCH₂), 0.15 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 143.4 (SiCHCH), 139.7, 137.1, 128.5 (SiCH), 128.2, 128.1, 127.9, 124.1, 121.9, 26.0 (SiCH₂), -3.4 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₇H₁₉BrSi [M]⁺ 330.0439, found 330.0439.

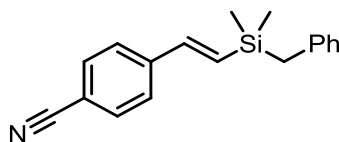
(E)-Benzyl(4-fluorostyryl)dimethylsilane (149)



Conditions A: 42 mg, 0.155 mmol, 65%.

R_f 0.31 (5% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 1601, 1507, 1248, 1227, 1156, 831, 699; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.39 (2H, dd, $J = 8.5, 5.5$ Hz, ArH), 7.23 (2H, d, $J = 7.5$ Hz, ArH), 7.09 (1H, t, $J = 7.5$ Hz, ArH), 7.04-7.01 (4H, m, ArH), 6.81 (1H, d, $J = 19.0$ Hz, SiCHCH), 6.34 (1H, d, $J = 19.0$ Hz, SiCH), 2.22 (2H, s, SiCH₂), 0.15 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 162.6 (d, $^1J_{\text{C-F}} = 246$ Hz), 143.4 (SiCHCH), 139.8, 134.4 (d, $^4J_{\text{C-F}} = 3.5$ Hz), 128.2, 128.1, 127.9 (d, $^3J_{\text{C-F}} = 8.0$ Hz), 127.0 (SiCH), 124.0, 115.4 (d, $^2J_{\text{C-F}} = 22.0$ Hz), 26.1 (SiCH₂), -3.4 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₇H₁₉FSi [M]⁺ 270.1240, found 270.1233.

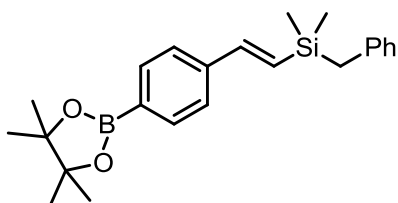
(E)-4-(2-Benzyl(dimethylsilyl)vinyl)benzonitrile (150)



Conditions B: 50 mg, 0.179 mmol, 75%.

R_f 0.25 (5% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 2957, 2227, 1603, 1493, 1249, 1206, 830, 700; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.63 (2H, d, J = 8.0 Hz), 7.49 (2H, d, J = 8.0 Hz), 7.25 (2H, t, J = 7.5 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.04 (2H, d, J = 7.5 Hz), 6.84 (1H, d, J = 19.0 Hz, SiCHCH), 6.61 (1H, d, J = 19.0 Hz, SiCH), 2.25 (2H, s, SiCH₂), 0.19 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 142.7 (SiCHCH), 142.2, 139.3, 132.7 (SiCH), 132.3, 128.2, 126.8, 124.2, 118.9 (CN), 111.1, 25.8 (SiCH₂), -3.5 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₁₈H₁₉NSi [M+Na]⁺ 300.1179, found 300.1170.

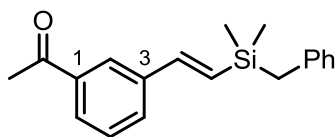
(*E*)-Benzyltrimethyl[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)styryl]silane (151)



Conditons A: 140 mg, 0.373 mmol, 78%; Conditons B: 154 mg, 0.411 mmol, 86%.

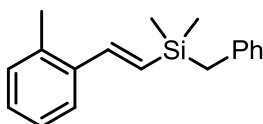
R_f 0.58 (20% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 2980, 1706, 1509, 1358, 1272, 1143, 1087, 857; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.83 (2H, d, J = 8.0 Hz, ArH), 7.46 (2H, d, J = 8.0 Hz, ArH), 7.25 (2H, t, J = 7.5 Hz, ArH), 7.11 (1H, t, J = 7.5 Hz, ArH), 7.06 (2H, d, J = 7.5 Hz, ArH), 6.90 (1H, d, J = 19.0 Hz, SiCHCH), 6.55 (1H, d, J = 19.0 Hz, SiCH), 2.26 (2H, s, SiCH₂), 1.39 (12H, s, 2 x C(CH₃)₂), 0.18 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 144.7 (SiCHCH), 140.8, 139.8, 135.1, 128.8 (SiCH), 128.3, 128.2, 125.7, 124.1, 83.8 (OC(CH₃)₂), 26.1(SiCH₂), 24.9 (C(CH₃)₂), -3.3 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₂₃H₃₁BO₂Si [M+Na]⁺ 401.2083, found 401.2066.

m/z (ESI+) 401 [M+Na]⁺, 381, 289, 217, 129; HRMS: Found [M+Na]⁺, 401.2066. C₂₃H₃₁BO₂Si requires [M+Na]⁺ 401.2083.

(E)-1-[3-(2-Benzyldimethylsilylvinyl)phenyl]ethanone (153)

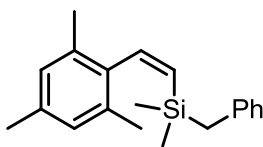
Conditions A: 65 mg, 0.220 mmol, 92%.

R_f 0.29 (10% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3024, 2956, 1685, 1599, 1493, 1247, 833, 796; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 8.00 (1H, t, $J = 1.5$ Hz, H5), 7.86 (1H, dt, $J = 7.5, 1.5$ Hz, H6), 7.62 (1H, d, $J = 7.5$ Hz, H4), 7.44 (1H, t, $J = 7.5$ Hz, H2), 7.24 (2H, t, $J = 7.5$ Hz, ArH), 7.10 (1H, t, $J = 7.5$ Hz, ArH), 7.07 (2H, d, $J = 7.5$ Hz, ArH), 6.90 (1H, d, $J = 19.0$ Hz, SiCHCH), 6.54 (1H, d, $J = 19.0$ Hz, SiCH), 2.64 (3H, s, COCH_3), 2.25 (2H, s, SiCH_2), 0.18 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 198.1 (CO), 143.6 (SiCHCH), 139.7, 138.7 (C3), 137.4 (C1), 130.8 (C4), 129.3 (SiCH), 128.8 (C2), 128.3, 128.2, 127.9 (C6), 126.2 (C5), 124.1, 26.7 (COCH_3), 26.0 (SiCH_2), -3.4 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{19}\text{H}_{22}\text{OSi}$ $[\text{M}+\text{Na}]^+$ 317.1332, found 317.1328.

(E)-Benzyldimethyl(2-methylstyryl)silane (154)

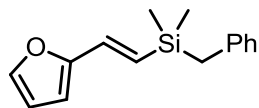
Conditions B: 53 mg, 0.198 mmol, 83%.

R_f 0.54 (10% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3023, 2955, 1600, 1493, 1206, 831, 741, 697; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.49 (1H, d, $J = 7.5$ Hz, ArH), 7.24-7.05 (9H, m, ArH + SiCHCH) 6.33 (1H, d, $J = 19.0$ Hz, SiCH), 2.35 (3H, s, CH_3), 2.24 (2H, s, SiCH_2), 0.16 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 142.5 (SiCHCH), 139.9, 137.6, 135.3, 130.3, 129.2 (SiCH), 128.3, 128.1, 127.8, 126.1, 125.3, 124.0, 26.2 (SiCH_2), 19.6 (CH_3), -3.3 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (FI+) calc. for $\text{C}_{18}\text{H}_{22}\text{Si}$ $[\text{M}]^+$ 266.1491, found 266.1493.

(Z)-Benzyldimethyl(2,4,6-trimethylstyryl)silane (155)

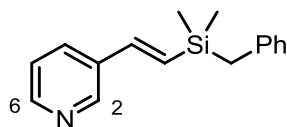
Conditions B: 20 mg, 0.069 mmol, 29%.

R_f 0.64 (5% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3024, 2952, 1614, 1599, 1493, 1247, 821, 697; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.23-7.18 (3H, m, ArH + SiCHCH), 7.06 (1H, t, $J = 7.5$ Hz, ArH), 6.96 (2H, d, $J = 7.5$ Hz, ArH), 6.81 (2H, s), 5.97 (1H, d, $J = 15.0$ Hz, SiCH), 2.27 (3H, s, *p*-CH₃), 2.12 (6H, s, 2 x *o*-CH₃), 2.00 (2H, s, SiCH₂), -0.27 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 146.2 (SiCHCH), 140.1, 136.9, 136.0, 135.0, 131.9 (SiCH), 128.2, 128.0, 127.6, 123.9, 26.1 (SiCH₂), 21.0 (*p*-CH₃), 20.4 (*o*-CH₃), -3.2 (Si(CH₃)₂); **HRMS** (FI⁺) calc. for C₂₀H₂₆Si [M]⁺ 294.1804, found 224.1812.

(E)-Benzyl(2-(furan-2-yl)vinyl)dimethylsilane (156)

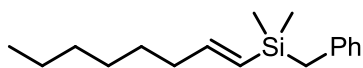
Conditions A: 50 mg, 0.206 mmol, 86%; Conditions B: 50 mg, 0.206 mmol, 86%.

R_f 0.50 (petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3024, 2956, 1600, 1493, 1452, 1249, 836, 698; δ_{H} **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.38 (1H, d, $J = 2.0$ Hz, ArH), 7.22 (2H, t, $J = 7.5$ Hz, ArH), 7.09 (1H, t, $J = 7.5$ Hz, ArH), 7.03 (2H, d, $J = 7.5$ Hz, ArH), 6.64 (1H, d, $J = 19.0$ Hz, SiCHCH), 6.39 (1H, dd, $J = 3.0, 2.0$ Hz, ArH), 6.31 (1H, d, $J = 19.0$ Hz, SiCH), 6.28 (1H, d, $J = 3.0$ Hz, ArH), 2.20 (2H, s, SiCH₂), 0.11 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 154.0, 142.3, 139.8, 132.1 (SiCHCH), 128.2, 128.1, 125.5 (SiCH), 124.0, 111.4, 108.2, 26.0 (SiCH₂), -3.5 (Si(CH₃)₂); **HRMS** (ESI⁺) calc. for C₁₅H₁₈OSi [M+Na]⁺ 265.1019, found 265.1019.

(E)-3-[2-(Benzyldimethylsilyl)vinyl]pyridine (157)

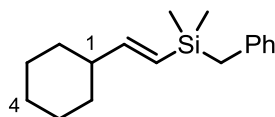
Conditions A: 27 mg, 0.108 mmol, 45%, Conditions C: 27 mg, 0.108 mmol, 49%.

R_f 0.26 (20% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3024, 2956, 1601, 1493, 1410, 1248, 1207, 700; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 8.61 (1H, d, $J = 2.0$ Hz, H2), 8.49 (1H, dd, $J = 4.5, 2.0$ Hz, H6), 7.73 (1H, dt, $J = 8.0, 2.0$ Hz, H4), 7.26 (1H, dd, $J = 8.0, 4.5$ Hz, H5), 7.22 (2H, t, $J = 8.0$ Hz, SiArH), 7.10 (1H, t, $J = 7.5$ Hz, SiArH), 7.03 (2H, d, $J = 7.5$ Hz, SiArH), 6.82 (1H, d, $J = 19.0$ Hz, SiCHCH), 6.53 (1H, d, $J = 19.0$ Hz, SiCH), 2.23 (2H, s, SiCH₂), 0.17 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 149.0, 148.6, 141.0 (SiCHCH), 139.5, 132.7, 130.6 (SiCH), 128.2, 128.1, 124.2, 123.4, 25.9 (SiCH₂), -3.5 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₁₆H₁₉NSi [M+H]⁺ 254.1360, found 254.1361.

(E)-Benzyldimethyl(oct-1-en-1-yl)silane (162)

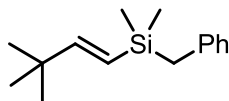
Conditions A: 48 mg, 0.184 mmol, 77%.

R_f 0.75 (petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 2926, 2856, 1616, 1493, 1452, 1248, 831, 698; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.21 (2H, t, $J = 7.5$ Hz, ArH), 7.07 (1H, t, $J = 7.5$ Hz, ArH), 7.00 (2H, d, $J = 7.5$ Hz, ArH), 6.01 (1H, dt, $J = 18.5, 6.5$ Hz, SiCHCH), 5.59 (1H, d, $J = 18.5$ Hz, SiCH), 2.12-2.09 (4H, m, SiCH₂ + CHCH₂), 1.54-1.29 (8H, m, 4 x CH₂), 0.92-0.89 (3H, m, CH₂CH₃), 0.03 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 148.8 (SiCHCH), 140.2, 128.8, 128.0, 127.4 (SiCH), 123.8, 36.8, 31.7, 28.8, 28.6, 26.3 (SiCH₂), 22.6, 14.1, -3.3 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₇H₂₈Si [M]⁺ 260.1960, found 260.1962.

(E)-Benzyl(2-cyclohexylvinyl)dimethylsilane (163)

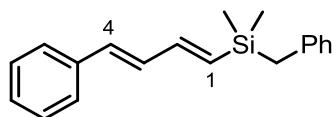
Conditions A: 50 mg, 0.191 mmol, 80%; Conditions B: 120 mg, 0.373 mmol, 78%.

R_f 0.75 (petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3024, 2924, 1602, 1493, 1450, 1247, 831, 698; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.21 (2H, t, $J = 7.5$ Hz, ArH), 7.08 (1H, t, $J = 7.5$ Hz, ArH), 7.01 (2H, d, $J = 7.5$ Hz, ArH), 5.96 (1H, dd, $J = 19.0, 6.0$ Hz, SiCHCH), 5.40 (1H, dd, $J = 19.0, 1.5$ Hz, SiCH), 2.12 (2H, s, SiCH₂), 2.00-1.94 (1H, m, H1_{eq}), 1.76-1.72 (4H, m, H2_{eq}+H3_{eq}+H5_{eq}+H6_{eq}), 1.69-1.65 (1H, m, H4_{eq}), 1.33-1.24 (2H, m, H3_{ax}+ H5_{ax}), 1.18 (1H, tt, $J = 12.5, 3.0$ Hz, H4_{ax}), 1.12-1.04 (2H, m, H2_{ax}+ H6_{ax}), 0.04 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 154.1 (SiCHCH), 140.3, 128.3 (SiCH), 128.0, 124.1, 123.8, 44.0 (C1), 32.3 (C2+C6), 26.3 (C3+C5), 26.2 (SiCH₂), 26.0 (C4), -3.3 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₇H₂₆Si [M]⁺ 258.1804, found 258.1807.

(E)-Benzyl(3,3-dimethylbut-1-en-1-yl)dimethylsilane (164)

Conditions A: 43 mg, 0.184 mmol, 77%.

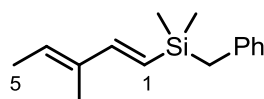
R_f 0.36 (petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 1602, 1493, 1245, 1206, 993, 830, 697; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.20 (2H, t, $J = 7.5$ Hz, ArH), 7.06 (1H, t, $J = 7.5$ Hz, ArH), 6.99 (2H, d, $J = 7.5$ Hz, ArH), 5.99 (1H, d, $J = 19.0$ Hz, SiCHCH), 5.48 (1H, d, $J = 19.0$ Hz, SiCH), 2.12 (2H, s, SiCH₂), 0.99 (9H, s, C(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 158.8 (SiCHCH), 140.3, 128.3, 127.9, 123.8, 120.5 (SiCH), 35.1 (C(CH₃)₃), 29.0 (C(CH₃)₃), 26.4 (SiCH₂), -3.3 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₅H₂₄Si [M]⁺ 232.1647, found 232.1645.

Benzyltrimethyl[(1*E*,3*E*)-4-phenyl-1,3-butadienyl]silane (165)

Conditions A: 63 mg, 0.225 mmol, 94%.

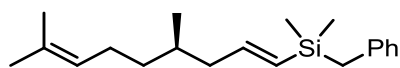
R_f 0.19 (petrol); **¹H NMR** (500 MHz, CDCl₃) δ_H 7.42 (2H, d, *J* = 7.5 Hz, ArH), 7.33 (2H, t, *J* = 7.5 Hz, ArH), 7.27-7.21 (3H, m, ArH), 7.09 (1H, t, *J* = 7.5 Hz, ArH), 7.03 (2H, d, *J* = 7.5 Hz, ArH), 6.79 (1H, dd, *J* = 15.5, 10.0 Hz, H3), 6.67 (1H, dd, *J* = 18.5, 10.0 Hz, H2), 6.58 (1H, d, *J* = 15.5 Hz, H4), 5.96 (1H, d, *J* = 18.5 Hz, H1), 2.19 (2H, s, SiCH₂), 0.10 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 145.1 (C2), 139.9, 137.1, 133.2 (C4), 132.6 (C1), 131.5 (C3), 128.6, 128.2, 128.1, 127.7, 126.5, 124.0, 26.1 (SiCH₂), -3.4 (Si(CH₃)₂).

The spectroscopic data was found to be in agreement with that reported by Oshima and co-workers.²⁵²

Benzyltrimethyl[(1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl]silane (166)

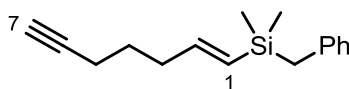
Conditions A: 45 mg, 0.196 mmol, 82%.

R_f 0.75 (10% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3025, 1680, 1637, 1600, 1249, 985, 904, 831; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.07 (1H, t, *J* = 7.5 Hz, ArH), 7.01 (2H, d, *J* = 7.0 Hz, ArH), 6.53 (1H, d, *J* = 19.0 Hz, H2), 5.65 (1H, d, *J* = 19.0 Hz, H1), 5.63 (1H, q, *J* = 7.0 Hz, H4), 2.15 (2H, s, SiCH₂), 1.76 (3H, d, *J* = 7.0 Hz, H4), 1.74 (3H, s, CH₃), 0.06 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 149.5 (C2), 140.2, 136.3 (C3), 128.7, 128.2 (C4), 128.0, 123.9, 122.8 (C1), 26.3 (SiCH₂), 14.0 (C5), 11.4 (CH₃), -3.3 (Si(CH₃)₂); **HRMS** (FI⁺) calc. for C₁₅H₂₂Si [M]⁺ 230.1491, found 230.1486.

(*R,E*)-Benzyl(4,8-dimethylnona-1,7-dien-1-yl)dimethylsilane (167)

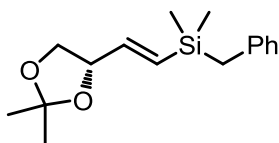
Conditions B: 58 mg, 0.194 mmol, 81%.

R_f 0.70 (10% ethyl acetate / petrol); **[α]²⁵_D** -38.2 (*c* = 0.96, CHCl₃); **IR** (thin film, *v*_{max} / cm⁻¹) 3025, 2956, 2913, 1615, 1601, 1248, 829, 697; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.08 (1H, t, *J* = 7.5 Hz, ArH), 7.01 (2H, d, *J* = 7.5 Hz, dt, ArH), 5.99 (1H, dt, *J* = 18.5, 6.5 Hz, H₂), 5.60 (1H, dt, *J* = 18.5, 1.5 Hz, H₁), 5.12 (1H, tt, *J* = 7.0, 1.5 Hz, H₇), 2.18-2.14 (3H, m, 1 x H₃ + SiCH₂), 1.71 (3H, s, CH₃), 1.63 (3H, s, CH₃), 1.57-1.51 (1H, m, H₄), 1.38-1.31 (1H, m, 1 x H₅), 1.20-1.12 (1H, m, 1 x H₅), 0.88 (3H, d, *J* = 6.5 Hz, CH₃), 0.05 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 147.3 (C₂), 140.2, 131.1 (C₈), 129.1 (C₁), 128.2, 128.0, 124.8 (C₇), 123.8, 44.5 (C₃), 36.7 (C₅), 32.3 (C₄), 26.3 (SiCH₂), 25.7 (CH₃), 25.6 (C₆), 19.4 (CH₃), 17.6 (CH₃), -3.3 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₂₀H₃₂Si [M]⁺ 300.2273, found 300.2279.

(*E*)-Benzyl(hept-1-en-6-ynyl)dimethylsilane (168)

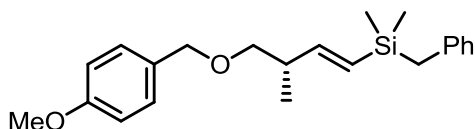
Conditions A: 46 mg, 0.189 mmol, 79%.

R_f 0.64 (30% ethyl acetate / petrol); **IR** (thin film, *v*_{max} / cm⁻¹) 3309, 3025, 1601, 1493, 1248, 904, 763, 699; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.07 (1H, t, *J* = 7.5 Hz, ArH), 7.00 (2H, d, *J* = 7.0 Hz, ArH), 5.97 (1H, dt, *J* = 18.5, 6.0 Hz, SiCHCH), 5.64 (1H, dt, *J* = 18.5, 1.5 Hz, SiCH), 2.25-2.20 (2H, m, H₃), 2.17 (2H, td, *J* = 7.5, 2.0 Hz, H₅), 2.12 (2H, s, SiCH₂), 1.97 (1H, t, *J* = 2.5 Hz, H₇), 1.66-1.60 (2H, m, H₄), 0.03 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 147.0 (C₂), 140.1, 128.8 (C₁), 128.2, 128.0, 123.9, 84.3 (C₆), 68.4 (C₇), 35.5 (C₃), 27.4 (C₄), 26.2 (SiCH₂), 17.8 (C₅), -3.4 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₆H₂₂Si [M]⁺ 242.1491, found 242.1487.

(*S,E*)-Benzyl(2,2-dimethyl-1,3-dioxolan-4-vinyl)dimethylsilane (170)

Conditions A: 40 mg, 0.146 mmol, 61%.

R_f 0.28 (10% ethyl acetate / petrol); **[α]²⁵_D** +16.4 (*c* = 1.01, CHCl₃); 99% *ee* (CHIRALPAK IC, 0.6% IPA / hexane, 1.3 mL/min, *t_R* (*S*) 3.82 min, *t_R* (*R*) 4.03 min); **IR** (thin film, *v*_{max} / cm⁻¹) 2987, 2360, 1600, 1494, 1249, 989, 834, 699; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.08 (1H, t, *J* = 7.5 Hz, ArH), 6.99 (2H, d, *J* = 7.5 Hz, ArH), 5.97 (1H, s, SiCHCH), 5.96 (1H, d, *J* = 1.5 Hz, SiCH), 4.51-4.47 (1H, m, CHO), 4.10 (1H, dd, *J* = 8.0, 6.0 Hz, 1xCH₂O), 3.56 (1H, t, *J* = 8.0 Hz, 1xCH₂O), 2.14 (2H, s, SiCH₂), 1.45 (3H, s, CH₃), 1.41 (3H, s, CH₃), 0.07 (3H, s, 1 x Si(CH₃)₂), 0.06 (3H, s, 1 x Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 144.1 (SiCHCH), 139.6, 131.9 (SiCH), 128.2, 128.1, 124.0, 109.4 (CO₂(CH₃)₂), 79.1 (CHO), 69.2 (CH₂O), 26.6 (CH₃), 25.9 (CH₃), 25.8 (SiCH₂), -3.5 (Si(CH₃)₂), -3.6 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₁₆H₂₄O₂Si [M+Na]⁺ 299.1438, found 299.1437.

(*S,E*)-Benzyl[4-(4-methoxybenzyl)oxy-3-methylbut-1-en-1-yl]dimethylsilane (171)

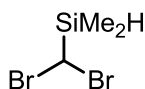
Conditions A: 58 mg, 0.163 mmol, 68%; Conditions B: 66 mg, 0.189 mmol, 79%.

R_f 0.43 (20% ethyl acetate / petrol); **[α]²⁵_D** -3.8 (*c* = 1.06, CHCl₃) (Conditions A), -3.4 (*c* = 0.47, CHCl₃) (Conditions B); 74% *ee* (Conditions A), 60% *ee* (Conditions B) (CHIRALPAK IB, 0.8% IPA / hexane, 1.3 mL/min, *t_R* (*S*) 3.53 min, *t_R* (*R*) 3.80 min); **IR** (thin film, *v*_{max} / cm⁻¹) 2957, 1613, 1513, 1247, 1090, 991, 831, 699; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.28 (2H, d, *J* = 8.5 Hz, ArH), 7.21 (2H, t, *J* = 7.5 Hz, ArH), 7.08 (1H, t, *J* = 7.5 Hz, ArH), 7.01 (2H, d, *J* = 7.5 Hz, ArH), 6.90 (2H, d, *J* = 8.5 Hz, ArH), 5.98 (1H, dd, *J* = 18.5, 6.5 Hz, H₂), 5.67 (1H, dd, *J* =

18.5, 1.5 Hz, H1), 4.47 (2H, s, OCH₂Ar), 3.09 (3H, s, OMe), 3.38 (1H, dd, $J = 9.0, 6.5$ Hz, 1 x H4), 3.27 (1H, dd, $J = 9.0, 7.0$ Hz, 1 x H4), 2.57-2.48 (1H, m, H3), 2.14 (2H, s, SiCH₂), 1.04 (3H, d, $J = 7.0$ Hz, Me), 0.06 (3H, s, 1 x Si(CH₃)₂), 0.05 (3H, s, 1 x Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 159.1, 150.5 (C2), 140.1, 130.7, 129.1, 128.3, 128.0, 127.0 (C1), 123.9, 113.7, 74.6 (C4), 72.5 (OCH₂Ar), 55.3 (OMe), 40.1 (C3), 26.2 (SiCH₂), 16.5 (Me), -3.5 (Si(CH₃)₂); HRMS (FI+) calc. for C₂₂H₃₀O₂Si [M+Na]⁺ 377.1907, found 377.1894.

The enantiopurity of the aldehyde substrate was determined by chiral HPLC analysis of the corresponding alcohol, obtained by NaBH₄ reduction of the aldehyde. Despite using the aldehyde immediately and without purification, the *ee* of an aliquot of the aldehyde removed at the time of setting up the silylolefinations was determined to be 80% (CHIRALPAK IC, 5% IPA / Hexane, 1.3 mL/min, *t_R* (*R*) 13.17 min, *t_R* (*S*) 14.35 min). Similar difficulties in preserving the stereochemical integrity of this aldehyde have been reported by Paquette and co-workers.¹⁵⁰

(Dibromomethyl)dimethylsilane (174)

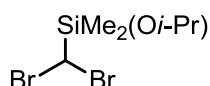


To a solution of bromoform (3.90 mL, 44.1 mmol, 1.00 eq) in THF (55 mL) at -90 °C was added *i*-PrMgCl in THF (2.0 M, 22.5 mL, 45.0 mmol, 1.02 eq) dropwise, maintaining the temperature of the solution below -80 °C. The resulting yellow solution was stirred at -90 °C for 15 min. A solution of chlorodimethylsilane (5.00 mL, 45.0 mmol, 1.02 eq) in THF (180 mL) was then added. The reaction mixture was stirred at -90 °C for 1 h before being allowed to warm to room temperature, upon which it was quenched with saturated NH₄Cl and stirred for a further 1 h. The organic layer was decanted, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by vacuum distillation to afford the title compound as a colourless oil (4.22 g, 41%).

b.p. 62-64 °C, 32 mbar (lit.²⁵³ 67-68 °C, 40 mmHg); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.20 (1H, d, *J* = 1.5 Hz, CHBr₂), 4.31-4.23 (1H, m, SiH), 0.35 (6H, d, *J* = 3.5 Hz, Si(CH₃)₂); **¹³C NMR** (100 MHz, CDCl₃) δ_C 32.9 (CHBr₂), -5.3 (Si(CH₃)₂).

The physical and spectroscopic data was found to be in agreement with that reported by Son and co-workers.²⁵⁴

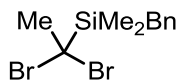
(Dibromomethyl)(isopropoxy)dimethylsilane (175)



To a solution of **174** (200 mg, 0.862 mmol, 1 eq) in isopropanol (130 μL, 1.72 mmol, 2 eq) was added dichloro(*p*-cymene)ruthenium(II) dimer (3 mg, 0.004 mmol, 0.5 mol%). Effervescence was observed and the resulting dark red solution was stirred over 4 h at room temperature. The reaction mixture was then filtered through a plug of silica gel washed with 10% ether in petrol and concentrated *in vacuo* as a colourless oil (250 mg, quant.).

IR (thin film, ν_{max} / cm⁻¹) 1444, 1260, 1095, 801; **¹H NMR** (500 MHz, CDCl₃) δ_H 5.15 (1H, s, CHBr₂), 4.21 (1H, sept, *J* = 6.0 Hz, OCH), 1.21 (6H, d, *J* = 6.0 Hz, OCH(CH₃)₂), 0.35 (6H, d, *J* = 3.5 Hz, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 66.7 (OCH), 35.0 (CHBr₂), 25.6 (OCH(CH₃)₂), -4.2 (Si(CH₃)₂).

Benzyl(1,1-dibromoethyl)dimethylsilane (183)

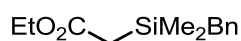


To a solution of diisopropylamine (96 μL, 0.683 mmol, 1.1 eq) in THF (0.6 mL) at 0 °C was added a solution of *n*-BuLi in THF (2.5 M, 260 μL, 0.652 mmol, 1.05 eq). The solution was stirred at 0 °C over 15 min then cooled to -78 °C. A solution of **144** in THF (1.2 mL) was added dropwise. After 30 min, methyl iodide (47 μL, 0.745 mmol, 1.2 eq) was added. The reaction mixture was stirred for a further 2 h, then poured onto aqueous 1M HCl and extracted

three times with ether. The combined organic layers were washed with saturated aqueous sodium thiosulphate and brine, dried over magnesium sulphate and concentrated *in vacuo* as a brown oil. The mixture was purified by column chromatography (petrol) to afford the title compound as a colourless oil (110 mg, 53%).

R_f 0.31 (petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3023, 2965, 1600, 1251, 821, 761, 698, 616; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.24 (2H, t, $J = 7.5$ Hz, ArH), 7.13 (1H, t, $J = 7.5$ Hz, ArH), 7.10 (2H, d, $J = 7.5$ Hz, ArH), 2.48 (3H, s, CH_3), 2.43 (2H, s, SiCH_2), 0.23 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 138.3, 128.5, 128.4, 124.7, 61.3 (CBr_2), 36.4 (CH_3), 23.1 (SiCH_2), -5.2 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (FI+) calc. for $\text{C}_{11}\text{H}_{16}\text{Br}_2\text{Si}$ $[\text{M}]^+$ 333.9388, found 333.9387.

Ethyl 2-(benzyldimethylsilyl)acetate (186)

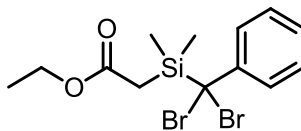


Zinc powder (1.00 g, 15.3 mmol, 1.2 eq), an iodine crystal and benzene (17 mL) were measured into a two-neck round bottomed flask fitted with a dropping funnel and water condenser under argon. The suspension was heated at 50 °C, and a solution of ethyl bromoacetate (1.80 mL, 15.9 mmol, 1.25 eq) in benzene (4 mL) and ether (4 mL) was added dropwise over 15 min. The reaction mixture was heated at reflux for 3 h, then cooled to room temperature and quenched with aqueous 1M HCl. The organic layer was decanted, washed with aqueous 1M HCl, saturated aqueous sodium carbonate and H_2O , dried over magnesium sulphate and concentrated *in vacuo* as a yellow oil. The mixture was purified by column chromatography to afford the title compound as a colourless oil (1.34 g, 45%).

R_f 0.31 (10% ethyl acetate–petrol); **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.24 (2H, t, $J = 7.5$ Hz, ArH), 7.10 (1H, t, $J = 7.5$ Hz, ArH), 7.05 (2H, d, $J = 7.5$ Hz, ArH), 4.11 (2H, q, $J = 7.0$ Hz, OCH_2), 2.20 (2H, s, CH_2Ph), 1.89 (2H, s, CHCO_2), 1.26 (3H, t, $J = 7.0$ Hz, CH_2CH_3), 0.10 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 172.8 (CO), 138.9, 128.3, 128.2, 124.3, 60.0 (OCH_2), 25.2, 25.0, 14.4 (CH_2CH_3), -3.4 ($\text{Si}(\text{CH}_3)_2$).

The spectroscopic data was found to be in agreement with that reported by Mahmoud and co-workers.²⁵⁵

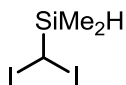
Ethyl 2-[(dibromophenylmethyl)dimethylsilyl]acetate (**188**)



To a solution of **186** (140 mg, 0.593 mmol, 1.0 eq) and *N*-bromosuccinimide (212 mg, 1.19 mmol, 2 eq) in carbon tetrabromide (1.2 mL) was added one crystal of benzoyl peroxide. The reaction mixture was heated at reflux for 1 h, filtered through a short pad of Celite® and concentrated *in vacuo* to afford the title compound as a colourless oil (224 mg, 96%).

R_f 0.30 (10% ethyl acetate–petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2979, 1720, 1244, 1146, 1095, 868, 825, 693; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.73 (2H, d, $J = 8.0$ Hz), 7.35 (2H, t, $J = 8.0$ Hz), 7.28 (1H, t, $J = 8.0$ Hz), 4.07 (2H, q, $J = 7.0$ Hz, OCH_2), 2.11 (2H, s, SiCH_2), 1.22 (3H, t, $J = 7.0$ Hz, CH_2CH_3), 0.36 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 171.7 (CO_2), 140.6, 128.5, 128.1, 128.0, 64.2 (CBr_2), 60.3 (OCH_2), 24.1 (SiCH_2), 14.3 (CH_2CH_3), –3.8 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (FI+) calc. for $\text{C}_{13}\text{H}_{18}\text{Br}_2\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 392.9516, found 392.9445.

(Diiodomethyl)dimethylsilane (**189**)



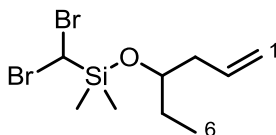
To a solution of iodoform (3.50 g, 8.83 mmol, 1.00 eq) in THF (11 mL) at –90 °C under argon was added a solution of ⁱPrMgCl in THF (1.25 M, 7.20 mL, 9.00 mmol, 1.02 eq) dropwise, maintaining the temperature of the solution below –80 °C. The resulting brown solution was stirred at –90 °C for 15 min. A solution of chlorodimethylsilane (1.00 mL, 9.00 mmol, 1.02 eq) in THF (3 mL) was then added, maintaining the temperature of the solution below –80 °C. The reaction was stirred at –90 °C for 1 h before being allowed to warm to room temperature, upon

which it was quenched with saturated aqueous ammonium chloride and stirred for a further 1 h at room temperature. The organic layer was decanted, dried over magnesium sulphate and concentrated *in vacuo* as a yellow oil. The mixture was purified by column chromatography (petrol) to afford the title compound as a pale yellow oil (1.25 g, 43%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.43 (1H, d, $J = 2.0$ Hz, CH_2), 4.28-4.24 (1H, m, SiH), 0.29 (6H, d, $J = 3.5$ Hz, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 22.1 (CH_2), -3.0 (CH_3).

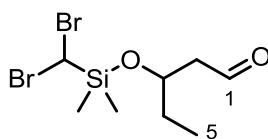
The spectroscopic data was found to be in agreement with that reported by Seyferth and co-workers.¹⁴⁷

Dibromomethyl(hex5-en-3-yloxy)dimethylsilane (196)



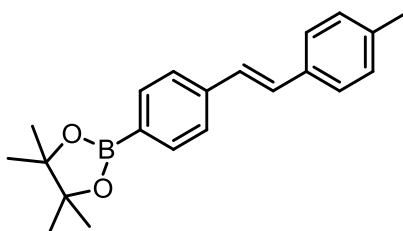
To a stirred mixture of **144** (441 mg, 1.90 mmol, 1.0 eq) and hex-5-en-3-ol (200 mg, 2.00 mmol, 1.05 eq) was added dichloro(*p*-cymene)ruthenium(II) dimer (6 mg, 0.01 mmol, 0.5 mol%). Effervescence was observed and the resulting dark red solution was stirred over 2.5 h at room temperature. A further portion of *hex-5-en-3-ol* (100 mg, 1.00 mmol, 1.0 eq) was added and the reaction stirred for an additional 3.5 h at room temperature. The reaction mixture was purified directly by column chromatography (10 $\rightarrow$ 20% ethyl acetate / petrol) to afford the title compound as a colourless oil (324 mg, 52%).

R_f 0.61 (10% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2967, 1603, 1433, 1257, 1094, 1055, 915, 839, 795; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 5.80 (1H, ddt, $J = 17.0, 10.0, 7.0$ Hz, H2), 5.13 (1H, s, CHBr_2), 5.11-5.06 (2H, m, H1), 3.86-3.81 (1H, m, H4), 2.31-2.22 (2H, m, H5), 0.91 (3H, t, $J = 7.5$ Hz, H6), 0.39 (6H, s, $\text{Si}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ_{C} 134.9 (C2), 117.2 (C1), 75.0 (C4), 41.1 (C3), 35.1 (CHBr_2), 29.4 (C5), 9.7 (C6), -4.0 ($\text{Si}(\text{CH}_3)_2$).

3-(Dibromomethyldimethylsilyl)-oxypentanal (195)

Through a solution of **196** (100 mg, 0.303 mmol, 1.0 eq) in dichloromethane (20 mL) at $-78\text{ }^{\circ}\text{C}$ was bubbled O_3 until saturation was observed (< 1 min). The reaction mixture was purged with O_2 for 10 min, after which the O_2 inlet was replaced with N_2 . Triphenylphosphine (120 mg, 0.455 mmol, 1.5 eq) was added and the solution was warmed to room temperature over 16 h. The solution was concentrated *in vacuo* as a pale yellow oil which was purified by column chromatography (5% ethyl acetate / petrol) to afford the title compound as a colourless oil (88 mg, 87%).

R_f 0.26 (5% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 2962, 2926, 1726, 1603, 1437, 1260, 1094, 801; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 9.85 (1H, t, $J = 2.0$ Hz, H1), 5.14 (1H, s, CHBr_2), 4.39-4.34 (1H, m, H3), 2.71 (1H, ddd, $J = 16.5, 7.0, 2.0$ Hz, 1xH2), 2.60 (1H, ddd, $J = 16.5, 4.5, 1.4$ Hz, 1xH2), 1.66-1.59 (2H, m, H4), 0.95 (3H, d, $J = 7.5$ Hz, H5), 0.43 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 201.5 (C1), 70.2 (C3), 50.4 (C2), 34.9 (CHBr_2), 30.4 (C4), 9.6 (C5), -4.0 ($1 \times \text{Si}(\text{CH}_3)_2$), -4.3 ($1 \times \text{Si}(\text{CH}_3)_2$).

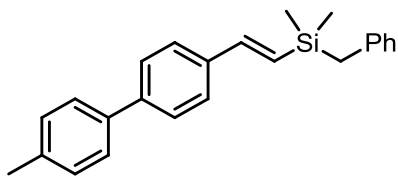
(E)-4,4,5,5-Tetramethyl-2-[4-(4-methylstyryl)phenyl]-1,3,2-dioxaborolane (197)

151 (50 mg, 0.132 mmol, 1.0 eq) and 4-iodotoluene (34 mg, 0.158 mmol, 1.2 eq) were dissolved in a solution of TBAF in THF (1.0M, 270 μL , 0.370 mmol, 2.0 eq) under argon and stirred at room temperature over 30 min. $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (4 mg, 0.003 mmol, 2.5 mol%) was added and the solution stirred at room temperature over 16 h. The reaction mixture was diluted

with ethyl acetate and filtered through a short plug of Celite[®]. The filtrate was washed with H₂O and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo* as brown solids. The mixture was purified by column chromatography (0 → 5% ether / petrol) to afford the title compound as off-white solids (20 mg, 48%).

R_f 0.41 (10% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 2978, 1603, 1510, 1359, 1145, 1089, 828, 654; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.80 (2H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.16 (1H, d, J = 16.5 Hz, CH), 7.07 (1H, d, J = 16.5 Hz, CH), 2.37 (3H, s, CH₃), 1.36 (12H, s, 2 x C(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 140.2, 137.7, 135.1, 134.4, 129.6 (CH), 129.4, 127.6 (CH), 126.5, 125.6, 83.7 (OC(CH₃)₂), 24.9 (C(CH₃)₂), 21.3 (CH₃); **HRMS** (ESI+) calc. for C₁₂H₂₅BO₂ [M+Na]⁺ 343.1844, found 343.1839.

(E)-Benzyltrimethyl[2-(4'-methyl-1,1'-biphenyl-4-yl)vinyl]silane (198)

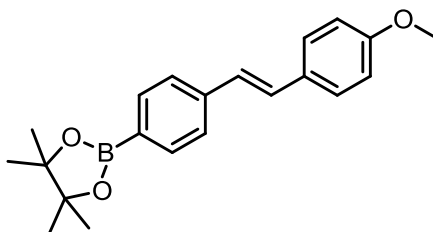


151 (70 mg, 0.185 mmol, 1.0 eq), 4-iodotoluene (48 mg, 0.222 mmol, 1.2 eq) and NaHCO₃ (62 mg, 0.740 mmol, 4.0 eq) were dissolved in DMSO (1.6 mL) and H₂O (80 μ L). The mixture was purged with N₂, then Pd(dppf)Cl₂ (7 mg, 0.009 mmol, 5 mol%) was added and the reaction was stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with H₂O (10 mL) and extracted with ether (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 5% ether / petrol) to afford the title compound as a white solid (50 mg, 0.146 mmol, 79%).

R_f 0.26 (5% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3024, 2956, 1601, 1493, 1360, 1247, 1147, 988; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.57 (2H, d, J = 8.0 Hz), 7.52 (2H, d, J = 8.0 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.23 (2H, t, J = 7.5 Hz), 7.10 (1H, t, J = 7.5 Hz), 7.05 (2H, d, J = 7.5 Hz), 6.89 (1H, d, J = 19.5 Hz, SiCHCH), 6.46 (1H, d, J = 19.5 Hz,

SiCH), 2.41 (3H, s, CH₃), 2.24 (2H, s, SiCH₂), 0.16 (6H, s, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 144.3 (SiCHCH), 140.8, 139.9, 137.8, 137.2, 137.0, 129.6, 128.3, 128.2, 127.3, 127.1 (SiCH), 126.9, 126.8, 124.1, 26.2 (SiCH₂), 21.2 (CH₃), -3.2 (Si(CH₃)₂); HRMS (FI+) calc. for C₂₄H₂₆Si [M]⁺ 342.1804, found 342.1803.

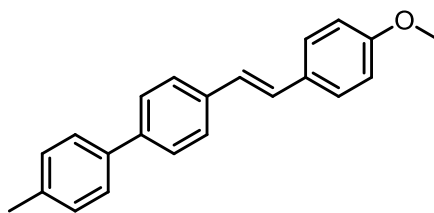
(E)-2-[4-(4-Methoxystyryl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S5)



151 (59 mg, 0.156 mmol, 1.0 eq) and 4-iodoanisole (44 mg, 0.187 mmol, 1.2 eq) were dissolved in a solution of TBAF in THF (1.0M, 312 μL, 0.312 mmol, 2.0 eq) under argon, and the mixture was stirred at room temperature for 30 min. Pd₂(dba)₃.CHCl₃ (4mg, 0.004 mmol, 2.5 mol%) was added and the solution was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a short plug of Celite[®]. The filtrate was washed with H₂O (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 10% ethyl acetate / petrol) to afford the title compound as an off-white solid (40 mg, 0.119 mmol, 76%).

R_f 0.29 (10% ethyl acetate / petrol); ¹H NMR (500 MHz, CDCl₃) δ_H 7.79 (2H, d, *J* = 8.0 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 7.48 (2H, d, *J* = 8.5 Hz), 7.14 (1H, d, *J* = 16.0 Hz, SiCHCH), 6.99 (1H, d, *J* = 16.0 Hz, SiCH), 6.91 (2H, d, *J* = 8.5 Hz), 3.84 (3H, s, OCH₃), 1.36 (12H, s, 2 x C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 159.4, 140.3, 135.1, 130.0, 129.2, 127.8, 126.5, 125.5, 114.1, 83.7, 55.3, 24.9.

The spectroscopic data was found to be in agreement with that reported by Evans and co-workers.²⁵⁶

(E)-4-(4-Methoxystyryl)-4'-methyl-1,1'-biphenyl (199)

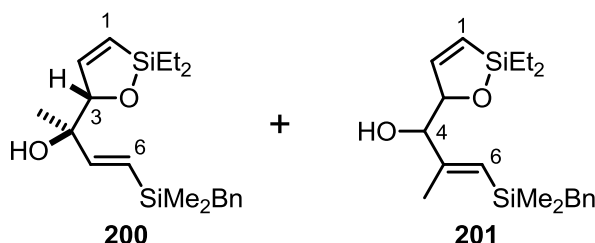
Hiyama Cross-Coupling: **198** (28 mg, 0.0817 mmol, 1.0 eq) and 4-iodoanisole (23 mg, 0.0981 mmol, 1.2 eq) were dissolved in a solution of TBAF in THF (1.0M, 165 μ L, 0.165 mmol, 2.0 eq) under argon, and the mixture was stirred at room temperature for 30 min. $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (2 mg, 0.002 mmol, 2.5 mol%) was added and the solution stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate and filtered through a short plug of Celite[®], and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 30% DCM / petrol) to afford the title compound as a white solid (18 mg, 0.060 mmol, 73%).

Suzuki Cross-Coupling: **S5** (10.0 mg, 0.0297 mmol, 1.0 eq), 4-iodotoluene (7.8 mg, 0.0357 mmol, 1.2 eq) and NaHCO_3 (10.0 mg, 0.119 mmol, 4.0 eq) were dissolved in DMSO (300 μ L) and H_2O (15 μ L). The mixture was purged with N_2 , $\text{Pd}(\text{dppf})\text{Cl}_2$ (1.5 mg, 0.0015 mmol, 5 mol%) was added and the reaction was stirred at 50 $^\circ\text{C}$ for 24 h. The reaction mixture was cooled to room temperature, then it was diluted with H_2O (1 mL) and extracted with ether (3 x 5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 30% DCM / petrol) to afford the title compound as a white solid (6.5 mg, 0.022 mmol, 73%).

R_f 0.20 (20% DCM / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3330, 1606, 1512, 1402, 969, 913, 820, 744; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.59 (2H, d, J = 8.5 Hz, *o*-ArCH₃), 7.56 (2H, d, J = 8.5 Hz, *m*-ArCH₃), 7.53 (2H, d, J = 8.0 Hz, ArH), 7.48 (2H, d, J = 8.5 Hz, *m*-ArOCH₃), 7.26 (2H, obs. d, ArH), 7.11 (1H, d, J = 16.5 Hz, CH), 7.02 (1H, d, J = 16.5 Hz, CH), 6.92 (2H, d, J = 8.5 Hz, *o*-ArOCH₃), 3.85 (3H, s, OCH₃), 2.41 (3H, s, CH₃); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 159.3,

139.8, 137.8, 137.0, 136.4, 130.2, 129.5, 128.1, 127.7, 127.1, 126.7, 126.6, 126.1, 114.1, 55.3 (OCH₃), 21.1 (CH₃); **HRMS** (FI⁺) calc. for C₂₂H₂₀O [M]⁺ 300.1514, found 300.1528.

***rac*-(*R,E*)-4-(Benzyldimethylsilyl)-2-[(*S*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl]but-3-en-2-ol (200) & *rac*-(*E*)-3-(Benzyldimethylsilyl)-1-(2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-2-methylprop-2-en-1-ol (201)**



To chromium(II) chloride (86 mg, 0.70 mmol, 6.0 eq) dried under vacuum and heat in a 10 mL round-bottomed flask was added THF (2 mL) and the resulting grey suspension was stirred for 30 min at room temperature. A solution of aldehyde **96** (0.116 mmol, 1.0 eq) and **145** (63 mg, 0.15 mmol, 1.3 eq) in THF (1 mL) was then added *via* syringe and the mixture stirred at room temperature over 16 h. The resulting purple suspension was diluted with ether, quenched with saturated aqueous EDTA.Na₂ and stirred at room temperature over 2 h. The organic layer was washed successively with distilled H₂O and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (5 → 20% ether / petrol) to afford the following compounds in a combined yield of 17% with a 1:1.3 distribution of **200:201**.

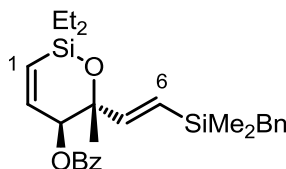
200: *R_f* 0.19 (10% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm⁻¹) 3459, 3024, 1601, 1493, 1411, 1376, 1248, 1031; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.20 (2H, t, *J* = 7.5 Hz, ArH), 7.06 (1H, t, *J* = 7.5 Hz, ArH), 6.98 (2H, d, *J* = 7.5 Hz, ArH), 6.84 (1H, dd, *J* = 10.5 and 1.5 Hz, H1), 6.27 (1H, dd, *J* = 10.5 and 2.5 Hz, H2), 5.98 (1H, d, *J* = 19.0 Hz, H6), 5.93 (1H, d, *J* = 19.0 Hz, H5), 4.55 (1H, dd, *J* = 2.5, 1.5 Hz, H3), 2.41 (1H, s, OH), 2.12 (2H, s, SiCH₂), 1.30 (3H, s, CH₃), 0.97 (3H, t, *J* = 8.0 Hz, 1 x Si(CH₂CH₃)₂), 0.91 (3H, t, *J* = 8.0 Hz, 1 x Si(CH₂CH₃)₂), 0.77-0.59 (4H, m, Si(CH₂CH₃)₂), 0.04 (3H, s, 1 x Si(CH₃)₂), 0.02 (3H, s, 1 x Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 149.8 (C1), 149.7 (C6), 139.9 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (C2), 126.2 (C5), 124.0 (Ar), 89.7 (C3), 75.7 (C4), 26.0 (SiCH₂), 24.4 (CH₃), 7.3 (Si(CH₂CH₃)₂), 6.8

(Si(CH₂CH₃)₂), 6.6 (Si(CH₂CH₃)₂), 6.4 (Si(CH₂CH₃)₂), -3.3 (Si(CH₃)₂), -3.6 (Si(CH₃)₂);

HRMS (ESI+) calc. for C₂₀H₃₂O₂Si₂ [M+Na]⁺ 383.1833, found 383.1832.

201: **R_f** 0.14 (10% ether / petrol); **IR** (thin film, $\nu_{\max}$ / cm⁻¹) 3464, 1601, 1493, 1248, 1122, 1030, 733, 699; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.21 (2H, t, J = 7.5 Hz, ArH), 7.07 (1H, t, J = 7.5 Hz, ArH), 7.04 (2H, d, J = 7.5 Hz, ArH), 6.69 (1H, dd, J = 10.5 and 1.5 Hz, H1), 6.07 (1H, dd, J = 10.5 and 2.5 Hz, H2), 5.50 (1H, s, H5), 4.55 (1H, dt, J = 8.0 and 2.0 Hz, H3), 3.65 (1H, dd, J = 8.0 and 1.5 Hz, H4), 2.84 (1H, d, J = 1.5 Hz, OH), 2.20 (2H, s, SiCH₂), 1.79 (3H, s, CH₃), 0.99-0.92 (6H, m, Si(CH₂CH₃)₂), 0.78-0.64 (4H, m, Si(CH₂CH₃)₂), 0.14 (3H, s, 1 x Si(CH₃)₂), 0.13 (3H, s, 1 x Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 153.2 (C6), 150.6 (C1), 140.1 (Ar), 128.2 (Ar), 128.1 (Ar), 126.6 (C2), 125.6 (C5), 124.0 (Ar), 85.4 (C3), 83.3 (C4), 26.4 (SiCH₂), 17.9 (C7), 7.1 (Si(CH₂CH₃)₂), 7.0 (Si(CH₂CH₃)₂), 6.8 (Si(CH₂CH₃)₂), 6.4 (Si(CH₂CH₃)₂), -1.9 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₂₀H₃₂O₂Si₂ [M+Na]⁺ 383.1833, found 383.1829.

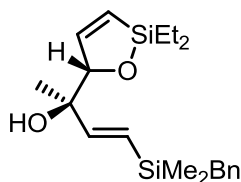
(5*S*,6*R*)-6-[(*E*)-2-(benzyltrimethylsilyl)vinyl]-2,2-diethyl-6-methyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl benzoate (204)



To chromium(II) chloride (116 mg, 0.942 mmol, 6.0 eq) dried under vacuum and heat was added THF (3 mL) and the resulting grey suspension was stirred for 30 min at 50 °C. A solution of **129** (50 mg, 0.157 mmol, 1.0 eq) and **144** (66 mg, 0.204 mmol, 1.3 eq) in THF (1 mL) was then added *via* syringe and the mixture stirred at 50 °C for 16 h. The resulting purple solution was diluted with ether, filtered through a pad of Celite[®], and rinsed with ether. The filtrate was washed twice with distilled H₂O and once with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatograph (0 → 5% ether / petrol) to afford the title compound as a pale yellow oil (36.1 mg, 49%).

$[\alpha]_{\text{D}}^{20}$ -108 (c 0.49, CHCl_3); R_f 0.24 (5% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 1724, 1601, 1493, 1267, 1207, 1110, 995, 710; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 8.06 (2H, d, $J = 7.5$ Hz, ArH), 7.58 (1H, t, $J = 7.5$ Hz, ArH), 7.46 (2H, t, $J = 7.5$ Hz, ArH), 7.15 (2H, t, $J = 7.5$ Hz, ArH), 7.03 (1H, t, $J = 7.5$ Hz, ArH), 6.92 (2H, d, $J = 7.5$ Hz, ArH), 6.73 (1H, dd, $J = 14.5, 3.5$ Hz, H2), 6.11 (1H, d, $J = 19.0$ Hz, H5), 6.09 (1H, dd, $J = 14.5, 1.5$ Hz, H1), 5.89 (1H, d, $J = 19.0$ Hz, H6), 5.46 (1H, dd, $J = 3.5, 1.5$ Hz, H3), 2.05 (2H, s, SiCH_2), 1.43 (3H, s, CH_3), 1.04-1.00 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.76-0.62 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), -0.01 (3H, s, 1 x $\text{Si}(\text{CH}_3)_2$), -0.04 (3H, s, 1 x $\text{Si}(\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 165.7 (CO_2), 151.2 (C5), 146.5 (C2), 139.8 (Ar *ipso*), 133.1 (Ar), 130.1 (Ar), 129.6 (Ar), 129.0 (C1), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 126.5 (C6), 123.9 (Ar), 77.2 (C4), 74.4 (C3), 25.8 (SiCH_2), 22.9 (CH_3), 7.0 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.7 ($\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.6 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), -3.6 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{27}\text{H}_{36}\text{O}_3\text{Si}_2$ $[\text{M}+\text{Na}]^+$ 487.2095, found 467.2078.

(*R,E*)-4-(Benzyldimethylsilyl)-2-[(*S*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl]but-3-en-2-ol [(+)-200]

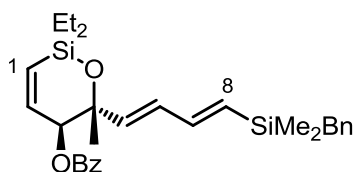


To a solution of **204** (9.0 mg, 0.0194 mmol, 1.0 eq) in MeOH (200 μL) was added K_2CO_3 (2.6 mg, 0.0194 mmol, 1.0 eq). The reaction was stirred at room temperature over 16 h and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 20% ether / petrol) to afford the title compound as a pale yellow oil (5.6 mg, 73%).

$[\alpha]_{\text{D}}^{20}$ $+99.3$ (c 0.33, CHCl_3).

The spectroscopic data was found to be in agreement with the racemic compound whose preparation is described above.

(5*S*,6*R*)-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 (205)

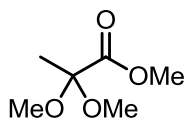


To chromium(II) chloride (107 mg, 0.871 mmol, 6.0 eq) dried under vacuum and heat was added THF (1.6 mL) and the resulting grey suspension was stirred for 30 min. A solution of **132** (50 mg, 0.145 mmol, 1.0 eq) and **145** (79 mg, 0.189 mmol, 1.3 eq) in THF (2 mL) was then added *via* syringe and the mixture stirred at room temperature for 16 h. The resulting purple suspension was diluted with ether, filtered through a pad of Celite[®], and rinsed with ether. The filtrate was washed twice with distilled H₂O and once with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatograph (0 → 5% ether / petrol) to afford the title compound as a pale yellow oil (57 mg, 80%).

$[\alpha]_{\text{D}}^{20}$ –120 (*c* 0.73, CHCl₃); **R_f** 0.47(5% ether / petrol); **IR** (thin film, ν_{max} / cm^{–1}) 2956, 1723, 1601, 1583, 1247, 1110, 1001, 698; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 8.08 (2H, d, *J* = 7.5 Hz, ArH), 7.61 (1H, t, *J* = 7.5 Hz, ArH), 7.49 (2H, t, *J* = 7.5 Hz, ArH), 7.19 (2H, t, *J* = 7.5 Hz, ArH), 7.06 (1H, t, *J* = 7.5 Hz, ArH), 6.99 (2H, d, *J* = 7.5 Hz, ArH), 6.72 (1H, dd, *J* = 14.5, 3.0 Hz, H2), 6.45 (1H, dd, *J* = 18.0, 10.0 Hz, H7), 6.36 (1H, dd, *J* = 15.0, 10.0 Hz, H6), 6.11 (1H, dd, *J* = 14.5, 2.0 Hz, H1), 5.86 (1H, d, *J* = 15.0 Hz, H5), 5.82 (1H, d, *J* = 18.0 Hz, H8), 5.48 (1H, dd, *J* = 3.0, 2.0 Hz, H3), 2.13 (2H, s, SiCH₂), 1.50 (3H, s, CH₃), 1.04 (6H, t, *J* = 8.0 Hz, Si(CH₂CH₃)₂), 0.77–0.65 (4H, m, Si(CH₂CH₃)₂), –0.04 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 165.7 (CO₂), 146.7 (C2), 144.8 (C7), 139.9 (C5), 139.0 (Ar *ipso*), 133.1 (Ar), 132.2 (C8), 131.7 (C6), 130.1 (Ar), 129.7 (Ar), 128.7 (C1), 128.5 (Ar), 128.2 (Ar), 128.1 (Ar), 123.9 (Ar), 75.7 (C3), 75.1 (C4), 26.0 (SiCH₂), 23.4 (CH₃), 7.0 (1 x Si(CH₂CH₃)₂), 6.7 (1 x Si(CH₂CH₃)₂), 6.6 (1 x Si(CH₂CH₃)₂), 6.5 (Si(1 x CH₂CH₃)₂), –3.5 (Si(CH₃)₂); **HRMS** (ESI+) calc. for C₂₉H₃₈O₃Si₂ [M+Na]⁺ 513.2252, found 513.2248.

7.4 The enol ether and amine coupling partners

Methyl 2,2-dimethoxypropanoate (**214**)

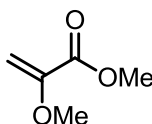


To a solution of methyl pyruvate (8.9 mL, 98.0 mol, 1.0 eq) and trimethylorthoformate (13.9 mL, 127 mmol, 1.3 eq) in MeOH (30 mL) in a flask connected to a distillation set up was added concentrated H₂SO₄ (0.05 mL). The solution was stirred at reflux for 5 h, during which 20 mL of solvent was removed by distillation. The resulting solution was cooled to 10 °C and quenched with a 0.05M solution of KOH. After continuous extraction with ether overnight, the organic layer was dried over MgSO₄ and concentrated *in vacuo* as a pale yellow oil. The crude mixture was purified by vacuum distillation to afford the title compound as a colourless oil (12.5 g, 86%).

bp 72 °C, 23 mbar (lit. 65-66 °C, 11 mbar); **¹H NMR** (400 MHz, CDCl₃) δ_H 3.82 (3H, s, CO₂CH₃), 3.30 (6H, s, 2 x OCH₃), 1.54 (3H, s, CH₃).

The physical and spectroscopic data was found to be in agreement with that reported by Wenkert and co-workers.¹⁶⁷

Methyl 2-methoxyacrylate (**211**)

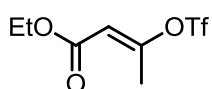


p-Toluenesulfonic acid (242 mg, 1.27 mmol, 0.015 eq) and **214** (12.5 g, 84.4 mmol, 1.0 eq) were heated at 140 °C over 4 h in a flask fitted with a short-path distillation apparatus to collect methanol. The collecting flask was replaced and the mixture distilled to afford the title compound as a colourless oil (3.30 g, 34%).

bp 150-154 °C (lit. 151-154 °C); **¹H NMR** (200 MHz, CDCl₃) δ_H 5.37 (1H, d, *J* = 3.0 Hz, 1 x CH₂), 4.64 (1H, d, *J* = 3.0 Hz, 1 x CH₂), 3.83 (3H, s, OCH₃), 3.67 (3H, s, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 197.5 (CO₂CH₃), 163.5 (CH₂), 152.0 (C(OCH₃)), 93.6 (CO₂CH₃), 55.7 (OCH₃).

The physical and spectroscopic data was found to be in agreement with that reported by Sanchez and co-workers.¹⁶⁷

(*E*)-Ethyl-3-(trifluoromethylsulfonyloxy)but-2-enoate (215)

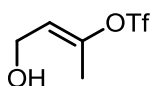


To a solution of ethyl acetoacetate (1.0 mL, 7.91 mmol, 1.0 eq) in hexane (40 mL) at 0 °C was added aqueous tetramethylammonium hydroxide solution (14 mL (25% wt.), 39.5 mmol, 5 eq) and H₂O (10 mL). The biphasic mixture was stirred vigorously for 5 min and triflic anhydride (3.0 mL, 19.8 mmol, 2.5 eq) was added dropwise over 5 min. The reaction mixture was stirred for 30 min, and then diluted with H₂O. The mixture was extracted once with ethyl acetate and the organic layer washed with H₂O and brine, dried over magnesium sulphate and concentrated *in vacuo* as an orange oil (1.40 g, 67%) which was used without further purification.

R_f 0.63 (30% ethyl acetate / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.96 (1H, d, *J* = 1.0 Hz, CH), 4.23 (2H, q, *J* = 7.0 Hz, CH₂CH₃), 2.52 (3H, d, *J* = 1.0 Hz, Me), 1.32 (3H, t, *J* = 7.0 Hz, CH₂CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 164.2, 161.9, 154.3, 118 (q, *J*_{CF} 320 Hz), 113.3, 61.2, 18.4, 14.1.

The spectroscopic data was found to be in agreement with that reported by Frantz and co-workers.¹⁶⁸

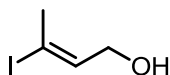
(*E*)-4-Hydroxybut-2-en-2-yl trifluoromethanesulfonate (210)



To a solution of **215** (500 mg, 1.91 mmol, 1.0 eq) in dichloromethane (19 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of DIBALH in hexanes (1.0 M, 4.2 mL, 4.20 mmol, 2.2 eq). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min then warmed gradually to room temperature over 1.5 h. The reaction mixture was quenched with saturated aqueous sodium and potassium tartrate and stirred vigorously for 30 min, and then extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulphate and concentrated *in vacuo* as a yellow oil. The mixture was purified by column chromatography (0 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a yellow oil (338 mg, 80%).

R_f 0.21 (30% ethyl acetate–petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3374, 1695, 1393, 1250, 1211, 1145, 993, 889; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 5.78 (1H, td, $J = 7.0, 1.0$ Hz, CH), 4.24 (2H, d, $J = 7.0$, CH_2OH), 2.12 (3H, s, CH_3); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 148.8, 120.6, 57.8, 16.6.

(E)-3-Iodobut-2-en-1-ol (S6)

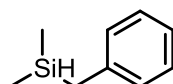


To a solution of *iso*-butylmagnesium chloride (4.9 mL [2.0 M in ether], 9.8 mmol, 2.3 eq) in ether (8 mL) at $0\text{ }^{\circ}\text{C}$ was added titanocene dichloride (53 mg, 0.21 mmol, 5 mol%). The mixture was stirred at $0\text{ }^{\circ}\text{C}$ over 10 min, after which a solution of 2-butyne-1-ol (320 μL , 4.28 mmol, 1.0 eq) in ether (5 mL) was added dropwise over 10 min and the resulting light brown suspension was warmed to room temperature over 3 h. The mixture was cooled to $0\text{ }^{\circ}\text{C}$ and a solution of iodine (1.14 g, 4.49 mmol, 1.05 eq) in ether (5 mL) was added dropwise over 10 min. The reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ over 2 h, followed by quenching with saturated aqueous ammonium chloride and stirring at room temperature for a further 2 h. The mixture was filtered through Celite[®] and extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium thiosulphate, dried over magnesium sulphate and concentrated *in vacuo* as a brown oil. The mixture was purified by column chromatography (0 $\rightarrow$ 25% ethyl acetate in petrol) to afford the title compound as a yellow oil (178 mg, 21%).

R_f 0.26 (30% ethyl acetate–petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 6.42 (1H, td, *J* = 7.0, 1.5 Hz, CH), 4.10 (2H, d, *J* = 7.0 Hz, CH₂OH), 2.47 (3H, s, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 139.7 (CH), 98.6 (C(CH₃)I), 59.9 (CH₂OH), 28.0 (CH₃).

The spectroscopic data was found to be in agreement with that reported by Katsumura and co-workers.²⁵⁷

Benzyltrimethylsilane

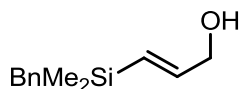


The title compound was prepared on a 69.2 mmol scale in a similar manner to benzylchlorodimethylsilane, replacing dichlorodemethylsilane with chlorodimethylsilane. The crude mixture was purified by vacuum distillation to afford the title compound as a colourless oil (6.94 g, 67%).

bp 70 °C, 20 mbar (lit.²⁵⁵ 72 °C, 24 mbar); **¹H NMR** (500 MHz, CDCl₃) δ_H 7.25 (2H, t, *J* = 7.5 Hz, ArH), 7.10 (1H, t, *J* = 7.5 Hz, ArH), 7.05 (2H, d, *J* = 7.5 Hz, ArH), 3.96 (1H, sept, *J* = 3.5 Hz, SiH), 2.17 (2H, d, *J* = 3.5 Hz, SiCH₂), 0.08 (6H, d, *J* = 3.5 Hz, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) 140.0, 128.3, 128.1, 124.2, 24.2, −4.7.

The spectroscopic data was found to be in agreement with that reported by Brennan and co-workers.²⁵⁸

(*E*)-3-(Benzyltrimethylsilyl)prop-2-en-1-ol (213)



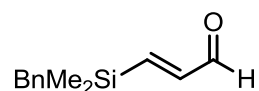
A solution of bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate hydrate (7.0 mg, 0.017 mmol, 0.5 mol%) in acetone (11 mL) was purged with N₂. Propargyl alcohol (220 μL, 3.66 mmol, 1.1 eq) and benzyltrimethylsilane (500 mg, 3.33 mmol, 1.0 eq) were added and the solution stirred at room temperature over 16 h. The solution was concentrated *in vacuo* and the resulting yellow

oil purified by column chromatography to afford the title compound as a colourless oil (518 mg, 75%).

R_f 0.22 (30% ether / petrol); **¹H NMR** (500 MHz, CDCl₃) δ_H 7.22 (2H, t, *J* = 7.5 Hz, ArH), 7.08 (1H, t, *J* = 7.5 Hz, ArH), 7.00 (2H, d, *J* = 7.5 Hz, ArH), 6.17 (1H, dt, *J* = 19.0 and 4.5 Hz, SiCHCH), 5.90 (1H, dt, *J* = 19.0 and 2.0 Hz, SiCH), 4.18 (2H, ddd, *J* = 6.0, 4.5 and 2.0 Hz, CH₂OH), 2.15 (2H, s, SiCH₂), 1.42 (1H, t, *J* = 6.0 Hz, OH), 0.07 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 146.0, 139.8, 128.2, 128.1, 127.4, 124.0, 65.5, 25.9, -3.5.

The spectroscopic data were found to be in agreement with that reported by Denmark and co-workers.¹²²

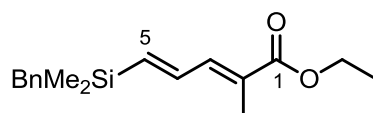
(*E*)-3-(Benzyldimethylsilyl)acrylaldehyde (S7)



To a solution of **213** (140 mg, 0.678 mmol, 1.0 eq) in DCM (3.5 mL) was added activated MnO₂ (589 mg, 6.78 mmol, 10 eq). The reaction mixture was stirred under reflux for 4 h, then cooled to room temperature and filtered through a pad of Celite[®] and rinsed with ether. The filtrate was concentrated *in vacuo* to afford the title compound as a colourless oil (122 mg, 88%) which was used in the next step without further purification.

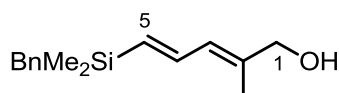
R_f 0.50 (20% ether–petrol); **¹H NMR** (500 MHz, CDCl₃) δ_H 9.50 (1H, d, *J* = 7.5 Hz, CHO), 7.24 (2H, t, *J* = 7.5 Hz, ArH), 7.14 (1H, d, *J* = 18.5 Hz, SiCH), 7.11 (1H, t, *J* = 7.5 Hz, ArH), 7.00 (2H, d, *J* = 7.5 Hz, ArH), 6.49 (1H, dd, *J* = 18.5 and 7.5 Hz, SiCHCH), 2.24 (2H, s, SiCH₂), 0.18 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 194.5, 156.6, 144.9, 138.4, 128.4, 128.1, 124.6, 25.0, -3.9.

The spectroscopic data were found to be in agreement with that reported by Denmark and co-workers.¹²²

(2E,4E)-Ethyl 5-(benzyldimethylsilyl)-2-methylpenta-2,4-dienoate (212)

To a suspension of sodium hydride (12 mg, 60% in mineral oil, 0.294 mmol, 1.5 eq) in THF (1 mL) at 0 °C was added a solution of triethyl 2-phosphopropionate (70 mg, 0.29 mmol, 1.5 eq). The reaction mixture was stirred at 0 °C over 45 min, then a solution of **S7** (40 mg, 0.20 mmol, 1.0 eq) was added, and the solution warmed to room temperature over 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted three times with ether. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (5 → 10% ether / petrol) to afford the title compound as a colourless oil (45 mg, 80%).

R_f 0.52 (10% ether / petrol); **¹H NMR** (500 MHz, CDCl₃) δ_H 7.22 (2H, t, *J* = 7.5 Hz, ArH), 7.13 (1H, dt, *J* = 11.0 and 1.0 Hz, H₃), 7.09 (1H, t, *J* = 7.5 Hz, ArH), 7.01 (2H, d, *J* = 7.5 Hz, ArH), 6.78 (1H, dd, *J* = 18.5 and 11.0 Hz, H₄), 6.26 (1H, d, *J* = 18.5 Hz, H₅), 4.23 (2H, q, *J* = 7.0 Hz, OCH₂), 2.19 (2H, s, SiCH₂), 1.96 (3H, d, *J* = 1.0 Hz, CH₃), 1.32 (3H, t, *J* = 7.0 Hz, CH₂CH₃), 0.11 (6H, s, Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_C 168.6 (C1), 141.0 (C5), 139.8 (C4), 139.7 (C3), 139.4 (C2), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 124.1 (Ar), 60.6 (OCH₂), 25.8 (SiCH₂), 14.3 (CH₂CH₃), 12.8 (CH₃), -3.5 (Si(CH₃)₂); **HRMS** (ESI⁺) calc. for C₁₇H₂₄O₂Si [M+Na]⁺ 311.1438, found 311.1438.

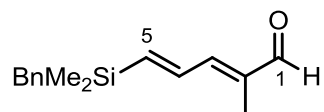
(2E,4E)-5-(Benzyldimethylsilyl)-2-methylpenta-2,4-dien-1-ol (219)

To a solution of **212** (43 mg, 0.15 mmol, 1.0 eq) in DCM (600 μL) at -78 °C was added a solution of DIBALH in hexanes (330 μL, 1.0 M, 0.328 mmol, 2.2 eq) dropwise. The solution was stirred at -78 °C over 2 h, and quenched with methanol (80 μL), and diluted with ether (2 mL) and a saturated aqueous solution of Rochelle's salts (1 mL). The mixture was stirred

vigorously at room temperature over 3 h, and extracted three times with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a colourless oil (32 mg, 89%).

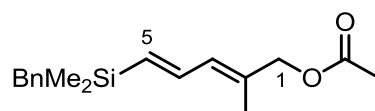
R_f 0.23 (30% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3320, 3081, 3060, 3024, 1600, 1493, 1248, 830; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.22 (2H, t, $J = 7.5$ Hz, ArH), 7.08 (1H, t, $J = 7.5$ Hz, ArH), 7.02 (2H, d, $J = 7.5$ Hz, ArH), 6.75 (1H, dd, $J = 18.5$ and 10.5 Hz, H4), 6.09 (1H, dt, $J = 10.5$ and 1.0 Hz, H3), 5.84 (1H, d, $J = 18.5$ Hz, H5), 4.09 (2H, d, $J = 6.0$ Hz, H1), 2.17 (2H, s, SiCH_2), 1.82 (3H, s, CH_3), 1.43 (1H, t, $J = 6.0$ Hz, OH), 0.08 (6H, s, $\text{Si}(\text{CH}_3)_2$); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 140.4 (C4), 139.9 (C2), 138.3 (Ar), 131.9 (C5), 128.2 (Ar), 128.1 (Ar), 127.5 (C3), 124.0 (Ar), 68.3 (C1), 26.1 (SiCH_2), 14.2 (CH_3), -3.3 ($\text{Si}(\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{15}\text{H}_{22}\text{OSi}$ $[\text{M}+\text{Na}]^+$ 269.1332, found 269.1326.

(2E,4E)-5-(Benzyldimethylsilyl)-2-methylpenta-2,4-dienal (218)



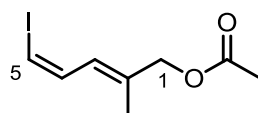
To a solution of **219** (90 mg, 0.375 mmol, 1.0 eq) in DCM (1.5 mL) was added activated MnO_2 (326 mg, 3.75 mmol, 10 eq). The reaction mixture was stirred under reflux for 5 h, then cooled to room temperature and filtered through a pad of Celite[®] and rinsed with ether. The filtrate was concentrated *in vacuo* to afford the title compound as a colourless oil (87 mg, 95%) which was used in the next step without further purification.

R_f 0.30 (10% ether–petrol); **IR** (thin film, ν_{max} / cm^{-1}) 1681, 1624, 1600, 1493, 1251, 1056, 999, 834; **¹H NMR** (400 MHz, CDCl_3) δ_{H} 9.47 (1H, d, $J = 7.5$ Hz, CHO), 7.23 (2H, t, $J = 7.5$ Hz, ArH), 7.10 (1H, t, $J = 7.5$ Hz, ArH), 7.01 (2H, d, $J = 7.5$ Hz, ArH), 6.93 (1H, dd, $J = 18.0$ and 11.0 Hz, H4), 6.78 (1H, d, $J = 11.0$ Hz, H3), 6.43 (1H, d, $J = 18.0$ Hz, H5), 2.21 (2H, s, SiCH_2), 1.86 (3H, s, Me_2), 0.15 (6H, s, $\text{Si}(\text{CH}_3)_2$).

(2E,4E)-5-(Benzyldimethylsilyl)-2-methylpenta-2,4-dien-1-yl acetate (220)

To a solution of **219** (30 mg, 0.122 mmol, 1.0 eq) in ether (200 μ L) was added acetic anhydride (23 μ L, 0.243 mmol, 2.0 eq) and Et₃N (51 μ L, 0.365 mmol, 3.0 eq). The reaction mixture was stirred at room temperature over 5 h, then quenched with cold H₂O. The aqueous layer was extracted three times with ether and the combined organic layers was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 40% ether / petrol) to afford the title compound as a colourless oil (35 mg, quant.).

R_f 0.51 (30% ether / petrol); ¹H NMR (500 MHz, CDCl₃) δ _H 7.22 (2H, t, *J* = 7.5 Hz, ArH), 7.08 (1H, t, *J* = 7.5 Hz, ArH), 7.02 (2H, d, *J* = 7.5 Hz ArH), 6.73 (1H, dd, *J* = 18.5, 10.5 Hz, H₄), 6.08 (1H, d, *J* = 10.5, H₃), 5.88 (1H, d, *J* = 18.5 Hz, H₅), 4.53 (2H, s, H₁), 2.16 (2H, s, SiCH₂), 2.10 (3H, s, CO₂CH₃), 1.82 (3H, s, Me₂), 0.08 (6H, s, 2 x SiCH₃); ¹³C NMR (125 MHz, CDCl₃) δ _C 170.8, 140.0, 139.8, 133.2, 133.0, 130.5, 128.2, 128.1, 124.0, 69.4, 26.0, 20.9, 14.6, -3.3.

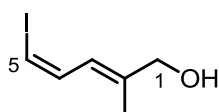
(2E,4Z)-5-Iodo-2-methylpenta-2,4-dien-1-yl acetate (221)

To a solution of **220** (22 mg, 0.076 mmol, 1.0 eq) in HFIP (380 μ L) at 0 °C in the dark was added Ag₂CO₃ (6.0 mg, 0.023 mmol, 0.3 eq) and *N*-iodosuccinimide (23 mg, 0.092 mmol, 1.2 eq). The reaction mixture was stirred at 0 °C for 10 min, then quenched with H₂O. The aqueous layer was extracted three times with ether, and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (5 $\rightarrow$ 10% ether / petrol) to afford the title compound as a colourless oil (18 mg, 89%).

R_f 0.24 (10% ether / petrol); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ_{H} 6.93 (1H, dd, $J = 10.5, 7.5$ Hz, H4), 6.38 (1H, d, $J = 7.5$ Hz, H3), 6.22 (1H, d, $J = 10.5$ Hz, H5), 4.57 (2H, s, H1), 2.13 (3H, s, CO_2CH_3), 1.83 (3H, s, Me2).

The spectroscopic data was found to be in agreement with that reported by Negishi and co-workers.¹¹⁰

(2*E*,4*Z*)-5-Iodo-2-methylpenta-2,4-dien-1-ol (222)

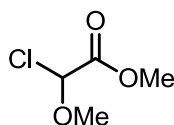


To a solution of **221** (33 mg, 0.12 mmol, 1.0 eq) in MeOH (1.5 mL) in the dark was added K_2CO_3 (35 mg, 0.25 mmol, 2.0 eq). The reaction mixture was stirred at room temperature in the dark over 4 h, then quenched with H_2O . The aqueous layer was extracted three times with ether, and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 30% ether / petrol) to afford the title compound as a colourless oil (13 mg, 47%).

R_f 0.21 (30% ether / petrol); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ_{H} 6.53 (1H, dd, $J = 10.5, 7.5$ Hz, H4), 6.31 (1H, dq, $J = 10.5, 1.5$ Hz, H3), 5.95 (1H, d, $J = 7.5$ Hz, H5), 3.58 (2H, d, $J = 5.5$ Hz, H1), 1.37 (3H, d, $J = 1.5$ Hz, Me2), 0.73 (1H, t, $J = 5.5$ Hz, OH); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ_{C} 143.5, 134.4, 124.6, 82.7, 15.0.

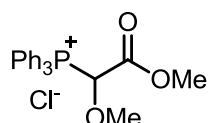
The spectroscopic data was found to be in agreement with that reported by de Lera and co-workers.²⁵⁹

Methyl 2-chloro-2-methoxyacetate (224)



To PCl_5 (3.75 g, 18.0 mmol, 1.1 eq) in a round-bottom flask fitted with a reflux condenser was carefully added methyl dimethoxyacetate (2.0 mL, 16.4 mmol, 1.0 eq) dropwise. After initial bubbling had ceased, the mixture was stirred at 140 °C over 4.5 h. The reflux condenser was replaced with a short path distillation apparatus and the reaction mixture was purified by short path distillation to afford the title compound as a colourless oil (3.5 g) which was used immediately in the next step.

(1,2-Dimethoxy-2-oxoethyl)triphenylphosphonium chloride (223)

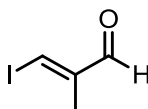


To a solution of **224** (3.5 g, 16.4 mmol, 1.0 eq) in DCM (5 mL) was added PPh_3 (4.30 g, 16.4 mmol, 1.0 eq). The solution was stirred at room temperature over 16 h to provide a yellow solution. The reaction was carefully concentrated *in vacuo* and the thick oily residue was washed two times with ether. The sticky solid was dried under vacuum over 24 h to produce a foamy solid which was crushed with a spatula and dried under vacuum for a further 24 h to provide the Wittig salt **223** as a yellow hygroscopic foam (6.04 g, 92% over two steps). The salt was stored in the glovebox and could be rapidly manipulated in air when required.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 8.62 (1H, d, $J = 13.5$ Hz, CH), 7.97 (6H, dd, $J = 13.0, 7.5$ Hz, *ortho*-ArH), 7.75 (3H, dd, $J = 7.5, 6.5$ Hz *para*-ArH), 7.67-7.62 (6H, m, *meta*-ArH), 3.87 (3H, s, CO_2Me), 3.56 (3H, s, OCH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 127.3, 134.9, 134.7 (d, $J = 10$ Hz), 130.0 (d, $J = 13$ Hz), 117.5, 76.1, 62.5 (d, $J = 10$ Hz), 53.1.

The spectroscopic data was found to be in agreement with that reported by Crimmins and co-workers.¹⁷⁵

(E)-3-Iodo-2-methylacrylaldehyde (229)

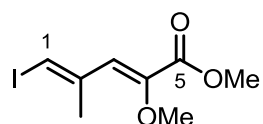


MnO₂ (2.20 g, 25.3 mmol, 10 eq) was added to a solution of **115** (500 mg, 2.53 mmol, 1.0 eq) in ether (25 mL). The reaction mixture was stirred at room temperature for 3 h, then filtered through a pad of Celite[®] and rinsed with ether. The filtrate was concentrated *in vacuo* to afford the title compound as a yellow oil (370 mg, 75%) which was used in the next step immediately without further purification.

R_f 0.33 (10% ether / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 9.53 (1H, s, CHO), 7.82 (1H, s, CH), 1.93 (3H, s, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 189.5, 150.8, 109.5, 16.4.

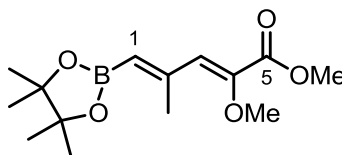
The spectroscopic data were found to be in agreement with that reported by White and co-workers.²⁶⁰

(2E,4E)-Methyl 5-iodo-2,4-dimethylpenta-2,4-dienoate (227)



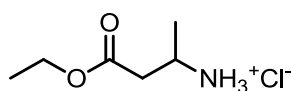
To a solution of **223** (2.95 g, 7.36 mmol, 5.2 eq) in acetonitrile (4.7 μL) was added DBU (1.06 mL, 7.08 mmol, 5.0 eq). The dark yellow solution was stirred at room temperature for 30 min. To the resulting creamy brown suspension was added a solution of **229** (278 mg, 1.42 mmol, 1.0 eq) in acetonitrile (1 mL). The reaction mixture was stirred at 80 °C over 16 h and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 10% ether / petrol) to afford the title compound as a pale yellow oil (285 mg, 71%).

R_f 0.27 (10% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 1717, 1619, 1434, 1347, 1241, 1101, 1037, 777; **¹H NMR** (500 MHz, CDCl₃) δ_H 6.87 (1H, s, H1), 6.58 (1H, s, H3), 3.81 (3H, s, CO₂CH₃), 3.71 (3H, s, OCH₃), 2.13 (3H, s, CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ_C 164.6 (C5), 143.8 (C4), 141.9 (C2), 123.9 (C3), 90.3 (C1), 59.9 (OCH₃), 52.2 (CO₂CH₃), 23.2 (CH₃); **HRMS** (ESI⁺) calc. for C₈H₁₁IO₃ [M+Na]⁺ 304.9645, found 304.9643.

(2Z,4E)-Methyl 2-methoxy-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-2,4-dienoate (228)

To a solution of **227** (143 mg, 0.507 mmol, 1.0 eq), bis(pinacolato)diboron (386 mg, 1.52 mmol, 3.0 eq) and potassium acetate (149 mg, 1.52 mmol, 3.0 eq) in DMSO (1.7 mL) was added Pd(dppf)Cl₂ (12 mg, 0.015 mmol, 3 mol%). The reaction was stirred at 80 °C for 1 h in a preheated oil bath, then cooled to room temperature and diluted with ether. The mixture was washed two times with H₂O, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography to afford a 1:3 mixture of the title compound and bis(pinacolato)diboron (496 mg, 27% purity by mass, 93%).

R_f 0.25 (10% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 1724, 1246, 1213, 1124, 983, 850; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 6.59 (1H, s, H3), 5.62 (1H, s, H1), 3.80 (3H, s, OCH₃), 3.69 (3H, s, CO₂CH₃), 2.28 (3H, s, Me₂), 1.27 (12H, s, 2 x C(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) δ_{C} 177.3, 152.4, 145.4, 129.0, 83.2, 60.1, 52.1, 24.6, 19.9.

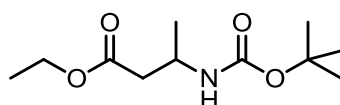
4-Ethoxy-4-oxobutan-2-ammonium chloride (S8)

To a two-neck round-bottomed flask charged with EtOH (47 mL), fitted with a reflux condenser and cooled to 0 °C was added SOCl₂ (3.1 mL, 42.7 mmol, 1.1 eq). The solution was stirred at 0 °C for 30 min, after which 3-aminobutanoic acid (4.00 g, 38.8 mmol, 1.0 eq) was added in one portion. The reaction mixture was stirred at room temperature for 1 h, then at 40 °C for 3 h. The reaction flask was cooled to room temperature and its contents concentrated *in vacuo* to afford the title compound as a thick colourless oil which was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ_H 5.18 (3H, br s, NH₃), 4.16 (2H, q, *J* = 7.0 Hz, OCH₂), 3.60-3.52 (1H, m, CHN), 2.57 (2H, t, *J* = 7.5 Hz, CH₂CO₂Et), 1.30 (3H, d, *J* = 6.5 Hz, CHCH₃), 1.26 (3H, t, *J* = 7.0 Hz, OCH₂CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 171.5 (CO₂), 60.8 (CHN), 44.4 (OCH₂), 41.3 (CH₂), 21.1 (CHCH₃), 14.1 (OCH₂CH₃).

The spectroscopic data was found to be in agreement with that reported by Zwierzak and co-workers.²⁶¹

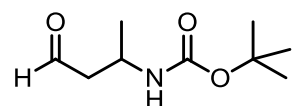
Ethyl 3-[(*tert*-butoxycarbonyl)amino]butanoate (233)



To a solution of **S8** (200 mg, 1.19 mmol, 1.0 eq) in DCM (30 mL) was added Et₃N (360 μL, 2.62 mmol, 2.2 eq). The reaction mixture was cooled to 0 °C and a solution of Boc₂O (273 mg, 1.25 mmol, 1.05 eq) in DCM (4.7 mL) was added dropwise followed by DMAP (cat.). The reaction mixture was allowed to warm to room temperature over 16 h, then quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with ethyl acetate and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (30 % ethyl acetate / petrol) to afford the title compound as a colourless oil (210 mg, 76%).

R_f 0.33 (20% ethyl acetate / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 4.93 (1H, br s, NH), 4.15 (2H, q, *J* = 7.5 Hz, OCH₂), 4.04 (1H, br s, CHN), 2.54-2.44 (2H, m, CH₂CO₂Et), 1.47 (9H, s, C(CH₃)₃), 1.27 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.21 (3H, d, *J* = 6.5 Hz, CHCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 171.5 (CO₂), 155.0 (NCO₂), 79.2 (C(CH₃)₃), 60.5 (OCH₂), 43.5 (CHN), 40.8 (CH₂CO₂), 28.4 (C(CH₃)₃), 20.4 (CHCH₃), 14.2 (OCH₂CH₃).

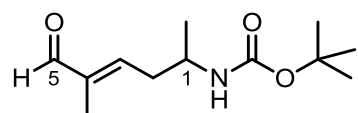
The spectroscopic data was found to be in agreement with that reported by Millenium Pharmaceuticals Inc.²⁶²

***tert*-Butyl (4-oxobutan-2-yl)carbamate (234)**

Racemic preparation: To a solution of **233** (600 mg, 2.60 mmol, 1.0 eq) in DCM (6.5 mL) at -78°C was added DIBALH (1.0 M in hexanes, 5.19 mL, 5.19 mmol, 2.0 eq) dropwise down the side of the flask over 30 min. The solution was stirred at -78°C for 45 min and quenched with saturated aqueous Na^+/K^+ tartrates. The mixture was allowed to warm to room temperature gradually over 30 min before dilution with ether (20 mL). The cooling bath was removed and the mixture stirred vigorously at room temperature for 2 h. The aqueous layer was extracted twice with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a colourless oil (300 mg, 62%).

R_f 0.22 (20% ethyl acetate / petrol); **¹H NMR** (400 MHz, CDCl_3) δ_{H} 9.77 (1H, t, $J = 2.0$ Hz, CHO), 4.67 (1H, br s, NH), 4.15 (1H, br s, CHN), 2.66-2.56 (2H, m, CH_2CHO), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.24 (3H, d, $J = 7.0$ Hz, CHCH_3); **¹³C NMR** (100 MHz, CDCl_3) δ_{C} 200.9 (CHO), 155.0 (NCO_2), 79.6 ($\text{C}(\text{CH}_3)_3$), 50.5 (CHN), 42.3 (CH_2), 28.3 ($\text{C}(\text{CH}_3)_3$), 20.9 (CHCH_3).

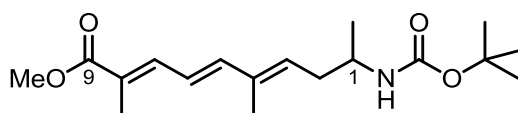
The spectroscopic data was found to be in agreement with that reported by Helmchen and co-workers.²⁶³

***(E)*-tert-Butyl (5-methyl-6-oxohex-4-en-2-yl)carbamate (232)**

A solution of **234** (402 mg, 2.15 mmol, 1.0 eq) and **235** (1.03 g, 3.22 mmol, 1.5 eq) in toluene (14 mL) was stirred at 80°C over 20 h. The reaction mixture was diluted with ether (10 mL), filtered through filter paper under gravity and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a pale yellow oil (444 mg, 91%).

R_f 0.35 (130% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3349, 2976, 2932, 1684, 1647, 1366, 1248, 1170; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 9.42 (1H, s, H5), 6.52 (1H, t, $J = 7.0$ Hz, H3), 4.42 (1H, br s, NH), 3.91 (1H, br s, H1), 2.53 (2H, t, $J = 7.0$ Hz, H2), 1.76 (3H, s, Me4), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.19 (3H, d, $J = 6.5$ Hz, Me1); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 195.1 (C5), 155.1 (CO_2), 150.0 (C3), 141.1 (C4), 79.5 ($\text{C}(\text{CH}_3)_3$), 45.9 (C1), 36.5 (C2), 28.3 ($\text{C}(\text{CH}_3)_3$), 20.8 (Me1), 9.4 (Me4); **HRMS** (ESI+) calc. for $\text{C}_{12}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{Na}]^+$ 250.1414, found 250.1409.

(2E,4E,6E)-Methyl 9-[(*tert*-butoxycarbonyl)amino]-2,6-dimethyldeca-2,4,6-trienoate (231)

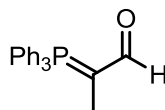


To 2,2,4,4,6,6 tetramethylpiperidine (636 mg, 3.74 mmol, 2.3 eq) at -20 °C was added *n*-BuLi (2.5 M in hexanes, 1.50 mL, 3.74 mmol, 2.3 eq) slowly. To the resulting pale yellow suspension obtained after stirring at -20 °C for 15 min was slowly added a solution of **236** (73% by mass, 1.28 g, 3.74 mmol, 2.3 eq) in THF (10 mL). The resulting brown solution was stirred at -20 °C for 30 min, before a solution of **232** (370 mg, 1.63 mmol, 1.0 eq) in THF (2.5 mL) was added. The reaction mixture was allowed to gradually warm to room temperature of 4 h, then quenched with saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted thrice with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a bright yellow oil (471 mg, 89%) and **232** (41 mg, 11%).

R_f 0.39 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3362, 1707, 1519, 1366, 1234, 1169, 1108, 751; **¹H NMR** (400 MHz, C_6D_6) δ_{H} 7.52 (1H, d, $J = 9.5$ Hz, H7), 6.36 (1H, dd, $J = 15.0, 9.5$ Hz, H6), 6.30 (1H, d, $J = 15.0$ Hz, H5), 5.41 (1H, t, $J = 7.5$ Hz, H3), 4.10 (1H, d, $J = 7.0$ Hz, NH), 3.82-3.77 (1H, m, H1), 3.49 (3H, s, OCH_3), 2.12-2.02 (2H, m, H2), 1.98 (3H, s, Me8), 1.58 (3H, s, Me4), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.80 (3H, d, $J = 6.5$ Hz, Me1); **¹³C NMR** (100 MHz, C_6D_6) δ_{C} 168.4 (CO_2CH_3), 155.1 (NHCO_2), 144.4 (C6), 139.3 (C7), 136.2 (C4), 133.1

(C3), 126.3 (C8), 122.1 (C5), 78.6 (C(CH₃)₃), 51.3 (OCH₃), 46.6 (C1), 35.8 (C2), 28.5 (C(CH₃)₃), 20.3 (Me1), 12.9 (Me8), 12.3 (Me4); **HRMS** (ESI+) calc. for C₁₈H₂₉NO₄ [M+Na]⁺ 346.1989, found 346.1990.

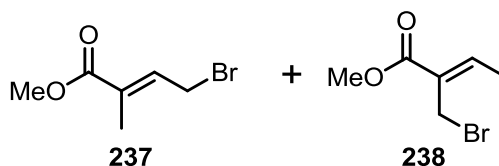
2-(Triphenylphosphoranylidene)propanal (235)



NaH (60% in mineral oil, 3.23 g, 80.0 mmol, 3.0 eq) was washed with pentane (2 x 10 mL) then suspended in THF (81 mL). Ethyltriphenylphosphonium bromide (10.0 g, 26.9 mmol, 1.0 eq) was added in two portions at room temperature and the mixture was stirred at room temperature over 16 h. The resulting yellow suspension was then cooled to 0 °C and ethyl formate (5.40 mL, 67.3 mmol, 2.5 eq) was added dropwise over 5 min. The mixture was stirred at 0 °C for 2 h, then at room temperature for 2 h, affording an off-white suspension. The reaction was cooled to 0 °C and carefully quenched with 1M HCl (80 mL). The pH of the aqueous layer was adjusted to pH=8 with 10% aqueous NaOH. The aqueous layer was extracted two times with DCM and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to afford white solids. The crude solids were purified by recrystallisation from ether/DCM and dried in air to afford the title compound as a off-white powder (4.83 g, 56%).

mp 204-206 °C, ether / DCM (lit. 213-217 °C benzene/hexane); **¹H NMR** (400 MHz, CDCl₃) δ_H 8.04 (1H, d, *J* = 5.0 Hz, CHO), 7.62-7.52 (15H, m, ArH), 1.87 (3H, d, *J* = 13.5 Hz, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 133.9 (d, *J* = 10 Hz), 132.9 (d, *J* = 3Hz), 129.1 (d, *J* = 12.0 Hz), 124.3 (d, *J* = 90 Hz), 10.9 (d, *J* = 10.5 Hz).

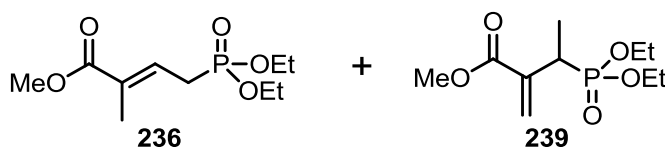
The physical and spectroscopic data was found to be in agreement with that reported by Kiyooka and co-workers.²⁶⁴

(E)-Methyl 4-bromo-2-methylbut-2-enoate (237) & (Z)-methyl 2-(bromomethyl)but-2-enoate (238)

To a solution of methyl tiglate (500 mg, 4.38 mmol, 1.0 eq) in CCl_4 (2.2 mL) in a 10 mL vial was added *N*-bromosuccinimide (780 mg, 4.38 mmol, 1.0 eq). The vial was capped, sealed and heated to 80 °C over 16 h. The reaction mixture was cooled to room temperature and directly purified by column chromatography (10 → 20% ether / petrol) to afford the title compounds as a inseparable 2:1 mixture of **237**:**238** (759 mg, 89%).

R_f 0.33 (10% ethyl acetate / petrol); ^1H NMR (200 MHz, CDCl_3) δ_{H} **major regioisomer 237** 6.92 (1H, tq, $J = 8.5, 1.5$ Hz, CH), 4.03 (2H, d, $J = 8.5$ Hz, CH_2Br), 3.76 (3H, s, OCH_3), 1.92 (3H, t, $J = 1.5$ Hz, CH_3), **minor regioisomer 238** 7.07 (1H, q, $J = 7.5$ Hz, CH), 4.24 (2H, s, CH_2Br), 3.80 (3H, s, OCH_3), 1.92 (3H, d, $J = 7.5$ Hz, CH_3).

The spectroscopic data of the major regioisomer and minor isomer was found to be in agreement with that reported by Rohmer²⁶⁵ and Loh²⁶⁶ respectively.

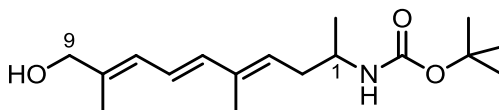
(E)-Methyl 4-(diethoxyphosphoryl)-2-methylbut-2-enoate (236) & Methyl 3-(diethoxyphosphoryl)-2-methylenebutanoate (239)

A mixture of **237** and **238** (759 mg, 3.88 mmol, 1.00 eq), and triethyl phosphite (699 μL , 4.07 mmol, 1.05 eq) were sealed in a vial and heated at 120 °C over 3 h. The reaction mixture was purified by column chromatography (5% MeOH / DCM) to afford the title compounds as an inseparable 2.7:1 mixture of **236** and **239**.

R_f 0.30 (5% DCM / MeOH); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ_{H} **major regioisomer 236** 6.83-6.69 (1H, m, CH), 4.20-4.03 (4H, m, 2 x OCH_2), 3.75 (3H, s, OCH_3), 2.75 (2H, ddd, $J = 23.5, 8.0, 0.5$ Hz, CH_2P), 1.93-1.87 (3H, m, CH_3), 1.33 (6H, t, $J = 7.0$ Hz, 2 x OCH_2CH_3).

The spectroscopic data of the major regioisomer was found to be in agreement with that reported by Rainier and co-workers.¹⁹⁵

***tert*-Butyl [(4*E*,6*E*,8*E*)-10-hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl]carbamate (241)**

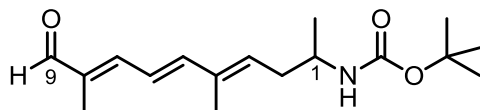


To a solution of **231** (237 mg, 0.733 mmol, 1.0 eq) in DCM (1.8 mL) at -70 °C was slowly added a solution of DIBALH in hexanes (1.0M, 2.2 mL, 2.20 mmol, 3.0 eq). The solution was allowed to warm to -50 °C over 1 h, then quenched at that temperature with a saturated solution of sodium and potassium tartrates (2 mL) and diluted with ether (3 mL). The cooling bath was removed and the mixture was stirred vigorously while warming to room temperature until two clear layers formed. The aqueous layer was extracted two times with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (20 $\rightarrow$ 30% ethyl acetate / petrol) to afford the title compound as a colourless oil (197 mg, 91%).

R_f 0.25 (40% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3344, 1686, 1391, 1366, 1251, 1170, 1054, 969; $^1\text{H NMR}$ (500 MHz, C_6D_6) δ_{H} 6.47 (1H, dd, $J = 15.0, 11.0$ Hz, H6), 6.30 (1H, d, $J = 15.0$ Hz, H5), 6.20 (1H, dd, $J = 11.0$ Hz, H7), 5.42 (1H, t, $J = 7.5$ Hz, H3), 4.13 (1H, br d, $J = 5.0$ Hz, NH), 3.88 (2H, d, $J = 5.0$ Hz, H9), 3.83 (1H, br s, H1), 2.16-2.13 (1H, m, 1 x H2), 2.09-2.05 (1H, m, 1 x H2), 1.71 (3H, s, Me4), 1.68 (3H, s, Me8), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.34 (1H, br s, OH), 0.85 (3H, d, $J = 7.0$ Hz, Me1); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ_{C} 155.3 (NHCO_2), 137.6 (C5), 137.3 (C8), 136.5 (C4), 128.7 (C3), 125.5 (C7), 123.0 (C6), 78.6 ($\text{C}(\text{CH}_3)_3$), 68.4

(C9), 46.9 (C1), 35.8 (C2), 28.6 (C(CH₃)₃), 20.4 (Me1), 14.2 (Me8), 12.7 (Me4); **HRMS** (FI+) calc. for C₁₇H₂₉NO₃ [M]⁺ 295.2148, found 295.2147.

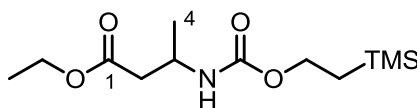
***tert*-Butyl [(4*E*,6*E*,8*E*)-5,9-dimethyl-10-oxodeca-4,6,8-trien-2-yl]carbamate (**240**)**



To a solution of **241** (240 mg, 0.812 mmol, 1.0 eq) in DCM (8.1 mL) over 4 Å molecular sieves was added NMO (381 mg, 3.25 mmol, 4.0 eq) and TPAP (14.3 mg, 0.0406 mmol, 5 mol%). The reaction mixture was stirred at room temperature in the dark over 6 h, then concentrated *in vacuo*. The residue was purified by column chromatography (20 → 30% ethyl acetate / petrol) to afford the title compound as a yellow oil (196 mg, 82%).

R_f 0.30 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 1712, 1665, 1605, 1364, 1168, 995, 963, 850; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 9.42 (1H, s, H9), 6.45 (1H, d, *J* = 10.5 Hz, H7), 6.34 (1H, dd, *J* = 15.0, 10.5 Hz, H6), 6.27 (1H, d, *J* = 15.0 Hz, H5), 5.54 (1H, t, *J* = 7.5 Hz, H3), 4.12 (1H, br s, NH), 3.80 (1H, br s, H1), 2.11-2.04 (1H, m, 1 x H2), 2.02-1.94 (1H, m, 1 x H2), 1.79 (3H, s, Me8), 1.55 (3H, s, Me4), 1.46 (9H, s, C(CH₃)₃), 0.82 (3H, d, *J* = 6.5 Hz, Me1); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 193.6 (CHO), 155.2 (CO₂), 148.4 (C7), 145.7 (C5), 137.4 (C8), 136.2 (C4), 134.8 (C3), 121.8 (C6), 78.7 (C(CH₃)₃), 46.7 (C1), 36.2 (C2), 28.6 (C(CH₃)₃), 20.5 (Me1), 12.3 (Me4), 9.6 (Me8); **HRMS** (ESI+) calc. for C₁₇H₂₇NO₃ [M+Na]⁺ 316.1883, found 316.1875.

Ethyl 3-[(2-trimethylsilylethoxy)carbonyl]aminobutanoate (244**)**

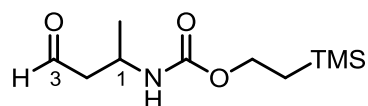


To a stirring mixture of 2-(trimethylsilyl)ethanol (99 mg, 0.84 mmol, 1.1 eq) and K₂CO₃ (348 mg, 2.51 mmol, 3.3 eq) in toluene (2.5 mL) at 0 °C was added a solution of triphosgene (84 mg, 0.28 mmol, 0.37 eq) in toluene (2.5 mL) dropwise. After stirring at room temperature for 1 h, a

solution of **S8** (100 mg, 0.762 mmol, 1.0 eq) in toluene (2.5 mL) was added and the mixture stirred at room temperature over 16 h. The reaction was quenched with 1% aqueous HCl (5 mL) and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to afford a colourless oil. The crude mixture was purified by column chromatography (20 → 30% ethyl acetate / petrol) to afford the title compound as a colourless oil (100 mg, 48%).

R_f 0.59 (30% ethyl acetate / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.07 (1H, br s, NH), 4.17-4.09 (5H, m, overlapping OCH₂CH₃ + OCH₂ + H₃), 4.09 (1H, br s, H₃), 2.51 (2H, d, *J* = 5.5 Hz, H₂), 1.27 (3H, t, *J* = 7.5 Hz, OCH₂CH₃), 1.24 (3H, d, *J* = 7.0 Hz, H₄), 0.98 (1H, t, *J* = 8.5 Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 171.5 (CONH), 155.9 (C1), 62.9 (OCH₂), 60.5 (OCH₂CH₃), 43.8 (C₃), 40.6 (C₂), 20.4 (C₄), 17.7 (SiCH₂), 14.2 (OCH₂CH₃), -1.5 (Si(CH₃)₃); **HRMS** (ESI+) calc. for C₁₂H₂₅NO₄Si [M+Na]⁺ 298.1445, found 298.1439.

2-(Trimethylsilyl)ethyl (4-oxobutan-2-yl)carbamate (**245**)

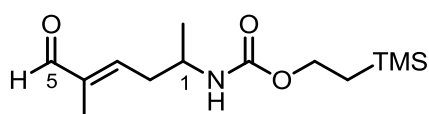


To a solution of **244** (86 mg, 0.31 mmol, 1.0 eq) in DCM (800 μL) at -78 °C was added DIBALH (1.0 M in hexanes, 630 μL, 0.63 mmol, 2.0 eq) dropwise down the side of the flask over 30 min. The solution was stirred at -78 °C for 45 min and quenched with saturated aqueous Na⁺/K⁺ tartrates. The mixture was allowed to warm to room temperature gradually over 30 min before dilution with ether (1 mL). The cooling bath was removed and the mixture stirred vigorously at room temperature for 2 h. The aqueous layer was extracted twice with ether and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a colourless oil (54 mg, 75%).

R_f 0.21 (20% ethyl acetate / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_H 9.77 (1H, s, H3), 4.76 (1H, br s, NH), 4.22-4.12 (3H, m, overlapping OCH₂ + H1), 2.68 (1H, ddd, *J* = 17.0, 6.0, 2.0 Hz, 1 x H2), 2.61 (1H, dd, *J* = 17.0, 5.5 Hz, 1 x H2), 1.27 (3H, d, *J* = 6.5 Hz, Me1), 0.97 (2H, t, *J* = 8.5 Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃).

The spectroscopic data was found to be in agreement with that reported by Haraldur Guðmundsson (EAA Group).²⁶⁷

(*E*)-2-(Trimethylsilyl)ethyl (5-methyl-6-oxohex-4-en-2-yl)carbamate (247)

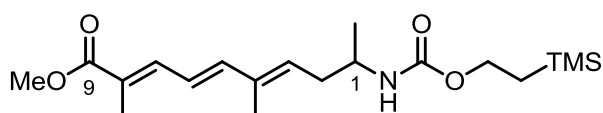


A solution of **245** (54 mg, 0.23 mmol, 1.0 eq) and **235** (111 mg, 0.35 mmol, 1.5 eq) in toluene (1.5 mL) was stirred at 80 °C over 16 h. The resulting brown solution was concentrated *in vacuo* and the residue was purified by column chromatography (10 → 30% ethyl acetate / petrol) to afford the title compound as a pale yellow oil (54 mg, 86%).

R_f 0.26 (30% ethyl acetate / petrol); **¹H NMR** (200 MHz, CDCl₃) δ_H 9.43 (1H, s, H5), 6.52 (1H, td, *J* = 7.5, 1.5 Hz, H3), 4.48 (1H, br s, NH), 4.15 (2H, t, *J* = 8.5 Hz, OCH₂), 4.02-3.89 (1H, m, H1), 2.55 (2H, t, *J* = 7.0 Hz, H2), 1.76 (3H, s, Me4), 1.22 (3H, d, *J* = 6.5 Hz, Me1), 0.97 (2H, t, *J* = 8.5 Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃).

The spectroscopic data was found to be in agreement with that reported by Haraldur Guðmundsson (EAA Group).²⁶⁷

(2*E*,4*E*,6*E*)-Methyl 2,6-dimethyl-9-[(2-(trimethylsilyl)ethoxycarbonyl]aminodeca-2,4,6-trienoate (246)



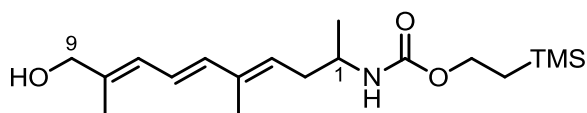
To 2,2,4,4,6,6 tetramethylpiperidine (60 mg, 0.42 mmol, 2.3 eq) at −20 °C was added *n*-BuLi (2.5 M in hexanes, 170 μL, 0.424 mmol, 2.3 eq) slowly. To the resulting pale yellow suspension

obtained after stirring at $-20\text{ }^{\circ}\text{C}$ for 15 min was slowly added a solution of **236** (70% by mass, 152 mg, 0.424 mmol, 2.3 eq) in THF (0.4 mL). The resulting brown solution was stirred at $-20\text{ }^{\circ}\text{C}$ for 30 min, before a solution of **247** (50 mg, 0.18 mmol, 1.0 eq) in THF (1.0 mL) was added. The reaction mixture was allowed to gradually warm to room temperature of 4 h, then quenched with saturated aqueous ammonium chloride (1.5 mL). The aqueous layer was extracted thrice with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a bright yellow oil (54 mg, 81%).

R_f 0.39 (20% ethyl acetate / petrol); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ_{H} 7.52 (1H, d, $J = 10.0$ Hz, H7), 6.38 (1H, dd, $J = 15.0, 10.0$ Hz, H6), 6.34 (1H, d, $J = 15.0$ Hz, H5), 5.42 (1H, t, $J = 7.5$ Hz, H3), 4.30 (2H, dd, $J = 9.5, 7.5$ Hz, OCH_2), 4.15 (1H, br s, NH), 3.84 (1H, app br s, H1), 3.49 (3H, s, OCH_3), 2.12-2.07 (1H, m, 1 x H2), 2.03-1.98 (1H, m, 1 x H2), 1.99 (3H, s, Me8), 1.59 (3H, s, Me4), 1.00 (2H, dd, $J = 9.5, 7.5$ Hz, SiCH_2), 0.84 (3H, d, $J = 6.5$ Hz, Me1), -0.06 (9H, s, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ_{C} 168.5 (CO_2CH_3), 156.0 (NHCO_2), 144.3 (C6), 139.3 (C7), 136.3 (C4), 132.9 (C3), 126.5 (C8), 122.3 (C5), 62.8 (OCH_2), 51.3 (OCH_3), 47.1 (C1), 35.9 (C2), 20.5 (Me1), 18.2 (SiCH_2), 13.0 (Me8), 12.4 (Me4), -1.5 ($\text{Si}(\text{CH}_3)_3$).

The spectroscopic data was found to be in agreement with that reported by Haraldur Guðmundsson (EAA Group).²⁶⁷

2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*)-10-hydroxy-5,9-dimethyldeca-4,6,8-trien-2-yl]carbamate (S9)

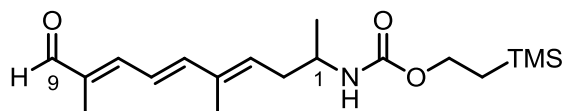


To a solution of **246** (54 mg, 0.15 mmol, 1.0 eq) in DCM (370 μL) at $-70\text{ }^{\circ}\text{C}$ was slowly added DIBALH (1.0M in hexanes, 440 μL , 0.44 mmol, 3.0 eq). The solution was allowed to warm to $-50\text{ }^{\circ}\text{C}$ over 1 h, then quenched at that temperature with a saturated solution of sodium and potassium tartrates (0.5 mL) and diluted with ether (0.5 mL). The cooling bath was removed

and the mixture was stirred vigorously while warming to room temperature until two clear layers formed. The aqueous layer was extracted two times with ether and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (30 → 40% ethyl acetate / petrol) to afford the title compound as a colourless oil (41 mg, 82%).

R_f 0.20 (30% ethyl acetate / petrol); **¹H NMR** (400 MHz, C₆D₆) δ_H 6.49 (1H, dd, *J* = 15.0, 11.0 Hz, H6), 6.32 (1H, d, *J* = 15.0 Hz, H5), 6.21 (1H, dd, *J* = 11.0 Hz, H7), 5.45 (1H, t, *J* = 7.0 Hz, H3), 4.37 (1H, br d, *J* = 5.0 Hz, NH), 4.28 (2H, t, *J* = 8.0 Hz, OCH₂), 3.90 (3H, app br s, H9 + H1), 2.21-2.14 (1H, m, 1 x H2), 2.12-2.05 (1H, m, 1 x H2), 1.73 (3H, s, Me4), 1.69 (3H, s, Me8), 0.99 (2H, t, *J* = 8.0 Hz, SiCH₂), 0.90 (3H, d, *J* = 6.5 Hz, Me1), 1.55 (1H, br s, OH), -0.06 (9H, s, Si(CH₃)₃). The spectroscopic data was found to be in agreement with that reported by Haraldur Gudmundsson (EAA Group).²⁶⁷

2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*)-5,9-dimethyl-10-oxodeca-4,6,8-trien-2-yl]carbamate (248)

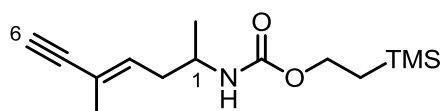


To a solution of **S9** (30 mg, 0.088 mmol, 1.0 eq) in DCM (880 μL) over 4 Å molecular sieves was added NMO (41 mg, 0.35 mmol, 4.0 eq) and TPAP (1.5 mg, 0.0044 mmol, 5 mol%). The reaction mixture was stirred at room temperature in the dark over 7 h, then concentrated *in vacuo*. The residue was purified by column chromatography (10 → 30% ethyl acetate / petrol) to afford the title compound as a yellow oil (20 mg, 68%).

R_f 0.42 (30% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 1671, 1607, 1527, 1249, 1192, 1060, 859, 837; **¹H NMR** (500 MHz, C₆D₆) δ_H 9.43 (1H, s, H9), 6.44 (1H, d, *J* = 11.0 Hz, H7), 6.35 (1H, dd, *J* = 15.0, 11.0 Hz, H6), 6.28 (1H, d, *J* = 15.0 Hz, H5), 5.55 (1H, t, *J* = 7.5 Hz, H3), 4.17 (1H, br s, NH), 4.31 (2H, d, *J* = 8.0 Hz, OCH₂), 3.91-3.87 (1H, m, H1), 2.13-2.10 (1H, m, 1 x H2), 2.04-1.99 (1H, m, 1 x H2), 1.81 (3H, s, Me8), 1.56 (3H, s, Me4), 1.00 (2H, d,

$J = 8.0$ Hz, SiCH₂)0.85 (3H, d, $J = 6.5$ Hz, Me1), -0.07 (9H, s, Si(CH₃)₃); ¹³C NMR (125 MHz, C₆D₆) δ_C 193.5 (CHO), 156.0 (CO₂), 148.2 (C7), 145.6 (C5), 137.5 (C8), 136.3 (C4), 134.6 (C3), 121.9 (C6), 62.9 (OCH₂), 47.1 (C1), 36.2 (C2), 20.6 (Me1), 18.2 (SiCH₂), 12.3 (Me4), 9.6 (Me8), -1.5 (Si(CH₃)₃); HRMS (ESI+) calc. for C₁₈H₃₁NO₃Si [M+Na]⁺ 360.1965, found 360.1955.

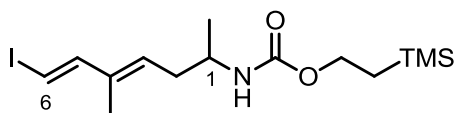
(E)-2-(Trimethylsilyl)ethyl (5-methylhept-4-en-6-yn-2-yl)carbamate (249)



A solution of LiHMDS in THF (1.0 M, 880 μ L, 0.88 mmol, 1.2 eq) was diluted with THF (3 mL) and cooled to -78 °C. TMSCHN₂ in hexanes (2.0 M, 440 μ L, 0.88 mmol, 1.2 eq) was added slowly and the resulting solution was stirred at -78 °C over 30 min. A solution of **247** (200 mg, 0.737 mmol, 1.0 eq) in THF (4.4 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, then allowed to warm to room temperature over 1.5 h. The reaction was quenched with saturated NH₄Cl and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate / petrol) to afford the title compound as a colourless oil (131 mg, 66%).

R_f 0.27 (20% ether / petrol); IR (thin film, $\nu_{\max}$ / cm⁻¹) 3314, 1690, 1531, 1251, 1061, 834; ¹H NMR (400 MHz, CDCl₃) δ_H 5.95 (1H, dd, $J = 7.5, 1.0$ Hz, H3), 4.46 (1H, br s, NH), 4.14 (1H, t, $J = 8.5$ Hz, OCH₂), 3.79 (1H, app br s, H1), 2.80 (1H, s, H6), 2.32-2.27 (2H, m, H2), 1.82 (3H, s, Me4), 1.15 (3H, d, $J = 6.5$ Hz, Me1), 0.98 (2H, t, $J = 8.5$ Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 156.0 (CONH), 134.7 (C3), 119.5 (C4), 86.4 (C5), 74.2 (C6), 62.8 (OCH₂), 46.5 (C1), 35.3 (C2), 20.4 (Me1), 17.7 (SiCH₂), 17.2 (Me4), -1.5 (Si(CH₃)₃); HRMS (ESI+) calc. for C₁₄H₂₅NO₂Si [M+Na]⁺ 290.1547, found 290.1541.

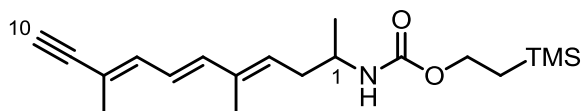
2-(Trimethylsilyl)ethyl [(4E,6E)-7-iodo-5-methylhepta-4,6-dien-2-yl]carbamate (250)



To a suspension of HZrCp₂Cl (124 mg, 0.449 mmol, 1.2 eq) in THF (2.5 mL) was added a solution of **249** (100 mg, 0.374 mmol, 1.0 eq) in THF (2.5 mL) dropwise. The reaction mixture was stirred at room temperature over 1 h then cooled to 0°C. A solution of I₂ (142 mg, 0.561 mmol, 1.5 eq) in THF (2.5 mL) was added dropwise and the reaction was warmed to room temperature over 3 h. The reaction was quenched with saturated Na₂S₂O₃ and diluted with ether. The aqueous layer was extracted two times with ether and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 20% ether / petrol) to afford the title compound as a yellow oil (50 mg, 34%).

R_f 0.22 (20% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3323, 1688, 1530, 1331, 1249, 1059, 942, 836; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 6.95 (1H, d, J = 14.5 Hz, H5), 6.10 (1H, d, J = 14.5 Hz, H6), 5.37 (1H, t, J = 7.5 Hz, H3), 4.32 (1H, br s, NH), 4.03 (1H, t, J = 8.5 Hz, OCH₂), 3.68 (1H, app br s, H1), 2.20-2.12 (2H, m, H2), 1.62 (3H, s, Me4), 1.03 (3H, d, J = 6.5 Hz, Me1), 0.86 (2H, t, J = 8.5 Hz, SiCH₂), -0.07 (9H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 169.3, 155.9, 149.7, 136.7, 129.9, 74.4, 62.7, 46.9, 35.2, 20.3, 18.2, 11.8, -1.5; **HRMS** (ESI+) calc. for C₁₄H₂₄INO₂Si [M+Na]⁺ 418.0670, found 418.0652.

2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*)-5,9-dimethylundeca-4,6,8-trien-10-yn-2-yl]carbamate (**251**)

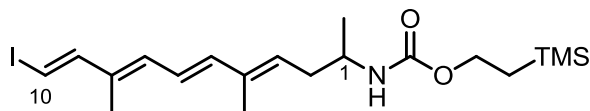


A solution of LiHMDS in THF (1.0 M, 330 μ L, 0.33 mmol, 1.2 eq) was diluted with THF (1 mL) and cooled to -78 °C. TMSCHN₂ in hexanes (2.0 M, 166 μ L, 0.33 mmol, 1.2 eq) was added slowly and the resulting solution was stirred at -78 °C over 30 min. A solution of **248** (93 mg, 0.276 mmol, 1.0 eq) in THF (1.8 mL) was added dropwise. The reaction mixture was

stirred at -78°C for 1 h, then allowed to warm to room temperature over 1.5 h. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (20% ether / petrol) to afford the title compound as a colourless oil (40 mg, 43%) and recover aldehyde **248** (19 mg, 20%).

R_f 0.42 (20% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3311, 1719, 1250, 1062, 962, 861, 837; **¹H NMR** (400 MHz, C_6D_6) δ_{H} 6.66 (1H, d, $J = 11$ Hz, H7), 6.31 (1H, dd, $J = 15.0, 11.0$ Hz, H6), 6.15 (1H, d, $J = 15.0$ Hz, H5), 5.36 (1H, t, $J = 7.5$ Hz, H3), 4.29 (1H, t, $J = 8.5$ Hz, OCH_2), 4.22 (1H, br s, NH), 3.85 (1H, app br s, H1), 2.79 (1H, s, H10), 2.15-2.08 (1H, m, 1 x H2), 2.06-1.98 (1H, m, 1 x H2), 1.81 (3H, s, Me4), 1.59 (3H, d, $J = 6.5$ Hz, Me1), 0.99 (2H, t, $J = 8.5$ Hz, SiCH_2), -0.07 (9H, s, $\text{Si}(\text{CH}_3)_3$); **¹³C NMR** (100 MHz, C_6D_6) δ_{C} 155.9, 139.8, 138.0, 136.3, 130.9, 126.2, 122.3, 117.0, 87.9, 77.5, 62.7, 47.2, 35.8, 20.4, 18.1, 17.4, 12.4, -1.5 ; **HRMS** (ESI+) calc. for $\text{C}_{19}\text{H}_{31}\text{NO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 356.2016, found 356.2011.

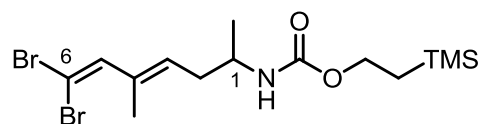
2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*)-11-iodo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl]carbamate (252**)**



To a suspension of HZrCp_2Cl (37 mg, 0.14 mmol, 1.2 eq) in THF (0.8 mL) was added a solution of **251** (40 mg, 0.12 mmol, 1.0 eq) in THF (0.8 mL) dropwise. The reaction mixture was stirred at room temperature over 1 h then cooled to 0°C . A solution of I_2 (61 mg, 0.24 mmol, 2.0 eq) in THF (0.8 mL) was added dropwise and the reaction was warmed to room temperature over 3 h. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and diluted with ether. The aqueous layer was extracted two times with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 20% ether / petrol) to afford the title compound as a 2:1 mixture of geometrical isomers (26 mg, 47%).

R_f 0.34 (20% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 1688, 1535, 1505, 1249, 1062, 962, 860, 836; **¹H NMR** (400 MHz, C₆D₆) δ_{H} **major isomer** 7.06 (1H, d, J = 14.5 Hz, H9), 6.36 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.26 (1H, d, J = 15.0 Hz, H5), 5.99 (1H, d, J = 14.5 Hz, H10), 5.54 (1H, d, J = 11.0 Hz, H7), 5.45 (1H, t, J = 7.5 Hz, H3), 4.30 (2H, t, J = 8.0 Hz, OCH₂), 4.16 (1H, br s, NH), 3.88 (1H, app br s, H1), 2.14-2.09 (1H, m, 1 x H2), 2.07-1.99 (1H, m, 1 x H2), 1.64 (3H, s, Me4), 1.49 (3H, s, Me8), 1.00 (2H, t, J = 8.0 Hz, SiCH₂), 0.85 (2H, d, J = 6.5 Hz, Me1), – 0.07 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, C₆D₆) δ_{C} 156.0, 149.7, 140.1, 136.6, 134.7, 133.2, 130.4, 128.6, 122.7, 62.7, 47.1, 35.9, 18.1, 12.5, 11.9, –1.6; **HRMS** (ESI+) calc. for C₁₉H₃₂INO₂Si [M+H]⁺ 462.1320, not found.

(*E*)-2-(Trimethylsilyl)ethyl (7,7-dibromo-5-methylhepta-4,6-dien-2-yl)carbamate (253)

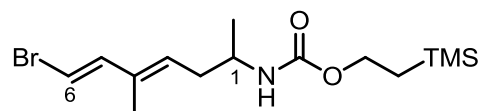


To a solution of PPh₃ (530 mg, 2.02 mmol, 4.0 eq) in DCM (4 mL) at 0 °C was added CBr₄ (155 mg, 1.01 mmol, 2.0 eq). The bright yellow solution was stirred at 0 °C for 10 min before Et₃N (70 μ L, 0.51 mmol, 1.0 eq) was added and the mixture stirred for a further 5 min. A solution of **247** (137 mg, 0.51 mmol, 1.0 eq) in DCM (1 mL) was added and the reaction was stirred at 0°C for 3 h. The reaction was quenched with saturated NaHCO₃ and the aqueous layer was extracted two times with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 10% ether / petrol) to afford the title compound as a colourless oil (116 mg, 53%).

R_f 0.30 (20% ether / petrol); **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.94 (1H, s, H5), 5.64 (1H, t, J = 7.0 Hz, H3), 4.47 (1H, m, NH), 4.14 (1H, t, J = 8.0 Hz OCH₂), 3.81 (1H, app br s, H1), 2.27 (2H, t, J = 6.5 Hz, H2), 1.86 (3H, s, Me4), 1.16 (3H, d, J = 6.5 Hz, Me1), 0.97 (2H, t, J = 8.5 Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 156.0 (CONH), 140.5 (C5), 134.1 (C4), 130.3 (C3), 86.8 (C6), 62.8 (OCH₂), 46.6 (C1), 35.1 (C2), 20.6 (Me1), 17.7

(SiCH₂), 15.5 (Me₄), -1.5 (Si(CH₃)₃); **HRMS** (ESI⁺) calc. for C₁₄H₂₅Br₂NO₂Si [M+Na]⁺ 447.9914, found 447.9919.

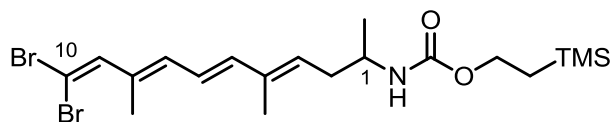
2-(Trimethylsilyl)ethyl [(4*E*,6*E*)-7-bromo-5-methylhepta-4,6-dien-2-yl]carbamate (254)



To a mixture of **253** (29 mg, 0.068 mmol, 1.0 eq) and diethyl phosphite (26 μ L, 0.20 mmol, 3.0 eq) in a vial was added Et₃N (28 μ L, 0.20 mmol, 3.0 eq). The reaction was stirred at room temperature over 16 h, upon which it was diluted with ether (1.5 mL), filtered through a Celite[®] pad and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 30% ether / petrol) to afford the title compound as a colourless oil (14.5 mg, 62%).

R_f 0.24 (20% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3323, 1688, 1530, 1331, 1249, 1059, 942, 836; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.74 (1H, d, J = 13.5 Hz, H₅), 6.20 (1H, d, J = 13.5 Hz, H₆), 5.49 (1H, t, J = 7.5 Hz, H₃), 4.45 (1H, br s, NH), 4.14 (1H, t, J = 8.5 Hz, OCH₂), 3.80 (1H, app br s, H₁), 2.35-2.22 (2H, m, H₂), 1.74 (3H, s, Me₄), 1.14 (3H, d, J = 6.5 Hz, Me₁), 0.97 (2H, t, J = 8.5 Hz, SiCH₂), 0.04 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 156.0 (CONH), 141.6 (C₅), 134.7 (C₄), 129.2 (C₃), 104.1 (C₆), 62.8 (OCH₂), 46.8 (C₁), 35.3 (C₂), 20.6 (Me₁), 17.7 (SiCH₂), 12.4 (Me₄), -1.5 (Si(CH₃)₃); **HRMS** (ESI⁺) calc. for C₁₄H₂₄BrNO₂Si [M+Na]⁺ 370.0808, found 370.0792.

2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*)-11,11-dibromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl]carbamate (255)

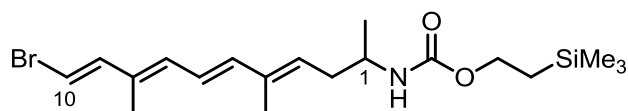


To a solution of PPh₃ (137 mg, 0.52 mmol, 4.0 eq) in DCM (0.5 mL) at 0 °C was added CBr₄ (40 mg, 0.26 mmol, 2.0 eq). The bright yellow solution was stirred at 0 °C for 10 min before Et₃N (18 μ L, 0.13 mmol, 1.0 eq) was added and the mixture stirred for a further 5 min. A

solution of **248** (44 mg, 0.13 mmol, 1.0 eq) in DCM (0.8 mL) was added and the reaction was stirred at 0°C for 7 h. The reaction was quenched with H₂O and the aqueous layer was extracted two times with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (10 → 30% ether / petrol) to afford the title compound as a colourless oil (13.7 mg, 21%).

R_f 0.38 (30% ether / petrol); **IR** (thin film, ν_{max} / cm⁻¹) 3325, 2953, 1692, 1530, 1250, 1060, 859, 837; **¹H NMR** (400 MHz, C₆D₆) δ_{H} 6.89 (1H, s, H9), 6.35 (1H, dd, J = 15.0, 9.5 Hz, H6), 6.28 (1H, d, J = 15.0 Hz, H5), 6.10 (1H, d, J = 9.5 Hz, H7), 5.47 (1H, t, J = 7.0 Hz, H3), 4.31 (1H, t, J = 8.0 Hz OCH₂), 4.12 (1H, d, J = 8.5 Hz, NH), 3.87 (1H, app br s, H1), 2.14-2.08 (1H, m, 1 x H2), 2.06-1.99 (1H, m, 1 x H2), 1.85 (3H, s, Me8), 1.64 (3H, s, Me4), 0.99 (2H, t, J = 8.5 Hz, SiCH₂), 0.85 (3H, d, J = 6.5 Hz, Me1), -0.06 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, C₆D₆) δ_{C} 156.0, 141.2, 140.6, 136.6, 135.5, 131.9, 130.8, 128.6, 122.5, 62.7, 47.1, 35.9, 20.5, 18.1, 15.3, 12.5, -1.5; **HRMS** (ESI+) calc. for C₁₉H₃₁Br₂NO₂Si [M+Na]⁺ 514.0383, found 514.0371.

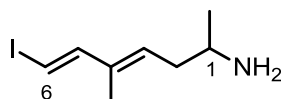
2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*E*,10*E*)-11-bromo-5,9-dimethylundeca-4,6,8,10-tetraen-2-yl]carbamate (256**)**



To a mixture of **255** (13.7 mg, 0.0278 mmol, 1.0 eq) and diethyl phosphite (100 μ L, 0.776 mmol, 28 eq) in a vial was added Et₃N (20 μ L, 0.14 mmol, 5.0 eq). The reaction was stirred at room temperature over 16 h, upon which it was diluted with ether (1.5 mL) and filtered through a Celite[®] pad. The filtrate was washed with H₂O and the aqueous layer was extracted two times with ether. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (10 → 30% ether / petrol) to afford the title compound as a colourless oil (5.0 mg, 43%).

R_f 0.56 (20% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 1689, 1250, 1204, 1062, 963, 861, 837; **¹H NMR** (400 MHz, C₆D₆) δ_{H} 6.75 (1H, d, J = 13.5 Hz, H9), 6.36 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.24 (1H, d, J = 13.5 Hz, H10), 6.00 (1H, d, J = 15.0 Hz, H5), 5.92 (1H, d, J = 11.0 Hz, H7), 5.44 (1H, t, 7.5 Hz, H3), 4.32-4.28 (1H, m, OCH₂), 4.11 (1H, br s, NH), 3.86 (1H, app br s, H1), 2.16-2.08 (1H, m, 1 x H2), 2.06-1.99 (1H, m, 1 x H2), 1.64 (3H, s, Me8), 1.50 (3H, s, Me4), 0.99 (2H, t, J = 8.5 Hz, SiCH₂), 0.85 (3H, d, J = 6.5 Hz, Me1), -0.07 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, C₆D₆) δ_{C} 156.0, 142.1, 140.3, 139.8, 133.3, 133.1, 130.2, 125.7, 122.8, 62.7, 47.1, 20.5, 18.1, 15.3, 12.9, 12.2, -1.5; **HRMS** (ESI+) calc. for C₁₉H₃₂BrNO₂Si [M+Na]⁺ 436.1268, found 463.1278.

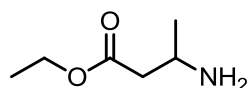
(4E,6E)-7-Iodo-5-methylhepta-4,6-dien-2-amine (S10)



To a solution of **250** (24 mg, 0.061 mmol, 1.0 eq) in THF (1.2 mL) at 0 °C was added TBAF in THF (1.0 M, 120 μ L, 0.120 mmol, 2.0 eq) dropwise. The solution was warmed to room temperature overnight and a second portion of TBAF in THF (1.0 M, 120 μ L, 0.120 mmol, 2.0 eq) was added. After stirring at room temperature over 48 h, the reaction mixture was quenched with saturated NaHCO₃. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a yellow oil (11 mg, 72%) which was used without further purification.

¹H NMR (400 MHz, C₆D₆) δ_{H} 6.98 (1H, d, J = 14.5 Hz, H5), 5.90 (1H, d, J = 14.5 Hz, H6), 5.16 (1H, t, J = 7.0 Hz, H3), 3.04 (2H, br s, NH₂), 2.67-2.59 (1H, m, H1), 1.81 (2H, t, J = 7.0 Hz, H2), 1.35 (3H, s, Me4), 0.84 (3H, d, J = 6.5 Hz, Me1).

Ethyl 3-aminobutanoate (S11)

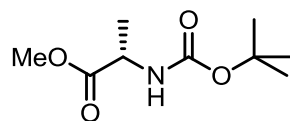


A solution of **S8** (3.93 g, 23.4 mmol, 1.0 eq) in CHCl_3 (150 mL) was washed with a 1M solution of NaOH in brine. The organic layer was dried over Na_2SO_4 , concentrated *in vacuo* and the residue was purified by vacuum distillation to afford the title compound as a colourless oil (1.83 g, 60%).

bp 68 °C, 20 mbar (lit.²⁶⁸ 60-61 °C, 13 Torr); **^1H NMR** (400 MHz, CDCl_3) δ_{H} 4.07 (2H, q, J = 7.0 Hz, OCH_2), 3.35-3.27 (1H, m, CHN), 2.33 (1H, dd, J = 15.5, 4.5 Hz, 1 x $\text{CH}_2\text{CO}_2\text{Et}$), 2.21 (1H, dd, J = 15.5, 8.5 Hz, 1 x $\text{CH}_2\text{CO}_2\text{Et}$), 1.19 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.05 (3H, d, J = 6.5 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 172.5, 60.3, 44.4, 44.1, 23.6, 14.3.

The spectroscopic data was found to be in agreement with that reported by Palmieri and co-workers.²⁶⁹

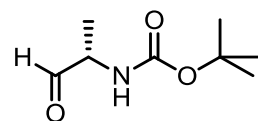
(S)-Methyl 2-[(*tert*-butoxycarbonyl)amino]propanoate (S12)



To a biphasic mixture of L-alanine methyl ester·HCl (3.00 g, 21.5 mmol, 1.00 eq) in THF/ H_2O (36 mL/36 mL) was added NaHCO_3 (3.97 g, 47.3 mmol, 2.20 eq) followed by Boc anhydride (4.93 g, 22.6 mmol, 1.05 eq). The reaction was stirred at room temperature over 16 h, then the aqueous layer was extracted three times with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to afford a viscous colourless oil. The crude mixture was purified by column chromatography (10 → 30% ethyl acetate / petrol) to afford the title compound as a viscous colourless oil (4.05 g, 93%).

R_f 0.38 (20% ethyl acetate / petrol); **^1H NMR** (200 MHz, CDCl_3) δ_{H} 5.03 (1H, br s, NH), 4.36-4.28 (1H, m, CH), 3.75 (3H, s, OCH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.38 (3H, d, J = 7.0 Hz, CHCH_3).

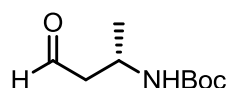
The spectroscopic data was found to be in agreement with that recorded by Park and co-workers.²⁷⁰

(S)-tert-Butyl (1-oxopropan-2-yl)carbamate (265)

To a solution of **S12** (660 mg, 3.25 mmol, 1.0 eq) in DCM (325 mL) at $-78\text{ }^{\circ}\text{C}$ was added DIBALH (1.0 M in hexanes, 6.50 mL, 6.50 mmol, 2.0 eq) dropwise down the side of the flask over 30 min. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and quenched with saturated aqueous Na^+/K^+ tartrates. The mixture was allowed to warm to room temperature gradually over 30 min before dilution with ether (10 mL). The cooling bath was removed and the mixture stirred vigorously at room temperature for 2 h. The aqueous layer was extracted twice with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate / petrol) to afford the title compound as a colourless oil (200 mg, 36%).

$[\alpha]_{\text{D}}^{20} +22.1$ (c 1.0, CHCl_3); R_f 0.38 (20% ethyl acetate / petrol); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 9.57 (1H, s, CHO), 5.10 (1H, br s, NH), 4.26-4.23 (1H, m, CH), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.35 (3H, d, $J = 7.0\text{ Hz}$, CHCH_3).

The spectroscopic data was found to be in agreement with that reported by Matsuya and co-workers.²¹⁵

(S)-tert-Butyl (4-oxobutan-2-yl)carbamate [(S)-234]

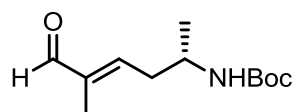
To a solution of (methoxymethyl)triphenylphosphonium chloride (394 mg, 1.15 mmol, 2.0 eq) in THF (3 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of NaHMDS in THF (2.0 M, 490 μL , 0.981 mmol, 1.7 eq). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ over 30 min before a solution of **265** (100 mg, 0.577 mmol, 1.0 eq) in THF (0.8 mL) was added. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ for 2 h and quenched with H_2O (3 mL). The aqueous layer was extracted two times with ethyl acetate and

the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to afford a yellow oil. The oil was dissolved in THF (2.9 mL) and 1M HCl (0.6 mL) was added. The mixture was stirred at room temperature for 3 h, then quenched with saturated NaHCO₃ and diluted with ethyl acetate. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (20 → 30% ethyl acetate / petrol) to afford the title compound as a pale yellow oil (76 mg, 70%).

$[\alpha]_{\text{D}}^{20} -21.6$ (*c* 1.0, CHCl₃).

The spectroscopic data was found to be in agreement with the racemic compound whose preparation is described above.

(*S,E*)-*tert*-Butyl (5-methyl-6-oxohex-4-en-2-yl)carbamate [(*S*)-232]



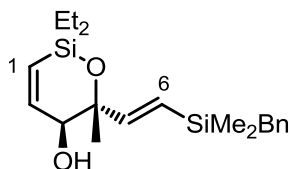
The enantioenriched compound was prepared on a 0.774 mmol scale in an identical manner to that described for the racemic compound above. Purification by column chromatography afforded the title compound as a pale yellow oil (110 mg, 63%).

$[\alpha]_{\text{D}}^{20} -30.6$ (*c* 1.0, CHCl₃); 79% *ee* (CHIRALPAK IA, 3% IPA / hexane, 1.3 mL/min, *t_R* (*S*) 8.76 min, *t_R* (*R*) 9.59 min).

The spectroscopic data was found to be in agreement with the racemic compound whose preparation is described above.

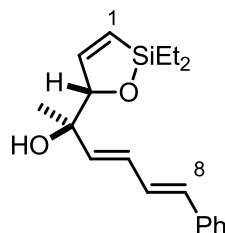
7.5 Towards assembling incednam by orthogonal cross-couplings

(5*S*,6*R*)-6-[(*E*)-2-(Benzyldimethylsilyl)vinyl]-2,2-diethyl-6-methyl-5,6-dihydro-2H-1,2-oxasilin-5-ol (**284**)



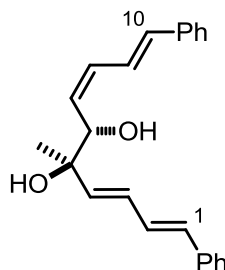
To a solution of **204** (18 mg, 0.0387 mmol, 1.0 eq) in ether (200 μ L) at -78°C was added MeLi•LiBr complex (1.5 M in ether, 57 μ L, 0.0851 mmol, 2.2 eq) dropwise. The reaction mixture was warmed to 0°C over 1 h, then to room temperature over another 1 h, then quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was separated and extracted three times with ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatograph (0 $\rightarrow$ 10% ether / petrol) to afford the title compound as a colourless oil (10 mg, 71%) and recover some of the starting material (1.9 mg, 11%).

$[\alpha]_{\text{D}}^{20} +48.2$ (c 0.81, CHCl_3); R_f 0.25 (10% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3451, 1493, 1249, 1216, 1058, 996, 887, 698; **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.21 (2H, t, $J = 7.5$ Hz, ArH), 7.08 (1H, t, $J = 7.5$ Hz, ArH), 6.98 (2H, d, $J = 7.5$ Hz, ArH), 6.69 (1H, dd, $J = 14.5, 2.5$ Hz, H2), 6.06 (1H, d, $J = 19.0$ Hz, H5), 5.92 (1H, dd, $J = 14.5, 2.5$ Hz, H1), 5.85 (1H, d, $J = 19.0$ Hz, H6), 3.93-3.91 (1H, m, H3), 2.16 (2H, s, SiCH_2), 1.51 (1H, d, $J = 5.5$ Hz, OH), 1.26 (3H, s, CH_3), 1.00-0.93 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.69-0.53 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.11 (6H, s, $\text{Si}(\text{CH}_3)_2$); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 152.8 (C5), 150.6 (C2), 140.1 (Ar *ipso*), 128.2 (Ar), 128.1 (Ar), 126.6 (C6), 126.2 (C1), 124.1 (Ar), 78.4 (C4), 73.2 (C3), 26.2 (SiCH_2), 20.2 (CH_3), 7.1 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.8 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.7 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.6 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), -3.2 (1 x $\text{Si}(\text{CH}_3)_2$), -3.4 (1 x $\text{Si}(\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{20}\text{H}_{32}\text{O}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 383.1833, found 383.1822.

***rac*-(3*E*,5*E*)-2-(2,2-Diethyl-2,5-dihydro-1,2-oxasilol-5-yl)-6-phenylhexa-3,5-dien-2-ol (291)**

To a solution of **106** (55 mg, 0.163 mmol, 1.0 eq), *trans*-2-phenylvinylboronic acid (29 mg, 0.195 mmol, 1.2 eq) and Ba(OH)₂·8H₂O (77 mg, 0.245 mmol, 1.5 eq) in DMF (3 mL) degassed by bubbling through with nitrogen (balloon) was added (dppf)PdCl₂ (18 mg, 0.024 mg, 0.15 eq). The mixture was stirred at room temperature over 5 h and then diluted with ethyl acetate, washed three times with brine, dried over magnesium sulphate and concentrated *in vacuo* as a brown oil. The mixture was purified by flash chromatography (10 → 20% ether / petrol) to afford the title compound as a yellow oil (20 mg, 39%).

R_f 0.31 (20% ether / petrol); **¹H NMR** (200 MHz, CDCl₃) δ_H 7.42-7.21 (5H, m, ArH), 6.97 (1H, dd, *J* = 10.5, 1.5 Hz, H2), 6.76 (1H, dd, *J* = 15.0, 10.0 Hz, H7), 6.55 (1H, d, *J* = 14.0 Hz, H8), 6.49 (1H, dd, *J* = 15.0, 10.0 Hz, H6), 6.18 (1H, dd, *J* = 10.5, 2.5 Hz, H1), 5.79 (1H, d, *J* = 15.0 Hz, H5), 4.61 (1H, dd, *J* = 2.5, 1.5 Hz, H3), 2.57 (1H, s, OH), 1.39 (3H, s, CH₃), 1.01-0.88 (6H, m, 2 x CH₂CH₃), 0.77-0.61 (4H, m, 2 x CH₂CH₃).

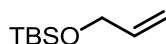
***rac*-(1*E*,3*E*,7*Z*,9*E*)-5-Methyl-1,10,diphenyldeca-1,3,7,9-tetraene-5,6-diol (292)**

291 (20 mg, 0.064 mmol, 1.0 eq) was dissolved in a solution of TBAF in THF (1.0 M, 0.13 mL, 0.13 mmol, 2.0 eq) and stirred under argon for 10 min. β-Bromostyrene (9 μL, 0.07 mmol, 1.1 eq) and [(η³-C₃H₅)PdCl]₂ (1 mg, 0.002 mmol, 2.5 mol%) were added successively. The reaction

mixture was stirred at room temperature for 3 h, then diluted with a solution of 70% ethyl acetate in hexane, filtered through a pad of silica and concentrated *in vacuo* as a yellow oil. The crude product was purified by flash chromatography (10 → 50% ethyl acetate / petrol) to afford the title compound as an orange oil (14 mg, 67%) which was further purified by HPLC to provide analytically pure samples.

R_f 0.18 (30% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3406, 3061, 3029, 1714, 1599, 1494, 1450, 697; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.43 (2H, d, J = 7.5 Hz, ArH), 7.39 (2H, d, J = 7.5 Hz, ArH), 7.35-7.30 (4H, m, ArH), 7.28-7.21 (2H, m, ArH) 7.12 (1H, ddd, J = 15.5, 11.0, 1.0 Hz, H9), 6.79 (1H, dd, J = 15.5, 10.5 Hz, H2), 6.64 (1H, d, J = 15.5, H10), 6.59 (1H, d, J = 15.5 Hz, H1), 6.55 (1H, dd, J = 15.5, 10.5 Hz, H3), 6.38 (1H, t, J = 11.0, H8), 5.96 (1H, d, J = 15.5 Hz, H4), 5.50 (1H, t, J = 10.0 Hz, H7), 4.60 (1H, ddd, J = 9.0, 5.0, 0.5 Hz, H6), 2.47 (1H, s, OH), 2.05 (1H, d, J = 5.0 Hz, OH), 1.38 (3H, s, CH_3); **¹³C NMR** (125 MHz, CDCl_3) δ_{C} 137.1, 136.8, 135.6 (C4), 135.3 (C10), 133.1 (C8), 132.9 (C1), 130.6 (C3), 128.7, 128.6 (C7), 128.5, 128.3 (C2), 128.0, 127.6, 126.6, 126.4, 123.6 (C9), 75.4 (C5), 74.5 (C6), 24.4 (CH_3); **HRMS** (ESI+) calc. for $\text{C}_{23}\text{H}_{24}\text{O}_2$ $[\text{M}+\text{Na}]^+$ 355.1669, found 355.1660.

(Allyloxy)(*tert*-butyl)dimethylsilane (S13)



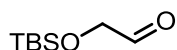
To a solution of allyl alcohol (500 mg, 8.61 mmol, 1.0 eq) in DCM (35 mL) was added TBSCl (1.43 g, 9.47 mmol, 1.1 eq), imidazole (878 mg, 12.9 mmol, 1.5 eq) and DMAP (2 crystals, cat.) sequentially. The reaction was stirred at room temperature for 90 min, then quenched with saturated aqueous sodium bicarbonate. The biphasic mixture was stirred vigorously until two clear layers formed. The aqueous layer was extracted twice with DCM and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to afford the title compound which was used without further purification.

¹H NMR (400 MHz, CDCl_3) δ_{H} 5.98-5.88 (1H, m, CH), 5.28 (1H, dd, J = 17.0, 1.5 Hz, 1 x CH_2), 5.09 (1H, dd, J = 10.5, 1.5 Hz, 1 x CH_2), 4.19-4.18 (2H, m, OCH_2), 0.92 (9H, s,

$\text{C}(\text{CH}_3)_3$, 0.08 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 137.5, 113.9, 64.1, 25.9, 18.4, -5.3.

The spectroscopic data was found to be in agreement with that reported by Williard and co-workers.²⁷¹

(*tert*-Butyldimethylsiloxy)acetaldehyde (294)

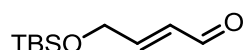


Ozone was bubbled through a solution of **S13** (8.61 mmol, 1.0 eq) in DCM (50 mL) at -78 °C. Once the solution turned blue, the supply of ozone was replaced with O_2 , and the solution was purged for 10 min. To the resulting colourless solution was added triphenylphosphine (4.97 g, 18.9 mmol, 2.2 eq) in three portions. The reaction mixture was stirred at -78 °C for 5 min, then allowed to warm to room temperature over 1 h. When the reaction was determined to be complete by TLC, the reaction mixture was concentrated *in vacuo* (at 200 mbar). The residue was purified by vacuum distillation to afford the title compound as a colourless oil (1.20 g, 80% over two steps).

bp 68-70 °C, 20 mbar (lit.²⁷² 65 °C, 23 mbar); ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.71 (1H, s, CHO), 4.22 (2H, m, OCH_2), 0.94 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.11 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 202.2, 69.6, 25.7, 18.3, -5.4.

The spectroscopic data was found to be in agreement with that reported by Charette and co-workers.²⁷³

(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-2-enal (295)



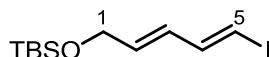
(Formylmethyl)triphenylphosphonium chloride (978 mg, 2.87 mmol, 1.0 eq) and triethylamine (480 μL , 3.44 mmol, 1.2 eq) in toluene (50 mL) was stirred at room temperature for 15 min. A solution of **294** (500 mg, 2.87 mmol, 1.0 eq) in toluene (7 mL) was added and

stirred at room temperature over 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatograph (10% ethyl acetate / petrol) to afford the title compound as a colourless oil (408 mg, 65%).

¹H NMR (200 MHz, CDCl₃) δ_H 9.62 (1H, d, *J* = 8.0 Hz, CHO), 6.90 (1H, dt, *J* = 15.5, 3.0 Hz, CHCH₂), 6.41 (1H, ddt, *J* = 15.5, 8.0, 2.0 Hz, CHCHO), 4.46 (2H, dd, *J* = 3.0, 2.0 Hz, OCH₂), 0.93 (9H, s, C(CH₃)₃), 0.10 (6H, s, Si(CH₃)₂).

The spectroscopic data was found to be in agreement with that reported by Ramachandran and co-workers.²⁷⁴

***tert*-Butyl[(2*E*,4*E*)-5-iodopenta-2,4-dien-1-yloxy]dimethylsilane (293)**



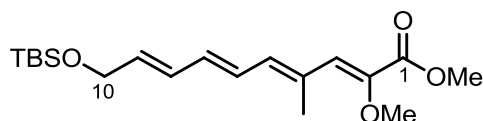
To chromium(II) chloride (490 mg, 3.99 mmol, 8.0 eq) dried under vacuum and heat was added THF (8 mL) and the resulting grey suspension was stirred for 90 min at room temperature. The solution was cooled to 0 °C before a solution of **295** (100 mg, 0.499 mmol, 1.0 eq) and iodoform (393 mg, 0.998 mmol, 2.0 eq) in THF (4 mL) was then added *via* syringe and the mixture stirred at 0 °C for 2 h. The resulting reddish-brown solution was diluted with ether, washed twice with distilled H₂O, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 5% ether / petrol + 1% Et₃N) to afford the dienyl iodide as a 5.3:1 mixture of *E/E* and *E/Z* isomers.

To the mixture of isomers was added a solution of freshly prepared sodium methoxide in methanol (1M, 250 μL, 0.250 mmol, 0.5 eq). The reaction mixture was stirred at 65 °C for 1 h and the resulting solution was diluted with ether and quenched with distilled H₂O. The aqueous layer was extracted twice with ether and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 → 2% ether / petrol + 1% Et₃N) to afford the title compound as a colourless oil (60 mg, 37%).

¹H NMR (200 MHz, C₆D₆) δ_{H} 6.86 (1H, dd, $J = 14.5, 10.5$, C4), 6.00 (1H, ddt, $J = 15.0, 10.5, 2.0$, C3), 5.86 (1H, d, $J = 14.5$, C5), 5.38 (1H, dt, $J = 15.0, 4.5$ Hz, C2), 3.86 (2H, dd, $J = 4.5, 2.0$ Hz, C1), 0.96 (9H, s, C(CH₃)₃), 0.01 (6H, s, Si(CH₃)₂).

The spectroscopic data was found to be in agreement with that reported by Negishi and co-workers.²⁷⁵

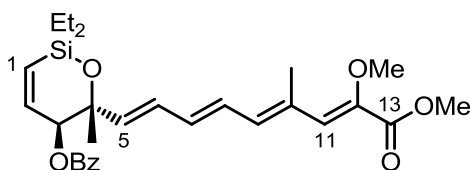
(2Z,4E,6E,8E)-Methyl 10-[(*tert*-butyldimethylsilyl)oxy]-2-methoxy-4-methyldeca-2,4,6,8-tetraenoate (296)



To a mixture of **293** (11 mg, 0.0339 mmol, 1.0 eq), **228** (14.5 mg, 0.0407 mmol, 1.2 eq) and K₃PO₄ (43 mg, 0.203 mmol, 6.0 eq) in THF (450 μ L) and H₂O (230 μ L) was added Pd(dppf)Cl₂ (3.0 mg, 0.0034 mmol, 10 mol%). The biphasic mixture was stirred in the dark at room temperature over 16 h, then at 40 °C for a further 2 h. The reaction mixture was diluted with ethyl acetate (1 mL) and washed with distilled H₂O. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (0 $\rightarrow$ 20% ether / petrol + 1% Et₃N) to afford the title compound as a yellow oil (7.0 mg, 59%) and recover **293** (1.9 mg, 17%).

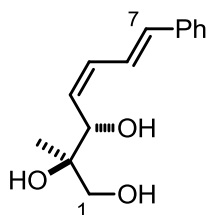
R_f 0.18 (10% ether / petrol + 1% Et₃N); **IR** (thin film, ν_{max} / cm⁻¹) 1750, 1720, 1253, 1104, 967, 837, 778; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 6.86 (1H, s, H3), 6.53-6.41 (2H, overlapping dd, H6 + H8), 6.30-6.22 (2H, overlapping dd, H5 + H7), 5.73 (1H, dt, $J = 15.0, 5.0$ Hz, H9), 4.12 (2H, d, $J = 5.0$ Hz, H10), 3.50 (3H, s, OCH₃), 3.40 (3H, s, CO₂CH₃), 2.04 (3H, s, CH₃), 1.00 (9H, s, C(CH₃)₃), 0.07 (Si(CH₃)₂); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 164.8 (C1), 144.8 (C2), 136.5 (C5), 135.7 (C7), 134.9 (C9), 133.3 (C6), 130.2 (C4), 128.9 (C3), 128.5 (C8), 63.6 (C10), 59.9 (OCH₃), 51.4 (CO₂CH₃), 26.1 (C(CH₃)), 18.6 (C(CH₃)), 15.2 (CH₃), -5.1 (Si(CH₃)₂); **HRMS** (FI+) calc. for C₁₉H₃₂O₄Si [M]⁺ 352.2070, not found.

(5*S*,6*R*)-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 (297)



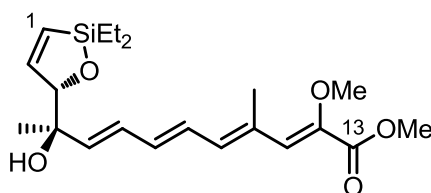
To a mixture of **227** (82 mg, 0.291 mmol, 1.0 eq), **140** (150 mg, 0.320 mmol, 1.1 eq) and Ti_2CO_3 (273 mg, 0.582 mmol, 2.0 eq) in THF (2.3 mL) and H_2O (0.6 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (24 mg, 0.029 mmol, 10 mol%). The biphasic mixture was stirred in the dark at room temperature over 5 h. The reaction mixture was diluted with ether and filtered through a Celite[®] pad. The filtrate was dried over MgSO_4 , concentrated *in vacuo* and the residue was purified by column chromatography (10 $\rightarrow$ 30% ether / petrol + 1% Et_3N) to afford the title compound as a yellow oil (95.2 mg, 66%) and **227** (5.8 mg, 7%).

$[\alpha]_{\text{D}}^{20}$ -115 (c 0.28, CHCl_3); R_f 0.21 (15% ether / petrol + 1% Et_3N); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2876, 1689, 1586, 1265, 1107, 993, 712; **^1H NMR** (500 MHz, C_6D_6) δ_{H} 8.21 (2H, d, J = 7.0 Hz, ArH), 7.13 (1H, t, J = 7.0 Hz, ArH), 7.07 (2H, t, J = 7.0 Hz, ArH), 6.83 (1H, s, H11), 6.73 (1H, dd, J = 14.5, 3.0 Hz, H2), 6.65 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.45 (1H, dd, J = 14.5, 11.5 Hz, H8), 6.22 (1H, d, J = 11.5, H9), 6.10 (1H, dd, J = 14.5, 11.5 Hz, H7), 5.97 (1H, d, J = 15.0, H5), 5.87 (1H, dd, J = 14.5, 2.0 Hz, H1), 5.84 (1H, dd, J = 3.0, 2.0 Hz, H3), 3.49 (3H, s, OCH_3), 3.39 (3H, s, CO_2CH_3), 2.01 (3H, s, Me10), 1.58 (3H, s, Me4), 1.03 (3H, t, J = 8.0 Hz, 1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 1.01 (3H, t, J = 8.0 Hz, 1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.71-0.56 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ_{C} 165.6 (CO_2Ar), 164.8 (CO_2CH_3), 147.5 (C2), 144.9 (C12), 140.0 (C5), 136.5 (C9), 135.7 (C7), 133.3 (C10), 133.2 (Ar), 130.7 (Ar), 130.0 (Ar), 129.8 (C6), 129.3 (C8), 128.8 (overlapping C11 + C1), 128.7 (Ar), 76.4 (C4), 75.4 (C3), 59.9 (OCH_3), 51.4 (CO_2CH_3), 23.9 (Me4), 15.2 (Me10), 7.5 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 7.0 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.9 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 6.8 (1 x $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **HRMS** (ESI+) calc. for $\text{C}_{28}\text{H}_{36}\text{O}_6\text{Si}$ $[\text{M}+\text{Na}]^+$ 519.2173 found 519.2161.

***rac*-(2*R*,3*S*,4*Z*,6*E*)-2,3-Dimethyl-7-phenylhepta-4,6-diene-1,2,3-triol (298)**

60 (20 mg, 0.0924 mmol, 1.1 eq) was dissolved in a solution of TBAF in THF (1.0 M, 0.17 mL, 0.167 mmol, 2.0 eq) and stirred under argon for 10 min. Bromostyrene (11 μ L, 0.0840 mmol, 1.0 eq) and $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ (1 mg, 0.0021 mmol, 2.5 mol%) were added successively. The reaction mixture was stirred at room temperature for 24 h, then diluted with a solution of 70% ethyl acetate in hexane, filtered through a pad of silica and concentrated *in vacuo* as a yellow oil. The crude product was purified by flash chromatography (50 $\rightarrow$ 100% ethyl acetate / petrol) to afford the title compound as a colourless oil (14 mg, 65%).

R_f 0.09 (50% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3368, 2927, 1450, 1043, 1002, 949, 740, 692; **¹H NMR** (500 MHz, CDCl_3) 7.32-7.25 (5H, m, Ph), 7.08 (1H, dd, $J = 15.5, 11.5$ Hz, H6), 6.64 (1H, d, $J = 15.5$ Hz, H7), 6.39 (1H, t, $J = 11.5$ Hz, H5), 5.55 (1H, t, $J = 10.5$ Hz, H4), 4.72 (1H, d, $J = 9.5$ Hz, H3), 3.88 (1H, d, $J = 11.5$ Hz, $1\times\text{CH}_2\text{OH}$), 3.51 (1H, d, $J = 11.5$ Hz, $1\times\text{CH}_2\text{OH}$), 1.51 (3H, s, Me); **¹³C NMR** (125 MHz, CDCl_3) 136.8, 135.5 (C7), 133.0 (C5), 128.7, 128.5 (C4), 128.1, 126.6, 123.3 (C6), 74.2 (C2), 74.0 (C3), 67.5 (C1), 20.9 (CH_3); **HRMS** (ESI+) calc. for $\text{C}_{15}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 257.1148 found 257.1151.

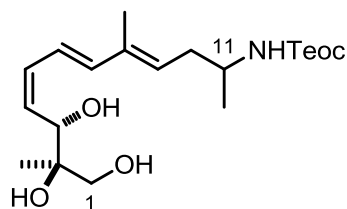
(*R*,2*Z*,4*E*,6*E*,8*E*)-Methyl 10-[(*S*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-10-hydroxy-2-methoxy-4-methylundeca-2,4,6,8-tetraenoate (302)

To a solution of **297** (26 mg, 0.052 mmol, 1.0 eq) in MeOH (520 μ L) was added K_2CO_3 (14 mg, 0.10 mmol, 1.0 eq). The reaction mixture was stirred at room temperature in the dark over 3 h,

then diluted with ether and quenched with saturated NH_4Cl . The aqueous layer was extracted two times with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (20 $\rightarrow$ 40% ether / petrol) to afford the title compound as a bright yellow oil (14 mg, 66%).

$[\alpha]_{\text{D}}^{20} +110$ (c 0.35, CHCl_3); R_f 0.21 (30% ether / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 1717, 1616, 1350, 1259, 1103, 991, 820, 697; **^1H NMR** (400 MHz, C_6D_6) δ_{H} 6.86 (1H, s, H11), 6.74 (1H, dd, J = 10.5, 1.5 Hz, H1), 6.57 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.49 (1H, dd, J = 14.5, 11.5 Hz, H8), 6.28 (1H, d, J = 11.5, H9), 6.23 (1H, dd, J = 14.5, 11.0 Hz, H7), 5.96 (1H, dd, J = 10.5, 2.0 Hz, H2), 5.72 (1H, d, J = 15.0, H5), 4.55 (1H, dd, J = 2.0, 1.5 Hz, H3), 3.50 (3H, s, OCH_3), 3.40 (3H, s, CO_2CH_3), 2.07 (3H, s, Me10), 1.32 (3H, s, Me4), 0.94 (6H, t, J = 8.0 Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_2$), 0.73-0.49 (4H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_2$); **^{13}C NMR** (100 MHz, C_6D_6) δ_{C} 164.8, 150.6, 144.8, 139.3, 136.5, 135.6, 133.3, 130.0, 128.9, 128.7, 127.8, 90.3, 75.0, 59.9, 51.4, 24.7, 15.2, 7.5, 7.1, 77.0, 6.7; **HRMS** (ESI+) calc. for $\text{C}_{21}\text{H}_{32}\text{O}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 415.1911 found 415.1915.

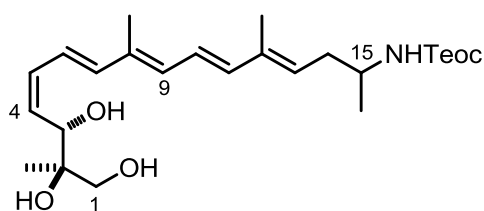
***rac*-2-(Trimethylsilyl)ethyl [(4*E*,6*E*,8*Z*,10*S*,11*R*)-10,11,12-trihydroxy-5,11-dimethyldodeca-4,6,8-trien-2-yl]carbamate (303)**



60 (7.5 mg, 0.035 mmol, 1.0 eq) and **250** (15 mg, 0.038 mmol, 1.1 eq) were dissolved in a solution of TBAF in THF (1.0 M, 69 μL , 0.069 mmol, 2.0 eq) and stirred under argon for 10 min. $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ (0.3 mg, 0.0009 mmol, 2.5 mol%) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction was directly purified by column chromatography (20 $\rightarrow$ 100% ethyl acetate / petrol) to afford the title compound as a bright yellow oil that turned brown on standing (8.6 mg, 57%) and recover **60** (2.5 mg, 33%) in addition to **250** (5.9 mg, 39%).

R_f 0.16 (70% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 3340, 1689, 1539, 1251, 1056, 947, 860, 837; **¹H NMR** (500 MHz, C₆D₆) 6.61 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.24 (1H, d, J = 15.0 Hz, H7), 6.13 (1H, t, J = 11.0 Hz, H5), 5.42 (1H, t, J = 7.5 Hz, H9), 5.39-5.34 (1H, m, H4), 4.70 (1H, d, J = 9.0 Hz, H3), 4.28 (4H, t, J = 8.5 Hz, overlapping OCH₂ + NH), 3.87 (1H, br s, H11), 3.77 (1H, d, J = 11.0 Hz, 1 x H1), 3.44 (1H, d, J = 11.0 Hz, 1 x H1), 2.50 (1H, t, J = 7.5 Hz, OH), 2.15-2.09 (1H, m, 1 x H10), 2.07-2.02 (1H, m, 1 x H10), 1.67 (3H, s, Me8), 1.39 (1H, s, OH), 1.13 (3H, s, Me2), 1.02-0.98 (2H, m, SiCH₂), 0.85 (3H, d, J = 6.5 Hz, Me11), – 0.05 (9H, s, Si(CH₃)₃); **¹³C NMR** (125 MHz, C₆D₆) 156.3, 140.3, 132.9, 129.7, 124.6, 122.4, 74.7, 74.3, 67.9, 62.9, 47.3, 35.9, 21.1, 18.2, 12.8, –1.5; **HRMS** (ESI+) calc. for C₂₀H₃₇NO₅ [M+Na]⁺ 422.2333 found 422.2320.

***rac*-2-(Trimethylsilyl)ethyl [(2*S*,4*E*,6*E*,8*E*,10*E*,12*Z*,14*S*,15*R*)-14,15,16-trihydroxy-5,9,15-trimethylhexadeca-4,6,8,10,12-pentaen-2-yl]carbamate (305)**

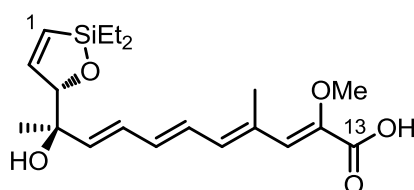


60 (8.1 mg, 0.038 mmol, 1.0 eq) and **252** (26 mg, 0.056 mmol, 1.5 eq) were dissolved in a solution of TBAF in THF (1.0 M, 83 μL , 0.083 mmol, 2.2 eq) and stirred under argon for 10 min. $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ (0.4 mg, 0.0010 mmol, 2.5 mol%) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction was directly purified by column chromatography (20 $\rightarrow$ 100% ethyl acetate / petrol) to afford the title compound as a bright yellow oil that turned brown on standing (7.5 mg, 43%).

R_f 0.25 (70% ethyl acetate / petrol); **IR** (thin film, $\nu_{\max}$ / cm^{-1}) 1689, 1537, 1250, 1061, 1050, 961, 837, 695; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 6.72-6.65 (1H, m, H6), 6.57 (1H, dd, J = 15.0, 11.5 Hz, H10), 6.36 (2H, d, J = 15.0 Hz, overlapping H7 + H11), 6.25 (1H, d, J = 11.5 Hz, H9), 6.19 (1H, app t, J = 10.5 Hz, H5), 5.49 (1H, t, J = 7.5 Hz, H13), 5.44-5.39 (1H, m, H4), 4.66 (1H, d, J = 9.5 Hz, H3), 4.20 (2H, t, J = 8.0 Hz, OCH₂), 4.20 (1H, br s, NH), 3.90-3.82 (1H, m,

H15), 3.70 (1H, d, $J = 11.0$ Hz, 1 x H1), 3.37 (1H, d, $J = 11.0$ Hz, 1 x H1), 2.20-2.13 (1H, m, 1 x H14), 2.10-2.04 (1H, m, 1 x H14), 1.82 (3H, s, Me8), 1.70 (3H, s, Me12), 1.10 (3H, s, Me2), 1.00 (2H, t, $J = 8.0$ Hz, SiCH₂), 0.88 (3H, d, $J = 6.5$ Hz, Me15), -0.06 (9H, s, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ_c 156.1, 140.4, 139.3, 136.7, 134.0, 133.0, 132.9, 130.0, 128.9, 123.6, 123.0, 74.4, 67.8, 62.7, 47.2, 36.1, 21.0, 18.1, 12.8, 12.6, -1.5 ; HRMS (ESI+) calc. for C₂₅H₄₃NO₅ [M+Na]⁺ 488.2803 found 488.2785.

(*R,2Z,4E,6E,8E*)-10-[(*S*)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-10-hydroxy-2-methoxy-4-methylundeca-2,4,6,8-tetraenoic acid (306)

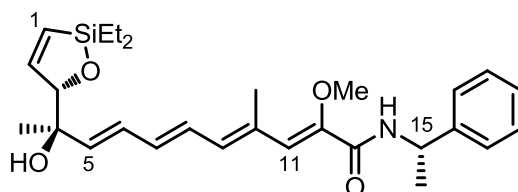


To a solution of **297** (60 mg, 0.121 mmol, 1.0 eq) in 1,4-dioxane (1.2 mL) was added an aqueous solution of KOH (1 M, 1.2 mL, 1.21 mmol, 10 eq) dropwise. The mixture was stirred at room temperature in the dark over 5 h, then diluted with ethyl acetate (2 mL) and brine (2 mL). The pH of the aqueous layer was adjusted to pH 3 with 1 M HCl before it was extracted three times with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (20 → 50% ethyl acetate / petrol) to afford the title compound as a bright yellow oil (30 mg, 65%).

$[\alpha]_D^{20} +148$ (c 0.49, CHCl₃); R_f 0.26 (70% ethyl acetate / petrol); IR (thin film, ν_{max} / cm⁻¹) 3421, 1716, 1615, 1263, 1230, 1108, 819, 735; ¹H NMR (500 MHz, C₆D₆) δ_H 6.97 (1H, s, H11), 6.73 (1H, dd, $J = 10.5, 3.0$ Hz, H1), 6.57 (1H, dd, $J = 15.0, 11.0$ Hz, H6), 6.45 (1H, dd, $J = 14.5, 11.5$ Hz, H8), 6.24 (1H, d, $J = 11.5$, H9), 6.22 (1H, dd, $J = 14.5, 11.0$ Hz, H7), 5.96 (1H, dd, $J = 10.5, 1.5$ Hz, H2), 5.74 (1H, d, $J = 15.0$, H5), 4.55 (1H, t, $J = 2.0$ Hz, H3), 3.47 (3H, s, OCH₃), 2.02 (3H, s, Me10), 1.32 (3H, s, Me4), 0.95 (6H, t, $J = 8.0$ Hz, Si(CH₂CH₃)₂), 0.76-0.51 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (125 MHz, C₆D₆) δ_c 169.8, 150.6, 143.9, 139.7, 137.9, 136.4,

133.2, 131.3, 130.5, 130.0, 111.9, 90.4, 75.1, 60.2, 24.8, 15.0, 7.6, 7.2, 7.1, 6.8; **HRMS** (ESI+) calc. for $C_{20}H_{30}O_5Si$ $[M+Na]^+$ 401.1755 found 401.1763.

(R,2Z,4E,6E,8E)-10-[(S)-2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl]-10-hydroxy-2-methoxy-4-methyl-N-[(S)-1-phenylethyl]undeca-2,4,6,8-tetraenamide (307)



To a solution of **306** (6.1 mg, 0.0016 mmol, 1.0 eq) and (*S*)-1-phenylethylamine (2.9 mg, 0.024 mmol, 1.5 eq), HOBT (2.4 mg, 0.018 mmol, 1.1 eq) and EDC·HCl (4.0 mg, 0.021 mmol, 1.3 eq) in DCM (160 μ L) was added DIPEA (3.0 μ L, 0.018 mmol, 1.1 eq). The reaction was stirred at room temperature over 1.5 h, then diluted with DCM and quenched with 0.1 M aqueous HCl. The aqueous layer was extracted three times with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (10 $\rightarrow$ 40% ethyl acetate / petrol) to afford the title compound as an orange oil (2.0 mg, 26%).

R_f 0.23 (20% ethyl acetate / petrol); **IR** (thin film, ν_{max} / cm^{-1}) 3304, 1638, 1533, 1492, 1030, 994, 699; **¹H NMR** (500 MHz, C_6D_6) δ_H 7.12 (2H, t, J = 7.5 Hz, ArH), 7.07 (1H, s, H11), 7.06 (1H, t, J = 7.5 Hz, ArH), 7.02 (2H, d, J = 7.5 Hz, ArH), 6.76 (1H, dd, J = 10.5, 1.5 Hz, H1), 6.59 (1H, dd, J = 15.0, 11.0 Hz, H6), 6.48 (1H, dd, J = 14.5, 11.5 Hz, H8), 6.29 (1H, d, J = 11.5 Hz, H9), 6.20 (1H, dd, J = 14.5, 11.0 Hz, H7), 5.96 (1H, dd, J = 10.5, 2.0 Hz, H2), 5.73 (1H, d, J = 15.0 Hz, H5), 5.37 (1H, quintet, J = 7.5 Hz, H15), 4.55 (1H, dd, J = 2.0, 1.5 Hz, H3), 3.11 (3H, s, OCH₃), 2.99 (1H, s, OH), 2.47 (1H, br s, NH), 1.98 (3H, s, Me10), 1.32 (3H, s, Me4), 1.23 (3H, d, J = 7.5 Hz, Me15), 0.94 (6H, t, J = 8.0 Hz, Si(CH₂CH₃)₂), 0.68-0.50 (4H, m, Si(CH₂CH₃)₂); **¹³C NMR** (125 MHz, C_6D_6) δ_C 163.0, 150.7, 144.0, 139.2, 136.0, 135.4, 132.2, 131.1, 129.9, 128.8, 128.5, 128.3, 127.4, 126.7, 126.5, 90.3, 75.0, 60.6, 48.8, 24.7, 21.8, 14.8, 7.5, 7.1, 7.0, 6.7; **HRMS** (ESI+) calc. for $C_{28}H_{39}NO_4Si$ $[M+Na]^+$ 504.2541 found 504.2537.

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