Approaches to the Synthesis of Non-Natural Carbohydrates *via* Silicon Tethered Ene and Allyl Transfer Reactions

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ASLIB ABSTRACT

Approaches to the Synthesis of Non-Natural Carbohydrates *via* Silicon Tethered Ene and Allyl Transfer Reactions

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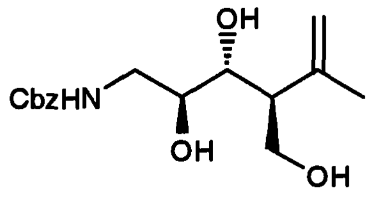
The efficiency of an intermolecular synthetic transformation can be improved by temporarily linking reaction components together. The addition of a tether leads to enhanced regio- and stereocontrol by restraining the mobility of the reacting partners, effectively transforming an intermolecular reaction into its intramolecular counterpart. Silicon tethers are associated with an expanding range of applications, including hydrosilylations, cycloadditions and radical reactions. This project has continued work pioneered by the Robertson group into silicon tethered Type I ene cyclisations, extending the methodology to incorporate *O*-linked ene precursors with the intention of applying this chemistry to the stereoselective synthesis of non-natural carbohydrates.

This investigation encompassed advances in the area made concurrently within the Robertson group and extended the scope of the ene protocol by successfully incorporating latent functionality into the R-group side chain. In addition, a new route to the *O*-linked ene precursors was established employing silylcyanohydrin chemistry. In general, the ene reactions proceeded stereoselectively to generate the expected oxasilacyclohexanols, which could be cleaved oxidatively to afford 1,2,4-triols. The formation of the major diastereomer was consistent with ene cyclisation proceeding through a *trans*-decalin type transition state (e.g. leading to compound 1).

During our attempts to effect ene cyclisation in the *O*-linked prenyl systems we observed an unexpected side reaction, resulting from intramolecular allylic transfer. Further studies revealed that this novel process could be initiated thermally to generate 1,2-homoallylic diols with excellent levels of stereoselectivity. Tethered *E*- and *Z*-crotylsilanes were found to be equally receptive to this process.

Although attempts to apply the silicon tethered allyl transfer chemistry to aldimines and glycosides failed, an extension of the methodology to incorporate cyclohexadienylsilanes was successful and provided interesting synthetic intermediates for elaboration to carbasugars.



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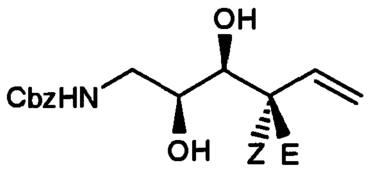

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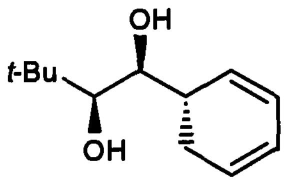

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My time available to spend on research would have been lessened considerably had it not been for the combined talents of the Dyson Perrins technical staff; the great stores team; Levi, Lee, Dave and especially Ralph for always keeping something useful in the basement. Thanks to the workshop guys for being omni-present to fix our temperamental water still and other Lab 61 artefacts. I acknowledge the mass spec. service in the DP and at Swansea, and thank Tim, Barbara and Tina for their efficiency in providing helpful NMR data.

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I am particularly grateful to Drs Gemmell-Evans for their dedicated proof reading in exchange for some jam and a second-hand rabbit hutch. Finally, I would like to thank my parents for their continued encouragement and support throughout my seemingly protracted education, I promise I will get a proper job now.

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Abbreviations

Ac	acetyl
acac	acetylacetone
AIBN	2,2'-azo*bis*isobutyronitrile
All	allyl
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis-(diphenylphosphino)-1,1'-binapthyl
BINOL	1,1'-binapthalene-2,2'-diol
BMDMS	bromomethyldimethylsilyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
B.p.	boiling point
Bu	butyl
CAB	chiral acyloxy borane
cat.	catalytic amount
Cbz	benzyloxycarbonyl
CI	chemical ionisation
COD	cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphor sulfonic acid
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
d.e.	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DIBAL	di-*iso*-butylaluminium hydride
DMAC	dimethylaluminium chloride
DMAP	4-*N,N*-dimethylamino pyridine
DMF	*N,N*-dimethylformamide
DMP	dimethoxypropane
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPPA	diphenylphosphoryl azide
dppp	1,3-*bis*(diphenylphosphino) propane
d.r.	diastereomeric ratio
2,6-DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DVDS	1,3-divinyl-1,1,3,3-tetramethyldisiloxane
EDA	ethyl diazoacetate
e.e.	enantiomeric excess
EI	electron impact
eq.	equivalent
e.r.	enantiomeric ratio
ES	electrospray ionisation
Et	ethyl
FI	field ionisation
GCMS	gas chromatography mass spectrometry
GCT	gas chromatography/time of flight mass spectrometry
HMBC	heteronuclear multiple-bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosporamide
HMQC	heteronuclear multiple-quantum correlation
hr	hour
hv	photolysis
i-	*ipso-*
IBX	*o*-iodoxybenzoic acid
Im.	imidazole
IDCP	iodonium dicollidine perchlorate
IMDA	intramolecular Diels-Alder
IR	infrared
iso/*i*-Pr	*iso*-propyl
LCT	liquid chromatography/time of flight mass spectroscopy
LDA	lithium di-*iso*-propylamide
lit.	literature value
M	molar
MAPh	methyl aluminium*bis*(2,6-diphenylphenoxide)
Me	methyl
Mes	mesityl
min	minute
MOM	methoxymethyl
MMTr	monomethoxytrityl

M.p.	melting point
MS	molecular sieves
m/z	mass to charge ratio
n.O.e.	nuclear Overhauser effect
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
N-PSP	*N*-phenylseleno phthalimide
o-	*ortho-*
oct	octanoate
p-	*para-*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
py.	pyridine
RCM	ring closing metathesis
R_f	retention factor
RT	room temperature
TA	transannular
tlc	thin layer chromatography
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBS	*tert*-butyldimethylsilane
TBDPS	*tert*-butyldiphenylsilane
TBHP	*tert*-butylhydroperoxide
TEA	triethylamine
tert/*t*-Bu	tertiary-butyl
TES	triethylsilane
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilane
TPAP	tetra-*N*-propylammonium perruthenate
TPS	triphenylsilane
Ts	4-methylphenylsulfonyl
UV	ultra violet
w/v	weight to volume ratio

Part 1

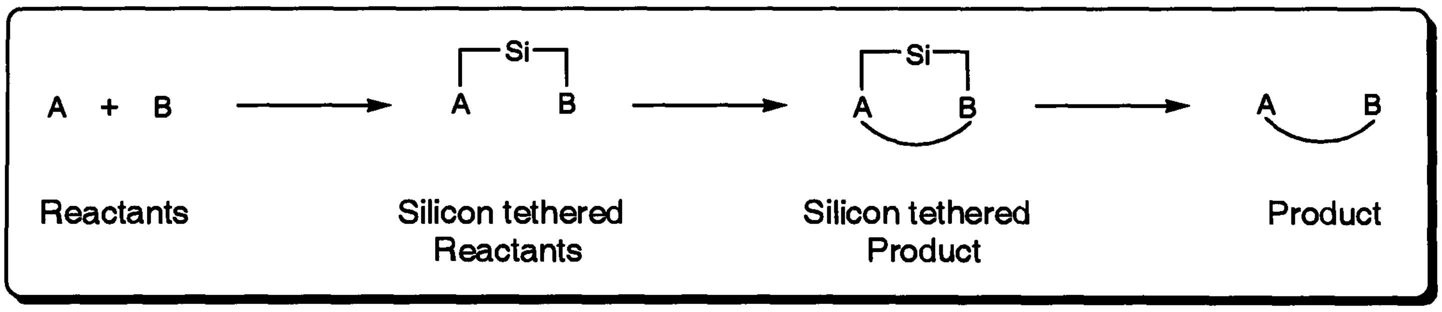
Silicon Tethered Ene Cyclisations

Chapter 1

Silicon Tethered Reactions

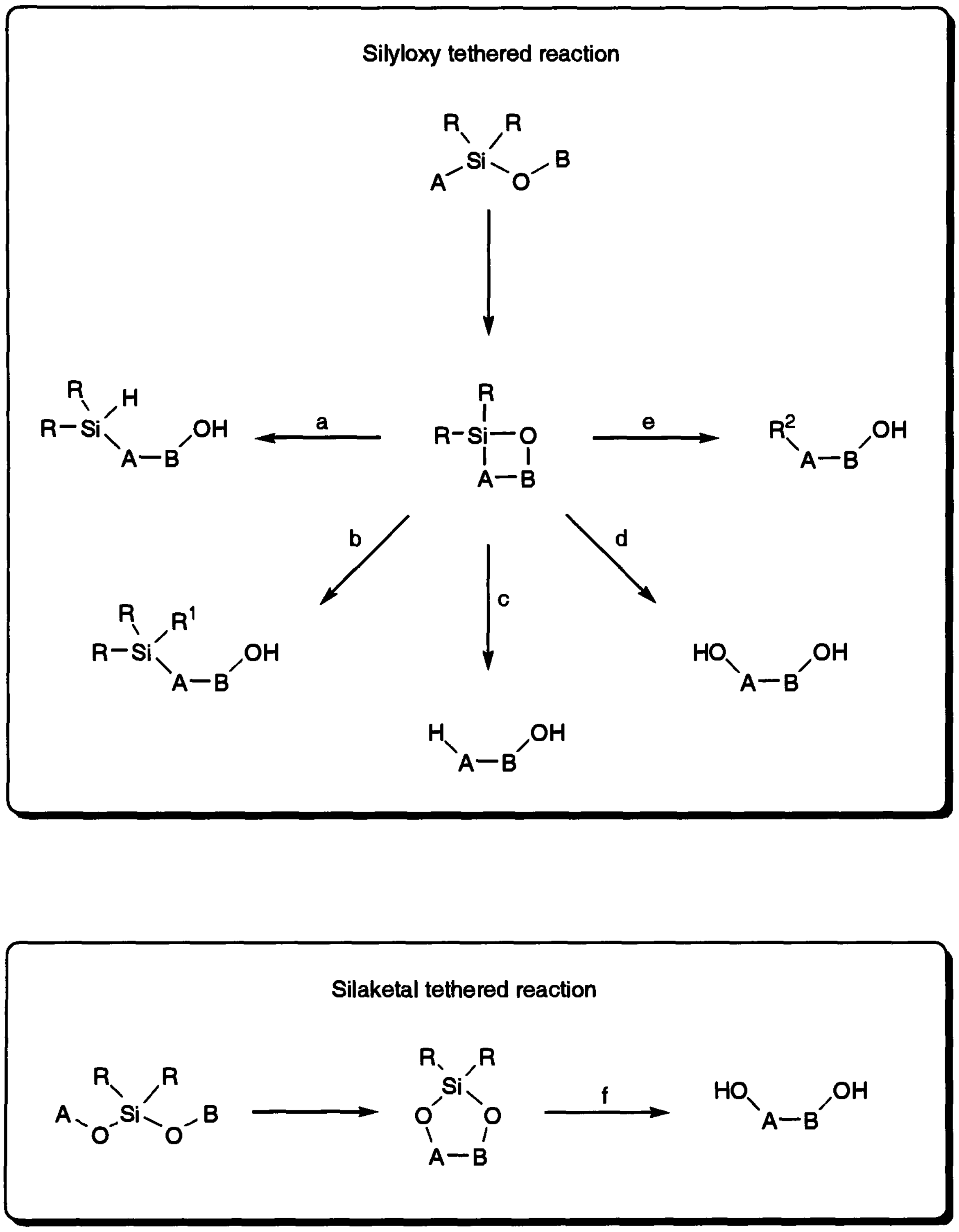
1.0 Introduction

In recent years the importance of temporary tethers in organic synthesis has become ever more apparent.[1] Tethered systems transform an intermolecular reaction into its intramolecular equivalent. The unimolecular transition state generated by the addition of a tethering component leads to enhanced regio- and stereocontrol by restraining the degrees of freedom of the reacting partners. The restriction in mobility imparted by temporary intramolecularity lessens entropic demands and can lead to increased rates and milder reaction conditions. Once the benefits of the temporary connection have been exploited, and the linker removed, a compound which is otherwise inaccessible by intermolecular means may result. Consequently a tethered reaction can be of greater synthetic value than the analogous intermolecular process (Scheme 1.01).



Scheme 1.01

The role of silicon as the 'disposable' component in tethered systems has been well documented in the literature since the concept was first introduced by Stork[2] and Nishiyama[3] in the mid 1980s. The silyl group has proved to be an advantageous choice for the temporary connector due to its inertness to assorted reaction conditions and the ease with which it can be selectively removed. In conjunction with its versatile tethering ability, silicon can also impart masked functionality; silyl tethers can simply be detached by protodesilylation or converted into a wide variety of functional groups (Scheme 1.02). It is this combined flexibility which underlines the increasing popularity of silicon-assisted processes.



a) $LiAlH_4$; b) R^1Li; c) *t*-BuOK, DMSO or TBAF, DMF; d) Tamao or Woerpel oxidation; e) R^2X, Pd, F^-; f) F^-.

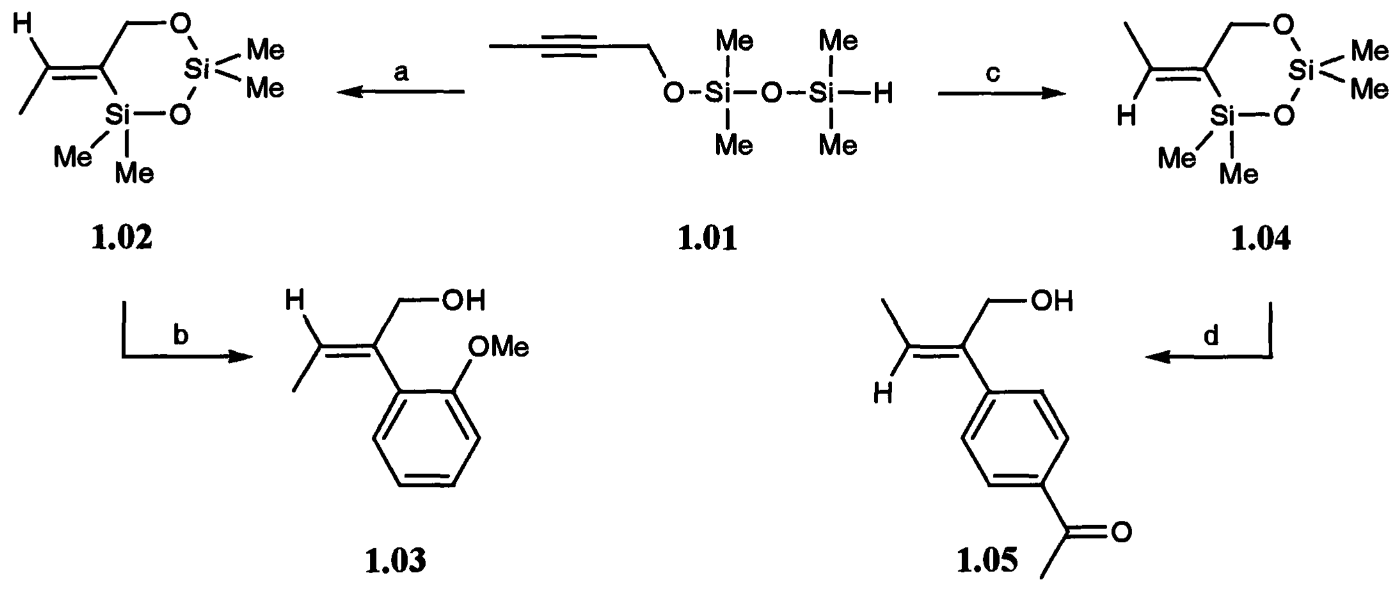
Scheme 1.02

To date, two excellent reviews of silicon tethered chemistry have been published;[4,5] this chapter will cover subsequent advances in the field, categorised according to reaction type. Whenever possible, the categories will highlight recent examples where the silicon tethered methodology is refined to an extent, that allows its application to the elegant syntheses of complex organic molecules.

1.1 Hydro- and Carbosilylations

Silicon heterocycles function as important synthetic intermediates; their versatility in organic transformations is amply documented in the literature.[6] A multitude of silacycle syntheses (predominantly five-membered silacycles) proceed *via* intramolecular hydrosilylation; this process has been the focus of study of several groups and provides a convenient stereoselective route to substituted 1,3-diols *via* oxidative cleavage of the silicon-carbon bond.[1,4,7]

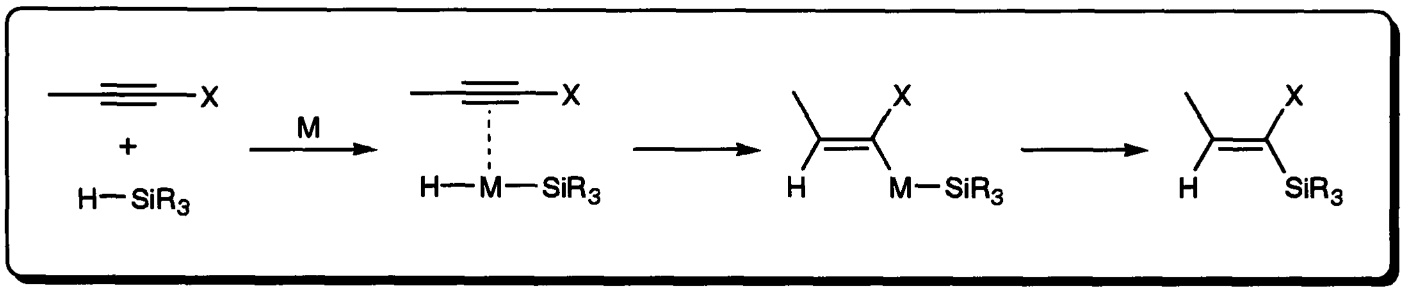
More recent additions to the literature include Denmark's intramolecular hydrosilylation and silicon-assisted cross-coupling methodology, as an expedient route to regio- and stereodefined allylic alcohols (Scheme 1.03).[8]



a) [RuCl$_2$(C$_6$H$_6$)]$_2$ 6.3 mol%, Δ (82%); b) TBAF-dioxane, ArI, Pd(dba)$_2$ 5.0 mol%, RT–40 °C, 70 hr (65%); c) Pt(DVDS) 0.3%, *i*-Pr$_2$NEt, 0 °C (60%); d) TBAF-dioxane, ArI, Pd(dba)$_2$ 5.0 mol%, RT, 10 hr (82%).

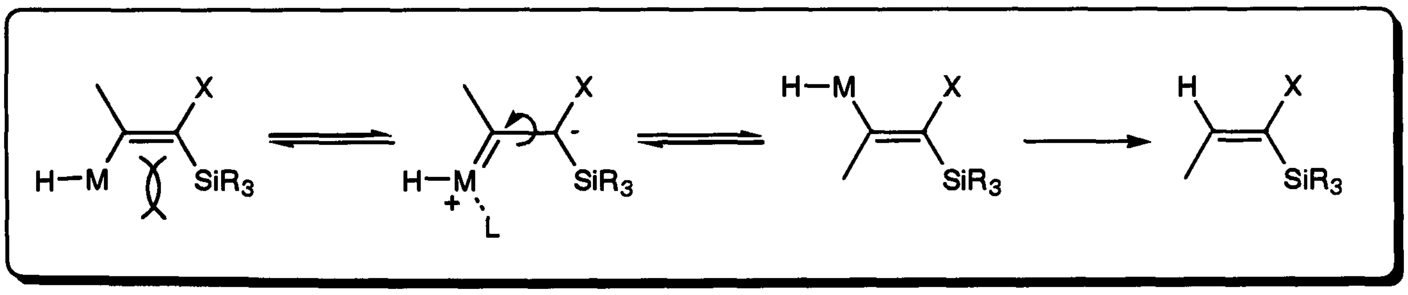
Scheme 1.03

The divergent stereochemistry of intermediate disiloxanes **1.02** and **1.04** results from the ability of the transition metal catalyst to direct the mode of cyclisation and addition of the Si-H bond. Substrate **1.01** underwent *syn* hydrosilylation with a Pt(0) catalyst to furnish the *E*-alkenylsilane **1.04**. The hydrosilylation is thought to proceed *via* the Chalk-Harrod mechanism (Scheme 1.04); initial oxidative addition of the hydrosilane to the catalyst generates a hydrido-silyl complex which coordinates to the alkyne. Subsequent *cis* addition of the Si-H bond and reductive elimination releases the *E*-vinylsilane and regenerates the catalyst.[9]



Scheme 1.04

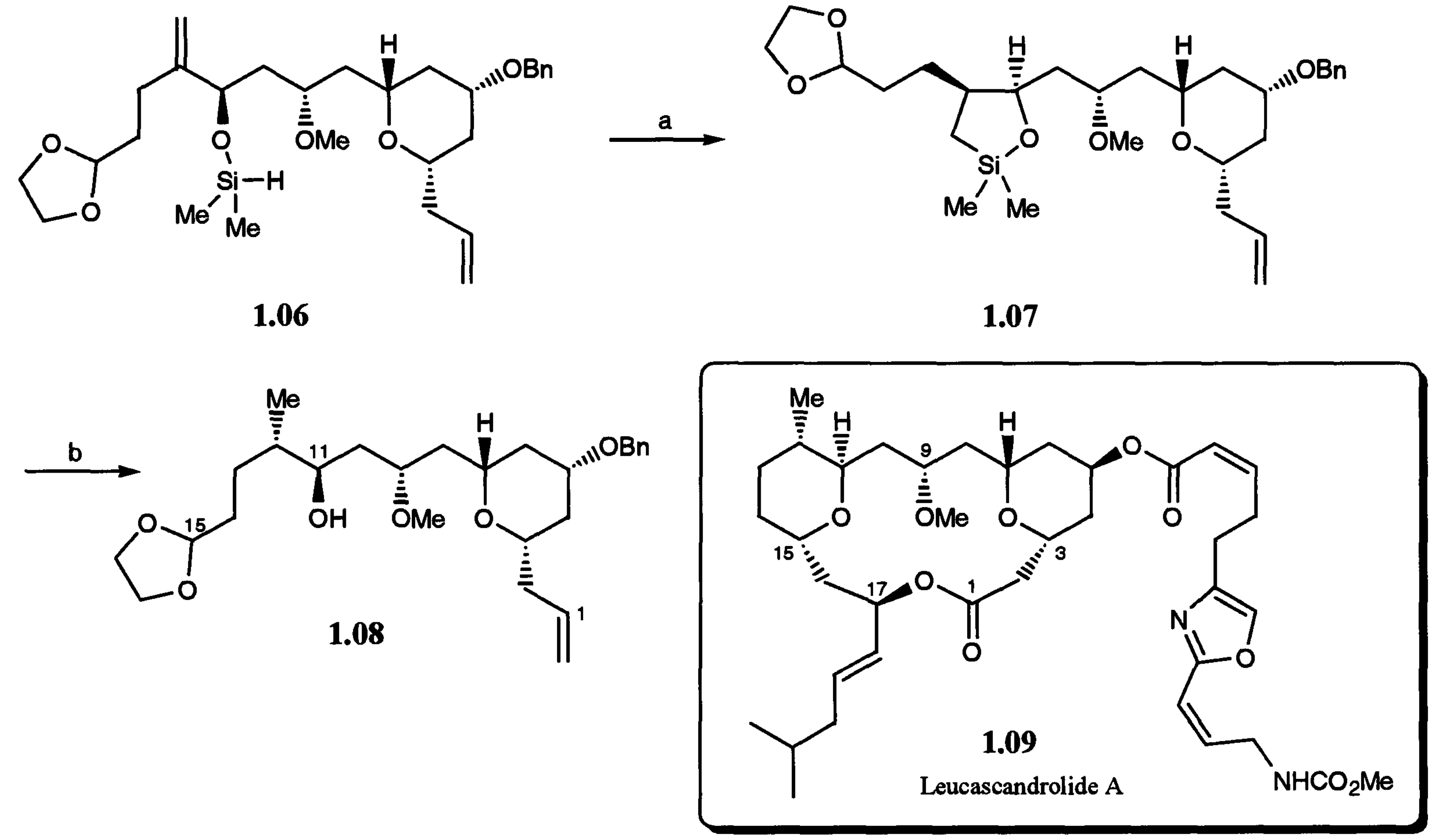
Anti-selectivity was observed with the use of a ruthenium arene complex, which results from an alternative mechanism, in which silyl migration to the coordinated alkyne proceeds in preference to hydride migration. The initial insertion orients the metal and silyl moiety *cis* on the vinyl organometallic, however, metal-assisted isomerisation proceeds *via* a zwitterionic carbene-like intermediate to generate the *Z*-alkenylsilane. The driving-force for isomerisation, leading to the thermodynamically less stable *Z*-vinyl silane, is the relief of steric strain between the metal and the adjacent silane (Scheme 1.05).



Scheme 1.05

Widenhoefer has demonstrated the use of a cationic palladium(II) complex to catalyse the intramolecular hydrosilylation of 4-pentenylsilanes to form silacyclohexanes with excellent regioselectivity.[10]

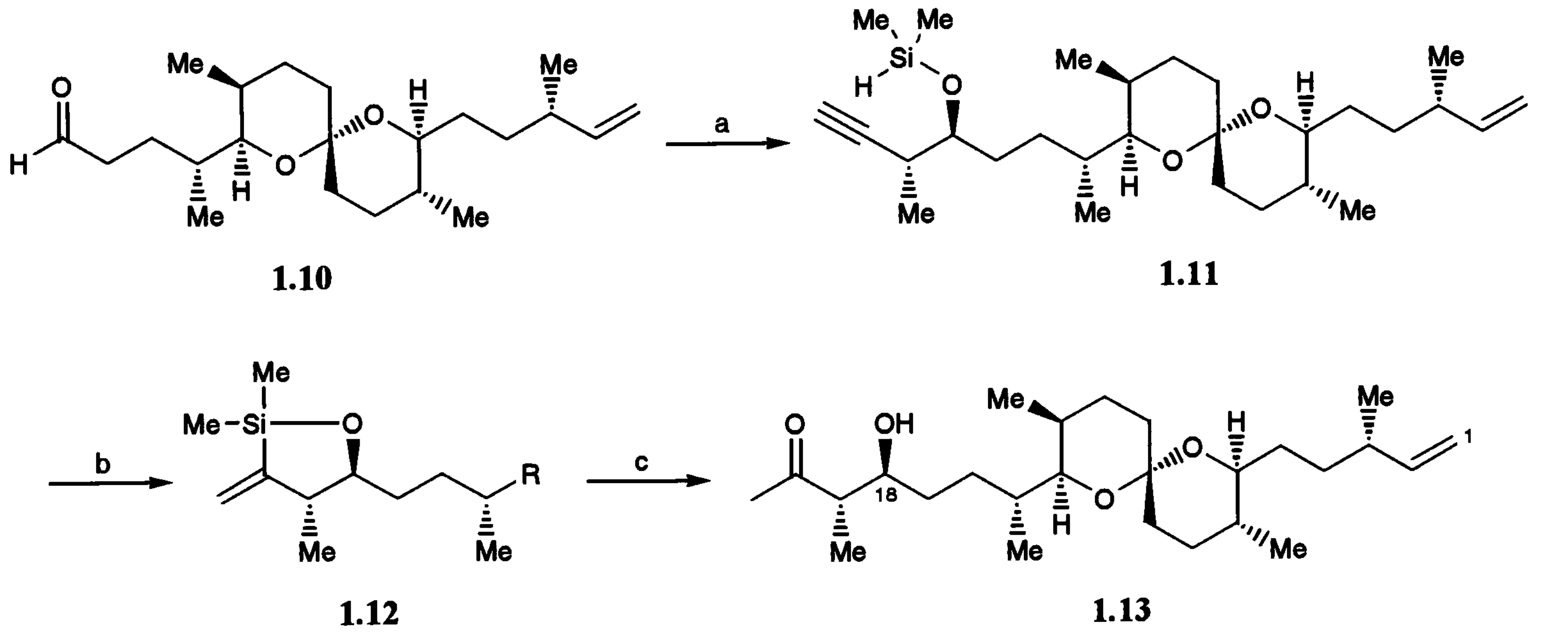
Several key steps in targeted syntheses have been facilitated by the use of intramolecular hydrosilylation reactions; Kozmin's studies toward the synthesis of leucascandrolide A (**1.09**), a cytotoxic 18-membered macrolide isolated from the marine sponge *Leucascandra caveolata*, involved an intramolecular hydrosilylation to selectively install the C_{12} stereocentre in the C_1-C_{15} segment (**1.08**) (Scheme 1.06).[11]

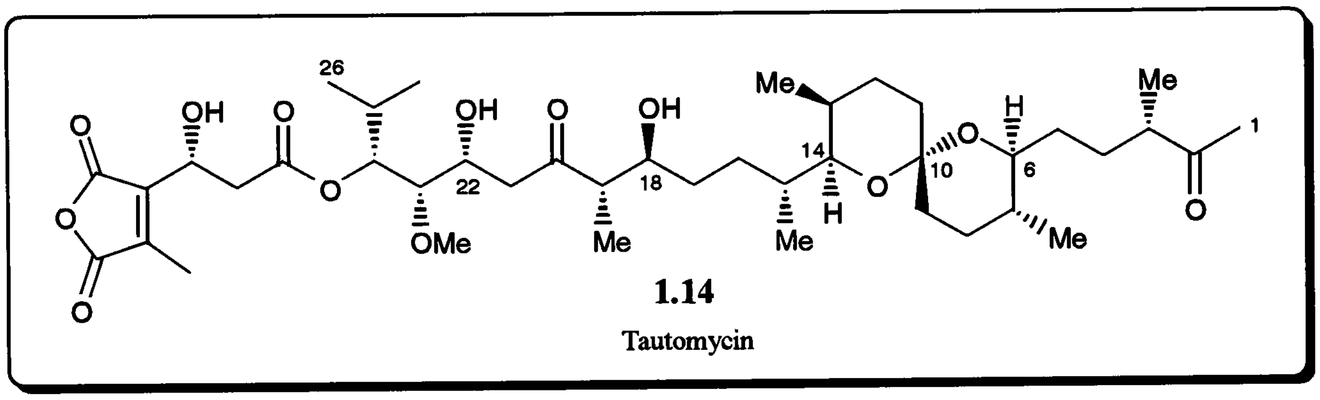


a) H_2PtCl_6 0.3 mol%, 50 °C, (d.r. = 87:13); b) TBAF-THF, 70 °C (54% two steps).

Scheme 1.06

In the synthesis of the C_1-C_{21} fragment of the protein phosphatase inhibitor tautomycin (**1.14**), Marshall and co-workers demonstrated the use of a tethered hydrosilylation-oxidation protocol to install the terminal β-hydroxy ketone subunit (Scheme 1.07).[12]



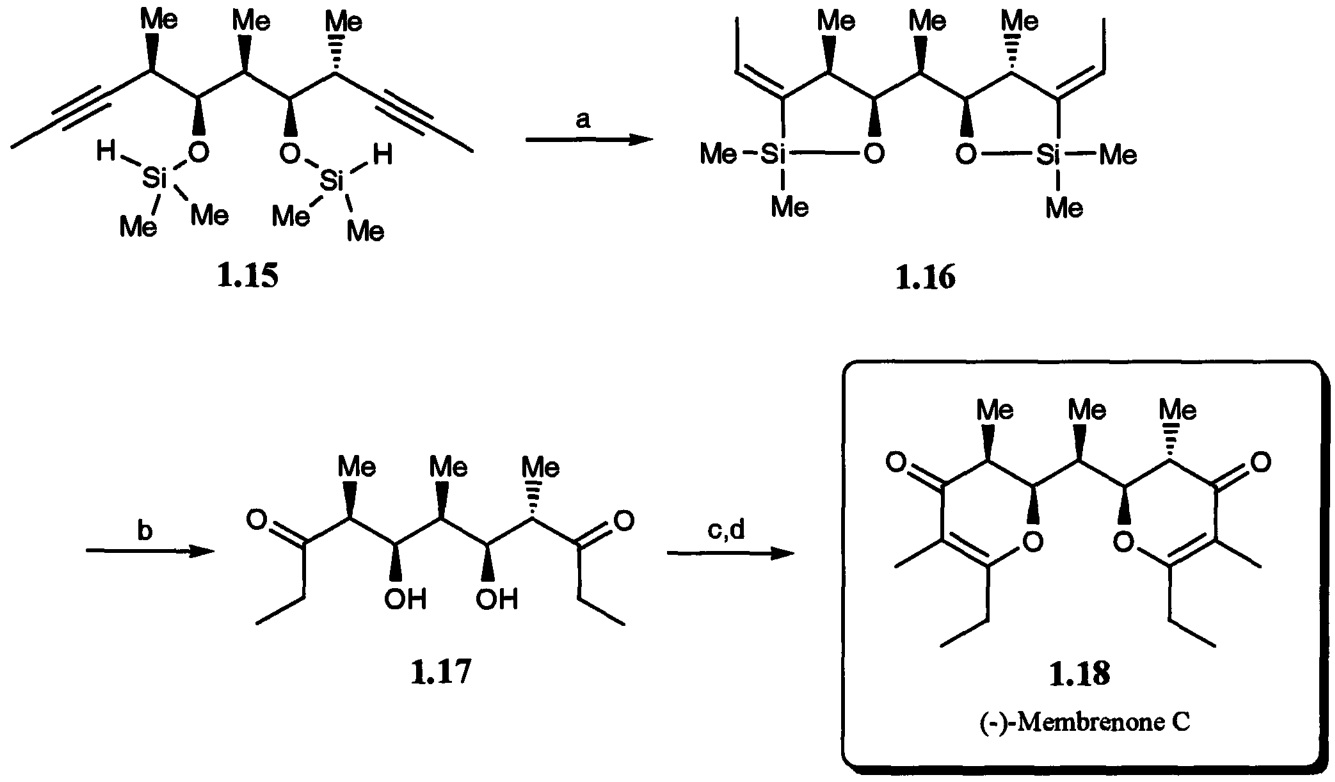


1.14
Tautomycin

a) 1-(*S*)-Methylprop-2-ynyl methanesulfonate, $Pd(OAc)_2$ 0.5 mol%, PPh_3, Et_2Zn (82%), then $HN(SiMe_2H)_2$; b) H_2PtCl_6 0.5 mol%, 60 °C; c) H_2O_2, KF, $KHCO_3$, MeOH (82% three steps).

Scheme 1.07

Marshall applied a similar bis-intramolecular hydrosilylation-oxidation strategy to the total synthesis of the polypropionate marine defence compound (–)-membrenone C (**1.18**). Hydrosilylation of di-alkyne precursor **1.15** and Tamao oxidation of the derived bis-cyclic siloxane **1.16** furnished diol **1.17**. Immediate acylation and double aldol condensation afforded the desired target compound **1.18** (Scheme 1.08).[13]

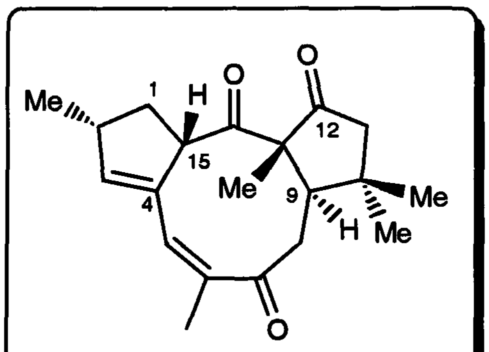


a) H_2PtCl_6 0.6 mol%, 75 °C (100%); b) H_2O_2, KF, $KHCO_3$, MeOH-THF;

c) $EtCO_2H$, DCC, DMAP (46% two steps); d) $TiCl_4$, *i*-Pr_2NEt (51%).

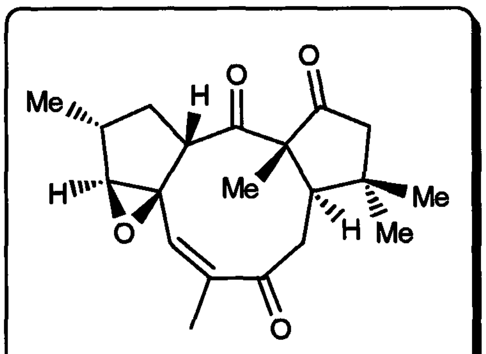
Scheme 1.08

In an effort to prepare diterpenoids jatrophatrione (**1.19**) and citlalitrione (**1.20**), Paquette reported the use of a stereocontrolled intramolecular hydrosilylation-oxidation sequence to oxygenate cleanly at the C_{12} position (Scheme 1.09). These novel diterpenoids are of interest as they possess an unprecedented [5.9.5] tricyclic core and exhibit impressive biological activity as tumour-inhibitory agents.[14]



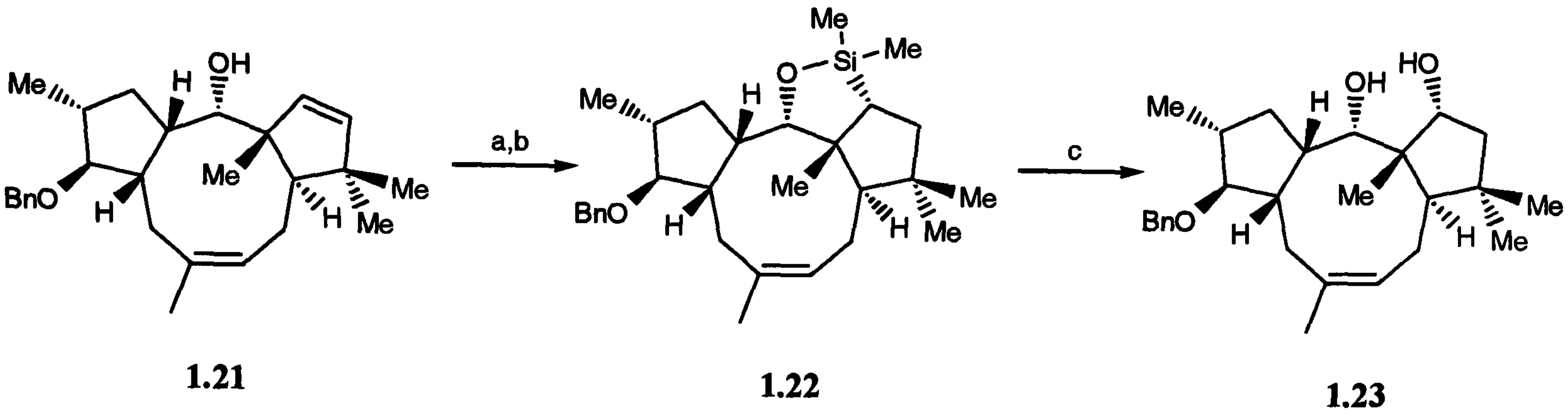
1.19

Jatrophatrione



1.20

Citlalitrione

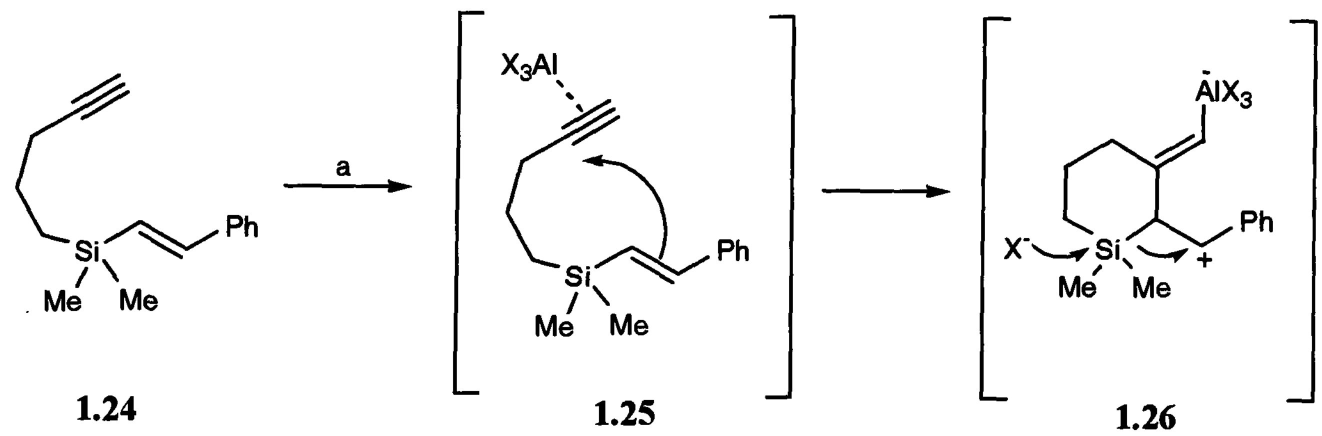


1.21 1.22 1.23

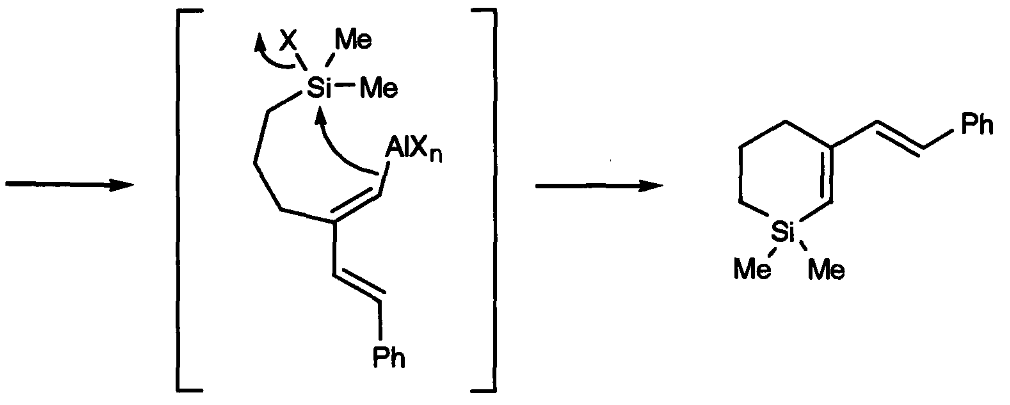
a) Me_2SiHCl, TEA; b) H_2PtCl_6, HMDS (80% two steps); c) H_2O_2, KF, $KHCO_3$, DMF (93%).

Scheme 1.09

Carbosilylations are less prevalent than their hydro- counterparts; a noteworthy example can be found in Yamamoto's methodology for the preparation of six-membered silacycles from unactivated alkynes. The Lewis acid catalysed intramolecular vinylsilylation of alkynylvinylsilane **1.24** proceeded in an *exo-trans* fashion to give **1.28** in excellent yield (Scheme 1.10). The proposed mechanism involves stereoselective formation of aluminium ate complex **1.26** *via* co-ordination of the Lewis acid to the alkyne with concurrent *exo*-attack of the vinylsilane moiety on the electron deficient alkynyl carbon. Dissipation of the β-carbocation by cleavage of the silicon-carbon bond generated intermediate **1.27** and subsequent rearrangement afforded the *trans*-silacycle **1.28**.[15]



1.24 1.25 1.26



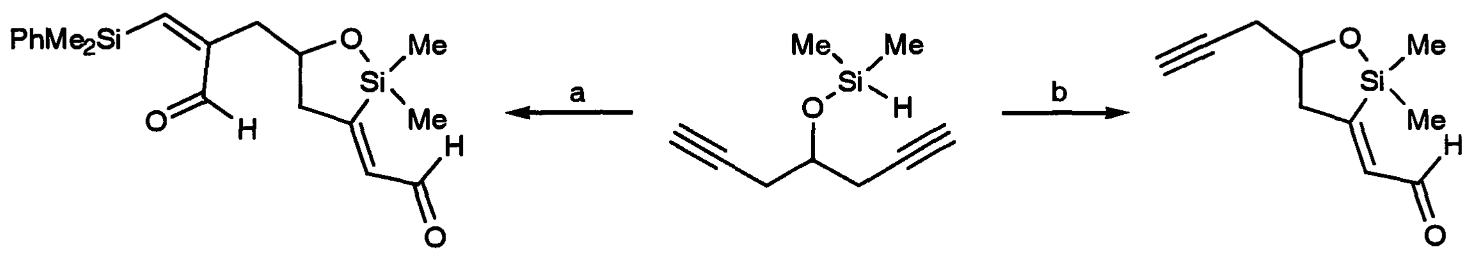
1.27 **1.28**

a) $EtAlCl_2$ (cat.), 0 °C–RT (92%).

Scheme 1.10

1.2 Silylformylation

Tethered silylformylation, which involves trapping of the catalytic intermediates of intramolecular hydrosilylation with carbon monoxide, has been extensively studied by Ojima.[16] These rhodium-catalysed reactions proceed with excellent regioselectivity and have been applied to the double silylformylation and desymmetrisation of silyloxyalkadiynes (Scheme 1.11).

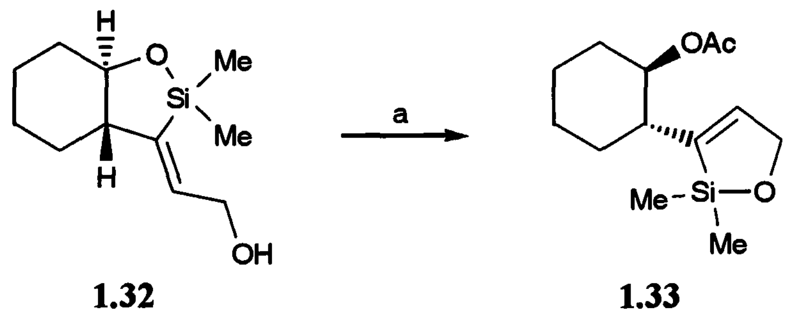


1.30 **1.29** **1.31**

a) $PhMe_2SiH$, $Rh(acac)(CO)_2$, CO (100%); b) $Rh(acac)(CO)_2$, CO (98%).

Scheme 1.11

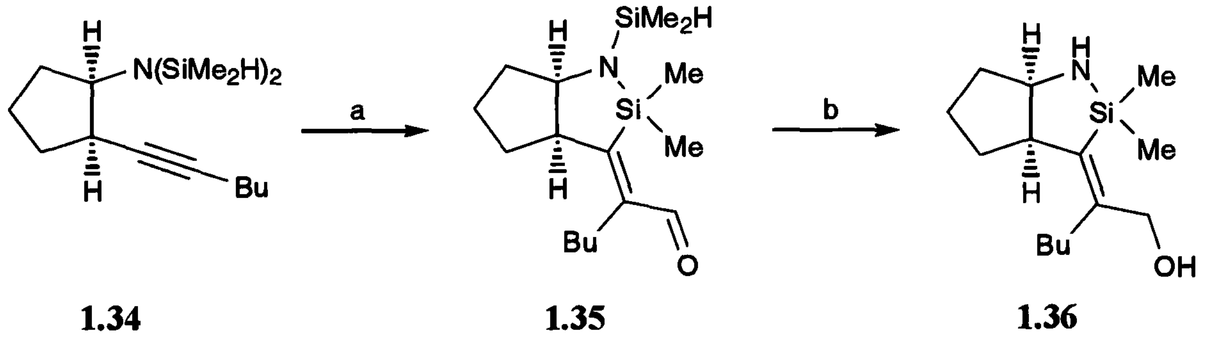
The resulting oxasilacyclopentanes could be converted into oxasilacyclopentenes *via* a novel DMAP-catalysed rearrangement (Scheme 1.12).



a) Ac_2O, TEA, DMAP 5.0 mol% (76%).

Scheme 1.12

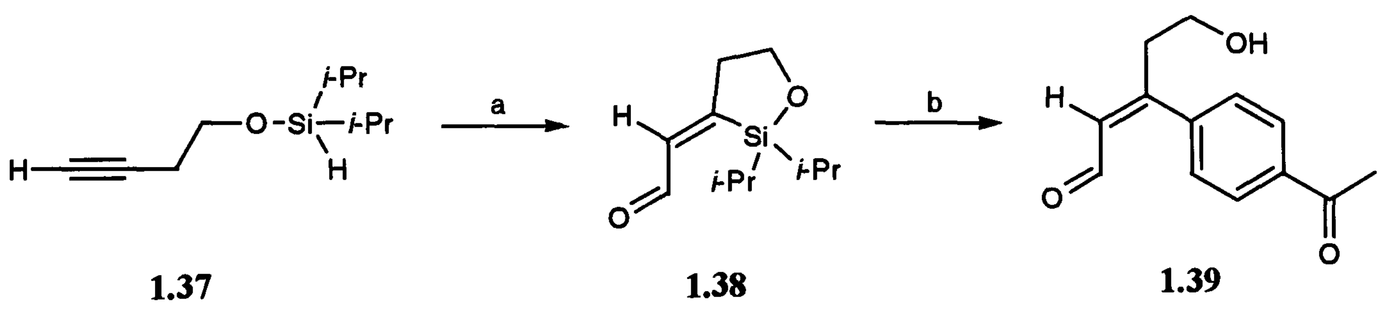
Ojima has also investigated the application of tethered silylformylation to bis(silylamino)alkynes as an expedient route to aminoformylvinylsilanes (Scheme 1.13).[17]



a) $Rh(acac)(CO)_2$, CO, 60 °C; b) $NaBH_4$ then *aq.* NH_4Cl (84% two steps).

Scheme 1.13

In an extension of his hydrosilylation cross-coupling methodology (see Scheme 1.03), Denmark has recently developed a novel tandem intramolecular silylformylation and silicon-assisted cross-coupling reaction as a means of accessing geometrically defined α,β-unsaturated aldehydes (Scheme 1.14).[18]



a) $[Rh(CN\textit{t}\text{-}Bu)_4][Co(CO)_4]$, CO, 70 °C (72%);

b) ArI, $[(allyl)PdCl]_2$ 5.0 mol%, CuI 10 mol%, $[\text{-MeSi(H)O-}]_{3\text{-}5}$ 2.5 mol%, $KF.2H_2O$, RT (91%).

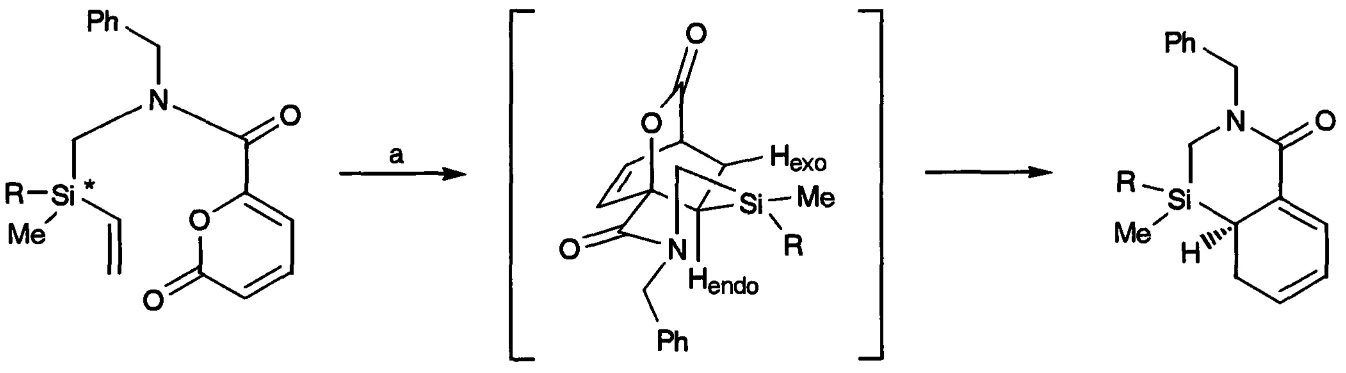
Scheme 1.14

1.3 Cycloadditions

1.3.1 Diels-Alder reactions

The intramolecular Diels-Alder reaction (IMDA) lends itself ideally to silicon tethering; a number of groups have used silicon to connect diene and dienophile components temporarily as a means of improving regio- and stereoselectivity during the construction of polycyclic ring systems. The IMDA precursors have been synthesised with a variety of silyl linkages producing silane, silyloxy, silaketal and siloxane bridged silatrienes, each possessing relatively robust Si-C or Si-O bonds.[1,4,7]

Coelho *et al.* have focused their attention on Si-chiral systems. Enantiomerically enriched silatriene **1.40** was shown to undergo thermal inverse-electron demand IMDA reaction, followed by retro Diels-Alder CO_2 extrusion to furnish silaisoquinolinone **1.42** in good yield, unfortunately the sequence only proceeded with moderate diastereoselectivity (Scheme 1.15).[19]

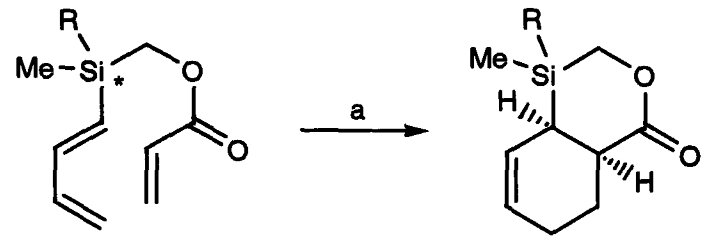


1.40 **1.41** **1.42**

R = C_6H_{11} a) Toluene, Δ (76%, d.e. = 58%).

Scheme 1.15

Much higher diastereoselectivity was observed with the Lewis acid catalysed IMDA reaction of chiral silatriene **1.43**, which furnished *endo*-cycloadduct **1.44** as the major isomer (Scheme 1.16).[20]

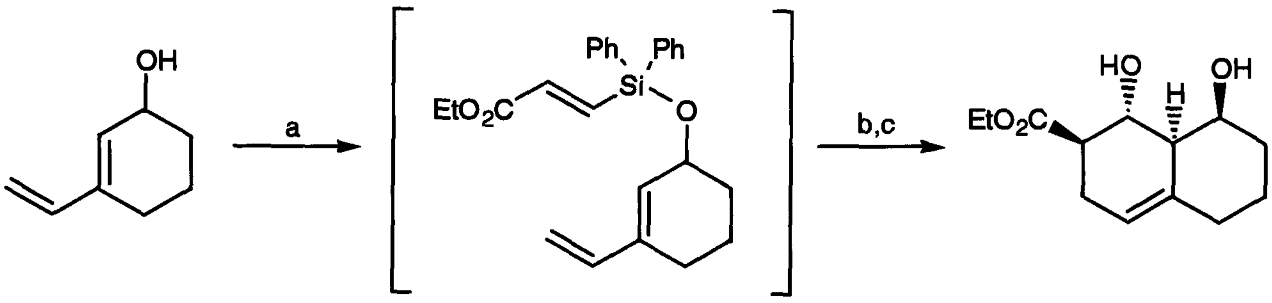


1.43 **1.44**

R = 2-MeOPh a) $EtAlCl_2$, DCM (74%, d.r. = 4:5:90:1).

Scheme 1.16

Sieburth reported the use of vinylsilanes as dienophiles in IMDA methodology applied to the synthesis of highly oxygenated cycloadducts, such as bicyclic diol **1.47** (Scheme 1.17).[21]

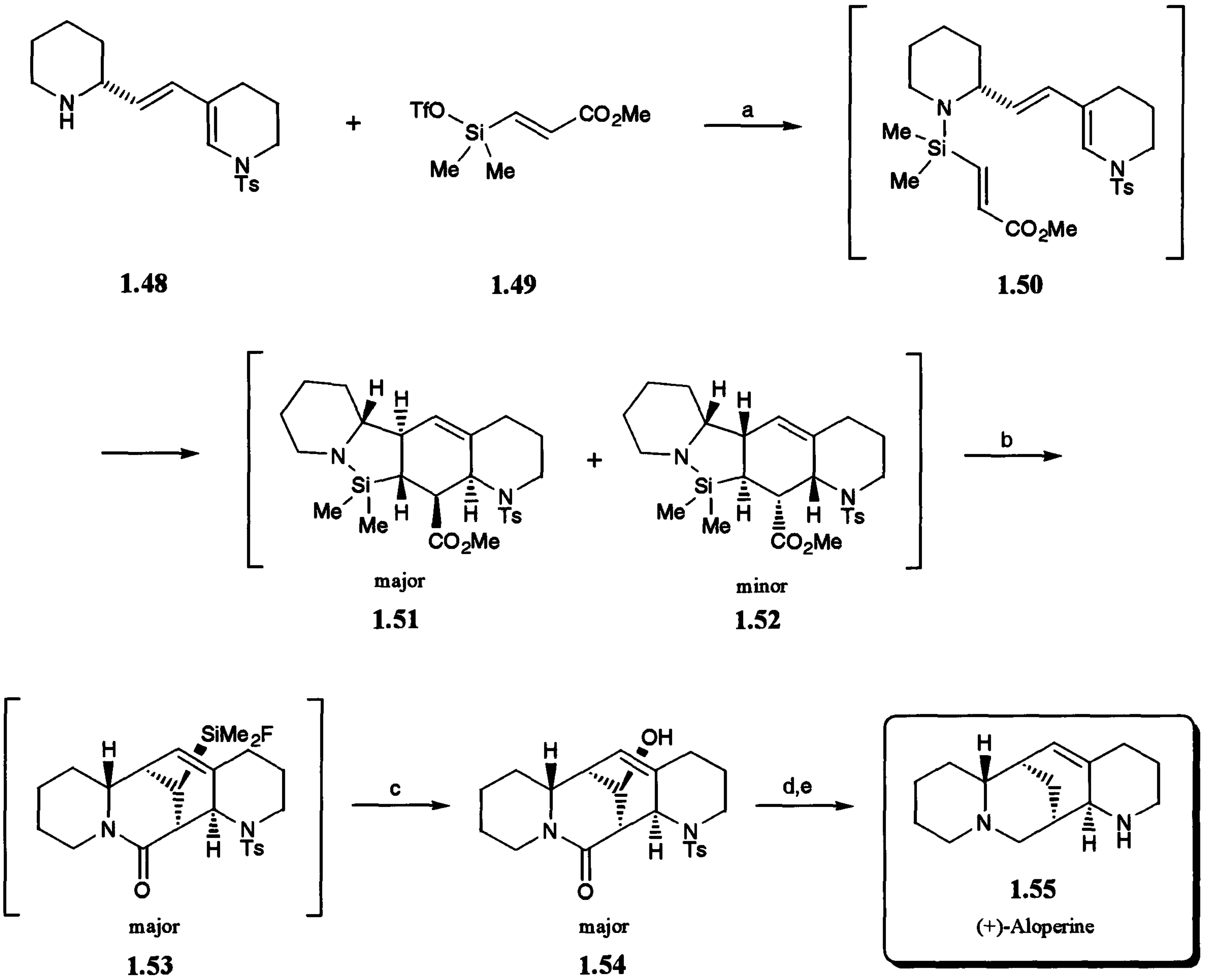


1.45 **1.46** **1.47**

a) EtO_2C-CH=CH-Si(OTf)Ph_2, py.; b) 80 °C; c) H_2O_2, KHF_2 (70% three steps).

Scheme 1.17

An example which clearly illustrates the synthetic utility of the silyl tethered IMDA reaction is Overman's total synthesis of (+)-aloperine (Scheme 1.18).[22] This lupinine alkaloid, first isolated from the seeds and leaves of *Sophora alopecuroides* L, a plant long associated with Chinese folk-medicine, is of interest for its anti-inflammatory properties. A key feature of Overman's synthesis is the employment of an uncommon *N*-silylamine tether during the construction of the bridged tetracyclic skeleton. The Si-N bond is inherently unstable, prone to hydrolysis, and is hence seldom utilised in synthesis; in Overman's tethered IMDA protocol, several of the key intermediates were not isolated for this very reason. Diels-Alder cycloaddition of triene **1.50** proceeded to give cycloadducts **1.51** and **1.52** (5:1), subsequent lactamisation and Tamao oxidation led to tetracyclic alcohols **1.54** (major and minor). Two additional steps enabled completion of the first total synthesis of (+)-aloperine (**1.55**) in an overall yield of 29% from **1.48**.



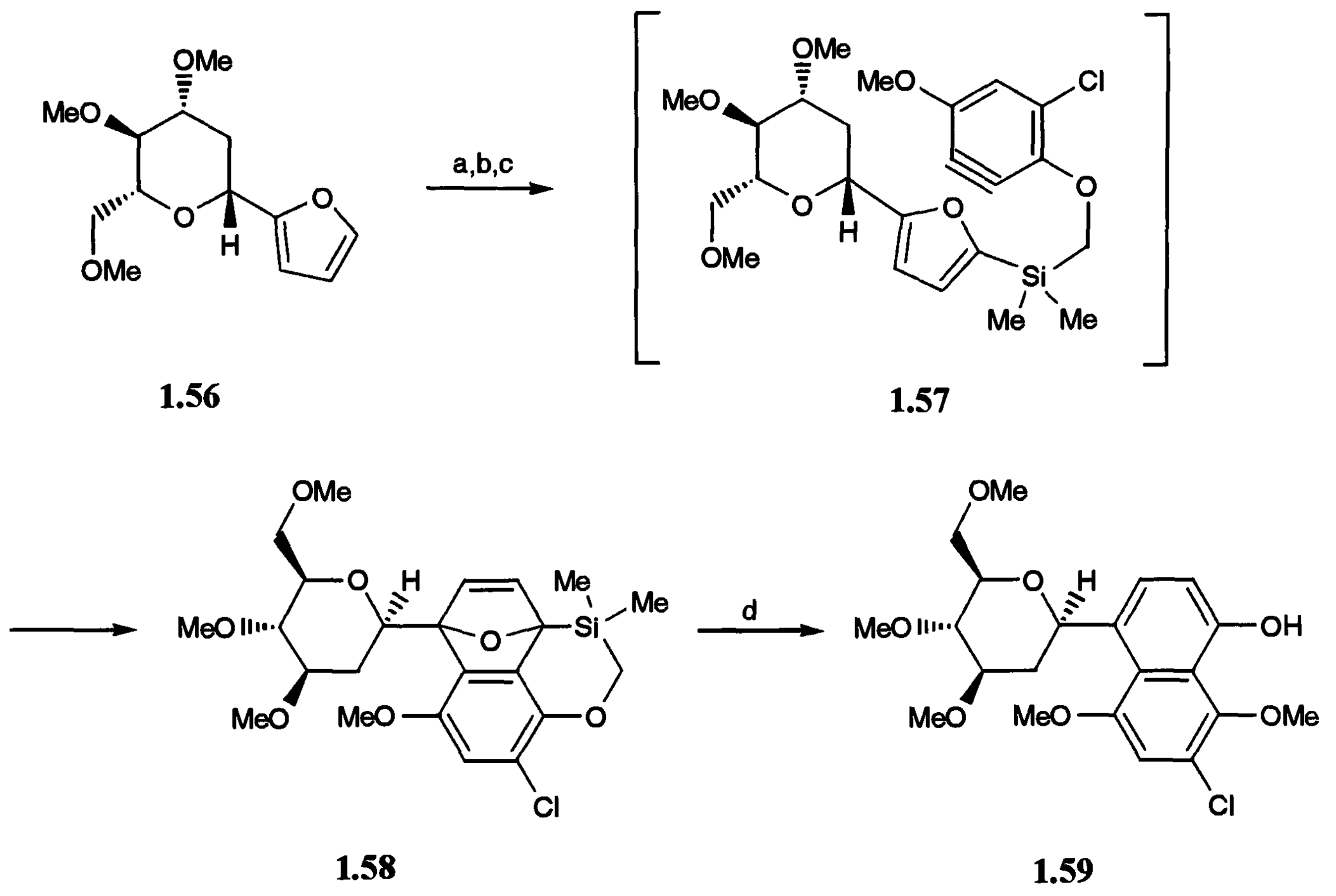
a) TEA, 0 °C–RT (76%); b) HF.py., RT, then Δ;

c) H_2O_2, KF, $KHCO_3$, MeOH-THF, Δ (63% and 13%, two steps);

d) $C_6F_5OC(S)Cl$, DMAP, then Bu_3SnH, AIBN, Δ (70%); e) $LiAlH_4$, RT (88%).

Scheme 1.18

In a recent synthesis of unsymmetrical *C*-aryl glycosides, a silicon tethered IMDA reaction was used by Martin and co-workers to prepare **1.59** (Scheme 1.19). Intermolecular Diels-Alder reactions of unsymmetrical benzynes generally proceed with poor regioselectivity,[23] in this case the temporary silicon connection dictates the regiochemistry of the benzyne-furan cycloaddition.[24]



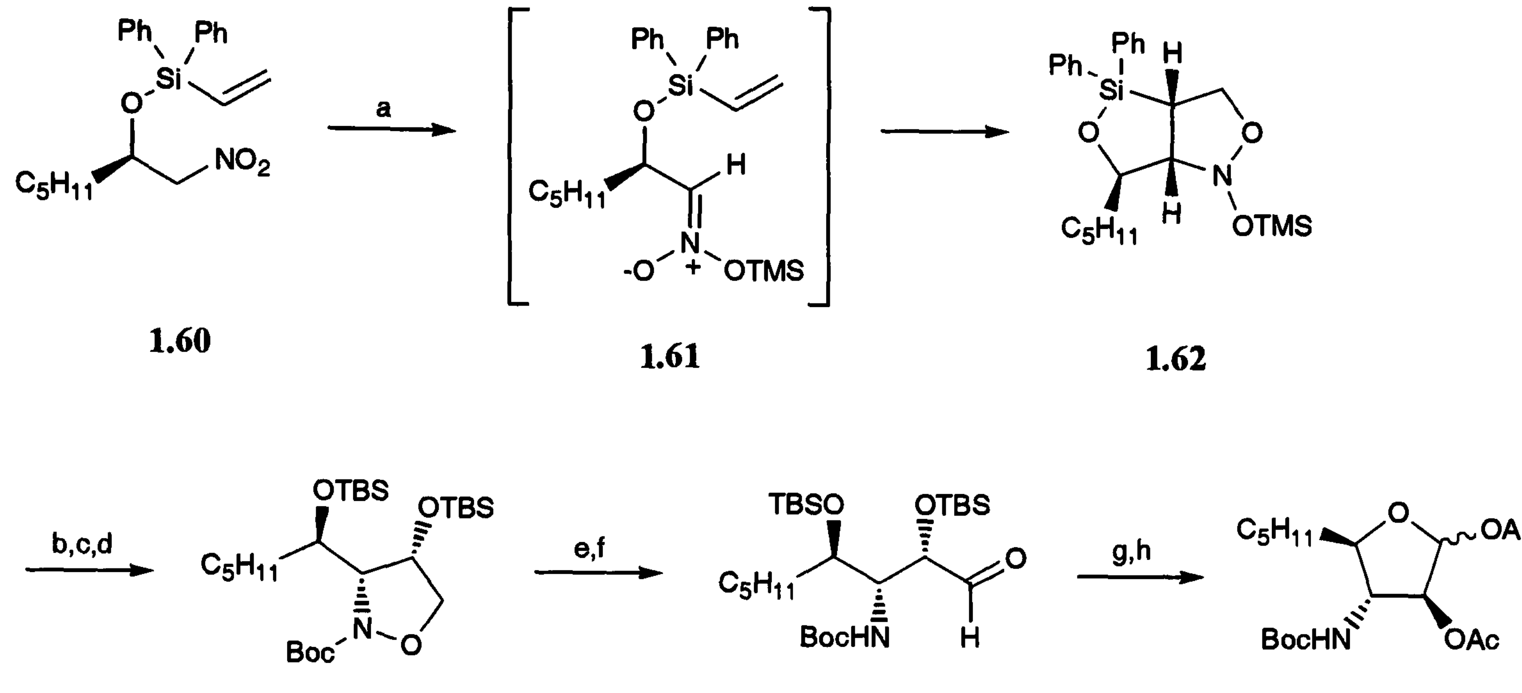
1.56 1.57 1.58 1.59

a) LDA, -78 °C then $Me_2Si(Cl)CH_2Br$ (73%); b) 2,6-dichloro-4-methoxyphenol, K_2CO_3, Bu_4NI (83%); c) *s*-BuLi, -95 °C to -5 °C (68%); d) TBAF-THF, DMF, RT then TFA, -5 °C–RT (90%).

Scheme 1.19

1.3.2 [3+2] Cycloadditions

Since the feasibility of silyl tethered 1,3-dipolar cycloadditions was first demonstrated by Rosini,[25] a number of groups have employed silicon based tethers to ensure high diastereofacial selectivity in azomethine ylide, nitrile oxide and silyl nitronate cycloadditions.[26,27] In recent studies directed towards the synthesis of stereodefined aminopolyols, Ishikawa employed a silicon tethered [3+2] nitrone cycloaddition elegantly to construct biologically important aminosugars. The cycloadduct derived from **1.61** was readily converted *via* Tamao oxidation into isoxazolidine **1.63** and then elaborated further to the desired aminoribose derivative **1.65** (Scheme 1.20).[28]



1.60 1.61 1.62

1.63 1.64 1.65

a) TMSCl, TEA, 0 °C–RT (99%, d.r. = 5:1); b) H_2, Pd/C, Boc_2O, RT (42%);

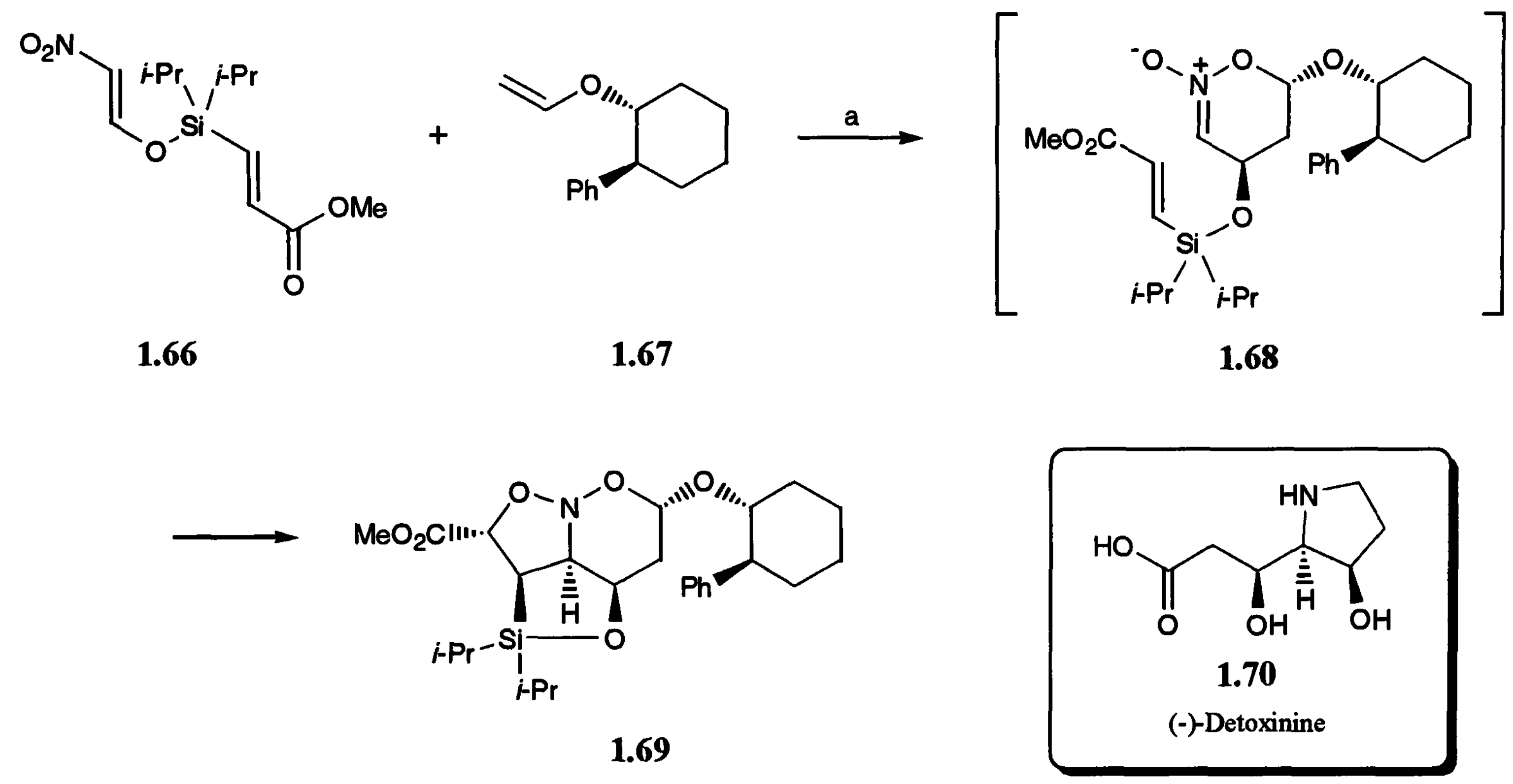
c) H_2O_2, KF, $KHCO_3$, MeOH-THF, RT; d) TBS-OTf, TEA, RT (46% two steps); e) $Mo(CO)_6$, Δ;

f) SO_3.py., TEA, DMSO (57% two steps); g) TBAF; h) Ac_2O, TEA, DMAP, RT (52% two steps).

Scheme 1.20

The synthetic expediency of tethered [3+2] nitrone cycloadditions is clearly demonstrated in Denmark's adept synthesis of (–)-detoxinine (**1.70**), a highly functionalised amino acid, which forms the core scaffold of constituent depsipeptides of the detoxin complex.[29] Co-administration of the detoxin complex with the nucleoside antibiotic blasicidin S induces a reduction in the cytotoxicity of the antibiotic without decreasing its effectiveness against rice blast disease.

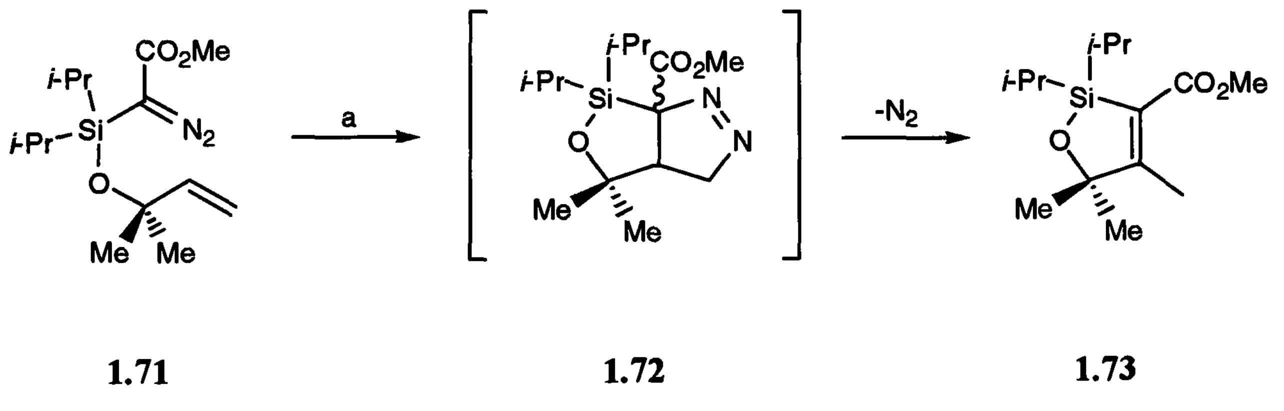
The tandem [4+2]/[3+2] cycloaddition proceeded *via* an intermolecular, inverse-electron demand hetero Diels-Alder reaction of nitroalkene **1.66** with chiral auxiliary **1.67**[30] and subsequent intramolecular [3+2] cyclisation of intermediate **1.68** (Scheme 1.21). The remarkable stereocontrol (d.r. = 27 :1) results from an *exo* approach of **1.67**, and direction of the dipolarophile on to the same face by the silicon tether.



a) MAPh, -78 °C to -15 °C, 14.5 hr (60%).

Scheme 1.21

Maas *et al.* have investigated the tethered [3+2] cycloaddition of unsaturated α-silyl-α-diazoacetates. For example cycloaddition of the diazo dipole and the tethered alkene generated silacycle **1.73** after nitrogen extrusion from the intermediate bicyclic pyrazole **1.72** (Scheme 1.22).[31]

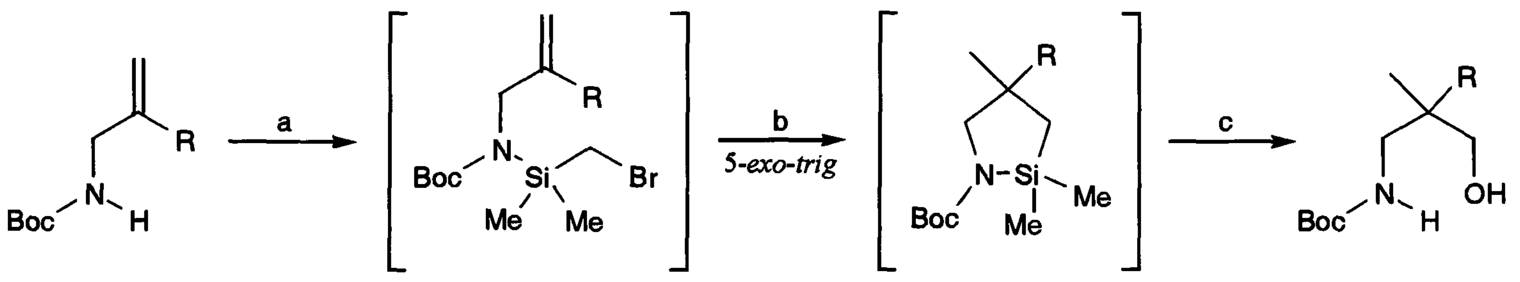


a) Xylene, 142 °C, 3 hr (63%).

Scheme 1.22

1.4 Radical reactions

A key synthetic process widely receptive to silicon tethered methodology is the radical cyclisation reaction. Since the concept of silicon mediated intramolecular hydroxymethylation was first demonstrated by Nishiyama[3] and Stork,[2] a number of groups have utilised bromomethyldimethylsilyl (BMDMS) ethers as a means of elaborating allylic alcohols stereoselectively *via* 5-*exo-trig* radical cyclisation.[1,4,7] Most recently, Malacria has investigated a nitrogen version of the BMDMS radical cyclisation (analogous to Nishiyama's original silyl ether series) for the novel construction of γ-amino alcohols. Interestingly, this group observed complete regioselectivity from their silicon-nitrogen tethered substrates, with cyclisation proceeding exclusively through the 5-*exo-trig* mode. Conversely, in Nishiyama's series, although cyclisation occurred predominantly through the 5-*exo* mode for crotyl systems, the 6-*endo* mode was often observed in allylic systems lacking terminal alkene functionality. Malacria's protocol provided an expedient one-pot synthesis of 1,3-amino alcohols and constituted the first use of an *N*-silyl linkage in radical chemistry (Scheme 1.23).[32]



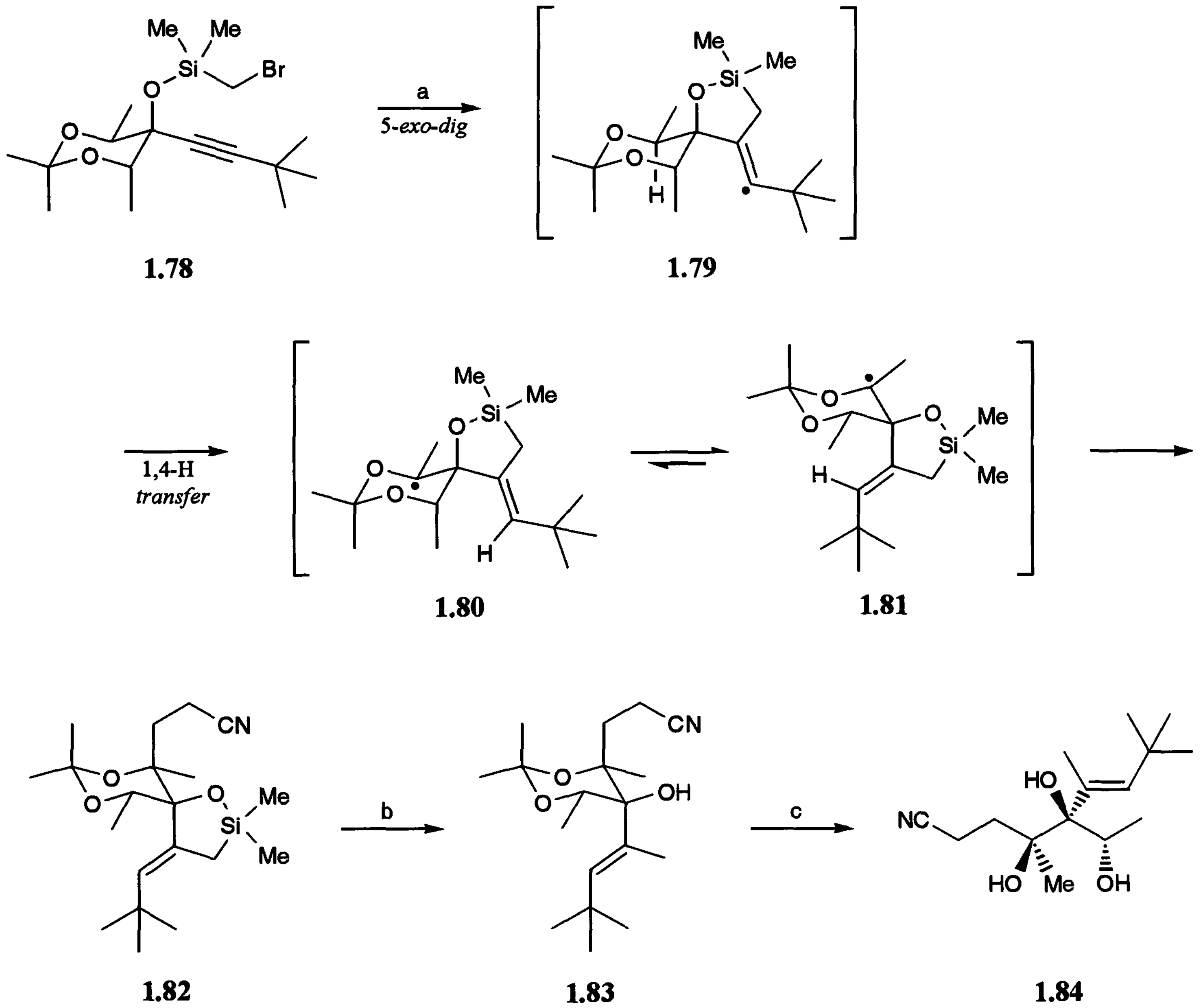
1.74 **1.75** **1.76** **1.77**

a) *n*-BuLi, BMDMSCl; b) Bu_3SnH, AIBN, *hv*, -10 °C;

c) H_2O_2, KF, $KHCO_3$, MeOH-THF, RT (R = H, 75%; R = Me, 42%; three steps).

Scheme 1.23

Malacria has also developed the silyl tethered 5-*exo-dig* cyclisation and has successfully applied this methodology to a number of radical cascade sequences. The initial 5-*exo-dig* reactions are often accompanied by radical translocation;[33] mainly through hydrogen transfer processes.[34] The enantioselective synthesis of triol **1.84** (Scheme 1.24) was achieved *via* an uncommon 1,4-H transfer; in this reaction 5-*exo-dig* cyclisation of the tethered silyl methyl radical and subsequent hydrogen transfer to the resulting vinyl radical **1.79** generated the stabilised intermediate **1.81**. Intermolecular trapping of this anomeric radical with acrylonitrile gave adduct **1.82** which was cleaved to furnish the enantiopure triol **1.84** in excellent yield.[35]

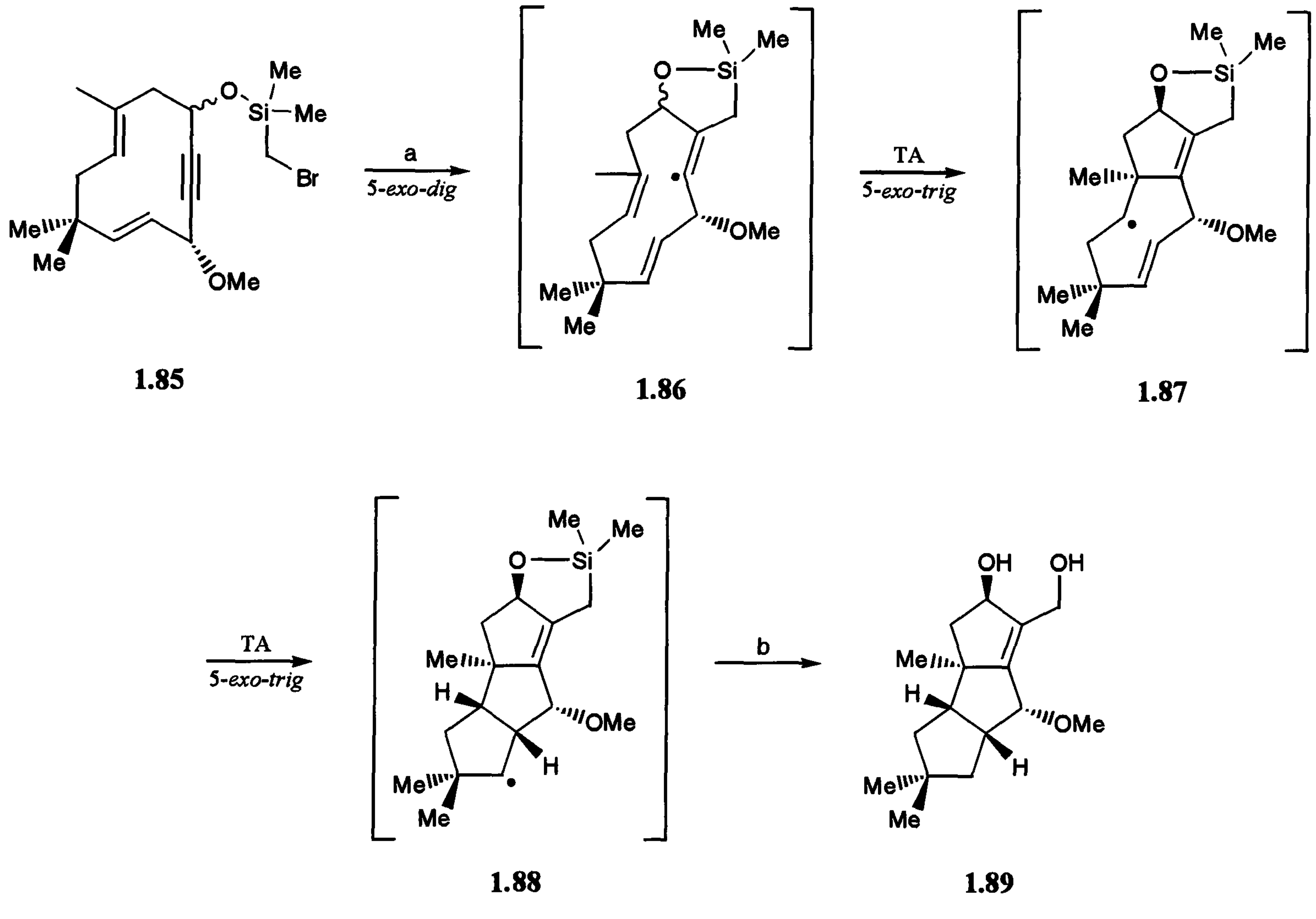


a) acrylonitrile, Bu_3SnH, AIBN, *hv*, RT (56%); b) TBAF-SiO_2, 60 °C (85%);

c) AcOH, H_2O, 60 °C (100%).

Scheme 1.24

Malacria and co-workers have applied a transannular radical cascade strategy to the diastereoselective synthesis of linear triquinane **1.89** (Scheme 1.25). The vinyl radical resulting from initial 5-*exo-dig* cyclisation of BMDMS precursor **1.85**, was shown to undergo a tandem transannular (TA) 5-*exo-trig*/8-*endo-trig*, 5-*exo-trig*/5-*endo-trig* cascade to generate tetracyclic intermediate **1.88**. The methylene radical was subsequently reduced and the silacycle oxidatively cleaved to afford the functionalised triquinane **1.89**. The *E*,*E*-geometry of the alkenyl bonds in the templating ring (**1.85**) was key to the success of the transannular cascade; when the *Z*,*E*-isomer was subjected to the same reaction conditions, cyclisation of the generated vinyl radical proceeded regioselectively in a 6-*endo* mode.[36]

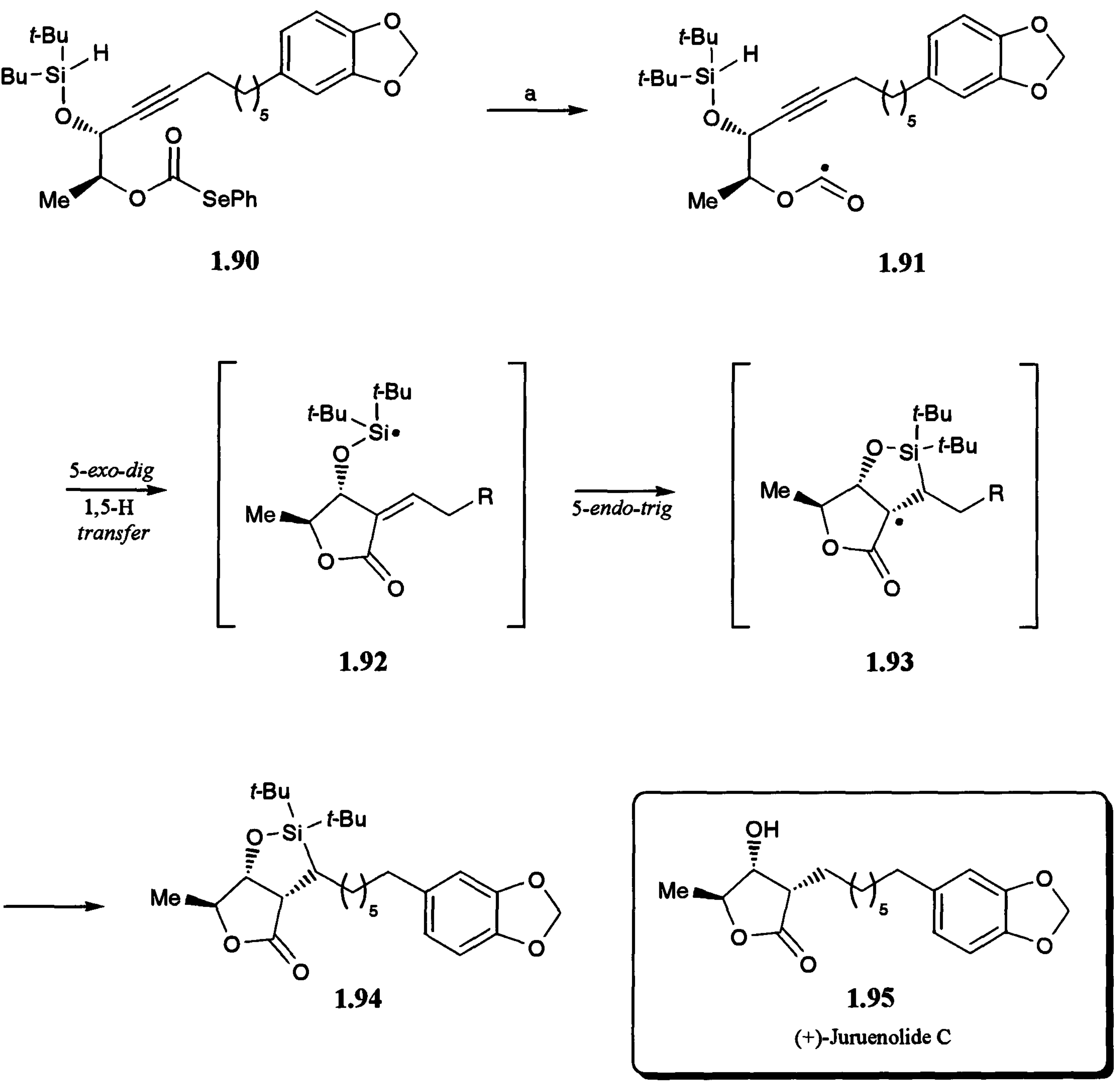


a) Ph_3SnH, AIBN, Δ; b) H_2O_2, KF, $KHCO_3$, MeOH-THF (45% two steps).

Scheme 1.25

Silicon tethered radical cascades have proven pivotal to a number of natural product syntheses.[1,4,7] Clive *et al.* employed a tethered radical sequence in their synthesis of (+)-

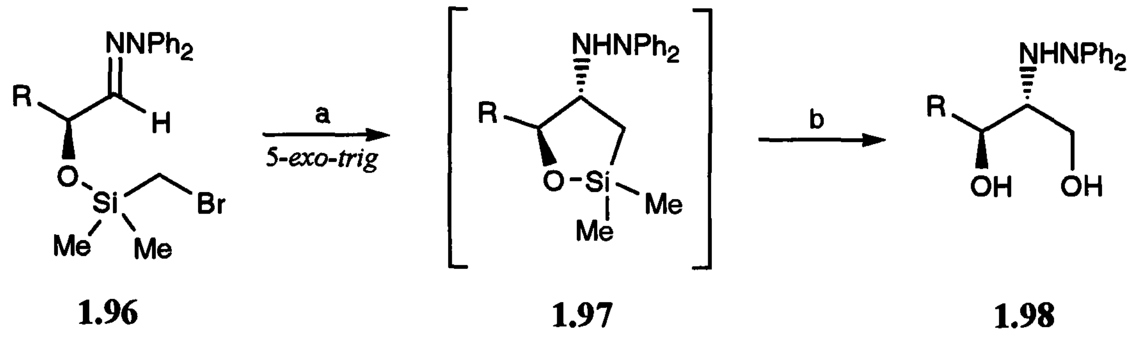
juruenolide C (**1.95**) (Scheme 1.26).[37] This natural γ-lactone, isolated from the seedlings of the myristicaceous Amazonian tree *Virola surinamensis*, is known to exhibit anti-fungal activity against *Cladiosporium cladisporiolides*. Clive's synthesis pertinently demonstrates an alternative to the intramolecular hydrosilylation reaction, incorporated within consecutive radical cyclisations. Activation of the phenylseleno carbonate moiety of precursor **1.90** generated acyl radical **1.91** which underwent 5-*exo-dig* cyclisation and intramolecular hydrogen transfer to generate silicon centred radical **1.92**. 5-*Endo-trig* cyclisation gave the desired γ-lactone **1.94** which was converted in five further steps into (+)-juruenolide C (**1.95**).



a) Ph_3SnH, AIBN, Δ (79%).

Scheme 1.26

Friestad's stereocontrolled radical addition to chiral hydrazones *via* the BMDMS radical donor **1.96** (Scheme 1.27) provided access to a range of chiral 2-hydrazino-1,3-diols (**1.98**) as precursors to α-branched amines.[38]

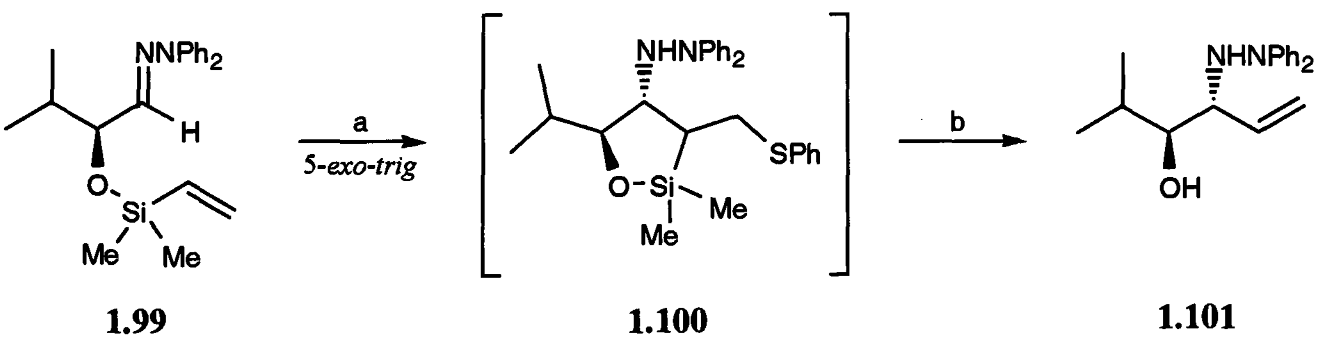


a) Bu_3SnH, AIBN, 80 °C;

b) H_2O_2, KF, $KHCO_3$, MeOH-THF (R = Me, 76%; R = *i*-Bu, 68%; R = *i*-Pr, 80%; R = Ph, 57%; two steps).

Scheme 1.27

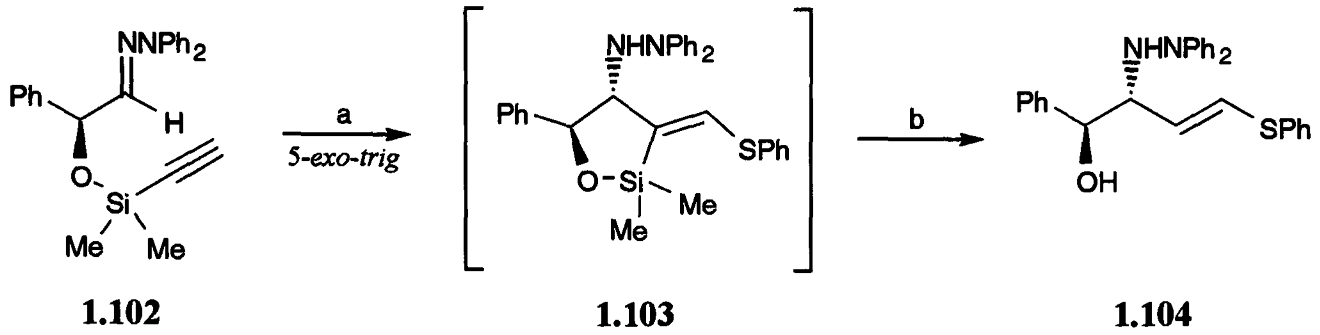
Tethering the radical acceptor also endows a high level of regio- and stereocontrol, as illustrated by Friestad's stereoselective synthesis of substituted vinylgylcinol **1.101** (Scheme 1.28).[39] Friestad's tethered radical addition process is equivalent to an intermolecular vinylation, but proceeded with opposing stereoselectivity.



a) PhSH, AIBN, Δ; b) KF (89% two steps).

Scheme 1.28

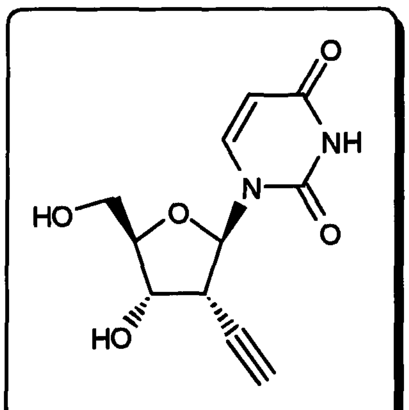
In an extension of this work *E*-vinylsulfides were obtained by thiyl radical activation of silicon tethered alkyne **1.102** and cyclisation of the resulting vinyl radical to install the vinylsulfide moiety after protodesilylation of the intermediate silacycle **1.103**. The newly-formed vinylsulfides are aldehyde equivalents, hence Friestad's protocol is effectively the synthetic counterpart of an acetaldehyde Mannich reaction (Scheme 1.29).[40]



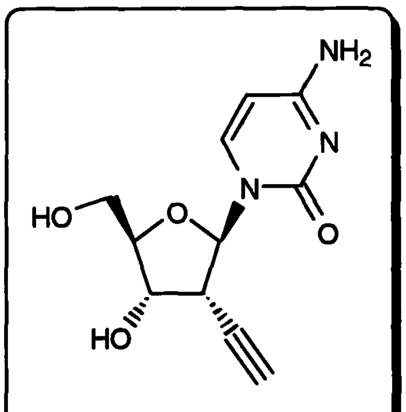
a) PhSH, AIBN, Δ; b) TBAF-THF (70% two steps).

Scheme 1.29

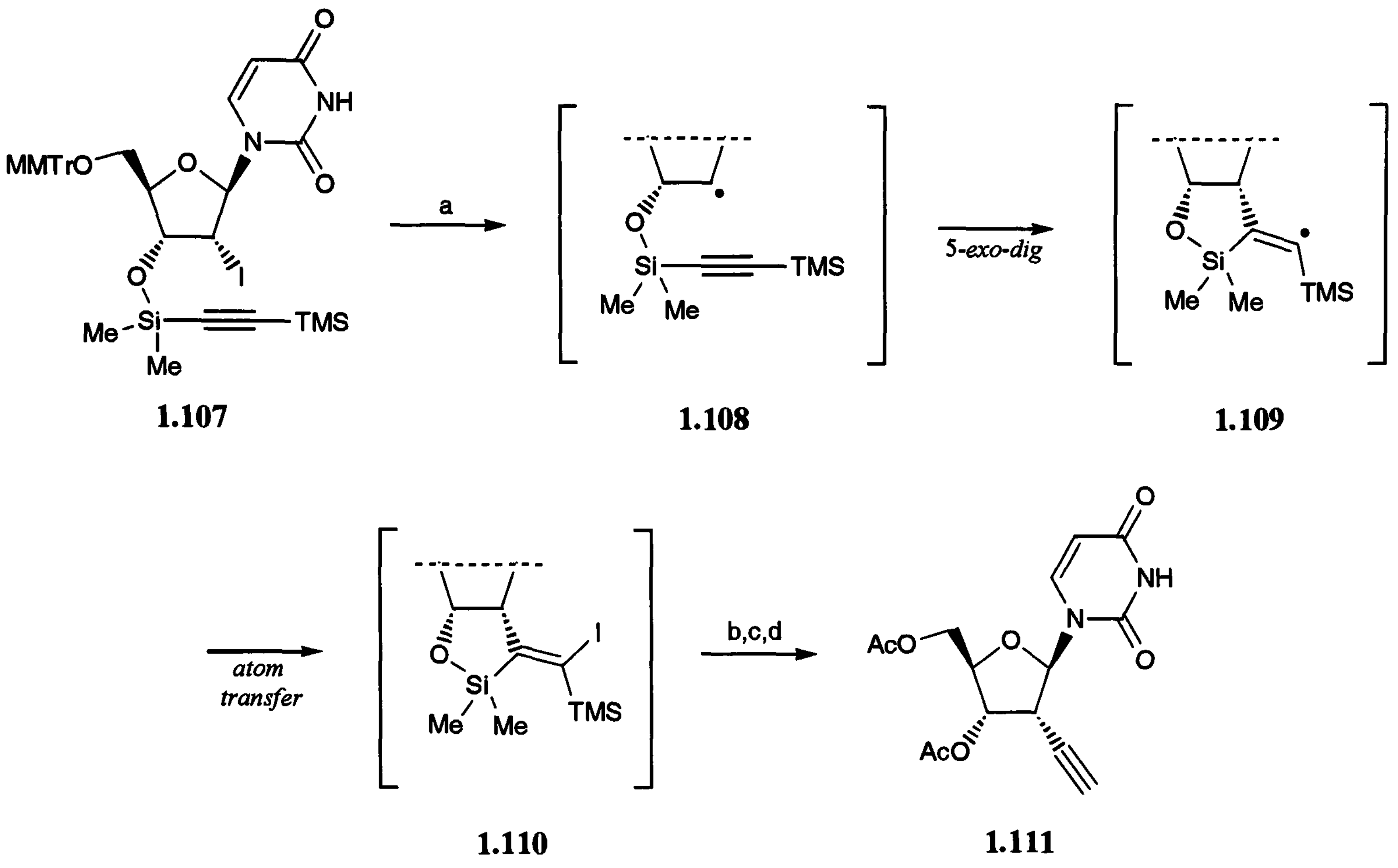
Shuto and co-workers have employed silyl tethered radical acceptors to install functionality selectively in branched sugar nucleosides, including hydroxyethyl and vinyl substituents.[41] Most recently this methodology was applied to alkynyl tethers, to introduce an ethynyl group stereoselectively at an aliphatic carbon centre during the synthesis of potential nucleoside anti-metabolites (**1.105** and **1.106**). From alkynyl acceptor **1.107**, the 5-*exo*-cyclised radical **1.109** was trapped by atom transfer to form intermediate **1.110**. Treatment with a fluoride ion source promoted elimination to the desired ethynyl derivative **1.111** (Scheme 1.30).[42]



1.105



1.106



a) Et_3B, O_2; b) TBAF-THF; c) *aq*. TFA; d) Ac_2O, py. (67% four steps).

Scheme 1.30

1.5 Alkene and alkyne metathesis

The now ubiquitous ring closing metathesis (RCM) procedure has also succumbed to the silicon tethering treatment.[43] This approach proved popular for the diastereoselective cross-coupling of alkenols in the preparation of ene-diols.[44] Tethered olefin metathesis is not limited to the use of silaketals; siloxane and silylether tethers have also been employed in this capacity.[45]

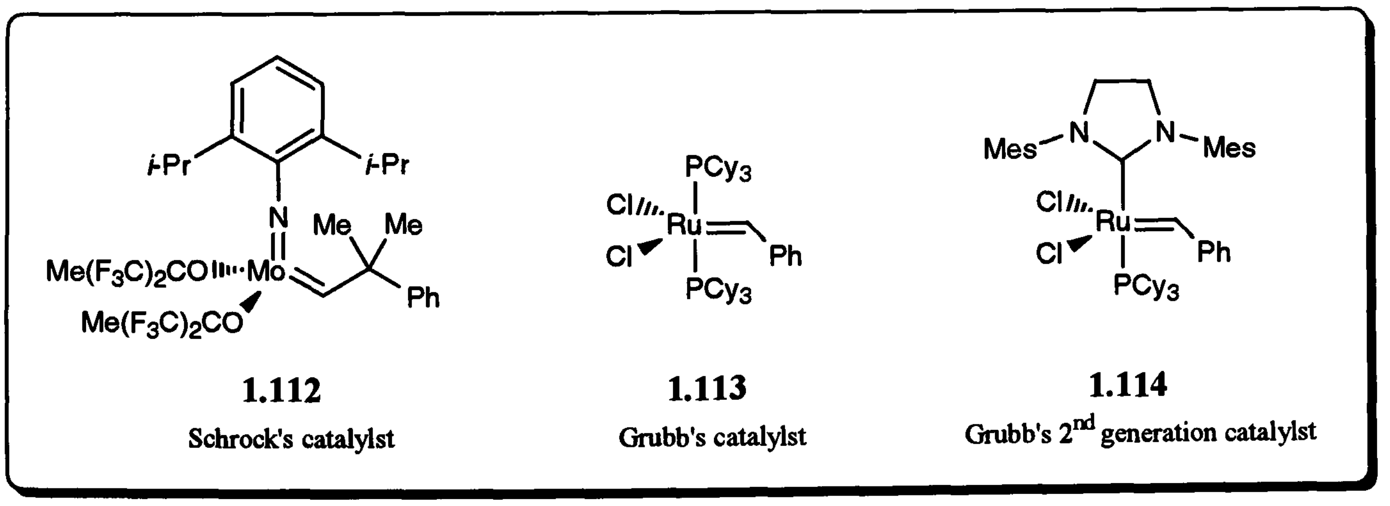
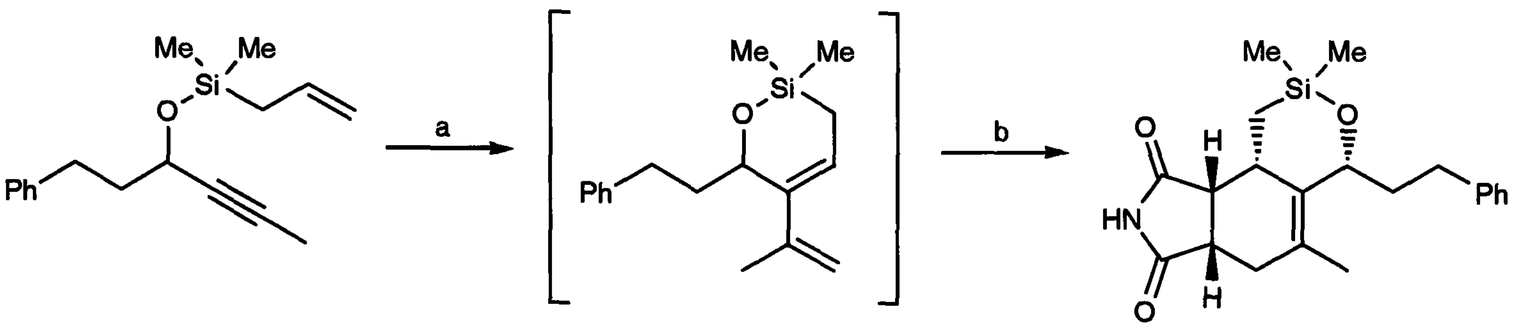


Figure 1.01

Reports of alkene-alkyne cross metathesis are relatively limited due to regioselectivity issues but, in an attempt to circumvent these problems, Dixneuf and co-workers explored the use of silicon tethers to endow an increased level of regiocontrol during ene-yne metathesis.[46]

Comparable methodology has been successfully applied to the synthesis of complex Diels-Alder precursors by Yao (Scheme 1.31).[47]

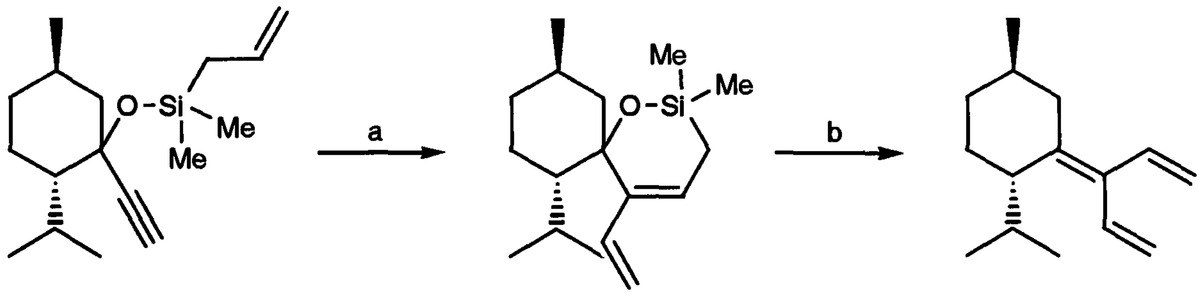


1.115 **1.116** **1.117**

a) Grubbs' 2nd generation catalyst (**1.114**) 1.0 mol%, Δ; b) Maleimide, Δ (70% two steps).

Scheme 1.31

Most recently Dixneuf has employed a ruthenium catalyst to promote the cyclic rearrangement of silylated enynes, as a route to novel terpene derivatives such as **1.120** (Scheme 1.32).[48]

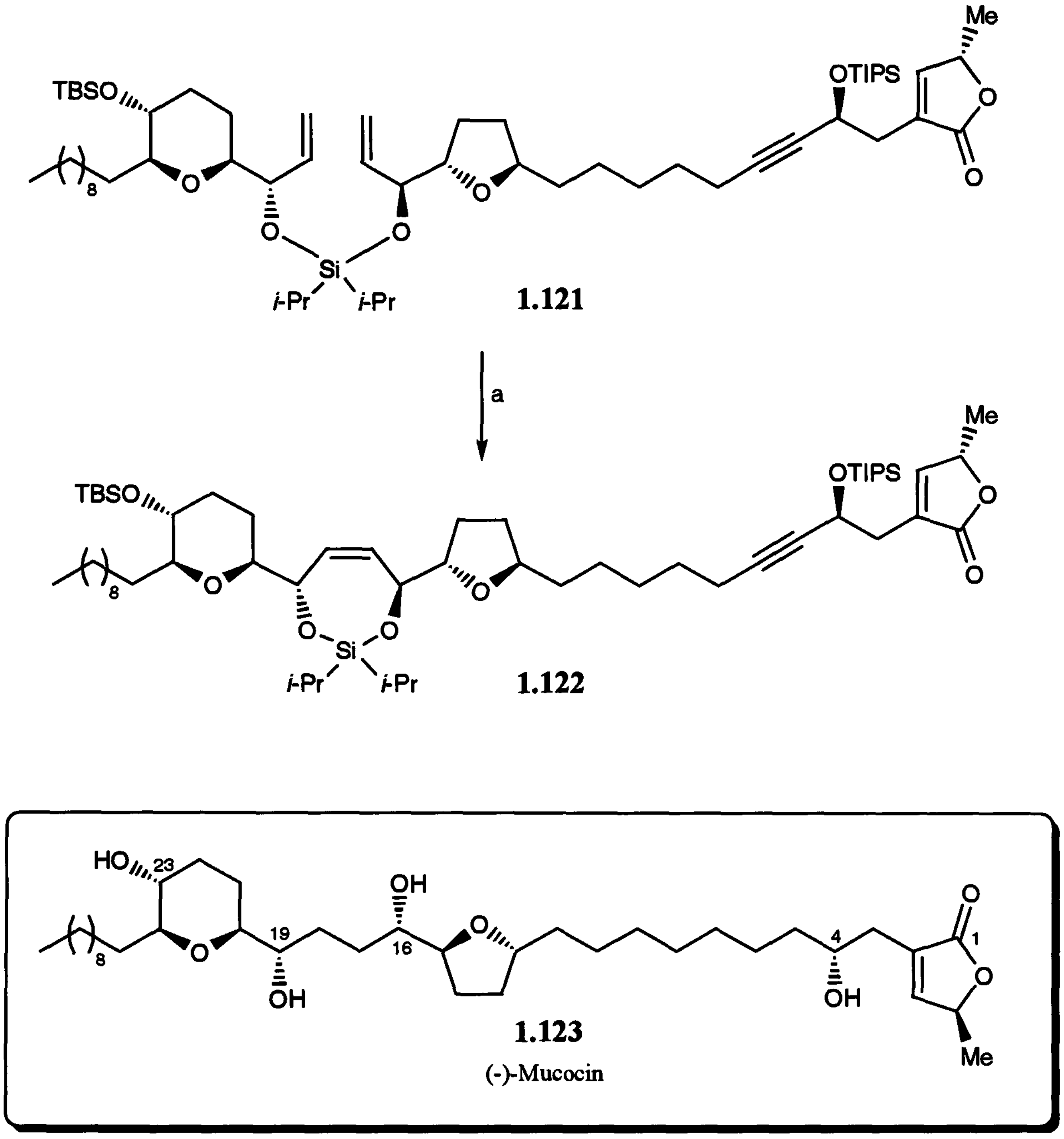


1.118 **1.119** **1.120**

a) $[RuCl_2(p\text{-cymene})]_2$ 2.5 mol%, 1,3-bis(mesityl)imidazolinium chloride 5.0 mol%, Cs_2CO_3 10.0 mol%, 80 °C, 16 hr (76%); b) TBAF, -78 °C–RT, 16 hr (70%).

Scheme 1.32

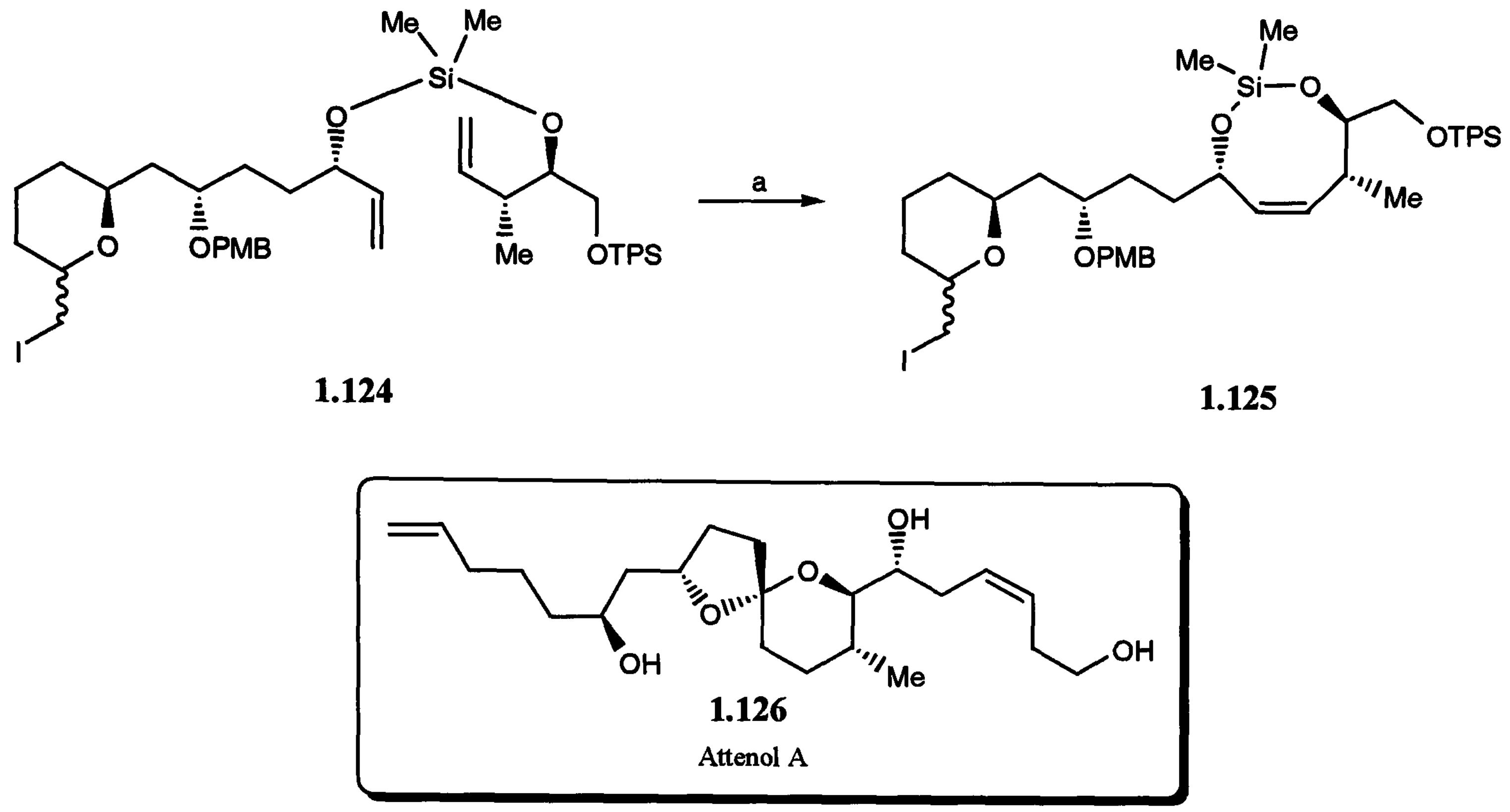
Several groups have exploited the synthetic utility of the silyl tethered alkene RCM process in target directed syntheses. Evans' synthesis of the potent anti-tumour agent (–)-mucocin (**1.123**), involved a silicon tethered RCM reaction to install the pseudo C_2-symmetric 1,4-diol core of this complex annonaceous acetogenin (Scheme 1.33).[49]



a) Grubbs' catalyst (**1.113**), Δ (83%).

Scheme 1.33

Similarly, Eustache's preparation of the cytotoxic spiroacetal attenol A (**1.126**) utilised a silaketal tethered RCM strategy to fuse the two highly functionalised subunits of silyloxy-diene **1.124** (Scheme 1.34).[50]



1.124 **1.125**

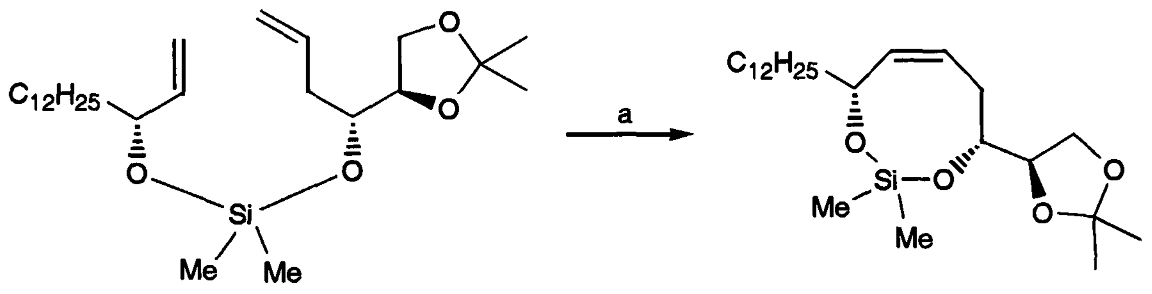
1.126

Attenol A

a) Schrock's catalyst (**1.112**) 10.0 mol%, RT, 24 hr (22%).

Scheme 1.34

In a simpler variant of this chemistry, Eustache employed a silicon tethered RCM reaction for the synthesis of cyclic silaketal intermediate **1.128** as a potential synthetic route to acetogenins (Scheme 1.35).[51]

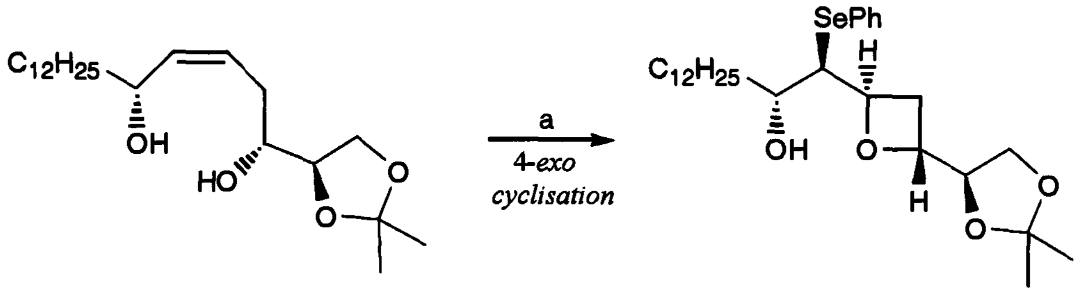


1.127 **1.128**

a) Grubbs' catalyst (**1.113**) 20.0 mol%, Δ, 48 hr (68%).

Scheme 1.35

Subsequent attempts to convert the (*Z*)-2-ene-1,5-diol **1.129** into a tetrahydrofuran, *via* 5-*endo* electrophilic selenocyclisation, revealed an unexpected 4-*exo* reaction pathway, resulting in the exclusive formation of oxetane **1.130** (Scheme 1.36).

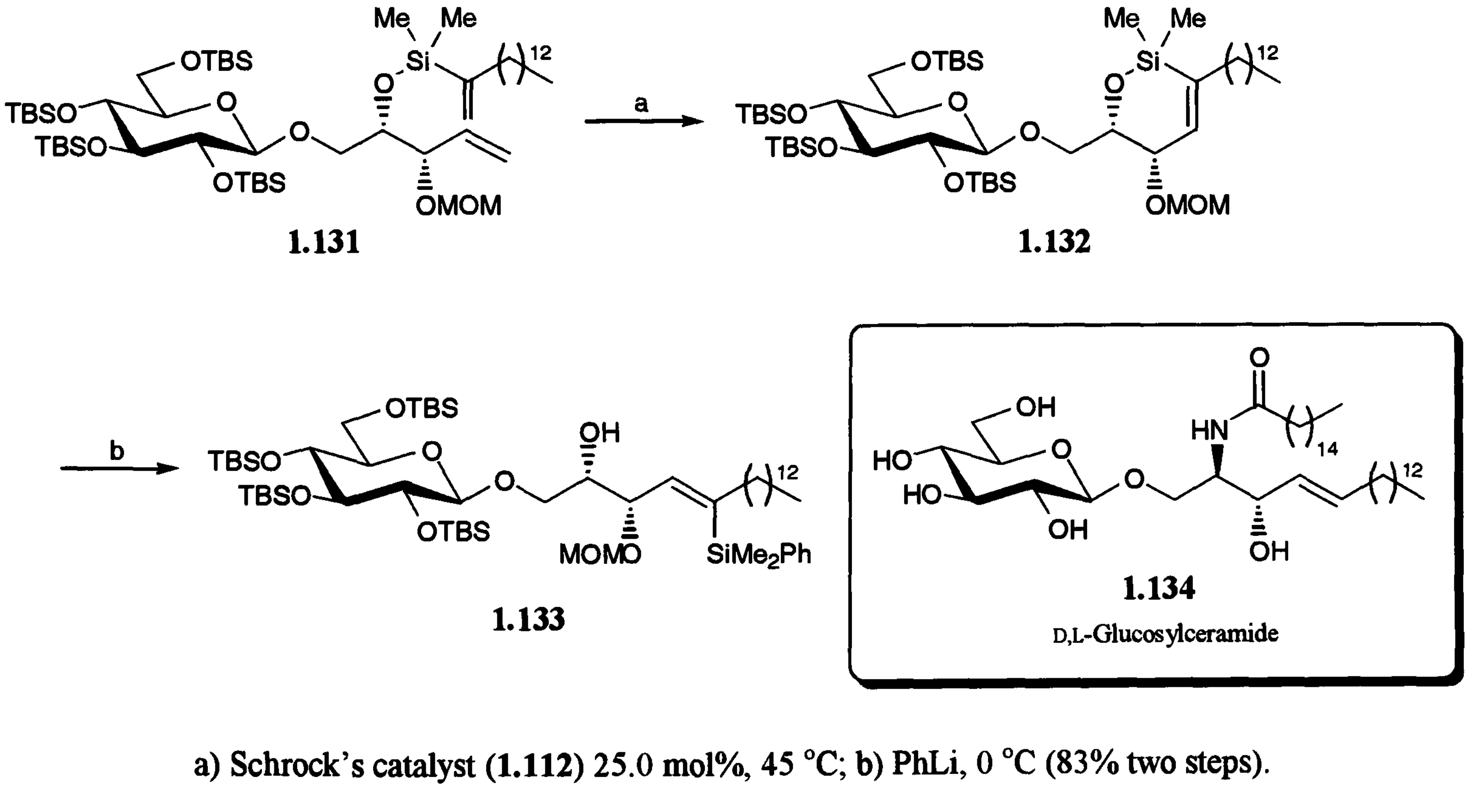


1.129 **1.130**

a) *N*-PSP, CSA (cat.), -78 °C–RT, 16 hr then 2,2-DMP, CSA (cat.), RT, 16 hr (75%).

Scheme 1.36

A number of groups have applied metathesis strategies to the field of carbohydrate chemistry;[52] Barrett employed Schrock's catalyst (**1.112**) with vinylsilyl ether **1.131** to install the *trans*-disubstituted double bond in his synthesis of D,L-glucosylceramide (**1.134**), a biologically important glycosphingolipid (Scheme 1.37).[53]

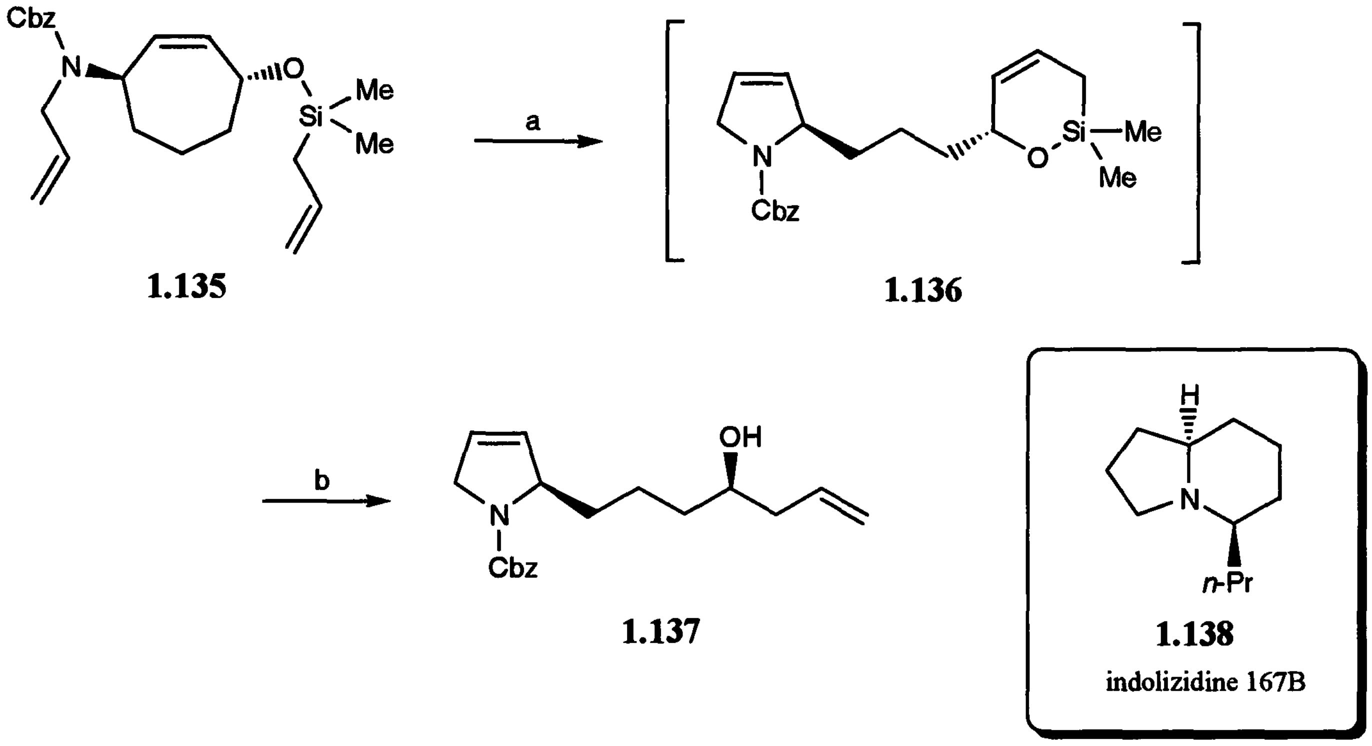


1.131 **1.132** **1.133** **1.134** D,L-Glucosylceramide

a) Schrock's catalyst (**1.112**) 25.0 mol%, 45 °C; b) PhLi, 0 °C (83% two steps).

Scheme 1.37

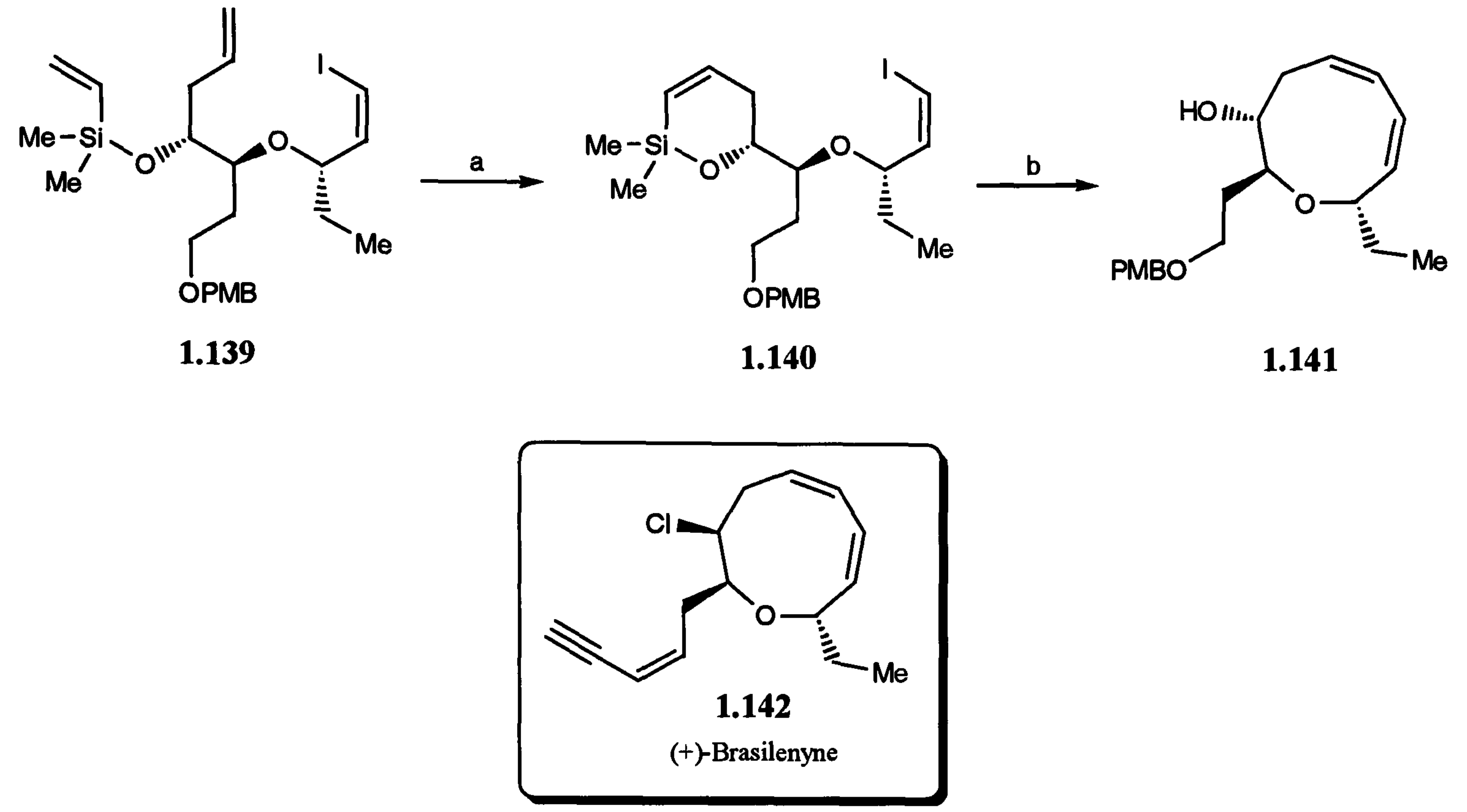
In an effort to prepare neuro-transmission inhibiting alkaloids, Blechert *et al.* developed a ruthenium-catalysed tandem ring-rearrangement metathesis for the enantioselective synthesis of (–)-indolizidine 167B (**1.138**) (Scheme 1.38).[54]



a) Grubbs' catalyst (**1.113**) 5.0 mol%, Δ,4 hr; b) TBAF, 0 °C–RT (92% two steps).

Scheme 1.38

A silicon tethered metathesis-Heck sequence has been developed by Denmark and applied to an imaginative synthesis of (+)-brasilenyne (**1.142**). This anti-feedant, isolated from the sea hare *Aplysia brasiliana*, possesses a synthetically demanding endocyclic 1,3-*cis*,*cis*-diene unit. Denmark *et al.* successfully overcame this challenge with their novel metathesis-intramolecular cross-coupling strategy; vinylsilyl ether **1.139** underwent RCM to give cycloalkenylsiloxane **1.140**, subsequent silicon-assisted Heck coupling completed construction of the cyclic ether skeleton of (+)-brasilenyne (**1.142**) (Scheme 1.39).[55]



1.139 **1.140** **1.141**

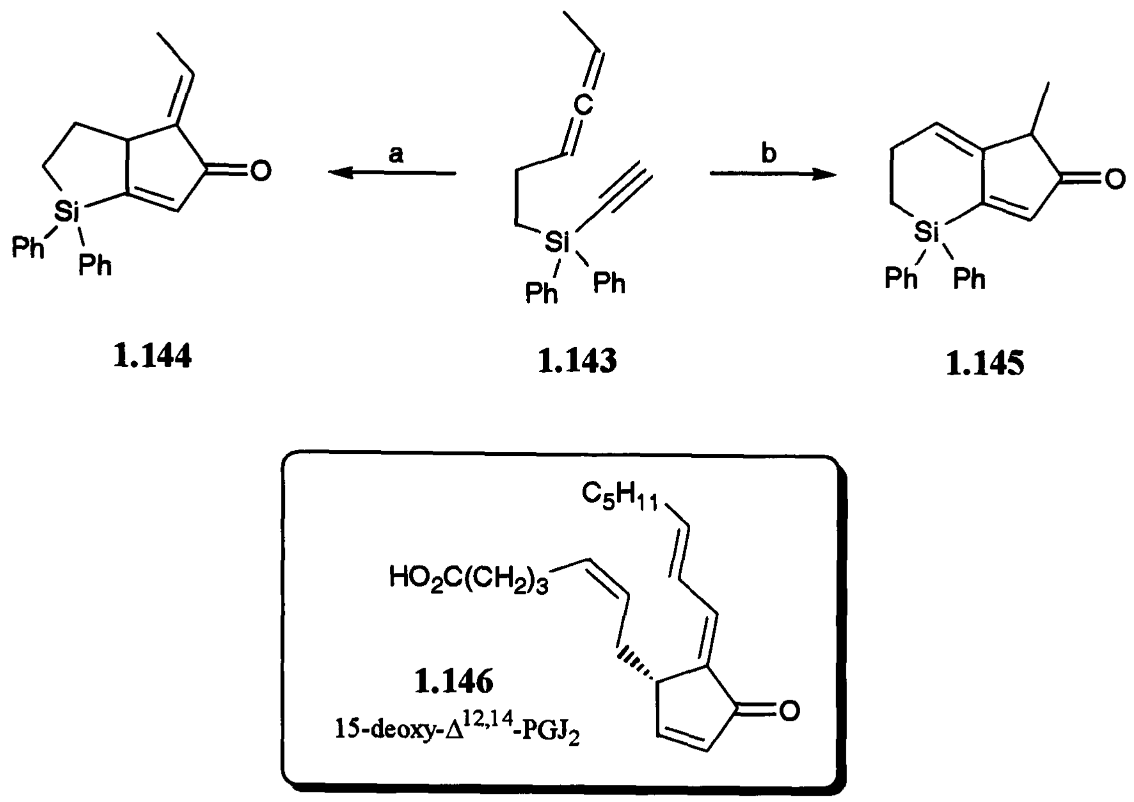
1.142
(+)-Brasilenyne

a) Schrock's catalyst (**1.112**) 5.0 mol%, RT, 1 hr (92%); b) $[(allyl)PdCl]_2$ 7.5 mol%, TBAF, RT, 60 hr (61%).

Scheme 1.39

1.6 Cyclocarbonylation and Pauson-Khand reactions

Carbonylative couplings offer an expedient method for the rapid assembly of substituted carbocycles bearing a carbonyl moiety. The Pauson-Khand reaction (PKR); a three component [2+2+1] cyclisation of an alkene, an alkyne and carbon monoxide, provides a reliable and convenient method for the construction of cyclopentenone derivatives. However, the intermolecular PKR is not regioselective with respect to the alkene and is also mainly restricted to the use of strained olefins. The analogous silicon tethered PKR has been examined by both Pagenkopf and Brummond as a means of increasing the regiocontrol of cycloaddition. Brummond and co-workers are seeking to apply their tethered PKR methodology to the synthesis of α-alkylidene cyclopentenones, the core skeletal unit of prostaglandin 15-deoxy-$\Delta^{12,14}$-PGJ_2 (**1.146**) (Scheme 1.40).[56]



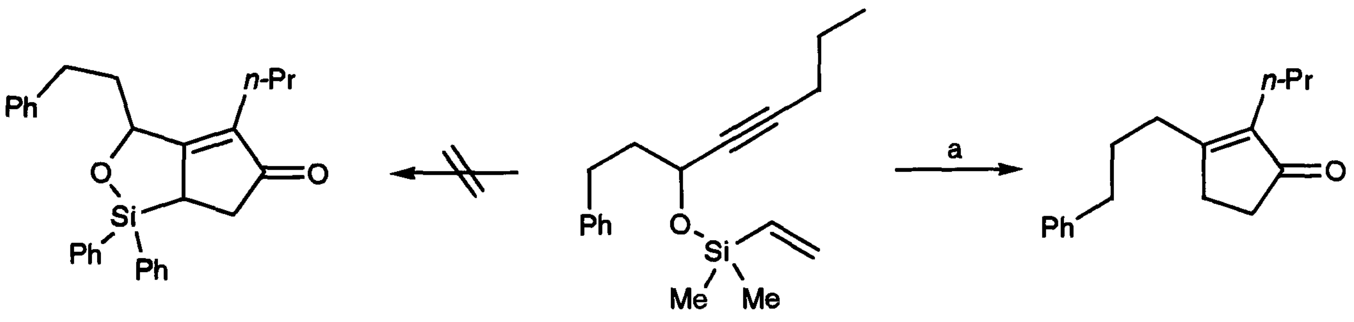
1.144 **1.143** **1.145**

1.146
15-deoxy-$\Delta^{12,14}$-PGJ$_2$

a) $Mo(CO)_6$, 90 °C (64%); b) $[Rh(CO)_2Cl]_2$ 5.0 mol%, CO, 90 °C (64%).

Scheme 1.40

Pagenkopf wished to adopt a similar approach for the preparation of isoprostanes, prostaglandin mimics which feature *cis*-dialkyl stereochemistry at the cyclopentane ring. Unfortunately, this group were not able to isolate the desired cyclopentenone core **1.148** due to the predominance of a competing reaction pathway (Scheme 1.41).[57] The formation of **1.149** is thought to result from fragmentation of the Si-C bond of bicyclic enone **1.148**, culminating in reduction of the propargylic carbon. Interestingly, this process is the regiocontrolled equivalent of an intermolecular PKR reaction of an alkyne with ethylene gas.[58]

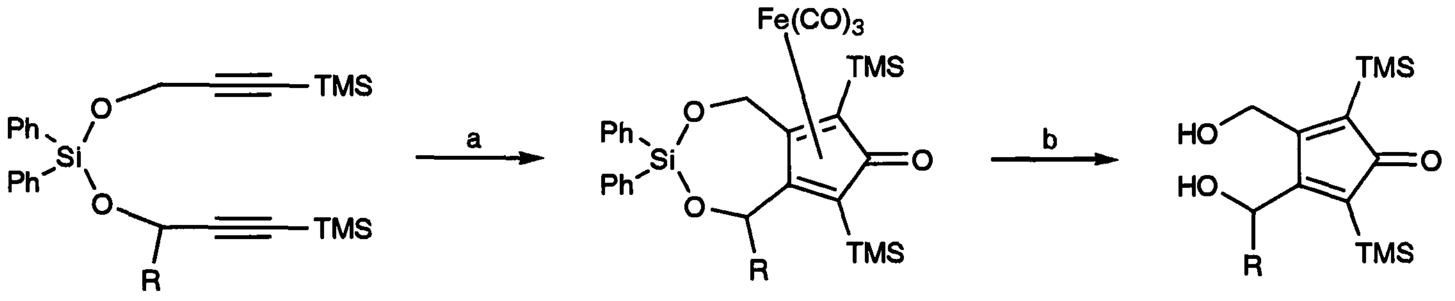


1.148 **1.147** **1.149**

a) $Co_2(CO)_8$, H_2O 1.0 mol%, Δ, 24 hr (62%).

Scheme 1.41

Carbonylative alkyne-alkyne couplings, which form cyclopentadienones, are less common than the equivalent alkene-alkyne reactions. Shibata and Pearson have both investigated the silaketal tethered cyclocarbonylation of diynes catalysed by octacarbonyldicobalt and pentacarbonyliron respectively.[59] Pearson's protocol allows for a cross-coupling of non-identical alkyne units, that generate unsymmetrically substituted cyclopentadienone derivatives (Scheme 1.42).



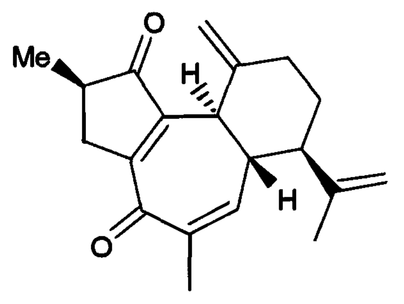
1.150 **1.151** **1.152**

a) $Fe(CO)_5$, CO, Δ, 24 hr (R = Me, 83%; R = Ph, 47%); b) Me_3NO, 0 °C, 4 hr (R = Me, 66%; R = Ph, 74%).

Scheme 1.42

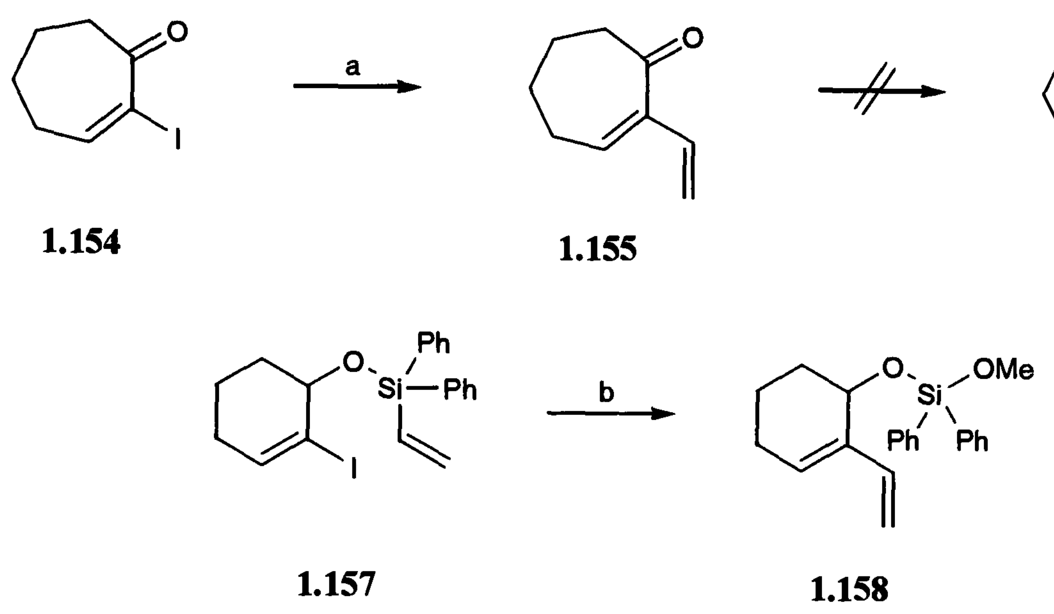
1.7 Heck and Stille coupling

The silicon tethered Heck reaction has been investigated by both Keese and Young for the alkenylation of five and six-membered carbocycles.[60] In an effort to prepare curcusone A (**1.153**), a potential anti-cancer therapeutic compound, Young *et al.* developed a silicon tethered version of the Heck reaction as an alternative to a problematic and low-yielding Stille coupling. During model studies, the silicon based approach to intermediate **1.158** proved far superior to the inherently toxic Stille reaction (Scheme 1.43).



1.153

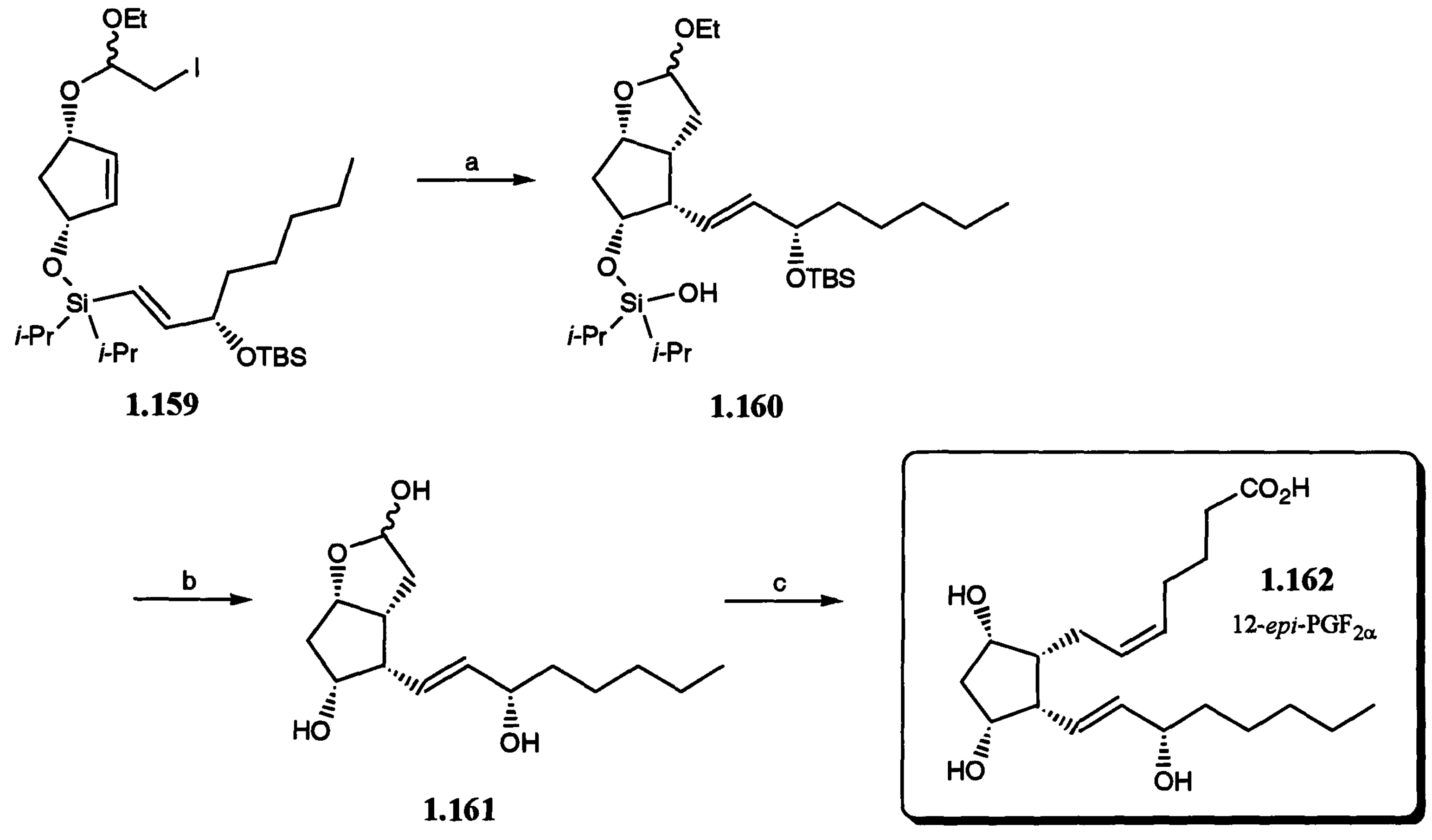
Curcusone A



a) $Bu_3SnCH{=}CH_2$, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, NMP (27%); b) $(Ph_3P)_4Pd$, TEA, MeOH (89%).

Scheme 1.43

A silicon tethered Heck/sila-Stille cross-coupling protocol has recently been applied by Cha and co-workers to the elegant syntheses of a series of pharmacologically important prostaglandin mimics. Synthesis of isoprostane 12-*epi*-$PGF_{2\alpha}$ (**1.162**) was accomplished *via* an adept cascade sequence, employing dual tethers to define the stereochemistry of the *epi*-prostaglandin side-chains (Scheme 1.44).[61]



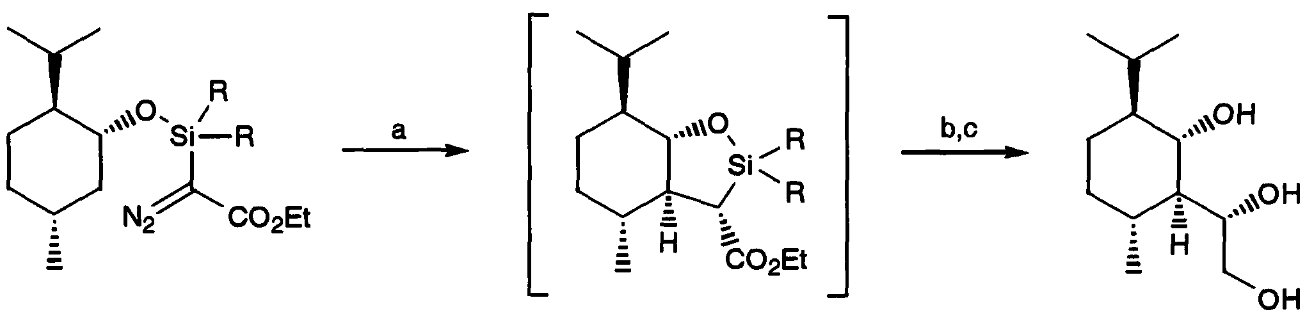
a) $Pd(OAc)_2$, dppp, TEA (51%); b) *aq.* HCl (74%);

c) (4-carboxybutyl)triphenylphosphonium bromide, KHMDS (55%).

Scheme 1.44

1.8 Carbene insertions

Marsden has developed a novel strategy for the stereoselective synthesis of 1,2,4-triols *via* carbenoid insertions of silicon tethered diazoacetates. The derived oxasilacyclopentane **1.164** was oxidatively cleaved after reduction of the pendant ester, to furnish the desired polyol **1.165** (Scheme 1.45).[62] The moderate yield of **1.165** results from a competing elimination pathway during the Tamao-oxidation step.



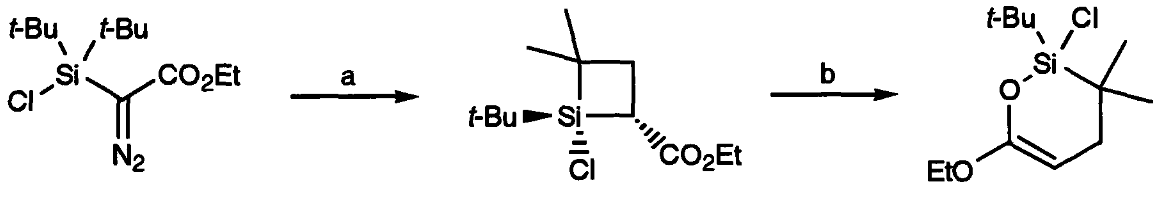
1.163 **1.164** **1.165**

a) $Rh_2(oct)_4$ 3.0 mol%, Δ; b) DIBAL, -78 °C;

c) H_2O_2, KF, $KHCO_3$, DMF, 80 °C (R = *i*-Pr, 30%; R = Et, 35% three steps).

Scheme 1.45

Maas and co-workers have also examined the intramolecular carbene reactions of silyl diazoacetates.[63] The tethered C-H insertion of a photochemically generated carbene allowed access to silacyclobutane **1.167**, which underwent a thermal [1,3]-shift to form oxasilacyclohexene **1.168** (Scheme 1.46).[64]



1.166 **1.167** **1.168**

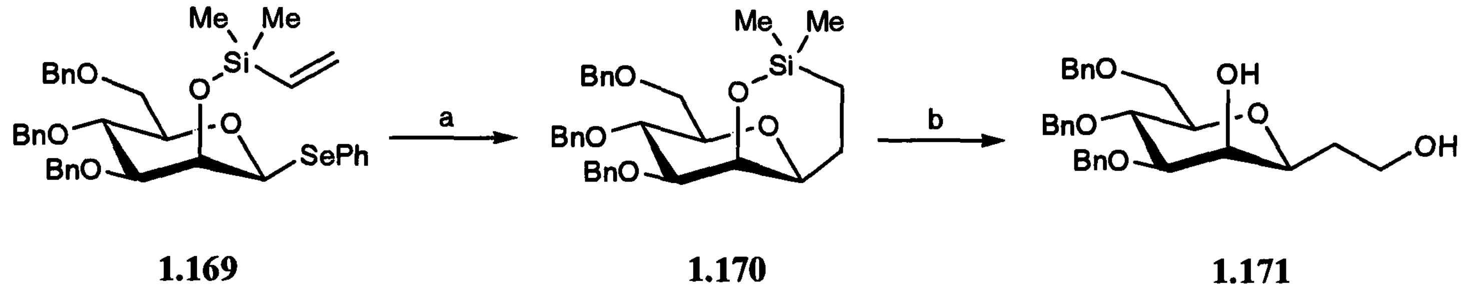
a) *hν* (100%); b) Toluene, 85 °C (36%).

Scheme 1.46

1.9 Glycosylations

Since Stork *et al.* first demonstrated the use of temporary silyl tethers to control the regio- and stereochemistry of radical-induced glycosylation,[65] a number of groups have applied similar methodology to the synthesis of *C*-glycosides.[1,4,7,66,67]

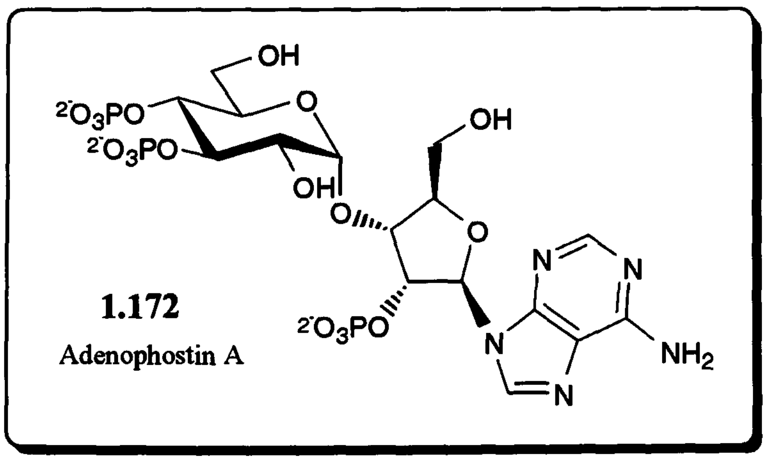
Allyl- and vinylsilyl radical acceptors have been examined by Shuto *et al.* for the stereoselective generation of *C*-glycosides.[68] At elevated temperatures, provided that the concentration of Bu_3SnH was kept low, the radical cyclisation proceeded in a 6-*endo* fashion to furnish the β-*C*-mannoside **1.171** exclusively (Scheme 1.47).

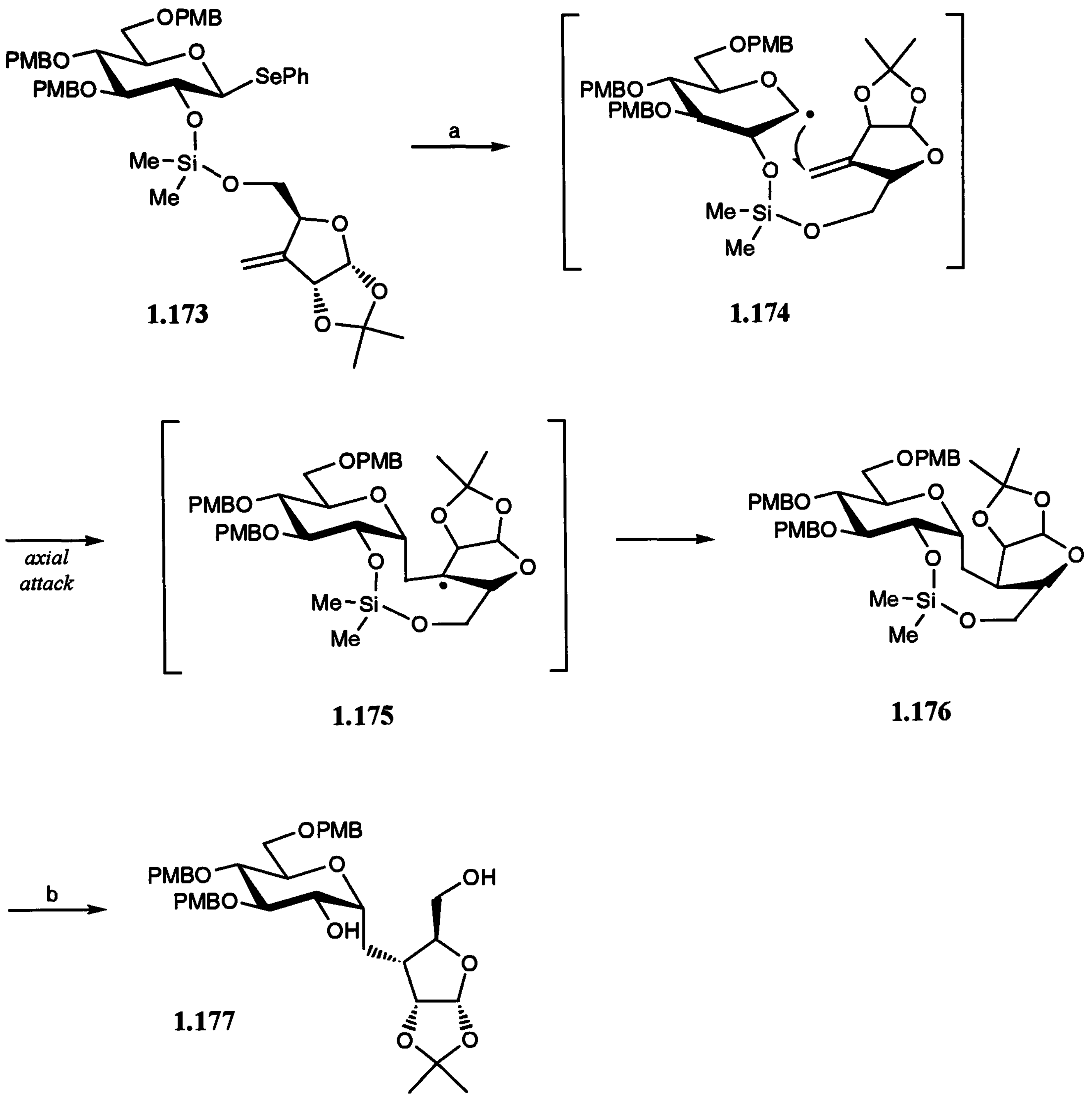


a) Bu_3SnH, AIBN, PhCl, Δ; b) H_2O_2, KF, $KHCO_3$, MeOH-THF (74% two steps).

Scheme 1.47

Shuto has also applied a silyl tethered radical coupling approach to his synthesis of the *C*-glycoside analogue of adenophostin A (**1.172**), a potent IP_3 receptor agonist (Scheme 1.48).[69]

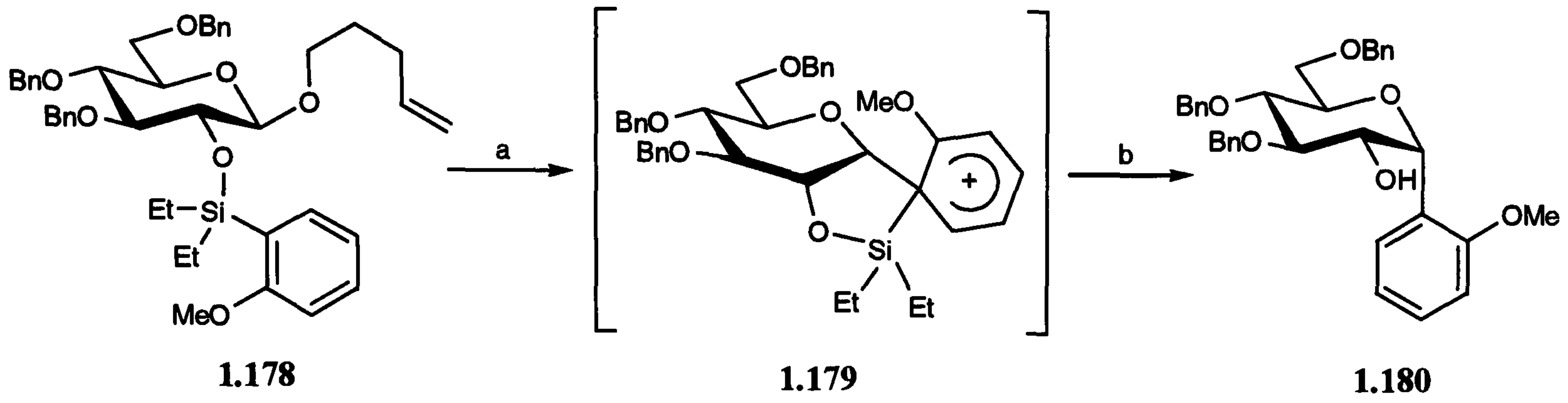




a) Bu_3SnH, AIBN, Δ; b) TBAF-THF (α:β = 3:1, 66% two steps).

Scheme 1.48

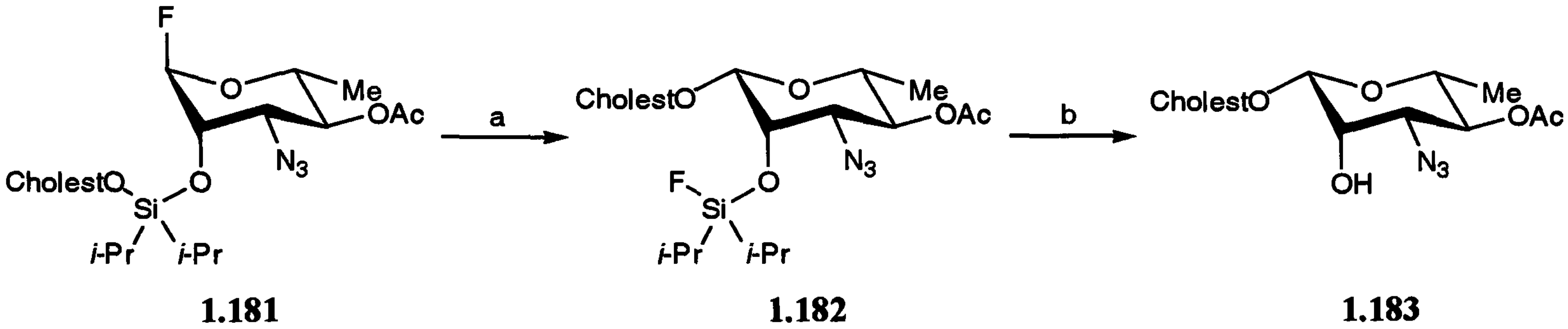
Martin *et al.* employed a silicon tether to deliver the aromatic aglycon in the stereodirected synthesis of *C*-aryl glycosides. Electrophilic *ipso*-desilylation of **1.179** gave exclusive access to the α-*C*-aryl glucoside **1.180**, possessing the elusive 1,2-*cis*-configuration (Scheme 1.49).[70]



a) IDCP; b) TBAF (72% two steps).

Scheme 1.49

In an extension of Stork's pioneering work on β-selective intramolecular *O*-aglycon delivery (IAD),[71] Rychnovsky demonstrated the utility of a silyl-IAD protocol for β-selective glycosylation with D-mycosamine (Scheme 1.50).[72]



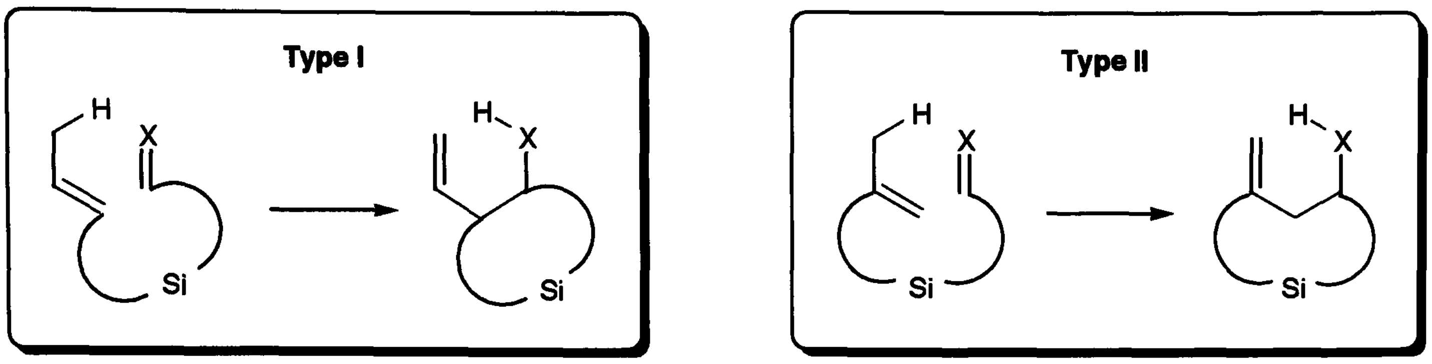
a) Cp_2ZrCl_2, $AgClO_4$, 4Å MS (73%); b) TBAF (100%).

Scheme 1.50

1.10 Ene reactions

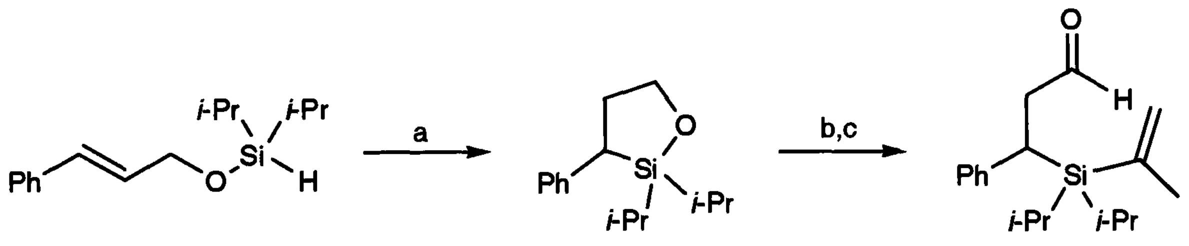
The Robertson group are interested in developing silicon tethered ene methodology as a method for the stereoselective generation of polylols; which could in turn be used as intermediates in the synthesis of non-natural carbohydrates.

The nomenclature of the tethered ene cyclisation is ascribed to Oppolzer and Snieckus who define the reaction type according to the point of attachment of the tether to the ene component (Scheme 1.51).[73]



Scheme 1.51

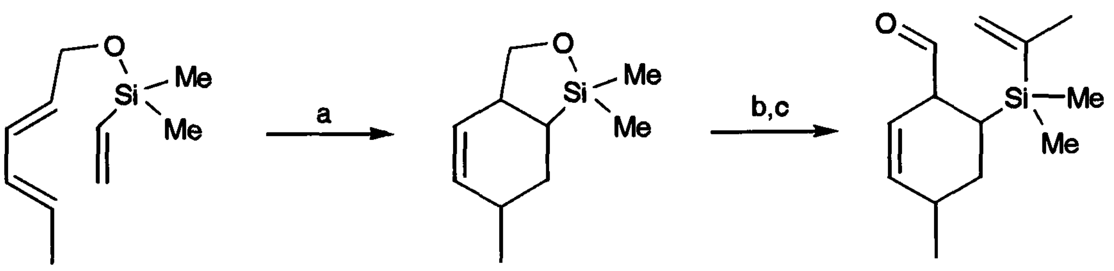
Early work in the Robertson group focused on *C*-linked Type II silicon tethered carbonyl ene reactions.[74,75] The ene precursors themselves were prepared either *via* silicon tethered hydrosilylation or by a silyl tethered IMDA reaction, with organometallic ring-opening of the intermediate oxasilacyclopentanes (Scheme 1.52 and Scheme 1.53).[76]



1.184 **1.185** **1.186**

a) $(Ph_3P)_3RhCl$ 0.2 mol%, 4Å MS (100%); b) 2-propenyllithium, -78 °C (66%); c) PDC, 4Å MS, 0 °C-RT (64%).

Scheme 1.52

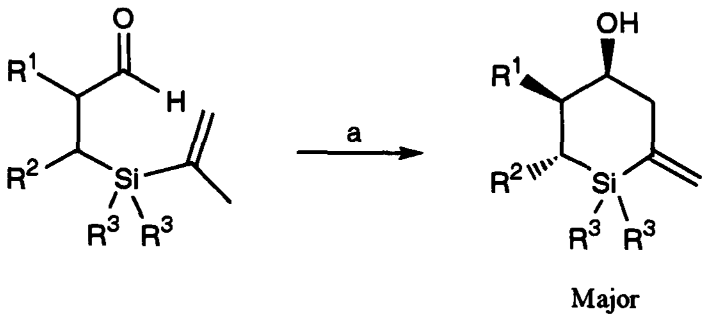


1.187 **1.188** **1.189**

a) Toluene, 170 °C; b) 2-propenyllithium, -78 °C (67% two steps); c) PDC, 4Å MS, 0 °C–RT (65%).

Scheme 1.53

The Lewis acid catalysed ene reactions proceeded with a high degree of stereoselectivity to generate a range of novel substituted silacyclohexanols (Scheme 1.54 and Scheme 1.55).



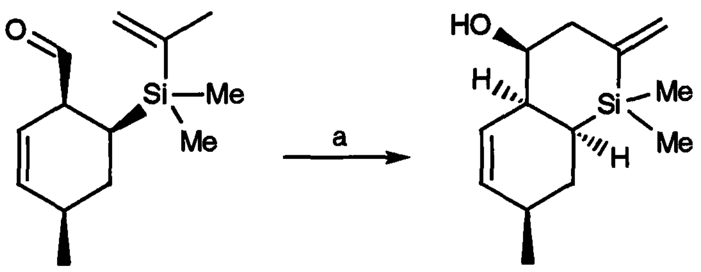
1.190 **1.191**

a) MeAlCl$_2$, -78 °C.

Scheme 1.54

R^1	R^2	R^3	Yield %
H	H	Me	80
Me	H	Me	80
H	Me	Me	69
i-Pr	H	Me	84
Bn	H	Me	79
H	Ph	*i*-Pr	76

Table 1.01

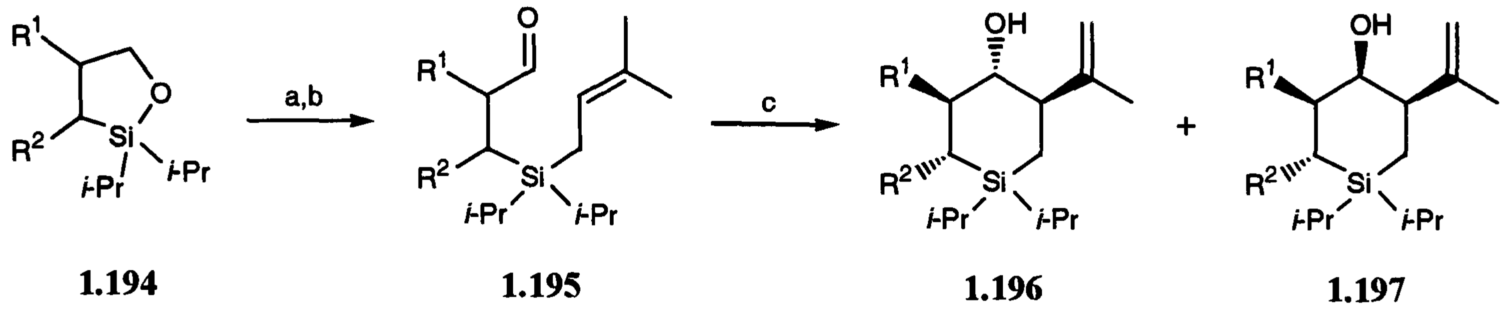


1.192 **1.193**

a) MeAlCl$_2$, -78 °C (88%).

Scheme 1.55

Subsequently, the group's attention moved to Type I silicon tethered carbonyl ene cyclisations.[74,77] The Type I variant offers the advantage of formation of two new stereocentres, compared to one generated by the Type II process (Scheme 1.56).[78]

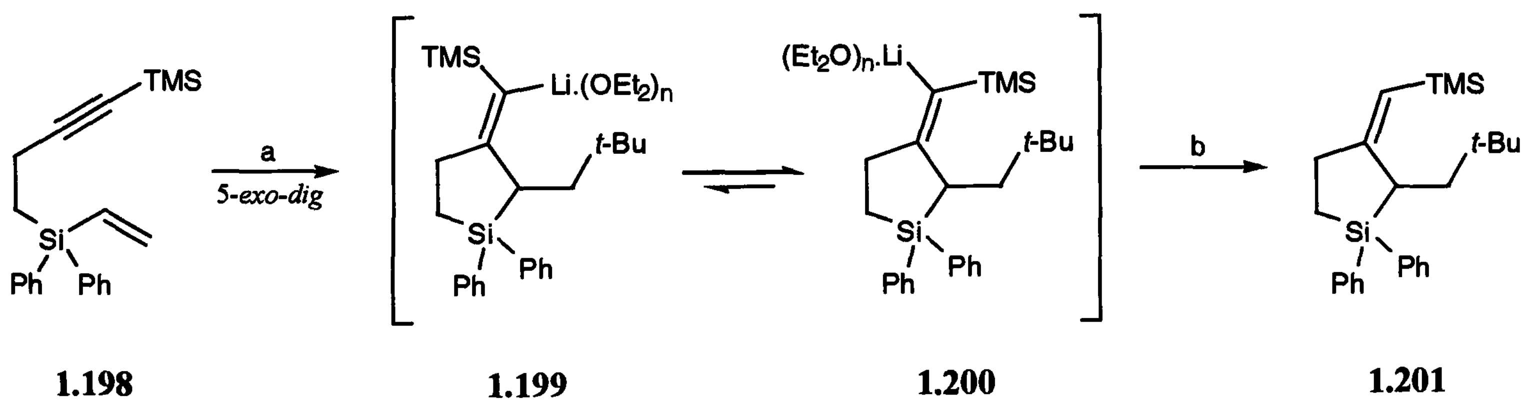


a) prenyllithium, -78 °C; b) PDC, 4Å MS, 0 °C–RT (R^1 = Ph, R^2 = H, 62%; R^1 = H, R^2 = Ph, 40%; two steps); c) Me_2AlCl, RT (R^1 = Ph, R^2 = H, 61% and 13%; R^1 = H, R^2 = Ph, 50% and 9%).

Scheme 1.56

1.11 Miscellaneous

Taylor has developed a tandem intermolecular-intramolecular carbolithiation sequence in order to prepare substituted silacyclopentanes regioselectively. The lithiated homopropargyl silane **1.198** cyclised in a 5-*exo-dig* fashion to give **1.201**, predominantly as the *Z*-isomer; the observed selectivity is thought to result from steric repulsion between the ether-solvated lithium and the pendant *t*-butyl group (Scheme 1.57).[79]



a) *t*-BuLi, RT; b) H_3O^+ (78%).

Scheme 1.57

1.12 Conclusions

This introductory chapter has provided an insight into the extensive field of 'temporary silicon connection' methodology, demonstrating that silyl tethers are associated with a plethora of applications, including hydrosilylations, cycloadditions and radical reactions. This ubiquitous process has also been applied to more recently established areas of synthetic methodology such as RCM, and is still finding new applications, including our own tethered ene protocol. The examples presented in this chapter have illustrated the versatility of silicon tethers in organic transformations and their ability to facilitate key steps in targeted syntheses.

Despite widening popularity, silicon tethered processes are often restricted by the limited methodology available for assembling the tethered systems; as a result, novel protocols for the preparation of silanes, and pertinent methods for the rapid and efficient assembly of silicon tethered substrates are continually sought.

The subsequent chapters of this thesis will present our developments in the area of silicon tethered ene methodology, illustrating new routes to ene precursors and reporting their behaviour under our established ene conditions. We will also demonstrate the utility of these substrates to allyl transfer reactions, with the second part of the thesis dedicated to this novel process. Finally, we will present the first application of our methodology to carbasugar synthesis.

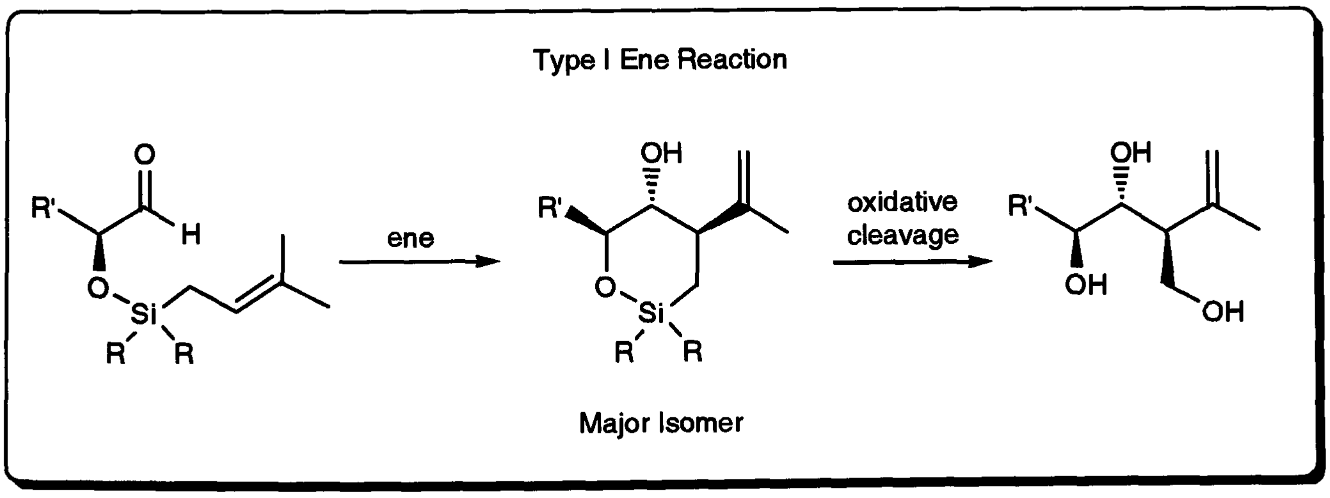
Chapter 2

Synthesis and Investigation of *O*-Linked Prenyl Tethers

2.0 Introduction

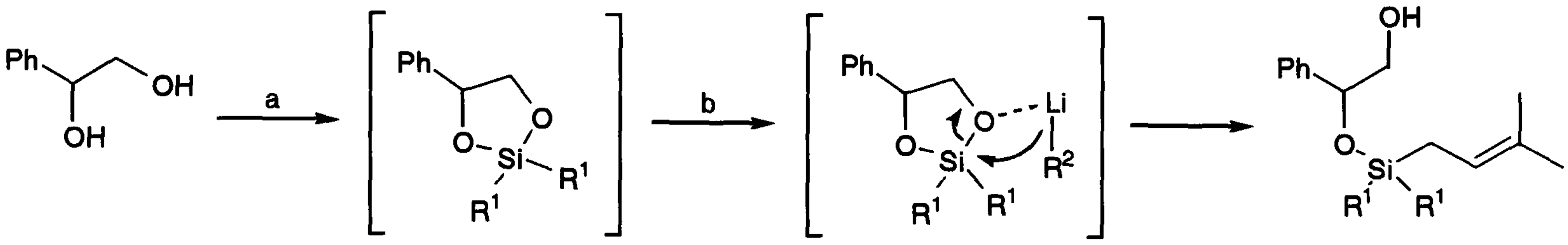
The intramolecular Type I carbonyl ene reaction presents an attractive method for C-C bond formation, generating two contiguous stereocentres, with a high degree of stereocontrol. Recent work in the Robertson group has seen a transition in the focus of our studies from the silicon tethered Type I carbonyl ene cyclisation of all-carbon systems (Section 1.10)[74,77] to the synthesis and investigation of *O*-linked ene precursors,[80] the *C*-linked systems being of limited synthetic use due to the relatively immovable silicon residing within the ene product.

The addition of an *O*-linkage, incorporating an electron withdrawing group on silicon, offers the advantage of selective removal of the silicon atom from the ene product oxasilacycle by way of oxidative cleavage of the Si-C bond. Overall, this methodology provides a flexible and stereoselective route to 1,2,4-triols with alkene functionality (Scheme 2.01)[80,81] which have the potential to be elaborated into a variety of carbohydrate-like scaffolds. These polyol templates, derived from non-carbohydrate precursors,[82] could prove useful intermediates in target syntheses.



Scheme 2.01

Our established route for construction of the *O*-linked ene precursor is based on Kuwajima's procedure for the selective silylation of the internal hydroxyl of a terminal 1,2-diol.[83] Kuwajima's one-pot protocol was adapted by our group to employ prenyllithium (prepared *in situ* from the prenyl stannane) to ring-open the intermediate siladioxolane **2.03** regioselectively (Scheme 2.02).[80,81] Deprotonation of diol **2.01**, addition of the dialkylchlorosilane, and subsequent evolution of hydrogen generated siladioxolane **2.02** *in situ*. It is possible that co-ordination of prenyllithium to the sterically less encumbered 1°-hydroxyl dictates the regioselectivity of the ring-opening, with predominant formation of the kinetic 2°-silylated product **2.04**.

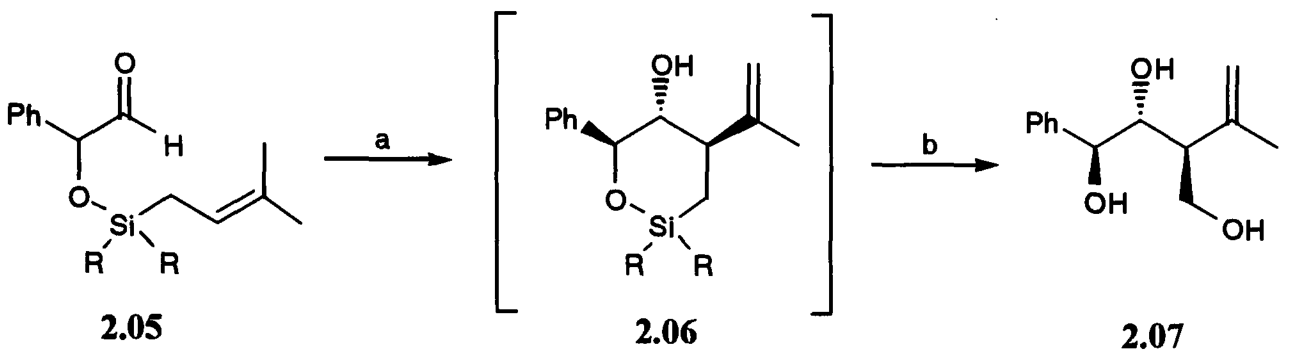


2.01 **2.02** **2.03** **2.04**

a) n-BuLi, R_2SiHCl; b) R^2Li = prenyllithium, TMEDA (R^1 = *t*-Bu, 77%; R^1 = *i*-Pr, 42%; two steps).

Scheme 2.02

Oxidation of the 1°-hydroxyl with IBX offered reliable access to the α-silyloxy aldehyde **2.05** as the ene precursor. The ensuing DMAC catalysed ene reaction gave the *trans,trans*-silacyclohexanol (±)-**2.06** as the major diastereomer. The oxasilacycle was cleaved oxidatively to furnish the desired triol (±)-**2.07**, effectively generating two additional stereocentres, starting from just one in the ene precursor (Scheme 2.03).[80,81]



a) Me_2AlCl, RT (R = *t*-Bu, 38%; R = *i*-Pr, 40%); b) H_2O_2, KF, $KHCO_3$, MeOH-THF, Δ (R = *i*-Pr, 17%).

Scheme 2.03

Unfortunately this route suffered from two major drawbacks. It was determined that cyclic siloxanes in which the silicon atom bears *tert*-butyl groups fail to succumb to oxidative cleavage, even under the most forcing conditions. This is attributed to steric encumbrance by the bulky substituents preventing nucleophilic attack at silicon. Repeating the sequence with less sterically demanding *iso*-propyl substituents allowed the ene product to be oxidised as desired, but the initial Kuwajima process for preparing the required 2°-silylated diol was much less efficient.

To date, the effort expended on the synthesis of *O*-linked prenyl tethered systems *via* the Kuwajima route had only proven partially successful;[80] evaluation of these preliminary results indicated that the project could move forward if a better method for preparing the desired *O*-linked silicon tethered ene precursors could be found. Hence, the initial aims of this project were:

- to develop and evaluate alternatives to the Kuwajima protocol, establishing a reliable synthetic method for assembling the ene and enophile components on silicon.

- to prepare *O*-linked silicon tethered ene precursors where the silicon bears two *iso*-propyl groups, in order for the resulting oxasilacycles to be cleavable.

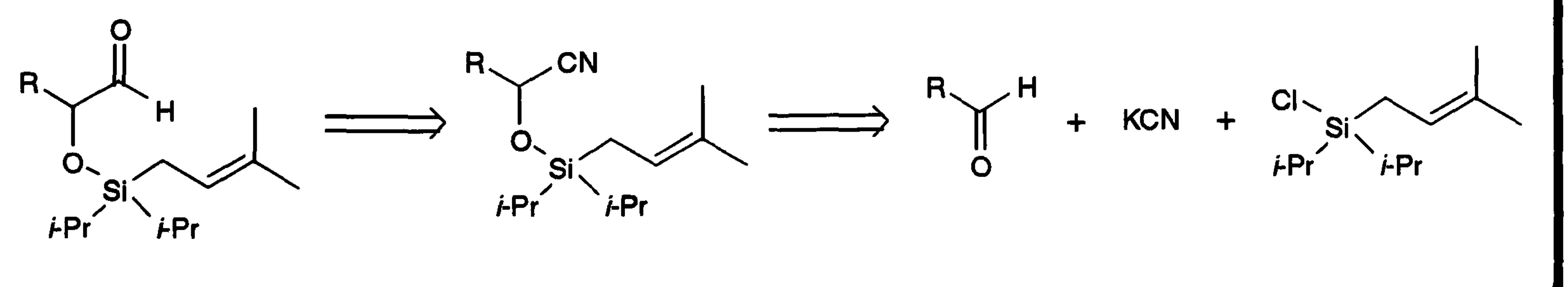
We were also interested in developing a synthetic route which would avoid stannane intermediates; the use of tin is becoming unfavourable in synthesis due to its inherent toxicity, and problems associated with its removal during purification.

This project continues work pioneered by the Robertson group into *O*-linked silicon tethered Type I ene cyclisations,[80] with an overall objective to apply the optimised methodology to the stereoselective synthesis of non-natural carbohydrates.

2.1 New routes to ene precursors

The previous method utilised by our group to synthesise prenylsilanes proceeded *via* formation of prenyllithium *in situ* from a stannane precursor, which in turn is derived from the reaction of prenylmagnesium chloride with a stannyl chloride.[80] Considering the drawbacks associated with stannane intermediates an alternative method for preparing the prenyl silyl substrates was sought.

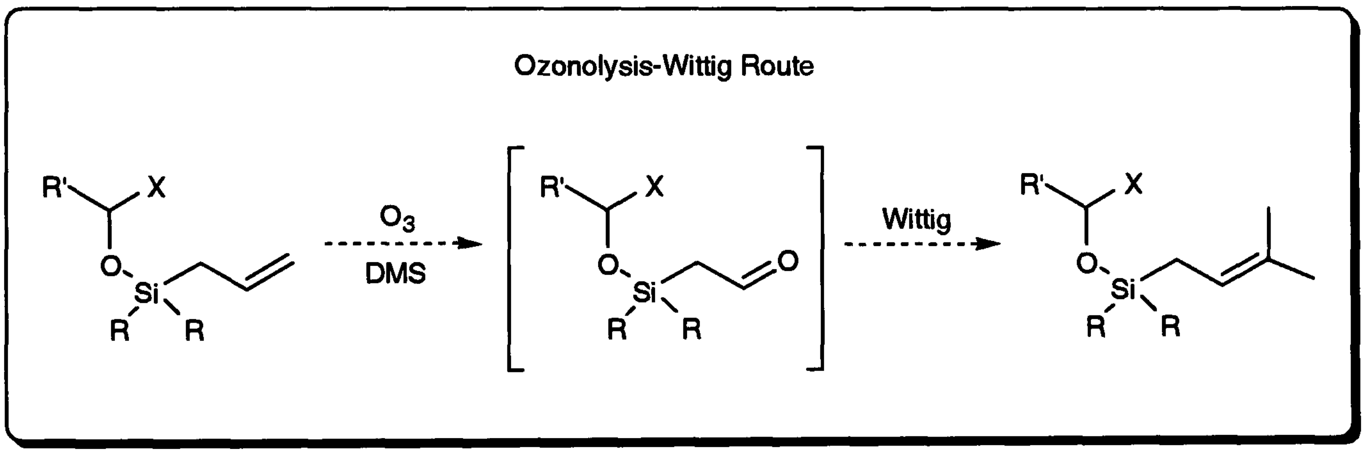
Our first objective was to develop a practical synthetic route for the assembly of the two halves of the ene precursor on a silicon tether bearing two *iso*-propyl groups. It was envisaged that this could be achieved by adapting a method precedented by Cava *et al.* based on silyl cyanohydrin chemistry (Scheme 2.04).[84] This protocol would allow access to the ene precursor in just two steps, after routine reduction of the nitrile moiety.



Scheme 2.04

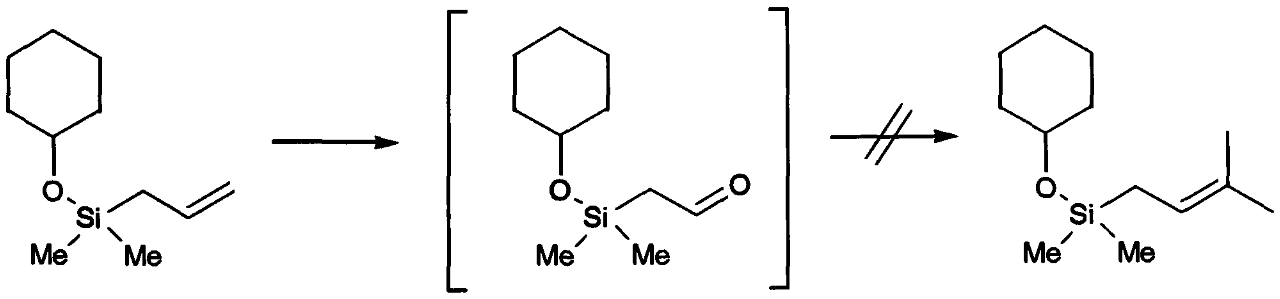
Before the cyanohydrin chemistry could be attempted it was necessary to prepare prenyldi(*iso*-propyl)silyl chloride as the silicon component. Initial investigations commenced with the generation of prenyl Grignard, followed by *in situ* trapping with a chlorosilane. Unfortunately this approach failed, with test reactions employing TBSCl resulting in the formation of the prenyl dimer and TBS-prenyl transfer product.[85]

An alternative strategy was based on the idea of obtaining prenyl silanes from more readily accessible allylsilyl substrates. It was envisaged that allylsilanes could be ozonised *in situ* to form α-silyl aldehyde intermediates; subsequent installation of the *iso*-propyl component *via* Wittig olefination would furnish the desired prenyl substituent on the silicon tether (Scheme 2.05).[86]

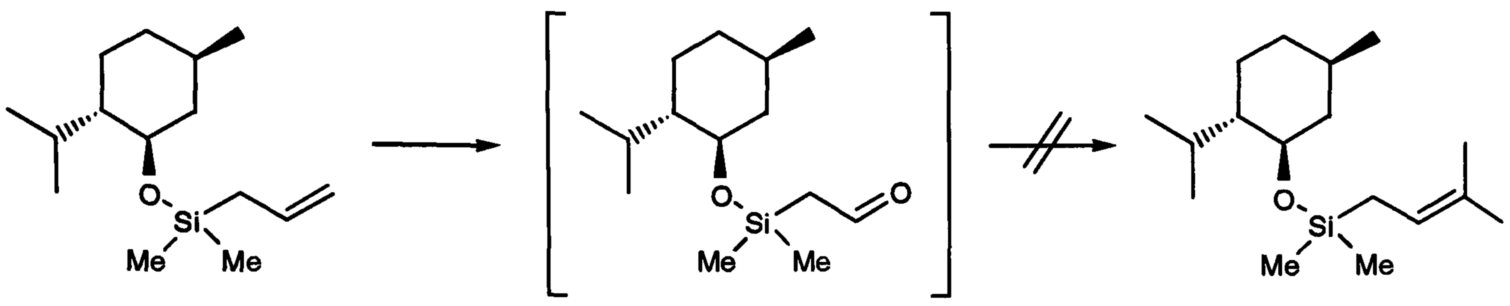


Scheme 2.05

Exploratory model studies with commercially available allyl(dimethyl)chlorosilane, coupled to cyclohexanol or menthol, failed to generate the desired products (Scheme 2.06).



2.08 **2.09** **2.10**

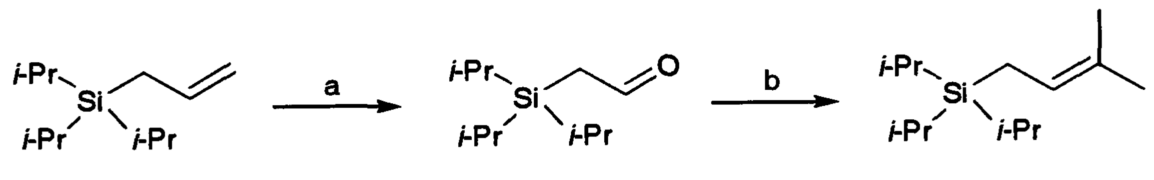


2.11 **2.12** **2.13**

O_3, DCM, -78 °C then DMS, -78 °C–0 °C; then $Me_2C{=}PPh_3$, -78 °C–RT.

Scheme 2.06

^{1}H NMR analysis of the multiple decomposition products provided some evidence of rearrangement of the fragile α-(alkyloxy)dimethylsilyl aldehyde to a silyl vinyl ether; we postulated that increasing the steric bulk around silicon might overcome this problem. Hence, subsequent work in this area concentrated on *iso*-propyl analogues (Scheme 2.07, Scheme 2.08). Model studies indicated that the ozonolysis-Wittig process does indeed work well when silicon bears relatively large alkyl substituents. Hence, allyl-TIPS (**2.14**) was successfully converted to prenyl-TIPS (**2.16**) in excellent yield. To our surprise the intermediate tri(*iso*-propyl)silanylacetaldehyde **2.15** was readily isolated and proved remarkably stable to chromatography on silica,[87] with 20% of the tri(*iso*-propyl)silanyloxyethene rearrangement product observed.

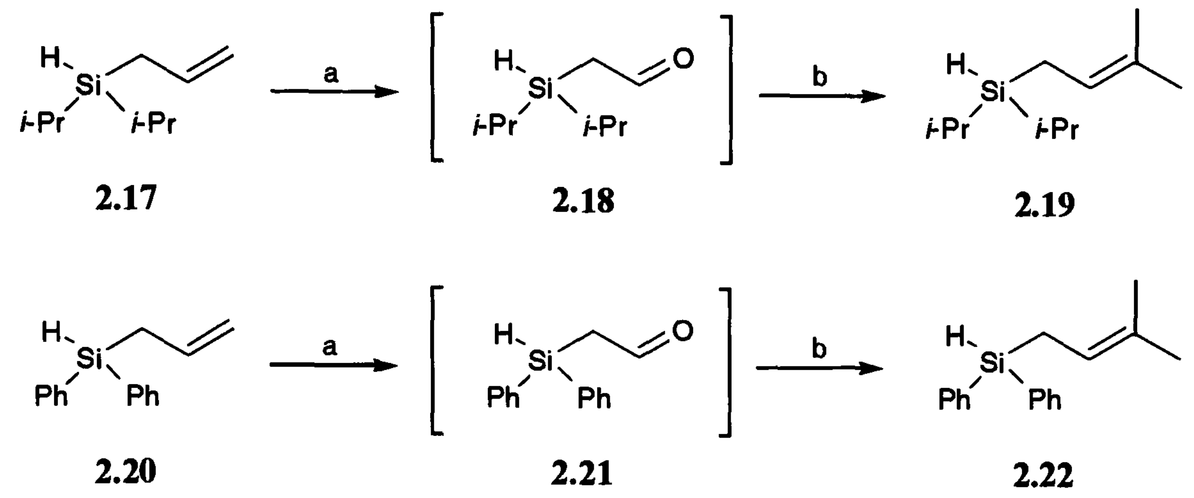


2.14 **2.15** **2.16**

a) O_3, DCM, -78 °C then DMS, -78 °C–RT (61%); b) $Me_2C{=}PPh_3$, -45 °C–RT (81%).

Scheme 2.07

As expected, reduction in steric bulk around silicon was accompanied by lower product yields; in the case of allyldi(*iso*-propyl)silane **2.17**, the prenyl derivative **2.19** was only isolated in 48% yield. The poor yield of **2.22** reflects the use of smaller, more electron withdrawing phenyl substituents leading to *in situ* decomposition of the intermediate silanylacetaldehyde (Scheme 2.08).

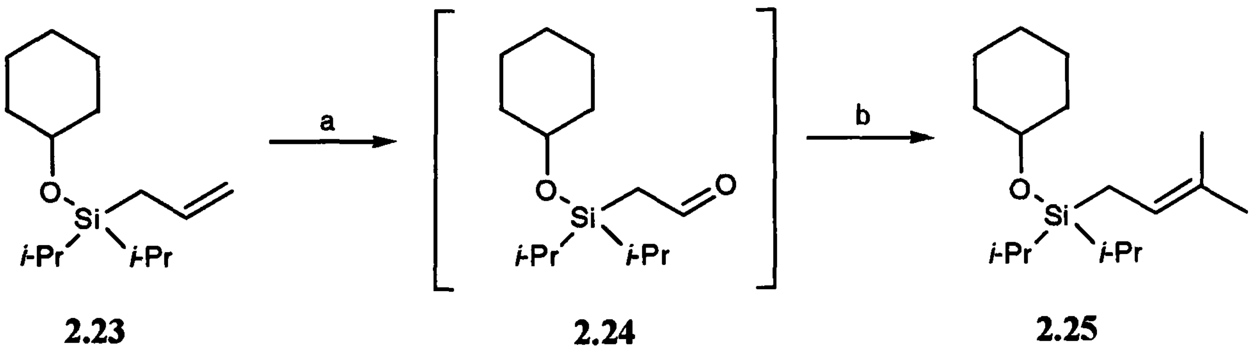


a) O_3, Sudan Red 7B, DCM, -78 °C then DMS, -78 °C–RT;

b) $Me_2C{=}PPh_3$, -45 °C–RT (**2.19** 48%; **2.22** 7%; two steps).

Scheme 2.08

The next objective was to re-introduce the silyl moiety bearing two *iso*-propyl substituents, with alkoxy functionality; this would provide a more exacting test of our ozonolysis-Wittig methodology. This was achieved *via* a one-pot procedure to generate cyclohexyloxyallylsilane **2.23** directly from di(*iso*-propyl)dichlorosilane; unfortunately this method was slightly hampered by competing generation of di(*iso*-propyl)diallylsilane (**2.27**). Silylation of cyclohexanol *in situ* produced model precursor **2.23** for our ozonolysis-Wittig chemistry, which proceeded in an unoptimised 50% yield (Scheme 2.09).

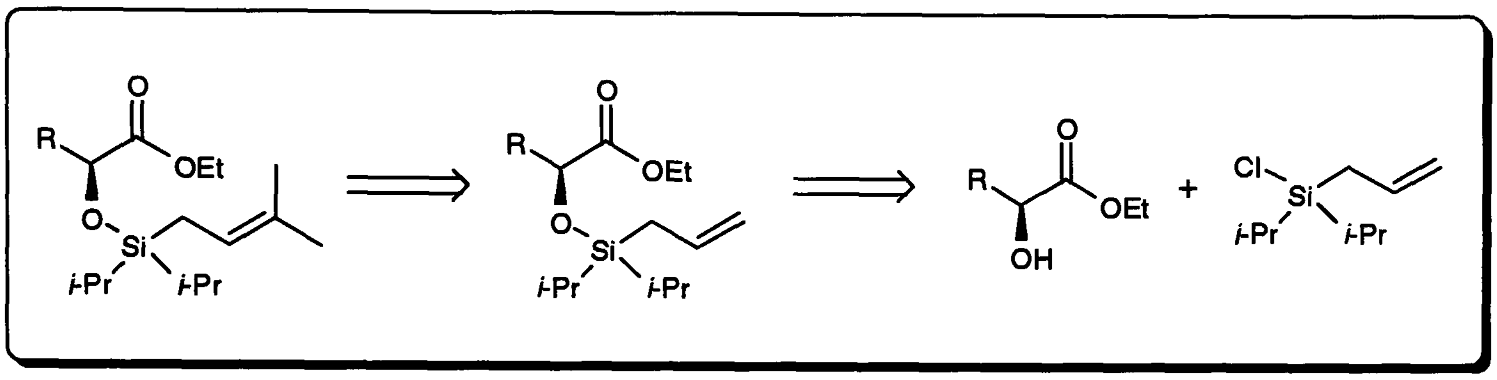


a) O_3, DCM, -78 °C then DMS, -78 °C–RT; b) $Me_2C{=}PPh_3$, -45 °C–RT (50% two steps).

Scheme 2.09

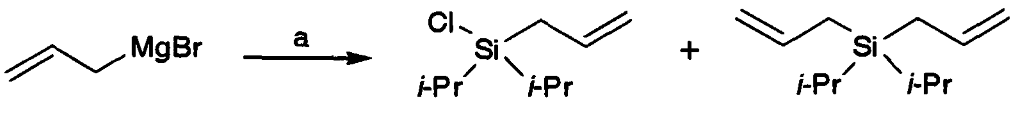
2.2 Di(*iso*-propyl)prenylsilyloxy system

Confident that the ozonolysis-Wittig route could be an effective way to construct the ene precursor, efforts focused on the application of this methodology to readily available α-hydroxy esters, which would be converted to the corresponding, enantiomerically pure, ene precursors after DIBAL reduction (Scheme 2.10).



Scheme 2.10

Our first approach was to repeat the one-pot procedure employed in the synthesis of alkoxy silane **2.23**; unfortunately this route was low yielding and again hampered by the generation of substantial quantities of the diallylsilane **2.27**. To circumvent this problem we attempted to isolate the desired allylchlorosilane **2.26** by Kugelrohr distillation but, this proved troublesome, producing a mixture of the mono and di-substituted allylsilanes which co-distilled (Scheme 2.11).

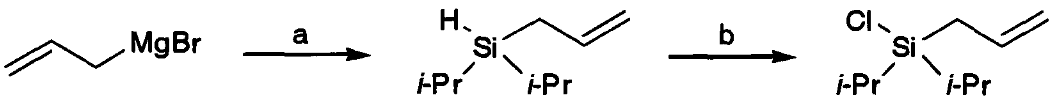


2.26 **2.27**

a) i-Pr_2SiCl_2, THF, -45 °C–RT (**2.26**:**2.27** = 5:2, 83%).

Scheme 2.11

The problem of di-addition was eventually overcome by following a stepwise approach to the required chlorosilane. The allyl component was attached *via* Grignard addition to di(*iso*-propyl)chlorosilane, followed by chlorination of the resulting hydrosilane, using a procedure adapted from Ishikawa's precedent.[88] The desired allylchlorosilane **2.26** was isolated as the sole product, in excellent yield, after reduced pressure distillation (Scheme 2.12). This two-step protocol subsequently became our method of choice for the preparation of substituted chlorosilanes.

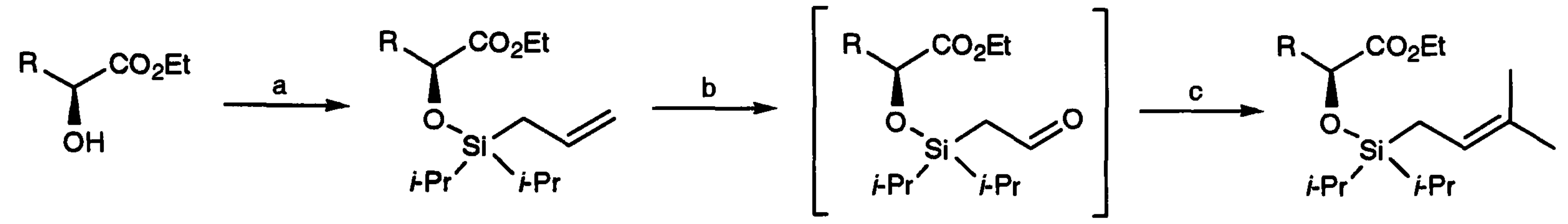


2.17 **2.26**

a) $i\text{-}Pr_2SiHCl$, THF, 0 °C–40 °C (99%); b) $CuCl_2$, CuI (cat.), THF, RT (98%).

Scheme 2.12

Subsequent silylation of (*S*)-ethyl lactate and (*S*)-ethyl mandelate (**2.28**) under standard conditions produced the requisite precursors for the ozonolysis-Wittig chemistry. Unfortunately, attempts to install the *iso*-propyl unit in this way proved disappointing; evidence from the ^1H NMR spectra indicated substantial decomposition of the α-silyloxy ester precursors. The addition of Sudan Red 7B as an indicator during ozonolysis, to limit over oxidation,[89] did not improve matters greatly but did enable isolation of the desired prenyl-substituted substrate **2.33** albeit in very poor yield (Scheme 2.13).



2.28 R = Ph
2.29 R = Ph
2.30 R = Me
2.31 R = Ph
2.32 R = Me
2.33 R = Ph

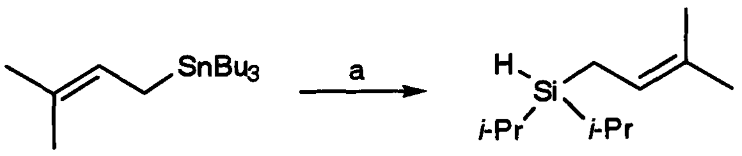
a) allyldi(*iso*-propyl)chlorosilane (**2.26**), TEA, DMAP (cat.), DMF, 80 °C (**2.29** 94%; **2.30** 87%);

b) O_3, Sudan Red 7B, DCM, -78 °C then DMS, -78 °C–RT; c) $Me_2C{=}PPh_3$, -45 °C–RT (**2.33** 18%; two steps).

Scheme 2.13

This disappointment was compounded by the fact that there was insufficient material available to carry forward to the ene studies. To by-pass the limitations of the ozonolysis-Wittig chemistry we opted to revert to a tin-assisted route in order to generate precursor **2.33** more efficiently.

Tributylprenyl stannane **2.34** was prepared employing Naruta's ultrasound-mediated Barbier procedure.[90] Transmetallation of the stannane with *n*-BuLi generated prenyllithium, which was trapped *in situ* by di(*iso*-propyl)chlorosilane. The desired prenylsilane **2.19** was isolated in good yield after separation from the tin residues by flash column chromatography on silica gel (Scheme 2.14).

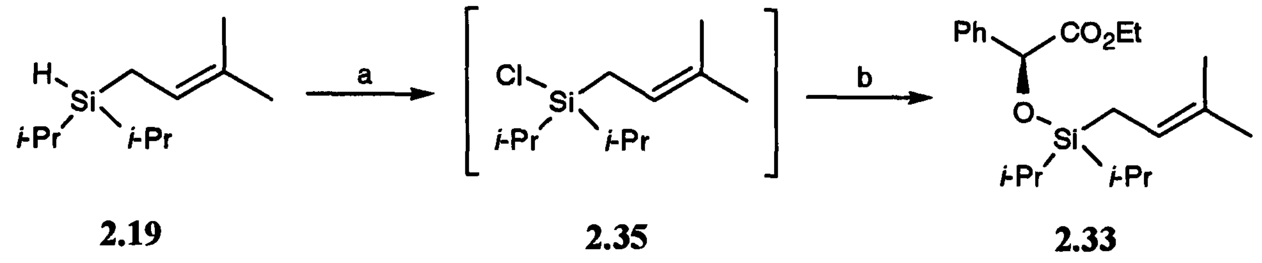


2.34 **2.19**

a) *n*-BuLi, -78 °C then i-Pr_2SiHCl, -78 °C–RT (85%).

Scheme 2.14

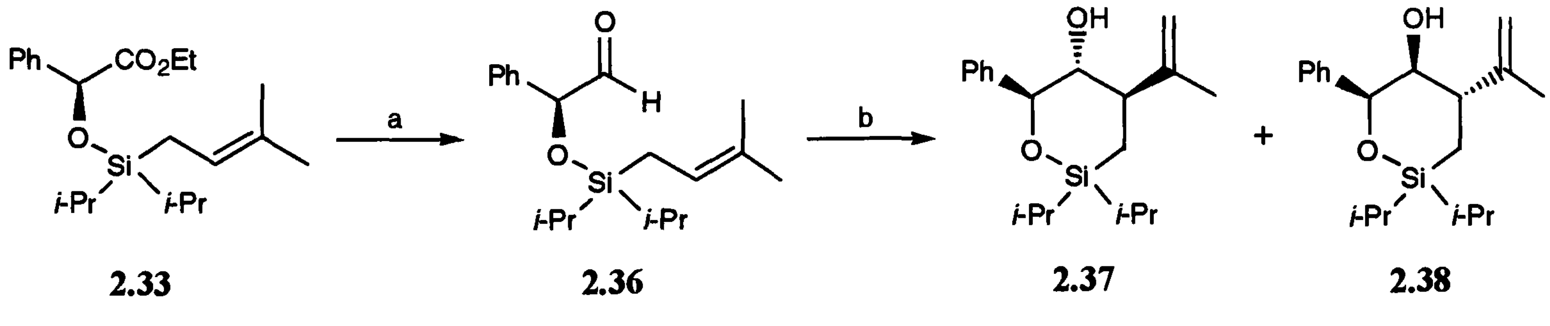
Prenyldi(*iso*-propyl)chlorosilane (**2.35**) was prepared *in situ* employing Ishikawa's copper-mediated chlorination protocol,[88] providing access to the desired α-silyloxy ester **2.33** in excellent yield (Scheme 2.15).



a) $CuCl_2$, CuI (cat.), THF, RT; b) (*S*)-ethyl mandelate (**2.28**), TEA, DMAP (cat.), DMF, 60 °C (81% two steps)

Scheme 2.15

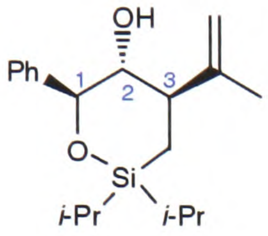
DIBAL reduction of ester **2.33** furnished a suitable precursor (**2.36**) for our ene studies. The ene reaction was carried out under the optimised conditions for cyclisation of *O*-linked systems, established previously within the group.[80,91] The DMAC-mediated cyclisation furnished two isolable ene products **2.37** and **2.38** (Scheme 2.16). ^1H NMR analysis of the crude reaction mixture indicated partial cleavage of the Si-O bond, which may explain, in part, the moderate reaction yield.



a) DIBAL, -78 °C (92%); b) Me_2AlCl, RT (43% and 9%).

Scheme 2.16

Coupling constant analysis and qualitative n.O.e. difference spectra of the major ene product **2.37** (Appendix 3) indicated a *trans* tri-equatorial disposition of the ring substituents; the CH(OH) resonance appeared as a double doublet (*J* 10.2 and 8.8 Hz), consistent with di-axial couplings to adjacent protons (Figure 2.01).



2.37

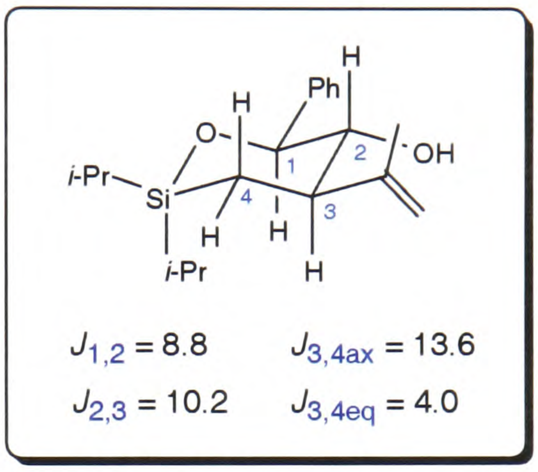
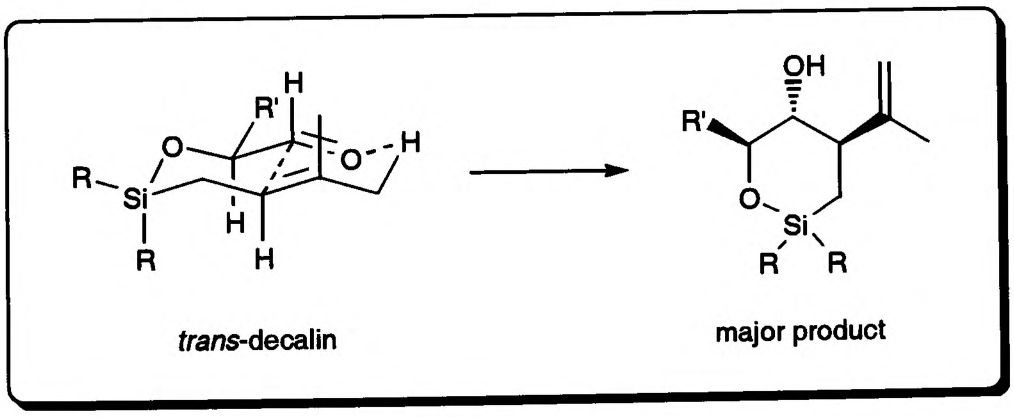


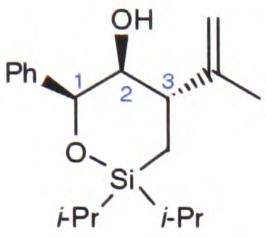
Figure 2.01

Formation of the major product can be rationalized in terms of preferential cyclisation through a *trans*-decalin like ene transition state, to generate a *trans,trans* oxasilacycle, where the ene and enophile components adopt a chair-like conformation, with bulky substituents lying in equatorial sites (Scheme 2.17).



Scheme 2.17

Qualitative n.O.e. difference spectra (Appendix 3) and coupling constant analysis of the minor ene product **2.38** suggested that the OH and vinyl groups occupy axial sites around the ring. Interestingly, ^{1}H-^{1}H constants for the C**H**(OH) resonance suggest distorted axial-equatorial (*J* 2.8 Hz) and equatorial-equatorial (*J* 6.8 Hz) couplings to neighbouring protons (Figure 2.02).



2.38

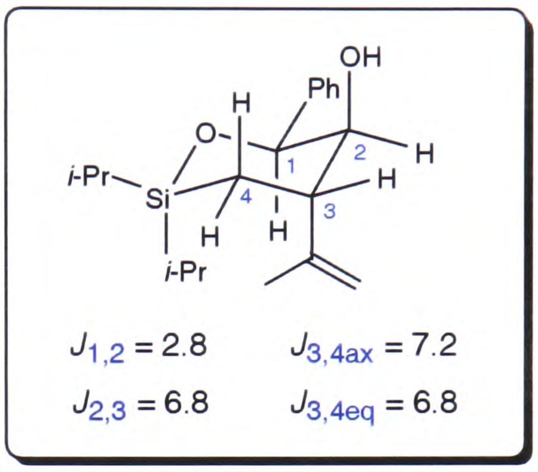


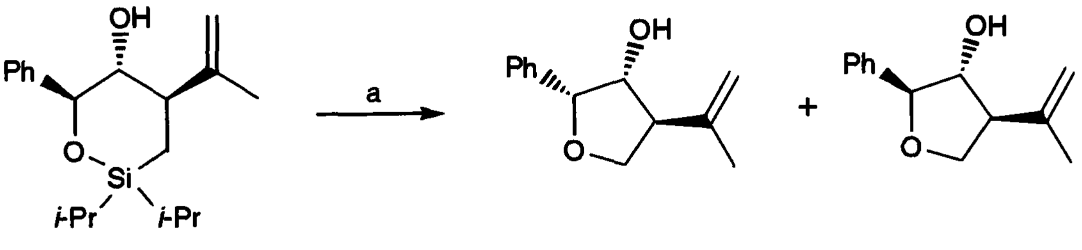
Figure 2.02

From the range of *O*-linked prenyl ene precursors, possessing α-phenyl substitution, investigated previously in our group, the *trans,trans* ene product was major in all cases (see Scheme 2.03). The stereochemistry of the minor ene product was more ambiguous, but had been assigned as the *cis,cis* isomer on the basis of an expected *cis*-decalin type transition state.[80]

Re-examination of those preliminary results suggested that the relative stereochemistry of the minor oxasilacycle may in fact vary depending on the silyl substituents.[81,92] The minor *cis,trans* product generated from Type I ene reaction of precursor **2.36** is consistent with this proposal, suggesting that the reaction may proceed through a more open transition state or perhaps through a chair-boat conformation. The exact reasons for distortion in the transition state, which would account for the observed stereochemistry of **2.38**, remain unclear. It is possible that the bulky *iso*-propyl substituents on silicon would have some bearing on the outcome of the reaction.

With **2.37** in hand, the next objective was to effect oxidative cleavage of the silacyclohexanol. It is well established that silicon-carbon bonds, where silicon bears one or more electron withdrawing group(s), such as fluorine or oxygen, can be cleaved oxidatively under a variety of conditions to provide a hydroxyl moiety. In essence, selective cleavage requires a fluoride ion source to activate silicon and a peroxide to effect the Si-C oxidation. This process has been the focus of study of several groups and has been the subject of a recent review,[93] with the most notable contributions to the field made by Tamao and Kumada,[94] Fleming,[95] and more recently Woerpel.[96]

Oxidative cleavage of the Si-C bond of oxasilacycle **2.37** was performed under Tamao-Kumada conditions;[94] however, instead of furnishing the expected triol, the process yielded an inseparable mixture of diastereomeric tetrahydrofurans **2.39a** and **2.39b**, with 76% recovered starting material (Scheme 2.18). This unexpected result was later ascribed to the unintended use of acidic sodium hydrogensulfate during the aqueous work up.



2.37 **2.39a** **2.39b**

a) H_2O_2, KF, $KHCO_3$, MeOH-THF, Δ (**a**:**b** = 2:1, 19%).

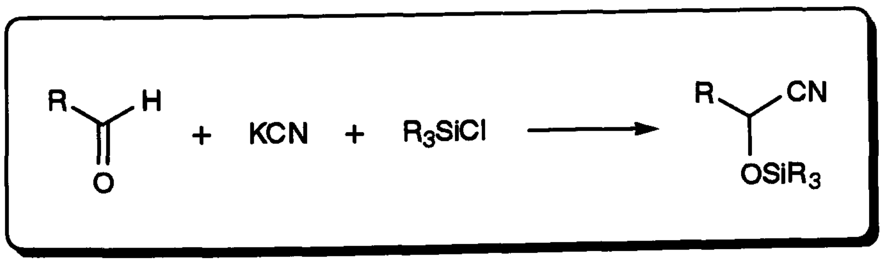
Scheme 2.18

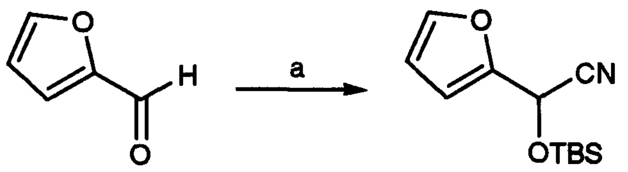
The diastereomeric ratio of **2.39** was determined from the 500 MHz ^{1}H NMR spectrum and was observed to be 2:1 in favour of **2.39a**. The stereochemical assignment was made on the basis of qualitative n.O.e. data (Appendix 3).

At this point we decided to move away from the α-silyloxy ester systems towards more robust silylcyanohydrin-based substrates, returning to our original proposal of adapting Cava's literature protocol (see Scheme 2.04).[84] Although Cava's route is not asymmetric, the primary purpose was to investigate the viability of the one-pot process and subsequently to explore the behaviour of the silylcyanohydrin substrates under the ozonolysis-Wittig conditions.

Cava has limited his study of this reaction to bulky, commercially available, chlorosilanes for the preparation of *O*-trialkylsilyl cyanohydrins;[84] our initial task was to extend this work by examining the ability of allylchlorosilane **2.26** to partake in a similar process.

Investigations commenced with test reactions performed with commercially available aldehydes and chlorosilanes (Table 2.01). To our surprise the reactions would not complete, even with prolonged reaction times, when performed under the conditions described by Cava *et al.*[84] Elevating the temperature appeared to have no beneficial effect; modifications with added 18-crown-6[97] or lithium ethoxide[98] did not improve matters greatly. Changing the reaction solvent did have some bearing on the progress of the reaction; with the use of a less polar solvent such as DCM the yield of **2.40** improved, but we were still unable to drive the reaction to completion (Scheme 2.19).





2.40

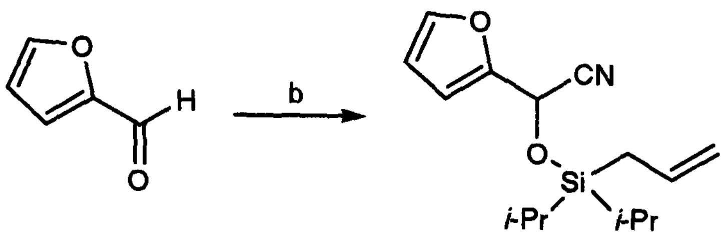
a) TBSCl, KCN.

Scheme 2.19

Aldehyde	Chlorosilane	Solvent	Conditions	Yield %
Benzaldehyde	TIPSCl	MeCN	ZnI_2 (cat.), 40 hr, RT	not isolated
“	“	“	ZnI_2 (cat.), 44 hr, RT–70 °C	“
“	TBSCl	“	ZnI_2 (cat.), 22 hr, RT	“
“	“	“	ZnI_2 (cat.), 44 hr, RT–70 °C	“
2-Furaldehyde	“	“	ZnI_2 (cat.), 23 hr, RT	16 (**2.40**)
“	“	“	ZnI_2 (cat.), 20 hr, 70 °C	15
“	”	“	ZnI_2 (cat.), 43 hr, RT–70 °C	10
“	“	“	18-crown-6, 72 hr, RT	39
“	“	“	LiOEt, 48 hr, RT	34
“	“	“	ZnI_2 (cat.),))), 23 hr, RT	29
“	“	“	ZnI_2 (cat.),))), 70 hr, RT	40
“	“	DMF	ZnI_2 (cat.),))), 75 hr, RT	38
“	“	DCM	ZnI_2 (cat.),))), 27 hr, RT	32
“	”	“	ZnI_2 (cat.),))), 70 hr, RT	58
“	”	THF	ZnI_2 (cat.),))), 76 hr, 25 °C	92

Table 2.01

The problem was eventually alleviated when acetonitrile was substituted for THF, as in Kurihara's comparable protocol which employed LiCN in the absence of a Lewis acid catalyst.[99] Initial sonication of the reaction mixture was also found to assist the dissolution of KCN (Scheme 2.20).

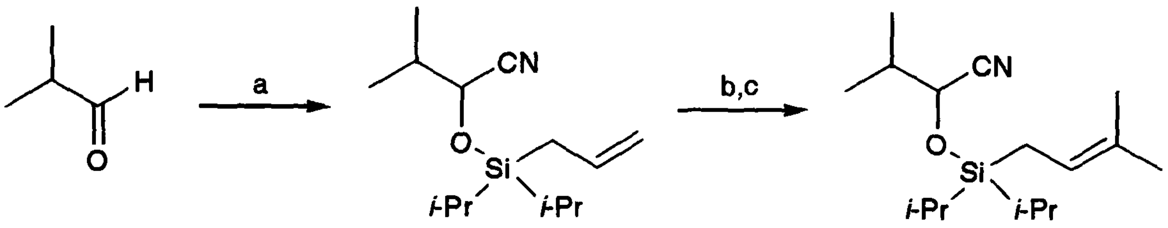


2.41

a) allyldi(*iso*-propyl)chlorosilane (**2.26**), KCN, ZnI_2 (cat.),))) THF, 90 hr, 25 °C (78%).

Scheme 2.20

With the silylcyanohydrin protocol optimised, allyldi(*iso*-propyl)chlorosilane (**2.26**) was employed to generate **2.42** from *iso*-butyraldehyde. The ozonolysis-Wittig sequence was performed, with limited success, to construct the desired prenyl tether (Scheme 2.21).



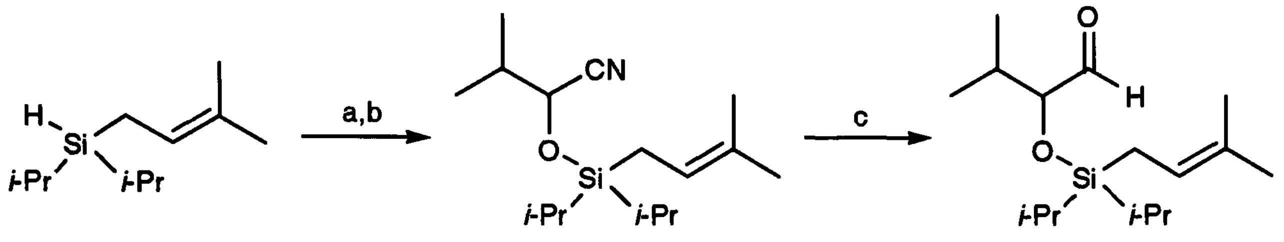
2.42 **2.43**

a) allyldi(*iso*-propyl)chlorosilane (**2.26**), KCN, ZnI_2 (cat.),))) THF, 50 hr, 25 °C (85%);

b) O_3, Sudan Red 7B, DCM, -78 °C then DMS, -78 °C–RT; c) $Me_2C{=}PPh_3$, -45 °C–RT (36% two steps).

Scheme 2.21

As in the synthesis of α-silyloxy substrate **2.33**, the silylcyanohydrin precursor (**2.43**) could also be prepared more efficiently by recourse to prenylsilane **2.19** (prepared *via* a tin-assisted route). Subsequent DIBAL reduction furnished the ene precursor in satisfactory yield (Scheme 2.22).[100]



2.19 **2.43** **2.45**

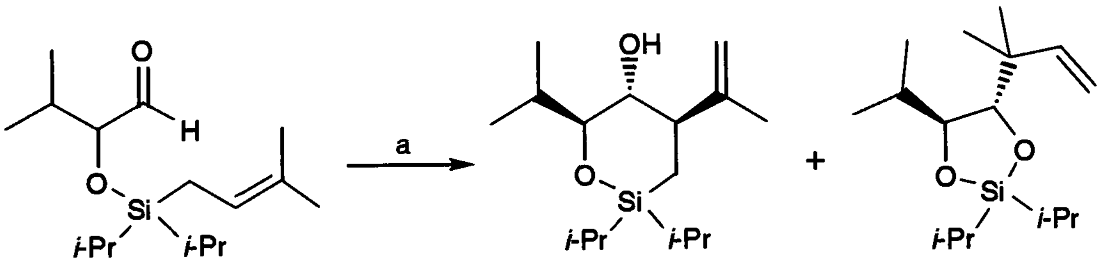
a) $CuCl_2$, CuI (cat.), THF, RT;

b) 2-hydroxy-3-methylbutyronitrile (**2.44**), TEA, DMAP, DCM, RT (83% two steps);

c) DIBAL, -78 °C (64%).[101]

Scheme 2.22

Substrate **2.45** (α-substituent = *i*-Pr) was expected to react in an analogous fashion to ene precursor **2.36** (α-substituent = Ph); however, treatment of **2.45** with DMAC at RT revealed an interesting mode of reactivity. The cyclisation generated just one isolable ene product **2.46**, accompanied by a novel silacycle which showed peaks in its 400 MHz ^1H NMR spectrum indicative of a terminal vinylic group. This compound was later identified as the siladioxolane **2.47** resulting from intramolecular allylic transfer (Scheme 2.23).



2.45 **2.46** **2.47**

a) Me_2AlCl, RT (37% and 39%).

Scheme 2.23

The ene product was confirmed as the expected *trans,trans* cyclic siloxane by 400 MHz ^1H NMR coupling constant analysis and quantitative n.O.e. data (Figure 2.03, Table 2.02).

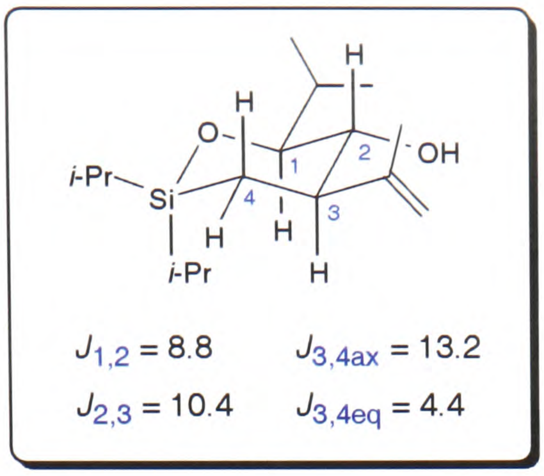


Figure 2.03

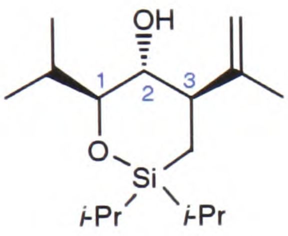
		Enhancement %				
	Irradiate	H^1	H^2	H^3	$=\mathbf{CH_2}$	$C(\mathbf{CH_3})=$
	H^2	1.1	-	0.9	1.0	6.8
	H^3	6.8	1.2	-	5.3	3.4
	$=\mathbf{CH_2}$	0.0	0.9	3.9	-	3.2
2.46	$C(CH_3)=$	0.5	5.6	2.5	4.0	-

Table 2.02

The relative stereochemistry of siladioxolane **2.47** was assigned with the aid of quantitative n.O.e. data (Table 2.03).

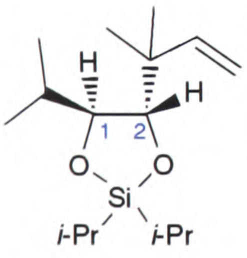
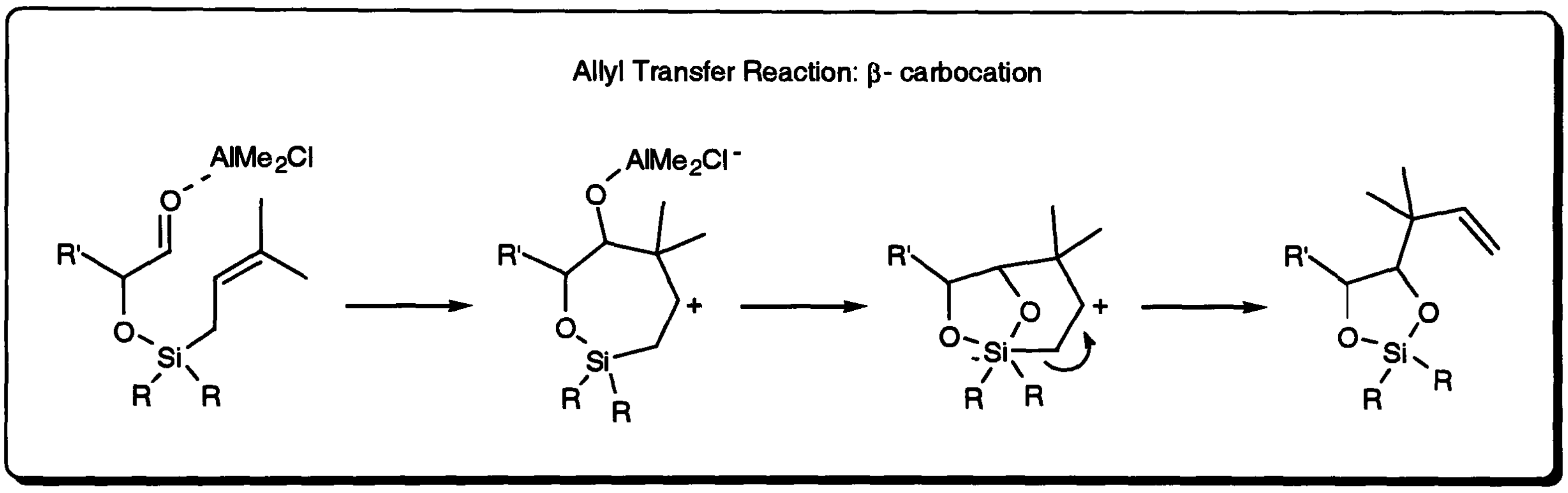
		Enhancement %						
	Irradiate	H^1	H^2	$\mathbf{CH}{=}CH_2$	$CH{=}\mathbf{CH_2}$	$C(\mathbf{CH_3})_2$	$\mathbf{CH}(CH_3)_2$	$CH(\mathbf{CH_3})_2$
	H^1	-	2.5	1.8	0.7	6.0	3.2	3.8
2.47	H^2	1.3	-	2.5	0.2	5.8	3.1	4.4

Table 2.03

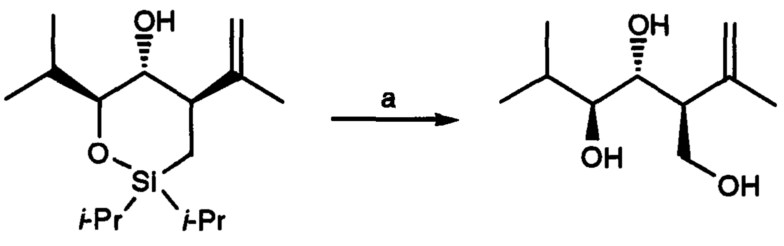
This intriguing result suggested that allylic transfer operates in competition with the ene cyclisation and could possibly account for the moderate mass balance observed in previous ene studies.[80]

At the time, we postulated that the ability of precursor **2.45** to stabilise a build up of positive charge β- to silicon may account for the competitive allyl transfer reaction in the presence of DMAC (Scheme 2.24). Considering the similarity of substrates **2.36** and **2.45** it is difficult to propose a satisfactory explanation for their dichotomous behaviour under identical DMAC-mediated ene conditions. Interestingly, later work suggested that the allyl transfer process could proceed efficiently in the absence of a Lewis acid catalyst.



Scheme 2.24

Cleavage of the Si-C bond of silacyclohexanol **2.46** was attempted initially under Tamao-Kumada conditions,[94] but this failed to yield any of the desired product, returning starting material after 3 days at reflux. Oxidative cleavage was then performed under Woerpel's more forcing conditions,[96] with limited success, furnishing triol **2.48** in just 22% yield (Scheme 2.25).



2.46 **2.48**

a) TBHP, DMF, 0 °C then $CsOH.H_2O$, TBAF, RT–70 °C (22%).

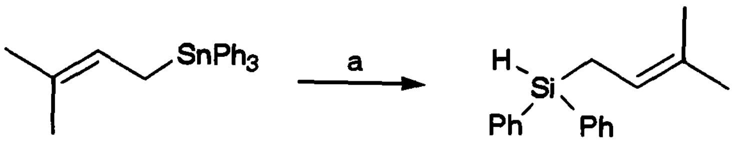
Scheme 2.25

The poor yield obtained from this conversion was attributed to the steric hindrance of the two bulky *iso*-propyl substituents impeding nucleophilic attack at silicon, and to decomposition of the ene product under the harsh basic reaction conditions.

2.3 Diphenylprenylsilyloxy system

Considering the poor results obtained from the oxidative cleavage of di(*iso*-propyl)silyl derivatives **2.37** and **2.46**, we set out to prepare less sterically encumbered diphenylsilyl ene precursors. Fleming has shown that phenyl-substituted silanes succumb readily to oxidative cleavage.[95] It was hoped that phenyl substituents would confer the appropriate balance of effective size and electronic activation, leading to an improvement in the conversion of the ene product to the desired triol.

Resigned to the fact that we could not efficiently circumvent the use of tin during the synthesis of the requisite prenylsilyl ene precursors, the diphenylsilane was prepared directly from the prenylstannane. Use of triphenylstannane **2.49** was found to be superior to tributylstannane **2.34**, enabling facile separation of the non-polar silane from the tin residues.[102] Prenyl(diphenyl)silane **2.22** was isolated in excellent yield following addition of prenyllithium to diphenylchlorosilane (Scheme 2.26). Addition of TMEDA to the reaction mixture proved detrimental, leading to predominant formation of the di-substituted silane, *via* displacement of the silyl hydride by the organolithium.[103]

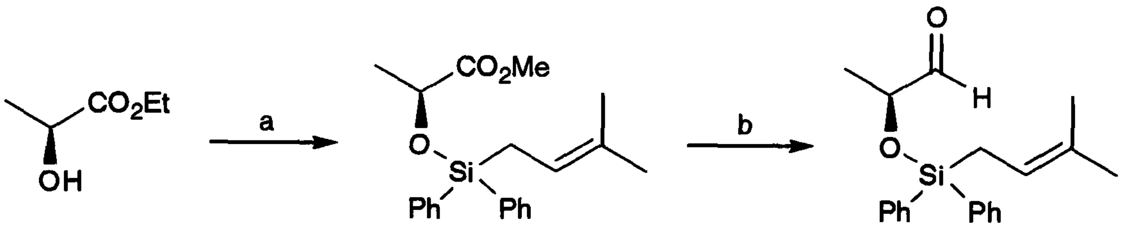


2.49 **2.22**

a) *n*-BuLi, -78 °C then Ph_2SiHCl, -78 °C–RT (97%).

Scheme 2.26

At this time we became aware of Piers' use of a borane Lewis acid catalyst to activate silanes for the reduction of carbonyls and for the silylation of hindered hydroxyls.[104] Concurrent work within the group demonstrated that the tris(pentafluorophenyl)borane catalyst could be employed to couple allylsilanes to α-hydroxy esters readily, with no apparent detriment to the allylic substituent.[80] Consequently this approach was adopted for the preparation of **2.50** from commercially available (*S*)-ethyl lactate (Scheme 2.27).

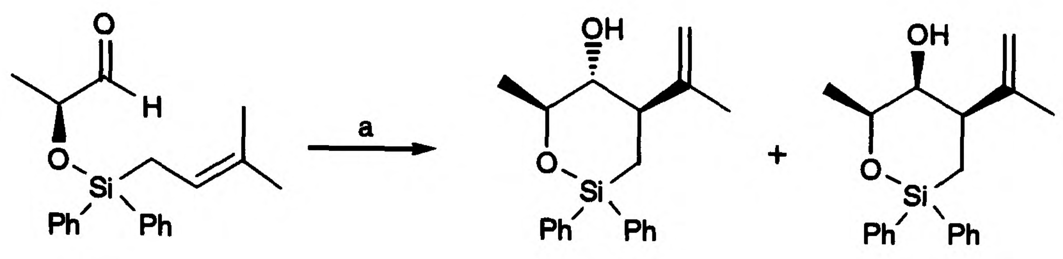


2.50 **2.51**

a) prenyl(diphenyl)silane (**2.22**), $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (70%); b) DIBAL, -78 °C (61%).

Scheme 2.27

Ene cyclisation of aldehyde **2.51** proceeded smoothly under our standard DMAC-mediated conditions to afford the separable, diastereomeric, silacyclohexanols **2.52** and **2.53**, free of allyl transfer products (Scheme 2.28).



2.51 **2.52** **2.53**

a) Me_2AlCl, RT (48% and 5%).

Scheme 2.28

The stereochemistry of both the major and minor ene products was initially assigned on the basis of their 400 MHz ^1H NMR spectra and supporting n.O.e. data (Figure 2.04 and Figure 2.05). Reassuringly, the major product appeared analogous to the *trans,trans* oxasilacyles obtained from the cyclisation of di(*iso*-propyl)silyl ene precursors **2.36** and **2.45**.

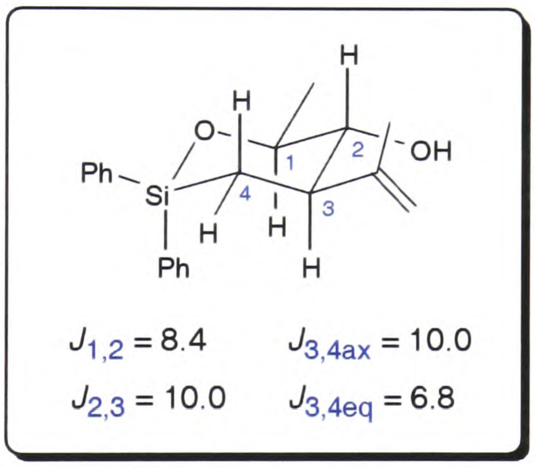


Figure 2.04

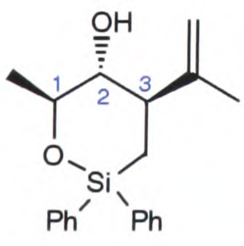
		Enhancement %					
	Irradiate	H^1	H^2	H^3	$=CH_2$	$C(CH_3)=$	$CH(CH_3)$
 **2.52**	H^1	-	1.0	5.6	0.0	0.0	2.2
	H^2	2.3	-	2.3	1.5	10.3	3.9
	H^3	7.1	1.5	-	3.9	0.0	0.0

Table 2.04

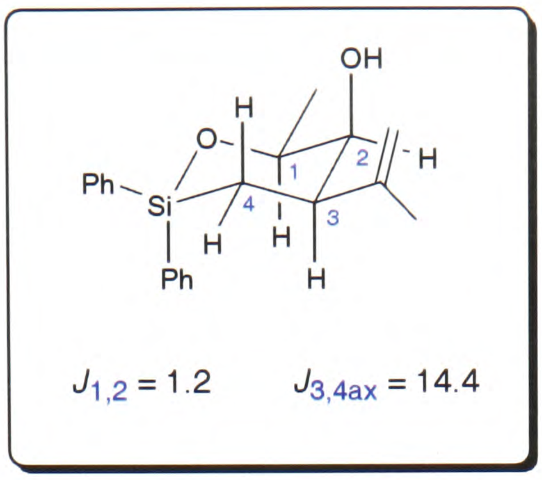


Figure 2.05

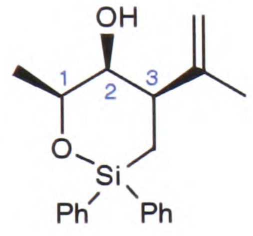
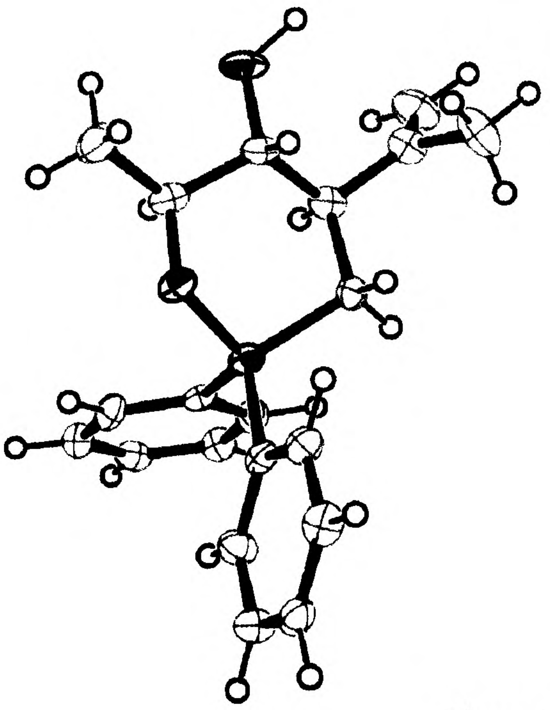
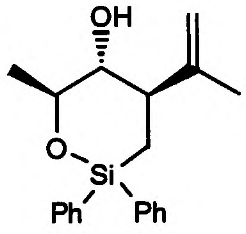
		Enhancement %					
	Irradiate	H^1	H^2	H^3	$=CH_2$	$C(CH_3)=$	$CH(CH_3)$
 **2.53**	H^1	-	8.4	8.5	0.0	0.0	3.3
	H^2	7.8	-	6.4	0.7	5.7	3.3
	H^3	8.2	6.5	-	1.9	6.0	0.0

Table 2.05

Our stereochemical assignment of **2.52** was later confirmed by single crystal X-ray analysis (Figure 2.06 and Appendix 1).

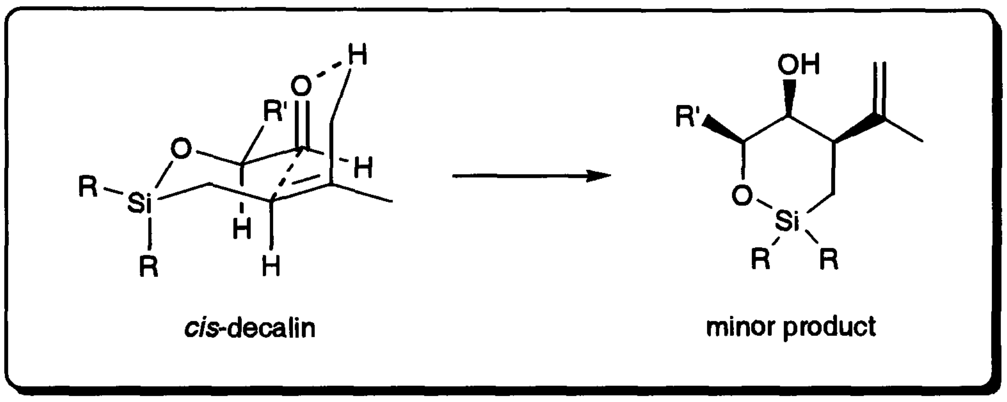




2.52

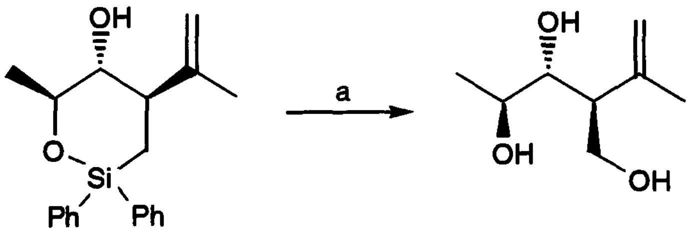
Figure 2.06

Interestingly, the minor product gained from ene cyclisation of precursor **2.51** is consistent with cyclisation through a *cis*-decalin type transition state (Scheme 2.29). This preference for the *cis,cis* isomer (compared to *cis,trans* isomer **2.38**) would appear to result from the diphenyl-substitution of the ene precursor. Furthermore, the electron withdrawing nature of these substituents reduces the ability of silicon to stabilise positive charge at the β-position, which disfavours the allyl transfer process. The relative size of the α-substituent may also be a contributing factor; compared to phenyl (**2.36**) or *iso*-propyl (**2.45**) substituents the small α-methyl group of precursor **2.51** would present minimal $A^{1,3}$ strain (consistent with the Houk model) favouring cyclisation through the *cis*-decalin pathway.



Scheme 2.29

Pleasingly, oxidative cleavage of the major silacyclohexanol **2.52**, under Tamao-Kumada conditions, proceeded more readily than the related di(*iso*-propyl)silyloxy derivatives to afford the desired triol **2.54** in excellent yield (Scheme 2.30).



2.52 **2.54**

a) H_2O_2, KF, $KHCO_3$, MeOH-THF, RT (88%).

Scheme 2.30

2.4 Conclusions

We have examined a variety of routes to *O*-linked silicon tethered ene precursors and assessed the ability of these substrates to undergo stereoselective ene cyclisation. In the course of these studies we observed a competing allyl transfer process; this course of reactivity is reported on further in Chapter 3.

Our investigations have demonstrated that phenyl substituents on silicon ease oxidative cleavage of the ene product, allowing efficient access to stereodefined triols. It is hoped that the four-step sequence developed for the synthesis of **2.54** can be extended to incorporate more elaborate functionality.

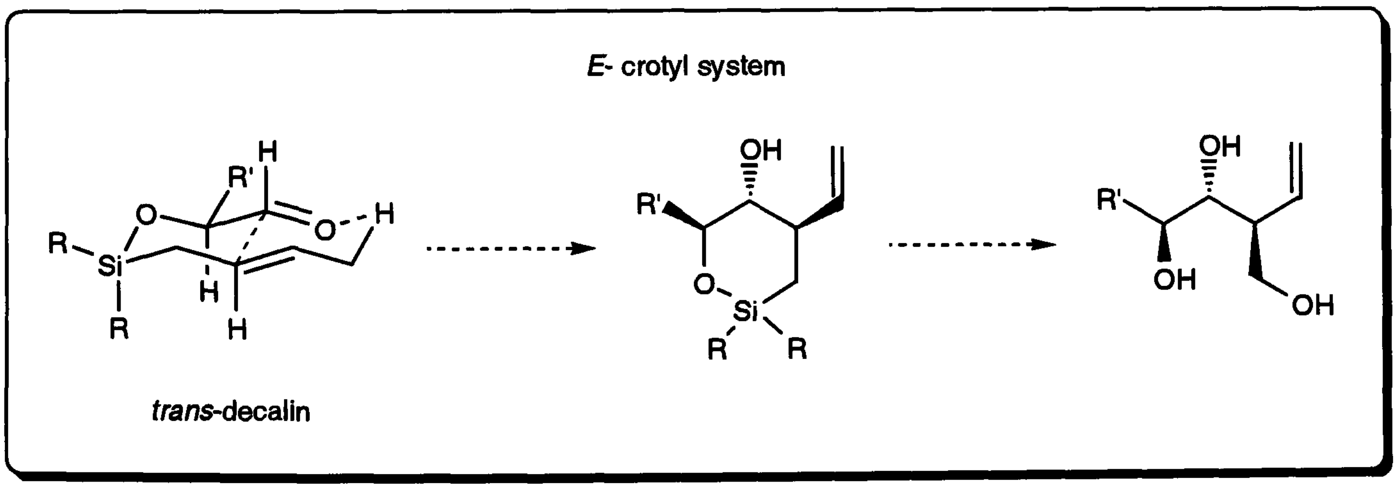
Chapter 3

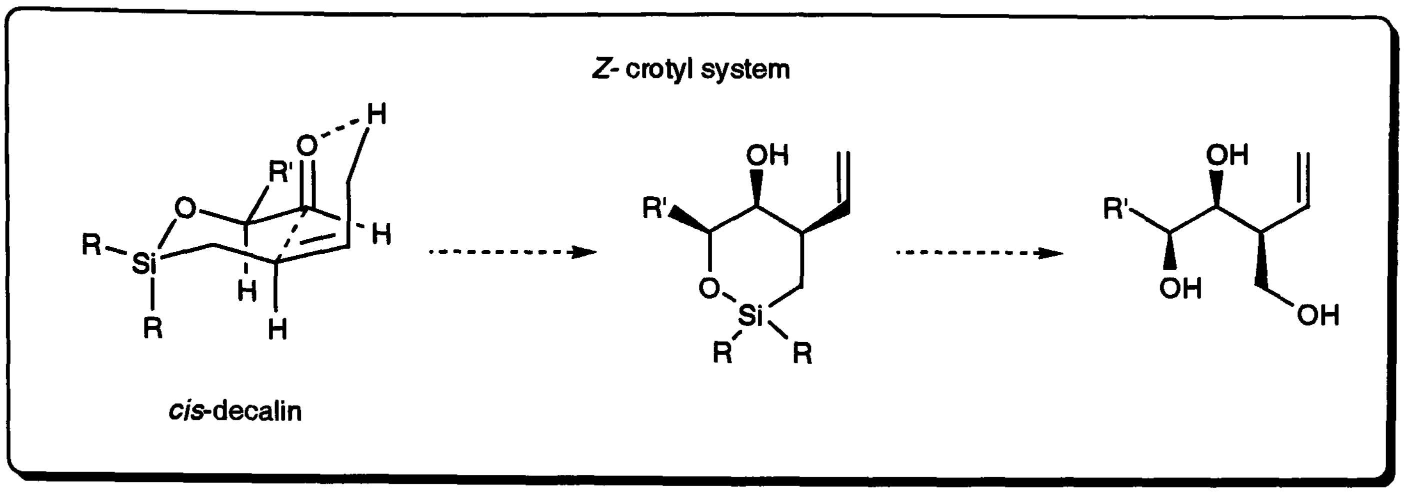
Synthesis and Investigation of Functionalised Side Chain

3.0 Introduction

Prior to this point all the *O*-linked substrates possessed inert side chains, merely for synthetic expediency, therefore it was of interest to study the compatibility of side chain functionality with the ene cyclisation.

A parallel area of interest concerned silicon tethered crotyl systems which, in principle, would enable stereospecific access to ene cyclised products. In Chapter 2 the major and minor ene products arising from prenyl substrate **2.51** could be ascribed to proton abstraction from either the *E*- or *Z*- methyl group respectively. Moving to a crotyl system should limit access to either the *trans,trans* or *cis,cis* oxasilacycle depending on the geometry of the crotyl substituent (Scheme 3.01). The *E*-crotyl substrate should cyclise preferentially through a *trans*-decalin type transition state; the *Z*-crotyl substrate through a *cis*-decalin-like conformation, generating either *anti,anti* or *syn,syn* triols after oxidation of the intermediate oxasilacycles.





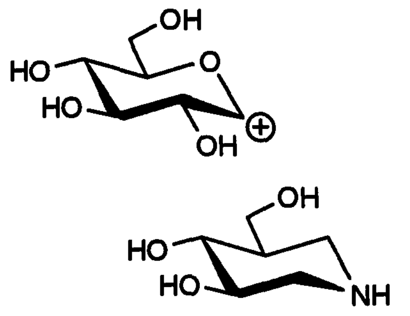
Scheme 3.01

In view of the fact that, at the time, preliminary investigations of crotyl systems had recently been initiated within the group,[80] it seemed logical to incorporate both these objectives within a targeted carbohydrate synthesis; a suitable precursor would combine a tethered crotyl silane, capable of exploiting the ordered transition state arrangement of the ene cyclisation, with latent functionality in the form of a suitably protected side chain.

Our silicon tethered ene methodology has the potential to facilitate an array of carbohydrate syntheses, including branched sugars and *C*-linked disaccharides. The incorporation of nitrogen into the *O*-linked systems had not been previously explored and it was hoped that such an approach would bring diversity to our silicon tethered ene chemistry. Thus, an initial area of investigation was concerned with the synthesis of non-natural iminosugars as potential glycosidase inhibitors.[105,106]

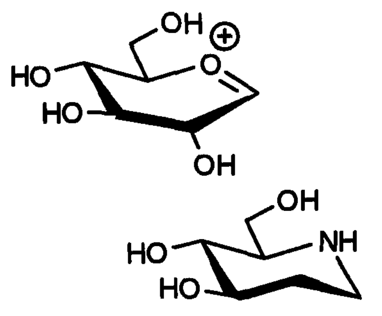
3.1 Attempted isofagomine synthesis

The potent glycosidase inhibitor isofagomine was selected as our first target (Figure 3.01).[107] Compounds of this type, capable of accepting positive charge at the anomeric position, act as effective transition state mimics during enzymatic glycosylation, binding to the glycosidase by imitating the shape and partial charge of the intermediate formed during glycosidic bond cleavage.[107] The naturally occurring iminosugar fagomine (**3.02**) (Figure 3.02) mimics the oxonium ion intermediate formed during glycosylation and is only mildly active in this respect. In contrast its non-natural analogue isofagomine (**3.01**), first synthesised by Bols *et al.* in 1994, is an extremely powerful β-glucosidase inhibitor of the 1-*N*-iminosugar class and has been identified as a possible therapeutic agent for Type II diabetes (K_i = 0.11 μM).[105-107]



3.01
(+)-Isofagomine

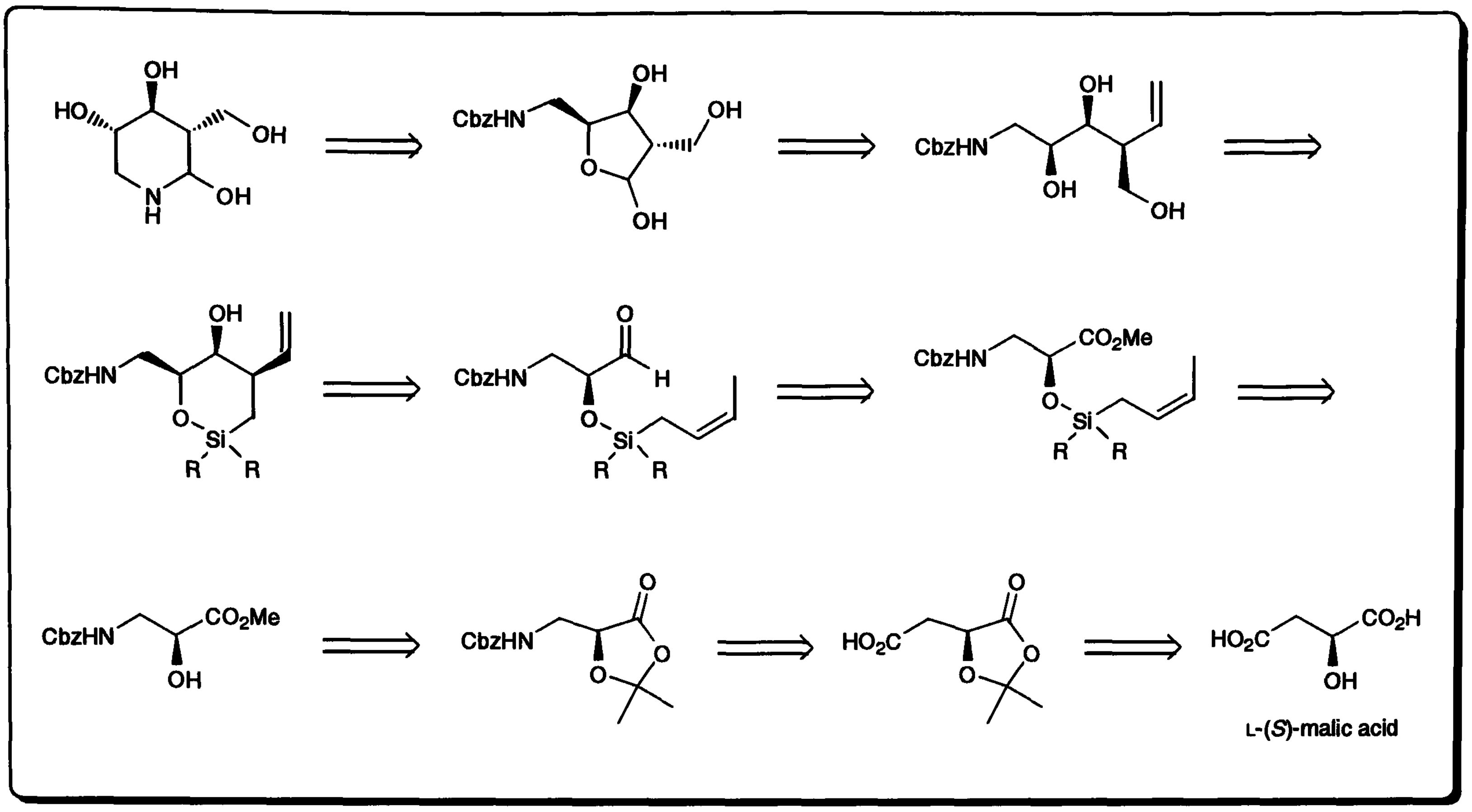
Figure 3.01



3.02
Fagomine

Figure 3.02

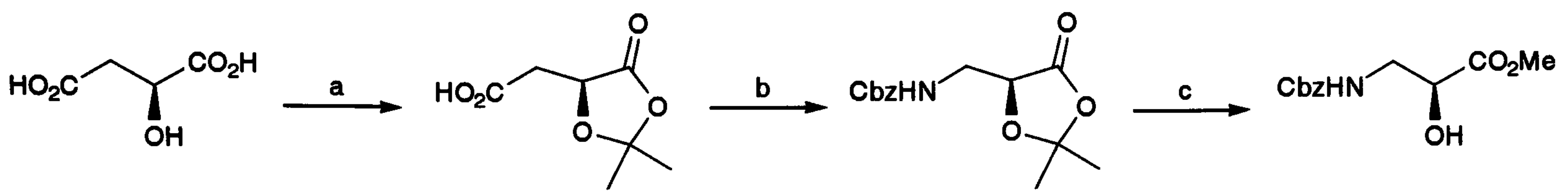
The conceived synthesis would allow access to the basic iminosugar unit in nine steps from the inexpensive starting material L-(*S*)-malic acid (Scheme 3.02). Reduction of the hemiaminal would generate (–)-isofagomine,[108] whereas elimination of the hydroxyl group would result in the formation of an iminoglycal, which may exhibit inherent biological activity.



Scheme 3.02

It was envisaged that the proposed route to isofagomine would prove sufficiently flexible to allow access to several stereoisomers, and various other iminosugar derivatives by analogous procedures, once the basic route had been completed and optimised.

Investigations commenced with the synthesis of isoserine derivative **3.05**, required as the 'enophile' component. Protection of L-(*S*)-malic acid was effected with 2,2-dimethoxypropane and catalytic CSA.[109] Conversion of the carboxylic acid moiety of **3.03** to the carbamate-protected isoserine acetonide (**3.04**) was achieved in one pot. Treatment with diphenyl phosphoryl azide generated the acyl azide, which underwent Curtius rearrangement spontaneously, under the reaction conditions, to the isocyanate. This reactive species was trapped *in situ* by benzyl alcohol to furnish the desired isoserine acetonide **3.04** in good yield. Subsequent acid catalysed methanolysis afforded the carbamate-protected isoserine ester **3.05** in good overall yield on a multi-gram scale (Scheme 3.03).



3.03 **3.04** **3.05**

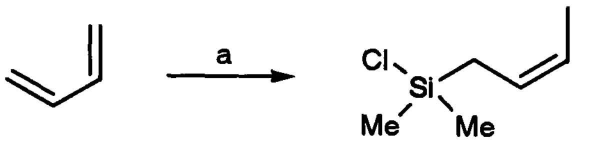
a) 2,2-DMP, CSA (cat.), RT (65%); b) DPPA, TEA then BnOH RT–70 °C, 16 hr (80%); c) MeOH, CSA (cat.), RT (85%).

Scheme 3.03

This approach is a more efficient version of the original step-wise Curtius procedure presented independently by Suzuki and Milewska.[110,111] A similar step-wise process has been developed by Burger *et al.* for the preparation of various *N*-protected hexafluoroacetonide derivatives.[112] It was hoped that our condensed route would, if required, prove sufficiently flexible to accommodate a range of alcohols, allowing a number of different carbamate protecting groups to be incorporated into the end product.

The preparation of Z-crotyl(dimethyl)chlorosilane (**3.06**) has literature precedent,[113] hence this silane was initially selected with some reservations concerning the minimal steric bulk around silicon and how this might influence the outcome of the ene reaction; previous studies with a dimethyl-substituted system had observed cleavage of the allyl substituent from the silane under the Lewis acidic conditions.[74] If this choice of silyl moiety proved capricious, methods for the preparation of the diphenyl-substituted silane would be explored as earlier work had indicated that phenyl substituents on silicon were beneficial in the oxidative cleavage step (Section 2.3).

In practice, nickel-catalysed hydrosilylation of butadiene with dimethylchlorosilane provided the *Z*-crotyl-substituted chlorosilane **3.06** in excellent yield (Scheme 3.04).[113]

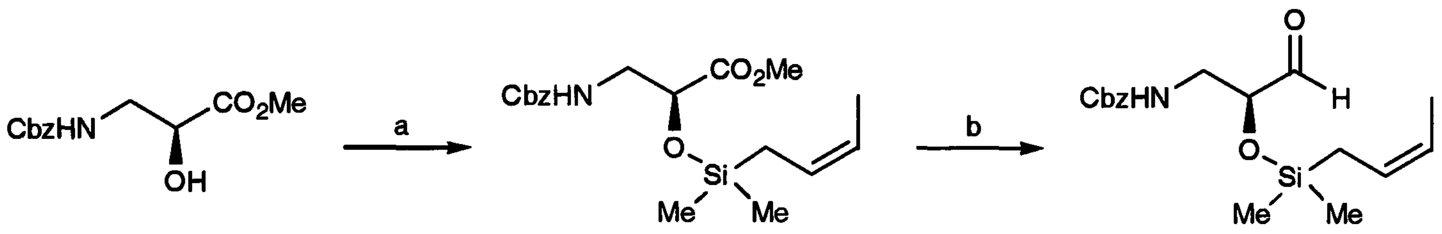


3.06

a) Ni(acac)$_2$ 3.0 mol%, Me$_2$SiHCl, 100 °C (89%).

Scheme 3.04

Silylation of isoserine ester **3.05** with the dimethylchlorosilane **3.06** under standard conditions generated the desired *Z*-crotyl substrate **3.07**. Subsequent DIBAL reduction of the methyl ester to aldehyde **3.08** generally proceeded in good yield albeit with some recovery of starting material (Scheme 3.05).



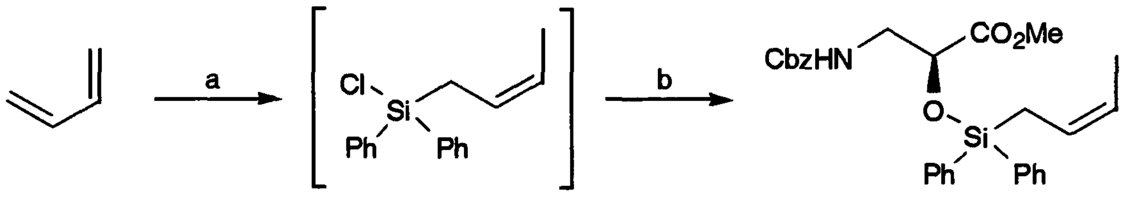
3.05 **3.07** **3.08**

a) *Z*-crotyl(dimethyl)chlorosilane (**3.06**), TEA, DMAP (cat.), DMF, 0 °C–40 °C (78%); b) DIBAL, -78 °C (72%).

Scheme 3.05

With precursor **3.08** in hand an ene reaction was attempted under the standard conditions. The DMAC catalysed ene reaction was expected to proceed preferentially through a *cis*-decalin transition state to furnish the *cis,cis* cyclic siloxane as the major diastereomer (see Scheme 3.01). Unfortunately, no products of ene cyclisation could be isolated, precursor **3.08** simply decomposed; this was attributed to poor *Z*-crotyl(dimethyl)silyloxy aldehyde stability under the Lewis acidic conditions of the ene reaction. Examination of the 200 MHz ^{1}H NMR spectrum of the crude product mixture confirmed the formation of a small quantity of diol, resulting from allylic transfer.

Since the dimethylsilyl variant **3.08** had proved labile under our established ene conditions we decided to investigate the more sterically encumbered diphenylsilyl derivative. Attempts to repeat the hydrosilylation protocol with diphenylchlorosilane, trapping the resulting *Z*-crotylchlorosilane (**3.09**) with isoserine ester **3.05**, returned very poor yields of the desired product **3.10** and considerable amounts of polymerised butadiene. The poor yield was ascribed to steric hindrance imparted by the phenyl substituents slowing the rate of hydrosilylation, together with the hydrolytic instability of the intermediate chlorosilane **3.09** (Scheme 3.06).

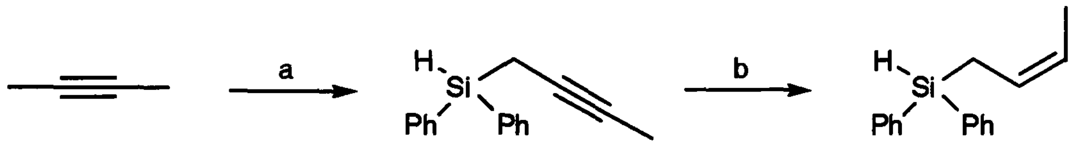


3.09 **3.10**

a) Ni(acac)$_2$ 3.0 mol%, Ph$_2$SiHCl, 100 °C; b) isoserine ester **3.05**, TEA, DMAP (cat.), DMF, 0 °C–40 °C (11%).

Scheme 3.06

Fortuitously, at this time a method became available for the synthesis of *Z*-crotyl(diphenyl)silane **3.12**. The procedure, developed concurrently in our group,[80] employed *t*-BuLi to deprotonate 2-butyne, the resulting organolithium intermediate being trapped with diphenylchlorosilane, without rearrangement, to give propargylic silane **3.11**. The desired *Z*-crotylsilane **3.12** was isolated in satisfactory yield, free of the *E*-isomer, after selective reduction of the alkyne bond with DIBAL (Scheme 3.07).[80,114]

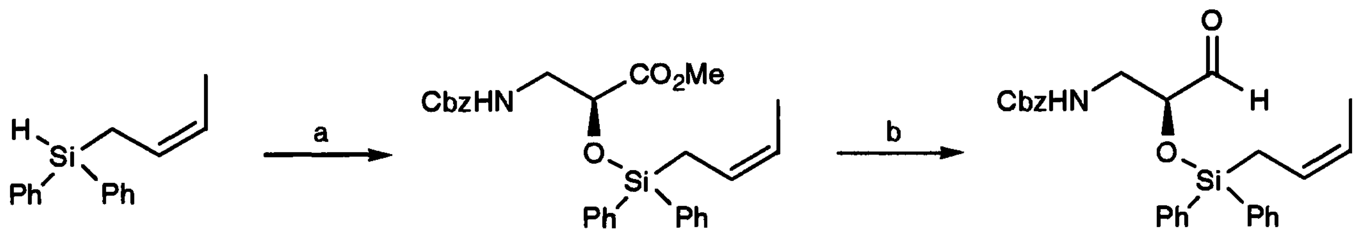


3.11 **3.12**

a) *t*-BuLi, TMEDA, -78 °C–RT then Ph$_2$SiHCl, -78 °C–RT (96%); b) DIBAL, Δ, then H$_3$O$^+$ (65%).

Scheme 3.07

With silane **3.12** in hand silylation of the isoserinate was readily achieved, employing Piers' protocol, to furnish **3.10** in 77% yield. Although DIBAL reduction of the resulting ester provided access to the desired ene precursor **3.13**, this conversion often proceeded in only moderate yield, which was attributed in part to over-reduction, coupled with a tendency of the aldehyde to decompose on silica gel. (Scheme 3.08).

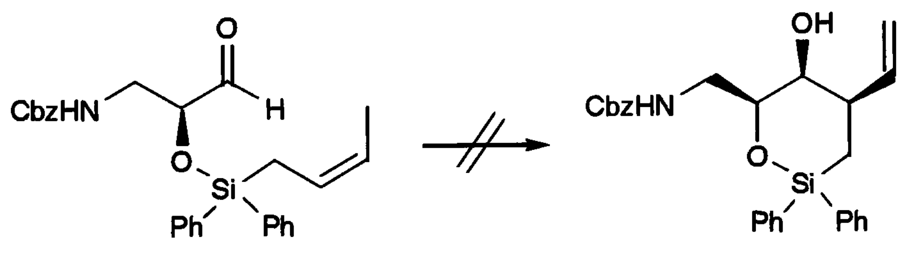


3.12 **3.10** **3.13**

a) isoserine ester **3.05**, $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (77%); b) DIBAL, -78 °C (76%).

Scheme 3.08

The *Z*-crotyldiphenyl substrate **3.13** failed to react in a useful manner under our established Type I ene conditions and application of DMAC at RT resulted in no products of ene cyclisation, **3.13** merely undergoing rapid decomposition, again with some ^{1}H NMR evidence of allyl transfer amongst the multiple products (Scheme 3.09).



3.13 **3.14**

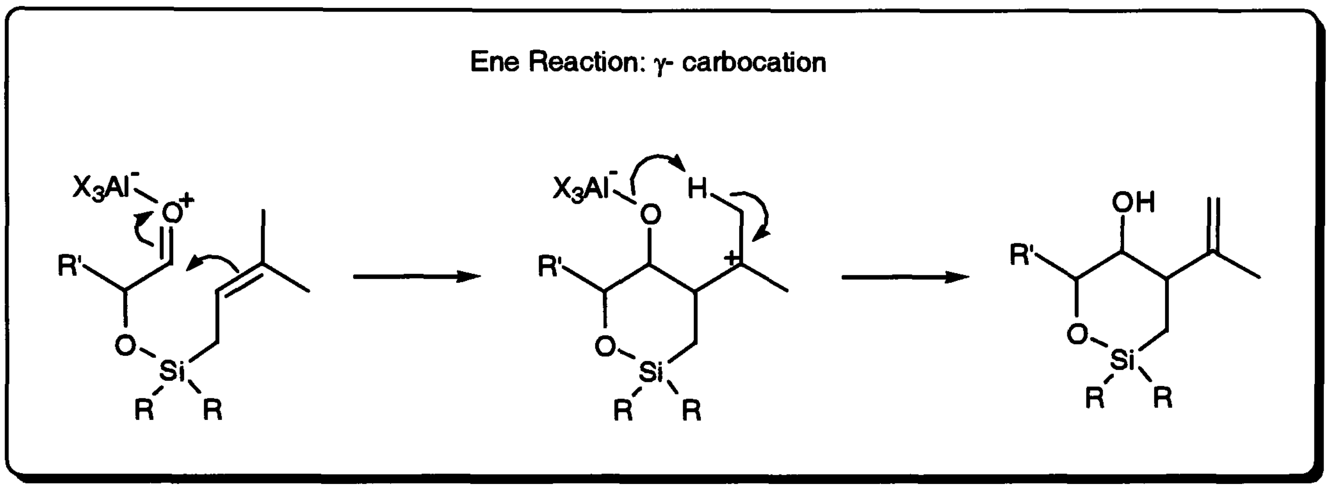
Me_2AlCl, RT.

Scheme 3.09

It soon became clear that Type I ene cyclisation of crotyl silanes was not viable under the conditions explored. Before abandoning this mode of reaction completely, we decided to repeat the ene chemistry with a prenylsilyl derivative, to confirm that our lack of success was indeed due to the crotyl substituent and could not be attributed to the polar, protic side-chain.

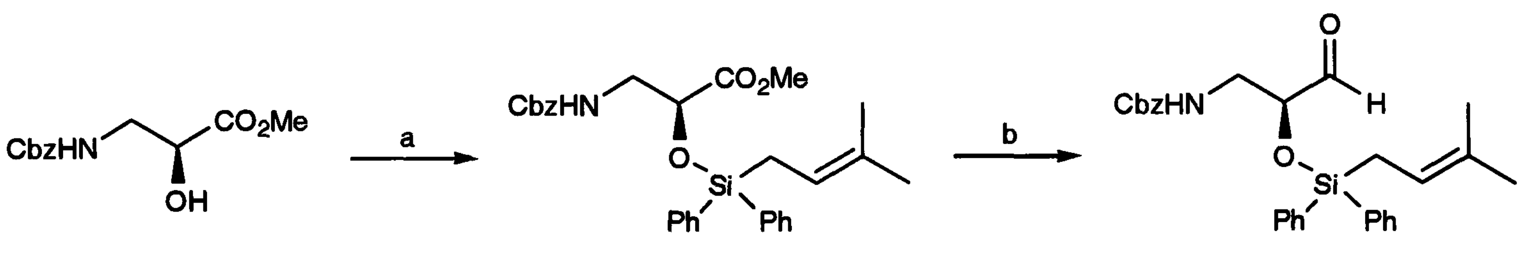
3.2 Aminotriol synthesis

The prenyl systems are biased to undergo ene cyclisation due to the electron donating ability of the two terminal methyl groups, which enables stabilisation of a partial positive charge γ-to silicon (Scheme 3.10).



Scheme 3.10

Preparation of the prenylsilyl derivative followed the established route and silylation of isoserine ester **3.05** with the prenyl(diphenyl)silane **2.22** proceeded uneventfully. However, reduction of the ester with DIBAL proved troublesome; it was almost impossible to ascertain the extent of conversion to aldehyde **3.16** due to the streaking of the product during tlc (Scheme 3.11).

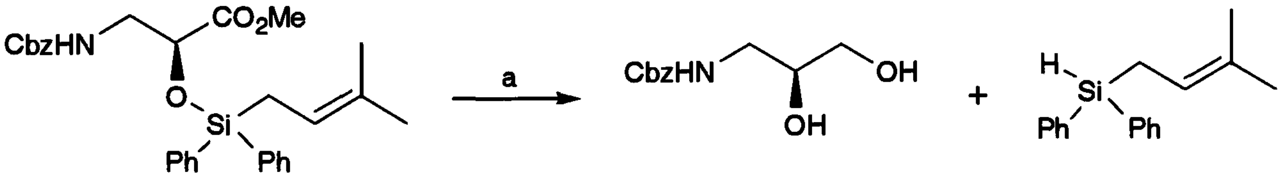


3.05 **3.15** **3.16**

a) prenyl(diphenyl)silane (**2.22**), $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (78%); b) DIBAL, -78 °C (68%).

Scheme 3.11

Under these conditions the aldehyde often became contaminated with over-reduced products and we decided to pursue a reduction-oxidation strategy in an attempt to optimise the overall conversion to **3.16**. The use of lithium aluminium hydride proved too severe, resulting in the addition of hydride to silicon and cleavage of **3.15**, regenerating the prenylsilane **2.22** and furnishing diol **3.17** (Scheme 3.12).[115]

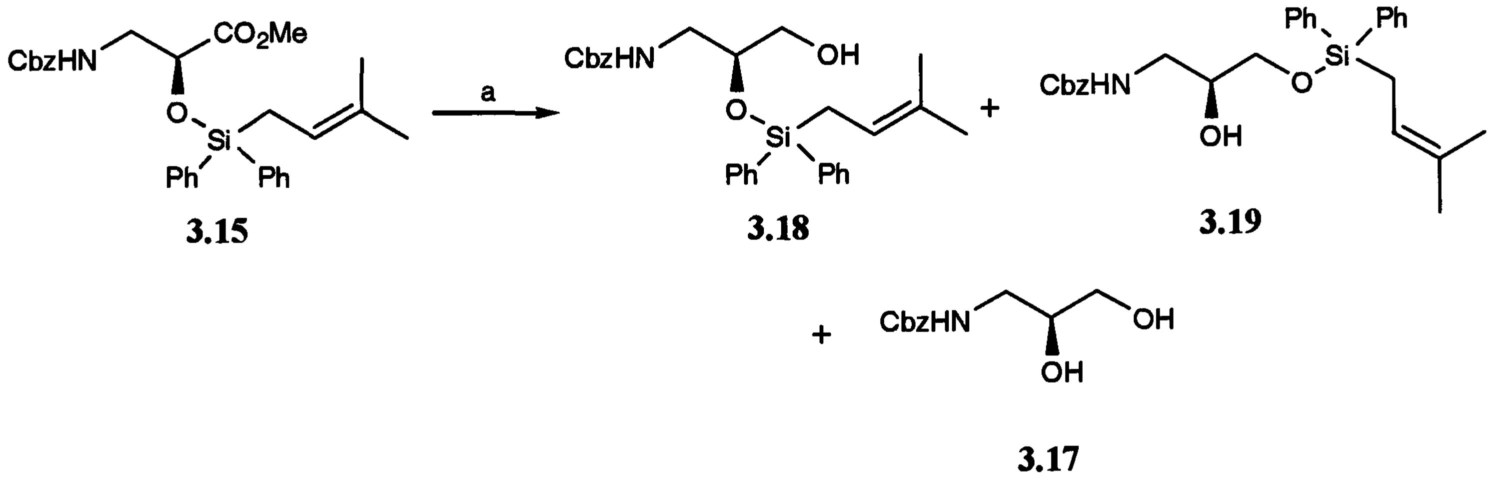


3.15 **3.17** **2.22**

a) $LiAlH_4$, -78 °C (42% and 31%).

Scheme 3.12

The use of sodium borohydride did little to improve matters; inspection of the 400 MHz ^1H NMR spectrum provided evidence of silyl migration, indicating a complex product mixture containing **3.18**, the unwanted 1°-silylated diol (**3.19**) and the desilylated product (**3.17**) (Scheme 3.13).

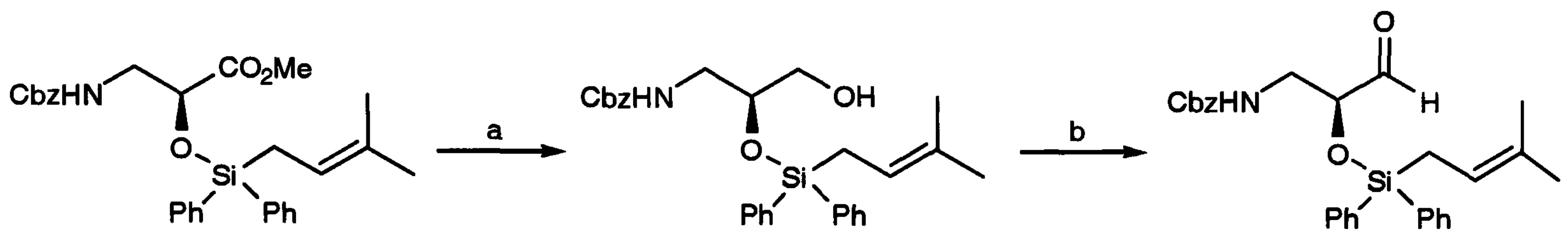


3.15 **3.18** **3.19** **3.17**

a) $NaBH_4$, 0 °C–RT (68% overall).

Scheme 3.13

Ultimately, reduction with excess DIBAL proved to be the best option; the 400MHz ^{1}H NMR spectrum of **3.18** confirmed the presence of an internally protected diol, with loss of the OH coupling to the CH_2 signal on addition of D_2O. Although, the desired aldehyde **3.16** was isolated cleanly in comparable overall yield after Swern oxidation, the two-step strategy offered no great advantage over direct reduction (Scheme 3.14).

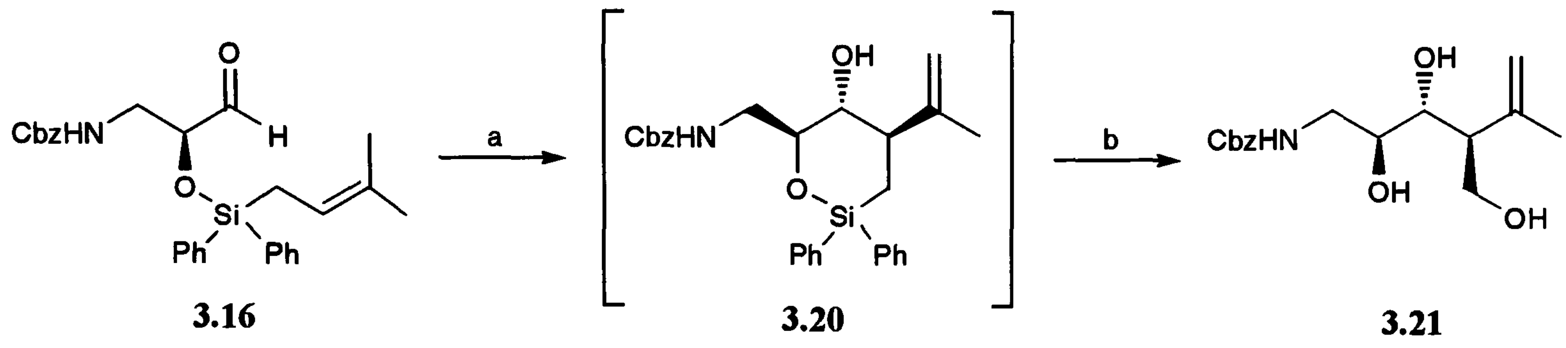


3.15 **3.18** **3.16**

a) DIBAL, -78 °C (51%); b) oxalyl chloride, TEA, DMSO, -78 °C–RT (94%).

Scheme 3.14

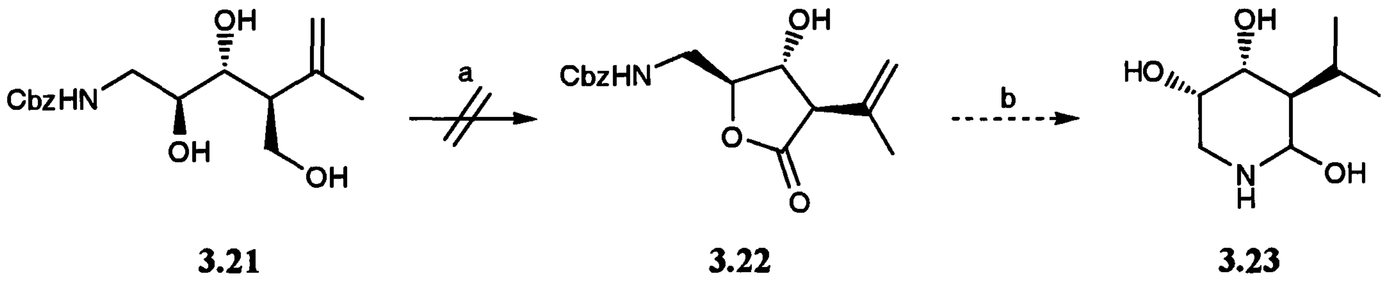
Treatment of aldehyde **3.16** with DMAC proceeded uneventfully at RT to furnish a single ene product, tentatively assigned as the *trans,trans* isomer on the basis of 400 MHz ^{1}H NMR analysis of the crude product. Expecting oxasilacyclic intermediate **3.20** to be labile to chromatography on silica gel, the crude material was carried forward to the next step without purification. Oxidative cleavage of the Si-C bond under Tamao-Kumada conditions furnished the desired aminotriol **3.21** in 47% yield (Scheme 3.15). The moderate conversion in this reaction was attributed to the dual problem of solvation and recovery of the aminotriol during aqueous work-up.



a) Me_2AlCl, RT; b) H_2O_2, KF, $KHCO_3$, MeOH-THF, RT (47% two steps).

Scheme 3.15

Eager to confirm the stereochemistry of the aminotriol (**3.21**) we decided to try to promote an oxidative cyclisation, selective oxidation of terminal 1,4-diols having literature precedent.[116] Disappointingly, attempts to oxidise the 1°-hydroxyl of **3.21** with either Ag_2CO_3 on Celite®, PCC, or TPAP all failed to induce lactonisation, resulting instead in unproductive decomposition (Scheme 3.16).



a) Ag_2CO_3-Celite® or PCC or TPAP; b) H_2, Pd/C.

Scheme 3.16

Undeterred by stability issues, we repeated the ene sequence to isolate silacyclohexanol **3.20** in a surprisingly good yield of 52% following flash column chromatography on silica gel. The relative stereochemistry was then established by routine coupling constant analysis and n.O.e. data (Figure 3.03, Table 3.01).

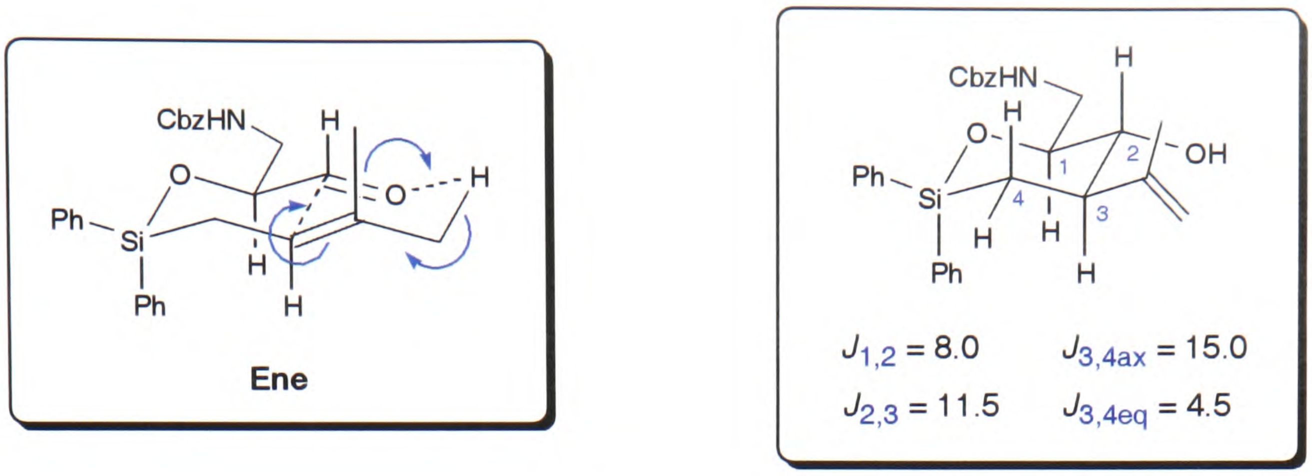


Figure 3.03

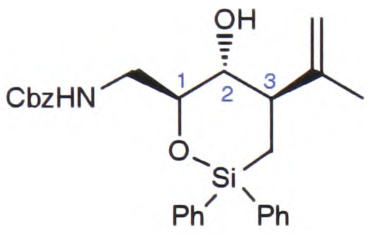
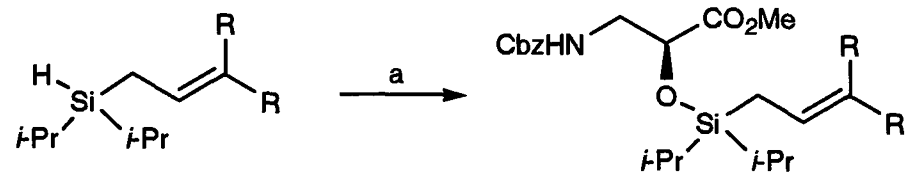
		Enhancement %					
	Irradiate	H^1	H^2	H^3	CH(OH)	=CH_2	C(CH_3)=
	H^1	-	1.5	6.2	1.4	0.0	0.0
	H^2	1.7	-	1.6	5.3	0.9	4.6
	H^3	7.4	1.4	-	1.2	4.7	0.0
3.20	CH(OH)	3.4	9.1	2.4	-	2.1	1.5

Table 3.01

This positive result led us to conclude that the failure of precursor **3.13** to cyclise under the conditions of the ene reaction was indeed due to the crotyl substituent and not a problem of side chain incompatibility. The presence of a crotyl substituent, compared to a prenyl substituent, reduces the ability of the system to stabilise a build-up of positive charge γ- to silicon (see Scheme 3.10). The favourable formation of a γ-stabilised carbocation is fundamental to the ene process; by moving to a crotyl substituent this pathway is disfavoured due to the associated loss in stabilisation. It is also postulated that a reduction in the overall bulk of the silicon group linked with a concurrent increase in ease of Si-O bond cleavage may also contribute to the failure of the ene cyclisations in the crotyl case.

We briefly directed our attention to the preparation of a di(*iso*-propyl)silyl-substituted ene precursor. Unfortunately Piers' tris(pentafluorophenyl)borane-catalysed silylation protocol was not equally applicable to *iso*-propyl substituted silanes. In the case of silanes **2.17** and **2.19** attempted borane-assisted coupling to isoserine ester **3.05**, under a variety of conditions, furnished **3.24** and **3.25** in optimal yields of just 7% and 11% respectively (Scheme 3.17).



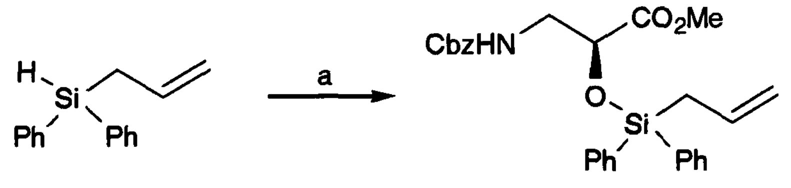
2.17 R = H
2.19 R = Me

3.24 R = H
3.25 R = Me

a) isoserine ester **3.05**, $B(C_6F_5)_3$ 10.0 mol%, toluene, Δ (**3.24** 7%; **3.25** 11%).

Scheme 3.17

In comparison the diphenylsilyl variant **3.26** was readily formed under milder conditions, with a lower catalyst loading (Scheme 3.18).



2.20

3.26

a) isoserine ester **3.05**, $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (70%)

Scheme 3.18

A combination of steric and electronic factors may account for this observed behaviour on moving from bulky alkyl groups on silicon to relatively small, electron withdrawing, phenyl substituents. Examination of the literature revealed no examples of Piers' method having been applied to the silylation of hindered hydroxyls with sterically demanding alkyl silanes. In fact Piers comments that both tri(*iso*-propyl)silane and tribenzylsilane are ineffective silylating agents, even under forcing conditions.[104]

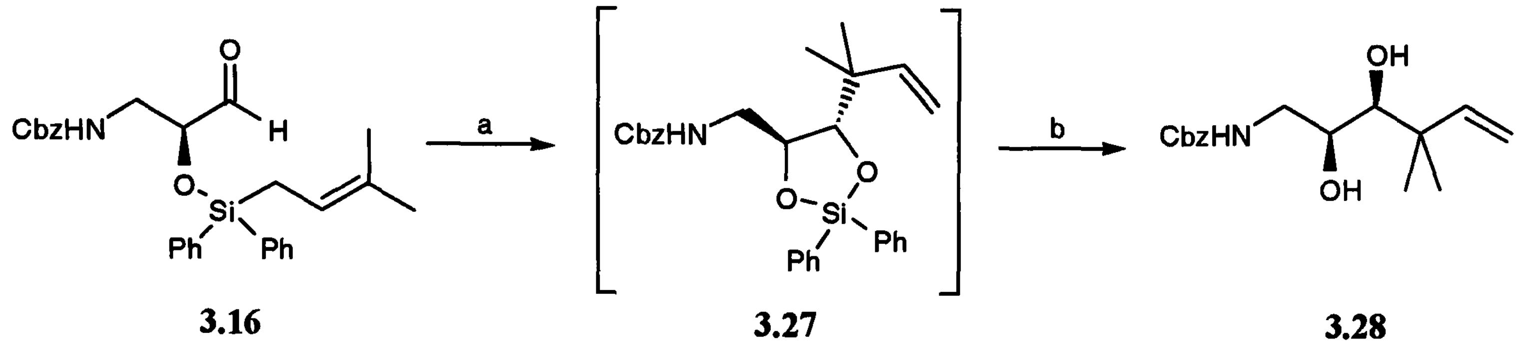
3.3 Aminodiol synthesis

Concerned that the delicate α-silyloxy aldehyde precursors were partially unstable to the Lewis acid employed in the ene reaction it was decided to attempt to induce cyclisation under neutral thermal conditions, in the hope that the substrates would be less liable to decompose.

Hence substrate **3.16** was dissolved in toluene and warmed to 120 °C in an attempt to optimise the yield of the ene products. The thermal behaviour of **3.16** was surprising; instead of the expected ene cyclisation, we observed a remarkably smooth conversion to siladioxolane **3.27** (Scheme 3.19) arising from allyl transfer of the prenyl component. Qualitative n.O.e. analysis of this intermediate suggested that the allyl transfer process proceeds with anti-Felkin-Ahn selectivity.

Isolation of siladioxolane **3.27** was attempted, by silica gel chromatography, without success due to the sensitivity of these compounds towards hydrolysis. It is quite feasible that this mode of reaction had competed with the ene cyclisation under the DMAC-mediated conditions, but the instability of the resulting diphenyl-substituted siladioxolanes contributed to the loss of this by-product. This result offers a possible explanation for the mediocre yields obtained from previous ene reactions.[80]

The crude siladioxolane **3.27** was desilylated directly employing KF in methanol with added hydrogen peroxide to aid the breakdown of silyl residues and generally ease purification. The aminodiol **3.28** was isolated in an excellent yield of 95% over two steps (Scheme 3.19).

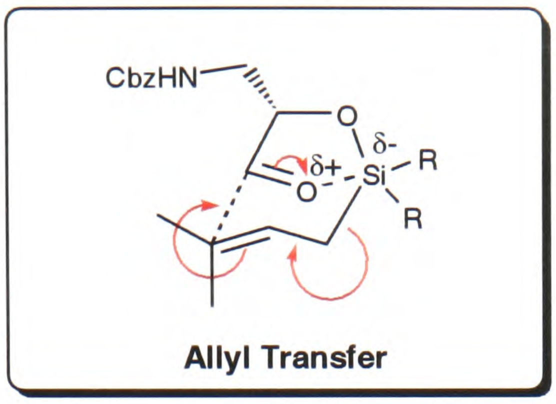


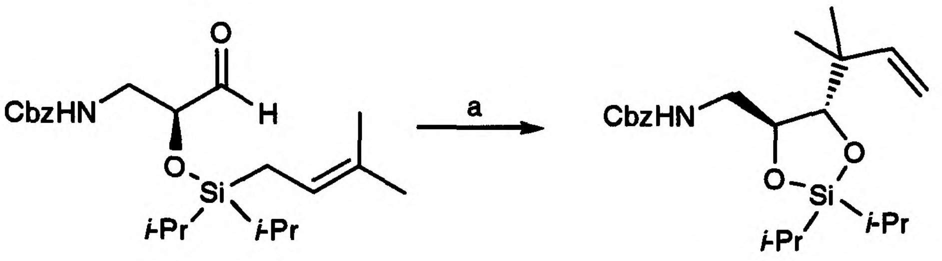
a) Toluene, 120 °C, 20 hr; b) H_2O_2, KF, MeOH, RT (95% two steps).

Scheme 3.19

In an attempt to improve the stability of the intermediate siladioxolane, the di(*iso*-propyl)-substituted variant **3.29** was subjected to the same thermal conditions; this time the substrate was dissolved in deuterated toluene and the progress of the allyl transfer reaction monitored by ^1H NMR. From the results obtained in Chapter 2 (Section 2.2) we proposed that the siladioxolane resulting from the di(*iso*-propyl) precursor should be isolable.

Pleasingly, the allyl transfer conditions were found to be general; applied to the di(*iso*-propyl)silyl analogue (**3.29**) the outcome paralleled that of the diphenylsilyl derivative, although the reaction time was slightly protracted. In this case the siladioxolane **3.30** was isolable and stable to chromatography on silica gel (Scheme 3.20).



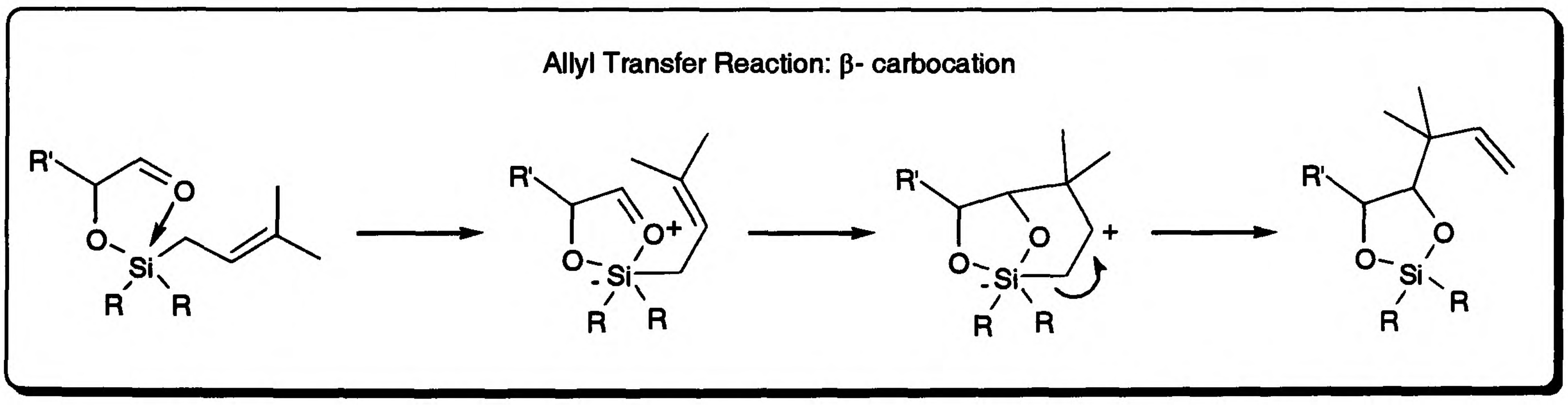


3.29 **3.30**

a) Toluene-d$_8$, 120 °C, 30 hr (91%).

Scheme 3.20

Under thermal conditions, the observed allyl transfer process could proceed *via* the generation of a β-stabilised carbocation; the absence of a Lewis acid limits the potential for competing decomposition pathways (Scheme 3.21).[117]



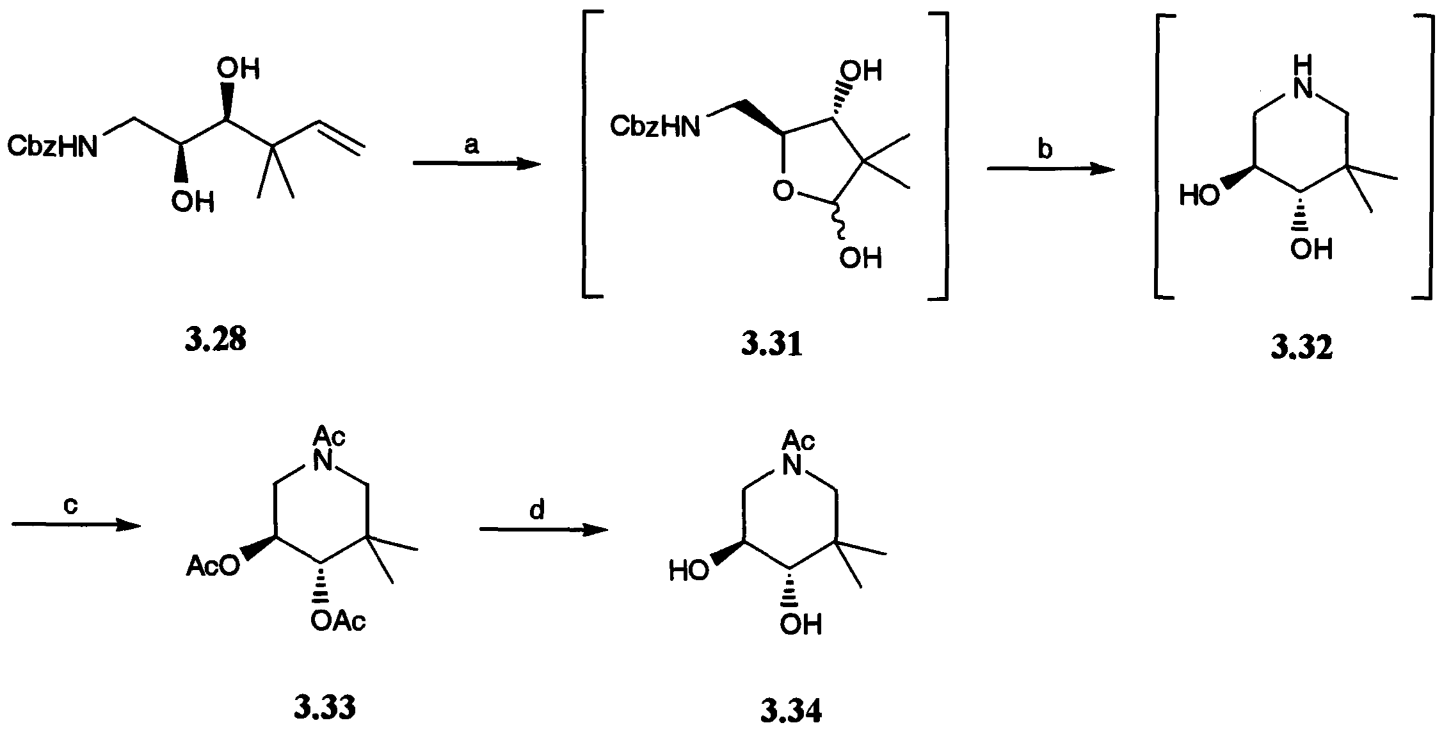
Scheme 3.21

3.4 Iminosugar synthesis

With aminodiol **3.28** in hand we decided to implement the final steps of our original isofagomine synthesis, which would lead to an unknown iminosugar derivative and also re-confirm the assigned stereochemistry of the diol.

We initially encountered some problems concerning the solubility of the unprotected diol (**3.28**) in DCM at -78 °C, leading to the recovery of appreciable amounts of starting material following ozonolysis. Subsequently the reaction temperature was raised to overcome this problem and the ozonolysis was performed successfully at -45 °C. The highly polar intermediate **3.31** was accompanied by many inseparable impurities and so the crude material was taken through directly to the hydrogenation step. Again, due to the high polarity of the resulting hydroxylated piperidine, it was necessary to acetylate compound **3.32** to aid purification prior to isolation. The drawback of this approach being the complex rotameric NMR spectrum exhibited by the product. However, with the aid of COSY, HMQC and HMBC experiments, the product was identified as compound **3.33**.

Attempts to deacetylate compound **3.33** with base-activated resin resulted in cleavage of the acetates from the two hydroxyls, but did not effect deprotection of the amine (Scheme 3.22).



a) O_3, Sudan Red 7B, DCM, -45 °C then Ph_3P–resin, -45 °C–RT; b) H_2, Pd/C, EtOH;

c) Ac_2O, py., DMAP (cat.), 0 °C–RT (18% three steps);

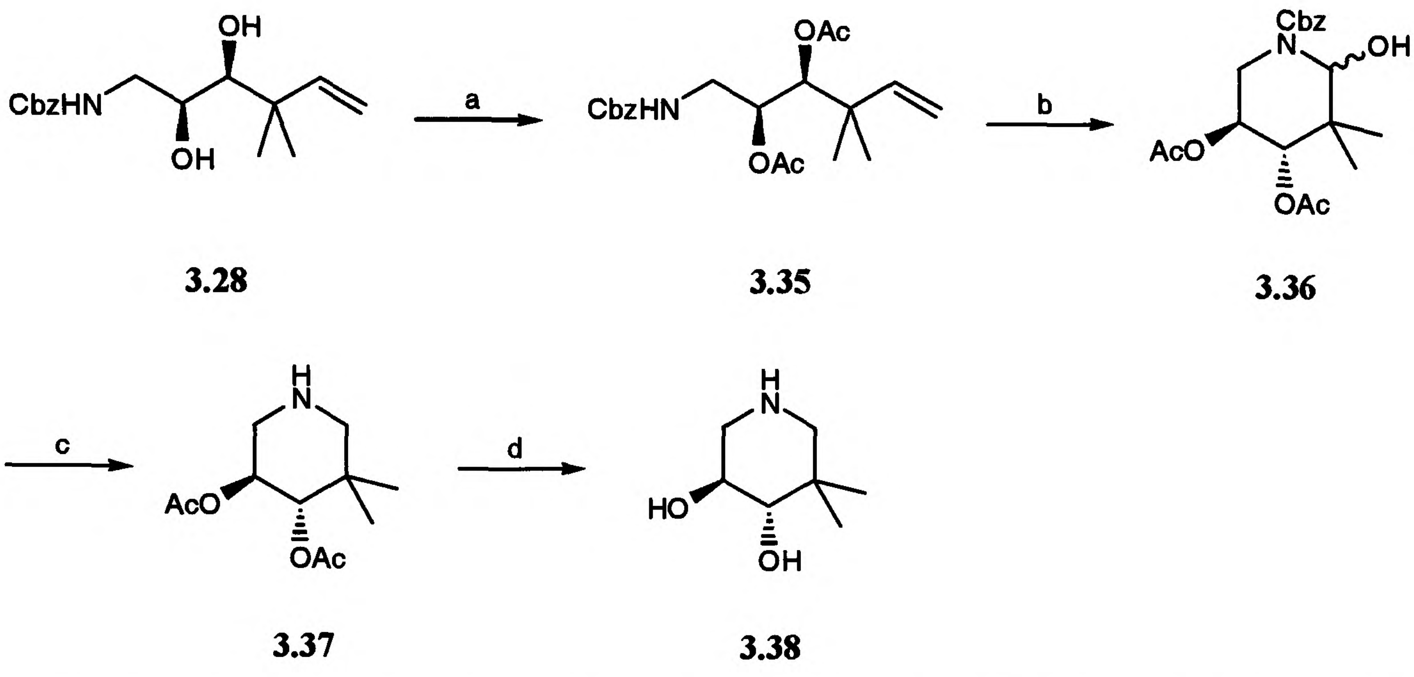
d) Amberlite® IRA (OH) resin, MeOH, 50 °C (94%).

Scheme 3.22

Since elaboration of the unprotected diol **3.28** had proven difficult it was decided to amend the order of the synthetic sequence, acetylating the diol first, before subjecting the alkene to ozonolysis. It was hoped that this would ease purification, allowing the intermediates to be isolated, and avoid the problem of *N*-protection in the final product.

Following routine acetylation, we were slightly surprised to find that the protected diol **3.35** also had limited solubility in DCM at low temperatures; again this problem was circumvented by performing the ozonolysis procedure in a mixture of DCM and methanol (5:1, v/v) at -45 °C. Use of dimethyl sulfide in the course of the same reaction also proved troublesome, leading to the inadvertent isolation of the intermediate ozonide,[118] following column chromatography of the anticipated product. To overcome the limitations of dimethyl sulfide, triphenyl phosphine was employed in its place to furnish hemiaminal **3.36** as a mixture of diastereomers, in good overall yield.

Hydrogenolysis of carbamate **3.36** was accompanied by reductive amination to give the protected dihydroxypiperidine **3.37**. Subsequent resin-mediated deprotection gave rise to the desired *gem*-dimethyl dihydroxypiperidine **3.38** in excellent yield (Scheme 3.23)



3.28 **3.35** **3.36** **3.37** **3.38**

a) Ac_2O, py., 0 °C–RT (97%); b) O_3, DCM-MeOH (5:1, v/v), -45 °C then PPh_3, -45°C–RT (d.r. = 2:1, 90%); c) H_2, Pd/C, EtOH (60%); d) Amberlite® IRA (OH) resin, MeOH, 50 °C (98%).

Scheme 3.23

Examination of the 400 MHz ^1H NMR spectrum confirmed a *trans* di-equatorial arrangement of the hydroxyls, the large ^1H-^1H coupling constant values (J 10.8 and 9.4 Hz) indicating di-axial coupling between the neighbouring protons (Figure 3.04), which also re-confirmed **3.28** as the *syn*-diol.

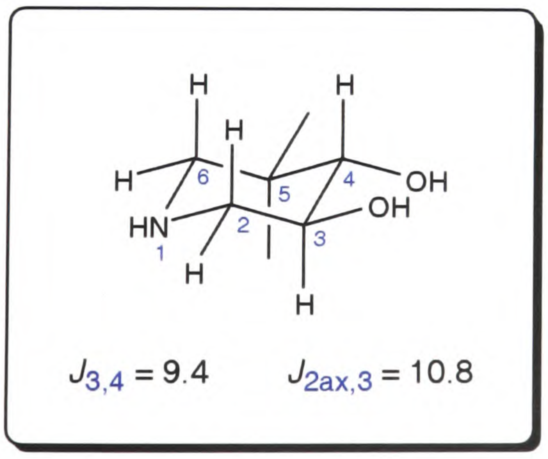


Figure 3.04

3.5 Conclusions

This study has extended the scope of our ene methodology, demonstrating that latent side chain functionality can be successfully incorporated within the ene precursor with no detriment to the overall sequence. This is exemplified by the formation of 2,3,5-aminotriol **3.21**. In association with this synthesis we have developed an expedient route to the useful isoserine derivative **3.05**.

Although the envisaged synthesis of isofagomine proved unsuccessful, during the course of the investigation we observed a silicon tethered allyl transfer process which proceeded stereoselectively under thermal conditions, generating 2,3-aminodiol **3.28**. This result parallels the equally unexpected siladioxolane discussed in Chapter 2 (Section 2.2); further investigations of this mode of reaction and preliminary applications are reported in Part 2 of this thesis.

Part 2

Silicon Tethered Allyl Transfer Reactions

Chapter 4

Silicon-Assisted Allylation

4.0 Introduction

The allylation of carbonyl derivatives is an essential preparative process in organic synthesis, providing access to important synthetic intermediates such as functionalised homoallylic alcohols and amines. The addition of allylic metal reagents provides a reliable method for controlling the stereochemistry of the forming C-C bond; the emergence of this process as a cornerstone in the field of asymmetric synthesis stems from Hoffman's pioneering work with crotylboronates[119] and Yamamoto's subsequent investigations with crotylstannanes.[120] A variety of allylic organometallic compounds have since been employed in this capacity,[121,122] but the most common allylic semi-metallic reagents remain those of boron (Type I),[123] tin (Type II)[124] and silicon (Type II).[125]

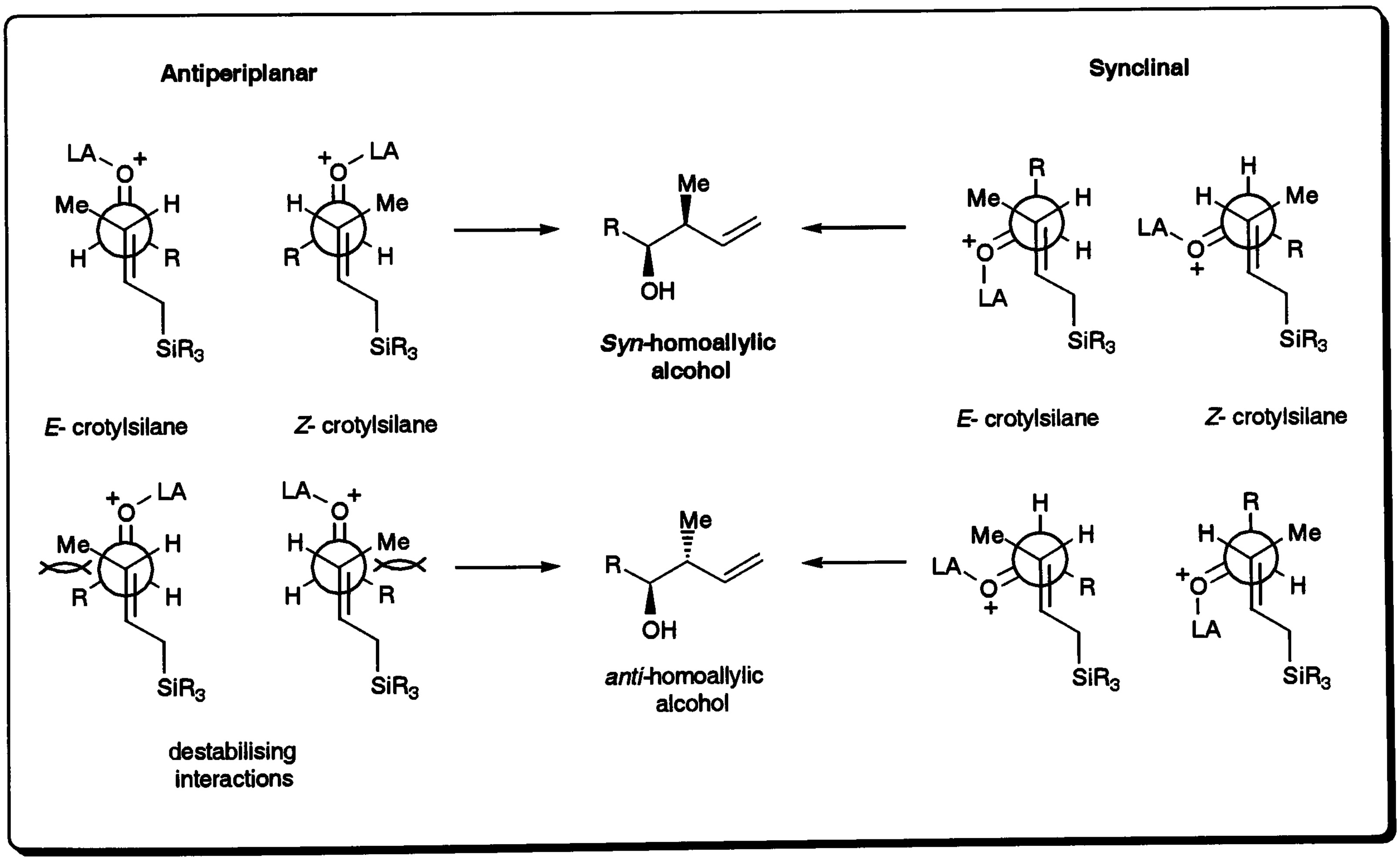
Of the Type II reagents employed to effect asymmetric transformations, the use of allylsilanes is most preferable due to their greater stability and lower toxicity when compared to the analogous stannanes. The ability of organosilicon reagents to act as both an electron donor and acceptor, to accommodate a variety of functional groups, and to tolerate a diverse range of reaction conditions, underpins the popularity of these versatile reagents in stereocontrolled synthesis. In this regard, silicon-mediated allylations are of great synthetic utility and have attracted much attention in the literature.[126,127]

This introductory chapter will focus solely on silicon allylation chemistry of carbonyl compounds and imine derivatives, giving a brief overview of the more prevalent silicon allylation reagents and highlighting key areas of stereoselective silicon-assisted allylation methodology.

4.1 Allylation of C=O groups with silicon reagents

Carbonyl allylation with silicon reagents was first described by Hosomi and Sakurai in the mid 1970s.[128] Since then the asymmetric synthesis of homoallylic alcohols by addition of allylic silanes to carbonyl compounds has been the focus of study for many groups; two comprehensive reviews which encompass this area of silicon chemistry have been published by Panek and Fleming.[129,7]

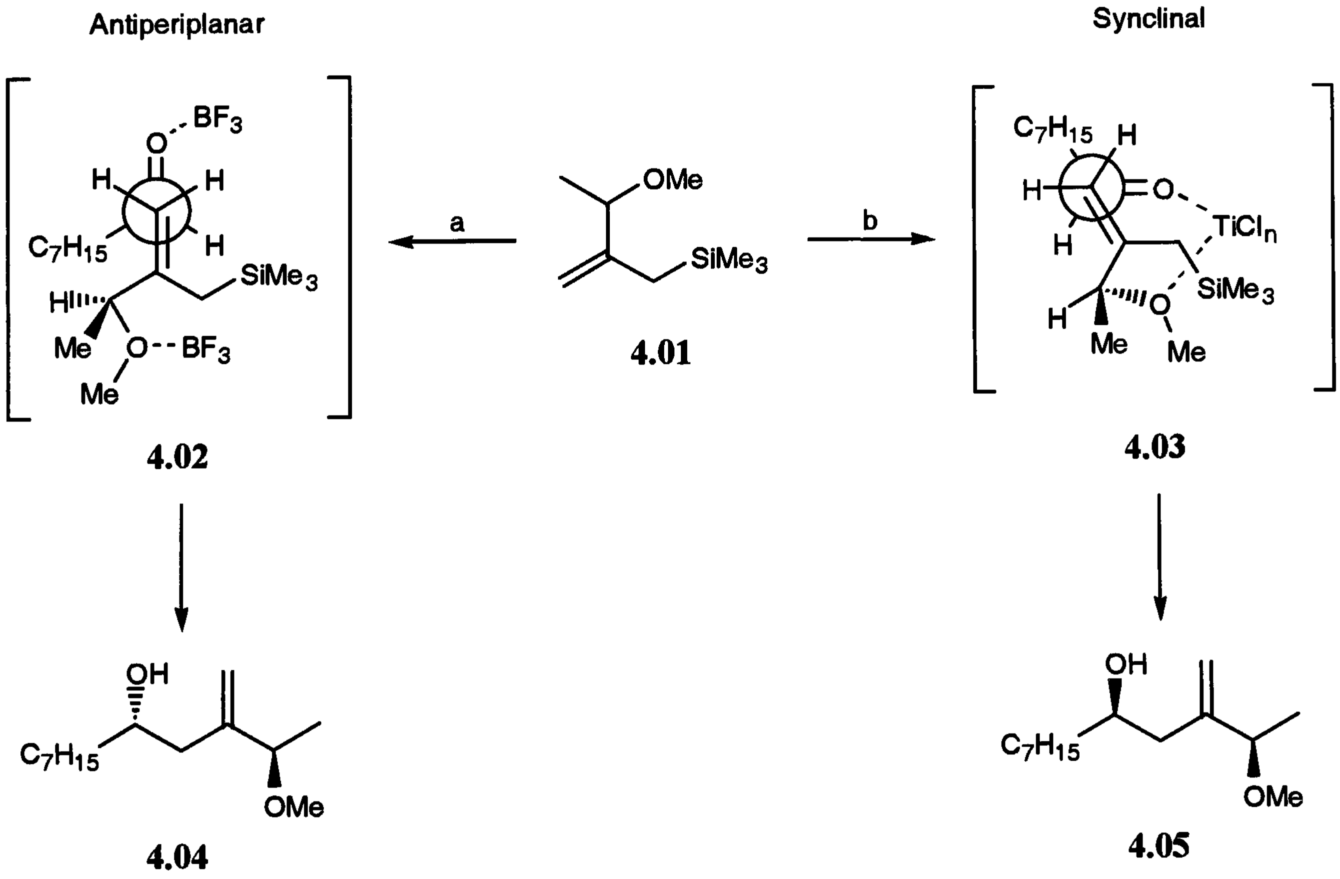
The Hosomi-Sakurai reaction traditionally involves addition of an allylsilane to a carbonyl compound promoted by a Lewis acid. In the case of Lewis acid-catalysed reactions of crotylsilanes, the addition proceeds non-stereospecifically to give the *syn* homoallylic alcohol as the major diastereomer, regardless of the geometry of the crotyl substituent (Scheme 4.01).



Scheme 4.01

This result has been ascribed to the preference for either an antiperiplanar arrangement of the open acyclic transition state, in order to minimise steric interactions between the γ-methyl group of the crotyl unit and the R-group of the carbonyl, or to a synclinal orientation, where the reacting π -bonds are oriented at an angle of 60° and steric interactions of the Lewis acid, coordinated to the oxygen lone pair and positioned *anti* to the R-group of the carbonyl, are minimised.[122] Mechanistic studies have indicated that the *anti*-S_E' arrangement is the most favourable pathway.[125,130,131]

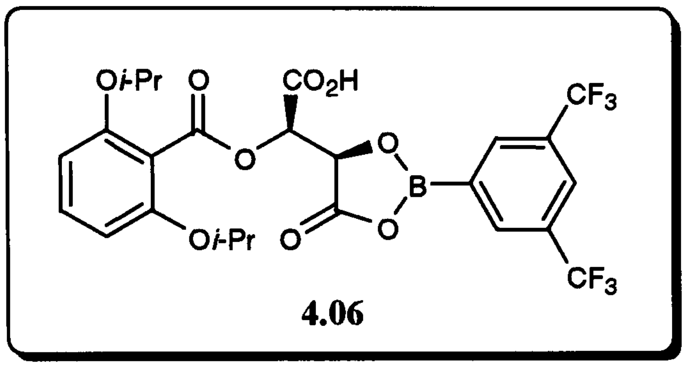
Notably, in the case of substituted allylsilanes, the stereochemistry of the resulting homoallylic alcohol can be influenced by the choice of Lewis acid. For example, monodentate Lewis acids, such as boron trifluoride etherate, give predominantly *anti*-selectivity. In contrast, by employing a chelating species, such as titanium tetrachloride, the diastereoselectivity is reversed due to the location and co-ordinating ability of the Lewis acid, resulting in *syn*-selectivity (Scheme 4.02).[121,129,7,132]



a) $C_7H_{15}CHO$, $BF_3.OEt_2$ (d.r. = 71:29); b) $C_7H_{15}CHO$, $TiCl_4$ (d.r. = 100:0).

Scheme 4.02

The use of chiral Lewis acids to catalyse enantioselective allylation reactions has become prevalent since Yamamoto first introduced chiral acyloxy boranes (**4.06**) in the early 1990s (Figure 4.01).[133]

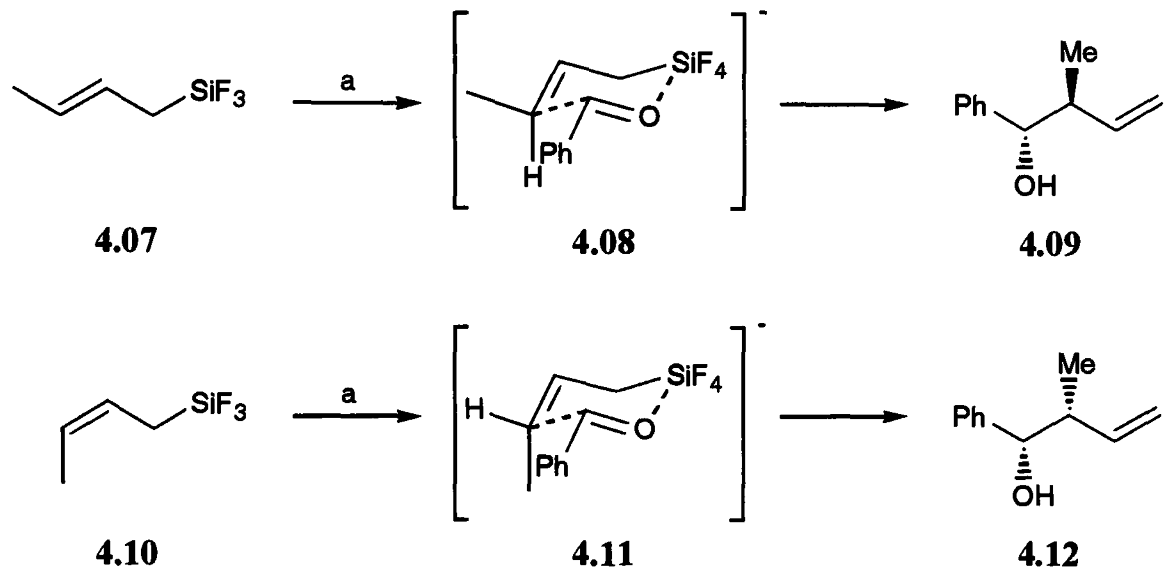


4.06

Figure 4.01

A wide variety of chiral allylation catalysts have appeared in the literature and have found application in a number of complex natural product syntheses.[122] Typical chiral Lewis acid complexes comprise of a strong Lewis acid, normally a borane or titanium(IV) species, coupled with a chiral ligand, such as BINOL or BINAP. The main disadvantage of chiral Lewis acid-catalysed additions is an overall lack of diastereocontrol; this problem has subsequently been addressed by the development of chiral Lewis bases, which will be discussed later in this chapter (Section 4.5).

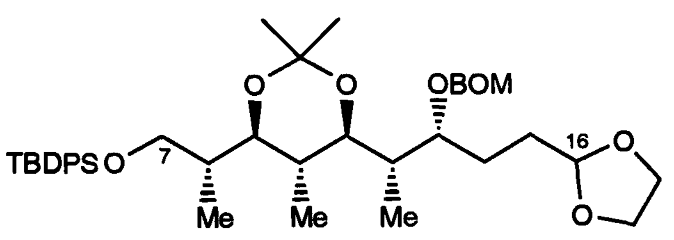
Increasing the innate Lewis acidity of silicon itself can be a useful method to effect carbonyl allylation by removing the need for an external Lewis acid. Ligation of small, highly electronegative substituents can lead to a dramatic increase in Lewis acidity at silicon. In the case of crotyltrifluorosilanes **4.07** and **4.10** this electron withdrawing effect has been exploited to enhance the diastereoselectivity of the reaction by effectively transforming the allylation into an intramolecular process (Type I mechanism) *via* the co-ordination of the carbonyl and silicon reagent (Scheme 4.03).[134]



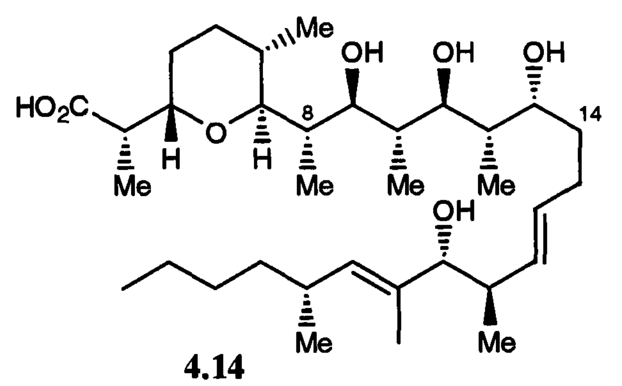
a) PhCHO, CsF (d.r. = 99:1).

Scheme 4.03

This principle has recently been extended by Roush, who developed the silylfluoride-promoted allylation procedure for the synthesis of *anti,anti*-dipropionate stereotriads from α-methyl-β-hydroxy aldehydes.[135] This methodology was applied to the synthesis of the C_7-C_{16} fragment of zincophorin (**4.14**), a potent zinc-binding antibiotic. Roush has suggested that the cyclisation proceeds through bicyclic transition state **4.16**, with the silane attached to the β-hydroxyl group of the aldehyde, allowing intramolecular transfer of the crotyl substituent (Scheme 4.04).[136]

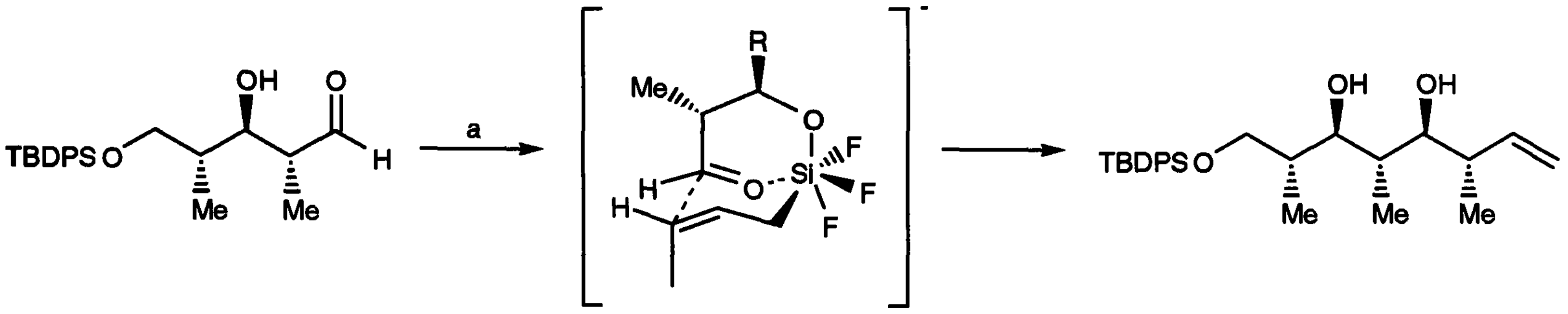


4.13



4.14

Zincophorin

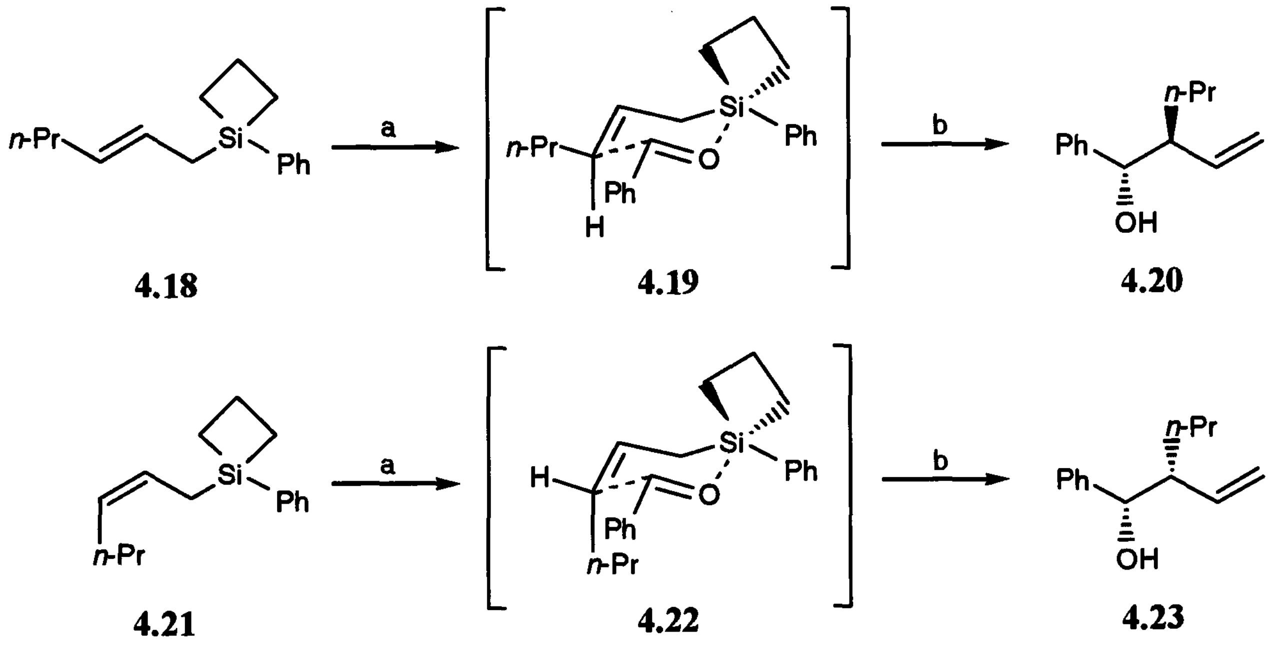


4.15 **4.16** **4.17**

a) Z-crotyltrifluorosilane (**4.10**), *i*-Pr_2NEt, 0 °C (75%, d.r. = 94:6).

Scheme 4.04

Confining the silicon atom within a small ring with a restricted tetrahedral geometry also results in an increased level of Lewis acidity,[137] a principle that has been illustrated by the work of Utimoto *et al.* (Scheme 4.05).[138] Co-ordination of a nucleophile to the silicon atom in silacyclobutane **4.18** releases strain by moving to a more favourable trigonal-bipyramidal geometry in five-membered chelate **4.19**. This ring strain activation effectively promoted intramolecular allyl transfer to the chelated aldehyde, which proceeded under thermal conditions with good diastereoselectivity, in the absence of any external catalyst.

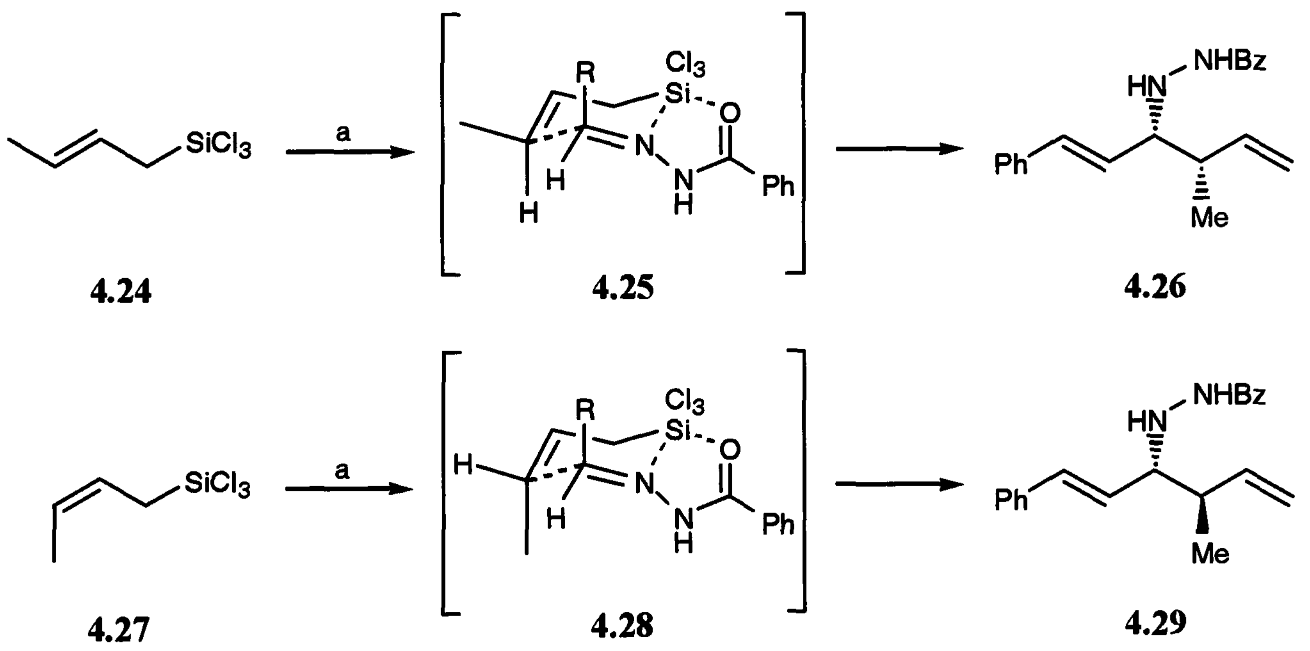


a) PhCHO, 130 °C; b) H_3O^+ (**4.20** 68%, d.r. = 95:5; **4.23** 66%, d.r. = 95:5).

Scheme 4.05

4.2 Allylation of C=N groups with silicon reagents

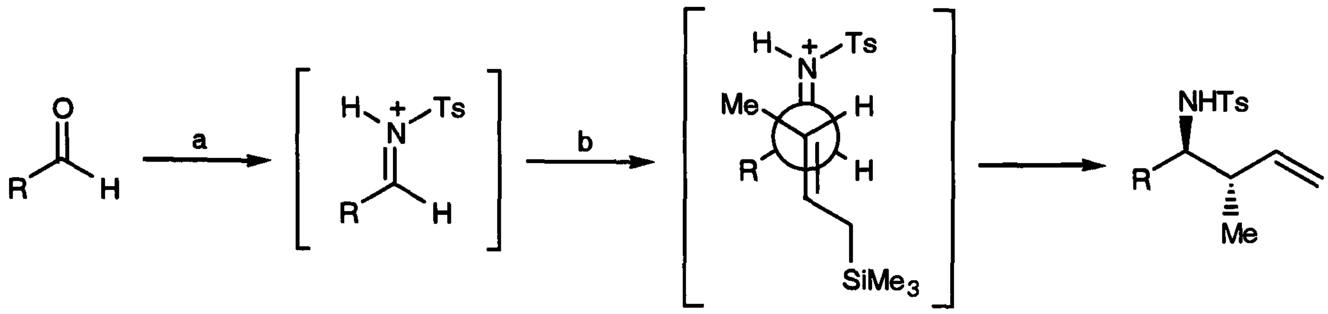
Asymmetric amine synthesis *via* allylic metal addition to the C=N bond of activated imino derivatives is of fundamental importance to the synthetic chemist; chiral homoallylic amines act as important intermediates in the syntheses of many biologically active nitrogen-containing molecules. Organosilanes have proven to be valuable reagents for the allylation of activated imine derivatives in a number of natural product syntheses.[127,7,139] However, compared to allylic metal additions to C=O bonds, imine allylations often suffer from poor reactivity and selectivity due in part to the reduced electrophilicity of the C=N bond.[140,141] Kobayashi has examined the use of benzoylhydrazones to address this problem.[142,143] The regio- and stereoselectivity can be successfully controlled in these additions *via* bidentate co-ordination of the hydrazone moiety of substrate **4.30** to the silicon atom of the crotyltrichlorosilane **4.24** forming a closed, chair-like transition structure organised around silicon (Scheme 4.06). The stereochemical outcome of the addition was contrary to that observed from tetracoordinate Lewis acid-mediated crotylation (Section 4.1).[121]



a) cinnamaldehyde benzoylhydrazone (**4.30**), DMF, 0 °C (**4.26** 82%, d.r. = 95:5; **4.29** 80%, d.r. = 97:3).

Scheme 4.06

It is well established that addition of electron withdrawing substituents, such as sulfonyl, sulfoxy or ester groups, to simple imines increases the electrophilicity of the C=N bond. Masuyama *et al.* formed a *N*-tosyliminium species *in situ* from a carbonyl substrate and tosylamine, in the presence of NCS and tin (II) chloride. Subsequent reaction of the iminium intermediate **4.32** with *E*-crotyltrimethylsilane provided access to the corresponding homoallylic amine with moderate diastereoselectivity (Scheme 4.07).[144]



4.31 **4.32** **4.33** **4.34**

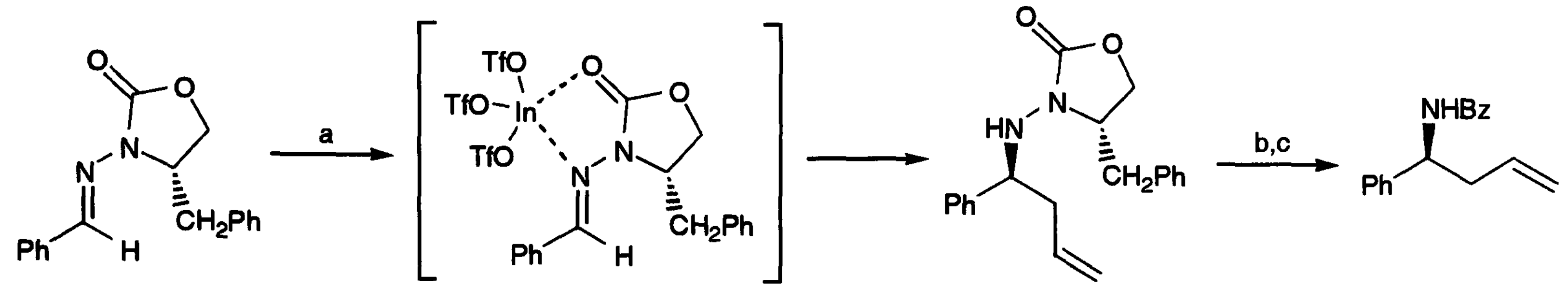
a) $TsNH_2$, $SnCl_2$, NCS, 0 °C;

b) *E*-crotyltrimethylsilane (R = Ph, 91%, d.r. = 89:11; R = *c*-C_6H_{11}, 62%, d.r. = 91:9).

Scheme 4.07

4.3 Dual activation of allylsilanes

Prior to addition, trialkyl-substituted allylsilane reagents normally require activation of the carbonyl moiety with a strong Lewis acid, to which the substrate may be labile.[145] In an attempt to overcome this drawback Friestad developed the novel strategy of dual activation of the allylsilane, employing two mild activators as opposed to a single strong promoter. Friestad used the soft Lewis acid indium (III) triflate in conjunction with TBAT, a fluoride ion source, to activate chiral *N*-acyl hydrazones towards allylation; the resulting chiral allylamines showed promising levels of enantioselectivity. It has been suggested that the allylation proceeds *via* attack of a fluoride-activated hypervalent-silane on indium chelated hydrazone **4.36** (Scheme 4.08).[146]



4.35 **4.36** **4.37** **4.38**

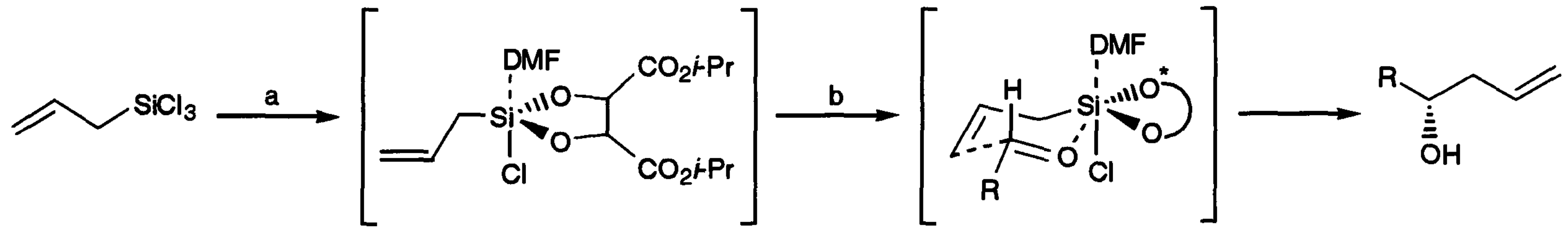
a) Si(allyl)$_4$, TBAT, In(OTf)$_3$ (78%, d.r. = 99:1); b) *n*-BuLi, (PhCO)$_2$O (81%); c) SmI$_2$, HMPA (93%).

Scheme 4.08

Shibasaki has also demonstrated the use of dual activation methodology, employing catalytic copper (I) chloride and TBAT with allyltrimethoxysilane to induce activation in a range of aldehydes and imines; the mechanism of this process is unknown, however a putative fluorosilicon species is thought to impart allylation.[147,148]

4.4 Pentacoordinate allylsilanes

The ability of silicon to expand its valence from the tetravalent to pentacoordinate species has been exploited by a number of groups in order to effect stereoselective allylation.[129,149] Wang *et al.* extended Hosomi's work with tartrate-based silicates,[150] by employing pentacoordinate silanes to promote the allylation of carbonyl derivatives. Chiral pentavalent species **4.40** was formed *in situ* following the addition of (+)-di(*iso*-propyl)tartrate to allyltrichlorosilane **4.39** in a strongly donating co-solvent; the diol-modified allylsilane reacted cleanly to afford the corresponding homoallylic alcohol **4.42** with decent e.e. (Scheme 4.09).[151]

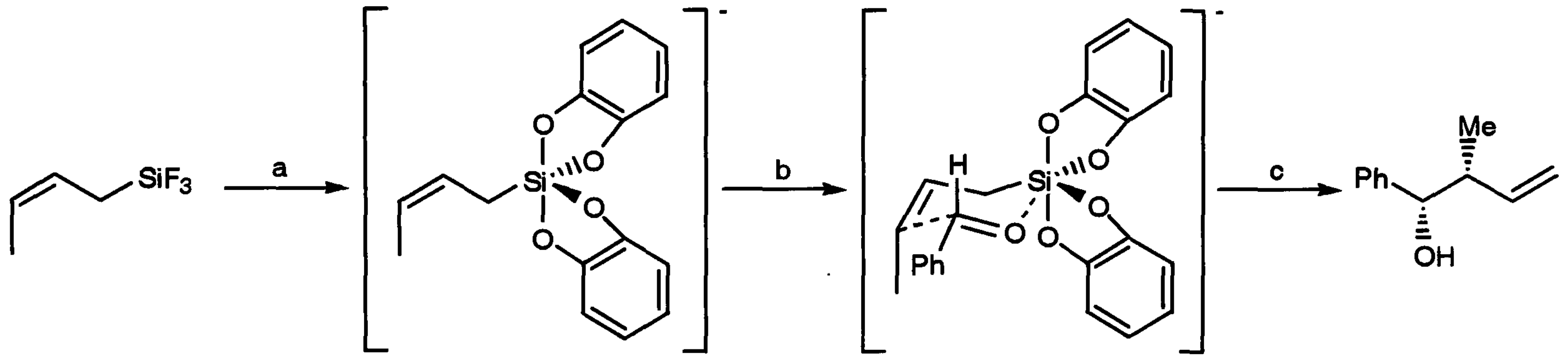


4.39 **4.40** **4.41** **4.42**

b) (+)-di(*iso*-propyl)tartrate, DMF; b) $CH_3(CH_2)_4CHO$ (R = $CH_3(CH_2)_4$, 52%, e.e. = 81%).

Scheme 4.09

Both Kira and Hosomi have used catechol-based pentacoordinate crotylsilanes in a similar manner, albeit with limited diastereoselectivity. The overall negative charge of the pentavalent intermediate **4.43** is stabilised by delocalisation into the electronegative ligands, resulting in electron deficiency at silicon and a consequent increase in the Lewis acidity at this centre (Scheme 4.10).[150,152]



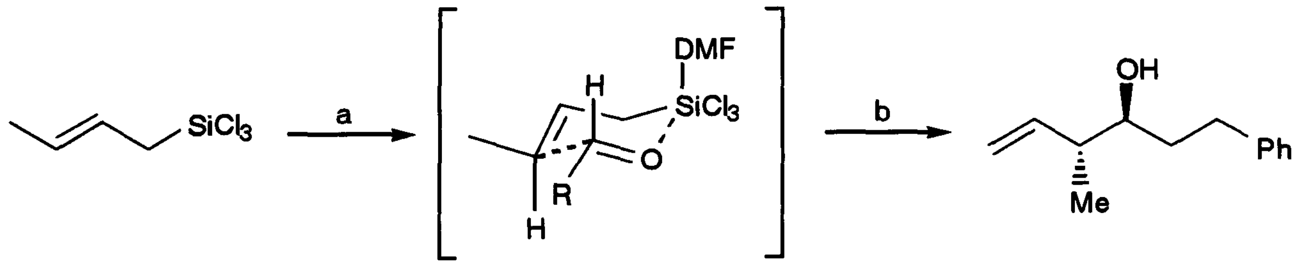
4.10 **4.43** **4.44** **4.12**

a) catechol, TEA; b) PhCHO, 80 °C; c) H_3O^+ (88%, d.r. = 90:10).

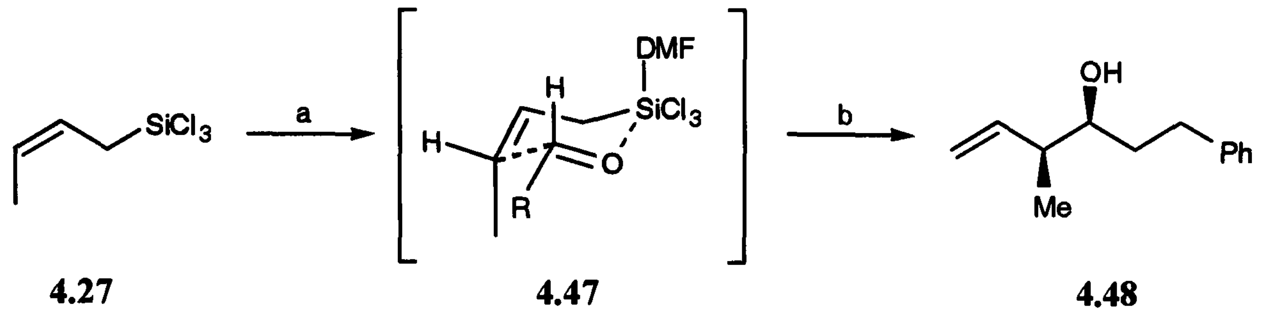
Scheme 4.10

4.5 Chiral Lewis bases

Kobayashi has examined the use of simple Lewis bases, such as HMPA, to activate allyltrichorosilanes towards carbonyl addition *via* the formation of hypervalent silicates. In the presence of donating co-solvents such as DMF the conditions are essentially neutral, yet the Hosomi-Sakurai reactions proceeded efficiently in the absence of additional catalysts (Scheme 4.11).[153]



4.24 **4.45** **4.46**



a) $Ph(CH_2)_2CHO$, DMF, 0 °C; b) H_3O^+ (**4.46** 87%, d.r. = 97:3; **4.48** 90%, d.r. = 99:1).

Scheme 4.11

The use of chiral Lewis bases to promote stereoselective allylation and crotylation is now emerging as a highly efficient method to prepare homoallylic alcohols and amines.[122,145] Excellent levels of enantio- and diastereoselectivity have been observed with chiral amine **4.49**,[154] urea **4.50**,[155] pyridine-*N*-oxides **4.51** and **4.52**,[156] formamides **4.53**,[157] phosphoramides **4.54**,[158] and sulfoxides **4.55**,[159] employed as allylation promoters (Figure 4.02).

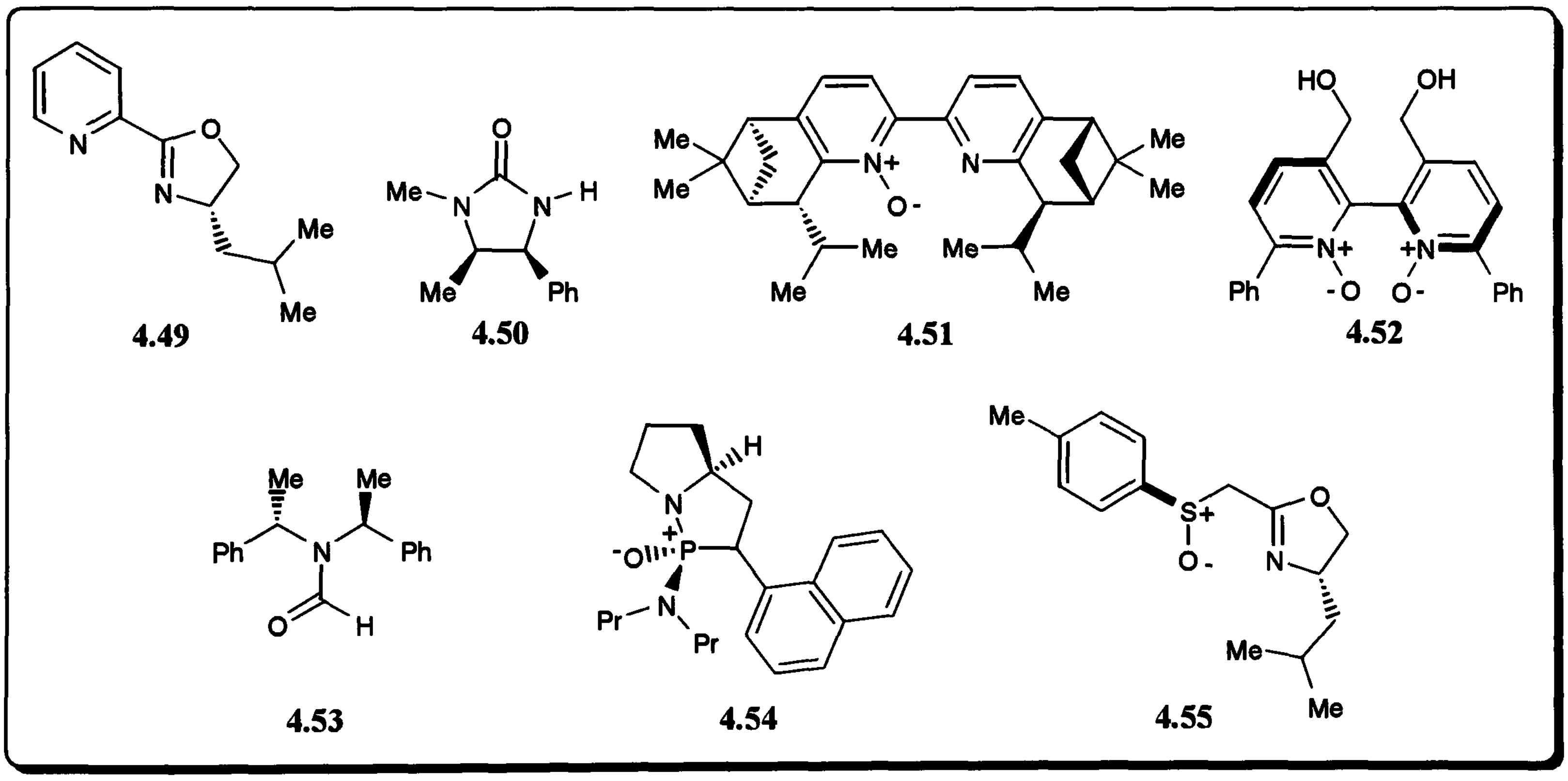
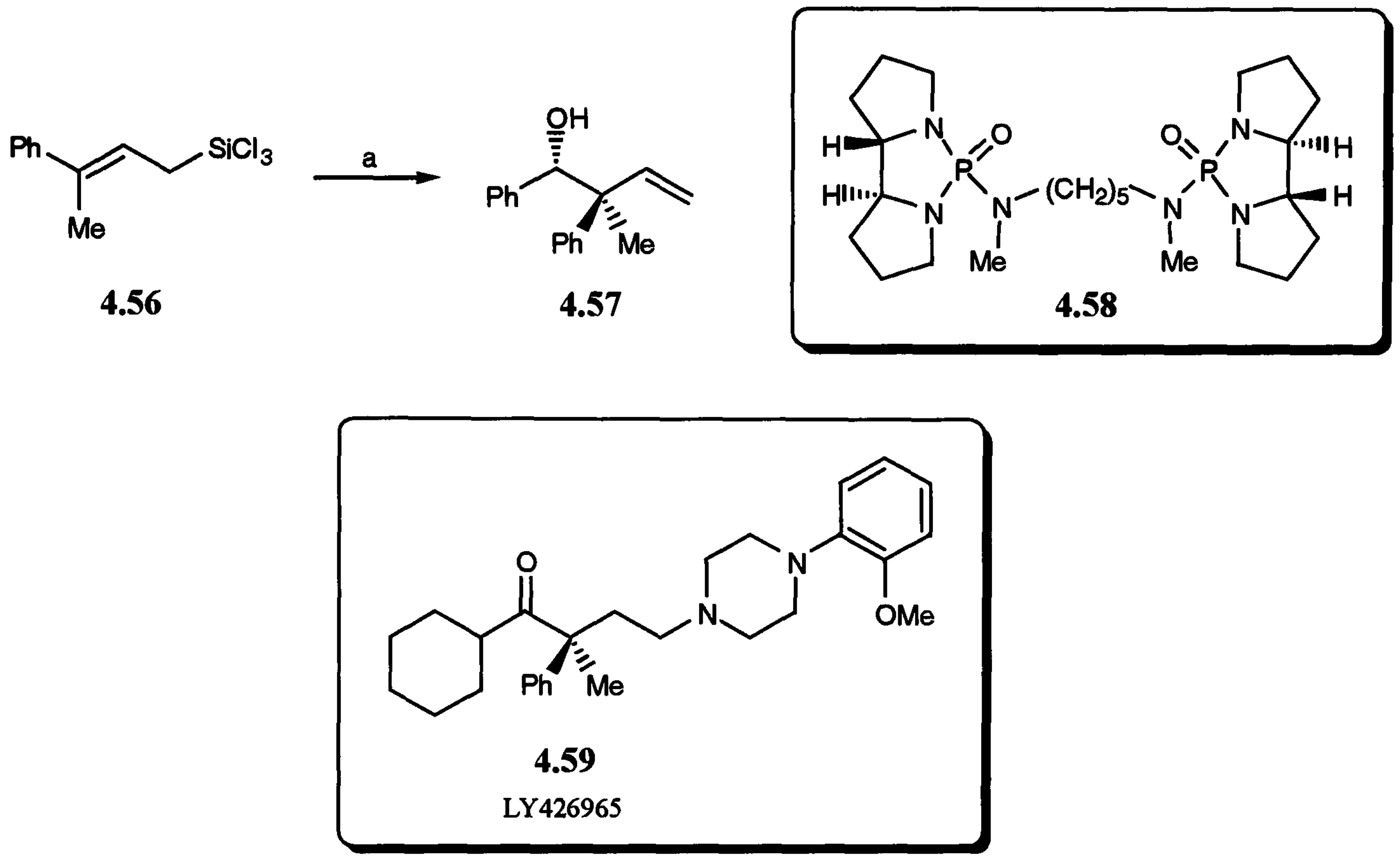


Figure 4.02

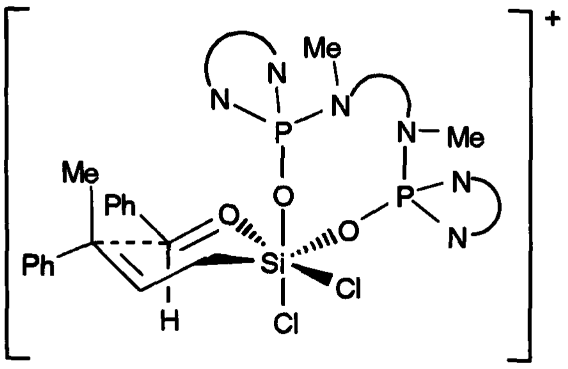
Chiral Lewis base methodology has been extensively studied by Denmark,[160] who was the first to investigate the use of chiral phosphoramides to generate reactive hypervalent allylsilicates *in situ*.[161] This strategy has recently been extended to dimeric activators, employed to construct stereogenic quaternary carbon centres enantioselectively.[162] Bisphosphoramide **4.58**, derived from 2,2'-bispyrrolidine, successfully catalysed the diastereoselective Hosomi-Sakurai reaction of benzaldehyde with γ,γ-disubstituted silane **4.56** to afford **4.57**, a key intermediate in the synthesis of arylpiperazine derivative LY426965 (**4.59**), a known serotonin antagonist (Scheme 4.12).[163]



a) PhCHO, **4.58** 10 mol%, Bu_4NI, DCM, -78 °C (64%, d.r. = 99:1; e.r. = 97:3).

Scheme 4.12

The allylation is thought to proceed through a six-membered cyclic transition state (Type I mechanism), with the chiral Lewis base (**4.58**) chelating to allylsilane **4.56** at its highly electropositive silicon centre. Loss of a chloride ion generated cationic octahedral species **4.60**, sufficient Lewis acidity being retained at this position to allow co-ordination of the carbonyl substrate, promoting transfer of the allyl substituent (Figure 4.03).[164]

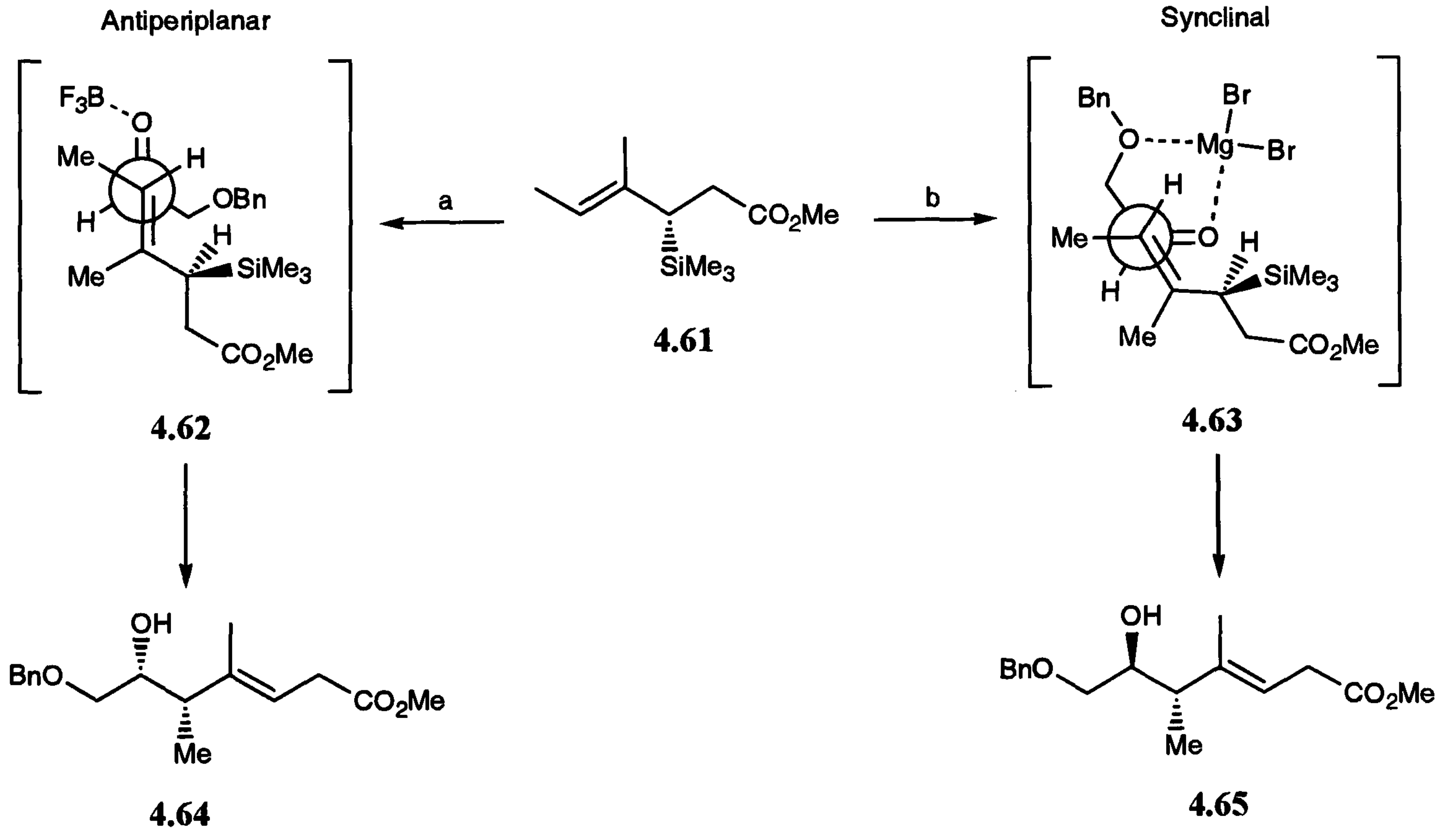


4.60

Figure 4.03

4.6 Lewis acid catalysed allylation with α-chiral silanes

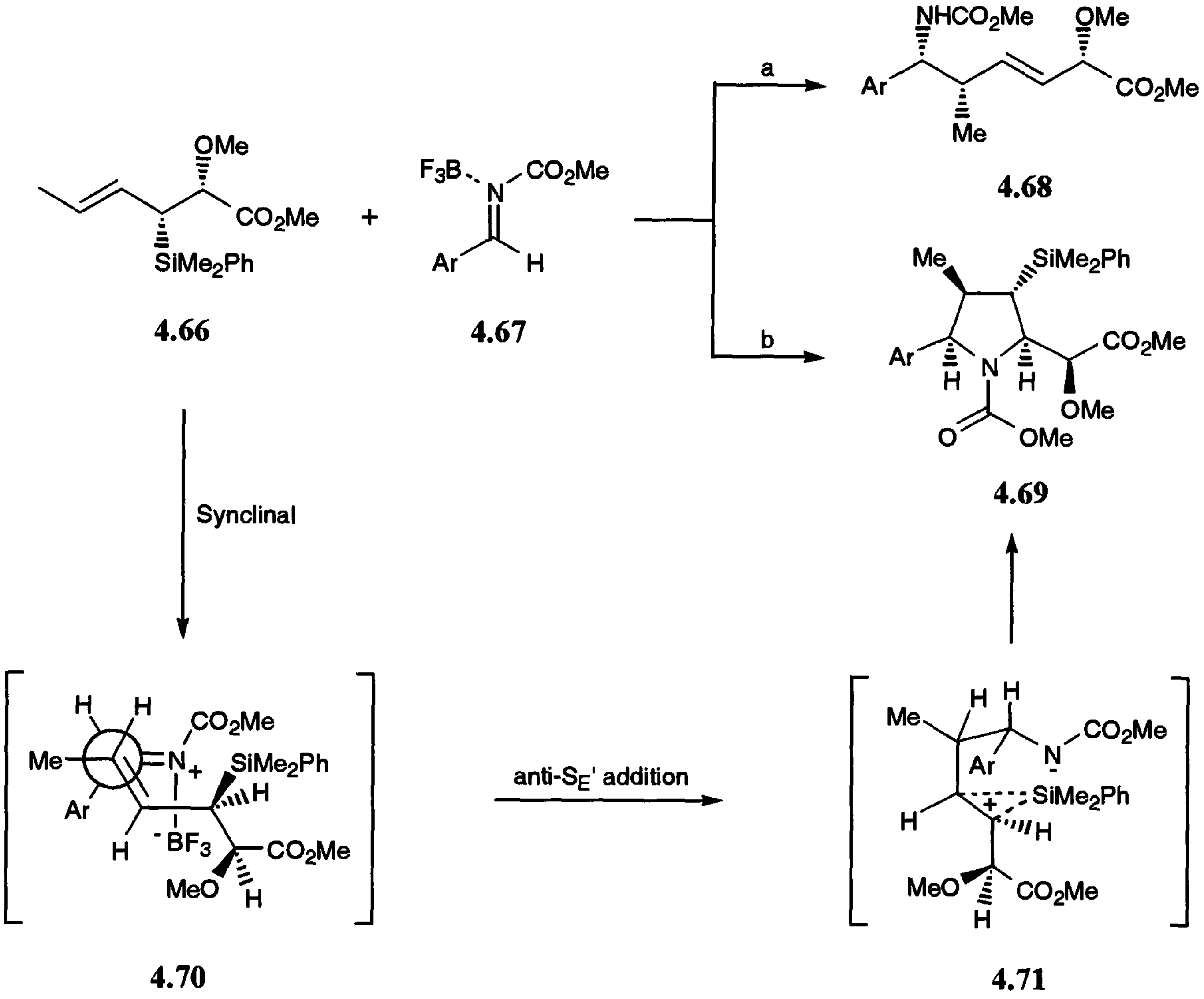
Several groups have reported the use of α-chiral silanes to impart stereoselectivity during allylation reactions.[129,7] Panek has studied this methodology extensively and employed α-chiral allylsilane reagents in the syntheses of chiral homoallylic alcohols (Scheme 4.13),[165] chiral tetrahydrofurans,[166] chiral homoallylic amines and functionalised pyrrolidines (Scheme 4.14).[167] In the case of chiral silane **4.61**, the diastereoselection of the Lewis acid-catalysed *E*-crotylation can be reversed by exerting the influence of chelation ($MgBr_2.OEt_2$) and non-chelation ($BF_3.OEt_2$) controlled conditions.



a) $BnOCH_2CHO$, $BF_3.OEt_2$, -78 °C (d.r. = 7:1); b) $BnOCH_2CHO$, $MgBr_2.OEt_2$, -25 °C (d.r. = 13:1).

Scheme 4.13

The diastereoselective synthesis of *syn* homoallylic carbamate **4.68** resulted from direct amino-crotylation of *N*-acyl imine **4.67** generated *in situ*. At lower temperatures silyl-functionalised pyrrolidine **4.69** was obtained, resulting from a [3+2] annulation pathway (Scheme 4.14).[167]

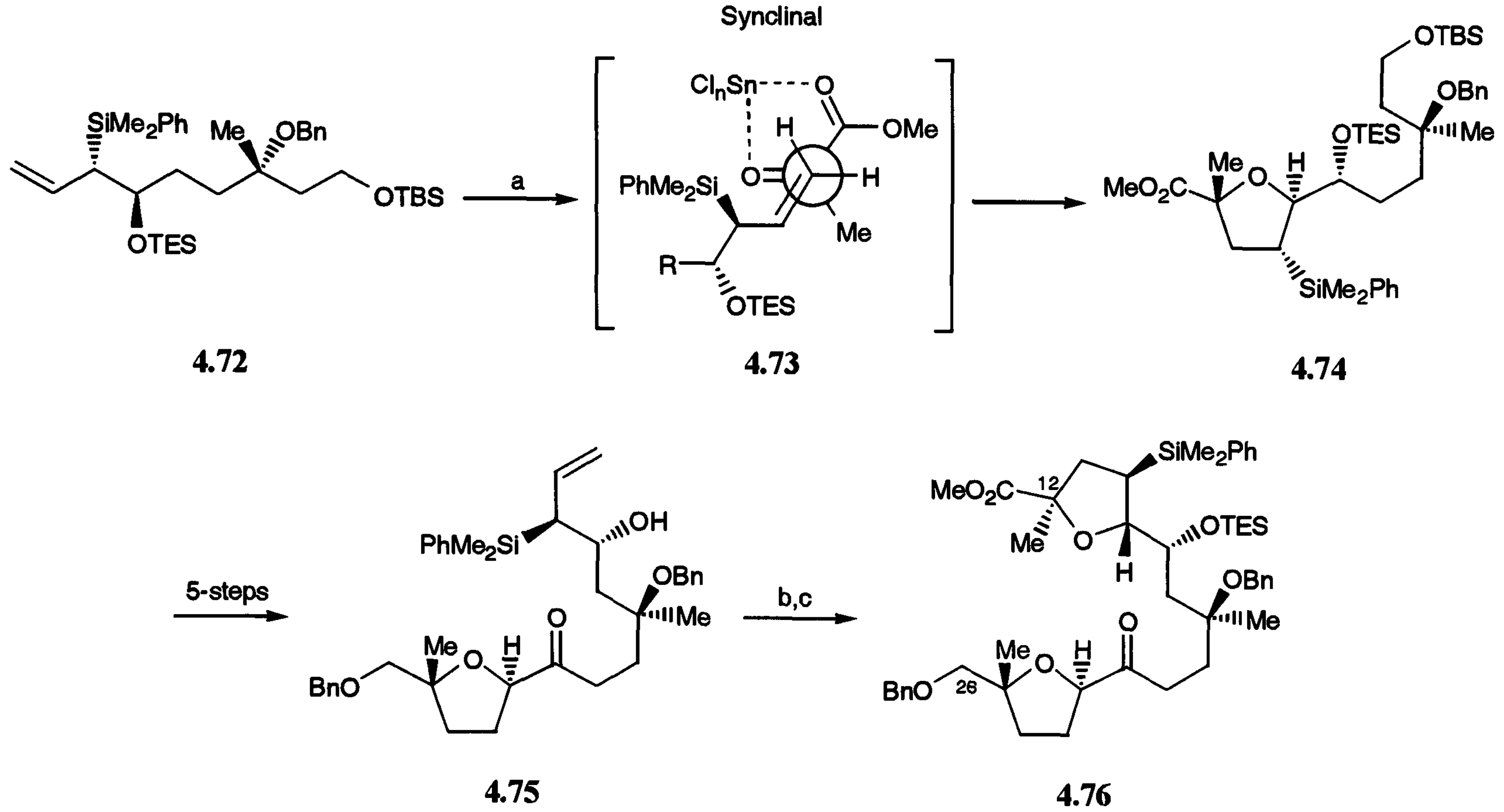


a) ArCHO, H_2NCO_2Me, $BF_3.OEt_2$, -20 °C (**4.68** 79%, d.r. = 9:1);

b) ArCHO, H_2NCO_2Me, $BF_3.OEt_2$, -100 °C to -78 °C (**4.69** 72%, d.r. = 20:1).

Scheme 4.14

Chiral tetrahydrofurans have been prepared in a similar manner by Roush *et al.* during studies toward the total the synthesis of the highly cytotoxic polyether macrolide Pectenotoxin II. The C_{11}-C_{26} sub-unit (**4.76**) was prepared *via* two stereoselective [3+2] annulation reactions of α-chiral allylsilanes **4.72** and **4.75** (Scheme 4.15).[168]

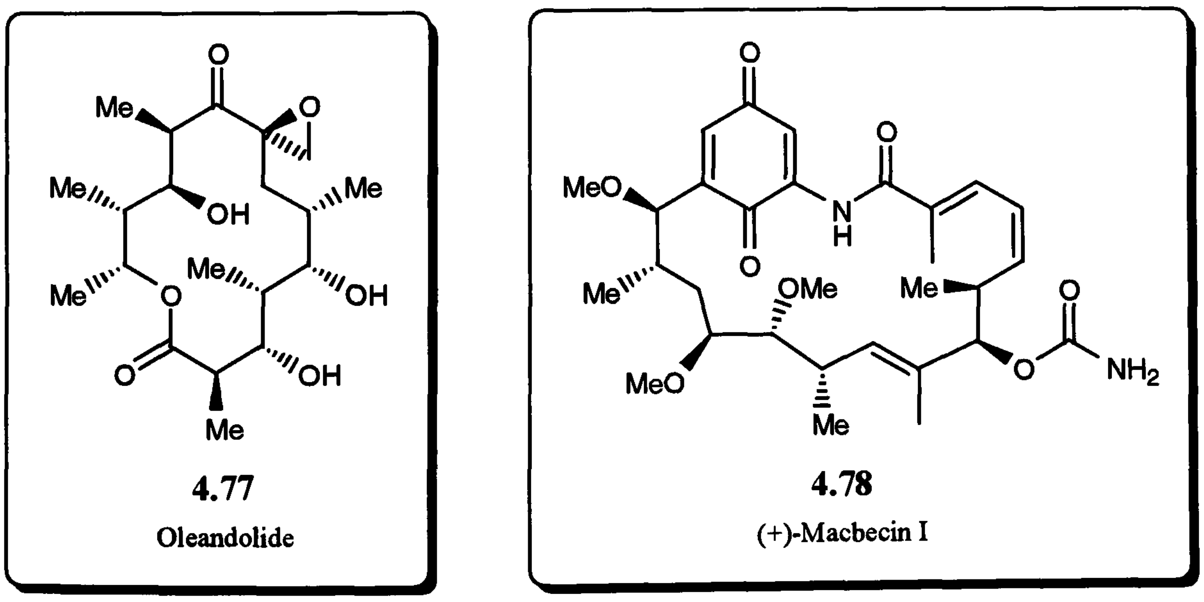


a) methyl pyruvate, $SnCl_2$, -78 °C (75%);

b) TESCl, Im., DMF; c) methyl pyruvate, $SnCl_2$, -78 °C (60% two steps).

Scheme 4.15

Panek applied his allylation strategy to the syntheses of several polypropionate derived macrolides,[169] such as oleandolide (**4.77**),[170] and a number of the ansamysin antibiotics,[171] including (+)-macbecin I (**4.78**) (Figure 4.04).[172]

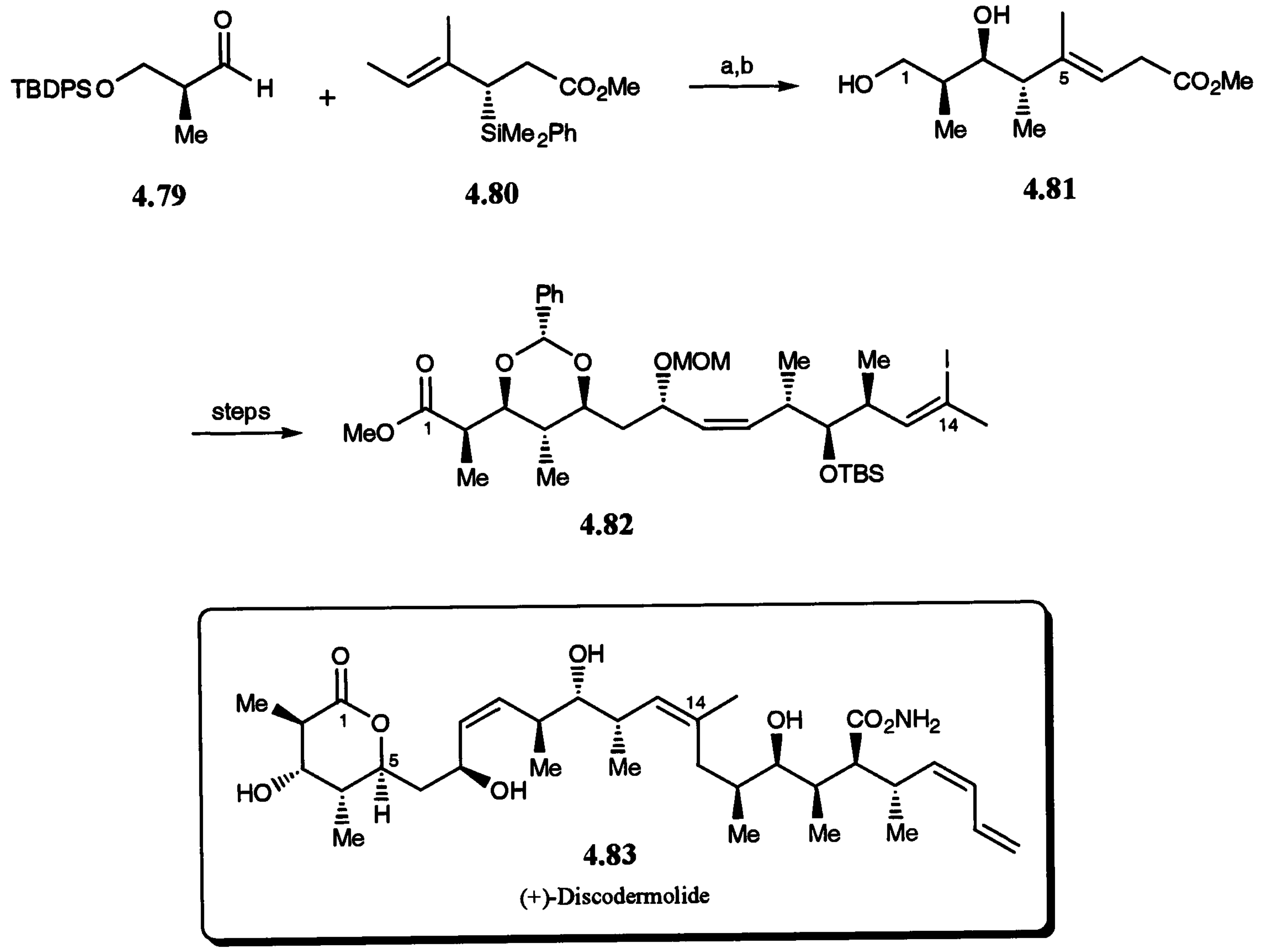


4.77
Oleandolide

4.78
(+)-Macbecin I

Figure 4.04

Of Panek's more recent syntheses,[173] his assembly of the C_1-C_{14} fragment (**4.82**) of cytotoxic marine metabolite (+)-discodermolide (**4.83**) provides a pertinent example of chiral *E*-crotylsilane bond construction methodology (Scheme 4.16).[174]

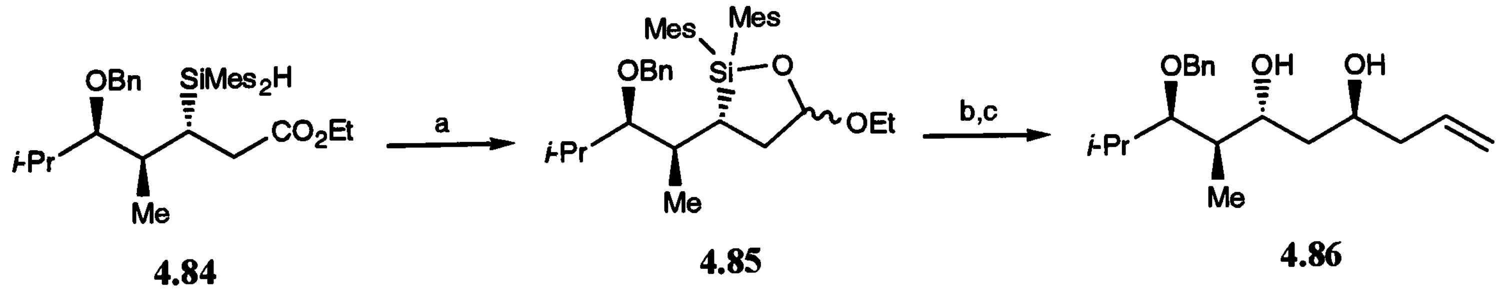


4.79 **4.80** **4.81** **4.82** **4.83**

a) $TiCl_4$, -78 °C; b) H_3O^+ (85%, d.r. = 30:1).

Scheme 4.16

Woerpel has devised a novel hydrosilylation-allylation methodology to generate polyols diastereoselectively from α-chiral silanes (Scheme 4.17).[175]



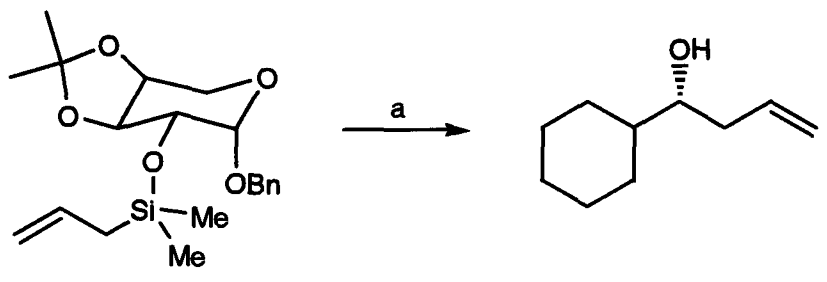
4.84 **4.85** **4.86**

a) TBAF 10 mol%, 0 °C (82%, d.r. = 85:15); b) allyltrimethylsilane, $BF_3.OEt_2$, -78 °C–0 °C (91%); c) TBHP, $CsOH.H_2O$, CsF, NMP (69%, d.r. = 99:1).

Scheme 4.17

4.7 Chiral auxiliaries

In an extension of Chan's work with silicon-bearing (–)-β-pinene,[176] pyrrolidine[177] and (–)-menthyloxy[178] ligands, Shing has attached allylsilanes to carbohydrate-based chiral auxiliaries in order to direct the stereoselectivity of the Hosomi-Sakurai reaction.[179] The Lewis acid-mediated allylation of simple aldehydes with chiral allylsilane **4.87**, derived from L-arabinose, allowed access to homoallylic alcohols with moderate enantioselectivity (Scheme 4.18).

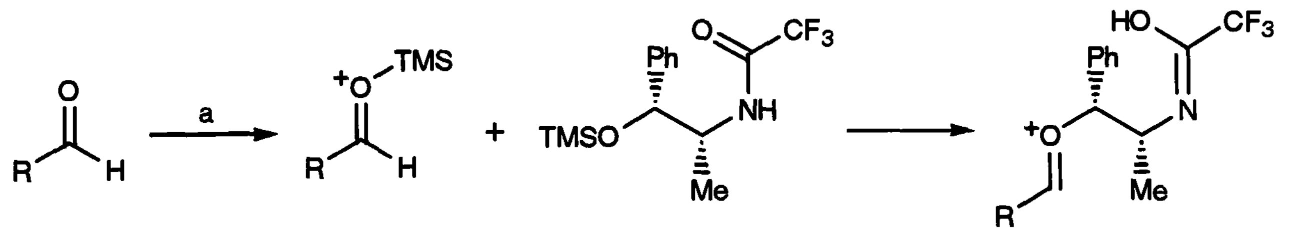


4.87 **4.88**

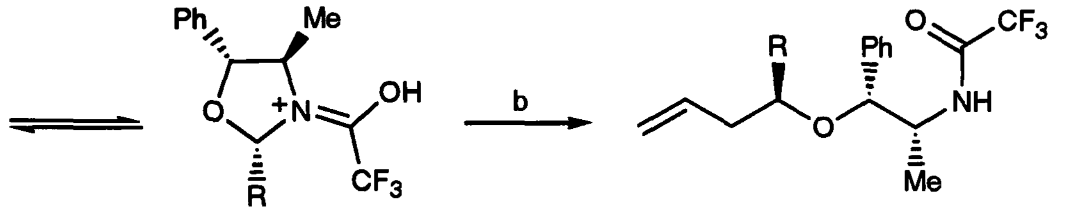
a) $(C_6H_{11})CHO$, $BF_3.OEt_2$, -78 °C (71%, e.e. = 38%).

Scheme 4.18

Tietze has examined the use of norpseudoephedrine to generate chiral auxiliary **4.93** *in situ*; stereoselective allylation of aliphatic aldehydes and ketones has been successfully achieved employing this strategy.[180] The oxonium ion **4.90** was formed initially *via* the reaction of the carbonyl substrate **4.89** with catalytic trimethylsilyltriflate; addition of norpseudoephedrine derivate **4.91** generated **4.92** which cyclised to form oxazolidinium ion intermediate **4.93** as the chiral auxiliary. Nucleophilic addition of allyltrimethylsilane to **4.93** produced the homoallylic ether **4.94** with excellent diastereoselectivity (Scheme 4.19). Subsequent deprotection furnishing the enantiopure homoallylic alcohol in 88% yield.



4.89 **4.90** **4.91** **4.92**



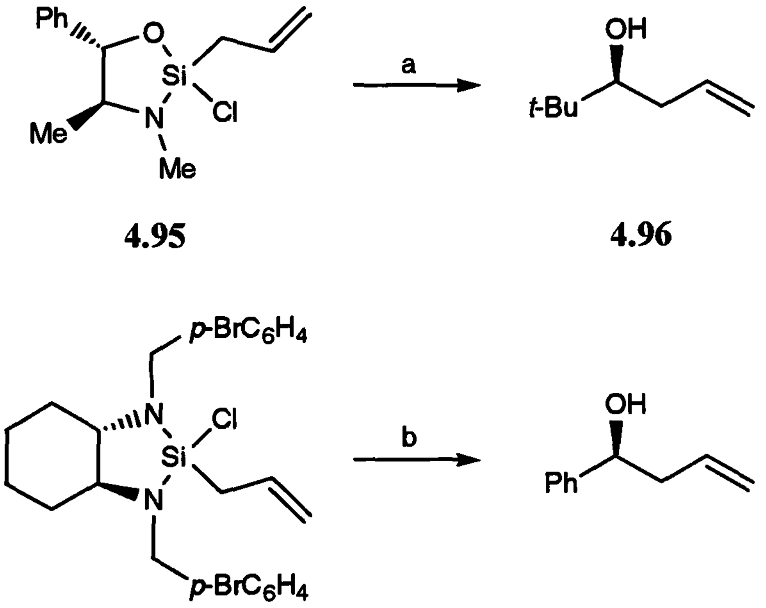
4.93 4.94

a) TMS-OTf, -78 °C; b) allyltrimethylsilane (R = *i*-Pr, 71%, d.e. = 99%).

Scheme 4.19

4.8 Strained silacycles

As discussed in Section 4.1, constraining silicon within a small ring leads to an associated increase in Lewis acidity; this has proved an effective way to activate allylsilanes towards addition to carbonyl derivatives. In an extension of Trombini's work with chiral tin complexes,[181] Leighton applied the same principle to strain-activated silacycles as a means to prepare homoallylic alcohols enantioselectively. Substituted-trichlorosilanes were treated with chiral 1,2-diols, 1,2-diamines and 1,2-amino alcohols to generate strained five-membered heterocycles, with silicon bearing allylic functionality (Scheme 4.20).[182]



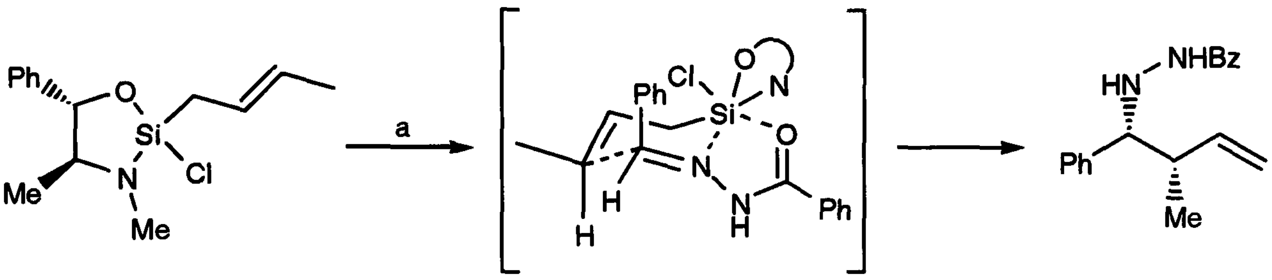
4.95 4.96

4.97 4.98

a) *t*-BuCHO, -10 °C (80%, e.e. = 96%); b) PhCHO, -10 °C (69%, e.e. = 98%).

Scheme 4.20

Leighton has recently expanded this methodology to encompass the diastereoselective crotylation of acylhydrazones to facilitate the synthesis of chiral amines. Although the exact mode of reaction is not known, it has been postulated that the hydrazone bis-chelates to the strained silacycle forming hexacoordinate siliconate species **4.100** prior to allylation (Scheme 4.21).[183]



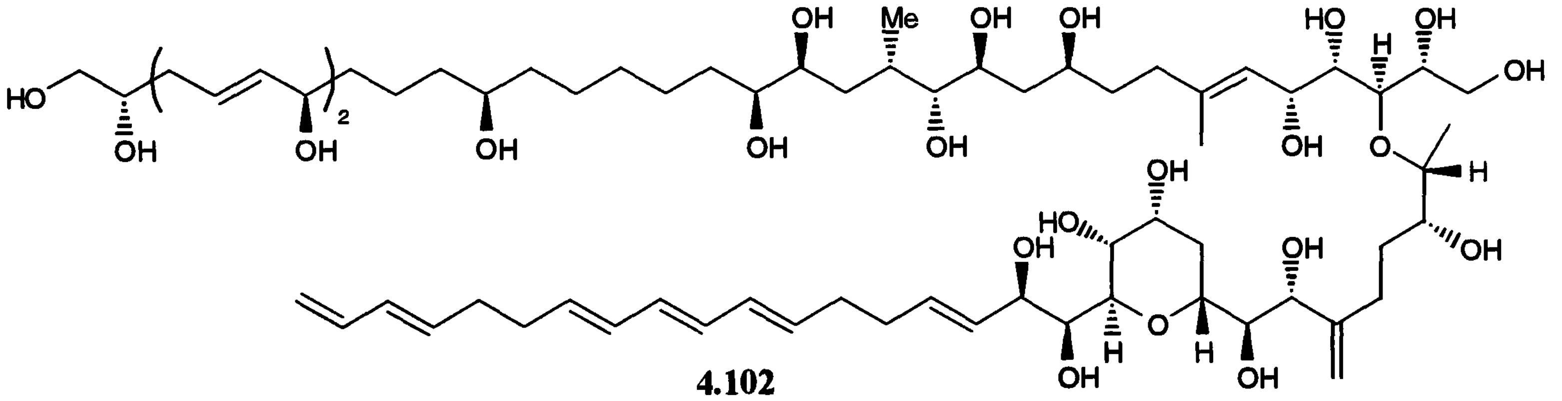
4.99 **4.100** **4.101**

a) benzaldehyde benzoylhydrazone, DCM, 10 °C (89%, d.r. = 95:5, e.e. = 97%).

Scheme 4.21

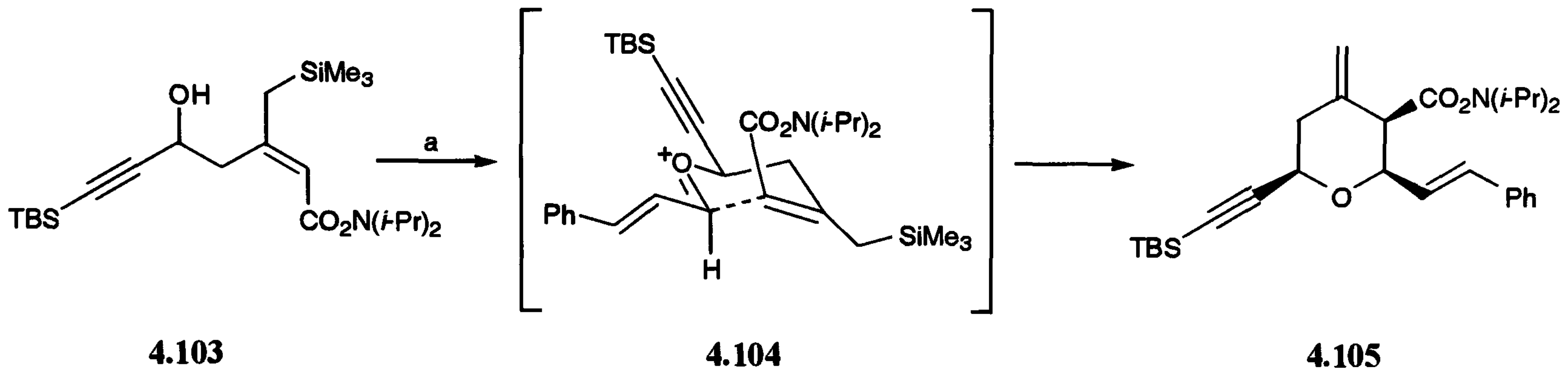
4.9 Exocyclic intramolecular allylation

Exocyclic intramolecular Hosomi-Sakurai reactions, in which the participating silane is located outside the forming ring, have been investigated by a number of groups.[121,7] For example, Markó *et al.* examined the intramolecular allylation reaction of oxonium intermediate **4.104** to synthesise *exo*-methylene tetrahydropyran **4.105**. Polysubstituted tetrahydropyrans are a common structural sub-unit of polyhydroxy-polyenes of the amphidinol class (Scheme 4.22).[184]



4.102

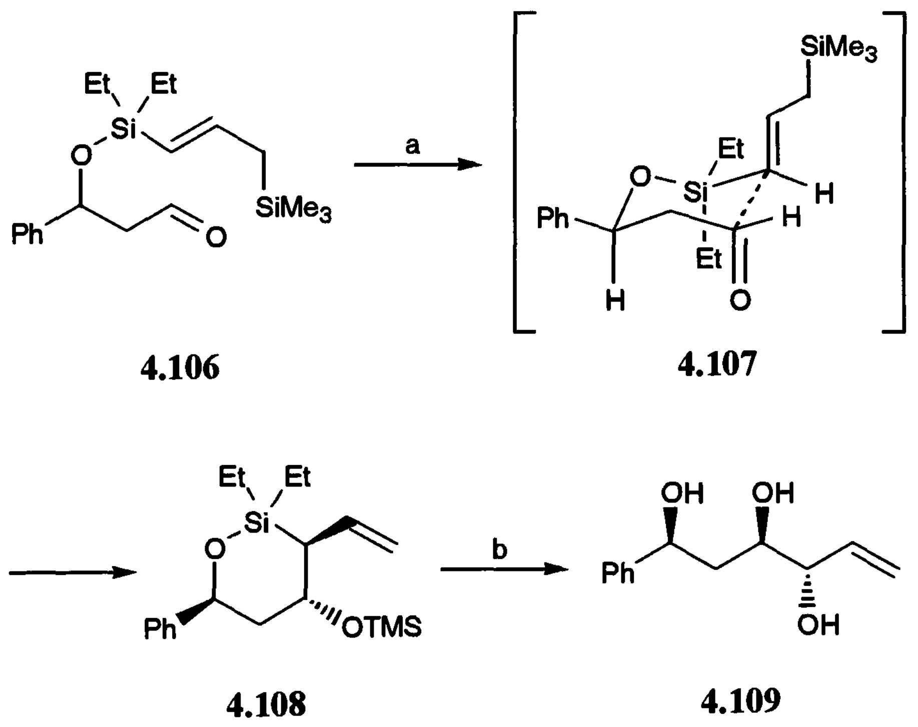
Amphidinol III



a) (*E*)-PhCH=CHCHO, $BF_3.OEt_2$, DCM, -78 °C–0 °C (63%, d.r. = 79:21).

Scheme 4.22

Cox has recently developed a novel silicon-tethered exocyclic intramolecular allylation reaction as a means to access stereodefined 1,2,4-triols (Scheme 4.23). Cyclisation of substrate **4.106** generated oxasilacyclic product **4.108**, as the major diastereomer, in which the silane tether remained intact. The reacting silane was exocyclic with respect to the proposed transition state (**4.107**) and was cleaved during the course of the allylation. The preference for the *exo*-silane to adopt a pseudo-axial orientation is thought to be the result of a steric requirement to reduce interactions between the allylsilane appendage and the ethyl substituents of the silicon tether.[185]

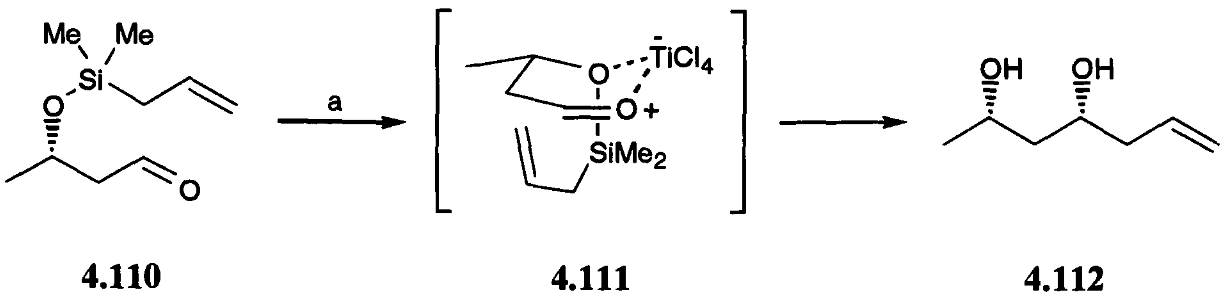


a) TMS-OTf, 2,6-DTBMP, DCM, -78°C (88%, d.r. = 4:1); b) H_2O_2, KF, $KHCO_3$, MeOH-THF (73%).

Scheme 4.23

4.10 Endocyclic intramolecular allylation

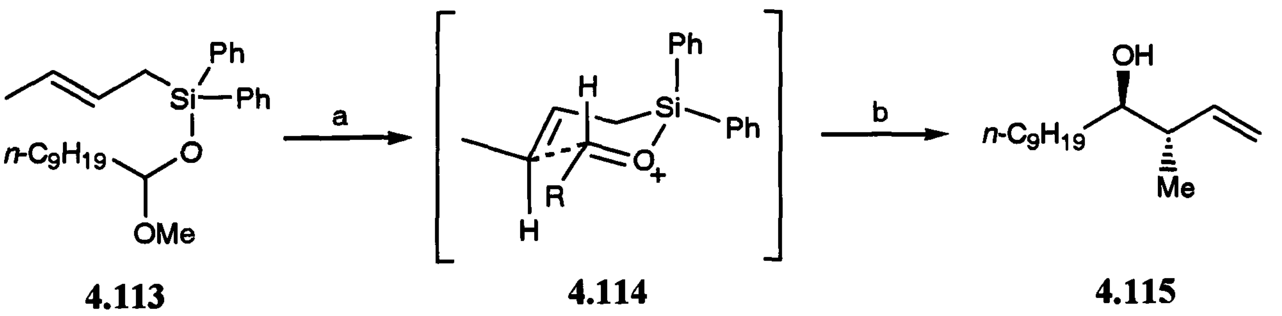
A growing number of examples of silicon tethered endocyclic allylation are being reported in the literature. This area of silicon tethered methodology stemmed from Reetz's study of the behaviour of substrate **4.110** with a variety of Lewis acids. Reetz's findings indicated that the stereoselectivity of the silicon tethered allylation was dictated by the choice of Lewis acid, and only proceeded through an intramolecular pathway when catalysed by chelating Lewis acid titanium (IV) chloride (Scheme 4.24).[186]

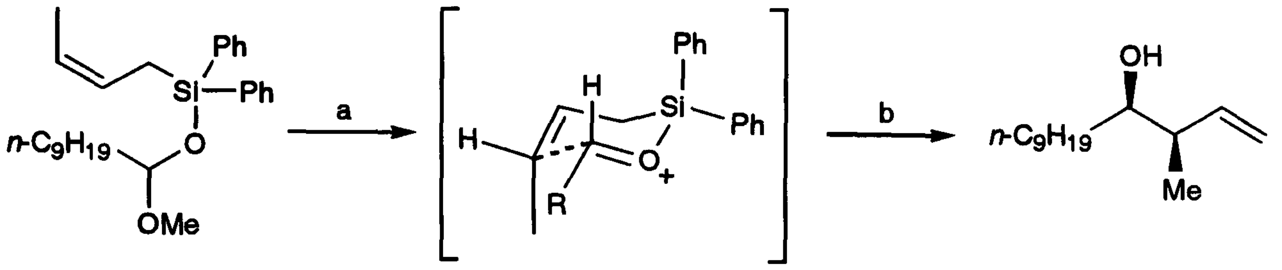


a) $TiCl_4$ (70%, d.r. = 92:8).

Scheme 4.24

The lack of stereospecificity observed with Lewis acid-mediated intermolecular crotylation (Section 4.1) has been addressed by Oshima *et al.* By tethering the crotyl substituents, the addition process was forced to proceed in a stereoselective manner through a cyclic transition state, with *E*- and *Z*-crotylsilyl acetals **4.115** and **4.118** providing *anti*- and *syn*-homoallylic alcohols respectively (Scheme 4.25).[187]



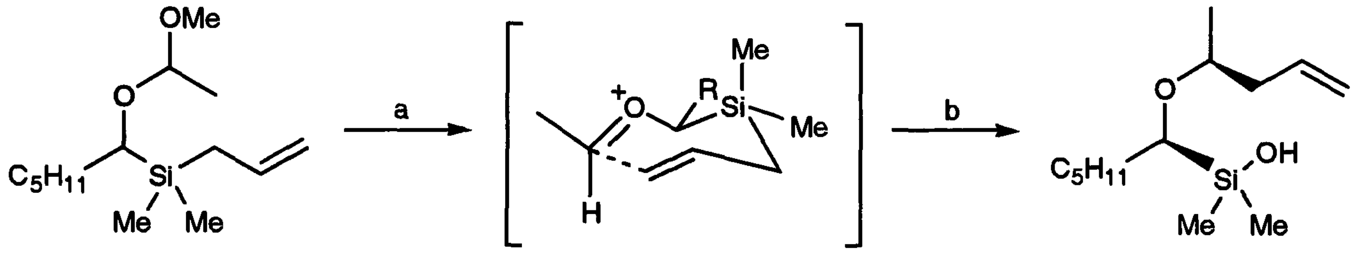


4.116 **4.117** **4.118**

a) $TiCl_4$, -78 °C; b) TBAF-THF (**4.115** 70%, d.r. = 91:9; **4.118** 70%, d.r. = 93:7).

Scheme 4.25

In a related process, Linderman prepared silyl-substituted mixed acetal **4.119** for intramolecular allylation. Oxonium ion **4.120** was generated *in situ* and subsequent S_E' synclinal transfer of the allyl substituent, *via* a seven-membered cyclic transition state, furnished **4.121** in good yield (Scheme 4.26).[188]

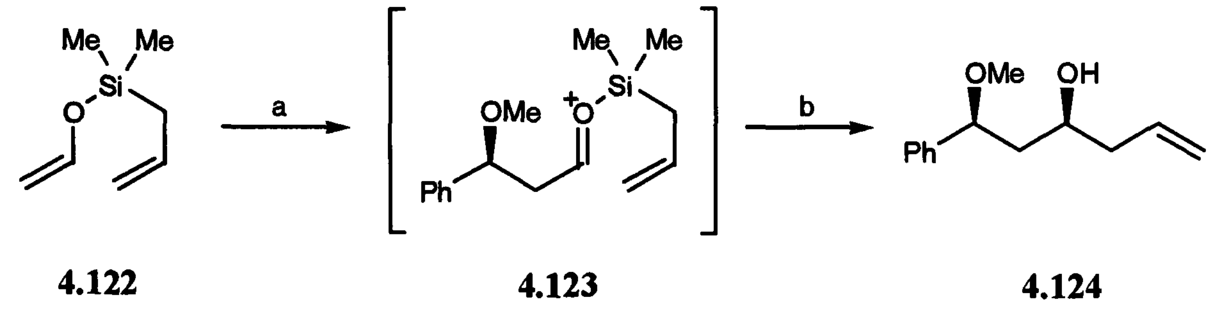


4.119 **4.120** **4.121**

a) TMS-OTf, DCM, -78 °C b) SiO_2-H_2O (70%).

Scheme 4.26

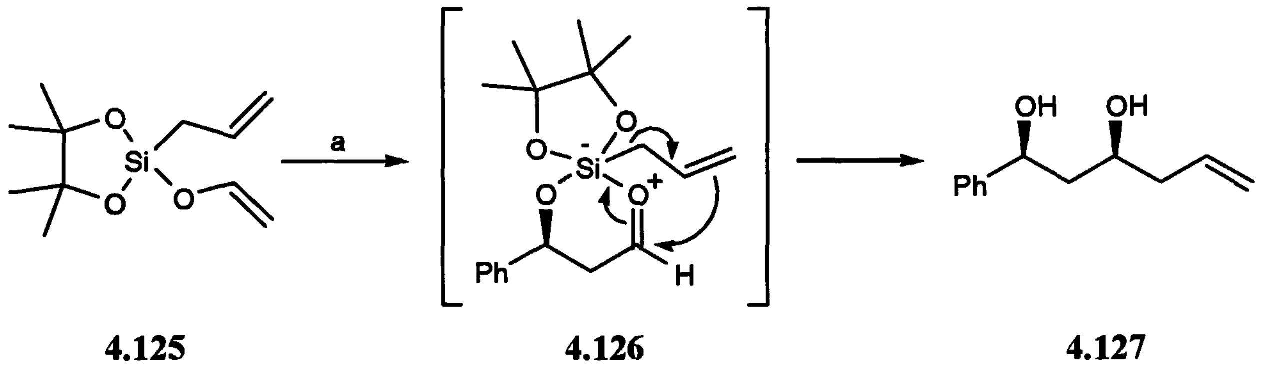
A further example of intramolecular nucleophilic delivery is demonstrated by Berrisford's approach to 1,3-diols. The tandem intermolecular aldol-intramolecular allylation process resulted in the rapid construction of *syn*-diol derivative **4.124**, although only modest levels of diastereoselectivity were observed (Scheme 4.27).[189]



a) $PhCH(OMe)_2$, $BF_3.OEt_2$, DCM, -40 °C; b) KF (77%, d.r. = 62:38).

Scheme 4.27

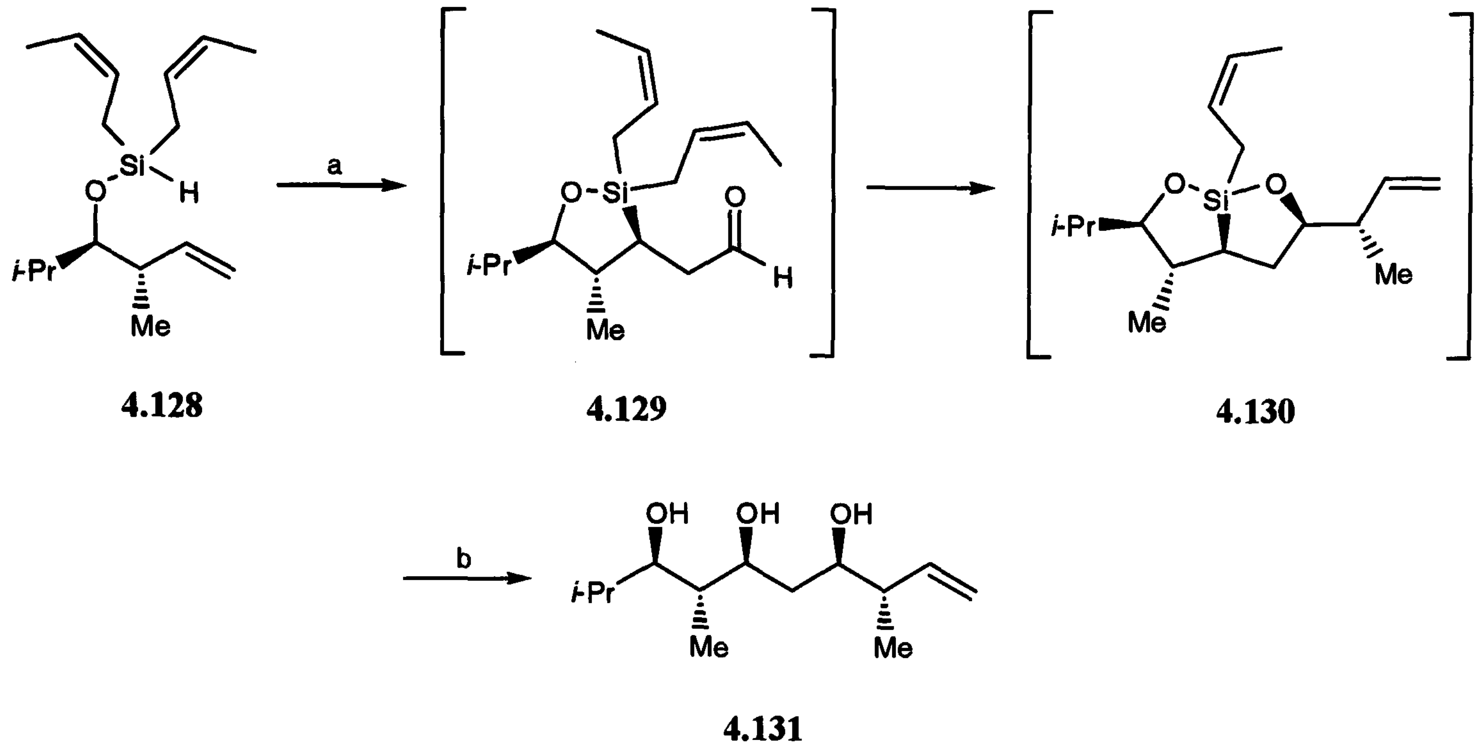
Leighton's research in this area has been prolific; 1,3-diol **4.127** was prepared *via* an analogous tandem intermolecular aldol-intramolecular allylation process, employing strain-activated silacycle **4.125** (Scheme 4.28).[190]



a) PhCHO, 40 °C (60%, d.r. = 11:1).

Scheme 4.28

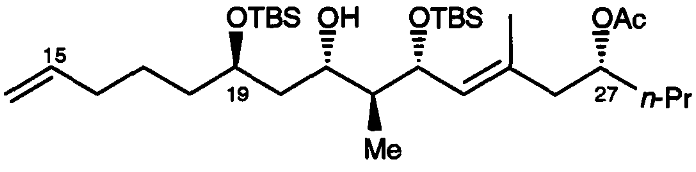
Leighton *et al.* also developed a silicon tethered approach for the rapid assembly of polyketide fragments, by combining rhodium-catalysed silylformylation with strain release activated intramolecular crotylation (Scheme 4.29).[191] This novel process can be employed to generate up to three stereocentres simultaneously, controlled by the stereochemistry of the starting material. Recent investigations have indicated that the procedure can be used iteratively to generate repeating 1,3-diol motifs stereoselectively.[192]



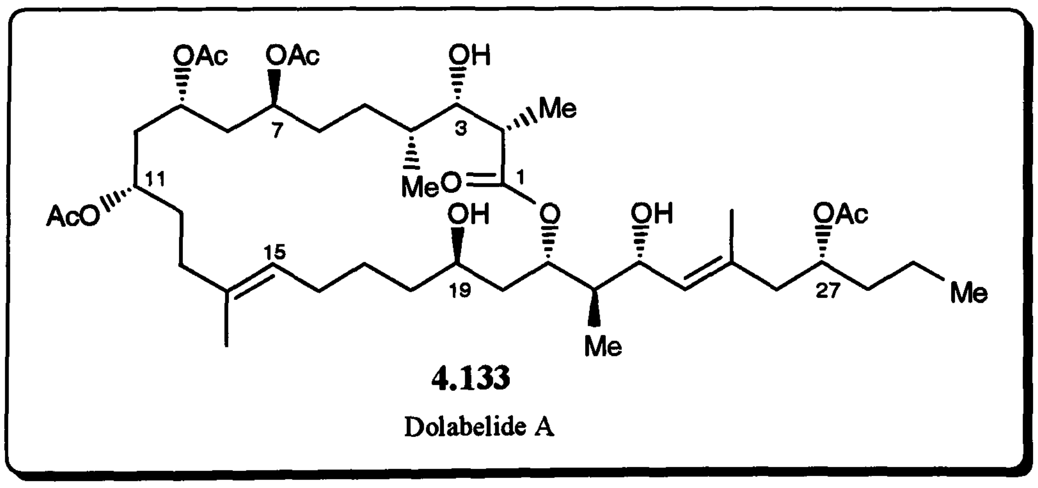
a) Rh(acac)(CO)$_2$ 3.0 mol%, CO, 60 °C; b) H$_2$O$_2$, NaHCO$_3$, MeOH-THF, Δ (67%, d.r. = 92:8).

Scheme 4.29

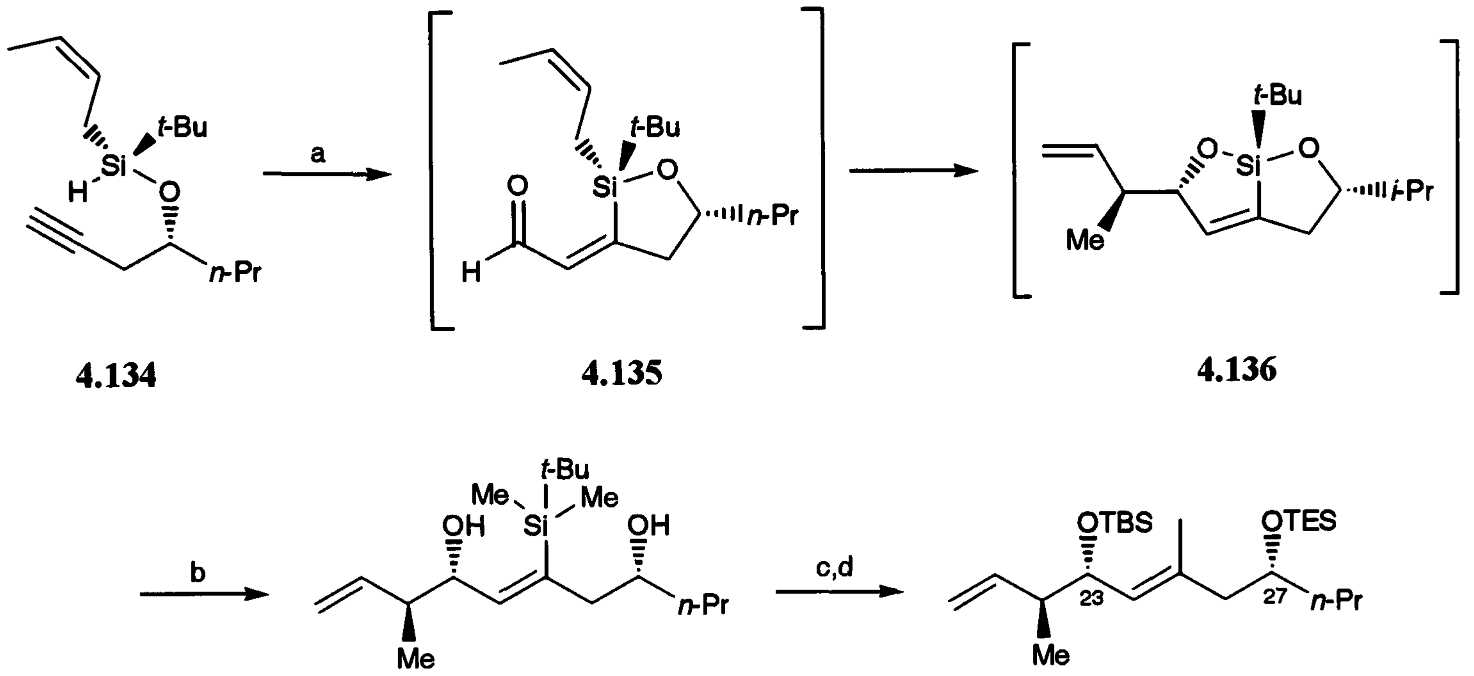
A key step in Leighton's recent synthesis of the C$_{15}$-C$_{30}$ fragment (**4.132**) of cytotoxic marine macrolide dolabelide A (**4.133**) was facilitated by the application of his tandem silylformylation-crotylsilylation methodology (Scheme 4.30).[193]



4.132



4.133
Dolabelide A



4.134 4.135 4.136

4.137 4.138

a) {Rh(acetone)$_2$[P(OPh)$_3$]$_2$}$^+$BF$_4^-$ 2.0 mol%, CO, 60 °C; b) MeLi (56%, d.r. = 4:1; two steps);

c) TESCl, TEA, -20 °C (74%); d) *n*-BuLi then CuBr.DMS, DMPU, MeI (92%).

Scheme 4.30

4.11 Conclusions

This chapter has introduced a selection of innovative methodologies developed to effect allylation of carbonyl derivatives and has underlined the importance of silicon-assistance in facilitating these processes. Several of the examples given in this introduction demonstrate the utility of organosilicon reagents in controlling the stereochemical outcome of the Hosomi-Sakurai reaction.

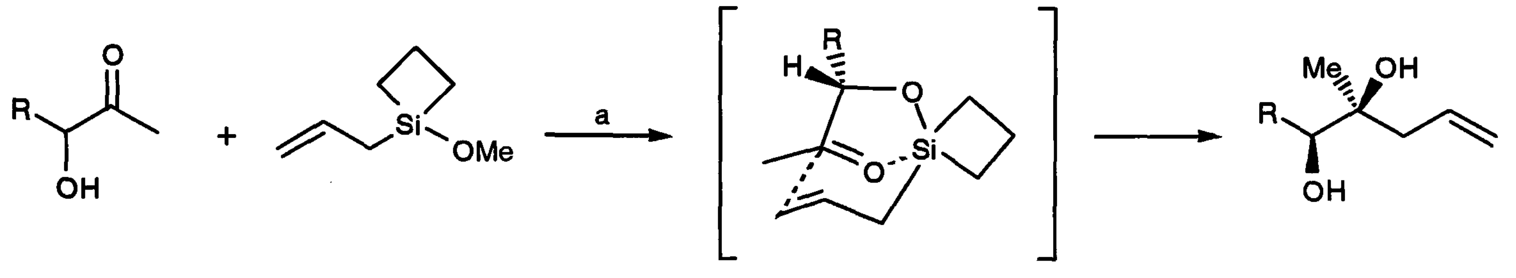
The following chapters will describe our own efforts to effect stereoselective intramolecular allylation of carbonyl derivatives reliant on the innate Lewis acidity of strained, hypervalent silicon, in the absence of external Lewis acid catalysis.

Chapter 5

Investigation of Carbonyl Allyl Transfer Reactions

5.0 Introduction

Our investigations of the Type I ene reactions of *O*-linked precursors in Chapter 3 had indicated that an unexpected mode of reaction predominated over the ene process under thermal conditions. Cognisant of the work of Utimoto involving pre-coordination of the carbonyl moiety to form activated intermediate **5.03** (Scheme 5.01),[138] we anticipated, that in our system, allyl transfer occurred similarly *via* mutual co-ordination of the silicon and the carbonyl oxygen, activating the carbonyl toward nucleophilic delivery of the tethered prenyl substituent.

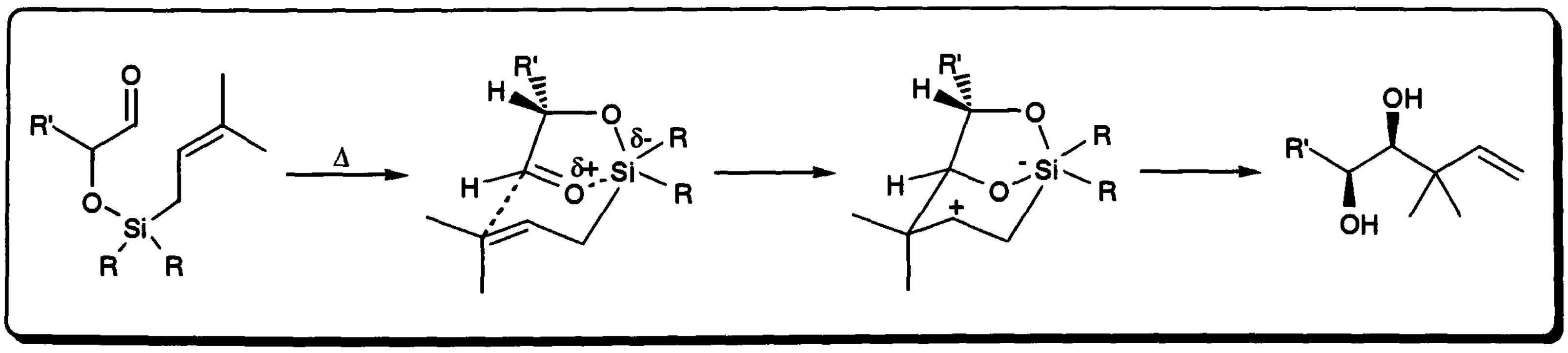


5.01 **5.02** **5.03** **5.04**

a) 100 °C then H_3O^+.

Scheme 5.01

With the allyl Si-C bond oriented co-planar with the C=C π -system, the system could stabilise a build up of positive charge β- to silicon (Scheme 5.02).



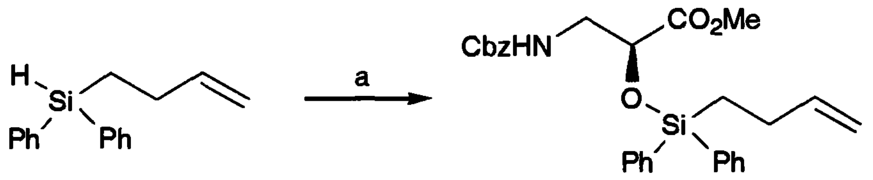
Scheme 5.02

The discovery of this high-yielding, stereoselective, thermal allyl transfer reaction diverted our attention away from the ene studies toward this novel allylation process. Since we had shown that silicon tethered allyl transfer with prenyl systems was viable under thermal conditions, giving rise to 1,2-diols stereoselectivity, attempts were made to develop an analogous process employing crotyl substrates. It was envisaged that the silicon tether would direct the attack of the crotyl substituent, generating methyl-diols stereoselectively.

5.1 Synthesis of *E*-crotyl system

With the *Z*-crotyl precursor **3.13** already in hand, attention now focussed on the preparation of the *E*-crotyl system. This was readily achieved by following a protocol developed within the group,[80] employing a commercially available iridium(I) complex, as a pre-catalyst, to isomerise the terminal double bond of a homoallylic silane *in situ*.[114]

Isoserine ester **3.05** was coupled with 3-butenyldiphenylsilane,[194] in the usual manner, to furnish the desired isomerisation precursor **5.05** in good yield (Scheme 5.03).

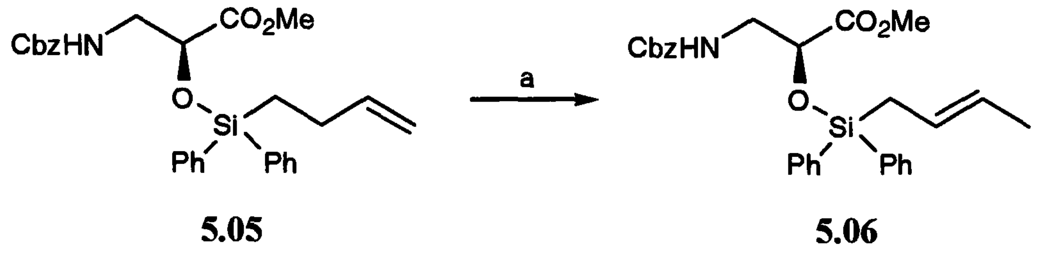


5.05

a) isoserine ester **3.05**, $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (70%).

Scheme 5.03

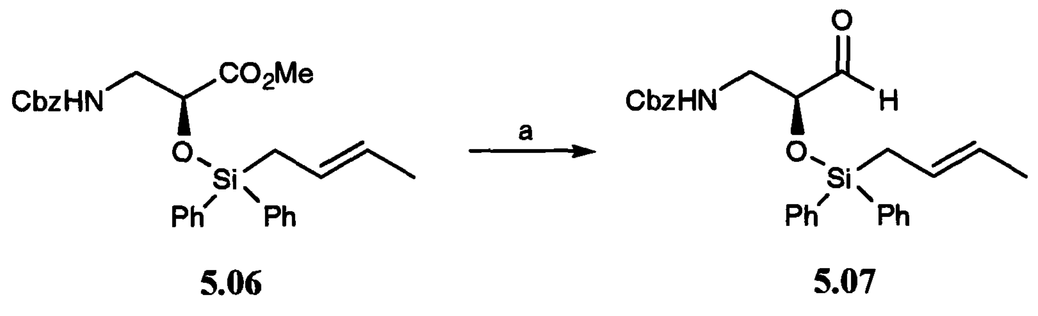
In an extension of Matsuda's work involving rhodium and iridium catalysed C=C bond migrations of simple trialkyl silanes,[195] pre-catalyst (1,5-cyclooctadiene)bis (methyldiphenylphosphine)iridium (I) hexafluorophosphate was employed, after hydrogen-activation, to isomerise the terminal double bond of **5.05** to the more stable internal position, generating the required *E*-crotyl substituent exclusively (Scheme 5.04).[196] Careful temperature regulation, controlled pre-activation of the catalyst and removal of excess hydrogen were required in order to ensure that further migration of the C=C bond, to the vinylic silane, was avoided.[197]



a) $[(COD)Ir(PPh_2Me)_2]^+PF_6^-$ 1.0mol%, H_2, DCM, -78 °C–0 °C (100%).

Scheme 5.04

Subsequent DIBAL reduction of ester **5.06** furnished the desired *E*-crotyl precursor for our thermal allyl transfer studies (Scheme 5.05). It should be noted that this substrate proved particularly unstable and was found to decompose upon standing at RT.

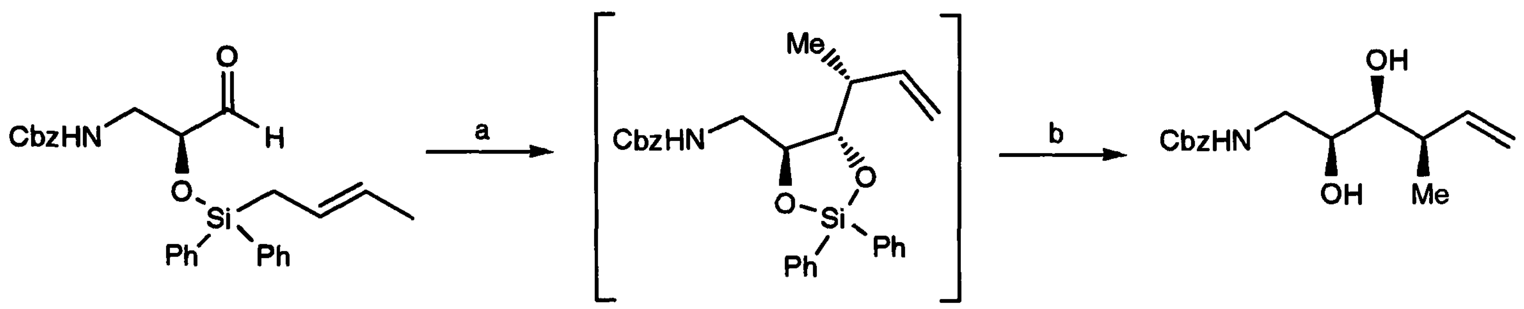


a) DIBAL, -78 °C (50%).

Scheme 5.05

5.2 Thermal allyl transfer of *Z*- and *E*-crotyl systems

Considering the lability of precursor **5.07**, the thermal allyl transfer reaction of the *E*-crotyl substrate proceeded very smoothly; heating a dilute solution of **5.07** at 130 °C in a sealed tube resulted in a single product being observed from ^1H NMR analysis of reaction aliquots. The crude product (**5.08**) was carried through directly to the deprotection step, as previous diphenyl-substituted siladioxolanes had proven unstable with respect to hydrolysis on silica gel. Subsequently, 1,2-homoallylic diol **5.09** was isolated cleanly in 80% yield (Scheme 5.06).

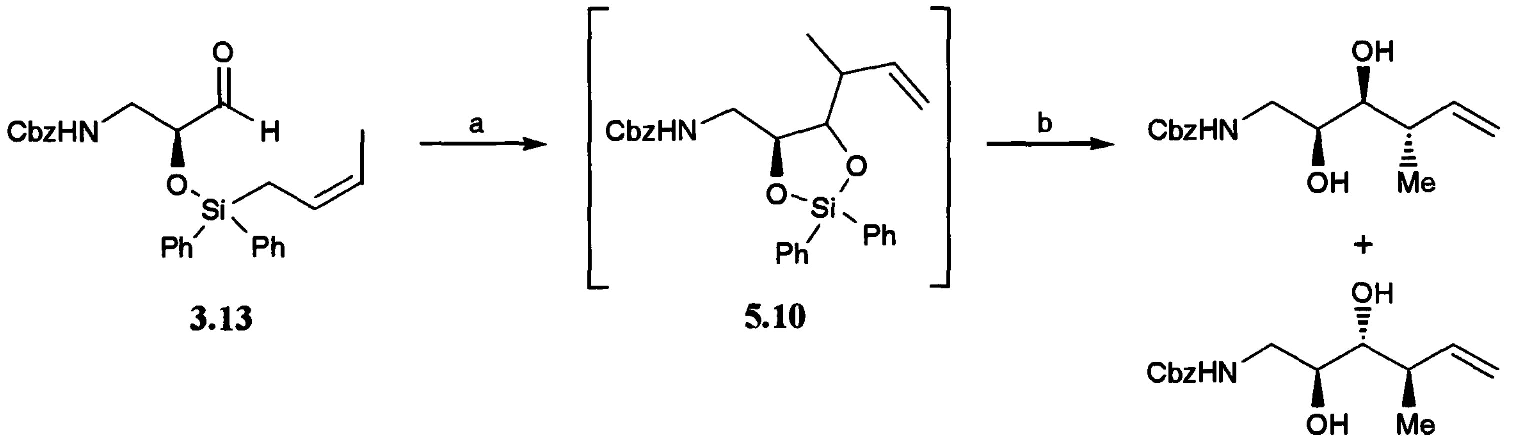


5.07 **5.08** **5.09**

a) Toluene, 130 °C, 17 hr; b) H_2O_2, KF, MeOH, RT (80% two steps).

Scheme 5.06

Under the same conditions the *Z*-crotyl system produced diastereomeric allyl transfer products **5.11** and **5.12** in yields of 78% and 7% respectively (Scheme 5.07).



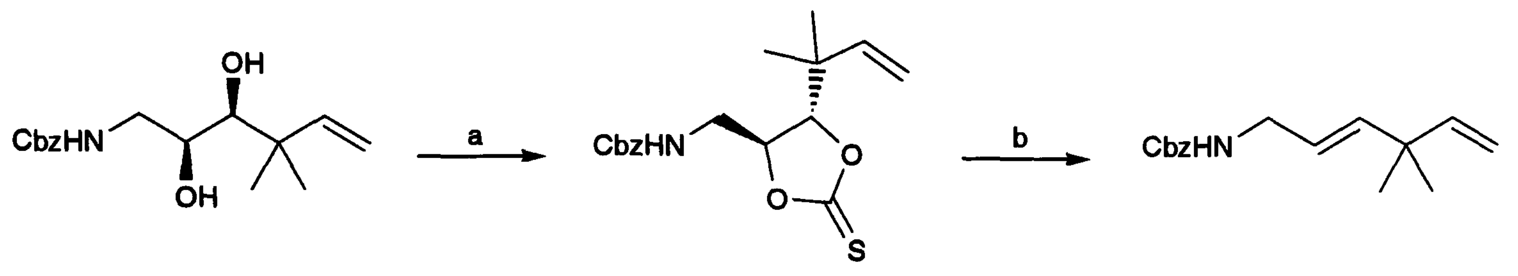
3.13 **5.10** **5.11** **5.12**

a) Toluene, 130 °C, 24 hr; b) H_2O_2, KF, MeOH, RT (**5.11** 78%; **5.12** 7%; two steps).

Scheme 5.07

5.3 Confirmation of diol stereochemistry

In order to establish the stereochemistry of the newly generated 1,2-homoallylic diols rapidly, we decided to adopt a Corey-Winter approach. A model study with 1,2-diol **3.28**, generated previously from the prenyl system (Section 3.3), confirmed the efficiency of this process (Scheme 5.08).

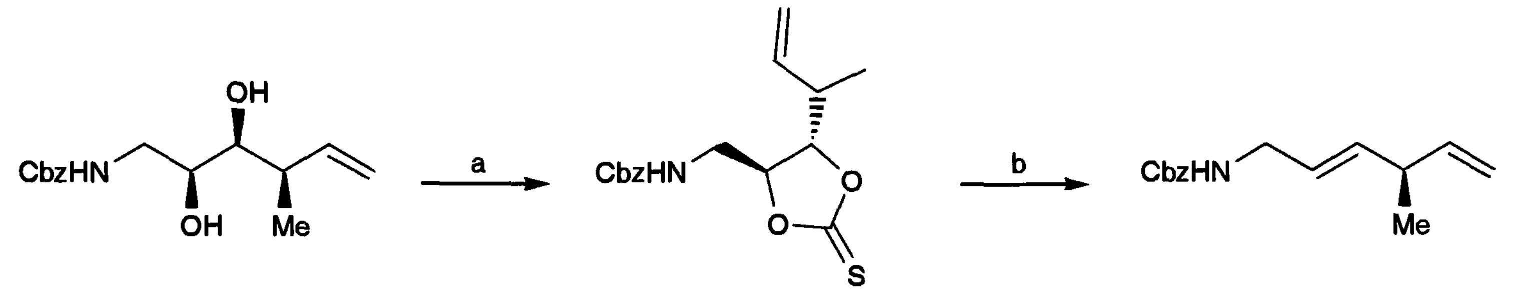


3.28 **5.13** **5.14**

a) $(Im)_2C{=}S$, THF, Δ (89%); b) $P(OEt)_3$, Δ (85%).

Scheme 5.08

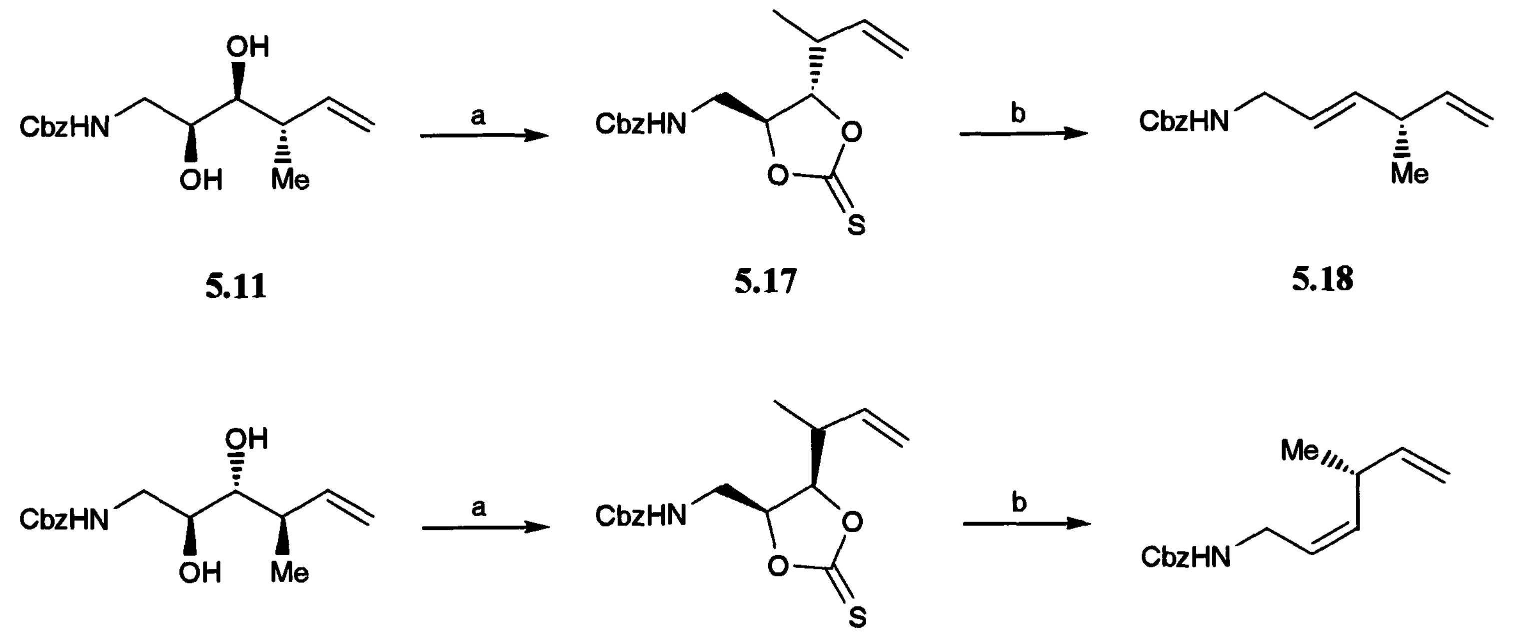
Hence, the thiocarbonates of **5.15**, **5.17** and **5.19** were prepared, and subsequent selective elimination generated a range of methyl dienes (Scheme 5.09 and Scheme 5.10).



5.09 **5.15** **5.16**

a) $(Im)_2C{=}S$, THF, Δ (93%); b) $P(OEt)_3$, Δ (98%).

Scheme 5.09



5.11 **5.17** **5.18**

5.12 **5.19** **5.20**

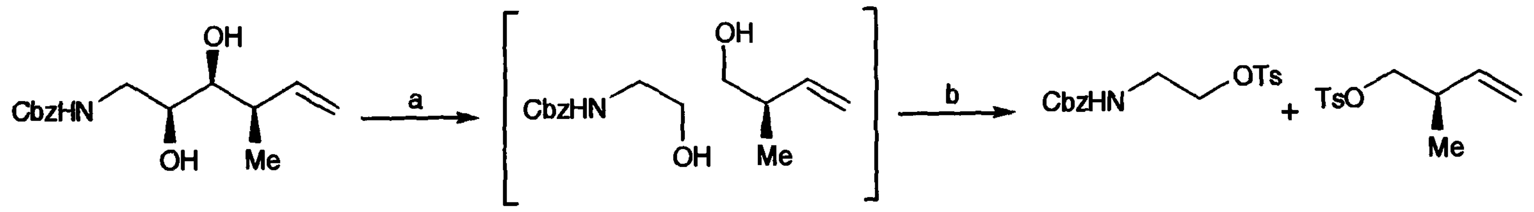
a) $(Im)_2C{=}S$, THF, Δ (**5.17** 97%; **5.19** 75%); b) $P(OEt)_3$, Δ (**5.18** 85%; **5.20** 64%).

Scheme 5.10

The double bond geometry was established by *J* value analysis of the respective ^{1}H NMR spectra of compounds **5.16**, **5.18** and **5.20**. In the case of major products **5.16** and **5.18**, which reassuringly possessed equal and opposite $[\alpha]_D$ values, the CH=CH coupling constants (*J* 15.6 Hz and *J* 15.5 Hz) were consistent with an *E*-configuration, confirming the precursors **5.09** and **5.11** as *syn*-diols. The diene **5.20**, resulting from minor product **5.12**, gave a coupling constant value (*J* 11.0 Hz) consistent with *Z*-alkene geometry, confirming that the minor diastereomer **5.12** possessed an *anti*-diol configuration.

5.4 Methyl group stereochemistry

The geometry of the crotyl unit in the precursor should dictate the stereochemistry at the allylic position of the product. In order to confirm the methyl group stereochemistry of major diastereomers **5.09** and **5.11**, we decided initially to cleave the diols oxidatively and correlate the $[\alpha]_D$ values of the allylic fragments with those of known enantiomers.[198] Unfortunately this approach was hindered by the volatility of the intermediates which formed azeotropes with the reaction solvent, and by the small scale of the attempted cleavage.[199] As a result of this volatility the 2-methylbut-3-enol fragment proved impossible to isolate and an attempt was made to trap intermediate **5.22** as its tosylate **5.24** (Scheme 5.11).[200] Unfortunately, subsequent $[\alpha]_D$ measurements proved inconclusive.

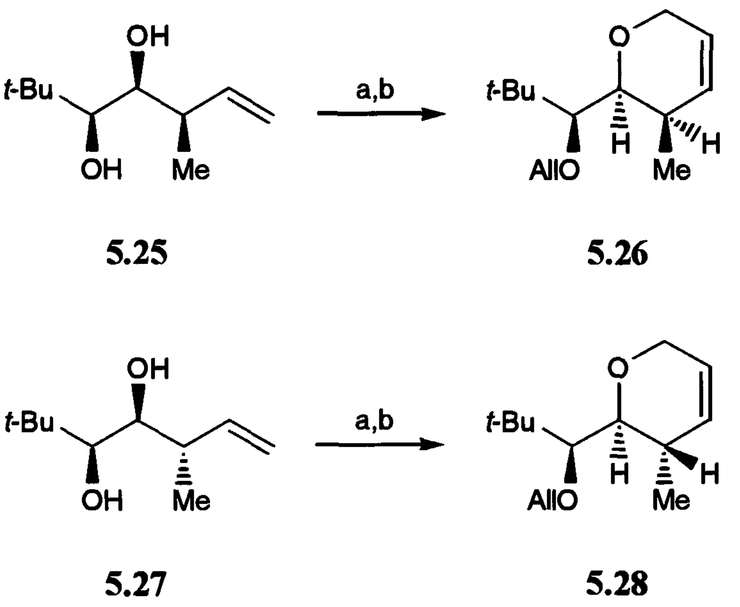


5.09 **5.21** **5.22** **5.23** **5.24**

a) $NaIO_4$-SiO_2, RT then $NaBH_4$; b) TsCl, py.

Scheme 5.11

Since attempts to confirm the methyl group stereochemistry in this manner proved capricious, the relative orientation of the methyl substituents was assigned as being analogous to those of related model crotyl systems. This work, performed concurrently within the Robertson group,[80] involved coupling constant analysis of rigid dihydropyrans, prepared from analogous 1,2-homoallylic diols *via* bis-allylation and RCM of the resulting allyl ethers (Scheme 5.12).[114,201]



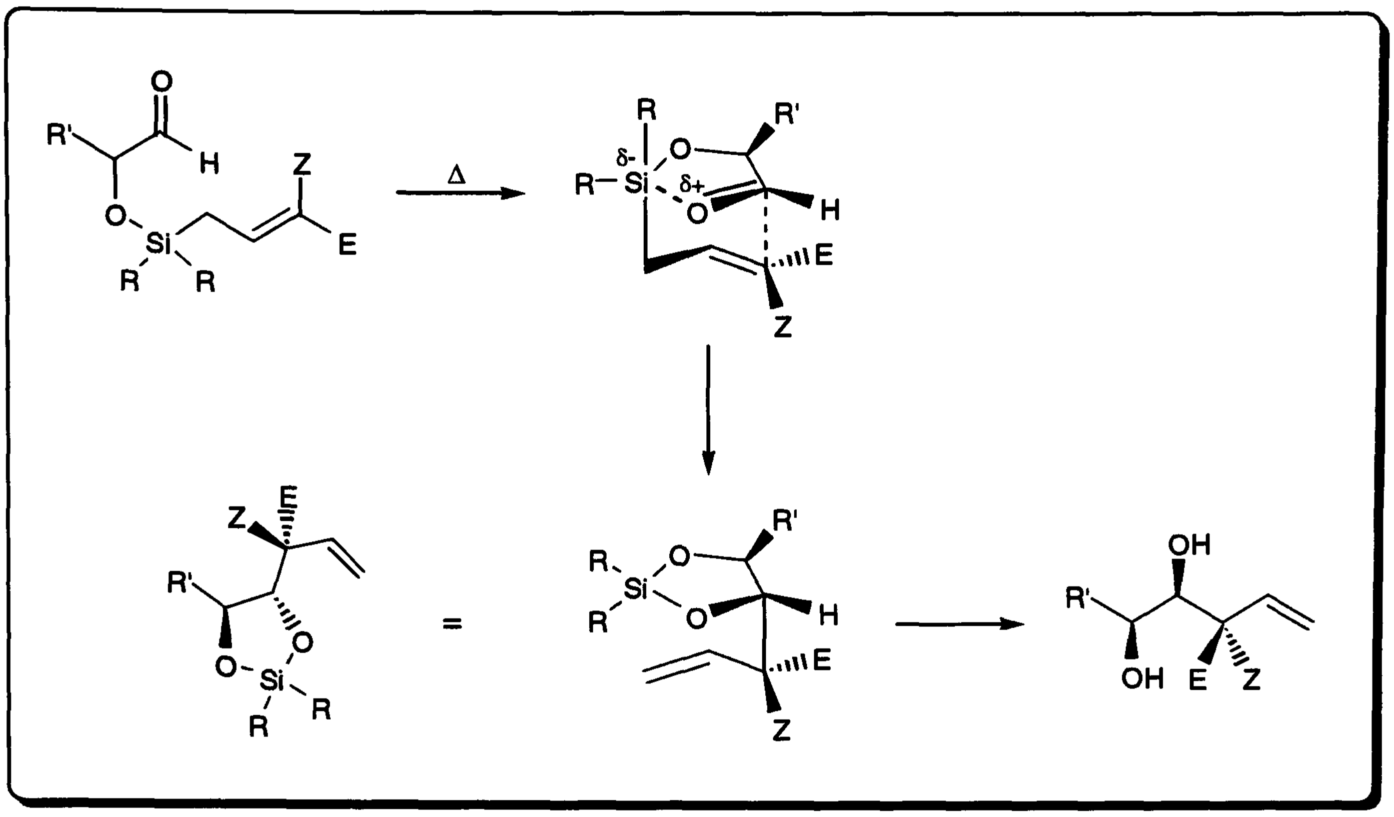
a) NaH, allyl bromide;

b) Grubbs' 2nd generation catalyst (**1.114**) 2.0 mol%, RT (**5.26** 43%; **5.28** 28%; two steps).

Scheme 5.12

5.5 Transition state model

Our proposed transition state model for the thermal allyl transfer process involves co-operative[138] pre-activation of the silicon and aldehyde by their mutual co-ordination. Allylic transfer then occurs through a chair-like arrangement from the face opposite the side chain substituent ensuring that the addition proceeds, predominantly, with anti-Felkin-Ahn selectivity (Scheme 5.13). Interestingly, the relative stereochemistry of the methyl substituent at the allylic position and the adjacent hydroxyl is reversed (*E*→ *syn*, *Z*→ *anti*) when compared with the stereoselectivity normally observed from intermolecular allylations that proceed *via* cyclic six-membered transition states (*E*→ *anti*, *Z*→ *syn*, see Section 4.1).



Scheme 5.13

We postulate that the minor *anti*-diol **5.12**, generated from the *Z*-crotyl substrate **3.13**, results from allyl transfer from the same face as the side chain substituent. Hence, the stereoselectivity of this process may be enhanced by increasing the steric bulk at this position.

5.6 Conclusions

This chapter summarises our first efforts in the direction of thermal carbonyl allyl transfer methodology, demonstrating the efficacy of this process during the synthesis of homoallylic aminodiols **5.09** and **5.11**, which result from ordered intramolecular allylic transfer of *E*- and *Z*-crotyl substituents.

This chemistry adds to the range of allylation protocols currently available, but offers a number of advantages over conventional methods; most notably, our procedure functions stereoselectively under thermal conditions without the need for an additive Lewis acid catalyst to promote allylation. This method parallels the growing number of reported protocols (Chapter 4) which demonstrate the advantage of inducing Lewis acidity at silicon, *via* ligation or strain-assisted activation, to effect allylation.

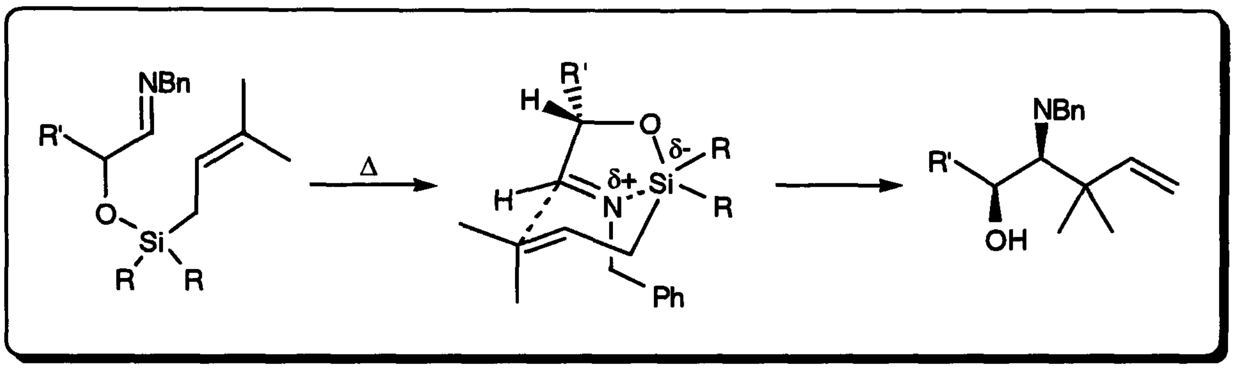
Subsequent chapters will describe our efforts to explore the viability of the tethered intramolecular allyl transfer process when applied to more demanding systems.

Chapter 6

Investigation of Aldimine Allyl Transfer Reactions

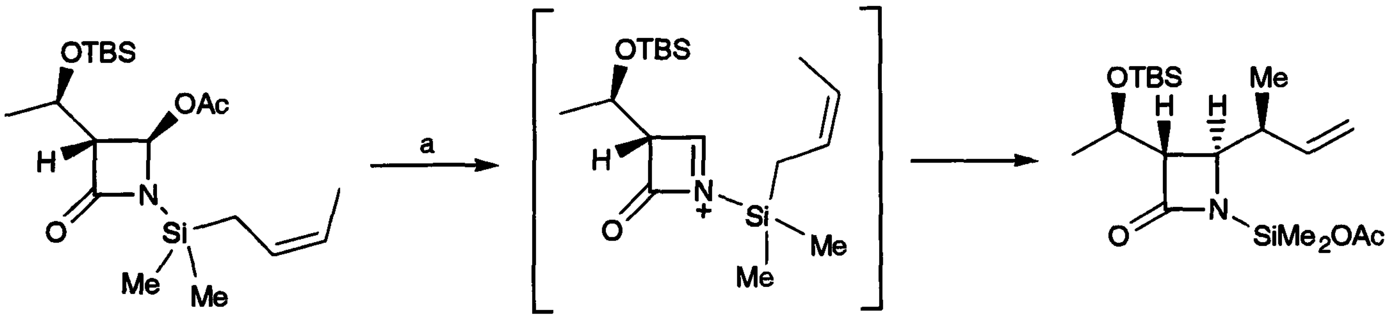
6.0 Introduction

Having optimised the methodology connected with the carbonyl system we were keen to effect analogous silicon tethered allyl transfer methodology with an *O*-linked imine variant. It was envisaged that this chemistry would constitute a novel approach to 1,2-homoallylic aminols with predictable control of stereochemistry (Scheme 6.01).



Scheme 6.01

To date, relatively few examples of silicon tethered nucleophilic delivery to imine derivatives have appeared in the literature.[4,7,139] Of the examples reported, Uyeo's use of an *N*-silyl tether to facilitate a Sakurai-type crotylation of β-lactam precursor **6.01** nicely illustrates the synthetic potential of these processes (Scheme 6.02).[202]

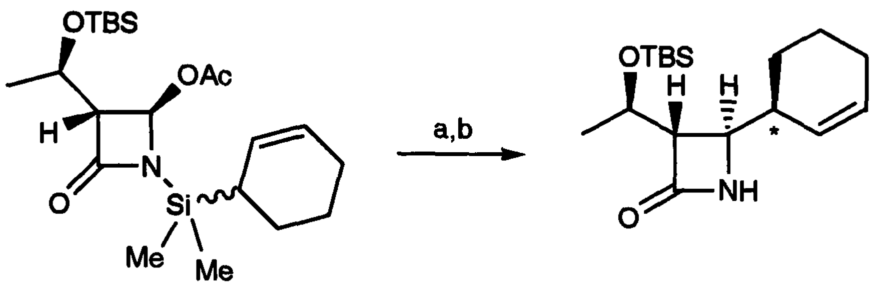


6.01 **6.02** **6.03**

a) TMS-OTf, DCM, 0 °C (84%).

Scheme 6.02

In an extension of this work, tethered cyclohexenylsilane **6.04** was shown to add stereoselectively to iminium species **6.05** (Scheme 6.03).[203]

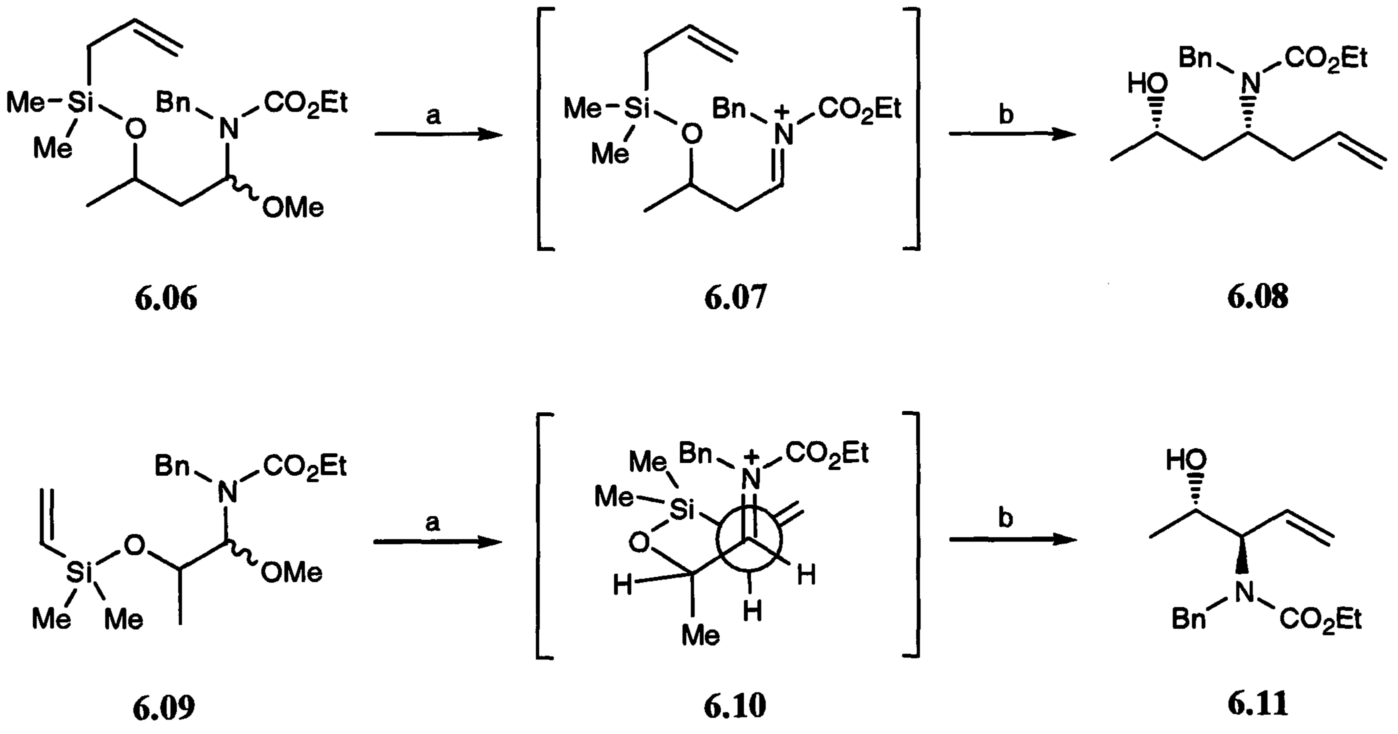


6.04 **6.05**

a) TMS-OTf, DCM, 0 °C; b) TBAF (71%, d.r = 8:2).

Scheme 6.03

Hioki *et al.* have reported Lewis acid-mediated Hosomi-Sakurai reactions of iminium intermediates, employed to generate *anti*-1,2- and *syn*-1,3-aminoalcohols stereoselectively (Scheme 6.04).[204]



6.06 **6.07** **6.08**

6.09 **6.10** **6.11**

a) $BF_3.OEt_2$, DCM, 0 °C; b) TBAF (**6.08** 86%, d.r = 51:1; **6.11** 98%, d.r = 300:1).

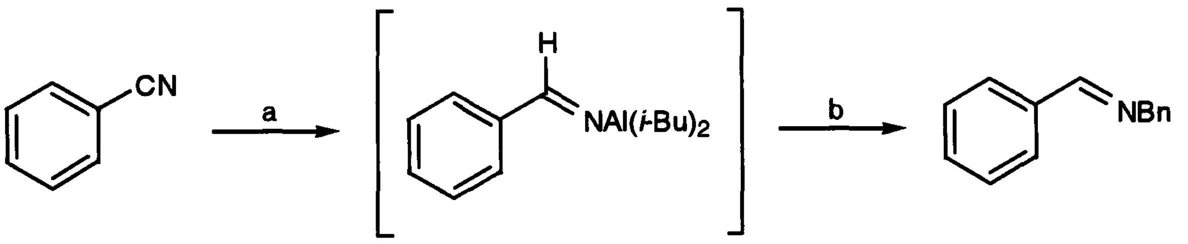
Scheme 6.04

The potential advantage offered by our methodology is the ability to induce allylation without the need for any additional catalysts or reagents.

6.1 α-Silyloxy imine synthesis

It was envisaged that the aldimine precursors could be synthesised using the methodology developed for the preparation of the silylcyanohydrins in Chapter 2. An in-depth examination of the literature revealed Brussee's potentially useful transimination protocol, for the preparation of *N*-substituted β-ethanolamines, which we hoped could be adapted to allow access to the benzylated imine directly from the cyanohydrin.[205]

A test reaction was performed with benzonitrile to ascertain the viability of halting Brussee's protocol at the *N*-Aryl imine stage. The nitrile was initially reduced with DIBAL at low temperature, before a solution of ammonium bromide in dry methanol was added to destroy any excess reducing agent and to convert the imine-aluminium complex **6.12** to the free imine. Conversion of the primary imine to the more stable *N*-substituted secondary imine was achieved *via* the addition of excess benzylamine; subsequently *N*-benzylidenebenzylamine **6.13** was isolated in excellent yield following reduced pressure distillation (Scheme 6.05).



6.12 **6.13**

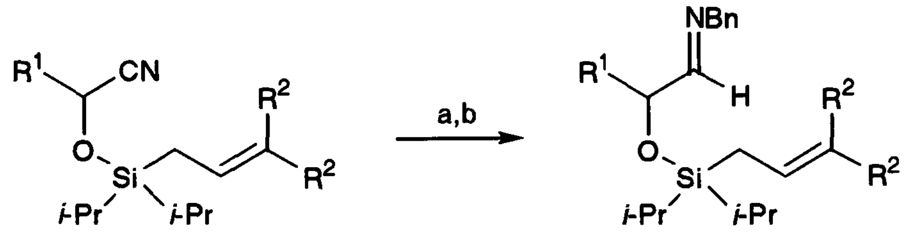
a) DIBAL, DCM, -78 °C; b) NH_4Br in MeOH then $BnNH_2$, -78 °C–RT (91% two steps).

Scheme 6.05

Encouraged by the result of the test reaction, attention focussed on the application of Brussee's procedure to our silylcyanohydrin systems. Although a diphenyl-substituted silicon would confer enhanced activation, a known limitation of such systems was the intrinsic instability of the intermediate siladioxolanes (Section 3.3). To this end, cyanohydrins **2.42**,

2.43 and **6.14** were chosen, bearing *iso*-propyl substituents on silicon, in order to confer a suitable level of stability to the anticipated oxazasilolidines.

Pleasingly, application of the reduction-transimination protocol to cyanohydrins **2.42**, **2.43** and **6.14** furnished the desired benzyl imines **6.15**, **6.16** and **6.17** in excellent yield (Scheme 6.06). It was found that these imines could be stored at low temperature for reasonable periods of time with negligible decomposition.



2.42 R^1 = *i*-Pr, R^2 = H
2.43 R^1 = *i*-Pr, R^2 = Me
6.14 R^1 = Ph, R^2 = H

6.15 R^1 = *i*-Pr, R^2 = H
6.16 R^1 = *i*-Pr, R^2 = Me
6.17 R^1 = Ph, R^2 = H

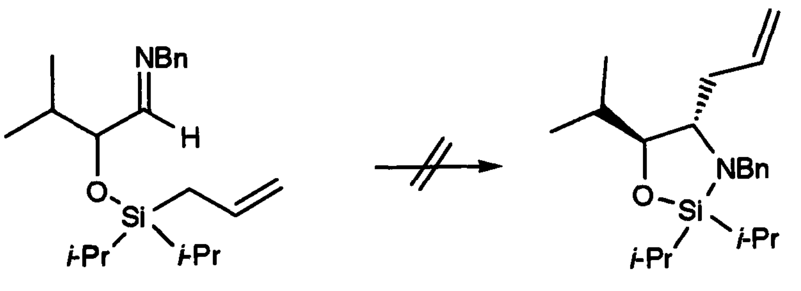
a) DIBAL, DCM, -78 °C;

b) NH_4Br in MeOH then $BnNH_2$, -78 °C–RT (**6.15** 93%; **6.16** 86%; **6.17** 98%; two steps).

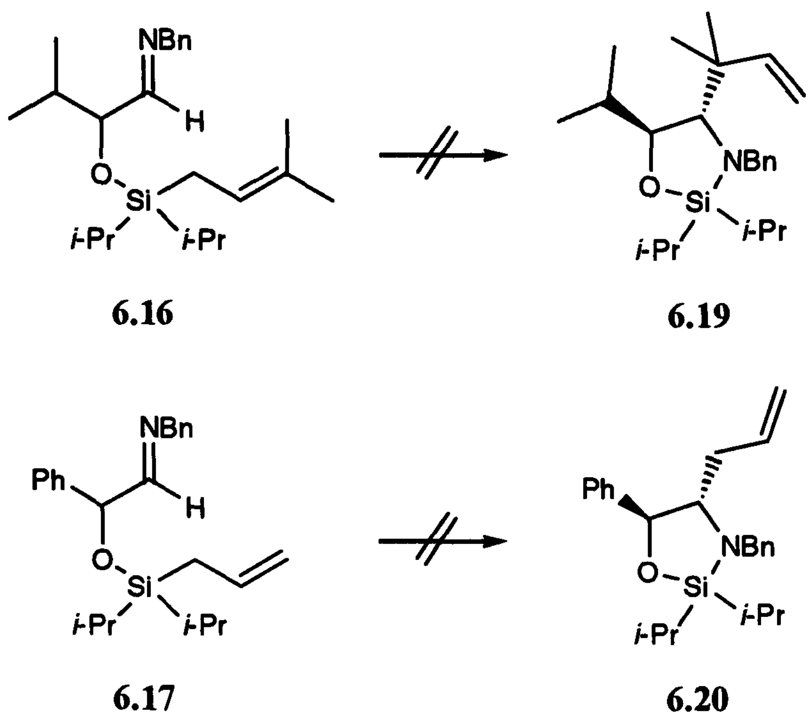
Scheme 6.06

6.2 Attempted allyl transfer reactions

Attempts to induce thermal allyl transfer of substrates **6.15**, **6.16** and **6.17** under the standard conditions failed, more forcing conditions merely resulting in decomposition (Scheme 6.07).



6.15 **6.18**



Toluene-d_8, 130 °C, up to four days or toluene, 150 °C–200 °C, 20 hr; (no product observed by ^{1}H NMR).

Scheme 6.07

In an attempt to activate the C=N bond, benzyl imines **6.15**, **6.16** and **6.17** were treated with a variety of Lewis acids, which resulted in unproductive decomposition in all cases.[206] Addition of trimethylsilyl triflate had no beneficial effect either. Attempts to improve the electrophilicity of the azomethine carbon by treatment with methyl iodide also led to complex mixtures of products, with limited evidence of *N*-alkylation.

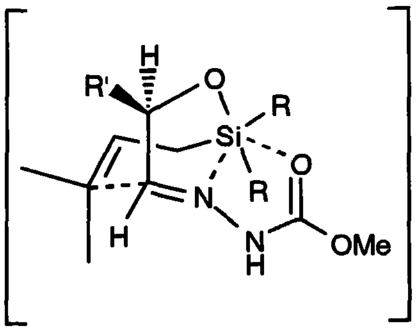
The failure to induce allylation in these systems would, most likely, result from the reduced electrophilicity of the C=N bond compared to the analogous carbonyl systems.[140] With regard to the proposed transition state of our thermal allyl transfer protocol, it is possible that the *N*-benzyl substituent would lead to steric crowding at the imine terminus, and could contribute to the inability of silicon to activate the imine. The benzyl moiety could also interfere with the approach of the prenyl substituent to the azomethine carbon. Depleted Lewis acidity could also be a contributing factor, compounded by our choice of *iso*-propyl substituents on silicon. These combined steric and electronic factors may account for the overall lack of reactivity of the aldimine systems.

As both the thermal and Lewis acidic conditions proved to be unviable for allylation, we considered the possibility of inducing an ene cyclisation in the case of prenyl-substituted precursor **6.16**; in the event no such reaction was observed[207] but this result was not altogether surprising since ene reactions of unactivated imines are relatively uncommon.[208]

We next considered the preparation of more activated substituted imines. However, previous attempts to install *N*-tosylimines in similar systems, employing Weinreb's *N*-sulfinyl *p*-toluenesulfonamide method for enolisable aldehydes,[209] had failed.[74]

Cognisant of Kobayashi's aldimine allylation work with benzoylhydrazones,[142] we became aware of the latest application of Leighton's strain-activation methodology,[210] in which a range of imine derivatives had been screened for reactivity towards intermolecular allylation with strained five-membered silacycles bearing allylic substitution at silicon (Chapter 4). Of the imine derivatives tested,[211] acylhydrazones had proved the most successful.

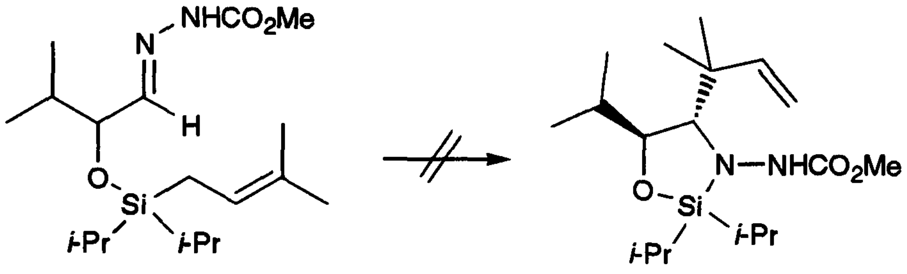
Incorporation of a hydrazone moiety would offer enhanced chelating ability, and we anticipated the possibility of inducing bidentate co-ordination at the silicon atom of the substrate, forming a closed transition structure organised around silicon (Figure 6.01).



6.21

Figure 6.01

Hydrazone **6.22** was prepared from the previously synthesised aldehyde **2.45** in acceptable yield (53%). Heating a solution of substrate **6.22** in deuterated toluene, in a sealed tube, at 130 °C for several days failed to induce thermal allyl transfer; similarly in deuterated DMF, hydrazone **6.22** failed to undergo thermal rearrangement at temperatures ranging from 150 °C to 170 °C for up to five days, although decomposition was observed (Scheme 6.08).



6.22 **6.23**

Toluene-d_8, 130 °C, up to four days or

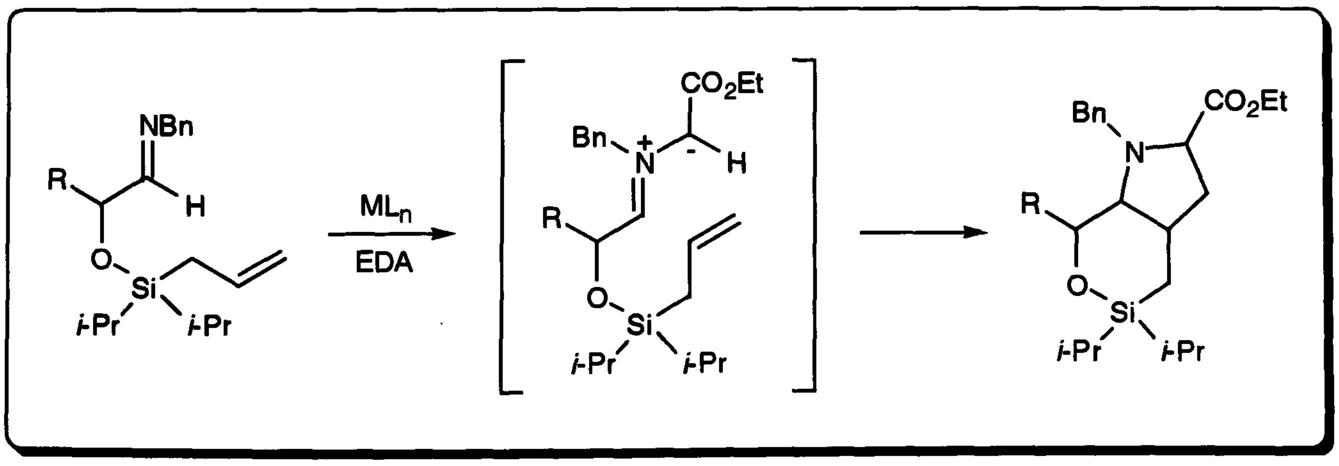
DMF-d_7, 150 °C–170 °C, up to five days; (no product observed by ^{1}H NMR).

Scheme 6.08

Neither thermal nor Lewis acidic conditions had yielded any fruitful results, and so our investigation into silicon tethered aldimine allylation was terminated at this time.

6.3 Attempted azomethine ylide cycloaddition

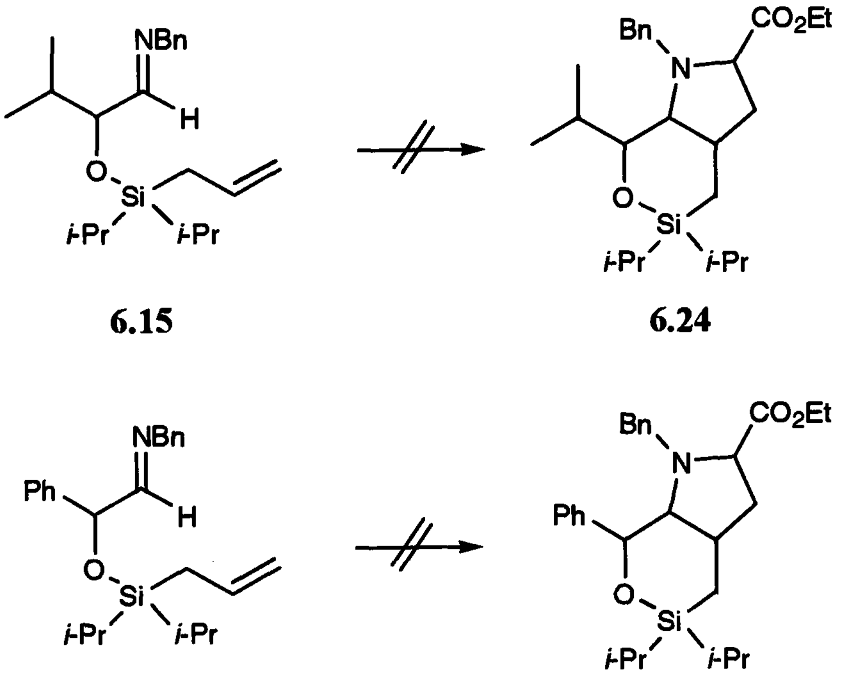
In a final attempt to find a useful application for the benzyl imine substrates, we next investigated the viability of a silicon tethered azomethine ylide cycloaddition (Scheme 6.09).



Scheme 6.09

Provided that the aldimine could be activated with a suitable metallocarbenoid, this method might allow access to the necine base core of pyrrolizidine alkaloids. Although construction of functionalised pyrrolidines *via* 1,3-dipolar cycloaddition processes are not uncommon,[212] convergent protocols in which the azomethine ylide is generated in the presence of a tethered dipolarophile are less well known.[26]

Treatment of a solution of aldimine (**6.15** or **6.17**) and rhodium(II) acetate dimer in toluene with a dilute solution of ethyl diazoacetate, added *via* syringe pump over 1 hr (to reduce the likelihood of carbenoid dimerisation), did not result in cycloaddition even after prolonged heating; only starting material was isolated, contaminated with uncharacterisable material (Scheme 6.10).



6.15 **6.24**

6.17 **6.25**

$Rh_2(OAc)_4$, EDA over 1 hr, toluene, 80 °C, 5–12 hr; (no product observed by ^1H NMR).

Scheme 6.10

Varying the temperature, solvent, catalyst loading and the rate of addition all resulted in uncharacterisable products of decomposition.

Padwa has suggested that imine purity is an important factor in metallocarbenoid cycloadditions;[213] the presence of trace amounts of residual benzylamine, employed to effect the transimination, or enolised by-products may have had a detrimental effect on the rhodium(II) catalyst.

A number of groups have reported the use of copper salts to effect azomethine ylide cycloaddition, copper (II) acetylacetonate being particularly popular.[212] Scheidt *et al.* have recently described the use of copper(I) triflate employed in the catalytic three-component assembly of an *N*-aryl imine, α-diazo ester and an alkyne during the synthesis of functionalised pyrrolidines.[214] Unfortunately, the employment of copper salts had no beneficial effect on our system. In light of these results this area of research was abandoned.

6.4 Conclusions

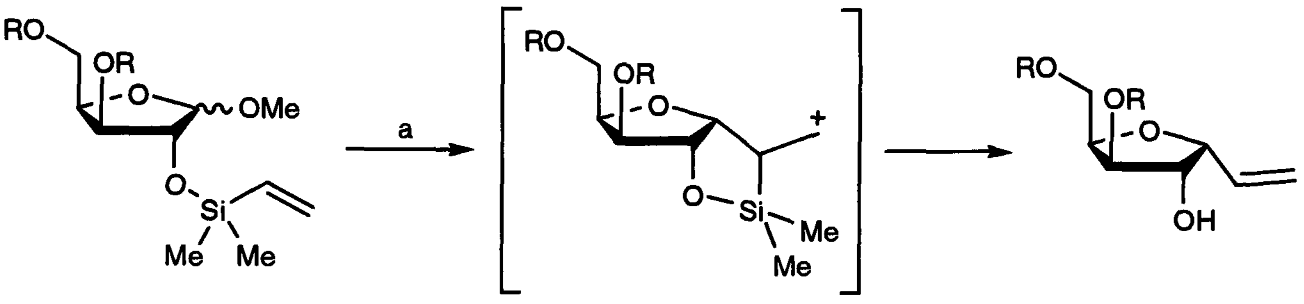
This chapter has described efforts to test the flexibility of our thermal allyl transfer methodology and effect a similar process in related *O*-linked aldimine systems. Although unsuccessful, this investigation has demonstrated a useful one-pot transimination procedure for the preparation of *N*-aryl imines from silylcyanohydrins.

Chapter 7

Investigation of Thermal Glycosylation

7.0 Introduction

A number of groups have employed silicon tethers to facilitate aglycon delivery (Section 1.9),[4,7,66] however, reports of carbon-centred nucleophile delivery are more limited.[5] Martin *et al.* reported the Lewis acid-mediated synthesis of *C*-furanoside **7.03**, in which a carbon nucleophile was delivered intramolecularly from the C-2 silyloxy tether of precursor **7.01** to the anomeric position *via* intermediate **7.02** (Scheme 7.01).[215]



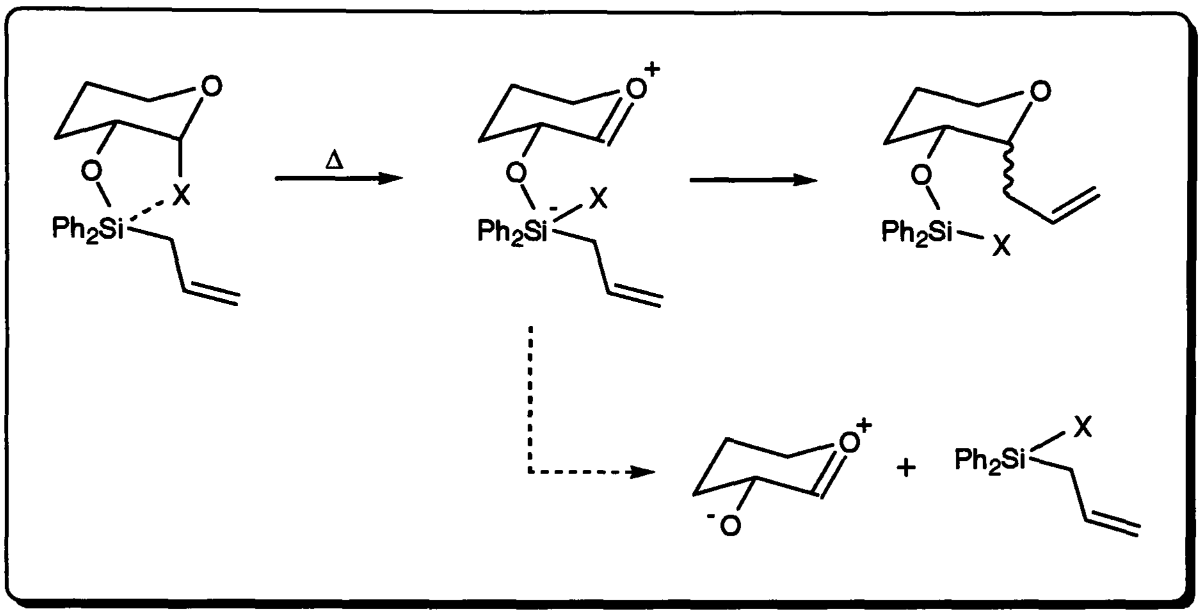
7.01 **7.02** **7.03**

R = *p*-chlorobenzyl a) $SnCl_4$, DCM, RT (35%).

Scheme 7.01

As a consequence of the results described in Chapter 5, in which co-operative activation had enabled allylic transfer in α-silyloxyaldehyde systems, we decided to investigate the viability of silicon tethered glycosylation employing thermal allyl transfer.

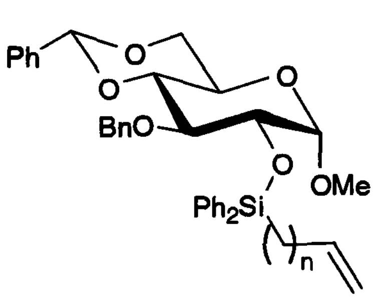
Martin's Lewis acid-mediated *C*-glycosylation[215] led us to postulate whether a 2-*O*-diphenylsilyl substituent would act as an internal Lewis acid to activate an anomeric leaving group and effect intramolecular nucleophile delivery. It is conceivable that a suitably silylated α-glucoside may orient the silyl moiety in close enough proximity to the anomeric centre to induce co-operative activation. Transfer of the anomeric substituent to silicon could, at the same time, facilitate intramolecular allylation of the oxonium intermediate *via* transfer of the *C*-nucleophile from the siliconate. At the outset we envisaged co-operative desilylation as an alternative reaction pathway that could render the transfer process unsuccessful (Scheme 7.02).



Scheme 7.02

7.1 Methyl glucopyranoside systems

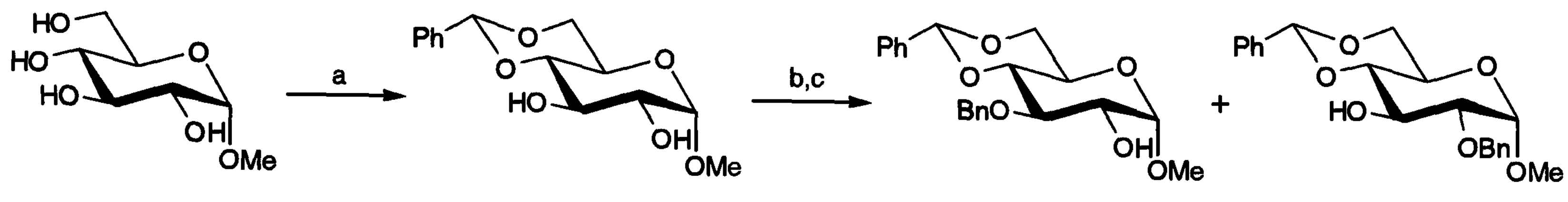
For relative ease of synthesis, methyl glycosides **7.04** and **7.05** were chosen as our first target precursors (Figure 7.01).



7.04 n = 0 and **7.05** n = 1.

Figure 7.01

Access to the free C-2 hydroxyl group of *gluco*-derivative **7.07** was achieved starting from methyl-α-D-glucopyranoside. Standard benzylidene acetal protection followed by stannane-mediated benzylation furnished a mixture of 2-OH and 3-OH protected methyl glycosides (Scheme 7.03).



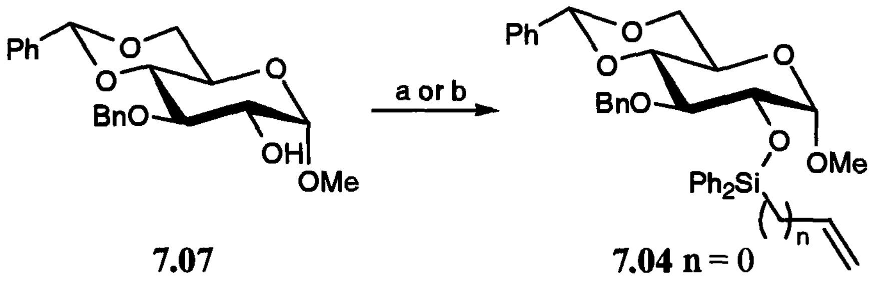
7.06 **7.07** **7.08**

a) PhCH(OMe)$_2$, CSA (cat.), DMF, 20 Torr, 55–60 °C (76%); b) Bu$_2$SnO, PhMe, Δ;

c) BnBr, Bu$_4$NI, PhMe, Δ (**7.07** 26%; **7.08** 40%; two steps).

Scheme 7.04

Subsequent silylation of substrate **7.07** with either allyl- or vinyl(diphenyl)chlorosilane furnished the desired α-methyl glycosides **7.04** and **7.05** in acceptable overall yield (Scheme 7.04).



7.07

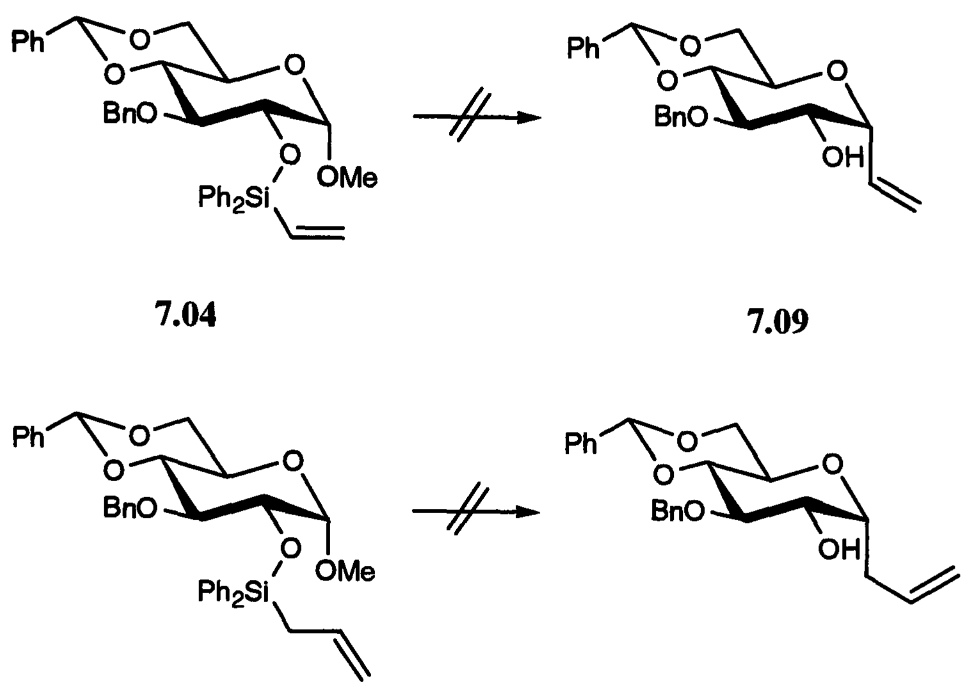
7.04 n = 0
7.05 n = 1

a) vinyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, 0 °C–40 °C (**7.04** 99%);

b) allyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, RT–60 °C (**7.05** 95 %).

Scheme 7.04

Heating samples of **7.04** and **7.05** in toluene, in a sealed tube, at a range of temperatures for up to five days simply returned starting material unchanged (Scheme 7.05).



7.04 **7.09**

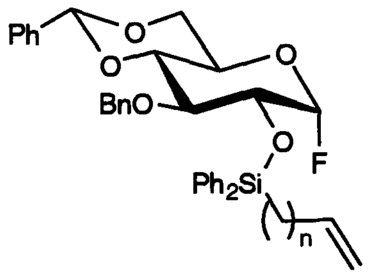
7.05 **7.10**

Toluene-d$_8$, 130 °C, up to five days or toluene, 150 °C–180 °C, three days; (no product observed by ^{1}H NMR).

Scheme 7.05

7.2 Glycosyl fluoride systems

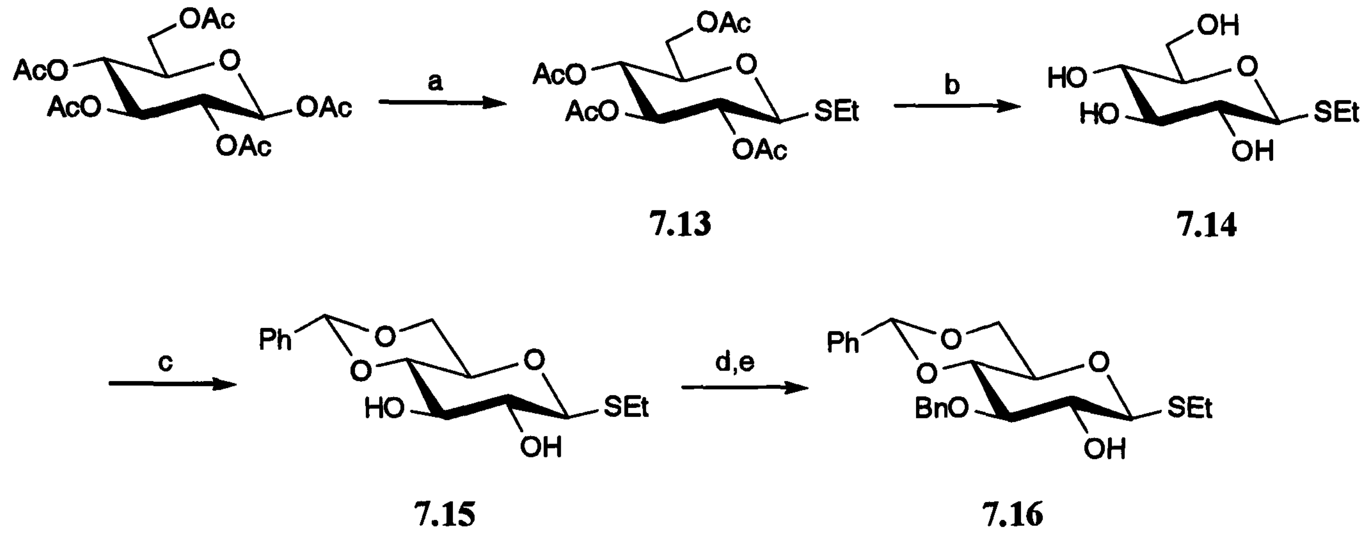
In light of these results the glycosyl fluoride derivatives **7.11** and **7.12** were envisaged as our next targets (Figure 7.02).[216] Considering the fluorophilicity of silicon, we anticipated the Si-F bond strength (810 kJ mol^{-1}) to be a potential driving force for nucleophile transfer.



7.11 n = 0 and **7.12** n = 1.

Figure 7.02

Treatment of glucose pentaacetate with ethane thiol in the presence of boron trifluoride etherate gave the thioglycoside **7.13**, which was deacetylated cleanly under Zemplén conditions to furnish compound **7.14** in good yield. Subsequent benzylidene acetal protection and selective 3-OH benzylation furnished substrate **7.16** in reasonable yield (Scheme 7.06).



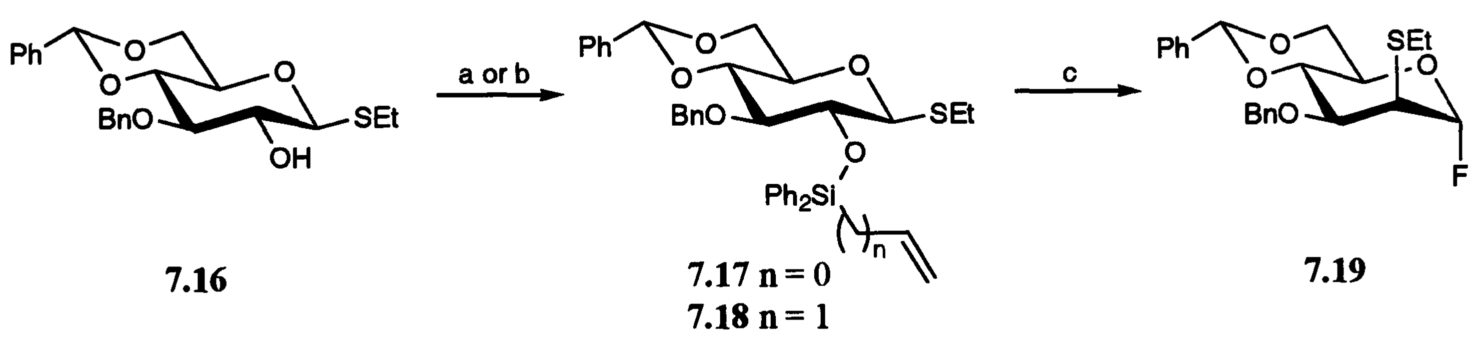
a) EtSH, $BF_3.OEt_2$, DCM, 0 °C (93%); b) NaOMe (cat.), MeOH, RT (99%);

c) $PhCH(OMe)_2$, CSA (cat.), DMF, 20 Torr, 55–60 °C (82%);

d) Bu_2SnO, MeOH, Δ; e) BnBr, CsF, DMF, RT (60%; two steps).

Scheme 7.06

Silylation of compound **7.16** with vinyl- and allyl(diphenyl)chlorosilane afforded thioglycosides **7.17** and **7.18** respectively. Initially, introduction of fluoride at the anomeric position proved troublesome; treatment of thioglycoside **7.18** with diethylamino sulfur trifluoride (DAST), a versatile reagent commonly employed in fluoro-dehydroxylations, led to the 2-deoxy-thioethyl glycoside **7.19** under NIS activation (Scheme 7.07).



a) vinyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, RT–40 °C (**7.17** 79%);

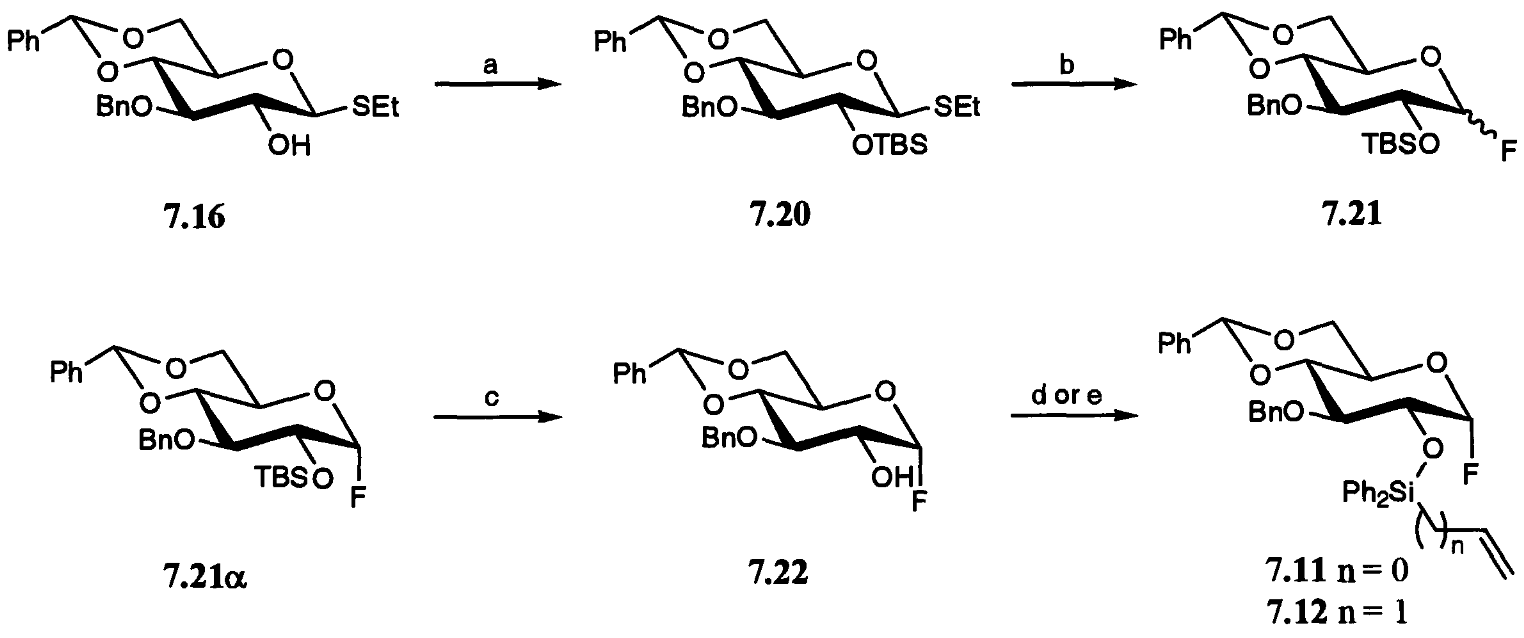
b) allyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, RT–60 °C (**7.18** 76 %);

c) DAST, NIS, DCM, -10 °C–RT (90%).

Scheme 7.07

This result was not entirely surprising, Nicolaou *et al.* had observed similar behaviour of 2-hydroxy-thioglycosides, reporting the formation of analogous glycosyl fluorides resulting from 1,2-migration of the thioalkyl group.[217] In the case of substrate **7.18** migration would presumably be triggered by iodonium ion activation of the allyl C=C bond, the intermediate sulfonium ion would then be trapped *in situ* by DAST-generated fluoride.

To circumvent this problem we opted to protect the C-2 hydroxyl of thioglycoside **7.16** as the TBS ether, repeat the DAST sequence, deprotect and then reinstall the silyloxy group at C-2. In the event this indirect approach proceeded uneventfully to furnish the desired allyl and vinyl substituted glycosyl fluorides **7.11** and **7.12** in good yield (Scheme 7.08).



a) TBSCl, TEA, DMAP (cat.), DMF, RT–50 °C (69%);

b) DAST, NIS, DCM, -10 °C–RT (**7.21α** 60%; **7.21β** 22%); c) TBAF-THF, 0 °C (82%);

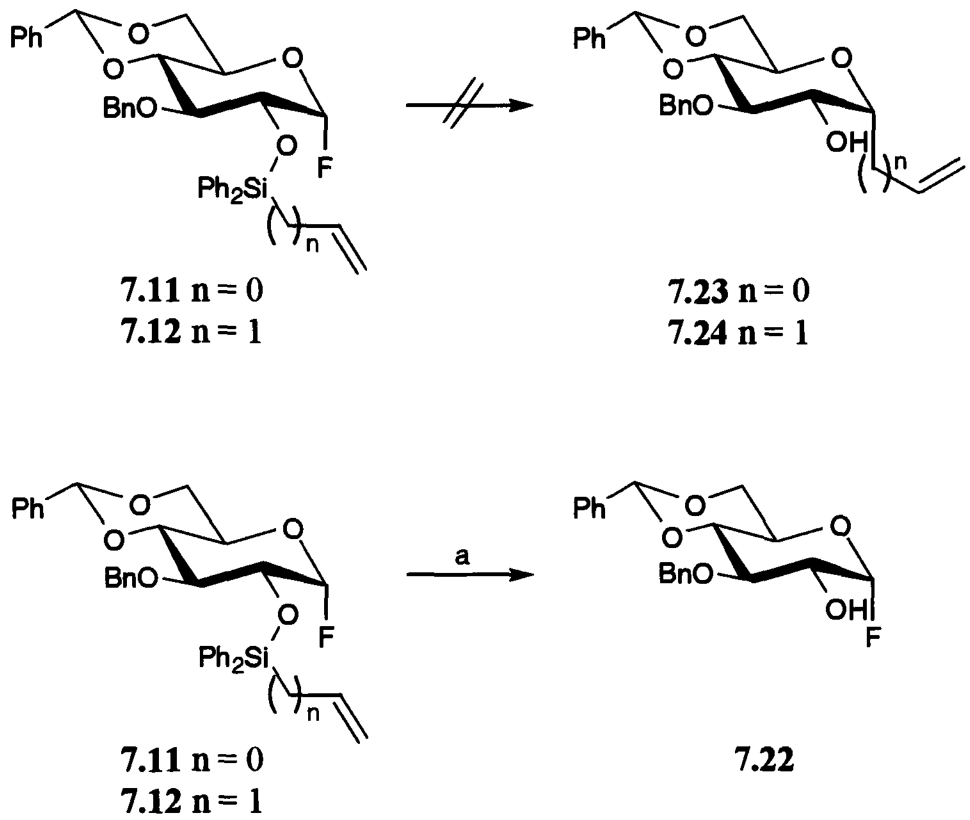
d) vinyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, RT–50 °C (**7.11** 80%);

e) allyl(diphenyl)chlorosilane, TEA, DMAP (cat.), DMF, RT–50 °C (**7.12** 96 %).

Scheme 7.08

In the case of fluoro-substrates **7.11** and **7.12**, as with the methyl glycosides, starting material was recovered unchanged with no evidence of allyl migration under thermal conditions.

Attempts to induce thermal allyl transfer in DMF were instigated; test reactions with glycosyl fluoride derivatives **7.11** and **7.12** in deuterated DMF, heating to 130 °C in a sealed NMR tube, failed to afford any evidence of allyl transfer when monitored by ^{1}H NMR. Continued heating for three days at 170 °C resulted solely in desilylation, forming alcohol **7.22** (Scheme 7.09).



7.11 n = 0
7.12 n = 1

7.23 n = 0
7.24 n = 1

7.11 n = 0
7.12 n = 1

7.22

Toluene, 130 °C–150 °C, up to six days (no product observed by ^{1}H NMR);

a) DMF-d_7, 130 °C–170 °C, three days (observed by ^{1}H NMR and tlc).

Scheme 7.09

Unfortunately both glycoside systems had failed to cleave the anomeric substituent under our thermal allyl transfer conditions, suggesting that diphenyl-substituted silicon was not sufficiently Lewis acidic to confer co-operative pre-activation and hence promote intramolecular allylation. At this point we decided to abandon our investigations in this area.

7.3 Conclusions

Attempts to extend the scope of the thermal allyl transfer methodology with application to intramolecular glycosylation proved unviable. The next chapter will present an alternative application of this methodology to the field of carbohydrate chemistry.

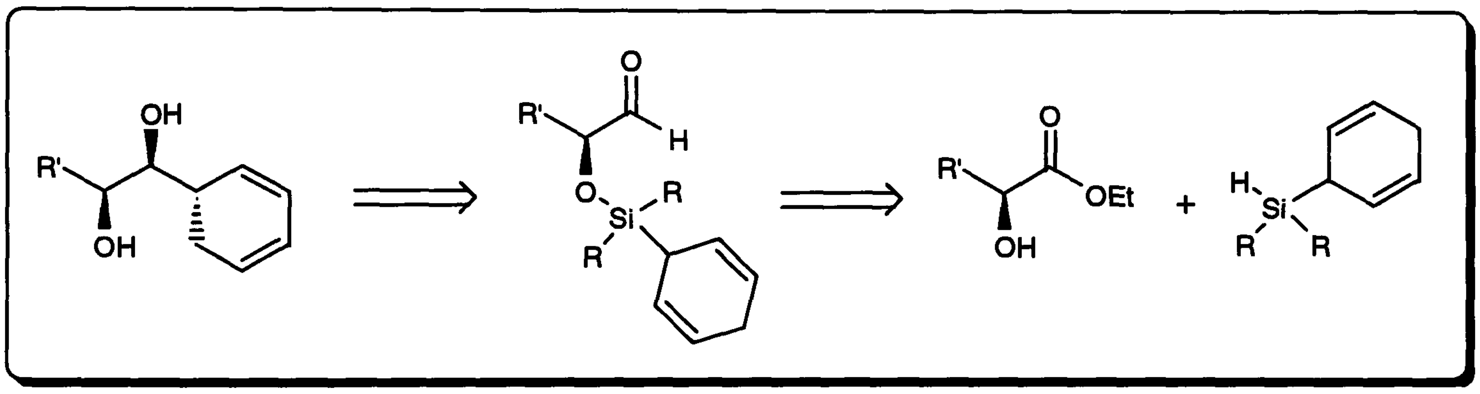
Chapter 8

Cyclohexadienyl Allyl Transfer

8.0 Introduction

Seeking to extend the scope of the silicon tethered allyl transfer methodology, unsaturated cyclohexyl systems were envisaged as a means to incorporate functionality into the allyl transfer products. Elaboration of the resulting cyclohexadienes would constitute a flexible method for the synthesis of *pseudo*-sugars[218] from non-carbohydrate precursors.[82]

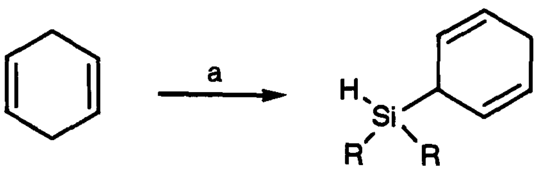
Our anticipated precursor would again result from elaboration of an α-hydroxy ester, with retrosynthetic analysis based on a cyclohexadienylsilane (Scheme 8.01).



Scheme 8.01

8.1 Cyclohexadienylsilane synthesis

Landais and Woerpel have both prepared trialkyl- and triaryl-substituted cyclohexadienylsilanes *via* Birch reduction of the corresponding arenes or *via* lithiation of 1,4-cyclohexadiene.[219,220] In the event, the bis-substituted phenyl and *iso*-propyl variants were readily prepared by adapting the 1,4-cyclohexadiene literature methods (Scheme 8.02).



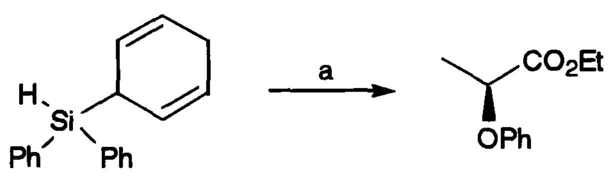
8.01 R = Ph
8.02 R = *i*-Pr

a) *s*-BuLi, TMEDA, -78 °C to -45 °C then R_2SiHCl, -45 °C–RT (**8.01** 100%; **8.02** 96%).

Scheme 8.02

8.2 α-Silyloxy ester system

Initial attempts to couple the cyclohexadienylsilanes with α-hydroxy esters proved troublesome; Piers' tris(pentafluorophenyl)borane catalyst was not compatible with the cyclohexadienyl system, producing the unexpected phenyl ether **8.03** in modest yield (Scheme 8.03).[221]



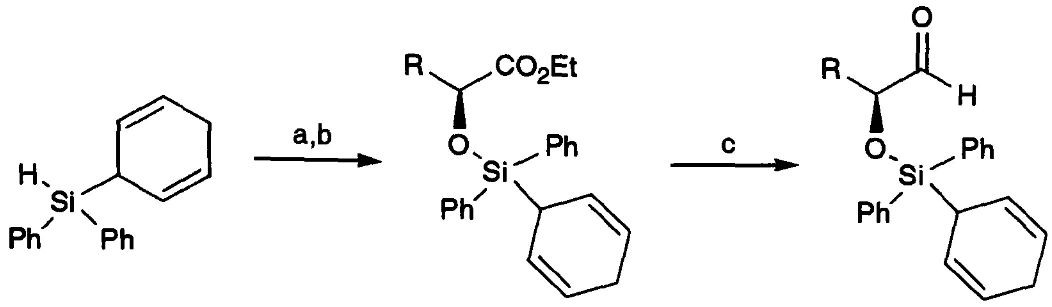
8.01 **8.03**

a) (*S*)-ethyl lactate, $B(C_6F_5)_3$ 5.0 mol%, DCM, Δ (20%).

Scheme 8.03

The di(*iso*-propyl)cyclohexadienylsilane (**8.02**) did not behave well under the established copper-mediated chlorination conditions and we sought a more reliable alternative to effect silylation. A survey of the literature revealed a number of possible procedures for both direct and indirect silylation and we briefly explored these methods.[222] Unfortunately none proved any more efficient than Ishikawa's copper-mediated protocol; the majority of cases resulted in substantial decomposition. At this point we abandoned attempts to initiate coupling of the di(*iso*-propyl)silane **8.02** and continued our investigations with the diphenyl-variant **8.01**.

Silylation of (*S*)-ethyl lactate and (±)-ethyl mandelate with cyclohexadienylsilane **8.01** under standard conditions produced the requisite precursors **8.06** and **8.07** following DIBAL reduction, however these compounds proved difficult to isolate by chromatography (Scheme 8.04).



8.01

8.04 R = Me
8.05 R = Ph

8.06 R = Me
8.07 R = Ph

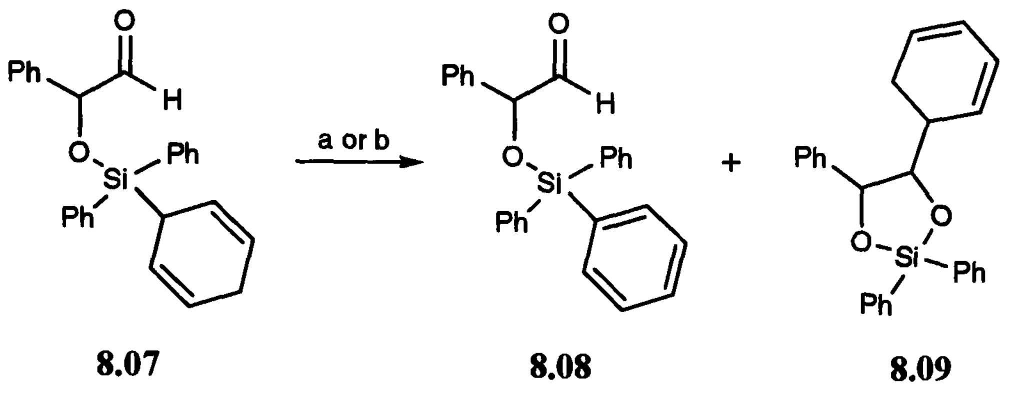
a) $CuCl_2$, CuI (cat.), THF, RT;

b) (*S*)-ethyl lactate or (±)-ethyl mandelate, TEA, DMAP (cat.), DMF, RT–40 °C

(**8.04** 70%; **8.05** 88%; two steps); c) DIBAL, -78 °C (**8.06** 55%; **8.07** 31%).

Scheme 8.04

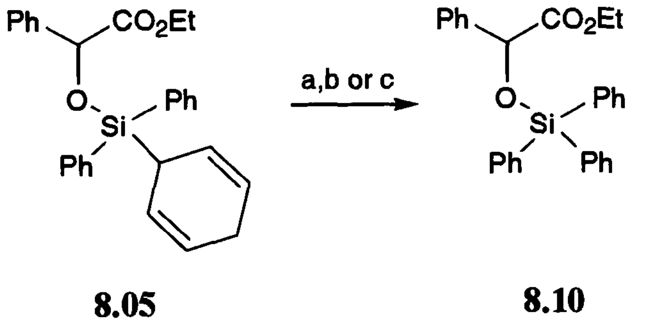
Compounds **8.06** and **8.07** were subjected to the allyl transfer conditions previously shown to be successful (toluene-d_8, 130 °C, sealed NMR tube). α-Methylsilyloxy aldehyde **8.06** underwent decomposition to a multi-component mixture. Likewise, in the case of the α-phenylsilyloxy aldehyde **8.07** a mixture of products was observed, however, at 80 °C the aromatised product **8.08** was obtained almost exclusively, with just a trace of compound **8.09** apparent in the crude ^1H NMR spectrum (Scheme 8.05).



a) Toluene-d_8, 130 °C, 1 hr (observed by ^{1}H NMR); b) toluene-d_8, 80 °C, 4 hr (observed by ^{1}H NMR).

Scheme 8.05

In order to study the thermal behaviour of the cyclohexadienyl substrates more closely, test reactions were performed with α-silyloxy ester **8.05**; the level of aromatisation was monitored by GCMS and ^{1}H NMR. Heating a solution of ethyl ester **8.05** in deuterated toluene, in a sealed NMR tube at 120 °C, resulted in complete aromatisation after just 2 hr. The model studies revealed that degassing the precursor solutions prior to heating slowed the rate of substrate degradation considerably. Hence, heating a thoroughly degassed solution of **8.05** at 120 °C successfully limited the auto-oxidation, with less than 20% of the triphenylsilyl product **8.10** observed after 5 hr (Scheme 8.06).[223]

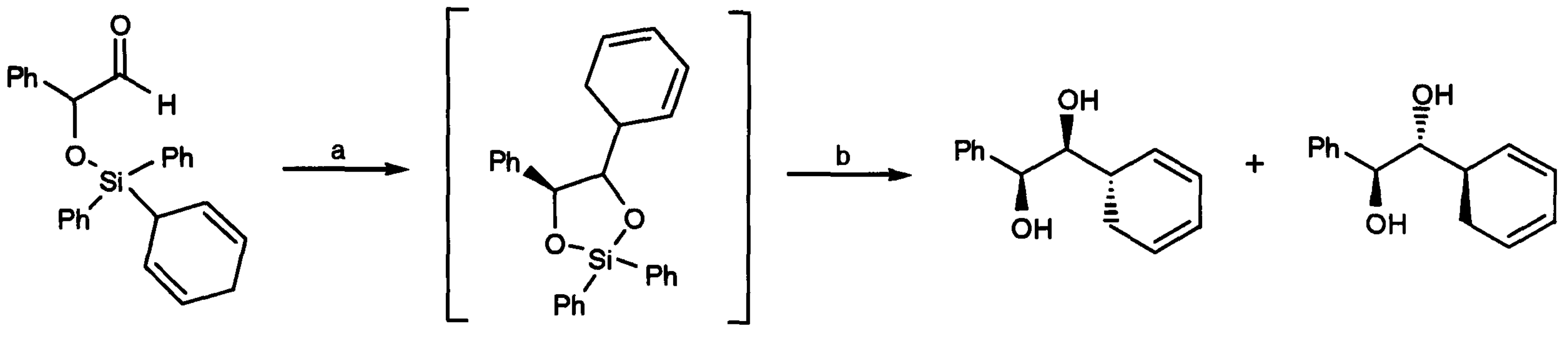


a) Toluene-d_8, 0.05 M, 80 °C, 4 hr (100%); b) toluene-d_8, 0.05 M, 120 °C, 2 hr (100%);

c) toluene-d_8, 0.05 M, 120 °C, 5 hr (< 20% conversion observed by ^{1}H NMR and GCMS).

Scheme 8.06

Subsequently, solutions of α-phenylsilyloxy aldehyde **8.07** were degassed and pleasingly the thermal allyl transfer products **8.11** and **8.12** were isolated, albeit in moderate yield (Scheme 8.07).

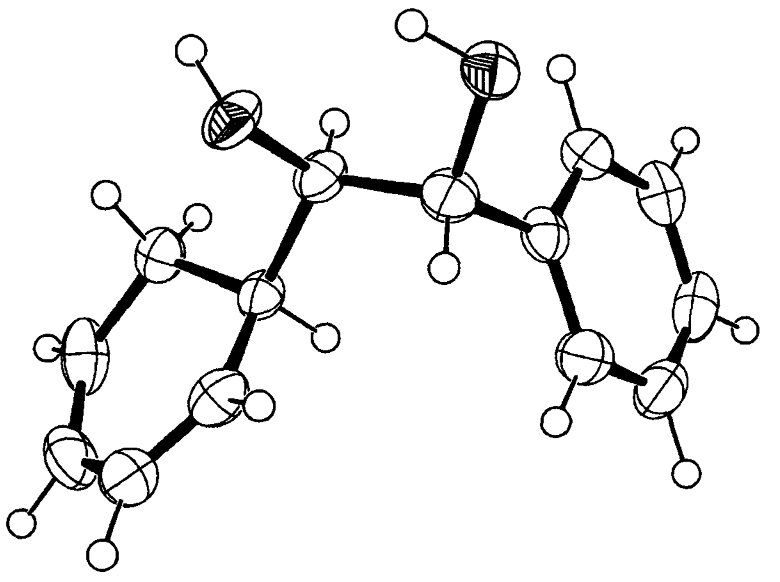


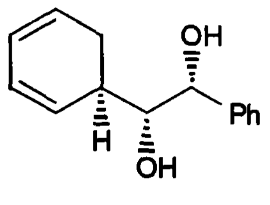
8.07 **8.09** **8.11** **8.12**

a) Toluene, 120 °C, 20 hr; b) H_2O_2, KF, MeOH, RT (**8.11** 19%; **8.12** 6%; two steps).

Scheme 8.07

The relative stereochemistry of major diastereomer **8.11** was determined by single crystal X-ray analysis (Figure 8.01 and Appendix 2).

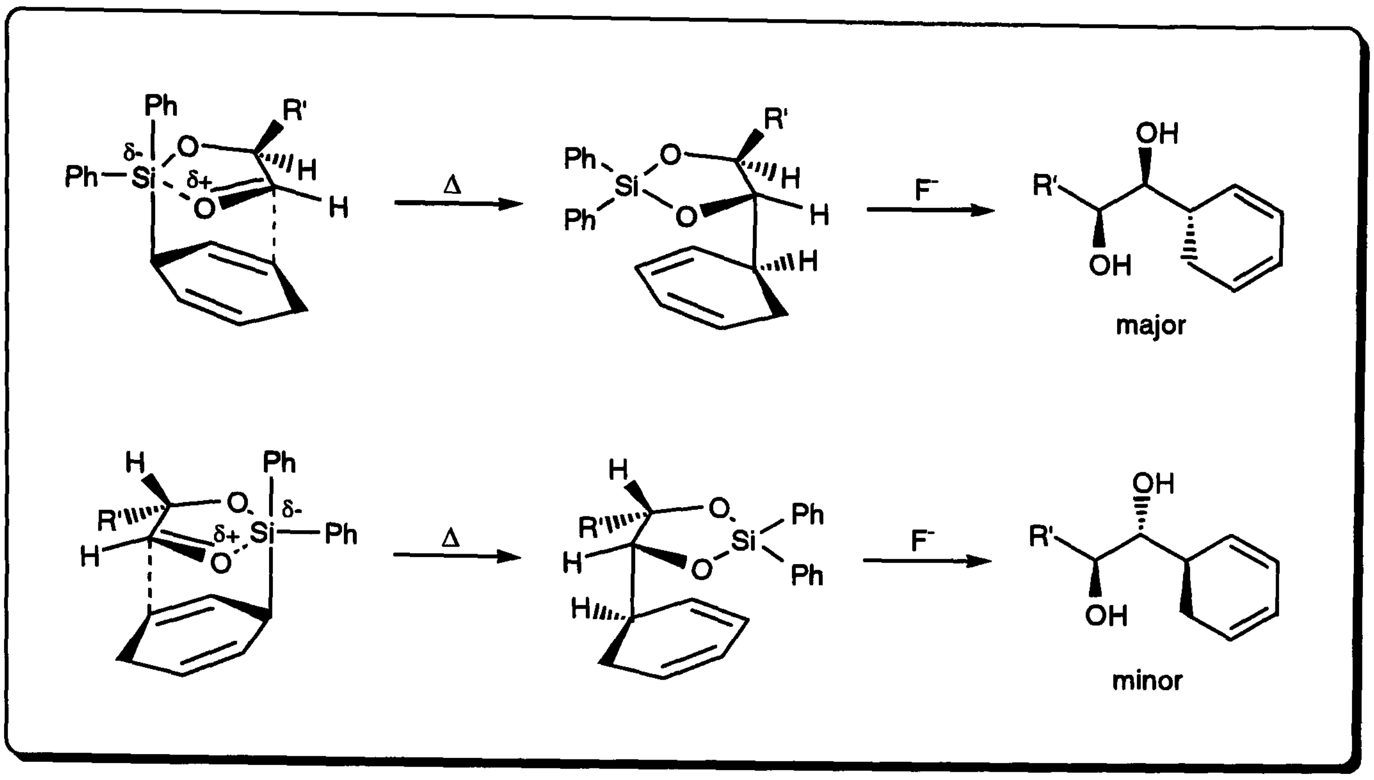




8.11

Figure 8.01

The modest diastereoselectivity of the thermal allyl transfer most likely results from the inability of the α-phenyl substituent of substrate **8.07** to direct nucleophile delivery exclusively to one face of the oxonium intermediate (Scheme 8.08).

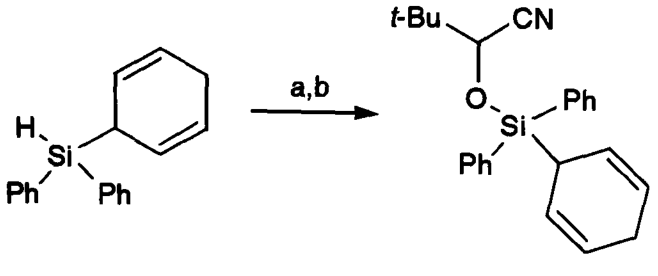


Scheme 8.08

8.3 *O*-Silylcyanohydrin system

From our transition state model (Section 5.5) we postulated that facial selectivity should be enhanced by increasing the effective size of the R-group side chain. As the ethyl lactate and ethyl mandelate derivatives had proven inconveniently labile we abandoned the α-hydroxy ester systems in favour of silylcyanohydrins. The *tert*-butyl cyanohydrin **8.13** was prepared in good yield, and we anticipated that this sterically demanding substrate would direct nucleophilic attack solely to the opposite face, generating a single diastereomer.

Efforts to couple cyanohydrin **8.13** with cyclohexadienylsilane **8.01** led to an optimisation of the established silylation procedure, in which degradation of the cyclohexadienylsilane could be limited by increasing the copper (I) iodide loading to 10 mol%; in addition, reducing the time in the presence of evolved HCl reduced associated protodesilylation. Furthermore, excess DMAP in DCM was found to promote silylation more efficiently than TEA in DMF with catalytic DMAP (Scheme 8.09).



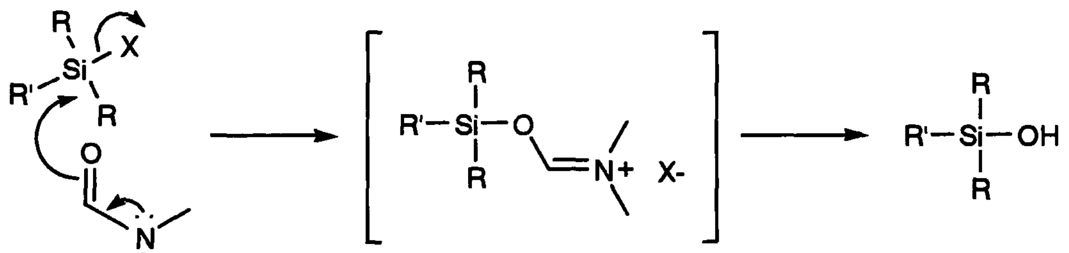
8.01 **8.14**

a) $CuCl_2$, CuI (cat.), THF, RT;

b) 2-hydroxy-3,3-dimethylbutyronitrile (**8.13**), TEA, DMAP, DCM, RT (98% two steps).

Scheme 8.09

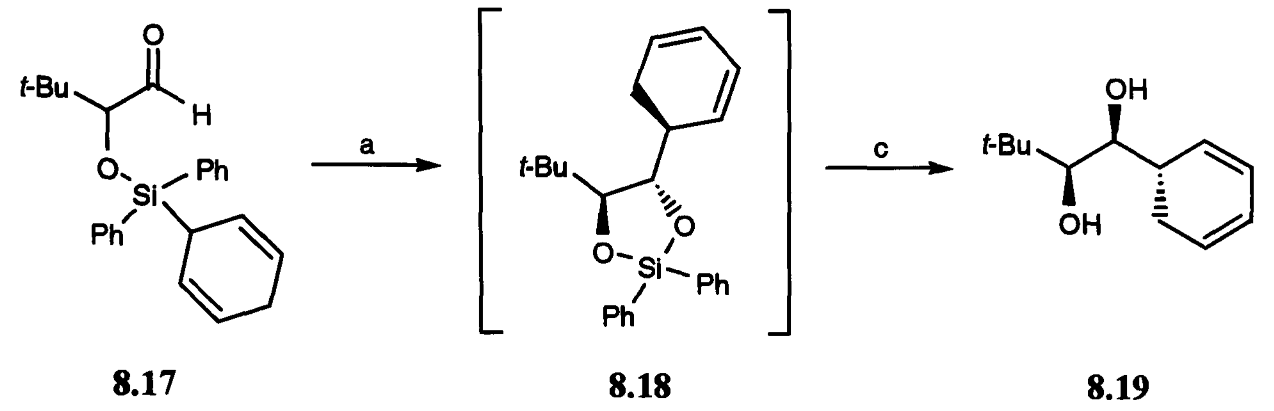
We were pleased to find validation for this method in the comments of Malacria *et al.* regarding the inhibiting effects of DMF on bromosilylation. Malacria suggested that addition of a halosilane to DMF formed intermediate **8.15** which, upon aqueous work up, resulted in the formation of silanol **8.16** as the main product; our experiences certainly support this conjecture (Scheme 8.10).[224]



8.15 **8.16**

Scheme 8.10

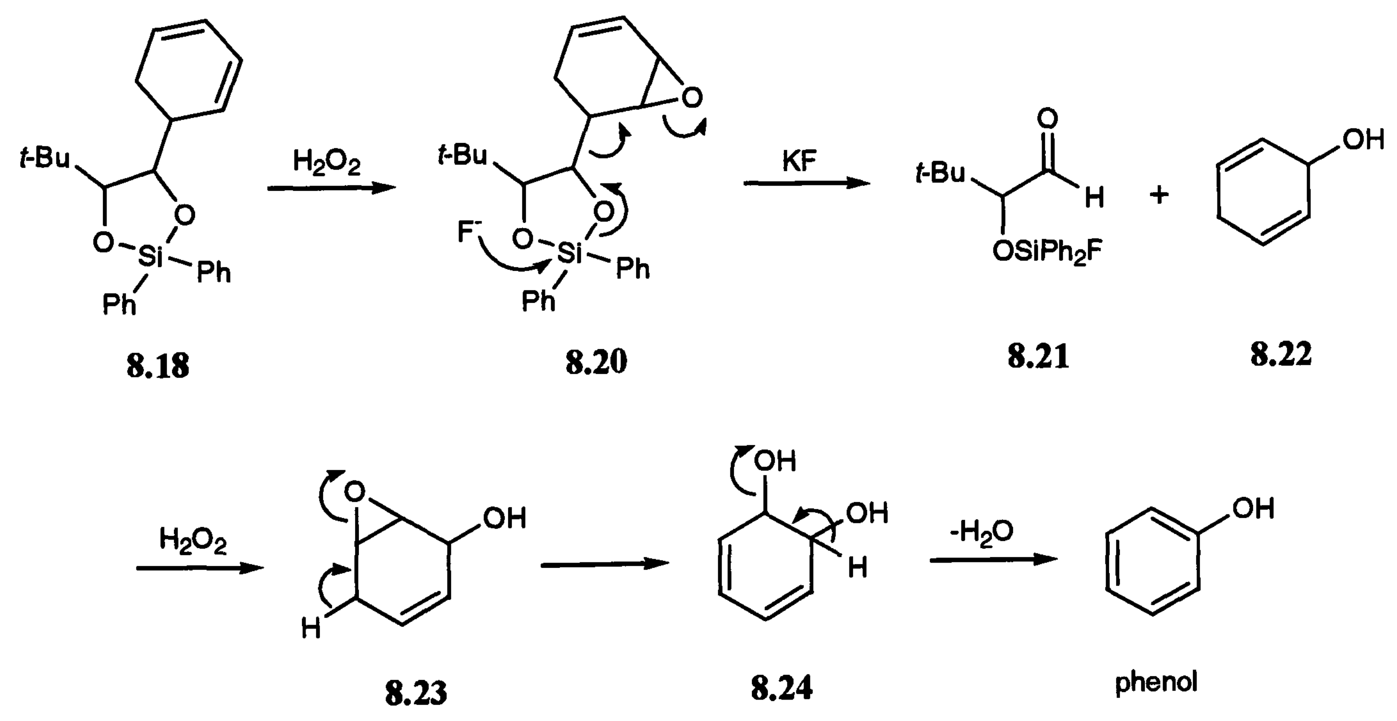
Substrate **8.14** proved less labile towards DIBAL reduction than the corresponding α-hydroxy ester systems, and once subjected to the allyl transfer conditions, nucleophile delivery to aldehyde **8.17** proceeded with excellent selectivity to generate a single diol (**8.19**) in 30% yield over two steps (Scheme 8.11).



a) Toluene, 130 °C, 18 hr; b) H_2O_2, KF, MeOH, RT (30% two steps).

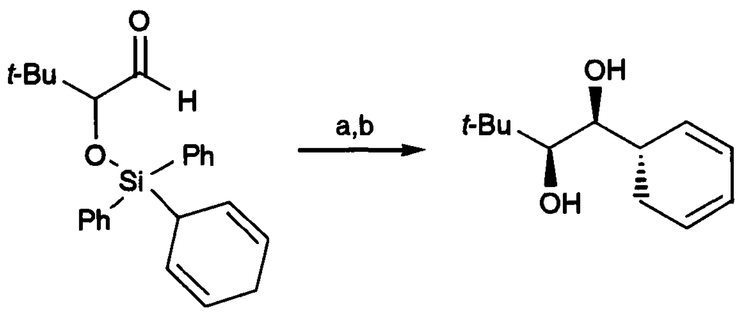
Scheme 8.11

Initially it was assumed that the relatively poor yield of the allyl transfer product **8.19** was due to preferential aromatisation of cyclohexadienyl precursor **8.17** in spite of systematic degassing. This lability towards auto-oxidation would be in keeping with our previous results, but was thought not to account solely for the reduced yield of the end product **8.19**. Closer examination of the chromatographed reaction products revealed, to our surprise, a substantial quantity of phenol. The presence of this unanticipated by-product indicated that the poor yield of **8.19** was largely a reflection of oxidative decomposition of the intermediate siladioxolane **8.18**, most likely resulting from the peroxide additive employed to assist deprotection (Scheme 8.12).



Scheme 8.12

Hence, we were delighted to find that the yield of diol **8.19** increased dramatically after switching the reagent employed to effect desilylation (Scheme 8.13).



8.17 **8.19**

a) Toluene, 130 °C, 18 hr; b) TBAF-THF, 0 °C–RT (86% two steps).

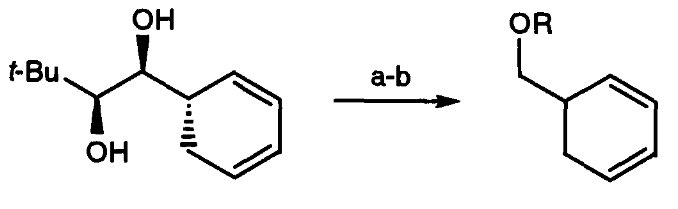
Scheme 8.13

8.4 Carbasugar syntheses

With a reasonable quantity of diol **8.19** in hand, we proceeded to elaborate the endocyclic diene component to furnish our envisaged *pseudo*-sugar sub-unit. As a 'first generation' application we decided to cleave the diol moiety of substrate **8.19** to gain access to simple carbasugar scaffolds. It is hoped that future applications will take advantage of the additional stereogenic centres and leave the diol unit intact (Chapter 9).

Carbasugars, in which the endocyclic oxygen has been replaced with a methylene unit, resemble monosaccarides in shape, size and functionality and, accordingly, are glycomimetics. These compounds mirror the polarity and conformation of the parent carbohydrate but lack a glycosidic linkage, which precludes glycosylation. The ability of these polyhydroxylated cyclohexanes to function as glycosidase inhibitors underlines their importance as potential therapeutic agents.[82]

Unfortunately, our first approach led to a mixture of uncharacterisable products following attempted double-dihydroxylation of substrates **8.25** or **8.26** with osmium tetroxide (Scheme 8.14).



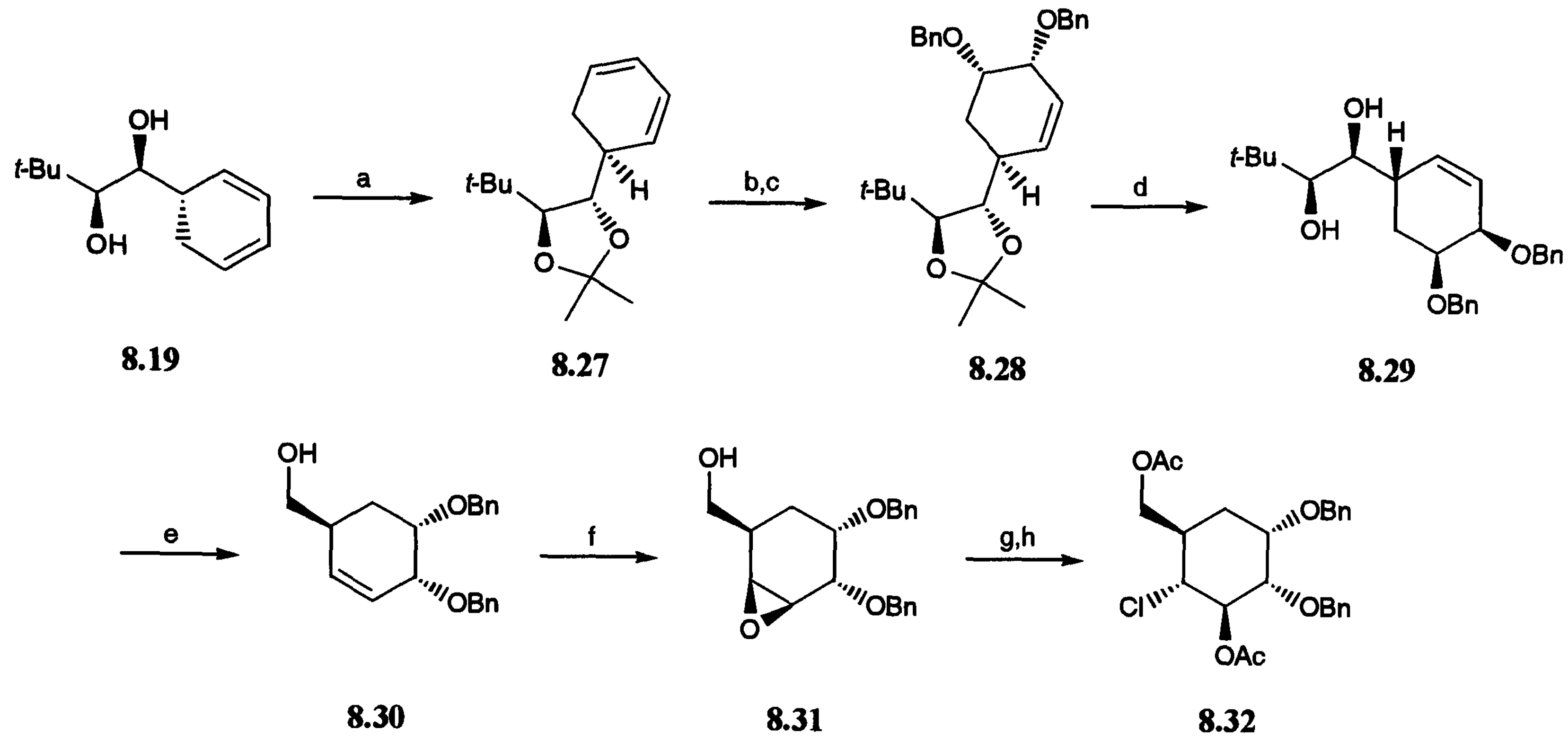
8.19

8.25 R = H
8.26 R = TBS

a) $NaIO_4$-SiO_2, RT then $NaBH_4$ (**8.25** 81%); b) TBSCl, Im., DMF, RT (**8.26** 100%).

Scheme 8.14

Our second approach involved initial acetonide protection of the diol moiety but; osmium-mediated oxidation furnished a single hydroxylated product **8.28** in relatively poor yield. It appears that the dihydroxylation occurred exclusively at the remote alkene, *anti* to the acetonide moiety, suggesting that this bulky appendage blocks access to the homoallylic double bond and forces the osmium reagent to approach the more remote π -system. However, loss of the tetra-hydroxylated product during aqueous work-up cannot be ruled out and may account for the modest reaction yield. Subsequent TFA-mediated deprotection and periodate cleavage furnished *pseudo*-glycal **8.30** in good yield. Epoxidation of the homoallylic alkene with vanadyl acetylacetonate and TBHP generated compound **8.31** which was cleaved regioselectively with HCl to afford chloro-carbasugar **8.32** as a unique diastereomer (Scheme 8.15). Due to lack of material further elaboration of **8.32** was not attempted and the synthesis was terminated at this point. However we anticipate that a halo-substituent may provide a suitable handle for functionalisation in related systems in the future.



a) 2,2-DMP, CSA (cat.), RT (80%); b) OsO_4 (cat.), NMO, THF, RT;

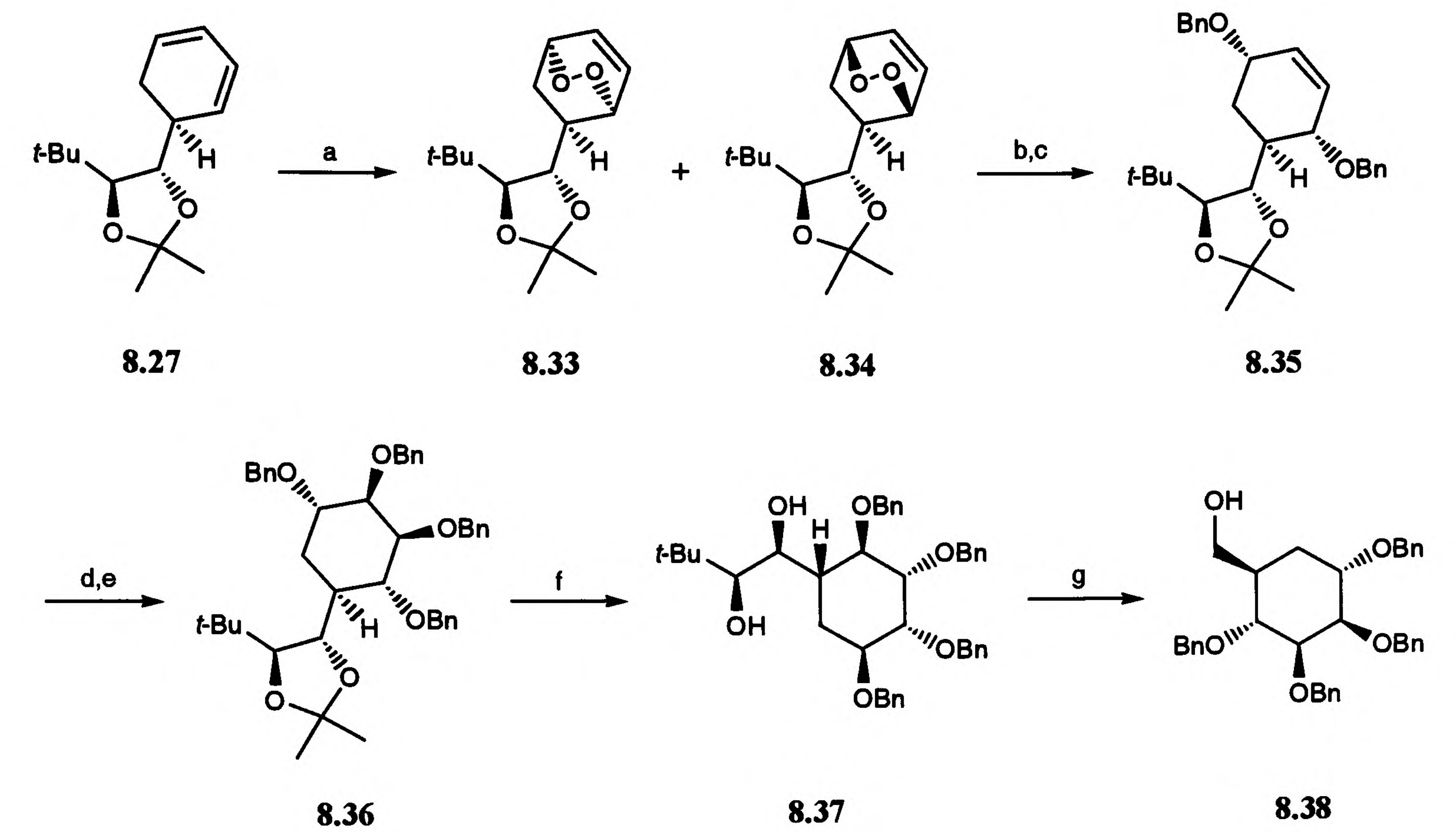
c) BnBr, NaH, DMF, 0 °C–RT (33% two steps); d) *aq.* TFA, RT (99%);

e) $NaIO_4$, THF-H_2O, RT then $NaBH_4$ (80%); f) $VO(acac)_2$, TBHP, DCM, 0 °C–RT (54%);

g) *aq.* HCl, THF-H_2O, RT; h) Ac_2O, py., DMAP (cat.), RT (95% two steps).

Scheme 8.15

In the third approach, acetonide **8.27** was subjected to singlet oxygen addition to furnish a mixture of endoperoxides. Due to their similar R_f values, separation of **8.33** and **8.34** by flash column chromatography, although possible, proved difficult. Subsequent reductive cleavage and benzylation of endoperoxide **8.33** provided the protected ene-diol **8.35**; osmylation and benzylation under standard conditions afforded the benzylated tetrol unit **8.36** in good yield. Finally, TFA-mediated deprotection of **8.36** and periodate cleavage of diol **8.37** furnished benzylated *pseudo*-mannose **8.38** (Scheme 8.16).[225]



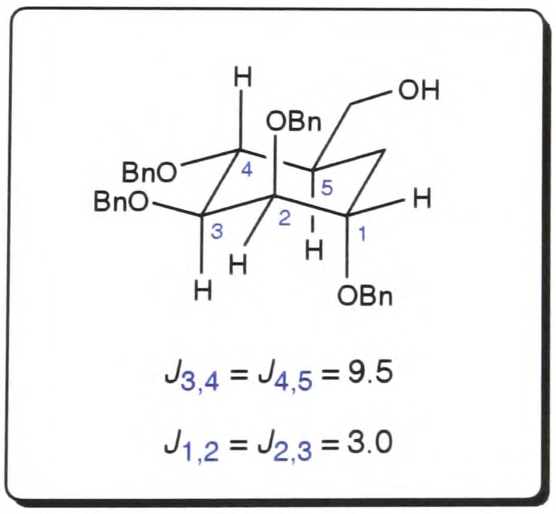
a) O_2, $h\nu$, methylene blue, DCM, -78 °C (**8.33**:**8.34** = 2:1, 76%); b) $LiAlH_4$, THF, 0 °C–RT;

c) BnBr, NaH, DMF, 0 °C–RT (81% two steps); d) OsO_4 (cat.), NMO, THF, RT;

e) BnBr, NaH, DMF, 0 °C–RT (77% two steps); f) *aq*. TFA, RT (93%); g) $NaIO_4$-SiO_2, RT then $NaBH_4$ (77%).

Scheme 8.16

The relative stereochemistry of the *pseudo*-mannopyranoside **8.38** was assigned by coupling constant analysis (Figure 8.02).



$J_{3,4} = J_{4,5} = 9.5$

$J_{1,2} = J_{2,3} = 3.0$

Figure 8.02

8.5 Conclusions

We have successfully expanded the scope of the silicon tethered thermal allyl transfer methodology to incorporate cyclohexadienylsilanes. Employment of a *tert*-butyl directing group resulted in completely stereoselective intramolecular allyl transfer of the cyclohexadienyl unit to afford diol **8.19** in a yield of 77% over four steps from the cyanohydrin.

The first application of this chemistry was developed by elaborating the diene unit to generate polysubstituted cyclohexanes, which are carbasugar scaffolds.

The endocyclic diene unit offers a number of options in terms of functionalisation and in this regard it is envisaged that more elaborate cyclohexadienyl transfer precursors would provide access to a novel range of *pseudo*-sugars that may be of biological relevance, this topic will be discussed further in Chapter 9.

Chapter 9

Conclusions and Future Work

9.0 Conclusions

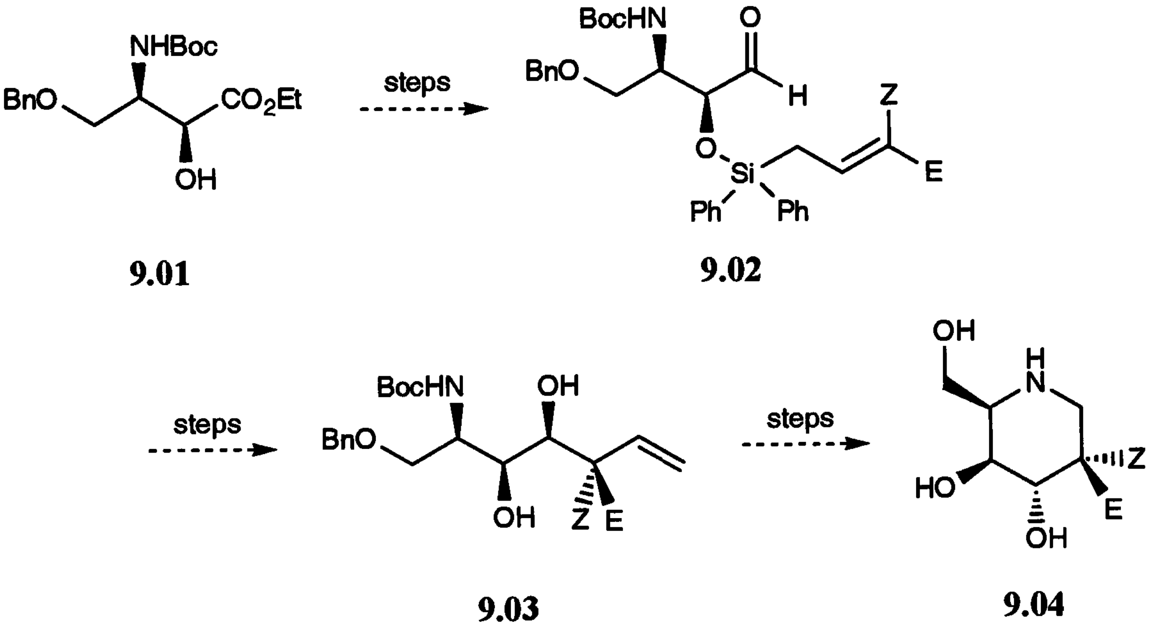
This project has continued work in the field of Type I silicon tethered ene chemistry, extending the methodology already developed within the group for the synthesis of complex *O*-linked ene precursors. A variety of routes to silicon tethered ene precursors have been explored and the subsequent ene reactions evaluated. In general, the cyclisations proceeded *via* the predicted stereochemical course to furnish oxasilacyclohexanols in reasonable yield. The diphenyl-substituted oxasilacycles succumbed readily to oxidative cleavage to afford stereodefined 1,2,4-triols.

During the course of our ongoing efforts to develop efficient, stereocontrolled routes to polyhydroxylated intermediates we discovered an ordered allyl transfer process that proceeded with excellent levels of stereoselectivity under thermal activation. The second part of this thesis has provided an account of our investigations into this novel process and has described the elaboration of the resulting intermediates. Coupled with the choice of *E*- or *Z*-crotylsilane substitution, our studies have shown that three contiguous stereocentres can be installed in a stereocontrolled manner in a relatively short synthetic sequence. Additional functionality was readily concealed within the R-group side chain, to furnish 1,2,3-aminodiols in high overall yield.

An investigation into the viability of the tethered intramolecular allyl transfer process was conducted employing more demanding systems. The reaction sequence was successfully applied to the synthesis of diastereomeric cyclohexadienes, which proved useful intermediates for the construction of more complex polyhydroxylated molecules.

9.1 Future Work

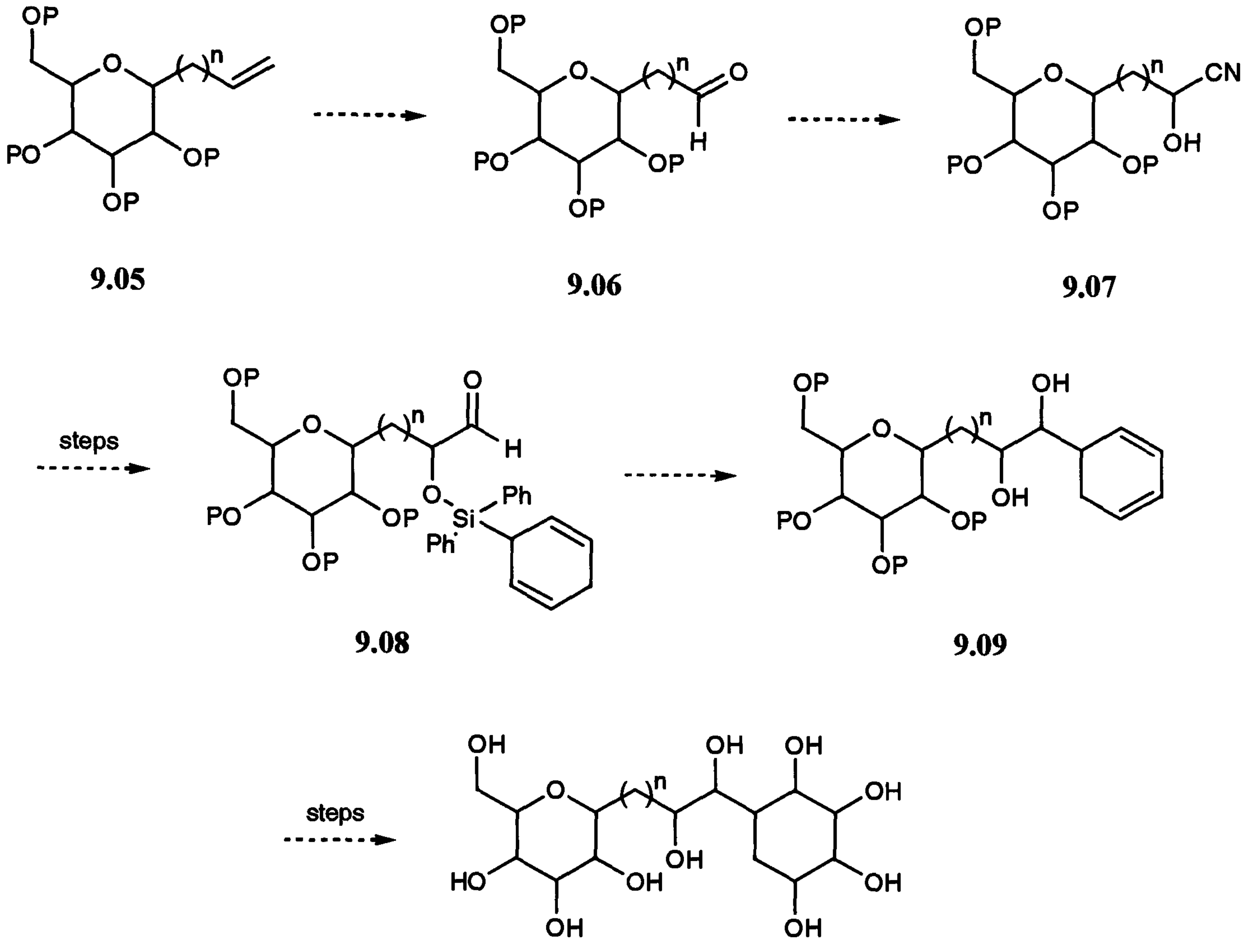
A number of polyhydroxylated and aminated synthons are available, with predictable relative stereochemistry, *via* application of our generic thermal allyl transfer methodology. Of the possible avenues of investigation open to us we envisage the project continuing in the area of carbohydrate synthesis. For example, a suitably protected β-amino ester could be elaborated to provide a general and practical route to fagomine-type iminosugars, such as **9.04** (Scheme 9.01).



Scheme 9.01

Based on readily accessible cyclohexadienylsilanes, many possibilities exist for the preparation of novel carbohydrate derivatives and *psuedo*-sugars. Future work may concentrate on the synthesis of these cyclic intermediates.

Replacement of an *O*-glycosidic linkage with a non-hydrolysable *C*-link confers a greater degree of stability to the sugar substrate *in vivo*, with associated biological effects arising from modifications to intra- and inter-cellular processes and recognition events. As a result *C*-glycosides and *C*-linked disaccharides often possess potent pharmacological properties.[82] In this context, the silacyclohexadienyl transfer methodology offers a method to build-up a *psuedo*-sugar component onto an appropriately protected monosaccharide following allylation. In our systems the *C*-linkage of the carba-*C*-disaccharides would possess hydroxy functionality that may alter biological activity (Scheme 9.02).



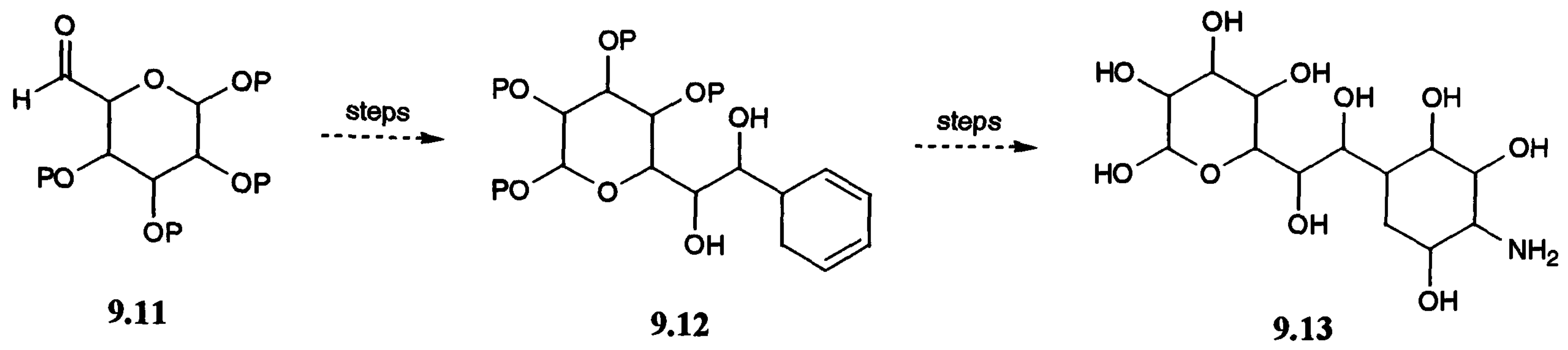
9.05 9.06 9.07

9.08 9.09

9.10

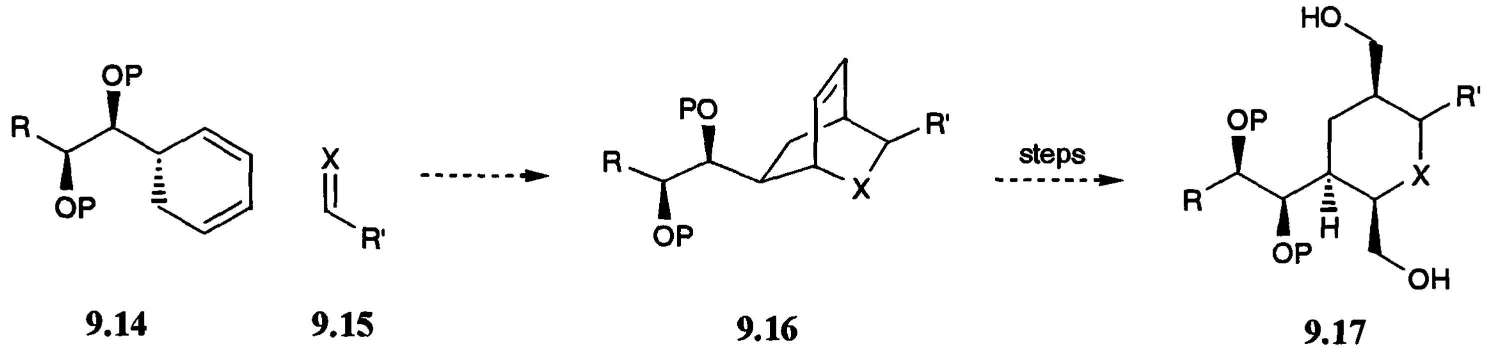
Scheme 9.02

In a similar approach, elaboration of simple monosaccharides *via* the C-6 aldehyde, could afford related hydroxy-*C*-linked carbasugars. Amino-carbasugars represent another class of potential glycosidase inhibitors; application of Sharpless' asymmetric aminohydroxylation (AA) procedure, or Donohoe's tethered aminohydroxylation (TA) process,[226] should allow access to such systems (Scheme 9.03).



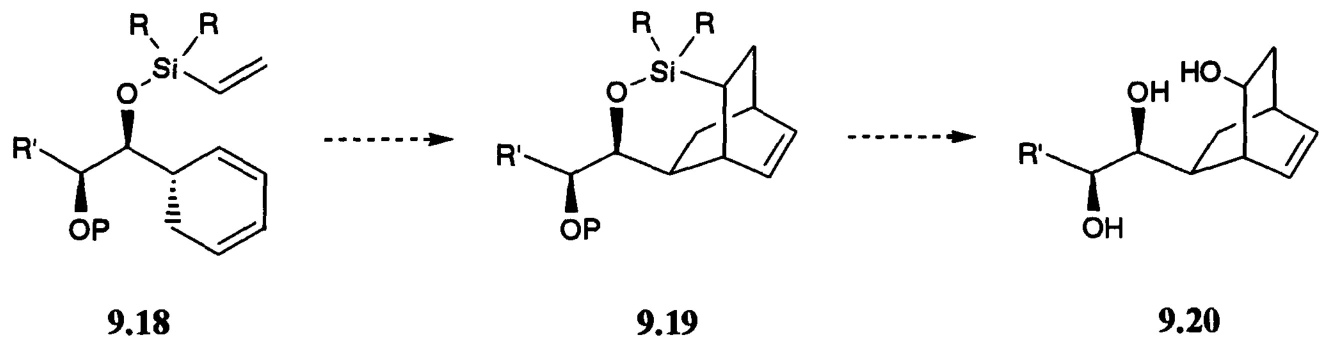
Scheme 9.03

More speculative applications include the formation of Diels-Alder adducts with the cyclohexadienyl intermediate. Cleavage of the double bond in **9.16** *via* ozonolysis would generate branched a *pseudo*-sugar (Scheme 9.04).



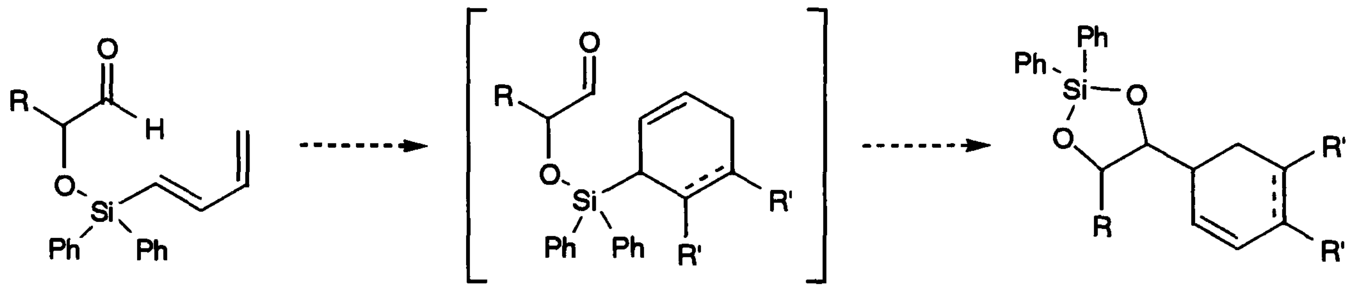
Scheme 9.04

It would also be of interest to investigate the viability of a silicon tethered dienophile. Such an approach would incorporate latent functionality at silicon, permitting further elaboration of the cycloadduct either by oxidative cleavage, protodesilylation or Hiyama-type ring-opening (Scheme 9.05).



Scheme 9.05

Functionalised cyclohexenylsilanes formed *in situ* by Diels-Alder reaction could, in principle, partake in a thermal cascade to form highly functionalised transfer products such as **9.23** (Scheme 9.06).



9.21 **9.22** **9.23**

Scheme 9.06

These selected examples illustrate that the project can progress in a number of interesting directions. It is hoped that future applications of silicon tethered allyl transfer chemistry will provide a range of interesting intermediates for synthetic elaboration.

Experimental

General Procedures

Reagents and Solvents

Solvents and commercially available reagents were dried and purified before use where appropriate, using standard procedures;[227] copper (II) chloride was recrystallised from HCl (2.5 M) and dried at 150 °C under reduced pressure; potassium cyanide and nickel (II) acetylacetonate were dried at 150 °C under reduced pressure; sodium hydride (60% dispersion in mineral oil) was washed with THF and dried under reduced pressure; imidazole was recrystallised from hot ethanol; benzaldehyde and 2-furaldehyde were distilled under reduced pressure from sodium carbonate; *iso*-butyraldehyde was distilled under argon from calcium sulfate; benzyl alcohol was fractionally distilled under argon; benzylamine dried with sodium hydroxide and distilled under reduced pressure; pyridine was distilled under argon from calcium hydride and stored over potassium hydroxide; TEA and TMEDA were distilled under argon from calcium hydride and stored over 4Å molecular sieves; acetonitrile, toluene, DMF and DMSO were distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves; methanol was distilled under argon from magnesium methoxide and stored over 4Å molecular sieves; DCM was distilled from calcium hydride; THF and diethyl ether were distilled from sodium and benzophenone under argon; 'petrol' refers to the fraction of petroleum ether which boils in the range of 30–40 °C and was redistilled prior to use; water was distilled. All other solvents and reagents were used as supplied, without prior purification.

For reactions requiring anhydrous conditions experiments were carried out in oven-dried glassware under an argon atmosphere. ACE pressure tubes were washed with a saturated solution of potassium hydroxide in ethanol, rinsed sequentially with water and acetone, oven-dried and the thread sealed with PTFE tape before use. Where stated, reactions were degassed by passing a rapid flow of argon through the solution for 20–30 min, depending on scale.

Chromatography

Thin layer chromatography (tlc) was performed using Merck aluminium backed 0.2 mm Kieselgel 60 F_{254} pre-coated plates. Plates were visualised by the quenching of UV fluorescence ($\lambda_{max.}$ 254 nm) then stained and heated with one of four solutions as appropriate: (i) 6% vanillin (w/v) and 1% sulfuric acid (v/v) in ethanol; (ii) 5% ammonium molybdate (w/v) and 0.2% cerium (IV) sulfate (w/v) in 5% *aq.* sulfuric acid (v/v); (iii) 5% *dodeca*-molybdophosphoric acid (w/v) in ethanol; (iv) 4% sulfuric acid (v/v) in ethanol. Retention factors (R_f) are reported with the solvent system used in parentheses.

Flash column chromatography was performed on Merck 60 silica gel with a particle size of 40–63 μm; the solvent system being quoted in parentheses. The general method was adapted from the procedure reported by Still and co-workers;[228] the column was loaded with a slurry, prepared by pre-mixing silica gel with the eluent.

Melting and Boiling Points

Melting points were determined using a Griffin heated metal block apparatus and are uncorrected. Boiling points were measured either by using a short path distillation unit or with Kugelrohr apparatus at the pressure specified.

Polarimetry

Optical rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 mL.

Infrared Spectroscopy

Infrared spectra were recorded as thin films on NaCl plates or as KBr disks using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Absorption maxima (ν_{max}) were recorded in wavenumbers (cm^{-1}) and are classified as strong (s), medium (m), weak (w) and broad (br).

Nuclear Magnetic Resonance Spectroscopy

Proton (^1H) NMR spectra were recorded on the following spectrometers: Bruker AMX-500 (500 MHz); Bruker DQX-400 or DPX-400 (400 MHz); Bruker DPX-200 or Varian Gemini 200 (200 MHz). Chemical shifts (δ_H) are reported in parts per million (ppm) down-field of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift and coupling constants using COSY and n.O.e. experiments where appropriate.[229] Abbreviations used in the description of multiplicities are singlet (s), doublet (d), triplet (t), quartet (q), septet (sept) multiplet (m) and broad (br). Coupling constants (*J*) are quoted to the nearest 0.1 Hz.

Carbon-13 (^{13}C) NMR spectra were recorded on the following spectrometers: Bruker AMX-500 (125.7 MHz); Bruker DQX-400 or DPX-400 (100.6 MHz); Bruker DPX-200 (50.3 MHz). Chemical shifts (δ_C) are reported in parts per million (ppm) down-field of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift using DEPT, HMQC and HMBC experiments where appropriate.

Fluorine-19 (^{19}F) NMR spectra were recorded on a Bruker DPX-400 (376.5 MHz) spectrometer. Chemical shifts (δ_F) are reported in parts per million (ppm).

Mass Spectrometry

Low resolution mass spectra were recorded on the following machines: Micromass GCT (CI, EI or FI), VG Trio-1 GCT (CI or EI), Micromass LCT (ES), Micromass Platform (APCI or ES). High resolution mass spectra (HRMS) were recorded either by the author using a Micromass GCT (CI or EI) or by Dr N. Oldham and Mr R. Proctor using a Micromass AutoSpec-oaToF (CI or EI) or a Micromass LCT (ES). HRMS were also performed by the EPSRC National Mass Spectrometry Service Centre, Department of Chemistry, University of Wales, Swansea. Mass to charge ratios (*m/z*) are reported in Daltons with percentage abundance in parentheses. For peaks other than MH^+ and MNH_4^+, only those with an intensity of 10% or higher are quoted.

Elemental analysis

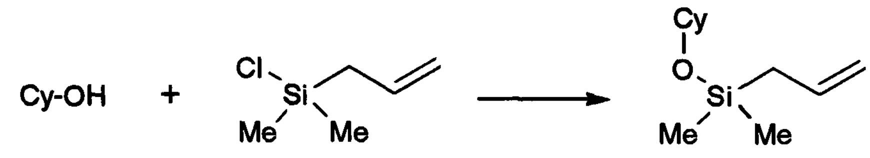
Microanalysis was performed by Elemental Microanalysis Ltd., Okehampton.

X-Ray Crystallography

Single crystal X-ray analysis was performed by Mr Stephen Bell of the Robertson group. The data were collected on an Enraf Nonius Kappa CCD diffractometer, Data collection: COLLECT; cell refinement: DENZO and SCALEPACK; data reduction: DENZO and SCALEPACK; programs used to solve structure: SIR92 and SIR97; program used to refine structure: CRYSTALS; molecular graphics: ORTEP-3; software used to prepare material for publication: CRYSTALS. All structures were refined on setting F.

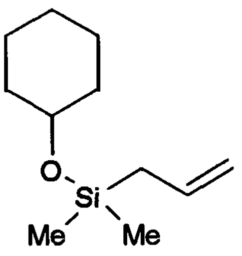
Chapter 2 Compounds

General procedure for (alkoxy)dimethylprop-2-enylsilane synthesis



To a stirred solution of the alcohol (6.00 mmol), DMAP (37.0 mg, 0.30 mmol) and TEA (1.0 mL, 7.20 mmol) in anhydrous THF (15.0 mL) was added allyl(dimethyl)chlorosilane (964 μL, 6.60 mmol) dropwise. The reaction mixture was stirred at RT for 16 hr and then partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (2 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (2 × 50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The resulting pale yellow oil was purified by reduced pressure distillation (Kugelrohr) to furnish the alkoxysilane.

(Cyclohexyloxy)dimethylprop-2-enylsilane[230]

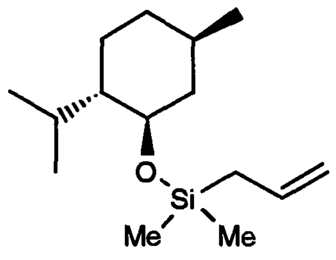


2.08

Colourless oil (1.05 g, 88%). R_f 0.83 (2:1, petrol:diethyl ether); Kugelrohr oven 90–95 °C at 1.0 mmHg; ν_{max}/cm^{-1} (thin film) 3078w, 2935s, 2858m, 1631m, 1451m, 1420w, 1375w, 1255s, 1157w, 1086s, 1026w, 995m, 909s, 875s, 875m, 836m, 735s, 648w; δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 1.07–1.81 (10H, m, 5 × CH_2), 1.60 (2H, dt, *J* 8.0 and 1.2, $SiCH_2$), 3.57 (1H, tt, *J* 8.8 and 4.0, OCH), 4.83 (1H, ddt, *J* 10.2, 2.0 and 1.2, $CH{=}CH_EH$), 4.87 (1H, ddt, *J* 17.8, 2.0 and 1.2, $CH{=}CHH_Z$), 5.78 (1H, ddt, *J* 17.8, 10.2 and 8.0, $CH{=}CH_2$);

δ_C (100.6 MHz, $CDCl_3$) -1.95 ($Si(CH_3)_2$), 24.3 (CH_2), 25.0 ($SiCH_2$), 25.5 (CH_2), 35.9 (CH_2), 71.1 (OCH), 113.2 ($CH{=}CH_2$), 134.2 ($CH{=}CH_2$); *m/z* (GCMS CI^+) 199 (MH^+, 32%), 174 (70), 157 (M^+-C_3H_5, 19), 118 (15), 92 (100), 74 (23); Accurate mass (CI^+): Found 199.1520, $C_{11}H_{23}OSi$ (MH^+) requires 199.1518.

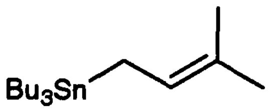
[(−)-Menthyloxy]dimethylprop-2-enylsilane[178]



2.11

Colourless oil (1.23 g, 81%). R_f 0.62 (2:1, petrol:diethyl ether); Kugelrohr oven 100–105 °C at 1.0 mmHg, [lit.,[178] 102–103 °C at 1.0 mmHg]; $[\alpha]_D^{25}$ −46.7 (*c* 1.05, chloroform, [lit.,[231] $[\alpha]_D$ −59.7]); ν_{max}/cm^{-1} (thin film) 3078w, 2956s, 2920s, 2870s, 1632m, 1456w, 1420w, 1385w, 1370w, 1346w, 1253s, 1179w, 1157m, 1108s, 1083s, 1069s, 1054m, 1000w, 932m, 879s, 838s, 751w, 646w; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, $\mathrm{Si(C\mathbf{H}_3)_2}$), 0.74 (3H, d, *J* 6.8, $\mathrm{CHC\mathbf{H}_3}$), 0.77–0.90 (1H, m, H-3_{ax}), 0.90 (6H, d, *J* 6.8, $\mathrm{CH(C\mathbf{H}_3)_2}$), 0.93 (1H, dt, *J* 12.8 and 9.6, H-4_{ax}), 1.01 (1H, dt, *J* 12.2 and 10.4, H-6_{ax}), 1.14 (1H, ddt, *J* 12.4, 10.4 and 2.4, H-2), 1.31–1.44 (1H, m, H-5), 1.56–1.67 (2H, m, H-3_{eq} and H-4_{eq}), 1.63 (2H, br d, *J* 8.8, $\mathrm{SiC\mathbf{H}_2}$), 1.86 (1H, ddt, *J* 12.2, 4.2 and 2.0, H-6_{eq}), 2.16 (1H, septd, *J* 6.8 and 2.4, $\mathrm{C\mathbf{H}(CH_3)_2}$), 3.41 (1H, dt, *J* 10.4 and 4.2, H-1), 4.85 (1H, ddt, *J* 10.0, 2.4 and 1.2, $\mathrm{CH{=}C\mathbf{H}_{\mathit{E}}H}$), 4.89 (1H, ddt, *J* 16.8, 2.4 and 1.2, $\mathrm{CH{=}CH\mathbf{H}_{\mathit{Z}}}$), 5.79 (1H, ddt, *J* 16.8, 10.0 and 8.8, $\mathrm{C\mathbf{H}{=}CH_2}$); δ_C (100.6 MHz, $CDCl_3$) -1.78 and -1.57 ($Si(CH_3)_2$), 15.9 ($CHCH_3$), 21.2 and 22.3 ($CH(CH_3)_2$), 22.8 (C-4), 25.1 ($CH(CH_3)_2$), 25.4 ($SiCH_2$), 31.6 (C-5), 34.5 (C-3), 45.4 (C-6), 49.9 (C-2), 72.6 (C-1), 113.4 ($CH{=}CH_2$), 134.3 ($CH{=}CH_2$); *m/z* (GCMS CI^+) 255 (MH^+, 19%), 230 (10), 169 (43), 156 (11), 139 (33), 116 (100), 92 (56), 81 (21), 74 (22), 58 (18); Accurate mass (CI^+): Found 255.2140, $C_{15}H_{31}OSi$ (MH^+) requires 255.2144.

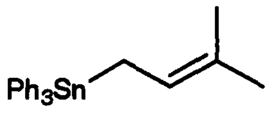
Tributyl(3-methylbut-2-enyl)stannane[90]



2.34

A mixture of magnesium powder (1.13 g, 46.5 mmol), a few crystals of iodine, tributylstannyl chloride (9.63 mL, 35.5 mmol) and anhydrous THF (45.0 mL) was placed in a Quickfit conical flask equipped with rubber septum. The reaction vessel was placed in an ultrasonic cleaning bath and sonicated for 30 min. 3-Methylbut-2-enyl chloride (5.00 mL, 44.4 mmol) was added over 15 min and the suspension was sonicated for a further 1 hr. The reaction was quenched by the addition of saturated *aq.* NH_4Cl soln. (50 mL), stirred for 15 min and filtered through a glass sinter. The filtrate was extracted with diethyl ether (3 × 50 mL); the combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product as a pale yellow oil. Purification by reduced pressure distillation (B.p. 124–127 °C at 1.0 mmHg, [lit.[90] 105–107 °C at 0.01 mmHg]) gave stannane **2.34** as a colourless oil (10.2 g, 80%). R_f 0.72 (5:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 2958s, 2924s, 2873s, 2883s, 1662w, 1464m, 1418w, 1376m, 1340w, 1292w, 1249w, 1182w, 1149w, 1118m, 1071m, 1001w, 960w, 874w, 846m, 800w, 705m; δ_H (400 MHz, $CDCl_3$) 0.85 (6H, t, *J* 8.0, $Sn(\mathbf{CH_2}(CH_2)_2CH_3)_3$), 0.91 (9H, t, *J* 7.2, $Sn((CH_2)_3\mathbf{CH_3})_3$), 1.26–1.36 (6H, m, $Sn(CH_2\mathbf{CH_2}CH_2CH_3)_3$), 1.46–1.53 (6H, m, $Sn((CH_2)_2\mathbf{CH_2}CH_3)_3$), 1.59 and 1.69 (2 × 3H, 2 × s, $=C(\mathbf{CH_3})_2$), 1.66 (2H, d, *J* 8.8, $Sn\mathbf{CH_2}CH=$), 5.31 (1H, br t, *J* 8.8, $\mathbf{CH}=C(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$) 9.3 ($Sn(\mathbf{C}H_2(CH_2)_2CH_3)_3$), 10.6 ($Sn\mathbf{C}H_2CH=$), 13.6 ($Sn((CH_2)_3\mathbf{C}H_3)_3$), 17.4 and 25.5 ($C(\mathbf{C}H_3)_2$), 27.4 ($Sn(CH_2\mathbf{C}H_2CH_2CH_3)_3$), 29.2 ($Sn((CH_2)_2\mathbf{C}H_2CH_3)_3$), 122.9 ($\mathbf{C}H=C(CH_3)_2$), 125.3 ($=\mathbf{C}(CH_3)_2$); *m/z* (GCMS EI^+) 359 ($M^{120}Sn^+$, 37%), 357 ($M^{118}Sn^+$, 20), 355 ($M^{116}Sn^+$, 10), 233 (16), 177 (100), 69 (52), 55 (29).

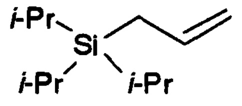
Triphenyl(3-methylbut-2-enyl)stannane[90]



2.48

A mixture of magnesium powder (1.13 g, 46.5 mmol), a few crystals of iodine, triphenylstannyl chloride (13.7 g, 35.5 mmol) and anhydrous THF (45.0 mL) was placed in a Quickfit conical flask equipped with rubber septum. The reaction vessel was placed in an ultrasonic cleaning bath and sonicated for 30 min. 3-Methylbut-2-enyl chloride (5.00 mL, 44.4 mmol) was added over 15 min and the suspension was sonicated for a further 1 hr. The reaction was quenched by the addition of saturated *aq.* NH_4Cl soln. (50 mL), stirred for 15 min and filtered through a glass sinter. The filtrate was extracted with diethyl ether (3 × 50 mL); the combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product as a pale peach solid. Recrystallisation from heptane furnished triphenyl(3-methylbut-2-enyl)stannane **2.48** as a white solid (9.10 g, 61%). R_f 0.74 (diethyl ether); M.p. 59–62 °C (from heptane) [lit.,[232] 61–63 °C]; ν_{max}/cm^{-1} (KBr disc) 3061m, 2964m, 2917m, 1479w, 1428s, 1374w, 1074m, 1021w, 996w, 848w, 806w, 727s, 698s; δ_H (400 MHz, $CDCl_3$) 1.47 and 1.67 (2 × 3H, 2 × s, =C(C**H**$_3$)$_2$), 2.38 (2H, br d, *J* 8.8, SnC**H**$_2$), 5.50 (1H, br t, *J* 8.8, C**H**=C(CH$_3$)$_2$), 7.35–7.76 (15H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.7 ($SnCH_2$), 17.6 and 25.5 (=C(CH$_3$)$_2$), 120.5 (CH=C(CH$_3$)$_2$), 128.6 (Ph), 128.9 (Ph), 137.1 (Ph), 137.5 (*i*-Ph), 139.0 (=C(CH$_3$)$_2$); *m/z* (GCMS FI$^+$) 420 ($M^{120}Sn^+$, 100%), 418 ($M^{118}Sn^+$, 68), 416 ($M^{116}Sn^+$, 29); (GCMS EI$^+$) 351 ($M^{120}Sn^+$-C_5H_9, 66%), 349 ($M^{118}Sn^+$-C_5H_9, 51), 347 ($M^{116}Sn^+$-C_5H_9, 35), 309 (46), 307 (38), 305 (12), 197 (65), 195 (50), 193 (30), 154 (100), 153 (41), 151 (20), 77 (60).

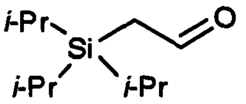
Tri(*iso*-propyl)prop-2-enylsilane[233]



2.14

To a stirred solution of tri(*iso*-propyl)chlorosilane (4.28 mL, 20.0 mmol) in anhydrous THF (20.0 mL) cooled to 0 °C was added allylmagnesium bromide (2.0 M in THF, 10.5 mL, 21.0 mmol) dropwise over 10 min; the cloudy suspension was warmed to 40 °C for 2 hr. The reaction mixture was cooled to RT and quenched by the addition of ice (~100 mL); the mixture was stirred until the layers separated and became homogeneous. The organic phase was washed with saturated *aq.* NaCl soln. (3 × 50 mL) and the combined aqueous phases back extracted with diethyl ether (2 × 100 mL). The combined organic fractions were dried (Na_2SO_4) and the solvents removed *in vacuo* to furnish a pale yellow oil. Purification by reduced pressure distillation (Kugelrohr oven 65–70 °C at 1.0 mmHg) gave silane **2.14** as a colourless oil (3.91 g, 99%). R_f 0.83 (3:1, petrol;diethyl ether); ν_{max}/cm^{-1} (thin film) 3076w, 2943s, 2891s, 2867s, 1630m, 1464m, 1421w, 1384w, 1367w, 1158w, 1041w, 1016w, 991w, 885s, 884s, 735m, 655m; δ_H (400 MHz, $CDCl_3$) 1.00–1.19 (21H, m, 3 × $\mathbf{CH(CH_3)_2}$), 1.67 (2H, dt, *J* 8.0 and 1.2, $\mathrm{Si}\mathbf{CH_2}$), 4.84 (1H, ddt, *J* 10.0, 2.4 and 1.2, $\mathrm{CH{=}C}\mathbf{H}_E\mathrm{H}$), 4.94 (1H, ddt, *J* 16.8, 2.4 and 1.2, $\mathrm{CH{=}CH}\mathbf{H}_Z$), 5.90 (1H, ddt, *J* 16.8, 10.0 and 8.0, $\mathbf{CH}\mathrm{{=}CH_2}$); δ_C (100.6 MHz, $CDCl_3$) 11.0 (3 × $CH(CH_3)_2$), 17.3 ($SiCH_2$), 18.6 (3 × $CH(CH_3)_2$), 112.7 ($CH{=}CH_2$), 136.0 ($CH{=}CH_2$); *m/z* (GCMS EI$^+$) 198 (MH$^+$, 3%), 157 (M$^+$-C_3H_5, 100), 115 (50), 99 (22), 85 (74), 73 (65), 59 (80), 43 (41).

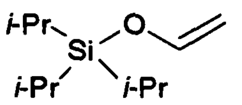
Tri(*iso*-propyl)silanylacetaldehyde[234]



2.15

A solution of allyltri(*iso*-propyl)silane **2.14** (723 μL, 3.00 mmol) in anhydrous DCM (60.0 mL) was cooled to -78 °C. Ozone was passed through the solution until a blue colouration persisted; excess ozone was purged from the system with argon. Dimethyl sulfide (264 μL, 3.60 mmol) was added and the reaction mixture stirred at -78 °C for 1 hr and then warmed to RT over 16 hr. The mixture was partitioned between water (50 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (2 × 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. Purification by flash column chromatography (silica gel, 19:1, petrol:diethyl ether → 9:1, petrol:diethyl ether) gave aldehyde **2.15** as a colourless oil (372 mg, 61%) and tri(*iso*-propyl)silanyloxyethene (122 mg, 20%) as a minor by-product. R_f 0.43 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 2944m, 2892w, 2868m, 2713w, 1705s (C=O), 1466m, 1386w, 1368w, 1163w, 1130m, 1017w, 883m, 786w, 679m; δ_H (400 MHz, $CDCl_3$) 1.00–1.10 (21H, m, 3 × **$CH(CH_3)_2$**), 2.28 (2H, d, *J* 4.4, Si**CH_2**), 9.76 (1H, t, *J* 4.4, **CHO**); δ_C (100.6 MHz, $CDCl_3$) 11.3 (3 × **C**H($CH_3)_2$), 18.4 (3 × CH(**CH_3**$)_2$), 33.0 (Si**CH_2**), 200.6 (**C**HO); *m/z* (GCMS CI$^+$) 218 (MNH_4^+, 24%), 201 (MH^+, 100), 174 (45), 157 (12), 147 (11), 130 (43), 102 (16), 74 (12).

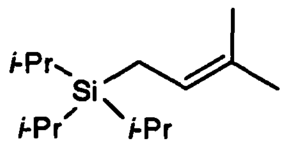
Tri(*iso*-propyl)silanyloxyethene



R_f 0.73 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 2944s, 2868s, 1465m, 1411w, 1382w, 1370m, 1320m, 1192m, 1107s (Si-O), 1057s, 1019m, 1000m, 980m, 902w, 883m, 822w, 762w, 725w, 689w, 656w; δ_H (400 MHz, $CDCl_3$) 0.01–1.10 (21H, m, 3 × **$CH(CH_3)_2$**), 4.01 (1H, d, *J* 5.6, CH=**CH_E**H), 4.40 (1H, d, *J* 12.4, CH=CH**H_Z**), 6.48 (1H, dd, *J* 12.4 and 5.6, **CH**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 11.4 (3 × **C**H($CH_3)_2$), 18.5 (3 × CH(**CH_3**$)_2$), 94.2

($CH=CH_2$), 148.2 ($CH=CH_2$) *m/z* (GCMS CI$^+$) 218 (MNH_4^+, 22%), 201 (MH^+, 100), 174 (37), 147 (11), 130 (22), 102 (12), 74 (13).

Tri(*iso*-propyl)-3-methylbut-2-enylsilane[233]



2.16

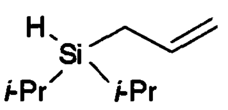
A solution of allyltri(*iso*-propyl)silane **2.14** (482 μL, 2.00 mmol) in anhydrous DCM (40.0 mL) was cooled to -78 °C. Ozone was passed through the solution until a blue colouration persisted; excess ozone was purged from the system with argon. Dimethyl sulfide (176 μL, 2.40 mmol) was added and the reaction mixture stirred at -78 °C for 1 hr and then warmed to RT over 3.5 hr. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (3.46 g, 8.00 mmol) in anhydrous THF (35.0 mL) cooled to -78 °C was added *n*-BuLi (1.6 M in hexanes, 4.40 mL, 7.00 mmol). The blood-red solution was stirred for 1.5 hr at -78 °C then warmed to RT over 1.5 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 3 hr. The reaction mixture was partitioned between water (50 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (3 × 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether and petrol (1:1, v/v), and the combined extracts were filtered through Celite® and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, petrol → 9:1, petrol:diethyl ether) to furnish silane **2.16** as a colourless oil (366 mg, 81%) and tri(*iso*-propyl)silanyloxyethene (9.0 mg, 2%). R_f 0.63 (petrol); ν_{max}/cm^{-1} (thin film) 2942s, 2867s, 1463m, 1404w, 1383m, 1346w, 1244w, 1158m, 1099m, 1070w, 999w, 918w, 883s, 845w, 812w, 738s, 712s; δ_H (400 MHz, $CDCl_3$) 0.90–1.09 (21H, m, 3 × $CH(CH_3)_2$), 1.50

(2H, d, *J* 8.4, Si**CH**$_2$), 1.63 and 1.69 (2 × 3H, 2 × s, =C(**CH**$_3$)$_2$), 5.22 (1H, br t, *J* 8.4, **CH**=C(CH$_3$)$_2$); δ_C (100.6 MHz, CDCl$_3$) 10.8 (SiCH$_2$), 11.1 (3 × CH(CH$_3$)$_2$), 17.6 and 25.8 (=C(CH$_3$)$_2$), 18.6 (3 × CH(CH$_3$)$_2$), 120.9 (CH=C(CH$_3$)$_2$), 128.0 (=C(CH$_3$)$_2$); *m/z* (GCMS EI$^+$) 226 (M$^+$, 9%), 157 (M$^+$-C$_5$H$_9$, 50), 115 (49), 99 (24), 87 (60), 73 (61), 59 (100).

General procedure for prop-2-enylsilane synthesis

To a stirred solution of the chlorosilane (5.00 mmol) in anhydrous THF (5.0 mL) cooled to 0 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 5.50 mL, 5.50 mmol) dropwise over 5 min; the cloudy suspension was warmed to 40 °C for 2 hr. The reaction was cooled to RT and quenched by the addition of ice and saturated *aq.* NH$_4$Cl soln. (20 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic phases washed with saturated *aq.* NaCl soln. (2 × 50 mL) and dried (MgSO$_4$). The solvent was removed *in vacuo* and the resulting pale yellow oil was purified by flash column chromatography (silica gel, petrol).

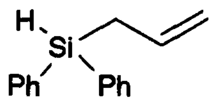
Di(*iso*-propyl)prop-2-enylsilane



2.17

Colourless oil (775 mg, 99%). R$_f$ 0.76 (petrol); ν_{max}/cm^{-1} (thin film) 2942s, 2891s, 2865s, 2100s (Si-H), 1632s, 1463s, 1420w, 1385m, 1366w, 1242w, 1193w, 1160m, 1068w, 1045w, 1003s, 931m, 918m, 895s, 806s, 732m, 710m, 693m; δ_H (400 MHz, CDCl$_3$) 0.95–1.08 (14H, m, 2 × **CH**(**CH**$_3$)$_2$), 1.67 (2H, ddt, *J* 8.0, 3.2 and 1.2, Si**CH**$_2$), 3.45-3.49 (1H, m, Si**H**), 4.85 (1H, ddt, *J* 10.0, 2.0 and 1.2, CH=**CH**$_E$H), 4.94 (1H, ddt, *J* 16.8, 2.0 and 1.2, CH=CH**H**$_Z$), 5.87 (1H, ddt, *J* 16.8, 10.0 and 8.0, **CH**=CH$_2$); δ_C (100.6 MHz, CDCl$_3$) 10.4 (2 × CH(CH$_3$)$_2$), 16.3 ($SiCH_2$), 18.6 and 18.9 (2 × $CH(CH_3)_2$), 113.1 ($CH{=}CH_2$), 135.7 ($CH{=}CH_2$); *m/z* (GCMS CI^+) 174 (MNH_4^+, 100%), 157 (MH^+, 29), 132 (30), 90 (18), 76 (23), 60 (14); Accurate mass (EI^+): Found 156.1338, $C_9H_{20}Si$ (M^+) requires 156.1334.

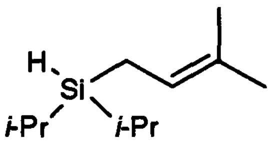
Diphenyl(prop-2-enyl)silane[194]



2.20

On a 5.11 mmol scale the reaction gave silane **2.20** as a colourless oil (1.13 g, 99%). R_f 0.40 (petrol); ν_{max}/cm^{-1} (thin film) 3135w, 3069s, 3051s, 3000s, 2973m, 2917w, 2885w, 2125s (Si-H), 1956w, 1884w, 1818w, 1766w, 1630s, 1589m, 1568w, 1486m, 1428s, 1391m, 1329w, 1302w, 1264w, 1190m, 1155m, 1116s, 1066w, 1041w, 991m, 929m, 899m, 807s, 697s, 586s; δ_H (400 MHz, $CDCl_3$) 2.27 (2H, ddt, *J* 8.0, 3.4 and 1.2, $Si\mathbf{CH_2}$), 5.00 (1H, t, *J* 3.4, Si**H**), 5.02 (1H, ddt, *J* 10.4, 2.0 and 1.2, $CH{=}\mathbf{CH}_E H$), 5.08 (1H, ddt, *J* 17.2, 2.0 and 1.2, $CH{=}CH\mathbf{H}_Z$), 5.97 (1H, ddt, *J* 17.2, 10.4 and 8.0, $\mathbf{CH}{=}CH_2$), 3.71–7.78 (6H, m, Ph), 3.82–3.86 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 19.9 ($SiCH_2$), 114.9 ($CH{=}CH_2$), 128.1 (Ph), 129.8 (Ph), 133.7 (Ph), 133.8 (*i*-Ph), 135.3 ($CH{=}CH_2$); *m/z* (GCMS CI^+) 242 (MNH_4^+, 100%), 200 (82), 183 (M^+-C_3H_5, 14); Accurate mass (CI^+): Found 242.1369, $C_{15}H_{20}NSi$ (MNH_4^+) requires 242.1365.

(3-Methylbut-2-enyl)di(*iso*-propyl)silane

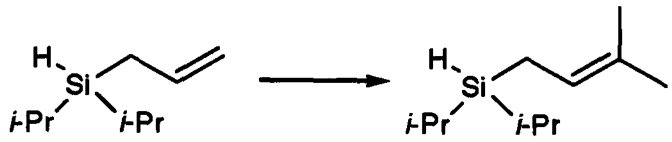


2.19

To a stirred solution of prenyl(tributyl)stannane **2.34** (3.27 g, 9.10 mmol) in anhydrous THF (45.0 mL) cooled to -78 °C was added *n*-BuLi (1.6 M in hexanes, 5.69 mL, 9.10 mmol) dropwise over 5 min and the mixture was stirred for 2.5 hr. Di(*iso*-propyl)chlorosilane (1.55 mL, 9.10 mmol) was added and the mixture was stirred at -78 °C for a further 1.5 hr. The solution was warmed to RT and the solvent removed *in vacuo*. The crude residue was triturated with petrol, the petrol extracts were filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol) to furnish silane **2.19** as a colourless oil (1.43 g, 85%). R_f 0.91 (petrol); ν_{max}/cm^{-1} (thin film) 2925s, 2864s, 2098s (Si-H), 1463s, 1377m, 1343w, 1244w, 1159m, 1098w, 1071w, 1003m, 918w, 882m, 857m, 828m, 804s, 730m, 696m, 648m; δ_H (400 MHz, $CDCl_3$) 0.97–1.08 (14H, m, 2 × $CH(CH_3)_2$), 1.51 (2H, br d, *J* 8.3, $SiCH_2$), 1.61 and 1.69 (2 × 3H, 2 × s, $=C(CH_3)_2$), 3.42–3.45 (1H, m, SiH), 5.20 (1H, br t, *J* 8.3, $CH=C(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$) 10.2 ($SiCH_2$), 10.6 (2 × $CH(CH_3)_2$), 17.5 and 25.7 ($=C(CH_3)_2$), 18.7 and 18.9 (2 × $CH(CH_3)_2$), 120.2 ($CH=C(CH_3)_2$), 128.8 ($=C(CH_3)_2$); *m/z* (GCMS CI^+) 202 (MNH_4^+, 100%), 185 (MH^+, 9), 132 (24), 105 (28), 90 (11), 76 (16); Accurate mass (GCMS EI^+): Found 184.1658, $C_{11}H_{24}Si$ (M^+) requires 184.1647.

On a 5.86 mmol scale the prenyl(triphenyl)stannane (**2.48**) procedure gave **2.19** as a colourless oil (702 mg, 65%).

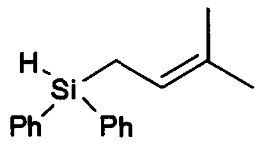
Alternative procedure from 2.17



A solution of allyldi(*iso*-propyl)silane **2.17** (621 mg, 3.97 mmol) and Sudan Red 7B indicator (20.0 μL, 0.05% w/v in DCM) in anhydrous DCM (79.0 mL) was cooled to -78 °C. Ozone was passed through the solution until the magenta colouration dispersed; excess ozone was purged from the system with argon. Dimethyl sulfide (350 μL, 4.77 mmol) was added and the reaction mixture stirred at -78 °C for 1.5 hr and then warmed to RT over 30 min. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (3.43 g, 7.94 mmol) in anhydrous

THF (32.0 mL) cooled to -45 °C was added *n*-BuLi (1.6 M in hexanes, 4.20 mL, 6.72 mmol). The blood-red solution was stirred for 1.5 hr at -45 °C then warmed to RT over 2 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 2 hr. The reaction mixture was partitioned between water (200 mL) and DCM (100 mL). The aqueous phase was extracted with DCM (3 × 50 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (2 × 50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether, the ethereal extracts were filtered through Celite® and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, petrol) to furnish silane **2.19** as a colourless oil (353 mg, 48%).

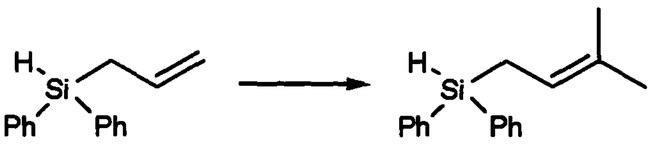
(3-Methylbut-2-enyl)diphenylsilane[235]



2.22

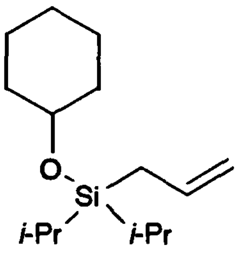
To a stirred solution of prenyl(triphenyl)stannane **2.48** (1.04 g, 2.48 mmol) in anhydrous THF (25.0 mL) cooled to -78 °C was added *n*-BuLi (1.6 M in hexanes, 1.55 mL, 2.48 mmol) dropwise over 5 min and the mixture was stirred for 1.5 hr. Diphenylchlorosilane (490 μL, 2.50 mmol) was added and the mixture was stirred at -78 °C for a further 1 hr. The solution was warmed to RT and the solvent removed *in vacuo*. The crude residue was triturated with petrol, and the petrol extracts were filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol) to furnish **2.22** as a colourless oil (606 mg, 97%). R_f 0.67 (10:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3086m, 3068s, 3050s, 3020s, 2999s, 2966s, 2912s, 2879s, 2855m, 2122s (Si-H), 1955w, 1883w, 1818w, 1765w, 1665w, 1589m, 1486m, 1450m, 1428s, 1404w, 1376m, 1343w, 1330w, 1302w, 1264w, 1224w, 1189w, 1156s, 1117s, 1066w, 998m, 858s, 835s, 804s, 734s, 698s; δ_H (400 MHz, $CDCl_3$) 1.53 and 1.73 (2 × 3H, 2 × s, $=C(\mathbf{CH_3})_2$), 2.09 (2H, dd, *J* 8.4 and 3.2, $Si\mathbf{CH_2}$), 4.91 (1H, t, *J* 3.2, Si**H**), 5.30 (1H, br t, *J* 8.4, $\mathbf{CH}=C(CH_3)_2$), 7.40–7.48 (6H, m, Ph), 7.57–7.74 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.1 ($SiCH_2$), 17.6 and 25.7 ($=C(CH_3)_2$), 118.3 ($CH=C(CH_3)_2$), 127.8 (Ph), 129.6 (Ph), 131.0 ($=C(CH_3)_2$), 134.3 (*i*-Ph), 135.2 (Ph); *m/z* (GCMS CI^+) 270 (MNH_4^+, 100%), 253 (MH^+, 29), 199 (85), 192 (36), 183 (50), 139 (22), 105 (20), 78 (16); Accurate mass (ES^+): Found 270.1682, $C_{17}H_{24}NSi$ (MNH_4^+) requires 270.1678; Found: C 80.56, H 8.34, $C_{17}H_{20}Si$ requires: C 80.89, H 7.99.

Alternative procedure from 2.20



A solution of allyl(diphenyl)silane **2.20** (492 mg, 2.19 mmol) and Sudan Red 7B indicator (10.0 μL, 0.05% w/v in DCM) in anhydrous DCM (44.0 mL) was cooled to -78 °C. Ozone was passed through the solution until the magenta colouration dispersed; excess ozone was purged from the system with argon. Dimethyl sulfide (193 μL, 2.63 mmol) was added and the mixture stirred at -78 °C for 1 hr and then warmed to RT over 30 min. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (1.89 g, 4.37 mmol) in anhydrous THF (18.0 mL) cooled to -45 °C was added *n*-BuLi (1.6 M in hexanes, 2.33 mL, 3.73 mmol). The blood-red solution was stirred for 1 hr at -45 °C then warmed to RT over 2 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 2 hr. The reaction mixture was partitioned between water (100 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (3 × 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (2 × 50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether, the ethereal extracts were filtered through Celite® and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, petrol) to furnish silane **2.22** as a colourless oil (39.6 mg, 7%).

(Cyclohexyloxy)di(*iso*-propyl)prop-2-enylsilane

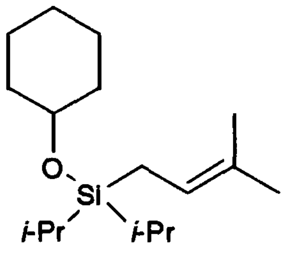


2.23

To a stirred solution of di(*iso*-propyl)dichlorosilane (722 μL, 4.00 mmol) in anhydrous THF (20.0 mL) cooled to -78 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 3.20 mL, 3.20 mmol) dropwise over 5 min. The reaction mixture was stirred for 2 hr at -78 °C and then warmed to RT and the THF removed *in vacuo*. The residue was taken up in anhydrous DMF (12.0 mL) and treated with imidazole (327 mg, 4.80 mmol), DMAP (24.0 mg, 0.20 mmol) and cyclohexanol (333 μL, 3.20 mmol). The mixture was heated at 80 °C for 4 hr, cooled to RT and poured into saturated *aq*. NH_4Cl soln. (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 25 mL); the combined organic fractions were washed with saturated *aq*. NaCl soln. (2 × 25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, petrol) to furnish alkoxysilane **2.23** as a colourless oil (555 mg, 69%). R_f 0.80 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3078w, 2934s, 2865s, 1630m, 1464m, 1372m, 1245w, 1155m, 1134m, 1100s, 1053m, 1020m, 997m, 932w, 884m, 859m, 821m, 782m, 746m; δ_H (400 MHz, $CDCl_3$) 0.95–1.09 (14H, m, 2 × **CH(CH$_3$)$_2$**), 1.16–1.39 (5H, m, 2 × **CH$_2$** and **CH**), 1.46–1.52 (1H, m, **CH**), 1.72 (2H, dt, *J* 8.4 and 1.2, SiC**H$_2$**), 1.69–1.83 (4H, m, 2 × **CH$_2$**), 3.66 (1H, tt, *J* 9.0 and 3.6, OC**H**), 4.85 (1H, ddt, *J* 10.0, 2.4 and 1.2, CH=C**H$_E$**H), 4.95 (1H, ddt, *J* 16.8, 2.4 and 1.2, CH=CH**H$_Z$**), 5.88 (1H, ddt, *J* 16.8, 10.0 and 8.4, C**H**=CH$_2$); δ_C

(100.6 MHz, $CDCl_3$) 12.8 (2 × $CH(CH_3)_2$), 17.5 and 17.6 (2 × $CH(CH_3)_2$), 19.3 ($SiCH_2$), 24.0 (CH_2), 25.6 (CH_2), 35.8 (CH_2), 70.8 (OCH), 113.3 ($CH{=}CH_2$), 134.9 ($CH{=}CH_2$); *m/z* (GCMS CI^+) 255 (MH^+, 4%), 230 (100), 213 (M^+-C_3H_5, 79), 148 (25); Accurate mass (CI^+): Found 255.2139, $C_{15}H_{31}OSi$ (MH^+) requires 255.2144.

(Cyclohexyloxy)di(*iso*-propyl)-3-methylbut-2-enylsilane

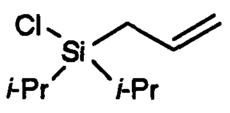


2.25

A stirred solution of silane **2.23** (240 mg, 0.94 mmol) in anhydrous DCM (20.0 mL) was cooled to -78 °C. Ozone was passed through the solution until a blue colouration persisted; excess ozone was purged from the system with argon. Dimethyl sulfide (83.0 µL, 1.13 mmol) was added and the reaction mixture was stirred at -78 °C for 2 hr and then warmed to RT over 1 hr. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (1.63 g, 3.77 mmol) in anhydrous THF (15.0 mL) cooled to -45 °C was added *n*-BuLi (1.6 M in hexanes, 2.06 mL, 3.30 mmol). The blood-red solution was warmed to RT over 2 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 3 hr. The reaction mixture was partitioned between water (50 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (3 × 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether and petrol (1:1, v/v), the combined extracts filtered through Celite® and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 29:1, petrol:diethyl ether) to furnish alkoxysilane **2.25** as a colourless oil (131 mg, 50%). R_f 0.68 (29:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film)

2933s, 2865s, 1464m, 1450m, 1374w, 1245w, 1153w, 1099s, 1052m, 1020w, 998m, 919w, 883m, 859m, 824w, 781w, 742m, 720w; δ_H (400 MHz, $CDCl_3$) 0.90–1.05 (14H, m, 2 × $CH(CH_3)_2$), 1.16–1.38 (5H, m, 2 × **CH_2** and **CH**), 1.46–1.53 (1H, m, **CH**), 1.56 (2H, d, *J* 8.0, $Si\mathbf{CH_2}$), 1.63 and 1.68 (2 × 3H, 2 × s, $=C(\mathbf{CH_3})_2$), 1.70–1.82 (4H, m, 2 × **CH_2**), 3.65 (1H, tt, *J* 8.8 and 4.0, O**CH**), 5.21 (1H, br t, *J* 8.0, **CH**$=C(CH_3)_2$); δ_C (100.6 MHz, $CDCl_3$) 12.9 (2 × $CH(CH_3)_2$ and $SiCH_2$), 17.5 and 17.6 (2 × $CH(CH_3)_2$ and CH_3), 24.0 (CH_2), 25.6 (CH_2), 35.8 (CH_2), 70.9 (OCH), 119.9 ($CH=C(CH_3)_2$), 128.8 ($=C(CH_3)_2$); *m/z* (GCMS CI^+) 283 (MH^+, 8%), 230 (100), 213 (M^+-C_5H_9, 18), 148 (14); Accurate mass (CI^+): Found 283.2454, $C_{17}H_{35}OSi$ (MH^+) requires 283.2457.

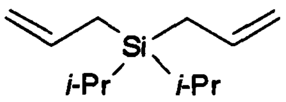
Chlorodi(*iso*-propyl)prop-2-enylsilane



2.26

To a stirred solution of dichlorodi(*iso*-propyl)silane (3.00 mL, 16.6 mmol) in anhydrous THF (50.0 mL) cooled to -45 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 16.6 mL, 16.6 mmol) dropwise over 30 min; the cloudy suspension was warmed slowly to RT over 3 hr. The solvent was removed *in vacuo* and the residue distilled under reduced pressure (Kugelrohr oven 100–105 °C at 18.0 mmHg) to furnish chlorosilane **2.26** as a colourless oil contaminated with diallylsilane **2.27** (2.63 g, 5:2, 83%).

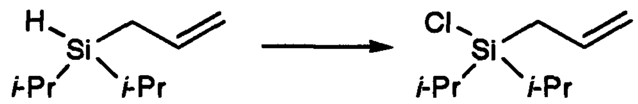
Di(*iso*-propyl)di(prop-2-enyl)silane[236]



2.27

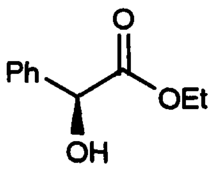
Colourless oil.[237] R_f 0.85 (2:1, petrol;diethyl ether); ν_{max}/cm^{-1} (thin film) 3078w, 2943s, 2892s, 2867s, 1630s, 1464m, 1420w, 1392w, 1246w, 1157m, 1057w, 992m, 932w, 893s, 784w; δ_H (200 MHz, $CDCl_3$) 0.98–1.10 (14H, m, 2 × $CH(CH_3)_2$), 1.65 (4H, dt, *J* 8.0 and 1.2, 2 × $SiCH_2$), 4.86 (2H, ddt, *J* 10.0, 2.0 and 1.2, 2 × $CH=CH_EH$), 4.94 (2H, ddt, *J* 17.2, 2.0 and 1.2, 2 × $CH=CHH_Z$), 5.87 (2H, ddt, *J* 17.2, 10.0 and 8.0, 2 × $CH=CH_2$); δ_C (50.3 MHz, $CDCl_3$) 11.3 (2 × $CH(CH_3)_2$), 17.7 (2 × $SiCH_2$), 18.1 (2 × $CH(CH_3)_2$), 113.1 (2 × $CH=CH_2$), 135.3 (2 × $CH=CH_2$); *m/z* (GCMS CI^+) 214 (MNH_4^+, 7%), 197 (MH^+, 100), 172 (14), 155 (M^+-C_3H_5, 28), 147 (54), 130 (96), 105 (25), 88 (19), 77 (13), 60 (11).

Alternative procedure from 2.17[88]



A flame-dried two-necked flask (100 mL) was charged with anhydrous $CuCl_2$ (6.10 g, 45.4 mmol) and anhydrous CuI (108 mg, 0.57 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round bottomed flask (100 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (45.0 mL) was added followed by allyldi(*iso*-propyl)silane **2.17** (3.55 g, 22.7 mmol) and the orange suspension stirred for 21 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon; THF was removed from the filtrate *in vacuo* to give a crude product which was distilled under reduced pressure into a flask cooled to -78 °C, to furnish chlorosilane **2.26** as a colourless oil (4.24 g, 98%). R_f 0.50 (2:1, petrol:diethyl ether); B.p. 38–40 °C (0.2 mmHg); ν_{max}/cm^{-1} (thin film) 3081m, 2984s, 2870s, 1632s, 1465s, 1419w, 1387m, 1368w, 1247w, 1191w, 1166m, 1070m, 993s, 901s, 883s, 768m, 734m; δ_H (500 MHz, $CDCl_3$) 1.10–1.14 (12H, m, 2 × $CH(CH_3)_2$), 1.16–1.25 (2H, m, 2 × $CH(CH_3)_2$), 1.88 (2H, dt, *J* 8.0 and 1.5, $SiCH_2$), 4.96 (1H, ddt, *J* 10.0, 2.0 and 1.5, $CH=CH_EH$), 5.02 (1H, ddt, *J* 17.0, 2.0 and 1.5, $CH=CHH_Z$), 5.84 (1H, ddt, *J* 17.0, 10.0 and 8.0, $CH=CH_2$); δ_C (125.7 MHz, $CDCl_3$) 13.8 (2 × $CH(CH_3)_2$), 17.0 (2 × $CH(CH_3)_2$), 20.6 ($SiCH_2$), 115.0 ($CH=CH_2$), 132.6 ($CH=CH_2$); *m/z* (GCMS CI^+) 210 ($M^{37}ClNH_4^+$, 6%), 208 ($M^{35}ClNH_4^+$, 22), 193 ($M^{37}ClH^+$, 8), 191 ($M^{35}ClH^+$, 25), 168 (32), 166 (100), 148 (11), 138 (31), 93 (22), 74 (41), 63 (19), 60 (15); Accurate mass (CI^+): Found 191.1027, $C_9H_{20}Si^{35}Cl$ (MH^+) requires 191.1023.

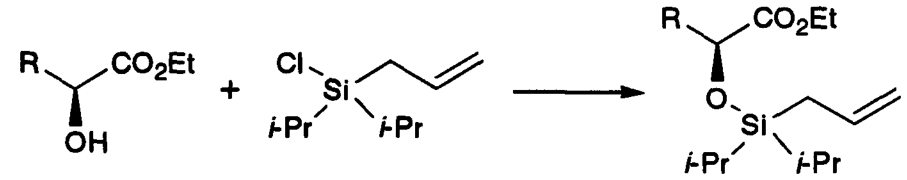
(*S*)-Ethyl mandelate[238]



2.28

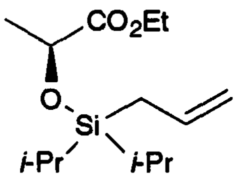
To a stirred solution of (*S*)-(+)-mandelic acid (5.00 g, 32.9 mmol) in ethanol (33.0 mL) was added $NiCl_2{\cdot}6H_2O$ (782 mg, 3.29 mmol) and the resulting green solution heated at reflux for 12 hr. The reaction was cooled to RT and the solvent removed *in vacuo*; the crude residue was taken up in diethyl ether (200 mL) and washed successively with water (2 x 50 mL), saturated *aq.* $NaHCO_3$ soln. (2 x 50 mL) and saturated *aq.* NaCl soln. (50 mL). The organic phase was separated and dried (Na_2SO_4) and the solvent removed *in vacuo* to furnish ester **2.28** as a colourless syrup (5.46 g, 92%) which solidified upon standing. The product was used without further purification. R_f 0.65 (diethyl ether); M.p. 30–33 °C [lit.,[239] 33–34 °C]; $[\alpha]_D^{20}$ +136.8 (*c* 1.01, chloroform) [lit.,[239] $[\alpha]_D^{25}$ +132.9 (*c* 1.00, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3440s (br, O-H), 3087w, 3075w, 3033w, 2985m, 2939w, 2905w, 1936w, 1981w, 1732s (C=O), 1601w, 1587w, 1492m, 1473m, 1456m, 1386m, 1344w, 1304m, 1262m, 1210s, 1186s, 1094s, 1068s, 1023m, 935w, 911w, 862w; δ_H (200 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.2, $OCH_2\mathbf{CH_3}$), 3.89 (1H, d, *J* 6.0, **OH**), 4.05–4.34 (2H, m, $O\mathbf{CH_2}CH_3$), 5.17 (1H, d, *J* 6.0, **CH**Ph), 7.26–7.49 (5H, m, Ph); δ_C (50.3 MHz, $CDCl_3$) 13.9 ($OCH_2\mathbf{C}H_3$), 61.9 ($O\mathbf{C}H_2CH_3$), 73.0 (**C**HPh), 126.6 (Ph), 128.3 (Ph), 128.5 (Ph), 138.6 (*i*-Ph), 173.6 (CO_2); *m/z* (GCMS CI^+) 198 (MNH_4^+, 100%), 180 (MH^+, 69), 165 (21), 163 (17), 121 (18), 105 (59), 94 (41), 91 (74), 82 (22), 78 (47), 58 (46).

General procedure for α-silyloxy ester synthesis



To a stirred solution of the α-hydroxy ester (1.00 mmol), DMAP (0.05 mmol) and TEA (1.20 mmol), in anhydrous DMF (5.0 mL), was added chlorosilane **2.26** (1.20 mmol). The solution was warmed to 80 °C for 12 hr, then cooled to RT and partitioned between water (25 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 39:1, petrol:diethyl ether).

(*S*)-Ethyl 2-[(prop-2-enyl)di(*iso*-propyl)silanyloxy]propanoate

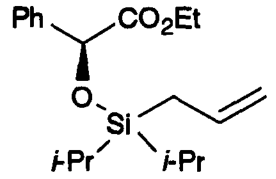


2.30

On a 3.42 mmol scale the reaction gave ester **2.30** as a colourless oil (807 mg, 87%). R_f 0.74 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –24.6 (*c* 1.03, chloroform); ν_{max}/cm^{-1} (thin film) 3078w, 2944s, 2868s, 1755s (C=O), 1630m, 1465m, 1420w, 1373m, 1346w, 1273m, 1146s, 1062s, 1024m, 975m, 933w, 884s, 860w, 749m; δ_H (400 MHz, $CDCl_3$) 1.00–1.09 (14H, m, 2 × $CH(CH_3)_2$), 1.28 (3H, t, *J* 7.0, OCH_2CH_3), 1.41 (3H, d, *J* 6.4, $OCHCH_3$), 1.73 (2H, ~d, *J* 8.0, $SiCH_2$), 4.12–4.24 (2H, m, OCH_2CH_3), 4.40 (1H, q, *J* 6.4, $OCHCH_3$), 4.86 (1H, ddt, *J* 10.4, 2.0 and 1.2, $CH{=}CH_EH$), 4.95 (1H, ddt, *J* 16.8, 2.0 and 1.2, $CH{=}CHH_Z$), 5.86 (1H, ddt, *J* 16.8, 10.4 and 8.0, $CH{=}CH_2$); δ_C (100.6 MHz, $CDCl_3$) 12.5 (2 × $CH(CH_3)_2$), 14.1 (OCH_2CH_3), 17.0 and 17.3 (2 × $CH(CH_3)_2$), 18.8 ($SiCH_2$), 21.5 ($OCHCH_3$), 60.7 (OCH_2CH_3), 68.4 ($OCHCH_3$), 113.9 ($CH{=}CH_2$), 134.2 ($CH{=}CH_2$), 174.0 (CO_2); *m/z* (GCMS

EI$^+$) 272 (M$^+$, 4%), 231 (M$^+$-C_3H_5, 70), 229 (50), 203 (25), 195 (12), 159 (35), 157 (40), 145 (17), 133 (86), 131 (100), 117 (15), 113 (19), 103 (41), 101 (26), 89 (18), 85 (19), 75 (25); Accurate mass (EI$^+$): Found 272.1813, $C_{14}H_{28}O_3Si$ (M$^+$) requires 272.1808.

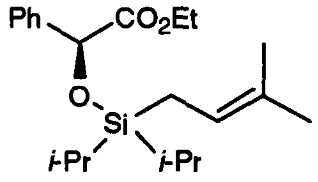
(*S*)-Ethyl [(prop-2-enyl)di(*iso*-propyl)silanyloxy]phenylacetate



2.29

On a 1.47 mmol scale the reaction gave ester **2.29** as a colourless oil (459 mg, 94%). R$_f$ 0.69 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +43.8 (*c* 1.04, chloroform); ν_{max}/cm^{-1} (thin film) 3076w, 3032w, 2944s, 2867s, 1760s (C=O), 1734s, 1630m, 1495w, 1464m, 1419w, 1388w, 1368w, 1262m, 1132s, 1071m, 1029m, 995w, 884s; δ_H (400 MHz, $CDCl_3$) 0.97–1.12 (14H, m, 2 × $CH(CH_3)_2$), 1.22 (3H, t, *J* 7.2, OCH_2CH_3), 1.75 (2H, dt, *J* 8.0 and 1.2, $SiCH_2$), 4.08–4.21 (2H, m, OCH_2CH_3), 4.85 (1H, ddt, *J* 10.4, 2.0 and 1.2, $CH=CH_EH$), 4.93 (1H, ddt, *J* 16.8, 2.0 and 1.2, $CH=CHH_Z$), 5.32 (1H, s, CHPh), 5.82 (1H, ddt, *J* 16.8, 10.4 and 8.0, $CH=CH_2$), 7.26–7.34 (3H, m, Ph), 7.47–7.49 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.5 (2 × $CH(CH_3)_2$), 14.0 (OCH_2CH_3), 17.3 and 17.4 (2 × $CH(CH_3)_2$), 18.9 ($SiCH_2$), 61.0 (OCH_2CH_3), 74.4 (CHPh), 114.1 ($CH=CH_2$), 126.3 (Ph), 128.0 (Ph), 128.2 (Ph), 134.0 ($CH=CH_2$), 139.3 (*i*-Ph), 172.0 (CO_2); *m/z* (GCMS CI$^+$) 335 (MH$^+$, 17%), 293 (M$^+$-C_3H_5, 100), 265 (13); Accurate mass (CI$^+$): Found 335.2036, $C_{19}H_{31}O_3Si$ (MH$^+$) requires 335.2042.

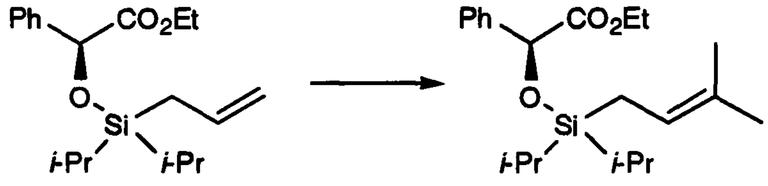
(*S*)-Ethyl [(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]phenylacetate



2.33

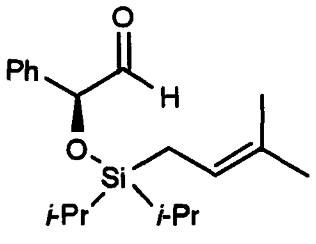
A flame-dried two-necked flask (50 mL) was charged with anhydrous $CuCl_2$ (729 mg, 5.42 mmol) and anhydrous CuI (51.6 mg, 0.27 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (11.0 mL) was added followed by prenyldi(*iso*-propyl)silane **2.19** (500 mg, 2.71 mmol) and the orange suspension stirred for 5 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane (**2.35**) in THF was added *via* cannula to a stirred solution of (*S*)-ethyl mandelate **2.28** (326 mg, 1.81 mmol), DMAP (11.0 mg, 0.09 mmol) and TEA (757 μL, 5.43 mmol) in anhydrous DMF (30.0 mL). The reaction mixture was warmed to 60 °C for 16 hr, then cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 50:1, petrol:diethyl ether) to furnish ester **2.33** as a colourless oil (532 mg, 81%). R_f 0.27 (29:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +20.5 (*c* 1.01, chloroform); ν_{max}(thin film)/cm^{-1} 3032w, 2943s, 2867s, 1757s (C=O), 1733s, 1495w, 1464m, 1454m, 1369w, 1262m, 1133s, 1071m, 1029m, 999w, 949w, 918w, 883m, 834m; δ_H (400 MHz, $CDCl_3$) 0.95–1.08 (14H, m, 2 × $\mathbf{CH(CH_3)_2}$), 1.22 (3H, t, *J* 7.2, $OCH_2\mathbf{CH_3}$), 1.56 and 1.63 (2 × 3H, 2 × s, $=C(\mathbf{CH_3})_2$), 1.59 (2H, ~d, *J* 8.2, $Si\mathbf{CH_2}$), 4.10–4.18 (2H, m, $O\mathbf{CH_2}CH_3$), 5.12 (1H, br t, *J* 8.2, $\mathbf{CH}=C(CH_3)_2$), 5.28 (1H, s, **CH**Ph), 7.27–7.36 (3H, m, Ph), 7.49–7.52 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.4 ($SiCH_2$), 12.5 (2 × $CH(CH_3)_2$), 14.1 (OCH_2CH_3), 16.9, 17.3 and 17.6 (2 × $CH(CH_3)_2$ and CH_3), 25.8 (CH_3), 61.0 (OCH_2CH_3), 74.4 (CHPh), 118.6 ($CH=C(CH_3)_2$), 126.3 (Ph), 126.4 (Ph), 128.2 (Ph), 129.7 ($=C(CH_3)_2$), 139.4 (*i*-Ph), 172.1 (CO_2); *m/z* (GCMS CI^+) 380 (MNH_4^+, 16%), 293 (M^+-C_5H_9, 100), 91 (27); Accurate mass (CI^+): Found 380.2624, $C_{21}H_{38}NO_3Si$ (MNH_4^+) requires 380.2621.

Alternative procedure from 2.29



A solution of allylsilane **2.29** (214 mg, 0.64 mmol) and Sudan Red 7B indicator (5.0 μL, 0.05% w/v in DCM) in anhydrous DCM (13.0 mL) was cooled to -78 °C. Ozone was passed through the solution until the magenta colouration dispersed; excess ozone was purged from the system with argon. Dimethyl sulfide (56.0 μL, 0.76 mmol) was added and the mixture stirred at -78 °C for 1 hr and then warmed to RT over 30 min. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (1.10 g, 2.54 mmol) in anhydrous THF (10.0 mL) cooled to -45 °C was added *n*-BuLi (2.5 M in hexanes, 916 μL, 2.29 mmol). The blood-red solution was stirred for 30 min at -45 °C then warmed to RT over 1 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 2.5 hr. The reaction mixture was partitioned between water (50 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (2 x 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (2 x 50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether and petrol (1:1, v/v); the combined extracts were filtered through Celite® and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 29:1, petrol:diethyl ether) to furnish ester **2.33** as a colourless oil (41.3 mg, 18%).

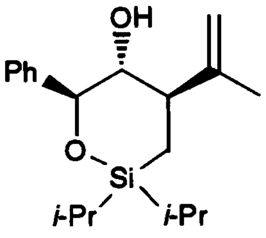
(*S*)-[(3-Methylbut-2-enyl)di(*iso*-propyl)silanyloxy]phenylacetaldehyde



2.36

To a stirred solution of ester **2.33** (300 mg, 0.83 mmol) in anhydrous DCM (8.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 1.24 mL, 1.24 mmol) dropwise and the solution stirred at -78 °C for 1 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (2 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (20% w/v, 25 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (2 × 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50:1, petrol: diethyl ether) to furnish aldehyde **2.36** as a colourless oil (244 mg, 92%). R_f 0.73 (3:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +4.91 (*c* 1.14, chloroform); ν_{max}(thin film)/cm^{-1} 2957m, 2944m, 2921m, 2892m, 2867s, 1735s (C=O), 1464w, 1452w, 1376w, 1262m, 1115m, 1072w, 882w, 841w, 746m, 698s; δ_H (400 MHz, $CDCl_3$) 0.96–1.14 (14H, m, 2 × C**H**(C**H**$_3$)$_2$), 1.56 and 1.63 (2 × 3H, 2 × br s, =C(C**H**$_3$)$_2$), 1.60 (2H, ~d, *J* 8.0, SiC**H**$_2$), 5.06 (1H, d, *J* 2.2, C**H**Ph), 5.12 (1H, tsept, *J* 8.0 and 1.2, C**H**=C(CH_3)$_2$), 7.30–7.44 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.6 ($SiCH_2$), 12.7 (2 × $CH(CH_3)_2$), 17.3 and 17.4 (2 × $CH(CH_3)_2$), 17.6 and 25.8 (=$C(CH_3)_2$), 80.0 (CHPh), 118.6 (CH=$C(CH_3)_2$), 126.4 (Ph), 128.3 (Ph), 128.7 (Ph), 130.1 (=$C(CH_3)_2$), 136.8 (*i*-Ph), 199.6 (CHO); *m/z* (GCMS CI$^+$) 319 (M$^+$, 100%), 249 (M$^+$-C_5H_9, 26), 206 (21); Accurate mass (CI$^+$): Found 319.2102, $C_{19}H_{31}O_2Si$ (MH$^+$) requires 319.2093.

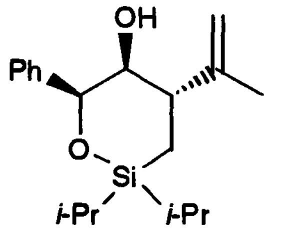
(3*S*,4*R*,5*R*)-1,1-Di(*iso*-propyl)-2-oxa-3-phenyl-5-(propen-2-yl)silinan-4-ol



2.37

To a stirred solution of aldehyde **2.36** (240 mg, 0.75 mmol) in anhydrous DCM (7.5 mL) at RT was added DMAC (1.0 M in hexanes, 750 µL, 0.75 mmol). After 30 min the reaction was quenched by the addition of saturated *aq.* Na_2SO_4 soln. (5 mL) and the mixture partitioned between water (20 mL) and diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (2 × 20 mL); the combined organic layers were washed with saturated *aq.* NaCl soln. (40 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting pale yellow oil was purified by flash column chromatography (silica gel, 35:1, petrol:diethyl ether) to furnish the major product **2.37** as a colourless oil (103 mg, 43%) and a minor product **2.38** as a colourless oil (21.6 mg, 9%). R_f 0.55 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −25.0 (*c* 1.38, chloroform); ν_{max}/cm^{-1} (thin film) 3479m (br, O-H), 3066w, 3032w, 2941s, 2892m, 2864m, 1643w, 1495w, 1462m, 1454m, 1409w, 1382w, 1245w, 1203w, 1178m, 1099m, 1082m, 1060s, 1038m, 1028m, 991m, 944w, 917w, 882s, 846s, 801w, 765s, 744m, 698s, 679m, 658m, 621m, 589s; δ_H (400 MHz, $CDCl_3$) 0.86 (1H, dd, *J* 14.6 and 4.0, SiCH**H**$_{eq}$), 1.00 (1H, dd, *J* 14.6 and 13.6, SiC**H**$_{ax}$H), 1.05–1.27 (14H, m, 2 × C**H**(C**H**$_3$)$_2$), 1.65 (1H, d, *J* 2.0, CH(O**H**)), 1.76 (3H, s, C(C**H**$_3$)=), 2.68 (1H, ddd, *J* 13.6, 10.2 and 4.0, SiCH$_2$C**H**), 3.28 (1H, ddd, *J* 10.2, 8.8 and 2.0, C**H**(OH)), 4.62 (1H, d, *J* 8.8, C**H**Ph), 4.87 and 4.91 (2 × 1H, 2 × br s, C(CH$_3$)=C**H**$_2$), 7.28–7.48 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 10.9 (SiCH$_2$), 12.0 and 12.9 (2 × **C**H(CH$_3$)$_2$), 17.2 and 17.3 (CH(**C**H$_3$)$_2$), 17.6 (C(**C**H$_3$)=), 17.7 and 17.8 (CH(**C**H$_3$)$_2$), 49.6 (SiCH$_2$**C**H), 74.5 (**C**H(OH)), 80.6 (**C**HPh), 112.4 (C(CH$_3$)=**C**H$_2$), 127.1 (Ph), 127.9 (Ph), 128.3 (Ph), 142.6 (*i*-Ph), 148.4 (**C**(CH$_3$)=); *m/z* (GCMS CI$^+$) 336 (MNH$_4^+$, 38%), 319 (MH$^+$, 52), 301 (100), 275 (24), 249 (57), 211 (39), 199 (49), 171 (70); Accurate mass (CI$^+$): Found 319.2095, $C_{19}H_{31}O_2Si$ (MH$^+$) requires 319.2093.

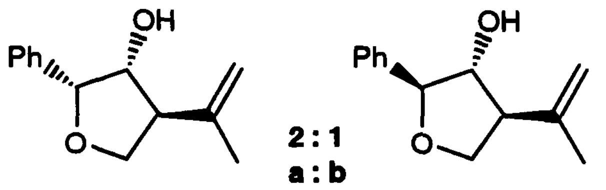
(3*S*,4*S*,5*S*)-1,1-Di(*iso*-propyl)-2-oxa-3-phenyl-5-(propen-2-yl)silinan-4-ol



2.38

R$_f$ 0.57 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −15.0 (*c* 0.40, chloroform); ν_{max}/cm^{-1} (thin film) 3460m (br, O-H), 3065w, 3029w, 2941s, 2865s, 1643w, 1494w, 1462m, 1452m, 1383w, 1246w, 1200w, 1176w, 1145w, 1088m, 1063m, 1028m, 931w, 882s, 847w, 819w, 743w, 701s; δ_H (400 MHz, CDCl$_3$) 0.90–1.20 (16H, m, SiC**H**$_2$ and 2 × C**H**(C**H**$_3$)$_2$), 1.56 (1H, d, *J* 5.6, CH(O**H**)), 1.86 (3H, s, C(C**H**$_3$)=), 2.72 (1H, dt, *J* 7.2 and 6.8, SiCH$_2$C**H**), 3.93 (1H, ddd, *J* 6.8, 5.6 and 2.8, C**H**(OH)), 4.87 and 4.90 (2 × 1H, 2 × br s, C(CH$_3$)=C**H**$_2$), 5.09 (1H, d, *J* 2.8, C**H**Ph), 7.25–7.45 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 6.81 (SiCH$_2$), 12.8 and 13.7 (2 × CH(CH$_3$)$_2$), 17.2, 17.3, 17.5 and 17.6 (2 × CH(CH$_3$)$_2$), 20.8 (C(CH$_3$)=), 45.4 (SiCH$_2$CH), 73.6 (CH(OH)), 74.6 (CHPh), 111.4 (C(CH$_3$)=CH$_2$), 126.3 (Ph), 127.3 (Ph), 128.2 (Ph), 140.8 (*i*-Ph), 147.8 (C(CH$_3$)=); *m/z* (GCMS CI$^+$) 336 (MNH$_4^+$, 13%), 319 (MH$^+$, 34), 301 (100), 275 (14), 249 (42), 211 (24), 199 (35), 171 (37); Accurate mass (CI$^+$): Found 336.2356, $C_{19}H_{34}NO_2Si$ (MNH$_4^+$) requires 336.2359.

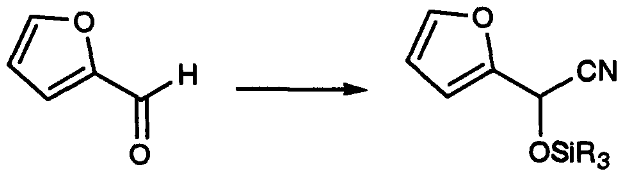
(2*R*,3*R*,4*S*)-2-Phenyl-4-(propen-2-yl)tetrahydrofuran-3-ol and (2*S*,3*R*,4*S*)-2-Phenyl-4-(propen-2-yl)tetrahydrofuran-3-ol



2.39

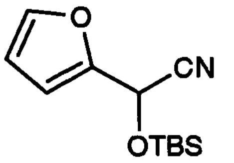
To a solution of oxasilinane **2.37** (98.0 mg, 0.31 mmol) in methanol (2.0 mL) and THF (2.0 mL) was added KF (54.0 mg, 0.93 mmol), $KHCO_3$ (62.1 mg, 0.62 mmol) and H_2O_2 (35% in water, 151 μL, 1.55 mmol) and the resulting mixture heated at reflux for 16 hr.[240] The reaction mixture was allowed to cool to RT, quenched by the addition of saturated *aq.* $NaHSO_4$ soln. (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated *aq.* NaCl soln. (40 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting material was purified by flash column chromatography (silica gel, diethyl ether) to furnish the inseparable diastereomeric tetrahydrofurans **2.39a** and **2.39b**, as a colourless oil (12.7 mg, 2:1, 19%), and recovered oxasilinane **2.37** (74.0 mg, 76%). R_f 0.40 (diethyl ether); ν_{max}/cm^{-1} (thin film) 3368s (br, O-H), 3066w, 3025w, 2921m, 1643w, 1453w, 1377w, 1195w, 1095w, 1019w, 897w, 759w, 701m; δ_H (500 MHz, $CDCl_3$) 1.72 (3H, br s, C(**CH**$_3$)=, diastereomer **A**), 1.82 (3H, br s, C(**CH**$_3$)=, diastereomer **B**), 2.16 (1H, td, *J* 7.5 and 4.5, OCH_2**CH**, **A**), 2.32 (1H, dt, *J* 5.5 and 5.5, OCH_2**CH**, **B**), 2.53 (2H, br s, 2 × **OH**, **A** and **B**), 3.68 (1H, dd, *J* 11.0 and 4.5, **OCHH**$_b$, **A**), 3.77 (2H, ~d, *J* 5.5, **OCH**$_2$, **B**), 3.85 (1H, dd, *J* 11.0 and 7.5, **OCH**$_a$H, **A**), 3.98 (1H, t, *J* 5.5, **CH**(OH), **B**), 4.20 (1H, dd, *J* 7.5 and 4.5, **CH**(OH), **A**), 4.77 (1H, d, *J* 5.5, **CH**Ph, **B**), 4.80 and 4.97 (2 × 1H, 2 × br s, $C(CH_3)=$**CH**$_2$, **A**), 4.81 (1H, d, *J* 4.5, **CH**Ph, **A**), 4.95 and 5.08 (2 × 1H, 2 × br s, $C(CH_3)=$**CH**$_2$, **B**), 7.30–7.42 (10H, m, 2 × Ph, **A** and **B**); δ_C (125.7 MHz, $CDCl_3$) 21.8 ($C(CH_3)=$, **A**), 21.9 ($C(CH_3)=$, **B**), 49.6 (OCH_2CH, **A**), 50.4 (OCH_2CH, **B**), 62.7 (OCH_2, **B**), 63.4 (OCH_2, **A**), 74.5 (CHPh, **B**), 75.2 (CHPh, **A**), 75.4 (CH(OH), **B**), 76.0 (CH(OH), **A**), 113.7 ($C(CH_3)=CH_2$, **A**), 115.6 ($C(CH_3)=CH_2$, **B**), 126.7 (Ph), 127.4 (Ph), 127.9 (Ph), 128.0 (Ph), 128.2 (Ph), 128.4 (Ph), 139.8 (*i*-Ph), 141.0 (*i*-Ph), 143.0 ($C(CH_3)=$, **B**), 143.5 ($C(CH_3)=$, **A**); *m/z* (CI^+) 222 (MNH_4^+, 29%), 205 (MH^+, 37), 187 (100), 175 (50), 169 (26), 157 (54), 137 (25), 132 (13), 115 (12), 105 (75), 91 (38), 85 (29), 78 (20), 69 (82), 58 (14); Accurate mass (CI^+): Found 222.1489, $C_{13}H_{20}NO_2$ (MNH_4^+) requires 222.1494.

General procedure for silylcyanohydrin synthesis



To a stirred suspension of 2-furaldehyde (166 μL, 2.00 mmol), KCN (521 mg, 8.00 mmol) and ZnI_2 (12.7 mg, 0.04 mmol) in anhydrous THF (10.0 mL) was added the chlorosilane (2.40 mmol). The reaction vessel was placed in an ultrasonic cleaning bath, sonicated for 20 min and then stirred at 25 °C for 3–4 days. THF was removed *in vacuo*, the crude residue triturated with diethyl ether and the ethereal extracts filtered through Celite®. The filtrate was washed successively with water (3 × 20 mL), saturated *aq.* NaCl soln. (50 mL), then dried (Na_2SO_4) and the solvents removed *in vacuo* to furnish a pale yellow oil. Purification by flash column chromatography (silica gel, 9:1, petrol:diethyl ether) gave the silylcyanohydrin as a colourless oil

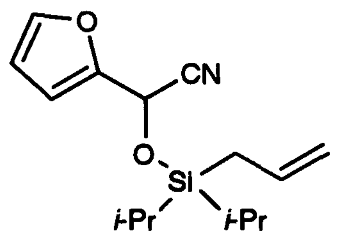
Furan-2-yl-[(*tert*-butyldimethyl)silanyloxy]acetonitrile[241]



2.40

2.40 colourless oil (436 mg, 92%). R_f 0.43 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3174w, 3126w, 2971s, 2932s, 2888m, 2860s, 2241w (C≡N), 1500w, 1473m, 1492m, 1391w, 1363w, 1306w, 1256s, 1190w, 1148s, 1089s, 1015m, 960w, 940w, 910w; δ_H (200 MHz, $CDCl_3$) 0.14 and 0.17 (2 × 3H, 2 × s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 5.56 (1H, s, CHCN), 6.39 (1H, dd, *J* 3.2 and 1.8, CH=), 6.53 (1H, dt, *J* 3.2 and 0.8, CH=), 7.44 (1H, dd, *J* 1.8 and 0.8, CH=); δ_C (50.3 MHz, $CDCl_3$) –5.30 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.4 ($SiC(CH_3)_3$), 58.0 (CHCN), 109.4 (CH=), 110.7 (CH=), 117.2 (C≡N), 143.8 (CH=), 148.5 (=C(O)CH); *m/z* (GCMS CI^+) 255 (MNH_4^+, 29%), 211 (100), 197 (24), 180 (74), 106 (18).

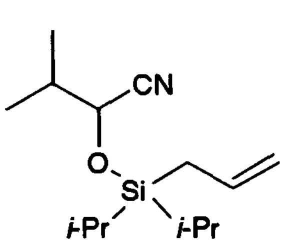
Furan-2-yl-[(prop-2-enyl)di(*iso*-propyl)silanyloxy]acetonitrile



2.41

2.41 colourless oil (434 mg, 78%). R_f 0.50 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3079w, 2947s, 2894m, 2869s, 2245w (C≡N), 1631m, 1500w, 1464m, 1420w, 1389w, 1304w, 1246w, 1152s, 1092s, 1015m, 960w, 905m, 884s, 829m, 808m, 746s; δ_H (400 MHz, $CDCl_3$) 1.00–1.15 (14H, m, 2 × $\mathbf{CH(CH_3)_2}$), 1.82 (2H, dt, *J* 8.0 and 1.2, $\mathbf{SiCH_2}$), 4.94 (1H, ddt, *J* 10.0, 2.0 and 1.2, $CH{=}\mathbf{CH_E}H$), 5.04 (1H, ddt, *J* 16.8, 2.0 and 1.2, $CH{=}CH\mathbf{H_Z}$), 5.68 (1H, s, **CH**CN), 5.87 (1H, ddt, *J* 16.8, 10.0 and 8.0, $\mathbf{CH}{=}CH_2$), 6.41 (1H, dd, *J* 3.6 and 1.8, **CH**=), 6.54 (1H, dd, *J* 3.6 and 0.4, **CH**=), 7.46 (1H, dd, *J* 1.8 and 0.4, **CH**=); δ_C (100.6 MHz, $CDCl_3$) 12.4 (2 × $CH(CH_3)_2$), 17.2 and 17.4 (2 × $CH(CH_3)_2$), 18.5 ($SiCH_2$), 58.1 (CHCN), 109.4 (CH=), 110.7 (CH=), 115.0 ($CH{=}CH_2$), 117.2 (C≡N), 133.2 ($CH{=}CH_2$), 143.7 (CH=), 148.5 (=C(O)CH); *m/z* (GCMS CI^+) 295 (MNH_4^+, 14%), 268 (16), 253 (75), 236 (M^+-C_3H_5, 100); Accurate mass: (ES^+) Found 295.1843, $C_{15}H_{27}N_2O_2Si$ (MNH_4^+) requires 295.1842.

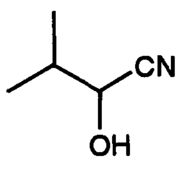
3-Methyl-2-[(prop-2-enyl)di(*iso*-propyl)silanyloxy]butyronitrile



2.42

To a stirred suspension of *iso*-butyraldehyde (400 µL, 4.40 mmol), KCN (1.15 g, 17.6 mmol) and ZnI_2 (28.7 mg, 0.09 mmol) in anhydrous THF (20.0 mL) was added chlorosilane **2.26** (1.01 g, 5.29 mmol). The reaction vessel was placed in an ultrasonic cleaning bath, sonicated for 1 hr and then stirred at 25 °C for 50 hr. THF was removed *in vacuo*, the crude residue triturated with diethyl ether and the ethereal extracts filtered through Celite®. The filtrate was washed successively with water (3 × 25 mL), saturated *aq.* NaCl soln. (50 mL), then dried (Na_2SO_4) and the solvents removed *in vacuo* to furnish a pale yellow oil. Purification by flash column chromatography (silica gel, 19:1, petrol:diethyl ether) gave silylcyanohydrin **2.42** as a colourless oil (945 mg, 85%). R_f 0.83 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3079w, 2964s, 2869s, 2238w (C≡N), 1631m, 1464m, 1390m, 1371w, 1249w, 1110s, 1066m, 994m, 883m, 826m, 804m, 752m; δ_H (400 MHz, $CDCl_3$) 1.00–1.20 (20H, m, 2 × SiC**H**(C**H**$_3$)$_2$ and CH(C**H**$_3$)$_2$), 1.80 (2H, dt, *J* 8.0 and 1.2, SiC**H**$_2$), 1.99 (1H, septd, *J* 6.8 and 5.2, C**H**(CH$_3$)$_2$), 4.40 (1H, d, *J* 5.2, C**H**CN), 4.92 (1H, ddt, *J* 10.0, 2.0 and 1.2, CH=C**H**$_E$H), 5.02 (1H, ddt, *J* 16.8, 2.0 and 1.2, CH=CH**H**$_Z$), 5.87 (1H, ddt, *J* 16.8, 10.0 and 8.0, C**H**=CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 12.4 (2 × SiCH(CH$_3$)$_2$), 16.9, 17.3 and 17.5 (2 × SiCH(CH$_3$)$_2$ and CH(CH$_3$)$_2$), 18.5 (SiCH$_2$), 34.1 (CH(CH$_3$)$_2$), 68.0 (CHCN), 114.7 (CH=CH$_2$), 119.0 (C≡N), 133.4 (CH=CH$_2$); *m/z* (GCMS CI$^+$) 271 (MNH_4^+, 20%), 254 (MH^+, 13), 229 (100), 212 (M^+-C_3H_5, 35), 202 (27), 185 (14); Accurate mass (ES$^+$): Found 271.2202, $C_{14}H_{31}N_2OSi$ (MNH_4^+) requires 271.2206.

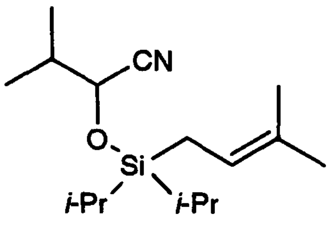
2-Hydroxy-3-methylbutyronitrile[242]



2.44

To a stirred solution of $NaHSO_3$ (25.1 g, 240 mmol) in water (80.0 mL) cooled to 0 °C was added *iso*-butyraldehyde (7.27 mL, 80.0 mmol). After 30 min a solution of KCN (20.8 g, 320 mmol) in water (400 mL) was added dropwise over 40 min; the resulting solution was stirred at RT for 5 hr. The reaction mixture was extracted with diethyl ether (3 × 150 mL) and the combined organic extracts washed with HCl (5.0 M, 250 mL), saturated *aq.* NaCl soln. (250 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by reduced pressure distillation (B.p. 81–83 °C at 5.0 Torr, [lit.,[243] 66–67 °C at 0.1 Torr]) to give cyanohydrin **2.44** as a pale yellow oil (7.41 g, 93%). R_f 0.28 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3435s (br, O-H), 2969s, 2937m, 2879m, 2248w (C≡N), 1639w, 1471m, 1391m, 1373m, 1348w, 1324w, 1255w, 1181w, 1135w, 1064s, 1017m, 973m, 954m, 880w, 826w, 796w; δ_H (400 MHz, $CDCl_3$) 1.06 and 1.09 (2 × 3H, 2 × d, *J* 6.8, $CH(CH_3)_2$), 2.04 (1H, septd, *J* 6.8 and 6.4, $CH(CH_3)_2$), 3.44 (1H, d, *J* 6.4, CH(OH)), 4.27 (1H, t, *J* 6.4, CHCN); δ_C (100.6 MHz, $CDCl_3$) 17.2 and 17.7 ($CH(CH_3)_2$), 33.0 ($CH(CH_3)_2$), 67.0 (CHCN), 119.3 (C≡N); *m/z* (GCMS CI^+) 117 (MNH_4^+, 100%), 90 (26), 72 (10); Accurate mass: (CI^+) Found 117.1028, $C_5H_{13}N_2O$ (MNH_4^+) requires 117.1028.

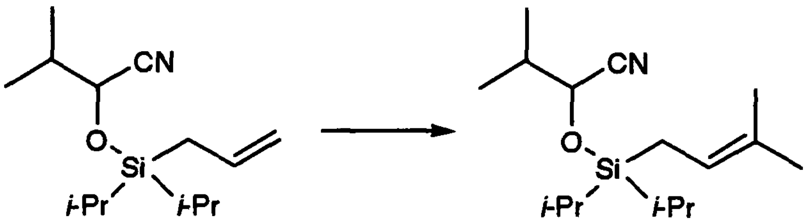
3-Methyl-2-[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]butyronitrile



2.43

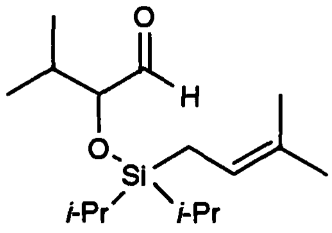
A flame-dried two-necked flask (50 mL) was charged with anhydrous $CuCl_2$ (1.46 g, 10.9 mmol) and anhydrous CuI (51.6 mg, 0.27 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (22.0 mL) was added followed by prenyldi(*iso*-propyl)silane **2.19** (1.00 g, 5.42 mmol) and the orange suspension stirred for 20 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane (**2.35**) in THF was added *via* cannula to a stirred solution of cyanohydrin **2.44** (267 mg, 2.70 mmol), DMAP (1.65 g, 13.5 mmol) and TEA (1.88 mL, 13.5 mmol) in anhydrous DCM (27.0 mL). The reaction was stirred at RT for 5 hr, then partitioned between saturated *aq*. $NaHCO_3$ soln. (100 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol → 100:1, petrol:diethyl ether) to furnish silylcyanohydrin **2.43** as a colourless oil (627 mg, 83%). R_f 0.80 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3052w, 2964s, 2893s, 2868s, 2240w (C≡N), 1464s, 1388m, 1372m, 1351w, 1247w, 1224w, 1185m, 1161m, 1110s, 1061s, 997m, 958w, 920w, 883s, 827s, 800m, 746m, 724m; δ_H (500 MHz, $CDCl_3$) 0.98–1.15 (20H, m, 2 × $SiCH(CH_3)_2$ and $CH(CH_3)_2$), 1.64 and 1.70 (2 × 3H, 2 × s, $=C(CH_3)_2$), 1.65 (2H, ~d, *J* 8.5, $SiCH_2$), 1.98 (1H, septd, *J* 6.5 and 5.0, $CH(CH_3)_2$), 4.35 (1H, d, *J* 5.0, CHCN), 5.19 (1H, br t, *J* 8.5, $CH=C(CH_3)_2$); δ_C (125.7 MHz, $CDCl_3$) 12.2 ($SiCH_2$), 12.4 (2 × $SiCH(CH_3)_2$), 16.8 and 25.7 ($=C(CH_3)_2$), 17.0, 17.2, 17.5 and 17.6 (2 × $SiCH(CH_3)_2$ and $CH(CH_3)_2$), 34.1 ($CH(CH_3)_2$), 67.9 (CHCN), 117.9 ($CH=(CH_3)_2$), 118.9 (C≡N), 130.3 ($=C(CH_3)_2$); *m/z* (GCMS CI^+) 299 (MNH_4^+, 100%), 282 (MH^+, 36), 255 (42), 229 (80), 212 (M^+-C_5H_9, 47), 185 (28), 147 (25), 130 (35); Accurate mass: (ES^+) Found 299.2518, $C_{16}H_{35}N_2OSi$ (MNH_4^+) requires 299.2519.

Alternative procedure from 2.42



A solution of silylcyanohydrin **2.42** (536 mg, 2.12 mmol) and Sudan Red 7B indicator (10.0 μL, 0.05% w/v in DCM) in anhydrous DCM (40.0 mL) was cooled to -78 °C. Ozone was passed through the solution until the magenta colouration dispersed; excess ozone was purged from the system with argon. Dimethyl sulfide (186 μL, 2.54 mmol) was added and the reaction mixture stirred at -78 °C for 30 min and then warmed to RT over 1 hr. Meanwhile, to a suspension of *iso*-propyltriphenylphosphonium iodide (1.83 g, 4.23 mmol) in anhydrous THF (16.0 mL) cooled to -45 °C was added *n*-BuLi (1.6 M in hexanes, 2.38 mL, 3.81 mmol). The blood-red solution was stirred for 30 min at -45 °C then warmed to RT over 1 hr. Both solutions were cooled to -45 °C and the ylide added *via* cannula to the solution of silylacetaldehyde. The solution was stirred at -45 °C for 30 min and then warmed to RT over 3 hr. The mixture was partitioned between water (100 mL) and DCM (50 mL). The aqueous phase was extracted with DCM (3 x 25 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (2 x 50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude residue was triturated with diethyl ether and petrol (1:1, v/v), the extracts filtered through Celite® and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, petrol) to furnish silylcyanohydrin **2.43** as a colourless oil (213 mg, 36%).

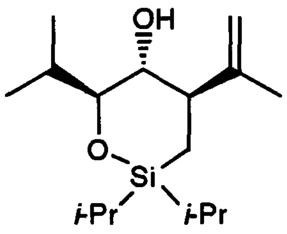
3-Methyl-2-[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]butyraldehyde



2.45

To a stirred solution of silylcyanohydrin **2.43** (68.6 mg, 0.24 mmol) in anhydrous heptane (2.0 mL) cooled to -78 °C was added DIBAL (1.0 M in heptane, 268 µL, 0.27 mmol) dropwise and the solution stirred at -78 °C for 45 min. The reaction mixture was diluted with ethyl acetate (1.2 mL) and quenched by the addition of *aq.* tartaric acid soln. (60% w/v, 600 µL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (25 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 49:1, petrol:diethyl ether) to furnish aldehyde **2.45** as a colourless oil (44.4 mg, 64%). R$_f$ 0.83 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 2965s, 2944s, 2893s, 2868s, 1736s (C=O), 1464m, 1387w, 1246w, 1162w, 1099m, 1066m, 996w, 883m, 837w, 814w, 789w, 746m, 722m; δ_H (500 MHz, $CDCl_3$) 0.96 and 1.00 (2 × 3H, 2 × d, *J* 7.0, $CH(CH_3)_2$), 1.03–1.07 (14H, m, 2 × Si**C**H(CH_3)$_2$), 1.57 (2H, br d, *J* 8.0, Si**CH**$_2$) 1.60 (3H, ~s) and 1.67 (3H, d, *J* 1.5, =C(**CH**$_3$)$_2$), 2.02 (1H, septd, *J* 7.0 and 5.0, **CH**(CH_3)$_2$), 3.83 (1H, dd, *J* 5.0 and 2.5, O**CH**), 5.15 (1H, tsept, *J* 8.0 and 1.5, **CH**=C(CH_3)$_2$), 9.60 (1H, d, *J* 2.5, **CHO**); δ_C (125.7 MHz, $CDCl_3$) 12.7 ($SiCH_2$), 12.8 (2 × $SiCH(CH_3)_2$), 16.8 and 18.1 ($CH(CH_3)_2$), 17.4 (2 × $SiCH(CH_3)_2$), 17.6 and 25.7 (=$C(CH_3)_2$), 32.4 ($CH(CH_3)_2$), 81.9 (OCH), 118.5 ($CH=(CH_3)_2$), 129.8 (=$C(CH_3)_2$), 205.1 (CHO); *m/z* (GCMS CI$^+$) 285 (MH$^+$, 27%), 241 (30), 229 (35), 215 (M$^+$-C_5H_9, 76), 203 (95), 148 (100), 137 (17); Accurate mass (ES$^+$): Found 285.2256, $C_{16}H_{33}O_2Si$ (MH$^+$) requires 285.2250.

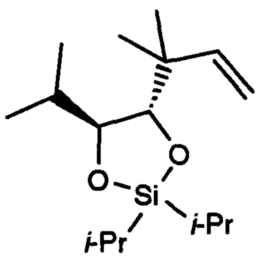
rel-(3*S*,4*R*,5*R*)-1,1,3-Tri(*iso*-propyl)-2-oxa-5-(propen-2-yl)silinan-4-ol



2.46

To a stirred solution of aldehyde **2.45** (41.2 mg, 0.15 mmol) in anhydrous DCM (1.5 mL) at RT was added DMAC (1.0 M in hexanes, 131 μL, 0.13 mmol). After 30 min the reaction was quenched by the addition of saturated *aq.* Na_2SO_4 soln. (2.5 mL) and the mixture partitioned between water (5 mL) and diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL); the combined organic layers were washed with saturated *aq.* NaCl soln. (2 × 10 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 18:1, petrol:diethyl ether) to furnish the ene product **2.46** as a colourless oil (15.4 mg, 37%) and the allyl transfer product **2.47** as a colourless oil (16 mg, 39%). R_f 0.41 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3554m (br, O-H), 2957s, 2866s, 1642w, 1464m, 1383w, 1246w, 1180w, 1152w, 1101w, 1044s, 882m, 841w, 794w, 747w; δ_H (400 MHz, $CDCl_3$) 0.72 (1 H, dd, *J* 14.8 and 4.4, $\mathrm{SiCH}\mathbf{H}_{\mathbf{eq}}$), 0.80 (1H, dd, *J* 14.8 and 13.2, $\mathrm{SiC}\mathbf{H}_{\mathbf{ax}}\mathrm{H}$), 0.88 and 0.99 (2 × 3H, 2 × d, *J* 6.8, $\mathrm{CH(}\mathbf{CH_3}\mathrm{)_2}$), 0.93–1.08 (14H, m, 2 × $\mathrm{SiC}\mathbf{H}\mathrm{(}\mathbf{CH_3}\mathrm{)_2}$), 1.61 (1H, d, *J* 1.6, $\mathrm{CH(O}\mathbf{H}\mathrm{))}$, 1.76 (3H, br s, $\mathrm{C(}\mathbf{CH_3}\mathrm{)=}$), 2.14 (1H, septd, *J* 6.8 and 1.6, $\mathbf{CH}\mathrm{(CH_3)_2}$), 2.43 (1H, ddd, *J* 13.2, 10.4 and 4.4, $\mathrm{SiCH_2}\mathbf{CH}$), 3.16 (1H, ddd, *J* 10.4, 8.8 and 1.6, $\mathbf{CH}\mathrm{(OH))}$, 3.48 (1H, dd, *J* 8.8 and 1.6, $\mathbf{CH}\mathrm{CH(CH_3)_2}$), 4.88 and 4.91 (2 × 1H, 2 × br s, $\mathrm{C(CH_3)=}\mathbf{CH_2}$); δ_C (100.6 MHz, $CDCl_3$) 10.6 ($SiCH_2$), 12.0 and 12.6 (2 × $SiCH(CH_3)_2$), 14.0 and 17.1 ($CH(CH_3)_2$), 17.2, 17.5, 17.6, 17.7 and 20.0 (2 × $SiCH(CH_3)_2$ and $C(CH_3)=$), 29.3 ($CH(CH_3)_2$), 50.6 ($SiCH_2CH$), 70.1 (CH(OH)), 81.1 ($CHCH(CH_3)_2$), 113.2 ($C(CH_3)=CH_2$), 148.3 ($C(CH_3)=$); *m/z* (GCMS CI$^+$) 302 (MNH_4^+, 4%), 285 (MH$^+$, 100), 267 (26), 241 (43), 215 (41), 213 (39), 203 (17), 173 (25), 169 (41), 148 (53), 137 (20), 121 (13), 104 (15), 81 (18); Accurate mass (ES$^+$): Found 285.2253, $C_{16}H_{33}O_2Si$ (MH$^+$) requires 285.2250.

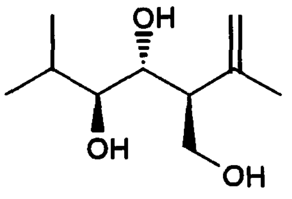
rel-(3*S*,4*S*)-3-(1,1-Dimethylprop-2-enyl)-2,5-dioxa-1,1,4-tri(*iso*-propyl)silolane



2.47

R_f 0.76 (9:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 2961s, 2869s, 1465m, 1385w, 1024s, 1006s, 916w, 884m, 844m; δ_H (400 MHz, $CDCl_3$) 0.91 and 1.01 (2 × 3H, 2 × d, *J* 6.8, $\mathrm{CH(}\mathbf{CH_3}\mathrm{)_2}$), 0.90–1.16 (18H, m, 2 × $\mathrm{SiCH(}\mathbf{CH_3}\mathrm{)_2}$ and $\mathrm{C(}\mathbf{CH_3}\mathrm{)_2}$), 1.53–1.65 (2H, m, 2 × $\mathrm{SiC}\mathbf{H}\mathrm{(CH_3)_2}$), 1.68 (1H, septd, *J* 6.8 and 3.2, $\mathbf{CH}\mathrm{(CH_3)_2}$), 3.56 (1H, d, *J* 7.2, $\mathbf{CH}\mathrm{(O)C(CH_3)_2}$), 3.63 (1H, dd, *J* 7.2 and 3.2, $\mathbf{CH}\mathrm{(O)CH(CH_3)_2}$), 5.00* (1H, dd, *J* 16.8 and 1.6, $\mathrm{CH=CH}\mathbf{H}_{\mathbf{Z}}$), 5.01* (1H, s, CH=CH$_E$H), 5.88* (1H, "dd", *J* 16.8 and 10.8, CH=CH$_2$);[244] δ_C (100.6 MHz, CDCl$_3$) 13.3 (2 × SiCH(CH$_3$)$_2$), 17.1, 18.2, 22.4 and 24.6 (2 × SiCH(CH$_3$)$_2$ and C(CH$_3$)$_2$), 15.6 and 20.9 (CH(CH$_3$)$_2$), 32.3 (CH(CH$_3$)$_2$), 40.9 (C(CH$_3$)$_2$), 80.5 (CH(O)CH(CH$_3$)$_2$), 83.5 (CH(O)C(CH$_3$)$_2$), 112.2 (CH=CH$_2$), 144.9 (CH=CH$_2$); *m/z* (GCMS CI$^+$) 285 (MH$^+$, 27%), 241 (31), 229 (33), 215 (84), 203 (100), 148 (92), 137 (16); Accurate mass (EI$^+$): Found 284.2176, $C_{16}H_{32}O_2Si$ (M$^+$) requires 284.2172.

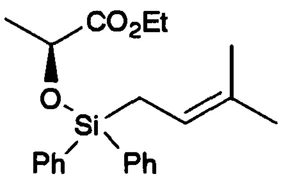
rel-(3*S*,4*R*,5*S*)-3-(Hydroxymethyl)-2,6-dimethylhept-1-en-4,5-diol[96]



2.48

To a stirred solution of TBHP (70% in water, 676 mg, 5.25 mmol) in DMF (2.0 mL) cooled to 0 °C was added CsOH.H$_2$O (705 mg, 4.20 mmol). The viscous suspension was allowed to warm to RT then a solution of oxasilinane **2.46** (100 mg, 0.35 mmol) in DMF (2.0 mL) was added dropwise over 10 min; TBAF (1.0 M in THF, 1.75 mL, 1.75 mmol) was added and the mixture warmed to 70 °C. After 2.5 hr the reaction mixture was cooled to RT, quenched by the addition of solid Na$_2$S$_2$O$_3$ (~ 500 mg) and the solvents removed *in vacuo*. The residue was partitioned between water (50 mL) and diethyl ether (25 mL); the aqueous phase was separated and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The resulting pale yellow oil was purified by flash column chromatography (silica gel, diethyl ether) to furnish triol **2.48** as colourless needles (14.5 mg, 22%). R$_f$ 0.26 (diethyl ether); M.p. 78–80 °C (from chloroform); ν_{max}/cm^{-1} (KBr disc) 3560s (br, O-H), 3082w, 3019w, 2962s, 2993s, 2874m, 1640w, 1466m, 1368w, 1342w, 1299w, 1216s, 1181w, 1088m, 1041m, 1001m, 988m, 940w, 896m, 757s, 669m; δ_H (400 MHz, D$_2$O) 0.69 and 0.80 (2 × 3H, 2 × d, *J* 7.0, $CH(CH_3)_2$), 1.65 (3H, s, $C(CH_3)=$), 1.85 (1H, septd, *J* 7.0 and 2.4, $CH(CH_3)_2$), 2.54 (1H, ddd, *J* 9.6, 6.2 and 3.6, $CHCH_2OH$), 3.26 (1H, dd, *J* 9.2 and 2.4, $CH(OH)CH(CH_3)_2$), 3.52 (1H, dd, *J* 9.2 and 3.6, $CH(OH)$), 3.60 (1H, dd, *J* 11.0 and 6.2, CH_aHOH), 3.66 (1H, dd, *J* 11.0 and 9.6, CHH_bOH), 4.74 and 4.91 (2 × 1H, 2 × br s, $C(CH_3)=CH_2$); δ_C (100.6 MHz, D_2O) 14.0 and 19.8 ($CH(CH_3)_2$), 21.8 ($C(CH_3)=$), 28.3 ($CH(CH_3)_2$), 50.4 ($CHCH_2OH$), 62.5 (CH_2OH), 71.2 ($CH(OH)$), 75.6 ($CH(OH)CH(CH_3)_2$), 115.5 ($C(CH_3)=CH_2$), 143.3 ($C(CH_3)=$); *m/z* (ES^-) 187 ($M-H^+$, 100%), 170 (M^+-H_2O, 21), 154 (17); Accurate mass (ES^-): Found 187.1330, $C_{10}H_{19}O_3$ ($M-H^+$) requires 187.1334.

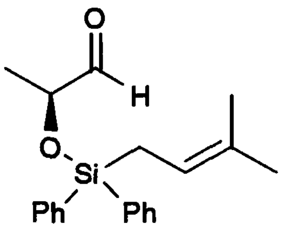
(*S*)-Ethyl 2-[(3-methylbut-2-enyl)diphenylsilanyloxy]propanoate[104]



2.50

To a stirred solution of silane **2.22** (794 mg, 3.15 mmol) and (*S*)-(–)-ethyl lactate (357 μL, 3.15 mmol) in anhydrous DCM (10.0 mL) was added tris(pentafluorophenyl)borane (80.6 mg, 0.16 mmol) and the reaction mixture heated at reflux for 16 hr. The solution was allowed to cool to RT and then partitioned between water (25 mL) and diethyl ether (25 mL), the aqueous layer was separated and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 10:1, petrol:diethyl ether) to furnish the product as a colourless oil (807 mg, 70%). R_f 0.64 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –36.1 (*c* 0.79, chloroform); ν_{max}/cm^{-1} (thin film) 3070m, 3050m, 2981m, 2912m, 1751s (C=O), 1590w, 1446m, 1429s, 1375m, 1272w, 1198m, 1118s, 1061m, 1023m, 976m, 817m, 735s, 701s; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.41 and 1.65 (2 × 3H, 2 × d, *J* 1.2, $=C(CH_3)_2$), 1.43 (3H, d, *J* 6.8, $OCHCH_3$), 2.12 (2H, br d, *J* 8.0, SiC**H**$_2$), 4.05–4.13 (2H, m, $CO_2C\mathbf{H}_2CH_3$), 4.38 (1H, q, *J* 6.8, OC**H**CH$_3$), 5.24 (1H, tsept, *J* 8.0 and 1.2, C**H**=C(CH$_3$)$_2$), 7.36–7.47 (6H, m, Ph), 7.62–7.71 (4H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 14.0 ($CO_2CH_2CH_3$), 16.2 (SiCH$_2$), 17.6 and 25.8 (=C(CH$_3$)$_2$), 21.2 (OCHCH$_3$), 60.7 ($CO_2CH_2CH_3$), 68.8 (OCHCH$_3$) 117.2 (CH=C(CH$_3$)$_2$), 127.7 (Ph), 129.9 (Ph), 131.3 (=C(CH$_3$)$_2$), 134.4 (*i*-Ph), 134.9 (Ph), 173.6 (CO$_2$); *m/z* (ES$^+$) 391 (MNa$^+$, 100%), 300 (MH$^+$-C$_5$H$_9$, 11); Accurate mass (ES$^+$): Found 386.2157, $C_{22}H_{32}NO_3Si$ (MNH$_4^+$) requires 386.2151.

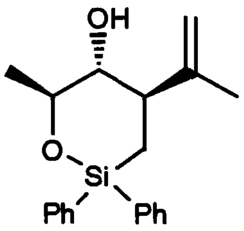
(*S*)-2-[(3-Methylbut-2-enyl)diphenylsilanyloxy]propionaldehyde



2.51

To a stirred solution of ester **2.50** (530 mg, 1.44 mmol) in anhydrous DCM (15.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 2.16 mL, 2.16 mmol) dropwise and the solution stirred at -78 °C for 45 min. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (2 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 20 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (2 x 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (40 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 30:1, petrol: diethyl ether) to furnish aldehyde **2.51** as a colourless oil (285 mg, 61%). R$_f$ 0.26 (10:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ −14.7 (*c* 1.10, chloroform); ν_{max}/cm^{-1} (thin film) 3070m, 3050m, 3024m, 2975m, 2913m, 2856m, 2803w, 1960w, 1889w, 1822w, 1739s (C=O), 1590w, 1429s, 1376m, 1160m, 1118s, 1011m, 998m, 967w, 859w, 816m, 734s, 701s; δ_H (400 MHz, CDCl$_3$) 1.29 (3H, d, *J* 6.8, OCHC**H**$_3$), 1.43 and 1.66 (2 x 3H, 2 x d, *J* 1.2, =C(C**H**$_3$)$_2$), 2.12 (2H, br d, *J* 8.0, $SiCH_2$), 4.19 (1H, qd, *J* 6.8 and 1.2, $OCHCH_3$), 5.23 (1H, tsept, *J* 8.0 and 1.2, $CH=C(CH_3)_2$), 7.38–7.48 (6H, m, Ph), 7.61–7.68 (4H, m, Ph), 9.46 (1H, d, *J* 1.2, CHO); δ_C (100.6 MHz, $CDCl_3$) 16.1 ($SiCH_2$), 17.6 and 25.7 ($=C(CH_3)_2$), 18.4 ($OCHCH_3$), 74.3 ($OCHCH_3$) 116.9 ($CH=C(CH_3)_2$), 127.9 (Ph), 130.2 (Ph), 131.7 ($=C(CH_3)_2$), 134.2 (*i*-Ph), 134.7 (Ph), 203.5 (CHO); *m/z* (GCMS CI^+) 342 (MNH_4^+, 39%), 325 (MH^+, 34), 255 (M^+-C_5H_9, 100), 243 (20), 216 (82), 78 (19); Accurate mass (CI^+): Found 342.1891, $C_{20}H_{28}NO_2Si$ (MNH_4^+) requires 342.1889.

(3*S*,4*R*,5*R*)-2-Oxa-1,1-diphenyl-3-methyl-5-(propen-2-yl)silinan-4-ol

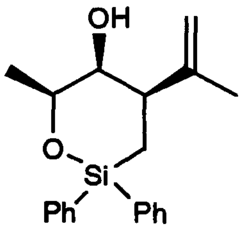


2.52

To a stirred solution of aldehyde **2.51** (228 mg, 0.70 mmol) in anhydrous DCM (7.0 mL) at RT was added DMAC (1.0 M in hexanes, 634 μL, 0.63 mmol). After 20 min the reaction was quenched by the addition of saturated *aq.* Na_2SO_4 soln. (5 mL) and the mixture partitioned between water (25 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL); the combined organic layers were washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 30:1, petrol:diethyl ether) to furnish the major product **2.52** as colourless needles (109 mg, 48%) and a minor product **2.53** as a colourless syrup (11.0 mg, 5%). R_f 0.38 (2:1, petrol:diethyl ether); M.p. 82–85 °C (from diethyl ether); $[\alpha]_D^{22}$ –25.0 (*c* 0.62, chloroform); ν_{max}/cm^{-1} (KBr disc) 3521m (O-H), 3071m, 2970m, 2878m, 1635w, 1590w, 1489w, 1430s, 1371m, 1334w, 1307w, 1264w, 1180w, 1157m, 1120s, 1072s, 1037m, 1018s, 997m, 978s, 941w, 910m, 892w, 824w, 804m, 772m, 743s, 712s, 701s; δ_H (400 MHz, $CDCl_3$) 1.32–1.36 (2H, m, $SiCH_2$), 1.47 (3H, d, *J* 6.0,

$CHCH_3$), 1.80 (3H, br s, $C(CH_3)$=), 2.51 (1H, td, *J* 10.0 and 6.8, $SiCH_2CH$), 3.25 (1H, dd, *J* 10.0 and 8.4, CH(OH)), 3.88 (1H, qd, *J* 8.4 and 6.0, $CHCH_3$), 4.88 and 4.94 (2 × 1H, 2 × br s, $C(CH_3)=CH_2$), 7.33–7.50 (6H, m, Ph), 7.54–7.57 (2H, m, Ph), 7.67–7.71 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.0 ($SiCH_2$), 17.7 ($C(CH_3)$=), 21.8 ($CHCH_3$), 49.8 ($SiCH_2CH$), 74.4 (CH(OH)), 74.5 ($CHCH_3$), 113.8 ($C(CH_3)=CH_2$), 127.9 (Ph), 128.2 (Ph), 130.1 (Ph), 130.3 (Ph), 133.9 (*i*-Ph), 134.3 (Ph), 134.8 (*i*-Ph), 147.5 ($C(CH_3)$=); *m/z* (GCMS CI^+) 342 (MNH_4^+, 16%), 325 (MH^+, 45), 307 (21), 281 (20), 255 (75), 247 (95), 233 (26), 216 (57), 203 (100), 181 (14), 156 (24), 138 (14), 109 (24); Accurate mass (CI^+): Found 342.1879, $C_{20}H_{28}NO_2Si$ (MNH_4^+) requires 342.1889.

(3*S*,4*S*,5*R*)-2-Oxa-1,1-diphenyl-3-methyl-5-(propen-2-yl)silinan-4-ol

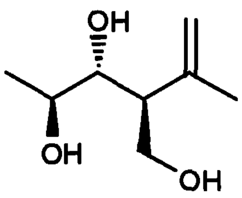


2.53

R_f 0.33 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –44.4 (*c* 0.50, chloroform); ν_{max}/cm^{-1} (thin film) 3455s (br, O-H), 3069m, 2973m, 2930m, 1643m, 1428s, 1375w, 1261w, 1118s, 1070m, 997m, 957m, 914w, 852w, 821w, 782m, 737s, 699s; δ_H (400 MHz, $CDCl_3$) 1.11 (1H, dd, *J* 14.4 and 3.2, $SiCHH_{eq}$), 1.43 (3H, d, *J* 6.8, $CHCH_3$), 1.49 (1H, t, *J* 14.4, $SiCH_{ax}H$), 1.70 (1H, br s, CH(OH)), 1.84 (3H, br s, $C(CH_3)$=), 2.46 (1H, br d, *J* 14.4, $SiCH_2CH$), 3.66 (1H, ~s, CH(OH)), 4.14 (1H, qd, *J* 6.8 and 1.2, $CHCH_3$), 4.96–4.99 (2H, m, $C(CH_3)=CH_2$), 7.33–7.49 (6H, m, Ph), 7.57–7.61 (2H, m, Ph), 7.68–7.71 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 8.2 ($SiCH_2$), 20.8 ($CHCH_3$), 22.0 ($C(CH_3)$=), 46.3 ($SiCH_2CH$), 71.9 (CH(OH)), 73.2 ($CHCH_3$), 111.1 ($C(CH_3)=CH_2$), 127.9 (Ph), 128.2 (Ph), 130.1 (Ph), 130.3 (Ph), 133.9 (*i*-Ph), 134.3 (Ph), 134.4 (*i*-Ph), 148.5 ($C(CH_3)$=); *m/z* (ES^+) 342 (MNH_4^+, 87%), 325 (MH^+, 20), 299 (85), 291

(44), 279 (50), 247 (61), 226 (19), 217 (65), 209 (88), 172 (100), 150 (71); Accurate mass (ES$^+$): Found 342.1878, $C_{20}H_{28}NO_2Si$ (MNH$_4^+$) requires 342.1889.

(2*S*,3*R*,4*S*)-4-(Hydroxymethyl)-5-methylhex-5-en-2,3-diol

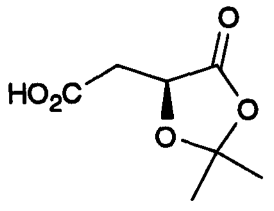


2.54

To a solution of oxasilinane **2.52** (88.1 mg, 0.27 mmol) in methanol (5.0 mL) and THF (5.0 mL) was added KF (47.3 mg, 0.81 mmol), $KHCO_3$ (54.4 mg, 0.54 mmol) and H_2O_2 (35% in water, 130 μL, 1.36 mmol). The mixture was stirred for 16 hr at RT, filtered through Celite® and the solvent removed *in vacuo*. The residue was triturated with diethyl ether, the extracts were filtered and the solvent removed *in vacuo*. The resulting material was purified by flash column chromatography (silica gel, 1:2, petrol:diethyl ether) to furnish triol **2.54** as a colourless syrup (38.3 mg, 88%). R_f 0.18 (ethyl acetate); $[\alpha]_D^{22}$ +1.67 (*c* 0.60, chloroform); ν_{max}/cm^{-1} (thin film) 3368s (br, O-H), 3078w, 2970m, 2929m, 1644m, 1450m, 1376m, 1282w, 1134w, 1073s, 1040s, 983m, 897m; δ_H (400 MHz, DMSO-d$_6$) 1.07 (3H, d, *J* 6.0, CH(OH)C**H**$_3$), 1.70 (3H, s, C(C**H**$_3$)=), 2.44 (1H, dt, *J* 7.2 and 4.4, C**H**CH$_2$OH), 3.35 (1H, ddd, *J* 7.2, 5.6 and 4.4, C**H**(OH)CH(OH)CH$_3$), 3.40–3.54 (3H, m, C**H**(OH)CH$_3$ and C**H**$_2$OH), 4.25 (1H, d, *J* 5.6, CH(O**H**)CH(OH)CH$_3$), 4.27 (1H, d, *J* 5.6, CH(O**H**)CH$_3$), 4.33 (1H, t, *J* 5.2, CH$_2$O**H**), 4.73 and 4.75 (2 × 1H, 2 × br s, C(CH$_3$)=C**H**$_2$); δ_C (100.6 MHz, DMSO-d$_6$) 20.9 (CH(OH)CH$_3$), 23.2 (C(CH$_3$)=), 51.1 (CHCH$_2$OH), 62.7 (CH$_2$OH), 68.0 (CH(OH)CH$_3$), 75.2 (CH(OH)CH(OH)CH$_3$), 113.7 (C(CH$_3$)=CH$_2$), 145.7 (C(CH$_3$)=); *m/z* (ES$^-$) 159 (M–H$^+$, 100%), 157 (10); Accurate mass (ES$^-$): Found 159.1029, $C_8H_{15}O_3$ (M–H$^+$) requires 159.1021.

Chapter 3 Compounds

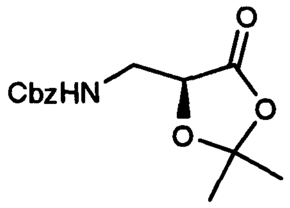
(+)-(*S*)-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid



3.03

To a stirred suspension of L-(*S*)-malic acid (40.1 g, 0.30 mol) in 2,2-dimethoxypropane (150 mL) was added CSA (1.40 g, 6.03 mmol) and the reaction mixture was stirred at RT for 5.5 hr. The reaction was quenched by the addition of dilute *aq.* $NaHCO_3$ soln. (0.5% w/v, 200 mL); diluted with DCM (200 mL) and the aqueous phase acidified to pH 2–3 with HCl (1.0 M). The aqueous layer was separated, re-acidified and extracted with DCM (3 × 100 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (250 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was recrystallised from chloroform/petrol to furnish acetonide **3.03** as colourless needles (33.7 g, 65%). R_f 0.47 (ethyl acetate); M.p. 105–107 °C (from chloroform) [lit.,[245] 105–107 °C]; $[\alpha]_D^{20}$ +5.70 (*c* 1.07, chloroform) [lit.,[246] $[\alpha]_D^{22}$ +6.90 (*c* 0.94, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3269m (O-H), 2987w, 2943w, 2900w, 1764s (C=O), 1736s (C=O), 1386w, 1343w, 1281w, 1220w, 1169w, 1129m, 926w, 805w; δ_H (200 MHz, $CDCl_3$) 1.57 and 1.63 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.86 (1H, dd, *J* 17.3 and 6.4, CH_aHCO_2H), 3.01 (1H, dd, *J* 17.3 and 4.0, CHH_bCO_2H), 4.72 (1H, dd, *J* 6.4 and 4.0, $CH(OR)CO_2R'$), 9.98 (1H, br s, CO_2H); δ_C (50.3 MHz, $CDCl_3$) 25.8 and 26.7 ($C(CH_3)_2$), 36.0 (CH_2CO_2H), 70.4 ($CH(OR)CO_2R'$), 111.4 ($C(CH_3)_2$), 171.9 (CO_2H), 175.1 ($CH(OR)CO_2R'$); *m/z* ($APCI^+$) 175 (MH^+, 3%), 131 (28), 122 (100), 102 (24). Found: C 47.81, H 5.78, $C_7H_{10}O_5$ requires: C 48.28, H 5.79.

(–)-(*S*)-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-ylmethyl)carbamic acid benzyl ester

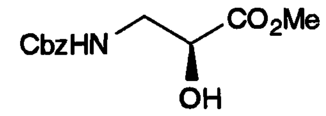


3.04

To a stirred suspension of acetonide **3.03** (11.0 g, 63.2 mmol) in anhydrous toluene (168 mL) was added DPPA (15.0 mL, 69.5 mmol) followed by TEA (9.70 mL, 69.5 mmol) dropwise over ~5 min. The solution was stirred at RT for 15 min, after which time the mixture became homogeneous, then benzyl alcohol (6.54 mL, 63.3 mmol) was added and the reaction warmed to 70 °C and stirred for 16 hr.[247] The reaction mixture was cooled to RT and quenched by the addition of saturated *aq.* $NaHCO_3$ soln. (200 mL). The resulting solution was partitioned between water (200 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 100 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (250 mL), dried ($MgSO_4$) and the solvents removed *in vacuo* to afford a brown syrup. The crude product was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish carbamate **3.04** as a viscous pale yellow oil (14.1 g, 80%). R_f 0.45 (diethyl ether); $[\alpha]_D^{20}$ –1.69 (*c* 1.01, chloroform); ν_{max}/cm^{-1} (thin film) 3350m (br, N-H), 3066w, 3035w, 2994s, 2942s, 1792s (C=O), 1716s (C=O), 1530m, 1456w, 1388m, 1331w, 1239s, 1136s, 994w, 902w, 841w, 775w, 739w, 698w; δ_H (400 MHz, $CDCl_3$) 1.53 and 1.55 (2 × 3H, 2 × s, C(C**H**$_3$)$_2$), 3.57 (1H, ddd, *J* 14.4, 6.2 and 5.2, NHC**H$_a$**H), 3.63–3.73 (1H, m, NHCH**H$_b$**), 4.48 (1H, ~t, *J* 5.2, C**H**(OR)CO$_2$R'), 5.07 and 5.14 (2 × 1H, 2 × d, *J* 12.2, C**H**$_2$Ph), 5.21–5.27 (1H, m, N**H**), 7.27–7.35 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 25.8 and 26.9 (C(CH$_3$)$_2$), 41.4 (NHCH$_2$), 67.0 (CH$_2$Ph), 73.4 (CH(OR)CO$_2$R'), 111.3 (C(CH$_3$)$_2$), 128.2 (Ph), 128.4 (Ph), 128.5 (Ph), 136.2 (*i*-Ph), 156.3 (C=O, Cbz), 171.5 (CH(OR)CO$_2$R'); *m/z* (APCI$^+$) 280 (MH$^+$, 29%), 236 (91), 222 (12), 196 (11), 143 (100); Accurate mass (ES$^+$):

Found 280.1189, $C_{14}H_{18}NO_5$ (MH^+) requires 280.1185; Found: C 60.04, H 6.22, $C_{14}H_{17}NO_5$ requires: C 60.21, H 6.14.

(+)-(*S*)-Methyl *N*-(benzyloxycarbonyl)isoserinate

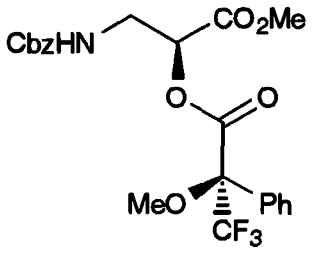


3.05

To a stirred solution of carbamate **3.04** (11.8 g, 42.4 mmol) in anhydrous methanol (42.0 mL) was added CSA (197 mg, 0.85 mmol) and the reaction mixture stirred at RT until no starting material remained by tlc (~6 hr). Methanol was removed *in vacuo* and the residual oil dissolved in diethyl ether (200 mL), washed with saturated *aq.* $NaHCO_3$ soln. (200 mL) and the aqueous phase back-extracted with diethyl ether (2 × 50 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a pale yellow syrup. Purification by flash column chromatography (silica gel, 1:4, petrol:diethyl ether) afforded the protected isoserine **3.05** as a colourless syrup which solidified upon standing (9.09 g, 85%). R_f 0.30 (diethyl ether); M.p. 39–41 °C (from toluene/petrol) [lit.,[248] 43 °C]; $[\alpha]_D^{20}$ +17.8 (*c* 1.01, chloroform) [lit.,[248] $[\alpha]_D^{20}$ +18.8 (*c* 1.42, methanol)]; ν_{max}/cm^{-1} (KBr disc) 3355s (br, N-H, O-H), 3037w, 2955w, 1750s (C=O), 1722s (C=O), 1686s, 1539s, 1498w, 1456m, 1440m, 1400w, 1373w, 1338w, 1305m, 1277s, 1225m, 1205m, 1157w, 1127m, 1107m, 1067w, 973w, 755m, 699m; δ_H (400 MHz, $CDCl_3$) 3.50–3.61 (2H, m, NHC**H**$_2$), 3.65 (1H, d, *J* 5.2, CH(O**H**)), 3.75 (3H, s, CO_2C**H**$_3$), 4.19–4.30 (1H, m, C**H**(OH)), 5.08 (2H, s, C**H**$_2$Ph), 5.43 (1H, br t, *J* 5.2, N**H**), 7.28–7.37 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 44.2 (NHCH$_2$), 52.8 (CO_2CH_3), 66.9 (CH$_2$Ph), 70.1 (CH(OH)), 128.1 (Ph), 128.3 (Ph), 128.5 (Ph), 136.3 (*i*-Ph), 156.7 (C=O, Cbz), 173.4 (CO_2CH_3); *m/z* (APCI$^+$) 254 (MH^+, 15%), 210 (100), 146 (11), 120 (59); Accurate mass (ES$^+$): Found 254.1024,

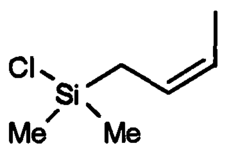
$C_{12}H_{16}NO_5$ (MH^+) requires 254.1028; Found: C 56.90, H 6.05, $C_{12}H_{15}NO_5$ requires: C 56.91, H 5.97.

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(*R*)-methoxy(trifluoromethyl)phenylacetoxy]-isoserinate



To a stirred solution of isoserinate **3.05** (25.0 mg, 0.10 mmol), DCC (41.0 mg, 0.20 mmol) and DMAP (6.1 mg, 0.05 mmol) in anhydrous DCM (2.0 mL) was added Mosher's acid (47.0 mg, 0.20 mmol) and the reaction mixture stirred at RT until a white precipitate of DCU formed (~10–15 min). The mixture was filtered and washed with diethyl ether (2 x 5 mL); the filtrate was washed successively with dilute HCl (1.0 M, 5 mL), saturated *aq.* $NaHCO_3$ soln. (5 mL) and saturated *aq.* NaCl soln. (5 mL). The organic fraction was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the derivatised ester. Derivatisation with (±)-methoxy(trifluoromethyl)phenylacetic acid gave the diastereomeric esters; δ_F (376.5 MHz, $CDCl_3$) −71.61 and −71.93; derivatisation with (*R*)-methoxy(trifluoromethyl)phenylacetic acid gave a single ester; δ_F (376.5 MHz, $CDCl_3$) −71.93; *m/z* (GCMS CI^+) 487 (MNH_4^+, 21%), 470 (MH^+, 12), 426 (18), 376 (100), 336 (11), 318 (11), 224 (17), 189 (31); Accurate mass (CI^+): Found 487.1696, $C_{22}H_{26}N_2O_7F_3$ (MNH_4^+) requires 487.1692. Enantiomeric excess was determined as being >99%.

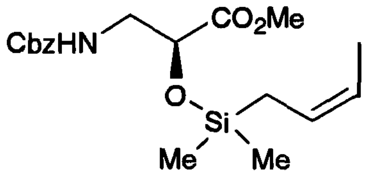
Chlorodimethyl(*Z*-but-2-enyl)silane



3.06

1,3-Butadiene (1.51 g, 27.9 mmol) was condensed into a sealed tube cooled to -45 °C; dimethylchlorosilane (2.20 mL, 19.8 mmol) and Ni(acac)$_2$ (216 mg, 0.84 mmol) were added and the mixture heated at 100 °C for 3.5 hr. The crude product was distilled under reduced pressure into a flask cooled to -78 °C, to furnish chlorosilane **3.06** as a colourless oil (2.63 g, 89%). R$_f$ 0.23 (2:1, petrol:diethyl ether); B.p. 42–44 °C at 15 Torr, [lit.,[249] 43 °C at 15 Torr]; ν_{max}/cm^{-1} (thin film) 3020s, 2964s, 2921s, 1649m, 1397m, 1363m, 1259s, 1156m, 1068s, 991m, 911m; δ_H (400 MHz, CDCl$_3$) 0.41 (6H, s, Si(C**H**$_3$)$_2$), 1.61 (3H, dd, *J* 6.0 and 1.2, =CHC**H**$_3$), 1.82 (2H, d, *J* 8.4, SiC**H**$_2$), 5.41–5.50 (2H, m, C**H**=C**H**CH$_3$); δ_C (100.6 MHz, CDCl$_3$) 1.01 and 1.30 (Si(CH$_3$)$_2$), 12.7 (=CHCH$_3$), 20.1 (SiCH$_2$), 123.2 (=CHCH$_3$), 124.0 (CH=CHCH$_3$); *m/z* (GCMS EI$^+$) 150 (M^{37}Cl$^+$, 15%), 148 (M^{35}Cl$^+$, 100), 133 (11), 76 (12).

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(*Z*-but-2-enyl)dimethylsilanyloxy]isoserinate

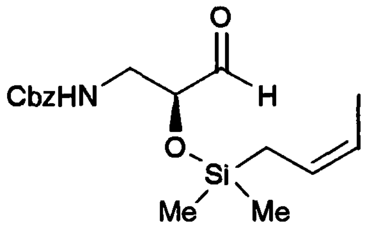


3.07

To a stirred solution of methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (431 mg, 1.70 mmol), DMAP (11.0 mg, 0.09 mmol) and TEA (284 μL, 2.04 mmol) in anhydrous DMF (25.0 mL) cooled to 0 °C was added chlorosilane **3.06** (303 mg, 2.04 mmol) dropwise. The solution was stirred at RT for 30 min and then warmed to 40 °C for 4 hr. The reaction mixture was cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (50 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish ester **3.07** as a colourless syrup (482 mg, 78%). R$_f$ 0.52 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −14.1 (*c* 1.03, chloroform); ν_{max}/cm^{-1} (thin film)

3360s (br, N-H), 3066w, 3016m, 2955s, 1728s (C=O), 1648w, 1517m, 1455m, 1439m, 1397w, 1363w, 1253s, 1142s, 991m, 905w, 841m, 735w, 697w, 677w; δ_H (400 MHz, $CDCl_3$) 0.09 and 0.15 (2 × 3H, 2 × s, **$Si(CH_3)_2$**), 1.57 (3H, d, *J* 4.8, =CH**CH_3**), 1.62 (2H, dd, *J* 6.6 and 3.8, Si**CH_2**), 3.43 (1H, ~dt, *J* 13.6 and 6.0, NHC**H_a**H), 3.56 (1H, ddd, *J* 13.6, 6.0 and 4.8, NHCH**H_b**), 3.72 (3H, s, CO_2**CH_3**), 4.34 (1H, dd, *J* 6.0 and 4.8, OC**H**), 5.08 and 5.12 (2 × 1H, 2 × d, *J* 12.6, **CH_2**Ph), 5.17 (1H, br t, *J* 6.0, N**H**), 5.36–5.44 (2H, m, C**H**=C**H**CH_3), 7.30–7.36 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) -2.24 and -1.92 ($Si(CH_3)_2$), 12.7 (=$CHCH_3$), 17.9 ($SiCH_2$), 44.7 ($NHCH_2$), 52.2 (CO_2CH_3), 66.8 (CH_2Ph), 70.7 (OCH), 122.8 (=$CHCH_3$), 124.4 (CH=$CHCH_3$), 128.1 (Ph), 128.3 (Ph), 128.5 (Ph), 136.4 (*i*-Ph), 156.2 (C=O, Cbz), 171.9 (CO_2CH_3); *m/z* (ES^+) 404 (MK^+, 4%), 388 (MNa^+, 50), 383 (MNH_4^+, 15), 366 (MH^+, 3), 310 (M^+-C_4H_7, 100), 278 (10); Accurate mass (ES^+): Found 383.1994, $C_{18}H_{31}N_2O_5Si$ (MNH_4^+) requires 383.2002.

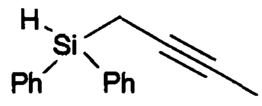
(*S*)-*N*-(Benzyloxycarbonyl)[(*Z*-but-2-enyl)dimethylsilanyloxy]isoserinal



3.08

To a stirred solution of silyl isoserinate **3.07** (572 mg, 1.56 mmol) in anhydrous DCM (31.0 mL) cooled to -78 °C was added DIBAL (1.0 M in heptane, 2.34 mL, 2.34 mmol) dropwise and the solution stirred at -78 °C for 2 hr. The reaction was quenched by the addition of *aq.* tartaric acid soln. (60% w/v, 5 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 20 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (2 × 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 2:1, petrol:diethyl ether) to furnish aldehyde **3.08** as a colourless oil (377 mg, 72%). R_f 0.64 (diethyl ether, [streaks]); $[\alpha]_D^{22}$ –11.4 (*c* 1.02, chloroform); ν_{max}/cm^{-1} (thin film) 3351m (br, N-H), 3132w, 3066w, 3015m, 2958m, 1710s (C=O), 1648w, 1521s, 1455m, 1397w, 1363w, 1331w, 1255s, 1150s, 1017m, 990m, 906w, 841s, 809m, 776w, 754m, 735w, 697m, 680w; δ_H (500 MHz, $CDCl_3$) 0.16 and 0.18 (2 × 3H, 2 × s, $Si(CH_3)_2$), 1.57 (3H, d, *J* 5.2, $=CHCH_3$), 1.63 (2H, d, *J* 6.5, $SiCH_2$), 3.47–3.51 (2H, m, $NHCH_2$), 4.18 (1H, t, *J* 5.2, OCH), 5.08 and 5.13 (2 × 1H, 2 × d, *J* 12.0, CH_2Ph), 5.09 (1H, br s, NH), 5.39–3.46 (2H, m, $CH=CHCH_3$), 7.31–7.39 (5H, m, Ph), 9.63 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) –2.02 and –1.87 ($Si(CH_3)_2$), 12.6 ($=CHCH_3$), 17.8 ($SiCH_2$), 42.5 ($NHCH_2$), 66.9 (CH_2Ph), 76.2 (OCH), 123.0 ($=CHCH_3$), 124.1 ($CH=CHCH_3$), 128.0 (Ph), 128.1 (Ph), 128.4 (Ph), 136.1 (*i*-Ph), 156.1 (C=O, Cbz), 201.5 (CHO); *m/z* ($APCI^+$) 336 (MH^+, 20%), 292 (31), 236 (57), 219 (15), 161 (22), 129 (100), 120 (90), 116 (10); Accurate mass (ES^+): Found 336.1623, $C_{17}H_{26}NO_4Si$ (MH^+) requires 336.1631.

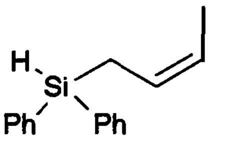
(But-2-ynyl)diphenylsilane[80,114]



3.11

To a stirred solution of 2-butyne (1.57 mL, 20.0 mmol) and TMEDA (3.02 mL, 20.0 mmol) in anhydrous THF (20.0 mL) cooled to -78 °C was added *t*-BuLi (1.7 M in pentane, 12.4 mL, 21.0 mmol) dropwise and the solution stirred for 30 min at -78 °C and then warmed to RT over 30 min. The reaction mixture was re-cooled to -78 °C and diphenylchlorosilane (3.90 mL, 20.0 mmol) was added. The resulting solution was stirred for 30 min at -78 °C, RT for 1 hr and then partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol) to give silane **3.11** as a colourless oil (4.52 g, 96%). R_f 0.18 (pentane); ν_{max}/cm^{-1} (thin film) 3069m, 3049m, 3011m, 2916m, 2880w, 2854w, 2134s (Si-H), 1957w, 1915w, 1820w, 1588w, 1567w, 1486w, 1428s, 1395w, 1331w, 1303w, 1263w, 1179m, 1117s, 1066w, 1028w, 998w, 807s, 733s, 697s, 674s; δ_H (400 MHz, $CDCl_3$) 1.83 (3H, t, *J* 2.8, ≡C**CH$_3$**), 2.15 (2H, dq, *J* 3.2 and 2.8, Si**CH$_2$**), 5.08 (1H, t, *J* 3.2, Si**H**), 7.39–7.55 (6H, m, Ph), 7.72–7.74 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 3.00 ($SiCH_2$), 3.62 (≡CCH_3), 74.9 (C≡C), 75.7 (**C**≡C), 127.8 (Ph), 129.9 (Ph) 133.0 (*i*-Ph), 135.2 (Ph); *m/z* (GCMS EI$^+$) 236 (M$^+$, 18%), 221 (23), 183 (M$^+$-C_4H_5, 100), 158 (15), 105 (60), 53 (21); Accurate mass (EI$^+$): Found 236.1022, $C_{16}H_{16}Si$ (M$^+$) requires 236.1021; Found C 81.35, H 6.99, $C_{16}H_{16}Si$ requires C 81.30, H 6.82.

(*Z*-But-2-enyl)diphenylsilane[80,114]

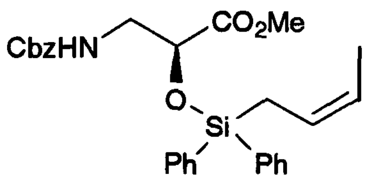


3.12

To a stirred solution of silane **3.11** (4.50 g, 19.0 mmol) was added DIBAL (1.0 M in heptane, 38.0 mL, 38.0 mmol) and the solution heated at reflux for 5 hr. The reaction was cooled to RT and poured into a mixture of dilute HCl (1.0 M, 50 mL), ice (100 mL) and diethyl ether (100 mL) and stirred for 15 min. The layers were separated and the aqueous phase extracted with diethyl ether (2 × 100 mL); the combined organic fractions were washed with dilute HCl (1.0 M, 2 × 100 mL), saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol) to give *Z*-crotylsilane **3.12** as a colourless oil (2.96 g, 65%). R_f 0.36 (petrol); ν_{max}/cm^{-1} (thin film) 3087m, 3069s, 3050m, 3017s, 2962m, 2926m, 2858m, 2125s (Si-H), 1956w, 1883w, 1818w, 1766w, 1649m, 1589m, 1486m, 1428s, 1396m, 1362m, 1330w, 1302w, 1262w, 1152m, 1118s, 1066w, 1028w, 990m, 908s, 808s, 732s, 698s, 647m; δ_H (400 MHz, $CDCl_3$)

1.57 (3H, d, *J* 6.0, =CHC**H**$_3$), 2.16 (2H, dd, *J* 8.0 and 3.6, SiC**H**$_2$), 4.95 (1H, t, *J* 3.6, Si**H**), 5.45–5.65 (2H, m, C**H**=C**H**CH$_3$), 7.41–7.50 (6H, m, Ph), 7.64–7.68 (4H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 12.7 (=CHCH$_3$), 13.6 (SiCH$_2$), 123.4 (CH=CHCH$_3$), 124.8 (CH=CHCH$_3$), 128.0 (Ph), 129.7 (Ph), 134.1 (*i*-Ph), 135.2 (Ph); *m/z* (GCMS CI$^+$) 256 (MNH$_4^+$, 44%), 239 (MH$^+$, 16), 200 (100), 183 (M$^+$-C$_4$H$_7$, 96), 122 (14), 105 (36); Accurate mass (CI$^+$): Found 256.1520, C$_{16}$H$_{22}$NSi (MNH$_4^+$) requires 256.1522.

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(*Z*-but-2-enyl)diphenylsilanyloxy]isoserinate

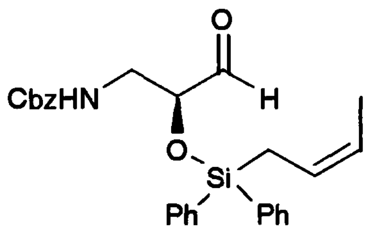


3.10

To a stirred solution of *Z*-crotyl(diphenyl)silane **3.12** (1.05 g, 4.40 mmol) and methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (1.11 g, 4.38 mmol) in anhydrous DCM (4.5 mL), was added tris(pentafluorophenyl)borane (112 mg, 0.22 mmol) and the reaction mixture heated at reflux for 16 hr. The solution was allowed to cool to RT and then partitioned between water (50 mL) and diethyl ether (50 mL); the aqueous layer was separated and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish the product as a colourless syrup (1.65 g, 77%). R$_f$ 0.35 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −13.6 (*c* 1.07, chloroform); ν_{max}/cm^{-1} (thin film) 3427m (br, N-H), 3070m, 3049m, 3017m, 2952m, 1725s (C=O), 1650w, 1590w, 1515s, 1455m, 1429s, 1396w, 1364w, 1332w, 1215s, 1119s, 991m, 910w, 781m, 737s, 700s, 648m; δ_H (400 MHz, CDCl$_3$) 1.45 (3H, d, *J* 5.6, =CHC**H**$_3$), 2.20 (2H, d, *J* 7.6, SiC**H**$_2$), 3.56 (2H, ~t, *J* 5.6, NHC**H**$_2$), 3.58 (3H, s, CO$_2$C**H**$_3$), 4.39 (1H, t, *J* 5.6, OC**H**), 5.08 and 5.11 (2 × 1H, 2 × d, *J* 13.0, C**H**$_2$Ph), 5.15 (1H, br t, *J* 5.6, N**H**), 5.37–

5.53 (2H, m, CH=CHCH$_3$), 7.30–7.46 (10H, m, Ph), 7.55–7.63 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 12.6 (=CHCH$_3$), 15.3 (SiCH$_2$), 44.8 (NHCH$_2$), 52.0 (CO$_2$CH$_3$), 66.9 (CH$_2$Ph), 71.5 (OCH), 123.4 (=CHCH$_3$), 124.1 (CH=CHCH$_3$), 127.9 (Ph), 128.1 (Ph), 128.5 (Ph), 129.5 (Ph), 130.2 (Ph), 133.5 (*i*-Ph), 134.8 (Ph), 136.4 (*i*-Ph, Cbz), 156.2 (C=O, Cbz), 171.5 (CO$_2$CH$_3$); *m/z* (ES$^+$) 512 (MNa$^+$, 100%), 507 (MNH$_4$$^+$, 27); Accurate mass (ES$^+$): Found 507.2322, $C_{28}H_{35}N_2O_5Si$ (MNH$_4$$^+$) requires 507.2315.

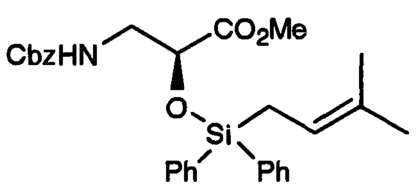
(*S*)-*N*-(Benzyloxycarbonyl)[(*Z*-but-2-enyl)diphenylsilanyloxy]isoserinal



3.13

To a stirred solution of silyl isoserinate **3.10** (1.01 g, 2.06 mmol) in anhydrous DCM (20.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 3.10 mL, 3.10 mmol) dropwise and the solution stirred at -78 °C for 1.5 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (5 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 50 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (50 mL), dried (Na$_2$SO$_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 3:1, petrol:diethyl ether) to furnish aldehyde **3.13** as a colourless syrup (720 mg, 76%). R$_f$ 0.28 (1:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ –1.67 (*c* 1.02, chloroform); ν_{max}/cm^{-1} (thin film) 3425s (br, N-H), 3070m, 3049m, 3017m, 2935m, 2858w, 1704s (C=O), 1650w, 1590w, 1515s, 1455m, 1429s, 1394w, 1363w, 1331w, 1257s, 1152s, 1117s, 1027w, 990m, 911m, 857w; δ_H (400 MHz, CDCl$_3$) 1.46 (3H, d, *J* 6.0, =CHCH$_3$), 2.19–2.29 (2H, m, SiCH$_2$), 3.45 and 3.59 (2 x 1H, 2 x ~dt, *J* 14.4 and 5.2, NHCH$_2$), 4.26 (1H, t, *J* 5.2, OCH), 5.06–5.08 (1H, m, NH), 5.07 and 5.11 (2 × 1H, 2 × d, *J* 12.4, CH_2Ph), 5.40–5.56 (2H, m, $CH{=}CHCH_3$), 7.32–7.49 (10H, m, Ph), 7.63–7.69 (5H, m, Ph), 9.59 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 12.7 ($=CHCH_3$), 15.3 ($SiCH_2$), 42.6 ($NHCH_2$), 66.9 (CH_2Ph), 123.2 ($=CHCH_3$), 124.4 ($CH{=}CHCH_3$), 127.9 (Ph), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 130.5 (Ph), 133.3 (*i*-Ph), 134.8 (Ph), 136.3 (*i*-Ph, Cbz), 156.2 (C=O, Cbz), 201.0 (CHO); *m/z* ($APCI^+$) 460 (MH^+, 35%), 416 (29), 404 (16), 360 (35), 253 (50), 246 (22), 192 (99), 180 (18), 120 (100), 105 (12); Accurate mass (ES^+): Found 460.1943, $C_{27}H_{30}NO_4Si$ (MH^+) requires 460.1944.

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(3-methylbut-2-enyl)diphenylsilanyloxy]isoserinate

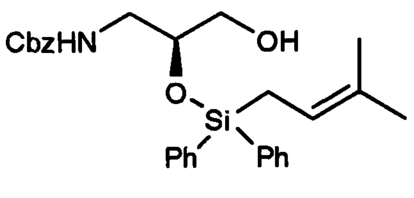


3.15

To a stirred solution of prenyl(diphenyl)silane **2.22** (1.42 g, 5.64 mmol) and methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (1.43 g, 5.64 mmol) in anhydrous DCM (6.0 mL), was added tris(pentafluorophenyl)borane (144 mg, 0.28 mmol) and the reaction mixture heated at reflux for 16 hr. The solution was allowed to cool to RT and then partitioned between water (50 mL) and diethyl ether (50 mL); the aqueous layer was separated and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish ester **3.15** as a colourless syrup (2.22 g, 78%). R_f 0.41 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −14.0 (*c* 1.03, chloroform); ν_{max}/cm^{-1} (thin film) 3442m (br, N-H), 3070m, 3049m, 3027m, 2953m, 2926m, 2855m, 1754s (C=O), 1727s (C=O), 1590w, 1515s, 1454m, 1429s, 1402w, 1376m, 1221s, 1120s, 997m, 839w, 817m, 735s, 700s; δ_H (400 MHz, $CDCl_3$) 1.39 and 1.62 (2 × 3H, 2 × s, $=C(CH_3)_2$), 2.11 (2H, d, *J* 8.0, $SiCH_2$), 3.54 (2H, ~t, *J* 5.2, $NHCH_2$), 3.58 (3H, s,

$CO_2C\mathbf{H}_3$), 4.37 (1H, t, *J* 5.2, OC**H**), 5.08 (2H, br s, C**H**$_2$Ph), 5.12 (1H, t, *J* 5.2, N**H**), 5.19 (1H, t, *J* 8.0, C**H**=C(CH$_3$)$_2$), 7.33–7.64 (15 H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.9 ($SiCH_2$), 17.6 and 25.7 (=C(CH$_3$)$_2$), 44.8 ($NHCH_2$), 52.0 (CO_2CH_3), 66.8 (CH_2Ph), 71.4 (OCH), 116.8 (CH=C(CH$_3$)$_2$), 127.8 (Ph), 127.9 (Ph), 128.1 (Ph), 130.1 (Ph), 130.2 (Ph), 131.8 (=C(CH$_3$)$_2$), 133.8 (*i*-Ph), 134.9 (Ph), 136.4 (*i*-Ph, Cbz), 156.2 (C=O, Cbz), 171.5 (CO_2CH_3); *m/z* (CI^+) 521 (MNH_4^+, 5%), 434 (M^+-C_5H_9,11), 413 (52), 230 (13), 163 (100), 108 (21); Accurate mass (ES^+): Found 521.2467, $C_{29}H_{37}N_2O_5Si$ (MNH_4^+) requires 521.2472.

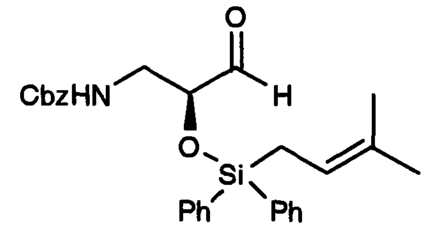
(*S*)-*N*-(Benzyloxycarbonyl)[(3-methylbut-2-enyl)diphenylsilanyloxy]isoserinol



3.18

To a stirred solution of silyl isoserinate **3.15** (118 mg, 0.23 mmol) in anhydrous DCM (2.5 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 580 μL, 0.58 mmol) dropwise and the solution stirred at -78 °C for 3 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (2 mL). The mixture was warmed to RT and partitioned between dilute HCl (1.0 M, 25 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic extracts washed with dilute HCl (1.0 M, 50 mL), saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish isoserinol **3.18** as a colourless oil (57.0 mg, 51%). R_f 0.16 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −10.1 (*c* 1.05, chloroform); ν_{max}/cm^{-1} (thin film) 3425m (br, N-H), 3350m (br, O-H), 3069w, 3049w, 2963m, 2925m, 2876m, 1706s (C=O), 1589w, 1517m, 1454w, 1428m, 1402w, 1376w, 1345w, 1261m, 1150m, 1117s, 1053m, 998m, 844w, 816w, 774w, 733s, 700s; δ_H (400 MHz, $CDCl_3$) 1.41 and 1.64 (2 x 3H, 2 x s, =C(C**H**$_3$)$_2$), 2.08 (2H, d, *J* 8.0, SiC**H**$_2$), 2.77 (1H, br s, CH$_2$O**H**), 3.17 (1H, ddd, *J* 14.4, 5.2 and 4.4, NHC**H**$_a$H), 3.48 (1H, ddd, *J* 14.4, 5.2 and 4.0, NHCH**H**$_b$), 3.49 (2H, d, *J* 5.2, C**H**$_2$OH), 3.92 (1H, ddt, *J* 5.2, 5.2, 4.4 and 4.0, OC**H**), 5.03 (1H, br t, *J* 5.2, N**H**), 5.08 and 5.12 (2 × 1H, 2 × d, *J* 12.2, C**H**$_2$Ph), 5.20 (1H, br t, *J* 8.0, C**H**=C(CH$_3$)$_2$), 7.30–7.68 (15H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 16.0 (SiCH$_2$), 17.6 and 25.8 (=C(CH$_3$)$_2$), 43.2 (NHCH$_2$), 63.1 (CH$_2$OH), 67.0 (CH$_2$Ph), 72.3 (OCH), 117.1 (CH=C(CH$_3$)$_2$), 128.0 (Ph), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 130.2 (Ph), 131.9 (=C(CH$_3$)$_2$), 134.4 (*i*-Ph), 134.7 (Ph), 136.3 (*i*-Ph, Cbz), 157.8 (C=O, Cbz); *m/z* (ES$^+$) 498 (MNa$^+$, 56%), 493 (MNH$_4^+$, 100), 476 (MH$^+$, 29), 406 (30), 398 (11); Accurate mass (ES$^+$): Found 498.2078, $C_{28}H_{33}NO_4NaSi$ (MNa$^+$) requires 498.2077.

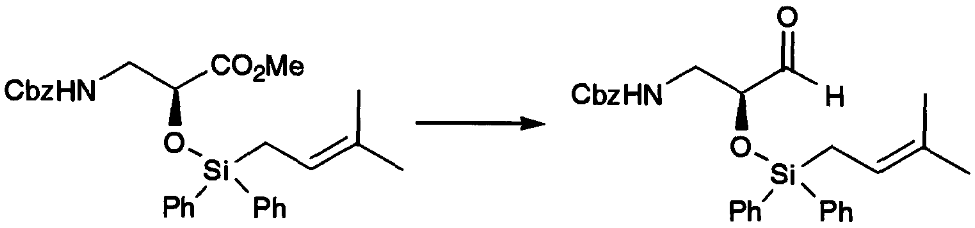
(*S*)-*N*-(Benzyloxycarbonyl)[(3-methylbut-2-enyl)diphenylsilanyloxy]isoserinal



3.16

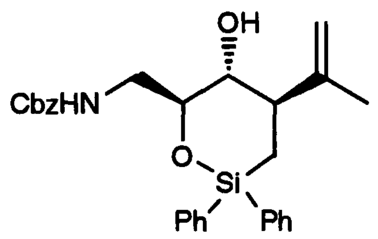
To a stirred solution of oxalyl chloride (11.5 μL, 0.13 mmol) in anhydrous DCM (1.0 mL) cooled to -78 °C was added DMSO (15.0 μL, 0.21 mmol). After 10 min a cooled solution of isoserinol **3.18** (50.0 mg, 0.11 mmol) in anhydrous DCM (1.0 mL) was added *via* cannula. After a further 10 min TEA (59.0 μL, 0.42 mmol) was added; the resulting cloudy mixture was stirred for 15 min at -78 °C and then allowed to warm to RT over 1 hr. The reaction mixture was partitioned between water (15 mL) and diethyl ether (15 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (50 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 2:1, petrol:diethyl ether) to furnish aldehyde **3.16** as a colourless syrup (46.7 mg, 94%). R$_f$ 0.30 (1:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ −1.00 (*c* 1.03, chloroform); ν_{max}/cm^{-1} (thin film) 3442m (br, N-H), 3069w, 3049w, 2965m, 2925m, 1724s (C=O), 1590w, 1517m, 1454w, 1429m, 1377w, 1331w, 1258m, 1154m, 1119s, 998w, 817w, 734s, 700s; δ_H (500 MHz, $CDCl_3$) 1.39 and 1.64 (2 × 3H, 2 × s, $=C(CH_3)_2$), 2.14 (2H, d, *J* 8.0, $SiCH_2$), 3.46 and 3.57 (2 × 1H, 2 × dt, *J* 14.0 and 4.5, $NHCH_2$), 4.23 (1H, t, *J* 4.5, OCH), 5.02 (1H, br s, NH), 5.06 and 5.10 (2 × 1H, 2 × d, *J* 12.2, CH_2Ph), 5.21 (1H, t, *J* 8.0, $CH=C(CH_3)_2$), 7.32–7.64 (15H, m, Ph), 9.58 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 15.8 ($SiCH_2$), 17.6 and 25.6 ($=C(CH_3)_2$), 42.6 ($NHCH_2$), 66.8 (CH_2Ph), 77.1 (OCH), 116.6 ($CH=C(CH_3)_2$), 127.8 (Ph), 128.0 (Ph), 128.1 (Ph), 128.4 (Ph), 130.3 (Ph), 132.1 ($=C(CH_3)_2$), 133.4 (*i*-Ph), 134.7 (Ph), 136.2 (*i*-Ph, Cbz), 156.1 (C=O, Cbz), 201.1 (CHO); *m/z* (APCI$^+$) 474 (MH$^+$, 10%), 430 (13), 360 (36), 343 (31), 253 (48), 192 (100), 149 (17), 120 (98), 106 (11); Accurate mass (ES$^+$): Found 474.2102, $C_{28}H_{32}NO_4Si$ (MH$^+$) requires 474.2100.

Alternative procedure from 3.15



To a stirred solution of silyl isoserinate **3.15** (1.11 g, 2.20 mmol) in anhydrous DCM (22.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 3.30 mL, 3.30 mmol) dropwise and the solution stirred at -78 °C for 2 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (5 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 50 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 3:1, petrol:diethyl ether) to furnish aldehyde **3.16** as a colourless syrup (708 mg, 68%).

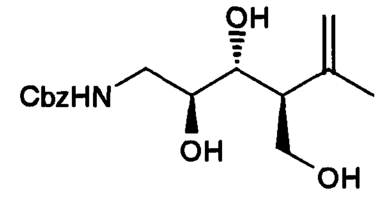
(3*S*,4*R*,5*R*)-3-[(Benzyloxycarbonyl)amino]methyl-2-oxa-1,1-diphenyl-5-(propen-2-yl)silinan-4-ol



3.20

To a stirred solution of aldehyde **3.16** (230 mg, 0.49 mmol) in anhydrous DCM (5.0 mL) at RT was added DMAC (1.0 M in hexanes, 540 µL, 0.54 mmol). After 30 min the reaction was quenched by the addition of saturated *aq.* Na_2SO_4 soln. (5 mL) and the mixture partitioned between water (10 mL) and diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL); the combined organic layers were washed with saturated *aq.* NaCl soln. (40 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The resulting syrup was purified by flash column chromatography (silica gel, 3:1, petrol:diethyl ether) to furnish oxasilacycle **3.20** as a colourless foam (118 mg, 52%). R_f 0.32 (1:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ +7.00 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3427m (br, N-H, O-H), 3069m, 2926m, 1703s (C=O), 1590w, 1518s, 1455m, 1429s, 1374w, 1261s, 1118s, 1070s, 1038m, 987m, 909w, 802w, 768w, 737s, 699s; δ_H (500 MHz, $CDCl_3$) 1.38 (1H, t, *J* 15.0, $SiC\mathbf{H}_{ax}H$), 1.43 (1H, dd, *J* 15.0 and 4.5, $SiCH\mathbf{H}_{eq}$), 1.85 (3H, s, $C(C\mathbf{H}_3)=$), 2.67 (1H, ddd, *J* 15.0, 11.5 and 4.5, $SiCH_2C\mathbf{H}$), 3.23 (1H, br s, $CH(O\mathbf{H})$), 3.44 (1H, ~dd, *J* 11.5 and 8.0, $C\mathbf{H}(OH)$), 3.58 (1H, ~dt, *J* 14.0 and 4.5, $NHC\mathbf{H}_aH$), 3.81 (1H, ddd, *J* 14.0, 8.0 and 4.5, $NHCH\mathbf{H}_b$), 3.89 (1H, ~td, J 8.0 and 4.5, $NHCH_2C\mathbf{H}$), 4.92 and 4.95 (2 × 1H, 2 × br s, $C(CH_3)=C\mathbf{H}_2$), 5.22 and 5.27 (2 × 1H, 2 × d, *J* 12.0, $C\mathbf{H}_2Ph$), 5.49 (1H, t, *J* 4.5, N**H**), 7.41–7.76 (15H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.4 ($SiCH_2$), 17.7 ($C(CH_3)=$), 44.6 ($NHCH_2$), 48.7 ($SiCH_2CH$), 67.0 (CH_2Ph), 70.4 (CH(OH)), 77.3 ($NHCH_2CH$), 112.6 ($C(CH_3)=CH_2$), 128.0 (Ph), 128.2 (Ph), 128.4 (Ph), 128.6 (Ph), 130.4 (Ph), 133.3 (*i*-Ph), 134.3 (Ph), 136.6 (*i*-Ph, Cbz), 147.9 ($C(CH_3)=$), 157.6 (C=O, Cbz);[250] *m/z* ($APCI^+$) 474 (MH^+, 91%), 430 (59), 366 (36), 340 (49), 322 (23), 253 (30), 240 (100), 198 (23), 192 (62), 120 (75), 107 (31); Accurate mass (ES$^+$): Found 474.2101, $C_{28}H_{32}NO_4Si$ (MH$^+$) requires 474.2100.

(2*S*,3*R*,4*S*)-1-[(Benzyloxycarbonyl)amino-4-hydroxymethyl-5-methylhex-5-en-2,3-diol

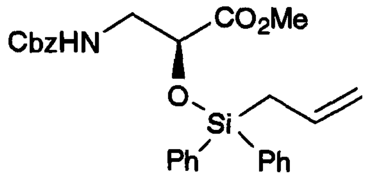


3.21

To a solution of crude oxasilinane **3.20**[251] in methanol (6.5 mL) and THF (6.5 mL) was added KF (220 mg, 3.79 mmol), $KHCO_3$ (253 mg, 2.53 mmol) and H_2O_2 (35% in water, 620 μL, 6.32 mmol). The mixture was stirred for 16 hr at RT, filtered through Celite® and the solvent removed *in vacuo*. The residue was triturated with diethyl ether, the extracts filtered and the solvent removed *in vacuo*. The resulting material was purified by flash column chromatography (silica gel, 1:2, petrol:diethyl ether) to give aminotriol **3.21** as a colourless glassy solid (182 mg, 47%). The product was then recrystallised from methanol to furnish colourless needles. R_f 0.24 (ethyl acetate); M.p 65–67 °C (from methanol); $[\alpha]_D^{22}$ +8.57 (*c* 1.02, chloroform); ν_{max}/cm^{-1} (KBr disc) 3319s (br, N-H, O-H), 3091w, 3067w, 3039w, 2954m, 2920m, 2887m, 1694s (C=O), 1642w, 1541s, 1462m, 1434w, 1326w, 1275s, 1238w, 1151m, 1103m, 1070m, 1046m, 1027m, 970m, 893m; δ_H (500 MHz, DMSO-d_6) 1.71 (3H, s, C(C**H**$_3$)=), 2.42–2.51 (1H, m, C**H**C(CH$_3$)=), 2.97 (1H, dt, *J* 12.5 and 6.0, NHC**H**$_a$H), 3.34–3.43 (2H, m, CH$_2$C**H**(OH) and NHCH**H**$_b$), 3.46–3.58 (3H, m, CH$_2$CH(OH)C**H**(OH) and C**H**$_2$OH), 4.36 (1H, t, *J* 5.0, CH$_2$O**H**), 4.53 (1H, d, *J* 5.5, CH$_2$CH(OH)CH(O**H**)), 4.55 (1H, d, *J* 6.0, CH$_2$CH(O**H**)), 4.77 (2H, br s, C(CH$_3$)=C**H**$_2$), 5.02 (2H, s, C**H**$_2$Ph), 6.92 (1H, t, *J* 6.0, N**H**), 7.30–7.37 (5H, m, Ph); δ_C (125.7 MHz, DMSO-d_6) 23.4 (C(CH$_3$)=), 45.5 (NHCH$_2$), 50.5 (CHC(CH$_3$)=), 62.5 (CH$_2$OH), 66.1 (CH$_2$Ph), 71.4 (CH$_2$CH(OH)), 72.2 (CH$_2$CH(OH)CH(OH)), 114.2 (C(CH$_3$)=CH$_2$), 128.6 (2 × Ph), 129.2 (Ph), 138.1 (*i*-Ph), 145.3

(C(CH$_3$)=), 157.4 (C=O, Cbz); *m/z* (APCI$^+$) 310 (MH$^+$, 14%), 266 (39), 158 (100), 128 (18); Accurate mass (ES$^+$): Found 310.1658, $C_{16}H_{24}NO_5$ (MH$^+$) requires 310.1654.

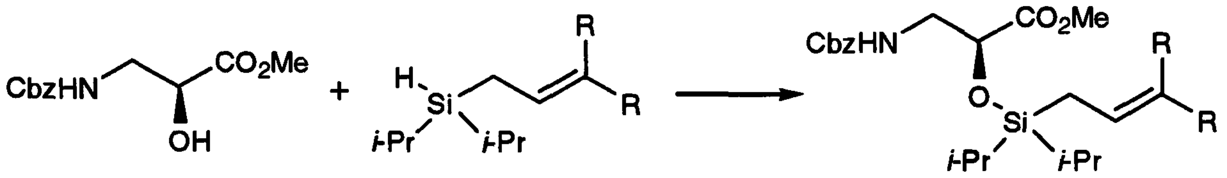
(*S*)-Methyl *N*-(benzyloxycarbonyl)[(prop-2-enyl)diphenylsilanyloxy]isoserinate



3.26

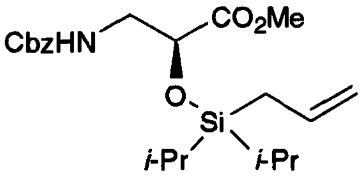
To a stirred solution of allyl(diphenyl)silane **2.20** (355 mg, 1.58 mmol) and methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (400 mg, 1.58 mmol) in anhydrous DCM (1.6 mL), was added tris(pentafluorophenyl)borane (41.0 mg, 0.08 mmol) and the reaction mixture heated at reflux for 16 hr. The solution was allowed to cool to RT and then partitioned between water (25 mL) and diethyl ether (25 mL); the aqueous layer was separated and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (25 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish ester **3.26** as a colourless syrup (525 mg, 70%). R$_f$ 0.39 (1:1, petrol:diethyl ether); $[\alpha]_D^{20}$ –10.6 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3424m (br, N-H), 3070m, 3001m, 2951m, 1962w, 1892w, 1760s (C=O), 1724s (C=O), 1630m, 1590w, 1516s, 1455m, 1370w, 1247s, 1119s, 997m, 902w, 773m, 738s, 700s; δ_H (400 MHz, CDCl$_3$) 2.26 (2H, d, *J* 8.0, SiC**H**$_2$), 3.53–3.58 (2H, m, NHC**H**$_2$), 3.59 (3H, s, CO$_2$C**H**$_3$), 4.40 (1H, t, *J* 5.0, OC**H**), 4.92 (1H, ddt, *J* 10.0, 2.0 and 1.2, CH=C**H**$_E$H), 4.97 (1H, ddt, *J* 17.0, 2.0 and 1.2, CH=CH**H**$_Z$), 5.07 and 5.11 (2 × 1H, 2 × d, *J* 12.4, C**H**$_2$Ph), 5.14 (1H, br t, *J* 5.2, N**H**), 5.83 (1H, ddt, *J* 17.0, 10.0 and 8.0, C**H**=CH$_2$), 7.29–7.68 (15H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 21.8 (SiCH$_2$), 44.7 (NHCH$_2$), 52.0 (CO$_2$CH$_3$), 66.8 (CH$_2$Ph), 71.5 (OCH), 115.6 (CH=CH$_2$), 127.8 (Ph), 127.9 (Ph), 128.1 (Ph), 128.5 (Ph), 130.3 (Ph), 132.6 (Ph), 133.4 (*i*-Ph), 134.9 (CH=CH$_2$), 136.4 (*i*-Ph, Cbz), 156.2 (C=O, Cbz), 171.5 (CO_2CH_3); *m/z* (ES^+) 498 (MNa^+, 10%), 493 (MNH_4^+, 100), 476 (MH^+, 3), 434 (M^+-C_3H_5, 51); Accurate mass (ES^+): Found 493.2163, $C_{27}H_{33}N_2O_5Si$ (MNH_4^+) requires 493.2159.

General procedure for α-silyloxy ester synthesis



To a stirred solution of the di(*iso*-propyl)silane (1.00 mmol) and methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (0.90 mmol) in anhydrous toluene (5.0 mL), was added tris(pentafluorophenyl)borane (0.10 mmol) and the reaction mixture heated at reflux for 24 hr. The solution was allowed to cool to RT and then partitioned between water (25 mL) and diethyl ether (25 mL); the aqueous layer was separated and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether).

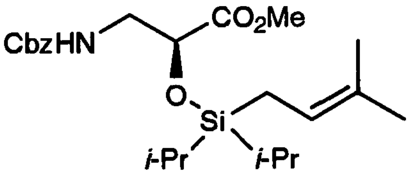
(*S*)-Methyl *N*-(benzyloxycarbonyl)[(prop-2-enyl)di(*iso*-propyl)silanyloxy]isoserinate



3.24

On a 0.59 mmol scale the reaction gave **3.24** as a colourless syrup (16.0 mg, 7%). R_f 0.35 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −7.86 (*c* 1.01, chloroform); ν_{max}/cm^{-1} (thin film) 3368m (br, N-H), 3068m, 3034w, 2944s, 2892m, 2866s, 1756s (C=O), 1728s (C=O), 1630w, 1517m, 1463m, 1384w, 1366w, 1248m, 1143m, 1070w, 996m, 883m, 830w, 750w, 697m; δ_H (400 MHz, $CDCl_3$) 0.97–1.04 (14H, m, 2 × $CH(CH_3)_2$), 1.73 (2H, d, *J* 8.0, $SiCH_2$), 3.51–3.55 (2H, m, NHC**H**$_2$), 3.72 (3H, s, CO$_2$C**H**$_3$), 4.44 (1H, t, *J* 5.0, OC**H**), 4.88 (1H, ~dd, *J* 10.0 and 1.6, CH=C**H**$_E$H), 4.96 (1H, ~dd, *J* 17.0 and 1.6, CH=CH**H**$_Z$), 5.08 and 5.13 (2 × 1H, 2 × d, *J* 12.0, C**H**$_2$Ph), 5.12–5.15 (1H, m, N**H**), 5.84 (1H, ddt, *J* 17.0, 10.0 and 8.0, C**H**=CH$_2$), 7.25–7.41 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 12.6 (2 × CH(CH$_3$)$_2$), 17.3 and 17.4 (2 × CH(CH$_3$)$_2$), 18.7 (SiCH$_2$), 45.0 (NHCH$_2$), 52.1 (CO$_2$CH$_3$), 66.8 (CH$_2$Ph), 71.1 (OCH), 114.3 (CH=CH$_2$), 128.1 (2 × Ph), 128.5 (Ph), 133.9 (CH=CH$_2$), 136.5 (*i*-Ph), 156.3 (C=O, Cbz), 171.3 (CO$_2$CH$_3$); *m/z* (ES$^+$) 425 (MNH$_4^+$, 100%), 408 (MH$^+$, 6), 366 (M$^+$-C$_3$H$_5$, 82); Accurate mass (ES$^+$): Found 425.2470, C$_{21}$H$_{37}$N$_2$O$_5$Si (MNH$_4^+$) requires 425.2472.

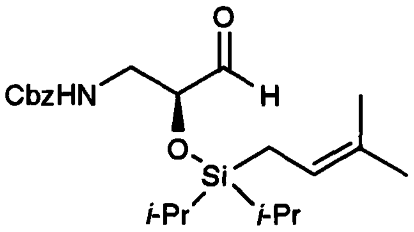
(*S*)-Methyl *N*-(benzyloxycarbonyl)[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]isoserinate



3.25

On a 2.44 mmol scale the reaction gave **3.25** as a colourless syrup (120 mg, 11%). R$_f$ 0.37 (1:1, petrol:diethyl ether); $[\alpha]_D^{20}$ –6.60 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3361m (br, N-H), 3033w, 2946s, 2867s, 1761s (C=O), 1729s (C=O), 1514m, 1456m, 1376w, 1248m, 1143s, 1097w, 995m, 883m, 844w, 814w, 748s, 697m; δ_H (400 MHz, CDCl$_3$) 1.03–1.14 (14H, m, 2 × C**H**(C**H**$_3$)$_2$), 1.58 (2H, ~d, *J* 8.0, SiC**H**$_2$), 1.60 and 1.67 (2 × 3H, 2 × br s, =C(C**H**$_3$)$_2$), 3.46–3.59 (2H, m, NHC**H**$_2$), 3.72 (3H, s, CO$_2$C**H**$_3$), 4.40 (1H, t, *J* 5.0, OC**H**), 5.08 and 5.13 (2 × 1H, 2 × d, *J* 12.4, C**H**$_2$Ph), 5.11–5.18 (2H, m, C**H**=C(CH$_3$)$_2$ and N**H**), 7.27–7.39 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 12.4 (SiCH$_2$), 12.7 (2 × CH(CH$_3$)$_2$), 17.3 and 17.4 (2 × CH(CH$_3$)$_2$), 17.6 and 25.8 (=C(CH$_3$)$_2$), 45.1 (NHCH$_2$), 52.0 (CO$_2$CH$_3$), 66.8 (CH$_2$Ph), 71.1 (OCH), 118.4 (CH=C(CH$_3$)$_2$), 128.1 (2 × Ph), 128.5 (Ph), 130.0 (=C(CH$_3$)$_2$), 136.4 (*i*-Ph), 156.2 (C=O, Cbz), 172.0 (CO_2CH_3); *m/z* (CI^+) 453 (MNH_4^+, 100%), 436 (MH^+, 13), 838 (15); Accurate mass (ES^+): Found 453.2786, $C_{23}H_{41}N_2O_5Si$ (MNH_4^+) requires 453.2785.

(*S*)-*N*-(Benzyloxycarbonyl)[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]isoserinal

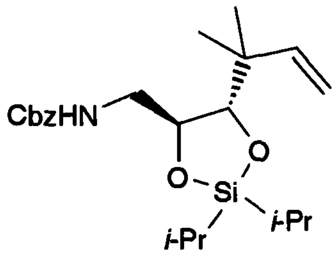


3.29

To a stirred solution of silyl isoserinate **3.25** (82.6 mg, 0.19 mmol) in anhydrous DCM (2.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 290 μL, 0.29 mmol) dropwise and the solution stirred at -78 °C for 1 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (1 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 15 mL) and diethyl ether (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (25 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 8:1, petrol:ethyl acetate) to furnish aldehyde **3.29** as a colourless syrup (59.5 mg, 77%). R_f 0.63 (diethyl ether, [streaks]); $[\alpha]_D^{20}$ −1.90 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3349m (br, N-H), 3066w, 3034w, 2944s, 2892m, 2867s, 1732s (C=O), 1517m, 1456m, 1403w, 1377w, 1347w, 1328w, 1256s, 1153s, 1128s, 1098m, 1002m, 920w, 883m, 844w, 815w, 775w, 747m, 697m; δ_H (400 MHz, $CDCl_3$) 0.98–1.14 (14H, m, 2 × **CH(CH₃)₂**), 1.59 and 1.67 (2 × 3H, 2 × br s, =C(**CH₃**)₂), 1.60 (2H, ~d, *J* 8.0, Si**CH₂**), 3.42 (1H, ~dt, *J* 14.0 and 5.0, NHCH**$_a$**H), 3.58 (1H, ddd, *J* 14.0, 7.2 and 5.0, NHCH**H$_b$**), 4.18 (1H, t, *J* 5.0, OC**H**), 5.08 and 5.12 (2 × 1H, 2 × d, *J* 12.0, **CH₂**Ph), 5.12–5.19 (2H, m, C**H**=C(CH₃)₂ and N**H**), 7.30–7.39 (5H, m, Ph), 9.62 (1H, s, C**H**O); δ_C (100.6 MHz, $CDCl_3$) 12.4 ($SiCH_2$), 12.6 (2 × $CH(CH_3)_2$), 17.3 and 17.4 (2 × $CH(CH_3)_2$), 17.7 and 25.8 (=$C(CH_3)_2$), 43.0 ($NHCH_2$), 66.9 (CH_2Ph), 76.3

(OCH), 118.2 (CH=C(CH$_3$)$_2$), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 130.4 (=C(CH$_3$)$_2$), 136.3 (*i*-Ph), 156.2 (C=O, Cbz), 202.2 (CHO); *m/z* (CI$^+$) 423 (MNH$_4^+$, 29%), 406 (MH$^+$, 91), 366 (13), 336 (M$^+$-C$_5$H$_9$, 100), 315 (49), 272 (30), 218 (21), 169 (35), 148 (75), 108 (25); Accurate mass (ES$^+$): Found 423.2680, C$_{22}$H$_{39}$N$_2$O$_4$Si (MNH$_4^+$) requires 423.2679.

(3*S*,4*S*)-3-[(Benzyloxycarbonyl)amino]methyl-4-(1,1-dimethylprop-2-enyl)-2,5-dioxa-1,1-di(*iso*-propyl)silolane

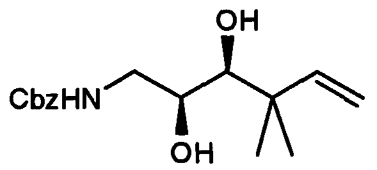


3.30

A solution of aldehyde **3.29** (48.9 mg, 0.12 mmol) in toluene-d$_8$ (600 μL) was heated at 120 °C in a sealed NMR tube and the reaction progress monitored by ^{1}H NMR. After 30 hr the reaction was cooled to RT and the solvent removed *in vacuo*. Purification by flash column chromatography (silica gel, 5:1, petrol:diethyl ether) gave siladioxolane **3.30** as a colourless oil (44.7 mg, 91%). R$_f$ 0.58 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –33.1 (*c* 0.55, chloroform); ν_{max}/cm^{-1} (thin film) 3338m (br, N-H), 2946s, 2867s, 1724s (C=O), 1513m, 1465m, 1382w, 1248m, 1148w, 1073m, 1041m, 918w, 883w, 849w, 797w, 752w, 696m; δ_H (400 MHz, CDCl$_3$) 1.00–1.02 (14H, m, 2 × **CH(CH$_3$)$_2$**), 1.04 and 1.08 (2 × 3H, 2 × br s, C(**CH$_3$**)$_2$), 3.02 (1H, ddd, *J* 13.0, 8.0 and 3.8, NH**CH$_a$**H), 3.42 (1H, d, *J* 8.0, **CH**(O)C(CH$_3$)$_2$), 3.60 (1H, ddd, *J* 13.0, 8.0 and 2.8, NHCH**H$_b$**), 3.84 (1H, td, *J* 8.0 and 2.8, NHCH$_2$**CH**(O)), 5.02–5.14 (2H, m, CH=**CH$_2$**), 5.09 and 5.15 (2 × 1H, 2 × d, *J* 12.2, **CH$_2$**Ph), 5.23–5.30 (1H, m, **NH**), 5.90* (1H, "dd", *J* 17.6 and 10.8, **CH**=CH$_2$), 7.31–7.39 (5H, m, Ph);[244] δ_C (100.6 MHz, CDCl$_3$) 12.5 and 12.7 (2 × CH(CH$_3$)$_2$), 16.8 and 16.9 (2 × CH(CH$_3$)$_2$), 22.6 and 24.0 (C(CH$_3$)$_2$), 40.6 (C(CH$_3$)$_2$), 46.7 (NHCH$_2$), 66.7 (CH$_2$Ph), 75.5 (NHCH$_2$CH(O)), 83.8 (CH(O)C(CH$_3$)$_2$), 113.2

($CH{=}CH_2$), 128.1 (2 × Ph), 128.8 (Ph), 136.5 (*i*-Ph), 143.9 ($CH{=}CH_2$) 156.3 (C=O, Cbz); *m/z* (APCI$^+$) 406 (MH$^+$, 46%), 363 (100), 280 (10), 255 (10), 122 (10); Accurate mass (ES$^+$): Found 406.2408, $C_{22}H_{36}NO_4Si$ (MH$^+$) requires 406.2413.

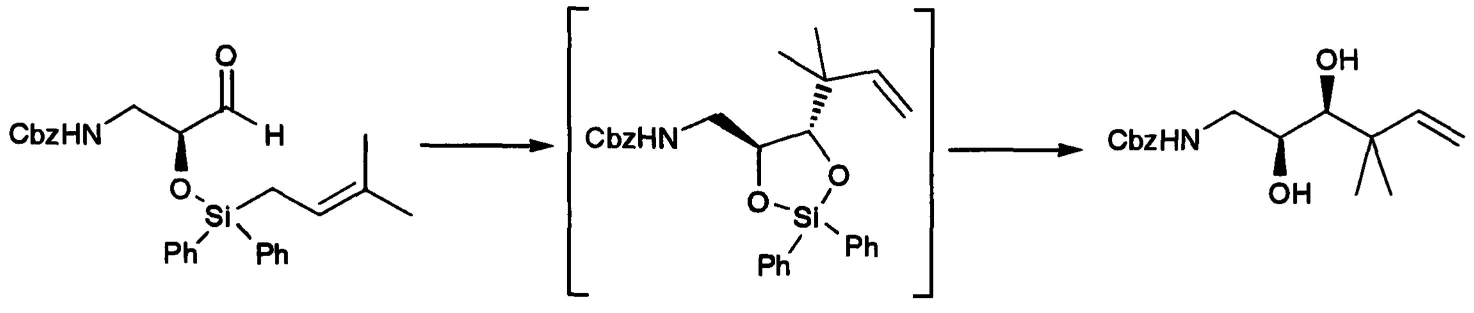
(2*S*,3*S*)-1-[(Benzyloxycarbonyl)amino-4,4-dimethylhex-5-en-2,3-diol



3.28

To a stirred solution of siladioxolane **3.30** (41.3 mg, 0.10 mmol) in methanol (1.0 mL) was added KF (17.4 mg, 0.30 mmol) and the reaction mixture was stirred at RT for 16 hr. The solvent was removed *in vacuo*; the crude residue was triturated with diethyl ether and the combined extracts were filtered through Celite® and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 1:2, petrol:diethyl ether) to give aminodiol **3.28** as a colourless glassy solid (26.2 mg, 89%). R_f 0.49 (diethyl ether); $[\alpha]_D^{22}$ −10.9 (*c* 1.01, chloroform); ν_{max}/cm^{-1} (KBr disc) 3428s and 3399s (br, N-H, O-H), 3084w, 3034w, 2946m, 1694s (C=O), 1638w, 1538m, 1455m, 1415m, 1271s, 1145m, 1106m, 1012m, 914m, 844w, 824w, 736m, 697s; δ_H (400 MHz, DMSO-d_6) 0.95 and 0.96 (2 × 3H, 2 × s, $C(\mathbf{CH_3})_2$), 2.97 (2H, ~t, *J* 6.0, $NH\mathbf{CH_2}$), 3.03 (1H, br d, *J* 8.2, $\mathbf{CH}(OH)C(CH_3)_2$), 3.57–3.64 (1H, m, $NHCH_2\mathbf{CH}(OH)$), 4.17 (1H, d, *J* 8.2, $CH(O\mathbf{H})C(CH_3)_2$), 4.36 (1H, d, *J* 7.2, $NHCH_2CH(O\mathbf{H})$), 4.90 (1H, dd, *J* 10.8 and 1.4, $CH{=}\mathbf{CH}_EH$), 4.92 (1H, dd, *J* 17.6 and 1.4, $CH{=}CH\mathbf{H}_Z$), 4.98 and 5.03 (2 × 1H, 2 × d, *J* 12.4, $\mathbf{CH_2}Ph$), 5.87 (1H, dd, *J* 17.6 and 10.8, $\mathbf{CH}{=}CH_2$), 7.20 (1H, br t, *J* 6.0, N**H**), 7.29–7.38 (5H, m, Ph); δ_C (100.6 MHz, DMSO-d_6) 22.0 and 24.9 ($C(CH_3)_2$), 41.2 ($C(CH_3)_2$), 45.3 ($NHCH_2$), 65.1 (CH_2Ph), 67.6 ($NHCH_2CH(OH)$), 75.3 ($CH(OH)C(CH_3)_2$), 111.3 ($CH{=}CH_2$), 127.7 (Ph), 127.8 (Ph), 128.4 (Ph), 137.3 (*i*-Ph), 146.4 ($CH{=}CH_2$) 156.3 (C=O, Cbz); *m/z* (APCI$^+$) 294 (MH$^+$, 16%), 250 (100), 160 (21), 142 (40), 104 (18); Accurate mass (ES$^+$): Found 294.1708, $C_{16}H_{24}NO_4$ (MH$^+$) requires 294.1705.

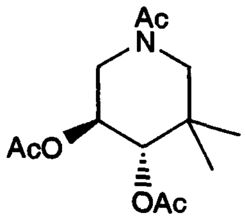
Alternative procedure from 3.16



3.27

A stirred solution of aldehyde **3.16** (743 mg, 1.57 mmol) in anhydrous toluene (8.0 mL) was heated at 120 °C in a base-washed sealed tube. After 20 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo* to furnish the crude siladioxolane **3.27.** R_f 0.83 (diethyl ether); δ_H (400 MHz, toluene-d$_8$) 1.06 (2 × 3H, 2 × s, C(C**H**$_3$)$_2$), 3.15 (1H, ~dt, *J* 14.0 and 6.4, NHC**H$_a$**H), 3.42 (1H, ddd, *J* 14.0, 6.4 and 3.2, NHCH**H$_b$**), 3.80 (1H, d, *J* 6.4, C**H**(O)C(CH$_3$)$_2$), 4.20 (1H, td, *J* 6.4 and 3.2, NHCH$_2$C**H**(O)), 4.90 (1H, t, *J* 6.4, N**H**), 4.94–5.12 (4H, m, CH=C**H$_2$** and C**H$_2$**Ph), 5.90* (1H, "dd", *J* 17.4 and 11.0, C**H**=CH$_2$), 6.93–7.33 (11H, m, Ph), 7.61–7.72 (4H, m, Ph);[244] δ_C (100.6 MHz, toluene-d$_8$) 22.8 and 24.1 (C(CH$_3$)$_2$), 41.6 (C(CH$_3$)$_2$), 47.4 (NHCH$_2$), 67.1 (CH$_2$Ph), 77.0 (NHCH$_2$CH(O)), 84.8 (CH(O)C(CH$_3$)$_2$), 114.0 (CH=CH$_2$), 128.1 (Ph), 128.5 (Ph), 128.7 (Ph), 128.9 (Ph), 129.0 (Ph), 132.4 (*i*-Ph), 133.5 (*i*-Ph), 135.4 (Ph), 135.6 (Ph), 135.8 (Ph), 135.9 (Ph), 137.9 (*i*-Ph, Cbz), 144.2 (CH=CH$_2$) 156.9 (C=O, Cbz); *m/z* (APCI$^+$) 474 (MH$^+$, 100%), 430 (81), 396 (77), 352 (60), 306 (84), 262 (58), 160 (60), 122 (36). The crude product was dissolved in methanol (15.0 mL); KF (274 mg, 4.72 mmol) and H_2O_2 (35% in water, 1.5 mL) were added and the reaction mixture was stirred at RT for 3 hr. The solvent was removed *in vacuo*; the crude residue was triturated with diethyl ether and the combined extracts were filtered through Celite® and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 1:2, petrol:diethyl ether) to give aminodiol **3.28** as a colourless glassy solid (447 mg, 95%).

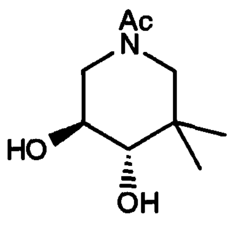
(3*S*,4*S*)-1-*N*-Acetyl-3,4-di-*O*-acetyl-5,5-dimethyl-3,4-dihydroxypiperidine



3.33

A stirred solution of aminodiol **3.28** (470 mg, 1.60 mmol) and Sudan Red 7B indicator (10.0 μL, 0.05% w/v in DCM) in anhydrous DCM (32.0 mL) was cooled to -45 °C. Ozone was passed through the solution until the magenta colouration dispersed; excess ozone was purged from the system with argon. Triphenylphosphine resin (3.0 mmol/g, 600 mg, 2.00 mmol) was added and the reaction mixture stirred at -45 °C for 30 min and then warmed to RT over 1.5 hr. The resin was removed by filtration through a short plug of silica gel and Celite® and the solvents removed from the filtrate *in vacuo*. The crude product was dissolved in absolute ethanol (15.0 mL), palladium on carbon (10 wt%, 55.0 mg, 0.05 mmol) was added and the flask purged with argon and then with hydrogen. The reaction mixture was stirred vigorously at RT under a positive pressure of hydrogen for 12 hr. The flask was purged with argon and the mixture filtered through Celite® to remove the palladium catalyst; the residue was washed with ethanol (3 × 5 mL) and the filtrate concentrated *in vacuo*. The residual yellow foam was taken up in anhydrous DCM (5.0 mL) and the solution cooled to 0 °C; pyridine (650 μL, 8.04 mmol), DMAP (4.9 mg, 0.04 mmol) and acetic anhydride (1.5 mL, 16.0 mmol) were added and the reaction mixture warmed to RT. After 3.5 hr the solution was cooled to 0 °C and quenched by the dropwise addition of saturated *aq.* $NaHCO_3$ soln. (20 mL). The mixture was partitioned between water (25 mL) and diethyl ether (25 mL); the aqueous layer was separated and extracted with diethyl ether (3 × 25 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 15 mL) to remove traces of pyridine and the crude product purified by flash column chromatography (silica gel, ethyl acetate) to furnish the acetylated piperidine **3.33** as a colourless syrup (76.8 mg, 18%). R_f 0.29 (ethyl acetate); $[\alpha]_D^{22}$ +8.62 (*c* 0.55, chloroform); ν_{max}/cm^{-1} (thin film) 2965m, 1743s (C=O), 1653s, 1439m, 1395w, 1370m, 1294w, 1242s, 1044s, 940w, 904w, 880w, 799m; δ_H (500 MHz, DMSO-d_6) 0.83, 0.86, 0.89 and 0.92 (4 × 3H, 4 × s, 2 × $C(CH_3)_2$), 1.97, 1.99, 2.02 and 2.05 (6 × 3H, 6 × s, 4 × OAc and 2 × NAc), 2.66 (1H, dd, *J* 12.5 and 10.5, H-2_{ax}, major rotamer **M$_r$**), 2.70 (1H, d, *J* 13.5, H-6_{ax}, minor rotamer **m$_r$**), 3.12 (1H, d, *J* 13.5, H-6_{ax}, **M$_r$**), 3.14 (1H, dd, *J* 13.5 and 10.0, H-2_{ax}, **m$_r$**), 3.52 (1H, dd, *J* 13.5 and 12.5, H-6_{eq}, **M$_r$**), 3.95 (1H, ddd, *J* 13.5, 5.0 and 2.0, H-2_{eq}, **m$_r$**), 3.98 (1H, dd, *J* 13.5 and 2.0, H-6_{eq}, **m$_r$**), 4.52 (1H, ddd, *J* 12.5, 5.5 and 2.5, H-2_{eq}, **M$_r$**), 4.65 (1H, ddd, *J* 10.5, 9.5 and 5.5, H-3, **M$_r$**), 4.78 (1H, ddd, *J* 10.0, 9.0 and 5.0, H-3, **m$_r$**), 4.84 (1H, d, *J* 9.0, H-4, **m$_r$**), 4.85 (1H, d, *J* 9.5, H-4, **M$_r$**); δ_C (125.7 MHz, DMSO-d_6) 19.1 and 19.8 ($C(CH_3)_2$), 21.4, 21.5, 21.9 and 22.1 (6 × **Ac**), 24.5 and 24.8 ($C(CH_3)_2$), 37.1 and 37.7 (2 × $C(CH_3)_2$), 43.2 (C-2, **M$_r$**), 48.2 (C-2, **m$_r$**), 50.8 (C-6, **m$_r$**), 55.5 (C-6, **M$_r$**), 68.3 (C-3, **M$_r$**), 68.9 (C-3, **m$_r$**), 77.5 (2 × C-4, **M$_r$** and **m$_r$**), 169.4, 169.6, 170.5 and 170.8 (**C**=O, 6 × **Ac**); *m/z* (APCI$^+$) 272 (MH$^+$, 100%), 230 (10), 212 (11); Accurate mass (ES$^+$): Found 272.1497, $C_{13}H_{22}NO_5$ (MH$^+$) requires 272.1498.

(3*S*,4*S*)-1-*N*-Acetyl-5,5-dimethyl-3,4-dihydroxypiperidine

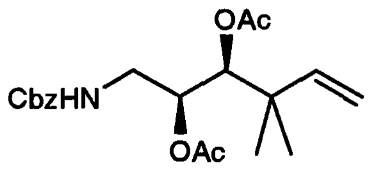


3.34

To a stirred solution of acetylated piperidine **3.33** (73.7 mg, 0.27 mmol) in anhydrous methanol (5.5 mL) was added freshly activated Amberlite® IRA 400 (OH) resin (2.7 mL)[252] and the suspension stirred vigorously at 50 °C for 12 hr. The reaction mixture was cooled to RT and the resin removed by filtration through a glass sinter; washed with methanol (3 × 15 mL) and the filtrate concentrated *in vacuo* to give piperidine **3.34** as a colourless syrup (47.7

mg, 94%). R_f 0.05 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3400s (br, O-H), 2963m, 2872m, 1624s (C=O), 1451s, 1365m, 1292w, 1251w, 1219w, 1101m, 1066m, 1042s, 1002m, 909w, 875w; δ_H (400 MHz, DMSO-d_6) 0.69, 0.76, 0.88 and 0.94 (4 × 3H, 4 × s, 2 × $C(\mathbf{CH_3})_2$), 1.95 and 2.01 (2 × 3H, 2 × s, 2 × N**Ac**), 2.23 (1H, dd, *J* 12.4 and 10.8, H-2$_{ax}$, major rotamer $\mathbf{M_r}$), 2.35 (1H, d, *J* 12.8, H-6$_{ax}$, minor rotamer $\mathbf{m_r}$), 2.76 (1H, dd, *J* 13.2 and 10.0, H-2$_{ax}$, $\mathbf{m_r}$), 2.81 (1H, d, *J* 13.2, H-6$_{ax}$, $\mathbf{m_r}$), 2.91 (1H, d, *J* 9.0, H-4, $\mathbf{M_r}$), 2.93 (1H, d, *J* 8.4, H-4, $\mathbf{m_r}$), 3.18 (1H, ddd, *J* 10.8, 9.0 and 5.6, H-3, $\mathbf{M_r}$), 3.33 (1H, ddd, *J* 10.0, 8.4 and 5.2, H-3, $\mathbf{m_r}$), 3.39 (1H, dd, *J* 13.2 and 2.4, H-6$_{eq}$, $\mathbf{M_r}$), 3.73 (1H, ddd, *J* 13.2, 5.2 and 2.4, H-2$_{eq}$, $\mathbf{m_r}$), 3.94 (1H, dd, *J* 12.8 and 2.4, H-6$_{eq}$, $\mathbf{m_r}$), 4.40 (1H, ddd, *J* 12.4, 5.6 and 2.4, H-2$_{eq}$, $\mathbf{M_r}$), 4.80 and 4.90 (2 × 2H, 2 × br s, 4 × O**H**, $\mathbf{M_r}$ and $\mathbf{m_r}$); δ_C (100.6 MHz, DMSO-d_6) 18.5 and 19.2 ($C(\mathbf{C}H_3)_2$), 22.0 and 22.1 (2 × **A**c), 25.6 and 25.8 ($C(\mathbf{C}H_3)_2$), 37.2 and 37.9 (2 × $\mathbf{C}(CH_3)_2$), 47.2 (C-2, $\mathbf{M_r}$), 51.7 (C-6, $\mathbf{m_r}$), 51.9 (C-2, $\mathbf{m_r}$), 56.7 (C-6, $\mathbf{M_r}$), 68.0 (C-3, $\mathbf{M_r}$), 68.7 (C-3, $\mathbf{m_r}$), 80.1 and 80.2 (2 × C-4, $\mathbf{M_r}$ and $\mathbf{m_r}$), 169.0 (**C**=O, 2 × **Ac**); *m/z* (ES$^+$) 188 (MH$^+$, 100%), 160 (18); Accurate mass (ES$^+$): Found 188.1293, $C_9H_{18}NO_3$ (MH$^+$) requires 188.1287.

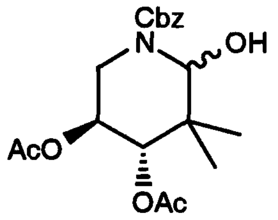
(2*S*,3*S*)-1-(Benzyloxycarbonyl)amino-2,3-di-*O*-acetyl-4,4-dimethylhex-5-en-2,3-diol



3.35

To a stirred solution of aminodiol **3.28** (320 mg, 1.10 mmol) in anhydrous DCM (11.0 mL) cooled to 0 °C was added pyridine (222 μL, 2.75 mmol) and acetic anhydride (520 μL, 5.51 mmol) and the reaction mixture warmed slowly to RT. After 16 hr the solution was cooled to 0 °C and quenched by the dropwise addition of saturated *aq.* $NaHCO_3$ soln. (20 mL). The mixture was partitioned between water (50 mL) and diethyl ether (50 mL); the aqueous layer was separated and extracted with diethyl ether (3 × 25 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 25 mL) to remove traces of pyridine and the crude product purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish the acetylated diol **3.35** as a colourless oil (401 mg, 97%). R_f 0.63 (diethyl ether); $[\alpha]_D^{20}$ –26.4 (*c* 3.06, chloroform); ν_{max}/cm^{-1} (thin film) 3359m (br, N-H), 3066w, 3034w, 2972s, 1743s (C=O), 1638w, 1527m, 1456w, 1418w, 1373m, 1223s, 1148w, 1112w, 1035m, 971w, 915w, 776w, 737w, 698w; δ_H (400 MHz, $CDCl_3$) 1.00 and 1.06 (2 × 3H, 2 × s, $C(\mathbf{CH}_3)_2$), 1.98 and 2.16 (2 × 3H, 2 × s, 2 × **OAc**), 3.08 (1H, ~dt, *J* 14.4 and 5.6, $NH\mathbf{CH_a}H$), 3.35 (1H, ~dt, *J* 14.4 and 7.2, $NHC\mathbf{HH_b}$), 4.85 (1H, d, *J* 2.0, $\mathbf{CH}(OAc)C(CH_3)_2$), 4.97 (1H, br d, *J* 17.6, $CH{=}CH\mathbf{H}_Z$), 4.99 (1H, br d, *J* 10.8, $CH{=}C\mathbf{H}_EH$), 5.07 and 5.11 (2 × 1H, 2 × d, *J* 12.4, $\mathbf{CH}_2Ph$), 5.13 (1H, br t, *J* 5.6, **NH**), 5.26 (1H, ddd, *J* 7.2, 5.6 and 2.0, $NHCH_2\mathbf{CH}(OAc)$), 5.91 (1H, dd, *J* 17.6 and 10.8, $\mathbf{CH}{=}CH_2$), 7.27–7.37 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 20.7 and 21.0 (2 × **Ac**), 23.1 and 24.7 ($C(\mathbf{CH}_3)_2$), 40.2 ($\mathbf{C}(CH_3)_2$), 42.4 ($NH\mathbf{CH}_2$), 66.8 ($\mathbf{CH}_2Ph$), 69.4 ($NHCH_2\mathbf{CH}(OAc)$), 77.1 ($\mathbf{CH}(OAc)C(CH_3)_2$), 112.1 ($CH{=}\mathbf{CH}_2$), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 136.5 (*i*-Ph), 143.3 ($\mathbf{CH}{=}CH_2$) 156.2 (**C**=O, Cbz), 170.1 and 171.2 (**C**=O, 2 × **Ac**); *m/z* (ES^+) 400 (MNa^+, 100%), 395 (MNH_4^+, 27), 378 (MH^+, 47), 334 (23); Accurate mass (ES^+): Found 400.1734, $C_{20}H_{27}NO_6Na$ (MNa^+) requires 400.1736.

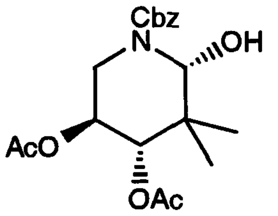
(3*S*,4*S*)-1-*N*-(Benzyloxycarbonyl)-3,4-di-*O*-acetyl-5,5-dimethyl-3,4,6-trihydroxypiperidine



3.36

A stirred solution of aminodiol **3.35** (400 mg, 1.06 mmol) in anhydrous DCM and methanol (5:1, v/v, 24.0 mL) was cooled to -45 °C. Ozone was passed through the solution until a blue colouration persisted; excess ozone was purged from the system with argon. Triphenylphosphine (695 mg, 2.65 mmol) was added and the reaction mixture stirred at -45 °C for 1 hr and then warmed to RT. After 4.5 hr the solvents were removed *in vacuo* and the crude hemiaminal purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish the major diastereomer **3.36a** as a colourless foam (243 mg, 60%) and the minor diastereomer **3.36b** as a colourless syrup (120 mg, 30%).

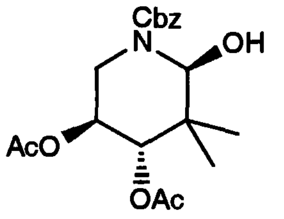
(3*S*,4*S*,6*R*)-1-*N*-(Benzyloxycarbonyl)-3,4-di-*O*-acetyl-5,5-dimethyl-3,4,6-trihydroxypiperidine



3.36a

R$_f$ 0.52 (diethyl ether); $[\alpha]_D^{22}$ +8.24 (*c* 2.15, chloroform); ν_{max}/cm^{-1} (thin film) 3443m (br, O-H), 3033w, 2970m, 2007m, 1746s (C=O), 1709s (C=O), 1498w, 1429m, 1370m, 1326m, 1227s, 1168w, 1130m, 1106w, 1040s, 993w, 969w, 921w, 897w, 846w, 815w, 755w, 699w, 646w, 600m; δ_H (400 MHz, CDCl$_3$) 0.98 and 1.04 (2 × 3H, 2 × s, C(CH$_3$)$_2$), 2.01 and 2.06 (2 × 3H, 2 × s, 2 × OAc), 3.19 (1H, dd, *J* 12.0 and 10.0, H-2$_{ax}$), 4.15–4.30 (1H, m, H-2$_{eq}$), 5.02 (1H, dt, *J* 10.0, 10.0 and 6.4, H-3), 5.10 and 5.15 (2 × 1H, 2 × d, *J* 12.0, CH$_2$Ph), 5.35 (1H, d, *J* 10.0, H-4), 5.40 (1H, br s, H-6), 7.31–7.39 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 19.3 and 23.1 ($C(CH_3)_2$), 20.8 and 20.9 (2 × Ac), 40.4 (C-2), 40.6 ($C(CH_3)_2$), 67.8 (CH_2Ph), 68.2 (C-3), 73.9 (C-4), 83.0 (C-6), 128.0 (Ph), 128.3 (Ph), 128.6 (Ph), 135.9 (*i*-Ph), 156.3 (C=O, Cbz), 170.4 and 170.5 (C=O, 2 × Ac); *m/z* (ES^+) 402 (MNa^+, 100%), 397 (MNH_4^+, 26), 362 (MH^+-H_2O, 72), 318 (24); Accurate mass (ES^+): Found 402.1530, $C_{19}H_{25}NO_7Na$ (MNa^+) requires 402.1529.

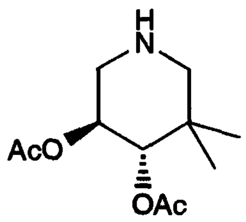
(3*S*,4*S*,6*S*)-1-*N*-(Benzyloxycarbonyl)-3,4-di-*O*-acetyl-5,5-dimethyl-3,4,6-trihydroxypiperidine



3.36b

R_f 0.45 (diethyl ether); $[\alpha]_D^{22}$ +1.87 (*c* 2.68, chloroform); ν_{max}/cm^{-1} (thin film) 3450m (br, O-H), 3033w, 2963m, 1745s (C=O), 1704s (C=O), 1498w, 1429m, 1372m, 1329m, 1244s, 1188m, 1164m, 1121m, 1036s, 1001m, 966w, 933w, 913w, 834w, 739w, 699m, 603m; δ_H (400 MHz, $CDCl_3$) 1.05 and 1.11 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.95 and 2.12 (2 × 3H, 2 × s, 2 × OAc), 3.59 and 4.02 (2 × 1H, 2 × ~br d, *J* 14.6, H-2_{ax} and H-2_{eq}), 4.78–4.81 (1H, m, H-3), 4.82 (1H, d, *J* 1.2, H-6), 5.12 and 5.21 (2 × 1H, 2 × d, *J* 12.0, CH_2Ph), 5.34 (1H, d, *J* 6.8, H-4), 7.30–7.38 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 20.8 (2 × Ac), 20.9 and 24.4 ($C(CH_3)_2$), 37.9 (C-2), 40.7 ($C(CH_3)_2$), 67.4 (CH_2Ph), 68.3 (C-3), 74.0 (C-6), 82.2 (C-4), 127.9 (Ph), 128.2 (Ph), 128.6 (Ph), 136.2 (*i*-Ph), 155.7 (C=O, Cbz), 169.3 and 169.5 (C=O, 2 × Ac); *m/z* (ES^+) 402 (MNa^+, 100%), 397 (MNH_4^+, 11), 362 (MH^+-H_2O, 62), 318 (30); Accurate mass (ES^+): Found 402.1522, $C_{19}H_{25}NO_7Na$ (MNa^+) requires 402.1529.

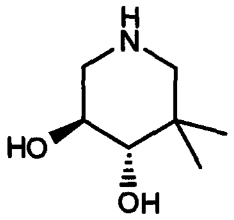
(3*S*,4*S*)-3,4-Di-*O*-acetyl-5,5-dimethyl-3,4-dihydroxypiperidine



3.37

To a stirred solution of hemiaminal **3.36** (188 mg, 0.50 mmol) in absolute ethanol (5.0 mL) was added palladium on carbon (10 wt%, 26.4 mg, 0.025 mmol) and the flask purged with argon and then with hydrogen. The reaction mixture was stirred vigorously at RT under a positive pressure of hydrogen for 16 hr. The flask was purged with argon and the mixture filtered through Celite® to remove the palladium catalyst; the residue was washed with ethanol (3 × 10 mL) and the filtrate concentrated *in vacuo* to give the crude product as a white solid. Recrystallisation from chloroform/diethyl ether furnished piperidine **3.37** as colourless needles (68.1 mg, 60%). R_f 0.11 (ethyl acetate); M.p. 189–190 °C (from chloroform/diethyl ether); $[\alpha]_D^{22}$ +14.5 (*c* 0.62, chloroform); ν_{max}/cm^{-1} (KBr disc) 3465m (br, N-H), 3065m, 2982m, 2889m, 2822w, 2786m, 2746, 2698m, 2659m, 2565w, 2511w, 2438w, 1743s (C=O), 1568w, 1462w, 1430w, 1373m, 1289w, 1236s, 1192w, 1135w, 1101w, 1050m, 1024w, 1011w, 949w, 935w, 893w, 869w, 642w, 603w, 594w; δ_H (400 MHz, $CDCl_3$) 1.13 and 1.23 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.11 and 2.14 (2 × 3H, 2 × s, 2 × OAc), 2.94 and 3.04 (2 × 1H, 2 × d, *J* 13.0, H-6_{ax} and H-6_{eq}), 3.18 (1H, dd, *J* 13.6 and 6.0, H-2_{ax}), 3.44 (1H, dd, *J* 13.6 and 3.6, H-2_{eq}), 4.87 (1H, d, *J* 6.0, H-4), 5.05 (1H, ddd, *J* 6.0, 6.0 and 3.6, H-3), 9.99 (1H, br s, NH); δ_C (100.6 MHz, $CDCl_3$) 20.6 and 21.0 (2 × Ac), 22.3 and 24.3 ($C(CH_3)_2$), 33.9 ($C(CH_3)_2$), 43.3 (C-2), 50.9 (C-6), 65.6 (C-3), 72.9 (C-4), 169.5 (C=O, 2 × Ac); *m/z* (ES^+) 230 (MH^+, 100%); Accurate mass (ES^+): Found 230.1393, $C_{11}H_{20}NO_4$ (MH^+) requires 230.1392.

(3*S*,4*S*)-5,5-Dimethyl-3,4-dihydroxypiperidine

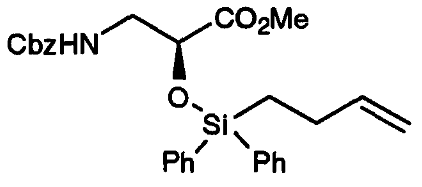


3.38

To a stirred solution of acetylated piperidine **3.37** (41.3 mg, 0.18 mmol) in anhydrous methanol (3.6 mL) was added freshly activated Amberlite® IRA 400 (OH) resin (1.8 mL) and the suspension stirred vigorously at RT for 12 hr.[252] The resin was removed by filtration through a glass sinter; washed with methanol (3 × 5 mL) and the filtrate concentrated *in vacuo* to give the crude product as a white solid. Recrystallisation from methanol/diethyl ether furnished piperidine **3.38** as colourless needles (25.7 mg, 98%). R$_f$ 0.10 (2:1, ethyl acetate:methanol); M.p. 43–45 °C (from methanol/diethyl ether); $[\alpha]_D^{20}$ +63.1 (*c* 0.70, methanol); ν_{max}/cm^{-1} (KBr disc) 3276s (br, N-H, O-H), 2927s, 2859s, 2824s, 1654w, 1541w, 1468m, 1454m, 1421m, 1362m, 1273w, 1169w, 1110m, 1082m, 1048m, 994w, 932m, 913m, 901m, 783w, 635m; δ_H (400 MHz, D_2O) 0.78 and 0.79 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.18 (1H, dd, *J* 12.8 and 10.8, H-2$_{ax}$), 2.24 (1H, d, *J* 13.2, H-6$_{ax}$), 2.44 (1H, dd, *J* 13.2 and 1.6, H-6$_{eq}$), 2.96 (1H, ddd, *J* 12.8, 5.4 and 1.6, H-2$_{eq}$), 3.02 (1H, d, *J* 9.4, H-4), 3.46 (1H, ddd, *J* 10.8, 9.4 and 5.4, H-3); δ_C (100.6 MHz, D_2O) 17.8 and 25.1 ($C(CH_3)_2$), 36.9 ($C(CH_3)_2$), 50.6 (C-2), 56.3 (C-6), 69.1 (C-3), 80.7 (C-4); *m/z* (ES$^+$) 146 (MH$^+$, 100%); Accurate mass (ES$^+$): Found 146.1187, $C_7H_{16}NO_2$ (MH$^+$) requires 146.1181.

Chapter 5 Compounds

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(but-3-enyl)diphenylsilanyloxy]isoserinate

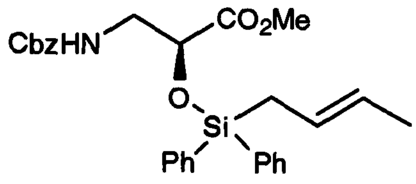


5.05

To a stirred solution of but-3-enyl(diphenyl)silane[80,114] (934 mg, 3.92 mmol) and methyl (*S*)-*N*-(benzyloxycarbonyl)isoserinate **3.05** (992 g, 3.92 mmol) in anhydrous DCM (4.0 mL), was added tris(pentafluorophenyl)borane (100 mg, 0.20 mmol) and the reaction mixture heated at reflux for 16 hr. The solution was allowed to cool to RT and then partitioned between water (50 mL) and diethyl ether (50 mL); the aqueous layer was separated and extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish **5.05** as a colourless syrup (1.34 g, 70%). R_f 0.26 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –16.2 (*c* 1.03, chloroform); ν_{max}/cm^{-1} (thin film) 3355m (br, N-H), 3070m, 3001m, 2951m, 1726s (C=O), 1638w, 1589w, 1515m, 1429m, 1244m, 1118s, 996m, 910w, 740m, 700s; δ_H (400 MHz, $CDCl_3$) 1.26-1.38 (2H, m, $\mathbf{SiCH_2}$), 2.07–2.22 (2H, m, $\mathbf{CH_2}$CH=), 3.54 (2H, ~t, *J* 5.6, NH$\mathbf{CH_2}$), 3.58 (3H, s, $CO_2\mathbf{CH_3}$), 4.34 (1H, t, *J* 5.6, O**CH**), 4.91 (1H, ~dd, *J* 10.4 and 1.6, CH=C$\mathbf{H_E}$H), 5.00 (1H, ~dd, *J* 16.8 and 1.6, CH=CH$\mathbf{H_Z}$), 5.08 (2H, s, $\mathbf{CH_2}$Ph), 5.11 (1H, br t, *J* 5.6, **NH**), 5.89 (1H, ddt, *J* 16.8, 10.4 and 6.4, **CH**=CH_2), 7.26–7.50 (10H, m, Ph), 7.56–7.60 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.8 ($SiCH_2$), 26.8 (CH_2CH=), 44.7 ($NHCH_2$), 52.0 (CO_2CH_3), 66.8 (CH_2Ph), 71.3 (OCH), 113.2 (CH=CH_2), 128.0 (Ph), 128.1 (Ph), 128.5 (Ph), 130.3 (Ph), 133.6 (*i*-Ph), 134.8 (Ph), 134.9 (Ph), 136.4 (*i*-Ph, Cbz), 140.8 (CH=CH_2), 156.0

(C=O, Cbz), 171.5 (CO_2CH_3); *m/z* (ES^+) 512 (MNa^+, 100%), 490 (MH^+, 22), 194 (20); Accurate mass (ES^+): Found 490.2050, $C_{28}H_{32}NO_5Si$ (MH^+) requires 490.2050.

(*S*)-Methyl *N*-(benzyloxycarbonyl)[(*E*-but-2-enyl)diphenylsilanyloxy]isoserinate[80,195]

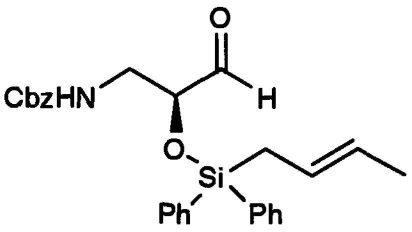


5.06

(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium (I) hexafluorophosphate (20.3 mg, 0.024 mmol) was dissolved in anhydrous DCM (3.5 mL) and cooled to -78 °C. The Ir (I) catalyst was activated by passing hydrogen through the solution until the colour changed from blood-red to colourless. The reaction vessel was purged with argon to remove any remaining hydrogen and the solution was warmed to 0 °C. A solution of ester **5.05** (1.15 g, 2.35 mmol) in anhydrous DCM (12.0 mL) was cooled to 0 °C and then added *via* cannula to the solution of pre-activated catalyst. The resulting mixture was stirred at 0 °C and the reaction progress monitored by ^1H NMR. After 35 min the solvent was removed *in vacuo*; the resulting material was triturated with diethyl ether, the extracts filtered though a short plug of silica gel and Celite® and the solvents removed from the filtrate *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 4:1, petrol:diethyl ether) to furnish the isomerised product **5.06** as a colourless oil (1.15 g, 100%). R_f 0.44 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –10.3 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3360m (br, N-H), 3070m, 3048m, 3015m, 2952m, 2884m, 2854w, 1754s (C=O), 1727s (C=O), 1590w, 1515s, 1429s, 1303m, 1245s, 1119s, 998m, 967m; δ_H (400 MHz, C_6D_6) 1.61 (3H, ~dd, *J* 6.2 and 1.0, =CH**CH_3**), 2.30 (2H, br d, *J* 8.0, Si**CH_2**), 3.27 (3H, s, CO_2**CH_3**), 3.61 (2H, ~t, *J* 5.6, NH**CH_2**), 4.52 (1H, t, *J* 5.6, O**CH**), 4.98 (1H, t, *J* 5.6, N**H**), 5.11 and 5.16 (2 × 1H, 2 × d, *J* 12.0, **CH_2**Ph), 5.42–5.69 (2H, m, **CH**=**CH**CH_3), 7.25–7.34 (10H, m, Ph), 7.78–7.81 (5H, m, Ph); δ_C (100.6 MHz, C_6D_6) 18.4

(=$CHCH_3$), 20.5 ($SiCH_2$), 45.3 ($NHCH_2$), 51.6 (CO_2CH_3), 66.9 (CH_2Ph), 72.1 (OCH), 125.2 (CH=$CHCH_3$), 126.4 (CH=$CHCH_3$), 128.4–128.8 (Ph), 130.5 (Ph), 134.7 (*i*-Ph), 135.6 (Ph), 135.8 (Ph), 137.5 (*i*-Ph, Cbz), 156.5 (C=O, Cbz), 171.6 (CO_2CH_3);[250] *m/z* (ES^+) 512 (MNa^+, 90%), 507 (MNH_4^+, 40), 490 (MH^+, 14), 434 (M^+-C_4H_7, 100), 412 (17); Accurate mass (ES^+): Found 512.1862, $C_{28}H_{31}NO_5Si$ (MNa^+) requires 512.1869.

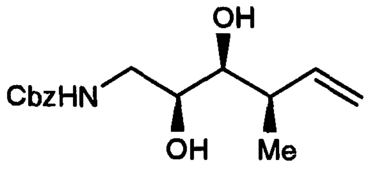
(*S*)-*N*-(Benzyloxycarbonyl)[(*E*-but-2-enyl)diphenylsilanyloxy]isoserinal



5.07

To a stirred solution of silyl isoserinate **5.06** (1.14 g, 2.33 mmol) in anhydrous DCM (23.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 3.50 mL, 3.50 mmol) dropwise and the solution stirred at -78 °C for 2 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (5 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 50 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic extracts washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 3:1, petrol:diethyl ether) to furnish aldehyde **5.07** as a colourless syrup (537 mg, 50%). R_f 0.21 (1:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ +1.27 (*c* 1.02, chloroform); ν_{max}/cm^{-1} (thin film) 3423m (br, N-H), 3069m, 3049m, 3014m, 2932m, 2854w, 1722s (C=O), 1517s, 1454w, 1428m, 1258m, 1153m, 1118s, 998w, 968w, 910w, 739s, 700s; δ_H (500 MHz, C_6D_6) 1.48 (3H, d, *J* 6.5, =$CHCH_3$), 2.06–2.15 (2H, m, $SiCH_2$), 3.15 and 3.28 (2 x 1H, ~dt, *J* 14.0 and 5.5, $NHCH_2$), 3.97 (1H, t, *J* 5.5, OCH), 4.58 (1H, t, *J* 5.5, NH), 4.96 and 5.02 (2 x 1H, 2 x d, *J* 12.5, CH_2Ph), 5.32 (1H, dq, *J* 15.8 and 6.5, CH=$CHCH_3$), 5.46 (1H, dt, *J* 15.8 and 8.0, CH=CHCH$_3$), 7.16–7.25 (10H, m, Ph), 7.54–7.72 (5H, m, Ph), 9.27 (1H, br s, CHO); δ_C (125.7 MHz, C_6D_6) 18.5 (=CHCH$_3$), 20.5 (SiCH$_2$), 43.0 (NHCH$_2$), 67.2 (CH$_2$Ph), 77.6 (OCH), 125.0 (CH=CHCH$_3$), 126.8 (CH=CHCH$_3$), 128.1–135.5 (Ph), 134.6 (*i*-Ph), 137.5 (*i*-Ph, Cbz), 156.6 (C=O, Cbz), 200.2 (CHO);[250] *m/z* (ES$^+$) 477 (MNH$_4^+$, 100%), 460 (MH$^+$, 73); Accurate mass (ES$^+$): Found 460.1946, $C_{27}H_{30}NO_4Si$ (MH$^+$) requires 460.1944.

(2*S*,3*S*,4*R*)-1-(Benzyloxycarbonyl)amino-4-methylhex-5-en-2,3-diol

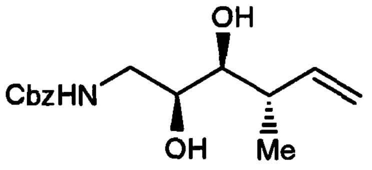


5.09

A stirred solution of aldehyde **5.07** (419 mg, 0.91 mmol) in anhydrous toluene (4.5 mL) was heated at 130 °C in a base-washed sealed tube. After 17 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The crude siladioxolane was dissolved in methanol (9.0 mL); KF (159 mg, 2.74 mmol) and H_2O_2 (35% in water, 1.0 mL) were added and the reaction mixture was stirred at RT for 4 hr. The solvent was removed *in vacuo*; the crude residue was triturated with diethyl ether and the combined extracts were filtered through Celite® and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to give diol **5.09** as a colourless crystalline solid (205 mg, 80%). R$_f$ 0.27 (diethyl ether); M.p. 82–85 °C (from diethyl ether); $[\alpha]_D^{22}$ –3.00 (*c* 1.01, chloroform); ν_{max}/cm^{-1} (KBr disc) 3456m and 3343m (br, N-H, O-H), 2974m, 2951m, 2906m, 1671s (C=O), 1552s, 1441m, 1350m, 1277s, 1131s, 1054m, 1036m, 916m, 780w, 750m; δ_H (400 MHz, DMSO-d$_6$) 1.00 (3H, d, *J* 6.4, CH(C**H**$_3$)), 2.31–2.41 (1H, m, C**H**(CH$_3$)), 3.01–3.10 (3H, m, NHC**H**$_2$ and C**H**(OH)CH(CH$_3$)), 3.52 (1H, ddt, *J* 13.6, 6.8 and 2.0, NHCH$_2$C**H**(OH)), 4.18 (1H, d, *J* 8.0, CH(O**H**)CH(CH$_3$)), 4.37 (1H, d, *J* 6.8, NHCH$_2$CH(O**H**)), 4.94 (1H, dd, *J* 10.2 and 2.0, CH=C**H**$_E$H), 5.00 and 5.03 (2 × 1H, 2 × d, *J* 12.6, C**H**$_2$Ph), 5.02 (1H, ddd, *J* 17.2, 2.0 and 1.2, CH=CH**H**$_Z$), 5.71 (1H, ddd, *J* 17.2, 10.2 and

8.0, CH=CH$_2$), 7.11 (1H, t, J 5.6, NH), 7.30–7.40 (5H, m, Ph); δ$_C$ (100.6 MHz, DMSO-d$_6$) 17.3 (CH(CH$_3$)), 41.1 (CH(CH$_3$)), 45.1 (NHCH$_2$), 66.0 (CH$_2$Ph), 70.1 (NHCH$_2$CH(OH)), 74.9 (CH(OH)CH(CH$_3$)), 115.1 (CH=CH$_2$), 128.6 (Ph), 129.2 (2 × Ph), 138.1 (*i*-Ph), 142.8 (CH=CH$_2$), 157.2 (C=O, Cbz); *m/z* (ES$^+$) 302 (MNa$^+$, 100%), 280 (MH$^+$, 37), 236 (81); Accurate mass (ES$^+$): Found 302.1371, $C_{15}H_{21}NO_4Na$ (MNa$^+$) requires 302.1368.

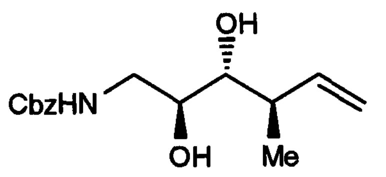
(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)amino-4-methylhex-5-en-2,3-diol



5.11

A stirred solution of aldehyde **3.13** (490 mg, 1.07 mmol) in anhydrous toluene (5.5 mL) was heated at 130 °C in a base-washed sealed tube. After 24 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo* to furnish the crude siladioxolane **5.10** R$_f$ 0.60 (1:2, petrol:diethyl ether); δ$_H$ (400 MHz, toluene-d$_8$) 1.12 (3H, d, *J* 7.2, CH(CH$_3$)), 2.25–2.29 (1H, m, CH(CH$_3$)), 3.15 (1H, ~dt, *J* 13.6 and 6.4, NHCH$_a$H), 3.39 (1H, ddd, *J* 13.6, 6.4 and 3.2, NHCHH$_b$), 3.86 (1H, dd, *J* 6.4 and 3.6, CH(OH)CH(CH$_3$)), 4.14 (1H, dt, *J* 6.4 and 3.2, NHCH$_2$CH(OH)), 4.84 (1H, t, *J* 6.4, NH), 4.90–5.04 (2H, m, CH=CH$_2$), 4.98 and 5.07 (2 × 1H, 2 × d, *J* 12.0, CH$_2$Ph), 5.92 (1H, ddd, *J* 17.6, 10.0 and 8.0, CH=CH$_2$), 7.05–7.25 and 7.61–7.75 (15H, m, Ph); δ$_C$ (100.6 MHz, toluene-d$_8$) 17.1 (CH(CH$_3$)), 42.3 (CH(CH$_3$)), 45.3 (NHCH$_2$), 66.7 (CH$_2$Ph), 77.8 (NHCH$_2$CH(OH)), 81.3 (CH(OH)CH(CH$_3$)), 116.1 (CH=CH$_2$), 128.2–128.9 (Ph), 134.7–135.3 (Ph), 130.7 (*i*-Ph), 137.7 (*i*-Ph, Cbz), 139.5 (CH=CH$_2$) 156.2 (C=O, Cbz);[250] *m/z* (APCI$^+$) 460 (MH$^+$, 100%), 416 (58), 382 (37), 338 (60), 292 (58), 248 (41), 183 (16). The crude product was dissolved in methanol (10.5 mL); KF (187 mg, 3.22 mmol) and H_2O_2 (35% in water, 1.0 mL) were added and the reaction mixture was stirred at RT for 14 hr. The solvent was removed *in vacuo*; the crude residue was triturated with diethyl ether and the combined extracts were filtered through Celite® and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to give the major product **5.11** as a colourless crystalline solid (233 mg, 78%) and a minor product **5.12** as a colourless semi-solid (22.1 mg, 7%). R_f 0.24 (diethyl ether); M.p. 77–79 °C (from diethyl ether); $[\alpha]_D^{22}$ −19.4 (*c* 1.08, chloroform); ν_{max}/cm^{-1} (KBr disc) 3481m and 3348m (br, N-H, O-H), 3066m, 3034m, 2980m, 2932m, 2884m, 1672s (C=O), 1643m, 1548s, 1440m, 1276s, 1109m, 1034m, 906m, 752m; δ_H (400 MHz, DMSO-d_6) 0.92 (3H, d, *J* 7.2, CH(**CH$_3$**)), 2.33 (1H, ddq, *J* 7.2, 7.2 and 6.8, **CH**(CH$_3$)), 2.98–3.14 (3H, m, NH**CH$_2$** and **CH**(OH)CH(CH$_3$)), 3.49 (1H, ddt, *J* 10.8, 6.4 and 3.6, NHCH$_2$**CH**(OH)), 4.22 (1H, d, *J* 6.8, CH(**OH**)CH(CH$_3$)), 4.49 (1H, d, *J* 6.4, NHCH$_2$CH(**OH**)), 4.94 (1H, dd, *J* 10.0 and 1.2, CH=C**H$_E$**H), 4.96–5.01 (1H, m, CH=CH**H$_Z$**), 4.99 and 5.03 (2 × 1H, 2 × d, *J* 12.6, **CH$_2$**Ph), 5.89 (1H, ddd, *J* 17.6, 10.0 and 7.2, **CH**=CH$_2$), 7.11 (1H, t, *J* 5.6, **NH**), 7.29–7.38 (5H, m, Ph); δ_C (100.6 MHz, DMSO-d_6) 17.5 (CH(CH$_3$)), 40.6 (CH(CH$_3$)), 44.7 (NHCH$_2$), 66.0 (CH$_2$Ph), 70.4 (NHCH$_2$CH(OH)), 75.2 (CH(OH)CH(CH$_3$)), 114.6 (CH=CH$_2$), 128.5 (Ph), 129.2 (2 × Ph), 138.1 (*i*-Ph), 142.9 (CH=CH$_2$), 157.2 (C=O, Cbz); *m/z* (ES$^+$) 302 (MNa$^+$, 100%), 280 (MH$^+$, 33), 236 (82); Accurate mass (ES$^+$): Found 302.1363, $C_{15}H_{21}NO_4Na$ (MNa$^+$) requires 302.1368.

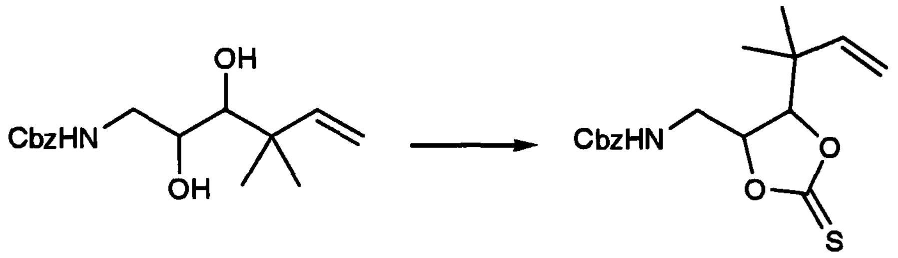
(2*S*,3*R*,4*R*)-1-(Benzyloxycarbonyl)amino-4-methylhex-5-en-2,3-diol



5.12

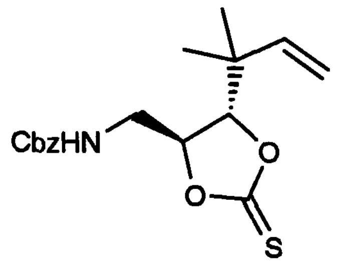
R_f 0.33 (diethyl ether); $[\alpha]_D^{22}$ +17.5 (*c* 0.49, chloroform); ν_{max}/cm^{-1} (KBr disc) 3400s and 3338s (br, N-H, O-H), 3069m, 3037m, 3000m, 2958m, 2928m, 2869m, 1667s (C=O), 1547s, 1440m, 1367w, 1282m, 1149w, 1071m, 1011w, 971w, 919w; δ_H (400 MHz, DMSO-d_6) 0.99 (3H, d, *J* 7.2, CH(**CH$_3$**)), 2.48–2.55 (1H, m, **CH**(CH$_3$)), 2.92 (1H, ddd, *J* 13.2, 8.2 and 5.6, NHC**H**$_a$H) 3.11 (1H, ddd, *J* 8.2, 6.0 and 2.8, C**H**(OH)CH(CH$_3$)), 3.30 (1H, ddt, *J* 8.2, 6.4 and 2.8, NHCH$_2$C**H**(OH)), 3.37 (1H, ddd, *J* 13.2, 5.6 and 2.8, NHCH**H**$_b$), 4.58 (1H, d, *J* 6.4, NHCH$_2$CH(O**H**)), 4.63 (1H, d, *J* 6.0, CH(O**H**)CH(CH$_3$)), 4.96 (1H, dd, *J* 10.4 and 2.4, CH=C**H**$_E$H), 4.98 and 5.03 (2 × 1H, 2 × d, *J* 12.8, C**H**$_2$Ph), 4.99 (1H, dd, *J* 17.2 and 2.4, CH=CH**H**$_Z$), 5.80 (1H, ddd, *J* 17.2, 10.4 and 8.4, C**H**=CH$_2$), 6.95 (1H, t, *J* 5.6, N**H**), 7.30–7.37 (5H, m, Ph); δ_C (100.6 MHz, DMSO-d$_6$) 18.5 (CH(CH$_3$)), 39.6 (CH(CH$_3$)), 45.4 (NHCH$_2$), 66.1 (CH$_2$Ph), 71.5 (NHCH$_2$CH(OH)), 76.4 (CH(OH)CH(CH$_3$)), 115.6 (CH=CH$_2$), 128.6 (Ph), 129.2 (2 × Ph), 139.1 (*i*-Ph), 141.2 (CH=CH$_2$), 157.3 (C=O, Cbz); *m/z* (ES$^+$) 302 (MNa$^+$, 100%), 280 (MH$^+$, 25), 236 (60); Accurate mass (ES$^+$): Found 302.1371, $C_{15}H_{21}NO_4Na$ (MNa$^+$) requires 302.1368.

General procedure for thiocarbonate synthesis



To a stirred solution of the diol (0.10 mmol) in anhydrous THF (2.0 mL) was added 1,1-thiocarbonyldiimidazole (0.20 mmol) and the mixture heated at reflux. After 20 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The crude thiocarbonate was purified by flash column chromatography (silica gel, 3:2, petrol:diethyl ether).

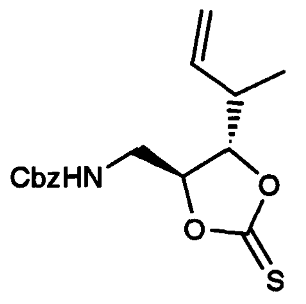
(4*S*,5*S*)-5-[(Benzyloxycarbonyl)amino]methyl-4-(1,1-dimethylprop-2-enyl)-1,3-dioxolane-2-thione



5.13

On a 0.12 mmol scale the reaction gave thiocarbonate **5.13** as a colourless oil (37.5 mg, 89%). R_f 0.62 (diethyl ether); $[\alpha]_D^{22}$ +15.4 (*c* 1.51, chloroform); ν_{max}/cm^{-1} (thin film) 3337s (br, N-H), 3088w, 3034w, 2971m, 1704s (C=O), 1520s, 1455m, 1282s, 1166s, 1092w, 1049m, 978s, 929m; δ_H (400 MHz, $CDCl_3$) 1.13 and 1.14 (2 × 3H, 2 × s, C($\mathbf{CH_3}$)$_2$), 3.44–3.56 (2H, m, NH$\mathbf{CH_2}$), 4.41 (1H, d, *J* 6.0, **CH**(OR)C(CH_3)$_2$), 4.64 (1H, td, *J* 6.0 and 4.4, NHCH_2**CH**(OR)), 5.10 and 5.16 (2 × 1H, 2 × d, *J* 12.4, $\mathbf{CH_2}$Ph), 5.20 (1H, d, *J* 17.6, CH=CH$\mathbf{H_Z}$), 5.21 (1H, t, *J* 6.4, **NH**), 5.25 (1H, d, *J* 10.4, CH=C$\mathbf{H_E}$H), 5.74 (1H, dd, *J* 17.6 and 10.4, **CH**=CH_2), 7.31–7.40 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 21.5 and 22.6 (C(CH_3)$_2$), 39.9 (C(CH_3)$_2$), 43.4 (NHCH_2), 67.4 (CH_2Ph), 81.9 (NHCH_2CH(OR)), 89.7 (CH(OR)C(CH_3)$_2$), 116.7 (CH=CH_2), 128.1 (Ph), 128.4 (Ph), 128.6 (Ph), 135.8 (*i*-Ph), 139.6 (CH=CH_2), 153.2 (C=S), 156.7 (C=O, Cbz); *m/z* (ES^+) 358 (MNa^+, 29%), 336 (MH^+, 100), 209 (28); Accurate mass (ES^+): Found 336.1270, $C_{17}H_{22}NO_4S$ (MH^+) requires 336.1270.

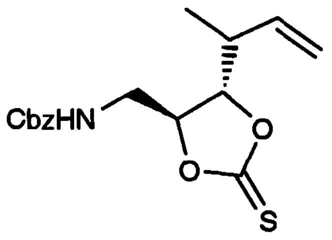
(4*S*,5*S*)-5-[(Benzyloxycarbonyl)amino]methyl-4-(1-methylprop-2-enyl)-1,3-dioxolane-2-thione



5.15

On a 0.10 mmol scale the reaction gave thiocarbonate **5.15** as a colourless oil (30.4 mg, 95%). R_f 0.58 (diethyl ether); $[\alpha]_D^{22}$ +22.0 (*c* 1.17, chloroform); ν_{max}/cm^{-1} (thin film) 3412s (br, N-H), 2968m, 1705s (C=O), 1623m, 1455w, 1292s, 1164m, 1045w, 975w, 738w, 697m; δ_H (400 MHz, CDCl$_3$) 1.18 (3H, d, *J* 6.8, CH(C**H**$_3$)), 2.54–2.65 (1H, m, C**H**(CH$_3$)), 3.52–3.56 (2H, m, NHC**H**$_2$), 4.49 (1H, t, *J* 7.0, C**H**(OR)CH(CH$_3$)), 4.66 (1H, dt, *J* 7.0 and 4.0, NHCH$_2$C**H**(OR)), 5.10 and 5.16 (2 × 1H, 2 × d, *J* 12.2, C**H**$_2$Ph), 5.20–5.29 (3H, m, CH=C**H**$_2$ and N**H**), 5.66 (1H, ddd, *J* 17.6, 9.6 and 8.0, C**H**=CH$_2$), 7.32–7.41 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 15.5 (CH(CH$_3$)), 41.4 (CH(CH$_3$)), 42.7 (NHCH$_2$), 67.4 (CH$_2$Ph), 83.5 (NHCH$_2$CH(OR)), 86.4 (CH(OR)CH(CH$_3$)), 119.2 (CH=CH$_2$), 128.1 (Ph), 128.4 (Ph), 128.6 (Ph), 135.4 (CH=CH$_2$), 135.8 (*i*-Ph), 153.1 (C=S), 156.7 (C=O, Cbz); *m/z* (ES$^+$) 344 (MNa$^+$, 12%), 322 (MH$^+$, 100), 301 (13), 195 (11); Accurate mass (ES$^+$): Found 322.1112, $C_{16}H_{20}NO_4S$ (MH$^+$) requires 322.1113.

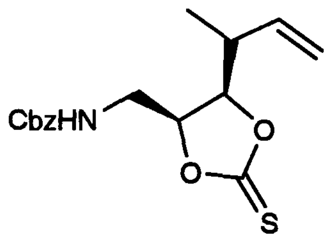
(4*S*,5*S*)-5-[(Benzyloxycarbonyl)amino]methyl-4-(1-methylprop-2-enyl)-1,3-dioxolane-2-thione



5.17

On a 0.084 mmol scale the reaction gave thiocarbonate **5.17** as a colourless oil (26.2 mg, 97%). R_f 0.54 (diethyl ether); $[\alpha]_D^{22}$ +10.3 (*c* 1.31, chloroform); ν_{max}/cm^{-1} (thin film) 3326m (br, N-H), 3066w, 3033w, 2969m, 1801w, 1710s (C=O), 1521m, 1455w, 1336s, 1290s, 1170m, 1045m, 999m, 928m, 735m, 698m; δ_H (400 MHz, CDCl$_3$) 1.16 (3H, d, *J* 6.8, CH(C**H**$_3$)), 2.60 (1H, ddq, *J* 7.6, 6.8 and 6.8, C**H**(CH$_3$)), 3.51–3.57 (2H, m, NHC**H**$_2$), 4.64 (1H, dd, *J* 6.8 and 4.4, C**H**(OR)CH(CH$_3$)), 4.67 (1H, td, *J* 6.0 and 4.4, NHCH$_2$C**H**(OR)), 5.10 and 5.15 (2 × 1H, 2 × d, *J* 12.2, C**H**$_2$Ph), 5.19–5.28 (3H, m, CH=C**H**$_2$ and N**H**), 5.71 (1H, ddd, *J* 17.6, 10.4 and 7.6, CH=CH$_2$), 7.31–7.43 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 14.6 (CH(CH$_3$)), 40.2 (CH(CH$_3$)), 42.7 (NHCH$_2$), 67.4 (CH$_2$Ph), 82.7 (NHCH$_2$CH(OR)), 86.6 (CH(OR)CH(CH$_3$)), 119.0 (CH=CH$_2$), 128.1 (Ph), 128.4 (Ph), 128.6 (Ph), 135.1 (CH=CH$_2$), 135.8 (*i*-Ph), 154.1 (C=S), 156.8 (C=O, Cbz); *m/z* (APCI$^+$) 322 (MH$^+$, 48%), 236 (27), 182 (44), 171 (51), 153 (100); Accurate mass (ES$^+$): Found 322.1109, $C_{16}H_{20}NO_4S$ (MH$^+$) requires 322.1113.

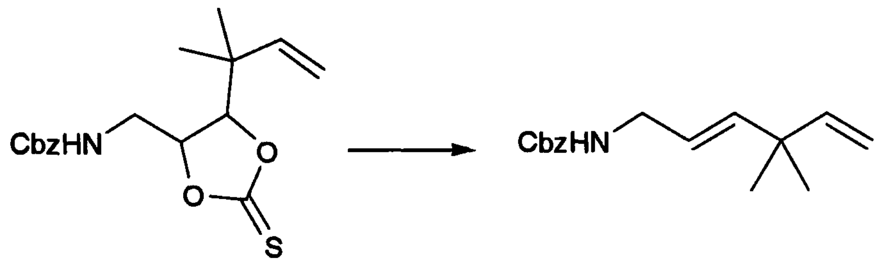
(4*R*,5*S*)-5-[(Benzyloxycarbonyl)amino]methyl-4-(1-methylprop-2-enyl)-1,3-dioxolane-2-thione



5.19

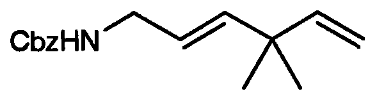
On a 0.048 mmol scale the reaction gave thiocarbonate **5.19** as a colourless oil (11.6 mg, 75%). R$_f$ 0.58 (diethyl ether); $[\alpha]_D^{22}$ −101.8 (*c* 0.57, chloroform); ν_{max}/cm^{-1} (thin film) 3124s (br, N-H), 2965m, 1701s (C=O), 1519m, 1451w, 1298s, 1160m, 975m; δ_H (400 MHz, CDCl$_3$) 1.20 (3H, d, *J* 7.2, CH(C**H**$_3$)), 2.58–2.69 (1H, m, C**H**(CH$_3$)), 3.39 (1H, ddd, *J* 14.8, 9.6 and 4.4, NHC**H$_a$**H), 3.85 (1H, ddd, *J* 14.8, 8.2 and 2.6, NHCH**H$_b$**), 4.71 (1H, t, *J* 7.4, C**H**(OR)CH(CH$_3$)), 4.97 (1H, ddd, *J* 9.6, 7.4 and 2.6, NHCH$_2$C**H**(OR)), 5.11 and 5.14 (2 × 1H, 2 × d, *J* 12.4, C**H$_2$**Ph), 5.19–5.26 (3H, m, CH=C**H$_2$** and N**H**), 5.82 (1H, ddd, *J* 17.6, 10.4 and 7.6, C**H**=CH$_2$), 7.32–7.41 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 17.4 (CH(CH$_3$)), 37.1 (CH(CH$_3$)), 39.6 (NHCH$_2$), 67.3 (CH$_2$Ph), 82.8 (NHCH$_2$CH(OR)), 86.5 (CH(OR)CH(CH$_3$)), 118.0 (CH=CH$_2$), 128.1 (Ph), 128.3 (Ph), 128.6 (Ph), 136.6 (CH=CH$_2$), 136.7 (*i*-Ph), 154.5 (C=S), 157.1 (C=O, Cbz); *m/z* (ES$^+$) 322 (MH$^+$, 74%), 304 (19), 183 (41), 154 (100); Accurate mass (ES$^+$): Found 322.1115, $C_{16}H_{20}NO_4S$ (MH$^+$) requires 322.1113.

General procedure for diene synthesis



A stirred solution of the thiocarbonate (0.10 mmol) in triethylphosphite (2.0 mL) was heated at reflux. After 2.5 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The residual oil was azeotroped with toluene (3 × 5 mL) and the crude diene purified by flash column chromatography (silica gel, 9:1, petrol:diethyl ether).

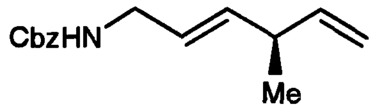
1-(Benzyloxycarbonyl)amino-4,4-dimethylhexa-2(*E*),5-diene



5.14

On a 0.084 mmol scale the reaction gave diene **5.14** as a colourless oil (18.6 mg, 85%). R_f 0.55 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3336m (br, N-H), 3066w, 3034w, 2963m, 2869w, 1702s (C=O), 1529m, 1456w, 1360w, 1246s, 1135m, 975m, 914m; δ_H (400 MHz, CDCl$_3$) 1.10 (6H, 2 × s, C(C**H**$_3$)$_2$), 3.80 (2H, t, *J* 6.0, NHC**H**$_2$), 4.76 (1H, br s, N**H**), 4.94 (1H, dd, *J* 10.8 and 1.2, CH=C**H**$_E$H), 4.95 (1H, dd, *J* 17.2 and 1.2, CH=CH**H**$_Z$), 5.12 (2H, s, C**H**$_2$Ph), 5.41 (1H, dt, *J* 15.8 and 6.0, NHCH$_2$C**H**=), 5.61 (1H, dt, *J* 15.8 and 1.2, =C**H**C(CH$_3$)$_2$), 5.80 (1H, dd, *J* 17.2 and 10.8, C**H**=CH$_2$), 7.30–7.39 (5H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 26.8 (C(CH$_3$)$_2$), 39.0 (C(CH$_3$)$_2$), 43.1 (NHCH$_2$), 66.7 (CH$_2$Ph), 110.9 (CH=CH$_2$), 122.6 (NHCH$_2$CH=), 128.1 (2 × Ph), 128.5 (Ph), 136.6 (*i*-Ph), 141.4 (=CHC(CH$_3$)$_2$), 146.7 (CH=CH$_2$), 156.8 (C=O, Cbz); *m/z* (APCI$^+$) 260 (MH$^+$, 29%), 215 (44), 199 (100), 156 (27), 151 (87); Accurate mass (CI$^+$): Found 260.1649, $C_{16}H_{22}NO_2$ (MH$^+$) requires 260.1651.

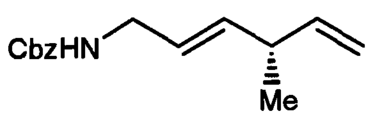
(4*R*)-1-(Benzyloxycarbonyl)amino-4-methylhex-2(*E*),5-diene



5.16

On a 0.063 mmol scale the reaction gave diene **5.16** as a colourless oil (15.1 mg, 98%). R_f 0.62 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –6.58 (*c* 0.73, chloroform); ν_{max}/cm^{-1} (thin film) 3336m (br, N-H), 3033w, 2964m, 2922m, 1703s (C=O), 1530m, 1455m, 1363w, 1250s, 1134w, 1046w, 972m; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.2, CH($\mathbf{CH_3}$)), 2.80–2.91 (1H, m, **CH**(CH_3)), 3.80 (2H, ~t, *J* 5.6, NH$\mathbf{CH_2}$), 4.77 (1H, br s, N**H**), 4.97 (1H, ~dt, *J* 10.4 and 1.6, CH=C$\mathbf{H_E}$H), 4.99 (1H, ~dt, *J* 17.2 and 1.6, CH=CH$\mathbf{H_Z}$), 5.12 (2H, s, $\mathbf{CH_2}$Ph), 5.46 (1H, dt, *J* 15.6 and 5.6, $NHCH_2$**CH**=), 5.58 (1H, dd, *J* 15.6 and 6.4, =**CH**CH(CH_3)), 5.76 (1H, ddd, *J* 17.2, 10.4 and 6.8, **CH**=CH_2), 7.31–7.38 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 19.6 (CH(CH_3)), 39.9 (CH(CH_3)), 42.9 ($NHCH_2$), 66.7 (CH_2Ph), 113.2 (CH=CH_2), 124.9 ($NHCH_2$CH=), 128.1 (2 × Ph), 128.5 (Ph), 136.6 (*i*-Ph), 136.8 (=CHC(CH_3)$_2$), 142.2 (CH=CH_2), 156.1 (C=O, Cbz); *m/z* (ES^+) 268 (MNa^+, 100%), 263 (MNH_4^+, 30), 255 (14), 246 (MH^+, 84), 241 (10), 236 (20); Accurate mass (ES^+): Found 246.1488, $C_{15}H_{20}NO_2$ (MH^+) requires 246.1494.

(4*S*)-1-(Benzyloxycarbonyl)amino-4-methylhex-2(*E*),5-diene

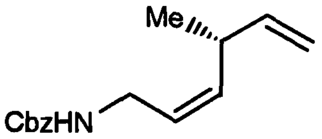


5.18

On a 0.068 mmol scale the reaction gave diene **5.18** as a colourless oil (13.7 mg, 82%). R_f 0.62 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +6.22 (*c* 0.37, chloroform); ν_{max}/cm^{-1} (thin film) 3420s (br, N-H), 3094m, 3028m, 2963m, 2920w, 1695s (C=O), 1638m, 1529m, 1454w, 1247s, 1132w, 1045w, 970w, 912w; δ_H (500 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.5, CH($\mathbf{CH_3}$)), 2.86 (1H, ddq, *J* 7.0, 6.5 and 6.5, **CH**(CH_3)), 3.80 (2H, ~t, *J* 5.5, NH$\mathbf{CH_2}$), 4.78 (1H, br s, N**H**), 4.97

(1H, ~dt, *J* 10.0 and 1.5, CH=CH$_E$H), 5.00 (1H, ~dt, *J* 17.0 and 1.5, CH=CHH$_Z$), 5.12 (2H, s, CH$_2$Ph), 5.46 (1H, dt, *J* 15.5 and 5.5, NHCH$_2$CH=), 5.59 (1H, dd, *J* 15.5 and 6.5, =CHCH(CH$_3$)), 5.76 (1H, ddd, *J* 17.0, 10.0 and 7.0, CH=CH$_2$), 7.30–7.39 (5H, m, Ph); δ_C (125.7 MHz, CDCl$_3$) 19.5 (CH(CH$_3$)), 39.8 (CH(CH$_3$)), 42.8 (NHCH$_2$), 66.6 (CH$_2$Ph), 113.1 (CH=CH$_2$), 124.8 (NHCH$_2$CH=), 128.0 (2 × Ph), 128.4 (Ph), 136.4 (*i*-Ph), 136.6 (=CHC(CH$_3$)$_2$), 142.1 (CH=CH$_2$), 156.1 (C=O, Cbz); *m/z* (ES$^+$) 268 (MNa$^+$, 100%), 246 (MH$^+$, 13), 152 (8); Accurate mass (ES$^+$): Found 246.1493, $C_{15}H_{20}NO_2$ (MH$^+$) requires 246.1494.

(4*R*)-1-(Benzyloxycarbonyl)amino-4-methylhex-2(*Z*),5-diene

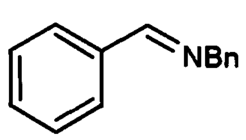


5.20

On a 0.035 mmol scale the reaction gave diene **5.20** as a colourless oil (5.5 mg, 64%). R$_f$ 0.60 (1:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +51.9 (*c* 0.27, chloroform); ν_{max}/cm^{-1} (thin film) 3335m (br, N-H), 3066w, 3014w, 2963m, 2927m, 1702s (C=O), 1524m, 1455w, 1260s, 1096m, 1028m, 914w, 799m, 697m; δ_H (500 MHz, CDCl$_3$) 1.09 (3H, d, *J* 6.5, CH(CH$_3$)), 3.15–3.26 (1H, m, CH(CH$_3$)), 3.83 and 3.90 (2 × 1H, 2 × dt, *J* 15.0 and 5.0, NHCH$_2$), 4.72 (1H, br s, NH), 4.95 (1H, ~dt, *J* 10.5 and 1.0, CH=CH$_E$H), 5.00 (1H, ~d, *J* 17.0, CH=CHH$_Z$), 5.12 (2H, s, CH$_2$Ph), 5.38–5.44 (1H, m, NHCH$_2$CH=), 5.43 (1H, dd, *J* 11.0 and 6.5, =CHCH(CH$_3$)), 5.76 (1H, ddd, *J* 17.0, 10.5 and 6.5, CH=CH$_2$), 7.31–7.37 (5H, m, Ph); δ_C (125.7 MHz, CDCl$_3$) 20.5 (CH(CH$_3$)), 35.7 (CH(CH$_3$)), 38.1 (NHCH$_2$), 66.6 (CH$_2$Ph), 112.9 (CH=CH$_2$), 124.7 (NHCH$_2$CH=), 128.0 (2 × Ph), 128.4 (Ph), 136.4 (*i*-Ph), 136.7 (=CHC(CH$_3$)$_2$), 142.1 (CH=CH$_2$), 156.1 (C=O, Cbz); *m/z* (ES$^+$) 268 (MNa$^+$, 100%), 155 (16); Accurate mass (ES$^+$): Found 268.1314, $C_{15}H_{19}NO_2Na$ (MNa$^+$) requires 268.1313.

Chapter 6 Compounds

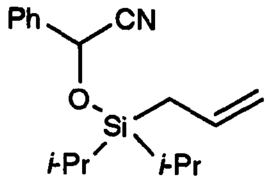
N-Benzylidenebenzylamine[205]



6.13

To a stirred solution of benzonitrile (510 μL, 5.00 mmol) in anhydrous DCM (40.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 12.5 mL, 12.5 mmol) dropwise and the solution stirred at -78 °C for 3 hr. A solution of NH_4Br (1.22 g, 12.5 mmol) in anhydrous methanol (20.0 mL) was added *via* cannula, after 5 min benzylamine (1.10 mL, 10.1 mmol) was added and the reaction mixture warmed to RT over 14hr. The suspension was filtered through Celite® and the filtrate partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (2 x 50 mL); the combined organic fractions were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the crude product as a pale yellow oil. Purification by reduced pressure distillation (B.p. 134–137 °C at 1.0 mmHg, [lit.,[253] 101 °C at 0.1 mmHg]) gave **6.13** as a colourless oil (889 mg, 91%). ν_{max}/cm^{-1} (thin film) 3085m, 3062m, 3028m, 2871m, 2840m, 1957w, 1885w, 1813w, 1644s, 1580m, 1496m, 1452s, 1379w, 1343w, 1312w, 1292w, 1027m, 753s, 694s; δ_H (400 MHz, $CDCl_3$) 4.93 (2H, s, CH_2Ph), 7.34–7.53 (8H, m, Ph), 7.88–7.93 (2H, m, Ph), 8.47 (1H, s, CH=NBn); δ_C (100.6 MHz, $CDCl_3$) 65.1 (CH_2Ph), 126.9 (Ph), 128.1 (Ph), 128.4 (Ph), 128.7 (Ph), 129.0 (Ph), 130.9 (Ph), 136.3 (*i*-Ph), 139.5 (*i*-Ph), 162.0 (CH=NBn); *m/z* ($APCI^+$) 196 (MH^+, 100%).

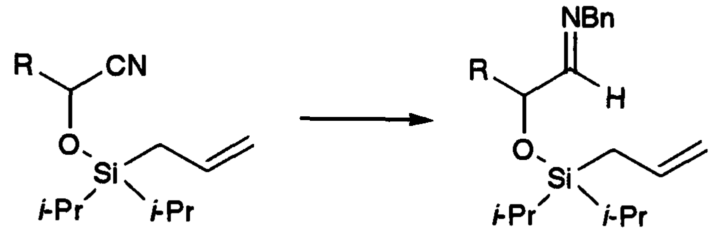
2-[(Prop-2-enyl)di(*iso*-propyl)silanyloxy]phenylacetonitrile



6.14

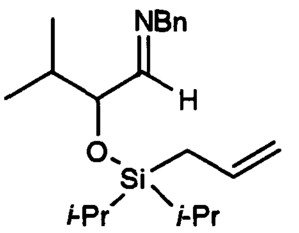
To a stirred suspension of benzaldehyde (900 μL, 8.85 mmol), KCN (2.31 g, 35.5 mmol) and ZnI_2 (57.5 mg, 0.18 mmol) in anhydrous THF (45.0 mL) was added chlorosilane **2.26** (2.02 g, 10.6 mmol). The reaction vessel was placed in an ultrasonic cleaning bath, sonicated for 1 hr and then stirred at 25 °C for 6 days. THF was removed *in vacuo*, the crude residue triturated with diethyl ether and the ethereal extracts filtered through Celite®. The filtrate was washed successively with water (3 × 50 mL), saturated *aq*. NaCl soln. (100 mL), then dried (Na_2SO_4) and the solvents removed *in vacuo* to furnish a yellow oil. Purification by flash column chromatography (silica gel, 30:1, petrol:diethyl ether) gave silylcyanohydrin **6.14** as a colourless oil (1.70 g, 67%). R_f 0.67 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3077w, 3034w, 2946s, 2893m, 2868s, 2239w (C≡N), 1630m, 1494w, 1462m, 1389w, 1195m, 1165m, 1114s, 1100s, 1072s, 995m, 900m; δ_H (400 MHz, $CDCl_3$) 1.00–1.25 (14H, m, 2 × **$CH(CH_3)_2$**), 1.84 (2H, d, *J* 8.0, $SiCH_2$), 4.93 (1H, dd, *J* 10.0 and 1.6, $CH{=}CH_EH$), 5.02 (1H, dd, *J* 16.8 and 1.6, $CH{=}CHH_Z$), 5.64 (1H, s, **CHCN**), 5.86 (1H, ddt, *J* 16.8, 10.0 and 8.0, $CH{=}CH_2$), 7.39–7.45 (3H, m, Ph), 7.47–7.51 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.5 (2 × $CH(CH_3)_2$), 17.2 and 17.3 (2 × $CH(CH_3)_2$), 18.6 ($SiCH_2$), 64.1 (CHCN), 115.0 ($CH{=}CH_2$), 119.3 (C≡N), 126.1 (Ph), 128.9 (Ph), 129.3 (Ph), 133.2 ($CH{=}CH_2$), 136.6 (*i*-Ph); *m/z* (GCMS CI^+) 305 (MNH_4^+, 16%), 261 (49), 246 (MH^+-C_3H_5, 100), 238 (36), 221 (10), 130 (29), 105 (10); Accurate mass (ES^+): Found 305.2058, $C_{17}H_{29}N_2OSi$ (MNH_4^+) requires 305.2049.

General procedure for imine synthesis



To a stirred solution of silylcyanohydrin (1.00 mmol) in anhydrous DCM (10.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 2.5 mmol) dropwise and the solution stirred at -78 °C for 2 hr. A solution of NH_4Br (2.5 mmol) in anhydrous methanol (5.0 mL) was added *via* cannula, after 5 min benzylamine (2.0 mmol) was added and the reaction mixture warmed to RT over 16 hr. The suspension was filtered through Celite® and the filtrate concentrated *in vacuo*; the residual oil was azeotroped with toluene (3 × 25 mL) to remove traces of benzylamine. The crude benzyl imine was used without further purification.[254]

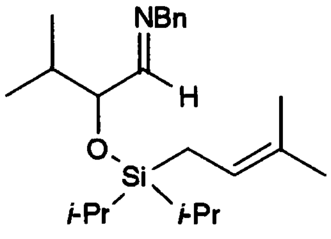
3-Methyl-2-[(prop-2-enyl)di(*iso*-propyl)silanyloxy]butylidenebenzylamine



6.15

On a 2.09 mmol scale the reaction gave benzyl imine **6.15** as a pale yellow oil (699 mg, 93%). R_f 0.76 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3076w, 3029w, 2960s, 2943s, 2893m, 2867s, 1672w, 1630w, 1464m, 1386w, 1366w, 1159w, 1086m, 1062m, 994w, 883m; δ_H (400 MHz, $CDCl_3$) 0.93–1.09 (20H, m, 2 × **SiCH(CH$_3$)$_2$** and CH(**CH$_3$**)$_2$), 1.69 (2H, d, *J* 8.0, Si**CH$_2$**), 1.85–1.95 (1H, m, **CH**(CH$_3$)$_2$), 4.05 (1H, t, *J* 6.0, O**CH**), 4.61 (2H, s, **CH$_2$**Ph), 4.84 (1H, dd, *J* 10.0 and 2.0, CH=**CH$_E$**H), 4.92 (1H, dd, *J* 16.8 and 2.0, CH=CH**H$_Z$**), 5.83 (1H, ddt, *J* 16.8, 10.0 and 8.0, **CH**=CH$_2$), 7.25–7.37 (5H, m, Ph), 7.64 (1H, d, *J* 6.0, **CH**=NBn); δ_C (100.6 MHz, $CDCl_3$) 12.8 (2 × SiCH(CH$_3$)$_2$), 17.5 and 17.6 (2 × SiCH(CH$_3$)$_2$), 18.1 (CH(CH$_3$)$_2$), 19.5 (SiCH$_2$), 33.9 (CH(CH$_3$)$_2$), 64.8 (CH$_2$Ph), 79.2 (OCH), 113.8 (CH=CH$_2$), 127.0 (Ph), 128.2 (Ph), 128.5 (Ph), 134.4 ($CH=CH_2$), 138.7 (*i*-Ph), 167.7 (CH=NBn); *m/z* (ES^+) 346 (MH^+, 100%), 336 (11), 304 (M^+-C_3H_5, 50), 216 (20); Accurate mass (ES^+): Found 346.2559, $C_{21}H_{36}NOSi$ (MH^+) requires 346.2566.

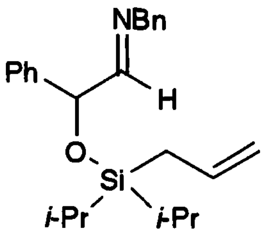
3-Methyl-2-[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]butylidenebenzylamine



6.16

On a 2.76 mmol scale the reaction gave benzyl imine **6.16** as a pale yellow oil (887 mg, 86%). R_f 0.70 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3088w, 3064w, 3029w, 2960s, 2892s, 2866s, 1672m, 1604w, 1496w, 1464m, 1385m, 1367m, 1347w, 1296w, 1247w, 1223w, 1158m, 1086s, 1062s, 999m, 960w, 919w, 883m, 823m, 744m, 730m, 697m, 648m; δ_H (400 MHz, $CDCl_3$) 0.93–1.07 (20H, m, 2 × $SiCH(C\mathbf{H}_3)_2$ and $CH(C\mathbf{H}_3)_2$), 1.52–1.57 (2H, m, $SiC\mathbf{H}_2$), 1.59 and 1.66 (2 × 3H, 2 × d, *J* 1.2, $=C(C\mathbf{H}_3)_2$), 1.89 (1H, septd, *J* 6.8 and 5.8, $C\mathbf{H}(CH_3)_2$), 4.04 (1H, t, *J* 5.8, OC**H**), 4.58 and 4.63 (2 × 1H, 2 × d, *J* 14.0, $C\mathbf{H}_2Ph$), 5.16 (1H, tsept, *J* 8.4 and 1.2, $C\mathbf{H}=C(CH_3)_2$), 7.25–7.37 (5H, m, Ph), 7.64 (1H, dt, *J* 5.8 and 1.6, C**H**=NBn); δ_C (100.6 MHz, $CDCl_3$) 12.8 (2 × $SiCH(CH_3)_2$), 13.1 ($SiCH_2$), 17.5 and 17.7 (2 × $SiCH(CH_3)_2$), 17.6 and 25.8 ($=C(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 34.0 ($CH(CH_3)_2$), 64.8 (CH_2Ph), 79.1 (OCH), 119.1 ($CH=(CH_3)_2$), 127.0 (Ph), 128.1 (Ph), 128.4 (Ph), 129.2 (*i*-Ph), 138.8 ($=C(CH_3)_2$), 167.9 (CH=NBn); *m/z* (ES^+) 391 (MNH_4^+, 74%), 374 (MH^+, 100), 279 (24), 268 (33), 227 (75), 223 (14), 216 (12); Accurate mass: (ES^+) Found 374.2877, $C_{23}H_{40}NOSi$ (MH^+) requires 374.2879.

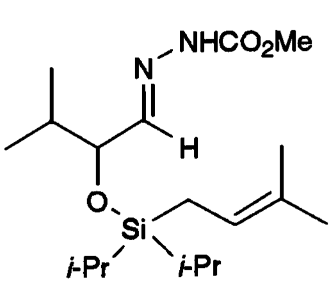
2-Phenyl-2-[(prop-2-enyl)di(*iso*-propyl)silanyloxy]ethylidenebenzylamine



6.17

On a 1.88 mmol scale the reaction gave benzyl imine **6.17** as a pale yellow oil (702 mg, 98%). R_f 0.55 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3063w, 3029m, 2943s, 2892m, 2866s, 1671w, 1630m, 1603w, 1494m, 1463s, 1453s, 1386w, 1364w, 1159m, 1093s, 1064s, 1028m, 994m; δ_H (400 MHz, $CDCl_3$) 0.98–1.15 (12H, m, 2 × $CH(\mathbf{CH_3})_2$), 1.63–1.71 (2H, m, 2 × $\mathbf{CH}(CH_3)_2$), 1.74 (2H, dt, *J* 8.0 and 1.2, $Si\mathbf{CH_2}$), 4.55 and 4.61 (2 × 1H, 2 × d, *J* 13.8, $\mathbf{CH_2}Ph$), 4.83 (1H, ddt, *J* 10.0, 2.0 and 1.2, $CH{=}C\mathbf{H_E}H$), 4.90 (1H, ddt, *J* 16.8, 2.0 and 1.2, $CH{=}CH\mathbf{H_Z}$), 5.43 (1H, d, *J* 6.0, $OC\mathbf{H}$), 5.79 (1H, ddt, *J* 16.8, 10.0 and 8.0, $\mathbf{CH}{=}CH_2$), 7.16–7.52 (10H, m, Ph), 7.67 (1H, d, *J* 6.0, $\mathbf{CH}{=}NBn$); δ_C (100.6 MHz, $CDCl_3$) 12.6 (2 × $CH(CH_3)_2$), 17.4 and 17.6 (2 × $CH(CH_3)_2$), 19.4 ($SiCH_2$), 64.4 (CH_2Ph), 76.8 (OCH), 114.0 ($CH{=}CH_2$), 125.3–129.0 (Ph), 134.0 ($CH{=}CH_2$), 138.6 (*i*-Ph), 140.7 (*i*-Ph), 166.4 ($CH{=}NBn$);^{250} *m/z* (ES^+) 402 (MNa^+, 100%), 380 (MH^+, 32), 292 (13), 250 (48), 225 (84), 190 (11); Accurate mass (ES^+): Found 380.2407, $C_{24}H_{34}NOSi$ (MH^+) requires 380.2410.

3-Methyl-2-[(3-methylbut-2-enyl)di(*iso*-propyl)silanyloxy]butylidene-*N*-carboxy methyl hydrazone



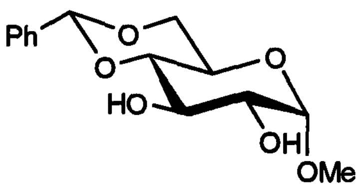
6.22

To a stirred solution of aldehyde **2.45** (150 mg, 0.53 mmol) in absolute ethanol (2.0 mL) was added hydrazinocarboxylate (50.0 mg, 0.55 mmol) and the solution stirred at RT for 12 hr.

The solvent was removed *in vacuo* and the resulting material was purified by flash column chromatography (silica gel, 5:1, petrol:diethyl ether → 2:1, petrol:diethyl ether) to furnish hydrazone **6.22** as colourless needles (151 mg, 81%). R_f 0.45 (1:1, petrol:diethyl ether); M.p. 92–94 °C (from diethyl ether); ν_{max}/cm^{-1} (KBr disc) 3434w (br, N-H), 3214m, 3065w, 2963m, 2931m, 2866m, 1732m, 1708s (C=O), 1563m, 1463w, 1437w, 1352w, 1269s, 1197w, 1159w, 1086m, 1065m, 1033m, 1013w, 962w, 883w, 824w, 734w, 660w; δ_H (400 MHz, $CDCl_3$) 0.92 and 0.94 (2 × 3H, 2 × d, *J* 7.0, CH($\mathbf{CH_3}$)$_2$), 0.97–1.07 (14H, m, 2 × Si**CH**($\mathbf{CH_3}$)$_2$), 1.54 (2H, br d, *J* 7.8, Si$\mathbf{CH_2}$) 1.60 and 1.67 (2 × 3H, 2 × s, =C($\mathbf{CH_3}$)$_2$), 1.84 (1H, septd, *J* 7.0 and 6.4, **CH**(CH_3)$_2$), 3.82 (3H, s, $NHCO_2\mathbf{CH_3}$), 4.15 (1H, t, *J* 6.4, O**CH**), 5.15 (1H, tsept, *J* 7.8 and 1.2, **CH**=C(CH_3)$_2$), 7.04 (1H, br s, **CH**=N-$NHCO_2CH_3$) 7.80 (1H, br s, **NH**CO_2CH_3); δ_C (100.6 MHz, $CDCl_3$) 12.8 (2 × SiCH(CH_3)$_2$), 13.1 (SiCH_2), 17.5 and 17.7 (2 × SiCH(CH_3)$_2$), 17.6 and 25.8 (=C(CH_3)$_2$), 17.9 (CH(CH_3)$_2$), 34.2 (CH(CH_3)$_2$), 53.4 ($NHCO_2CH_3$), 76.6 (OCH), 118.9 (CH=(CH_3)$_2$), 129.5 (CH=N-NHR), 138.6 (=C(CH_3)$_2$), 173.5 (CO_2); *m/z* (ES^+) 379 (MNa^+, 100%), 357 (MH^+, 12), 287 (M^+-C_5H_9, 47), 153 (10); Accurate mass: (ES^+) Found 379.2405, $C_{18}H_{36}N_2O_3SiNa$ (MNa^+) requires 379.2393.

Chapter 7 Compounds

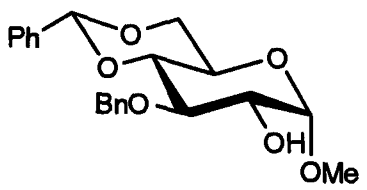
Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside[255]



7.06

To a solution of methyl-α-D-glucopyranoside (10.1 g, 52.0 mmol) in anhydrous DMF (52.0 mL) was added benzaldehyde dimethyl acetal (8.62 mL, 57.2 mmol) and CSA (2.42 g, 10.4 mmol). The reaction flask was placed on a rotary evaporator at a pressure of 20 Torr and a temperature of 55–60 °C. After 1 hr the solution was concentrated *in vacuo* employing toluene (2 × 25 mL) to azeotropically remove residual DMF. Dilute *aq.* $NaHCO_3$ soln. (2.0% w/v, 50 mL) was added and the suspension heated at 100 °C until the precipitate was finely dispersed; the mixture was cooled to RT, filtered through a glass sinter and the product washed successively with water (2 × 25 mL) and pentane (3 × 25 mL). The crude white solid was recrystallised from chloroform/petrol to furnish **7.06** as colourless crystals (11.2 g, 76%). R_f 0.28 (diethyl ether); M.p. 165–167 °C (from chloroform) [lit.,[256] 165.4–166.8 °C]; $[\alpha]_D^{20}$ +89.1 (*c* 1.10, chloroform) [lit.,[257] $[\alpha]_D$ +92.0 (*c* 5.00, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3448s (br, O-H), 3067w, 3042w, 2975m, 2937m, 2918m, 2875m, 1651w, 1452m, 1374s, 1331m, 1277w, 1212m, 1169m, 1143m, 1121m, 1075s, 1028s, 998s, 932w, 923w, 753s, 697s, 678w, 650m; δ_H (400 MHz, $CDCl_3$) 3.42 (3H, s, OCH_3), 3.46 (1H, t, *J* 9.4, H-4), 3.59 (1H, dd, *J* 9.4 and 3.2, H-2), 3.71 (1H, t, *J* 9.4, H-6_{ax}), 3.78 (1H, dt, *J* 9.4 and 4.0, H-5), 3.91 (1H, t, *J* 9.4, H-3), 4.27 (1H, dd, *J* 9.4 and 4.0, H-6_{eq}), 4.74 (1H, d, *J* 3.2, H-1), 5.51 (1H, s, CHPh), 7.35–7.39 (3H, m, Ph), 7.48–7.51 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 55.9 (OCH_3), 62.8 (C-5), 69.4 (C-6), 71.9 (C-3), 73.2 (C-2), 81.4 (C-4), 100.3 (C-1), 102.3 (CHPh), 126.8 (Ph), 127.3 (Ph), 128.5 (Ph), 128.8 (Ph), 129.7 (Ph), 137.5 (*i*-Ph); *m/z* (GCMS CI$^+$) 283 (MH$^+$, 100%), 251 (13), 74 (19).

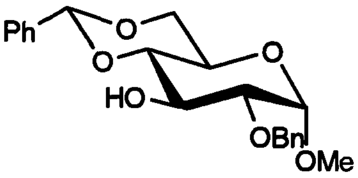
Methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[255]



7.07

To a stirred solution of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **7.06** (5.00 g, 17.7 mmol) in benzene (177 mL) was added Bu_2SnO (4.85 g, 19.5 mmol). The reaction vessel was equipped with a Dean-Stark trap and the suspension heated at reflux for 16 hr with azeotropic removal of water. The solution was cooled to RT and concentrated *in vacuo* to a volume of ~100 mL; benzyl bromide (2.33 mL, 19.5 mmol) and Bu_4NI (7.20 g, 19.5 mmol) were added and the resulting mixture heated at reflux. After 4 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*; the crude residue was triturated with methanol, the methanol extracts were filtered through Celite® and the solvent removed *in vacuo*. The resulting yellow solid was purified by flash column chromatography (silica gel, 3:1, petrol:diethyl ether → 1:1, petrol:diethyl ether) to furnish both **7.07** (1.71 g, 26%) and **7.08** (2.64 g, 40%) as colourless crystals. R_f 0.40 (diethyl ether); M.p. 180–182 °C (from toluene) [lit.,[258] 180–181 °C]; $[\alpha]_D^{22}$ +76.6 (*c* 1.04, chloroform) [lit.,[258] $[\alpha]_D^{25}$ +80.0 (*c* 0.12, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3316s (br, O-H), 3090w, 3028w, 2930m, 2871m, 1498w, 1452m, 1388m, 1368m, 1330w, 1283w, 1213m, 1174m, 1143m, 1075s, 1030s, 993s, 967m; δ_H (400 MHz, $CDCl_3$) 2.34 (1H, d, *J* 6.8, 2-OH), 3.46 (3H, s, OCH_3), 3.66 (1H, t, *J* 9.6, H-4), 3.71–3.76 (1H, m, H-2), 3.77 (1H, t, *J* 9.6, H-6$_{ax}$), 3.82 (1H, t, *J* 9.6, H-3), 3.85 (1H, dt, *J* 9.6 and 4.4, H-5), 4.32 (1H, dd, *J* 9.6 and 4.4, H-6$_{eq}$), 4.81 and 4.98 (2 × 1H, 2 × d, *J* 11.6, CH_2Ph), 4.82 (1H, d, *J* 3.2, H-1), 5.58 (1H, s, CHPh), 7.27–7.41 (8H, m, Ph), 7.49–7.53 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 55.4 (OCH_3), 62.6 (C-5), 69.0 (C-6), 72.3 (C-2), 74.8 (CH_2Ph), 78.8 (C-3), 81.9 (C-4), 99.8 (C-1), 101.3 (CHPh), 126.0 (Ph), 127.7 (Ph), 128.0 (Ph), 128.2 (Ph), 128.4 (Ph), 128.9 (Ph), 137.3 (*i*-Ph), 138.4 (*i*-Ph); *m/z* (GCMS ES^-) 371 ($M-H^+$, 100%), 313 (23), 299 (18), 281 (51), 267 (16), 255 (16); Accurate mass: (ES^-) Found 371.1501, $C_{21}H_{23}O_6$ ($M-H^+$) requires 371.1495.

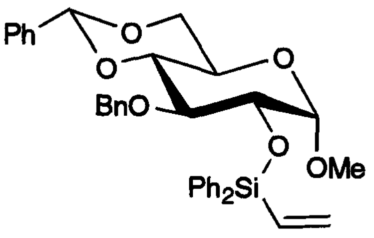
Methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside



7.08

R_f 0.54 (diethyl ether); M.p. 122–124 °C (from toluene) [lit.,[259] 122–124 °C]; $[\alpha]_D^{22}$ +35.3 (*c* 1.02, chloroform) [lit.,[260] $[\alpha]_D^{26}$ +35.2 (*c* 0.10, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3468m (br, O-H), 3060m, 2998m, 2956m, 2927m, 2867m, 2042m, 1498m, 1456m, 1379m, 1359m, 1333m, 1312m, 1273m, 1244w, 1212m, 1149s, 1091s, 923m, 851w, 751s, 700s, 679m, 660m; δ_H (400 MHz, $CDCl_3$) 2.61 (1H, d, *J* 2.4, 3-O**H**), 3.39 (3H, s, OC**H**$_3$), 3.48 (1H, dd, *J* 9.6 and 3.6, H-2), 3.51 (1H, t, *J* 9.6, H-4), 3.71 (1H, t, *J* 10.2, H-6_{ax}), 3.83 (1H, ddd, *J* 10.2, 9.6 and 4.8, H-5), 4.16 (1H, dt, *J* 9.6 and 2.4, H-3), 4.27 (1H, dd, *J* 10.2 and 4.8, H-6_{eq}), 4.63 (1H, d, *J* 3.6, H-1), 4.72 and 4.80 (2 × 1H, 2 × d, *J* 12.0, C**H**$_2$Ph), 5.53 (1H, s, C**H**Ph), 7.33–7.42 (8H, m, Ph), 7.49–7.52 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 55.4 (OCH_3), 62.0 (C-5), 69.0 (C-6), 70.2 (C-3), 73.3 (CH_2Ph), 79.6 (C-2), 81.2 (C-4), 98.6 (C-1), 102.0 (CHPh), 126.3 (Ph), 128.1 (Ph), 128.3 (Ph), 128.6 (Ph), 129.0 (Ph), 129.1 (Ph), 137.1 (*i*-Ph), 137.9 (*i*-Ph); *m/z* (ES^-) 403 (100%), 371 ($M-H^+$, 36); Accurate mass: (ES^-) Found 371.1494, $C_{21}H_{23}O_6$ ($M-H^+$) requires 371.1495.

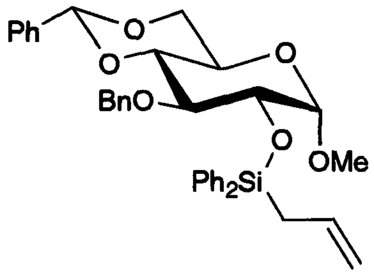
Methyl-2-*O*-[(vinyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside



7.04

To a stirred solution of methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **7.07** (507 mg, 1.36 mmol), DMAP (8.6 mg, 0.07 mmol) and TEA (229 μL, 1.64 mmol) in anhydrous DMF (14.0 mL) cooled to 0 °C was added vinyl(diphenyl)chlorosilane (451 μL, 2.04 mmol) dropwise. The solution was stirred at RT for 30 min and then warmed to 40 °C for 16 hr. The reaction mixture was cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (3 × 25 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 15:1, petrol:ethyl acetate) gave **7.04** as a colourless syrup (782 mg, 99%). R_f 0.45 (5:1, petrol:ethyl acetate); $[\alpha]_D^{22}$ −11.1 (*c* 0.62, chloroform); ν_{max}/cm^{-1} (thin film) 3089w, 3069m, 3050m, 3010w, 2934m, 2912m, 2866m, 1591m, 1497w, 1454m, 1429s, 1405m, 1374m, 1264w, 1175m, 1120s, 1112s, 1088s, 1052s, 998s, 967m, 843m, 740s, 712s; δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s, OCH_3), 3.61 (1H, t, *J* 9.2, H-4), 3.71 (1H, t, *J* 10.4, H-6$_{ax}$), 3.88 (1H, ddd, *J* 10.4, 9.2 and 5.0, H-5), 4.02 (1H, dd, *J* 9.2 and 3.6, H-2), 4.07 (1H, t, *J* 9.2, H-3), 4.27 (1H, dd, *J* 10.4 and 5.0, H-6$_{eq}$), 4.49 (1H, d, *J* 3.6, H-1), 4.78 and 4.92 (2 × 1H, 2 × d, *J* 11.4, CH_2Ph), 5.55 (1H, s, CHPh), 5.96 (1H, dd, *J* 20.4 and 3.6, CH=CHH_Z), 6.29 (1H, dd, *J* 14.8 and 3.6, CH=CH_EH), 6.55 (1H, dd, *J* 20.4 and 14.8, CH=CH_2), 7.26–7.51 (12H, m, Ph), 7.64–7.71 (8H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 55.0 (OCH_3), 62.4 (C-5), 69.1 (C-6), 74.1 (C-3), 75.1 (CH_2Ph), 78.8 (C-2), 82.1 (C-4), 100.3 (C-1), 101.2 (CHPh), 126.1–134.6 (Ph), 134.1 (*i*-Ph), 135.1 (CH=CH$_2$), 137.4 (*i*-Ph), 137.6 (CH=CH$_2$), 138.7 (*i*-Ph);[250] *m/z* (ES$^+$) 581 (MH$^+$, 100%), 451 (24), 257 (90), 225 (67), 171 (15); Accurate mass: (ES$^+$) Found 581.2354, $C_{35}H_{37}O_6Si$ (MH$^+$) requires 581.2359.

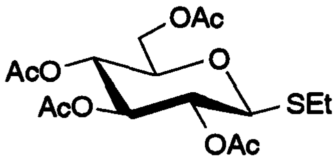
Methyl-2-*O*-[(prop-2-enyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside



7.05

A flame-dried two-necked flask (50 mL) was charged with anhydrous CuCl$_2$ (726 mg, 5.40 mmol) and anhydrous CuI (26.7 mg, 0.14 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round-bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (10.0 mL) was added followed by allyl(diphenyl)silane **2.20** (606 mg, 2.70 mmol) and the orange suspension stirred for 16 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane in THF was added *via* cannula to a stirred solution of methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **7.07** (502 mg, 1.35 mmol), DMAP (8.6 mg, 0.07 mmol) and TEA (760 μL, 5.45 mmol) in anhydrous DMF (15.0 mL). The reaction mixture was warmed to 60 °C for 6 hr, then cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (3 × 25 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 15:1, petrol:ethyl acetate) afforded **7.05** as a colourless syrup (786 mg, 98%). R$_f$ 0.28 (4:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −17.0 (*c* 1.00, chloroform); ν_{max}/cm^{-1} (thin film) 3069m, 3048m, 3028w, 3000w, 2973w, 2913m, 2866m, 1959w, 1890w, 1821w, 1630m, 1590w, 1496w, 1454m, 1428s, 1374m, 1331w, 1311w, 1112s, 1089s, 1053s, 1029m, 996s, 931w, 900m, 844m, 735s, 699s; δ_H (400 MHz, $CDCl_3$) 2.24 (1H, dt, *J* 8.0 and 1.2, Si**CH**$_2$), 3.27 (3H, s, O**CH**$_3$), 3.57 (1H, t, *J* 9.2, H-4), 3.68 (1H, t, *J* 10.4, H-6$_{ax}$), 3.83 (1H, ddd, *J* 10.4, 9.2 and 4.8, H-5), 3.93 (1H, dd, *J* 9.2 and 3.6, H-2), 4.02 (1H, t, *J* 9.2, H-3), 4.24 (1H, dd, *J* 10.4 and 4.8, H-6$_{eq}$), 4.35 (1H, d, *J* 3.6, H-1), 4.76 and 4.93 (2 × 1H, 2 × d, *J* 11.2, **CH**$_2$Ph), 4.86 (1H, ddt, *J* 10.0, 2.0 and 1.2, CH=**CH**$_E$H), 4.90 (1H, ddt, *J* 17.2, 2.0 and 1.2, CH=CH**H**$_Z$), 5.53 (1H, s, **CH**Ph), 5.82 (1H, ddt, *J* 17.2, 10.0 and 8.0, **CH**=CH$_2$), 7.26–7.48 (12H, m, Ph), 7.64–7.67 (8H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 22.1 ($SiCH_2$), 54.9 (OCH_3), 62.2 (C-5), 68.9 (C-6), 73.9 (C-2), 75.1 (CH_2Ph), 78.6 (C-3), 82.0 (C-4), 100.1 (C-1), 101.1 (CHPh), 115.3 ($CH=CH_2$), 125.9–135.9 (Ph), 132.9 ($CH=CH_2$), 133.8 (*i*-Ph), 137.3 (*i*-Ph), 138.6 (*i*-Ph);[250] *m/z* (ES$^+$) 617 (MNa$^+$, 43%), 612 (MNH_4^+, 74), 595 (MH$^+$, 100); Accurate mass: (ES$^+$) Found 595.2515, $C_{36}H_{39}O_6Si$ (MH$^+$) requires 595.2516.

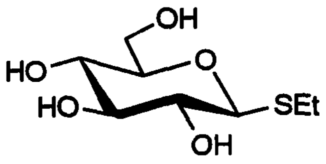
Ethyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside



7.13

To a stirred solution of β-D-glucose pentaacetate (16.1 g, 41.2 mmol) in anhydrous DCM (205 mL) was added ethane thiol (9.30 mL, 124 mmol) and the mixture cooled to 0 °C. After 15 min $BF_3.OEt_2$ was added (7.60 mL, 61.8 mmol) dropwise over 5 min and the solution stirred at 0 °C for 4.5 hr. The reaction was quenched by the addition of saturated *aq.* $NaHCO_3$ soln. (150 mL) and stirred for 30 min at RT. The aqueous phase was extracted with DCM (2 × 100 mL) and the combined organic fractions were washed successively with saturated *aq.* $NaHCO_3$ soln. (250 mL) and saturated *aq.* NaCl soln. (250 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was recrystallised from diethyl ether/petrol to furnish **7.13** as colourless crystals (15.1 g, 93%). R_f 0.41 (2:1, toluene:diethyl ether); M.p. 84–85 °C (from diethyl ether) [lit.,[261] 83–84 °C]; $[\alpha]_D^{22}$ –27.5 (*c* 1.04, chloroform) [lit.,[261] $[\alpha]_D^{22}$ –29.2 (*c* 1.00, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 2964m, 2890m, 1752s (C=O), 1644w, 1449m, 1375s, 1211s, 1050s, 957w, 909m, 825w, 785w, 679w, 639w, 601m, 560w; δ_H (400 MHz, CDCl$_3$) 1.25 (3H, t, *J* 7.4, SCH$_2$C**H**$_3$), 1.99, 2.01, 2.04 and 2.06 (4 × 3H, 4 × s, 4 × OAc), 2.61–2.72 (2H, m, SC**H**$_2$CH$_3$), 3.70 (1H, ddd, *J* 10.0, 4.8 and 2.4, H-5), 4.12 (1H, dd, *J* 12.4 and 2.4, H-6$_b$), 4.23 (1H, dd, *J* 12.4 and 4.8, H-6$_a$), 4.49 (1H, d, *J* 10.0, H-1), 5.02 (1H, dd, *J* 10.0 and 9.2, H-2), 5.07 (1H, dd, *J* 10.0 and 9.2, H-4), 5.21 (1H, t, *J* 9.2, H-3); δ_C (100.6 MHz, CDCl$_3$) 14.8 (SCH$_2$CH$_3$), 20.6 and 20.7 (4 × **A**c), 24.1 (SCH$_2$CH$_3$), 62.1 (C-6), 68.3 (C-4), 69.8 (C-2), 73.9 (C-3), 75.8 (C-5), 83.5 (C-1), 169.3, 169.4, 170.2 and 170.6 (**C**=O, 4 × Ac); *m/z* (ES$^+$) 415 (MNa$^+$, 85%), 410 (MNH$_4^+$, 100); Accurate mass: (ES$^+$) Found 410.1487, $C_{16}H_{28}NO_9S$ (MNH$_4^+$) requires 410.1485.

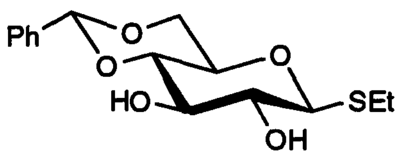
Ethyl-1-thio-β-D-glucopyranoside[262]



7.14

To a stirred solution of ethyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **7.13** (14.2 g, 36.2 mmol) in anhydrous methanol (180 mL) was added NaOMe (196 mg, 3.63 mmol) and the mixture was stirred at RT for 2 hr. The reaction was neutralised by the addition of Amberlite® 15 (H$^+$) resin (~1 g) and the suspension stirred vigorously at RT for 10 min. The resin was removed by filtration through Celite®; washed with methanol (3 × 5 mL) and the filtrate concentrated *in vacuo* to furnish ethyl-1-thio-β-D-glucopyranoside **7.14** as a white foam (8.07 g, 99%). The product was used without further purification. R_f 0.21 (9:1, ethyl acetate:methanol); $[\alpha]_D^{22}$ −55.6 (*c* 0.98, methanol) [lit.,[261] $[\alpha]_D^{24}$ −53.5 (*c* 0.74, methanol)]; ν_{max}/cm^{-1} (thin film) 3367s (br, O-H), 2962m, 2927m, 2875m, 1640m, 1593m, 1449m, 1354m, 1268m, 1030s, 881w; δ_H (400 MHz, D_2O) 1.11 (3H, t, *J* 7.4, SCH_2CH_3), 2.51–2.68 (2H, m, SCH_2CH_3), 3.15 (1H, dd, *J* 9.6 and 9.0, H-2), 3.23 (1H, t, *J* 9.0, H-4), 3.30 (1H, ddd, *J* 9.0, 5.6 and 2.0, H-5), 3.32 (1H, t, *J* 9.0, H-3), 3.53 (1H, dd, *J* 12.4 and 5.6, H-6$_a$), 3.73 (1H, dd, *J* 12.4 and 2.0, H-6$_b$), 4.38 (1H, d, *J* 9.6, H-1); δ_C (100.6 MHz, D_2O) 14.8 (SCH_2CH_3), 24.5 (SCH_2CH_3), 61.2 (C-6), 69.8 (C-4), 72.5 (C-2), 77.5 (C-3), 80.1 (C-5), 85.4 (C-1); *m/z* (ES$^-$) 223 (M−H$^+$, 100%); Accurate mass: (ES$^-$) Found 223.0647, $C_8H_{15}O_5S$ (M−H$^+$) requires 223.0640.

Ethyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[262]

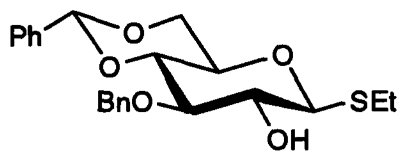


7.15

To a solution of ethyl-1-thio-β-D-glucopyranoside **7.14** (7.98 g, 35.6 mmol) in anhydrous DMF (35.0 mL) was added benzaldehyde dimethyl acetal (5.90 mL, 39.2 mmol) and CSA (1.65 g, 7.12 mmol). The reaction flask was placed on a rotary evaporator at a pressure of 20 Torr and a temperature of 55–60 °C. After 1 hr the solution was concentrated *in vacuo* employing toluene (2 × 25 mL) to azeotropically remove residual DMF. The residue was dissolved in DCM (150 mL) and washed with saturated *aq.* $NaHCO_3$ soln. (150 mL); the aqueous phase was extracted with DCM (3 × 50 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (150 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was recrystallised from chloroform/petrol to furnish **7.15** as colourless crystals (9.13 g, 82%). R_f 0.53 (ethyl acetate); M.p. 134–136 °C (from chloroform) [lit.,[263] 129–130 °C (from ethyl acetate)]; $[\alpha]_D^{22}$ −59.1 (*c* 1.15, chloroform) [lit.,[263] $[\alpha]_D^{25}$ –

59.0 (*c* 1.00, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3381m and 3290m (br, O-H), 3064w, 2974m, 2920m, 2873m, 1452m, 1376m, 1266w, 1217w, 1080s, 1033m, 1006m, 927w, 834w, 751m, 698m; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.4, SCH_2CH_3), 2.72–2.81 (2H, m, SCH_2CH_3), 3.49 (1H, dt, *J* 10.0 and 4.8, H-5), 3.50 (1H, dd, *J* 9.6 and 8.8, H-2), 3.57 (1H, dd, *J* 10.0 and 8.8, H-4), 3.77 (1H, t, *J* 10.0, H-6_{ax}), 3.82 (1H, t, *J* 8.8, H-3), 4.35 (1H, dd, *J* 10.0 and 4.8, H-6_{eq}), 4.46 (1H, d, *J* 9.6, H-1), 5.54 (1H, s, CHPh), 7.36–7.41 (3H, m, Ph), 7.48–7.52 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.3 (SCH_2CH_3), 24.8 (SCH_2CH_3), 68.6 (C-6), 70.5 (C-5), 73.2 (C-2), 74.5 (C-3), 80.4 (C-4), 86.6 (C-1), 101.9 (CHPh), 126.3 (Ph), 128.4 (Ph), 129.3 (Ph), 136.9 (*i*-Ph); *m/z* (ES^+) 330 (MNH_4^+, 56%), 313 (MH^+, 100), 207 (32); Accurate mass: (ES^+) Found 313.1098, $C_{15}H_{21}O_5S$ (MH^+) requires 313.1110.

Ethyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[264]

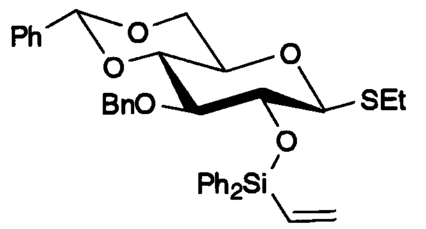


7.16

To a stirred solution of ethyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.15** (2.68 g, 8.58 mmol) in anhydrous methanol (52.0 mL) was added Bu_2SnO (2.35 g, 9.44 mmol) and the suspension heated at reflux for 3 hr. The solution was cooled to RT, concentrated *in vacuo* and azeotroped with toluene (3 × 25 mL). The residue was dissolved in anhydrous DMF (86.0 mL); CsF (1.56 g, 10.3 mmol) and benzyl bromide (1.54 mL, 12.9 mmol) were added and the resulting mixture was stirred at RT for 16 hr. The solution was concentrated *in vacuo* and the crude residue taken up in diethyl ether (100 mL) and washed successively with *aq.* KF soln. (1.0 M, 2 × 50 mL), water (50 mL) and saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude yellow solid was recrystallised from ethyl acetate/petrol to furnish ethyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside

7.16 as colourless crystals (2.06 g, 60%). R_f 0.65 (diethyl ether); M.p. 139–141 °C (from ethyl acetate) [lit.,[265] 145–146 °C (from diethyl ether)]; $[\alpha]_D^{22}$ –54.4 (*c* 0.97, chloroform) [lit.,[265] $[\alpha]_D$ –57.0 (*c* 0.87, chloroform)]; ν_{max}/cm^{-1} (KBr disc) 3368m (br, O-H), 3033w, 2971w, 2868m, 1453m, 1366m, 1273w, 1211w, 1087s, 1006m, 920w, 747m, 696m; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.4, SCH_2CH_3), 2.54 (1H, d, *J* 1.6, 2-OH), 2.70–2.83 (2H, m, SCH_2CH_3), 3.51 (1H, ddd, *J* 10.4, 9.2 and 5.2, H-5), 3.59 (1H, dt, *J* 9.2 and 1.6, H-2), 3.69 (1H, t, *J* 9.2, H-3), 3.73 (1H, t, *J* 9.2, H-4), 3.79 (1H, t, *J* 10.4, H-6_{ax}), 4.37 (1H, dd, *J* 10.4 and 5.2, H-6_{eq}), 4.48 (1H, d, *J* 9.2, H-1), 4.83 and 4.99 (2 × 1H, 2 × d, *J* 11.6, CH_2Ph), 5.59 (1H, s, CHPh), 7.28–7.43 (8H, m, Ph), 7.48–7.52 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.2 (SCH_2CH_3), 24.6 (SCH_2CH_3), 68.6 (C-6), 70.8 (C-5), 73.0 (C-2), 74.7 (CH_2Ph), 81.2 and 81.6 (C-3, C-4), 86.6 (C-1), 101.3 (CHPh), 126.0 (Ph), 127.8 (Ph), 128.0 (Ph), 128.3 (Ph), 128.4 (Ph), 129.0 (Ph), 137.2 (*i*-Ph) 138.3 (*i*-Ph); *m/z* (ES^+) 420 (MNH_4^+, 98%), 403 (MH^+, 100), 297 (59); Accurate mass: (ES^+) Found 403.1573, $C_{22}H_{27}O_5S$ (MH^+) requires 403.1579.

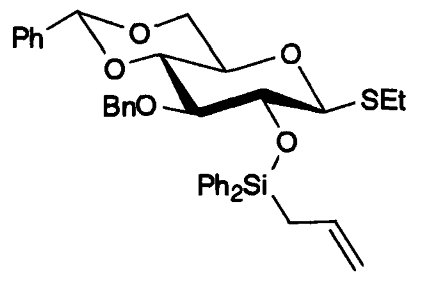
Ethyl-2-*O*-[(vinyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside



7.17

To a stirred solution of ethyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.16** (544 mg, 1.35 mmol), DMAP (8.6 mg, 0.07 mmol) and TEA (226 μL, 1.62 mmol) in anhydrous DMF (14.0 mL) was added vinyl(diphenyl)chlorosilane (358 μL, 1.62 mmol) dropwise. The solution was stirred at RT for 30 min and then warmed to 40 °C for 16 hr. The reaction mixture was cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 25 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 15:1, petrol:ethyl acetate) gave **7.17** as a colourless syrup (654 mg, 79%). R_f 0.50 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −78.1 (*c* 1.12, chloroform); ν_{max}/cm^{-1} (thin film) 3049m, 2973m, 2873m, 1591w, 1453m, 1428m, 1374m, 1317w, 1267w, 1216w, 1090s, 1029s, 996s, 922w, 832m, 751s, 704s; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.6, SCH$_2$**CH$_3$**), 2.52 and 2.63 (2 × 1H, 2 × dq, *J* 12.4 and 7.6, S**CH$_2$**CH$_3$), 3.53 (1H, ddd, *J* 10.4, 9.2 and 4.8, H-5), 3.67 (1H, t, *J* 9.2, H-4), 3.73 (1H, t, *J* 10.4, H-6$_{ax}$), 3.76–3.81 (2H, m, H-2 and H-3), 4.31 and 4.84 (2 × 1H, 2 × d, *J* 10.8, **CH$_2$**Ph), 4.37 (1H, dd, *J* 10.4 and 4.8, H-6$_{eq}$), 4.63 (1H, d, *J* 9.2, H-1), 5.50 (1H, s, **CH**Ph), 5.77 (1H, dd, *J* 20.4 and 3.6, CH=CH**H$_Z$**), 6.22 (1H, dd, *J* 14.8 and 3.6, CH=C**H$_E$**H), 6.59 (1H, dd, *J* 20.4 and 14.8, **CH**=CH$_2$), 7.00–7.77 (20H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.8 (SCH_2CH_3), 24.4 (SCH_2CH_3), 68.7 (C-6), 70.0 (C-5), 73.9 (CH_2Ph), 74.5 (C-2), 82.1 (C-4), 83.0 (C-3), 87.0 (C-1), 101.1 (CHPh), 125.9–135.6 (Ph), 134.1 (*i*-Ph), 134.6 (CH=CH_2), 137.2 (*i*-Ph), 137.3 (CH=CH_2), 138.6 (*i*-Ph);[250] *m/z* (ES$^+$) 628 (MNH$_4^+$, 100%), 611 (MH$^+$, 55), 536 (32), 505 (74), 427 (14), 195 (13); Accurate mass: (ES$^+$) Found 611.2288, $C_{36}H_{39}O_5SiS$ (MH$^+$) requires 611.2287.

Ethyl-2-*O*-[(prop-2-enyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside

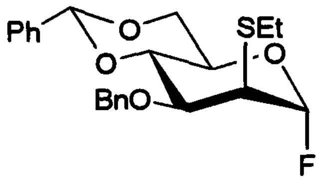


7.18

A flame-dried two-necked flask (50 mL) was charged with anhydrous $CuCl_2$ (600 mg, 4.46 mmol) and anhydrous CuI (11.4 mg, 0.06 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round-bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (11.0 mL) was added followed by allyl(diphenyl)silane **2.20** (500 mg, 2.23 mmol) and the orange suspension stirred for 24 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane in THF was added *via* cannula to a stirred solution of ethyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.16** (602 mg, 1.50 mmol), DMAP (9.8 mg, 0.08 mmol) and TEA (627 μL, 4.50 mmol) in anhydrous DMF (15.0 mL). The reaction mixture was warmed to 60 °C for 7 hr, then cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (3 × 25 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 15:1, petrol:ethyl acetate) afforded **7.18** as a colourless syrup (712 mg, 76%). R_f 0.53 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −79.3 (*c* 1.04, chloroform); ν_{max}/cm^{-1} (thin film) 3068w, 2973m, 2872m, 1629w, 1453w, 1427w, 1375m, 1091s, 1030m, 993m, 901w, 832w, 751s, 699s; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.6, $SCH_2\mathbf{CH_3}$), 2.23–2.29 (2H, m, $SiC\mathbf{H_2}$), 2.51 and 2.65 (2 × 1H, 2 × dq, *J* 12.4 and 7.6, $S\mathbf{CH_2}CH_3$), 3.52 (1H, ddd, *J* 10.4, 9.6 and 4.8, H-5), 3.64 (1H, dd, *J* 9.6 and 8.8, H-4), 3.66 (1H, dd, *J* 9.2 and 8.4, H-2), 3.72 (1H, t, *J* 10.4, H-6_{ax}), 3.79 (1H, dd, *J* 8.8 and 8.4, H-3), 4.36 (1H, dd, *J* 10.4 and 4.8, H-6_{eq}), 4.37 and 4.92 (2 × 1H, 2 × d, *J* 10.8, $\mathbf{CH_2}Ph$), 4.61 (1H, d, *J* 9.2, H-1), 4.84 (1H, dd, *J* 13.2 and 1.6, $CH{=}C\mathbf{H_E}H$), 4.88 (1H, dd, *J* 17.2 and 1.6, $CH{=}CH\mathbf{H_Z}$), 5.49 (1H, s, **CH**Ph), 5.77 (1H, ddt, *J* 17.2, 13.2 and 8.0, $\mathbf{CH}{=}CH_2$), 7.00–7.66 (20H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.8 (SCH_2CH_3), 22.7 ($SiCH_2$), 24.5 (SCH_2CH_3), 68.7

(C-6), 69.9 (C-5), 74.1 (CH_2Ph), 74.5 (C-2), 82.0 (C-4), 82.9 (C-3), 86.9 (C-1), 101.1 (CHPh), 114.9 ($CH=CH_2$), 125.9–135.5 (Ph), 133.3 (*i*-Ph), 134.3 ($CH=CH_2$), 137.2 (*i*-Ph), 138.5 (*i*-Ph);[250] *m/z* (CI^+) 642 (MNH_4^+, 27%), 625 (MH^+, 17), 583 (M^+-C_3H_5, 14), 565 (12), 519 (100), 477 (20), 457 (13); Accurate mass: (CI^+) Found 625.2473, $C_{37}H_{41}O_5SiS$ (MH^+) requires 625.2444.

2-Ethylthio-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-fluoro-α-D-mannopyranoside[266]

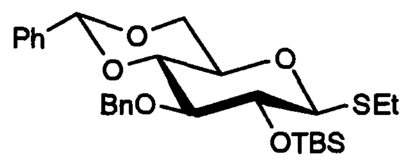


7.19

To a stirred solution of ethyl-2-*O*-[(prop-2-enyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.18** (241 mg, 0.39 mmol) in anhydrous DCM (4.0 mL) cooled to -10 °C was added DAST (77.0 μL, 0.58 mmol) dropwise. The solution was warmed to RT over 10 min and NIS (104 mg, 0.46 mmol) added in one portion. The reaction mixture was stirred at RT for 1 hr, then diluted with DCM (25 mL) and quenched by the addition of saturated *aq.* $NaHCO_3$ soln. and saturated *aq.* $Na_2S_2O_3$ soln. (1:1, v/v, 50 mL). The aqueous phase was extracted with DCM (3 x 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual orange oil was purified by flash column chromatography (silica gel, 20:1, petrol:ethyl acetate) to afford **7.19** as a colourless oil (142 mg, 90%). R_f 0.56 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ +12.7 (*c* 0.93, chloroform); ν_{max}/cm^{-1} (thin film) 3065w, 3033w, 2976m, 2928m, 2870m, 1497w, 1454m, 1380m, 1329w, 1314w, 1299w, 1265m, 1218m, 1153s, 1103s, 1005s, 956s, 919m, 799w, 748m, 698s; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.6, $SCH_2C\mathbf{H_3}$), 2.75 (2H, q, *J* 7.6, $SC\mathbf{H_2}CH_3$), 3.39 (1H, td, *J* 4.6 and 1.2, H-2), 3.83 (1H, dt, *J* 10.4 and 1.2, H-6_{ax}), 4.01 (1H, ddd, *J* 10.4, 9.6 and 4.6, H-5), 4.14 (1H, t, *J* 9.6, H-4), 4.24

(1H, dd, *J* 9.6 and 4.6, H-3), 4.31 (1H, dd, *J* 10.4 and 4.6, H-6_{eq}), 4.77 and 4.89 (2 × 1H, 2 × d, *J* 12.0, CH_2Ph), 5.64 (1H, s, CHPh), 5.77 (1H, dd, *J* 52.0 and 1.2, H-1), 7.30–7.43 (8H, m, Ph), 7.49–7.54 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.6 (SCH_2CH_3), 28.1 (SCH_2CH_3), 49.7 (d, C-2), 66.3 (C-5), 68.3 (C-6), 73.2 (CH_2Ph), 74.0 (C-3), 79.3 (C-4), 101.6 (CHPh), 109.2 (d, C-1), 126.1 (Ph), 127.7 (Ph), 128.2 (Ph), 128.4 (Ph), 129.0 (Ph), 137.3 (*i*-Ph), 138.2 (*i*-Ph); δ_F (376.5 MHz, $CDCl_3$) −121.2 (F-1); *m/z* (CI^+) 422 (MNH_4^+, 48%), 405 (MH^+, 100), 385 (57), 345 (12), 315 (15), 235 (24), 106 (21), 91 (20); Accurate mass: (CI^+) Found 405.1528, $C_{22}H_{26}O_4FS$ (MH^+) requires 405.1535.

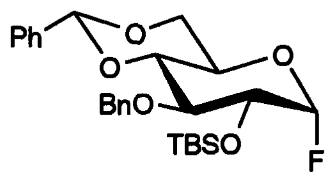
Ethyl-2-*O*-[(*tert*-butyldimethyl)silanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside



7.20

To a stirred solution of ethyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.16** (200 mg, 0.50 mmol), DMAP (3.7 mg, 0.03 mmol) and TEA (105 μL, 0.75 mmol) in anhydrous DMF (5.0 mL) was added *tert*-butyldimethylsilyl chloride (90.4 mg, 0.60 mmol) and the reaction mixture warmed to 50 °C for 16 hr. The solution was cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 15:1, petrol:diethyl ether) to furnish **7.20** as a colourless syrup (177 mg, 69%). R_f 0.20 (10:1, petrol:diethyl ether); $[\alpha]_D^{22}$ −88.8 (*c* 0.48, chloroform); ν_{max}/cm^{-1} (thin film) 3066w, 3034w, 2956m, 2928m, 2857m, 1472w, 1454w, 1369m, 1249m, 1168w, 1135m, 1093s, 1029m, 994m, 855m, 838m, 779m, 749m, 697m; δ_H (400 MHz, $CDCl_3$) 0.07 and 0.09 (2 × 3H, 2 × s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.32 (3H, t, *J* 7.6, SCH_2CH_3), 2.65–2.81 (2H, m, SCH_2CH_3), 3.51 (1H, ddd, *J* 10.2, 9.6 and 4.8, H-5), 3.61 (1H, t, *J* 8.8, H-2), 3.66 (1H, t, *J* 8.8, H-3), 3.74 (1H, dd, *J* 9.6 and 8.8, H-4), 3.79 (1H, t, *J* 10.2, H-6_{ax}), 4.38 (1H, dd, *J* 10.2 and 4.8, H-6_{eq}), 4.48 (1H, d, *J* 8.8, H-1), 4.73 and 5.03 (2 × 1H, 2 × d, *J* 11.2, CH_2Ph), 5.50 (1H, s, CHPh), 7.26–7.39 (8H, m, Ph), 7.42–7.45 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) –5.30 and –3.60 ($Si(CH_3)_2$), 15.0 (SCH_2CH_3), 18.3 ($SiC(CH_3)_3$), 24.9 (SCH_2CH_3), 26.0 ($SiC(CH_3)_3$), 68.8 (C-6), 70.0 (C-5), 74.1 (C-2), 74.5 (CH_2Ph), 82.2 (C-4), 83.2 (C-3), 87.3 (C-1), 101.2 (CHPh), 125.5–128.9 (Ph), 137.3 (*i*-Ph), 138.6 (*i*-Ph);[250] *m/z* (CI^+) 517 (MH^+, 6%), 455 (12), 411 (100), 349 (13), 303 (16), 279 (12), 219 (39), 161 (10), 129 (13), 108 (28), 91 (79); Accurate mass: (CI^+) Found 517.2439, $C_{28}H_{41}O_5SiS$ (MH^+) requires 517.2444.

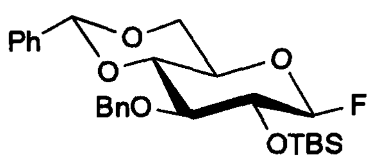
2-*O*-[(*tert*-Butyldimethyl)silanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside[266]



7.21α

To a stirred solution of ethyl-2-*O*-[(*tert*-butyldimethyl)silanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7.20** (142 mg, 0.27 mmol) in anhydrous DCM (3.0 mL) cooled to -10 °C was added DAST (55.0 µL, 0.42 mmol) dropwise. The solution was warmed to RT over 10 min and NIS (74.1 mg, 0.33 mmol) added in one portion. The reaction mixture was stirred at RT for 1 hr, then diluted with DCM (25 mL) and quenched by the addition of saturated *aq*. $NaHCO_3$ soln. and saturated *aq*. $Na_2S_2O_3$ soln. (1:1, v/v, 50 mL). The aqueous phase was extracted with DCM (3 × 25 mL) and the combined organic fractions were washed with saturated *aq*. NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 20:1, petrol:diethyl ether) to afford both the α-anomer (76.3 mg, 60%) and the β-anomer (28.5 mg, 22%) as colourless crystals. R_f 0.21 (10:1, petrol:diethyl ether); M.p. 93–95 °C; $[\alpha]_D^{22}$ −14.8 (*c* 0.64, chloroform); ν_{max}/cm^{-1} (KBr disc) 3035w, 2984w, 2951m, 2928m, 2856m, 1470w, 1378m, 1248w, 1177m, 1142s, 1089s, 1070m, 1048w, 1028m, 1018w, 997m, 976w, 861m, 835m, 784m, 763m, 742m, 698s; δ_H (400 MHz, $CDCl_3$) 0.11 and 0.12 (2 × 3H, 2 × s, $Si(CH_3)_2$), 0.94 (9H, s, $SiC(CH_3)_3$), 3.68 (1H, t, *J* 9.6, H-4), 3.74 (1H, t, *J* 10.0, H-6_{ax}), 3.76 (1H, ddd, *J* 25.2, 9.6 and 2.8, H-2), 3.92 (1H, t, *J* 9.6, H-3), 4.02 (1H, ddd, *J* 10.0, 9.6 and 4.8, H-5), 4.36 (1H, dd, *J* 10.0 and 4.8, H-6_{eq}), 4.78 and 4.92 (2 × 1H, 2 × d, *J* 11.2, CH_2Ph), 5.48 (1H, dd, *J* 52.6 and 2.8, H-1), 5.57 (1H, s, CHPh), 7.28–7.41 (8H, m, Ph), 7.46–7.49 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) −4.96 ($Si(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 64.6 (C-5), 68.6 (C-6), 73.1 (d, C-2), 75.3 (CH_2Ph), 78.3 (C-3), 81.2 (C-4), 101.4 (CHPh), 107.3 (d, C-1), 126.0 (Ph), 127.3 (Ph), 128.1 (Ph), 128.2 (Ph), 129.0 (Ph), 137.1 (*i*-Ph), 138.3 (*i*-Ph); δ_F (376.5 MHz, $CDCl_3$) −149.3 (F-1); *m/z* (CI^+) 475 (MH^+, 100%), 405 (45), 385 (25), 369 (18), 235 (10), 108 (27), 91 (56); Accurate mass: (CI^+) Found 475.2312, $C_{26}H_{36}O_5FSi$ (MH^+) requires 475.2316.

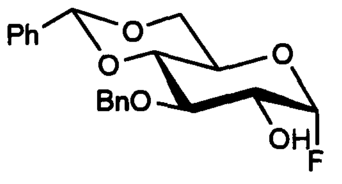
2-*O*-[(*tert*-Butyldimethyl)silanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-β-D-glucopyranoside



7.21β

R_f 0.26 (10:1, petrol:diethyl ether); M.p. 64–65 °C; $[\alpha]_D^{22}$ −43.0 (*c* 0.40, chloroform); ν_{max}/cm^{-1} (KBr disc) 3062w, 3034w, 2960m, 2928m, 2889m, 2857m, 1472w, 1451w, 1381w, 1253w, 1177w, 1139m, 1116s, 1093s, 1070w, 1049w, 1006m, 976w, 858m, 840m, 782m, 754m, 728m, 700m; δ_H (400 MHz, $CDCl_3$) 0.08 and 0.11 (2 × 3H, 2 × s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 3.62 (1H, ddd, *J* 10.2, 9.6 and 4.8, H-5), 3.67 (1H, dd, *J* 8.8 and 6.0, H-3), 3.74 (1H, dt, *J* 12.4 and 6.0, H-2), 3.82 (1H, t, *J* 10.2, H-6_{ax}), 3.83 (1H, dd, *J* 9.6 and 8.8, H-4), 4.42 (1H, dd, *J* 10.2 and 4.8, H-6_{eq}), 4.75 and 4.92 (2 × 1H, 2 × d, *J* 11.2, CH_2Ph), 5.20 (1H, dd, *J* 53.2 and 6.0, H-1), 5.58 (1H, s, CHPh), 7.27–7.40 (8H, m, Ph), 7.45–7.48 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) –4.86 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 65.4 (C-5), 68.7 (C-6), 74.4 (d, C-2), 74.6 (CH_2Ph), 80.9 and 81.1 (C-3 and C-4), 101.3 (CHPh), 110.0 (d, C-1), 126.0 (Ph), 127.6 (Ph), 128.1 (Ph), 128.2 (Ph), 129.0 (Ph), 137.0 (*i*-Ph), 138.1 (*i*-Ph); δ_F (376.5 MHz, $CDCl_3$) –135.8 (F-1); *m/z* (CI^+) 492 (MNH_4^+, 12%), 475 (MH^+, 40), 139 (12), 122 (23), 106 (100), 91 (28), 72 (19), 58 (29); Accurate mass: (CI^+) Found 475.2308, $C_{26}H_{36}O_5FSi$ (MH^+) requires 475.2316.

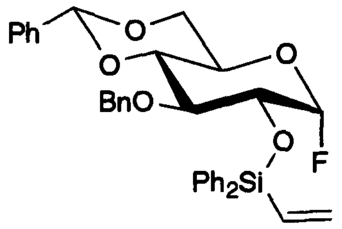
3-*O*-Benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside



7.22

To a stirred solution of 2-*O*-[(*tert*-Butyldimethyl)silanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside **7.21α** (73.3 mg, 0.15 mmol) in THF (3.0 mL) cooled to 0 °C was added TBAF (1.0 M in THF, 380 μL, 0.38 mmol) dropwise. The reaction mixture was stirred for 20 min at 0 °C and then quenched by the addition of saturated *aq.* NH_4Cl soln. (25 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to give **7.22** as colourless solid (45.7 mg, 82%). R_f 0.55 (diethyl ether); M.p. 171–172 °C; $[\alpha]_D^{22}$ +33.8 (*c* 1.17, chloroform); ν_{max}/cm^{-1} (KBr disc) 3291m (br, O-H), 3060w, 3032w, 2987m, 2929m, 2870m, 1453w, 1368m, 1212w, 1154s, 1115m, 1089s, 1071s, 1034m, 1017m, 964w, 918w, 886w, 771w, 742m, 694m; δ_H (500 MHz, $CDCl_3$) 2.35 (1H, dd, *J* 5.5 and 1.0, 2-OH), 3.72–3.81 (1H, m, H-2), 3.74 (1H, t, *J* 9.5, H-4), 3.78 (1H, dt, *J* 10.5 and 1.5, H-6_{ax}), 3.91 (1H, t, *J* 9.5, H-3), 4.04 (1H, ddd, *J* 10.5, 9.5 and 5.0, H-5), 4.37 (1H, dd, *J* 10.5 and 5.0, H-6_{eq}), 4.77 and 5.02 (2 × 1H, 2 × d, *J* 12.0, CH_2Ph), 5.58 (1H, s, CHPh), 5.67 (1H, dd, *J* 53.5 and 3.0, H-1), 7.30–7.43 (8H, m, Ph), 7.50–7.52 (2H, m, Ph); δ_C (125.7 MHz, $CDCl_3$) 64.7 (C-5), 68.4 (C-6), 71.9 (d, C-2), 74.8 (CH_2Ph), 77.9 (C-3), 81.1 (C-4), 101.3 (CHPh), 106.7 (d, C-1), 125.9 (Ph), 127.9 (Ph), 128.0 (Ph), 128.2 (Ph), 128.4 (Ph), 129.0 (Ph), 136.9 (*i*-Ph), 137.9 (*i*-Ph); δ_F (376.5 MHz, $CDCl_3$) −149.4 (F-1); *m/z* (ES^+) 361 (MH^+, 100%), 338 (16), 332 (38), 256 (29), 252 (25), 205 (23); Accurate mass: (ES^+) Found 361.1437, $C_{20}H_{22}O_5F$ (MH^+) requires 361.1451.

2-*O*-[(Vinyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside

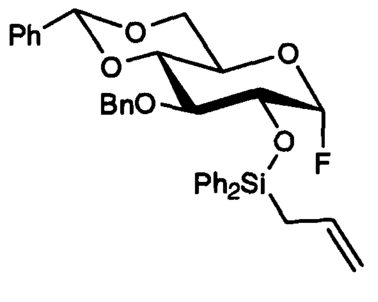


7.11

To a stirred solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside **7.22** (22.4 mg, 0.06 mmol), DMAP (cat.) and TEA (11.0 µL, 0.08 mmol) in anhydrous DMF (600 µL) was added vinyl(diphenyl)chlorosilane (17.7 µL, 0.08 mmol) dropwise. The solution was stirred at 50 °C for 16 hr. The reaction mixture was cooled to RT and partitioned between water (15 mL) and diethyl ether (15 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. Purification by flash column chromatography (silica gel, 15:1, petrol:diethyl ether) gave **7.11** as a colourless syrup (28.4

mg, 80%). R_f 0.53 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –37.4 (*c* 0.19, chloroform); ν_{max}/cm^{-1} (thin film) 3068m, 2926m, 2868m, 1591w, 1454w, 1429w, 1373w, 1122s, 1090s, 1028m, 1007m, 841w, 742m, 712m, 698s; δ_H (500 MHz, $CDCl_3$) 3.66 (1H, t, *J* 9.5, H-4), 3.69 (1H, dt, *J* 10.5 and 1.0, H-6$_{ax}$), 3.96 (1H, ddd, *J* 25.0, 9.5 and 3.0, H-2), 4.03 (1H, ddd, *J* 10.5, 9.5 and 5.0, H-5), 4.06 (1H, t, *J* 9.5, H-3), 4.32 (1H, dd, *J* 10.5 and 5.0, H-6$_{eq}$), 4.68 and 4.89 (2 × 1H, 2 × d, *J* 11.0, CH_2Ph), 5.36 (1H, dd, *J* 52.5 and 3.0, H-1), 5.53 (1H, s, CHPh), 5.95 (1H, dd, *J* 20.5 and 3.5, CH=CHH$_Z$), 6.29 (1H, dd, *J* 15.0 and 3.5, CH=CH$_E$H), 6.51 (1H, dd, *J* 20.5 and 15.0, CH=CH_2), 7.20–7.48 (16H, m, Ph), 7.62–7.68 (4H, m, Ph); δ_C (125.7 MHz, $CDCl_3$) 64.9 (C-5), 69.0 (C-6), 74.0 (d, C-2), 75.5 (CH_2Ph), 78.7 (C-3), 81.6 (C-4), 101.8 (CHPh), 107.3 (d, C-1), 126.5 (Ph), 128.0 (Ph), 128.4 (Ph), 128.5 (Ph), 128.6 (Ph), 128.7 (Ph), 129.4 (Ph), 130.7 (Ph), 133.7 (CH=CH_2), 134.2 (*i*-Ph), 137.6 (*i*-Ph), 138.4 (CH=CH_2), 138.8 (*i*-Ph);[250] δ_F (376.5 MHz, $CDCl_3$) –149.4 (F-1); *m/z* (CI$^+$) 569 (MH$^+$, 58%), 361 (19), 279 (48), 257 (15), 235 (27), 216 (20), 167 (18), 156 (11), 105 (38), 91 (100), 78 (35); Accurate mass: (CI$^+$) Found 569.2159, $C_{34}H_{34}O_5FSi$ (MH$^+$) requires 569.2159.

2-*O*-[(Prop-2-enyl)diphenylsilanyloxy]-3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside

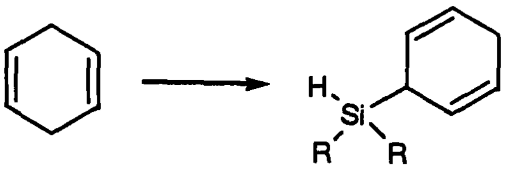


7.12

To a stirred solution of 3-*O*-benzyl-4,6-*O*-benzylidene-1-fluoro-α-D-glucopyranoside **7.22** (17.6 mg, 0.05 mmol), DMAP (cat.) and TEA (25.0 μL, 0.18 mmol) in anhydrous DMF (500 μL) was added crude allyl(diphenyl)chlorosilane (~0.15 M in THF, 533 μL, 0.08 mmol). The reaction mixture was warmed to 50 °C for 16 hr, then cooled to RT and partitioned between water (15 mL) and diethyl ether (15 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. Purification by flash column chromatography (silica gel, 15:1, petrol:diethyl ether) afforded **7.12** as a colourless syrup (27.3 mg, 96%). R_f 0.55 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –42.1 (*c* 0.66, chloroform); ν_{max}/cm^{-1} (thin film) 3069m, 2921m, 2868m, 1630w, 1454w, 1428w, 1373w, 1132s, 1091s, 1028m, 999m, 898w, 841w, 739m, 698s; δ_H (400 MHz, $CDCl_3$) 2.17–2.27 (2H, m, Si**CH₂**), 3.64 (1H, t, *J* 9.2, H-4), 3.69 (1H, dt, *J* 10.2 and 1.0, H-6_{ax}), 3.90 (1H, ddd, *J* 25.0, 9.2 and 2.8, H-2), 4.02 (1H, ddd, *J* 10.2, 9.2 and 5.2, H-5), 4.05 (1H, t, *J* 9.2, H-3), 4.31 (1H, dd, *J* 10.2 and 5.2, H-6_{eq}), 4.68 and 4.93 (2 × 1H, 2 × d, *J* 11.4, **CH₂**Ph), 4.89 (1H, ddt, *J* 10.4, 2.4 and 1.2, CH=**CH**$_E$H), 4.92 (1H, ddt, *J* 17.6, 2.4 and 1.2, CH=CH**H**$_Z$), 5.28 (1H, dd, *J* 52.6 and 2.8, H-1), 5.53 (1H, s, **CH**Ph), 5.83 (1H, ddt, *J* 17.6, 10.4 and 8.0, **CH**=CH_2), 7.25–7.48 (16H, m, Ph), 7.61–7.66 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 22.2 ($SiCH_2$), 64.4 (C-5), 68.5 (C-6), 73.4 (d, C-2), 75.1 (CH_2Ph), 78.2 (C-3), 81.2 (C-4), 101.3 (CHPh), 106.8 (d, C-1), 115.5 (CH=CH_2), 126.0 (Ph), 127.6 (Ph), 127.9 (Ph), 128.1 (Ph), 128.2 (Ph), 129.0 (Ph), 130.2 (Ph), 132.7 (CH=CH_2), 133.7 (*i*-Ph), 135.0 (Ph), 137.1 (*i*-Ph), 138.3 (*i*-Ph);[250] δ_F (376.5 MHz, $CDCl_3$) -149.1 (F-1); *m/z* (CI^+) 583 (MH^+, 16%), 285 (10), 230 (13), 131 (14), 106 (48), 91 (100), 78 (39); Accurate mass: (CI^+) Found 583.2306, $C_{35}H_{36}O_5FSi$ (MH^+) requires 583.2316.

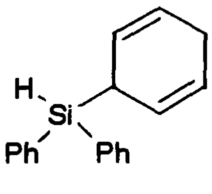
Chapter 8 Compounds

General procedure for cyclohexadienyl silane synthesis[219]



To a stirred solution of 1,4-cyclohexadiene (2.60 mL, 27.5 mmol) in anhydrous THF (37.5 mL) cooled to -78 °C was added TMEDA (3.77 mL, 25.0 mmol) and *s*-BuLi (1.0 M in cyclohexanes, 25.0 mL, 25.0 mmol) dropwise over 10 min. The yellow solution was warmed to -45 °C and stirred for 3 hr. The chlorosilane (25.0 mmol) in anhydrous THF (12.5 mL) was added and the mixture was stirred at -45 °C for a further 30 min. The solution was warmed to RT and the reaction quenched by the addition of saturated *aq.* NH_4Cl soln. (100 mL). The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, 40–60 petrol) to furnish the cyclohexadienyl silane.

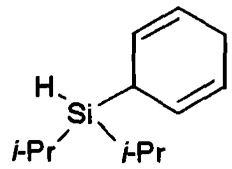
(Cyclohexa-2,5-dienyl)diphenylsilane



8.01

Colourless oil (6.56 g, 100%). R_f 0.35 (petrol); ν_{max}/cm^{-1} (thin film) 3068m, 3048m, 3025m, 2885w, 2854w, 2820m, 2125s (Si-H), 1956w, 1884w, 1819w, 1667w, 1622w, 1588w, 1486w, 1428s, 1331w, 1293w, 1190w, 1158w, 1115s, 1066w, 1052w, 998w, 931w, 893m, 803s, 726s, 698s; δ_H (400 MHz, $CDCl_3$) 2.36–2.46 and 2.61–2.72 (2 × 1H, 2 × m, CH_2), 2.95–3.03 (1H, m, SiC**H**), 4.83 (1H, d, *J* 3.2, SiH), 5.57–5.63 (2H, m, 2 × CH=C**H**), 5.76–5.82 (2H, m, 2 × CH=CH), 7.37–7.47 (6H, m, Ph), 7.64–7.68 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 26.2 (CH_2), 28.4 (SiCH), 123.2 (2 × CH=CH), 125.2 (2 × CH=CH), 127.9 (Ph), 129.7 (Ph), 132.9 (*i*-Ph), 135.5 (Ph); *m/z* (GCMS CI^+) 280 (MNH_4^+, 38%), 263 (MH^+, 53), 200 (100), 183 (58), 139 (12), 123 (39), 105 (19); Accurate mass (CI^+): Found 280.1511, $C_{18}H_{22}NSi$ (MNH_4^+) requires 280.1522.

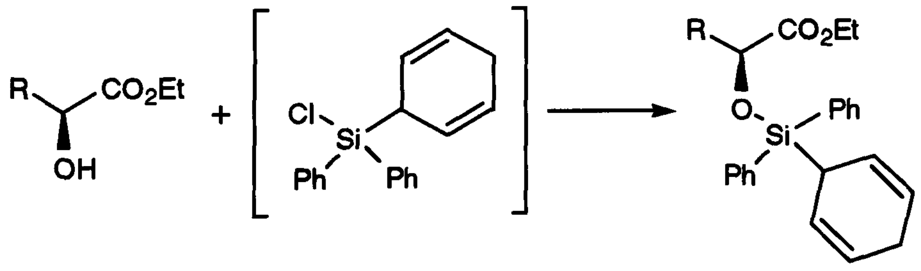
(Cyclohexa-2,5-dienyl)di(*iso*-propyl)silane



8.02

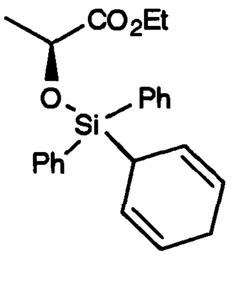
Colourless oil (4.69 g, 96%). R_f 0.61 (petrol); ν_{max}/cm^{-1} (thin film) 3025m, 2941s, 2890s, 2864s, 2821m, 2093s (Si-H), 1624w, 1462m, 1384w, 1366w, 1291w, 1244w, 1108m, 1053w, 1004m, 897m, 883m, 824m, 801s, 732s, 653m, 625m; δ_H (400 MHz, $CDCl_3$) 1.08–1.11 (14H, m, 2 × **CH**(CH_3)$_2$), 2.54–2.62 (1H, m, SiCH), 2.70–2.78 (2H, m, CH_2), 3.44–3.46 (1H, m, SiH), 5.52–5.58 (2H, m, 2 × CH=**CH**), 5.70–5.76 (2H, m, 2 × **CH**=CH); δ_C (100.6 MHz, $CDCl_3$) 10.4 (2 × CH(CH_3)$_2$), 19.1 and 19.2 (2 × CH(CH_3)$_2$), 26.1 (CH_2), 26.4 (SiCH), 121.6 (2 × CH=CH), 126.6 (2 × CH=CH); *m/z* (GCMS CI^+) 212 (MNH_4^+, 72%), 195 (MH^+, 100), 147 (20), 132 (51), 130 (34), 104 (13), 90 (45), 76 (15); Accurate mass (CI^+): Found 195.1564, $C_{12}H_{23}Si$ (MH^+) requires 195.1569.

General procedure for α-silyloxy ester synthesis



A flame-dried two-necked flask (50 mL) was charged with anhydrous $CuCl_2$ (2.00 mmol) and anhydrous CuI (0.025 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round-bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (5.0 mL) was added followed by the cyclohexadienylsilane (1.00 mmol) and the orange suspension stirred for 25 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane in THF was added *via* cannula to a stirred solution of the α-hydroxy ester (0.50 mmol), DMAP (0.025 mmol) and TEA (1.50 mmol) in anhydrous DMF (20.0 mL). The reaction mixture was warmed to 40 °C for 16 hr, then cooled to RT and partitioned between water (50 mL) and diethyl ether (25 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 20:1, petrol:diethyl ether) to furnish the α-silyloxy ester.

(*S*)-Ethyl 2-[(cyclohexa-2,5-dienyl)diphenylsilanyloxy]propanoate

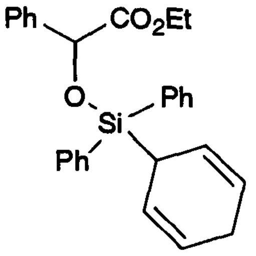


8.04

On a 1.91 mmol scale the reaction gave **8.04** as a colourless oil (254 mg, 70%). R_f 0.58 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –36.8 (*c* 0.98, chloroform); ν_{max}/cm^{-1} (thin film) 3070w, 3027m, 2982m, 2935w, 2889w, 2820w, 1750s (C=O), 1590w, 1455w, 1429m, 1374w, 1274w, 1199w, 1119s, 1061m, 1023w, 976w, 894w, 779w, 739m, 700s; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.2, $OCH_2C\mathbf{H_3}$), 1.42 (3H, d, *J* 6.8, $OCHC\mathbf{H_3}$), 2.11–2.22 and 2.53–2.64 (2 x 1H, 2 x m, $\mathbf{CH_2}$), 3.12–3.19 (1H, m, SiC**H**), 4.07 (2H, q, *J* 7.2, $OC\mathbf{H_2}CH_3$), 4.40 (1H, q, *J* 6.8,

$OCHCH_3$), 5.50–5.56 (2H, m, 2 × CH=CH), 5.80–5.86 (2H, m, 2 × CH=CH), 7.34–7.50 (6H, m, Ph), 7.60–7.72 (4H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 21.2 ($OCHCH_3$), 26.1 (CH_2), 30.1 (SiCH), 60.7 (OCH_2CH_3), 68.9 ($OCHCH_3$), 123.4 (2 × CH=CH), 124.6 (2 × CH=CH), 127.6 (Ph), 132.9 (*i*-Ph), 133.9 (Ph), 135.4 (Ph), 174.0 (CO_2); *m/z* (GCMS CI^+) 396 (MNH_4^+, 12%), 299 (M^+-C_6H_7, 100), 271 (18), 244 (20), 199 (17); Accurate mass (CI^+): Found 299.1112, $C_{17}H_{19}O_3Si$ (M^+-C_6H_7) requires 299.1103.

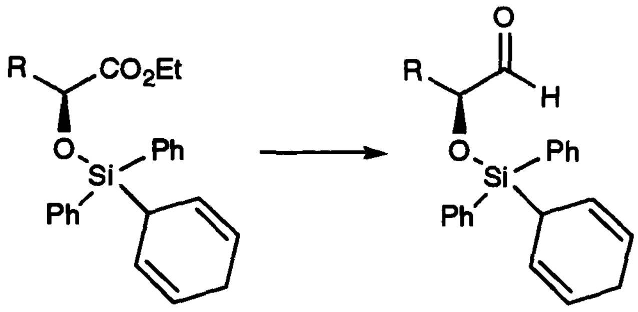
Ethyl [(cyclohexa-2,5-dienyl)diphenylsilanyloxy]phenylacetate



8.05

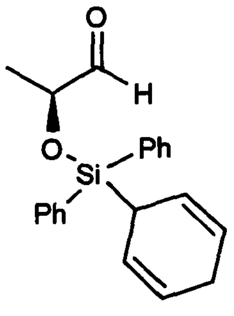
On a 3.81 mmol scale the reaction gave **8.05** as a colourless oil (737 mg, 88%). R_f 0.53 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3069w, 3028m, 3000w, 2980w, 2936w, 2889w, 2856w, 2821w, 1960w, 1892w, 1824w, 1752s (C=O), 1590w, 1494w, 1454w, 1429m, 1264m, 1206m, 1178m, 1120s, 1072m, 1028m, 948w, 892m, 836m; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, t, *J* 7.2, OCH_2CH_3), 2.06–2.17 and 2.50–2.61 (2 × 1H, 2 × m, CH_2), 3.12–3.19 (1H, m, SiCH), 4.00 (2H, 2 × dq, *J* 10.8 and 7.2, OCH_2CH_3), 5.29 (1H, s, OCHPh), 5.50–5.55 (2H, m, 2 × CH=CH), 5.78–5.86 (2H, m, 2 × CH=CH), 7.30–7.74 (15H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 13.9 (OCH_2CH_3), 26.0 (CH_2), 30.1 (SiCH), 61.0 (OCH_2CH_3), 74.8 (CHPh), 123.6 (2 × CH=CH), 124.3 (2 × CH=CH), 126.6–135.5 (Ph), 132.5 (*i*-Ph), 138.7 (*i*-Ph), 171.6 (CO_2);[250] *m/z* (GCMS CI^+) 458 (MNH_4^+, 17%), 361 (M^+-C_6H_7, 100), 207 (13), 199 (22), 182 (55); Accurate mass (CI^+): Found 361.1257, $C_{22}H_{21}O_3Si$ (M^+-C_6H_7) requires 361.1260.

General procedure for α-silyl aldehyde synthesis



To a stirred solution of the α-silyloxy ester (0.5 mmol) in anhydrous DCM (5.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 0.75 mmol) dropwise and the solution stirred at -78 °C for 45 min. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (2 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (30% w/v, 25 mL) and diethyl ether (25 mL). The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20:1, petrol:diethyl ether) to furnish the aldehyde.[267]

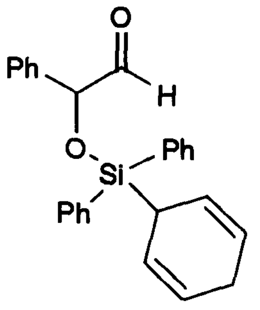
(*S*)-2-[(Cyclohexa-2,5-dienyl)diphenylsilanyloxy]propionaldehyde



8.06

Colourless oil (91.3 mg, 55%). R_f 0.42 (2:1, petrol:diethyl ether, [streaks]); $[\alpha]_D^{22}$ −17.1 (*c* 0.86, chloroform); ν_{max}/cm^{-1} (thin film) 3070w, 3027m, 2978w, 2932w, 2888w, 2854w, 2820w, 1737s (C=O), 1428s, 1376w, 1118s, 1013w, 998w, 697w, 894w, 741m, 700s; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.2, $OCHCH_3$), 2.15–2.26 and 2.56–2.67 (2 × 1H, 2 × m, CH_2), 3.11–3.18 (1H, m, SiCH), 4.26 (2H, br q, *J* 7.2, $OCHCH_3$), 5.53–5.59 (2H, m, 2 × CH=CH), 5.77–5.85 (2H, m, 2 × C**H**=CH), 7.38–7.50 (6H, m, Ph), 7.65–7.69 (4H, m, Ph), 9.67 (1H, br s, CHO); δ_C (100.6 MHz, $CDCl_3$) 18.4 ($OCHCH_3$), 26.1 (CH_2), 29.9 (SiCH), 74.5 ($OCHCH_3$), 123.7 (2 × CH=CH), 124.2 (2 × CH=CH), 127.9 (Ph), 130.3 (Ph), 132.8 (*i*-Ph), 135.4 (Ph), 203.6 (CHO); *m/z* (GCMS CI^+) 335 (MH^+, 66%), 281 (19), 255 (M^+-C_6H_7, 100), 224 (74), 216 (32); Accurate mass (CI^+): Found 335.1472, $C_{21}H_{23}O_2Si$ (MH^+) requires 335.1467.

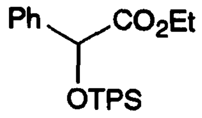
[(Cyclohexa-2,5-dienyl)diphenylsilanyloxy]phenylacetaldehyde



8.07

Colourless oil (61.4 mg, 31%). R_f 0.49 (2:1, petrol:diethyl ether, [streaks]); ν_{max}/cm^{-1} (thin film) 3069m, 3049w, 3028m, 2955w, 2924w, 2889w, 2854w, 2820w, 1960w, 1891w, 1825w, 1736s (C=O), 1590w, 1489w, 1453w, 1429s, 1191m, 1118s, 1073m, 1051m, 1028m, 924w, 895w, 853w, 741m, 711s, 699s; δ_H (400 MHz, $CDCl_3$) 2.10–2.21 and 2.55–2.65 (2 × 1H, 2 × m, CH_2), 3.14–3.22 (1H, m, SiC**H**), 5.20 (1H, d, *J* 1.6, C**H**Ph), 5.53–5.60 (2H, m, 2 × CH=C**H**), 5.78–5.86 (2H, m, 2 × C**H**=CH), 7.30–7.75 (15H, m, Ph), 9.59 (1H, d, *J* 1.6, CHO); δ_C (100.6 MHz, $CDCl_3$) 26.1 (CH_2), 30.0 (SiCH), 80.6 (CHPh), 123.2 (2 × CH=CH), 124.4 (2 × CH=CH), 126.5–136.1 (Ph and *i*-Ph), 198.9 (CHO);[250] *m/z* (GCMS CI^+) 397 (MH^+, 20%), 224 (100), 197 (47), 180 (33), 163 (14); Accurate mass (CI^+): Found 397.1602, $C_{26}H_{25}O_2Si$ (MH^+) requires 397.1624.

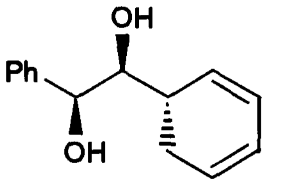
(Triphenylsilanyloxy)phenylacetaldehyde



8.10

To a stirred solution of (±)-ethyl mandelate (323 μL, 2.00 mmol), DMAP (6.1 mg, 0.05 mmol) and TEA (335 μL, 2.40 mmol) in anhydrous DMF (20.0 mL) was added triphenylsilyl chloride (708 mg, 2.40 mmol) and the reaction mixture warmed to 60 °C for 8 hr. The solution was cooled to RT and partitioned between water (100 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (2 x 50 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual viscous oil was purified by flash column chromatography (silica gel, 20:1, petrol:diethyl ether) to furnish **8.10** as a colourless syrup (774 mg, 88%). R_f 0.50 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3069m, 3049m, 3028w, 3008w, 2936w, 2904w, 1962w, 1895w, 1826w, 1752s (C=O), 1691w, 1590w, 1486w, 1454w, 1429s, 1369w, 1264m, 1207m, 1178m, 1118s, 1071m, 1028m, 998w, 880w, 864w, 836m, 742m, 728m, 712s, 699s; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.2, OCH_2CH_3), 3.91 and 3.97 (2 x 1H, 2 x dq, *J* 10.8 and 7.2, OCH_2CH_3), 5.37 (1H, s, CHPh), 7.32–7.55 (15H, m, Ph), 7.67–7.71 (5H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 13.9 (OCH_2CH_3), 61.0 (OCH_2CH_3), 74.9 (CHPh), 126.7–135.6 (Ph), 133.5 (*i*-Ph), 138.6 (*i*-Ph), 171.5 (CO_2);[250] *m/z* (GCMS CI$^+$) 456 (MNH_4^+, 10%), 439 (MH^+, 2), 361 (M^+-C_6H_5, 100), 259 (16), 196 (12), 105 (24), 78 (15); Accurate mass (CI$^+$): Found 456.1994, $C_{28}H_{30}NO_3Si$ (MNH_4^+) requires 456.1995.

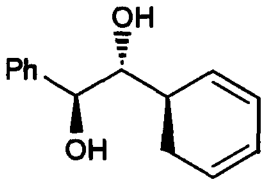
rel-(1*S*,2*S*)-1-[rel-(1*S*)-Cyclohexa-2,4-dienyl]-2-phenylethan-1,2-diol



8.11

A degassed solution of crude aldehyde **8.07**[268] in anhydrous toluene (5.0 mL) was heated at 120 °C in a base-washed sealed tube. After 20 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The crude siladioxolane was dissolved in methanol (5.0 mL); KF (90.1 mg, 1.55 mmol) and H_2O_2 (35% in water, 500 μL) were added and the reaction mixture was stirred at RT for 2 hr. The solvent was removed *in vacuo* and the residue taken up in diethyl ether (25 mL) and washed with water (25 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL) and the combined organic fractions were washed with saturated *aq*. NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 5:1, petrol:diethyl ether) to furnish both **8.11** (20.5 mg, 19%) and **8.12** (6.9 mg, 6%) as colourless crystals. R_f 0.54 (diethyl ether); M.p. 100–103 °C (from chloroform); ν_{max}/cm^{-1} (KBr disc) 3392s (br, O-H), 3036m, 2921w, 1951w, 1891w, 1818w, 1691w, 1600w, 1494w, 1452w, 1429w, 1409w, 1198w, 1116m, 1064m, 1026m, 971w, 919w, 842w, 761m, 700s; δ_H (500 MHz, $CDCl_3$) 2.24-2.29 (2H, m, =CH**CH_2**), 2.31 (1H, d, *J* 5.0, CH(O**H**)CH), 2.43 (1H, dddd, *J* 10.5, 4.5, 4.0 and 2.5, CH(OH)C**H**), 2.78 (1H, br s, CH(O**H**)Ph), 3.64 (1H, dt, *J* 10.5 and 5.0, C**H**(OH)CH), 4.73 (1H, ~d, *J* 5.0, C**H**(OH)Ph), 5.81 (1H, dt, *J* 9.5 and 4.5, =C**H**CH_2), 5.86 (1H, dd, *J* 9.5 and 4.5, C**H**=CHCH_2), 5.87–5.91 (1H, m, C**H**=CH), 6.06 (1H, dd, *J* 9.5 and 4.5, CH=C**H**), 7.29–7.40 (5H, m, Ph); δ_C (125.7 MHz, $CDCl_3$) 26.5 (=CHCH_2), 34.5 (CH(OH)CH), 74.2 (CH(OH)Ph), 79.1 (CH(OH)CH), 123.7, 125.0, 126.2 and 126.3 (CH=CH-CH=CHCH_2), 126.5 (Ph), 127.9 (Ph), 128.5 (Ph), 141.0 (*i*-Ph); *m/z* (CI^+) 234 (MNH_4^+, 100%), 217 (MH^+, 18), 199 (22), 154 (12), 137 (16), 121 (30), 105 (15), 91 (17); Accurate mass (CI^+): Found 234.1493, $C_{14}H_{20}NO_2$ (MNH_4^+) requires 234.1494.

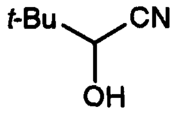
rel-(1*R*,2*S*)-1-[rel-(1*R*)-Cyclohexa-2,4-dienyl]-2-phenylethan-1,2-diol



8.12

R$_f$ 0.58 (diethyl ether); M.p. 75–77 °C (from chloroform); ν_{max}/cm^{-1} (KBr disc) 3428s (br, O-H), 3015s, 2925m, 2873m, 1954w, 1885w, 1813w, 1719w, 1604w, 1494m, 1454m, 1429m, 1410m, 1392m, 1216s, 1078m, 1060m, 1023s, 973w, 924w, 843w, 755s, 702s; δ_H (500 MHz, CDCl$_3$) 1.97 (1H, d, *J* 5.0, CH(O**H**)CH), 2.24–2.33 (3H, m, =CHC**H$_2$** and CH(O**H**)Ph), 2.54-2.61 (1H, m, CH(OH)C**H**), 3.80 (1H, dt, *J* 9.5 and 5.0, C**H**(OH)CH), 4.79 (1H, ~d, *J* 5.0, C**H**(OH)Ph), 5.80 (1H, dt, *J* 9.5 and 4.0, =C**H**CH$_2$), 5.87-5.90 (1H, m, C**H**=CH), 5.91 (1H, dd, *J* 9.5 and 4.0, C**H**=CHCH$_2$), 6.03 (1H, ~dd, *J* 9.5 and 5.0, CH=C**H**), 7.31–7.44 (5H, m, Ph); δ_C (125.7 MHz, CDCl$_3$) 26.4 (=CHCH$_2$), 34.3 (CH(OH)CH), 75.1 (CH(OH)Ph), 78.1 (CH(OH)CH), 123.9, 125.6, 125.7 and 126.0 (CH=CH-CH=CHCH$_2$), 126.9 (Ph), 127.8 (Ph), 128.4 (Ph), 140.5 (*i*-Ph); *m/z* (CI$^+$) 234 (MNH$_4^+$, 52%), 217 (MH$^+$, 40), 199 (74), 183 (24), 154 (29), 136 (43), 121 (50), 105 (100), 94 (69), 78 (73); Accurate mass (CI$^+$): Found 234.1471, $C_{14}H_{20}NO_2$ (MNH$_4^+$) requires 234.1494.

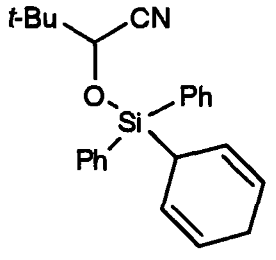
2-Hydroxy-3,3-dimethylbutyronitrile[242]



8.13

To a stirred solution of NaHSO$_3$ (12.6 g, 120 mmol) in water (40.0 mL) cooled to 0 °C was added trimethylacetaldehyde (4.40 mL, 40.0 mmol). After 30 min a solution of KCN (10.4 g, 160 mmol) in water (200 mL) was added dropwise over 20 min; the resulting solution was stirred at RT for 4 hr. The reaction mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were washed with HCl (5.0 M, 150 mL), saturated *aq*. NaCl soln. (150 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting colourless waxy solid was used without further purification (3.98 g, 88%). R_f 0.29 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3436s (br, O-H), 2967s, 2912m, 2876m, 2247w (C≡N), 1638w, 1480m, 1467m, 1398m, 1370s, 1321w, 1292w, 1243m, 1187w, 1077s, 1023s, 949m, 934m, 863w, 766w; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 3.49 (1H, br s, CH(OH)), 4.12 (1H, d, *J* 6.6, CHCN); δ_C (100.6 MHz, $CDCl_3$) 24.9 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 70.5 (CHCN), 119.2 (C≡N); *m/z* (GCMS CI^+) 131 (MNH_4^+, 92%), 104 (100), 87 (90), 70 (56); Accurate mass: (CI^+) Found 131.1185, $C_6H_{15}N_2O$ (MNH_4^+) requires 131.1184.

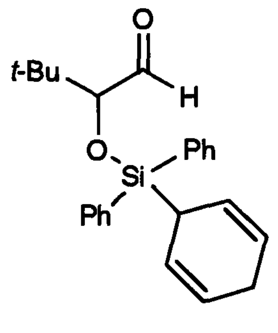
2-[(Cyclohexa-2,5-dienyl)diphenylsilanyloxy]-3,3-dimethylbutyronitrile



8.14

A flame-dried two-necked flask (50 mL) was charged with anhydrous $CuCl_2$ (1.03 g, 7.66 mmol) and anhydrous CuI (72.6 mg, 0.38 mmol). The flask was equipped with a flame-dried Schlenk filter attached to a second round-bottomed flask (50 mL). All joints were sealed with PTFE tape and the apparatus purged several times with argon. Anhydrous THF (15.0 mL) was added followed by cyclohexadienylsilane **8.01** (1.00 g, 3.81 mmol) and the orange suspension stirred for 12 hr at RT. The apparatus was inverted and the inorganics filtered off by suction under argon. The solution of crude chlorosilane in THF was added *via* cannula to a stirred solution of cyanohydrin **8.13** (216 mg, 1.91 mmol), DMAP (584 mg, 4.78 mmol) and TEA (531 µL, 3.81 mmol) in anhydrous DCM (20.0 mL). The reaction mixture was stirred at RT for 22 hr, then partitioned between saturated *aq.* $NaHCO_3$ soln. (100 mL) and diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL), the combined organic layers were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting oil was purified by flash column chromatography (silica gel, petrol → 50:1, petrol:diethyl ether) to furnish silylcyanohydrin **8.14** as a colourless oil (700 mg, 98%). R$_f$ 0.58 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3071w, 3050w, 3028m, 2966m, 2873w, 2821w, 2245w (C≡N), 1961w, 1892w, 1824w, 1591w, 1477m, 1465w, 1429s, 1398w, 1368m, 1335w, 1193w, 1119s, 1035s, 1014s, 994s, 894w, 827m, 778w, 740s, 699s, 625s, 614s; δ_H (400 MHz, CDCl$_3$) 1.05 (9H, s, C(C**H**$_3$)$_3$), 2.07 (1H, dtt, *J* 13.6, 5.2, 5.2, 2.8 and 2.8, C**H**$_a$H), 2.53–2.63 (1H, m, CH**H**$_b$), 3.26–3.34 (1H, m, SiC**H**), 4.04 (1H, s, C**H**CN), 5.56–5.62 (2H, m, 2 × CH=C**H**), 5.83–5.93 (2H, m, 2 × C**H**=CH), 7.41–7.75 (10H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 25.1 (C(CH$_3$)$_3$), 26.1 (CH$_2$), 29.6 (SiCH), 36.3 (C(CH$_3$)$_3$), 71.6 (CHCN), 118.7 (C≡N), 123.8 and 124.2 (2 × CH=CH), 127.9 (Ph), 130.6 (Ph), 131.3 (*i*-Ph), 135.6 (Ph); *m/z* (GCMS CI$^+$) 391 (MNH$_4^+$, 100%), 374 (MH$^+$, 10), 311 (37), 294 (M$^+$-C$_6$H$_7$, 26), 267 (14), 215 (13), 198 (10); Accurate mass (CI$^+$): Found 294.1302, C$_{18}$H$_{20}$NOSi (M$^+$-C$_6$H$_7$) requires 294.1314.

2-[(Cyclohexa-2,5-dienyl)diphenylsilanyloxy]-3,3-dimethylbutyraldehyde

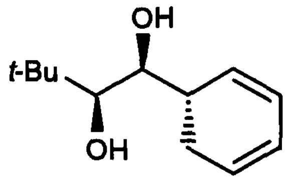


8.17

To a stirred solution of silylcyanohydrin **8.14** (920 mg, 2.46 mmol) in anhydrous DCM (25.0 mL) cooled to -78 °C was added DIBAL (1.0 M in DCM, 3.70 mL, 3.70 mmol) dropwise and the solution stirred at -78 °C for 3 hr and then warmed to -45 °C and stirred for a further 2 hr. The reaction was quenched by the addition of a saturated solution of tartaric acid in methanol (5 mL). The mixture was warmed to RT and partitioned between *aq.* tartaric acid soln. (20% w/v, 50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3

× 25 mL) and the combined organic extracts were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 50:1, petrol:diethyl ether) to furnish aldehyde **8.17** as a colourless syrup (842 mg, 91%). R_f 0.60 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3070w, 3028w, 2962m, 2871w, 2820w, 1734s (C=O), 1590w, 1478w, 1429s, 1396w, 1366m, 1190w, 1119s, 1035s, 1014s, 994m, 935w, 894m, 841m, 740s, 699s, 624s, 614s; δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, $C(CH_3)_3$), 2.03 (1H, dtt, *J* 13.6, 5.2, 5.2, 2.8 and 2.8, CH_aH), 2.49–2.60 (1H, m, CHH_b), 3.15–3.22 (1H, m, SiCH), 3.67 (1H, d, *J* 2.6, OCH), 5.48–5.58 (2H, m, 2 × CH=CH), 5.76–5.89 (2H, m, 2 × CH=CH), 7.35–7.77 (10H, m, Ph), 9.58 (1H, d, *J* 2.6, CHO); δ_C (100.6 MHz, $CDCl_3$) 25.9 ($C(CH_3)_3$), 26.0 (CH_2), 29.9 (SiCH), 36.1 ($C(CH_3)_3$), 85.1 (OCH), 123.7 and 124.2 (2 × CH=CH), 127.9 (Ph), 134.4 (Ph), 134.0 (*i*-Ph), 135.6 (Ph), 203.5 (CHO); *m/z* (GCMS CI$^+$) 377 (MH$^+$, 49%), 315 (26), 311 (28), 297 (M^+-C_6H_7, 100), 216 (17), 198 (20), 181 (28), 179 (24), 163 (42); Accurate mass (CI$^+$): Found 297.1304, $C_{18}H_{21}O_2Si$ (M^+-C_6H_7) requires 297.1311.

rel-(1*S*,2*S*)-1-[rel-(1*S*)-Cyclohexa-2,4-dienyl]-3,3-dimethylbutan-1,2-diol

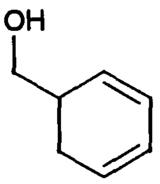


8.19

A degassed solution of aldehyde **8.17** (842 mg, 2.24 mmol) in anhydrous toluene (12.0 mL) was heated at 130 °C in a base-washed sealed tube. After 18 hr the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The crude siladioxolane was dissolved in THF (22.0 mL) cooled to 0 °C and TBAF (1.0 M in THF, 5.60 mL, 5.60 mmol) added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then warmed to RT and stirred for a further 1.5 hr. The reaction was quenched by the addition of saturated *aq.* NH_4Cl

soln. (50 mL). The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 10:1, petrol:diethyl ether) to furnish diol **8.19** as colourless crystals (376 mg, 86%). R_f 0.39 (1:1, petrol:diethyl ether); M.p. 86–88 °C (from diethyl ether); ν_{max}/cm^{-1} (KBr disc) 3445s and 3338s (br, O-H), 3040m, 2957s, 2868m, 2821w, 1480w, 1428w, 1392w, 1361w, 1307w, 1102m, 1050m, 1016m, 986w, 932w, 872w, 852w, 830w, 772w, 740w, 689s; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(C**H**$_3$)$_3$), 2.16 (1H, dddd, *J* 13.2, 11.2, 4.4 and 2.0, =CHC**H**$_a$H), 2.31 (1H, dddd, *J* 13.2, 9.2, 4.4 and 2.0, =CHCH**H**$_b$), 2.32 (1H, d, *J* 6.8, CH(O**H**)CH), 2.43–2.52 (1H, m, CH(OH)C**H**), 2.48 (1H, d, *J* 6.8, CH(O**H**)C(CH$_3$)$_3$), 3.25 (1H, d, *J* 6.8, C**H**(OH)C(CH$_3$)$_3$), 3.73 (1H, t, *J* 6.8, C**H**(OH)CH), 5.78 (1H, dt, *J* 9.6 and 4.4, =C**H**CH$_2$), 5.86–5.94 (2H, m, C**H**=CHCH$_2$ and C**H**=CH), 6.03 (1H, ~dd, *J* 9.6 and 4.4, CH=C**H**); δ_C (100.6 MHz, $CDCl_3$) 25.4 (C(**C**H$_3$)$_3$), 26.0 (=CH**C**H$_2$), 35.1 (**C**(CH$_3$)$_3$), 38.0 (CH(OH)**C**H), 70.7 (**C**H(OH)CH), 77.2 (**C**H(OH)C(CH$_3$)$_3$), 124.3, 125.6, 125.7 and 126.9 (**C**H=**C**H-**C**H=**C**HCH$_2$); *m/z* (CI^+) 214 (MNH_4^+, 43%), 197 (MH^+, 100), 179 (94), 163 (18), 134 (45), 126 (17), 114 (34), 109 (43), 98 (30), 94 (41), 85 (26), 78 (70), 58 (35); Accurate mass (CI^+): Found 197.1536, $C_{12}H_{21}O_2$ (MH^+) requires 197.1541.

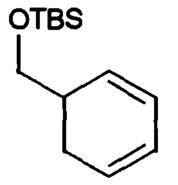
5-Hydroxymethylcyclohexa-1,3-diene[269]



8.25

To a stirred suspension of $NaIO_4$ on silica gel (25 wt%, 1.71 g, 2.00 mmol) in THF (2.0 mL) was added a solution of diol **8.19** (79.0 mg, 0.40 mmol) in THF (2.0 mL). The reaction mixture was stirred vigorously at RT for 3 hr and then filtered through Celite® and washed with THF (2 × 2 mL). The filtrate was added dropwise to a stirred solution of $NaBH_4$ (60.5 mg, 1.60 mmol) in THF (2.0 mL) and methanol (1.0 mL) and stirred at RT for 25 min. The reaction was quenched by the addition of saturated *aq.* NH_4Cl soln. (25 mL); the aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (silica gel, 10:1, petrol:diethyl ether) to furnish **8.25** as a colourless oil (35.8 mg, 81%). R_f 0.38 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3369s (br, O-H), 3037m, 2929m, 2871m, 1450w, 1429m, 1364w, 1127m, 1027s, 910m, 733m, 698s, 678s; δ_H (400 MHz, $CDCl_3$) 1.49 (1H, br s, $CH_2O\mathbf{H}$), 2.19 (1H, dddd, *J* 15.2, 10.8, 4.0 and 2.0, $=CHC\mathbf{H_a}H$), 2.34 (1H, dddd, *J* 15.2, 10.8, 4.4 and 2.0, $=CHCH\mathbf{H_b}$), 2.46–2.55 (1H, m, $C\mathbf{H}CH_2OH$), 3.60 (1H, dd, *J* 12.2 and 6.6, $C\mathbf{H_a}HOH$), 3.63 (1H, dd, *J* 12.2 and 6.2, $CH\mathbf{H_b}OH$), 5.70 (1H, dd, *J* 9.6 and 4.0, $C\mathbf{H}=CH$), 5.78 (1H, ~dt, *J* 10.8 and 4.4, $=C\mathbf{H}CH_2$), 5.86–5.91 (1H, m, $C\mathbf{H}=CHCH_2$), 5.99 (1H, dd, *J* 9.6 and 5.2, $CH=C\mathbf{H}$); δ_C (100.6 MHz, $CDCl_3$) 25.1 ($=CHCH_2$), 35.7 ($CHCH_2OH$), 65.3 (CH_2OH), 123.8, 125.5, 125.7 and 126.8 ($CH=CH$-$CH=CHCH_2$); *m/z* (GCMS CI^+) 128 (MNH_4^+, 100%), 111 (MH^+, 60), 96 (20), 94 (49), 70 (50); Accurate mass (CI^+): Found 111.0814, $C_7H_{11}O$ (MH^+) requires 111.0810.

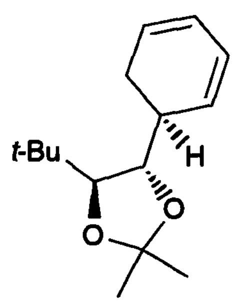
5-[(*tert*-Butyldimethyl)silanyloxy]methylcyclohexa-1,3-diene



8.26

To a stirred solution of 5-hydroxymethylcyclohexa-1,3-diene **8.25** (55.1 mg, 0.50 mmol) and imidazole (68.1 mg, 1.00 mmol) in anhydrous DMF (2.0 mL) was added *tert*-butyldimethylsilyl chloride (90.4 mg, 0.60 mmol) and the reaction mixture was stirred at RT for 16 hr. The solution was partitioned between water (20 mL) and diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, petrol) to furnish **8.26** as a colourless oil (112 mg, 100%). R_f 0.30 (petrol); ν_{max}/cm^{-1} (thin film) 3038m, 2954s, 2928s, 2886s, 2856s, 1656w, 1472s, 1464s, 1430m, 1410m, 1387m, 1361m, 1257s, 1198w, 1177w, 1105s, 1006m, 988w, 968m, 938m, 894m, 836s, 814m, 775s, 677s, 667s; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, 2 × s, $Si(\mathbf{CH_3})_2$), 0.91 (9H, s, $SiC(\mathbf{CH_3})_3$), 2.08–2.18 (1H, m, $=CHC\mathbf{H_a}H$), 2.25 (1H, dddd, *J* 13.2, 8.4, 4.0 and 2.0, $=CHCH\mathbf{H_b}$), 2.43–2.54 (1H, m, $\mathbf{CH}CH_2OTBS$), 3.54 (2H, d, *J* 6.4, $\mathbf{CH_2}OH$), 5.69 (1H, dd, *J* 9.6 and 4.0, $\mathbf{CH}=CH$), 5.76 (1H, ~dt, *J* 9.6 and 4.0, $=\mathbf{CH}CH_2$), 5.84–5.90 (1H, m, $\mathbf{CH}=CHCH_2$), 5.93 (1H, ~ddt, *J* 9.6, 5.2 and 1.2, $CH=\mathbf{CH}$); δ_C (100.6 MHz, $CDCl_3$) –5.35 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_2$), 25.0 ($=CHCH_2$), 25.9 ($C(CH_3)_2$), 35.9 ($CHCH_2OTBS$), 67.3 (CH_2OTBS), 123.9, 124.7, 125.6 and 127.7 ($CH=CH-CH=CHCH_2$); *m/z* (GCMS CI^+) 225 (MH^+, 64%), 184 (19), 167 (11), 131 (22), 106 (44), 93 (100); Accurate mass (CI^+): Found 225.1680, $C_{13}H_{25}OSi$ (MH^+) requires 225.1675.

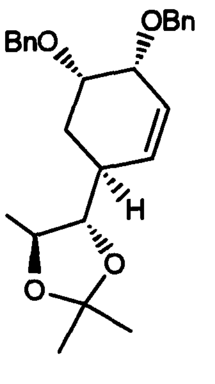
rel-(4*S*,5*S*)-5-(*tert*-Butyl)-4-[rel-(1*S*)-cyclohexa-2,4-dienyl]-2,2-dimethyl-1,3-dioxolane



8.27

To a stirred solution of diol **8.19** (350 mg, 1.78 mol) in 2,2-dimethoxypropane (5.0 mL) was added CSA (21.0 mg, 0.09 mmol) and the reaction mixture was stirred at RT for 1.5 hr. The reaction mixture was partitioned between saturated *aq.* $NaHCO_3$ soln. (50 mL) and diethyl ether (50 mL); the aqueous phase was separated and extracted with diethyl ether (3 × 25 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (50 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 20:1, petrol:diethyl ether) to furnish acetonide **8.27** as a colourless oil (337 g, 80%). R_f 0.74 (5:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3041w, 2983m, 2957m, 2871m, 1480w, 1468w, 1430w, 1395w, 1378m, 1368s, 1249s, 1208m, 1162m, 1115w, 1077m, 1053m, 1027m, 994w, 973w, 928w, 872w, 700m, 681m, 659w; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, $C(C\mathbf{H}_3)_3$), 1.41 (6H, 2 × s, $C(C\mathbf{H}_3)_2$), 2.13–2.19 (2H, m, $=CHC\mathbf{H}_2$), 2.51–2.61 (1H, m, $CH(OR)C\mathbf{H}$), 3.67 (1H, d, *J* 6.0, $C\mathbf{H}(OR)C(CH_3)_3$), 3.87 (1H, t, *J* 6.0, $C\mathbf{H}(OR)CH$), 5.76–5.83 (1H, m, $=C\mathbf{H}CH_2$), 5.91–5.96 (2H, m, $C\mathbf{H}=CHCH_2$ and $C\mathbf{H}=CH$), 5.98–6.04 (1H, m, $CH=C\mathbf{H}$); δ_C (100.6 MHz, $CDCl_3$) 26.2 ($C(CH_3)_3$), 27.1 ($=CHCH_2$), 27.5 and 28.4 ($C(CH_3)_2$), 33.4 ($C(CH_3)_3$), 37.8 ($CH(OR)CH$), 79.6 ($CH(OR)CH$), 86.7 ($CH(OR)C(CH_3)_3$), 108.6 ($C(CH_3)_2$), 124.7, 125.0, 125.6 and 127.0 ($CH=CH-CH=CHCH_2$); *m/z* (GCMS CI^+) 237 (MH^+, 100%), 179 (78), 157 (94), 148 (51), 126 (13); Accurate mass (CI^+): Found 237.1854, $C_{15}H_{25}O_2$ (MH^+) requires 237.1855.

rel-(4*S*,5*S*)-5-(*tert*-Butyl)-4-[rel-(1*S*,4*R*,5*S*)-4,5-dibenzyloxycyclohexa-2-enyl]-2,2-dimethyl-1,3-dioxolane

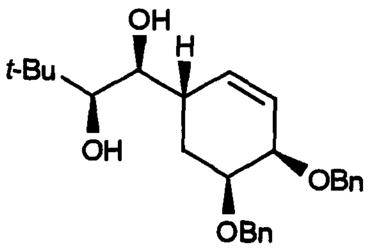


8.28

To a stirred solution of dioxolane **8.27** (172 mg, 0.73 mol) in THF (7.0 mL) was added NMO (171 mg, 1.46 mmol) and OsO_4 (10.2 mg, 0.04 mmol), the reaction mixture was stirred at RT for 3 hr. The reaction was quenched by the addition of dilute *aq.* Na_2SO_3 soln. (10% w/v, 10 mL) and the mixture was partitioned between water (50 mL) and ethyl acetate (50 mL); the aqueous phase was separated and extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residue was azeotroped with toluene (3 × 10 mL) and then dissolved in anhydrous DMF (7.0 mL) and the solution cooled to 0 °C. Benzyl bromide (695 μL, 5.84 mmol) was added, followed by NaH (140 mg, 5.83 mmol). The reaction mixture was allowed to warm slowly to RT over 16 hr. The solution was cooled to 0 °C and quenched by the dropwise addition of methanol (2 mL); the resulting mixture was partitioned between water (50 mL) and diethyl ether (50 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 50 mL); the combined organic fractions were washed with saturated *aq.* NaCl soln. (100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 15 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 10:1, petrol:diethyl ether) gave **8.28** as a colourless oil (107 mg, 33%). R_f 0.48 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3087w, 3063w, 3030w, 2981m, 2955m, 2926m, 2870m, 1949w, 1871w, 1809w, 1725w, 1651w, 1606w, 1496w, 1479w, 1454m, 1378m, 1368m, 1332w, 1247m, 1214m, 1167w, 1114s, 1074s, 1028s, 933w, 908w, 902w, 871w, 816w, 735s, 698s; δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, $C(\mathbf{CH_3})_3$), 1.35 and 1.38 (2 × 3H, 2 × s, $C(\mathbf{CH_3})_2$), 1.57 (1H, ddd, *J* 13.6, 9.0 and 2.0, $\mathbf{CH_{ax}}H$), 2.04 (1H, ddd, *J* 13.6, 6.8 and 5.4, $CH\mathbf{H_{eq}}$), 2.61–2.68 (1H, m, CH(OR)C**H**), 3.65 (1H, d, *J* 7.0, **CH**(OR)$C(CH_3)_3$), 3.70 (1H, dd, *J* 7.0 and 4.4, **CH**(OR)CH), 4.02 (1H, ddd, *J* 5.4, 2.0 and 2.0, **CH**(OBn)CH_2), 4.05–4.09 (1H, m, **CH**(OBn)CH=), 4.61 and 4.68 (2 × 1H, 2 × d, *J* 12.4, $\mathbf{CH_2}$Ph), 4.66 and 4.72 (2 × 1H, 2 × d, *J* 12.6, $\mathbf{CH_2}$Ph), 5.85 (1H, br d, *J* 10.6, **CH**=CH), 5.99 (1H, br d, *J* 10.6, CH=**CH**), 7.27–7.42 (10H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 26.2 ($C(CH_3)_3$), 27.5 and 28.1 ($C(CH_3)_2$), 30.0 (CH_2), 33.0 ($C(CH_3)_3$), 36.2 (CH(OR)CH), 70.2 (CH_2Ph), 71.4 (CH_2Ph), 72.7 (CH(OBn)CH_2), 74.1 (CH(OBn)CH=), 80.5 (CH(OR)CH), 85.9

(CH(OR)C(CH3)3), 108.3 (C(CH3)2), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.9 (Ph), 128.3 (Ph and CH=CH), 129.4 (CH=CH), 138.8 (*i*-Ph), 139.0 (*i*-Ph); *m/z* (ES$^+$) 473 (MNa$^+$, 89%), 468 (MNH$_4^+$, 100), 343 (62), 279 (20); Accurate mass (ES$^+$): Found 451.2856, $C_{29}H_{39}O_4$ (MH$^+$) requires 451.2848.

rel-(1*S*,2*S*)-1-[rel-(1*S*,4*R*,5*S*)-4,5-Dibenzyloxycyclohexa-2-enyl]-3,3-dimethylbutan-1,2-diol

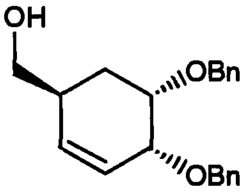


8.29

To a stirred solution of dioxolane **8.28** (80.0 mg, 0.18 mmol) in water (3.0 mL) was added TFA (6.0 mL) and the mixture was stirred at RT for 2 hr. The solution was concentrated *in vacuo* employing toluene (3 × 10 mL) to azeotropically remove water. The residual yellow oil was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish diol **8.29** as a colourless oil (72.0 mg, 99%). R$_f$ 0.23 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3429m (br, O-H), 3088w, 3064w, 3031w, 2954s, 2868m, 1951w, 1875w, 1812w, 1648w, 1606w, 1496w, 1478w, 1454m, 1395m, 1363m, 1306w, 1254w, 1206w, 1090s, 1075s, 1028m, 1014m, 957w, 910m, 855w, 805w, 735s, 698s; δ_H (400 MHz, CDCl$_3$) 0.92 (9H, s, C(C**H**3)3), 1.50 (1H, ddd, *J* 13.8, 8.6 and 1.6, C**H**$_{ax}$H), 2.12 (1H, ddd, *J* 13.8, 7.0 and 5.6, CH**H**$_{eq}$), 2.25 and 2.31 (2 × 1H, 2 × br s, CH(O**H**)CH and CH(O**H**)C(CH3)3), 2.55 (1H, dddd, *J* 8.6, 5.6, 5.6 and 2.4, CH(OH)C**H**), 3.17 (1H, br s, C**H**(OH)C(CH3)3), 3.61 (1H, d, *J* 5.6, C**H**(OH)CH), 3.94–3.99 (1H, m, C**H**(OBn)CH2), 4.02–4.05 (1H, m, C**H**(OBn)CH=), 4.59 and 4.67 (2 × 1H, 2 × d, *J* 12.4, C**H**2Ph), 4.69 (2H, s, C**H**2Ph), 5.85 (1H, br d, *J* 10.4, C**H**=CH), 5.92 (1H, br d, *J* 10.4, CH=C**H**), 7.26–7.43 (10H, m, Ph); δ_C (100.6 MHz, CDCl$_3$) 25.9 (C(CH3)3), 27.3 (CH2), 35.0 (C(CH3)3), 39.0 (CH(OH)CH), 70.6 (CH2Ph), 71.1

(CH$_2$Ph), 71.2 (CH(OH)CH), 72.4 (CH(OBn)CH$_2$), 74.0 (CH(OBn)CH=), 77.1 (CH(OH)C(CH$_3$)$_3$), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.9 (Ph), 128.2 (Ph), 128.3 (Ph and CH=CH), 130.1 (CH=CH), 138.7 (*i*-Ph), 139.0 (*i*-Ph); *m/z* (ES$^+$) 433 (MNa$^+$, 100%), 428 (MNH$_4^+$, 34), 303 (17), 279 (71); Accurate mass (ES$^+$): Found 428.2809, C$_{26}$H$_{38}$NO$_4$ (MNH$_4^+$) requires 428.2801.

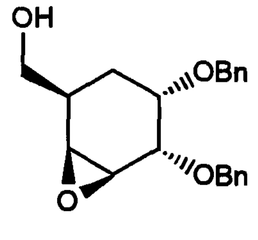
rel-(1*S*,2*R*,5*S*)-1,2-Dibenzyloxy-5-hydroxymethylcyclohex-3-en-1,2-diol



8.30

To a stirred solution of diol **8.29** (71.1 mg, 0.17 mmol) in THF (3.0 mL) and water (1.0 mL) was added NaIO$_4$ (167 mg, 0.78 mmol). The reaction mixture was stirred vigorously at RT for 2.5 hr and then quenched by the addition of saturated *aq.* NaCl soln. (25 mL). The resulting mixture was extracted with ethyl acetate (3 × 15 mL); the combined organic fractions were dried (MgSO$_4$) and the solvents removed *in vacuo*. The residue was dissolved in methanol (4.0 mL) and the resulting solution cooled to 0 °C; NaBH$_4$ (32.9 mg, 0.87 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated *aq.* NH$_4$Cl soln. (15 mL); the aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The resulting pale yellow oil was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish **8.30** as a colourless oil (45.1 mg, 80%). R$_f$ 0.40 (diethyl ether); ν_{max}/cm^{-1} (thin film) 3434m (br, O-H), 3062w, 3029w, 2923m, 2869s, 1955w, 1876w, 1817w, 1724w, 1654w, 1604w, 1496w, 1454m, 1390w, 1359w, 1336w, 1306w, 1206w, 1098s, 1071s, 1038s, 1028s, 910w, 803w, 736s, 697s; δ_H (400 MHz, CDCl$_3$) 1.54 (1H, ddd, *J* 13.6, 8.0 and 2.0, C**H**$_{ax}$H), 1.57 (1H, br s, 6-**OH**), 2.18 (1H, dt, *J* 13.6 and 6.8, CH**H**$_{eq}$), 2.62 (1H, ddddd, *J* 8.0, 6.8, 6.0, 5.4 and 2.4, H-5), 3.55 (1H, dd, *J* 10.6 and 5.4, H-6$_a$), 3.59 (1H, dd, *J* 10.6 and 6.0, H-6$_b$), 3.92–3.97 (1H, m, H-1), 4.02–4.05 (1H, m, H-2), 4.60 and 4.67 (2 × 1H, 2 × d, *J* 12.4, C**H**$_2$Ph), 4.69 and 4.72 (2 × 1H, 2 × d, *J* 12.8, C**H**$_2$Ph), 5.79 (1H, br d, *J* 10.4, H-4), 5.85 (1H, br d, *J* 10.4, H-3), 7.26–7.43 (10H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 27.0 (CH_2), 36.2 (C-5), 66.2 (C-6), 70.7 (CH_2Ph), 70.9 (CH_2Ph), 72.4 (C-1), 73.7 (C-2), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.8 (Ph), 128.0 (C-3), 128.3 (Ph), 130.8 (C-4), 138.8 (*i*-Ph), 138.9 (*i*-Ph); *m/z* (ES^+) 347 (MNa^+, 65%), 342 (MNH_4^+, 100), 325 (MH^+, 14), 217 (19); Accurate mass (ES^+): Found 347.1626, $C_{21}H_{24}O_3Na$ (MNa^+) requires 347.1623.

rel-(1*S*,2*S*,3*S*,4*S*,5*R*)-1,2-Dibenzyloxy-3,4-epoxy-5-hydroxymethylcyclohexan-1,2-diol

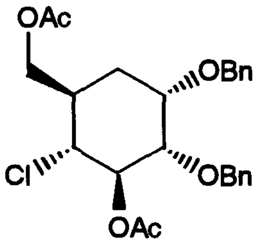


8.31

To a blue-green suspension of $VO(acac)_2$ (1.6 mg, 0.006 mmol) in anhydrous DCM (1.5 mL) cooled to 0 °C was added **8.30** (36.3 mg, 0.11 mmol) in anhydrous DCM (1.0 mL). After 10 min TBHP (5.0 M in decane, 34.0 μL, 0.17 mmol) was added and the dark red solution stirred vigorously for 1 hr at 0 °C and then warmed to RT. After 6 hr the reaction was quenched by the addition of dilute *aq.* Na_2SO_3 soln. (10% w/v, 10 mL) and the mixture extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:1, petrol:diethyl ether) to furnish epoxide **8.31** as a colourless oil (20.5 mg, 54%). R_f 0.29 (diethyl ether); ν_{max}/cm^{-1} (thin film) 3436m (br, O-H), 3058w, 3023w, 2928m, 2870m, 1496w, 1453m, 1355w, 1325w, 1312w, 1261w, 1206w, 1112s, 1095s, 1072s, 1027m, 800w, 734m, 698s; δ_H (400 MHz, $CDCl_3$) 1.12

(1H, ddd, *J* 14.2, 10.2 and 1.6, $CH_{ax}H$), 1.83 (1H, dt, *J* 14.2 and 6.4, CHH_{eq}), 2.38–2.47 (1H, m, H-5), 3.28 (1H, br d, *J* 3.8, H-3), 3.38–3.42 (1H, m, H-4), 3.62 (1H, d, *J* 3.8, H-2), 3.75 (2H, dd, *J* 6.0 and 4.0, H-6), 3.77–3.82 (1H, m, H-1), 4.63 and 4.68 (2 × 1H, 2 × d, *J* 12.2, CH_2Ph), 4.67 and 4.71 (2 × 1H, 2 × d, *J* 12.0, CH_2Ph), 7.30–7.44 (10H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 22.8 (CH_2), 32.7 (C-5), 53.9 (C-3), 54.6 (C-4), 64.9 (C-6), 71.2 (CH_2Ph), 71.4 (C-1), 71.6 (CH_2Ph), 75.1 (C-2), 127.6 (Ph), 127.7 (Ph), 128.3 (Ph), 128.4 (Ph), 138.8 (*i*-Ph), 138.9 (*i*-Ph); *m/z* (ES^+) 363 (MNa^+, 100%), 358 (MNH_4^+, 12), 255 (13); Accurate mass (ES^+): Found 363.1569, $C_{21}H_{24}O_4Na$ (MNa^+) requires 363.1572.

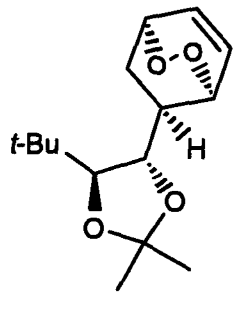
rel-(1*S*,2*S*,3*R*,4*R*,5*R*)-3-*O*-Acetyl-1,2-dibenzyloxy-4-chloro-5-acetoxymethylcyclohexan-1,2,3-triol



8.32

To a stirred solution of epoxide **8.31** (6.0 mg, 0.018 mmol) in THF (1.5 mL) and water (300 μL) was added dilute HCl (1.0 M, 50.0 μL). The reaction mixture was stirred at RT for 16 hr and then concentrated *in vacuo* employing toluene (3 × 2.5 mL) to azeotropically remove water. The residue was dissolved in anhydrous DCM (1.0 mL); pyridine (15.0 μL, 0.19 mmol), DMAP (cat.) and acetic anhydride (34.0 μL, 0.36 mmol) were added and the reaction mixture was stirred at RT for 1.5 hr. The solution was cooled to 0 °C and quenched by the dropwise addition of saturated *aq.* $NaHCO_3$ soln. (1.0 mL). The mixture was partitioned between water (5 mL) and diethyl ether (5 mL); the aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (15 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish **8.32** as a colourless oil (7.7 mg, 95%). R_f 0.28 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3065w, 3031w, 2959m, 2930m, 2873m, 1743s (C=O), 1497w, 1454w, 1371m, 1229s, 1072m, 1038m, 906w, 768w, 738w, 698m, 672w; δ_H (400 MHz, $CDCl_3$) 1.31 (1H, ddd, *J* 14.4, 12.8 and 2.0, **CH$_{ax}$H**), 2.00 (1H, dt, *J* 14.4 and 3.8, **CHH$_{eq}$**), 2.06 and 2.10 (2 × 3H, 2 × s, 2 × **OAc**), 2.40–2.50 (1H, m, H-5), 3.32 (1H, dd, *J* 10.0 and 2.6, H-2), 3.76 (1H, dd, *J* 11.2 and 10.0, H-4), 3.93–3.96 (1H, m, H-1), 4.20 (1H, dd, *J* 11.2 and 2.2, H-6$_a$), 4.31 (1H, dd, *J* 11.2 and 4.4, H-6$_b$), 4.50 and 4.61 (2 × 1H, 2 × d, *J* 12.4, **CH$_2$Ph**), 4.64 and 4.77 (2 × 1H, 2 × d, *J* 12.0, **CH$_2$Ph**), 5.63 (1H, t, *J* 10.0, H-3), 7.28–7.38 (10H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 20.6 and 20.8 (2 × **Ac**), 30.4 (**CH$_2$**), 37.5 (C-5), 60.6 (C-4), 64.5 (C-6), 71.8 (C-1), 72.0 (CH$_2$Ph), 72.1 (CH$_2$Ph), 74.6 (C-3), 80.9 (C-2), 127.3 (Ph), 127.4 (Ph), 127.6 (Ph), 128.2 (Ph), 128.3 (Ph), 137.9 (*i*-Ph), 138.3 (*i*-Ph), 169.6 and 170.6 (C=O, 2 × **Ac**); *m/z* (ES$^+$) 483 (MNa$^+$, 67%), 478 (MNH$_4^+$, 100), 454 (17), 279 (15), 153 (13); Accurate mass (ES$^+$): Found 478.1994, $C_{25}H_{33}NO_6Cl$ (MNH$_4^+$) requires 478.1996.

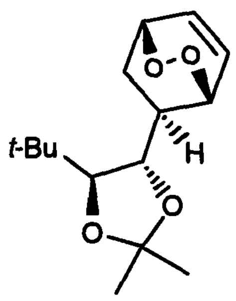
rel-(1*S*,4*S*,7*R*)-7-[rel-(4*S*,5*S*)-5-(*tert*-Butyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3-dioxabicyclo[2.2.2]-oct-5-ene



8.33

A stirred solution of dioxolane **8.27** (261 mg, 1.10 mol) and methylene blue indicator (20.0 μL, 0.05% w/v in DCM) in anhydrous DCM (165 mL) was cooled to -78 °C. The resulting mixture was irradiated with a tungsten filament lamp (300 Watt) while oxygen was passed through the solution; after 4.5 hr the solution was warmed to RT and filtered through a short plug of silica gel and Celite®; the residue was washed with DCM (3 × 20 mL) and the filtrate concentrated *in vacuo*. The resulting material was purified by flash column chromatography (silica gel, 5:1, petrol:diethyl ether) to furnish the diastereomeric endoperoxides **8.33** and **8.34** as colourless crystals (225 mg, 2:1, 76%).[270] R_f 0.44 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (KBr disc) 2961s, 2871m, 1480w, 1469w, 1441w, 1396w, 1380m, 1370s, 1335w, 1301w, 1247s, 1216s, 1175w, 1157m, 1094w, 1073m, 1053m, 1028m, 996w, 960w, 948w, 881w, 867w, 756s, 711w, 667m; δ_H (400 MHz, CDCl$_3$) 0.89 (9H, s, C(C**H**$_3$)$_3$), 1.18 (1H, ddd, *J* 13.2, 4.8 and 1.6, CH**H**$_{eq}$), 1.41 and 1.47 (2 × 3H, 2 × s, C(C**H**$_3$)$_2$), 2.35 (1H, ddd, *J* 13.2, 9.2 and 4.4, C**H**$_{ax}$H), 2.75 (1H, dddd, *J* 9.2, 9.2, 4.8 and 3.2, CH(OR)C**H**), 3.40 (1H, dd, *J* 9.2 and 4.8, C**H**(OR)CH), 3.67 (1H, d, *J* 4.8, C**H**(OR)C(CH$_3$)$_3$), 4.64–4.68 (1H, m, C**H**(O$_2$)CH$_2$), 4.87–4.91 (1H, m, C**H**(O$_2$)CH=), 6.68–6.71 (2H, m, C**H**=C**H**); δ_C (100.6 MHz, CDCl$_3$) 26.1 (C(**C**H$_3$)$_3$), 27.0 (**C**H$_2$), 27.5 and 28.6 (C(**C**H$_3$)$_2$), 33.4 (**C**(CH$_3$)$_3$), 38.8 (CH(OR)**C**H), 70.2 (**C**H(O$_2$)CH$_2$), 72.2 (**C**H(O$_2$)CH=), 80.1 (**C**H(OR)CH), 88.8 (**C**H(OR)C(CH$_3$)$_3$), 109.6 (**C**(CH$_3$)$_2$), 131.3 (**C**H=CH), 132.4 (CH=**C**H); *m/z* (GCMS CI$^+$) 286 (MNH$_4^+$, 7%), 269 (MH$^+$, 45), 253 (64), 211 (100), 194 (37), 185 (90), 177 (51), 169 (33), 157 (33).; Accurate mass (CI$^+$): Found 286.2014, $C_{15}H_{28}NO_4$ (MNH$_4^+$) requires 286.2018.

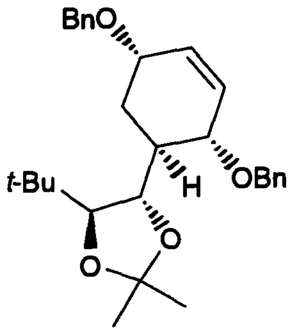
rel-(1*R*,4*R*,7*R*)-7-[rel-(4*S*,5*S*)-5-(*tert*-Butyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3-dioxabicyclo[2.2.2]-oct-5-ene



8.34

R_f 0.42 (1:1, petrol:diethyl ether); ν_{max}/cm^{-1} (KBr disc) 3066w, 3017m, 2983m, 2960s, 2871m, 1480w, 1468w, 1458w, 1441w, 1396w, 1380m, 1370s, 1335w, 1301w, 1247s, 1216s, 1179w, 1157m, 1087m, 1068m, 1053m, 1027m, 994w, 960w, 926w, 908w, 867w, 757s, 711w, 668m; δ_H (400 MHz, $CDCl_3$) 0.99 (9H, s, $C(CH_3)_3$), 1.39 and 1.47 (2 × 3H, 2 × s, $C(CH_3)_2$), 1.60 (1H, ddd, *J* 13.2, 10.8 and 2.0, $CH_{ax}H$), 1.80 (1H, ddd, *J* 13.2, 4.8 and 4.0, CHH_{eq}), 1.91 (1H, dddd, *J* 10.8, 10.8, 4.8 and 1.6, CH(OR)C**H**), 3.68 (1H, d, *J* 3.4, C**H**(OR)$C(CH_3)_3$), 4.28 (1H, dd, *J* 10.8 and 3.4, C**H**(OR)CH), 4.61–4.66 (1H, m, C**H**$(O_2)CH_2$), 4.89–4.93 (1H, m, C**H**(O_2)CH=), 6.66–6.69 (1H, m, CH=C**H**), 6.77 (1H, ddd, *J* 8.4, 6.4 and 2.0, C**H**=CH); δ_C (100.6 MHz, $CDCl_3$) 25.2 (CH_2), 26.3 ($C(CH_3)_3$), 27.9 and 29.3 ($C(CH_3)_2$), 34.0 ($C(CH_3)_3$), 39.2 (CH(OR)CH), 70.3 ($CH(O_2)CH_2$), 71.6 ($CH(O_2)$CH=), 78.7 (CH(OR)CH), 89.7 (CH(OR)$C(CH_3)_3$), 109.8 ($C(CH_3)_2$), 132.4 (CH=CH), 132.8 (CH=CH); *m/z* (GCMS CI^+) 269 (MH^+, 46%), 253 (20), 211 (25), 195 (20), 185 (100), 175 (21).; Accurate mass (CI^+): Found 269.1756, $C_{15}H_{25}O_4$ (MH^+) requires 269.1753.

rel-(4*S*,5*S*)-5-(*tert*-Butyl)-4-[rel-(1*S*,2*S*,5*S*)-2,5-dibenzyloxycyclohexa-3-enyl]-2,2-dimethyl-1,3-dioxolane



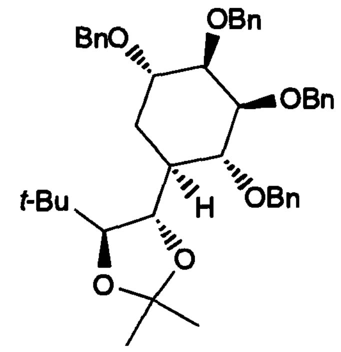
8.35

To a stirred solution of endoperoxide **8.33** (20.0 mg, 0.075 mol) in anhydrous THF (1.5 mL) cooled to 0 °C was added $LiAlH_4$ (7.2 mg, 0.19 mmol) and the reaction mixture stirred at 0 °C for 30 min and then RT for 15 min. The reaction mixture was re-cooled to 0 °C and quenched by the dropwise addition of saturated *aq.* potassium sodium tartrate soln. (1.5 mL) and stirred for 15 min. The mixture was partitioned between water (15 mL) and ethyl acetate (15 mL); the aqueous phase was separated and extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo* to furnish the ene-diol as a pale yellow solid; δ_H (400 MHz,

$\mathrm{CDCl_3}$) 0.94 (9H, s, $\mathrm{C(C\mathbf{H}_3)_3}$), 1.37 (1H, td, *J* 13.6 and 3.4, $\mathrm{C\mathbf{H}_{ax}H}$), 1.46 and 1.48 (2 × 3H, 2 × s, $\mathrm{C(C\mathbf{H}_3)_2}$), 1.69 (1H, br s, $\mathrm{CH(O\mathbf{H})CH_2}$), 1.77 (1H, dt, *J* 13.6 and 2.8, $\mathrm{CH\mathbf{H}_{eq}}$), 2.08 (1H, ddt, *J* 8.8, 3.4 and 2.8, $\mathrm{CH(OR)C\mathbf{H}}$), 3.89 (1H, dd, *J* 8.8 and 5.2, $\mathrm{C\mathbf{H}(OR)CH}$), 3.92 (1H, d, *J* 5.2, $\mathrm{C\mathbf{H}(OR)C(CH_3)_3}$), 4.00 (1H, br s, $\mathrm{CH(O\mathbf{H})CH{=}}$), 4.18–4.23 (1H, m, $\mathrm{C\mathbf{H}(OH)CH_2}$), 4.28 (1H, br d, *J* 8.8, $\mathrm{C\mathbf{H}(OH)CH{=}}$), 5.85–5.87 (2H, m, $\mathrm{C\mathbf{H}{=}C\mathbf{H}}$). The crude ene-diol was azeotroped with toluene (3 × 5 mL) and then dissolved in anhydrous DMF (3.0 mL) and the solution cooled to 0 °C. Benzyl bromide (36.0 μL, 0.30 mmol) was added, followed by NaH (7.2 mg, 0.30 mmol) and the reaction mixture was warmed slowly to RT over 16 hr. The solution was cooled to 0 °C and quenched by the dropwise addition of methanol (500 μL); the resulting mixture was partitioned between water (25 mL) and diethyl ether (15 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 15 mL); the combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried ($\mathrm{MgSO_4}$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 10 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 5:1, petrol:diethyl ether) gave **8.35** as a colourless oil (27.2 mg, 81%). R_f 0.40 (5:1, petrol:diethyl ether); $\nu_{max}/\mathrm{cm^{-1}}$ (thin film) 3030w, 2952m, 2869m, 1497w, 1480w, 1454w, 1377w, 1367m, 1240m, 1216w, 1170w, 1065s, 1028m, 914w, 733m, 697s; δ_H (400 MHz, $\mathrm{CDCl_3}$) 0.91 (9H, s, $\mathrm{C(C\mathbf{H}_3)_3}$), 1.37 and 1.40 (2 × 3H, 2 × s, $\mathrm{C(C\mathbf{H}_3)_2}$), 1.82 (1H, ddd, *J* 14.0, 11.6 and 4.0, $\mathrm{C\mathbf{H}_{ax}H}$), 1.95 (1H, ~ddt, *J* 14.0, 3.6 and 1.0, $\mathrm{CH\mathbf{H}_{eq}}$), 2.37 (1H, dddd, *J* 11.6, 8.0, 3.6 and 2.0, $\mathrm{CH(OR)C\mathbf{H}}$), 3.71 (1H, dd, *J* 8.8 and 2.0, $\mathrm{C\mathbf{H}(OR)CH}$), 3.96 (1H, ddd, *J* 4.0, 4.0 and 3.6, $\mathrm{C\mathbf{H}(OBn)CH_2}$), 4.13 (1H, d, *J* 8.8, $\mathrm{C\mathbf{H}(OR)C(CH_3)_3}$), 4.35 (1H, ~ddt, *J* 8.0, 2.6 and 1.0, $\mathrm{C\mathbf{H}(OBn)CH{=}}$), 4.54 and 4.70 (2 × 1H, 2 × d, *J* 11.4, $\mathrm{C\mathbf{H}_2Ph}$), 4.60 (2H, s, $\mathrm{C\mathbf{H}_2Ph}$), 5.98 (1H, ~ddt, *J* 10.2, 4.0 and 1.0, $\mathrm{C\mathbf{H}{=}CH}$), 6.06 (1H, dd, *J* 10.2 and 2.6, $\mathrm{CH{=}C\mathbf{H}}$), 7.26–7.40 (10H, m, Ph); δ_C (100.6 MHz, $\mathrm{CDCl_3}$) 26.3 ($\mathrm{C(CH_3)_3}$), 27.4 and 27.8 ($\mathrm{C(CH_3)_2}$), 32.2 ($\mathrm{CH_2}$), 32.5 ($\mathrm{C(CH_3)_3}$), 36.2 ($\mathrm{CH(OR)CH}$), 69.6 ($\mathrm{CH_2Ph}$), 70.4 ($\mathrm{CH(OBn)CH_2}$), 70.7 ($\mathrm{CH_2Ph}$), 73.5

(CH(OBn)CH=), 80.5 (CH(OR)CH), 84.8 (CH(OR)C(CH$_3$)$_3$), 107.1 (C(CH$_3$)$_2$), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 128.2 (CH=CH), 128.3 (Ph), 128.4 (Ph), 131.4 (CH=CH), 138.5 (*i*-Ph), 140.0 (*i*-Ph); *m/z* (ES$^+$) 473 (MNa$^+$, 100%), 468 (MNH$_4^+$, 57), 451 (MH$^+$, 12), 343 (98), 285 (23); Accurate mass (ES$^+$): Found 473.2668, C$_{29}$H$_{38}$O$_4$Na (MNa$^+$) requires 473.2668.

rel-(4*S*,5*S*)-5-(*tert*-Butyl)-4-[rel-(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3,4,5-tetra(benzyloxy)cyclohexyl]-2,2-dimethyl-1,3-dioxolane

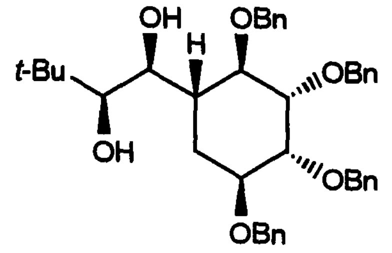


8.36

To a stirred solution of ene-diol **8.35** (24.1 mg, 0.053 mmol) in THF (2.5 mL) was added NMO (6.9 mg, 0.059 mmol) and OsO$_4$ (cat.), the reaction mixture was stirred at RT for 1 hr. The reaction was quenched by the addition of dilute *aq.* Na$_2$SO$_3$ soln. (10% w/v, 2.5 mL) and the mixture partitioned between water (10 mL) and ethyl acetate (10 mL); the aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with saturated *aq.* NaCl soln. (25 mL), dried (MgSO$_4$) and the solvents removed *in vacuo*. The residue was azeotroped with toluene (3 × 5 mL) and then dissolved in anhydrous DMF (2.5 mL) and the solution cooled to 0 °C. Benzyl bromide (26 μL, 0.22 mmol) was added, followed by NaH (5.5 mg, 0.23 mmol). The reaction mixture was allowed to warm slowly to RT over 12 hr. The solution was cooled to 0 °C and quenched by the dropwise addition of methanol (500 μL); the resulting mixture was partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL); the combined organic fractions were washed with saturated *aq.*

NaCl soln. (25 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was azeotroped with toluene (2 × 10 mL) to remove traces of DMF. Purification by flash column chromatography (silica gel, 7:1, petrol:diethyl ether) gave benzylated tetraol **8.36** as a colourless oil (27.4 mg, 77%). R_f 0.30 (7:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3056w, 3030w, 2978w, 2952m, 2932m, 2869m, 1496w, 1453m, 1367m, 1247w, 1208w, 1072s, 1027m, 734m, 697s; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, $C(\mathbf{CH_3})_3$), 1.39 and 1.47 (2 × 3H, 2 × s, $C(\mathbf{CH_3})_2$), 1.74 (1H, ~dt, *J* 14.2 and 4.0, $CH\mathbf{H_{eq}}$), 2.04 (1H, ddd, *J* 14.2, 11.2 and 4.0, $\mathbf{CH_{ax}}H$), 2.24 (1H, dddd, *J* 11.2, 8.2, 4.0 and 4.0, $CH(OR)\mathbf{CH}$), 3.73 (1H, ddd, *J* 4.0, 4.0 and 3.6, $\mathbf{CH}(OBn)CH_2$), 3.81 (1H, dd, *J* 4.0 and 3.6, $\mathbf{CH}(OBn)CH(OBn)$), 3.84–3.87 (1H, m, $\mathbf{CH}(OR)CH$), 3.89 (1H, dd, *J* 8.2 and 3.6, $CH(OBn)\mathbf{CH}(OBn)$), 4.09 (1H, d, *J* 7.2, $\mathbf{CH}(OR)C(CH_3)_3$), 4.18 (1H, t, *J* 8.2, $\mathbf{CH}(OBn)CH$), 4.43 and 4.49 (2 × 1H, 2 × d, *J* 11.6, $\mathbf{CH_2}Ph$), 4.57 and 4.66 (2 × 1H, 2 × d, *J* 11.6, $\mathbf{CH_2}Ph$), 4.64 and 4.72 (2 × 1H, 2 × d, *J* 12.2, $\mathbf{CH_2}Ph$), 4.70 (2H, s, $\mathbf{CH_2}Ph$), 7.23–7.38 (20H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 26.4 ($C(\mathbf{CH_3})_3$), 27.4 and 28.5 ($C(\mathbf{CH_3})_2$), 30.8 ($\mathbf{CH_2}$), 32.8 ($\mathbf{C}(CH_3)_3$), 33.2 ($CH(OR)\mathbf{CH}$), 71.2 ($\mathbf{CH_2}Ph$), 72.5 ($\mathbf{CH_2}Ph$), 72.6 ($\mathbf{CH_2}Ph$), 72.7 ($\mathbf{CH_2}Ph$), 74.9 ($\mathbf{CH}(OBn)CH_2$), 76.5 ($\mathbf{CH}(OBn)CH$), 77.0 ($\mathbf{CH}(OBn)CH(OBn)$), 80.0 ($CH(OBn)\mathbf{CH}(OBn)$), 82.1 ($\mathbf{CH}(OR)CH$), 86.9 ($\mathbf{CH}(OR)C(CH_3)_3$), 107.8 ($\mathbf{C}(CH_3)_2$), 127.3 (Ph), 127.4 (Ph), 127.5 (Ph), 127.7 (Ph), 127.9 (Ph), 128.2 (Ph), 128.3 (Ph), 138.7 (*i*-Ph), 138.8 (*i*-Ph), 138.9 (*i*-Ph), 139.0 (*i*-Ph);[250] *m/z* (ES$^+$) 687 (MNa$^+$, 45%), 682 (MNH_4^+, 30), 665 (MH$^+$, 100), 515 (12), 454 (14), 413 (12), 391 (18), 342 (19), 301 (15), 279 (19), 226 (20); Accurate mass (ES$^+$): Found 665.3836, $C_{43}H_{53}O_6$ (MH$^+$) requires 665.3842.

rel-(1*S*,2*S*)-1-[rel-(1*R*,2*R*,3*S*,4*R*,5*S*)-2,3,4,5-Tetra(benzyloxy)cyclohexyl]-3,3-dimethylbutan-1,2-diol

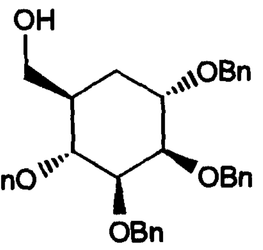


8.37

To a stirred solution of dioxolane **8.36** (23.3 mg, 0.18 mmol) in THF (2.0 mL) and water (1.0 mL) was added TFA (2.0 mL) and the mixture was stirred at RT for 1.5 hr. The solution was concentrated *in vacuo* employing toluene (3 × 10 mL) to azeotropically remove water. The residue was purified by flash column chromatography (silica gel, 5:1, petrol:diethyl ether) to furnish diol **8.37** as a colourless oil (20.3 mg, 93%). R$_f$ 0.35 (2:1, petrol:diethyl ether); ν_{max}/cm^{-1} (thin film) 3435m (br, O-H), 3064w, 3030w, 2949m, 2927m, 2865w, 1496w, 1454m, 1390w, 1363w, 1309w, 1207w, 1097s, 1066s, 1028m, 734s, 697s; δ_H (400 MHz, CDCl$_3$) 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.52 (1H, ddd, *J* 14.2, 12.0 and 2.8, C**H**$_{ax}$H), 1.92 (1H, ddd, *J* 14.2, 4.0 and 3.6, CH**H**$_{eq}$), 2.09 (1H, dddd, *J* 12.0, 9.2, 7.6 and 4.0, CH(OH)C**H**), 3.13 (1H, br s, C**H**(OH)C(CH$_3$)$_3$), 3.69 (1H, ddd, *J* 3.6, 3.6 and 2.8, C**H**(OBn)CH$_2$), 3.78 (1H, d, *J* 7.6, C**H**(OH)CH), 3.83 (1H, dd, *J* 3.6 and 2.8, C**H**(OBn)CH(OBn)), 3.93 (1H, dd, *J* 9.2 and 2.8, CH(OBn)C**H**(OBn)), 4.00 (1H, t, *J* 9.2, C**H**(OBn)CH), 4.34 and 4.54 (2 × 1H, 2 × d, *J* 12.0, C**H**$_2$Ph), 4.59 (2H, s, C**H**$_2$Ph), 4.61 and 4.73 (2 × 1H, 2 × d, *J* 12.0, C**H**$_2$Ph), 4.71 and 5.08 (2 × 1H, 2 × d, *J* 10.8, C**H**$_2$Ph), 7.23–7.36 (20H, m, Ph); δ_C (125.7 MHz, CDCl$_3$) 26.3 (C(CH$_3$)$_3$), 26.8 (CH$_2$), 34.9 (C(CH$_3$)$_3$), 39.7 (CH(OH)CH), 70.8 (CH$_2$Ph), 72.5 (CH$_2$Ph), 72.9 (CH$_2$Ph), 73.0 (CH(OH)CH), 74.0 (CH$_2$Ph), 74.1 (CH(OBn)CH$_2$), 76.1 (CH(OBn)CH(OBn)), 77.1 (CH(OH)C(CH$_3$)$_3$), 81.1 (CH(OBn)CH), 81.7 (CH(OBn)CH(OBn)), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 127.9 (Ph), 128.2 (Ph), 128.3 (Ph), 137.7 (*i*-Ph), 138.2 (*i*-Ph), 138.3 (*i*-Ph), 138.5 (*i*-Ph);[250] *m/z* (ES$^+$) 647

(MNa$^+$, 66%), 625 (MH$^+$, 100); Accurate mass (ES$^+$): Found 625.3526, $C_{40}H_{49}O_6$ (MH$^+$) requires 625.3529.

rel-(1*S*,2*R*,3*S*,4*R*,5*R*)-1,2,3,4,-Tetra(benzyloxy)-5-hydroxymethylcyclohexane



8.38

To a stirred suspension of $NaIO_4$ on silica gel (25 wt%, 85.6 mg, 0.10 mmol) in THF (1.0 mL) was added a solution of diol **8.37** (11.6 mg, 0.019 mmol) in THF (1.0 mL). The reaction mixture was stirred vigorously at RT for 3 hr and then filtered through Celite® and washed with THF (2 × 2 mL). The filtrate was added dropwise to a stirred solution of $NaBH_4$ (3.8 mg, 0.10 mmol) in THF (1.0 mL) and methanol (500 µL) and stirred at RT for 25 min. The reaction was quenched by the addition of saturated *aq.* NH_4Cl soln. (5 mL); the aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic fractions were washed with saturated *aq.* NaCl soln. (15 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, 1:1, petrol:diethyl ether) to furnish benzylated pseudo-mannopyranose **8.38** as a colourless oil (7.7 mg, 77%). R_f 0.57 (diethyl ether); ν_{max}/cm^{-1} (thin film) 3469m (br, O-H), 3090w, 3063w, 3030m, 2923m, 2861m, 1953w, 1877w, 1813w, 1724w, 1605w, 1513w, 1496m, 1453m, 1391w, 1362w, 1323w, 1306w, 1251w, 1234w, 1207w, 1154w, 1091s, 1073s, 1028m, 911w, 734s, 697s; δ_H (500 MHz, $CDCl_3$) 1.64 (1H, ddd, *J* 14.0, 12.5 and 3.0, **CH$_{ax}$H**), 1.73 (1H, dt, *J* 14.0 and 3.5, **CHH$_{eq}$**), 2.04 (1H, dddt, *J* 12.5, 9.5, 6.5, 6.5 and 3.5, H-5), 2.23 (1H, br s, 6-**OH**), 3.64 (2H, br t, *J* 6.5, H-6), 3.68 (1H, ddd, *J* 3.5, 3.0 and 3.0, H-1), 3.80 (1H, t, *J* 3.0, H-2), 3.84 (1H, t, *J* 9.5, H-4), 3.89 (1H, dd, *J* 9.5 and 3.0, H-3), 4.32 and 4.48 (2 × 1H, 2 × d, *J* 12.0, **CH$_2$**Ph), 4.59 and 4.76 (2 × 1H, 2 × d, *J* 12.0, **CH$_2$**Ph), 4.60 and 4.67 (2 × 1H, 2 × d, *J* 11.0, **CH$_2$**Ph), 4.69 and 5.03 (2 × 1H, 2 × d, *J* 11.0, CH$_2$Ph), 7.26–7.39 (20H, m, Ph); δ_C (125.7 MHz, CDCl$_3$) 26.8 (CH$_2$), 39.0 (C-5), 65.9 (C-6), 70.7 (CH$_2$Ph), 72.5 (CH$_2$Ph), 72.9 (CH$_2$Ph), 74.6 (C-1), 74.9 (CH$_2$Ph), 76.0 (C-2), 80.5 (C-4), 82.2 (C-3), 127.2 (Ph), 127.3 (Ph), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 128.1 (Ph), 128.2 (Ph), 128.3 (Ph), 128.4 (Ph), 138.3 (*i*-Ph), 138.4 (*i*-Ph), 138.5 (*i*-Ph), 138.6 (*i*-Ph); *m/z* (ES$^+$) 561 (MNa$^+$, 100%), 539 (MH$^+$, 69), 454 (26), 391 (33), 342 (18), 326 (22); Accurate mass (ES$^+$): Found 539.2792, $C_{35}H_{39}O_5$ (MH$^+$) requires 539.2797.

References and Footnotes

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(NHCH$_2$CH(OH)), 128.1 (Ph), 128.3 (Ph), 128.6 (Ph), 136.1 (*i*-Ph), 156.2 (C=O, Cbz); *m/z* (CI$^+$) 243 (MNH$_4^+$, 33%), 226 (MH$^+$, 100), 200 (16), 182 (66), 169 (22), 108 (19), 91 (22).

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[221] Data for phenyl ether **8.03**; R_f 0.40 (2:1, petrol:diethyl ether); $[\alpha]_D^{22}$ –29.7 (*c* 1.01, chloroform); ν_{max}/cm^{-1} (thin film) 3072w, 3051w, 2984m, 2937m, 2909w, 1752s (C=O), 1592w, 1447m, 1430m, 1375m, 1305m, 1273m, 1204m, 1126s, 1062m, 1023m, 985m, 895w, 861w, 809w, 741m, 720s, 701s; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.2, $OCH_2\mathbf{CH_3}$), 1.44 (3H, d, *J* 6.8, $OCH\mathbf{CH_3}$), 4.08–4.16 (2H, m, $O\mathbf{CH_2}CH_3$), 4.60 (1H, q, *J* 6.8, $O\mathbf{CH}CH_3$), 7.35–7.47 (3H, m, Ph), 7.72–7.77 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 21.0 ($OCHCH_3$), 60.8 (OCH_2CH_3), 68.3 ($OCHCH_3$), 127.8 (Ph), 130.5 (Ph), 132.1 (*i*-Ph), 135.1 (Ph), 173.4 (CO_2); *m/z* (GCMS EI^+) 194 (M^+, 7%), 181 (22), 107 (17), 98 (40), 91 (100).

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[267] Aldehydes **8.06** and **8.07** are particularly unstable to flash column chromatography on silica gel.

[268] Prepared from 0.51 mmol of ester **8.05**.

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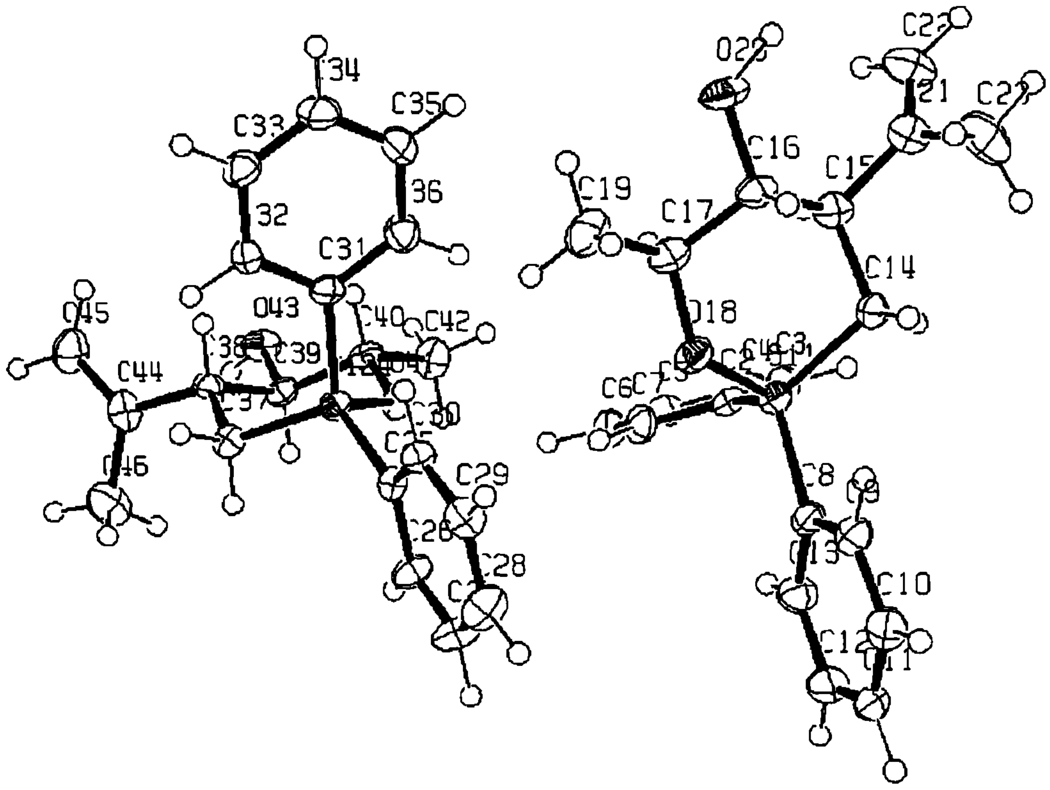
[270] The diastereomeric endoperoxides **8.33** and **8.34** were only partially separable by flash column chromatography.

Appendix 1

X-ray crystal structure data for 2.52



Crystal Data

Molecular Formula: $C_{20}H_{24}O_2Si$

$M_r = 324.50$

Crystal Class: Monoclinic

$a = 10.5057\ (3)$ Å

$b = 9.5503\ (3)$ Å

$c = 18.6166\ (7)$ Å

$\beta = 100.8199\ (11)^\circ$

$V = 1834.6\ (1)$ Å^3

$Z = 4$

Crystal Size: 0.40 × 0.20 × 0.10 mm

Space Group: $P2_1$

$D_x = 1.175$ Mg m^{-3}

Colourless plate

Data Collection and Processing

Diffractometer type Kappa CCD

Scan type 2θ/ω

Radiation type Mo Kα

$\lambda = 0.71073$ Å

Cell parameters from 4193 reflections

8132 measured reflections

4422 independent reflections

2157 reflections with $I > 3.00u(I)$

$R_{int} = 0.04$

$\theta_{max} = 27.467^\circ$

$\theta = 5–27^\circ$

$\mu = 0.135$ mm^{-1}

$T = 150$ K

$h = -13 \rightarrow 13$

$k = -12 \rightarrow 12$

$l = -24 \rightarrow 24$

Refinement

Refinement on F

$R = 0.0345$

$wR = 0.0387$

$S = 1.0985$

2157 reflections

139 parameters

$\Delta\rho_{max} = 0.23$ e Å^{-3}

$\Delta\rho_{max} = -0.24$ e Å^{-3}

Bond lengths (Å)

Si1 – C2	1.860 (4)
Si2 – C8	1.857 (4)
Si1 – C14	1.857 (4)
Si1 – O18	1.653 (3)
C2 – C3	1.405 (5)
C2 – C7	1.392 (5)
C3 – C4	1.388 (6)
C4 – C5	1.382 (6)
C5 – C6	1.391 (6)
C6 – C7	1.392 (6)
C8 – C9	1.395 (6)
C8 – C13	1.396 (6)
C9 – C10	1.396 (6)
C10 – C11	1.391 (6)
C11 – C12	1.367 (6)
C12 – C13	1.393 (6)
C14 – C15	1.551 (6)

C15 – C16	1.551 (6)
C15 – C21	1.513 (6)
C16 – C17	1.526 (6)
C16 – O20	1.429 (5)
C17 – O18	1.442 (5)
C17 – C19	1.522 (6)
C21 – C22	1.327 (7)
C21 – C23	1.496 (6)
Si24 – C25	1.856 (4)
Si24 – C31	1.855 (4)
Si24 – C37	1.852 (4)
Si24 – O41	1.661 (3)
C25 – C26	1.396 (5)
C25 – C30	1.403 (5)
C26 – C27	1.385 (6)
C27 – C28	1.402 (6)
C28 – C29	1.376 (6)

C29 – C30	1.383 (6)
C31 – C32	1.407 (5)
C31 – C36	1.403 (6)
C32 – C33	1.385 (5)
C33 – C34	1.380 (6)
C34 – C35	1.392 (6)
C35 – C36	1.378 (6)
C37 – C38	1.540 (5)
C38 – C39	1.545 (5)
C38 – C44	1.536 (5)
C39 – C40	1.533 (5)
C39 – O43	1.433 (5)
C40 – O41	1.430 (4)
C40 – C42	1.521 (5)
C44 – C45	1.321 (6)
C44 – C46	1.503 (6)

Bond Angles (°)

C2 – Si1 – C8	110.9 (17)
C2 – Si1 – C14	111.12 (18)
C8 – Si1 – C14	112.9 (18)
C2 – Si1 – O18	110.1 (16)
C8 – Si1 – O18	108.0 (17)
C14 – Si1 – O18	103.5 (16)
Si1 – C2 – C3	122.0 (3)
Si1 – C2 – C7	121.0 (3)
C3 – C2 – C7	117.1 (4)
C2 – C3 – C4	121.6 (4)
C3 – C4 – C5	119.9 (4)
O4 – C5 – C6	120.1 (4)
C5 – C6 – C7	119.3 (4)
C2 – C7 – C6	122.1 (4)
Si1 – C8 – C9	120.7 (3)
Si1 – C8 – C13	122.3 (3)
C9 – C8 – C13	116.9 (4)
C8 – C9 – C10	122.0 (4)
C9 – C10 – C11	119.3 (4)
C10 – C11 – C12	119.9 (4)
C11 – C12 – C13	120.5 (4)
C8 – C13 – C12	121.5 (4)
Si1 – C14 – C15	109.5 (3)

C14 – C15 – C16	110.2 (3)
C14 – C15 – C21	113.0 (3)
C16 – C15 – C21	110.1 (3)
C15 – C16 – C17	112.8 (3)
C15 – C16 – O20	110.3 (3)
C17 – C16 – O20	106.8 (3)
C16 – C17 – O18	110.6 (3)
C16 – C17 – C19	112.6 (3)
O18 – C17 – C19	107.2 (3)
Si1 – O18 – C17	118.1 (2)
C15 – C21 – C22	120.9 (4)
C15 – C21 – C23	117.6 (4)
C22 – C21 – C23	121.5 (4)
C25 – Si24 – C31	109.0 (17)
C25 – Si24 – C37	116.6 (18)
C31 – Si24 – C37	111.6 (17)
C25 – Si24 – O41	106.6 (16)
C31 – Si24 – O41	110.0 (16)
C37 – Si24 – O41	102.6 (15)
Si24 – C25 – C26	121.4 (3)
Si24 – C25 – C30	121.6 (3)
C26 – C25 – C30	116.9 (4)
C25 – C26 – C27	121.8 (4)

C26 – C27 – C28	119.9 (4)
C27 – C28 – C29	119.2 (4)
C28 – C29 – C30	120.5 (4)
C25 – C30 – C29	121.7 (4)
Si24 – C31 – C32	122.1 (3)
Si24 – C31 – C36	120.6 (3)
C32 – C31 – C36	117.2 (3)
C31 – C32 – C33	121.5 (4)
C32 – C33 – C34	119.9 (4)
C33 – C34 – C35	119.9 (4)
C34 – C35 – C36	120.2 (4)
C31 – C36 – C35	121.3 (4)
Si24 – C37 – C38	109.2 (3)

C37 – C38 – C39	111.2 (3)
C37 – C38 – C44	113.0 (3)
C39 – C38 – C44	109.6 (3)
C38 – C39 – C40	113.1 (3)
C38 – C39 – O43	110.9 (3)
C40 – C39 – O43	106.3 (3)
C39 – C40 – O41	110.8 (3)
C39 – C40 – C42	112.6 (3)
O41 – C40 – C42	108.0 (2)
Si24 – O41 – C40	118.0 (2)
C38 – C44 – C45	120.7 (4)
C38 – C44 – C46	117.4 (4)
C45 – C44 – C46	121.9 (4)

Fractional atomic coordinates and equivalent isotropic displacement parameters (Å)

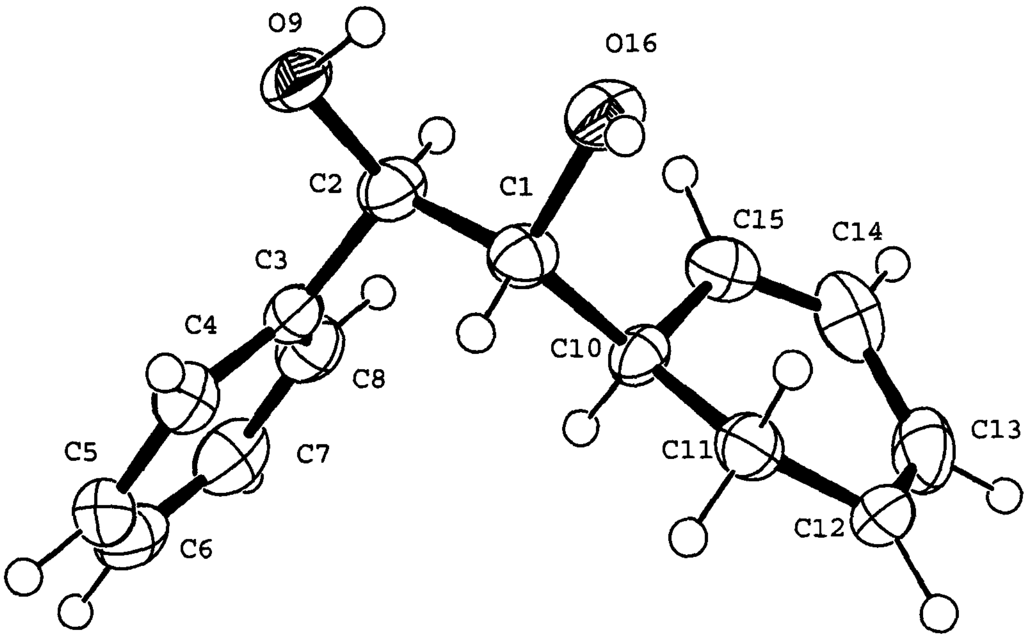
Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
Si1	0.7756 (1)	0.64423 (12)	0.40770 (6)	0.0229
C2	0.8992 (4)	0.5385 (4)	0.3723 (2)	0.0233
O3	1.0145 (4)	0.4946 (4)	0.4177 (2)	0.0287
O4	1.1079 (4)	0.4192 (4)	0.3905 (2)	0.0283
O5	1.0877 (4)	0.3844 (4)	0.3171 (2)	0.0302
O6	0.9750 (4)	0.4266 (5)	0.2705(2)	0.0321
C7	0.8827 (4)	0.5032 (4)	0.2986 (2)	0.0293
C8	0.7976 (4)	0.8339 (4)	0.3916 (2)	0.0236
C9	0.7199 (4)	0.9333 (4)	0.4174 (2)	0.0291
C10	0.7386 (4)	1.0768 (5)	0.4096 (2)	0.0331
C11	0.8380 (4)	1.1227 (4)	0.3754 (2)	0.0310
C12	0.9154 (4)	1.0273 (5)	0.3496 (2)	0.0360
C13	0.8957 (4)	0.8843 (4)	0.3573 (2)	0.0321
C14	0.7747 (4)	0.6026 (4)	0.5050 (2)	0.0252
C15	0.7153 (4)	0.4552 (4)	0.5104 (2)	0.0274
C16	0.5783 (4)	0.4477 (4)	0.4619 (2)	0.0270
C17	0.5807 (4)	0.4632 (4)	0.3806 (2)	0.0290
O18	0.6286 (2)	0.5994 (3)	0.36550 (14)	0.0273
C19	0.4471 (4)	0.4468 (6)	0.3328 (3)	0.0431
O20	0.5195 (3)	0.3155 (3)	0.47081 (17)	0.0361
C21	0.7093 (4)	0.4135 (5)	0.5881 (2)	0.0336
C22	0.7496 (5)	0.2884 (6)	0.6138 (3)	0.0505
C23	0.6579 (5)	0.5189 (6)	0.6349 (3)	0.0529
Si24	0.7294 (1)	0.28771 (12)	0.07654 (6)	0.0214
C25	0.7094 (4)	0.4748 (4)	0.0991 (2)	0.0226
C26	0.7915 (4)	0.5780 (4)	0.0803 (2)	0.0288
C27	0.7768 (5)	0.7179 (5)	0.0966 (3)	0.0387
C28	0.6778 (4)	0.7586 (5)	0.1333 (2)	0.0380
C29	0.5957 (4)	0.6585 (4)	0.1520 (2)	0.0296
C30	0.6099 (4)	0.5194 (4)	0.1345 (2)	0.0257

C31	0.6108 (4)	0.1815 (4)	0.1152 (2)	0.0225
C32	0.4923 (4)	0.1377 (4)	0.0727 (2)	0.0268
C33	0.4015 (4)	0.0652 (5)	0.1032 (2)	0.0309
C34	0.4272 (4)	0.0325 (5)	0.1767 (2)	0.0370
C35	0.5444 (4)	0.0727 (5)	0.2199 (2)	0.0396
C36	0.6343 (4)	0.1458 (5)	0.1896 (2)	0.0333
C37	0.7253 (4)	0.2455 (4)	-0.0210 (2)	0.0243
C38	0.7811 (4)	0.0978 (4)	-0.02680 (19)	0.0222
C39	0.9193 (4)	0.0854 (4)	0.0191 (2)	0.0221
C40	0.9240 (4)	0.1065 (4)	0.1012 (2)	0.0228
O41	0.8794 (2)	0.2433 (3)	0.11548 (14)	0.0238
C42	1.0598 (4)	0.0881 (5)	0.1460 (2)	0.0342
O43	0.9725 (3)	-0.0508 (3)	0.01130 (15)	0.0288
C44	0.7820 (4)	0.0537 (4)	-0.1060 (2)	0.0299
C45	0.7423 (4)	-0.0724 (5)	-0.1296 (2)	0.0391
C46	0.8324 (5)	0.1578 (5)	-0.1544 (2)	0.0440
H31	1.0299 (4)	0.5175 (4)	0.4711 (2)	0.0353
H41	1.1899 (4)	0.3897 (4)	0.4235 (2)	0.0347
H51	1.1549 (4)	0.3302 (4)	0.2974 (2)	0.0373
H61	0.9594 (4)	0.4001 (5)	0.2176 (2)	0.0399
H71	0.8032 (4)	0.5361 (4)	0.2645 (2)	0.0364
H91	0.6493 (4)	0.8997 (4)	0.4424 (2)	0.0405
H101	0.6804 (4)	1.1454 (5)	0.4280 (2)	0.0384
H111	0.8524 (4)	1.2253 (4)	0.3697 (2)	0.0404
H121	0.9878 (4)	1.0598 (5)	0.3257 (2)	0.0458
H131	0.9522 (4)	0.8152 (4)	0.3379 (2)	0.0392
H141	0.8654 (4)	0.6048 (4)	0.5336 (2)	0.0323
H142	0.7209 (4)	0.6732 (4)	0.5255 (2)	0.0323
H151	0.7748 (4)	0.3882 (4)	0.4919 (2)	0.0358
H161	0.5267 (4)	0.5262 (4)	0.4776 (2)	0.0299
H171	0.6398 (4)	0.3881 (4)	0.3687 (2)	0.0392
H191	0.4527 (4)	0.4563 (6)	0.2799 (3)	0.0507
H192	0.3896 (4)	0.5218 (6)	0.3463 (3)	0.0507
H193	0.4105 (4)	0.3529 (6)	0.3413 (3)	0.0507
H221	0.7442 (5)	0.2629 (6)	0.6652 (3)	0.0632
H222	0.7855 (5)	0.2199 (6)	0.5822 (3)	0.0632
H231	0.6584 (5)	0.4790 (6)	0.6846 (3)	0.0756
H232	0.7130 (5)	0.6050 (6)	0.6394 (3)	0.0756
H233	0.5671 (5)	0.5435 (6)	0.6113 (3)	0.0756
H261	0.8615 (4)	0.5491 (4)	0.0537 (2)	0.0353
H271	0.8380 (5)	0.7896 (5)	0.0837 (3)	0.0458
H281	0.6660 (4)	0.8591 (5)	0.1458 (2)	0.0473
H291	0.5240 (4)	0.6871 (4)	0.1775 (2)	0.0366
H301	0.5488 (4)	0.4481 (4)	0.1480 (2)	0.0365
H321	0.4743 (4)	0.1591 (4)	0.0192 (2)	0.0355
H331	0.3166 (4)	0.0380 (5)	0.0724 (2)	0.0390
H341	0.3622 (4)	-0.0204 (5)	0.1990 (2)	0.0487
H351	0.5636 (4)	0.0476 (5)	0.2730 (2)	0.0476
H361	0.7175 (4)	0.1761 (5)	0.2212 (2)	0.0456

H371	0.7785 (4)	0.3152 (4)	-0.0425 (2)	0.0297
H372	0.6337 (4)	0.2489 (4)	-0.0481 (2)	0.0297
H381	0.7221 (4)	0.0331 (4)	-0.00636 (19)	0.0284
H391	0.9715 (4)	0.1601 (4)	0.0005 (2)	0.0304
H401	0.8653 (4)	0.0333 (4)	0.1154 (2)	0.0271
H421	1.0581 (4)	0.1006 (5)	0.1992 (2)	0.0440
H422	1.1177 (4)	0.1603 (5)	0.1302 (2)	0.0440
H423	1.0931 (4)	-0.0075 (5)	0.1378 (2)	0.0440
H451	0.7433 (4)	-0.1001 (5)	-0.1812 (2)	0.0468
H452	0.7117 (4)	-0.1402 (5)	-0.0956 (2)	0.0468
H461	0.8285 (5)	0.1183 (5)	-0.2045 (2)	0.0588
H462	0.9243 (5)	0.1804 (5)	-0.1322 (2)	0.0588
H463	0.7789 (5)	0.2449 (5)	-0.1577 (2)	0.0588
H11	0.5016 (3)	0.2842 (3)	0.52163 (17)	0.0500
H60	1.0206 (3)	-0.0726 (3)	-0.02952 (15)	0.0500

Appendix 2

X-ray crystal structure data for 8.11



Crystal Data
Molecular Formula: $C_{14}H_{16}O_2$
$M_r = 216.28$
Crystal Class: Orthorhombic
$a = 8.4023$ (2) Å
$b = 16.1062$ (4) Å
$c = 17.4221$ (6) Å
$V = 2357.72$ (11) Å^3
$Z = 8$
Crystal Size: 0.50 × 0.30 × 0.20 mm
Space Group: *Pnaa*
$D_x = 1.219$ Mg m^{-3}
Colourless plate

Data Collection and Processing
Diffractometer type Kappa CCD
Scan type 2θ/ω
Radiation type Mo Kα
$\lambda = 0.71073$ Å
Cell parameters from 2930 reflections
5322 measured reflections
2687 independent reflections
1655 reflections with $I > 3.00u(I)$
$R_{int} = 0.02$
$\theta_{max} = 27.486$ °
$\theta = 5$–27 °
$\mu = 0.080$ mm^{-1}
$T = 150$ K
$h = -10 \rightarrow 10$
$k = -20 \rightarrow 20$
$l = -22 \rightarrow 22$

Refinement
Refinement on F
$R = 0.0559$
$wR = 0.0659$
$S = 1.1058$
1655 reflections
145 parameters
$\Delta\rho_{max} = 0.65$ e Å^{-3}
$\Delta\rho_{max} = -0.26$ e Å^{-3}

Bond lengths (Å)

C1 - C2	1.521 (3)
C1 - C10	1.542 (3)
C1 - O16	1.449 (3)
C2 - C3	1.499 (3)
C2 - O9	1.450 (3)
C3 - C4	1.396 (3)
C3 - C8	1.386 (3)
C4 - C5	1.384 (4)
C5 - C6	1.377 (4)
C6 - C7	1.363 (4)
C7 - C8	1.387 (4)
C10 - C11	1.524 (3)
C10 - C15	1.488 (3)
C11 - C12	1.497 (4)
C12 - C13	1.325 (4)
C13 - C14	1.460 (4)
C14 - C15	1.313 (4)

Bond Angles (°)

C2 - C1 - C10	115.0 (19)
C2 - C1 - O16	106.5 (18)
C10 - C1 - O16	109.0 (19)
C1 - C2 - C3	112.3 (19)
C1 - C2 - O9	107.2 (18)
C3 - C2 - O9	109.1 (19)
C2 - C3 - C4	121.8 (2)
C2 - C3 - C8	119.6 (2)
C4 - C3 - C8	118.6 (2)
C3 - C4 - C5	120.1 (2)
C4 - C5 - C6	120.3 (2)

C5 - C6 - C7	120.2 (2)
C6 - C7 - C8	120.2 (2)
C3 - C8 - C7	120.6 (2)
C1 - C10 - C11	108.3 (18)
C1 - C10 - C15	115.7 (2)
C11 - C10 - C15	112.0 (19)
C10 - C11 - C12	113.0 (2)
C11 - C12 - C13	120.3 (2)
C12 - C13 - C14	120.7 (2)
C13 - C14 - C15	120.9 (3)
C10 - C15 - C14	120.9 (2)

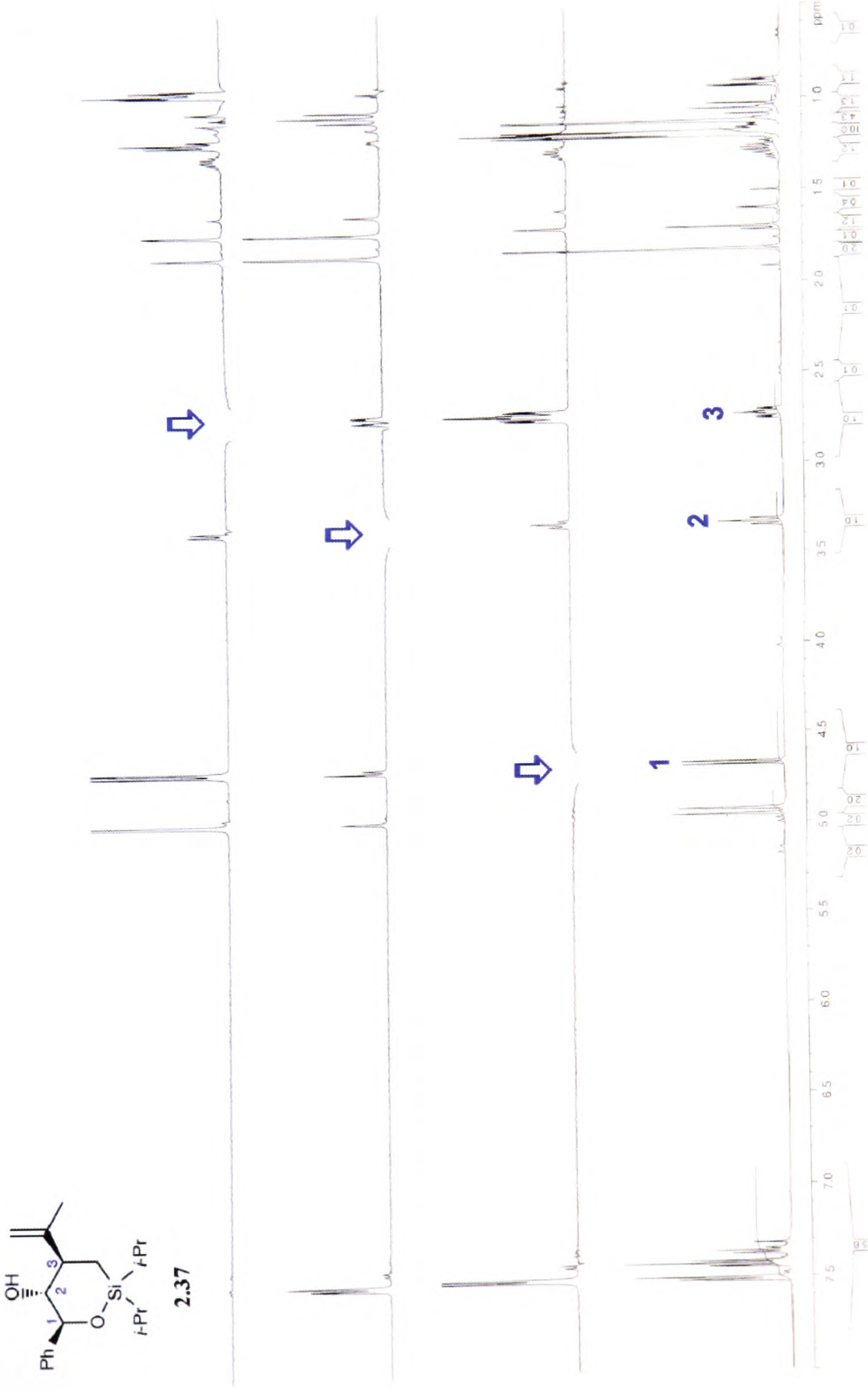
Fractional atomic coordinates and equivalent isotropic displacement parameters (Å)

Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
C1	0.1177 (3)	0.13026 (14)	0.84909 (13)	0.0326
C2	0.2865 (3)	0.13086 (15)	0.81772 (13)	0.0350
C3	0.3683 (3)	0.04887 (14)	0.82787 (13)	0.0318
C4	0.3277 (3)	-0.02044 (15)	0.78389 (13)	0.0365
C5	0.4018 (3)	-0.09588 (15)	0.79695 (15)	0.0416
C6	0.5171 (3)	-0.10286 (18)	0.85278 (16)	0.0466
C7	0.5581 (3)	-0.03563 (19)	0.89597 (16)	0.0477
C8	0.4851 (3)	0.04041 (16)	0.88354 (14)	0.0396
O9	0.2761 (2)	0.1496 (1)	0.73645 (9)	0.0365

C10	0.1050 (3)	0.12039 (14)	0.93691 (12)	0.0290
C11	-0.0681 (3)	0.10227 (14)	0.95695 (14)	0.0344
C12	-0.1017 (3)	0.10884 (16)	1.04112 (17)	0.0461
C13	-0.0121 (4)	0.15663 (18)	1.08544 (15)	0.0514
C14	0.1187 (3)	0.20480 (18)	1.05293 (16)	0.0495
C15	0.1708 (3)	0.19005 (15)	0.98320 (15)	0.0378
O16	0.04639 (19)	0.20858 (11)	0.8269 (1)	0.0387
H11	0.0620 (3)	0.08066 (14)	0.82737 (13)	0.0415
H21	0.3508 (3)	0.17307 (15)	0.84622 (13)	0.0448
H41	0.2453 (3)	-0.01520 (15)	0.74272 (13)	0.0453
H51	0.3716 (3)	-0.14554 (15)	0.76573 (15)	0.0512
H61	0.5707 (3)	-0.15749 (18)	0.86153 (16)	0.0567
H71	0.6407 (3)	-0.04124 (19)	0.93697 (16)	0.0588
H81	0.5168 (3)	0.08981 (16)	0.91475 (14)	0.0503
H101	0.1753 (3)	0.07336 (14)	0.95288 (12)	0.0370
H111	-0.0942 (3)	0.04469 (14)	0.93958 (14)	0.0421
H112	-0.1369 (3)	0.14293 (14)	0.92903 (14)	0.0421
H121	-0.1918 (3)	0.07682 (16)	1.06415 (17)	0.0557
H131	-0.0348 (4)	0.15983 (18)	1.14171 (15)	0.0624
H141	0.1702 (3)	0.24922 (18)	1.08441 (16)	0.0590
H151	0.2539 (3)	0.22672 (15)	0.96000 (15)	0.0471
H3	-0.05599 (19)	0.19628 (11)	0.8066 (1)	0.0500
H4	0.1874 (2)	0.1855 (1)	0.72963 (9)	0.0500

Appendix 3

Qualitative n.O.e. Spectra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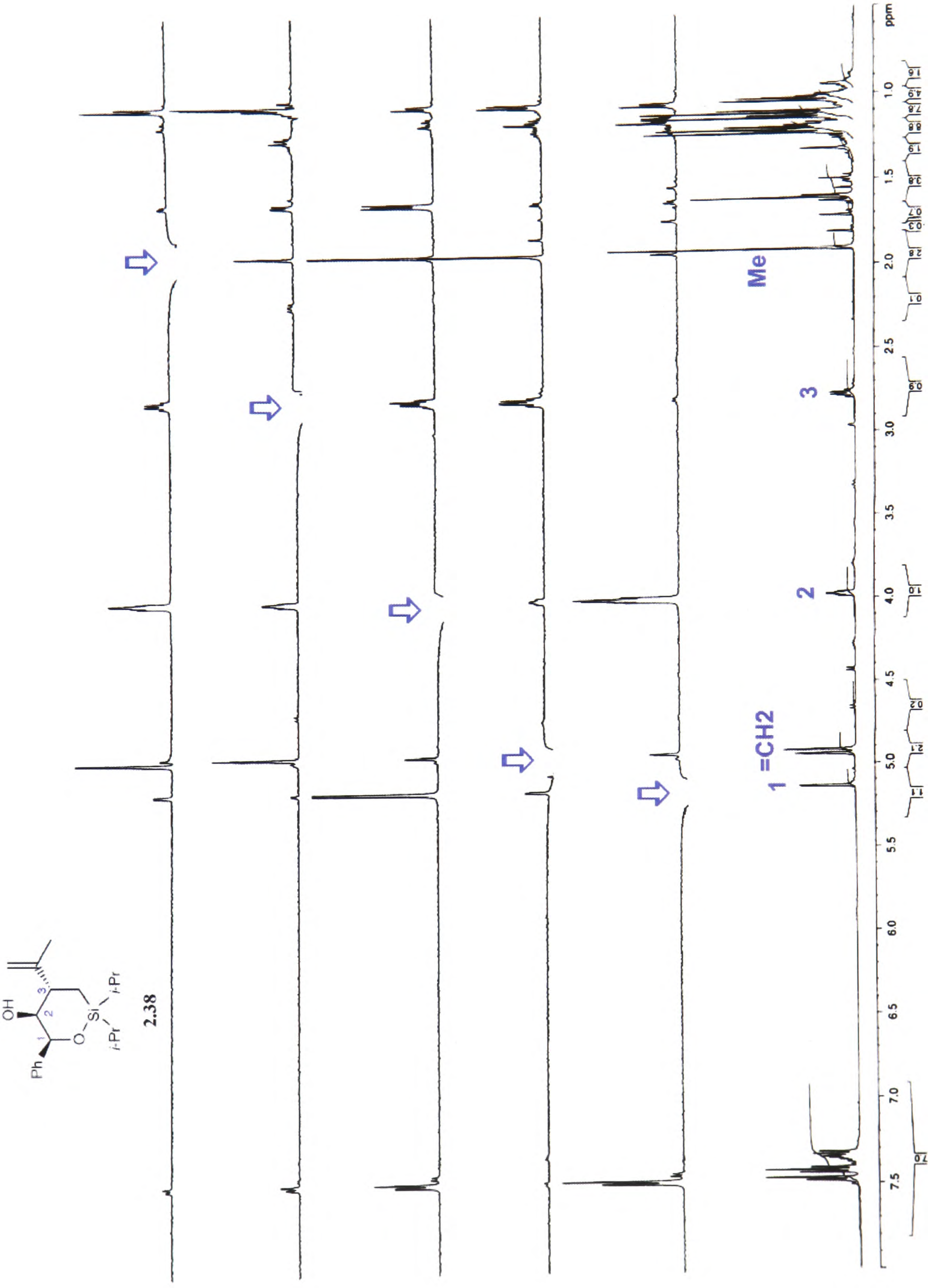
Ph
OH
O
Si
i-Pr
i-Pr
1
2
3
Me
3
2
1 =CH2
ppm
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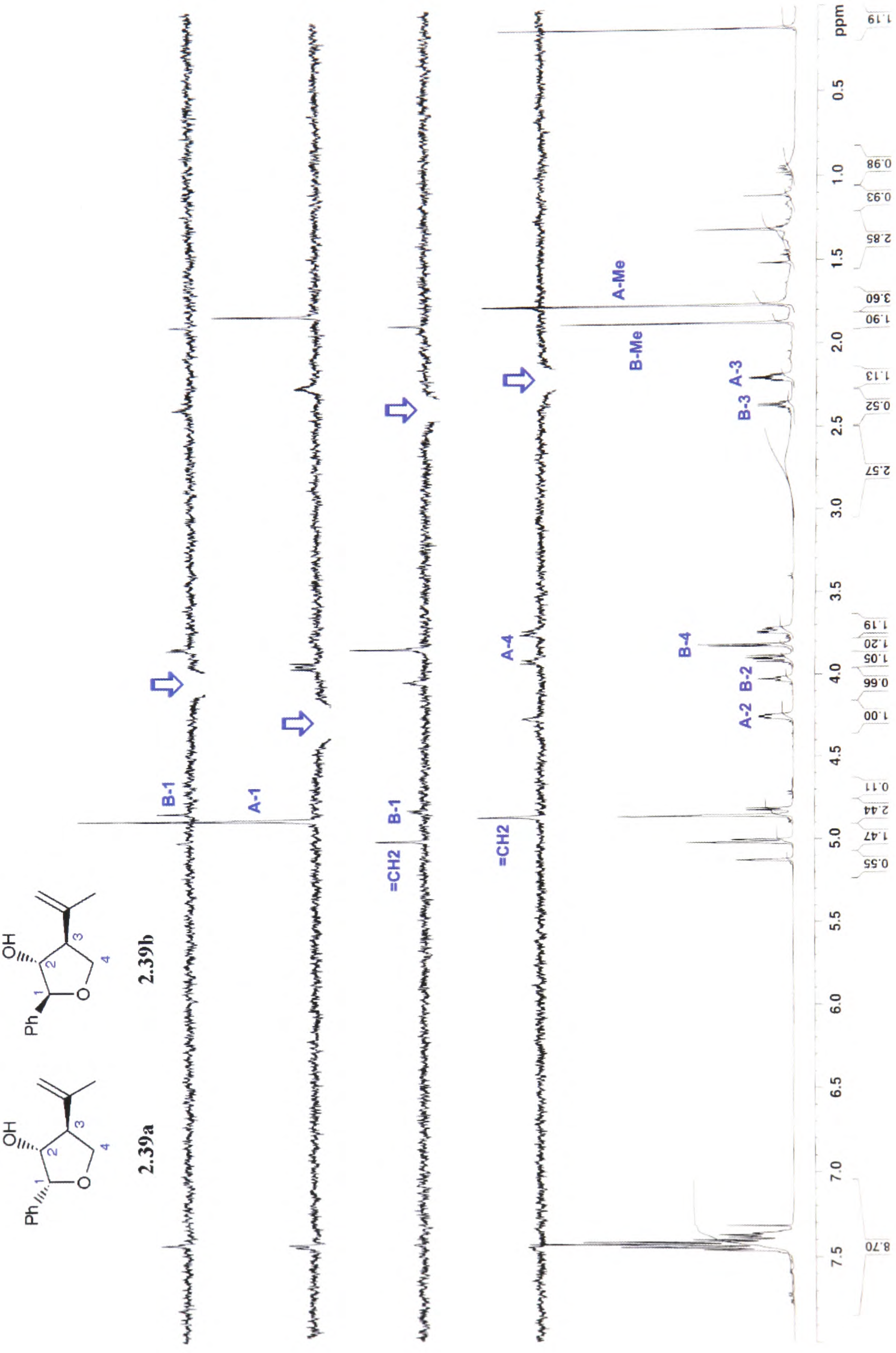
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

2.38


Ph
OH
O
1
2
3
4
2.39a
2.39b
B-1
A-1
=CH2
B-1
=CH2
A-4
B-4
A-2
B-2
A-Me
B-Me
A-3
B-3
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.19
0.98
0.93
2.85
3.60
1.90
1.13
0.52
2.57
1.19
1.20
1.05
0.66
1.00
0.11
2.44
1.47
0.55
8.70