UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

Stereoselective Synthesis of *all-C* Quaternary Stereocentres using Non-Enolisable 1,3-Dialdehydes

Catherine Oakes

Thesis for the Degree of Doctor of Philosophy

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ABSTRACT

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STEREOSELECTIVE SYNTHESIS OF *ALL-C* QUATERNARY STEREOCENTRES USING NON-ENOLISABLE 1,3-DIALDEHYDES

By Catherine Oakes

The efficient synthesis of *all-C* quaternary centres as part of an acyclic contiguous stereoarray is a highly challenging synthetic operation. Investigations have been carried out into using non-enolisable 1,3-dialdehydes, under $MgBr_2 \bullet OEt_2$ chelation control, as small building blocks for the synthesis of *all-C* quaternary centre as part of a stereoarray. Initial investigations focussed on developing controlled monoadditions to non-enolisable dialdehydes with allylation, hydroxyallylation and aldol reactions to give products containing two or three contiguous stereocentres, including an *all-C* quaternary stereocentre, with good stereocontrol. Interestingly it was found that the diastereoselection of monoaddition was different when the dialdehyde contained a pendant benzyloxy group in contrast to a pendant trityl or TBDPS ether group. The diastereoselection of additions to dialdehydes has been rationalised by considering the reactive conformations involved to form the observed diastereoisomer products of these addition reactions.

A double addition process to the non-enolisable 1,3-dialdehyde with a benzyloxy group has been described. It has been found that the second addition is highly diastereoselective and is effective with a range of nucleophiles to give products containing four or five contiguous stereocentres, including an *all-C* quaternary stereocentre, as part of a stereoarray. The high level of diastereoselectivity of this second addition has again been rationalised by considering the reactive conformation involved.

Finally, attempts have been made toward the formation of enantioenriched stereoarrays containing an *all-C* quaternary stereocentre. Investigations focussed on using Evans' BOX ligands and chiral reagents in reactions with non-enolisable 1,3-dialdehydes.

Contents

DECLARATION OF AUTHORSHIP

I , CATHERINE OAKES declare that the thesis entitled 'STEREOSELECTIVE SYNTHESIS OF *ALL-C* QUATERNARY STEREOCENTRES, USING NON-ENOLISABLE 1,3-DIALDEHYDES' and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
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Signed: ……..

Date:…….

Preface

The research described in this thesis was carried out under the supervision of Dr. Bruno Linclau at the University of Southampton between October 2007 and August 2011. No part of this thesis has previously been submitted for a degree. All work is my own unless otherwise stated.

Acknowledgements

I would like to thank Bruno for all his patience, encouragement and supervision throughout the last four years and for the opportunity to undertake this PhD.

I would also like to thank my industrial supervisors, firstly Vicki, then Andrew and more recently Karl for all of their input and suggestions. I'd also like to thank everyone at GSK Tonbridge who made me feel so welcome and were always willing to help during my time there on placement.

Past and present member of the Linclau group have been a constant source of assistance and laughter both in and out of the lab throughout the past four years. Special mention should go to Nathan who has not only put up with working with me, but also living with me for the last two years; but throughout has been the source of many useful conversations and encouragement about chemistry and less useful conversations about many other things!

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I would like to thank my family for being a constant support throughout over 20 years of education. Special thanks also go to my church, Life Church Southampton, for being like a family to me for the past four years. To my friends, too numerous to mention, for the banter and Sunday afternoon adventures and to my life group for their love, support and prayers, I can't thank you enough. Lastly I'd like to thank Jesus, my saviour, for His complete and undeserved faithfulness towards me.

Abbreviations

ADD	1,1’-(Azodicarbonyl)dipiperidine
AM1	Austin model 1
aq	Aqueous
Ar	Aryl
ax	Axial
BOX	Bisoxazoline
Bn	Benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CAMP	Cyclohexyl-O-anisylmethyl phosphine
δ	Chemical shift
d	Doublet
dd	Doublet of doublets
dq	Doublet of quartets
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diisopopylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N Dimethylformamide
DMSO	Dimethylsulfoxide
d.r	Diastereomeric ratio
EDC	*N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide
EDG	Electron donating group
ee	Enantiomeric excess
eq	Equatorial
equiv.	Equivalents

EtOAc	Ethyl Acetate
ESI	Electrospray ionisation
EWG	Electron withdrawing group
g	Gram
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IR	Infra Red
J	Coupling constant
LCMS	Liquid Chromatography Mass Spectrometry
LDA	Lithium diisopropylamine
LRMS	Low Resolution Mass Spectroscopy
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet
M	Molar
MEM	Methoxy ethoxy methyl
mg	Milligram
MHz	Mega hertz
mL	Millilitre
mmol	Millimoles
MOP	(diphenylphosphanyl)-2’-methoxy-1,1’binaphthyl
Mp	Melting point
Ms	Mesyl
nOe	Nuclear Overhauser effect
NMR	Nuclear Magnetic Resonance
PCA	Principle Component Analysis
PCC	Pyridinium chlorochromate

ppm	Parts per million
q	Quartet
qd	Quartet of doublets
quin.	Quintet
RCM	Ring Closing Metathesis
r.t	Room Temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	Tert-butyldimethylsilyl
TBDPS	Tert-butyldiphenylsilyl
TCDI	1,1-Thiocarbonyldiimidazole
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosyl
UV	Ultra Violet

Chapter 1. Introduction

1.1 Synthesis of *all–C* quaternary centres

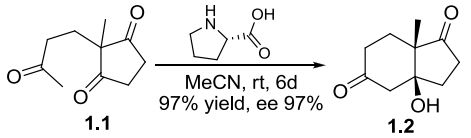
In the past several decades impressive progress has been made in the field of stereoselective synthesis. However the diastereoselective and enantioselective construction of carbon atoms bonded to four different carbon substituents (*all*-carbon quaternary centres) still poses a significant challenge for synthesis.[1] The creation of *all-C* quaternary centres is complicated by steric repulsion between the carbon substituents[2] and further complicated in acyclic systems due to the number of degrees of freedom associated with these structures.[3] However a number of successful methodologies have been reported in this area.[2-5] These include cycloadditions, in particular Diels Alder reactions,[6] Pd catalysed coupling reactions,[7-9] alkylations of enolates with both chiral auxilliaries[10-13] and metal catalyzed additions[14, 15] and sigmatropic rearrangements.[16, 17] Desymmetrisation of a prochiral or *meso* compound containing a quaternary carbon is an additional stereoselective method used to form *all-C* quaternary centres.

1.1.2 Desymmetrisation

Desymmetrisation of an achiral or *meso* compound to yield products with a greater degree of stereocomplexity is a powerful synthetic tool. When a plane of symmetry is present in a bifunctional molecule the two halves are usually enantiotopic. An enantioselective reaction will convert an achiral or *meso* compound into enantioenriched products. This can be achieved by the use of a chiral reagent, catalyst[18] or enzyme.[19] A diastereoselective desymmetrisation reaction will convert an achiral or *meso* compound into diastereoisomers by diastereotopic facial selectivity. Desymmetrisation is a useful synthetic method in the formation of *all-C* quaternary stereocentres; it allows the conversion of an *all-C* quaternary prochiral centre to a stereogenic centre. This has been achieved by organocatalytic aldol cyclisations,[20-24] intramolecular Wittig reactions[25, 26] and Pd catalysed coupling reactions.[27-31]

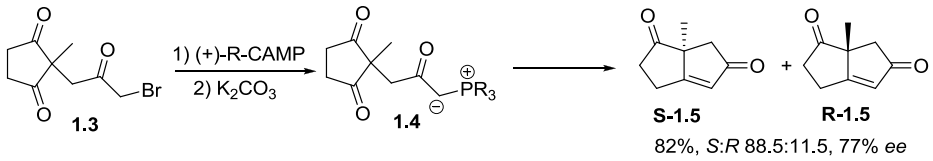
1.1.2.1 Desymmetrisation to form *all-C* quaternary centres

An elegant early example of desymmetrisation of an achiral compound containing an *all-C* quaternary prochiral centre to form an *all-C* quaternary stereocentre was shown concurrently by Eder *et. al.*[20] and Hajos and Parrish.[21] They reported that prochiral triketones such as **1.1** can be transformed into ketols **1.2**[21] or enediones[20] in excellent yields and ee's by an intramolecular asymmetric, amino acid catalysed aldol cyclisation (Scheme 1.1).



Scheme 1.1. Asymmetric, amino acid mediated aldol cyclisation.[21]

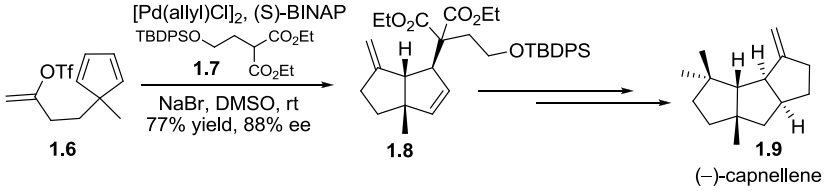
Trost and Curran have also reported the desymmetrisation of 1,3 cyclopentadiones to form an *all-C* quaternary stereocentre. This has been achieved using an intramolecular Wittig annulation to yield fused five membered ring enedione **1.5** (Scheme 1.2). This is potentially a versatile intermediate in the synthesis of a number of biologically active fused five-membered ring natural products.[25, 26]



Scheme 1.2. Intramolecular Wittig anulation of cyclopentadione **1.3**.

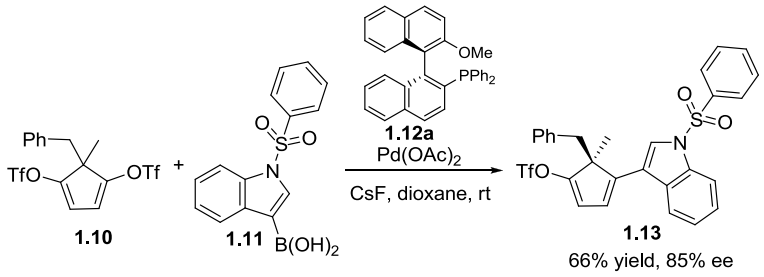
The enantioselective intramolecular Heck reaction is extremely effective in C-C bond construction. No other method for catalytic asymmetric synthesis of *all-C* quaternary centres has been utilised with such a broad range of substrates. This methodology has already been demonstrated in the synthesis of several natural products containing *all-C* quaternary stereocentres. The most common strategy of desymmetrisation applied in this field is the differentiation of enantiotopic olefinic bonds in molecules with prochiral *all-C* quaternary centres.[27]

The Pd catalysed intramolecular Heck cyclisation to form *all-C* quaternary centres was first demonstrated by Shibasaki *et. al.*[28] The basic strategy employed involves enantiotopic group selective ring closure of the prochiral monocyclic compound using a Pd catalyst with a chiral ligand.[28, 32] This methodology has expanded to incorporate a carbanion capture process[33] and this reaction has been successfully employed in the catalytic asymmetric total synthesis of (–)-$\Delta^{9(12)}$-Capnellene (Scheme 1.3).[34]



Scheme 1.3 Use of the asymmetric Heck desymmetrisation in the total synthesis of (–)-$\Delta^{9(12)}$-Capnellene.

Willis *et. al.* have also utilised Pd-catalysed coupling reactions in the desymmetrisation of their cyclic ditriflates, such as **1.10**.[29] Reaction of the ditriflate (**1.10**) with a chiral palladium catalyst allows selective oxidative addition, yielding an enantioenriched vinyl-palladium species. This coupled with a nucleophilic partner (**1.11**) yields the enantioenriched desymmetrised product (**1.13**) containing an *all-C* quaternary stereocentre (Scheme 1.4). It was found that this methodology was effective in both Suzuki[30] and carbonylation[31] reactions using $Pd(OAc)_2$ and MOP-ligand **1.12** and its variants (Scheme 1.4).

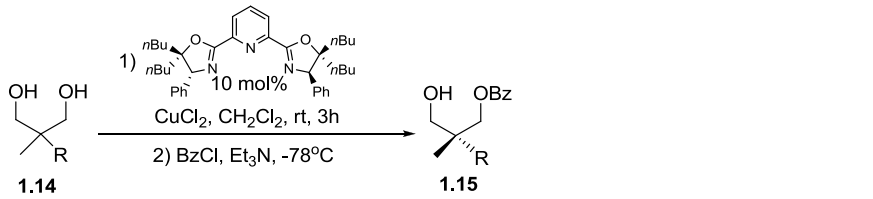


Scheme 1.4. Enantioselective desymmetrisation of cyclic ditriflates with a Suzuki reaction.

1.1.2.2 Desymmetrisation of 1,3-Propanediols

Kang *et. al.* have previously reported the Cu(II) catalysed desymmetrisation of glycerols to synthesize *tert*-alcohols[35, 36] and serinols to synthesize *tert*-alkylamines[37] using bisoxazolines

as chiral ligands. The stereochemical outcomes of these reactions have been rationalised by analysing the chelated intermediates between the Cu-catalysts and the substrates through two heteroatoms at 1,2- rather than 1,3-positions. They have applied this methodology to the desymmetrisation of 2,2-disubstituted 1,3-propanediols to form *all-C* quaternary stereocentres. In the desymmetrisation of these 2,2-(*all*-carbon) disubstituted 1,3-propanediols, the substrates can only coordinate with the catalyst through the two hydroxyls at the 1,3 positions. However the prochiral centre is located in the 2-position and therefore further from the chiral ligand adding a further challenge to the desymmetrisation of 2,2-disubstituted 1,3-propanediols. It was found that Cu(II) pyridinebisoxazolines (Pybox) were effective catalysts in the desymmetrisation of 2,2-disubstituted 1,3-propanediols through monobenzoylation (Scheme 1.5). This methodology was found to be effective for a wide range of different 2,2-disubstituted 1,3-propanediols.



Scheme 1.5. Enantioselective desymmetrisation of **1.14**.

The mechanism and stereochemical outcome of this reaction has been rationalised by analysing the chelated intermediate between the Cu(II) catalyst and the diol **1.14** (Figure 1.1).

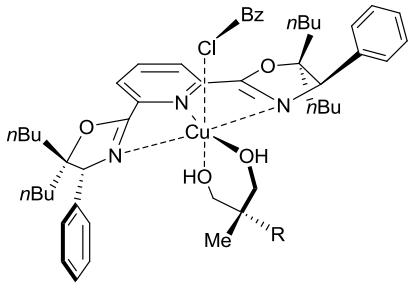


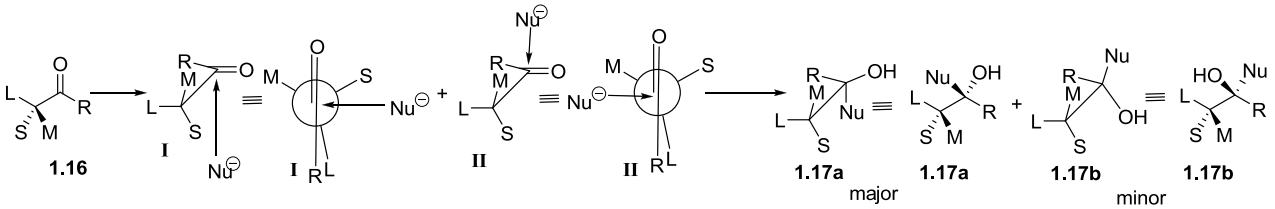
Figure 1.1. Pybox ligand chelated to diol **1.14**.

It is believed that the Pybox-Cu(II) catalyst forms an octahedral complex with the 1,3-diol and benzoyl chloride to transfer the benzoyl cation to the closest hydroxyl group. In this

proposed transition state the tridentate Pybox is situated equatorially, benzoyl chloride axially and diol **1.14** both equatorially and axially. Based on sterics, the smaller methyl group will occupy the smaller space near the 4-phenyl substituent of the oxazoline ring leading to the observed stereochemical outcome.[38]

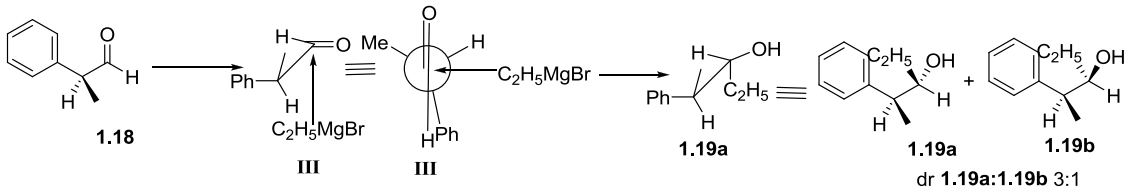
1.2 Control of diastereoselection in addition to carbonyls

A model to explain the stereoselectivity of additions of nucleophiles to carbonyls was first put forward by Cram in 1952.[39] This stated that additions to different faces of a carbonyl adjacent to a stereogenic centre **1.16** occur at different rates due to the difference in size of the two out of plane groups M and S attached to the stereogenic centre that hinder the approach of the nucleophile. In the transition state **I** and **II** the carbonyl group is assumed to be antiperiplanar to the largest of the three substituents, L, on the adjacent carbon. This places S and M on different sides of the carbonyl group and the nucleophile will preferentially attack from the side of the small substituent S (**I**), leading to **1.17a** as the major product, known as the Cram product (Scheme 1.6).[40-42]



Scheme 1.6. Cram's Rule based on sterics.

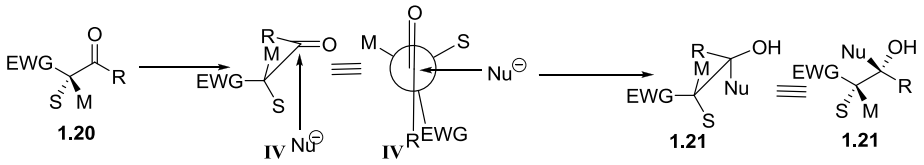
Cram's rule has successfully been able to predict the relative stereochemistry of additions to many α-chiral carbonyl compounds. An example of this is the Grignard addition to 2-Phenylpropionaldehyde **1.18** (Scheme 1.7).[39]



Scheme 1.7. Prediction of diastereoselectivity of addition to **1.18** based on Cram's rule.

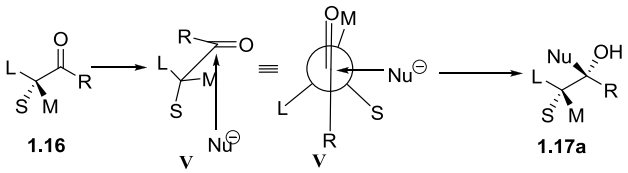
1.2.1 Felkin Anh

Cram's rule is an effective tool at explaining the preferred diastereoselection in additions to carbonyls if no polar substituents are present on the α-stereocentre. However if the α-stereocentre contains polar groups such as Cl or trimethylsiloxy they assume the position of L regardless of more sterically demanding substituents being present. This observation can not be explained by Cram's rule. Cornforth has modified Cram's rule to state that electron withdrawing substituents (EWG) on the α carbon assume the role of L in the transition state **IV** (Scheme 1.8). This would minimize the dipole moment as the dipoles are antiparallel, so aiding the polarization of the carbonyl and lowering the energy of the transition state.[43]



Scheme 1.8. Cornforth model.

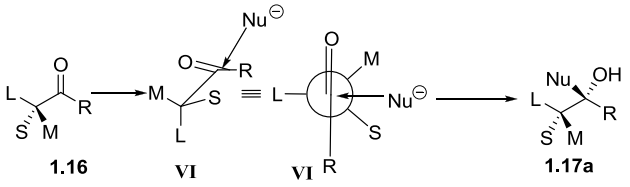
In both the Cram[39] and the Cornforth[43] models the large group on the α carbon L and the R group on the carbonyl (especially in ketones) are eclipsed due to the steric bulk of the carbonyl being overestimated. Analysis by Karabatsos[44-46] stressed that attack of the nucleophile should occur via the least sterically hindered pathway. Due to the rapid addition of nucleophiles to carbonyls and the exothermic nature of these additions led to the assumption that little bond making and breaking had occurred in the transition states. Therefore Karabatsos proposed that the nature of the transition state for nucleophilic additions to carbonyls should be reactant like as opposed to product like. It is put forward that the least sterically hindered reactant like transition state would place medium group, M, on the α carbon in a position that eclipses the carbonyl, with the nucleophile attacking the carbonyl past the small group on the α-stereocentre (**V**, Scheme 1.9). This leads to the same major diastereoisomer **1.17a** as Cram's rule.[44]



Scheme 1.9. Karabatsos model.

The Cram and Karabatsos models were further refined by Felkin. It was suggested that by increasing the steric size of R would increase the strain in transition states **I** (Scheme 1.6) and **V** (Scheme 1.9), destabilising these transition states. Therefore the bulkier R, the less stereoselective these reactions should be. This however is not what is observed experimentally.

Felkin suggested that a single, internally consistent model, encompassing both open chain and cyclic carbonyl compounds can be put forward to interpret the steric outcome of additions to carbonyls based on four principles. Firstly, that the transition states are reactant like rather than product like. Secondly, that torsional strain involving partial bonds in the transition states represents a large fraction of the strain between fully formed bonds. This implies that in open chain carbonyl compounds the preferred conformation for the transition state **VI** is staggered (Scheme 1.10). Thirdly, that the dominant steric interaction in the transition state involves the incoming nucleophile and R, rather than the carbonyl oxygen as assumed by Cram and Karabatsos. On this basis **VI** would be the least strained of the six possible staggered conformations. Fourthly, polar effects stabilise transition states where any EWG is furthest from the incoming nucleophile and destabilise all other transition states.[47]



Scheme 1.10. Felkin model.

Felkin, however failed to explain why the repulsion between the incoming nucleophile and an EWG on the α carbon had to be minimized in the transition state. Felkin model **VI** also breaks down in the case of aldehydes when R=H. In this case the steric interaction between R and the group on the α centre is removed, so it would be expected that M would be next to R rather than next to the carbonyl. This would lead to the wrong diastereoisomer being predicted.

Ab initio calculations by Anh and Eisenstein on propanal and 2-chloropropanal show that σ–π mixing occurs in the carbonyl group. Due to this the π–electron cloud becomes dissymmetric; the electron density is greater on one diastereotopic face than the other. From this it is assumed that a nucleophilic reagent would attack preferentially on the positive face of the carbonyl.[48] These calculations successfully predict the same stereochemical outcome as Cram's rule[39] for propanal and Cornforth's rule[43] for 2-chloropropanal. Anh's work was further extended to suggesting when there is an EWG on the α carbon, the best acceptor σ* orbital, i.e. σ^*_{C-EWG}, will be aligned parallel to the π and π* orbitals of the carbonyl. This allows delocalisation of electron density by hyperconjugation from the reaction centre towards EWG, so stabilising the incoming anion (Figure 1.2).[49]

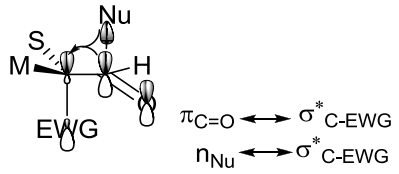


Figure 1.2. Anh Model.

Calculations by Bürgi/Dunitz[50, 51] and Anh/Eisenstein[48, 52] showed that the nucleophile approached the carbonyl at a 103° angle with respect to the carbonyl, rather than the 90° angle that was initially assumed. This explains why even in the case of aldehydes, where R=H, S must be next to R in the transition state (Figure 1.3).

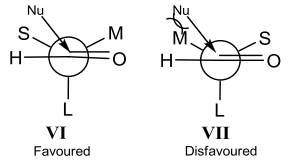
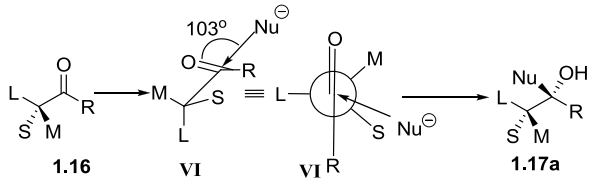


Figure 1.3. Bürgi-Dunitz trajectory.

Anh first postulated that asymmetric induction in addition to carbonyls is controlled by both electronic and steric factors.[48] From all of these contributions evolved a new model, known as the Felkin Anh rule. The Felkin Anh rule states that substituent L is placed orthogonal to the carbonyl group, allowing the nucleophile to attack *anti* to L and so minimizing steric repulsion. The definition of L was broadened so that the pivotal role of electronic factors in stabilising the transition state with the incoming nucleophile was recognised (Figure 1.2).

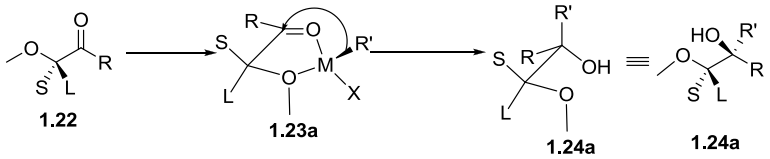
The Felkin-Anh reaction pathway is preferred to the Cram conformation (Scheme 1.6) as it leads directly to a staggered conformation in the product. The Felkin-Anh model still leads to diastereoisomer **1.17a** as the favoured product (Scheme 1.11); however it is a more reliable method of predicting and explaining the stereochemical outcome of additions to carbonyls.[41]



Scheme 1.11. Felkin–Anh Model.

1.2.2 Cram Chelate

Cram, in his seminal paper on control of asymmetric induction, observed that in systems where the asymmetric centre in the starting material carried a group capable of complexing with an organometallic reagent, a different stereochemical outcome was observed. A model, known as the Cram chelate, was put forward. Chelation occurs between a metal cation, the carbonyl group and one of the substituents of the α-stereocentre. The substrate is then locked into a relatively rigid, five membered ring which fixes the conformation of the reacting species. This places the remaining two substituents on the α-stereocentre on different sides of the carbonyl group. A nucleophile will preferentially attack the carbonyl from the side of the smaller substituent, leading to **1.24a** as the major, Cram-chelate product (Scheme 1.12).[39]

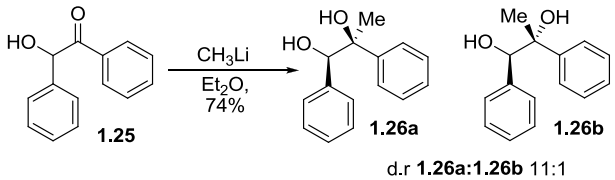


Scheme 1.12. Cram chelate model.

1.2.2.1 1,2-Induction

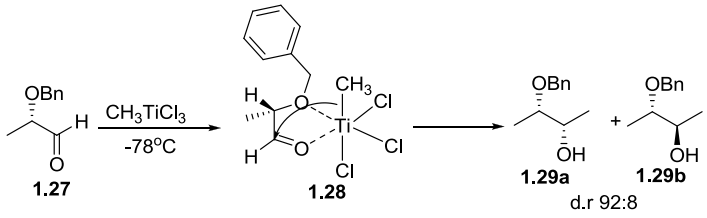
Initial examples of 1,2-induction following the Cram chelate model involved additions of Grignards and alkyl lithium's to α-alkoxy and α-hydroxy carbonyl compounds.[39, 40, 53, 54] In

these reactions it was believed that the organometallic reagent chelated to the carbonyl and the hydroxyl or alkoxy oxygen to form intermediate **1.23a** (Scheme 1.12) and delivered the nucleophile to the least sterically hindered face. An example of this is shown by the addition of MeLi to 1,2-diphenyl-2-hydroxy-1-propanone **1.25**, which gave **1.26a**, the Cram-chelate product, as the major diastereoisomer with a diastereomeric ratio of 11:1 (Scheme 1.13).[54]



Scheme 1.13. MeLi addition to **1.25** following Cram-chelate model.

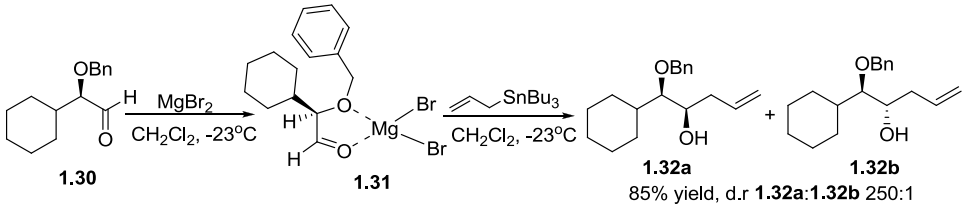
Unfortunately the diastereoselectivity of these type of additions can vary from excellent (96:4) to poor (55:45).[55] There are few cases where the use of Grignard reagents gives good diastereoselectivity, however the diastereomeric ratio of aldol additions of lithium enolates to α-alkoxy aldehydes is poor.[56] Reetz developed a chelation controlled methylation of aldehydes and ketones using CH_3TiCl_3.[57] Lewis acid CH_3TiCl_3 has been shown to methylate both aldehydes[58] and ketones[59] in good diastereoselectivity. CH_3TiCl_3 will chelate to both the aldehydic oxygen and the benzyloxyether oxygen of aldehyde **1.27** to form chelate **1.28**. The methyl is delivered from the top face, past the small proton to give **1.29a** as the major diastereoisomer (d.r 92:8, **1.29a**:**1.29b**) (Scheme 1.14).[58]



Scheme 1.14. Reetz H_3CTiCl_3 methylation by chelation control.

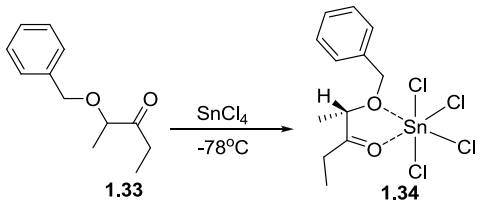
The number of reagents $RTiCl_3$ is limited; therefore a more general method of chelation controlled additions to carbonyls had to be developed. The Lewis acid-induced activation of carbonyl compounds towards nucleophilic addition by reagents such as enol silanes (Mukaiyama aldol),[60] allylsilanes[61] and dialkylzinc[56] is known. Therefore an alkoxy aldehyde should chelate to a Lewis acid capable of bis-ligation such as $TiCl_4$, $SnCl_4$ or

MgX_2. The intermediate chelate then formed should react with a carbon nucleophile such as allylsilanes, enol ethers or allystannanes in intermolecular reactions. This idea has been found to be a general principle in the stereoselective formation of C-C bonds. α-Alkoxy aldehydes and ketones have been found, under chelation control with $TiCl_4$, ZnI_2, $MgBr_2$, $MgCl_2$ and $SnCl_4$, to react with allylsilanes, allylstannanes, silyl enolethers and dienes in chelation controlled Diels Alder reactions with 1,2-asymmetric induction usually being 90-100% (Scheme 1.15).[55, 56, 62-69]



Scheme 1.15. Allylation of α-alkoxy aldehyde under $MgBr_2$ chelation control.[68]

The model for the Cram chelate was developed as the likely intermediate from the known relative stereochemistry of the observed products. Reetz *et. al.* synthesised crystalline $SnCl_4$ complexes of α-alkoxy carbonyl compounds (Scheme 1.16). X-ray structural analysis showed the chelate **1.34** to be monomeric with the tin hexa–coordinate, but in a distorted octahedral environment. The stannacycle is not planar due to the tin pointing towards the methyl group at the chiral centre. The methyl group on the chiral centre shields the bottom diastereotopic face of the carbonyl, with the puckering of the ring enhancing this effect (Figure 1.4); this leads to the observed diastereoselection of additions to Cram-chelates.[66]



Scheme 1.16. Formation of crystalline Sn Cram-chelate.

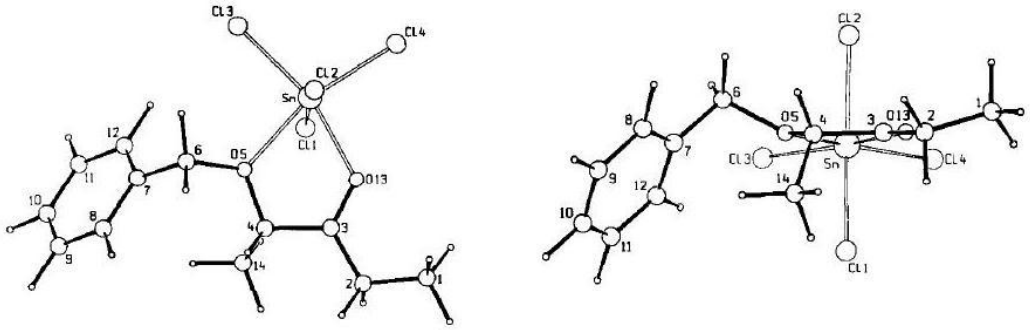
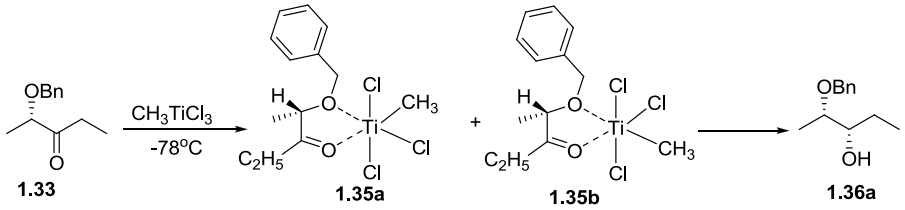


Figure 1.4. X-rays of Sn Cram chelate **1.34**.

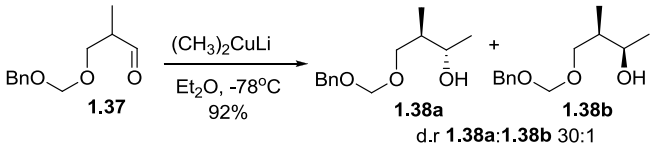
Reetz also observed the solution phase Cram chelate between **1.33** and CH_3TiCl_3 by low temperature ^{13}C NMR. The ^{13}C NMR spectrum recorded directly after addition of CH_3TiCl_3 to **1.33** the carbonyl peak displayed a downfield shift of 11 ppm relative to the uncomplexed ketone **1.33**. The complexation of the ether should lead to a downfield shift of the signals of the two C atoms bound directly to oxygen; this is observed. The ^{13}C NMR spectrum displayed two chelates present, **1.35a** and **1.35b** leading to chelation controlled diastereoisomer **1.36a** as the only observed product (Scheme 1.17).[59]



Scheme 1.17. Formation of Cram chelate **1.35** which is observable by ^{13}C NMR.

1.2.2.2 1,3-Induction

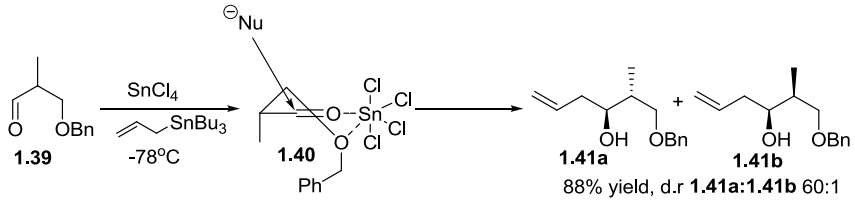
Although addition of Grignards and alkyl lithiums to α-alkoxyaldehydes and ketones was successful in high stereoselectivity (Scheme 1.13), additions of Grignards and alkyl lithiums to β-alkoxyaldehydes proceeded with low asymmetric induction. Still *et. al.* found that lithium dimethylcuprate was an effective source of methyl nucleophile. In additions to β-alkoxyaldehyde **1.37** the reaction proceeded with a high yield and excellent diastereoselectivity (d.r **1.38a**:**1.38b** 30:1) to give the chelation controlled product (Scheme 1.18).[70]



Scheme 1.18. 1,3 chelation controlled methylation of **1.37**.

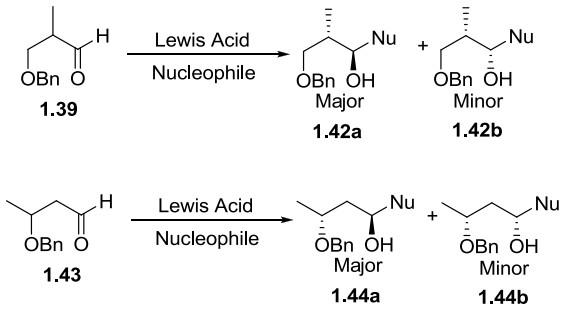
The level of 1,3 induction in additions of lithium dialkylcuprates to β-alkoxyaldehydes dropped off as the size of the alkyl group on the cuprate increased. Surprisingly Me_2CuLi showed almost no stereoselectivity when no α-substituent was present. Asymmetric induction was also severely reduced in additions of Me_2CuLi to α-alkoxyaldehydes, suggesting where Grignards have a preference for α-chelation (5 membered ring chelate) organocuprates display a preference for β-chelation (6 membered ring chelate).[70]

Reetz *et. al.* had previously shown that compounds of the type $RTiCl_3$ can alkylate α-alkoxyaldehydes (Scheme 1.13).[57] They found the same methodology was applicable to the alkylation of β-alkoxyaldehydes.[71] As with 1,2-induction, this methodology was further developed where a β-alkoxyaldehyde chelated to $TiCl_4$; this chelate was capable of reacting with a silyl enol ether in an intermolecular reaction with good yields and diastereoselectivity.[71] This idea has been developed to be a general principle in the stereoselective formation of C-C bonds with compounds capable of 1,3-chelation. β-Alkoxy aldehydes and ketones have been found, under chelation control with $TiCl_4$, $ZnBr_2$, $MgBr_2$, $AlCl_3$, Et_2AlCl and $SnCl_4$, to react with allylsilanes, allylstannanes, silyl enolethers and dienes in chelation controlled Diels Alder reactions with 1,3-asymmetric induction usually being 90-100%.[62, 63, 65, 71-73] The diastereoselection of these reactions can be deduced by considering the 1,3-chelate that is formed between the Lewis acid and the β-alkoxyaldehyde or ketone.



Scheme 1.19. Allylation of β-alkoxy aldehyde under $SnCl_4$ chelation control.[73]

Investigations into the origins of stereoselectivity in chelation controlled nucleophilic additions to β-alkoxyaldehydes have been carried out by Keck *et. al.* Variable temperature NMR spectroscopy experiments on the solution structures of the Lewis acid complexes with β-alkoxyaldehydes revealed details of the structure of the chelates and the resultant diastereoselection.[74, 75] The diastereofacial selectivity for nucleophilic additions to β-alkoxyaldehydes **1.39** and **1.43** in the presence of bidentate Lewis acids is widely reported in the literature (Scheme 1.20).[65, 71-73]



Scheme 1.20. Diastereoselection in additions to **1.39** and **1.43**.

Interpretations of the observed diastereoselection within the literature place the substituent in the C_2 or C_3 position *pseudo*-equatorial in the presumed intermediate complex.[55] Variable temperature NMR spectroscopy of the complexes formed between aldehydes **1.39** and **1.43** with $TiCl_4$, $SnCl_4$ and $MgBr_2 \bullet OEt_2$ revealed the structure of the intermediate chelates formed in solution (Figure 1.5).[74]

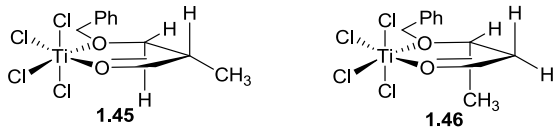


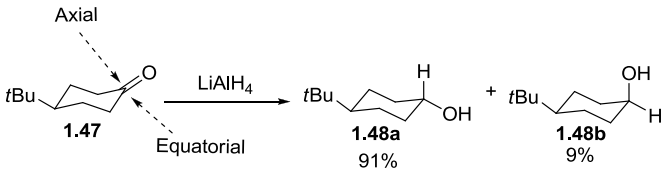
Figure 1.5. Solution structures of the $TiCl_4$ complexes of **1.39** (**1.45**) and **1.43** (**1.46**).

It was found that aldehyde **1.39** chelates with $TiCl_4$ to form chelate **1.45**, a rigid and 'conformationally locked' structure. Coupling constants between the protons at C_3 and C_2 ($J_{ax\text{-}ax}$ = 9.7 Hz, $J_{ax\text{-}eq}$ = 3.5 Hz) shows that the methyl group at C_2 is in a *pseudo*-equatorial position. The same results are observed when **1.39** is complexed with $SnCl_4$ and $MgBr_2 \bullet OEt_2$. Nucleophilic attack on the *Si*, to go *via* the more favourable chair transition state would lead to the observed diastereoselection with **1.42a** as the major diastereoisomer.

NMR experiments of **1.43** showed that no single chelate was formed with $SnCl_4$. However, with $TiCl_4$ and $MgBr_2 \bullet OEt_2$ the formation of a discrete bidentate complex was observed, with complex formation favoured at lower temperatures. Coupling in the ^1H NMR showed the methyl group at C_3 must occupy a *pseudo*-axial position, as shown in **1.46**. This relieves the $A^{1,3}$-like interactions between the C_3 methyl group and the benzyl group on the oxygen. It is believed that this $A^{1,3}$-like interaction is responsible for the conformation of chelates derived from **1.43** in solution, there are also no significant 1,3-diaxial interactions present to disfavour this conformation. The favourability of chelate **1.46** is what is believed to lead to the high levels of diastereofacial selectivity in chelation controlled additions to **1.43**.[74] This work has shown the structures of Cram chelates in solution for 1,3-induction reactions, the importance of minimising unfavourable interactions in these chelates and the effect this has on the observed diastereoselectivity.[74, 75]

1.2.3 Cieplak Model

The role of sterics in the stereoinduction of additions to carbonyl groups has never been in question. However sterics alone fail to fully explain the diastereoselection of additions to all carbonyl groups in the literature, notably additions to 4-*tert*-butylcyclohexanone **1.47**. The diastereoselection of nucleophilic additions to 4-*tert*-butylcyclohexanone is determined by two competitive factors; steric hinderance directing the nucleophile into the equatorial position (**1.48b**) and a 'non-steric' factor directing nucleophiles into the axial position (**1.48a**). In the $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone axial addition of the hydride dominates (Scheme 1.21).[76]



Scheme 1.21. $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone.

Anh suggested that the 'non-steric' factor was an electronic factor in which the axial transition state was stabilised by interaction with the σ* antibonding orbitals of the axial C_2 and C_6 bonds (Figure 1.2).[49, 77]

Cieplak suggested an alternative electronic factor controlling π face selection in his seminal paper in 1981.[78] Cieplak proposed that π-face selection is not only controlled by steric strain, but by resonance interactions between the newly forming bond and the substituents on the α centre to the reacting carbonyl. The dominant interaction in the bond forming process is electron delocalisation from the σ orbitals (hyperconjugation) of the α centre into the σ* orbital of the bond forming ($\sigma^*_{\ddagger}$), the low lying LUMO of the transition state (Figure 1.6). Although this electron donation weakens the bond forming, the net effect is stabilization of the transition state due to the increase in bonding between the α centre and the bonding centre. Therefore the relative stability of the transition state for bond formation of nucleophilic addition to carbonyls depends not only on the size of substituents S, M and L, but also on their σ donor capability. According to the Cieplak model the nucleophile will approach the carbonyl antiperiplanar to the substituent in the α position that is the best σ donor,[78, 79] the opposite approach to that proposed by the polar Felkin Anh model.[49]

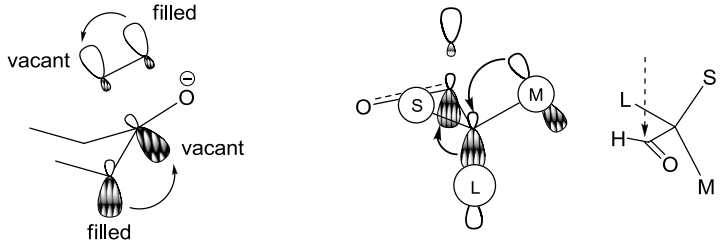


Figure 1.6. Cieplak model of hyperconjugation to stabilise transition state.

Applying the Cieplak model to the $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone there is a $\sigma_{C\text{-}C}$ bond and a $\sigma_{C\text{-}H}$ bond in the α position that could donate into the $\sigma^*_{\ddagger}$ orbital. Hyperconjugative assistance from $\sigma_{C\text{-}C}$ would increase the stabilisation energy of the equatorial approach, whereas hyperconjugative assistance from $\sigma_{C\text{-}H}$ would increase the stabilisation energy of the axial approach (Figure 1.7).[78] It is known that C-H bonds are better σ donors than C-C bonds.[79-81] Therefore the Cieplak model correctly predicts that

axial approach of the hydride in the $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone will dominate (Scheme 1.21).

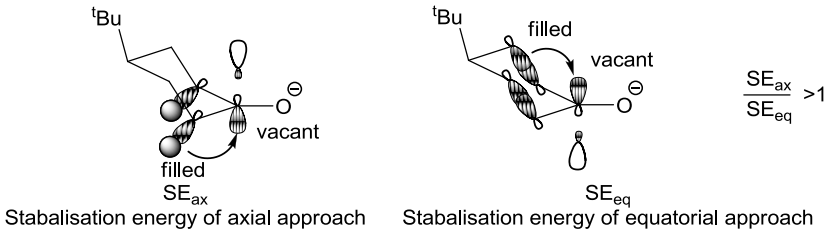
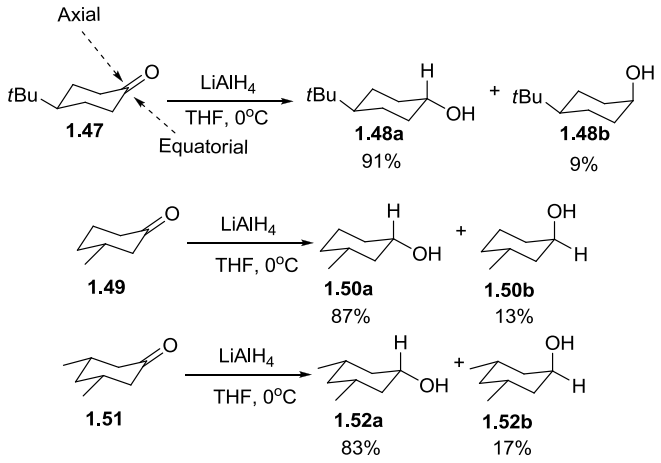


Figure 1.7. Cieplak model of hyperconjugation in additions to 4-*tert*-butylcyclohexanone.

1.2.3.1 Remote Substitution

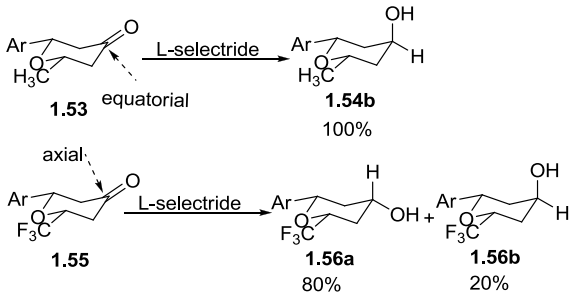
If the Cieplak model is correct, then an increase in the electron donating ability of the $\sigma_{C\text{-}C}$ bonds in the cyclohexanone ring should lead to an increase in yield of the product from the equatorial approach of the nucleophile. Alkyl substitution in the C3 and C5 positions increases the σ-donor abilities of the C-C bonds in the cyclohexanone ring.[82] Accordingly, the relative yields of the product of equatorial approach increases in metal hydride reductions of 3- and 3,5-alkylcyclohexanones (Scheme 1.22).[83, 84] This suggests a selective stabilisation of the equatorial transition state due to an increased electron donating ability of the $\sigma_{C\text{-}C}$ bonds in the cyclohexanone ring, fitting with the Cieplak model.[78]



Scheme 1.22. Increase in equatorial approach with C3 and C5 alkyl substitution.

Danishefsky has shown that using L-selectride, the diastereoselection of the reduction of pyranones can be completely reversed by changing the substitution at C3 following the

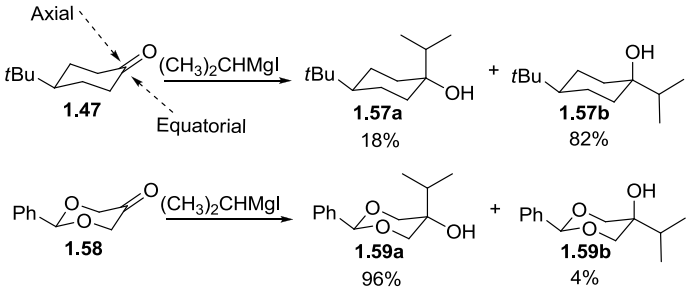
Cieplak model. An EDG such as a methyl at C3, **1.53**, increases the electron donating ability of $\sigma_{C\text{-}C}$ bond, therefore promoting equatorial approach of the reducing agent to give **1.54b** exclusively. Substitution at C3 with an EWG, **1.55**, reduces the σ donor ability of the ring C-C bond, promoting axial approach, to give **1.56a** as the major product (Scheme 1.23).[85, 86]



Scheme 1.23. Reversal in diastereoselection of hydride reduction by C3 substitution.

1.2.3.2 Heterocyclohexanones

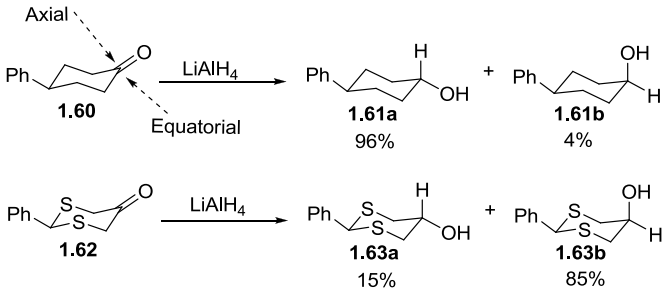
The electron donating ability of typical σ bonds increases in the following order: $\sigma_{CO} < \sigma_{CN} < \sigma_{CC} < \sigma_{CS}$. Therefore replacing C3 and C5 in a cyclohexanone with O will, according to the Cieplak model, destabilise the equitorial transition state as the C-O bond is a poorer electron donor than the C-C bond. It is expected that this would therefore lead to an increase in the yield of the axial product. It is observed that the yield of the axial product of addition of Grignards to **1.58** is much greater than the yield of the axial product of addition of Grignards to **1.47** (Scheme 1.24).[78]



Scheme 1.24. Grignard additions to cyclohexanones and dioxanones.

Replacement of C3 and C5 in a cyclohexanone with S should promote equatorial approach of nucleophiles according to the Cieplak model as C-S bonds are better σ donors than C-C bonds. Metal hydride reduction of cyclohexanone **1.60** displays axial approach. However

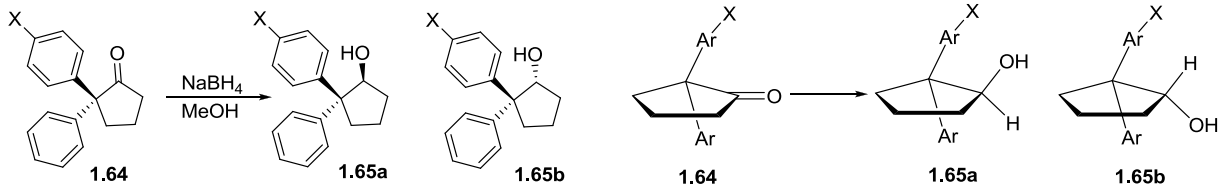
introduction of S into the cyclohexanone ring in the β position results in the reversal of the usual preference for axial approach, to display equatorial approach (Scheme 1.25).[78]



Scheme 1.25. Hydride reduction of cyclohexanone **1.60** and thioxanone **1.62**.

1.2.3.3 Nucleophilic addition to sterically unbiased carbonyls

Using the sterically unbiased system of 5-substitued 2-adamantanones, le Noble *et. al.* has shown that reduction of these adamantanone systems occurs with excellent π-facial diastereoselection in fitting with hyperconjugative σ assistance.[87] This is also supported by Haltermans work with 2,2-diarylcyclopentanones (Scheme 1.26, Table 1.1).[88]



Scheme 1.26. Reduction of sterically unbiased 2,2-diarylcyclopentanones.

Table 1.1. Reduction of sterically unbiased 2,2-diarylcyclopentanones.

Entry	X	% 1.65a	% 1.65b
1	NO_2	21	79
2	Cl	37	63
3	Br	37	63
4	H	50	50
5	OCH_3	57	43
6	O^-	70	30
7	NH_2	64	36

The Cieplak model states that the hydride will approach the carbonyl antiperiplanar to the substituent in the α position that is the best σ donor. In entry 1, where X is NO_2, the phenyl

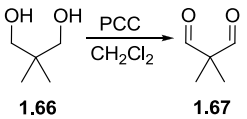
ring is the most electron rich substituent in the α position, therefore the C-Ph bond is the best σ donor. The hydride will attack antiperiplanar to the C-Ph bond to stabilise the transition state, giving **1.65b** as the major diastereoisomer. However when X is an EDG (entries 5-7), the substituted aromatic becomes the most electron rich ring and the C-ArX bond the best σ donor. Hyperconjugative σ assistance to stabilise the transition state causes the hydride to attack antiperiplanar to the C-ArX bond, giving **1.65a** as the major diastereoisomer.[88]

1.3 Non-enolisable dialdehydes

Non-enolisable 1,3-dialdehydes are a potentially useful and versatile class of compounds especially in bidirectional synthesis. However 1,3-dialdehydes have been rarely used in synthesis due to their instability[89] and perceived difficulty in preparation and isolation.[90]

1.3.1 Synthesis of 1,3-dialdehydes

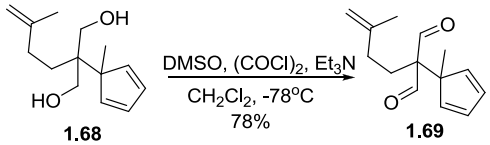
There are few reported examples of the synthesis of 1,3-dialdehydes from the corresponding 1,3-propanediols. PCC has been used as an oxidant in the preparation of 2,2-substituted 1,3-dialdehydes, however with no reported yields (Scheme 1.27).[91, 92]



1.66 **1.67**

Scheme 1.27. PCC oxidation of 2,2-dimethyl-1,3-propanediol **1.66**.[91]

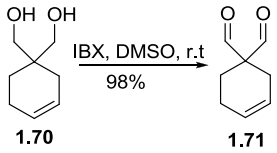
The most commonly reported oxidation procedure in the synthesis of 1,3-dialdehydes is the Swern oxidation (Scheme 1.28). However yields from this oxidation can vary from very low to good.[90, 93-96]



1.68 **1.69**

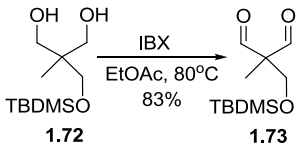
Scheme 1.28. Swern oxidation to form 1,3-dialdehyde **1.69**.[90]

More recently, it has been reported that IBX, the precursor to Dess-Martin periodinane, can effectively oxidise primary and secondary alcohols to aldehydes and ketones.[97] It has been shown that IBX can oxidise 1,3-diols, such as **1.70**, to their corresponding 1,3-dialdehydes in good yields (Scheme 1.29).[97, 98]



Scheme 1.29. IBX oxidation via the Santagostino procedure.[97]

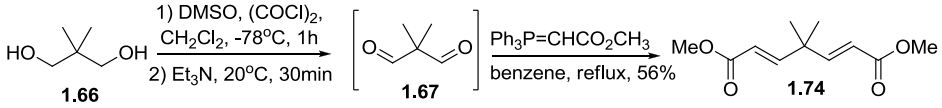
IBX is virtually insoluble in most organic solvents; it is only soluble in DMSO. The limitations of DMSO as a solvent include, the need for an aqueous work up which may promote hydration, oligomerization and self-condensation of the dialdehyde, as well as difficulty in the separation of oxidation by products. This has motivated the synthesis of solid phase analogues of IBX (polystyrene and silica bound), expanding the range of viable solvents and facilitating the recovery and reuse of the oxidant.[99, 100] Finney demonstrated that IBX is an effective heterogeneous oxidant in most organic solvents. At elevated temperatures, IBX is sufficiently soluble in most organic solvents to allow clean oxidation of alcohols to their corresponding aldehydes and ketones. It was found that EtOAc and DCE were the optimum solvents as they are inert and all oxidant by-products from the reaction are insoluble at room temperature, so no purification is require beyond simple filtration.[101] The Finney modification of the Santagostino IBX oxidation procedure has been found to be effective for the oxidation of 1,3-diols to their corresponding 1,3-dialdehydes, in good yields, with no need for purification (Scheme 1.30).[102]



Scheme 1.30. IBX oxidation of **1.72** by the Finney modification of the Santagistino procedure.[102]

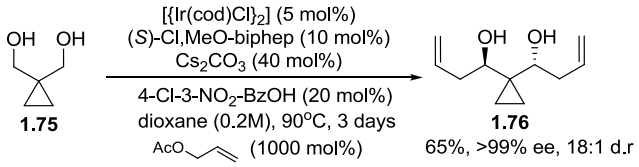
1.3.2 Reactions of 1,3-dialdehydes

1,3-Dialdehydes are known to be unstable and often difficult to isolate.[96] However they have been utilised in synthesis by being formed *in situ* and reacted immediately, without isolation. An example of this is the oxidation, followed by Wittig reaction of diol **1.66** to form diester **1.74** (Scheme 1.31).[93]



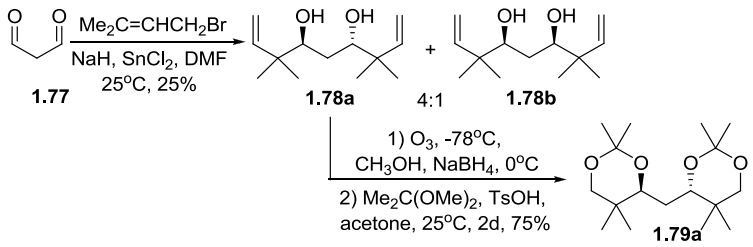
Scheme 1.31. *In situ* formation of dialdehyde **1.67** followed by Wittig reaction.

Krische *et. al.* have overcome the instability of 1,3-dialdehydes by using 1,3-propanediols as dialdehyde synthons in a highly diastereoselective bidirectional allylation process. The enantioselective method for carbonyl allylation of 1,3-propanediols from the alcohol oxidation level takes place using iridium catalyzed transfer hydrogenation conditions, using allyl acetate as an allyl donor. The reactant alcohol acts as both a source of hydrogen and an aldehyde precursor, allowing formation of enantioenriched allylic alcohols directly from the alcohol oxidation level *via* a transient aldehyde (Scheme 1.32).[89]



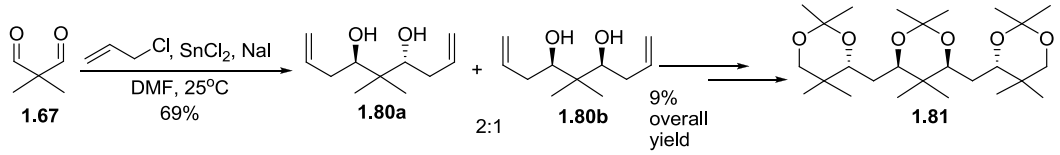
Scheme 1.32. Iridium catalysed, enantioselective carbonyl allylation of diol **1.75**.

However it has been shown that it is possible to isolate and use 1,3-dialdehydes in synthesis. Hoffmann *et. al.* have demonstrated that isolated 1,3-dialdehydes can be utilised as small building blocks in the bidirectional synthesis of skipped polyols. It was found that malondialdehyde **1.77** could react with allyl chloride[103] and prenyl bromide under substrate control to preferentially give the *anti* 1,3-diol **1.78a** (Scheme 1.33).[104]



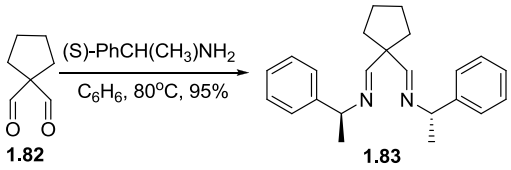
Scheme 1.33. Formation of skippd polyols *via* addition to malonaldehyde **1.77**.[104]

This work has been further extended to give the *meso* polyols by the allylation of non-enolisable 1,3-dialdehyde **1.67**, which this time preferentially gives the *syn* 1,3-diol **1.80b** in a 2:1 ratio. However it was found that both diastereoisomers could be utilised to form the desired tetrakis-acetonide **1.81** (Scheme 1.34).[104, 105]



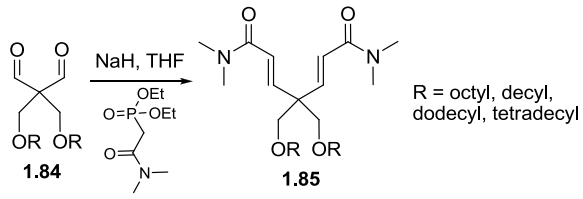
Scheme 1.34. Bidirectional synthesis of polyols from non-enolisable 1,3-dialdehydes.[104]

Non-enolisable 1,3-dialdehydes have also been used as substrates in the synthesis of chiral β-diimine ligands. Condensation of dialdehydes with a chiral amines yields chiral β-diimines (Scheme 1.35). These chiral β-diimines can form complexes with Pd and be used in asymmetric synthesis.[94]



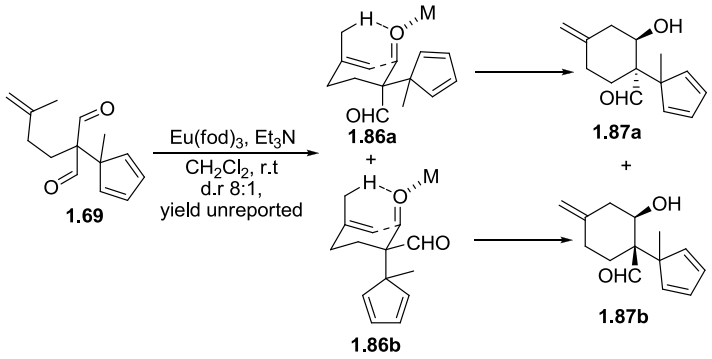
Scheme 1.35. Condensation of dialdehyde **1.82** to give chiral β-diimine **1.83**.

Dialdehydes have also been used in the Horner–Wadsworth–Emmons reaction to form intermediates in the synthesis of cationic surfactants (Scheme 1.36). This is the first reported case of the Horner–Wadsworth–Emmons reaction being performed on dialdehydes.[95]



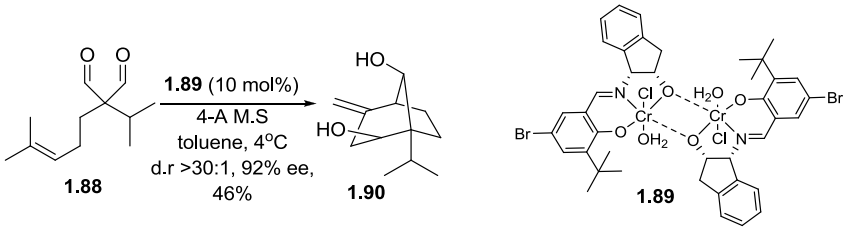
Scheme 1.36. Horner–Wadsworth–Emmons reaction on dialdehyde **1.84**.

Ziegler *et. al.* have shown that non-enolisable 1,3-dialdehydes can be desymmetrised by a Lewis acid catalysed ene cyclisation reaction. The reaction should proceed *via* a chair type transition state, with the newly generated hydroxyl in an axial orientation. Due to the steric bulk of the methylcyclopentadienyl group, this should occupy the equatorial position in the transition state to give **1.87a** as the major diastereoisomer (Scheme 1.37).[90]



Scheme 1.37. Ene cyclisation in the desymmetrisation of dialdehyde **1.69**.

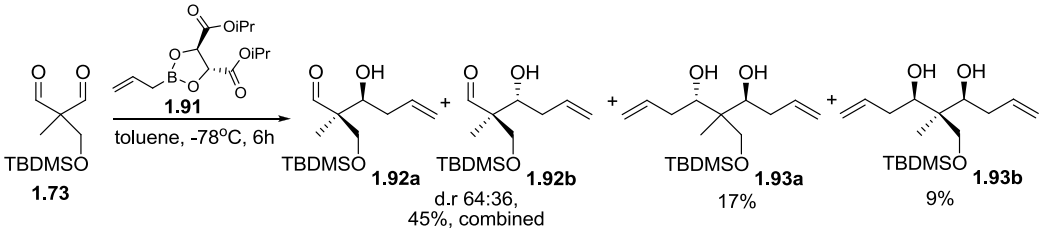
This methodology has been further developed to a tandem ene cyclisation to form products containing up to three contiguous stereocentres in good diastereo and enantioselectivity (Scheme 1.38).[106]



Scheme 1.38. Tandem ene cyclisation of dialdehyde **1.88**.

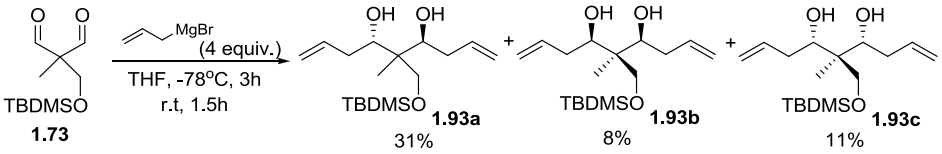
Unpublished work within the Linclau group has shown that dialdehyde **1.73** will react with Roush's allylboronate.[107] Surprisingly the reaction did not go to completion despite 8 equiv.

of allylboronate **1.90** being used; monoallylation products **1.92a** and **1.92b** were isolated along with bisallylation products **1.93a** and **1.93b** (Scheme 1.39).[108]



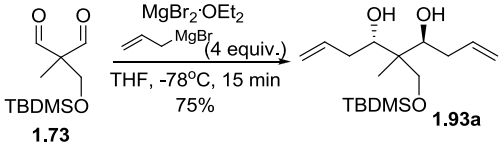
Scheme 1.39. Allylation of dialdehyde **1.73** with Roush's allylboronate **1.91**.

These results suggest that the second allylation is considerably slower than the first. It is believed that this is due to steric hinderance next to the remaining aldehyde after the first allylation has taken place. Bisallylation of **1.73** was more successful using allyl Grignards and allylstannane reagents. Corresponding with Hoffmann's observations,[104] formation of the *pseudo-C_2* symmetric **1.93a** was favoured over formation of *meso* compounds **1.93b** and **1.93c** (Scheme 1.40).[108]



Scheme 1.40. Bisallylation of **1.73** with allyl Grignards.

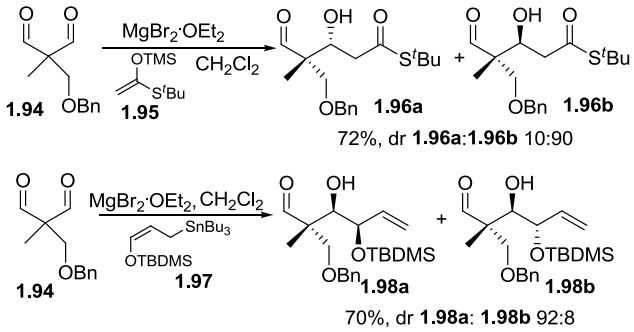
Interestingly it was found that when **1.73** was chelated to $MgBr_2$•OEt_2, the bisallylation with allyl Grignard proceeded to give only **1.93a**, the *pseudo- C_2* symmetric product in 75% yield (Scheme 1.41). By comparing results from the bisallylation of **1.73** with and without $MgBr_2$•OEt_2, it could be seen that additions to dialdehyde **1.73** under $MgBr_2$•OEt_2 activation proceeded in higher yields and diastereoselectivity.[109]



Scheme 1.41. Bisallylation of **1.73** with allyl Grignards under $MgBr_2$•OEt_2 activation.

1.4 Aims of the work

The focus of this project was to investigate the use of non-enolisable 1,3 dialdehydes as small building blocks in the synthesis of *all-C* quaternary stereocentres as part of a stereoarray. Non-enolisable 1,3-dialdehydes contain a prochiral *all-C* quaternary centre. Therefore controlled monoaddition to one of the aldehydes would form an *all-C* quaternary stereocentre as part of a stereoarray in a desymmetrisation reaction. Previous work within the Linclau group has shown that non-enolisable 1,3-dialdehyde **1.94** will react with allylstannnes and silyl enol ethers in allylation, hydroxyallylation and Mukaiyama aldol reactions, with the prochiral quaternary centre in **1.94** being transformed into an chiral centre with excellent diastereoselectivity (Scheme 1.42).[109]



Scheme 1.42. Previous work within the group on monoaddition to dialdehyde **1.94**.

The specific objectives of this project were to expand the scope of reactions on non-enolisable 1,3-dialdehydes and rationalise the observed stereochemistry. We also aimed to investigate the corresponding enantioselective additions to non-enolisable 1,3-dialdehydes and explore the synthetic scope of this methodology in the synthesis of natural product fragments.

1.4.1 Expanding the scope of reactions and rationalising diastereoselectivity

Preliminary results indicated that allylstannations and Mukaiyama aldol reactions with **1.94** are high yielding and very stereoselective (Scheme 1.42). These reactions are very versatile and were to be investigated in more detail. Of particular interest was the diastereoselectivity

of the reaction. The γ-substitution on the allylstannanes and β-substitution on enolates is associated with the formation of an additional stereocentre at C4, giving three contiguous stereocentres. The associated C3-C4 stereoselectivity is controlled by the acyclic transition state for the respective C-C bond formations. Therefore additions of a range of different substituted allylstannanes and enolates (Figure 1.8) were to be investigated.

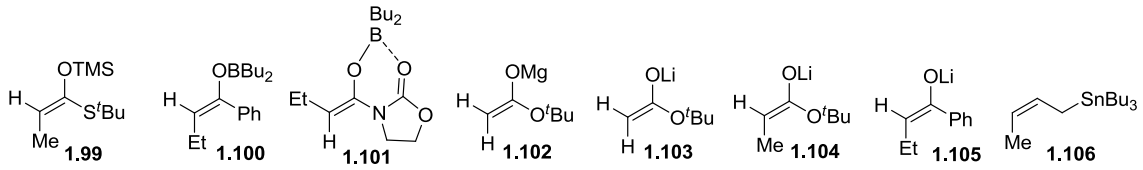


Figure 1.8. Range of nucleophiles to react with non-enolisable 1,3-dialdehydes.

The C2-C3 diastereoselection and diastereoselectivity depends on aldehyde facial differentiation. We aimed to investigate the hydroxyallylation and Mukaiyama aldol reactions of other non-enolisable 1,3-dialdehydes (Figure 1.9). The results of these reactions we hoped would further our understanding into the model of chelation and the significance of the two groups attached to the prochiral centre in the diastereoselectivities of the additions to non-enolisable 1,3-dialdehydes.

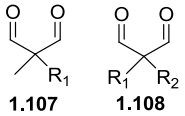


Figure 1.9. Non-enolisable 1,3-dialdehydes.

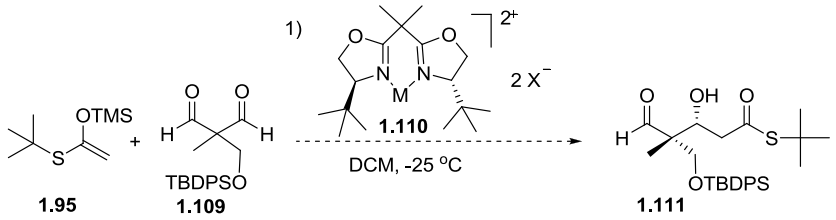
The major and minor diastereoisomers formed in these reactions were to be isolated and the relative stereochemistry identified by X-ray crystallography, chemical correlation and nOe experiments. We aimed to rationalise the diastereoselection and diastereoselectivities observed in these reactions and to put forward a stereochemical model for nucleophilic additions to non-enolisable 1,3-dialdehydes.

1.4.2 The enantioselective synthesis of *all-C* quaternary stereocentres

We hoped to extend the methodology developed to achieve the enantioselective synthesis of quaternary stereocentres. The non-enolisable 1,3-dialdehydes substrates should offer a good opportunity for employing chiral catalysts, with chelation leading to structurally defined activated species. Chelation of (enolisable) 1,3-dicarbonyl groups is well precedented,

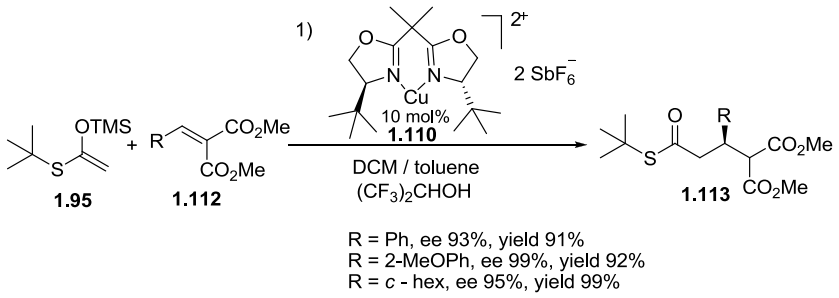
however to the best of our knowledge there are no known examples of chelation of non-enolisable 1,3-dialdehydes. We have chosen to focus on Evans bisoxazoline catalysts for our investigations as these have a proven track record for bidentate activation of 1,3-dicarbonyl species.[14, 110-112]

We intended to start our investigations around the Mukaiyama aldol reaction of non-enolisable 1,3-dialdehydes using Evans bisoxazoline ligands (Scheme 1.43). Our approach is centred around establishing the optimum chelate geometry to obtain maximum enantiodifferentiation by the chiral ligand.



Scheme 1.43. Enantioselective Mukaiyama aldol reaction of **1.109**.

There is literature precedent of a Mukaiyama Michael reaction on a malonate chelated with a Cu(box) catalyst (91% yield, 93% *ee*), where the two carbonyl oxygens chelate to the metal, adopting a boat conformation with the metal atom at the apex (Scheme 1.43).[111] We expected that the catalyst substrate complex between our dialdehyde and M(box) catalyst would adopt the same conformation and hoped to obtain X-ray structures of this complex to aid rationalisation of the stereochemical outcome of the reaction. There is also literature precedent of enantioselective Mukaiyama aldol reactions of chelated 1,2-dicarbonyls with Evans bisoxazoline catalysts in the case of pyruvates (99% yield, 98% *ee*).[14] However to the best of our knowledge there is no example of an addition to a carbonyl group of a 1,3-dicarbonyl species which is chelated with $[M(Box)]^{2+}$.

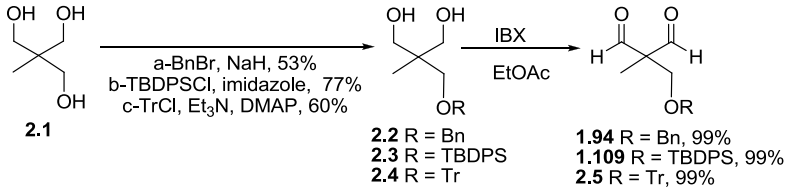


Scheme 1.43. Michael Mukaiyama reaction on malonate **1.112**.[111]

Chapter 2. Monoaddition reactions to non-enolisable 1,3-dialdehydes

2.1 Synthesis of non-enolisable 1,3-dialdehyde starting materials

Work has focussed on investigating the reactions of benzyloxy dialdehyde **1.94**, TBDPS ether dialdehyde **1.109** and trityl ether dialdehyde **2.5**. These non-enolisable 1,3-dialdehydes were synthesised in two steps from the cheap, commercially available triol **2.1**, by monoprotection,[102] followed by IBX oxidation by the Finney modification[101] of the Santagostino procedure (Scheme 2.1).[97]

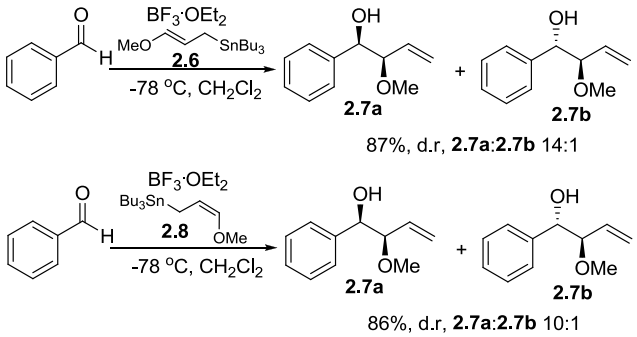


Scheme 2.1. Synthesis of non-enolisable 1,3-dialdehydes **1.94**, **1.109** and **2.5**.[109]

2.2 Hydroxyallylation reactions

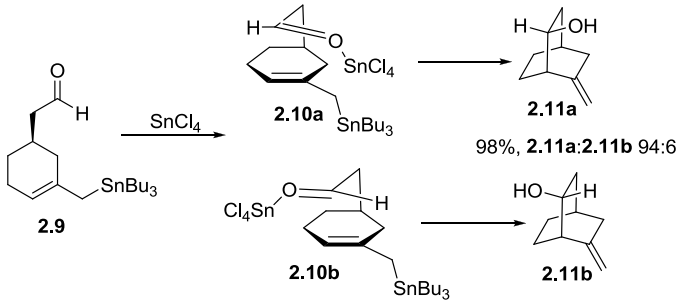
2.2.1 Introduction

Investigations into the stereoselective synthesis of carbohydrates and other polyoxygenated materials from acyclic precursors has led to the development of the hydroxyallylation reaction between aldehydes and (γ-alkoxyallyl)metal reagents.[113, 114] It has been shown that γ-alkoxyallylstannane reagents are highly diastereoselective in the synthesis of *syn* 1,2-diols[113] regardless of the *E/Z* geometry of the γ-alkoxyallylstannane reagent (Scheme 2.2).[114] γ-Alkoxyallylstannanes have become the most widely used synthetic equivalents of the 1-hydroxyallyl anion due to their easy purification and storability.[115]



Scheme 2.2. Hydroxyallylation of benzaldehyde with E and Z γ-methoxyallylstannanes.[114]

It is believed that the Lewis acid promoted reaction of aldehydes with γ-alkoxyallylstannanes occurs stereoconvergently to give the *syn* adducts *via* an acyclic transition state.[116] Denmark has shown that the synclinal transition state is favoured over the antiperiplanar transition state in additions of allylstannanes. In the Lewis acid promoted cyclisation of **2.9**, the reaction yields proximal product **2.11a** as the major diastereoisomer. This must form *via* synclinal transition state **2.10a**, whereas the minor distal diastereoisomer **2.11b** must form from the antiperiplanar transition state **2.10b** (Scheme 2.3).[117]



Scheme 2.3 Intramolecular allylation showing favouring of the synclinal approach.

Denmark suggested that the synclinal transition state is favoured over the less sterically hindered antiperiplanar transition state due to stereoelectronic effects. The synclinal transition state **2.10a** would minimise the charge separation in the intermediate **A** formed in the reaction (Figure 2.1). The synclinal orientation also allows a secondary orbital interaction between the HOMO of the allyl group and the LUMO of the complexed aldehyde, which is absent in the antiperiplanar orientation (Figure 2.1).[117]

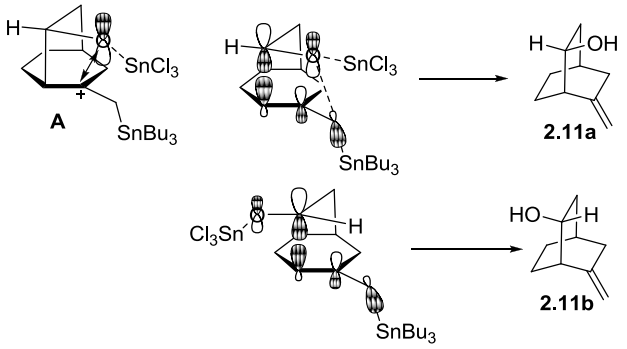
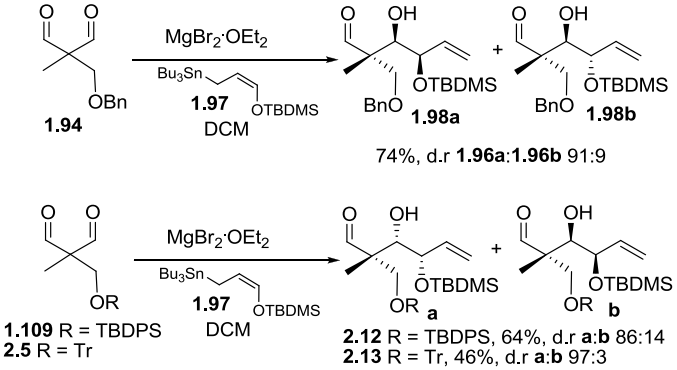


Figure 2.1. Secondary orbital overlap showing preference for synclinal approach.

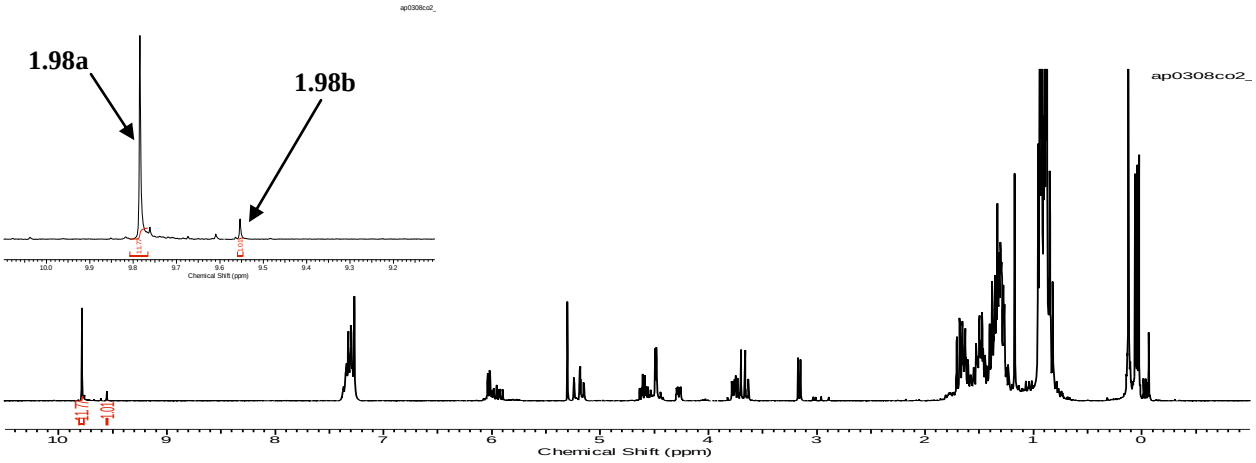
2.2.2 Previous work within the group

Previous work within the Linclau group has shown that non enolisable 1,3-dialdehydes will react cleanly under $MgBr_2 \bullet OEt_2$ activation. Dialdehydes **1.94**, **1.109** and **2.5** will undergo a hydroxyallylation reaction with the achiral γ-siloxy allylstannane **1.97** (Scheme 2.4).[109]

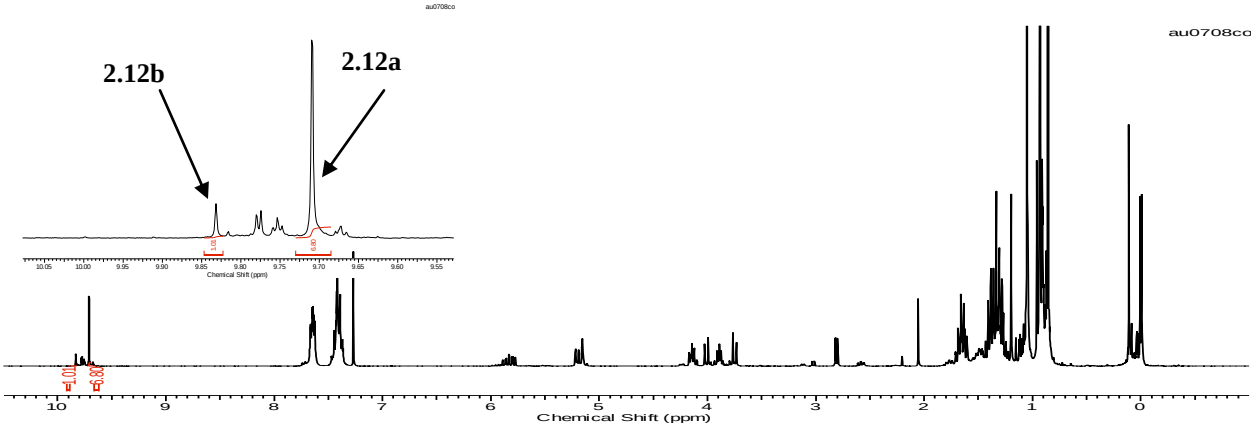


Scheme 2.4. Hydroxyallylation of dialdehydes **1.94**, **1.109** and **2.5**.

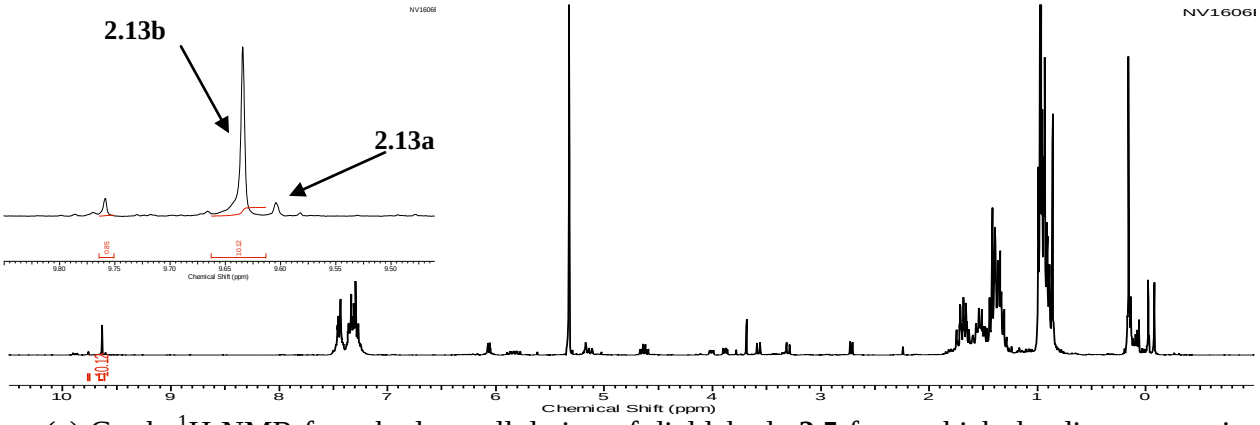
The d.r from the hydroxyallylation reactions were calculated from integration of the aldehydic peaks of the crude ^{1}H NMR spectra (Figure 2.2). For the hydroxyallylation reaction of benzyloxy dialdehyde **1.94** it was observed that the aldehydic peak for the major diastereoisomer was downfield and the minor upfield in the ^{1}H NMR spectrum. The opposite was observed for the hydroxyallylation of siloxy dialdehyde **1.109** and trityl ether dialdehyde **2.5**. It was therefore suspected that the hydroxyallylation of dialdehyde **1.94** displays the opposite diastereoselection to the hydroxyallylation of dialdehydes **1.109** and **2.5**.[109]



(a) Crude ^{1}H NMR from hydroxyallylation of dialdehyde **1.94** from which the diastereomeric ratio is calculated.



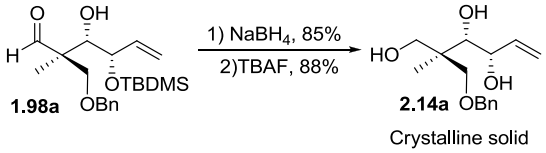
(b) Crude ^{1}H NMR from hydroxyallylation of dialdehyde **1.109** from which the diastereomeric ratio is calculated.



(c) Crude ^{1}H NMR from hydroxyallylation of dialdehyde **2.5** from which the diastereomeric ratio is calculated.

Figure 2.2. Crude ^{1}H NMR's from hydroxyallylation of **1.94**, **1.109** and **2.5**, from which the d.r was calculated.

The relative stereochemistry of **1.98a**, the major diastereoisomer from the hydroxyallylation of dialdehyde **1.94** had been identified by X-ray crystallography.[109] Major and minor diastereoisomer **1.98a** and **1.98b** were separated by preparative HPLC, followed by $NaBH_4$ mediated reduction of **1.98a** and desilylation formed triol **2.14a**, which was a crystalline solid (Scheme 2.5). X-ray crystallography showed that major diastereoisomer **1.98a** displayed a *syn* relationship between the hydroxyl and siloxy groups, which is expected from hydroxyallylation reactions,[115] and an *anti* relationship between the larger pendant benzyloxy group on the quaternary centre and the hydroxyl group (Figure 2.3).



Scheme 2.5. Reduction and desilylation of **1.98a**.

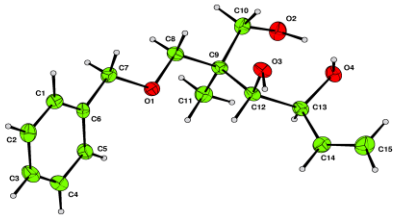


Figure 2.3. X-Ray structure of **2.14a.**

Unfortunately neither the equivalent triol of minor diastereoisomer **1.98b**, nor the products of the hydroxyallylation reactions on dialdehydes **1.109** and **2.5**, were crystalline. Therefore the relative stereochemistry of **1.98b** and **2.12a** and **b** and **2.13a** and **b** could not be identified by this method.[109]

2.2.3 Results of optimisation of hydroxyallylation reaction on dialdehyde 2.5

The hydroxyallylation reactions on dialdehydes **1.94** and **1.109** had been optimised to proceed in good yields and good to excellent diastereoselectivities (Scheme 2.4). However the hydroxyallylation reaction on dialdehyde **2.5**, despite showing excellent diastereoselectivity (d.r, 97:3), proceeded in poor yields (46%).[109] Work was carried out to improve the yield of the hydroxyallylation of **2.5**. The results of these investigations are summarised in Table 2.1.

Table 2.1. Summary of development work on hydroxyallylation of dialdehyde **2.5**.

Entry	Scale (mmol)	Time (min)	Temp. (°C)	% Yield [a]	d.r [b]
1[109]	0.70	180	–25	46	97:3
2	2.51	180	–25	27	93:7
3	2.51	180	–30	57	97:3
4	3.63	210	–30	64	95:5

[a] – Isolated yield of **2.13** after column chromatography.

[b] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude from the hydroxyallylation reaction.

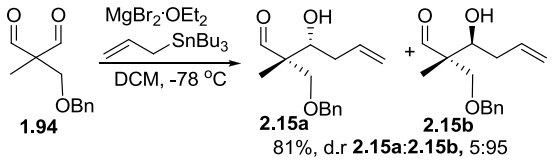
In entries 1 and 2 the hydroxyallylation reaction was carried out at –25 °C for 3 h. Despite giving an excellent d.r, the yield of **2.13** was poor. This could be attributed to the higher temperature the reaction was carried out at. Due to the low nucleophilicity of siloxyallylstannanes, the Lewis acid promoted hydroxyallylation reaction must be carried out at higher temperatures than analogous reactions with more nucleophilic reagents, such as allyl tributylstannane. The higher temperature allows Lewis acid mediated cleavage of certain acid sensitive groups, which can compete with the desired addition process and lead to a complex mixture of side products.[113] In entry 3 the hydroxyallylation of **2.5** was carried out at –30 °C for 3 h; this led to an increase in yield (57%). In entry 4 the reaction was left longer, 3 h 30 min at –30 °C. This led to the best observed results, 64% yield and d.r 95:5.

2.3 Allylation reactions

Allylation of aldehydes with allyltributylstannanes is widely reported in the literature.[67, 68, 73, 113, 118-120] These allylations are often promoted by a Lewis acid, with the reaction occurring by addition to a Lewis acid – aldehyde complex *via* an acyclic transition state.[118] $MgBr_2 \bullet OEt_2$[113] and $MgI_2 \bullet OEt_2$[120] have been shown to be effective Lewis acids in the promotion of the allylation of a wide range of aldehydes with allyl tributylstannane under mild conditions (Scheme 1.15).[68]

2.3.1 Previous work within the group

Previous work within the Linclau group has shown that non enolisable 1,3-dialdehydes will react cleanly under $MgBr_2 \bullet OEt_2$ activation. Dialdehyde **1.94** will react with the achiral allyl tributylstannane (Scheme 2.6).

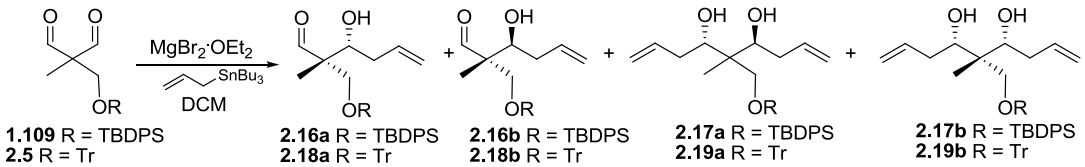


Scheme 2.6. Allylation of dialdehyde **1.94**.

By carrying out the reaction in dilute conditions (59 mL $mmol^{-1}$) and having an excess of dialdehyde **1.94**, the reaction can be controlled to give only monoaddition, yielding **2.15**, which contains two contiguous stereocentres, in good yields and excellent diastereoselectivity.[109] The prochiral centre of **1.94** is transformed into an *all-C* quaternary centre.

2.3.2 Results - Allylation of dialdehydes 1.109 and 2.5

The allylation of dialdehydes **1.109** and **2.5** (Scheme 2.7) were initially attempted with the same conditions used for the allylation of dialdehyde **1.94** (–78 °C, 0.75 equiv. allyl tributylstannane). In the case of dialdehyde **2.5** the allylation was low yielding (40%) and with dialdehyde **1.109** no reaction occurred. Investigations were carried out into the development and optimisation of the allylation of dialdehydes **1.109** and **2.5**, the results of which are summarised in Table 2.2.



Scheme 2.7. Allylation of dialdehydes **1.109** and **2.5**.

Table 2.2. Development work on allylations of dialdehydes **1.109** and **2.5**.

Entry	SM	Scale (mmol)	Equiv. allyltin	Dilution (mL mmol^{-1})	Time (min)	Temp. (°C)	Yield of mono addition product [a] (%)	Yield of double addition product [a] (%)	d.r [b] a:b
1	**1.94**	0.97	0.75	39	2	–78	81 (**2.15**)	-	5:95
2	**1.109**	1.13	0.75	67	30	–78	-	-	-
3	**1.109**	1.13	1	67	180	–78	-	-	-
4	**1.109**	1.36	1	61	180	–78 –[c]	61 (**2.16**)	17 (**2.17**)	72:28
5	**1.109**	1.20	0.90	60	180	–78- –50	31 (**2.16**)[d]	-	70:30
6	**1.109**	1.07	1	60	120	–25	77 (**2.16**)	1 (**2.17**)	72:28
7	**2.5**	1.39	1	61	180	–78	40 (**2.18**)	-	84:16
8	**2.5**	1.41	1	60	120	–25	53 (**2.18**)	-	92:8

[a] – Isolated yield after column chromatography.

[b] – For the monoaddition products, calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude from the hydroxyallylation reaction (see chapter 7, Figure 7.1, 7.2 and 7.3).

[c] – Reaction stirred for 150 min at –78 °C then removed from the ice bath and allowed to warm for 30 min.

[d] – 21% recovery of starting dialdehyde **1.109**.

The mono allylation reaction on dialdehyde **1.109** (entry 2) using similar conditions to the allylation conditions of dialdehyde **1.94** (entry 1) was unsuccessful and gave a complex mixture of products. When the allylation reaction was attempted on dialdehyde **2.5** (entry 7), with 1 equiv. of allyltributylstannane and allowed to react for longer, it gave 40% mono allylated aldehyde **2.18** as product. However when the same conditions were attempted with dialdehyde **1.109** (entry 3) no reaction was observed. By looking at the more developed hydroxyallylation reactions as analogous to the allylation reactions, it can be seen that the hydroxyallylation reactions on dialdehydes **1.109** and **2.5** occur at a slower rate and are lower yielding than the hydroxyallylation reaction of dialdehyde **1.94**. This suggests that the reactive complex that forms between dialdehydes **1.109** and **2.5** and $MgBr_2 \bullet OEt_2$ is less reactive than the reactive complex that forms between dialdehyde **1.94** and $MgBr_2 \bullet OEt_2$. Therefore attempting the allylation of **1.109** and **2.5** at a higher temperature than the allylation of **1.94** may lead to a more successful reaction. In entry 4, allyl tributylstannane was added to dialdehyde **1.109** at –78 °C and stirred for 2 h 30 min, after which no reaction

was apparent by TLC. The reaction was then removed from the ice bath and allowed to warm for 30 min. By TLC it appeared to have gone to completion giving a 61% isolated yield of **2.16**; however the d.r was poor (72:28), it was thought that this could be attributed to the rate at which the reaction was warmed. Double addition product **2.17** was also isolated in 17% yield. In entry 5 the reaction was warmed in a more controlled fashion; allyl tributylstannane was added to **1.109** at –78 °C and stirred for 30 min. The reaction was then allowed to warm to –50 °C over 2 h 30 min. This gave a poorer yield (31%) of **2.16** with a 21% recovery of starting material and no improvement in d.r. The poor yield can be attributed to the reaction not going to completion. The poor d.r could be expected as the d.r for the analogous hydroxyallylation of dialdehyde **1.109** is only 86:14. Allyl tributylstannane is smaller than the hydroxyallylating reagent **1.97** and can therefore be expected to display reduced facial selectivity, possibly explaining the poorer d.r. In entry 6 the allylation of **1.109** was attempted at –25 °C with 1 equiv. of allyl tributylstannane and allowed to react for 2 h. This yielded 77% **2.16** with a d.r of 72:28; only a trace amount of double addition product **2.17** was observed.

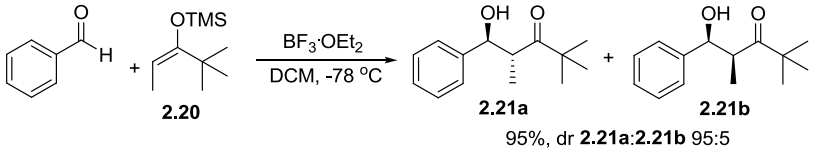
Following the optimisation of the allylation of dialdehyde **1.109**, the allylation of dialdehyde **2.5** was attempted using the optimum conditions found (entry 8). This yielded 53% of **2.18** with excellent diastereoselectivity (d.r 92:8). These results of a lower yield and improved diastereoselectivity for allylations to **2.5** compared with **1.109** are analogous to the hydroxyallylation results.

2.4 Mukaiyama Aldol reactions

2.4.1 Introduction

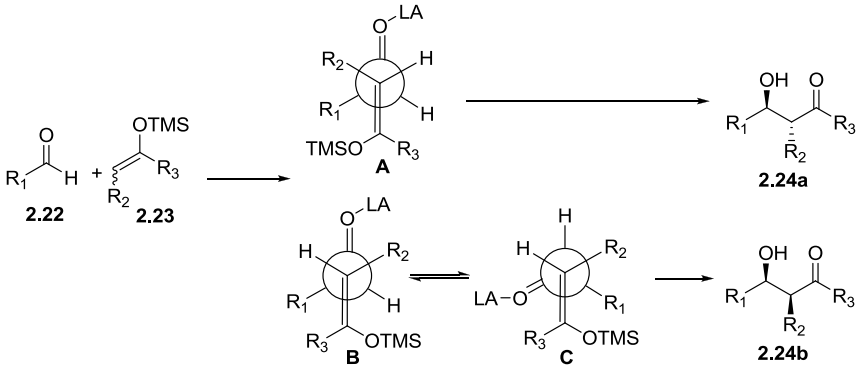
Mukaiyama *et. al.* developed an aldol reaction between silyl enol ethers and aldehydes and ketones in the presence of Lewis acids (Scheme 2.8).[121] Mixed aldol reactions can afford a mixture of self- and cross-addition products. However it was found that the Mukaiyama aldol reaction is selective for cross-aldol addition type products in good yields. The Mukaiyama aldol reaction was initially developed using $TiCl_4$ as the Lewis acid activating

the carbonyl,[121] however it has been found to be effective with a wide range of Lewis acids.[122]



Scheme 2.8. Mukaiyama aldol reaction on benzaldehyde in good yields and d.r.[123]

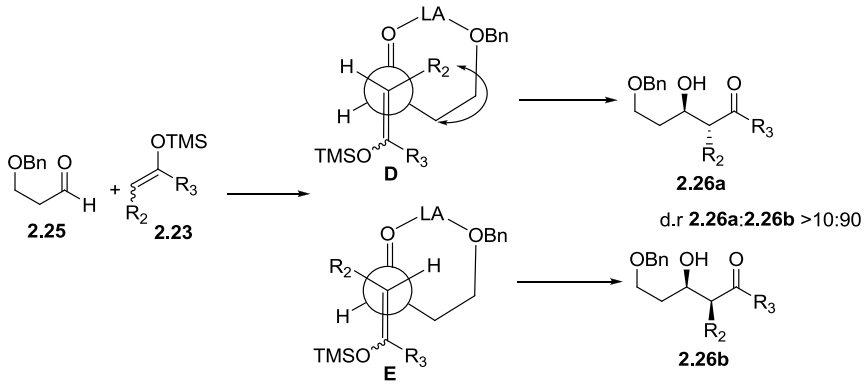
In the Mukaiyama aldol reaction, the Lewis acid coordinates to the carbonyl oxygen leading to its activation, no transmetallation occurs in the reaction. Therefore it is widely believed that the Mukaiyama aldol reaction occurs *via* an open or extended transition state. This leads to the best agreement with the observed stereochemical results.[124, 125] The proposed open transition state model assumes that the uncomplexed oxygens are as remote as possible to minimise dipolar repulsion; steric repulsive interactions of the substituents are also minimised (Scheme 2.9).



Scheme 2.9. Mukaiyama aldol transition states.

Good *anti* selectivity (**2.24a**) was observed independently of the double bond geometry when R_2 was small and R_3 was a sterically bulky group; therefore favouring transition state **A** over **B** and **C**.[123, 126-128] When R_2 is a large bulky group the transition state **B** is favoured, leading to predominantly *syn* diastereoselection.[129]

By using aldehydes capable of chelation such as **2.25** and polydentate Lewis acids, a reversal of the high levels of *anti* diastereoselection was found and high levels of *syn* selectivity were observed (Scheme 2.10).[62]

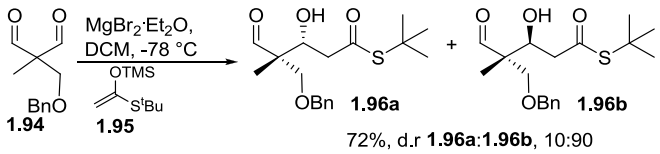


Scheme 2.10. Mukaiyama aldol reaction under chelation control leading to *syn* products.

As a result of chelation, in transition state **D** there is a repulsive steric interaction between R_2 and the side chain of the aldehyde, leading to *anti* product **2.26a** being disfavoured. Transition state **E** relieves this steric interaction, leading to the observed preference for the *syn* diastereoisomer **2.26b**. In all cases this *syn* preference was independent of the geometry of the enol silane.[62]

2.4.2 Previous work within the group

Previous work within the Linclau group has shown that non enolisable 1,3-dialdehyde **1.94** will react with the achiral silyl thioester enolate **1.95** in good yields and d.r in the Mukaiyama aldol reaction (Scheme 2.11).



Scheme 2.11. Mukaiyama aldol reaction on dialdehyde **1.94**.

By carrying out the reaction in dilute conditions (19 mL $mmol^{-1}$) and having an excess of dialdehyde **1.94** the reaction can be controlled to give only monoaddition, yielding **1.96**, which contains two contiguous stereocentres, in good yields and excellent diastereoselectivity.[109] The prochiral centre of **1.94** is transformed into an *all-C* quaternary centre.

The d.r of the allylation was calculated from the integration of the aldehydic peaks in the ^{1}H NMR (Figure 2.4).

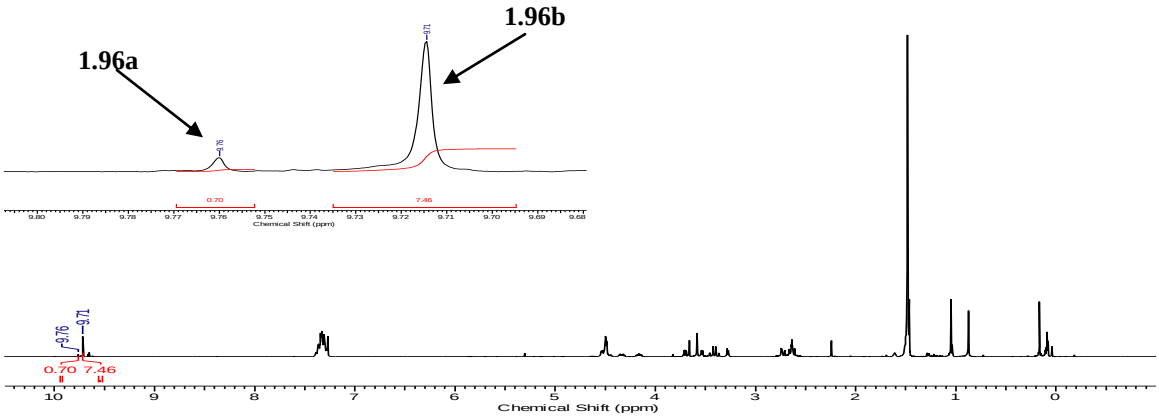
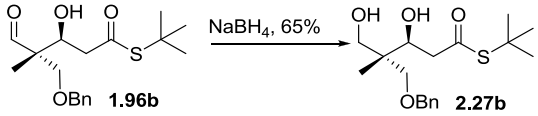


Figure 2.4. Crude ^{1}H NMR from allylation of dialdehyde **1.94**.

The relative stereochemistry of **1.96b**, the major diastereoisomer from the Mukaiyama aldol reaction of dialdehyde **1.94**, has been identified by X-ray crystallography. Major and minor diastereoisomers **1.96b** and **1.96a** were separated by preparative HPLC. Major diastereoisomer **1.96b** was reduced with $NaBH_4$ to form diol **2.27b**, which was a crystalline solid (Scheme 2.12, Figure 2.5).[109]



Scheme 2.12. Reduction and desilylation of **1.96b**.

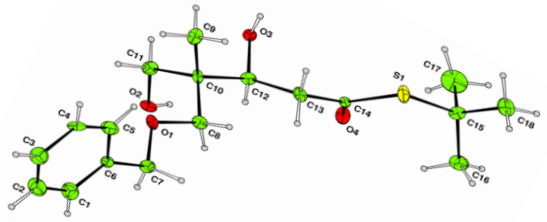
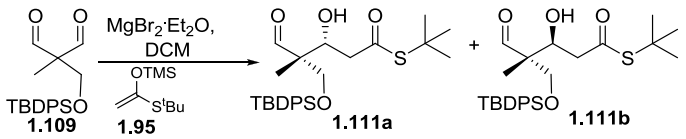


Figure 2.5. X-Ray structure of **2.27b**.

2.4.3 Results - Mukaiyama Aldol reaction of TBDPS dialdehyde 1.109

The diastereoselective Mukaiyama aldol reaction of **1.109** was attempted and optimised (Scheme 2.13). A summary of the Mukaiyama aldol reactions of dialdehyde **1.109** are shown in Table 2.3.



Scheme 2.13. Diastereoselective Mukaiyama aldol reaction of **1.109**.

Table 2.3. Summary of Mukaiyama aldol reactions on dialdehyde **1.109**.

Entry	Equiv. $MgBr_2$•OEt_2	Equiv. 1.109	Temp. (°C)[a]	Time (min)	% Yield [b]	d.r [c]
1	3	1	–78	360	-	-
2	0	1	–25	120	-	-
3	4.5	1.5	–45	90	47	72:28
4	3	1	–25	120	50	70:30
5	3	1	–45	180	50	75:25
6	1	1	–45	180	51	67:33
7	3	1	–25	90	52	70:30
8	3	1	–25	60	52	72:28
9	1	1	–20	120	53	68:32

[a] – Reagents added at –78 °C and then warmed to the temperature given.

[b] – Isolated yield of **1.111** after column chromatography.

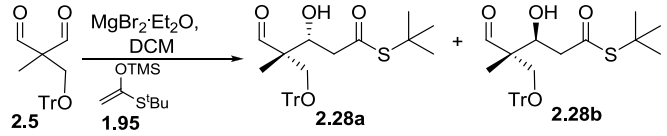
[c] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude (Figure 7.4).

In entry 1 the Mukaiyama aldol reaction of **1.109** was attempted with the same conditions as were successful with the Mukaiyama aldol reaction of **1.94**. This gave no reaction. This is unsurprising as the allylation reaction which is successful with dialdehyde **1.94** at –78 °C is unsuccessful with dialdehyde **1.109**; however the allylation reaction of **1.109** is successful at –25 °C. When the Mukaiyama aldol reaction on **1.109** was attempted at –25 °C (entries 4, 7 and 8) it was successful in reasonable yields but poor d.r's. In entries 3 and 5 the reaction was attempted at –45 °C, this led to a slight improvement in the d.r (75:25 in entry 5) however not significantly. In entries 6 and 9 it was shown that the Mukaiyama aldol reaction of dialdehyde **1.109** occurred with only slightly reduced d.r's (68:32) and no effect on yield when 1 equiv. of $MgBr_2$•OEt_2 was used rather than the usual 3 equiv. In entry 2 the Mukaiyama reaction of dialdehyde **1.109** was attempted with no $MgBr_2$•OEt_2. This gave no reaction, so showing the need for the Lewis acid in the reaction to activate the dialdehyde.

From these results it was found that the optimum conditions to carry out the Mukaiyama aldol reaction on dialdehyde **1.109** were using 3 equiv. of $MgBr_2 \bullet OEt_2$, 1 equiv. of dialdehyde **1.109** and 1 equiv. of silyl enol ether **1.95** at –25 °C (Table 2.3, entry 8).

2.4.4 Results - Mukaiyama Aldol reaction of trityl dialdehyde 2.5

Work has been carried out towards the Mukaiyama aldol reaction of trityl ether dialdehyde **2.5** with silyl enol ether **1.95** (Scheme 2.14). The results are summarised in Table 2.4.



Scheme 2.14. Mukaiyama aldol reaction of **2.5**.

Table 2.4. Summary of Mukaiyama aldol reactions on dialdehyde **2.5**.

Entry	Equiv. 1.95	Temp. (°C) [a]	% Yield [b]	d.r [c] 2.28a:2.28b
1	1	–55	0	-
2	1	–40	25	87:13
3	1.5	–25	57	70:30
4	1.5	–40	52	90:10

[a] – Reagents added at –78 °C and then warmed to the temperature given.

[b] – Isolated yield after column chromatography.

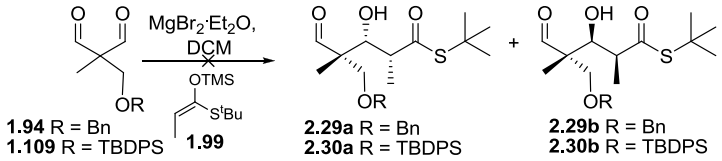
[c] – Calculated from the integration of the aldehyde peaks on the ^1H NMR of the crude (Figure 7.5).

In entry 1 the Mukaiyama aldol reaction on **2.5** was attempted at –55 °C, this gave no reaction. It had been shown that the Mukaiyama aldol reaction of **1.109** (Scheme 2.13) required temperatures above –40 °C for a reaction. In entry 2 the Mukaiyama aldol reaction of **2.5** was attempted at –40 °C, this successfully formed **2.28** in reasonable d.r (87:13) but poor yield (25%). In entry 3 the reaction was attempted with an increase of silyl enol ether **1.95**, 1.5 equiv., and at –25 °C. This gave an improved yield of 57% but a decrease in d.r, 70:30 due to the higher temperature. Entry 4 shows that when the reaction was carried out at

a lower temperature (–40 °C) with 1.5 equiv. of **1.95** the yield is reasonable (52%) and the d.r is good (90:10).

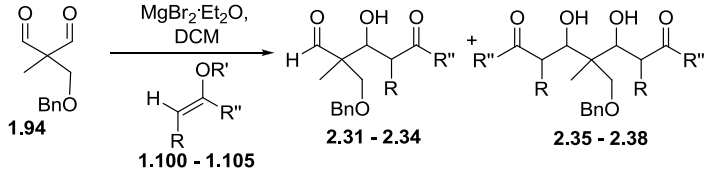
2.5 Screen of aldol reactions

The hydroxyallylation reaction has been achieved, reacting allylstannane **1.97** with dialdehyde **1.94**, **1.109** and **2.5** to give products containing three contiguous stereocentres, including an *all-C* quaternary centre. It was hoped the use of substituted silyl enol ether **1.99**, to further develop the Mukaiyama aldol reaction on our 1,3-dialdehydes, would form products with a greater degree of stereocomplexity (three contiguous stereocentres). However when this was attempted on dialdehydes **1.94 a**nd **1.109** no reaction was observed (Scheme 2.15). It is believed that because of the extra steric bulk of the added substitution of silyl enol ether **1.99**, a silyl enol ether is not reactive enough to form **2.29** or **2.30**.



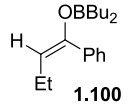
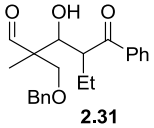
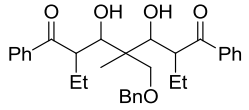
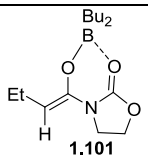
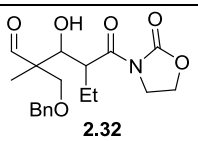
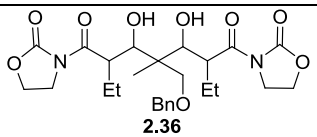
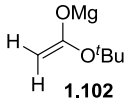
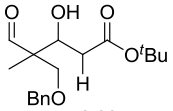
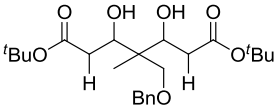
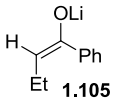
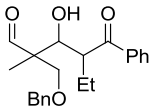
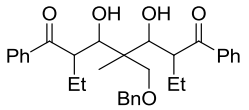
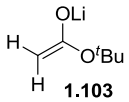
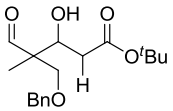
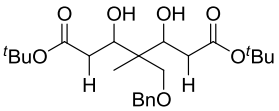
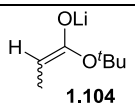
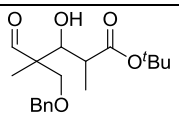
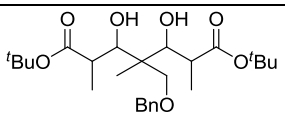
Scheme 2.15. Attempted Mukaiyama aldol reaction with substituted silyl enol ether **1.99**.

It was therefore decided to investigate different metal enolates in aldol reactions on dialdehyde **1.94** (Scheme 2.16). The results of these investigations are summarised in Table 2.5.



Scheme 2.16. Attempted aldol reactions on dialdehyde **1.94**.

Table 2.5. Summary of aldol reactions on dialdehyde **1.94**.

Entry	Enolate [a]	Mono-addition product	Double addition Product	Yield[b]	d.r[c]
1	 **1.100**	 **2.31**	 **2.35**	-	-
2	 **1.101**	 **2.32**	 **2.36**	-	-
3	 **1.102**	 **2.33**	 **2.37**	-	-
4	 **1.105**	 **2.31**	 **2.35**	-	-
5	 **1.103**	 **2.33**	 **2.37**	46% (**2.33**) 26% (**2.37**)	83:17 95:5[d]
6	 **1.104**	 **2.34**	 **2.38**	39% (**2.34**) 7% (**2.38**)	44:30:20:6 -

[a] – 1.5 equiv. of enolate, except **1.102** which was 1.2 equiv.

[b] – Isolated yield after column chromatography.

[c] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude (Figures 7.6 and 7.8).

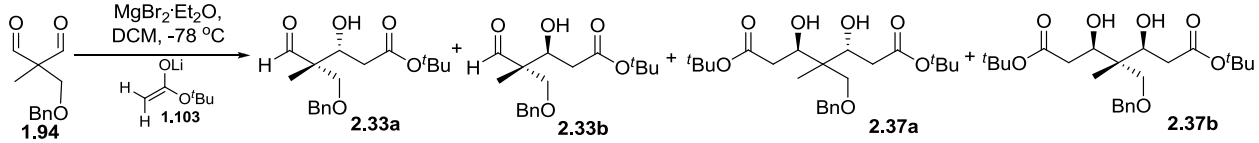
[d] – Calculated from the integration of the Me peaks on the ^{1}H NMR of the isolated **2.37** after column chromatography (Figure 7.7).

We believe that our Mukaiyama aldol reactions, where the dialdehyde is activated with $MgBr_2 \bullet OEt_2$, occur *via* an acyclic transition state. Literature precedents that boron enolates will react *via* a cyclic transition state,[130] however Heathcock *et. al.* have shown that a boron

enolate of an oxazolidinone can react *via* an acyclic transition state.[131] Therefore in entry 1 the aldol reaction of **1.94** was attempted with boron enolate **1.100**; this gave no reaction. It was thought that this is because boron enolates require more than one chelate to react.[131] In view of this, the aldol reaction of **1.94** was attempted with boron enolate **1.101** that contains an oxazolidinone (entry 2). This also gave no reaction. It was thought that these reactions could be failing due to complications with having a 'mixed metal' reaction which could disturb the dialdehyde $MgBr_2 \bullet OEt_2$ chelate. Heathcock's acyclic boron enolate aldol reactions used BBu_2OTf as the Lewis acid promoter.[131] Aldol reactions using Mg enolates have been reported,[132] however when the aldol reaction of **1.94** was attempted using Mg enolate **1.102** the reaction also failed (entry 3). In entry 4 the aldol reaction was attempted with the more reactive Li enolate **1.105**. This reaction also failed; this could be due to the terminal substitution or that an aryl Li enolate is not reactive enough. In entry 5 the aldol reaction was attempted with the more reactive unsubstituted terminal Li ester enolate **1.103**. This reaction was successful giving 46% of the mono addition product **2.33** and 26% of the double addition product **2.37** in good d.r's. To achieve the extra substitution in the aldol reactions of dialdehyde **1.94**, substituted Li ester enolate **1.104** was employed (entry 6). This yielded 39% of **2.34** in a poor d.r.

2.5.1 Optimisation of aldol reaction with Li ester enolate 1.103

Optimisation work has been carried out on improving the yield and d.r. of the aldol reaction between dialdehyde **1.94** and Li ester enolate **1.103** (Table 2.5, entry 5; scheme 2.17). Results of this work are summarised in Table 2.6.



Scheme 2.17. Aldol reaction with Li ester enolate **1.103**.

Table 2.6. Summary of aldol reactions between **1.94** and **1.103**.

Entry	Scale (mmol 1.94)	Temp. (°C)	Dilution (ml $mmol^{-1}$)	Time (min)	Equiv. 1.103	Yield [a] (2.33)	Yield [a] (2.37)	d.r [b] 2.33a:b	d.r [c] 2.37a:b
1	0.57	–78	10.5	180	1.5	46	26	17:83	95:5
2	0.97	–78	20.6	210	1.5	31	28	23:77	97:3
3	0.97	–78	10.3	10	1.5	29	17	17:83	98:2
4	0.97	–78	10.3	60	1	20	16	17:83	95:5
5	0.97	–78	14.4	30	0.75	31[d]	20[d] 38[e]	23:77	99:1
6	0.97	–83	10.3	120	1.5	28	17	19:81	96:4
7	3.80	–78	10.5	90	1.5	38	34	22:78	96:4

[a] – Isolated yield after column chromatography.

[b] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude (Figure 7.6).

[c] – Calculated from the integration of the Me peaks on the ^{1}H NMR of the isolated **2.37** after column (Figure 7.7)

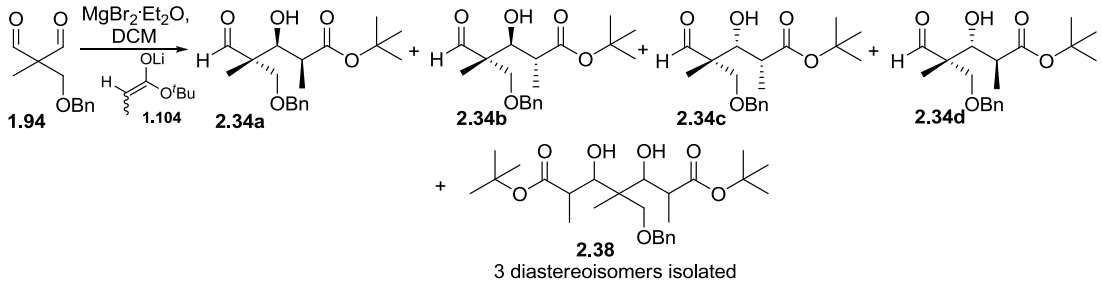
[d]– Yield of enolate to products (enolate limiting reagent)

[e]– Yield of enolate to product (2 enolate equiv. to 1 product)

Much of the development of the aldol reaction between **1.94** and **1.103** focussed on limiting the formation of double addition product **2.37**. In entry 2 the reaction was carried out in more dilute conditions in an attempt to reduce the yield of double addition product **2.37**. This was unsuccessful and appeared to have a detrimental effect on the overall yield of the reaction. It also appeared that more dilute conditions had a damaging effect on the diastereoselectivity of the reaction (entries 2 and 5). In entry 3 the reaction time was reduced to just 10 min, this did lower the yield of **2.37**; however the yield of monoaddition product **2.33** was also compromised. Lowering the equiv. of enolate **1.103** (entries 4 and 5) led to a lower overall yield for the reaction but failed to limit formation of **2.37**. In entry 6 the aldol reaction was performed at a lower temperature (–83 °C); this failed to improve the diastereoselectivity of the reaction.

2.5.2 Optimisation of aldol reaction with Li ester enolate 1.104

Optimisation work was carried out to improve the yield and d.r. of the aldol reaction between dialdehyde **1.94** and Li ester enolate **1.104** (Table 2.5, entry 6; scheme 2.18). Results of this work are summarised in Table 2.7.



Scheme 2.18. Aldol reaction with Li ester enolate **1.104**.

Table 2.7. Summary of aldol reactions between **1.94** and **1.104**.

Entry	Scale (mmol 1.94)	Temp. (°C)	Dilution (ml mmol^{-1})	Time (min)	Equiv. 1.104	Yield[a] % 2.34	Yield[a] % 2.38	d.r [b] 2.34a:b:c:d
1	2.42	–78	10.7	120	1.5	39	7	44:30:20:6
2	0.73	–25	11.0	120	1.5	28	17	21:25:30:24
3	0.73	–78	11.0	120	1.5	20	14	42:25:24:9
4	0.73	–78	11.0	120	2	26	22	30:29:29:12
5	0.97	–83	19.6	120	2	37	22	40:35:17:8
6	0.97	–78	19.6	25	2	46	21	39:26:23:11
7	4.85	–78	15.1	90	1.8	47	35	44:30:17:9
8	4.85	–78	15.1	90	1.8	56	21	51:27:13:9

[a] – Isolated yield after column chromatography.

[b] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude (Figure 7.8).

The yield and d.r of the aldol reaction to form **2.34** was initially poor (entry 1). In entry 2 the reaction was attempted at –25 °C in an attempt to improve the yield. The higher reaction temperature resulted in an increase in the yield of double addition product **2.38**, a reduction in the yield of monoaddition product **2.34** and a reduced diastereoselectivity. The number of equiv. of **1.104** were increased to two (entry 4). This resulted in an increased yield of double addition product **2.38**; however the yield of monoaddition product **2.34** remained poor. The

aldol reaction was attempted in more dilute conditions (entries 5-8); this gave an improved yield of monoaddition product **2.34**. Shorter reaction times (entries 6-8) also improved the yield of **2.34**, limiting formation of **2.38**. In entry 5 the reaction was attempted at –83 °C to improve the diastereomeric ratio. However, it appears the largest improvement in diastereoselectivity was caused by carrying out the reaction in more dilute conditions (entries 5-8). However the diastereomeric ratios of the aldol reaction between dialdehyde **1.94** and enolate **1.104** remain disappointing. The *E/Z* ratio of lithium enolate **1.104** formation from *t*-butyl propionate is known to be 95:5.[133, 134] However the *syn/anti* ratio of aldol products using Li enolate **1.104** is dependant on the aldehyde used.[134-137] Aliphatic aldehydes have been found to give better *syn/anti* ratios (5:95) than aromatic aldehydes (49:51).[137] In this context the diastereoselectivity of our aldol reaction between the Li enolate of *t*-butyl propionate **1.104** and dialdehyde **1.94** are still disappointing.

2.6 Identification of diastereoisomers from monoaddition reactions.

2.6.1 Identification of diastereoisomers from hydroxyallylation reactions

The relative stereochemistry of the major and minor diastereoisomers from the hydroxyallylation reaction on dialdehydes **1.94**, **1.109** and **2.5** have been identified by chemical correlation and X-ray crystallography.

2.6.1.1 Identification of the relative stereochemistry of 1.98b

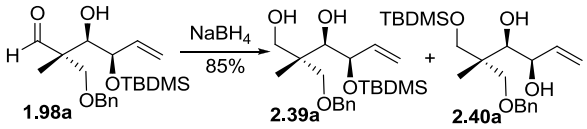
The relative configuration of the major diastereoisomer **1.98a** from the hydroxyallylation reaction was known. The reduced and desilylated product **2.14a** is crystalline and the relative stereochemistry had been determined by X-ray crystallography (Scheme 2.5).[109] However the structure of the minor diastereoisomer **1.98b** was not known and the equivalent reduced and desilylated product **2.14b** was not crystalline.[109] Therefore it was decided to investigate the relative stereochemistry of **1.98b** by chemical correlation.

It was postulated the structure of the minor diastereoisomer **1.98b** had a *syn* relationship between the hydroxyl and silyloxy groups. It was assumed that allyl stannane **1.97** showed

the opposite facial selectivity in the minor diastereoisomer, but approached the aldehyde in the same orientation to give the expected *syn* relationship that is common in hydroxyallylation reactions.[115] As shown below, removal of the stereochemistry at the quaternary centre of **1.98a** and **1.98b** should give the same compound, proving the *syn* diastereoselection in minor diastereoisomer **1.98b**.

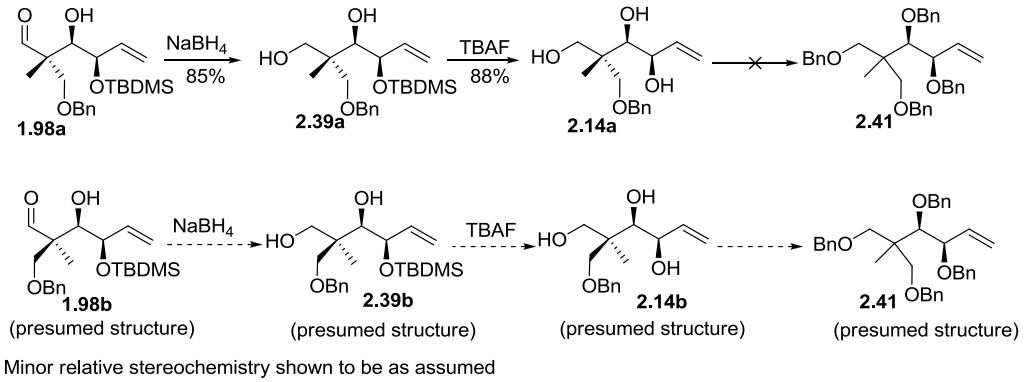
2.6.1.1.1 Per-benzylation

Reduction of **1.98** by $NaBH_4$ results in migration of the TBDMS group to the primary alcohol to give an inseparable mixture of products **2.39** and **2.40** (Scheme 2.19). [109]



Scheme 2.19. Migration of TBDMS group in $NaBH_4$ reduction.

For characterisation purposes the silyl group therefore needs to be removed using TBAF to form **2.14**. If the stereochemistry of **1.98b** is as expected, per-benzylation of **2.14a** and **2.14b** would remove the stereochemistry at the quaternary centre and should give the same compound, **2.41** (Scheme 2.20). Reduction of compound **1.98a** with $NaBH_4$ proceeded in 85% yield. Desilylation of the mixture of **2.39a** and **2.40a** with TBAF proceeded with 88% yield.



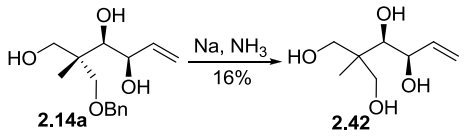
Scheme 2.20. Attempted per-benzylation of **2.14a**.

However per-benzylation using NaH / benzyl bromide or benzyl trichloroacetimidate[138] of **2.14a** failed. The ^1H NMR showed a mixture of products. The LRMS also showed a

mixture of products; however the major peak in the LRMS had a mass of 469, suggesting that two of the free hydroxyls had benzylated, but with no regioselectivity. The LRMS also showed that compound **2.41a** was not formed; this was probably due to the molecule being too sterically crowded for the third benzyl group to add. Due to these results the reduction, desilylation and perbenzylation of minor diastereoisomer **1.98b** was not attempted.

2.6.1.1.2 Birch Reduction

Removal of the benzyl group on compounds **2.14a** and **2.14b** would also remove the stereochemistry at the quaternary centre; both compounds would form tetraol **2.42** (Scheme 2.21). It was decided to do this *via* a Birch reduction[139] to maintain the double bond so the NMR would be more distinctive.

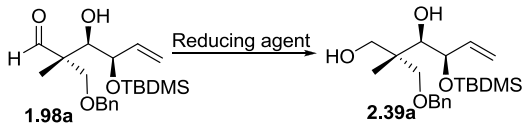


Scheme 2.21. Birch reduction of **2.14a**.

Birch reduction on **2.14a** was successful, however the yield of **2.42** was low, only 16%. In the Birch reduction there is a decrease in molecular weight of 34%; because of this, the low yield of the reaction and the small quantities of **1.98b** that were produced from each hydroxyallylation reaction, it was decided to abandon these attempts.

2.6.1.1.3 Investigation into Reduction reactions

An alternative way to remove the benzyl group would be by hydrogenolysis.[140] However because of the loss of mass in the removal of the benzyl group and the low quantities of **1.98b** it would be preferable to not remove the TBDMS group as well. In the reduction of **1.98** with $NaBH_4$, TBDMS migration is observed giving mixture of products (Scheme 2.19), which complicates the structural identification.[109] To not remove the TBDMS protecting group, a reduction reaction had to be found in which the TBDMS group did not migrate. A number of different reducing agents were screened. The results of these reduction reactions (Scheme 2.22) are summarised in Table 2.8.



Scheme 2.22. Reduction of aldehyde **1.98a**.

Table 2.8. Summary of reduction experiments.

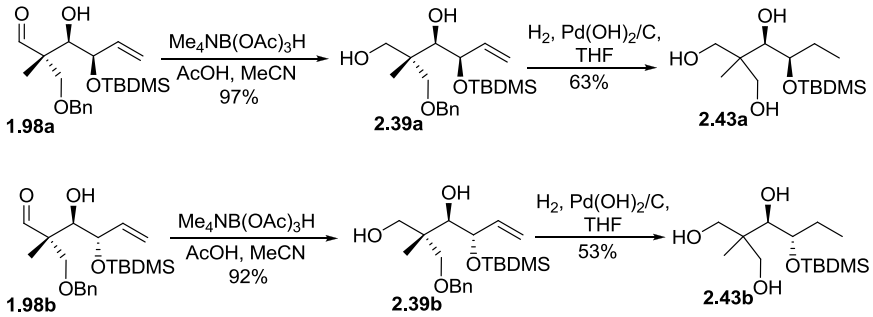
Entry	Reducing Agent	% Yield [a]	TBDMS migration
1	$NaBH_4$	85%	Yes
2	$LiAlH_4$	29%	Yes
3	BH_3	60%	No
4	$Me_4NB(OAc)_3H$	97%	No

[a] – Isolated yield of **2.39a** after column chromatography.

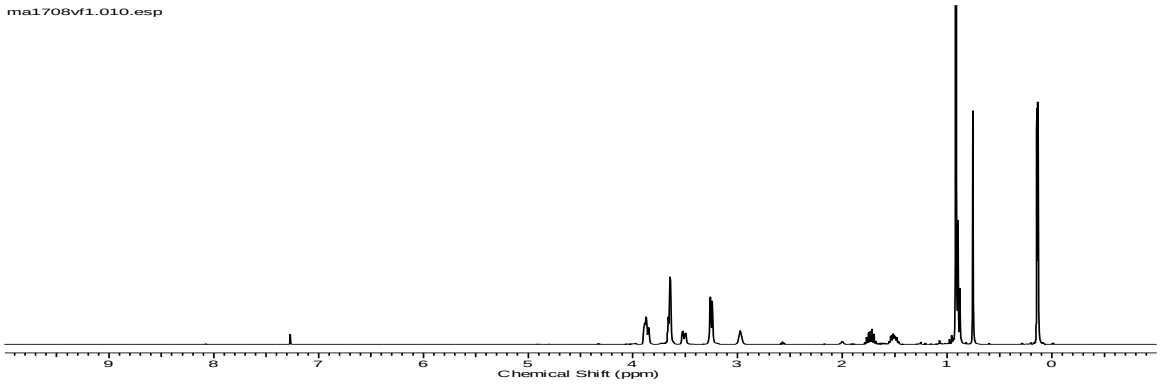
In entry 4 reduction of **1.98a** with $Me_4NB(OAc)_3H$[141] prevented migration of the TBDMS group. The isolated yield of **2.39a** was also best when using $Me_4NB(OAc)_3H$. It was therefore decided to use the $Me_4NB(OAc)_3H$ method for future reduction reactions. This allowed the allylic hydroxyl to remain protected, to give more versatility in the derivatisation of **2.39** to find the structure of the minor diastereoisomer **1.98b**.

2.6.1.1.4 Hydrogenolysis

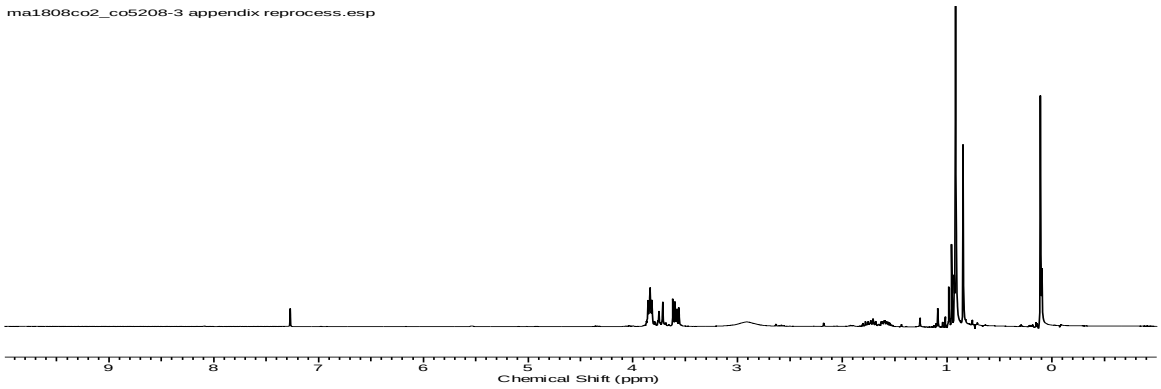
Reduction of **1.98b** with $Me_4NB(OAc)_3H$ proceeded in near quantitative yield (Scheme 2.23). Hydrogenolysis of compound **2.39a** was successful and produced triol **2.43a**. Hydrogenolysis of compound **2.39b** was also successful, however it did not produce the expected compound **2.43a** (Scheme 2.23). Much to our surprise the ^1H NMR of compounds **2.43a** and **2.43b** were different (Figure 2.6), leading to the conclusion that the siloxy and the hydroxyl groups are *anti* in compound **2.43b**, and therefore also *anti* in the minor diastereoisomer **1.98b** from the hydroxyallylation reaction.



Scheme 2.23. Hydrogenolysis of diol **2.39**.



(a) ^{1}H NMR spectrum of **2.43a**



(b) ^{1}H NMR spectrum of **2.43b**

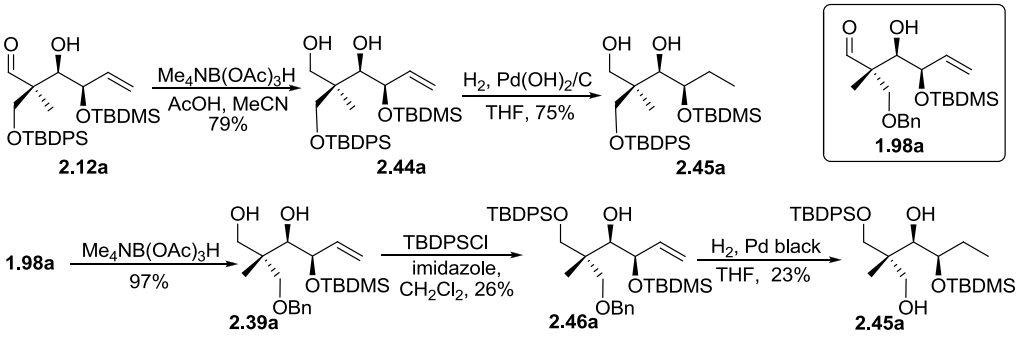
Figure 2.6. ^{1}H NMR spectra of **2.43a** and **2.43b** proving the anti relationship between the hydroxyl and siloxy groups in **1.98b**.

The relative stereochemistry of **1.98b** could only be identified at a late stage through a hydroxyallylation - Grignard addition sequence (for full details see chapter 4). It was found to be as shown (Scheme 2.23) with an *anti* relationship between the hydroxyl and larger benzyloxy group on the quaternary centre and an *anti* relationship between the hydroxyl and

siloxy group. The rationalisation for the observed stereochemistry in the hydroxyallylation of **1.94** will be fully explained in chapter 3.

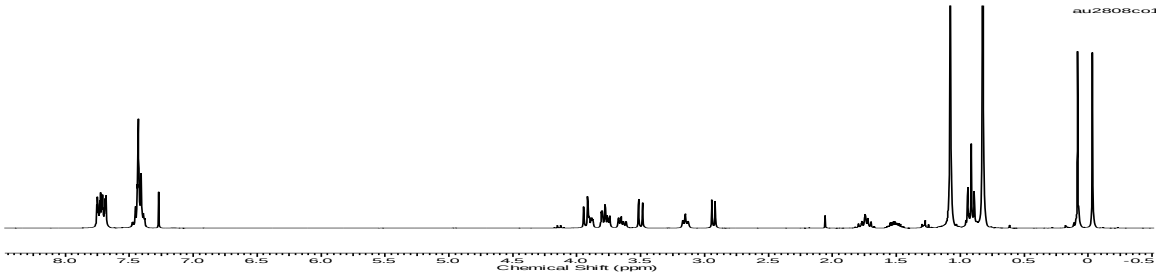
2.6.1.2 Identification of the relative stereochemistry of 2.12a

It was predicted that the hydroxyallylation reaction on dialdehyde **1.109** displayed the opposite diastereoselection to dialdehyde **1.94** (Scheme 2.4, Figure 2.2). The relative stereochemistry of **1.98a**, the major diastereoisomer from the hydroxyallylation of dialdehyde **1.94** is known. If the relative stereochemistry of **2.12a** is as expected, then reduction and hydrogenation of **2.12a** would give diol **2.45a**. Reduction, followed by TBDPS protection of the primary alcohol and hydrogenolysis of **1.98a** should also give diol **2.45a** (Scheme 2.24). Reduction of **2.12a** with $Me_4NB(OAc)_3H$[141] proceeded with 79% yield. Hydrogenation[140] of **2.44a** gave diol **2.45a** in 75% yield. Reduction of **1.98a**[141] proceeded in excellent yields to give **2.39a**. The primary alcohol was selectively protected with TBDPSCl with an unoptimised yield of 26%. Compound **2.46a** underwent hydrogenolysis[140] with Pd black to give **2.45a** (Scheme 2.24).

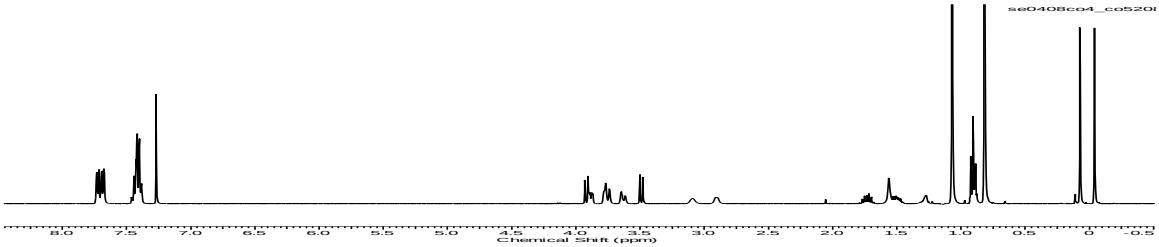


Scheme 2.24. Identification of relative stereochemistry of **2.12a**.

The ^{1}H NMR's of **2.45a** formed from the hydrogenation of **2.44a** and **2.45a** from the hydrogenolysis of **2.46a** showed formation of the same compound (Figure 2.7), proving the relative stereochemistry of **2.12a** to be as shown (Scheme 2.24).



^{1}H NMR of compound **2.45a** formed from the hydrogenation of compound **2.44a**



^{1}H NMR of compound **2.45a** formed from hydrogenolysis of compound **2.46a**

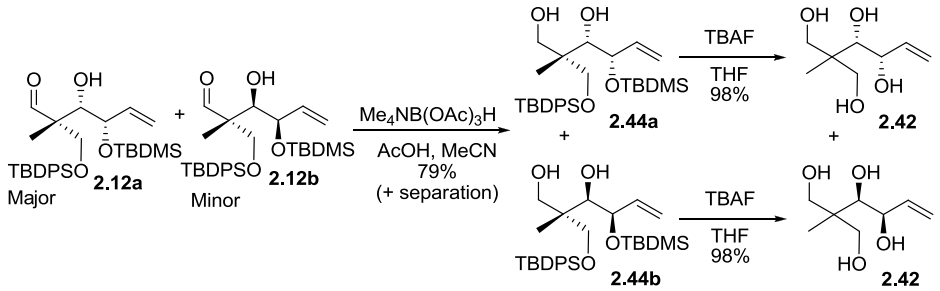
Figure 2.7. ^{1}H NMR's of compound **2.45a** formed from **2.44a** and **2.46a** respectively.

This proves that the diastereoselection of the hydroxyallylation reaction on dialdehyde **1.94** is different to the diastereoselection of the hydroxyallylation reaction on dialdehyde **1.109**. We predict that this is due to the differing transition states in the hydroxyallylation reaction of **1.94** and **1.109**. This will be rationalised and the observed diastereoselectivity explained in chapter 3.

2.6.1.3 Identification of the relative stereochemistry of 2.12b

The relative stereochemistry of minor diastereoisomer **2.12b**, from the hydroxyallylation reaction on dialdehyde **1.109**, was identified by correlation with major diastereoisomer **2.12a** whose relative stereochemistry had been established (see above). The inseparable mixture of diastereoisomers **2.12a** and **2.12b** was reduced with $Me_4NB(OAc)_3H$ to give diols **2.44a** and **2.44b** (Scheme 2.25), which were now separable by HPLC. Both diols were desilylated with TBAF, removing the stereochemistry at the quaternary centre to form **2.42**. The ^{1}H NMR's of **2.42** formed from **2.44a** and **2.44b** were identical (see chapter 7, Figure 7.9) so proving

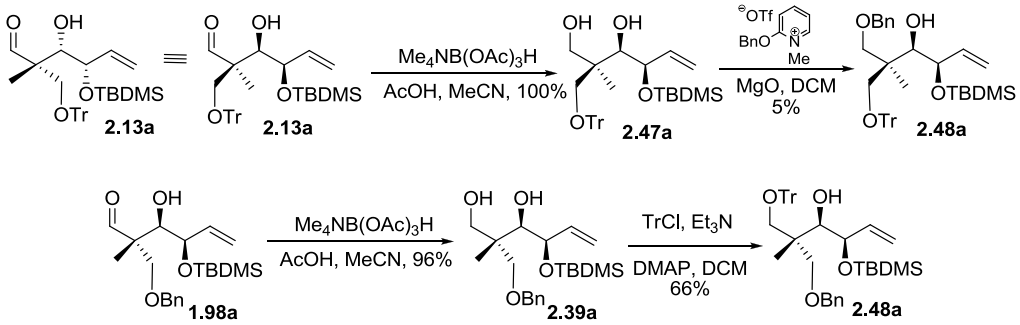
the *syn* relationship between the hydroxyl and siloxy group in **2.12b**; therefore the relative stereochemistry of **2.12b** must be as shown.



Scheme 2.25. Determination of the relative stereochemistry of minor diastereoisomer **2.12b**.

2.6.1.4 Identification of the relative stereochemistry of 2.13a

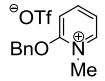
It is postulated that the diastereoselection for the hydroxyallylation reaction on dialdehyde **2.5** is the same as the known diastereoselectivity for the hydroxyallylation reaction on dialdehyde **1.109** and different to the diastereoselection for dialdehyde **1.94** (Figure 2.2, Scheme 2.4). The expected relative stereochemistry of **2.13a** (Scheme 2.4) had a *syn* relationship between the trityloxy methyl, hydroxyl and silyloxy groups. Benzylation of the primary alcohol of **2.47a** would give **2.48a**. Reduction and tritylation of **1.98a**, the relative stereochemistry of which is known, would also give **2.48a** (Scheme 2.26).



Scheme 2.26. Identification of relative stereochemistry of **2.13a**.

Reduction of **2.13a** with $Me_4NB(OAc)_3H$ proceeded with quantitative yields. A summary of the benzylation reactions carried out on compound **2.47a** is shown in Table 2.9.

Table 2.9. Summary of benzylation reactions on **2.47a**.

Entry	Reaction Conditions	Formation of 2.48a	% Yield [a]
1	BnBr, NaH, TBAI	Yes (Not isolated)	-
2	1) Bu_2SnO, 2)BnBr, TBAI[142]	No	-
3	 , MgO[143]	Yes	5% [b]

[a] – Isolated yield of **2.48a** after column chromatography.

[b] – 53% yield of recovered starting material **2.47a**.

When BnBr and NaH were used to benzylate the primary alcohol (entry 1) a mixture of products were formed. By ^{1}H NMR compound **2.48a** could be seen in this mixture, however the mixture could not be separated by column chromatography or HPLC. It is thought that the NaH deprotects both the primary and secondary alcohols of **2.47a**, allowing migration of the TBDMS group to give a small amount of deprotected allylic alcohol. The mixture of deprotected alcohols results in a mixture of benzylated products. In entry 2 benzylation of the primary alcohol of **2.47a** was attempted by making the stannylene acetal between the primary and secondary alcohols in order to protect the secondary alcohol, preventing migration of the TBDMS group. The stannylene acetal would then be opened with benzyl bromide, benzylating the primary alcohol.[142] By TLC the stannylene acetal was successfully formed *in situ;* however the ^{1}H NMR of the product after BnBr addition showed a mixture of compounds and loss of the TBDMS protecting group. In entry 3 benzylation of **2.47a** with 2-Benzyloxy-1-methylpyridinium triflate salt,[143] synthesised from 2-chloropyridine and benzyl alcohol,[144] was achieved, giving **2.48a** in 5% yield with 53% recovery of starting material **2.47a**.

Reduction of **1.98a** followed by tritylation of the primary alcohol gave **2.48a** in 66% yield. The ^{1}H NMR's of **2.48a** formed from the tritylation of **2.39a** and the benzylation of **2.47a** (Scheme 2.26) were the same (Figure 7.10), proving the relative stereochemistry of **2.13a**.

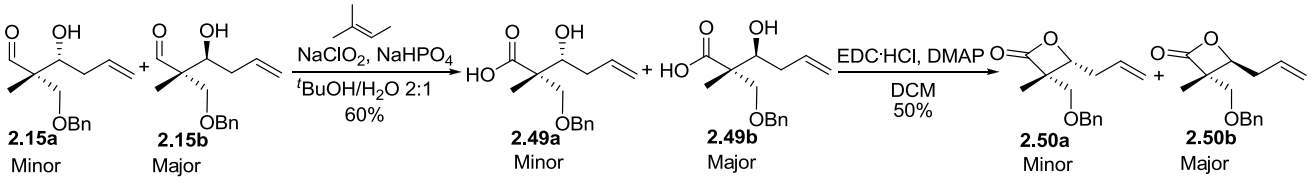
This proves that the diastereoselection of the hydroxyallylation reaction of dialdehyde **2.5** is the same as dialdehyde **1.109** and different to the diastereoselection of the hydroxyallylation reaction of dialdehyde **1.94**.

2.6.2 Identification of diastereoisomers from allylation reactions

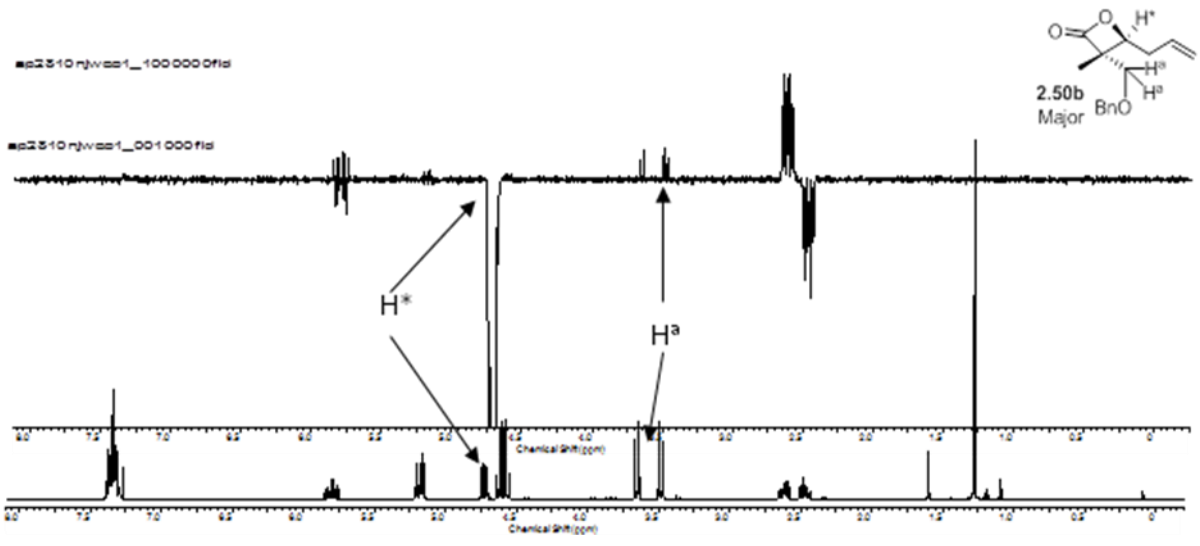
The relative stereochemistry of the major and minor diastereoisomers from the allylation reaction on dialdehydes **1.94** (Scheme 2.6), **1.109** and **2.5** (Scheme 2.7) have been identified by chemical correlation and nOe experiments.

2.6.2.1 Identification of the relative stereochemistry of 2.15a and 2.15b

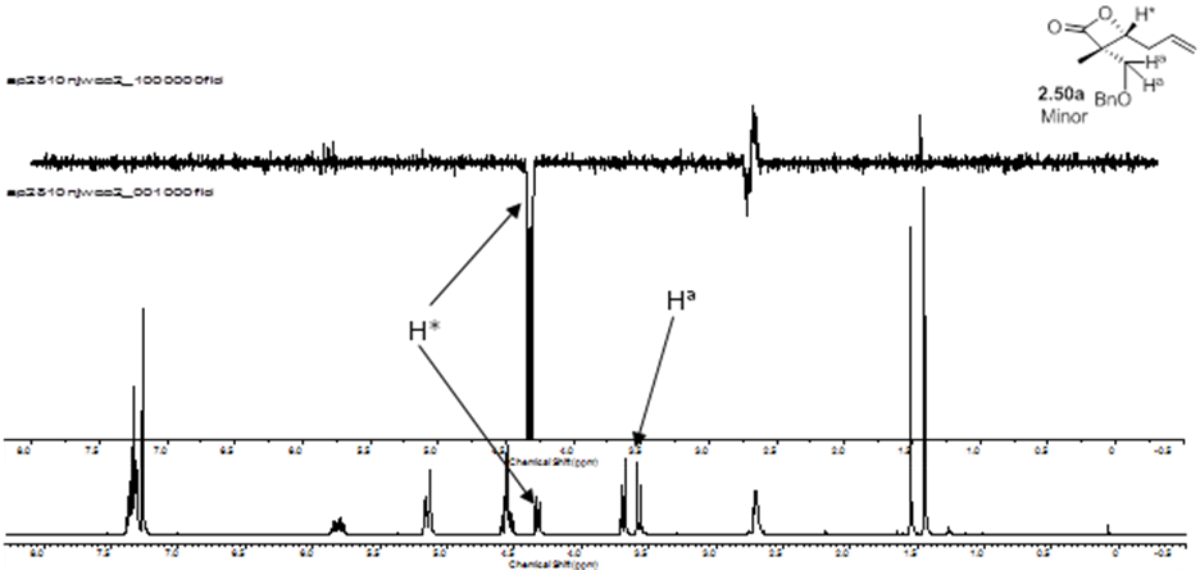
The relative stereochemistry of major and minor diastereoisomers **2.15b** and **2.15a**, from the allylation of benzyloxy dialdehyde **1.94**, were identified by oxidation of the aldehyde to the acid **2.49**, followed by cyclisation to form β-lactones **2.50b** and **2.50a** (Scheme 2.27) according to the method described by Mulzer.[145] The β-lactones were separated by HPLC and nOe experiments carried out to prove the relative stereochemistry (Figure 2.8).



Scheme 2.27. Formation of lactones **2.50a** and **2.50b**.



(a) nOe on major diastereoisomer **2.50b**



(b) nOe on minor diastereoisomer **2.50a**

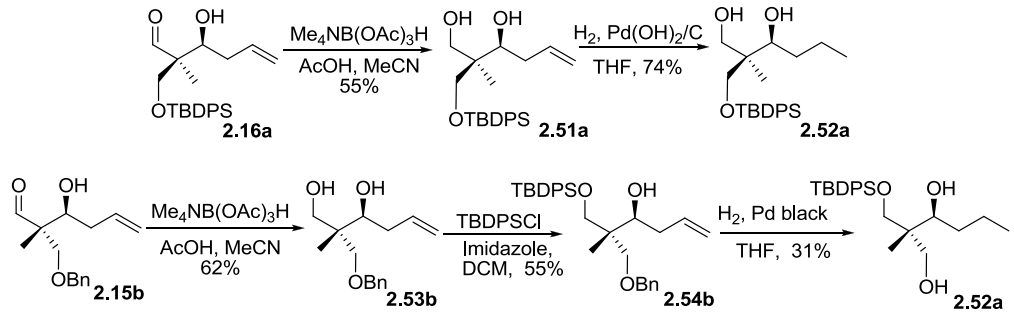
Figure 2.8. nOe experiments on **2.50b** and **2.50a** proving the relative stereochemistry of **2.15b** and **2.15a**.

From the nOe experiments on **2.50b**, when H* was irradiated a response was observed at benzylic protons H^a, proving that H* and H^a must be on the same face of the β-lactone ring. The relative stereochemistry of **2.50b** and therefore major diastereoisomer from the allylation **2.15b** must be as shown. When nOe experiments were performed on **2.50a**, no response was observed at benzylic protons H^a when H* was irradiated; however a nOe was observed between H* and the methyl protons. H* and H^a must be on opposite faces of the β-lactone ring and the relative stereochemistry of **2.50a** and therefore **2.15a**, the minor diastereoisomer from the allylation reaction, must be as shown.

2.6.2.2 Identification of the relative stereochemistry of 2.16a

The relative stereochemistry of major diastereoisomer **2.16a** was identified by correlation with major diastereoisomer **2.15b**, whose relative stereochemistry had been unambiguously identified by ^{1}H NMR nOe experiments (see above). This was achieved by reducing **2.16a** to form **2.51a**, followed by hydrogenation of the double bond to give **2.52a**. The major diastereoisomer **2.15b** was reduced to give **2.53b** and the primary alcohol was protected with

a TBDPS group to form **2.54b**. This was subjected to hydrogenolysis to give **2.52a** (Scheme 2.28).

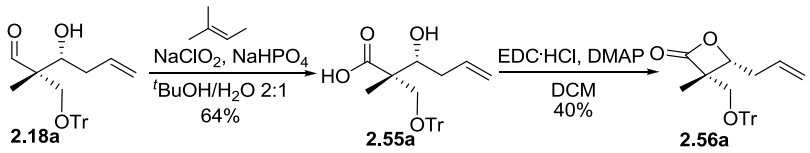


Scheme 2.28. Determination of the relative stereochemistry of **2.16a**.

The ^{1}H NMR's of **2.52a**, obtained by the hydrogenation of **2.51a** and hydrogenolysis **2.54b**, were identical proving the relative stereochemistry of **2.16a** (see chapter 7, Figure 7.13).

2.6.2.3 Identification of the relative stereochemistry of 2.18a

The relative stereochemistry of major diastereoisomer **2.18a** was identified by oxidation of the aldehyde to the acid **2.55a** and cyclisation to form β-lactone **2.56a** (Scheme 2.29). nOe experiments were carried out on β-lactone **2.56a**, proving the relative stereochemistry to be as shown (Figure 7.14).



Scheme 2.29. Formation of lactone **2.56a**.

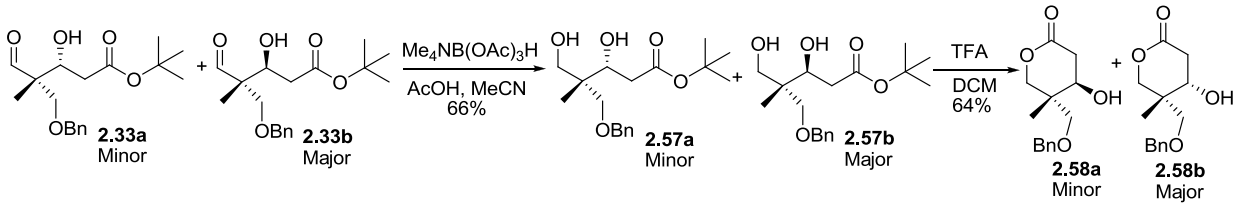
It has been proven, as with hydroxyallylation, that the diastereoselection of the allylation of dialdehydes **1.109** and **2.5** is opposite to the diastereoselection of the allylation of dialdehyde **1.94**. This will be rationalised and the observed diastereoselectivity explained in chapter 3.

2.6.3 Identification of diastereoisomers from aldol reactions

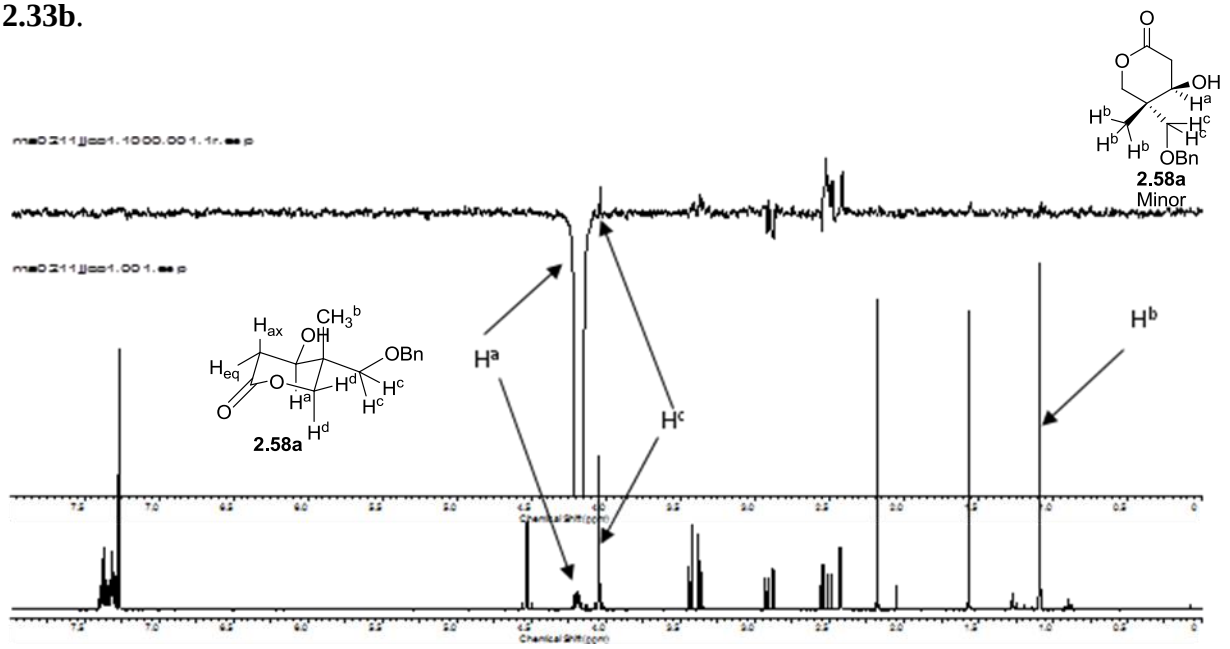
The aldol reactions with Li enolates of *t*-butyl acetate **1.103** and *t*-butyl propionate **1.104** on dialdehyde **1.94** have been achieved (Scheme 2.17 and 2.18). The relative stereochemistry of the diastereoisomers have been identified by nOe analysis.

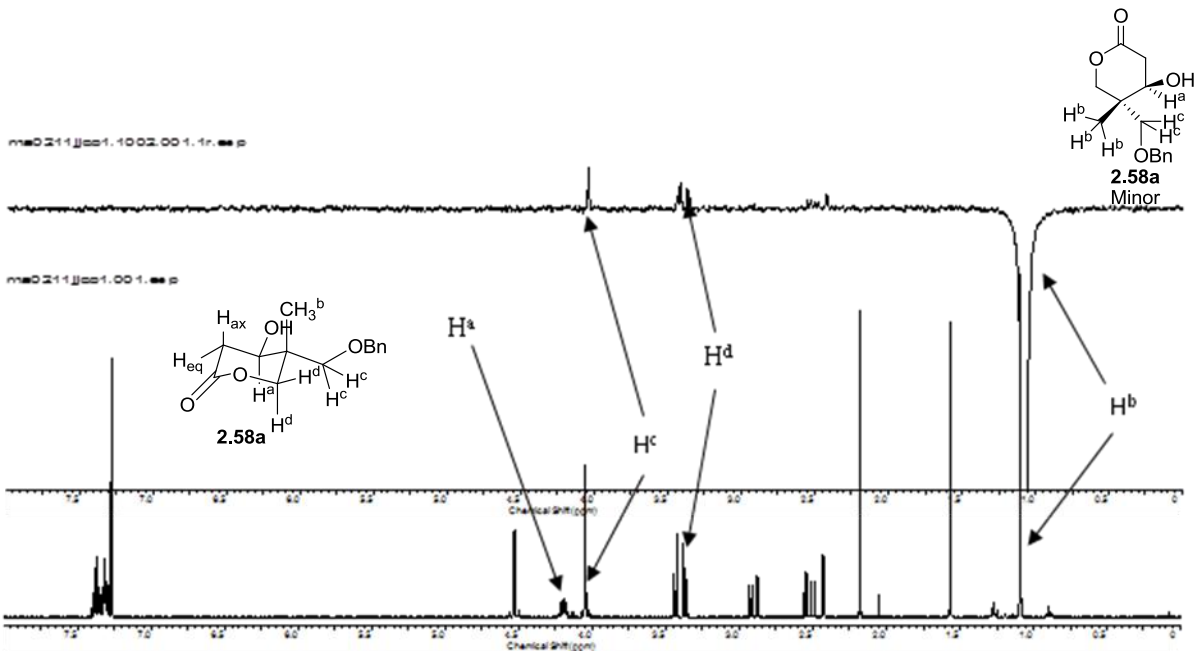
2.6.3.1 Identification of the relative stereochemistry of 2.33

The relative stereochemistry of monoaddition products **2.33a** and **2.33b** were identified by reduction with $Me_4NB(OAc)_3H$ of a mixture of **2.33a** and **2.33b** followed by cyclisation to give δ-lactone **2.58** in 64% yield (Scheme 2.30). The diastereoisomers could then be separated by preparative HPLC. nOe experiments on **2.58a** and **2.58b** identified the relative stereochemistry of the δ-lactones and in turn monoaddition products **2.33a** and **2.33b** (Figure 2.9).

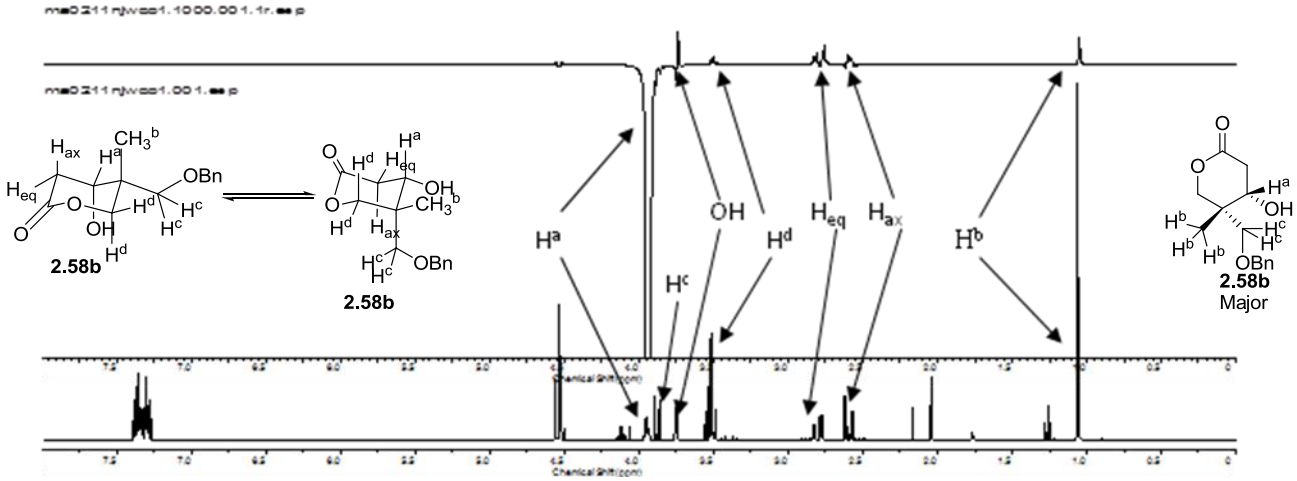


Scheme 2.30. Formation of δ-lactone **2.58** to identify relative stereochemistry of **2.33a** and **2.33b**.





(a) nOe's on **2.58a**.



(b) nOe on **2.58b**.

Figure 2.9. nOe's on **2.58a** and **2.58b** to identify relative stereochemistry.

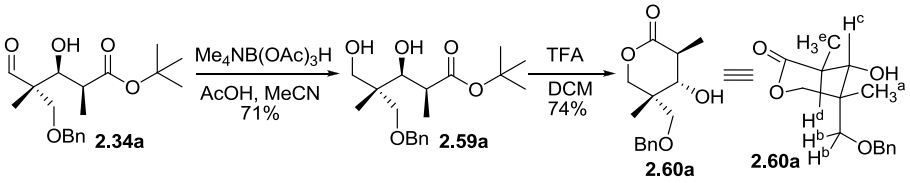
From the nOe experiments on **2.58a** when H^a was irradiated a response was observed at benzylic protons H^c and no response was observed at methyl protons H^b, proving that H^a and H^c must be on the same face of the δ-lactone ring. The relative stereochemistry of minor diastereoisomer **2.58a** and therefore minor diastereoisomer **2.33a** from the aldol of **1.94** must be as shown. When nOe experiments were performed on **2.58b**, no response was observed at benzylic protons H^c when H^a was irradiated; however an nOe was observed between H^a and

the methyl protons H^b. H^a and H^c must be on opposite faces of the δ-lactone ring **2.58b** and therefore the relative stereochemistry of lactone **2.58b** and the major diastereoisomer **2.33b** from the aldol reaction of dialdehyde **1.94** must be as shown (Scheme 2.30).

This is confirmed by *J* value analysis of lactones **2.58a** and **2.58b**. In lactone **2.58a** proton H^a is a ddd with J = 8.6, 6.5, 3.3 Hz. For these types of lactones a typical $J_{ax\text{-}ax}$ interaction is 9.9 Hz and $J_{eq\text{-}ax}$ interaction is 6.0 Hz[134] suggesting that H^a in lactone **2.58a** is axial and the relative stereochemistry is as shown. In lactone **2.58b** proton H^a is a q with J = 4.5 Hz. A typical $J_{eq\text{-}eq}$ and $J_{eq\text{-}ax}$ interaction is 6.0 Hz[134] suggesting that H^a in lactone **2.58b** is equatorial and the relative stereochemistry is as shown.

2.6.3.2 Identification of the relative stereochemistry of 2.34a

Major diastereoisomer **2.34a**, from the aldol reaction between **1.94** and **1.104** (Scheme 2.18), could be obtained pure after preparative HPLC. A mixture of **2.34b** and **2.34d** could also be isolated cleanly. The relative stereochemistry of monoaddition product **2.34a** was identified by reduction with $Me_4NB(OAc)_3H$, followed by cyclisation to give δ-lactone **2.60a** in 74% yield (Scheme 2.31). nOe experiments on **2.60a** identified the relative stereochemistry of the lactone and in turn monoaddition products **2.34a** to be as shown (Figure 7.15).

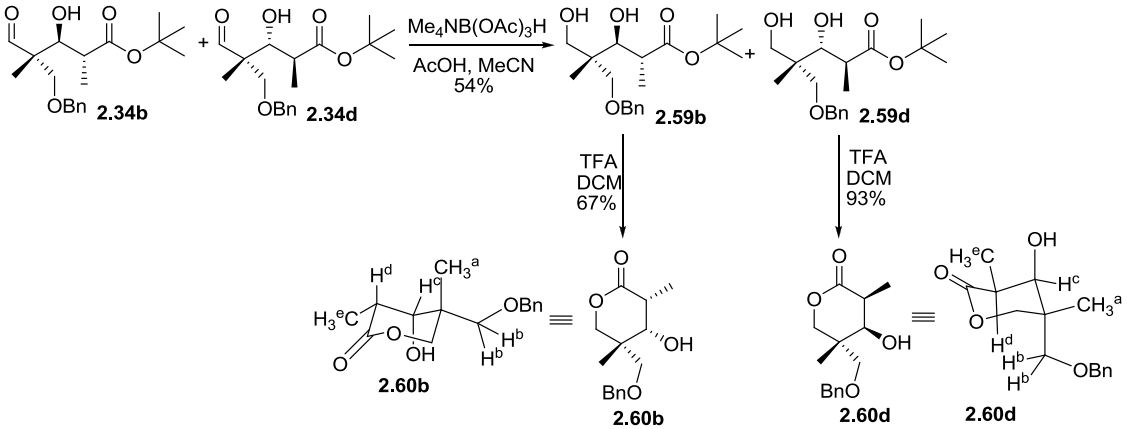


Scheme 2.31. Formation of lactone **2.60a** to identify relative stereochemistry of **2.34a**.

J value analysis of lactone **2.60a** revealed $J_{Hc\text{-}Hd}$ = 9.0 Hz. This value is consistent with an axial axial coupling,[134] suggesting that the **2.60a** chair is in the conformation shown with the methyl groups equatorial and the benzyloxy group axial.

2.6.3.3 Identification of the relative stereochemistry of 2.34b and 2.34d

The relative stereochemistry of monoaddition products **2.34b** and **2.34d** were identified by reduction with $Me_4NB(OAc)_3H$ to give **2.59b** and **2.59d**, which could be separated by preparative HPLC. Cyclisation of **2.59b** and **2.59d** with TFA gave δ-lactones **2.60b** and **2.60d** (Scheme 2.32). nOe experiments on **2.60b** (Figure 7.16) and **2.60d** (Figure 7.17) identified the relative stereochemistry of the δ-lactones and in turn monoaddition products **2.34b** and **2.34d**.



Scheme 2.32. Formation of lactones **2.60b** and **2.60d** to identify relative stereochemistry of **2.34b a**nd **2.34d**.

J value analysis of lactone **2.60b** revealed $J_{Hc\text{-}Hd}$ = 3.0 Hz. This value is consistent with an axial equatorial coupling[134] confirming the relative stereochemistry of **2.60b** suggested by the nOe experiments. *J* value analysis of lactone **2.60d** revealed $J_{Hc\text{-}Hd}$ = 3.5 Hz. This value is again consistent with an axial equatorial coupling[134] confirming the relative stereochemistry of **2.60d** suggested by the nOe experiments.

2.7 Conclusions

The allylation (Scheme 2.6 and 2.7), hydroxyallylation (Scheme 2.4) and Mukaiyama aldol (Scheme 2.11, 2.14 and 2.14) monoaddition reactions have all been achieved on dialdehydes **1.94**, **1.109** and **2.5** in good to excellent yields and diastereoselectivities to give products containing 2 or 3 contiguous stereocentres, including an *all*-C quaternary stereocentre. The

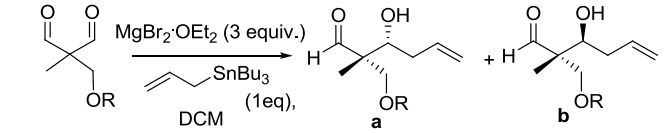
relative stereochemistry of the major and minor diastereoisomers from the allylation and hydroxyallylation reactions have been identified by X-ray crystallography, chemical correlation and nOe analysis. It has been found that monoadditions to dialdehydes **1.109** and **2.5** display opposite diastereoselection to monoaddition to dialdehyde **1.94**. The aldol reaction using Li enolates of esters **1.103** and **1.104** has been achieved on dialdehyde **1.94** in moderate yields and diastereoselectivities (Scheme 2.17 and 2.18), to give products containing two or three contiguous stereocentres, including an *all*-C quaternary stereocentre. The relative stereochemistry of the major and minor diastereoisomers from these aldol reactions has been identified by formation of the corresponding δ-lactone and nOe analysis.

Chapter 3. Rationalisation of diastereoselection

In this chapter a rationalisation of the observed diastereoselection of the reactions described in the previous chapter is put forward. With the relative stereochemistry of the major and minor diastereoisomers determined; the substrate conformation and nucleophile facial approach leading to the observed isomers is considered first.

3.1 Allylation reactions

The allylation of dialdehydes **1.94**, **1.109** and **2.5** has been achieved in moderate to good yields and good to excellent diastereoselectivity (Scheme 3.1). The allylation of **1.94** displays opposite diastereoselection to **1.109** and **2.5** suggesting that the reactions occur *via* a different reactive conformation.

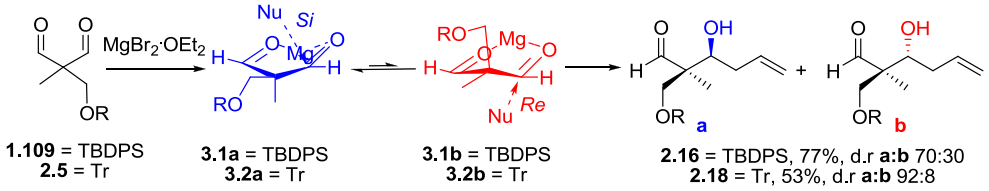


Scheme 3.1. Allylation of dialdehydes **1.94**, **1.109** and **2.5**

3.1.1 Rationalisation of the diastereoselection of allylation of dialdehydes 1.109 and 2.5

In the allylation reaction the $MgBr_2$•OEt_2 will chelate to both aldehyde groups, which leads to activation for the allyl stannation reaction. Previous work by Martin Jeffrey has shown that hydroxyallylation of $(TBDMSOCH_2)_2(CH_3)CCHO$ using $MgBr_2$•OEt_2 only results in recovery of the starting material, showing the $MgBr_2$•OEt_2 chelates to both aldehydes of **1.109** to activate it for reactions.[108] In the case of dialdehydes **1.109** and **2.5**, due to the steric bulk of the trityl and TBDPS groups, the ether oxygen is non-chelating.[146] It is proposed that the $MgBr_2$•OEt_2 chelate exists as a flattened boat reactive conformation **3.1a** (Scheme 3.2). Similar chelates have been proposed for β-formyl esters and amides[147] and malonates.[111] To form the major diastereoisomer **2.16a** or **2.18a** the allylstannane must approach the aldehyde on the *Si* face past the *pseudo* equatorial ether group. The A-value of a methyl group is 1.70

kcal mol^{-1}, whereas the A-value of a CH_2OTs, which in this case can be considered comparable to our $CH_2OTBDPS$, is 1.75 kcal mol^{-1}.[148] Therefore the steric differences between the methyl and ether groups are small. The minor diastereoisomer is thought to arise *via* the conformation after ring inversion. The nucleophile will approach the *Re* face of the aldehyde past the *pseudo* equatorial methyl group, with the ether group sitting in a *pseudo* axial position (**3.1b**) to yield the observed minor diastereoisomer **2.16b** or **2.18b**.

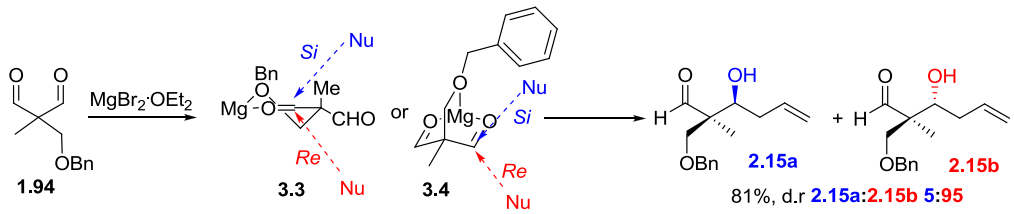


Scheme 3.2 Reactive conformations involved in the allylation of **1.109** and **2.5**

It is believed that as a trityl group is much larger than a TBDPS group, that difference in sterics leads to the improved diastereoselectivity observed in the allylation of **2.5**.

3.1.2 Rationalisation of the diastereoselection of allylation of dialdehyde 1.94

The allylation of dialdehyde **1.94** displays opposite diastereoselection to the allylation of dialdehydes **1.109** and **2.5** (Scheme 3.1). The diastereoselection of the allylation reaction on dialdehyde **1.94** could be rationalised from two different reactive conformations, **3.3** and **3.4**. It is known that benzyl ethers can chelate to Lewis acids.[39] In reactive conformation **3.3** the benzyl ether and one of the aldehydic oxygens chelate to the Mg(II) to form a half chair with the nucleophile attacking from the *Re* face past the smaller formyl group to give major diastereoisomer **2.15b** *via* a chair transition state. In reactive conformation **3.4** the benzyl ether oxygen and both aldehydic oxygens chelate to the Mg(II) forming a bridged complex. The nucleophile will then approach the less sterically hindered *Re* face to give major diastereoisomer **2.15b** (Scheme 3.3).



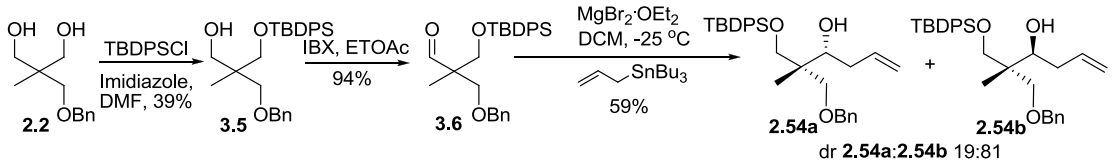
Scheme 3.3 Two possible reactive conformations leading to **2.15b**.

3.1.2.1 Variable temperature NMR experiments

It is known within the literature that $MgBr_2$•OEt_2 will form a bidentate chelate between an aldehydic oxygen and a benzyl ether oxygen. Keck *et. al.* have also shown that the structure of the six membered ring complex can be determined by ^{1}H NMR at low temperatures.[75,74] Previous low temperature ^{1}H NMR experiments on dialdehyde **1.94** with $MgBr_2$•OEt_2 have suggested that the benzyl ether oxygen is involved in chelation, as shown by a large difference in chemical shift of the OC**H$_2$**Ph upon $MgBr_2$•OEt_2 addition.[109] We attempted to identify the reactive conformation of dialdehyde **1.94** with $MgBr_2$•OEt_2 by running a series of ^{1}H and ^{13}C NMR's of dialdehyde **1.94** and $MgBr_2$•OEt_2 in CD_2Cl_2 at 0 °C, –25 °C and –60 °C (Figure 3.1). In these experiments only one aldehydic peak was present, this could suggest that both aldehydic oxygens are chelating to the Mg(II) with the reaction going *via* transition state **3.4**. However the single aldehydic environment in the ^{1}H NMR could be as a result of a rapid equilibrium shift in **3.3** between the two ring inversions. Interestingly it was also observed that the aldehydic peak of **1.94** did not shift in the ^{1}H NMR upon chelation to $MgBr_2$•OEt_2; although Keck also only observed a small downfield shift (0.08 ppm) in the aldehydic peak upon chelation to $MgBr_2$•OEt_2.[74] We also observed a shift downfield of the OC**H$_2$**Ph peak upon $MgBr_2$•OEt_2 chelation, suggesting that the benzyloxy oxygen of **1.94** chelates to $MgBr_2$•OEt_2. However due to the low temperatures these experiments were performed at, the resolution of the NMR's was poor and therefore these results do not exclude either **3.3** or **3.4**.

3.1.2.2 Control Experiments

It was also hoped to obtain further understanding of the diastereoselection of the allylation reaction on dialdehyde **1.94** by performing an allylation reaction on model compound **3.6**, where only the aldehydic oxygen and the benzyl ether oxygen could chelate to Mg(II) (Scheme 3.4).



Scheme 3.4. Allylation of aldehyde **3.6**.

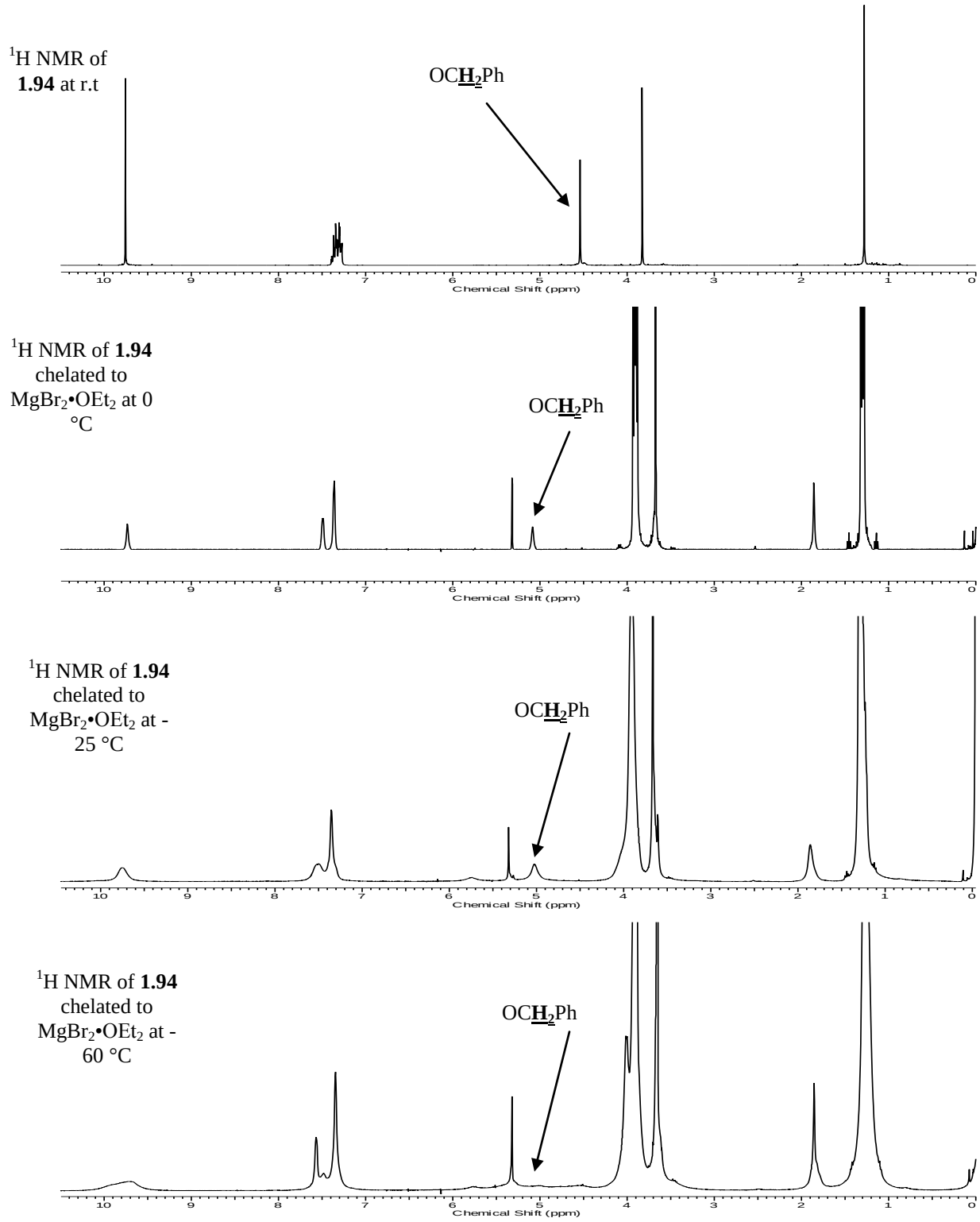
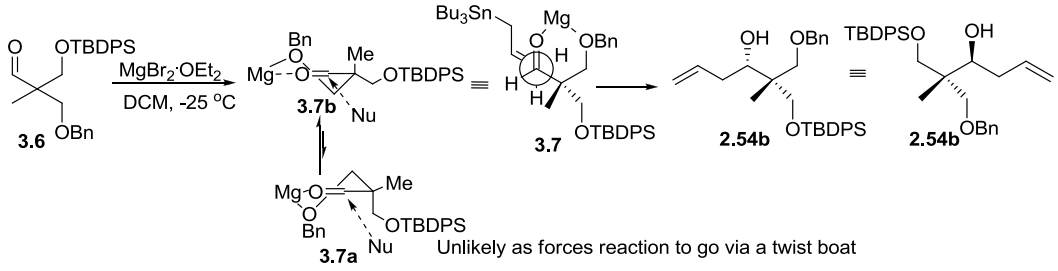


Figure 3.1 Variable temperature ^{1}H NMR's of **1.94** chelated to $MgBr_2$•OEt_2 showing only one aldehydic proton environment and worsening of resolution at lower temperatures.

Allylation of aldehyde **3.6** gave alcohol **2.54b** as the major diastereoisomer in reasonable yield and d.r (59%, d.r **2.54a**:**2.54b** 19:81, see chapter 7 Figure 7.11). The ^{1}H NMR spectrum of the major diastereoisomer corresponded with **2.54b** (Figure 7.12), which had previously been synthesised (Scheme 2.28), so proving the diastereoselection of this reaction.

As there are only two chelating oxygens in aldehyde **3.6** (the siloxy ether oxygen is non-chelating[146]) the reaction must go *via* a half chair reactive conformation. From the relative stereochemistry of the product **2.54b** we can assume the reactive conformation to be **3.7b**, with the allylstannane nucleophile approaching **3.7b** past the *pseudo* equatorial TBDPS ether group (Scheme 3.5).

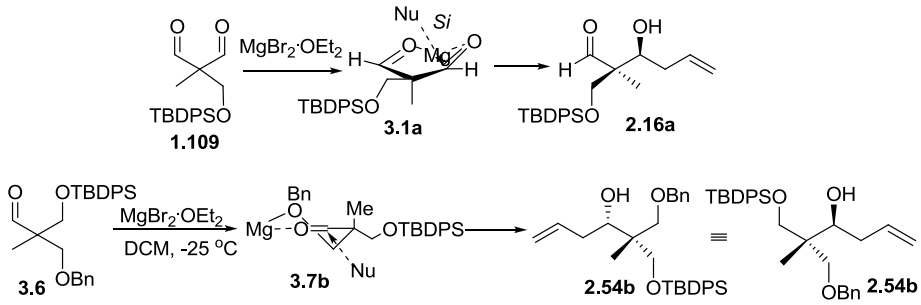


Scheme 3.5. Postulated reactive conformation for the allylation of aldehyde **3.6**.

If the reactive conformation for the allylation on dialdehyde **1.94** is half chair **3.3** (Scheme 3.3), then the allyl stannane nucleophile must approach past the *pseudo* equatorial formyl group, to give major diastereoisomer **2.15b**. However in the case of the allylation of **3.6**, the nucleophile is approaching the aldehyde past the TBDPS group (Scheme 3.5). The d.r of the allylation of **1.94** is 5:95, compared with the allylation of **3.6** which is 19:81. In the case of reactive conformation **3.3** the A-value for a formyl group is 0.8 kcal mol^{-1}, whereas the A-value for the methyl group is 1.7 kcal mol^{-1}.[148] This difference in steric bulk of the substituents on the α position could explain the excellent diastereoselectivity in the allylation of **1.94**. In the case of the allylation of **3.6**, the methyl and $CH_2OTBDPS$ have similar A-values,[148] so explaining the poorer diastereoselectivity.

From this work it can be seen that the facial preference of the allylation of aldehyde **3.6** is for the nucleophile to approach the reacting aldehyde past the *pseudo* equatorial TBDPS ether,

despite the similarity in sterics between the $CH_2OTBDPS$ and methyl according the A-values.[148] This adds strength to the postulated reactive conformations **3.1** and **3.2** for the allylations of dialdehydes **1.109** and **2.5**. In these reactions it is also assumed that the allylstannane nucleophile approaches the dialdehyde past the *pseudo* equatorial ether with the methyl *pseudo* axial (Scheme 3.6).

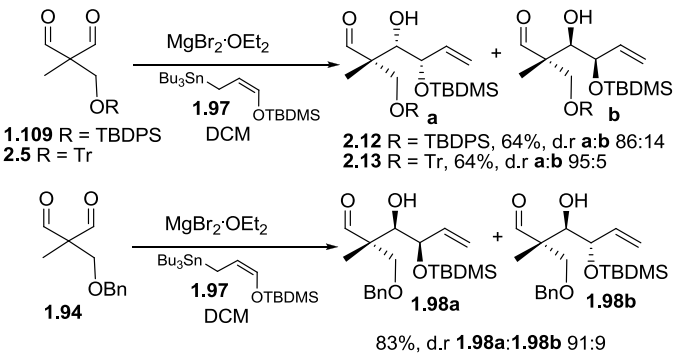


Scheme 3.6 Comparison between reactive conformations **3.1a** and **3.7b**

In our view the results of the variable temperature NMR experiments and the experiments on model compound **3.6** are inconclusive as to whether additions to dialdehyde **1.94** occur *via* reactive conformation **3.3** or **3.4** (Scheme 3.3). We however believe that dialdehyde **1.94** chelates to $MgBr_2 \bullet OEt_2$ to form bridged conformation **3.4**. It is known that $MgBr_2 \bullet OEt_2$ has up to six coordination points. Charette *et. al.* have also suggested tridentate chelate reactive conformations for benzyloxy aldehydes and $MgBr_2 \bullet OEt_2$.[149-151] With three chelating oxygens in dialdehyde **1.94** it seems likely that all three would coordinate to $MgBr_2 \bullet OEt_2$. The excellent facial selectivity of additions to **1.94**, especially in the hydroxyallylation reaction (Scheme 2.4) and double addition reactions (see chapter 4) where complete facial selectivity is observed, suggests the reactive conformation formed is a very different more rigid conformation such as **3.4**.

3.2 Hydroxyallylation reactions

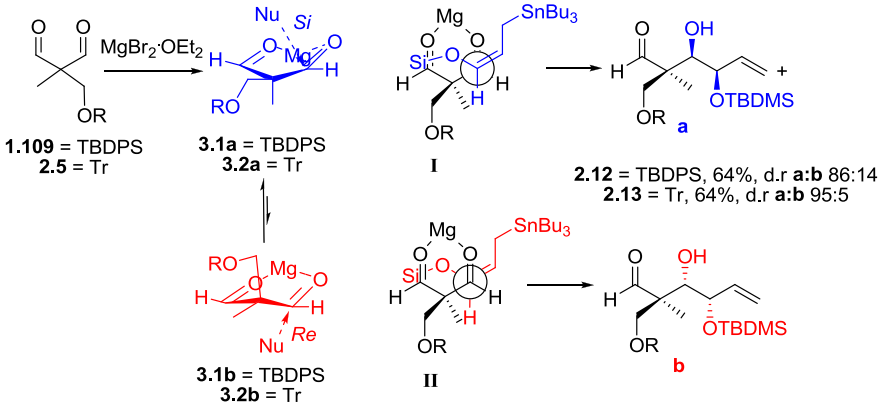
The hydroxyallylation of dialdehydes **1.94**, **1.109** and **2.5** have been achieved in good to excellent yields and good to excellent diastereoselectivity (Scheme 3.7). As with the allylation, the hydroxyallylation of **1.94** displays opposite facial selectivity to **1.109** and **2.5**.



Scheme 3.7. Hydroxyallylation of dialdehydes **1.94**, **1.109** and **2.5**

3.2.1 Rationalisation of the diastereoselection of hydroxyallylation of dialdehydes 1.109 and 2.5

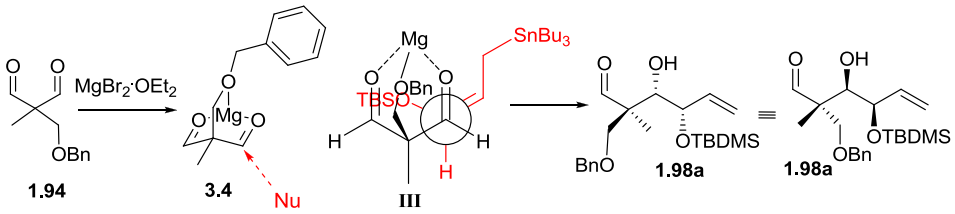
In accord with the allylation results, we believe that the hydroxyallylation of dialdehydes **1.109** and **2.5** also goes *via* reactive conformations **3.1** and **3.2**. The same *syn* relationship between the pendant ether group on the quaternary centre and the hydroxyl group is observed from the hydroxyallylation in major diastereoisomers **2.12a** and **2.13a** as in major diastereoisomers **2.16a** and **2.18a** from the allylation reaction. This suggests that allylstannane **1.97** is also approaching from the *Si* face, in the least sterically hindered orientation (**I**), to give the observed *syn* relationship between the hydroxyl and siloxy groups, which is expected from hydroxyallylation reactions,[115] yielding **2.12a** or **2.13a** as the major diastereoisomer (Scheme 3.8). The stereochemistry of the minor diastereoisomers can be explained by *Re* face approach after ring inversion of **3.1b** or **3.2b** to give the observed *anti* relationship between the hydroxyl and the pendant ether group.



Scheme 3.8 Rationalisation of diastereoselection of hydroxyallylation reaction of **1.109** and **2.5**.

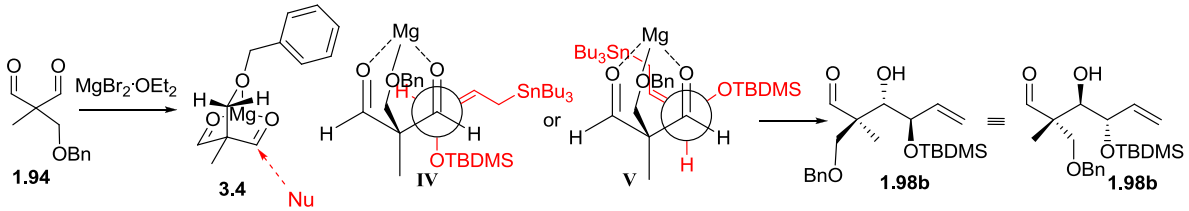
3.2.2 Rationalisation of the diastereoselection of hydroxyallylation of dialdehyde 1.94

When dialdehyde **1.94** chelates with $MgBr_2$•OEt_2 we postulate that it forms bridged reactive conformation **3.4**. The observed major diastereoisomer **1.98a** is formed by allylstannane **1.97** approaching the *Re* face of **3.4**, as in the allylation, to give the *anti* relationship between the hydroxyl and benzyloxy group. As with the hydroxyallylation of **1.109** and **2.5**, allylstannane **1.97** will approach **3.4** in the least sterically hindered orientation to give the observed *syn* relationship between the hydroxyl and siloxy groups (Scheme 3.9).



Scheme 3.9. Rationalisation for the formation of major diastereoisomer **1.98a**.

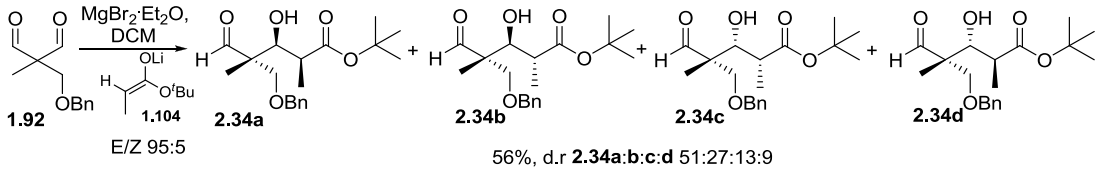
Surprisingly it was found that minor diastereoisomer **1.98b** displayed an *anti* relationship between the hydroxyl and benzyloxy group and an *anti* relationship between the siloxy and hydroxyl groups. Therefore to form **1.98b**, **1.97** must show the same aldehyde facial selectivity, approaching the *Re* face. It is believed that this is because of the large steric bulk of allylstannane **1.97** (*c.f.* allyl tributylstannane), the methylene protons on **3.4** are blocking the *Si* face. However the opposite face of the allylstannane must react (**IV** or **V**) to give the *anti* relationship between the hydroxyl and siloxy groups (Scheme 3.10).



Scheme 3.10. Rationalisation for the formation of minor diastereoisomer **1.98b**.

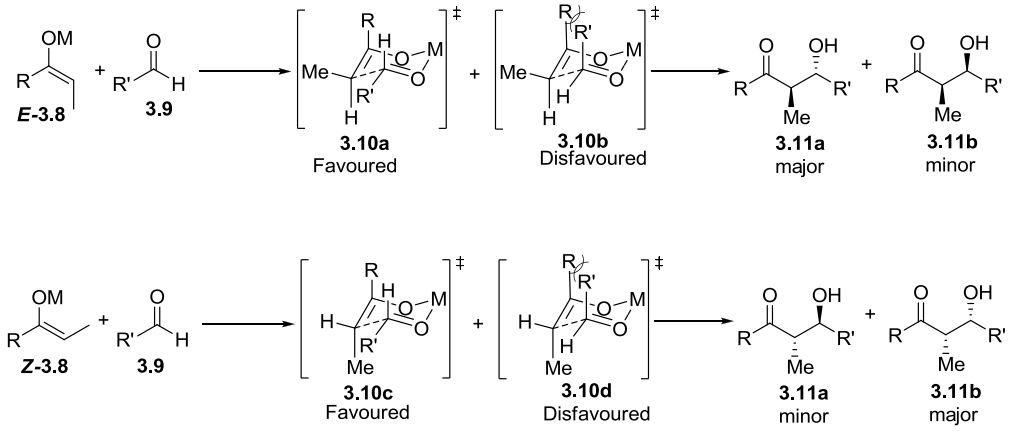
3.3 Aldol reactions

The aldol reaction of dialdehyde **1.94** with Li ester enolate **1.104** has been achieved in moderate yields and diastereoselectivity (Scheme 3.11). The *E/Z* ratio for the formation of lithium enolate **1.104** from *t*-butyl propionate is known to be 95:5.[133, 134] However the *syn/anti* ratio of aldol products using Li enolate **1.104** is variable dependent on the aldehyde used.[134-137] Aliphatic aldehydes have been found to give better *syn/anti* ratios (up to 5:95) than aromatic aldehydes (49:51).[137]



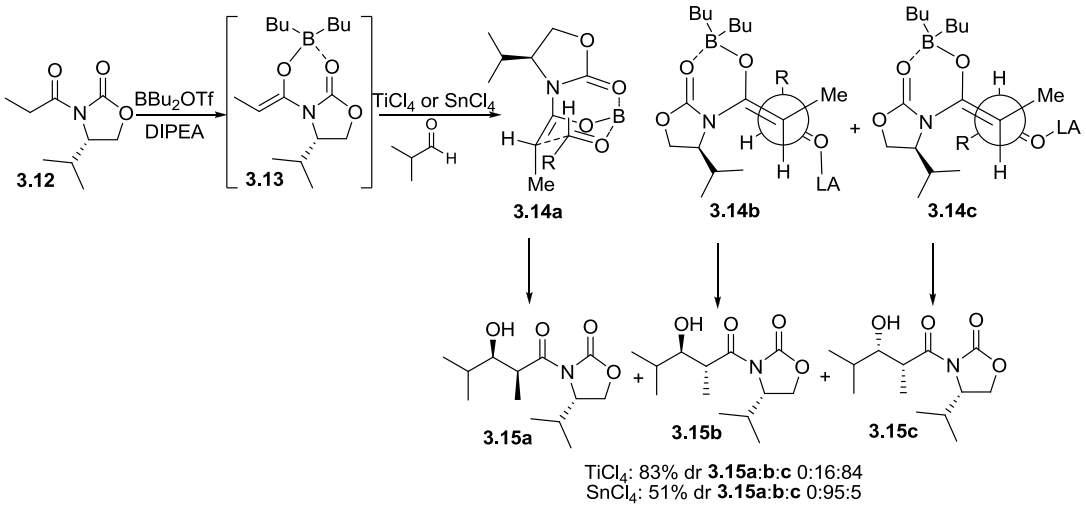
Scheme 3.11. Aldol reaction of **1.94** with Li ester enolate **1.104**.

Typically aldol reactions with Li enolates occur *via* cyclic Zimmerman – Traxler transition states, where the metal on the enolate coordinates to the reacting aldehyde to form a chair like six membered transition state. *E* enolates lead to *anti* products and *Z* enolates lead to *syn* products. This selectivity is controlled by the unfavourable 1,3-diaxial interactions that would exist in the transition state, leading to the opposite selectivity (Scheme 3.12).[130]



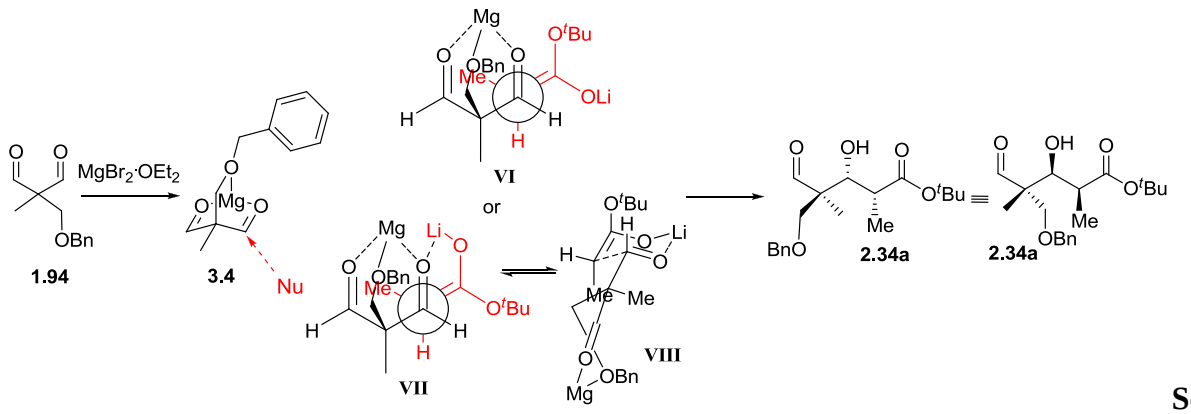
Scheme 3.12 Zimmerman – Traxler transition states controlling aldol reactions.

Heathcock *et. al.* has shown that boron enolates of imide **3.12** will react with an already coordinated aldehyde *via* an open, acyclic transition state, with only trace amounts of the product *via* the cyclic transition state (**3.14a**) being observed (Scheme 3.13). It is believed that this reaction is successful as the reaction with the chelated aldehyde is much faster than the reaction with the uncoordinated aldehyde.[131, 152]



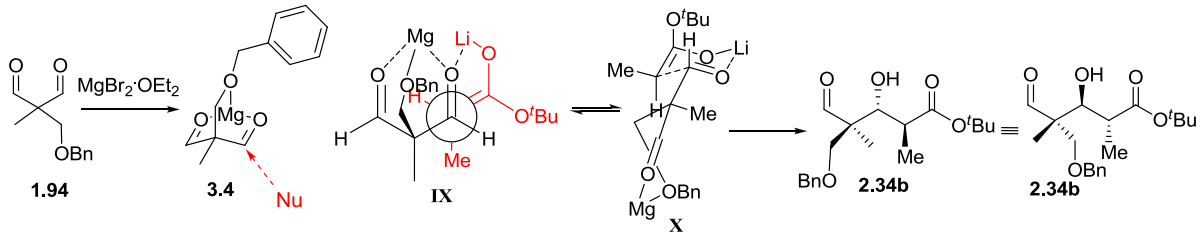
Scheme 3.13 Heathcock's boron enolate aldol reactions[152]

We believe that the mixture of diastereoisomers and poor diastereoselectivity in our aldol reaction of **1.94** (Scheme 3.11) is as a result of the reaction going *via* both the open acyclic and closed cyclic transition states. The major diastereoisomer **2.34a** is a *syn* aldol product from an *E* enolate, suggesting that it is formed from a Heathcock type acyclic transition state (**VI**). However in the literature there is variability in d.r's from aldol reactions using enolate **1.104**,[134-137] suggesting the enolate may scramble. If this is the case, the formation of **2.34a** can be rationalised from ***Z*-1.104**. One of the Mg aldehydic oxygen bonds in **3.4** will break as the reacting aldehyde chelates to the Li enolate to form a Zimmerman – Traxler transition state (**VIII**), which would lead to major diastereoisomer **2.34a** (Scheme 3.14).



Scheme 3.14. Rationalisation for the formation of major diastereoisomer **2.34a**.

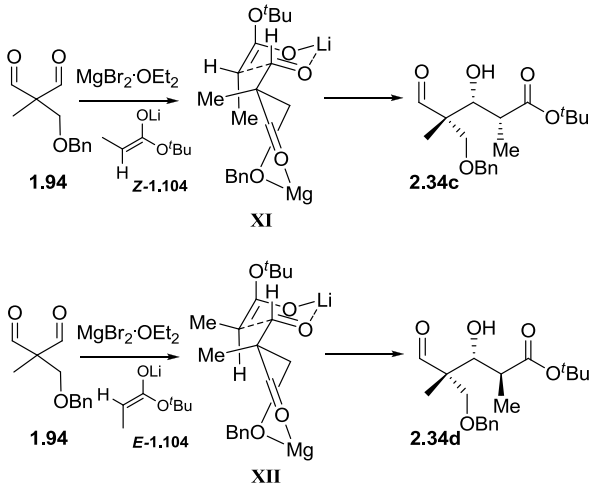
Medium diastereoisomer **2.34b** is an *anti* aldol product from an *E* enolate and can therefore be explained by Zimmerman – Traxler transition state **IX**, where all three oxygens remain coordinated to the Mg and there is an additional interaction between the Li enolate and the reaction aldehydic oxygen. The formation of **2.34b** can also be explained by transition state **X**, where the Mg aldehydic oxygen chelate breaks and the reacting aldehyde chelates to the Li of the enolate (Scheme 3.15).



Scheme 3.15. Rationalisation for the formation of major diastereoisomer **2.34b**.

Minor diastereoisomers **2.34c** and **2.34d** both have a *syn* relationship between the hydroxyl and benzyloxy group, suggesting the aldehyde must display opposite facial selectivity. The hydroxyallylation reaction (Scheme 3.7), which also gives products containing 3 contiguous stereocentres, on dialdehyde **1.94** only yields two diastereomeric products, with the allyl stannane nucleophile **1.97** displaying complete facial selectivity. Enolate **1.104** is thought to be sterically larger than allyl stannane nucleophile **1.97** (the A-value of a methyl group is 1.70 kcal mol^{-1}, whereas the A-value of the OTBDMS group in the equivalent position on **1.97** is 1.06 kcal mol^{-1}).[148] This suggests that chelate **3.4** is broken in the aldol reaction and

minor diastereoisomers **2.34c** and **2.34d** must be formed *via* Zimmerman – Traxler type transition states (Scheme 3.16).



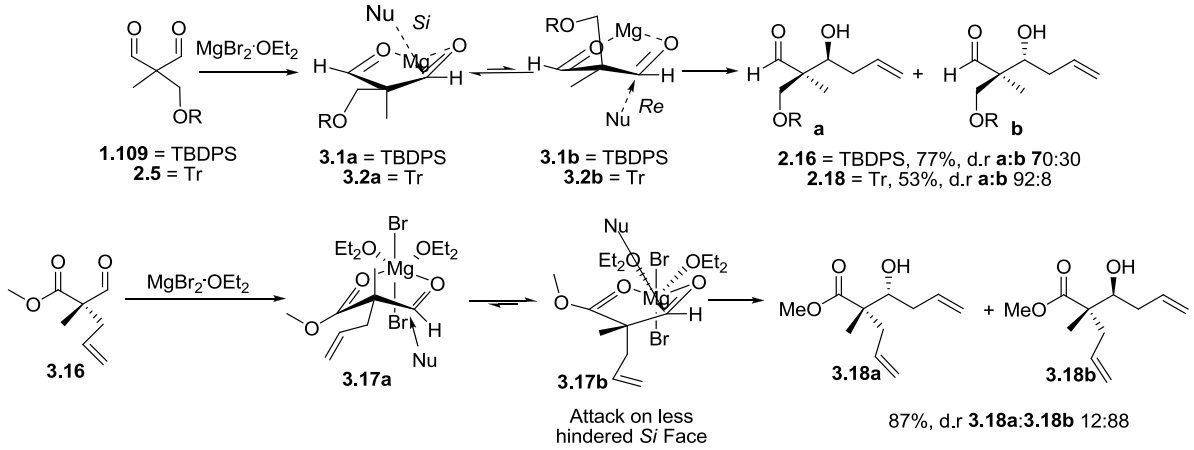
Scheme 3.16 Rationalisation for the formation of **2.34c** and **2.34d**

Further investigations would be required to clarify these models. However in view of the disappointing yields and diastereoselectivities, the aldol reaction of propionate derived enolates to malonaldehydes has not been investigated further.

3.4 Refinement of the model

3.4.1 Allylation of 3-oxo esters

While finalising the model for the stereoselection of malonaldehydes, Mulzer published a related allylstannations process of 3-oxo esters upon $MgBr_2 \bullet OEt_2$ activation.[145, 147] To our surprise the Mulzer results did not correspond to our model (Scheme 3.17). The ensuing investigations led to a refinement of our proposed model.



Scheme 3.17. Allylation of Mulzer's 3-oxo ester **3.16** compared with allylation of **1.109** and **2.5**.

3-Oxo ester **3.16** can be considered analogous to dialdehydes **1.109** and **2.5** in that the two carbonyl oxygens will chelate Mg(II) to form a flattened boat reactive conformation. Reactive conformations **3.1a** and **3.2a** of dialdehydes **1.109** and **2.5** place the ether group *pseudo* equatorial to give the observed *syn* relationship between the hydroxyl group and the large ether group on the quaternary centre. However the major diastereoisomer from the allylation of **3.16** displays an *anti* relationship between the hydroxyl and the larger allyl group on the quaternary centre.[145] The larger allyl group must therefore occupy the *pseudo* axial position in reactive conformation **3.17b** to give major diastereoisomer **3.18b** (Scheme 3.17).

3.4.2 DFT Calculations – Nathan Bartlett

To understand the differences in diastereoselection between our dialdehyde systems and Mulzer's 3-oxo ester systems, Nathan Bartlett within the Linclau group carried out DFT modelling on both systems. It was found that in the 3-oxo ester system, 1,2-allylic strain is present between the ester and the group *pseudo* equatorial in the reactive conformation. This forces the smaller group in the 3-oxo ester system to occupy the *pseudo* equatorial position in the reactive conformation (**3.17b**). In the dialdehyde system this 1,2-allylic strain is relieved and the dominant interaction is 1,4-flagpole strain between the bromine of $MgBr_2$•OEt_2 and the *pseudo* axial group. This forces the smaller methyl group on the quaternary centre of the

dialdehyde to occupy the *pseudo* axial position in the reactive conformation (**3.1a**) leading to the observed diastereoselection (Figure 3.2).[153]

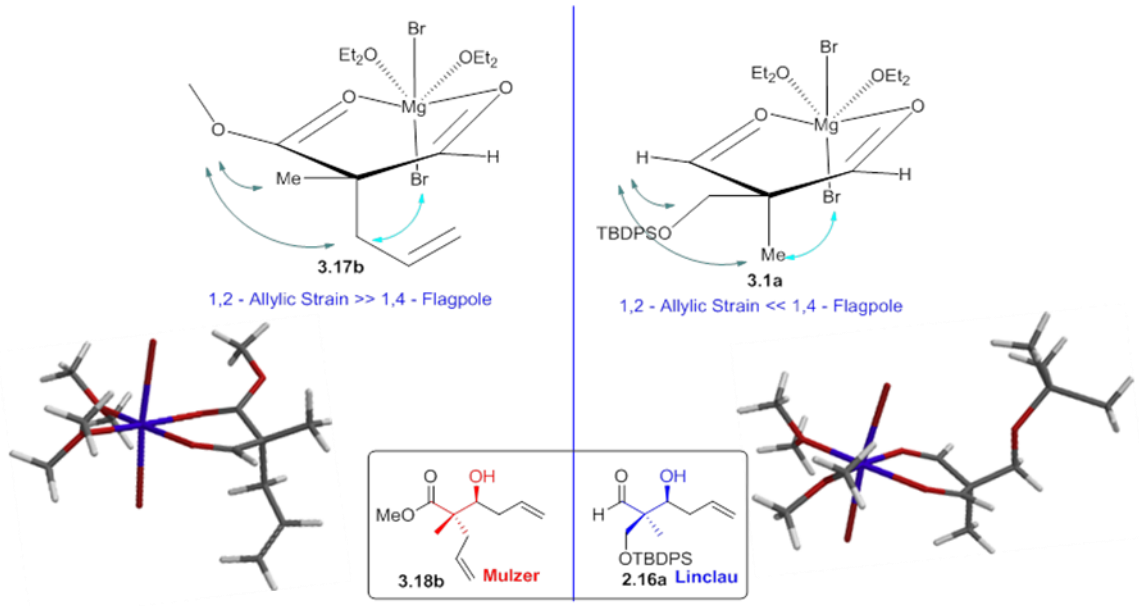
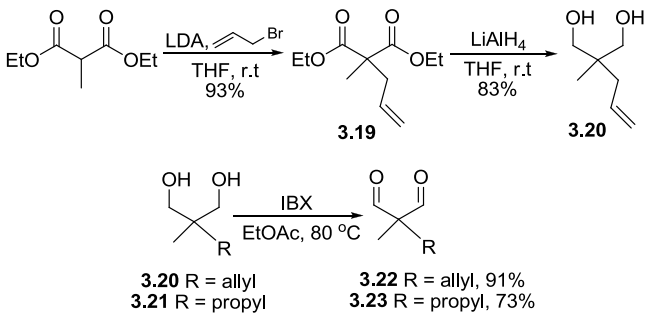


Figure 3.2 Results of DFT modelling on **3.17b** and **3.1a**.[153]

3.4.3 Allylation of allyl dialdehyde 3.22 and propyl dialdehyde 3.23

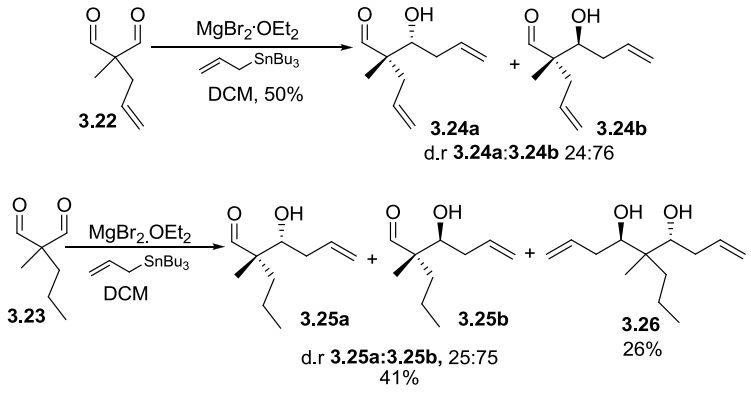
If additions to 3-oxo esters are controlled by 1,2-allylic strain, then allylation of allyl dialdehyde **3.22** should display the same diastereoselection as our 1,3-dialdehyde systems and opposite to Mulzer's 3-oxo esters, leading to a product having a *syn* relationship between the large group on the quaternary centre and the hydroxyl. To eliminate any possibility of the diastereoselection of the allylation of **3.16** or **3.22** being controlled by interactions between the allyl group and the carbonyl or Mg(II), the allylation was also carried out on propyl dialdehyde **3.23** (Scheme 3.19).

Dialdehyde **3.22** was prepared by addition of allyl bromide to diethylmethyl malonate to give **3.19**. $LiAlH_4$ reduction followed by IBX oxidation gave dialdehyde **3.22** in excellent yields (Scheme 3.18). Commercially available propyl diol underwent IBX oxidation to yield propyl dialdehyde **3.23** in excellent yields.



Scheme 3.18. Preparation of allyl and propyl dialdehydes **3.22** and **3.23**.

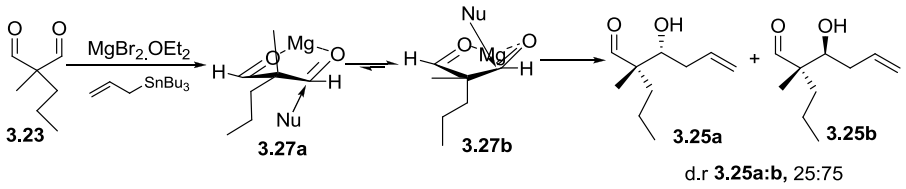
The allylation of dialdehyde **3.22** was carried out in 50% yield and 76:24 d.r (see chapter 7, Figure 7.18). The allylation of propyl dialdehyde **3.23** was carried out in 41% yield and 75:25 d.r (Figure 7.19). In this case double addition product **3.26** was also isolated in 26% yield (Scheme 3.19); therefore the d.r for the monoaddition to **3.23** is taken assuming that the rate of the second allylation is the same for both **3.25a** and **3.25b**.



Scheme 3.19. Allylation of allyl dialdehyde **3.22** and propyl dialdehyde **3.23**.

Surprisingly the diastereoselection of the allylation reaction of allyl dialdehyde **3.22** and propyl dialdehyde **3.23** (Scheme 3.19) was found to be the same as in Mulzer's 3-oxo ester system (Scheme 3.17). Interestingly the diastereoselectivity of the allylation of dialdehydes **3.22** and **3.23** (76:24 and 75:25) were significantly worse than 3-oxo ester **3.16** (88:12). This suggests that although the 1,2-allylic strain is not the origin of the diastereoselection of the addition to **3.22** and **3.16**, it is enhancing the diastereoselectivity of additions to 3-oxo ester system **3.16**.

An explanation for the observed diastereoselection in the allylation of allyl dialdehyde **3.22** and propyl dialdehyde **3.23** (Scheme 3.19) is that in these cases there are no additional factors controlling the diastereoselection of these reactions and they are controlled by sterics alone (Scheme 3.20).



Scheme 3.20 Rationalisation for the observed diastereoselection in the allylation of **3.23**.

The $MgBr_2$•OEt_2 will chelate the two aldehydic oxygens of **3.23** to form the flattened boat reactive conformation **3.27**. It is expected that **3.27a**, with the smaller methyl group *pseudo* axial, would be the more stable reactive conformation, as the 1,4-flagpole strain between the *pseudo* axial group and a bromine of $MgBr_2$•OEt_2 would be minimised. However the least sterically hindered approach for the allylstannane is past the smaller *pseudo* equatorial methyl group (**3.27b**); and this leads to the observed major diastereoisomer **3.25b**. This suggests that although **3.27a** may be the most stable reactive conformation, the activation energy to form **3.25b** from **3.27b** is less than the activation energy to form **3.25a** from **3.27a**, resulting in **3.25b** as the observed major diastereoisomer. If this is the case then the observed opposite diastereoselection for dialdehydes **1.109** and **2.5** (Scheme 3.2) must involve an additional factor above sterics. We propose that the Cieplak model can explain the stereochemical outcome in these cases.

3.4.4 Rationalisation using the Cieplak Model

The Cieplak model states that a nucleophile will approach a carbonyl antiperiplanar to the α substituent which is the most electron rich and therefore the best σ donor (Figure 3.3).[154]

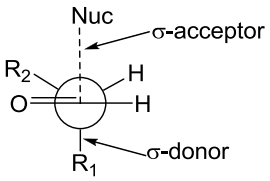
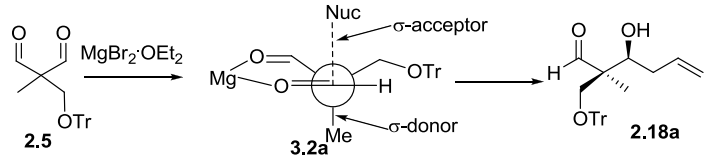


Figure 3.3 Cieplak model.

In the case of the addition to dialdehydes **1.109** and **2.5**, the silyloxy methyl group or trityloxy methyl group are worse σ donors compared to a methyl group. The methyl group

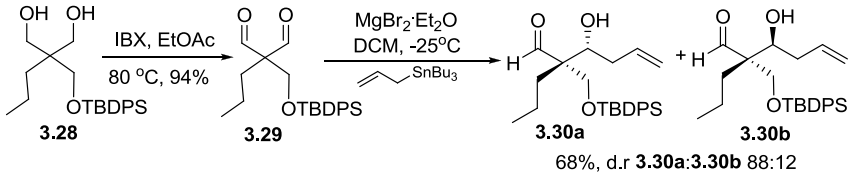
should therefore sit antiperiplanar to the approach of the nucleophile, in the *pseudo* axial position, in the reactive conformation (Scheme 3.21). The observed major diastereoisomer **2.16a** or **2.18a** is the expected diastereoisomer that would be formed based on this model.



Scheme 3.21 Rationalisation of the observed diastereoselection using the Cieplak model.

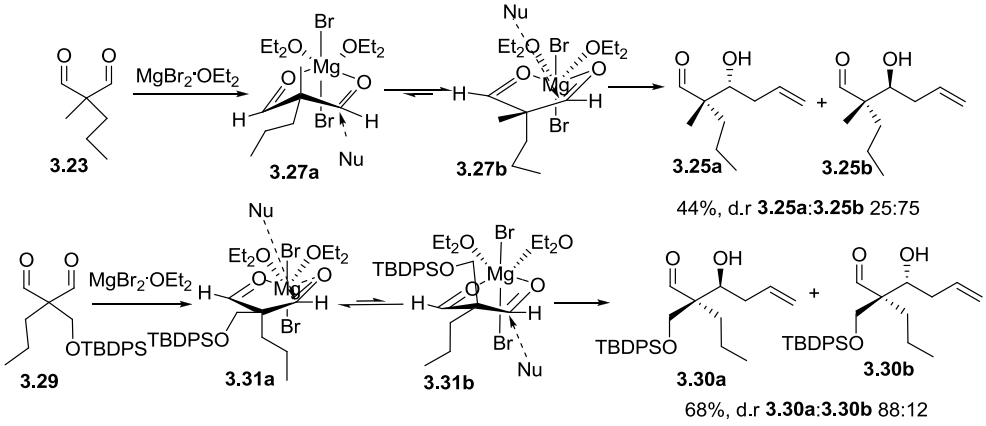
3.4.5 Confirmation with propyl, TBDPS ether dialdehyde 3.29

Diol **3.28** had been previously prepared with the Linclau group.[155] Oxidation with IBX gave dialdehyde **3.29**. The allylation of **3.29** was carried out in 68% yield and d.r **3.30a**:**3.30b** of 88:12 (Scheme 3.22, Figure 7.20).



Scheme 3.22 Allylation of dialdehyde **3.29**.

By comparing the allylation of propyl methyl dialdehyde **3.23** and TBDPS propyl dialdehyde **3.29**, to form the observed major diastereoisomers in both cases the propyl group must occupy the *pseudo* axial position in the reactive conformation (Scheme 3.23).



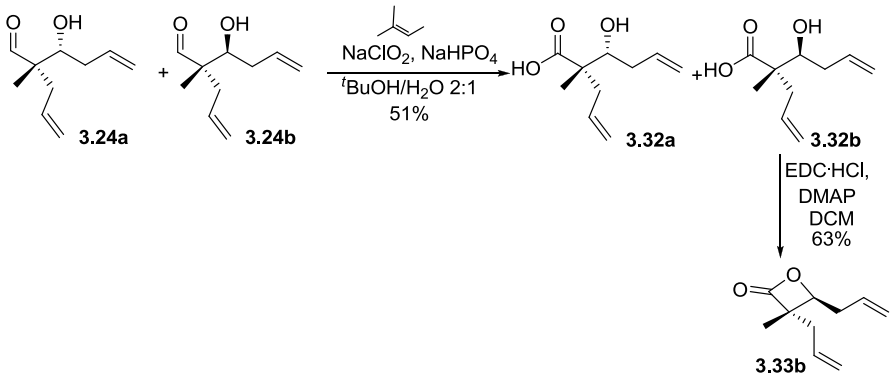
Scheme 3.23 Reactive conformations for the allylation of **3.23** and **3.29**.

In the case of **3.23** the propyl group is in the *pseudo* axial position to minimise steric hinderance for the addition. In the case of **3.29**, with the A-value of the propyl group 0.75 kcal mol^{-1}, and the A-value of the $CH_2OTBDPS$ is expected to be approximately 0.75 kcal mol^{-1},[148] there is little steric difference between these groups; however the d.r from the allylation of **3.29** (88:12) is greater than the d.r from the allylation of **3.23** (75:25). We believe that this greater level of observed diastereoselection in the allylation of **3.29** can be explained by the Cieplak model. The propyl group is a better σ donor than the TBDPS ether. Therefore nucleophilic approach to dialdehyde **3.29** antiperiplanar to the propyl group will better stabilise the transition state, due to hyperconjugative assistance from the propyl group, than approach antiperiplanar to the TBDPS ether,[79] leading to **3.30a** as the major diastereoisomer. The better d.r for the allylation of **3.29** compared to the allylation of **1.109** (72:28) is similarly explained, as a propyl group will be a better σ donor than a methyl group. The Cieplak model can also explain the difference in diastereoselectivity in additions to siloxy dialdehyde **1.109** trityloxy dialdehyde **2.5** (92:8) (Scheme 3.2). A trityl ether is more electron withdrawing than a silyl ether; therefore addition antiperiplanar to a trityloxy group will destabalise the transition state to a greater extent than addition antiperiplanar to a OTBDPS group.

3.5 Identification of diastereoisomers

3.5.1 Identification of diastereoisomers from the allylation of 3.22

The relative stereochemistry of the major diastereoisomer **3.24b** from the allylation of **3.22** (Scheme 3.19) was identified by oxidation of the aldehyde to carboxylic acid **3.32**, at which point the major and minor diastereoisomers could be separated by preparative HPLC. Cyclisation of **3.32b** formed β-lactone **3.33b** (Scheme 3.24).

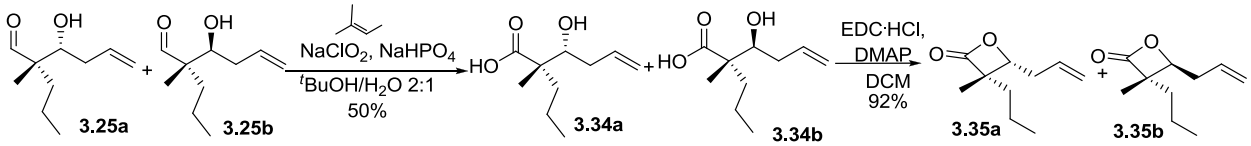


Scheme 3.24. Identification of relative stereochemistry of major diastereoisomer **3.24b** from the allylation of dialdehyde **3.22**.

The ^{1}H and ^{13}C NMR data from **3.33b** matched that given in the literature,[145] proving the relative stereochemistry of the major diastereoisomer **3.24b** from the allylation reaction of **3.22**.

3.5.2 Identification of diastereoisomers from the allylation of 3.23

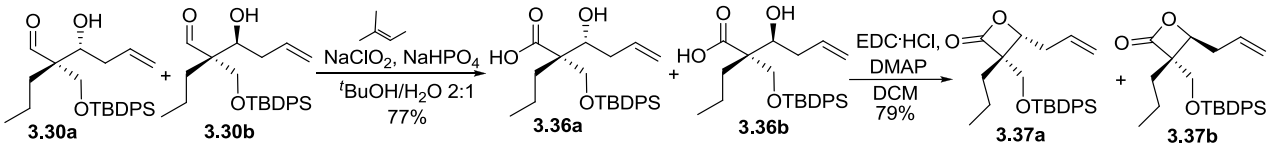
The relative stereochemistry of **3.25b**, major diastereoisomer from the allylation of **3.23** (Scheme 3.19), was determined by oxidising the mixture of **3.25a** and **3.25b** to give acids **3.34a** and **3.34b**. Cyclisation of **3.34a** and **3.34b** with EDC•HCl gave β-lactone **3.35** (Scheme 3.25). An analytically pure sample of major diastereoisomer **3.35b** could be obtained by preparative HPLC. nOe experiments allowed the relative stereochemistry to be determined (Figure 7.21).



Scheme 3.25 Formation of lactone **3.35b** to identify the relative stereochemistry of major diastereoisomer **3.25b**.

3.5.3 Identification of diastereoisomers from the allylation of 3.29

The allylation of **3.29** was carried out in 68% yield and d.r **3.30a**:**3.30b** of 88:12 (Scheme 3.22). The relative stereochemistry of major and minor diastereoisomers **3.30a** and **3.30b** was identified by formation of the corresponding β-lactones according to Mulzer's method (Scheme 3.26).[145]



Scheme 3.26. Formation of β lactone **3.37** to identify the relative stereochemistry of **3.30**.

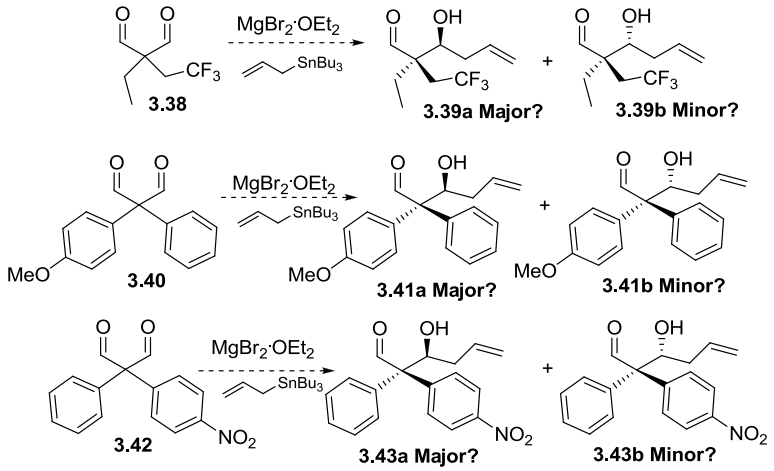
Major and minor lactones **3.37a** and **3.37b** could be separated by preparative HPLC and nOe analysis (Figures 7.22 and 7.23) allowed the relative stereochemistry to be determined.

3.7 Conclusions

We have put forward a rationalisation for the diastereoselection of additions to dialdehydes **1.94**, **1.109** and **2.5** by suggesting reactive conformations. We postulate that additions to dialdehydes **1.109** and **2.5** go *via* flattened boat reactive conformations **3.1** and **3.2**, with nucleophilic approach to the less sterically hindered *Si* face to give the observed major diastereoisomers (Scheme 3.2). Work has suggested that additions to dialdehyde **1.94** display opposite facial selectivity, as the reactions occur *via* a different bridged reactive conformation **3.4** (Scheme 3.3). We have also rationalised the *anti* relationship between the hydroxyl and siloxy group in minor diastereoisomer **1.98b**. Allylstannane **1.97** approaches the same *Re* face of dialdehyde **1.94** as with the major diastereoisomer, however the opposite face of **1.97** reacts (Scheme 3.10).

The cause of the observed diastereoselection in additions to dialdehydes has also been investigated. We propose that the diastereoselection of additions to dialdehydes are controlled by the Cieplak model; this model places the best σ donor on the quaternary centre in the *pseudo* axial position (Scheme 3.21). To strengthen this proposal, further

investigations are suggested. We suggest that the diastereoselection of allylations of dialdehydes with substituents which are sterically similar but electronically different are investigated. Dialdehydes **3.38** with an ethyl and trifluoroethyl, **3.40** and **3.42** with two electronically different aryl groups (similar to Halterman's work)[88] are suggested (Scheme 3.27).

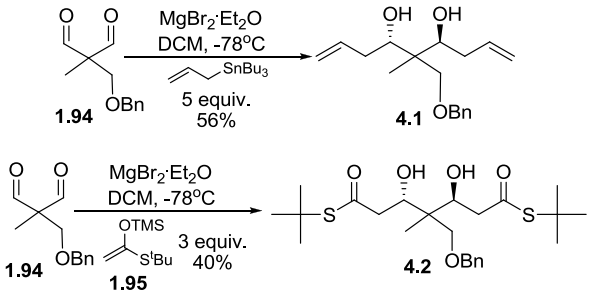


Scheme 3.27. Suggested allylation reactions to probe the Cieplak model.

Chapter 4. Double addition reactions

4.1 Previous work within the group - Mukaiyama aldol and allylation reactions

Previous work within the group found that treatment of dialdehyde **1.94** with an excess of silyl enol ether **1.95** or allyl tributylstannane, in more concentrated conditions, led to a double addition sequence (Scheme 4.1). In both cases only the *pseudo*-C_2-symmetric diastereoisomers **4.1** and **4.2** were isolated. The relative stereochemistry of **4.1** and **4.2** were derived by ^{1}H NMR analysis which shows diastereotopic hydroxyls, therefore the molecule must contain an *anti* 1,3-diol.[109]



Scheme 4.1. Double allylation and Mukaiyama aldol of **1.94**.

In the case of the hydroxyallylation reaction, treatment of **1.94** with an excess of γ-siloxy allylstannane **1.97** results only in monoaddition (Scheme 2.4).[109] It is believed that this is because of the added steric bulk of **1.97** compared to allyl tributylstannane, preventing a second addition.

4.2 The hydroxyallylation – Grignard/MeLi sequence

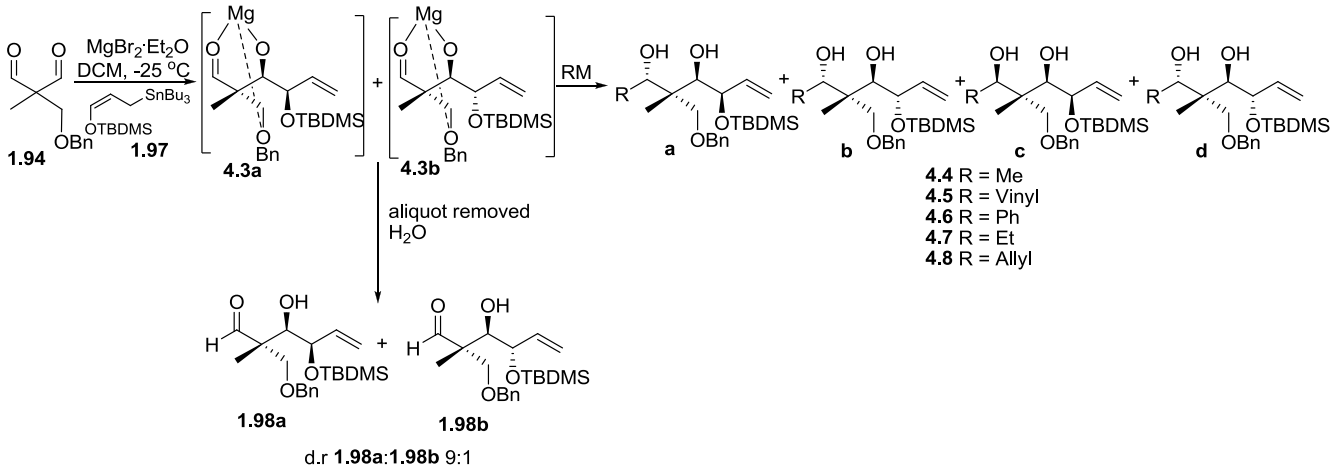
4.2.1 Previous work with the group

The knowledge that hydroxyallylation only results in monoaddition was then exploited to achieve a sequence using a second, stronger nucleophile for the second step. The hydroxyallylation reaction of **1.94** was carried out in the usual way and monitored by TLC. After completion of hydroxyallylation an aliquot of the reaction mixture was removed and

worked up to identify the d.r of the mono-hydroxyallylation reaction. A second, more reactive nucleophile was added and reacted with the unreacted aldehyde to form products containing four contiguous stereocentres, including an *all*-C quaternary centre (Scheme 4.2). Preliminary results showed that MeLi and vinyl Grignard were effective as the second nucleophile.[109] For reasons of clarity these results are discussed amongst other results.

4.2.2 Results of hydroxyallylation – Grignard/MeLi double addition reactions

We have shown that the double hydroxyallylation – Grignard/MeLi addition reactions occur in good yields and diastereoselectivities for a range of different Grignard reagents and MeLi (Scheme 4.2). The results of these reactions are summarised in Table 4.1.



Scheme 4.2. Double hydroxyallylation – Grignard/MeLi addition to **1.94**.

Table 4.1. Summary of double hydroxyallylation – Grignard/MeLi additions to **1.94**.

Entry	RM	d.r [a] 1.98a:1.98b	Product	% Yield [b]	d.r [c] a:b:c:d
1	MeLi	90:10	**4.4**	51	79:12:9:0[109]
2	MeMgBr	93:7	**4.4**	56	87:9:4:0
3	VinylMgBr	90:10	**4.5**	67	>90:10<:0:0[d][109]
4	PhMgBr	90:10	**4.6**	59	90:10:0:0
5	EtMgBr	89:11	**4.7**	60	88:12:0:0
6	AllylMgBr	90:10	**4.8**	51	>90:10<:0:0[d]

[a] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude from an aliquot taken from the hydroxyallylation reaction.

[b] – Isolated yield after column chromatography.

[c] – Determined by ^{1}H NMR analysis (Figure 4.1 (entry 2), see chapter 7, Figure 7.25 (entry 4) and 7.26 (entry 5))

[d] – Precise diastereomeric ratio could not be determined (Figure 7.24 and 7.27).

Preliminary results by Elena Cini revealed that the hydroxyallylation – MeLi addition sequence yielded three diastereoisomers (entry 1). A derivative of major diastereoisomer **4.4a** was a crystalline solid and the relative stereochemistry identified by X-ray crystallography. Preliminary results also revealed that the hydroxyallylation – vinyl Grignard addition sequence yielded only two diastereoisomers (entry 3).[109] We were unsure as to whether the third diastereoisomer (**4.4c**) was formed because of steric differences between adding a methyl or a vinyl group or differences between an alkyl lithium nucleophile and a Grignard. The same double addition sequence was attempted using MeMgBr as the second nucleophile (entry 2). The third *syn* 1,3-diol diastereoisomer **4.4c** was observed in this reaction by ^{1}H NMR (Figure 4.1). This suggests that the facial selectivity in the second addition is controlled by the size of the second nucleophile. However MeMgBr did give an improved diastereomeric ratio compared with MeLi (87:9:4 *cf* 79:12:9) suggesting Grignard reagents are better nucleophiles for additions to dialdehydes.

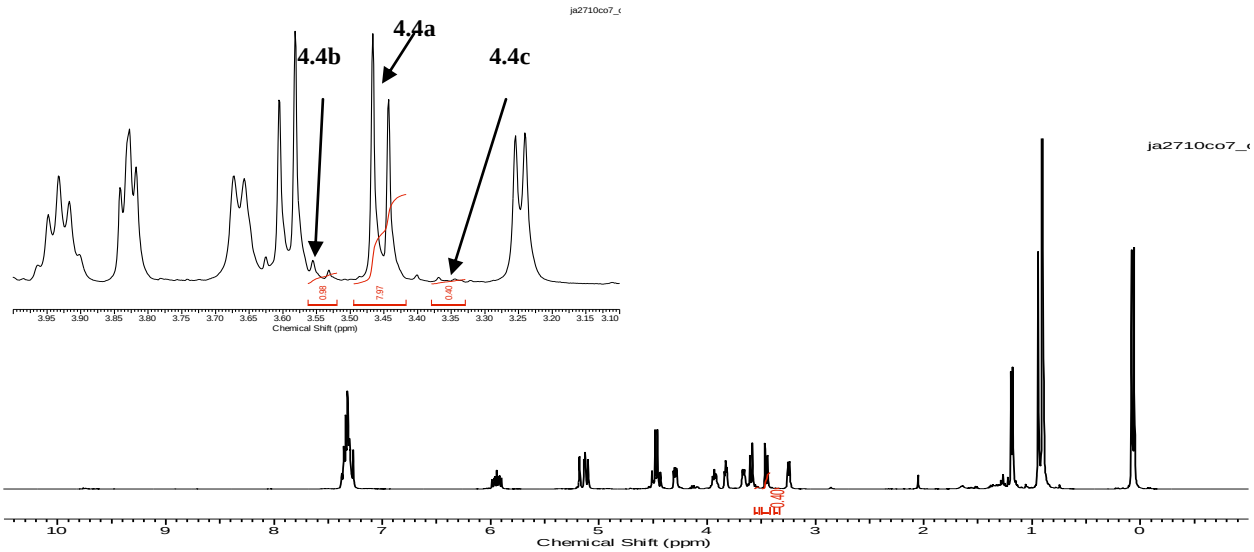
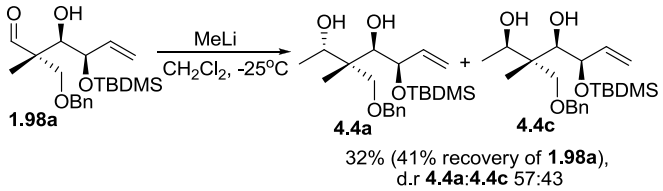
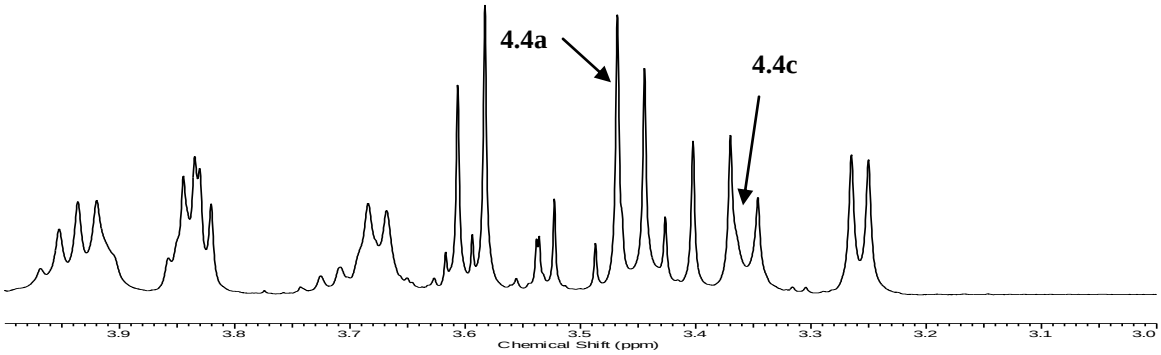


Figure 4.1. ^{1}H NMR of **4.4** after chromatography from which d.r was determined and the presence of **4.4c** was identified.

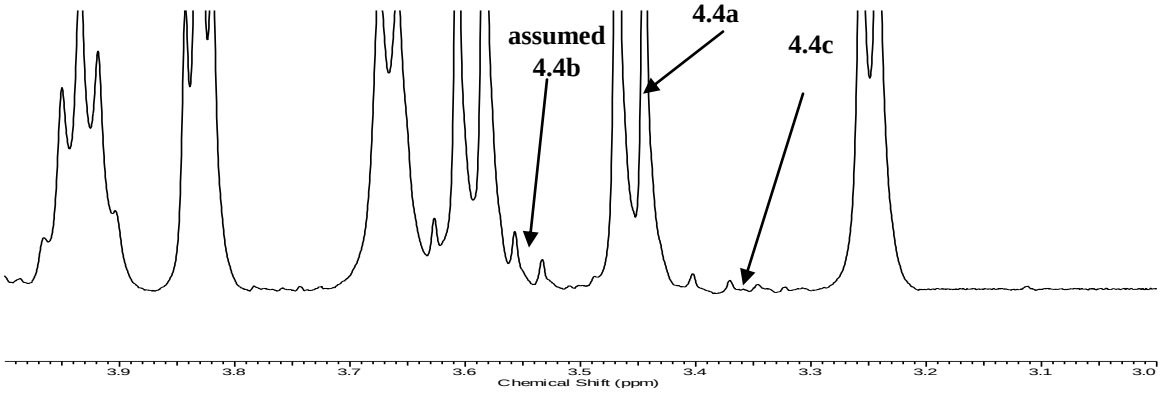
Identification of the peaks for **4.4a**, **4.4b** and **4.4c** was determined by carrying out MeLi addition on isolated **1.98a** without $MgBr_2$•OEt_2 chelation (Scheme 4.3) to give a mixture of **4.4a** and **4.4c**. From this it could be determined which peaks related to which diastereoisomer and so calculate the d.r (Figure 4.2).



Scheme 4.3. MeLi addition to **1.98a**.



(a) Expansion of crude ^{1}H NMR of MeLi addition to **1.98a**



(b) Expansion of crude ^{1}H NMR of MeMgBr addition after hydroxyallylation of dialdehyde **1.94**

Figure 4.2 Determination of peaks relating to **4.4a**, **4.4b** and **4.4c**.

Entries 2-6 (Table 4.1) show that the hydroxyallylation – Grignard double addition sequence is effective for a range of Grignards in good yields and excellent diastereoselectivity. For all

Grignard reagents, other than MeMgBr, the second addition appears to be completely diastereoselective with only the *anti*-1,3-diol observed.

4.3 Rationalisation of diastereoselection

All of the double addition reactions carried out on dialdehyde **1.94** appear to be highly diastereoselective for the *anti*-1,3-diol (*pseudo*-C_2 symmetric) product. It is believed that after the first addition, which occurs in the usual fashion, all three chelating oxygens remain attached to the $MgBr_2$•OEt_2, two remain chelated and the reacted aldehydic oxygen forms a covalent O-Mg bond to form **4.3a** and **4.3b**. The hydroxyallyl side chain is then blocking the *Si* face in the bridged reactive intermediate, so the 2nd nucleophile has to approach from the *Re* face to give the *anti* 1,3 diol relationship (Figure 4.3). Using a sterically smaller second nucleophile, such as MeLi or MeMgBr (Scheme 4.2), a minor amount of *Si* face approach is observed to yield **4.4c**.

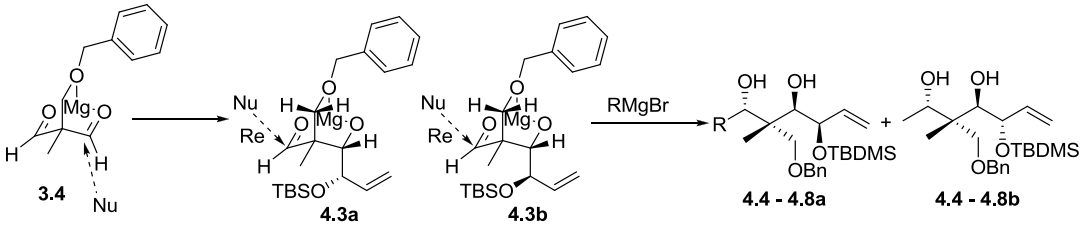
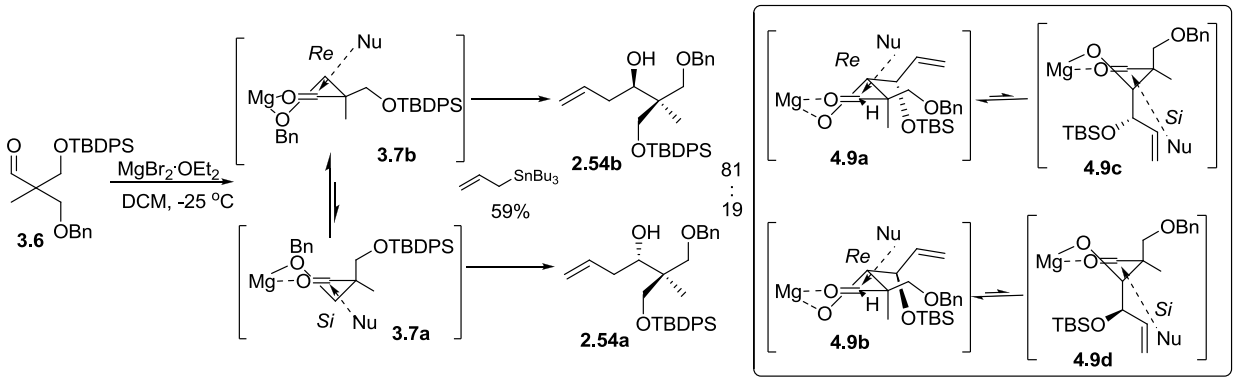


Figure 4.3 Possible rationalisation of *anti* 1,3-diol relationship displayed after double addition to dialdehyde **1.94**.

If after the first addition, formation of the covalent Mg-O bond caused the chelate between the Mg and the benzyl ether oxygen to break, the second addition would be expected to go *via* half chair reactive conformation **4.9**. The allylation of model compound **3.6** has been reported in the previous chapter (Scheme 4.4). Aldehyde **3.6** has a chelating benzyl ether oxygen and a non-chelating TBDPS ether oxygen and therefore must form a half chair reactive conformation (**3.7**) with $MgBr_2$•OEt_2.

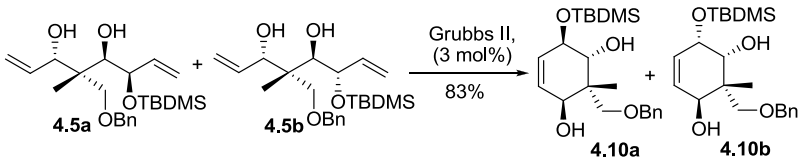


Scheme 4.4 Allylation of aldehyde **3.6**.

In this allylation reaction it was found that the d.r was 81:19, suggesting that a minor diastereoisomer should be expected when the reaction is going *via* a half chair reactive intermediate. In the double addition reactions of dialdehyde **1.94** a minor diastereoisomer as a result of the second addition is only observed with small MeLi or MeMgBr nucleophiles (Scheme 4.2); the products almost exclusively show the *anti* 1,3-diol relationship. This suggests that the double addition reactions occur *via* the bridged intermediates **4.3** (Figure 4.3).

4.4 RCM

Diol **4.5**, product from a double addition reaction on dialdehyde **1.94**, can undergo a RCM reaction with Grubbs II to form cyclohexene **4.10** in good yields (Scheme 4.5).[156, 157] This could be a potentially interesting substrate in the synthesis of cyclitol derivatives and complex carbohydrates as it contains four contiguous stereocentres, including an *all*-C quaternary stereocentre and a double bond that could be dihydroxylated or undergo epoxidation.

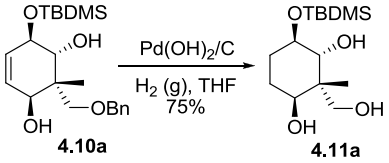


Scheme 4.5 RCM of double addition product **4.5**.

It was found that the large difference in polarity of major and minor diastereoisomer **4.10a** and **4.10b** allowed easy separation by column chromatography.

4.4.1 Identification of 1.98b, minor diastereoisomer from the hydroxyallylation of 1.94

After hydrogenolysis of major diastereoisomer **4.10a**, it was found that triol **4.11a** (Scheme 4.6) was a crystalline solid whose relative stereochemistry was assigned by X-ray crystallography (Figure 4.4).



Scheme 4.6 Hydrogenolysis of major diastereoisomer **4.10a**.

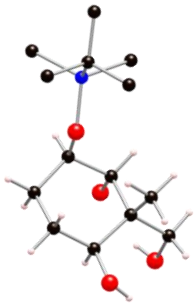
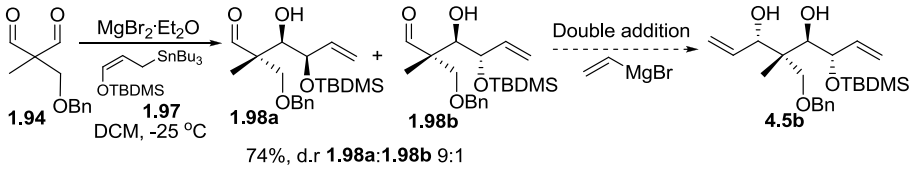


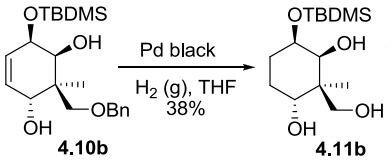
Figure 4.4 X-ray structure of **4.11a**

This double addition / RCM sequence was used to unambiguously assign the relative stereochemistry of the minor hydroxyallylation diastereoisomer **1.98b** (Scheme 4.7). After double addition sequence with vinyl Grignard (Scheme 4.2), RCM on **4.5a** and **4.5b** allowed for isolation of **4.10b** (Scheme 4.5).



Scheme 4.7 Hydroxyallylation of **1.94**

Hydrogenolysis of minor diastereoisomer **4.10b** gave **4.11b** as an oil, which after column chromatography and trituration with hexane gave a white solid (Scheme 4.8). This was recrystallised from diisopropyl ether and hexane to give fine crystalline needles which were submitted for X-ray analysis, revealing the relative stereochemistry of **4.11b** to be as shown (Figure 4.5).



Scheme 4.8 Hydrogenolysis of **4.10b**

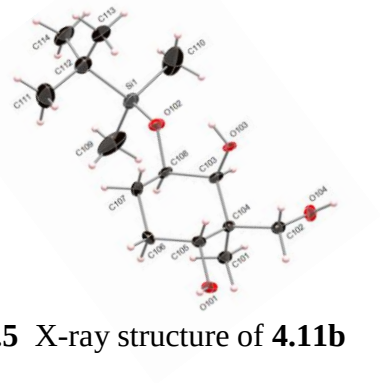


Figure 4.5 X-ray structure of **4.11b**

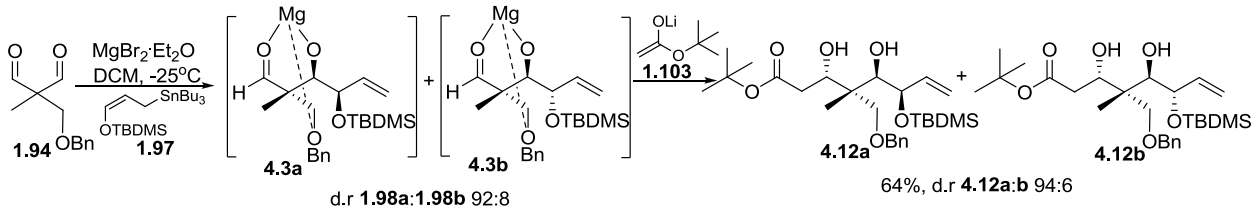
Identification of the relative stereochemistry of **4.11b** by X-ray crystallography has confirmed the relative stereochemistry of the minor diastereoisomer **4.5b**, from the hydroxyallylation - Grignard addition sequence, as also displaying an *anti* 1,3-diol moiety. Diol **4.5b** therefore must be a result of the minor diastereoisomer from the hydroxyallylation reaction, with the Grignard addition being completely diastereoselective (Scheme 4.2). The X-ray of **4.11b** has therefore also revealed the relative stereochemistry of **1.98b**, the minor diastereoisomer from the hydroxyallylation reaction of **1.94**, to be as shown (Scheme 4.7).

4.5 Hydroxyallylation – Aldol reactions

The monoaddition aldol reaction on **1.94** using Li - enolates of *t*-butyl acetate (**1.103**) and *t*-butyl propionate (**1.104**) has been developed (Scheme 2.17 and 2.18). The hydroxyallylation - aldol double addition sequence was attempted using acetate and propionate enolates **1.103** and **1.104**.

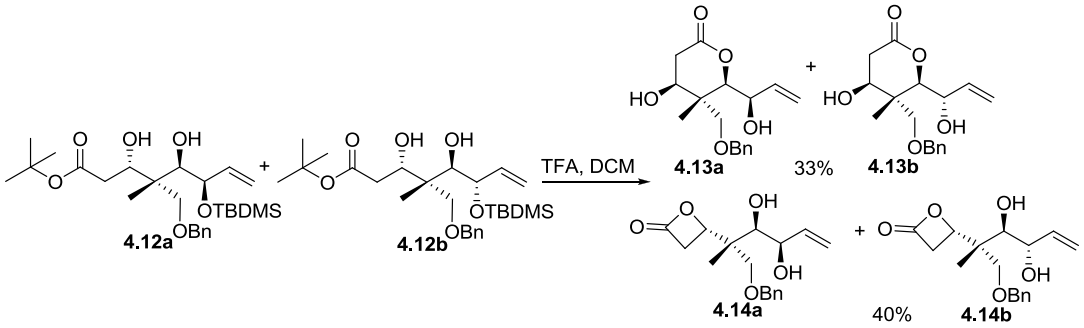
4.5.1 Hydroxyallylation – Aldol with 1.103

The hydroxyallylation - aldol reaction with Li - enolate **1.103** has been carried out in good yields and diastereoselectivity to give products containing four contiguous stereocentres, including an *all*-C quaternary stereocentre (Scheme 4.9).



Scheme 4.9 Hydroxyallylation, followed by aldol with **1.103** on dialdehyde **1.94**

Only two diastereoisomers **4.12a** and **4.12b** were identified from this double addition reaction, but were inseparable by HPLC. The relative stereochemistry of major diastereoisomer **4.12a** was identified by ester hydrolysis, causing cyclisation and concomitant desilylation to yield δ-lactone **4.13** and tentatively assigned β-lactone **4.14** (Scheme 4.10). The IR carbonyl stretching frequency for **4.13a** was 1721 cm^{-1},[158] typical for a δ-lactone; compared with 1786 cm^{-1} for **4.14a**, typical for a β-lactone. Preparative HPLC isolated an analytically pure sample of **4.13a** and nOe experiments identified the relative stereochemistry of the δ-lactone **4.13a** (see chapter 7, Figure 7.29).



Scheme 4.10 Formation of lactones **4.13** and **4.14**.

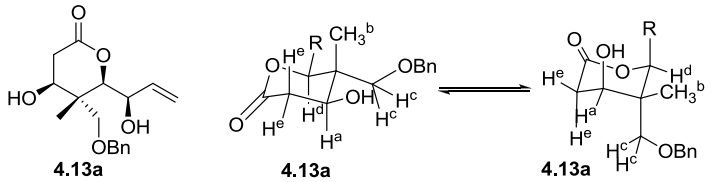


Figure 4.6. Potential chair conformations of **4.13a**.

Analysis of the ^{1}H NMR of **4.13a** revealed that proton H^a appeared as a t (J = 7.1 Hz) rather than the expected dd. Both H^e_{ax} and H^e_{eq} exist as dd with $J_{Ha\text{-}He}$ = 7.3 Hz and 6.6 Hz. These J values are close enough to cause the signal for H^a to merge into a triplet and 7.3 and 6.6 Hz are typical values for an axial equatorial coupling and an equatorial equatorial coupling.[134] However AM1 semi-empirical calculations (carried out by Nathan Bartlett) show large differences in the angles between H^a and H^e_{ax} and H^e_{eq}[153] suggesting that the chair conformation of **4.13a** is in equilibrium between the ring inversions, resulting in the defined triplet for H^a (Figure 4.6), and explaining the observed nOe between H^a and H^b and H^d and H^b (Figure 7.29).

Interestingly it was discovered that a sample of β-lactone **4.14a**, after one month in the freezer, had almost quantitatively converted to δ-lactone **4.13a** (Figure 4.7). This suggests that the β-lactone **4.14** is the kinetic product of the cyclisation, however **4.13** is the thermodynamic product.

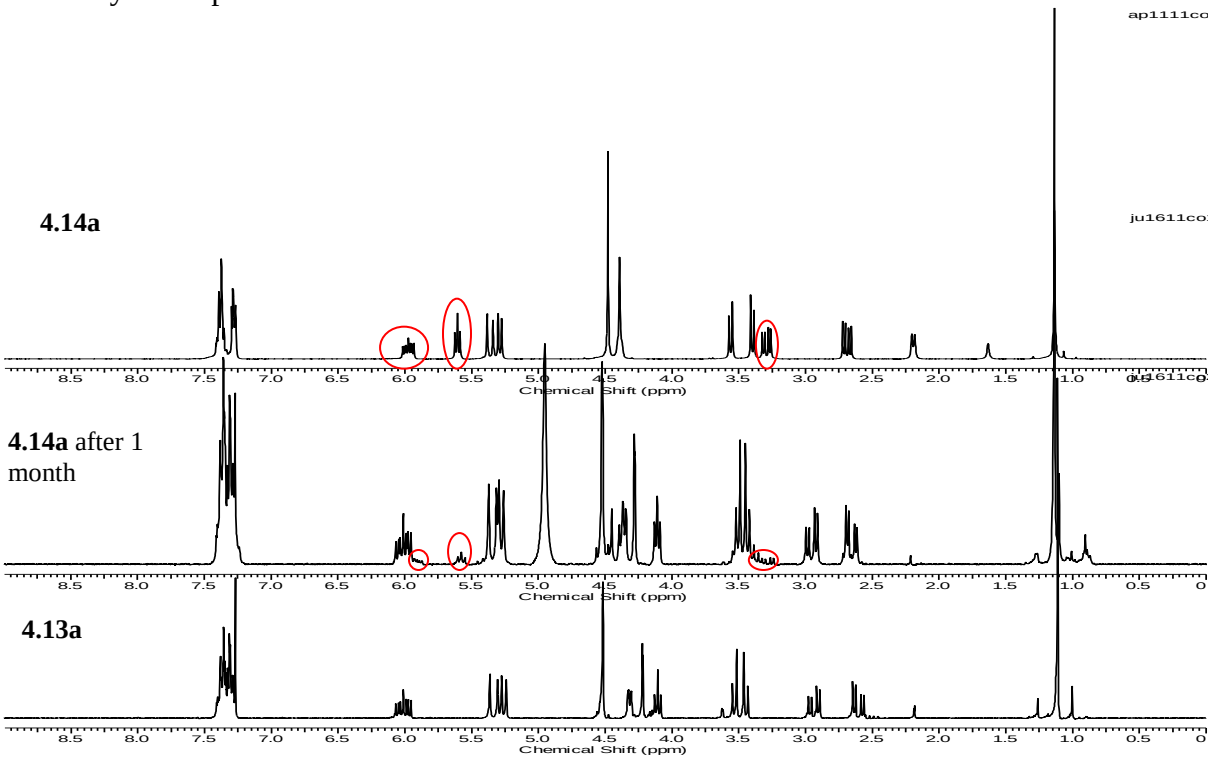
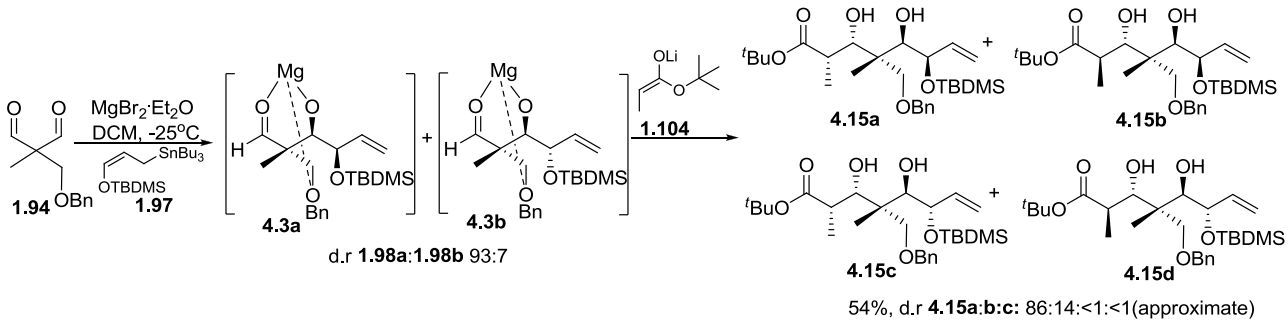


Figure 4.7. Conversion of **4.14a** to **4.13a**

4.5.2 Hydroxyallylation – Aldol with 1.104

The hydroxyallylation – aldol sequence with Li enolate **1.104** has been carried out in good yields and diastereoselectivity to give products containing five contiguous stereocentres, including an *all*-C quaternary stereocentre (Scheme 4.11).

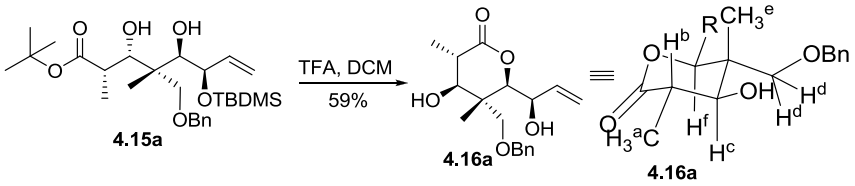


Scheme 4.11 Hydroxyallylation, followed by aldol with **1.104** on dialdehyde **1.94**

Four diastereoisomers were isolated from this reaction, however an accurate d.r could not be calculated as there was no baseline separation of the diastereoisomers in the ^{1}H NMR. An approximate d.r was calculated using the C**H**CH_3 peaks where **4.15a** and **4.15b** could be distinguished. However the C**H**CH_3 peak of **4.15d** overlapped with the C**H**CH_3 peak of **4.15a** and the C**H**CH_3 peak of **4.15c** overlapped with other peaks in the crude ^{1}H NMR (Figure 7.30). The four diastereoisomers were separated by preparative HPLC, with less than 1% of pure **4.15c** and **4.15d** isolated. This allowed the approximate d.r of 86:14:<1:<1 to be put forward.

4.5.2.1 Identification of relative stereochemistry of 4.15a

The relative stereochemistry of major diastereoisomer **4.15a** was identified by ester hydrolysis, causing cyclisation and concomitant desilylation to yield δ-lactone **4.16a** (Scheme 4.12). nOe experiments on **4.16a** identified the relative stereochemistry of the δ-lactone (Figure 7.31).

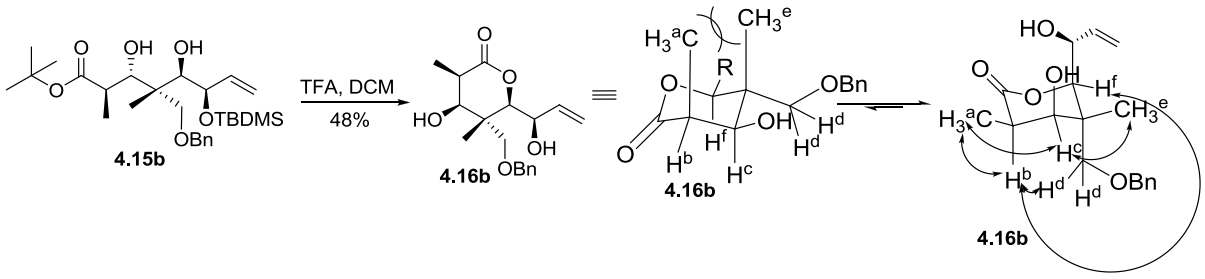


Scheme 4.12 Formation of δ-lactone **4.16a**

Analysis of the ^{1}H NMR spectrum of **4.16a** revealed H^b to be a multiplet. Double irradiation of methyl group H^a clarified the coupling of H^b to be a doublet, revealing $J_{Hb\text{-}Hc}$ = 9.8 Hz which is consistent with a $J_{ax\text{-}ax}$ interaction.[134] This suggests that **4.16a** exists in the chair conformation shown (Scheme 4.12), with the benzyloxy group and the side chain, R, equatorial.

4.5.2.2 Identification of relative stereochemistry of 4.15b

The relative stereochemistry of major diastereoisomer **4.15b** was identified by ester hydrolysis causing cyslisation and concomitant desilylation to yield δ-lactone **4.16b** (Scheme 4.13).



Scheme 4.13 Formation of δ-lactone **4.16b**

Analysis of the ^{1}H NMR spectrum of **4.16b** revealed H^b to be a qd. Double irradiation of methyl group H^a clarified the coupling of H^b to H^c, revealing $J_{Hb\text{-}Hc}$ = 4.7 Hz which is consistent with a $J_{ax\text{-}eq}$ coupling.[159] DFT calculations by Nathan Bartlett showed the conformation of **4.16b** with the highest population to be the chair with the two methyl groups equatorial and the benzyloxy group and side chain axial.[153] This is likely to be because of the unfavourability of the 1,3-diaxial interaction between the two methyl groups in the ring inversion chair conformation. This suggests that **4.16b** exists in the chair conformation shown (Scheme 4.13) with the benzyloxy group and the side chain axial. nOe experiments on **4.16b** fitted this being the relative stereochemistry and conformation of the δ-lactone (Figure 7.32).

It is however surprising that the medium diastereoisomer from the hydroxyallylation - aldol double addition should be **4.15b**. It is expected that the d.r of monohydroxyallylation to be reflected in the ratio of the double addition products. Although the d.r of **4.15** is approximate (Figure 7.30), it does suggest that the medium diastereoisomer formed (14%) should be the product of the minor diastereoisomer from the hydroxyallylation and the major diastereoisomer from the aldol reaction (**4.15c**). Hence we checked whether the observed NMR data could fit the structure of **4.16c**, which would be obtained from **4.15c** (minor hydroxyallylation – major aldol product). DFT calculations by Nathan Bartlett found that the highest populated possible low energy conformation of **4.16c** placed the benzyloxy group and the side chain in the equatorial position on the chair (Figure 4.8) as in **4.16a**.[153]

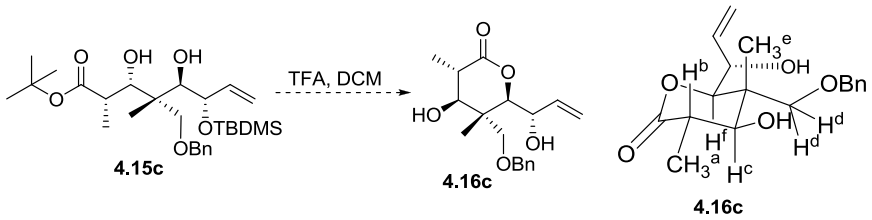


Figure 4.8 Highest populated conformation of **4.16c** according to DFT calculations.[153]

DFT results revealed the expected $J_{Hb\text{-}Hc}$ value of the axial axial coupling in this conformation to be 8.1 Hz.[153] The observed $J_{Hb\text{-}Hc}$ coupling of the medium δ-lactone was found to be 4.7 Hz which is consistent with a $J_{ax\text{-}eq}$ coupling and not a $J_{ax\text{-}ax}$ coupling. The nOe of the δ-lactone also did not match **4.16c** in the conformation shown (Figure 4.8) as a response was observed between H^b and H^f, which have a 1,4-diaxial relationship in **4.16c** (Figure 7.32). This suggests that the medium lactone is **4.16b** and it exists in the chair conformation shown (Scheme 4.13).

The medium diastereoisomer from the hydroxyallylation - aldol double addition with Li enolate **1.104** on dialdehyde **1.94** is therefore **4.15b**. This is a result of the major diastereoisomer from the hydroxyallylation and the minor diastereoisomer from the aldol reaction and is in fitting with the poor d.r observed in the monoaddition aldol reaction of **1.104** with **1.94** (Scheme 2.18). It is believed that the inconsistencies of the d.r of the monohydroxyallylation and the d.r of **4.15** are as a result of the difficulties of obtaining an accurate d.r for **4.15** (Figure 7.30). The small amount of **4.15c** and **4.15d** isolated can be attributed to difficulties in separation of the diastereoisomers.

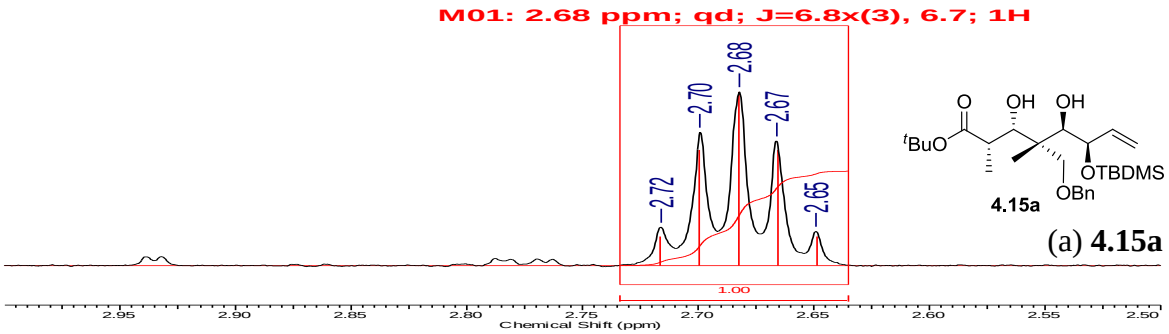
4.5.2.3 Identification of relative stereochemistry of 4.15c and 4.15d

Minor diastereoisomer **4.15c** and **4.15d** were identified by comparison of their ^{1}H NMR's with **4.15a** and **4.15b**. It is believed that both **4.15c** and **4.15d** result from **4.3b**, the minor diastereoisomer from the hydroxyallylation. Proton C**H**CH_3 in **4.15a** is a qd with a *J* coupling of 6.8, 6.7 Hz. The same proton in **4.15b** is a qd with a *J* coupling of 7.2, 2.8 Hz. It is known that there is a *syn* relationship between the methyl and hydroxyl groups in **4.15a** and an *anti* relationship in **4.15b**. The C**H**CH_3 protons in **4.15c** and **4.15d** also appear as a qd

in the ^{1}H NMR. In **4.15c** J = 7.1, 6.1 Hz, suggesting the same *syn* relationship as in **4.15a**. In **4.15d** J = 7.3, 2.0 Hz, suggesting the same *anti* relationship as in **4.15d** (Figure 4.9). It is therefore suggested that **4.15c** and **4.15d** have the relative stereochemistry as shown (Scheme 4.11). This analysis confirms the assignments from the nOe's of the lactones **4.16a** and **4.16b** (Scheme 4.12 and 4.13) confirming that there is a different relationship between the methyl and the hydroxyl from the second addition in **4.15a** and **4.15b**.

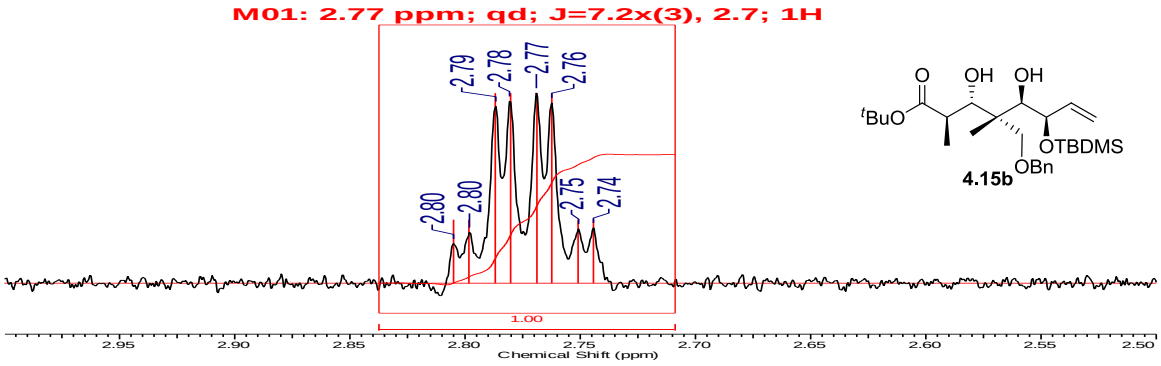
4.6 Conclusions

A one pot, two component hydroxyallylation – Grignard/MeLi double addition sequence on dialdehyde **1.94** has been achieved to form products containing four contiguous stereocentres, including an *all-C* quaternary centre in good yields and excellent diastereoselectivities. It has been demonstrated that the hydroxyallylation – Grignard double addition is effective for a range of different Grignard reagents (Scheme 4.2). It has been shown that the second addition after hydroxyallylation is highly stereoselective, giving almost exclusively the *anti* 1,3-diol and this high diastereoselectivity has been rationalised (Figure 4.3). A RCM performed on double addition product **4.5** has been utilised to identify the relative stereochemistry of **1.98b**, the minor diastereoisomer from the hydroxyallylation reaction of **1.94** (Figure 4.5) and the relative stereochemistry of double addition products **4.5a** and **4.5b**. The hydroxyallylation – aldol double addition reaction has also been achieved using enolates **1.103** to give products containing four contiguous stereocentres (Scheme 4.9) and **1.104** to give products containing five contiguous stereocentres (Scheme 4.11), including an *all*-C quaternary stereocentre in good yields and good diasteroselectivites. The relative stereochemistry of the products from these double addition reactions have been identified by formation of the δ-lactone (Scheme 4.12 and 4.13) and subsequent nOe experiments and ^{1}H NMR analysis.

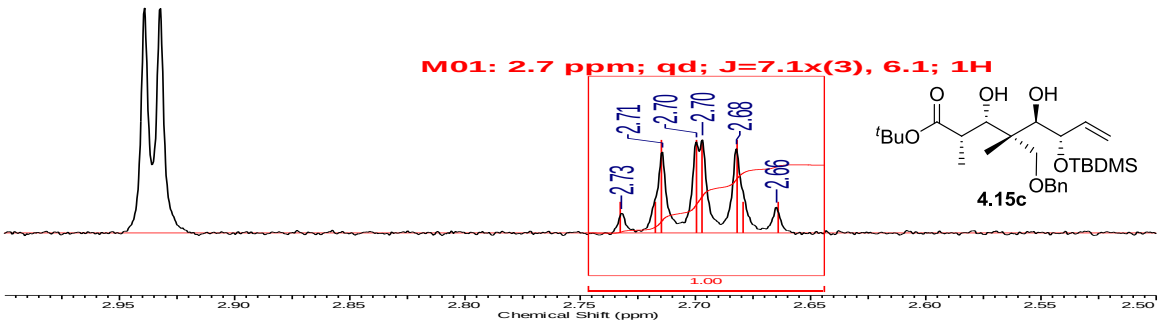


(a) **4.15a**

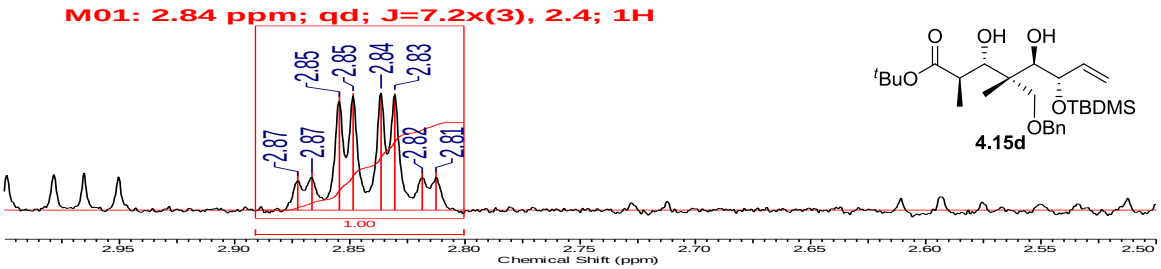
C**H**CH$_3$



(b) **4.15b** C**H**CH$_3$



(c) **4.15c** C**H**CH$_3$



(d) **4.15d** C**H**CH$_3$

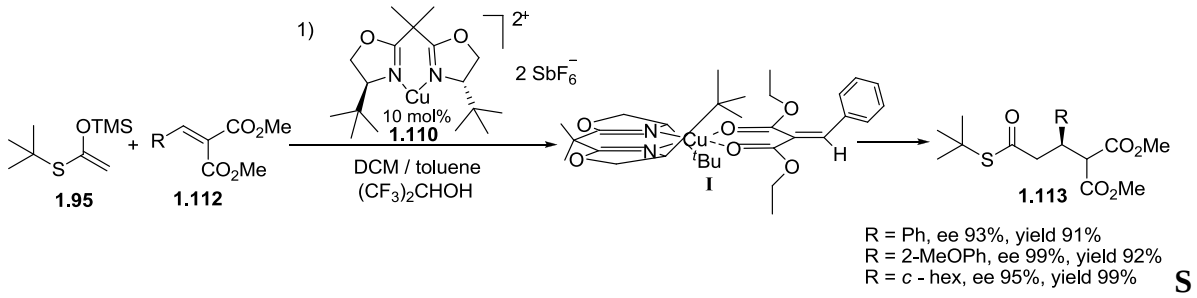
Figure 4.9 C**H**CH$_3$ peaks of **4.15** diastereoisomers in ^{1}H NMR's

Chapter 5. Synthesis of enantioenriched *all*-C quaternary centres

5.1 Chiral Ligands

5.1.1 Evans box ligands

Evans' bisoxazoline catalysts have a proven record for the bidentate activation of 1,3-dicarbonyl species.[14, 110-112] The Evans bisoxazoline will coordinate with the metal, often Cu(II), to form the active catalyst. This then coordinates with the 1,3-dicarbonyl species, giving differentiation between the two faces of the electrophile. Evans' bisoxazoline catalysts have demonstrated excellent enantioinduction in the Michael Mukaiyama reaction of **1.95** with **1.112** (Scheme 5.1).

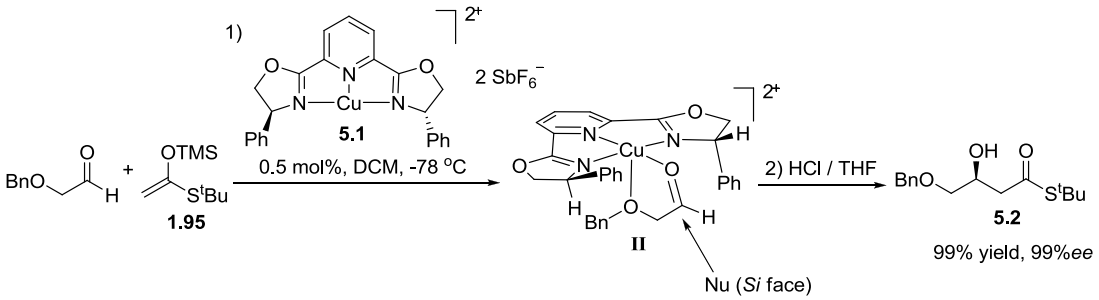


S

cheme 5.1. Enantioselective Michael Mukaiyama reaction using bisoxazoline ligand **1.110**.[111]

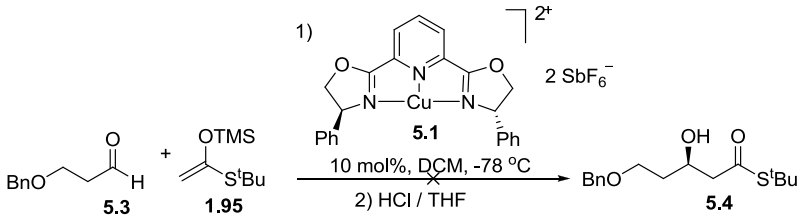
The Evans bisoxazoline catalyst coordinates with **1.112** to form intermediate **I**. The *Re* face of the coordinated carbonyl is shielded by the *tert*-butyl substituent on the ligand, permitting approach of the silyl enol ether from the *Si* face only. This leads to the shown product **1.113** in excellent enantioselectivity (93-99% *ee*).[111]

Evans *et.al* has shown that [Cu((*S*,*S*)py-box)](SbF$_6$)$_2$ complex **5.1** catalyses the addition of silyl enol ether **1.95** to benzyloxyacetaldehyde in excellent yields and enantioselectivity. It is believed the reaction requires a five coordinate Cu(II) catalyst – substrate complex (**II**) with the Cu(II) in a square pyramidal geometry (Scheme 5.2).[112]



Scheme 5.2 Cu(II) py-box catalysed Mukaiyama aldol reaction of benzyloxyacetaldehyde.

However the [Cu((*S*,*S*)py-box)](SbF$_6$)$_2$ **5.1** failed to catalyse the Mukaiyama aldol reaction on aldehyde **5.3**, with an additional methylene unit in the tether compared to benzyloxyacetaldehyde (Scheme 5.3).

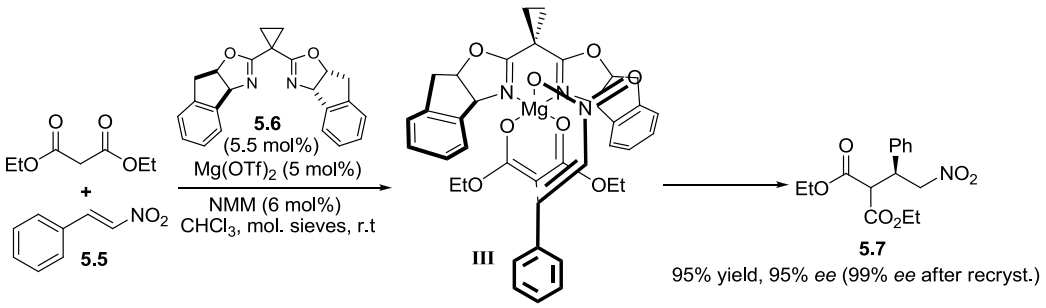


Scheme 5.3 Failed Cu(II) py-box Mukaiyama aldol reaction of **5.3**.

Stereochemical models suggest the five membered chelate with benzyloxyacetaldehyde complements the ligand pocket available in [Cu(Ph-pybox)]-(SbF$_6$)$_2$, whereas the six membered chelate for aldehyde **5.3** adopts a chair or twist boat conformation which undergoes significant steric interactions with the pybox ligand framework.[112] Our 1,3-dialdehydes **1.94** and **1.109** would form reactive conformations **3.4** and **3.1** (Scheme 3.2 and 3.3) respectively. These conformations are expected to cause the same steric interactions with the pybox ligand framework as aldehyde **5.3**, so for our investigations it was decided to focus on the bisoxazoline ligands above the pyridine(bisoxazoline) ligands.

Bisoxazoline ligand have also been shown to form effective catalysts with Mg(II).[160-165] Barnes *et.al.* have shown that Mg(II) bisoxazoline (**5.6**) complex will catalyse the enolisation addition reaction of diethylmalonate to nitroolefin **5.5** in excellent yields and enantioselectivity. The authors believe the transition state complex **III** has square pyramidal

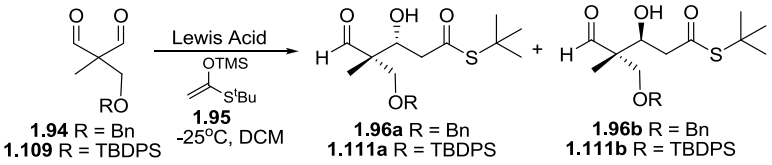
geometry with the ligand and enolate in the plane and the incipient nitronate anion stabilised by an interaction with the axial coordination site on the metal (Scheme 5.4).[166]



Scheme 5.4 Mg(II) bisoxazoline catalysed addition to diethylmalonate.

5.1.1.1 Lewis acid screen

Most literature precedent of enantioselective reactions with Evans' bisoxazoline ligands uses Cu(II) as the Lewis acid.[111, 112] However all the diastereoselective reactions of dialdehydes **1.94**, **1.109** and **2.5** have been carried out using $MgBr_2$•OEt_2. When initial work was carried out, $MgBr_2$•OEt_2 was found to form a chelate with non-enolisable 1,3-dialdehydes.[109] A wide range of Lewis acids were screened to find other Lewis acids that would effectively activate the Mukaiyama aldol reaction of dialdehydes **1.94** and **1.109** (Scheme 5.5). A summary of the results of these reactions are shown in Table 5.1.



Scheme 5.5. Diastereoselective Mukaiyama aldol reaction of **1.94** and **1.109**, Lewis acid screen.

Table 5.1. Summary of Lewis acid screen on Mukaiyama aldol reactions on dialdehydes **1.92** and **1.107**.

Entry	Dialdehyde	Lewis Acid	Conversion to 1.96 or 1.111 by HPLC [a]
1	**1.109**	$Sc(OTf)_3$	-
2	**1.109**	$Y(OTf)_3$	0.5%
3	**1.109**	$In(OTf)_3$	-
4	**1.109**	$Bi(OTf)_3$	-
5	**1.109**	LiCl	-
6	**1.109**	$TiCl_4$	2%
7	**1.109**	$Ti(O^iPr)_4$	-
8	**1.109**	$CuCl_2$	1%
9	**1.109**	$Cu(OTf)_2$	5%
10	**1.109**	$Cu(SbF_6)_2$	8%
11	**1.109**	$NiBr_2$	0.5%
12	**1.109**	$Ni(SbF_6)_2$	8%
13	**1.109**	$ZrCl_4$	18%
14	**1.109**	$Zn(OAc)_2$	-
15	**1.109**	$AlEt_2Cl$	3%
16	**1.109**	CaI_2	1%
17	**1.109**	$Sr(O^iPr)_2$	3%
18	**1.109**	SrI_2	-
19	**1.109**	$Mg(OTf)_2$	3%
20	**1.109**	$Mg(ClO_4)$	2%
21	**1.109**	MgI_2	43%
22	**1.109**	$MgBr_2 \bullet OEt_2$	59%
23	**1.94**	$Sc(OTf)_3$	1%
24	**1.94**	$Y(OTf)_3$	0.6%
25	**1.94**	$In(OTf)_3$	1%
26	**1.94**	$Cu(OTf)_2$	-
27	**1.94**	$NiBr_2$	-
28	**1.94**	$ZrCl_4$	1%
29	**1.94**	$Zn(OAc)_2$	-
30	**1.94**	$AlEt_2Cl$	-
31	**1.94**	CaI_2	11%
32	**1.94**	$Sr(O^iPr)$	1%
33	**1.94**	SrI_2	2%
34	**1.94**	$Mg(OTf)_2$	0.5%
35	**1.94**	$Mg(ClO_4)$	24%
36	**1.94**	MgI_2	11%
37	**1.94**	$MgBr_2 \bullet OEt_2$	52%

[a] - % conversion to **1.96** or **1.111** determined by observing product peak in HPLC trace.

In the Mukaiyama aldol reaction of dialdehyde **1.109** (Scheme 5.5) a range of transition and heavy metals were screened as the Lewis acid (entries 1-4). The reactions were monitored by analytical HPLC and after 18 h no peak was observed on the HPLC trace correlating to **1.111**; however there was a reduction in the level of starting material and an impurity peak appeared that by LCMS had a mass of 436. It is believed that this is an aldehyde degradation product. Ti(IV) Lewis acids were screened (entries 6-7), these, by HPLC, showed no consumption of starting material. A range of Cu(II) Lewis acids (entries 8-10) were looked at as there is literature precedent of these chelating to 1,3-dicarbonyls.[111] By HPLC there was only a small amount of conversion to product **1.111**. It was also observed that the larger the counter ion the greater the conversion of **1.109** to **1.111**. However in the case of $Cu(OTf)_2$ (entry 9) and $Cu(SbF_6)_2$ (entry 10), where there is greater conversion to **1.111** (5% and 8% respectively) there is also more of the aldehyde degradation impurity present.

Lewis acids with similar properties to $MgBr_2 \bullet OEt_2$, according to a PCA (Principle Component Analysis) diagram of Lewis acids, were screened (entries 11-15). These also showed little conversion by HPLC. The Ni(II) Lewis acids (entries 11-12) showed little consumption of starting materials. $ZrCl_4$ (entry 13) showed 18% conversion to **1.111**, however the HPLC trace was messy showing the formation of many different impurities. Zn(II) (entry 14) is more Lewis acidic than $MgBr_2 \bullet OEt_2$, however when screened showed no consumption of starting materials. $AlEt_2Cl$ (entry 15) showed only 3% conversion to **1.111**; however it showed a small amount of the dialdehyde degradation impurity.

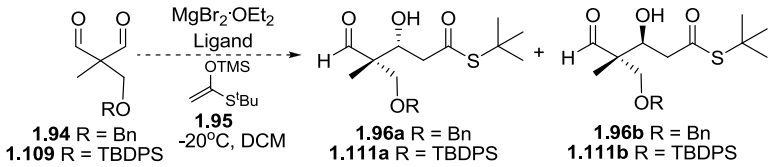
In entries 16-22 a series of group 2 Lewis acids were screened. CaI_2 (entry 16) showed no consumption of starting materials by HPLC. Sr(II) Lewis acids (entries 17-18) also displayed little conversion to **1.111**. $Mg(OTf)_2$ (entry 19) and $Mg(ClO_4)$ (entry 20) displayed little conversion to **1.111** with very little consumption of starting material. MgI_2 (entry 21) showed 43% conversion to **1.111** by HPLC after 1 h. However at that point the reaction appeared to stop and no more starting material was consumed despite the reaction being left longer. $MgBr_2 \bullet OEt_2$ (entry 22) displayed 59% conversion to **1.111** by HPLC, making it the optimum Lewis acid tested for activating dialdehyde **1.109**.

The Lewis acid screen for the Mukaiyama aldol reaction of dialdehyde **1.94** (Scheme 5.5) displayed the same trend as that for dialdehyde **1.109**. A wide range of Lewis acids (entries 23-30) were screened which displayed no conversion to **1.96**. A series of group 2 Lewis acids were also screened. CaI_2 (entry 31) displayed 11% conversion to **1.96**, however the HPLC trace was messy showing many impurities formed and a lot of unreacted starting material. Sr(II) Lewis acids screened (entries 32-33) displayed very little conversion to **1.96**. $Mg(OTf)_2$ (entry 34) showed little consumption of starting material by HPLC. $Mg(ClO_4)$ (entry 35) showed 24% conversion to **1.96** by HPLC after 1 h, however after this the reaction appeared to stop with no more starting material consumed. MgI_2 (entry 36) displayed 11% conversion to **1.96** by HPLC; however the rest of the HPLC trace was messy suggesting the formation of many different impurities. $MgBr_2 \bullet OEt_2$ displayed 52% conversion to **1.96** by HPLC making it the optimum Lewis acid screened for activating dialdehyde **1.94**.

The Lewis acid screen suggests that group 2 Lewis acids are required to chelate to dialdehydes **1.94** and **1.109**. It also shows that $MgBr_2 \bullet OEt_2$ is the best Lewis acid for chelating to both dialdehyde **1.109** (entry 22) and dialdehyde **1.94** (entry 37).

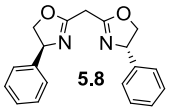
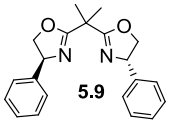
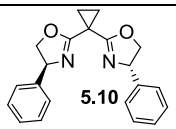
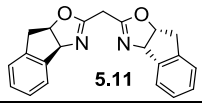
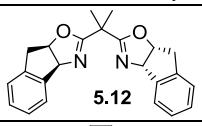
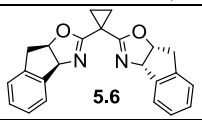
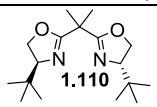
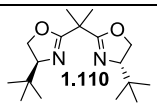
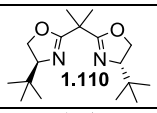
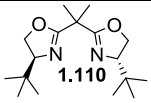
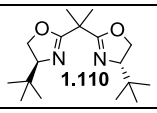
5.1.1.2 Ligand screen

Having found that $MgBr_2 \bullet OEt_2$ was the optimum Lewis acid to activate the Mukaiyama aldol reaction of dialdehydes **1.94** and **1.109**, the enantioselective Mukaiyama aldol reaction using a range of Evans' bisoxazoline ligands (Scheme 5.6) was attempted. A summary of the results of these reactions are shown in Table 5.2.



Scheme 5.6. Attempted enantioselective Mukaiyama aldol reaction of **1.94** and **1.109**.

Table 5.2. Summary of chiral ligand screen on Mukaiyama aldol reactions on dialdehydes **1.94** and **1.109**.

Entry	Dialdehyde	Chiral Ligand	Equiv. of catalyst	Conversion by HPLC [a]
1	**1.109**	-	2	52%
2	**1.109**	-	1	36%
3	**1.109**	 5.8	1	-
4	**1.109**	 5.9	1	-
5	**1.109**	 5.10	1	-
6	**1.109**	 5.11	1	-
7	**1.109**	 5.12	1	-
8	**1.109**	 5.6	1	-
9	**1.109**	 1.110	1	-
10	**1.109**	 1.110	1	-
11	**1.109**	 1.110	2	-
12	**1.94**	 1.110	1	-
13	**1.94**	 1.110	2	-

[a] - % conversion to **1.96** or **1.111** determined by observing product peak in HPLC trace.

The ligand screen reactions were carried out by adding the ligand in CH_2Cl_2 to $MgBr_2 \bullet OEt_2$ and stirring at r.t for 30 min to pre-form the catalyst. The reaction mixture was cooled to -20

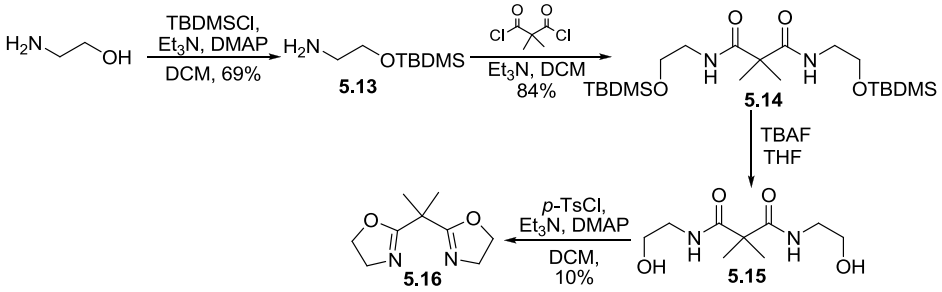
°C and dialdehyde in CH_2Cl_2 was added and the reaction mixture stirred at –20 °C for 20 min. A solution of silyl enol ether **1.95** in CH_2Cl_2 was then added and the reaction stirred at –20 °C for 2 h and monitored by HPLC.

The Mukaiyama aldol reactions were attempted with the Evans' bisoxazoline ligands (entries 3-13) and no reaction was observed, the analytical HPLC trace showed no consumption of starting materials. It was initially thought that water could be present in the reaction mixture causing the reactions to fail; however when the water content was measured on a Karl Fisher apparatus it was found to be 0.105% which is considered analytically insignificant.

When the Mukaiyama aldol reaction on dialdehyde **1.109** was carried out in the same conditions, with the same batch of starting materials as in entries 3-13 but with no bisoxazoline ligand (entries 1-2) conversion to **1.111** was observed. It was therefore suggested that when the Evans' bisoxazoline ligands chelate to the Mg(II) the metal centre becomes sterically crowded. This could then prevent the dialdehyde chelating to the Mg(II), explaining the lack of reactivity.

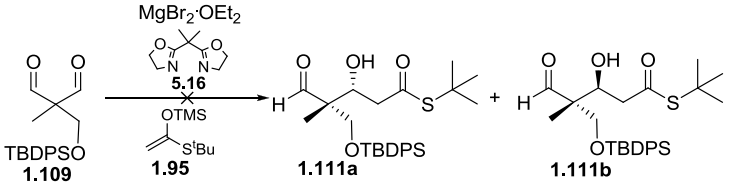
It was decided to do a test reaction with the unsubstituted bisoxazoline **5.16** (Scheme 5.8) to confirm if the metal centre was too sterically crowded due to the substituents on the ligand, or due to the steric bulk of the bisoxazoline causing the dialdehyde not to chelate.

The unsubstituted bisoaxazoline **5.16** was synthesised by TBDMS protection of ethanolamine to yield **5.13**, followed by double nucleophilic addition onto dimethyl malonylchloride to give **5.14**. Deprotection with TBAF gave crude **5.15** followed by cyclisation gave bisoxazoline **5.16** in 10% yield (Scheme 5.7).



Scheme 5.7. Preparation of bisoxazoline **5.16**.

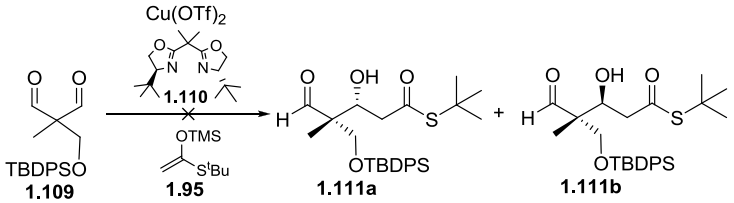
Bisoxazoline **5.16** was used in the test Mukaiyama aldol reaction of dialdehyde **1.109** with silyl enol ether **1.95** (Scheme 5.8).



Scheme 5.8. Attempted Mukaiyama aldol reaction on dialdehyde **1.109** with bisoxazoline **5.16**.

The reaction was carried out by adding bisoxazoline **5.16** to freshly prepared $MgBr_2$•OEt_2 in CH_2Cl_2. Dialdehyde **1.109** was then added, followed by silyl enol ether **1.95** and the reaction stirred at –25 °C for 2 h. No reaction was observed by TLC and so the reaction was warmed to 0 °C, after 2 h no reaction was observed and so the reaction was warmed to r.t, stirred for 2 h and quenched. The crude ^{1}H NMR showed just starting material. This agrees with the postulate that when the bisoxazoline chelates to the $MgBr_2$•OEt_2 the metal centre is too sterically crowded for the dialdehyde to also chelate, resulting in no reaction being observed.

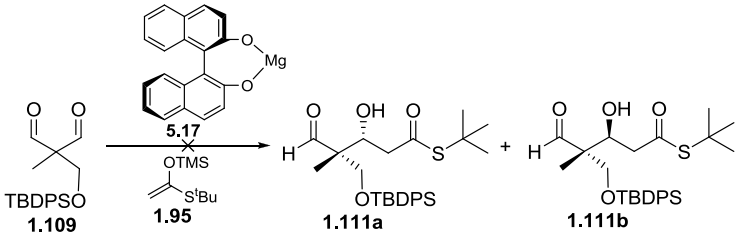
Mg(II) is a small metal. This could be a reason why both the ligand and dialdehyde were unable to chelate. Cu(II) is a larger metal, however it has been shown that this does not activate our dialdehydes in Mukaiyama aldol reactions. However it is known that metals display different properties when they are chelated and Cu(II) is widely known to activate dicarbonyls while also being chelated to bisoxazoline.[111] It was therefore decided to attempt the Mukaiyama aldol reaction of **1.109** with $Cu(OTf)_2$ and bisoxazoline **1.110** (Scheme 5.9). However when this reaction was attempted, no reaction was observed.



Scheme 5.9. Attempted enantioselective Mukaiyama aldol reaction on dialdehyde **1.109** with $Cu(OTf)_2$.

5.1.2 Magnesium Binaphtholate

Ishihara *et. al.* have shown that Mg(II)-Binaphtholate can be used as a chiral catalyst for the enantioselective direct Mannich-type reaction with malonates.[167] We attempted to use this Mg(II)-Binaphtholate to activate dialdehyde **1.109** in an enantioselective Mukaiyama aldol reaction (Scheme 5.10).



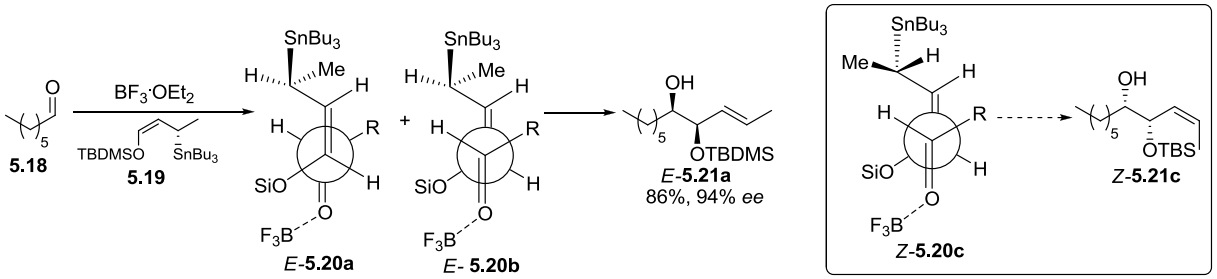
Scheme 5.10. Attempted enantioselective Mukaiyama aldol reaction on dialdehyde **1.109** with Mg(II)-Binaphtholate.

The Mg(II)-Binaphtholate was synthesised by adding *n*Bu_2Mg to a suspension of binaphthol and $MgSO_4$ in toluene at –20 °C.[167] Dialdehyde **1.109** was then added, followed by silyl enol ether **1.95**. The reaction was stirred at –20 °C for 4 h and slowly warmed to r.t and stirred overnight at r.t. The crude ^{1}H NMR showed only starting materials, the reaction failed.

5.2 Chiral Reagents

It has been shown that achiral aldehydes can react with chiral reagents to give enantioenriched products, with the chirality of the reagent being transferred to the product. Marshall has shown that achiral aldehydes will react with chiral allylstannanes[168] and chiral allenic stannanes[169, 170] with excellent chirality transfer to give enantioenriched products.[171] The hydroxyallylation of **5.18** with α-alkoxy allylic stannane **5.19** proceeds with excellent yields and enantioselectivity (Scheme 5.11).[168] It is believed the reaction proceeds *via* a non-chelated acyclic transition state in the antiperiplanar orientation (*E*-**5.20a**), first proposed by Yamamoto,[125] to give the major enantiomer *E*-**5.21a**. The minor enantiomer is believed to arise from transition state *E*-**5.20b** with the stannane pointing towards the reacting carbonyl. Marshall does not mention the formation of *Z*-**5.21c**; however in the hydroxyallylation

reaction with the equivalent α-alkoxy allylic stannane with a BOM group rather than a TBDMS group the *Z* isomer is reported.[171] It is believed formation of *Z*-**5.21c** would arise from transition state *Z*-**5.20c**.



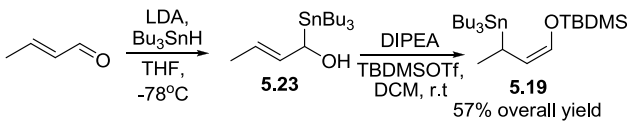
Scheme 5.11. Diastereoselective hydroxyallylation with a chiral allylstannane.

5.2.1 Chiral allylstannane

Attempts to form enantioenriched products, containing an *all-C* quaternary centre, using a chiral reagent were initially attempted using enantiopure chiral allylstannanes in the hydroxyallylation reaction (Scheme 5.13). The allylstannanes were prepared by Marshall's method.[172, 173] This hydroxyallylation reaction should be analogous to the hydroxyallylation reaction developed on dialdehyde **1.94** with achiral γ-siloxy allylstannane **1.97** (Scheme 2.4).

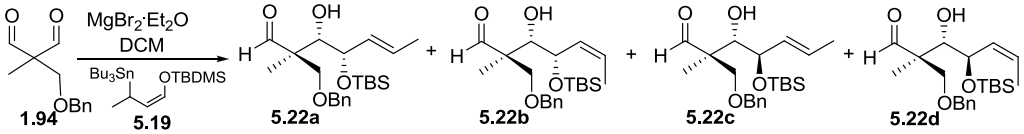
5.2.1.1 Hydroxyallylation reaction with racemic allylstannane 5.19

The hydroxyallylation reaction of **1.94** (Scheme 5.13) was first optimised using the racemic allylstannane **5.19**, before it was attempted using the enantiopure reagent. Allylstannane **5.19** was prepared by the addition of $SnBu_3Li$ to crotonaldehyde to give the crude allylstannane alcohol.[173] The crude **5.23** was treated with DIPEA followed by TBDMSOTf at 0 °C and warmed to r.t over 3 h to perform the protection of the alcohol and isomerisation to yield allylstannane **5.19** (Scheme 5.12).[172, 173]



Scheme 5.12. Preparation of racemic allylstannane **5.19**.

The intermediate **5.23** and allylstannane **5.19** are relatively unstable; so after purification of **5.19** by column chromatography, reaction with **1.94** (Scheme 5.13) was performed the same day. Four diastereoisomers are expected from this reaction (Scheme 5.13). A summary of the results of the hydroxyallylation reactions are shown in Table 5.3.



Scheme 5.13. Hydroxyallylation of dialdehyde **1.94** using an racemic **5.19**.

Table 5.3. Summary of hydroxyallylation reactions on dialdehyde **1.94**.

Entry	Temp. (°C)	Time (min)	Conc. (mmol mL^{-1})	Equiv. of 5.19	Yield [a] (%)	d.r [b] (a:b:c:d)
1	–25	150	0.05	2	38	78:10:6:6
2	–25	180	0.05	2	49	82:8:6:4
3	–25	210	0.10	2	31	79:13:5:3
4	–10	180	0.05	2	59	74:14:7:5
5	–25	150	0.05	3	63	84:8:5:3

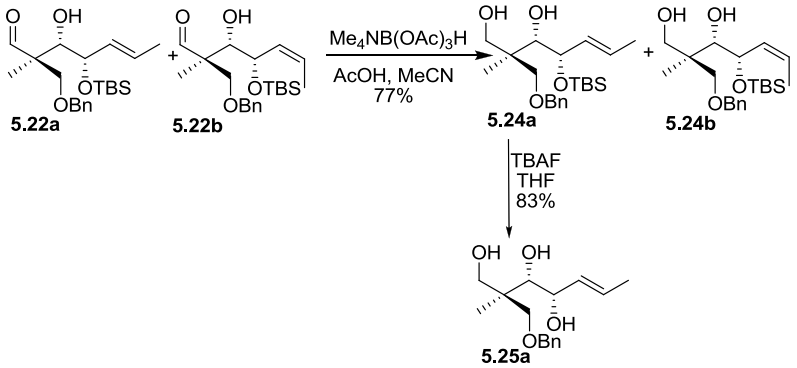
[a] – Isolated yield after column chromatography.

[b] – Calculated from the integration of the aldehyde peaks on the ^{1}H NMR of the crude (Figure 7.33).

In entry 1 the hydroxyallylation was attempted using the same conditions that the previous hydroxyallylation on dialdehyde **1.94** used. This gave **5.22** as the product in poor yield (38%) and d.r (78:10:6:6). When the reaction was left longer (entry 2) the yield was only slightly improved. In entry 3 the hydroxyallylation was attempted in more concentrated conditions, hoping this would increase the yield. This had the opposite effect, causing reduction in yield. When the reaction was attempted at higher temperature the yield was improved (entry 4), however there was degradation in the diastereoselectivity. In entry 5 the hydroxyallylation was attempted with an increased number of equivalents of allylstannane **5.19**, this gave an improved yield (63%) with an acceptable diastereoselectivity (84:8:5:3).

5.2.1.2 Identification of relative stereochemistry of diastereoisomer 5.22a

Diastereoisomers **5.22a** and **5.22b** could be separated by column chromatography from diastereoisomers **5.22c** and **5.22d**. Reduction of **5.22a** and **5.22b** with $Me_4NB(OAc)_3H$ gave a mixture of **5.24a** and **5.24b** which could be separated by preparative HPLC. Desilylation with TBAF gave **5.25a** as a white solid (Scheme 5.14).



Scheme 5.14. Identification of major diastereoisomer **5.25a**.

Following recrystallisation with diisopropyl ether and hexane; X-ray crystallography identified the relative stereochemistry of **5.25a** (Figure 5.1), so confirming **5.22a** as the major diastereoisomer from the hydroxyallylation of **1.94** with allylstannane **5.19**.

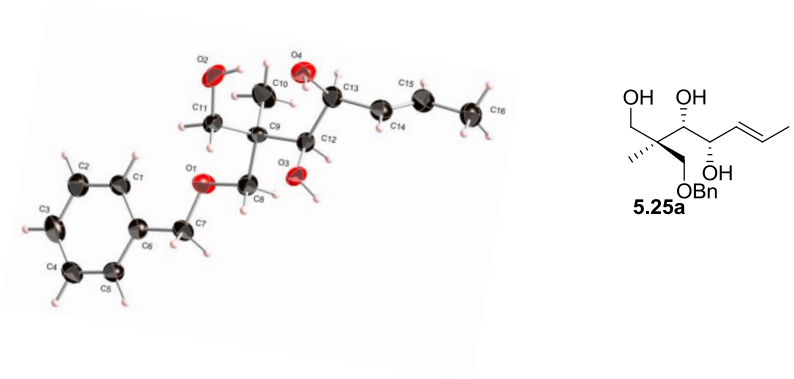


Figure 5.1. X-ray of diastereoisomer **5.25a**

5.2.1.3 Identification of relative stereochemistry of diastereoisomer 5.22c

The relative stereochemistry of the larger of the two minor diastereoisomers, **5.22c** was identified by double irradiation NMR experiments. A mixture of the two minor diastereoisomers **5.22c** and **5.22d** were isolated by column chromatography. The allylic peaks of **5.22c** and **5.22d** were separate in the ^{1}H NMR. When the allylic peak of **5.22c** was doubly irradiated the double bond region became clearer, as there was only coupling between the other =CH (Figure 5.2). A *J* value of 15.1 Hz was obtained, suggesting that diastereoisomer **5.22c** contains *E* double bond geometry. Major diastereoisomer **5.22a** also contains *E* double bond geometry; it is therefore assumed that the relative stereochemistry in **5.22c** is the same as in the minor diastereoisomer **1.98b** from the analogous hydroxyallylation reaction with the terminal allyl group.

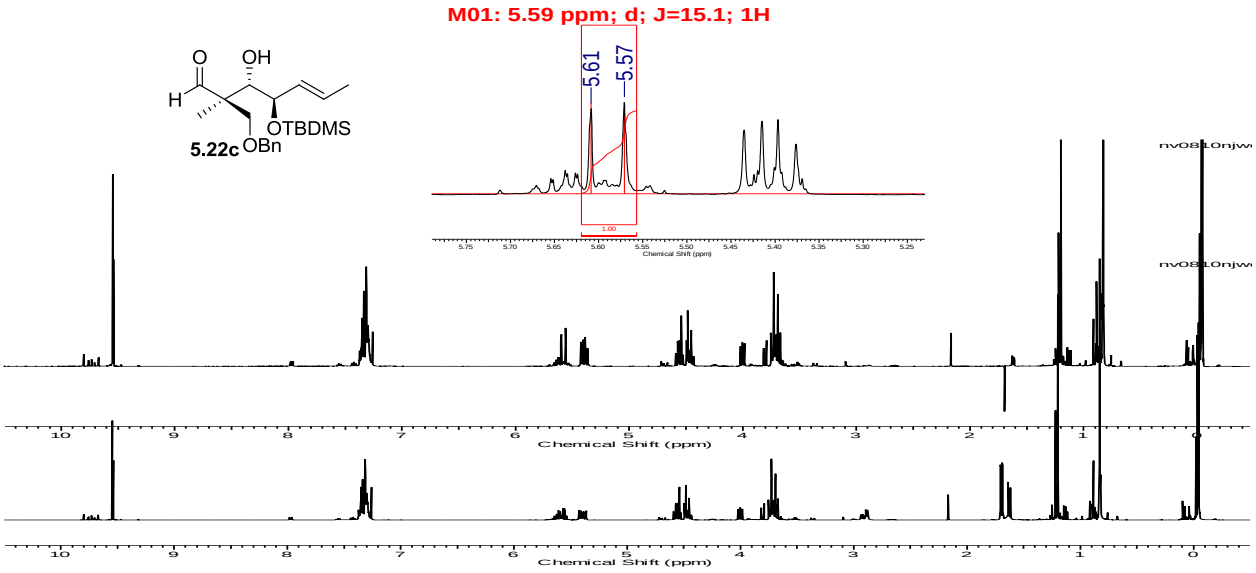
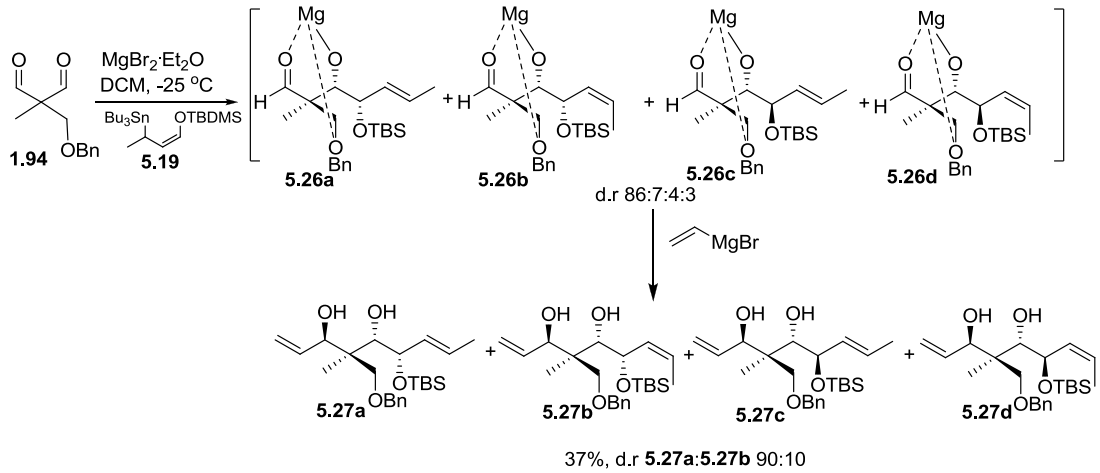


Figure 5.2. Double irradiation of **5.22c**.

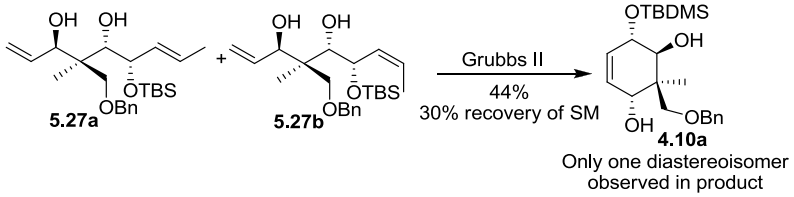
5.2.1.4 Identification of relative stereochemistry of diastereoisomer 5.22b

The double addition sequence of the hydroxyallylation with **5.19** followed by addition of vinyl Grignard has been achieved. A mixture of the major diastereoisomer **5.27a** and medium diastereoisomer **5.27b** were isolated by column chromatography (Scheme 5.15).



Scheme 5.15. Double addition reaction on dialdehyde **1.94**.

A RCM reaction on the mixture of **5.27a** and **5.27b** with Grubbs II catalyst yielded just one product, **4.10a** (Scheme 5.16), with 30% recovery of the starting material (d.r of recovered **5.27a:b** 96:4). This result suggests the relative stereochemistry of **5.22b** is the same as **5.22a**; however **5.22b** must display *Z* double bond geometry as opposed to the known *E* geometry displayed in **5.22a**.



Scheme 5.16. RCM on **5.24a** and **5.24b** to yield just one diastereoisomer, **4.10a**.

5.2.1.5 Rationalisation of the diastereoselection of the hydroxyallylation reaction with 5.19 on dialdehyde 1.94

The observed diastereoselection from the hydroxyallylation of **1.94** with **5.19** (Scheme 5.12) can be rationalised by considering the reactive conformations. $MgBr_2$•OEt_2 will chelate with dialdehyde **1.94** to form the bridged intermediate **3.4**. Assuming the stannane is always pointing away from the aldehyde to achieve the correct orbital overlap for the reaction to occur; four diastereoisomers can arise from approach of the two reagent faces on each aldehyde. The least sterically hindered approach leads to the formation of the observed major diastereoisomer **5.22a** (Figure 5.3).

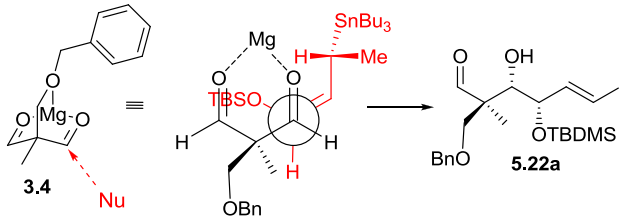


Figure 5.3. Rationalisation for the formation of major diastereoisomer **5.22a**.

The formation of the observed medium diastereoisomer **5.22b** occurs by allylstannane **5.19** approaching in the same orientation as in Figure 5.3, however with the other aldehyde. Therefore the Me points towards the dialdehyde to give the *Z* double bond geometry (Figure 5.4).

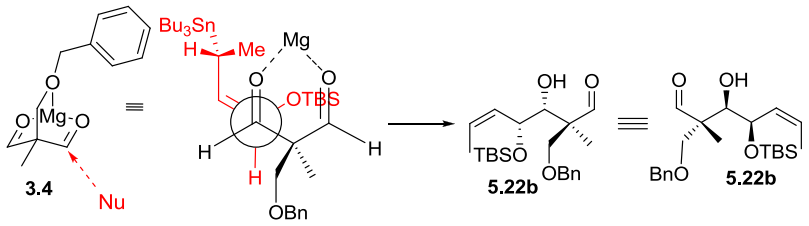


Figure 5.4. Rationalisation of the medium diastereoisomer **5.22b**.

Formation of the larger of the minor diastereoisomer **5.22c** is rationalised by the opposite face of allylstannane **5.19** reacting with the same face of dialdehyde **1.94** in the least sterically hindered orientation (Figure 5.5).

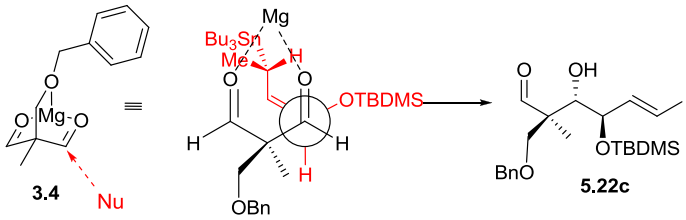


Figure 5.5. Rationalisation of the formation of **5.22c**.

The formation of the observed minor diastereoisomer **5.22d** occurs by allylstannane **5.19** approaching in the same orientation as in Figure 5.5, however with the other aldehyde. Therefore the Me points towards the dialdehyde to give the *Z* double bond geometry (Figure 5.6).

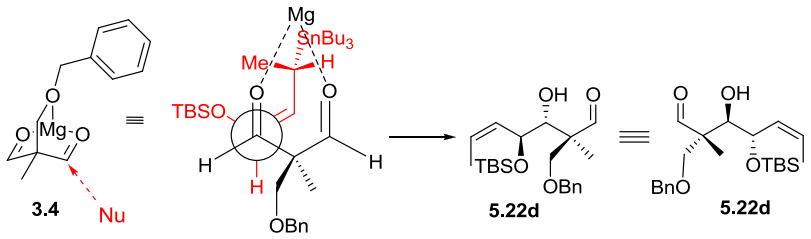
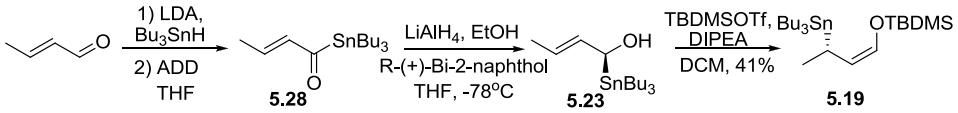


Figure 5.6. Rationalisation of the formation of **5.22d**.

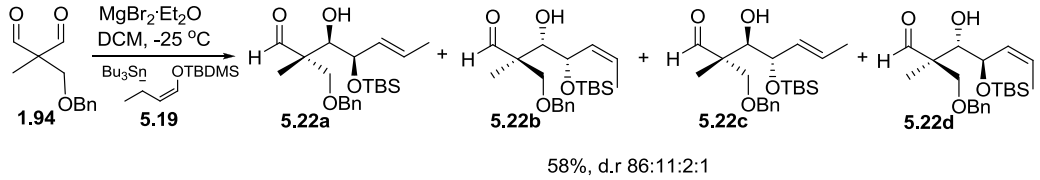
5.2.1.6 Hydroxyallylation of 1.94 with chiral allylstannane 5.19

Having developed the reaction with the racemic allylstannane **5.19** the reaction was attempted with chiral **5.19**. Allylstannane **5.19** was prepared enantioselectively according to the procedure by Marshall (Scheme 5.17).[172, 173]



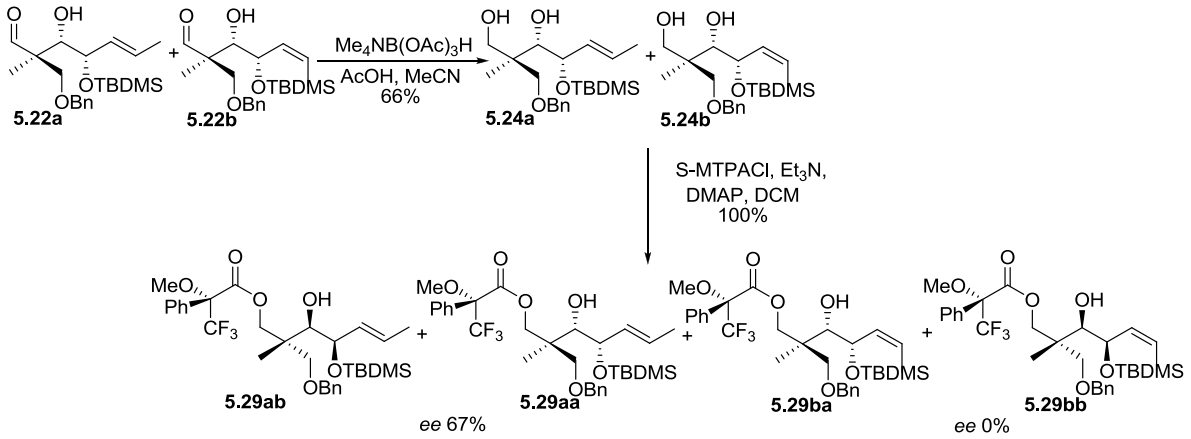
Scheme 5.17 Preparation of chiral **5.19**.

The reaction with the chiral allylstannane **5.19** with dialdehyde **1.94** proceeded in the usual fashion (Scheme 5.18).

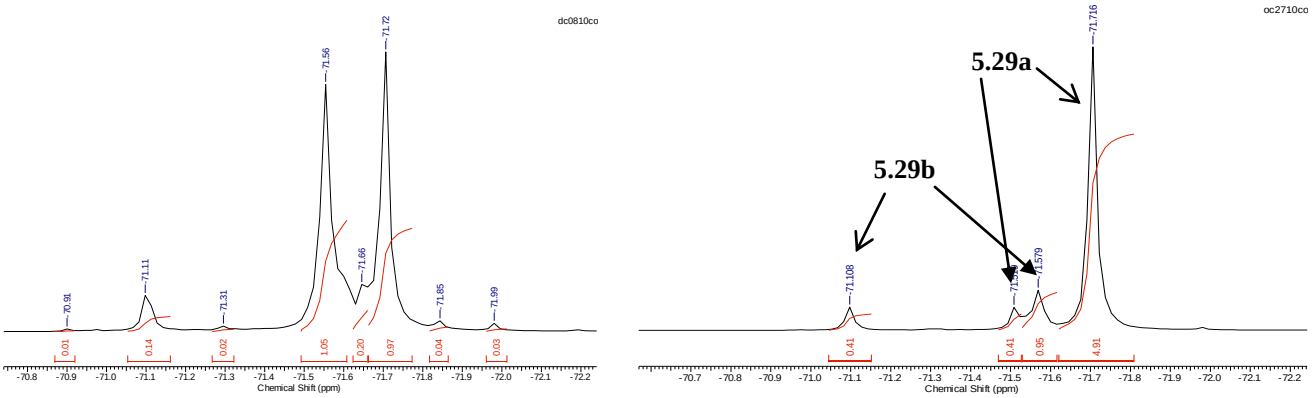


Scheme 5.18. Hydroxyallylation with chiral allylstannane **5.19**.

The *ee* was determined using Mosher's esters (Scheme 5.19). Unfortunately the Mosher's ester diastereoisomers, **5.29**, did not fully separate in the ^{19}F NMR (Figure 5.7), therefore an accurate *ee* could not be determined. However a rough *ee* was determined from the ^{19}F NMR which showed major diastereoisomer **5.22a** to have 67% *ee* and surprisingly medium diastereoisomer **5.22b** to have 0% *ee*.



Scheme 5.19. Formation of Mosher's ester's to determine the *ee*.



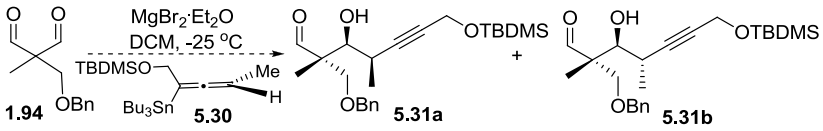
Racemate Chiral

Figure 5.7. ^{19}F NMR of **5.29** from which the *ee* was determined.

These results were disappointing and as a result it was decided to not continue development of the hydroxyallylation with chiral **5.19**.

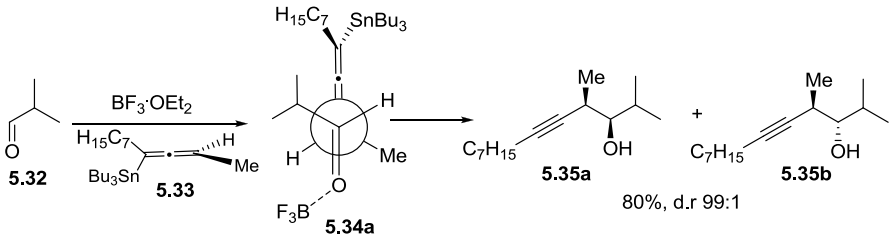
5.2.2 Chiral allenic stannane

Investigations have been carried out towards the formation of enantioenriched *all-C* quaternary centres as part of a stereoarray using chiral allenic stannanes (Scheme 5.20).



Scheme 5.20. Reaction of enantiopure allenic stannane **5.30** with dialdehyde **1.94**.

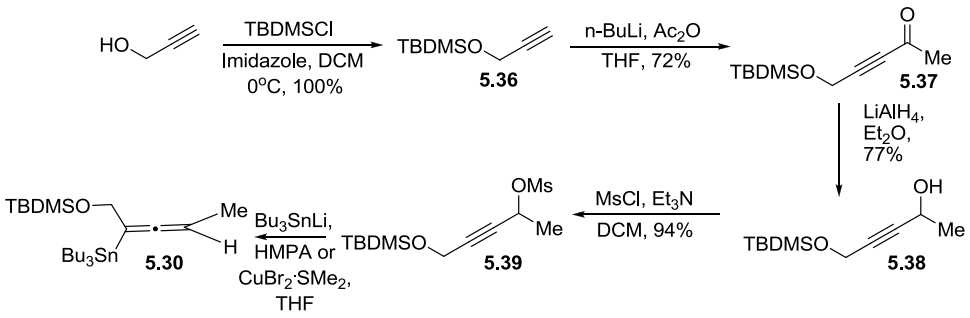
There is literature precedent of the reaction of chiral allenic stannanes with achiral aldehydes, with the enantiomeric excess of the reagent being transferred to the product. It is believed that addition of allenic stannane **5.33** to **5.32** takes place *via* transition state **5.34a**, where the reagents adopt a Felkin Anh geometric arrangement, with the stannane pointing away from the carbonyl to give major diastereoisomer **5.35a** (Scheme 5.21).[170]



Scheme 5.21. Reaction of a chiral allenic stannane with an achiral aldehyde.

5.2.2.1 Preparation of allenic stannane 5.30

It was decided to first develop the reaction on the racemic allenic stannane **5.30**. Allenic stannane **5.30** was prepared by the method described by Marshall (Scheme 5.22).[169] Propargyl alcohol was protected with TBDMSCl, then acetylated, reduced with $LiAlH_4$ and mesylated with MsCl to give **5.39** in good yields.



Scheme 5.22. Formation of allenic stannane **5.30**.

The stannylation to form allenic stannane **5.30** was initially low yielding. Therefore optimisation of this reaction was carried out. The results of this optimisation is summarised in Table 5.4.

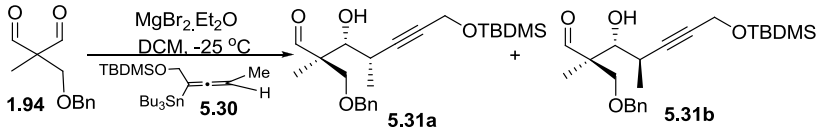
Table 5.4 Summary of optimisation of the stannylation to form **5.30**.

Entry	Reagent	Temp.(°C)	Bu_3SnLi equiv.	Yield (%)
1	HMPA	r.t	1.3	0
2	HMPA	0	1.3	2
3	$CuBr•SMe_2$	–78 - –20	1.3	9
4	$CuBr•SMe_2$	–60	1.3	36
5	$CuBr•SMe_2$	–60	2	66

The stannylation of **5.39** was initially attempted using the procedure described by Marshall[169] (entries 1 and 2) using HMPA and Bu_3SnLi, however these reactions were either unsuccessful or proceeded in extremely poor yields. An alternative procedure to form allenic stannanes was found that used $CuBr•SMe_2$ to form the stannylcuprate.[174] In entry 3 the reaction was performed using $CuBr•SMe_2$ at –78 °C and warmed to –20 °C over 3 h; this gave an improved yield of 9%. In entry 4 the reaction was carried at –60 °C for 3 h; this gave a much improved yield of 36%, however by TLC residual starting material could be observed. The equiv. of Bu_3SnLi were increased to two (entry 5), yielding 66% of **5.30**.

5.2.2.2 Development of reaction of racemic 5.30 with dialdehyde 1.94

Development of the reaction between racemic allenic stannane **5.30** and dialdehyde **1.94** was carried out (Scheme 5.23). The results of these investigations are summarised in Table 5.5.



Scheme 5.23. Reaction of racemic allenic stannane **5.30** with dialdehyde **1.94**.

Table 5.5. Summary of development work on the reaction between **1.94** and **5.30**.

Entry	Scale (mmol)	Temp. (°C)	Equiv. 5.30	Yield (%)	d.r [a]
1	0.12	–25	2	70	83:17
2	0.29	–40 - –25	2	34	80:20
3	1.24	–25	2	39	76:24
4	1.03	–40	2	31	72:28
5	0.81	–25	3	35	76:24

[a] – d.r. calculated from the aldehydic peaks on the crude ^{1}H NMR (Figure 7.35).

The reaction was initially attempted on a small scale (entry 1) and displayed promising results with a good yield (70%) and d.r (83:17). However when the reaction was attempted on a larger scale (entry 3) the yield of **5.31** was poor (39%) and the d.r disappointing (76:24). In entries 2 and 4 the reaction was carried out at –40 °C to attempt to improve the d.r, however this was unsuccessful and resulted in reduced yields. In entry 5 the reaction was attempted with 3 equiv. of allenic stannane **5.30**. This also failed to improve the yield or d.r. It is thought that the results reported in entry 1 can be explained by experimental error, resulting in a high yield due to the small scale of the reaction. In respect to these poor results it was decided to halt this work rather than pursuing this reaction to attempt it with the chiral allenic stannane.

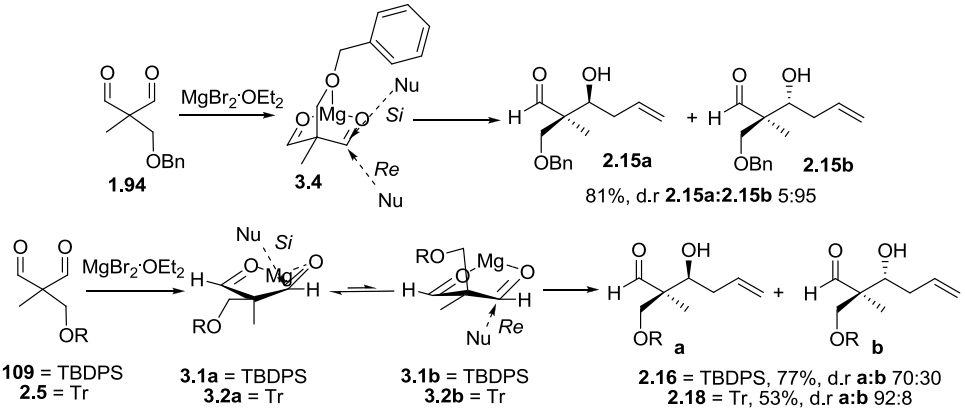
5.3 Conclusions

The formation of enantioenriched *all-C* quaternary stereocentres from non-enolisable 1,3-dialdehydes has been attempted. Initial attempts to achieve an enantioselective Mukaiyama aldol reaction on dialdehydes **1.94** and **1.109** (Scheme 5.6) using Evans' BOX ligands[111] were unsuccessful. It is thought that this is because when the ligand chelates to the Mg(II) to form the chiral catalyst, the metal centre becomes too sterically crowded for the dialdehyde to also chelate, causing the reaction to fail. Surprisingly it was found that when the reaction was attempted with a range of other Lewis acids, including Cu(II) (Table 5.1) these also failed to activate the dialdehydes.

The formation of enantioenriched *all-C* quaternary stereocentres has also been attempted by the addition of chiral allylstannnes and allenic stannanes to dialdehyde **1.94** (Scheme 5.18 and 5.23 respectively). Addition of chiral allylstannane **5.19** to **1.94** proceeded with moderate yields and d.r's and poor *ee*'s. Addition of allenic stannane **5.30** to **1.94** proceeded with poor yields and moderate diastereoselectivity. With respect to these disappointing results it was decided not to pursue the addition of chiral reagents to our dialdehydes to form enantioenriched *all-C* quaternary stereocentres.

Chapter 6. Project Summary

The subject of the PhD was to investigate addition processes on 1,3-dialdehyde substrates. The mono allylation, hydroxyallylation and Mukaiyama aldol reaction has been achieved on dialdehydes **1.94**, **1.109** and **2.5** in good yields and diastereoselectivities to give products containing up to three contiguous stereocentres, including an *all-C* quaternary stereocentre. Interestingly it was found that the diastereoselection of additions to dialdehyde **1.94** displayed a different diastereoselection to additions to dialdehydes **1.109** and **2.5**. It is believed that this is because of differences in chelation of the dialdehydes to $MgBr_2 \bullet OEt_2$ leading to different reactive conformations (Scheme 6.1).



Scheme 6.1 Differences in diastereoselection in monoadditions to dialdehydes.

It is put forward that the diastereoselection in the monoadditions to dialdehydes **1.109** and **2.5** can be explained by the Cieplak model.[79] To form major diastereoisomer **2.16a** from the allylation of **1.109**, $MgBr_2 \bullet OEt_2$ must chelate to the two aldehydic oxygens to form a flattened boat reactive conformation with the ether group *pseudo* equatorial, **3.1a**. From a steric point of view, it is puzzling that the nucleophile should approach the dialdehyde past the larger group in the *pseudo* equatorial position, rather than the reactive conformation with the smaller group in the *pseudo* equatorial position. However the Cieplak model states that a nucleophile will approach constrained carbonyl groups perpendicular to the substituent in the α position that is the best σ donor.[78] In the cases of dialdehydes **1.109** and **2.5** the best σ donor in the α position is the methyl group which would lead to reactive conformations **3.1a** and **3.2a** yielding the major diastereoisomers as observed. To strengthen this proposal,

further investigations are suggested. We suggest that the diastereoselection of allylations of dialdehydes with substituents which are sterically similar but electronically different are investigated. Dialdehydes **3.38** with an ethyl and trifluoroethyl, **3.40** and **3.42** with two electronically different aryl groups (similar to Halterman's work)[88] are suggested (Scheme 3.27).

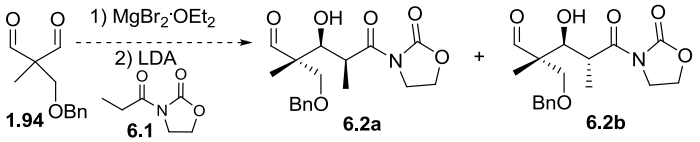
It has been found that after monohydroxyallylation on dialdehyde **1.94** a second addition reaction is possible with high diastereoselectivity. It has been found that with Grignards larger than MeMgBr the second addition is completely diastereoselective for the *anti*-1,3-diol. This has again been rationalized by considering the likely reactive conformation involved (Figure 4.3). It has been found that the hydroxyallylation – Grignard double addition reaction is successful for a range of Grignard reagents, giving products containing four contiguous stereocentres, including an *all-C* quaternary centre, in a one pot, two step reaction from prochiral dialdehyde **1.94** in good yields and excellent diastereoselectivity. It has also been found that the hydroxyallylation – aldol double addition reaction is effective using Li enolates **1.103** and **1.104** to yield products containing up to five contiguous stereocentres in good yields and diastereoselectivities (Scheme 4.9 and 4.11). The relative stereochemistries of the products of these reactions have been identified by formation of the corresponding δ-lactones and nOe and ^{1}H NMR analysis (Scheme 4.12 and 4.13).

Attempts have also been made towards the formation of enantioenriched *all-C* quaternary stereocentres as part of a stereoarray. Initial investigations looked to use Evans' bisoxazoline ligands[110] to induce an enantioselective Mukaiyama aldol reaction on dialdehyde **1.109** (Scheme 5.6). However it was found that while the Mukaiyama aldol reaction of **1.109** worked well without the ligand, when a bisoxazoline ligand was added, the reaction failed. It is believed that this is because when the ligand chelates to the metal centre the Mg(II) becomes too sterically crowded for the dialdehyde to also chelate, resulting in no reaction.

The formation of enantioenriched *all-C* quaternary stereocentres has also been attempted by the addition of chiral allylstannnes and allenic stannanes to dialdehyde **1.94**. Addition of chiral allylstannane **5.17** to **1.94** proceeded with moderate yields and d.r's and poor ee's

(Scheme 5.18). Addition of allenic stannane **5.27** to **1.94** proceeded with poor yields and moderate diastereoselectivity (Scheme 5.23). With respect to these disappointing results it was decided not to pursue the addition of chiral reagents to our dialdehydes to form enantioenriched *all-C* quaternary stereocentres any further.

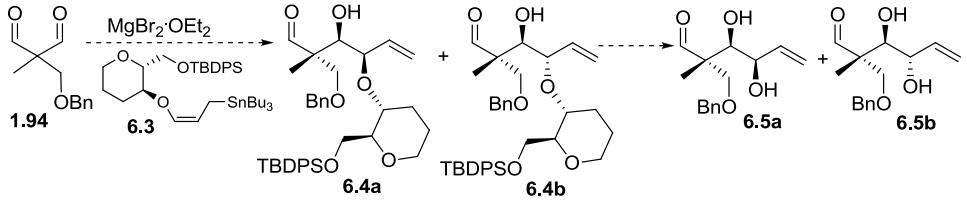
It is suggested that a chiral auxiliary approach is preferable for obtaining enantioenriched products by additions to non-enolisable 1,3-dialdehydes and this would be the focus of any future work within this project. Chiral auxiliaries are widely reported in the literature as being effective in the formation of enantioenriched products from aldol reactions.[175-177] However in our screen of aldol reactions it was found that only Li enolates of esters were effective nucleophiles in reactions with dialdehyde **1.94** (Scheme 2.16, Table 2.5). Unfortunately within the literature, metal enolates derived from chiral acetate and propionate esters exhibit low levels of aldol asymmetric induction that rarely exceed 50% *ee*.[130] In our aldol screen the Li enolate of oxazolidinones was not attempted. It is known that the Li enolate of oxazolidinone derivatives can be formed[178] and can react in aldol reactions.[179] It is suggested that the aldol reaction of the Li enolate of an oxazolidinone derivative is attempted with dialdehydes **1.94** and **1.109** (Scheme 6.2) and that if successful, this is further developed to use a chiral oxazolidinone derivative as a chiral auxiliary to form enantioenriched products.



Scheme 6.2 Aldol reaction with Li enolate of **6.1**

Previously Martin Jeffrey in the Linclau group showed that dialdehyde **1.73** will undergo an allylation reaction with Roush's allylboronate (Scheme 1.39).[107] Further investigations should be made into developing this reaction with dialdehydes **1.94**, **1.109** and **2.5**; investigating the effect of $MgBr_2 \bullet OEt_2$ on the diastereoselectivity of the reaction and determining the *ee* of the products. It is hoped this could provide a route to form enantioenriched *all-C* quaternary stereocentres as part of a stereoarray in any further development of this project.

Carbohydrate chiral auxiliaries have also been widely reported within the literature, particularly in allylation and hydroxyallylation reactions with aldehydes to yield enantioenriched products.[149, 180-183] It is hoped to apply this methodology to achieve the hydroxyallylation of dialdehydes **1.94**, **1.109** and **2.5** with allylstannanes with carbohydrate chiral auxiliaries to give enantioenriched products (Scheme 6.3).



Scheme 6.3. Hydroxyallylation of **1.94** with **6.3**, an allylstannane with a carbohydrate chiral auxiliary.

Chapter 7. Experimental

General Method

All reaction vessels were flame dried under vacuum and cooled under nitrogen prior to use. All water sensitive experiments were carried out under nitrogen atmosphere, using dry solvents. For the reactions performed at low temperatures, dry ice was used as a cryogenic substance.

DCM, Et_3N and EtOAc were distilled from CaH_2; THF, Benzene and Et_2O from Na/benzophenone. MeCN was dried over molecular sieves. All chemical reagents were ordered from Acros Organics, Aldrich, Alfa Aesar.

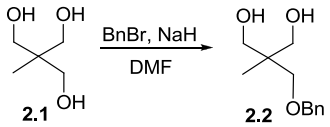
All reactions, except the Mukaiyama aldol reactions, were monitored by TLC (Kiesgel 60 F_{254} MERCK Art. 5735 aluminium sheet). The TLC dye is a solution of *p*-anisaldehyde (186ml of EtOH, 6.9 mL of H_2SO_4, 2.1 mL of AcOH, 5.1 mL of *p*-anisaldehyde). For the compounds containing a phenyl group, a revelation under UV light (λ = 254nm) was done as well. Mukaiyama aldol reactions were monitored by HPLC (Agilent Zorbax SB-C18 column, 1.8 micron, 3.0 x 50 mm) with eluents 0.05% TFA in H_2O and 0.05% TFA in MeCN.

NMR spectra were recorded on a BRUKER AV300 at 300 MHz (^1H) and 75 MHz (^{13}C), or on a BRUKER AV400 at 400 MHz (^1H) and 100 MHz (^{13}C) using the residual solvent as the internal standard. The coupling constants (*J*) are expressed in Hertz and the chemical shift in ppm.

IR spectra were recorded on a THERMO MATSON Fourier Transform spectrometer. The wave numbers (υ) are given in cm^{-1}.

LRMS spectra were accomplished with ThermoQuest Trace MS, single quadrupol GC. This instrument was used for electron ionisation (EI) and chemical ionisation (CI) spectra. HRMS spectra were recorded on a VG Analytical 70-250-SE normal geometry, double focusing. This apparatus was used for all the HRMS.

2-Benzyloxymethyl-2-methyl-propane-1,3-diol (2.2)



To a stirred solution of **2.1** (9.00 g, 75.0 mmol, 3 equiv.) in DMF (150 mL) at 0 °C was added NaH (0.88 g, 25.0 mmol, 1 equiv.). After stirring for 15 min benzylbromide (3.00 mL, 25.0 mmol, 1 equiv.) was added over 1 h and the reaction mixture stirred at r.t for 16 h. The solvent was evaporated and the oil purified by column chromatography (petroleum ether / EtOAc, 50:50) to give **2.2** as a white solid (2.79 g, 13.3 mmol, 53%).

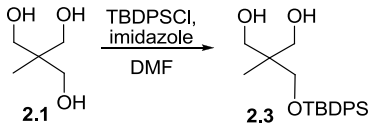
^{1}H NMR (400MHz, $CDCl_3$): δ 7.38 – 7.27 (5 H, m, Ar**H**), 4.53 (2 H, s, C**H**$_2$Ph), 3.73 (2 H, dd, *J* = 10.8, 4.8 Hz, C**H**H**O**H), 3.61 (2 H, dd, *J* = 11.0, 7.0 Hz, C**H**H**O**H), 3.47 (2 H, s, C**H**$_2$OBn), 2.34 (2 H, dd, *J* = 7.0, 5.1 Hz, O**H**), 0.83 (3 H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (Ar**C**), 128.5 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 75.7 (**C**H_2OH), 73.7 (**C**H_2OBn), 68.1 (**C**H_2Ph), 40.8 (**C**CH_3), 17.2 (**C**H_3) ppm.

Mp: 58 – 59 °C.

Data corresponds to previous data[109]

2-(*tert*-Butyldiphenylsilanyloxymethyl)-2-methylpropane-1,3-diol (2.3).



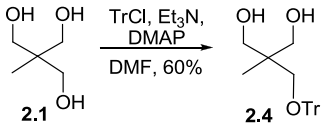
To a stirred solution of **2.1** (1.31 g, 10.9 mmol, 3 equiv.) and imidazole (0.49 g, 7.20 mmol, 2 equiv.) in DMF (20 mL) was added TBDPSCl (1.00 g, 3.64 mmol, 1 equiv.) dropwise over 10 min. The reaction mixture was stirred at r.t for 24 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The organics were washed with H_2O, brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude colourless oil was purified by column chromatography (hexane / acetone 75:25) to give **2.3** as a pale yellow oil (1.01 g, 2.82 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.62 (4 H, m, Ar**H**), 7.52 – 7.35 (6 H, m, Ar**H**), 3.75 (2 H, d, *J* = 10.9 Hz, C**H**H**O**H), 3.65 (2 H, s, C**H**$_2$OTBDPS), 3.61 (2 H, d, *J* = 10.9 Hz, C**H**H**O**H), 1.09 (9 H, s, C(C**H**$_3$)$_3$), 0.81 (3 H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6 (Ar**C**H), 132.9 (Ar**C**), 129.9 (Ar**C**H), 127.8 (Ar**C**H), 68.5 (**C**H_2OTBDPS), 68.0 (**C**H_2OH), 41.6 (**C**$(CH_2OH)_2$), 26.9 (C(**C**$H_3)_3$), 19.2 (**C**$(CH_3)_3$), 16.8 (**C**H_3) ppm. [102]

Data corresponds to the literature data [102]

2-Trityloxymethyl-2-methylpropane-1,3-diol (2.4).



To a stirred solution of **2.1** (12.00 g, 99.9 mmol, 3 equiv.) in DMF (200 mL) was added Et_3N (4.60 mL, 33.3 mmol, 1 equiv.), followed by DMAP (407 mg, 3.33 mmol, 0.1 equiv.) and chlorotriphenylmethane (9.28 g, 33.3 mmol, 1 equiv.). The reaction was stirred at 60 °C for 12 h, the solvent evaporated and the yellow oil purified by column chromatography (petroleum ether / EtOAc, 50:50) to give **2.4** as a white solid (7.20 g, 19.9 mmol, 60% yield).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.50 – 7.29 (15 H, m, Ar**H**), 3.70 (2 H, dd, *J* = 11.2, 5.3 Hz, C**H**HOH), 3.59 (2 H, dd, *J* = 11.0, 6.7 Hz, C**H**HOH), 3.18 (2 H, s, CH_2OTr), 2.12 (2 H, dd, *J* = 6.6, 5.5 Hz, O**H**), 0.89 (3 H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (Ar**C**), 128.6 (Ar**C**H), 127.9 (Ar**C**H), 127.2 (Ar**C**H), 86.9 (**C**Ph), 68.3 (**C**H_2OH), 67.0 (**C**H_2OTr), 41.2 (**C**CH_3), 17.4 (**C**H_3) ppm.

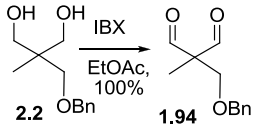
Mp: 119 – 121 °C.

Data corresponds to previous data[109]

General Procedure for the synthesis of 1,3 Dialdehydes 1.94, 1.109, 2.5 [102]

To a suspension of IBX (6 equiv.) in EtOAc (10 mL) was added *via* cannula a solution of diol (1.00 g, 1 equiv.) in EtOAc (10 mL). The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled in an ice bath for 1 h and then filtered. The filter cake was washed with EtOAc and the combined filtrates concentrated in *vacuo* to give a pale yellow oil (100% yield).

2-Benzyloxymethyl-2-methyl malonaldehyde (1.94).

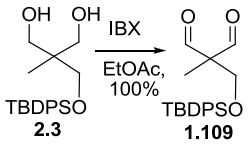


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (2 H, s, C**H**O), 7.38 – 7.28 (5 H, m, Ar**H**), 4.53, (2 H, s, C**H$_2$**Ph), 3.82 (2 H, s, C**H$_2$**OBn), 1.28 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0 (**C**HO), 137.1 (Ar**C**), 128.4 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 73.7 (**C**H_2OBn), 70.7 (**C**H_2Ph), 62.8 (**C**CH_3), 13.3 (**C**H_3) ppm.

Data corresponds to previous data[109]

2-(*tert*-Butyldiphenylsilanyloxymethyl)-2-methyl malonaldehyde (1.109).

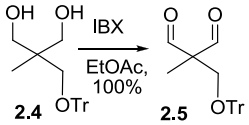


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (2 H, s, C**H**O), 7.69 – 7.59 (4 H, m, Ar**H**), 7.51 – 7.37 (6 H, m, Ar**H**), 4.03 (2 H, s, C**H$_2$**OTBDPS), 1.25 (3 H, s, C**H$_3$**), 1.06 (9 H, s, SiC(C**H$_3$**)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5 (**C**HO), 135.6 (Ar**C**H), 132.3 (Ar**C**), 130.1 (Ar**C**H), 127.9 (Ar**C**H), 65.3 (**C**H_2OTBDPS), 64.1 (**C**CH_3), 26.7 (SiC(**C**H_3)$_3$), 19.2 (Si**C**$(CH_3)_3$), 12.8 (**C**H_3) ppm.

Data corresponds to the literature data. [102]

2-Trityloxymethyl-2-methyl malonaldehyde (2.5).

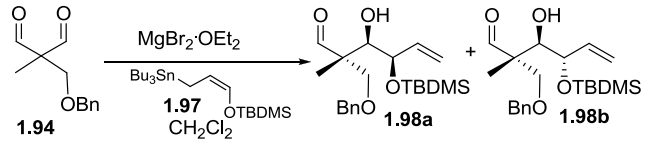


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (2 H, s, C**H**O), 7.49 – 7.26 (15 H, Ar**H**), 3.56 (2 H, s, C**H$_2$**OTr), 1.24 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2 (**C**HO), 142.9 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.4 (Ar**C**H), 84.9 (**C**Ph_3), 64.5 (**C**H_2OTr), 45.6 (**C**CH_3), 13.3 (**C**H_3) ppm.

Data corresponds to previous data[109]

(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(tert-butyldimethylsilanonyloxy)-3-hydroxy-2-methylhex-5-enal (1.98a) & (*rac*-2*S*,3*R*,4*S*)-2-Benzyloxymethyl-4-(tert-butyldimethylsilanonyloxy)-3-hydroxy-2-methylhex-5-enal (1.98b)



1,2-Dibromoethane (1.13 mL, 13.07 mmol, 3 equiv.) was added to a suspension of magnesium turnings (317 mg, 13.07 mmol, 3 equiv.) in Et_2O (13.5 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (22.5 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (900 mg, 4.36 mmol, 1 equiv.) in CH_2Cl_2 (31.5 mL). After addition of the dialdehyde the reaction mixture becomes a yellow solution. After 20 min of stirring, allyltin **1.97** (4.02 g, 8.72 mmol, 2 equiv.) in CH_2Cl_2 (36 mL) was added *via* cannula and the reaction stirred at –25 °C for 2 h 45 min. The reaction was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. After dilution with CH_2Cl_2, the organic phase was washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 95:5) to give 1.37 g of **1.98** (3.62 mmol, 83% yield) as a colourless oil (diastereomeric ratio on the crude **1.98a**:**1.98b** 93:7). The two diastereoisomers were separated by HPLC (hexane / acetone, 95:5).

Data for compound 1.98a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1 H, s, C**H**O), 7.35 – 7.26 (5 H, m, Ar**H**), 5.99 – 5.90 (1 H, m, C**H**=CH_2), 5.22 – 5.14 (2 H, m, C**H$_2$**=CH), 4.50 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.46 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.26 (1 H, dd, *J* = 7.5, 3.5 Hz, C**H**OTBDMS), 3.75 (1 H, dd, *J* = 7.0, 3.5 Hz, C**H**OH), 3.70 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 3.63 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 3.12 (1 H, d, *J* = 6.5 Hz, O**H**), 1.16 (3 H, s, CC**H$_3$**), 0.88 (9 H, s, SiC(C**H$_3$**)$_3$), 0.05 (3 H, s, C**H$_3$**Si), 0.03 (3 H, s, C**H$_3$**Si) ppm.

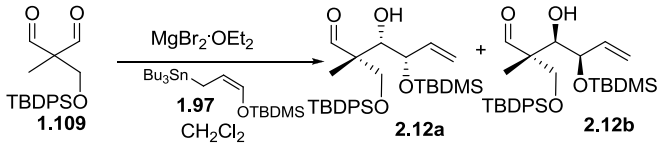
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6 (**C**HO), 139.0 (**C**H=CH_2), 137.7 (Ar**C**), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 117.0 (**C**H_2=CH), 77.9 (**C**HOH), 74.3 (**C**HOTBDMS), 73.6 (C**H$_2$**OBn), 73.3 (C**H$_2$**Ph), 53.5 (**C**CH_3), 25.9 (SiC(**C**H_3)$_3$), 18.1 (Si**C**CH_3), 14.9 (**C**H_3C), -3.6 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

Data for compound 1.98b: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.56 (1 H, s, C**H**O), 7.38 – 7.30 (5 H, m, Ar**H**), 5.84 – 5.76 (1 H, m, C**H**=CH_2), 5.23 – 5.17 (2 H, m, C**H$_2$**=CH), 4.56 (1 H, d, *J* = 12.0 Hz, C**H**HPh), 4.46 (1 H, d, *J* = 12.0 Hz, C**H**HPh), 4.05 (1 H, t, *J* = 7.5 Hz, C**H**OTBDMS), 3.77 (1 H, t, *J* = 7.0 Hz, C**H**OH), 3.75 (1 H, d, *J* = 9.5 Hz, C**H**HOBn), 3.68 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 2.96 (1 H, d, *J* = 6.5 Hz, O**H**), 1.22 (3 H, s, CC**H$_3$**), 0.84 (9 H, s, SiC(C**H$_3$**)$_3$), -0.01 (3 H, s, C**H$_3$**Si), -0.03 (3 H, s, C**H$_3$**Si).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4 (**C**HO), 138.6 (**C**H=CH_2), 137.5 (Ar**C**), 128.5 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 118.1 (**C**H$_2$=CH), 77.4 (**C**HOH), 76.2 (**C**HOTBDMS), 73.9 (**C**H$_2$OBn), 72.4 (**C**H$_2$Ph), 52.2 (**C**CH$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 15.9 (**C**H$_3$C), -3.9 (**C**H$_3$Si), -4.5 (**C**H$_3$Si) ppm.

Data corresponds to previous data[109]

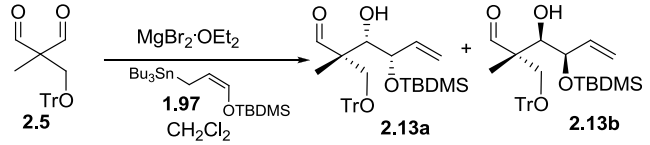
(*rac*-2*S*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-3-hydroxy-2-methylhex-5-enal (2.12a) & (*rac*-2*S*,3*R*,4R)-4-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-3-hydroxy-2-methylhex-5-enal (2.12b).



1,2-Dibromoethane (656 µL, 7.61 mmol, 3 equiv.) was added to a suspension of magnesium turnings (185 mg, 7.61 mmol, 3 equiv.) in Et_2O (8 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (12.5 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula, of dialdehyde **1.109** (900 mg, 2.54 mmol, 1 equiv.) in CH_2Cl_2 (17.5 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min allyltin **1.97** (2.34 g, 5.08 mmol, 2 equiv.) in CH_2Cl_2 (20 mL) was added *via* cannula and the reaction stirred at –25 °C for 3 h. The reaction was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. After dilution with CH_2Cl_2, the organic phase was washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 70:30) to give 854 mg (1.62 mmol, 64% yield) of **2.12** as a colourless oil

(diastereomeric ratio on the crude **2.12a**:**2.12b** 86:14). The diastereoisomers could not be separated at this stage, but were obtained pure after aldehyde reduction.

(*rac*-2*S*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-2-methyl-2-trityloxymethylhex-5-enal (2.13a) & (*rac*-2*S*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-2-methyl-2-trityloxymethylhex-5-enal (2.13b)



1,2-Dibromoethane (0.65 mL, 7.53 mmol, 3 equiv.) was added to a suspension of magnesium turnings (183 mg, 7.53 mmol, 3 equiv.) in Et_2O (7.7 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (14 mL) was added and the reaction mixture was cooled to –30 °C before addition, *via* cannula, of the dialdehyde **2.5** (900 mg, 2.51 mmol, 1 equiv.) in CH_2Cl_2 (17 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. The reaction mixture was stirred at –30 °C for 20 min then allyltin **1.97** (2.32 g, 5.02 mmol, 2 equiv.) in CH_2Cl_2 (23 mL) was added *via* cannula and the reaction stirred at –30 °C for 3 h 30 min. The reaction was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. After dilution with CH_2Cl_2, the organic phase was washed with brine and dried over Na_2SO_4, before removal of the solvent. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 95:5) to give 851 mg of **2.13** (1.61 mmol, 64%) as a colourless oil (diastereomeric ratio on the crude **2.13a**:**2.13b** 95:5). Major diastereoisomer **2.13a** was obtained pure after preparative HPLC (95:5 hexane / acetone).

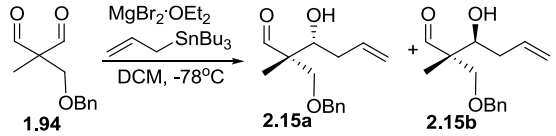
Data for compound 2.13a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (1 H, s, C**H**O), 7.62 – 7.21 (15 H, m, Ar**H**), 5.86 (1 H, ddd, *J* = 17.0, 10.6, 7.5 Hz, C**H**=CH_2), 5.30 – 5.06 (2 H, m, C$\mathbf{H_2}$=CH), 4.03 (1 H, dd, *J* = 7.6, 3.6 Hz, C**H**OTBDMS), 3.92 (1 H, dd, *J* = 6.8, 3.5 Hz, C**H**OH), 3.61 (1 H, d, *J* = 9.3 Hz, C**HH**OTr), 3.33 (1 H, d, *J* = 9.3 Hz, C**HH**OTr), 2.76 (1 H, d, *J* = 7.0 Hz, CHO**H**), 1.38 (3 H, s, C$\mathbf{H_3}$C), 0.89 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.00 (3 H, s, C$\mathbf{H_3}$Si), -0.05 (3 H, s, C$\mathbf{H_3}$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4 (**C**HO), 143.5 (Ar**C**), 138.7 (**C**H=CH_2) 128.8 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 127.4 (Ar**C**H), 127.2 (Ar**C**H), 117.5 (**C**H_2=CH), 86.7 (**C**Ph_3), 77.3 (**C**HOH), 73.9 (**C**HOTBDMS), 65.3

(**C**H_2OTr), 53.8 (**C**CH_3), 25.9 (SiC(**C**H_3)$_3$), 18.0 (Si**C**CH_3), 15.1 (**C**H_3C), -3.6 (**C**H_3Si), -4.7 (**C**H_3Si) ppm.

Data corresponds to previous data[109]

(*rac*-2*S*,3*R*)-2-Benzyloxymethyl-3-hydroxy-2-methylhex-5-enal (2.15a) & (*rac*-2*S*,3*S*)-2-Benzyloxymethyl-3-hydroxy-2-methylhex-5-enal (2.15b)



1,2-Dibromoethane (247 μL, 2.91 mmol, 4.5 equiv.) was added to a suspension of magnesium turnings (71 mg, 2.91 mmol, 4.5 equiv.) in Et_2O (4.5 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of the Et_2O, CH_2Cl_2 (10 mL) was added and the reaction mixture was cooled to –78 °C before addition *via* cannula of dialdehyde **1.94** (200 mg, 0.97 mmol 1.5 equiv.) in CH_2Cl_2 (14 mL). After 20 min of stirring, allyl tributylstannane (198 μL, 0.65 mmol, 1 equiv.) in CH_2Cl_2 (14 mL) was added *via* cannula. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixure was purified by column chromatography (petroleum ether / EtOAc 90:10), then purified by preparative HPLC (hexane / EtOAc 92:8) to give 130 mg of **2.15b** as colourless oil (d.r. **2.15a**:**2.15b** 5:95 from crude ^{1}H NMR, Figure 7.1) (0.52 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (1 H, s, C**H**O), 7.38 – 7.27 (5 H, m, Ar**H**), 5.90 – 5.82 (1 H, m, C**H**=), 5.17 – 5.12 (2 H, m, C**H$_2$**=), 4.53 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.49 (1 H, d, *J* = 12.1 Hz, CH**H**Ph), 4.05 – 4.03 (1 H, m, C**H**OH), 3.66 (1 H, d, *J* = 9.3 Hz, C**H**HOBn), 3.60 (1 H, d, *J* = 9.3 Hz, CH**H**OBn), 2.66 (1 H, d, *J* = 4.0 Hz, O**H**), 2.32 – 2.10 (2 H, m, C**H$_2$**CH=), 1.09 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5 (**C**HO), 137.4 (Ar**C**), 135.0 (**C**H=), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 118.0 (**C**H_2=), 73.7 (**C**H_2Ph), 73.0 (**C**H_2OBn), 72.3 (**C**HOH), 54.0 (CH_3**C**), 36.5 (**C**H_2CH=), 13.3 (**C**H_3C) ppm.

Data corresponds to previous data[109]

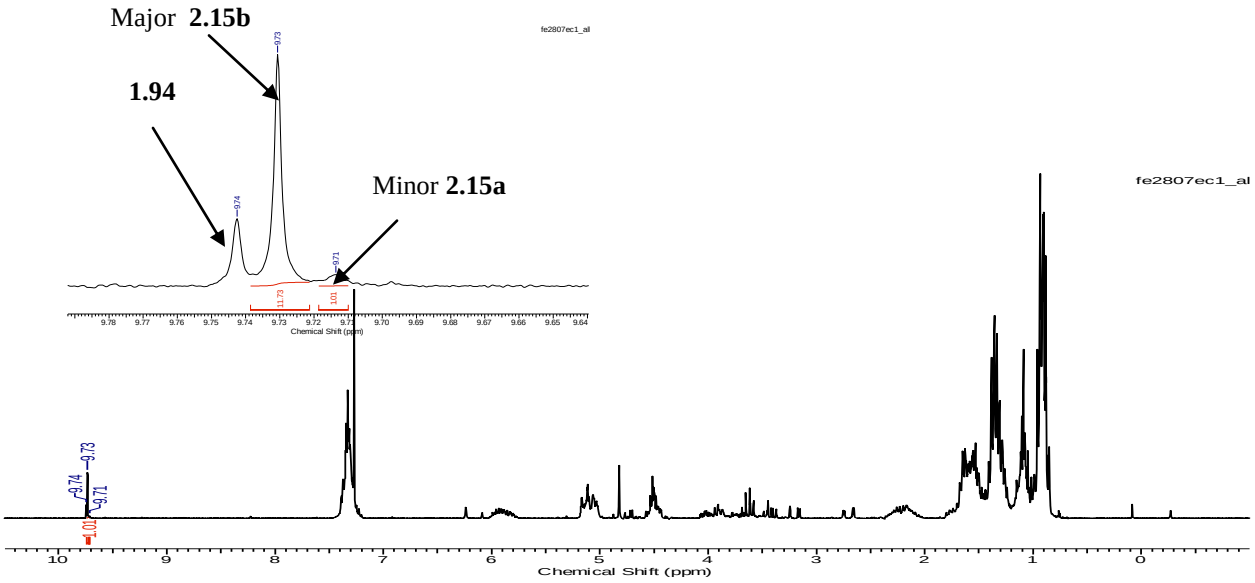
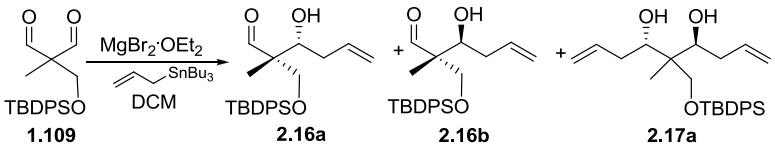


Figure 7.1. Crude ^{1}H NMR from allylation of dialdehyde **1.94** showing how the d.r of **2.15** was calculated.

(*rac*-2*S*,3*R*)- (2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-hydroxy-2-methylhex-5-enal (2.16a) & (*rac*-2*S*,3*S*)- (2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-hydroxy-2-methylhex-5-enal (2.16b) & (*rac*-4S,6S)-5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-methyl-nona-1,8-diene-4,6-diol (2.17a)



1,2-Dibromoethane (278 μL, 3.22 mmol, 3 equiv.) was added to a suspension of magnesium turnings (78 mg, 3.22 mmol, 3 equiv.) in Et_2O (9 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (18 mL) was added and the reaction mixture was cooled to –78 °C before addition *via* cannula of dialdehyde **1.109** (380 mg, 1.07 mmol, 1 equiv.) in CH_2Cl_2 (22 mL). After 20 min of stirring at –78 °C, allyl tributylstannane (348 μL, 1.07 mmol, 1 equiv.) in CH_2Cl_2 (24 mL) was added *via* cannula at –78 °C and stirred for 30 min. The reaction mixture was stirred at –25 °C for 2 h. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, before removal of the solvent in *vacuo*. The crude

mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 328 mg of **2.16** as a colourless oil (dias ratio **2.16a**:**2.16b** 72:28, Figure 7.2) (83 mmol, 77 %). The product was further purified by HPLC (9:1, hexane / EtOAc) to separate the diastereoisomers and trace amounts (5 mg, 0.01 mmol, 1%) of **2.17a** was isolated.

Data for compound 2.16a: IR (neat): 3497 (br), 3072 (w), 2931 (m), 2858 (m), 1726 (s), 1641 (w), 1589 (w), 1472 (m), 1427 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (1 H, s, C**H**O), 7.75 – 7.60 (4 H, m, Ar**H**), 7.51 – 7.37 (6 H, m, Ar**H**), 5.88 (1 H, dddd, *J* = 16.5, 10.7, 7.8, 6.1 Hz, C**H**=CH_2), 5.20 – 5.09 (2 H, m, CH=C**H$_2$**), 4.05 (1 H, ddd, *J* = 10.1, 4.9, 2.7 Hz, C**H**OH), 3.91 (1 H, d, *J* = 10.3 Hz, C**HH**OTBDPS), 3.88 (1 H, d, *J* = 10.4 Hz, C**HH**OTBDPS), 2.54 (1 H, d, *J* = 5.3 Hz, CHO**H**), 2.35 – 2.22 (1 H, m, C**HH**CH=), 2.22 – 2.09 (1 H, m, C**HH**CH=), 1.07 (9 H, s, C(C**H$_3$**)$_3$), 1.04 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (**C**HO), 135.6 (Ar**C**), 135.0 (**C**H=CH_2), 132.6 (Ar**C**), 132.4 (Ar**C**H), 130.0 (Ar**C**H), 127.8 (Ar**C**H), 118.1 (**C**H_2=CH), 72.5 (**C**HOH), 66.0 (**C**H_2OTBDPS), 55.0 (CH_3**C**), 36.9 (**C**H_2CH=), 26.8 (SiC(**C**H_3)$_3$, 19.2(Si**C**$(CH_3)_3$, 13.2 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 419 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 419.2013 $[M+Na]^+$; found: 419.2014 $[M+Na]^+$.

Data for compound 2.16b: IR (neat): 3496 (br), 3072 (w), 2931 (m), 2858 (m), 1724 (s), 1641 (w), 1589 (w), 1472 (m), 1427 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1 H, s, C**H**O), 7.79 – 7.57 (4 H, m, Ar**H**), 7.55 – 7.35 (6 H, m, Ar**H**), 5.96 – 5.80 (1 H, m, C**H**=CH_2), 5.22 – 5.10 (2 H, m, CH=C**H$_2$**), 4.18 (1 H, dt, *J* = 10.2, 2.6 Hz, C**H**OH), 3.84 (1 H, d, *J* = 10.5 Hz, C**HH**OTBDPS), 3.80 (1 H, d, *J* = 10.4 Hz, C**HH**OTBDPS), 2.64 (1 H, d, *J* = 3.4 Hz, CHO**H**), 2.34 – 2.23 (1 H, m, C**HH**CH=), 2.23 – 2.03 (1 H, m, C**HH**CH=), 1.07 (9 H, s, C(C**H$_3$**)$_3$), 1.03 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1 (**C**HO), 135.6 (Ar**C**), 135.0 (**C**H=CH_2), 132.5 (Ar**C**), 132.4 (Ar**C**), 130.0 (Ar**C**H), 127.8 (Ar**C**H), 118.1 (**C**H_2=CH), 71.8 (**C**HOH), 66.7 (**C**H_2OTBDPS), 55.2 (CH_3**C**), 36.2 (**C**H_2CH=), 26.8 (SiC(**C**H_3)$_3$, 19.2 (Si**C**$(CH_3)_3$, 12.3 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 419 $[M+Na]^+$ (56%), 451 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 419.2013 $[M+Na]^+$; found: 419.2006 $[M+Na]^+$.

Data for compound 2.17a: IR (neat): 3375 (br), 3072 (m), 2931 (s), 2858 (m), 1641 (m), 1589 (w), 1472 (m), 1427 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.59 (4 H, m, Ar**H**), 7.53 – 7.35 (6 H, m, Ar**H**), 6.00 – 5.81 (2 H, m, C**H**=CH_2), 5.21 – 5.05 (4 H, m, CH=C**H$_2$**), 4.02 (1 H, dt, *J* = 9.5, 3.5 Hz, C**H**OH), 3.85 – 3.73 (1 H, m, C**H**OH), 3.79 (1 H, d, *J* = 10.5 Hz, C**HH**OTBDPS), 3.59 (1 H, d, *J* = 10.5 Hz, C**HH**OTBDPS), 3.26 (1 H, d, *J* = 5.0 Hz, CHO**H**), 2.77 (1 H, d, *J* = 4.0 Hz, CHO**H**), 2.44 – 2.31 (1 H, m, C**HH**CH=), 2.27 – 2.06 (3 H, m, 2 x C**HH**CH= and C**HH**CH=), 1.09 (9 H, s, C(C**H$_3$**)$_3$), 0.86 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4 (**C**H=CH_2), 136.2 (**C**H=CH_2), 135.7 (Ar**C**H), 132.8 (Ar**C**), 129.9 (Ar**C**H), 127.8 (Ar**C**H), 117.5 (**C**H_2=CH), 117.1 (**C**H_2=CH), 75.7 (**C**HOH), 73.6 (**C**HOH), 66.7 (**C**H_2OTBDPS), 44.8 (CH_3**C**), 36.8 (**C**H_2CH=), 35.9 (**C**H_2CH=), 27.0 (SiC(**C**H_3)$_3$, 19.2 (Si**C**$(CH_3)_3$, 16.2 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 461 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 461.2482 $[M+Na]^+$; found: 461.2490 $[M+Na]^+$.

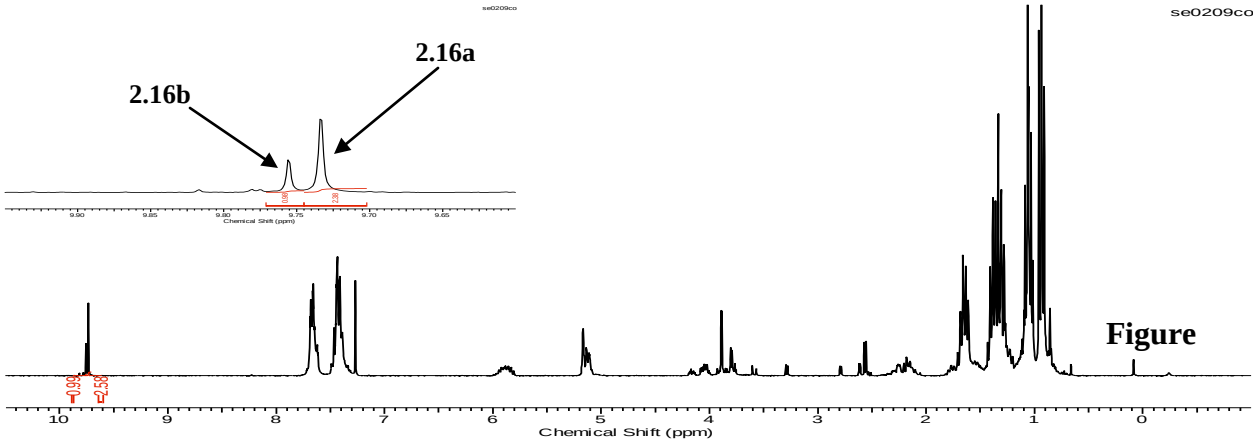
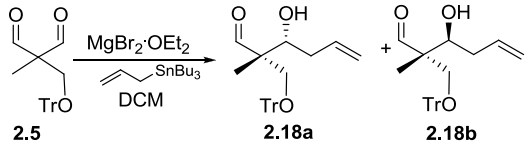


Figure 7.2 Crude ^{1}H NMR from allylation of dialdehyde **1.109**.

(*rac*-2*S*,3*R*)-3-Hydroxy-2-methyl-2-trityloxymethylhex-5-enal (2.18a) and (*rac*-2*S*,3*S*)-3-Hydroxy-2-methyl-2-trityloxymethylhex-5-enal (2.18b)



1,2-Dibromoethane (364 μL, 4.23 mmol, 3 equiv.) was added to a suspension of magnesium turnings (103 mg, 4.23 mmol, 3 equiv.) in Et_2O (12 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (24 mL) was added and the reaction mixture

was cooled to –78 °C before addition *via* cannula of dialdehyde **2.5** (505 mg, 1.41 mmol 1 equiv.) in CH_2Cl_2 (29 mL). After 20 min of stirring at –78 °C, allytributylstannane (459 μL, 1.41 mmol, 1 equiv.) in CH_2Cl_2 (32 mL) was added *via* cannula at –78 °C and stirred 30 min. The reaction mixture was warmd to –25 °C and stirred for 2 h. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, before removal of the solvent in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 299 mg of **2.18** as a colourless oil (d.r. **2.18a**:**2.18b** 92:8, Figure 7.3) (0.74 mmol, 53%) and then further purified by HPLC (85:15, hexane / acetone) to separate the diastereoisomers.

Data for compound 2.18a: IR (neat): 3493 (br), 3059 (w), 2931 (w), 1724 (s), 1641 (w), 1556 (w), 1490 (m), 1448 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1 H, s, C**H**O), 7.56 – 7.43 (6 H, m, Ar**H**), 7.41 – 7.23 (9 H, m, Ar**H**), 5.92 – 5.74 (1 H, m, C**H**=CH_2), 5.21 – 4.97 (2 H, m, C**H$_2$**=CH), 4.10 – 3.96 (1 H, m, C**H**OH), 3.54 (1 H, d, *J* = 9.0 Hz, C**H**HOTr), 3.41 (1 H, d, *J* = 9.0 Hz, C**H**HOTr), 2.44 (1 H, d, *J* = 5.5 Hz, CHO**H**), 2.21 – 2.07 (1 H, m, C**H**HCH=), 2.00 – 1.82 (1 H, m, C**H**HCH=), 1.08 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9 (**C**HO), 143.2 (**C**H=CH_2), 135.0 (Ar**C**), 128.6 (Ar**C**H), 127.9 (Ar**C**H), 127.2 (Ar**C**H), 117.9 (**C**H_2=CH), 87.2 (**C**Ph_3), 72.5 (**C**HOH), 64.7 (**C**H_2OTr), 54.4 (CH_3**C**), 36.5 (**C**H_2CH=), 13.8 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 423 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 423.1936 $[M+Na]^+$; found: 423.1929 $[M+Na]^+$, calculated: 455.2198 $[M+Na+MeOH]^+$; found: 455.2189 $[M+Na+MeOH]^+$.

Data for compound 2.18b: IR (neat): 3481 (br), 3059 (w), 3032 (w), 2924 (m), 1724 (s), 1641 (w), 1556 (w), 1490 (m), 1449 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (1 H, s, C**H**O), 7.52 – 7.39 (6 H, m, Ar**H**), 7.39 – 7.20 (9 H, m, Ar**H**), 5.92 – 5.72 (1 H, m, C**H**=CH_2), 5.19 – 5.00 (2 H, m, C**H$_2$**=CH), 4.19 (1 H, d, *J* = 9.0 Hz, C**H**OH), 3.41 (1 H, d, *J* = 9.5 Hz, C**H**HOTr), 3.27 (1 H, d, *J* = 9.5 Hz, C**H**HOTr), 2.54 (1 H, br. s., CHO**H**), 2.17 – 1.85 (2 H, m, C**H$_2$**CH=), 1.06 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8 (**C**HO), 143.1 (**C**H=CH_2), 135.0 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.3 (Ar**C**H), 118.0 (**C**H_2=CH), 87.0 (**C**Ph_3), 71.5 (**C**HOH), 65.6 (**C**H_2OTr), 54.4 (CH_3**C**), 35.8 (**C**H_2CH=), 12.4 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 423 $[M+Na]^+$ (93%), 455 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 423.1936 $[M+Na]^+$; found: 423.1929 $[M+Na]^+$, calculated: 455.2198 $[M+Na+MeOH]^+$; found: 455.2189 $[M+Na+MeOH]^+$.

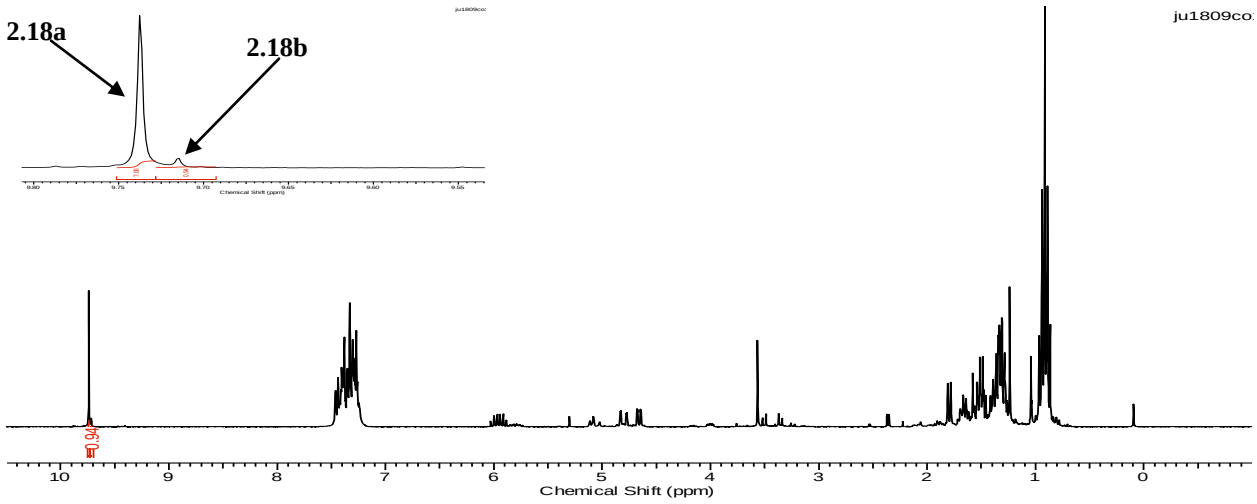
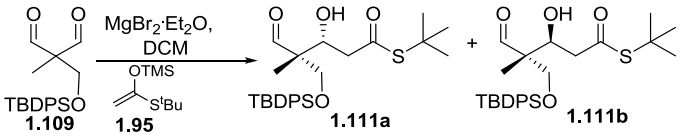


Figure 7.3. Crude ^{1}H NMR from allylation of dialdehyde **2.5**.

(*rac*-2*R*,3*S*)-4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-4-methyl-5-oxo-pentanethioic acid *S*-*tert*-butyl ester (1.111a) & (*rac*-2*R*,3*R*)-4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-4-methyl-5-oxo-pentanethioic acid *S*-*tert*-butyl ester (1.111b)



1,2-Dibromoethane (359 µL, 4.17 mmol, 3 equiv.) was added to a suspension of magnesium turnings (101 mg, 4.17 mmol, 3 equiv.) in Et_2O (7 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (7 mL) was added and the reaction mixture was cooled to –78 °C before addition, *via* cannula of the dialdehyde **1.109** (491 mg, 1.39 mmol, 1 equiv.) in CH_2Cl_2 (8 mL). After addition of the dialdehyde the reaction mixture becomes a pale yellow solution. After 20 min of stirring, silyl enol ether **1.95** (284 mg, 1.39 mmol, 1

equiv.) in CH_2Cl_2 (12 mL) at –78 °C was added *via* cannula and allowed to react at –25 °C for 1 h. The reaction was quenched with aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2 and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 350 mg (0.72 mmol, 52 % yield) of a colourless oil (d.r on the crude **1.111a**:**1.111b** 72:28, Figure 7.4). The diastereoisomers were separated by preparative HPLC (hexane :EtOAc, 85:15).

Data for compound 1.111a: IR (neat): 3492 (br), 3071 (w), 2961 (m), 2930 (m), 2858 (m), 1728 (s), 1679 (s), 1589 (w), 1472 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (1 H, s, C**H**O), 7.71 – 7.55 (4 H, m, Ar**H**), 7.50 – 7.30 (6 H, m, Ar**H**), 4.61 (1 H, dt, *J* = 9.4, 3.2 Hz, C**H**OH), 3.73 (2 H, s, C**H$_2$**OTBDPS), 3.19 (1 H, d, *J* = 3.5 Hz, CHO**H**), 2.67 – 2.52 (2 H, m, CHOHC**H$_2$**CO), 1.48 (9 H, s, SC(C**H$_3$**)$_3$), 1.05 (9 H, s, SiC(C**H$_3$**)$_3$), 0.98 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (**C**HO), 199.9 (**C**OS), 135.6 (Ar**C**H), 132.5 (Ar**C**), 130.0 (Ar**C**H), 127.9 (Ar**C**H), 69.5 (**C**HOH), 66.3 (**C**H_2OTBPDS), 54.9 (CH_3**C**), 48.7 (S**C**$(CH_3)_3$), 45.9 (**C**H_2CO), 29.8 (SC(**C**$H_3)_3$), 26.8 (SiC(**C**$H_3)_3$), 19.2 (Si**C**$(CH_3)_3$), 12.3 (C**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 544 $[M+K+NH_4]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 541.2420 $[M+Na+MeOH]^+$; found: 541.2400 $[M+Na+MeOH]^+$.

Data for compound 1.111b: IR (neat): 3492 (br), 3071 (w), 2961 (m), 2930 (m), 2858 (m), 1728 (s), 1679 (s), 1589 (w), 1472 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (1 H, s, C**H**O), 7.69 – 7.57 (4 H, m, Ar**H**), 7.50 – 7.30 (6 H, m, Ar**H**), 4.50 (1 H, dt, *J* = 8.6, 4.2 Hz, C**H**OH), 3.87 (1 H, d, *J* = 10.4 Hz, C**HH**OTBDPS), 3.82 (1 H, d, *J* = 10.4 Hz, C**HH**OTBDPS), 3.16 (1 H, d, *J* = 4.7 Hz, CHO**H**), 2.68 – 2.56 (2 H, m, CHOHC**H$_2$**CO), 1.47 (9 H, s, SC(C**H$_3$**)$_3$), 1.05 (9 H, s, SiC(C**H$_3$**)$_3$), 1.00 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5 (**C**HO), 200.1 (**C**OS), 135.6 (Ar**C**H), 132.5 (Ar**C**), 129.9 (Ar**C**H), 127.8 (Ar**C**H), 69.3 (**C**HOH), 65.3 (**C**H_2OTBPDS), 54.9 (CH_3**C**), 48.6 (S**C**$(CH_3)_3$), 46.5 (**C**H_2CO), 29.7 (SC(**C**$H_3)_3$), 26.8 (SiC(**C**$H_3)_3$), 19.2 (Si**C**$(CH_3)_3$), 12.8 (C**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 544 $[M+K+NH_4]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 541.2420 $[M+Na+MeOH]^+$; found: 541.2400 $[M+Na+MeOH]^+$.

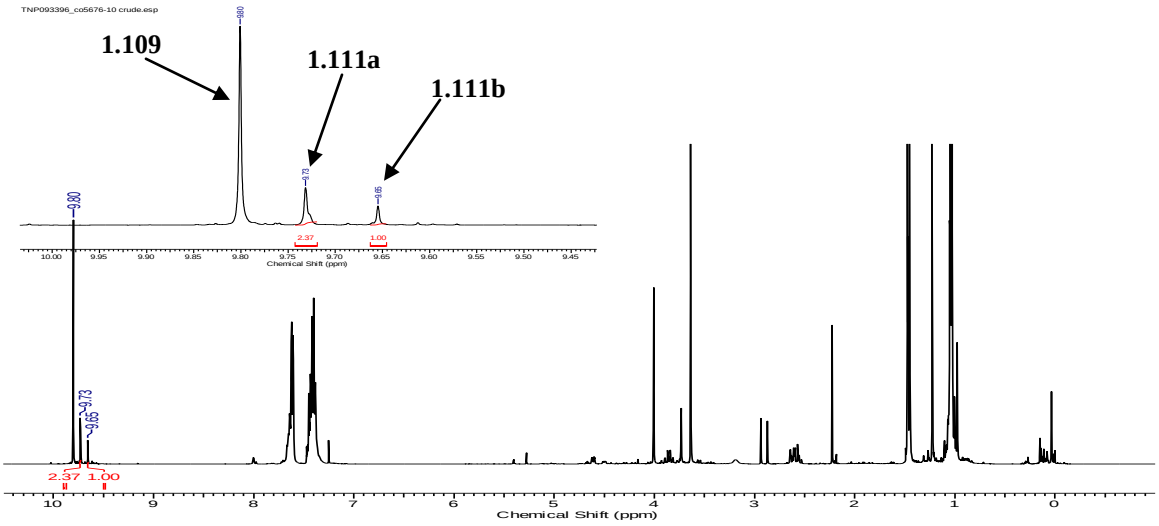
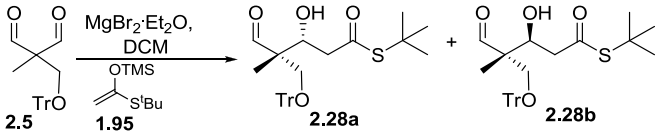


Figure 7.4. Crude ^{1}H NMR from Mukaiyama aldol reaction on **1.109** from which the d.r was calculated.

(*rac*-2*R*,3*S*)-3-Hydroxy-4-methyl-5-oxo-4-trityloxymethyl-pentanethioic acid *S*-*tert*-butyl ester (2.28a) & (*rac*-2*R*,3*R*)-3-Hydroxy-4-methyl-5-oxo-4-trityloxymethyl-pentanethioic acid *S*-*tert*-butyl ester (2.28b)



1,2-Dibromoethane (346 µL, 4.02 mmol, 3 equiv.) was added to a suspension of magnesium turnings (98 mg, 4.02 mmol, 3 equiv.) in Et_2O (8.5 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (8 mL) was added and the reaction mixture was cooled to –78 °C before addition, *via* cannula of the dialdehyde **2.5** (480 mg, 1.23 mmol, 1 equiv.) in CH_2Cl_2 (7 mL). After addition of the dialdehyde the reaction mixture became a pale yellow solution. After 20 min of stirring, silyl enol ether **1.95** (410 mg, 2.01 mmol, 1.5 equiv.) in CH_2Cl_2 (18 mL) at –78 °C was added *via* cannula and allowed to react at –40 °C for 2 h 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ and allowed to warm to r.t. The organics were extracted with CH_2Cl_2 and dried over Na_2SO_4, filtered and concentrated in

vacuo. The crude mixture was purified by column chromatography with petroleum ether / EtOAc 95:5 to give 342 mg (52% yield) of a colourless oil (d.r on the crude 90:10, Figure 7.5). The diastereoisomers were separated by preparative HPLC (hexane / EtOAc, 9:1).

Data for compound 2.28a: IR (neat): 3502 (br), 3058 (w), 2964 (m), 2924 (m), 1727 (s), 1678 (s), 1597 (w), 1490 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (1 H, s, C**H**O), 7.56 – 7.27 (15 H, m, Ar**H**), 4.68 (1 H, ddd, *J* = 10.2, 3.4, 2.5 Hz, C**H**OH), 3.35 (1 H, d, *J* = 9.5 Hz, C**HH**OTr), 3.19 (1 H, d, *J* = 9.5 Hz, C**HH**OTr), 3.14 (1 H, d, *J* = 3.5 Hz, CHO**H**), 2.43 (1 H, dd, *J* = 15.6, 10.2 Hz, C**HH**CHOH), 2.34 (1 H, dd, *J* = 15.6, 2.4 Hz, C**HH**CHOH), 1.50 (9 H, s, $SC(CH_3)_3$), 1.02 (3 H, s, CCH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1 (**C**HO), 199.8 (**C**OS), 143.1 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.3 (Ar**C**H), 87.0 (**C**$(Ph)_3$), 69.2 (**C**HOH), 65.3 (**C**H_2OTr), 54.0 (CH_3**C**), 48.6 (S**C**$(CH_3)_3$), 45.2 (**C**H_2CO), 27.8 ($SC(CH_3)_3$), 12.4 (CCH_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 545 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 545.2338 $[M+Na+MeOH]^+$; found: 545.2340 $[M+Na+MeOH]^+$.

Data for compound 2.28b: IR (neat): 3431 (br), 3058 (w), 2964 (m), 1724 (s), 1596 (w), 1489 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (1 H, s, C**H**O), 7.55 – 7.40 (6 H, m, Ar**H**), 7.37 – 7.21 (9 H, m, Ar**H**), 4.48 (1 H, dd, *J* = 9.8, 2.5 Hz, C**H**OH), 3.44 (1 H, d, *J* = 9.4 Hz, C**HH**OTr), 3.38 (1 H, d, *J* = 9.3 Hz, C**HH**OTr), 3.04 (1 H, br., CHO**H**), 2.50 (1 H, dd, *J* = 15.7, 2.6 Hz, C**HH**CHOH), 2.41 (1 H, dd, *J* = 15.8, 9.9 Hz, C**HH**CHOH), 1.48 (9 H, s, $SC(CH_3)_3$), 1.04 (3 H, s, CCH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (**C**HO), 199.9 (**C**OS), 143.2 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.2 (Ar**C**H), 87.2 (**C**$(Ph)_3$), 69.7 (**C**HOH), 64.4 (**C**H_2OTr), 54.1 (CH_3**C**), 48.6 (S**C**$(CH_3)_3$), 46.2 (**C**H_2CO), 29.7 ($SC(CH_3)_3$), 13.6 (CCH_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 545 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 545.2338 $[M+Na+MeOH]^+$; found: 545.2340 $[M+Na+MeOH]^+$.

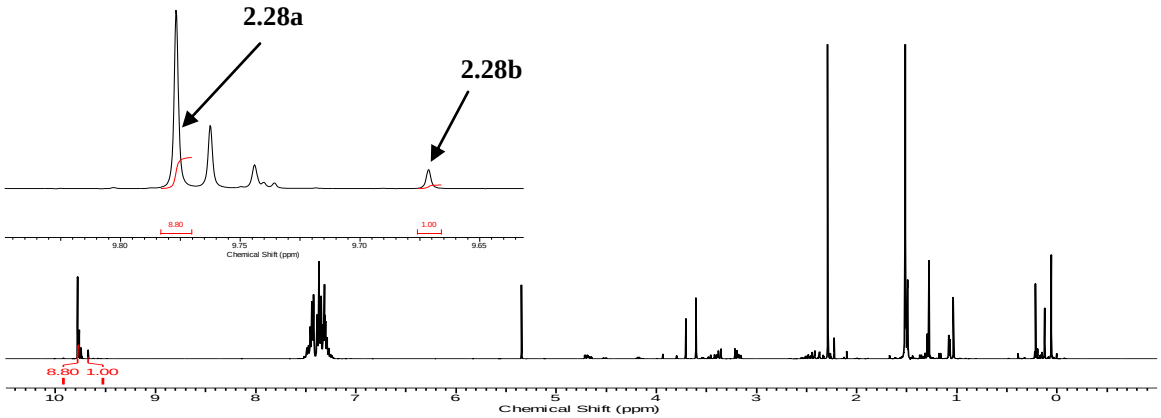
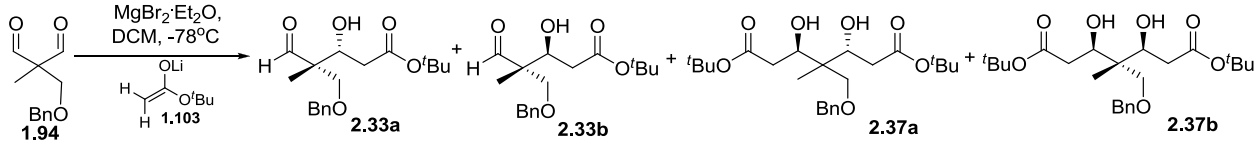


Figure 7.5. Crude ^{1}H NMR showing how the d.r. of **2.28** was calculated.

(*rac*-3*R*,4*S*)-4-Benzyloxymethyl-3-hydroxy-4-methyl-5-oxo-pentanoic acid *tert*-butyl ester (2.33a) & (*rac*-3*R*,4*R*)-4-Benzyloxymethyl-3-hydroxy-4-methyl-5-oxo-pentanoic acid *tert*-butyl ester (2.33b) & (*rac*-3R,5R)-4-Benzyloxymethyl-3,5-dihydroxy-4-methyl-heptanedioic acid di-*tert*-butyl ester (2.37a) & (*rac*-3S,4S,5R)-4-Benzyloxymethyl-3,5-dihydroxy-4-methyl-heptanedioic acid di-*tert*-butyl ester (2.37b)



1,2-Dibromoethane (146 µL, 1.70 mmol, 3 equiv.) was added to a suspension of magnesium turnings (42 mg, 1.70 mmol, 3 equiv.) in Et_2O (3 mL) and stirred at r.t for 30 min to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (3 mL) was added and the reaction mixture was cooled to –78 °C before addition, *via* cannula of the dialdehyde **1.94** (117 mg, 0.57 mmol, 1 equiv.) in CH_2Cl_2 (3 mL). After addition of the dialdehyde the reaction mixture became a pale yellow solution and was stirred at –78 °C for 20 min. Seperately to DIPA (119 µL, 0.85 mmol, 1.5 equiv.) in Et_2O (1 mL) at –78 °C was added *n*-BuLi (2.5 M in Et_2O) (0.34 mL, 0.85 mmol, 1.5 equiv). After 15 min *t*-Butyl acetate (114 µL, 0.85 mmol, 1.5 equiv.) was added and the reaction stirred at –78 °C for 15 min to form the lithium enolate **1.103**. The lithium enolate **1.103** at –78 °C was added *via* cannula to the dialdehyde chelate and stirred at –78 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl and allowed to warm to r.t. The organics were extracted with CH_2Cl_2 and dried over $MgSO_4$, filtered and concentrated in

vacuo. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 83 mg (0.26 mmol, 46% yield) of a colourless oil of **2.33** (d.r on the crude **2.33a**:**2.33b** 13:87, Figure 7.6) and 50 mg (0.11 mmol, 26% yield) of **2.37** (d.r on chromatographed product **2.37a**:**2.37b**, 95:5, Figure 7.7) as a colourless oil. After preparative HPLC (hexane :EtOAc, 85:15) an analytically pure sample of **2.33a** (3 mg), **2.33b** (5 mg), **2.37a** (24 mg) and **2.37b** (4 mg) were isolated.

Data for compound 2.33a: IR (neat): 3474 (br), 2978 (m), 2933 (w), 1728 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (1 H, s, C**H**O), 7.41 – 7.28 (5 H, m, Ar**H**), 4.53 (2 H, s, C**H**$_2$Ph), 4.39 (1 H, ddd, *J* = 8.9, 4.8, 4.4 Hz, C**H**OH), 3.71 (1 H, d, *J* = 9.4 Hz, C**HH**OBn), 3.68 (1 H, d, *J* = 9.5 Hz, C**HH**OBn), 2.46 – 2.36 (2 H, m, C**H**$_2$CHOH), 1.47 (9 H, s, OC(C**H**$_3$)$_3$), 1.06 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (**C**HO), 172.1 (**C**OO*t*Bu), 137.7 (Ar**C**), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 81.5 (O**C**(CH$_3$)$_3$), 73.7 (**C**H$_2$Ph), 71.5 (**C**H$_2$OBn), 69.7 (**C**HOH), 53.8 (CH$_3$**C**), 37.9 (**C**H$_2$CO), 28.1 (OC(**C**H$_3$)$_3$), 13.5 (**C**H$_3$C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 377 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 377.1940 $[M+Na+MeOH]^+$; found: 377.1929 $[M+Na+MeOH]^+$.

Data for compound 2.33b: IR (neat): 3515 (br), 2979 (m), 2935 (w), 2863 (w), 1727 (s), 1497 (w), 1477 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (1 H, s, C**H**O), 7.46 – 7.15 (5 H, m, Ar**H**), 4.52 (1 H, d, *J* = 12.2 Hz, C**HH**Ph), 4.48 (1 H, d, *J* = 12.2 Hz, C**HH**Ph), 4.44 (1 H, dt, *J* = 9.4, 3.5 Hz, C**H**OH), 3.62 (1 H, d, *J* = 9.4 Hz, C**HH**OBn), 3.58 (1 H, d, *J* = 9.4 Hz, C**HH**OBn), 3.47 (1 H, d, *J* = 3.5 Hz, CHO**H**), 2.46 – 2.34 (2 H, m, C**H**$_2$CHOH), 1.48 (9 H, s, OC(C**H**$_3$)$_3$), 1.06 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1 (**C**HO), 172.1 (**C**OO*t*Bu), 137.5 (Ar**C**), 128.5 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 81.6 (O**C**(CH$_3$)$_3$), 73.6 (**C**H$_2$Ph), 72.4 (**C**H$_2$OBn), 69.6 (**C**HOH), 53.6 (CH$_3$**C**), 37.4 (**C**H$_2$CO), 28.1 (OC(**C**H$_3$)$_3$), 13.1 (**C**H$_3$C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 377 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 377.1940 $[M+Na+MeOH]^+$; found: 377.1929 $[M+Na+MeOH]^+$.

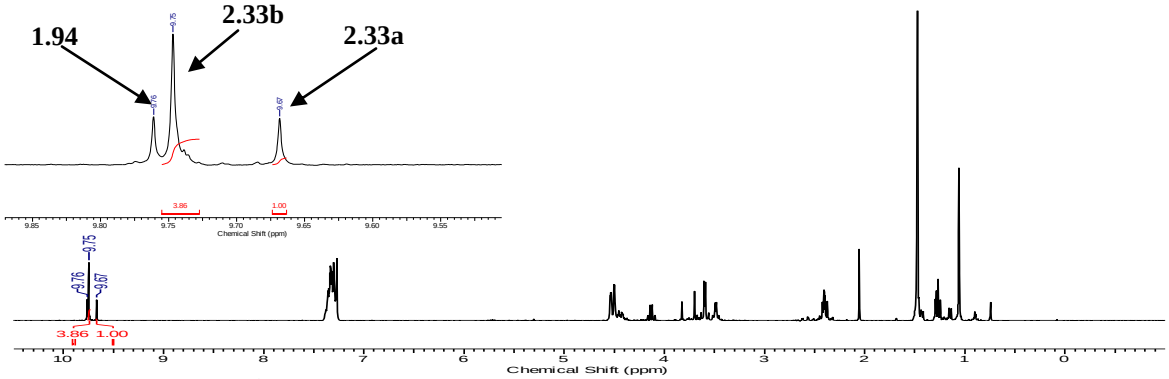


Figure 7.6. Crude ^{1}H NMR showing how the d.r. for **2.33** was calculated.

Data for compound 2.37a: IR (neat): 3471 (br), 2977 (m), 2932 (w), 1725 (s), 1455 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (5 H, m, Ar**H**), 4.52 (1 H, d, *J* = 12.2 Hz, C**H**HPh), 4.47 (1 H, d, *J* = 13.2 Hz, C**H**HPh), 4.28 (1 H, dt, *J* = 9.7, 3.7 Hz, C**H**OH), 4.14 (1 H, ddd, *J* = 9.9, 4.6, 3.2 Hz, C**H**OH), 3.88 (1 H, d, *J* = 4.8 Hz, CHO**H**), 3.76 (1 H, d, *J* = 4.3 Hz, CHO**H**), 3.49 (1 H, d, *J* = 9.5 Hz, C**H**HOBn), 3.41 (1 H, d, *J* = 9.5 Hz, C**H**HOBn), 2.59 – 2.39 (4 H, m, C**H$_2$**CHOH), 1.48 (18 H, s, OC(C**H$_3$**)$_3$), 0.90 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (**C**OO*t*Bu), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 81.1 (O**C**(CH$_3$)$_3$), 81.0 (O**C**(CH$_3$)$_3$), 73.5 (**C**H$_2$Ph), 73.1 (**C**HOH), 72.8 (**C**H$_2$OBn), 71.7 (**C**HOH), 43.7 (CH$_3$**C**), 38.7 (**C**H$_2$CO), 37.7 (**C**H$_2$CO), 28.1 (OC(**C**H$_3$)$_3$), 16.0 (**C**H$_3$C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 461 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 461.2510 $[M+Na]^+$; found: 461.2499 $[M+Na]^+$.

Data for compound 2.37b: IR (neat): 3512 (br), 2977 (m), 2933 (w), 1728 (s), 1455 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.28 (5 H, m, Ar**H**), 4.53 (2 H, s, C**H$_2$**Ph), 4.20 (2 H, ddd, *J* = 10.5, 5.8, 2.3 Hz, C**H**OH), 3.60 (2 H, s, C**H$_2$**OBn), 3.50 (2 H, d, *J* = 5.8 Hz, CHO**H**), 2.59 (2 H, dd, *J* = 15.8, 2.4 Hz, C**H**HCHOH), 2.38 (2 H, dd, *J* = 15.8, 10.5 Hz, C**H**HCHOH), 1.48 (18 H, s, OC(C**H$_3$**)$_3$), 0.75 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (**C**OO*t*Bu), 137.7 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 81.0 (O**C**$(CH_3)_3$), 73.7 (**C**H_2Ph), 72.7 (**C**H_2OBn), 70.9 (**C**HOH), 44.2 (CH_3**C**), 38.0 (**C**H_2CO), 28.1 (OC(**C**H_3)$_3$), 14.2 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 461 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 461.2510 $[M+Na]^+$; found: 461.2507 $[M+Na]^+$.

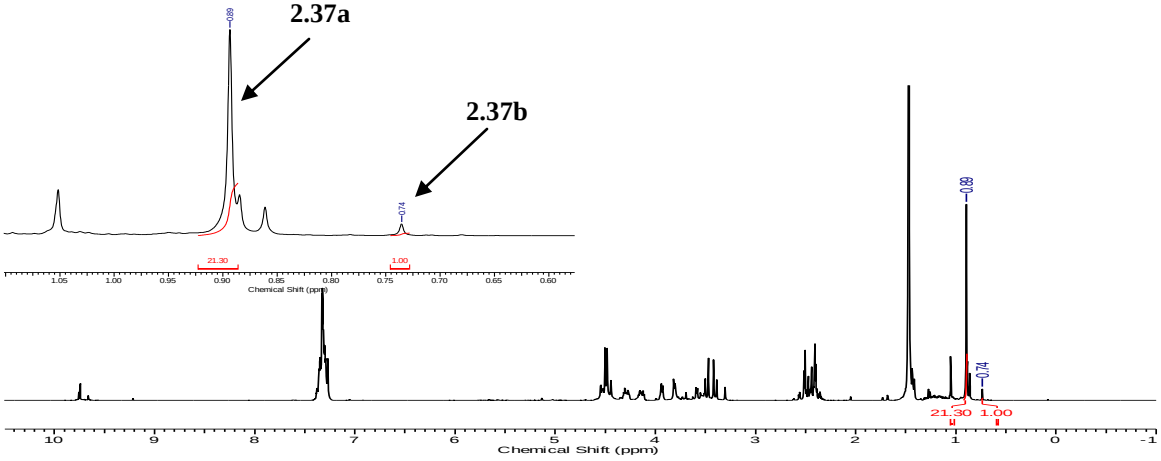
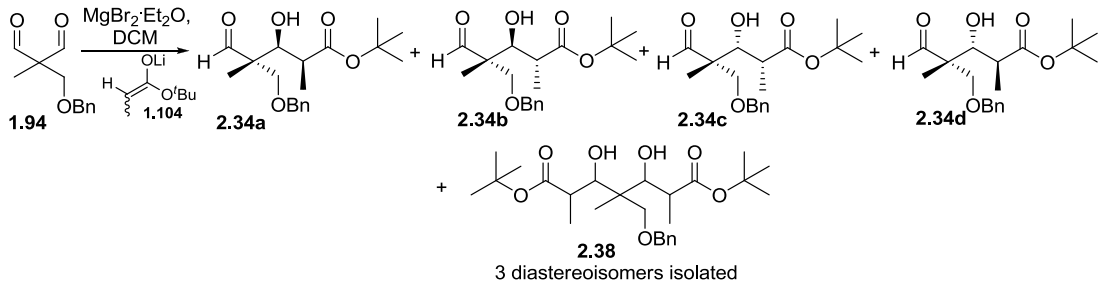


Figure 7.7. ^{1}H NMR of chromatographed **2.37** showing how the d.r. was calculated.

(*rac*-2*S*,3*S*,4*S*)-4-Benzyloxymethyl-3-hydroxy-2,4-dimethyl-5-oxo-pentanoic acid *tert*-butyl ester (2.34a) & (*rac*-2*R*,3*S*,4*S*)-4-Benzyloxymethyl-3-hydroxy-2,4-dimethyl-5-oxo-pentanoic acid *tert*-butyl ester (2.34b) & (*rac*-2*R*,3*R*,4*S*)-4-Benzyloxymethyl-3-hydroxy-2,4-dimethyl-5-oxo-pentanoic acid *tert*-butyl ester (2.34c) & (*rac*-2*S*,3*R*,4*S*)-4-Benzyloxymethyl-3-hydroxy-2,4-dimethyl-5-oxo-pentanoic acid *tert*-butyl ester (2.34d) & *rac*- 4-Benzyloxymethyl-3,5-dihydroxy-2,4,6-trimethyl-heptanedioic acid di-*tert*-butyl ester (2.38)



1,2-Dibromoethane (1.25 mL, 14.5 mmol, 3 equiv.) was added to a suspension of magnesium turnings (354 mg, 14.5 mmol, 3 equiv.) in Et_2O (12 mL) and stirred at r.t for 30 min to obtain $MgBr_2 \bullet OEt_2$. After removal of Et_2O, CH_2Cl_2 (36 mL) was added and the reaction mixture was cooled to –78 °C before addition, *via* cannula of the dialdehyde **1.94** (1.00 g, 4.85 mmol, 1 equiv.) in CH_2Cl_2 (37 mL). After addition of the dialdehyde the reaction mixture became a pale yellow solution and was stirred at –78 °C for 20 min. Separately to DIPA (1.20 mL, 8.73 mmol, 1.8 equiv.) in Et_2O (5 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes) (3.49 mL, 8.73 mmol, 1.8 equiv). After 15 min *t*-Butyl propionate (1.31 mL, 8.73 mmol, 1.8 equiv.) was added and the reaction stirred at –78 °C for 15 min to form the lithium enolate **1.104**. The lithium enolate **1.104** at –78 °C was added *via* cannula to the dialdehyde chelate and stirred at –78 °C for 1.5 h. The reaction was quenched with sat. aq. NH_4Cl and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 913 mg (2.76 mmol, 56% yield) of a colourless oil of **2.34** (d.r on the crude product, 51:27:13:9, Figure 7.8) and 475 mg (1.02 mmol, 21% yield) of a colourless oil of **2.38**. The diastereoisomers **2.34a**, **2.34b**, **2.34d** and three diastereoisomers of **2.38** were separated by preparatorive HPLC (hexane / acetone, 90:10).

Data for compound 2.34a: IR (neat): 3493 (br. m), 2978 (m), 2935 (w), 1720 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (1 H, s, C**H**O), 7.42 – 7.20 (5 H, m, Ar**H**), 4.52 (2 H, s, C**H**$_2$Ph), 4.22 (1 H, t, *J* = 4.8 Hz, C**H**OH), 3.72 (1 H, d, *J* = 9.6 Hz, C**HH**OBn), 3.68 (1 H, d, *J* = 9.1 Hz, C**HH**OBn), 3.30 (1 H, d, *J* = 4.5 Hz, CHO**H**), 2.57 (1 H, qd, *J* = 7.2, 4.8 Hz, C**H**CH_3), 1.45 (9 H, s, C(C**H$_3$**)$_3$), 1.17 (3 H, d, *J* = 7.6 Hz, CHC**H$_3$**), 1.12 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1 (**C**HO), 175.4 (**C**OO*t*Bu), 137.4 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 81.2 (O**C**$(CH_3)_3$), 74.1 (**C**HOH), 73.8 (**C**H_2Ph), 73.7 (**C**H_2OBn), 53.9 (CH_3**C**), 42.3 (**C**HCH_3), 28.0 (OC(**C**$H_3)_3$), 14.7 (**C**H_3C), 12.6 (**C**H_3CH) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 391 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 359.1829 $[M+Na]^+$; found: 359.1827 $[M+Na]^+$.

Data for compound 2.34b: IR (neat): 3459 (br. m), 2977 (m), 2935 (w), 1723 (s), 1708 (m), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (1 H, s, C**H**O), 7.40 – 7.23 (5 H, m, Ar**H**), 4.49 (2 H, s, C**H**$_2$Ph), 4.20 (1 H, d, *J* = 9.1 Hz, CHO**H**), 3.95 (1 H, dd, *J* = 9.6, 3.0 Hz, C**H**OH), 3.70 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.56 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.59 (1 H, qd, *J* = 7.1, 3.0 Hz, C**H**CH_3), 1.45 (9 H, s, C(C**H**$_3$)$_3$), 1.31 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 1.09 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8 (**C**HO), 176.3 (**C**OO*t*Bu), 137.6 (Ar**C**), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.5 (Ar**C**H), 81.8 (O**C**$(CH_3)_3$), 76.1 (**C**HOH), 73.6 (**C**H_2Ph), 72.7 (**C**H_2OBn), 55.0 (CH_3**C**), 40.0 (**C**HCH_3), 27.9 (OC(**C**$H_3)_3$), 17.2 (**C**H_3CH), 13.9 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 391 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 359.1829 $[M+Na]^+$; found: 359.1827 $[M+Na]^+$.

Data for compound 2.34d: IR (neat): 3444 (br. m), 2977 (m), 2935 (w), 1723 (s), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (1 H, s, C**H**O), 7.39 – 7.28 (5 H, m, Ar**H**), 4.55 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.51 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.17 (1 H, d, *J* = 8.6 Hz, CHO**H**), 4.01 (1 H, dd, *J* = 8.6, 3.5 Hz, C**H**OH), 3.77 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.58 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 2.49 (1 H, qd, *J* = 7.2, 3.5 Hz, C**H**CH_3), 1.43 (9 H, s, C(C**H**$_3$)$_3$), 1.28 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 1.11 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8 (**C**HO), 176.5 (**C**OO*t*Bu), 137.6 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 81.8 (O**C**$(CH_3)_3$), 75.1 (**C**HOH), 73.6 (**C**H_2Ph), 72.5 (**C**H_2OBn), 55.3 (CH_3**C**), 40.7 (**C**HCH_3), 27.9 (OC(**C**$H_3)_3$), 17.1 (**C**H_3CH), 13.1 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 359 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 359.1829 $[M+Na]^+$; found: 359.1827 $[M+Na]^+$.

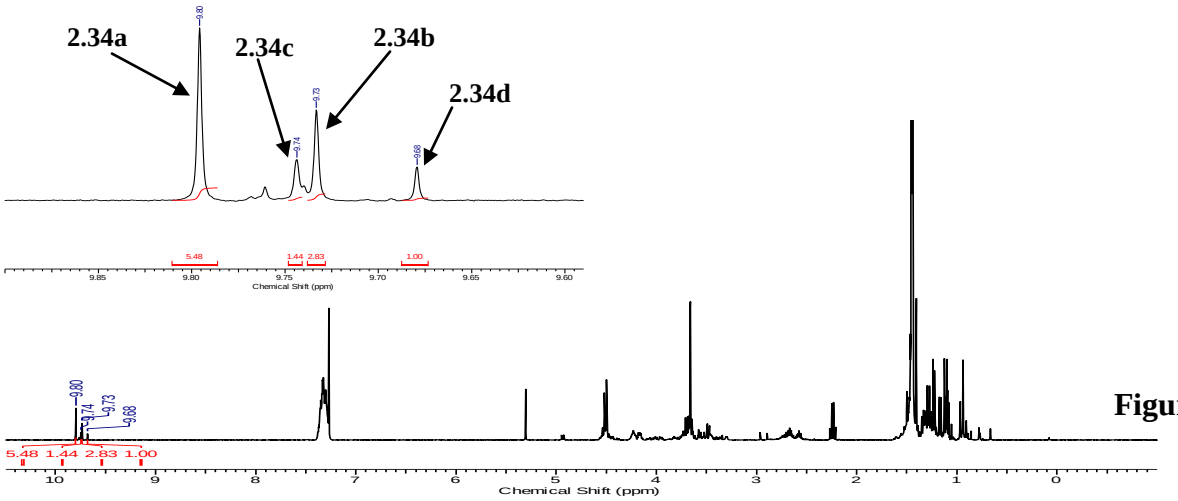


Figure 7.8. Crude ^{1}H NMR of **2.34** showing how the d.r. was calculated.

Data for compound 2.38a: IR (neat): 3453 (br. m), 2976 (m), 2934 (w), 1723 (s), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.24 (5 H, m, Ar**H**), 4.49 (2 H, s, C**H**$_2$Ph), 4.23 (1 H, t, *J* = 4.8 Hz, C**H**OH), 4.16 (1 H, t, *J* = 5.5 Hz, C**H**OH), 3.68 (1 H, d, *J* = 4.5 Hz, CHO**H**), 3.65 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.49 (1 H, d, *J* = 5.1 Hz, CHO**H**), 3.47 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.75 – 2.61 (2 H, m, C**H**CH_3), 1.45 (9 H, s, C(C**H**$_3$)$_3$), 1.44 (9 H, s, C(C**H**$_3$)$_3$), 1.28 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 1.23 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.94 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3 (**C**OO*t*Bu), 176.2 (**C**OO*t*Bu), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 80.6 (O**C**$(CH_3)_3$), 80.5 (O**C**$(CH_3)_3$), 75.4 (**C**HOH), 74.8 (**C**HOH), 73.6 (**C**H_2OBn), 73.5 (**C**H_2Ph), 60.3 (CH_3**C**), 42.2 (**C**HCH_3), 41.7 (**C**HCH_3), 28.0 (OC(**C**$H_3)_3$), 27.9 (OC(**C**$H_3)_3$), 16.8 (**C**H_3C), 13.7 (**C**H_3CH), 13.3 (**C**H_3CH) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 489 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 489.2823 $[M+Na]^+$; found: 489.2839 $[M+Na]^+$.

Data for compound 2.38b: IR (neat): 3498 (br. m), 2977 (m), 2934 (w), 1725 (s), 1456 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.28 (5 H, m, Ar**H**), 4.51 (2 H, s, C**H**$_2$Ph), 4.15 (2 H, t, *J* = 5.8 Hz, C**H**OH), 3.66 (2 H, s, C**H**$_2$OBn), 3.35 (2 H, d, *J* = 6.6 Hz, CHO**H**), 2.75 (2 H, qd,

J = 7.1, 5.5 Hz, C**H**CH_3), 1.46 (18 H, s, C(C**H**$_3$)$_3$), 1.23 (6 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.78 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6 (**C**OO*t*Bu), 137.5 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 80.6 (O**C**$(CH_3)_3$), 73.9 (**C**H_2Ph), 73.8 (**C**H_2OBn), 73.4 (**C**HOH), 45.9 (CH_3**C**), 42.0 (**C**HCH_3), 28.0 (OC(**C**H_3)$_3$), 14.6 (**C**H_3C), 13.8 (**C**H_3CH) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 489 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 489.2823 $[M+Na]^+$; found: 489.2837 $[M+Na]^+$.

Data for compound 2.38c: IR (neat): 3488 (br. m), 2976 (m), 2935 (w), 1726 (s), 1701 (m), 1456 (m) cm^{-1}.

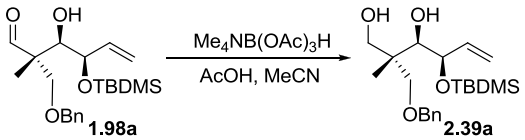
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (5 H, m, Ar**H**), 4.55 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.45 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.25 (1 H, d, *J* = 9.6 Hz, CHO**H**), 4.08 (1 H, dd, *J* = 9.3, 1.8 Hz, C**H**OH), 3.89 (1 H, dd, *J* = 9.9, 7.8 Hz, C**H**OH), 3.83 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.52 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.36 (1 H, d, *J* = 10.1 Hz, CHO**H**), 2.87 (1 H, qd, *J* = 7.2, 1.5 Hz, C**H**CH_3), 2.56 (1 H, quin, *J* = 7.1 Hz, C**H**CH_3), 1.46 (9 H, s, C(C**H**$_3$)$_3$), 1.44 (9 H, s, C(C**H**$_3$)$_3$), 1.40 (3 H, d, *J* = 7.6 Hz, CHC**H**$_3$), 1.23 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.66 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3 (**C**OO*t*Bu), 174.7 (**C**OO*t*Bu), 137.1 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 80.2 (O**C**$(CH_3)_3$), 76.3 (**C**HOH), 74.9 (**C**HOH), 73.8 (**C**H_2OBn), 73.6 (**C**H_2Ph), 46.6 (CH_3**C**), 43.4 (**C**HCH_3), 38.2 (**C**HCH_3), 27.9 (OC(**C**H_3)$_3$), 27.9 (OC(**C**H_3)$_3$), 18.4 (**C**H_3C), 14.9 (**C**H_3CH), 14.3 (**C**H_3CH) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 489 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 489.2823 $[M+Na]^+$; found: 489.2815 $[M+Na]^+$.

(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(tert-butyl-dimethyl-silanonyloxy)-2-methyl-hex-5-ene-1,3-diol (2.39a).



To a solution of $Me_4NB(OAc)_3H$ (2.78 g, 10.57 mmol, 5 equiv.) and AcOH (1.21 mL, 21.13 mmol, 10 equiv.) in MeCN (33 mL) was added a solution of aldehyde **1.98a** (800 mg, 2.11 mmol, 1 equiv.) in MeCN (7 mL). The reaction mixture was stirred at r.t for 1 h. The

reaction mixture was quenched with sat. aq. NH_4Cl. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the combined organic extracts washed with brine and dried with anhydrous Na_2SO_4. The reaction mixture was filtered and the solvent removed. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 6:4) to give 740 mg of **2.39a** as a colourless oil (1.94 mmol, 92%).[141]

IR (neat): 3429 (br), 2953 (m), 2929 (s), 2856 (s), 1497 (w), 1471 (m), 1454 (m), 1390 (m) cm^{-1}.

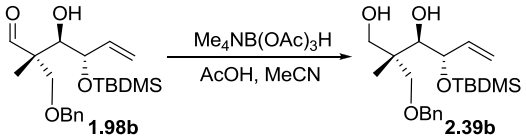
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (5 H, m, Ar**H**), 6.01 (1 H, ddd, *J* = 17.5, 9.9, 7.9 Hz, C**H**=CH_2), 5.28 – 5.09 (2 H, m, C**H$_2$**=CH), 4.55 (1 H, d, *J* = 11.7 Hz, C**H**HPh), 4.50 (1 H, d, *J* = 11.7 Hz, CH**H**Ph), 4.35 (1 H, dd, *J* = 7.3, 3.5 Hz, C**H**OTBDMS), 3.78 – 3.62 (3 H, m, C**H**OH and C**H$_2$**OH), 3.58 (1 H, d, *J* = 9.3 Hz, C**H**HOBn), 3.53 (1 H, d, *J* = 9.3 Hz, CH**H**OBn), 3.34 (1 H, d, *J* = 6.4 Hz, CHO**H**), 3.25 (1 H, t, *J* = 5.6 Hz, CH_2O**H**), 0.99 (3 H, s, CC**H$_3$**) 0.96 (9 H, s, SiC(C**H$_3$**)$_3$), 0.13 (3 H, s, C**H$_3$**Si), 0.11 (3 H, s, C**H$_3$**Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (**C**H=CH_2), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.7 (Ar**C**H), 116.2 (**C**H_2=CH), 77.3 (**C**HOH), 75.6 (**C**H_2OH), 74.6 (**C**HOTBDMS), 73.5 (**C**H_2OBn), 68.9 (**C**H_2Ph), 43.0 (**C**CH_3), 25.9 (SiC(**C**H_3)$_3$), 18.1 (Si**C**CH_3), 16.4 (**C**H_3C), -3.6 (**C**H_3Si), -4.7 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 403 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 403.2275 $[M+Na]^+$; found: 403.2272 $[M+Na]^+$

(*rac*-2*S*,3*R*,4*S*)-2-Benzyloxymethyl-4-(tert-butyl-dimethyl-silanonyloxy)-2-methyl-hex-5-ene-1,3-diol (2.39b)



60 mg of **1.98b** (0.16 mmol, 1 equiv.) was transformed to 56 mg of **2.39b** (0.15 mmol, 92% yield) according to the method above.

IR (neat): 3418 (br), 2953 (m), 2928 (s), 2884 (m), 2856 (s), 1471 (m), 1462 (m), 1455 (m) cm^{-1}.

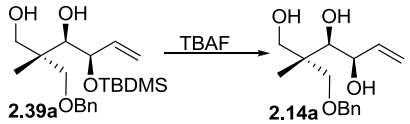
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.21 (5 H, m, Ar**H**), 6.00 (1 H, ddd, *J* = 16.9, 10.7, 7.6 Hz, C**H**=CH_2), 5.28 – 5.08 (2 H, m, C**H**$_2$=CH), 4.52 (2 H, s, C**H**$_2$Ph), 4.27 (1 H, dd, *J* = 7.6, 3.7 Hz, C**H**OTBDMS), 3.98 – 3.85 (1 H, m, C**H**OH), 3.78 – 3.58 (2 H, m, C**H**$_2$OH), 3.55 (1 H, d, *J* = 9.0 Hz, C**HH**OBn), 3.48 (1 H, d, *J* = 9.0 Hz, C**HH**OBn), 0.90 (12 H, s, CC**H**$_3$ and SiC(C**H**$_3$)$_3$), 0.08 (3 H, s, C**H**$_3$Si), 0.05 (3 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0 (Ar**C**), 137.7 (**C**H=CH_2), 128.4 (Ar**C**H), 127.6 (Ar**C**H), 117.2 (**C**H_2=CH), 77.2 (**C**HOH), 75.8 (**C**H_2OH), 75.8 (**C**HOTBDMS), 73.6 (**C**H_2OBn), 68.6 (**C**H_2Ph), 42.1 (**C**CH_3), 25.8 (SiC(**C**H_3)$_3$), 18.1 (Si**C**$(CH_3)_3$), 15.8 (**C**H_3C), -4.2 (**C**H_3Si), -4.8 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 403 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 403.2275 $[M+Na]^+$; found: 403.2272 $[M+Na]^+$.

(*rac*-2*S*,3*R*,4*R*)-2-(benzyloxymethyl)-2-methylhex-5-ene-1,3,4-triol (2.14a)



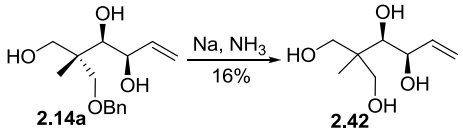
TBAF (750 µL of 1.0 M solution in THF, 0.75 mmol, 1.5 equiv.) was added dropwise to a solution of diol **2.39a** (190 mg, 0.50 mmol, 1 equiv.) in THF (3.3 mL). The reaction was stirred for 30 min at r.t then the solvent removed in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / acetone, 7:3) to give 117 mg of a colourless oil (0.44 mmol, 88% yield). This was crystallised to give **2.14a** as fine white needles.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.08 (5 H, m, Ar**H**), 6.03 – 5.76 (1 H, m, C**H**=CH_2), 5.45 – 5.04 (2 H, m, C**H**$_2$=CH), 4.41 (2 H, s, C**H**$_2$Ph), 4.22 (1 H, br.s, C**H**OHCH=CH_2; simplifies to dd, *J* = 5.3, 1.1 Hz upon treatment with D_2O), 3.84 (1 H, d, *J* = 11.3 Hz, CC**H**OH), 3.71 – 3.48 (4 H, m, 3 x O**H** and C**HH**OH; simplifies to 3.72 – 3.56 (1H, m, C**HH**OH) upon treatment with D_2O), 3.48 – 3.25 (3 H, m, C**HH**OH and C**H**$_2$OBn), 0.88 (3 H, s, CC**H**$_3$) ppm.

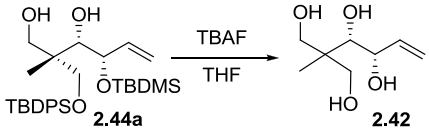
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2 (**C**H=CH_2), 137.3 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 115.6 (**C**H_2=CH), 77.4 (C**C**HOH), 77.1 (**C**H_2OH), 73.6 (**C**H_2OBn), 70.5 (**C**HOTBDMS), 64.8 (**C**H_2Ph), 43.2 (**C**CH_3), 16.7 (**C**H_3C) ppm.

Data corresponds to previous data[109]

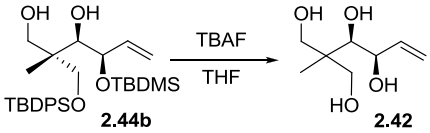
(*rac-3,4 -syn*)-2-(Hydroxymethyl)-2-methylhex-5-ene-1,3,4-triol (2.42).



Na (0.5 g, 21.83 mmol, 55 equiv.) was dissolved in NH_3 (20 mL) at –78 °C to give a deep blue solution. A solution of triol **2.14a** (100 mg, 0.38 mmol, 1 equiv.) in Et_2O (1 mL) was added slowly and the reaction mixture stirred at –78 °C for 50 min. Solid NH_4Cl was added in small portions until the blue colour had disappeared. The reaction mixture was warmed to r.t, evaporating the NH_3. EtOAc was added to the reaction mixture to give a white suspension. The reaction mixture was filtered and the solvent removed in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / acetone, 1:1) and further purified by HPLC (acetone / hexane 7:3) to give 11 mg of a colourless oil (0.06 mmol, 16%).[139]



To a solution of **2.44a** (50 mg, 0.09 mmol, 1 equiv.) in THF (5 mL) was added TBAF (82 µL, 0.11 mmol, 3 equiv.) dropwise. The reaction mixture was stirred at r.t for 45 min and the solvent removed in *vacuo*. The crude was purified by column chromatography (petroleum ether / acetone 1:1) and further purified by HPLC (acetone / hexane 7:3) to give 16 mg of **2.42** as a colourless oil (0.09 mmol, 98% yield).



20 mg of **2.44b** (0.04 mmol, 1 equiv.) was transformed to 8 mg of **2.42** (0.04 mmol, 100 % yield) according to the method above.

IR (neat): 3371 (br), 2475 (br), 1456 (m) cm^{-1}.

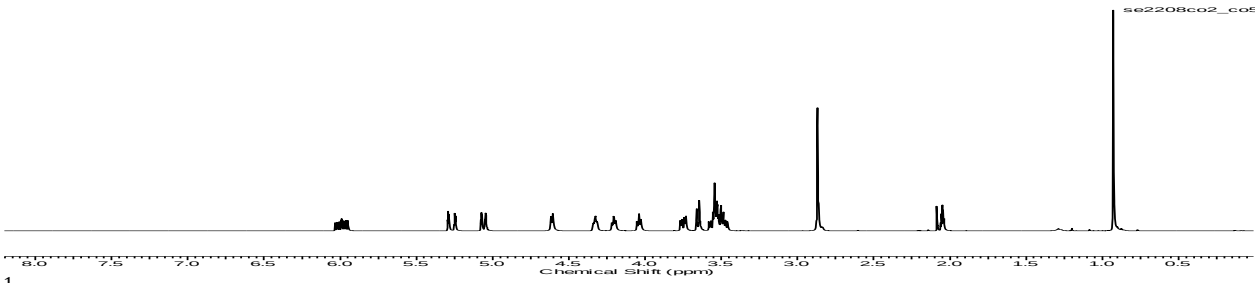
^{1}H NMR (400 MHz, d_6-acetone): δ 5.99 (2 H, ddd, *J* = 17.2, 10.5, 5.4 Hz, C**H**=CH_2), 5.27 (1 H, dt, *J* = 17.3, 1.8 Hz, C**HH**=CH), 5.06 (1 H, dt, *J* = 10.5, 1.8 Hz, C**HH**=CH), 4.61 (1 H, d, *J* = 5.1 Hz, CHO**H**), 4.39 – 4.27 (1 H, m, C**H**(OH)CH=CH_2), 4.21 (1 H, t, *J* = 5.3 Hz, CH_2O**H**), 4.04 (1 H, t, *J* = 5.4 Hz CH_2O**H**), 3.75 (1 H, dd, *J* = 10.9, 4.6 Hz C**HH**OH), 3.65

(1 H, d, *J* = 6.8 Hz, C**H**H**H**OH), 3.59 – 3.41 (4 H, m, 2 x C**H**H**H**OH and CC**H**OH and O**H**), 0.93 (3 H, s, C**H**$_3$) ppm.

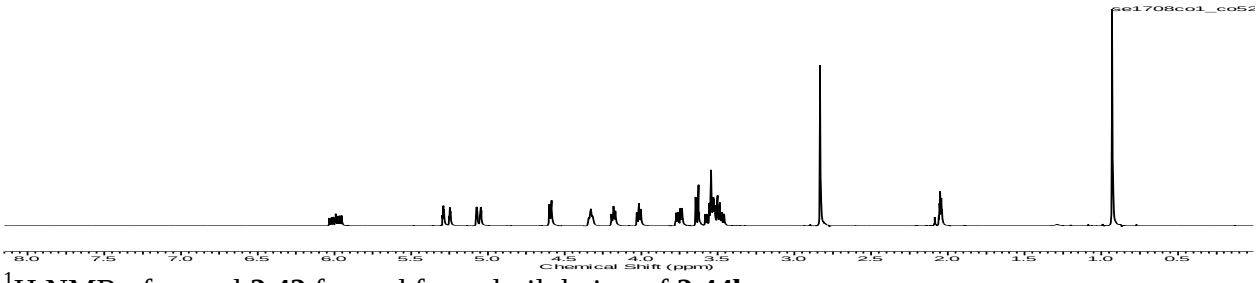
^{13}C NMR (100 MHz, d_6-acetone): δ 141.8 (**C**H=CH$_2$), 114.6 (**C**H$_2$=CH), 77.7 (C**C**HOH), 71.5 (**C**HOHCH=CH$_2$), 67.7 (**C**H$_2$OH), 65.4 (**C**H$_2$OH), 44.8 (**C**CH$_3$), 17.4 (**C**H$_3$C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 315 $[M+Na]^+$ (93%), 607 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 315.1962 $[M+Na]^+$; found: 315.1956 $[M+Na]^+$.



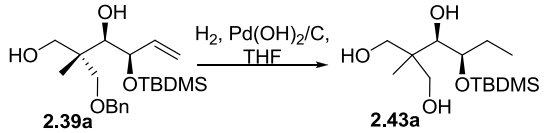
^{1}H NMR of tetraol **2.42** formed from desilylation of **2.44a**



^{1}H NMR of tetraol **2.42** formed from desilylation of **2.44b**

Figure 7.9. ^{1}H NMR's of compound **2.42** formed from **2.44a** and **2.44b** respectively.

(*rac*-3*R*,4*R*)-4-(tert-butyldimethylsilyloxy)-2-(hydroxymethyl)-2-methylhexane-1,3-diol (2.43a)



To a solution of diol **2.39a** (100 mg, 0.26 mmol, 1 equiv.) in THF (5 mL) was added 20% Pd(OH)$_2$/C (18 mg, 0.18 equiv. by weight). The reaction mixture was placed under a H_2 (g) atmosphere and stirred at r.t for 18 h. The black reaction suspension was filtered through celite and washed with Et_2O. The filtrate was concentrated and the crude mixture purified by

column chromatography (petroleum ether / acetone, 1:1) to give 48 mg of **2.43a** as a colurless oil (0.15 mmol, 63%).[140]

Data for compound 2.43a: IR (neat): 3386 (br), 2955 (m), 2930 (m), 2882 (w), 2858 (w), 1463 (m), 1460 (w) cm^{-1}.

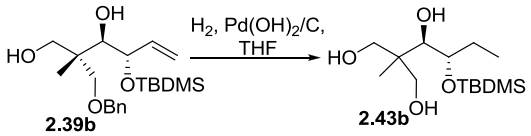
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 – 3.77 (2 H, m, C**H**H**O**H and C**H**OTBDMS), 3.64 (3 H, br. s., CC**H**OH and C**H$_2$**OH), 3.55 – 3.44 (1 H, m, C**H**H**O**H), 3.43 – 3.31 (1 H, m, O**H**), 3.31 – 3.23 (1 H, m, O**H**), 3.12 (1 H, m, O**H**), 1.83 – 1.36 (2 H, m, C**H$_2$**CH_3), 0.95 –0.84 (12 H, m, C**H$_3$**CH_2 and SiC(C**H$_3$**)$_3$), 0.75 (3 H, s, CC**H$_3$**), 0.14 (3 H, s, SiC**H$_3$**), 0.13 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 74.6 (**C**H_2OH), 71.9 (**C**HOTBDMS), 69.7 (C**C**HOH), 67.8 (**C**H_2OH), 43.3 (**C**CH_3), 29.2 (**C**H_2CH_3), 26.4 (**C**H_3CH_2), 18.5 (Si**C**CH_3), 16.1 (**C**H_3C), 9.4 (SiC(**C**H_3)$_3$), -3.0 (**C**H_3Si), -4.0 (**C**H_3Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 315 $[M+Na]^+$ (93%), 607 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity), calculated: 315.1962 $[M+Na]^+$, found: 315.1956 $[M+Na]^+$.

***(rac*-3*R*,4*S*)-4-(tert-butyldimethylsilyloxy)-2-(hydroxymethyl)-2-methylhexane-1,3-diol (2.43b)**



75 mg of **2.39b** (0.20 mmol, 1 equiv.) was transformed to 31 mg of **2.43b** (0.11 mmol, 53% yield) according to the method above.

Data for compound 2.43b: IR (neat): 3364 (br), 2955 (m), 2930 (m), 2883 (w), 2857 (w), 1464 (m) cm^{-1}.

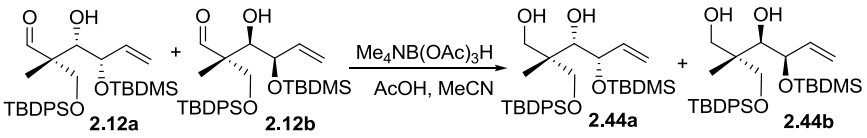
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (3 H, ddd, *J* = 5.5, 3.0, 2.8 Hz, C**H**OTBDMS and C**H$_2$**OH), 3.77 – 3.67 (1 H, m, C**H**OH), 3.59 (2 H, dd, *J* = 11.2, 6.1 Hz, C**H$_2$**OH), 1.85 – 1.49 (2 H, m, C**H$_2$**CH_3), 0.96 (3 H, t, *J* = 7.5 Hz, C**H$_3$**CH_2), 0.92 (9 H, s, SiC(C**H$_3$**)$_3$), 0.85 (3 H, s, CC**H$_3$**), 0.16 – 0.07 (6 H, m, (C**H$_3$**)$_2$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 77.3 (**C**HOTBDMS), 74.8 (C**C**HOH), 69.6 (**C**H_2OH), 67.9 (**C**H_2OH), 42.2 (**C**CH_3), 26.0 (**C**H_3CH_2), 25.0 (**C**H_2CH_3), 18.1 (Si**C**CH_3), 16.0 (**C**H_3C), 10.1 (SiC**C**H_3), -4.4 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 315 $[M+Na]^+$ (70%), 607 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 315.1962 $[M+Na]^+$, found: 315.1956 $[M+Na]^+$.

(*rac*-2*S*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-2-methylhex-5-ene-1,3-diol (2.44a) and (*rac*-2*S*,3*R*,4*R*)-4-(*tert*-butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-2-methylhex-5-ene-1,3-diol (2.44b).



To a solution of $Me_4NB(OAc)_3H$ (1.75 g, 6.64 mmol, 5 equiv.) and AcOH (761 µL, 13.29 mmol, 10 equiv.) in MeCN (30 mL) was added a solution of a mixture of major and minor diastereoisomers **2.12a** and **2.12b** (700 mg, 1.33 mmol, 1 equiv.) in MeCN (5 mL). The reaction mixture was stirred at r.t for 90 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the organics extracts washed with brine and dried with anhydrous Na_2SO_4. The reaction mixture was filtered and the solvent removed. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 556 mg of **2.44** as a colourless oil (1.05 mmol, 79%) and further purified by HPLC (hexane / acetone 85:15) to separate the diastereoisomers.[141]

Data for compound 2.44a: IR (neat): 3462 (br), 3072 (w), 2955 (m), 2929 (m), 2885 (m), 2857 (m), 1590 (w), 1471 (m), 1427 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.62 (4 H, m, Ar**H**), 7.50 – 7.35 (6 H, m, Ar**H**), 6.00 (1 H, ddd, *J* = 17.5, 10.1, 7.7 Hz., C**H**=CH_2), 5.24 – 5.08 (2 H, m, C**H$_2$**=CH), 4.33 (1 H, dd, *J* = 7.5, 3.4 Hz, C**H**OTBDMS), 3.83 (1 H, d, *J* = 9.9 Hz, C**HH**OTBDPS), 3.73 (1 H, dd, *J* = 6.4, 3.4 Hz, C**H**OH), 3.71 – 3.60 (2 H, m, C**H$_2$**OH), 3.58 (1 H, d, *J* = 9.8 Hz, C**HH**OTBDPS), 3.07 – 2.97 (2 H, m, CH_2O**H** and CHO**H**), 1.07 (9 H, s, SiC(C**H$_3$**)$_3$

(TBDMS)), 0.90 (3 H, s, C**H**$_3$C), 0.85 (9 H, s, SiC(C**H**$_3$)$_3$ (TBDPS)), 0.04 (3 H, s, SiC**H**$_3$), 0.02 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8 (**C**H=CH$_2$), 135.7 (Ar**C**H), 133.2 (Ar**C**), 132.8 (Ar**C**), 129.7 (Ar**C**H), 127.8 (Ar**C**H), 116.1 (**C**H$_2$=CH), 77.2 (**C**HOH), 74.3 (**C**HOTBDMS), 68.8 (**C**H$_2$OH), 68.4 (**C**H$_2$OTBDPS), 43.9 (**C**CH$_3$), 26.9 (SiC(**C**H$_3$)$_3$ (TBDMS)), 25.9 (SiC(**C**H$_3$)$_3$ (OTBDPS)), 19.3 (Si**C**CH$_3$), 18.1 (Si**C**CH$_3$), 16.0 (**C**H$_3$C), -3.5 (**C**H$_3$Si), -4.7 (**C**H$_3$Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 551 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 551.2983 $[M+Na]^+$; found: 551.2984 $[M+Na]^+$.

Data for compound 2.44b: IR (neat): 3481 (br), 3072 (w), 2929 (m), 2885 (w), 2857 (m),1472 (m), 1427 (m) cm^{-1}.

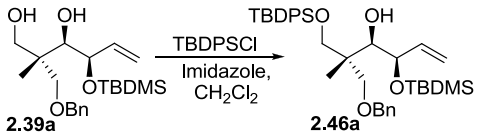
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 – 7.62 (4 H, m, Ar**H**), 7.50 – 7.35 (6 H, m, Ar**H**), 5.92 (1 H, ddd, *J* = 17.5, 10.1, 7.8 Hz, C**H**=CH$_2$), 5.19 – 5.00 (2 H, m, C**H$_2$**=CH), 4.25 (1 H, dd, *J* = 7.8, 3.6 Hz, C**H**OTBDMS), 3.76 (1 H, dd, *J* = 11.2, 5.4 Hz, C**HH**OH), 3.71 – 3.61 (4 H, m, C**HH**OH and C**H$_2$**OTBDPS and C**H**OH), 3.22 (1 H, d, *J* = 6.4 Hz, CHO**H**), 2.99 (1 H, t, *J* = 6.1 Hz, CH$_2$O**H**), 1.08 (9 H, s, SiC(C**H$_3$**)$_3$ (TBDMS)), 0.92 (3 H, s, C**H$_3$**C), 0.89 (9 H, s, SiC(C**H$_3$**)$_3$ (TBDPS)), 0.05 (3 H, s, SiC**H$_3$**), 0.05 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5 (**C**H=CH$_2$), 135.7 (Ar**C**H), 133.0 (Ar**C**), 132.9 (Ar**C**), 129.8 (Ar**C**H), 127.7 (Ar**C**H), 116.5 (**C**H$_2$=CH), 77.2 (**C**HOH), 74.3 (**C**HOTBDMS), 68.5 (**C**H$_2$OH), 68.3 (**C**H$_2$OTBDPS), 43.6 (**C**CH$_3$), 26.9 (SiC(**C**H$_3$)$_3$ (TBDMS)), 25.9 (SiC(**C**H$_3$)$_3$ (OTBDPS)), 19.2 (Si**C**CH$_3$), 18.1 (Si**C**CH$_3$), 15.7 (**C**H$_3$C), -3.5 (**C**H$_3$Si), -4.7 (**C**H$_3$Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 551 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 551.2983 $[M+Na]^+$; found: 551.2985 $[M+Na]^+$.

(*rac*-2*R*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-2-methylhex-5-ene-1,3-diol (2.46a).



2.39a **2.46a**

To a solution of diol **2.39a** (150 mg, 0.39 mmol, 1 equiv.) and imidazole (53 mg, 0.78 mmol, 2 equiv.) in CH_2Cl_2 (8 mL) was added TBDPSCl (112 µL, 0.43 mmol, 1.1 equiv.) dropwise. The reaction mixture was stirred at r.t for 24 h. The reaction mixture was poured into H_2O,

the organics extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and the solvent evaporated in *vacuo*. The crude was purified by column chromatography (petroleum ether / EtOAc 90:10) and further purified by preparative HPLC (hexane / EtOAc, 95:5) to give 63 mg of **2.46a** as a colourless oil (0.10 mmol, 26%).

IR (neat): 2954 (m), 2929 (s), 2885 (m), 2856 (s), 1472 (m), 1427 (m) cm^{-1}.

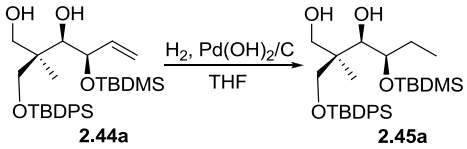
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.60 (4 H, m, Ar**H**), 7.48 – 7.20 (11 H, m, Ar**H**), 5.95 (1 H, ddd, *J* = 17.5, 10.1, 7.7 Hz, C**H**=CH_2), 5.15 – 4.98 (2 H, m, C**H$_2$**=CH), 4.52 (1 H, d, *J* = 11.8 Hz, C**HH**Ph), 4.45 (1 H, d, *J* = 11.9 Hz, C**HH**Ph), 4.33 (1 H, dd, *J* = 7.6, 2.7 Hz, C**H**OTBDMS), 3.83 (1 H, d, *J* = 9.7 Hz, C**HH**OTBDPS), 3.67 (1 H, d, *J* = 9.3 Hz, C**HH**OTBDPS), 3.64 (1 H, d, *J* = 8.5 Hz, C**HH**OBn), 3.57 (1 H, dd, *J* = 6.4, 2.6 Hz, C**H**OH), 3.45 (1 H, d, *J* = 8.9 Hz, C**HH**OBn), 3.05 (1 H, d, *J* = 6.9 Hz, CHO**H**), 1.06 (9 H, s, SiC(C**H$_3$**)$_3$ (TBDMS)), 1.03 (3 H, s, C**H$_3$**C), 0.86 (9 H, s, SiC(C**H$_3$**)$_3$ (TBDPS)), 0.01 (3 H, s, SiC**H$_3$**), 0.00 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4 (**C**H=CH_2), 138.6 (Ar**C**), 135.7 (Ar**C**H), 133.7 (Ar**C**), 133.6 (Ar**C**), 129.5 (Ar**C**H), 128.2 (Ar**C**H), 127.5 (Ar**C**H), 127.4 (Ar**C**H), 115.4 (**C**H_2=CH), 76.4 (**C**HOH), 74.2 (**C**HOTBDMS), 73.3 (**C**H_2Ph), 72.9 (**C**H_2OBn), 66.7 (**C**H_2OTBDPS), 44.3 (**C**CH_3), 26.9 (SiC(**C**H_3)$_3$ (TBDMS)), 25.9 (SiC(**C**H_3)$_3$ (OTBDPS)), 19.4 (Si**C**CH_3), 18.1 (Si**C**CH_3), 15.8 (**C**H_3C), -3.5 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 642 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 641.3453 $[M+Na]^+$; found: 641.3448 $[M+Na]^+$.

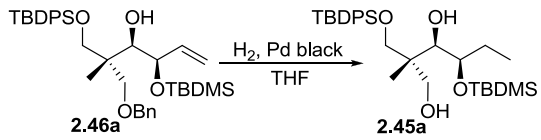
(*rac*-2*S*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldiphenylsilanyloxymethyl)-2-methyl-hexane-1,3-diol (2.45a).



2.44a **2.45a**

To a solution of diol **2.44a** (100 mg, 0.19 mmol, 1 equiv.) in THF (5 mL) was added 20% $Pd(OH)_2$/C (18 mg, 0.18 equiv. by weight). The reaction mixture was placed under a H_2 (g) atmosphere and stirred at r.t for 18 h. The black reaction suspension was filtered through celite and washed with Et_2O. The filtrate was concentrated in *vacuo* and the crude mixture

purified by column chromatography (petroleum ether / acetone 90:10) to give 76 mg of **2.45a** as a colurless oil (0.14 mmol, 75%).[140]



To a solution of **2.46a** (40 mg, 0.065 mmol, 1 equiv.) in THF (2 mL) was added Pd black (7.2 mg, 0.18 equiv. by weight). The reaction mixture was placed under a H_2 (g) atmosphere and stirred at r.t for 18 h. The black reaction suspension was filtered through celite and washed with Et_2O. The filtrate was concentrated in *vacuo* and the crude mixture purified by column chromatography (petroleum ether / EtOAc, 85:15) and further purified by HPLC (hexane / EtOAc, 85:15) to give 8 mg of **2.45a** as a colourless oil (0.015 mmol, 23%).

IR (neat): 3469 (br), 2956 (m) 2930 (m), 2883 (w), 2857 (m), 1590 (w), 1472 (m), 1427 (m) cm^{-1}.

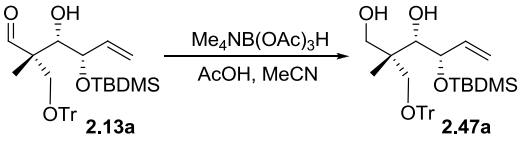
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.62 (4 H, m, Ar**H**), 7.52 – 7.34 (6 H, m, Ar**H**), 3.93 (1 H, d, *J* = 9.7 Hz, C**H**HOTBDPS), 3.89 (1 H, td, *J* = 4.1, 1.4 Hz, C**H**OTBDMS), 3.83 – 3.72 (2 H, m, C**H**OH and C**H**HOH), 3.64 (1 H, dd, *J* = 11.3, 6.2 Hz, C**H**HOH), 3.50 (1 H, d, *J* = 9.7 Hz, CH**H**OTBDPS), 1.85 – 1.65 (1 H, m, C**H**HCH_3), 1.61 – 1.42 (1 H, m, CHHCH_3), 1.08 (9 H, s, SiC(C**H**$_3$)$_3$ (TBDMS)), 0.92 (3 H, t, *J* = 7.5 Hz, C**H**$_3$$CH_2$), 0.82 (12 H, s, SiC(C**H**$_3$)$_3$ (TBDPS) and C**H**$_3$C), 0.08 (3 H, s, SiC**H**$_3$), -0.03 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7 (Ar**C**H), 135.6 (Ar**C**H), 133.2 (Ar**C**), 132.7 (Ar**C**), 129.7 (Ar**C**H), 127.7 (Ar**C**H), 72.6 (**C**HOH), 71.6 (**C**HOTBDMS), 68.8 (**C**H_2OH), 68.5 (**C**H_2OTBDPS), 43.7 (**C**CH_3), 28.9 (**C**H_2CH_3), 26.8 (SiC(**C**H_3)$_3$ (TBDMS)), 25.9 (SiC(**C**H_3)$_3$ (OTBDPS)), 19.3 (Si**C**CH_3), 18.0 (Si**C**CH_3), 15.4 (**C**H_3C), 9.1 (**C**H_3CH_2), -3.5 (**C**H_3Si), -4.5 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 553 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 553.3140 $[M+Na]^+$; found: 553.3134 $[M+Na]^+$ (100%).

(*rac*-2*S*,3*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-methyl-2-trityloxymethylhex-5-ene-1,3-diol (2.47a).



To a solution of $Me_4NB(OAc)_3H$ (241 mg, 0.91 mmol, 5 equiv.) and AcOH (105 µL, 1.83 mmol, 10 equiv.) in MeCN (4 mL) was added a solution of aldehyde **2.13a** (100 mg, 0.18 mmol, 1 equiv.) in MeCN (1 mL). The reaction mixture was stirred at r.t for 90 min. The reaction mixture was quenched with sat. aq. NH_4Cl. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the organics extracts washed with brine and dried with anhydrous Na_2SO_4. The reaction mixture was filtered and the solvent removed. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 6:4) to give 102 mg of **2.47a** as a colourless oil (0.18 mmol, 100%).[141]

IR (neat): 3476 (br), 3059 (m), 3023 (w), 2954 (s), 2928 (s), 2884 (m), 2856 (s), 1717 (w), 1597 (w), 1490 (m), 1471 (m), 1449 (s) cm^{-1}.

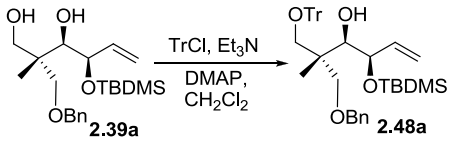
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.17 (15 H, m, Ar**H**), 5.97 (1 H, ddd, *J* = 17.7, 10.0, 7.7 Hz, C**H**=CH_2), 5.23 – 4.99 (2 H, m, C**H$_2$**=CH), 4.25 (1 H, dd, *J* = 7.7, 3.7 Hz, C**H**OTBDMS), 3.82 – 3.70 (1 H, m, C**H**OH), 3.62 (2 H, dd, *J* = 6.3, 3.6 Hz, C**H$_2$**OH), 3.40 (1 H, d, *J* = 9.0 Hz, C**H**HOTr), 3.07 (1 H, d, *J* = 9.0 Hz, C**H**HOTr), 3.03 (1 H, d, *J* = 6.0 Hz, CHO**H**), 2.80 (1 H, t, *J* = 6.5 Hz, CH_2O**H**), 1.00 (3 H, s, CC**H$_3$**), 0.89 (9 H, s, SiC(C**H$_3$**)$_3$), 0.07 (3 H, s, C**H$_3$**Si), 0.05 (3 H, s, C**H$_3$**Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (Ar**C**), 143.3 (Ar**C**), 139.7 (**C**H=CH_2), 128.9 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**H), 116.3 (**C**H_2=CH), 86.9 (**C**$(Ph)_3$), 77.2 (**C**HOH), 74.4 (**C**HOTBDMS), 68.3 (**C**H_2OTr), 67.4 (**C**H_2OH), 43.5 (**C**CH_3), 25.9 (SiC(**C**$H_3)_3$), 18.1 (Si**C**CH_3), 17.0 (**C**H_3C), -3.5 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

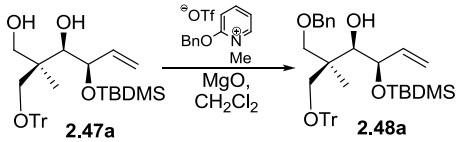
LRMS (ESI+): $^m/_z$ (rel. intensity) 555 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 555.2901 $[M+Na]^+$; found: 555.2909 $[M+Na]^+$.

(*rac*-2*R*,3*R*,4*R*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-1-trityloxy-hex-5-en-3-ol (2.48a).



To a solution of diol **2.39a** (100 mg, 0.26 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added Et_3N (54.5 μL, 0.39 mmol, 1.5 equiv.), DMAP (3 mg, 0.026 mmol, 0.1 equiv.) and chlorotriphenylmethane (81 mg, 0.29 mmol, 1.1 equiv.) and stirred at r.t for 16 h. The reaction mixture was poured into H_2O, the organics washed with sat. aq. NH_4Cl and H_2O. The combined organic extracts were dried with Na_2SO_4 and the solvent removed in *vacuo*. The crude mixture was purified by column chromatography (hexane / acetone 9:1) to give 107 mg of **2.48a** as a colourless oil (0.17 mmol, 66%).



To a suspension of 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate[144] (133 mg, 0.38 mmol, 2 equiv.) and MgO (15 mg, 0.38 mmol, 2 equiv.) in toluene (4 mL) was added diol **2.47a** (100 mg, 0.19 mmol, 1 equiv.) in toluene (2 mL). The reaction suspension was heated to 90 °C for 63 h. The reaction mixture was cooled to r.t, filtered through celite, washed with CH_2Cl_2 and concentrated in *vacou*. The crude brown oil was purified by column chromatography (hexane / acetone 95:5) and further purified by HPLC (hexane / acetone 95:5) to give a pale brown oil of **2.48a** (6 mg, 0.0096 mmol, 5% yield) with 53% recovery of starting material.[143]

IR (neat): 3529 (br), 3060 (w), 3031 (w), 2928 (m), 2856 (m), 1490 (m), 1471 (m), 1449 (s), 1389 (m) cm^{-1}.

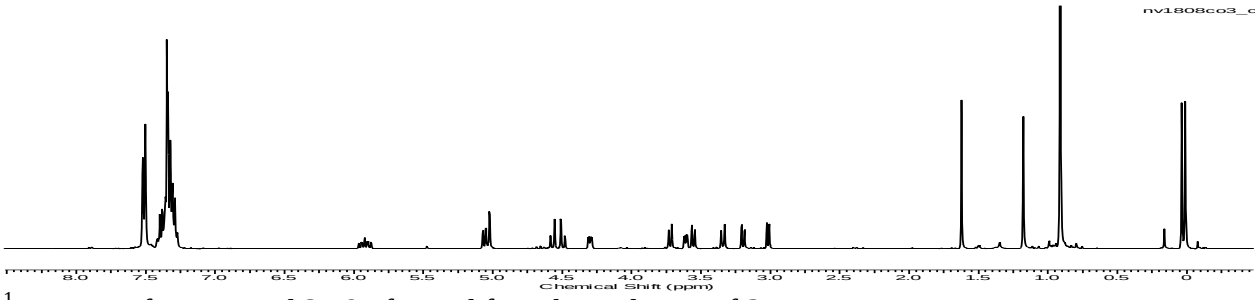
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.40 (6 H, m, Ar**H**), 7.35 – 7.17 (14 H, m, Ar**H**), 5.84 (1 H, ddd, *J* = 17.3, 10.5, 7.8 Hz, C**H**=CH_2), 5.05 – 4.89 (2 H, m, C**H$_2$**=CH), 4.49 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.42 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.22 (1 H, dd, *J* = 7.7, 2.9 Hz, C**H**OTBDMS), 3.64 (1 H, d, *J* = 8.9 Hz, C**HH**OTr), 3.53 (1 H, dd, *J* = 7.1, 3.1 Hz, C**H**OH), 3.48 (1 H, d, *J* = 8.9 Hz, C**HH**OTr), 3.26 (1 H, d, *J* = 8.7 Hz, C**HH**OBn), 3.12 (1 H, d, *J* =

8.8 Hz, C**H**<u>**H**</u>OBn), 2.94 (1 H, d, *J* = 7.2 Hz, CHO<u>**H**</u>), 1.10 (3 H, s, CC<u>$\mathbf{H_3}$</u>), 0.84 (9 H, s, SiC(C<u>$\mathbf{H_3}$</u>)$_3$), -0.04 (3 H, s, C<u>$\mathbf{H_3}$</u>Si), -0.07 (3 H, s, C<u>$\mathbf{H_3}$</u>Si) ppm.

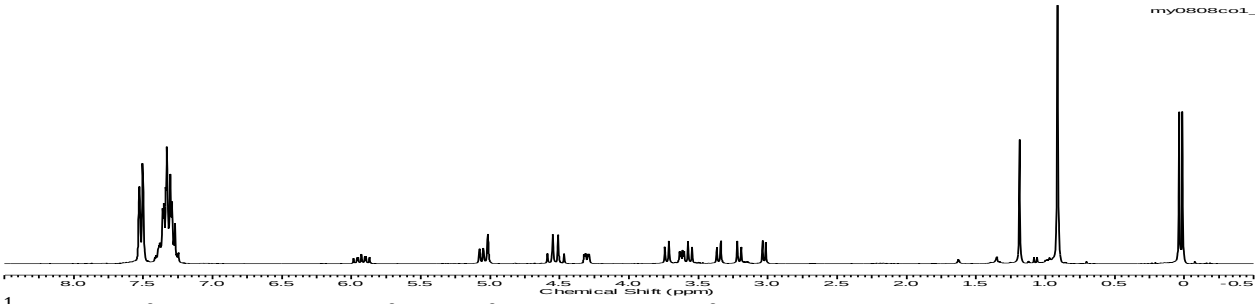
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (Ar<u>**C**</u>), 140.2 (<u>**C**</u>H=CH_2), 138.6 (Ar<u>**C**</u>), 128.8 (Ar<u>**C**</u>H), 128.2 (Ar<u>**C**</u>H), 127.6 (Ar<u>**C**</u>H), 127.4 (Ar<u>**C**</u>H), 127.3 (Ar<u>**C**</u>H), 126.8 (Ar<u>**C**</u>H), 115.5 (<u>**C**</u>H_2=CH), 86.3 (<u>**C**</u>$(Ph)_3$), 77.2 (<u>**C**</u>HOH), 74.0 (<u>**C**</u>HOTBDMS), 73.4 (<u>**C**</u>H_2OTr), 73.2 (<u>**C**</u>H_2OBn), 65.8 (<u>**C**</u>H_2Ph), 43.6 (<u>**C**</u>CH_3), 25.9 (SiC(<u>**C**</u>$H_3)_3$), 18.0 (Si<u>**C**</u>CH_3), 17.2 (<u>**C**</u>H_3C), -3.5 (<u>**C**</u>H_3Si), -4.6 (<u>**C**</u>H_3Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 645 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 645.3371 $[M+Na]^+$; found: 645.3372 $[M+Na]^+$.



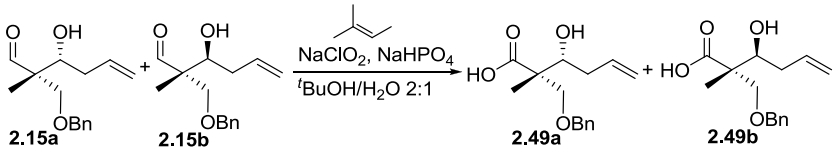
^{1}H NMR of compound **2.48a** formed from benzylation of **2.47a**.



^{1}H NMR of compound **2.48a** formed from tritylation of **2.39a**.

Figure 7.10. ^{1}H NMR's of compound **2.48a** formed from **2.47a** and **2.39a** respectively

(*rac*-2*S*,3*R*)-2-Benzyloxymethyl-3-hydroxy-2-methyl-hex-5-enoic acid (2.49a) & (*rac*-2*S*,3*S*)-2-Benzyloxymethyl-3-hydroxy-2-methyl-hex-5-enoic acid (2.49b)



To a solution of **2.15a** and **2.15b** (150 mg, 0.61 mmol, 1 equiv.) in *t*-BuOH (2 mL) was added 2-methyl-2-butene (273 µL, 2.24 mmol, 3.7 equiv.) at r.t. A solution of $NaClO_2$ (99 mg, 1.09 mmol, 1.8 equiv.) and $NaHPO_4$ (174 mg, 1.45 mmol, 2.4 equiv) in H_2O (1 mL) was added to the reaction and the reaction mixture was stirred at r.t for 5 h. Na_2SO_3 (137 mg, 1.09 mmol, 1.8 equiv.) was added to consume the excess $NaClO_2$ and the reaction stirred for 10 min. The reaction mixture was poured into CH_3Cl and the organics extracted and washed with H_2O, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude oil. The crude was purified by column chromatography (petroleum ether / EtOAc, 8:2) to give **2.49a** and **2.49b** (96 mg, 0.36 mmol, 60% yield) as a colourless oil. An analytically pure sample of major diastereoisomer **2.49b** (9 mg) was obtained after repeated HPLC (hexane / acetone, 9:1).

Data for 2.49b: IR (neat): 3447 (br. s), 3065 (m), 2979 (m), 2916 (m), 1704 (s), 1642 (w), 1496 (w), 1454 (m) cm^{-1}.

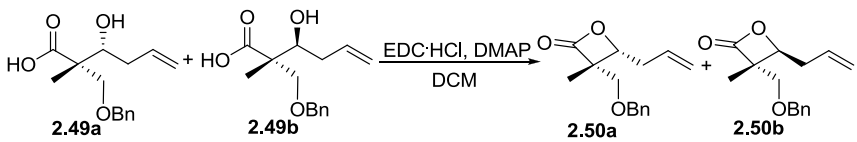
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.29 (5 H, m, Ar**H**), 5.96 – 5.78 (1 H, m, C**H**=CH_2), 5.20 – 5.07 (2 H, m, C**H$_2$**=CH), 4.58 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.53 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 3.96 (1 H, dd, *J* = 10.3, 2.8 Hz, C**H**OH), 3.73 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 3.63 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 2.39 – 2.26 (1 H, m, C**H**HCH=), 2.24 – 2.07 (1 H, m, C**H**HCH=), 1.26 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (**C**HO), 137.3 (Ar**C**), 134.9 (**C**H=), 128.5 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 118.0 (**C**H_2=), 74.1 (**C**H_2OBn), 73.8 (**C**H_2Ph), 73.6 (**C**HOH), 50.9 (CH_3**C**), 36.6 (**C**H_2CH=), 16.8 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 287 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 287.1259 $[M+Na]^+$; found: 287.1257 $[M+Na]^+$.

(*rac*-3*S*,4*R*)-4-Allyl-3-benzyloxymethyl-3-methyl-oxetan-2-one (2.50a) and (*rac*-3*S*,4*S*)-4-Allyl-3-benzyloxymethyl-3-methyl-oxetan-2-one (2.50b)



To a solution of **2.49a** and **2.49b** (60 mg, 0.23 mmol, 1 equiv.) in CH_2Cl_2 (1.5 mL) was added EDC•HCl (65 mg, 0.34 mmol, 1.5 equiv.) and DMAP (56 mg, 0.46 mmol, 2 equiv.)

and the reaction mixture stirred at r.t for 4 h. The reaction was quenched with brine, the organics extracted with CH_2Cl_2 and dried over $MgSO_4$ filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1 petroleum ether / EtOAc) to give **2.50a** and **2.50b** (28 mg, 0.11 mmol, 50% yield). Further purification by preparative HPLC (85:15 hexane / EtOAc) separated the diastereoisomers.

Data for 2.50a: IR (neat): 2973 (w), 2864 (w), 1824 (s), 1644 (w), 1497 (w), 1454 (m) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5 H, m, Ar**H**), 5.82 (1 H, dddd, *J* = 16.6, 13.2, 9.8, 6.7 Hz, C**H**=CH_2), 5.21 – 5.09 (2 H, m, C**H$_2$**=CH), 4.58 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.53 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.33 (1 H, dd, *J* = 7.9, 6.0 Hz, C**H**OCO), 3.69 (1 H, d, *J* = 10.2 Hz, C**HH**OBn), 3.57 (1 H, d, *J* = 10.0 Hz, C**HH**OBn), 2.78 – 2.63 (2 H, m, C**H$_2$**CH=), 1.45 (3 H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (**C**OO), 137.3 (**C**H=), 132.4 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.8 (Ar**C**H), 118.2 (**C**H_2=), 82.1 (**C**HOCO), 73.6 (**C**H_2Ph), 68.4 (**C**H_2OBn), 58.6 (CH_3**C**), 34.1 (**C**H_2CH=), 18.0 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 146 $[3MeCN+Na]^+$ (100%), 310 $[M+Na+MeCN]^+$ (52%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 301.1410 $[M+Na+MeOH]^+$; found: 301.1407 $[M+Na+MeOH]^+$.

Data for 2.50b: IR (neat): 2979 (w), 2862 (w), 1818 (s), 1699 (m), 1643 (w), 1496 (w), 1455 (m) cm^{-1}.

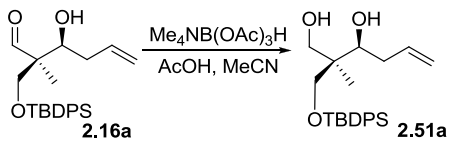
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (5 H, m, Ar**H**), 5.80 (1 H, dddd, *J* = 17.1, 10.5, 6.5 Hz, C**H**=CH_2), 5.23 – 5.11 (2 H, m, C**H$_2$**=CH), 4.73 (1 H, dd, *J* = 8.0, 6.4 Hz, C**H**OCO), 4.62 (1 H, d, *J* = 12.2 Hz, C**HH**Ph), 4.56 (1 H, d, *J* = 12.3 Hz, C**HH**Ph), 3.65 (1 H, d, *J* = 9.7 Hz, C**HH**OBn), 3.48 (1 H, d, *J* = 9.7 Hz, C**HH**OBn), 2.69 – 2.55 (1 H, m, C**HH**CH=), 2.54 – 2.41 (1 H, m, C**HH**CH=), 1.28 (3 H, s, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (**C**OO), 137.4 (Ar**C**), 131.8 (**C**H=CH_2), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**CH**), 118.5 (**C**H_2=CH), 77.3 (**C**HOCO), 73.4 (**C**H_2Ph), 70.9 (**C**H_2OBn), 58.7 (CH_3**C**), 34.4 (**C**H_2CH=), 11.8 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 146 $[3MeCN+Na]^+$ (100%), 310 $[M+Na+MeCN]^+$ (72%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 301.1410 $[M+Na+MeOH]^+$; found: 301.1407 $[M+Na+MeOH]^+$.

(*rac*-2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-methyl-hex-5-ene-1,3-diol (2.51a)



To a solution of $Me_4NB(OAc)_3H$ (566 mg, 2.14 mmol, 5 equiv.) and AcOH (246 µL, 4.29 mmol, 10 equiv.) in MeCN (6 mL) was added a solution of **2.16a** (170 mg, 0.43 mmol, 1 equiv.) in MeCN (1 mL). The reaction mixture was stirred at r.t for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the organics extracts washed with brine and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 95 mg of **2.51a** as a colourless oil (0.24 mmol, 55%) and further purified by HPLC (hexane / acetone 85:15).

IR (neat): 3406 (br), 3072 (w), 2930 (m), 2857 (m), 1647 (w), 1472 (m), 1427 (m) cm^{-1}.

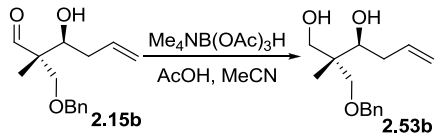
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.62 (4 H, m, Ar**H**), 7.55 – 7.35 (6 H, m, Ar**H**), 5.90 (1 H, dddd, *J* = 17.7, 9.5, 8.1, 5.9 Hz, C**H**=CH_2), 5.19 – 5.09 (2 H, m, C$\mathbf{H_2}$=CH), 3.85 – 3.75 (3 H, m, C**H**OH, C**HH**OH, C**HH**OTBDPS), 3.61 (1 H, d, *J* = 10.0 Hz, C**HH**OTBDPS), 3.57 (1 H, d, *J* = 11.0 Hz, C**HH**OH), 2.45 – 2.33 (1 H, m, C**HH**CH=), 2.20 – 2.09 (1 H, m, C**HH**CH=), 1.09 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.82 (3 H, s, SiC$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1 (**C**H=CH_2), 135.6 (Ar**C**H), 132.8 (Ar**C**), 129.9 (Ar**C**H), 127.8 (Ar**C**H), 117.8 (**C**H_2=CH), 74.1 (**C**HOH), 68.4 (**C**H_2OH), 67.9 (**C**H_2OTBDPS), 43.2 (**C**CH_3), 36.5 (**C**H_2CH=), 26.9 (SiC(**C**H_3)$_3$), 19.2 (Si**C**CH_3), 15.9 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 421 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 421.2169 $[M+Na]^+$; found: 421.2174 $[M+Na]^+$.

(*rac*-2*S*,3*S*)-2-Benzyloxymethyl-2-methyl-hex-5-ene-1,3-diol (2.53b).



To a solution of $Me_4NB(OAc)_3H$ (531 mg, 2.02 mmol, 5 equiv.) and AcOH (230 µL, 4.03 mmol, 10 equiv.) in MeCN (4 mL) was added a solution of aldehyde **2.15b** (100 mg, 0.40 mmol, 1 equiv.) in MeCN (1 mL). The reaction mixture was stirred at r.t for 80 min. The reaction mixture was quenched with sat. aq. NH_4Cl. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 62 mg of **2.53b** as a colourless oil (0.25 mmol, 62%).

IR (neat): 3388 (br), 3068 (m), 3030 (w), 2879 (s), 1640 (w), 1496 (w), 1454 (m) cm^{-1}.

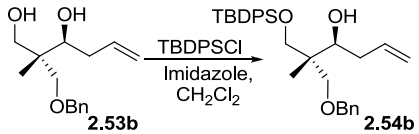
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5 H, m, Ar**H**), 5.90 – 5. 77 (1 H, m, C**H**=CH_2), 5.21 – 5.10 (2 H, m, C**H$_2$**=CH), 4.54 (1 H, d, *J* = 12.0 Hz, C**H**HPh), 4.50 (1 H, d, *J* = 12.2 Hz, CH**H**Ph), 3.89 (1 H, d, *J* = 10.5 Hz, C**H**OH), 3.75 (1 H, dd, *J* = 11.2, 4.3 Hz, C**H**HOH), 3.66 (1 H, d, *J* = 9.9 Hz, CH**H**OH), 3.50 (2 H, s, C**H$_2$**OBn), 2.78 (1 H, br. s., CH_2O**H**), 2.50 (1 H, d, *J* = 2.5 Hz, CHO**H**), 2.37 – 2.24 (1 H, m, C**H**HCH=), 2.20 – 2.08 (1 H, m, CH**H**CH=), 0.82 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (Ar**C**), 136.0 (**C**H=CH_2), 128.5 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 117.8 (**C**H_2=CH), 75.8 (**C**H_2OBn), 73.6 (**C**HOH & **C**H_2Ph), 68.2 (**C**H_2OH), 42.6 (**C**CH_3), 36.1 (**C**H_2CH=), 15.5 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 273 $[M+Na]^+$ (100%).

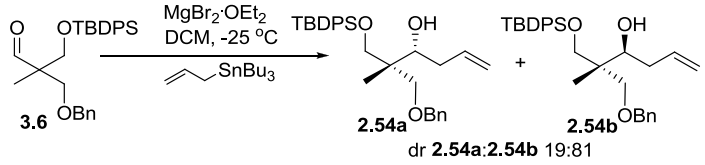
HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 273.1461 $[M+Na]^+$; found: 273.1465 $[M+Na]^+$.

(*rac*-2*R*,3*S*)-2-Benzyloxymethyl-1-(*tert*-butyl-diphenyl-silanyloxy)-2-methyl-hex-5-en-3-ol (2.54b)



To a solution of diol **2.53b** (45 mg, 0.18 mmol, 1 equiv.) and imidazole (25 mg, 0.36 mmol, 2 equiv.) in CH_2Cl_2 (4 mL) was added TBDPSCl (52 µL, 0.20 mmol, 1.1 equiv.) dropwise. The reaction mixture was stirred at r.t for 24 h. The reaction mixture was poured into H_2O, the organics extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and the

solvent evaporated in *vacuo*. The crude was purified by column chromatography (petroleum ether / EtOAc 95:5) to give 48 mg of **2.54b** as a colourless oil (0.10 mmol, 55%).



1,2-Dibromoethane (233 µL, 2.7 mmol, 3 equiv.) was added to a suspension of magnesium turnings (66 mg, 2.7 mmol, 3 equiv.) in Et_2O (6 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (10 mL) was added and the reaction mixture cooled to –25 °C before addition, *via* cannula of aldehyde **3.6** (400 mg, 0.90 mmol, 1 equiv.) in CH_2Cl_2 (14 mL). After addition of the aldehyde the reaction mixture became a yellow solution. After 20 min allyl tributylstannane (558 µL, 1.8 mmol, 2 equiv.) in CH_2Cl_2 (16 mL) was added *via* cannula and the reaction was stirred at –25 °C for 2 h. The reaction was hydrolysed with sat. aq. $NaHCO_3$, the organics washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 95:5) to give 258 mg (0.53 mmol, 59% yield) of **2.54** as a colourless oil (d.r from crude ^{1}H NMR 19:81, Figure 7.11). An analytically pure sample of **2.54b** (14 mg) was obtained after preparative HPLC (hexane / EtOAc 92:8).

Data for compound 2.54b: IR (neat): 3494 (br), 3071 (m), 2946 (m), 2930 (s), 2883 (m), 2857 (s), 1640 (w). 1589 (w), 1472 (m) 1454 (w) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.59 (4 H, m, Ar**H**), 7.49 – 7.18 (11 H, m, Ar**H**), 5.93 (1 H, dddd, *J* = 16.9, 10.0, 7.2, 6.9 Hz, C**H**=CH_2), 5.10 (1 H, d, *J* = 6.9 Hz, C**H**H=CH), 5.07 (1 H, s, CH**H**=CH), 4.49 (2 H, s, C$\mathbf{H_2}$Ph), 3.82 – 3.58 (3 H, m, C$\mathbf{H_2}$OTBDPS and C**H**OH), 3.55 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 3.47 (1 H, d, *J* = 9.0 Hz, CH**H**OBn), 3.29 (1 H, d, *J* = 4.5 Hz, CHO**H**), 2.38 – 2.22 (1 H, m, C**H**HCHOH), 2.20 – 2.00 (1 H, m, CH**H**CHOH), 1.06 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.93 (3 H, s, CC$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6 (Ar**C**), 135.6 (**C**H=CH_2), 133.1 (Ar**C**), 129.7 (Ar**C**H), 128.3 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 116.5 (**C**H_2=CH), 76.0 (**C**HOH), 74.5 (**C**H_2OBn), 73.5 (**C**H_2Ph), 66.9 (**C**H_2OTBDPS), 43.4 (**C**CH_3), 36.6 (**C**H_2CH=CH_2) 26.9 (SiC(**C**H_3)$_3$), 19.3 (Si**C**$(CH_3)_3$), 16.6 (C**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 511 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 511.2639 $[M+Na]^+$; found: 511.2640 $[M+Na]^+$.

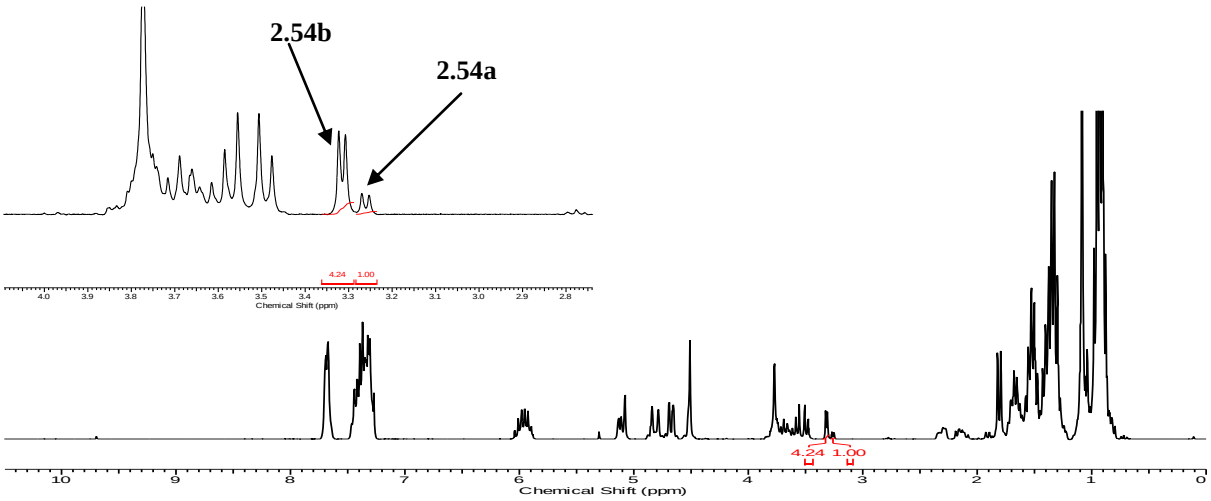
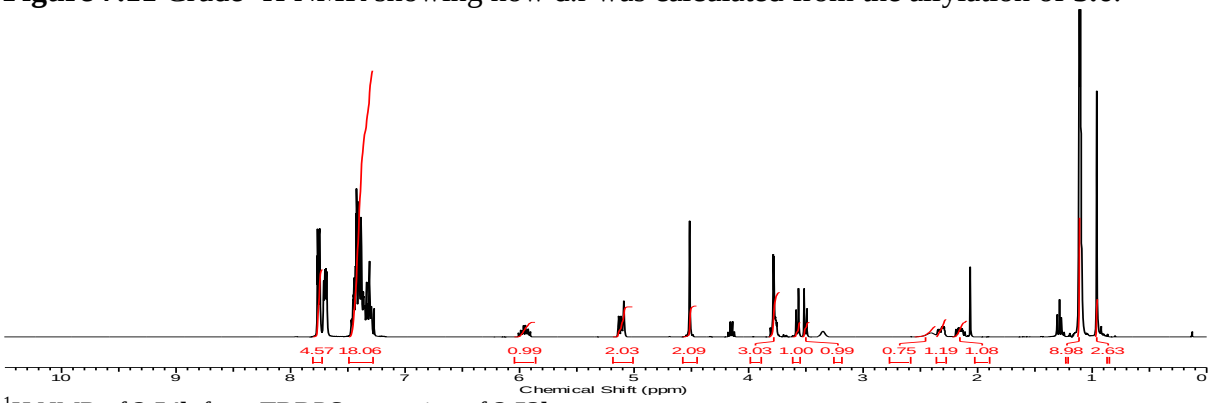
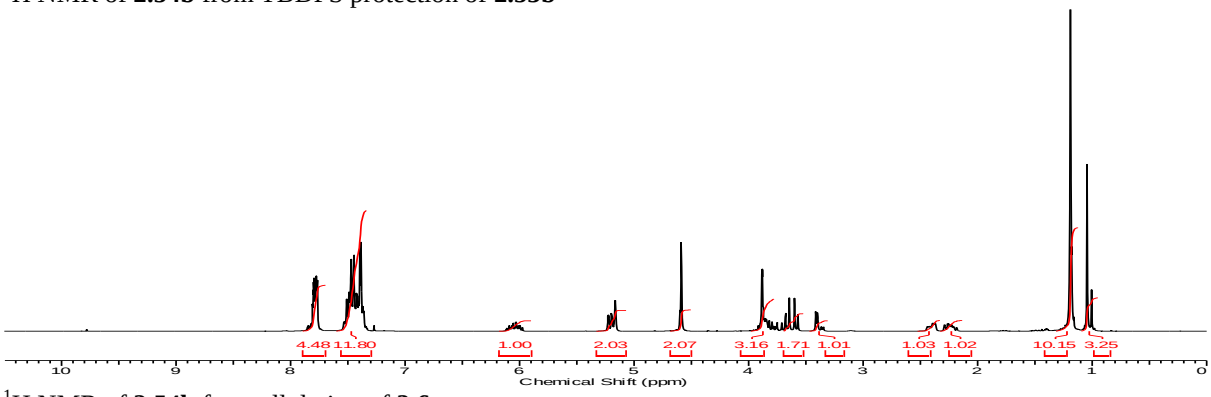


Figure 7.11 Crude ^{1}H NMR showing how d.r was calculated from the allylation of **3.6**.



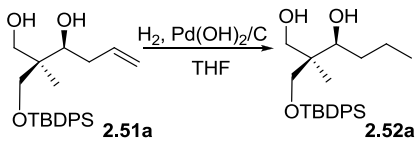
^{1}H NMR of **2.54b** from TBDPS protection of **2.53b**



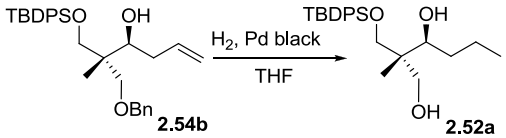
^{1}H NMR of **2.54b** from allylation of **3.6**

Figure 7.12 ^{1}H NMR's of **2.54b** from TBDPS protection of **2.53b** and allylation of **3.6** proving the diastereoselection of the allylation of **3.6**.

(*rac*-2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-methyl-hexane-1,3-diol (2.52a)



To a solution of diol **2.51a** (90 mg, 0.23 mmol, 1 equiv.) in THF (5 mL) was added 20% $Pd(OH)_2/C$ (16 mg, 0.18 equiv. by weight). The reaction mixture was placed under a H_2 (g) atmosphere and stirred at r.t for 20 h. The black reaction suspension was filtered through celite and washed with Et_2O. The filtrate was concentrated and the crude mixture purified by column chromatography (petroleum ether / EtOAc 80:20) to give 68 mg of **2.52a** as a colurless oil (0.17 mmol, 74%).[140]



To a solution of **2.54b** (45 mg, 0.09 mmol, 1 equiv.) in THF (3 mL) was added Pd black (8 mg, 0.18 equiv. by weight). The reaction mixture was placed under a H_2 (g) atmosphere and stirred at r.t for 48 h. The black reaction suspension was filtered through celite and washed with CH_2Cl_2. The filtrate was concentrated and the crude mixture purified by column chromatography (petroleum ether / EtOAc, 80:20) to give 12 mg of **2.52a** as a colourless oil (0.028 mmol, 31%) (50% yield recovery of the starting material **2.54b**).

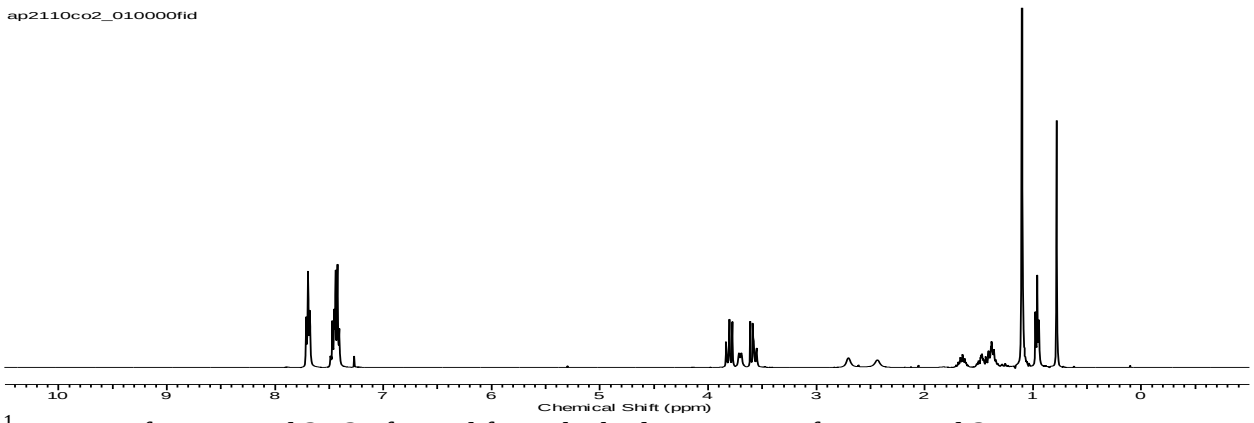
IR (neat): 3373 (br), 2957 (m), 2931 (m), 2858 (m), 1471 (m), 1427 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.61 (4 H, m, Ar**H**), 7.54 – 7.37 (6 H, m, Ar**H**), 3.82 (1 H, d, *J* = 12.7 Hz, C**H**HOH), 3.78 (1 H, d, *J* = 10.3 Hz, C**H**HOTBDPS), 3.70 (1 H, d, *J* = 8.9 Hz, C**H**OH), 3.60 (1 H, d, *J* = 10.3 Hz, CHHOTBDPS), 3.57 (1 H, d, *J* = 11.3 Hz, CHHOH), 2.70 (1 H, br. s., CHO**H**), 2.44 (1 H, br. s., CH_2O**H**), 1.75 – 1.58 (1 H, m, CH_2CHHCH_3), 1.54 – 1.31 (3 H, m, C**H**$_2$CHHCH_3), 1.10 (9 H, s, SiC(C**H**$_3$)$_3$), 0.96 (3 H, t, *J* = 7.2 Hz, CH_2C**H**$_3$), 0.78 (3 H, s, C**H**$_3$C) ppm.

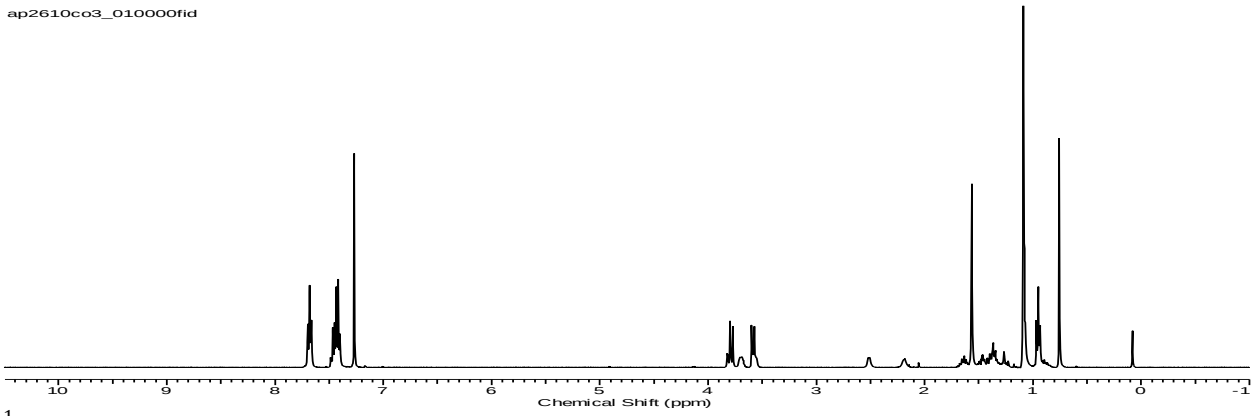
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6 (Ar**C**H), 132.7 (Ar**C**), 129.9 (Ar**C**H), 127.8 (Ar**C**H), 75.3 (**C**HOH), 68.3 (**C**H_2OH), 67.9 (**C**H_2OTBDPS), 43.3 (**C**CH_3), 33.7 (**C**H_2CH_3), 26.9 (SiC(**C**H_3)$_3$), 19.8 (**C**$H_2CH_2CH_3$) 19.2 (Si**C**CH_3), 16.1 (**C**H_3C), 14.1 (**C**H_3CH_2) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 423 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 423.2326 $[M+Na]^+$; found: 423.2324 $[M+Na]^+$.



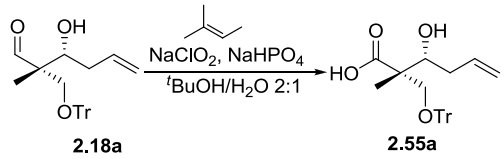
^{1}H NMR of compound **2.52a** formed from the hydrogenation of compound **2.51a**



^{1}H NMR of compound **2.52a** formed from hydrogenolysis of compound **2.54b**

Figure 7.13. Identification of relative stereochemistry of **2.16a** by correlation.

(*rac*-2*S*,3*R*)-3-Hydroxy-2-methyl-2-trityloxymethyl-hex-5-enoic acid (2.55a)



2.18a **2.55a**

To a solution of **2.18a** (100 mg, 0.25 mmol, 1 equiv.) in *t*-BuOH (2 mL) was added 2-methyl-2-butene (98 µL, 0.92 mmol, 3.7 equiv.) at r.t. A solution of $NaClO_2$ (54 mg, 0.60 mmol, 2.4 equiv.) and $NaHPO_4$ (72 mg, 0.60 mmol, 2.4 equiv) in H_2O (1 mL) was added to the reaction and the reaction mixture was stirred at r.t for 4 h. Na_2SO_3 (150 mg, 1.19 mmol, 4.8 equiv.) was added to consume the excess $NaClO_2$ and the reaction stirred for 10 min. The reaction mixture was poured into CH_3Cl and the organics extracted and washed with

H_2O, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude oil. The crude was purified by column chromatography (petroleum ether : EtOAc, 8:2) to give **2.55a** (67 mg, 0.16 mmol, 64% yield) as a colourless oil.

Data for 2.55a: IR (neat): 3058 (br. s), 1700 (s), 1641 (m), 1490 (w), 1449 (m) cm^{-1}.

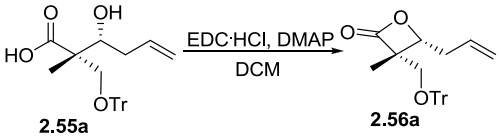
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.39 (5 H, m, Ar**H**), 7.37 – 7.18 (10 H, m, Ar**H**), 5.86 – 5.68 (1 H, m, C**H**=CH_2), 5.10 (1 H, d, *J* = 9.6 Hz, C**H**H=CH), 5.05 (1 H, d, *J* = 17.7 Hz, CH**H**=CH), 3.99 (1 H, dd, *J* = 10.1, 2.0 Hz, C**H**OH), 3.41 (2 H, s, C**H$_2$**OTr), 2.09 (1 H, dd, *J* = 13.1, 5.1 Hz, C**H**HCH=), 1.87 (1 H, ddd, *J* = 13.4, 9.6, 9.3 Hz, C**H**HCH=), 1.30 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2 (**C**OOH), 143.2 (**C**H=CH_2), 134.8 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.3 (Ar**C**H), 118.2 (**C**H_2=CH), 73.2 (**C**HOH), 66.0 (**C**H_2OTr), 50.8 (**C**CH_3), 36.5 (**C**H_2CH=), 17.1 (**C**H_3C) ppm.

LRMS (ESI-): $^m/_z$ (rel. intensity) 415 $[M-H]^-$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 439.1880 $[M+Na]^+$; found: 439.1885 $[M+Na]^+$.

(*rac*-3*S*,4*R*)-4-Allyl-3-methyl-3-trityloxymethyl-oxetan-2-one (2.56a)



2.55a **2.56a**

To a solution of **2.55a** (40 mg, 0.096 mmol, 1 equiv.) in CH_2Cl_2 (1.5 mL) was added EDC•HCl (27 mg, 0.14 mmol, 1.5 equiv.) and DMAP (23 mg, 0.19 mmol, 2 equiv.) and the reaction mixture stirred at r.t for 4 h. The reaction was quenched with brine, the organics extracted with CH_2Cl_2 and dried over $MgSO_4$ filtered and concentrated in *vacuo*. The crude was purified by column chromatography (8:2 petroleum ether / EtOAc) to give **2.56a** (15 mg, 0.038 mmol, 40% yield).

Data for 2.56a: IR (neat): 3059 (w), 2873 (w), 1822 (s), 1642 (w), 1491 (m), 1449 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.24 (15 H, m, Ar**H**), 5.63 (1 H, dddd, *J* = 17.2, 10.5, 6.7, 6.6 Hz, C**H**=CH_2), 5.02 (1 H, dd, *J* = 10.6, 1.3 Hz, C**H**H=CH), 4.91 (1 H, dd, *J* = 17.4, 1.3 Hz, CH**H**=CH), 4.33 (1 H, dd, *J* = 8.1, 6.1 Hz, C**H**OCO), 3.46 (1 H, d, *J* = 9.6 Hz,

C**HH**OTr), 3.19 (1 H, d, *J* = 10.1 Hz, C**HH**OTr), 2.64 – 2.43 (2 H, m, C$\mathbf{H_2}$CH=), 1.46 (3 H, s), C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (**C**OO), 143.1 (Ar**C**), 132.3 (**C**H=), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.2 (Ar**C**H), 118.0 (**C**H_2=), 87.1 (**C**Ph_3), 82.1 (**C**HOCO), 61.8 (**C**H_2OTr), 58.6 (CH_3**C**), 34.7 (**C**H_2CH=), 18.2 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 462 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 421.1774 $[M+Na]^+$; found: 421.1771 $[M+Na]^+$.

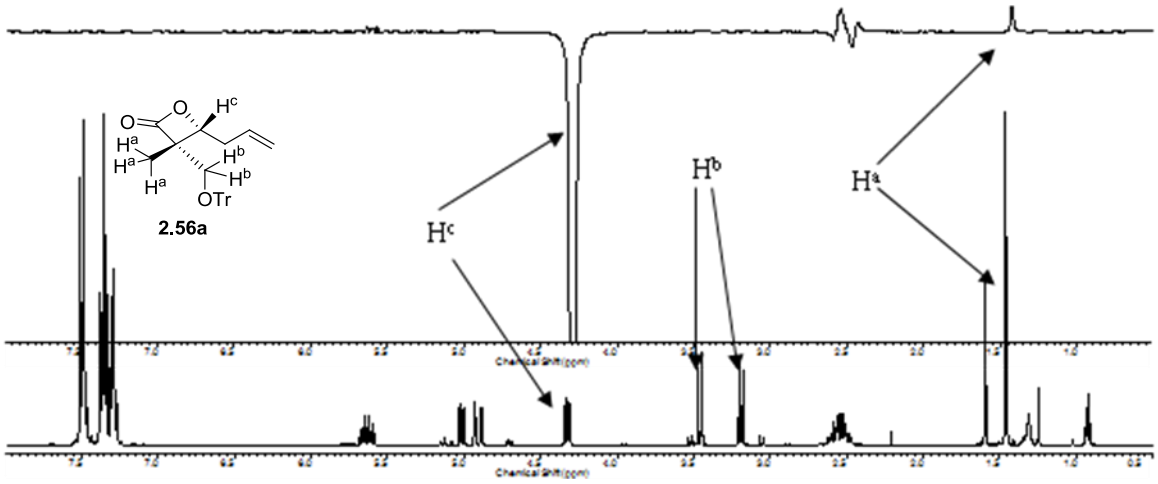


Figure 7.14 nOe experiment on **2.56a** proving the relative stereochemistry of **2.18a**

From the nOe experiment on **2.56a** when H^c was irradiated an NOE was observed at H^a and no response at H^b so proving that H^c is on the same side of the β-lactone ring as the methyl and opposite to the trityl ether. Therefore the relative stereochemistry of **2.56a** is as shown.

(rac-3*R*,4*S*)-4-Benzyloxymethyl-3,5-dihydroxy-4-methyl-pentanoic acid *tert*-butyl ester (2.57a) & (rac-3*S*,4*S*)-4-Benzyloxymethyl-3,5-dihydroxy-4-methyl-pentanoic acid *tert*-butyl ester (2.57b)

To a solution of $Me_4NB(OAc)_3H$ (1.19 g, 4.51 mmol, 5 equiv.) and AcOH (517 µL, 9.03 mmol, 10 equiv.) in MeCN (20 mL) was added a solution of aldehyde **2.34a** and **2.34b** (291

mg, 0.90 mmol, 1 equiv.) in MeCN (6 mL). The reaction mixture was stirred at r.t for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the combined organic extracts washed with brine and dried with anhydrous Na_2SO_4. The reaction mixture was filtered and the solvent removed. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 192 mg of **2.57** as a colourless oil (0.59 mmol, 66%). Further purification by preparative HPLC (9:1 hexane / acetone) allowed an analytical sample of **2.57a** (4 mg) and an analytical sample of **2.57b** (13 mg) to be isolated.

Data for compound 2.57a: IR (neat): 3441 (br. m), 2975 (m), 2934 (w), 2874 (w), 1724 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.29 (5 H, m, Ar**H**), 4.55 (1 H, d, *J* = 12.1 Hz, C**H**H**H**Ph), 4.51 (1 H, d, *J* = 12.1 Hz, C**H**H**H**Ph), 4.24 (1 H, d, *J* = 10.5 Hz, C**H**OH), 3.68 (1 H, d, *J* = 10.9 Hz, C**H**H**H**OH), 3.65 (1 H, d, *J* = 8.7 Hz, C**H**H**H**OBn), 3.58 (1 H, d, *J* = 2.8 Hz, CHO**H**), 3.52 (1 H, d, *J* = 11.2 Hz, C**H**H**H**OH), 3.45 (1 H, d, *J* = 9.0 Hz, C**H**H**H**OBn), 2.91 (1 H, br. s. , CH_2O**H**), 2.54 (1 H, dd, *J* = 16.2, 2.5 Hz, C**H**H**H**CO), 2.41 (1 H, dd, *J* = 16.2, 10.4 Hz, C**H**H**H**CO), 1.48 (9 H, s, $C(C\mathbf{H_3})_3$), 0.82 (3 H, s, $CC\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (**C**OO*t*Bu), 138.0 (Ar**C**), 128.5 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 81.3 ($O\mathbf{C}(CH_3)_3$), 74.8 (**C**H_2OBn), 73.7 (**C**H_2Ph), 70.9 (**C**HOH), 69.0 (**C**H_2OH), 42.4 ($CH_3\mathbf{C}$), 37.5 (**C**H_2CO), 28.1 ($OC(\mathbf{C}H_3)_3$), 15.6 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 347 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 347.1829 $[M+Na]^+$; found: 347.1825 $[M+Na]^+$.

Data for compound 2.57b: IR (neat): 3434 (br. m), 2976 (m), 2934 (w), 2876 (w), 1723 (s), 1454 (m) cm^{-1}.

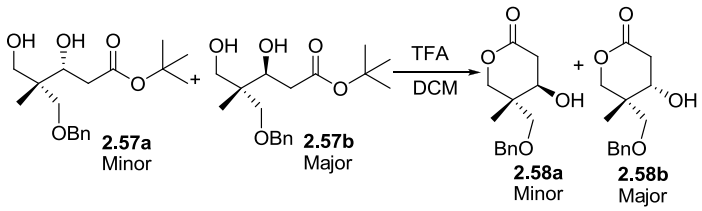
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.29 (5 H, m, Ar**H**), 4.54 (1 H, m, *J* = 12.1 Hz, C**H**H**H**Ph), 4.48 (1 H, d, *J* = 12.3 Hz, C**H**H**H**Ph), 4.27 (1 H, ddd, *J* = 8.0, 4.8, 3.0 Hz, C**H**OH), 3.74 – 3.64 (2 H, m, C$\mathbf{H_2}$OH), 3.60 (1 H, d, *J* = 3.2 Hz, CHO**H**), 3.48 (1 H, d, *J* = 9.2 Hz, C**H**H**H**OBn), 3.43 (1 H, d, *J* = 9.1 Hz, C**H**H**H**OBn), 2.92 (1 H, t, *J* = 5.5 Hz, CH_2O**H**), 2.43 – 2.38 (2 H, m, C$\mathbf{H_2}$CO), 1.48 (9 H, s, $C(C\mathbf{H_3})_3$), 0.83 (3 H, s, $CC\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (**C**OO*t*Bu), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 81.4 (O**C**$(CH_3)_3$), 74.9 (**C**H_2OBn), 73.5 (**C**H_2Ph), 71.3 (**C**HOH), 68.1 (**C**H_2OH), 42.3 (CH_3**C**), 37.3 (**C**H_2CO), 28.1 (OC(**C**$H_3)_3$), 15.1 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 347 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 347.1829 $[M+Na]^+$; found: 347.1836 $[M+Na]^+$.

(*rac*-4*R*,5*R*)-5-Benzyloxymethyl-4-hydroxy-5-methyl-tetrahydro-pyran-2-one (2.58a) & (*rac*-4*S*,5*R*)-5-Benzyloxymethyl-4-hydroxy-5-methyl-tetrahydro-pyran-2-one (2.58b)



TFA (1.11 mL, 15 mmol, 60 equiv.) was added to a solution of ester **2.57a** and **2.57b** (80 mg, 0.25 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) and the reaction stirred at r.t for 22 h. The reaction mixture was concentrated in *vacuo* and the resultant crude oil purified by column chromatography (1:1 petroleum ether / EtOAc) to give 40 mg (0.16 mmol, 64% yield) of **2.58** as a colourless oil. The diastereoisomers were separated by preparative HPLC (7:3, hexane / acetone).

Data for compound 2.58a: IR (neat): 3435 (br. m), 2968 (w), 2866 (m), 1715 (s), 1472 (w), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5 H, m, Ar**H**), 4.55 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.52 (1 H, d, *J* = 12.0 Hz, C**H**HPh), 4.19 (1 H, ddd, *J* = 8.6, 6.5, 3.3 Hz, C**H**OH), 4.05 (1 H, d, *J* = 11.6 Hz, C**H**HOBn), 4.02 (1 H, d, *J* = 11.6 Hz, C**H**HOBn), 3.43 (1 H, d, *J* = 9.1 Hz, C**H**HOCO), 3.37 (1 H, d, *J* = 10.2 Hz, C**H**HOCO), 2.90 (1 H, dd, *J* = 18.3, 6.6 Hz, C**H**HCHOH), 2.52 (1 H, dd, *J* = 18.4, 8.5 Hz, C**H**HCHOH), 2.41 (1 H, d, *J* = 3.3 Hz, CHO**H**), 1.09 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (**C**OO), 137.3 (Ar**C**), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.7 (Ar**C**H), 74.1 (**C**H_2OCO), 73.7 (**C**H_2Ph), 72.5 (**C**H_2OBn), 67.9 (**C**HOH), 38.7 (CH_3**C**), 36.0 (**C**H_2CHOH), 13.3 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 305 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 305.1359 $[M+Na+MeOH]^+$; found: 305.1357 $[M+Na+MeOH]^+$.

Data for compound 2.58b: IR (neat): 3435 (br. m), 2968 (w), 2866 (m), 1715 (s), 1472 (w), 1454 (m) cm^{-1}.

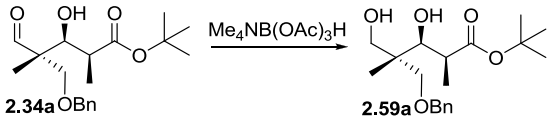
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (5 H, m, Ar**H**), 4.55 (2 H, d, *J* = 11.1 Hz, C**H**HOBn & C**H**HPh), 4.50 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 3.95 (1 H, q, *J* = 4.5 Hz, C**H**OH), 3.88 (1 H, d, *J* = 11.1 Hz, C**H**HOBn), 3.74 (1 H, d, *J* = 3.5 Hz, CHO**H**), 3.56 (1 H, d, *J* = 9.6 Hz, C**H**HOCO), 3.51 (1 H, d, *J* = 9.6 Hz, C**H**HOCO), 2.81 (1 H, dd, *J* = 18.2, 5.1 Hz, C**H**HCHOH), 2.60 (1 H, dd, *J* = 18.2, 5.1 Hz, C**H**HCHOH), 1.06 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (**C**OO), 136.8 (Ar**C**), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 127.7 (Ar**C**H), 73.9 (**C**H_2OCO), 73.8 (**C**H_2Ph), 71.8 (**C**H_2OBn), 71.0 (**C**HOH), 37.6 (CH_3**C**), 36.7 (**C**H_2CHOH), 18.6 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 305 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 305.1359 $[M+Na+MeOH]^+$; found: 305.1357 $[M+Na+MeOH]^+$.

***Rac*-(2*S*,3*S*,4*S*)-4-Benzyloxymethyl-3,5-dihydroxy-2,4-dimethyl-pentanoic acid *tert*-butyl ester (2.59a).**



To a solution of $Me_4NB(OAc)_3H$ (574 mg, 2.08 mmol, 5 equiv.) and AcOH (238 µL, 4.16 mmol, 10 equiv.) in MeCN (12 mL) was added a solution of aldehyde **2.34a** (140 mg, 0.42 mmol, 1 equiv.) in MeCN (2 mL). The reaction mixture was stirred at r.t for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tartrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the combined organic extracts washed with brine and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 102 mg of **2.59a** as a colourless oil (0.30 mmol, 71%).

Data for compound 2.59a: IR (neat): 3430 (br. m), 2975 (m), 2934 (w), 2879 (w), 1723 (s), 1454 (m) cm^{-1}.

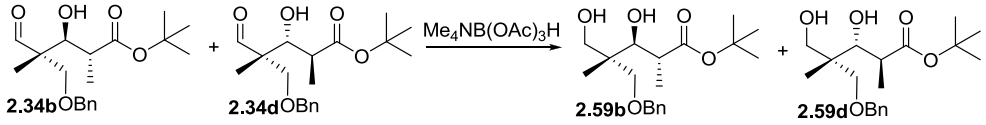
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (5 H, m, Ar**H**), 4.52 (2 H, s, C**H**$_2$Ph), 4.14 (1 H, t, *J* = 4.3 Hz, C**H**OH), 3.71 (1 H, dd, *J* = 11.1, 5.1 Hz, C**H**HOH), 3.60 (1 H, dd, *J* = 10.6, 3.5 Hz, CH**H**OH), 3.52 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.47 (1 H, d, *J* = 8.6 Hz, CH**H**OBn), 3.23 (1 H, d, *J* = 4.5 Hz, CHO**H**), 2.82 (1 H, t, *J* = 6.1 Hz, CH_2O**H**), 2.63 (1 H, qd, *J* = 7.1, 4.5 Hz, C**H**CH_3), 1.46 (9 H, s, C(C**H**$_3$)$_3$), 1.26 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.91 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (**C**OO*t*Bu), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 80.9 (O**C**$(CH_3)_3$), 75.6 (**C**H_2OBn), 74.2 (**C**HOH), 73.6 (**C**H_2Ph), 68.3 (**C**H_2OH), 43.3 (CH_3**C**), 41.8 (**C**HCH_3), 28.0 (OC(**C**H_3)$_3$), 16.6 (**C**H_3C), 13.2 (**C**H_3CH) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 361 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 361.1985 $[M+Na]^+$; found: 361.1977 $[M+Na]^+$.

***Rac*-(2*R*,3*S*,4*S*)-4-Benzyloxymethyl-3,5-dihydroxy-2,4-dimethyl-pentanoic acid *tert*-butyl ester (2.59b) and *rac*-(2*S*,3*R*,4*S*)-4-Benzyloxymethyl-3,5-dihydroxy-2,4-dimethyl-pentanoic acid *tert*-butyl ester (2.59d).**



404 mg of **2.34b** and **2.34d** (1.20 mmol, 1 equiv.) were transformed to 218 mg of **2.59b** and **2.59d** (0.64 mmol, 54% yield) according to the method above. The diastereoisomers were separated by preparative HPLC (hexane / acetone 85:15) to give 61 mg pure **2.59b** and 38 mg pure **2.59d** and 92 mg mixed fraction.

Data for compound 2.59b: IR (neat): 3445 (br), 2976 (m), 2935 (w), 2878 (w), 1700 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (5 H, m, Ar**H**), 4.49 (1 H, d, *J* = 12.6 Hz, C**H**HPh), 4.46 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.28 (1 H, d, *J* = 9.1 Hz, CHO**H**), 3.81 (1 H, dd, *J* = 8.8, 2.3 Hz, C**H**OH), 3.71 (1 H, dd, *J* = 11.1, 3.5 Hz, C**H**HOH), 3.64 (1 H, dd, *J* = 11.1, 7.1 Hz, CH**H**OH), 3.44 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.38 (1 H, d, *J* = 9.1 Hz, CH**H**OBn), 2.91 (1 H, dd, *J* = 7.6, 4.5 Hz, CH_2O**H**), 2.57 (1 H, qd, *J* = 7.3, 2.0 Hz, C**H**CH_3), 1.46 (9 H, s, C(C**H**$_3$)$_3$), 1.33 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.85 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (**C**OO), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 81.6 (**C**$(CH_3)_3$), 77.5 (**C**HOH), 75.5 (**C**H_2OBn), 73.5 (**C**H_2Ph), 69.3 (**C**H_2OH), 43.9 (**C**CH_3), 39.2 (**C**HCH_3) 27.9 (OC(**C**$H_3)_3$), 18.0 (**C**HCH_3), 14.7 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 361 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 361.1985 $[M+Na]^+$; found: 361.1991 $[M+Na]^+$.

Data for compound 2.59d: IR (neat): 3457 (br), 2975 (m), 2934 (w), 2877 (w), 1698 (s), 1454 (m) cm^{-1}.

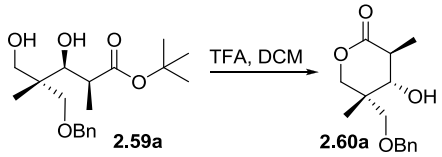
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (5 H, m, Ar**H**), 4.58 (1 H, d, *J* = 12.1 Hz, C**H**H**H**Ph), 4.50 (1 H, d, *J* = 12.1 Hz, C**H**H**H**Ph), 4.28 (1 H, d, *J* = 9.1 Hz, CHO**H**), 3.81 (1 H, dd, *J* = 9.3, 1.8 Hz, C**H**OH), 3.74 (1 H, d, *J* = 8.6 Hz, C**H**H**H**OBn), 3.69 (1 H, dd, *J* = 11.1, 4.5 Hz, C**H**H**H**OH), 3.60 (1 H, dd, *J* = 11.6, 7.6 Hz, C**H**H**H**OH), 3.38 (1 H, d, *J* = 8.6 Hz, C**H**H**H**OBn), 3.01 (1 H, dd, *J* = 7.6, 5.1 Hz, CH_2O**H**), 2.70 (1 H, qd, *J* = 7.2, 2.0 Hz, C**H**CH_3), 1.44 (9 H, s, C(C**H$_3$**)$_3$), 1.38 (3 H, d, *J* = 7.1 Hz, CHC**H$_3$**), 0.77 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5 (**C**OO), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 81.5 (**C**$(CH_3)_3$), 76.5 (**C**HOH), 75.7 (**C**H_2OBn), 73.6 (**C**H_2Ph), 69.6 (**C**H_2OH), 43.9 (**C**CH_3), 38.9 (**C**HCH_3), 27.9 (OC(**C**$H_3)_3$), 18.2 (**C**HCH_3), 15.5 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 361 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 361.1985 $[M+Na]^+$; found: 361.1992 $[M+Na]^+$.

***Rac*-(3*S*,4*S*,5*R*)-5-Benzyloxymethyl-4-hydroxy-3,5-dimethyl-tetrahydro-pyran-2-one (2.60a)**



TFA (988 µL, 13.30 mmol, 60 equiv.) was added to a solution of ester **2.59a** (75 mg, 0.22 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) and the reaction stirred at r.t for 16 h. The reaction mixture was concentrated in *vacuo* and the resultant crude oil purified by column chromatography (1:1 petroleum ether:EtOAc) to give 43 mg (0.16 mmol, 74% yield) of **2.60a** as a colourless oil.

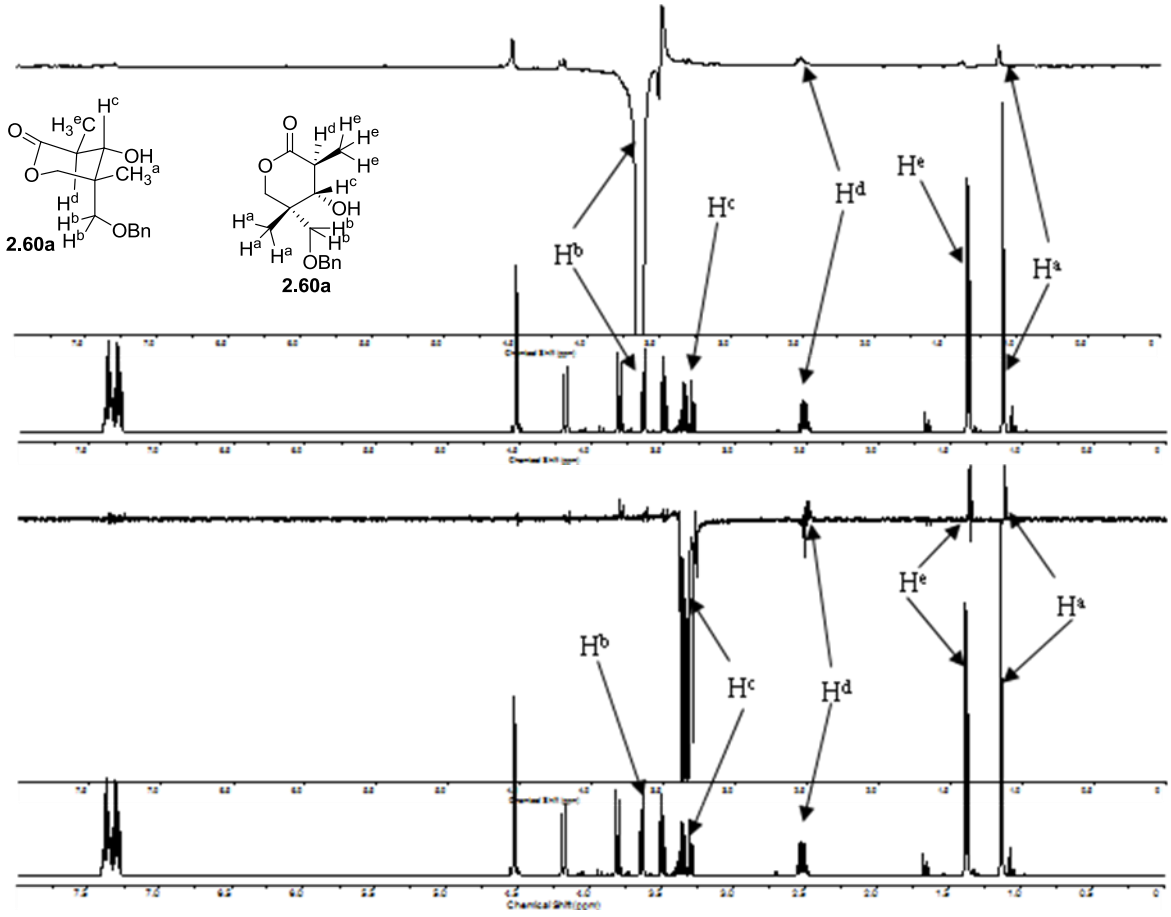
IR (neat): 3437 (br), 2974 (w), 2877 (m), 1718 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.26 (5 H, m, Ar**H**), 4.52 (2 H, s, C**H**$_2$Ph), 4.19 (1 H, d, *J* = 11.6 Hz, C**H**HOCO), 3.81 (1 H, d, *J* = 11.6 Hz, CHHOCO), 3.63 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.50 (1 H, d, *J* = 9.6 Hz, CHHOBn), 3.40 – 3.30 (2 H, m, C**H**O**H**), 2.52 (1 H, qd, *J* = 9.0, 6.8 Hz, C**H**CH_3), 1.37 (3 H, d, *J* = 6.6 Hz, CC**H**$_3$), 1.13 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 (**C**OO), 136.8 (Ar**C**), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 127.7 (Ar**C**H), 77.8 (**C**HOH), 73.9 (**C**H_2Ph), 72.5 (**C**H_2OBn), 71.5 (**C**H_2OCO), 42.4 (**C**HCH_3), 39.2 (CH_3**C**), 20.2 (**C**H_3C), 13.9 (**C**H_3CH) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 328 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 287.1254 $[M+Na]^+$; found: 287.1259 $[M+Na]^+$.



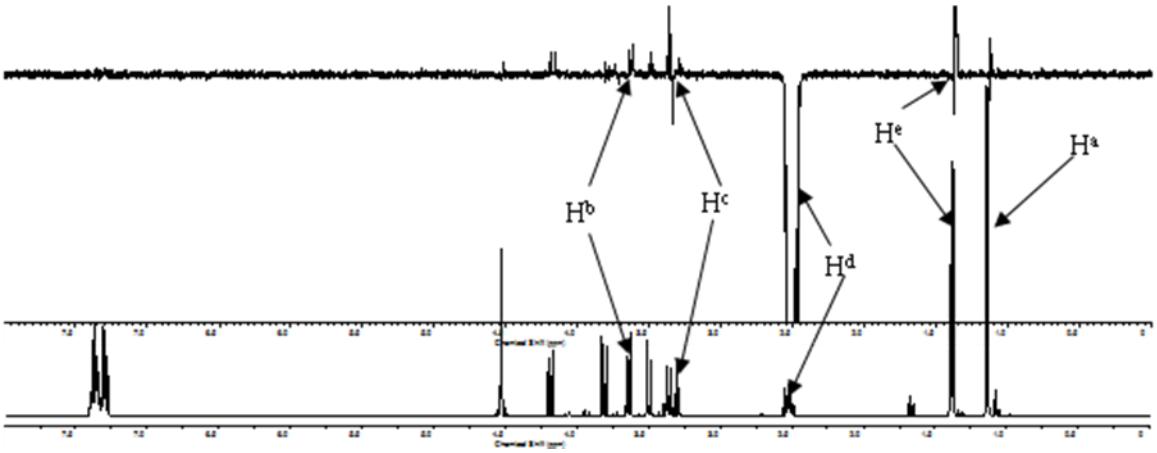
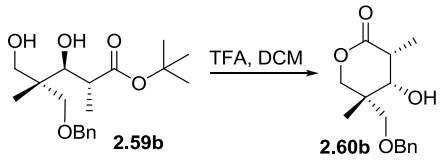


Figure 7.15. nOe's on **2.60a** to identify relative stereochemistry.

From the nOe experiments on **2.60a** when H^b was irradiated a response was observed at H^d and no response was observed H^c, so proving that H^b and H^d must be on the same face of the lactone ring and H^c on the opposite face. When H^c was irradiated an nOe response was observed at H^e and H^a, showing that H^c, H^e and H^a are on the same face of the δ-lactone **2.60a**. A response was also observed at H^d and is proably a result of the hydroxyl also being irradiated. These show the relative stereochemistry of lactone ring **2.60a** and therefore monoaddition product **2.34a** to be as shown (Scheme 2.31).

***Rac*-(3*R*,4*S*,5*R*)-5-Benzyloxymethyl-4-hydroxy-3,5-dimethyl-tetrahydro-pyran-2-one (2.60b)**



61 mg of ester **2.59b** (0.18 mmol, 1 equiv.) was transformed to 32 mg of lactone **2.60b** (0.12 mmol, 67% yield) according to the method above.

IR (neat): 3457 (br), 2978 (w), 2904 (m), 1731 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5 H, m, Ar**H**), 4.53 (2 H, s, C**H$_2$**Ph), 4.48 (1 H, d, *J* = 11.1 Hz, C**H**HOCO), 3.87 (1 H, d, *J* = 11.6 Hz, C**H**HOCO), 3.84 (1 H, d, *J* = 3.0 Hz, C**H**OH), 3.74 (1 H, br. s. , CHO**H**), 3.58 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.45 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.68 (1 H, qd, *J* = 6.9, 3.0 Hz, C**H**CH_3), 1.32 (3 H, d, *J* = 6.6 Hz, CHC**H$_3$**), 1.05 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7 (**C**OO), 136.9 (Ar**C**), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.7 (Ar**C**H), 75.4 (**C**HOH), 75.0 (**C**H_2Ph), 73.8 (**C**H_2OBn), 71.9 (**C**H_2OCO), 38.7 (CH_3**C**), 38.4 (**C**HCH_3), 19.4 (**C**H_3C), 12.2 (**C**H_3CH) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 287 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 287.1254 $[M+Na]^+$; found: 287.1258 $[M+Na]^+$.

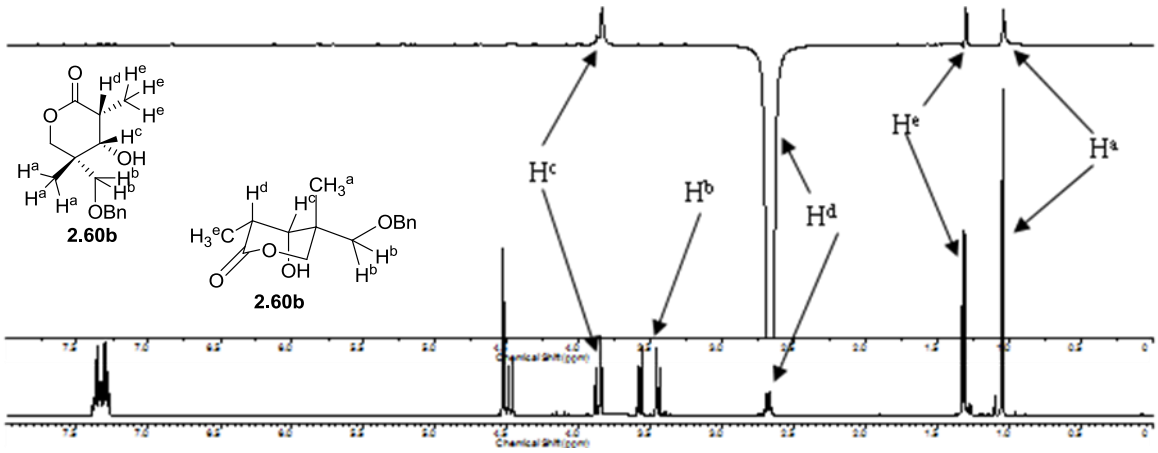
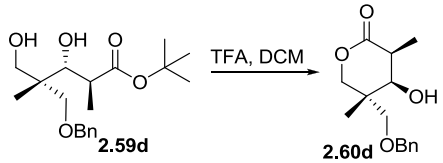


Figure 7.16. nOe on **2.60b** to identify relative stereochemistry.

From the nOe experiments on **2.60b** when H^d was irradiated a response was observed at H^c, H^e and H^a and no response was observed H^b. This shows that H^d must be on the same face of the δ-lactone ring as H^c and H^a and on the opposite face to H^b. This shows the relative stereochemistry of δ-lactone ring **2.60b** and therefore monoaddition product **2.34b** to be as shown (Scheme 2.32).

***Rac*-(3*S*,4*R*,5*R*)-5-Benzyloxymethyl-4-hydroxy-3,5-dimethyl-tetrahydro-pyran-2-one (2.60d)**



38 mg of ester **2.59d** (0.11 mmol) was transformed to 27 mg of lactone **2.60d** (0.10 mmol, 93% yield) according to the method above.

IR (neat): 3451 (br), 2980 (w), 2877 (m), 1726 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.27 (5 H, m, Ar**H**), 4.53 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.47 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.18 (1 H, d, *J* = 11.1 Hz, C**H**HOCO), 4.09 (1 H, d, *J* = 11.6 Hz, C**H**HOCO), 3.95 (1 H, d *J* = 3.5 Hz, C**H**OH), 3.44 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.37 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.75 (1 H, qd, *J* = 7.0, 3.8 Hz, C**H**CH_3), 2.08 (1 H, br. s. , CHO**H**), 1.30 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 1.11 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 (**C**OO), 137.7 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.5 (Ar**C**H), 74.1 (**C**H_2OBn), 73.5 (**C**H_2Ph), 72.6 (**C**HOH), 72.2 (**C**H_2OCO), 39.7 (CH_3**C**), 38.8 (**C**HCH_3), 17.7 (**C**H_3C), 12.2 (**C**H_3CH) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 328 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 287.1254 $[M+Na]^+$; found: 287.1250 $[M+Na]^+$.

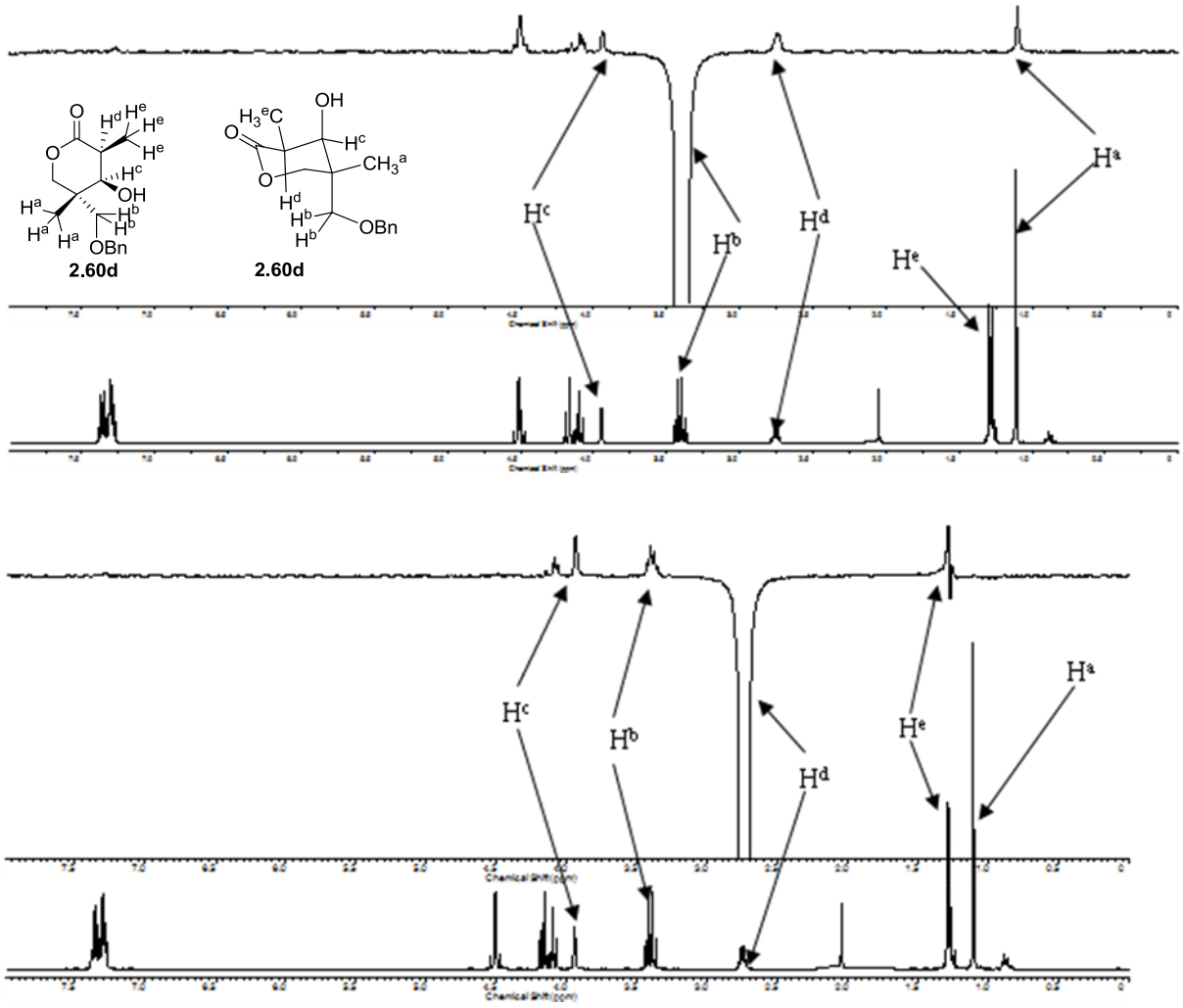
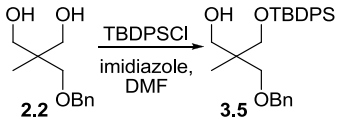


Figure 7.17. nOe's on **2.60d** to identify relative stereochemistry.

From the nOe experiments on **2.60d** when H^d was irradiated a response was observed at H^c, H^b and H^e and no response was observed H^a. This shows that H^d must be on the same face of the lactone ring as H^c and H^b and on the opposite face to H^a. When H^b was irradiated a nOe response was observed at H^c, H^d and H^a and no response was observed H^e. Therefore H^b must be on the same face of the δ-lactone ring as H^c and H^b and on the opposite face to methyl group H^e. This shows the relative stereochemistry of δ-lactone ring **2.60d** and therefore monoaddition product **2.34d** to be as shown (Scheme 2.32).

3-Benzyloxy-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-2-methyl-propan-1-ol (3.5)



2.2 **3.5**

To a stirred solution of diol **2.2** (1.00 g, 4.76 mmol, 1 equiv.) and imidazole (647 mg, 9.51 mmol, 2 equiv.) in DMF (18 mL) was added TBDPSCl (1.36 mL, 5.23 mmol, 1.1 equiv.) dropwise over 10 min. The reaction mixture was stirred at r.t for 24 h. The reaction mixture was poured into H_2O and the organics extracted with Et_2O. The organics were washed with H_2O and brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude colourless oil was purified by column chromatography (petroleum ether / EtOAc, 7:3) to give a colourless oil (822 mg, 1.83 mmol, 39% yield).

Data for compound 3.5: IR (neat): 3441 (br), 2953 (m), 3070 (w), 2930 (s), 2856 (s), 1589 (w), 1471 (m), 1454 (m), 1390 (m) cm^{-1}.

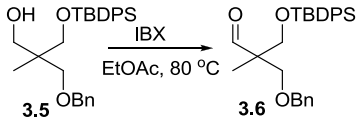
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (4 H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 7.51 – 7.25 (11 H, m, Ar**H**), 4.54 (2 H, s, C**H$_2$**Ph), 3.75 – 3.68 (2 H, m, C**H$_2$**OTBDPS), 3.66 (2 H, dd, *J* = 5.9, 3.1 Hz, C**H$_2$**OH), 3.60 (1 H, d, *J* = 8.9 Hz, C**H**HOBn), 3.51 (1 H, d, *J* = 8.8 Hz, C**H**HOBn), 2.79 (1 H, t, *J* = 6.0 Hz), 1.10 (9 H, s, SiC(C**H$_3$**)$_3$), 0.94 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2 (Ar**C**), 135.6 (Ar**C**H), 133.2 (Ar**C**), 129.7 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 74.7 (**C**H_2OBn), 73.5 (**C**H_2Ph), 69.0 (**C**H_2OH), 67.5 (**C**H_2OTBDPS), 41.5 (**C**$(CH_2OH)_2$), 26.9 (C(**C**$H_3)_3$), 19.2 (**C**$(CH_3)_3$), 17.3 (**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity): 471 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity): calculated: 471.2326 $[M+Na]^+$; found: 471.2323 $[M+Na]^+$.

3-Benzyloxy-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-2-methyl-propionaldehyde (3.6)



To a suspension of IBX (1.50 g, 5.35 mmol, 3 equiv.) in EtOAc (8 mL) was added *via* cannula a solution of alcohol **3.5** (800 mg, 1.78 mmol, 1 equiv.) in EtOAc (7 mL). The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled in an ice bath for 1 h and filtered. The filter cake was washed with EtOAc and the combined filtrates concentrated to give a pale yellow oil (751 mg, 1.68 mmol, 94% yield).

Data for compound 3.6: IR (neat): 3070 (w); 2930 (m); 2857 (m); 1729 (s); 1589 (w) cm^{-1}

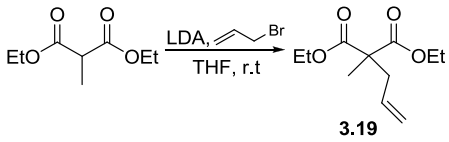
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (1 H, s, C**H**O), 7.81 – 7.54 (3 H, m, Ar**H**), 7.50 – 7.19 (12 H, m, Ar**H**), 4.52 (2 H, s, C$\mathbf{H_2}$Ph), 3.86 (1 H, d, *J* = 10.0 Hz, C**H**HOTBDPS), 3.80 (1 H, d, *J* = 10.0 Hz, C**H**HOTBDPS), 3.70 (1 H, d, *J* = 8.9 Hz, C**H**HOBn), 3.65 (1 H, d, *J* = 8.8 Hz, C**H**HOBn), 1.11 (3 H, s, CC$\mathbf{H_3}$), 1.04 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9 (**C**HO), 138.1 (Ar**C**), 135.6 (Ar**C**H), 133.0 (Ar**C**), 129.7 (Ar**C**H), 127.7 (Ar**C**H), 127.4 (Ar**C**H), 74.7 (**C**H_2OBn), 73.5 (**C**H_2Ph), 70.9 (**C**H_2OBn), 65.0 (**C**H_2OTBDPS), 53.0 (**C**$(CH_2OH)_2$), 26.8 (C(**C**H_3)$_3$), 19.3 (**C**$(CH_3)_3$), 14.7 (**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 469 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 469.2169 $[M+Na]^+$, found: 469.2174 $[M+Na]^+$.

2-Allyl-2-methyl-malonic acid diethyl ester (3.19)



To a solution of DIPA (9.0 mL, 65 mmol, 1.1 equiv.) in THF (60 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes) (26.0 mL, 65 mmol, 1.1 equiv) then a solution of diethylmethyl malonate (10.0 mL, 59 mmol, 1 equiv.) in THF (50 mL) at –78 °C. The reaction was warmed to 0 °C and stirred for 1 h. Allyl bromide (10.2 mL, 117 mmol, 2 equiv.) in THF (10 mL) was added dropwise to the reaction and the reaction warmed to r.t and stirred for 1 h 30 min. The reaction was quenched with sat. aq. NH_4Cl and the organics extracted with Et_2O, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude

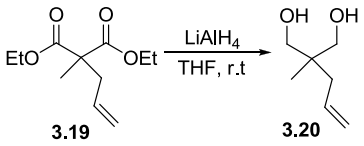
mixture was purified by distillation under reduced pressure (0.6 mbar, 60–62 °C) to give 11.7 g of a colourless oil (55 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (1 H, ddt, *J* = 17.0, 10.0, 7.4, 7.4 Hz, C**H**=CH_2), 5.15 – 4.98 (2 H, m, C**H$_2$**=CH), 4.17 (4 H, q, *J* = 7.0 Hz, C**H$_2$**CH_3), 2.60 (2 H, d, *J* = 7.3 Hz, C**H$_2$**CH_3), 1.38 (3 H, s, C**H$_3$**), 1.24 (6 H, t, *J* = 7.2 Hz, CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (**C**=O), 132.7 (**C**H=CH_2), 119.0 (**C**H_2=CH), 61.2 (**C**H_2CH_3), 53.4 (**C**CO_2Et), 40.0 (**C**H_2CHCH_2), 19.7 (C**C**H_3), 14.0 (**C**H_3CH_2O) ppm.

This corresponds to data in the literature[184]

2-Allyl-2-methyl-propane-1,3-diol (3.20)



3.19 **3.20**

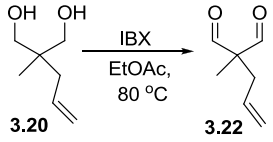
To a suspension of $LiAlH_4$ (4.43 g, 117 mmol, 5 equiv.) in THF (50 mL) at 0 °C was added diester **3.19** (5 g, 23 mmol, 1 equiv) in THF (25 mL). The reaction was stirred 0 °C for 15 min and allowed to warm to r.t and stirred for 20 min. The reaction was slowly quenched with H_2O and the organics extracted with Et_2O, washed with brine and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 1:1) to give 2.5 g of a colourless oil of diol **3.20** (19 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (1 H, ddt, *J* = 16.2, 10.8, 7.6, 7.6 Hz, C**H**=CH_2), 5.15 – 5.01 (2 H, m, C**H$_2$**=CH), 3.54 (2 H, d, *J* = 10.8 Hz, C**H**H**O**H), 3.50 (2 H, d, *J* = 10.8 Hz, C**H**H**O**H), 2.87 (2 H, d, *J* = 8.4 Hz, CH_2O**H**), 2.10 (2 H, d, *J* = 7.5 Hz, C**H$_2$**$CHCH_2$), 0.83 (3 H, s, C**H$_3$**C) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2 (**C**H=CH_2), 117.8 (**C**H_2=CH), 69.9 (**C**H_2OH), 39.2 (**C**CH_2OH), 38.6 (**C**H_2CHCH_2), 18.4 (C**C**H_3) ppm.

This corresponds to data in the literature[185]

2-Allyl-2-methyl-malonaldehyde (3.22)



To a suspension of IBX (6.50 g, 23.05 mmol, 6 equiv.) in EtOAc (10 mL) was added *via* cannula a solution of diol **3.20** (500 mg, 3.84 mmol, 1 equiv.) in EtOAc (10 mL). The reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled in an ice bath for 1 h and then filtered. The filter cake was washed with EtOAc and the combined filtrates concentrated to give 443 mg of a pale yellow oil (3.51 mmol, 91% yield).

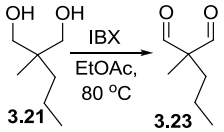
IR (neat): 3435 (w), 3033 (w), 2980 (w), 2935 (w), 1708 (s), 1641 (w), 1456 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (2 H, s, C**H**O), 5.65 (1 H, ddt, *J* = 17.3, 9.8, 7.4, 7.4 Hz, C**H**=CH_2), 5.19 – 5.14 (1 H, m, C**H**H=CH), 5.13 – 5.09 (1 H, m. CH**H**=CH), 2.57 (1 H, t, *J* = 1.1 Hz, C**H**HCH=), 2.56 (1 H, t, *J* = 1.1 Hz, CH**H**CH=), 1.29 (3 H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2 (**C**HO), 130.8 (**C**H=CH_2), 120.1 (**C**H_2=CH), 61.9 (**C**CH_3), 36.5 (**C**H_2CH=), 14.7 (**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) compound did not fly.

2-Methyl-2-propyl-malonaldehyde (3.23)



To a suspension of IBX (6.36 g, 22.70 mmol, 6 equiv.) in EtOAc (8 mL) was added *via* cannula a solution of diol **3.21** (500 mg, 3.78 mmol, 1 equiv.) in EtOAc (8 mL). The reaction mixture was stirred at 80 °C for 4 h 30 min. The reaction mixture was cooled in an ice bath for 1 h and then filtered. The filter cake was washed with EtOAc and the combined filtrates concentrated to give 354 mg of a pale yellow oil (2.72 mmol, 73% yield).

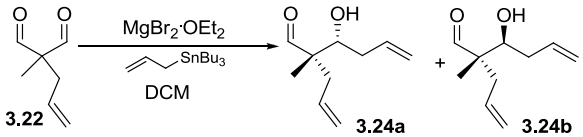
IR (neat): 2962 (m), 2936 (w), 2874 (w), 1708 (s), 1465 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (2 H, s, C**H**O), 1.84 – 1.75 (2 H, m, C**H$_2$**CH_2), 1.36 – 1.23 (2 H, m, CH_2C**H$_2$**), 1.29 (3 H, s, CC**H$_3$**), 0.94 (3 H, t, *J*=7.3 Hz, CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0 (**C**HO), 62.5 (**C**CH_3), 34.6 (**C**H_2CH_2), 17.3 (CH_2**C**H_2), 14.5 (**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 320 $[2M+Na+MeCN]^{+}$ (100%).

(*rac*-2S,3S)-2-Allyl-3-hydroxy-2-methyl-hex-5-enal (3.24b)



1,2-Dibromoethane (303 µL, 4.45 mmol, 3 equiv.) was added to a suspension of magnesium turnings (108 mg, 4.45 mmol, 3 equiv.) in Et_2O (7 mL) and stirred at r.t for 30 min. After removal of Et_2O by vacuum to leave a white solid of $MgBr_2$•OEt_2, CH_2Cl_2 (8 mL) was added and the reaction mixture was cooled to –78 °C. Dialdehyde **3.22** (189 mg, 1.50 mmol, 1 equiv.) was added, *via* cannula, in CH_2Cl_2 (10 mL). After addition of the dialdehyde the reaction mixture became a pale yellow solution. The reaction mixture was stirred at –78 °C for 20 min then allyl tributylstannane (731 µL, 2.25 mmol, 2 equiv.) in CH_2Cl_2 (12 mL) was added *via* cannula and the reaction stirred at –78 °C for 6 h. The reaction was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. After dilution with CH_2Cl_2, the organic phase was washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 90:10) to give 127 mg of **3.24a** and **3.24b** (0.75 mmol, 50%) as a colourless oil (diastereomeric ratio on the crude **3.24a:3.24b** 24:76, Figure 7.18). An analytically pure sample of major diastereoisomer **3.24b** (11 mg) was obtained pure after preparative HPLC (95:5 hexane / acetone).

Data for compound 3.24b: IR (neat): 3461 (br.s), 3077 (w), 2978 (m), 2912 (m), 2725 (m), 1716 (s), 1640 (m), 1458 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (1 H, s, C**H**O), 5.90 – 5.77 (1 H, m, =C**H**CH_2CHOH), 5.77 – 5.63 (1 H, m, =C**H**CH_2C), 5.23 – 5.05 (4 H, m, C**H$_2$**=CH), 3.82 (1 H, d, *J* = 11.0 Hz, C**H**OH), 2.41 – 2.25 (3 H, m, CC**H$_2$** & CHO**H**), 2.19 – 1.98 (2 H, m, C**H$_2$**CHOH), 1.08 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5 (**C**HO), 134.8 (**C**H=CH_2), 132.4 (**C**H=CH_2), 118.9 (**C**H_2=CH), 118.6 (**C**H_2=CH), 72.9 (**C**HOH), 53.0 (**C**CH_3), 38.0 (C**C**H_2CH=), 36.1 (CHOH**C**H_2CH=), 14.4 (**C**H_3C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 359 $[2M+Na]^+$ (77%), 400 $[2M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 223.1305 $[M+Na+MeOH]^+$; found: 223.1307 $[M+Na+MeOH]^+$.

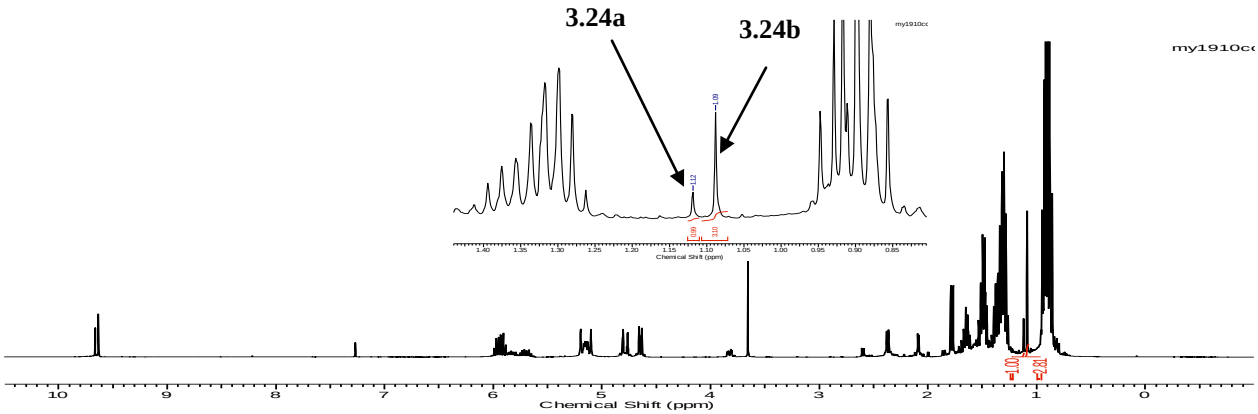
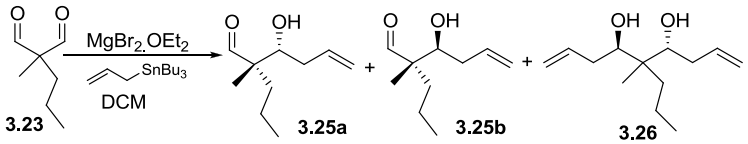


Figure 7.18 Crude ^{1}H NMR of allylation on allyl dialdehyde **3.24**, showing how the d.r. was calculated from integration of the methyl peaks.

(*rac*-2S,3R)-3-Hydroxy-2-methyl-2-propyl-hex-5-enal (3.25a) & (*rac*-2S,3S)-3-Hydroxy-2-methyl-2-propyl-hex-5-enal (3.25b) & (*rac*-4*R*,6*R*)-5-Methyl-5-propyl-nona-1,8-diene-4,6-diol (3.26)



d.r **a:b**, 25:75

1,2-Dibromoethane (666 µL, 7.73 mmol, 3 equiv.) was added to a suspension of magnesium turnings (188 mg, 7.73 mmol, 3 equiv.) in Et_2O (12 mL) and stirred at r.t for 30 min. After removal of Et_2O by vacuum to leave a white solid of $MgBr_2$•OEt_2, CH_2Cl_2 (14 mL) was added and the reaction mixture was cooled to –78 °C. Dialdehyde **3.23** (330 mg, 2.58 mmol, 1 equiv.) in CH_2Cl_2 (19 mL) was added, *via* cannula. After addition of the dialdehyde the reaction mixture became a pale yellow solution. The reaction mixture was stirred at –78 °C for 20 min then allyl tributylstannane (1.30 mL, 3.86 mmol, 1.5 equiv.) in CH_2Cl_2 (19 mL) was added *via* cannula and the reaction stirred at –78 °C for 2 h, warmed to –20 °C and stirred at –20 °C for 2 h. The reaction was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. After dilution with CH_2Cl_2, the organic phase was washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 80:20) to give 179 mg of **3.25a** and **3.25b**

(1.05 mmol, 41%) as a colourless oil (diastereomeric ratio on the crude **3.25a:3.25b** 25:75, Figure 7.19). Double addition product **3.26** (142 mg, 0.69 mmol, 26 %) was also isolated.

Data for compound 3.25a and 3.25b (mixture): IR (neat): 3457 (br.s), 3077 (w), 2960 (m), 2936 (m), 2874 (m), 2716 (w), 1719 (s), 1642 (m), 1466 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (1 H, s, C**H**O (**3.25a**)), 9.57 (1 H, s, C**H**O (**3.25b**)), 5.93 – 5.78 (1 H + 1 H, m, C**H**=CH_2), 5.23 – 5.11 (2 H + 2 H, m, CH=C**H$_2$**), 3.86 (1 H, dt, *J* = 10.6, 2.8 Hz, C**H**OH (**3.25b**)), 3.75 (1 H, ddd, *J* = 10.4, 3.0, 2.8 Hz, C**H**OH (**3.25a**)), 2.39 – 2.24 (1 H + 1 H, m, C**HH**CH=), 2.17 – 2.10 (1 H + 1 H + 1 H, m, C**HH**CH= (**3.25a** and **3.25b**) and CHO**H** (**3.25b**)), 1.98 (1 H, d, *J* = 4.0 Hz, CHO**H** (**3.25a**)), 1.81 – 1.70 (1 H, m, C**HH**CH_2CH_3 (**3.25a**)), 1.64 – 1.45 (1 H + 2 H, m, C**HH**CH_2CH_3 (**3.25a**) and C**H$_2$**CH_2CH_3 (**3.25b**)), 1.37 – 1.12 (2 H + 2 H, m, C**H$_2$**CH_3), 1.10 (3 H, s, CC**H$_3$** (**3.25a**)), 1.07 (3 H, s, CC**H$_3$** (**3.25b**)), 0.93 (3 H, t, *J* = 6.1 Hz, C**H$_3$**CH_2 (**3.25a**)), 0.91 (3 H, t, *J* = 7.1 Hz, C**H$_3$**CH_2 (**3.25b**)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9 (**C**HO (**3.25a**)), 206.8 (**C**HO (**3.25b**)), 135.1 (**C**H=CH_2 (**3.25a**)), 135.0 (**C**H=CH_2 (**3.25b**)), 118.7 (**C**H_2=CH (**3.25a**)), 118.6 (**C**H_2=CH (**3.25b**)), 73.7 (**C**HOH (**3.25a**)), 72.7 (**C**HOH (**3.25b**)), 53.4 (**C**CH_3 (**3.25b**)), 53.0 (**C**CH_3 (**3.25a**)), 36.9 (C**C**H_2CH_2 (**3.25a**)), 36.0 (**C**H_2CH= (**3.25b**)), 36.0 (**C**H_2CH= (**3.25a**)), 34.8 (C**C**H_2CH_2 (**3.25a**)), 17.3 (**C**H_2CH_3 (**3.25a**)), 17.2 (**C**H_2CH_3 (**3.25b**)), 15.4 (**C**H_3C (**3.25a**)), 14.9 (**C**H_3CH_2 (**3.25a**)), 14.8 (**C**H_3C (**3.25b**)), 13.8 (**C**H_3CH_2 (**3.25b**)) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 454 $[2M+NH_4+Na+MeCN+MeOH]^+$ (100%)

Data for compound 3.26: IR (neat): 3332 (br.s), 3076 (w), 2959 (s), 2873 (m), 1641 (m), 1466 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (2 H, ddddd, *J* = 18.8, 8.2, 8.1, 6.1, 2.3 Hz, C**H**=CH_2), 5.24 – 5.05 (4 H, m, C**H$_2$**=CH), 3.69 (1 H, d, *J* = 10.1 Hz, C**H**OH), 3.63 (1 H, d, *J* = 10.6 Hz, C**H**OH), 3.14 (1 H, br. s., CHO**H**), 2.99 (1 H, d, *J* = 4.0 Hz, CHO**H**), 2.43 – 2.11 (4 H, m, C**H$_2$**CHOH), 1.66 (1 H, td, *J* = 13.0, 4.3 Hz, C**HH**CH_2CH_3), 1.49 – 1.36 (1 H, m, CH_2C**HH**CH_3), 1.32 – 1.19 (1 H, m, CH_2C**HH**CH_3), 1.18 - 1.05 (1 H, m, C**HH**CH_2CH_3), 0.93 (3 H, t, *J* = 7.3 Hz, C**H$_3$**CH_2), 0.89 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3 (**C**H=CH_2), 117.8 (**C**H_2=CH), 117.6 (**C**H_2=CH), 76.5 (**C**HOH), 76.1 (**C**HOH), 42.0 (**C**CH_3), 36.3 (**C**H_2CH=), 35.4 (C**C**H_2CH_2), 19.3 (**C**H_3C), 16.4 (**C**H_2CH_3), 15.1 (**C**H_3CH_2) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 276 $[M+Na+MeCN]^{+}$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 235.1669 $[M+Na]^{+}$; found: 235.1671 $[M+Na]^{+}$.

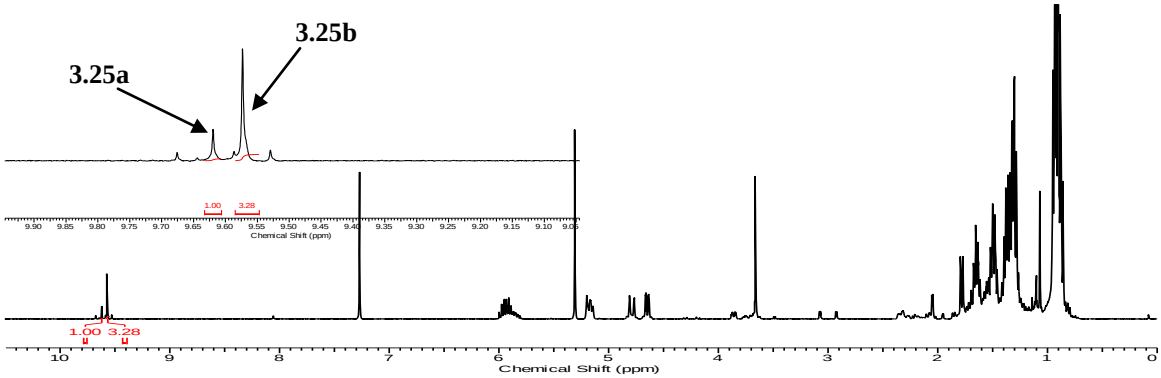
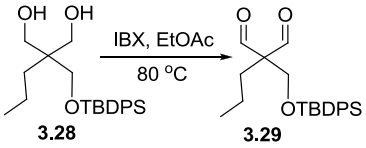


Figure 7.19. Crude ^{1}H NMR of allylation on propyl dialdehyde **3.25**, showing how the d.r. was calculated from integration of the aldehyde peaks.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-2-propyl malonaldehyde (3.29).



To a suspension of IBX (2.17 g, 7.75 mmol, 6 equiv.) in EtOAc (4 mL) was added *via* cannula a solution of diol **3.28** (500 mg, 1.29 mmol, 1 equiv.) in EtOAc (5 mL). The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled in an ice bath for 1 h and then filtered. The filter cake was washed with EtOAc and the combined filtrates concentrated to give 462 mg (1.21 mmol, 94% yield) as a pale yellow oil.

IR (neat): 3071 (w), 2959 (m), 2932 (m), 2858 (m), 1710 (s), 1468 (m) cm^{-1}.

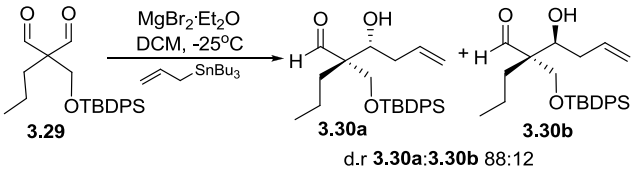
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (2 H, s, C**H**O), 7.66 – 7.56 (4 H, m, Ar**H**), 7.49 – 7.37 (6 H, m, Ar**H**), 4.03 (2 H, s, C$\mathbf{H_2}$OTBDPS), 1.78 – 1.66 (2 H, m, C$\mathbf{H_2}$$CH_2CH_3$), 1.23 – 1.15 (2 H, m, $CH_2C\mathbf{H_2}CH_3$), 1.03 (9 H, s, SiCC$\mathbf{H_3}$), 0.87 (3 H, t, J = 7.3 Hz, $CH_2CH_2C\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4 (**C**HO), 135.6 (Ar**C**H), 132.4 (Ar**C**), 130.0 (Ar**C**H), 127.9 (Ar**C**H), 67.0 (**C**CH_3), 64.1 (**C**H_2OTBDPS), 30.8 (**C**$H_2CH_2CH_3$), 26.7 (SiC(**C**$H_3)_3$), 19.2 (Si**C**$(CH_3)_3$), 17.2(CH_2**C**H_2CH_3), 14.5 (CH_2CH_2**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 437 $[M+Na+MeOH]^{+}$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 437.2119 $[M+Na+MeOH]^{+}$; found: 437.2121 $[M+Na+MeOH]^{+}$.

(2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-2-propyl-hex-5-enal (3.30a) & (2*R*,3*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-2-propyl-hex-5-enal (3.30b)



1,2-Dibromoethane (300 μL, 3.48 mmol, 3 equiv.) was added to a suspension of magnesium turnings (85 mg, 3.48 mmol, 3 equiv.) in Et_2O (9 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (15.5 mL) was added and the reaction mixture was cooled to –78 °C before addition *via* cannula of dialdehyde **3.29** (445 mg, 1.16 mmol, 1 equiv.) in CH_2Cl_2 (19 mL). After 20 min of stirring at –78 °C, tributyl allylstannane (358 μL, 1.16 mmol, 1 equiv.) in CH_2Cl_2 (21.5 mL) was added *via* cannula at –78 °C and stirred for 30 min. The reaction mixture warmed to –25 °C and stirred for 1 h 30 min. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, before removal of the solvent in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 335 mg of **3.30** as a colourless oil (d.r 88:12 from crude ^{1}H NMR, Figure 7.20) (0.79 mmol, 68%). The product was further purified by HPLC (9 : 1, hexane / EtOAc) to yield an analytical sample of major diastereoisomer **3.30a** (10 mg) and 243 mg of mixture of **3.30a** and **3.30b**.

Data for compound 3.30a: IR (neat): 3495 (br), 3072 (w), 2958 (m), 2932 (m), 2858 (m), 1723 (s), 1641 (w), 1589 (w), 1467 (m), 1427 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (1 H, s, C**H**O), 7.75 – 7.60 (4 H, m, Ar**H**), 7.51 – 7.35 (6 H, m, Ar**H**), 6.00 – 5.85 (1 H, m, C**H**=CH_2), 5.13 (1 H, d, *J* = 9.6 Hz, CH=C**H**H), 5.13 (1 H, d, *J* = 18.7 Hz, CH=C**H**H), 4.06 (1 H, d, *J* = 10.6 Hz, C**H**HOTBDPS), 4.09 – 4.02 (1 H, m, C**H**OH), 3.78 (1 H, d, *J* = 10.6 Hz, C**H**HOTBDPS), 3.04 (1 H, d, *J* = 6.6 Hz, CHO**H**), 2.40 – 2.29 (1 H, m, C**H**HCH=), 2.29 – 2.20 (1 H, m, C**H**HCH=), 1.59 – 1.49 (2 H, m, C**H$_2$**CH_2CH_3), 1.19 – 1.10 (2 H, m, CH_2C**H$_2$**CH_3), 1.07 (9 H, s, C(C**H$_3$**)$_3$), 0.85 (3 H, t, *J* = 7.6 Hz, CH_2CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (**C**HO), 135.8 (Ar**C**H), 135.4 (**C**H=CH_2), 132.5 (Ar**C**), 132.2 (Ar**C**), 130.0 (Ar**C**H), 127.8 (Ar**C**H), 117.7 (**C**H_2=CH), 73.5 (**C**HOH), 63.9 (**C**H_2OTBDPS), 57.5 (CH_2CH_2**C**), 36.7 (**C**H_2CH=), 31.9 (**C**$H_2CH_2CH_3$), 26.9 (SiC(**C**$H_3)_3$), 19.1 (Si**C**$(CH_3)_3$, 16.9 (CH_2**C**H_2CH_3), 13.2 (CH_2CH_2**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 447 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 447.2326 $[M+Na]^+$; found: 447.2334 $[M+Na]^+$.

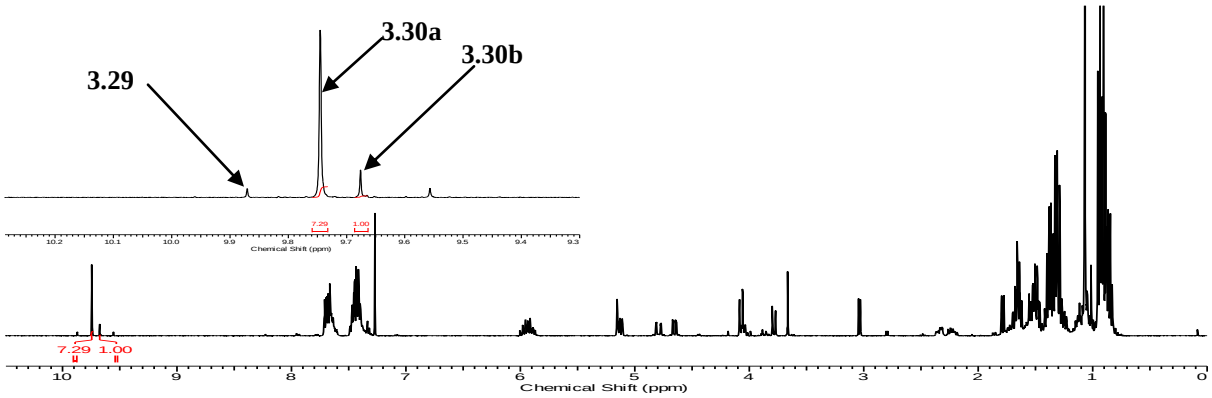
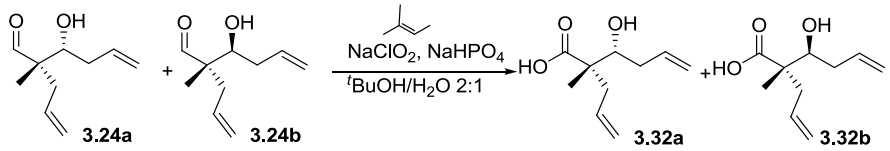


Figure 7.20. Crude ^{1}H NMR of **3.30** showing how the d.r was calculated.

(*rac*-2*S*,3*R*)-2-Allyl-3-hydroxy-2-methyl-hex-5-enoic acid (3.32a) & (*rac*-2*S*,3*S*)-2-Allyl-3-hydroxy-2-methyl-hex-5-enoic acid (3.32b)



To a solution of **3.24a** and **3.24b** (200 mg, 1.19 mmol, 1 equiv.) in *t*-BuOH (4 mL) was added 2-methyl-2-butene (496 µL, 4.40 mmol, 3.7 equiv.) at r.t. A solution of $NaClO_2$ (258 mg, 2.85 mmol, 2.4 equiv.) and $NaHPO_4$ (342 mg, 2.85 mmol, 2.4 equiv) in H_2O (2 mL) was added to the reaction and the reaction mixture was stirred at r.t for 4 h. Na_2SO_3 (120 mg, 0.95 mmol, 0.8 equiv.) was added to consume the excess $NaClO_2$ and the reaction stirred for 10 min. The reaction mixture was poured into CH_3Cl and the organics extracted and washed with H_2O, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude oil. The crude was purified by column chromatography (petroleum ether / EtOAc, 8:2) to give **3.32a** and **3.32b** (111 mg, 0.61 mmol, 51% yield) as a colourless oil. The diastereoisomers were separated by preperative HPLC (hexane : EtOAc, 9:1).

Data for 3.32a: IR (neat): 3447 (br. s), 3078 (m), 2981 (m), 2920 (m), 1707 (s), 1641 (w), 1469 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95 – 5.75 (2 H, m, C**H**=CH_2), 5.25 – 5.06 (4 H, m, C**H$_2$**=CH), 3.80 (1 H, dd, *J* = 10.4, 2.3 Hz, C**H**OH), 2.58 (1 H, dd, *J* = 13.9, 6.9 Hz, CC**H**HCH=), 2.45 – 2.25 (2 H, m, CC**HH**CH= & C**H**HCHOH), 2.21 – 2.09 (1 H, m, C**H**HCHOH), 1.24 (3 H, sm CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (**C**OOH), 134.9 (**C**H=CH_2), 133.5 (**C**H=CH_2), 118.8 (**C**H_2=CH), 118.6 (**C**H_2=CH), 74.2 (**C**HOH), 50.2 (**C**CH_3), 40.0 (C**C**H_2CH=), 37.0 (CHOH**C**H_2), 17.5 (**C**H_3C) ppm.

LRMS (ESI-): $^{m}/_{z}$ (rel. intensity) 183 $[M-H]^-$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 207.0992 $[M+Na]^+$; found: 207.0994 $[M+Na]^+$.

Data for 3.32b: IR (neat): 3447 (br. s), 3077 (m), 2980 (m), 2929 (m), 2943 (m), 1695 (s), 1641 (m), 1467 (w) cm^{-1}.

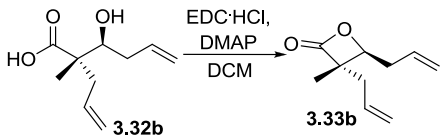
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 – 5.67 (2 H, m, C**H**=CH_2), 5.23 – 5.06 (4 H, m, C**H$_2$**=CH), 3.76 (1 H, dd, *J* = 10.4, 1.9 Hz, C**H**OH), 2.50 (1 H, dd, *J* = 13.7, 7.2 Hz, CC**H**HCH=), 2.45 – 2.31 (2 H, m, CC**HH**CH= & C**H**HCHOH), 2.15 – 2.04 (1 H, m, C**H**HCHOH), 1.18 (3 H, sm CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5 (**C**OOH), 134.8 (**C**H=CH_2), 132.8 (**C**H=CH_2), 119.0 (**C**H_2=CH), 118.5 (**C**H_2=CH), 74.3 (**C**HOH), 50.5 (**C**CH_3), 40.7 (C**C**H_2CH=), 36.3 (CHOH**C**H_2), 17.1 (**C**H_3C) ppm.

LRMS (ESI-): $^{m}/_{z}$ (rel. intensity) 183 $[M-H]^-$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 207.0992 $[M+Na]^+$; found: 207.0994 $[M+Na]^+$.

(*rac*-3*S*,4*S*)-3,4-Diallyl-3-methyl-oxetan-2-one (3.33b)



To a solution of **3.32b** (50 mg, 0.27 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) was added EDC•HCl (79 mg, 0.41 mmol, 1.5 equiv.) and DMAP (66 mg, 0.54 mmol, 2 equiv.) and the reaction mixture stirred at r.t for 5 h. The reaction was quenched with brine, organics extracted with CH_2Cl_2 and dried over $MgSO_4$ filtered and concentrated in *vacuo*. The crude was purified by

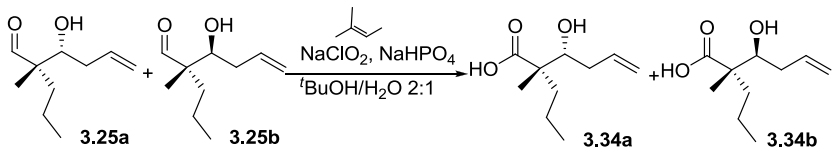
column chromatography (9:1 petroleum ether / EtOAc) to give **3.33b** (28 mg, 0.17 mmol, 63% yield).

Data for 3.33b: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.88 – 5.68 (2 H, m, C**H**=CH_2), 5.27 – 5.09 (4 H, m, C**H$_2$**=CH), 4.40 (1 H, dd, *J* = 8.0, 6.2 Hz, C**H**OCO), 2.68 – 2.34 (4 H, m, C**H$_2$**CH=), 1.30 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1 (**C**OO), 131.7 (**C**H=CH_2), 131.7 (**C**H=CH_2), 120.0 (**C**H_2=CH), 118.7 (**C**H_2=CH), 79.2 (**C**HOCO), 57.1 (**C**CH_3), 40.1 (**C**H_2CH=CH_2), 34.8 (**C**H_2CH=CH_2), 14.5 (**C**H_3C) ppm.

This corresponds to data from the literature.[145]

(*rac*-2*S*,3*R*)-3-Hydroxy-2-methyl-2-propyl-hex-5-enoic acid (3.34a) & (*rac*-2*S*,3*S*)-3-Hydroxy-2-methyl-2-propyl-hex-5-enoic acid (3.34b)



To a solution of **3.25a** and **3.25b** (100 mg, 0.59 mmol, 1 equiv.) in *t*-BuOH (3 mL) was added 2-methyl-2-butene (245 µL, 2.17 mmol, 3.7 equiv.) at r.t. A solution of $NaClO_2$ (128 mg, 1.42 mmol, 2.4 equiv.) and $NaHPO_4$ (170 mg, 1.42 mmol, 2.4 equiv) in H_2O (1.5 mL) was added to the reaction and the reaction mixture was stirred at r.t for 16 h. Na_2SO_3 (179 mg, 1.42 mmol, 2.4 equiv.) was added to consume the excess $NaClO_2$ and the reaction stirred for 10 min. The reaction mixture was poured into CH_3Cl and the organics extracted and washed with H_2O, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude oil. The crude was purified by column chromatography (petroleum ether / EtOAc, 7:3) to give **3.34a** and **3.34b** (54 mg, 0.29 mmol, 50% yield) as a colourless oil. An analytical sample of major diastereoisomer **3.34b** (5 mg) was isolated by preparative HPLC (hexane / EtOAc, 75:25).

Data for 3.34b: **IR** (neat): 3447 (br. s), 3077 (w), 2960 (m), 2874 (m), 1701 (s), 1642 (m), 1468 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 – 5.80 (1 H, m, C**H**=CH_2), 5.22 – 5.09 (2 H, m, C**H$_2$**=CH), 3.79 (1 H, dd, *J* = 10.6, 2.0 Hz, C**H**OH), 2.43 – 2.31 (1 H, m, C**H**HCH=), 2.21 – 1.99 (1 H, m, C**H**HCH=), 1.69 (1 H, td, *J* = 12.9, 4.5 Hz, C**H**HCH_2CH_3), 1.50 (1 H, td, *J* =

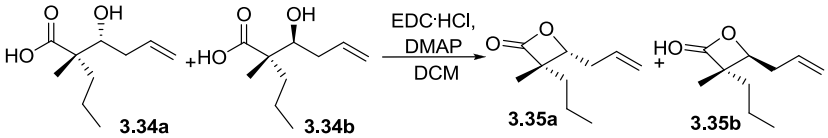
13.0, 4.3 Hz, C**H**<u>**H**</u>CH_2CH_3), 1.43 – 1.31 (1 H, m, C<u>**H**</u>**H**CH_3), 1.30 – 1.20 (1 H, m, C**H**<u>**H**</u>CH_3), 1.16 (3 H, s, CC<u>**H**$_3$</u>), 0.92 (3 H, t, *J* = 7.3 Hz, CH_2C<u>**H**$_3$</u>) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1 (<u>**C**</u>OOH), 135.2 (<u>**C**</u>H=CH_2), 118.0 (<u>**C**</u>H_2=CH), 74.7 (<u>**C**</u>HOH), 50.7 (<u>**C**</u>CH_3), 38.8 (C<u>**C**</u>H_2CH_2), 36.2 (CHOH<u>**C**</u>H_2), 17.6 (<u>**C**</u>H_2CH_3), 16.6 (<u>**C**</u>H_3C), 14.5 (<u>**C**</u>H_3CH_2) ppm.

LRMS (ESI-): $^m/_z$ (rel. intensity) 185 $[M-H]^-$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 209.1148 $[M+Na]^+$; found: 209.1155 $[M+Na]^+$.

(*rac*-3*S*,4*R*)-4-Allyl-3-methyl-3-propyl-oxetan-2-one (3.35a) & (*rac*-3*S*,4*S*)-4-Allyl-3-methyl-3-propyl-oxetan-2-one (3.35b)



To a solution of **3.34a** and **3.34b** (20 mg, 0.11 mmol, 1 equiv.) in CH_2Cl_2 (1.5 mL) was added EDC•HCl (31 mg, 0.16 mmol, 1.5 equiv.) and DMAP (26 mg, 0.21 mmol, 2 equiv.) and the reaction mixture stirred at r.t for 5 h. The reaction was quenched with brine, the organics extracted with CH_2Cl_2 and dried over $MgSO_4$ filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1, petroleum ether / EtOAc) to give **3.35a** and **3.35b** (17 mg, 0.10 mmol, 92% yield). An analytically pure sample of major diastereoisomer **3.35b** (3 mg) was isolated after preparative HPLC (hexane / acetone 93:7). nOe analysis on **3.35b** identified the relative stereochemistry (Figure 7.21).

Data for 3.35b: IR (neat): 2962 (m), 2875 (w), 1817 (s), 1643 (w), 1459 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (1 H, dddd, *J* = 17.1, 10.4, 6.8, 6.7 Hz, C<u>**H**</u>=CH_2), 5.30 – 5.12 (2 H, m, C<u>**H**$_2$</u>=CH), 4.35 (1 H, dd, *J* = 7.8, 6.3 Hz, C<u>**H**</u>OCO), 2.65 – 2.54 (1 H, m, C<u>**H**</u>**H**CH=), 2.51 – 2.38 (1 H, m, C**H**<u>**H**</u>CH=), 1.75 – 1.64 (2 H, m, CC<u>**H**$_2$</u>CH_2), 1.56 – 1.47 (1 H, m, C<u>**H**</u>**H**CH_3), 1.39 – 1.30 (1 H, m, C**H**<u>**H**</u>CH_3), 1.29 (3 H, s, CC<u>**H**$_3$</u>), 0.97 (3 H, t, *J* = 7.3 Hz, CH_2C<u>**H**$_3$</u>) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8 (<u>**C**</u>OO), 131.9 (<u>**C**</u>H=CH_2), 118.7 (<u>**C**</u>H_2=CH), 80.3 (<u>**C**</u>HOCO), 57.7 (<u>**C**</u>CH_3), 38.00 (C<u>**C**</u>H_2CH_2), 34.9 (<u>**C**</u>H_2CH=), 17.6 (<u>**C**</u>H_2CH_3), 14.3 (<u>**C**</u>H_3C), 14.2 (<u>**C**</u>H_3CH_2) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 241 $[M+MeOH+MeCN]^+$ (90%).

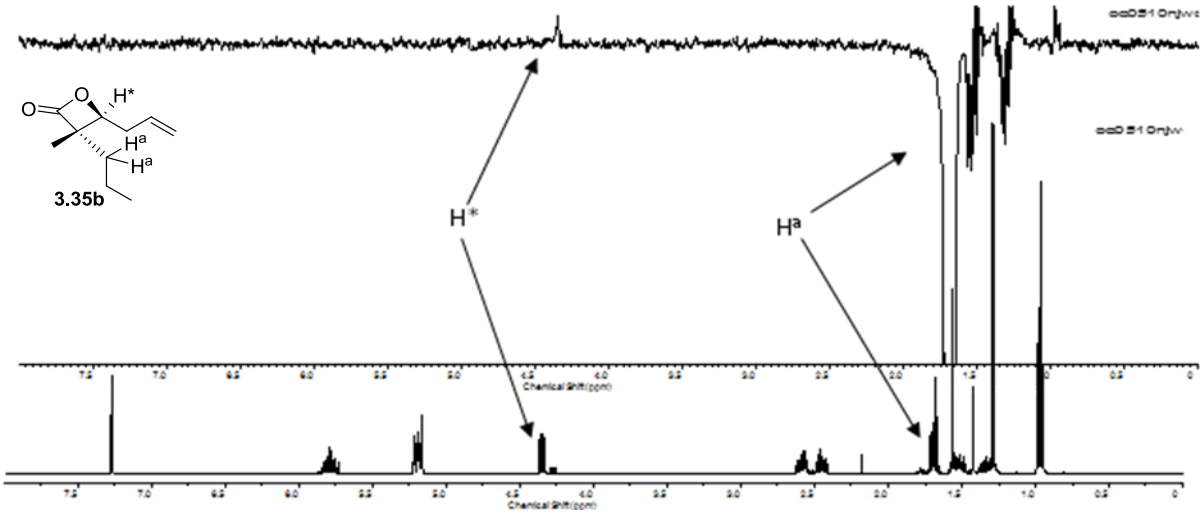
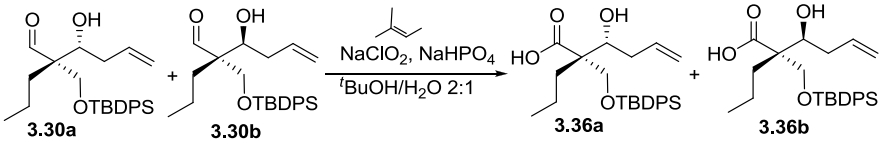


Figure 7.21. nOe experiment on **3.35b** proving the relative stereochemistry

From the nOe experiment on **3.35b** when H^a was irradiated a nOe was observed at H*, so proving the relative stereochemistry is as shown.

(*rac*-2*S*,3*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-2-propyl-hex-5-enoic acid (3.36a) & (*rac*-2*S*,3*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-2-propyl-hex-5-enoic acid (3.36b).



To a solution of **3.30a** and **3.30b** (200 mg, 0.47 mmol, 1 equiv.) in *t*-BuOH (4 mL) was added 2-methyl-2-butene (184 µL, 1.74 mmol, 3.7 equiv.) at r.t. A solution of $NaClO_2$ (102 mg, 1.13 mmol, 2.4 equiv.) and $NaHPO_4$ (135 mg, 1.13 mmol, 2.4 equiv) in H_2O (2 mL) was added to the reaction and the reaction mixture was stirred at r.t for 4 h. Na_2SO_3 (150 mg, 1.19 mmol, 2.53 equiv.) was added to consume the excess $NaClO_2$ and the reaction stirred for 10 min. The reaction mixture was poured into CH_3Cl and the organics extracted and washed with H_2O, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give crude oil. The crude was purified by column chromatography (petroleum ether / EtOAc, 7:3) to give **3.36a** and **3.36b** (160 mg, 0.36 mmol, 77% yield) as a colourless oil. An analytically pure sample of major diastereoisomer **3.36a** (14 mg) was isolated after preperative HPLC (hexane / acetone, 8:2) and 143 mg of a mixture of **3.36a** and **3.36b** was isolated.

Data for compound 3.36a: IR (neat): 3072 (br), 2959 (s), 2932 (s), 2859 (m), 1702 (s), 1469 (m), 1427 (s) cm^{-1}.

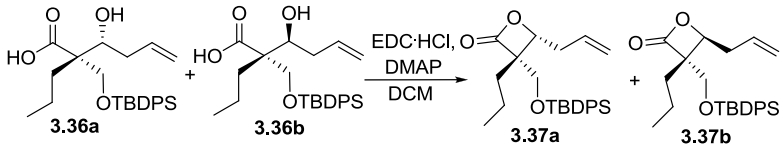
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.62 (4 H, m, Ar**H**), 7.50 – 7.35 (6 H, m, Ar**H**), 5.85 (1 H, dddd, *J* = 14.1, 10.1, 8.1, 6.1 Hz, C**H**=CH_2), 5.22 – 5.09 (2 H, m, CH=C**H$_2$**), 4.04 (1 H, dd, *J* = 10.6, 2.0 Hz, C**H**OH), 3.92 (1 H, d, *J* = 10.6 Hz, C**HH**OTBDPS), 3.87 (1 H, d, *J* = 11.1 Hz, C**HH**OTBDPS), 2.41 – 2.31 (1 H, m, C**HH**CH=), 2.16 – 2.02 (1 H, m, C**HH**CH=), 1.80 – 1.65 (2 H, m, C**H$_2$**CH_2CH_3), 1.25 – 1.13 (2 H, m, CH_2C**H$_2$**CH_3), 1.09 (9 H, s, C(C**H$_3$**)$_3$), 0.88 (3 H, t, *J* = 7.6 Hz, CH_2CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0 (**C**OOH), 135.7 (Ar**C**H), 134.8 (**C**H=CH_2), 132.3 (Ar**C**), 130.1 (Ar**C**H), 127.9 (Ar**C**H), 118.6 (**C**H_2=CH), 72.9 (**C**HOH), 63.7 (**C**H_2OTBDPS), 54.5 (CH_2CH_2**C**), 36.6 (**C**H_2CH=), 33.5 (**C**$H_2CH_2CH_3$), 26.9 (SiC(**C**H_3)$_3$), 19.2 (Si**C**$(CH_3)_3$, 17.4 (CH_2**C**H_2CH_3), 14.5 (CH_2CH_2**C**H_3) ppm.

LRMS (ESI-): $^{m}/_{z}$ (rel. intensity) 439 $[M-H]^-$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 463.2275 $[M+Na]^+$; found: 463.2280 $[M+Na]^+$.

(3*S*,4*R*)-4-Allyl-3-(*tert*-butyl-diphenyl-silanyloxymethyl)-3-propyl-oxetan-2-one (3.37a) & (3*S*,4*S*)-4-Allyl-3-(*tert*-butyl-diphenyl-silanyloxymethyl)-3-propyl-oxetan-2-one (3.37b)



To a solution of **3.36a** and **3.36b** (130 mg, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added EDC•HCl (85 mg, 0.44 mmol, 1.5 equiv.) and DMAP (72 mg, 0.59 mmol, 2 equiv.) and the reaction mixture stirred at r.t for 5 h. The reaction was quenched with brine, the organics extracted with CH_2Cl_2 and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1 petroleum ether / EtOAc) to give **3.37a** and **3.37b** (98 mg, 0.23 mmol, 79% yield). The diastereoisomers were separated by preparative HPLC (hexane / acetone 97:3) to give 51 mg **3.29a** and 6 mg **3.37b** and 12 mg of mixture of **3.37a** and **3.37b**. nOe analysis on **3.37a** (Figure 7.22) and **3.37b** (Figure 7.23) identified the relative stereochemistry.

Data for compound 3.37a: IR (neat): 3072 (w), 2959 (m), 2932 (m), 2859 (m), 1821 (s), 1468 (m), 1427 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.64 (4 H, m, Ar**H**), 7.51 – 7.36 (6 H, m, Ar**H**), 5.82 (1 H, ddt, *J* = 17.0, 10.5, 6.7, 6.7 Hz, C**H**=CH_2), 5.13 (1 H, d, *J* = 8.7 Hz, CH=C**HH**), 5.10 (1 H, d, *J* = 18.3 Hz, CH=C**HH**), 4.41 (1 H, dd, *J* = 8.4, 5.6 Hz, C**H**OCO), 3.88 (1 H, d, *J* = 10.9 Hz, C**HH**OTBDPS), 3.82 (1 H, d, *J* = 10.4 Hz, C**HH**OTBDPS), 2.90 – 2.69 (2 H, m, C**H$_2$**CH=), 1.72 – 1.62 (2 H, m, C**H$_2$**CH_2CH_3), 1.47 – 1.34 (1 H, m, CH_2C**HH**CH_3), 1.33 – 1.18 (1 H, m, CH_2C**HH**CH_3), 1.08 (9 H, s, C(C**H$_3$**)$_3$), 0.90 (3 H, t, *J* = 7.2 Hz, CH_2CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9 (**C**OO), 135.8 (**C**H=CH_2), 135.6 (Ar**C**H), 132.1 (Ar**C**), 130.0 (Ar**C**H), 127.9 (Ar**C**H), 118.3 (**C**H_2=CH), 79.9 (**C**HOCO), 64.1 (**C**COO), 61.6 (**C**H_2OTBDPS), 34.0 (**C**H_2CH=), 33.7 (**C**$H_2CH_2CH_3$), 26.8 (SiC(**C**H_3)$_3$), 19.2 (Si**C**$(CH_3)_3$, 17.7 (CH_2**C**H_2CH_3), 14.3 (CH_2CH_2**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 486 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 445.2169 $[M+Na]^+$; found: 445.2171 $[M+Na]^+$.

Data for compound 3.37b: IR (neat): 3072 (w), 2959 (m), 2932 (m), 2859 (m), 1821 (s), 1469 (m), 1427 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 – 7.62 (4 H, m, Ar**H**), 7.51 – 7.35 (6 H, m, Ar**H**), 5.81 (1 H, ddt, *J* = 17.1, 10.5, 6.5, 6.5 Hz, C**H**=CH_2), 5.18 (1 H, d, *J* = 18.4 Hz, CH=C**HH**), 5.13 (1 H, d, *J* = 9.1 Hz, CH=C**HH**), 4.72 (1 H, dd, *J* = 8.4, 5.9 Hz, C**H**OCO), 3.97 (1 H, d, *J* = 10.7 Hz, C**HH**OTBDPS), 3.67 (1 H, d, *J* = 10.6 Hz, C**HH**OTBDPS), 2.69 – 2.57 (1 H, m, C**HH**CH=), 2.52 – 2.41 (1 H, m, C**HH**CH=), 1.82 – 1.69 (1 H, m, C**HH**CH_2CH_3), 1.63 – 1.52 (1 H, m, C**HH**CH_2CH_3), 1.33 – 1.20 (2 H, m, CH_2C**H$_2$**CH_3), 1.07 (9 H, s, C(C**H$_3$**)), 0.89 (3 H, t, *J* = 7.1 Hz, CH_2CH_2C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (**C**OO), 135.7 (**C**H=CH_2), 135.6 (Ar**C**H), 132.2 (Ar**C**), 130.0 (Ar**C**H), 127.9 (Ar**C**H), 118.3 (**C**H_2=CH), 77.4 (**C**HOCO), 63.6 (**C**COO), 63.0 (**C**H_2OTBDPS), 34.2 (**C**H_2CH=), 28.6 (**C**$H_2CH_2CH_3$), 26.7 (SiC(**C**H_3)$_3$), 19.3 (Si**C**$(CH_3)_3$, 17.7 (CH_2**C**H_2CH_3), 14.6 (CH_2CH_2**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 486 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 445.2169 $[M+Na]^+$; found: 445.2172 $[M+Na]^+$.

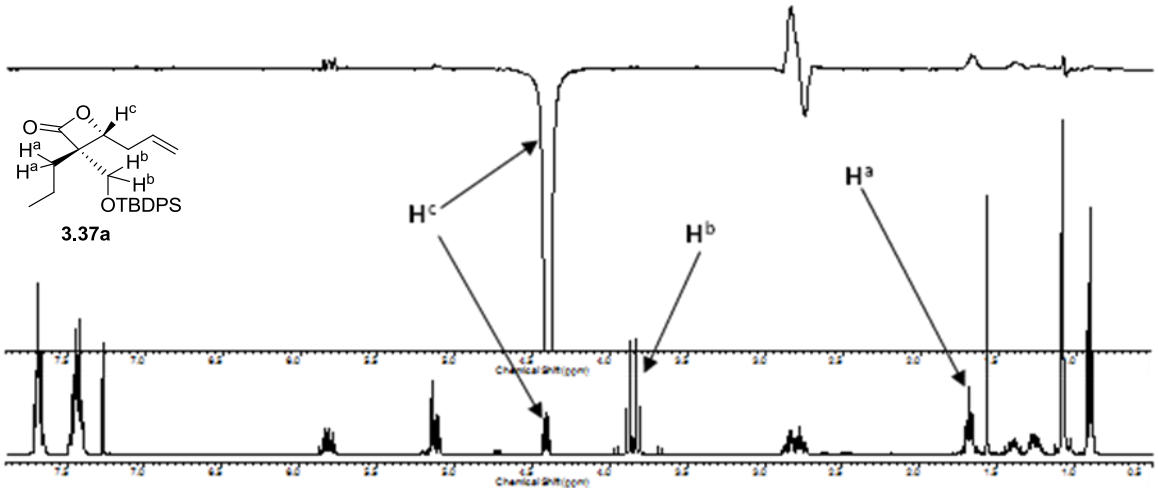


Figure 7.22. nOe experiment on **3.37a** proving the relative stereochemistry

From the nOe experiment on **3.37a** when H^c was irradiated an nOe was observed at H^a and no response at H^b so proving that H^c is on the same side of the lactone ring as the propyl chain and opposite to the $CH_2OTBDPS$ group. Therefore the relative stereochemistry of **3.37a** is as shown.

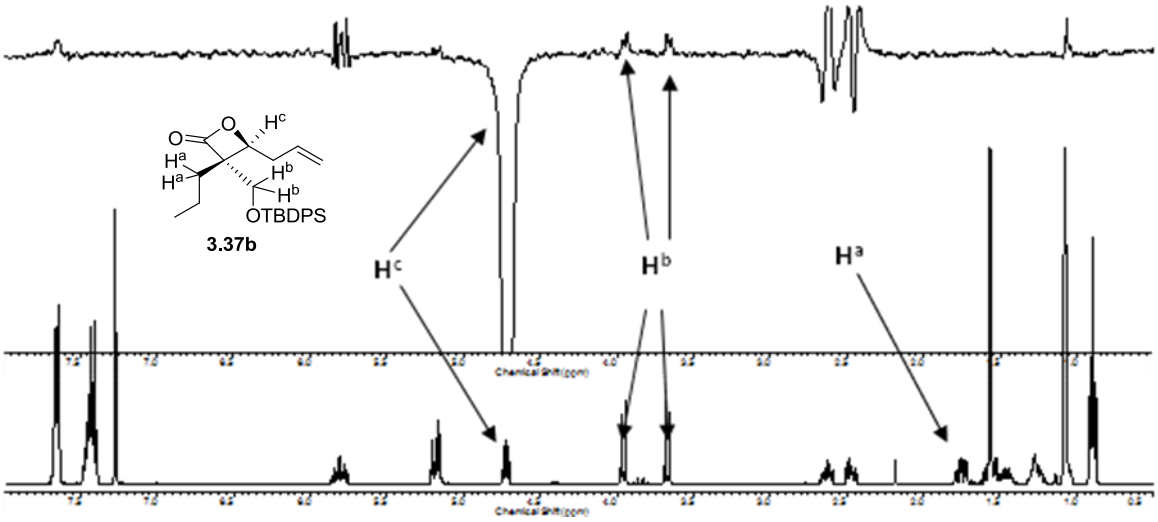
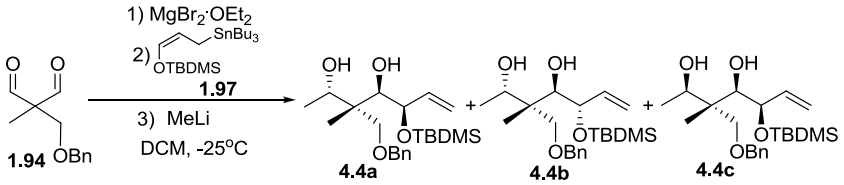


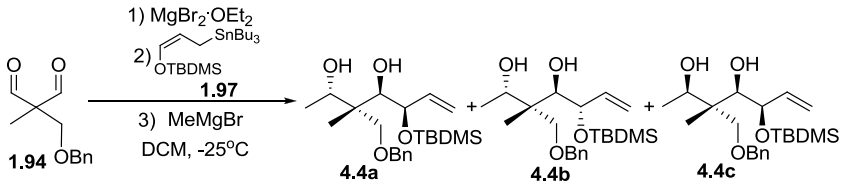
Figure 7.23 nOe experiment on **3.37b** proving the relative stereochemistry

From the nOe experiment on **3.37b**, when H^c was irradiated a nOe was observed at H^b and no response at H^a so proving that H^c is on the same side of the β-lactone ring as the $CH_2OTBDPS$ group and opposite to the propyl chain. Therefore the relative stereochemistry of **3.37b** is as shown.

(*rac*-2*S*,3*R*,4*R*,5*R*)-3-Benzyloxymethyl-5-(*tert*-butyldimethyl-silanyloxy)-3-methylhept-6-ene-2,4-diol (4.4a) and (*rac*-2*S*,3*R*,4*R*,5*S*)-3-Benzyloxymethyl-5-(*tert*-butyldimethyl-silanyloxy)-3-methylhept-6-ene-2,4-diol (4.4b) and (*rac*-2*R*,3*R*,4*R*,5*R*)-3-Benzyloxymethyl-5-(*tert*-butyldimethyl-silanyloxy)-3-methylhept-6-ene-2,4-diol (4.4c)



1,2-Dibromoethane (1.00 mL, 11.61 mmol, 3 equiv.) was added to a suspension of magnesium turnings (282 mg, 11.61 mmol, 3 equiv.) in Et_2O (12 mL) and stirred for 30 min at r.t obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (20 mL) was added and the reaction mixture was cooled to –25 °C before addition *via* cannula of dialdehyde **1.94** (800 mg, 3.87 mmol, 1 equiv.) in CH_2Cl_2 (28 mL). The reaction mixture was stirred at –25 °C for 20 min. A solution of **1.97** (3.57 mg, 7.74 mmol, 2 equiv) in CH_2Cl_2 (34 mL) at –25 °C was added *via* cannula and the reaction stirred at –25 °C for 2 h. A 1 mL aliquot was taken from the reaction mixture to determine that ratio of monoaddtition products (d.r. **1.98a**:**1.98b** 91:9). MeLi (1.6 M sol. in Et_2O) (9.68 mL, 15.48 mmol, 4 equiv) was then added dropwise. The reaction mixture was stirred at –25 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography (petroleum ether / EtOAc, 90:10) gave **4.4** as a colourless oil (772 mg, 1.96 mmol, 51%, d.r. 79:12:9). Major diastereoisomer **4.4a** (514 mg) was obtained pure after preparative HPLC (hexane / EtOAc, 95:5).



1,2-Dibromoethane (526 µL, 6.11 mmol, 3 equiv.) was added to a suspension of magnesium turnings (149 mg, 6.11 mmol, 3 equiv.) in Et_2O (7 mL) and stirred for 30 min at r.t obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (10 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of dialdehyde **1.94** (420 mg, 2.04 mmol, 1

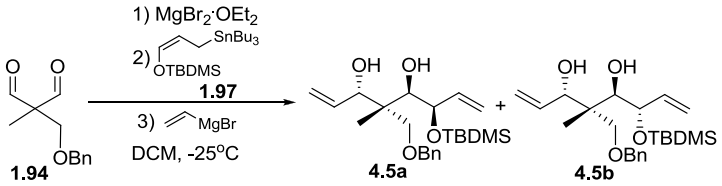
equiv.) in CH_2Cl_2 (15 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min of stirring, allyl tin **1.97** (1.88 g, 4.08 mmol, 2 equiv.) in CH_2Cl_2 (17 mL) was added *via* cannula and allowed to react for 2 h. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r. was determined by ^{1}H NMR (**1.98a**:**1.98b** 93:7). Methyl magnesium bromide (3.0 M sol. in Et_2O) (2.72 mL, 8.16 mmol, 4 equiv.) was added dropwise and the reaction mixture stirred at –25 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 456 mg (1.16 mmol, 56%, d.r 87:9:4) of **4.4** as a colourless oil. Major diastereoisomer **4.4a** (298 mg) was obtained pure after preparative HPLC (hexane / EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (5 H, m, Ar**H**), 5.94 (1 H, ddd, *J* = 17.3, 10.3, 7.9 Hz, C**H**=CH_2), 5.21 – 5.07 (2 H, m, C**H$_2$**=CH), 4.50 (1 H, d, *J* = 11.9 Hz, C**H**H**H**Ph), 4.45 (1 H, d, *J* = 11.9 Hz, C**H**H**H**Ph), 4.30 (1 H, dd, *J* = 8.0, 4.0 Hz, C**H**OTBDMS), 3.93 (1 H, t, *J* = 6.5 Hz, C**H**OHCH$_3$), 3.83 (1 H, dd, *J* = 5.8, 4.0 Hz, C**H**OHCHOTBDMS), 3.65 (1 H, d, *J* = 6.5 Hz, CHO**H**CH$_3$), 3.59 (1 H, d, *J* = 9.4 Hz, C**H**H**H**OBn), 3.46 (1 H, d, *J* = 9.5 Hz, C**H**H**H**OBn), 3.24 (1 H, d, *J* = 5.9 Hz, CHO**H**CHOTBDMS), 1.19 (3 H, d, *J* = 6.5 Hz, C**H$_3$**CHOH), 0.94 (3 H, s, CC**H$_3$**), 0.90 (9 H, s, SiC(C**H$_3$**)$_3$), 0.08 (3 H, s, SiC**H$_3$**), 0.06 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (**C**H=), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 116.2 (**C**H$_2$=), 76.2 (**C**HOHCHOTBDMS), 74.3 (**C**HOTBDMS), 73.7 (**C**H$_2$OBn), 73.5 (**C**H$_2$Ph), 72.7 (**C**HOHCH$_3$), 44.7 (CH$_3$**C**), 25.9 (SiC(**C**H$_3$)$_3$), 18.1 (**C**H$_3$CHOH), 18.1 (Si**C**(CH$_3$)$_3$), 16.5 (**C**H$_3$C), -3.4 (Si**C**H$_3$), -4.7 (Si**C**H$_3$) ppm.

This corresponds to previous data within the group[109]

(*rac*-2*S*,3*R*,4*R*,5*R*)-4-Benzyloxymethyl-6-(*tert*-butyldimethylsilanyloxy)-4-methylocta-1,7-diene-3,5-diol (4.5a) and (*rac*-2*S*,3*R*,4*R*,5*S*)-4-Benzyloxymethyl-6-(*tert*-butyldimethylsilanyloxy)-4-methylocta-1,7-diene-3,5-diol (4.5b)



1,2-Dibromoethane (1.13 mL, 13.07 mmol, 3 equiv.) was added to a suspension of magnesium (317 mg, 13.07 mmol, 3 equiv.) in Et_2O (13.5 mL) and stirred for 30 min at r.t to obtain $MgBr_2 \bullet OEt_2$. After removal of Et_2O, CH_2Cl_2 (22.5 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (900 mg, 4.36 mmol, 1 equiv.) in CH_2Cl_2 (31.5 mL). After addition of the dialdehyde the reaction mixture becomes a yellow solution. After 20 min of stirring, allyl tin **1.97** (4.02 g, 8.72 mmol, 2 equiv.) in CH_2Cl_2 (36 mL) was added *via* cannula and allowed to react for 2 h. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r. was determined by ^{1}H NMR (**1.98a**:**1.98b** 9:1). Vinyl magnesium bromide (1.0 M sol. in THF) (17.44 mL, 17.44 mmol, 4 equiv.) was added dropwise and the reaction mixture stirred at –25 °C for 45 min. The reaction was quenched with aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 1.18 g (2.90 mmol, 67% yield) of **4.5** as a colourless oil. Further purification by preparative HPLC (hexane : acetone 9:1) allowed isolation of an analytically pure sample of **4.5a** (23 mg).

Data for compound 4.5a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.23 (5 H, m, Ar**H**), 6.06 – 5.85 (2 H, m, C**H**=CH_2), 5.40 – 5.04 (4 H, m, C**H**$_2$=CH), 4.48 (1 H, d, *J* = 11.9 Hz, C**H**HPh), 4.42 (1 H, d, *J* = 12.0 Hz, CH**H**Ph), 4.35 – 4.21 (2 H, m, C**H**OHCH= & C**H**OTBDMS), 3.90 (1 H, dd, *J* = 6.1, 3.7 Hz, C**H**OHCHOTBDMS), 3.83 (1 H, d, *J* = 7.6 Hz, CHO**H**CH=), 3.55 (1 H, d, *J* = 9.4 Hz, C**H**HOBn), 3.41 (1 H, d, *J* = 9.5 Hz, C**H**HOBn), 3.22 (1 H, d, *J* = 6.1 Hz, CHO**H**CHOTBDMS), 0.97 (3 H, s, CC**H**$_3$), 0.91 (9 H, s, SiC(C**H**$_3$)$_3$), 0.08 (3 H, s, SiC**H**$_3$), 0.06 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0 (**C**H=), 137.7 (Ar**C**), 137.6 (**C**H=), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 116.2 (**C**H_2=), 116.1 (**C**H_2=), 77.9 (**C**HOTBDMS), 75.2 (**C**HOHCH=), 74.1

(**C**H_2Ph), 73.7 (**C**HOTBDMS), 73.4 (**C**H_2OBn), 44.7 (CH_3**C**), 25.9 (SiC(**C**H_3)$_3$), 18.0 (**C**H_3C), 15.9 (Si**C**(CH_3)$_3$), -3.4 (Si**C**H_3), -4.7(Si**C**H_3) ppm.

This corresponds to previous data[109]

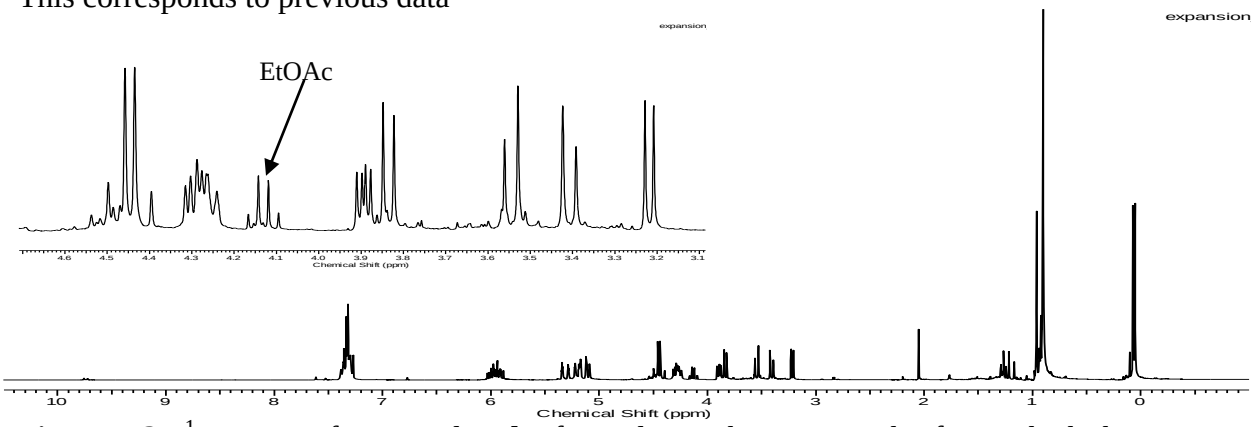
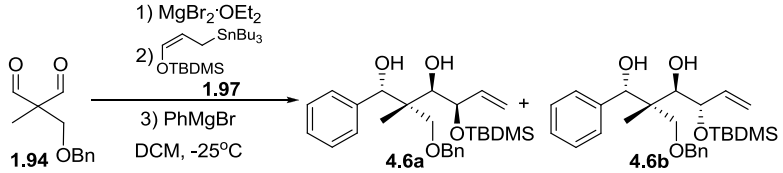


Figure 7.24 ^{1}H NMR of **4.5a** and **4.5b** after column chromatography from which the major and minor diastereoisomers could not be distinguished enough to determine a d.r by integration.

(*rac*-2*S*,3*R*,4*R*,5*R*)-2-Benzyloxymethyl-4-(*tert*-butyldimethylsilanyloxy)-2-methyl-1-phenylhex-5-ene-1,3-diol (4.6a) and (*rac*-2*S*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-4-(*tert*-butyldimethylsilanyloxy)-2-methyl-1-phenylhex-5-ene-1,3-diol (4.6b)



1,2-Dibromoethane (532 µL, 6.18 mmol, 3 equiv.) was added to a suspension of magnesium turnings (150 mg, 6.18 mmol, 3 equiv.) in Et_2O (6.5 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (11 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (425 mg, 2.06 mmol, 1 equiv.) in CH_2Cl_2 (15 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min of stirring, allyl tin **1.97** (1.90 g, 4.12 mmol, 2 equiv.) in CH_2Cl_2 (17 mL) was added *via* cannula and allowed to react for 2 h 30 min. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give the crude, from which the d.r was determined by ^{1}H NMR (**1.98a**:**1.98b** 90:10). Phenyl magnesium bromide (1.0 M sol. in THF) (8.24 mL, 8.24 mmol, 4 equiv.) was added dropwise and the reaction mixture warmed

to –20 °C and stirred for 15 min. The reaction was quenched with sat. aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography with petroleum ether / EtOAc 9:1 to give 560 mg (1.23 mmol, 60% yield, d.r 9:1, Figure 7.25) of **4.6** as a waxy white solid. Further purification by preparative HPLC (hexane : acetone 9:1) allowed isolation of an analytically pure sample of **4.6a** (19 mg).

Data for compound 4.6a: IR (neat): 3417 (br), 3063 (w), 3030 (w), 2953 (m), 2928 (s), 2884 (m), 2856 (s), 1495 (w), 1471 (m) 1454 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.18 (10 H, m, Ar**H**), 5.95 (1 H, ddd, *J* = 17.3, 10.2, 8.0 Hz, C**H**=CH_2), 5.06 – 5.18 (2 H, m, C**H**$_2$=CH), 4.94 (1 H, d, *J* = 7.8 Hz, C**H**OHPh), 4.63 (1 H, d, *J* = 7.8 Hz, CHO**H**Ph), 4.49 (1 H, d, *J* = 11.8 Hz, C**H**H**H**Ph), 4.43 (1 H, d, *J* = 11.7 Hz, C**H**H**H**Ph), 4.31 (1 H, dd, *J* = 8.0, 3.6 Hz, C**H**OTBDMS), 4.02 (1 H, dd, *J* = 6.0, 3.6 Hz, C**H**OHCHOTBDMS), 3.50 (1 H, d, *J* = 9.5 Hz, C**H**H**H**OBn), 3.34 (1 H, d, *J* = 6.1 Hz, CHO**H**CHOTBDMS), 3.23 (1 H, d, *J* = 9.5 Hz, C**H**H**H**OBn), 0.90 (9 H, s, SiC(C**H$_3$**)$_3$), 0.88 (3 H, s, CC**H$_3$**), 0.06 (3 H, s, SiC**H$_3$**), 0.06 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4 (Ar**C**), 140.1 (**C**H=), 137.5 (Ar**C**), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 127.1 (Ar**C**H), 116.2 (**C**H_2=), 79.4 (**C**HOHPh), 74.8 (**C**HOHCHOTBDMS), 74.2 (**C**HOTBDMS), 73.5 (**C**H_2Ph), 73.0 (**C**H_2OBn), 45.1 (CH_3**C**), 25.9 (SiC(**C**H_3)$_3$), 18.1 (**C**H_3C), 16.4 (Si**C**$(CH_3)_3$), -3.4 (Si**C**H_3), -4.6 (Si**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 479 $[M+Na]^+$ (49%), 935 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 479.2588 $[M+Na]^+$; found: 479.2585 $[M+Na]^+$.

Mp: 49 – 51 °C.

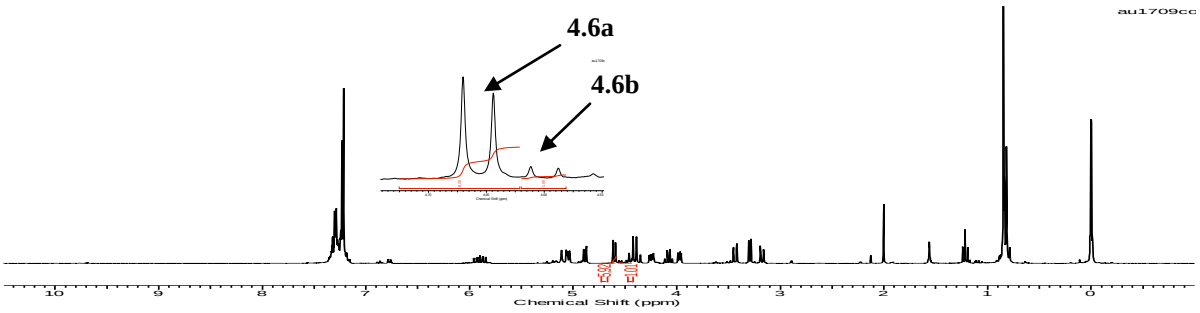
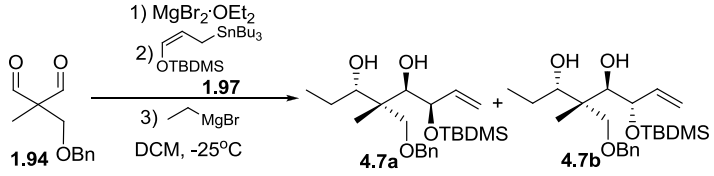


Figure 7.25 ^{1}H NMR of **4.6a** and **4.6b** after column chromatography showing how the d.r was calculated.

(*rac*-2*S*,3*R*,4*R*,5*R*)-4-Benzyloxymethyl-6-(*tert*-butyldimethylsilanyloxy)-4-methyloct-7-ene-3,5-diol (4.7a) and (*rac*-2*S*,3*R*,4*R*,5*S*)-4-Benzyloxymethyl-6-(*tert*-butyldimethylsilanyloxy)-4-methyloct-7-ene-3,5-diol (4.7b)



1,2-Dibromoethane (501 µL, 5.81 mmol, 3 equiv.) was added to a suspension of magnesium turnings (141 mg, 5.81 mmol, 3 equiv.) in Et_2O (6 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (10 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (395 mg, 1.91 mmol, 1 equiv.) in CH_2Cl_2 (14 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min of stirring, allyl tin **1.97** (1.76 g, 3.88 mmol, 2 equiv.) in CH_2Cl_2 (16 mL) was added *via* cannula and allowed to react for 2 h 30 min. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r was determined by ^{1}H NMR (**1.98a**:**1.98b** 89:11). Ethyl magnesium bromide (1.0 M sol. in THF) (7.76 mL, 7.76 mmol, 4 equiv.) was added dropwise and the reaction mixture warmed to –20 °C and stirred for 15 min. The reaction was quenched with sat. aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 485 mg (1.13 mmol, 59% yield, d.r

88:12, Figure 7.26) of **4.7** as a colourless oil. Further purification by preparative HPLC (hexane : acetone 92:8) isolated an analytically pure sample of **4.7a** (22 mg).

Data for compound 4.7a: IR (neat): 3456 (br), 2955 (m), 2929 (s), 2857 (m), 1497 (w), 1471 (m) 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (5 H, m, Ar**H**), 5.95 (1 H, ddd, *J* = 17.3, 10.2, 8.0 Hz, C**H**=CH_2), 5.21 – 5.02 (2 H, m, C**H$_2$**=CH), 4.49 (1 H, d, *J* = 11.9 Hz, C**H**HPh), 4.43 (1 H, d, *J* = 11.9 Hz, CH**H**Ph), 4.31 (1 H, dd, *J* = 8.0, 3.8 Hz, C**H**OTBDMS), 3.83 (1 H, dd, *J* = 6.0, 3.8 Hz, C**H**OHCHOTBDMS), 3.61 – 3.52 (2 H, m, C**H**OHCH_2 and C**H**HOBn), 3.47 – 3.39 (2 H, m, CH**H**OBn and CHO**H**CH_2), 3.28 (1 H, d, *J* = 5.9 Hz, CHO**H**CHOTBDMS), 1.65 – 1.51 (1 H, m, C**H**HCH_3), 1.42 – 1.28 (1 H, m, CH**H**CH_3), 1.03 (3 H, t, *J* = 7.3 Hz, C**H$_3$**CH_2), 0.95 (3 H, s, CC**H$_3$**), 0.91 (9 H, s, SiC(C**H$_3$**)$_3$), 0.08 (3 H, s, SiC**H$_3$**), 0.06 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (**C**H=), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.6 (Ar**C**H), 116.1 (**C**H_2=), 78.6 (**C**HOHCH_2), 76.5 (**C**HOHCHOTBDMS), 74.3 (**C**HOTBDMS), 73.8 (**C**H_2OBn), 73.5 (**C**H_2Ph), 44.8 (CH_3**C**), 25.9 (SiC(**C**H_3)$_3$), 24.7 (**C**H_2CH_3), 18.0 (Si**C**(CH_3)$_3$), 16.7 (**C**H_3C), 11.6 (**C**H_3CH_2), -3.4 (Si**C**H_3), -4.6 (Si**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 431 $[M+Na]^+$ (61%), 839 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 431.2588 $[M+Na]^+$; found: 431.2583 $[M+Na]^+$.

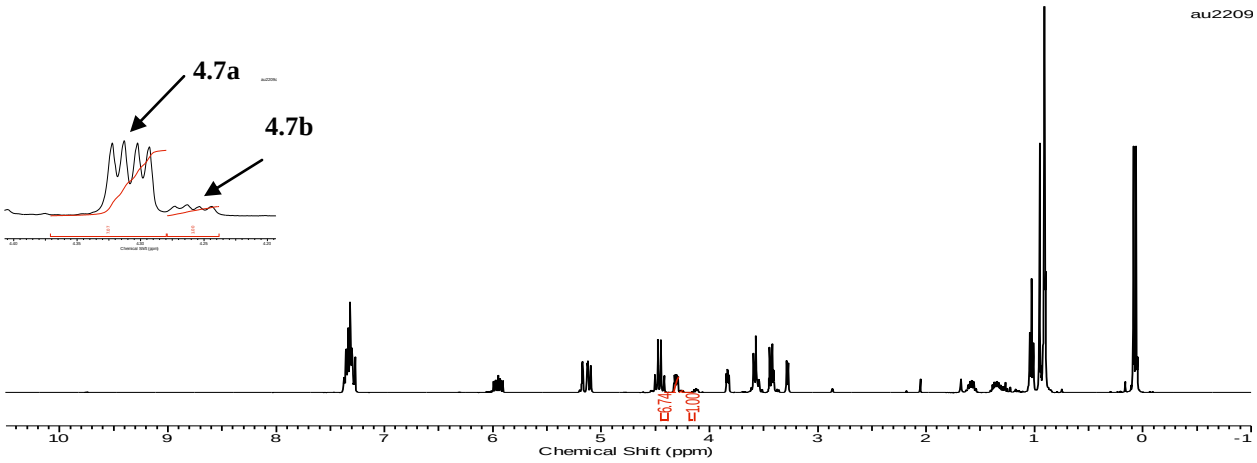
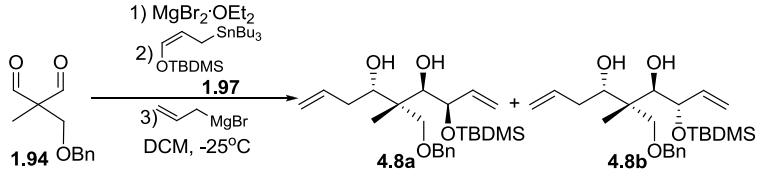


Figure 7.26 ^{1}H NMR of **4.7a** and **4.7b** after column chromatography from which the d.r was calculated.

(*rac*-2*S*,3*R*,4*R*,5*R*)-5-Benzyloxymethyl-3-(*tert*-butyldimethylsilanyloxy)-5-methylnona-1,8-diene-4,6-diol (4.8a) and (*rac*-2*S*,3*R*,4*R*,5*S*)-5-Benzyloxymethyl-3-(*tert*-butyldimethylsilanyloxy)-5-methylnona-1,8-diene-4,6-diol (4.8b).



1,2-Dibromoethane (527 µL, 6.11 mmol, 3 equiv.) was added to a suspension of magnesium turnings (149 mg, 6.11 mmol, 3 equiv.) in Et_2O (6.5 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (10 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (420 mg, 2.04 mmol, 1 equiv.) in CH_2Cl_2 (15 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min of stirring, allyl tin **1.97** (1.89 g, 4.07 mmol, 2 equiv.) in CH_2Cl_2 (17 mL) was added *via* cannula and allowed to react for 2 h 30 min. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give the crude, from which the d.r. was determined by ^{1}H NMR (**1.98a**:**1.98b** 9:1). Allyl magnesium bromide (1.0 M sol. in Et_2O) (8.15 mL, 8.15 mmol, 4 equiv.) was added dropwise and the reaction mixture warmed to –15 °C and stirred for 15 min. The reaction was quenched with sat. aq. NH_4Cl and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 436 mg (1.04 mmol, 51% yield) of **4.8** as a colourless oil. The ratio of diastereoisomers could not be determined by ^{1}H NMR (Figure 7.27). Further purification by preparative HPLC (hexane / acetone 92:8) allowed isolation of an analytically pure sample of **4.8a** (17 mg).

Data for compound 4.8a: IR (neat): 3454 (br), 3073 (w), 2953 (m), 2929 (s), 2885 (m), 2857 (s), 1640 (w), 1497 (w), 1471 (m) 1462 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (5 H, m, Ar**H**), 6.02 – 5.87 (2 H, m, C**H**=CH_2), 5.21 – 5.02 (4 H, m, C**H$_2$**=CH), 4.50 (1 H, d, *J* = 12.0 Hz, C**H**HPh), 4.45 (1 H, d, *J* = 11.9 Hz, C**H**HPh), 4.31 (1 H, dd, *J* = 8.0, 3.8 Hz, C**H**OTBDMS), 3.86 – 3.72 (2 H, m, C**H**OHCHOTBDMS and C**H**OHCH_2), 3.58 (1 H, d, *J* = 9.4 Hz, C**H**HOBn), 3.47 (1 H, d, *J* = 9.4 Hz, C**H**HOBn), 3.40 (1 H, d, *J* = 6.3 Hz, CHO**H**), 3.30 (1 H, d, *J* = 6.0 Hz, CHO**H**), 2.44

– 2.32 (1 H, m, C**H**HCH_3), 2.22 – 2.08 (1 H, m, C**H**HCH_3), 0.98 (3 H, s, CC$\underline{\mathbf{H_3}}$), 0.90 (9 H, s, SiC(C$\underline{\mathbf{H_3}}$)$_3$), 0.08 (3 H, s, SiC$\underline{\mathbf{H_3}}$), 0.06 (3 H, s, SiC$\underline{\mathbf{H_3}}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (**C**H=CH_2), 137.9 (Ar**C**), 137.0 (**C**H=CH_2), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 116.3 (**C**H_2=), 116.2 (**C**H_2=), 76.5 (**C**HOH), 76.3 (**C**HOH), 74.3 (**C**HOTBDMS), 73.6 (**C**H_2OBn), 73.5 (**C**H_2Ph), 44.7 (CH_3**C**), 36.9 (**C**H_2CH=), 25.9 (SiC(**C**H_3)$_3$), 18.1 (Si**C**(CH_3)$_3$), 16.6 (**C**H_3C), -3.4 (Si**C**H_3), -4.6 (Si**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 443 $[M+Na]^+$ (49%), 864 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 443.2588 $[M+Na]^+$; found: 443.2576 $[M+Na]^+$.

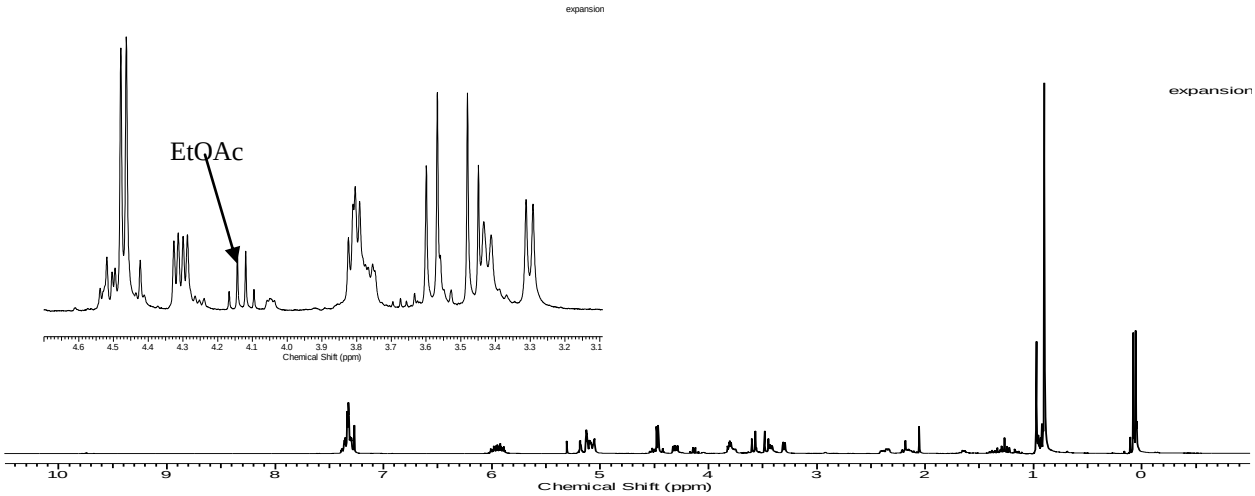
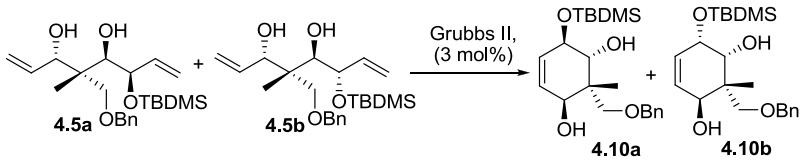


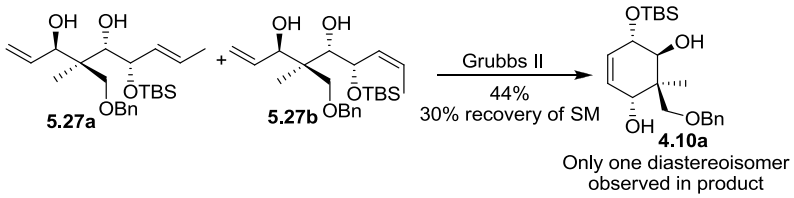
Figure 7.27 ^{1}H NMR of **4.8a** and **4.8b** after column chromatography from which the major and minor diastereoisomers could not be distinguished enough to determine a d.r by integration.

(*rac*-1*R*,2*R*,3*S*,6*R*)-2-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-cyclohex-4-ene-1,3-diol (4.10a) & (*rac*-1*R*,2*R*,3*S*,6*S*)-2-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-cyclohex-4-ene-1,3-diol (4.10b)



Grubbs 2nd generation catalyst [156, 157] (47 mg, 0.06 mmol, 3 equiv.) was added to a solution of a mixture of the major and minor diastereoisomers of diol **4.5a** and **4.5b** (750 mg, 1.84

mmol, 1 equiv.) in refluxing benzene (15 mL). The brown suspension was stirred at 70 °C for 45 min. The solution was allowed to cool to r.t and concentrated in *vacuo* to give crude brown oil. The crude was purified by column chromatography (petroleum ether / EtOAc 8:2) to separate the major diastereoisomer **4.10a** (505 mg) and minor diastereoisomer **4.10b** (70 mg) (overall yield, 575mg, 1.52 mmol, 83%).



Grubbs 2nd generation catalyst (6 mg, 0.007 mmol, 0.03 equiv.) was added to a solution of diols **5.27a** and **5.27b** (100 mg, 0.24 mmol, 1 equiv.) in refluxing toluene (4 mL). The brown suspension was stirred at 70 °C for 5 h. The solution was allowed to cool to r.t and concentrated in *vacuo* to give crude brown oil. The crude was purified by column chromatography with petroleum ether / EtOAc 8:2 to give **4.10a** (40 mg, 0.11 mmol, 44%).

Data for compound 4.10a: IR (neat): 3426 (br), 3031 (w), 2953 (m), 2928 (s), 2856 (s), 1497 (w), 1471 (m) 1455 (m) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.23 (5H, m, Ar**H**), 5.71 (1H, dd, *J* = 10.2, 1.5 Hz, =C**H**CHOH), 5.64 (1H, d, *J* = 10.2 Hz, =C**H**CHOTBDMS), 4.57 (1H, d, *J* = 11.9 Hz, C**H**HPh), 4.53 (1H, d, *J* = 11.9 Hz, C**H**HPh), 4.34 (1H, br. s., =CHC**H**OH), 4.00 (1H, d, *J* = 3.0 Hz, C**H**OTBDMS), 3.77 (1H, d, *J* = 3.5 Hz, CHCHO**H**), 3.72 (1H, t, *J* = 3.6 Hz, CHC**H**OH), 3.67 (1H, d, *J* = 9.0 Hz, C**H**HOBn), 3.44 (1H, d, *J* = 9.2 Hz, C**H**HOBn), 1.80 (1H, d, *J* = 6.3 Hz, =CHCHO**H**), 1.04 (3H, s, CC**H$_3$**), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 0.11 (3H, s, SiC**H$_3$**), 0.10 (3H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4 (Ar**C**), 129.5 (=**C**HCHOH), 129.3 (=**C**HCHOTBDMS), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 78.3 (CH**C**HOH), 76.0 (**C**H$_2$OBn), 73.8 (**C**H$_2$Ph), 70.9 (**C**HOTBDMS), 67.7 (=CH**C**H), 41.5 (**C**CH$_3$), 25.7 (SiC(**C**H$_3$)$_3$), 18.0 (Si**C**(CH$_3$)$_3$), 15.6 (C**C**H$_3$), -4.7 (Si**C**H$_3$), -4.8 (Si**C**H$_3$) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 401 $[M+Na]^+$ (100%), 779 $[2M+Na]^+$ (49%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 401.2119 $[M+Na]^+$; found: 401.2114 $[M+Na]^+$.

Data for compound 4.10b: IR (neat): 3539 (br), 3031 (w), 2953 (m), 2929 (s), 2883 (m), 2857 (s), 1497 (w), 1471 (m) 1454 (w) cm^{-1}.

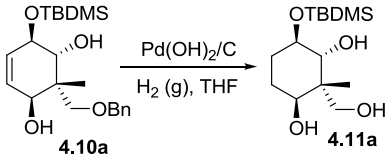
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.21 (5H, m, Ar**H**), 5.70 (1H, dt, *J* = 10.3, 2.0 Hz, =C**H**CHOH), 5.44 (1H, dq, *J* = 10.3, 2.0 Hz, =C**H**CHOTBDMS), 4.63 (1H, d, *J* = 12.1 Hz, C**H**HPh), 4.60 – 4.52 (2H, m, C**H**HPh and =CHC**H**OH), 4.34 (1H, dd, *J* = 3.7, 2.4 Hz, C**H**OHCHOTBDMS), 4.06 (1H, d, *J* = 8.5 Hz, C**H**HOBn), 3.54 (1H, dd, *J* = 3.6, 1.6 Hz, C**H**OTBDMS), 3.46 (1H, d, *J* = 8.4 Hz, C**H**HOBn), 3.00 (1H, d, *J* = 2.3 Hz, =CHO**H**), 2.83 (1H, s, CHO**H**CHOTBDMS), 0.99 (3H, s, CC**H**$_3$), 0.92 (9H, s, SiC(C**H**$_3$)$_3$), 0.14 (3H, s, SiC**H**$_3$), 0.12 (3H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8 (Ar**C**), 131.4 (=**C**HCHOH), 128.5 (Ar**C**H), 127.8 (Ar**C**H), 127.6 (Ar**C**H), 126.3 (=**C**HCHOTBDMS), 78.2 (**C**H$_2$OBn), 74.1 (**C**HOTBDMS), 73.8 (**C**H$_2$Ph), 70.6 (=CH**C**HOH), 67.7 (**C**HOHCHOTBDMS), 44.2 (**C**CH$_3$), 25.7 (SiC(**C**H$_3$)$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 13.8 (C**C**H$_3$), -4.6 (Si**C**H$_3$), -4.9 (Si**C**H$_3$) ppm.

LRMS (ESI +): $^m/_z$ (rel. intensity) 401 $[M+Na]^+$ (71%), 779 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 401.2119 $[M+Na]^+$; found: 401.2117 $[M+Na]^+$.

(*rac*-1*S*,2*R*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxymethyl-2-methyl-cyclohexane-1,3-diol (4.11a)



To a suspension of $Pd(OH)_2/C$ (36 mg, 0.18 equiv. by weight) in THF (10 mL) was added diol **4.10a** (200 mg, 0.53 mmol, 1 equiv.). The flask was evacuated and purged with H_2 (g) and stirred at r.t overnight. The reaction mixture was filtered through celite with Et_2O and concentrated in *vacuo* to give a white solid. The crude white solid was recrystallised from diisopropyl ether and hexane to give **4.11a** as a fine white crystalline solid (115 mg, 0.40 mmol, 75%).[140]

Data for compound 4.11a: IR (neat): 3335 (br), 2953 (s), 2930 (s), 2885 (m), 2857 (m), 1471 (m) 1454 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (1 H, dd, *J* = 11.0, 2.8 Hz, C**H**HOH), 3.79 (1 H, td, *J* = 7.4, 4.1 Hz, C**H**OTBDMS), 3.73 (1 H, br. s., CH_2C**H**OH), 3.67 (1 H, d, *J* = 6.8 Hz, C**H**OHCHOTBDMS), 3.37 (1 H, dd, *J* = 10.9, 8.2 Hz, C**H**HOH), 3.14 (1 H, dd, *J*=7.9, 2.9

Hz, $CH_2O\underline{\mathbf{H}}$), 2.98 (1 H, s, CHO**H**CHOTBDMS), 1.89 – 1.56 (5 H, m, $C\underline{\mathbf{H}_2}C\underline{\mathbf{H}_2}$ and $CH_2CHO\underline{\mathbf{H}}$), 1.21 (3 H, s, $CC\underline{\mathbf{H}_3}$), 0.90 (9 H, s, $SiC(C\underline{\mathbf{H}_3})_3$), 0.10 (6 H, s, $Si(C\underline{\mathbf{H}_3})_2$ ppm.

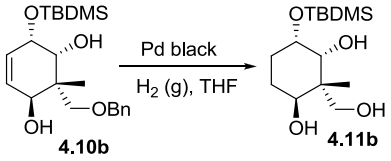
^{13}C NMR (100 MHz, $CDCl_3$): δ 79.9 (**C**HOHCHOTBDMS), 72.5 (**C**HOTBDMS), 70.9 ($CH_2\underline{\mathbf{C}}HOH$), 68.1 ($\underline{\mathbf{C}}H_2OH$), 43.5 ($\underline{\mathbf{C}}CH_3$), 27.9 ($\underline{\mathbf{C}}H_2CH_2$), 26.9 ($CH_2\underline{\mathbf{C}}H_2$), 25.8 ($SiC(\underline{\mathbf{C}}H_3)_3$), 17.9 ($C\underline{\mathbf{C}}H_3$), 16.9 ($Si\underline{\mathbf{C}}(CH_3)_3$), -4.3 ($Si\underline{\mathbf{C}}H_3$), -4.8 ($Si\underline{\mathbf{C}}H_3$) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 313 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 313.1806 $[M+Na]^+$; found: 313.1808 $[M+Na]^+$.

Mp: 137 –138 °C

(*rac*-1*S*,2*R*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxymethyl-2-methyl-cyclohexane-1,3-diol (4.11b).



To a suspension of Pd black (14 mg, 0.18 equiv. by weight) in THF (4 mL) was added **4.10b** (80 mg, 0.21 mmol, 1 equiv.). The flask was evacuated and purged with H_2 (g) and stirred at r.t overnight. The reaction mixture was filtered through celite with Et_2O and concentrated in *vacuo* to give a colourless oil. The crude was purified by column chromatography (petroleum ether / EtOAc 6:4) to give a colourless oil which was triturated with hexane to give a white solid. The white solid was recrystallised from diisopropyl ether and hexane to give **4.11b** as a fine white crystalline solid (22 mg, 0.08 mmol, 38%). [140]

Data for compound 4.11b: IR (neat): 3373 (br), 2953 (s), 2930 (s), 2883 (m), 2857 (s), 1471 (m) 1454 (m) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (1H, ddd, *J* = 11.8, 7.5, 3.8 Hz, $CH_2C\underline{\mathbf{H}}OH$), 3.88 (1H, ddd, *J* = 10.8, 5.4, 3.1 Hz, C**H**OTBDMS), 3.75 (1H, dd, *J* = 11.2, 1.4 Hz, C**HH**OH), 3.67 – 3.56 (2H, m, C**HH**OH, C**H**OHCHOTBDMS), 3.44 (1H, dd, *J* = 9.5, 1.9 Hz, CHO**H**CHOTBDMS), 2.73 (1H, s, $CH_2O\underline{\mathbf{H}}$), 2.54 (1H, d, *J* = 3.8 Hz, $CH_2CHO\underline{\mathbf{H}}$), 1.84 – 1.45 (4H, m, $C\underline{\mathbf{H}_2}C\underline{\mathbf{H}_2}$), 0.89 (9H, s, $SiC(C\underline{\mathbf{H}_3})_3$), 0.82 (3H, s, $CC\underline{\mathbf{H}_3}$), 0.08 (6H, s, $Si(C\underline{\mathbf{H}_3})_2$) ppm.

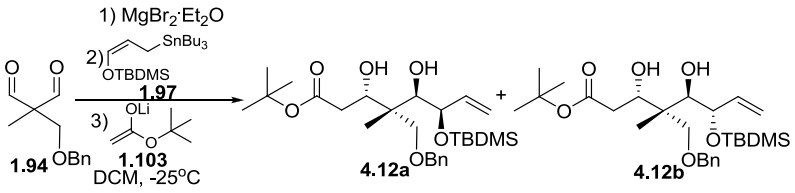
^{13}C NMR (100 MHz, $CDCl_3$): δ 79.7 (**C**HOHCHOTBDMS), 70.1 (**C**H_2OH), 69.4 (**C**HOTBDMS), 67.2 (CH_2**C**HOH), 42.8 (**C**CH_3), 27.5 (**C**H_2**C**H_2), 25.7 (SiC(**C**$H_3)_3$), 18.0 (Si**C**$(CH_3)_3$), 13.0 (C**C**H_3), -4.6 (Si**C**H_3), -4.9 (Si**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 313 $[M+Na]^+$ (70%), 603 $[2M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 313.1806 $[M+Na]^+$; found: 313.1801 $[M+Na]^+$.

Mp: 64 – 66 °C.

(*rac*-3*S*,4*R*,5*R*,6*R*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-4-methyl-oct-7-enoic acid *tert*-butyl ester (4.12a) & (*rac*-3*S*,4*R*,5*R*,6*S*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-4-methyl-oct-7-enoic acid *tert*-butyl ester (4.12b)



1,2-Dibromoethane (1.23 mL, 14.24 mmol, 3 equiv.) was added to a suspension of magnesium turnings (347 mg, 14.24 mmol, 3 equiv.) in Et_2O (15 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of Et_2O, CH_2Cl_2 (25 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula, of dialdehyde **1.94** (980 mg, 4.75 mmol, 1 equiv.) in CH_2Cl_2 (33 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min, allyl tin **1.97** (4.38 g, 9.50 mmol, 2 equiv.) in CH_2Cl_2 (40 mL) was added *via* cannula and allowed to react for 2 h. An aliquot was removed, hydrolysed with aqueous $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r was determined by ^{1}H NMR (**1.98a**:**1.98b** 92:8). Seperately to DIPA (2.13 mL, 15.21 mmol, 3.2 equiv.) in THF (18 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes) (6.08 mL, 15.21 mmol, 3.2 equiv). After 15 min *t*-butyl acetate (1.91 mL, 14.24 mmol, 3 equiv.) was added and the reaction stirred at –78 °C for 15 min to form the lithium enolate. The lithium enolate at –78 °C was added *via* cannula to the hydroxyallylation reaction and stirred at –25 °C for 10 min. The reaction was quenched with aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, filtered and

concentrated in *vacuo*. The crude mixture was purified by column chromatography with petroleum ether / EtOAc 9:1 to give 1.52 g (3.07 mmol, 64% yield) of a colourless oil (d.r on the chromatographed product 94:6, Figure 7.28). An analytical sample of major diastereoisomer **4.12a** (23 mg) was obtained cleanly after preparative HPLC (hexane:acetone 95:5) and 1.36 g of a mixture of **4.12a** and **4.12b** was obtained after HPLC.

Data for compound 4.12a: IR (neat): 3481 (br. m), 2930 (m), 2858 (m), 1728 (s), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (5 H, m, Ar**H**), 5.95 (1 H, ddd, *J* = 17.6, 10.0, 7.8 Hz, C**H**=CH_2), 5.15 (1 H, d, *J* = 17.2 Hz, CH=C**HH**), 5.10 (1 H, d, *J* = 10.6 Hz, CH=C**HH**), 4.49 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.43 (1 H, d, *J* = 11.6 Hz, C**HH**Ph), 4.32 (1 H, dd, *J* = 8.1, 3.5 Hz, C**H**OTBDMS), 4.22 (1 H, ddd, *J* = 10.6, 6.1, 2.5 Hz, C**H**OHCH_2), 3.75 (1 H, d, *J* = 5.6 Hz, CHO**H**CH_2), 3.70 (1 H, dd, *J* = 6.6, 3.5 Hz, C**H**OHCHOTBDMS), 3.55 (1 H, d, *J* = 9.6 Hz, C**HH**OBn), 3.47 (1 H, d, *J* = 9.6 Hz, C**HH**OBn), 3.36 (1 H, d, *J* = 6.6 Hz, CHO**H**), 2.60 (1 H, dd, *J* = 15.2, 2.0 Hz, C**HH**COO), 2.41 (1 H, dd, *J* = 15.7, 10.6 Hz, C**HH**COO), 1.47 (9 H, s, OC(C**H$_3$**)$_3$), 0.96 (3 H, s, CC**H$_3$**), 0.90 (9 H, s, SiC(C**H$_3$**)$_3$), 0.07 (3 H, s, SiC**H$_3$**), 0.05 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (**C**OO*t*Bu), 140.0 (**C**H=CH_2), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.6 (Ar**C**H), 116.1 (CH=**C**H_2), 80.6 (O**C**$(CH_3)_3$), 76.7 (**C**HOH), 74.4 (**C**HOTBDMS), 73.8 (**C**HOH), 73.4 (**C**H_2Ph & **C**H_2OBn), 44.5 (CH_3**C**), 39.1 (**C**H_2COO), 28.1 (OC(**C**$H_3)_3$), 25.9 (SiC(**C**$H_3)_3$), 18.1 (Si**C**$(CH_3)_3$), 16.1 (**C**H_3C), -3.5 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 517 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 517.2956 $[M+Na]^+$; found: 517.2952 $[M+Na]^+$.

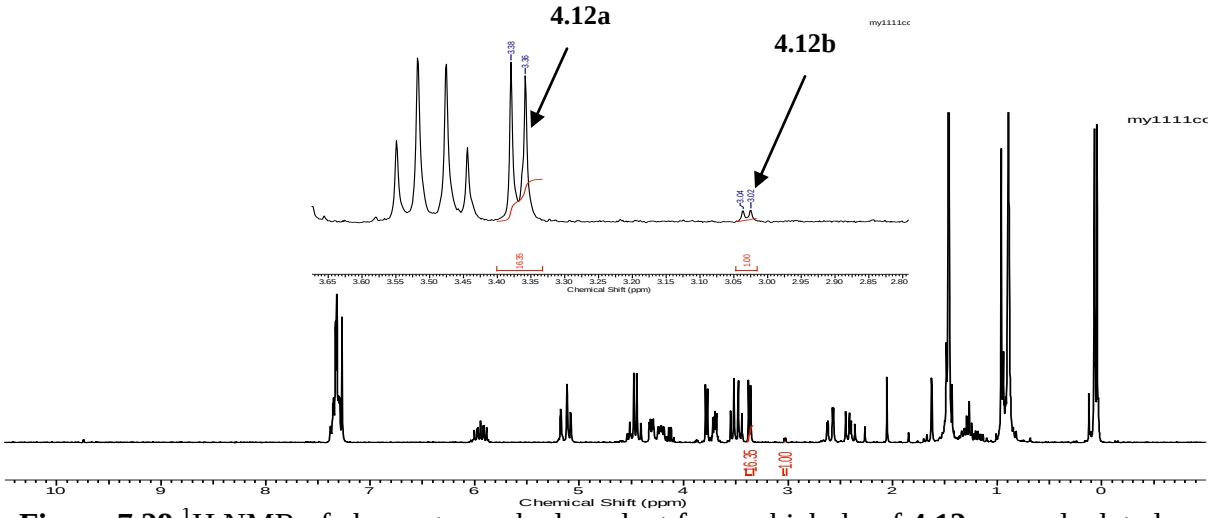
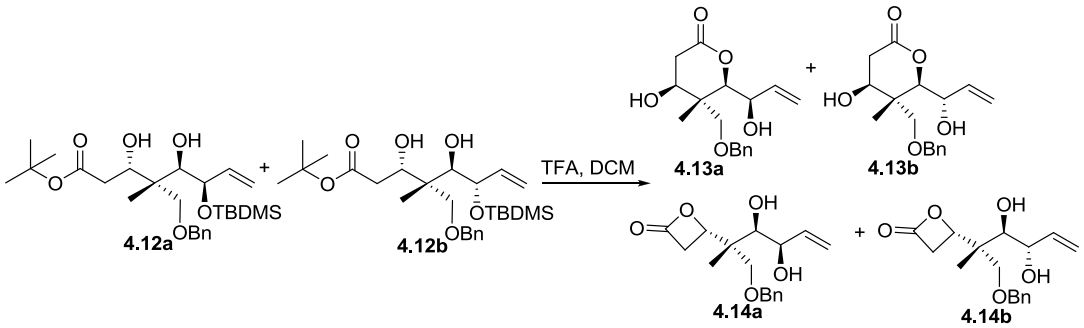


Figure 7.28 ^{1}H NMR of chromatographed product from which d.r of **4.12** was calculated.

(*rac*-4*S*,5*R*,6*R*)-5-Benzyloxymethyl-4-hydroxy-6-((*R*)-1-hydroxy-allyl)-5-methyl-tetrahydro-pyran-2-one (4.13a) & (*rac*-4*S*,5*R*,6*R*)-5-Benzyloxymethyl-4-hydroxy-6-((*S*)-1-hydroxy-allyl)-5-methyl-tetrahydro-pyran-2-one (4.13b) & *Rac*-(*S*)-4-((1*S*,2*R*,3*R*)-1-Benzyloxymethyl-2,3-dihydroxy-1-methyl-pent-4-enyl)-oxetan-2-one (4.14a) & *Rac*-(*S*)-4-((1*S*,2*R*,3*S*)-1-Benzyloxymethyl-2,3-dihydroxy-1-methyl-pent-4-enyl)-oxetan-2-one (4.14b)



TFA (8.74 mL, 117.64 mmol, 60 equiv.) was added to a solution of ester **4.12a** and **4.12b** (970 mg, 1.96 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) and the reaction stirred at r.t for 16 h. The reaction mixture was concentrated in *vacuo* and the resultant crude oil purified by column chromatography (1:1 petroleum ether / EtOAc) to give 200 mg (0.65 mmol, 33% yield) of **4.13** as a colourless oil and 241 mg (0.79 mmol, 40% yield) of **4.14** as a colourless oil. Further purification by preparative HPLC (hexane / acetone 57:43) isolated an analytical

sample of **4.13a** (14 mg) and purification by preparative HPLC (hexane / acetone 75:25) isolated an analytically pure sample of **4.14a** (13 mg).

Data for compound 4.13a: IR (neat): 3401 (br. s), 2866 (m), 1721 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.28 (5 H, m, Ar**H**), 6.01 (1 H, ddd, *J* = 17.1, 10.5, 6.3 Hz, C**H**=CH_2), 5.33 (1 H, d, *J* = 17.2 Hz, C**H**H=CH), 5.26 (1 H, d, *J* = 10.6 Hz, CH=CH**H**), 4.54 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.49 (1 H, d, *J* = 12.1 Hz, CH**H**Ph), 4.32 (1 H, dd, *J* = 6.3, 1.3 Hz, C**H**OHCH), 4.22 (1 H, d, *J* = 2.0 Hz, C**H**OCO), 4.11 (1 H, t, *J* = 7.1 Hz, C**H**OHCH_2), 3.53 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.45 (1 H, d, *J* = 9.1 Hz, CH**H**OBn), 2.93 (1 H, dd, *J* = 18.9, 7.3 Hz, C**H**HCO), 2.60 (1 H, dd, *J* = 18.7, 6.6 Hz, CH**H**CO), 1.11 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (**C**OO), 137.5 (**C**H=CH_2), 137.3 (Ar**C**), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.7 (Ar**C**H), 117.5 (CH=**C**H_2), 83.0 (**C**HOCO), 73.6 (**C**H_2Ph), 73.2 (**C**H_2OBn), 70.9 (**C**HOHCH=), 67.3 (**C**HOHCH_2), 41.5 (CH_3**C**), 36.3 (**C**H_2COO), 12.1 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 370 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 361.1617 $[M+Na+MeOH]^+$; found: 361.1622 $[M+Na+MeOH]^+$.

Data for compound 4.14a: IR (neat): 3436 (br. m), 2866 (m), 1786 (s), 1745 (s), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.25 (3 H, m, Ar**H**), 7.24 – 7.12 (2 H, m, Ar**H**), 5.89 (1 H, ddd, *J* = 17.1, 10.5, 5.9 Hz, C**H**=CH_2), 5.52 (1 H, t, *J* = 8.0 Hz, C**H**OCO), 5.30 (1 H, d, *J* = 17.1 Hz, C**H**H=CH), 5.19 (1 H, d, *J* = 9.2 Hz, CH=CH**H**), 4.40 (2 H, s, C**H**$_2$Ph), 4.31 (2 H, br. s, C**H**OHCH= & CC**H**OH), 3.48 (1 H, d, *J* = 10.0 Hz, C**H**HOBn), 3.31 (1 H, d, *J* = 10.1 Hz, CH**H**OBn), 3.21 (1 H, dd, *J* = 18.3, 7.6 Hz, C**H**HCO), 2.60 (1 H, dd, *J* = 18.3, 8.5 Hz, CH**H**CO), 2.11 (1 H, d, *J* = 9.1 Hz, CHO**H**CH=), 1.05 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (**C**OO), 137.4 (**C**H=CH_2), 136.8 (Ar**C**), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 128.0 (Ar**C**H), 117.3 (CH=**C**H_2), 80.8 (C**C**HOH), 73.5 (**C**H_2Ph), 72.3 (**C**HOCO), 70.2 (**C**HOHCH=), 69.9 (**C**H_2OBn), 41.2 (CH_3**C**), 33.5 (**C**H_2COO), 10.6 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 370 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 361.1622 $[M+Na+MeOH]^{+}$; found: 361.1622 $[M+Na+MeOH]^{+}$.

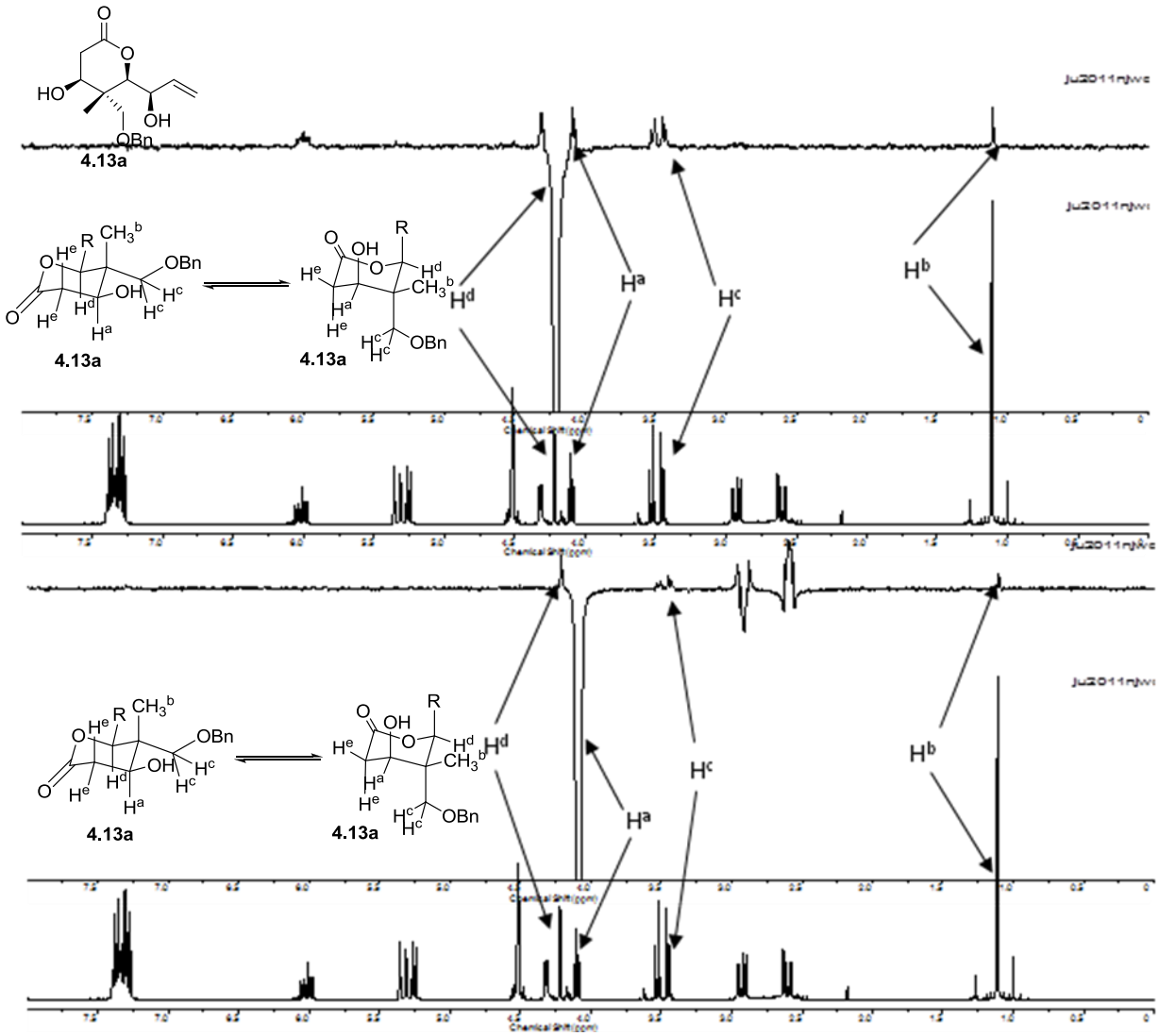
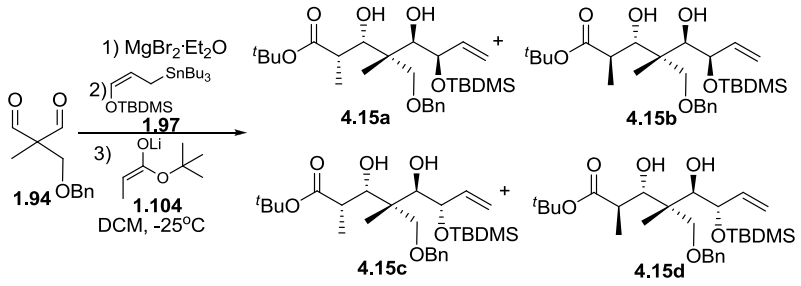


Figure 7.29. nOe's of **4.13a**

When H^{d} was irradiated, a response was observed from H^{a} and H^{c}, suggesting these were on the same side of the ring. When H^{a} was irradiated a response was observed from H^{c} and H^{d} suggesting this was also on the same side of the ring, this allowed the relative stereochemistry of **4.13a** to be deduced.

(*rac*-2*S*,3*S*,4*R*,5*R*,6*R*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-2,4-dimethyl-oct-7-enoic acid *tert*-butyl ester (4.15a) & (*rac*-2*R*,3*S*,4*R*,5*R*,6*R*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-2,4-dimethyl-oct-7-enoic acid *tert*-butyl ester (4.15b) & (*rac*-2*S*,3*S*,4*R*,5*R*,6*S*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-2,4-dimethyl-oct-7-enoic acid *tert*-butyl ester (4.15c) & (*rac*-*2R*,3*S*,4*R*,5*R*,6*S*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-3,5-dihydroxy-2,4-dimethyl-oct-7-enoic acid *tert*-butyl ester (4.15d)



1,2-Dibromoethane (1.23 mL, 14.24 mmol, 3 equiv.) was added to a suspension of magnesium turnings (347 mg, 14.24 mmol, 3 equiv.) in Et_2O (15 mL) and stirred for 30 min at r.t to obtain $MgBr_2{\bullet}OEt_2$. After removal of Et_2O, CH_2Cl_2 (25 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of dialdehyde **1.94** (980 mg, 4.75 mmol, 1 equiv.) in CH_2Cl_2 (33 mL). After addition of the dialdehyde the reaction mixture became a yellow solution. After 20 min, allyl tin **1.97** (4.38 g, 9.50 mmol, 2 equiv.) in CH_2Cl_2 (40 mL) at –25 °C was added *via* cannula and allowed to react for 2 h. An aliquot was removed, hydrolysed with aqueous $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r was determined by ^{1}H NMR (**1.98a**:**1.98b** 93:7). Separately to DIPA (2.13 mL, 15.21 mmol, 3.2 equiv.) in THF (18 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes) (6.08 mL, 15.21 mmol, 3.2 equiv). After 15 min *t*-Butyl propionate (2.15 mL, 14.24 mmol, 3 equiv.) was added and the reaction stirred at –78 °C for 15 min to form the lithium enolate **1.104** (*E/Z* 95:5)[1]. The lithium enolate **1.104** at –78 °C was added *via* cannula to the hydroxyallylation reaction and stirred at –25 °C for 10 min. The reaction was quenched with aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography with petroleum ether / EtOAc 9:1 to give 1.31 g (2.57 mmol, 54% yield) of a colourless oil (approx. d.r on the crude 86:14:<1:<1, Figure 7.30). The

diastereoisomers were separated by preparative HPLC (hexane / acetone 95:5) to give 624 mg of mixtures of **4.15a**, **b**, **c** and **d**, 536 mg of **4.15a**, 53 mg of **4.15b**, 1 mg **4.15c** and 1 mg of **4.15d**.

Data for compound 4.15a: IR (neat): 3481 (br. m), 2956 (m), 2932 (m), 2884 (w), 2858 (m), 1729 (m), 1700 (s), 1458 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (5 H, m, Ar**H**), 5.95 (1 H, ddd, *J* = 17.4, 9.9, 8.1 Hz, C**H**=CH_2), 5.15 (1 H, d, *J* = 17.2 Hz, CH=C**H**H), 5.10 (1 H, d, *J* = 10.6 Hz, CH=C**H**H), 4.51 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.43 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.33 (1 H, dd, *J* = 8.1, 3.5 Hz, C**H**OTBDMS), 4.13 (1 H, t, *J* = 6.1 Hz, C**H**OHCHCO), 3.80 (1 H, dd, *J* = 6.3, 3.8 Hz, C**H**OHCHOTBDMS), 3.75 (1 H, d, *J* = 6.1 Hz, CHO**H**CHCO), 3.65 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.48 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.34 (1 H, d, *J* = 6.6 Hz, CHO**H**CHOTBDMS), 2.68 (1 H, qd, *J* = 6.8, 6.7 Hz, C**H**CH_3), 1.43 (9 H, s, OC(C**H**$_3$)$_3$), 1.22 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.96 (3 H, s, CC**H**$_3$), 0.90 (9 H, s, SiC(C**H**$_3$)$_3$), 0.08 (3 H, s, SiC**H**$_3$), 0.05 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (**C**OO*t*Bu), 140.0 (**C**H=CH_2), 138.0 (Ar**C**), 128.4 (Ar**C**H), 127.6 (Ar**C**H), 116.1 (CH=**C**H_2), 80.1 (O**C**$(CH_3)_3$), 76.9 (**C**HOHCHOTBDMS), 75.8 (**C**HOHCHCH_3), 74.2 (**C**HOTBDMS), 73.6 (**C**H_2Ph), 73.5 (**C**H_2OBn), 45.6 (CH_3**C**), 42.5 (**C**HCOO), 28.0 (OC(**C**$H_3)_3$), 25.9 (SiC(**C**$H_3)_3$), 18.1 (Si**C**$(CH_3)_3$), 16.6 (**C**H_3C), 13.9 (**C**H_3CH), -3.5 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 531 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 531.3112 $[M+Na]^+$; found: 531.3100 $[M+Na]^+$.

Data for compound 4.15b: IR (neat): 3481 (br. m), 2956 (m), 2932 (m), 2884 (w), 2858 (m), 1729 (s), 1700 (m), 1458 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (5 H, m, Ar**H**), 5.98 (1 H, ddd, *J* = 17.7, 10.1, 8.1 Hz, C**H**=CH_2), 5.13 (1 H, d, *J* = 16.7 Hz, CH=C**H**H), 5.06 (1 H, d, *J* = 9.1 Hz, CH=C**H**H), 4.54 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.43 (1 H, d, *J* = 9.1 Hz, CHO**H**CHCO), 4.38 (1 H, d, *J* = 11.1 Hz, C**H**HPh), 4.35 (1 H, dd, *J* = 7.6, 2.5 Hz, C**H**OTBDMS), 3.83 (1 H, dd, *J* = 9.1, 2.5 Hz, C**H**OHCHCO), 3.70 (1 H, dd, *J* = 8.1, 2.5 Hz, C**H**OHCHOTBDMS), 3.64 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.42 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.37 (1 H, d, *J* = 7.6 Hz, CHO**H**CHOTBDMS), 2.77 (1 H, qd, *J* = 7.2, 2.8 Hz, C**H**CH_3), 1.43 (9 H, s, OC(C**H**$_3$)$_3$), 1.31

(3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.94 (3 H, s, CC**H**$_3$), 0.89 (9 H, s, SiC(C**H**$_3$)$_3$), 0.03 (3 H, s, SiC**H**$_3$), 0.03 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8 (**C**OO*t*Bu), 140.1 (**C**H=CH_2), 138.3 (Ar**C**), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 115.6 (CH=**C**H_2), 80.8 (O**C**$(CH_3)_3$), 78.6 (**C**HOHCHCH_3), 77.2 (**C**HOHCHOTBDMS), 74.5 (**C**HOTBDMS), 73.4 (**C**H_2OBn), 73.3 (**C**H_2Ph), 46.2 (CH_3**C**), 40.2 (**C**HCOO), 28.0 (OC(**C**H_3)$_3$), 25.9 (SiC(**C**H_3)$_3$), 18.2 (**C**H_3C), 18.1 (Si**C**$(CH_3)_3$), 15.7 (**C**H_3CH), -3.4 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 531 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 531.3112 $[M+Na]^+$; found: 531.3112 $[M+Na]^+$.

Data for compound 4.15c: IR (neat): 3502 (br. m), 2954 (m), 2931 (m), 2885 (w), 2858 (m), 1727 (s), 1458 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (5 H, m, Ar**H**), 6.03 (2 H, ddd, *J* = 17.6, 10.2, 7.6 Hz, C**H**=CH_2), 5.22 – 5.10 (2 H, m, CH=C**H**$_2$), 4.53 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.45 (1 H, d, *J* = 12.1 Hz, CH**H**Ph), 4.29 (1 H, dd, *J* = 7.8, 3.8 Hz, C**H**OTBDMS), 4.20 (1 H, t, *J* = 5.8 Hz, C**H**OHCHCO), 4.03 (1 H, t, *J* = 3.3 Hz, C**H**OHCHOTBDMS), 3.65 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.63 (1 H, d, *J* = 5.6 Hz, CHO**H**CHCO), 3.53 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.94 (1 H, d, *J* = 2.5 Hz, CHO**H**CHOTBDMS), 2.70 (1 H, qd, *J* = 7.1, 6.1 Hz, C**H**CH_3), 1.44 (9 H, s, OC(C**H**$_3$)$_3$), 1.21 (3 H, d, *J* = 7.1 Hz, CHC**H**$_3$), 0.94 (3 H, s, CC**H**$_3$), 0.89 (9 H, s, SiC(C**H**$_3$)$_3$), 0.07 (3 H, s, SiC**H**$_3$), 0.04 (3 H, s, SiC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3 (**C**OO*t*Bu), 137.7 (**C**H=CH_2), 136.9 (Ar**C**), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 117.2 (CH=**C**H_2), 80.2 (O**C**$(CH_3)_3$), 77.2 (**C**HOHCHOTBDMS), 75.4 (**C**HOHCHCH_3), 72.3 (**C**HOTBDMS), 73.6 (**C**H_2OBn), 73.2 (**C**H_2Ph), 44.8 (CH_3**C**), 42.4 (**C**HCOO), 28.0 (OC(**C**H_3)$_3$), 25.9 (SiC(**C**H_3)$_3$), 17.6 (Si**C**$(CH_3)_3$), 15.6 (**C**H_3C), 13.8 (**C**H_3CH), -4.1 (**C**H_3Si), -4.7 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 531 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 531.3112 $[M+Na]^+$; found: 531.3118 $[M+Na]^+$.

Data for compound 4.15d: IR (neat): 3444 (br. m), 2956 (m), 2932 (m), 2884 (w), 2858 (m), 1727 (s), 1700 (w), 1458 (m) cm^{-1}.

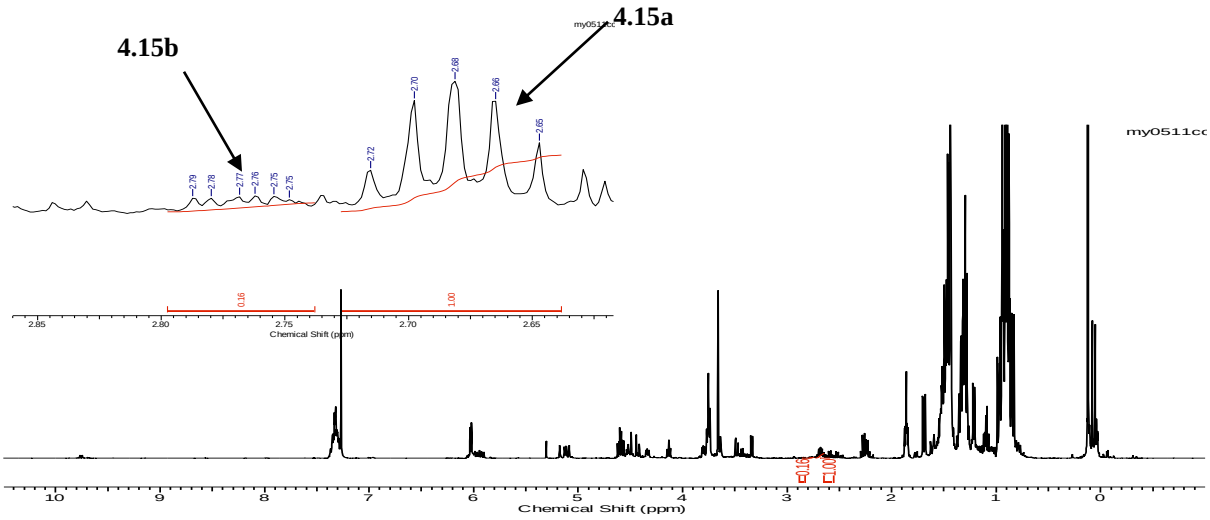
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (5 H, m, Ar**H**), 5.98 (1 H, ddd, *J* = 17.6, 10.0, 7.8 Hz, C**H**=CH_2), 5.13 (1 H, dd, *J* = 10.1, 1.5 Hz, CH=C**H**H), 5.04 (1 H, dd, *J* = 17.2, 1.0 Hz, CH=C**H**H), 4.57 (1 H, d, *J* = 11.6 Hz, C**H**HPh), 4.57 (1 H, d, *J* = 9.1 Hz, CHO**H**CHCO),

4.41 (1 H, d, *J* = 12.1 Hz, C**H**<u>**H**</u>Ph), 4.29 (1 H, dd, *J* = 7.8, 3.8 Hz, C<u>**H**</u>OTBDMS), 3.83 (1 H, dd, *J* = 6.8, 2.3 Hz, C<u>**H**</u>OHCHCO), 3.80 (1 H, t, *J* = 4.0 Hz, C<u>**H**</u>OHCHOTBDMS), 3.65 (1 H, d, *J* = 9.6 Hz, C<u>**H**</u>**H**OBn), 3.41 (1 H, d, *J* = 9.1 Hz, C**H**<u>**H**</u>OBn), 3.06 (1 H, d, *J* = 4.0 Hz, CHO<u>**H**</u>CHOTBDMS), 2.84 (1 H, qd, *J* = 7.3, 2.0 Hz, C<u>**H**</u>CH_3), 1.43 (9 H, s, OC(C<u>**H**</u>$_3$)$_3$), 1.34 (3 H, d, *J* = 7.1 Hz, CHC<u>**H**</u>$_3$), 0.91 (3 H, s, CC<u>**H**</u>$_3$), 0.88 (9 H, s, SiC(C<u>**H**</u>$_3$)$_3$), 0.04 (3 H, s, SiC<u>**H**</u>$_3$), 0.02 (3 H, s, SiC<u>**H**</u>$_3$) ppm.

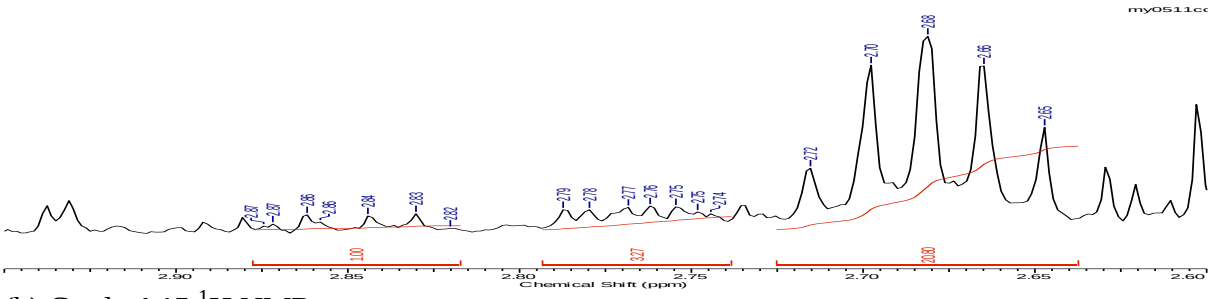
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2 (<u>**C**</u>OO*t*Bu), 138.6 (<u>**C**</u>H=CH_2), 138.2 (Ar<u>**C**</u>), 128.3 (Ar<u>**C**</u>H), 127.7 (Ar<u>**C**</u>H), 127.6 (Ar<u>**C**</u>H), 116.8 (CH=<u>**C**</u>H_2), 81.0 (O<u>**C**</u>$(CH_3)_3$), 78.6 (<u>**C**</u>HOHCHCH_3), 77.2 (<u>**C**</u>HOHCHOTBDMS), 76.0 (<u>**C**</u>HOTBDMS), 73.5 (<u>**C**</u>H_2OBn), 73.1 (<u>**C**</u>H_2Ph), 45.5 (CH_3<u>**C**</u>), 39.8 (<u>**C**</u>HCOO), 28.0 (OC(<u>**C**</u>H_3)$_3$), 25.9 (SiC(<u>**C**</u>H_3)$_3$), 18.5 (<u>**C**</u>H_3C), 18.1 (Si<u>**C**</u>$(CH_3)_3$), 14.8 (<u>**C**</u>H_3CH), -4.1 (<u>**C**</u>H_3Si), -4.6 (<u>**C**</u>H_3Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 531 $[M+Na]^+$ (100%).

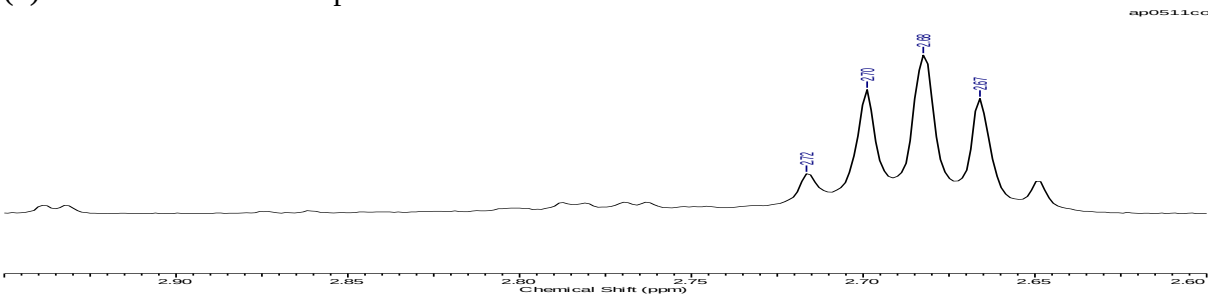
HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 531.3112 $[M+Na]^+$; found: 531.3113 $[M+Na]^+$.



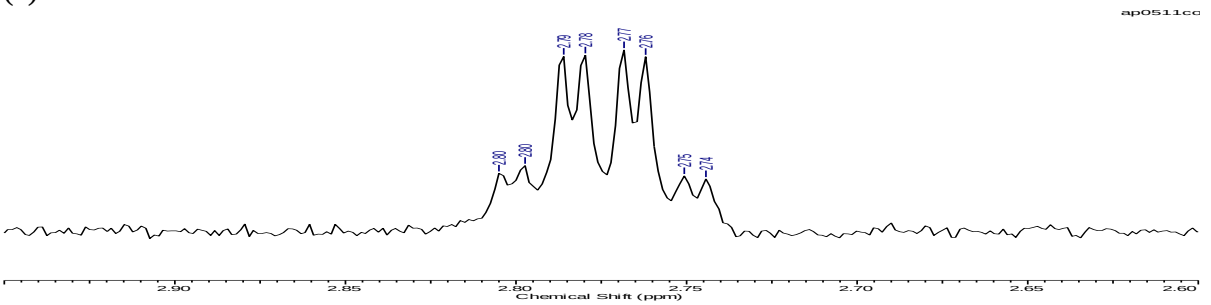
(a) **4.15** Crude ^{1}H NMR



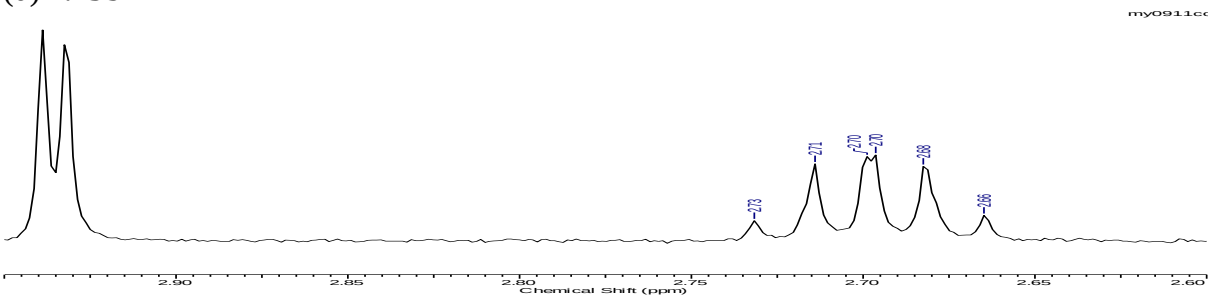
(b) Crude **4.15** ^{1}H NMR spectrum



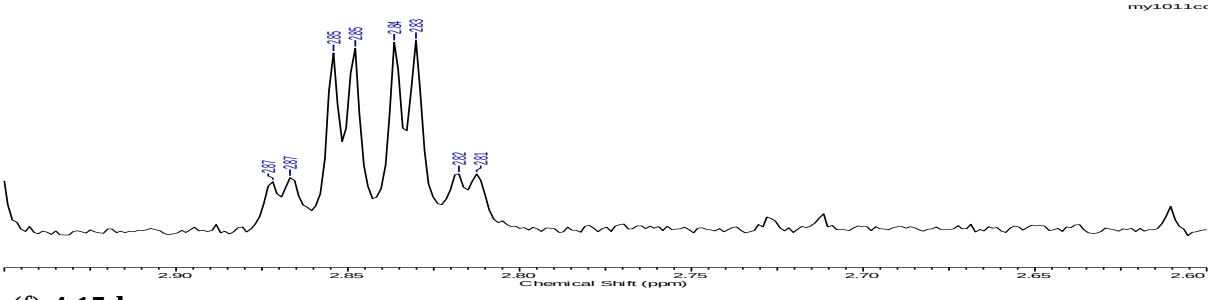
(c) **4.15a**



(d) **4.15b**



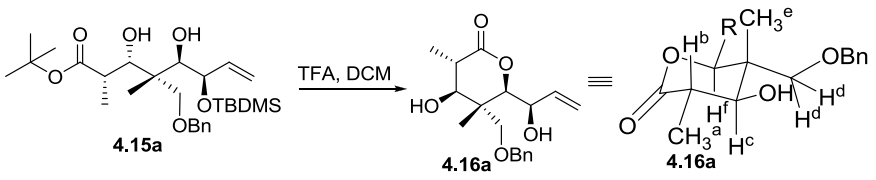
(e)**4.15c**



(f) **4.15d**

Figure 7.30. Crude ^{1}H NMR from which the d.r was calculated from the C**H**CH$_3$ peaks.

(*rac*-3*S*,4*S*,5*R*,6*R*)-5-Benzyloxymethyl-4-hydroxy-6-((*R*)-1-hydroxy-allyl)-3,5-dimethyl-tetrahydro-pyran-2-one (4.16a)



TFA (438 µL, 5.90 mmol, 60 equiv.) was added to a solution of ester **4.15a** (50 mg, 0.10 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) and the reaction stirred at r.t for 16 h. The reaction mixture was concentrated in *vacuo* and the resultant crude oil purified by column chromatography (1:1 petroleum ether:EtOAc) to give 19 mg (0.06 mmol, 59% yield) of **4.16a** as a colourless oil.

IR (neat): 3410 (br. m), 2981 (w), 2880 (m), 1716 (s), 1455 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (5 H, m, Ar**H**) 5.95 (1 H, ddd, *J* = 17.0, 10.6, 6.1 Hz, C**H**=CH_2), 5.31 (1 H, dt, *J* = 17.2, 1.2 Hz, CH=C**H**H), 5.23 (1 H, dt, *J* = 10.4, 1.2 Hz, CH=C**H**H), 4.51 (2 H, s, C**H$_2$**Ph), 4.28 (1 H, tt, *J* = 7.3, 1.0 Hz, C**H**OHCH=), 4.19 (1 H, d, *J* = 2.3 Hz, C**H**OCO), 3.81 (1 H, dd, *J* = 9.7, 4.9 Hz, C**H**OHCHCH$_3$), 3.59 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.47 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.58 (1 H, d, *J* = 4.9 Hz, CHO**H**CHCH$_3$), 2.57 – 2.49 (1 H, m, C**H**CH$_3$), 2.36 (1 H, d, *J* = 8.7 Hz, CHO**H**CH=), 1.41 (3 H, d, *J* = 7.1 Hz, CC**H$_3$**), 1.04 (3 H, s, CC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (**C**OO), 137.8 (**C**H=CH_2), 137.3 (Ar**C**), 128.6 (Ar**C**H), 128.2 (Ar**C**H), 127.8 (Ar**C**H), 117.0 (CH=**C**H$_2$), 81.7 (**C**HOCO), 73.7 (**C**H$_2$Ph), 73.5 (**C**H$_2$OBn), 72.2 (**C**HOHCHCH$_3$), 70.8 (**C**HOHCH=), 41.9 (CH$_3$**C**), 41.0 (**C**HCH$_3$), 15.1 (**C**H$_3$CH), 10.3 (**C**H$_3$C) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 384 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 343.1516 $[M+Na]^+$; found: 343.1524 $[M+Na]^+$.

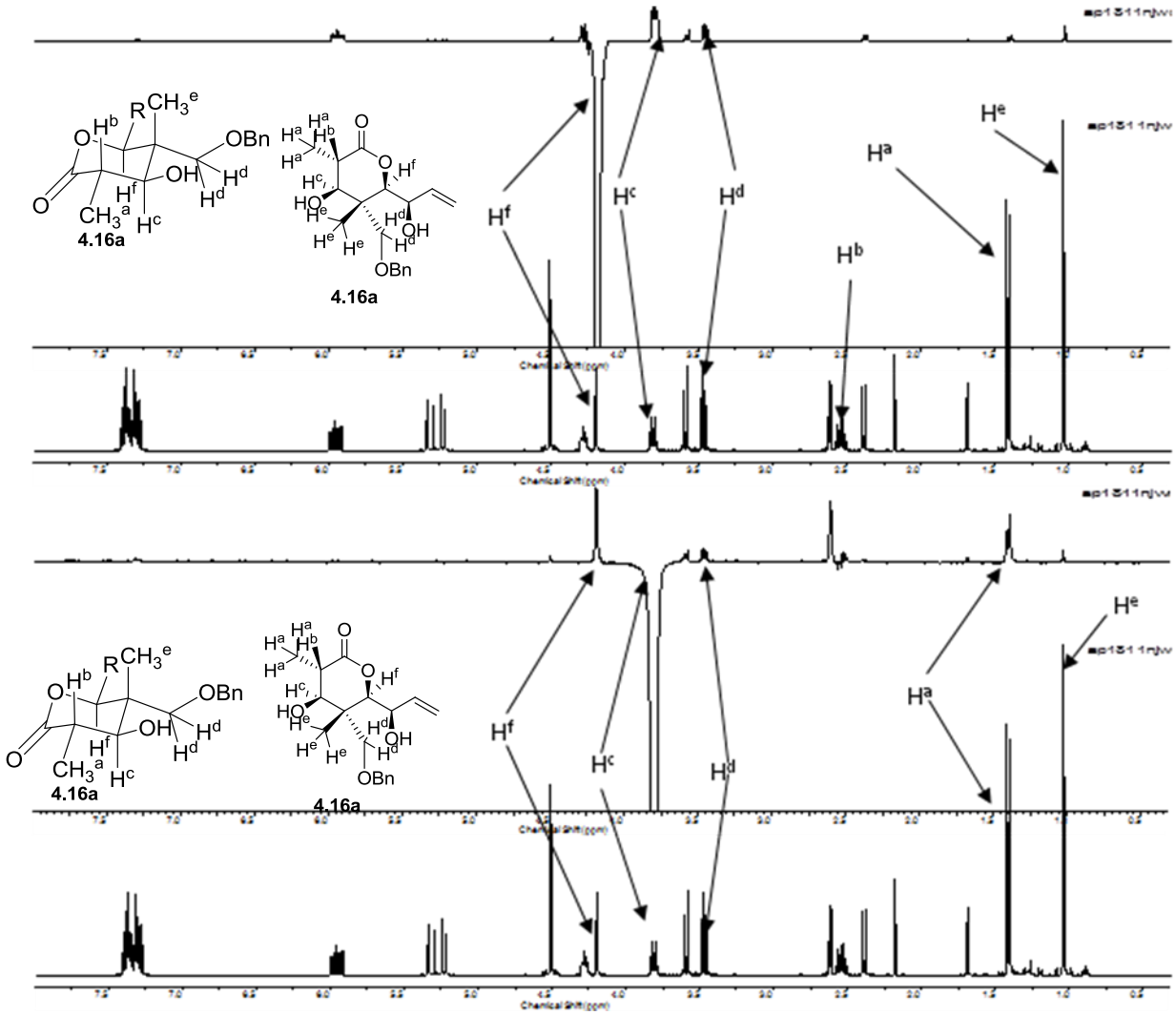
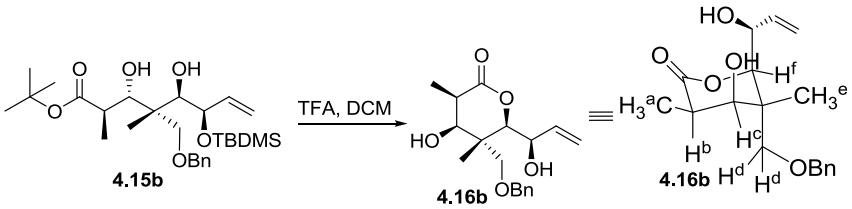


Figure 7.31. nOe's of **4.16a**

When H^f was irradiated, a response was observed from H^c and H^d, suggesting these were on the same side of the ring. When H^c was irradiated a response was observed from H^a, H^d and H^f suggesting this was also on the same side of the ring, this allowed the relative stereochemistry of **4.16a** to be deduced.

(*rac*-3*R*,4*S*,5*R*,6*R*)-5-Benzyloxymethyl-4-hydroxy-6-((*R*)-1-hydroxy-allyl)-3,5-dimethyl-tetrahydro-pyran-2-one (4.16b)



50 mg of ester **4.15b** (0.10 mmol) was transformed to 15 mg of lactone **4.16b** (0.05 mmol, 48% yield) according to the method above.

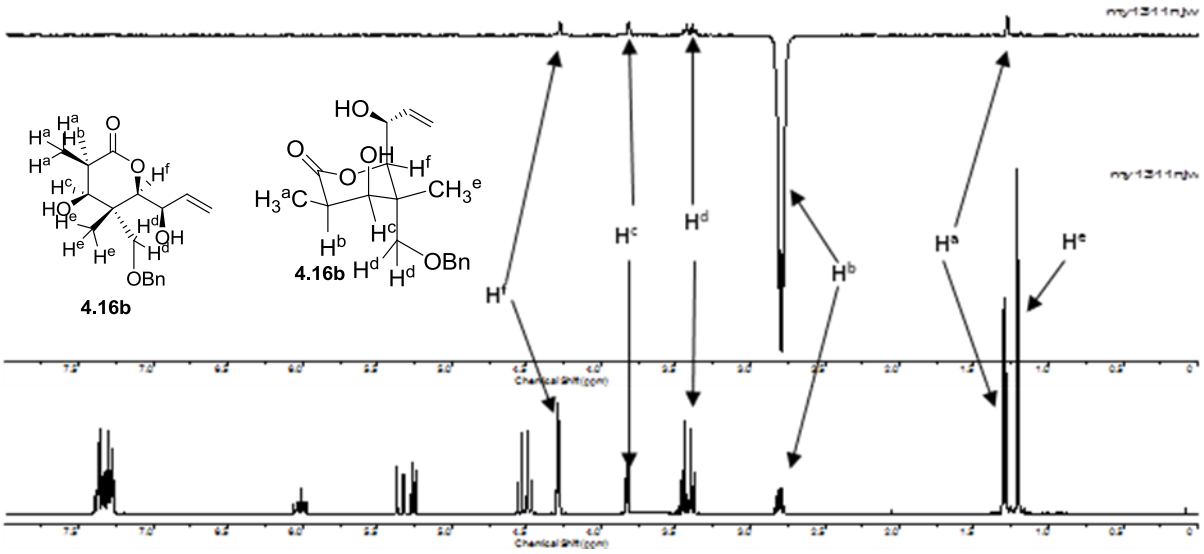
IR (neat): 3298 (br. m), 2982 (w), 2881 (m), 1730 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (5 H, m, Ar**H**), 6.01 (1 H, ddd, *J* = 17.3, 10.2, 6.8 Hz, C**H**=CH_2), 5.35 (1 H, d, *J* = 17.2 Hz, CH=C**H**H), 5.26 (1 H, d, *J* = 10.6 Hz, CH=C**H**H), 4.55 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.48 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.34 – 4.21 (2 H, m, C**H**OCO & C**H**OHCH=), 3.83 (1 H, d, *J* = 4.5 Hz, C**H**OHCHCH_3), 3.77 – 3.48 (2 H, m, CHO**H**), 3.45 (1 H, d, *J* = 9.1 Hz, C**H**HOBn), 3.39 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 2.81 (1 H, qd, *J* = 6.9, 4.5 Hz, C**H**CH_3), 1.30 (3 H, d, *J* = 7.1 Hz, CC**H**$_3$), 1.21 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6 (**C**OO), 137.5 (Ar**C**), 137.1 (**C**H=CH_2), 128.5 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 118.1 (CH=**C**H_2), 83.7 (**C**HOCO), 75.4 (**C**H_2Ph), 73.5 (**C**H_2OBn), 72.9 (**C**HOHCHCH_3), 71.1 (**C**HOHCH=), 42.6 (CH_3**C**), 38.9 (**C**HCH_3), 16.1 (**C**H_3CH), 12.1 (**C**H_3C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 384 $[M+Na+MeCN]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 343.1508 $[M+Na]^+$; found: 343.1524 $[M+Na]^+$.



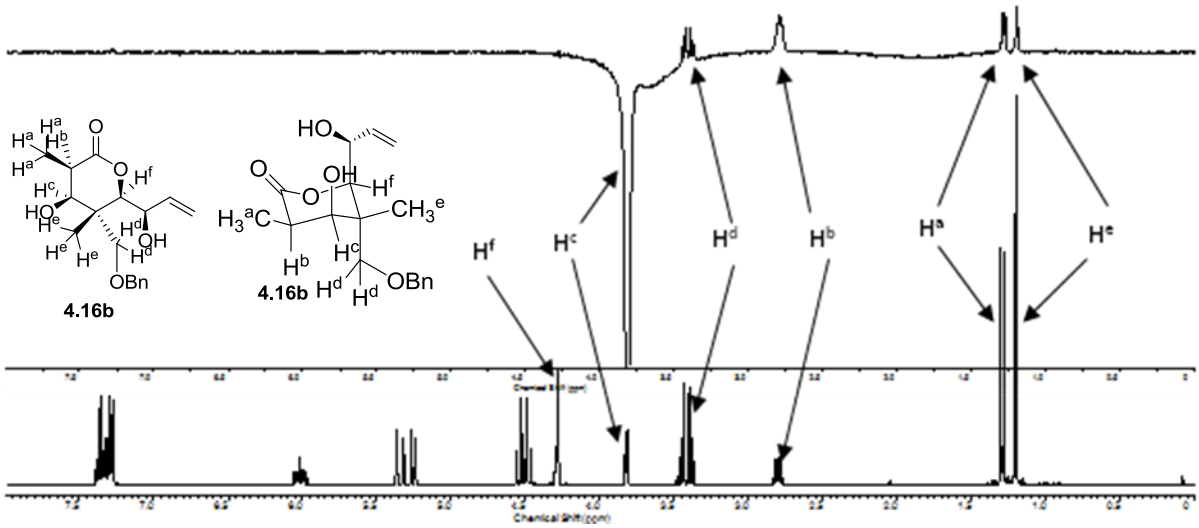
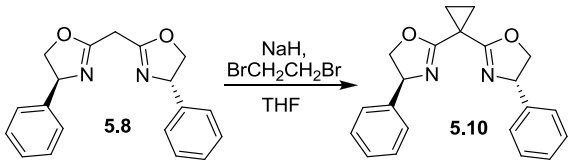


Figure 7.32. nOe's of **4.16b**

When H^b was irradiated a response was observed from H^f, H^a, H^c and H^d suggesting this was on the same side of the ring. When H^c was irradiated a response was observed from H^b and H^d suggesting that these were on the same side of the ring as H^c. Responses were also observed from H^a and H^e this corresponds with the chair conformation of **4.16b** suggested as both H^a and H^e sit equatorial and are therefore close in space to H^c. This would not be the case if **4.16b** existed in the ring inversion conformation as the H^c would then have a 1,2-diaxial relationship to H^a and H^e, therefore no response would be expected. This allowed the relative stereochemistry and conformation of **4.16b** to be deduced.

(*S*)-4,5-dihydro-2-(1-((*S*)-4,5-dihydro-4-phenyloxazol-2-yl)cyclopropyl)-4-phenyloxazole (5.10)



To a solution of **5.8** (70 mg, 0.23 mmol, 1 equiv.) in THF (2 mL) at 0 °C was added NaH (60% w/w dispersion on mineral oil) (28 mg, 0.69 mmol, 3 equiv.) and the reaction stirred at 0 °C for 30 min. 1,1-Dibromoethane (24 µL, 0.28 mmol, 1.2 equiv) was added dropwise to the reaction at 0 °C and the reaction warmed to 50 °C and stirred for 5 h. The reaction was quenched with aq. NH_4Cl and the organics extracted with CH_2Cl_2, washed with brine and

dried over $MgSO_4$, filtered and concentrated in *vacuo* to give crude orange oil. The crude was purified by column chromatography (hexane / acetone, 9:1) to give **5.7** as a yellow oil (38 mg, 0.11 mmol, 49%).

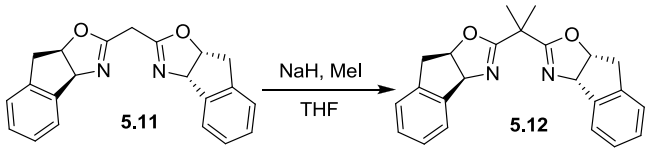
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.20 (10 H, m, Ar**H**), 5.22 (2 H, dd, *J* = 10.0, 7.9 Hz, C**H**HO), 4.69 (2 H, dd, *J* = 10.1, 8.4 Hz, C**H**HO), 4.17 (2 H, t, *J* = 8.1 Hz, C**H**Ph), 1.58 – 1.48 (4 H, m C(C$\mathbf{H_2}$)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (**C**=N), 142.3 (Ar**C**), 128.7 (Ar**C**H), 127.5 (Ar**C**H), 126.6 (Ar**C**H), 75.4 (**C**H_2O), 69.5 (**C**HPh), 36.1 (**C**$(CH_2)_2$), 15.8 (C(**C**$H_3)_2$) ppm.

[α]$_D$: -90.41° (*c* 2.00, CH_2Cl_2, 27 °C); lit. -92.75° (*c* 1.77, CH_2Cl_2, 20 °C)

This corresponds to data in the literature [161]

(3a*S*,8a*R*)-8,8a-dihydro-2-(2-((3a*S*,8a*R*)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)propan-2-yl)-3aH-indeno[1,2-d]oxazole (5.12)



5.11 5.12

To a solution of **5.11** (70 mg, 0.21 mmol, 1 equiv.) in THF (1 mL) at 0 °C was added NaH (60% w/w dispersion on mineral oil) (27 mg, 0.64 mmol, 3 equiv.) and the reaction stirred at 0 °C for 30 min. A solution of MeI (40 µL, 0.64 mmol, 3 equiv) in THF (1 mL) was added dropwise to the reaction at 0 °C and the reaction allowed to warm to r.t and stirred for 4 h. The reaction was quenched with aq. NH_4Cl and the organics extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo* to give cream solid (41 mg, 0.11 mmol, 54%).

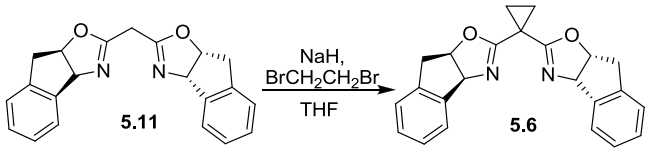
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.41 (2 H, m, Ar**H**), 7.35 – 7.15 (6 H, m, Ar**H**), 5.51 (2 H, d, *J* = 8.0 Hz, C**H**N), 5.24 (2 H, ddd, *J* = 7.9, 7.2, 1.9 Hz, CH_2C**H**O), 3.29 (2 H, dd, *J* = 17.9, 7.1 Hz, C**H**HPh), 2.94 (2 H, d, *J* = 17.8 Hz, C**H**HPh) 1.41 (6 H, s, CC$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (**C**=N), 141.8 (Ar**C**), 139.7 (Ar**C**), 128.3 (Ar**C**H), 127.3 (Ar**C**H), 125.6 (Ar**C**H), 125.0 (Ar**C**H), 83.2 (CH_2**C**HO), 76.4 (N**C**HPh), 39.6 (**C**H_2Ph), 38.7 (**C**$(CH_3)_2$), 23.8 (C(**C**$H_3)_2$) ppm.

[α]$_D$ -461.8° (*c* 2.00, CH_2Cl_2, 26 °C); lit. -453.0° (*c* 1.00, CH_2Cl_2, 22 °C)

This corresponds to data in the literature [161]

(3aS,8aR)-8,8a-dihydro-2-(1-((3aS,8aR)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)cyclopropyl)-3aH-indeno[1,2-d]oxazole (5.6)



To a solution of **5.11** (70 mg, 0.21 mmol, 1 equiv.) in THF (2 mL) at 0 °C was added NaH (60% w/w dispersion on mineral oil) (27 mg, 0.64 mmol, 3 equiv.) and the reaction stirred at 0 °C for 30 min. 1,1-Dibromoethane (22 µL, 0.25 mmol, 1.2 equiv) was added dropwise to the reaction at 0 °C and the reaction warmed to 50 °C and stirred for 3 h. The reaction was quenched with aq. NH_4Cl and the organics extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo* to give **5.6** as a cream solid (72 mg, 0.20 mmol, 96 %).

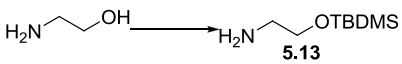
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.36 (2 H, m, Ar**H**), 7.28 – 7.16 (6 H, m, Ar**H**), 5.51 (2 H, d, *J* = 8.0 Hz, C**H**N), 5.31 (2 H, ddd, *J* = 7.9, 7.0, 2.0 Hz, CH_2C**H**O), 3.37 (2 H, dd, *J* = 17.9, 7.0 Hz, C**H**HPh), 3.18 (2 H, dd, *J* = 17.9, 1.6 Hz, C**H**HPh) 1.40 – 1.28 (4 H, m C(C$\mathbf{H_2}$)$_2$)ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (**C**=N), 141.6 (Ar**C**), 139.5 (Ar**C**), 128.2 (Ar**C**H), 127.2 (Ar**C**H), 125.4 (Ar**C**H), 125.0 (Ar**C**H), 83.2 (CH_2**C**HO), 76.2 (N**C**HPh), 39.5 (**C**H_2Ph), 18.2 (**C**$(CH_2)_2$), 15.6 (C(**C**$H_3)_2$) ppm.

[α]$_D$ -355.4° (*c* 2.00, CH_2Cl_2, 26 °C), lit; -349.3° (*c* 1.19, CH_2Cl_2, 20 °C)

This corresponds to data in the literature [161]

2-(*tert*-Butyl-dimethyl-silanyloxy)-ethylamine (5.13)



To a solution of ethanolamine (500 mg, 8.19 mmol, 1equiv.) and DMAP (100 mg, 0.819 mmol, 0.1 equiv.) in CH_2Cl_2 (20 ML) at 0 °C was added Et_3N (1.7 mL, 12.29 mmol, 1.5 equiv.). TBDMSCl (1.36 g, 9.01 mmol, 1.1 equiv.) was added portionwise and the reaction warmed to r.t and stirred for 5 h 30 min. The reaction was quenched with H_2O and the

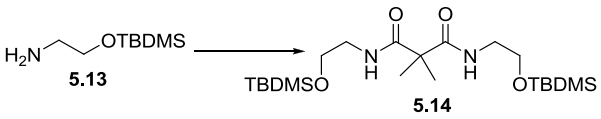
organics extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* to give 992 mg (5.66 mmol, 69% yield) of **5.13** as a thick oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (2 H, t, *J* = 5.3 Hz, C**H**$_2$OTBDMS), 2.77 (2 H, t, *J* = 5.3 Hz, C**H**$_2$NH$_2$), 1.41 (2 H, br. s., N**H**$_2$), 0.90 (9 H, s, SiC(C**H**$_3$)$_3$), 0.06 (6 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 65.3 (**C**H$_2$OTBDMS), 44.4 (**C**H$_2$NH$_2$), 25.9 (SiC**C**H$_3$), 18.3 (Si**C**CH$_3$), -5.3 (Si**C**H$_3$) ppm.

This corresponds to data from the literature [186]

***N,N'*-Bis-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2,2-dimethyl-malonamide (5.14)**



To a solution of **5.13** (990 mg, 5.65 mmol, 3 equiv.) and Et_3N (2.6 mL, 18.8 mmol, 10 equiv.) in CH_2Cl_2 (7 mL) was added dimethylmalonylchloride (299 µL, 1.88 mmol, 1 equiv.). The reaction was stirred at r.t for 2 h. The reaction was diluted with CH_2Cl_2 (5 mL) and quenched with 1 M HCl (5 mL) and the organics extracted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ then brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1, CH_2Cl_2 / MeOH) to give 706 mg (1.58 mmol, 84% yield) of **5.14** as a thick yellow oil.

IR (neat): 3322(m), 2928 (m), 2858 (m), 1645 (s), 1530 (s), 1470 (m) cm^{-1}.

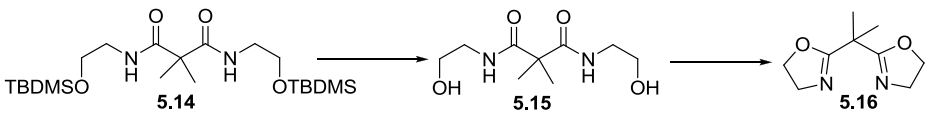
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (2 H, br. s., N**H**$_2$), 3.67 (4 H, t, *J* = 5.3 Hz, C**H**$_2$OTBDMS), 3.36 (4 H, q, *J* = 5.2 Hz, C**H**$_2$NH), 1.46 (6 H, s, CC**H**$_3$), 0.91 (18 H, s, SiC(C**H**$_3$)$_3$), 0.07 (12 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (**C**ONH), 61.5 (**C**H$_2$OTBDMS), 49.3 (**C**(CH$_3$)$_2$), 41.9 (**C**H$_2$NH$_2$), 25.8 (SiC**C**H$_3$), 24.0 (C(**C**H$_3$)$_2$), 18.2 (Si**C**CH$_3$), -5.4 (Si**C**H$_3$) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 469 [M+Na]$^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 469.2888 [M+Na]$^+$; found: 469.2889 [M+Na]$^+$.

***N,N'*-Bis-(2-hydroxy-ethyl)-2,2-dimethyl-malonamide (5.16)**



To a solution of **5.14** (650 mg, 1.5 mmol, 1 equiv.) in THF (14 mL) was added TBAF (1.0 M in THF) (4.5 mL, 4.5 mmol, 3 equiv.). The reaction was stirred at r.t for 1 h. The reaction mixture was concentrated *in vacuo* to give crude **5.15**.

To a solution of **5.15** in CH_2Cl_2 (6 mL) was added DMAP (18 mg, 0.15 mmol, 0.1 equiv.) followed by Et_3N (0.9 mL, 6.6 mmol, 4.4 equiv.). The reaction was placed in a water bath and a solution of *p*TsCl (572 mg, 3.0 mmol, 2 equiv.) in CH_2Cl_2 (1 mL) was added and the reaction was stirred at r.t for 20 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with sat. aq. NH_4Cl. The organics were extracted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude oil was purified by column chromatography (9:1, CH_2Cl_2 / MeOH) to give 26 mg (0.14 mmol, 10% yield) of **5.16** as a pale yellow oil.

IR (neat): 3406 (br), 2982 (m), 2858 (m), 1653 (s), 1469 (w) cm^{-1}.

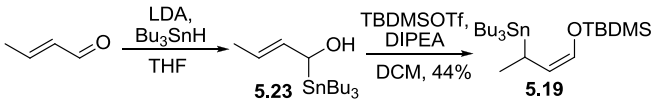
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (4 H, t, *J* = 9.6 Hz, C**H**$_2$N=), 3.86 (4 H, t, *J* = 9.3 Hz, C**H**$_2$O), 1.51 (6 H, s, C(C**H**$_3$)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (**C**=N), 68.0 (**C**H_2N=), 54.3 (**C**H_2O), 38.6 (**C**$(CH_3)_2$), 24.2 (C(**C**$H_3)_2$) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 183 $[M+H]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 205.0947 $[M+Na]^+$; found: 205.0949 $[M+Na]^+$.

***Rac-tert*-Butyl-dimethyl-((*Z*)-3-tributylstannanyl-but-1-enyloxy)-silane (5.19)**



To a solution of DIPA (2.9 mL, 20.6 mmol, 1.2 equiv.) in THF (50 mL) at 0 °C was added *n*BuLi (1.6 M solution in hexanes) (12.9 mL, 20.6 mmol, 1.2 equiv.) and the reaction mixture stirred at 0 °C for 10 min. Tributyl tinhydride (5.6 mL, 20.6 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at 0 °C for 25 min and cooled to –78 °C. Crotonaldehyde (1.42 mL, 17.2 mmol, 1 equiv.) in THF (8 mL) was added and the reaction mixture stirred at –78 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl and the organics extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give crude allyltin alcohol **5.23** as a yellow oil.

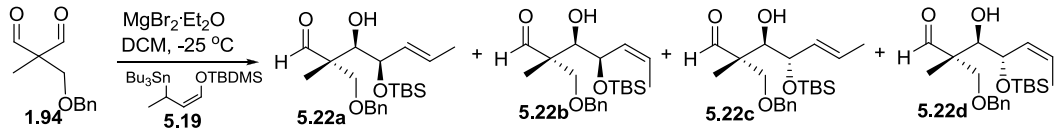
To a solution of crude allyltin alcohol **5.23** in CH_2Cl_2 (48 mL) at 0 °C was added DIPEA (9.0 mL, 51.6 mmol, 3 equiv.) followed by TBDMSOTf (5 g, 18.9 mmol, 1.1 equiv.) and the reaction was warmed to r.t over 3 h. The reaction was quenched with H_2O and the organics extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (hexane) to give **5.19** (4.66 g, 9.78 mmol, 57 %) as a colourless oil.

Data for 5.19: IR (neat): 3021 (w), 2955 (s), 2927 (m), 2865 (m), 1695 (s), 1640 (m), 1463 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (1 H, dd, *J* = 6.0, 1.0 Hz, C**H**OTBDMS), 4.48 (1 H, dd, *J* = 11.0, 5.5 Hz, C**H**CHSnBu_3), 2.60 – 2.48 (1 H, m, C**H**SnBu_3), 1.58 – 1.22 (18 H, m, Sn((C**H**$_2$)$_3$$CH_3$)$_3$), 0.94 (9 H, s, SiC(C**H**$_3$)$_3$), 0.90 (9 H, t, *J* = 7.3 Hz, CH_2C**H**$_3$), 0.12 (3 H, s, SiC**H**$_3$), 0.11 (3 H, s, SiC**H**$_3$) ppm.

This corresponds to data from the literature[173]

(*E*)-(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enal (5.22a) & (*Z*)-(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enal (5.22b) & (*E*)-(*rac*-2*S*,3*R*,4*S*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enal (5.22c) & (*Z*)-(*rac*-2*S*,3*R*,4*S*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enal (5.22d)



1,2-Dibromoethane (290 μL, 3.36 mmol, 3 equiv.) was added to a suspension of magnesium turnings (82 mg, 3.36 mmol, 3 equiv.) in Et_2O (4 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of the ether, CH_2Cl_2 (5 mL) was added and the reaction mixture was cooled to –25 °C before addition *via* cannula of dialdehyde **1.94** (230 mg, 1.12 mmol 1 equiv.) in CH_2Cl_2 (7 mL) at –25 °C. After 20 min of stirring, allytin **5.19** (1.60 g, 3.36 mmol, 3 equiv.) in CH_2Cl_2 (11 mL) at –25 °C was added *via* cannula and the reaction mixture stirred at –25 °C for 2 h 30 min. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixure was purified by

column chromatography (petroleum ether/EtOAc 90:10) to give 277 mg of **5.22** as colourless oil (d.r. **5.22a**:**5.22b**:**5.22c**:**5.22d** 84:8:5:3, Figure 7.33) (0.71 mmol, 63%). Further purification by by preparative HPLC (9:1 hexane:EtOAc) isolated an analytically pure sample of major diastereoisomer **5.19a** (11 mg), a mixture of **5.19a** and **5.19b** (196 mg) and a mixture of **5.19c** and **5.19d** (16 mg).

Data for 5.22a: IR (neat): 3515 (br. w), 2929 (m), 2856 (m), 1720 (m), 1641 (w), 1497 (w), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1 H, s, C**H**O), 7.40 – 7.22 (5 H, m, Ar**H**), 5.68 – 5.50 (2 H, m, **H**C=C**H**), 4.51 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.47 (1 H, d, *J* = 12.1 Hz, C**H**HPh), 4.22 (1 H, dd, *J* = 7.5, 3.5 Hz, C**H**OTBDMS), 3.74 (1 H, dd, *J* = 6.5, 3.5 Hz, C**H**OH), 3.72 (1 H, d, *J* = 9.0 Hz, C**H**HOBn), 3.62 (1 H, d, *J* = 9.0 Hz, **CH**HOBn), 3.10 (1 H, d, *J* = 6.5 Hz, CHO**H**), 1.69 (3 H, d, *J* = 5.0 Hz, =CHC**H$_3$**), 1.16 (3 H, s, CC**H$_3$**), 0.88 (9 H, s, SiC(C**H$_3$**)$_3$), 0.05 (3 H, s, SiC**H$_3$**), 0.02 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7 (**C**HO), 137.8 (Ar**C**), 131.9 (**C**H=), 128.6 (**C**H=), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.5 (Ar**C**H), 77.9 (**C**HOH), 73.9 (**C**HOTBDMS), 73.6 (**C**H_2Ph), 73.2 (**C**H_2OBn), 53.5 (CH_3**C**), 25.9 (SiC(**C**H_3)$_3$), 18.1 (Si**C**$(CH_3)_3$), 17.6 (=CH**C**H_3), 14.7 (**C**H_3C), -3.5 (Si**C**H_3), -4.6 (Si**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 415 $[M+Na]^+$ (36%), 447 $[M+Na+MeOH]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 415.2275 $[M+Na]^+$; found: 415.2278 $[M+Na]^+$.

Data for 5.22c and 5.22d (mixture): IR (neat): 3501 (br. w), 2929 (m), 2856 (m), 1722 (m), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (1 H, s, C**H**O (**5.22c**)), 9.55 (1 H, s, C**H**O (**5.22d**)), 7.40 – 7.28 (10 H, m, Ar**H**), 5.66 – 5.53 (1 H + 1 H, m, =C**H**CH_3 (**5.22c** and **5.22d**)), 5.45 – 5.35 (1 H + 1 H, m, =C**H**CHOTBDMS (**5.22c** and **5.22d**)), 4.58 (1 H, d, *J* = 11.6 Hz, C**H**HPh (**5.22d**)), 4.57 (1 H, d, *J* = 12.1 Hz, C**H**HPh (**5.22c**)), 4.52 – 4.42 (1 H + 1 H + 1 H, m, C**H**HPh (**5.22c** and **5.22d**) and C**H**OTBDMS (**5.22d**)), 4.02 (1 H, dd, *J* = 8.1, 6.6 Hz, C**H**OTBDMS (**5.22c**)), 3.81 (1 H, d, *J* = 9.1 Hz, C**H**HOBn (**5.22d**)), 3.77 – 3.67 (1 H + 2 H + 1 H + 1 H, m, C**H**HOBn (**5.22d**) and C**H$_2$**OBn (**5.22c**) and C**H**OH (**5.22c** and **5.22d**)), 2.93 (1 H, d, *J* = 7.1 Hz, CHO**H** (**5.22d**)), 2.89 (1 H, d, *J* = 6.6 Hz, CHO**H** (**5.22c**)), 1.71 (3 H, dd, *J* = 6.6, 1.5 Hz, C**H$_3$**CH= (**5.22c)**), 1.64 (3 H, dd, *J* = 7.1, 1.5 Hz, C**H$_3$**CH= (**5.22d)**), 1.23 (3 H, s, CC**H$_3$** (**5.22d**)), 1.21 (3 H, s, CC**H$_3$** (**5.22d**)), 0.84 (9 H + 9 H, s, SiC(C**H$_3$**)$_3$ (**5.22c** and

5.22d)), -0.01 (3 H, s, SiC**H**$_3$ (**5.22d**)), -0.02 (3 H, s, SiC**H**$_3$ (**5.22c**)), -0.03 (3 H, s, SiC**H**$_3$ (**5.22d**)), -0.03 (3 H, s, SiC**H**$_3$ (**5.22c**)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4 (**C**HO (**5.22c**)), 202.0 (**C**HO (**5.22d**)), 137.6 (Ar**C** (**5.22c**)), 137.5 (Ar**C** (**5.22d**)), 131.5 (=**C**HCHOTBDMS (**5.22c**)), 131.3 (=**C**HCHOTBDMS (**5.22d**)), 129.8 (=**C**HCH$_3$ (**5.22c**)), 129.6 (=**C**HCH$_3$ (**5.22d**)), 128.5 (Ar**C**H), 128.4 (Ar**C**H), 128.0 (Ar**C**H), 127.9 (Ar**C**H), 127.9 (Ar**C**H), 127.3 (Ar**C**H), 77.8 (**C**HOH (**5.22d**)), 77.5 (**C**HOH (**5.22c**)), 75.8 (**C**HOTBDMS, (**5.22c**)), 74.0 (**C**H$_2$Ph (**5.22d**)), 73.8 (**C**H$_2$Ph (**5.22c**)), 72.5 (**C**H$_2$OBn (**5.22d**)), 72.3 (**C**H$_2$OBn (**5.22c**)), 69.9 (**C**HOTBDMS, (**5.22d**)), 52.2 (CH$_3$**C**), 25.9 (SiC(**C**H$_3$)$_3$), 18.1 (Si**C**(CH$_3$)$_3$ (**5.22c**)), 18.0 (Si**C**(CH$_3$)$_3$ (**5.22d**)), 17.7 (=CH**C**H$_3$ (**5.22c**)), 16.0 (**C**H$_3$C, (**5.22d**)), 15.8 (**C**H$_3$C, (**5.22c**)), 13.8 (=CH**C**H$_3$ (**5.22d**)), -3.8 (Si**C**H$_3$ (**5.22c**)), -4.1 (Si**C**H$_3$ (**5.22d**)), -4.5 (Si**C**H$_3$ (**5.22c**)), -4.6 (Si**C**H$_3$ (**5.22d**)) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 415 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 415.2275 $[M+Na]^+$; found: 415.2279 $[M+Na]^+$.

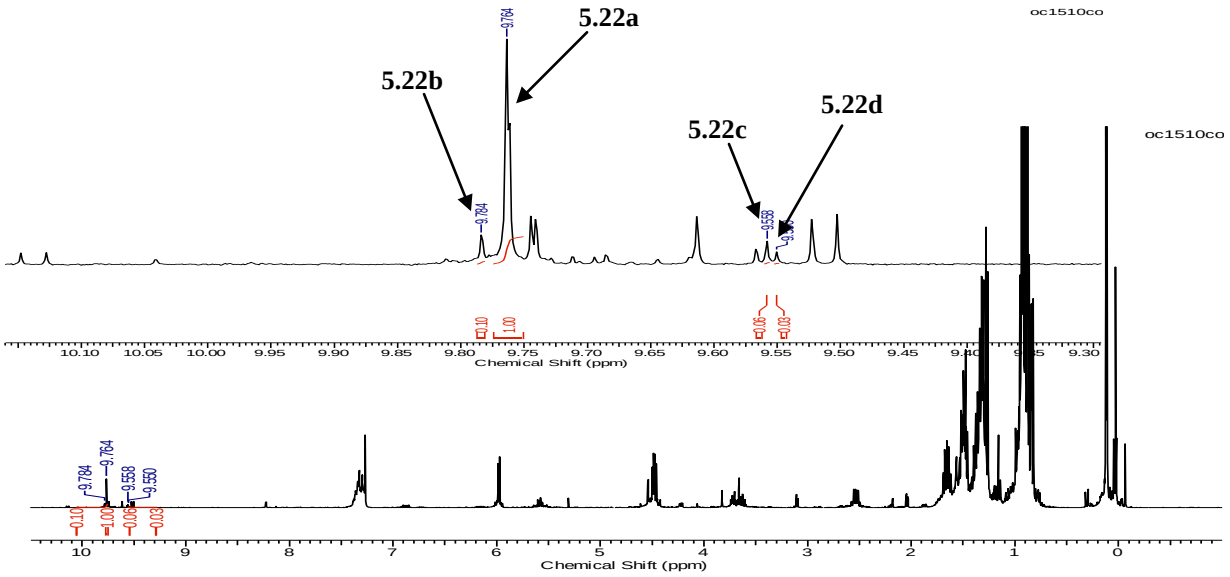
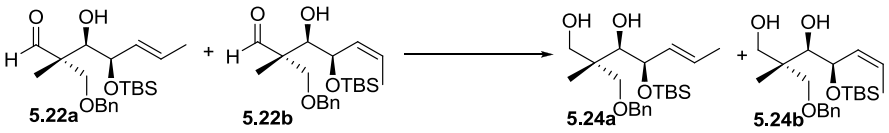


Figure 7.33. Crude ^{1}H NMR from hydroxyallylation of **1.94** from which the d.r was calculated.

(*E*)-(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-hept-5-ene-1,3-diol (5.24a) & (*Z*)-(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-hept-5-ene-1,3-diol (5.24b)



To a solution of $Me_4NB(OAc)_3H$ (334 mg, 1.27 mmol, 5 equiv.) and AcOH (143 µL, 2.55 mmol, 10 equiv.) in MeCN (6 mL) was added a solution of aldehyde **5.22a** and **5.22b** (100 mg, 0.25 mmol, 1 equiv.) in MeCN (2 mL). The reaction mixture was stirred at r.t for 1 h 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution. After effervescence had ceased, the solution was treated with 1.0 M aq. Na^+/K^+ tatrate solution and stirred for 20 min. The white aqueous solution was extracted with EtOAc, the organics extracts washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether / EtOAc 8:2) to give 76 mg of a **5.24** (0.19 mmol, 77%) as a colourless oil. The diastereoisomers were separated by preparative HPLC (hexane : EtOAc 78:22) to give **5.24a** (63 mg) and **5.24b** (10 mg).

Data for compound 5.24a: IR (neat): 3470 (br), 2954 (s), 2931 (s), 2885 (m), 2857 (s), 1454 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.29 (5 H, m, Ar**H**), 5.66 – 5.53 (2 H, m, C**H**=C**H**), 4.50 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.46 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.24 (1 H, dd, *J* = 7.1, 4.0 Hz, C**H**OTBDMS), 3.72 – 3.59 (3 H, m, C$\mathbf{H_2}$OH and C**H**OH), 3.49 (2 H, s, C$\mathbf{H_2}$OBn), 3.23 (1 H, d, *J* = 6.1 Hz, CHO**H**), 3.14 (1 H, t, *J* = 6.1 Hz, CH_2O**H**), 1.68 (3 H, d, *J* = 4.5 Hz, =CHC$\mathbf{H_3}$), 0.92 (3 H, s, CC$\mathbf{H_3}$), 0.90 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.08 (3 H, s, C$\mathbf{H_3}$Si), 0.04 (3 H, s, C$\mathbf{H_3}$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1 (Ar**C**), 132.8 (**C**H=), 128.4 (Ar**C**H), 127.8 (**C**H=), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 77.1 (**C**HOH), 75.7 (**C**H_2OBn), 74.2 (**C**HOTBDMS), 73.5 (**C**H_2OPh), 68.9 (**C**H_2OH), 42.8 (**C**CH_3), 25.9 (SiC**C**H_3), 18.1 (Si**C**CH_3), 17.6 (**C**H_3CH=), 16.1 (**C**H_3C), -3.4 (**C**H_3Si), -4.6 (**C**H_3Si) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 417 $[M+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 417.2432 $[M+Na]^+$; found: 417.2433 $[M+Na]^+$.

Data for compound 5.24b: IR (neat): 3445 (br), 2954 (s), 2930 (s), 2885 (m), 2857 (s), 1468 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5 H, m, Ar**H**), 5.66 – 5.55 (2 H, m, C**H**=), 4.57 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.49 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.34 – 4.27 (1 H, m,

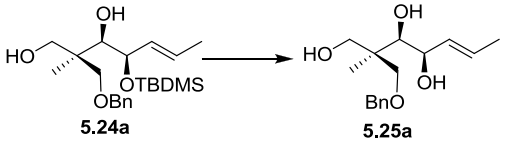
C**H**OTBDMS), 3.70 – 3.60 (3 H, m, C**H**$_2$OH and C**H**OH), 3.50 (2 H, s, C**H**$_2$OBn), 3.42 (1 H, d, *J* = 8.6 Hz, CH$_2$O**H**), 3.08 (1 H, d, *J* = 6.6 Hz, CHO**H**), 1.69 (2 H, d, *J* = 5.1 Hz, =CHC**H**$_3$), 0.89 (9 H, s, SiC(C**H**$_3$)$_3$), 0.88 (3 H, s, CC**H**$_3$), 0.07 (3 H, s, C**H**$_3$Si), 0.04 (3 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1 (Ar**C**), 132.9 (**C**H=), 128.4 (Ar**C**H), 127.6 (**C**H=), 127.5 (Ar**C**H), 77.2 (**C**HOH), 74.8 (**C**H$_2$OBn), 73.6 (**C**HOTBDMS), 72.0 (**C**H$_2$OPh), 69.8 (**C**H$_2$OH), 40.6 (**C**CH$_3$), 25.9 (SiC**C**H$_3$), 18.1 (Si**C**CH$_3$), 17.6 (**C**H$_3$CH=), 16.3 (**C**H$_3$C), -3.3 (**C**H$_3$Si), -4.6 (**C**H$_3$Si) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 417 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 417.2432 $[M+Na]^+$; found: 417.2431 $[M+Na]^+$.

(E)-(*rac*-2*S*,3*R*,4*R*)-2-Benzyloxymethyl-2-methyl-hept-5-ene-1,3,4-triol (5.25a)



5.24a **5.25a**

TBAF (1.0 M solution in THF) (228 µL, 0.23 mmol, 1.5 equiv.) was added dropwise to a solution of diol **5.24a** (60 mg, 0.15 mmol, 1 equiv) in THF (2 mL). The reaction was stirred at r.t for 1 h. The solvent removed in *vacuo*. The crude mixture was purified by column chromatography (petroleum ether : EtOAc 1:1) to give 35 mg (0.12 mmol, 83%) of a white solid. The solid was recrystallised from diisopropyl ether and hexane to give a crystalline white solid.

Data for compound 5.25a: IR (neat): 3330 (br), 3030 (w), 2877 (m), 1453 (s) cm^{-1}.

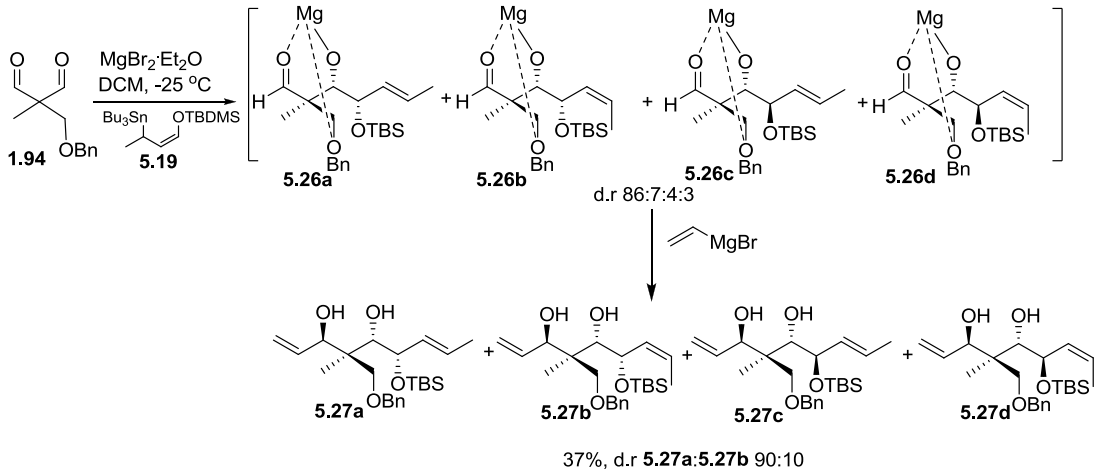
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.21 (5 H, m, Ar**H**), 5.79 – 5.66 (1 H, m, =C**H**CH$_3$), 5.61 (1 H, ddd, *J* = 15.7, 6.6, 1.5 Hz, =C**H**CHOH), 4.46 (2 H, s, C**H**$_2$Ph), 4.20 (1 H, d, *J* = 6.6 Hz, C**H**OHCH=), 3.88 (1 H, d, *J* = 11.1 Hz, C**H**HOBn), 3.62 – 3.54 (2 H, m, CC**H**OH and CHO**H**CH=), 3.48 – 3.34 (5 H, m, C**H**HOBn and C**H**$_2$O**H** and CCHO**H**), 1.68 (3 H, d, *J* = 6.1 Hz, C**H**$_3$CH=), 0.91 (3 H, s, CC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4 (Ar**C**), 132.0 (=**C**HCHOH), 128.5 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (=**C**HCH$_3$), 77.9 (C**C**HOH), 77.3 (**C**H$_2$OH), 73.7 (**C**H$_2$Ph), 70.5 (**C**HOHCH=), 65.0 (**C**H$_2$OBn), 43.2 (**C**CH$_3$), 17.7 (**C**H$_3$CH=), 16.7 (**C**H$_3$C) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 303 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 303.1567 $[M+Na]^+$; found: 303.1570 $[M+Na]^+$.
Mp: 72 –73 °C

(*E*)-(3*R*,4*S*,5*S*,6*S*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-nona-1,7-diene-3,5-diol (5.27a) & (*Z*)-(3*R*,4*S*,5*S*,6*S*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-nona-1,7-diene-3,5-diol (5.27b) & (*E*)-(3*R*,4*S*,5*S*,6*R*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-nona-1,7-diene-3,5-diol (5.27c) & (*Z*)-(3*R*,4*S*,5*S*,6*R*)-4-Benzyloxymethyl-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-nona-1,7-diene-3,5-diol (5.27d)



1,2-Dibromoethane (477 µL, 5.53 mmol, 3 equiv.) was added to a suspension of magnesium turnings (134.4 mg, 5.53 mmol, 3 equiv.) in Et_2O (8 mL) and stirred for 30 min at r.t to obtain $MgBr_2{\bullet}OEt_2$. After removal of Et_2O, CH_2Cl_2 (8 mL) was added and the reaction mixture was cooled to –25 °C before addition, *via* cannula of the dialdehyde **1.94** (380 mg, 1.21 mmol, 1 equiv.) in CH_2Cl_2 (12 mL). After addition of the dialdehyde the reaction mixture becomes a yellow solution. After 20 min of stirring, allyl tin **5.19** (2.63 g, 5.53 mmol, 3 equiv.) in CH_2Cl_2 (18 mL) was added *via* cannula and allowed to react for 3 h. An aliquot was removed, hydrolysed with sat. aq. $NaHCO_3$, the organic phase washed with brine and dried over $MgSO_4$, before removal of the solvent to give crude, from which the d.r. was determined by ^{1}H NMR (**5.22a**:**5.22b**:**5.22c**:**5.22d** 86:7:4:3). Vinyl magnesium bromide (1.0 M sol. in THF) (7.37 mL, 7.37 mmol, 4 equiv.) was added dropwise and the reaction mixture stirred at –25 °C for 45 min. The reaction was quenched with aq. NH_4Cl sol. and allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column

chromatography (petroleum ether / EtOAc 9:1) to give 284 mg (0.68 mmol, 37% yield) of **5.27a** and **5.27b** as a colourless oil (d.r 9:1, from ^{1}H NMR of **5.27** after column chromatography, Figure 7.34). An analytically pure sample of **5.27a** (13 mg) was obtained after preparative HPLC (9:1 hexane / acetone).

Data for 5.27a: IR (neat): 3446 (br. m), 2928 (m), 2856 (m), 1497 (w), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.24 (5 H, m, Ar**H**), 5.98 (1 H, ddd, *J* = 17.1, 10.7, 6.1 Hz, C**H**=CH_2), 5.60 – 5.51 (2 H, m, C**H**=C**H**CH_3), 5.31 (1 H, d, *J* = 16.7 Hz, C**HH**=CH), 5.20 (1 H, d, *J* = 10.6 Hz, C**HH**=CH), 4.46 (1 H, d, *J* = 11.6 Hz, C**HH**Ph), 4.42 (1 H, d, *J* = 12.1 Hz, C**HH**Ph), 4.29 – 4.20 (2 H, m, =CHC**H**OH & C**H**OTBDMS), 3.93 – 3.82 (2 H, m, C**H**OHCHOTBDMS & =CHCHO**H**), 3.53 (1 H, d, *J* = 9.6 Hz, C**HH**OBn), 3.39 (1 H, d, *J* = 9.6 Hz, C**HH**OBn), 3.24 (1 H, d, *J* = 5.6 Hz, CHO**H**CHOTBMDS), 1.67 (3 H, d, *J* = 5.1 Hz, C**H$_3$**CH=), 0.95 (3 H, s, CC**H$_3$**), 0.89 (9 H, s, SiC(C**H$_3$**)$_3$), 0.06 (3 H, s, SiC**H$_3$**), 0.03 (3 H, s, SiC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8 (Ar**C**), 137.7 (**C**H=CH_2), 133.1 (=**C**HCH_3), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.7 (=**C**HCHOTBDMS), 127.6 (Ar**C**H), 116.2 (**C**H$_2$=), 78.0 (**C**HOTBDMS), 75.4 (**C**HOHCHOTBDMS), 73.9 (=CH**C**HOH), 73.8 (**C**H$_2$Ph), 73.5 (**C**H$_2$OBn), 44.6 (CH_3**C**), 25.9 (SiC(**C**H$_3$)$_3$), 18.1 (Si**C**(CH$_3$)$_3$), 17.6 (**C**H$_3$CH=), 15.9 (C**C**H$_3$), -3.3 (Si**C**H$_3$), -4.6 (Si**C**H$_3$) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 443 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 443.2588 $[M+Na]^+$; found: 443.2595 $[M+Na]^+$.

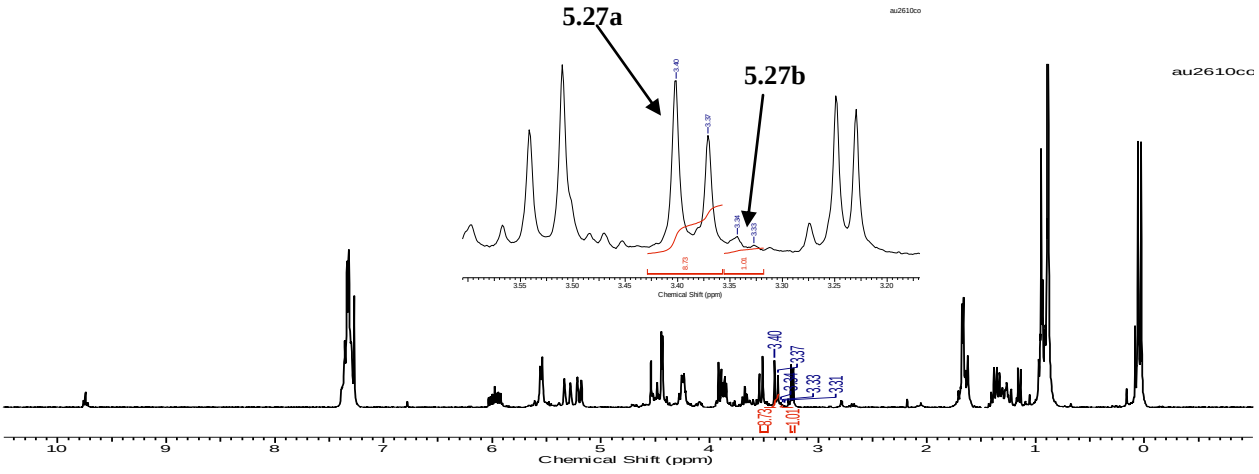
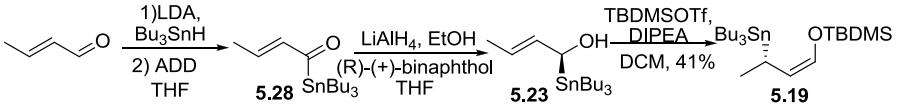


Figure 7.34. ^{1}H NMR after chromatography of **5.27** double hydroxyallylation - vinyl Grignard addition to dialdehyde **1.94**, showing how the d.r. was calculated.

***tert*-Butyl-dimethyl-((Z)-(*S*)-3-tributylstannanyl-but-1-enyloxy)-silane (5.19)**



To a solution of DIPA (2.72 mL, 19.4 mmol, 1.2 equiv.) in THF (88 mL) at 0 °C was added *n*BuLi (2.5M solution in hexanes) (12.1 mL, 19.4 mmol, 1.2 equiv.) and the reaction mixture stirred at 0 °C for 15 min. Tributyl tinhydride (5.2 mL, 19.4 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at 0 °C for 15 min and cooled to –78 °C. Crotonaldehyde (1.40 mL, 17.2 mmol, 1 equiv.) in THF (22 mL) was added and the reaction mixture stirred at –78 °C for 30 min. 1,1-Azodicarbonyl (4.90 g, 19.4 mmol, 1.2 equiv.) was added and the reaction allowed to warm to 0 °C and stirred for 15 min. The reaction was quenched with sat. aq. NH_4Cl and the organics extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give crude acyl stannane **5.28** as an orange oil.

To a solution of $LiAlH_4$ (1.0M solution in THF) (31 mL, 31.0 mmol, 1.8 equiv) in THF (90 mL) was added EtOH (1.8 mL, 31.0 mmol, 1.8 equiv.) over 30 min and the resultant white suspension stirred at r.t for 30 min. A solution of R-(+)-1,1'-bi-2-naphthol (8.9 g, 31.0 mmol, 1.8 equiv.) in THF (60 mL) was added over 1 h and the reaction warmed to reflux over 50 min, then cooled slowly to –78 °C. Crude acyl stannane **5.28** in THF (20 mL) was added over 1 h and the reaction stirred at –78 °C for 23 h. The reaction was quenched with MeOH (4 mL) followed by sat. aq. NH_4Cl and allowed to warm to r.t. The organics were extracted and the aqueous layer treated with 3% aq. HCl and extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The resultant oil was triturated with hexane and filtered to recover solid R-(+)-1,1'-bi-2-naphthol (7.69 g, 86%). The filtrate was concentrated in *vacuo* to give crude chiral allyltin alcohol **5.23**.

To a solution of crude allyltin alcohol **5.23** in CH_2Cl_2 (48 mL) at 0 °C was added DIPEA (9.00 mL, 51.6 mmol, 3 equiv.) followed by TBDMSOTf (4.35 mL, 18.9 mmol, 1.1 equiv.) and the reaction was warmed to r.t over 3 h. The reaction was quenched with H_2O and the organics extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (hexane) to give **5.19** (3.34 g, 7.01 mmol, 41%) as a colourless oil.

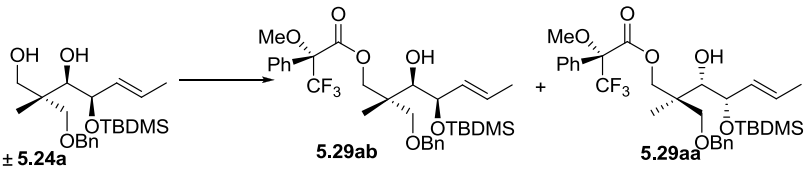
IR (neat): 3021 (w), 2955 (s), 2927 (m), 2865 (m), 1695 (s), 1640 (m), 1463 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (1 H, dd, *J* = 6.0, 1.0 Hz, C**H**OTBDMS), 4.48 (1 H, dd, *J* = 11.0, 5.5 Hz, C**H**CHSnBu_3), 2.60 – 2.48 (1 H, m, C**H**SnBu_3), 1.58 – 1.22 (18 H, m, Sn((C**H**$_2$)$_3$CH_3)$_3$), 0.94 (9 H, s, SiC(C**H**$_3$)$_3$), 0.90 (9 H, t, *J* = 7.3 Hz, CH_2C**H**$_3$), 0.12 (3 H, s, SiC**H**$_3$), 0.11 (3 H, s, SiC**H**$_3$) ppm.

[α]$_D$ +127.8 (*c* 2.0, $CHCl_3$, 26 °C), lit. +130.6 (*c* 2.24, $CHCl_3$, 28 °C)[187]

This corresponds to data from the literature[173]

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (*E*)-(2*R*,3*R*,4*R*)-2-benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enyl ester (5.29ab) & (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (*E*)-(2*S*,3*S*,4*S*)-2-benzyloxymethyl-4-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-methyl-hept-5-enyl ester (5.29aa)



To a solution of ±**5.24a** (25 mg, 0.063 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added Et_3N (88 µL, 0.63 mmol, 10 equiv.) and DMAP (1 mg, 0.0063 mmol, 0.1 equiv.) followed by S-MTPACl (24 µL, 0.126 mmol, 2 equiv.). The reaction was stirred at r.t. for 20 h. The reaction was quenched with sat. aq. NH_4Cl and the organics extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1 petroleum ether:EtOAc) to give 38 mg (0.062 mmol, 99% yield) of **5.29aa** and **5.29ab** as a colourless oil.

Data for compound 5.29aa and 5.29ab: IR (neat): 3535 (br), 2954 (m), 2931 (m), 2885 (w), 2857 (m), 1750 (s), 1453 (m) cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ 7.23 – 6.97 (20 H, m, Ar**H**), 5.58 – 5.46 (2 H, m, =C**H**CHOTBDMS), 5.40 – 5.28 (2 H, m, =C**H**CH_3), 4.79 (1 H, d, *J* = 10.6 Hz, C**H**HPh), 4.71 (1 H, d, *J* = 11.1 Hz, C**H**HPh), 4.67 (1 H, d, *J* = 11.1 Hz, CH**H**Ph), 4.57 (1 H, d, *J* = 10.6 Hz, CH**H**Ph), 4.28 – 4.14 (6 H, m, C**H**$_2$CO and C**H**OTBDMS), 3.68 (1 H, dd, *J* = 5.6, 4.0 Hz, C**H**OH), 3.63 (1 H, dd, *J* = 5.6, 4.0 Hz, C**H**OH), 3.44 (3 H, s, C**H**$_3$O), 3.42 (3 H, s, C**H**$_3$O), 3.40 – 3.31 (4 H, m, C**H**$_2$OBn), 3.04 (1 H, d, *J* = 5.1 Hz, CHO**H**), 2.99 (1 H, d, *J* = 5.6 Hz, CHO**H**), 1.42 (3 H, t, *J* = 2.0 Hz, C**H**$_3$CH=), 1.41 (3 H, dd, *J* = 2.0, 1.5 Hz,

C**H**$_3$CH=), 1.04 (3 H, s, CC**H**$_3$), 1.02 (3 H, s, CC**H**$_3$), 0.90 (18 H, s, SiC(C**H**$_3$)$_3$), 0.02 (3 H, s, C**H**$_3$Si), 0.01 (3 H, s, C**H**$_3$Si), 0.01 (3 H, s, C**H**$_3$Si), 0.00 (3 H, s, C**H**$_3$Si) ppm.

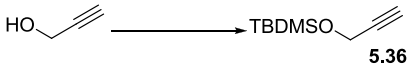
^{13}C NMR (100 MHz, C_6D_6): δ 169.9 (**C**OO), 139.1 (Ar**C**), 133.8 (**C**H=), 133.8 (**C**H=), 133.7 (Ar**C**), 130.0 (**C**H=), 130.0 (**C**H=), 129.0 (Ar**C**H), 129.0 (Ar**C**H), 76.3 (**C**HOH), 76.3 (**C**HOH), 74.9 (**C**HOTBDMS), 73.9 (C**H**$_2$OCO), 73.1 (**C**H$_2$OBn), 73.0 (**C**H$_2$OBn), 69.7 (C**H**$_2$Ph), 69.6 (C**H**$_2$Ph), 55.7 (**C**H$_3$O), 55.7 (**C**H$_3$O), 43.1 (**C**CH$_3$), 43.1 (**C**CH$_3$), 26.5 (SiC**C**H$_3$), 26.4 (**C**COO), 18.6 (Si**C**CH$_3$), 17.8 (**C**H$_3$CH=), 16.4 (**C**H$_3$C), 16.3 (**C**H$_3$C), -2.8 (**C**H$_3$Si), -4.1 (**C**H$_3$Si) ppm.

^{19}F NMR (282 MHz, C_6D_6): δ -71.60 (3 F, br. s., C**F**$_3$), -71.38 (3 F, br. s., C**F**$_3$) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 633 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 633.2830 $[M+Na]^+$; found: 633.2825 $[M+Na]^+$.

tert-Butyl-dimethyl-prop-2-ynyloxy-silane (5.36)



5.36

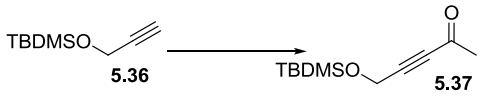
TBDMSCl (14.8 g, 98 mmol, 1.1 equiv.) and imidazole (12.1 g, 178 mmol, 2 equiv.) were added to a solution of propargylalcohol (5.0 g, 89 mmol, 1 equiv.) in CH_2Cl_2 (35 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction was quenched with H_2O and the organics extracted with CH_2Cl_2 and dried over Na_2SO_4, filtered and concentrated in *vacuo* to give 15.2 g (89 mmol, 100%) of **5.36** as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 (2 H, d, *J* = 2.0 Hz, C**H**$_2$OTBDMS), 2.39 (1 H, t, *J* = 2.5 Hz, ≡C**H**), 0.91 (9 H, s, SiC(C**H**$_3$)$_3$), 0.13 (6 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 82.4 (CH_2**C**≡), 72.8 (≡**C**H), 51.5 (**C**H$_2$OTBDMS), 25.8 (SiC**C**H$_3$), 18.3 (Si**C**CH$_3$), -5.2 (Si**C**H$_3$) ppm.

This corresponds to data from the literature [188]

5-(*tert*-Butyl-dimethyl-silanyloxy)-pent-3-yn-2-one (5.37)



5.36 **5.37**

To a solution of **5.36** (8.46 g, 49.8 mmol, 1 equiv.) in THF (170 mL) at –78 °C was added *n*BuLi (2.5M in Hexanes) (19.9 mL, 49.8 mmol, 1 equiv.) and the reaction mixture was

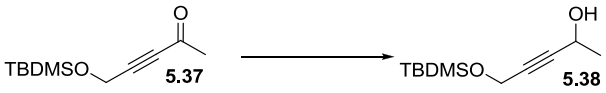
stirred at –78 °C for 15 min. Acetic anhydride (9.39 mL, 99.3 mmol, 2 equiv.) was added and the reaction warmed to r.t over 2 h 30 min and stirred at r.t for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl and the organics were extracted with Et_2O, washed with $NaHCO_3$, then H_2O and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (9:1 petroleum ether: EtOAc) to give 7.62 g (35.88 mmol, 72% yield) of **5.37** as a colourless oil.[189]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (2 H, s, C**H**$_2$OTBDMS), 2.35 (3 H, s, COC**H**$_3$), 0.92 (9 H, s, SiC(C**H**$_3$)$_3$), 0.14 (6 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.0 (**C**OCH_3), 90.1 (≡**C**CO), 84.3 (CH_2**C**≡), 51.5 (**C**H_2OTBDMS), 32.5 (**C**H_3CO), 25.7 (SiC**C**H_3), 18.2 (Si**C**CH_3), -5.2 (Si**C**H_3) ppm.

This corresponds to data from the literature[190]

5-(*tert*-Butyl-dimethyl-silanyloxy)-pent-3-yn-2-ol (5.38)



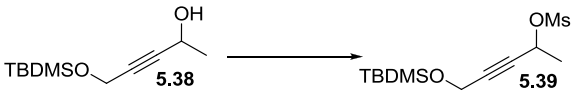
To a suspension of $LiAlH_4$ (1.0 M in THF) (16.8 mL, 16.8 mmol, 1.2 equiv.) in Et_2O (200 mL) at –78 °C was added a solution of **5.37** (3.00 g, 14.1 mmol, 1 equiv.) in Et_2O (50 mL) and the reaction stirred at –78 °C for 1 h 30 min. The reaction was quenched with 10% aq. HCl and allowed to warm to r.t. The organics were extracted with Et_2O and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (petroleum ether / acetone, 9:1) to give 2.34 g (10.92 mmol, 77% yield) of **5.38** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (1 H, td, *J* = 6.6, 1.5 Hz, C**H**OH), 4.34 (2 H, d, *J* = 2.0 Hz, C**H**$_2$OTBDMS), 1.89 (1 H, d, *J* = 5.1 Hz, CHO**H**), 1.45 (3 H, d, *J* = 6.6 Hz, C**H**$_3$CHOH), 0.91 (9 H, s, SiC(C**H**$_3$)$_3$), 0.12 (6 H, s, C**H**$_3$Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 86.6 (CH_2**C**≡), 82.7 (≡**C**CHOH), 58.3 (**C**HOH), 51.7 (**C**H_2OTBDMS), 25.8 (SiC**C**H_3), 24.2 (**C**H_3CHOH), 18.3 (Si**C**CH_3), -5.1 (Si**C**H_3) ppm.

This corresponds to data from the literature[190]

Methanesulfonic acid 4-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-but-2-ynyl ester (5.39)



To a solution of **5.38** (3.20 g, 14.9 mmol, 1 equiv.) in CH_2Cl_2 (96 mL) at –78 °C was added Et_3N (4.16 mL, 29.9 mmol, 2 equiv.) followed by MsCl (1.73 mL, 22.4 mmol, 1.5 equiv.). The reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and allowed to warm to r.t. The organics were extracted with Et_2O, washed with brine and dried over $MgSO_4$, filtered and concentrated in *vacuo* to give 4.11 g (14.1 mmol, 94% yield) of **5.39** as a pale yellow oil.

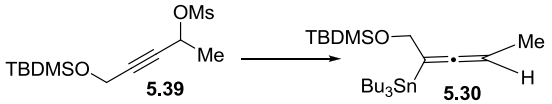
IR (neat): 2932 (m), 2858 (m), 1470 (w), 1359 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 – 5.26 (1 H, m, C**H**OH), 4.36 (2 H, d, *J* = 2.0 Hz, C**H$_2$**OTBDMS), 3.10 (3 H, s, C**H$_3$**S), 1.63 (3 H, d, *J* = 6.6 Hz, C**H$_3$**CHOMs), 0.90 (9 H, s SiC(C**H$_3$**)$_3$), 0.11 (6 H, s, C**H$_3$**Si) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 87.0 (CH_2**C**≡), 81.0 (≡**C**CHOMs), 68.1 (**C**HOMs), 51.4 (**C**H_2OTBDMS), 39.1 (**C**H_3S), 25.7 (SiC**C**H_3), 22.5 (**C**H_3CHOMs), 18.2 (Si**C**CH_3), -5.3 (Si**C**H_3) ppm.

This corresponds to data from the literature[169]

***tert*-Butyl-dimethyl-(2-tributylstannanyl-penta-2,3-dienyloxy)-silane (5.30)**



*n*BuLi (2.5 M in hexanes) (5.50 mL, 13.68 mmol, 2 equiv.) was added to a solution of DIPA (1.92 mL, 13.68 mmol, 2 equiv.) in THF (30 mL) at 0 °C and the reaction stirred for 30 min. Tributyl tin hydride (3.69 mL, 13.68 mmol, 2 equiv.) was added to the reaction and stirred at 0 °C for 15 min to form Bu_3SnLi. This was added to a suspension of $CuBr_2{\cdot}SMe_2$ (2.81 g, 13.68 mmol, 2 equiv.) in THF (10 mL) at –60 °C and stirred at –60 °C for 30 min. A solution of **5.39** (2.00 g, 6.84 mmol, 1 equiv.) in THF (26 mL) was added dropwise to the reaction and the reaction was stirred at –60 °C for 4 h. The reaction was quenched with sat. aq. NH_4Cl containing 1% w/w NaCN and allowed to warm to r.t. The organics were extracted with Et_2O, washed with H_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by column chromatography (petroleum ether) to give 2.19 g (4.49 mmol, 66% yield) of **5.30** as a colourless oil.

IR (neat): 2956 (s), 2928 (s), 2856 (m), 2018 (m), 1975 (w), 1935 (w), 1462 (w) cm^{-1}.

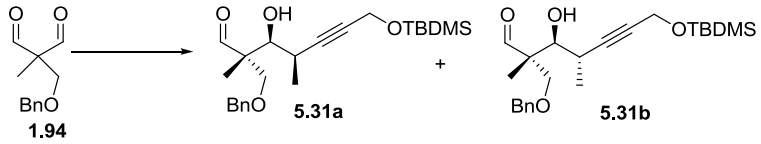
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 – 4.63 (1 H, m, =C**H**), 4.26 (2 H, tdd, *J* = 14.2, 3.0, 1.5 Hz, C**H$_2$**OTBDMS), 1.62 (3 H, d, *J* = 7.1 Hz, =CC**H$_3$**), 1.57 – 1.45 (6 H, m, $(CH_3CH_2CH_2C\mathbf{H_2})_3Sn$), 1.38 – 1.26 (6 H, m, $(CH_3CH_2C\mathbf{H_2}CH_2)_3Sn$), 0.91 (9 H, s, $SiC(C\mathbf{H_3})_3$), 0.98 – 0.87 (15 H, m, $C\mathbf{H_3}C\mathbf{H_2}(CH_2)_2Sn$), 0.07 (6 H, s, $C\mathbf{H_3}Si$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5 (=**C**=), 95.7 (CH_2**C**=), 77.9 (=**C**CH_3), 64.7 (**C**H_2OTBDMS), 29.1 (**C**H_2Sn), 27.3 (**C**H_2CH_2Sn), 26.0 (SiC**C**H_3), 22.5 (**C**H_3CHOMs), 18.5 (Si**C**CH_3), 14.2 (**C**H_3C=), 13.7 (**C**$H_3(CH_2)_3$Sn), 10.4 (CH_3**C**$H_2(CH_2)_2$Sn), -5.3 (Si**C**H_3) ppm.

LRMS (ESI+): $^m/_z$ (rel. intensity) 454 $[M-^tBu+Na]^+$ (100%).

HRMS (ESI+): $^m/_z$ (rel. intensity) calculated: 511.2389 $[M+Na]^+$; found: 511.2380 $[M+Na]^+$.

(*rac*-2*S*,3*S*,4*R*)-2-Benzyloxymethyl-7-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2,4-dimethyl-hept-5-ynal (5.31a) & (*rac*-2*S*,3*S*,4*S*)-2-Benzyloxymethyl-7-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2,4-dimethyl-hept-5-ynal (5.31b)



1,2-Dibromoethane (76 μL, 0.88 mmol, 3 equiv.) was added to a suspension of magnesium turnings (21 mg, 0.88 mmol, 3 equiv.) in Et_2O (1 mL) and stirred for 30 min at r.t to obtain $MgBr_2$•OEt_2. After removal of the ether, CH_2Cl_2 (1.2 mL) was added and the reaction mixture was cooled to –40 °C before addition *via* cannula of dialdehyde **1.94** (60 mg, 0.29 mmol 1 equiv.) in CH_2Cl_2 (2 mL) at –40 °C. After 20 min of stirring, allenic stannane **5.30** (285 mg, 0.58 mmol, 2 equiv.) in CH_2Cl_2 (2.8 mL) at –40 °C was added *via* cannula and the reaction mixture stirred at –40 °C for 1 h and the reaction warmed to –25 °C and stirred for 1.5 h. The reaction mixture was hydrolysed with sat. aq. $NaHCO_3$ and then allowed to warm to r.t. The organics were extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$, before removal of the solvent. The crude mixure was purified by column chromatography (petroleum ether / EtOAc 9:1) to give 40 mg of **5.31a** and **5.31b** as colourless oil (d.r. **5.31a**:**5.31b** 80:20, Figure 7.35) (0.10 mmol, 34%). The diastereoisomers were separated by preparative HPLC (9:1 hexane / EtOAc).

Data for 5.31a: IR (neat): 3483 (br. w), 2954 (s), 2931 (s), 2858 (s), 2360 (m), 2340 (w), 2039 (m), 1978 (w), 1719 (m), 1457 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (1 H, s, C**H**O), 7.41 – 7.28 (5 H, m, Ar**H**), 4.54 (2 H, d, *J* = 11.9 Hz, C**H**HPh), 4.52 (2 H, d, *J* = 12.0 Hz, CH**H**Ph), 4.20 (2 H, d, *J* = 2.0 Hz, C$\mathbf{H_2}$OTBDMS), 3.96 (1 H, d, *J* = 9.6 Hz, C**H**HOBn), 3.76 (1 H, d, *J* = 9.6 Hz, CH**H**OBn), 3.70 (1 H, t, *J* = 9.1 Hz, C**H**OH), 2.98 (1 H, d, *J* = 9.2 Hz, CHO**H**), 2.56 (1 H, m, C**H**CH_3), 1.32 (3 H, d, *J* = 6.8 Hz, CHC$\mathbf{H_3}$), 1.27 (3 H, s, CC$\mathbf{H_3}$), 0.91 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.11 (6 H, s, SiC$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4 (**C**HO), 137.2 (Ar**C**), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 127.8 (Ar**C**H), 77.9 (**C**HOH), 77.2 (**C**H_2Ph), 76.7 (**C**H_2OBn), 74.1 (≡**C**$CHCH_3$), 72.7 (≡**C**CH_2OTBDMS), 53.6 (CH_3**C**), 51.8 (**C**H_2OTBDMS), 30.5 (**C**HCH_3), 25.8 (SiC(**C**H_3)$_3$), 18.3 (Si**C**$(CH_3)_3$), 18.1 (CH**C**H_3), 17.1 (**C**H_3C), -5.2 (Si**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 427 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 427.2275 $[M+Na]^+$; found: 427.2277 $[M+Na]^+$.

Data for 5.31b: IR (neat): 3459 (br. w), 2954 (s), 2932 (s), 2858 (s), 2360 (m), 2340 (w), 2039 (w), 2017 (m), 1976 (w), 1718 (m), 1456 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (1 H, s, C**H**O), 7.44 – 7.28 (5 H, m, Ar**H**), 4.55 (1 H, d, *J* = 11.8 Hz, C**H**HPh), 4.48 (1 H, d, *J* = 11.9 Hz, CH**H**Ph), 4.23 (2 H, d, *J* = 2.0 Hz, C$\mathbf{H_2}$OTBDMS), 4.03 (1 H, dd, *J* = 8.9, 6.3 Hz, C**H**OH), 3.70 (1 H, d, *J* = 9.2 Hz, C**H**HOBn), 3.66 (1 H, d, *J* = 9.2 Hz, CH**H**OBn), 2.85 (1 H, d, *J* = 6.3 Hz, CHO**H**), 2.66 – 2.53 (1 H, m, C**H**CH_3), 1.32 (3 H, d, *J* = 6.8 Hz, CHC$\mathbf{H_3}$), 1.16 (3 H, s, CC$\mathbf{H_3}$), 0.91 (9 H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.11 (6 H, s, SiC$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2 (**C**HO), 137.2 (Ar**C**), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 83.1 (≡**C**$CHCH_3$), 83.1 (≡**C**CH_2OTBDMS), 77.2 (**C**HOH), 73.9 (**C**H_2Ph), 73.8 (**C**H_2OBn), 54.5 (**C**H_2OTBDMS), 51.7 (CH_3**C**), 29.2 (**C**HCH_3), 25.8 (SiC(**C**H_3)$_3$), 18.4 (CH**C**H_3), 17.4 (Si**C**$(CH_3)_3$), 13.6 (**C**H_3C), -5.2 (Si**C**H_3) ppm.

LRMS (ESI+): $^{m}/_{z}$ (rel. intensity) 427 $[M+Na]^+$ (100%).

HRMS (ESI+): $^{m}/_{z}$ (rel. intensity) calculated: 405.2456 $[M+H]^+$; found: 405.1348 $[M+H]^+$.

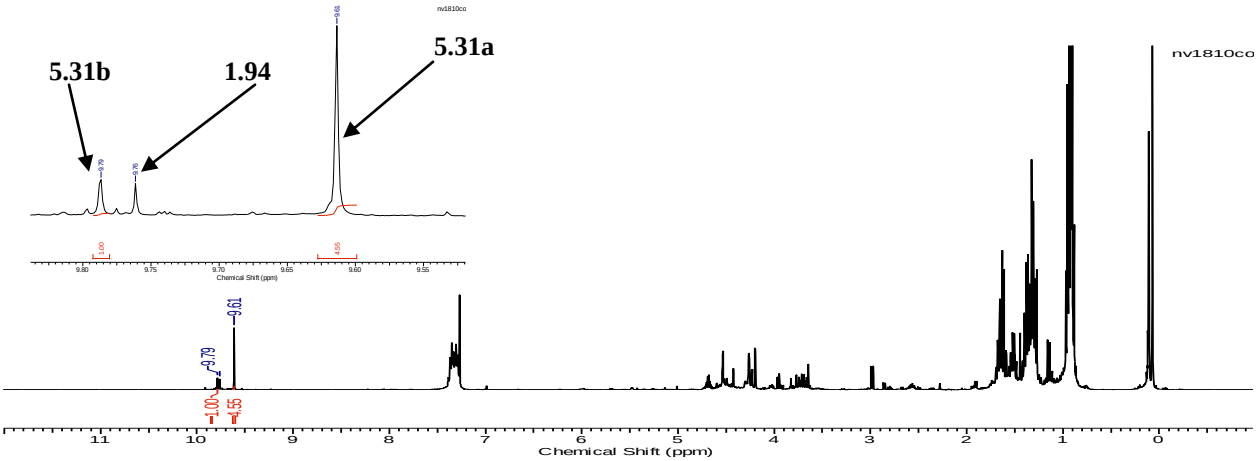


Figure 7.35 Crude ^{1}H NMR from the reaction between **5.30** and **1.94** showing how the d.r was calculated.

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APPENDIX

Appendix A

X-Ray Structure of 4.11a

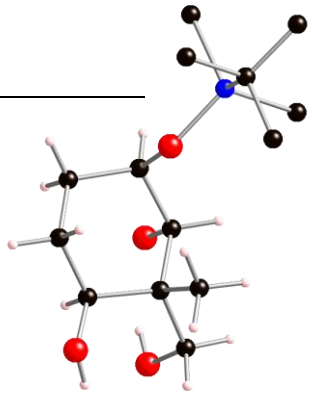


Table 1. Crystal data and structure refinement details.

Identification code	**2009sot0547**	
Empirical formula	$C_{14}H_{30}O_4Si$	
Formula weight	290.47	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 6.7205(6) Å	α = 76.828(5)°
	b = 9.9305(11) Å	β = 81.198(7)°
	c = 13.2467(16) Å	γ = 80.692(7)°
Volume	843.23(16) Å^3	
Z	2	
Density (calculated)	1.144 Mg / m^3	
Absorption coefficient	0.147 mm^{-1}	
F(000)	320	
Crystal	Rod; Colourless	
Crystal size	0.2 × 0.05 × 0.02 mm^3	
θ range for data collection	3.09 – 25.03°	
Index ranges	$-7 \le h \le 7$, $-11 \le k \le 11$, $-15 \le l \le 15$	
Reflections collected	12838	
Independent reflections	2959 [R_{int} = 0.0697]	
Completeness to θ = 25.03°	99.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9971 and 0.9612	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2959 / 0 / 181	
Goodness-of-fit on F^2	1.119	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0672, *wR2* = 0.1233	
R indices (all data)	*R1* = 0.0977, *wR2* = 0.1383	
Largest diff. peak and hole	0.263 and –0.290 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located in the difference map and then placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2149(5)	–1070(3)	2014(3)	24(1)	1
C2	1696(4)	–1903(3)	3130(3)	24(1)	1
C3	3489(4)	–2253(3)	3789(2)	23(1)	1
C4	5375(4)	–2891(3)	3150(2)	24(1)	1
C5	5862(5)	–1979(3)	2082(3)	26(1)	1
C6	4068(5)	–1744(4)	1449(3)	27(1)	1
C7	–386(5)	1772(4)	529(3)	37(1)	1
C8	–1623(5)	1419(4)	2855(3)	37(1)	1
C9	1694(5)	3265(3)	1810(3)	29(1)	1
C10	3475(6)	3450(4)	936(3)	45(1)	1
C11	75(6)	4559(4)	1638(3)	41(1)	1
C12	2479(5)	3144(4)	2861(3)	34(1)	1
C13	3886(5)	–942(3)	4111(3)	30(1)	1
C14	2913(5)	–3289(3)	4811(3)	27(1)	1
O1	2380(3)	344(2)	2012(2)	24(1)	1
O2	1088(3)	–3193(2)	3023(2)	28(1)	1
O3	2807(3)	–4665(2)	4682(2)	31(1)	1
O4	7131(3)	–3110(2)	3694(2)	32(1)	1
Si2	540(1)	1664(1)	1805(1)	24(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.437(4)	C5–C6	1.530(4)
C1–C6	1.526(4)	C7–Si2	1.864(4)
C1–C2	1.532(4)	C8–Si2	1.857(3)
C2–O2	1.449(4)	C9–C10	1.536(5)
C2–C3	1.544(4)	C9–C12	1.536(5)
C3–C13	1.532(4)	C9–C11	1.542(5)
C3–C14	1.542(4)	C9–Si2	1.880(3)
C3–C4	1.544(4)	C14–O3	1.429(4)
C4–O4	1.437(4)	O1–Si2	1.654(2)
C4–C5	1.516(4)		

O1–C1–C6	109.2(2)	C1–C6–C5	111.2(3)
O1–C1–C2	111.2(3)	C10–C9–C12	108.8(3)
C6–C1–C2	111.1(3)	C10–C9–C11	109.3(3)
O2–C2–C1	105.8(3)	C12–C9–C11	108.5(3)
O2–C2–C3	108.8(2)	C10–C9–Si2	110.0(2)
C1–C2–C3	115.5(2)	C12–C9–Si2	110.7(2)
C13–C3–C14	106.2(3)	C11–C9–Si2	109.6(2)
C13–C3–C2	110.3(3)	O3–C14–C3	114.5(3)
C14–C3–C2	109.2(2)	C1–O1–Si2	123.36(18)
C13–C3–C4	111.7(2)	O1–Si2–C8	110.30(15)
C14–C3–C4	110.7(3)	O1–Si2–C7	110.00(15)
C2–C3–C4	108.8(3)	C8–Si2–C7	108.58(17)
O4–C4–C5	107.9(2)	O1–Si2–C9	105.64(13)
O4–C4–C3	110.7(3)	C8–Si2–C9	110.84(16)
C5–C4–C3	112.7(3)	C7–Si2–C9	111.47(16)
C4–C5–C6	110.4(3)		

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	21(2)	23(2)	29(2)	–4(1)	–5(1)	–4(1)
C2	19(2)	23(2)	29(2)	–6(1)	1(1)	–5(1)
C3	18(2)	28(2)	23(2)	–2(1)	–2(1)	–6(1)
C4	19(2)	27(2)	26(2)	–2(1)	–4(1)	–5(1)
C5	21(2)	29(2)	25(2)	–2(1)	1(1)	–3(1)
C6	29(2)	29(2)	22(2)	–4(1)	–2(1)	–3(1)
C7	38(2)	37(2)	37(2)	–6(2)	–14(2)	1(2)
C8	27(2)	41(2)	42(2)	–12(2)	3(2)	–7(2)
C9	33(2)	24(2)	28(2)	–4(2)	–2(2)	–3(1)
C10	47(2)	43(2)	45(3)	–8(2)	10(2)	–20(2)
C11	48(2)	28(2)	48(3)	–10(2)	–15(2)	0(2)
C12	29(2)	34(2)	43(2)	–12(2)	–3(2)	–9(2)
C13	30(2)	30(2)	31(2)	–6(2)	–5(2)	–6(2)
C14	26(2)	31(2)	24(2)	–5(2)	1(1)	–7(1)
O1	24(1)	21(1)	29(1)	–4(1)	–6(1)	–4(1)
O2	21(1)	25(1)	37(1)	–3(1)	–5(1)	–7(1)
O3	31(1)	30(1)	33(2)	0(1)	–8(1)	–9(1)
O4	20(1)	38(2)	32(2)	6(1)	–6(1)	–6(1)
Si2	22(1)	27(1)	25(1)	–5(1)	–2(1)	–3(1)

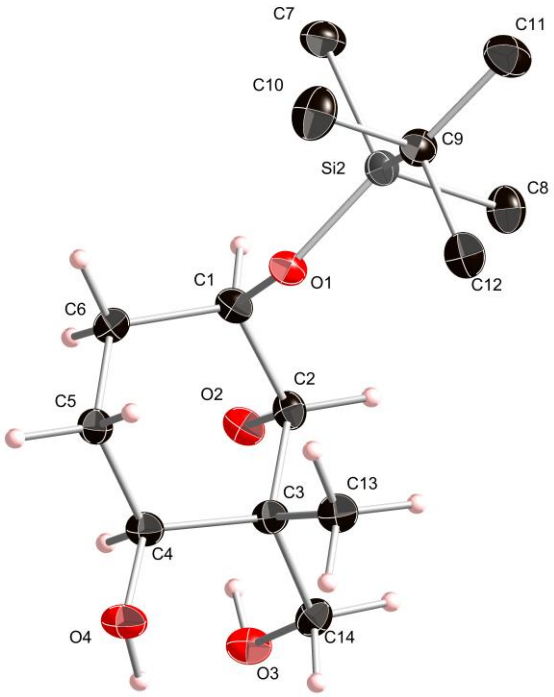
Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	982	–1055	1624	29	1
H2	529	–1374	3502	29	1
H4	5114	–3814	3054	29	1
H5A	7080	–2432	1705	32	1
H5B	6166	–1069	2163	32	1
H6A	4403	–1135	759	32	1
H6B	3822	–2649	1331	32	1
H7A	772	1771	–20	56	1
H7B	–1322	2634	362	56	1
H7C	–1093	968	574	56	1
H8A	–2222	593	2828	55	1
H8B	–2651	2243	2757	55	1
H8C	–1137	1290	3536	55	1
H10A	4092	4271	957	68	1
H10B	2978	3578	258	68	1
H10C	4492	2619	1035	68	1
H11A	–1020	4472	2220	61	1
H11B	–481	4630	983	61	1
H11C	698	5399	1602	61	1
H12A	3122	3970	2839	52	1
H12B	3476	2307	2994	52	1
H12C	1340	3079	3421	52	1
H13A	2650	–553	4500	45	1
H13B	4276	–250	3486	45	1
H13C	4986	–1187	4555	45	1
H14A	3925	–3346	5295	33	1
H14B	1577	–2918	5143	33	1
H2A	–178	–3163	3168	41	1
H3	2145	–4616	4183	47	1
H94	6984	–3735	4236	47	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2A···O4^{i}	0.84	1.83	2.666(3)	171.1
O3–H3···O2	0.84	1.97	2.658(3)	138.5
O4–H94···O3^{ii}	0.84	1.88	2.710(3)	167.3

Symmetry transformations used to generate equivalent atoms:
(i) x–1,y,z (ii) –x+1,–y–1,–z+1

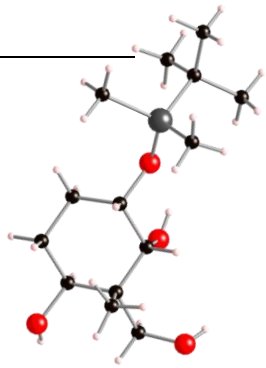


Thermal ellipsoids drawn at the 35% probability level, methyl hydrogens from TBDMS omitted for clarity.

Appendix B

X-Ray Structure of 4.11b

Table 1. Crystal data and structure refinement details.



Identification code	**2009sot0388**	
Empirical formula	$C_{14}H_{30.50}O_{4.25}Si$	
	$C_{14}H_{30}O_4Si$, 0.25(H_2O)	
Formula weight	294.97	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 6.8663(3) Å	α = 64.7881(18)°
	b = 22.2825(8) Å	β = 89.127(2)°
	c = 24.5254(8) Å	γ = 89.570(2)°
Volume	3394.5(2) $Å^3$	
Z	8 (4 molecules in the asymmetric unit)	
Density (calculated)	1.154 Mg / m^3	
Absorption coefficient	0.148 mm^{-1}	
F(000)	1300	
Crystal	Needle; Colourless	
Crystal size	0.4 × 0.02 × 0.02 mm^3	
θ range for data collection	2.97 – 25.03°	
Index ranges	$-8 \le h \le 7$, $-26 \le k \le 26$, $-29 \le l \le 29$	
Reflections collected	44593	
Independent reflections	11879 [R_{int} = 0.1389]	
Completeness to θ = 25.03°	99.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9970 and 0.9469	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11879 / 393 / 736	
Goodness-of-fit on F^2	1.094	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1564, *wR2* = 0.2788	
R indices (all data)	*R1* = 0.2359, *wR2* = 0.3183	
Largest diff. peak and hole	0.842 and –0.615 e $Å^{-3}$	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the water whose torsion angle was allowed to refine.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	383(4)	1717(1)	8736(1)	33(1)	1
O101	4381(9)	2858(3)	5810(3)	25(1)	1
O102	1707(10)	2225(3)	8158(3)	31(2)	1
O103	2555(10)	3405(3)	7211(2)	27(2)	1
O104	–196(9)	4017(3)	6012(3)	29(2)	1
C101	342(14)	2609(4)	6286(4)	26(2)	1
C102	1691(13)	3746(4)	6006(4)	23(2)	1
C103	1437(13)	2919(4)	7102(3)	22(2)	1
C104	1844(13)	3005(4)	6454(4)	22(2)	1
C105	3969(14)	2796(4)	6405(4)	24(2)	1
C106	4407(14)	2093(4)	6862(4)	27(2)	1
C107	3996(14)	2027(4)	7502(4)	27(2)	1
C108	1973(15)	2227(4)	7569(4)	29(2)	1
C109	–810(20)	1095(7)	8559(5)	81(5)	1
C110	–1470(20)	2236(7)	8910(6)	79(5)	1
C111	3500(20)	864(7)	9321(6)	73(4)	1
C112	2000(17)	1339(6)	9411(4)	44(3)	1
C113	3112(17)	1892(6)	9488(5)	47(3)	1
C114	740(20)	964(6)	9978(5)	61(4)	1
Si2	6176(4)	4569(1)	7648(1)	24(1)	1
O201	3177(9)	6074(3)	4684(2)	24(1)	1
O202	4351(9)	4829(3)	7176(2)	24(1)	1
O203	1287(9)	4850(3)	6488(3)	23(1)	1
O204	–1186(9)	6248(3)	5888(3)	28(2)	1
C201	2935(14)	6607(4)	5584(4)	24(2)	1
C202	4(13)	6018(4)	5519(4)	24(2)	1
C203	2322(12)	5463(4)	6365(4)	18(2)	1
C204	2100(13)	5935(4)	5696(4)	19(2)	1
C205	3195(13)	5623(4)	5314(4)	20(2)	1
C206	5291(13)	5472(4)	5490(4)	24(2)	1
C207	5522(13)	5023(4)	6171(4)	22(2)	1
C208	4396(14)	5299(4)	6557(3)	23(2)	1
C209	7443(16)	3865(5)	7579(4)	37(2)	1
C210	7918(16)	5252(5)	7492(4)	39(3)	1
C211	3390(18)	3767(5)	8486(5)	47(3)	1
C212	4903(16)	4296(4)	8407(4)	32(2)	1
C213	3830(16)	4896(5)	8431(5)	41(3)	1
C214	6424(18)	4031(6)	8911(5)	51(3)	1
Si3	6509(4)	10431(1)	2348(1)	24(1)	1
O301	3247(9)	8933(3)	5308(2)	24(1)	1

O302	4615(9)	10186(3)	2815(2)	25(1)	1
O303	1446(9)	10157(3)	3499(3)	24(1)	1
O304	–995(9)	8761(3)	4104(3)	27(2)	1
C301	3100(13)	8390(4)	4408(4)	26(2)	1
C302	106(13)	9002(4)	4461(4)	23(2)	1
C303	2507(13)	9551(4)	3623(4)	21(2)	1
C304	2242(13)	9074(4)	4294(4)	18(2)	1
C305	3285(13)	9385(4)	4674(3)	20(2)	1
C306	5383(13)	9545(4)	4496(4)	23(2)	1
C307	5664(14)	9989(4)	3823(4)	25(2)	1
C308	4626(13)	9712(4)	3440(3)	21(2)	1
C309	7668(17)	11155(5)	2393(4)	39(3)	1
C310	8312(14)	9749(5)	2522(4)	31(2)	1
C311	3883(19)	11213(5)	1470(5)	54(3)	1
C312	5391(15)	10665(5)	1590(4)	32(2)	1
C313	4312(16)	10067(5)	1576(4)	39(3)	1
C314	6944(17)	10899(5)	1091(4)	46(3)	1
Si4	614(4)	13396(1)	1282(1)	32(1)	1
O401	4368(9)	12139(3)	4195(2)	26(2)	1
O402	1679(10)	12801(3)	1850(3)	30(2)	1
O403	2580(10)	11614(3)	2787(3)	30(2)	1
O404	–178(9)	10967(3)	3999(3)	26(1)	1
C401	282(13)	12380(4)	3734(4)	24(2)	1
C402	1700(13)	11257(4)	3997(4)	26(2)	1
C403	1415(15)	12079(4)	2909(4)	28(2)	1
C404	1832(13)	11987(4)	3562(4)	21(2)	1
C405	3916(14)	12206(4)	3593(3)	22(2)	1
C406	4352(15)	12915(4)	3147(4)	30(2)	1
C407	3961(15)	12991(5)	2503(4)	31(2)	1
C408	1923(15)	12788(5)	2441(4)	30(2)	1
C409	1780(20)	14223(6)	1127(5)	64(4)	1
C410	–1988(19)	13462(7)	1447(6)	65(4)	1
C411	3156(16)	13137(5)	512(4)	40(3)	1
C412	975(16)	13204(6)	625(5)	42(3)	1
C413	–45(19)	12540(6)	755(5)	56(3)	1
C414	120(20)	13762(7)	54(5)	64(4)	1
O1W	7605(9)	7509(3)	4991(3)	25(1)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–O102	1.652(7)	Si3–O302	1.653(7)
Si1–C109	1.820(13)	Si3–C309	1.850(9)
Si1–C110	1.876(14)	Si3–C310	1.860(9)
Si1–C112	1.880(11)	Si3–C312	1.879(9)
O101–C105	1.431(10)	O301–C305	1.448(9)
O102–C108	1.452(10)	O302–C308	1.444(9)
O103–C103	1.449(10)	O303–C303	1.446(9)
O104–C102	1.427(10)	O304–C302	1.433(9)
C101–C104	1.532(12)	C301–C304	1.542(11)
C102–C104	1.550(11)	C302–C304	1.507(12)
C103–C108	1.525(12)	C303–C308	1.516(13)
C103–C104	1.538(11)	C303–C304	1.542(11)
C104–C105	1.546(13)	C304–C305	1.562(11)
C105–C106	1.519(12)	C305–C306	1.499(13)
C106–C107	1.535(12)	C306–C307	1.532(12)
C107–C108	1.483(13)	C307–C308	1.515(11)
C111–C112	1.551(16)	C311–C312	1.528(14)
C112–C113	1.533(15)	C312–C314	1.527(14)
C112–C114	1.540(15)	C312–C313	1.543(13)
Si2–O202	1.646(6)	Si4–O402	1.635(6)
Si2–C210	1.847(11)	Si4–C410	1.844(13)
Si2–C209	1.856(10)	Si4–C412	1.847(11)
Si2–C212	1.895(10)	Si4–C409	1.897(12)
O201–C205	1.441(9)	O401–C405	1.457(9)
O202–C208	1.431(9)	O402–C408	1.451(10)
O203–C203	1.454(9)	O403–C403	1.431(11)
O204–C202	1.456(9)	O404–C402	1.446(10)
C201–C204	1.517(11)	C401–C404	1.537(12)
C202–C204	1.497(12)	C402–C404	1.520(11)
C203–C208	1.499(12)	C403–C408	1.544(13)
C203–C204	1.534(11)	C403–C404	1.555(11)
C204–C205	1.567(11)	C404–C405	1.529(13)
C205–C206	1.503(12)	C405–C406	1.520(12)
C206–C207	1.549(11)	C406–C407	1.541(12)
C207–C208	1.530(12)	C407–C408	1.504(14)
C211–C212	1.525(14)	C411–C412	1.537(15)
C212–C214	1.542(14)	C412–C413	1.545(15)
C212–C213	1.544(13)	C412–C414	1.545(14)

O102–Si1–C109	110.9(5)	O102–Si1–C112	108.4(5)
O102–Si1–C110	107.1(5)	C109–Si1–C112	112.6(6)
C109–Si1–C110	110.7(8)	C110–Si1–C112	106.8(6)

C108–O102–Si1	128.6(6)	C206–C205–C204	112.2(7)
O104–C102–C104	112.6(7)	C205–C206–C207	112.5(7)
O103–C103–C108	109.0(7)	C208–C207–C206	111.4(7)
O103–C103–C104	109.0(7)	O202–C208–C203	107.0(7)
C108–C103–C104	112.1(7)	O202–C208–C207	110.8(6)
C101–C104–C103	109.3(7)	C203–C208–C207	112.5(7)
C101–C104–C105	113.1(7)	C211–C212–C214	110.9(9)
C103–C104–C105	109.2(7)	C211–C212–C213	108.0(9)
C101–C104–C102	108.9(7)	C214–C212–C213	109.5(8)
C103–C104–C102	110.2(7)	C211–C212–Si2	109.8(6)
C105–C104–C102	106.0(7)	C214–C212–Si2	109.4(8)
O101–C105–C106	109.7(7)	C213–C212–Si2	109.1(6)
O101–C105–C104	110.5(7)	O302–Si3–C309	109.8(4)
C106–C105–C104	112.4(7)	O302–Si3–C310	111.1(4)
C105–C106–C107	109.9(7)	C309–Si3–C310	110.2(5)
C108–C107–C106	111.5(7)	O302–Si3–C312	103.1(4)
O102–C108–C107	109.8(7)	C309–Si3–C312	111.2(4)
O102–C108–C103	107.1(7)	C310–Si3–C312	111.2(4)
C107–C108–C103	113.7(8)	C308–O302–Si3	126.8(5)
C113–C112–C114	108.9(9)	O304–C302–C304	112.5(7)
C113–C112–C111	108.6(11)	O303–C303–C308	109.6(7)
C114–C112–C111	110.6(10)	O303–C303–C304	109.2(6)
C113–C112–Si1	109.4(7)	C308–C303–C304	112.8(7)
C114–C112–Si1	109.3(8)	C302–C304–C303	109.8(7)
C111–C112–Si1	110.2(8)	C302–C304–C301	109.5(7)
O202–Si2–C210	110.0(4)	C303–C304–C301	109.3(7)
O202–Si2–C209	110.4(4)	C302–C304–C305	108.6(7)
C210–Si2–C209	109.6(5)	C303–C304–C305	107.9(7)
O202–Si2–C212	102.4(4)	C301–C304–C305	111.7(7)
C210–Si2–C212	112.7(4)	O301–C305–C306	106.9(6)
C209–Si2–C212	111.5(4)	O301–C305–C304	110.8(7)
C208–O202–Si2	128.1(6)	C306–C305–C304	112.8(7)
O204–C202–C204	112.5(7)	C305–C306–C307	112.8(7)
O203–C203–C208	108.9(6)	C308–C307–C306	111.5(7)
O203–C203–C204	108.9(6)	O302–C308–C307	111.0(7)
C208–C203–C204	113.9(7)	O302–C308–C303	105.8(6)
C202–C204–C201	109.1(7)	C307–C308–C303	112.7(7)
C202–C204–C203	111.1(7)	C314–C312–C311	109.7(9)
C201–C204–C203	109.0(7)	C314–C312–C313	108.7(8)
C202–C204–C205	108.0(6)	C311–C312–C313	107.1(9)
C201–C204–C205	111.6(7)	C314–C312–Si3	111.0(7)
C203–C204–C205	108.1(6)	C311–C312–Si3	109.7(6)
O201–C205–C206	107.2(7)	C313–C312–Si3	110.4(6)
O201–C205–C204	110.3(6)	O402–Si4–C410	111.3(5)

O402–Si4–C412	106.5(4)	C401–C404–C403	107.8(7)
C410–Si4–C412	112.1(5)	O401–C405–C406	108.2(6)
O402–Si4–C409	110.0(5)	O401–C405–C404	111.6(7)
C410–Si4–C409	107.1(7)	C406–C405–C404	113.7(7)
C412–Si4–C409	109.8(6)	C405–C406–C407	109.2(7)
C408–O402–Si4	125.1(5)	C408–C407–C406	112.0(8)
O404–C402–C404	113.3(7)	O402–C408–C407	110.2(8)
O403–C403–C408	108.9(7)	O402–C408–C403	107.1(7)
O403–C403–C404	108.4(7)	C407–C408–C403	112.9(8)
C408–C403–C404	111.5(7)	C411–C412–C413	108.8(9)
C402–C404–C405	106.6(7)	C411–C412–C414	108.5(9)
C402–C404–C401	109.4(7)	C413–C412–C414	109.9(10)
C405–C404–C401	113.4(7)	C411–C412–Si4	110.5(7)
C402–C404–C403	110.2(7)	C413–C412–Si4	108.8(8)
C405–C404–C403	109.5(7)	C414–C412–Si4	110.3(8)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	37(2)	34(2)	21(1)	–6(1)	2(1)	–2(1)
O101	32(4)	26(3)	22(3)	–15(3)	3(3)	–6(3)
O102	50(4)	27(3)	16(3)	–9(3)	3(3)	–6(3)
O103	53(4)	18(3)	10(3)	–7(3)	–5(3)	–2(3)
O104	35(4)	17(3)	30(3)	–6(3)	–5(3)	–1(3)
C101	38(6)	21(5)	17(4)	–7(4)	2(4)	–4(4)
C102	34(6)	17(4)	18(4)	–7(4)	0(4)	–7(4)
C103	26(5)	27(5)	11(4)	–7(4)	1(4)	–3(4)
C104	31(5)	18(4)	15(4)	–7(4)	–3(4)	1(4)
C105	36(5)	18(4)	20(4)	–11(4)	–2(4)	–4(4)
C106	36(6)	20(5)	28(5)	–14(4)	–1(4)	7(4)
C107	40(6)	14(4)	19(4)	–1(4)	0(4)	0(4)
C108	53(6)	22(5)	9(4)	–4(4)	–3(4)	–2(4)
C109	107(12)	79(10)	30(6)	2(7)	–1(7)	–65(9)
C110	72(10)	74(10)	49(8)	12(7)	18(7)	21(8)
C111	71(10)	74(10)	64(9)	–20(8)	3(7)	35(8)
C112	52(7)	47(7)	28(5)	–12(5)	0(5)	9(6)
C113	58(8)	53(7)	29(6)	–17(5)	–10(5)	3(6)
C114	95(11)	52(8)	20(5)	0(5)	–1(6)	–4(7)
Si2	36(2)	20(1)	16(1)	–7(1)	–4(1)	4(1)
O201	34(4)	18(3)	14(3)	0(3)	10(3)	–7(3)
O202	33(4)	20(3)	17(3)	–5(3)	3(3)	–4(3)
O203	32(4)	14(3)	19(3)	–4(3)	–1(3)	1(3)
O204	45(4)	13(3)	26(3)	–9(3)	–6(3)	5(3)
C201	33(6)	17(4)	22(5)	–7(4)	2(4)	–8(4)
C202	36(6)	20(4)	19(4)	–13(4)	8(4)	–4(4)
C203	25(5)	12(4)	24(4)	–14(4)	6(4)	–6(4)
C204	26(5)	14(4)	18(4)	–6(3)	5(4)	–7(4)
C205	38(5)	8(4)	17(4)	–8(3)	3(4)	–3(4)
C206	33(5)	22(5)	18(4)	–9(4)	–1(4)	–8(4)
C207	29(5)	20(4)	16(4)	–5(4)	–4(4)	–2(4)
C208	45(6)	7(4)	12(4)	0(3)	3(4)	–5(4)
C209	52(7)	28(5)	30(5)	–11(5)	1(5)	1(5)
C210	45(7)	41(6)	25(5)	–8(5)	–5(5)	–2(5)
C211	70(8)	39(6)	36(6)	–19(5)	21(6)	–21(6)
C212	57(7)	22(5)	20(5)	–11(4)	3(5)	1(5)
C213	45(7)	46(6)	33(6)	–18(5)	–3(5)	4(5)
C214	74(9)	51(7)	26(6)	–15(5)	–15(6)	14(6)

Si3	34(2)	22(1)	16(1)	−7(1)	0(1)	−1(1)
O301	33(4)	25(3)	13(3)	−5(3)	3(3)	6(3)
O302	31(4)	23(3)	15(3)	−3(3)	−3(3)	2(3)
O303	37(4)	14(3)	18(3)	−4(3)	2(3)	0(3)
O304	37(4)	19(3)	28(3)	−10(3)	−4(3)	−2(3)
C301	31(5)	20(5)	22(5)	−6(4)	−7(4)	6(4)
C302	30(5)	18(4)	20(4)	−7(4)	−3(4)	−2(4)
C303	32(5)	12(4)	21(4)	−9(4)	−4(4)	11(4)
C304	28(5)	9(4)	15(4)	−4(3)	−4(4)	4(3)
C305	28(5)	18(4)	14(4)	−7(4)	−7(4)	1(4)
C306	41(6)	18(4)	17(4)	−13(4)	−8(4)	7(4)
C307	29(5)	19(4)	28(5)	−11(4)	−2(4)	1(4)
C308	34(5)	15(4)	11(4)	−3(3)	−6(4)	4(4)
C309	63(8)	27(5)	26(5)	−9(4)	−7(5)	−13(5)
C310	31(6)	34(5)	30(5)	−15(5)	1(4)	4(4)
C311	90(10)	40(6)	30(6)	−14(5)	−25(6)	23(6)
C312	46(6)	27(5)	23(5)	−11(4)	−4(4)	−3(5)
C313	53(7)	41(6)	26(5)	−18(5)	3(5)	−13(5)
C314	68(8)	43(6)	19(5)	−5(5)	4(5)	−14(6)
Si4	40(2)	31(2)	19(1)	−5(1)	−1(1)	4(1)
O401	43(4)	19(3)	18(3)	−8(3)	−8(3)	8(3)
O402	53(4)	22(3)	18(3)	−11(3)	−1(3)	5(3)
O403	51(4)	23(3)	17(3)	−10(3)	3(3)	6(3)
O404	43(4)	15(3)	22(3)	−10(3)	8(3)	−2(3)
C401	29(5)	24(5)	22(5)	−13(4)	3(4)	2(4)
C402	46(6)	14(4)	20(4)	−9(4)	4(4)	4(4)
C403	41(6)	23(5)	19(4)	−7(4)	−4(4)	4(4)
C404	37(5)	15(4)	14(4)	−8(3)	4(4)	−1(4)
C405	46(6)	15(4)	6(4)	−5(3)	3(4)	1(4)
C406	40(6)	27(5)	23(5)	−9(4)	0(4)	2(4)
C407	47(6)	22(5)	23(5)	−8(4)	2(4)	0(4)
C408	50(6)	26(5)	19(4)	−14(4)	−5(4)	4(4)
C409	107(12)	38(7)	45(7)	−13(6)	−28(7)	−3(7)
C410	72(10)	74(9)	60(8)	−38(8)	−16(7)	24(8)
C411	56(7)	39(6)	24(5)	−11(5)	2(5)	3(5)
C412	44(7)	51(7)	33(6)	−19(5)	−9(5)	7(5)
C413	77(9)	46(7)	57(7)	−34(6)	−7(7)	−19(6)
C414	88(10)	77(9)	25(6)	−20(6)	−23(6)	35(8)
O1W	40(4)	19(3)	19(3)	−13(3)	−3(3)	6(3)

Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H901	5592	2868	5753	38	1
H903	2839	3251	7577	40	1
H904	–105	4428	5898	44	1
H10A	463	2136	6556	38	1
H10B	573	2674	5869	38	1
H10C	–972	2762	6325	38	1
H60D	2670	4003	6111	28	1
H60E	1997	3793	5594	28	1
H103	19	2997	7146	26	1
H105	4853	3104	6484	29	1
H90F	5790	1986	6824	32	1
H90G	3588	1776	6783	32	1
H90D	4206	1561	7795	32	1
H90E	4920	2308	7595	32	1
H108	1054	1899	7534	34	1
H10D	–1717	1314	8228	121	1
H10E	–1519	784	8915	121	1
H10F	178	853	8438	121	1
H11A	–818	2504	9082	118	1
H11B	–2431	1946	9200	118	1
H11C	–2127	2528	8539	118	1
H11D	4054	572	9710	110	1
H11E	4541	1124	9046	110	1
H11F	2847	596	9148	110	1
H11G	2184	2185	9564	70	1
H11H	3869	2148	9121	70	1
H11I	3994	1695	9830	70	1
H11J	1578	707	10318	91	1
H11K	–149	664	9905	91	1
H11L	–25	1283	10072	91	1
H801	4302	6101	4536	36	1
H803	1842	4533	6767	34	1
H804	–1381	6658	5699	42	1
H20A	2792	6912	5158	36	1
H20B	4318	6558	5687	36	1
H20C	2234	6784	5835	36	1
H20D	–93	6339	5091	28	1
H20E	–509	5587	5557	28	1
H203	1706	5675	6611	22	1

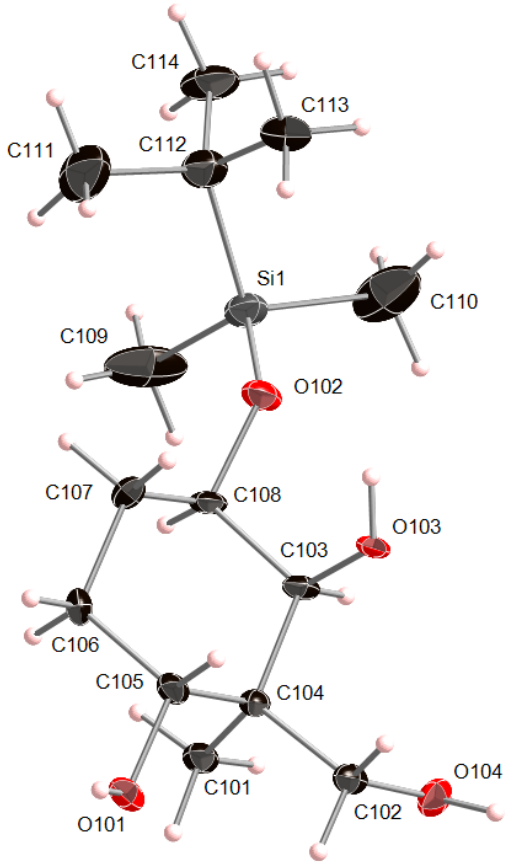
H205	2524	5203	5371	24	1
H20F	5995	5894	5387	29	1
H20G	5893	5250	5255	29	1
H20H	5039	4572	6262	27	1
H20I	6919	4987	6275	27	1
H208	5058	5712	6525	27	1
H20J	6489	3525	7613	56	1
H20K	8398	3674	7902	56	1
H20L	8112	4024	7187	56	1
H21A	8273	5452	7063	59	1
H21B	9090	5078	7732	59	1
H21C	7315	5589	7598	59	1
H21D	2765	3618	8884	71	1
H21E	4030	3389	8452	71	1
H21F	2404	3953	8173	71	1
H21G	2926	5083	8094	61	1
H21H	4782	5235	8401	61	1
H21I	3102	4752	8812	61	1
H21J	7357	4383	8858	76	1
H21K	7116	3654	8892	76	1
H21L	5767	3888	9304	76	1
H301	2140	8943	5455	36	1
H703	1776	10448	3158	36	1
H704	–1001	8344	4270	41	1
H30A	2949	8088	4836	38	1
H30B	4485	8438	4296	38	1
H30C	2409	8210	4164	38	1
H80D	–47	8693	4891	28	1
H80E	–420	9439	4407	28	1
H303	1943	9338	3376	26	1
H305	2591	9803	4620	24	1
H80F	6112	9126	4600	28	1
H80G	5936	9769	4731	28	1
H777	5153	10438	3731	30	1
H30G	7072	10030	3721	30	1
H308	5310	9300	3474	25	1
H30D	6661	11472	2386	59	1
H30E	8558	11369	2048	59	1
H30F	8398	11008	2768	59	1
H31A	8777	9607	2934	46	1
H31B	9415	9906	2238	46	1
H31C	7694	9373	2485	46	1
H31D	4482	11582	1523	81	1
H31E	2787	11039	1754	81	1
H31F	3414	11370	1057	81	1
H31G	3743	10196	1178	58	1

H31H	3276	9923	1884	58	1
H31I	5233	9701	1657	58	1
H31J	7932	10552	1177	69	1
H31K	7560	11303	1072	69	1
H31L	6337	10993	704	69	1
H601	4829	11760	4400	40	1
H603	2605	11723	2415	45	1
H604	−144	10785	3761	40	1
H40A	−1016	12260	3653	36	1
H40B	494	12856	3494	36	1
H40C	382	12275	4163	36	1
H451	2717	11009	3888	31	1
H452	1970	11209	4409	31	1
H403	6	11990	2877	34	1
H405	4818	11907	3499	27	1
H70D	5730	13022	3180	36	1
H70E	3516	13226	3237	36	1
H655	4167	13459	2214	37	1
H654	4902	12715	2401	37	1
H408	984	13107	2490	36	1
H40D	1630	14313	1482	97	1
H40E	1149	14575	782	97	1
H40F	3171	14207	1035	97	1
H41A	−2682	13070	1469	98	1
H41B	−2541	13861	1126	98	1
H41C	−2123	13493	1833	98	1
H41D	3690	12752	851	61	1
H41E	3839	13539	471	61	1
H41F	3329	13077	140	61	1
H41G	−5	12461	391	84	1
H41H	−1403	12560	875	84	1
H41I	627	12178	1082	84	1
H41J	771	14182	−27	96	1
H41K	−1282	13806	118	96	1
H41L	310	13653	−290	96	1
H1W	6800(100)	7380(50)	4810(40)	60	1
H2W	7070(120)	7670(50)	5210(40)	60	1

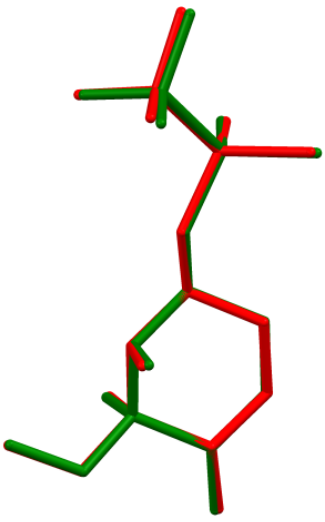
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O103–H903···O102	0.84	2.25	2.725(8)	115.7
O104–H904···O203	0.84	2.26	2.787(8)	121.0
O303–H703···O302	0.84	2.28	2.712(9)	112.2
O303–H703···O403	0.84	2.43	3.060(8)	132.9
O203–H803···O202	0.84	2.24	2.704(8)	114.5
O203–H803···O103	0.84	2.33	3.068(8)	147.7
O403–H603···O402	0.84	2.30	2.739(8)	113.3
O404–H604···O303	0.84	2.07	2.795(8)	144.3
O101–H901···O201^{i}	0.84	2.30	2.736(8)	113.1
O201–H801···O101^{i}	0.84	2.29	2.736(8)	113.4
O1W–H1W···O101^{i}	0.84(2)	1.99(4)	2.800(8)	161(9)
O401–H601···O301^{ii}	0.84	1.92	2.721(8)	157.8
O301–H301···O404^{iii}	0.84	1.95	2.753(8)	158.7
O304–H704···O1W^{iv}	0.84	2.16	2.870(9)	141.8

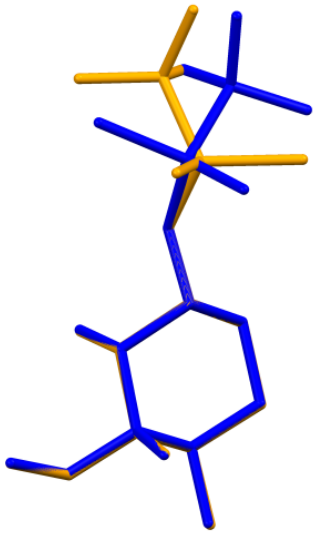
Symmetry transformations used to generate equivalent atoms:
(i) –x+1,–y+1,–z+1 (ii) –x+1,–y+2,–z+1 (iii) –x,–y+2,–z+1
(iv) x–1,y,z



One of the 4 independent molecules in the asymmetric unit, thermal ellipsoids drawn at the 35% probability level



Molecules 1 and 4

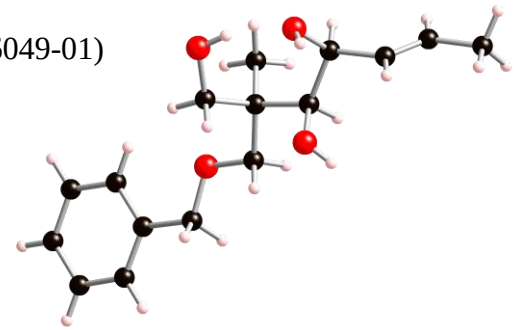


Molecules 2 and 3

Appendix C

X-Ray Crystal structure of 5.25a

Table 1. Crystal data and structure refinement details.



Identification code	**2010sot1103** (CO6049-01)
Empirical formula	$C_{16}H_{24}O_4$
Formula weight	280.35
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.4394(13) Å
	b = 6.1489(7) Å β = 101.195(6)°
	c = 20.7893(19) Å
Volume	1559.9(3) Å^3
Z	4
Density (calculated)	1.194 Mg / m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	608
Crystal	Lath; Colourless
Crystal size	0.12 × 0.03 × 0.02 mm^3
θ range for data collection	3.34 – 25.03°
Index ranges	$-14 \le h \le 14$, $-7 \le k \le 7$, $-24 \le l \le 24$
Reflections collected	12669
Independent reflections	2750 [R_{int} = 0.1215]
Completeness to θ = 25.03°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9983 and 0.9899
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2750 / 3 / 195
Goodness-of-fit on F^2	1.121
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1208, *wR2* = 0.1878
R indices (all data)	*R1* = 0.2147, *wR2* = 0.2288
Largest diff. peak and hole	0.358 and –0.247 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: Aromatic, methylenic and methine hydrogens were placed in calculated positions and refined using a riding model. Methyl hydrogens were placed in calculated positions and the torsion angle allowed to refine. Hydroxyl hydrogens were refined using distance restraints (0.84) only.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	9610(3)	3519(7)	1063(2)	51(1)	1
O2	6682(4)	506(8)	280(3)	68(2)	1
O3	6556(4)	6283(7)	364(2)	47(1)	1
O4	5515(4)	3100(8)	–561(2)	55(1)	1
C1	11228(5)	967(10)	1777(3)	45(2)	1
C2	12058(5)	–342(12)	2121(3)	50(2)	1
C3	12677(5)	395(13)	2708(3)	54(2)	1
C4	12463(5)	2394(12)	2954(3)	49(2)	1
C5	11644(5)	3666(11)	2605(3)	47(2)	1
C6	11021(4)	2985(10)	2017(3)	39(2)	1
C7	10136(5)	4441(11)	1659(3)	44(2)	1
C8	8788(5)	4913(10)	709(3)	47(2)	1
C9	7932(5)	3590(10)	235(3)	37(1)	1
C10	8474(6)	2400(13)	–258(3)	61(2)	1
C11	7421(5)	1985(10)	650(3)	43(2)	1
C12	7111(5)	5339(10)	–112(3)	39(2)	1
C13	6261(5)	4670(11)	–718(3)	45(2)	1
C14	5613(5)	6607(11)	–1033(3)	53(2)	1
C15	5687(6)	7472(12)	–1568(3)	62(2)	1
C16	5049(6)	9401(11)	–1866(3)	59(2)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C7	1.404(6)	C5–C6	1.380(8)
O1–C8	1.424(7)	C6–C7	1.499(8)
O2–C11	1.411(7)	C8–C9	1.536(8)
O3–C12	1.433(7)	C9–C10	1.520(8)
O4–C13	1.420(7)	C9–C11	1.528(8)
C1–C6	1.381(8)	C9–C12	1.560(8)
C1–C2	1.392(8)	C12–C13	1.536(8)
C2–C3	1.387(9)	C13–C14	1.514(9)
C3–C4	1.377(9)	C14–C15	1.253(9)
C4–C5	1.374(8)	C15–C16	1.493(9)

C7–O1–C8	112.2(5)	C11–C9–C8	107.0(5)
C6–C1–C2	120.4(6)	C10–C9–C12	110.8(5)
C3–C2–C1	119.6(7)	C11–C9–C12	113.6(5)
C4–C3–C2	120.2(6)	C8–C9–C12	104.0(5)
C5–C4–C3	119.3(6)	O2–C11–C9	114.0(5)
C4–C5–C6	121.8(6)	O3–C12–C13	109.1(5)
C5–C6–C1	118.7(6)	O3–C12–C9	108.6(4)
C5–C6–C7	119.4(6)	C13–C12–C9	118.6(5)
C1–C6–C7	121.9(5)	O4–C13–C14	108.5(5)
O1–C7–C6	111.6(5)	O4–C13–C12	111.8(5)
O1–C8–C9	110.6(5)	C14–C13–C12	111.6(5)
C10–C9–C11	111.0(5)	C15–C14–C13	126.4(7)
C10–C9–C8	110.1(5)	C14–C15–C16	125.5(8)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	40(2)	56(3)	51(3)	–12(2)	–8(2)	12(2)
O2	71(4)	35(3)	87(4)	5(3)	–8(3)	–15(3)
O3	49(3)	30(3)	56(3)	–3(2)	–1(2)	8(2)
O4	42(3)	55(3)	65(3)	–6(3)	2(2)	–10(3)
C1	40(4)	50(4)	41(4)	0(3)	2(3)	–2(3)
C2	40(4)	55(4)	54(4)	7(4)	4(3)	3(3)
C3	32(4)	82(6)	48(4)	15(4)	8(3)	1(4)
C4	40(4)	64(5)	40(4)	3(4)	1(3)	–9(3)
C5	49(4)	44(4)	45(4)	–1(3)	5(3)	–8(3)
C6	29(3)	44(4)	43(3)	3(3)	7(3)	–4(3)
C7	36(3)	54(4)	39(3)	–1(3)	3(3)	–4(3)
C8	38(3)	43(4)	55(4)	5(3)	–3(3)	–2(3)
C9	39(3)	37(3)	36(3)	–9(3)	5(3)	–3(3)
C10	52(4)	80(5)	50(4)	–2(4)	5(3)	14(4)
C11	46(4)	33(3)	46(4)	0(3)	2(3)	0(3)
C12	37(3)	37(3)	42(3)	5(3)	0(3)	–4(3)
C13	41(4)	48(4)	45(4)	5(3)	3(3)	0(3)
C14	53(4)	51(4)	50(4)	–2(4)	1(3)	–7(4)
C15	69(5)	60(5)	55(4)	2(4)	4(4)	–8(4)
C16	61(5)	55(4)	57(4)	5(4)	3(3)	9(4)

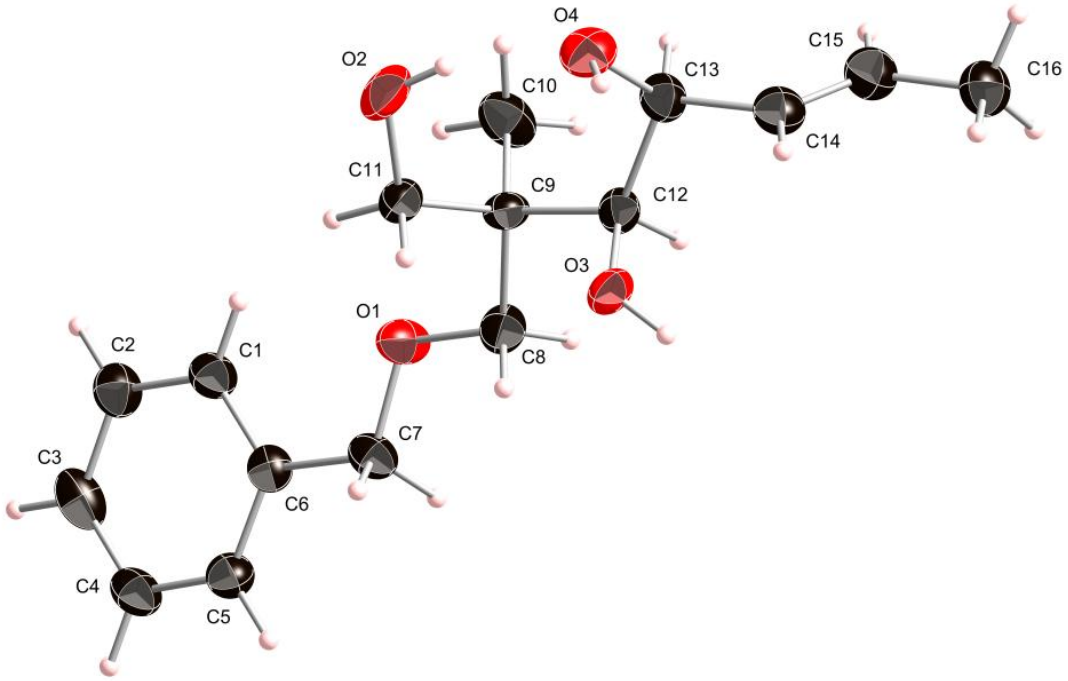
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H92	6230(60)	1090(140)	–20(30)	120(40)	1
H93	6560(50)	7640(30)	350(30)	50(20)	1
H94	5030(50)	3730(120)	–410(30)	90(30)	1
H1	10802	468	1374	53	1
H2	12198	–1730	1955	60	1
H3	13252	–483	2941	65	1
H4	12876	2888	3360	59	1
H5	11504	5051	2773	56	1
H7A	9590	4712	1938	52	1
H7B	10459	5857	1572	52	1
H8A	9133	5991	459	56	1
H8B	8425	5713	1021	56	1
H10A	8763	3462	–533	92	1
H10B	7933	1472	–536	92	1
H10C	9075	1500	–25	92	1
H11A	8015	1153	931	51	1
H11B	7031	2814	943	51	1
H12	7562	6523	–256	47	1
H13	6658	4015	–1045	54	1
H14	5100	7227	–802	63	1
H15	6191	6847	–1804	75	1
H16A	4562	9894	–1577	88	1
H16B	4611	9000	–2294	88	1
H16C	5555	10575	–1922	88	1

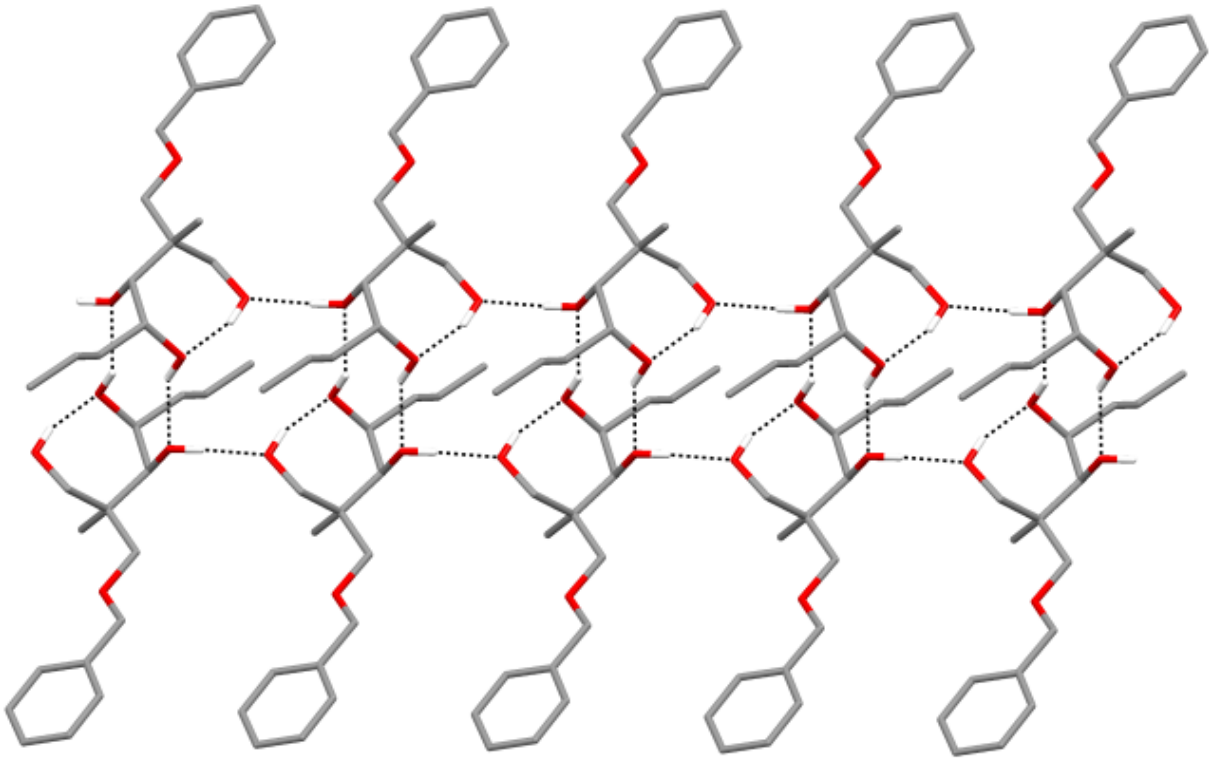
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O3–H93···O2^{i}	0.84(2)	1.78(2)	2.609(6)	174(6)
O2–H92···O4	0.84(2)	1.78(4)	2.592(7)	161(10)
O4–H94···O3^{ii}	0.83(2)	1.99(5)	2.713(7)	145(7)

Symmetry transformations used to generate equivalent atoms:
(i) x,y+1,z (ii) –x+1,–y+1,–z



Thermal ellipsoids drawn at the 35% probability level



Part of a hydrogen bonded chain that extends along the *b* direction.