Alkylation of Planar Chiral Cationic π-Allylmolybdenum Complexes - The Total Synthesis of Cryptophycin 4.

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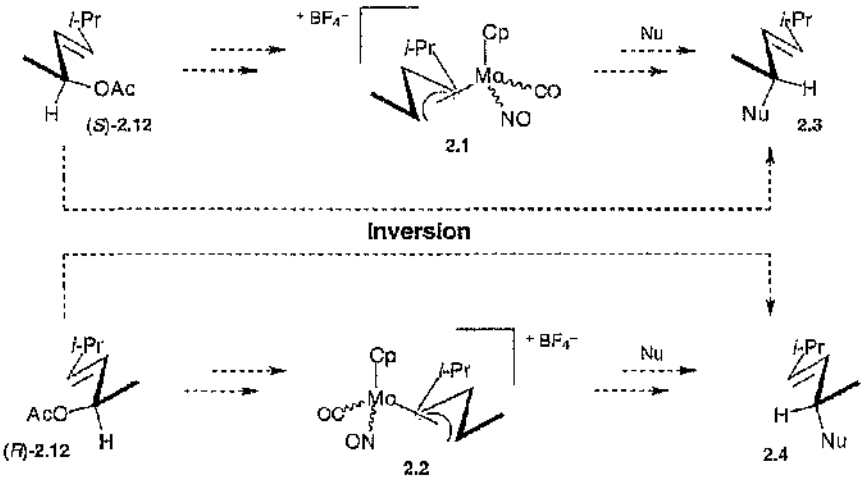
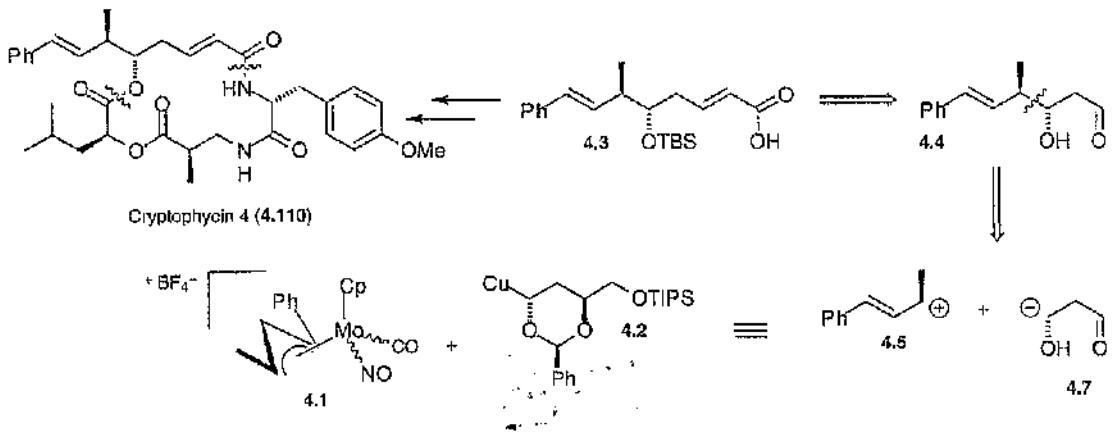
Abstract

We have investigated the alkylation of planar chiral cationic π-allylmolybdenum complexes **2.1** and **2.2** with a variety of functionalised α-alkoxyalkylcopper(I) nucleophiles. Complexes **2.1** and **2.2** are readily formed from the corresponding homochiral allylic acetates (*S*)- and (*R*)-**2.12** and a suitable Mo(0) source with retention of facial stereochemistry (Scheme 1). Excellent selectivity for attack *anti* to the metal fragment yields products of overall inversion of configuration, **2.3** and **2.4**. Good regiocontrol (typically > 8:1) results from steric discrimination between the termini of the allyl unit. The selectivity is obtained without the need to control central chirality at the metal, in contrast to literature precedent.



Scheme 1.

We have applied the methodology to natural product synthesis. Cryptophycin 4 (**4.110**) was prepared *via* the coupling of novel cationic complex **4.1** and homochiral nucleophile **4.2** as synthetic equivalents for synthons **4.5** and **4.7** respectively (Scheme 2).



Scheme 2.

For Vicki

Contents

Preface

The research described in this thesis was carried out under the supervision of Professor P. J. Kocienski at the University of Southampton between October 1996 and December 1996, and at the University of Glasgow between January 1997 and July 2000. No part of this thesis has been previously submitted for a degree at this or any other University. Part of this thesis has been previously published:

- J. A. Christopher, P. J. Kocienski, and M. J. Procter, *Synlett*, 1998, 425.

- J. A. Christopher, P. J. Kocienski, A. Kuhl, and R. Bell, *Synlett*, 2000, 463.

- A. Kuhl, J. A. Christopher, L. J. Farrugia, and P. J. Kocienski, *Manuscript submitted*, 2000.

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Finally, I wish to thank my friends and family for their support.

Abbreviations

Ac	acetyl
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CALB	*Candida antarctica* B-lipase
CAN	ammonium cerium(IV) nitrate
cat.	catalyst / catalytic
CI	chemical ionisation
COSY	correlation spectroscopy
Cp	cyclopentadienyl ligand
m-CPBA	*meta*-chloroperbenzoic acid
d	day(s)
DBB	4,4-di-*tert*-butylbiphenylide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCDT	dicyclododecyl tartrate
de / dr	diastereomeric excess / ratio
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL / Dibal	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA / DIEA	*N*,*N*-diisopropylethylamine
DIPS	diisopropyl sulfide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one
DMS	dimethyl sulfide
ee / er	enantiomeric excess / ratio
EI	electron impact
Et	ethyl
FAB	fast atom bombardment
FDDP	pentafluorophenyl diphenylphosphinate
GCMS	gas-chromatography mass spectroscopy
h	hour(s)
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum coherence
HPLC	high performance liquid chromatography

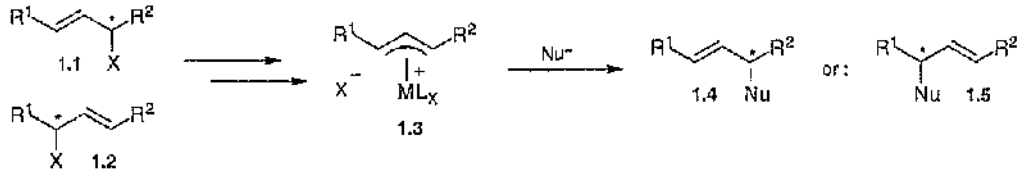
HRMS	high resolution mass spectroscopy
Hz	Hertz
Im	imidazole
LDA	lithium diisopropylamide
LDBB	lithium 4,4-di-*tert*-butylbiphenylide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LN	lithium naphthalenide
LRMS	low resolution mass spectroscopy
Me	methyl
min	minute(s)
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser enhancement
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium toluene-*p*-sulfonate
Piv / Pv	trimethylacetyl
Pyr / Py	pyridine
rt	room temperature
t (tert.)	tertiary
TBME	*tert*-butyl methyl ether
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl or tetramethylsilane
Tp	hydrotris(1-pyrazolyl)borate ligand
Ts	*p*-tolylsulfonyl
Tyr	tyrosine
UV	ultra violet
VAZO® 88	1,1′-azobis(cyclohexanecarbonitrile)

Chapter 1 - Cationic η^3-allylmolybdenum complexes.

1.1 - Introduction.

Extensive investigations over the past three decades have been carried out in the area of nucleophilic attack upon allylic ligands π-bonded to transition metals. The use of palladium in *catalytic* allylic alkylations has been most extensively investigated, with enantioselective variants of the reaction being well established since the first report in 1977.[1] Catalytic applications are not restricted to palladium, with alternative metals including molybdenum, nickel, iridium, ruthenium, iron, platinum, tungsten, cobalt and rhodium being utilised.[2-4] In a stoichiometric fashion, molybdenum and iron have been the metals of choice,[5-8] with molybdenum being relatively unexplored in applications to organic synthesis until recent years.

The strategy of having a metal bound to an allylic cation equivalent (**1.3**, Scheme 1.1) is a powerful one. The metal serves a dual purpose: stabilising the allylic cation, and directing nucleophilic attack upon one face of the planar allyl unit. For the general procedure outlined below to be of use to the synthetic chemist, several factors need to be controlled: (a) formation of planar chiral electrophilic complexes **1.3** from suitable enantiomerically pure precursors **1.1** / **1.2**; (b) subsequent attack on the face of the planar allyl ligand opposite to that blocked by the metal; (c) regioselection between the two allylic termini on steric or electronic grounds; (d) control of double-bond geometry in products **1.4** / **1.5**; (e) facile removal of the metal from the olefin product.



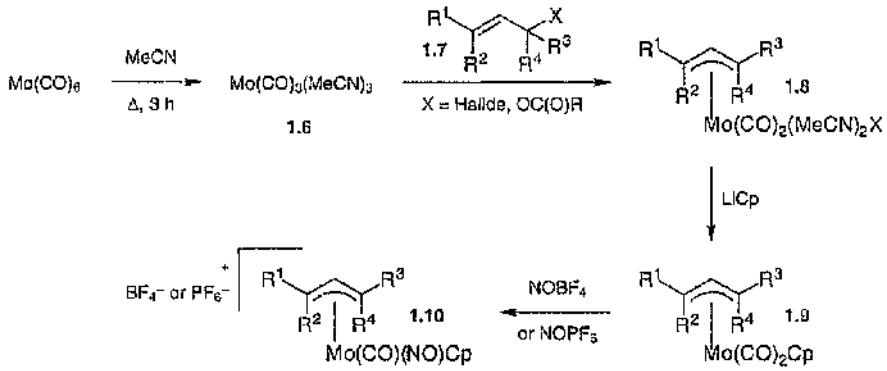
Scheme 1.1.

The above aims can be satisfied by the use of planar chiral cationic η^3-allylmolybdenum complexes based on the CpMo(CO)(NO) fragment. Chapter 1 will discuss the development of cationic η^3-allylmolybdenum complexes and examine their potential for use in asymmetric synthesis.

1.2 - Preparation of neutral and cationic η^3-allylmolybdenum complexes.

1.2.1 - Oxidative addition to zerovalent molybdenum.

The most popular method for formation of neutral η^3-allylmolybdenum complexes **1.9** is the oxidative addition of an allylic precursor **1.7** to $Mo(CO)_3(MeCN)_3$ (**1.6**) (Scheme 1.2).[9, 10] Ligand displacement with an anionic spectator group such as cyclopentadienyl (Cp) (or hydrotris(1-pyrazolyl)borate (Tp) - see section 1.3) yields **1.9**. Neutral complexes **1.9** are stable 18-electron species and unreactive towards nucleophiles. Activation to the highly electrophilic cationic tetrafluoroborate or hexafluorophosphate complex **1.10** $[(\eta^3\text{-allyl})Mo(CO)(NO)Cp]^+X^-$ ($X = BF_4$ or PF_6) is readily achieved by treatment of neutral complex **1.9** with nitrosonium tetrafluoroborate or hexafluorophosphate.



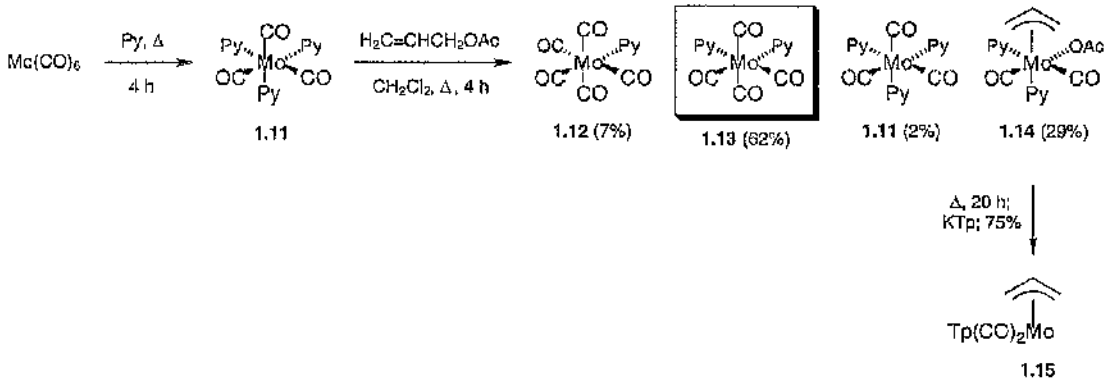
Scheme 1.2.

Whilst $Mo(CO)_3(MeCN)_3$[11] is the most common Mo(0) source, other variants include $Mo(CO)_3(DMF)_3$,[12] $Mo(CO)_3(py)_3$[13] and $Mo(CO)_3(PhMe)$.[14] $Mo(CO)_3$(diglyme) and $(DME)_2Mo_2(CO)_6$ have also been briefly investigated by Liebeskind.[15] An investigation of $Mo(CO)_3(py)_3$ by Kuhl and Kocienski[16] and the subsequent development of the related reagent $Mo(CO)_4(py)_2$ is discussed below in section 1.2.2.

The allylic reagent **1.7** can vary, with allylic acetates or halides being the most widely used. Allylic trifluoroacetates, relatively common precursors in palladium-based allylic alkylation chemistry,[17-19] have only limited use in the formation of π-allylmolybdenum species.[20] Liebeskind has used allylic diphenylphosphinate esters in the preparation of neutral $(\eta^3\text{-allyl})Mo(CO)_2Cp$ complexes.[15, 21]

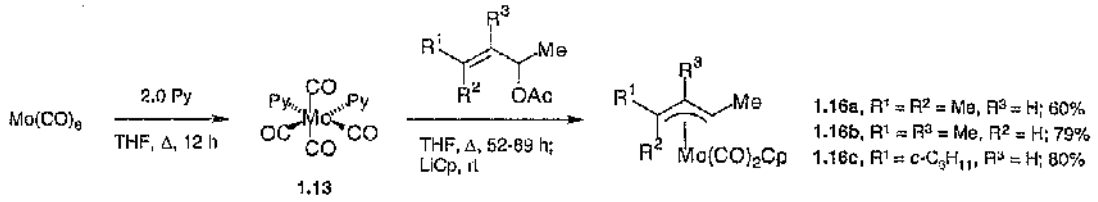
1.2.2 - The development of $Mo(CO)_4(py)_2$ as a reagent for the preparation of η^3-allylmolybdenum complexes.[16]

$Mo(CO)_3(py)_3$[13] was reported by Pearson to be a superior reagent to other zerovalent molybdenum sources for the preparation of η^3-allylmolybdenum complexes.[22] A variety of neutral complexes were prepared in good to excellent yield, some of which could only be obtained inefficiently using $Mo(CO)_3(MeCN)_3$ or $Mo(CO)_3(DMF)_3$. Problems encountered with the use of $Mo(CO)_3(py)_3$ within the Kocienski group stimulated Kuhl to investigate the reagent, using ^{95}Mo NMR[23] to elucidate the reaction pathways involved. $Mo(CO)_3(py)_3$ (**1.11**) was readily formed from $Mo(CO)_6$ by refluxing in pyridine for 4 h (Scheme 1.3). Following Pearson's protocol, the oxidative addition of allyl acetate to **1.11** in CH_2Cl_2 was investigated. After 4 h, the major component of the reaction mixture was *cis*-$[Mo(CO)_4(py)_2]$ (**1.13**, 62%) together with only 2% of **1.11**, $Mo(CO)_5(py)$ (**1.12**, 7%) and the expected η^3-allylmolybdenum(II) complex **1.14** (29%). A gradual increase in the concentration of **1.14** was mirrored by a decrease in **1.13**, and after a further 20 h, neutral complex **1.15** was isolated in 75% yield following ligand exchange.



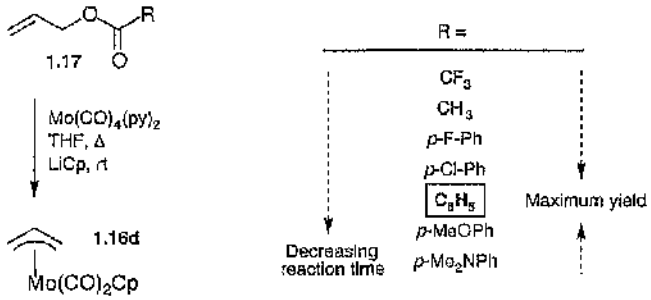
Scheme 1.3.

$Mo(CO)_4(py)_2$ (**1.13**), the reagent apparently responsible for the oxidative addition, was quantitatively prepared in THF from $Mo(CO)_6$ and 2 equivalents of pyridine (Scheme 1.4). *In situ* reaction with an allylic acetate followed by displacement of the remaining pyridine and acetate ligands with LiCp yielded a variety of neutral η^3-allylmolybdenum complexes in excellent yield and purity, including hindered complexes **1.16a-1.16c** which could not be obtained with $Mo(CO)_3(MeCN)_3$.



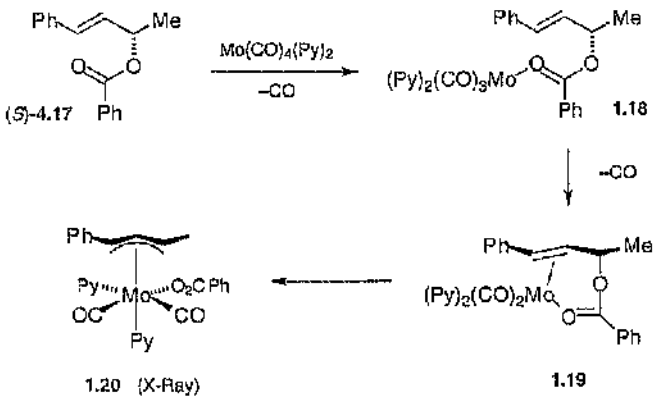
Scheme 1.4.

Kuhl also investigated the influence of the leaving group on the oxidative addition using a series of allyl esters **1.17** (Scheme 1.5). A dependence on the donor capacity of the leaving group was established. Optimal yield of allyl complex **1.16d** and reaction time was obtained with the benzoate leaving group. Reaction time continued to decrease as the donor capacity increased (R = Ph → *p*-MeOPh → *p*-Me_2NPh) but a detrimental effect upon yield was observed.



Scheme 1.5.

The trend in donating ability supports the mechanism proposed by Kuhl (Scheme 1.6), illustrated for the oxidative addition of enantiopure benzoate (*S*)-**4.17** (see Chapter 4, section 4.2) to $Mo(CO)_4(py)_2$. Decarbonylation of $Mo(CO)_4(py)_2$ is followed by coordination of the transient 16-electron species with the carbonyl group of benzoate **4.17** to give **1.18**. Following the loss of a further carbonyl ligand from **1.18**, and coordination of molybdenum to the olefin, intermediate **1.19** collapses to give molybdenum(II) complex **1.20**.

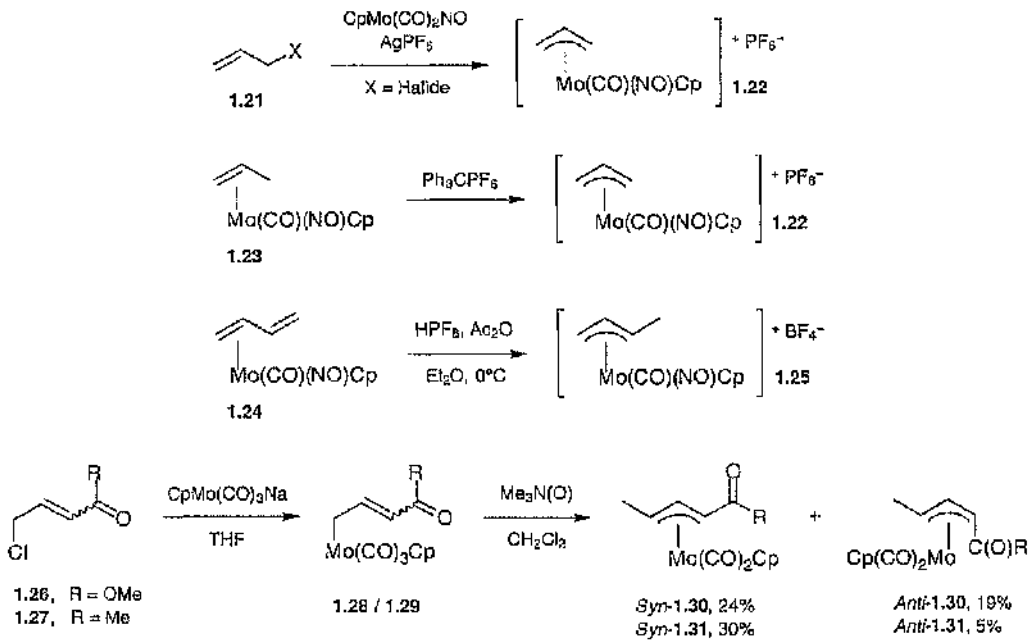


Scheme 1.6.

An X-ray structure of **1.20** was obtained[24, 25] and revealed that: (a) the carboxylate and allyl ligands were *cis*; (b) Mo(II) complex **1.20** had been formed with overall retention of configuration from benzoate **4.17**. Both observations support the above mechanism. The $Mo(CO)_4(py)_2$ reagent parallels $Mo(CO)_3(MeCN)_3$ in the retentive stereochemistry of oxidative addition (see section 1.5.2), but also has distinct advantages in terms of reactivity and efficiency, and yields neutral complexes of higher purity. The formation of **1.20** (and hence the corresponding $CpMo(CO)_2$-complex) with retention of configuration satisfies one of the fundamental requirements of the η^3-allylmolybdenum chemistry.

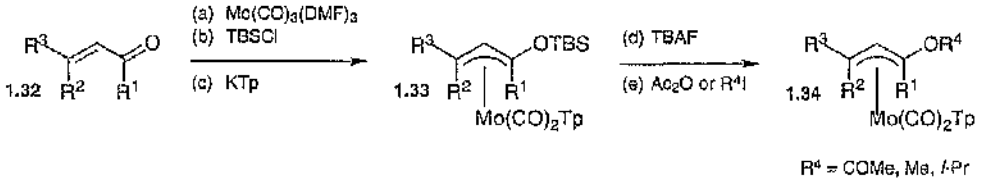
1.2.3 - Alternative routes to neutral and cationic complexes.

A variety of other routes to neutral and cationic η^3-allylmolybdenum complexes exist (Scheme 1.7). McCleverty has reported the direct synthesis of cationic complex **1.22** from $CpMo(CO)_2NO$, $AgPF_6$ and an allylic halide,[26] and syntheses based on hydride abstraction from $CpMo(CO)(NO)(\eta^2$-olefin) complexes (e.g. **1.23**)[9] or protonation of $CpMo(CO)(NO)(\eta^2$-diene) complexes (e.g. **1.24**)[27] have also been described. Liu has reported the preparation of functionalised complexes **1.30** and **1.31** (as separable mixtures of *syn* and *anti* isomers) from allylic chlorides **1.26** and **1.27** *via* halide displacement with $CpMo(CO)_3Na$.[28] $Me_3N(O)$ promoted decarbonylation of the intermediate η^1-species **1.28** / **1.29** produces **1.30** / **1.31**. The *syn* / *anti* product ratio presumably represents the *E* / *Z* ratio of the starting allylic chlorides,[29] since the isolated *syn* and *anti* η^3-complexes **1.30** and **1.31** were found not to interconvert, even at elevated temperatures.



Scheme 1.7.

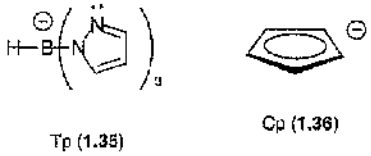
Liebeskind has described the preparation of cyclic and acyclic (η^3-allyl)Mo(CO)$_2$Tp complexes **1.33** bearing electron-donating substituents by treatment of cyclic and acyclic α,β-unsaturated enals and enones **1.32** with Mo(CO)$_3$(DMF)$_3$ and TBSCl (Scheme 1.8).[30] Desilylation and alkylation or acylation can be performed on the (*tert*-butylsilyl)oxy-substituted complexes **1.33**, yielding 1-acetoxy or 1-alkoxy substituted complexes **1.34**.



Scheme 1.8.

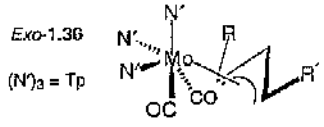
1.3 - The choice of spectator ligand; Cyclopentadienyl (Cp) *vs* hydrotris(1-pyrazolyl)borate (Tp) - and the complications of *Syn-Anti* and *Exo-Endo* isomerisation.

The hydrotris(1-pyrazolyl)borate (Tp, **1.35**) ligand is isoelectronic with the η^5-cyclopentadienyl ligand (Cp, **1.36**) (Scheme 1.9), as both are anionic, six-electron donor ligands. In recent years, the Tp ligand has increasingly been used in place of Cp and offers several advantages:[31] (a) KTp is a readily available, air-stable solid (LiCp readily deteriorates unless stored and used under anaerobic and anhydrous conditions, and is best prepared freshly); (b) Cp is too basic and nucleophilic to be used with sensitive, functionalised systems; (c) Tp-bearing complexes are generally more robust and easy to handle than the sensitive Cp-analogues.



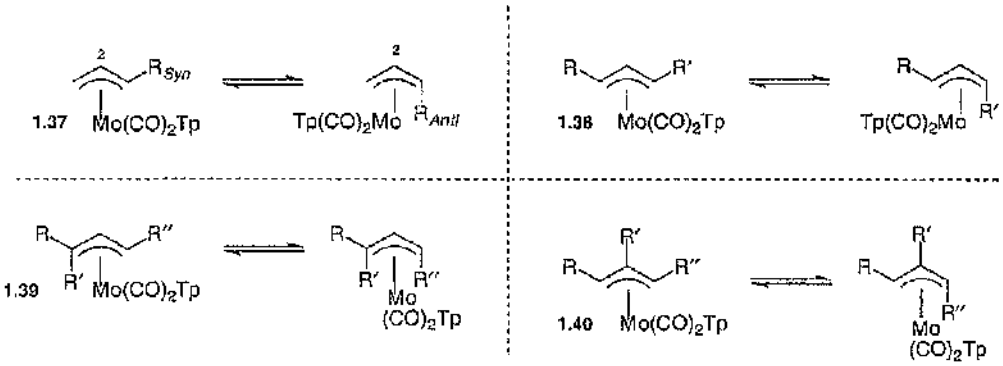
Scheme 1.9.

Liebeskind disclosed a study of the formation of (η^3-allyl)Mo(CO)$_2$Tp complexes **1.36** (Scheme 1.10) from allylic acetates and Mo(CO)$_3$(DMF)$_3$ in 1995,[31] building upon earlier work by Ipaktschi and Trofimenko.[32-34] Unlike the related Cp-complexes (see section 1.4.1), (η^3-allyl)Mo(CO)$_2$Tp complexes exist solely as *exo* isomers.[31, 35]



Scheme 1.10.

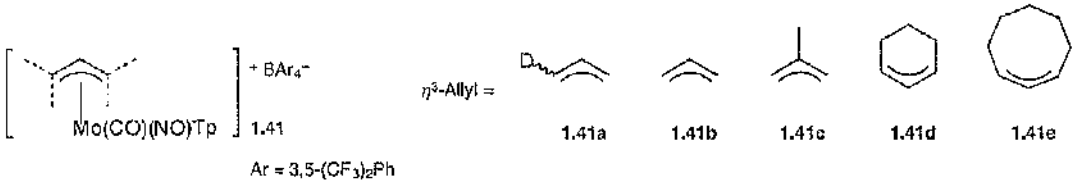
The utility of (η^3-allyl)Mo(CO)$_2$Tp and [(η^3-allyl)Mo(CO)(NO)Tp]$^+$ systems is complicated by *syn-anti* isomerisation of terminal allylic substituents (Scheme 1.11), a phenomenon with only very meagre precedent in the analogous Cp-based systems. The descriptors *syn* and *anti* refer to the configuration of the substituent relative to that at C2 of the allyl. Liebeskind observed several general trends: (a) the *anti* stereoisomer is favoured at equilibrium for 1°, 2° and 3° alkyl, CO_2Me and OAc substituents; (b) aryl and OMe substituents show a preference for *syn* stereochemistry at equilibrium; (c) 1-monosubstituted complexes (**1.37**) require elevated temperatures (100°C, 2 h) to equilibrate; (d) 1,3-di- (**1.38**), 1,1,3-tri- (**1.39**) and 1,2,3-trisubstituted complexes (**1.40**) equilibrate at ambient temperature in solution.



Scheme 1.11.

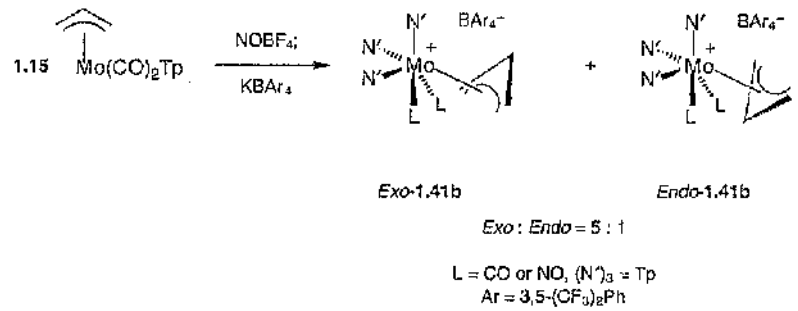
X-ray studies of several of the above complexes rationalised the observed trends: steric hindrance between *syn*-substituents and two of the pyrazole groups on the Tp ligand render the *anti*-isomers more stable. The exceptions are the methoxy and aryl substituents, which maintain a preference for the *syn*-configuration, as the *anti*-configuration involves a significant distortion away from the allyl plane with the resulting impairment of resonance delocalisation.

Information regarding *syn-anti* isomerisation of the corresponding cationic Tp(CO)(NO)Mo(η^3-allyl) systems is sparse. A single report from Liebeskind has disclosed the synthesis and characterisation of deuterated complex **1.41a** and symmetrically substituted systems **1.41b-1.41e** (Scheme 1.12).[35] Replacement of the BF_4 counterion by BAr_4 [Ar = 3,5-$(CF_3)_2$Ph] gave complexes of sufficient stability to enable thorough spectroscopic investigation.



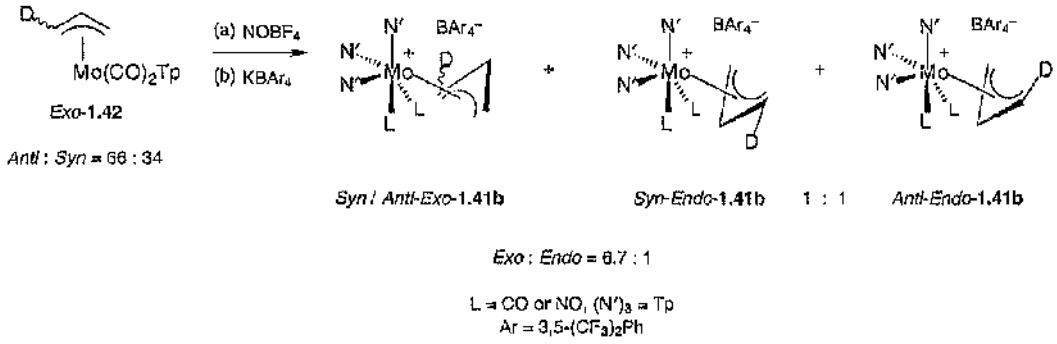
Scheme 1.12.

In contrast to the parent neutral dicarbonyl Tp complexes, acyclic cationic complexes **1.41a** and **1.41b** exhibit both *exo* and *endo* isomers (Scheme 1.13). Complex **1.41c** existed solely as the *endo* isomer and cyclic complexes **1.41d / 1.41e** as purely *exo*. Complex **1.41b** showed no change in *exo*:*endo* ratio by ^{1}H NMR upon warming to 50°C. Together with other NMR evidence, this lead Liebeskind to conclude that the *exo* and *endo* isomers did not interconvert under the conditions explored.



Scheme 1.13.

The formation of *endo* isomers from acyclic complexes **1.41a**-**1.41c** but not from the cyclic systems **1.41d / 1.41e** prompted Liebeskind to explore the mechanism of ligand exchange and *endo* isomer formation. Deuterated complex **1.41b** was used in the investigation, formed from neutral dicarbonyl precursor **1.42** in which the *anti*-*syn* deuterium ratio was 66 : 34 (Scheme 1.14).



Scheme 1.14.

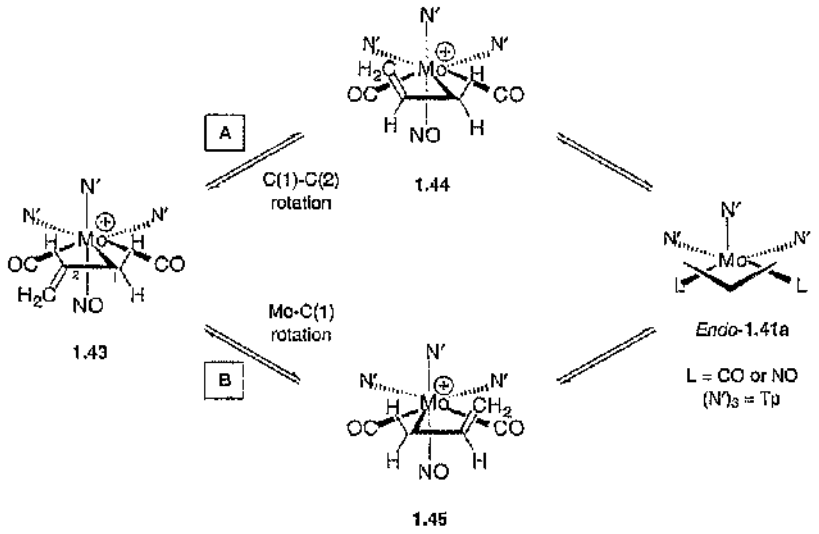
The *anti* : *syn* deuterium ratio in *endo*-**1.41b** was approximately 1 : 1, estimated by comparing the total integration of *anti*-protons in the *endo* isomers to that of the central allylic protons (H2) (Scheme 1.14). The 1 : 1 ratio represents a decrease from the 66 : 34 ratio *exo*-*anti* : *exo*-*syn* in the parent neutral complex **1.42**.

Liebeskind drew the following mechanistic conclusions:

(1) The carbonyl-nitrosyl ligand exchange process occurs through an η^1-allyl intermediate **1.43** (Scheme 1.15, illustrated for allyl complex **1.41a**). Intermediate **1.43** is formed *via* electrophilic addition of NO^+ to neutral dicarbonyl complex **1.15** with slippage of the allyl unit from a η^3- to a η^1-arrangement.

(2) The *endo* isomer is formed solely by rotation about the C(1)-C(2) bond in η^1-intermediate **1.43** (pathway A).

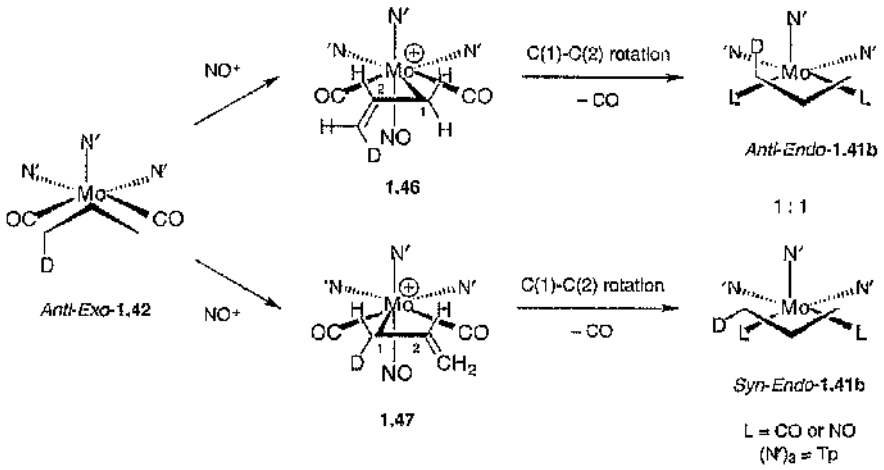
(3) Formation of the *endo* isomer by rotation about the Mo-C(1) axis in intermediate **1.43** (pathway B) is discounted; since this mode of rotation will not convert a *syn*-substituent to *anti* or vice-versa, and hence will not explain the deuterium scrambling observed in **1.41b**.



Scheme 1.15.

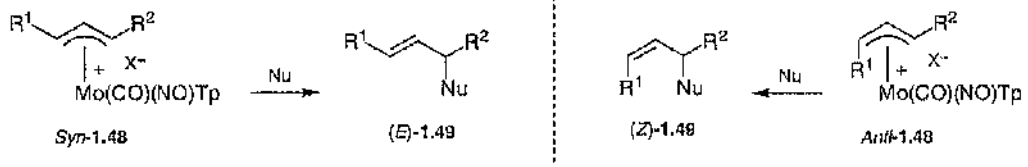
(4) A mixture of pathways A and B was discounted on the grounds that the 1 : 1 *syn-endo*-**1.41b** : *anti-endo*-**1.41b** ratio observed is equal to that predicted to arise *via* pathway A alone. Scheme 1.16 below illustrates how pathway A leads to an equal ratio of *syn* and *anti* substituents, assuming equal population of η^1-intermediates **1.46** / **1.47**. The deuterium is arbitrarily shown as *anti* in *exo*-**1.42**, an analogous process would scramble a *syn* deuterium substituent.

(5) The formation of *endo*-**1.41b** exclusively by pathway A accounts for the formation of *endo* cation isomers in acyclic Tp systems alone; *cyclic* η^1-allyl analogues of **1.46** / **1.47** cannot freely rotate about the C(1)-C(2) allyl bond.



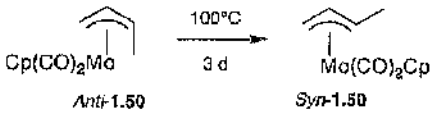
Scheme 1.16.

Similar η^3-η^1-η^3 mechanisms have been proposed for *endo-exo* isomerisation with concomitant scrambling of *syn-anti* substituents in CpM(CO)(η^3-allyl) complexes (M = Fe or Ru).[36, 37] The meagre precedent established by Liebeskind indicates that acyclic cationic Tp(CO)(NO)Mo(η^3-allyl) complexes are formed as static mixtures of *exo* and *endo* conformers, presumably in a kinetic ratio. *Syn-anti* scrambling of the terminal deuterium atom in complex **1.42** upon formation of the cation, together with the dynamic equilibration of *syn-anti* isomers in the corresponding neutral dicarbonyl precursors (*via* a similar $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ mechanism)[31] suggests that *acyclic* cationic Tp-based systems **1.48** are likely to be of limited use in synthesis. Nucleophilic attack upon *syn* and *anti*-**1.48** (arbitrarily at the R^2 terminus) would result in geometrical olefin isomers (*E*)- and (*Z*)-**1.49** respectively (Scheme 1.17).



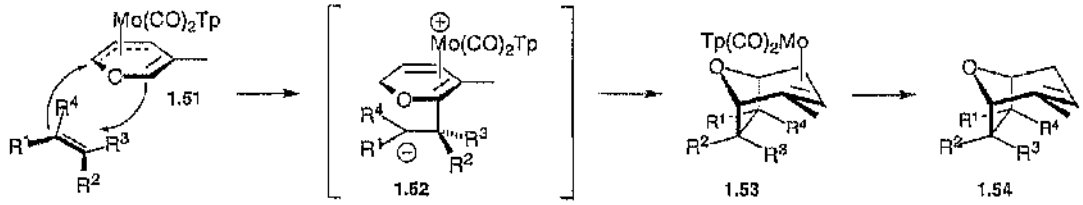
Scheme 1.17.

The cyclopentadienyl systems popularised by Faller do not generally exhibit *syn-anti* isomerisation, presumably as a result of the lower steric bulk of Cp compared to Tp. In one reported case of *syn-anti* isomerisation in a Cp-system, crotyl complex *anti*-**1.50** isomerised to *syn*-**1.50** upon heating to 100°C for 3 days (Scheme 1.18). The preference for the *syn*-isomer is the opposite to that favoured by Tp-complexes.[38]



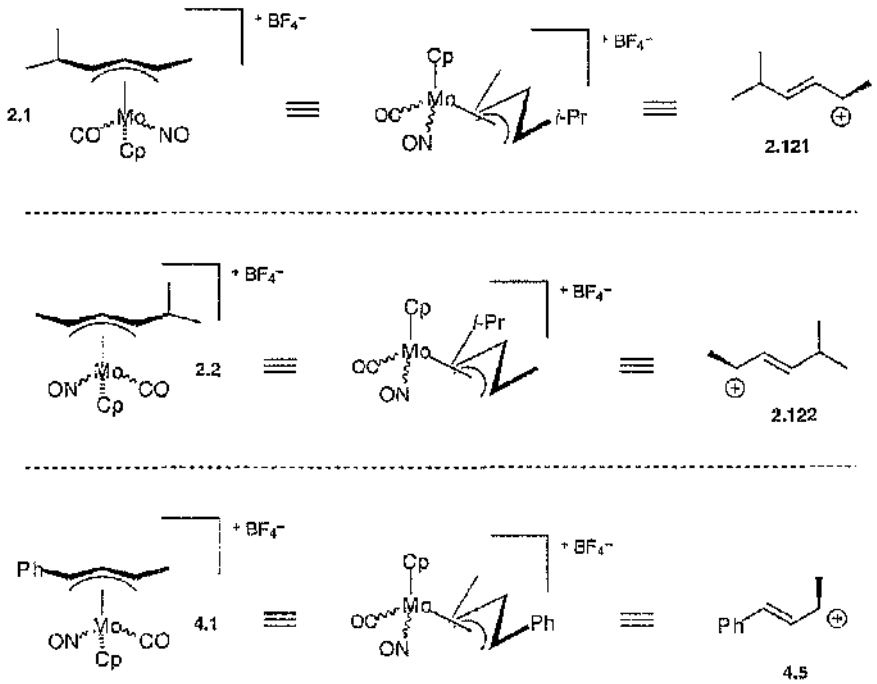
Scheme 1.18.

Cyclic systems cannot undergo *syn-anti* isomerisation because of geometrical constraints, and the Tp ligand can be used without complication. The recent use of enantiopure *neutral* complex **1.51** in a series of [5+2] cycloaddition reactions to form oxabicyclo[3.2.1]octenes **1.54** illustrates the point (Scheme 1.19).[39]



Scheme 1.19.

The work presented in this thesis in chapters 2 and 4 utilises planar chiral acyclic cationic (cyclopentadienyl)molybdenum complexes **2.1** / **2.2** and **4.1** (Scheme 1.20) as equivalents for the enantiopure, geometrically pure allylic cation synthons **2.121** / **2.122** and **4.5** respectively. Whilst the benefits of the analogous Tp systems discussed in this section are acknowledged, the possible complications resulting from *syn* / *anti* isomerisation of unsymmetrically substituted cationic complexes precluded their use in our work.

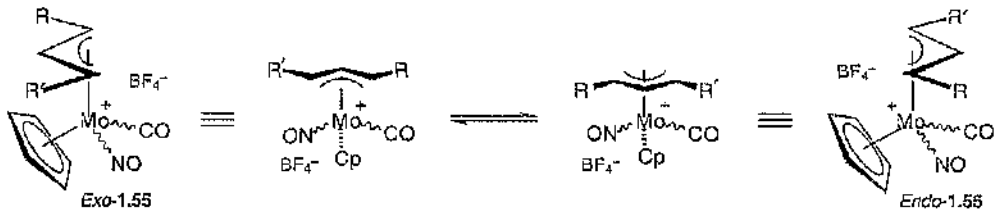


Scheme 1.20.

1.4 - Nucleophilic attack upon cationic CpMo(CO)(NO)(η^3-allyl) complexes.

1.4.1 - Mechanism of *exo-endo* isomerisation in Cp-based complexes and an examination of the factors governing stereo- and regiocontrol in alkylation.

The existence of $CpMo(CO)_2(\eta^3\text{-}C_3H_5)$ as a mixture of isomers was first observed by King[40] in 1966 and later proposed to result from differing orientations of the allyl group with respect to the Cp-ring (Scheme 1.21).[41] The $CpMo(CO)(NO)(\eta^3\text{-}C_3H_5)$ cation (**1.55**, R = R′ = H) was also found to exhibit similar behaviour.[42] In contrast to the Tp-systems, all neutral and cationic Cp-based complexes freely interconvert in solution without exchange of *syn* and *anti*-substituents. The orientational isomers are termed *exo* and *endo*,[42] with the *exo* rotamer defined as that in which the substituent at the central carbon (C2) of the allyl ligand is proximal to the cyclopentadienyl ligand, and the *endo* as that where the allyl ligand has rotated through 180 degrees to place the C2 substituent distal to cyclopentadienyl.



Scheme 1.21.

In contrast to the η^3-η^1-η^3 mechanism observed for the Tp-systems which enables *syn* and *anti*-substituents to interconvert, the mechanism of rotamer interconversion for the cyclopentadiene based complexes is one of 'pseudorotation' about the Mo-allyl axis.[43-46] A similar mode of interconversion has been described for the analogous $[(\eta^5\text{-}C_5Me_5)Re(CO)_2(\eta^3\text{-}C_3H_5)][BF_4]$ complex.[47] *Exo-endo* isomerisation does not change the face of the allyl ligand which is blocked by the metal, only the orientation of the ligand with respect to the Cp-group.

Factors affecting the regio- and stereochemistry of nucleophilic attack upon cationic complexes have been analysed by Faller and Kochi. The vast majority of the work was carried out with a limited range of nucleophiles: enamines, enolates, hydride, thiophenoxide and malonate derivatives. The complicated kinetic pathways have led to much uncertainty and contradiction over the years, with many concepts being revised with time. Nevertheless, the following conclusions have been drawn:

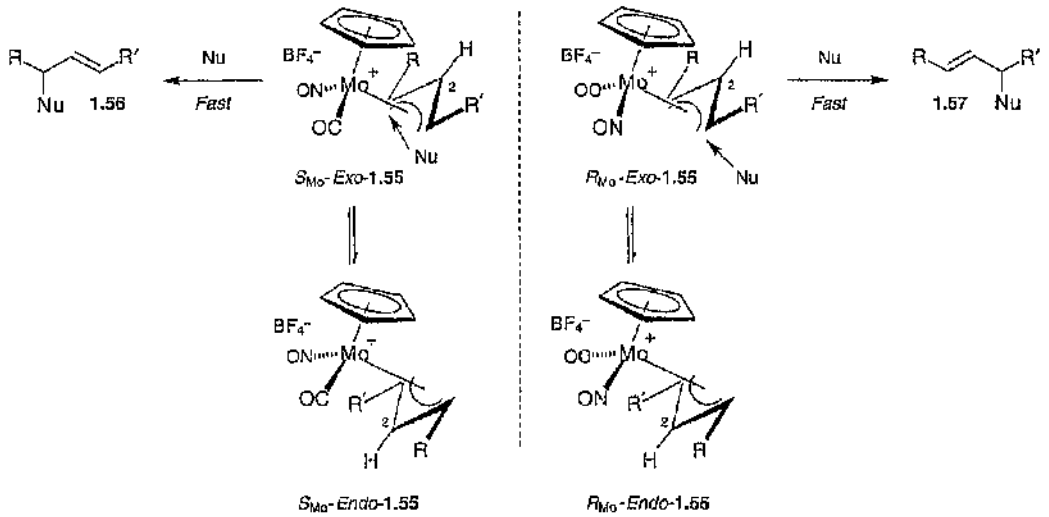
(a) Nucleophiles attack the face of the planar allylic ligand *anti* to the metal.[48]

(b) Regiochemistry of attack is governed by the stereochemistry at molybdenum. Addition occurs *cis* to the nitrosyl group, in accordance with attack at the point of lowest electron density on the allyl ligand. The selectivity is rationalised by a consideration of the electronegativities of C and N, and the different back bonding properties of CO and NO. The electronic distribution at the metal is distorted, leading in turn to a polarisation of the allyl ligand.[46, 49]

(c) Carbonyl-nitrosyl exchange is unselective.[50]

(d) The *exo*-isomer reacts faster than the *endo*-isomer, and as the *exo*- and *endo*-isomers are in rapid equilibrium under the reaction conditions kinetic selection for the *exo*-isomer can occur.[46, 51, 52] The isomerisation is generally catalysed by the nucleophile.[9]

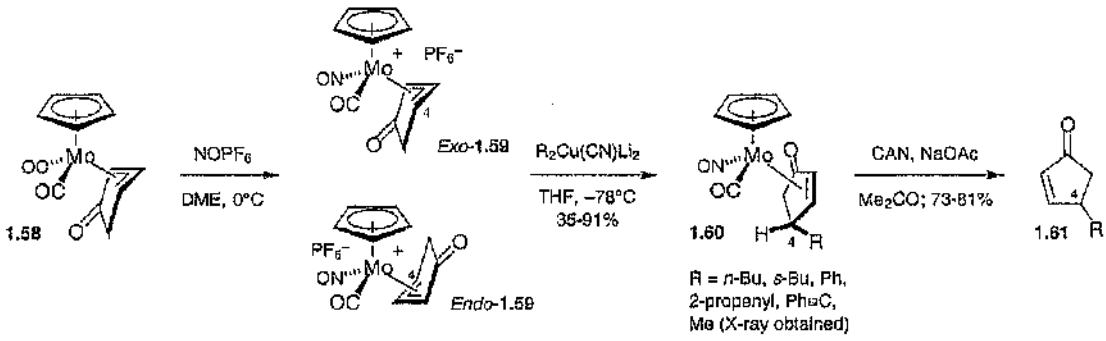
The implication of conclusions (b)-(d) for alkylation of an unsymmetrically disubstituted complex **1.55** is that the central chirality at molybdenum governs regioselectivity (Scheme 1.22): complexes S_{Mo}-*Exo*-**1.55** and R_{Mo}-*Exo*-**1.55** giving rise to regioisomeric products **1.56** and **1.57** respectively. (Priority for assigning the stereochemistry at Mo: $\eta^5 > \eta^3 > NO > CO$).[53]



Scheme 1.22.

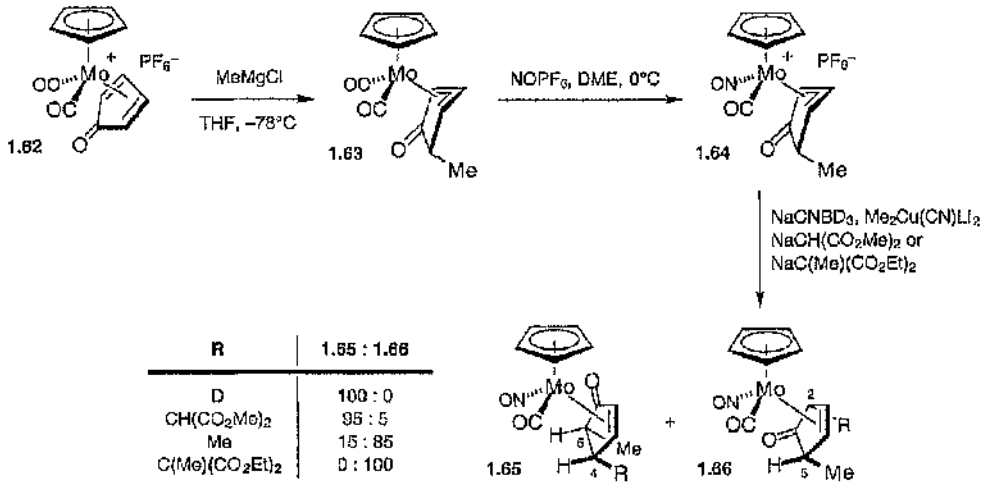
Liebeskind has described the addition of higher order cyanocuprates to functionalised complex **1.59** (Scheme 1.23),[54] giving olefinic complexes **1.60** and ultimately α,β-unsaturated ketones **1.61** with a high degree of regioselectivity. ^{1}H NMR spectroscopic data for olefinic complexes **1.60** indicated in each case the presence of predominantly a single diastereomer, leading Liebeskind to infer that the CO → NO$^+$ exchange (**1.58** → **1.59**) was

highly diastereoselective. Spectroscopic analysis (including the estimation of *endo-exo* rotamer composition) of cationic η^3-complex **1.59** was not available because of instability in solution, but a crystal structure of intermediate **1.60** (R = Me) was obtained. The X-ray structure indicated that the observed products had arisen from nucleophilic addition either *trans* to the nitrosyl ligand in *exo*-**1.59** or *cis* to the nitrosyl in *endo*-**1.59**, in stark contrast to Faller's predictions. Liebeskind was unable to rationalise the apparent diastereoselectivity of the ligand exchange process. Similarly, the precise rationale for the failure of the nitrosyl to control nucleophilic attack was unclear, although a product-like transition state favouring conjugated products **1.60** arising from attack at C4 was suggested.



Scheme 1.23.

Liebeskind also looked at the formation of disubstituted pentenone products **1.65** and **1.66**[54] (Scheme 1.24). Nucleophilic addition to (η^4-cyclopentadiene)(η^5-cyclopentadiene)dicarbonyl molybdenum cation **1.62** yielded substituted neutral dicarbonyl complex **1.63**. Subsequent activation by ligand exchange yielded electrophile **1.64**, on which a second nucleophilic attack could be performed, more hindered nucleophiles ($Me_2Cu(CN)Li_2$ or $NaC(Me)(CO_2Et)_2$) attacking predominantly the less sterically demanding 2-position.



R	1.65 : 1.66
D	100 : 0
$CH(CO_2Me)_2$	95 : 5
Me	15 : 85
$C(Me)(CO_2Et)_2$	0 : 100

Scheme 1.24.

Liebeskind's work is important for several reasons:

(a) Reaction of cationic η^3-allylmolybdenum complexes with 'hard' nucleophiles is rare.

(b) Nucleophilic attack *cis* to nitrosyl in *exo*-**1.59** and *exo*-**1.64** is not observed.

(c) Carbonyl → nitrosyl exchange is apparently highly diastereoselective.

(d) Both electronic and steric demands of the allylic ligand play a role in determining regioselectivity, overriding the nitrosyl directing effect. The dependence on steric factors is mirrored by precedent from the Kocienski group (section 1.5.3).

(e) The disubstituted cyclopentenone syntheses exemplify an important advantage that stoichiometric η^3-allylmolybdenum complexes have over catalytic allylic alkylations: the directing influence of the metal fragment can be multiplied in sequential additions to the same substrate.

1.4.2 - Methods for demetallation following nucleophilic attack.

Several procedures have been described for cleavage of the CpMo(CO)(NO) fragment from product olefins:

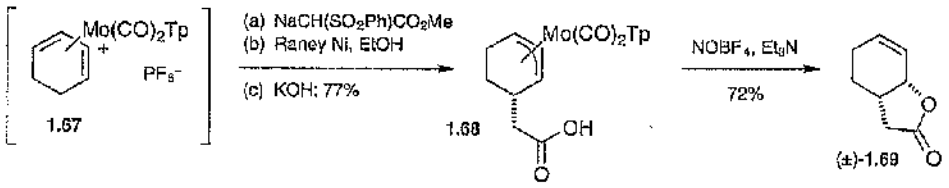
(a) Exposure of a chloroform solution of the crude material to air.[9] The procedure is mild, but slow, reaction times of a day or more generally being required. As described in chapters 2 and 4, we have found that bubbling gaseous oxygen through the crude solution provides a more rapid alternative.

(b) High pressure CO cleaves the olefin from molybdenum, releasing $CpMo(CO)_2(NO)$.[9]

(c) Strong base - if the olefin can withstand the conditions.[9]

(d) Oxidation by ammonium cerium(IV) nitrate (CAN), often buffered by NaOAc.[55]

(e) Pearson has used intramolecular attack upon a cationic Mo(CO)(NO)Cp(η^3-allyl) system by a pendant acid to effect simultaneous lactonisation and olefin decomplexation (Scheme 1.25).[56] Noteworthy in the sequence below is the excellent stability of the $Mo(CO)_2Tp$ moiety during functional group manipulations.

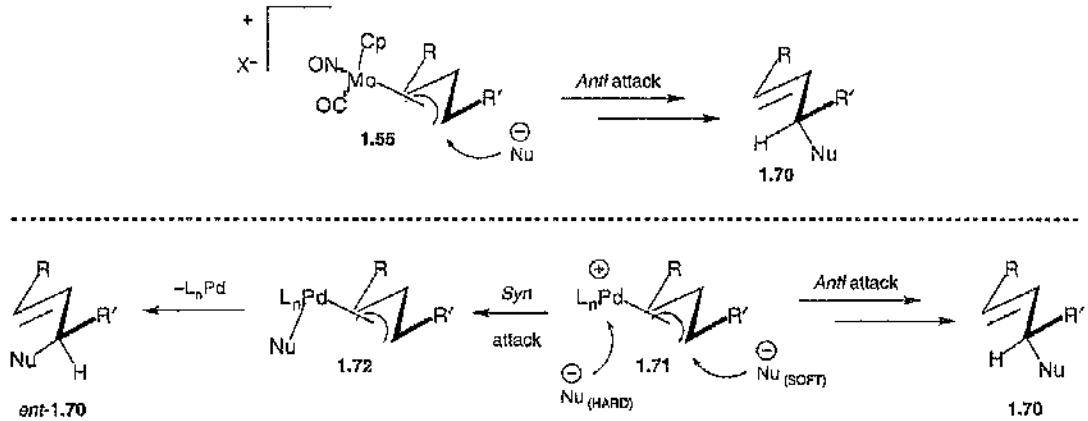


Scheme 1.25.

1.5 - Stereochemical issues.

1.5.1 - Asymmetric synthesis *via* resolved complexes.

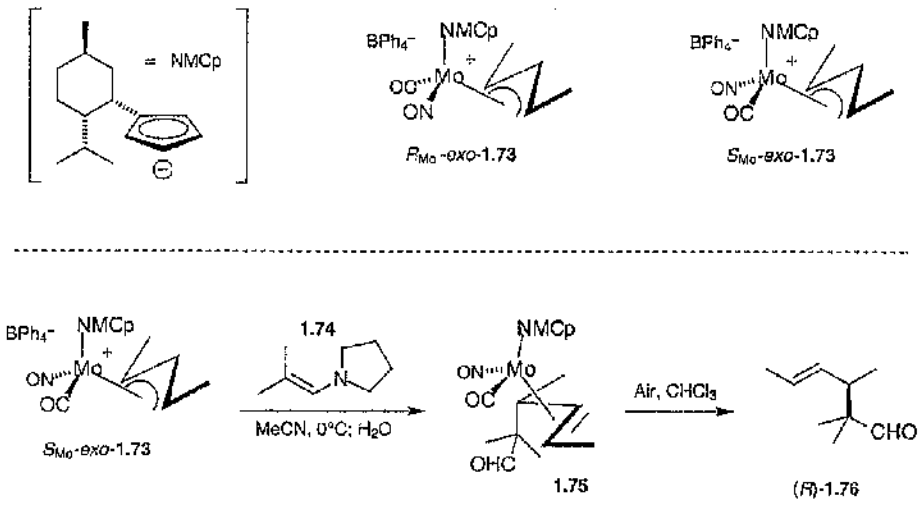
The (η^3-allyl)Mo(CO)$_2$Cp and [(η^3-allyl)Mo(CO)(NO)Cp]$^+$ BF$_4^-$ systems popularised by Faller are configurationally stable; the metal moiety cannot migrate from one enantioface of the planar allyl ligand to the other. If it can be arranged for one face of the allyl ligand to be specifically blocked by the molybdenum fragment, then an incoming nucleophile will specifically attack the opposite face, *anti* to the metal (Scheme 1.26). Herein lies an important difference between palladium-catalysed and stoichiometric Mo allylic alkylation reactions: palladium forms coordinatively unsaturated 16-electron η^3-allyl electrophilic complexes **1.71**, whereas the metal in [(η^3-allyl)Mo(CO)(NO)Cp]$^+$ BF$_4^-$ complexes is a coordinatively saturated 18-electron species. A nucleophile attacking the allyl ligand should therefore only be able to do so from the face *anti* to molybdenum, which acts as a steric shield, blocking the *syn*-face. In the palladium case however, there is the possibility for nucleophilic attack *syn* or *anti* to the metal fragment. In general, "soft" nucleophiles (such as stabilised carbanions) attack *anti*, whereas "hard" nucleophiles (organometallic reagents for example) can initially attack the palladium, before alkylation *via* reductive elimination of intermediate **1.72**.[2]



Scheme 1.26.

Carbonyl-nitrosyl ligand exchange results in a chiral molybdenum centre, a racemic mixture if the η^3-ligand is symmetrical. Faller used a neomenthylcyclopentadienyl (NMCp) ligand as

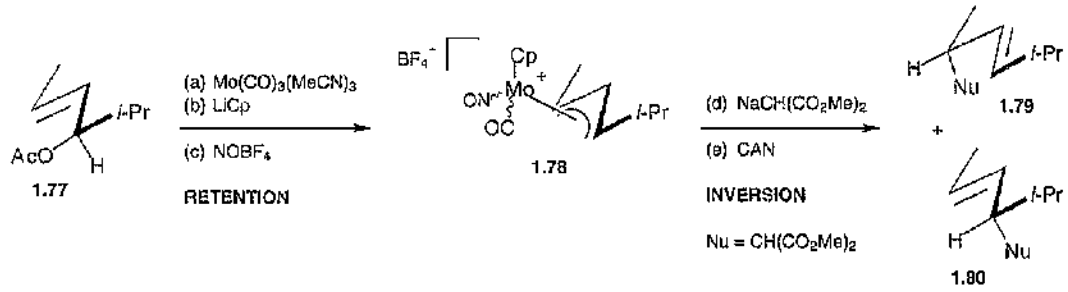
a substitute for Cp to form diastereomeric complexes **1.73** (Scheme 1.27), which were subsequently separated by crystallisation.[51] Coupling of cation S_{Mo}-**1.73** with enamine **1.74** yielded optically pure olefin **1.76** following oxidation.



Scheme 1.27.

1.5.2 - Formation of planar chiral complexes from enantiopure allylic esters.

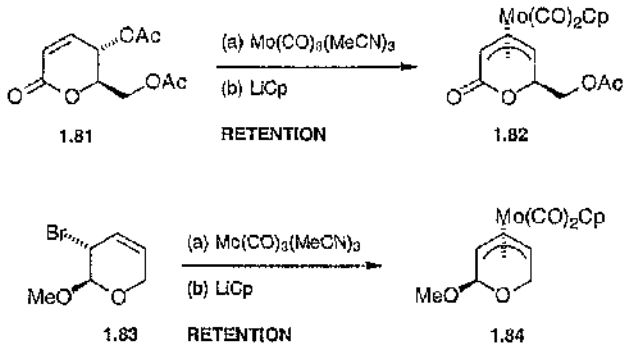
Enantiofacial control without the need for resolution is possible, as demonstrated by Faller in a study designed to elucidate the stereochemical pathway of Mo-*catalysed* asymmetric alkylations (Scheme 1.28).[50] Oxidative addition of enantiopure allylic acetate **1.77** to $Mo(CO)_3(MeCN)_3$ occurred with clean *retention* of configuration, yielding products of overall *inversion* following nucleophilic attack upon cationic complex **1.78**. In line with the precedented directing effect of the nitrosyl ligand, nucleophilic attack yielded an equimolar mixture of regioisomers **1.79** and **1.80**.



Scheme 1.28.

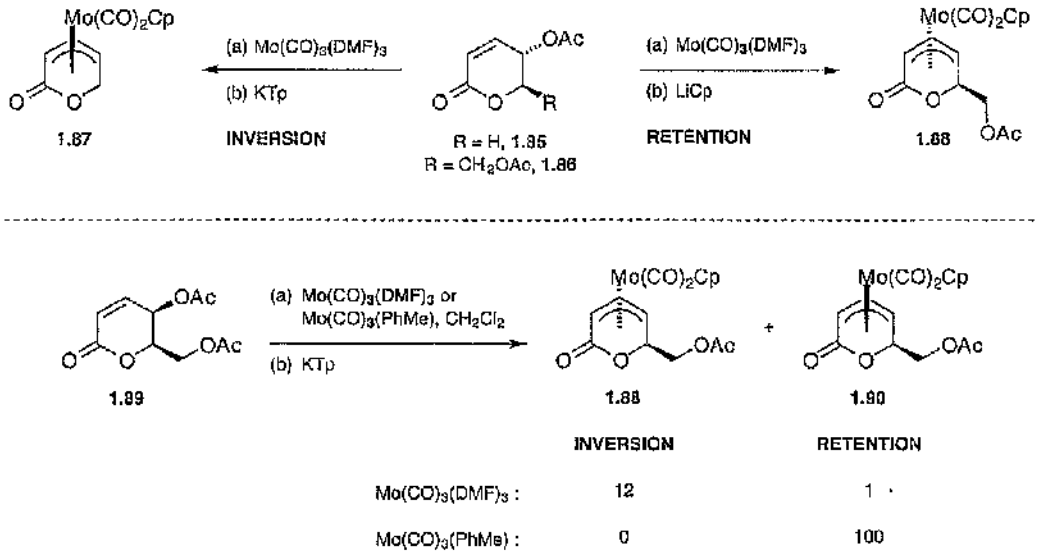
The retentive oxidative addition of acyclic allylic acetate *ent*-**1.77** to $Mo(CO)_3(MeCN)_3$ demonstrated by Faller was confirmed by Kocienski in the synthesis of Salinomycin,[57] (see

section 1.5.3) and complemented by Liebeskind for cyclic acetate **1.81** and bromide **1.83** (Scheme 1.29).[58, 59]



Scheme 1.29.

Further investigation of cyclic systems by Liebeskind revealed that cleanly retentive oxidative addition pathways cannot be universally assumed for alternative Mo(0) systems (Scheme 1.30).[60] Dihydropyranone **1.86**, when treated with $Mo(CO)_3(DMF)_3$ in CH_2Cl_2 gave **1.88**, the product of overall retention. In contrast, diastereomeric dihydropyranone **1.89** gave a 12 : 1 mixture of inversion (**1.88**) and retention (**1.90**) products with $Mo(CO)_3(DMF)_3$. Retentive product **1.90** could be prepared independently using $Mo(CO)_3(PhMe)$ as the Mo(0) source. $Mo(CO)_3(DMF)_3$ could be utilised with acetate **1.85** to yield complex **1.87** *via* inversion.



Scheme 1.30.

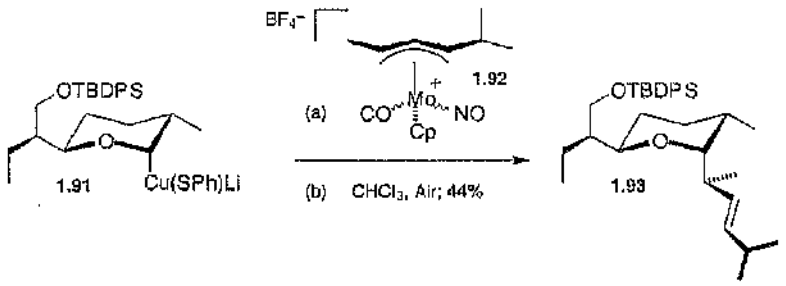
Liebeskind concluded that retentive or invertive pathways were both feasible, depending upon a number of factors including the nature and effective concentration of the Mo(0) source, temperature, and steric constraints imposed by the substrate. Only $Mo(CO)_3(MeCN)_3$,

$Mo(CO)_3(PhMe)$ and $Mo(CO)_4(py)_2$ appear to be unambiguous sources of Mo(0) for retentive oxidative addition pathways, with $Mo(CO)_3(DMF)_3$ giving inversion under appropriate conditions.

Homochiral allylic esters are readily available, the corresponding alcohols being obtained by several methods, including kinetic resolution *via* Sharpless asymmetric epoxidation, enzymatic resolution or from the chiral pool. Coupling with the reliable $Mo(CO)_3(MeCN)_3$, $Mo(CO)_3(PhMe)$ or $Mo(CO)_4(py)_2$ reagents should therefore allow access to enantiopure η^3-allylmolybdenum complexes. A restriction to the use of allylic acetates is their rather low reactivity compared to the corresponding halides, however, as described in section 1.2.2, an allylic benzoate provides a more reactive substitute. Liebeskind has used achiral or racemic allylic diphenylphosphinate esters in combination with $Mo(CO)_6$ in refluxing MeCN as an alternative to the allylic acetate / $Mo(CO)_3(MeCN)_3$ combination.[15, 21] At the time of writing (July 2000) nothing further has been reported, and the use of these substrates for the formation of enantiopure complexes has yet to be explored.

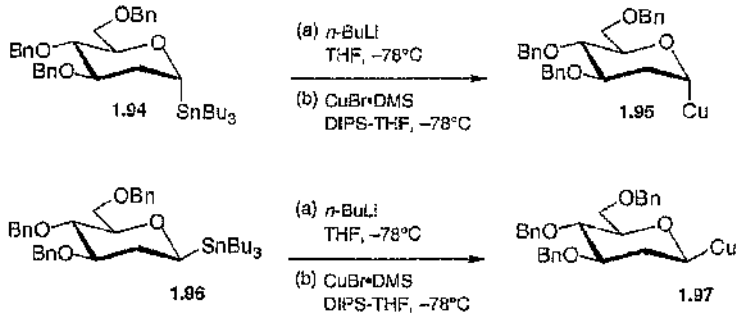
1.5.3 - Regioselectivity in alkylation of unsymmetrically substituted complexes.

In contrast to Faller's observations, Kocienski found that attack of cuprate nucleophile **1.91** upon planar chiral substituted complex **1.92** gave a single regioisomeric product **1.93** following oxidative decomplexation of the metal (Scheme 1.31).[57, 61]



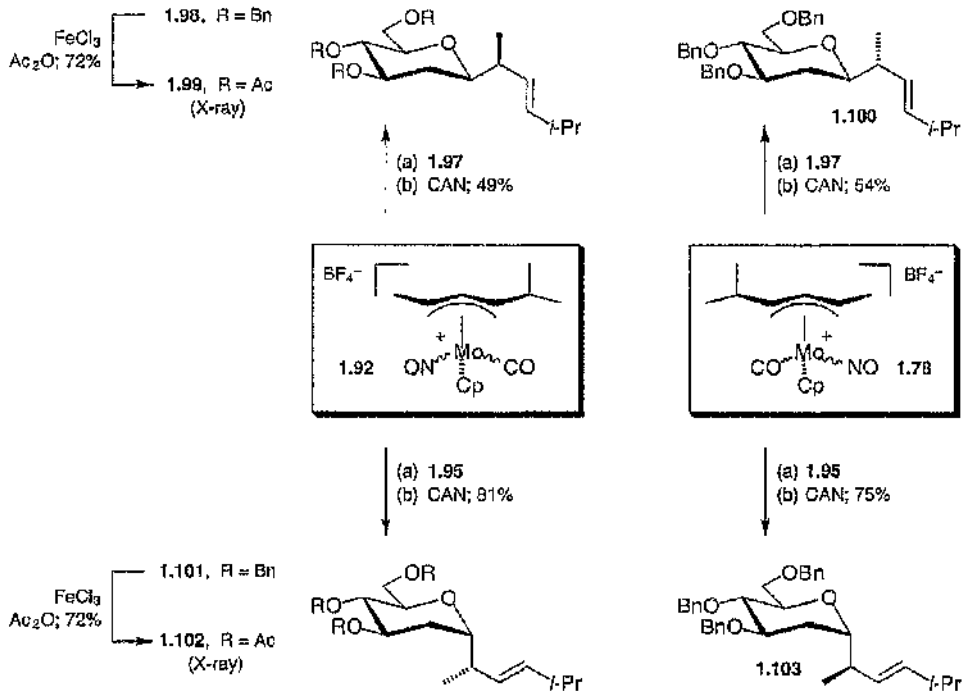
Scheme 1.31.

Further precedent was established[53, 61] using configurationally stable organocopper(I) nucleophiles **1.95** and **1.97**,[62] derived from the corresponding stannanes **1.94** and **1.96**[63, 64] at low temperature (Scheme 1.32).



Scheme 1.32.

Coupling of **1.95** and **1.97** with complexes **1.78** and **1.92** (Scheme 1.33) gave in each of the 4 cases predominantly the olefin arising from attack at the less sterically hindered terminus of the allylic unit (regioselectivity ≥ 8:1). X-ray structures of derivatives of olefins **1.98** and **1.101** established that: (a) the stereochemistry of the α-glucosylcopper(I) reagent was retained in the alkylation; (b) the geometry of the double bond was retained from acetate *ent*-**1.77**; (c) clean overall inversion had occurred with respect to **1.77**.



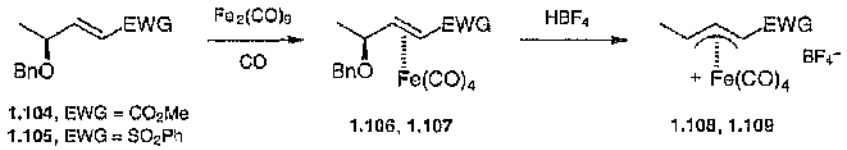
Scheme 1.33.

The Kocienski precedent established that the electronic directing effect of the nitrosyl ligand could be overcome on the grounds of steric differentiation between the methyl and *iso*-propyl allylic termini, negating the need to control central chirality. Furthermore, the work revealed the potential for the use of functionalised α-alkoxyalkylcopper(I) nucleophiles in conjunction

with planar chiral cationic complexes, simultaneously creating 2 stereocentres with excellent control.

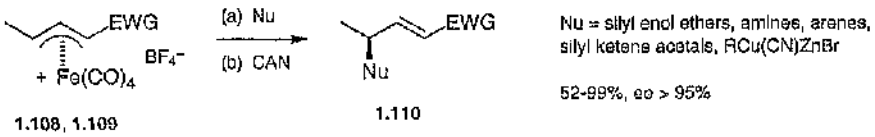
1.6 - Parallels between stoichiometric molybdenum- and iron-based η^3-allyl chemistry.

The stoichiometric use of planar chiral cationic η^3-allyliron complexes has been investigated by Enders in recent years (Scheme 1.34), and parallels the molybdenum chemistry discussed above.[65] In common with the above strategy, an optically pure allylic substrate (**1.104 / 1.105**) serves as a precursor to planar chiral complex **1.108 / 1.109**. In contrast to the molybdenum chemistry, inversion of configuration is observed in formation of complexes **1.108 / 1.109**. The stereocomplementarity of the Mo- and Fe-systems originates from the different roles played by the allylic leaving group. In the molybdenum case, an ester is used to tether the metal, directing it to the same face of the allylic unit, resulting in excellent retentive formation of the planar chiral allyl complex. In the iron-based systems, the allylic ether acts simply as a steric shield, forcing the iron moiety to coordinate to the opposite face of the olefin (intermediates **1.106 / 1.107**), before formation of the η^3-array in a subsequent step. Cationic complexes **1.108 / 1.109** are obtained in good yield and optical purity (>95%) following purification by repeated precipitation.



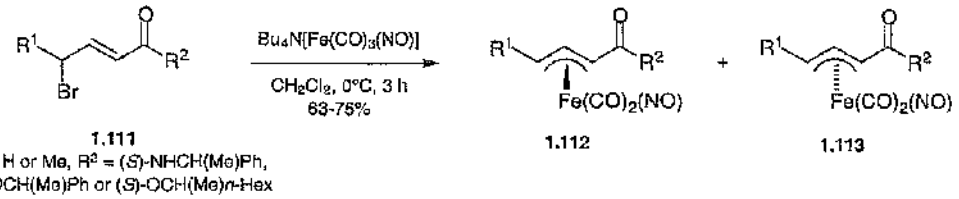
Scheme 1.34.

The regioselectivity complications arising from central chirality in cationic π-allylmolybdenum systems do not occur with complexes **1.108 / 1.109**, as the iron is achiral. Complete γ-regiocontrol is obtained on electronic grounds, directed by the electron-withdrawing effect of the sulfone or ester group (Scheme 1.35). Olefins **1.110** are products of overall retention of configuration with respect to the starting allylic ether (*via* double inversion), nucleophilic attack occurring *anti to* the metal.



Scheme 1.35.

Nakanishi has described the preparation of analogous $Fe(CO)_2(NO)(\eta^3$-allyl) complexes **1.112** and **1.113** (Scheme 1.36).[66] Although formally neutral, the ability of the nitrosyl ligand to act as a one, two or three-electron donor allows the complexes to react with nucleophiles *and* electrophiles. Planar chiral complexes **1.112** and **1.113** are formed from allylic bromides **1.111** bearing chiral amide or ester auxiliary groups.[67] The diastereomeric complexes are readily separable by column chromatography.

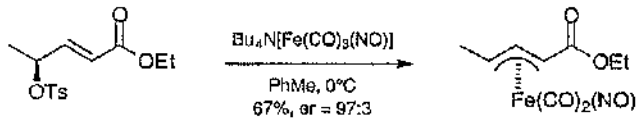


1.111
R^1 = H or Me, R^2 = (*S*)-NHCH(Me)Ph, (*R*)-OCH(Me)Ph or (*S*)-OCH(Me)*n*-Hex

1.112 **1.113**

Scheme 1.36.

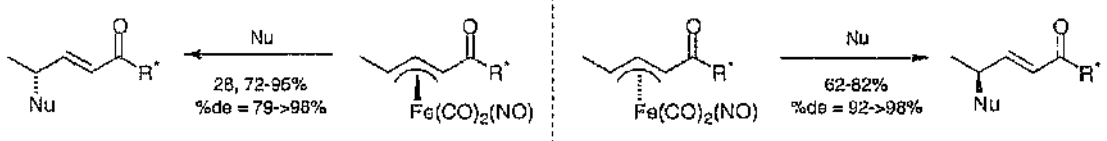
Alternatively, complexes **1.115** can be formed from optically active allylic substrates (e.g. tosylate **1.114**) (Scheme 1.37), the stereoselectivity being highly dependant upon the nature of the leaving group and the solvent.[68]



1.114 **1.115**

Scheme 1.37.

As expected, complexes **1.112** and **1.113** are aminated or alkylated with excellent regioselectivity as for the analogous Enders systems (Scheme 1.38).[69]

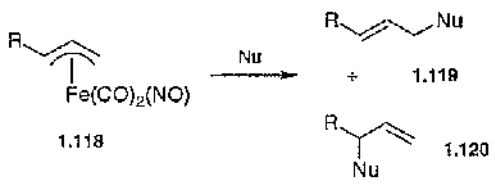


1.116 **1.112** **1.113** **1.117**

Nu = $BnNH_2$, BnNHMe, $NaCH(CO_2Me)_2$, $NaCH(COMe)(CO_2Et)$, $NaCH(CN)_2$

Scheme 1.38.

Monosubstituted complexes **1.118** have also been investigated (Scheme 1.39).[66, 69, 70] Alkylation with sodiodiethylmalonate gives predominantly substitution at the less hindered allyl terminus. Amination is more problematic; phenyl and ester substituents on the allyl give complete regioselectivity, but alkyl substituents result in a mixture of regioisomers.



R	Nu	1.119 : 1.120
Me	$NaCH(CO_2Et)_2$	83 : 17
Me	$BnNH_2$	63 : 37
Ph	$NaCH(CO_2Et)_2$	100 : 0
Ph	$BnNH_2$	100 : 0
n-C_5H_{11}	$BnNH_2$	82 : 18
CO_2Me	$BnNH_2$	100 :0

Scheme 1.39.

1.7 - Conclusions.

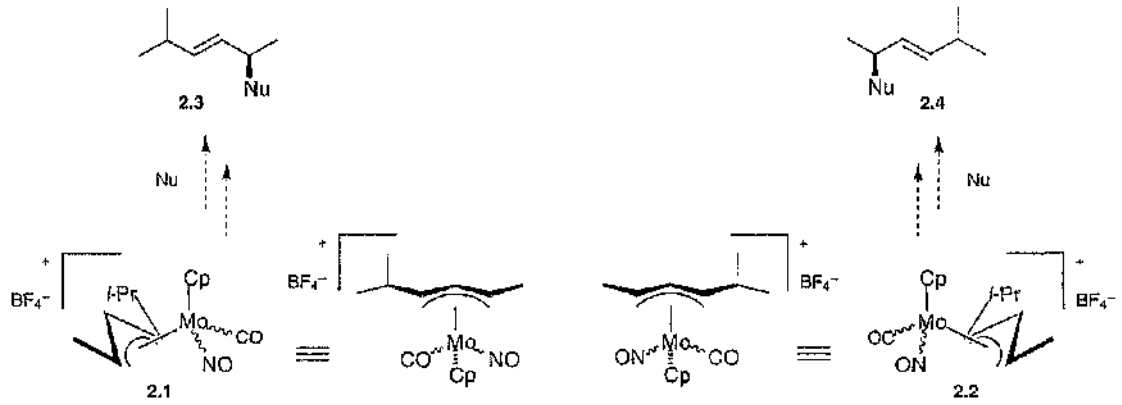
The requirements set out in section 1.1 for asymmetric synthesis using planar chiral η^3-allylmolybdenum complexes have been met. Faller, Liebeskind and Kuhl have shown that formation of planar chiral neutral complexes with clean retention from optically active precursors is feasible, and that nucleophilic attack occurs *anti* to the metal. Furthermore, Kocienski has shown that good regiocontrol using an unsymmetrically substituted complex can be obtained without the need to control central chirality.

The molybdenum based chemistry mirrors similar iron based work, but has the advantage of excellent facial stereocontrol without reliance upon recrystallisation or chromatography. The Kocienski work with functionalised, configurationally stable chiral organocopper(I) nucleophiles demonstrates the potential for the application of planar chiral η^3-allylmolybdenum complexes to asymmetric synthesis.

The work contained in this thesis in chapters 2 and 4 builds upon the knowledge of η^3-allylmolybdenum complexes described here in chapter 1, with an ultimate application of the strategy to natural product synthesis.

Chapter 2 - Alkylation of substituted η^3-allylmolybdenum complexes.

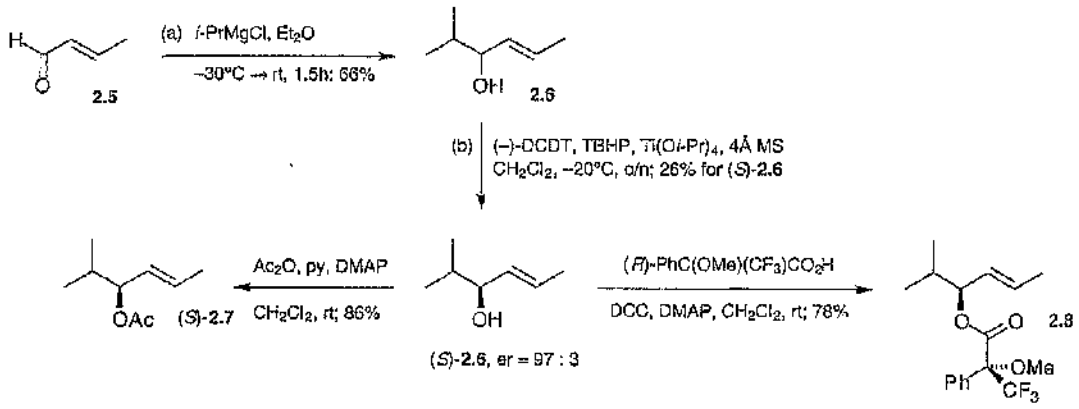
Chapter 2 will describe an expanded range of nucleophiles compatible with planar chiral cationic complexes **2.1** and **2.2** (Scheme 2.1). We show that the good regiocontrol with alkylcopper(I) nucleophiles described in the previous chapter is general for a number of readily available substrates. The nucleophiles chosen were not aimed at specific synthetic targets, but in most cases contain functionality which would allow further elaboration of the olefin products.



Scheme 2.1

2.1 - Synthesis of η^3-allylmolybdenum complexes 2.1 and 2.2.

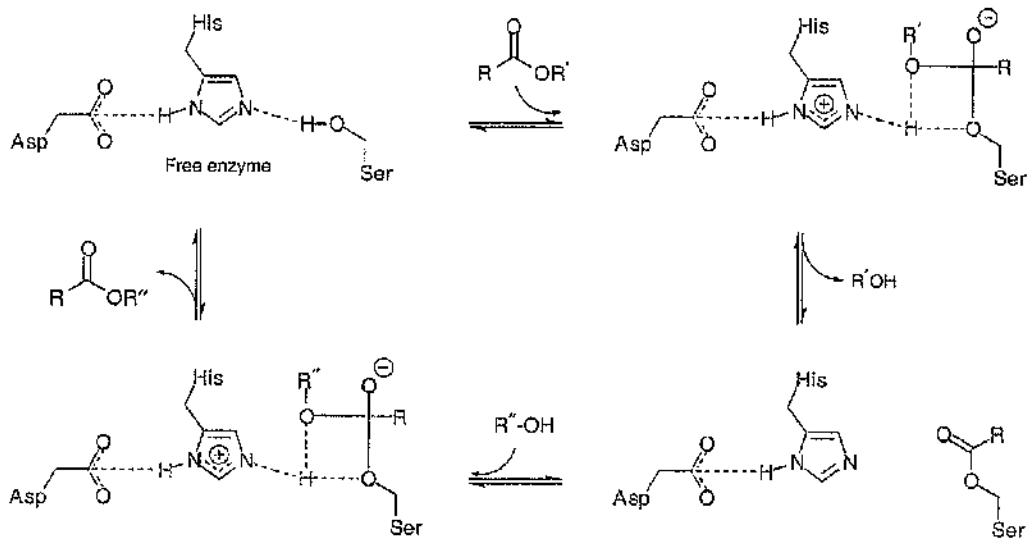
We have used two procedures to secure enantiopure allylic precursors to complexes **2.1** and **2.2**. Initial work utilised kinetic resolution *via* Sharpless asymmetric epoxidation,[71] allylic acetate (*S*)-**2.7** being obtained in moderate overall yield in three steps from crotonaldehyde **2.5** (Scheme 2.2). The enantiomeric ratio at C3 of intermediate alcohol (*S*)-**2.6** was estimated as 97:3 *via* formation of the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate ester **2.8** and ^{1}H / ^{19}F NMR spectroscopic analysis. The corresponding (*R*)-alcohol and acetate were prepared in similar fashion (29%, er = 93:7 and 87% respectively).



Scheme 2.2

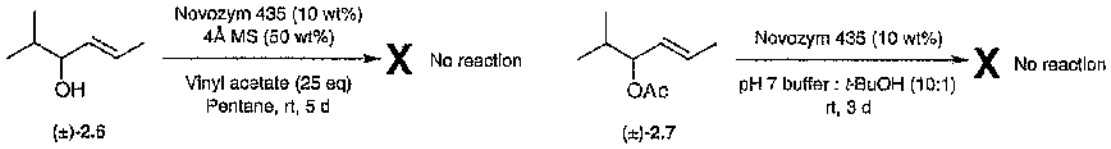
The kinetic resolution procedure was reliable in terms of the enantiopurity of allylic alcohol (*R*)- or (*S*)-**2.6**, but as with all resolutions, the sequence is wasteful, the epoxide formed being of no use to us. We subsequently turned our attention to an alternative enzymatic resolution, which would allow access to either enantiomer of acetate **2.7** from a common precursor.

Novozym 435 is the trade name of the recombinant, immobilised B-component lipase from the yeast *Candida antarctica*, and is particularly efficient and robust, catalysing a diverse range of regio- and enantioselective syntheses.[72] The enantiospecificity of the enzyme has been predicted based on the crystal structure and modelling of the active site region, indicating that only (*R*)-enantiomers should be able to form the intermediates required for catalysis.[73] Uppenberg and co-workers have resolved the amino acid sequence and three dimensional structure of CALB (*Candida antarctica* B-lipase) and postulated the general mechanism shown in Scheme 2.3.[73] The catalytically active serine residue is located at the bottom of a deep, narrow pocket approximately 10 x 4Å wide and 12Å deep,[72] and CALB exhibits a high degree of substrate selectivity which is related to the limited amount of space available in the active-site pocket.



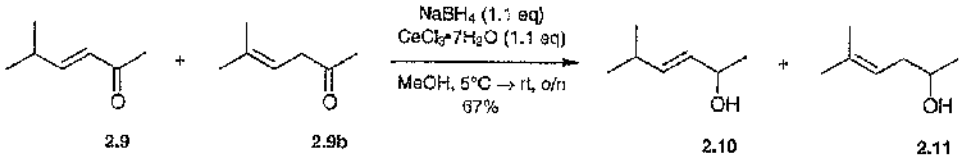
Scheme 2.3

Attempts to acetylate (±)-**2.6** under standard conditions[74] (Novozym 435, vinyl acetate, 4Å MS and pentane at ambient temperature) were fruitless, ^{1}H NMR spectroscopy of the crude reaction indicating < 5% acetylation after 5 days (Scheme 2.4). Attention then turned to the saponification of racemic allylic acetate **2.7**, but treatment with Novozym 435 in a 10 : 1 pH 7 Buffer : *t*-BuOH mixture[75] similarly failed to produce any alcohol product after 3 days at ambient temperature.



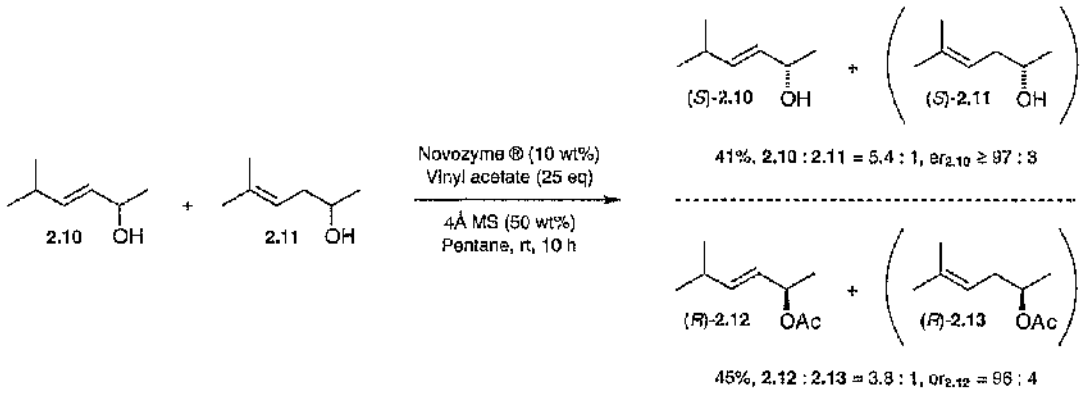
Scheme 2.4

As an alternative we decided to investigate the use of allylic alcohol **2.10** which offered reduced steric congestion around the hydroxyl group, presumably the cause of the incompatibility of **2.6** and **2.7** with CALB. Preparation of racemic alcohol **2.10** (Scheme 2.5) was straightforward, but our task was complicated by the commercial availability of enone **2.9** in only 75% purity, the remainder being isomer **2.9b**. Reduction yielded a mixture of inseparable, volatile alcohols **2.10** / **2.11** in the approximate ratio 4.7 : 1. The corresponding acetates **2.12** / **2.13** (Scheme 2.6) were also inseparable; however, it was hoped that complex formation from a mixture would be possible as **2.13** would not react with the Mo(0) source to form an η^3-intermediate. Undesired acetate **2.13** (b.p. 60-62°C / 13 mmHg[76]) was judged to be volatile enough to be removed upon prolonged drying *in vacuo*.



Scheme 2.5

Alcohols (±)-**2.10** / (±)-**2.11** were subjected to the standard Novozym acetylation conditions (Scheme 2.6),[74] reaction proceeding quickly and efficiently to yield acetates (*R*)-**2.12** / (*R*)-**2.13** in 45% yield and alcohols (*S*)-**2.10** / (*S*)-**2.11** in 41% yield. The reaction was followed periodically by ^{1}H NMR spectroscopic analysis of crude reaction samples, ≥50% conversion being attained after 7.5 h at ambient temperature. Saponification of a portion of acetates (*R*)-**2.12** / (*R*)-**2.13** allowed the estimation of the enantiomeric excesses of alcohol (*S*)-**2.10** and acetate (*R*)-**2.12** as ≥95% and 92% respectively *via* (*R*)-acetylmandelate ester formation and ^{1}H NMR analysis.

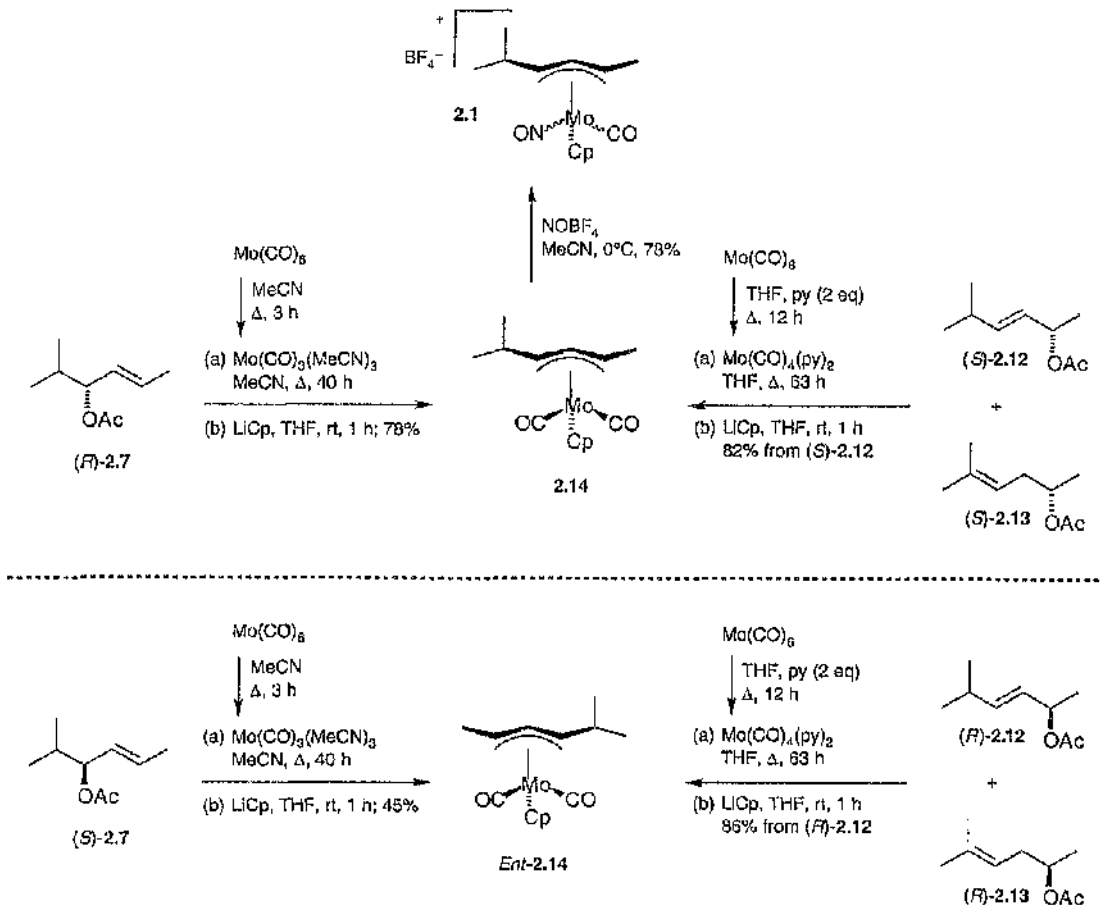


Scheme 2.6

Our early studies into the formation and use of η^3-allylmolybdenum complexes used the $Mo(CO)_3(MeCN)_3$ based procedure described in Chapter 1.[9] Neutral complex **2.14** was formed from allylic acetate (*R*)-**2.7** in 78% yield, and complex *ent*-**2.14** in 73% yield from (*S*)-**2.7** (Scheme 2.7). Complex **2.14** was isolated as a dark-red oil after purification by column chromatography under inert atmosphere.[57] ^{1}H and ^{13}C NMR spectroscopy indicated that the purity of material prepared using the Faller procedure was reasonable, but contamination of **2.14** by minor unidentified products was obvious. Nevertheless, conversion into complex **2.1** by ligand exchange using nitrosonium tetrafluoroborate was straightforward, and the cationic species was isolated as a fine yellow solid in 78% yield by precipitation in cold ether and filtration under inert atmosphere. The yield of cationic complex **2.1** was capricious, a minimum volume of MeCN being necessary to prevent **2.1** being deposited as an oil. Stringent precautions were needed to exclude moisture and air from the sensitive solid cationic complexes, which readily decomposed taking on a sticky, green

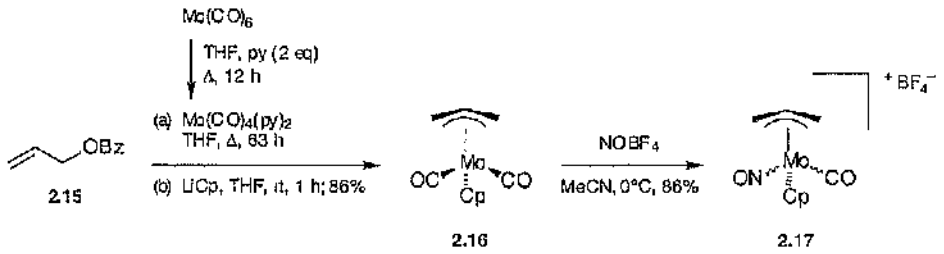
appearance. Tetrafluoroborate salts such as **2.1** and **2.2** are well precedented to be sensitive to moisture, a suggested decomposition route being decarbonylation promoted by fluoride ion liberated from hydrolysis of the BF_4 anion.[35, 77] The precedented unselective ligand exchange in formation of cationic complex **2.1** was confirmed by ^1H and ^{13}C NMR spectroscopy. Complex **2.1** initially appeared as a mixture of 2 major isomers in an approximately equimolar ratio, along with a further pair of minor isomers. The major isomers are assigned as *endo* conformers, on the basis of observations from Faller that cationic (η^3-allyl)Mo(CO)(NO)Cp species are formed as kinetically controlled mixtures of isomers.[42, 78] The mixture gradually proceeds towards thermodynamic equilibrium, eventually favouring the conformer which was thermodynamically favoured in the parent neutral complex. Neutral complex **2.14** exists in solution as a 5 : 1 *exo* : *endo* mixture, assignment based on the characteristic upfield *exo* resonance (δ –1743) in the ^{95}Mo spectrum and the existence of similarly substituted complexes predominantly in *exo*-conformations.[78]

The use of $Mo(CO)_4(py)_2$[16] (see Chapter 1, section 1.2.2) provided a viable alternative to the original Faller protocol, allowing the formation of neutral complexes **2.14** and *ent*-**2.14** in high yield and excellent purity as judged from ^1H / ^{13}C NMR spectroscopy (Scheme 2.7). The use of a mixture of acetate isomers **2.12 / 2.13** did not hamper formation of the neutral complex. Periodic analysis of the crude reaction mixture by ^1H NMR spectroscopy revealed complete consumption of allylic acetate within 58-63 h. LiCp ligand exchange in the normal fashion yielded neutral complex **2.14** uncontaminated by acetate **2.13**, which was volatile enough to be removed by prolonged drying *in vacuo*.



Scheme 2.7

Similarly, unsubstituted allyl complex **2.16** was prepared in 86% yield from allyl benzoate and $Mo(CO)_4(py)_2$ (Scheme 2.8). In contrast to the substituted cationic complexes, allyl cationic complex **2.17** readily precipitated in cold Et_2O, and was isolated in 86% yield as a fine yellow solid.

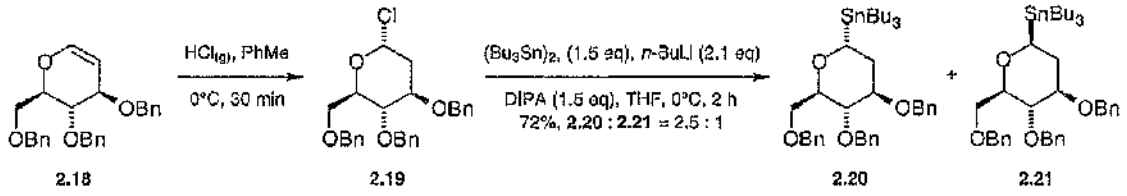


Scheme 2.8

A drawback with using a mixture of acetates **2.12 / 2.13** in combination with $Mo(CO)_4(py)_2$ is the lengthy reaction time for oxidative addition; 63 h compared to 40 h with $Mo(CO)_3(MeCN)_3$ and acetate **2.7**. The greater reactivity of $Mo(CO)_4(py)_2$ compared to $Mo(CO)_3(MeCN)_3$ is illustrated by the reaction times required for oxidative addition of benzoate **4.17** (see Chapter 4), 18 h and 28 h respectively. The mechanism for formation of

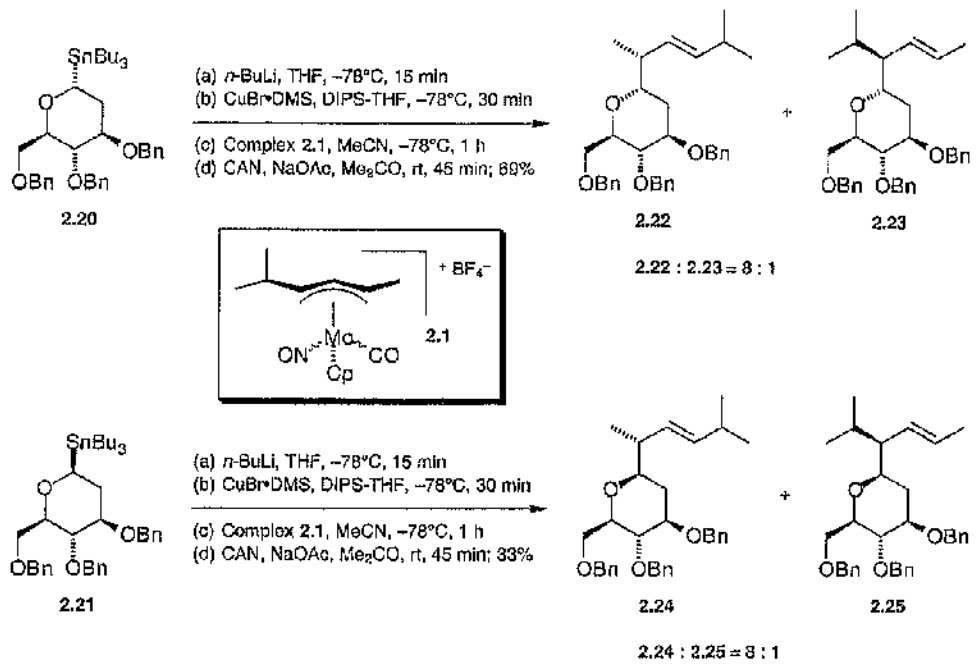
η^3-allylmolybdenum complexes from $Mo(CO)_4(py)_2$ is described in Chapter 1 (section 1.2.2). Coordination of the carbonyl oxygen of an allylic ester occurs prior to departure of a ligand from the metal, coordination of Mo to the olefin and collapse of the system to give the η^3-arrangement. Competing coordination of a substrate incapable of forming an η^3-intermediate would inhibit coordination of the allylic acetate and decrease the rate of oxidative addition.

To overcome difficulties encountered in the isolation of complexes **2.1** and **2.2**, we performed the ligand-exchange and alkylation procedures without isolation, minimising the opportunity for decomposition of the sensitive tetrafluoroborate salts. In order to ascertain whether the strategy was viable, the C-glycoside syntheses described in Chapter 1 (section 1.5.3) were revisited.[53, 61]A method previously utilised within the Kocienski group was used to secure stannanes **2.20** and **2.21**.[61] Procter had found that retention was the dominant mode of reaction when substitution of α-chloroether **2.19** using tributylstannyl lithium generated in the presence of 0.6 equivalents of excess *n*-BuLi and 1.5 equivalents of di*iso*-propylamine was used.[61] A single electron transfer (SET) pathway was tentatively proposed as the most likely mechanism. Similar processes have been described in the displacement of halides with trimethyltin anions.[79-81] Readily separable axial and equatorial stannanes **2.20** and **2.21** were prepared in good overall yield from glucal **2.18** (Scheme 2.9), with the axial stannane **2.20** dominating in an approximate 2.5 : 1 ratio.



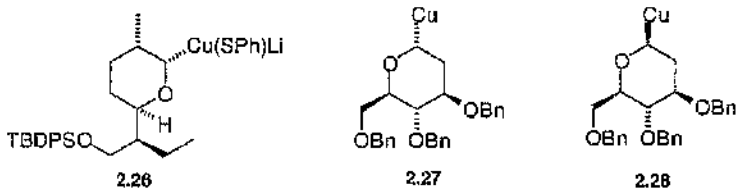
Scheme 2.9

Coupling of stannanes **2.20** or **2.21** with cationic complex **2.1** *via* the corresponding alkylcopper(I) reagent was performed as previously described.[61] The only procedural difference was the addition of complex **2.1** (which had been isolated by precipitation) as a solution in a minimal volume of acetonitrile rather than as a solid. Olefins **2.22** and **2.24** respectively were isolated as the major products after decomplexation using CAN (Scheme 2.10). Analysis of ^1H NMR spectra allowed the regioselectivity to be conservatively estimated as 8:1 in each case, as estimated from the differing olefinic signals for each regioisomer (see experimental section for details). Comparison of yields and regioselectivity with previous work showed that addition of **2.1** as a solution had no detrimental effect upon yield or regioselectivity.



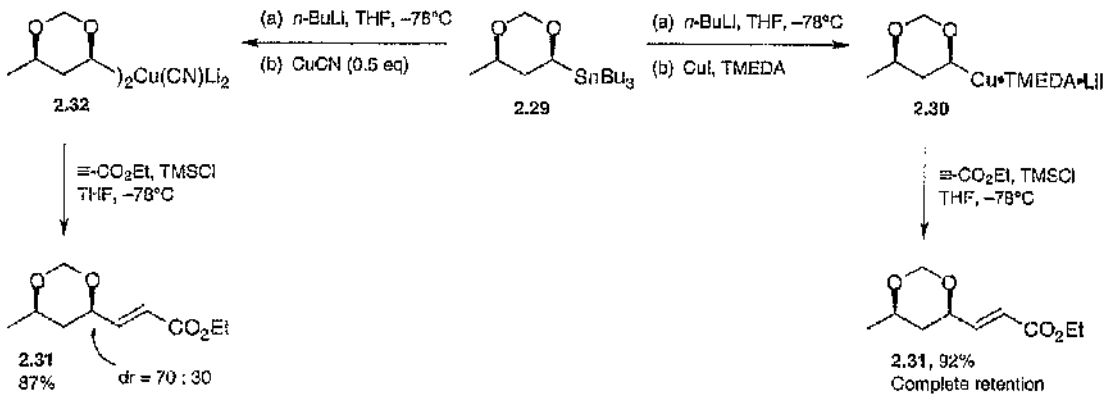
Scheme 2.10

It had been established by Procter that alkyllithium nucleophiles were not compatible with complexes such as **2.1**, transmetallation to copper being necessary before alkylation could occur.[61] One unknown factor which will determine the synthetic utility of prospective chiral nucleophiles is the configurational stability of alkylcopper(I) species. In 1980, Still demonstrated that transmetallation of α-alkoxyorganostannanes to the corresponding alkyllithium species occurs with retention, as does reaction with electrophiles.[82] In recent years, this precedent has been greatly expanded upon.[83-85] In contrast, only meagre precedent exists for the configurational stability of cyclic α-alkoxyalkylcopper(I) reagents at low temperature, including that already described for alkylcopper(I) reagents **2.26-2.28** (Scheme 2.11).



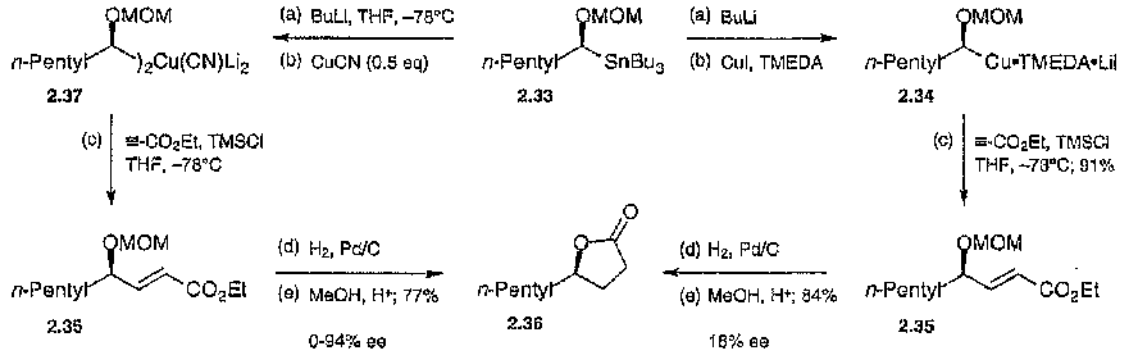
Scheme 2.11

Linderman has shown that the precise nature of the copper species is important. The TMEDA-copper reagent **2.30** reacted with ethyl propiolate to yield **2.31** with complete retention, but the corresponding higher order cyanocuprate **2.32** resulted in only partial retention (Scheme 2.12).[86]



Scheme 2.12

The situation for acyclic α-alkoxyalkylcopper(I) reagents is even less well established. Linderman described the addition of TMEDA-copper reagent **2.34** (prepared from stannane **2.33** of 98% ee) to ethyl propiolate to ultimately give lactone **2.36** in only 18%ee (Scheme 2.13). Similarly, the related higher order cyanocuprate **2.37** led to lactone products with widely varying (0-97%) degrees of retention of configuration.[86, 87]



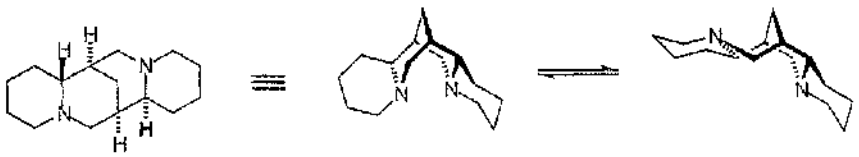
Scheme 2.13

With the above precedent in mind, we approached the search for nucleophiles compatible with complexes **2.1** and **2.2** with the knowledge that retention of configuration at the nucleophile cannot be assumed using chiral alkylcopper(I) nucleophiles.

2.3 - Alkylation of complexes 2.1 and 2.2.

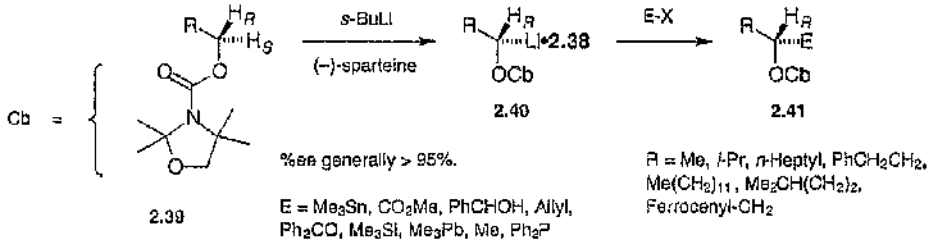
2.3.1 - Nucleophiles derived by (–)-sparteine-mediated enantioselective deprotonation.

(–)-Sparteine (**2.38**, Scheme 2.14) is a readily available lupine alkaloid which in recent years has found widespread use in enantioselective synthesis due to its ability to serve as a chiral bidentate ligand in the conformation **2.38a**.[83]



Scheme 2.14

(–)-Sparteine was first used in enantioselective synthesis in 1968 when Nozaki and co-workers reported the addition of organolithium and organomagnesium reagents to carbonyl compounds to yield products with up to 22% ee.[88, 89] The chiral ligand has since been utilised in a wide variety of enantioselective processes, an area which has been thoroughly reviewed.[83, 90-92] Hoppe has described the deprotonation of achiral carbamates **2.39** with *s*-butyllithium and (–)-sparteine, the carbamate serving to stabilise the α-lithio derivatives by chelation.[83, 93-95] The deprotonation proceeds with reliable selectivity for the *pro-S*-proton to give enantioenriched products **2.41** of stereoretention after electrophile addition (Scheme 2.15).



Scheme 2.15

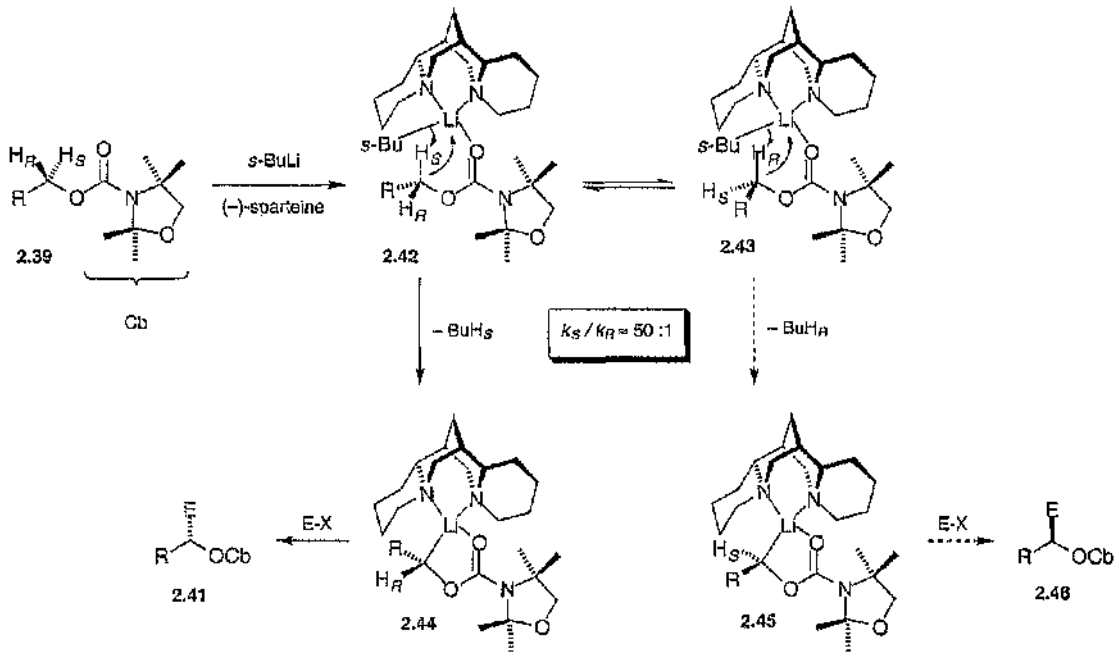
A series of mechanistic investigations allowed Hoppe to rationalise the mechanism of the (–)-sparteine-mediated deprotonation, with the following conclusions:[83, 96]

(1) Lithiated alkyl carbamates **2.40** are configurationally stable in the form of TMEDA or (–)-sparteine complexes under the reaction conditions.

(2) The deprotonation is kinetically controlled, which determines the stereochemical course of the reaction.

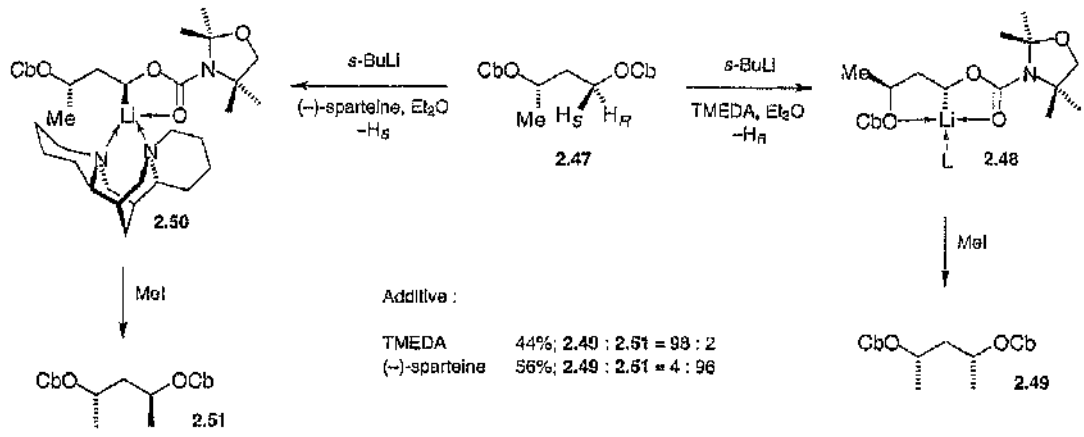
(3) The *pro-S*-proton is abstracted with high selectivity under the influence of (–)-sparteine.

It was concluded that prior to the deprotonation occurring, a complex of *s*-butyllithium, (–)-sparteine and the carbamate forms virtually irreversibly. Proton transfer in aggregate **2.42** is an intramolecular process in which abstraction of the *pro-S*-proton occurs more rapidly than abstraction of the *pro-R*-proton in conformation **2.43**, leading to an excess of **2.41** over enantiomer **2.46** following retentive electrophile incorporation (Scheme 2.16).



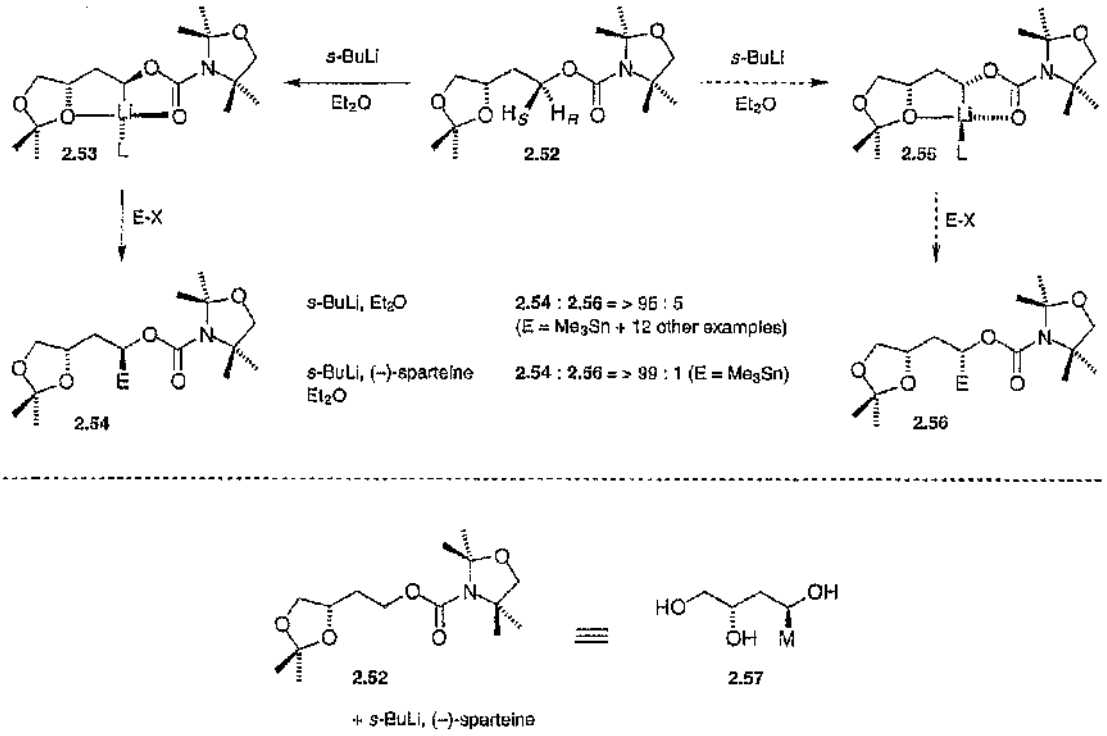
Scheme 2.16

Hoppe has also investigated heterosubstituted alkyl carbamates, in which chiral induction is possible if a good donor substituent is attached to a stereogenic carbon atom γ- or δ- to the carbamate. In a favourable case, substrate directed or (–)-sparteine mediated lithiation can be utilised to produce diastereomeric products. Dicarbamate **2.47** (Scheme 2.17) serves as an elegant example of the principle, methylated compound **2.49** being formed with good substrate-directed selectivity in the absence of (–)-sparteine.[97] In the presence of (–)-sparteine, lithiation is directed in the opposite fashion, the internal chelate effect being overridden by the more powerful chelating effect of the diamine.



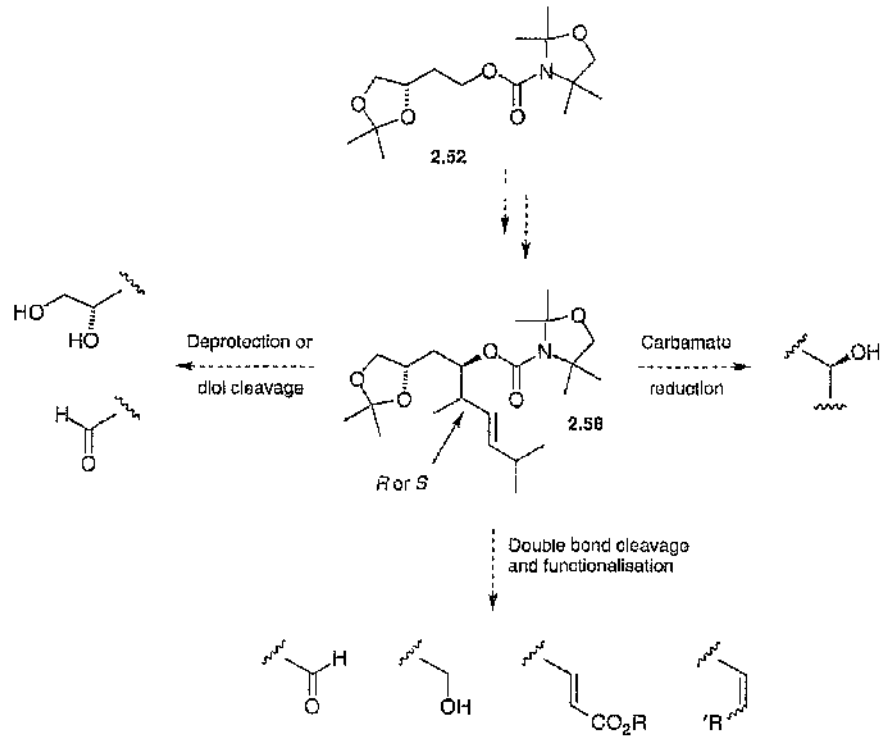
Scheme 2.17

In the case of acetonide **2.52** (Scheme 2.18), the inherent substrate-directed selectivity and the external selectivity derived from (–)-sparteine form a matched pair, both favouring abstraction of the *pro-S*-proton.[98] Lithiation and substitution in the absence of a chelating ligand returns **2.54** in excellent (> 95:5) diastereomeric excess, which, in the case of the specific example using Me_3SnCl as electrophile, is further increased to > 99:1 in the presence of (–)-sparteine. Use of the enantiomeric (+)-sparteine results in an inversion of selectivity to 28:72, a reflection of the now mismatched internal and external inductions. Carbamate **2.52** thus forms a synthetic equivalent for the (1*S*,3*S*)-1,3,4-trihydroxybutanide ion **2.57**. As is described in chapter 4, an equivalent for the related (1*S*,3*R*)-1,3,4-trihydroxybutanide ion has been utilised in the total synthesis of the natural product Cryptophycin 4.



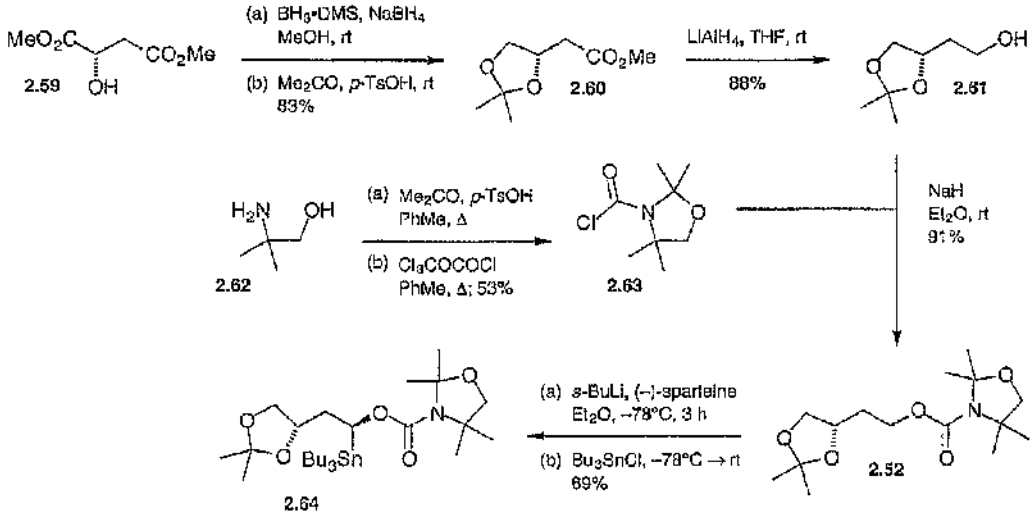
Scheme 2.18

We were interested in the union of masked triol synthon **2.57** and cationic complexes **2.1** or **2.2**, an attractive prospect as the resulting olefin product **2.58** would contain two newly formed vicinal stereocentres (Scheme 2.19). The stereochemistry at C1 is fixed as (*R*)- by the lithiation step, the outcome of transmetallation to copper and alkylation was unknown at the time. The C2 centre could be fixed as (*R*)- or (*S*)-, by the choice of planar chiral electrophile **2.1** or **2.2** respectively. Versatile olefin **2.58** offers many possibilities for further elaboration.



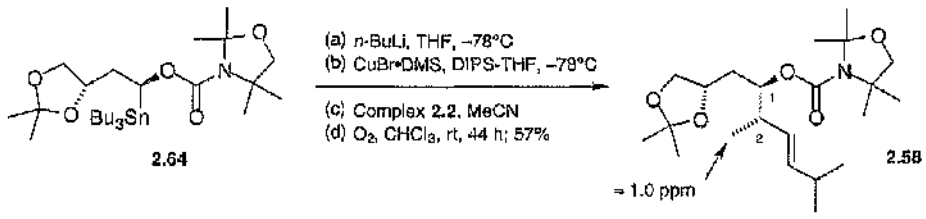
Scheme 2.19

Carbamate **2.52** was derived in four straightforward steps from dimethyl (*S*)-malate **2.59** (Scheme 2.20). Selective reduction[99] was followed by protection of the crude diol, reduction of ester **2.60** and coupling with chloride **2.63**.[94, 100, 101] Metallation of **2.52** in the presence of (–)-sparteine and stannylation yielded stannane **2.64** in good yield as a single diastereomer within the limits of ^{1}H and ^{13}C NMR spectroscopy .



Scheme 2.20

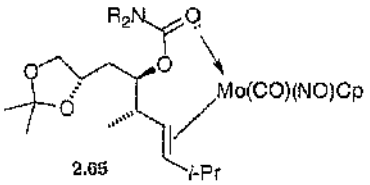
From stannane **2.64**, tin-lithium exchange using *n*-BuLi followed by transmetallation to copper using a slight excess of CuBr•DMS as a solution in di*iso*propylsulfide and THF generated the required alkylcopper(I) nucleophile. A freshly prepared solution of electrophilic complex **2.2** in MeCN was added directly. Following standard aqueous workup olefin product **2.58** was released by oxidative decomplexation of the metal fragment, and was obtained in good overall yield from stannane **2.64** (Scheme 2.21). ^{1}H NMR spectroscopy indicated the dominance of one diastereomeric product, backed up by GCMS data which revealed a mixture of 4 isomers in the approximate ratio 95 : 2 : 2 : 1. The absolute stereochemistry of the major olefin isomer is assigned as below and reflects two assumptions - firstly, that addition to complex **2.2** proceeded *anti* to the metal, ample precedent for which is now available. Secondly, the more contentious assumption of overall retention at C1 is made (see below). The regiochemistry resulting from alkylation of complex **2.2** is assigned as that resulting from nucleophilic attack predominantly at the less hindered allyl terminus of **2.2** on the basis of 2D NMR spectroscopy. The expected chemical shifts of a methyl group in an allylic or vinylic position (approximately 1.0-1.1 and 1.7 ppm respectively) also support the assigned regiochemistry.[102, 103]



Scheme 2.21

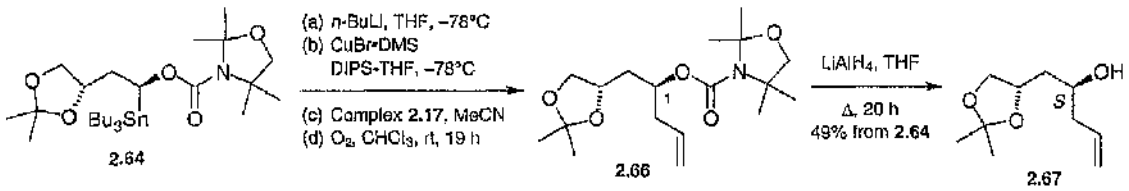
Two procedures have been used throughout our work with η^3-allylmolybdenum complexes to cleave the metal fragment from the olefin following nucleophilic attack. The first protocol is the treatment of an acetone solution of the crude material with ammonium cerium(IV) nitrate (CAN), adding CAN portionwise until decomplexation is complete.[55] Progress of the cleavage is easily followed by TLC, a characteristic, polar, UV active spot represents the (η^2-olefin)Mo(CO)(NO)Cp species, typically appearing as a faint-yellow spot in visible light. The less polar olefin spot was almost always faintly present following aqueous workup, indicating partial decomplexation of material before the oxidation step. An alternative procedure was developed from Faller's precedent for decomplexation by exposure of a chloroform solution of the crude material to air.[9] As described in Chapter 4, we experienced difficulties in the CAN-mediated decomplexation of a substrate containing an acetonide-protected diol moiety. We subsequently bubbled gaseous oxygen through a chloroform solution of the crude material. Reaction was generally completed overnight, and simplified the workup protocol by eliminating a second aqueous extraction stage. The procedure was subsequently adopted for most of the systems described in Chapter 2. In the case of the

crude material obtained from the above coupling reaction, the decomplexation using oxygen alone was slow, minimal progress being observed overnight. Discussion with a co-worker in the Kocienski group indicated that the rate of decomplexation could be enhanced by visible light. Indeed, decomplexation was complete within a further 24 h simply with illumination from a 150W household light bulb. The reluctance of the metal fragment to depart the olefin can be rationalised by coordination of the neighbouring Lewis-basic carbamate oxygen to the metal (Scheme 2.22), providing stabilisation of the (η^2-olefin)Mo(CO)(NO)Cp species **2.65**.



Scheme 2.22

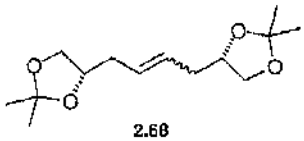
To establish the overall effect upon the C1 stereochemistry in the tin → lithium → copper → carbon sequence forming olefin **2.58**, we needed to relate the C1 stereochemistry to a known compound. Using allyl complex **2.17** allowed us to relate the olefin derived from stannane **2.64** to alcohol **2.67**. Alcohol **2.67** and the corresponding (1*R*)-epimer are known, **2.67** having been reported as an intermediate in the synthesis of the natural product Milbemycin.[104, 105] In similar fashion to the preparation of olefin **2.58**, stannane **2.64** was converted to the corresponding alkylcopper(I) reagent and coupled with complex **2.17**, to reveal olefin **2.66** after decomplexation as a 98:2 ratio of isomers by GCMS. Reductive cleavage of the carbamate group[106] proceeded uneventfully yielding alcohol **2.67** in 49% overall yield from stannane **2.64** (Scheme 2.23). The stereochemistry at C1 was confirmed as *S* by comparison of optical rotation and ^{1}H / ^{13}C NMR spectroscopic data for **2.67** with literature values.



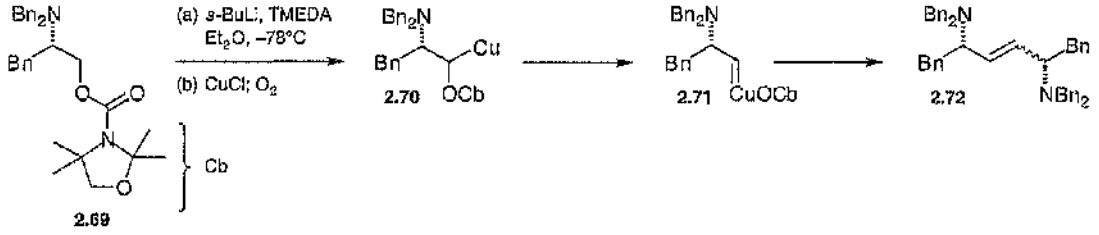
Scheme 2.23

Carbamate **2.66** was contaminated with an inseparable byproduct, tentatively assigned as **2.68** on the basis of ^{1}H and ^{13}C NMR spectroscopic data. Hoppe has described the formation of olefins (*E*)- and (*Z*)-**2.72** by deprotonation of carbamate **2.69**, transmetallation to copper and introduction of oxygen (Scheme 2.24).[106] Copper carbene **2.71** was proposed as an

intermediate.[107, 108] In our system, adventitious oxygen could explain the observance of **2.68**, formed by a similar process from carbamate **2.64**.



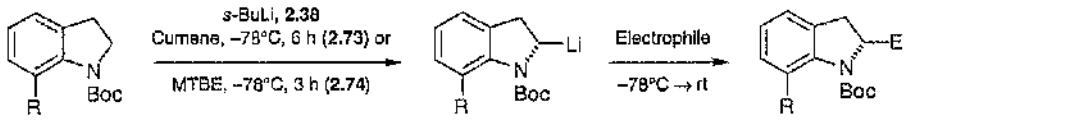
2.68



Scheme 2.24

With the synthesis of alcohol **2.67** having confirmed overall retention at C1, by analogy we have assumed overall retention in the preparation of olefin **2.58**. It can therefore be concluded that stannane **2.64** serves as a reliable precursor to the (1*S*,3*S*)-1,3,4-trihydroxybutanide ion **2.57** in coupling with η^3-allylmolybdenum complexes **2.2** and **2.17**. In principle the technique of deprotonation α- to a carbamate group and alkylation with complexes **2.2** or **2.17** could be applied to a multitude of other substrates such as those illustrated above in Scheme 2.15. The generality of the retentive lithium-copper transmetallation would have to be verified for specific substrates, but the meagre precedent provided by carbamate **2.64** is encouraging.

Continuing the theme of (–)-sparteine assisted enantioselective deprotonations, we became interested in work reported by Beak which allows access to chiral indoline structures. Beak described the asymmetric deprotonation of *N*-Boc indoline (**2.73**) and *N*-Boc 7-chloroindoline (**2.74**) with *s*-BuLi and (–)-sparteine, and the subsequent reaction of enantioenriched organolithium **2.75** or **2.76** with a range of electrophiles (Scheme 2.25).[109]



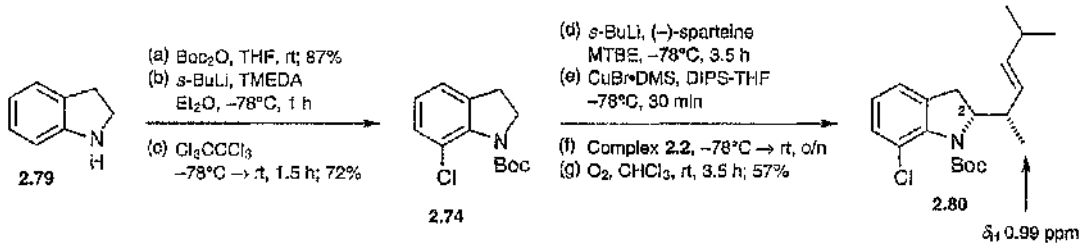
2.73, R = H
2.74, R = Cl

2.75, R = H
2.76, R = Cl

2.77, R = H, 11-70%, %ee = 36->98%
2.78, R = Cl, 32-90%, %ee = 0, 73-78%

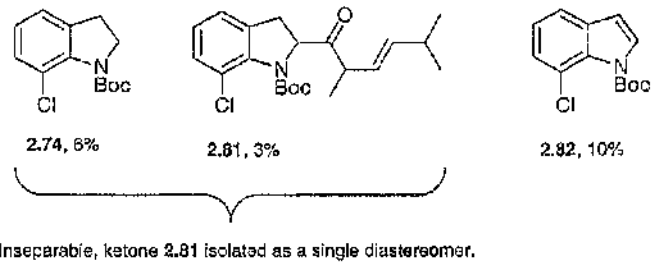
Scheme 2.25

Substituted indoline **2.74** was easily prepared in two steps by standard procedures.[110] Following *N*-protection, the C7 position was selectivity lithiated under conditions described by Iwao (*s*-BuLi / TMEDA) and blocked by chlorination. It should be noted that a complication with the use of indoline **2.73** is competing lithiation at C7, minimised but not eliminated by the use of cumene as a solvent[109] and for this reason we chose to use the chlorinated substrate. Asymmetric lithiation under Beak conditions was followed by transmetallation to copper using CuBr•DMS in the fashion described above and coupling with cationic complex **2.2** (Scheme 2.26). Oxidative decomplexation (O_2, $CHCl_3$ or CAN, Me_2CO) yielded a mixture of olefins **2.80** in 57% overall yield.



Scheme 2.26

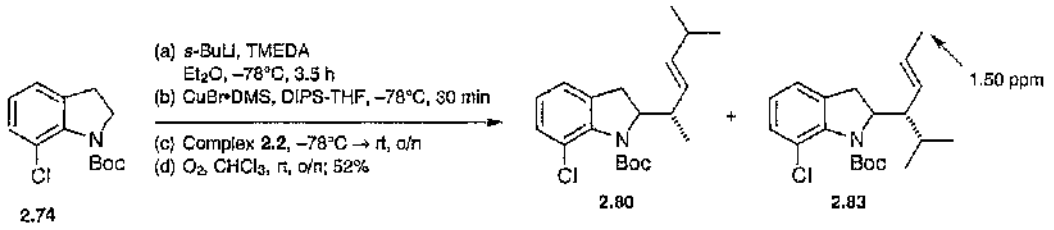
Analysis of the mixture by GCMS revealed the presence of 4 isomers, in the approximate ratio 4 : 9 : 81 : 6. The major product will have the absolute stereochemistry depicted above if the key assumption of overall retention of configuration at C2 from alkyllithium **2.76** to indoline **2.80** is made, as discussed below. Regioselectivity was good, the major diastereomer being assigned as **2.80** above on the basis of 2D NMR spectroscopy and on the shift of the allylic methyl group. The absolute stereochemistry of the methyl group is based on an assumption of *anti* attack upon complex **2.2**. In addition to the expected olefin products, an inseparable mixture of ketone product **2.81** and recovered starting material was isolated, as was indole **2.82**[109] (presumably arising by oxidation of unreacted indoline **2.74** under the decomplexation conditions) (Scheme 2.27).



Scheme 2.27

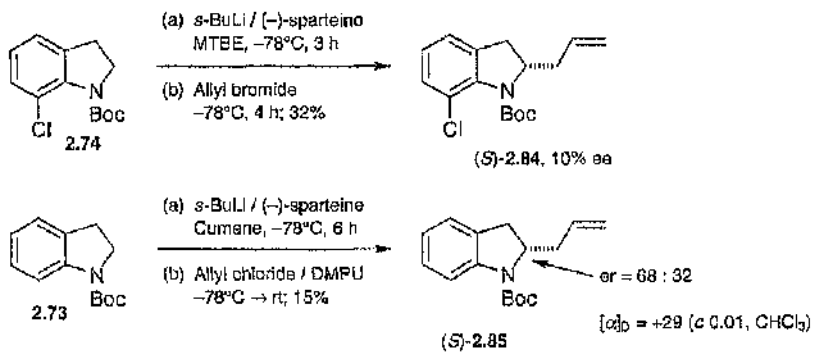
Repeating the coupling reaction using a combination of *s*-BuLi and TMEDA for the initial deprotonation step resulted in a 52% yield of a mixture of the same 4 olefin isomers by

GCMS in the approximate ratios 20 : 4 : 29 : 27. Again a trace of ketone **2.81** (<2%, apparently a single diastereomer) was observed, together with indole **2.82** (15%) and **2.74** (4%). The formation of the same 4 diastereomeric compounds under the non-asymmetric lithiation conditions indicate that one of the 3 minor diastereomers obtained in the original coupling reaction is due to moderate stereocontrol at C2. The remaining two diastereomers are tentatively assigned as regioisomeric olefins **2.83** on the basis of the observation of an allylic methyl signal resonating at approximately 1.5 ppm (Scheme 2.28). Although the overall diastereoselectivity in the original coupling is excellent (81 : 19) it is vexing to note that in the coupling of the corresponding racemic alkylcopper(I) nucleophile, regioselectivity was poor.



Scheme 2.28

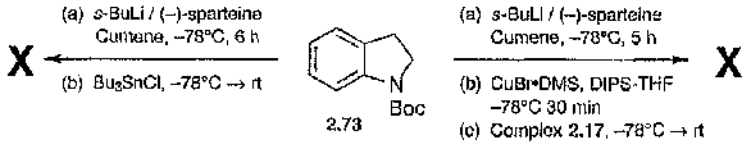
As with the previous example there was a need to determine the absolute stereochemistry at C2, using allyl complex **2.17** as a model electrophile. Beak had formed indoline **2.84** (Scheme 2.29) in poor yield and only 10% ee under the *s*-BuLi / (–)-sparteine conditions and regrettably, no optical rotation data was reported. Allylation of the corresponding unsubstituted substrate **2.73** gave a sample of (*S*)-**2.85** in 15% yield with a slight excess of the (*S*)-enantiomer (er = 68 : 32). Fortunately, the optical rotation of the sample enriched in the (*S*)-enantiomer was recorded, giving us a basis for comparison.



Scheme 2.29

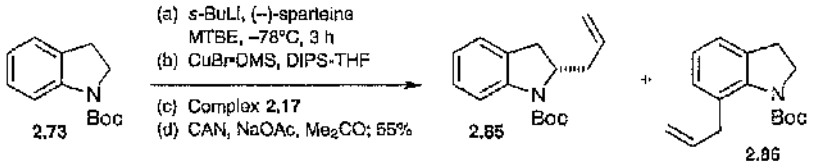
Our initial efforts were hampered by the inefficient deprotonation of indoline **2.73** compared to the chlorinated analogue. Optimised conditions reported by Beak utilised cumene as

solvent and a 6 h reaction time at –78°C. Lithiation / substitution sequences in alternative solvents such as TBME gave poorer yields and / or a greater proportion of products resulting from lithiation and substitution at C7. Unfortunately, in our hands, lithiation, transmetallation to copper and coupling with allyl complex **2.17** failed completely in cumene, returning only starting material **2.73** (Scheme 2.30). Similarly, lithiation in cumene and trapping with tributyltin chloride was inefficient on a large (25 mmol) scale, only the merest trace of stannylation apparent by TLC, despite scaling the concentration appropriately from the Beak protocol.



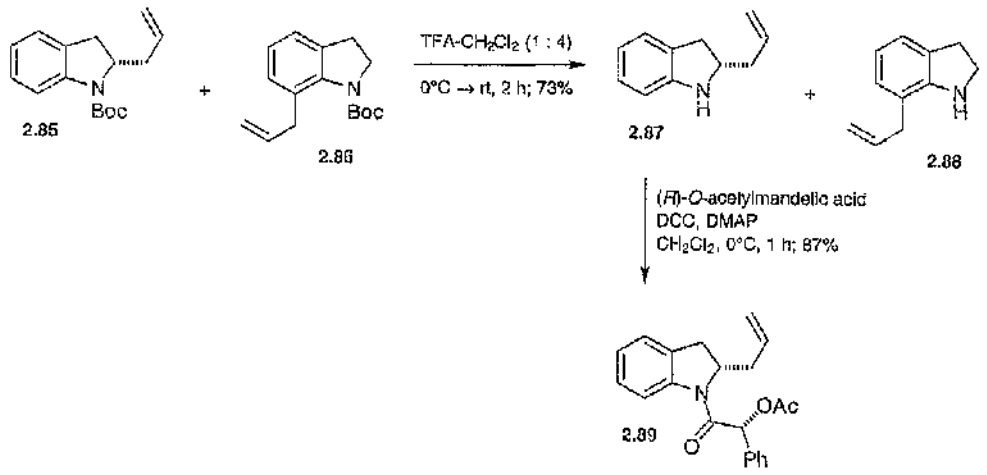
Scheme 2.30

We decided to turn to TBME as solvent despite the anticipated poor chemoselectivity. Lithiation with *s*-BuLi / (–)-sparteine, transmetallation to copper, and reaction with **2.17** yielded an inseparable equimolar mixture of 2- and 7-substituted indolines **2.85 / 2.86** (55%) together with 9% of recovered indoline **2.73** (Scheme 2.31). Comparison of the sign of optical rotation of the mixture **2.85 / 2.86** [+44.2, (*c* 0.55, $CHCl_3$)] to that reported by Beak [+29 (*c* 0.01, $CHCl_3$), 36% ee] indicated that the lithiation, transmetallation and allylation sequence returned material with predominantly the (2*S*)-configuration we had assumed in the original coupling procedure with complex **2.2**.



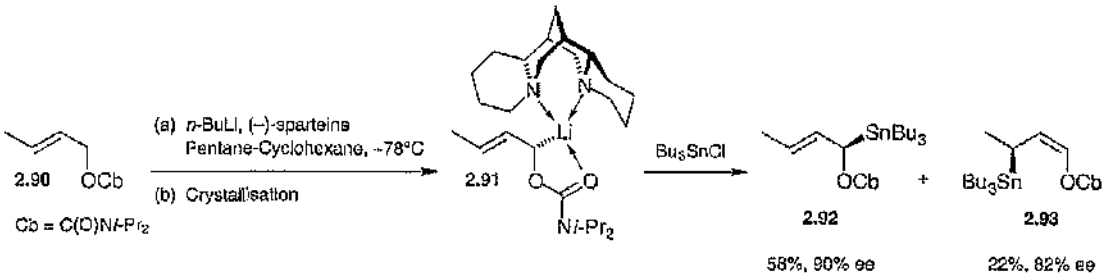
Scheme 2.31

N-Deprotection allowed the separation of the regioisomeric amines **2.87** and **2.88**, and 2-substituted isomer **2.87** was converted into the corresponding amide **2.89** under DCC conditions in good yield (Scheme 2.32). Only a single diastereomer was apparent by ^1H / ^{13}C NMR spectroscopy and GCMS, indicating excellent stereocontrol in the retentive transmetallation-substitution sequence. It is worth noting that the union of allyl complex **2.17** with indoline **2.73** represents an improvement in efficiency over the Beak conditions for allylation of indolines **2.73 / 2.74**.



Scheme 2.32

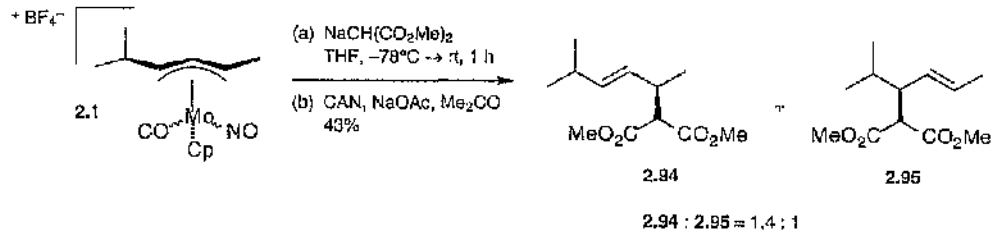
Further application of (–)-sparteine mediated enantioselective deprotonation to a nucleophile derived from crotyl carbamate **2.90**[111] failed (Scheme 2.33). Hoppe has shown that deprotonation of carbamate **2.90** under carefully controlled conditions allowed the selective crystallisation of alkyllithium•(–)-sparteine complex **2.91**, which could then be trapped with an electrophile (e.g. Bu_3SnCl) to yield stannane isomers **2.92** and **2.93** in good yield. Unfortunately, we found that deprotonation under the Hoppe conditions, followed by transmetallation to copper and reaction with allyl complex **2.17** resulted in a complex mixture of products from which nothing of value could be obtained.



Scheme 2.33

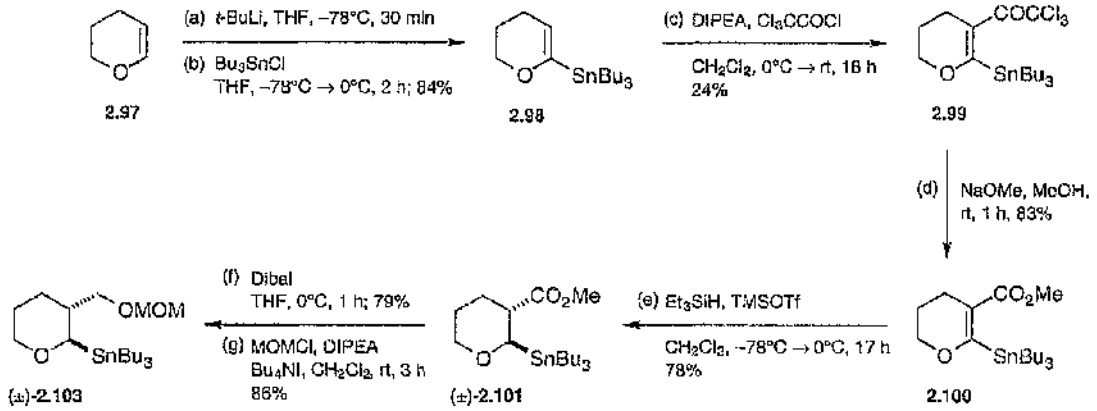
2.3.2 - Further nucleophiles.

We have confirmed the poor regioselectivity described by Faller in the coupling of sodiodimethylmalonate with complex **2.1**. In our hands isomers **2.94** and **2.95** were formed in 43% yield in a 1.4 : 1 ratio (Scheme 2.34), a slight selectivity for attack at the less hindered allyl terminus, but nevertheless greatly reduced regioselectivity compared to other nucleophile systems.



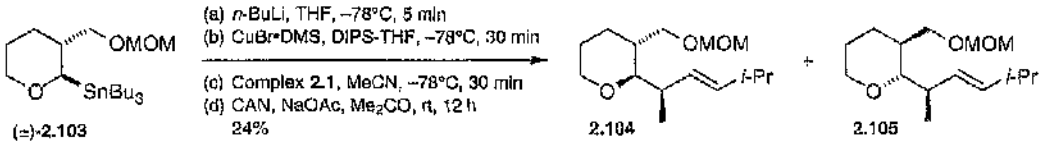
Scheme 2.34

A number of other simple nucleophiles were investigated, and the general trend of good regioselectivity continued. Stannane (±)-**2.103** was synthesised in straightforward fashion by the route below, based on a series of communications by Quayle (Scheme 3.35).[112-115] Deprotonation[116] of 3,4-dihydro-2*H*-pyran (**2.97**) and stannylation yielded **2.98**. Acylation at C3 under the reported conditions[113] proceeded inefficiently to yield stannane **2.99** which was subsequently converted into ester **2.100**. Double-bond reduction yielded pyran **2.101**, from which stannane **2.103** was obtained in a further 2 steps.



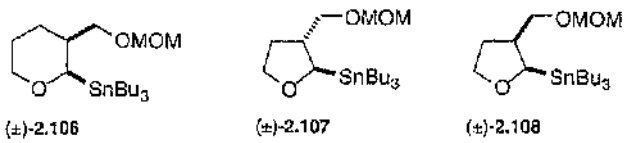
Scheme 2.35

In the normal fashion, stannane **2.103** was converted into the corresponding alkylcopper(I) reagent and coupled with complex **2.1** to yield olefin products **2.104** / **2.105** (Scheme 2.36), in low (though unoptimised) yield, both of which were regioisomerically pure within the limits of NMR spectroscopy. The maintenance of *trans*- relative stereochemistry between C2 and C3 (and hence by analogy retention of configuration at C2 from stannane (±)-**2.103**) in both olefins is confirmed by the large coupling between H2 and H3 (^3J 9-9.6 Hz).



Scheme 2.36

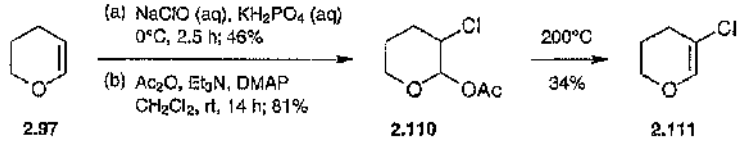
In principle the Quayle route could have been adapted to prepare similar substrates **2.106-2.108** (Scheme 2.37). Conversion of *trans* substrates (±)-**2.103** and (±)-**2.107** to the corresponding *cis*-isomers is possible by deprotonation α- to the tributylstannyl moiety at low temperature, followed by a protic quench.[117, 118]



(±)-2.106 (±)-2.107 (±)-2.108

Scheme 2.37

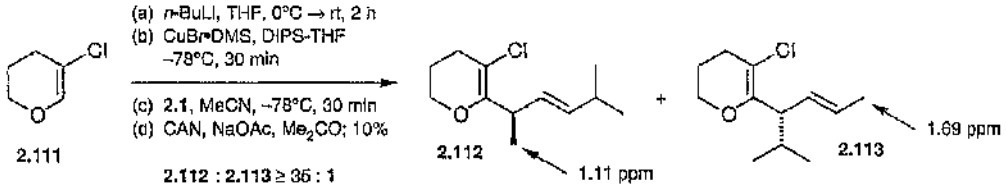
Chlorinated dihydropyran **2.111** was straightforwardly obtained (Scheme 2.38) from dihydropyran **2.97** by chlorohydration,[119] acetylation and pyrolysis.[120]



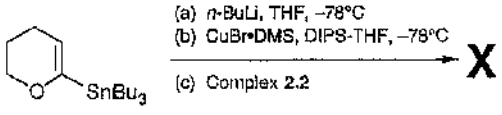
2.97 2.110 2.111

Scheme 2.38

Deprotonation of chloride **2.111**, transmetallation to copper in the normal fashion and reaction with complex **2.1** yielded olefin **2.112** in only 10% yield (Scheme 2.39). Despite the poor yield, olefin **2.112** was isolated in excellent regioselectivity (≥ 35 : 1). Only a trace of the regioisomeric olefin (**2.113**) was observed in the ^{1}H NMR spectrum, with doublets at 1.11 and 1.69 ppm being used to assign olefins **2.112** and **2.113** respectively. Stannane **2.98** was investigated as a similar system to that derived from chloride **2.111**. Disappointingly, tin-lithium exchange, transmetallation to copper, and reaction with cationic complex **2.2** failed to yield any olefin product.



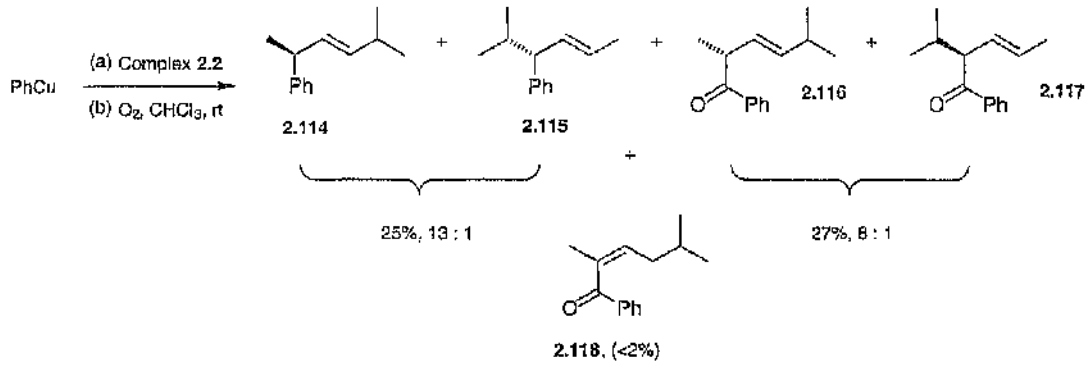
2.111 2.112 2.113



2.98

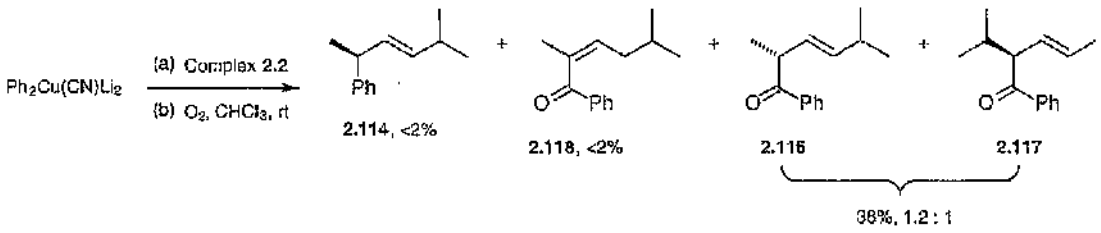
Scheme 2.39

As will be described in Chapter 4, we have successfully coupled PhCu with substituted η^3-allylmolybdenum complex **4.1** and a minor ketone byproduct apparently arising from attack upon the carbonyl ligand of **4.1** was observed. PhCu was coupled with complex **2.2** in order to see if a similar product would be obtained. The expected olefin regioisomers **2.114** and **2.115** were obtained with excellent (13 : 1) regioselectivity in 25% isolated yield (Scheme 2.40). The regioisomers were identified by reference to literature data.[121, 122] Ketone regioisomers **2.116** and **2.117** were also isolated in 27% yield, in an 8 : 1 ratio, together with isomeric ketone **2.118** (< 2%). The stereochemistry suggested for **2.116** and **2.117** is that which would be obtained if the phenyl nucleophile initially attacked the carbonyl ligand and then transferred directly to the face of the allyl ligand *syn* to the metal.



Scheme 2.40

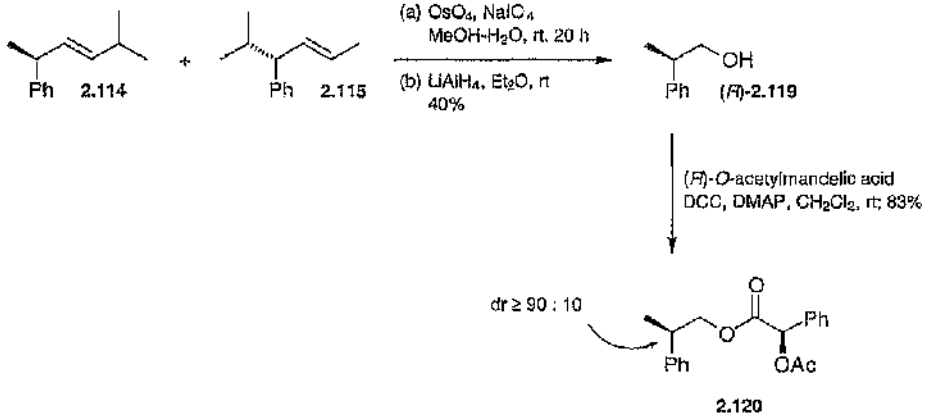
As an alternative nucleophile to PhCu, higher order cyanocuprate $Ph_2Cu(CN)Li_2$ was investigated, which has been successfully used by Liebeskind in couplings with cationic π-allyl molybdenum complexes.[54] However, only a trace (<2%) of alkylation products **2.114 / 2.115** were obtained (Scheme 2.41), together with ketones **2.116 / 2.117** in 38% yield and almost equimolar ratio, and 2% of isomeric ketone **2.118.**



Scheme 2.41

The absolute stereochemistry and enantiopurity of olefin **2.114** was established by dihydroxylation and *in-situ* diol cleavage, followed by reduction of the resulting aldehyde (Scheme 2.42). Comparison of the sign of optical rotation for alcohol **2.119** with literature values allowed the absolute stereochemistry to be identified as *R*, as expected *via* a process of

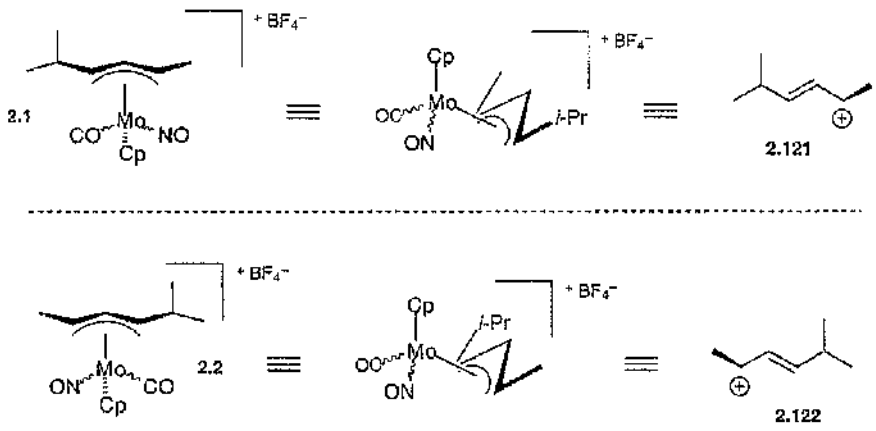
retention-inversion from acetate (*R*)-**2.12**. The enantiomeric ratio at C1 was conservatively estimated to be ≥ 90 : 10 *via* formation of the (*R*)-*O*-acetylmandelate ester **2.120** and comparison of the integration of the acetate methyl signals at 2.14 ppm and 2.15 ppm (minor and major diastereomers respectively) with reference to an authentic sample of esters formed from (±)-**2.119**.



Scheme 2.42

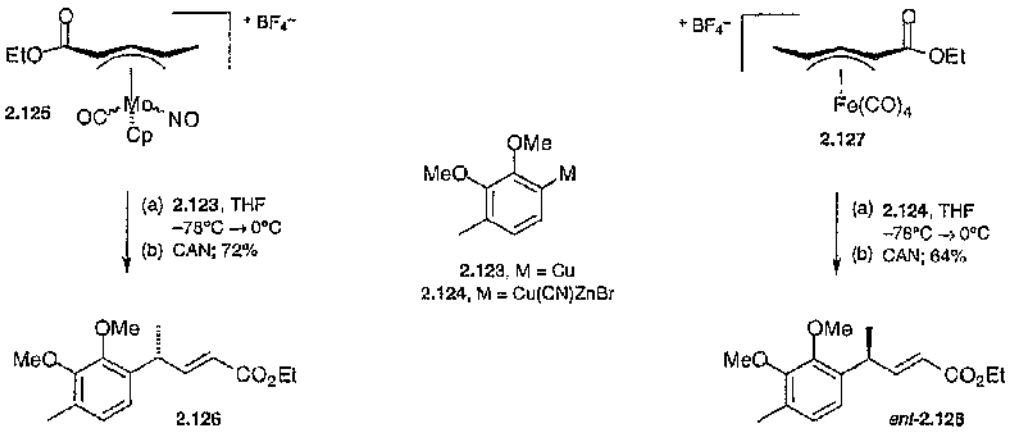
2.4 - Conclusions.

We have demonstrated that the good regioselectivity observed by Procter[61] in the coupling of alkylcopper(I) nucleophiles with substituted complexes **2.1** and **2.2** is general for a wide range of functionalised substrates. Regioselectivities have typically been ≥ 8 : 1. The regioselectivity reflects a triumph of steric discrimination over the failure to control central chirality inherent in the indiscriminate carbonyl-nitrosyl exchange process. Complexes **2.1** and **2.2** have been shown to be reliable synthetic equivalents for cationic synthons **2.121** and **2.122** (Scheme 2.43).



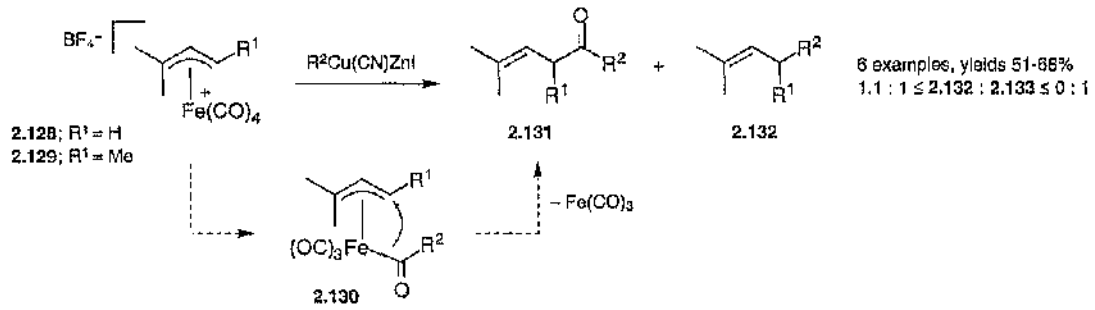
Scheme 2.43

The range of substrates we have studied indicates that sp^3-hybridised nucleophiles perform well, whereas sp^2-based systems such as **2.98**, **2.111** and phenyl are problematic. The variability of success encountered with these substrates and the presence of products arising from attack at the carbonyl ligand of complex **2.1 / 2.2** are interesting factors to note. With such systems it is likely that the compatibility of the nucleophile and electrophile will be finely balanced, with harmony of the coupling partners dependant upon the precise nature of the allylic ligand and nucleophile. For example, arylcopper(I) reagent **2.123** has been used within the Kocienski group to alkylate functionalised molybdenum complex **2.125**[123] (Scheme 2.44), without complication from carbonylated products. Similarly, the zinc-copper based nucleophile **2.124** gave *ent*-**2.126** in good yield using Enders' iron complex **2.127**[124] as the electrophile.



Scheme 2.44

In contrast to the Enders complex, a variety of zinc-copper based reagents reacted with the similar η^3-allyltetracarbonyl complexes **2.128** and **2.129** to give carbonylated products **2.131** as well as olefins **2.132**, in varying ratios (Scheme 2.45).[125] The proposed mechanism was one of initial addition to a carbon-monoxide ligand to form metal-acyl intermediate **2.130.** Ketone **2.131** was subsequently formed *via* migration of the acyl to the less-substituted allylic terminus and loss of $Fe(CO)_3$.



Scheme 2.45

In our molybdenum chemistry, yields over the two step alkylation-decomplexation sequences remain moderate to poor, though the cases described in this chapter have not been individually optimised. The Achilles heel of the process is the oxidative cleavage procedure,[5] with a need in the future for an exploration of alternative methods. In general, we have found that the alkylation procedures are more efficient on a moderate (3-7 mmol) rather than small (<1 mmol) scale. We also observed better yields using the higher quality neutral complexes formed using the $Mo(CO)_4(py)_2$ based preparation procedure.

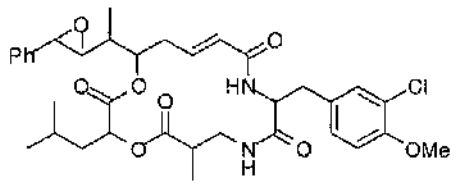
Having established the utility of complexes **2.1** and **2.2** where steric bias in the allylic ligand allows good regiocontrol, we moved to a system of more complexity. Chapter 3 introduces the Cryptophycin series of natural products which provided our next challenge. Chapter 4 describes our approach to Cryptophycin 4, and describes our investigation of an η^3-allylmolybdenum complex with substituents on the allylic ligand which could have both a steric and electronic impact upon regioselectivity.

Chapter 3 - The Cryptophycin series of natural products.

Chapter 3 will describe the isolation and biological activity of the Cryptophycin family of natural products, potent antiproliferative compounds which show excellent antitumour activity. Previous total syntheses of the Cryptophycins and analogues will be discussed briefly, focusing on the control of absolute stereochemistry in a key fragment. The literature up to and including May 2000 has been covered.

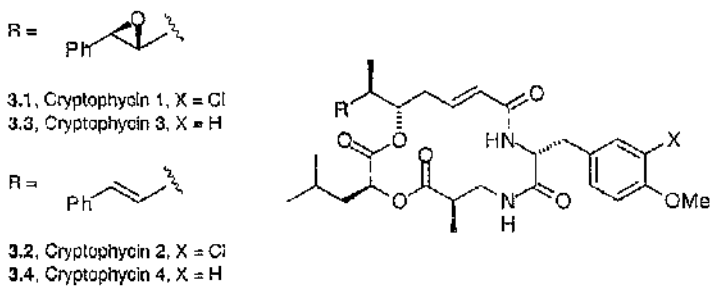
3.1 – Isolation of the Cryptophycins.

In 1990, as part of an algae screening program, Schwartz and co-workers reported the isolation of a novel depsipeptide from *Nostoc* sp. ATCC 53789 which was active against fungi and yeast of the genus *Cryptococcus*.[126] The general structure **3.1** was proposed and named Cryptophycin. Studies into the use of Cryptophycin as an antifungal agent were discontinued due to toxicological concerns.



3.1

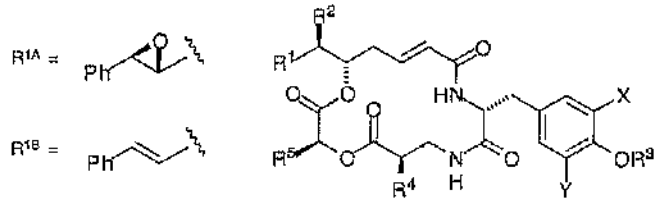
Interest in the area was revitalised in 1994, when Moore reported that the lipophilic extract of the blue-green alga (cyanobacterium) *Nostoc* sp. GSV 224 was strongly cytotoxic.[127] The major cytotoxin, Cryptophycin 1 (**3.1**) (initially named Cryptophycin A) was isolated, together with 3 minor constituents, Cryptophycins 2-4 (or B, C, D, **3.2**-**3.4**) (Scheme 3.1). Mass spectral data and NMR spectroscopic analysis, combined with degradation experiments elucidated the relative and absolute stereochemistry of Cryptophycins 1-4. The tyrosine portion in Cryptophycins 1 and 3 was initially assigned as L and corrected to D in a later publication following total synthesis.[127, 128]



Scheme 3.1.

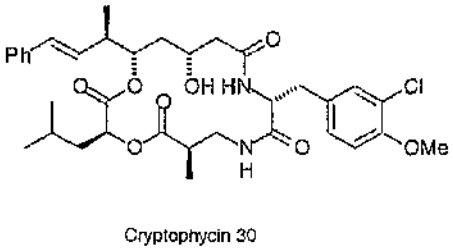
To date, a total of 25 naturally occurring members of the Cryptophycin series have been isolated from *Nostoc* sp. GSV 224, as shown below (Table 1, Scheme 3.2).[127, 129-131]

Table 1 - Naturally occurring Cryptophycins.

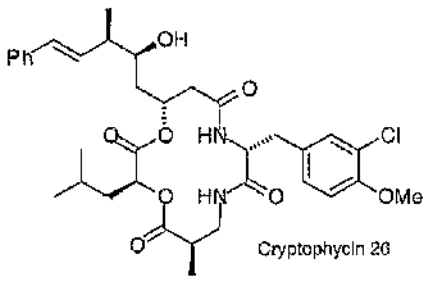


Cryptophycin	R^1	R^2	R^3	R^4	R^5	X	Y
1	R^{1A}	Me	Me	Me	*i*-Bu	Cl	H
2	R^{1A}	Me	Me	Me	*i*-Bu	H	H
3	R^{1B}	Me	Me	Me	*i*-Bu	Cl	H
4	R^{1B}	Me	Me	Me	*i*-Bu	H	H
16	R^{1A}	Me	H	Me	*i*-Bu	Cl	H
17	R^{1B}	Me	H	Me	*i*-Bu	Cl	H
18	R^{1B}	Me	Me	Me	(*S*)-CH(Me)Et	Cl	H
19	R^{1B}	Me	Me	Me	$CHMe_2$	Cl	H
21	R^{1A}	Me	Me	H	*i*-Bu	Cl	H
23	R^{1A}	Me	H	Me	*i*-Bu	Cl	Cl
24[a]	R^{1A}	Me	Me	H	*i*-Bu	H	H
28	R^{1B}	H	Me	Me	*i*-Bu	Cl	H
29	R^{1B}	Me	Me	H	*i*-Bu	Cl	H
31	R^{1A}	Me	Me	Me	*i*-Bu	Cl	Cl
40	R^{1A}	H	Me	Me	*i*-Bu	Cl	H
43	R^{1B}	Me	H	Me	*i*-Bu	H	H
45	R^{1B}	Me	H	Me	*i*-Bu	Cl	Cl
46[b]	R^{1B}	Me	Me	Me	*i*-Bu	Cl	H
49	R^{1B}	Me	Me	Me	*n*-Pr	Cl	H
50	R^{1A}	Me	Me	Me	*n*-Pr	Cl	H
54	R^{1A}	Me	Me	Me	(*S*)-CH(Me)Et	Cl	H
175	R^{1B}	Me	Me	Me	*i*-Bu	Cl	Cl
176	R^{1A}	Me	Me	H	*i*-Bu	Cl	H

[a] Cryptophycin 24 ≡ Arenastatin A. [b] *L*-Tyr not *D*-Tyr



Cryptophycin 30



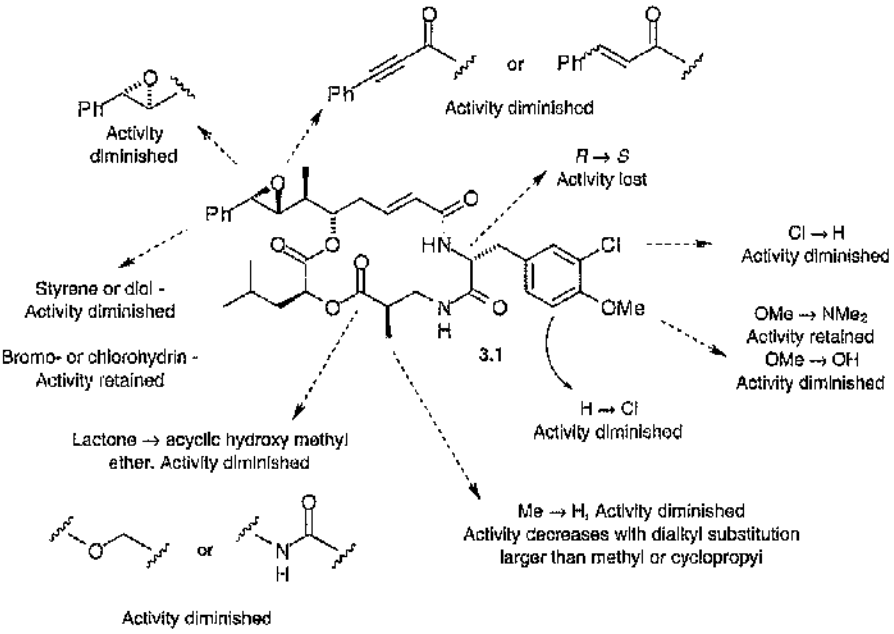
Cryptophycin 26

Scheme 3.2.

Cryptophycin 24 has an identical structure to Arenastatin A, which was isolated from the marine sponge *Dysidea arenaria*, and independently reported by Kitagawa and co-workers in 1994.[132]

3.2 – Biological activity of the Cryptophycins.

Early investigations by Moore and co-workers revealed cytotoxicity IC_{50} values as low as 0.01 nM for the most active member of the Cryptophycin family, Cryptophycin 1. Three human tumour cell lines were investigated: KB (nasopharyngeal carcinoma), LoVo (colorectal adenocarcinoma) and SKOV3 (ovarian carcinoma).[129, 130] *In vivo* cytotoxicity data obtained from other members of the Cryptophycin family, and from synthetic analogues revealed the structure-activity relationships depicted below (Scheme 3.3).[127, 129-131, 133-137]



Scheme 3.3.

The Cryptophycins exhibit antitumour activity by the inhibition of tubulin polymerisation into microtubules.[138] Microtubules are dynamic assemblies within cells and are involved in a range of cellular activities including the maintenance of cell structure, cell motility, cell proliferation and the regulation of membrane transport processes. The Cryptophycins bind to tubulin, inhibit microtubule polymerisation, and depolymerise preformed microtubules *in vitro*.[139] The mode of action of the Cryptophycins bears similarities to other clinically used antimicrotubule agents (Vinblastine, Colchicine and Paclitaxel) although the mode of action is most closely related to Vinblastine.[138, 139] In addition, the Cryptophycins are poor substrates

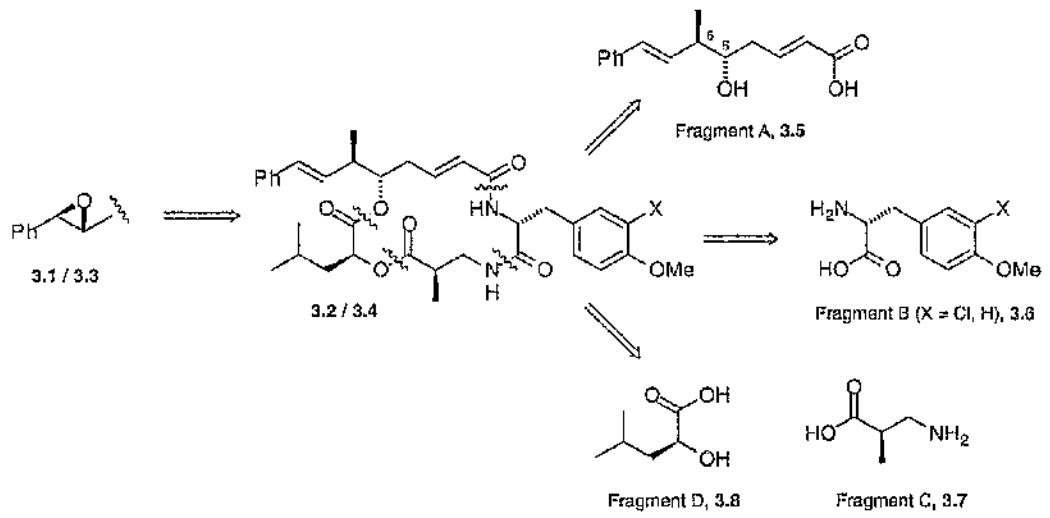
for the drug-efflux pump P-glycoprotein, a property which may prove useful in the chemotherapy of drug-resistant tumours.[138]

3.3 – Synthetic approaches towards the Cryptophycins.

3.3.1 – Retrosynthesis

Since the isolation of the first members of the Cryptophycin family and reports of the impressive biological activity a great deal of synthetic interest has developed. Several total syntheses of Cryptophycins and analogues have been reported to date.[128, 133-137, 140-147]

The Cryptophycin skeleton can be viewed in a retrosynthetic fashion as being built up from four fragments, A – D (Scheme 3.4). Fragments B and D (**3.6 / 3.8**) are easily accessed from commercially available D-tyrosine and L-leucic acid respectively. β-Amino acid fragment C (**3.7**) presents few synthetic problems, being readily available from the chiral pool in a minimum number of steps, leaving fragment A (**3.5**) as the major synthetic challenge.

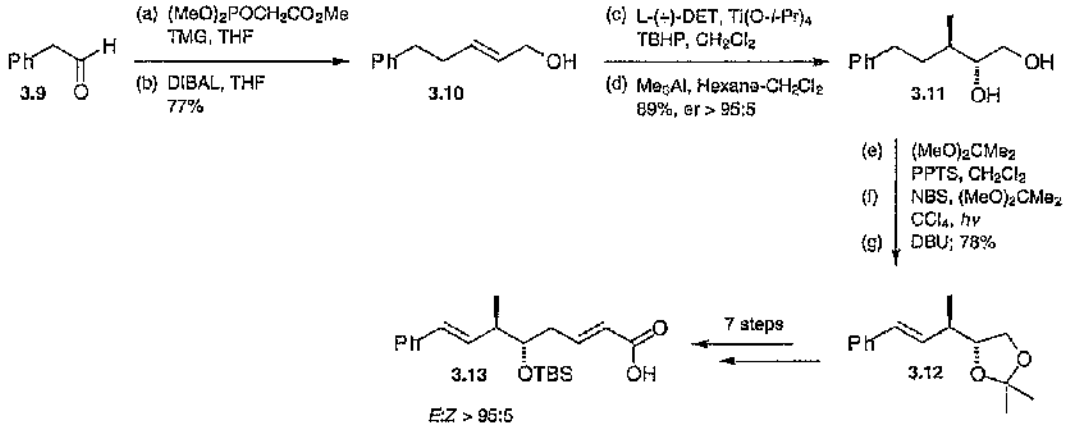


Scheme 3.4.

The following sections deal briefly with the many published synthetic approaches to fragment A of the Cryptophycin family, focusing on the key steps involved in securing the C5 and C6 *anti* stereochemistry.

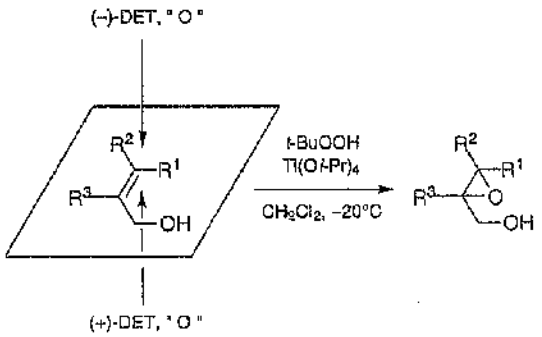
3.3.2 – The Moore-Tius strategies.[128, 148]

The first total synthesis of Cryptophycins 1 and 3 was reported in 1995 by Moore, Tius and co-workers.[128] The route to acid **3.13** is lengthy, though efficient (Scheme 3.5). The C5 and C6 stereocentres are introduced *via* Sharpless asymmetric epoxidation,[71] followed by epoxide opening with trimethylaluminium. Protection, benzylic bromination and immediate dehydrobromination introduce the styryl double bond into **3.12**, from where standard manipulation affords **3.13**.



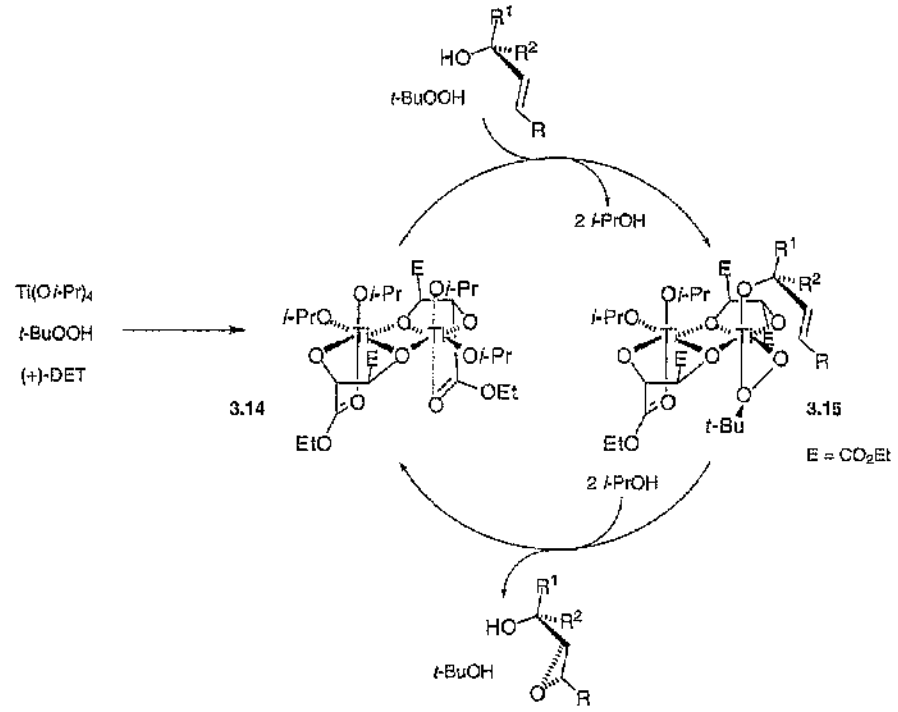
Scheme 3.5.

The efficient and reliable Sharpless asymmetric epoxidation procedure plays a crucial role in several of the routes to Cryptophycin fragment A described in this chapter. The mnemonic below (Scheme 3.6) serves as a reminder of the general stereofacial selectivity obtained from the epoxidation.[149]



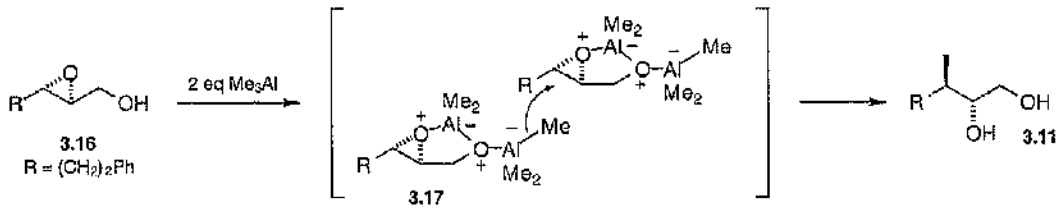
Scheme 3.6.

The catalytic cycle below (Scheme 3.7) has been proposed to account for the observed enantioselectivity, with dimer **3.15** postulated as the structure of the 'loaded' catalyst at the time of oxygen transfer.[150]



Scheme 3.7.

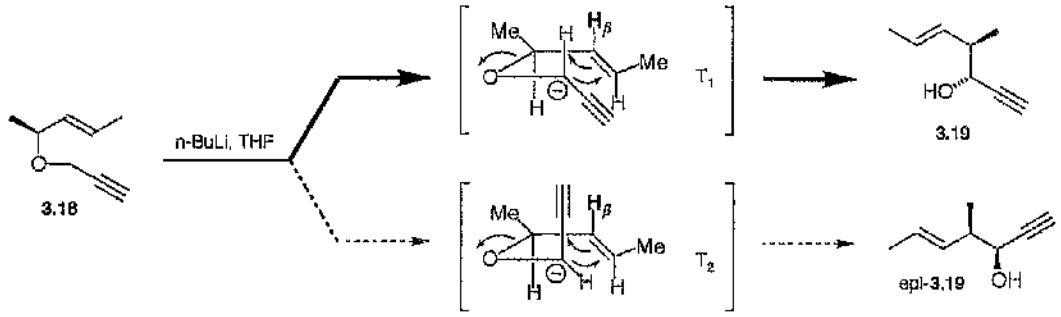
Opening of epoxide **3.16** proceeds with inversion of configuration and places the methyl substituent remote to the primary hydroxyl group.[151] The mechanism below was proposed, with clean inversion of stereochemistry resulting from S_N2-type reaction of the tight ion pair **3.17** (Scheme 3.8). Two equivalents of Me_3Al are required; the first generates an aluminium alkoxide from the free hydroxyl group, and the second coordinates between the epoxy-oxygen and the hydroxyl oxygen. The epoxide is subsequently cleaved by a liberated methyl anion, yielding diol **3.11**.



Scheme 3.8.

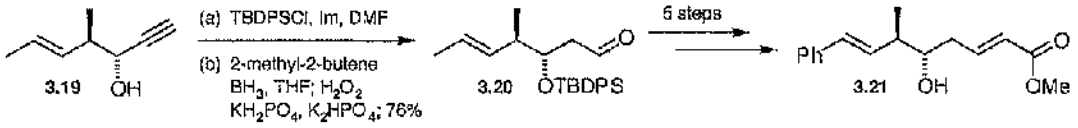
A later report by Moore and Tius revealed the formation of fragment A utilising a [2,3]-Wittig rearrangement of propargyl ether **3.18** as the key stereodetermining step (Scheme 3.9).[148] As described by Nakai and Mikami in their studies of the [2,3]-Wittig rearrangement, the reaction occurs with efficient transfer of chirality.[152] The stereoselectivity can be predicted by a consideration of the 5-membered transition states T_1 and T_2 below. A

pseudo-1,3-diaxial interaction between the olefinic proton H_β and the alkyne in transition state T_2 favours T_1 and results in the dominance of *threo* alcohol product **3.19**.



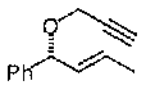
Scheme 3.9.

After silyl protection, selective monohydroboration of the terminal alkyne with disiamylborane (prepared *in situ* from 2-methyl-2-butene) yielded aldehyde **3.20**, which was further elaborated into ester **3.21** (Scheme 3.10).



Scheme 3.10.

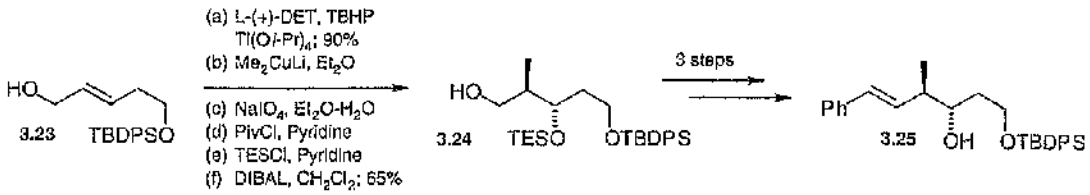
Initial attempts to rearrange ether **3.22** were unsuccessful due to competing rearrangement pathways, necessitating the introduction of the phenyl group into the molecule at a later stage.



3.22

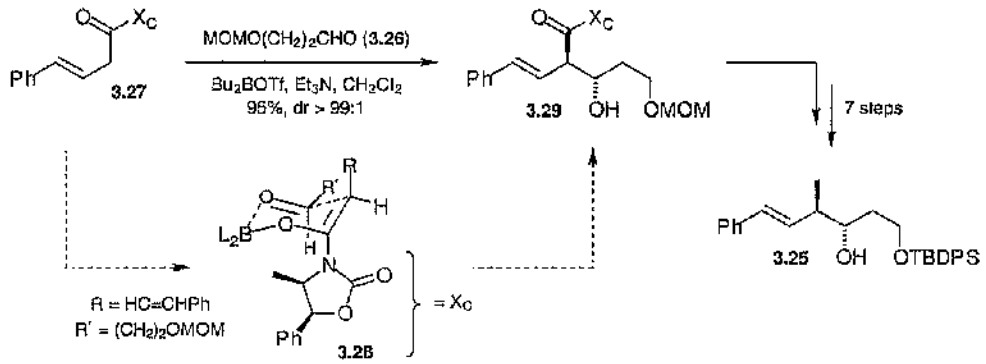
3.3.3 - Kobayashi-Kitagawa routes.[141, 153]

Two synthetic routes reported by Kobayashi and Kitagawa yield protected 1,3-diol **3.25** (Scheme 3.11) as the fragment A equivalent, relying on a later Wittig-Horner olefination of the corresponding aldehyde to elaborate the target molecule. In the first approach the required *trans* stereochemistry is introduced *via* Sharpless asymmetric epoxidation of allylic alcohol **3.23** and subsequent epoxide opening with Me_2CuLi. The outcome of the epoxide opening step is not discussed, but judging from the overall efficiency of the conversion of **3.23** to protected triol **3.24**, selectivity for formation of the 1,3-diol must be good. Chelation of the nucleophile to the free hydroxyl group has been proposed in similar systems to account for 1,3-selectivity.[154]



Scheme 3.11.

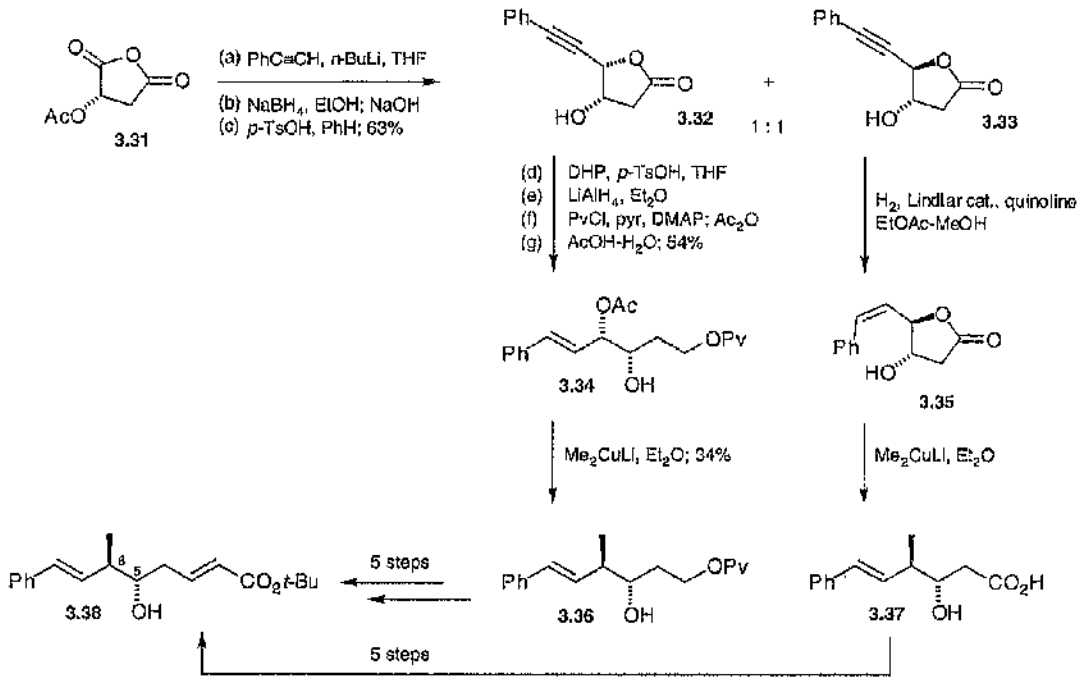
The second route (Scheme 3.12) utilises a highly diastereoselective addition of aldehyde **3.26** to carboximide **3.27** to ultimately reveal protected diol **3.25** after auxiliary cleavage, deoxygenation and protecting group manipulation. The excellent diastereoselectivity for this boron-mediated aldol reaction can be explained by Zimmerman-Traxler transition state **3.28**.[155, 156] Steric hindrance is minimised by placing the aldehyde substituent (R′) in an equatorial position, and as drawn below the chiral auxiliary substituents are orientated away from the centre of the 6-membered transition state.



Scheme 3.12.

3.3.4 - The Lavallée approach.[142]

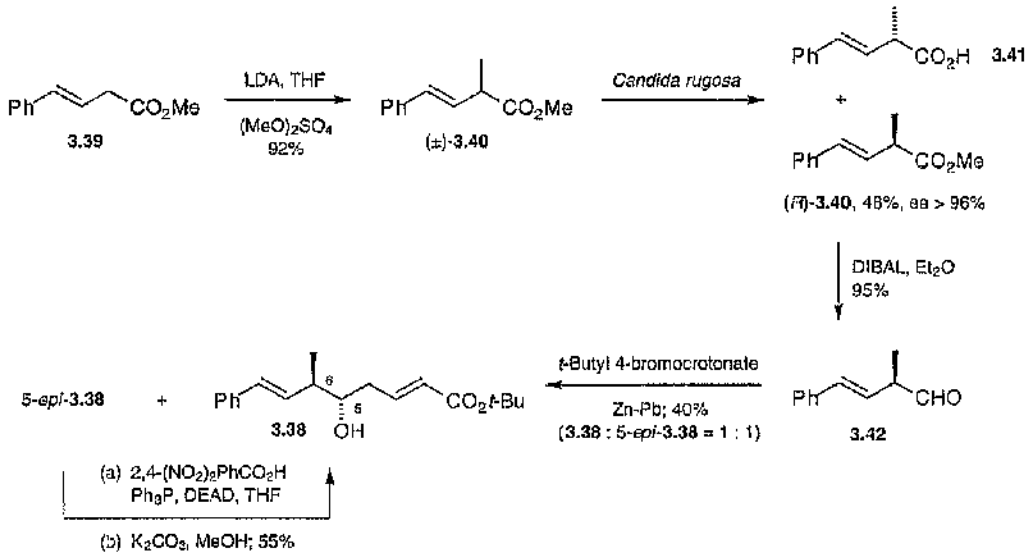
Lavallée uses the commercial availability of (*S*)-(–)-2-acetoxysuccinic anhydride (**3.31**) to install the C5 stereocentre in hydroxyester **3.38** (Scheme 3.13). Unselective addition of lithium phenylacetylide to **3.31** followed by reduction and protection provides separable butyrolactones **3.32** and **3.33**. Lactone **3.32** was converted into protected triol **3.34**, and treatment with Me_2CuLi installed the required methyl group. Alcohol **3.36** was isolated in poor yield from the mixture of S_N2 and S_N2' products, and straightforwardly converted into ester **3.38**. Epimeric butyrolactone **3.33** was transformed into acid **3.37** by Lindlar reduction and treatment with Me_2CuLi. The second step is precedented to occur both with retention of configuration at the electrophilic centre, and with olefin isomerisation.[157]



Scheme 3.13.

3.3.5 – The Sih chemoenzymatic method.[143]

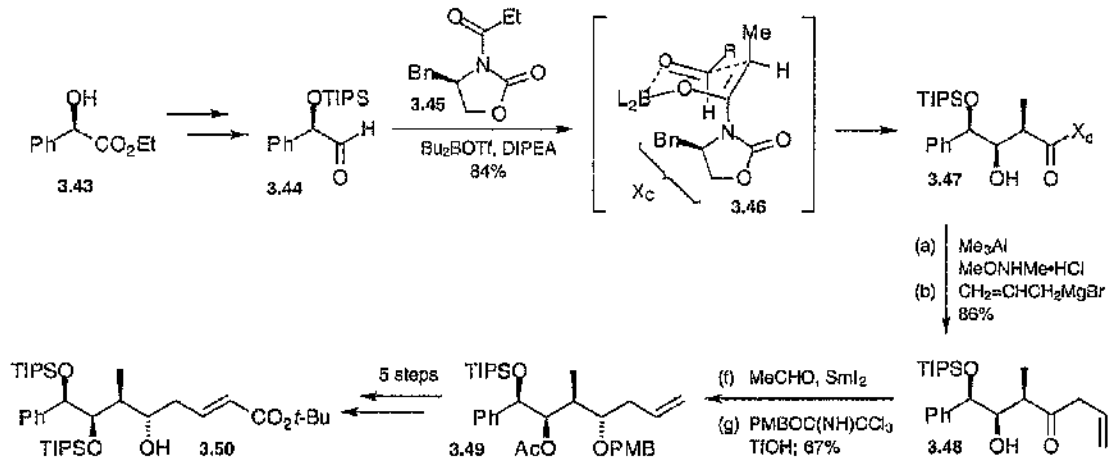
The key step in the Sih synthesis of ester **3.38** is the resolution of racemic ester **3.40** *via* lipase catalysed enantioselective hydrolysis (Scheme 3.14). Utilisation of 2-propanol-treated *Candida rugosa* lipase yielded ester (*R*)-**3.40** with excellent enantiopurity. Reformatzky reaction of corresponding aldehyde **3.42** with *t*-butyl 4-bromocrotonate promoted by Zn-Pb couple produced diastereomers **3.38** and *epi*-**3.38** in poor yield, from which the undesired epimer was transformed into **3.38** isomer *via* Mitsonobu inversion.



Scheme 3.14.

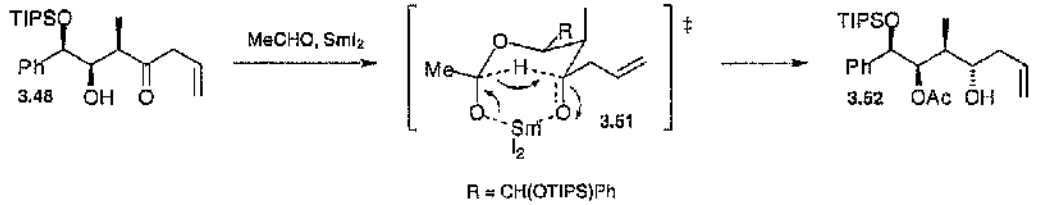
3.3.6 – The Leahy synthesis.[140]

Leahy incorporates the means for introducing the epoxide present in Cryptophycins 1 and 2 into the synthesis of fragment A, as discussed below in section 3.3.12. Aldehyde **3.44** (derived from (*R*)-ethyl mandelate **3.43**) yields alcohol **3.47** after reaction with amide **3.45** under standard Evans aldol conditions (Scheme 3.15).[158] In common with the Kobayashi-Kitagawa route described above (section 3.3.3), transition state **3.46** can be invoked to rationalise the observed stereoselectivity of the aldol reaction. Transamidation of amide **3.47** followed by allylation secured ketone **3.48**. Finally, an intramolecular samarium-catalysed Tishchenko reaction[159] with acetaldehyde was used to introduce the final stereocentre with concomitant differentiation of the hydroxyl groups.



Scheme 3.15.

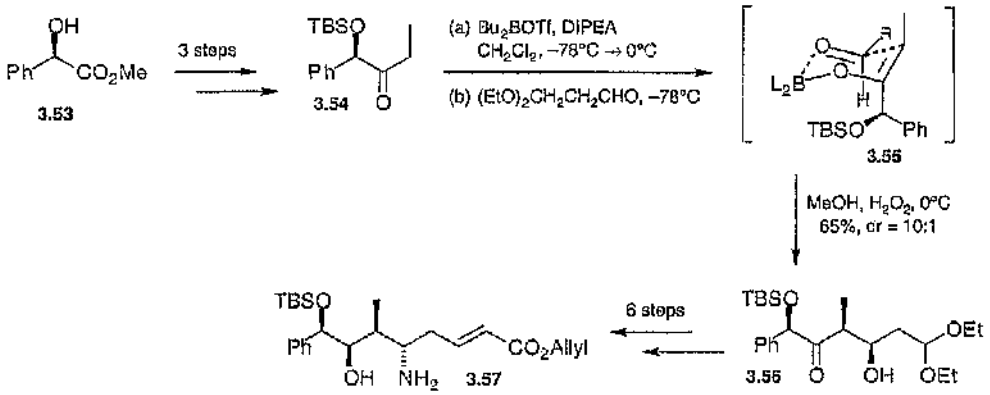
The mechanistic rationale proposed by Evans for the selectivity of the Tishchenko reaction is illustrated below (Scheme 3.16).[159] Coordination of the aldehyde and hydroxyketone **3.48** to samarium is followed by hemiacetal formation. Intramolecular hydride transfer in transition state **3.51** yields acetate **3.52**.



Scheme 3.16.

Amine **3.57**, an intermediate *en route* to unit A of an unstable aza-analogue of Cryptophycin 1 was also synthesised in a broadly similar fashion by Tius from (*R*)-methyl mandelate **3.53**

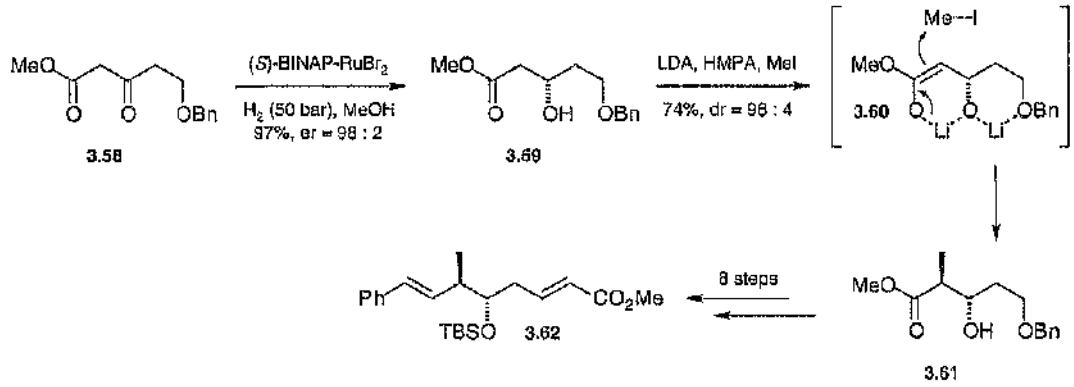
(Scheme 3.17).[147] The chirality of ketone **3.54** dictates the configuration of transition state **3.55** in the boron-mediated aldol reaction, the bulky silyloxy group being orientated away from the 6-membered ring.



Scheme 3.17.

3.3.7 – The Georg procedure.[160]

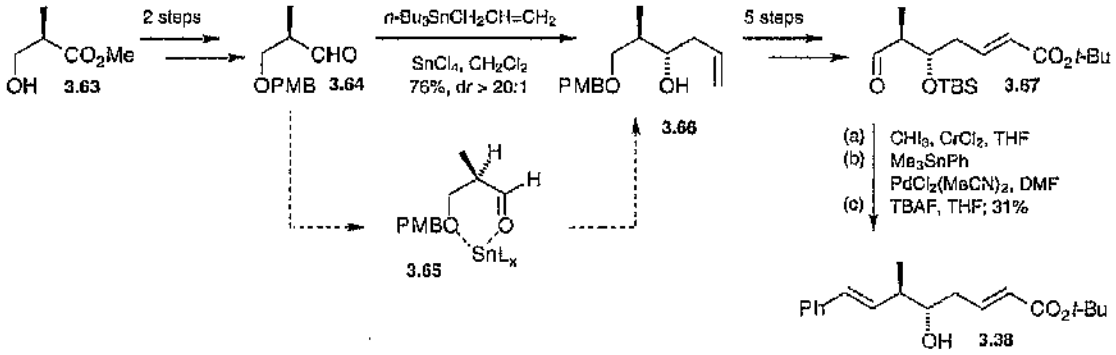
The stereochemistry required in fragment A is introduced at an early stage in the synthesis reported by Georg (Scheme 3.18). Ruthenium catalysed asymmetric hydrogenation of β-keto ester **3.58** yielded hydroxy ketone **3.59** in excellent yield and enantiopurity. Alkylation gave ester **3.61** with excellent *trans* selectivity, presumably *via* attack upon chelate **3.60** from the less hindered upper face.



Scheme 3.18.

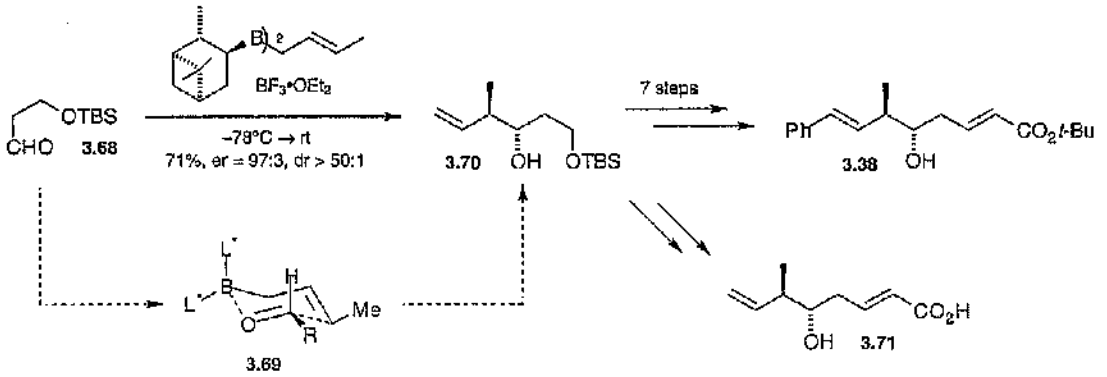
3.3.8 – The White syntheses.[144, 145]

White has described two approaches to fragment A. In the first route (Scheme 3.19), one stereocentre is derived from the chiral pool, methyl (*R*)-3-hydroxy-2-methylpropionate (**3.63**) being converted to aldehyde **3.64**. The second stereocentre is then secured by the diastereoselective addition of allyl tributylstannane, *anti*-alcohol **3.66** presumably arising *via* chelated intermediate **3.65**. After standard manipulation to aldehyde **3.67**, a Takai reaction[161] with iodoform followed by coupling of the resulting (*E*)-iodoalkene with phenyltrimethylstannane under Stille conditions yields ester **3.38**.



Scheme 3.19.

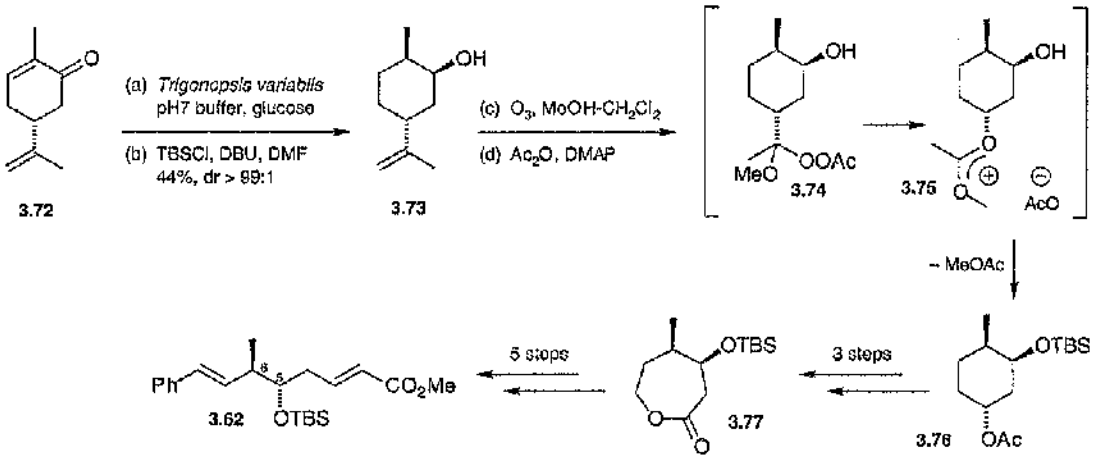
The second White approach utilises an asymmetric crotylboration protocol to produce key allylic alcohol **3.70** (Scheme 3.20). Independently, the same approach was reported by researchers at Eli Lilly.[162] The highly enantio- and diastereoselective crotylboration can be rationalised by 6-membered transition state **3.69**, the absolute configuration of which is determined by the geometry of the isopinocampheyl ligands (L*).[163] The White and Eli Lilly strategies diverge from alcohol **3.70**, standard manipulation allowing White to reveal ester **3.38** in a further seven steps. The Eli Lilly route ultimately incorporates the versatile terminal double bond of **3.71** into the Cryptophycin skeleton, before introduction of the phenyl group in a later Pd-catalysed coupling step.



Scheme 3.20.

3.3.9 – The Eli Lilly bioreductive strategy.[164]

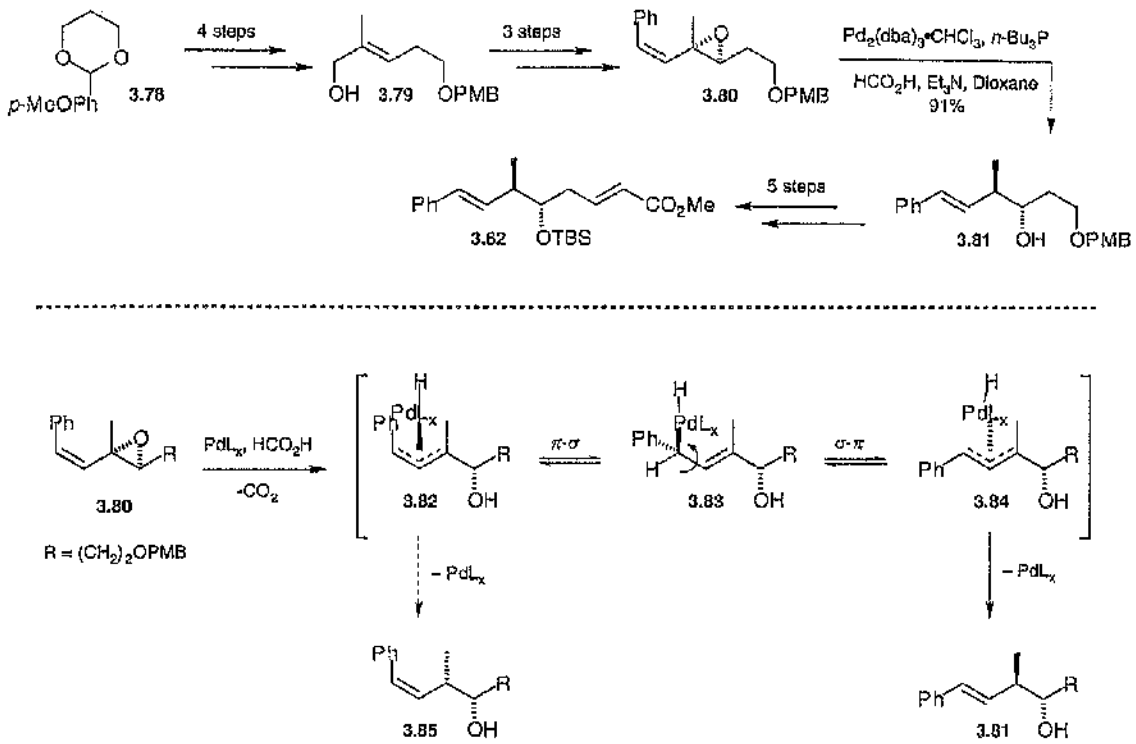
The key to a second approach reported by Eli Lilly is the bioreduction of readily available (*R*)-carvone **3.72** (Scheme 3.21). Reduction with *Trigonopsis variablis* produced alcohol **3.73** without the need for chromatographic purification. Two stereocentres are set in place with excellent selectivity, which ultimately translate to C5 and C6 in fragment A. Ozonolysis followed by Criegee rearrangement[165] produced acetate **3.76** which was subsequently elaborated into ester **3.62.**



Scheme 3.21.

3.3.10 – The Shimizu Palladium catalysed route.[166]

Shimizu reported the elegant palladium-catalysed reductive ring-opening of optically active alkenyl oxirane **3.80** (secured *via* Sharpless asymmetric epoxidation of alcohol **3.79**) to selectively yield homoallylic alcohol **3.81** (Scheme 3.22). (*Z*)-Alkenyloxirane **3.80** forms π-allylpalladium species **3.82** which isomerises *via* a π-σ-π interconversion mechanism (**3.82** $\rightarrow$ **3.83** $\rightarrow$ **3.84**), yielding thermodynamically favoured *syn*-π-allylpalladium species **3.84**. Intramolecular hydride attack subsequently yields the desired olefin **3.81**.



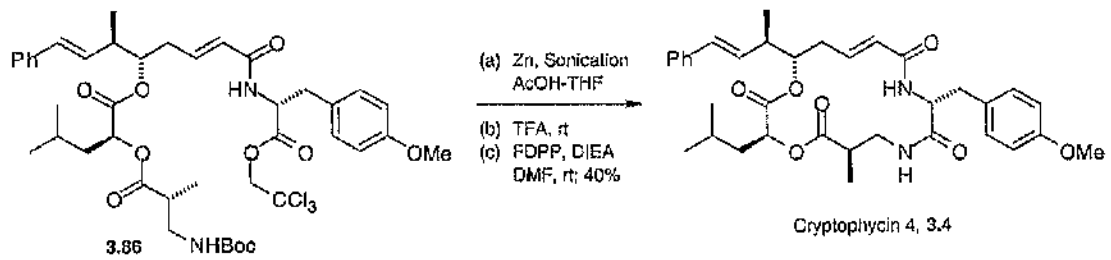
Scheme 3.22.

3.3.11 - Macrocyclisation procedures.

Three main strategies have been used to furnish the macrocyclic Cryptophycins and analogues, differing in the position of final ring closure.

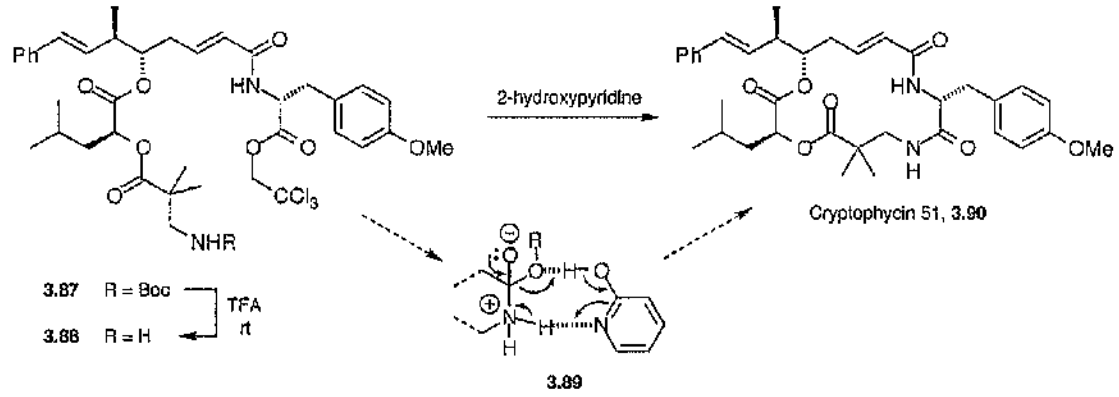
(a) - The Moore-Tius approach.[128]

The strategy pioneered by Moore and Tius in the first reported synthesis of a member of the Cryptophycin family featured macrolactamisation at the junction between fragments B and C (Scheme 3.23).[128] Treatment of ester **3.86** with TFA followed by cleavage of the trichloroethyl ester revealed the free amine and acid functionalities. Macrolactamisation was promoted by pentafluorophenyl diphenylphosphinate (FDPP), giving the cyclised Cryptophycin (**3.4**) in moderate yield over 3 steps.



Scheme 3.23.

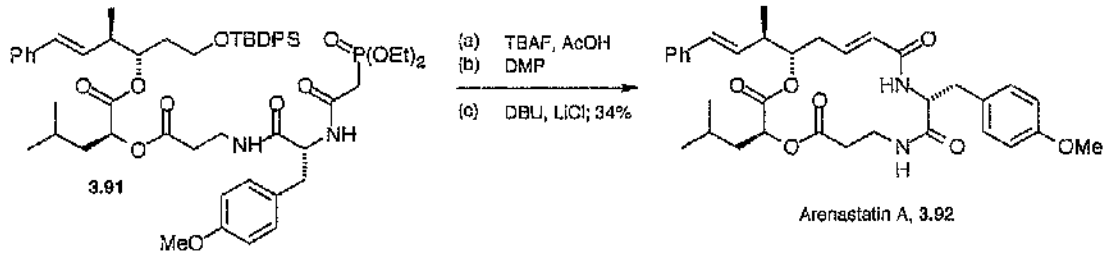
Fray has communicated a similar strategy for the formation of Cryptophycin macrocycles under mild conditions (Scheme 3.24).[167] Following *N*-deprotection of ester **3.87**, 2-hydroxypyridine was used to promote ring closure. 2-Hydroxypyridine stabilises tetrahedral intermediate **3.89**, favouring proton transfer, loss of trichloroethanol and lactamisation. The mild Fray conditions minimise byproducts occurring in the Moore - Tius cyclisation procedure.



Scheme 3.24.

(b) - The Kitagawa approach.[141]

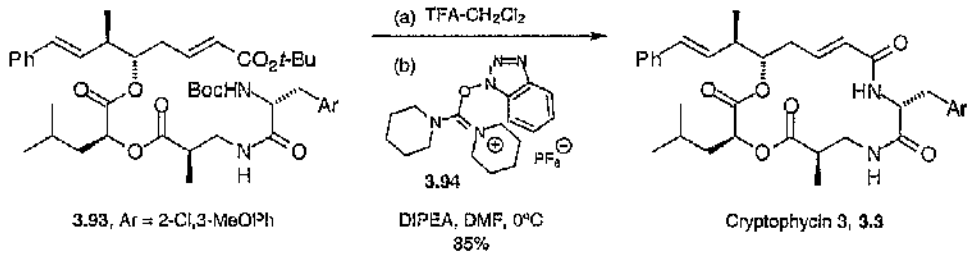
In the total synthesis of Arenastatin A (Cryptophycin 24, **3.92**), Kitagawa closed the ring *via* formation of the C2-C3 double bond under intramolecular Wittig-Horner conditions from phosphonate **3.91** (Scheme 3.25).



Scheme 3.25.

(c) The Lavallée procedure.[142]

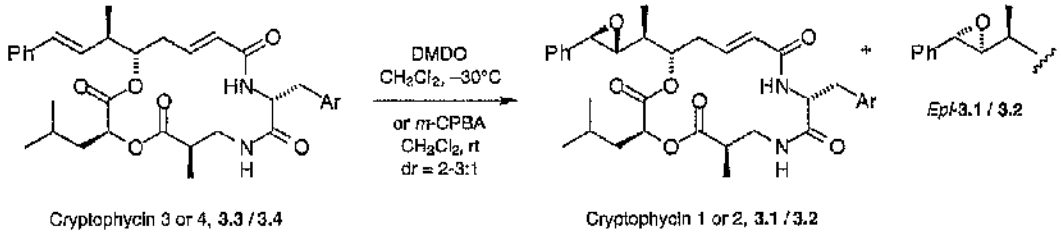
Lavallée chose macrolactamisation between units A and B to close the Cryptophycin macrocycle (Scheme 3.26), utilising an acid-labile *tert*-butyl ester which was removed simultaneously with the *N*-Boc protection in ester **3.93**. Cyclisation of the resulting amino acid was promoted by *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-bis(pentamethylene) uronium hexafluorophosphate (**3.94**).



Scheme 3.26.

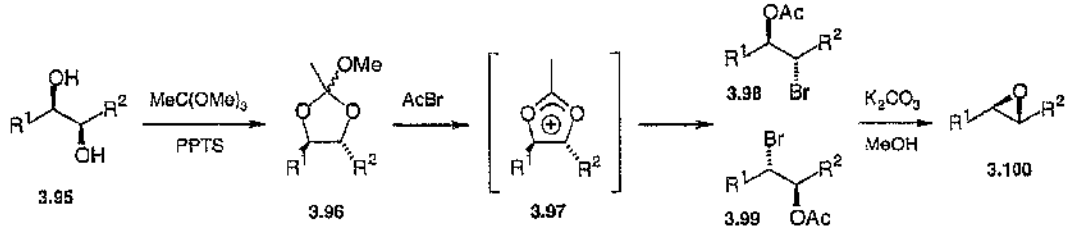
3.3.12 - Strategies for the introduction of the Unit A epoxide moiety.

Two general strategies for the introduction of the β-epoxide pharmacophore present in the most active members of the Cryptophycins (e.g. **3.1** and **3.2**) have been described. The first and most common is the introduction of the epoxide in a final step using *m*-CPBA[134-136, 143, 162] or dimethyldioxirane (DMDO)[141, 144, 145, 153] (Scheme 3.27). Diastereoselectivity for the epoxidation is poor, 3 : 1 in favour of the desired β-isomer (**3.1** / **3.2**) at best, with isolated yields in the region of 50% following reverse-phase HPLC separation.



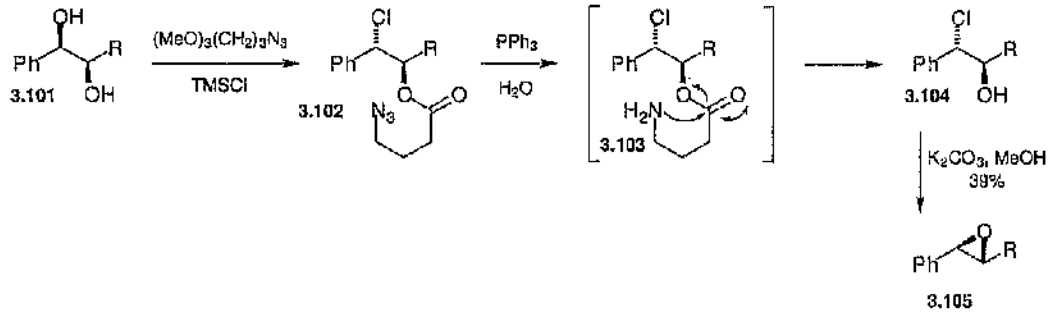
Scheme 3.27.

The second general epoxidation strategy, first applied by Leahy,[140] (section 3.3.6) draws upon precedent from Sharpless for the *in-situ* conversion of vicinal diols into epoxides (Scheme 3.28).[168] Formation of a cyclic orthoester **3.96** is followed by the addition of acetyl bromide, and the resulting acetoxy halides **3.98** / **3.99** reveal epoxide **3.100** upon acetate cleavage and cyclisation using potassium carbonate in methanol.



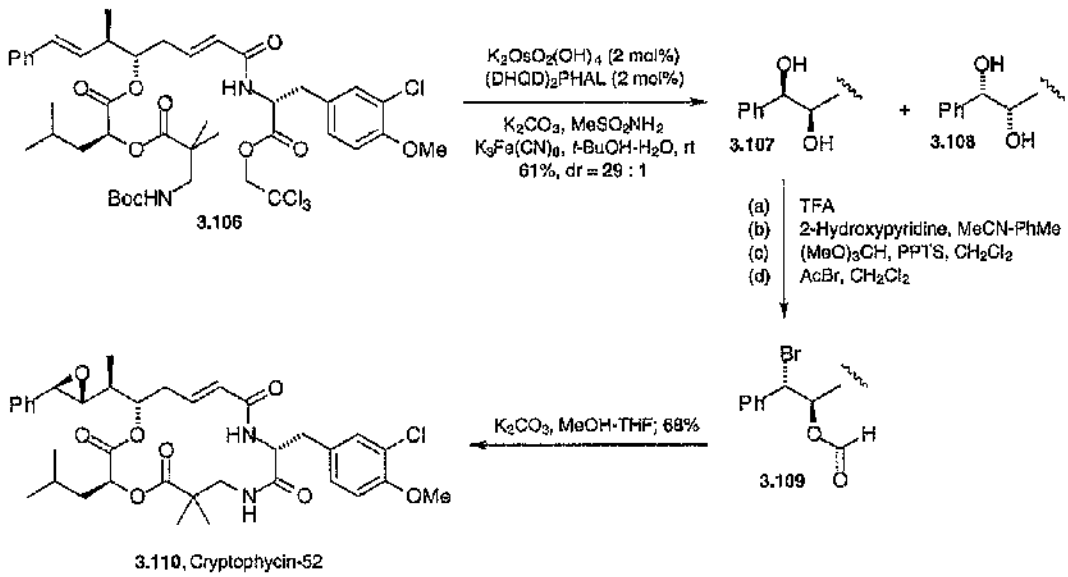
Scheme 3.28.

In the Cryptophycins, the base-sensitive ester linkages present are incompatible with the basic transesterification step required to reveal the α-hydroxy halide precursor to the epoxide, necessitating a modification of the Sharpless protocol (Scheme 3.29). The use of 4-azido-1,1,1-trimethoxybutane in place of trimethyl orthoacetate allowed cleavage of azidobutyrate **3.102** under reductive conditions *via* intramolecular lactamisation of intermediate **3.103**.[140]



Scheme 3.29.

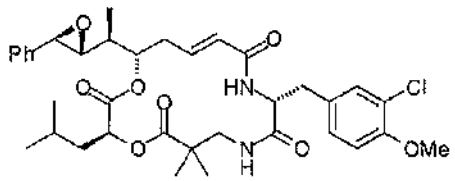
The Leahy strategy was later adapted by Moore and Moher and incorporated into a late stage of the original Moore-Tius route (section 3.3.2), using Sharpless Asymmetric Dihydroxylation to install the required diol (Scheme 3.30).[169] Dihydroxylation of styrene **3.106** under optimised conditions allowed the isolation of β-diol **3.107** with excellent (29 : 1) diastereoselectivity. Macrocyclisation under Fray conditions was followed by conversion *via* the orthoformate to formate ester **3.109**. The use of an orthoformate in place of an orthoacetate allowed cleavage of the formate ester under mildly basic conditions, leaving the other ester linkages intact, and gave epoxide **3.110** in excellent overall yield.



Scheme 3.30

3.4 – Conclusions.

The Cryptophycins have stimulated great synthetic interest over the short time since their potential as antitumour compounds was revealed in 1994. At the time of writing (May 2000) Eli Lilly and Company report that Cryptophycin 52 (LY 355703, **3.110**) is in Phase II clinical trials as a proposed treatment for multiple solid tumours.[135, 170]

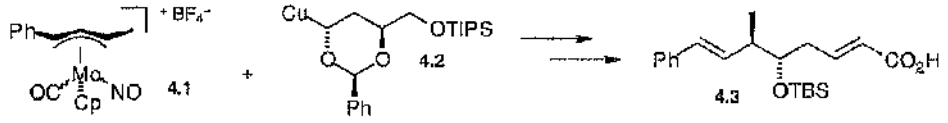


Cryptophycin 52, **3.110**
(LY 355703)

Numerous synthetic routes to the Cryptophycins and analogs, and especially to the key Fragment A motif have been published. Many of the routes to fragment A rely heavily upon standard, well established methodology, such as the Sharpless asymmetric epoxidation, asymmetric boron-mediated aldol or asymmetric crotylboration reactions. The Glasgow route to Cryptophycin fragment A, and thence to the total synthesis of Cryptophycin 4 will be discussed in the following chapter. We use novel molybdenum-based asymmetric carbon-carbon bond forming methodology to control the C5 and C6 stereocentres in fragment A.

Chapter 4 - The Total Synthesis of Cryptophycin 4.

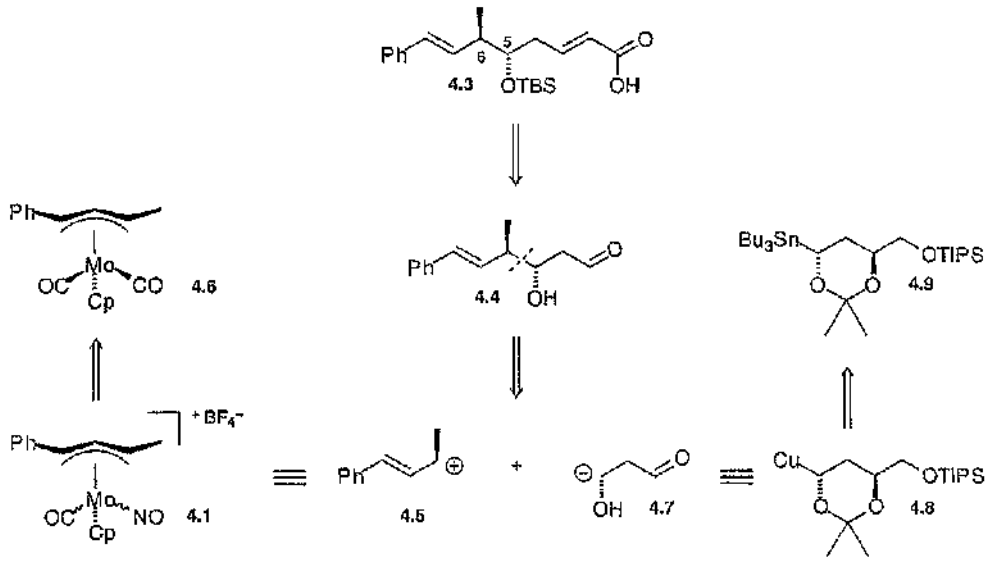
Chapter 4 will describe the Glasgow approach to (2*E*,5*S*,6*R*,7*E*)-5-(*tert*-butyldimethylsilanyloxy)-6-methyl-8-phenylocta-2,7-dienoic acid **4.3** and from there to the total synthesis of Cryptophycin 4. The synthesis of **4.3** provided an opportunity to apply the molybdenum-based methodology described in Chapters 1 and 2 to natural product synthesis, and utilises a strategy whereby the C5 and C6 stereocentres are introduced in a single synthetic operation. Our approach (Scheme 4.1) entails coupling of organocopper(I) nucleophile **4.2** with novel planar chiral cationic η^3-allyl molybdenum complex **4.1**.



Scheme 4.1

4.1 - Retrosynthesis

In common with previous Cryptophycin syntheses described in Chapter 3, our initial target molecule was protected hydroxy acid **4.3** as an equivalent for fragment A (Scheme 4.2). With a reliable route to **4.3** in hand we planned to complete the synthesis of Cryptophycin 4 mainly following precedent established by Moore and co-workers.[128] Hydroxy aldehyde **4.4** was envisaged to be a precursor to **4.3**, disconnection across the key C5-C6 bond leading to the chiral synthons **4.5** and **4.7**.



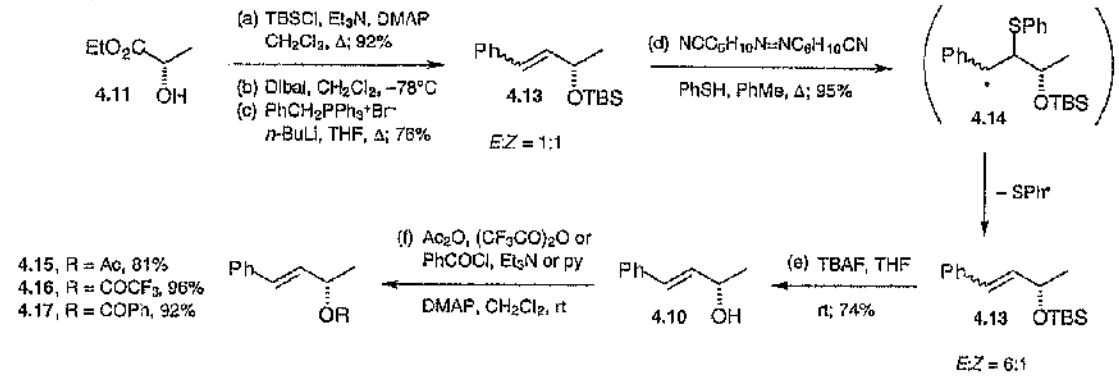
Scheme 4.2

We envisaged that cationic synthon **4.5** could be represented by the novel cationic molybdenum complex **4.1**, which, if available in planar chiral form, would allow the C6 methyl stereochemistry to be controlled by addition of a suitable nucleophile *anti* to the face blocked by the metal. At the commencement of the work, little guiding precedent was available regarding the regioselectivity of nucleophilic attack upon complex **4.1**. Key issues were the electronic effect of phenyl conjugation and the relative steric effects of phenyl *vs* methyl.

As for the nucleophilic coupling partner, we initially envisaged novel organocopper(I) nucleophile **4.8** as an equivalent to synthon **4.7**. The 1,2-diol array in intermediate **4.9** has two key strategic functions: (a) it acts as a stereochemical marker and (b) it serves as a latent aldehyde. The strategy outlined in Scheme 4.2 requires the successful synthesis and union of complex **4.1** and nucleophile **4.8**. Routes to the two key intermediates will be dealt with in the following sections.

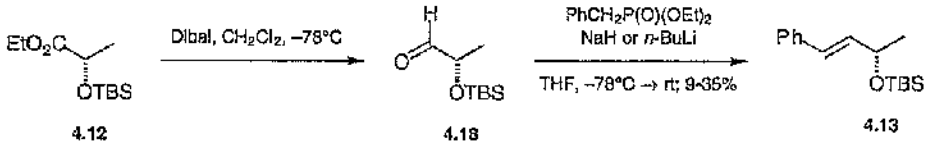
4.2 - Preparation of allylic alcohol derivatives - precursors to neutral π-allyl molybdenum complex 4.6.

Neutral complex **4.6**, the immediate precursor to cationic species **4.1** required the preparation of enantiopure allylic alcohol **4.10**[171] (Scheme 4.3). From cheap (~£16 / L) and readily available (*S*)-ethyl lactate (**4.11**), alcohol **4.10** could be secured in 5 steps. Silyl protection, reduction and Wittig reaction of the resulting lactaldehyde[172] yielded an equimolar mixture of (*E*)- and (*Z*)-styryl isomers **4.13**. Treatment of the mixture with thiophenol and 1,1′-azobis(cyclohexanecarbonitrile) (VAZO® 88) in refluxing toluene[148] smoothly isomerised the mixture to favour the desired (*E*)-styrene, presumably *via* addition of PhS• to the olefin, rotation of benzylic radical **4.14** and reformation of the double bond. Similar isomerisations of 2-alkenoic esters, styrenes and non-conjugated olefins using PhSSPh with or without AIBN have been described.[173-175] Fluorodesilylation and recrystallisation secured isomerically pure (*E*)-allylic alcohol **4.10** in 74% yield and ≥92% ee as estimated *via* ^{1}H NMR analysis of the corresponding (*R*)-*O*-acetyl mandelate ester. Allylic ester derivatives **4.15**-**4.17** were subsequently prepared from **4.10** in good yield.



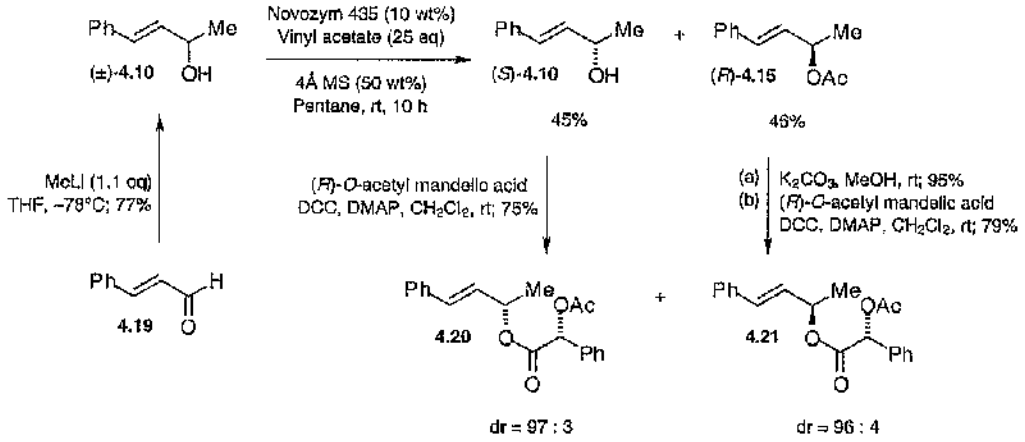
Scheme 4.3

Allylic alcohol **4.10** was prepared on a > 40 mmol scale, but the route was inelegant. Horner-Emmons elongation of (*S*)-*O*-(*tert*-butyldimethylsilyl)lactaldehyde **4.18**[172] (Scheme 4.4) with diethyl benzylphosphonate[176] yielded styrene **4.13** in only poor yield under standard conditions,[177] and the Wittig reaction - isomerisation sequence was more efficient on a large scale.



Scheme 4.4

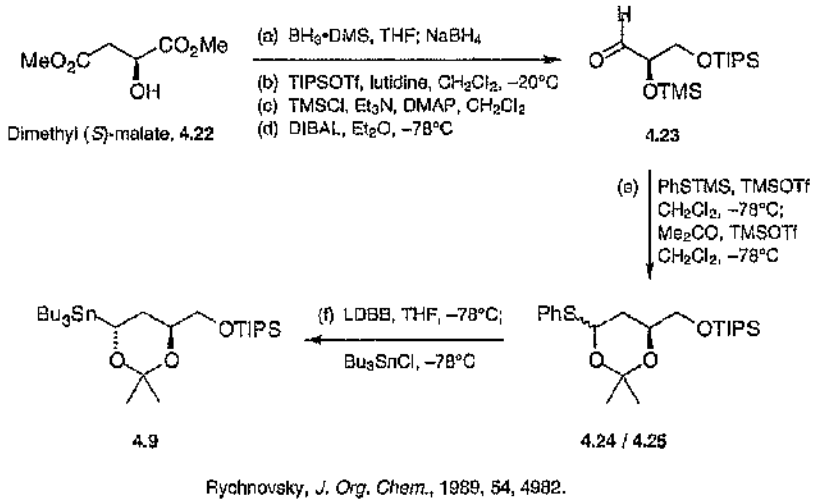
An alternative preparation of allylic alcohol **4.10** involved the use of Novozym 435[72] to resolve the racemate (see Chapter 2, section 2.1). Racemic alcohol **4.10**, easily obtained by the addition of methyl lithium to cinnamaldehyde **4.19**,[178] was treated with Novozym 435 in the presence of vinyl acetate (Scheme 4.5). Enantioselective acetylation of the racemate gave acetate (*R*)-**4.15** (46% yield) and alcohol (*S*)-**4.10** (45% yield). Saponification of a portion of acetate **4.15** allowed the estimation of the enantiomeric ratios of alcohol **4.10** and acetate **4.15** to be estimated as 97:3 and 96:4 respectively *via* formation of (*R*)-*O*-acetyl mandelate esters **4.20** and **4.21** and ^{1}H NMR spectroscopic analysis.



Scheme 4.5

4.3 - Synthesis of stannane 4.9.

Isopropylidene-protected stannane **4.9** was initially targeted as a precursor to the nucleophile in the key Cryptophycin coupling step, as it was hoped that tin-lithium exchange and lithium-copper transmetallation would both proceed retentively at low temperature. A communication from Rychnovsky formed the basis of initial attempts to secure stannane **4.9** (Scheme 4.6).[179] Dimethyl (*S*)-malate **4.22** was converted into aldehyde **4.23**, from which thioacetals **4.24 / 4.25** were obtained by treatment of **4.23** with (phenylthio)trimethylsilane (PhSTMS) and catalytic trimethylsilyl triflate (TMSOTf), followed by acetone and catalytic TMSOTf. Reductive lithiation and stannylation at low temperature concluded the reported route to stannane **4.9**.

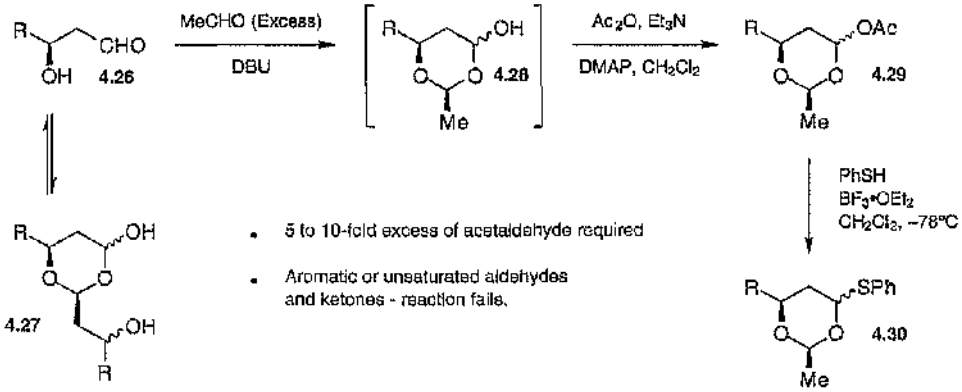


Rychnovsky, *J. Org. Chem.*, 1989, 54, 4982.

Scheme 4.6

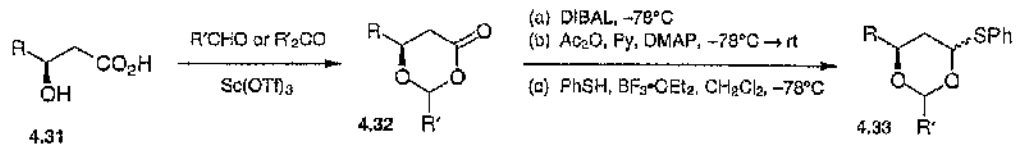
In our hands the original Rychnovsky procedure proved unsuccessful: treatment of aldehyde **4.23** under the above conditions returning none of the desired *O,S*-acetals **4.24 / 4.25**, and an alternative route was investigated. Justification for this decision arrived after the conclusion of the Cryptophycin work when in 1999 Rychnovsky acknowledged that the original procedure was unsatisfactory and poorly reproducible, quoting decomposition of the product into the phenylthioacetal of the starting aldehyde, the phenylthioacetal of acetone and a variety of unidentified products under the reaction conditions.[180, 181] Fortuitously, two alternative routes to 4-(phenylthio)-1,3-dioxanes such as **4.24 / 4.25** existed, the second of which was modified successfully to secure stannane **4.9**.

In the first alternative route (Scheme 4.7),[180-182] β-hydroxy aldehyde **4.26**, which exists as a mixture with its unsymmetrical dimer **4.27**, is treated with an excess of acetaldehyde under DBU catalysis and the resulting hemiacetal **4.28** acetylated *in situ* to yield acetate **4.29**. Exchange of acetate for thiophenol under Lewis acidic conditions yielded 4-(phenylthio)-1,3-dioxane **4.30**. The intermediacy of acetate **4.29** is necessary due to the instability of hemiacetal **4.28**, which, if isolated, would spontaneously lose acetaldehyde to return β-hydroxy aldehyde **4.26**.



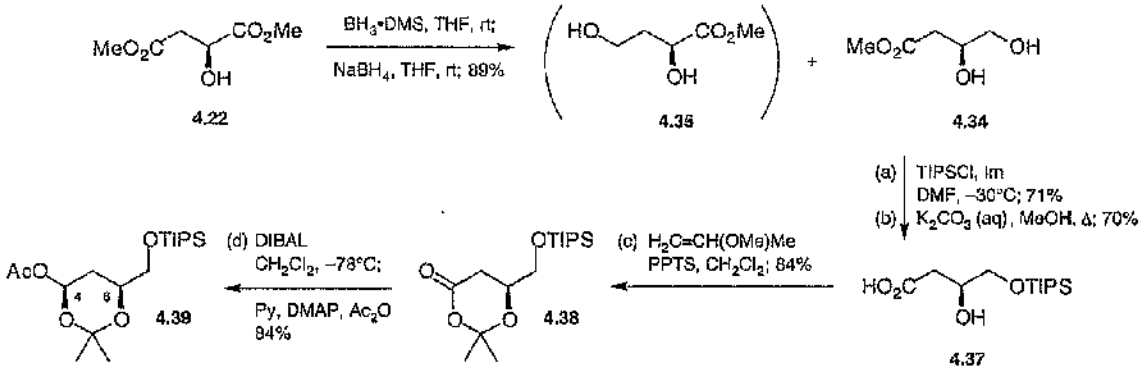
Scheme 4.7

The second route[180, 181, 183] (Scheme 4.8) relies on the reduction and *in situ* acetylation of 1,3-dioxan-4-ones **4.32**, prepared from β-hydroxy acids and excess aldehyde under protic or Lewis acidic catalysis. DIBAL reduction and *in-situ* acetylation of the resulting unstable hemiacetal yields an α-acetoxy ether which can be converted into **4.33** under Lewis acidic conditions as above. The second, more general route is successful for the preparation of 1,3-dioxan-4-ones derived from aliphatic or aromatic aldehydes and also from ketones.



Scheme 4.8

The second route allowed us to access acetate **4.39** in 5 steps from dimethyl (*S*)-malate **4.22** (Scheme 4.9). Reduction of dimethyl (*S*)-malate by the procedure of Moriwake[99] gave the desired 1,2-diol **4.34** together with the 1,3-diol **4.35** (7:1 respectively). The diols were identified by comparison of their ^{1}H NMR spectra with literature data.[184-186] The reaction was less selective than reported perhaps because the $NaBH_4$ was of inferior quality leading to longer reaction times. The contaminant isomer was readily removed chromatographically following selective silylation of the primary hydroxyl group[187] and saponification of the methyl ester to yield hydroxyacid **4.37**. Dioxanone **4.38** was subsequently prepared using 2-methoxypropene and catalytic PPTS.[188] DIBAL reduction and acetylation proceeded uneventfully under Rychnovsky conditions to yield acetate **4.39** exclusively as the (4*S*,6*S*)-isomer shown.



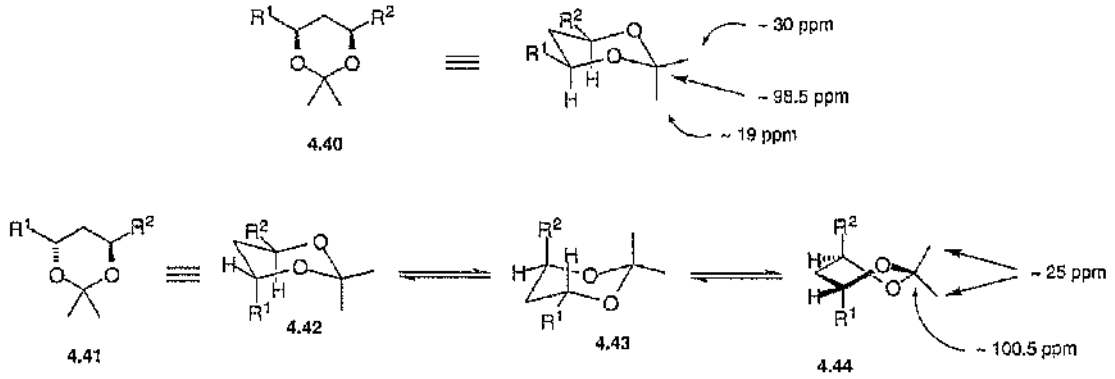
Scheme 4.9

For the Cryptophycin 4 synthesis, the configuration at C4 is irrelevant at this stage (or at that of the phenylthio acetal which follows) since the required C4 stereochemistry is only put in place by a subsequent reductive lithiation - stannylation step. For convenience however, it is useful to note that the relative configurations of acetonides derived from *syn*- and *anti*-1,3-diols can be assigned from the ^{13}C NMR shifts of the acetal carbon and acetal methyl carbons (Scheme 4.10).[189, 190] Rychnovsky correlated the ^{13}C NMR spectra of more than 200 known compounds of general structure **4.40** or **4.41** and drew the following conclusions:

- *Syn*-1,3-diol acetonides **4.40** exhibit acetal methyl carbon shifts at approximately 19 and 30 ppm. The acetonide exists in a well-defined chair conformation with the C4 and C6 substituents both placed in equatorial positions.

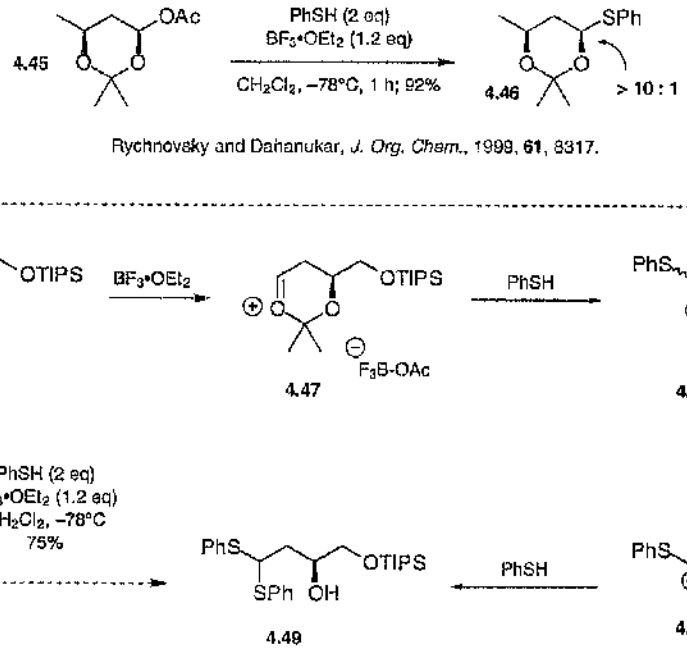
- *Anti*-1,3-diol acetonides **4.41** exhibit acetal methyl carbon shifts at approximately 25 ppm. The acetonide exists in a twist-boat conformation **4.44** in order to avoid 1,3-diaxial interactions that would be present in chair conformations **4.42** and **4.43**.

- The acetal methyl carbon shifts are reliable indicators of 1,3-diol acetonide stereochemistry, (except where R^1 or R^2 = CN) but the acetal carbon shift (~98.5 ppm *Syn* and ~100.5 ppm *Anti*) is not as reliable and should be used with caution.



Scheme 4.10

The formation of a single acetate diastereomer **4.39** is unsurprising, and in accordance with the good *syn* diastereoselectivity (4:1 -> 10:1) observed by Rychnovsky in the reduction and *in-situ* acetylation of similar dioxanone precursors.[183, 191] Presumably acetate **4.39** represents the kinetic product resulting from axial hydride attack upon the carbonyl group of **4.38**, followed by stereoselective acetylation.[183] Transformation of acetate **4.39** into *O,S*-acetals **4.24 / 4.25** was problematic (Scheme 4.11), despite precedent from Rychnovsky for the conversion of similar acetates, such as **4.45** depicted below, simply using thiophenol and stoichiometric $BF_3{\cdot}OEt_2$ as a promoter.[183] In our hands, treatment of acetate **4.39** under the literature conditions using stoichiometric $BF_3{\cdot}OEt_2$ yielded *S,S*-acetal **4.49** as the sole product in 75% yield. A plausible mechanism is proposed below, with desired sulphides **4.24 / 4.25** being initially formed *via* the intermediacy of oxonium ion **4.47**, followed by Lewis acid mediated departure of acetone and the formation of *S,S*-acetal **4.49** after attack of thiophenol upon the stabilised cation **4.48**.



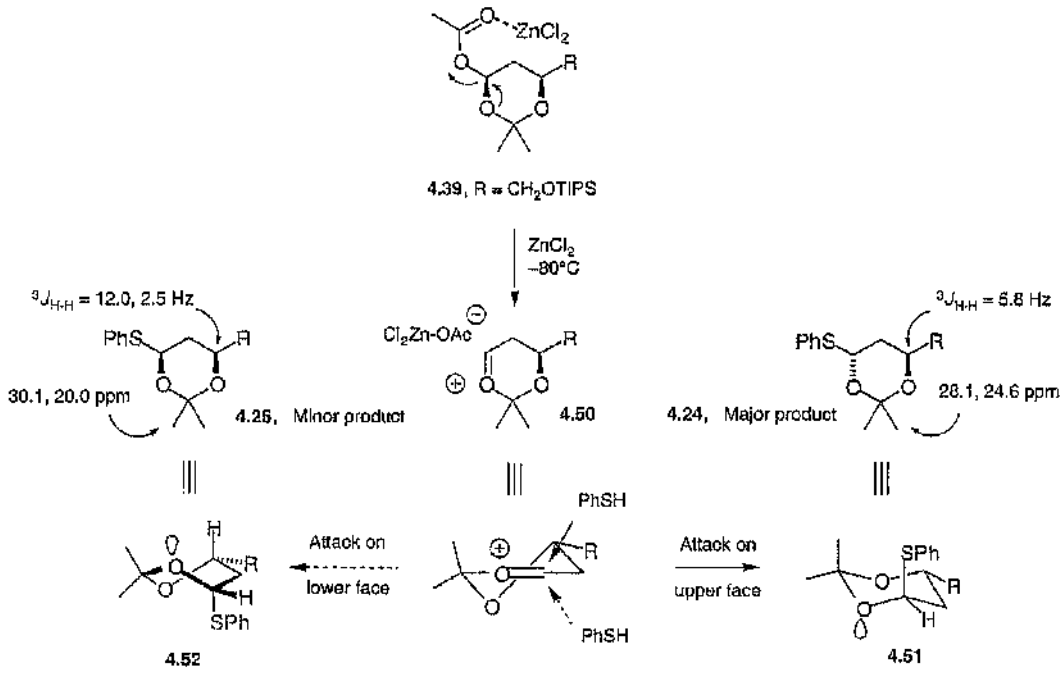
Scheme 4.11

A variety of alternative conditions were subsequently investigated, as summarised in the table below:

Entry	Conditions	Yield (%) of 4.24 / 4.25	Yield (%) of 4.49
1	2.0 PhSH, 1.2 BF_3•OEt_2 CH_2Cl_2, –78°C, 1 h	0 (-)	75
2	1.1 PhSTMS, BF_3•OEt_2 (cat) CH_2Cl_2, –78°C, 40 min	3 (-)	0
3	1.1 PhSTMS, 5 mol% $ZnCl_2$ CH_2Cl_2, –60°C, 5 min	81 (73 : 27)	0
4	1.1 PhSH, 5 mol% $ZnCl_2$ CH_2Cl_2, –80°C, 1.5 h	81 (81 : 19)	Trace by TLC
5	1.05 eq PhSH, 4 mol% $ZnCl_2$ CH_2Cl_2, –30°C, 15 min	87 (10 : 90)	Trace by TLC

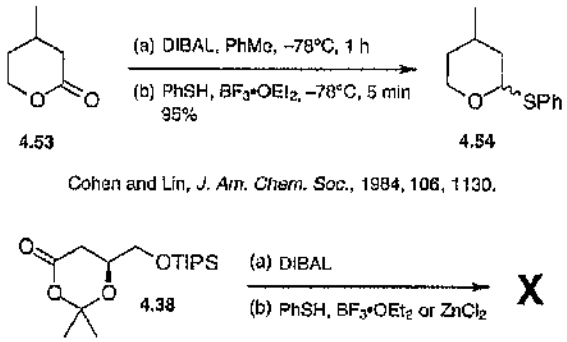
Use of PhSTMS in place of PhSH with BF_3•OEt_2 promotion gave a trace of the desired products **4.24 / 4.25** but the combination of PhSTMS and $ZnCl_2$ at low temperature allowed sulphides **4.24 / 4.25** to be isolated in 81% yield. *Syn*-isomer **4.25** was readily identified by the acetal methyl carbon shifts (δ 30.1, 20.0 ppm) which were in close agreement with literature values (δ 30.0, 19.9 ppm).[189] The good selectivity for the *anti* isomer **4.24** at low temperature supports predictions made by Deslongchamps for the addition of nucleophiles to a cyclic 6-membered oxonium ion (Scheme 4.12).[192] Attack on oxonium ion **4.50** from the

upper face will result in chair conformation **4.51**, which is equivalent to the observed major product **4.24**. Taking into account the restriction for the antiperiplanar arrangement of an oxygen lone pair with the newly formed C-S bond, attack upon the lower face of the oxonium ion would result in the strained and unfavourable twist-boat conformation **4.52**. Other Lewis acids screened in conjunction with PhSTMS include TMSOTf (decomposition), $Sc(OTf)_3$ (decomposition), $SnCl_4$ (decomposition to **4.49**) and $Ti(O^iPr)_4$ (no reaction).



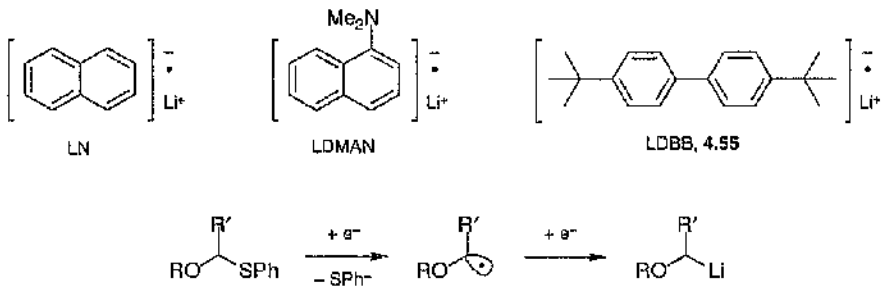
Scheme 4.12

Subsequent experimentation revealed that the reaction temperature was not critical and neither was the use of PhSTMS, more conveniently thiophenol itself could be used (Entries 3-5). An alternative preparation of *O,S*-acetals **4.24 / 4.25** was briefly investigated (Scheme 4.13). Cohen has reported the one-pot synthesis of *O,S*-acetal **4.54** from lactone **4.53** by DIBAL reduction and treatment of the crude aluminium salt with thiophenol and $BF_3{\bullet}OEt_2$ at low temperature,[193] a route apparently not applied dioxanone systems such as **4.38** by Rychnovsky. The original Cohen conditions were applied to dioxanone **4.38** in an attempt to avoid the intermediacy of acetate **4.39**, but were unsuccessful, as was the use of DIBAL followed by $ZnCl_2$ and PhSH.



Scheme 4.13

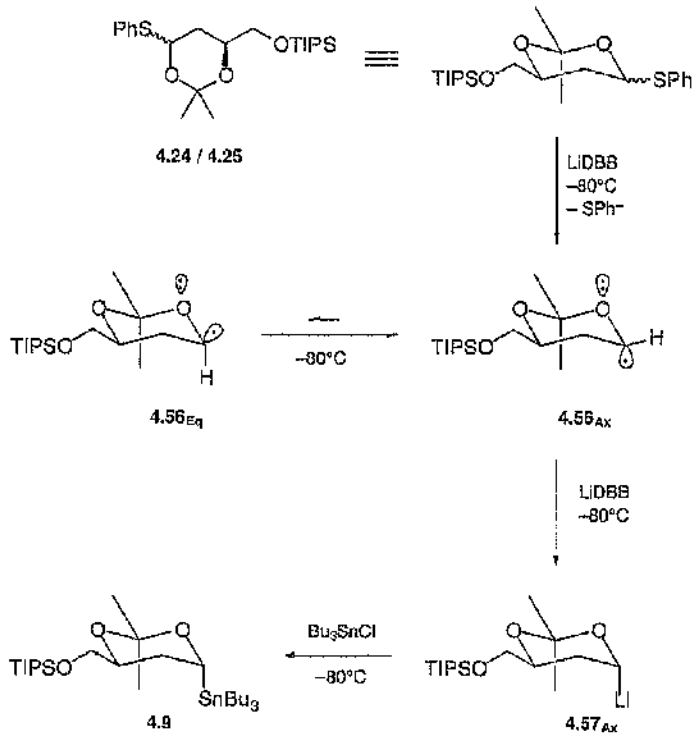
With a viable route to sulphides **4.24 / 4.25** now in place, the key step in the synthesis of stannane **4.9** could be addressed. The axial stereochemistry at C4 is set in place by a reductive lithiation and stannylation sequence, converting a mixture of diastereomeric sulphides to a single stannane diastereomer. Reductive lithiation of α-(phenylthio)ethers originated in 1980 when Cohen reported the formation of α-lithioethers from a variety of precursors by treatment with lithium 1-(dimethylamino)naphthalenide (LDMAN) or lithium naphthalenide (LN) (Scheme 4.14).[194] An advantage of using LDMAN is that the 1-(dimethylamino)naphthalene (DMAN) byproduct is readily removed from the reaction mixture with a dilute acid wash during workup. Reductive lithiation proceeds *via* electron transfer followed by carbon-sulfur bond cleavage and departure of thiophenoxide anion. The resulting carbon radical is further reduced by a second equivalent of the aromatic radical anion to give a carbanion. The efficiency of electron transfer from the radical anion increases with the steric bulk of the aromatic group, leading to the widespread use of lithium di-*tert*-butylbiphenylide (LDBB, **4.55**).[195, 196]



Scheme 4.14

In the case of a cyclic six-membered α-(phenylthio)ether system, axially substituted products are formed with excellent selectivity if lithiation and reaction with an electrophile are carried out at low temperature.[193, 197] The selectivity results from the "radical anomeric effect" illustrated below (Scheme 4.15). The first equivalent of the aromatic radical anion forms radical **4.56** which can rapidly interconvert between pseudo axial and pseudo equatorial

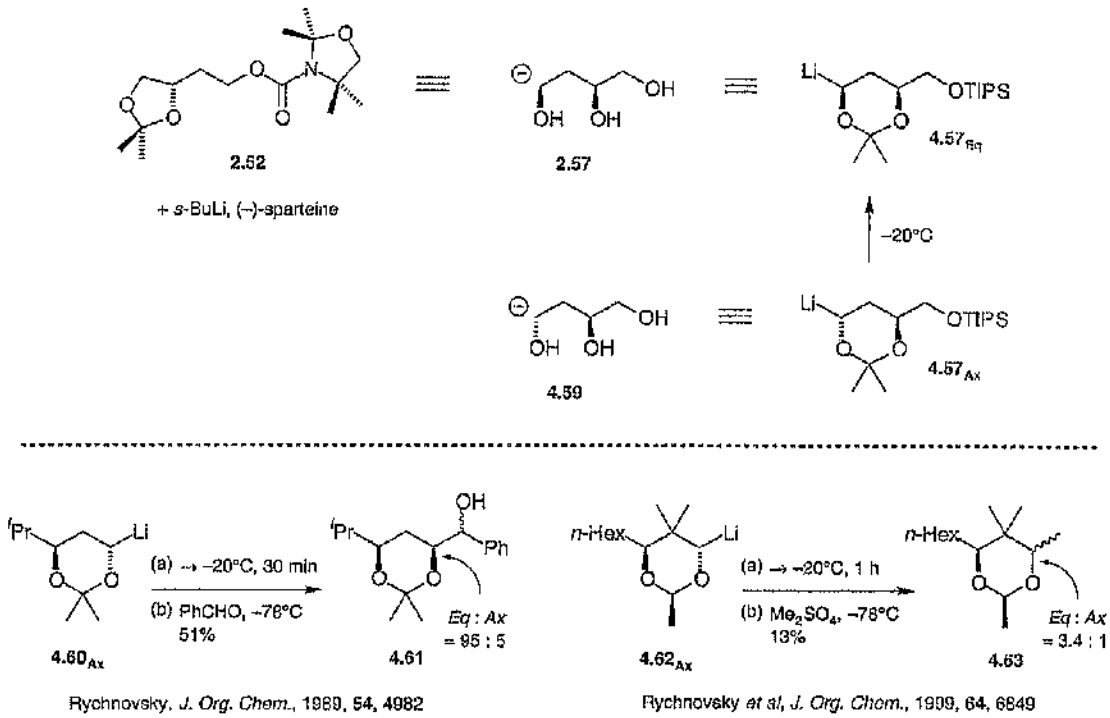
orientations, even at low temperature.[198] Repulsion between the SOMO and the nearby oxygen lone pair in radical **4.56$_{Eq}$** results in radical **4.56$_{Ax}$** being favoured, and leads solely to kinetic organolithium species **4.57$_{Ax}$** following donation of a second electron.



Scheme 4.15

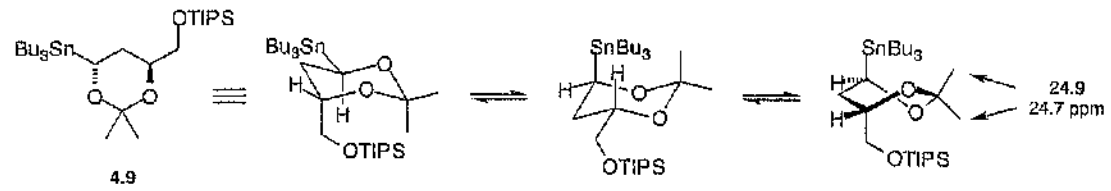
The kinetically formed axial alkyllithium **4.57$_{Ax}$** (and the corresponding stannane **4.9**) have the correct configuration required for the synthesis of Cryptophycin 4; however, thermal equilibration of axial organolithium **4.57$_{Ax}$** to the diastereomeric species **4.57$_{Eq}$** is possible (Scheme 4.16).[193] The resulting alkyllithium would then be a synthetic equivalent for the (1*S*,3*S*)-1,3,4-trihydroxybutanide ion **2.57**, an alternative form of which results from deprotonation of carbamate **2.52** in the presence of (–)-sparteine as described in Chapter 2.

Rychnovsky has reported the equilibration of the related axial alkyllithium **4.60** by warming to –20°C before re-cooling to –78°C and alkylation (Scheme 4.16). Equatorially substituted product **4.61** was formed with excellent stereoselectivity, albeit with the penalty of a lower yield due to competing protonation of the alkyllithium during equilibration.[179] Later studies of the equilibration of a range of 4-lithio-1,3-dioxanes similar to **4.57** and **4.60** have revealed a marked substrate dependence, with unhindered acetals equilibrating rapidly and efficiently, but with more hindered substrates such as **4.62** being problematic, steric hindrance reducing the rate of equilibration and increasing the rate of protonation by the solvent.[180, 181]



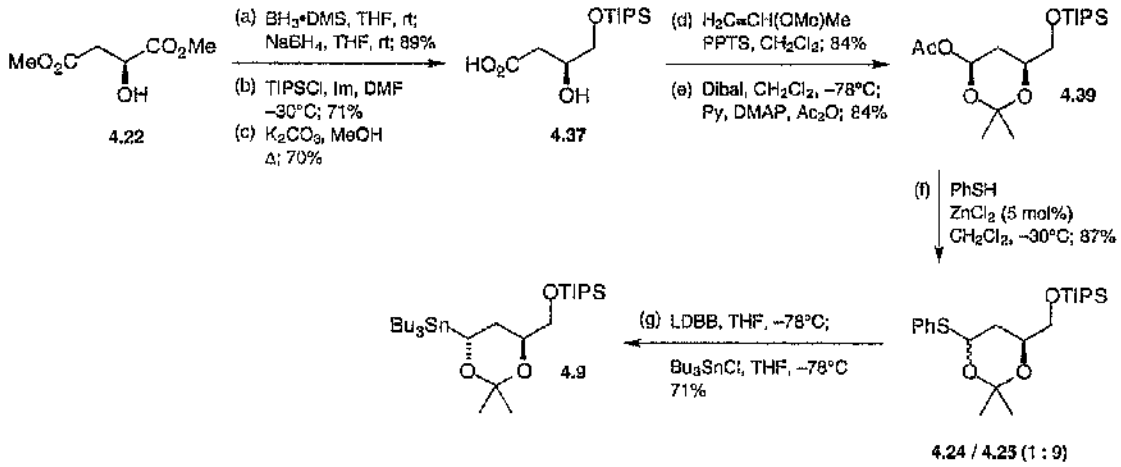
Scheme 4.16

LDBB (as a solution in THF) was prepared by a slight modification to the method of Freeman.[196] Reaction of lithium metal with 4,4′-di-*tert*-butylbiphenyl (DBB) often proceeded slowly and due to the intense dark blue colour of the resulting LDBB solution, it was difficult to assess when the lithium had been completely consumed. It was more practical to use an excess of Li to DBB in a known volume of THF and essentially perform a 'titration' of the LDBB solution by reaction with a small quantity of sulphides **4.24** / **4.25**. LDBB solution was added dropwise to a mixture of the sulphides in THF at –78°C until the dark blue colour of the radical anion persisted, at which time TLC confirmed the absence of sulphide and completion of the reductive lithiation. The concentration of the LDBB solution could then be calculated and the bulk of the solution used in a larger reaction, scaling the quantity of the sulphides appropriately. With this practical modification, stannane **4.9** could be produced efficiently, trapping organolithium $\mathbf{4.57_{Ax}}$ with Bu_3SnCl at low temperature. Stannane **4.9** was identified as the desired axially substituted isomer by comparison of the acetal methyl carbon shifts (δ 24.9, 24.7 ppm, Scheme 4.17) with those reported by Rychnovsky (δ 24.7, 24.5 ppm).[189] The epimeric equatorial stannane has significantly different chemical shifts for the acetal methyls (δ 29.9, 18.6 ppm).[189] In principle, axial organolithium species **4.57** could have been directly transmetallated to the corresponding alkylcopper, but this was not done for convenience and also because meagre precedent suggests that the thiophenoxide anion formed during reductive lithiation can act as a nucleophile with cationic molybdenum complexes.[61]



Scheme 4.17

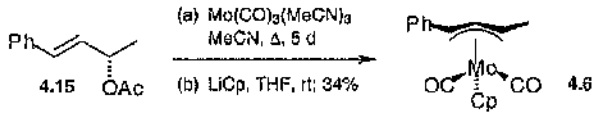
Our final route to stannane **4.9**, the immediate precursor to organocopper(I) nucleophile **4.2** is summarised below (Scheme 4.18).



Scheme 4.18

4.4 - Preparation of neutral complex 4.6 and initial attempts at the key coupling step.

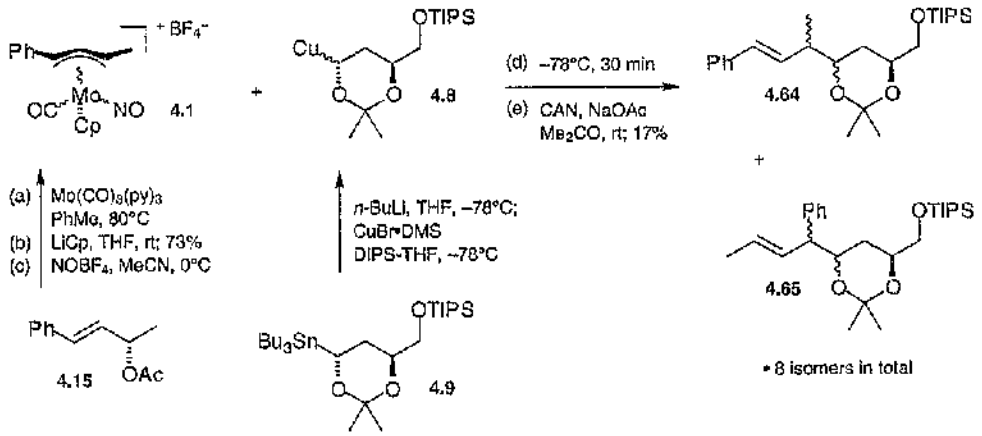
With viable routes to stannane **4.9** and allylic alcohol **4.10** in place, we turned our attention to the formation and use of neutral complex **4.6**, which proved more difficult than had been initially envisaged. Oxidative addition of acetate **4.15** to $Mo(CO)_3(MeCN)_3$ was slow (Scheme 4.19), requiring 5 days in refluxing acetonitrile for completion by TLC. The isolated yield of neutral complex **4.6** following ligand exchange with LiCp was poor (34%). To overcome the problem of the low reactivity of **4.6**, two approaches were considered, to increase the reactivity of the allylic ester or to increase the reactivity of the Mo(0) complex to which the allylic ester oxidatively adds.



Scheme 4.19

The second approach was investigated initially, as various systems of the type $Mo(CO)_3(L)_3$ are known, where L = DMF,[12] pyridine[13] or $(L)_3$ = PhMe[14] amongst others. $Mo(CO)_3(DMF)_3$ has found wide applicability as a Mo(0) source for the formation of π-allyl molybdenum complexes, but has the practical limitation of being difficult to handle,[22] and more seriously for our purposes the stereochemical consequences of the oxidative addition of enantiopure allylic acetate systems vary with several factors such as temperature, solvent and rate of addition of acetate.[60] Of the various possible Mo(0) sources, $Mo(CO)_3(py)_3$, first reported in 1935 by Hieber appeared promising.[13] Pearson has compared the rate of reaction of various allylic acetate systems with $Mo(CO)_3(py)_3$ and $Mo(CO)_3(MeCN)_3$, concluding that the pyridine based system is of greatly increased reactivity.[22]

$Mo(CO)_3(py)_3$ was prepared from $Mo(CO)_6$ by refluxing in pyridine for 3 hours, followed by cooling and precipitation with pentane, yielding a yellow crystalline solid in 86% yield.[22] As hoped, $Mo(CO)_3(py)_3$ was more reactive than $Mo(CO)_3(MeCN)_3$, oxidative addition with acetate **4.15** being complete by TLC within 3 h in refluxing toluene, or 20 h at 90°C, to give neutral complex **4.6** in 73% yield. $Mo(CO)_3(MeCN)_3$ is known to react with enantiopure allylic acetates with retention of configuration,[50, 53, 57-59] but the consequences of oxidative addition to $Mo(CO)_3(py)_3$ were unknown. It soon became apparent that stereocontrolled oxidative addition was not occurring, as coupling of alkylcopper(I) reagent **4.8** with cationic complex **4.1** gave a complex mixture of olefin products **4.64** and **4.65** in poor yield (17%), following oxidative decomplexation with CAN (Scheme 4.20). The isolation of a trace amount of olefins corresponding to diol analogs of **4.64** and **4.65** indicated that the acetonide diol protecting group was not stable under the CAN decomplexation conditions. Analytical HPLC and GCMS studies revealed a total of 8 diastereomeric olefins **4.64** and **4.65** were present, indicating not only that neutral complex **4.6** had been formed without complete facial control, but also that nucleophile **4.8** was configurationally unstable and exhibited poor regioselectivity in coupling with electrophile **4.1**.



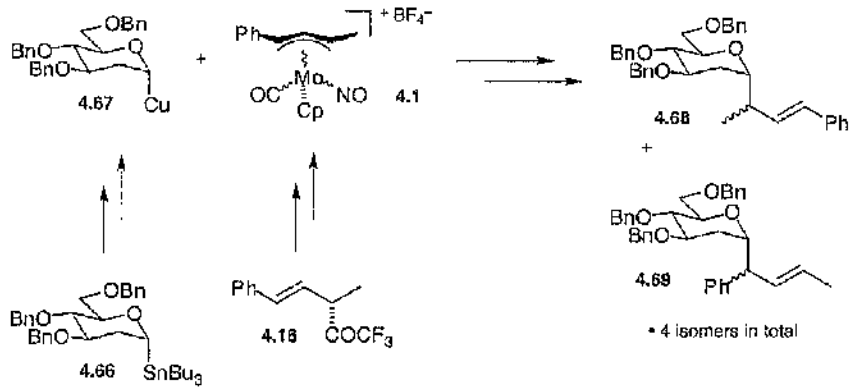
Scheme 4.20

Investigations into the use of $Mo(CO)_3(py)_3$ were discontinued, as it appeared that a lengthy investigation of reaction parameters such as temperature, solvent and concentration would have been required before a judgement upon its viability as a Mo(0) source could be made, and the more attractive option of increasing the activity of the allylic ester component was investigated. Kuhl has subsequently investigated the $Mo(CO)_3(py)_3$ system, and established that $Mo(CO)_4(py)_2$ is the main component in solution, as described in Chapter 1, section 1.2.2. Application of the $Mo(CO)_4(py)_2$ system to the Cryptophycin investigation is described later in this chapter.

4.5 - Alterations to the electrophilic and nucleophilic coupling partners used in the Fragment A key step.

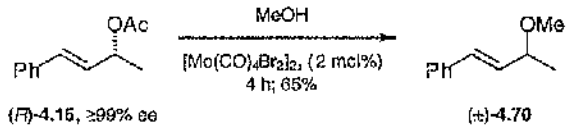
The formation of a total of 8 diastereomers in the reaction of cationic complex **4.1** and the nucleophile derived from stannane **4.9** indicated that three separate problems were occurring in the attempted coupling reaction. The two most serious problems, those involving the failure to control the stereochemistry at both of the newly formed stereocentres are discussed below, and the third problem, that of the poor regiocontrol in nucleophilic addition to cationic complex **4.1**, is dealt with in sections 4.7 and 4.8.

To overcome the problem of the lack of facial selectivity in the formation of neutral complex **4.6** from an enantiopure allylic ester precursor, we returned to the $Mo(CO)_3(MeCN)_3$ system, as precedent suggested this source of zerovalent molybdenum for stereocontrolled oxidative addition to form η^3-allyl complexes was the most reliable.[50, 53, 57-59] The need for a more activated leaving group in an analogous system to acetate **4.15** was obvious. As an extreme alternative, trifluoroacetate **4.16**[17] was synthesised. Trifluoroacetate **4.16** could be prepared, purified by column chromatography and used immediately, but was unstable upon storage, a neat sample decomposing to a black oil upon storage overnight at ambient temperature. Unsurprisingly, oxidative addition of **4.16** to $Mo(CO)_3(MeCN)_3$ was much faster than that of the corresponding acetate, addition being complete after 12 h at rt followed by 1 h at reflux, or after 2 d at rt. Trifluoroacetate **4.16** was not a viable precursor to planar chiral cationic complex **4.1**, as coupling of **4.1** with nucleophile **4.67** (derived from stannane **4.66**[64]) resulted in a complex mixture of products following decomplexation (Scheme 4.21). The presence of four C-glycosides was indicated by a complex mixture of signals in the vinylic region of the ^{1}H NMR spectrum, and four methyl doublet resonances. The mixture of products is presumed to be **4.68** and **4.69** below, as the configurational stability of nucleophile **4.67** in coupling with η^3-allylmolybdenum complexes has already been established.[53, 61]



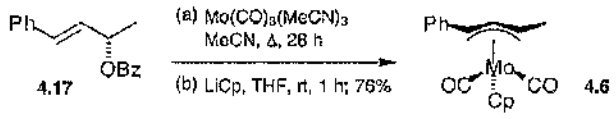
Scheme 4.21

The loss of facial control in the formation of **4.6** is probably due to racemisation of trifluoroacetate **4.16** under the reaction conditions. When a sample of **4.16** was treated under the conditions originally used for the oxidative addition (rt, o/n; Δ, 1 h) in the absence of $Mo(CO)_3(MeCN)_3$ and then concentrated *in vacuo*, ^1H NMR spectroscopy indicated significant decomposition with multiple peaks in the δ 6.50-5.00 ppm region and the crude mixture was optically inactive. Decomposition and loss of optical activity in the absence of $Mo(CO)_3(MeCN)_3$ ruled out the possibility of a racemisation mechanism involving coordination of the carbonyl group of **4.16** to molybdenum and ionisation to form an allylic cation and a coordinated trifluoroacetate anion. An ionic, S_N1-like mechanism of this type has been proposed by Kocovsky and co-workers to explain racemisation in the formation of allylic ether **4.70** in an investigation of Lewis-acid type Mo(II) catalysed allylic substitutions (Scheme 4.22).[199]



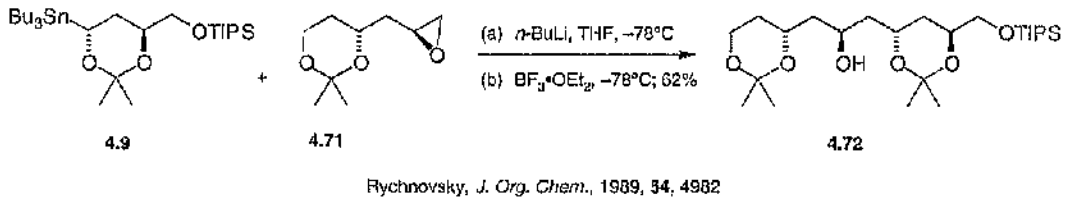
Scheme 4.22

The chemical and configurational instability of trifluoroacetate **4.16** obviously precluded its use, and an alternative ester with greater reactivity than acetate **4.15** was found in the form of crystalline benzoate **4.17** (Scheme 4.23).[200] Oxidative addition of **4.17** to $Mo(CO)_3(MeCN)_3$ was complete by TLC after 28 h in refluxing MeCN, and after LiCp ligand exchange in the normal fashion, neutral complex **4.6** was isolated in good yield (76%). With the precedent that oxidative addition of enantiopure allylic acetates to $Mo(CO)_3(MeCN)_3$ is cleanly retentive, it was assumed that the problem of facial control in the formation of neutral complex **4.6** was now overcome, and attention turned to the problems encountered with the configurational instability of alkylcopper reagent **4.8**.

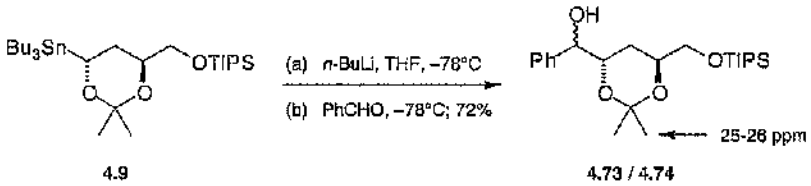


Scheme 4.23

Tin-lithium exchange of stannane **4.9** and retentive reaction with electrophile **4.71** has been reported by Rychnovsky (Scheme 4.24).[179] We confirmed the configurational stability of organolithium $\mathbf{4.57_{Ax}}$ by reaction with benzaldehyde to return axial alcohols **4.73** and **4.74**. Retention at C4 was indicated by the characteristic acetal methyl carbon shifts.

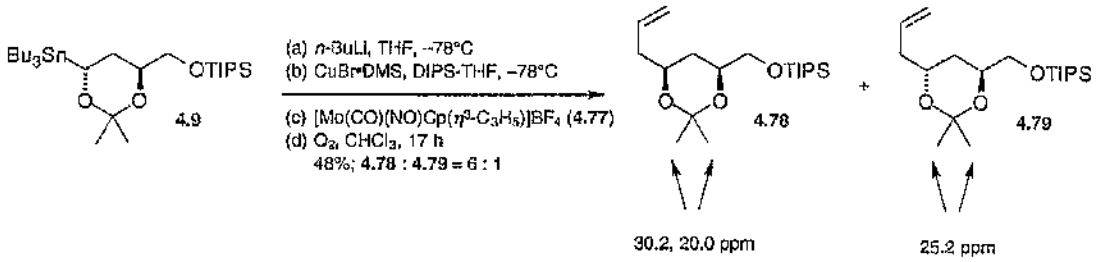


Rychnovsky, *J. Org. Chem.*, 1989, 54, 4982



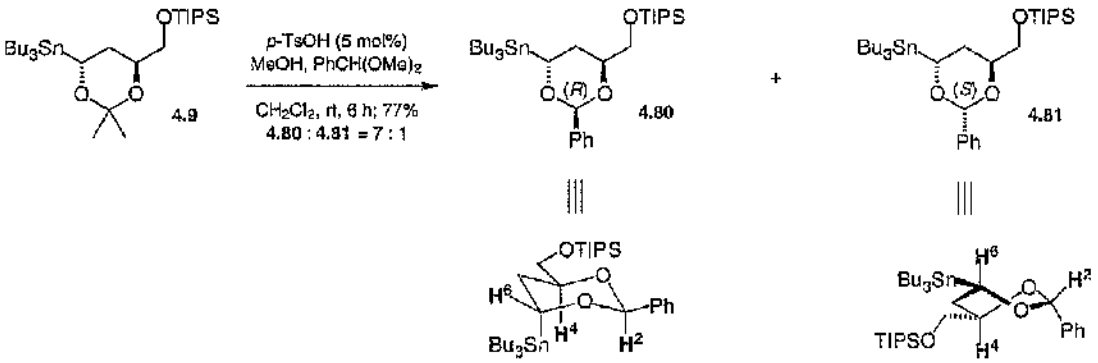
Scheme 4.24

Configurational instability of organocopper(I) reagent **4.8** therefore appeared to be the problem, and in order to confirm this, **4.8** was coupled with simple allyl molybdenum complex **4.77** to yield olefins **4.78** and **4.79** in a 6 : 1 ratio (Scheme 4.25). Oxidative cleavage of the metal fragment was achieved by bubbling a stream of O_2 through a chloroform solution of the crude η^2-olefin molybdenum products, an extension of a precedented protocol utilising decomplexation by exposure to air.[9] The new procedure allowed the isolation of olefins **4.78** and **4.79** without the complication of cleavage of the acetonide protecting group, and was subsequently adopted for all other decomplexation steps in the Cryptophycin investigation. The configuration of the major (equatorial) isomer **4.78** was identified by the large diaxial coupling between H6 and H5 (J 11.6 Hz) and confirmed by the acetal methyl ^{13}C shifts.



Scheme 4.25

The origin of the configurational instability of the organocopper(I) species **4.8** is presumably an unfavourable steric interaction between the axial methyl group of the acetonide protecting group and the axial copper substituent. To minimise this steric interaction, the isopropylidene acetal was changed to a benzylidene acetal, with the consequent replacement of the axial methyl group by a proton. α-Hydroxy stannanes are reasonably unstable,[201] and a one-pot transacetalisation strategy was employed, converting stannane **4.9** into a 7 : 1 mixture of acetal isomers **4.80** and **4.81** under acidic conditions in the presence of methanol and an excess of benzaldehyde dimethyl acetal (Scheme 4.26).[202] Isomers **4.80** and **4.81** were separable by repeated column chromatography. Undesired stannane **4.81** could be recycled under the above conditions, yielding an 11 : 1 mixture of isomers **4.80** and **4.81** in 83% yield. Major isomer **4.80** was identified as the desired (2*R*)-epimer shown below, where the bulky phenyl group occupies an equatorial position. The conformation of **4.80** was based upon nOe studies, with enhancements of H2 observed upon irradiation of H4, and vice-versa. Similarly, minor isomer **4.81** had the (2*S*)-configuration, the larger than expected ^3J coupling of H^6 to H^5 (13.7 Hz) presumably resulting from the distortion of the ring to alleviate steric strain between the diaxial phenyl and tributylstannyl groups at C2 and C6 respectively. nOe studies suggested a twist-boat conformation for stannane **4.81**, as suggested by Rychnovsky for the analogous acetonide protected stannane **4.9**.

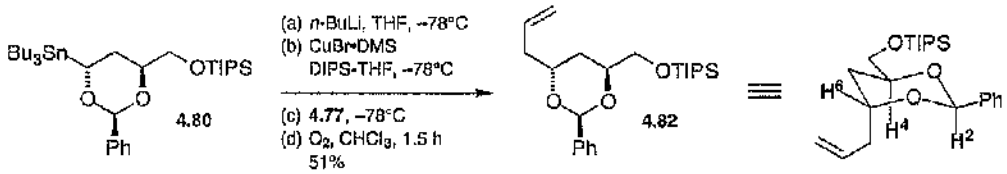


	ppm	^3J (Hz)	nOe
H^2	5.81	-	16% → H^4
H^4	4.26	10.7, 6.9, 5.2, 2.4	10% → H^2
H^6	5.16	6.4	-

	ppm	^3J (Hz)	nOe
H^2	5.73	-	13% → H^6
H^4	4.17-4.12	-	6% → H^5
H^6	4.59	13.7, 2.3	14% → H^2

Scheme 4.26

The configurational stability of the alkylcopper(I) reagent **4.2** derived from stannane **4.80** was established by coupling with allyl cationic complex **4.77**, to yield a single olefin product **4.82** in moderate yield after decomplexation (Scheme 4.27). Retention of the axial configuration at C6 is indicated by the small (^3J = 6.9 Hz) coupling between the C6-proton and the two methylene protons at C5, and confirmed by nOe studies, with a 16% enhancement of H6 observed upon irradiation of the acetal proton and a 12% enhancement in the opposite direction. Zero enhancement of H6 upon irradiation of H4 and vice-versa was also seen.

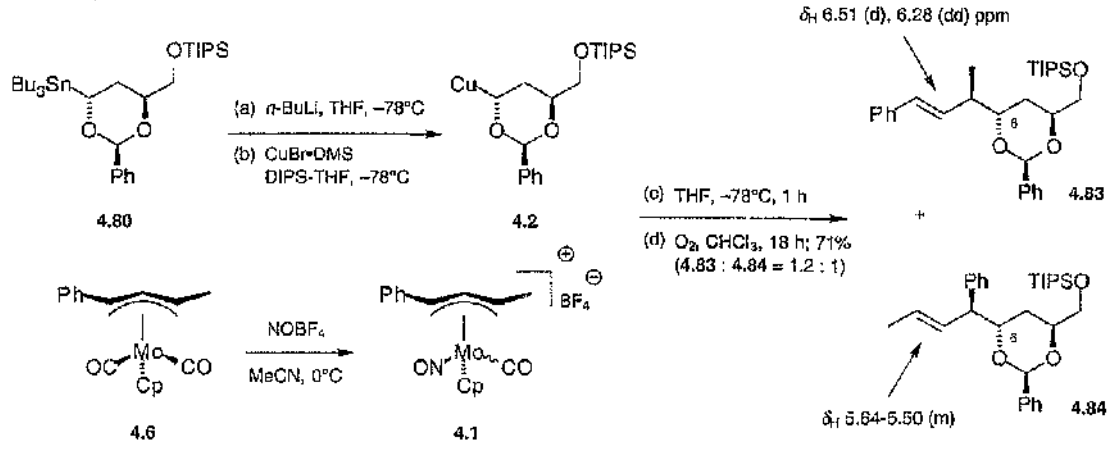


	ppm	^3J (Hz)	nOe
H^2	5.84	-	16% → H4
H^4	4.18	11.0, 5.9, 2.5	10% → H2
H^6	4.35	6.9	-

Scheme 4.27

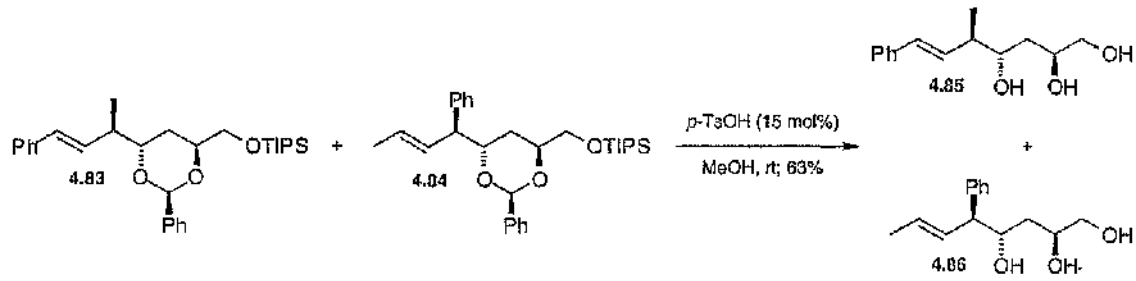
4.6 - Completion of the total synthesis of Cryptophycin 4.

We were now in a position to address the key coupling step in the Cryptophycin fragment A synthesis again, with modified electrophilic and nucleophilic coupling partners. Stannane **4.80** was converted in the normal fashion to organocopper(I) reagent **4.2** and a freshly prepared solution of complex **4.1** in MeCN was added at low temperature. After a 1 hr reaction time, aqueous workup was followed by decomplexation (O_2, $CHCl_3$) and a mixture of olefins **4.83** and **4.84** was isolated in 71% yield (Scheme 4.28). ^{1}H NMR spectroscopy revealed a ratio of **4.83** : **4.84** of 1.2 : 1, estimated by integration of the vinylic proton peaks at 6.51 / 6.28 ppm and 5.64-5.50 ppm respectively. A mixture of a further pair of regioisomeric olefins was also obtained in <5% yield, subsequently identified as epimers at C6 as described below in section 4.7, indicating that the configurational stability of alkylcopper(I) species **4.2** was excellent though not perfect.



Scheme 4.28

Regiosiomeric olefins **4.83** and **4.84** were inseparable, but cleavage of the silyl and acetal protecting groups in one step under acidic conditions allowed the isolation of triols **4.85** and **4.86** which could be separated, albeit with some difficulty, by column chromatography (Scheme 4.29).

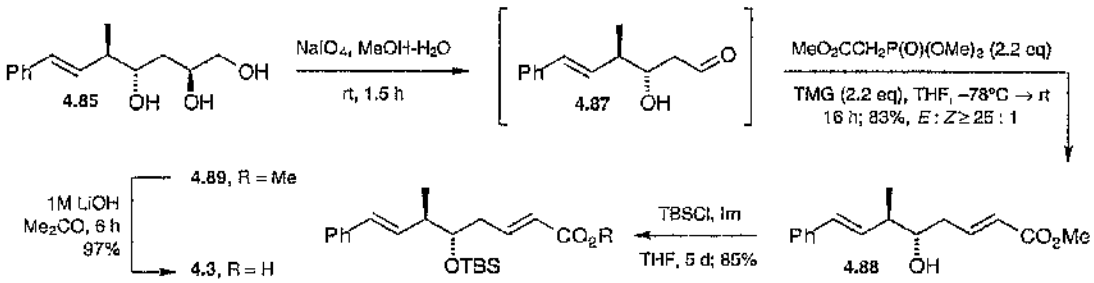


Scheme 4.29

Desired triol **4.85** was subjected to sodium periodate-mediated oxidation to reveal β-hydroxy aldehyde **4.87** which was isolated and used without further purification (Scheme 4.30). A Wadsworth-Horner-Emmons olefination using trimethylphosphonoacetate and tetramethylguanidine in THF at low temperature[128] subsequently yielded ester **4.88**. Analysis of the ^{1}H NMR spectrum of **4.88** revealed that the newly formed (*E*)-olefin was geometrically pure within the limits of NMR spectroscopy. An initial attempt at the olefination using *n*-BuLi and trimethylphosphonoacetate at 0°C[203] was unsuccessful, the desired olefin product only being isolated in 19% overall yield, and as a 4:1 mixture of *E*:*Z* isomers. Comparison of spectroscopic data and optical rotation for **4.88** to that of the literature compound confirmed the absolute stereochemistry at C5 and C6, which up to now had been assumed in structures **4.83** and **4.85**, and by analogy in regioisomeric compounds **4.84** and **4.86**. The comparison of spectroscopic data indicated the key coupling step between complex **4.1** and organocopper(I) reagent **4.2** had occurred with overall retention at the

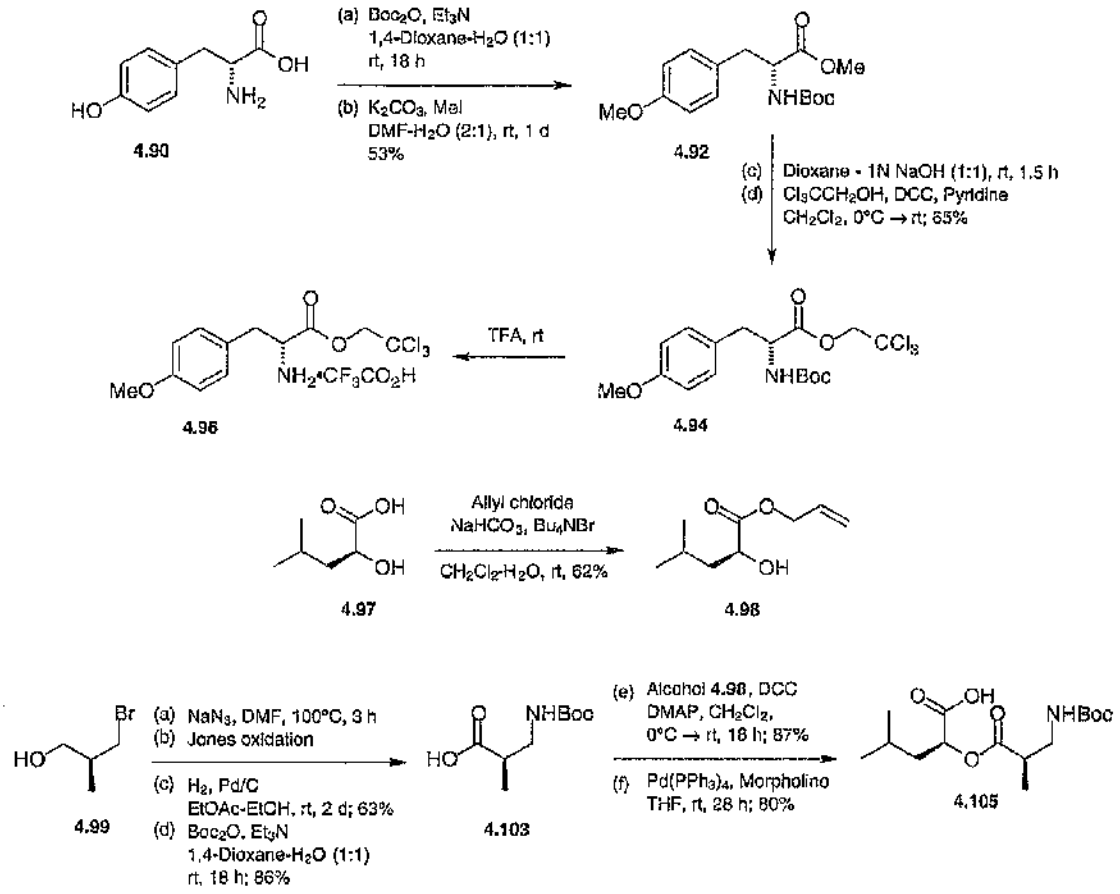
carbon of **4.2** which originally bore the tributylstannyl moiety, and confirmed the formation of neutral complex **4.6** from benzoate **4.17** with retention.

Formation of olefin **4.88** constituted a formal synthesis of Cryptophycin 4, and from here onwards precedent established by Moore and Tius was utilised to a large extent to complete the total synthesis.[128] The free hydroxyl group in ester **4.88** was efficiently, albeit slowly protected as the *tert*-butyldimethylsilyl ether by treatment with an excess of TBSCl and imidazole in THF at ambient temperature (Scheme 4.30). The analogous transformation using TBSOTf and 2,6-lutidine yielded silyl ether **4.89** in only 63% yield, together with the corresponding δ-hydroxy acid (15%). Lithium hydroxide mediated ester cleavage[128] yielded acid **4.3**, from where the elaboration of the remaining 3 fragments of the Cryptophycin skeleton could be addressed.



Scheme 4.30

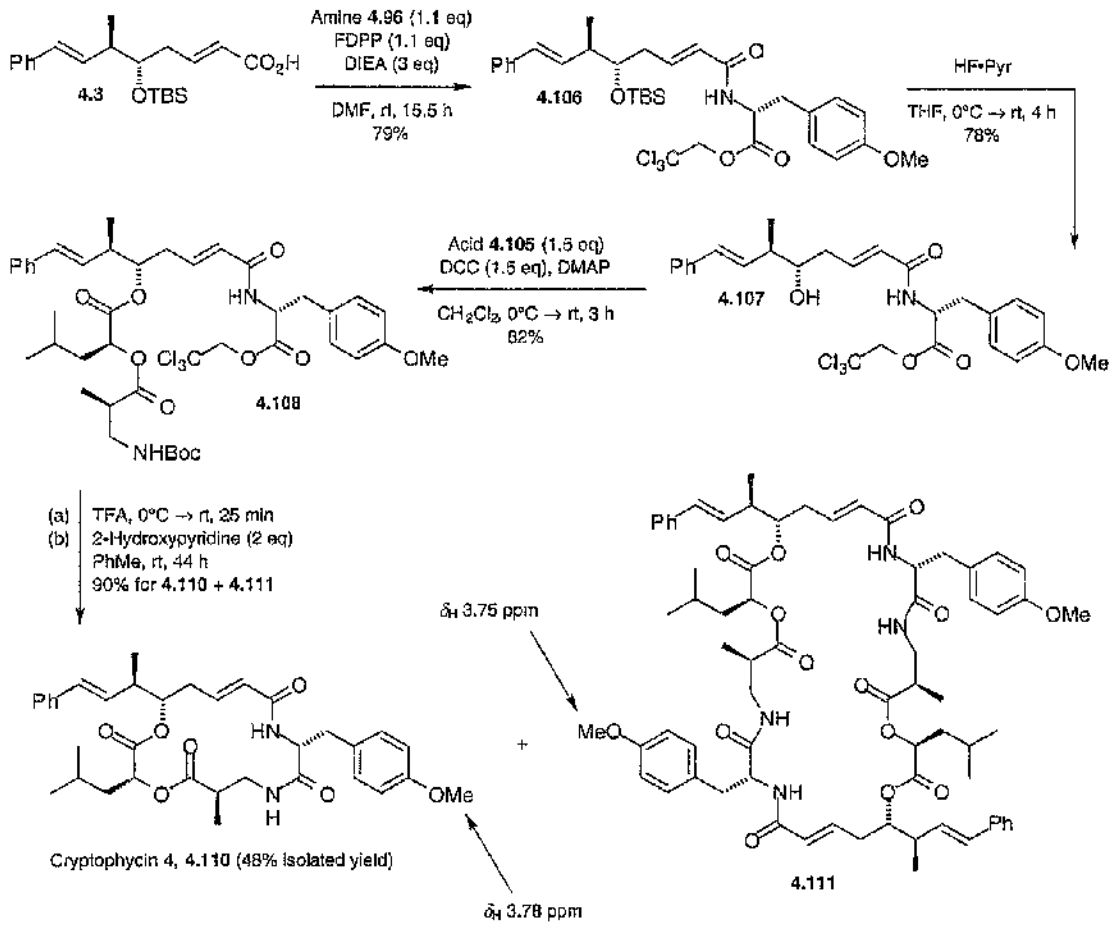
D-Tyrosine (**4.90**) was elaborated to trichloroethyl ester **4.94** in a straightforward four step sequence (Scheme 4.31); amino protection, dimethylation, selective cleavage of the methyl ester and DCC-mediated esterification of the resulting acid with trichloroethanol.[128, 204, 205] Treatment of ester **4.94** with neat TFA yielded trifluoroacetate salt **4.96** which was dried *in vacuo* and used immediately without further purification. Cryptophycin fragments C and D were prepared according to standard procedures without difficulty. Allylation of commercially available L-leucic acid[128] yielded ester **4.98** which was coupled under DCC conditions with acid **4.103**, prepared from (*R*)-3-bromo-2-methyl-propanol **4.99** by displacement of the bromide with azide, Jones oxidation, azide reduction and Boc-protection of the resulting amine.[142] Pd-catalysed allyl cleavage yielded fragment C-D acid **4.105**.[128]



Scheme 4.31

Amide **4.106** was prepared in 79% yield under conditions reported by Moore and Tius using pentafluorophenyl diphenylphosphinate (FDPP) promotion (Scheme 4.32).[128] Cleavage of the *tert*-butyldimethylsilyl ether protection proceeded efficiently using pyridinium poly(hydrogen fluoride) in THF solution. Attempted cleavage using aqueous acetic acid in THF[206] was unsuccessful. Coupling of alcohol **4.107** with fragment C-D acid **4.105** then yielded ester **4.108** in good yield, from where a cyclisation protocol communicated by Fray[167] was used to complete the total synthesis of Cryptophycin 4. TFA mediated Boc cleavage was followed by basic workup and dissolution of the crude amine in toluene (0.02M), to which 2-hydroxypridine (2 eq) was added. A smooth cyclisation occurred (48 h, rt) to yield a mixture of Cryptophycin 4 (**4.110**) and a component subsequently identified as dimer **4.111**. The ratio of **4.110** to **4.111** was estimated as 4 : 1, based on the integration of the tyrosine methoxy singlets at 3.78 and 3.75 ppm respectively in the ^{1}H NMR spectrum. The overall combined yield of **4.110** and **4.111** for the Boc cleavage-cyclisation protocol was 90%, and after separation by preparative TLC pure Cryptophycin 4 was obtained in 48% isolated yield from **4.108**. Spectroscopic data were in excellent accordance with those reported by Moore and Tius, concluding the total synthesis of Cryptophycin 4.[128] Increasing the dilution of the cyclisation reaction from the 0.02M which had been specified by Fray to

0.005M increased the ratio of **4.110** to **4.111** to 9 : 1, albeit with a lower overall yield (59%), and an extended reaction time (4 d).



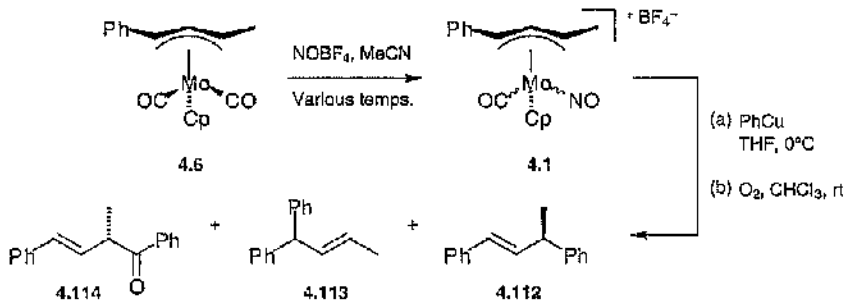
Scheme 4.32

4.7 - Studies directed towards improving regiocontrol in the coupling of complex 4.1 and nucleophile 4.2.

Minimal regiocontrol was observed in the addition of organocopper(I) reagent **4.2** to cationic complex **4.1** in the synthesis of Cryptophycin 4, in contrast to alkylations described in Chapter 2 using complexes **2.1** / **2.2** in which good regioselectivity between the methyl and *iso*-propyl termini of the allylic unit had been observed. The poor regioselectivity exhibited by complex **4.1** is presumably a reflection of the similar steric requirements of the phenyl and methyl termini, allowing the electronic directing effect of the nitrosyl ligand to be the dominant factor affecting regioselection.[50] The minimal selectivity in carbonyl - nitrosyl exchange was illustrated by ^{1}H NMR spectroscopy of **4.1**, the relative ratios of diastereomers at the metal centre approximately paralleling the observed ratio of olefin products following alkylation. Complex **4.1** initially appeared as a pair of 2 major isomers, in the approximate

ratio 1.2 : 1. Upon standing in CD_3CN solution, the mixture isomerised to a mixture of 4 compounds, presumably 2 pairs of *exo* and *endo* isomers, in the ratio 2.3 : 2 : 1 : 1.2, as estimated from the intensities of cyclopentadienyl singlets at 5.69, 6.11, 6.22, and 6.02 ppm respectively, indicating minimal selectivity in the ligand exchange step.[50]

It was hoped that the diastereoselectivity of carbonyl - nitrosyl exchange, and consequently the regioselectivity of nucleophilic attack upon complex **4.1**, could be biased by varying the temperature at which ligand exchange was performed. Phenylcopper was chosen as a simple nucleophile for the investigation (Scheme 4.33). The results of a series of alkylations are summarised in the table below. Interestingly, in each case a significant amount (8-13%) of ketone byproduct **4.114** was isolated, apparently arising *via* attack of the nucleophile upon the carbonyl ligand of **4.1** prior to acylation of the η^3-ligand. Despite a mixture of regioisomeric 'normal' alkylation products **4.112** and **4.113** being obtained, ketone **4.114** was isolated as a single regioisomer. The (*S*)-stereochemistry suggested for **4.114** is that which would result from attack *syn* to the metal, though the absolute configuration of **4.114** has not been determined.



Scheme 4.33

Entry	Temperature of cation formation	Overall yield of 4.112 / 4.113	4.112 : 4.113	Yield of 4.114
1	18°C	73%	1 : 2.3	8%
2	0°C	59%	1 : 2.1	10%
3	–40°C	50%	1 : 1.4	11%
4	–80°C[a]	47%	1 : 1.8	13%
5	18°C[a]	56%	1 : 2.5	10%
6	18°C[b]	53%	1 : 3.8	13%
7	18°C[c]	62%	1 : 2.1	10%

[a] Complex **4.1** prepared in EtCN solution as opposed to MeCN.

[b] Cation added to phenyl copper solution at –80°C as opposed to 0°C.

[c] $N_{2(g)}$ bubbled through cation solution before addition to PhCu solution at 0°C.

Several observations were made from the above experiments ;

(a) In all cases the proportion of regioisomer **4.113** arising from nucleophilic attack upon the phenyl terminus of the allylic unit dominates, in contrast to the use of Cryptophycin nucleophile **4.2**, where a slight (≈ 1.2 : 1) preference for attack at the methyl terminus is apparent.

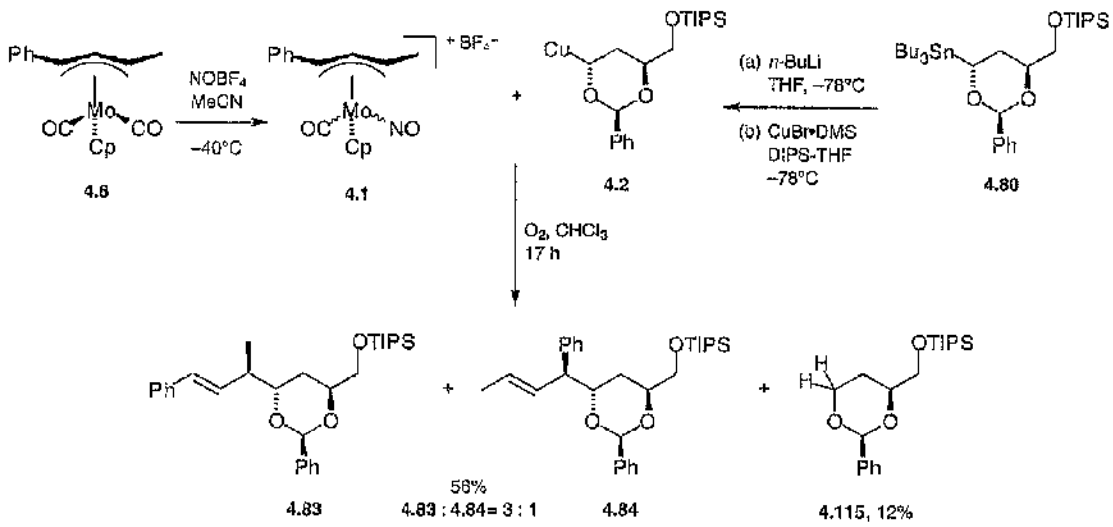
(b) As the temperature at which cationic complex **4.1** is formed in MeCN solution decreases, the proportion of alkylation product resulting from attack at the methyl terminus of the allylic unit increases. (Entries 1-3).

(c) The use of MeCN as a solvent for the formation of cationic complex **4.1** is restricted by the freezing point (mp = –48°C) and it was envisaged that the use of EtCN (mp = –93°C) would allow a further biasing of the regioselectivity in favour of isomer **4.112**. However, the use of EtCN as a solvent for cation formation at –80°C resulted in a greater proportion of isomer **4.113** than had been observed at –40°C in MeCN, as was also the case at rt (entry 5 *vs* entry 1), indicating that the nature of the solvent as well as the reaction temperature plays a role in the carbonyl-nitrosyl exchange process.

(d) Lowering the temperature of the nucleophile solution from 0°C to –80°C before addition of the electrophile solution resulted in greater selectivity for the 'undesired' sense of attack and formation of **4.113**. (Entries 1 and 6). However, in the Cryptophycin case the need for the nucleophile to be kept at low temperature (–80°C) precludes operation at 0°C and the apparent favourable effect upon regioselectivity.

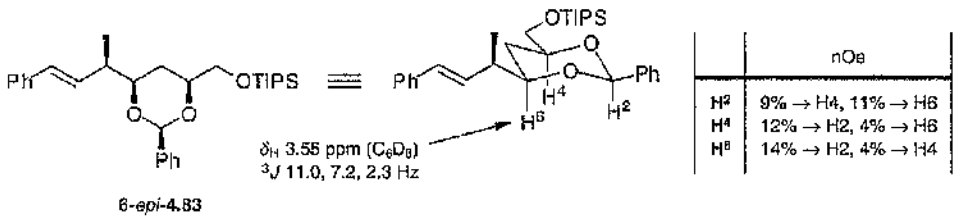
(e) Thoroughly degassing the solution of cationic complex before addition to the PhCu solution did not reduce the yield of ketone **4.114**, allowing dissolved carbon monoxide in the reaction medium to be discounted as the origin of the carbonyl group. Ketone **4.114** has optical activity, although the absolute configuration of the methyl group in **4.114** has not been determined.

The most favourable regiocontrol with PhCu as nucleophile was obtained when carbonyl-nitrosyl exchange was performed at –40°C and these conditions were applied to the coupling of nucleophile **4.2** with complex **4.1** (Scheme 4.34). The desired regioisomeric dioxane **4.83** was obtained together with regioisomer **4.84** in approximately a 3 : 1 ratio, a moderate improvement over the 1.2 : 1 ratio obtained initially. A minor, inseparable contaminant was identified as oxane **4.115** by independent synthesis (*n*-BuLi, THF, –78°C, 30 min; NH_4Cl, ≈100%) from stannane **4.80**.



Scheme 4.34

As in the initial coupling reaction *en route* to Cryptophycin 4, a small amount (7%) of a mixture of 2 further olefin regioisomers 6-*epi*-**4.83** and 6-*epi*-**4.84** was also obtained (Scheme 4.35), tentatively assigned as epimers at C6 on the basis of a large (^3J 11.0 Hz) coupling between H6 and H5 in 6-*epi*-**4.83**. The assignment was confirmed by nOe experiments, with large enhancements being observed between H2 and H4 and vice versa, and between H2 and H6 and vice versa, indicating that protons at positions 2, 4 and 6 all occupy axial orientations.

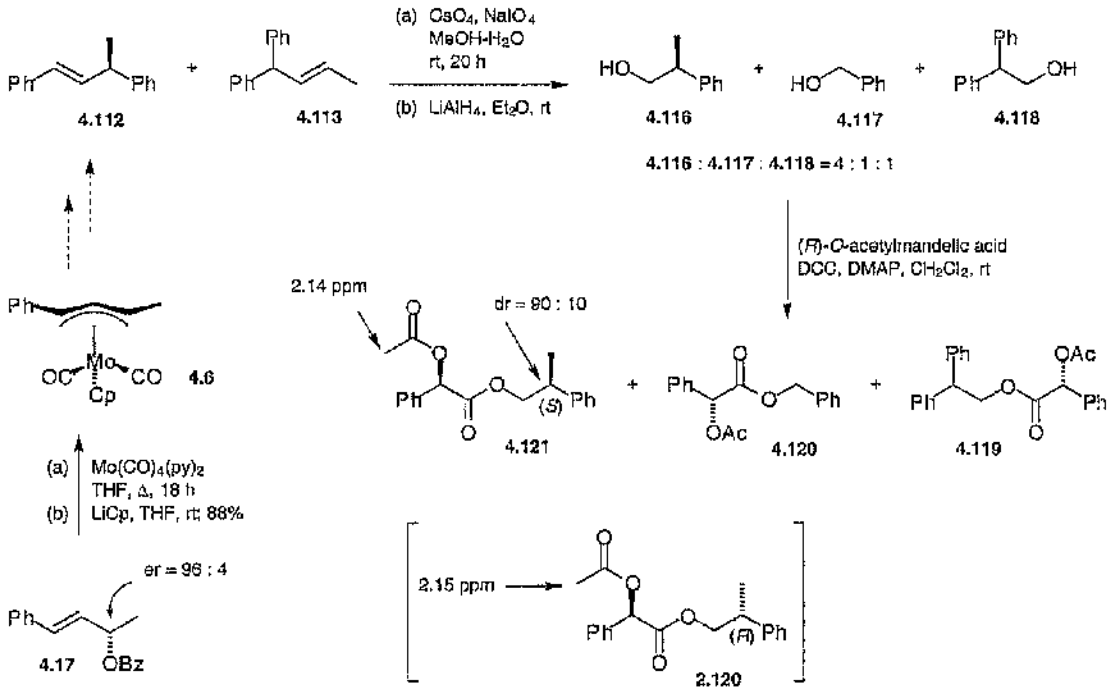


Scheme 4.35

The above studies using complex **4.1** and PhCu or nucleophile **4.2** were carried out with neutral complex **4.6** which had been prepared using $Mo(CO)_4(py)_2$ as the Mo(0) source, rather than $Mo(CO)_3(MeCN)_3$ which was used in the initial synthesis of Cryptophycin 4. Formation of the same olefin isomers **4.83** and **4.84** which had been observed in the initial coupling procedure confirmed that formation of neutral complex **4.6** was cleanly retentive, as in the case with $Mo(CO)_3(MeCN)_3$ and benzoate **4.17**.

The retentive nature of the oxidative addition of benzoate **4.17** to $Mo(CO)_4(py)_2$ was also confirmed by derivatisation of olefin **4.112** isolated from the addition of PhCu to neutral

complex **4.6** (Scheme 4.36). Olefin regioisomers **4.112** and **4.113** were barely separable by column chromatography which complicated matters to an extent. Despite this, it was envisaged that oxidative cleavage of the olefins followed by reduction would result in a mixture of alcohols **4.116**, **4.117** and **4.118**, which could be further derivatised as (*R*)-*O*-acetylmandelate esters in order to identify the absolute stereochemistry of the methyl group in olefin **4.112**, and estimate the enantiopurity. A mixture of olefins **4.112** and **4.113** (**4.112** : **4.113** = 5 : 1) was subjected to dihydroxylation and diol cleavage using OsO_4 (10 mol%) and $NaIO_4$ to yield a mixture of crude aldehydes. Reduction using $LiAlH_4$ yielded an inseparable mixture of alcohols **4.116**, **4.117** and **4.118** in an approximate 4 : 1 : 1 ratio. Subsequent esterification with (*R*)-*O*-acetylmandelic acid yielded ester **4.121** (and esters **4.119** and **4.120**).



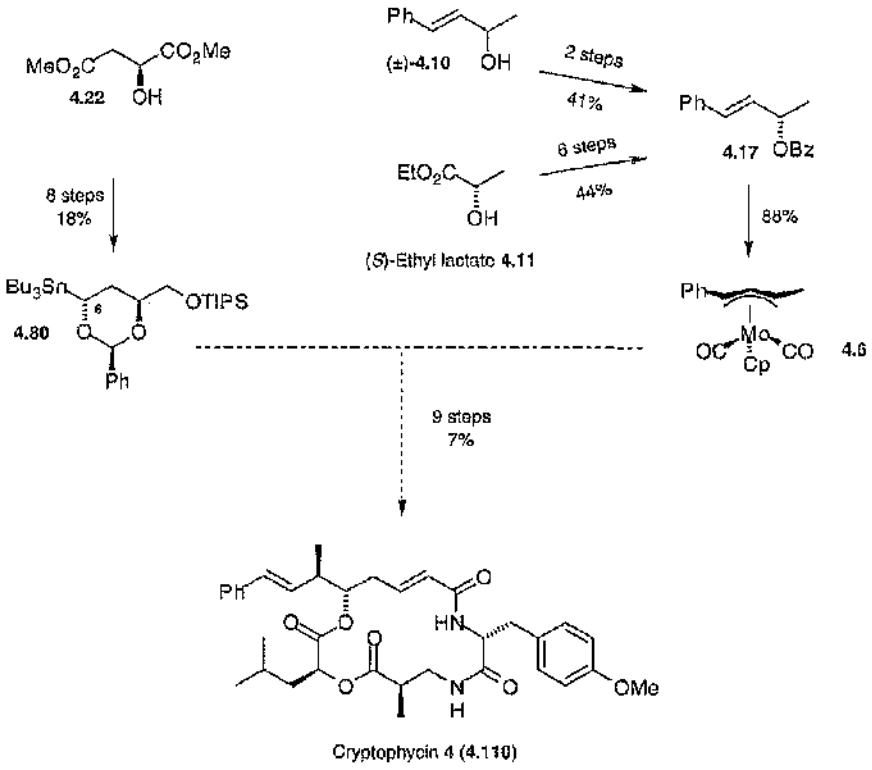
Scheme 4.36

As described in Chapter 2 (section 2.3), ester **2.120** had been prepared from a sample of (*R*)-**2.119** (identified as the (*R*)-enantiomer by comparison of the direction of the optical rotation with the literature value), and a mixture of esters (*RS*)-**4.121** had been prepared from (±)-**4.116**. Comparison of ^{1}H NMR data for ester **4.121** with that for **2.120** and (*RS*)-**4.121** allowed the stereochemistry of **4.116** (and by analogy that of olefin **4.112**) to be confirmed as *S*. The diastereomeric ratio at the methyl centre of ester **4.121** was conservatively estimated as 90 : 10 by integration of the acetate methyl singlets at 2.14 and 2.15 ppm ($CDCl_3$ + TMS) for the major and minor diastereomers respectively. Acetate singlets from esters **4.119** and **4.120** (at 2.18 and 2.08 ppm) did not interfere with the estimation of the dr of ester **4.121**.

The estimation of the diastereomeric ratio above should be viewed with some caution. Acetate methyl singlets from the diastereomeric esters formed from (±)-**4.116** and (*R*)-*O*-acetylmandelic acid were not completely baseline separated in ^{1}H NMR spectra run in $CDCl_3$, CD_3OD, C_6D_6 or CD_3CN. Attempts to analyse the dr by analytical HPLC or GCMS failed, with separation of peaks from the diastereomeric esters not being possible. Benzoate **4.17** (from which olefins **4.112** and **4.113** were ultimately derived) was itself estimated to have an enantiomeric ratio of 96 : 4. With the caveat that the estimated er of 90 : 10 for olefin **4.112** incorporates a degree of inaccuracy, it is nevertheless indicative that the oxidative addition of benzoate **4.17** to $Mo(CO)_4(py)_2$ and subsequently the addition of PhCu to complex **4.1** occurred in each case with excellent stereocontrol, giving olefin **4.112** as the product of overall inversion of configuration.

4.8 - Conclusions and future directions.

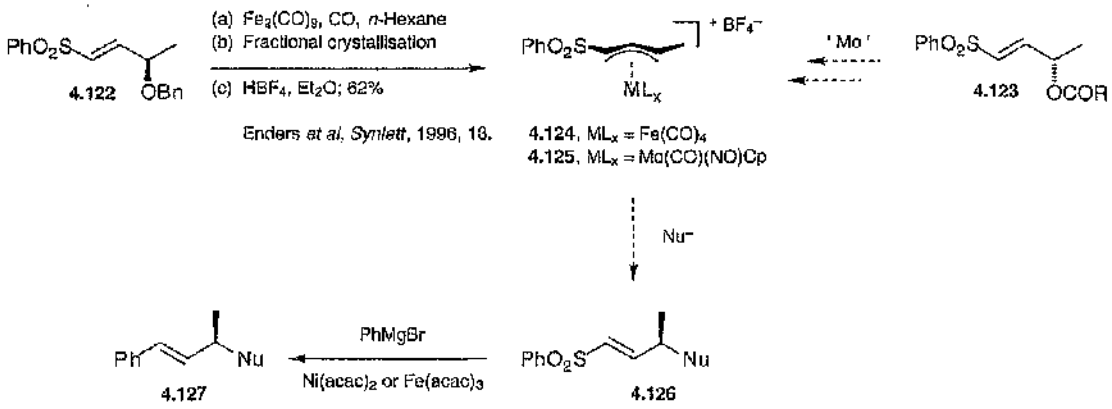
The synthesis of acid **4.3** and subsequently the total synthesis of Cryptophycin 4 has been achieved, utilising the ambitious union of novel cationic complex **4.1** and nucleophile **4.2**. Excellent control of two newly formed stereocentres has been achieved, albeit with poor regiocontrol. Viable routes to the electrophilic and nucleophilic coupling partner precursors **4.6** and **4.80** (Scheme 4.37) have been established, with serious problems encountered in both areas successfully overcome. Neutral complex **4.6** is prepared in enantiopure form *via* benzoate **4.17**, itself derived cheaply and easily from (*S*)-ethyl lactate **4.11** or by enzymatic resolution of (±)-**4.10**. Stannane **4.80** is similarly prepared from the chiral pool, with an efficient and highly selective reductive lithiation step securing the key (6*R*)-stereocentre which ultimately translates into C5 of Cryptophycin fragment A. Our synthesis of Cryptophycin 4 incorporates a high degree of flexibility, either enantiomer of complex **4.6** being available from the appropriate benzoate, and the epimeric nucleophile in principle being available *via* equilibration of alkyllithium **4.57**, or from carbamate **2.52** (Chapter 2, section 2.3.1). Either configuration at C5 and C6 in acid **4.3** could therefore be accessed by our synthetic route if desired.



Scheme 4.37

Regiocontrol in additions to complex **4.1** remains disappointing. Model studies using PhCu as nucleophile indicated that slight control over the site of nucleophilic attack could be obtained by varying the temperature at which carbonyl - nitrosyl exchange in the formation of **4.1** is performed, and also indicated that the regioselectivity is substrate dependant.

A long term solution to the problem of regiocontrol could possibly be provided by Enders' sulfone complex **4.124**[207] or the analogous molybdenum version **4.125** (Scheme 4.38). Formation of iron complex **4.124** is stereocomplementary to the molybdenum route, as oxidative addition occurs with inversion of configuration with respect to the allylic precursor. The regioselectivity of attack upon sulfone complex **4.124** is precedented to be excellent, the electron withdrawing effect of the sulfone group directing the nucleophile to the other end of the η^3-allyl unit, to yield vinyl sulfone **4.126** after decomplexation.[207] Nickel or iron catalysed coupling of Grignard reagents with vinylic sulfones has been reported to occur with a high degree of retention of olefin geometry,[208-211] which would in principle allow access to the Cryptophycins or analogs from vinyl sulfone **4.126**, and provide a flexible alternative to the use of problematic complex **4.1**.


(a) $Fe_2(CO)_9$, CO, *n*-Hexane
(b) Fractional crystallisation
(c) HBF_4, Et_2O; 62%
Enders *et al*, *Synlett*, 1996, 18.
4.122
4.123
4.124, $ML_x = Fe(CO)_4$
4.125, $ML_x = Mo(CO)(NO)Cp$
Nu⁻
PhMgBr
$Ni(acac)_2$ or $Fe(acac)_3$
4.126
4.127

Scheme 4.38

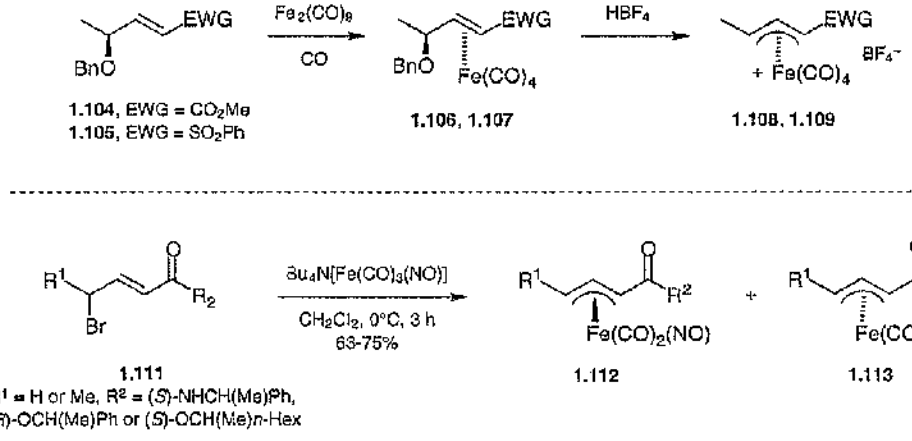
Chapter 5 - Summary of results and conclusions.

The following chapter briefly compares and contrasts allylic alkylation using planar chiral cationic η^3-allylmolybdenum complexes with: (a) stoichiometric iron-mediated allylic alkylations; (b) palladium-catalysed allylic alkylations. The achievements described in this thesis are summarised.

5.1 - Comparison between iron- and molybdenum-mediated stoichiometric allylic alkylation procedures.

As described earlier (Chapter 1, Section 1.6) important parallels exist between the stoichiometric use of cationic η^3-allylmolybdenum and cationic or neutral iron complexes. Enders' complexes **1.108 / 1.109** (Scheme 5.1) can be obtained with good control of planar chirality from enantiomerically pure allylic ethers **1.104 / 1.105**, the enantiopurity being dependant upon purification by repeated precipitation.[65, 124, 207] The steric bulk of the allylic ether directs the metal fragment in to the opposite face of the olefin, initially forming olefin complexes **1.106 / 1.107**. A second step forms cationic complexes **1.108 / 1.109** with overall inversion of configuration from **1.104 / 1.105**.

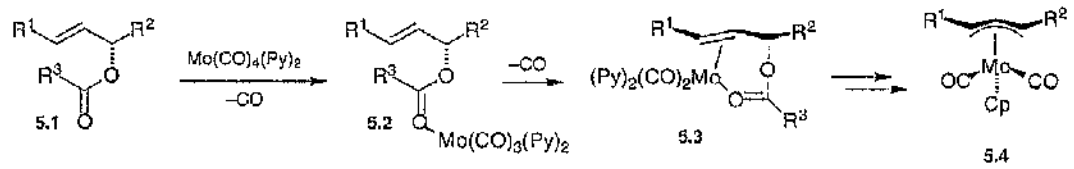
Control of chirality in formation of Nakanishi's complexes **1.112 / 1.113** relies upon the use of an attached chiral auxiliary to facilitate the separation of diastereomeric complexes.[66, 67] The stereoselectivity of an alternative preparation from optically active substrates is highly dependant upon the leaving group and solvent.[68]



Scheme 5.1.

Control of planar chirality in the formation of neutral (η^3-allyl)Mo(CO)$_2$Cp complexes **5.4** (precursors to the electrophilic cationic complexes) is highly reliable (Scheme 5.2), depending only upon the optical purity of readily available allylic esters. Tethering of

molybdenum to allylic ester **5.1** directs the metal to the face of the olefin proximal to the ester. Neutral complex **5.4** is formed with clean retention of configuration, which complements inversion obtained with iron.



Scheme 5.2.

Both the Enders and Nakanishi complexes are achiral at the metal, and as a result regioselectivity between the allylic termini is controlled by steric or electronic factors alone. In contrast, regiocontrol in the molybdenum chemistry is complicated by a dependence upon central chirality, though the effects are subtle, and in favourable cases can be overcome.

5.2 - Advantages of stoichiometric molybdenum-mediated allylic alkylation over palladium-catalysed procedures.

The stoichiometric nature of the molybdenum chemistry described in this thesis may be interpreted as disadvantageous on economic grounds, but the basic feedstock, $Mo(CO)_6$, is relatively cheap (25 p / mmol). Several important advantages of the molybdenum methodology over palladium-catalysed allylic alkylation procedures should be noted:

- $CpMo(CO)_2(\eta^3\text{-allyl})$ and $[CpMo(CO)(NO)(\eta^3\text{-allyl})]^+$ systems are not prone to rearrangement *via* $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ pathways, which allows the *syn-anti* isomerisation of terminal substituents.

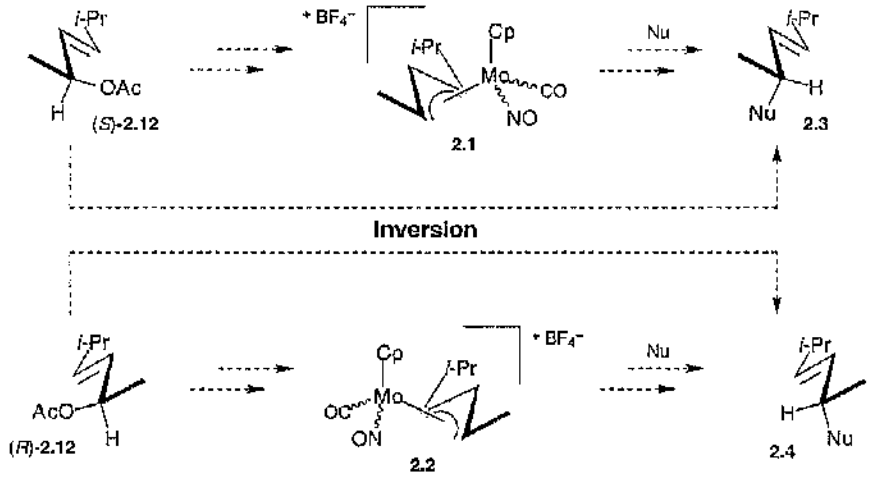
- The Mo-complexes are coordinatively saturated, 18-electron systems containing non-labile ligands, resulting in nucleophilic attack *anti* to the metal. *Anti* or *syn* modes of attack are both possible in palladium-mediated alkylations, depending on the nature of the nucleophile.

- Mo-complexes tolerate both soft and "hard" nucleophiles; the use of hard nucleophiles in palladium-catalysed systems is comparatively rare. The combination of molybdenum complexes with the functionalised, chiral α-heteroalkylcopper(I) nucleophiles described in this thesis has no parallel in Pd-systems.

- The directing influence of the molybdenum fragment can be used to direct sequential additions to the same substrate.

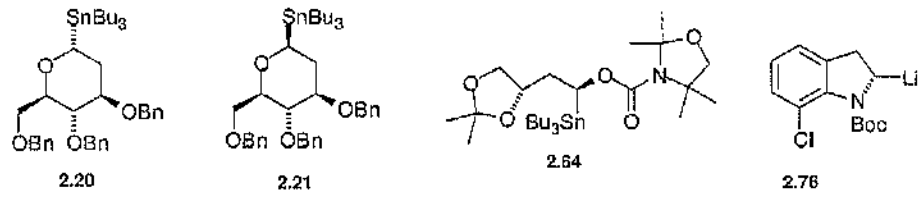
5.3 - Summary of results.

We have investigated the alkylation of planar chiral complexes **2.1** and **2.2** with a variety of functionalised α-alkoxyalkylcopper(I) nucleophiles (Scheme 5.3). Good regioselectivity (typically > 8:1) for attack at the less sterically-hindered methyl terminus of the allyl ligand is observed. In contrast to literature precedent,[50] the regioselectivity is achieved without the need to control the central chirality at molybdenum. Complexes **2.1** and **2.2** are readily available from the corresponding enantiopure allylic acetates (*S*)- and (*R*)-**2.12** and $Mo(CO)_3(MeCN)_3$ or $Mo(CO)_4(py)_2$ with clean retention of facial stereochemistry. Nucleophilic attack subsequently occurs *anti* to the metal fragment, yielding olefin products **2.3** and **2.4** with overall inversion with respect to the starting acetate.



Scheme 5.3.

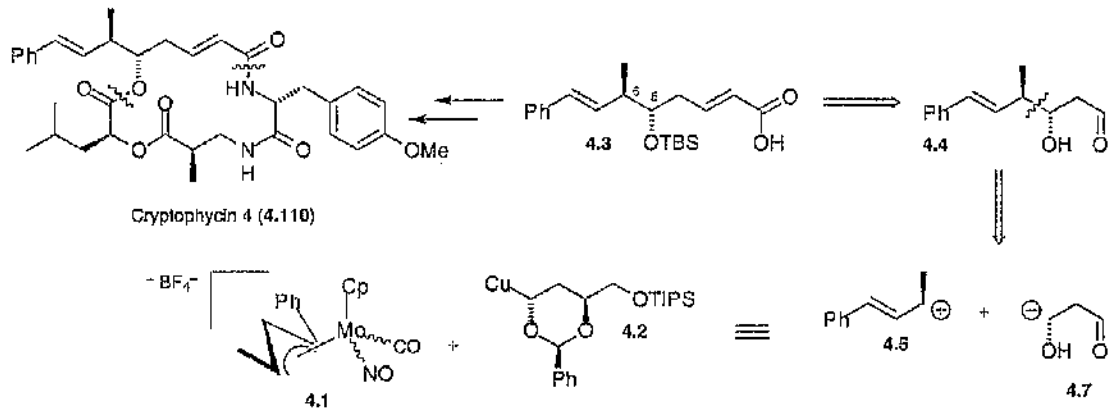
Use of configurationally stable alkylcopper(I) nucleophiles derived from stannanes **2.20**, **2.21** and **2.64**, and from chiral alkyllithium **2.76** demonstrates the ability of the methodology to simultaneously form two stereocentres with excellent control (Scheme 5.4).



Scheme 5.4.

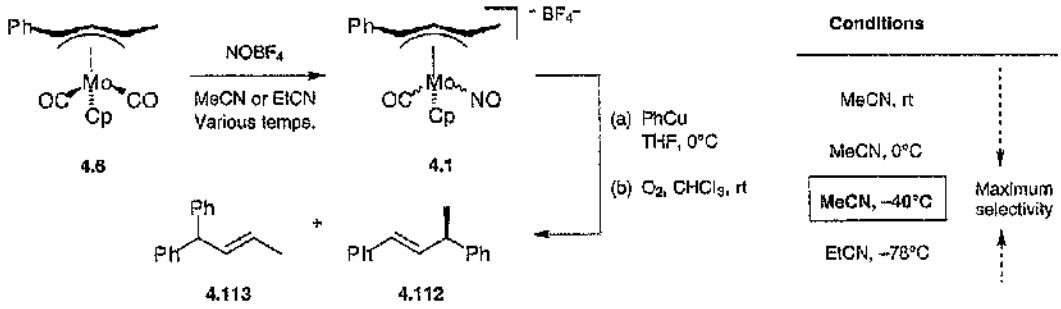
The molybdenum-based methodology was extended to the synthesis of Cryptophycin 4 (**4.110**) (Scheme 5.5). The key step involved the coupling of nucleophile **4.2** with novel

planar chiral cationic complex **4.1**, to secure the absolute stereochemistry at C5 and C6 in acid **4.3**. The complete route to Cryptophycin 4 is illustrated in Scheme 5.7.



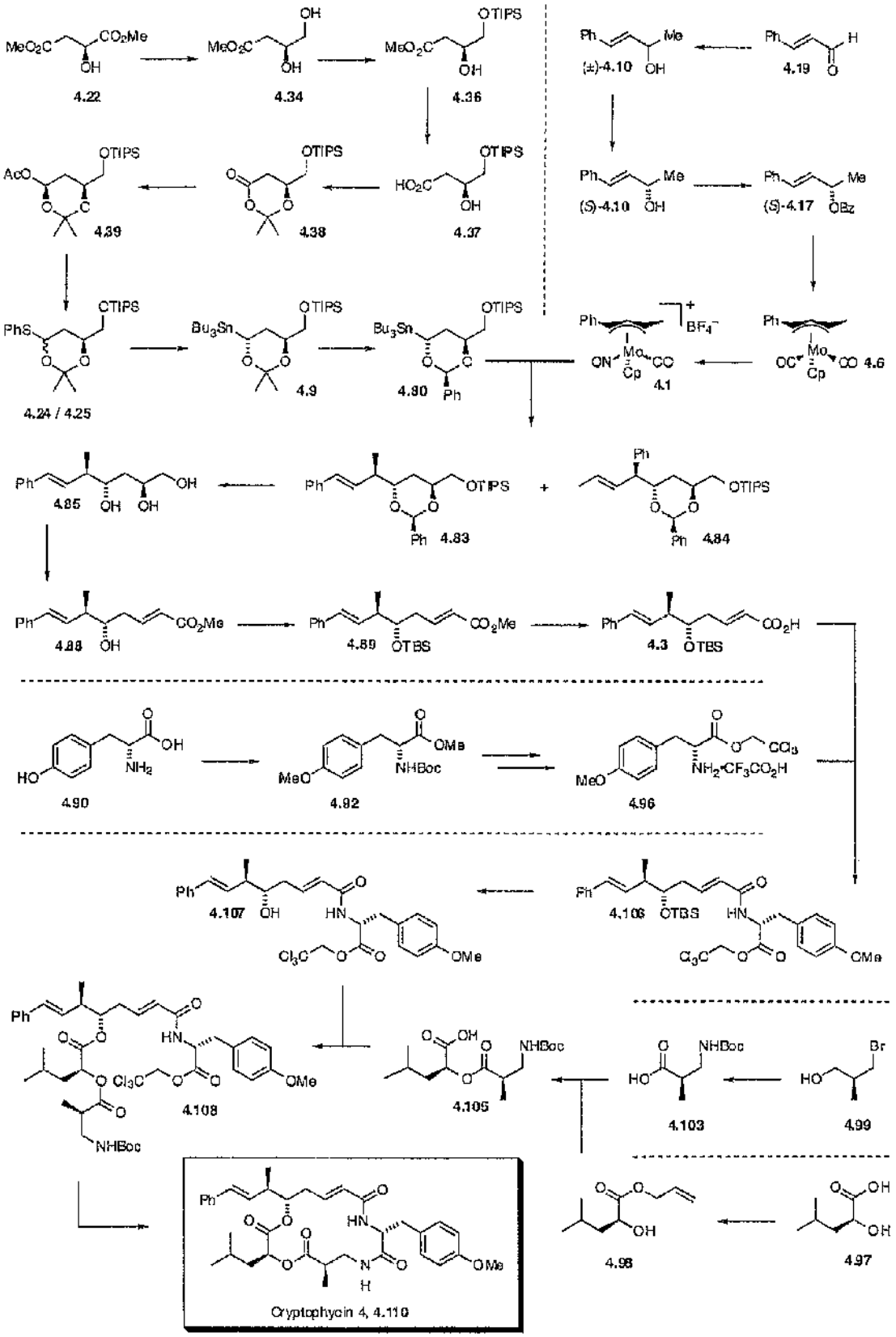
Scheme 5.5.

Regioselectivity in the coupling of complex **4.1** and nucleophile **4.2** was minimal, only a slight preference for attack at the methyl terminus (1.2 : 1) being observed. The lack of regiocontrol presumably reflects poor steric differentiation between the phenyl and methyl termini, and the precedented directing effect of the nitrosyl ligand in complex RS_{Mo}-**4.1**.[45, 49] Using PhCu as a model nucleophile we investigated the effect of temperature upon selectivity of CO → NO^+ exchange in forming complex **4.1** (Scheme 5.6). We inferred that decreasing the temperature resulted in an increasing diastereoselectivity in cation formation, as evidenced by an increasing preference for attack at the 'desired' methyl terminus of **4.1**. The optimum conditions were –40°C in MeCN, poorer selectivity obtained *via* ligand exchange at –78°C in EtCN indicated that the nature of the solvent as well as temperature plays a role in ligand exchange selectivity.



Scheme 5.6.

Applying the optimised conditions to the Cryptophycin key step enhanced the regioselectivity to 3 : 1 in favour of desired olefin **4.83** (Scheme 5.7).


4.22
4.34
4.36
4.37
4.38
4.39
4.24 / 4.25
4.9
4.80
4.1
4.6
(±)-4.10
4.19
(S)-4.10
(S)-4.17
4.85
4.83
4.84
4.88
4.89
4.3
4.90
4.92
4.96
4.107
4.106
4.108
4.105
4.103
4.99
4.98
4.97
Cryptophycin 4, 4.110

Scheme 5.6.

In conclusion, excellent enantiofacial selectivity is achieved in alkylations using η^3-allylmolybdenum complexes, resulting from: (a) reliable control of planar chirality in formation of the complexes from enantiomerically pure precursors; (b) subsequent attack *anti* to the metal fragment. Regioselectivity in alkylation of unsymmetrically disubstituted complexes is more problematic, and governed mainly by central chirality. Ligand asymmetry at the metal results in an electronic distortion of the allyl ligand, a subtle effect which can be overcome in favourable cases on steric grounds. We have found that solvent and temperature effects can affect the diastereoselectivity at the metal in formation of cationic complexes.

The applicability of the molybdenum-based methodology to stereocontrolled carbon-carbon bond formation within the context of a challenging natural product synthesis has been demonstrated, and paves the way for future work on more complex target molecules. We are optimistic that a combination of the best features of the molybdenum chemistry (reliable control of central chirality) and Enders' iron-methodology (excellent regiocontrol on electronic grounds) will successfully overcome the problem of regiocontrol in the Cryptophycin synthesis.

Chapter 6 - Experimental.

6.1 - General experimental details.

Reactions requiring anhydrous conditions were conducted in glassware which had been flame-dried or oven-dried overnight, under an atmosphere of dry nitrogen unless otherwise specified. Diethyl ether, tetrahydrofuran and *tert*-butylmethyl ether (TBME) were freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Dichloromethane, pentane, acetonitrile, cumene and toluene were freshly distilled from CaH_2 under nitrogen. Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure (*ca* 15 mmHg, water aspirator). Methanol was freshly distilled from magnesium methoxide under nitrogen prior to use. Hexanes used for column chromatography refers to the fraction of petroleum ether boiling in the range 40-60°C and were distilled before use.

Cyclopentadiene (Cp) was cracked freshly from dicyclopentadiene under inert atmosphere and used immediately. $Mo(CO)_6$ and $NOBF_4$ were purchased from Acros and Lancaster respectively and used without further purification. (–)-Sparteine was purified by Kugelrohr distillation immediately prior to use. CuBr•DMS was prepared by the procedure of Taylor[212] and purified by recrystallisation before use. All other commercially available reagents were purchased from standard suppliers (Aldrich, Acros, Lancaster, Avacado) and typically used as supplied or purified by standard methods.[213] Al_2O_3 refers to activated neutral alumina, purchased from Acros (Cat. No. 19041-0010) and used as received without deactivation unless otherwise specified. Eluants used in the purification of complexes **2.14**, **2.16** and **4.6** were degassed with dry nitrogen for 20-30 minutes before use. Commercial *n*-butyllithium, *s*-butyllithium and phenyllithium solutions were titrated against 1,3-diphenylacetone-*p*-tosylhydrazone prior to use.[214]

Organic extracts were dried using magnesium sulphate ($MgSO_4$) unless otherwise specified, and were concentrated using a Buchi rotary evaporator at diaphragm pump or water aspirator pressure (5-20 mmHg). All aqueous solutions (e.g. NH_4Cl, $NaHCO_3$) were saturated unless otherwise specified, the exception being aqueous ammonia (35% solution). All reactions were magnetically stirred unless otherwise specified and were monitored by Thin Layer Chromatography (TLC) using Macherey-Nagel Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), 20wt% phosphomolybdic acid (PMA) in ethanol, anisaldehyde, vanillin followed by H_2SO_4, potassium permanganate or ceric sulphate solutions. Flash chromatography was performed on Fisher Scientific 'Matrex Silica 60' silica gel (35-70 micron particle size, Code No. S/0683/70). Preparative TLC was performed on Macherey-Nagel SIL G-200 UV_{254} pre-coated glass sheets, 20 x 20 cm, layer thickness 2 mm.

Melting points were recorded using open capillary tubes (except for complexes **2.14**, **2.16** and **4.6** which were recorded in sealed capillary tubes) on a Griffin melting point apparatus and are uncorrected. Specific optical rotations ($[\alpha]_D$) were measured at ambient temperature (21±3°C) on an Optical Activity polAAr 2000 polarimeter using a 5 mL cell with a 1 dm path length or a 0.5 mL cell with a 0.05 dm path length. Infra-red (IR) spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer using a thin film supported between NaCl plates or a KBr disk, unless otherwise specified. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, br = broad, weak absorbtions are not recorded.

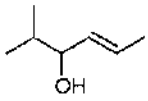
^1H and ^{13}C NMR spectra were recorded in Fourier Transform mode at the field strength specified, on a Bruker AM360 or Bruker DPX 400 spectrometer. All spectra were obtained in $CDCl_3$, C_6D_6 or CD_3CN solution in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform

(δ_H 7.27, δ_C 77.2), benzene (δ_H 7.27, δ_C 128.4) or acetonitrile (δ_H 2.00, δ_C 117.7) unless specified otherwise. Multiplicities in ^{1}H NMR spectra are quoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are reported in Hz. Numbers in parenthesis following the chemical shift in the ^{13}C spectra refer to the number of protons attached to the carbon as disclosed by the Distortionless Enhancement by Phase Transfer (DEPT) technique, with secondary pulses at 90° and 135°. Signal assignments are based on COSY and HMQC correlations, and / or by reference to standard texts.[102, 103] The numbering of ^{1}H and ^{13}C NMR spectroscopic data refers to the illustration of the compound directly underneath the name. ^{19}F and ^{95}Mo NMR spectra were recorded on a Bruker WP200SY spectrometer, operating at 188 MHz and 13 MHz field strengths respectively. ^{19}F NMR spectra were referenced externally to $FCCl_3$ at 0°C and ^{95}Mo NMR spectra were referenced externally to $Na_2[MoO_4]$.[23, 215, 216]

Low and high resolution mass spectra were run on a JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parenthesis, by the peak intensity relative to the base peak (100%). GCMS was performed on the above spectrometer, using a Chrompack WCOT Fused Silica column (25m x 0.25mm, CP-SIL 8CB-MS stationary phase), initial temperature and heating rates are specified for individual cases. Microanalytical data was recorded at the University of Glasgow by Mrs. K. Wilson.

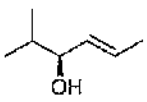
6.2 - Experimental Procedures from Chapter 2.

(4*E*)-2-Methylhex-4-en-3-ol (2.6).



The title compound was prepared by a modification of the literature procedure[217]: Mg turnings (9.6 g, 397 mmol) were stirred overnight under N_2 at rt before being suspended in Et_2O (150 mL) and 1,2-dibromoethane (0.05 mL) was added. 2-Chloropropane (36 mL, 397 mmol) was added at a rate sufficient to maintain a moderate reflux, with slight heating (heat gun) applied to initiate reflux. After the addition of 2-chloropropane was complete, the dark solution was added dropwise to a solution of freshly distilled crotonaldehyde (23.2 g, 331 mmol) in Et_2O (150 mL) at –30°C under N_2. After warming to rt over 1.5 h, 2M HCl (200 mL) was added cautiously and the phases separated. The aqueous phase was extracted with Et_2O (2 x 50 mL), and the combined organic phases dried, filtered and concentrated *in vacuo*. Purification by short path distillation (b.p. = 58°C / 30 mmHg) yielded the title compound (24.9 g, 220 mmol, 66%) as a clear oil. Spectroscopic data were in accordance with literature data.[218]

(3*S*,4*E*)-2-Methylhex-4-en-3-ol (2.6).



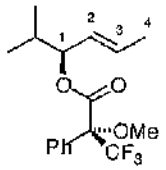
The kinetic resolution of allylic alcohol (±)-**2.6** was performed on a 45.6 mmol scale using (–)-dicyclododecyl tartrate according to the general procedure reported by Sharpless.[71] Purification by Kugelrohr distillation (b.p. 150-160°C / 760 mmHg) followed by column chromatography (SiO_2, Et_2O : hexanes = 1 :

3) yielded the title compound (1.34 g, 11.8 mmol, 26%) as a clear oil. The enantiomeric ratio at C3 was estimated as 97:3 *via* formation of the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate ester as described below.

$[\alpha]_D$ = +8.5 (*c* 1.20, $CHCl_3$). Lit. $[\alpha]_D$ (enantiomer) = –12.9 (*c* 4.75, $CHCl_3$).[50]

In a similar fashion (3*R*,4*E*)-alcohol **2.6** ($[\alpha]_D$ = –11.4 (*c* 4.97, $CHCl_3$))was prepared in 29% yield on a 107 mmol scale using (+)-dicyclododecyl tartrate. The enantiomeric ratio at C3 was estimated to be 93:7 *via* formation of the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate ester.

(2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid (1*S*,2*E*)-1-isopropylbut-2-enyl ester (2.8).



DCC (160 mg, 0.78 mmol) was added to a solution of alcohol (*S*)-**2.6** (44 mg, 0.39 mmol), (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (136 mg, 0.58 mmol) and DMAP (5 mg) in CH_2Cl_2 (10 mL) at 0°C under N_2. The cloudy white solution was allowed to warm to rt with stirring over 60 h before filtration and concentration *in vacuo*. Et_2O (20 mL) and 2M HCl (10 mL) were added and the phases were separated. The organic layer was washed with 2M HCl (10 mL) and aqueous $NaHCO_3$ (2 x 20 mL) and the organic phase dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) yielded the title compound (100 mg, 0.30 mmol, 78%) as a clear oil. The diastereomeric ratio at C1 was estimated as 97 : 3 *via* integration of trifluoromethyl singlet peaks in the ^{19}F NMR spectrum: δ_F (188 MHz, $CDCl_3$) = –71.9 and –71.8 ppm ((1*S*)- and (1*R*)-diastereomers respectively), or alternatively *via* ^1H NMR spectroscopic analysis, comparing the integration of H4 signals at 5.34 (ddq, *J* 15.2, 8.2, 1.8, (1*S*)-isomer) and 5.47 (ddq, *J* 15.3, 8.4, 1.7, (1*R*)-isomer) with reference to a sample of (1*RS*)-ester formed from (±)-**2.6**.

$[\alpha]_D$ = +60.0 (*c* 0.4, $CHCl_3$).

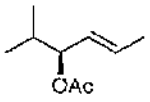
IR (film): ν = 2957 s, 2932 s, 2876 m, 2850 m, 1749 s, 1451 m, 1255 s, 1179 s, 1123 s, 1081 m, 1017 m, 992 m, 967 m cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.50 (2H, m, Ph), 7.43-7.37 (3H, m, Ph), 5.79 (1H, dq, *J* 15.3, 6.5, H3), 5.34 (1H, ddq, *J* 15.3, 8.2, 1.6, H2), 5.18 (1H, dd, *J* 8.2, 6.0, H1), 3.56 (3H, d, $^5J_{C\text{-}F}$ 1.1, OMe), 1.92-1.86 (1H, m, C<u>H</u>Me$_2$), 1.70 (3H, dd, *J* 6.5, 1.6, H4), 0.94 (3H, d, *J* 6.7, CH(<u>Me</u>)Me), 0.91 (3H, d, *J* 6.8, CH(Me)<u>Me</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (0, O<u>C</u>(O)R), 132.6 (0, Ph), 132.0 (1, C3), 129.6 (1, Ph), 128.4 (2C, 1, Ph), 127.8 (2C, 1, Ph), 126.7 (1, C2), 123.6 (0, q, $^1J_{C\text{-}F}$ 288, CF_3), 84.9 (0, q, $^2J_{C\text{-}F}$ 27, <u>C</u>(CF_3)(OMe)Ph), 83.0 (1, C1), 55.7 (3, OMe), 32.1 (1, <u>C</u>HMe$_2$), 18.3 (2C, 3, CH<u>Me</u>$_2$), 17.9 (3, C4).

LRMS (CI$^+$ mode, NH_3): *m/z* = 348.2 [$(M+NH_4)^+$, 100 %], 252.1 (25), 114.1 (63).

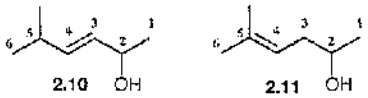
Acetic acid (1*S*,2*E*)-1-isopropyl-but-2-enyl ester (2.7).



A mixture of alcohol (*S*)-**2.6** (1.15 g, 10.1 mmol), acetic anhydride (1.3 mL, 14.1 mmol), pyridine (1.1 mL, 14.1 mmol) and DMAP (20 mg) in CH_2Cl_2 (20 mL) was stirred at rt under N_2 for 60 h before the addition of 2M HCl (15 mL) and CH_2Cl_2 (40 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 6) yielded the title compound (1.35 g, 8.7 mmol, 86%) as a clear fragrant oil. Spectroscopic data were in accordance with literature data.[219]

$[\alpha]_D$ = –29.5 (*c* 1.12, $CHCl_3$). Lit. $[\alpha]_D$ (enantiomer) = +37.6 (*c* 4.71, $CHCl_3$).[50]

5-Methyl-3-hexen-2-ol (2.10) and 5-methyl-4-hexen-2-ol (2.11).



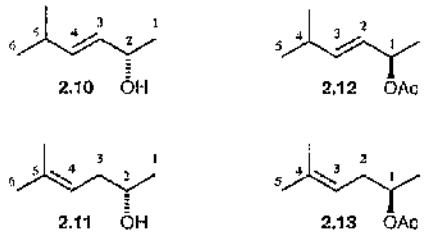
To a solution of 5-methyl-3-hexen-2-one **2.9** (24.9 g, 222 mmol, Aldrich, 75% pure - remainder 5-methyl-4-hexen-2-one (**2.9b**)) in MeOH (400 mL) at rt was added $CeCl_3 \cdot 7H_2O$ (90.8 g, 244 mmol) and the clear solution stirred under N_2 for 30 min before cooling to 0°C. $NaBH_4$ (9.22 g, 244 mmol) was added portionwise over 30 min maintaining the internal temperature below 5°C. The cloudy white solution was stirred at 5°C for 30 min and then at rt overnight before cooling to 5°C and careful addition of aqueous NH_4Cl (250 mL). The aqueous phase was saturated with NaCl and extracted with Et_2O (3 x 100 mL), and the combined organic phases washed with brine (100 mL), dried, filtered and concentrated *in vacuo* to yield a fragrant, volatile clear oil which was purified by short path distillation (b.p. = 66°C / 20 mmHg, Lit. b.p. = 60-62°C / 16 mmHg (**2.10**), 57°C / 11 mmHg (**2.11**)[76, 219]) to give an inseparable mixture of the title compounds (17.0 g, 149 mmol, 67%). ^{1}H NMR spectroscopy revealed a ratio of **2.10** : **2.11** of 4.7 : 1, estimated by integration of H1 signals at 4.25 ppm (1H, dq, *J* 6.4, 6.4) and 3.79 ppm (1H, sextet, *J* 6.1) for **2.10** and **2.11** respectively.

IR and ^{1}H NMR spectroscopic data for **2.10**[219] and **2.11**[220] were in accordance with literature data.

^{13}C NMR for **2.10** (100 MHz, $CDCl_3$): δ = 138.2 (1, C4), 131.3 (1, C3), 69.2 (1, C2), 30.7 (1, C5), 23.6 (3, C1), 22.4 (2C, 3, C6 and C5-Me).

^{13}C NMR for **2.11** (100 MHz, $CDCl_3$): δ = 135.3 (0, C5), 120.3 (1, C4), 68.1 (1, C2), 38.2 (2, C3), 26.1 (3, C5-Me), 22.9 (3, C1), 18.1 (3, C6).

(2*S*)-5-Methyl-3-hexen-2-ol (2.10), (2*S*)-5-Methyl-4-hexen-2-ol (2.11), Acetic acid (1*R*)-1,4-dimethylpent-2-enyl ester (2.12) and **Acetic acid (1*R*)-1,4-dimethylpent-3-enyl ester (2.13).**



A mixture of alcohols (±)-**2.10** and (±)-**2.11** (14.9 g, 130 mmol, **2.10** : **2.11** = 4.7 : 1), vinyl acetate (60 mL, 650 mmol), activated crushed 4Å MS (50 wt%, 7.43 g) and Novozym 435 (10 wt%, 1.49 g) in pentane (120 mL) was shaken until ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated ≥ 50% conversion (7.5 h). The mixture was filtered and carefully concentrated *in vacuo* (~15 mmHg, 15-20°C bath temp.) to give a clear oil which was purified by column chromatography (SiO_2, Et_2O : hexanes = 2 : 8) to yield a mixture of the title acetates (9.18 g, 58.8 mmol, 45%) as a volatile clear oil. ^{1}H NMR spectroscopy revealed a ratio of (*R*)-**2.12** : (*R*)-**2.13** of 3.8 : 1, estimated by integration of H2 signals at 5.25 ppm (1H, dq, *J* 6.4, 6.4) and 4.82 ppm (1H, sextet, *J* 6.4) for **2.12** and **2.13** respectively. Further elution yielded a mixture of the title alcohols (6.16 g, 52.9 mmol, 41%; $[\alpha]_D$ = –7.5 (*c* 1.04, $CHCl_3$), (*S*)-**2.10** : (*S*)-**2.11** = 5.4 : 1 by ^{1}H NMR spectroscopy as described above).

Data for a 3.8 : 1 mixture of acetates (*R*)-**2.12** and (*R*)-**2.13**:

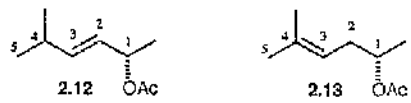
$[\alpha]_D$ = +67.4 (*c* 1.16, $CHCl_3$).

IR and ^{1}H NMR spectroscopic data for the mixture of **2.12** and **2.13** were in accordance with literature data.[219, 220]

^{13}C NMR for **2.12** (100 MHz, $CDCl_3$): δ = 170.3 (0, COMe), 140.0 (1, C3), 126.7 (1, C2), 71.0 (1, C1), 30.7 (1, C4), 22.1 (2C, C5 and C4-Me), 21.4 (3, COMe), 20.4 (3, C1-Me).

^{13}C NMR for **2.13** (100 MHz, $CDCl_3$): δ = 170.0 (0, COMe), 134.4 (0, C4), 119.3 (1, C3), 70.4 (1, C1), 34.5 (2, C2), 25.8 (3, C4-Me), 21.3 (3, COMe), 19.4 (3, C1-Me), 17.9 (3, C5).

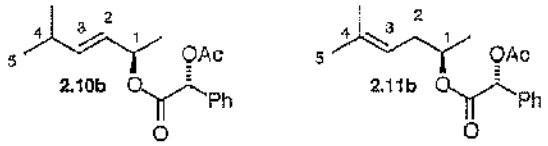
Acetic acid (1*S*)-1,4-dimethylpent-2-enyl ester (2.12) and **Acetic acid (1*S*)-1,4-dimethylpent-3-enyl ester (2.13).**



A mixture of the title acetates (**2.12** : **2.13** = 5.8 : 1, $[\alpha]_D$ = –56.4 (*c* 1.64, $CHCl_3$)) was prepared from a mixture of alcohols (*S*)-**2.10** and (*S*)-**2.11** (**2.10** : **2.11** = 5.4 : 1) in 81% yield on a 48.2 mmol scale by an analogous procedure to that described above for acetate **2.7**. Purification by short-path distillation (b.p. =

70-71°C / 15 mmHg, Lit. b.p. = 60-62°C / 13 mmHg[76]) gave the title compounds as a clear colourless fragrant oil. Spectroscopic data were as described above.

(*R*)-Acetoxyphenylacetic acid (1*R*)-1,4-dimethylpent-2-enyl ester (2.10b) and (*R*)-Acetoxyphenylacetic acid (1*R*)-1,4-dimethylpent-3-enyl ester (2.11b).



A mixture of acetates (*R*)-**2.12** and (*R*)-**2.13** (**2.12** : **2.13** = 3.8 : 1, 141 mg, 0.90 mmol), K_2CO_3 (14 mg) and MeOH (5 mL) was stirred at rt for 20 h before concentration *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 4 : 6) yielded a mixture of alcohols (*R*)-**2.10** and (*R*)-**2.11** (45 mg, 0.39 mmol), which were dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C under N_2. DCC (122 mg, 0.59 mmol), (*R*)-*O*-acetoxyphenylacetic acid (92 mg, 0.47 mmol) and DMAP (2.4 mg) were added and the mixture stirred at 0°C for 30 min, and then at rt for 1 h before filtration and concentration *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 3 : 7) yielded an inseparable mixture of the title compounds (102 mg, 0.35 mmol, 90%) in the approximate ratio **2.10b** : **2.11b** = 3 : 1. The diastereomeric ratio at C1 for allylic ester **2.10b** was estimated as 96 : 4 *via* integration of the following signals in the ^{1}H NMR spectrum: H2 (major isomer of **2.10b**) at 5.19 ppm (ddd, *J* 15.6, 6.4, 1.2) *vs* H3 (major isomer of **2.11b**) at 5.68 ppm (dd, *J* 14.8, 6.4), with reference to a sample of (1*RS*)-**2.10b** and (1*RS*)-**2.11b** formed from (±)-**2.10** and (±)-**2.11**.

$[\alpha]_D$ = -58.7 (*c* 1.02, $CHCl_3$).

IR (film): ν = 2954 s, 2928 m, 2868 m, 1739 s, 1455 m, 1374 m, 1232 s, 1219 s, 1176 m, 1051 m, 965 m cm^{-1}.

LRMS (CI^+ mode, NH_3): *m/z* = 308.1 [$(M+NH_4)^+$, 100 %], 212.0 (38), 114.1 (30), 97.1 (25).

NMR data for **2.10b**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.44 (2H, m, Ph), 7.41-7.35 (3H, m, Ph), 5.90 (1H, s, C<u>H</u>(OAc)Ph), 5.42 (1H, ddd, *J* 15.6, 6.7, 1.1, H3), 5.36 (1H, pentet, *J* 6.4, H1), 5.19 (1H, ddd, *J* 15.6, 6.4, 1.1, H2), 2.19 (3H, s, CO<u>Me</u>), 2.19-2.08 (1H, m, H4), 1.31 (3H, d, *J* 6.4, C1-Me), 0.86 (3H, d, *J* 6.8, H5), 0.85 (3H, d, *J* 6.8, C4-Me).

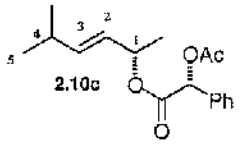
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (0, O<u>C</u>OR), 168.2 (0, O<u>C</u>OR), 140.5 (1, C3), 134.0 (0, Ph), 129.2 (1, Ph), 128.8 (2C, 1, Ph), 127.9 (2C, 1, Ph), 125.7 (1, C2), 74.8 (1, <u>C</u>H(OAc)Ph), 72.7 (1, C1), 30.6 (1, C4), 22.1 (2C, 3, C5 and C4-<u>Me</u>), 20.9 (3, CO<u>Me</u>), 20.4 (3, C1-<u>Me</u>).

NMR data for **2.11b**:

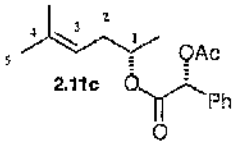
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.44 (2H, m, Ph), 7.41-7.35 (3H, m, Ph), 5.96 (1H, s, C<u>H</u>(OAc)Ph), 4.92 (1H, sextet, *J* 6.4, H1), 4.79 (1H, broad t, *J* 7.4, H3), 2.19 (3H, s, CO<u>Me</u>), 2.19-2.05 (2H, m, H2), 1.54 (3H, s, C4-Me), 1.46 (3H, s, H5), 1.25 (3H, d, *J* 6.4, C1-Me).

^{13}C NMR (100 MHz, $CDCl_3$, partial data - some signals obscured by the major diastereomer **2.10b**): δ = 168.6 (0, O<u>C</u>OR), 134.5 (0, C4 or Ph), 118.9 (1, C3), 74.9 (1, <u>C</u>H(OAc)Ph), 72.8 (1, C1), 34.3 (2, C2), 25.8 (3, C4-<u>Me</u>), 19.6 (3, C1-<u>Me</u>), 17.8 (3, C5).

(*R*)-Acetoxyphenylacetic acid (1*S*)-1,4-dimethylpent-2-enyl ester (2.10c) and **(*R*)-Acetoxyphenylacetic acid (1*S*)-1,4-dimethylpent-3-enyl ester (2.11c).**



2.10c



2.11c

A mixture of the title esters (**2.10c** : **2.11c** = 6 : 1) was prepared from a mixture of alcohols (*S*)-**2.10** and (*S*)-**2.11** (5.4 : 1) in 83% yield on a 0.68 mmol scale by an analogous procedure to that described above for esters **2.10b** and **2.11b**. The diastereomeric ratio at C1 for **2.10c** was estimated as ≥ 97 : 3 *via* integration of the following signals in the ^{1}H NMR spectrum: H3 (major isomer of **2.10c**) at 5.68 ppm (dd, *J* 14.8, 6.4) *vs* H2 (minor isomer of **2.10c**) at 5.19 ppm (ddd, *J* 15.6, 6.4, 1.2), with reference to a sample of (1*RS*)-**2.10c** and (1*RS*)-**2.11c** formed from (±)-**2.10** and (±)-**2.11**.

$[\alpha]_D$ = – 91.5 (*c* 1.63, $CHCl_3$).

IR (film): ν = 2961 s, 2923 m, 2869 m, 1747 s, 1374 m, 1265 m, 1374 m, 1232 s, 1182 m, 1056 m cm^{-1}.

LRMS (CI$^+$ mode, NH_3): *m/z* = 308.1 [$(M+NH_4)^+$, 100 %], 212.1 (30), 114.1 (25), 97.1 (24).

NMR data for **2.10c**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.45 (2H, m, Ph), 7.41-7.27 (3H, m, Ph), 5.91 (1H, s, C<u>H</u>(OAc)Ph), 5.68 (1H, dd, *J* 14.8, 6.4, H3), 5.43-5.32 (2H, m, H1 and H2), 2.35-2.23 (1H, m, H4), 2.19 (3H, s, OCO<u>Me</u>), 1.17 (3H, d, *J* 6.0, C1-Me), 0.97 (6H, d, *J* 6.8, H5 and C4-Me).

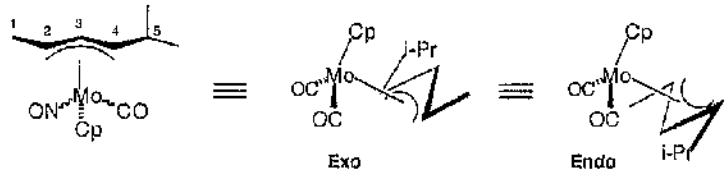
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (0, O<u>C</u>OR), 168.2 (0, O<u>C</u>OR), 140.8 (1, C3), 134.1 (0, Ph), 129.2 (1, Ph), 128.8 (2C, 1, Ph), 127.7 (2C, 1, Ph), 125.8 (1, C2), 74.8 (1, <u>C</u>H(OAc)Ph), 72.9 (1, C1), 30.7 (1, C4), 22.1 (2C, 3, C5 and C4-<u>Me</u>), 20.8 (3, CO<u>Me</u>), 20.0 (3, C1-<u>Me</u>).

NMR data for **2.11c**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.45 (2H, m, Ph), 7.41-7.27 (3H, m, Ph), 5.89 (1H, s, C<u>H</u>(OAc)Ph), 5.08 (1H, broad t, *J* 7.4, H3), 4.92 (1H, sextet, *J* 6.4, H1), 2.35-2.23 (2H, m, H2), 2.19 (3H, s, OCO<u>Me</u>), 1.69 (3H, s, C4-Me), 1.61 (3H, s, H5), 1.08 (3H, d, *J* 6.4, C1-Me).

^{13}C NMR (100 MHz, $CDCl_3$, partial data - some signals obscured by the major diastereomer **2.10c**): δ = 170.3 (0, OCOR), 168.4 (0, OCOR), 134.8 (0, C4 or Ph), 127.7 (1, Ph), 118.9 (1, C3), 74.8 (1, CH(OAc)Ph), 72.8 (1, C1), 34.3. (2, C2), 25.9 (3, C4-Me), 19.1 (3, C1-Me), 18.0 (3, C5).

(2*R*,4*S*)-(η^5-Cyclopentadienyl)(5-methyl-2,3,4-η-hex-3-en-2-yl)(dicarbonyl)molybdenum (2.14).



The title compound was prepared in 73% yield as a dark-red oil by the procedure of Kocienski on a 6.7 mmol scale,[57] or alternatively as below:[16]

To a solution of $Mo(CO)_6$ (1.70 g, 6.44 mmol) in THF (30 mL) under N_2 was added pyridine (1.04 mL, 12.9 mmol) and the solution brought to reflux. After refluxing for 12 h a solution of acetates (*R*)-**2.12** and (*R*)-**2.13** (**2.12** : **2.13** = 3.8 : 1, 1.21 g, 6.12 mmol of **2.12**) in THF (5 mL + 2 x 1 mL) was added dropwise *via* syringe to the red-orange solution, which was refluxed for a further 63 h before cooling to rt over 1 h. LiCp (21 mL of a 0.33M solution in THF (prepared immediately before use from freshly cracked Cp (1.03 g, 15.6 mmol) and *n*-BuLi (6.7 mL of a 2.32M solution in hexanes, 15.6 mmol) in THF (40 mL), rt, 15 min under N_2) was added and the dark red-brown solution stirred at rt under N_2 for 1 h. The solution was transferred *via* syringe to a round-bottomed flask and concentrated *in vacuo* to a volume of approximately 20 mL, before purification by column chromatography (Al_2O_3, degassed hexanes-Et_2O, 1:1, under N_2) and prolonged (3 h, 30°C, ~5 mmHg) concentration in vacuo. The title compound (1.66 g, 5.27 mmol, 86% from **2.12**) was obtained as a red-yellow oil which solidified upon drying *in vacuo* overnight. Complex **2.14** was generally used without further purification, but for analytical purposes purification by recrystallisation from pentane under an atmosphere of N_2 gave fine yellow needles. ^{1}H NMR spectroscopy indicated an approximate *exo* : *endo* ratio of 5 : 1, as judged by the integration of H3 signals at 3.95 and 3.45 ppm respectively. Spectroscopic data for the title compound has previously been reported.[57]

m.p. = 65-67°C (dec, pentane). Lit. m.p. = 65-67°C (hexane).[57]

$[\alpha]_D$ = –20.6 (*c* 2.10, $CHCl_3$). Lit. $[\alpha]_D$ = –150.0 (*c* 0.08, $CHCl_3$).[57]

IR (KBr): ν = 2954 m, 1936 s, 1848 s, 1377 m, 1006 m cm^{-1} - in accordance with literature data.[57]

^{1}H and ^{13}C NMR data for the major (*Exo*) isomer were in accordance with literature data.[57]
^{1}H and ^{13}C NMR data for the minor (*Endo*) isomer:

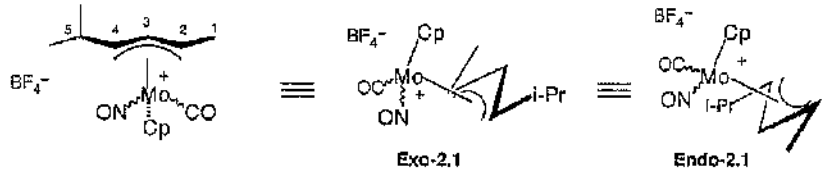
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.20 (5H, s, Cp), 3.45 (1H, t, *J* 10.0, H3), 2.63 (1H, dq, *J* 10.0, 6.0, H2), 2.37 (1H, t, *J* 9.6, H4), 2.02 (1H, ddt, *J* 13.2, 9.2, 6.6, H5), 1.88 (3H, d, *J* 6.0, H1), 1.22 (3H, d, *J* 6.4, H6), 1.13 (3H, d, *J* 6.8, H6').

^{13}C NMR (100 MHz, $CDCl_3$): δ = 240.4 (2C, 0, CO), 90.6 (5C, 1, Cp), 90.5 (1, C3), 67.6 (1, C4), 51.0 (1, C2), 33.7 (1, C5), 28.1 (3, C1), 25.3 (3, C6), 20.5 (3, C6').

^{95}Mo NMR (13 MHz, THF): δ_{exo} = –1743, δ_{endo} = –1559. *Exo* : *endo* = 5 : 1.[221]

By an analogous procedure, enantiomeric complex *ent*-**2.14** was prepared in 82% yield from a mixture of acetates (*S*)-**2.12** / (*S*)-**2.13** (5.8 : 1) on a 6.1 mmol scale, or in 45% yield on a 5.2 mmol scale by the literature procedure.[57]

(2*S*,4*R*)-(η^5-Cyclopentadienyl)(5-methyl-2,3,4-η-hex-3-en-2-yl)(carbonyl)(nitrosyl) molybdenum tetrafluoroborate (2.1).



Cationic complex **2.1** (or **2.2**) was routinely prepared in a minimum volume (*ca* 2-3 mL / mmol) of freshly distilled MeCN at 0°C under N_2 by the addition of $NOBF_4$ (1.1 eq) and transferred directly *via* cannula to a solution of the nucleophile. For characterisation purposes the title compound was prepared in 78% yield on a 4.9 mmol scale from neutral complex (2*S*,4*R*)-**2.14** according to the published procedure.[57] Complex **2.1** was isolated as a mixture of 2 major isomers (presumably a pair of *endo* isomers),[42, 78] in the approximate ratio 1 : 1, a minor pair of *exo*-isomers was also observable.

IR (solution in CD_3CN): ν = 2076 s, 1716 s cm^{-1}

^1H NMR (400 MHz, CD_3CN) Data for *endo* isomers: δ = 6.09 (5H, s, Cp), 6.05 (5H, s, Cp), 5.24 (1H, t, *J* 12.6, H3), 5.12 (1H, br t, *J* 13.0, H3), 4.36-4.28 (1H, m, H2), 3.93 (1H, dd, *J* 13.0, 9.8, H4), 3.64 (1H, dd, *J*13.2, 4.8, H4), 3.31 (1H, dq, *J* 12.0, 6.1, H2), 2.82-2.62 (2H, m, H5), 2.39 (3H, d, *J* 6.4, Me), 2.13 (3H, d, *J* 6.4, Me), 1.44 (3H, d, *J* 6.4, Me), 1.38 (3H, d, *J* 6.8, Me), 1.23 (3H, d, *J* 6.4, Me), 0.96 (3H, d, *J* 6.9, Me). Partial data for the *exo* isomers: δ = 6.21 (5H, s, Cp), 6.19 (5H, s, Cp), 3.83-3.74 (2H, m), 2.57-2.48 (2H, m), 2.22 (3H, d, *J* 6.0, Me), 1.38 (3H, d, *J* 6.8, Me), 1.34 (3H, d, *J* 6.8, Me), 1.32 (3H, d, *J* 6.8, Me), 1.29 (3H, d, *J* 6.8, Me), 1.26 (3H, d, *J* 6.8, Me), remaining peaks obscured by the major isomers.

^{13}C NMR (100 MHz, CD_3CN, mixture of *endo* and *exo* isomers): δ = 215.8 (0, CO), 215.0 (0, CO), 211.3 (0, CO), 211.0 (0, CO), 110.1 (1), 109.7 (1), 108.6 (1), 106.7 (1), 102.8 (5C, 1), 101.6 (5C, 1), 101.5 (5C, 1), 100.6 (5C, 1), 94.4 (1), 94.1 (2C, 1), 93.9 (1), 89.4 (1), 87.2 (1), 78.1 (1), 75.6 (1), 35.3 (1), 34.4 (1), 30.9 (1), 30.4 (1), 26.4 (3), 25.5 (3), 25.3 (3), 24.4 (3), 23.9 (3), 22.7 (3), 21.3 (3), 21.1 (3), 20.7 (3), 19.4 (3), 18.7 (3), 18.2 (3).

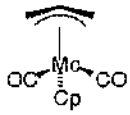
LRMS (CI^+ mode, NH_3): *m/z* = 318 [$(M+H)^+$ (^{98}Mo), 100 %], 316 [$(M+H)^+$ (^{96}Mo), 73 %], 287 (14), 286 (11). The expected Mo isotope patterns are present.

HRMS (EI mode): found [$M^{+\bullet}$], 317.0310. $C_{13}H_{17}O_2{}^{98}Mo$ requires 317.0316. Found [$M^{+\bullet}$], 315.0296. $C_{13}H_{17}O_2{}^{96}Mo$ requires 315.0312. The expected Mo isotope patterns are present.

Benzoic acid allyl ester (2.15).

Benzoate **2.15** was prepared on a 258 mmol scale by the procedure of Tamaru.[222] Purification by short-path distillation (b.p. = 112-114°C / 10 mmHg, Lit. b.p. = 109-111°C / 15 mmHg[223]) gave the title compound (41.0 g, 253 mmol, 98%) as a clear oil. Spectroscopic data were in accordance with literature data.[224, 225]

(η^5-Cyclopentadienyl)(η^3-propenyl)(dicarbonyl)molybdenum (2.16 / 4.76)



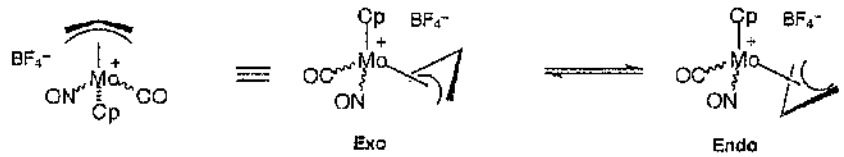
To a solution of $Mo(CO)_6$ (3.0 g, 11.4 mmol) in THF (140 mL) under N_2 was added pyridine (1.8 mL, 22.7 mmol) and the solution brought to reflux. After refluxing for 12 h a solution of benzoate **2.15** (1.75 g, 10.8 mmol) in THF (5 mL + 5 mL) was added dropwise *via* syringe to the red-orange solution, which was refluxed for a further 12 h before cooling to rt over 1 h. LiCp (31.0 mL of a 0.40M solution in THF (prepared immediately before use from freshly cracked Cp (1.29 mg, 19.6 mmol) and *n*-BuLi (8.4 mL of a 2.32M solution in hexanes) in THF (40 mL), rt, 15 min under N_2)) was added and the dark red-brown solution stirred at rt under N_2 for 1 h. The solution was transferred *via* syringe to a round-bottomed flask and concentrated *in vacuo* to a volume of approximately 20 mL. Purification by column chromatography (Al_2O_3, degassed hexanes-Et_2O, 1:1, under N_2) yielded the title compound (2.39 g, 9.26 mmol, 86%) as a yellow fine crystalline solid. Spectroscopic data were in accordance with literature data.[15] ^{1}H NMR spectroscopy indicated that **2.16** existed as a mixture of *exo* and *endo* isomers (3.3 : 1) in good agreement with literature data.[15, 78]

Complex **2.16** was generally used without further purification, but for analytical purposes purification by recrystallisation from Et_2O / pentane under an atmosphere of N_2 gave fine yellow needles.

m.p. = 136-139°C (dec, Et_2O / pentane). Lit. m.p. = 135-138°C (Et_2O / heptane).[15]

^{95}Mo NMR (13 MHz, THF): $\delta_{exo} = -1856$, $\delta_{endo} = -1648$. *Exo* : *endo* = 2 : 1,[221] in good agreement with literature data.[78]

(η^5-Cyclopentadienyl)(η^3-propenyl)(carbonyl)(nitrosyl)molybdenum tetrafluoroborate (2.17 / 4.77)



Cationic complex **2.17** was routinely prepared in a minimum volume (*ca* 2-3 mL / mmol) of freshly distilled MeCN at 0°C under N_2 by the addition of $NOBF_4$ (1.1 eq) and transferred directly *via* cannula to a

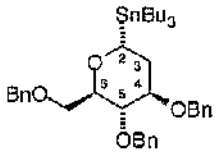
solution of the nucleophile. However, for characterisation purposes the title compound was prepared in 92% yield on a 6.2 mmol scale in an analogous fashion to complex **2.17** above.

^{1}H NMR spectroscopy indicated that **2.17** existed as a mixture of *exo* and *endo* isomers, in an initial ratio of *endo* : *exo* = 5 : 1, equilibrating to *endo* : *exo* = 1 : 5.5 after 27 h in CD_3CN at rt. The *endo* and *exo* resonances were assigned by reference to ^{1}H and ^{13}C NMR spectroscopic data for the corresponding hexafluorophosphate analogue of **2.17**,[226] and the ratio was estimated *via* integration of H2 peaks at 5.47 and 5.09 ppm for *endo* and *exo* respectively.

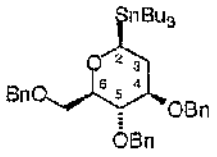
^{1}H NMR (400 MHz, CD_3CN): *Endo* isomer: δ = 6.24 (5H, s, Cp), 5.47 (1H, ddt, *J* 14.0, 12.6, 7.1, H2), 4.83 (1H, dd, *J* 7.1, 3.4, H1 or H3), 4.15 (1H, ddd, *J* 7.3, 3.5, 0.5, H1 or H3), 3.54 (1H, dd, *J* 12.5, 1.0, H1 or H3), 3.00 (1H, d, *J* 14.0, H1 or H3); *Exo* isomer : δ = 6.09 (5H, s, Cp), 5.09 (1H, tt, *J* 14.0, 7.6, H2), 4.92 (1H, dd, *J* 7.5, 3.3, H1 or H3), 4.70 (1H, dd, *J* 7.9, 3.2, H1 or H3), 3.42 (1H, d, *J* 13.4, H1 or H3), 3.15 (1H, d, *J* 13.4, H1 or H3).

^{13}C NMR (100 MHz, CD_3CN): *Endo* isomer: δ = 207.7 (0, CO), 113.8 (1, C2), 101.5 (5C, 1, Cp), 67.8 (2, C1 or C3), 59.8 (2, C1 or C3); *Exo* isomer: δ = 210.7 (0, CO), 100.5 (6C, Cp + C2), 67.9 (2, C1 or C3), 64.1 (2, C1 or C3).

(2*R*,4*R*,5*S*,6*R*)-(4,5-Bisbenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)tributyl stannane (2.20) and **(2*S*,4*R*,5*S*,6*R*)-(4,5-Bisbenzyloxy-6-benzyloxymethyltetrahydro pyran-2-yl)tributylstannane (2.21)**



2.20

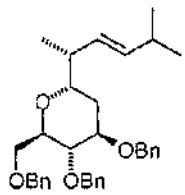


2.21

The title compounds were prepared over 2 steps from tri-*O*-benzyl D-glucal (**2.18**) on a scale of 4.8 mmol according to the procedure described by Procter.[61] Purification by column chromatography allowed the isolation of stannanes **2.20** (3.47 g, 4.91 mmol, 51%) and **2.21** (1.41 g, 1.99 mmol, 21%) as clear oils. Spectroscopic data for both compounds were in accordance with literature data.[64]

$[\alpha]_D$ (**2.20**) = +31 (*c* 6.6, $CHCl_3$). Lit. $[\alpha]_D$ = +26 (*c* 5.5, $CHCl_3$)[64]
$[\alpha]_D$ (**2.21**) = –9.4 (*c* 1.9, $CHCl_3$). Lit. $[\alpha]_D$ = –9.3 (*c* 1.8, $CHCl_3$)[64]

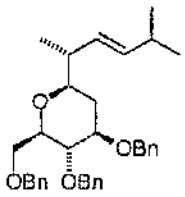
(2*R*,3*R*,4*R*,6*S*)-2,3-Bisbenzyloxy-4-benzyloxymethyl-6-[(1*R*,2*E*)-1,4-dimethylpent-2-enyl]tetrahydropyran (2.22).



The title compound was prepared in 69% yield on a 1.3 mmol scale from stannane **2.20** according to the method previously described.[61] Spectroscopic data were in accordance with those reported previously.[61] The

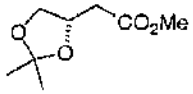
regioselectivity in formation of olefin **2.22** was estimated as 8 : 1, based on the integration of the following vinylic proton resonances in the ^{1}H NMR spectrum: δ 5.45-5.31 (2H, m, major isomer, 1H m, minor regioisomer) *vs* 5.12 (1H, dd, *J* 15.3, 8.9, minor isomer).

(2*R*,3*R*,4*R*,6*R*)-2,3-Bisbenzyloxy-4-benzyloxymethyl-6-[(1*R*,2*E*)-1,4-dimethylpent-2-enyl]tetrahydropyran (2.24).



The title compound was prepared in 33% yield on a 0.24 mmol scale from stannane **2.21** according to the method previously described.[61] Spectroscopic data were in accordance with those reported previously.[61] The regioselectivity in formation of olefin **2.24** was estimated as 8 : 1, based on the integration of the following vinylic proton resonances in the ^{1}H NMR spectrum: δ 5.43 (1H, dd, 15.5, 6.6, major regioisomer) + 5.46-5.33 (2H, m, minor regioisomer) *vs* 5.25 (1H, 15.5, *J* , 8.0, 1.0, major regioisomer).

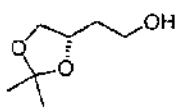
[(4*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl]acetic acid methyl ester (2.60)



The title compound was prepared by a procedure adapted from the literature:[99, 101] Methyl (3*S*)-3,4-dihydroxybutanoate (prepared from dimethyl (*S*)-malate **2.59** on a scale of 153 mmol according to the procedure of Moriwake[99] as a clear oil and used crude) was dissolved in acetone (300 mL) and *p*-TsOH•H_2O (1.46 g, 7.65 mmol) was added. The cloudy white suspension was stirred at rt for 2.5 d before the addition of Et_3N (0.5 mL) and concentration *in vacuo*. The residue was partitioned between CH_2Cl_2 (150 mL) and aqueous $NaHCO_3$ (150 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases dried, filtered and concentrated *in vacuo* to give a pale yellow oil which was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 1) to yield the title compound as a clear oil (16.1 g, 92.2 mmol, 60% over two steps from **2.59**). Spectroscopic data were in accordance with literature data.[227]

$[\alpha]_D$ = +9.05 (*c* 10.4, Me_2CO). Lit. $[\alpha]_D$ = +8.69 (*c* 10, Me_2CO).[227]

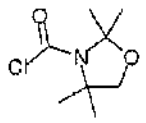
2-[(4*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl]ethanol (2.61).



The title compound was prepared in 88% yield on a 83.6 mmol scale by the method of Luk.[100] Spectroscopic data were in accordance with literature data.[100, 228]

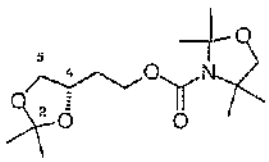
$[\alpha]_D$ = –2.72 (*c* 4.97, MeOH). Lit. $[\alpha]_D$ (enantiomer) = +2.49 (*c* 5.12, MeOH).[100]

2,2,4,4-Tetramethyloxazolidine-3-carbonyl chloride (2.63).



The title compound was prepared in 70% yield on a 46.0 mmol scale by the method of Hoppe[94] and purified by short-path distillation (b.p. = 79-81°C / 1.5 mmHg, Lit. b.p. = 73-74 / 3 mmHg[94]). Spectroscopic data were in accordance with literature data.[94]

2,2,4,4-Tetramethyloxazolidine-3-carboxylic acid [(4*S*)-2-(2,2-dimethyl[1,3]dioxolan-4-yl)]ethyl ester (2.52).



The title compound was prepared in 91% yield as a clear colourless oil on a 32.0 mmol scale by the method of Hoppe.[94] ^{1}H NMR spectroscopic data were in accordance with literature data.[98]

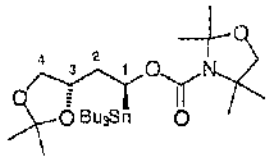
$[\alpha]_D = -9.47$ (*c* 5.08, MeOH) Lit. $[\alpha]_D = -11.4$ (*c* 5.3, MeOH).[98]

IR (film): ν = 2982 s, 2937 s, 2871 m, 1700 s, 1457 m, 1410 s, 1353 s, 1262 m, 1211 m, 1158 m, 1097 m, 1069 m cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (0.55C, 0, O$\underline{C}$(O)NR_2), 152.8 (0.45C, 0, O$\underline{C}$(O)NR_2), 109.1 (0, C2), 96.0 (0.55C, 0, N$\underline{C}Me_2O$), 94.9 (0.45C, 0, N$\underline{C}Me_2O$), 76.5 (0.55C, 2, O$\underline{C}H_2CMe_2$), 76.2 (0.45C, 2, O$\underline{C}H_2CMe_2$), 73.4 (1, C4), 69.5 (2, C5), 61.6 (2, $\underline{C}H_2OC(O)N$), 60.7 (0.45C, 0, N$\underline{C}Me_2$), 59.8 (0.55C, 0, N$\underline{C}Me_2$), 33.3 (2, $\underline{C}H_2CH_2OC(O)N$), 27.1 (2C, 3, Me), 26.7 (3, Me), 25.8 (3, Me), 25.4 (3, Me), 24.3 (3, Me).

^{13}C NMR (100 MHz, $CDCl_3$, 52°C): δ = 138.4, 109.2, 76.6, 73.6, 69.6, 61.7, 33.5, 27.2, 26.8, 25.8, 25.6, 24.4, 3 quaternary signals were not observed.

2,2,4,4-Tetramethyloxazolidine-3-carboxylic acid (1*S*)-2-[(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-1-(tributylstannanyl)ethyl ester (2.64).



s-BuLi (22.9 mL of a 1.28M solution in cyclohexane : hexane (92:8), 29.4 mmol) was added dropwise to a solution of carbamate **2.52** (8.04 g, 26.7 mmol) and (–)-sparteine (6.88 g, 29.4 mmol) in Et_2O (140 mL) at

–78°C under N_2. The clear yellow solution was stirred at –78°C for 3 h before the dropwise addition of tributyltin chloride (10.9 mL, 40.0 mmol) and the solution was allowed to warm gradually to rt overnight (~12 h). 1M HCl (100 mL) and Et_2O (50 mL) were added and after stirring for 10 min the phases were separated. The aqueous phase was extracted with Et_2O (2 x 50 mL), and the combined organic phases washed with brine (50 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 4) gave the title compound (10.8 g, 18.3 mmol, 69%) as a clear colourless oil.

$[\alpha]_D$ = +15.3 (*c* 0.85, $CHCl_3$).

IR (film): ν = 2953 s, 2922 s, 2877 m, 1680 s, 1399 s, 1382 s, 1261 m, 1208 m, 1070 s cm^{-1}.

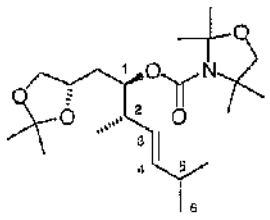
^1H NMR (400 MHz, $CDCl_3$): δ = 4.76 (1H, dt, *J* 9.6, 4.1, H1), 4.17 (1H, septet, *J* 6.2, H3), 4.10 (1H, dd, *J* 6.0, 6.0, H4), 3.72 (2H, s, OCH_2CMe_2), 3.55 (1H, dt, *J* 3.1, 7.4, H4), 2.31-2.20 (1H, m, H2), 1.95 (1H, ddd, *J* 14.4, 6.8, 4.1, H2'), 1.55-1.26 (30H, m, $SnBu_3$, Me), 0.92-0.85 (15H, $SnBu_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (0.6C, 0, $OC(O)NR_2$), 152.6 (0.4C, 0, $OC(O)NR_2$), 109.1 (0, CMe_2), 96.1 (0.6C, 0, $NCMe_2O$), 94.8 (0.4C, 0, $NCMe_2O$), 76.5 (0.6C, 2, OCH_2CMe_2), 76.2 (0.4C, 2, OCH_2CMe_2C), 74.7 (1, C3), 69.6 (2, C4), 67.7 (1, C1), 60.8 (0.4C, 0, $NCMe_2CH_2$), 59.6 (0.6C, 0, $NCMe_2CH_2$), 38.5 (2, C2), 29.3 (3C, 2, $Sn(CH_2CH_2CH_2Me)_3$, $^3J_{C\text{-}Sn}$ 9.8), 27.7 (3C, 2, $Sn(CH_2CH_2CH_2Me)_3$, $^2J_{C\text{-}Sn}$ 28.8), 27.2 (3, Me), 26.9 (0.5C, 3, Me), 26.7 (0.5C, 3, Me), 25.8 (3, Me), 25.5 (2C, 3, Me), 24.4 (0.5C, 3, Me), 24.3 (0.5C, 3, Me), 13.9 (3C, 3, $Sn(CH_2CH_2CH_2Me)_3$), 10.1 (3C, 2, $Sn(CH_2CH_2CH_2Me)_3$, $^1J_{C\text{-}Sn}$ 162.9, 155.9).

LRMS (CI mode, isobutane): *m/z* = 592.0 [$(M+H)^+$, 11 %], 590.1 (10), 534.0 (100), 532.0 (75), 476.0 (8), 474.0 (6), 291.0 (6), 289.0 (5).

Found: C, 54.99; H, 9.04; N, 2.28. $C_{27}H_{53}NO_5Sn$ requires: C, 54.92; H, 9.05; N, 2.37 %.

2,2,4,4-Tetramethyloxazolidine-3-carboxylic acid (1*R*,2*S*,3*E*)-1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,5-dimethylhex-3-enyl ester (2.58).



n-BuLi (4.6 mL of a 1.42M solution in hexanes, 6.5 mmol) was added dropwise to a solution of stannane **2.64** (3.49 g, 5.92 mmol) in THF (100 mL) at –78°C under N_2. The light-yellow solution was stirred at –78°C for 30 min before cooling to approximately –90°C and the dropwise addition of a solution of CuBr•DMS (1.46 g, 7.10 mmol) in di*iso*propylsulfide (2.5 mL) and THF (10 mL). The brown-orange solution was allowed to warm to –78°C over 45 min before re-cooling to approximately –90°C and the dropwise addition of a solution of cationic complex **2.2** (which had been freshly prepared from neutral complex **2.14** (1.55 g, 4.93 mmol) and $NOBF_4$ (633 mg, 5.42 mmol) in MeCN (10 mL) at 0°C for 10 min). After warming to –78°C and stirring for 1.5 h, aqueous NH_4Cl (40 mL), Et_2O (30 mL) and aqueous

NH_3 (5 mL) were added and the mixture warmed to rt. After filtration of the mixture through celite, and thorough washing of the celite with Et_2O (2 x 30 mL) the phases were separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried, filtered and concentrated *in vacuo*. The resulting yellow-brown oil was dissolved in $CHCl_3$ (250 mL) and stirred at rt with O_2 bubbling through the solution for 44 h, and illumination from a standard household light-bulb (150W) for the last 26 h. The dark-brown mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 (5 mL) and flushed through a plug of SiO_2 (4 cm depth, Et_2O) before purification by column chromatography (SiO_2, Et_2O : hexanes, 0 : 1 → 1 : 1) to yield the title olefin (1.12 g, 2.28 mmol, 57%) as a pale yellow oil. Stannane **2.64** (93 mg, 0.23 mmol, 4%) was also recovered.

$[\alpha]_D$ = +10.3 (*c* 1.3, $CHCl_3$).

IR (film): ν = 2978 s, 2939 s, 2872 m, 1694 s, 1399 s, 1377 s, 1259 m, 1209 m, 1094 m, 1064 s cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.45 (1H, dd, *J* 15.6, 6.3, H4), 5.31 (1H, dd, *J* 15.6, 7.9, H3), 4.83 (1H, dt, *J* 9.9, 3.9, H1), 4.15-4.07 (2H, m, C<u>H</u>OCMe$_2$, C<u>H</u>$_A$H$_B$OCMe$_2$), 3.75 (2H, s, OC<u>H$_2$</u>CMe$_2$), 3.58-3.52 (1H, m, CH$_A$<u>H$_B$</u>OCMe$_2$), 2.44-2.34 (1H, m, H2), 2.25 (1H, octet, *J* 6.8, H5), 1.98 (1H, dt, *J* 9.9, 4.7, CH(OAllyl)C<u>H$_A$</u>H$_B$), 1.70-1.63 (1H, m, CH(OAllyl)CH$_A$<u>H$_B$</u>), 1.55 (6H, br s, Me), 1.41 (3H, s, Me), 1.40 (3H, s, Me), 1.38 (3H, s, Me), 1.32 (3H, s, Me), 1.03 (1.5H, d, *J* 6.8, C2-Me), 1.02 (1.5H, d, *J* 6.8, C2-Me), 0.96 (6H, d, *J* 6.8, H6, C5-Me).

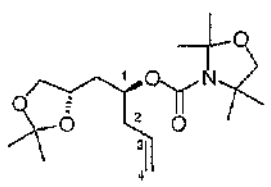
^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7 (0.6C, 0, O<u>C</u>(O)NR$_2$), 152.6 (0.4C, 0, O<u>C</u>(O)NR$_2$), 139.4 (1, C3 or C4), 127.9 (0.6C, 1, C3 or C4), 127.8 (0.4C, 1, C3 or C4), 108.9 (0, O<u>C</u>Me$_2$O), 96.1 (0.6C, 0, O<u>C</u>Me$_2$N), 95.0 (0.4C, 0, O<u>C</u>Me$_2$N), 76.6 (0.6C, 2, O<u>C</u>H$_2$CMe$_2$), 76.2 (0.4C, 2, O<u>C</u>H$_2$CMe$_2$), 74.9 (1, C1 or <u>C</u>HOCMe$_2$), 73.7 (1, C1 or <u>C</u>HOCMe$_2$), 69.7 (2, <u>C</u>H$_2$CMe$_2$), 60.8 (0.4C, 0, N<u>C</u>Me$_2$CH$_2$), 59.9 (0.6C, 0, N<u>C</u>Me$_2$CH$_2$), 41.0 (1, C2), 36.3 (2, CH(OAllyl)<u>C</u>H$_2$), 31.2 (1, C5), 27.1 (3, Me), 26.8 (3, Me), 25.8 (3, Me), 25.7 (0.5C, 3, Me), 25.6 (0.5C, 3, Me), 25.4 (3, Me), 24.4 (3, Me), 22.7 (3, C6), 22.6 (3, C5-Me), 17.0 (C2-Me).

GCMS (160°C, 1 min, 3°C min^{-1} → 200°C, 5°C → 250°C) showed 4 isomers in the ratio 1 : 95 : 2 : 2, retention times 9.32, 10.03, 10.19, 10.36 respectively.

LRMS (CI mode, isobutane): *m/z* = 398.2 [$(M+H)^+$, 95 %], 340.2 (100), 225.2 (62), 167.2 (59).

Found: C, 66.56; H, 9.83; N, 3.47. $C_{22}H_{39}NO_5$ requires: C, 66.47; H, 9.89; N, 3.52 %.

2,2,4,4-Tetramethyloxazolidine-3-carboxylic acid (1*S*)-1-[(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]but-3-enyl ester (2.66).



To a solution of stannane **2.64** (4.09 g, 6.93 mmol) in THF (100 mL) at –78°C under N_2 was added *n*-BuLi (5.4 mL of a 1.42M solution in hexanes, 7.6 mmol) dropwise and the resulting light-yellow solution stirred at –78°C for 20 min before cooling to approximately –90°C and dropwise addition of a solution of CuBr•DMS (1.71 g, 8.32 mmol) in di*iso*propylsulfide (3 mL) and THF (10 mL). After stirring at –78°C for 30 min the orange-brown solution was re-cooled to –90°C and a solution of cationic complex **2.17** (which had been freshly prepared from neutral complex **2.16** (1.12 g, 4.34 mmol) and $NOBF_4$ (558 mg, 4.77 mmol) in MeCN (12 mL) at 0°C for 10 min) was added *via* cannula keeping the internal temperature below –75°C. The brown solution was stirred at –78°C for 1 h before aqueous work-up and decomplexation (O_2, light, rt, 19 h) as described above for olefin **2.58**. Concentration *in vacuo* and purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 4) yielded the title compound (1.45 g, 4.25 mmol, 61%) as a pale yellow oil. Alkane **2.52** (103 mg, 0.34 mmol, 5%) was also isolated by column chromatography. ^1H NMR spectroscopy indicated that olefin **2.66** had been isolated as a 11 : 1 mixture with impurity **2.68**, estimated by comparison of the integration of the following peaks: 5.84-5.72 (1H, m, H3 (**2.66**)) *vs* 5.57-5.49 ppm (2H, m, **2.68**).

$[\alpha]_D$ = + 22.1 (*c* 1.02, $CHCl_3$).

IR (film): ν = 2984 s, 2938 m, 2873 m, 1696 s, 1399 s, 1379 s, 1334 m, 1259 m, 1210 m, 1159 m, 1095 s, 1064 s cm^{-1}.

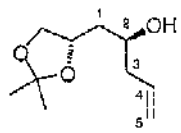
^1H NMR (400 MHz, $CDCl_3$): δ = 5.84-5.72 (1H, m, H3), 5.10 (1H, d, *J* 17.9, H4), 5.09 (1H, d, *J* 9.5, H4'), 4.99-4.93 (1H, m, H1), 4.15 (1H, br pentet, *J* 6.4, C<u>H</u>OCMe$_2$), 4.09 (1H, dd, *J* 7.6, 5.8, C<u>H</u>$_A$H$_B$OCMe$_2$), 3.72 (2H, s, NC(Me)$_2$C<u>H</u>$_2$O), 3.56 (1H, t, *J* 7.6, CH$_A$<u>H</u>$_B$OCMe$_2$), 4.47-2.37 (2H, m, H2), 2.03-1.93 (1H, m, CH(OAllyl)C<u>H</u>$_A$CH$_B$), 1.81-1.71 (1H, m, CH(OAllyl)CH$_A$C<u>H</u>$_B$), 1.55 (3H, s, Me), 1.53 (3H, s, Me), 1.51 (3H, s, Me), 1.41-1.33 (12H, m, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4 (0.6C, 0, O<u>C</u>(O)NR$_2$), 151.6 (0.4C, 0, O<u>C</u>(O)NR$_2$), 133.8 (1, C3), 118.3 (2, C4), 109.1 (0, N<u>C</u>(Me)$_2$O), 96.1 (0.6C, 0, O<u>C</u>(Me)$_2$O), 95.0 (0.4C, 0, O<u>C</u>(Me)$_2$O), 76.5 (0.6C, 2, NC(Me)$_2$<u>C</u>H$_2$), 76.2 (0.4C, 2, NC(Me)$_2$<u>C</u>H$_2$), 73.3 (1, <u>C</u>HOCMe$_2$), 71.1 (1, C1), 69.6 (2, <u>C</u>H$_2$OCMe$_2$), 60.8 (0.4C, 0, N<u>C</u>(Me)$_2$CH$_2$), 59.9 (0.6C, 0, N<u>C</u>(Me)$_2$CH$_2$), 39.5 (0.6C, 2, <u>C</u>H$_2$CH=CH$_2$), 39.4 (0.4C, 2, <u>C</u>H$_2$CH=CH$_2$), 38.0 (0.6C, 2, CH(OAllyl)C<u>H</u>$_2$), 37.9 (0.4C, 2, CH(OAllyl)C<u>H</u>$_2$), 27.2 (3, Me), 26.9 (3, Me), 25.8 (3, Me), 25.7 (0.5C, 3, Me), 25.6 (0.5C, 3, Me), 25.5 (0.5C, 3, Me), 25.4 (0.5C, 3, Me), 24.4 (3, Me).

LRMS (EI mode GCMS, 150°C, 2 min, 5°C min^{-1} → 200°C, 10°C → 250°C, rt = 6.31 min): *m/z* = 341 [($M^{+\bullet}$), 2%], 326 (100), 158 (85), 156 (35), 101 (87). A minor diastereomer (2%) was observed, with a retention time of 6.47 min.

HRMS (CI mode, isobutane): found $[M+H]^+$, 342.2283. $C_{18}H_{32}O_5N$ requires 342.2280.

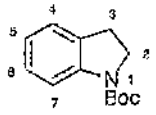
(2*S*)-1-[(4*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl]pent-4-en-2-ol (2.67).



A solution of olefin **2.66** (1.08 g, 3.16 mmol) in THF (25 mL) was added dropwise over 5 min to a suspension of $LiAlH_4$ (480 mg, 12.7 mmol) in THF (35 mL) at 0°C under N_2. The mixture was then refluxed for 4 d (with the addition of a further 480 mg of $LiAlH_4$ after 44 h) before cooling to 0°C and the addition of H_2O (0.9 mL), followed by 15% aqueous NaOH (0.9 mL) and H_2O (2.7 mL). The mixture was brought back to reflux for 30 min before cooling to rt and filtration through celite, washing the celite thoroughly with THF (3 x 15 mL). The filtrate was concentrated *in vacuo* and purification by column chromatography (Et_2O : hexanes = 3 : 7 → 1 : 1) yielded the title compound (475 mg, 2.55 mmol, 81%) as a clear oil. Spectroscopic data were in accordance with literature data.[104, 105]

$[\alpha]_D$ = +11.9 (*c* 3.20) Lit. $[\alpha]_D$ = +14.6 (*c* 3.33, $CHCl_3$).[104]

2,3-Dihydroindole-1-carboxylic acid *tert*-butyl ester (2.73)

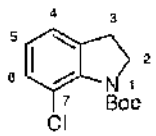


The title compound was prepared on a 75.6 mmol scale according to the procedure of Iwao.[229] Purification by short-path distillation (b.p. = 95-97°C / 0.1 mmHg, Lit. b.p. = 83-84°C / 0.1 mmHg[229]) gave the title compound (14.4 g, 65.8 mmol, 87%) as a clear oil which solidified upon standing and was purified further by recrystallisation from hexanes. ^1H NMR and IR spectroscopic data were in accordance with literature data.[110] ^{13}C NMR spectroscopic data ($CDCl_3$, rt) were in accordance with the partial data reported by Meyers, and in common with the literature report not all quaternary carbons were visible.[230]

m.p. = 43-45°C (hexanes). Lit. m.p. = 42-45°C (from the melt).[229]

^{13}C NMR (100 MHz, $CDCl_3$, 52°C): δ = 152.8 (0), 142.9 (0), 131.4 (0), 127.5 (1), 124.8 (1), 122.3 (1), 115.0 (1), 80.9 (0), 47.8 (2), 28.7 (3C, 3), 27.5 (2).

7-Chloro-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (2.74)

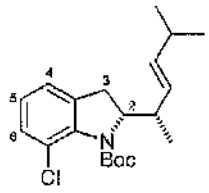


The title compound was prepared in 72% yield on a scale of 14.8 mmol according to the method of Iwao.[110] Purification by column chromatography yielded the title compound as a pale yellow solid which was purified further by recrystallisation from pentane. ^1H NMR and IR spectroscopic data were in accordance with literature data.[110]

m.p. = 84.5-85.5°C (pentane) Lit. 84.5-85°C (pentane).[110]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (0, $\underline{C}O_2{}^tBu$), 140.7 (0, Ph), 137.2 (0, Ph), 129.1 (1, Ph), 125.3 (1, Ph), 124.2 (0, Ph), 122.9 (1, Ph), 81.6 (0, $\underline{C}Me_3$), 51.5 (2, C2), 30.1 (2, C3), 28.3 (3C, 2, $C\underline{Me}_3$).

(2*R*)-7-Chloro-2-[(1*S*,3*E*)-1,4-dimethylpent-2-enyl]-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (2.80).



s-BuLi (4.3 mL of a 1.28M solution in cyclohexane : hexane (92:8), 5.54 mmol) was added dropwise to a solution of (–)-sparteine (1.30 g, 5.54 mmol) in *tert*-butyl methyl ether (70 mL) at –78°C under N_2. The solution was stirred for 10 min before the slow addition of a pre-cooled (–78°C) solution of indoline **2.74** (1.17 g, 4.62 mmol) in *tert*-butyl methyl ether (50 mL) *via* cannula, ensuring the internal solution temperature did not rise above –75°C. The solution was stirred at –78°C for 3.5 h before cooling to approximately –85°C and addition of a solution of CuBr•DMS (1.23 g, 6.01 mmol) in diisopropyl sulfide (4 mL) and THF (6 mL) ensuring the internal solution temperature did not rise above –75°C. The orange solution was stirred at –78°C for 30 min before cooling to approximately –85°C and adding a solution of complex **2.2** (which had been freshly prepared from neutral complex *ent*-**2.14** (1.21 g, 3.85 mmol) and $NOBF_4$ (495 mg, 4.24 mmol) in MeCN (10 mL) at 0°C for 10 min) *via* cannula. The brown solution was allowed to gradually warm to rt over 14 h before aqueous work-up in an identical fashion to that described above for olefin **2.58**. The crude material following aqueous work-up was dissolved in Me_2CO (250 mL) and $NaOAc•3H_2O$ (7.5 g) added, followed by CAN (2.5 g). The orange-brown mixture was stirred at rt for 3 h before concentration *in vacuo* and addition of Et_2O (100 mL) and H_2O (100 mL). After stirring for 10 min the mixture was filtered through celite, the phases were separated and the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to yield a brown oil. Purification by column chromatography (SiO_2, Et_2O : hexanes = 5 : 95 → 10 : 90) yielded the title olefin (766 mg, 2.19 mmol, 57% from neutral complex *ent*-**2.14**) as a pale yellow oil. Further elution yielded an inseparable mixture of ketone **2.81** and indoline **2.74** (111 mg, **2.81** : **2.74** = 1 : 3, approximately 3% and 6% respectively, R_f (Et_2O : hexanes = 1 : 9): **2.80** = 0.40, **2.74** / **2.81** = 0.23). Indole **2.82**[109] (165 mg, 0.66 mmol, 14%) was also isolated. ^{1}H NMR indicated that **2.80** was obtained as a mixture of isomers, GCMS (150°C, 2 min, 5°C min^{-1} → 200°C, 10°C min^{-1} → 250°C) showed 4 isomers in the ratio 4 : 9 : 81 : 6, retention times 8.66, 9.11, 9.50, 9.78 min respectively. NMR data is quoted for the major isomer.

$[\alpha]_D$ = +9.42 (*c* 1.38, $CHCl_3$).

IR (film) ν = 2961 s, 2931 m, 1702 s, 1454 s, 1366 s, 1327 s, 1244 m, 1162 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (1H, d, *J* 8.0, Ph), 7.01 (1H, d, *J* 7.2, 0.4, Ph), 6.93 (1H, t, *J* 7.6, Ph), 5.30 (1H, ddd, *J* 15.3, 6.4, 0.8, CH=C<u>H</u>CHMe$_2$), 5.06 (1H, ddd, *J* 15.3, 8.2, 1.4, C<u>H</u>=CHCHMe$_2$), 4.45 (1H, ddd, *J* 8.5, 5.4, 1.2, H2), 3.35 (1H, dd, *J* 16.0, 8.5, H3), 2.61 (1H, d, *J* 16.0, H3'), 2.24 (1H, ddq, *J* 13.2, 1.2, 6.7, C<u>H</u>Me), 2.08 (1H, dseptet, *J* 1.1, 6.7, C<u>H</u>Me$_2$), 1.54 (9H, s, C<u>Me</u>$_3$), 0.99 (3H, d, *J* 6.8, CH<u>Me</u>), 0.82 (3H, d, *J* 6.8, CH<u>Me</u>(Me)), 0.80 (3H, *J* 6.8, CHMe(<u>Me</u>)).

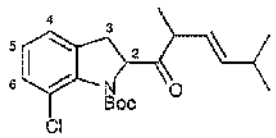
^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8 (0, <u>C</u>O$_2$*t*-Bu), 140.9 (0, Ph), 138.3 (1, CH=<u>C</u>HCHMe$_2$), 136.9 (0, Ph), 128.8 (1, Ph), 127.7 (1, <u>C</u>H=CHCHMe$_2$), 125.2 (1, Ph), 124.3 (0, Ph), 122.7 (1, Ph), 81.4 (0,

$\underline{C}Me_3$), 66.9 (1, C1), 42.2 (1, $\underline{C}HMe$), 33.4 (2, C2), 31.0 (1, $\underline{C}HMe_2$), 28.4 (3C, 3, $C\underline{Me}_3$), 22.6 (3, $CH\underline{Me}(Me)$), 22.3 (3, $CHMe(\underline{Me})$), 16.7 (3, CHMe).

LRMS (EI mode): *m/z* = 349 [($M^{+\bullet}$), 2 %], 276 (3), 252 (6), 152 (100), 117 (11), 57 (97).

Found: C, 68.50; H, 7.89; N, 3.96. Calc. for $C_{20}H_{28}ClNO_2$: C, 68.65; H, 8.07; N, 4.00%.

Spectroscopic data for **8-Chloro-2-(2,5-dimethylhex-3-enoyl)-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (2.81)**:



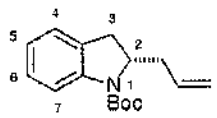
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-6.94 (3H, m, Ph), 5.24 (1H, dd, *J* 15.7, 6.0, CH=C$\underline{H}$CHMe$_2$), 5.17 (1H, dd, *J* 15.7, 7.8, C$\underline{H}$=CHCHMe$_2$), 4.93 (1H, dd, *J* 10.0, 2.0, H2), 3.82 (1H, dq, *J* 7.0, 7.1, C(O)C$\underline{H}$Me), 3.48 (1H, dd, *J* 16.4, 10.0, H3), 3.19 (1H, dd, *J* 16.4, 2.0, H3'), 1.99-1.91 (1H, m, C$\underline{H}$Me$_2$), 1.17 (3H, d, *J* 6.8, C(O)CH$\underline{Me}$), 0.71 (3H, d, *J* 6.8, CH$\underline{Me}$(Me)), 0.70 (3H, d, *J* 6.7, CHMe($\underline{Me}$)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8 (0, $\underline{C}$(O)CHMe), 153.6 (0, $\underline{C}O_2{}^t$Bu), 140.5 (1, $\underline{C}$H=CHCHMe$_2$), 139.9 (0, Ph), 135.0 (0, Ph), 129.4 (1, Ph), 125.7 (1, CH=$\underline{C}$HCHMe$_2$ or Ph), 124.7 (1, CH=$\underline{C}$HCHMe$_2$ or Ph), 124.1 (0, Ph), 123.0 (1, Ph), 82.6 (0, $\underline{C}Me_3$), 69.3 (1, C2), 44.2 (1, C(O)$\underline{C}$HMe), 33.0 (2, C3), 30.8 (1, $\underline{C}HMe_2$), 28.3 (3C, 3, $C\underline{Me}_3$), 22.2 (3, $CH\underline{Me}(Me)$), 22.0 (3, $CHMe(\underline{Me})$), 17.4 (3, C(O)$\underline{C}$HMe).

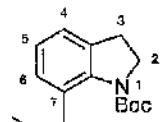
LRMS (EI mode GCMS, 150°C, 2 min, 5°C min^{-1} → 200°C, 10°C → 250°C, rt = 11.87 min): *m/z* = 377 [$M^{+\bullet}$, 3 %], 304 (4), 277 (7), 152 (100), 151 (11), 117 (17), 57 (79).

HRMS (GCMS, EI$^+$ mode): found [$M^{+\bullet}$], 377.1756. $C_{21}H_{28}O_3N^{35}Cl$ requires 377.1758.

(2*S*)-2-Allyl-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (2.85) and **7-Allyl-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (2.86).**



2.85



2.86

s-BuLi (6.4 mL of a 1.30M solution in cyclohexane : hexane (92:8), 8.25 mmol) was added dropwise to a solution of indoline **2.73** (1.39 g, 6.4 mmol) and (–)-sparteine (1.93 g, 8.25 mmol) in *tert*-butyl methyl ether (65 mL) at –78°C under N_2. The light yellow solution was stirred at –78°C for 3.25 h before cooling to approximately –90°C and addition of a solution of CuBr•DMS (1.83 g, 8.89 mmol) in di*iso*propyl sulfide (5 mL) and THF (7 mL) dropwise, ensuring the internal solution temperature did not rise above –75°C. After stirring for 40 min at –78°C the solution was cooled to approximately –85°C and a solution of cationic complex **2.17** (which had been freshly prepared from neutral complex **2.16** (2.69 g, 10.4 mmol) and $NOBF_4$ (1.34 g, 11.4 mmol) in MeCN (20 mL) at 0°C for 10 min) was added dropwise over 10 min. The dark-brown solution was allowed to warm slowly to rt under N_2 overnight, before aqueous work-up in an

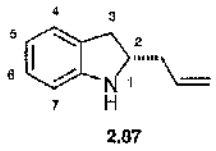
identical fashion to that described above for olefin **2.58**. Decomplexation was performed using the CAN mediated procedure described above for olefin **2.80**. Purification by column chromatography (SiO_2, PhMe : hexanes = 1 : 1 → 100 : 0 followed by Et_2O : hexanes = 1 : 9) yielded a mixture of the title compounds as a pale yellow oil (901 mg, 3.47 mmol, 55%; R_f = 0.39 in PhMe) and recovered indoline **2.73** (130 mg, 0.59 mmol, 9%; R_f = 0.24 in PhMe). ^1H NMR spectroscopy revealed an approximately equimolar ratio of **2.85** and **2.86**. ^1H and ^{13}C NMR spectroscopic data for **2.85** and ^1H NMR data for **2.86** were in accordance with literature data.[109]

$[\alpha]_D$ = +44.2 (*c* 0.55, $CHCl_3$).

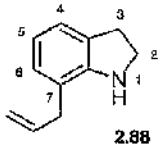
IR (film, 1 : 1 mixture of **2.85** / **2.86**): ν = 2975 m, 1703 s, 1484 s, 1453 m, 1391 s, 1333 m, 1293 m, 1168 s, 1139 m cm^{-1}.

^{13}C NMR (**2.86**) (100 MHz, $CDCl_3$): δ = 154.0 (0, $\underline{C}O_2{}^t$Bu), 142.3 (0, Ph), 138.3 (0, Ph), 137.1 (1, $\underline{C}H{=}CH_2$), 134.8 (0, Ph), 128.8 (1, Ph), 124.7 (1, Ph), 116.0 (2, CH=$\underline{C}H_2$), 115.4 (1, Ph), 80.8 (0, $\underline{C}Me_3$), 51.2 (2, C2), 37.9 (2, $\underline{C}H_2CH{=}CH_2$), 29.8 (2, C3), 28.6 (3C, C$\underline{Me}_3$).

(2*S*)-2-Allyl-2,3-dihydro-1*H*-indole (2.87) and 7-Allyl-2,3-dihydro-1*H*-indole (2.88).



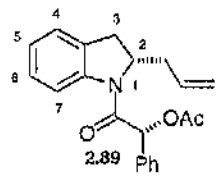
2.87



2.88

Trifluoroacetic acid (2 mL) was added to a solution of indolines **2.85** and **2.86** (≈ 1 : 1, 742 mg, 2.86 mmol) in CH_2Cl_2 (8 mL) at 0°C under N_2. The orange-brown solution was stirred at 0°C for 30 min and then at rt for 1.5 h before concentration *in vacuo* to give a purple-red oil which was dissolved in Et_2O (25 mL) and washed with 0.5M NaOH (2 x 25 mL). The combined aqueous phases were extracted with Et_2O (2 x 25 mL) and CH_2Cl_2 (3 x 25 mL) and the combined organic phases washed with brine (25 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : PhMe = 2 : 98 → 5 : 95) yielded indoline **2.87** (233 mg, 1.46 mmol, 51%; R_f = 0.51 in Et_2O : PhMe = 5 : 95) and indoline **2.88** (100 mg, 0.63 mmol, 22%; R_f = 0.34 in Et_2O : PhMe = 5 : 95) as clear oils. Spectroscopic data for **2.87**[230] ($[\alpha]_D$ = –54.3 (*c* 1.18, $CHCl_3$)) and for **2.88**[231] were in accordance with literature data.

Acetic acid 2-[(2*S*)-2-allyl-2,3-dihydroindol-1-yl]-2-oxo-1-phenylethyl ester (2.89).



2.89

A solution of DCC (87 mg, 0.42 mmol) and (*R*)-*O*-acetoxyphenylacetic acid (82 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was cooled to 0°C under N_2 and stirred for 15 min before the addition *via* cannula of a solution of indoline **2.87** (56 mg, 0.35 mmol) in CH_2Cl_2 (10 mL). The cloudy mixture was stirred at 0°C under N_2 for

1 h before concentration *in vacuo*. EtOAc (25 mL) was added to the residue and the mixture filtered before the addition of 0.5M HCl (15 mL). The phases were separated and the organic phase washed with 0.5M HCl (15 mL) and aqueous $NaHCO_3$ (2 x 15 mL). The two aqueous phases were extracted separately with EtOAc (2 x 15 mL) and the combined organic phases dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 4 : 6) yielded the title compound (102 mg, 0.30 mmol, 87%) as a colourless oil. ^1H and ^{13}C NMR spectroscopic analysis indicated the presence of a single diastereomer within the limits of detection.

$[\alpha]_D = -121.9$ (*c* 2.04, $CHCl_3$).

IR (film): ν = 1739 s, 1670 s, 1599 m, 1481 s, 1458 m, 1411 s, 1371 m, 1229 s, 1184 m, 1045 s, 956 m, 919 m, 755 s cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (1H, d, *J* 8.1, Ph), 7.52 (2H, t, *J* 2.9, Ph), 7.46-7.38 (3H, m, Ph), 7.23 (1H, t, *J* 7.7, Ph), 7.15 (1H, d, *J* 7.2, Ph), 7.05 (1H, t, *J* 7.4, Ph), 6.18 (1H, s, C<u>H</u>(OAc)Ph), 5.79 (1H, ddt, *J* 17.0, 10.0, 7.0, C<u>H</u>=CH_2), 5.19 (1H, d, *J* 17.0, CH=C<u>H</u>$_2$), 5.16 (1H, d, *J* 10.0, CH=C<u>H</u>$_2$), 4.32 (1H, br t, *J* 8.5, H2), 3.02 (1H, dd, *J* 15.8, 8.5, H3), 2.86-2.72 (2H, m, C<u>H</u>$_A$H$_B$CH=CH_2, H3'), 2.49 (1H, dt, *J* 14.4, 7.9, CH_AC<u>H</u>$_B$CH=CH_2), 2.24 (3H, s, OC(O)<u>Me</u>).

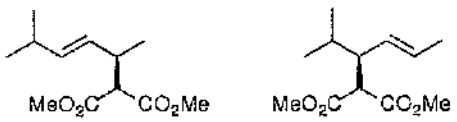
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (0, O<u>C</u>(O)R), 165.8 (0, O<u>C</u>(O)R), 142.1 (0, Ph), 133.9 (0, Ph), 133.0 (1, <u>C</u>H=CH_2), 130.3 (0, Ph), 129.9 (1, Ph), 129.4 (2C, 1, Ph), 128.9 (2C, 1, Ph), 127.8 (1, Ph), 125.0 (1, Ph), 124.7 (1, Ph), 119.0 (2, CH=<u>C</u>H$_2$), 118.2 (1, Ph), 75.0 (1, <u>C</u>H(OAc)Ph), 58.3 (1, <u>C</u>2), 39.1 (2, <u>C</u>H$_2$CH=CH_2), 33.7 (2, C3), 21.0 (3, OC(O)<u>Me</u>).

LRMS (EI+ mode): *m/z* = 335.4 [$M^{+\bullet}$, 24 %], 294.3 (26), 177.2 (17), 149.2 (44), 118.2 (100), 84.0 (49).

GCMS (150°C, 1 min, 5°C min^{-1} → 250°C, rt = 14.73 min) indicated the presence of a single amide diastereomer, within the limits of detection.

HRMS (EI^+ mode): found [$M^{+\bullet}$], 335.1521. $C_{21}H_{21}NO_3$ requires 335.1521.

2-[(1*R*,2*E*)-1,4-Dimethylpent-2-enyl]malonic acid dimethyl ester (2.94) and 2-[(1*S*,2*E*)-1-Isopropylbut-2-enyl]malonic acid dimethyl ester (2.95).



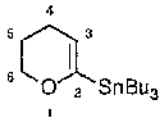
2.94 **2.95**

NaH (382 mg, 9.55 mmol) was washed with THF (2 x 5 mL), suspended in THF (100 mL) and cooled to 0°C under N_2, before the dropwise addition of dimethyl malonate (1.09 mL, 9.55 mmol) over 10 min. After warming to rt and stirring for 15 min the solution was cooled to –78°C and a solution of cationic complex **2.1** (which had been freshly prepared from neutral complex **2.14** (1.50 g, 4.76 mmol) and $NOBF_4$ (613 mg, 5.25 mmol) in MeCN (15 mL) at 0°C for 10 min) was added dropwise. After warming to rt over 1 h and stirring at rt for 2 h the mixture was concentrated *in vacuo* and re-dissolved in Me_2CO (100 mL). NaOAc•$3H_2O$ (5.0 g) was added and rapid stirring commenced before the addition of CAN (2.87 g, 5.24

mmol). The dark-brown solution was stirred for 17 h with the addition of further portions of CAN (1.30 g, 2.38 mmol) after 30 min, 1 h and 2 h. Following aqueous work-up in the fashion described above for olefin **2.80**, purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) yielded an inseparable mixture of the title compounds (470 mg, 2.06 mmol, 43%) as a pale yellow oil. Spectroscopic data were in accordance with literature data.[232] The regioisomeric ratio was estimated as **2.84** : **2.85** = 1.4 : 1 by ^1H NMR spectroscopy, comparing the integration of H2 doublets at 3.51 ppm (*J* 9.8) and 3.25 ppm (*J* 3.25) for **2.85** and **2.84** respectively.

$[\alpha]_D$ = +15.6 (*c* 1.40, $CHCl_3$).

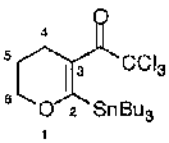
Tributyl(5,6-dihydro-4*H*-pyran-2-yl)stannane (2.98).



t-BuLi (12.1 mL of a 1.7M solution in pentane, 20.6 mmol) was added to a solution of 3,4-dihydro-2*H*-pyran (1.98 g, 20.6 mmol) in THF (5 mL) at –78°C under N_2. The flask was transferred to an ice-bath, and stirred at 0°C for 30 min before cooling to –78°C and adding tributyltin chloride (6.15 mL, 22.66 mmol). The solution was allowed to warm to room temperature with stirring under N_2 over 2 h, before pouring into ether (50 mL) and aqueous NH_4Cl (1 mL). After rapid stirring for 5 min the phases were separated and the organic phase washed with brine (2 x 50 mL), dried, filtered and concentrated *in vacuo* to give a clear oil. Purification by distillation (b.p. 101°C / 0.1 mmHg, Lit. b.p. = 105-110°C / 0.1 mmHg[233]) gave the title compound (13.9 g, 37.3 mmol, 84%) as a clear oil. IR and ^1H NMR spectroscopic data were in accordance with literature data.[233]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (0, C2), 112.5 (1, $^2J_{C\text{-}Sn}$ 31.7, C3), 66.2 (2, $^3J_{C\text{-}Sn}$ 10.3, C6), 29.2 (3C, 2, $^3J_{C\text{-}Sn}$ 10.1, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 27.4 (3C, 2, $^2J_{C\text{-}Sn}$ 27.7, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 23.4 (2, C5), 21.4 (2, $^3J_{C\text{-}Sn}$ 16.1, C4), 13.8 (3C, 3, $Sn(CH_2CH_2CH_2\underline{Me})_3$), 9.6 (3C, 2, $^1J_{C\text{-}Sn}$ 171.8, 164.4, $Sn(\underline{C}H_2CH_2\underline{C}H_2Me)_3$).

2,2,2-Trichloro-1-[2-(tributylstannanyl)-5,6-dihydro-4*H*-pyran-3-yl]ethanone (2.99).



Trichloroacetyl chloride (0.30 mL, 2.72 mmol) was added dropwise over 5 min to a solution of stannane **2.98** and *N*,*N*-diisopropylethylamine (0.05 mL, 0.27 mmol) in CH_2Cl_2 (9 mL) at 0°C under N_2. The solution was allowed to warm to rt over 2 h, and stirred for a further 16 h. The red-orange solution was then poured into 5% aqueous $NaHCO_3$ (20 mL) and the phases separated. The organic phase was washed with H_2O (2 x 25 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, hexanes) gave the title compound (335 mg, 0.65 mmol, 24%) as a clear oil.

IR (film): ν = 2954 s, 2922 s, 1662 m, 1464 m, 1252 m, 1168 s, 812 m, 722 s cm^{-1}.

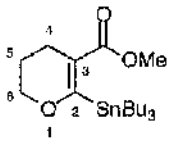
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (2H, t, *J* 5.2, H6), 2.75 (2H, t, *J* 6.4, H4), 1.92-1.86 (2H, m, H5), 1.59-1.47 (6H, m, $Sn(CH_2CH_2\underline{C}H_2Me)_3$), 1.31 (6H, apparent sextet, *J* 7.2, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 1.03-0.99 (6H, m, $Sn(\underline{C}H_2CH_2CH_2Me)_3$), 0.89 (9H, t, *J* 7.2, $Sn(CH_2CH_2CH_2\underline{Me})_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9 (0, $\underline{C}OCCl_3$), 182.2 (0, C2), 116.2 (0, C3), 97.3 (0, $CO\underline{C}Cl_3$), 68.5 (2, $^3J_{C\text{-}Sn}$ 9.8, C6), 29.2 (3C, 2, $^3J_{C\text{-}Sn}$ 10.1, $Sn(CH_2CH_2\underline{C}H_2Me)_3$), 27.8 (3C, 2, $^2J_{C\text{-}Sn}$ 30.4, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 23.2 (2, $^3J_{C\text{-}Sn}$ 7.8, C4), 21.3 (2, C5), 13.7 (3C, 3, $Sn(CH_2CH_2CH_2\underline{Me})_3$), 11.7 (3C, 2, $^1J_{C\text{-}Sn}$ 183.1, 175.1, $Sn(\underline{C}H_2CH_2CH_2Me)_3$).

LRMS (CI mode, NH_3): *m/z* = 536.1 [$(M+NH_4)^+$, 36 %], 519.1 [$(M+H)^+$, 29 %], 461.1 (100), 427.0 (66), 359.1 (60).

HRMS (CI mode, isobutane): found $[M+H]^+$, 519.0638. $C_{19}H_{34}{}^{35}Cl_3O_2{}^{120}Sn$ requires 519.0632.

2-(Tributylstannanyl)-5,6-dihydro-4*H*-pyran-3-carboxylic acid methyl ester (2.100).



Na (30 mg) was added to a solution of stannane **2.99** (325 mg, 0.63 mmol) in MeOH (5 mL) at rt under N_2. After stirring at rt for 1 h, the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, CH_2Cl_2 : hexanes = 1 : 5) gave the title compound (226 mg, 0.52 mmol, 83%) as a clear oil.

IR (film): ν = 2954 s, 2922 s, 2872 m, 2852 m, 1690 s, 1560 s, 1290 s, 1264 s, 1156 m, 1096 s, 1076 m cm^{-1}.

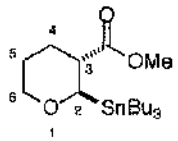
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (2H, t, *J* 5.1, H6, H6'), 3.69 (3H, s, OMe), 2.29 (2H, t, *J* 6.4, H4, H4'), 1.87-1.81 (2H, m, H5, H5'), 1.54-1.46 (6H, m, $Sn(CH_2CH_2\underline{C}H_2Me)_3$), 1.31 (6H, apparent sextet, *J* 7.3, $Sn(CH_2C\underline{H}_2CH_2Me)_3$), 0.99-0.95 (6H, m, $Sn(\underline{C}H_2CH_2CH_2Me)_3$), 0.89 (9H, t, *J* 7.3, $Sn(CH_2CH_2CH_2\underline{Me})_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5 (0, $\underline{C}O_2Me$), 170.2 (0, C2), 113.9 (0, C3), 67.1 (2, $^3J_{C\text{-}Sn}$ 10.6, C6), 51.2 (3, $CO_2\underline{Me}$), 29.2 (3C, 2, $^3J_{C\text{-}Sn}$ 10.2, $Sn(CH_2CH_2\underline{C}H_2Me)_3$), 27.5 (3C, 2, $^2J_{C\text{-}Sn}$ 30.2, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 21.6 (2, C4), 21.0 (2, C5), 13.9 (3C, 3, $Sn(CH_2CH_2CH_2\underline{Me})_3$), 11.5 (3C, 2, $^1J_{C\text{-}Sn}$ 183.9, 173.9, $Sn(\underline{C}H_2CH_2CH_2Me)_3$).

LRMS (CI mode, NH_3): *m/z* = 433.2 [$(M+H)^+$, 6 %], 392.2 (33), 375.1 (100), 373.1 (77).

Found: C, 53.00; H, 8.48. $C_{19}H_{36}O_3Sn$ requires: C, 52.92; H, 8.42 %.

***Trans*-2-(Tributylstannanyl)tetrahydropyran-3-carboxylic acid methyl ester (2.101).**



Trimethylsilyl trifluoromethanesulfonate (1.62 mL, 8.94 mmol) was added dropwise to a solution of stannane **2.100** (1.29 g, 2.98 mmol) and triethylsilane (4.76 mL, 29.8 mmol) in CH_2Cl_2 (100 mL) at –78°C under N_2. After stirring at –78°C for 30 min the solution was allowed to warm to rt before adding aqueous $NaHCO_3$ (50 mL). The phases were separated, the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic phases washed with brine (50 mL), dried, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 5 : 95) gave the title compound (1.19 g, 2.74 mmol, 92%) as a clear oil.

IR (film): ν = 2954 s, 2930 s, 2872 m, 2852 m, 1732 s, 1462 m, 1436 m, 1150 m, 1074 s, 1016 m cm^{-1}.

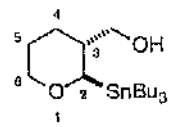
^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (1H, ddd, *J* 11.2, 3.6, 2.0, H6), 3.61 (1H, d, *J* 11.2, H2), 3.64 (3H, s, $CO_2\underline{Me}$), 3.26 (1H, dt, *J* 2.0, 11.2, H6'), 2.82 (1H, ddd, *J* 11.2, 11.0, 3.5, H3), 2.10-2.06 (1H, m, H4), 1.69-1.61 (3H, m, H4', H5, H5'), 1.53-1.45 (6H, m, $Sn(CH_2CH_2C\underline{H}_2Me)_3$), 1.31 (6H, apparent sextet, *J* 7.3, $Sn(CH_2C\underline{H}_2CH_2Me)_3$), 0.92-0.84 (6H, m, $Sn(C\underline{H}_2CH_2CH_2Me)_3$), 0.89 (9H, t, *J* 7.4, $Sn(CH_2CH_2CH_2\underline{Me})_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (0, $\underline{C}O_2Me$), 75.3 (1, $^1J_{C\text{-}Sn}$ 199.9, 189.9, C2), 70.3 (2, $^3J_{C\text{-}Sn}$ 19.5, C6), 51.7 (3, $CO_2\underline{Me}$), 46.9 (1, C3), 29.2 (4C, 2, $^3J_{C\text{-}Sn}$ 9.9, $Sn(CH_2CH_2\underline{C}H_2Me)_3$, C4), 27.6 (3C, 2, $^2J_{C\text{-}Sn}$ 27.8, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 25.8 (2, C5), 13.9 (3C, 3, $Sn(CH_2CH_2CH_2\underline{Me})_3$), 9.0 (3C, 2, $^1J_{C\text{-}Sn}$ 160.9, 153.8, $Sn(\underline{C}H_2CH_2CH_2Me)_3$).

LRMS (CI mode, NH_3): *m/z* = 452.3 [$(M+NH_4)^+$, 50 %], 450.3 (35), 394.2 (57), 377.1 (100).

Found: C, 52.45; H, 8.91. $C_{19}H_{38}O_3Sn$ requires: C, 52.68; H, 8.84 %.

***Trans*-[2-(Tributylstannanyl)tetrahydropyran-3-yl]methanol (2.102).**



To a solution of stannane **2.101** (316 mg, 0.73 mmol) in THF (5 mL) at 0°C under N_2 was added diisobutylaluminium hydride (0.26 mL, 1.46 mmol). The solution was stirred at 0°C for 1 h before adding dropwise a solution of sodium potassium tartrate (2.0 g) in H_2O (5 mL). The mixture was stirred at rt for 3 h before the addition of ether (50 mL) and separation of phases. The aqueous phase was extracted with ether (2 x 15 mL), and the combined organic phases washed with brine (25 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 1 : 9) gave the title compound (234 mg, 0.58 mmol, 79%) as a clear oil.

IR (film): ν = 3404 br m, 2954 s, 2926 s, 2872 m, 2850 m, 1464 m, 1074 s, 1024 m, 868 m cm^{-1}.

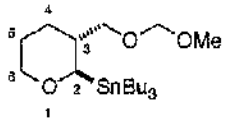
^1H NMR (400 MHz, $CDCl_3$): δ = 3.86-3.82 (1H, m, H6), 3.60 (1H, d, *J* 10.0, H2), 3.51-3.46 (1H, m, CH_AH_BOH), 3.42-3.37 (1H, m, CH_AH_BOH), 3.26 (1H, dt, *J* 4.0, 10.4, H6'), 2.01-1.89 (3H, m, H3 and H4, H4' or H5, H5'), 1.69-1.61 (2H, m, H4, H4' or H5, H5'), 1.55-1.47 (6H, m, $Sn(CH_2CH_2CH_2Me)_3$), 1.32 (6H, apparent sextet, *J* 7.4, $Sn(CH_2CH_2CH_2Me)_3$), 0.92-0.88 (6H, m, $Sn(CH_2CH_2CH_2Me)_3$), 0.90 (9H, t, *J* 7.4, $Sn(CH_2CH_2CH_2Me)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.7 (1, $^1J_{C\text{-}Sn}$ 205.0, 196.0, C2), 70.8 (2, $^3J_{C\text{-}Sn}$ 19.4, C6), 65.7 (2, $^3J_{C\text{-}Sn}$ 4.7, CH_2OH), 43.2 (1, C3), 29.4 (3C, 2, $^3J_{C\text{-}Sn}$ 9.8, $Sn(CH_2CH_2CH_2Me)_3$), 28.5 (2, $^3J_{C\text{-}Sn}$ 18.2, C4), 27.6 (3C, 2, $^2J_{C\text{-}Sn}$ 27.4, $Sn(CH_2CH_2CH_2Me)_3$), 26.1 (2, C5), 13.9 (3C, 3, $Sn(CH_2CH_2CH_2Me)_3$), 9.4 (3C, 2, $^1J_{C\text{-}Sn}$ = 157.9, 150.9, $Sn(CH_2CH_2CH_2Me)_3$).

LRMS (CI mode, isobutane): *m/z* = 405.2 [$(M+H)^+$, 20 %], 353.2 (25), 347.1 (100).

Found: C, 53.33; H, 9.34. $C_{18}H_{38}O_2Sn$ requires: C, 53.35; H, 9.45 %.

***trans*-Tributyl(3-methoxymethoxymethyl-tetrahydropyran-2-yl)stannane (2.103).**



Chloromethyl methyl ether (0.09 mL, 1.15 mmol) was added to a solution of stannane **2.102** (234 mg, 0.58 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.15 mmol) and tetrabutylammonium iodide (11 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) at rt under N_2. The solution was stirred at rt for 3 h before the addition of aqueous $NaHCO_3$ (20 mL) and separation of phases. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers washed with brine (20 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 1 : 49) gave the title compound (225 mg, 0.50 mmol, 86%) as a clear oil.

IR (film): ν = 2954 s, 2926 s, 2872 m, 2850 m, 1464 m, 1154 m, 1114 m, 1074 s, 1044 s, 922 m cm^{-1}.

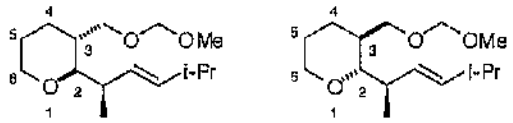
^1H NMR (400 MHz, $CDCl_3$): δ = 4.56 (2H, s, OCH_2OMe), 3.85 (1H, br d, *J* 10.8, H6), 3.58 (1H, d, *J* 10.4, H2), 3.34 (3H, s, OCH_2OMe), 3.33-3.26 (2H, m, CH_2OMOM), 3.23 (1H, dt, *J* 10.8, 3.1, H6'), 2.12-2.03 (1H, m, H3), 1.96-1.88 (1H, m, H4), 1.74-1.58 (2H, m, H5, H5'), 1.56-1.42 (7H, m, H4', $Sn(CH_2CH_2CH_2Me)_3$), 1.31 (6H, apparent sextet, *J* 7.3, $Sn(CH_2CH_2CH_2Me)_3$), 0.92-0.86 (6H, m, $Sn(CH_2CH_2CH_2Me)_3$), 0.89 (9H, t, *J* 7.2, $Sn(CH_2CH_2CH_2Me)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.6 (2, OCH_2OMe), 78.0 (1, $^1J_{C\text{-}Sn}$ 208.5, 199.1, C2), 70.7 (2, $^3J_{C\text{-}Sn}$ 20.1, C6 or CH_2OMOM), 70.4 (2, $^3J_{C\text{-}Sn}$ 3.8, C6 or CH_2OMOM), 55.3 (3, CH_2OMe), 41.1 (1, C3), 29.4 (3C, 2, $^3J_{C\text{-}Sn}$ 9.8, $Sn(CH_2CH_2CH_2Me)_3$), 29.2 (2, $^3J_{C\text{-}Sn}$ 18.6, C4), 27.7 (3C, 2, $^2J_{C\text{-}Sn}$ 27.4, $Sn(CH_2CH_2CH_2Me)_3$), 26.3 (2, C5), 13.9 (3C, 3, $Sn(CH_2CH_2CH_2Me)_3$), 9.4 (3C, 2, $^1J_{C\text{-}Sn}$ 158.3, 151.2, $Sn(CH_2CH_2CH_2Me)_3$).

LRMS (CI mode, NH_3): *m/z* = 468.3 [$(M+NH_4)^+$, 31 %], 408.2 (100), 391.2 (96).

Found: C, 53.23; H, 9.32. $C_{20}H_{42}O_3Sn$ requires: C, 53.47; H, 9.42 %.

(2*R*,3*R*)- and (2*S*,3*S*)-2-[(1*R*,2*E*)-1,4-Dimethylpent-2-enyl]-3-methoxymethoxymethyl-tetrahydropyran (2.104 / 2.105).



n-BuLi (0.44 mL of a 2.33M solution in hexanes, 1.03 mmol) was added to a solution of stannane **2.103** (424 mg, 0.94 mmol) in THF (10 mL) at –78°C under N_2. The solution was stirred at –78°C for 10 min before cooling to –90°C and adding *via* cannula a precooled (–90°C) solution of CuBr•DMS (232 mg, 1.13 mmol) in diisopropyl sulfide (0.8 mL) and THF (1.0 mL), maintaining the reaction temperature below –75°C. The orange-brown solution was allowed to warm to –78°C over 30 min before cooling to –90°C and adding a solution of complex **2.1** in MeCN (3 mL) *via* cannula. After warming to –78°C and stirring for 30 min aqueous work-up and decomplexation using the CAN mediated procedure were performed as described above for olefin **2.80**. Purification by column chromatography (SiO_2, Et_2O : hexanes = 5 : 95) gave the title compounds as clear oils.

Data for the less polar isomer (R_f = 0.43, ether : hexanes = 1 : 9):

$[\alpha]_D$ = +63.0 (*c* 0.47, $CHCl_3$).

IR (film): ν = 2956 s, 2928 s, 1464 m, 1154 m, 1110 s, 1042 s, 1004 m, 976 m, 920 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.45-5.36 (2H, m, C<u>H</u>=C<u>H</u>), 4.59 (2H, s, OC<u>H</u>$_2$OMe), 3.99 (1H, ddt, *J* 4.0, 2.0, 10.9, H6), 3.46 (1H, dd, *J* 9.6, 3.6, C<u>H</u>$_A$H$_B$OMOM), 3.39 (1H, dd, *J* 9.6, 6.4, CH$_A$<u>H</u>$_B$OMOM), 3.36 (3H, s, O<u>Me</u>), 3.32 (1H, dd, *J* 10.9, 3.4, H6'), 3.11 (1H, dd, *J* 9.6, 2.4, H2), 2.42-2.33 (1H, m, C<u>H</u>Me), 2.31-2.23 (1H, m, C<u>H</u>Me$_2$), 1.93-1.87 (1H, m, H4 or H5), 1.71-1.54 (3H, m, H3, H4, H4' or H3, H5, H5'), 1.50-1.40 (1H, m, H4' or H5'), 1.07 (3H, d, *J* 6.9, CH<u>Me</u>), 0.98 (3H, d, *J* 6.7, CH(<u>Me</u>)Me), 0.98 (3H, d, *J* = 6.7, CH(Me)<u>Me</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6 (1, <u>C</u>H=CH), 128.0 (1, CH=<u>C</u>H), 96.7 (2, O<u>C</u>H$_2$OMe), 83.2 (1, C2), 68.8 (2, C6 or <u>C</u>H$_2$OMOM), 68.6 (2, C6 or <u>C</u>H$_2$OMOM), 55.3 (3, OMe), 38.8 (1, <u>C</u>HMe), 38.5 (1, <u>C</u>HMe$_2$), 31.3 (1, <u>C</u>HMe$_2$), 27.7 (2, C4 or C5), 26.4 (2, C4 or C5), 23.0 (3, CH(<u>Me</u>)Me), 22.9 (3, CH(Me)<u>Me</u>), 19.0 (3, CH<u>Me</u>).

LRMS (EI^+ mode): *m/z*: = 256.2 [$(M^{+\bullet})$, 5%], 159.0 (12), 129.1 (10), 97.0 (100), 81.0 (9), 55(12).

Found: C, 70.14; H, 10.92. $C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.01 %.

Data for the more polar isomer (R_f = 0.35, ether : hexanes = 1 : 9):

$[\alpha]_D$ = –9.0 (*c* 0.72, $CHCl_3$).

IR (film): ν = 2956 s, 2930 s, 2868 m, 1464 m, 1380 m, 1152 m, 1110, s, 1042 s, 994 m, 970 m, 922 m cm^{-1}.

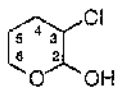
^1H NMR (400 MHz, $CDCl_3$): δ = 5.48 (1H, ddd, *J* 15.6, 7.1, 0.8, C<u>H</u>=CHCHMe$_2$), 5.37 (1H, dd, *J* 15.6, 6.3, CH=C<u>H</u>CHMe$_2$), 4.60 (2H, s, OC<u>H$_2$</u>OMe), 3.93 (1H, ddt, *J* 3.6, 1.6, 10.8, H6), 3.47 (1H, dd, *J* 9.7, 4.6, C<u>H$_A$</u>H$_B$OMOM), 3.40 (1H, dd, *J* 9.7, 6.0, CH$_A$<u>H$_B$</u>OMOM), 3.37-3.31 (1H, m, H6'), 3.36 (3H, s, OMe), 3.08 (1H, dd, *J* 9.0, 3.1, H2), 2.39 (1H, dquintet, *J* 3.1, 7.1, C<u>H</u>Me), 2.25 (1H, octet, *J* 6.7, C<u>H</u>Me$_2$), 1.91 (1H, ddq, *J* 12.8, 4.0, 1.6, H4), 1.80-1.71 (1H, m, H3), 1.63-1.56 (2H, m, H5, H5'), 1.47-1.37 (1H, m, H4), 0.98 (3H, d, *J* 7.1, CH<u>Me</u>), 0.97 (6H, d, *J* 6.7, CH<u>Me$_2$</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7 (1, CH=<u>C</u>HCHMe$_2$), 131.4 (1, <u>C</u>H=CHCHMe$_2$), 96.8 (2, O<u>C</u>H$_2$OMe), 83.2 (1, C2), 69.4 (2, C6 or <u>C</u>H$_2$OMOM), 67.9 (2, C6 or <u>C</u>H$_2$OMOM), 55.4 (3, OMe), 37.9 (1, C3 or <u>C</u>HMe), 37.3 (1, C3 or <u>C</u>HMe), 31.1 (1, <u>C</u>HMe$_2$), 27.3 (2, C5), 26.0 (2, C4), 22.9 (3, CH(<u>Me</u>)Me), 22.8 (3, CH(Me)<u>Me</u>), 14.1 (3, CH<u>Me</u>).

LRMS (EI$^+$ mode): *m/z*: = 256 [($M^{+\bullet}$), 6%], 159 (9), 129 (8), 97 (100), 81 (9), 69 (11), 55 (15).

Found: C, 70.10; H, 10.94. $C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.01 %.

3-Chlorotetrahydropyran-2-ol (2.109)



The title compound was prepared in 46% yield on a 120 mmol scale according to the general procedure of Descotes and Soula.[119] Purification by recrystallisation (Et_2O / hexanes) gave the title compound as white crystals. ^1H NMR and IR data have been previously reported.[234]

m.p. = 59-61°C (Et_2O / hexanes) Lit. m.p. 60-62°C.[235]

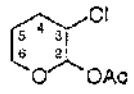
IR (KBr): ν = 3321 br s, 2962 s, 2930 m, 2876 s, 1432 m, 1350 s, 1294 m, 1180 s, 1152 s, 1105 s, 1063 s, 943 s, 770 s cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.93 (1H, d, *J* 1.9, H2), 4.77 (1H, d, *J* 5.8, H2), 4.12-4.08 (1H, m, H3), 4.04-3.98 (2H, m, H6, H6), 3.94 (2H, s, OH), 3.76 (1H, ddd, *J* 4.3, 5.8, 8.6, H3), 3.60-3.52 (1H, m, H6'), 3.59 (1H, ddd, *J* 3.2, 8.7, 11.6, H6'), 2.35-2.29 (1H, m, H4), 2.23-2.14 (1H, m, H4), 2.04-1.97 (1H, m, H4'), 1.91-1.76 (3H, m, H4', H5, H5), 1.66-1.50 (2H, m, H5', H5').

^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.1 (1, C2), 92.9 (1, C2), 64.2 (2, C6), 63.0 (2, C6), 59.7 (1, C3), 58.5 (1, C3), 30.9 (2, C4), 29.2 (2, C4), 24.0 (2, C5), 22.4 (2, C5).

LRMS (EI$^+$ mode): m/z = 136.01 (M^+, 40%), 119.00 [$(M-OH)^+$, 33%], 107.98 (47), 90.05 (100), 75.43 (56), 62.55 (100), 54.29 (85).

Acetic acid 3-chlorotetrahydropyran-2-yl ester (2.110)



To a solution of lactol **2.109** (814 mg, 5.96 mmol) in CH_2Cl_2 (20 mL) at rt under N_2 was added acetic anhydride (0.7 mL, 7.15 mmol), triethylamine (1.0 mL, 7.15 mmol), and DMAP (10 mg). The solution was stirred at rt for 14 h before addition of 1M HCl (50 mL) and separation of the phases. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic phases were washed with brine (50 mL), dried and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) gave the title compound (891 mg, 4.99 mmol, 84%) as a clear oil. ^{1}H NMR (CCl_4) and IR data have been previously reported.[236]

IR (film): ν = 2960 m, 1760 s, 1438 m, 1372 m, 1228 s, 1204 s, 1144 m, 1072 s, 1040 m, 1008 m, 950 s cm^{-1}.

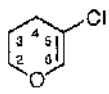
^{1}H NMR (400 MHz, $CDCl_3$): (Approximately 4 : 1 ratio of *trans* : *cis* isomers[236]) *Trans* isomer: δ = 5.82 (1H, d, *J* 5.2, H2), 3.99 (1H, ddd, *J* 11.6, 7.6, 3.9, H6), 3.94 (1H, dt, *J* 7.2, 4.6, H3), 3.70 (1H, ddd, *J* 11.6, 6.6, 3.9, H6'), 2.42-2.34 (1H, m, H4), 1.89-1.82 (2H, m, H4', H5), 1.69-1.59 (1H, m, H5'); *Cis* isomer: δ = 6.13 (1H, d, *J* 3.2, H2), 4.14-4.09 (1H, m, H3), 3.92-3.84 (1H, m, H6), 3.73-3.69 (1H, m, H6'), 2.20-2.06 (1H, m, H4'), 2.42-2.34 (1H, m, H4), 1.89-1.82 (2H, m, H5, H5').

^{13}C NMR (100 MHz, $CDCl_3$): *Trans* isomer: δ = 169.2 (0, COMe), 94.3 (1, C2), 64.2 (2, C6), 55.3 (1, C3), 29.5 (2, C4), 22.3 (2, C5), 21.0 (3, COMe); *Cis* isomer: δ = 169.5 (0, COMe), 91.0 (1, C2), 61.2 (2, C6), 55.5 (1, C3), 28.5 (2, C4), 25.2 (2, C5), 20.9 (3, COMe).

LRMS (CI mode, isobutane): m/z = 179 [$(M+H)^+$, 5%], 136 (7), 119 (100).

HRMS (CI mode, isobutane): found $[M+H]^{+\bullet}$, 179.0472. $C_7H_{12}{}^{35}ClO_3$ requires 179.0475.

5-Chloro-3,4-dihydro-2*H*-pyran (2.111)



The title compound was prepared in 34% yield on a 39.8 mmol scale according to the procedure of Summerbell and Lunk.[120] Purification by short-path distillation (b.p. 54°C / 30 mmHg, Lit. b.p. = 140-142°C / 760 mmHg[120]) gave a clear oil. ^{1}H NMR data has been previously reported.[237]

IR (film): ν = 2936 m, 2876 m, 1760 m, 1654 m, 1272 m, 1222 s, 1158 s, 1092 m, 1054 m, 1028 m, 986 m, 922 m, 854 m cm^{-1}.

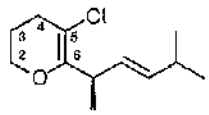
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (1H, s, H6), 3.93 (2H, dd, *J* 5.2, 5.2, H2), 2.31 (2H, dt, *J* 6.4, 1.6, H4), 1.97 (2H, tt, *J* 6.4, 5.2, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7 (1, C6), 110.9 (0, C5), 65.3 (2, C2), 27.9 (2, C4), 23.2 (2, C3).

LRMS (EI^+ mode): *m/z*: 120 [(M^+, $C_5H_7{}^{37}ClO$], 42%), 118 [(M^+, $C_5H_7{}^{35}ClO$], 92%), 89 (40%), 83 (100%), 62 (44%), 53 (53%).

HRMS (EI^+ mode): found [$M^{+\bullet}$], 118.0186. $C_5H_7{}^{35}ClO$ requires 118.0185.

5-Chloro-6-[(1*R*,3*E*)-1,4-dimethylpent-2-enyl]-3,4-dihydro-2*H*-pyran (2.112)



n-BuLi (3.0 mL of a 2.23M solution in hexanes, 6.62 mmol) was added to a solution of pyran **2.111** (747 mg, 6.30 mmol) in THF (10 mL) under N_2. The solution was allowed to warm to rt and stirred for 2 h before cooling to –80°C and addition of a solution of CuBr•DMS (1.69 g, 8.19 mmol) in diisopropylsulfide (5.2 mL) and THF (6.7 mL) dropwise over 10 min, keeping the internal temperature below –75°C. The brown solution was stirred at –80°C for 30 min before cooling to –90°C and addition of complex **2.1** (1.27 g, 3.15 mmol) in MeCN (3 mL) dropwise. After warming to –78°C and stirring for 30 min aqueous work-up and decomplexation using the CAN mediated procedure were performed as described above for olefin **2.80**. Purification by column chromatography (SiO_2, Et_2O : hexanes = 5 : 95) gave the title compound (65 mg, 0.30 mmol, 10%) as a clear oil.

$[\alpha]_D$ = +50.4 (*c* 0.83, $CHCl_3$).

IR (film): ν = 2958 s, 2931 m, 2868 m, 1249 m, 1092 s, 1078 m, 1020 m, 1007 m, 971 m, 944 m cm^{-1}.

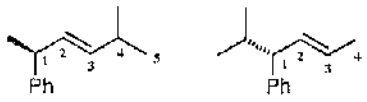
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (1H, dd, *J* 15.5, 5.8, C<u>H</u>=CHCHMe$_2$ or CH=C<u>H</u>CHMe$_2$), 5.39 (1H, dd, *J* 15.5, 6.4, C<u>H</u>=CHCHMe$_2$ or CH=C<u>H</u>CHMe$_2$), 3.94 (2H, t, *J* 5.1, H2, H2′), 3.57 (1H, pentet, *J* 6.9, C<u>H</u>Me or C<u>H</u>Me$_2$), 2.35-2.31 (2H, m, H4, H4′), 2.26 (1H, dq, *J* 9.7, 6.5, C<u>H</u>Me or C<u>H</u>Me$_2$), 1.96-1.89 (2H, m, H3, H3′), 1.11 (3H, d, *J* 7.0, CH<u>Me</u>), 0.98 (6H, d, *J* 6.8, CH<u>Me$_2$</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9 (0, C6), 137.4 (1, <u>C</u>H=CHCHMe$_2$ or CH=<u>C</u>HCHMe$_2$), 128.0 (1, <u>C</u>H=CHCHMe$_2$ or CH=<u>C</u>HCHMe$_2$), 105.1 (0, C5), 66.2 (2, C2), 37.6 (1, <u>C</u>HMe or <u>C</u>HMe$_2$), 31.0 (1, <u>C</u>HMe or <u>C</u>HMe$_2$), 29.2 (2, C3 or C4), 24.0 (2, C3 or C4), 22.7 (2C, 2, CH<u>Me$_2$</u>), 17.8 (3, CH<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 232.0 [$(M+NH_4)^+$, 45 %], 215.0 [$(M+H)^+$, 100 %], 179.0 (30).

HRMS (EI^+ mode): found [$M^{+\bullet}$], 214.1122. $C_{12}H_{19}{}^{35}ClO$ requires 214.1124.

(1*S*,2*E*)-(1,4-Dimethylpent-2-enyl)benzene (2.114) and **(1*R*,2*E*)-(1-Isopropylbut-2-enyl)benzene (2.115).**



2.114 2.115

To a solution of phenyllithium (2.0 mL of a 1.81M solution in cyclohexane / ether, 3.54 mmol) in THF (60 mL) at 0°C under N_2 was added a solution of CuBr•DMS (850 mg, 4.13 mmol) in di*iso*-propyl sulfide (2 mL) and THF (4 mL) *via* cannula. The dark green-black solution was stirred at 0°C under N_2 for 30 min before cooling to –78°C and the addition of a solution of cationic complex **2.2** (which had been freshly prepared from neutral complex *ent*-**2.14** (928 mg, 2.95 mmol) and $NOBF_4$ (379 mg, 3.25 mmol) in MeCN (15 mL) at 0°C for 10 min) dropwise. After stirring at –78°C for 2 h, aqueous work-up and decomplexation using the O_2 mediated procedure were performed as described above for olefin **2.58** (without illumination). Purification by column chromatography (SiO_2, Et_2O : hexanes = 5 : 95) gave an inseparable mixture of the title compounds (128 mg, 0.73 mmol, 25%) as a clear oil in the approximate ratio 13 : 1, as estimated by comparison of the integration of H5 (**2.114**) and H4 (**2.115**), at 3.33 ppm (1H, ddq, *J* 6.9, 6.9) and 2.78 ppm (1H, t, *J* 9.0) respectively. Further elution yielded ketones **2.116** and **2.117** (164 mg, 0.81 mmol, 27%) in the approximate ratio **2.116** : **2.117** = 8 : 1, followed by a trace (<2%) of isomeric ketone **2.118**. (R_f (Et_2O : hexanes = 5 : 95): **2.114** / **2.115** = 0.79, **2.116** / **2.117** = 0.50, **2.118** = 0.34).

$[\alpha]_D$ = + 4.42 (*c* 0.86, $CHCl_3$, 13 : 1 ratio of **2.114** : **2.115**).

IR (film, 13 : 1 mixture of olefins **2.114** / **2.115**): ν = 3017 m, 2959 s, 2930 m, 2868 m, 1496 m, 1454 m, 972 m cm^{-1}. (IR data for **2.115** has been previously reported).[121]

LRMS (EI$^+$ mode): *m/z* = 174.1 [$M^{+\bullet}$, 40 %], 131.1 (100), 118.1 (49), 105.1 (42), 91.0 (32).

NMR Data for **2.114**: (Undetailed ^{1}H NMR data has been reported previously[122])

^{1}H NMR (400 MHz, C_6D_6, referenced to added TMS): δ = 7.16-7.04 (5H, m, Ph), 5.57 (1H, ddd, *J* 15.4, 6.6, 0.9, H2), 5.40 (1H, ddd, *J* 15.4, 6.6, 1.2, H3), 3.33 (1H, dq, *J* 6.9, 6.9, H1), 2.19 (1H, apparent octet, *J* 6.7, H4), 1.28 (3H, d, *J* 7.2, C1-Me), 0.94 (3H, d, *J* 6.4, H5), 0.93 (3H, d, *J* 6.8, C4-Me).

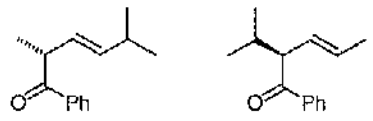
^{13}C NMR (100 MHz, C_6D_6, referenced to added TMS): δ = 146.7 (0, Ph), 136.3 (1, C3), 132.5 (1, C2), 128.6 (2C, 1, Ph), 127.5 (2C, 1, Ph), 126.2 (1, Ph), 42.5 (1, C1), 31.3 (1, C4), 22.8 (3, C5), 22.7 (3, C4-Me), 21.8 (3, C1-Me).

NMR Data for **2.115**: (^{1}H NMR data were in accordance with literature data[121])

^{13}C NMR (100 MHz, C_6D_6, referenced to added TMS): δ = 145.2 (0, Ph), 134.5 (1, Ph, C2 or C3), 128.5 (2C, 1, Ph), 128.2 (2C, 1, Ph), 126.1 (1, Ph, C2 or C3), 125.4 (1, Ph, C2 or C3), 57.7 (1, C1), 33.3 (1, $\underline{C}HMe_2$), 21.3 (3, CH$\underline{Me}$(Me)), 21.0 (3, CHMe($\underline{Me}$)), 18.0 (3, CH$\underline{Me}$).

An analogous coupling procedure was performed as detailed above using 4.7 mmol of $Ph_2Cu(CN)Li_2$ (prepared as described by Liebeskind[54]) and 3.2 mmol of neutral complex *ent*-**2.14**. Aqueous work-up and decomplexation using the O_2 mediated procedure were performed as described above for olefin **2.58** (without illumination). Purification by column chromatography (SiO_2, Et_2O : hexanes = 2 : 98) gave ketones **2.116** and **2.117** (**2.116** : **2.117** = 1.2 : 1, 240 mg, 1.19 mmol, 38%), <2% of ketone **2.118** and <2% of olefins **2.114** / **2.115**.

Data for: **(2*R*,3*E*)-2,5-Dimethyl-1-phenylhex-3-en-1-one (2.116)** and **(2*S*,3*E*)-2-Isopropyl-1-phenylpent-3-en-1-one (2.117)**.



2.116 2.117

IR (film): ν = 2950 s, 2924 m, 2876 m, 1677 s, 1455 m, 1202 m, 976 s, 706 s cm^{-1}

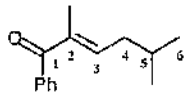
$[\alpha]_D$ = –50.7 (*c* 1.34)

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00-7.79 (2H, m, Ph (**2.116** / **2.117**)), 7.57-7.53 (1H, m, Ph (**2.116** / **2.117**)), 7.48-7.44 (2H, m, Ph (**2.116** / **2.117**)), 5.61-5.47 (2H, m, H3, H4 (**2.116** / **2.117**)), 4.10 (1H, pentet, *J* 6.8, H2 (**2.116**)), 3.71 (1H, t, *J* 8.6, H2 (**2.117**)), 2.29-2.217 (1H, m, H5 (**2.116**), C<u>H</u>Me$_2$ (**2.117**)), 1.60 (3H, d, *J* 6.0, H5 (**2.117**)), 1.30 (3H, d, *J* 6.8, C2-Me (**2.116**)), 0.95 (3H, d, *J* 6.7, H6 (**2.116**)), 0.94 (3H, d, *J* 6.7, C5-Me (**2.116**)), 0.83 (6H, d, *J* 6.6, CH<u>Me</u>$_2$ (**2.116**)).

^{13}C (100 MHz, $CDCl_3$): δ = 202.3 (0, C1 (**2.117**)), 202.0 (0, C1 (**2.116**)), 140.1 (1, C3 or C4 (**2.116**)), 137.8 (0, Ph), 136.7 (0, Ph), 133.0 (1, Ph, C3 or C4), 132.9 (1, Ph, C3 or C4), 129.3 (1, Ph, C3 or C4), 129.1 (1, Ph, C3 or C4), 128.7 (3C, 1, Ph, C3 or C4), 128.6 (2C, Ph), 128.5 (1, Ph, C3 or C4), 128.3 (1, Ph, C3 or C4), 127.2 (1, Ph, C3 or C4), 127.1 (1, Ph, C3 or C4), 58.3 (1, C2 (**2.117**)), 44.8 (1, C2 (**2.116**)), 31.2 (1, C5 (**2.116**)), 30.8 (1, <u>C</u>HMe$_2$ (**2.117**)), 22.4 (2C, 3, C6, C5-<u>Me</u> (**2.116**)), 21.5 (3, C5 or CH<u>Me</u>$_2$ (**2.117**)), 20.0 (3, C5 or CH<u>Me</u>$_2$ (**2.117**)), 18.2 (3, C5 or CH<u>Me</u>$_2$ (**2.117**)), 17.9 (3, C5).

LRMS (EI^+ mode): *m/z* = 202 [$M^{+\bullet}$, 19 %], 159.1 (44), 105.0 (100), 77.0 (100), 55.0 (45).

Data for: **(2*E*)-2,5-Dimethyl-1-phenylhex-2-en-1-one (2.118)**.



IR (film): ν = 2955 m, 2929 m, 1654 s, 1446 m, 1319 m, 1277 s, 912 m cm^{-1}.

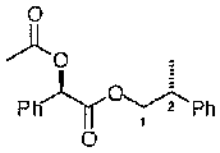
^1H NMR (400 MHz, $CDCl_3$): δ = 7.70-7.34 (5H, m, Ph), 6.37 (1H, td, *J* 7.4, 1.3, H3), 2.24 (2H, t, *J* 6.8, H4), 2.02 (3H, s, Me), 1.80 (1H, septet, *J* 6.7, H5), 0.86 (6H, d, *J* 6.6, H6, C5-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3 (0, COPh), 146.0 (1, C3), 139.0 (0, Ph or C2), 137.2 (0, Ph or C2), 131.5 (1, Ph), 129.4 (2C, 1, Ph), 128.2 (2C, 1, Ph), 38.4 (2, C4), 28.6 (1, C5), 22.7 (2C, 3, C6), 12.8 (3, C2).

LRMS (EI$^+$ mode): *m/z* = 202 [$M^{+\bullet}$, 41 %], 159 (54), 145 (59), 105 (100), 91 (19), 77 (68).

HRMS (EI$^+$ mode): found [$M^{+\bullet}$], 202.1359. $C_{14}H_{18}O$ requires 202.1358.

(*R*)-Acetoxyphenylacetic acid (2*R*)-2-phenylpropyl ester (2.120).



To a mixture of olefins **2.114** and **2.115** (87 mg, 0.50 mmol, **2.114** : **2.115** = 13 : 1) in MeOH (6 mL) and H_2O (6 mL) was added OsO_4 (0.66 mL of a 0.1M solution in H_2O, 0.07 mmol) and sodium periodate (538 mg, 2.52 mmol) and the dark solution stirred at rt for 15 h. Et_2O (20 mL) and H_2O (20 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic phases were dried, filtered and concentrated *in vacuo* to yield a black oil which was dissolved in MeOH (20 mL), cooled to 0°C, and $NaBH_4$ (238 mg, 6.0 mmol) added. The solution was stirred at 0°C for 5 min and at rt for 15 min before concentration *in vacuo* and the addition of Et_2O (20 mL) and H_2O (20 mL). The phases were separated and the aqueous phase extracted with Et_2O (2 x 20 mL). The combined organic phases were dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 3 : 7) yielded (*R*)-2-phenylpropan-1-ol (**2.119**, 27 mg, 0.20 mmol, 40%) as a clear oil. Spectroscopic data for **2.119** ($[\alpha]_D$ = +5.9 (*c* 2.7, $CHCl_3$), Lit. $[\alpha]_D$ = +16.5 (*c* 1.47)[238]) were in accordance with literature data.[238, 239]

Alcohol **2.119** (27 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (10 mL) and (*R*)-*O*-acetoxyphenylacetic acid (46 mg, 0.24 mmol), DMAP 12 mg, 0.01 mmol) and DCC (61 mg, 0.30 mmol) were added. The cloudy mixture was stirred at rt for 2 h before filtration and addition of 0.5M HCl (10 mL). The phases were separated and the organic phase washed with aqueous $NaHCO_3$ (10 mL), before extraction of both aqueous phases separately with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 5 : 95 → 1 : 9) yielded the title compound (52 mg, 0.17 mmol, 83%) as a clear oil.

The dr at C2 for ester **2.120** was conservatively estimated as ≥ 90 : 10 from the integration of acetate methyl singlets at 2.14 and 2.15 ppm (minor and major isomers respectively) with reference to an authentic sample of (2*RS*)-**2.120**.

$[\alpha]_D$ = –73.8 (c 0.4, $CHCl_3$).

IR (film): ν = 3031 m, 2966 m, 1744 s, 1454 m, 1273 m, 1231 s, 1176 m, 1056 m, 699 m cm^{-1}.

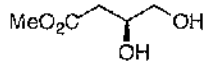
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.34 (5H, m, Ph), 7.26-7.19 (3H, m, Ph), 7.09-7.07 (2H, m, Ph), 5.89 (1H, s, CH(OAc)Ph), 4.26-4.17 (2H, m, H1, H1'), 3.03 (1H, sextet, *J* 7.0, H2), 2.15 (3H, s, COMe), 1.20 (3H, d, *J* 7.0, C2-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (0, $\underline{C}O_2R$), 168.9 (0, $\underline{C}O_2R$), 142.8 (0, Ph), 134.0 (0, Ph), 129.3 (1, Ph), 128.9 (2C, 1, Ph), 128.6 (2C, 1, Ph), 127.8 (2C, 1, Ph), 127.4 (2C, 1, Ph), 126.8 (1, Ph), 74.7 (1, Ph$\underline{C}$H(OR)CO_2R), 70.5 (2, O$\underline{C}H_2$), 39.0 (1, C$\underline{H}$(Me)Ph), 20.9 (3, C(O)$\underline{Me}$), 17.9 (3, CH($\underline{Me}$)Ph).

LRMS (CI$^+$ mode, isobutane): *m/z* = 313.1 [(M+H)$^+$, 70 %], 253.0 (48), 225.1 (100), 207.1 (37), 118.1 (33).

6.3 - Experimental Procedures from Chapter 4.

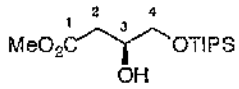
(3*S*)-3,4-Dihydroxybutyric acid methyl ester (4.34).



Diol **4.34** was prepared in 89% yield on a 89.3 mmol scale by the method of Moriwake and co-workers.[99] Spectroscopic data were in accordance with literature data.[186]

$[\alpha]_D$ = –23.2 (*c* 1.22, $CHCl_3$). Lit. $[\alpha]_D$ = –24.6 (*c* 1.00, $CHCl_3$).[186]

(3*S*)-3-Hydroxy-4-(triisopropylsilanyloxy)butyric acid methyl ester (4.36).



To a solution of diol **4.34** (12.0 g, 89.3 mmol) and imidazole (12.2 g, 178.6 mmol) in *N*,*N*-dimethylformamide (100 mL) at 0°C under N_2 was added triisopropylsilyl chloride (20.1 mL, 93.8 mmol). The solution was stirred at rt for 30 h before pouring into hexanes (250 mL) and H_2O (75 mL). The phases were separated and the organic phase washed with H_2O (2 x 50 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ethyl acetate : hexanes = 1 : 9) gave the title compound (18.5 g, 63.6 mmol, 71%) as a clear oil.

$[\alpha]_D$ = –7.2 (*c* 1.06, $CHCl_3$).

IR (film): ν = 3481 br m, 2944 s, 2867 s, 1736 s, 1463 m, 1439 m, 1123 m, 1066 m, 883 m cm^{-1}.

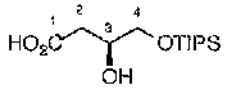
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (1H, ddq, *J* 7.6, 5.8, 4.8, H3), 3.72 (1H, dd, *J* 9.8, 4.9, H4), 3.71 (3H, s, CO_2Me), 2.91 (1H, d, *J* 4.8, OH), 3.66 (1H, dd, *J* 9.8, 5.8, H4′), 2.58 (1H, dd, *J* 16.0, 4.8, H2), 2.52 (1H, dd, *J* 16.0, 7.6, H2′), 1.06 (18H, d, *J* 5.6, Si(CH$\underline{Me}_2$)$_3$), 1.15-1.04 (3H, m, Si($\underline{C}$HMe$_2$)$_3$.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (0, C1), 68.8 (1, C3), 66.6 (2, C4), 51.9 (3, $CO_2\underline{Me}$), 38.0 (2, C2), 18.1 (6C, 3, Si(CH($\underline{Me}$)$_2$)$_3$), 12.0 (3C, 1, Si($\underline{C}$H(Me)$_2$)$_3$).

LRMS (CI mode, isobutane): *m/z* = 291.2 [(M+H)$^+$, 100 %], 247.1 (15).

Found: C, 57.81; H, 10.37. Calc. for $C_{14}H_{30}O_4Si$: C, 57.89; H, 10.41%.

(3*S*)-3-Hydroxy-4-(triisopropylsilanyloxy)butyric acid (4.37).



To a solution of ester **4.36** (38.6 g, 132.9 mmol) in MeOH (600 mL) was added 10% aqueous potassium carbonate solution (270 mL) and the mixture refluxed for 1.5 h. After cooling to rt, the mixture was acidified to pH 2 with 2M HCl. After extraction with Et_2O (2 x 250 mL) and washing with brine (200 mL), the organic phase was dried, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ethyl acetate : hexanes = 2 : 8 → 1:1) gave the title compound (27.1 g, 98.1 mmol, 74%) as a clear oil.

$[\alpha]_D$ = –7.2 (*c* 0.83, $CHCl_3$).

IR (film): ν = 3460 br w, 2937 m, 2861 m, 1713 s, 1469 s, 1123 m, 1062 w, 884 m, 798 m, 681 m cm^{-1}.

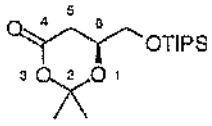
^1H NMR (400 MHz, $CDCl_3$): δ = 6.50 (1H, br s, OH), 4.17-4.07 (1H, m, H3), 3.73 (1H, dd, *J* 9.8, 4.9, H4), 3.68 (1H, dd, *J* 9.8, 5.7, H4′), 2.63 (1H, dd, *J* 16.2, 4.6, H2), 2.56 (1H, dd, *J* 16.2, 7.9, H2′), 1.05 (18H, d, *J* 5.7, $Si(CH\underline{Me}_2)_3$), 1.15-1.05 (3H, m, $Si(C\underline{H}Me_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (0, C1), 68.7 (1, C3), 66.4 (2, C4), 38.1 (2, C2), 18.0 (6C, 3, $Si(CH\underline{Me}_2)_3$), 12.0 (3C, 1, $Si(\underline{C}HMe_2)_3$).

LRMS (CI mode, isobutane): *m/z* = 277 [$(M+H)^+$, 100 %], 259 (14), 233 (23), 173 (19).

Found: C, 56.22; H, 10.03. Calc. for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.21%.

(6*S*)-2,2-Dimethyl-6-(triisopropylsilanyloxymethyl)-[1,3]dioxan-4-one (4.38).



To a solution of acid **4.37** (7.45 g, 27.0 mmol) and 2-methoxypropene (3.10 mL, 32.3 mmol) in CH_2Cl_2 (250 mL) at rt under N_2 was added pyridinium *p*-toluenesulfonate (339 mg, 1.35 mmol). The clear solution was stirred at rt for 3 h before concentration *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 4 : 6) gave the title compound (7.15 g, 22.6 mmol, 84%) as a clear oil. Further elution yielded acid **4.37** (730 mg, 2.64 mmol, 10%).

$[\alpha]_D$ = –38.4 (*c* 1.10, $CHCl_3$).

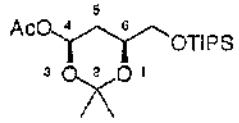
IR (film): ν = 2945 s, 2864 s, 1746 s, 1464 m, 1387 m, 1295 m, 1142 m, 883 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (1H, tt, *J* 7.1, 4.8, H6), 3.81 (1H, dd, *J* 10.4, 4.8, CH_2OTIPS), 3.74 (1H, dd, *J* 10.4, 4.8, CH_2OTIPS), 2.59 (2H, d, *J* 7.1, H5, H5'), 1.59 (3H, s, C<u>Me</u>(Me)), 1.57 (3H, s, CMe(<u>Me</u>)), 1.05 (18H, d, *J* 5.2, Si(CH<u>Me</u>$_2$)$_3$), 1.14-1.03 (3H, m, Si(C<u>H</u>Me$_2$)$_3$).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1 (0, C4), 106.1 (0, C2), 68.7 (1, C6), 65.6 (2, CH_2OTIPS), 31.8 (2, C5), 29.1 (3, C<u>Me</u>(Me)), 25.0 (3, CMe(<u>Me</u>)), 18.0 (6C, 3, Si(CH<u>Me</u>$_2$)$_3$), 12.0 (3C, 1, Si(<u>C</u>HMe$_2$)$_3$).

LRMS (CI mode, isobutane): *m/z* = 317.3 [$(M+H)^+$, 100 %], 259.2 (16).

Found: C, 60.71; H, 10.07. Calc. for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19%.

Acetic acid (4*S*,6*S*)-2,2-dimethyl-6-(triisopropylsilanyloxymethyl)-[1,3]dioxan-4-yl ester (4.39).



To a solution of dioxanone **4.38** (19.1 g, 60.4 mmol) in CH_2Cl_2 (180 mL) at –78°C under N_2 was added neat DIBAL (11.3 mL, 63.4 mmol) dropwise. After stirring –78°C for 1 h, pyridine (14.6 mL, 181 mmol), 4-dimethylaminopyridine (8.11 g, 66.4 mmol) in CH_2Cl_2 (50 mL) and acetic anhydride (22.8 mL, 241 mmol) were added and the clear solution stirred at –78°C for a further 1.5 h before the addition of aqueous NH_4Cl (100 mL) and aqueous sodium potassium tartrate (100 mL). The solution was allowed to warm to rt with vigorous stirring over 1 h. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with ice-cold 1M $NaHSO_4$ (3 x 100 mL), aqueous $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried, filtered and concentrated *in vacuo* to yield the crude product as a clear oil. Purification by column chromatography (SiO_2, ether : hexanes = 1 : 9) gave the title compound (18.3 g, 50.7 mmol, 84%) as a clear oil. ^{13}C NMR spectroscopy indicated that acetate **4.39** was a single diastereomer, identified as the *syn* 1,3-diol acetonide isomer by reference to the shifts of the acetonide methyl signals, and to the coupling constants of H4.[189, 190]

$[\alpha]_D$ = –5.1 (*c* 1.26, $CHCl_3$).

IR (film): ν = 2941 s, 2893 m, 2865 s, 1757 s, 1466 m, 1385 m, 1364 m, 1225 s, 1144 s, 1039 s, 996 m cm^{-1}.

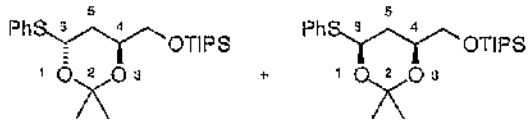
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (1H, dd *J* 10.0, 3.0, H4), 4.01 (1H, dddd, *J* 11.7, 6.3, 4.8, 2.5, H6), 3.81 (1H, dd, *J* 9.8, 5.0, CH_2OTIPS), 3.61 (1H, dd, *J* 9.6, 6.4, CH_2OTIPS), 2.11 (3H, s, COMe), 1.96 (1H, dt, *J* 12.4, 2.8, H5), 1.56-1.43 (1H, m, H5'), 1.52 (3H, s, C<u>Me</u>(Me)), 1.44 (3H, s, CMe(<u>Me</u>)), 1.13-1.01 (3H, m, Si(C<u>H</u>Me$_2$)$_3$), 1.05 (18H, d, *J* 4.8, Si(CH<u>Me</u>$_2$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (0, <u>C</u>OMe), 100.7 (0, C2), 89.6 (1, C4), 69.5 (2, CH_2OTIPS), 66.8 (1, C6), 33.1 (2, C5), 29.8 (3, C<u>Me</u>(Me)), 21.4 (3, CO<u>Me</u>), 20.9 (3, CMe(<u>Me</u>)), 18.1 (6C, 3, Si(CH<u>Me</u>$_2$)$_3$), 12.1 (3C, 1, Si(<u>C</u>HMe$_2$)$_3$).

LRMS (CI mode, NH_3): *m/z* = 378.3 [$(M+NH_4)^+$, 67 %], 318.3 (100), 301.2 (92).

Found: C, 59.95; H, 9.88. Calc. for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06%.

(4*S*,6*R*)-(2,2-Dimethyl-6-phenylsulfanyl-[1,3]dioxan-4-ylmethoxy)triisopropylsilane (4.24) and (4*S*,6*S*)-(2,2-Dimethyl-6-phenylsulfanyl-[1,3]dioxan-4-ylmethoxy) triisopropylsilane (4.25).



4.24 4.25

To a solution of acetate **4.39** (9.90 g, 27.5 mmol) in CH_2Cl_2 (110 mL) at –70°C under N_2 was added phenylthiotrimethylsilane (5.5 mL, 28.8 mmol) and $ZnCl_2$ (0.82 mL of a 1.0 M solution in ether, 0.82 mmol) dropwise. The light brown solution was stirred at –70°C for 17 h before addition of 1M NaOH (50 mL) and warming to rt. The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with 1M NaOH (50 mL) and brine (50 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 2 : 98 → 4 : 96) gave a mixture of the title compounds (9.74 g, 23.7 mmol, 86%) as a clear oil. ^1H and ^{13}C NMR spectroscopy indicated a ratio of **4.24** : **4.25** of approximately 7:3.[189, 190] For analytical purposes, a sample of isomers **4.24** and **4.25** was separated by careful column chromatography.

Alternative procedure: $ZnCl_2$ (1.9 mL of a 1.0M solution in ether, 1.9 mmol) was added dropwise to a solution of acetate **4.39** (17.4 g, 48.4 mmol) and thiophenol (5.2 mL, 50.8 mmol) in CH_2Cl_2 (240 mL) at –30°C under N_2. After stirring for 15 min at –30°C, 1M NaOH (100 mL) was added and the mixture allowed to warm to rt. Work-up and purification as above yielded a mixture of the title compounds (17.3 g, 42.1 mmol) as a clear oil. ^1H and ^{13}C NMR indicated a ratio of **4.24** : **4.25** of approximately 1:9.[189, 190]

Spectroscopic data for sulphide **4.24**: (R_f = 0.85, Et_2O : PhMe = 2 : 98)

$[\alpha]_D$ = +85.0 (*c* 0.22, $CHCl_3$).

IR (film): ν = 2942 s, 2859 s, 1586 w, 1461 m, 1382 m, 1215 w, 1137 m, 1114 m, 873 m, 688 m cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.52-7.47 (2H, m, Ph), 7.33-7.22 (3H, m, Ph), 5.50 (1H, t, *J* 5.8, H6), 4.17 (1H, ddt, *J* 10.2, 4.7, 5.5, H4), 3.80 (1H, dd, *J* 10.2, 5.5, CH_2OTIPS), 3.64 (1H, dd, *J* 10.2, 5.7, CH_2OTIPS), 2.08 (1H, ddd, *J* 13.5, 10.1, 6.0, H5), 1.99 (1H, ddd, *J* 13.5, 5.7, 4.7, H5'), 1.61 (3H, s, C<u>Me</u>(Me)), 1.38 (3H, s, CMe(<u>Me</u>)), 1.14-1.04 (3H, m, Si(C<u>H</u>$Me_2)_3$), 1.07 (18H, d, *J* 4.5, Si(CH<u>Me</u>$_2)_3$).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 135.6 (0, Ph), 131.0 (2C, 1, Ph), 129.0 (2C, 1, Ph), 127.1 (1, Ph), 101.1 (0, C2), 78.6 (1, C4 or C6), 67.8 (1, C4 or C6), 66.5 (2, CH_2OTIPS), 34.0 (2, C5), 28.1 (3, C<u>Me</u>(Me)), 24.6 (3, CMe(<u>Me</u>)), 18.1 (6C, 3, Si(CH<u>Me</u>$_2)_3$), 12.1 (3C, 1, Si(<u>C</u>H$Me_2)_3$).

LRMS (FAB$^+$ mode): *m/z* = 433.4 [(M+Na)$^+$, 22 %], 335.4 (14), 301.4 (47), 243.3 (82), 173.2 (100), 157.2 (73), 115.3 (43).

HRMS (FAB$^+$ mode, PEG): found $[M+Na]^+$, 433.2210. $C_{22}H_{38}O_3SSiNa$ requires 433.2209.

Spectroscopic data for sulphide **4.25**: (R_f = 0.78, Et_2O : PhMe = 2 : 98)

Compound **4.25** has been previously described, with only the following ^{13}C NMR data reported: δ = 30.0 (Me), 19.9 (Me) ppm.[189]

$[\alpha]_D$ = –54.2 (*c* 0.36, $CHCl_3$).

IR (film): ν = 2938 s, 2859 s, 1462 w, 1379 w, 1138 m, 1117 m, 955 m, 881 m, 689 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.48 (2H, m, Ph), 7.32-7.23 (3H, m, Ph), 5.31 (1H, dd, *J* 12.0, 2.5, H6), 4.02 (1H, dddd, *J* 11.3, 6.4, 4.9, 2.4, H4), 3.76 (1H, dd, *J* 9.8, 4.9, CH_2OTIPS), 3.54 (1H, dd, *J* 9.8, 6.4, CH_2OTIPS), 1.98 (1H, dt, *J* 12.9, 12.5, H5), 1.61-1.52 (1H, m, H5'), 1.55 (3H, s, C<u>Me</u>(Me)), 1.52 (3H, s, CMe(<u>Me</u>)), 1.12-1.04 (3H, m, Si(C<u>H</u>$Me_2)_3$), 1.04 (18H, d, *J* 4.5, Si(CH<u>Me</u>$_2)_3$).

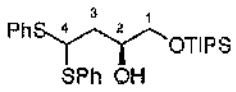
^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3 (0, Ph), 131.4 (2C, 1, Ph), 129.0 (2C, 1, Ph), 127.3 (1, Ph), 100.3 (0, C2), 77.7 (1, C4 or C6), 70.5 (1, C4 or C6), 66.9 (2, CH_2OTIPS), 34.0 (2, C5), 30.1 (3, C<u>Me</u>(Me)), 20.0 (3, CMe(<u>Me</u>)), 18.1 (6C, 3, Si(CH<u>Me</u>$_2)_3$), 12.1 (3C, 1, Si(<u>C</u>H$Me_2)_3$).

LRMS (CI mode, NH_3): *m/z* = 428.2 [$(M+NH_4)^+$, 34 %], 370.2 (39), 318.2 (69), 301.2 (100), 283.2 (81), 260.2 (31), 151.1 (39).

HRMS (CI$^+$ mode, isobutane): found $[M+H]^+$, 411.2389. $C_{22}H_{39}O_3SSi$ requires 411.2389.

Found (for a mixture of isomers): C, 64.36; H, 9.41. Calc. for $C_{22}H_{38}O_3SSi$: C, 64.34; H, 9.33%.

4,4-Bis-phenylsulfanyl-1-(triisopropylsilanyloxy)butan-2-ol (4.49)



The title compound was obtained in an initial attempt to synthesise sulphides **4.24** and **4.25** by the following procedure: A solution of acetate **4.39** (57 mg, 0.16 mmol) and thiophenol (0.03 mL, 0.32 mmol) in CH_2Cl_2 (5 mL) was cooled to –78°C under N_2 and BF_3•OEt_2 (0.02 mL, 0.19 mmol) was added dropwise. After stirring at –78°C for 1 h, 1M NaOH (2 mL) was added, the mixture was warmed to rt and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases washed with 1M NaOH (2 x 10 mL), brine (10 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) gave the title compound (55 mg, 0.12 mmol, 75%) as a clear oil.

$[\alpha]_D$ = –8.1 (*c* 0.42, $CHCl_3$).

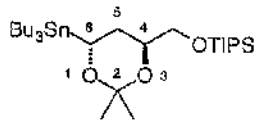
IR (film): ν = 2569 w, 3491 w, 2943 s, 2866 s, 1582 m, 1477 m, 1464 m, 1117 m, 882 m, 791 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.50 (2H, m, Ph), 7.46-7.43 (2H, m, Ph), 7.33-7.23 (6H, m, Ph), 4.74 (1H, dd, *J* 10.5, 4.1, H4), 4.16-4.11 (1H, m, H2), 3.70 (1H, dd, *J* 9.8, 3.7, H1), 3.50 (1H, dd, *J* 9.8, 6.4, H1'), 2.50 (1H, d, *J* 4.8, OH), 2.09 (1H, ddd, *J* 14.2, 9.9, 4.1, H3), 1.79 (1H, ddd, *J* 14.2, 10.5, 3.1, H3'), 1.07-0.99 (3H, m, $Si(C\underline{H}Me_2)_3$), 1.03 (18H, d, *J* 4.8, $Si(CH\underline{Me}_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3 (0, Ph), 134.0 (0, Ph), 133.0 (2C, 1, Ph), 132.7 (2C, 1, Ph), 129.1 (4C, 1, Ph), 127.9 (1, Ph), 127.8 (1, Ph), 69.5 (1, C2), 67.3 (2, C1), 54.8 (1, C4), 39.6 (2, C3), 18.1 (6C, 3, $Si(CH\underline{Me}_2)_3$), 12.0 (3C, 1, $Si(\underline{C}HMe_2)_3$).

LRMS (CI mode, NH_3): *m/z* = 480.0 [$(M+NH_4)^+$, 3 %], 370.1 (23), 335.1 (100), 174.1 (9).

(4*S*,6*R*)-[2,2-Dimethyl-6-(tributylstannanyl)-[1,3]dioxan-4-ylmethoxy]triisopropylsilane (4.9).



LDBB was prepared by a modification to the method of Freeman and Hutchinson:[196] A mixture of Li (3.24 g, 467 mmol), DBB (12.5 g, 46.7 mmol) and THF (160 mL) was stirred at 0°C for 48 h under a static Ar atmosphere. A mixture of sulphides **4.24 / 4.25** (188 mg, 0.46 mmol) in THF (20 mL) was cooled to –78°C under N_2 and LDBB solution (5.8 mL) added dropwise until lithiation was complete, as apparent by the maintenance of a dark-blue solution colour and TLC analysis. Bu_3SnCl (0.13 mL, 0.48 mmol) was added dropwise and the solution stirred at –78°C for 10 min before the addition of H_2O (3 mL) and removal of the cold bath. The remaining LDBB solution was added dropwise to a solution of sulphides **4.24 / 4.25** (4.23 g, 10.3 mmol) in THF (100 mL) at –78°C and the resulting dark-blue solution stirred at –78°C for 10 min before the addition of Bu_3SnCl (2.9 mL, 10.8 mmol) dropwise. After stirring for 10 min, H_2O (100 mL) and Et_2O (100 mL) were added and the cold bath removed. The two reaction mixtures were combined and the phases separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases washed with 0.5M NaOH (3 x 50 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, hexanes → ether : hexanes = 1 : 99) gave the title compound (4.96 g, 8.38 mmol, 81%) as a clear oil. ^{13}C NMR spectroscopy indicated the presence of a single isomer, identified as the expected axially substituted isomer by reference to the chemical shifts of the acetonide methyl signals.[189, 190]

Compound **4.9** has been previously described, with only the following ^{13}C NMR data reported: δ = 24.7 (Me), 24.5 (Me) ppm.[189]

$[\alpha]_D$ = –17.2 (*c* 1.02, $CHCl_3$).

IR (film): ν = 2949 s, 2928 s, 2870 s, 1465 m, 1382 m, 1225 m, 1143 m, 1101 m, 1068 w, 1002 m, 878 m, 692 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (1H, dd, *J* 11.3, 6.3, H6), 3.90 (1H, dq, *J* 8.8, 5.9, H4), 3.75 (1H, dd, *J* 10.0, 5.8, CH_2OTIPS), 3.62 (1H, dd, *J* 10.0, 5.8, CH_2OTIPS), 2.11 (1H, dt, *J* 5.9, 12.1, H5), 1.69 (1H, ddd, *J* 12.7, 8.9, 6.2, H5'), 1.58-1.46 (6H, m, $Sn(CH_2CH_2C\underline{H}_2Me)$, 1.36-1.26 (6H, m,

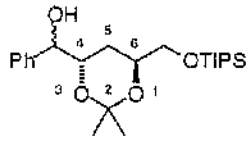
$Sn(CH_2C\underline{H}_2CH_2Me)$, 1.32 (3H, s, C$\underline{Me}$(Me)), 1.29 (3H, s, CMe($\underline{Me}$)), 1.13-1.05 (3H, m, Si($C\underline{H}Me_2)_3$), 1.07 (18H, d, J 4.4, Si($CH\underline{Me}_2)_3$), 0.93-0.84 (15H, m, $Sn(C\underline{H}_2CH_2CH_2Me)_3$, $Sn((CH_2)_3\underline{Me})_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.4 (0, C2), 68.1 (1, C4), 66.7 (2, CH_2OTIPS), 59.8 (1, C6), 34.1 (2, C5), 29.3 (3C, 2, $^3J_{C\text{-}Sn}$ 10.4, $Sn(CH_2C\underline{H}_2C\underline{H}_2Me)_3$), 27.8 (3C, 2, $^2J_{C\text{-}Sn}$ 25.2, $Sn(CH_2\underline{C}H_2CH_2Me)_3$), 24.9 (3, C$\underline{Me}$(Me)), 24.7 (3, CMe($\underline{Me}$)), 18.1 (6C, 3, Si($CH\underline{Me}_2)_3$), 13.9 (3C, 3, $Sn((CH_2)_3\underline{Me})_3$), 12.2 (3C, 1, Si($\underline{C}HMe_2)_3$), 8.8 (3C, 2, $^1J_{C\text{-}Sn}$ 161.0, 150.9, $Sn(\underline{C}H_2CH_2CH_2Me)_3$).

LRMS (EI$^+$ mode): m/z = 591.2 [$M^{+\bullet}$, 0.1%], 535.2 (19), 477.2 (40), 291.1 (100), 243.2 (75), 157.1 (74), 115.0 (38).

Found: C, 56.90; H, 9.98. Calc. for $C_{28}H_{60}O_3SiSn$: C, 56.85; H, 10.22%.

[(4*S*,6*S*)-2,2-Dimethyl-6-(triisopropylsilanyloxymethyl)-[1,3]dioxan-4-yl]-(*RS*)-phenylmethanol (4.73 and 4.74).



To a solution of stannane **4.8** (171 mg, 0.29 mmol) in THF (15 mL) at –78°C under N_2 was added *n*-BuLi (0.14 mL of a 2.29 M solution in hexanes, 0.35 mmol) dropwise. The light yellow solution was stirred at –78°C for 10 min before adding dropwise a solution of benzaldehyde (0.03 mL, 0.32 mmol) in THF (1 mL), which had been dried by standing with freshly activated 4Å sieves for 10 min. The clear solution was stirred at –78°C for 25 min before the addition of aqueous NH_4Cl (10 mL) and Et_2O (10 mL) and warming to rt. The phases were separated and the aqueous phase extracted with Et_2O (3 x 20 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 2 : 8) gave the title compounds (85 mg, 0.21 mmol, 72%) as a clear oil. ^1H NMR spectroscopy revealed that **4.73** and **4.74** were formed as an approximately equimolar mixture. Careful column chromatography allowed separation of the isomers for characterisation purposes.

Data for the less polar isomer: (R_f = 0.45, Et_2O : hexanes = 2 : 8)

$[\alpha]_D$ = –33.5 (*c* 0.60, $CHCl_3$).

IR (film): ν = 3462 br m, 2946 s, 2871 s, 1458 m, 1378 m, 1222 m, 1112 m, 1022 m, 882 m, 696 m, 681 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, referenced to added TMS): δ = 7.37-7.24 (5H, m, Ph), 4.92 (1H, t, J 2.3, C$\underline{H}$(OH)Ph), 4.03 (1H, ddd, 9.6, 6.0, 3.6, H4), 3.90-3.83 (1H, m, H6), 3.64 (1H, dd, J 10.4, 16.4, CH_2OTIPS), 3.54 (1H, dd, J 10.4, 4.8, CH_2OTIPS), 2.58 (1H, d, J 2.2, OH), 1.94 (1H, ddd, J 13.2, 10.0, 6.4, H5), 1.39 (3H, s, C$\underline{Me}$(Me)), 1.37 (3H, s, CMe($\underline{Me}$)), 1.14 (1H, ddd, J 13.0, 9.0, 6.0, H5'), 1.06-0.98 (3H, m, Si($C\underline{H}Me_2)_3$), 1.00 (18H, d, J 2.0, Si($CH\underline{Me}_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6 (0, Ph), 128.3 (2C, 1, Ph), 127.6 (1, Ph), 126.3 (2C, 1, Ph), 100.7 (0, $\underline{C}Me_2$), 74.6 (1, $\underline{C}$H(OH)Ph), 70.5 (1, C4), 68.7 (1, C6), 66.5 (2, CH_2OTIPS), 26.9 (2, C5), 25.6 (3, C$\underline{Me}$(Me)), 25.0 (3, CMe($\underline{Me}$)), 18.1 (6C, 3, Si($CH\underline{Me}_2)_3$), 12.1 (3C, 1, Si($\underline{C}HMe_2)_3$).

LRMS (CI^+ mode, isobutane): *m/z* = 409.3 [$(M+H)^+$, 6], 351.2 (100), 333.2 (80), 307.2 (32), 289.2 (22), 177.1 (72), 159.1 (14).

Found: C, 67.66; H, 9.89. Calc. for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87%.

Data for the more polar isomer: (R_f = 0.35, Et_2O : hexanes = 2 : 8)

$[\alpha]_D$ = –6.5 (*c* 1.55, $CHCl_3$).

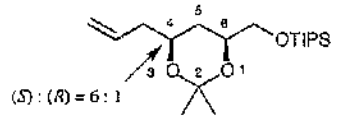
IR (film): ν = 3466 br m, 2939 s, 2865 s, 1464 m, 1381 m, 1223 m, 1136 m, 1108 m, 1020 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, referenced to added TMS): δ = 7.38-7.26 (5H, m, Ph), 4.49 (1H, dd, *J* 8.0, 1.6, C<u>H</u>(OH)Ph), 3.95-3.87 (2H, m, H4, H6), 3.64 (1H, dd, *J* 10.4, 6.0, CH_2OTIPS), 3.52 (1H, dd, *J* 10.4, 5.2, CH_2OTIPS), 3.03 (1H, d, *J* 2.0, OH), 1.62 (1H, ddd, *J* 13.0, 9.9, 6.4, H5), 1.42 (3H, s, C<u>Me</u>(Me)), 1.40 (3H, s, CMe(<u>Me</u>)), 1.22 (1H, ddd, *J* 13.0, 9.1, 5.7, H5'), 1.08-0.97 (3H, m, Si(C<u>H</u>$Me_2)_3$), 1.00 (18H, d, *J* 2.0, Si(CH<u>Me</u>$_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3 (0, Ph), 128.6 (2C, 1, Ph), 128.4 (1, Ph), 127.5 (2C, 1, Ph), 101.0 (0, <u>C</u>Me_2), 77.5 (1, <u>C</u>H(OH)Ph), 71.8 (1, C4 or C6), 68.1 (1, C4 or C6), 66.4 (2, CH_2OTIPS), 30.8 (2, C5), 25.4 (3, C<u>Me</u>(Me)), 25.0 (3, CMe(<u>Me</u>)), 18.1 (6C, 3, Si(CH<u>Me</u>$_2)_3$), 12.1 (3C, 1, Si(C<u>H</u>$Me_2)_3$).

LRMS (CI^+ mode): *m/z* = 426.2 [$(M+NH_4)^+$, 4], 368.2 (37), 351.2 (100), 333.2 (9), 194.1 (15).

(4*S*,6*RS*)-(6-Allyl-2,2-dimethyl-[1,3]dioxan-4-ylmethoxy)triisopropylsilane (4.79).



n-BuLi (0.15 mL of a 2.29 M solution in hexanes, 0.35 mmoL) was added to a solution of stannane **4.9** (190 mg, 0.32 mmol) in THF (20 mL) at –78°C under N_2. The solution was stirred at –78°C for 5 min before cooling to –90°C and adding *via* cannula a solution of CuBr•DMS (79 mg, 0.39 mmol) in diisopropyl sulfide (0.3 mL) and THF (0.3 mL) maintaining the reaction temperature below –80°C. The orange solution was stirred at –78°C for 30 min before cooling to –90°C and dropwise addition of a solution of complex **4.77** (which had been freshly prepared from neutral complex **4.76** (91 mg, 0.35 mmol) and $NOBF_4$ (45 mg, 0.39 mmol) in MeCN (4 mL), 0°C, 20 min). The brown solution was allowed to warm to –78°C over 30 min before addition of aqueous NH_3 (5 mL), aqueous NH_4Cl (10 mL) and Et_2O (25 mL) and removal of the cooling bath. After warming to room temperature the mixture was filtered through celite, rinsing with Et_2O (3 x 25 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined organic phases were washed with brine (50 mL), dried, filtered and concentrated *in vacuo*. The crude products were dissolved in analytical grade chloroform (50 mL), and stirred at rt with a stream of O_2 bubbling through the solution for 17 h. The solvent was removed *in vacuo* to give a brown oil. Purification by column chromatography (SiO_2, Et_2O : hexanes = 2 : 98) gave the title compound (53 mg, 0.15 mmol, 48%) as a clear oil.

^{1}H NMR spectroscopy indicated that olefin **4.79** was present as a mixture of epimers at the C4 position. (Isomers inseparable by column chromatography). The major isomer was determined to be the (6*S*)-epimer by the large (^3J 11.6) coupling of H6 to H5 (C_6D_6). ^{13}C NMR spectroscopic data confirmed the assignment, acetonide methyl carbon shifts at 30.2 and 20.0 ppm being indicative of the stereochemistry.[189, 190] The minor (6*R*)-isomer exhibited acetonide methyl carbon shifts at 25.2 ppm (2C, 3). The ratio of equatorial : axial isomers was estimated from ^{1}H NMR spectroscopy ($CDCl_3$) comparing the integration of signals at: 3.79-3.72 (2 overlapping dd, 1 each from (6*R*)- and (6*S*)-isomers) and 3.63 (1H, dd, (6*R*)-isomer).

$[\alpha]_D$ = –12.8 (*c* 1.06, $CHCl_3$).

IR (film): ν = 2943 s, 2866 s, 1642 w, 1464 m, 1379 m, 1261 m, 1200 m, 1172 m, 1114 s, 994 m, 883 m, 681 w cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, data for the (6*S*)-isomer): δ = 5.90-5.80 (1H, m, C<u>H</u>=CH$_2$), 5.06-5.01 (2H, m, CH=C<u>H</u>$_2$), 3.88 (1H, ddt, *J* 11.6, 2.5, 5.5, H4), 3.80 (1H, dd, *J* 9.7, 5.2, CH$_2$OTIPS), 3.69 (1H, ddt, *J* 11.6, 2.4, 6.0, H6), 3.57 (1H, dd, *J* 9.7, 2.2, CH$_2$OTIPS), 2.34-2.27 (1H, m, C<u>H</u>$_A$H$_B$CH=CH$_2$), 2.14-2.07 (1H, m, CH$_A$<u>H</u>$_B$CH=CH$_2$), 1.50 (3H, s, C<u>Me</u>(Me)), 1.45 (1H, dt, *J* 12.8, 2.6, H5), 1.30 (3H, s, CMe(<u>Me</u>)), 1.26-1.17 (1H, m, H5'), 1.11 (18H, d, *J* 2.8, Si(CH<u>Me</u>$_2$)$_3$), 1.15-1.08 (3H, m, Si(C<u>H</u>Me$_2$)$_3$).

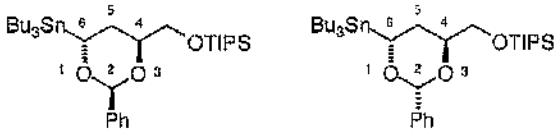
^{13}C NMR (100 MHz, $CDCl_3$, (6*S*)-isomer): δ = 134.4 (1, <u>C</u>H=CH$_2$), 117.2 (2, CH=<u>C</u>H$_2$), 98.6 (0, <u>C</u>Me$_2$), 70.2 (1, C4), 68.7 (1, C6), 67.4 (2, CH$_2$OTIPS), 41.1 (2, <u>C</u>H$_2$CH=CH$_2$), 33.9 (2, C5), 30.2 (3, C<u>Me</u>(Me)), 20.0 (3, CMe(<u>Me</u>)), 18.1 (6C, 3, Si(CH<u>Me</u>$_2$)$_3$), 12.2 (3C, 1, Si(<u>C</u>HMe$_2$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$, (6*S*)-isomer): δ = 134.7 (1, <u>C</u>H=CH$_2$), 117.0 (2, CH=<u>C</u>H$_2$), 100.3 (0, <u>C</u>Me$_2$), 68.1 (1, C6 or C4), 66.7 (2, CH$_2$OTIPS), 66.5 (1, C6 or C4), 40.4 (2, <u>C</u>H$_2$CH=CH$_2$), 34.4 (2, C5), 25.2 (2C, 3, C<u>Me</u>$_2$), 18.1 (6C, 3, Si(CH<u>Me</u>$_2$)$_3$), 12.2 (3C, 1, Si(<u>C</u>HMe$_2$)$_3$).

LRMS (CI$^+$ mode): *m/z* = 343.2 [(M+H)$^+$, 5], 285.2 (100), 267.2 (26), 241.2 (20), 217.2 (7), (173.1 (13), 111.1 (32).

Found: C, 66.75; H, 11.09. Calc. for $C_{19}H_{38}O_3Si$: C, 66.61; H, 11.18%.

(2*R*,4*S*,6*R*)-Triisopropyl[2-phenyl-6-(tributylstannanyl)-[1,3]dioxan-4-ylmethoxy]silane (4.80) and (2*S*,4*S*,6*R*)-Triisopropyl[2-phenyl-6-(tributylstannanyl)-[1,3]dioxan-4-ylmethoxy]silane (4.81).



4.80 4.81

To a solution of stannane **4.9** (4.32 g, 7.30 mmol), methanol (0.9 mL, 21.9 mmol) and benzaldehyde dimethylacetal (5.5 mL, 36.5 mmol) in CH_2Cl_2 (120 mL) at rt under N_2 was added *p*-TsOH (69 mg, 0.37 mmol). The solution was stirred at rt for 7 h before concentration *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 2 : 98) gave the title compounds (4.17 g, 6.52 mmol, 89%) as a

clear oil. ^{1}H NMR spectroscopy indicated a mixture of **4.80** / **4.81** in the approximate ratio 7 : 1, based on the integration of H2 singlets at 5.81 and 5.73 ppm respectively. Separation of isomers was possible by careful repetitive column chromatography (SiO_2, PhMe : hexanes = 1 : 3). The major isomer was identified as the 2*R* isomer **4.80** by nOe studies.

Data for the 2*R*-isomer (**4.80**): (R_f = 0.13, PhMe : hexanes = 1 : 3)

$[\alpha]_D$ = +20.6 (*c* 1.61, $CHCl_3$).

IR (film): ν = 2922 s, 2860 s, 1460 m, 1378 w, 1107 m, 1004 w, 883 w, 796 w, 755 m, 687 m, 595 w cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.93-7.90 (2H, m, Ph), 7.36-7.22 (3H, m, Ph), 5.81 (1H, s, H2), 5.15 (1H, apparent d, *J* 6.4, H6), 4.26 (1H, dddd, *J* 10.7, 6.9, 5.2, 2.4, H4), 4.18 (1H, dd, *J* 9.7, 5.0, CH_2OTIPS), 3.89 (1H, dd, *J* 9.7, 7.2, CH_2OTIPS), 2.56 (1H, ddd, *J* 13.3, 10.8, 6.4, H5), 2.07 (1H, br dd, *J* 13.3, 1.4, H5'), 1.76-1.63 (6H, m, Sn($CH_2CH_2C\underline{H}_2$Me), 1.49 (6H, sextet, *J* 7.3, Sn($CH_2C\underline{H}_2CH_2$Me), 1.27-1.12 (12H, m, Sn($CH_2CH_2CH_2\underline{Me}$ + Si($C\underline{H}Me_2$)$_3$), 1.22 (18H, d, *J* 2.8, Si($CH\underline{Me}_2$)$_3$), 1.04 (6H, t, *J* 7.2, Sn($C\underline{H}_2CH_2CH_2$Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1 (0, Ph), 128.8 (1, Ph), 128.4 (2C, 1, Ph), 126.2 (2C, 1, Ph), 100.6 (1, C2), 77.4 (1, C4), 74.4 (1, C6), 66.6 (2, CH_2OTIPS), 33.9 (2, C5), 29.3 (3C, 2, $^3J_{C\text{-}Sn}$ = 10.2, Sn($CH_2CH_2\underline{C}H_2$Me)$_3$), 27.7 (3C, 2, $^2J_{C\text{-}Sn}$ = 27.8, Sn($CH_2\underline{C}H_2CH_2$Me)$_3$), 18.2 (6C, 3, Si($CH\underline{Me}_2$)$_3$), 13.8 (3C, 3, Sn($(CH_2)_3\underline{Me}$)$_3$), 12.1 (1, 3C, Si($\underline{C}HMe_2$)$_3$), 10.3 (3C, 2, $^1J_{C\text{-}Sn}$ 150.1, 143.6, Sn($\underline{C}H_2CH_2CH_2$Me)$_3$).

LRMS (CI^+ mode): *m/z* = 641.2 [$(M+H)^+$, 35], 583.1 (100), 581.1 (76), 533.2 (32), 475.1 (18), 291.1 (44), 289.1 (34), 243.2 (22), 107.1 (86).

Found: C, 60.17; H, 9.41. Calc. for $C_{32}H_{60}O_3SiSn$: C, 60.09; H, 9.46%.

Data for the 2*S*-isomer (**4.81**): (R_f = 0.22, PhMe : hexanes = 1 : 3)

$[\alpha]_D$ = –2.14 (*c* 1.54, $CHCl_3$).

IR (film): ν = 2960 s, 2864 s, 1460 s, 1380 m, 1114 m, 1073 m, 1018 m, 881 m, 798 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.44 (2H, m, Ph), 7.36-7.28 (3H, m, Ph), 5.73 (1H, s, H2), 4.59 (1H, dd, *J* 13.7, 2.3, H6), 4.35 (1H, t, *J* 9.0, CH_2OTIPS), 4.17-4.12 (1H, m, H4), 4.01 (1H, dd, *J* 9.5, 5.2, CH_2OTIPS), 2.59 (1H, dt, *J* 6.1, 13.8, H5), 1.85 (1H, ddd, *J* 13.8, 2.3, 1.1, H5'), 1.61-1.51 (6H, m, Sn($CH_2CH_2C\underline{H}_2$Me)$_3$), 1.31 (6H, sextet, *J* 7.2, Sn($CH_2C\underline{H}_2CH_2$Me)$_3$), 1.18-1.08 (3H, m, Si($C\underline{H}Me_2$)$_3$), 1.10 (18H, d, *J* 5.2, Si($CH\underline{Me}_2$)$_3$), 0.99-0.94 (6H, m, Sn($C\underline{H}_2CH_2CH_2$Me)$_3$), 0.90 (9H, t, *J* 7.4, Sn($CH_2CH_2CH_2\underline{Me}$)$_3$).

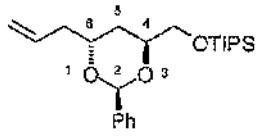
^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0 (0, Ph), 128.5 (1, Ph), 128.2 (2C, 1, Ph), 126.2 (2C, 1, Ph), 97.9 (1, C2), 73.1 (1, C4), 68.1 (1, C6), 61.8 (2, CH_2OTIPS), 30.1 (2, C5), 29.3 (3C, 2, $^3J_{C\text{-}Sn}$ 10.2, Sn($CH_2CH_2\underline{C}H_2$Me)$_3$), 27.9 (3C, 2, $^2J_{C\text{-}Sn}$ 26.8, Sn($CH_2\underline{C}H_2CH_2$Me)$_3$), 18.2 (6C, 3, Si($CH\underline{Me}_2$)$_3$),

13.9 (3C, 3, $Sn((CH_2)_3\underline{Me})_3$), 12.1 (3C, 1, $Si(\underline{C}HMe_2)_3$), 8.6 (3C, 2, $^1J_{C\text{-}Sn}$ 160.6, 153.6, $Sn(\underline{C}H_2CH_2CH_2Me)_3$).

LRMS (CI^+ mode): m/z = 641.0 [$(M+H)^+$, 49%], 583.0 (100), 581.0 (75), 533.0 (31), 351.1 (42), 291.0 (69), 289.0 (53).

Found: C, 60.07; H, 9.36. Calc. for $C_{32}H_{60}O_3SiSn$: C, 60.09; H, 9.46%.

(2*S*,4*S*,6*R*)-(6-Allyl-2-phenyl-[1,3]dioxan-4-ylmethoxy)triisopropylsilane (4.82).



Olefin **4.82** was prepared in an analogous fashion to olefin **4.79** on a scale of 0.25 mmol of stannane **4.80** and 0.28 mmol of neutral complex **4.76**. Purification by column chromatography (SiO_2, Et_2O : hexanes = 3 : 97) gave the title compound (50 mg, 0.13 mmol, 51%) as a clear oil. ^1H and ^{13}C NMR spectroscopy indicated the presence of a single isomer, identified as the (6*S*)-isomer on the basis of the small (*J* 6.9) coupling between H6 and H5. nOe experiments confirmed the assignment, with large (12-16%) enhancements observed between H6 and H2, and no enhancement observed between H4 and H6 when either position was irradiated.

$[\alpha]_D$ = +17.5 (*c* 0.59 $CHCl_3$).

IR (film): ν = 2866 s, 1463 m, 1383 m, 1216 m, 1118 s, 1069 m, 1027 m, 995 s, 918 m, 883 s, 754 s, 697 m cm^{-1}.

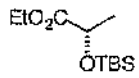
^1H NMR (400 MHz, $CDCl_3$): δ = 7.51-7.48 (2H, m, Ph), 7.38-7.30 (3H, m, Ph), 5.88 (1H, ddt, *J* 16.8, 10.0, 7.3, $C\underline{H}=CH_2$), 5.84 (1H, s, H2), 5.21-5.13 (2H, m, $CH=C\underline{H}_2$), 4.35 (1H, m, apparent q, *J* 6.9, H6), 4.18 (1H, ddt, *J* 11.0, 2.5, 5.9, H4), 3.93 (1H, dd, *J* 9.9, 5.4, CH_2OTIPS), 3.69 (1H, dd, *J* 9.9, 6.4, CH_2OTIPS), 2.87 (1H, dt, *J* 14.4, 7.3, $C\underline{H}_AH_BCH=CH_2$), 2.55 (1H, dt, *J* 14.4, 7.3, $CH_A\underline{H}_BCH=CH_2$), 2.00 (1H, ddd, *J* 13.8, 11.2, 6.2, H5), 1.74 (1H, ddd, *J* 13.5, 2.5, 1.3, H5'), 1.15-1.03 (3H, m, $Si(C\underline{H}Me_2)_3$), 1.08 (18H, d, *J* 5.2, $Si(CH\underline{Me}_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1 (0, Ph), 134.7 (1, $\underline{C}H=CH_2$), 128.8 (1, Ph), 128.3 (2C, 1, Ph), 126.3 (2C, 1, Ph), 117.6 (2, $CH=\underline{C}H_2$), 94.4 (1, $\underline{C}HPh$), 73.2 (1, C4), 72.3 (1, C6), 66.9 (2, CH_2OTIPS), 35.6 (2, $\underline{C}H_2CH=CH_2$), 30.3 (2, C5), 18.2 (6C, 3, $Si(CH\underline{Me}_2)_3$), 12.1 (3C, 1, $Si(\underline{C}HMe_2)_3$).

LRMS (CI^+ mode): m/z = 391.1 [$(M+H)^+$, 100], 347.1 (8), 285.1 (50), 261.1 (11), 241.1 (11), 111.1 (13), 107.1 (12).

Found: C, 70.65; H, 9.73. Calc. for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.81%.

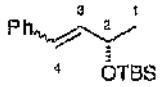
(2*S*)-2-(*tert*-Butyldimethylsilanyloxy)propionic acid ethyl ester (4.12).



A solution of (*S*)-ethyl lactate **11** (12.2 g, 104 mmol), *tert*-butyldimethylsilyl chloride (15.6 g, 104 mmol), triethylamine (15.2 mL, 109 mmol) and 4-dimethylaminopyridine (500 mg) in CH_2Cl_2 (200 mL) was refluxed under N_2 for 1 d. After cooling to rt the mixture was filtered through celite, and the celite washed with hexanes (50 mL). The filtrate was washed with 2M HCl (100 mL) and H_2O (100 mL), dried, filtered and concentrated *in vacuo*. Purification by short-path distillation (b.p. 102°C / 15 mmHg) yielded the title compound (22.2 g, 95.5 mmol, 92%) as a clear oil. Spectroscopic data were in accordance with literature data.[240]

$[\alpha]_D$ = –25.0 (*c* 1.05, $CHCl_3$). Lit. $[\alpha]_D$ = –30.0 (*c* 2.50, $CHCl_3$).[240]

(1*S*,2*E*)-*tert*-Butyldimethyl(1-methyl-3-phenylallyloxy)silane (*E*)-4.13 and (1*S*,2*Z*)-*tert*-Butyldimethyl(1-methyl-3-phenylallyloxy)silane (*Z*)-4.13.



To a solution of silyl ether **4.12** (23.3 g, 100 mmol) in CH_2Cl_2 (400 mL) at –78°C under N_2 was added diisobutylaluminium hydride (102 mL of a 1.0M solution in hexanes, 102 mmol) dropwise. After stirring for 10 min at –78°C, acetone (12 mL) and aqueous Na_2SO_4 (60 mL) were added and the cooling bath removed. After vigorous stirring at rt for 1 h, solid Na_2SO_4 (90 g) was added and stirring continued for a further 1 h. The mixture was filtered through celite and the residue washed thoroughly with CH_2Cl_2 (3 x 100 mL) before concentration *in vacuo* yielded crude (*S*)-*O*-(*tert*-butyldimethylsilyl)lactaldehyde (**4.18**) as a clear oil which was immediately used without further purification.

n-BuLi (62 mL of a 2.03M solution in hexanes, 125 mmol) was added to a suspension of benzyltriphenylphosphonium bromide (52.2 g, 121 mmol) in THF (200 mL) at rt under N_2. After stirring at rt for 10 min the dark red solution was brought to reflux before the dropwise addition of a solution of crude aldehyde **4.18** in THF (20 mL). Reflux was continued for 30 min before the orange suspension was cooled to rt and aqueous NH_4Cl (100 mL) and H_2O (100 mL) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried, filtered and concentrated *in vacuo* to yield a pale yellow suspension of crude olefins (*E*)-**4.13** and (*Z*)-**4.13** and triphenylphosphine oxide. The mixture was suspended in hexanes (150 mL) and filtered, washing with hexanes (2 x 50 mL). The filtrate was concentrated and purification by column chromatography (SiO_2, ether : hexanes = 5 : 95) gave the title compounds (20.1 g, 76.7 mmol, 76%) as a pale yellow oil. ^1H NMR spectroscopy indicated an approximately equimolar mixture of geometrical isomers.

$[\alpha]_D$ = –48.65 (*c* 1.11, $CHCl_3$).

IR (film): ν = 2960 s, 2932 s, 2848 m, 1466 w, 1378 w, 1255 s, 1063 s, 834 s, 778 s cm^{-1}.

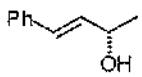
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.18 (10H, m, Ph), 6.50 (1H, d, *J* 15.6), 6.37 (1H, d, *J* 12.0), 6.21 (1H, dd, *J* 15.6, 5.6), 5.68 (1H, dd, *J* 12.0, 8.8), 4.77 (1H, dq, *J* 8.8, 6.0), 4.47 (1H, dq, *J* 6.0, 6.2), 1.34 (3H, d, *J* 6.3), 1.30 (3H, d, *J* 6.3), 0.92 (9H, s), 0.82 (9H, s), 0.10 (3H, s), 0.09 (3H, s), –0.07 (3H, s), –0.12 (3H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7 (1, Ph, C2 or C3), 137.4 (0, Ph), 137.3 (0, Ph), 135.0 (1, Ph, C2 or C3), 128.8 (2C, 1, Ph), 128.7 (2C, 1, Ph), 128.3 (2C, 1, Ph), 128.1 (1, Ph, C2 or C3), 127.5 (1, Ph, C2 or C3), 127.4 (1, Ph, C2 or C3), 127.0 (1, Ph, C2 or C3), 126.6 (2C, 1, Ph), 69.6 (1, C1), 65.3 (1, C1), 26.1 (3C, 3, $SiMe_2C\underline{Me}_3$), 26.0 (3C, 3, $SiMe_2C\underline{Me}_3$), 24.8 (3, C1-Me), 24.6 (3, C1-Me), 18.5 (0, $SiMe_2\underline{C}Me_3$), 18.3 (0, $SiMe_2\underline{C}Me_3$), –4.3 (2C, 3, $Si\underline{Me}_2CMe_3$), –4.6 (2C, 3, $Si\underline{Me}_2CMe_3$).

Isomerisation of olefins (*EZ*)-4.13.

A solution of olefins **4.13** (*E* : *Z* ≈ 1:1, 30.8 g, 117 mmol), thiophenol (1.2 mL, 11.8 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (865 mg, 3.54 mmol) in PhMe (600 mL) was brought to reflux under N_2. After refluxing for 2 d the pale yellow solution was cooled to rt, and washed with 0.5M NaOH (2 x 100 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL) and the combined organic phases dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether : hexanes = 5 : 95) gave **4.13** (29.1 g, 111 mmol, 95%) as a pale yellow oil. ^{1}H NMR spectroscopy indicated an approximate ratio of *E* : *Z* isomers of 6:1, based on the integration of H4 doublets at 6.50 and 6.37 ppm respectively.

(2*S*,3*E*)-4-Phenylbut-3-en-2-ol (4.10).

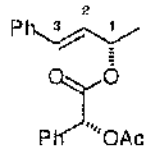


Tetrabutylammonium fluoride trihydrate (22.0 g, 69.7 mmol) was added to a solution of olefins **4.13** (15.3 g, 58.1 mmol, *E* : *Z* = 6 : 1) in THF (200 mL) at rt under N_2. The dark red-brown solution was stirred at rt under N_2 for 4.5 h before addition of aqueous NH_4Cl (100 mL) and Et_2O (100 mL). The phases were separated, and the aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give a yellow-brown oil. Purification by column chromatography (SiO_2, ethyl acetate : hexanes = 1 : 9 → 2 : 8) gave a mixture of alcohols (*EZ*)-**4.10** (7.71 g, 52.0 mmol, 90%) as a light yellow oil which solidified upon standing. Further purification by recrystallisation from hexanes-CH_2Cl_2 (6:1) yielded (*E*)-**4.10** (6.38 g, 43.1 mmol, 74%) as a pale yellow crystalline solid. Spectroscopic data were in accordance with literature data.[241, 242]

m.p. = 29-30°C (hexanes-CH_2Cl_2) Lit. m.p. = 31-33°C.[171]

$[\alpha]_D$ = –24.8 (*c* 0.87, $CHCl_3$). Lit. $[\alpha]_D$ = +34.2 (enantiomer) (*c* 1.77, $CHCl_3$).[200]

(*R*)-Acetoxyphenylacetic acid (1*S*)-1-methyl-3-phenylallyl ester (4.20)



To a solution of alcohol **4.10** (41 mg, 0.28 mmol), (*R*)-*O*-acetoxyphenylacetic acid (59 mg, 0.30 mmol) and DMAP (2 mg, 0.01 mmol) in CH_2Cl_2 (10 mL) at 0°C under N_2 was added DCC (86 mg, 0.41 mmol). The cloudy solution was stirred at 0°C for 10 min and at rt for 50 min before filtering through celite and washing with Et_2O. After drying, filtration and concentration *in vacuo*, purification by column chromatography (SiO_2, ether : hexanes = 3 : 7) gave the title compound (76 mg, 0.23 mmol, 84%) as a clear oil.

The diastereomeric ratio at C1 was estimated as 97 : 3 *via* integration of the H3 signals in the ^{1}H NMR spectrum: δ = 6.56 (d, *J* 16.0, (1*S*)-diastereomer), δ = 6.26 (d, *J* 16.0, (1*R*)-diastereomer), with reference to a sample of (1*RS*)-ester formed from (±)-**4.10**.

$[\alpha]_D$ = –107.7 (*c* 2.32, $CHCl_3$).

IR (film): ν = 3054 w, 3030 m, 2978 m, 2930 w, 1755 s, 1492 w, 1448 w, 1368 m, 1225 s, 1173 s, 1049 s, 970 m cm^{-1}.

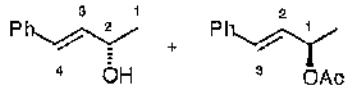
^{1}H NMR (400 MHz, $CDCl_3$ referenced to added TMS): δ = 7.50-7.19 (10H, m, Ph), 6.58 (1H, d, *J* 16.0, H3), 6.16 (1H, dd, *J* 16.0, 6.4, H2), 5.95 (1H, s, C<u>H</u>(OAc)Ph), 5.55 (1H, ddq, *J* 6.4, 1.1, 6.5, H1), 2.17 (3H, s, OCO<u>Me</u>), 1.27 (3H, d, *J* 6.5,C1-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (0, O<u>C</u>OR), 168.2 (0, O<u>C</u>OR), 136.3 (0, Ph), 134.0 (0, Ph), 131.9 (1, C3), 129.2 (1, C2 or Ph), 128.8 (2C, 1, Ph), 128.6 (2C, 1, Ph), 128.0 (2C, 1, C2 and / or Ph), 127.7 (2C, 1, Ph), 126.7 (2C, 1, Ph), 74.8 (1, <u>C</u>H(OAc)Ph), 72.6 (1, C1), 20.8 (3, CO<u>Me</u>), 20.0 (3, C1-<u>Me</u>).

LRMS (EI$^+$ mode): *m/z* = 324.2 [$M^{+\bullet}$, 2%], 264.2 (7), 131.1 (100), 118.1 (40), 107.1 (32), 91.1 (20), 43.0 (17).

HRMS (EI$^+$ mode): found [$M^{+\bullet}$], 324.1359. $C_{20}H_{20}O_4$ requires 324.1362.

Alternative procedure for the preparation of **(2*S*,3*E*)-4-Phenylbut-3-2-ol (4.10)** and **(1*R*,2*E*)-Acetic acid 1-methyl-3-phenylallyl ester (4.15)**:



A suspension of Novozym 435 (66 mg), crushed activated 4Å molecular sieves (330 mg), (±)-**4.10** (660 mg, 4.45 mmol) and vinyl acetate (10.3 mL, 111 mmol) in pentane (20 mL) was shaken gently at rt for 10 h. ^{1}H NMR analysis of the crude reaction mixture indicated ≥ 50% conversion. After filtration and concentration *in*

vacuo, purification by column chromatography (SiO_2, ether : hexanes = 2 : 8 → 4 : 6) gave acetate **4.15** (390 mg, 2.05 mmol, 46%) as a clear oil, and alcohol **4.10** (300 mg, 2.02 mmol, 45%) as a clear oil which solidified upon standing.

Data for alcohol **4.10**:

$[\alpha]_D$ = –34.1 (*c* 2.34, $CHCl_3$). Lit. $[\alpha]_D$ = +34.2 (enantiomer) (*c* 1.77, $CHCl_3$).[200]

Spectroscopic data were in accordance with literature data.[241, 242]

The enantiomeric ratio at C2 for alcohol **4.10** was estimated as 97:3 *via* formation of the corresponding (*R*)-*O*-acetoxyphenylacetic ester **4.20** by an analogous procedure to that detailed above.

Data for acetate **4.15**:

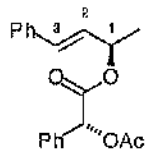
$[\alpha]_D$ = +143.1 (*c* 3.38, $CHCl_3$). Lit. $[\alpha]_D$ = +151.1 (*c* 5.27, $CHCl_3$).[243]

^1H and IR spectroscopic data were in accordance with literature data.[244]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (0, COMe), 136.5 (0, Ph), 131.7 (1, Ph, C2 or C3), 129.0 (1, Ph, C2 or C3), 128.7 (2C, 1, Ph), 128.0 (1, Ph, C2 or C3), 126.7 (2C, 1, Ph), 71.1 (1, C1), 21.5 (3, COMe), 20.5 (3, C1-Me).

The enantiomeric ratio at C1 for acetate **4.15** was estimated as 96:4 by cleavage of the acetate (10 wt% K_2CO_3, MeOH, rt, 15 h) and formation of the corresponding (*R*)-*O*-acetoxyphenylacetic ester **4.21** by an analogous procedure to that detailed above.

(*R*)-Acetoxyphenylacetic acid (1*R*)-1-methyl-3-phenylallyl ester (4.21)



$[\alpha]_D$ = –2.6 (*c* 1.40, $CHCl_3$).

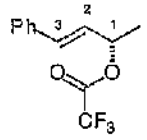
IR (film): ν = 3054 w, 3034 m, 2974 m, 2930 w, 1763 s, 1743 s, 1492 m, 1448 m, 1372 s, 1225 s, 1173 s, 1049 s, 970 s, 926 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$ referenced to added TMS): δ = 7.49-7.18 (10H, Ph), 6.26 (1H, d, *J* 16.0, H3), 5.98 (1H, dd, *J* 16.0, 6.2, H2), 5.95 (1H, s, CH(OAc)Ph), 5.55 (1H, ddq, *J* 6.4, 1.2, 6.2, H1), 2.19 (3H, s, OCOMe), 1.42 (3H, d, *J* 6.4, C1-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (0, OCOR), 168.2 (0, OCOR), 136.3 (0, Ph), 134.0 (0, Ph), 131.4 (1, C3), 129.4 (1, C2 or Ph), 128.9 (2C, 1, Ph), 128.6 (3C, 1, Ph), 128.0 (3C, 1, Ph), 127.9 (1, C2 or Ph), 126.6 (1, Ph), 74.8 (1, CH(OAc)Ph), 72.4 (1, C1), 20.9 (3, COMe), 20.4 (3, C1-Me).

LRMS (CI$^+$ mode, NH_3): m/z = 342.1 [$(M+NH_4)^+$, 14%], 212.1 (14), 131.1 (100).

(1*S*,2*E*)-Trifluoroacetic acid 1-methyl-3-phenylallyl ester (4.16).



Freshly distilled trifluoroacetic anhydride (2.5 mL, 11.5 mmol), was added to a solution of alcohol **4.10** (854 mg, 5.76 mmol), triethylamine (1.8 mL, 12.7 mmol) and DMAP (10 mg) in CH_2Cl_2 (5 mL) at 0°C under N_2. The solution was allowed to warm to rt with stirring over 3 h and H_2O (30 mL) added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with aqueous K_2HPO_4 solution (2 x 30 mL) and H_2O (30 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) gave the title compound (1.15 g, 4.70 mmol, 82%) as a clear oil.

Trifluoroacetate **4.16** has previously been described, but no data reported.[17]

$[\alpha]_D$ = –94.8 (*c* 0.83, $CHCl_3$).

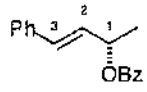
IR (film): ν = 3058 w, 3031 w, 2987 m, 2934 w, 1781 s, 1377 w, 1222 m, 1160 s, 1027 m, 969 w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.29 (5H, m, Ph), 6.72 (1H, d, *J* 15.9, H1), 6.20 (1H, dd, *J* 15.9, 7.4, H2), 5.70 (1H, dq, *J* 6.7, 6.5, H3), 1.57 (3H, d, *J* 6.5, H4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0 (0, q, $^2J_{C\text{-}F}$ 42.0, $\underline{C}OCF_3$), 135.7 (0, Ph), 134.4 (1, Ph, C1 or C2), 128.9 (2C, 1, Ph), 128.8 (1, Ph, C1 or C2), 127.0 (1, Ph, C1 or C2), 126.1 (1, Ph, C1 or C2), 114.8 (0, q, $^1J_{C\text{-}F}$ 286.0, CO$\underline{C}F_3$), 76.6 (1, C3), 20.1 (3, C4).

LRMS (EI mode): m/z = 244.2 [$M^{+\bullet}$, 60 %], 149.1 (28), 131.1 (100), 115.1 (50), 91.1 (49), 57.2 (29).

(1*S*,2*E*)-Benzoic acid 1-methyl-3-phenylallyl ester (4.17).



To a solution of alcohol **4.10** (3.82 g, 25.8 mmol) and DMAP (10 mg) in CH_2Cl_2 (30 mL) at rt under N_2 was added benzoyl chloride (3.3 mL, 28.4 mmol) and triethylamine (4.0 mL, 28.4 mmol). The solution was stirred at rt for 18 h before the addition of 2M HCl (30 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give a pale-yellow solid. Purification by recrystallisation from hexanes gave the title compound (5.89 g, 23.3 mmol, 90%) as a white solid.

Optical rotation and b.p. data for benzoate **4.17** have been previously reported.[200]

m.p. = 79-80°C (hexanes).

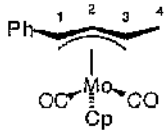
$[\alpha]_D$ = +1.46 (*c* 7.56, $CDCl_3$). Lit. $[\alpha]_D$ = +0.42 (*c* 8.16 $CHCl_3$).[200]

IR (KBr): ν = 3057 w, 3028 m, 2979 w, 2921 w, 1709 s, 1633 m, 1450 m, 1327 m, 1274 s, 1147 m, 1070 m, 974 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$ referenced to added TMS): δ = 8.10-8.06 (2H, m, Ph), 7.55-7.21 (8H, m, Ph), 6.69 (1H, d, *J* 16.0, H3), 6.30 (1H, dd, *J* 16.0, 6.6, H2), 5.79 (1H, ddq, *J* 6.5, 1.1, 6.5, H1), 1.54 (3H, d, *J* 6.5, C1-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (0, COPh), 136.5 (0, Ph), 133.0 (1, Ph, C2 or C3), 131.8 (1, Ph, C2 or C3), 131.1 (0, Ph), 129.7 (2C, 1, Ph, C2 or C3), 129.0 (1, Ph, C2 or C3), 128.7 (2C, 1, Ph, C2 or C3), 128.5 (2C, 1, Ph, C2 or C3), 128.0 (1, Ph, C2 or C3), 126.7 (2C, 1, Ph, C2 or C3), 71.7 (1, C1), 20.6 (3, C1-Me).

(1*R*,3*S*)-(η^5-Cyclopentadienyl)(1-phenyl-1,2,3-η-but-3-enyl)(dicarbonyl)molybdenum (4.6).



Procedure 1) - A solution of molybdenum hexacarbonyl (4.20 g, 15.9 mmol) in acetonitrile (140 mL) was brought to reflux under N_2 and refluxed for 3 h to give a clear yellow solution. A solution of benzoate **4.17** (3.35 g, 13.3 mmol) in MeCN (50 mL) was added *via* cannula and reflux was continued for 28 h before the solution was cooled to rt. A solution of cyclopentadienyllithium (freshly prepared by the addition of *n*-BuLi (8.9 mL of a 1.71M solution in hexanes) to freshly cracked cyclopentadiene (965 mg, 14.6 mmol) in THF (35 mL) at 0°C under N_2 followed by stirring of the light-yellow solution at 0°C for 15 min) was added *via* cannula and the red solution stirred at rt for 1 h before concentration *in vacuo*. Purification by column chromatography (Al_2O_3, degassed CH_2Cl_2, under N_2 atmosphere) gave the title compound (3.53 g, 10.1 mmol, 76%) as a red-orange crystalline solid which was dried *in vacuo* overnight before use.

Procedure 2)[16] - To a solution of $Mo(CO)_6$ (512 mg, 1.94 mmol) in THF (25 mL) under N_2 was added pyridine (0.31 mL, 3.88 mmol) and the solution brought to reflux. After refluxing for 12 h a solution of benzoate **4.17** (465 mg, 1.84 mmol) in THF (1 mL + 0.5 mL) was added dropwise *via* syringe to the red-orange solution, which was refluxed for a further 18 h before cooling to rt over 1 h. LiCp (7.1 mL of a 0.29M solution in THF (prepared immediately before use from freshly cracked Cp (328 mg, 5.0 mmol) and *n*-BuLi (2.27 ml of a 2.19M solution in hexanes) in THF (15 mL), rt, 15 min under N_2)) was added and the dark red-brown solution stirred at rt under N_2 for 1 h. The solution was transferred *via* syringe to a round-bottomed flask and concentrated *in vacuo* to a volume of approximately 10 mL, before purification by column chromatography (Al_2O_3, degassed hexanes-Et_2O, 2:1, under N_2) and concentration *in vacuo*. The title compound was obtained as a fine yellow crystalline solid (597 mg, 1.71 mmol, 88%).

Complex **4.6** was generally used without further purification, but for analytical purposes it could be purified further by recrystallisation from pentane to give fine yellow needles.

m.p. = 85-88°C. (Et_2O / Pentane).

$[\alpha]_D$ = +8.0 (*c* 0.67, $CHCl_3$)

IR (KBr): ν = 1917 s, 1839 s, 812 m, 757 m, 695 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$ referenced to added TMS): δ = 7.30-7.19 (3H, m, Ph), 7.12-7.08 (2H, m, Ph), 5.10 (5H, s, Cp), 4.88 (1H, t, *J* 9.6, H2), 2.35 (1H, d, *J* 10.0, H1), 1.86 (3H, d, *J* 6.0, H4), 1.78-1.73 (1H, m, H3).

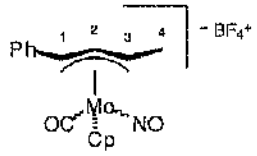
^{13}C NMR (100 MHz, $CDCl_3$): δ = 239.7 (0, CO), 239.6 (0, CO), 142.1 (0, Ph), 128.6 (2C, 1, Ph), 125.9 (1, Ph), 125.1 (2C, 1, Ph), 93.9 (5C, 1, Cp), 68.5 (1, C2), 58.8 (1, C3), 58.4 (1, C1), 21.2 (3, C4).

^{95}Mo NMR (13 MHz, THF): δ_{exo} = –1617, δ_{endo} = –1412. *exo* : *endo* = 13 : 1.[221]

LRMS (EI mode): *m/z* = 350.2 [$(M(^{98}Mo)^{+\bullet}$, 25 %], 322.2 [$(M(^{98}Mo)\text{-}CO)^+$, 20%], 292.2 (100). The expected Mo isotope patterns are present.

Found: C, 58.60; H, 4.69. Calc. for $C_{17}H_{16}O_2Mo$: C, 58.63; H, 4.63%.

(1*R*,3*S*)-(η^5-Cyclopentadienyl)(1-phenyl-1,2,3-η-but-3-enyl)(carbonyl)(nitrosyl) molybdenum tetrafluoroborate (4.1)



Cationic complex **4.1** was routinely prepared in a minimum volume (*ca* 2-3 mL / mmol) of freshly distilled MeCN at 0°C under N_2 by the addition of $NOBF_4$ (1.1 eq) and transferred directly *via* cannula to a solution of the nucleophile. However, for characterisation purposes the title compound was prepared on a 3.4 mmol scale and transferred to Et_2O (200 mL) at 0°C under N_2 to yield a light-brown solid after cooling to –60°C for 15 min. Cationic complex **4.1** (518 mg, 1.20 mmol, 36%) was isolated by filtration under an atmosphere of N_2.

IR (solution in CD_3CN): ν = 2080 s, 1720 s cm^{-1}

^1H (360 MHz, CD_3CN): Complex **4.1** was initially isolated as a mixture of 2 major isomers (presumably a pair of *endo* isomers),[42, 78] in the approximate ratio 1.2 : 1 which equilibrated to a mixture of 4 isomers upon standing in CD_3CN for 24 h, in a ratio of approximately 2.3 : 2 : 1 : 1.2, as estimated by the integrations of Cp singlets at 5.69, 6.11, 6.22 and 6.02 ppm respectively.

^{1}H NMR data for the initial (*endo*) isomers: δ = 7.54-7.35 (10H, m, Ph), 6.11 (5H, s, Cp), 5.69 (5H, s, Cp), 6.23-5.93 (2H, m, H2), 5.28 (1H, d, *J* 11.7, H1), 5.20 (1H, d, *J* 13.4, H1), 3.95 (1H, dq, *J* 12.9, 6.2, H3), 3.76 (1H, d, dq, *J* 12.3, 6.2, H3), 2.47 (3H, d, *J* 5.9, H4), 2.30 (3H, d, *J* 6.3, H4); partial data for the *exo*-isomers: δ = 6.22 (5H, s, Cp), 6.02 (5H, s, Cp), 4.77 (1H, d, *J* 13.8, H1), 4.51-4.44 (2H, m, H3), 4.40 (1H, d, *J* 13.0, H1), 2.42 (3H, d, *J* 6.4, H4). Signals for H2 and the second H4 doublet obscured by major isomer peaks at 6.23-5.93 ppm and 2.30 ppm respectively.

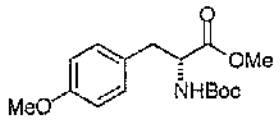
^{13}C NMR (100 MHz, CD_3CN, equilibrium mixture of 4 *endo* and *exo* isomers): δ = 214.9 (0), 213.9 (0), 211.0 (0), 209.5 (0), 136.8 (0), 135.8 (0), 135.4 (0), 134.0 (0), 131.4 (2C, 1), 130.7 (2C, 1), 130.0 (2C, 1), 129.8 (2C, 1), 129.7 (2C, 1), 129.5 (2C, 1), 129.4 (2C, 1), 128.0 (2C, 1), 127.7 (2C, 1), 127.6 (2C, 1), 106.7 (1), 106.5 (1), 104.2 (1), 103.3 (5C, 1), 102.5 (5C, 1), 102.4 (5C, 1), 101.8 (5C, 1), 101.0 (1), 94.6 (1), 93.4 (1), 92.3 (1), 88.0 (1), 83.3 (1), 80.6 (1), 76.8 (1), 74.6 (1), 21.1 (3), 19.6 (3), 18.9 (3), 18.2 (3).

^{95}Mo NMR (13 MHz, MeCN): δ = –1293, –1339, –1383 ppm, in the approximate ratio 1 : 2.5 : 4, with approximate line widths 210 Hz, 206 Hz, 290 Hz respectively.[221]

LRMS (FAB mode, nitrobenzyl alcohol matrix): *m/z* = 352.1 [M(^{98}Mo)$^{+\bullet}$, 98%], 324.1 [(M(^{98}Mo)–CO)$^+$, 100%], 289.1 (30). The expected Mo isotope patterns are present.

HRMS (FAB mode, nitrobenzyl alcohol matrix): found [$M^{+\bullet}$], 352.0235. $C_{16}H_{16}O_2N^{98}Mo$ requires 352.0238. Found [$M^{+\bullet}$], 350.0246. $C_{16}H_{16}O_2N^{96}Mo$ requires 350.0235. The expected Mo isotope patterns are present.

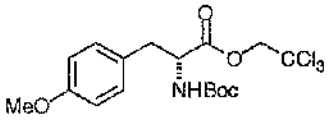
(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propionic acid methyl ester (4.92).



Ester **4.92** was prepared as a clear oil in 53% yield over two steps from D-Tyrosine on a scale of 6.0 mmol according to literature procedures.[204, 205] Spectroscopic data were in accordance with literature data.[245]

$[\alpha]_D$ = –4.7 (*c* 2.4, MeOH) Lit. $[\alpha]_D$ (enantiomer) = +5.9 (*c* 2.5, MeOH).[204]

(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propionic acid 2,2,2-trichloroethyl ester (4.94).

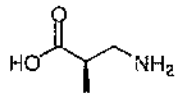


Ester **4.94** was prepared in 65% yield over 2 steps from ester **4.92** on a scale of 3.08 mmol according to literature procedures.[128, 204] The title compound was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 4) and recrystallisation from EtOAc. Spectroscopic data were in accordance with literature data.[128]

m.p. = 111-112°C (EtOAc) Lit. m.p. = 115-116°C.[128]

$[\alpha]_D$ = –8.60 (*c* 6.3, $CHCl_3$) Lit. $[\alpha]_D$ = –12.0 (*c* 12.0, $CHCl_3$).[128]

(2*R*)-3-Amino-2-methylpropionic acid (4.102).

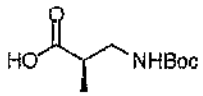


Acid **4.102** was prepared in 63% yield over 3 steps on a 9.28 mmol scale by the method of Lavallée and co-workers.[142] Spectroscopic data were in accordance with literature data.[142]

m.p. = 184-185°C (MeOH / EtOAc). Lit. m.p. = 179-181°C.[142] (MeOH / EtOAc)

$[\alpha]_D$ = –14.2 (*c* 3.4, H_2O) Lit. $[\alpha]_D$ = –14.7 (*c* 2.6, H_2O).[142]

(2*R*)-3-*tert*-Butoxycarbonylamino-2-methylpropionic acid (4.103).

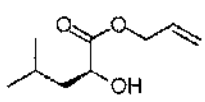


A solution of amino acid **4.102** (601 mg, 5.83 mmol), di-*tert*-butyl dicarbonate (1.46 g, 6.70 mmol) and triethylamine (1.22 mL, 8.75 mmol) in 1,4-dioxane (10 mL) and H_2O (10 mL) was stirred at rt for 18 h. The mixture was concentrated *in vacuo* and diluted with H_2O (50 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase washed with EtOAc (3 x 25 mL). The aqueous phase was acidified to pH 1 with 1M HCl and re-extracted with EtOAc (3 x 25 mL). The organic phases were washed with brine (25 mL), dried, and concentrated *in vacuo* to give the title compound (619 mg, 3.04 mmol) as a clear oil which slowly solidified. A further batch of acid **4.103** (397 mg, 1.95 mmol) was isolated from the first organic phase after solvent removal *in vacuo* to give a total crude mass of the title compound of 1.02 g (5.00 mmol, 86%) which was used without further purification. A sample was purified for analytical purposes by recrystallisation from Et_2O. Spectroscopic data were in accordance with literature data.[128]

m.p. = 67-68°C. (Et_2O). Lit. m.p. = 69.5-70.5°C. (Et_2O)[128]

$[\alpha]_D$ = –20.4 (*c* 1.39, MeOH). Lit. $[\alpha]_D$ –18.4 (*c* 2.0, MeOH).[128]

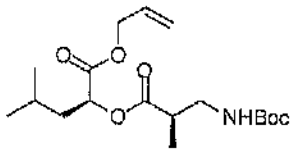
(2*S*)-2-Hydroxy-4-methylpentanoic acid allyl ester (4.98).



The title compound was prepared as a pale yellow oil in 62% yield on a scale of 8.04 mmol by the procedure of Moore, Tius and co-workers.[128] Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = –8.7 (*c* 0.91, $CHCl_3$) Lit. $[\alpha]_D$ = –8.4 (*c* 1.1, $CHCl_3$).[128]

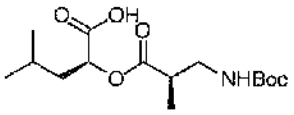
(2*S*)-2-[(3*R*)-3-*tert*-Butoxycarbonylamino-2-methylpropionyloxy]-4-methylpropionic acid allyl ester (4.104).



Ester **4.104** was prepared as a clear oil in 87% yield on a scale of 2.36 mmol by the method of Moore, Tius and co-workers.[128] Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = –43.8 (*c* 3.47, $CHCl_3$) Lit. $[\alpha]_D$ = –51.3 (*c* 3.41, $CHCl_3$).[128]

(2*S*)-2-[(3*R*)-3-*tert*-Butoxycarbonylamino-2-methylpropionyloxy]-4-methylpropionic acid (4.105)

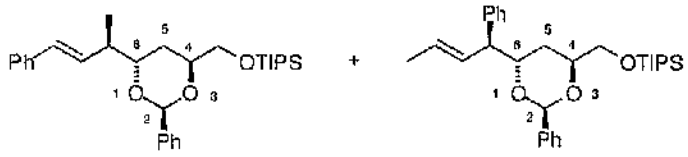


The title compound was prepared as a clear oil which solidified upon standing in 80% yield on a scale of 1.87 mmol by the method of Moore, Tius and co-workers.[128] Recrystallisation from Et_2O gave clear needles. Spectroscopic data were in accordance with literature data.[128]

m.p. = 73-74.5°C (Et_2O).

$[\alpha]_D$ = –51.9 (*c* 3.77, $CHCl_3$) Lit. $[\alpha]_D$ = –47.9 (*c* 4.70, $CHCl_3$).[128]

Triisopropyl[(2*S*,4*S*,6*S*)-6-[(1*R*,2*E*)-1-methyl-3-phenylallyl]-2-phenyl-[1,3]dioxan-4-ylmethoxy]silane (4.83) and **Triisopropyl-[(2*S*,4*S*,6*S*)-2-phenyl-6-[(1*S*)-1-phenylbut-2-enyl]-[1,3]dioxan-4-ylmethoxy]silane (4.84).**



n-BuLi (5.4 mL of a 1.71M solution in hexanes) was added dropwise to a solution of stannane **4.80** (5.40 g, 8.45 mmol) in THF (150 mL) at –80°C under N_2. After the light-yellow solution was stirred at –80°C for 1 h, a solution of CuBr•DMS (2.08 g, 10.14 mmol) in di*iso*-propylsulfide (7 mL) and THF (8.5 mL) was added *via* cannula, maintaining the internal solution temperature below –80°C. The orange-brown solution was stirred at –80°C for 1 h under N_2 before the addition of cationic complex **4.1** (freshly prepared: nitrosonium tetrafluoroborate (1.28 g, 11.0 mmol) was added to a solution of neutral complex **4.6** (3.53 g, 10.1 mmol, prepared by procedure 1 above) in MeCN (20 mL) at 0°C and the yellow solution stirred at 0°C under N_2 for 15 min) *via* cannula. The light-brown solution was stirred at –80°C for 1 h before the addition of aqueous

NH_4Cl (40 mL) and aqueous NH_3 (10 mL) and removal of the cooling bath. After reaching room temperature, the mixture was filtered through celite, washing thoroughly with Et_2O (50 mL). The phases were separated, and the aqueous phase extracted with Et_2O (2 x 50 mL), and the combined organic phases washed with brine (100 mL), dried, filtered and concentrated *in vacuo*. The crude material was dissolved in $CHCl_3$ (250 mL) and stirred at rt for 17 h with a stream of O_2 bubbling through the brown solution. Removal of solvent *in vacuo* yielded a dark brown oil which was purified by column chromatography (SiO_2, Et_2O : hexanes = 2 : 98) to give a mixture of the title compounds (2.90 g, 6.03 mmol, 71% from stannane **4.80**) as a pale yellow oil. ^1H NMR revealed a ratio of **4.83** : **4.84** of approximately 1.2 : 1 (in favour of the desired isomer), estimated by integration of the vinylic proton peaks at 6.51 and 6.28 ppm (**4.83**) and 5.64-5.50 ppm (**4.84**).

$[\alpha]_D$ = +23.3 (*c* 1.50, $CHCl_3$) (1.2:1 mixture of **4.83** : **4.84**).

IR (film) ν = 2942 s, 2866 s, 1462 m, 1382 w, 1117 s, 1069 m, 1028 m, 1014 m, 995 m, 882 m, 795 w, 748 m, 696 s, 660 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.17 (19H, m, Ph), 7.05-7.04 (1H, m, Ph), 6.51 (1H, d, *J* 15.9, PhC<u>H</u>=CHR (**4.83**)), 6.28 (1H, dd, *J* 15.9, 8.4, PhCH=C<u>H</u>R (**4.83**)), 5.85 (1H, s, C<u>H</u>Ph, (**4.83**)), 5.76 (1H, s, C<u>H</u>Ph (**4.84**)), 5.64-5.50 (2H, m, MeC<u>H</u>=C<u>H</u>R (**4.84**)), 4.44 (1H, dd, *J* 11.1, 5.0 (**4.84**)), 4.27-3.90 (6H, m), 3.72 (2H, ddd, *J* 10.0, 6.6, 1.4 (**4.83**)), 3.19 (1H, q, *J* 8.3), 2.11 (1H, ddd, *J* 13.5, 2.5, 1.5 (**4.84**)), 2.02-1.90 (3H, m), 1.66 (3H, dd, *J* 5.6, 0.8 (**4.84**)), 1.13 (3H, d, *J* 6.4, Me (**4.83**)), 1.12-1.00 (42H, m, $Si(CHMe_2)_3$).

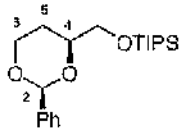
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (0, Ph), 139.1 (0, Ph), 138.9 (0, Ph), 137.8 (0, Ph), 133.5 (1, PhCH=<u>C</u>HR (**4.83**)), 132.2 (1, CH=CH, (**4.84**)), 130.1 (Ph<u>C</u>H=CHR (**4.83**)), 128.8 (2C, 1, Ph), 128.7 (2C, 1, Ph), 128.6 (1, Ph or CH=CH, (**4.84**)), 128.4 (1, Ph or CH=CH, (**4.84**)), 128.3 (2C, 1, Ph), 128.2 (2C, 1, Ph), 128.1 (2C, 1, Ph), 127.9 (1, Ph or CH=CH, (**4.84**)), 127.2 (1, Ph or CH=CH, (**4.84**)), 126.6 (1, Ph or CH=CH, (**4.84**)), 126.3 (2C, 1, Ph), 126.2 (2C, 1, Ph), 125.9 (2C, 1, Ph), 94.8 (1, <u>C</u>HPh (**4.83**)), 94.3 (1, <u>C</u>HPh, (**4.84**)), 76.6 (1), 74.8 (1), 73.3 (1), 73.1 (1), 66.8 (2C, 2), 50.0 (1), 37.6 (1, PhCH=CH<u>C</u>HMeR, (**4.83**)), 28.9 (2), 28.7 (2), 18.2 (14C, 3, Me + $Si(CH\underline{Me}_2)_3$), **12.2** (6C, 1, $Si(\underline{C}HMe_2)_3$).

LRMS (CI mode, isobutane): *m/z* = 481 [$(M+H)^+$, 17 %], 393 (21), 375 (58), 351 (100), 307 (25), 245 (44).

Found: C, 74.86; H, 9.41. Calc. for $C_{30}H_{44}O_3Si$: C, 74.95; H, 9.22.

Olefins **4.83** and **4.84** were also prepared in 56% yield (**4.83** : **4.84** = 3 : 1) on a scale of 0.56 mmol of stannane **4.80** by an analogous procedure to that described above using neutral complex **4.6** prepared by procedure 2 above. The mixture of the title compounds was contaminated by oxane **4.115**, identified by independent preparation by an analogous procedure to that detailed for alcohols **4.73** and **4.74** above, using aqueous NH_4Cl solution in place of benzaldehyde as the electrophile.

Data for **(2*S*,4*S*)-Triisopropyl-(2-phenyl-[1,3]dioxan-4-ylmethoxy)silane (4.115):**



$[\alpha]_D$ = –1.96 (*c* 1.02, $CHCl_3$).

IR (film): ν = 2943 s, 2863 s, 1465 m, 1385 w, 1236 w, 1147 m, 1109 s, 1029 m, 881 m, 758 w, 694 w cm^{-1}.

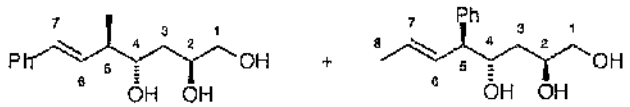
^1H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.51 (2H, m, Ph), 7.40-7.32 (3H, m, Ph), 5.56 (1H, s, H2), 4.33 (1H, dd, *J* 11.1, 4.5, H6), 4.04-3.97 (2H, m, H4, H6'), 3.94 (1H, dd, *J* 9.7, 5.2, CH_2OTIPS), 3.71 (1H, dd, *J* 9.7, 6.7, CH_2OTIPS), 1.86 (1H, ddt, *J* 11.8, 5.3, 12.1, H5), 1.74 (1H, br dd, *J* 13.3, 1.2, H5'), 1.18-1.11 (3H, m, $Si(C\underline{H}(Me)_2)_3$, 1.09 (18H, d, *J* 5.2, $Si(CH(\underline{Me})_2)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8 (0, Ph), 128.9 (1, Ph), 128.3 (2C, 1, Ph), 126.3 (2C, 1, Ph), 101.4 (1, C2), 77.9 (1, C4), 67.2 (2, C6), 66.6 (2, CH_2OTIPS), 28.8 (2, C5), 18.1 (6C, 3, $Si(CH(\underline{Me})_2)_3$), 12.1 (3C, 1, $Si(\underline{C}H(Me)_2)_3$).

LRMS (CI mode, isobutane): *m/z* = 351.3 [$(M+H)^+$, 85 %], 307.2 (53), 245.3 (100).

Found: C, 68.49; H, 9.65. Calc. for $C_{20}H_{34}O_3Si$: C, 68.32; H, 9.78%.

(2*R*,4*S*,5*R*,6*E*)-5-Methyl-7-phenyl-hept-6-ene-1,2,4-triol (4.85) and **(2*R*,4*S*,5*S*,6*E*)-5-Phenyl-oct-6-ene-1,2,4-triol (4.86).**



4.85 4.86

To a solution of oxanes **4.83** and **4.84** (**4.83** : **4.84** = 1.2:1, 2.77 g, 5.76 mmol) in MeOH (100 mL) at rt was added *p*-toluenesulfonic acid monohydrate (164 mg, 0.86 mmol). The pale yellow solution was stirred at rt for 1 d before solvent removal *in vacuo*. Purification by column chromatography (SiO_2, EtOAc) yielded a mixture of the title compounds (861 mg, 3.64 mmol, 63%) as a pale yellow oil. Careful repetitive column chromatography allowed the separation of isomers. Triol **4.86** solidified upon standing and was recrystallised from Et_2O to give fine needles.

Data for isomer **4.85**:

$[\alpha]_D$ = +103.6 (*c* 1.10, MeOH).

IR (film): ν = 3465 br s, 2935 m, 2873 m, 1452 m, 1388 m, 1365 m, 1329 m, 1082 m, 992 m, 972 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.23 (5H, m, Ph), 6.49 (1H, d, *J* 16.1, H7), 6.12 (1H, dd, *J* 16.1, 8.7, H6), 4.05-3.99 (1H, m, H2), 3.80-3.76 (1H, m, H4), 3.67 (1H, dd, *J* 11.1, 3.6, H1), 3.54 (1H, dd, *J* 11.1, 7.0, H1'), 2.41 (1H, br sextet, *J* 7.3, H5), 1.75 (1H, ddd, *J* 14.4, 8.7, 2.5, H3), 1.60 (1H, ddd, *J* 14.4, 9.3, 3.5, H3'), 1.12 (3H, d, *J* 6.8, C5-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (0, Ph), 132.3 (1, C6 or C7), 131.6 (1, C6 or C7), 128.8 (2C, 1, Ph), 127.7 (1, Ph), 126.4 (2C, 1, Ph), 72.3 (1, C2), 69.6 (1, C4), 66.9 (2, C1), 44.2 (1, C5), 36.4 (2, C3), 16.9 (3, C5-Me).

LRMS (CI mode, NH_3): *m/z* = 254.2 [$(M+NH_4)^+$, 100 %], 237.1 (28), 219.1 (22).

Found: C, 71.15; H, 8.70. Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.

Data for isomer **4.86**:

m.p. = 110-111°C (Et_2O).

$[\alpha]_D$ = –69.1 (*c* 1.65, MeOH).

IR (KBr):*v* = 3397 br s, 2959 w, 2940 w, 2917 w, 2890 w, 1112 m, 1082 m, 1070 s, 1025 s, 963 m, 702 m cm^{-1}.

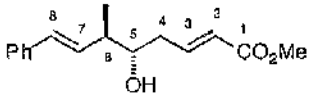
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.30 (2H, m, Ph), 7.26-7.17 (3H, m, Ph), 5.65-5.53 (2H, m, H6 and H7), 4.13 (1H, dt, *J* 2.5, 8.8, H4), 4.07-4.01 (1H, m, H2), 3.65 (1H, dd, *J* 11.1, 3.5, H1), 3.53 (1H, dd, *J* 11.1, 7.0, H1'), 3.30 (1H, t, *J* 8.2, H5), 2.94 (1H, br s, OH), 2.18 (1H, br s, OH), 1.88 (1H, ddd, *J* 14.5, 8.7, 2.6, H3), 1.68 (3H, d, *J* 5.0, H8), 1.63 (1H, br s, OH), 1.55 (1H, ddd, *J* 14.5, 9.1, 3.5, H3').

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4 (0, Ph), 130.8 (1, Ph, C6 or C7), 129.2 (2C, 1, Ph), 128.5 (2C, 1, Ph), 128.4 (1, Ph, C6 or C7), 127.2 (1, Ph, C6 or C7), 72.1 (1, C4), 69.7 (1, C2), 67.1 (2, C1), 56.7 (1, C5), 36.8 (2, C3), 18.3 (3, C8).

LRMS (CI mode, NH_3): *m/z* = 254.2 [$(M+NH_4)^+$, 100 %], 236.2 (30), 219.2 (8), 116.1 (12).

Found: C, 71.27; H, 8.73. Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53.

(2*E*,5*S*,6*R*,7*E*)-5-Hydroxy-6-methyl-8-phenylocta-2,7-dienoic acid methyl ester (4.88).



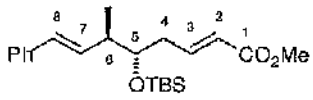
To a solution of triol **4.85** (125 mg, 0.53 mmol) in MeOH (15 mL) and H_2O (5 mL) at rt was added sodium periodate (170 mg, 0.79 mmol). The clear solution was stirred at rt for 1.5 h, after which time a white precipitate was present. Methanol was removed *in vacuo* and H_2O (30 mL) and CH_2Cl_2 (20 mL) were added. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried, filtered and concentrated *in vacuo* to afford crude aldehyde **4.87** as a clear oil (103

mg, 0.50 mmol) which was azeotroped with PhMe (2 x 20 mL) and used without further purification after further drying *in vacuo* for 1.5 h.

To a solution of aldehyde **4.87** in THF (17 mL) and trimethylphosphonoacetate (0.17 mL, 1.17 mmol) at –78°C under N_2 was added *N,N,N',N'*-tetramethylguanidine (0.15 mL, 1.17 mmol) in THF (5 mL) dropwise over 2 min. The clear solution was allowed to warm to rt with stirring over 16 h and stirred at rt for 42 h before the addition of H_2O (20 mL) and Et_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried, filtered and concentrated *in vacuo* to afford a pale-yellow oil. Purification by column chromatography (SiO_2, Et_2O : Cyclohexane = 2 : 8 → 4 : 6) yielded the title compound (114 mg, 0.44 mmol, 83%) as a clear colourless oil. Spectroscopic data were in accordance with literature data.[148]

$[\alpha]_D$ = +71.7 (*c* 1.20, $CHCl_3$). Lit. $[\alpha]_D$ = +55.2 (*c* 0.31, $CHCl_3$).[148]

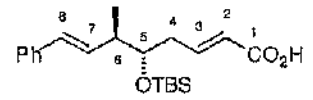
(2*E*,5*S*,6*R*,7*E*)-5-(*tert*-Butyldimethylsilanyloxy)-6-methyl-8-phenylocta-2,7-dienoic acid methyl ester (4.89).



To a solution of alcohol **4.88** (85 mg, 0.33 mmol) in DMF (15 mL) at rt under N_2 was added *tert*-butyldimethylsilyl chloride (198 mg, 1.32 mmol) and imidazole (98 mg, 1.32 mmol). The clear solution was stirred at rt under N_2 for 5 d before the addition of Et_2O (30 mL) and 1M HCl (40 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : Cyclohexane = 2 : 8) yielded the title compound (104 mg, 0.28 mmol, 85%) as a clear colourless oil. Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = +64.0 (*c* 0.50, $CHCl_3$). Lit. $[\alpha]_D$ = +68.2 (*c* 1.50, $CHCl_3$).[128]

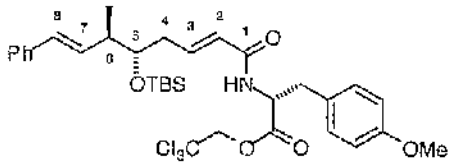
(2*E*,5*S*,6*R*,7*E*)-5-(*tert*-Butyldimethylsilanyloxy)-6-methyl-8-phenylocta-2,7-dienoic acid (4.3).



To a solution of methyl ester **4.89** (236 mg, 0.63 mmol) in acetone (10 mL) at rt was added 1M LiOH (8 mL). The cloudy light-yellow solution was stirred at rt for 6 h before the addition of Et_2O (20 mL). After washing with 1M HCl (2 x 20 mL) and brine (20 mL) the combined aqueous phases were extracted with Et_2O (2 x 20 mL). The combined organic phases were dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, EtOAc : Cyclohexane = 3 : 7 + 1% AcOH) yielded the title compound (219 mg, 0.61 mmol, 97%) as a clear colourless oil. Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = +90.8 (*c* 1.13, $CHCl_3$). Lit. $[\alpha]_D$ = +87.0 (*c* 1.40, $CHCl_3$).[128]

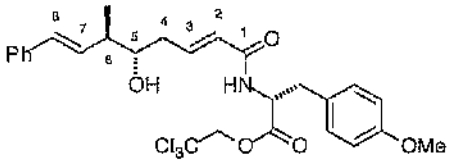
(2*R*)-2-[(2*E*,5*S*,6*R*,7*E*)-5-(*tert*-Butyldimethylsilanyloxy)-6-methyl-8-phenyl-octa-2,7-dienoylamino]-3-(4-methoxyphenyl)-propionic acid 2,2,2-trichloroethyl ester (4.106).



Amide **4.106** was prepared according to the method of Moore, Tius and co-workers[128] on a scale of 0.6 mmol of acid **4.3** and 0.6 mmol of TFA salt **4.96**. Salt **4.96** had been freshly prepared from ester **4.94** (263 mg, 0.6 mmol) by dissolution in neat trifluoroacetic acid (5 mL) at 0°C, followed by standing at rt for 1.5 h before concentration *in vacuo*, addition of PhMe (5 mL) and concentration *in vacuo*. Purification by column chromatography (SiO_2, Et_2O : Cyclohexane = 1 : 9 → 3 : 7) yielded the title compound (297 mg, 0.44 mmol, 79%) as a viscous clear oil. Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = +17.1 (*c* 2.28, $CHCl_3$). Lit. $[\alpha]_D$ = +18.2 (*c* 2.00, $CHCl_3$).[128]

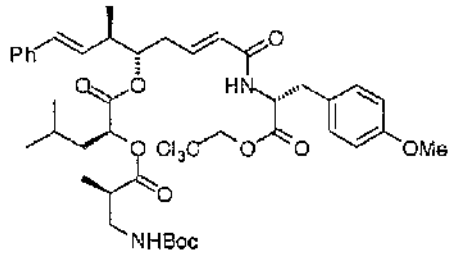
(2*R*)-2-[(2*E*,5*S*,6*R*,7*E*)-5-Hydroxy-6-methyl-8-phenyl-octa-2,7-dienoylamino]-3-(4-methoxyphenyl)-propionic acid 2,2,2-trichloroethyl ester (4.107).



To a solution of amide **4.106** (189 mg, 0.28 mmol) in THF (20 mL) at 0°C under N_2 in a polypropylene reaction vessel was added pyridinium poly(hydrogen fluoride) (5 mL) and the clear solution stirred at 0°C for 1 h then at rt for 3 h. The solution was diluted with Et_2O (20 mL), washed with H_2O (2 x 30 mL), aqueous $NaHCO_3$ (2 x 30 mL) and brine (2 x 20 mL), dried, filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 1 → 100 : 0) yielded the title compound (122 mg, 0.22 mmol, 78%) as a colourless clear oil. Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = −1.14 (*c* 1.75, $CHCl_3$). Lit. $[\alpha]_D$ = −1.50 (*c* 1.70, $CHCl_3$).[128]

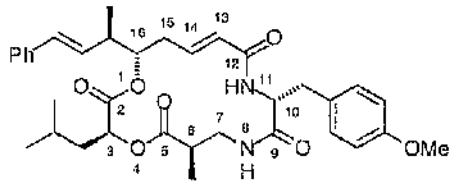
(2*S*)-2-[(2*R*)-3-*tert*-Butoxycarbonylamino-2-methylpropionyloxy]-4-methylpentanoic acid (1*S*,2*R*,3*E*)-1-{3-[(2*R*)-2-(4-methoxyphenyl)-1-(2,2,2-trichloroethoxycarbonyl)-ethylcarbamoyl]-allyl}-2-methyl-4-phenylbut-3-enyl ester (4.108).



Ester **4.108** was prepared according to the method of Moore, Tius and co-workers [128] on a scale of 0.15 mmol of alcohol **4.107** and 0.23 mmol of acid **4.105**. Purification by column chromatography (SiO_2, Et_2O : hexanes = 6 : 4) yielded the title compound (105 mg, 0.12 mmol, 82%) as a colourless clear oil. Spectroscopic data were in accordance with literature data.[128]

$[\alpha]_D$ = –9.8 (*c* 0.53, $CHCl_3$). Lit. $[\alpha]_D$ = –10.5 (*c* 0.56, $CHCl_3$).[128]

(3*S*,6*R*,10*R*,13*E*,16*S*)-3-Isobutyl-10-(4-methoxybenzyl)-6-methyl-16-[(1*R*,2*E*)-1-methyl-3-phenylallyl]-1,4-dioxa-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetraone (4.110) - Cryptophycin 4.



Ester **4.108** (29.8 mg, 0.04 mmol) was dissolved in trifluoroacetic acid (2 mL) at 0°C and stirred at rt for 25 min before concentration *in vacuo*. PhMe (5 mL) was added and the clear solution concentrated *in vacuo* before dissolution in Et_2O (5 mL) and washing with 0.5M NaOH (2 x 5 mL). The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic phases washed with brine (5 mL), dried, filtered and concentrated *in vacuo*. The crude amine was then dissolved in toluene (1.75 mL) and 2-hydroxypyridine (6.6 mg, 0.070 mmol) added in one portion. The clear solution was stirred at rt under N_2 for 44 h before being diluted with Et_2O (5 mL), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, EtOAc : hexanes = 1 : 1) followed by preparative TLC (SiO_2, EtOAc : hexanes = 6 : 4) gave Cryptophycin 4 (**4.110**) (10.2 mg, 0.017 mmol, 48% over 2 steps) as a clear semi-solid, which was further purified by crystallisation from EtOAc : hexanes (1:1) to give clear fine needles. (m.p. = 176-178°C) A minor component was also isolated by preparative TLC (0.7 mg, white amorphous solid), which was established to be dimer **4.111** on the basis of mass spectroscopic data.

$[\alpha]_D$ = +51.5 (*c* 0.20, $CHCl_3$) Lit. $[\alpha]_D$ = + 22.8 (*c* 0.2, $CHCl_3$).[128]

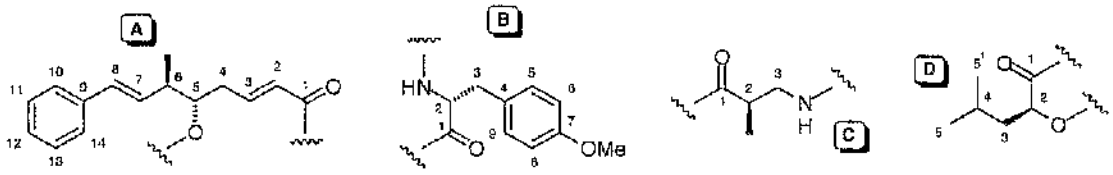
IR ($CHCl_3$): ν = 3403 w, 3273 w, 3003 s, 2956 s, 1743 s, 1727 s, 1676 s, 1519 s, 1249 s, 1182 s, 1123 m, 970 m cm^{-1} - in accordance with literature data.[127]

IR (KBr): ν = 3425 m, 3315 m, 2960 w, 2934 w, 1744 s, 1667 s, 1618 m, 1514 s, 1463 w, 1248 m, 1194 m, 1177 m, 1126 w, 1068 w, 1032 w, 973 w cm^{-1}.

LRMS (EI^+ mode): *m/z* = 604.4 [$M^{+\bullet}$, 7%], 378.2 (100), 227.2 (42), 161.1 (100), 121.1 (55), 44.0 (48).

HRMS (EI^+ mode): found [$M^{+\bullet}$], 604.3148. $C_{29}H_{42}O_5N$ requires 604.3149.

NMR data comparison for **4.110**: (Numbering system as specified by Moore *et al.*[127]).



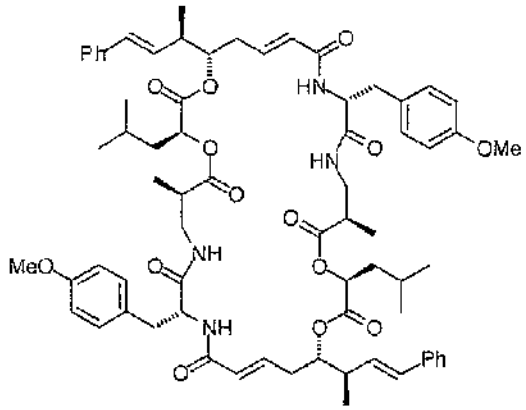
^{1}H NMR ($CDCl_3$, 400 MHz):

	Literature data[128]			Experimental data		
Proton	δ		***J* (Hz)**	δ		***J* (Hz)**
A Ph	7.35-7.20	5H, m	-	7.35-7.21	5H, m	-
B H5, H9	7.12	2H, d	8.8	7.12	2H, d	8.8
C NH	7.02	1H, dd	5.8, 4.3	7.05	1H, t	6.0
B H6, H8	6.81	2H, d	8.8	6.82	2H, d	8.4
A H3	6.71	1H, ddd	15.3, 10.3, 5.0	6.72	1H, ddd	15.2, 10.2, 5.0
A H8	6.41	1H, d	15.8	6.41	1H, d	15.6
A H7	6.01	1H, dd	15.8, 8.9	6.02	1H, dd	16.0, 8.8
A H2	5.74	1H, dd	15.3, 1.2	5.75	1H, d	15.2
B NH	5.62	1H, d	8.3	5.65	1H, d	8.0
A H5	5.02	1H, ddd	11.0, 6.3, 1.8	5.03	1H, ddd	11.1, 6.3, 1.7
D H2	4.84	1H, dd	9.9, 3.6	4.85	1H, dd	9.8, 3.4
B H2	4.80	1H, ddd	8.3, 7.0, 5.5	4.83-4.78	1H, m	-
B OMe	3.78	3H, s	-	3.79	3H, s	-
C H3	3.41	1H, ddd	13.5, 4.3, 4.3	3.41-3.38	2H, m	-
C H3'	3.36	1H, ddd	13.5, 7.5, 5.8			
B H3	3.14	1H, dd	14.4, 5.5	3.15	1H, dd	14.4, 5.2
B H3'	3.08	1H, dd	14.4, 7.0	3.08	1H, dd	14.4, 7.2
C H2	2.69	1H, m	-	2.73-2.66	1H, m	-
A H6, H4'	2.54	2H, m	-	2.59-2.51	2H, m	-
A H4	2.36	1H, ddd	14.5, 11.0, 10.3	2.38	1H, ddd	14.4, 10.8, 10.6
D H3, H4	1.65	2H, m	-	1.70-1.59	2H, m	-
D H3'	1.35	1H, m	-	1.38-1.32	1H, m	
C 2-Me	1.22	3H, d	7.5	1.23	3H, d	7.2
A 6-Me	1.13	3H, d	6.5	1.14	3H, d	6.8
D 5-Me	0.76	3H, d	6.5	0.77	3H, d	6.8
D 4-Me	0.72	3H, d	6.5	0.73	3H, d	6.4

^{13}C ($CDCl_3$, 100 MHz):

	Literature data[128]		Experimental data	
Carbon	δ	**Multiplicity**	δ	**Multiplicity**
C C1	175.9	-	176.0	0
B C1	171.2	-	171.2	0
D C1	170.8	-	170.8	0
A C1	165.3	-	165.3	0
B C7	158.6	-	158.5	0
A C3	141.5	-	141.6	1
A C9	136.7	-	136.7	0
A C8	131.8	-	131.8	1
B C5, C9	130.2	-	130.2	1
A C7	130.1	-	130.1	1
A C11, C13	128.6	-	128.6	1
B C4	128.5	-	128.4	0
A C12	127.6	-	127.5	1
A C10, C14	126.2	-	126.1	1
A C2	125.1	-	125.0	1
B C6, C8	114.1	-	114.1	1
A C5	77.1	-	77.2	1
D C2	71.6	-	71.6	1
B OMe	55.2	-	55.2	3
B C2	53.8	-	53.9	1
A C6	42.3	-	42.3	1
C C3	40.8	-	40.7	2
D C3	39.5	-	39.5	2
C C2	38.1	-	38.1	1
A C4	36.5	-	36.5	2
B C3	35.3	-	35.3	2
D C4	24.5	-	24.4	1
D C5	22.7	-	22.7	3
D 4-Me	21.1	-	21.2	3
A 6-Me	17.3	-	17.3	3
C 2-Me	14.2	-	14.2	3

(3*S*,6*R*,10*R*,13*E*,16*S*,19*S*,22*R*,26*R*,29*E*,32*S*)-3,19-Diisobutyl-10,26-bis-(4-methoxybenzyl)-6,22-dimethyl-16,32-bis-[(1*R*,2*E*)-1-methyl-3-phenylallyl]-1,4,17,20-tetraoxa-8,11,24,27-tetraazacyclotriaconta-13,29-dien-2,5,9,12,18,21,25,28-octaone (4.111):



$[\alpha]_D$ = +57.1 (*c* 0.04, $CHCl_3$).

IR ($CHCl_3$) ν = 3297 m, 2955 s, 2925 s, 2853 m, 1746 s, 1632 s, 1553 m, 1514 s, 1458 m, 1247 m, 1179 m, 1110 m cm^{-1}.

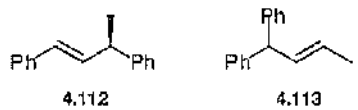
^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (2H, br s), 7.35-7.20 (10H, m), 7.10 (4H, d, *J* 8.6), 6.76 (4H, d, *J* 8.6), 6.77-6.70 (2H, m), 6.53 (2H, br s), 6.41 (2H, d, *J* 15.8), 6.02 (2H, dd, *J* 15.8, 8.7), 5.85 (2H, d, *J* 15.8), 5.18 (2H, br q, *J* 7.4), 5.08 (2H, ddd, *J* 9.9, 6.5, 3.3), 4.78 (2H, dd, *J* 9.9, 3.7), 3.76 (6H, s), 3.49-3.42 (4H, m), 3.11 (2H, dd, *J* 13.9, 5.7), 2.91 (2H, dd, *J* 13.9, 7.3), 2.67 (2H, br q, *J* 5.0), 2.56 (2H, dd, *J* 15.0, 6.6), 2.52-2.34 (6H, m), 1.44 (2H, ddd, *J* 14.2, 8.8, 3.7), 1.12 (6H, d, *J* 7.3), 1.08 (6H, d, *J* 6.8), 0.94-0.87 (2H, m), 0.78 (6H, d, *J* 6.5), 0.73 (6H, d, *J* 6.6).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 174.7 (2C), 172.3 (2C), 171.2 (2C), 165.5 (2C), 158.4 (2C), 139.4 (2C), 137.1 (2C), 131.8 (2C), 130.7 (4C), 130.5 (2C), 129.3 (2C), 128.8 (4C), 127.7 (2C), 126.4 (4C), 113.9 (4C), 76.3 (2C), 71.7 (2C), 55.3 (2C), 54.1 (2C), 42.3 (2C), 41.1 (2C), 39.7 (2C), 39.6 (2C), 38.3 (2C), 35.2 (2C), 29.9 (2C), 24.8 (2C), 23.1 (2C), 21.7 (2C), 17.1 (2C), 14.1 (2C).

LRMS (+ve ion FAB): *m/z* = 1232 [$(M+Na)^+$, 31%], 1046 (12), 844 (100), 804 (25), 801.7 (22), 745 (22), 743 (21), 705 (11).

HRMS (+ve ion FAB): found [$(M+Na)^+$], 1231.6187. $C_{70}H_{88}O_{14}N_4Na$ requires 1231.6195.

(1*R*,2*E*)-1,3-Diphenyl-1-butene (4.112) and (*E*)-1,1-Diphenylbut-2-ene (4.113).



4.112 4.113

Representative experimental procedure: To a solution of phenyllithium (1.47 mL of a 1.81M solution in cyclohexane / ether, 2.65 mmol) in THF (30 mL) at 0°C under N_2 was added a solution of CuBr•DMS (636 mg, 3.10 mmol) in di*iso*-propyl sulfide (1.5 mL) and THF (4 mL) *via* cannula. The dark green-black solution was stirred at 0°C under N_2 for 30 min before the addition of cationic complex **4.1** (formed immediately before use: $NOBF_4$ (284 mg, 2.43 mmol) was added to a solution of neutral complex **4.6** (770 mg, 2.21 mmol) in MeCN (10 mL) at 0°C under N_2, and the solution stirred at 0°C for 10 min before transfer). After stirring at 0°C for 1 h after the addition of cationic complex **4.1**, aqueous NH_4Cl (20 mL) and aqueous NH_3 (5 mL) were added and the solution allowed to warm to room temperature. Et_2O (30 mL) was added and the phases were separated, extracting the aqueous phase with Et_2O (2 x 30 mL). The combined organic phases were washed with brine (30 mL), dried, filtered and concentrated *in vacuo* to give a brown oil which was dissolved in $CHCl_3$ (300 mL) and stirred at rt with a stream of O_2 bubbling through the solution for 17 h. Concentration *in vacuo* and adsorbtion of the crude material onto silica was followed by purification by column chromatography (SiO_2, hexanes) to yield a mixture of the title compounds (272 mg, 1.31 mmol, 59%) in the approximate ratio **4.112** : **4.113** = 1 : 2.1, as estimated from ^1H NMR spectroscopy *via* integration of the corresponding vinylic proton resonances: δ 6.39 (1H, d, *J* 5.2) and 6.35 (1H, d, *J* 4.8) for **4.112** and δ 5.92 (1H, ddq, *J* 15.1, 7.7, 1.7) and 5.44 (1H, ddq, *J* 15.2, 1.2, 6.4) for **4.113**. Further elution yielded ketone **4.114** (53 mg, 0.22 mmol, 10%) as a clear oil.

^1H and ^{13}C NMR data for olefin **4.112** were in accordance with literature data.[246]

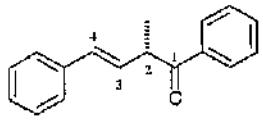
^1H NMR data (CCl_4) for olefin **4.113** has previously been reported.[247]

^1H NMR (400 MHz, $CDCl_3$, referenced to added TMS, **4.113**): δ = 7.38-7.18 (10H, Ph), 5.92 (1H, ddq, *J* 15.1, 7.7, 1.7, H2), 5.44 (1H, ddq, *J* 15.1, 1.2, 6.4, H3), 4.67 (1H, d, *J* 7.6, H1), 1.73 (3H, d, *J* 6.4, H4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4 (2C, 0, Ph), 133.7 (1, C2), 128.7 (4C, 1, Ph), 128.5 (4C, 1, Ph), 127.1 (1, C3), 126.3 (2C, 1, Ph), 54.3 (1, C1), 18.2 (3, C4).

LRMS (EI^+ mode, isobutane): *m/z* = 208.2 [$M^{+\bullet}$, 100 %], 193.2 (65), 165.1 (28), 115.1 (50).

(2*S*,3*E*)-2-Methyl-1,4-diphenylbut-3-en-1-one (4.114)



$[\alpha]_D$ = +25.3 (*c* 0.88, $CHCl_3$)

IR (film): ν = 3054 w, 3025 w, 2971 w, 2927 w, 1677 s, 1589 m, 1443 s, 1244 w, 1205 m, 961 s, 747 m, 703 s cm^{-1}.

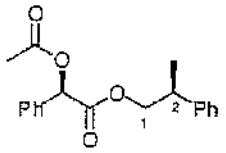
^1H NMR (400 MHz, $CDCl_3$, referenced to added TMS): δ = 8.03-8.00 (2H, m, Ph), 7.57-7.21 (8H, m, Ph), 6.52 (1H, d, *J* 16.0, H4), 6.36 (1H, dd, *J* 16.0, 8.0, H3), 4.32 (1H, br quintet, *J* 7.1, H2), 1.42 (3H, d, *J* 6.8, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2 (0, C1), 137.1 (0, Ph), 136.6 (0, Ph), 133.2 (2C, 1, Ph, C3 or C4), 131.8 (1, Ph, C3 or C4), 129.9 (2C, 1, Ph, C3 or C4), 128.8 (2C, 1, Ph, C3 or C4), 127.7 (4C, 1, Ph, C3 or C4), 126.4 (1, Ph, C3 or C4), 45.1 (1, C2), 17.9 (3, Me).

LRMS (CI mode, NH_3): *m/z* = 254.2 [$(M+NH_4)^+$, 100 %], 237.1 [$(M+H)^+$, 93 %], 200.1 (5).

HRMS (CI^+ mode): found [$M^{+\bullet}$], 236.1200. $C_{17}H_{16}O$ requires 236.1201.

(*R*)-Acetoxyphenylacetic acid (2*S*)-2-phenylpropyl ester (4.121).



To a mixture of olefins **4.112** and **4.113** (89 mg, 0.43 mmol, **4.112** : **4.113** = 5 : 1) in MeOH (6 mL) and H_2O (6 mL) was added OsO_4 (0.45 mL of a 0.1M solution in H_2O, 0.04 mmol) and sodium periodate (366 mg, 1.7 mmol) and the dark solution stirred at rt for 20 h. Et_2O (5 mL) and H_2O (5 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic phases were washed with aqueous $Na_2S_2O_3$ solution (2 x 10 mL) and brine (10 mL), dried, filtered and concentrated *in vacuo*. The resulting crude mixture of aldehydes was dissolved immediately in Et_2O (3 mL) and $LiAlH_4$ (65 mg, 1.7 mmol) added. The grey suspension was stirred at rt for 10 min before the dropwise addition of a 10% aqueous solution of KOH (10 mL) and Et_2O (5 mL). The mixture was stirred vigorously for 10 min before separation of the phases and extraction of the aqueous phase with Et_2O (2 x 5 mL). The combined organic phases were dried, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, Et_2O : hexanes = 3 : 7) yielded a mixture of alcohols **4.116**, **4.117** and **4.118** (40 mg) which were dissolved in CH_2Cl_2 (10 mL) and (*R*)-*O*-acetoxyphenylacetic acid (84 mg, 0.44 mmol), DMAP (2 mg, 0.01 mmol) and DCC (90 mg, 0.44 mmol) added. The cloudy mixture was stirred at rt for 2 h before filtration and purification by column chromatography (SiO_2, Et_2O : hexanes = 1 : 3) to yield a mixture of esters **4.119**-**4.121** (66 mg, **4.121** : **4.120** : **4.119** = 3.5 : 1 : 1).

The dr at C2 for ester **4.121** was conservatively estimated as 90 : 10 from the integration of acetate methyl singlets at 2.14 and 2.15 ppm (major and minor isomers respectively) with reference to an authentic sample of (*RS*)-**4.121**.

NMR spectroscopic data for ester **4.121**:

^{1}H NMR (400 MHz, $CDCl_3$, referenced to added TMS): δ = 7.29-7.11 (10H, m, Ph), 5.88 (1H, s, C<u>H</u>(OAc)Ph), 4.26 (1H, dd, *J* 10.8, 7.2, H1), 4.16 (1H, dd, *J* 10.8, 7.2, H1'), 3.04 (1H, sextet, *J* 7.2, H2), 2.14 (3H, s, CO<u>Me</u>), 1.18 (3H, d, *J* 6.8, C2-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (0, <u>C</u>O_2R), 168.9 (0, <u>C</u>O_2R), 142.8 (0, Ph), 133.9 (0, Ph), 129.2 (1, Ph), 128.9 (2C, 1, Ph), 128.6 (2C, 1, Ph), 127.6 (2C, 1, Ph), 127.4 (2C, 1, Ph), 126.8 (1, Ph), 74.6 (1, Ph<u>C</u>H(OR)CO_2R), 70.4 (2, O<u>C</u>H_2), 39.0 (1, C<u>H</u>(Me)Ph), 20.8 (3, C(O)<u>Me</u>), 17.9 (3, CH(<u>Me</u>)Ph).

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